Asymmetric copper-catalyzed fluorination of cyclic β-keto esters in a continuous-flow microreactor

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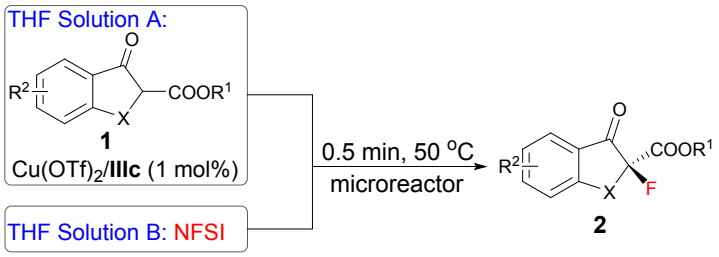
1. General information

Unless otherwise stated, all regents were purchased from commercial suppliers and used without purifications. Indanone carboxylate **1** were synthesized according to the known method[1]. Flash column chromatography was performed on silica-gel. ^{1}H and ^{13}C NMR were recorded in $CDCl_3$ on Bruker AVANCE III. TMS served as internal standard (d= 0 ppm) for ^{1}H NMR and $CDCl_3$ was used as internal standard (d= 77.0 ppm) for ^{13}C NMR; Chiral HPLC analyses were performed using JASCO LC-2000 Plus. Chiralpak AD-H, OB-H, OD-H, OJ-H and IC columns were purchased from Daicel Chemical Industries (Shanghai, China). The continuous synthesis was conducted using a commercially available continuous-flow system (syrris Asia), comprising (1) a corrosion-resistant dual pair syringe pump (one pair consists of a 50 μL and a 100 μL syringe), (2) a heater module, (3) a 250 μL internal volume borosilicate microreactor.

The microreactor system

The structure of the microreactor

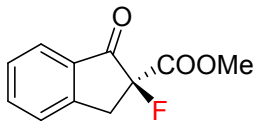
2. Typical experimental procedure for the enantioselective fluorination under continuous-flow conditions



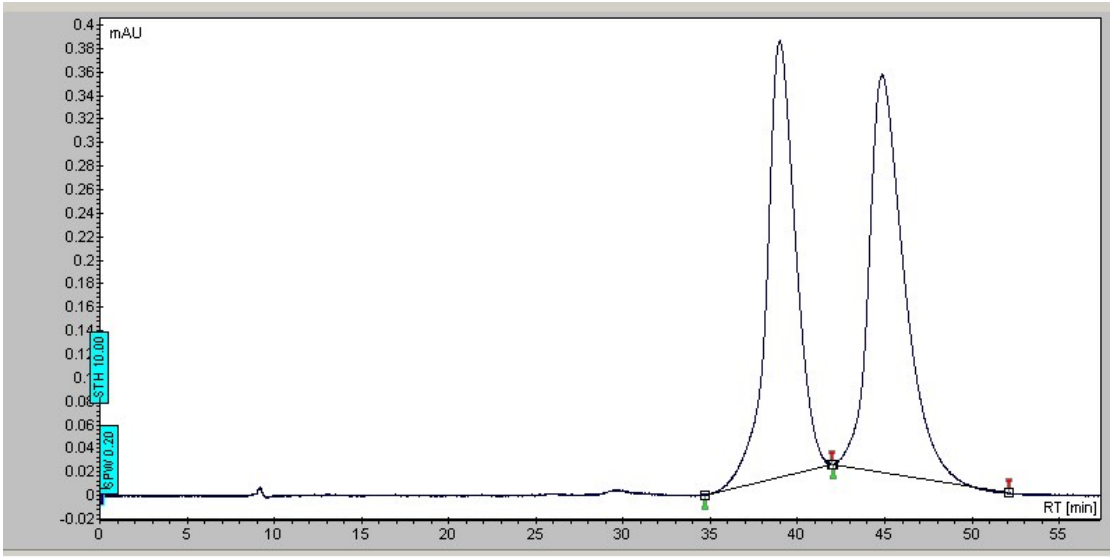
The fluorination reaction was conducted in a microreactor consisting of a 250 μL heated (50 °C) retention unit and two inlets. The solution A containing copper complex **IIIc**-$Cu(OTf)_2$ (0.01M), indanone carboxylate **1** (1.0 M) in THF and the solution B containing NFSI (1.2 M) in THF were prepared using standard volumetric techniques, and preheated to 50 °C. The two solutions were introduced seperately from the two inlet at the same flow rate of 250 μL min^{-1}. Total output was 500 μL min^{-1} (0.5 min of residence time). Typically, the reaction sample was collected for 2 mL. The reaction mixture was concentrated under reduced pressure. The crude product was purified by flash column chromatography eluting with ethyl acetate (EtOAc) and petroleum ether (PE) to afford the resulting product. The enantiomeric excess was determined by HPLC using a Chiralpak AD-H, OB-H, OD-H, OJ-H or IC columns.

3. Characterization and NMR spectra of resulting products

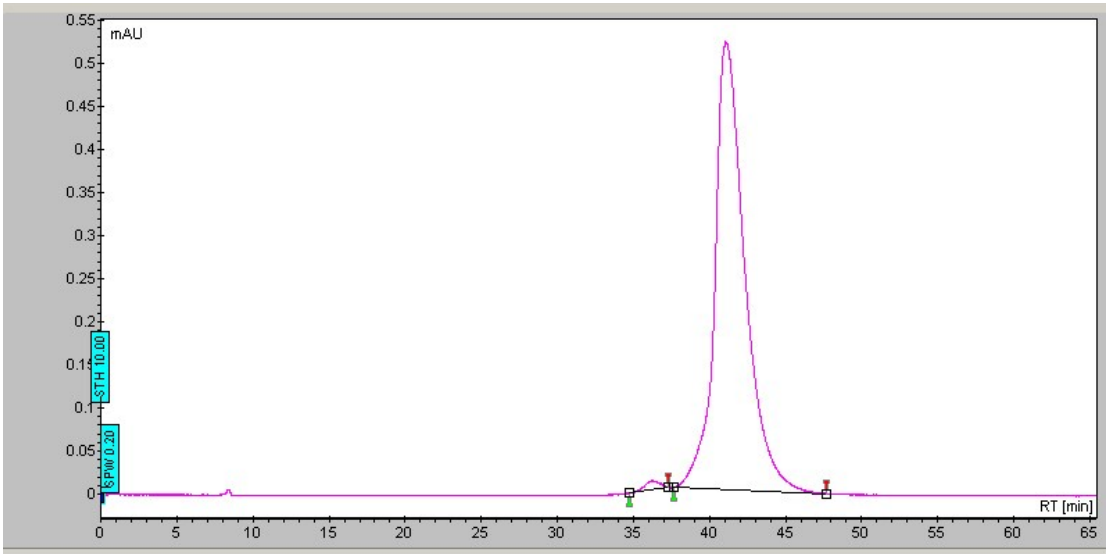
methyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2a)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as white solid. (99% yield, 206.0 mg) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.7 Hz, 1H), 7.64 (td, J = 7.5, 1.2 Hz, 1H), 7.48 – 7.36 (m, 2H), 3.74 (s, 4H), 3.79 – 3.67 (m, 1H), 3.37 (dd, J = 23.3, 17.6 Hz, 1H).^{13}C NMR (126 MHz, $CDCl_3$) δ 195.08 (d, J = 18.4 Hz), 167.72 (d, J = 27.8 Hz), 150.82 (d, J = 3.8 Hz), 136.76, 133.23, 128.67, δ 126.64 – 126.55 (m) 125.68, 94.61 (d, J = 201.6 Hz), 53.24, 38.26 (d, J = 23.8 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak OB-H column at 254 nm (n-hexane/*i*-PrOH = 70/30), 1.0 mL/min; Major enantiomer: t_R = 41.05 min, minor enantiomer: t_R =36.23 min. 98% *ee*.

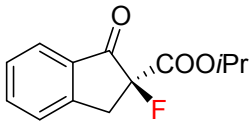


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	34.688	38.971	41.961	0.000	47.29	0.4	0.7	47.291
2	UNKNOWN	42.041	44.863	52.112	0.000	52.71	0.3	0.8	52.709
Total						100.00	0.7	1.5	100.000

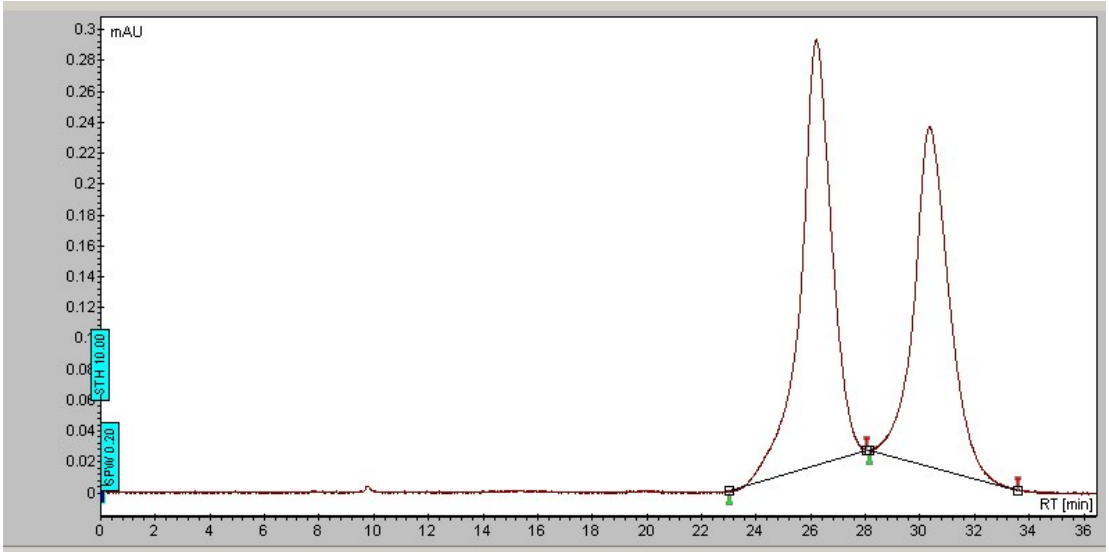


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	34.732	36.227	37.285	0.000	0.90	0.0	0.0	0.902
2	UNKNOWN	37.649	41.052	47.677	0.000	99.10	0.5	1.2	99.098
Total						100.00	0.5	1.2	100.000

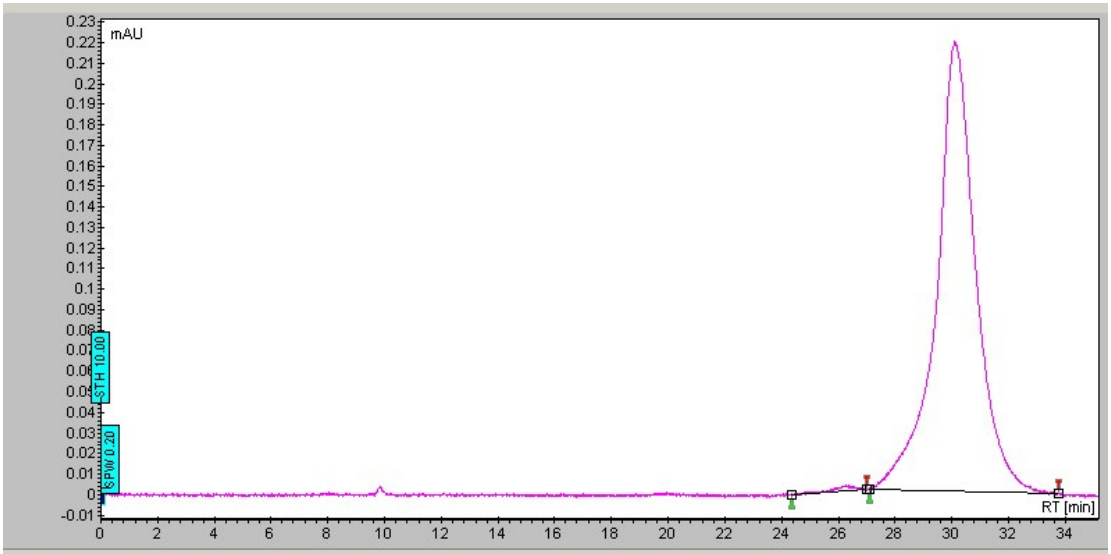
isopropyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2b)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as white solid (97% yield, 229.0 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.7 Hz, 1H), 7.65 – 7.58 (m, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.5 Hz, 1H), 5.05 (h, *J* = 6.2 Hz, 1H), 3.69 (dd, *J* = 17.6, 11.8 Hz, 1H), 3.33 (dd, *J* = 23.3, 17.6 Hz, 1H), 1.15 (ddd, *J* = 13.6, 6.3, 1.0 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.27 (d, *J* = 18.4 Hz), 166.74 (d, *J* = 27.6 Hz), 150.86 (d, *J* = 3.5 Hz), 136.54, 133.20, 128.45, 126.49, 125.37, 94.32 (d, *J* = 201.1 Hz), 70.55, 38.13 (d, *J* = 24.1 Hz), 21.37 (d, *J* = 13.8 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak OB-H column at 254 nm (n-hexane/*i*-PrOH = 90/10), 1.0 mL/min; Major enantiomer: t_R = 30.12 min, minor enantiomer: t_R = 26.28 min. 99% *ee*.

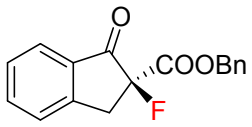


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.016	26.198	28.046	0.000	52.63	0.3	0.4	52.634
2	UNKNOWN	28.148	30.358	33.584	0.000	47.37	0.2	0.3	47.366
Total						100.00	0.5	0.7	100.000

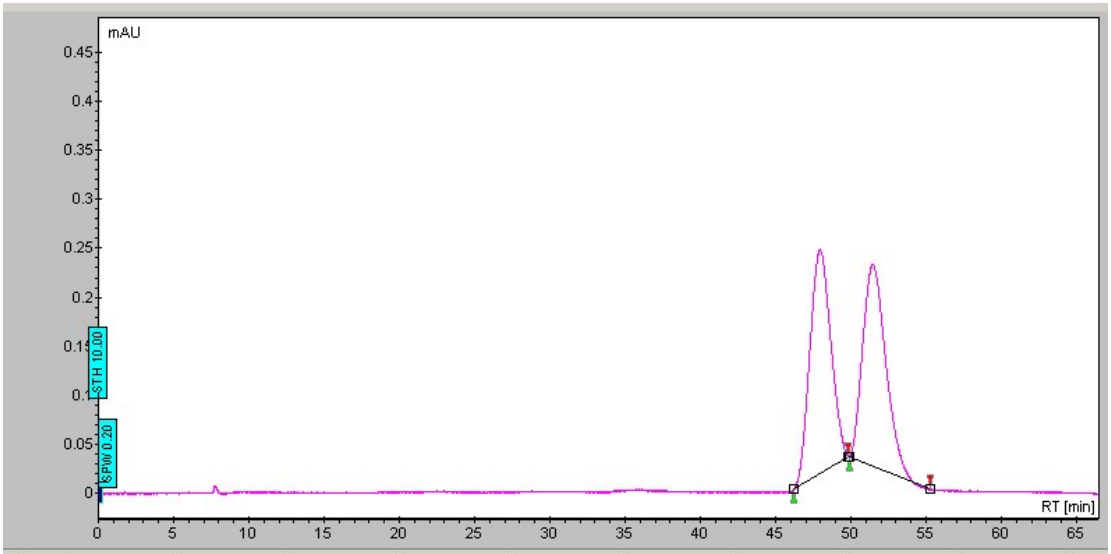


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Are	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24.356	26.278	27.003	0.000	0.55	0.0	0.0	0.546
2	UNKNOWN	27.101	30.118	33.765	0.000	99.45	0.2	0.4	99.454
Total						100.00	0.2	0.4	100.000

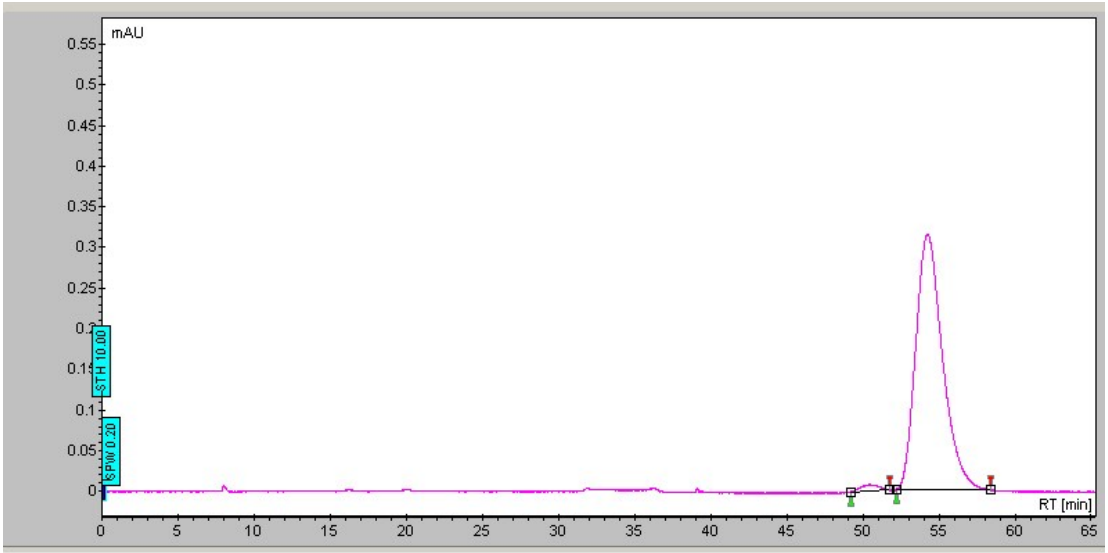
benzyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2c)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as white solid (94% yield, 267.0 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.95 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.79 (d, *J* = 7.7 Hz, 1H), 7.66 (td, *J* = 7.5, 1.3 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.48 – 7.39 (m, 2H), 7.32 – 7.25 (m, 3H), 5.30 – 5.15 (m, 2H), 3.79 – 3.73 (m, 1H), 3.45 – 3.35 (m, 1H).^{13}C NMR (151 MHz, $CDCl_3$) δ 195.15 (d, *J* = 18.2 Hz), 167.16 (d, *J* = 28.2 Hz), 150.88 (d, *J* = 3.7 Hz), 136.85, 135.97, 134.72, 133.22, 129.75, 129.54, 128.70, 128.64, 128.55, 126.71 (d, *J* = 1.2 Hz), 125.54, 94.69 (d, *J* = 201.4 Hz), 67.79, 38.23 (d, *J* = 24.1 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak AD-H column at 254 nm (n-hexane/*i*-PrOH = 97/3), 1.0 mL/min; Major enantiomer: t_R = 54.25 min, minor enantiomer: t_R = 50.45 min. 97% *ee*.

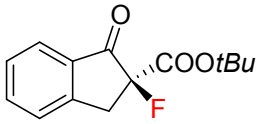


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	46.212	47.943	49.824	0.000	50.12	0.2	0.4	50.120
2	UNKNOWN	49.916	51.462	55.288	0.000	49.88	0.2	0.4	49.880
Total						100.00	0.4	0.7	100.000



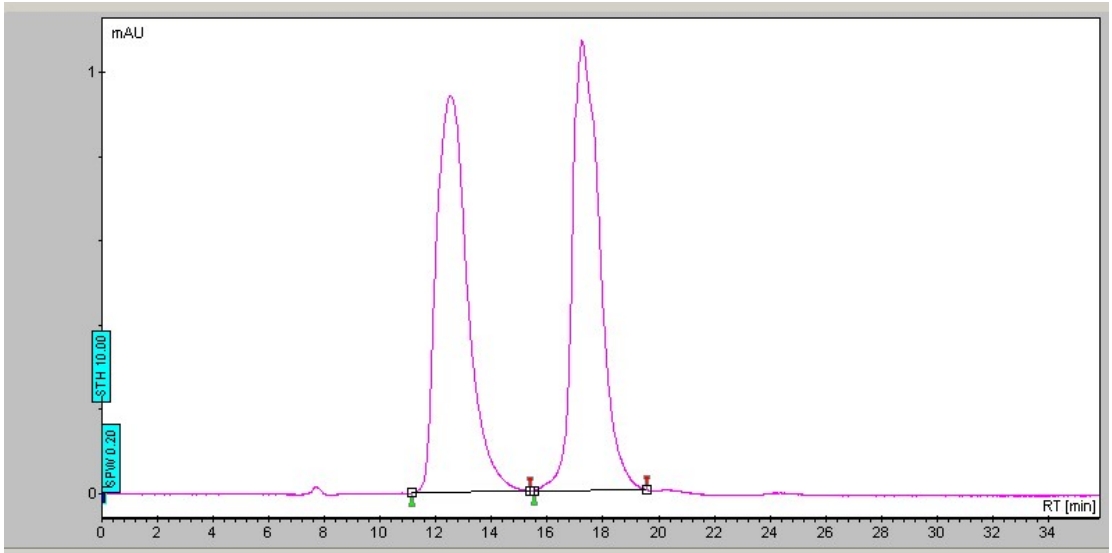
#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	49.217	50.449	51.765	0.000	1.69	0.0	0.0	1.687
2	UNKNOWN	52.220	54.247	58.406	0.000	98.31	0.3	0.6	98.313
Total						100.00	0.3	0.7	100.000

tert-butyl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2d)

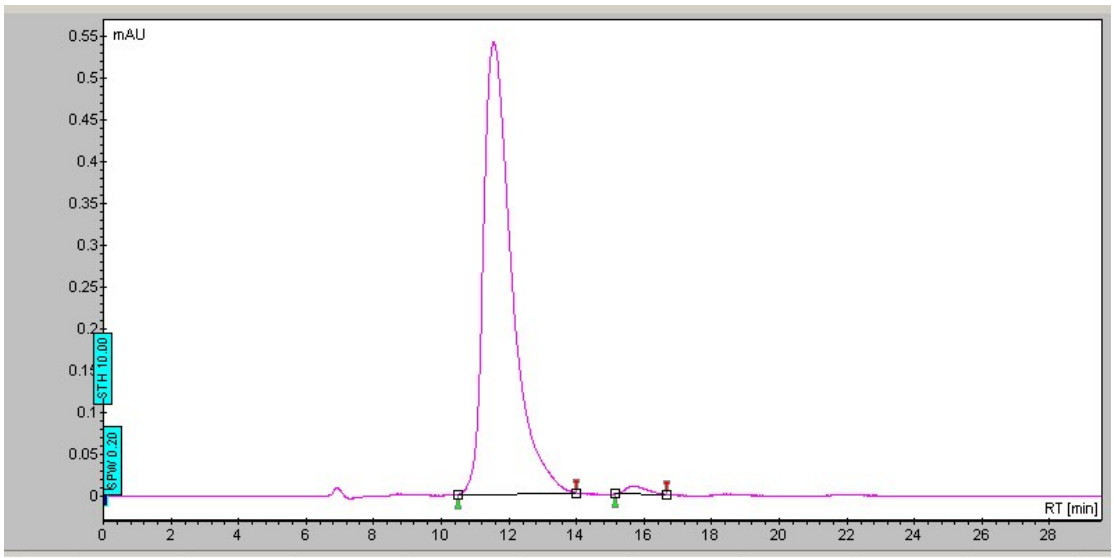


Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as white solid (97% yield, 242.6 mg).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (dd, *J* = 7.8, 0.6 Hz, 1H), 7.61 (td, *J* = 7.5, 1.2 Hz, 1H), 7.42 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.38 (ddd, *J* = 8.0, 7.2, 0.9 Hz, 1H), 3.71 – 3.58 (m, 1H), 3.32 (ddd, *J* = 22.9, 17.4, 1.0 Hz, 1H), 1.36 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.97 (d, *J* = 18.5 Hz), 166.44 (d, *J* = 27.7 Hz), 151.16 (d, *J* = 3.9 Hz), 136.64, 133.78, 128.66, 126.68, 125.61, 94.58 (d, *J* = 201.7 Hz), 84.31, 38.54 (d, *J* = 24.2 Hz). 28.02. The enantiomers were analyzed by HPLC using Daicel Chiralpak OB-H column at 254 nm (n-hexane/*i*-PrOH = 70/30), 1.0 mL/min; Major

enantiomer: t_R = 11.55 min, minor enantiomer: t_R = 15.68 min. 97% *ee*.

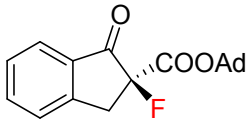


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	11.136	12.519	15.380	0.000	50.18	0.9	1.2	50.178
2	UNKNOWN	15.530	17.239	19.575	0.000	49.82	1.1	1.2	49.822
Total						100.00	2.0	2.4	100.000



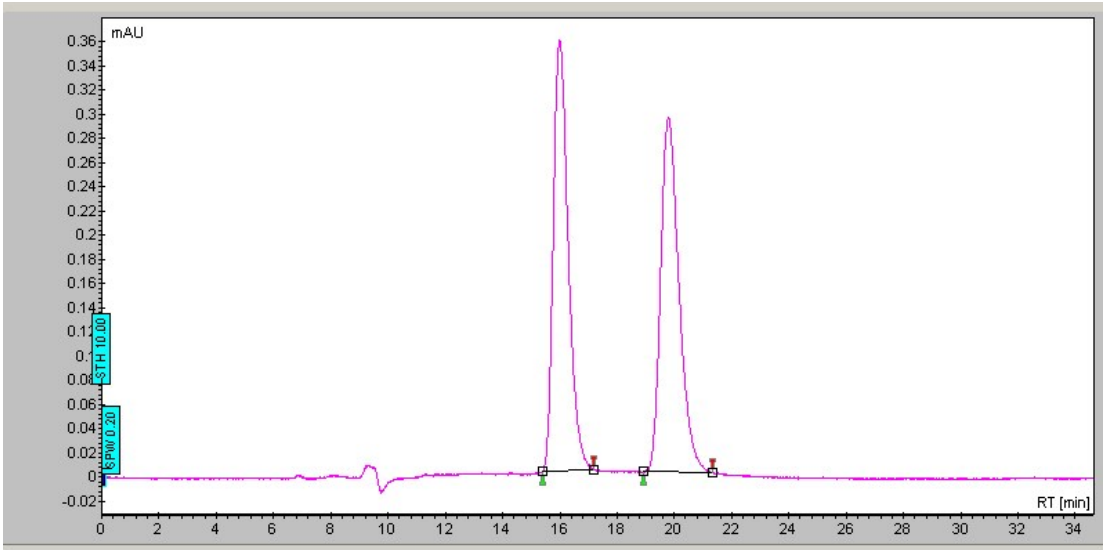
#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	10.494	11.546	13.991	0.000	98.71	0.5	0.5	98.715
2	UNKNOWN	15.144	15.679	16.666	0.000	1.29	0.0	0.0	1.285
Total						100.00	0.5	0.5	100.000

(3*R*,5*R*,7*R*)-Adamantan-1-yl (*S*)-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate(2e)

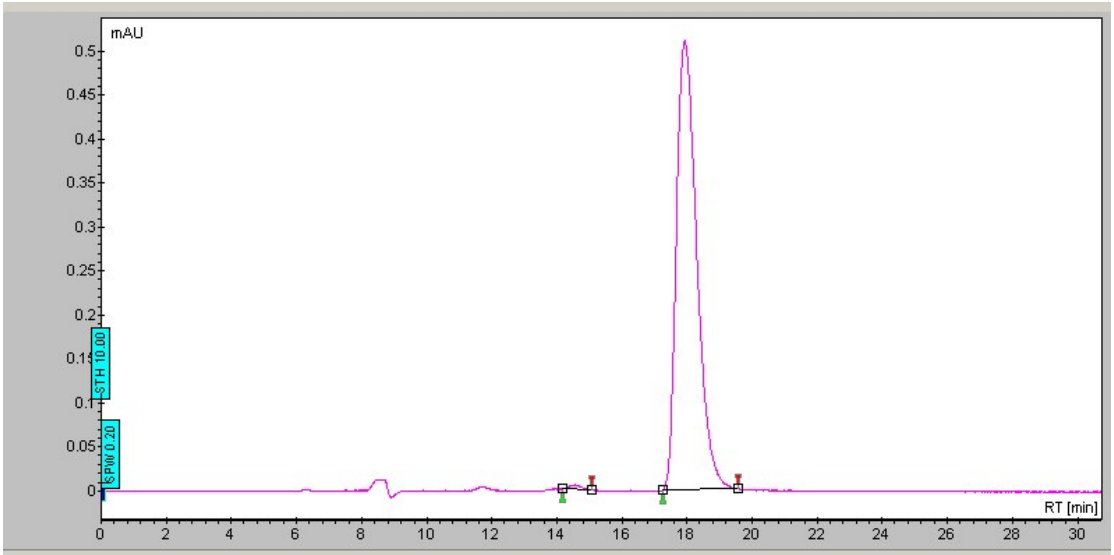


Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/10 (v/v) as white solid (80% yield, 262.5 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.8 Hz, 1H), 7.60 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 3.65 (dd, *J* = 17.5, 10.6 Hz, 1H), 3.30 (dd, *J* = 22.9, 17.4 Hz, 1H), 2.04 (s, 3H), 1.95 (s, 6H), 1.52 (s, 6H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.70 (d, *J* = 18.3 Hz), 165.62 (d, *J* = 28.0 Hz), 150.84 (d, *J* = 4.0 Hz), 136.30, 133.41, 128.27, 126.34 (d, *J* = 1.4 Hz), 125.14, 94.14 (d, *J* = 201.4 Hz), 83.90, 40.86, 38.26 (d, *J* = 23.9 Hz). 35.71, 30.69. The

enantiomers were analyzed by HPLC using Daicel Chiralpak AD-H column at 254 nm (n-hexane/*i*-PrOH = 90/10), 1.0 mL/min; Major enantiomer: t_R = 17.93 min, minor enantiomer: t_R = 14.55 min. 99% *ee*.

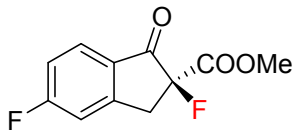


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	15.396	15.986	17.182	0.000	49.63	0.4	0.2	49.631
2	UNKNOWN	18.919	19.799	21.333	0.000	50.37	0.3	0.2	50.369
Total						100.00	0.6	0.4	100.000



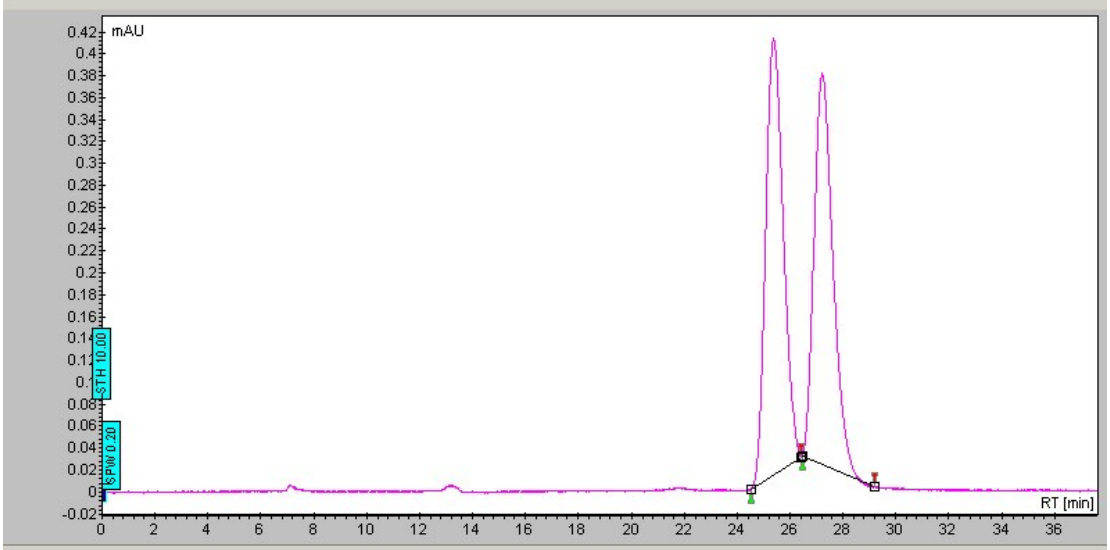
#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	14.174	14.546	15.074	0.000	0.61	0.0	0.0	0.606
2	UNKNOWN	17.258	17.932	19.570	0.000	99.39	0.5	0.4	99.394
Total						100.00	0.5	0.4	100.000

methyl (*S*)-2,5-difluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2f)

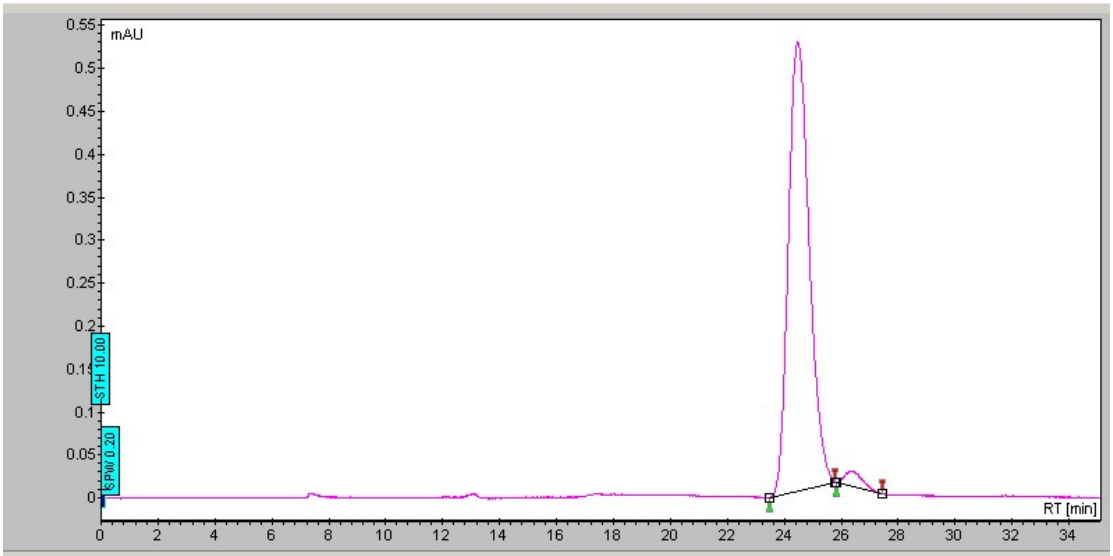


Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as white solid (95% yield, 214.7 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 1H), 7.63 – 7.55 (m, 1H), 7.21 – 7.16 (m, 1H), 3.80 (dd, *J* = 16.8, 10.8 Hz, 1H), 3.81 (s, 3H), 3.43 (ddd, *J* = 23.0, 18.0, 1.2 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.21 (d, *J* = 18.2 Hz), 169.04, 167.51, 167.32, 153.91 (dd, *J* = 10.6, 3.9 Hz), 128.16 (d, *J* = 10.7 Hz), 117.19 (d, *J* = 23.8 Hz), 113.60 (d, *J* = 23.0 Hz), 94.62 (d, *J*

= 202.3 Hz), 53.29, 38.08 (dd, J = 24.4, 2.3 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak OB-H column at 254 nm (n-hexane/*i*-PrOH = 90/10), 1.0 mL/min; Major enantiomer: t_R = 24.45 min, minor enantiomer: t_R = 26.40 min. 94% *ee*.

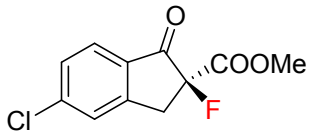


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24.534	25.385	26.421	0.000	50.96	0.4	0.3	50.963
2	UNKNOWN	26.474	27.211	29.200	0.000	49.04	0.4	0.3	49.037
Total						100.00	0.8	0.6	100.000



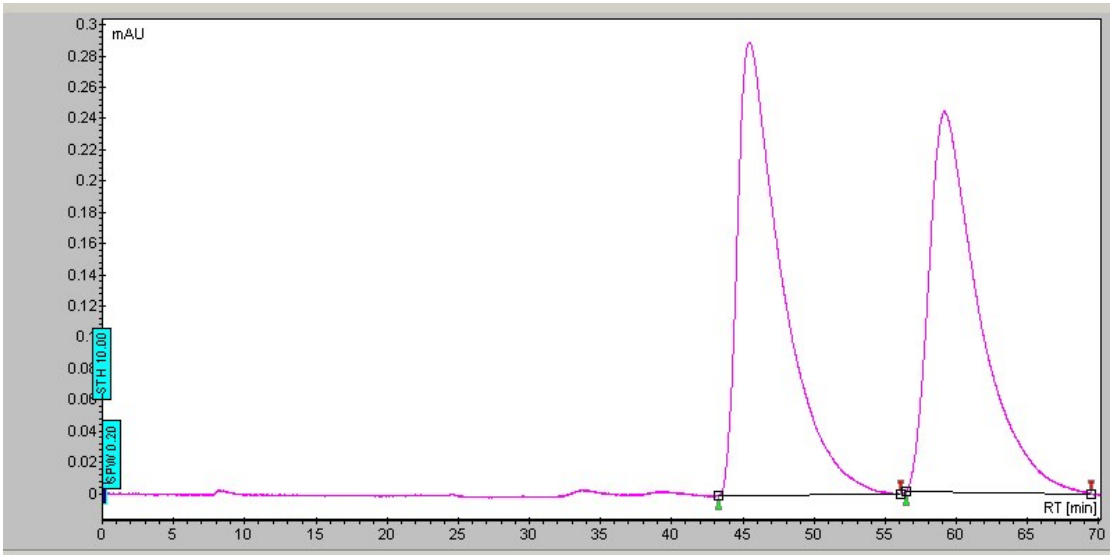
#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.479	24.452	25.777	0.000	97.22	0.5	0.4	97.221
2	UNKNOWN	25.826	26.398	27.441	0.000	2.78	0.0	0.0	2.779
Total						100.00	0.5	0.5	100.000

methyl (*S*)-5-chloro-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2g)

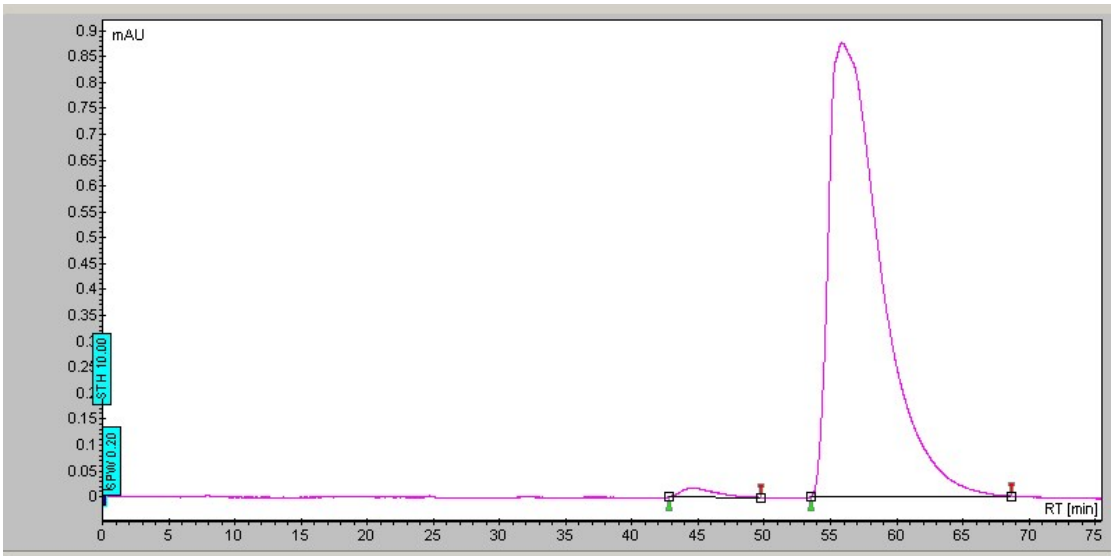


Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as white solid (91% yield, 220.2 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.2 Hz, 1H), 7.46 – 7.42 (m, 1H), 7.37 (dd, J = 8.2, 1.7 Hz, 1H), 3.73 (s, 3H), 3.71 (dd, J = 18.0, 10.9 Hz, 1H), 3.34 (dd, J = 23.0, 17.9 Hz, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 193.73 (d, J = 18.3 Hz), 167.32 (d, J = 28.0 Hz), 152.24 (d,

J = 3.9 Hz), 143.48, 131.59 (d, J = 1.3 Hz), 129.54 (d, J = 5.5 Hz), 126.92 (d, J = 1.4 Hz), 126.68 (d, J = 1.3 Hz), 94.50 (d, J = 202.4 Hz), 53.37, 37.91 (d, J = 24.2 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak OD-H column at 254 nm (n-hexane/*i*-PrOH = 99/1), 1.0 mL/min; Major enantiomer: t_R = 55.83 min, minor enantiomer: t_R = 44.60 min. 97% *ee*.

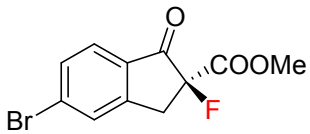


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	43.280	45.464	56.078	0.000	51.44	0.3	1.0	51.441
2	UNKNOWN	56.469	59.139	69.463	0.000	48.56	0.2	1.0	48.559
Total						100.00	0.5	2.0	100.000



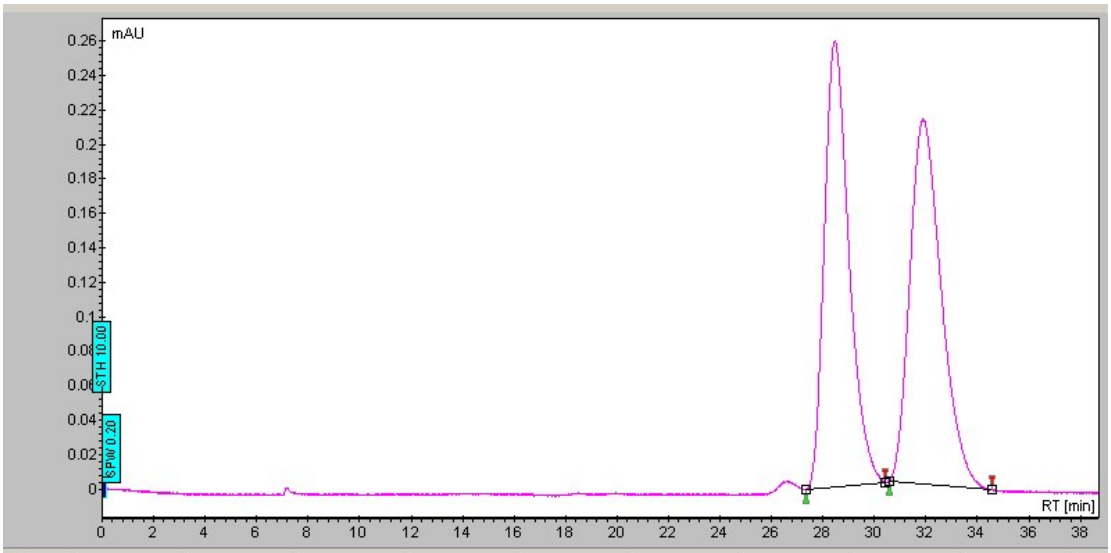
#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	42.801	44.597	49.742	0.000	1.30	0.0	0.1	1.304
2	UNKNOWN	53.528	55.833	68.671	0.000	98.70	0.9	4.0	98.696
Total						100.00	0.9	4.1	100.000

methyl (*S*)-5-bromo-2-fluoro-1-oxo-2,3-dihydro-1H-indene-2-carboxylate (2h)

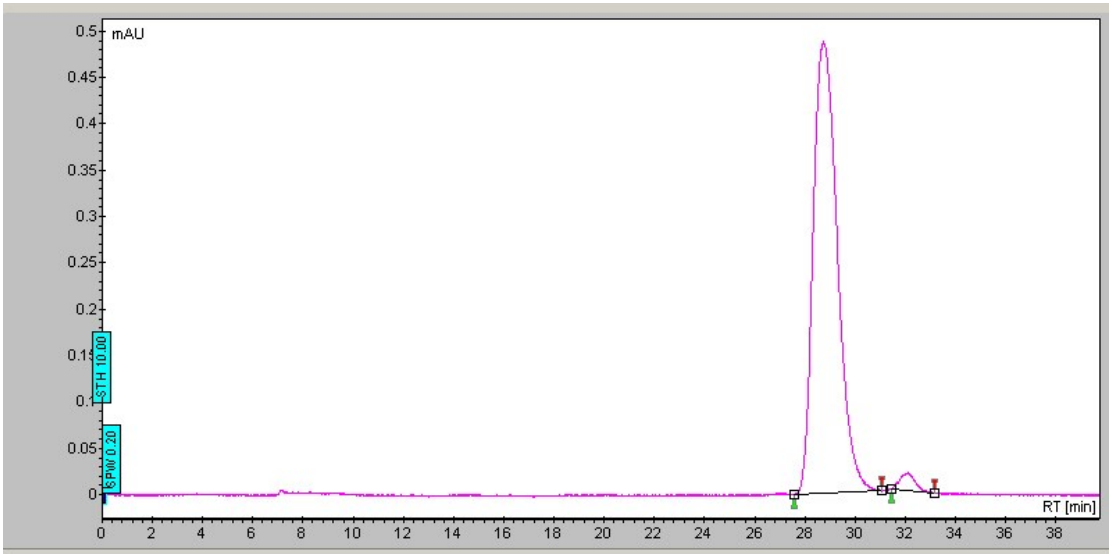


Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as yellow solid (97% yield, 277.4 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 1H), 7.54 (d, J = 8.4 Hz, 1H), 3.74 (s, 3H), 3.77 – 3.67 (m, 1H), 3.35 (dd, J = 23.0, 17.8 Hz, 1H).^{13}C NMR (151 MHz,

$CDCl_3$) δ 193.91 (d, J = 18.3 Hz), 167.29 (d, J = 28.1 Hz), 152.20 (d, J = 3.9 Hz), 132.43, 129.99, 129.81, 129.48, 126.70, 94.41 (d, J = 202.8 Hz) 53.36, 37.85 (d, J = 24.3 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak AD-H column at 254 nm (n-hexane/*i*-PrOH = 97/3), 1.0 mL/min; Major enantiomer: t_R = 28.73 min, minor enantiomer: t_R = 32.09 min. 95% *ee*.

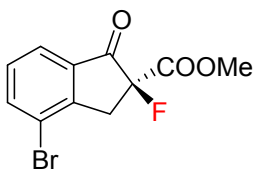


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27.341	28.451	30.415	0.000	48.79	0.3	0.3	48.790
2	UNKNOWN	30.577	31.891	34.568	0.000	51.21	0.2	0.3	51.210
Total						100.00	0.5	0.6	100.000



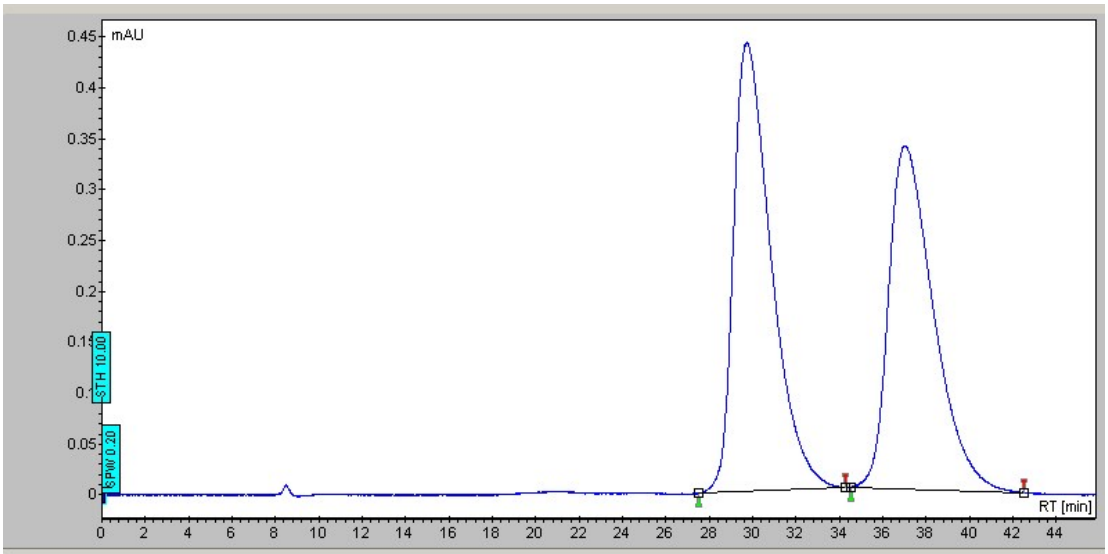
#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27.577	28.731	31.066	0.000	97.66	0.5	0.5	97.659
2	UNKNOWN	31.454	32.091	33.170	0.000	2.34	0.0	0.0	2.341
Total						100.00	0.5	0.6	100.000

methyl (*S*)-4-bromo-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2i)

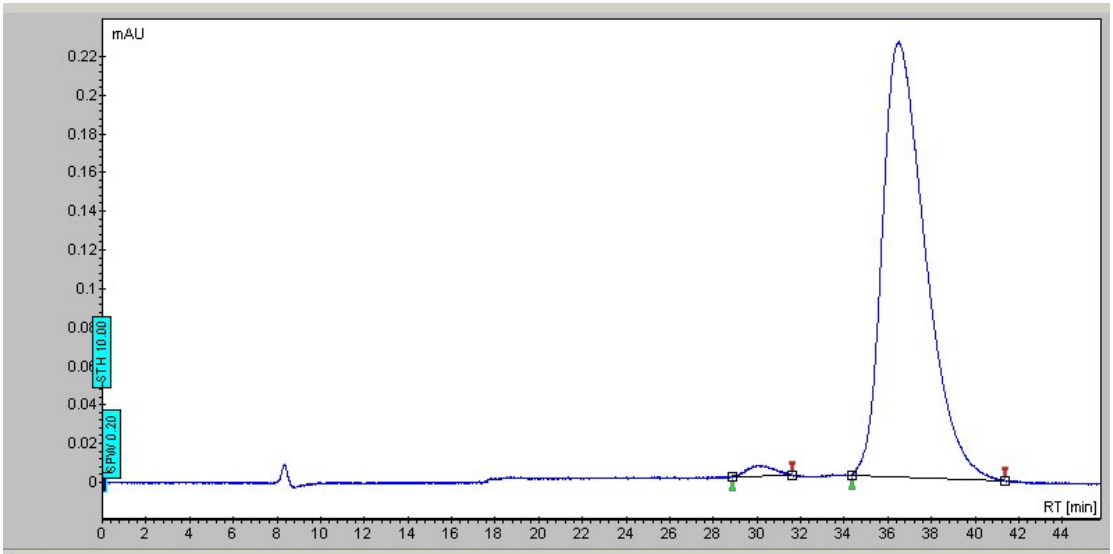


Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as yellow solid (87% yield, 249.5 mg). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (dd, J = 7.8, 1.0 Hz, 1H),

7.78 (d, J = 7.6 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 3.81(s, 3H)3.76 (dd, J = 18.0, 11.5 Hz, 1H), 3.35 (dd, J = 23.3, 18.1 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 194.40 (d, J = 18.4 Hz), 167.16 (d, J = 27.8 Hz), 150.55 (d, J = 4.0 Hz), 139.33, 135.04, 130.34, 124.29, 121.76, 93.98 (d, J = 202.3 Hz), 53.30, 39.22 (d, J = 24.8 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak OB-H column at 254 nm (n-hexane/*i*-PrOH = 70/30), 1.0 mL/min; Major enantiomer: t_R =36.48 min, minor enantiomer: t_R = 30.08 min. 97% *ee*.

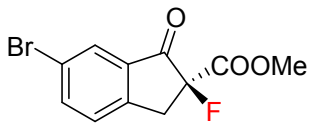


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27.517	29.745	34.284	0.000	52.22	0.4	0.9	52.222
2	UNKNOWN	34.540	37.037	42.520	0.000	47.78	0.3	0.8	47.778
Total						100.00	0.8	1.7	100.000

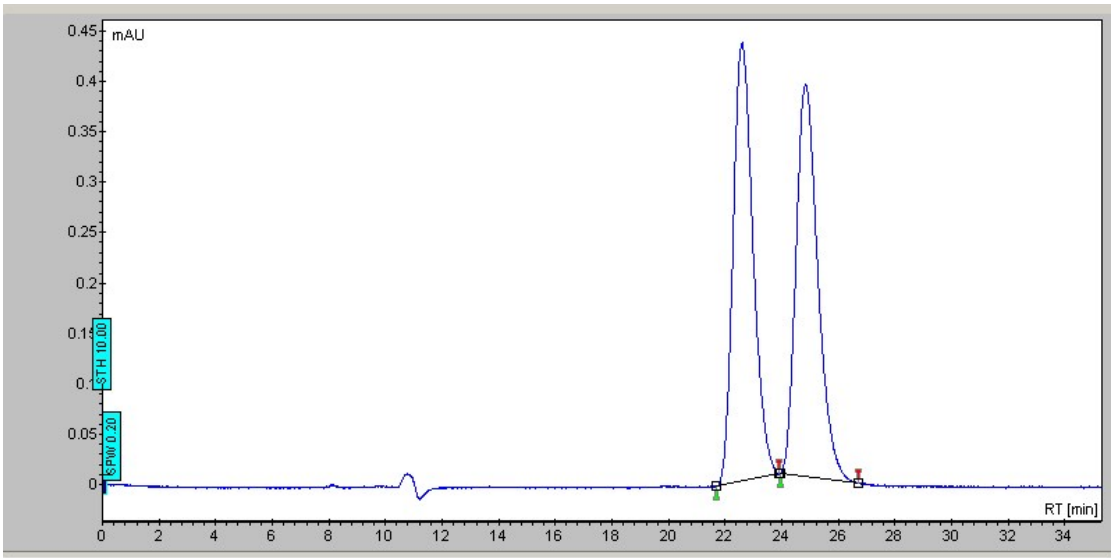


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
2	UNKNOWN	28.871	30.078	31.611	0.000	1.47	0.0	0.0	1.466
1	UNKNOWN	34.352	36.477	41.362	0.000	98.53	0.2	0.5	98.534
Total						100.00	0.2	0.5	100.000

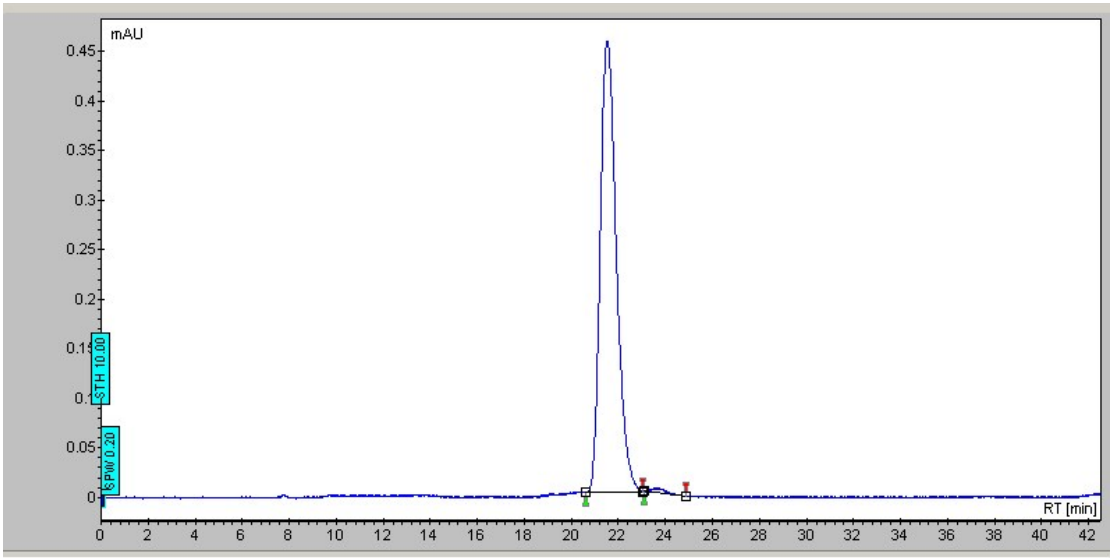
methyl (*S*)-6-bromo-2-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2j)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as yellow solid (91% yield, 260.2 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (d, J = 1.9 Hz, 1H), 7.82 (dd, J = 8.2, 2.0 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 3.83(s, 3H), 3.76 (dd, J = 17.7, 10.8 Hz, 1H), 3.40 (dd, J = 22.9, 17.7 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 193.80 (d, J = 18.4 Hz), 167.25 (d, J = 27.9 Hz), 149.30 (d, J = 3.9 Hz), 139.52, 134.94, 128.41, 128.13, 122.83, 94.61 (d, J = 202.9 Hz), 53.39, 37.92 (d, J = 24.2 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak AD-H column at 254 nm (n-hexane/*i*-PrOH = 90/10), 1.0 mL/min; Major enantiomer: t_R = 21.53 min, minor enantiomer: t_R = 23.68 min. 98% *ee*.

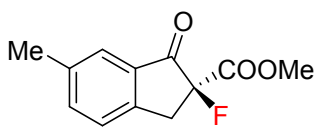


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	21.686	22.598	23.898	0.000	50.32	0.4	0.4	50.322
2	UNKNOWN	23.948	24.838	26.701	0.000	49.68	0.4	0.3	49.678
Total						100.00	0.8	0.7	100.000

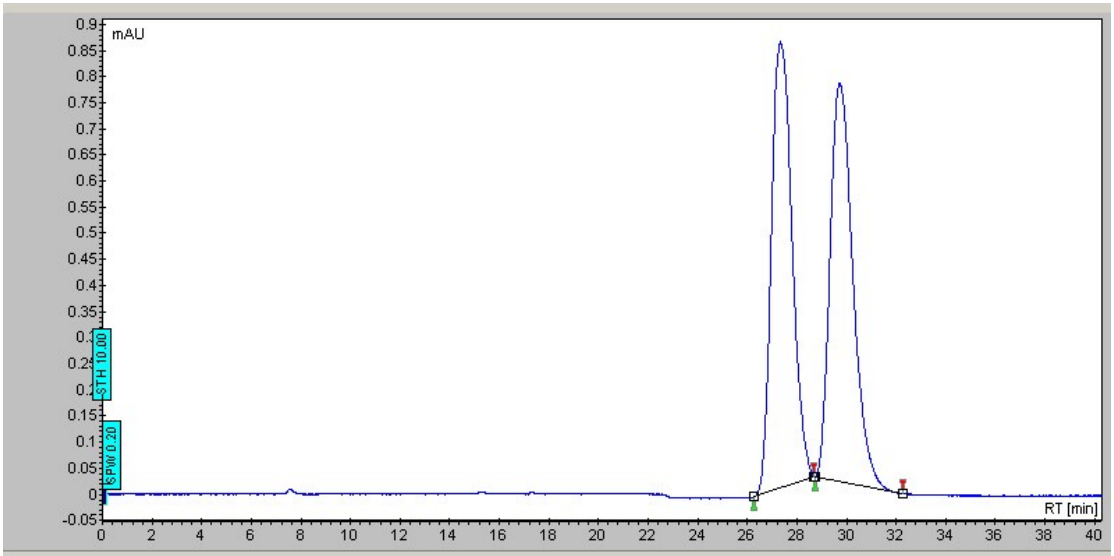


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	20.609	21.532	23.037	0.000	99.24	0.5	0.4	99.236
2	UNKNOWN	23.096	23.678	24.872	0.000	0.76	0.0	0.0	0.764
Total						100.00	0.5	0.4	100.000

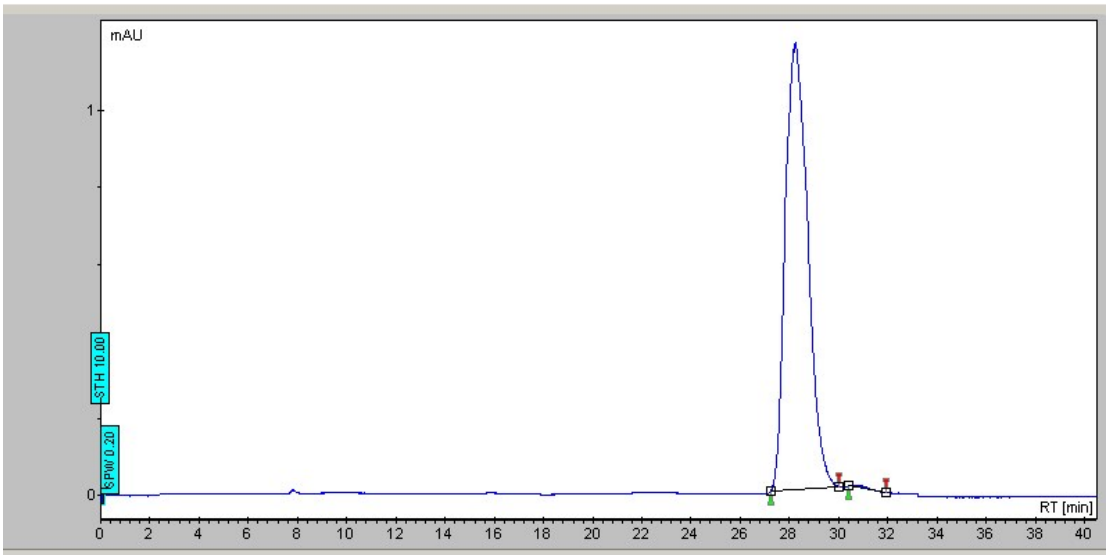
methyl (*S*)-2-fluoro-6-methyl-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2k)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as yellow solid (82% yield, 182.1 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J = 1.6 Hz, 1H), 7.45 (dd, J = 7.8, 1.7 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 3.72 (s, 3H), 3.67 (dd, J = 17.5, 11.0 Hz, 1H), 3.31 (dd, J = 23.3, 17.4 Hz, 1H), 2.35 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 195.10 (d, J = 18.2 Hz), 167.76 (d, J = 28.2 Hz), 148.22 (d, J = 3.7 Hz), 138.80, 138.02, 133.30, 126.21, 125.41, 94.93 (d, J = 201.3 Hz), 53.13, 37.88 (d, J = 23.8 Hz). 21.02. The enantiomers were analyzed by HPLC using Daicel Chiralpak AD-H column at 254 nm (n-hexane/*i*-PrOH = 97/3), 1.0 mL/min; Major enantiomer: t_R = 28.25 min, minor enantiomer: t_R = 30.81 min. 99% *ee*.

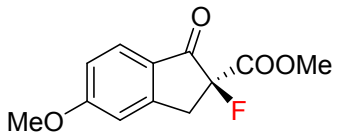


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	26.264	27.305	28.677	0.000	50.34	0.9	0.8	50.345
2	UNKNOWN	28.733	29.731	32.268	0.000	49.66	0.8	0.8	49.655
Total						100.00	1.6	1.6	100.000

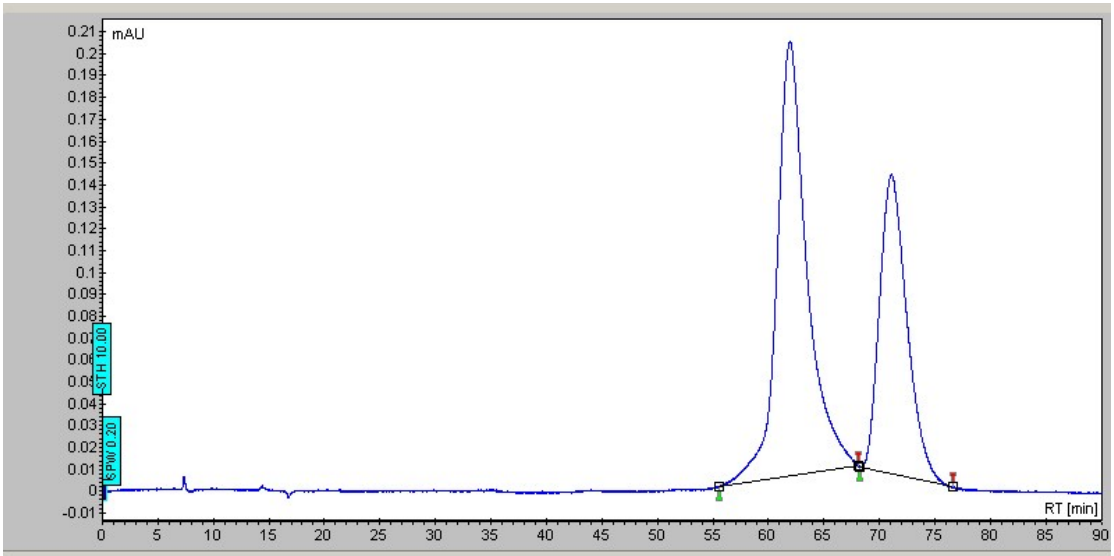


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	27.249	28.251	30.013	0.000	99.69	1.2	1.2	99.690
2	UNKNOWN	30.408	30.811	31.931	0.000	0.31	0.0	0.0	0.310
Total						100.00	1.2	1.2	100.000

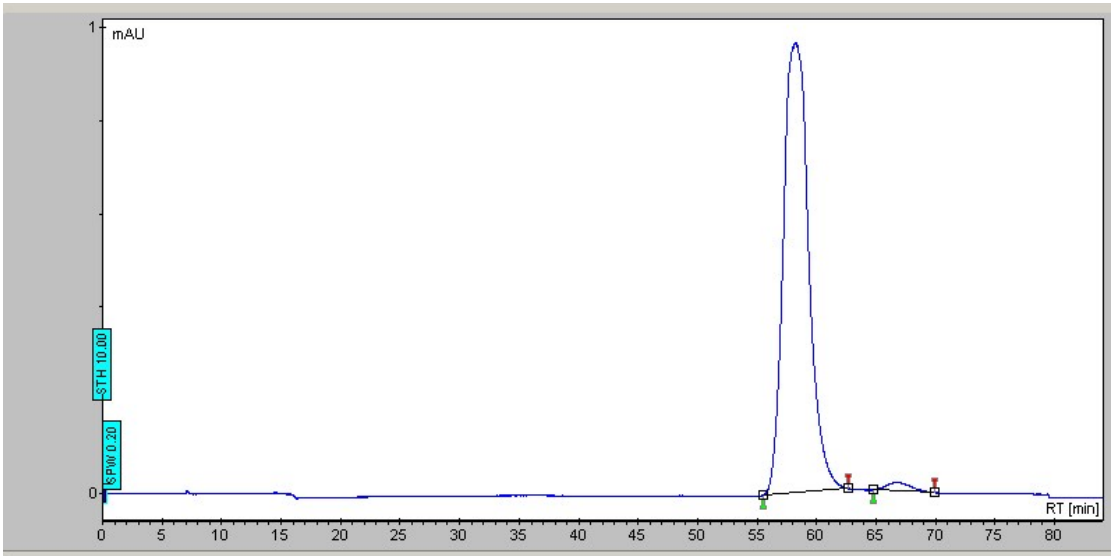
methyl (*S*)-2-fluoro-5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2l)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as yellow solid (97% yield, 230.9 mg).^{1}H NMR (600 MHz, $CDCl_3$) δ 7.66 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.89 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.84 (d, *J* = 2.3 Hz, 1H), 3.83 (d, *J* = 1.8 Hz, 3H), 3.72 – 3.70 (m, 3H), 3.66 (dd, *J* = 17.7, 11.1 Hz, 1H), 3.28 (dd, *J* = 23.1, 17.6 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 192.88 (d, *J* = 18.3 Hz), 167.84 (d, *J* = 28.2 Hz), 166.83, 153.99 (d, *J* = 4.0 Hz), 127.29, 126.05, 116.73, 109.65, 94.95 (d, *J* = 200.7 Hz), 55.81, 53.04, 38.07 (d, *J* = 24.1 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak AD-H column at 254 nm (n-hexane/*i*-PrOH = 97/3), 1.0 mL/min; Major enantiomer: t_R = 58.19 min, minor enantiomer: t_R = 66.83 min. 96% *ee*.

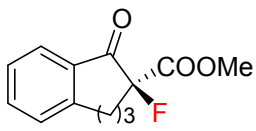


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	55.554	61.938	68.094	0.000	61.66	0.2	0.6	61.665
2	UNKNOWN	68.220	71.081	76.622	0.000	38.34	0.1	0.4	38.335
Total						100.00	0.3	1.0	100.000

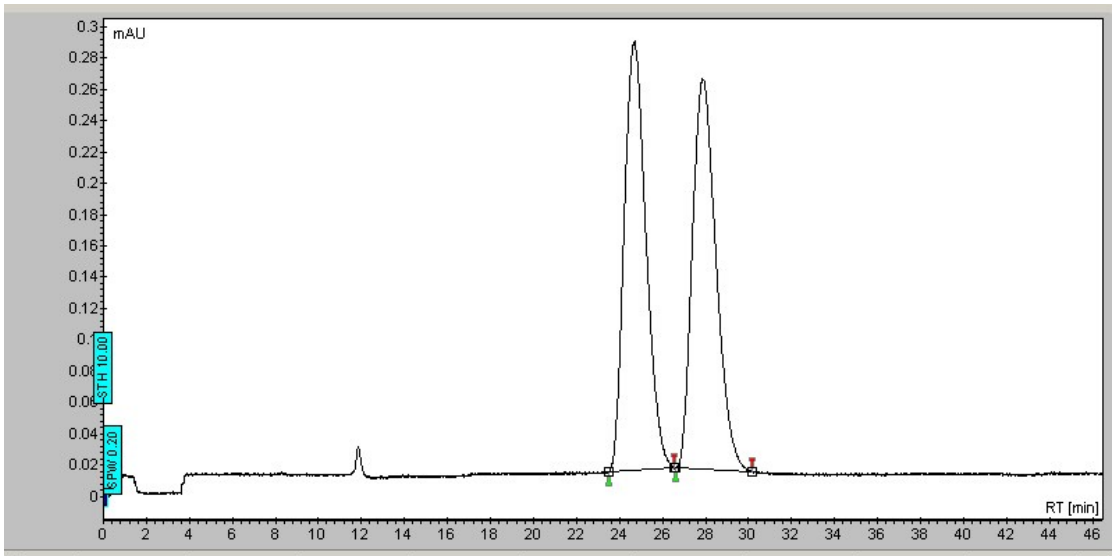


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	55.507	58.192	62.650	0.000	98.17	1.0	2.4	98.168
2	UNKNOWN	64.758	66.829	69.911	0.000	1.83	0.0	0.0	1.832
Total						100.00	1.0	2.4	100.000

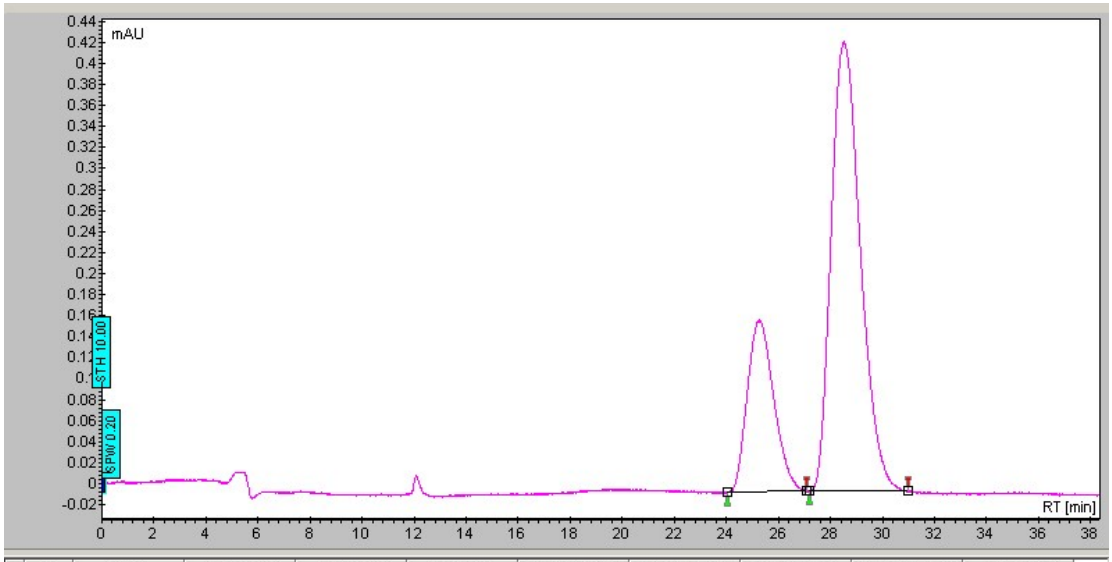
methyl (*S*)-6-fluoro-5-oxo-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (2m)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as yellow oil (48% yield, 113.3 mg). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.45 (td, *J* = 7.5, 1.4 Hz, 1H), 7.32 (td, *J* = 7.6, 1.1 Hz, 1H), 7.23 (d, *J* = 7.6 Hz, 1H), 3.84 (s, 3H), 3.13 (ddd, *J* = 16.0, 10.4, 3.0 Hz, 1H), 2.95 (ddt, *J* = 16.0, 7.7, 2.4 Hz, 1H), 2.63 (dddd, *J* = 35.8, 15.2, 7.3, 5.3 Hz, 1H), 2.30 (tdd, *J* = 15.2, 8.2, 5.2 Hz, 1H), 2.16 (dtdd, *J* = 15.4, 7.8, 5.1, 3.0 Hz, 1H), 1.93 (ddtd, *J* = 12.9, 10.8, 5.3, 2.7 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 198.73 (d, *J* = 27.0 Hz), 167.69 (d, *J* = 25.2 Hz), 140.73, 136.38, 132.37, 129.63, 129.35, 126.70, 99.22 (d, *J* = 195.8 Hz), 53.11, 33.44 (d, *J* = 1.9 Hz), 32.70 (d, *J* = 22.0 Hz). The enantiomers were analyzed by HPLC using Daicel Chiralpak IC column at 254 nm (n-hexane/*i*-PrOH = 90/10), 1.0 mL/min; Major enantiomer: t_R = 28.53 min, minor enantiomer: t_R = 25.27 min. 48% *ee*.

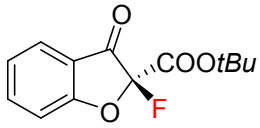


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	23.499	24.692	26.542	0.000	50.17	0.3	0.3	50.165
2	UNKNOWN	26.606	27.851	30.167	0.000	49.83	0.2	0.3	49.835
Total						100.00	0.5	0.6	100.000

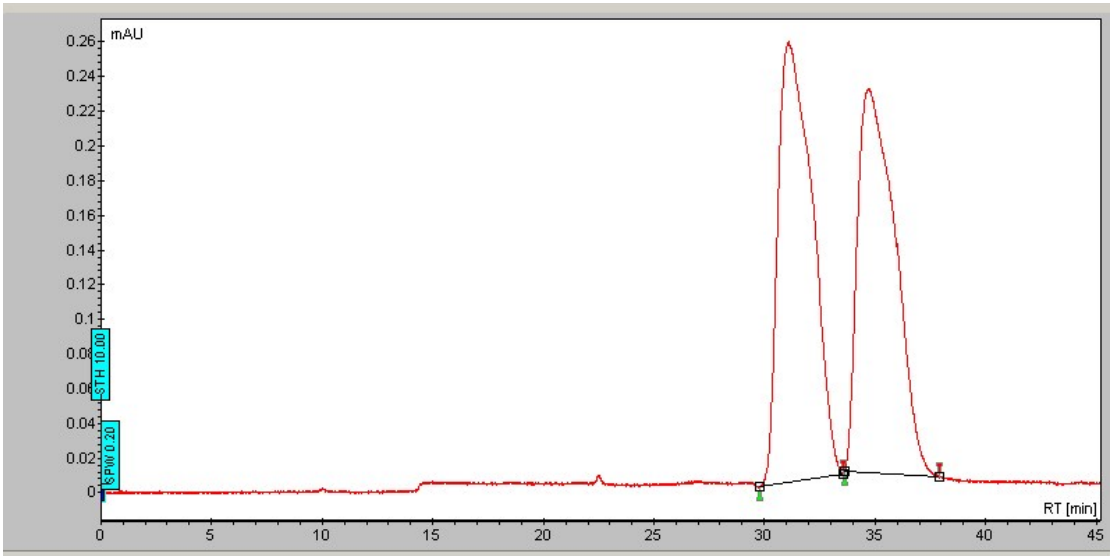


#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	24.042	25.265	27.087	0.000	25.79	0.2	0.2	25.785
2	UNKNOWN	27.194	28.531	30.987	0.000	74.21	0.4	0.6	74.215
Total						100.00	0.6	0.7	100.000

tert-butyl (*S*)-2-fluoro-3-oxo-2,3-dihydrobenzofuran-2-carboxylate (2n)



Purified by flash chromatography on silica gel, eluting with ethyl acetate/petroleum ether 1/30 (v/v) as yellow oil (84% yield, 211.7 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 – 7.51 (m, 2H), 7.35 – 6.87 (m, 2H), 1.48 (d, J = 1.1 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 190.36 (d, J = 18.3 Hz), 171.28 (d, J = 1.6 Hz), 161.10 (d, J = 36.0 Hz), 139.55, 125.66, 124.26, 117.58, 113.51, 103.18 (d, J = 250.1 Hz) 85.64, 27.69. The enantiomers were analyzed by HPLC using Daicel Chiralpak OJ-H column at 254 nm (n-hexane/*i*-PrOH = 99/1), 1.0 mL/min; Major enantiomer: t_R = 32.74 min, minor enantiomer: t_R = 29.52 min. 97% *ee*.



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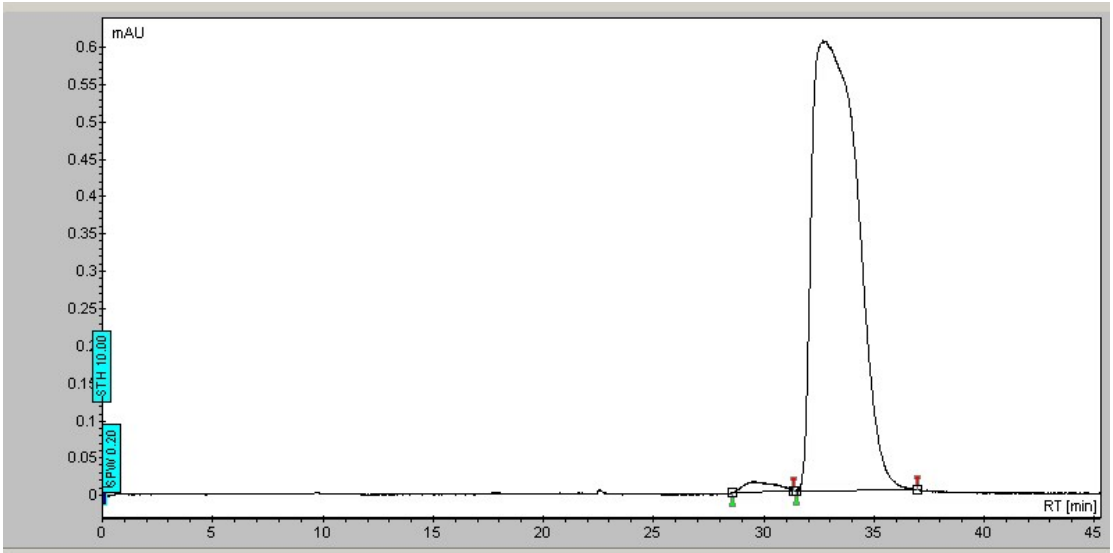
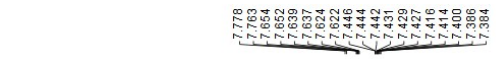
1	UNKNOWN	29.785	31.091	33.564	0.000	50.94	0.3	0.5	50.936
2	UNKNOWN	33.627	34.704	37.909	0.000	49.06	0.2	0.4	49.064
Total						100.00	0.5	0.9	100.000



#	Name	Start [Min]	Time [Min]	End [Min]	Ret. time Offset	Quantity [% Area]	Height [mAU]	Area [mAU.Min]	Area % [%]
1	UNKNOWN	28.576	29.518	31.352	0.000	1.57	0.0	0.0	1.566
2	UNKNOWN	31.478	32.744	36.966	0.000	98.43	0.6	1.4	98.434
Total						100.00	0.6	1.5	100.000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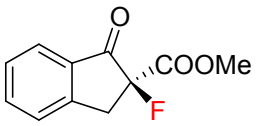
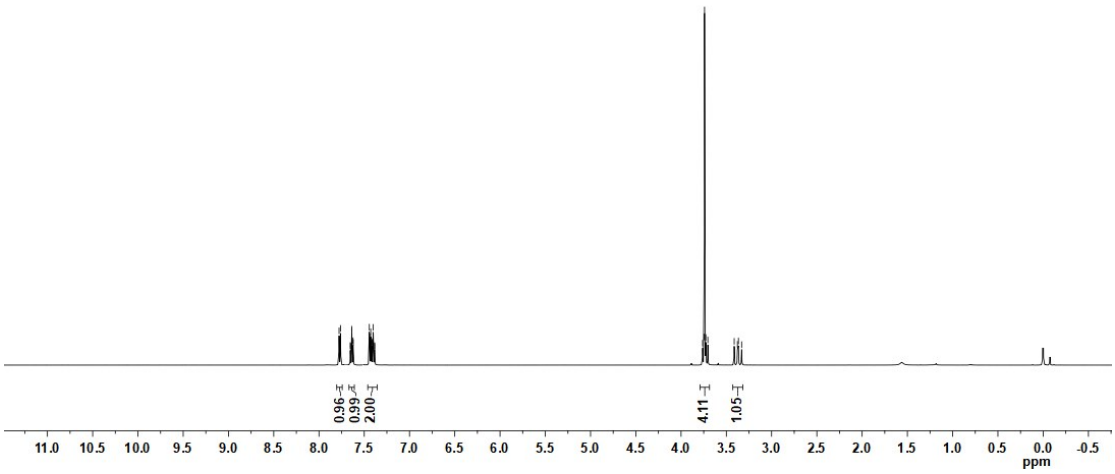
7.654
7.652
7.639
7.637
7.624
7.622
7.446
7.444
7.442
7.431
7.429
7.427
7.416
7.414
7.400
7.386
7.384
3.762
3.746
3.741
3.727
3.704
3.413
3.378
3.366
3.331


O
COOMe
F

2a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0.99
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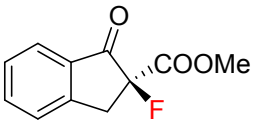
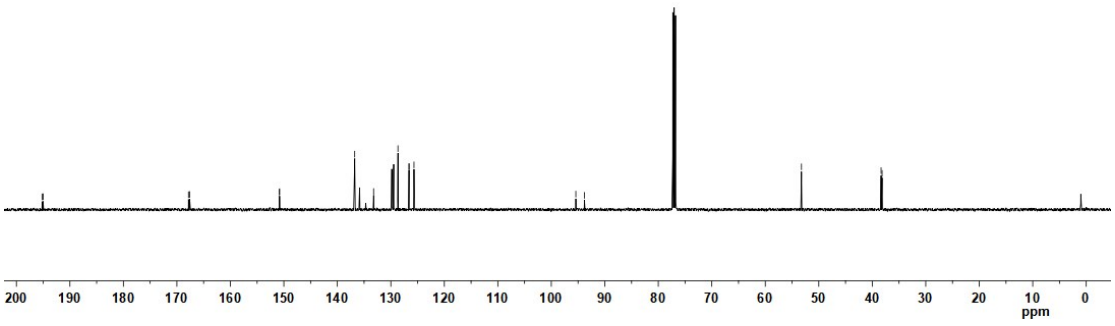
1.05
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm

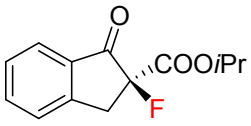

195.155
195.009
167.835
167.614
150.831
150.801
136.759
133.226
128.671
126.603
126.596
125.675
95.414
93.811
53.236
38.351
38.162


O
COOMe
F

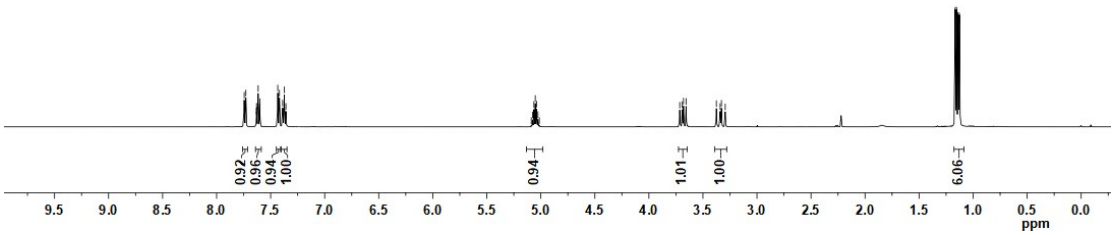
2a


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm


7.745
7.729
7.633
7.631
7.629
7.616
7.602
7.600
7.599
7.434
7.419
7.389
7.374
7.359
5.089
5.077
5.064
5.052
5.039
5.027
5.014
3.715
3.691
3.680
3.656
3.376
3.340
3.329
3.294
1.166
1.165
1.154
1.152
1.140
1.137
1.127
1.125


O
COO*i*Pr
F

2b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0.96
0.94
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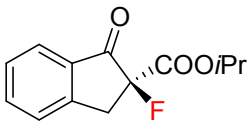
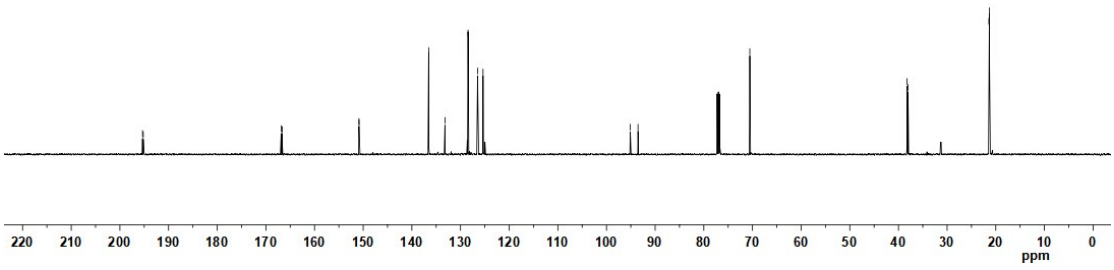
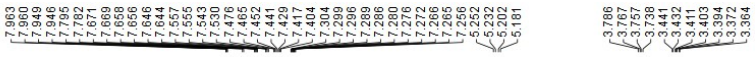
0.94
1.01
1.00
6.06
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm

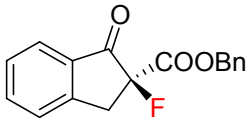

195.345
195.199
166.848
166.629
150.869
150.841
136.541
133.195
128.453
126.490
125.370
95.117
93.517
70.548
38.228
38.036
21.421
21.311


O
COO*i*Pr
F

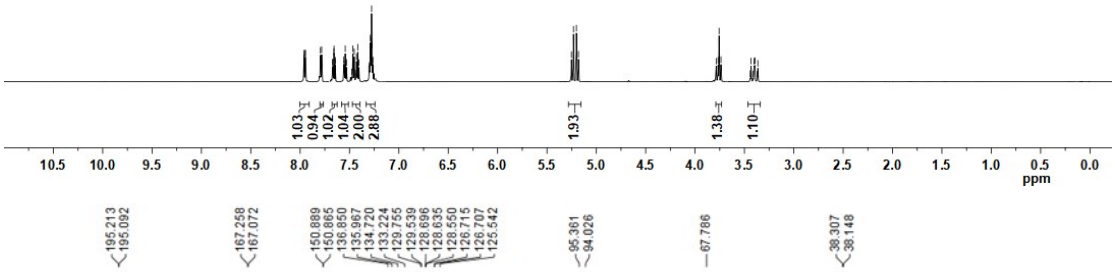
2b

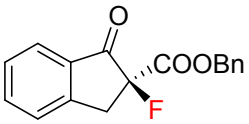

220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm





2c





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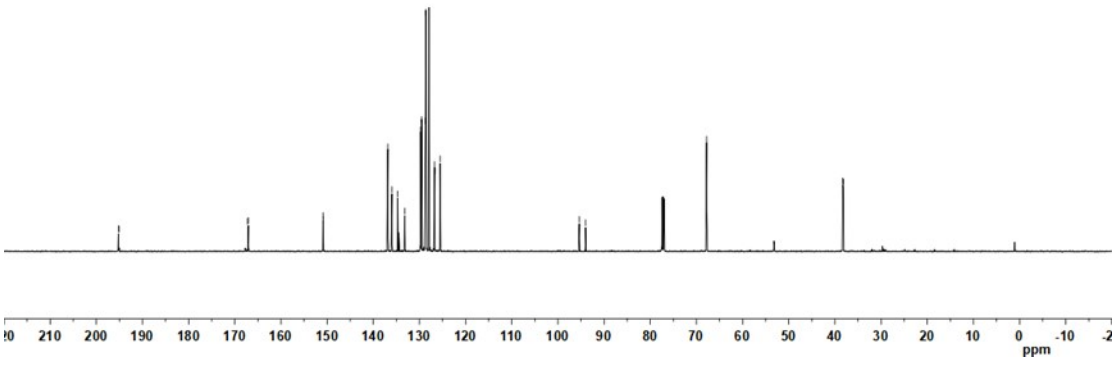

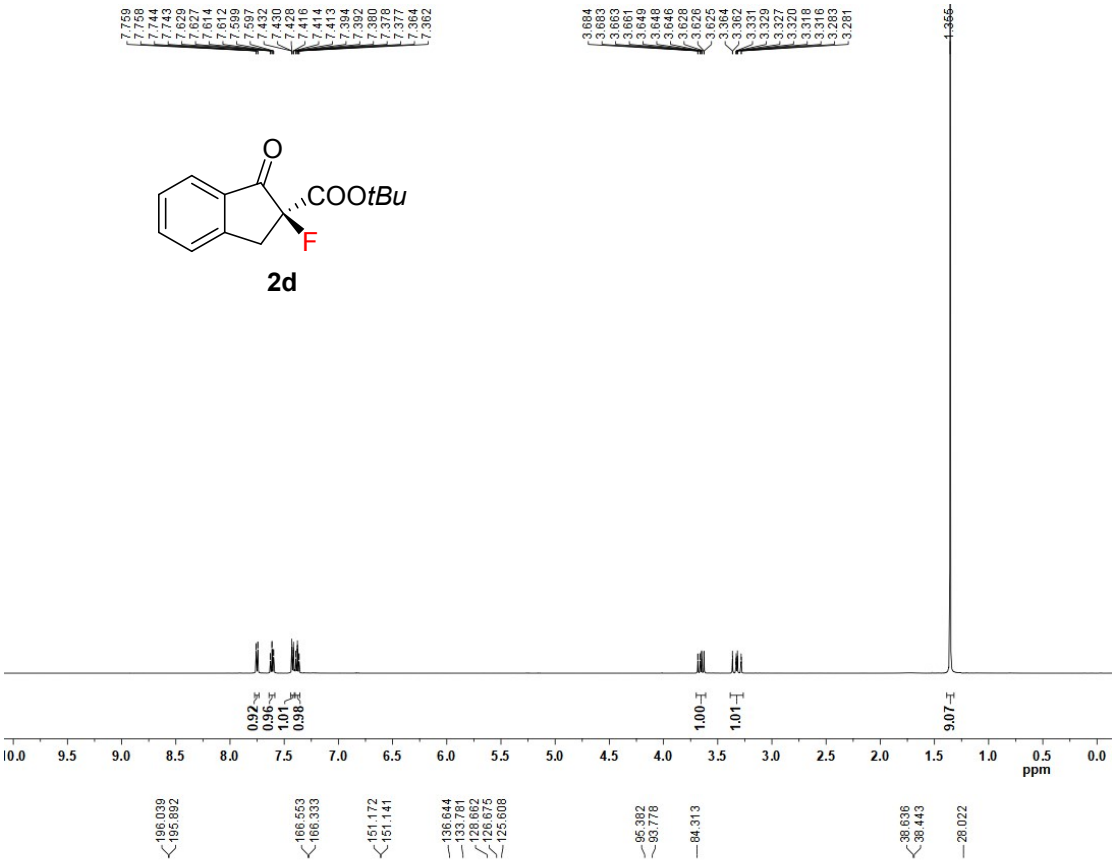
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7.627
7.614
7.612
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7.597
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7.430
7.428
7.416
7.414
7.413
7.394
7.392
7.380
7.378
7.377
7.364
7.362
3.684
3.683
3.663
3.661
3.649
3.648
3.646
3.628
3.626
3.625
3.364
3.362
3.331
3.329
3.327
3.320
3.318
3.316
3.283
3.281
1.365
O
COOtBu
F
0.92
0.96
1.01
0.98
1.00
1.01
9.07
ppm
196.039
195.892
166.553
166.333
151.172
151.141
136.644
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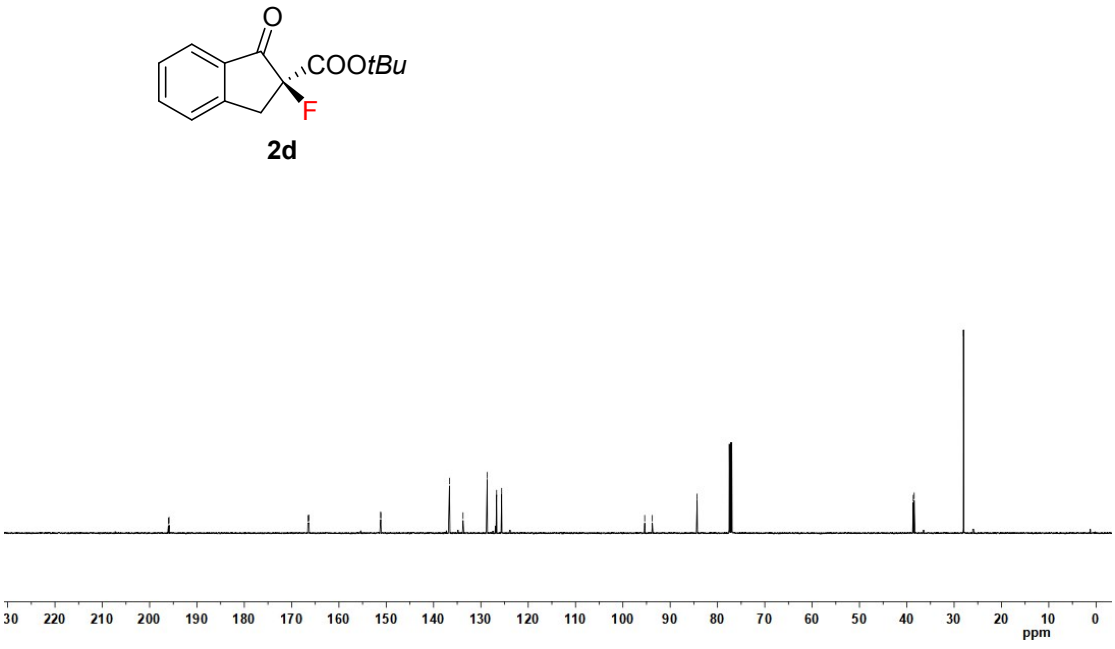
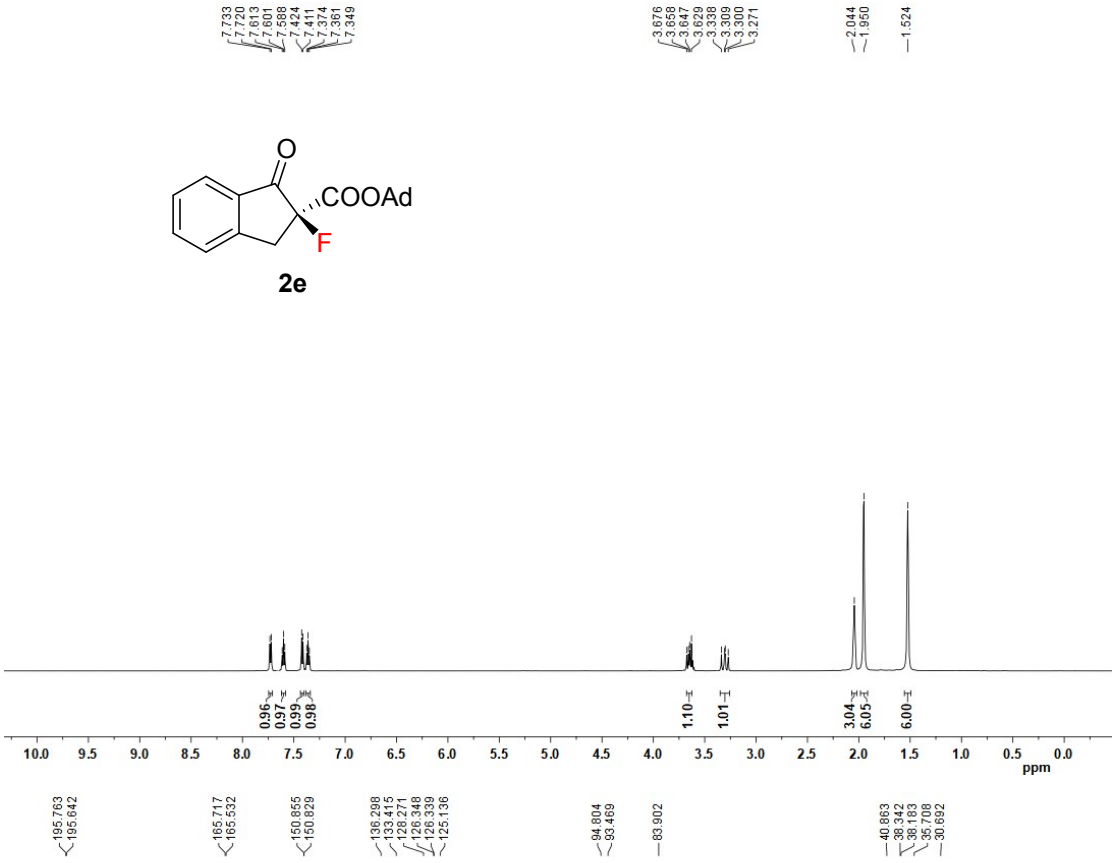
128.662
126.675
125.608
95.382
93.778
84.313
38.636
38.443
28.022

2d


O
COOtBu
F
ppm

2d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7.613
7.601
7.598
7.424
7.411
7.374
7.361
7.349
3.676
3.658
3.647
3.629
3.338
3.309
3.300
3.271
2.044
1.950
1.524
O
COOAd
F
2e
0.96
0.97
0.99
0.98
1.10
1.01
3.04
6.05
6.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
195.763
195.642
165.717
165.532
150.855
150.829
136.298
133.415
128.271
126.348
126.339
125.136
94.804
93.469
83.902
40.863
38.342
38.183
35.708
30.692
O
COOAd
F
2e
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm


7.998
7.995
7.992
7.990
7.984
7.981
7.978
7.613
7.610
7.608
7.598
7.596
7.587
7.584
7.197
7.194
7.183
7.180
7.169
7.165
3.825
3.805
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3.777
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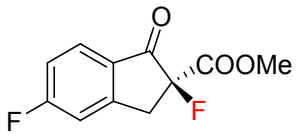
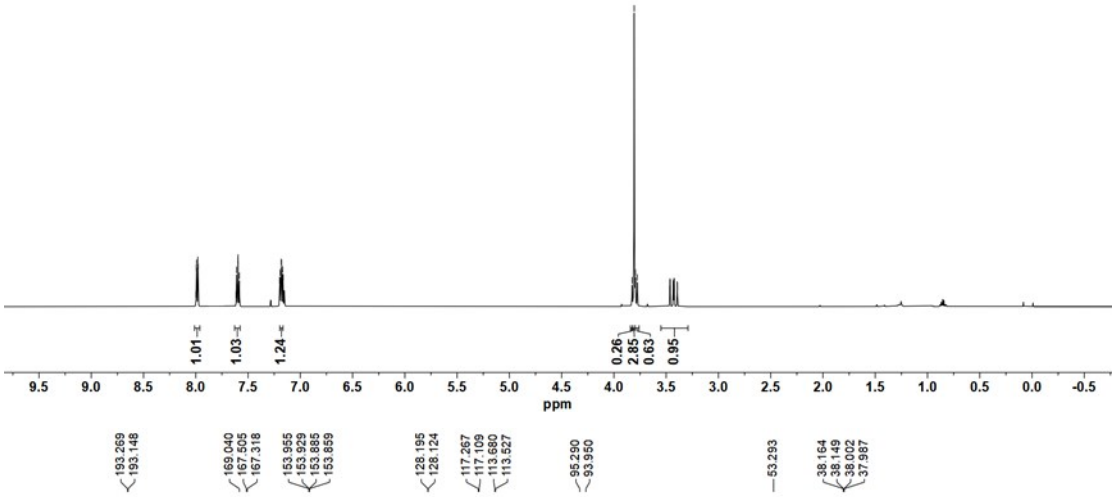
3.461
3.433
3.432
3.425
3.423
3.395
3.393


O
COOMe
F
F

2f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1.03
1.24
0.26
2.85
0.63
0.95
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
ppm
193.269
193.148
169.040
167.505
167.318
153.955
153.929
153.885
153.859
128.195
128.124
117.267
117.109
113.680
113.527
95.290
93.950
53.293
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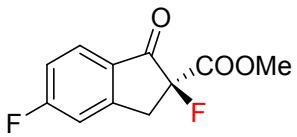
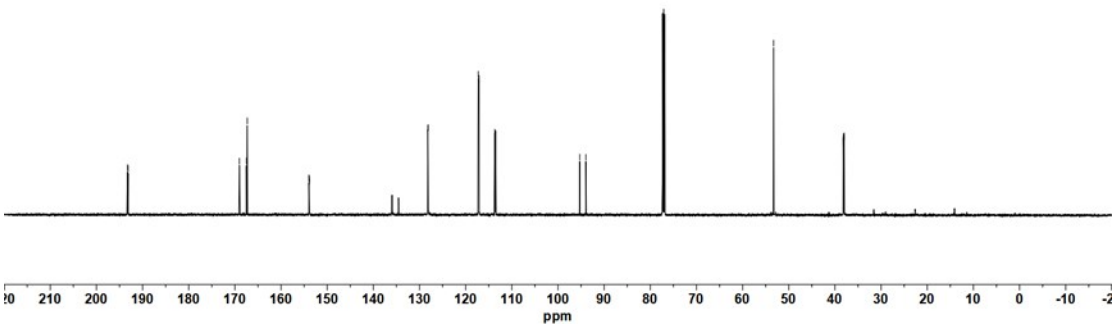
38.149
38.002
37.987


O
COOMe
F
F

2f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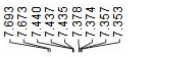
ppm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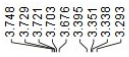
7.435
7.378
7.374
7.357
7.353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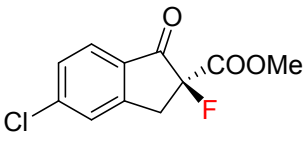
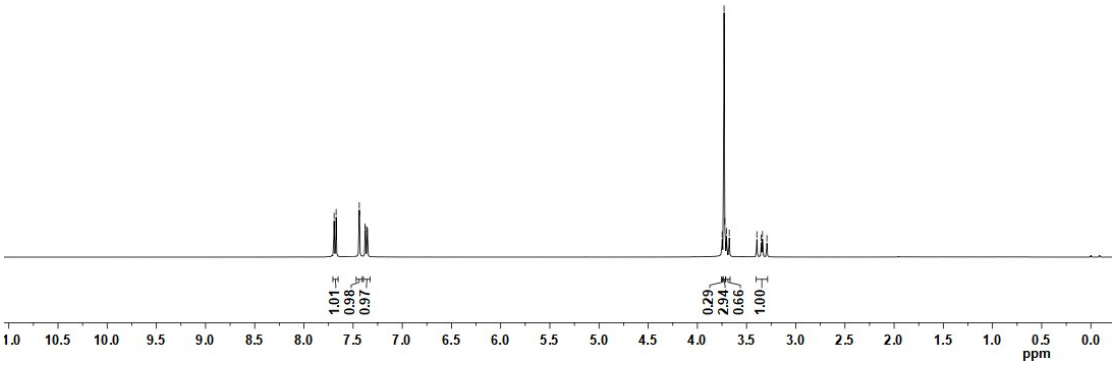
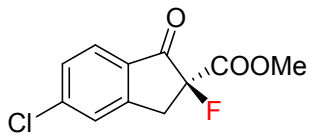
3.729
3.721
3.703
3.676
3.395
3.351
3.338
3.293


O
COOMe
Cl
F

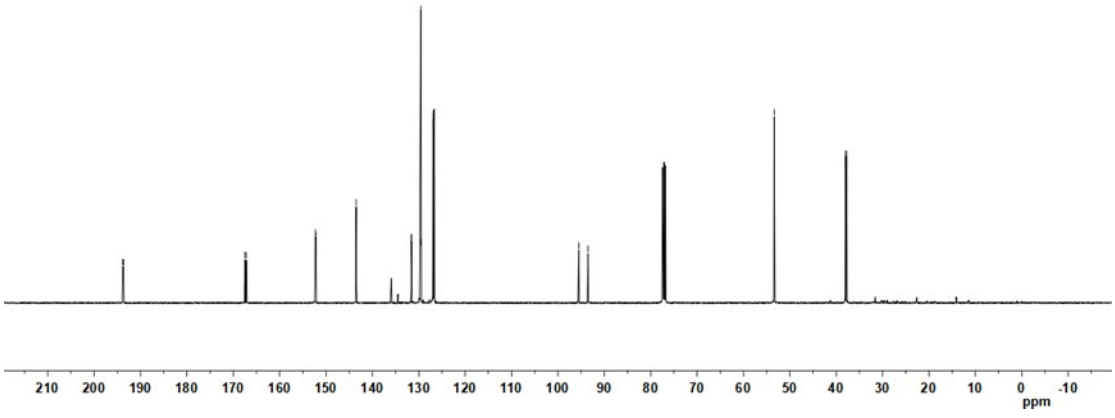
2g


1.01
0.98
0.97
0.29
2.94
0.66
1.00
1.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


193.822
193.640
167.460
167.182
152.256
152.217
143.481
131.597
131.584
129.567
129.513
126.929
126.914
126.688
126.675
95.510
93.498
53.372
38.028
37.788


O
COOMe
Cl
F

2g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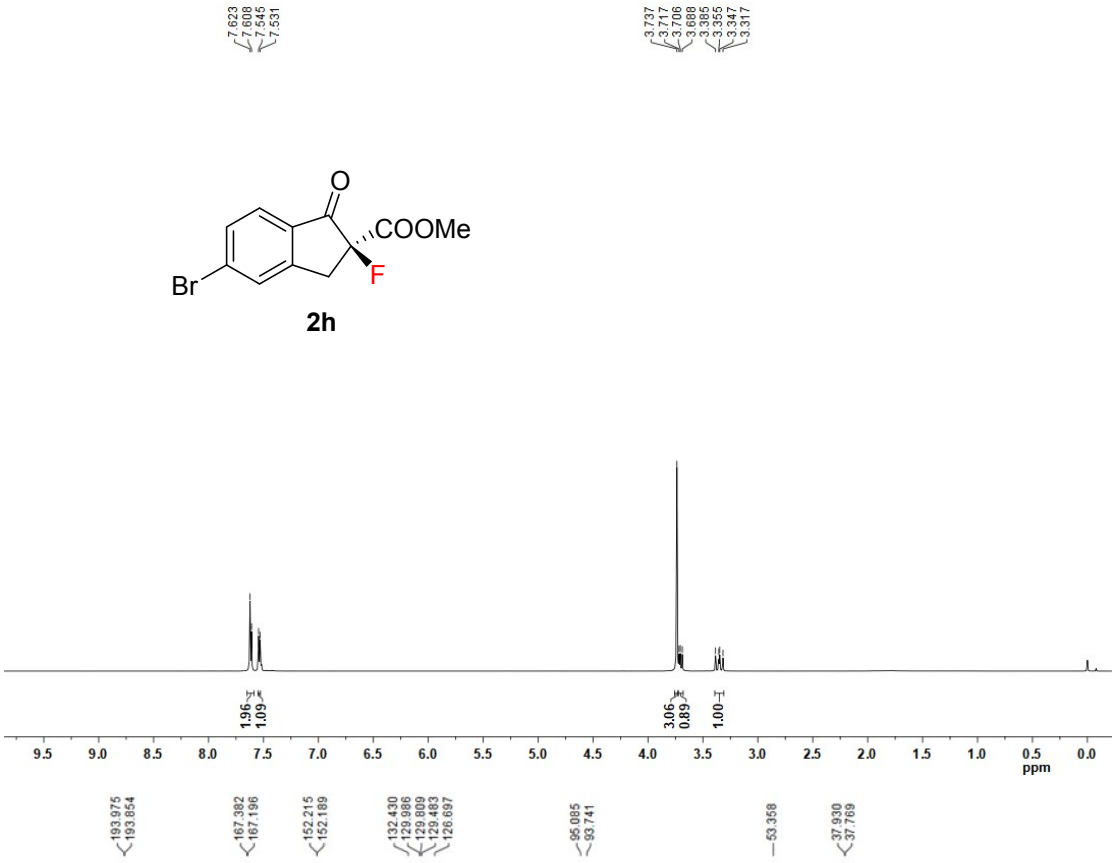
ppm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3.717
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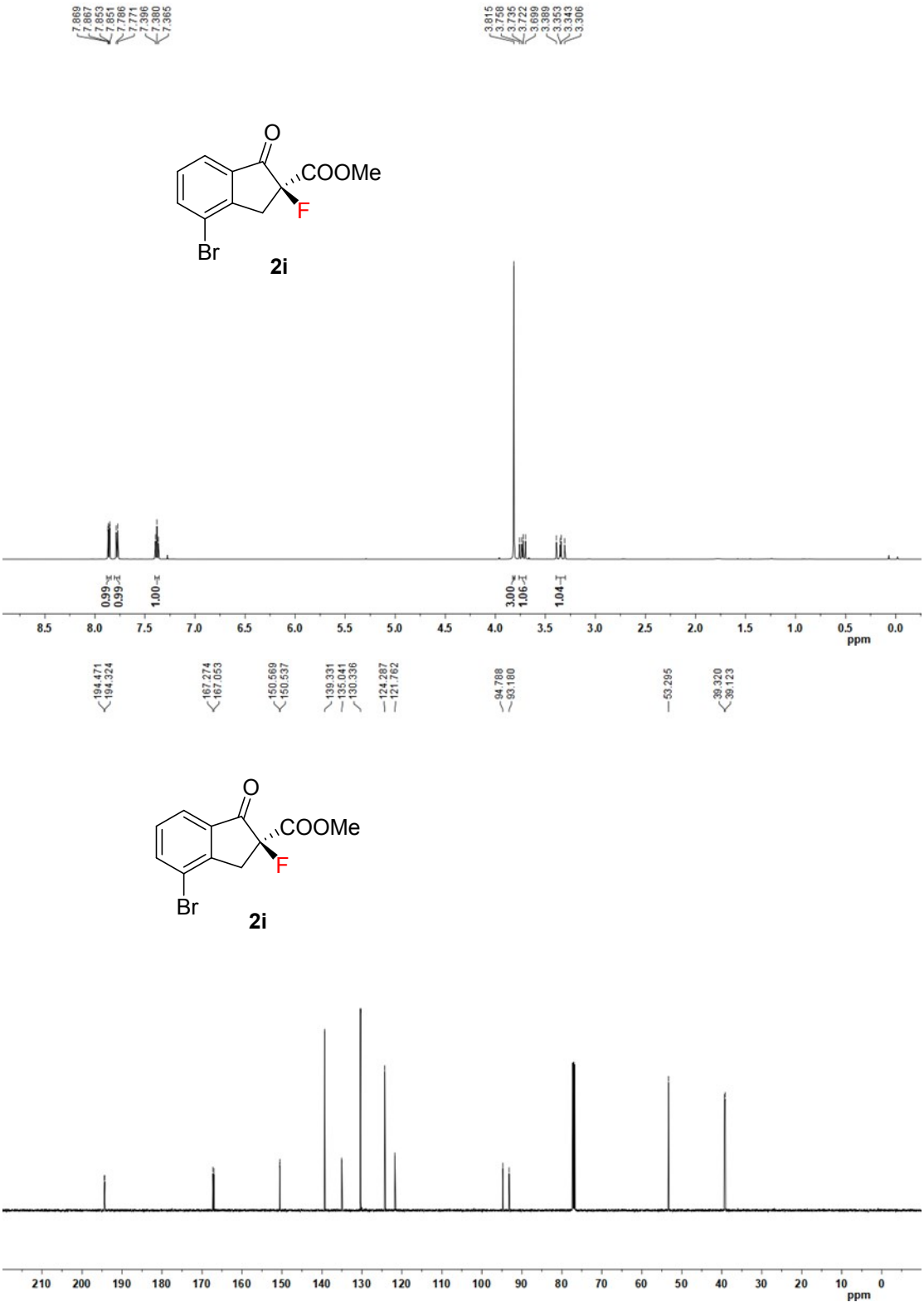
3.688
3.385
3.355
3.347
3.317
O
COOMe
Br
F
2h
1.96
1.09
3.06
0.89
1.00
ppm
193.975
193.854
167.382
167.196
152.215
152.189
132.430
129.986
129.809
129.483
126.697
95.085
93.741
53.358
37.930
37.769
O
COOMe
Br
F
2h
ppm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7.771
7.396
7.380
7.365
3.815
3.758
3.735
3.722
3.699
3.389
3.353
3.343
3.306
O
COOMe
F
Br
2i
0.99
0.99
1.00
3.00
1.06
1.04
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
194.471
194.324
167.274
167.053
150.569
150.537
139.331
135.041
130.336
124.287
121.762
94.788
93.180
53.295
39.320
39.123
O
COOMe
F
Br
2i
210
200
190
180
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140
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120
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100
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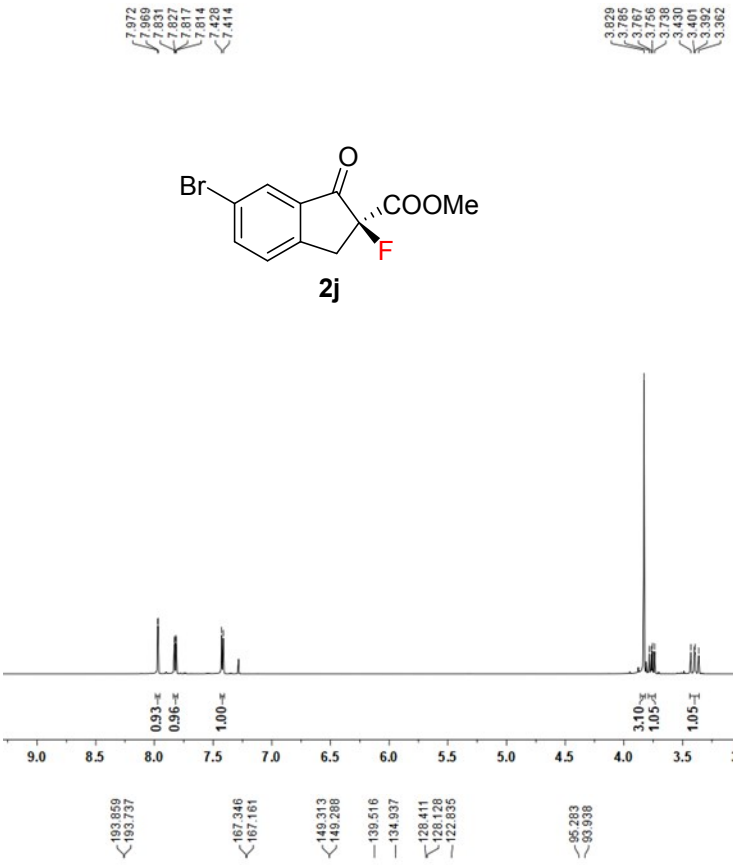
80
70
60
50
40
30
20
10
0
ppm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7.814
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7.414
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3.785
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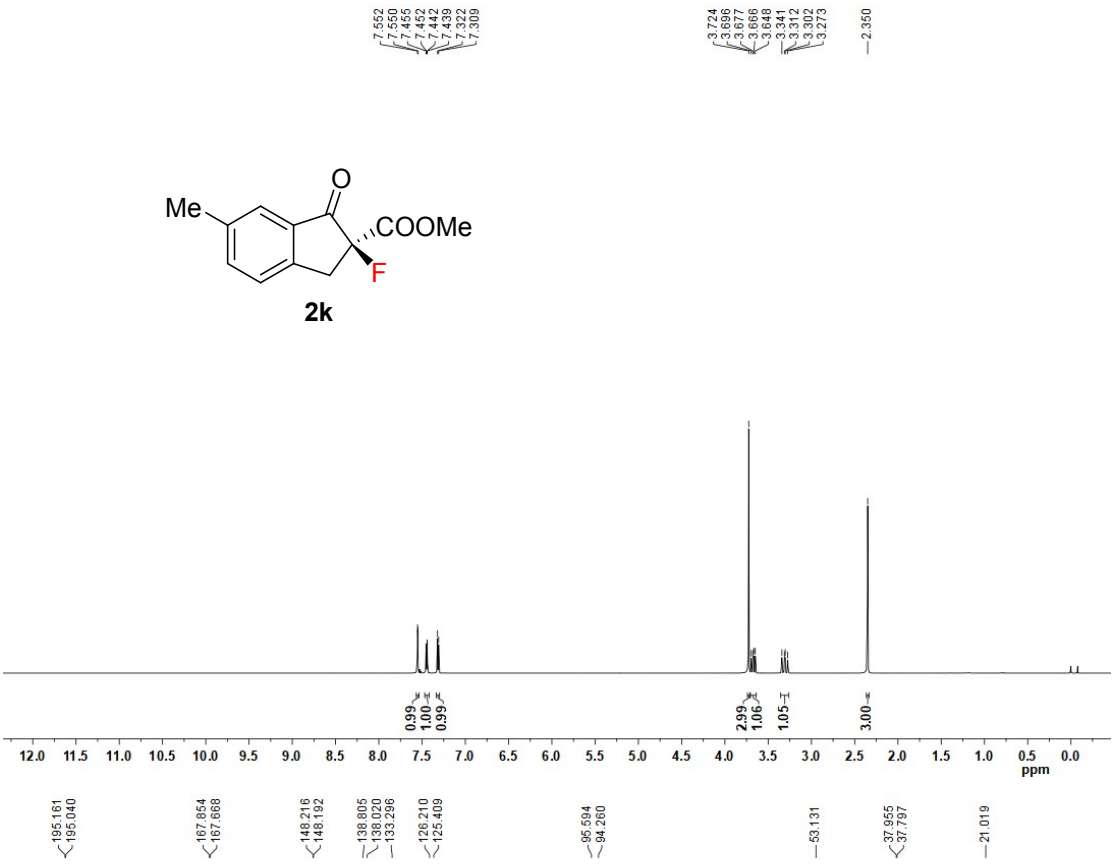
3.756
3.738
3.430
3.401
3.392
3.362
Br
O
COOMe
F
2j
0.93
0.96
1.00
3.10
1.05
1.05
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
193.859
193.737
167.346
167.161
149.313
149.288
139.516
134.937
128.411
128.128
122.835
95.283
93.938
53.387
37.996
37.836
Br
O
COOMe
F
2j
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm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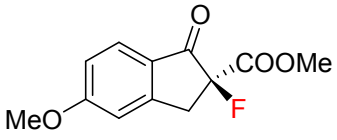
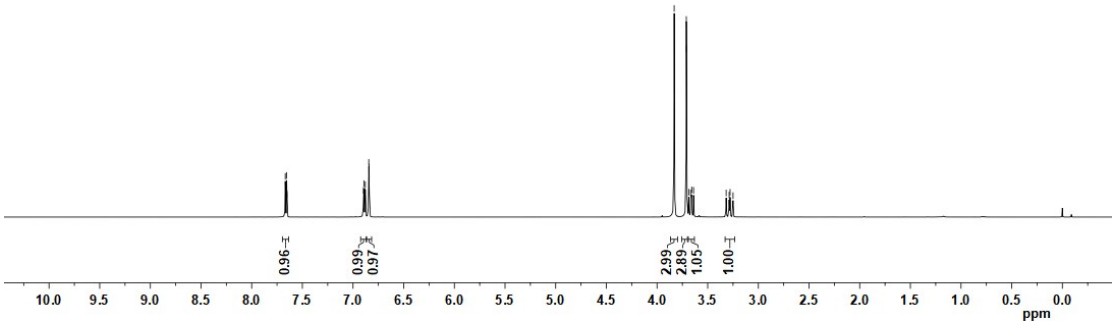
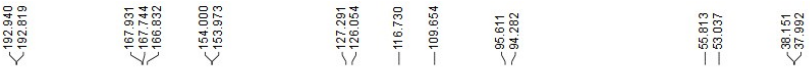
7.560
7.455
7.452
7.442
7.439
7.322
7.309
3.724
3.696
3.677
3.666
3.648
3.341
3.312
3.302
3.273
2.350
O
Me
COOMe
F
2k
0.99
1.00
0.99
2.99
1.06
1.05
3.00
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm
195.161
195.040
167.854
167.668
148.216
148.192
138.805
138.020
133.296
126.210
125.409
95.594
94.260
53.131
37.955
37.797
21.019
O
Me
COOMe
F
2k
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

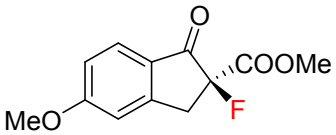

7.669
7.665
7.655
7.651
6.897
6.893
6.883
6.879
6.845
6.841
3.831
3.928
3.711
3.709
3.707
3.687
3.669
3.658
3.318
3.288
3.279
3.250


O
COOMe
F
MeO

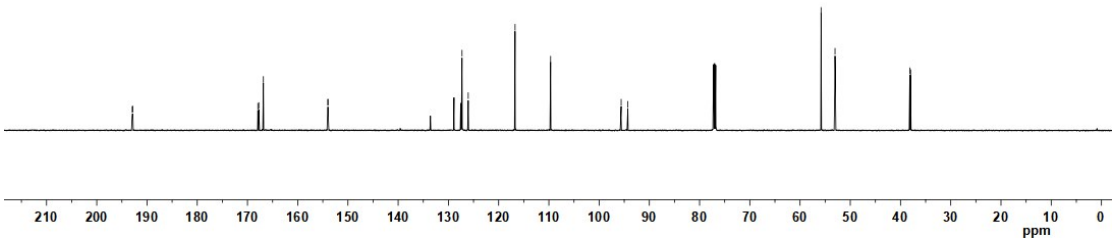
2l

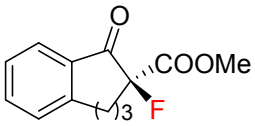

0.96
0.99
0.97
2.99
2.89
1.05
1.00
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
ppm


192.940
192.819
167.931
167.744
166.832
154.000
153.973
127.291
126.054
116.730
109.654
95.611
94.282
55.813
53.037
38.151
37.992

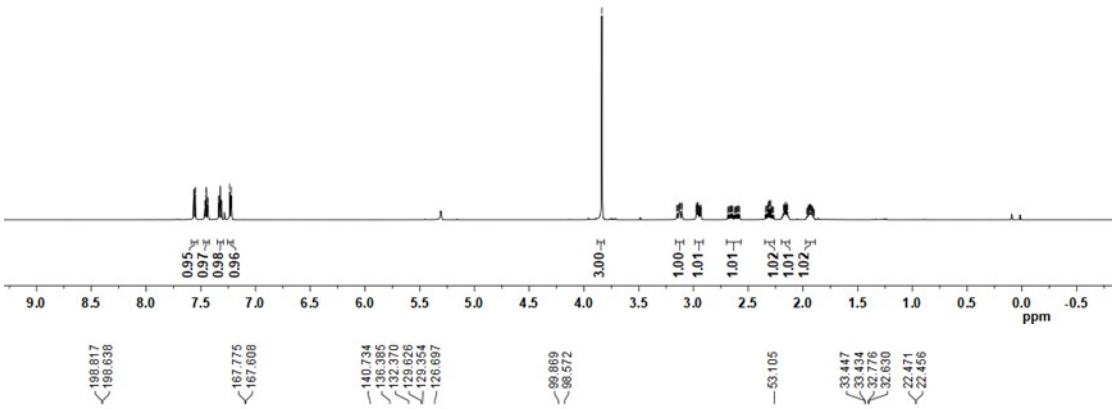

O
COOMe
F
MeO

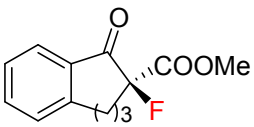
2l


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
ppm

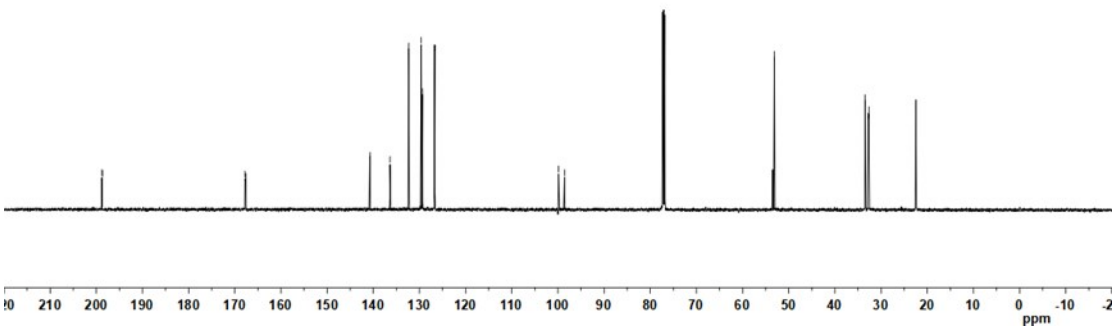

O
COOMe
3
F

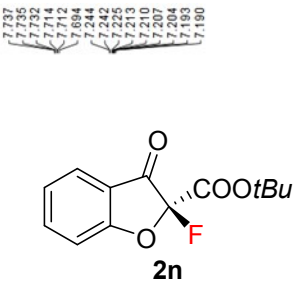
2m

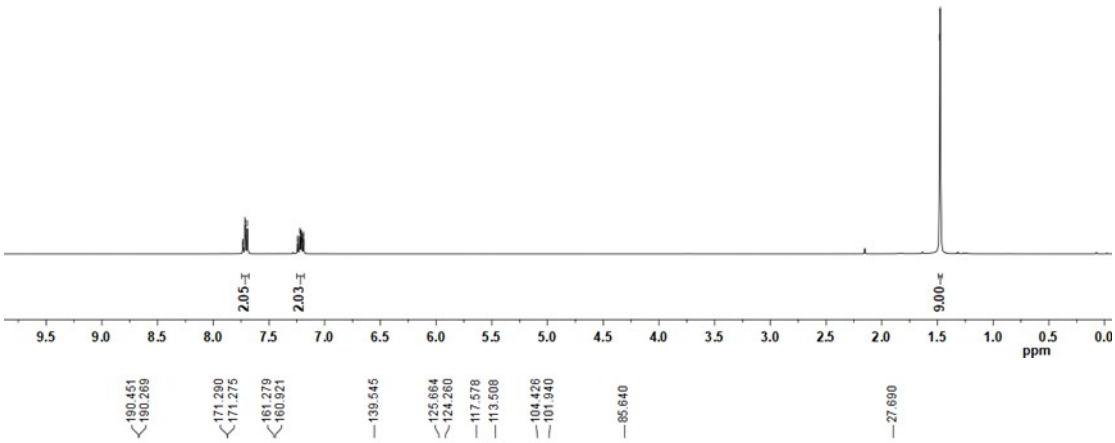

0.95
0.97
0.98
0.96
3.00
1.00
1.01
1.01
1.02
1.01
1.02
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
ppm
198.817
198.638
167.775
167.608
140.734
136.395
132.370
129.626
129.354
126.697
99.869
98.572
53.105
33.447
33.434
32.776
32.630
22.471
22.456

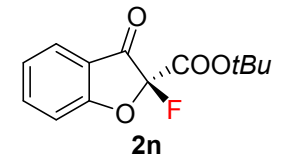

O
COOMe
3
F

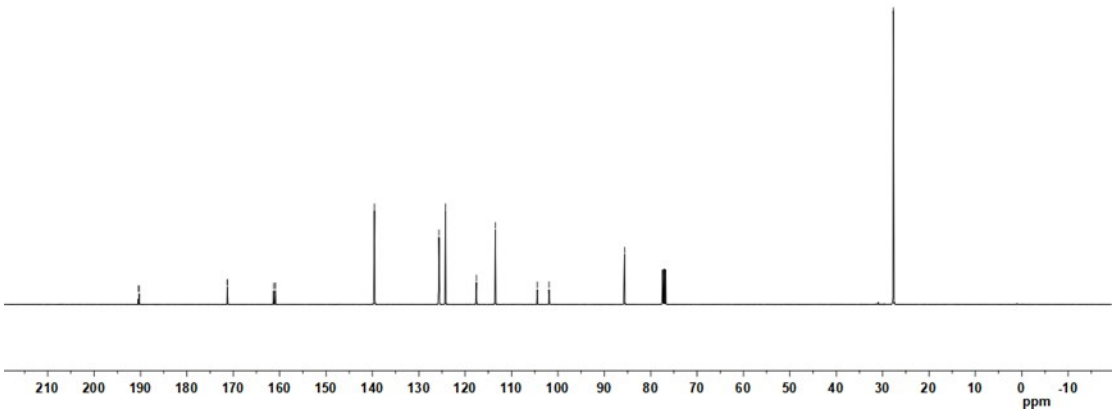
2m


210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
ppm









References

1 E. Bednářová, M. Dračínskỳ, Š. Malatinec, I. Císařová, F. Lamaty, M. Kotora, *Adv. Synth. Catal.* **2018**, *360*, 2869-2878.