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Stereoselective synthesis of 3-fluorotetrahydrofuran-3-carboxylate derivatives via the intramolecular cyclization reaction of erythro- and threo-α-allylated α-fluoro-β-hydroxy esters

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Abstract

When isomerically pure *erythro-* and *threo*-α-allylated-α-fluoro-β-hydroxy carboxylic acid esters were subjected to the intramolecular cyclization reaction with iodine and pyridine at −15 °C to ambient temperature for 6–9 h, the corresponding 3-fluorotetrahydrofuran-3-carboxylate derivatives were obtained in good yields as isomeric mixtures of the ratio of **3A**:**3B** = 10–20:90–80 or **4C**:**4D** = 28–39:72–61, respectively.

Keywords: 3-Fluorotetrahydrofuran-3-carboxylate; α-Allyl-α-fluoro-β-hydroxy ester; Intramolecular cyclization; Iodoetherification; Diastereoselectivity

1. Introduction

Polysubstituted terahydrofurans (THFs) are the fundamental subunits commonly encountered in natural products, such as polyether antibiotics [1], acetogenis [2] and C-glycosides [3]. Much attention is being denoted to the preparation of such compounds as one of the most challenging subjects in organic synthesis, since they can frequently exhibit high potency in biological activities. A number of synthetic approaches to polysubstituted tetrahydrofurans and related skeletons have hitherto been developed [4–11]. However, there are found few or no reports dealing with the synthesis of regio- and stereoselectively fluorinated tetrahydrofuran derivatives in the literature.

In close connection with our recent success in developing an efficient method for the diastereoselective synthesis of α-allylated α-fluoro-β-hydroxy esters [12], we intended to apply these isomerically pure compounds to prepare fluorine-containing heterocycles of biological interest.

This paper describes the intramolecular cyclization reaction of *erythro-* and *threo*-α-allylated α-fluoro-β-hydroxy carboxylates **1** and **2** by using iodine and amine, providing a convenient and stereoselective approach to various 3-fluorotetrahydrofuran-3-carboxylate derivatives **3** and **4**, which are difficult to access by other methods.

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2. Results and discussion

2.1. Intramolecular iodoetherification of erythro-isomers *1* and *2*

The starting esters erythro-**1** and **2** were readily prepared by the radical allylation reaction of α-bromo-α-fluoro-β-hydroxy carboxylates [13] with allylic stannanes in the presence of catalytic triethylborane in THF or isopropyl alcohol [12].

First, the reaction of *erythro*-α-methallyl-α-fluoro-β-hydroxy carboxylic acid ester (erythro-**1a**, R = Ph) was carried out under various reaction conditions, as shown in Scheme 1. Table 1 summarizes the results of these reactions. Thus, when *erythro*-**1a** was allowed to react with iodine (3.0 eq.) and pyridine (3.0 eq.) in THF, dichloromethane (CH_2Cl_2), or acetonitrile (MeCN) at room temperature for 3 h, the corresponding cyclization product **3a** was obtained as an isomeric mixture (**A**:**B** = 83–85:17–15) in 64–80% yields (Entries 1–3). The similar reactions in benzene or toluene took place with somewhat higher stereoselectivity (**A**:**B** = 88:12) (Entries 4, 5). Furthermore, even on treatment of *erythro*-**1a** with iodine and pyridine in toluene at −15 °C for 7 h, the reaction was completed to give the products **3aA** and **3aB** in a ratio of 90:10 (Entry 7).

The β-hydroxy esters *erythro*-**1** carrying various substituents R were subjected to the iodoetherification reaction under the conditions described in Entry 7 of Table 1. These results are tabulated in Table 2. The reaction of *erythro*-**1b**

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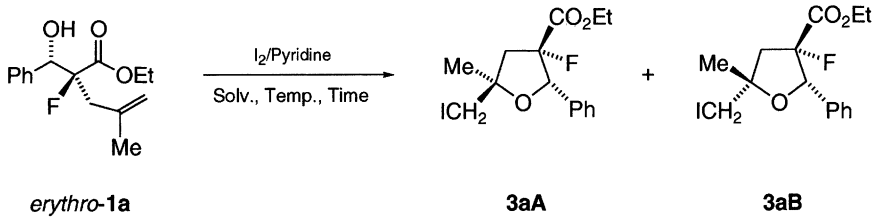


erythro-**1a** **3aA** **3aB**

Scheme 1.

Table 1
Intramolecular iodoetherification of *erythro*-**1a** with iodine and pyridine

Entry	Solvent	Temperature (°C)	Time (h)	Yield[a] (percentage of **3a**) (**A**:**B**)[b]
1	THF	Room temperature	3	64 (83:17)
2	CH_2Cl_2	Room temperature	3	80 (83:17)
3	MeCN	Room temperature	3	79 (85:15)
4	Benzene	Room temperature	3	77 (88:12)
5	Toluene	Room temperature	3	66 (88:12)
6	MeCN	−15	7	73 (87:13)
7	Toluene	−15	7	91 (90:10)

[a] Isolated yields.
[b] Determined by ^{19}F NMR before isolation.

and **1c** having aryl substituents R at −15 °C for 7 h proceeded smoothly to lead to the corresponding 3-fluorotetrahydrofuran-3-carboxylates **3b** and **3c** in good yields and in a stereoselective manner (Entries 2, 3), while the reaction of *erythro*-**1d** and **1f** carrying alkyl substituents R required a longer reaction time (9 h) for consumption of the starting ester (Entries 4, 5). It is worthy to note that the stereoselectivity, the ratio of **A**:**B**, for the reactions of *erythro*-**1** is fairly good and is scarcely affected by the kinds of the substituents R.

Next, the cyclization reaction of *erythro*-α-allylated esters **2** was conducted in a similar way (Scheme 2). As shown in Table 2, when erythro-**2a** was allowed to react with iodine and pyridine in toluene or MeCN at −15 °C for 7 h, the corresponding tetrahydrofuran-3-carboxylate **4a** was obtained in very low yield, the starting *erythro*-**2a** being recovered unchanged (Entries 6, 8). These results indicate that erythro-**2a** is less reactive than *erythro*-**1a**. This may be ascribed primarily to the difference in reactivity between the allyl and methallyl olefinic group. Raising the reaction temperature to room temperature allowed the reaction to proceed efficiently to afford the product **4a** in good yield, though the stereoselectivity was decreased to some extent, compared with that for the reaction of *erythro*-**1a** (Entries 7, 9). The reactions of other *erythro*-**2** having various substituents R with iodine and pyridine at ambient temperature for 6 h occurred smoothly to give the corresponding 3-fluorotetrahydrofuran-3-carboxylates **4** in good to excellent yields, whose isomer ratios **A**:**B** are around 80:20.

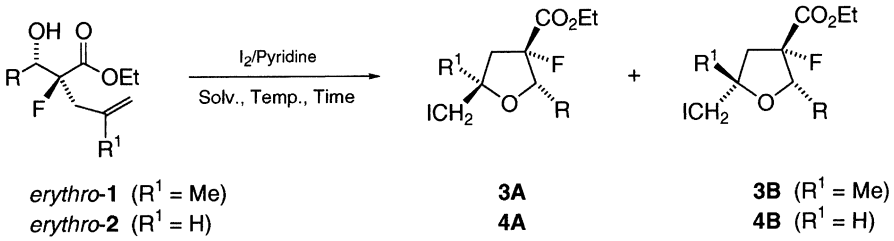
2.2. Intramolecular iodoetherification of threo-isomers *1* and *2*

The iodoetherification reaction was next examined employing another diastereoisomers of α-allylated α-fluoro-β-hydroxy esters, *threo*-**1** and **2** (Scheme 3), which were available from the reaction of α-bromo-α-fluoro-β-hydroxy

Table 2
Intramolecular iodoetherification of *erythro*-**1** and *erythro*-**2** by using iodine and pyridine

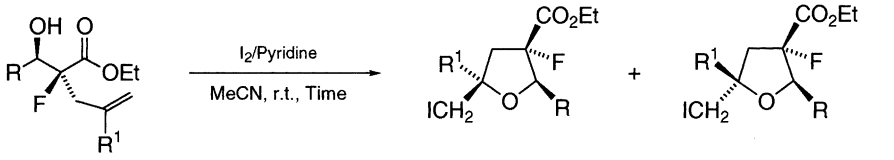
Entry	R		Solvent	Temperature (°C)	Time (h)	Yield[a] (percentage of **3** or **4**) (**A**:**B**)[b]
1	Ph	**1a**	Toluene	−15	7	91 (90:10)
2	*p*-MeC_6H_4	**1b**	Toluene	−15	7	58 (84:16)
3	*p*-$MeOC_6H_4$	**1c**	Toluene	−15	7	80 (86:14)
4	*n*-Pr	**1d**	Toluene	−15	9	82 (89:11)
5	*i*-Pr	**1f**	Toluene	−15	9	64 (89:11)
6	Ph	**2a**	Toluene	−15	7	9[c]
7	Ph	**2a**	Toluene	Room temperature	6	75 (82:18)
8	Ph	**2a**	MeCN	−15	7	13[d]
9	Ph	**2a**	MeCN	Room temperature	6	90 (80:20)
10	*p*-MeC_6H_4	**2b**	MeCN	Room temperature	6	82 (80:20)
11	*p*-$MeOC_6H_4$	**2c**	MeCN	Room temperature	6	68 (83:17)
12	*n*-Pr	**2d**	MeCN	Room temperature	6	88 (77:23)

[a] Yields are of pure products isolated by column chromatography.
[b] Determined by ^{19}F NMR prior to isolation.
[c] The starting ester *erythro*-**2a** was recovered in 80% yield.
[d] The starting ester *erythro*-**2a** was recovered in 68% yield.



erythro-**1** (R^1 = Me) **3A** **3B** (R^1 = Me)
erythro-**2** (R^1 = H) **4A** **4B** (R^1 = H)

Scheme 2.



threo-**1** (R^1 = Me) **3C** **3D** (R^1 = Me)
threo-**2** (R^1 = H) **4C** **4D** (R^1 = H)

Scheme 3.

esters with trimethylaluminum followed by the allylation with allylic stannanes and catalytic triethylborane [12]. As summarized in Table 3, on treating *threo*-**1a** with iodine and pyridine in toluene at −15 °C for 10 h, the reaction took place very reluctantly to result in only 14% yield of the corresponding cyclization product **3a**, and *threo*-**1a** was recovered in 81% yield (Entry 1). When the reaction temperature was raised to room temperature, the reaction proceeded efficiently and completed in 3 h to afford the product **3a** in good yield (Entry 2). Other *threo*-**1** carrying various substituents R were subjected to the reaction with iodine and pyridine in MeCN at room temperature for 3 h, the corresponding 3-fluorotetrahydrofuran-3-carboxylates **3** being given in good yields as diastereomeric mixtures of **C**:**D** = 61–72:39–28 (Entries 3–7). In addition, the esters *threo*-**2a**–**e** were also found to participate nicely in the cyclization reaction under similar conditions, the reaction time being 6 h, to provide the corresponding 3-fluorotetrahydrofuran derivatives **4** in good yields (Entries 8–12).

Table 3
Intramolecular iodoetherification of *threo*-**1** and *threo*-**2** by using iodine and pyridine

Entry	R		Time (h)	Yield[a] (percentage of **3** or **4**) (**C**:**D**)[b]
1	Ph	**1a**	10	14[c] (67:33)
2	Ph	**1a**	3	62 (66:34)
3	*p*-MeC_6H_4	**1b**	3	62 (65:35)
4	*p*-$MeOC_6H_4$	**1c**	3	71 (71:29)
5	*n*-Pr	**1d**	3	84 (71:29)
6	*n*-Hex	**1e**	3	78 (72:28)
7	*i*-Pr	**1f**	3	77 (61:39)
8	Ph	**2a**	6	65 (69:31)
9	*p*-MeC_6H_4	**2b**	6	71 (71:29)
10	*p*-MeOC6H4	**2c**	6	81 (70:30)
11	*n*-Pr	**2d**	6	82 (69:31)
12	*n*-Hex	**2e**	6	78 (69:31)

[a] Isolated yields.
[b] Determined by ^{19}F NMR.
[c] Performed at −15 °C in toluene. The ester *threo*-**1a** was recovered in 81% yield.

2.3. Mechanism for the iodoetherification reaction and the stereochemistry of 3 and 4

The NOE measurements in ^1H NMR made it possible to assign the relative stereochemistry of the products. Thus, the NOESY spectra were determined for the major isomers **3aA** and **3aC**, obtained from the reaction of *erythro*-**1a** and *threo*-**1a**, respectively. As shown in Fig. 1, these spectra of **3aA** and **3aC** exhibited cross peaks (circled in Fig. 1) between H_a and H_b or between H_c and H_d, respectively. Observation of the cross peaks strongly suggests that the hydrogen atom (H_a) at the C-2 position and the iodomethyl (H_b) group are *cis* in **3aA**, the hydrogen H_c and the methyl (H_d) group being *cis* in **3aC**.

The following possible mechanism is proposed for the stereoselective formation of 3-fluorotetrahydrofuran-3-carboxylate derivatives **3** and **4**, as depicted in Figs. 2 and 3. Thus, the electrophilic addition of iodine to the carbon–carbon double bond of an allylic group generates a bridged iodonium ion or carbocation species, which can undergo the intramolecular attack with a hydroxyl group in a 5-exo-trig [14] mode to produce the final product **3** or **4**. The stereoselectivity of this reaction may be explained as follows. Among the two possible envelope-type transition states **TS-I** and **TS-II** or **TS-III** and **TS-IV** for the reaction of the *erythro*- or *threo*-isomers of **1** and **2**, respectively, the former **TS-I** and **TS-III** may be more stable than the latter **TS-II** and **TS-IV** in which the bulky iodomethyl group occupies the axial position (Figs. 2 and 3). As a result, the cyclization will occur through **TS-I** or **TS-III**, leading preferentially to the major isomer **A** or **C**.

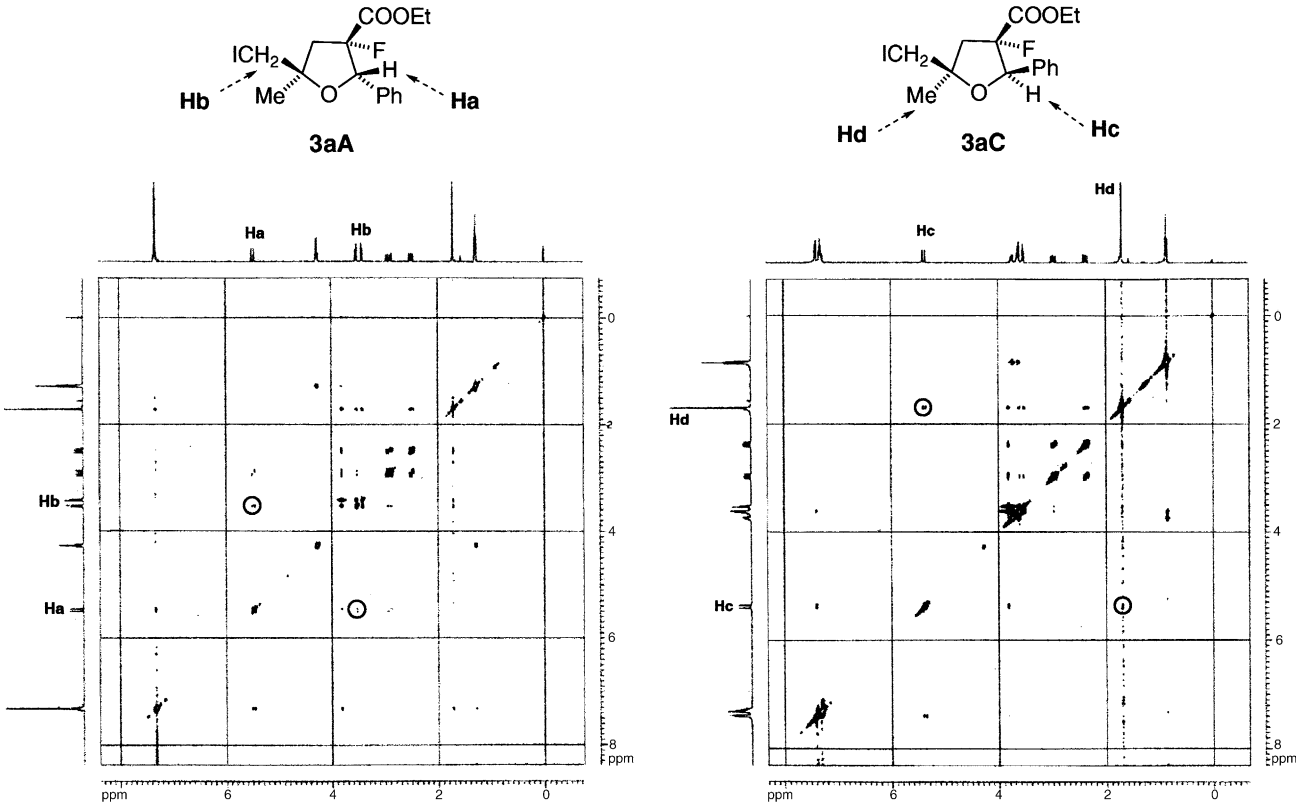


Fig. 1. NOESY spectra of the major isomers 3aA and 3aC obtained from the cyclization of *erythro*-**1a** and *threo*-**1a**.

In conclusion, we have developed a general and expedient route to the synthesis of stereochemically defined monofluorotetrahydrofuran derivatives, 3-fluorotetrahydrofuran-3-carboxylates **3** and **4**, based on the intramolecular iodoetherification of diastereomerically pure α-allylated α-fluoro-β-hydroxy esters **1** and **2** which can readily be prepared by our method [12].

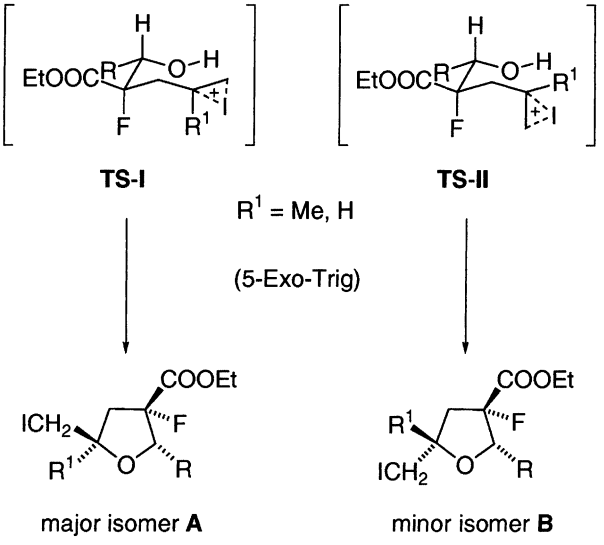


Fig. 2. Cyclization reaction of *erythro*-isomers of the β-hydroxy esters **1** and **2**.

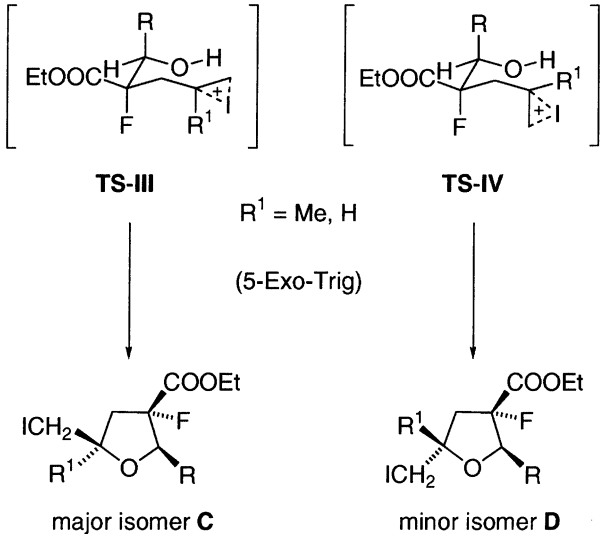


Fig. 3. Cyclization reaction of *threo*-isomers of the β-hydroxy esters **1** and **2**.

3. Experimental

3.1. Measurements and materials

Infrared spectra (IR) were recorded in a liquid film on a Shimadzu FTIR-8200A (PC) spectrophotometer. ^{1}H and ^{13}C NMR spectra were measured with a Bruker DRX 500

(500.13 MHz for ^{1}H and 125.75 MHz for ^{13}C) spectrometer in a chloroform-*d* ($CDCl_3$) solution with tetramethylsilane (Me_4Si) as an internal reference. NOESY spectra were determined with a Bruker DRX 500 (500.13 MHz) spectrometer. A JNM-EX90A (84.21 MHz) spectrometer was used to measure ^{19}F NMR spectra in $CDCl_3$ or a mixed solvent (MeCN/acetone = 1/1) using trichlorofluoromethane ($CFCl_3$) or trifluoroacetic acid (TFA) as an internal standard. Mass (MS) and high resolution mass spectra (HRMS) were taken on a JEOL JMS-700 mass spectrometer by an electron impact (EI) or chemical ionization (CI) method. The elemental analyses of products were conducted with a Yanaco CHN CORDER MT-5 instrument.

The starting *erythro*- and *threo*-α-allylated α-fluoro-β-hydroxy esters **1** and **2** were prepared highly stereoselectively by the reaction of α-bromo-α-fluoro-β-hydroxy esters with methallyl- or allyltributylstannane in the presence of a catalytic amount of triethylborane [12]. Tetrahydrofuran was freshly distilled from sodium benzophenone ketyl before use. Toluene and acetonitrile (MeCN) were distilled over calcium hydride and stored under argon. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. All reactions were carried out under an atmosphere of argon.

3.2. Typical procedure for the reaction of β-hydroxy ester erythro-**1** with iodine and pyridine

To a mixture of iodine (0.762 g, 3.0 mmol), toluene (2.0 ml) and pyridine (0.237 g, 3.0 mmol) was gradually added a solution of *eythro*-**1a** (0.266 g, 1.0 mmol) in toluene (2.0 ml) at −15 °C under an argon atmosphere. After stirring at −15 °C for 7 h, the mixture was quenched with a saturated aqueous NH_4Cl (25 ml). The resultant mixture was extracted with Et_2O (25 ml × 4) and the ethereal extracts were washed successively with 10% aqueous Na_2SO_3 (30 ml) and with a brine, followed by drying over anhydrous Na_2SO_4. Filtration and evaporation of solvents left a crude residue, which was purified by silica gel column chromatography (benzene) to afford pure product **3aA**,**B** (0.357 g, 0.911 mmol, 91% yield).

3.2.1. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-phenyltetrahydrofuran-3-carboxylate (***3aA***,***B***)

Yield 91%. IR (neat) (cm^{-1}): 2982 (w), 1759 (s), 1732 (s), 1454 (w), 1373 (m), 1335 (w), 1281 (vs), 1184 (s), 1150 (m), 1111 (s), 1088 (m), 1038 (vs). MS (CI) *m/z* (relative intensity): 393 (M + H, 100), 375 (10), 372 (22). HRMS (CI) calcd. for $C_{15}H_{19}FIO_3$ 393.0362 (M + H), found 393.0371. Anal. Calcd. for $C_{15}H_{18}FIO_3$: C, 45.94; H, 4.63. Found: C, 45.65; H, 4.12.

*3.2.1.1. Major isomer (**3aA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.29 (t, *J* = 7.2 Hz, 3H), 1.72 (s, 3H), 2.50 (dd, *J* = 21.0, 14.5 Hz, 1H), 2.91 (dd, *J* = 36.0, 14.5 Hz, 1H), 3.42 (d, *J* = 10.5 Hz, 1H), 3.54 (d, *J* = 10.5 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 2H), 5.48 (d, *J* = 24.5 Hz, 1H), 7.31–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.10, 16.51 (d, *J* = 1.7 Hz), 26.62, 48.17 (d, *J* = 22.0 Hz), 62.32, 81.84, 86.27 (d, *J* = 20.4 Hz), 101.32 (d, *J* = 204.1 Hz), 127.16, 128.14, 128.64, 133.58, 168.25 (d, *J* = 26.1 Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −93.7 (ddd, *J* = 36.0, 24.5, 21.0 Hz, 1F).

*3.2.1.2. Minor isomer (**3aB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.28 (t, *J* = 7.3 Hz, 3H), 1.67 (s, 3H), 2.65 (dd, *J* = 34.8, 14.5 Hz, 1H), 2.81 (dd, *J* = 25.5, 14.5 Hz, 1H), 3.51–3.56 (overlapped with the major isomer, 2H), 4.25–4.30 (overlapped with the major isomer, 2H), 5.40 (d, *J* = 24.0 Hz, 1H), 7.31–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.10, 15.50 (d, *J* = 1.8 Hz), 26.55, 47.75 (d, *J* = 21.9 Hz), 62.32, 81.48, 86.24 (d, *J* = 20.4 Hz), 100.67 (d, *J* = 204.4 Hz), 127.08, 128.14, 128.64, 133.60, 168.48 (d, *J* = 26.1 Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −90.1 to −91.8 (overlapped with the major isomer, 1F).

3.2.2. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-(4-methylphenyl)tetrahydrofuran-3-carboxylate (***3bA***,***B***)

Yield 58%. IR (neat) (cm^{-1}): 2982 (m), 2931 (m), 2874 (w), 1759 (vs), 1736 (vs), 1516 (m), 1435 (w), 1281 (vs), 1180 (s), 1150 (m), 1111 (s), 1038 (vs), 860 (w), 772 (m). MS (CI) *m/z* (relative intensity): 407 (M + H, 94), 389 (36), 386 (100), 361 (10). HRMS (CI) calcd. for $C_{16}H_{21}FIO_3$ (M + H) 407.0519, found 407.0516.

*3.2.2.1. Major isomer (**3bA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.29 (t, *J* = 7.2 Hz, 3H), 1.66 (s, 3H), 2.33 (s, 3H), 2.64 (dd, *J* = 34.8, 14.9 Hz, 1H), 2.80 (dd, *J* = 20.0, 14.9 Hz, 1H), 3.54 (d, *J* = 20.0 Hz, 1H), 3.52 (d, *J* = 20.0 Hz, 1H), 4.27 (q, *J* = 7.2 Hz, 2H), 5.37 (d, *J* = 25.0 Hz, 1H), 7.10–7.27 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.13, 15.56, 21.24, 26.58, 47.76 (d, *J* = 22.3 Hz), 62.35, 81.41, 86.26 (d, *J* = 20.8 Hz), 101.35 (d, *J* = 204.0 Hz), 125.87, 127.01, 128.93, 138.43, 168.59 (d, *J* = 24.5 Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −92.8 (ddd, *J* = 34.8, 25.0, 20.0 Hz, 1F).

*3.2.2.2. Minor isomer (**3bB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.29 (t, *J* = 7.3 Hz, 3H), 1.56 (s, 3H), 2.23 (s, 3H), 2.49 (dd, *J* = 21.0, 14.5 Hz, 1H), 2.90 (dd, *J* = 35.5, 14.5 Hz, 1H), 3.42 (d, *J* = 10.3 Hz, 1H), 3.61 (d, *J* = 10.3 Hz, 1H), 4.24–4.30 (overlapped with the major isomer, 2H), 5.44 (d, *J* = 24.0 Hz, 1H), 7.10–7.27 (m, 4H). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −91.50 (ddd, *J* = 35.5, 24.0, 21.0 Hz, 1F).

3.2.3. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-(4-methoxyphenyl)tetrahydrofuran-3-carboxylate (***3cA***,***B***)

Yield 80%. IR (neat) (cm^{-1}): 1755 (s), 1735 (s), 1515 (s), 1280 (s), 1249 (vs), 1176 (s), 1110 (m), 1064 (m), 798 (m). MS (EI) *m/z* (relative intensity): 422 (M^+, 9), 402 (100), 285 (16). HRMS (EI) calcd. for $C_{16}H_{20}FIO_4$ 422.0390, found

422.0386. Anal. Calcd. for $C_{16}H_{20}FIO_3$: C, 45.51; H, 4.77. Found: C, 45.52; H, 4.27.

*3.2.3.1. Major isomer (**3cA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.20 (t, $J = 7.2$ Hz, 3H), 1.62 (s, 3H), 2.40 (dd, $J = 21.0$, 14.5 Hz, 1H), 2.81 (dd, $J = 36.0$, 14.5 Hz, 1H), 3.33 (d, $J = 10.0$ Hz, 1H), 3.44 (d, $J = 10.0$ Hz, 1H), 3.70 (s, 3H), 4.18 (q, $J = 7.2$ Hz, 2H), 5.34 (d, $J = 20.0$ Hz, 1H), 6.70–6.82 (m, 2H), 7.16–7.20 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.14, 16.55, 26.68, 48.12 (d, $J = 21.8$ Hz), 55.23, 62.30, 81.60, 86.03 (d, $J = 20.0$ Hz), 101.32 (d, $J = 203.5$ Hz), 113.63, 125.54 (d, $J = 2.5$ Hz), 128.61, 159.91, 168.31 (d, $J = 25.5$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −93.0 (ddd, $J = 36.0$, 24.0, 21.0 Hz, 1F).

*3.2.3.2. Minor isomer (**3cB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.18–1.21 (overlapped with the major isomer, 3H), 1.57 (s, 3H), 2.55 (dd, $J = 34.8$, 14.8 Hz, 1H), 2.70 (dd, $J = 22.8$, 14.8 Hz, 1H), 3.31–3.34 (overlapped with the major isomer, 1H), 3.40–3.46 (overlapped with the major isomer, 1H), 3.68–3.72 (overlapped with the major isomer, 3H), 4.22–4.30 (overlapped with the major isomer, 2H), 5.26 (d, $J = 24.5$ Hz, 1H), 6.70–6.82 (overlapped with the major isomer, 2H), 7.16–7.20 (overlapped with the major isomer, 2H). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −92.2 to −93.4 (overlapped with the major isomer, 1F).

*3.2.4. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-propyltetrahydrofuran-3-carboxylate (**3dA**,**B**)*

Yield 82%. IR (neat) (cm^{-1}): 2963 (vs), 2936 (s), 2874 (m), 1759 (vs), 1736 (vs), 1458 (m), 1373 (s), 1285 (s), 1188 (s), 1096 (m), 1042 (s), 976 (m), 922 (w), 790 (w), 613 (s). MS (EI) *m/z* (relative intensity): 358 (M^+, 2), 338 (100), 286 (31), 217 (92), 197 (99), 113 (22). HRMS (EI) calcd. for $C_{12}H_{20}FIO_3$ 358.0441, found 358.0434.

*3.2.4.1. Major isomer (**3dA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.85 (t, $J = 7.3$ Hz, 3H), 1.27 (t, $J = 7.3$ Hz, 3H), 1.30–1.37 (m, 2H), 1.47 (s, 3H), 1.45–1.54 (m, 1H), 1.56–1.65 (m, 1H), 2.26 (dd, $J = 24.0$, 15.0 Hz, 1H), 2.68 (dd, $J = 33.5$, 15.0 Hz, 1H), 3.28 (d, $J = 10.0$ Hz, 1H), 3.33 (d, $J = 10.0$ Hz, 1H), 4.22 (q, $J = 7.3$ Hz, 2H), 4.16–4.28 (m, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.98, 14.10, 16.52 (d, $J = 1.9$ Hz), 18.95, 27.00, 30.54 (d, $J = 6.4$ Hz), 48.26 (d, $J = 22.3$ Hz), 62.20, 81.09, 84.26 (d, $J = 21.7$ Hz), 101.20 (d, $J = 201.1$ Hz), 169.04 (d, $J = 26.6$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −96.3 (ddd, $J = 33.5$, 24.0, 24.0 Hz, 1F).

*3.2.4.2. Minor isomer (**3dB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.83–0.87 (overlapped with the major isomer, 3H), 1.27 (t, $J = 7.3$ Hz, 3H), 1.30–1.37 (m, 2H), 1.45–1.54 (overlapped with the major isomer, 1H), 1.56–1.65 (overlapped with the major isomer, 1H), 1.45–1.48 (overlapped with the major isomer, 3H), 2.40 (dd, $J = 34.5$, 15.0 Hz, 1H), 2.59 (dd, $J = 24.0$, 15.0 Hz, 1H), 3.24 (d, $J = 10.0$ Hz, 1H), 3.28 (d, $J = 10.0$ Hz, 1H), 4.17–4.27 (m, 3H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.98, 14.10, 15.87, 18.91, 26.33, 30.85 (d, $J = 6.7$ Hz), 47.94 (d, $J = 22.2$ Hz), 62.20, 81.3, 84.56 (d, $J = 21.7$ Hz), 100.74 (d, $J = 200.9$ Hz), 169.14 (d, $J = 26.6$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −95.0 to −96.2 (overlapped with the major isomer, 1F).

*3.2.5. Ethyl 3-fluoro-5-(iodomethyl)-2-isopropyl-5-methyltetrahydrofuran-3-carboxylate (**3fA**,**B**)*

Yield 64%. IR (neat) (cm^{-1}): 3487 (m), 1739 (vs), 1323 (m), 1303 (m), 1226 (s), 1149 (w), 1126 (m), 1095 (w), 1049 (s), 1026 (s), 709 (s). MS (EI) *m/z* (relative intensity): 358 (M^+, 3), 338 (100), 294 (40), 217 (87), 137 (19). HRMS (EI) calcd. for $C_{12}H_{20}FIO_3$ 358.0441, found 358.0434.

*3.2.5.1. Major isomer (**3fA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.83 (d, $J = 7.0$ Hz, 3H), 1.03 (d, $J = 6.5$ Hz, 3H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.53 (s, 3H), 1.97–2.05 (m, 1H), 2.34 (dd, $J = 24.5$, 14.6 Hz, 1H), 2.68 (dd, $J = 23.5$, 14.6 Hz, 1H), 3.39 (d, $J = 10.3$ Hz, 1H), 3.35 (d, $J = 10.3$ Hz, 1H), 4.00 (dd, $J = 25.3$, $J = 9.3$ Hz, 1H), 4.29 (q, $J = 7.2$ Hz, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.04, 16.64, 17.89, 20.30, 26.87, 28.67 (d, $J = 5.8$ Hz), 49.32 (d, $J = 22.7$ Hz), 62.18, 80.70, 90.00 (d, $J = 21.6$ Hz), 100.87 (d, $J = 203.3$ Hz), 169.90 (d, $J = 26.6$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −96.3 to −97.4 (m, 1F).

*3.2.5.2. Minor isomer (**3fB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.82–0.85 (overlapped with the major isomer, 3H), 1.02–1.04 (overlapped with the major isomer, 3H), 1.33 (t, $J = 7.0$ Hz, 3H), 1.52–1.54 (overlapped with the major isomer, 3H), 1.98–2.05 (overlapped with the major isomer, 1H), 2.41 (dd, $J = 34.0$, 14.5 Hz, 1H), 2.63–2.74 (overlapped with the major isomer, 1H), 3.31 (d, $J = 9.5$ Hz, 1H), 3.34–3.38 (overlapped with the major isomer, 1H), 3.99 (dd, $J = 25.0$, 9.0 Hz, 1H), 4.28 (q, $J = 7.0$ Hz, 2H). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −95.4 to −96.5 (m, 1F).

*3.2.6. Ethyl 3-fluoro-5-(iodomethyl)-2-phenyltetrahydrofuran-3-carboxylate (**4aA**,**B**)*

Yield 90%. IR (neat) (cm^{-1}): 3032 (w), 2982 (m), 2935 (w), 1759 (vs), 1736 (vs), 1497 (w), 1454 (m), 1369 (m), 1269 (vs), 1231 (m), 1169 (m), 1110 (m), 1038 (s), 856 (w), 698 (m). MS (CI) *m/z* (relative intensity): 379 (M + H, 31), 257 (11), 117 (100). HRMS (CI) calcd. for $C_{14}H_{17}FIO_3$ (M + H) 379.0206, found 379.0161.

*3.2.6.1. Major isomer (**4aA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.26 (t, $J = 7.1$ Hz, 3H), 2.54 (ddd, $J = 36.0$, 13.9, 9.0 Hz, 1H), 2.71 (ddd, $J = 18.3$, 13.9, 6.3 Hz, 1H), 3.36–3.46 (m, 2H), 4.26 (q, $J = 7.1$ Hz, 2H), 4.54–4.59 (m, 1H), 5.47 (d, $J = 24.5$ Hz, 1H), 7.28–7.34 (m, 5H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.41, 13.97, 43.94 (d, $J = 22.8$ Hz), 62.20, 77.50, 86.08 (d, $J = 20.4$ Hz), 104.43 (d, $J = 203.4$ Hz), 126.83, 128.02, 128.43, 133.87 (d, $J = 3.5$ Hz), 167.85

(d, $J = 25.5$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −94.5 (ddd, $J = 36.0$, 24.5, 18.3 Hz, 1F).

*3.2.6.2. Minor isomer (**4aB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.25 (t, $J = 7.0$ Hz, 3H), 2.41 (ddd, $J = 25.0$, 14.8, 5.0 Hz, 1H), 2.88 (ddd, $J = 30.9$, 14.8, 8.4 Hz, 1H), 3.36–3.46 (overlapped with the major isomer, 2H), 4.23–4.28 (overlapped with the major isomer, 2H), 4.39–4.44 (m, 1H), 5.22 (d, $J = 23.0$ Hz, 1H), 7.28–7.34 (overlapped with the major isomer, 5H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 7.80, 13.97, 43.31 (d, $J = 22.9$ Hz), 62.17, 77.39, 87.25 (d, $J = 21.1$ Hz), 99.28 (d, $J = 203.6$ Hz), 127.00, 128.02, 128.50, 133.41 (d, $J = 3.1$ Hz), 168.63 (d, $J = 26.6$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −89.3 (ddd, $J = 30.9$, 25.0, 23.0 Hz, 1F).

*3.2.7. Ethyl 3-fluoro-5-(iodomethyl)-2-(4-methylphenyl)tetrahydrofuran-3-carboxylate (**4bA,B**)*

Yield 82%. IR (neat) (cm^{-1}): 3838 (m), 3749 (m), 3672 (m), 2360 (s), 1736 (vs), 1539 (m), 1520 (s), 1269 (vs), 1227 (w), 1165 (m), 1072 (m), 1034 (vs), 791 (s), 667 (s). Anal. Calcd. for $C_{15}H_{18}FIO_3$: C, 45.94; H, 4.63. Found: C, 45.84; H, 4.29.

*3.2.7.1. Major isomer (**4bA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.22 (t, $J = 7.2$ Hz, 3H), 2.25 (s, 3H), 2.48 (ddd, $J = 36.0$, 14.0, 9.0 Hz, 1H), 2.63 (ddd, $J = 18.3$, 14.0, 6.3 Hz, 1H), 3.34 (dd, $J = 10.0$, 7.5 Hz, 1H), 3.37 (dd, $J = 10.0$, 4.3 Hz, 1H), 4.21 (q, $J = 7.2$ Hz, 2H), 4.49–4.56 (m, 1H), 5.37 (d, $J = 25.0$ Hz, 1H), 7.06–7.18 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.36, 14.10, 21.19, 44.09 (d, $J = 22.6$ Hz), 62.31, 77.60, 86.23 (d, $J = 20.2$ Hz), 100.57 (d, $J = 202.8$ Hz), 126.88, 128.88, 130.87 (d, $J = 3.0$ Hz), 138.33, 168.11 (d, $J = 25.5$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −94.1 (ddd, $J = 36.0$, 25.0, 18.3 Hz, 1F).

*3.2.7.2. Minor isomer (**4bB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.21 (t, $J = 6.9$ Hz, 3H), 2.25 (s, 3H), 2.37 (ddd, $J = 25.0$, 14.7, 4.9 Hz, 1H), 2.84 (ddd, $J = 31.1$, 14.7, 8.4 Hz, 1H), 3.26–3.44 (overlapped with the major isomer, 2H), 4.20 (q, $J = 6.9$ Hz, 2H), 4.31–4.40 (m, 1H), 5.13 (d, $J = 23.0$ Hz, 1H), 7.06–7.18 (m, 4H). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −88.2 (ddd, $J = 31.1$, 25.0, 23.0 Hz, 1F).

*3.2.8. Ethyl 3-fluoro-5-(iodomethyl)-2-(4-methoxylphenyl)tetrahydrofuran-3-carboxylate (**4cA,B**)*

Yield 68%. IR (neat) (cm^{-1}): 2835 (w), 1755 (m), 1736 (m), 1612 (s), 1585 (m), 1515 (vs), 1461 (m), 1442 (m), 1369 (w), 1250 (vs), 1177 (s), 1111 (m), 1030 (vs), 979 (w), 979 (m). MS (EI) *m/z* (relative intensity): 408 (M^+, 17), 388 (100). HRMS (EI) calcd. for $C_{15}H_{18}FIO_4$ 408.0233, found 408.0240. Anal. Calcd. for $C_{15}H_{18}FIO_4$: C, 44.13; H, 4.44. Found: C, 44.37; H, 4.26.

*3.2.8.1. Major isomer (**4cA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.22 (t, $J = 7.0$ Hz, 3H), 2.49 (dd, $J = 36.5$, 14.0, 9.0 Hz, 1H), 2.68 (ddd, $J = 18.3$, 14.0, 6.3 Hz, 1H), 3.34 (dd, $J = 10.0$, 7.5 Hz, 1H), 3.38 (dd, $J = 10.0$, 4.5 Hz, 1H), 3.72 (s, 3H), 4.21 (q, $J = 7.0$ Hz, 2H), 4.49–4.55 (m, 1H), 5.35 (d, $J = 24.5$ Hz, 1H), 6.78–6.82 (m, 2H), 7.14–7.17 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.41, 14.12, 44.04 (d, $J = 22.7$ Hz), 55.21, 62.33, 77.50, 86.05 (d, $J = 19.8$ Hz), 100.57 (d, $J = 202.8$ Hz), 113.65, 125.84 (d, $J = 3.3$ Hz), 128.44, 159.86, 168.11 (d, $J = 25.6$ Hz). ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −94.5 (ddd, $J = 36.5$, 24.5, 18.3 Hz, 1F).

*3.2.8.2. Minor isomer (**4cB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 1.21 (t, $J = 7.0$ Hz, 3H), 2.37 (ddd, $J = 25.0$, 14.5, 5.0 Hz, 1H), 2.84 (ddd, $J = 31.0$, 14.5, 8.5 Hz, 1H), 3.70–3.73 (overlapped with the major isomer, 2H), 3.72 (s, 3H), 4.20 (q, $J = 7.0$ Hz, 2H), 4.32–4.40 (m, 1H), 5.10 (d, $J = 23.0$ Hz, 1H), 6.78–6.82 (m, 2H), 7.14–7.17 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.41, 14.12, 41.15 (d, $J = 24.2$ Hz), 62.33, 77.39, 128.55. ^{19}F NMR (MeCN/acetone = 1/1, TFA) δ: −88.6 (ddd, $J = 31.0$, 25.0, 23.0 Hz, 1F).

*3.2.9. Ethyl 3-fluoro-5-(iodomethyl)-2-propyltetrahydrofuran-3-carboxylate (**4dA,B**)*

Yield 88%. IR (neat) (cm^{-1}): 2963 (s), 2874 (m), 1759 (vs), 17340 (vs), 1466 (m), 1435 (m), 1369 (m), 1296 (s), 1265 (s), 1238 (m), 1173 (s), 1091 (s), 1041 (s), 984 (w), 860 (w), 763 (w), 613 (w). MS (CI) *m/z* (relative intensity): 345 (M + H, 100), 325 (66). HRMS (CI) calcd. for (M + H) $C_{11}H_{19}FIO_3$ 345.0363, found 345.0379.

*3.2.9.1. Major isomer (**4dA**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.93 (t, $J = 7.3$ Hz, 3H), 1.34 (t, $J = 7.3$ Hz, 3H), 1.30–1.44 (m, 2H), 1.51–1.69 (m, 2H), 2.39 (ddd, $J = 35.3$, 14.3, 8.8 Hz, 1H), 2.60 (ddd, $J = 20.0$, 14.3, 6.0 Hz, 1H), 3.30 (dd, $J = 9.9$, 7.5 Hz, 1H), 3.35 (dd, $J = 9.9$, 4.5 Hz, 1H), 4.26–4.33 (m, 1H), 4.30 (q, $J = 7.2$ Hz, 2H), 4.33–4.38 (m, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 7.64, 9.34, 14.04, 18.93, 30.50 (d, $J = 7.4$ Hz), 44.17 (d, $J = 22.9$ Hz), 62.22, 76.85, 84.56 (d, $J = 21.0$ Hz), 100.48 (d, $J = 200.2$ Hz), 168.78 (d, $J = 25.9$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −173.9 (ddd, $J = 35.3$, 20.0, 20.0 Hz, 1F).

*3.2.9.2. Minor isomer (**4dB**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.93 (t, $J = 7.5$ Hz, 3H), 1.22 (t, $J = 7.3$ Hz, 3H), 1.30–1.44 (overlapped with the major isomer, 2H), 1.51–1.69 (overlapped with the major isomer, 2H), 2.26 (ddd, $J = 26.8$, 14.5, 5.8 Hz, 1H), 2.78 (ddd, $J = 29.0$, 14.5, 8.0 Hz, 1H), 3.22 (dd, $J = 9.8$, 8.0 Hz, 1H), 4.09 (ddd, $J = 22.4$, 7.8, 5.5 Hz, 1H), 4.22–4.33 (overlapped with the major isomer, 4H), 4.33–4.38 (m, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 7.64, 9.34, 13.96, 18.66, 30.45 (d, $J = 5.9$ Hz), 43.87 (d, $J = 23.0$ Hz), 62.16, 77.76, 85.83 (d, $J = 22.0$ Hz), 99.58 (d, $J = 201.2$ Hz), 169.46 (d, $J = 26.9$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −169.4 (ddd, $J = 29.0$, 26.8, 22.4 Hz, 1F).

3.3. Typical procedure for the reaction of β-hydroxy ester threo-1 with iodine and pyridine

To a solution of iodine (0.762 g, 3.0 mmol), MeCN (2.0 ml) and pyridine (0.237 g, 3.0 mmol) was dropwise added a solution of *threo*-**1a** (0.266 g, 1.0 mmol) in MeCN (2.0 ml) at 0 °C. After being stirred at ambient temperature for 3 h, the mixture was quenched with a saturated aqueous NH_4Cl (25 ml). The resulting mixture was extracted with Et_2O (25 ml × 4). The combined extracts were washed with 10% aqueous Na_2SO_3 (30 ml) and a brine, and were dried over anhydrous Na_2SO_4, followed by filtration and concentration under vacuum. The residue was purified by silica gel column chromatography (benzene) to give pure product **3aC**,**D** (0.243 g, 0.620 mmol, 62% yield).

3.3.1. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-phenyltetrahydrofuran-3-carboxylate (*3aC*,*D*)

Yield 62%. IR (neat) (cm^{-1}): 3063 (w), 3032 (w), 2982 (w), 2936 (w), 2901 (w), 2874 (vs), 1755 (vs), 1497 (w), 1454 (w), 1377 (w), 1315 (w), 1258 (m), 1234(m), 1173 (m), 1126 (s), 1092 (m), 1057 (m), 1026 (w), 860 (w), 799 (w), 748 (w), 698 (m). MS (CI) *m/z* (relative intensity): 393 (M + H, 100), 247(8), 229 (6). HRMS (CI) calcd. for $C_{15}H_{19}FIO_3$ (M + H) 393.0362, found 393.

*3.3.1.1. Major isomer (**3aC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.86 (t, J = 7.2 Hz, 3H), 1.70 (s, 3H), 2.37 (dd, J = 23.3, 14.4 Hz, 1H), 2.96 (dd, J = 25.5, 14.4 Hz, 1H), 3.53 (d, J = 10.0 Hz, 1H), 3.55 (d, J = 10.0 Hz, 1H), 3.74 (q, J = 7.2 Hz, 2H), 5.37 (d, J = 25.0 Hz, 1H), 7.25–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.44, 14.18, 24.07, 45.06 (d, J = 20.1 Hz), 61.77, 81.42, 88.30 (d, J = 32.7 Hz), 103.93 (d, J = 197.3 Hz), 126.42, 127.97, 128.42, 135.70 (d, J = 4.8 Hz), 168.00 (d, J = 29.1 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −146.3 (ddd, J = 25.5, 25.0, 23.3 Hz, 1F).

*3.3.1.2. Minor isomer (**3aD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.86 (t, J = 7.1 Hz, 3H), 1.73 (s, 3H), 2.80 (m, 1H), 2.81 (dd, J = 20.5, 15.0 Hz, 1H), 3.58–3.64 (overlapped with the major isomer, 2H), 3.75 (q, J = 7.1 Hz, 2H), 5.34 (d, J = 25.0 Hz, 1H), 7.25–7.41 (m, 5H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.18, 15.21, 26.74, 46.90 (d, J = 20.1 Hz), 61.80, 82.78, 88.12 (d, J = 31.4 Hz), 104.62 (d, J = 195.9 Hz), 126.33, 128.02, 128.48, 135.68 (d, J = 6.3 Hz), 167.71 (d, J = 27.0 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −145.4 to −147.0 (overlapped with the major isomer, 1F).

3.3.2. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-(4-methylphenyl)tetrahydrofuran-3-carboxylate (*3bC*,*D*)

Yield 62%. IR (neat) (cm^{-1}): 2982 (m), 2932 (w), 2874 (w), 1755 (vs), 1516 (w), 1447 (w), 1377 (m), 1312 (m), 1258 (s), 1234 (m), 1173 (m), 1115 (s), 1061 (s), 1022 (m), 941 (w), 853 (w), 818 (w), 791 (w), 718 (w). MS (CI) *m/z* (relative intensity): 407 (M + H, 74), 389 (32), 386 (100), 286 (25). HRMS (CI) calcd. for $C_{16}H_{21}FIO_3$ 407.0519 (M + H), found 407.0495.

*3.3.2.1. Major isomer (**3bC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.89 (t, J = 7.3 Hz, 3H), 1.69 (s, 3H), 2.31 (s, 3H), 2.36 (dd, J = 30.0, 14.5 Hz, 1H), 2.95 (dd, J = 25.3, 14.5 Hz, 1H), 3.52 (d, J = 10.5 Hz, 1H), 3.61 (d, J = 10.5 Hz, 1H), 3.63–3.70 (m, 2H), 5.34 (d, J = 25.0 Hz, 1H), 7.08–7.30 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.42, 14.21, 21.11, 24.04, 46.84 (d, J = 20.3 Hz), 61.71, 81.31, 88.26 (d, J = 31.5 Hz), 103.99 (d, J = 196.7 Hz), 126.34, 128.60, 132.65 (d, J = 5.7 Hz), 138.12, 168.05 (d, J = 29.1 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −146.3 (ddd, J = 30.0, 25.3, 25.0 Hz, 1F).

*3.3.2.2. Minor isomer (**3bD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.90 (t, J = 7.0 Hz, 3H), 1.72 (s, 3H), 2.29–2.32 (overlapped with the major isomer, 3H), 2.73–2.76 (m, 1H), 2.80 (dd, J = 19.0, 15.0 Hz, 1H), 3.54 (d, J = 11.5 Hz, 1H), 3.59 (d, J = 11.5 Hz, 1H), 3.71–3.82 (m, 2H), 5.31 (d, J = 25.5 Hz, 1H), 7.08–7.30 (m, 4H). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −145.0 to −147.0 (overlapped with the major isomer, 1F).

3.3.3. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-(4-methoxyphenyl)tetrahydrofuran-3-carboxylate (*3cC*,*D*)

Yield 71%. IR (neat) (cm^{-1}): 2982 (m), 2936 (m), 2905 (w), 2839 (w), 1747 (vs), 1612 (s), 1585 (w), 1516 (s), 1462 (m), 1377 (s), 1304 (s), 1250 (s), 1173 (s), 1111 (s), 1034 (s), 941 (w), 853 (m), 829 (m), 795 (m), 768 (w), 725(w), 652 (w). MS (EI) *m/z* (relative intensity): 422 (M^+, 5), 402 (100), 286 (11), 111 (11). HRMS (EI) calcd. for $C_{16}H_{20}FIO_4$ 422.0390, found 422.0355.

*3.3.3.1. Major isomer (**3cC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.93 (t, J = 7.3 Hz, 3H), 1.68 (s, 3H), 2.35 (dd, J = 23.0, 14.2 Hz, 1H), 2.97 (dd, J = 25.8, 14.2 Hz, 1H), 3.52 (d, J = 10.5 Hz, 1H), 3.61 (d, J = 10.5 Hz, 1H), 3.65–3.80 (m, 2H), 3.78 (s, 3H), 5.33 (d, J = 25.5 Hz, 1H), 6.82–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.54, 14.21, 23.98, 46.76 (d, J = 20.6 Hz), 55.22, 61.75, 81.17, 88.10 (d, J = 31.8 Hz), 103.98 (d, J = 197.2 Hz), 113.38, 113.43, 127.85, 159.68, 168.09 (d, J = 29.4 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −146.4 (ddd, J = 25.8, 25.5, 23.0 Hz, 1F).

*3.3.3.2. Minor isomer (**3cD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.93 (t, J = 7.3 Hz, 3H), 1.72 (s, 3H), 2.75 (dd, J = 19.5, 14.9 Hz, 1H), 2.80 (dd, J = 23.8, 14.9 Hz, 1H), 3.50–3.63 (overlapped with the major isomer, 2H), 3.65–3.80 (overlapped with the major isomer, 2H), 3.77–3.79 (overlapped with the major isomer, 3H), 5.30 (d, J = 25.5 Hz, 1H), 6.82–7.35 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.21, 15.31, 26.76, 44.90 (d, J = 20.4 Hz), 55.22, 61.78, 82.56, 88.00 (d, J = 31.5 Hz), 104.66 (d, J = 195.7 Hz), 113.43, 127.74, 127.85, 159.72, 167.68 (d, J = 29.4 Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −146.2 (overlapped with the major isomer, 1F).

*3.3.4. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-propyltetrahydrofuran-3-carboxylate (**3dC,D**)*

Yield 84%. IR (neat) (cm^{-1}): 2963 (s), 2936 (m), 2874 (w), 1744 (vs), 1458 (w), 1377 (m), 1285 (s), 1227 (m), 1177 (m), 1107 (m), 1072 (s), 1061 (m), 980 (w). MS (EI) *m/z* (relative intensity): 358 (M^+, 1), 338 (2), 286 (15), 231 (32), 197 (100). HRMS (EI) calcd. for $C_{12}H_{20}FIO_3$ 358.0441, found 358.0439. Anal. Calcd. for $C_{12}H_2OFIO_3$: C, 40.24; H, 5.63. Found: C, 40.50; H, 5.51.

*3.3.4.1. Major isomer (**3dC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.92 (t, $J = 7.0$ Hz, 3H), 1.35 (t, $J = 7.0$ Hz, 3H), 1.38–1.53 (m, 4H), 1.57 (s, 3H), 2.29 (dd, $J = 22.0$, 14.5 Hz, 1H), 2.78 (dd, $J = 30.0$, 14.5 Hz, 1H), 3.34 (d, $J = 10.0$ Hz, 1H), 3.36 (d, $J = 10.0$ Hz, 1H), 4.15–4.35 (m, 3H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.72, 14.08, 16.57, 19.04, 25.15, 33.56 (d, $J = 4.8$ Hz), 46.40 (d, $J = 20.2$ Hz), 62.04, 81.33, 85.72 (d, $J = 28.4$ Hz), 103.14 (d, $J = 193.9$ Hz), 168.45 (d, $J = 28.2$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −148.8 (ddd, $J = 30.0$, 22.0, 22.0 Hz, 1F).

*3.3.4.2. Minor isomer (**3dD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.92 (t, $J = 7.0$ Hz, 3H), 1.34 (t, $J = 7.3$ Hz, 3H), 1.38–1.53 (overlapped with the major isomer, 4H), 1.54 (s, 3H), 2.61 (dd, $J = 28.0$, 15.0 Hz, 1H), 2.66 (dd, $J = 23.0$, 15.0 Hz, 1H), 3.42 (d, $J = 10.0$ Hz, 1H), 3.45 (d, $J = 10.0$ Hz, 1H), 4.15–4.35 (m, 3H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.72, 14.08, 15.01, 19.11, 27.31, 33.25 (d, $J = 3.8$ Hz), 45.23 (d, $J = 20.9$ Hz), 62.04, 81.56, 85.20 (d, $J = 28.4$ Hz), 103.02 (d, $J = 192.7$ Hz), 168.50 (d, $J = 30.8$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −149.8 (ddd, $J = 28.0$, 24.2, 23.0 Hz, 1F).

*3.3.5. Ethyl 3-fluoro-5-(iodomethyl)-5-methyl-2-hexyltetrahydrofuran-3-carboxylate (**3eC,D**)*

Yield 78%. IR (neat) (cm^{-1}): 2932 (m), 2858 (w), 1744 (s), 1462 (w), 1377 (w), 1281 (w), 1177 (w), 1069 (w). MS (CI) *m/z* (relative intensity): 401 (M + H, 96), 273 (10). HRMS (CI) calcd. for $C_{15}H_{27}FIO_3$ 401.0988 (M + H), found 401.0986.

*3.3.5.1. Major isomer (**3eC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.87 (t, $J = 7.0$ Hz, 3H), 1.24–1.49 (m, 10H), 1.35 (t, $J = 7.3$ Hz, 3H), 1.57 (s, 3H), 2.29 (dd, $J = 22.0$, 14.5 Hz, 1H), 2.78 (dd, $J = 30.0$, 14.5 Hz, 1H), 3.33 (d, $J = 10.3$ Hz, 1H), 3.36 (d, $J = 10.3$ Hz, 1H), 4.13–4.35 (m, 3H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.97, 14.08, 16.57, 22.47, 25.15, 25.72, 26.94, 31.54, 31.56 (d, $J = 4.7$ Hz), 46.41 (d, $J = 20.6$ Hz), 62.02, 81.33, 86.05 (d, $J = 28.2$ Hz), 103.12 (d, $J = 194.0$ Hz), 168.45 (d, $J = 28.6$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −148.7 (ddd, $J = 30.0$, 22.0, 22.0 Hz, 1F).

*3.3.5.2. Minor isomer (**3eD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.87 (t, $J = 7.0$ Hz, 3H), 1.24–1.49 (overlapped with the major isomer, 10H), 1.34 (t, $J = 7.00$ Hz, 3H), 1.54 (s, 3H), 2.60 (dd, $J = 28.3$, 14.8 Hz, 1H), 2.66 (dd, $J = 23.3$, 14.8 Hz, 1H), 3.41 (d, $J = 10.0$ Hz, 1H), 3.45 (d, $J = 10.0$ Hz, 1H), 4.13–4.35 (overlapped with the major isomer, 3H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 13.97, 14.08, 14.99, 16.57, 25.15, 25.77, 27.31, 31.23, 31.27, 45.25 (d, $J = 20.4$ Hz), 62.02, 81.57, 85.52 (d, $J = 28.3$ Hz), 103.01 (d, $J = 193.0$ Hz), 168.49 (d, $J = 28.6$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −149.6 (ddd, $J = 28.3$, 23.3, 22.0 Hz, 1F).

*3.3.6. Ethyl 3-fluoro-5-(iodomethyl)-2-isopropyl-5-methyltetrahydrofuran-3-carboxylate (**3fC,D**)*

Yield 77%. IR (neat) (cm^{-1}) δ: 2982 (m), 2936 (w), 2874 (w), 1755 (vs), 1740 (vs), 1470 (w), 1447 (w), 1373 (w), 1335 (w), 1265 (s), 1238 (m), 1177 (s), 1099 (m), 1072 (s), 860 (w), 795 (w). MS (EI) *m/z* (relative intensity): 358 (M^+, 1), 338 (18), 286 (41), 231 (46), 217 (100). HRMS (EI) calcd. for $C_{12}H_{20}FIO_3$ 358.0441, found 358.0450. Anal. Calcd. for $C_{12}H_{20}FIO_3$: C, 40.24; H, 5.63. Found: C, 40.37; H, 5.61.

*3.3.6.1. Major isomer (**3fC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.86–0.95 (m, 3H), 0.97–1.00 (m, 3H), 1.35 (t, $J = 7.3$ Hz, 3H), 1.57 (s, 3H), 1.74–1.85 (m, 1H), 2.29 (dd, $J = 23.8$, 14.3 Hz, 1H), 2.71 (dd, $J = 21.8$, 14.3 Hz, 1H), 3.45 (s, 2H), 3.84 (dd, $J = 22.5$, 9.5 Hz, 1H), 4.22–4.36 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 14.07, 15.26, 18.58, 19.86, 25.06, 29.19 (d, $J = 3.4$ Hz), 48.28 (d, $J = 21.2$ Hz), 61.99, 80.14 (d, $J = 3.0$ Hz), 91.06 (d, $J = 27.8$ Hz), 101.40 (d, $J = 196.2$ Hz), 169.55 (d, $J = 29.1$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −148.3 (ddd, $J = 23.8$, 22.5, 21.8 Hz, 1F).

*3.3.6.2. Minor isomer (**3fD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.86–0.95 (m, 3H), 0.97–1.00 (m, 3H), 1.34 (t, $J = 7.0$ Hz, 3H), 1.53 (s, 3H), 1.74–1.85 (m, 1H), 2.55 (dd, $J = 21.8$, 14.6 Hz, 1H), 2.64 (dd, $J = 23.5$, 14.6 Hz, 1H), 3.36 (d, $J = 9.8$ Hz, 1H), 3.37 (d, $J = 9.8$ Hz, 1H), 3.78 (dd, $J = 22.0$, 9.0 Hz, 1H), 4.22–4.36 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 15.26, 15.74, 18.58, 19.71, 26.65, 29.10 (d, $J = 3.3$ Hz), 47.03 (d, $J = 20.8$ Hz), 61.99, 80.49 (d, $J = 2.3$ Hz), 90.25 (d, $J = 27.6$ Hz), 101.69 (d, $J = 195.0$ Hz), 169.40 (d, $J = 28.6$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −172.6 (ddd, $J = 23.5$, 22.0, 21.8 Hz, 1F).

*3.3.7. Ethyl 3-fluoro-5-(iodomethyl)-2-phenyltetrahydrofuran-3-carboxylate (**4aC,D**)*

Yield 65%. IR (neat) (cm^{-1}): 3063 (w), 3032 (m), 2982 (s), 2901 (w), 1747 (vs), 1497 (w), 1454 (s), 1431 (m), 1373 (s), 1350 (s), 1300 (s), 1250 (s), 1211 (s), 1119 (s), 1053 (s), 1026 (s), 918 (w), 864 (m), 779 (w), 748 (s), 698 (s). MS (EI) *m/z* (relative intensity): 378 (M^+, 1), 358 (100), 272 (26), 231 (14). HRMS (EI) calcd. for $C_{14}H_{16}FIO_3$ 378.0128, found 378.0109.

*3.3.7.1. Major isomer (**4aC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.86 (t, $J = 7.3$ Hz, 3H), 2.50–2.60 (m, 2H), 3.42–3.53 (m, 2H), 3.60–3.86 (m, 2H), 4.28–4.36 (m, 1H), 5.24 (d, $J = 28.0$ Hz, 1H), 7.25–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$,

Me_4Si) δ: 5.95, 13.45, 42.68 (d, $J = 21.5$ Hz), 61.79, 77.35, 89.57 (d, $J = 31.9$ Hz), 103.62 (d, $J = 195.2$ Hz), 126.48, 128.06, 128.54, 135.75 (d, $J = 6.2$ Hz), 167.60 (d, $J = 28.2$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −147.9 (ddd, $J = 28.0$, 25.7, 25.3 Hz, 1F).

*3.3.7.2. Minor isomer (**4aD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.89 (t, $J = 7.5$ Hz, 3H), 2.40–2.60 (overlapped with the major isomer, 1H), 2.97 (ddd, $J = 23.4$, 14.4, 7.9 Hz, 1H), 3.42–3.56 (m, 2H), 3.60–3.86 (overlapped with the major isomer, 2H), 4.78–4.84 (m, 1H), 5.42 (t, $J = 21.5$ Hz, 1H), 7.25–7.38 (m, 5H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.13, 13.49, 40.26 (d, $J = 20.9$ Hz), 61.79, 79.59, 87.69 (d, $J = 29.4$ Hz), 103.09 (d, $J = 198.6$ Hz), 125.90, 128.18, 128.49, 136.10 (d, $J = 5.2$ Hz), 167.48 (d, $J = 28.0$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −151.6 (ddd, $J = 23.4$, 21.5, 21.5 Hz, 1F).

*3.3.8. Ethyl 3-fluoro-5-(iodomethyl)-2-(4-methylphenyl)tetrahydrofuran-3-carboxylate (**4bC,D**)*

Yield 71%. IR (neat) (cm^{-1}): 2982 (m), 2924 (w), 2901 (w), 1751 (vs), 1516 (w), 1431 (w), 1373 (m), 1342 (w), 1312 (m), 1296 (m), 1250 (s), 1215 (m), 1119 (m), 1053 (s), 1018 (m), 937 (w), 864 (w), 818 (w), 772 (w), 718 (w). MS (EI) *m/z* (relative intensity): 392 (M^+, 1), 372 (100), 271 (8), 199 (9). HRMS (EI) calcd. for $C_{15}H_{18}FIO_3$ 392.0284, found 392.0269.

*3.3.8.1. Major isomer (**4bC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.89 (t, $J = 7.3$ Hz, 3H), 2.29 (s, 3H), 2.50–2.60 (m, 2H), 3.40–3.55 (m, 2H), 3.65–3.80 (m, 2H), 4.28–4.35 (m, 1H), 5.21 (d, $J = 27.5$ Hz, 1H), 7.10–7.27 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 5.97, 13.42, 21.11, 42.59 (d, $J = 21.0$ Hz), 61.73, 77.27, 89.55 (d, $J = 31.4$ Hz), 103.65 (d, $J = 195.0$ Hz), 126.38, 128.66, 132.69 (d, $J = 6.3$ Hz), 138.25, 167.61 (d, $J = 28.3$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −148.0 (ddd, $J = 27.5$, 26.4, 25.9 Hz, 1F).

*3.3.8.2. Minor isomer (**4bD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.93 (t, $J = 7.0$ Hz, 3H), 2.31 (s, 3H), 2.45–2.55 (overlapped with the major isomer, 1H), 2.96 (ddd, $J = 23.4$, 14.4, 7.9 Hz, 1H), 3.43 (dd, $J = 10.0$, 8.5 Hz, 1H), 3.47 (dd, $J = 10.3$, 8.5 Hz, 1H), 3.65–3.80 (overlapped with the major isomer, 2H), 4.77–4.83 (m, 1H), 5.39 (d, $J = 21.5$ Hz, 1H), 7.10–7.27 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.15, 13.47, 21.11, 40.05 (d, $J = 20.5$ Hz), 61.76, 79.53, 87.75 (d, $J = 29.9$ Hz), 103.23 (d, $J = 194.9$ Hz), 125.79, 128.81, 133.05 (d, $J = 6.3$ Hz), 138.20, 167.46 (d, $J = 28.3$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −151.3 (ddd, $J = 23.4$, 22.1, 22.1 Hz, 1F).

*3.3.9. Ethyl 3-fluoro-5-(iodomethyl)-2-(4-methoxyphenyl)tetrahydrofuran-3-carboxylate (**4cC,D**)*

Yield 81%. IR (neat) (cm^{-1}): 2839 (w), 1751 (vs), 1612 (s), 1585 (w), 1516 (vs), 1443 (w), 1373 (w), 1304 (w), 1250 (vs), 1215 (w), 1177 (m), 1115 (m), 1034 (m), 829 (w). Anal. Calcd. for $C_{15}H_{18}FIO_4$: C, 44.13; H, 4.44. Found: C, 44.28; H, 4.29.

*3.3.9.1. Major isomer (**4cC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.92 (t, $J = 7.3$ Hz, 3H), 2.50–2.59 (m, 2H), 3.49–3.52 (m, 2H), 3.66–3.90 (m, 2H), 3.78 (s, 3H), 4.25–4.32 (m, 1H), 5.20 (d, $J = 28.0$ Hz, 1H), 6.83–6.86 (m, 2H), 7.18–7.30 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 6.15, 13.57, 42.59 (d, $J = 20.9$ Hz), 55.26, 61.80, 77.15, 89.44 (d, $J = 31.8$ Hz), 103.68 (d, $J = 195.2$ Hz), 113.43, 127.76, 127.89, 159.78, 167.68 (d, $J = 28.8$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −147.4 (ddd, $J = 28.0$, 25.9, 25.9 Hz, 1F).

*3.3.9.2. Minor isomer (**4cD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.96 (t, $J = 7.5$ Hz, 3H), 2.45–2.62 (m, 2H), 2.97 (ddd, $J = 23.5$, 14.0, 7.5 Hz, 1H), 3.49–3.52 (overlapped with the major isomer, 2H), 3.78–3.79 (overlapped with the major isomer, 3H), 3.66–3.90 (overlapped with the major isomer, 2H), 4.76–4.82 (m, 1H), 5.37 (d, $J = 21.5$ Hz, 1H), 6.83–6.86 (overlapped with the major isomer, 2H), 7.18–7.30 (overlapped with the major isomer, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.20, 13.62, 40.11 (d, $J = 20.9$ Hz), 55.26, 61.80, 79.45, 87.55 (d, $J = 30.0$ Hz), 103.13 (d, $J = 196.6$ Hz), 113.57, 127.27, 127.81, 159.74, 167.56 (d, $J = 28.7$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −151.0 (ddd, $J = 22.0$, 21.5, 21.5 Hz, 1F).

*3.3.10. Ethyl 3-fluoro-5-(iodomethyl)-2-propyltetrahydrofuran-3-carboxylate (**4dC,D**)*

Yield 82%. IR (neat) (cm^{-1}): 2963 (vs), 2874 (s), 1740 (vs), 1466 (m), 1435 (m), 1369 (s), 1304 (vs), 1250 (vs), 1153 (s), 1072 (s), 1042 (vs), 930 (w), 860 (w), 748 (w), 613 (m). Anal. Calcd. for $C_{11}H_{18}FIO_3$: C, 38.39; H 5.27. Found: C, 38.42; H, 5.00.

*3.3.10.1. Major isomer (**4dC**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.92 (t, $J = 7.3$ Hz, 3H), 1.28–1.43 (m, 2H), 1.35 (t, $J = 7.0$ Hz, 3H), 1.44–1.57 (m, 2H), 2.36 (ddd, $J = 31.0$, 13.9, 10.0 Hz, 1H), 2.48 (ddd, $J = 20.3$, 13.9, 5.0 Hz, 1H), 3.28 (dd, $J = 10.1$, 6.8 Hz, 1H), 3.36 (dd, $J = 10.1$, 5.0 Hz, 1H), 4.14–4.20 (m, 2H), 4.25–4.35 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 7.17, 13.73, 19.03, 32.61, 33.41, 42.70 (d, $J = 21.6$ Hz), 62.05, 77.76, 86.60 (d, $J = 28.5$ Hz), 102.29 (d, $J = 193.0$ Hz), 168.43 (d, $J = 27.9$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −151.1 (ddd, $J = 31.0$, 22.0, 20.4 Hz, 1F).

*3.3.10.2. Minor isomer (**4dD**).* ^{1}H NMR ($CDCl_3$, Me_4Si) δ: 0.90–0.95 (overlapped with the major isomer, 3H), 1.28–1.43 (overlapped with the major isomer, 2H), 1.34 (t, $J = 7.3$ Hz, 3H), 1.44–1.57 (overlapped with the major isomer, 2H), 2.33 (ddd, $J = 22.8$, 14.6, 5.0 Hz, 1H), 2.86 (ddd, $J = 24.4$, 14.6, 7.9 Hz, 1H), 3.25–3.31 (overlapped with the major isomer, 1H), 3.33–3.38 (overlapped with the major isomer, 1H), 4.09–4.13 (m, 1H), 4.25–4.35 (overlapped with the major isomer, 2H), 4.41–4.47 (m, 1H). ^{13}C NMR

($CDCl_3$, Me_4Si) δ: 9.08, 14.10, 18.93, 32.57, 33.46, 40.78 (d, $J = 21.1$ Hz), 62.05, 77.76, 85.26 (d, $J = 27.8$ Hz), 101.92 (d, $J = 194.6$ Hz), 168.31 (d, $J = 27.5$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −152.37 (ddd, $J = 24.4$, 22.8, 22.0 Hz, 1F).

*3.3.11. Ethyl 3-fluoro-5-(iodomethyl)-2-hexyltetrahydrofuran-3-carboxylate (**4eC**,**D**)*

Yield 78%. IR (neat) (cm^{-1}): 2928 (vs), 2858 (s), 1744 (vs), 1466 (s), 1435 (m), 1369 (m), 1304 (s), 1250 (vs), 1223 (s), 1153 (m), 1072 (s), 949 (w), 860 (w), 613 (m). Anal. Calcd. for $C_{14}H_{24}FIO_3$: C, 43.53; H, 6.26. Found: C, 43.58; H, 5.95.

*3.3.11.1. Major isomer (**4eC**).* ^1H NMR ($CDCl_3$, Me_4Si) δ: 0.87 (t, $J = 7.0$ Hz, 3H), 1.26–1.52 (m, 10H), 1.34 (t, $J = 7.3$ Hz, 3H), 2.36 (ddd, $J = 30.9$, 14.1, 10.1 Hz, 1H), 2.48 (ddd, $J = 20.0$, 14.1, 5.5 Hz, 1H), 3.28 (dd, $J = 10.0$, 7.0 Hz, 1H), 3.36 (dd, $J = 10.0$, 5.0 Hz, 1H), 4.13–4.20 (m, 2H), 4.23–4.35 (m, 2H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 7.19, 14.01, 22.51, 25.72, 28.97, 30.64, 31.46, 31.58, 42.75 (d, $J = 21.6$ Hz), 62.07, 77.80, 86.94 (d, $J = 28.9$ Hz), 102.29 (d, $J = 193.1$ Hz), 168.46 (d, $J = 28.0$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −151.0 (ddd, $J = 30.9$, 26.4, 20.0 Hz, 1F).

*3.3.11.2. Minor isomer (**4eD**).* ^1H NMR ($CDCl_3$, Me_4Si) δ: 0.85–0.89 (overlapped with the major isomer, 3H), 1.26–1.52 (overlapped with the major isomer, 10H), 1.34 (t, $J = 7.3$ Hz, 3H), 2.60 (ddd, $J = 24.4$, 14.4, 7.6 Hz, 1H), 2.29–2.38 (overlapped with the major isomer, 1H), 3.25–3.31 (m, 1H), 3.30–3.80 (m, 1H), 4.07–4.11 (m, 1H), 4.23–4.35 (overlapped with the major isomer, 2H), 4.40–4.47 (m, 1H). ^{13}C NMR ($CDCl_3$, Me_4Si) δ: 9.09, 14.13, 22.51, 25.63, 28.97, 30.61, 31.42, 31.58, 40.81 (d, $J = 20.9$ Hz), 62.07, 77.80, 85.59 (d, $J = 27.4$ Hz), 101.93 (d, $J = 193.9$ Hz), 168.33 (d, $J = 28.0$ Hz). ^{19}F NMR ($CDCl_3$, $CFCl_3$) δ: −152.3 (ddd, $J = 24.4$, 24.2, 24.2 Hz, 1F).

References

[1] J.W. Westley, Polyether Antibiotics, Naturally Occurring Acid Ionophores, Vols. I and II, Marcel Dekker, New York, 1982.
[2] A. Cavé, D. Cortes, B. Figadère, R. Hocquemiller, O. Laprévote, A. Laurens, M. Leboeuf, in: K.R. Downum, J. Romeo, H.H.A. Stafford (Eds.), Phytochemical Potential of Tropical Plants Recent Advances in Phytochemistry, Vol. 27, Plenum Press, New York, 1993.
[3] M.H.D. Postema, Tetrahedron 48 (1987) 8545–8599.
[4] T. Fukuyama, D. Schmid, D.P. Negri, Y. Kishi, Tetrahedron Lett. 31 (1978) 2741–2744.
[5] D.M. Walba, G.S. Stoudt, Tetrahedron Lett. 23 (1982) 727–730.
[6] S. Hatakeyama, K. Sakurai, K. Saijo, S. Takano, Tetrahedron Lett. 26 (1985) 1333–1336.
[7] H.U. Reissig, H. Holzinger, G. Glomsda, Tetrahedron 45 (1989) 3139–3150.
[8] A.R. Howell, G. Pattenden, J. Chem. Soc., Perkin Trans. 1 (1990) 2715–2719.
[9] G. Bojack, H. Bornowski, Tetrahedron 47 (1991) 9179–9186.
[10] S. Kobayashi, M. Sato, Y. Eguchi, M. Ohno, Tetrahedron Lett. 33 (1992) 1081–1084.
[11] G. Galatsis, J.J. Manwell, Tetrahedron Lett. 36 (1995) 8179–8182.
[12] T. Ishihara, K. Mima, T. Konno, H. Yamanaka, Org. Lett., submitted for publication.
[13] T. Ishihara, T. Matsuda, K. Imura, H. Matsui, H. Yamanaka, Chem. Lett. (1994) 2167–2170.
[14] J.E. Baldwin, J. Chem. Soc. Chem. Commun. (1976) 734–736.