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Intramolecular Diels–Alder reaction of α-fluoroacrylate derivatives promoted by novel bidentate aluminum Lewis acid

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Dedicated to Professor Iwao Ojima on the occasion of his 60th birthday.

Abstract

Intramolecular Diels–Alder (IMDA) reaction of α-fluoroacrylate derivatives **1a–e** having 1,7,9-decatrienoate system is efficiently promoted by the novel bidentate Lewis acid **A** generated in situ by mixing 3,3′,5,5′-tetrabromo-1,1′-biphenyl-2,2′-diol (Br_4BIPOL, 1 mol) and trimethylaluminum (2 mol). The IMDA reaction of α-fluoroacrylates proceeds via *endo*-boat transition state as in the case of the corresponding non-fluorinated acrylate.

Keywords: Diels–Alder reaction; α-Fluoroacrylate; 1,1′-Biphenyl-2,2′-diol derivative; Alkylaluminum; Bidentate Lewis acid

1. Introduction

It has been well documented that the intramolecular Diels–Alder (IMDA) reaction is a powerful mean for the stereoselective construction of highly functionalized polycyclic molecules [1–7]. In the IMDA reaction, the tether moiety connecting diene and dienophile parts often plays an important role on the reactivity of the substrate and the stereochemical outcome of the product [8]. For example, contrary to the IMDA reaction of hydrocarbon substrates or amide-tethered triene compounds, that of ester tethered substrates generally requires high temperature and long reaction time to get the cyclized product, but in some cases even fails to obtain any cyclized product [9–14]. The low reactivity of ester tethered substrate is explained by a preference of transoid geometry due to repulsive dipole interaction between carbonyl-oxygen and ethereal oxygen and steric repulsion between two alkyl substituents (R^1 and R^2), thereby the cisoid form, in which the diene and dienophile are in close proximity required for the IMDA reaction is more unfavorable [15–20]. Towards to this issue, we have demonstrated that a bidentate Lewis acid, which has bis-aluminated triflic amide structure, can nicely promote the IMDA reaction of ester tethered 1,7,9-decatrienoates [21–23]. The efficiency of this bidentate Lewis acid is possibly due to extensive restriction to the cisoid conformation and decrease in LUMO level of the dienophile part through the bidentate coordination of the ester group (Scheme 1).

Due to the unique physical and chemical properties of organofluorine compounds brought about by incorporation of fluorine atom into the molecule, organofluorine compounds have been attracting much attention, in particular in the field of medicinal chemistry and material science [24–26]. It would be expected that the Diels–Alder reaction of fluorinated dienophiles provides a powerful mean for the construction of fluorinated cyclic compounds. Indeed, several examples of fluorine-modified biologically active compounds such as L-glutamate [27–29], cantharidin and endothall [30], D-homosteroids [31], which were synthesized using the Diels–Alder reaction, were reported. In these examples, the intermolecular Diels–Alder reactions were employed, and as far as we know, there has been only one report on the intramolecular version using a trifluoromethylated olefin as a

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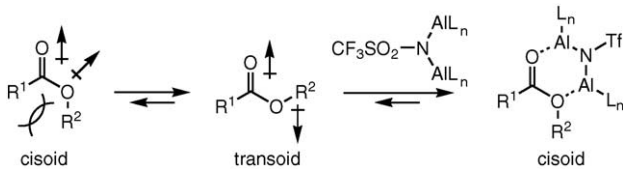


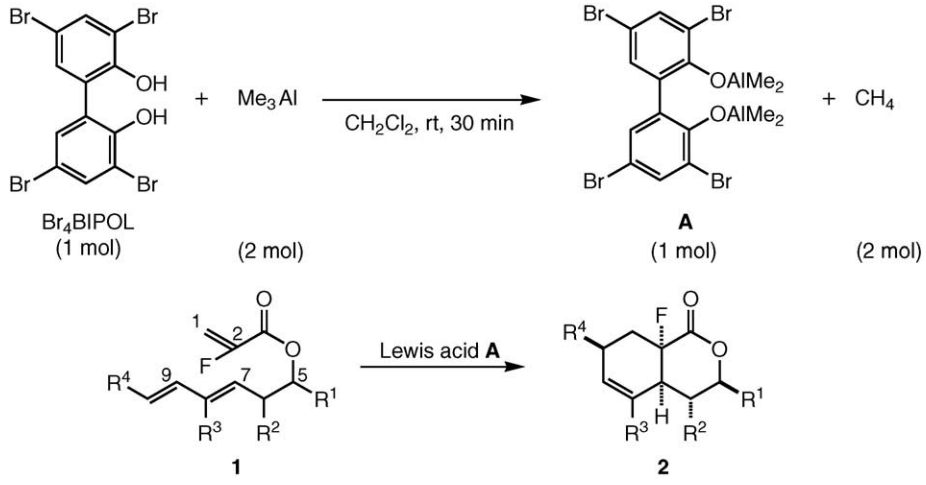
Scheme 1.

dienophile part [32]. Related to our ongoing study on the IMDA reaction of ester-tethered 1,7,9-decatrienoates efficiently promoted by a bidentate aluminated Lewis acid, we have examined the IMDA reaction of 1,7,9-decatrienoates having α-fluoroacrylate moiety. We found that the novel bidentate Lewis acid **A** generated in situ by mixing 3,3′,5,5′-tetrabromo-1,1′-biphenyl-2,2′-diol (Br_4BIPOL) and trimethylaluminum (2 equiv.) can efficiently promote the IMDA reaction of α-fluoroacrylate derivatives **1** having 1,7,9-decatrienoate system (Scheme 2). These results are the first successful examples of the IMDA reaction of α-fluoroacrylate derivatives and the detail is reported in this paper.

2. Results and discussion

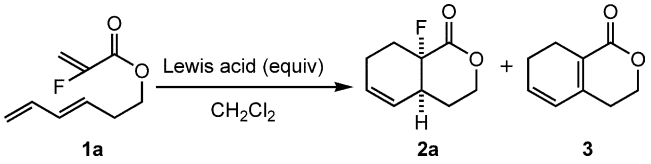
The IMDA reaction of 3,5-hexadienyl 2-fluoroacrylate **1a** was conducted under the various reaction conditions, in particular to find out an effective Lewis acid catalyst (Table 1). When the triflic amide-based aluminated Lewis acid TfN[Al(Me)Cl]$_2$ (1.1 equiv.), which showed the best efficiency as the catalyst in the IMDA reaction of non-fluorinated 1,7,9-decatrienoates was employed, the starting triene **1a** was consumed within 6 h at −24 °C giving rise to the desired cycloadduct **2a** in 35% yield along with the isolation of the defluorinated by-product **3** in some extent (entry 1). Since it was confirmed from the separate experiment that defluorination of the cycloadduct **2a** leading to **3** is promoted by the Lewis acid TfN[Al(Me)Cl]$_2$, less acidic Lewis acids TfN($AlMe_2$)$_2$ or TfN[Al(*i*-Bu)$_2$]$_2$ were examined. However, any significant improvement was not realized. Further efforts to find out an effective catalyst were made by changing the basic structure of the ligand, and 1,1′-biphenyl-2,2′-diol (BIPOL) was found to be an employable ligand. As shown in entry 2, the bis-aluminated BIPOL generated from 1,1′-biphenyl-2,2′-diol (1.1 equiv.) and Me_2AlCl (2.0 equiv.) promoted the IMDA reaction of **1a** at room temperature to give **2a** in 30% yield. Modification of BIPOL moiety by introducing bromine atoms led to more effective ligand. Thus, on using a combination of 3,3′-dibromo-1,1′-biphenyl-2,2′-diol (Br_2BIPOL) or 3,3′,5,5′-tetrabromo derivative (Br_4BIPOL) and Me_2AlCl increase in the yield of **2a** was observed, while with these Lewis acid defluorination of the cyclized product **2a** could not be prevented (entries 3, 4). A combination of Br_4BIPOL and Me_3Al instead of Me_2AlCl provided better results. That is, in the presence of 1.1 molar equivalent of Br_4BIPOL/2Me_3Al relative to **1a**, the IMDA product **2a** was obtained in 51% yield after 22 h at room temperature along with the recovery of **1a** (30%, entry 5), while at higher reaction temperature (60 °C) a significant decrease in the yield of **2a** due to defluorination reaction was observed (entry 8). The best result with **1a** was obtained when the reaction was carried out at room temperature using 1.5 molar equivalent of the present Lewis acids (entry 6). On the other hand, monodentate Lewis acid generated from mono-methylated Br_4BIPOL (Br_4BIPOL-OMe) and Me_3Al (1 equiv.) was found to be less effective. Thus, under the same reaction conditions with this Lewis acid, the IMDA product **2a** was obtained in only 23% yield along with the recovery of **1a** in 41% (entry 9). The *cis*-fused ring system in the product **2a** was determined based on the correlation between the fluorine atom and the angular hydrogen atom observed in the ^{19}F-^{1}H HOESY experiment [33].

As mentioned above, since we could find out an effective catalyst for the IMDA reaction of 3,5-hexadienyl 2-fluoroacrylate **1a**, we next examined the substituent effect



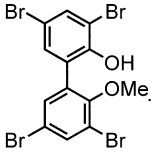
Scheme 2.

Table 1
Effect of bidentate Lewis acids on IMDA reaction of α-fluoroacrylate **1a**



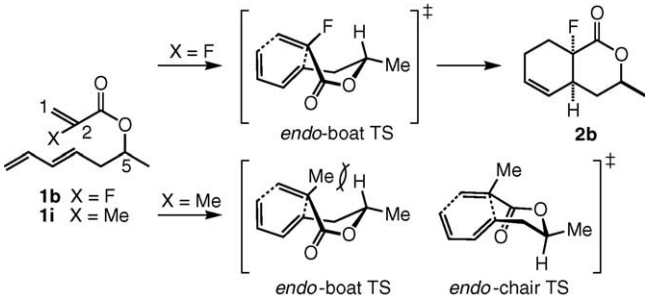
Entry	Lewis acid (equiv.)	Temperature (°C)	Time (h)	Yield[a] (%)	
				2	**3**
1	$TfN[Al(Me)Cl]_2$ (1.1)	−24	6	35	ND[b]
2	BIPOL + $2Me_2AlCl$ (1.1)	rt	9	30	ND[b]
3	Br_2BIPOL + $2Me_2AlCl$ (1.1)	rt	8	39	ND[b]
4[c]	Br_4BIPOL + $2Me_2AlCl$ (1.1)	rt	3	46	14
5[d]	Br_4BIPOL + $2Me_3Al$ (1.1)	rt	22	51	0
6[e]	Br_4BIPOL + $2Me_3Al$ (1.5)	rt	8	65	0
7[f]	Br_4BIPOL + $2Me_3Al$ (2.0)	rt	8	64	Trace
8[g]	Br_4BIPOL + $2Me_3Al$ (1.1)	60	10	41	26
9[h]	Br_4BIPOL-OMe + Me_3Al (3.0)	rt	8	23	0

[a] Isolated yield.
[b] Not determined.
[c] 18% of **1a** was recovered.
[d] 30% of **1a** was recovered.
[e] 13% of **1a** was recovered.
[f] 9% of **1a** was recovered.
[g] $ClCH_2CH_2Cl$ was used as solvent.
[h] 41% of **1a** was recovered

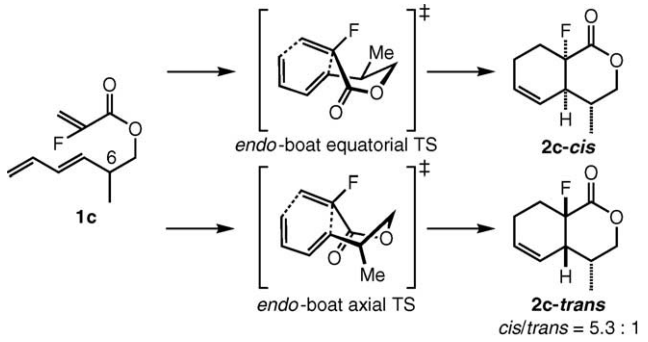


Br_4BIPOL-OMe

in the substrate **1b–e** on the reactivity and the diastereoselectivity. Results are summarized in Table 2. With these substrates, reaction proceeded at room temperature using 1.5 molar equivalent of Br_4BIPOL/$2Me_3Al$ to obtain the IMDA product in good yield and the position of substituent showed significant influence on the reactivity. Compared to the model substrate **1a**, 5-methyl derivative **1b** showed a similar reactivity to give the cyclized product **2b** in 71% yield as a single isomer (entry 2). Reaction of 6-methyl derivative **1c** required longer time (24 h) to give the product **2c** in 61% yield as a mixture of stereoisomers in a ratio of 5.3:1 (entry 3, see also Scheme 4). Both 8-methyl and 10-methyl derivatives **1d**, **1e** gave the corresponding IMDA product **2d**, **2e** as a single isomer. While **1d** showed high reactivity to give **2d** in 88% yield after 6 h, **1e** reacted slowly to give **2e** in moderate yield (42%). Contrary to α-fluoroacrylate **1a**, the chloro derivative **1f** or the methyl derivative **1g** did not react even at higher temperature (entries 6 and 7) and the corresponding acrylate itself **1h** showed somewhat lower reactivity to obtain the IMDA product **2h** in 58% yield after 42 h at 80 °C (entry 8 versus entry 1).



Scheme 3.



Scheme 4.

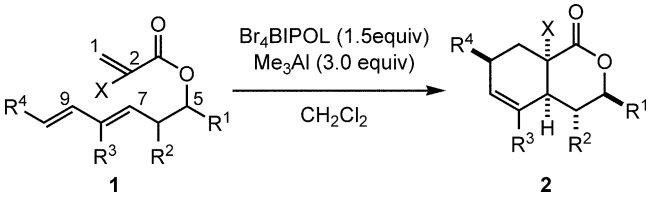
The structures of the products **2b–e** were determined by ^{19}F-^{1}H HOESY data or X-ray crystallographic analysis. Based on the structures of the products **2a–e**, all of which have *cis*-fused bicyclic structure, the IMDA reaction of α-fluoroacrylates proceeds via *endo*-boat transition state as in the case of the corresponding non-fluorinated acrylate [11,21]. These results may indicate that fluorine atom well mimics hydrogen in the present IMDA reaction, since the IMDA reaction of methacrylate **1i** (α-methyl instead of α-fluoro derivative **1b**) gave a diastereomer mixture of the cyclized products due to the steric interaction between α-methyl and 5-hydrogen substituents [21,22] (Scheme 3). 6-Methyl derivative **1c** gave the IMDA product as a mixture of **2c**-*cis* and **2c**-*trans* in a ratio of 5.3: 1, which would be formed via *endo*-boat-equatorial transition state and *endo*-boat axial transition state, respectively (Scheme 4).

In conclusion, we have demonstrated that a novel bidentate Lewis acid **A** in situ generated from Br_4BIPOL and Me_3Al can promote the IMDA reaction of α-fluoroacrylate derivatives to give the cycloadduct in good yield and with excellent stereoselectivity. These results are the first examples of the IMDA reaction of fluorinated triene systems and provide useful method for the stereoselective construction of fluorinated polycyclic molecules.

3. Experimental details

General: 2,2′-Biphenyl-1,1′-binol, trimethylaluminum (1.0 M in hexane) and dimethylaluminum chloride (1.0 M

Table 2
IMDA reaction of α-fluoroacrylate derivatives



1 2

Entry	1	X	R^1	R^2	R^3	R^4	Temperature (°C)	Time (h)	Yield[a] (%)		dr[b]
									2	1	
1	**1a**	F	H	H	H	H	rt	8	65	0	Single isomer
2	**1b**	F	Me	H	H	H	rt	8	71	0	Single isomer
3[c]	**1c**	F	H	Me	H	H	rt	24	61	8	5.3:1[d]
4	**1d**	F	H	H	Me	H	rt	6	88	0	Single isomer
5[c]	**1e**	F	H	H	H	Me	rt	12	42	0	Single isomer
6[e]	**1f**	Cl	H	H	H	H	80	12	No reaction		
7[e]	**1g**[f]	Me	H	H	H	H	80	41	No reaction		
8[e]	**1h**[f]	H	H	H	H	H	80	42	58	4	Single isomer

[a] Isolated yield.
[b] Based on ^{1}H-NMR.
[c] Trace amount of **3c** or ***3e*** (< 5% yield) was obtained.
[d] A ratio of *cis*/*trans*.
[e] Solvent; $ClCH_2CH_2Cl$.
[f] Ref. [21].

in hexane) are available commercially. 3,3′,5,5′-Tetrabromo-2,2′-biphenyl-1,1′-diol (Br_4BIPOL) was prepared according to the reported procedure [34]. All reactions were carried out under argon atmosphere. ^{1}H- and ^{13}C-NMR spectra were taken on a Bruker dpx400 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ for ^{1}H-NMR, and $CDCl_3$ (77.01 ppm) for ^{13}C-NMR as an internal standard, respectively. ^{19}F-NMR spectra were taken on a Bruker dpx400 spectrometer, and chemical shifts were reported in parts per million using benzotrifluoride as a standard. Infrared (IR) spectra were recorded on a JASCO FT/IR-620 infrared spectrophotometer. Mass spectra (MS) were obtained on a VG Auto Spec. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with RI detector.

3.1. General procedure for preparation of α-fluoroacrylate derivatives (*1*)

To a solution of 3,5-hexadiene-1-ol (491 mg, 5.0 mmol) in CH_2Cl_2 (10 mL), 2-fluoroacryloyl fluoride [35] (2.2 M in ether, 2.50 mL, 5.5 mmol) and triethylamine (0.63 mL, 6.0 mmol) were added at 0 °C. After being stirred at room temperature for 2 h, the reaction mixture was quenched by H_2O and extracted with diethyl ether. The organic layer was washed with brine and dried over $MgSO_4$. Purification by column chromatography (hexane/ether = 25:1) gave the product **1a** (731 mg, 4.2 mmol, 82%). By a similar procedure for the preparation of **1a**, the substrates **1b–e** were prepared from the corresponding dienyl alcohol and 2-fluoroacryloyl fluoride.

3.1.1. (3E)-3,5-hexadienyl 2-fluoroacrylate (*1a*)

Colorless oil. IR (neat) ν cm^{-1}; 1746. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 2.49 (2H, dd, J = 13.9, 6.8 Hz), 4.28 (2H, t, J = 6.8 Hz), 5.03 (1H, bd, J = 10.2 Hz), 5.15 (1H, bd, J = 16.6 Hz), 5.32 (1H, dd, J = 13.0, 3.2 Hz), 5.63–5.70 (1H, m), 5.66 (1H, dd, J = 43.0, 3.2 Hz), 6.14 (1H, dd, J = 13.9, 10.5 Hz), 6.30 (1H, dd, J = 16.6, 10.2, 10.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 31.7, 64.9, 102.7 (d, J = 15.2 Hz), 116.4, 128.8, 133.8, 136.6, 153.3 (d, J = 262.2 Hz), 160.3 (d, J = 36.6 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −54.4 (1F, dd, J = 43.0, 13.0 Hz) EI-MS *m*/*z*: 45.0 $[M\text{-}C_8H_{11}O_2]^+$, 73.0 $[M\text{-}C_7H_{11}O]^+$. Anal. Calcd for $C_9H_{11}FO_2$: C, 63.52; H, 6.52. Found: C, 63.48; H, 6.39.

3.1.2. (1S*,3E)-1-methyl-3,5-hexadienyl 2-fluoroacrylate (*1b*)

A 68% yield. Colorless oil. IR (neat) ν cm^{-1}; 1745. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.30 (3H, d, J = 6.3 Hz), 2.15–2.78 (2H, m), 5.02 (1H, d, J = 10.7 Hz), 5.05–5.11 (1H, m), 5.13 (1H, d, J = 16.9 Hz), 5.30 (1H, dd, J = 13.0, 3.1 Hz), 5.60–5.64 (1H, m), 5.62 (1H, dd, J = 44.0, 3.1 Hz), 6.11 (1H, dd, J = 16.0, 10.7 Hz), 6.29 (1H, ddd, J = 16.9, 10.7, 10.7 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 19.8, 39.2, 72.7, 102.8 (d, J = 15.4 Hz), 116.7, 128.9, 134.7, 137.0, 154.0 (d, J = 262.7 Hz), 160.3 (d, J = 36.7 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −54.2 (1F, dd, J = 44.0,

13.0 Hz) EI-MS *m/z*: 73.0 [*M*-$C_7H_{11}O$]$^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 64.97; H, 7.13.

3.1.3. (2R*,3E)-2-methyl-3,5-hexadienyl 2-fluoroacrylate (1c)

An 83% yield. Colorless oil. IR (neat) ν cm^{-1}; 1746. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.09 (3H, d, J = 6.8 Hz), 2.59–2.70 (1H, m), 4.05–4.20 (2H, m), 5.03 (1H, d, J = 10.2 Hz), 5.16 (1H, d, J = 17.9 Hz), 5.31 (1H, dd, J = 13.0, 3.2 Hz), 5.55–5.64 (1H, m), 5.65 (1H, dd, J = 43.0, 3.2 Hz), 6.12 (1H, dd, J = 15.1, 10.3 Hz), 6.31 (1H, ddd, J = 17.9, 10.2, 10.2 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 17.0, 36.3, 69.9, 103.1 (d, J = 15.2 Hz), 116.8, 132.1, 135.4, 137.2, 153.7 (d, J = 262.2 Hz), 160.7 (d, J = 36.5 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −54.3 (1F, dd, J = 43.0, 13.0 Hz). EI-MS *m/z*: 184 [*M*]$^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.20; H, 7.12.

3.1.4. (3E)-4-methyl-3,5-hexadienyl 2-fluoroacrylate (1d)

An 87% yield. Colorless oil. IR (neat) ν cm^{-1}; 1744. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.77 (3H, s), 2.56 (2H, dd, J = 14.1, 7.0 Hz), 4.26 (2H, t, J = 7.0 Hz), 4.99 (1H, d, J = 10.7 Hz), 5.14 (1H, d, J = 17.4 Hz), 5.31 (1H, dd, J = 13.0, 3.2 Hz), 5.46 (1H, dd, J = 7.0, 7.0 Hz), 5.65 (1H, dd, J = 43.0, 3.2 Hz), 6.37 (1H, dd, J = 17.4, 10.7 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 11.8, 27.6, 64.9, 102.6 (d, J = 15.2 Hz), 111.9, 126.4, 137.0, 140.9, 153.3 (d, J = 262.0 Hz), 160.4 (d, J = 36.4 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −54.2 (1F, dd, J = 43.0, 13.0 Hz). EI-MS *m/z*: 45.0 [*M*-$C_8H_{11}O_2$]$^+$, 73.0 [*M*-$C_7H_{11}O$]$^+$, 93.0 [*M*-$C_3H_4FO_2$]$^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.22; H, 7.12.

3.1.5. (3E,5E)-3,5-heptadienyl 2-fluoroacrylate (1e)

An 76% yield. Colorless oil. IR (neat) ν cm^{-1}; 1744. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.73 (3H, d, J = 6.7 Hz), 2.45 (2H, dd, J = 13.7, 6.8 Hz), 4.26 (2H, dd, J = 6.8, 6.8 Hz), 5.31 (1H, dd, J = 14.0, 3.2 Hz), 5.42–5.53 (1H, m), 5.57–5.68 (1H, m), 5.65 (1H, dd, J = 43.0, 3.2 Hz), 5.96–6.15 (2H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 18.0, 31.7, 65.2, 102.6 (d, J = 15.1 Hz), 125.3, 128.6, 131.1, 133.4, 153.3 (d, J = 262.0 Hz), 160.3 (d, J = 36.6 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −54.4 (1F, dd, J = 14.0, 43.0 Hz). EI-MS *m/z*: 184 [*M*]$^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.02; H, 7.10.

3.2. Preparation of α-chloroacrylate derivative (1f)

A mixture of 3,5-hexadiene-1-ol (491 mg, 5.0 mmol), 2-chloroacrylic acid (530 mg, 5.0 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC-HCl, 1.0 g, 5.5 mmol) in CH_2Cl_2 (5.0 mL) were stirred at room temperature for 5 h. After the reaction mixture was quenched by the addition of H_2O followed by extractive workup (diethyl ether), the residue was purified by silica gel column chromatography (hexane/ether = 25:1) to give the product **1f** (368 mg, 2.0 mmol, 39%).

3.2.1. (3E)-3,5-hexadienyl 2-chloroacrylate (1f)

Colorless oil. IR (neat) ν cm^{-1}; 1734. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 2.50 (3H, dd, J = 13.4, 6.7 Hz), 4.28 (2H, dd, J = 6.7, 6.7 Hz), 5.03 (1H, d, J = 10.0z), 5.14 (1H, d, J = 16.9 Hz), 5.61–5.72 (1H, m), 5.99 (1H, d, J = 1.3 Hz), 6.15 (1H, J = 15.2, 10.4 Hz), 6.32 (1H, J = 16.9, 15.2, 10.9 Hz), 6.50 (1H, d, J = 1.3 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ; 31.8, 65.5, 116.3, 125.7, 128.8, 131.4, 133.7, 136.5, 161.7. ESI-MS *m/z*: 187 [M + H]$^+$. HRMS Calcd for $C_9H_{12}ClO_2$ [M + H]$^+$: 187.0526. Found: 187.0524.

3.3. General procedure of Lewis acid mediated IMDA reactions of 1,7,9-decatrienoate derivatives

After a suspension of Br_4BIPOL (82 mg, 0.55 mmol) in CH_2Cl_2 (4.5 mL) was treated with trimethylaluminum (1.0 M in hexane, 1.1 mL, 1.1 mmol) for 30 min at room temperature, **1a** (85.0 mg, 0.50 mmol) in CH_2Cl_2 (2.5 mL) was added at room temperature. After being stirred for 8 h at the same temperature, the reaction mixture was quenched by 1 M HCl and extracted with diethyl ether. The organic layer was washed with brine and dried over $MgSO_4$. Purification by column chromatography on silica gel (hexane/AcOEt = 5:1) gave the product **2a** (55.5 mg, 65% yield).

3.3.1. (4aS*,8aS*)-8a-fluoro-3,4,4a,7,8,8a-hexahydro-1H-isochromen-1-one (2a)

Colorless oil. IR (neat) ν cm^{-1}; 1743. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.50–0.64 (1H, m), 0.77–0.92 (1H, m), 1.01–1.16 (1H, m), 1.21–1.36 (3H, m), 1.88–2.02 (1H, m), 3.63–3.88 (2H, m), 5.06–5.15 (1H, m), 5.52–5.63 (1H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 22.6 (d, J = 7.8 Hz), 27.0 (d, J = 3.5 Hz), 28.5 (d, J = 22.3 Hz), 38.2 (d, J = 21.9 Hz), 67.7, 91.5 (d, J = 180.6 Hz), 125.0 (d, J = 4.3 Hz), 128.9, 168.6 (d, J = 23.9 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −85.3 (1F, m). EI-MS *m/z*: 170.0 [*M*]$^+$. Anal. Calcd for $C_9H_{11}FO_2$: C, 63.52; H, 6.52. Found: C, 63.40; H, 6.58.

3.3.2. (3S*,4aS*,8aS*)-8a-fluoro-3-methyl-3,4,4a,7,8,8a-hexahydro-1H-isochromen-1-one (2b)

An 71% yield. Colorless oil. IR (neat) ν cm^{-1}; 1736. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.37 (3H, d, J = 6.3 Hz), 1.42 (1H, ddd, J = 14.6, 11.9, 11.9 Hz), 1.90–2.24 (4H, m), 2.27–2.38 (1H, m), 2.73–2.82 (1H, m), 4.63 (1H, dtd, J = 18.0, 6.3, 2.5 Hz), 5.50 (1H, bd, J = 10.1 Hz), 5.76–5.83 (1H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 21.4, 21.5 (d, J = 5.4 Hz), 27.3 (d, J = 23.5 Hz), 37.4 (d, J = 6.1 Hz), 38.4 (d, J = 22.8 Hz), 75.8, 91.1 (d, J = 181.4 Hz), 125.3, 126.8, 170.1 (d, J = 23.8 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −91.6 (1F, ddd, J = 30.0, 22.0, 10.0 Hz). EI-MS *m/z*: 184

$[M]^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.03; H, 6.96.

3.3.3. (4R*,4aR*,8aS*)-8a-fluoro-4-methyl-3,4,4a,7,8, 8a-hexahydro-1H-isochromen-1-one (**2c**-cis) and (4R*,4aS*,8aR*)-8a-fluoro-4-methyl-3,4,4a,7,8,8a-hexahydro-1H-isochromen-1-one (**2c**-trans)

An 61% yield (diastereomer mixture). Colorless oil. IR (neat) ν cm^{-1}; 1752. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; for *cis*-isomer: 1.04 (3H, d, J = 6.9 Hz), 1.73–1.87 (1H, m), 2.04–2.20 (1H, m), 2.23–2.34 (1H, m), 2.54–2.65 (1H, m), 2.65–2.84 (2H, m), 3.94 (1H, dd, J = 11.5, 11.5 Hz), 4.20 (1H, dd, J = 11.5, 4.3 Hz), 5.55–5.65 (1H, m), 5.91–6.00 (1H, m) for *trans*-isomer: 1.09 (3H, d, J = 6.8 Hz), 1.85–1.97 (1H, m), 1.97–2.36 (4H, m), 2.37–2.50 (1H, m), 4.14 (1H, dd, J = 10.9, 10.9 Hz), 4.22 (1H, ddd, J = 10.9, 4.7, 1.2 Hz), 5.55–5.62 (1H, m), 5.80–5.88 (1H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; for *cis*-isomer: 12.4, 23.9 (d, J = 10.3 Hz), 27.3, 29.8 (d, J = 21.3 Hz), 43.3 (d, J = 20.3 Hz), 72.3, 92.2 (d, J = 179.1 Hz), 120.2 (d, J = 6.9 Hz), 131.5 (d, J = 2.1 Hz), 167.4 (d, J = 23.9 Hz) for *trans*-isomer: 14.7, 21.9 (d, J = 6.4 Hz), 28.2 (d, J = 23. 1 Hz), 35.2 (d, J = 4.0 Hz), 45.1 (d, J = 21.6 Hz), 72.8, 91.2 (d, J = 180.4 Hz), 124.0 (d, J = 2.8 Hz), 127.6, 169.4 (d, J = 24.2 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −86.7 (1F, ddd, J = 29.0, 20.0, 9.0 Hz). EI-MS m/z: 184 $[M]^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.04; H, 7.11.

3.3.4. (4aS*,8aS*)-8a-fluoro-5-methyl-3,4,4a,7,8,8a-hexahydro-1H-isochromen-1-one (**2d**)

An 88% yield. White crystals. mp: 102–104 °C. IR (KBr) ν cm^{-1}; 1745. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.72 (3H, s), 1.77–1.89 (1H, m), 1.96–2.18 (3H, m), 2.22–2.35 (2H, m), 2.59–2.69 (1H, m), 4.32–4.40 (2H, m), 5.58 (1H, bs). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 21.3, 21.8 (d, J = 6.1 Hz), 27.1 (d, J = 5.8 Hz), 28.1 (d, J = 23.0 Hz), 43.5 (d, J = 22.3 Hz), 68.6, 92.5 (d, J = 182.2 Hz), 123.5, 130.8, 170.1 (d, J = 23.8 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −89.5 (1F, m). EI-MS m/z: 184 $[M]^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.16; H, 7.01.

3.3.5. (4aS*,7S*,8aS*)-8a-fluoro-7-methyl-3,4,4a,7,8, 8a-hexahydro-1H-isochromen-1-one (**2e**)

An 42% yield. White crystals. IR (KBr) ν cm^{-1}; 1743. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.06 (3H, d, J = 7.2 Hz), 1.50 (1H, ddd, J = 4.0, 14.0, 10.6 Hz), 1.72–1.84 (1H, m), 2.08–2.17 (1H, m), 2.22–2.31 (1H, m), 2.48–2.60 (1H, m), 2.66–2.69 (1H, m), 4.29–4.42 (2H, m), 5.52 (1H, ddd, J = 10.1, 4.0, 2.7 Hz), 5.71 (1H, bd, J = 10.1 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 20.6, 26.4 (d, J = 3.3 Hz), 30.0 (d, J = 8.1 Hz), 36.0 (d, J = 23.5 Hz), 38.5 (d, J = 23.6 Hz), 68.4, 91.4 (d, J = 184.2 Hz), 124.2, 134.0, 170.5 (d, J = 23.4 Hz). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; −90.1 (1F, ddd, J = 40.0, 20.0, 8.0 Hz). EI-MS m/z: 184 $[M]^+$. Anal. Calcd for $C_{10}H_{13}FO_2$: C, 65.20; H, 7.11. Found: C, 65.12; H, 7.02.

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