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Stereoselective cycloaddition–lactonization reaction of 2-allyl-4-pentenoic acids with polyfluoroalkyl iodides. An efficient synthesis of polyfluoroalkyl-containing bicyclolactone derivatives

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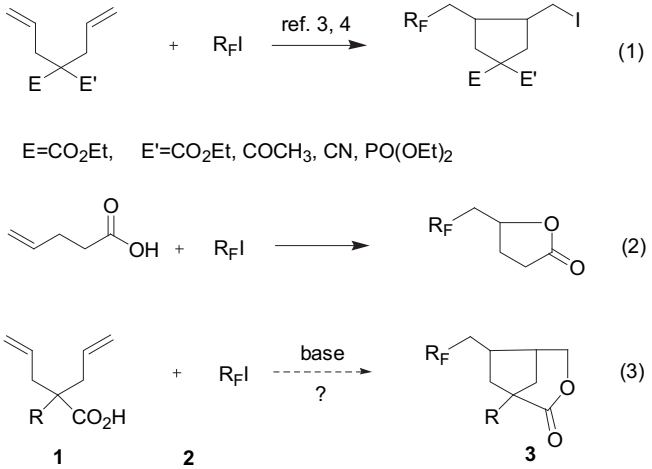
ABSTRACT

Polyfluoroalkyl-containing bicyclolactones were synthesized via the sodium dithionite-initiated cycloaddition–lactonization reaction of 2-allyl-4-pentenoic acids and polyfluoroalkyl iodides. The chemo- and stereo-selectivity of the cycloaddition–lactonization reaction strongly depended on the space hindrance of 2-substituent in 2-allyl-4-pentenoic acids. The reaction was believed to proceed through a tandem free radical addition-lactonization process.

1. Introduction

In past decades the radical reaction became increasingly attractive in the chemical synthesis field,[1] and many chemists have paid their attentions to the tandem free radical cycloaddition of compounds with several double or triple bonds to conveniently construct molecules bearing multi-cycled structure.[2–6] Brace[3] firstly reported the AIBN-initiated radical cycloaddition of 4-substituted 1,6-diene with polyfluoroalkyl iodides, and then Zhao[4] reported the same reaction initiated by sodium dithionite, both of the reactions predominantly provided the cis-cycloadducts. (Scheme 1).

Recently during the course of our study of the chemistry of polyfluoroalkyl iodides, we have demonstrated sodium dithionite-initiated addition-lactonization of 4-pentenoic acids and polyfluoroalkyl iodides can easily occur to afford polyfluoroalkyl-containing lactones.[7] On the basis of these results, we envisioned that the reaction of diallyl acetic acid with polyfluoroalkyl iodides would lead to the formation of fluoroalkylated biclyolactones via the tandem cycloaddition–lactonization process. However, for this reaction, due to the space hindrance of 2-allyl-4-pentenoic acids, there is a tendency that reaction is stopped at the stage of addition and no subsequent lactonization occurs. If we can control the selectivity of this reaction, it may be possible for us to develop an efficient method for the synthesis of polyfluoroalkyl-containing bicyclolactones. If this is feasible, diversity and regioselectivity are the advantages for this reaction since 2-allyl-4-pentenoic acids can accommodate different substituents at the different locations and



Scheme 1. The cycloaddition of 1,6-diene with polyfluoroalkyl iodides.

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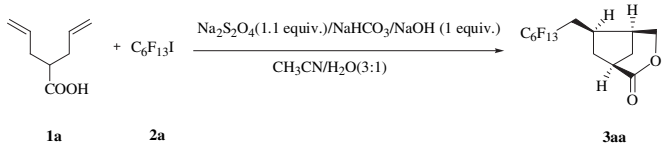
polyfluoroalkyl group, which can be transformed into other fluorine-containing group, can be organized into the bicyclones. Herein, we reported the sodium dithionite-initiated cycloaddition–lactonization reactions of 2-allyl-4-pentenoic acids **1a**–**c** with various polyfluoroalkyl iodies **2** to provide facile synthetic method for polyfluoroalkyl bicyclolactones **3** (Eq. 3, Scheme 1).

2. Results and discussion

2.1. The sodium dithionite-initiated reaction of 2-allyl-4-pentenoic acid with polyfluoroalkyl iodides

Using 2-allyl-4-pentenoic acid (**1a**) and perfluorohexanyl iodide (**2a**) as the starting point, we screened the reaction conditions; **1a** was resolved in fresh sodium hydroxide aqueous solution, then acetonitrile and R_FI were added, at last the mixture of sodium dithionite and sodium bicarbonate was introduced in several portions. Fortunately, the corresponding reaction in CH_3CN/H_2O (3:1) at 0 °C with 1.1 equiv of $Na_2S_2O_4$, 2.0 equiv of $NaHCO_3$, and 1.0 equiv of NaOH, afforded the expected bicyclolactone **3a** in 79% GC yield. Better results were obtained when the reaction was run at 25 °C for 6 h. While higher temperature and longer reaction time led to lower yields for **3a** (Table 1).

Table 1
The optimization of the reaction conditions



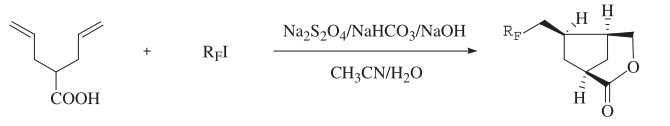
1a 2a 3aa

Entry	Substance	Temperature (°C)	Time (h)	Yield of **3aa**[a] (%)
1	**1a**	0	6	79
2	**1a**	25	6	85
3	**1a**	25	9	81
4	**1a**	40	6	76

[a] Yields determined by GC.

With the optimized conditions in hand, we turned our attention to investigate the scope of reaction. Besides **2a**, other fluoroalkyl iodides, such as $(CF_3)_2CFI$ (**2b**), $Cl(CF_2)_4I$ (**2c**), $Cl(CF_2)_2I$ (**2d**), and $PhSCF_2I$ (**2e**), could be employed. Thus the corresponding lactones **3ab**–**3ae** were obtained in 74–96%GC yields (entries 2–5 in Table 2).

Table 2
Sodium dithionite-initiated reaction of **1a** with polyfluoroalkyl iodides



1a 2a~2e 3aa~3ae

2a= $F(CF_2)_6I$; **2b**=$(CF_3)_2CFI$;
2c=$Cl(CF_2)_4I$; **2d**=$Cl(CF_2)_2I$;
2e=$PhSCF_2I$

4-(2)-*cis*-5(2)-*cis*

Entry	Substrate	R_FI	**3**	Yield of **3** (%)	Configuration of **3**
1	**1a**	$F(CF_2)_6I$	**3aa**	85[a] (92)[b]	4(2)-*cis*-5(2)-*cis*
2	**1a**	$(CF_3)_2CFI$	**3ab**	80 (89)	4(2)-*cis*-5(2)-*cis*
3	**1a**	$Cl(CF_2)_4I$	**3ac**	89 (96)	4(2)-*cis*-5(2)-*cis*
4	**1a**	$Cl(CF_2)_2I$	**3ad**	82 (90)	4(2)-*cis*-5(2)-*cis*
5	**1a**	$PhSCF_2I$	**3ae**	—[c] (74)	4(2)-*cis*-5(2)-*cis*

[a] Isolated yields.
[b] Yields in the parentheses determined by GC.
[c] The compound has not been separated.

Some typical results are summarized in Table 2. The following points should be noted. (1) For all chosen polyfluoroalkyl iodides, the reactions provided **3** in high yields with high chemo-selectivity. (2) For all chosen polyfluoroalkyl iodides, the reactions provided 4(2)-*cis*-5(2)-*cis*-**3** as major products with high stereo-selectivity. (3) The space effect of R_FI has little effect to the reaction results while $PhSCF_2I$ gave slightly lower yield. (4) The structure of the products is established by spectroscopic techniques, and in the case of **3ad**, is confirmed by the single crystal X-ray diffraction analysis (Fig. 2). For example, in the case of **3ab**, the NOE corrections between H_2 (δ=2.86–2.79) and H_4 (δ=2.56–2.48), along with between H_2 and H_5 (δ=2.35–2.41), exhibits that H_2, H_4, and H_5 are at the same side of the five-numbered ring (Fig. 1).

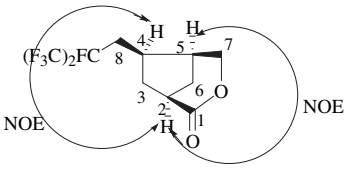


Figure 1. NOE correction from NOESY spectra of **3ab**.

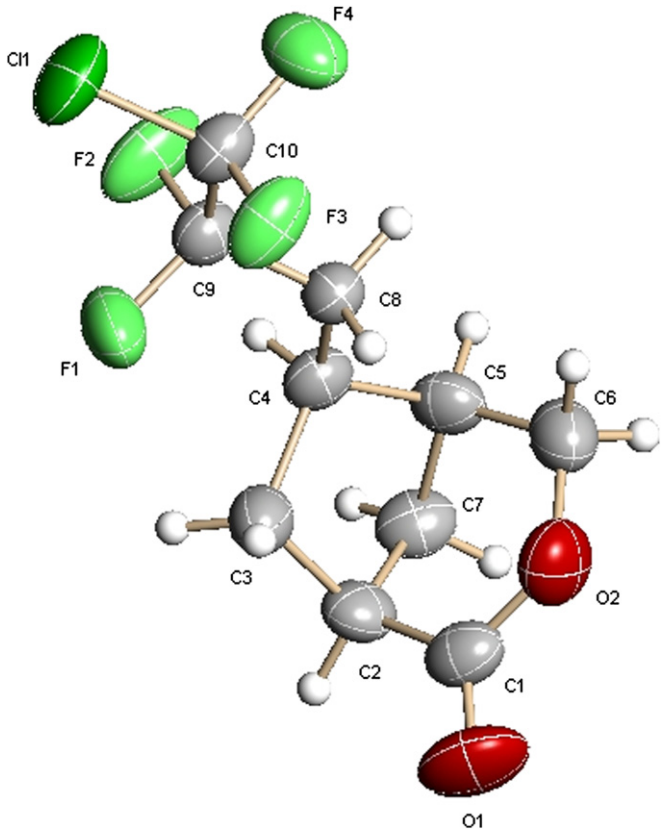
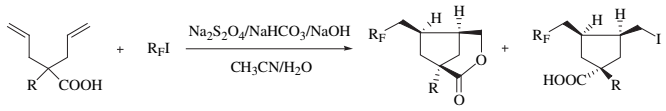


Figure 2. The three-dimensional perspective of molecule **3ad** (CCDC 730487).

2.2. The sodium dithionite-initiated reaction of 2-ethyl or benzyl-2-allyl-4-pentenoic acid with polyfluoroalkyl iodides

As shown in Table 3, under the same conditions, both of the sodium dithionite-initiated reactions of 2-ethyl-2-allyl-4-pentenoic acid (**1b**) and 2-benzyl-2-allyl-4-pentenoic acid (**1c**) with polyfluoroalkyl iodides could give the cycloaddition–lactonization product **3** but the yield of **3** was moderate. Besides **3**, cycloadducts **4** was obtained in moderate GC yields, which could not be converted to lactone **3** even by lengthening reaction time or increasing reaction temperature. Bulky R significantly hindered the lactonization

Table 3
The sodium dithionite-initiated reaction of **1b** or **1c** with polyfluoroalkyl iodides



1b,**1c** **2a~2e** **3ba~3cf** **4ba~4cf**

1b:R=C_2H_5; **1c**:R=$CH_2C_6H_5$

2a= $F(CF_2)_6I$; **2b**= $(CF_3)_2CFI$; **2c**= $Cl(CF_2)_4I$; **2d**= $Cl(CF_2)_2I$; **2e** = $PhSCF_2I$; **2f**= $F(CF_2)_4I$

Entry	Substrate	R_FI	**3**	**4**
1	**1b**	$F(CF_2)_6I$	**3ba**, 40[a] (58)[b] %, 4(2)-*cis*-5(2)-*cis*	**4ba**, 21 (37)%, 4(2)-*trans*-5(2)-*trans*
2	**1b**	$(CF_3)_2CFI$	**3bb**, 41(50)%, 4(2)-*cis*-5(2)-*cis*	**4bb**, — (42)%
3	**1b**	$Cl(CF_2)_2I$	**3bd**, 42 (56)%, 4(2)-*cis*-5(2)-*cis*	**4bd**, 30 (40)%, 4(2)-*trans*-5(2)-*trans*
4	**1b**	$Cl(CF_2)_4I$	**3bf**, 45 (47)%, 4(2)-*cis*-5(2)-*cis*	**4bf**, — (38)%
5	**1c**	$(CF_3)_2CFI$	**3cb**, 18 (38)%, 4(2)-*cis*-5(2)-*cis*	**4cb**, — (52)%
6	**1c**	$Cl(CF_2)_2I$	**3cd**, 20 (46)%, 4(2)-*cis*-5(2)-*cis*	**4cd**, — (41)%
7	**1c**	$PhSCF_2I$	**3ce**, —[c] (21)%, 4(2)-*cis*-5(2)-*cis*	**4ce**, — (32)%
8	**1c**	$F(CF_2)_4I$	**3cf**, 22 (40)%, 4(2)-*cis*-5(2)-*cis*	**4cf**, — (47)%

[a] Isolated yields.
[b] Yields in the parentheses were determined by GC.
[c] The compound has not been separated.

process (entry 3 in Table 2, entries 3 and 6 in Table 3). Nevertheless, it seemed that R_F did not affect the ratio of **3**/**4** in this reaction (entries 1–4 in Table 3).

The structure of products are fully confirmed by ^1H NMR, MS, IR, and elemental analysis or HRMS as well as X-ray analysis for **4ba** and **3ba** (Figs. 3 and 4). In the NOSEY spectra of **3cd**, NOE correction between H_9 and H_4 along with between H_9 and H_5 demonstrate that **3cd** is in 4(2)-*cis*-5(2)-*cis*-configuration (Fig. 5). While for **4bd**, due to the signal overlapping of H_4 and H_5, the configuration is determined by NOE correction between H_9 and H_7 along with between H_9 and H_8 (Fig. 6), which demonstrates that **4bd** is in 4(2)-*trans*-5(2)-*trans*-configuration. Similar conclusions are confirmed, for **4ba**, **4bb**, **4bc**, the major configurations are assigned to 4(2)-*trans*-5(2)-*trans*, while, for **3ba**, **3bb**, **3bc**, **3bd** **3cb**, **3ce**, **3cf**, the major configurations are assigned to 4(2)-*cis*-5(2)-*cis*.

We have tried to convert **4bd** into bicyclolactone under different base conditions (Table 4), but GC indicated no lactonization occurred. We speculate that because **4bd** possess 4(2)-*trans*-5(2)-*trans*-configuration, in which CH_2I and COOH lies in the opposite direction of the five-numbered ring, respectively, the far distance makes the iodolactonization hard to occur.

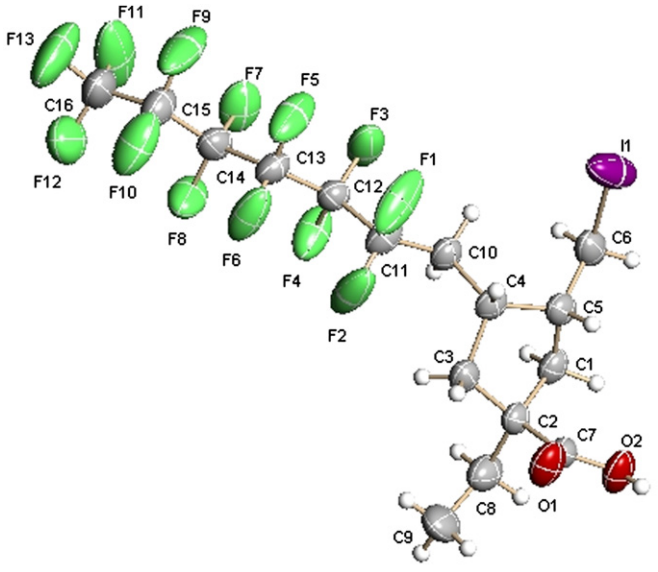


Figure 3. The three-dimensional perspective of molecule **4ba** (CCDC Number: 730907).

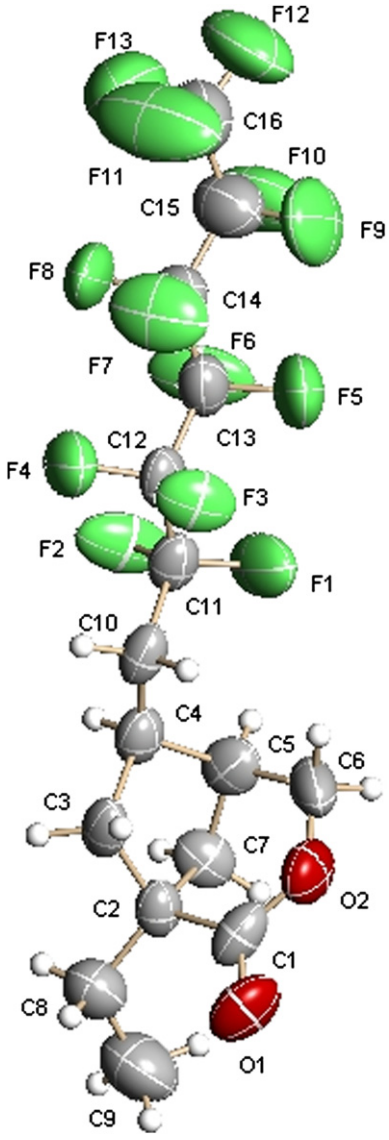


Figure 4. The three-dimensional perspective of molecule **3ba** (CCDC Number: 730906).

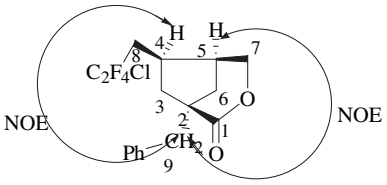


Figure 5. NOE correction from NOESY spectra of **3cd**.

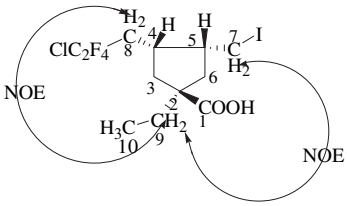


Figure 6. NOE correction from NOESY spectra of **4bd**.

Table 4
The iodolactonization reaction of **4bd** in the presence of various bases

Entry	Reaction conditions	Results
1	$NaHCO_3$, 25 °C	No reaction
2	NaOH, 25 °C	No reaction
3	NaOH, 60 °C	No reaction

The mixture of compound **4bd** (1 mmol) and base (3 mmol) in 10 ml water was stirred for 5 h, the reaction results were determined by TLC and GC.

2.3. Mechanism

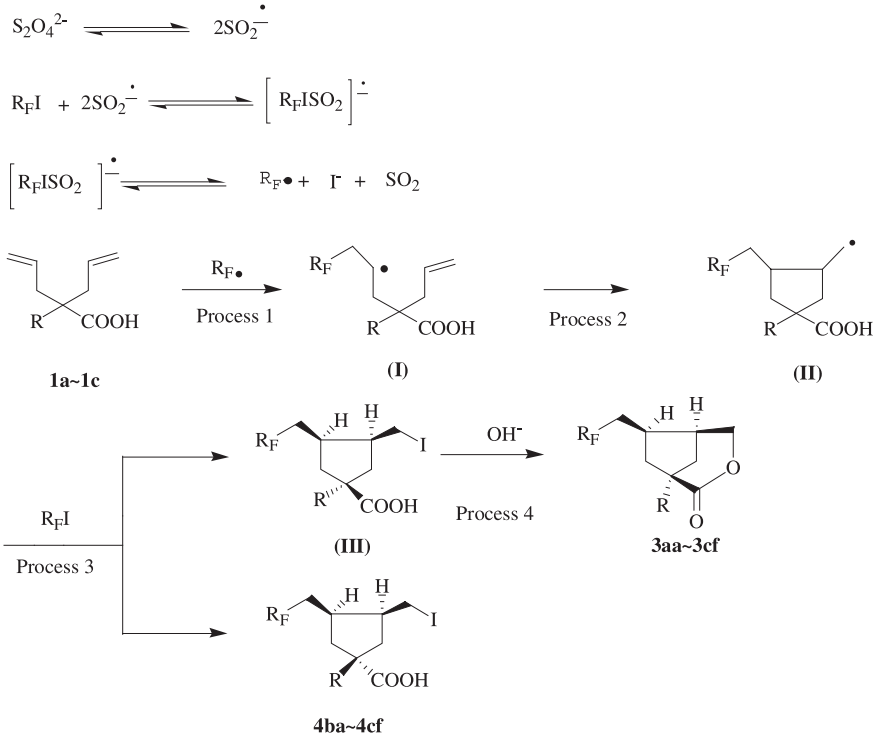
The mechanism is supposed as shown in (Scheme 2). After the polyfluoroalkyl radical $R_F^{\bullet}$ has been produced, the reaction processes continuous four steps: (1) $R_F^{\bullet}$ is added to one of the C=C and get intermediate **I**; (2) Radical cyclization occurs to get intermediate **II**; (3) **II** reacts with R_FI to get **III** and product **4**; (4) **III** is converted to **3** by iodolactonization.[8]

On the basis of the above mechanism we believe that the process (2) is the key step to determine the reaction's chemo- and stereoselectivity. The explanation is supposed as following (Scheme 3).

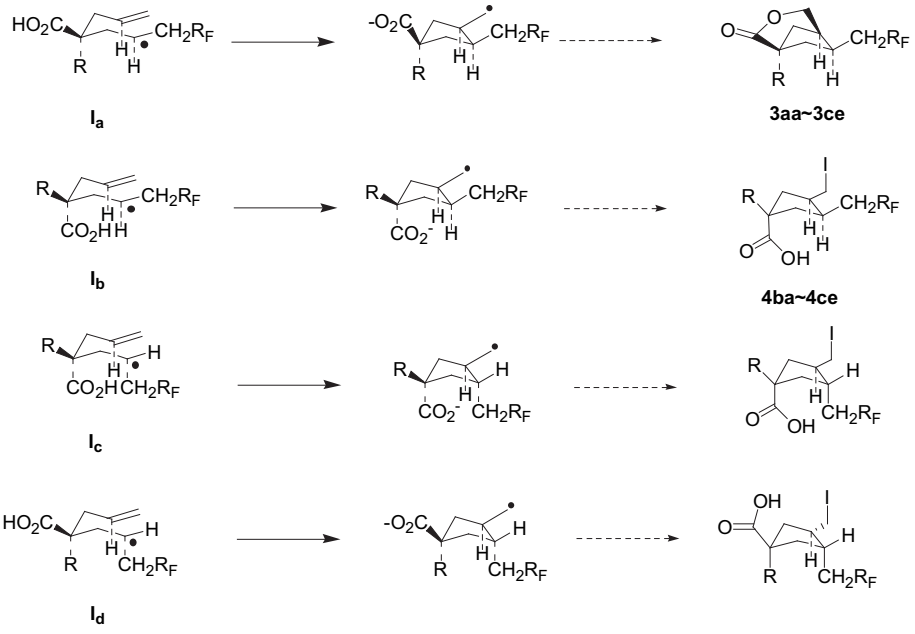
When cycloaddition occurs, the product's configuration mainly relies on the configuration of intermediate **I**. As shown in Scheme 3, intermediate **I** might possess four kinds of typical configurations, such as $\mathbf{I_a}$, $\mathbf{I_b}$, $\mathbf{I_c}$, and $\mathbf{I_d}$. For **1a** (R=H), $\mathbf{I_a}$ is the most stable configuration with CO_2H and R_FCH_2 at the equatorial bond of the chair-configuration, so 4(2)-*cis*-5(2)-*cis*-bicyclolactones **3aa**–**3af** are produced as the only product. For **1b** ($R=C_2H_5$) and **1c** ($R=CH_2C_6H_5$), with the increasing space hindrance, configuration $\mathbf{I_b}$ will be coexisted with configuration $\mathbf{I_a}$, thus 4(2)-*trans*-5(2)-*trans*-adducts **4ba**–**4ce** appears in the products and the ratio of **4**/**3** will be increased when 2-substituent changes from ethyl to benzyl. For the addition process of R_F does not appear in the rate-determined step, its effect to this reaction is not apparent. $\mathbf{I_c}$ and $\mathbf{I_d}$ are the unstable configuration with R_FCH_2 at the axial bond of the chair-configuration, therefore in our experimental conditions, no corresponding products are formed.

3. Conclusion

The reaction of 2-allyl-4-pentenoic acids with polyfluoroalkyl iodides has been developed to provide facile synthetic method for polyfluoroalkyl bicyclolactones **3**. For 2-allyl-4-pentenoic acid (**1a**), 4(2)-*cis*-5(2)-*cis*-bicyclolactone **3** was obtained as the major isomer in high yield and high stereoselectivity, while for 4-ethyl-2-allyl-4-pentenoic acid (**1b**) and 4-benzyl 2-allyl-4-pentenoic acid (**1c**), 4(2)-*cis*-5(2)-*cis*-bicyclolactones **3**, and 4(2)-*trans*-5(2)-*trans*-cycloadducts **4** were obtained in moderate yields and high stereoselectivity. 2-Substituent in 2-allyl-4-pentenoic acids plays an important role in the reaction's chemo- and stereoselectivity. The investigation of the reaction's applications is under way.



Scheme 2. Mechanism of the sodium dithionite-initiated reaction of **1** with **2**.



Scheme 3. Configuration explanation of the sodium dithionite-initiated reaction of **1** with **2**.

4. Experimental

4.1. General

All boiling points were uncorrected. ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker AC-500 (500 MHz) instrument with TMS and TFA as external references, respectively. Infrared spectra were measured on a Shimadzu IR-440. Mass spectra were recorded on a GC–MS-4021. X-ray data were measured at 293 K on a Bruker SMART CCD diffractomer with graphite monochromated Mo kα radiation.

4.2. Typical experimental procedure for the reaction of 1 with 2

2-Allyl-4-pentenoic acid **1**(**a**–**c**) (10.0 mmol) was dissolved in sodium hydroxide aqueous solution freshly prepared from sodium hydroxide (0.4 g, 10.0 mmol) in water (5 mL) and stirred while acetonitrile (15 mL) and R_FI (11.0 mmol) were added. To the solution was added the mixture of sodium dithionite (1.9 g, 11 mmol) and sodium bicarbonate (1.7 g, 20 mmol). The mixture was stirred at room temperature for 6 h to complete the reaction, then treated with water (about 50 mL) and shaken thoroughly. The mixture was extracted with ether (3×20 mL). The combined organic layer was washed with saturated brine solution and dried over anhydrous sodium sulfate. After evaporation of ether, the crude product was purified by column chromatography.

*4.2.1. 6-(2,2,3,3,4,4,5,5,6,6,7,7,7-Tridecafluoro-heptyl)-3-oxa-bicyclo [3.2.1]octan-2-one (**3aa**).* White Solid, mp: 73 °C ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.29–4.21 (2H, m, CO_2CH_2), 2.87–2.82 (1H, m, CH), 2.64–2.58 (1H, m, CH), 2.42 (1H, s, CH), 2.38–2.17 (3H, m, CH_2, $1/2CH_2$), 2.09 (1H, d, J=12.2, $1/2CH_2$), 1.87–1.83 (1H, m, $1/2CH_2$), 1.61–1.52 (1H, m, $1/2CH_2$). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −82.1 (3F, m), −114.8 (2F, m), −123.0 (2F, m), −124.1 (2F, m), −124.7 (4F, m), −127.4 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 174.6, 121.6–106.6 (6C, m, C_6F_{13}), 71.1, 42.1, 38.4, 36.1, 33.0 (1C, t, J=21.6), 33.0, 32.3. IR (film), ν (cm^{-1}): 2962, 1735, 1400, 1120, 920. EIMS (m/z): 458 (1.45), 414 (35.66), 399 (100.00), 387 (20.85), 81 (22.55), 55 (5.14). HRMS calcd for: $C_{14}H_{11}F_{13}O_2$: 458.0551, found: 458.0513.

*4.2.2. 6-(2,3,3,3-Tetrafluoro-2-trifluoromethyl-propyl)-3-oxa-bicyclo [3.2.1]octan-2-one (**3ab**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.31–4.18 (2H, m, CO_2CH_2), 2.86–2.79 (1H, m, CH), 2.56–2.48 (1H, m, CH), 2.41–2.27 (3H, m, $1/2CH_2$, CH_2), 2.23–2.14 (1H, m, 1/2CH), 2.06 (1H, d, J=12.2, $1/2CH_2$), 1.86–1.81 (1H, m, $1/2CH_2$), 1.46 (1H, d, d, J=5.6, 14.2, $1/2CH_2$). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −77.5 (3F, m), −78.1 (3F, m), −186.4 (1F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 174.4, 125.1–118.0 (2C, m, $2CF_3$), 94.0–91.3 (1C, m, CF), 70.7, 42.0, 38.6, 36.2, 33.6, 32.8, 30.9 (1C, d, J=19.8). IR (film), ν (cm^{-1}): 2966, 1732, 1439, 1183, 928, 732. EIMS (m/z): 264 (11.49), 249 (100.00), 237 (26.46), 231 (17.86), 95 (20.76), 81 (82.25), 67 (24.75), 55 (40.92). HRMS calcd for $C_{11}H_{11}F_7O_2$: 308.0647, found: 308.0647.

*4.2.3. 6-(5-Chloro-2,2,3,3,4,4,5,5-octafluoro-pentyl)-3-oxa-bicyclo [3.2.1]octan-2-one (**3ac**).* White Solid, mp: 54 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.37–4.28 (2H, m, CO_2CH_2), 2.95–2.91 (1H, m, CH), 2.69–2.60 (1H, m, CH), 2.48 (1H, s, CH), 2.45–2.28 (3H, m, $1/2CH_2$, CH_2), 2.15 (1H, d, J=12.2, $1/2CH_2$), 1.96–1.91 (1H, m, $1/2CH_2$), 1.60 (1H, d, d, J=5.5, 14.1, $1/2CH_2$). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −69.1 (2F, m), −114.8 (2F, m), −120.8 (2F, m), −124.0 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 173.0, 123.7–106.2 (4C, m, C_4F_8Cl), 69.5, 40.5, 36.7, 34.5, 31.4 (1C, t, J=21.6), 31.3, 30.7. IR (film), ν (cm^{-1}): 2954, 1735, 1467, 1133, 900, 742. EIMS (m/z): 330 (17.60), 317 (27.37), 315 (86.79), 302 (22.66), 293 (29.56), 95 (30.82), 81 (82.25), 67 (31.73), 55 (45.26). HRMS calcd for: $C_{12}H_{11}F_8ClO_2$ 374.0320, found: 374.0320.

*4.2.4. 6-(3-Chloro-2,2,3,3-tetrafluoro-propyl)-3-oxa-bicyclo[3.2.1] octan-2-one (**3ad**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.28–4.21 (2H, m, CO_2CH_2), 2.85–2.80 (1H, m, CH), 2.62–2.53 (1H, m, CH), 2.40 (1H, s (br), CH), 2.37–2.15 (3H, m, CH_2, $1/2CH_2$), 2.08 (1H, d, J=12.2, $1/2CH_2$), 1.89–1.82 (1H, m, $1/2CH_2$), 1.53 (1H, d, d, J=5.5, 14.2, $1/2CH_2$). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −72.5 (2F, m), −114.0 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 174.5, 126.7–115.5 (2C, m, ClC_2F_4), 70.9, 41.9, 38.1, 35.8, 32.7 (1C, t, J=10.9), 32.4, 30.0. IR (film), ν (cm^{-1}): 2954, 1742, 1468, 1152, 902, 751. EIMS (m/z): 244 (11.15), 230 (15.23), 217 (38.70), 215 (100.00), 202 (29.18), 181 (19.63), 95 (25.66), 81 (93.3), 67 (37.99), 55 (46.70). HRMS calcd for $C_{10}H_{11}ClF_4O_2$: 274.0384, found: 274.0383.

*4.2.5. 6-(2,2-Difluoro-2-(phenylthio)ethyl)-3-oxa-bicyclo[3.2.1]octan-2-one (**3ae**).* Colorless oil. ^{1}H NMR (CDCl3, 500 MHz) δ=7.60 (2H, d), 7.37–7.47 (3H, m), 4.23–4.33 (2H, m), 2.85–2.92 (1H, m), 2.58–2.67 (1H, m), 2.26–2.45 (4H, m), 2.06–2.12 (1H, m), 1.85–1.91 (1H, m), 1.53–1.59 (1H, m); ^{19}F NMR ($CDCl_3$, 470 MHz) δ=−72.82 (1F, AB, J=490.68 Hz, dd, J_1=11.28 Hz, J_2=18.8 Hz), −73.77 (1F, AB,

J=490.68 Hz, dd, J_1=13.16 Hz, J_2=17.86 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz) δ=174.90, 136.89, 130.71 (2C), 129.86 (2C), 130.20, 127.21 (1C, m), 71.30, 42.15, 41.15 (t, J=46.54 Hz), 38.21, 35.99, 344.56, 33.04. IR (film), ν (cm^{-1}). EIMS (m/z). HRMS calcd for: $C_{15}H_{16}F_2SO_2$ 298.0839, found: 298.0839. EIMS (m/z) 301 (6.03), 299 (16.70), 298 (87.45), 189 (21.29), 141 (21.52), 110 (100.00), 67 (16.59). IR (cm^{-1}) 2961, 1745, 1437, 1163, 946. HRMS calcd for $C_{15}H_{16}F_2O_2S$: 298.0839, found: 298.0839.

*4.2.6. 1-Ethyl-6-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoro-heptyl)-3-oxa-bicyclo[3.2.1]octan-2-one (**3ba**).* White Solid, mp: 78 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.5 (2H, d, J=2.0 CO_2CH_2), 2.66–2.59 (1H, m, CH), 2.42 (1H, s, CH), 2.32–2.14 (2H, m, CH_2), 2.07–1.93 (3H, m, CH_2, 1/2CH_2), 1.72–1.67(1H, m, 1/2CH_2), 1.58 (1H, d, d, J=6.1, 14.0, 1/2CH_2), 1.40–1.27 (1H, m, 1/2CH_2), 0.93–0.85 (3H, m, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −81.7 (3F, m), −114.7 (2F, m), −122.8 (2F, m), −123.8 (2F, m), −124.5 (2F, m), −127.1 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 175.5, 120.7–108.1 (6C, m, C_6F_{13}), 70.7, 50.6, 42.1, 38.7, 36.0, 32.6 (1C, t, J=21.6 Hz), 32.1, 27.7, 9.9. IR (film), ν (cm^{-1}): 2970, 1745, 1411, 1365, 1140, 1026, 902, 706. EIMS (m/z): 486 (15.88), 427 (12.97), 414 (14.38), 413 (100.00), 399 (17.44). HRMS calcd for: $C_{16}H_{15}F_{13}O_2$: 486.0864, found: 486.0865.

*4.2.7. 1-Ethyl-6-(2,3,3,3-tetrafluoro-2-trifluoromethyl-propyl)-3-oxa-bicyclo[3.2.1]octan-2-one (**3bb**).* White Solid, mp: 50 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.56–4.45 (2H, m, CO_2CH_2), 2.63–2.54 (1H, m, CH), 2.41 (1H, s, CH), 2.33–2.14 (2H, m, CH_2), 2.05–1.94 (3H, m, CH_2, 1/2CH_2), 1.70–1.66 (1H, m, 1/2CH_2), 1.53 (1H, d, d, J=6.1, 14.2, 1/2CH_2), 1.37–1.31 (1H, m, 1/2CH_2), 0.91–0.87 (3H, t, J=7.5, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −77.3 (3F, m), −77.9 (3F, m), −186.2 (1F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 176.1, 125.1–118.3 (2C, m, 2CF_3), 94.1–91.7 (1C, m, CF), 71.1, 51.1, 43.0, 39.7, 36.7, 34.2, 31.2 (1C, d, J=19.8 Hz), 28.4, 10.6. IR (film), ν (cm^{-1}): 2963, 1721, 1402, 1261, 1095, 800, 700. EIMS (m/z): 336 (16.08), 277 (16.39), 263 (100.00), 249 (21.05). HRMS calcd for: $C_{13}H_{15}F_7O_2$ 336.0960, found: 336.0960.

*4.2.8. 6-(3-Chloro-2,2,3,3-tetrafluoro-propyl)-1-ethyl-3-oxa-bicyclo[3.2.1]octan-2-one (**3bd**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.28–4.22 (2H, m, CO_2CH_2), 2.67–2.59 (1H, m, CH), 2.40 (1H, s, CH), 2.32–2.15 (H, m, 1/2CH_2), 2.08–1.95 (3H, m, CH_2, 1/2CH_2), 1.72–1.64 (1H, m, 1/2CH_2), 1.58 (1H, d, d, J=5.8, 14.1, 1/2CH_2), 1.38–1.33 (1H, m, 1/2CH_2), 0.94–0.87 (3H, t, J=7.5, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −72.4 (2F, m), −114.6 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 176.2, 124.4–115.9 (2C, m, ClC_2F_4), 71.3, 51.2, 42.7, 39.3, 36.6, 33.1, 33.0 (1C, t, J=21.8), 28.3, 10.6. IR (film), ν (cm^{-1}): 2963, 1742, 1440, 1261, 1091, 906, 799, 701. EIMS (m/z): 302 (15.10), 243 (14.85), 231 (27.49), 229 (100.00), 215 (15.17). HRMS calcd for: $C_{12}H_{15}ClF_4O_2$: 302.0697, found: 302.0697.

*4.2.9. 1-Ethyl-6-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-oxa-bicyclo[3.2.1]octan-2-one (**3bf**).* White Solid, mp: 59 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 4.5 (2H, d, J=2.0, CO_2CH_2), 2.68–2.60 (1H, m, CH), 2.42 (1H, s, CH), 2.38–2.13 (2H, m, CH_2), 2.06–1.95 (3H, m, CH_2 1/2CH), 1.70 (1H, d, d, J=4.8, 12.1 1/2CH_2), 1.58 (1H, d, d, J=5.8, 13.8, 1/2CH_2), 1.40–1.32 (1H, m, 1/2CH_2), 0.93–0.87 (3H, m, CH_3). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −81.9 (3F, m), −114.8 (2F, m), −125.4 (2F, m), −126.8 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 179.1, 121.0–110.0 (4C, m, C_4F_9), 71.1, 51.2, 42.7, 39.4, 36.7, 33.1 (1C, t, J=21.7 Hz), 32.7, 28.4, 10.6. IR (film), ν (cm^{-1}): 2963, 1743, 1398, 1260, 1112, 906, 801, 532. EIMS (m/z): 386 (15.53), 327 (15.03), 314 (12.40), 313 (100.00), 299 (18.97). HRMS calcd for: $C_{14}H_{15}F_9O_2$: 386.0928, found: 386.0931.

*4.2.10. 1-Benzyl-6-(3-chloro-2,2,3,3-tetrafluoro-propyl)-3-oxa-bicyclo[3.2.1]octan-2-one (**3cd**).* White Solid, mp: 57 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.24–7.14 (5H, m, C_6H_5), 4.25–4.14 (2H, m, CO_2CH_2), 3.30 (1H, d, J=13.8, CH) 2.70 (1H, d, J=13.8, CH), 2.58–2.48 (1H, m, 1/2CH_2), 2.34 (1H, s, 1/2CH_2), 2.28–2.09 (3H, m, CH_2, 1/2CH_2), 1.82 (1H, d, J=12.2, 1/2CH_2), 1.77–1.72 (1H, m, 1/2CH_2), 1.65–1.59 (1H, d, d, J=5.8, J=14.2, 1/2CH_2). ^{19}F NMR (470 MHz, $CDCl_3$), δ: −72.4 (2F,m), −114.5 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 176.0, 138.0, 131.4 (2C), 128.9 (2C), 127.3, 125.0–115.0 (2C, m, ClC_2F_4), 71.3, 51.4, 42.0, 40.2, 38.7, 36.7, 32.9 (1C, t, J=25.4 Hz), 32.7. IR (film), ν (cm^{-1}): 2962, 1726, 1446, 1398, 1261, 1082, 909, 799, 703. EIMS (m/z): 364 (39.39), 275 (11.76), 187 (14.92), 159 (100.00), 143 (19.19), 129 (16.26), 91 (53.12). HRMS calcd for: $C_{17}H_{17}ClF_4O_2$: 364.0853, found: 364.0847.

*4.2.11. 1-Benzyl-6-(2,2,3,3,4,4,5,5,5-nonafluoro-pentyl)-3-oxa-bicyclo[3.2.1]octan-2-one (**3cf**).* White Solid, mp: 62 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.29–7.07 (5H, m, C_6H_5), 4.23–4.13 (2H, m, CO_2CH_2), 3.30 (1H, d, J=13.8 CH) 2.70 (1H, m, J=13.8, CH), 2.58–2.48 (1H, m, 1/2CH_2), 2.35 (1H, s, 1/2CH_2), 2.28–2.09 (3H, m, CH_2, 1/2CH_2), 1.81 (1H, d, J=12.2, 1/2CH_2), 1.77–1.73 (1H, m, 1/2CH_2), 1.65–1.58 (1H, d, d, J=5.8, J=14.2, 1/2CH_2). ^{19}F NMR (470 MHz, $CDCl_3$), δ: -81.9 (3F, m), −114.8 (2F, m), −125.4 (2F, m), −126.8 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 174.3, 136.3, 129.7 (2C), 127.2 (2C), 125.6, 120.0–106.0 (4C, m, C_4F_9), 69.6, 49.7, 40.4, 38.5, 37.1, 35.0, 31.7 (1C, t, J=21.8 Hz), 30.8. IR (film), ν (cm^{-1}): 2962, 1730, 1396, 1225, 1020, 800, 700. EIMS (m/z): 448 (59.85), 357 (28.80), 313 (16.51), 187 (15.17), 159 (100.00), 129 (16.87) 91 (71.88). HRMS calcd for: $C_{19}H_{17}F_9O_2$: 448.1085, found: 448.1085.

*4.2.12. 1-Ethyl-3-(iodomethyl)-4-(2,2,3,3,4,4,5,5,6,6,7,7,7-tridecafluoroheptyl)cyclopentanecarboxylic acid (**4ba**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.18–3.09 (1H, m, 1/2CH_2I), 2.90–2.85 (1H, m, 1/2CH_2I), 2.55–2.35 (4H, m, 2CH_2), 2.27–2.21 (1H, m, 1/2CH_2CF_2), 2.03–1.90 (1H, m, 1/2CH_2CF_2), 1.68–1.59 (2H, m, CH_2), 1.48–1.37 (2H, m, CH_2CH_3), 0.83–0.72 (3H, m, CH_2CH_3). ^{19}F NMR (470 MHz, $CDCl_3$), δ: -82.2 (3F, m), -113.5–115.7 (2F, m), −123.1 (2F, m), −124.2 (2F, m), −124.8 (2F, m), −127.5 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 184.6, 121.5–106.9 (6C, m, C_6F_{13}), 54.1, 44.4, 42.8, 41.5, 35.6, 34.1, 31.1 (1C, t, J=21.6), 11.0, 8.5. IR (film), ν (cm^{-1}): 2968, 1688, 1464, 1206, 1087, 944, 652. EIMS (m/z): 614, 487 (34.69), 442 (33.19), 441 (100.00), 413 (26.17), 399 (73.65). HRMS calcd for: $C_{16}H_{16}F_{13}IO_2$ 613.9987, found: 613.9939.

*4.2.13. 3-(3-Chloro-2,2,3,3-tetrafluoropropyl)-1-ethyl-3-(iodomethyl)cyclopentanecarboxylic acid (**4bd**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 3.21–3.12 (1H, m, 1/2CH_2I), 2.98–2.90 (1H, m, 1/2CH_2I), 2.58–2.38 (4H, m, 2CH_2), 2.27–2.21 (1H, m, 1/2CH_2CF_2), 2.02–1.90 (1H, m, 1/2CH_2CF_2), 1.71–1.62 (2H, m, CH_2), 1.50–1.40 (2H, m, CH_2CH_3), 0.83–0.76 (3H, m, CH_2CH_3); ^{19}F NMR (470 MHz, $CDCl_3$), δ: -72.6 (2F, m), −112.4 to −116.1 (2F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 184.7, 124.3–118.0 (2C, m, ClC_2F_4), 54.0, 44.4, 42.9, 41.4, 35.6, 34.1, 30.8 (1C, t, J=21.8), 11.0, 8.7. IR (film), ν (cm-1): 2961, 1686, 1464, 1256, 1087, 940, 731. EIMS (m/z): 385 (M^+−COOH, 3.72), 303 (M^+−I, 3.72), 259 (19.81), 257 (100.00), 215 (19.23), 41 (8.68). HRMS calcd for: $C_{12}H_{16}F_4ClIO_2$ 429.9820, found: 429.9820.

*4.2.14. 1-Benzyl-3-(iodomethyl)-4-(2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl)cyclopentanecarboxylic acid (**4cb**).* Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$), δ: 7.29–7.07 (5H, m, C_6H_5), 3.18–3.09 (1H, m, 1/2CH_2I), 2.90 (2H, m, $CH_2C_6H_5$), 2.80–2.71 (1H, m, 1/2CH_2I), 2.52–2.34 (4H, m, 2CH_2), 2.22–2.16 (1H, m, 1/2CH_2CF_2), 1.95–1.87 (1H, m, 1/2CH_2CF_2), 1.62–1.54 (2H, m, CH_2); ^{19}F NMR (470 MHz, $CDCl_3$), δ: −76.9 (3F, m), −78.1 (3F, m), 185.8 (1F, m). ^{13}C NMR (125.8 MHz, $CDCl_3$), δ: 181.7, 136.1 (1C, 1/6C_6H_5), 128.8 (2C, 2/6C_6H_5), 127.4 (2C, 2/6C_6H_5), 126.0 (1C, 1/6C_6H_5), 122.0–117.0 (2C, m, 2CF_3), 90.0–92.5 (1C,m, CF), 52.8, 43.6, 42.7, 40.5, 39.6, 34.5, 27.2 (1C, d, J=19.6), 6.5. IR (film), ν (cm^{-1}): 2961, 1691, 1458, 1216, 1150, 960, 699. EIMS (m/z): 526 (1.01), 354 (11.47), 353 (41.49), 307

(39.36), 263 (14.33), 127 (17.15), 91 (100.00). HRMS calcd for: $C_{18}H_{18}F_7IO_2$ 526.0240, found: 526.0240.

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Supplementary data

Supplementary data associated with this article can found in online version, at doi:10.1016/j.tet.2010.07.002. These data include MOL files and InChIKeys of the most important compounds described in this article.

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