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Stereoselective synthesis of (*E*)-1-fluoro-1,3-enynes

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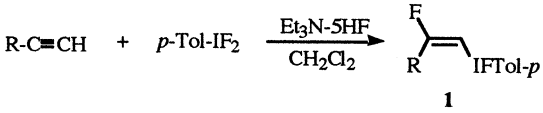
Abstract—1-Fluoro-1,3-enynes were stereoselectively prepared by the cross-coupling reaction of 1-alkynes with β-fluoroalkenyliodides obtained from (β-fluoroalkenyl)iodonium salts. As the reaction proceeds under mild conditions, polyfunctionalized 1-fluoro-1,3-enynes could be prepared, and the synthesis of a fluorinated analog of a natural compound was achieved using this method.

1. Introduction

Fluorinated compounds have been of great interest to synthetic and medicinal chemists due to the unique physical and biological properties imparted by fluorine.[1] Significant efforts have been exerted to achieve the synthesis of fluorinated enynes for their use as building blocks in the preparation of the fluorinated analogs of natural compounds.[2] Though the stereoselective syntheses of difluoro-1,3-enynes[3a–c] and 2-fluoro-1,3-enynes[3d,e] have been reported, selective methods for the 1-fluoro-1,3-enynes had been unknown. Recently, Mestdagh et al. reported the stereoselective synthesis of (*E*)-1-fluoro-1,3-enynes;[4] however, they prepared only simple substrates and, for application to the fluorinated analogs of natural compounds, the synthesis of polyfunctionalized substrates is necessary.[5]

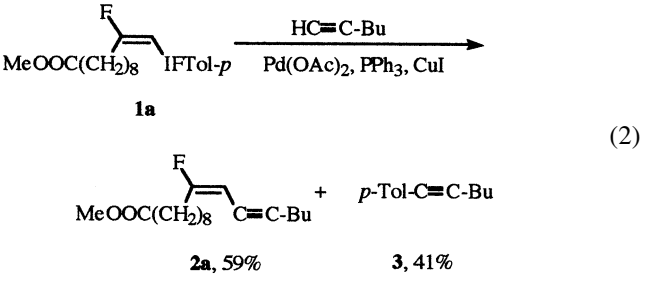
2. Results and discussion

Quite recently, we found that iodotoluene difluoride stereo- and regioselectively adds to 1-alkynes to give (*E*)-(β-fluoroalkenyl)(4-methylphenyl)iodonium fluorides (**1**) (Eq. (1)),[6] and then applied them to the synthesis of (*E*)-β-fluoro-α,β-unsaturated esters[7] and (*E*,*E*)-δ-fluoro-α,β,γ,δ-unsaturated carbonyl compounds.[8]



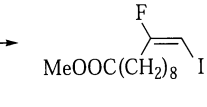
1 (1)

In order to develop a new methodology for 1-fluoro-1,3-enynes, the cross-coupling reaction of **1** with 1-alkynes was examined.[9] In the presence of a Pd catalyst, the reaction of **1a** with 1-hexyne took place to provide the desired fluoroenynes **2a** along with a significant amount of *p*-tolylhexyne (**3**) (Eq. (2)).



(2)

Application of hexynylstannane instead of hexyne gave a similar result, and the formation of **3** could not be suppressed.[10] As iodotoluene is formed in the reaction of **1a** with 1-hexyne and the cross-coupling reaction of iodotoluene with 1-hexyne proceeds under mild conditions,[11] the formation of **3** is unavoidable as long as **1a** is used. Therefore, we converted **1a** to (*E*)-2-fluoro-1-iodo-1-alkenes (**4a**)[6] (Eq. (3)) and examined the cross-coupling reaction with 1-hexyne (Table 1).



(3)

When 8 mol% of CuI to **4a** was used, a significant amount of the 1-hexyne dimer was formed (entry 1) and 2 equiv. of 1-hexyne was necessary to obtain **2a** in a good yield (entry 2).[12] By using 16 mol% of CuI, the formation of the dimer could be suppressed, and **2a** was obtained in good yield with 1.2 equiv. of 1-hexyne (entries 3–7). The best result was obtained when $Pd(OAc)_2$ and $2PPh_3$ were used as the catalyst, and Et_2NH was used as the solvent (entry 6).

Keywords: coupling reactions; fluorine and compounds; hypervalent elements.

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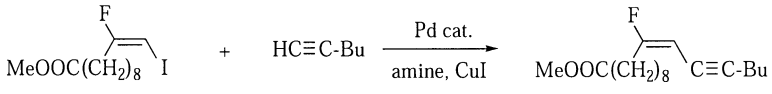
Table 1. Cross-coupling reaction of **4a** with 1-hexyne using various catalysts and amines



4a **2a**

Entry	So1vent	Catalyst	Amine[a]	CuI/**4a**	Hexyne/**4a**	Yield of **2a** (%)[b]
1	DMF	$Pd_2dba_3+4PPh_3$	Et_3N	0.08	1.2	–[c]
2	DMF	$Pd_2dba_3+4PPh_3$	Et_3N	0.08	2	80
3	DMF	$Pd_2dba_3+4PPh_3$	Et_3N	0.16	1.2	80
4	Et_3N	$Pd_2dba_3+4PPh_3$	–	0.16	1.2	80
5	Et_3N	$Pd(OAc)_2+2PPh_3$	–	0.16	1.2	77
6	Et_2NH	$Pd(OAc)_2+2PPh_3$	–	0.16	1.2	85
7	Et_2NH	$Pd_2dba_3+4PPh_3$	–	0.16	1.2	80

[a] 1.5 equiv. of amine to **4a** was used.
[b] Isolated yield based on **4a**.
[c] Most of **4a** remained unchanged.

Table 2. Stereoselective synthesis of (*E*)-(2-fluoroalkenyl)alkynes

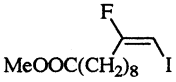
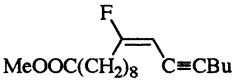
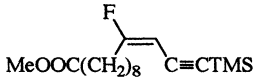
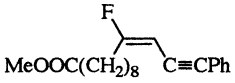
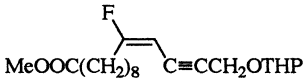
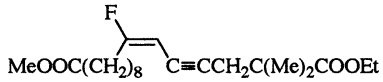
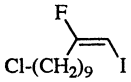
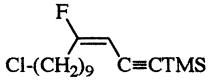
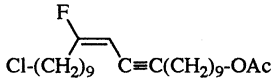
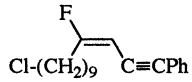
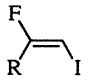
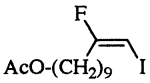
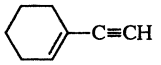
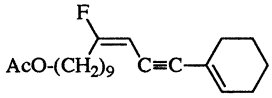
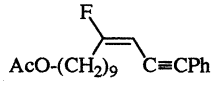
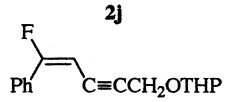
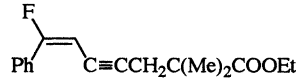
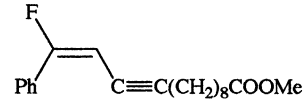
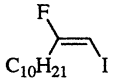
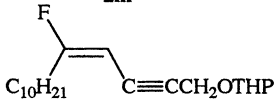
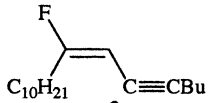
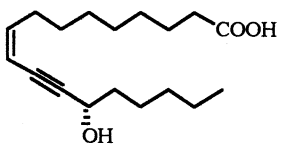
Entry		Alkyne	Product	Yield (%)[a]
1	 **4a**	BuC≡CH	 **2a**	85
2	**4a**	TMSC≡CH	 **2b**	80
3	**4a**	PhC≡CH	 **2c**	84
4	**4a**	$THPOCH_2C\equiv CH$	 **2d**	88
5	**4a**	$EtOOCC(CH_3)_2CH_2C\equiv CH$	 **2e**	77
6	 **4b**	TMSC≡CH	 **2f**	92
7	**4b**	$AcO\text{-}(CH_2)_9C\equiv CH$	 **2g**	78
8	**4b**	PhC≡CH	 **2h**	84

Table 2. (*continued*)

Entry		Alkyne	Product	Yield (%)[a]
9	 **4c**		 **2i**	78
10	**4c**	PhC≡CH	 **2j**	84
11	 **4d**	$THPOCH_2C{\equiv}CH$	 **2k**	85
12	**4d**	$EtOOCC(CH_3)_2CH_2C{\equiv}CH$	 **2l**	67
13*	**4d**	$MeOOC(CH_2)_8C{\equiv}CH$	 **2m**	90
14	 **4e**	$THPOCH_2C{\equiv}CH$	 **2n**	90
15	**4e**	BuC≡CH	 **2o**	78

If not otherwise mentioned, the reaction was carried out at room temperature for 12 h.
* Entry 13: The reaction was carried out at room temperature for 2.5 days.
[a] Isolated yield based on **4a**.

Under these reaction conditions, various 1-fluoro-1,3-enynes **2** could be stereoselectively prepared (>98%) from fluoroalkenyliodides **4** and 1-alkynes as shown in Table 2. As both the preparation of **4** and the cross-coupling reaction proceed under mild condtions, the introduction of various functional groups into **2** is possible. In order to show the usefulness of our method, the fluorinated analog of a biologically active compound was synthesized. Recently, an 11,12-dehydrocoriolic acid (**5**) was found to have stronger inhibitory activity than the natural coriolic acid against rice blast fungus.[13] We planned to synthesize the fluorinated analog of the dehydrocoriolic acid using our method. The reaction of methyl (*E*)-10-iodo-9-fluoro-9-decenoate (**7**), prepared from methyl 9-decynoate, with 1-octyn-3-ol (**8**)



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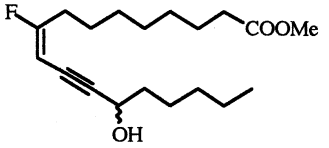
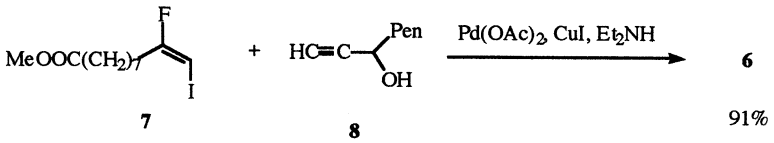


6



7 **8**

Scheme 1.

was carried out in the presence of a Pd catalyst and CuI to provide the (±)-9-fluorodehydrocoriolic acid methyl ester (**6**) in 91% yield directly (Scheme 1).

3. Conclusion

The stereoselective synthesis of (*E*)-1-fluoro-1,3-enynes was carried out by the cross-coupling reaction of 1-alkynes with (β-fluoroalkenyl)iodides obtained from (β-fluoroalkenyl)iodonium salts. As the reaction proceeds under mild conditions, polyfunctionalized 1-fluoro-1,3-enynes could be prepared. We also applied our method to the synthesis of a fluorinated analog of a natural compound.

4. Experimental

4.1. General

The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shift, δ, are referred to TMS (^{1}H) and $CFCl_3$ (^{19}F), respectively. The EI-low and high-resolution mass spectra were measured on a JEOL JMS-700TZ, JMS-FABmate or JMS-HX110. The elemental micro-analyses were done using a Yanagimoto CHN Corder MT-5. The Et_3N–5HF was prepared by the addition of freshly distilled Et_3N to anhydrous HF in Teflon™ PFA vessel at 0°C,[14] and can be kept in a Teflon™ PFA vessel. It is less corrosive and has a higher boiling point than anhydrous HF itself, but should be used in a bench hood with Teflon™ PFA apparatus. (Trimethylsilyl)acetylene, $Pd(OAc)_2$, Pd_2dba_3, PPh_3, 1-hexyne, phenylacetylene, and 1-ethynylcyclohexenol were purchased from Tokyo Kasei Co. Ltd. Propargyl alcohol, 10-undecynoic acid, and 10-undecyn-1-ol were also purchased from Tokyo Kasei Co. Ltd. and converted to the corresponding THP ether, methyl ester, and acetate, respectively. 1-Ethynylcyclohexene,[15] 11-chloro-1-dodecyne,[15] 1-octyn-3-ol,[15] and methyl 9-decynoate[16] were prepared from 1-ethynylcyclohexenol, 10-undecyn-1-ol, hexanal, and 9-decenoic acid, respectively, according to the literature. Ethyl 2,2-dimethyl-4-pentynoate was prepared from ethyl isobutyrate and propargyl bromide.[17]

4.1.1. Methyl (*E*)-11-iodo-10-fluoro-10-undecenoate (4a). *p*-Iodotoluene difluoride was prepared from iodotoluene by an electrochemical method in a divided cell made of Teflon™ PFA (25 ml×2) with a Nafion™ 117 cation exchange membrane. Each cell was equipped with a smooth platinum electrode (20×20 mm) and a magnetic stirrer bar. Et_3N–5HF (22 ml) was introduced into both cells, and *p*-iodotoluene (654 mg, 3 mmol) was added to the anodic cell. By passing 2 $Fmol^{-1}$ of electricity at a constant current (50 mA h^{-1}) at room temperature, the reaction was completed. The resulting Et_3N–5HF solution of *p*-iodotoluene difluoride was added at 0°C to a CH_2Cl_2 (6 ml) solution of methyl 10-undecynoate (392 mg, 2 mmol) in a reaction vessel made of Teflon™ PFA. After stirring for 1 h at 0°C, the mixture was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated under reduced pressure to give the crude (*E*)-(2-fluoro-10-methoxycarbonyl-1-decenyl)(4-methylphenyl)iodonium fluoride (**1a**), which was dissolved in CH_2Cl_2 (25 ml), and CuI (3.81 g, 20 mmol) and KI (3.32 g, 20 mmol) were then added. The reaction mixture was stirred at room temperature for 3 d and then extracted with CH_2Cl_2. The compound **4a** was isolated by column chromatography (silica gel/hexane–ether) in 80% yield as a pale yellow oil: IR (neat): 1735 (C=O), 1645 (C=C) cm^{-1}. ^{1}H NMR δ=5.67 (1H, d, *J*=17.8 Hz), 3.67 (3H, s), 2.50 (2H, dt, *J*=22.5, 7.3 Hz), 2.31 (2H, t, *J*=7.3 Hz), 1.64–1.51 (4H, m), 1.39–1.28 (8H, brs). ^{19}F NMR δ=−82.36 (1F, dt, *J*=17.8, 22.5 Hz). HRMS (EI) Calcd for $C_{11}H_{17}FIO$ (M^+−OMe) 300.0308, Found 300.0321.

4.1.2. (*E*)-11-Chloro-2-fluoro-1-iodo-1-undecene (4b). Pale yellow oil: IR (neat): 1649 (C=C) cm^{-1}. ^{1}H NMR δ=5.67 (1H, d, *J*=17.8 Hz), 3.53 (2H, t, *J*=6.6 Hz), 2.50 (2H, dt, *J*=22.4, 7.3 Hz), 1.81–1.73 (2H, m), 1.59–1.52 (2H, m), 1.44–1.30 (10H, m). ^{19}F NMR δ=−82.35 (1F, dt, *J*=17.8, 22.4 Hz). HRMS (EI) Calcd for $C_{11}H_{19}ClFI$ 332.0204, Found 332.0204.

4.1.3. (*E*)-11-Acetoxy-2-fluoro-1-iodo-1-undecene (4c). Pale yellow oil: IR (neat): 1740 (C=O), 1649 (C=C) cm^{-1}. ^{1}H NMR δ=5.67 (1H, d, *J*=17.8 Hz), 4.05 (2H, t, *J*=6.8 Hz), 2.50 (2H, dt, *J*=22.7, 7.3 Hz), 2.05 (3H, s), 1.64–1.53 (4H, m), 1.39–1.28 (10H, m). ^{19}F NMR δ=−82.48 (1F, dt, *J*=17.8, 22.7 Hz). HRMS (EI) Calcd for $C_{13}H_{22}IO_2$ (M^+−F) 337.0649, Found 337.0665.

4.1.4. (*E*)-1-Fluoro-1-phenyl-2-iodoethene (4d). Pale yellow oil: IR (neat): 1637 (C=C) cm^{-1}. ^{1}H NMR δ=7.81–7.78 (2H, m), 7.43–7.41 (3H, m), 6.14 (1H, d, *J*=19.5 Hz). ^{19}F NMR δ=−76.58 (1F, d, *J*=19.5 Hz). HRMS (EI) Calcd for C_8H_6FI 247.9498, Found 247.9523.

4.1.5. (*E*)-2-Fluoro-1-iodo-1-dodecene (4e). Pale yellow oil: IR (neat): 1645 (C=C) cm^{-1}. ^{1}H NMR δ=5.63 (1H, d, *J*=17.7 Hz), 2.46 (2H, dt, *J*=23.0, 7.6 Hz), 1.56–1.44 (2H, m), 1.32–1.20 (14H, m), 0.85 (3H, t, *J*=6.5 Hz). ^{19}F NMR δ=−82.25 (1F, dt, *J*=17.7, 23.0 Hz). HRMS (EI) Calcd for $C_{12}H_{22}FI$ 312.0750, Found 312.0742.

4.2. Cross-coupling reaction of 1-hexyne with (*E*)-(2-fluoro-10-methoxycarbonyl-1-decenyl)(4-methylphenyl)iodonium fluoride (1a)

A mixture of PPh_3 (26 mg, 0.1 mmol) and $Pd(OAc)_2$ (11 mg, 0.05 mmol) in DMF (10 ml) was stirred at room temperature under an atmosphere of nitrogen for 10 min. To the reaction mixture, 1-hexyne (98 mg, 1.2 mmol), **1a** prepared from methyl 10-undecynoate (196 mg, 1 mmol), Et_3N (150 mg, 1.5 mmol), and CuI (15 mg, 0.08 mmol) were successively added. The mixture was stirred at room temperature overnight and then poured into an aqueous NH_4Cl solution. The mixture was extracted with ether and the organic phase was dried over $MgSO_4$. Purification by column chromatography (silica gel/hexane–ether) gave **2a** in 59% yield with 41% of **3**.

4.3. Cross-coupling reaction of 1-alkyne with 2-fluoro-1-iodo-1-alkene (4)

4.3.1. Methyl (*E*)-10-fluoro-10-heptadecen-12-ynoate (2a). A mixture of **4a** (342 mg, 1 mmol), PPh_3 (26.2 mg, 0.1 mmol), $Pd(OAc)_2$ (11.3 mg, 0.05 mmol), CuI (32 mg, 0.16 mmol), 1-hexyne (98 mg, 1.2 mmol) in Et_2NH (10 ml) was stirred overnight at room temperature under an atmosphere of nitrogen. The reaction mixture was poured into an aqueous NH_4Cl solution and extracted with ether. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel/hexane–ether) gave **2a** in 85% yield as a pale yellow oil: IR (neat): 1741 (C=O) cm^{-1}. ^1H NMR δ=5.16 (1H, dt, J=14.0, 2.2 Hz), 3.67 (3H, s), 2.43 (2H, dt, J=22.0, 7.3 Hz), 2.31 (2H, t, J=7.3 Hz), 1.64–1.32 (18H, m), 0.92 (3H, t, J=7.3 Hz). ^{19}F NMR δ=−98.65 (1F, dt, J=14.0, 22.0 Hz). HRMS (EI) Calcd for $C_{18}H_{29}FO_2$ 296.2151, Found 296.2146.

4.3.2. Methyl (*E*)-10-fluoro-13-(trimethylsilyl)-10-tridecen-12-ynoate (2b). Pale yellow oil: IR (neat): 2142 (C≡C), 1742 (C=O) cm^{-1}. ^1H NMR δ=5.21 (1H, d, J=14.2 Hz), 3.67 (3H, s), 2.47 (2H, dt, J=22.0, 7.3 Hz), 2.31 (2H, t, J=7.6 Hz), 1.64–1.53 (4H, m), 1.32 (8H, brs), 0.18 (9H, s). ^{19}F NMR δ=−92.74 (1F, dt, J=14.2, 22.0 Hz). HRMS (EI) Calcd for $C_{17}H_{29}FO_2Si$ 312.1921, Found 312.1927.

4.3.3. Methyl (*E*)-10-fluoro-13-phenyl-10-tridecen-12-ynoate (2c). Pale yellow oil: IR (neat): 2209 (C≡C), 1739 (C=O) cm^{-1}. ^1H NMR δ=7.42–7.39 (2H, m), 7.33–7.30 (3H, m), 5.41 (1H, d, J=13.9 Hz), 3.66 (3H, s), 2.54 (2H, dt, J=22.0, 7.4 Hz), 2.28 (2H, t, J=7.6 Hz), 1.62–1.55 (4H, m), 1.38–1.31 (8H, m). ^{19}F NMR δ=−93.34 (1F, dt, J=13.9, 22.0 Hz). HRMS (EI) Calcd for $C_{20}H_{25}FO_2$ 316.1838, Found 316.1844.

4.3.4. Methyl (*E*)-10-fluoro-14-(2-tetrahydropyranyloxy)-10-tetradecen-12-ynoate (2d). Pale yellow oil: IR (neat): 2220 (C≡C), 1740 (C=O) cm^{-1}. ^1H NMR δ=5.22 (1H, dt, J=13.9, 2.2 Hz), 4.82 (1H, t, J=3.4 Hz), 4.44–4.33 (2H, m), 3.88–3.82 (1H, m), 3.67 (3H, s), 3.56–3.45 (1H, m), 2.45 (2H, dt, J=21.9, 7.3 Hz), 2.30 (2H, t, J=7.6 Hz), 1.87–1.53 (10H, m), 1.31 (8H, brs). ^{19}F NMR δ=−93.50 (1F, dt, J=13.9, 21.9 Hz). HRMS (EI) Calcd for $C_{20}H_{31}FO_4$ 354.2206, Found 354.2203.

4.3.5. Ethyl (*E*)-7-fluoro-15-methoxycarbonyl-2,2-dimethyl-6-pentadecen-4-ynoate (2e). Pale yellow oil: IR (neat): 1735 (C=O) cm^{-1}. ^1H NMR δ=5.16 (1H, dt, J=13.9, 2.2 Hz), 4.14 (2H, q, J=7.1 Hz), 3.67 (3H, s), 2.56 (2H, s), 2.42 (2H, dt, J=22.2, 7.6 Hz), 2.30 (2H, t, J=7.6 Hz), 1.64–1.52 (4H, m), 1.31–1.24 (17H, m). ^{19}F NMR δ=−96.62 (1F, dt, J=13.9, 22.2 Hz). HRMS (EI) Calcd for $C_{21}H_{33}FO_4$ 368.2363, Found 368.2356.

4.3.6. (*E*)-13-Chloro-4-fluoro-1-(trimethylsilyl)-3-tridecen-1-yne (2f). Pale yellow oil: IR (neat): 2142 (C≡C), 1656 (C=C) cm^{-1}. ^1H NMR δ=5.21 (1H, d, J=13.9 Hz), 3.53 (2H, t, J=6.6 Hz), 2.48 (2H, dt, J=21.4, 7.3 Hz), 1.81–1.74 (2H, m), 1.61–1.32 (12H, m), 0.19 (9H, s). ^{19}F NMR δ=−92.71 (1F, dt, J=13.9, 21.4 Hz). Anal. C, 63.44; H, 9.32. Found: C, 63.68; H, 9.22.

4.3.7. (*E*)-1-Acetoxy-22-chloro-13-fluoro-12-docosen-10-yne (2g). Pale yellow oil: IR (neat): 1741 (C=O), 1239 (C–OR) cm^{-1}. ^1H NMR δ=5.16 (1H, dt, J=14.4, 2.2 Hz), 4.05 (2H, t, J=6.8 Hz), 3.53 (2H, t, J=6.8 Hz), 2.44 (2H, dt, J=22.2, 7.4 Hz), 2.30 (2H, t, J=6.8Hz), 2.04 (3H, s), 1.80–1.73 (2H, m), 1.65–1.31 (26H, m). ^{19}F NMR δ=−97.67 (1F, dt, J=14.4, 22.2 Hz). HRMS (EI) Calcd for $C_{24}H_{40}ClFO_2$ 414.2701, Found 414.2715.

4.3.8. (*E*)-13-Chloro-4-fluoro-1-phenyl-3-tridecen-1-yne (2h). Pale yellow oil: IR (neat): 2207 (C≡C), 1489 (C=C) cm^{-1}. ^1H NMR δ=7.42–7.39 (2H, m), 7.33–7.29 (3H, m), 5.41 (1H, d, J=13.9 Hz), 2.54 (2H, dt, J=22.0, 7.3 Hz), 2.43 (2H, t, J=7.3 Hz), 1.64–1.49 (2H, m), 1.36–1.21 (2H, m), 1.11 (10H, brs). ^{19}F NMR δ=−93.32 (1F, dt, J=13.9, 22.0 Hz). HRMS (EI) Calcd for $C_{19}H_{24}ClF$ 306.1551, Found 306.1542.

4.3.9. (*E*)-1-Acetoxy-10-fluoro-13-(1-cyclohexenyl)-10-tridecen-12-yne (2i). Pale yellow oil: IR (neat): 1741 (C=O), 1238 (C–OR) cm^{-1}. ^1H NMR δ=6.05–6.07 (1H, m), 5.30 (1H, d, J=14.2 Hz), 4.05 (2H, t, J=6.8 Hz), 2.46 (2H, dt, J=21.9, 7.3 Hz), 2.13–2.10 (4H, m), 2.04 (3H, s), 1.67–1.53 (8H, m), 1.31 (10H, brs). ^{19}F NMR δ=−95.41 (1F, dt, J=14.2, 21.9 Hz). HRMS (EI) Calcd for $C_{21}H_{31}FO_2$ 334.2308, Found 334.2324.

4.3.10. (*E*)-1-Acetoxy-10-fluoro-13-phenyl-10-tridecen-12-yne (2j). Pale yellow oil: IR (neat): 1739 (C=O), 1240 (C–OR) cm^{-1}. ^1H NMR δ=7.42–7.39 (2H, m), 7.33–7.26 (3H, m), 5.41 (1H, d, J=13.9 Hz), 4.03 (2H, t, J=6.8 Hz), 2.55 (2H, dt, J=21.9, 7.3 Hz), 2.03 (3H, s), 1.68–1.56 (4H, m), 1.38–1.30 (10H, m). ^{19}F NMR δ=−93.29 (1F, dt, J=13.9, 21.9 Hz). HRMS (EI) Calcd for $C_{21}H_{27}FO_2$ 330.1995, Found 330.1991.

4.3.11. (*E*)-1-Fluoro-1-phenyl-5-(2-tetrahydropyranyloxy)-1-penten-3-yne (2k). Pale yellow oil: IR (neat): 2216 (C≡C) cm^{-1}. ^1H NMR δ=8.01–7.98 (2H, m), 7.43–7.33 (3H, m), 5.62 (1H, dt, J=2.4, 17.6 Hz), 4.85 (1H, t, J=3.6 Hz), 4.51–4.41 (2H, m), 3.89–3.83 (1H, m), 3.56–3.53 (1H, m), 1.89–1.51 (m, 6H). ^{19}F NMR δ=−102.19 (1F, d, J=17.6 Hz). HRMS (EI) Calcd for $C_{16}H_{17}FO_2$ 260.1212, Found 260.1206.

4.3.12. Ethyl (*E*)-7-fluoro-2,2-dimethyl-7-phenyl-6-hepten-4-ynoate (2l). Pale yellow oil: IR (neat): 1731 (C=O) cm^{-1}. ^1H NMR δ=8.02–7.98 (2H, m), 7.42–7.38 (3H, m), 5.59 (1H, dt, J=18.1, 2.7 Hz), 4.14 (2H, q, J=7.2 Hz), 2.66 (2H, s), 1.30 (6H, s), 1.23 (3H, t, J=7.2 Hz). ^{19}F NMR δ=−105.34 (1F, d, J=18.1 Hz). HRMS (EI) Calcd for $C_{17}H_{19}FO_2$ 274.1369, Found 274.1397.

4.3.13. Methyl (*E*)-13-fluoro-13-phenyl-12-tridecen-10-ynoate (2m). Pale yellow oil: IR (neat): 2215 (C≡C), 1739 (C=O) cm^{-1}. ^1H NMR δ=8.03–8.01 (2H, m), 7.42–7.38 (3H, m), 5.59 (1H, dt, J=18.3, 2.4 Hz), 3.66 (3H, s), 2.38–2.42 (2H, m), 2.29 (2H, t, J=7.6 Hz), 1.63–1.54 (4H, m), 1.42–1.40 (2H, m), 1.31 (6H, brs). ^{19}F NMR

δ=−106.34 (1F, d, J=18.3 Hz). HRMS (EI) Calcd for $C_{20}H_{25}FO_2$ 316.1838, Found 316.1824.

4.3.14. (*E*)-5-Fluoro-1-(2-tetrahydropyranyloxy)-4-pentadecen-2-yne (2n). pale yellow oil: IR (neat): 2220 (C≡C), 1664 (C=C) cm^{-1}. ^1H NMR δ=5.21 (1H, dt, J=14.0, 2.4 Hz), 4.82 (1H, t, J=3.4 Hz), 4.44–4.33 (2H, m), 3.88–3.83 (1H, m), 3.56–3.45 (1H, m), 2.46 (2H, dt, J=22.0, 7.3 Hz), 1.88–1.52 (8H, m), 1.31–1.20 (14H, m), 0.88 (3H, t, J=6.6 Hz). ^{19}F NMR δ=−93.47 (1F, dt, J=14.0, 22.0 Hz). HRMS (EI) Calcd for $C_{20}H_{33}FO_2$ 324.2464, Found 324.2451.

4.3.15. (*E*)-8-Fluoro-7-octadecen-5-yne (2o). Pale yellow oil: IR (neat): 2227 (C≡C), 1666 (C=C) cm^{-1}. ^1H NMR δ=5.16 (1H, dt, J=14.6, 2.2 Hz), 2.43 (2H, dt, J=22.0, 7.3 Hz), 2.29–2.32 (2H, m), 1.69–1.19 (20H, m), 0.92 (3H, t, J=7.1 Hz), 0.88 (3H, t, J=7.1 Hz). ^{19}F NMR δ=−97.66 (1F, dt, J=14.6, 22.0 Hz). HRMS (EI) Calcd for $C_{18}H_{31}F$ 266.2410, Found 266.2408.

4.3.16. Methyl (*E*)-9-fluoro-10-iodo-9-decenoate (7). Pale yellow oil: IR (neat): 1739 (C=O), 1650 (C=C) cm^{-1}. ^1H NMR δ=5.69 (1H, d, J=17.8 Hz), 3.67 (3H, s), 2.50 (2H, dt, J=22.4, 7.3 Hz), 2.31 (2H, t, J=7.6 Hz), 1.65–1.51 (4H, m), 1.38–1.21 (6H, brs). ^{19}F NMR δ=−82.53 (1F, dt, J=17.8, 22.4 Hz). HRMS (EI) Calcd for $C_{10}H_{15}FIO$ (M^+−OMe) 297.0152, Found 297.0162.

4.3.17. (*E*)-9-Fluoro-11,12-dehydrocoriolic acid methyl ester (6). Pale yellow oil: IR (neat): 3436 (C–OH), 2219 (C≡C), 1731 (C=O) cm^{-1}. ^1H NMR δ=5.21 (1H, dd, J=14.1, 2.0 Hz), 4.49 (1H, dt, J=1.4, 6.6 Hz), 3.67 (3H, s), 2.45 (2H, dt, J=22.2, 7.1 Hz), 2.38 (1H, brs), 2.31 (2H, t, J=7.6 Hz), 1.73–1.30 (18H, m), 0.90 (3H, t, J=6.8 Hz). ^{19}F NMR δ=−94.20 (1F, dt, J=14.1, 22.2 Hz). HRMS (EI) Calcd for $C_{19}H_{31}FO_3$ 326.2257, Found 326.2258. Anal. C, 69.91; H, 9.57. Found: C, 69.96; H, 9.52.

References

1. Hiyama, T. In *Organofluorine Compounds*; Springer: Berlin, 2000; pp. 137–182. Welch, J. T.; Eswarakrishnan, S. *Fluorine in Bioorganic Chemistry*; Wiley: New York, 1991.
2. Benayound, F.; Chen, L.; Moniz, G. A.; Zapata, A. J.; Hammond, G. B. *Tetrahedron* **1998**, *54*, 15541–15554. Zapata, A. J.; Gu, Y.; Hammond, G. B. *J. Org. Chem.* **2000**, *65*, 227–234.
3. (a) Yang, Z.-Y.; Burton, D. J. *Tetrahedron Lett.* **1990**, *31*, 1369–1372. (b) Yang, Z.-Y.; Burton, D. J. *J. Fluorine Chem.* **1991**, *53*, 307–326. (c) Ichikawa, J.; Ikeura, C.; Minamai, T. *J. Fluorine Chem.* **1993**, *63*, 281–285. (d) Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Tetrahedron Lett.* **1990**, *31*, 4449–4452. (e) Percy, J. M.; Wilkes, R. D. *Tetrahedron* **1997**, *53*, 14749–14762.
4. Eddarir, S.; Francesch, C.; Mestdagh, H.; Rolando, C. *Bull. Soc. Chim. Fr.* **1997**, *134*, 741–755.
5. Quite recently, Yamamoto et al. reported the stereoselective synthesis of (*Z*)-1-fluoro-1,3-enynes having perfluoroalkyl group, see: Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 796–802.
6. Hara, S.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Chem. Commun.* **1998**, 965–966.
7. Hara, S.; Yamamoto, K.; Yoshida, M.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **1999**, *40*, 7815–7818.
8. Yoshida, M.; Hara, S.; Fukuhara, T.; Yoneda, N. *Tetrahedron Lett.* **2000**, *41*, 3887–3890.
9. Radhakrishnan, U.; Stang, P. J. *Org. Lett.* **2001**, *3*, 859–860.
10. Hinkle, R. J.; Poulter, G. T.; Stang, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 11626–11627. Stang, P. J.; Blume, T.; Zhdankin, V. V. *Synthesis* **1993**, 35–36. Ryan, J. H.; Stang, P. J. *J. Org. Chem.* **1996**, *61*, 6162–6165.
11. Sonogashira, K. *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 3, pp. 521–549.
12. Hay, A. S. *J. Org. Chem.* **1962**, *27*, 3320–3321.
13. Kobayashi, Y.; Okamoto, S.; Shimazaki, T.; Ochiai, Y.; Sato, F. *Tetrahedron Lett.* **1987**, *28*, 3959–3962.
14. Chen, S.-Q.; Hatakeyama, T.; Fukuhara, T.; Hara, S.; Yoneda, N. *Electrochim. Acta* **1997**, *42*, 1951–1960.
15. Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: Amsterdam, 1971.
16. Khan, N. A. *Organic Syntheses Collected Volume IV*; 1963; pp. 969–972.
17. Cregge, R. J.; Herrmann, J. L.; Lee, C. S.; Richman, J. E.; Schlessinger, R. H. *Tetrahedron Lett.* **1973**, *14*, 2425–2428.