Pergamon

Tetrahedron: *Asymmetry* 9 (1998) 1979–1987

TETRAHEDRON: *ASYMMETRY*

Asymmetric Diels–Alder reactions of 2-fluoroacrylic acid derivatives. Part 1: The construction of fluorine substituted chiral tertiary carbon

Hisanaka Ito, Akio Saito and Takeo Taguchi *

Tokyo University of Pharmacy and Life Science, 1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

Received 27 April 1998; accepted 15 May 1998

Abstract

For the construction of chiral monofluorinated tertiary carbons, we have examined the asymmetric Diels–Alder reaction of 2-fluoroacrylic acid derivatives bearing a chiral oxazolidinone moiety. Under diethylaluminum chloride catalyzed conditions at −100°C, the reaction of **1** with isoprene proceeded smoothly with high diastereoselectivity.

1. Introduction

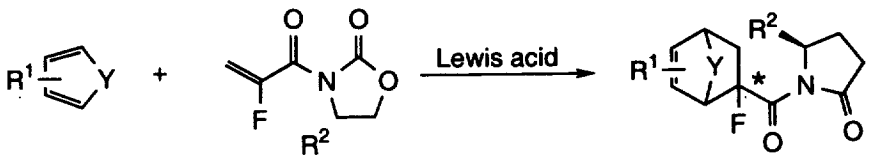
Development of an efficient construction method for enantiomerically pure fluorine-substituted tertiary carbons is of importance for the synthesis of biologically active fluorinated compounds.[1] The asymmetric Diels–Alder reaction of 2-fluoroacrylic acid derivatives could be one of the general approaches for the construction of such molecules. Although there have been a few reports on the Diels–Alder reaction of 2-fluoroacrylic derivatives,[2] the asymmetric version has not been reported. We report herein the Diels–Alder reaction of chiral 2-fluoroacrylic acid derivatives under Lewis acid catalyzed conditions (Scheme 1).

2. Results and discussion

The synthesis of chiral 2-fluoroacrylic acid derivatives bearing an oxazolidinone as a chiral auxiliary can be accomplished in three steps from methyl 2-fluoroacrylate **1** as illustrated in Scheme 2. Methyl 2-fluoroacrylate **1**[3] was converted to acid chloride **2** according to the literature procedure [(a) 2 N

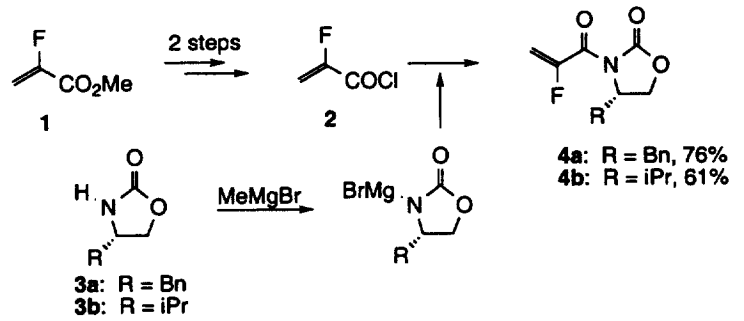
* Corresponding author.

0957-4166/98/$19.00
PII: S0957-4166(98)00195-5



Scheme 1.

NaOH/EtOH; (b) BzCl, hydroquinone, 160°C].[4] The reaction of **2** with the oxazolidinone moiety was achieved according to the Evans' procedure.[5] Thus, the treatment of chiral oxazolidinones **3a** and **3b** with methylmagnesium bromide and the following addition of **2** gave the desired compounds **4a** and **4b** in 76% and 61% yield (from **2**), respectively.



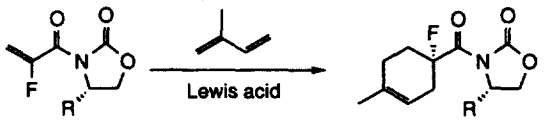
Scheme 2.

The Lewis acid promoted Diels–Alder reactions of **4a** and **4b** with isoprene are summarized in Table 1. In the presence of 1.5 equivalents of diethylaluminum chloride, the Diels–Alder reaction of **4a** and **4b** proceeded at −78°C to give cycloadducts **5a** in 60% yield with 70% de and **5b** in 40% yield with 59% de, respectively (entries 1, 2).[6] As in the case of non-fluorinated *N*-enoyloxazolidinone, these results indicate the importance of an aromatic group in the substituent (R) for π interaction in the transition state to achieve higher diastereoselectivity.[5] Determination of the diastereoselectivity was accomplished by the conversion of the cycloadduct to its benzyl ester (BnOLi/THF) and following HPLC analysis by using a chiral column. We also examined the effect of Lewis acid and reaction temperature. In all cases examined here, diastereomeric preference was not affected by the Lewis acid employed. The diastereoselectivity was significantly increased at low temperature in the presence of 1.5 equivalents of diethylaluminum chloride (entries 2, 4, and 5). The best result was obtained when 1.5 equivalents of diethylaluminum chloride was used at −100°C (entry 5, 59% yield, 90% de).

To examine the influence of the fluorine atom on *exo*/*endo* selectivity, the Diels–Alder reactions of **4a** with cyclopentadiene were conducted and the results are summarized in Table 2. Although the chemical yield of cycloadduct **6** was satisfactory in the presence of certain kinds of Lewis acid, the *exo*/*endo* selectivity was not as high as expected. Among the Lewis acids examined, titanium tetrachloride gave the *exo*-adduct in slight predominance. Both *exo*- and *endo*-adducts were obtained in higher diastereofacial selectivity (entry 3, *exo*; 96% de, *endo*; 95% de) than with isoprene.

The absolute stereochemistry of the adduct **6** was determined as shown in Scheme 3. After the Diels–Alder reaction of **4a** with cyclopentadiene at −100°C in the presence of 1.5 equivalents of diethylaluminum chloride and the separation of *endo*/*exo* isomers of **6**, **6**-*endo* and **6**-*exo* were converted to (−)-**10** and (−)-**11**, respectively. The known compound **8** ($[\alpha]_D^{25}$=59.3) was prepared by the asymmetric Diels–Alder reaction of **7** with cyclopentadiene at −78°C followed by benzyl esterification

Table 1
The Diels–Alder reaction of **4a** and **4b** with isoprene



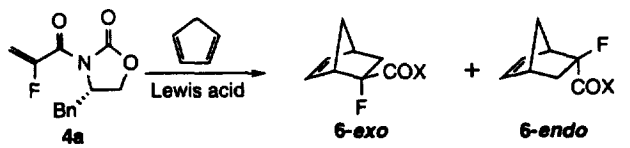
4a: R = Bn
4b: R = iPr

5a: R = Bn
5b: R = iPr

Entry	Substrate	Lewis acid	Equivalent	Temp. (°C)	Time (h)	Yield (%)[a,b]	de (%)[c]
1	**4b**	Et_2AlCl	1.5	-78	1	40	59
2	**4a**	Et_2AlCl	1.5	-78	1	60	70
3	**4a**	Et_2AlCl	0.95	-78	26	45	52
4	**4a**	Et_2AlCl	1.5	-85	1	48	75
5	**4a**	Et_2AlCl	1.5	-100	1.5	59	90
6	**4a**	$TiCl_4$	1.2	-78	1	39	44
7	**4a**	$ZrCl_4$	1.4	-78	1	78	55

a) All reactions were carried out in dichloromethane. b) Isolated yield. c) Diastereomeric excess was determined by HPLC analysis using a chiral column after conversion to its benzyl ester.

Table 2
The Diels–Alder reaction of **4a** with cyclopentadiene



4a

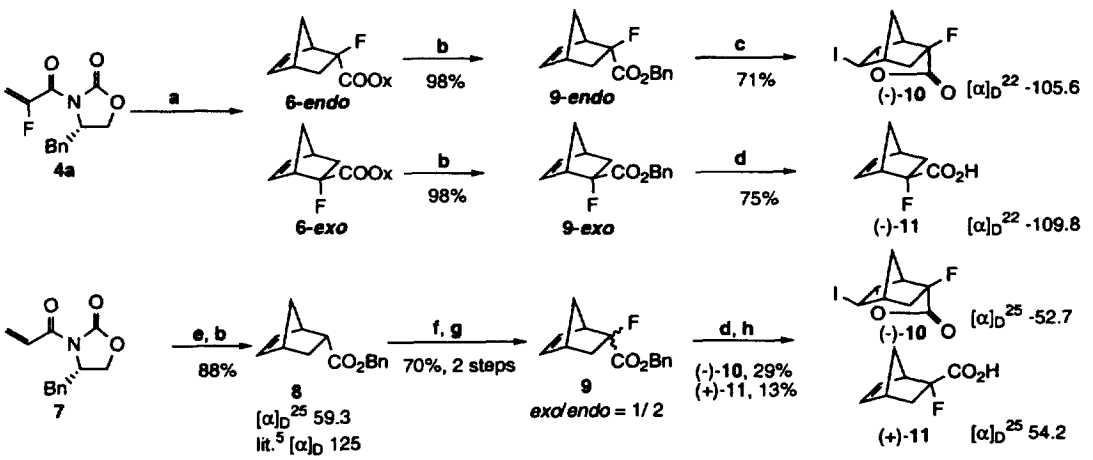
6-*exo*

6-*endo*

Entry	Lewis acid	Equivalent	Temp. (°C)	Time (h)	Yield (%)[a,b]	*exo* : *endo*[c]
1	Et_2AlCl	0.95	-78	1.5	91	1.6 : 1
2	Et_2AlCl	1.5	-78	0.5	88	1.0 : 1
3	Et_2AlCl	1.5	-100	0.75	80	1.0 : 1[d]
4	Me_3Al	1.1	-78	2.5	83	1.0 : 1
5	$TiCl_4$	1.2	-78	0.75	92	3.6 : 1
6	$SnCl_4$	1.1	-78	4	97	1.3 : 1

a) All reactions were carried out in dichloromethane. b) Isolated yield. c) The ratio of *endo* and *exo* forms was determined by 400 MHz ^1H NMR. d) *exo*; 96% de, *endo*; 95% de. Determined by HPLC analysis using a chiral column after reduction of **6** followed by benzoyl esterification.

(lit.[5] $[\alpha]_D^{25}$=125, in the literature, the Diels–Alder reaction was carried out at −100°C). Fluorination at the α-position of the carbonyl group in **8** was achieved by the following procedure. After conversion of **8** to its silyl enol ether, a fluorination reaction with *N*-fluoro-2,4,6-trimethylpyridinium triflate[7] afforded the fluoro ester **9** as an *endo*:*exo* isomeric mixture (2:1) in 70% yield. The *endo*/*exo* mixture could be separated by the iodolactonization. Through the determination of the specific rotation of the four compounds (Scheme 3), we could determine the absolute stereochemistries of the cycloadducts and reveal the nearly equal diastereofacial selectivity for both *endo*- and *exo*-adducts **6** in the Diels–Alder reaction of **4a** in the presence of 1.5 equivalents of diethylaluminum chloride at −100°C.



Reagent and conditions: **a** cyclopentadiene, 1.5 eq. of diethylaluminum chloride/CH_2Cl_2, -100 °C; **b** 1.5 eq. of BnOLi/THF, 0 °C-r.t.; **c** I_2, CH_3CN, r.t.; **d** 1*N* NaOH/THF, MeOH, r.t.; **e** cyclopentadiene, 1.5 eq. of diethylaluminum chloride/CH_2Cl_2, -78 °C; **f** LDA, TMSCl/THF, -40 °C-r.t.; **g** *N*-fluoro-2,4,6-trimethylpyridinium triflate, K_2CO_3/CH_2Cl_2, reflux; **h** I_2, KI, $NaHCO_3/H_2O$, 0 °C-r.t.

Scheme 3.

The mechanism of stereoselectivity could be considered as Fig. 1. Although we expected an abnormal facial selectivity caused by the fluorine–aluminum interaction,[8] the direction of asymmetric induction was similar to the Evans' result with non-fluorinated substrates.[5] That is, in the presence of more than 1 equivalent of diethylaluminum chloride, an aluminum atom coordinates to two carbonyl groups to form a six membered cyclic intermediate. The *Re* face of the fluorine-bearing carbon–carbon double bond of **4a** is sterically crowded by the benzyl group on the oxazolidinone moiety through a π interaction. In accordance with this hypothesis, the cycloaddition occurs selectively from the *Si* face on the dienophile **4a**.

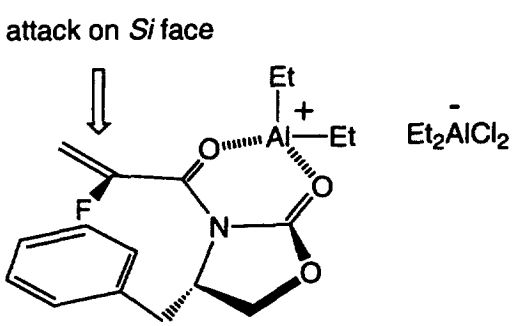


Fig. 1.

In summary, we have demonstrated that the Diels–Alder reaction of 2-fluoroacrylic acid bearing chiral oxazolidinone moieties provides an efficient construction method for chiral fluorine-substituted tertiary carbons. Along these lines, the synthesis of a fluorinated biologically active compound is currently under investigation.

3. Experimental

3.1. General

Melting points are uncorrected. Infrared absorption spectra were recorded using a Perkin–Elmer FTIR-1710. ^{1}H, and ^{13}C NMR spectra were obtained using Varian Gemini 300 (300 MHz), Bruker dpx 400 (400 MHz), and Bruker drx 500 (500 MHz). ^{19}F NMR spectra were obtained using a Bruker dpx 400. In the ^{1}H, ^{13}C, and ^{19}F NMR spectra, chemical shifts are expressed in δ (ppm) downfield from $CHCl_3$ (7.26 ppm), $CDCl_3$ (77.01 ppm), and benzotrifluoride (0 ppm), respectively. Mass spectra were recorded using HITACHI M-80, Finnigan MAT TSQ700, and VG Auto Spec. Column chromatography was performed on silica gel, Fuji silysia silica gel BW80S. All nonaqueous reactions were carried out under an argon atmosphere with freshly distilled solvents. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride.

3.2. (4S)-3-(2-Fluoropropenoyl)-4-(phenylmethyl)-2-oxazolidinone 4a

Under an argon atmosphere, to a solution of oxazolidinone **3a** (1.9 g, 10.7 mmol) in THF (100 ml) was added a solution of methylmagnesium bromide in THF (3 M, 3.6 ml, 10.8 mmol) at −78°C and the mixture was stirred for 10 min at −78°C, then for 10 min at 0°C. A solution of **2** (1.34 g, 12 mmol) in THF (5 ml) was added to the reaction mixture and recooled to −78°C. After being stirred for 45 min at −78°C, 2 h at 0°C, and 3 h at r.t., saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. After purification by silica gel column chromatography (hexane/ethyl acetate, 6/1), the compound **4a** (2.29 g, 9.13 mmol) was obtained in 85% yield (based on **3a**).

4a: Mp 80–82°C; $[\alpha]_D^{25}$ 82.1 (*c* 1.05, $CHCl_3$); IR (KBr) 1783, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.19–7.34 (5H, m), 5.45 (1H, dd, *J*=44.2, 3.9 Hz), 5.34 (1H, dd, *J*=14.7, 3.9 Hz), 4.67 (1H, m), 4.29 (1H, dd, *J*=9.0, 7.8 Hz), 4.21 (1H, dd, *J*=9.0, 4.8 Hz), 3.40 (1H, dd, *J*=13.5, 3.6 Hz), 2.84 (1H, dd, *J*=13.5, 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ 37.3, 55.7, 67.1, 102.0 (d, *J*=14.6 Hz), 127.5, 129.0, 129.3, 134.6, 152.3, 155.8 (d, *J*=267.5 Hz), 161.6 (d, *J*=35.9 Hz); ^{19}F NMR ($CDCl_3$) δ −44.7 (dd, *J*=44.2, 14.7 Hz). Anal. calcd for $C_{13}H_{12}FNO_3$: C, 62.65; H, 4.85; N, 5.62. Found: C, 62.71; H, 4.84; N, 5.66.

3.3. (4S)-3-(2-Fluoropropenoyl)-4-(i-propyl)-2-oxazolidinone 4b

According to a similar procedure for the preparation of **4a**, the isopropyl derivative **4b** was prepared in 68% yield from oxazolidinone **3b** (927 mg, 7.2 mmol) and acid chloride **2** (1.17 g, 8.1 mmol), and the final purification by silica gel column chromatography (hexane/ethyl acetate, 8/1).

4b: Mp 67–71°C; $[\alpha]_D^{28}$ 106.8 (*c* 1.57, $CHCl_3$); IR (KBr) 1800, 1694 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.38 (1H, dd, *J*=42.2, 3.9 Hz), 5.28 (1H, dd, *J*=12.9, 3.9 Hz), 4.45 (1H, ddd, *J*=8.8, 8.6, 4.9 Hz), 4.36 (1H, dd, *J*=8.7, 8.6 Hz), 4.23 (1H, dd, *J*=8.7, 4.9 Hz), 2.40 (1H, dqq, *J*=7.0, 7.0, 4.9 Hz), 0.92 (3H, d, *J*=7.0 Hz),

0.88 (3H, d, J=7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 15.1, 18.2, 28.3, 59.1, 64.4, 102.1 (d, J=14.4 Hz), 152.9, 156.0 (d, J=233.0 Hz), 161.9 (d, J=35.8 Hz); ^{19}F NMR ($CDCl_3$) δ −45.6 (dd, J=42.2, 12.9 Hz). Anal. calcd for $C_9H_{12}FNO_3$: C, 53.72; H, 6.01; N, 6.96. Found: C, 53.82; H, 5.95; N, 7.10.

3.4. Typical procedure of the Lewis acid mediated Diels–Alder reaction of 4. (4S)-3-[(4′S)-4′-Fluoro-1-methylcyclohexene-4′-carbonyl]-4-(phenylmethyl)-2-oxazolidinone 5a

Under an argon atmosphere, to a solution of **4a** (100 mg, 0.4 mmol) in CH_2Cl_2 (4 ml) was added a solution of diethylaluminum chloride (0.95 M in hexane, 0.63 ml, 0.6 mmol) at −100°C. After being stirred for 5 min, isoprene (0.8 ml, 8.0 mmol) was added to the reaction mixture at −100°C and the mixture was stirred at the same temperature for 1.5 h. After addition of saturated aqueous ammonium chloride, the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. After purification by silica gel column chromatography (hexane/ethyl acetate, 8/1), the compound **5a** (75.7 mg, 0.237 mmol) was obtained in 59% yield.

5a: $[\alpha]_D^{25}$ 97.3 (c 2.47, $CHCl_3$); IR (neat) 1792, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.20–7.37 (5H, m), 5.32 (1H, bs), 4.66 (1H, m), 4.25 (1H, dd, J=9.0, 7.3 Hz), 4.18 (1H, dd, J=9.0, 2.8 Hz), 3.31 (1H, dd, J=13.3, 3.0 Hz), 2.84 (1H, dd, J=13.3, 9.6 Hz), 2.48–2.93 (2H, m), 2.00–2.44 (4H, m), 1.73 (3H, s); ^{13}C NMR ($CDCl_3$) δ 23.7, 26.3, 29.3 (d, J=22.8 Hz), 32.5 (d, J=23.5 Hz), 38.1, 57.5, 67.0, 95.4 (d, J=187.8 Hz), 115.8, 127.8, 129.4, 129.8, 133.9, 135.5, 151.9, 173.2 (d, J=28.1 Hz); ^{19}F NMR ($CDCl_3$) δ −99.2 (m). Anal. calcd for $C_{18}H_{20}FNO_3$: C, 68.12; H, 6.35; N, 4.41. Found: C, 68.20; H, 6.50; N, 4.42.

3.5. (4S)-3-[(3′S,4′S,6′S)-4′-Fluoro-bicyclo[2.2.1]heptene-4′-carbonyl]-4-(phenylmethyl)-2-oxazolidinone **6**-exo *and (4S)-3-[(3′R,4′S,6′R)-4′-fluoro-bicyclo[2.2.1]heptene-4′-carbonyl]-4-(phenylmethyl)-2-oxazolidinone* **6**-endo

According to a similar procedure for the preparation of **5a**, the Diels–Alder reaction of **4a** (100 mg, 0.4 mmol) with cyclopentadiene (1.06 ml, 11 mmol) in the presence of diethylaluminum chloride (0.95 M in hexane, 0.63 ml, 0.6 mmol) was carried out at −100°C for 45 min. After extractive workup and purification by silica gel column chromatography (hexane/ethyl acetate, 8/1), a mixture of **6**-*endo* and **6**-*exo* (100.3 mg, 0.32 mmol) was obtained in 80% yield. Each isomer was separated by medium pressure liquid chromatography (hexane/ethyl acetate, 6/1).

6-*exo*: Mp 91–94°C; $[\alpha]_D^{22}$ −66.9 (c 1.05, $CHCl_3$); IR (KBr) 1796, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21–7.37 (5H, m), 6.51 (1H, dd, J=5.6, 3.0 Hz), 6.33 (1H, dd, J=5.6, 3.0 Hz), 4.67 (1H, m), 4.26 (1H, dd, J=9.0, 7.4 Hz), 4.19 (1H, dd, J=9.0, 3.3 Hz), 3.62 (1H, bs), 3.32 (1H, dd, J=13.4, 3.6 Hz), 2.96 (1H, bs), 2.88 (1H, dd, J=13.4, 9.3 Hz), 2.54 (1H, dt, J=13.6, 3.6 Hz), 1.50–1.80 (3H, m); ^{13}C NMR ($CDCl_3$) δ 37.8, 40.3 (d, J=20.2 Hz), 41.8, 48.4, 50.6 (d, J=20.6 Hz), 56.5, 66.6, 102.7 (d, J=197.7 Hz), 127.4, 128.9, 129.4, 132.1, 135.1, 140.8, 151.3, 171.8 (d, J=32.7 Hz); ^{19}F NMR ($CDCl_3$) δ −93.9 (dd, J=25.1, 14.1 Hz). HRMS calcd for $C_{18}H_{18}FNO_3$ 315.1271, found 315.1279.

6-*endo*: Mp 110–113°C; $[\alpha]_D^{23}$ 103.5 (c 1.02, $CHCl_3$); IR (KBr) 1783, 1691 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.21–7.36 (5H, m), 6.35 (1H, dd, J=5.6, 2.8 Hz), 6.03 (1H, dd, J=5.6, 2.8 Hz), 4.59 (1H, m), 4.22 (1H, dd, J=9.0, 6.9 Hz), 4.18 (1H, dd, J=9.0, 2.8 Hz), 3.65 (1H, bs), 3.27 (1H, dd, J=13.5, 3.3 Hz), 2.96 (1H, bs), 2.81 (1H, dd, J=13.5, 9.6 Hz), 2.17–2.31 (2H, m), 1.97 (1H, d, J=8.6 Hz), 1.75 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 37.5, 40.9, 41.0 (d, J=20.9 Hz), 48.0, 51.2 (d, J=21.8 Hz), 56.6, 66.3, 104.0 (d, J=198.8 Hz), 127.3, 128.9, 129.4, 132.0, 135.1, 141.3, 151.2, 169.5 (d, J=31.5 Hz); ^{19}F NMR ($CDCl_3$) δ −86.5 (dd, J=32.4, 19.0 Hz). HRMS calcd for $C_{18}H_{18}FNO_3$ 315.1271, found 315.1254.

3.6. (3R,4S,6R)-4-Benzyloxycarbonyl-4-fluoro-bicyclo[2.2.1]heptene 9-endo

Under an argon atmosphere, to a solution of BnOLi (prepared from 1.54 mmol of benzylalcohol and 1.19 mmol of *n*-BuLi) in THF (6 ml) was added a solution of **6**-*endo* (162 mg, 0.75 mmol) in THF (2 ml) at 0°C. After being stirred for 4 h, saturated aqueous ammonium chloride was added and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. After purification by silica gel column chromatography (hexane/ethyl acetate, 25/1), the compound **9**-*endo* (123 mg, 0.526 mmol) was obtained in 70% yield.

9-*endo*: $[\alpha]_D^{26}$ 30.4 (*c* 0.44, $CHCl_3$); IR (neat) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.30 (5H, m), 6.33 (1H, dd, *J*=5.4, 3.0 Hz), 5.84 (1H, dd, *J*=5.4, 3.0 Hz), 5.21 (1H, d, *J*=12.4 Hz), 5.18 (1H, d, *J*=12.4 Hz), 3.15 (1H, bs), 2.97 (1H, bs), 2.13–1.85 (3H, m), 1.76–1.68 (1H, m); ^{13}C NMR ($CDCl_3$) δ 39.8 (d, *J*=21.1 Hz), 41.7, 48.9, 52.0 (d, *J*=22.8 Hz), 67.4, 102.2 (d, *J*=195.3 Hz), 128.5, 128.7, 129.0, 131.5, 135.9, 142.3, 166.5 (d, *J*=34.3 Hz); ^{19}F NMR ($CDCl_3$) δ −86.5 (ddd, *J*=32.0, 18.0, 4.0 Hz). HRMS calcd for $C_{15}H_{15}FO_2$ 246.1056, found 246.1064.

3.7. (3S,4S,6S)-4-Benzyloxycarbonyl-4-fluoro-bicyclo[2.2.1]heptene 9-exo

The compound **9**-*exo* was obtained from **6**-*exo* according to the above mentioned procedure.

9-*exo*: $[\alpha]_D^{23}$ −135.5 (*c* 0.67, $CHCl_3$); IR (neat) 1739 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.42–7.39 (5H, m), 6.48 (1H, dd, *J*=5.6, 3.0 Hz), 6.10 (1H, dd, *J*=5.6, 3.0 Hz), 5.27 (2H, s), 3.22 (1H, bs), 2.98 (1H, bs), 2.40 (1H, ddd, *J*=13.1, 13.1, 3.6 Hz), 1.85 (1H, bd, *J*=9.1 Hz), 1.62–1.42 (1H, m), 1.47 (1H, ddd, *J*=24.3, 13.1, 4.1 Hz); ^{13}C NMR ($CDCl_3$) δ 40.4 (d, *J*=20.0 Hz), 42.6, 49.3, 51.9 (d, *J*=21.5 Hz), 67.7, 101.4 (d, *J*=195.5 Hz), 128.6, 128.8, 129.0, 132.8, 135.8, 140.6, 166.4 (d, *J*=27.3 Hz); ^{19}F NMR ($CDCl_3$) δ −94.6 (dd, *J*=24.3, 13.1 Hz). HRMS calcd for $C_{15}H_{15}FO_2$ 246.1056, found 246.1063.

3.8. (3S,3′S,5R,6R,6′R)-3-Fluoro-6-iodohexahydro-3,5-methano-2H-cyclopenta[b]-furan-2-one 10

To a solution of **9**-*endo* (20.9 mg, 0.086 mmol) in acetonitrile (2 ml) was added iodine (44 mg, 0.17 mmol) at ambient temperature and the mixture was stirred at the same temperature overnight. After addition of an aqueous $Na_2S_2O_3$ solution, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with brine dried over magnesium sulfate and concentrated under vacuum. After purification by silica gel column chromatography (hexane/ethyl acetate, 15/1), the compound **10** (17.2 mg, 0.061 mmol) was obtained in 71% yield.

10: Mp 59–63°C; $[\alpha]_D^{22}$ −105.6 (*c* 0.66, $CHCl_3$); IR (KBr) 1805 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.12 (1H, dd, *J*=4.2, 4.2 Hz), 3.83 (1H, d, *J*=2.6 Hz), 3.29 (1H, dd, *J*=7.1, 4.2 Hz), 2.79 (1H, bs), 2.45 (1H, dd, *J*=11.9, 1.3 Hz), 2.30 (1H, ddd, *J*=14.2, 4.7, 2.3 Hz), 2.14 (1H, bd, *J*=11.9 Hz), 2.06 (1H, ddd, *J*=14.2, 14.2, 4.2 Hz); ^{13}C NMR ($CDCl_3$) δ 26.7, 35.6, 42.1 (d, *J*=22.9 Hz), 46.6, 49.9 (d, *J*=20.0 Hz), 85.1, 93.0 (d, *J*=218.0 Hz), 172.8 (d, *J*=28.8 Hz); ^{19}F NMR ($CDCl_3$) δ −111.3 (m). HRMS calcd for $C_8H_8FIO_2$ 281.9553, found 281.9549.

3.9. (−)-(3R,4R,6R)-4-Carboxyl-4-fluoro-bicyclo[2.2.1]heptene 11

To a solution of **9**-*exo* (19.0 mg, 0.0785 mmol) in THF (1 ml) was added 0.3 ml of 1 N NaOH at ambient temperature and the mixture was stirred at the same temperature for 4 h. The reaction mixture was acidified to pH 4 by the addition of 10% HCl and then sodium chloride was added. The mixture was extracted with ethyl acetate three times. The organic layer was dried over magnesium sulfate and

concentrated under vacuum. After purification by silica gel column chromatography (ethyl acetate only), the compound **11** (9.2 mg, 0.059 mmol) was obtained in 75% yield.

11: $[\alpha]_D^{22}$ −109.8 (*c* 0.54, $CHCl_3$); IR (neat) 1717 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.50 (1H, dd, *J*=5.5, 3.0 Hz), 6.12 (1H, dd, *J*=5.5, 3.0 Hz), 3.27 (1H, bs), 3.03 (1H, bs), 2.42 (1H, ddd, *J*=13.1, 13.1, 3.5 Hz), 1.95 (1H, bd, *J*=8.1 Hz), 1.63–1.56 (1H, m), 1.51 (1H, ddd, *J*=23.0, 13.1, 4.0 Hz); ^{13}C NMR ($CDCl_3$) δ 39.6 (d, *J*=19.7 Hz), 41.5, 48.4, 51.1 (d, *J*=21.1 Hz), 100.0 (d, *J*=193.6 Hz), 131.8, 139.6, 177.7 (d, *J*=30.0 Hz); ^{19}F NMR ($CDCl_3$) δ −94.0 (dd, *J*=23.0, 13.1 Hz). HRMS calcd for $C_8H_9FO_2$ 156.0587, found 156.0582; Anal. calcd for $C_8H_9FO_2$: C, 61.53; H, 5.81. Found: C, 61.78; H, 5.94.

3.10. 4-Benzyloxycarbonyl-4-fluoro-bicyclo[2.2.1]heptene 9 (fluorination of compound 8)

Under an argon atmosphere, to a solution of LDA (prepared from 0.99 mmol of diisopropylamine and 0.82 mmol of n-BuLi) in THF (4 ml) was added a solution of **8** (162 mg, 0.75 mmol) in THF (2 ml) at −43°C. After being stirred for 30 min, chlorotrimethylsilane (0.13 ml, 1.02 mmol) was added to the reaction mixture at −43°C and the mixture was stirred at ambient temperature for 1 h. The reaction mixture was concentrated under vacuum. The residue was diluted with ether and filtered through a Celite pad and the filtrate was concentrated under vacuum. After addition of saturated aqueous ammonium chloride, the mixture was extracted with ethyl acetate and the organic layer was washed with brine, dried over magnesium sulfate, and concentrated under vacuum. A solution of the residue in CH_2Cl_2 (3 ml) was added to a mixture of *N*-fluoro-2,4,6-trimethylpyridinium triflate (261.8 mg, 0.91 mmol), anhydrous potassium carbonate (104 mg, 0.75 mmol) in CH_2Cl_2 (4.5 ml) at ambient temperature and the mixture was stirred under reflux overnight. The mixture was poured onto brine and extracted with ether. The organic layer was dried over magnesium sulfate and concentrated under vacuum. After purification by silica gel column chromatography (hexane/ethyl acetate, 25/1), compound **9** (123 mg, 0.53 mmol) was obtained as an *exo*:*endo* mixture (1:2) in 70% yield.

3.11. Preparation of (−)-10 and (+)-11 from the exo/endo *mixture of 9*

To a solution of an *exo*/*endo* mixture of **9** (123 mg, 0.53 mmol) in THF (0.1 ml) was added 4×0.5 ml of 1 N NaOH at ambient temperature over 4 h. The reaction mixture was acidified to pH 4 by the addition of 10% HCl and then sodium chloride was added. The mixture was extracted with ethyl acetate five times. The organic layer was dried over magnesium sulfate and concentrated under vacuum. The residue was treated with aqueous sodium bicarbonate (600 mg in 10 ml of water) at ambient temperature for 5 min. The mixture was washed with ether and the aqueous layer was cooled to 0°C. Powdered potassium iodide (1.1 g, 6.5 mmol) and iodine (305 mg, 1.2 mmol) were added to the aqueous reaction mixture and the mixture was stirred at ambient temperature for 18 h. Aqueous $Na_2S_2O_3$ was added to the reaction mixture which was then extracted with ether. The organic layer was dried over magnesium sulfate and concentrated under vacuum. After purification by silica gel column chromatography (hexane/ethyl acetate, 15/1), compound **10** (42.7 mg, 0.15 mmol) was obtained in 29% yield. The water layer was treated with 10% HCl until the pH of solution was 4 and sodium chloride was then added. The mixture was extracted with ethyl acetate five times. The organic layer was dried over magnesium sulfate and concentrated under vacuum to afford compound **11** (10.3 mg, 0.066 mmol) in 13% yield. (−)-**10**: $[\alpha]_D^{25}$ −52.7 (*c* 1.01, $CHCl_3$). (+)-**11**: $[\alpha]_D^{25}$ 54.2 (*c* 0.54, $CHCl_3$).

Acknowledgements

A generous donation of methyl 2-fluoroacrylate by Daikin Industries Co. is gratefully acknowledged. We also thank F-TECH, Inc. for the generous donation of *N*-fluoro-2,4,6-trimethylpyridinium triflate.

References

1. (a) Filler, R.; Kobayashi, Y. *Biomedicinal Aspects of Fluorine Chemistry*; Elsevier Biomedical Press and Kodansha Ltd, 1982. (b) Welch, J. T. *Tetrahedron* **1987**, *43*, 3123. (c) Resnati, G. *Tetrahedron* **1993**, *49*, 9385. (d) Fluoroorganic Chemistry: Synthetic Challenges and Biomedical Rewards; Tetrahedron Symposium-in Print No. 58; Resnati, G. and Soloshonok, V. A. Eds. *Tetrahedron* **1996**, *52*, 1. (e) Biomedical Frontiers of Fluorine Chemistry, Ojima, I.; McCarthy, J. R.; Welch, J. T. Eds., ACS Symposium Series 639, American Chemical Society: Washington, D.C., 1996. (f) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645.
2. (a) Kotikyan, Y. A.; Dyatkin, B. L.; Konstantinov, Y. S. *Izu. Akad. Nauk SSSR, Ser. Khim.* **1971**, 358. (b) Jeong, I. H.; Kim, Y. S.; Cho, K. Y.; Kim, K. J. *Bull. Korean Chem. Soc.* **1990**, *11*, 178.
3. Review for the preparation of 2-fluoroacrylate; Boguslavskaya, L. S.; Chuvatkin, N. N. *Macromol. Symp.* **1994**, *82*, 51.
4. Tolman, V.; Spronglová, P. *Collect. Czech. Chem. Commun.* **1983**, *48*, 319.
5. Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238.
6. Absolute stereochemistry was assigned by analogy with cyclopentadiene.
7. Umemoto, T.; Fukami, S.; Tomizawa, G.; Harasawa, K.; Kawada, K.; Tomita, K. *J. Am. Chem. Soc.* **1990**, *112*, 8563.
8. (a) Plenio, H. *Chem. Rev.* **1997**, *97*, 3363. Very recently, Maruoka et al. reported the interesting reactions involving the highly specific fluorine–aluminum interaction. (b) Ooi, T.; Kagoshima, N.; Maruoka, K. *J. Am. Chem. Soc.* **1997**, *119*, 5754. (c) Ooi, T.; Uraguchi, D.; Kagoshima, N.; Maruoka, K. *Tetrahedron Lett.* **1997**, *38*, 5679.