Stereoselective synthesis of insect sex pheromone analogs having a fluorine atom on their double bonds

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Abstract

Insect sex pheromone analogs having a fluorine atom on their double bonds, (9*E*,11*E*)-1-acetoxy-9-fluorotetradecadiene, (10*E*,12*E*)-13-fluorohexadecadien-1-ol, (9*Z*,11*E*)-1-acetoxy-9-fluorotetradecadiene, (10*E*,12*Z*)-13-fluorohexadecadien-1-ol were stereoselectively synthesized using cross-coupling reactions of alkenylboranes with (*E*)- or (*Z*)-2-fluoro-1-iodo-1-alkenes, stereoselectively prepared from 1-alkynes by our currently developed methods.

Keywords: Pheromone analogs, Fluorine, Conjugated diene, Cross-coupling reaction;

1. Introduction

Incorporation of fluorine atoms into bioactive compounds has been shown to mimic or inhibit the action of the parent compounds [1,2]. In this context, substitution of fluorine atoms for hydrogen in insect sex pheromones could be expected to disturb the perception of the natural pheromone by competitive binding of the fluorinated analogs with specific pheromone receptors, eventually leading to disruption of the mating communication system. Furthermore, the above substitution could increase the thermal and oxidative stability of the parent compounds, which might be of potential

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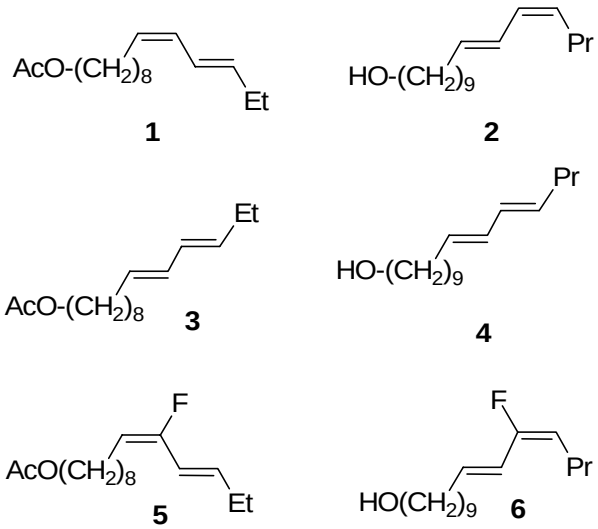
interest in field trials [3].

Many fluorinated analogs of insect pheromones have been synthesized and applied to field tests [3]. However, only a few analogs having a fluorine atom on their double bond have been reported [4-6].

(9*Z*,11*E*)-1-Acetoxytetradecadiene (**1**) [7] and (10*E*,12*Z*)-hexadecadien-1-ol (**2**) [8], having a conjugated (*Z*,*E*)-diene part, are known as insect sex pheromones of the Egyptian cotton leaf worm, *Spodoptera-Littorails*-Boisd, and silkworm moth, *Bombyx mori*, respectively. On the other hand, (9*E*,11*E*)-1-acetoxytetradecadiene (**3**) [9] and (10*E*,12*E*)-hexadecadien-1-ol (**4**) [10], having a conjugated (*E*,*E*)-diene part, are also known as insect sex pheromones of the light brown apple moth, *Epiphyas postvittana*, and legume podborer, *Maruca vitrata*, respectively. As for their analogs having a fluorine atom on their double bond, (9*E*,11*E*)-1-acetoxy-10-fluorotetradecadiene (**5**) and (10*E*,12*E*)-12-fluorohexadecadien-1-ol (**6**), a fluorinated analog of **1** and **2**, respectively, were previously synthesized [4] (Scheme 1).



Scheme 1

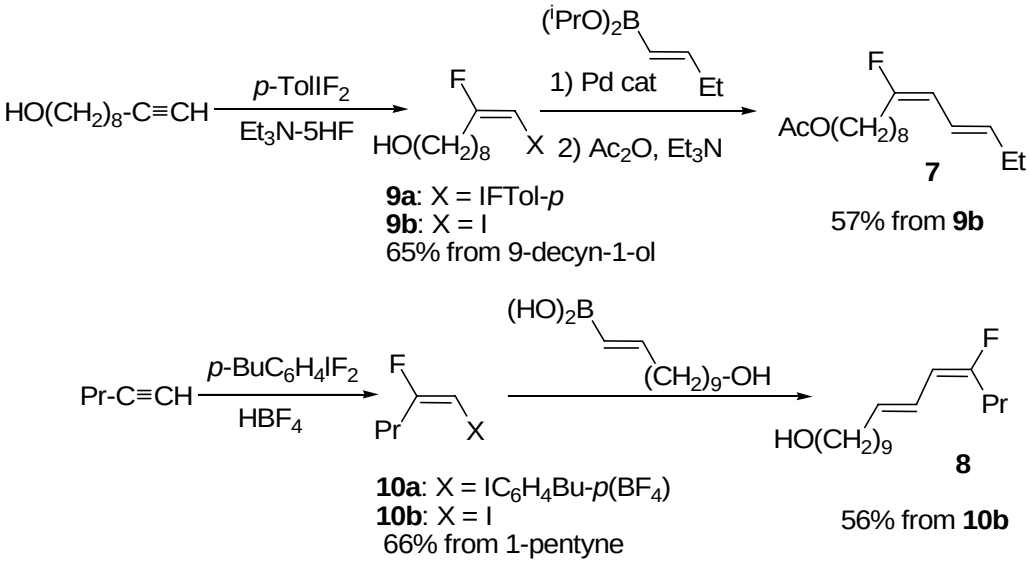
However, the fluorine atom always came to an inner position of the diene

function, because Wittig reaction with (*E*)- or (*Z*)-α-fluoro-α,β-unsaturated aldehydes was used for their synthesis. Quite recently, we succeeded in stereoselectively synthesizing both (*E*)-2-fluoro-1-iodo-1-alkenes [11,12] and (*Z*)-2-fluoro-1-iodo-1-alkenes [13] from 1-alkynes using hypervalent iodine compounds, and applied them to the synthesis of various fluoroalkadienes by a cross-coupling reaction with alkenylboranes [14]. We wish to report here an application of our method for the synthesis of insect sex pheromone analogs having a fluorine atom at the outer position of the diene functions, which were difficult to synthesize by the previous methods.

2. Results and Discussion

We initially synthesized (9*E*,11*E*)-1-acetoxy-9-fluorotetradecadiene (**7**) and (10*E*,12*E*)-13-fluorohexadcadien-1-ol (**8**) which are fluorinated analogs of **1** and **2**, respectively, by the cross-coupling reaction of (*E*)-9-fluoro-10-iodo-9-decen-1-ol (**9b**) with (*E*)-(1-butenyl)diisopropoxyborane, or (*E*)-2-fluoro-1-iodo-1-pentene (**10b**) with (*E*)-(11-hydroxy-1-undecenyl)boronic acid, respectively. The (*E*)-9-fluoro-10-iodo-9-decen-1-ol **9b** was prepared from 9-decyn-1-ol in 65% overall yield. The 9-decyn-1-ol was converted to (*E*)-10-hydoxy-2-fluoro-1-decenyliodonium fluoride (**9a**) by the reaction with Et_3N-5HF and *p*-iodotoluene difluoride (ITDF), electrochemically prepared from *p*-iodotoluene [11], and the resulting **9a,** without isolation, was converted to **9b** by the reaction with CuI and KI [11,15,16]. The cross-coupling reaction of (*E*)-(1-butenyl)diisopropoxyborane with **9b** using $Pd(PPh_3)_4$ as a catalyst was sluggish and a significant amount of a head-to-tail coupling by-product

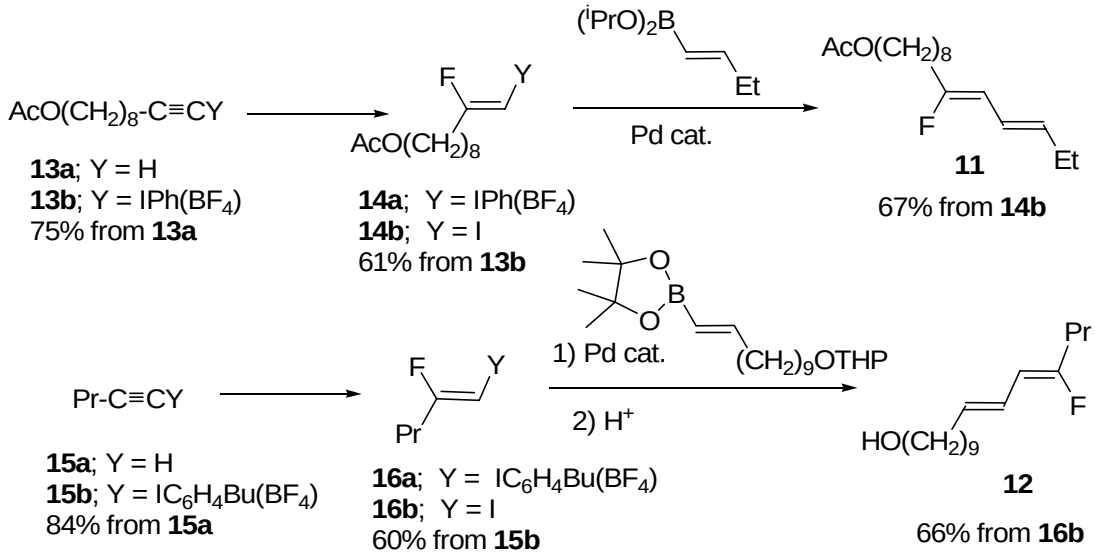
was formed as well as a normal coupling product [17]. This problem could be overcome by using $Pd(OAc)_2$-BINAP as catalyst and the desired **7** could be obtained in 57% yield from **9b** after acetylation of the hydoxyl group (Scheme 2). (*E*)-2-Fluoro-1-iodo-1-pentene (**10b**) was prepared from 1-pentyne in two steps by using *p*-iodo(butylbenzene) difluoride instead of ITDF because the separation of **10b** and iodotoluene, generated from ITDF, was difficult by both column chromatography and distillation. The cross-coupling reaction of **10b** with (*E*)-(11-hydroxy-1-undecenyl)boronic acid using $Pd(OAc)_2$-BINAP gave **8** in 56% yield. The coupling constant between F and H on the same double bond in **7** and **8** was 20.5-21.4 Hz which shows the stereochemistry of the F and H is *cis*, and that of the fluorine substituted double bond is *E* [18]. On the other hand, the coupling constant between two hydrogens on the other double bonds was 14.4-14.9 Hz which shows that the stereochemistry of the double bond is also *E* [19]. Therefore, the stereochemistry of the conjugated double bonds in **7** and **8** was shown to be (*E*,*E*).



Scheme 2

(9*Z*,11*E*)-1-Acetoxy-9-fluorotetradecadiene (**11**) and (10*E*,12*Z*)-13-fluorohexadecadien-1-ol (**12**), which are fluorinated analogs of **3** and **4**, were synthesized by the cross-coupling reactions of (*Z*)-1-acetoxy-9-fluoro-10-iodo-9-decene (**14b**) with (*E*)-(1-butenyl)diisopropoxyborane, or (*Z*)-2-fluoro-1-iodo-1-pentene (**16b**) with (*E*)-11-[(2-tetrahydropyranyloxy)-1-undecenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, respectively. The (*Z*)-1-acetoxy-9-fluoro-10-iodo-9-decene **14b** was stereoselectively synthesized from 1-acetoxy-9-decyne (**13a**) in three steps. The alkynyliodonium salt (**13b**) was directly prepared from **13a** in 75% yield by the reaction with iodosylbenzene and a catalytic amount of HgO [20]. The (*Z*)-fluoroiodoalkene **14b** could be obtained in 61% overall yield from **13b** without isolation of the (*Z*)-2-fluoro-1-alkenyliodonium salt (**14a**) by the treatment with 20% aq HF [13], followed by reaction with KI and CuI [13,15,16]. The palladium-catalyzed cross-coupling reaction of **14b** with (*E*)-(1-butenyl)diisopropoxyborane proceeded faster than that with **9b**, and **11** could be obtained in 67% yield by using $Pd(PPh)_4$ as a catalyst. 1-Pentynyliodonium salt (**15b**) was prepared from 1-pentyne with iodosyl(*p*-butylbenzene) instead of iodosylbenzene, and (*Z*)-2-fluoro-1-iodo-1-pentene **16b** was obtained in two steps from **15b** in 60% yield. The cross-coupling reaction of **16b** with (*E*)-11-[(2-tetrahydropyranyloxy)-1-undecenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, and subsequent removal of THP group gave **12** in 66% yield from **16b** (Scheme 3). The coupling constant between F and H on the same double bond was 36.3-36.8 Hz in **11** and **12**, which shows that the H and F occupy the *trans* configuration on the double bond and the stereochemistry of the double bond is *Z* [18]. On the other hand, the coupling constant of two hydrogens on the other double bond was 15.4 Hz which shows

that the double bond has *E* stereochemistry [19].



Scheme 3

3. Experimental

3.1. General methods

The IR spectra were recorded using a JASCO FT/IR-410. The ^{1}H NMR (400 MHz) spectra, ^{13}C NMR (100 MHz), and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ on a JEOL JNM-A400II FT NMR and the chemical shifts, δ, are referred to TMS (^{1}H and ^{13}C), and $CFCl_3$ (^{19}F), respectively. The EI-high-resolution mass spectra were measured on a JEOL JMS-700TZ. $Pd(PPh_3)_4$ was purchased from Tokyo Kasei Chemical. *S*-(-)-BINAP was purchased from Kanto Kagaku Chemical. $Pd(OAc)_2$, 50% HBF_4 in diethyl ether, 42% aq HBF_4, HgO, and $NaBF_4$ were purchased from Wako Pure Chemical Industries, Ltd. 20% aq HF was prepared by dilution of 46% aq HF

purchased from Wako Pure Chemical Industries, Ltd. Et_3N-5HF was prepared from Et_3N and anhydrous HF as described previously [21] but it is now obtainable from Tokyo Kasei Co. Ltd. All HF reagents including Et_3N-5HF should be handled in a bench hood with rubber gloves. (*E*)-(1-Butenyl)diisopropoxyborane [21], (*E*)-(11-hydroxy-1-undecenyl)boronic acid [22], and (*E*)-11-[(2-tetrahydropyranyloxy)-1-undecenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane [23,24] were prepared from the corresponding alkynes according to the literatures. 9-Decyn-1-ol and 10-undecyn-1-ol were prepared from the corresponding alkenes [25]. Iodotoluene difluoride [11], *p*-iodo(butylbenzene) difluoride [26], iodosylbenzene [26], and iodosyl(*p*-butylbenzene) [26] were prepared from the corresponding iodoarenes according to the literatures.

*4.2. Stereoselective synthesis of (9E,11E)-1-acetoxy-9-fluorotetradecadiene (**7**).*

*4.2.1. (E)-9-Fluoro-10-iodo-9-decen-1-ol (**9b**).*

To a CH_2Cl_2 (6 ml) solution of 9-decyn-1-ol (308 mg, 2 mmol) in a reaction vessel made of Teflon™ PFA, was added at 0 °C Et_3N-5HF solution (22 ml) of ITDF, prepared from *p*-iodotoluene (3 mmol) electrochemically [11]. After being stirred for 1 h at 0 °C, the mixture was poured into water (5 ml) and the separated aqueous layer was extracted with CH_2Cl_2 three times, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 ml), and added to a mixture of CuI (3.81 g, 20 mmol) and KI (3.32 g, 20 mmol) in CH_2Cl_2 (20 ml). After being stirred at room temperature for 3 h, the mixture was poured into water (5 ml) and the separated aqueous layer was extracted with CH_2Cl_2 three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.

Compound **9b** was isolated by column chromatography (silica gel / hexane-ether) in 65% yield (390 mg, 1.3 mmol) as a pale yellow oil. IR: (neat) ν 3335, 2929, 1650, 1073 cm^{-1}. ^1H NMR δ 1.25-1.42 (m, 9H), 1.50-1.63 (m, 4H), 2.50 (dt, *J* = 22.7, 7.6 Hz, 2H), 3.65 (t, *J* = 6.8 Hz, 2H,), 5.67 (d, *J* = 17.8 Hz, 1H). ^{19}F NMR δ -82.51 (dt, *J* = 17.8, 22.7 Hz, 1F). ^{13}C NMR δ 25.69 (CH_2, 2C), 28.64 (CH_2), 29.22 (CH_2), 29.24 (CH_2), 30.91 (d, J_{CF} = 26.4 Hz, CH_2CF=), 32.74 (CH_2), 54.75 (d, J_{CF} = 40.5 Hz, CIH=), 63.02 (CH_2O), 164.14 (d, J_{CF} = 264.4 Hz, CF=). HRMS (EI): Calcd for $C_{10}H_{18}FIO$: 300.0386. Found: 300.0370.

*4.2.2. (9E,11E)-1-Acetoxy-9-fluorotetradecadiene (**7**).*

A mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), *S*-(-)-BINAP (15.6 mg, 0.025 mmol), **9b** (150 mg, 0.5 mmol), (*E*)-(1-butenyl)diisopropoxyborane (184 mg, 1.0 mmol), 2 M aq KOH (0.5 ml, 1.0 mmol) in dioxane (3 ml) was stirred under N_2 atmosphere at 70 ºC for 6 h and then poured into aq $NaHCO_3$ (30 ml). The separated aqueous phase was extracted with ether three times, and the combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (3 ml), and to this solution, Ac_2O (122 mg, 1.2 mmol) and Et_3N (121 mg, 1.2 mmol) were added at room temperature. After being stirred for 12 h, the reaction mixture was poured into water (30 ml) and the separated aqueous phase was extracted with ether three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The product **7** was isolated by column chromatography (silica gel; hexane-diethyl ether) in 57% yield (77 mg, 0.28 mmol) from **9b**. IR: (neat) ν 2932, 1741, 1680, 1241 cm^{-1}. ^1H NMR δ 1.01 (t, *J* = 7.6 Hz, 3H), 1.26-1.42 (brs, 8H), 1.50-1.65 (m, 4H), 2.05 (s, 3H), 2.06-2.14 (m, 2H), 2.32 (dt, *J*

= 23.4, 7.3 Hz, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 5.58 (dt, *J* = 14.4, 6.8 Hz, 1H), 5.69 (dd, *J* = 20.5, 11.0 Hz, 1H), 5.90 (dd, *J* = 14.4, 11.0 Hz, 1H). ^{19}F NMR δ -104.78 (dt, *J* = 21.4, 22.6 Hz, 1F). ^{13}C NMR δ 13.69 (*C*H$_3$), 21.02 (*C*H$_2$), 25.87 (*C*H$_2$), 25.99 (*C*H$_2$), 26.32 (*C*H$_2$), 28.36 (d, J_{CF} = 27.3 Hz, *C*H$_2$CF=), 28.58 (*C*H$_2$), 28.83 (*C*H$_2$), 29.12 (*C*H$_2$), 29.20 (*C*H$_2$), 64.60 (*C*H$_2$O), 108.03 (d, J_{CF} = 27.3 Hz, CF=*C*H), 121.88 (d, J_{CF} = 11.5 Hz, =CH-*C*H=CH), 134.85 (d, J_{CF} = 9.0 Hz, =CH-CH=*C*H), 161.37 (d, J_{CF} = 252.0 Hz, *C*F=), 171.23 (*C*=O). HRMS (EI): Calcd for $C_{16}H_{27}FO_2$: 270.1995. Found: 270.1992.

*4.3. (10E,12E)-13-Fluorohexadecadien-1-ol (**8**).*

*4.3.1. (E)-2-Fluoro-1-iodo-1-pentene (**10b**).*

To a CH_2Cl_2 solution (10 ml) of *p*-iodo(butyl)benzene difluoride (894 mg, 3 mmol) was added 50% HBF_4 in diethyl ether (486 mg, 3 mmol) at -78 °C. After being stirred for 5 min, 1-pentyne (136 mg, 2 mol) was added and the mixture was stirred for 5 min at -78 °C. Then the mixture was poured into 5% aq $NaBF_4$ (20 ml) and extracted with CH_2Cl_2 four times. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 ml) and, added to a mixture of CuI (3.81 g, 20 mmol) and KI (3.32 g, 20 mmol) in DMF (5 ml). After being stirred at room temperature for 3 h, the mixture was poured into water (5 ml) and the separated aqueous layer was extracted with CH_2Cl_2 three times. The combined organic phase was dried over $MgSO_4$, carefully concentrated under reduced pressure. The residue was purified by column chromatography (silica gel/pentane-ether) to give a mixture of **10b** and *p*-iodo(butyl)benzene. After careful removal of the solvent under reduced pressure, the mixture was transferred into a distillation flask and the receiver was cooled with a

dry ice-MeOH bath. By keeping the flask under vacuum (0.1 mmHg) at 0 °C, pure **10b** could be collected in the cold trap in 66% yield (281 mg, 1.32 mmol) and *p*-iodo(butyl)benzene remained in the distillation flask.

IR: (neat) ν 2965, 1651, 1122, 1066 cm^{-1}. ^{1}H NMR δ 0.98 (t, *J* = 7.3 Hz, 3H), 1.55-1.64 (m, 2H), 2.49 (dt, *J* = 22.4, 7.3 Hz, 2H), 5.69 (d, *J* = 17.8 Hz, 1H). ^{19}F NMR δ -82.40 (dt, *J* = 22.4, 17.8 Hz, 1F). ^{13}C NMR δ 13.30 (*C*H_2), 19.24 (*C*H_2), 32.79 (d, J_{CF} = 25.6 Hz, *C*H_2CF=), 54.65 (d, J_{CF} = 39.7 Hz, *C*HI=), 163.98 (d, J_{CF} = 264.7 Hz, *C*F=). HRMS (EI): Calcd for C_5H_8FI: 213.9655. Found: 213.9657.

*4.3.2. (10E,12E)-13-Fluorohexadecadien-1-ol (**8**).*

Under N_2 atmosphere, a mixture of $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), *S*-(-)-BINAP (15.6 mg, 0.025 mmol), **10b** (107 mg, 0.5 mmol), (*E*)-(11-hydroxy-1-undecenyl)boronic acid (214 mg, 1.0 mmol), 2 M aq KOH (0.5 ml, 1.0 mmol) and EtOH (1 ml) in benzene (5 ml) was stirred under reflux for 2 h, and then poured into aq $NaHCO_3$ (30 ml). The separated aqueous phase was extracted with ether three times, and the combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography (silica gel; hexane-diethyl ether) afforded **8** in 56% yield (72 mg, 0.28 mmol). IR: (neat) ν 3345, 2927, 1679, 1145, 961 cm^{-1}. ^{1}H NMR δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.23-1.47 (m, 13H), 1.52-1.61 (m, 4H), 2.04-2.09 (dt, *J* = 7.1, 6.8 Hz, 2H), 2.30 (dt, *J* = 23.7, 7.3 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 5.58 (dt, *J* = 7.0, 14.9 Hz, 1H), 5.71 (dd, *J* = 20.5, 11.0 Hz, 1H), 5.91 (dd, *J* = 14.9, 11.0 Hz, 1H). ^{19}F NMR δ -104.91 (dt, *J* = 20.8, 23.5 Hz, 1F). ^{13}C NMR δ 13.47 (*C*H_3), 15.28 (*C*H_2), 19.75 (*C*H_2), 25.73 (*C*H_2), 29.17 (*C*H_2), 29.42 (*C*H_2, 2C), 29.55 (*C*H_2), 30.33 (d, J_{CF} = 27.2 Hz, *C*H_2CF=), 32.80 (*C*H_2), 32.99 (*C*H_2),

63.07 (*C*H_2O), 108.24 (d, J_{CF} = 26.5 Hz, *C*H=CF), 122.82 (d, J_{CF} = 10.8 Hz, =CH-*C*H=CH), 133.37 (d, J_{CF} = 9.9 Hz, =CH-CH=*C*H), 161.21 (d, J_{CF} = 251.4 Hz, CH=*C*F). HRMS (EI): Calcd for $C_{16}H_{29}FO$: 256.2202. Found: 256.2196.

*4.4. Synthesis of (9Z,11E)-1-acetoxy-9-fluorotetradecadiene (**11**).*

*4.4.1. 10-Acetoxy-1-decynyl(phenyl)iodonium tetrafluoroborate (**13b**).*

To a CH_2Cl_2 suspension (20 ml) of iodosylbenzene (1.32 g, 6 mmol) were added 42% aq HBF_4 (2.64 g, 30 mmol) and HgO (5.5 mg, 0.025 mmol). To the resulting two-phase reaction mixture, a colorless organic phase and a clear yellow aqueous phase, 1-acetoxy-10-decyne (980 mg, 5 mmol) was added at room temperature. The mixture was vigorously stirred for 30 min and a clear yellow color of the aqueous phase faded. The reaction mixture was added to 5% aq $NaBF_4$ (100 ml), and extracted with CH_2Cl_2 three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 ml) and a viscous liquid was condensed at the bottom by the addition of hexane (100 ml). The upper layer was removed by decantation and the viscous liquid was washed with hexane again. Finally, the solvent was completely removed under reduced pressure to give **13b** in 75% yield (1.82 g, 3.75 mmol) as a brown viscous liquid. IR (neat) ν 3045, 2932, 2184, 1732, 1470 cm^{-1}. ^{1}H NMR δ 1.21-1.44 (m, 8H), 1.52-1.70 (m, 4H), 2.06 (s, 3H), 2.64 (t, *J* = 7.1 Hz, 2H), 4.05 (t, *J* = 6.8 Hz, 2H), 7.55 (dd, *J* = 7.8, 7.8 Hz, 2H), 7.68 (dd, *J* = 7.3, 7.3 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 2H). ^{13}C NMR δ 20.65 (*C*H_3), 20.88 (*C*H_2), 25.56 (*C*H_2), 27.34 (*C*H_2), 28.29 (*C*H_2), 28.42 (*C*H_2), 28.57 (*C*H_2), 28.75 (*C*H_2), 64.75 (O*C*H_2), 113.67 (*C*≡C), 114.22 (C≡*C*), 132.57 (*Ar*, 3C), 132.83 (*Ar*), 133.87 (*Ar*, 2C), 172.03 (*C*=O).

*4.4.2. (Z)-1-Acetoxy-9-fluoro-10-iodo-9-decene (**14b**).*

A mixture of 20% aq HF (0.5 ml), **13b** (243 mg, 0.5 mmol), and 1,2-dichloroethane (2 ml) in a Teflon™ PFA vessel was stirred at 60 °C for 6 h. The reaction mixture was poured into 5% aq $NaBF_4$ (20 ml) and extracted with CH_2Cl_2 four times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 ml) and the mixture became turbid by the addition of hexane (40 ml). The viscous liquid settled down at the bottom by keeping the mixture in a refrigerator for 3 h and the clear upper liquid was removed by decantation. The residue was washed with hexane again, and the solvent was completely removed under reduced pressure to give **14a** as a viscous yellow liquid. The crude **14a** was dissolved in DMF (5 ml), and CuI (19 mg, 0.1 mmol) and KI (84mg, 0.5 mmol) were added. After being stirred at room temperature for 16 h, the reaction mixture was poured into 3M aq NH_4Cl (20 ml) and extracted with ether three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography gave **14b** in 61% overall yield (105 mg, 0.31 mmol) from **13b**. IR (neat) ν 3092, 2931, 1738, 1657, 1117 cm^{-1}. ^1H NMR δ 1.26 (brs, 8H), 1.45-1.67 (m, 4H), 2.05 (s, 3H), 2.33 (dt, *J* = 16.8, 7.6 Hz, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 5.18 (d, *J* = 34.4 Hz, 1H). ^{19}F NMR δ -80.00 (dt, *J* = 34.6, 7.6 Hz, 1F). ^{13}C NMR δ 20.83 (*C*H_3), 25.64 (*C*H_2, 2C), 28.36 (*C*H_2), 28.43 (*C*H_2), 28.85 (*C*H_2), 28.86 (*C*H_2), 32.55 (d, J_{CF} = 26.4 Hz, *C*H_2CF=), 50.62 (d, J_{CF} = 26.3 Hz, =*C*HI), 64.31 (O*C*H_2), 166.32 (d, J_{CF} = 260.8 Hz, *C*F=), 170.89 (*C*=O). HRMS (FAB): Calcd for $C_{12}H_{21}FO_2I$ ($M+H^+$): 343.0570. Found: 343.0578.

*4.4.3. (9Z,11E)-1-Acetoxy-9-fluorotetradecadiene (**11**).*

To a mixture of $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and (*E*)-(1-butenyl)diisopropoxyborane (111 mg, 0.6 mmol) in benzene (5 ml) were added a EtOH solution (0.5 ml) of KOH (56 mg, 1 mmol) and **14b** (172 mg, 0.5 mmol) at room temperature. After being stirred for 1 h at 80 °C, the reaction mixture was poured into aq NH_4Cl (15 ml), and extracted with ether three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 ml), and Ac_2O (153 mg, 1.5 mmol) and Et_3N (152 mg, 1.5 mmol) were added. After being stirred at room temperature for 12 h, the mixture was poured into water (40 ml) and extracted with CH_2Cl_2 three times. The combined organic phase was washed with aq $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. After purification by column chromatography (silica gel/ hexane-ether), **11** was isolated in 67% yield (91 mg, 0.34 mmol). IR (neat) ν 3065, 2931, 1741, 1686 cm^{-1}. ^1H NMR δ 1.01 (t, *J* = 7.6 Hz, 3H), 1.31 (brs, 8H), 1.45-1.67 (m, 4H), 2.05 (s, 3H), 2.10 (t, *J* = 7.3 Hz, 2H), 2.18 (m, 2H), 4.05 (t, *J* = 6.6 Hz, 2H), 5.18 (dd, *J* = 36.3, 10.7 Hz, 1H), 5.62 (dt, *J* = 15.4, 6.6 Hz, 1H), 6.26 (dd, *J* = 15.4, 10.8 Hz, 1H). ^{19}F NMR δ -107.13 (dt, *J* = 36.5, 17.7 Hz, 1F). ^{13}C NMR δ 13.75 (CH_3CH_2-), 21.20 (CH_3CO), 25.99 (CH_2), 26.03 (CH_2), 26.34 (CH_2), 28.73 (CH_2), 29.00 (CH_2), 29.27 (CH_2), 29.37 (CH_2), 32.15 (d, J_{CF} = 26.3 Hz, CH_2CF=), 64.77 (OCH_2), 106.51 (d, J_{CF} = 11.5 Hz, FC=*C*H), 120.86 (d, J_{CF} = 6.6 Hz, CH=*C*HCH=), 134.07 (d, J_{CF} = 3.3 Hz, *C*H=CHCH=), 159.32 (d, J_{CF} = 259.1 Hz, F*C*=CH), 171.43 (*C*=O). HRMS (EI): Calcd for $C_{16}H_{27}O_2F$: 270.1995. Found: 270.1995.

*4.5. Synthesis of (10E,12Z)-13-fluorohexadecadien-1-ol (**12**).*

*4.5.1. 1-Pentynyl(p-butylphenyl)iodonium tetrafluoroborate (**15b**).*

To a CH_2Cl_2 suspension (20 ml) of *p*-iodosyl(butylbenzene) (1.66 g, 6 mmol), a 42% aq HBF_4 (2.64 g, 30 mmol) and HgO (5.5 mg, 0.025 mmol) were added. To the resulting two-phase reaction mixture, a colorless organic phase and a clear yellow aqueous phase, was added 1-pentyne (**15a**) (340 mg, 5 mmol) at room temperature. The mixture was vigorously stirred for 30 min and the clear yellow color of the aqueous phase faded. The reaction mixture was added to 5% aqueous $NaBF_4$ (100 ml), and extracted with CH_2Cl_2 three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 ml) and a viscous liquid was condensed at the bottom by the addition of hexane (100 ml). The upper layer was removed by decantation and the viscous liquid was washed with hexane again. Finally, the solvent was completely removed under reduced pressure to give **15b** (1.74 g, 4.2 mmol) in 84% yield as a viscous liquid. IR: (neat) ν 2960, 2183, 1464, 1066 cm^{-1}. ^1H NMR δ 0.93 (t, *J* = 7.3 Hz, 3H), 0.98 (t, *J* = 7.6 Hz, 3H), 1.31-1.40 (m, 2H), 1.56-1.64 (m, 4H), 2.61 (t, *J* = 7.1 Hz, 2H), 2.68 (t, *J* = 7.8 Hz, 2H), 7.34 (d, *J* = 8.6 Hz, 2H), 7.94 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR δ 13.45 (*C*H_3), 13.94 (*C*H_3), 21.33 (*C*H_2), 22.36 (*C*H_2), 22.81 (*C*H_2), 33.22 (*C*H_2), 35.42 (*C*H_2), 110.74 (*C*≡C), 113.18 (C≡*C*), 132.87 (*Ar*, 2C), 134.07 (*Ar*, 3C), 149.01 (*Ar*).

*4.5.2.(Z)-2-Fluoro-1-iodo-1-pentene (**16b**).*

A mixture of 20% aq HF (0.5 ml), **15b** (207 mg, 0.5 mmol), and 1,2-dichloroethane (2 ml) in a Teflon™ PFA vessel was stirred at 60 °C for 6 h. The reaction mixture was poured into 5% aq $NaBF_4$ (20 ml) and extracted with CH_2Cl_2 four times. The combined organic phase was dried over $MgSO_4$ and concentrated under

reduced pressure. The residue was dissolved in CH_2Cl_2 (1 ml) and the mixture became turbid by the addition of hexane (40 ml). The viscous liquid settled down at the bottom by keeping the mixture in a refrigerator for 3h and the clear upper liquid was removed by decantation. The residue was washed with hexane again, and the solvent was completely removed under reduced pressure to give **16a** as a viscous yellow liquid. The crude **16a** was dissolved in DMF (5 ml), and CuI (19 mg, 0.1 mmol) and KI (83 mg, 0.5 mmol) were added. The mixture was stirred at room temperature for 16 h and then poured into a 3 M aq NH_4Cl (20 ml). The mixture was extracted with ether three times, and the combined organic phase was dried over $MgSO_4$, and carefully concentrated under reduced pressure. Purification by column chromatography (silica gel/pentane-ether) gave a mixture of **16b** and *p*-iodo(butylbenzene). After careful removal of the solvent, the mixture was transferred into a distillation flask and the receiver was cooled by a dry ice-MeOH bath. By keeping the flask under vacuum (0.1 mmHg) at 0 °C, pure **16b** could be collected in the cold trap in 60% overall yield from **15b** (64 mg, 0.3 mmol) and *p*-iodo(butyl)benzene remained in the distillation flask. IR: (neat) ν 3092, 2964, 1657, 1117 cm^{-1}. ^1H NMR δ 0.95 (t, *J* = 7.3 Hz, 3H), 1.5-1.61 (m, 2H), 2.32 (dt, *J* = 16.8, 7.6 Hz, 2H), 5.18 (d, *J* = 34.6 Hz, 1H). ^{19}F NMR δ -80.16 (dt, *J* = 34.6, 16.6 Hz, 1F). ^{13}C NMR δ 13.20 (CH_3), 19.22 (CH_2CH_3), 34.62 (d, *J* = 26.4Hz, CH_2CF), 50.80 (d, *J* = 26.3Hz, =CHI), 166.31 (d, *J* = 260.0Hz, CF=). HRMS (EI): Calcd for C_5H_8FI: 213.9655. Found: 213.9647.

*4.5.3. (10E,12Z)-13-fluorohexadecadien-1-ol (**12**).*

To a mixture of $Pd(PPh_3)_4$ (29 mg, 0.025 mmol) and (*E*)-11-[(2-tetrahydropyranyloxy)-1-undecenyl]-4,4,5,5-tetramethyl-1,3,2-dioxaborolane

(228 mg, 0.6 mmol) in benzene (5 ml) were added an EtOH solution (0.5 ml) of KOH (56 mg, 1 mmol) and **16b** (107 mg, 0.5 mmol) at room temperature. After being stirred for 1 h at 80 °C, the reaction mixture was poured into 3 M aq NH_4Cl (15 ml), and extracted with ether three times. The combined organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in MeOH (15 ml) and *p*-TsOH-H_2O (190 mg, 1 mmol) was added. After being stirred at room temperature for 4 h, the reaction mixture was diluted with CH_2Cl_2 (40 ml), washed with saturated $NaHCO_3$ (5 ml) and brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification by column chromatography provided **12** (85 mg) in 66% overall yield from **16b**. IR: (neat) ν 3412, 3055, 2925, 1685, 1066 cm^{-1}. ^1H NMR δ 0.94 (t, *J* = 7.3 Hz, 3H), 1.28-1.60 (m, 17H), 2.07 (dt, *J* = 7.1, *J* = 6.6 Hz, 2H), 2.16 (dt, *J* = 17.8, *J* =7.3 Hz, 2H), 3.64 (t, *J* = 6.3 Hz, 2H), 5.19 (dd, *J* = 36.3, *J* = 10.7 Hz, 1H), 5.57 (dt, *J* = 15.4, *J* = 7.1 Hz, 1H), 6.25 (dd, *J* = 15.4, *J* = 10.7 Hz, 1H). ^{19}F NMR δ -107.22 (dt, *J* = 36.8, *J* = 17.7 Hz, 1F). ^{13}C NMR δ 13.45 (*C*H_3), 19.52 (*C*H_2), 25.70 (*C*H_2), 29.14 (*C*H_2), 29.32 (*C*H_2), 29.38 (*C*H_2, 2C), 29.51 (*C*H_2), 32.78 (*C*H_2, 2C), 33.95 (d, *J* = 26.3 Hz, *C*H_2C(F)=), 63.06 (*C*H_2O), 106.44 (d, *J* = 12.3 Hz, *C*H=CF), 121.59 (d, *J* = 5.8 Hz, CH=*C*HCH=), 132.41 (*C*H=CHCH=), 158.94 (d, *J* = 259.2 Hz, =*C*F). HRMS (EI): Calcd for $C_{16}H_{29}OF$: 256.2202. Found: 256.2212.

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