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Synthesis of polyfluoroalkyl-γ-lactones from polyfluoroalkyl halides and 4-pentenoic acids

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Abstract—The polyfluoroalkyl-lactonization of 4-pentenoic acids having a substituent at the 2 or 3 position with the polyfluoroalkyl iodides initiated by sodium dithionite was realized in good yields. A new and efficient method for the synthesis of fluorine-containing γ-lactones is described. © 2003 Elsevier Science Ltd. All rights reserved.

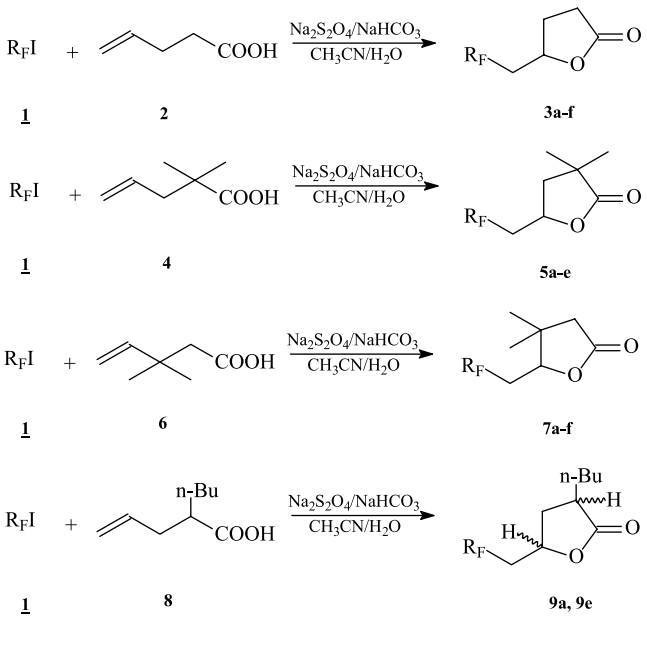
1. Introduction

Lactones represent a class of naturally occurring compounds with manifold biological activity.[1] Halolactonization is a most useful methodology for the synthesis of lactones.[2] It is utilized elegantly for stereoselective functional group incorporation and manipulation in (2*S*,3*R*,4*R*,5*S*)-trihydroxypipecolinic acid synthesis,[3] in total synthesis of tumor inhibitors, e.g. camptothecin[4] and in active insect anti-feedant synthesis.[5] Fluorine-containing lactones are especially important because of the significant effect conferred upon molecules by introduction of fluorine atom.[6] For example, 1-[2,4-dioxo-5-fluoro-(1*H*,3*H*)-pyrimidin-1-yl]-2-(2,3-dihydroxy-2-buten-4-olidylidene)ethane containing a 5-fluoro-substituted uracil ring showed the most significant antitumor activity against murine leukemia and murine mammary carcinoma.[7] 2-Fluorourocanic acid shows obvious changes in its inhibitory behavior towards protoenzymes.[8] In our ongoing studies into new potentially bioactive fluorinated compounds, we have investigated the synthesis of fluorine-containing lactones.

The addition reaction of polyfluoroalkyl iodides with unsaturated compounds, such as olefins and alkynes, initiated by sulfinatodehalogenation reagents (sodium dithionite) has been thoroughly studied in our laboratory.[9] In the case of 4-pentenoic acids, the corresponding polyfluoroalkylated γ-butyrolactones were obtained instead of the adducts as the main product under mild reaction conditions,[10] similar to the halolactonization reaction to give halolactones. It provided a new and convenient synthetic method for fluorine-containing γ-lactones. Herein we describe the results in full.

2. Results and discussion

Initially, the reactions of polyfluoroalkyl iodides R_FI with 4-pentenoic acid and analogues with a substituent at the 2 or 3 position to form polyfluoroalkyl substituted lactones in the presence of $Na_2S_2O_4$ were conducted to investigate the reactivity. It was found that polyfluoroalkyl iodides can



Scheme 1.

Keywords: polyfluoroalkyl iodide; γ-butyrolactones; sodium dithionite; polyfluoroalkyl-lactonization; 4-pentenoic acid.

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Table 1. The yields of compounds **3**, **5**, **7** and **9**

Entry	Time (h)	Product	Yield (%)
1	2	**3a**	81
2	2	**3b**	84
3	2	**3c**	86
4	2	**3d**	88
5	2	**3e**	87
6	2	**3f**	90
7	4	**5a**	86
8	4	**5b**	88
9	4	**5c**	92
10	4	**5d**	92
11	4	**5e**	90
12	5	**7a**	85
13	5	**7b**	80
14	5	**7c**	89
15	5	**7d**	89
16	5	**7e**	96
17	5	**7f**	86
18	5	**9a**	70
19	5	**9e**	62

smoothly react with **1** in the presence of sodium dithionite (**1/2/**$Na_2S_2O_4$=1.0:1.1:1.2) at room temperature in aqueous acetonitrile solution (CH_3CN/H_2O=3:1 (v/v)) for 2–5 h to give the corresponding lactones in good yields (Scheme 1 and Table 1).

When R_FI reacted with 4-pentenoic acid **2**, the yields were 81–90%, the reaction was complete in a short time (2 h). In the case of 2,2-dimethyl-4-pentenoic acid **4**, the yield was 86–92%, but the reaction took 4 h. This indicated that the polyfluoroalkyl-lactonization was more difficult to proceed because of the dimethyl group at the 2-position. In the case of 3,3-dimethyl-4-pentenoic acid **6**, the yield and the reaction time was similar. When R_FI reacted with 2-*n*-butyl-4-pentenoic acid **8**, the yield was lower (62–70%).

Table 2. The effect of inorganic base on the yield of lactone **7b**

Base	Yield (%)
Na_2CO_3	87
K_2CO_3	88
$NaHCO_3$	85
Without base	30

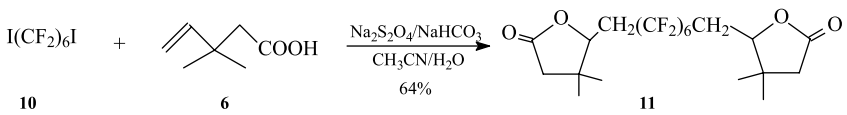
Perfluorodiodoalkane $I(CF_2)_6I$ **10** reacted with 3,3-dimethyl-4-pentenoic acid **6** to give the lactone **11** in 64% yield (Scheme 2). Alternatively, the lactone **7c** was obtained when $Cl(CF_2)_6I$ was treated with **6**. This indicated that the chlorine atom was inert under these reaction conditions.

Dibromodifluoromethane can react with **6** to give the bromodifluoromethyl substituted lactone **13** in 65% yield (Scheme 3).

In case of *n*-undecenoic acid **14**, the result was disappointing and no lactone was obtained. In this case, the addition product was obtained (Scheme 4).

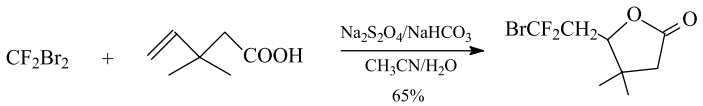
The adduct **16** was obtained as the major product when 3,3-dimethyl-4-pentenoic acid **6** was treated with $Cl(CF_2)_4I$ **1b** and $Na_2S_2O_4$ without the base. The adduct **16** was completely converted to the lactone **7b** with the addition of $NaHCO_3$ to continue the reaction (Scheme 5).

Further studies (Table 2) showed that if excess Na_2CO_3, K_2CO_3, or $NaHCO_3$ were used instead of NaOH, in the



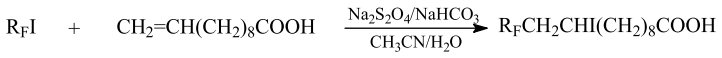
10 **6** **11**

Scheme 2.



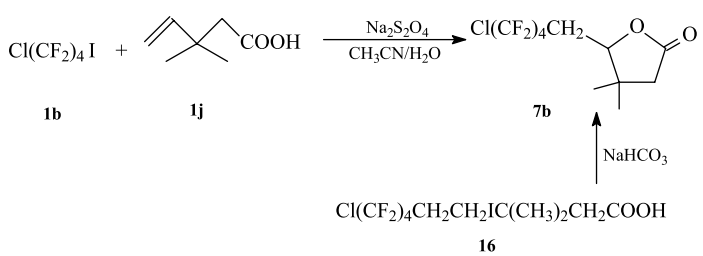
12 **6** **13**

Scheme 3.



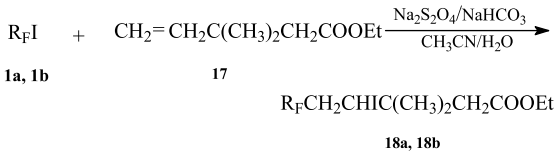
1b, 1e **14** **15b, 15e**

Scheme 4.



1b **1j** **7b** **16**

Scheme 5.

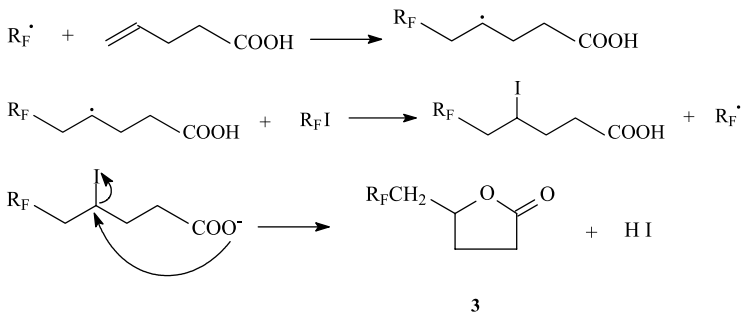


Scheme 6.

reaction of **1b** with **6**, the lactones were also obtained in good yields.

When ethyl 3,3-dimethyl-4-pentenoate **17** was employed with polyfluoroalkyl iodides (**1a**, **1b**), only addition products **18a**, **18b** were obtained without the formation of lactones (Scheme 6).

Halolactonization proceeds through the intramolecular cyclization of an iodonium ion with a carboxylate ion.[11,12] Thus, our reaction mechanism is different to the halolactonization reaction. It has been well documented that $Na_2S_2O_4$ is an excellent radical initiator of polyfluoroalkyl halides. The reaction is initiated by the SO_2 radical anion which exists in $Na_2S_2O_4$ solution. In the first step, SO_2 radical anion reacts with R_FI to produce R_F radical with the release of iodide anion and sulfur dioxide. The formed R_F radical attacks the unsaturated carboxylic acids at the less hindered end and yields a new radical which give the addition product by abstraction of iodide from another molecule of R_FI. Then the sequential nucleophilic cyclization of the adduct gives the lactone **3** (Scheme 7).



Scheme 7.

In conclusion, a convenient and efficient method of polyfluoroalkyl-lactonization by the reaction of 4-pentenoic acids with polyfluoroalkyl iodides initiated by sodium dithionite has been developed through sequential radical polyfluoroalkylation and nucleophilic cyclization.

3. Experimental

All boiling and melting points were uncorrected. IR spectra were recorded on IR-440 spectrometer using film or potassium bromide pellet. ^{19}F NMR spectra were recorded on a Varian EM-360L (56.4 MHz), FX-90Q (84.6 MHz) or Bruker AC-500 (500 MHz) spectrometers in $CDCl_3$ using TFA as external standard. Chemical shifts in ppm were positive for upfield shifts ($\delta_{CFCl_3}=\delta_{TFA}+76.8$ ppm). ^1H NMR spectra were recorded on Varian XL-200 (200 MHz) or Bruker AC-500 (500 MHz) spectrometers in $CDCl_3$. MS spectra were obtained on Finnigan GC-MS-4021 spectrometer and a Finnigan-8430 for high-resolution mass spectra (HRMS). Elemental data analysis were obtained by the elemental analysis group of Shanghai Institute of Organic Chemistry. The column chromatography was performed by using silica gel H with petroleum ether and ethyl acetate as the eluent.

3.1. General procedure of the reaction of unsaturated carboxylic acids with polyfluoroalkyl iodides

Unsaturated carboxylic acid (10 mmol) was dissolved in aqueous sodium hydroxide solution freshly prepared from 0.6 g sodium hydroxide in 5 mL water and stirred while acetonitrile (15 mL) and R_FI (11 mmol) was added. To the solution was added sodium dithionite (2.2 g) and sodium bicarbonate (1.70 g). The mixture was stirred at ambient temperature for 2–5 h to complete the reaction, then treated with about 50 mL of water and shaken thoroughly. The mixture was extracted with 3×20 mL of ether. The combined organic layer was washed with saturated brine solution and dried over anhydrous sodium sulfate. After evaporation of ether, the crude product was subjected to column chromatography to give the pure product.

3.1.1. 4-(2,2,3,3-Tetrafluoro-3-chloro-propyl)-γ-butyrolactone (3a). Bp 57–58°C/1 mm Hg; colorless oil; IR (KBr): 2950, 1780 (γ-lactone), 1430, 1420, 1190, 1130, 840, 800; ^1H NMR ($CDCl_3$) δ: 4.89–4.84 (1H, m, CH), 2.70–2.40 (5H, m, other hydrogen atoms), 2.04 (1H, m, CH); ^{19}F NMR ($CDCl_3$) δ: 72.5 (2F, s, $ClCF_2$), 113.1–113.5 (2F, m, CF_2CH_2); MS *m/z*: 235 (M^++1, 35.09), 105 (16.45), 103 (13.92), 57 (18.14), 56 (46.25), 55 (100.00). Anal. calcd for $C_7H_7ClF_4O_2$: C, 35.90; H, 3.00; F, 32.48. Found: C, 36.01; H, 3.04; F, 32.32.

3.1.2. 4-(2,2,3,3,4,4,5,5-Octafluoro-5-chloropentyl)-γ-butyrolactone (3b). Bp 62–64°C/1 mm Hg; colorless oil; IR (KBr): 2950, 1780 (γ-lactone), 1430, 1420, 1190, 1130, 840, 800; ^1H NMR ($CDCl_3$) δ: 4.87–4.82 (1H, m, CH), 2.75–2.50 (4H, m, 2×CH_2), 2.44–2.40 (1H, m, CH), 2.06–2.03 (1H, m, CH); ^{19}F NMR ($CDCl_3$) δ: 65.1 (2F, d, J=14.1 Hz, $ClCF_2$), 111.8 (2F, t, J=9.4 Hz, CF_2CH_2), 119.4 (2F, t, J=9.4 Hz, CF_2), 122.1 (2F, m, CF_2); MS *m/z*: 335 (M^++1, 100), 85 ($ClCF_2$, 31.92), 55 (CH_2=CHC=O, 15.44), 56 (6.01), 41 (4.40). Anal. calcd for $C_9H_7ClF_8O_2$: C, 32.33; H, 2.09; F, 45.50. Found: C, 32.53; H, 2.20; F, 45.48.

3.1.3. 4-(2,2,3,3,4,4,5,5,6,6,7,7-Dodecafluoro-7-chloroheptyl)-γ-butyrolactone (3c). Bp 75–76°C/1 mm Hg;

colorless oil; IR (KBr): 2950, 1780 (γ-lactone), 1430, 1420, 1190, 1130, 840, 800; ^{1}H NMR ($CDCl_3$) δ: 4.88–4.85 (1H, m, CH), 2.71–2.66 (1H, m, CH), 2.64–2.60 (2H, m, CH), 2.55–2.52 (1H, m, CH), 2.40–2.36 (1H, m, CH), 2.07–2.02 (1H, m, CH); ^{19}F NMR ($CDCl_3$) δ: 68.7 (2F, s, $ClCF_2$), 113.3 (2F, d, J=14.1 Hz, CF_2CH_2), 120.7 (2F, t, J=9.4 Hz, CF_2), 121.9 (2F, s, CF_2), 122.3 (2F, s, CF_2), 124.1 (2F, s, CF_2); MS *m/z*: 434 (20.43), 433 (16.85), 85 (100.00), 69 (11.81), 57 (12.27), 56 (29.22), 55 (83.00), 41 (10.76). Anal. calcd for $C_{11}H_7ClF_{12}O_2$: C, 30.41; H, 1.61; F, 52.53. Found: C, 30.67; H, 1.73; F, 52.25.

3.1.4. 4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-Hexadecafluoro-9-chlorononyl)-γ-butyrolactone (3d). Mp 45–46°C; colorless needles; IR (KBr): 2950, 1780 (γ-lactone), 1430, 1420, 1190, 1130, 840, 800; ^{1}H NMR ($CDCl_3$) δ: 4.88–4.85 (1H, m, CH), 2.72–2.69 (1H, m, CH), 2.63–2.58 (2H, m, CH), 2.48–2.45 (1H, m, CH), 2.39–2.36 (1H, m, CH), 2.05–2.01 (1H, m, CH); NMR ($CDCl_3$) δ: 68.7 (2F, t, J=14.1 Hz, $ClCF_2$), 113.2 (2F, t, J=9.4 Hz, CF_2CH_2), 120.7 (2F, d, J=9.4 Hz, CF_2), 121.8 (2F, s, CF_2), 122.2 (2F, s, CF_2), 122.4 (4F, d, J=9.4 Hz, 2×CF_2), 124.1 (2F, s, CF_2); MS *m/z*: 535 (M^++1, 12.95), 533 (25.65), 534 (35.40), 85 (100.00), 69 (14.94), 57 (12.36), 56 (32.78), 55 (88.06). Anal. calcd for $C_{13}H_7ClF_{16}O_2$ C, 29.21; H, 1.31; F, 56.90. Found: C, 29.27; H, 1.30; F, 56.88.

3.1.5. 4-(2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoroheptyl)-γ-butyrolactone (3e). Mp 39–40°C; colorless needles; IR (KBr): 3100–2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.87–4.86 (1H, m, CH), 2.07–2.01 (1H, m, CH), 2.30–2.70 (5H, m, other hydrogen atoms); ^{19}F NMR ($CDCl_3$) δ: 80.5 (3F, t, J=14.1 Hz, CF_3), 112.0–112.4 (2F, m, CF_2CH_2), 121.5 (2F, s, CF_2), 122.6 (2F, s, CF_2), 123.1 (2F, s, CF_2), 125.8 (2F, s, CF_2); MS *m/z*: 213 (6.54), 199 (4.52), 149 (12.63), 129 (16.87), 111 (20.64), 99 ($M^+-F(CF_2)_6$, 12.53), 98 (16.00), 85 ($M^+-F(CF_2)_6CH_2$, 43.35), 83 (42.88), 71 (47.89), 69 (67.66), 57 (88.91), 55 (96.75), 43 (100). Anal. calcd for $C_{11}H_7F_{13}O_2$: C, 31.58; H, 1.67; F, 59.09. Found: C, 31.26; H, 1.74; F, 59.35.

3.1.6. 4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-Heptadecafluorononyl)-γ-butyrolactone (3f). Mp 70–71°C; colorless needles; IR (KBr): 3100–2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.87–4.80 (1H, m, CH), 2.80–2.30 (5H, m, other hydrogen atoms), 2.05–2.01 (1H, m, CH); ^{19}F NMR ($CDCl_3$) δ: 80.5 (3F, s, CF_3), 112.4–112.8 (2F, m, CF_2CH_2), 121.6 (6F, s, 3×CF_2), 122.6 (4F, s, 2×CF_2), 125.8 (2F, s, CF_2); MS *m/z*: 521 (0.66), 520 (2.99), 519 (M^++1, 20.68), 474 (9.97), 461 (9.75), 131 (13.23), 95 (11.02), 85 ($M^+-F(CF_2)_8CH_2$, 98.47), 69 (28.87), 60 (12.08), 57 (16.14), 56 (34.52), 55 (100). Anal. calcd for $C_{13}H_7F_{17}O_2$: C, 30.12; H, 1.35; F, 62.36. Found: C, 30.10; H, 1.33; F, 62.33. HRMS: calcd for (M^+-CO_2), $C_{12}H_7F_{17}$: 474.0276, found: 474.0235.

3.1.7. 2,2-Dimethyl-4-(2,2,3,3-tetrafluoro-3-chloropropyl)-γ-butyrolactone (5a). Mp 89–90°C; colorless needles; IR (KBr): 2900, 1780 (γ-lactone), 1150, 780; ^{1}H NMR ($CDCl_3$) δ: 4.83–4.78 (1H, m, CH), 2.70–1.90 (4H, m, 2×CH_2), 1.31 (6H, s, 2×CH_3); ^{19}F NMR ($CDCl_3$) δ: 70.8 (2F, s, $ClCF_2$), 111.6–111.9 (2F, m, CF_2CH_2); MS *m/z*: 263 (M^++1, 24.26), 218 (M^+-CO_2, 15.14), 85 ($ClCF_2$, 23.27), 73 (16.07), 69 (100.00), 56 (30.02), 55 (CH_2=CHC=O, 24.19), 41 (71.57). Anal. calcd for $C_9H_{11}ClF_4O_2$; C, 41.14; H, 4.19; F, 28.95. Found: C, 41.14; H, 4.15; F, 29.12;

3.1.8. 2,2-Dimethyl-4-(2,2,3,3,4,4,5,5-octafluoro-5-chloropentyl)-γ-butyrolactone (5b). Mp 52–54°C; colorless needles; IR (KBr): 2900, 1780 (γ-lactone), 1480, 1200, 800; ^{1}H NMR ($CDCl_3$) δ: 4.83–4.79 (1H, m, CH), 2.70–1.90 (4H, m, 2×CH_2), 1.80 (6H, s, 2×CH_3); ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, s, $ClCF_2$), 112.1 (2F, m, CF_2CH_2), 119.1 (2F, s, CF_2), 122.1 (2F, s, CF_2); MS *m/z*: 363 (M^++1, 1.72), 320 ($M^+-C_3H_6$, 22.96), 318 (M^+-CO_2, 69.76), 303 (26.03), 85 ($ClCF_2$, 29.96), 69 (100.00), 56 (22.23), 55 (CH_2=CHC=O, 13.03), 41 (28.84). Anal. calcd for $C_{11}H_{11}ClF_8O_2$: C, 36.41; H, 3.03; F, 41.93. Found: C, 36.28; H, 3.02; F, 41.68.

3.1.9. 2,2-Dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7-dodecafluoro-7-chloroheptyl)-γ-butyrolactone (5c). Mp 80–82°C; colorless needles; IR (KBr): 2900, 1780 (γ-lactone), 1220, 1140, 680; ^{1}H NMR ($CDCl_3$) δ: 4.81–4.77 (1H, m, CH), 2.68–1.90 (4H, m, 2×CH_2), 1.29 (6H, d, J=5.0 Hz, 2×CH_3); ^{19}F NMR ($CDCl_3$) δ: 66.5 (2F, s, $ClCF_2$), 111.0–111.4 (2F, m, CF_2CH_2), 118.8 (2F, d, J=9.4 Hz, CF_2), 120.1 (4F, s, 2×CF_2), 123.1 (2F, d, J=9.4 Hz, CF_2); MS *m/z*: 463 (M^++1, 4.51), 418 (M^+-CO_2, 12.97), 85 ($ClCF_2$, 32.33), 69 (100.00), 57 (25.93), 55 (CH_2=CHC=O, 31.94), 41 (C_3H_5, 40.07). Anal. calcd for $C_{13}H_{11}ClF_{12}O_2$: C, 33.74; H, 2.39; F, 49.35. Found: C, 33.82; H, 2.35; F, 49.10.

3.1.10. 2,2-Dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluoro-9-chlorononyl)-γ-butyro lactone (5d). Mp 100°C; colorless needles; IR (KBr): 2960, 1780 (γ-lactone), 1440, 1250, 670; ^{1}H NMR ($CDCl_3$) δ: 4.84–4.79 (1H, m, CH), 2.68–1.90 (4H, m, 2×CH_2), 1.32 (6H, d, J=5.0 Hz, 2×CH_3); ^{19}F NMR ($CDCl_3$) δ: 61.1 (2F, s, $ClCF_2$), 111.1–111.5 (2F, m, CF_2CH_2), 118.6–118.9 (2F, m, CF_2), 120.1 (8F, s, 4×CF_2), 122.0–122.5 (2F, m, CF_2); MS *m/z*: 563 (M^++1, 37.46), 562 (M^+, 24.68), 518 (M^+-CO_2, 13.49), 85 ($ClCF_2$, 27.99), 69 (100.00), 56 (26.45), 55 (CH_2=CHC=O, 19.32), 41 (C_3H_5, 42.68). Anal. calcd for $C_{15}H_{11}ClF_{16}O_2$: C, 32.01; H, 1.97; F, 54.09. Found: C, 32.09; H, 1.94; F, 54.38.

3.1.11. 2,2-Dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)-γ-butyrolactone (5e). Mp 74°C; colorless needles; IR (KBr): 2980, 1780 (γ-lactone), 1200, 705; ^{1}H NMR ($CDCl_3$) δ: 4.80–4.76 (1H, m, CH), 2.70–1.90 (4H, m, 2×CH_2), 1.30 (6H, t, J=4.8 Hz, 2×CH_3); ^{19}F NMR ($CDCl_3$) δ: 81.4 (3F, t, J=14.1 Hz, CF_3), 113.3–113.6 (2F, m, CF_2CH_2), 122.4 (2F, s, CF_2), 123.5 (2F, s, CF_2), 124.1 (2F, s, CF_2), 126.5–126.9 (2F, m, CF_2); MS *m/z*: 447 (M^++1, 0.65), 402 (M^+-CO_2, 61.83), 387 (17.30), 361 (17.56), 113 (15.28), 83 (15.15), 69 (100.00), 56 (19.58), 41 (C_3H_5, 22.39). Anal. calcd for $C_{13}H_{11}F_{13}O_2$: C, 34.98; H, 1.47; F, 55.38. Found: C, 35.03; H, 1.38; F, 55.47.

3.1.12. 3,3-Dimetyl-4-(2,2,3,3-tetrafluoro-3-chloropropyl)-γ-butyrolactone (7a). Mp 55°C; colorless needles; IR (KBr): 2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 4.45 (1H, dd, J=7.7, 2.7 Hz, CH), 2.51–2.25 (4H, m, 2×CH_2), 1.22 (3H, s, CH_3),

1.06 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 71.2 (2F, s, $ClCF_2$), 112.4–112.8 (2F, m, CF_2CH_2); MS *m/z*: 265 (30.86), 264 (29.83), 263 (M^++1, 100), 243 (8.91), 113 (M^+−$Cl(CF_2)_2CH_2$, 8.05), 69 (13.82), 55 (8.61). Anal. calcd for $C_9H_{11}F_4O_2Cl$: C, 41.14; H, 4.19; F, 28.95. Found: C, 40.91 H, 3.92; F, 29.36.

3.1.13. 3,3-Dimethyl-4-(2,2,3,3,4,4,5,5-octafluoro-5-chloropentyl)-γ-butyrolactone (7b). Bp 92–94°C/ 1 mm Hg; colorless oil; IR (KBr): 2900, 1780 (γ-lactone), 1480, 1440, 1200–1100, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.46 (1H, dd, *J*=8.2, 2.6 Hz, CH), 2.51–2.26 (4H, m, 2×CH_2), 1.22–1.07 (6H, s, 2×CH_3); ^{19}F NMR ($CDCl_3$) δ: 67.8 (2F, s, $ClCF_2$), 112.4–112.8 (2F, m, CF_2CH_2), 119.4–119.8 (2F, m, CF_2), 122.3 (2F, s, CF_2); MS *m/z*: 365 (21.22), 364 (12.69), 363 (M^++1, 64.93), 343 (12.69), 113 (M^+−$Cl(CF_2)_4CH_2$, 29.35), 85 (13.74), 69 (17.91), 56 (100), 55 (15.09). Anal. calcd for $C_{11}H_{11}F_8O_2Cl$: C, 36.41; H, 3.03; F, 41.93. Found: C, 36.04; H, 2.94; F, 42.19.

3.1.14. 3,3-Dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7-dodecafluoro-7-chloroheptyl)-γ-butyrolactone (7c). Mp 54°C; colorless needles; IR (KBr): 3100–2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.47 (1H, dd, *J*=6.4, 2.5 Hz, CH), 2.53–2.28 (4H, m, 2×CH_2), 1.23 (3H, s, CH_3), 1.09 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 67.7 (2F, s, $ClCF_2$), 112.3–112.6 (2F, m, CF_2CH_2), 119.8 (2F, s, CF_2), 121.0–121.3 (4F, m, 2×CF_2), 122.9 (2F, s, CF_2); MS *m/z*: 465 (3.81), 464 (1.61), 463 (M^++1, 11.11), 113 (M^+−$Cl(CF_2)_6CH_2$, 25.44), 85 (15.73), 83 (9.67), 69 (20.34), 57 (8.32), 56 (100), 55 (13.16). Anal. calcd for $C_{13}H_{11}F_{12}O_2Cl$: C, 33.73; H, 2.38; F, 49.30. Found: C, 33.50; H, 2.22; F, 49.70.

3.1.15. 3,3-Dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9-hexadecafluoro-9-chlorononyl)-γ-butyrolactone (7d). Mp 79–80°C; colorless needles; IR (KBr): 3100–2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.48 (1H, dd, *J*=6.5, 2.5 Hz, CH), 2.52–2.28 (4H, m, 2×CH_2), 1.24 (3H, s, CH_3), 1.10 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 67.8 (2F, s, $ClCF_2$), 112.5 (2F, m, CF_2CH_2), 119.8 (2F, s, CF_2), 121.3–121.8 (8F, m, 4×CF_2), 122.8 (2F, s, CF_2); MS *m/z*: 565 (5.83), 564 (2.87), 563 (M^++1, 17.27), 479 (4.34), 477 (3.80), 131 (9.58), 113 (M^+−$Cl(CF_2)_8CH_2$, 19.52), 85 (15.80), 83 (10.17), 69 (22.47), 56 (100), 55 (14.20). Anal. calcd for $C_{15}H_{11}F_{16}O_2Cl$: C, 32.00; H, 1.96; F, 54.04. Found: C, 31.86; H, 1.93; F, 54.43.

3.1.16. 3,3-Dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)-γ-butyrolactone (7e). Mp 52–53°C; colorless needles; IR (KBr): 3100–2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.45 (1H, dd, *J*=7.3, 2.1 Hz, CH), 2.51–2.25 (4H, m, 2×CH_2), 1.21 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 80.7 (3F, s, CF_3), 112.0–112.7 (2F, m, CF_2CH_2), 121.0–121.4 (4F, m, 2×CF_2), 121.8–122.4 (4F, m, 2×CF_2), 126.0 (2F, s, CF_2); MS *m/z*: 449 (1.55), 448 (13.78), 447 (M^++1, 100), 427 (11.83), 401 (7.32), 113 (M^+−$F(CF_2)_6CH_2$, 12.85), 69 (13.25), 56 (38.27), 55 (6.59). Anal. calcd for $C_{13}H_{11}F_{13}O_2$: C, 34.98; H, 2.47; F, 55.38. Found: C, 34.65; H, 2.40; F, 55.02.

3.1.17. 3,3-Dimethyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-heptadecafluorononyl)-γ-butyrolactone (7f). Mp 82–83°C; colorless needles; IR (KBr): 3100–2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.45 (1H, dd, *J*=6.3, 2.1 Hz, CH), 2.51–2.25 (4H, m, 2×CH_2), 1.21 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 80.8 (3F, s, CF_3), 112.0–112.6 (2F, m, CF_2CH_2), 121.6 (6F, s, 3×CF_2), 122.1–122.4 (4F, m, 2×CF_2), 126.0 (2F, s, CF_2); MS *m/z*: 548 (1.95), 547 (M^++1, 12.38), 461 (5.95), 169 (3.93), 131 (8.45), 113 ($M^+F(CF_2)_8CH_2$, 23.26), 95 (9.72), 83 (10.25), 69 (27.97), 56 (100), 55 (12.44). Anal. calcd for $C_{15}H_{11}F_{17}O_2$: C, 32.97; H, 2.01; F, 59.16. Found: C, 33.00; H, 2.20; F, 59.32.

3.1.18. (*R*,*S*)-2-*n*-Butyl-4-(2,2,3,3-tetrafluoro-3-chloropropyl)-γ-butyrolactone (9a). Mp 88–89°C; colorless needles; IR (KBr): 2900, 1780 (γ-lactone), 1440, 1380, 1180, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.70–4.50 (1H, m, CH), 2.70–2.40 (2H, m), 2.20–1.80 (3H, m), 1.48–1.35 (6H, m, 3×CH_2), 0.95 (3H, t, *J*=4.4 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ: 70.8 (2F, s, CF_2Cl,), 111.8 (2F, m, CF_2CH_2); MS *m/z*: 292 (3.04), 291 (M^++1, 23.12), 290 (M^+, 9.52), 289 (68.61), 245 (12.34), 243 (31.90) 234 ($M^+C_4H_8$, 37.59), 203 (19.55), 149 (35.69), 100 (49.63), 73 (38.13), 55 (100), 43 (38.45). HRMS: calcd for $C_{11}H_{15}F_4O_2Cl$: 290.0766, found: 290.0731.

3.1.19. (*R*,*S*)-2-*n*-Butyl-4-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)-γ-butyrolactone (9e). Mp 122–123°C; colorless needles; IR (KBr): 2900, 1780 (γ-lactone), 1440, 1380, 1160, 940 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.65–4.50 (1H, m, CH), 2.70–2.40 (2H, m, CH_2), 2.10–1.80 (3H, m, CH_3), 1.48–1.34 (6H, m, 3×CH_2), 0.92 (3H, t, *J*=4.6 Hz, CH_3); ^{19}F NMR ($CDCl_3$) δ: 80.5 (3F, t, *J*=14.1 Hz, CF_3), 112.1 (2F, m, CF_2CH_2), 122.6 (6F, s, 3×CF_2), 126.0 (2F, s, CF_2); MS *m/z*: 475 (M^++1, 3.36), 474 (M^+, 2.28), 473 (7.96), 459 (18.85), 418 (M^+−C_4H_9, 85.99), 387 (9.25), 141 (19.31), 100 (51.38), 99 (36.32), 73 (83.63), 69 (48.85), 56 (29.80), 55 (100), 43 (46.61). HRMS: calcd for $C_{15}H_{14}F_{13}O_2$: 473.0881, found: 473.0833. HRMS: calcd for (M^+−C_4HO_8), $C_{11}H_7F_{13}O_2$: 418.0256, found: 418.0274.

3.1.20. 3,3,3′,3′-Tetramethyl-4,4′-(2,2,3,3,4,4,5,5,6,6,7,7-dodecafluorooctyl)-di-γ-butyrolactone (11). Mp 120–121°C; colorless needles; IR (KBr): 3100–2900, 1780 (γ-lactone), 1480, 1440, 1200, 1000, 800 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.45 (2H, dd, *J*=6.4, 2.6 Hz, 2×CH), 2.60–2.20 (8H, m, 4×CH_2), 1.21 (6H, s, 2×CH_3), 1.06 (6H, s, 2×CH_3); ^{19}F NMR ($CDCl_3$) δ: 112.2–112.6 (4F, m, 2×CF_2CH_2), 121.1–121.5 (4F, s, 2×CF_2), 122.7–123.1 (4F, m, 2×CF_2); MS *m/z*: 555 (M^++1, 0.51), 471 (19.78), 453 (11.10), 425 (33.43), 113 (12.76), 69 (13.05), 56 (100), 55 (14.37), 43 (12.97). Anal. calcd for $C_{20}H_{22}F_{12}O_4$: C, 43.32; H, 3.97; F, 41.16. Found: C, 43.61; H, 3.45; F, 41.37.

3.1.21. 3,3-Dimethyl-4-(2,2-difluoro-2-bromoethyl)-γ-butyrolactone (13). Mp 54–55°C; colorless needles; IR (KBr): 2900, 1780 (γ-lactone), 1200, 1080, 1040, 920 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.45 (1H, dd, *J*=7.2, 2.7 Hz, CH), 2.70–2.30 (4H, m, 2×CH_2), 1.20 (3H, s, CH_3), 1.06 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 42.5–43.4 (2F, m, CF_2Br); MS *m/z*: 259 (9.14), 257 (M^++1, 8.68), 227 (17.05), 131 (9.97), 113 (M^+−$BrCF_2$, 65.78), 109 (36.67),

103 (22.11), 69 (18.89), 57 (17.12), 56 (100). Anal. calcd for $C_8H_{11}F_2O_2Br$: C, 37.35; H, 4.28; F, 14.78. Found: C, 37.00; H, 4.23; F, 14.78.

3.1.22. 12,12,13,13,14,14,15,15-Octafluoro-15-chloro-10-iodopentadecanoic acid (15b). Mp 77–78°C; colorless needles; IR (KBr): 3500–2800, 1700, 1180, 1130, 1080, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.78 (1H, br, CO_2H), 4.37–4.32 (1H, m, CHI), 3.10– 2.70 (2H, m, CH_2CF_2), 2.35 (2H, t, J=7.4 Hz, CH_2CO), 1.90–1.20 (14H, m, other hydrogen atoms); ^{19}F NMR ($CDCl_3$) δ: 67.3 (2F, s, CF_2Cl), 112.8 (2F, m, CF_2CH_2), 119.1 (2F, s, CF_2), 122.3 (2F, s, CF_2); MS *m/z*: 549 (2.11), 547 (M^++1, 6.36), 529 (10.37), 419 (M^+−HI, 33.64), 401 (M^+−HI−H_2O, 100), 383 (40.48), 359 (17.08), 317 (33.30), 97 (29.80), 83 (36.89), 69 (72.10), 55 (77.86), 43 (28.08). Anal. calcd for $C_{15}H_{20}F_8O_2ClI$: C, 32.94; H, 3.67; F, 27.81. Found: C, 33.37; H, 3.67; F, 28.01. HRMS: calcd for (M^+−OH) $C_{15}H_{19}F_8OClI$: 528.9971, found: 529.0005.

3.1.23. 12,12,13,13,14,14,15,15,16,16,17,17,17-Trifluoro-10-iodoheptadecanioic acid (15e). Mp 66–67°C; colorless needles; IR (KBr): 3500–2800, 1700, 1180, 1130, 1080, 950 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 8.80 (1H, br, CO_2H), 4.37–4.34 (1H, m, CHI), 3.10–2.65 (2H, m, CH_2CF_2), 2.35 (2H, t, J=7.4 Hz, CH_2CO), 1.20–1.90 (14H, m, other hydrogen atoms); ^{19}F NMR ($CDCl_3$) δ: 80.1 (3F, s, CF_3), 112.6–112.9 (2F, m, CF_2CH_2), 121.6–121.9 (6F, m, 3×CF_2), 125.3 (2F, s, CF_2CF_3); MS *m/z*: 631 (M^++1, 1.91), 503 (M^+−HI, 33.47), 486 (18.37), 485 (M^+−HI−H_2O, 100), 467 (52.04), 443 (19.98), 401 (50.85), 97 (31.15), 83 (36.12), 69 (72.71), 55 (75.29), 43 (25.33). Anal. calcd for $C_{17}H_{20}F_{13}O_2I$: C, 32.38; H, 3.17; F, 39.21. Found: C, 32.74; H, 3.18; F, 39.66.

3.2. General procedure of the reaction of polyfluoroalkyl iodides with ethyl 3,3-dimethyl-4-pentenoate (17)

The mixture of polyfluoroalkyl iodides (12 mmol), **17** (1.70 g, 10 mmol), sodium dithionite (1.74 g), sodium bicarbonate (0.87 g), acetonitrile (15 mL) and water (10 mL) was stirred at ambient temperature for 2 h. Worked up as usual to give the pure product.

3.2.1. Ethyl 3,3-dimethyl-6,6,7,7-tetrafluoro-7-chloro-4-iodo-heptanoate (18a). Bp 54°C/1 mm Hg; colorless oil; IR (KBr): 2900, 1780, 1730, 1460, 1360, 1180, 1120, 1020 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.60 (1H, dd, J=4.9, 1.9 Hz, CHI), 4.19–4.12 (2H, m, CO_2CH_2), 3.10–2.30 (4H, m, 2×CH_2), 1.27 (3H, t, J=7.0 Hz, CH_3), 1.23 (3H, s, CH_3), 1.18 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 69.8 (2F, s, CF_2Cl), 112.6–112.9 (2F, m, CF_2CH_2); MS *m/z*: 421 (12.67), 420 (5.04), 419 (M^++1, 39.89), 293 (34.15), 291 (M^+−I, 87.38), 263 (20.47), 245 (28.46), 219 (32.62), 217 (100), 87 (14.89), 69 (23.33). HRMS: calcd for $C_{11}H_{16}F_4O_2ICl$: 417.9768, found: 417.9793.

3.2.2. Ethyl 3,3-dimethyl-6,6,7,7,8,8,9,9-octafluoro-9-chloro-4-iodononanoate (18b). Bp 56–58°C/1 mm Hg; colorless oil; IR (KBr): 2900, 1780, 1730, 1460, 1360, 1180, 1120, 1020, 840 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 4.60 (1H, dd, J=4.7, 1.9 Hz, CHI,), 4.18–4.13 (2H, m, CO_2CH_2), 3.10–2.65 (2H, m, CH_2CF_2), 2.60–2.40 (2H, m, CH_2), 1.26 (3H, t, J=7.0 Hz, CH_3), 1.23 (3H, s, CH_3), 1.14 (3H, s, CH_3); ^{19}F NMR ($CDCl_3$) δ: 66.8 (2F, s, $ClCF_2$), 113.8 (2F, m, CF_2CH_2), 118.8 (2F, s, CF_2), 122.1 (2F, s, CF_2); MS *m/z*: 521 (22.16), 520 (9.98), 519 (M^++1, 66.37), 391 (M^+−I, 100), 363 (14.60), 317 (24.68), 69 (10.47). Anal. calcd for $C_{13}H_{16}F_8O_2ICl$; C, 30.09; H, 3.08; F, 29.32. Found: C, 30.41; H, 3.09; F, 29.68.

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References

1. (a) Wang, C.; Rusell, G.-H. *J. Org. Chem.* **1999**, *64*, 2066. (b) Harding, K. E.; Tiner, T. H. *Comprehensive Organic Synthesis*, Trost, B. M., Ed.; Pregamon: New York, 1991; Vol. 4, p 363.
2. Brown, H. C.; Kulkarni, S. V.; Racherla, U. S. *J. Org. Chem.* **1994**, *89*, 365.
3. Heike, M.; Uli, K. *Synthesis* **2001**, 487.
4. M.-Lluisa, B.; Cecilia, J.; Joan, B. *Chem. Commun.* **2000**, 2459.
5. Edyta, P.; Zbigniew, C.; Jan, N.; Czeslaw, W. *J. Agric. Food Chem.* **2000**, *48*, 4973.
6. Wang, Z.; Lu, X.-Y. *Tetrahedron* **1995**, *51*, 2639.
7. Silvana, R.; Drazenka, S.; Tatjana, G.; Andreja, M.; Antonija, H. B.; Ante, N.; Jan, B.; Erik, D. C.; Mladen, M. *J. Med. Chem.* **2000**, *43*, 4806.
8. (a) Kirk, K. L.; Creveling, C. R. *Med. Res. Rev.* **1984**, *4*, 189. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123 and references cited therein.
9. (a) Wu, F.-H.; Huang, W.-Y. *Chin. J. Org. Chem.* **1997**, *17*, 106. (b) Huang, W.-Y.; Wu, F.-H. *Isr. J. Chem.* **1999**, *39*, 167.
10. Zou, X.-W.; Wu, F.-H. *Chin. Chem. Lett.* **2002**, *13*, 410.
11. Cambie, R. C.; Hayward, R. C.; Roberts, J. L.; Rutledge, P. S. *J. Chem. Soc. Perkin Trans. 1* **1974**, 1864.
12. Cambie, R. C.; Ng, K. S.; Rutledge, P. S.; Woodgate, P. D. *Aust. J. Chem.* **1979**, *32*, 2793.