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Journal of Fluorine Chemistry 124 (2003) 69–80
JOURNAL OF FLUORINE CHEMISTRY
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A novel reaction of allylic alcohols with hexafluoropropene-diethylamine adduct (PPDA) to form 2-fluoro-2-trifluoromethyl-4-alkenamide

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Received 2 May 2003; received in revised form 25 June 2003; accepted 2 July 2003

Abstract

Treatment of allylic alcohols with hexafluoropropene-diethylamine adduct (PPDA) afforded *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-4-alkenamides which were formed by the Claisen rearrangement of intermediary 2-alkenyl-1-diethylamino-2,3,3,3-tetrafluoro-1-propenyl ethers. Although (*E*)-allylic alcohols gave two diastereomeric products in about 1:1 ratio, (*Z*)-allylic alcohols gave the corresponding product as a single diastereomer.

Keywords: Hexafluoropropene-diethylamine adduct (PPDA); Allylic alcohol; *N*,*N*-Diethyl-2-fluoro-2-trifluoromethyl-4-alkenamide; Claisen rearrangement; Iodolactonization; 2-Fluoro-2-trifluoromethyl-5-iodo-4-alkanolide

1. Introduction

Hitherto, organofluoro compounds have been attracting much attention in the field of biological and material science because they show unique chemical, biological, and physical properties [1–5]. Hence, many reactions to construct organofluoro compounds were developed. We also reported a new synthetic process leading (*E*)-3-tosyl-2-alkenols (**I**) to 2-fluoro-3-tosylmethyl-2-trifluoromethyl-4-alkanolides (**II**) that are useful synthetic precursors for preparing various derivatives of 2-fluoro-2-trifluoromethyl-alkanoic acid [6,7]. The key step of this process is the reaction of **I** with hexafluoropropene-diethylamine adduct (PPDA). Although PPDA [8] is one of the reagents for converting a hydroxy group into fluorine atom [9–13], the reaction of **I** with PPDA did not form the corresponding 3-fluoro-1-alkenyl sulfone, but the compound **II** was produced (Scheme 1).

In this reaction, 1-diethylamino-2,3,3,3-tetrafluoro-1-propenyl 3-tosyl-2-propenyl ether (**III**) was thought to be an intermediate for the formation of **II**. It is likely that a Michael-type addition of the enamine moiety to the vinyl sulfone part occurs intramolecularly to form **II**. During our investigation to elucidate its reaction mechanism, we had a question: if the tosyl group does not exist in **III**, what reaction would occur? Our answer was a [3,3]sigmatropic rearrangement, the so-called Claisen rearrangement. The Claisen rearrangement was reported to provide a useful route for synthesizing organic fluoro compounds: (i) the Claisen rearrangement of allyl-2-chloro-1,2-difluorovinyl ethers to form 2-chloro-2-fluoro-4-alkenoic acids [14]; (ii) the Ireland–Claisen rearrangement for constructing 2-methoxy-3-trifluoromethyl-4-alkenoic acids from 4,4,4-trifluoro-2-butenyl methoxyacetates [15]; (iii) the Claisen rearrangement of intermediary silyl enol ethers of allyl-3,3,3-trifluoropropionates or 2,3,3,3-tetrafluoropropionates to yield 2-trifluoromethyl-4-alkenoic acids or 2-fluoro-2-trifluoromethyl-4-alkenoic acids respectively [16,17]; (iv) the Johnson–Claisen rearrangement of 1-ethoxyethenyl ethers, derived by the reaction of 1-trifluoromethyl-1-alken-3-ols with ethyl orthoacetate, to give ethyl 3-trifluoromethyl-4-alkenoates [18]; and (v) the Claisen rearrangement of allyl- or propargyl-1-cycloalkyl-2,3,3,3-tetrafluoropropenyl ethers to form 2-fluoro-2-trifluoromethyl-4-alkenones or 2-fluoro-2-trifluoromethyl-3,4-alkadienones, respectively [19]. Against these background, we initiated our investigation on the reaction of simple allylic alcohols (**1**) with PPDA that would form 2-alkenyl 1-diethylamino-2,3,3,3-tetrafluoropropenyl ether (**3**) as an intermediate (Scheme 2). Herein, we describe a novel Claisen rearrangement of **3** to form *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-4-alkenamides (**2**) [20].

2. Results and discussion

First, we subjected 1-alken-3-ols (**1**; R^2 = H) to the reaction with PPDA in the presence of *N*,*N*-diisopropylethylamine.

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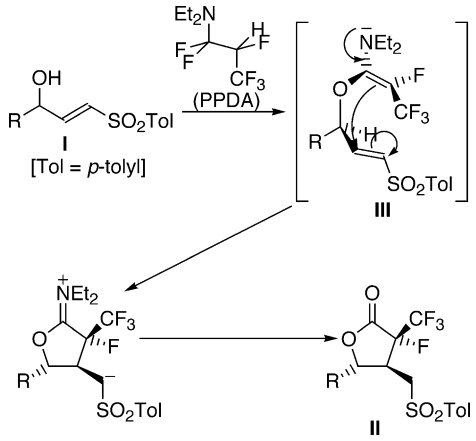
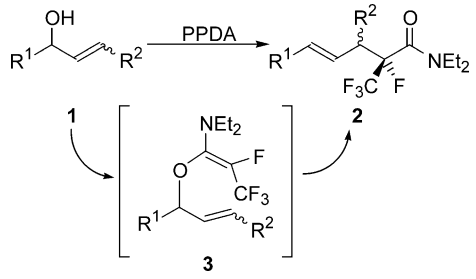
0022-1139/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/S0022-1139(03)00191-X



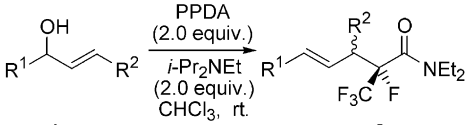
Scheme 1. Reaction of (*E*)-3-tosyl-2-alkenols with PPDA.



Scheme 2. Reaction of 2-alkenols with PPDA.

In this reaction, we found that *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-4-alkenamides (**2**) were formed. After a chloroform solution of PPDA (1 mol eq. to **1**) was dropwise added to a chloroform solution of l-hexen-3-ol (**1a**) and *N*,*N*-diisopropylethylamine (2 mol eq.), the resulting solution was stirred at room temperature (RT) for 55 h. The usual workup followed by chromatographic separation gave

Table 1
Formation of **2** from **1** and PPDA



1 **2**

Entry	**1**[a]	R^1	R^2	Time (h)	**2** (%)[b]
1	**1a**	*n*-Pr	H	55	90
2	**1b**	H	H	18	75
3	**1c**	Me	H	25	79
4	**1d**	*i*-Pr	H	111	70
5	**1e**	*n*-Bu	H	24	86
6	**1f** (*E*:*Z* = 88:12)	H	Me	18	96 (52:48)
7	**1g** (*E*:*Z* = 99:1)	H	*n*-Pr	18	79 (53:47)
8	**1h** (*E*:*Z* = 97:3)	H	Ph	25	29 (64:36)

[a] The value in parentheses is a geometric ratio (by ^{1}H NMR).
[b] The value in parentheses is a diastereomeric ratio (by HPLC).

N,*N*-diethyl-2-fluoro-2-trifluoromethyl-4-octenamide (**2a**) in 90% yield. This reaction was also applicable to 1-alken-3-ols such as allyl alcohol (**lb**), l-buten-3-ol (**1c**), 4-methyl-1-penten-3-ol (**1d**), and 1-hepten-3-ol (**1e**) to afford the corresponding **2** in comparable yields, as summarized in Table 1.

In the reaction of PPDA with 2-alken-1-ols (**1**; $R^2 \neq H$) having an inner C=C bond, two diastereomers of **2** would be formed. In fact, crotyl alcohol (**1f**), (*E*)-2-hexen-1-ol (**1g**), and cinnamyl alcohol (**1h**) gave a diastereomeric mixture of the corresponding **2** on similar treatment with PPDA. As shown in entries 6–8 of Table 1, two diastereomers were formed with a low selectivity. All of the **2** exhibited satisfactory spectral data for the proposed structures (see Section 4). Fortunately, a minor diastereomer of *N*,*N*-diethyl-2-fluoro-3-phenyl-2-trifluoromethyl-4-pentenamide

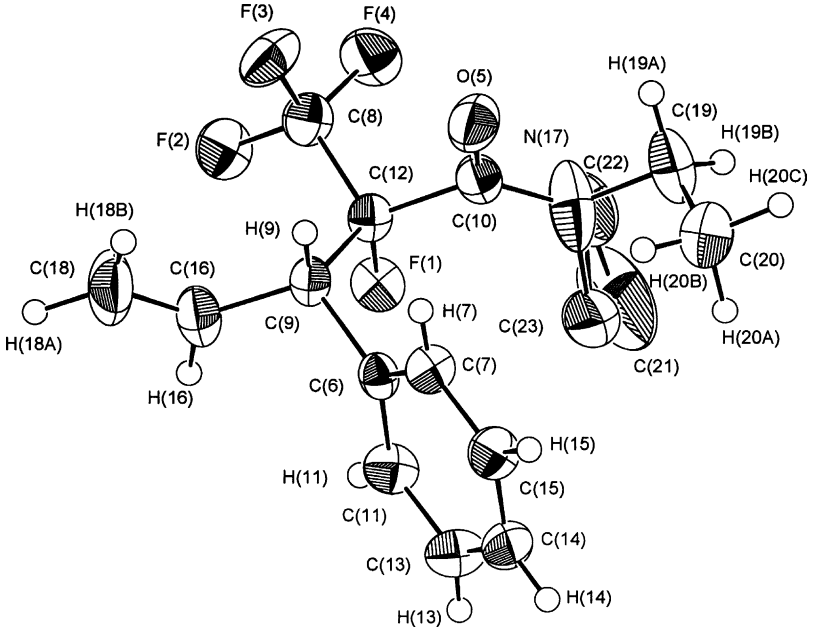
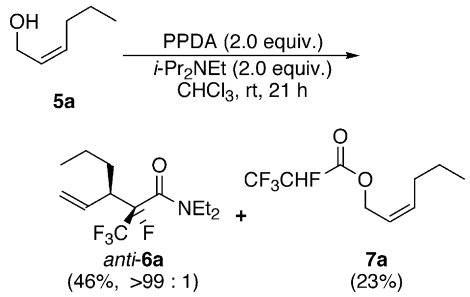
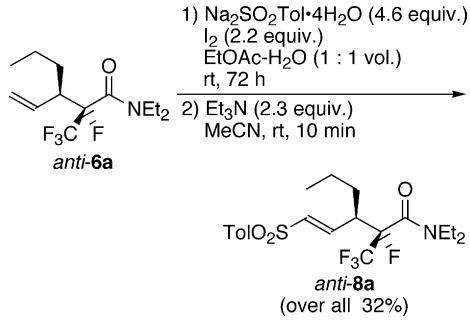


Fig. 1. ORTEP drawing of **2h** (minor).



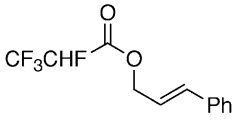
Scheme 3. Reaction of 2-hexen-1-ol (**5a**) with PPDA.



Scheme 4.

(**2h**) afforded a single crystal suitable for X-ray crystallographic analysis. Its ORTEP drawing is shown in Fig. 1 [20], which allowed us to confirm the structure of **2h** (minor).

However, the reaction of **1h** with PPDA in the presence of *N*,*N*-diisopropylethylamine was reported to afford cinnamyl 2,3,3,3-tetrafluoropropionate (**4**) [12]. This is different from our finding that **2h** was obtained on treatment of **1h** with PPDA and *N*,*N*-diisopropylethylamine for 25 h (entry 8 in Table 1). After several experiments, we succeeded in obtaining **4** by a reduction in the reaction time. Thus, we obtained **4** in 25% yield along with **2h** (14%) when **1h** was treated with PPDA for 1 h. These facts suggest that **3** ($R^1 = H$, $R^2 = Ph$) is formed as an intermediate for the production of **2h** (Scheme 2) and, if the reaction is quenched with water at an early stage, it is hydrolyzed to give **4**.



4

To our surprise, the reaction of (*Z*)-allylic alcohols with PPDA was found to proceed with a high diastereomeric selectivity. When (*Z*)-2-hexen-1-ol (**5a**) was allowed to react with PPDA in the presence of *N*,*N*-diisopropylethylamine, *N*,*N*-diethyl-2-fluoro-3-propyl-2-trifluoromethyl-4-pentenamide (**6a**) was formed in 46% yield along with 2-hexenyl 1,2,2,2-tetrafluoropropionate (**7a**) in 23% yield (Scheme 3). The formed **6a** consists of only one diastereomer. The stereochemistry of the product (**6a**) was confirmed by its derivation into *N*,*N*-diethyl-2-fluoro-3-propyl-5-tosyl-2-trifluoromethyl-4-pentenamide (**8a**), which was achieved by iodosulfonylation [21] followed by dehydroiodation (Scheme 4). The single-crystal X-ray crystallographic analysis of **8a** showed the *anti*-relationship between the fluorine atom at the 2-position and the propyl group at the 3-position (Fig. 2).

In order to improve the yield of **6**, we examined various reaction conditions. The results employing **5a** as a reactant are summarized in Table 2: a higher temperature accelerated the reaction to increase the yield of **6a** (entries 1–3). When the molar ratio of *N*,*N*-diisopropylethylamine:**5a** was

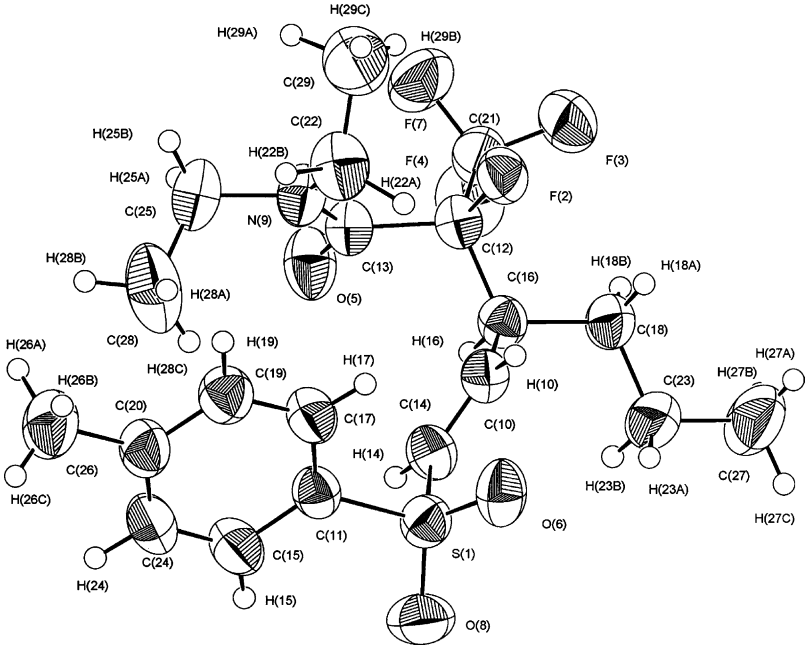


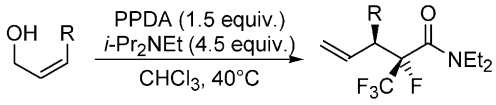
Fig. 2. ORTEP drawing of **8a**.

Table 2
Formation of **6a** from **5a** and PPDA[a,b]

Entry	PPDA (eq.)	*i*-Pr_2NEt (eq.)	Temperature (°C)	Yield (%)		
				6a	**7a**	**5a**
1	2.0	2.0	RT	51	28	6
2	2.0	2.0	30	55	8	7
3	2.0	2.0	40	58	3	–[c]
4	2.0	1.0	40	28	4	13
5	1.0	3.0	40	55	6	1
6	1.5	3.3	40	73	6	5
7	1.5	4.5	40	73	8	4
8	1.5	4.5	RT	15	37	46

[a] The geometric ratio of **5a** was *E*:*Z* = 6:94 (by ^{1}H NMR).
[b] The reaction time was 19–22 h.
[c] Not detected.

Table 3
Reaction of **5** with PPDA



5 **6**

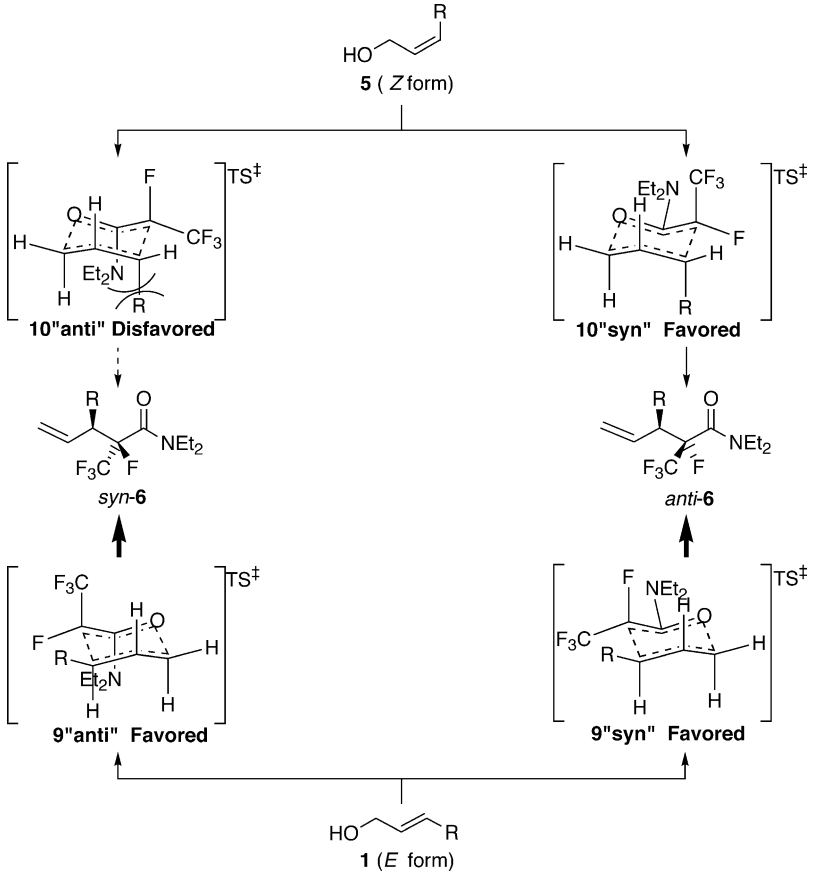
Entry	**5**[a]	**R**	Time (h)	**6** (%)[b]
1	**5a** (6:94)	*n*-Pr	22	73 (52)
2	**5b** (3:97)	Et	21	78 (65)
3	**5c** (1:>99)	*n*-C_9H_{19}	43	78 (50)
4	**5d** (2:98)	$Ph(Ch_2)_3$	32	76 (64)

[a] The value in parentheses is a geometric ratio of *E*:*Z* (by ^{1}H NMR).
[b] The yield of **6** was determined by ^{1}H NMR of crude mixture. The value in parentheses is an isolated yield.

increased up to 3.3–4.5 mol eq., the yield of **6a** became 73% (entries 6 and 7). Furthermore, the sufficient molar ratio of PPDA to **5a** was shown to be 1.5 eq. (entries 5–7). Thus, the recommended condition for the conversion of **5** to **6** is as follows: the reaction temperature, 40 °C; PPDA, 1.5 mol eq. (to **5**); *N*,*N*-diisopropylethylamine, 4.5 mol eq. (to **5**).

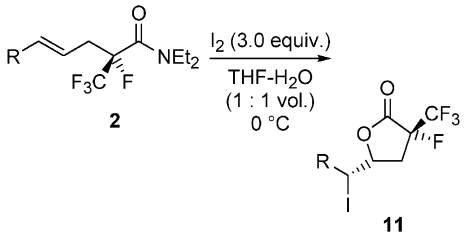
Using the above conditions, various **5** were subjected to the reaction with PPDA. All of the **5** examined herein afforded the corresponding **6** with an excellent selectivity (Table 3).

Although we do not have sufficient data for discussing the reaction mechanism at the present time, the formation of **2** from **1** is reasonably explained in terms of the Claisen rearrangement of the intermediary enamine derivative **3** of Scheme 2. For the highly stereoselective conversion of **5** to **6**, we propose a plausible mechanism depicted in Scheme 5. In the Claisen rearrangement of **1** and **5**, 2-alkenyl 1-diethylamino-2,3,3,3-tetrafluoro-1-propenyl ethers (**9** and **10**, respectively) would be formed intermediately. By semi-empirical molecular orbital calculation (PM3 method), the preferable



Scheme 5. Mechanism for the transformation of **5** into **6**.

Table 4
Reaction of iodolactonization of **2**



Entry	2	R	Time (h)	11 (%)[a]
1	**2a**	*n*-Pr	6	89 (90:10)
2	**2b**	H	7	95 (90:10)
3	**2c**	Me	6	95 (90:10)
4	**2d**	*i*-Pr	2	92[b]
5	**2e**	*n*-Bu	8	90 (90:10)

[a] Isolated yield. The value in parentheses is a diastereomeric ratio (by ^{1}H NMR).
[b] The diastereometic ratio could not be determined.

geometry of the enamine part in these intermediates was shown to be *E*. When the transition state for the Claisen rearrangement adopts a chair-like form, "*anti*" and "*syn*" states are possible. In *anti*-**10**, highly 1,3-repulsive interaction exists between the diethylamino and R groups. This implies that the Claisen rearrangement of **5** into **6** via **10** occurs with a high stereoselectivity. In contrast, the intermediary *anti*-**9** and *syn*-**9** are comparable in energy. This is the reason why the reaction of **1** with PPDA took place with a less stereoselectively.

Finally, we describe the easy derivation of **2** into 2-fluoro-5-iodo-2-trifluoromethyl-4-alkanolide (**11**). Treatment of **2** with I_2 in THF–water brought about the iodolactonization smoothly to afford the expected **11** in high yield, as shown in Table 4.

The reaction was so stereoselective that one diastereomer was predominantly formed. In the iodolactonization of **2** (R ≠ H), the formation of four diastereomers is possible. But, we obtained only two diastereomers of **11**. Since the iodolactonization reaction was known to take place with an extremely high stereoselectivity, the two diastereomers are estimated to result from the *cis–trans*-isomerism between the trifluoromethyl group at the 2-position and the substituent at the 4-position on the lactone ring. Fortunately, we also obtained single crystals for the tosyl-substituted product (**12b**) that was derived by the reaction with *p*-toluenethiolate anion and the subsequent oxidation with MCPBA from the major isomer of **11b**. The stereochemistry of **12b** was determined by X-ray crystallographic analysis (Fig. 3).

Hence, the major isomer of **11** was revealed to have *trans*-relationship between the substituents at the 2- and 4-positions.

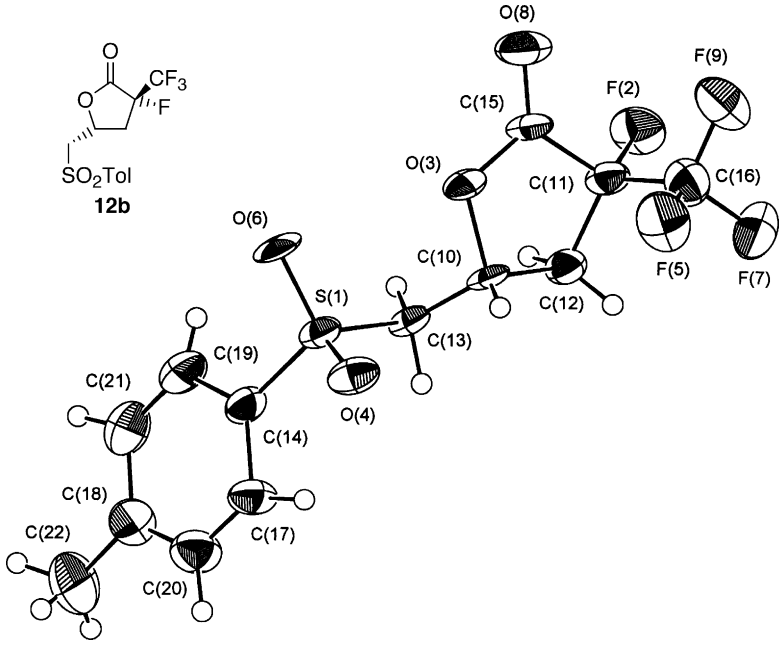
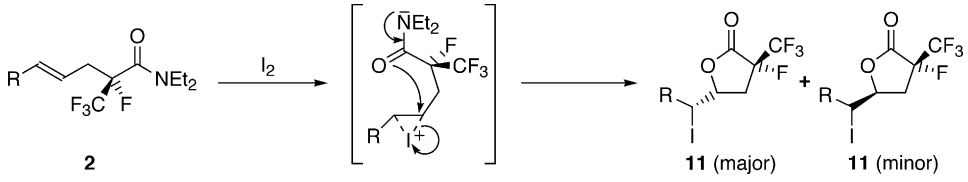


Fig. 3. ORTEP drawing of **12b**.



Scheme 6. Idolactonization of **2**.

This is in accordance with the stereochemical course (Scheme 6) of the iodolactonization that is similar to that reported in the iodolactonization of the usual 4-alkenamides [22].

3. Conclusion

In conclusion, the reaction of allylic alcohols (**1**) with PPDA in the presence of *N*,*N*-diisopropylethylamine affords *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-4-alkenamides (**2**) which, by iodolactonization, can be converted to 2-fluoro-5-iodo-2-trifluoromethyl-4-alkanolides (**11**) with a high stereoselectivity. The reaction of **1** with PPDA involves the Claisen rearrangement of an intermediary 2-alkenyl 1-diethylamino-2,3,3,3-tetrafluoro-1-propenyl ether (**3**). Interestingly, (*Z*)-2-alken-1-ols (**5**) react with PPDA to give the corresponding *anti*-*N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-4-alkenamides (**2**) with a high diastereomeric selectivity.

4. Experimental

4.1. General methods

Infrared spectra were recorded with JASCO FT/IR-350. ^{1}H NMR spectra were recorded on Varian GEMINI-2000 (300 MHz) or JEOL JNM LA-500 (500 MHz). ^{13}C NMR spectra were taken on Varian GEMINI-2000 (75 MHz). Microanalytical data were provided by the Analysis Center of Chiba University. Electron ionization mass spectrum (EIMS) were measured with JOEL JMS HX-110A and JMS 700T spectrometer. Analytical HPLC was performed on HITACHI L-6000 equipped with L-4000 UV detector or JASCO PU-980 equipped with UV-970 UV detector. Preparative HPLC was also performed on LC-908 (Japan Analytical Industry, Co. Ltd.). X-ray crystallographic analysis was performed on Mac Science MXC 18 diffractometer. Kugelrohr bulb-to-bulb distillation was carried out using SHIBATA GTO-250RS or GTO-350RS glass tube oven. The material used herein were obtained from commercial suppliers (Aldrich Chemical Co., Inc., Tokyo Kasei Kogyo Co., Ltd., Wako Pure Chemical Industries Ltd., Kanto Chemical Co., Inc., Nakarai Tesque, Inc.). PPDA was supplied from Tokyo Kasei Kogyo Co., Ltd. This reagent is the mixture of diethyl(perfluoropropyl)amine and diethyl(1-perfluoropropenyl)amine, the ratio of which was assumed to be 3:1 according to [8].

4.2. The reaction of terminal allylic alcohols with PPDA in the presence of N,N-diisopropylethylamine: A typical procedure

To a solution of 1-hexen-3-ol (**1a**) (2.00 g, 20 mmol) and *N*,*N*-diisopropylethylamine (7.0 ml, 40 mmol) in dry chloroform (20 ml), was dropwise added a solution of PPDA (7.1 ml, 40 mmol) in dry chloroform (20 ml) at room temperature over 30 min. After the solution was stirred at room temperature for 55 h, the reaction was quenched with water (10 ml) and the reaction mixture was extracted with chloroform (4 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (3 × 10 ml) and then with brine (2 × 10 ml), dried with $MgSO_4$, and evaporated in vacuo to give a brown oil (11.2 g). The residual crude mixture was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (12:1)] to give *N*,*N*-diethyl-2-fluoro-2-trifluoromethyl-4-octenamide (**2a**) (5.08 g: 90% yield).

4.2.1. N,N-Diethyl-2-fluoro-2-trifluoromethyl-4-octenamide (2a)

Colorless oil; bp 79 °C (bath temperature)/5 mmHg (short-path distillation); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.88 (t, 3H, $J = 7.3$ Hz, CH_3CH_2), 1.15 (t, 3H, $J = 7.1$ Hz, $CON(CH_2CH_3)$), 1.19 (t, 3H, $J = 7.1$ Hz, $CON(CH_2CH_3)$), 1.37 (sextet, 2H, $J = 7.3$ Hz, $CH_3CH_2CH_2$), 1.99 (q, 2H, $J = 7.1$ Hz, $CH_2CH_2CH{=}CH$), 2.63 (td, 1H, $J = 14.2$, 7.4 Hz, CH=CHCH(H)CF), 3.06 (ddd, 1H, $J = 36.4$, 14.5, 7.2 Hz, CH=CHCH(H)CF), 2.58–3.29 (m, 4H, $FCCON(CH_2CH_3)_2$), 5.33 (dt, 1H, $J = 15.3$, 7.5 Hz, CH=CHCH$_2$CF), 5.67 (dt, 1H, $J = 15.2$, 6.9 Hz, $CH_2CH_2CH{=}CH$); IR (neat): ν (cm^{-1}) 2966, 1651, 1448, 1435, 1277, 1198, 1167, 1119; Anal Calcd for $C_{13}H_{21}F_4NO$: C, 55.11; H, 7.47; N, 4.94. Found: C, 55.40; H, 7.43; N, 4.81.

4.2.2. N,N-Diethyl-2-fluoro-2-trifluoromethyl-4-pentenamide (2b)

Colorless oil; bp 95 °C/16 mmHg (Kugelrohr); ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) 1.15 (t, 3H, $J = 7.2$ Hz, $CON(CH_2CH_3)$), 1.19 (t, 3H, $J = 6.9$ Hz, $CON(CH_2CH_3)$), 2.69 (dq, 1H, $J = 19.1$, 7.2 Hz, CH_2=CHCH(H)CF), 3.14 (ddd, 1H, $J = 35.6$, 14.3, 6.9 Hz, CH_2=CHCH(H)CF), 3.39 (q, 2H, $J = 7.1$ Hz, $CON(CH_2CH_3)$ or $CON(CH(H)CH_3)(CH(H)CH_3)$), 3.30–3.43 (m, 1H, $FCCON(CH(H)CH_3)$), 3.56 (ddq, 1H, $J = 14.4$, 4.3, 7.1 Hz, $FCCON(CH(H)CH_3)$), 5.23 (dm, 1H, $J = 10.2$ Hz, CH(H)=CHCH$_2$CF), 5.27 (dq like, 1H, $J = 17.1$, 1.6 Hz, CH(H)=CHCH$_2$CF), 5.73 (ddt, 1H, $J = 17.1$, 10.0, 7.2 Hz, CH_2=CHCH$_2$); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) 12.36 ($CON(CH_2CH_3)$), 14.97 (d, $J = 2$ Hz), $FCCON(CH_2CH_3)$, 37.03 (d, $J = 23$ Hz, CH_2=CHCH$_2$CF), 42.65 (d, $J = 17$ Hz), $FCCON(CH_2CH_3)$, 43.36 ($CON(CH_2CH_3)$), 96.63 (dq, $J = 209$, 28 Hz, CF_3CFCO), 121.47 (CH_2=CHCH$_2$), 122.68 (qd, $J = 286$, 29 Hz, CF_3CFCO), 128.43 (d, $J = 3$ Hz, CH_2=CHCH$_2$CF), 162.64 (d, $J = 18$ Hz, CF_3CFCON); IR (neat): ν (cm^{-1}) 2985, 1651, 1438, 1364, 1278, 1200, 1168, 1117; Anal Calcd for $C_{10}H_{15}F_4NO$: C, 49.79; H, 6.27; N, 5.81. Found: C, 49.60; H, 6.20; N, 5.75.

4.2.3. N,N-Diethyl-2-fluoro-2-trifluoromethyl-4-hexenamide (2c)

Colorless oil; bp 98 °C/12 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.14 (t, 3H, $J = 7.0$ Hz, $CON(CH_2CH_3)$), 1.21 (t, 3H, $J = 7.1$ Hz, $CON(CH_2CH_3)$),

1.68 (d like, 3H, $J = 6.5$ Hz, CH_3CH=CH), 2.63 (ddd, 1H, $J = 21.6$, 14.4, 7.2 Hz, CH=CHC*H*(H)CF), 3.04 (ddd, 1H, $J = 35.9$, 14.3, 7.2 Hz, CH=CHCH(*H*)CF), 3.27–3.58 (m, 4H, FCCON(CH_2CH$_3$)$_2$), 5.35 (dtd like, 1H, $J = 14.7$, 7.3, 1.2 Hz, CH=C*H*CH$_2$CF), 5.68 (dq like, 1H, $J = 14.2$, 6.5 Hz, CH$_3$C*H*=CH); IR (neat): ν (cm^{-1}) 2976, 1651, 1448, 1437, 1364, 1276, 1199, 1115; Anal Calcd for $C_{11}H_{17}F_4NO$: C, 51.76; H, 6.71; N, 5.49. Found: C, 52.00; H, 6.71; N, 5.51.

4.2.4. N,N-Diethyl-2-fluoro-6-methyl-2-trifluoromethyl-4-heptenamide (**2d**)

Colorless oil; bp 100 °C/19 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.96 (d, 6H, $J = 6.7$ Hz, (CH_3)$_2$CH), 1.15 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.19 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3), 2.27 (octet, 1H, $J = 6.6$ Hz, (CH$_3$)$_2$C*H*CH), 2.61 (dt, 1H, $J = 14.1$, 7.3 Hz, CH=CHC*H*(H)CF), 3.04 (ddd, 1H, $J = 36.5$, 14.2, 7.2 Hz, CH=CHCH(*H*)CF), 3.27–3.57 (m, 4H, FCCON(CH_2-CH$_3$)$_2$), 5.28 (dt, 1H, $J = 15.2$, 7.0 Hz, CH=C*H*CH$_2$), 5.66 (dd, 1H, $J = 15.4$, 6.7 Hz, CHC*H*=CH); IR (neat): ν (cm^{-1}) 2966, 1651, 1448, 1435, 1363, 1278, 1200, 1119; Anal Calcd for $C_{13}H_{21}F_4NO$: C, 55.11; H, 7.47; N, 4.94. Found: C, 54.89; H, 7.31; N, 4.70.

4.2.5. N,N-Diethyl-2-fluoro-2-trifluoromethyl-4-nonenamide (**2e**)

Colorless oil; bp 120 °C/4 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.88 (t, 3H, $J = 7.1$ Hz, CH_3CH$_2$), 1.15 (t, 3H, $J = 6.9$ Hz, CON(CH$_2$CH_3)), 1.19 (t, 3H, $J = 6.9$ Hz, CON(CH$_2$CH_3)), 1.23–1.37 (m, 4H, CH$_3$-(CH_2)$_2$CH$_2$), 2.01 (q, 2H, $J = 6.6$ Hz, CH$_2$CH_2CH=CH), 2.62 (td, 1H $J = 14.2$, 7.2 Hz, CH=CHC*H*(H)CF), 3.05 (ddd, 1H, $J = 36.3$, 14.2, 7.1 Hz, CH=CHCH(*H*)CF), 3.29–3.58 (m, 4H, FCCON(CH_2CH$_3$)$_2$), 5.32 (dt, 1H, $J = 15.0$, 7.2 Hz, CH=C*H*CH$_2$), 5.67 (dt, 1H, $J = 15.1$, 6.9 Hz, CH$_2$C*H*=CH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.14 (CON(CH$_2$*C*H$_3$)), 14.60 (*C*H$_3$CH$_2$), 15.75 (d, $J = 3$ Hz, FCCON(CH$_2$*C*H$_3$)), 22.84 (CH$_3$*C*H$_2$CH$_2$), 31.94 (CH$_2$*C*H$_2$CH$_2$CH=CH), 33.00 (CH$_2$*C*H$_2$CH=CH), 36.66 (d, $J = 21$ Hz, CH=CH*C*H$_2$CF), 43.38 (d, $J = 18$ Hz, FCCON(*C*H$_2$CH$_3$)), 97.72 (dq, 208.4, 28.7 Hz, CF$_3$*C*FCO), 44.11 (CON(*C*H$_2$CH$_3$)), 120.22 (d, $J = 2.2$ Hz, CH$_2$CH=C*H*CH$_2$CF), 123.15 (qd, $J = 286$, 29 Hz, *C*F$_3$CFCO), 138.79 (CH$_2$*C*H=CHCH$_2$CF), 163.68 (d, $J = 20$ Hz, CF$_3$CF*C*ON); IR (neat): ν (cm^{-1}) 2933, 1651, 1448, 1364, 1276, 1198, 1119, 1082; Anal Calcd for $C_{14}H_{23}F_4NO + 0.2H_2O$: C, 55.88; H, 7.84; N, 4.65. Found: C, 55.92; H, 7.91; N, 4.59; HRMS Calcd for $C_{14}H_{23}F_4NO$: 297.1716. Found: 297.1717.

4.3. The reaction of (E)-internal allylic alcohols with PPDA in the presence of N,N-diisopropylethylamine: A typical procedure

To a solution of crotyl alcohol (E:$Z = 88$:12) (**1f**) (427 μl, 5.0 mmol) and *N*,*N*-diisopropylethylamine (1.7 ml, 10 mmol) in dry chloroform (5 ml), was dropwise added a solution of PPDA (1.8 ml, 10 mmol) in dry chloroform (5 ml) over 19 min under cooling with ice. After the solution was stirred at room temperature for 18 h, water (10 ml) was added to quench the reaction. The resulting reaction mixture was extracted with ether (4 × 8 ml). The combined organic layers were washed with saturated aqueous solution (20 ml) of $NaHCO_3$, dried with $MgSO_4$, and evaporated in vacuo to give a reddish brown oil (2.17 g). The residual crude mixture was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (6:1)] to give *N*,*N*-diethyl-2-fluoro-3-methyl-2-trifluoromethyl-4-pentenamide (**2f**) as a diastereomeric mixture (1.22 g: 96% yield). The diastereomeric ratio of **2f** was 52:48 which was determined by the HPLC analysis [YMC Pack, eluent: *n*-hexane–ethyl acetate (5:1)]. The diastereomers could be separated by preparative HPLC [YMC packed column: eluent; *n*-hexane–ethyl acetate (2:1)].

4.3.1. N,N-Diethyl-2-fluoro-3-methyl-2-trifluoromethyl-4-pentenamide (**2f**) (two diastereomeric mixture)

*4.3.1.1. Major diastereomer of **2f** (polar) [**2f** (major)].* Colorless oil; bp 120 °C (bath temperature)/16 mmHg (short-path distillation); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (d, 3H, $J = 7.0$ Hz, CH_3CHCF), 1.17 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.23 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 3.21–3.63 (m, 5H, CH$_2$=CHC*H*(CH$_2$)CF and FCCON(CH_2CH$_3$)$_2$), 5.15 (dd like, 1H, $J = 10.1$, 1.3 Hz, C*H*(H)=CHCH), 5.21 (dm, 1H, $J = 17.2$ Hz, CH(*H*)=CHCH), 5.68 (dt, 1H, $J = 17.0$, 9.5 Hz, CH$_2$=C*H*CH); IR (neat): ν (cm^{-1}) 2983, 1651, 1461, 1437, 1285, 1200, 1171, 1149; Anal Calcd for $C_{11}H_{17}F_4NO$: C, 51.76; H, 6.71; N, 5.49. Found: C, 51.83; H, 6.88; N, 5.47.

*4.3.1.2. Minor diastereomer of **2f** (less polar) [**2f** (minor)].* Colorless oil; bp 120 °C (bath temperature)/16 mmHg (short-path distillation); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.12 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.19 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3)), 1.20 (d, 3H, $J = 6.9$ Hz, CH_3CH), 3.19–3.53 (m, 5H, CH$_2$=CHC*H*(CH$_2$)CF and FCCON(CH_2CH$_3$)$_2$), 5.14 (d like, 1H, $J = 10.3$ Hz, C*H*(H)=CH), 5.20 (d, 1H, $J = 17.2$ Hz, CH(*H*)=CH), 5.76 (ddd, 1H, $J = 17.3$, 10.1, 8.3 Hz, CH$_2$=C*H*CH); IR (neat): ν (cm^{-1}) 2985, 1651, 1463, 1436, 1274, 1200, 1169, 1149; Anal Calcd for $C_{11}H_{17}F_4NO$: C, 51.76; H, 6.71; N, 5.49. Found: C, 51.72; H, 6.88; N, 5.53.

4.3.2. N,N-Diethy-2-fluoro-3-propyl-2-trifluoromethyl-4-pentenamide (**2g**) (two diastereomeric mixture)

The diastereomeric ratio of **2g** was 53:47 which was determined by HPLC analysis [YMC Pack, eluent: *n*-hexane–ethyl acetate (8:1)]. The diastereomers were separated by HPLC [YMC packed column: eluent; *n*-hexane–ethyl acetate (4:1)].

*4.3.2.1. Major diastereomer of **2g** (less polar) [**2g** (major)].* Colorless oil; bp 102 °C/4.5 mmHg (Kugelrohr); ^{1}H NMR

(300 MHz, $CDCl_3$): δ (ppm) 0.87 (t, 3H, $J = 7.0$ Hz, CH_3CH$_2$), 1.17 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.23 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.12–1.45 (m, 4H, CH$_3$(CH_2)$_2$CH), 3.10 (dtd, 1H, $J = 31.2$, 10.2, 2.9 Hz, CH$_2$=CHCH(CH$_2$)CF), 3.41 (q, 2H, $J = 7.1$ Hz, CON-(CH_2CH$_3$)), 3.35–3.49 (m, 1H, FCCON(CH(H)CH$_3$)), 3.58 (d sextet, 1H, $J = 7.1$, 4.7 Hz, FCCON(CH(H)CH$_3$)(CH$_2$-CH$_3$)), 5.18 (dm, 1H, $J = 16.9$ Hz, CH(H)=CHCH), 5.23 (dm like, 1H, $J = 10.2$ Hz, CH(H)=CHCH), 5.62 (dt, 1H, $J = 17.2$, 9.8 Hz, CH$_2$=CHCH); IR (neat): ν (cm^{-1}) 2965, 1651, 1462, 1447, 1287, 1202, 1169, 1142; Anal Calcd for $C_{13}H_{21}F_4NO$: C, 55.11; H, 7.47; N, 4.94. Found: C, 55.31; H, 7.58; N, 5.06.

*4.3.2.2. Minor diastereomer of **2g** (polar) [**2g** (minor)].* Colorless oil; bp 102 °C/4.5 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.90 (t, 3H, $J = 7.2$ Hz, CH_3CH$_2$), 1.11 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.19 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$CH_3)), 1.15–1.68 (m, 4H, CH$_3$(CH_2)$_2$CH), 3.03 (dtd, 1H, $J = 28.7$, 10.4, 3.3 Hz, CH$_2$=CHCH(CH$_2$)CF), 3.21 (sextet, 1H, $J = 6.9$ Hz, FCCON(CH(H)CH$_3$)(CH$_2$CH$_3$)), 3.48 (q, 1H, $J = 6.8$ Hz, CON(CH(H)CH$_3$)(CH$_2$CH$_3$)), 3.30–3.55 (m, 2H, FCCON(CH_2CH$_3$) or FCCON(CH(H)CH$_3$)(CH(H)CH$_3$)), 5.17 (dd, 1H, $J = 16.8$, 1.8 Hz, CH(H)=CHCH), 5.19 (dd, 1H, $J = 10.6$, 1.8 Hz, CH(H)=CHCH), 5.64 (dt, 1H, $J = 16.8$, 10.1 Hz, CH$_2$=CHCH); IR (neat): ν (cm^{-1}) 2966, 1651, 1462, 1447, 1272, 1200, 1168, 1107; Anal Calcd for $C_{13}H_{21}F_4NO$: C, 55.11; H, 7.47; N, 4.94. Found: C, 55.28; H, 7.46; N, 4.80.

*4.3.3. N,N-Diethyl-2-fluoro-3-phenyl-2-trifluoromethyl-4-pentenamide (**2h**) (two diastereomeric mixture)*

The diastereomeric ratio of **2h** was 64:36 (by the ^{1}H NMR). The diastereomers were separated by preparative HPLC [YMC packed column: eluent; *n*-hexane–ethyl acetate (3:1)].

*4.3.3.1. Major diastereomer of **2h** (less polar) [**2h** (major)].* Colorless crystals; mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.136 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$-CH_3)), 1.141 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 3.18–3.39 (m, 3H, FCCON(CH(H)CH$_3$)(CH_2CH$_3$)), 3.50 (sextet, 1H, $J = 6.9$ Hz, FCCON(CH(H)CH$_3$)(CH$_2$CH$_3$)), 4.34 (dd, 1H, $J = 30.8$, 9.0 Hz, CH$_2$=CHCH(Ph)CF), 5.21 (dm, 1H, $J = 10.2$ Hz, CH(H)=CHCH), 5.23 (dm, 1H, $J = 17.4$ Hz, CH(H)=CHCH), 6.22 (dt, 1H, $J = 17.0$, 10.2 Hz, CH$_2$=CHCH), 7.22–7.38 (m, 5H, Ph-H); IR (neat): ν (cm^{-1}) 2984, 1650, 1449, 1285, 1203, 1126, 1043, 748; Anal Calcd for $C_{16}H_{19}F_4NO$: C, 60.56; H, 6.04; N, 4.41. Found: C, 60.37; H, 5.98; N, 4.26.

*4.3.3.2. Minor diastereomer of **2h** (polar) [**2h** (minor)].* **2h** (*minor*) was recrystallized from *n*-hexane to give single crystals suitable for X-ray crystallographic analysis.

Colorless crystals; mp 49–50 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.82 (t, 3H, $J = 7.1$ Hz, CON(CH(CH$_2$CH_3)), 0.91 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 2.77–2.93 (m, 2H, FCCON(CH_2CH$_3$)(CH$_2$CH$_3$) or FCCON(CH(H)CH$_3$)-(CH(H)CH$_3$)), 3.04 (sextet d, 1H, $J = 7.2$, 4.3 Hz, FCCON-(CH(H)CH$_3$)(CH$_2$CH$_3$)), 3.38 (sextet, 1H, $J = 7.0$ Hz, FCCON(CH(H)CH$_3$)(CH$_2$CH$_3$)), 4.41 (dd, 1H, $J = 33.7$, 9.9 Hz, CH$_2$=CHCH(Ph)CF), 5.26 (d like, 2H, $J = 9.9$ Hz, CH(H)=CHCH), 5.30 (d like, 1H, $J = 17.4$ Hz, CH(H)=CHCH), 6.32 (dtq like, 1H, $J = 17.1$, 9.9, 1.1 Hz, CH$_2$=CHCHCCF$_3$), 7.22–7.33 (m, 5H, Ph-H); IR (KBr): ν (cm^{-1}) 2979, 1644, 1460, 1448, 1289, 1198, 1118, 1038 cm^{-1}; Anal Calcd for $C_{16}H_{19}F_4NO$: C, 60.56; H, 6.04; N, 4.41. Found: C, 60.60; H, 5.96; N, 4.38.

*4.4. The reaction of **1h** with PPDA in the presence of N,N-diisopropylethylamine during a shorten period of reaction time*

To a solution of **1h** (643 μl, 5.0 mmol) and *N*,*N*-diisopropylethylamine (1.7 ml, 10 mmol) in dry chloroform (5 ml), was dropwise added PPDA (1.8 ml, 10 mmol) in dry chloroform (5 ml) at room temperature over 17 min. After the solution was stirred for 1 h at room temperature, the reaction was quenched by the addition of water (5 ml). This reaction mixture was extracted with chloroform (4 × 8 ml). The combined organic layers were washed with saturated aqueous solution of $NaHCO_3$, dried with $MgSO_4$, and evaporated to give a yellow oil (2.24 g). The obtained crude mixture contained **2h** (14% yield) and cinnamyl 2,3,3,3-tetrafluoropropionate (**4**) (25% yield) by ^{1}H NMR analysis using naphthalene as an internal standard.

*4.4.1. Cinnamyl 2,3,3,3-tetrafluoropropionate (**4**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.96 (dd, 2H, $J = 6.7$, 1.2 Hz, OCH_2CH=CHPh), 5.14 (dq, 1H, $J = 46.2$, 6.5 Hz, CF$_3$CHFCO), 6.28 (dt, 1H, $J = 15.9$, 6.6 Hz, OCH$_2$CH=CHPh), 6.73 (d, 1H, $J = 15.8$ Hz, OCH$_2$CH=CHPh), 7.24–7.44 (m, 5H, Ph-H); IR (neat): ν (cm^{-1}) 3030, 1773, 1647, 1362, 1277, 1210, 1147, 1129. These spectral data are in accordance with those reported in [12].

4.5. The reaction of (Z)-internal allylic alcohols with PPDA in the presence of N,N-diisopropylethylamine: A typical procedure

To a solution of (*Z*)-2-hexen-1-ol (**5a**) (501.3 mg, 5.0 mmol) and *N*,*N*-diisopropylethylamine (3.9 ml, 23 mmol) in dry chloroform (5 ml), was dropwise added a solution of PPDA (1.3 ml, 7.5 mmol) in dry chloroform (3.8 ml) at room temperature over 11 min. After the resulting solution was stirred at 40 °C for 22 h, the reaction was quenched by the addition of water (10 ml). The reaction mixture was extracted with ether (4 × 10 ml). The combined organic layers were washed with 1N hydrochloric acid (3 × 10 ml) and then brine (3 × 10 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo to give a orange oil (3.22 g). The residual crude mixture was shown by ^{1}H NMR analysis to contain

6a (73% yield) and **7a** (7% yield). The crude mixture was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (8:1)] to give **6a** (743 mg: 52% yield). Its ^{1}H NMR analysis showed that **6a** consists of a single diastereomer.

4.5.1. *anti-N,N-Diethyl-2-fluoro-3-propyl-2-trifluoromethyl-4-pentenamide (**6a**)*

Colorless oil; bp 98 °C/8 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.90 (t, 3H, $J = 7.2$ Hz, C*H*$_3$CH$_2$), 1.11 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$C*H*$_3$)), 1.19 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$C*H*$_3$)), 1.15–1.69 (m, 4H, CH$_3$(C*H*$_2$)$_2$CH), 3.03 (1H, dtd, $J = 29.0$, 10.5, 3.2 Hz, CH$_2$=CHC*H*(CH$_2$)CF), 3.21 (1H, sextet, $J = 7.0$ Hz, FCCON(C*H*(H)CH$_3$)), 3.30–3.55 (3H, m, FCCON(C*H*(H)-CH$_3$)(C*H*$_2$CH$_3$)), 5.17 (dd, 1H, $J = 16.9$, 1.4 Hz, C*H*(H)=CH), 5.19 (dd, 1H, $J = 10.2$, 1.6 Hz, CH(*H*)=CH), 5.64 (1H, dt, $J = 16.8$, 10.2 Hz, CH$_2$=C*H*CH); IR (neat): ν (cm^{-1}) 2966, 1651, 1448, 1364, 1272, 1200, 1140, 1003; Anal Calcd for $C_{13}H_{21}F_4NO$: C, 55.11; H, 7.47; N, 4.94. Found: C, 55.37; H, 7.59; N, 4.99.

4.5.2. *2-Hexenyl 2,3,3,3-tetrafluoropropionate (**7a**)*

Colorless oil (hygroscopic); bp 64 °C/14 mmHg; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.92 (t, 3H, $J = 7.3$ Hz, C*H*$_3$CH$_2$), 1.42 (sextet, 2H, $J = 7.3$ Hz, CH$_3$C*H*$_2$CH$_2$), 2.12 (qd, 2H, $J = 7.4$, 1.2 Hz, CH$_2$C*H*$_2$CH=CH), 4.86 (d, 2H, $J = 6.9$ Hz, CH=CHC*H*$_2$O), 5.10 (dq, 1H, $J = 46.2$, 6.5 Hz, CF$_3$C*H*FCO), 5.57 (dtt, 1H, $J = 10.9$, 7.1, 1.5 Hz, CH$_2$CH=C*H*CH$_2$O), 5.75 (dtt, 1H, $J = 10.9$, 7.6, 1.1 Hz, CH$_2$C*H*=CHCH$_2$O); IR (neat): ν (cm^{-1}) 2964, 1774, 1648, 1362, 1276, 1216, 1200, 1148; Anal Calcd for $C_9H_{12}F_4O_2 + 0.75H_2O$: C, 44.73; H, 5.63. Found: C, 44.82; H, 5.36; LRMS (EI): *m/z* (rel. int.) 228 (M^+, 3%), 187 (5%), 129 (35%), 101 (41%), 82 (100%), 67 (79%), 41 (55%).

4.5.3. *anti-N,N-Diethyl-3-ethyl-2-fluoro-2-trifluoromethyl-4-pentenamide (**6b**)*

Colorless oil; bp 180 °C/2 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.88 (3H, t, $J = 7.4$ Hz, C*H*$_3$CH$_2$), 1.11 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$C*H*$_3$)), 1.19 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$C*H*$_3$)), 1.44 (dqd, 1H, $J = 11.5$, 7.3, 3.0 Hz, CH$_3$C*H*(H)CH), 1.67–1.85 (m, 1H, CH$_3$CH(*H*)CHCF), 2.92 (dddd, 1H, $J = 28.8$, 12.0, 8.9, 3.2 Hz, CH$_2$=CHC*H*(CH$_2$)CF), 3.21 (sextet, 1H, $J = 7.0$ Hz, FCCON(C*H*(H)CH$_3$)), 3.31–3.55 (m, 3H, FCCON-(C*H*(H)CH$_3$)(C*H*$_2$CH$_3$)), 5.18 (dd, 1H, $J = 17.0$, 1.9 Hz, C*H*(H)=CHCH), 5.22 (dd, 1H, $J = 10.2$, 1.8 Hz, CH(*H*)= CHCH), 5.64 (dt, 1H, $J = 17.0$, 10.0 Hz, CH$_2$=C*H*CH); IR (neat): ν (cm^{-1}) 1651, 1448, 1364, 1273, 1200, 1168, 1141, 1111; Anal Calcd for $C_{12}H_{19}F_4NO$: C, 53.52; H, 7.11; N, 5.20. Found: C, 53.62; H, 7.19; N, 5.12.

4.5.4. *anti-N,N-Diethyl-2-fluoro-3-nonyl-2-trifluoromethyl-4-pentenamide (**6c**)*

Colorless oil; bp 149 °C/2 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.88 (t, 3H, $J = 6.6$ Hz, C*H*$_3$CH$_2$), 1.11 (t, 3H, $J = 6.9$ Hz, CON(CH$_2$C*H*$_3$)), 1.19 (t, 3H, $J = 6.9$ Hz, CON(CH$_2$C*H*$_3$)), 1.05–1.38 (br s, 14H, CH$_3$(C*H*$_2$)$_7$CH$_2$), 1.45 (q like, 1H, $J = 10.9$ Hz, CH$_2$C*H*(H)-CHCF), 1.55–1.72 (br s, 1H, CH$_2$CH(*H*)CHCF), 3.01 (dtd, 1H, $J = 29.0$, 10.5, 2.9 Hz, CH$_2$=CHC*H*(CH$_2$)CF), 3.20 (sextet, 1H, $J = 7.0$ Hz, FCCON(C*H*(H)CH$_3$)(CH$_2$CH$_3$)), 3.28–3.56 (m, 3H, FCCON(C*H*(H)CH$_3$)(C*H*$_2$CH$_3$)), 5.17 (dm, 1H, $J = 16.9$ Hz, C*H*(H)=CHCH), 5.19 (dm, 1H, $J = 10.3$ Hz, CH(*H*)=CHCH)), 5.64 (dt, 1H, $J = 16.8$, 10.1 Hz, CH$_2$=C*H*CH); IR (neat): ν (cm^{-1}) 2927, 1651, 1463, 1447, 1435, 1273, 1200, 1186; Anal Calcd for $C_{19}H_{33}F_4NO$: C, 62.10; H, 9.05; N, 3.81. Found: C, 61.82; H, 8.85; N, 3.68.

4.5.5. *anti-N,N-Diethyl-2-fluoro-3-(3-phenylpropyl)-2-trifluoromethyl-3-pentenamide (**6d**)*

Colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.10 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$C*H*$_3$)), 1.17 (t, 3H, $J = 7.0$ Hz, CON(CH$_2$C*H*$_3$)), 1.42–1.58 (m, 2H, PhC*H*$_2$CH$_2$CH$_2$), 1.65–1.77 (m, 2H, PhCH$_2$C*H*$_2$CH$_2$), 2.49–2.60 (m, 1H, CH$_2$-C*H*(H)CHCF), 2.62–2.71 (m, 1H, CH$_2$CH(*H*)CHCF), 3.06 (dtd, 1H, $J = 28.9$, 10.2, 2.3 Hz, CH$_2$=CHC*H*(CH$_2$)CF), 3.20 (sextet, 1H, $J = 6.9$ Hz, FCCON(C*H*(H)CH$_3$)), 3.29–3.53 (m, 3H, FCCON(CH(*H*)CH$_3$)(C*H*$_2$CH$_3$)), 5.16 (dm, 1H, $J = 10.9$ Hz, C*H*(H)=CHCH), 5.18 (dm, 1H, $J = 17.0$ Hz, CH(*H*)=CHCH), 5.65 (dt, 1H, $J = 16.7$, 10.1 Hz, CH$_2$= C*H*CH), 7.14–7.30 (m, 5H, Ph-*H*); IR (neat): ν (cm^{-1}) 2937, 1651, 1453, 1363, 1273, 1200, 1129, 700; Anal Calcd for $C_{19}H_{25}F_4NO$: C, 63.50; H, 7.01; N, 3.90. Found: C, 63.60; H 7.08; N, 3.81.

4.6. *The preparation of anti-2-fluoro-3-propyl-5-tosyl-2-trifluoromethyl-4-pentenamide (**8a**)*

To a solution of **6a** (942 mg, 3.0 mmol) in ethyl acetate (10 ml) and water (10 ml), was added sodium *p*-tolylsulfinate tetrahydrate (3.42 g, 14 mmol) and iodine (1.30 g, 5.1 mmol). This reaction mixture was agitated at room temperature. When 26 h was passed, iodine (377 mg, 1.5 mmol) was added furthermore. The agitation was continued for 46 h furthermore. After the agitation, sodium sulfite (1 g, 8 mmol) and water (30 ml) was added to quench the reaction and this mixture was stirred until the color of iodine was disappeared. The resulting mixture was extracted with chloroform (5 × 10 ml). The obtained organic layer was washed with brine (2 × 20 ml), saturated sodium thiosulfate aqueous solution (1 × 20 ml), and brine (1 × 20 ml) again. The organic layer was dried with $MgSO_4$, and evaporated. As the result, 1.72 g of yellow oil was obtained.

The residual oil was dried in vacuo with phosphorous pentoxide. This oil was dissolved with acetonitrile (10 ml)–chloroform (10 ml). To this solution, was dropwise added triethylamine (0.96 ml, 6.9 mmol) over 10 min. After the resulting mixture was stirred for 10 min, the reaction was quenched with 1N hydrochloric acid (20 ml). The resulting mixture was extracted with chloroform (3 × 10 ml).

The combined organic layers were washed with 1N hydrochloric acid (1 × 10 ml) and brine (2 × 10 ml), dried over $MgSO_4$ and evaporated in vacuo to give a yellow oil (1.45 g). This oil was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (1:3) and chloroform] to afford **8a** (411 mg: 32% yield). **8a** was recrystallized from *n*-hexane–chloroform to give colorless crystals with good quality suitable to X-ray crystallographic analysis.

4.6.1. *anti-N,N-Diethyl-2-fluoro-3-propyl-2-trifluoromethyl-4-tosyl-3-pentenamide (**8a**)*

Colorless crystals; mp 124.9–125.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.88 (t, 3H, $J = 7.3$ Hz, CH_3CH$_2$), 1.06 (t, 3H, $J = 7.1$ Hz, CON(CH$_2$CH_3)), 1.18 (t, 3H, $J = 7.0$ Hz, CON(CH$_3$CH_3)), 1.02–1.40 (m, 2H, CH$_3$CH_2CH$_2$), 1.50–1.76 (m, 2H, CH$_2$CH_2CHCF), 2.44 (s, 3H, Tol-CH_3), 3.07–3.37 (m, 4H, FCCON(CH(H)CH$_3$)-(CH_2CH$_3$) and CH=CHCH(CH$_2$)CF), 3.49 (dqd, 1H, $J = 14.4$, 7.3, 4.8 Hz, FCCON(CH(*H*)CH$_3$)(CH$_2$CH$_3$)), 6.44 (d, 1H, $J = 15.1$ Hz, SO$_2$C*H*=CHCH), 6.79 (dd, 1H, $J = 15.2$, 10.2 Hz, SO$_2$CH=C*H*CH), 7.33 (d, 2H, $J = 8.0$ Hz, Tol-*H*), 7.73 (d, 2H, $J = 8.4$ Hz, Tol-*H*); IR (KBr): ν (cm^{-1}) 2971, 1644, 1319, 1273, 1197, 1182, 1170, 1148; Anal Calcd for $C_{19}H_{25}F_4NO$ C, 54.91; H, 6.22; N, 3.20. Found: C, 55.04; H, 6.09; N, 3.16.

4.7. *Typical procedure of the iodolactonization of **2***

To a solution of **2a** (3.68 g, 13.0 mmol) in 39 ml of THF and 39 ml of water, was added iodine (9.90 g, 39.0 mmol) at 0 °C. After the reaction mixture was stirred for 6 h, the reaction was quenched with 6.54 g of sodium sulfite. This reaction mixture was extracted with ether (4 × 10 ml). The combined organic layers were washed with saturated sodium thiosulfate aqueous solution (5 × 10 ml), brine (1 × 20 ml), 1N hydrochloric acid (2 × 10 ml) and brine (1 × 20 ml). The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residual oil was chromatographed on silica gel [eluent: *n*-hexane–ethyl acetate (12:1)] to give **11a** (4.44 g) as a mixture of two diastereomers in 95% yield. The diastereomeric ratio was determined by ^{1}H NMR to be 90:10.

4.7.1. *2-Fluoro-5-iodo-2-trifluoromethyl-4-octanolide (**11a**) (two diastereomeric mixture)*

Colorless oil; bp 136 °C/4 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer]: δ 0.98 (ppm) (t, 3H, $J = 7.1$ Hz, CH_3CH$_2$), 1.33–1.52 (m, 1H, CH$_3$CH(H)CH$_2$-CH), 1.59–1.97 (m, 3H, CH$_3$CH(*H*)CH_2CH), 2.57 (dddq like, 1H, $J = 25.7$, 15.1, 8.2, 0.9 Hz, CHCH(H)CFCF$_3$), 3.18 (ddd, 1H, $J = 14.9$, 8.1, 6.6 Hz, CHCH(*H*)CF), 4.12 (td, 1H, $J = 9.1$, 3.7 Hz, CH$_2$CH(I)CH), 4.45 (qd like, 1H, $J = 8.5$, 2.0 Hz, CHCH(O)CH$_2$); [minor isomer]: δ (ppm) 2.42 (dd like, 1H, $J = 15.5$, 8.9 Hz, CHCH(H)CF), 2.90–3.09 (m, CHCH(*H*)CFCF$_3$), 4.62 (td, $J = 8.7$, 5.7 Hz, CH$_2$CHCH), The other signals are overlapped with the signals of the major isomer; IR (neat): ν (cm^{-1}) 2963, 1806, 1335, 1210, 1145 1133, 1086, 1034; Anal Calcd for $C_9H_{11}F_4IO_2$: C, 30.53; H, 3.13. Found: C, 30.52; H, 3.19.

4.7.2. *2-Fluoro-5-iodo-2-trifluoromethyl-4-pentanolide (**11b**) (two diastereomeric mixture)*

The diastereomeric ratio of **11b** was determined by ^{1}H NMR to be 90:10.

Colorless oil; bp 88 °C/5 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer]: δ (ppm) 2.54 (dddq like, 1H, $J = 25.3$, 15.2, 7.5 Hz, CHCH(H)CFCF$_3$), 3.11 (ddd, 1H, $J = 15.3$, 10.8, 6.6 Hz, CHCH(*H*)CF), 3.35 (dd, 1H, $J = 15.3$, 10.8, 6.6 Hz, ICH(H)CH), 3.51 (dd, 1H, $J = 10.6$, 4.3 Hz, ICH(*H*)CH), 4.62 (m, 1H, CH$_2$CH(O)CH$_2$); [minor isomer]: δ (ppm) 2.69 (td, $J = 14.3$, 6.9 Hz, CHCH(H)CF), 4.77 (m, CH$_2$CH(O)CH$_2$). The other signals are overlapped with signals of the major isomer; IR (neat): ν (cm^{-1}) 2960, 1807, 1335, 1211, 1144, 1133, 1091, 1037; Anal Calcd for $C_6H_{15}F_4IO_2$: C, 23.10; H, 1.62. Found: C, 23.07; H: 1.61.

4.7.3. *2-Fluoro-5-iodo-2-trifluoromethyl-4-hexanolide (**11c**) (two diastereomeric mixture)*

The diastereomeric ratio of **11c** was shown by ^{1}H NMR to be 90:10.

Colorless oil; bp 106 °C/6 mmHg (a short-path distillation); ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer]: δ (ppm) 2.03 (d, 3H, $J = 6.9$ Hz, CH_3CHI), 2.54 (dddq like, 1H, $J = 25.6$, 15.1, 7.9, 1.3 Hz, CHCH(H)CFCF$_3$), 3.16 (ddd, 1H, $J = 15.1$, 8.6, 6.6 Hz, CHCH(*H*)CF), 4.16 (quintet like, 1H, $J = 6.8$ Hz, CH$_3$CH(I)CH), 4.37 (qd like, 1H, $J = 8.2$, 2.1 Hz, CHCH(O)CH$_2$); [minor isomer]: δ (ppm) 2.04 (d, $J = 6.9$ Hz, CH_3CHI), 2.36–2.44 (m, CHCH(H)CFCF$_3$), 2.88–3.04 (m, CHCH(*H*)CFCF$_3$), 4.53 (td, $J = 8.4$, 5.6 Hz, CHCH(O)CH$_2$); IR (neat): ν (cm^{-1}) 1802, 1336, 1208, 1139, 1091, 1068, 1037, 1014; Anal Calcd for $C_7H_7F_4IO_2$: C, 25.79; H, 2.16. Found: C, 26.08; H, 2.18; HRMS Calcd for $C_7H_7F_4IO_2$: 325.9429. Found: 325.9402.

4.7.4. *2-Fluoro-5-iodo-6-methyl-2-trifluoromethyl-4-heptanolide (**11d**) (two diastereomeric mixture)*

The diastereomeric ratio of **11d** was 90:10 which was determined by the ^{1}H NMR.

Colorless crystals; mp 57 °C (sublimed at 55 °C); ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer]: δ (ppm) 0.94 (d, 3H, $J = 6.6$ Hz, (CH_3)(CH$_3$)CH), 1.01 (d, 3H, $J = 6.6$ Hz, (CH$_3$)(CH_3)CH), 1.53 (d septet, 1H, $J = 6.5$, 2.9 Hz, (CH$_3$)$_2$CHCH), 2.55 (dddq like, 1H, $J = 25.7$, 15.3, 7.9, 1.3 Hz, CHCH(H)CFCF$_3$), 3.25 (ddd, 1H, $J = 15.4$, 9.3, 6.3 Hz, CHCH(*H*)CF), 4.11 (dd, 1H, $J = 10.3$, 2.9 Hz, CHCH(I)CH), 4.68 (dddd, 1H, $J = 2.1$ Hz, CHCH(O)CH$_2$); [minor isomer]: δ (ppm) 0.82 (d, 3H, $J = 6.63$ Hz, (CH_3)(CH$_3$)CH), 0.89 (d, 3H, $J = 6.5$ Hz, (CH$_3$)(CH_3)CH), 1.53 (d septet, 1H, $J = 6.5$, 2.9 Hz, (CH$_3$)$_2$CHCH), 2.43 (ddd, 1H, $J = 35.0$, 15.5, 8.8 Hz, CHCH(H)CF), 3.08 (ddd, 1H, $J = 22.5$, 15.6, 6.1 Hz, CHCH(*H*)CF), 4.05 (dd, 1H, $J = 10.3$, 2.9 Hz, CHCH(I)CH), 4.86 (ddd, 1H, $J = 10.3$,

9.0, 5.7 Hz, CHC*H*(O)CH_2), The other signals are overlapped with those of the major isomer; IR (neat): ν (cm^{-1}) 2965, 1788, 1467, 1341, 1200, 1137, 1033, 1001; Anal Calcd for $C_9H_{11}F_4IO_2$: C, 30.53; H, 3.13. Found: C, 30.50; H,2.99.

4.7.5. 2-Fluoro-5-iodo-2-trifluoromethyl-4-nonanolide (*11e*) (a mixture of two diastereomers)

The diastereomeric ratio of **11e** was 90:10 (by ^{1}H NMR).

Colorless oil; bp 110 °C/4 mmHg (Kugelrohr); ^{1}H NMR (300 MHz, $CDCl_3$) [major isomer]: δ (ppm) 0.94 (t, 3H, $J = 7.1$ Hz, CH_3CH$_2$), 1.11–1.50 (m, 3H, CH_3CH_2CH(H)-CH_2), 1.50–1.69 (m, 1H, CH_3CH_2CH(*H*)CH_2), 1.72–1.98 (m, 1H, CH_2CH(H)CH), 1.98–2.06 (m, 1H, CH_2CH(*H*)CH), 2.56 (dddq, 1H, $J = 25.7$, 15.1, 8.2, 1.4 Hz, CHC*H*(H)-$CFCF_3$), 3.17 (ddd, 1H, $J = 15.0$, 8.0 6.6 Hz, CHCH(*H*)CF), 4.11 (td, 1H, $J = 9.1$, 3.4 Hz, CHC*H*(I)CH), 4.45 (qd like, 1H, $J = 8.4$, 2.0 Hz, CHC*H*(O)CH_2); [minor isomer]: δ (ppm) 2.38–2.46 (m, CHC*H*(H)$CFCF_3$), 2.98 (ddd, $J = 29.0$, 15.9, 5.5 Hz, CHCH(*H*)CF), 4.62 (td, $J = 8.8$, 5.7 Hz, CH_2CH(I)CH). The other signals are overlapped with the signals of the major isomer; IR (neat): ν (cm^{-1}) 2960, 2873, 1807, 1466, 1335, 1212, 1144, 1038; Anal Calcd for $C_{10}H_{13}F_4IO_2$: C, 32.63; H, 3.56. Found: C, 32.59; H, 3.64.

4.8. The preparation of 2-fluoro-5-tosyl-2-trifluoromethyl-4-pentanolide (*12b*) from *11b*

To a solution of *p*-toluenethiol (187 mg, 1.5 mmol) in dimethyl sulfoxide (2 ml), was added sodium hydride (37 mg; dispersed in an oil; 50 wt.% content) at room temperature. This solution was stirred at the same temperature until gas evolution ceased. Then to the solution, was added dropwise a solution of **11b** (157 mg, 0.50 mmol) in dimethyl sulfoxide (2 ml) over 7 min. After 18 h stirring at room temperature, the reaction was quenched by the addition of diisopropyl ether (8 ml) and water (5 ml). The organic layer was separated, washed with saturated aqueous solution of $NaHCO_3$ (2×6 ml), dried over $MgSO_4$ and evaporated in vacuo to give a yellow oil (184 mg). The combined washings were again extracted with diisopropyl ether (4×6 ml). The resulting organic layer was washed with saturated aqueous solution of $NaHCO_3$ (2×10 ml), dried over $MgSO_4$ and evaporated in vacuo to give a yellow oil (21.7 mg). These residual crude mixtures were shown by ^{1}H NMR to mainly contain 2-fluoro-5-(*p*-tolylthio)-2-trifluoromethyl-4-pentanolide and *p*-toluenethiol. These crude mixtures were combined and then purified on silica gel chromatography two times [eluent: *n*-hexane–ethyl acetate; first (6:1), second (8:1)] to give 32.6 mg of 2-fluoro-5-(*p*-tolylthio)-2-trifluoromethyl-4-pentanolide (21% yield). To a solution of 2-fluoro-5-(*p*-tolylthio)-2-trifluoromethyl-4-pentanolide (21.7 mg, 0.070 mmol) in chloroform (1 ml) was added a solution of *m*-chloroperbenzoic acid (52.5 mg; 69–75 activity) in chloroform (2 ml) dropwise at 0 °C. The solution was stirred at room temperature for 7 h. The resulting solution was added a saturated aqueous solution of sodium thiosulfate (1 ml) and stirred over night. The resulting organic layer was separated and evaporated in vacuo. The residual oil was chromatographed on silica gel to give 17.5 mg of colorless solid containing **12b** (15.2 mg: 64% yield, by ^{1}H NMR). Further purification was performed on preparative HPLC [eluent: *n*-hexane–ethyl acetate (1:2)] to give **12b** (7.3 mg). **12b** was recrystallized from *n*-hexane–chloroform for single crystalline X-ray crystallography to determine the stereochemical relationship of the iodolactonization reaction.

4.8.1. 2-Fluoro-5-(p-tolylthio)-2-trifluoromethyl-4-pentanolide

Yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.35 (s, 3H, Tol-CH_3), 2.56 (dddq, 1H, $J = 25.6$, 15.1, 7.3, 1.2 Hz, CHCH(*H*)$CFCF_3$), 2.98 (ddd, 1H, $J = 15.1$, 12.2, 6.7 Hz, CHCH(*H*)CF), 3.05 (dd, 1H, $J = 14.1$, 8.2 Hz, SC*H*(H)CH), 3.37 (ddd, 1H, $J = 14.1$, 4.7, 0.6 Hz, SCH(*H*)CH), 4.61 (m, 1H, CH_2CH(O)CH_2), 7.15 (d, 2H, $J = 8.0$ Hz, Tol-*H*), 7.34 (dd, 2H, $J = 4.4$, 1.9 Hz, Tol-*H*); IR (KBr, neat): ν (cm^{-1}) 1800, 1334, 1209, 1179, 1092, 1179, 1092, 1015.

4.8.2. 2-Fluoro-5-tosyl-2-trifluoromethyl-4-pentanolid (*12b*)

Colorless crystals; mp 137.8–138.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.49 (s, 3H, Tol-CH_3), 2.76 (dddq like, 1H, $J = 24.7$, 15.5, 7.1, 1.0 Hz, CHC*H*(H)-$CFCF_3$), 3.20 (ddd, 1H, $J = 15.4$, 13.7, 6.9 Hz, CHCH(*H*)-CF), 3.42 (dd, 1H, $J = 14.1$, 7.8 Hz, SO_2CH(H)CH), 3.68 (dd, 1H, $J = 14.1$, 5.2 Hz, SO_2CH(*H*)CH), 5.03 (quintet like, 1H, $J = 7.3$ Hz, CH_2CH(O)CH_2), 7.82 (d, 2H, $J = 8.5$ Hz, Tol-*H*), 7.42 (d, 2H, $J = 8.3$ Hz, Tol-*H*); IR (KBr): ν (cm^{-1}) 1811, 1341, 1311, 1212, 1191, 1150, 1087, 1021; Anal Calcd for $C_{13}H_{12}F_4O_4S$: C, 45.89; H, 3.55. Found: C, 45.75; H, 3.57.

4.9. X-ray crystallography of compounds *2h* (minor), *8a*, and *12b*

Data collection was performed on a Mac Science MXC18 four-circle diffractometer with graphite monochromated Cu Kα radiation ($\lambda = 1.54178$ Å) using the θ–2θ scan technique. The structures were solved by direct methods and refined by full-matrix least-squares methods against *F* (SIR 92 [23] on a computer program package; maXus version 1.1 from MAC Science Co. Ltd.). All non-hydrogen atoms were refined with anisotropic displacement parameters and hydrogen atoms refined isotropically. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication nos. CCDC208379 for **2h** (minor), CCDC200797 for **8a**, and CCDC208380 for **12b**. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

*4.9.1. Crystal structural data of **2h** (minor)*

$C_{16}H_{19}F_4NO$; triclinic; space group P-1; unit-cell dimensions: $a = 8.397(3)$ Å, $b = 9.420(2)$ Å, $c = 11.280(4)$ Å, $\alpha = 95.80(2)^\circ$, $\beta = 97.32(3)^\circ$, $\gamma = 111.05(2)^\circ$, $V = 815.4(4)$ Å^3, $Z = 2$, $D_{calc} = 1.292$ g cm^{-3}. Intensity data were measured at 173 K. $\lambda = 1.5418$ Å) radiation. A total of 3425 reflections were measured, and 3099 were unique ($R_{int} = 0.014$). The final R and wR values were 0.066 and 0.070, respectively, based on 2482 observed reflections ($I > 3\sigma(I)$).

*4.9.2. Crystal structural data of **8a***

$C_{20}H_{27}F_4NO_3S$; triclinic; space group P-1; unit-cell dimensions: $a = 9.423(2)$ Å, $b = 10.360(2)$ Å, $c = 11.560(2)$ Å, $\alpha = 96.16(2)^\circ$, $\beta = 90.21(2)^\circ$ $\gamma = 97.50(2)^\circ$, $V = 1112.3(4)$ Å^3, $Z = 2$, $D_{calc} = 1.306$ g cm^{-3}. Intensity data were measured at 298 K. A total of 4467 reflections were measured, and 4217 reflections were unique ($R_{int} = 0.017$). The final R and wR values were 0.049 and 0.138, respectively, based on 3403 observed reflections ($I > 1.50\sigma(I)$).

*4.9.3. Crystal structural data of **12b***

$C_{13}H_{12}F_4O_4S$; monoclinic; space group $P2_1/a$; unit-cell dimensions: $a = 9.823(3)$ Å, $b = 27.343(7)$ Å, $c = 5.755(2)$ Å, $\alpha = 90.00(0)^\circ$, $\beta = 103.8(2)^\circ$, $\gamma = 90.00(0)^\circ$, $V = 1501.1(7)$ Å^3, $Z = 4$, $D_{calc} = 1.505$ g cm^{-3}. Intensity data were measured at 173 K. A total of 3170 reflections were measured, and 2958 reflections were unique ($R_{int} = 0.079$). The final R and wR values were 0.076 and 0.091, respectively, based on 1663 observed reflections ($I > 3\sigma(I)$).

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