ELSEVIER

Journal of Fluorine Chemistry 102 (2000) 61–67

JOURNAL OF FLUORINE CHEMISTRY

www.elsevier.com/locate/jfluchem

Preparation of 2,6-difluoromanoalogues derivatives

Yuzo Komatsu, Tomoya Kitazume*

Department of Bioengineering, Tokyo Institute of Technology, Nagatsuta, Midori-ku, Yokohama 226-8501, Japan

Received 5 June 1999; received in revised form 19 July 1999; accepted 20 August 1999

Dedicated to Professor Paul Tarrant on the occasion of his 85th birthday

Abstract

Design of the inhibitors for the phospholipase A_2 modified with fluorine(s) and total synthesis of 2,6-difluoromanoalogues derivatives, are described. © 2000 Elsevier Science S.A. All rights reserved.

Keywords: Bioactive materials; Inhibitor; Phospholipase A_2; Fluorine

1. Introduction

Since the discovery of the anti-inflammatory activity of manoalide [1] and/or manoalogues [2], research into the modification of those materials with functional group(s) and/or halogen atom(s), thus generating effective inhibitor of the phospholipase A_2 (PLA_2) [3–5], has been extensive in recent years. It is well known that the irreversible inactivation of cobra venom phospholipase A_2 by manoalide and manoalide analogues requires the opening of the lactone ring and the presence of the α,β-unsaturated aldehyde moiety (shown in Schemes 1 and 2) [2,6,7]. Recently, we reported that carbon–carbon double bond modified by a fluorine atom has significantly lower LUMO energy level than the corresponding nonfluorinated counterpart and has the similar values for the corresponding p_z orbital coefficients at the reaction sites, which demonstrates the higher electrophilic reactivity of those materials [8,9]. As a continuation of our interest in the synthesis of biological active materials modified with fluorine(s), which often exhibit unique physiochemical properties, we were intrigued by modification of 2- and/or 6-position on the manoalogues with a fluorine atom to increase the reactivity of α,β-unsaturated carbonyl compound.

Our basic strategy is based on the concept that fluorine-containing molecules might be constructed more easily by employing building blocks with appropriate functionalities. Herein, we report the synthesis of a difluorinated analog of manoalogues. Especially, we aimed to introduce fluorine atom(s) at position for the purpose of increasing the reactivity of aldehyde group in manoalogues.

2. Results and discussion

A convenient synthetic route to the desired materials is shown in Scheme 3 and/or Scheme 4. To obtain the desired fluoromanoalogues (**9a** and **9b**) derivative possessing fluorine atom(s), we required the *cis*- and/or *trans*-acetal derivatives (**4a** and **4b**) as a precursor.

At first, compound **1** was sought to undergo a Horner–Emmons reaction upon treatment with NaH–$(EtO)_2$-P(O)$CHFCO_2Et$ system in THF, giving satisfactory conversion of desired *cis*- and *trans*-compound **2**, and then the mixture was transformed into its thioacetal derivative by the reaction of ethanthiol in the presence of $BF_3{\cdot}Et_2O$. Then, for the purpose of obtaining either stereoisomer selectively, compound **3** was treated with DIBAL-H in diethyl ether at 0°C followed by quenching the reaction with 1 N HCl or saturated NH_4Cl aq. The final purification with column chromatography on silica gel using a mixture of *n*-hexane–ethyl acetate (3:1) as eluent, giving **4a** (13% yield) and **4b** (56% yield).

Pawson and Lovey have reported the preparation of the geometrical isomers of compound **6** by the reaction of triethyl fluorophosphonoacetate and pyruvaldehyde dimethyl acetal [10]. Their NMR spectral data shown in Table 1 suggest that the four-bond coupling constants ($^4J_{F,H}$) between the C-2 fluorine and C-3 methyl protons in compound A follow the pattern $^4J_{F,H}$ (*E*-isomer) $>{}^4J_{F,H}$ (*Z*-isomer) [11,12]. From this result, it seems that comparison of the coupling constants ($J_{F,H}$) supports the assignment of the geometrical isomers. The comparison of their NMR spectral data has led to the assignment of **4a** (*E*-isomer; $J_{F,H} = 2.4$ Hz) and **4b** (*Z*-isomer; $J_{F,H} = 1.2$ Hz) (shown in Table 1).

* Corresponding author.

0022-1139/00/$ – see front matter
PII: S0022-1139(99)00246-8

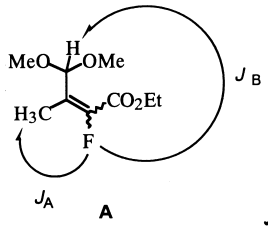
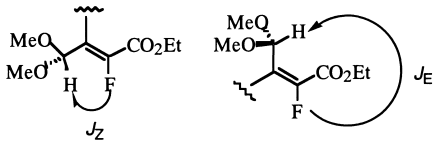


Table 1 H-F Coupling constants

	J_A	J_B
*E*isomer	4.40	2.45
*Z*isomer	3.18	1.47



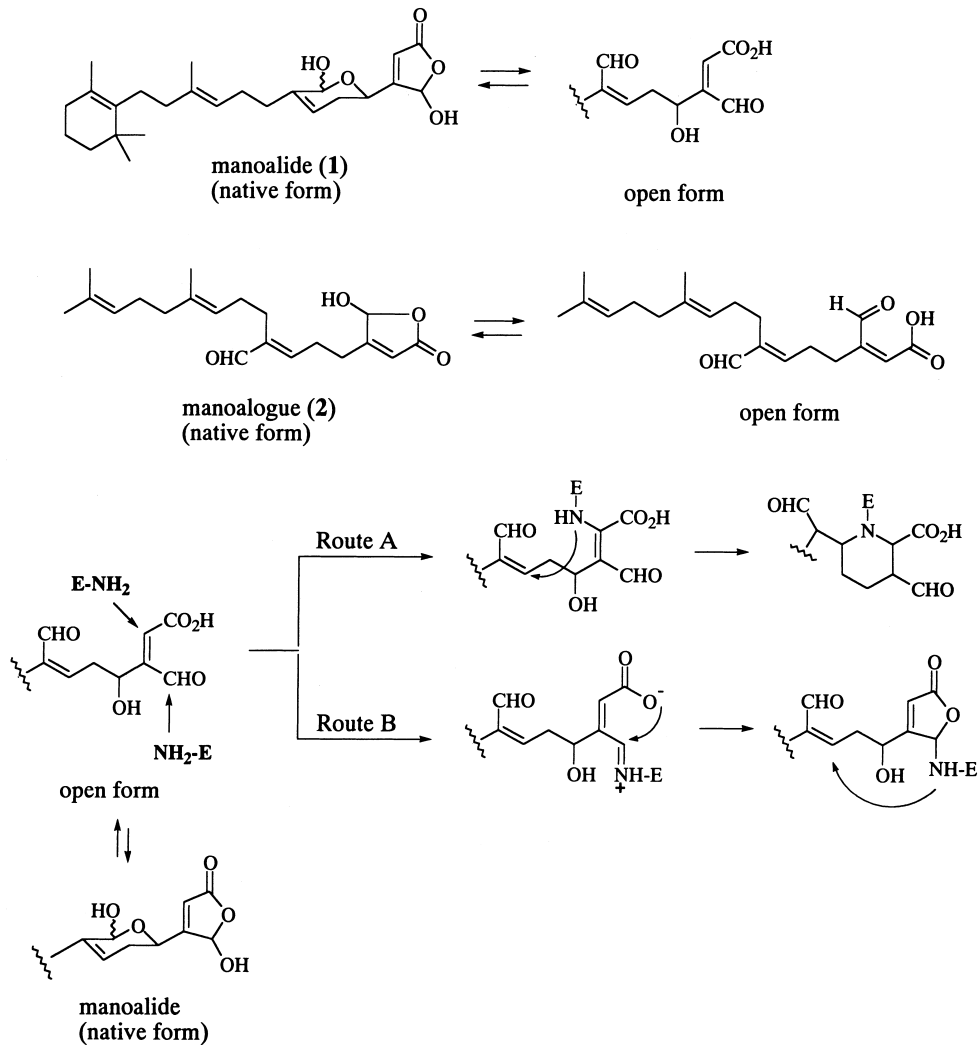
Z-isomer (J_Z) < *E*-isomer (J_E)

At the next stage, transformation of the obtained compounds **4a** and **4b** into 6-*cis*-2,6-difluoromanoalogue **9a** and/or 6-*trans*-2,6-difluoromanoalogue **9b** was investigated in detail (Schemes 3 and 4). After protecting the hydroxy group of compounds **4a** and **4b** with a mesyl moiety, the nucleophilic attack by the nucleophile derived from LDA–$CH_3(=NNMe_2)CH(OMe)_2$ in THF and hydrolysis led predominantly to the formation of compounds **5a** and **5b**. Then, Horner–Emmons reaction with $(EtO)_2P(O)CHFCO_2Et$ in THF was carried out, giving satisfactory conversion into the crude mixture of desired *cis*- and *trans*-compounds **6a** and **6b**. Treatment of the acetal derivatives with CF_3CO_2H in CH_2Cl_2 led to the fluorinated closed type of manoalogue derivatives **7a** and **7b**. Employment of Ag_2O–$BF_3{\cdot}Et_2O$ system followed by the hydrolysis with 40% H_2SO_4 furnished the desired 6-*cis*-2,6-difluoromanoalogue (**9a**) and 6-*trans*-2,6-difluoromanoalogue (**9b**).

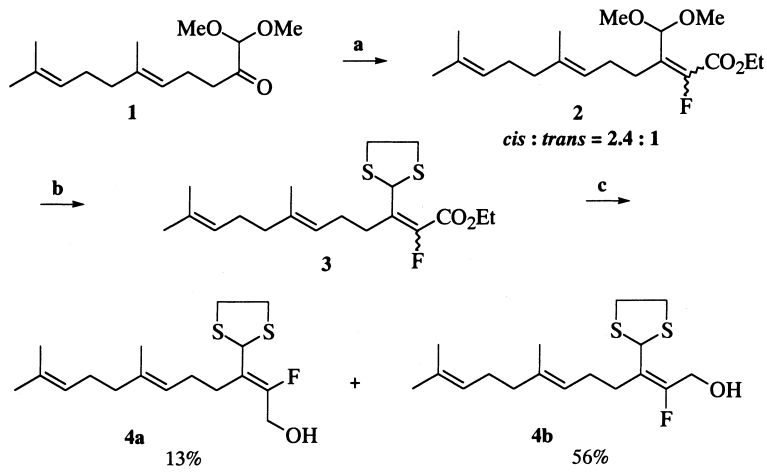
3. Experimental

3.1. General procedure

All commercially available reagents were used without further purification. Chemical shifts of ^1H (500 MHz) and



Scheme 1. Proposed schemes for the reaction of manoalide and manoalogue with cobra venom phospholipase A2: (a) involving two conjugate additions or (b) involving conjugate addition following Schiff base formation.



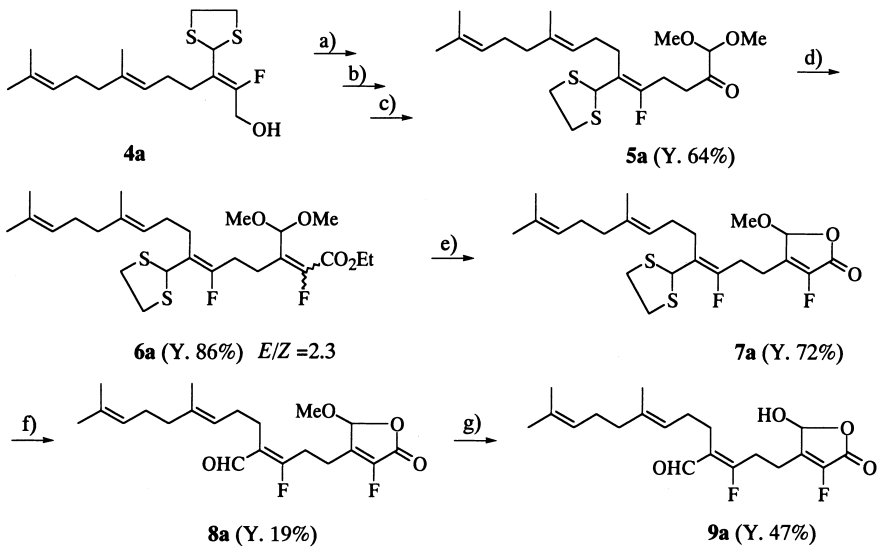
Scheme 2. (a) NaH, $(EtO)_2P(O)CHFCO_2Et$, THF, 25°C, Y, 93%; (b) $(CH_2SH)_2$, $BF_3{\cdot}OEt_2$, $Bu_4N^+I^-$, CH_2Cl_2, 0°C; (c) DIBAL-H, Et_2O, 0°C.

^{13}C NMR spectra were recorded in ppm (δ) downfield from the following internal standard (Me_4Si, δ 0.00, or $CHCl_3$, δ 7.24). The ^{19}F (470 MHz) NMR spectra were recorded in ppm downfield from the external trifluoroacetic acid (TFA) in $CDCl_3$. Yields quoted are those of the products actually isolated.

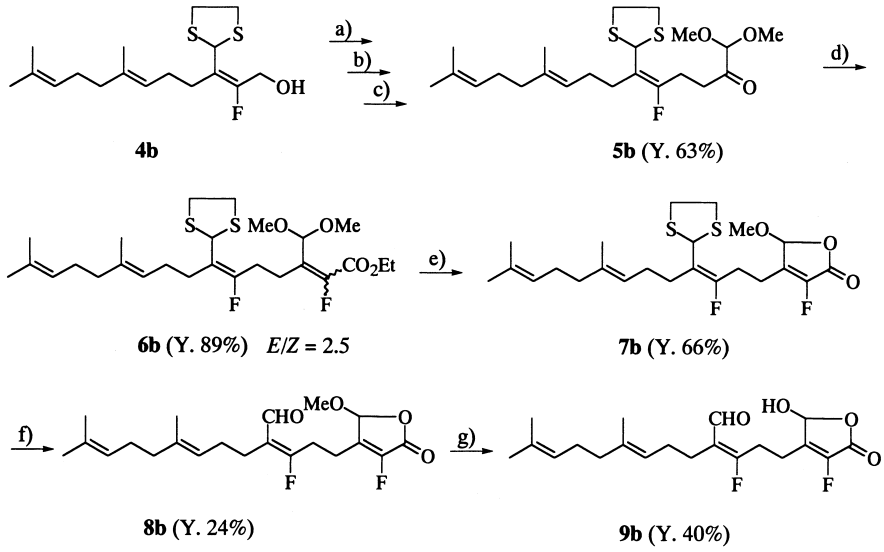
*3.1.1. 1,1-Dimethoxy-6,10-dimethyl-5(E),9-undecadien-2-one (**1**)*

To a solution of *N*-bromosuccinimide (3.91 g, 22 mmol) in dry CH_2Cl_2 (80 ml), dimethylsulfide (1.49 g, 24 mmol) was added dropwised at −40°C under an argon atmosphere. After stirring the whole at 0°C for 5 min, geraniol (3.09 g, 20 mmol) in dry CH_2Cl_2 (10 ml) was added to the mixture at −40°C. After stirring of 2 h at 0°C, the mixture was allowed to warm to room temperature. The mixture was poured into water (10 ml), and then oily materials were extracted with hexane. On removal of the solvent under high vacuum, the crude oily material is used in the next step.

To a solution of lithium diisopropylamide (2.43 g, 24 mmol) in dry THF (20 ml) at −10°C under an argon atmosphere, dimethylhydrazone of 1,1-dimethoxy-2-propanone (3.53 g, 22 mmol) in dry THF (10 ml) was added, and then the mixture was stirred for 30 min at 0°C. Geranylbromide in dry THF (10 ml) was added into the mixture at that temperature, and then the whole was stirred for 6 h at room temperature. After the whole was cooled with ice-water, the reaction mixture was quenched with saturated aq. NH_4Cl. The organic materials were extracted with diethyl ether. On removal of the solvent, the crude intermediate hydrazone was taken up in cold THF (100 ml) and shaken together with 40 ml of 2.0 N HCl. The mixture was then diluted with diethyl ether, and then the organic layer was separated. The organic materials were extracted with diethyl



Scheme 3. (a) MsCl, EtN, DMAP, LiCl/CH_2Cl_2, 25°C; (b) LDA, $CH_3C(=NNMe_2)CH(OMe)_2$, THF, −15°C to 25°C; (c) 2 N HCl, THF, 25°C, **4a** → **5a**; (d) NaH, THF, $(EtO_2)P(O)CHFCO_2Et$, 25°C; (e) TFA, CH_2Cl_2, 0°C; (f) Ag_2O, $BF_3{\cdot}OEt_2$, THF, H_2O, 0°C; (g) 40%, H_2SO_4, 1,4-dioxane, 25°C.



Scheme 4. (a) MsCl, EtN, DMAP, LiCl, CH_2Cl_2, 25°C; (b) LDA, $CH_3C(=NNMe_2)CH(OMe)_2$, THF, −15°C to 25°C; (c) 2 N HCl, THF, 25°C, **4b** → **5b**; (d) NaH, THF, $(EtO_2)P(O)CHFCO_2Et$, 25°C; (e) TFA, CH_2Cl_2, 0°C to 25°C; (f) Ag_2O, $BF_3{\cdot}OEt_2$, THF, H_2O, 0°C; (g) 40%, H_2SO_4, 1,4-dioxane, 25°C.sc4

ether, and the extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 10:1 *n*-hexane–ethyl acetate) afforded compounds **1** in 76% yield (3.87 g).

^{1}H NMR ($CDCl_3$): δ 1.59 (3 H, s), 1.62 (3 H, d, $J = 1.0$ Hz), 1.68 (3 H, d, $J = 1.2$ Hz), 1.93–1.98 (2 H, m), 2.01–2.07 (2 H, m), 2.24–2.30 (2 H, m), 2.58 (2 H, t, $J = 8.1$ Hz), 4.47 (1 H, s), 5.05–5.11 (2 H, m); ^{13}C NMR ($CDCl_3$): δ 15.99, 17.67, 21.58, 25.69, 26.63, 37.65, 39.65, 54.60 (2 C), 103.92, 122.53, 124.20, 131.41, 136.39, 205.50.

*3.1.2. Ethyl 3-dimethoxymethyl-7,11-dimethyl-2-fluoro-2(E), 6(E), 10-dodecatrienoate (**2a**), ethyl 3-dimethoxymethyl-7,11-dimethyl-2-fluoro-2(Z),6(E),10-dodecatrienoate (**2b**)*

To a solution of triethyl-2-fluoro-2-phosphonoacetate (1.54 g, 6 mmol) in dry THF (2.5 ml), a mixture of NaH (0.14 g, 6 mmol) in THF (10 ml) was added at 0°C under an argon atmosphere. After stirring of 30 min at room temperature, a mixture of acetal trienone **1** (1.27 g, 5 mmol) in dry THF (5 ml) was added, and then was stirred for 8 h at room temperature. After quenching with cold saturated aq. NH_4Cl, oily materials were extracted with ethyl acetate, and the extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 20:1 *n*-hexane–ethyl acetate) afforded *E*/*Z* mixture (ratio 2.4:1) of **2** in 93% yield (1.59 g).

E-isomer (**2a**): ^{1}H NMR ($CDCl_3$): δ 1.37 (3 H, t, $J = 7.1$ Hz), 1.60 (3 H, s), 1.61 (3 H, s), 1.68 (3 H, d, $J = 1.5$ Hz), 1.97–2.00 (2 H, m), 2.03–2.09 (2 H, m), 2.17–2.25 (2 H, m), 2.26–2.31 (2 H, m), 3.41 (6 H, s), 4.31 (2 H, q, $J = 7.1$ Hz), 5.07–5.12 (1 H, m), 5.16–5.21 (1 H, m), 5.82 (1 H, d, $J = 2.4$ Hz); ^{13}C NMR ($CDCl_3$): δ 14.09, 15.90, 17.67, 25.01 (d, $J = 4.7$ Hz), 25.70, 26.72, 27.38 (d, $J = 2.6$ Hz), 39.70, 55.52 (2 C), 61.61, 101.51 (d, $J = 10.0$ Hz), 123.60, 124.38, 131.31, 132.91 (d, $J = 11.5$ Hz), 135.96, 146.54 (d, $J = 260.1$ Hz), 160.77 (d, $J = 34.8$ Hz); ^{19}F NMR ($CDCl_3$): δ 49.3 (d, $J = 2.4$ Hz); IR (neat): 1726 (C=O), 1654 (C=C) cm^{-1}.

Z-isomer (**2b**): ^{1}H NMR ($CDCl_3$): δ 1.35 (3 H, t, $J = 7.3$ Hz), 1.60 (3 H, s), 1.62 (3 H, s), 1.68 (3 H, d, $J = 1.5$ Hz), 1.94–2.00 (2 H, m), 2.02–2.09 (2 H, m), 2.13–2.24 (2 H, m), 2.44–2.52 (2 H, m), 3.41 (6 H, s), 4.31(2 H, q, $J = 7.1$ Hz), 5.07–5.12 (1 H, m), 5.15–5.20 (1 H, m), 5.19 (1 H, d, $J = 1.5$ Hz); ^{13}C NMR ($CDCl_3$): δ 14.12, 15.96, 17.69, 24.85, 25.71, 26.74, 28.37 (d, $J = 3.4$ Hz), 39.73, 55.28 (2 C), 61.54, 101.18 (d, $J = 13.1$ Hz), 123.78, 124.42, 131.27, 131.64 (d, $J = 5.5$ Hz), 135.71, 145.72 (d, $J = 256.0$ Hz), 160.69 (d, $J = 35.7$ Hz); ^{19}F NMR ($CDCl_3$): δ 45 (s); IR (neat):1732 (C=O), 1654 (C=C) cm^{-1}.

*3.1.3. Ethyl 7,11-dimethyl-2-fluoro-3-(1,3-dithiolan-2-yl)-2(Z),6(E),10-dodecatrienoate (**3a**), ethyl 7,11-dimethyl-2-fluoro-3-(1,3-dithiolan-2-yl)-2(E),6(E),10-dodecatrienoate (**3b**)*

To a solution of acetal ester **2** (mixture of *E*- and *Z*-isomers, 1.78 g, 5.6 mmol) and *n*-Bu_4NI (0.206 g, 0.56 mmol) in CH_2Cl_2 (10 ml), $BF_3{\cdot}Et_2O$ (0.024 g, 0.28 mmol) and ethanedithiol was added at 0°C. The reaction mixture was stirred for 1 h, then poured into ice-water. Organic materials were extracted with ethyl acetate. The extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 1:2∼1:1 *n*-hexane–benzene) afforded *E*/*Z* mixture (ratio 4.2:1) of **3** in 73% yield (1.47 g).

E-isomer (**3a**): ^{1}H NMR ($CDCl_3$): δ 1.36 (3 H, t, $J = 7.3$ Hz), 1.61 (3 H, s), 1.64 (3 H, s), 1.69 (3 H, s), 1.96–2.01 (2 H, m), 2.04–2.11 (2 H, m), 2.26–2.37 (4 H, m),

3.27–3.34 (2 H, m), 3.34–3.41 (2 H, m), 4.30 (2 H, q, $J = 7.1$ Hz), 5.07–5.14 (1 H, m), 5.17–5.23 (1 H, m), 6.66 (1 H, d, $J = 3.2$ Hz); ^{19}F NMR ($CDCl_3$): δ 41.7 (d, $J = 2.8$ Hz).

Z-isomer (**3b**): ^{1}H NMR ($CDCl_3$): δ 1.35 (3 H, t, $J = 7.2$ Hz), 1.61 (3 H, s), 1.64 (3 H, s), 1.69 (3 H, s), 2.04–2.11 (4 H, m), 2.28–2.36 (2 H, m), 2.50–2.55 (2 H, m), 3.27–3.34 (2 H, m), 3.34–3.41 (2 H, m), 4.98 (2 H, q, $J = 7.1$ Hz), 5.07–5.13 (1 H, m), 5.16–5.22 (1 H, m), 5.88 (1 H, s); ^{19}F NMR ($CDCl_3$): δ 37.7 (s).

*3.1.4. 7,11-Dimethyl-3-(1,3-dithiolan-2-yl)-2-fluoro-2(Z),6(E),10-dodecatrien-1-ol (**4a**), 7,11-dimethyl-3-(1,3-dithiolan-2-yl)-2-fluoro-2(E),6(E),10-dodecatrien-1-ol (**4b**)*

To a solution of ditioacetal ester **3** prepared from **2** (3.36 g, 9.8 mmol) in dry Et_2O (20 ml), DIBAL-H (1.0 M, 22 ml, 22 mmol) was added at 0°C under an argon atmosphere. After the starting material was consummed, the reaction mixture was quenched with saturated aq. Na_2SO_4. Oily materials were extracted with diethyl ether, and then the extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 4:1∼3:1 *n*-hexane–ethyl acetate) afforded **4a** (0.42 g, yield 13%) and **4b** (1.81 g, yield 56%).

Compound **4a**: ^{1}H NMR ($CDCl_3$): δ 1.61 (3 H, s), 1.63 (3 H, s), 1.69 (3 H, d, $J = 1.0$ Hz), 1.97–2.02 (2 H, m), 2.04–2.11 (2 H, m), 2.16–2.22 (2 H, m), 2.23–2.30 (2 H, m), 3.23–3.30 (2 H, m), 3.33–3.39 (2 H, m), 4.23 (2 H, dd, $J = 22.0$, 6.4 Hz), 5.07–5.11 (1 H, m), 5.15–5.18 (1 H, m) 5.89 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 16.20, 17.71, 25.71, 26.50 (d, $J = 3.0$ Hz), 26.62, 30.44 (d, $J = 2.8$ Hz), 39.65, 39.95 (2 C), 49.29 (d, $J = 10.7$ Hz), 58.28 (d, $J = 30.0$ Hz), 117.43 (d, $J = 7.1$ Hz), 123.32, 124.18, 131.48, 136.35, 155.98 (d, $J = 254.5$ Hz); ^{19}F NMR ($CDCl_3$): δ 45.4 (t, $J = 22.0$ Hz); IR (neat): 3385 (OH), 1684 (C=C) cm^{-1}.

Compound **4b**: ^{1}H NMR ($CDCl_3$): δ 1.61 (3 H, s),1.64 (3 H, s), 1.69 (3 H, d, $J = 1.0$ Hz), 1.96–2.01 (2 H, m), 2.04–2.12 (2 H, m), 2.18–2.29, (4 H, m), 3.24–3.30 (2 H, m), 3.36–3.41 (2 H, m), 4.32 (2 H, dd, $J = 22.7$, 6.4 Hz), 5.11 (1 H, m), 5.20 (1 H, m), 5.51 (1 H, d, $J = 2.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 16.09, 17.70, 25.71, 26.53 (d, $J = 3.5$ Hz), 26.70, 28.63 (d, $J = 2.5$ Hz), 39.67, 40.11 (2 C), 52.66 (d, $J = 8.3$ Hz), 57.65 (d, $J = 31.0$ Hz), 118.57 (d, $J = 17.8$ Hz), 123.83, 124.38, 131.31, 135.71, 156.58 (d, $J = 254.9$ Hz); ^{19}F NMR ($CDCl_3$): δ 53.5 (dt, $J = 22.9$, 3.1 Hz); IR (neat): 3386 (OH), 1684 (C=C) cm^{-1}.

*3.1.5. 1,1-Dimethoxy-10,14-dimethyl-6-(1,3-dithiolan-2-yl)-5-fluoro-5(Z),9(E),13-pentadecatrien-2-one (**5a**)*

To a solution of compound **4a** (1.469 g, 4.44 mmol) in dry CH_2Cl_2 (20 ml), dimethylaminopyridine (0.326 g, 2.67 mmol), chloride (0.661 g, 5.78 mmol), triethylamine (0.495 g, 4.89 mmol), and LiCl (0.282 g, 6.66 mmol) were added sequentially. After stirring of 4 h at room temperature, the whole was poured into water. Oily materials were extracted with ethyl acetate, The whole was stirred room temperture for 4 h, then poured into water. The mixture was extracted with ethyl acetate, and then the extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 10: 1 *n*-hexane–ethyl acetate) afforded allyl chloride. This was used in the next step without further purification.

To a solution of lithium diisopropylamine (5.0 mmol) in THF (10 ml) at −10°C under argon atmosphere, dimethylhydrazone of 1,1-dimethoxy-2-propanone (5.5 mmol) in THF (10 ml) was added, and then the mixture was stirred for 30 min at 0°C. Allyl chloride in THF (10 ml) was added into the mixture at that temperature, and then the whole was stirred for 6 h at room temperature. After the whole was cooled with ice-water, the reaction mixture was quenched with saturated aq. NH_4Cl. The organic materials were extracted with diethyl ether. On removal of the solvent, the crude intermediate hydrazone was taken up in cold THF (20 ml) and shaken together with 10 ml of 2.0 N HCl. The mixture was then diluted with diethyl ether, and then the organic layer was separated. The organic materials were extracted with diethyl ether, and the extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 5: 1 *n*-hexane–ethyl acetate) afforded compound **5a** (1.20 g) in 63% yield.

^{1}H NMR ($CDCl_3$): δ 1.61 (3 H, s), 1.63 (3 H, s), 1.67 (3 H, d, $J = 0.8$ Hz), 1.94–2.00 (2 H, m) 2.04–2.09 (2 H, m), 2.09–2.15 (2 H, m), 2.19–2.25 (2 H, m), 2.54 (2 H, dt, $J = 22.0$, 7.3 Hz), 2.80 (2 H, t, $J = 7.1$ Hz) 3.20–3.26 (2 H, m), 3.31–3.36 (2 H, m), 3.41 (6 H, s), 4.48 (1 H, s), 5.07–5.12 (1 H, m), 5.13–5.18 (1 H, m), 5.89 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 16.14, 17.69, 22.87 (d, $J = 28.1$ Hz), 25.70, 26.66, 26.77, 29.83 (d, $J = 2.7$ Hz), 33.96, 39.67, 39.82 (2 C), 49.69 (d, $J = 11.5$ Hz), 54.76 (2 C), 103.89, 114.28 (d, $J = 8.8$ Hz), 123.59, 124.29, 131.32, 135.77, 157.05 (d, $J = 253.7$ Hz), 204.06; ^{19}F NMR ($CDCl_3$): δ 52.9 (t, $J = 21.4$ Hz); IR (neat): 1734 (C=O) cm^{-1}.

*3.1.6. 1,1-Dimethoxy-10,14-dimethyl-6-(1,3-dithiolan-2-yl)-5-fluoro-5(E),9(E),13-pentadecatrien-2-one (**5b**)*

In the above reaction, compound **4b** was used to give compound **5b** in 64% yield.

^{1}H NMR ($CDCl_3$): δ 1.61 (3 H, s), 1.62 (3 H, s), 1.67 (3 H, d, $J = 1.0$ Hz), 1.95–2.00 (2 H, m), 2.04–2.10 (2 H, m), 2.13–2.18 (2 H, m), 2.18–2.24 (2 H, m), 2.61 (2 H, dt, $J = 23.4$, 7.1 Hz), 2.81 (2 H, t, $J = 7.6$ Hz), 3.22–3.27 (2 H, m), 3.32–3.37 (2 H, m), 3.42 (6 H, s), 4.48 (1 H, s), 5.12–5.08 (1 H, m), 5.16–5.20 (1 H, m), 5.54 (1 H, d, $J = 3.2$ Hz); ^{13}C NMR ($CDCl_3$): δ 16.05, 17.68, 22.35 (d, $J = 28.3$ Hz), 25.71, 26.14 (d, $J = 4.0$ Hz), 26.73, 28.88, 34.42, 39.67, 39.98 (2 C), 53.47 (d, $J = 9.2$ Hz), 54.79 (2 C), 103.92, 115.45 (d, $J = 18.9$ Hz), 124.12, 124.41, 131.24, 135.38, 157.02 (d, $J = 252.7$ Hz), 204.08; ^{19}F NMR ($CDCl_3$): δ 60 (dt, $J = 22.9$, 3.0 Hz); IR (neat): 1734 (C=O) cm^{-1}.

*3.1.7. Ethyl 2,6-difluoro-3-dimethoxymethyl-11,15-dimethyl-7-(1,3-dithiolan-2-yl)-2,6(Z),10(E),14-hexadecatetraenoate (**6a**)*

To a solution of triethyl-2-fluoro-2-phosphonoacetate (1.54 g, 6 mmol) in dry THF (2.5 ml), a mixture of NaH (0.14 g, 6 mmol) in THF (10 ml) was added at 0°C under an argon atmosphere. After stirring of 30 min at room temperature, a mixture of acetal trienone **5a** (5 mmol) in dry THF (5 ml) was added, and then the whole was stirred for 8 h at room temperature. After quenching with cold saturated aq. NH_4Cl, oily materials were extracted with ethyl acetate, and the extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 20:1 *n*-hexane–ethyl acetate) afforded *E*/*Z* mixture (ratio 2.3:1) of **6a** in 86% yield.

E-isomer: ^{1}H NMR ($CDCl_3$): δ 1.37 (3 H, t, $J = 7.1$ Hz), 1.60 (3 H, s), 1.63 (3 H, s), 1.68 (3 H, s), 1.95–2.00 (2 H, m), 2.03–2.12 (4 H, m), 2.20–2.28 (2 H, m), 2.42–2.48 (2 H, m), 2.48–2.54 (2 H, m), 3.20–3.26 (2 H, m), 3.30–3.37 (2 H, m), 3.40 (6 H, s), 4.31 (2 H, q, $J = 7.1$ Hz), 5.07–5.12 (1 H, m), 5.12–5.20 (1 H, m), 5.83 (1 H, d, $J = 2.4$ Hz), 5.91 (1 H, s); ^{19}F NMR ($CDCl_3$): δ 53.7 (1 F, t, $J = 21.4$ Hz), 40.7 (1 F, d, $J = 3.1$ Hz).

Z-isomer: ^{1}H NMR ($CDCl_3$): δ 1.36 (3 H, t, $J = 7.3$ Hz), 1.61 (3 H, s), 1.63 (3 H, s), 1.68 (3 H, s), 1.95–2.00 (2 H, m), 2.03–2.12 (4 H, m), 2.19–2.28 (2 H, m), 2.48–2.54 (2 H, m), 2.67–2.72 (2 H, m), 2.68–2.73 (2 H, m), 3.18–3.25 (2 H, m), 3.31–3.38 (2 H, m), 3.39 (6 H, s), 4.31 (2 H, q, $J = 7.1$ Hz), 5.05–5.12 (1 H, m), 5.16–5.21 (1 H, m), 5.21 (1 H, d, $J = 1.5$ Hz), 5.91 (1 H, s); ^{19}F NMR ($CDCl_3$): δ 53.9 (1 F, t, $J = 22.7$ Hz), 36.5 (1 F, s).

*3.1.8. Ethyl 2,6-difluoro-3-dimethoxymethyl-11,15-dimethyl-7-(1,3-dithiolan-2-yl)-2,6(E),10(E),14-hexadecatetraenoate (**6b**)*

In the above reaction, compound **5b** was used to give compound **6b** in 89% yield (2.5:1 mixture of *E*-/*Z*-isomers).

E-isomer: ^{1}H NMR ($CDCl_3$): δ 1.36 (3 H, t, $J = 7.1$ Hz), 1.60 (3 H, s), 1.63 (3 H, s), 1.68 (3 H, s), 1.97–2.00 (2 H, m), 2.07–2.11 (2 H, m), 2.12–2.19 (2 H, m), 2.19–2.27 (2 H, m), 2.50–2.55 (2 H, m), 2.55–2.60 (2 H, m) 3.18–3.25 (2 H, m), 3.30–3.37 (2 H, m), 3.43 (6 H, s), 4.30 (2 H, q, $J = 7.1$ Hz), 5.05–5.12 (1 H, m), 5.16–5.22 (1 H, m), 5.50 (1 H, d, $J = 3.2$ Hz), 5.87 (1 H, d, $J = 2.5$ Hz); ^{19}F NMR ($CDCl_3$): δ 61.6 (1 F, dt, $J = 5.9$, 3.1 Hz), 40.7 (1 F, d, $J = 3.1$ Hz).

Z-isomer: ^{1}H NMR ($CDCl_3$): δ 1.37 (3 H, t, $J = 7.3$ Hz), 1.61 (3 H, s), 1.63 (3 H, s), 1.68 (3 H, s), 1.97–2.00 (2 H, m), 2.07–2.11 (2 H, m), 2.12–2.19 (2 H, m), 2.19–2.27 (2 H, m), 2.50–2.55 (2 H, m), 2.68–2.73 (2 H, m), 3.18–3.25 (2 H, m), 3.30–3.37 (2 H, m), 3.42 (6 H, s), 4.32 (2 H, q, $J = 7.1$ Hz), 5.05–5.12 (1 H, m), 5.16–5.22 (1 H, m), 5.22 (1 H, d, $J = 1.5$ Hz), 5.58 (1 H, d, $J = 3.4$ Hz); ^{19}F NMR ($CDCl_3$): δ 62.9 (t, $J = 24.4$, 3.1 Hz), 57.2 (s).

*3.1.9. 4-[8,12-Dimethyl-4-(1,3-dithiolan-2-yl)-3-fluoro-3(Z),7(E),11-tridecatrienyl]-3-fluoro-5-methoxy-2(5H)-furanone (**7a**)*

To a solution of compound **6a** (0.739 g, 1.43 mmol) in dry CH_2Cl_2 (5.0 ml), under argon and cooled to 0°C trifluoroacetic acid (1.1 eq) was added at 0°C under an argon atmosphere. After stirring of 6 h at room temperature, the mixture was poured into water. Oily materials were extracted with diethyl ether, and then the extract was washed with brine, dried over $MgSO_4$, and concentrated. Chromatography (silica gel, 4:1 *n*-hexane–ethyl acetate) afforded **7a** (0.47 g, yield 72%).

^{1}H NMR ($CDCl_3$): δ 1.61 (3 H, s), 1.63 (3 H, s), 1.69 (3 H, d, $J = 0.7$ Hz), 1.96–2.00 (2 H, m), 2.04–2.12 (4 H, m), 2.18–2.25 (2 H, m), 2.53–2.65 (4 H, m), 3.23–3.28 (2 H, m), 3.32–3.38 (2 H, m), 3.61 (3 H, s), 5.06–5.12 (1 H, m), 5.12–5.17 (1 H, m), 5.66 (1 H, d, $J = 5.1$ Hz) 5.88 (1 H, s); ^{13}C NMR ($CDCl_3$): δ 16.12, 17.69, 20.81 (d, $J = 3.0$ Hz), 25.70, 26.12 (d, $J = 2.4$ Hz), 26.62, 26.79 (d, $J = 3.4$ Hz), 29.84 (d, $J = 2.7$ Hz), 39.65 (2 C), 39.92 (2 C), 49.39 (d, $J = 11.1$ Hz), 57.36, 100.83 (d, $J = 11.5$ Hz), 115.78 (d, $J = 8.2$ Hz), 123.24, 124.16, 131.45, 134.53 (d, $J = 5.2$ Hz), 136.12, 146.66 (d, $J = 279.0$ Hz), 155.95 (d, $J = 254.1$ Hz), 162.58 (d, $J = 31.9$ Hz); ^{19}F NMR ($CDCl_3$): δ 16.4 (1 F, d, $J = 6.1$ Hz), 52.1 (1 F, t, $J = 21.4$ Hz); IR (neat): 1793 (C=O), 1719 (C=C) cm^{-1}.

*3.1.10. 4-[8,12-Dimethyl-4-(1,3-dithiolan-2-yl)-3-fluoro-3(E),7(E),11-tridecatrienyl]-3-fluoro-5-methoxy-2(5H)-furanone (**7b**)*

In the above reaction, compound **6b** was used to give compound **7b** in 65% yield.

^{1}H NMR ($CDCl_3$): δ 1.61 (3 H, s), 1.63 (3 H, s), 1.69 (3 H, d, $J = 0.9$ Hz), 1.96–2.01 (2 H, m), 2.04–2.11 (2 H, m), 2.14–2.24 (4 H, m), 2.54–2.71 (4 H, m), 3.22–3.28 (2 H, m), 3.34–3.39 (2 H, m), 3.62 (3 H, s), 5.08–5.13 (1 H, m), 5.16–5.21 (1 H, m), 5.36 (1 H, d, $J = 2.9$ Hz), 5.67 (1 H, d, $J = 5.1$ Hz); ^{13}C NMR ($CDCl_3$): δ 16.05, 17.69, 21.13 (d, $J = 3.2$ Hz), 25.71, 26.26, 26.33, 26.71, 28.77, 39.65 (2 C), 40.13 (2 C), 53.16 (d, $J = 8.8$ Hz), 57.31, 100.80 (d, $J = 11.5$ Hz), 116.97 (d, $J = 18.6$ Hz), 123.86, 124.36, 131.30, 134.15 (d, $J = 5.6$ Hz), 135.64, 147.02 (d, $J = 279.1$ Hz), 155.89 (d, $J = 252.8$ Hz), 162.64 (d, $J = 31.5$ Hz); ^{19}F NMR ($CDCl_3$): δ 16.8 (1 F, d, $J = 6$ Hz), 59.5 (1 F, dt, $J = 22.9$, 3.1 Hz); IR (neat): 1792 (C=O), 1718 (C=C) cm^{-1}.

*3.1.11. 4-[8,12-Dimethyl-3-fluoro-4-formyl-3(Z),7(E),11-tridecatrienyl]-3-fluoro-5-methoxy-2(5H)-furanone (**8a**)*

To a mixture solution of Ag_2O (0.18 g, 0.8 mmol), $BF_3{\cdot}Et_2O$ (0.11 g, 0.8 mmol), and 15% aqueous THF (3.0 ml), compound **7a** (0.183 g, 0.4 mmol) was dissolved in THF (1.5 ml) and was added dropwise at 0°C. The reaction mixture was stirred for 5 min at this temperature under argon. Et_2O then added, the precipitated salts were filtered, and the solution was washed with brine, then dried

over $MgSO_4$, and the solution was concentrated. The crude product was purified by column chromatography on silica gel, eluting with hexane/ethyl acetate (2:1) to give **8a** (0.029 g, yield 19%).

^{1}H NMR ($CDCl_3$): δ 1.57 (3 H, s), 1.60 (3 H, s), 1.68 (3 H, d, $J = 0.8$ Hz), 1.95–2.00 (2 H, m), 2.02–2.09 (4 H, m), 2.14–2.20 (2 H, m), 2.66–2.71 (2 H, m), 2.77–3.86 (2 H, m), 3.64 (3 H, s), 5.05–5.10 (2 H, m), 5.67 (1 H, d, $J = 5.1$ Hz), 10.14 (1 H, s); ^{19}F NMR ($CDCl_3$): δ 57.5 (1 F, t, $J = 21.4$ Hz), 17.2 (1 F, d, $J = 4.6$ Hz). HRMS calculated for $C_{21}H_{28}O_4F_2$ 382.1954, found *m/e* 382.1945.

*3.1.12. 4-[8,12-Dimethyl-3-fluoro-4-formyl-3(E),7(E),11-tridecatrienyl]-3-fluoro-5-methoxy-2(5H)-furanone (**8b**)*

In the above reaction, compound **7b** was used to give compound **8b** in 24% yield.

^{1}H NMR ($CDCl_3$): δ 1.57 (3 H, s), 1.60 (3 H, s), 1.68 (3 H, d, $J = 0.8$ Hz), 1.94–1.99 (2 H, m), 2.02–2.09 (4 H, m), 2.29–2.32 (2 H, m), 2.66–2.79 (2 H, m), 2.98–3.10 (2 H, m), 3.64 (3 H, s), 5.06–5.13 (2 H, m), 5.67 (1 H, d, $J = 5.1$ Hz), 9.82 (1 H, d, $J = 1.7$ Hz); ^{19}F NMR ($CDCl_3$): δ 81.8 (1 F, t, $J = 22.9$ Hz), 17.4 (1 F, d, $J = 4.6$ Hz). HRMS calculated for $C_{21}H_{28}O_4F_2$ 382.1954, found *m/e* 382.1967.

*3.1.13. 4-[8,12-Dimethyl-3-fluoro-4-formyl-3(Z),7(E),11-tridecatrienyl]-3-fluoro-5-hydroxy-2(5H)-furanone (**9a**)*

To a solution of compound **8a** (0.016 g, 0.042 mmol) in 1,4-dioxane (2 ml), H_2SO_4 (40%, 20 ml) was added. After stirring of 2 h at room temperature, the mixture was poured into water. Oily materials were extracted with diethyl ether, and then the extract was washed with brine, then dried over $MgSO_4$, and the solution was concentrated. Chromatography (silica gel, 1:1 *n*-hexane–ethyl acetate) afforded **9a** (0.0075 g, yield 47%).

^{1}H NMR ($CDCl_3$): δ 1.57 (3 H, s), 1.60 (3 H, s), 1.68 (3 H, s), 1.96–2.03 (2 H, m), 2.03–2.10 (4 H, m), 2.13–2.20 (2 H, m), 2.66–2.72 (2 H, m), 2.80–3.89 (2 H, m), 5.05–5.11 (2 H, m), 5.88 (1 H, d, $J = 4.5$ Hz), 10.43 (1 H, s); ^{19}F NMR ($CDCl_3$): δ 57.2 (1 F, t, $J = 22.8$ Hz), 15.3 (1 F, d, $J = 3.6$ Hz). HRMS calculated for $C_{20}H_{26}O_4F_2$ 368.1797, found *m/e* 368.1794.

*3.1.14. 4-[8,12-Dimethyl-3-fluoro-4-formyl-3(E),7(E),11-tridecatrienyl]-3-fluoro-5-hydroxy-2(5H)-furanone (**9b**)*

In the above reaction, compound **8b** was used to afford compound **9b** in 40% yield.

^{1}H NMR ($CDCl_3$): δ 1.57 (3 H, s), 1.60 (3 H, s), 1.68 (3 H, s), 1.94–2.00 (2 H, m), 2.03–2.11 (4 H, m), 2.29–2.31 (2 H, m), 2.66–2.80 (2 H, m), 3.00–3.15 (2 H, m), 5.04–5.13 (2 H, m), 5.67 (1 H, d, $J = 4.6$ Hz), 9.88 (1 H, d, $J = 1.7$ Hz); ^{19}F NMR ($CDCl_3$): δ 81.7 (1 F, t, $J = 22.9$ Hz), 15.1 (1 F, d, $J = 4.3$ Hz). HRMS calculated for $C_{20}H_{26}O_4F_2$ 368.1797, found *m/e* 368.1788.

References

[1] E.D. De Silva, P.J. Sheuer, Tetrahedron Lett. 21 (1980) 1611.
[2] L.J. Reynolds, B.P. Morgan, G.A. HiteE, D. Mihelich, E.A. Dennis, J. Am. Chem. Soc. 110 (1988) 5172.
[3] W.W. Wilkerson, Drugs of the Future 15 (1990) 140.
[4] M. Waite, J. Lipid Res. 26 (1985) 1379.
[5] I. Kudo, H.W. Chang, S. Hara, M. Murakami, K. Inoue, Dermatologica 179 (1989) 72.
[6] K.B. Glaser, R.S. Jacobs, Biochem. Pharmacol. 36 (1987) 2079.
[7] R.A. Deems, D. Lombardo, B.P. Morgan, E.D. Mihelich, E.A. Dennis, Biochem. Biophys. Acta 917 (1987) 258.
[8] N. Shinohara, J. Haga, T. Yamazaki, T. Kitazume, J. Org. Chem. 60 (1995) 4363.
[9] N. Shinohara, T. Yamazaki, T. Kitazume, Bioorg. Med. Chem. Lett. 5 (1995) 923.
[10] A.J. Lovey, B.A. Pawson, J. Med. Chem. 25 (1982) 71.
[11] G.L. Pattenden, B.C.L. Weedon, J. Chem. Soc. (1968) 1984.
[12] C.D. Poulter, J.C. Argyle, E.A. Mash, J. Am. Chem. Soc. 99 (1977) 957.