

Asymmetric Iodolactonization Utilizing Chiral Squaramides

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Supporting Information

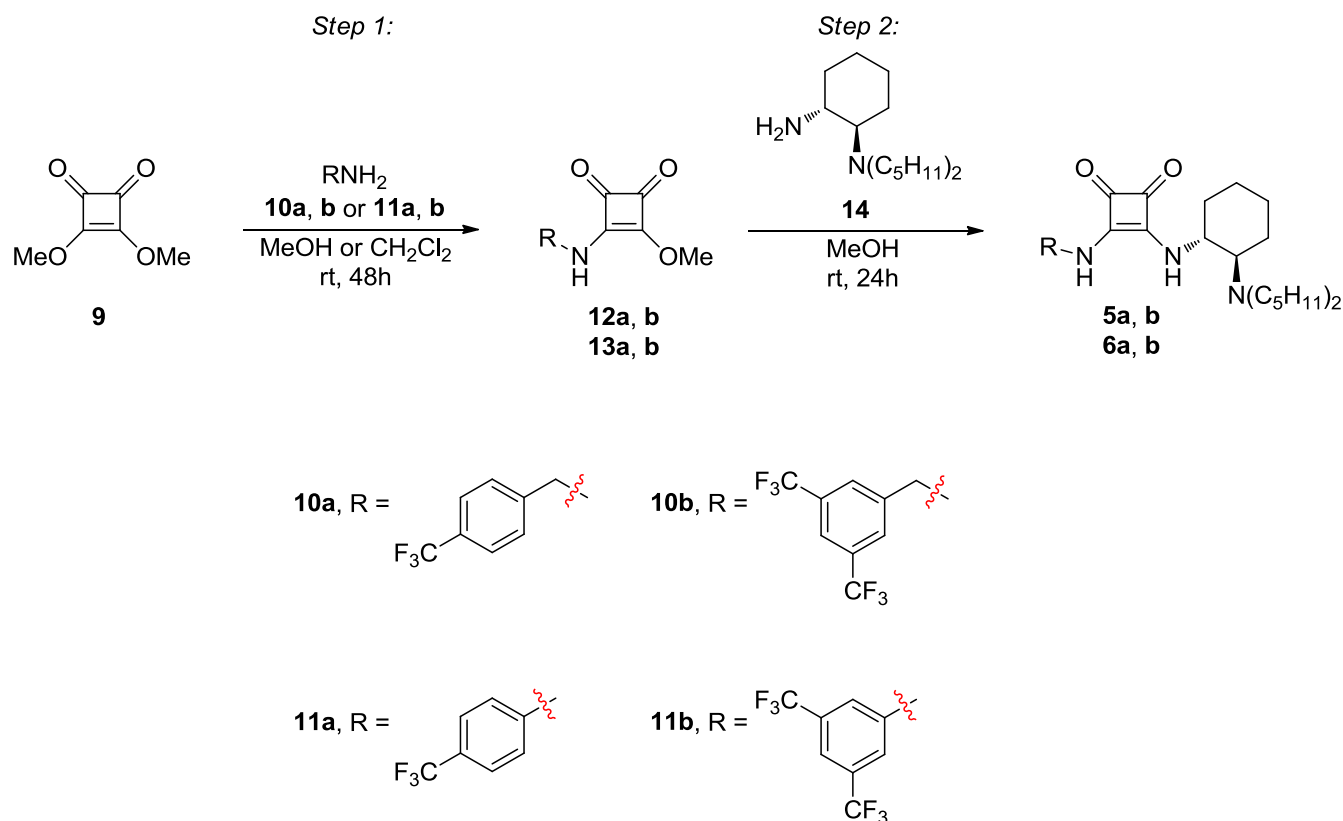
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General Information

All commercially available reagents and solvents were used in the form they were supplied without any further purification. The stated yields are based on isolated material. The melting points are uncorrected. Thin layer chromatography was performed on silica gel 60 F₂₅₄ aluminum-backed plates fabricated by Merck. Flash column chromatography was performed on silica gel 60 (40-63 μ m) fabricated by Merck. NMR spectra were recorded on a Bruker AVII-400 or a Bruker DPX-300 spectrometer at 400 MHz or 300 MHz respectively for ¹H NMR and at 100 MHz or 75 MHz respectively for ¹³C NMR. Coupling constants (*J*) are reported in hertz and chemical shifts are reported in parts per million (δ) relative to the central residual protium solvent resonance in ¹H NMR (CDCl₃ = δ 7.27, DMSO-*d*₆ = δ 2.50 and TFA-*d* = δ 11.50) and the central carbon solvent resonance in ¹³C NMR (CDCl₃ = δ 77.00 ppm and DMSO-*d*₆ = δ 39.43). Mass spectra were recorded at 70 eV on Waters Prospec Q spectrometer using EI as the method of ionization. High resolution mass spectra were recorded on Waters Prospec Q spectrometer using EI as the method of ionization. Optical rotations were measured using a 1 mL cell with a 1.0 dm path length on a Perkin Elmer 341 polarimeter. Determination of enantiomeric excess was performed by HPLC on an Agilent Technologies 1200 Series instrument with diode array detector set at 254 nm and equipped with a chiral stationary phase (Chiralpak AD-H 5 μ m 4.6 x 250 mm), applying the conditions stated. Alternatively, determination of enantiomeric excess was performed by GLC on a Varian 3380 instrument with split (1:30) injection, FID detector and equipped with a chiral stationary phase (Chiraldex G-TA 0.12 μ m 0.25 mm x 30 m), applying the conditions stated.

Preparation of Squaramide Catalysts

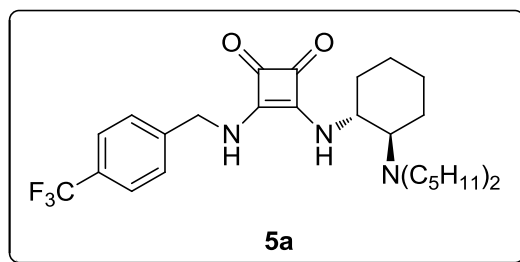


Scheme S-1 Synthetic route to chiral squaramides **5a**, **5b**, **6a** and **6b**.

General procedure for the preparation of squaramide catalysts (Scheme S-1): **Step 1.** 3,4-Dimethoxycyclobut-3-ene-1,2-dione (**9**) (1.0 equiv.) was suspended/dissolved in either MeOH or CH₂Cl₂ (0.07 M) and the amine **10a**, **b** or **11a**, **b** (1.1 equiv.) was added. The resulting mixture was stirred at ambient temperature for 48 hours. The mixture was then filtered; the collected solid residue was washed with ice-cold MeOH and dried *in vacuo* to afford the corresponding squaramate **12a**, **b**¹ or **13a**, **b**^{2, 3}. **Step 2.** 3-(Benzylamino)- or 3-(arylamino)-4-methoxycyclobut-3-ene-1,2-dione **12a**, **b** or **13a**, **b** (1.0 equiv.) was suspended in MeOH (0.07 M) and (1*R*,2*R*)-*N*¹,*N*¹-dipentylcyclohexane-1,2-diamine (**14**) (1.0 equiv.) was added. The resulting mixture was stirred at ambient temperature for 24 hours. The mixture was then filtered; the collected solid residue was washed with ice-cold MeOH and dried *in vacuo* to afford the corresponding squaramide **5a**, **b** or **6a**, **b**.

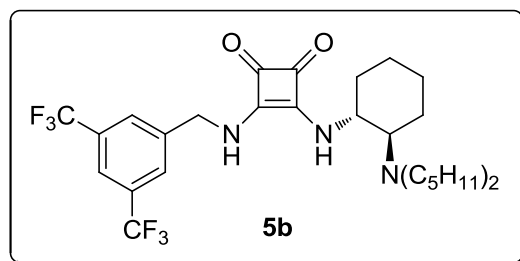
Notice! (1*R*,2*R*)-*N*¹,*N*¹-dipentylcyclohexane-1,2-diamine (**14**) was prepared according to literature procedure⁴ from commercially available (1*R*,2*R*)-cyclohexane-1,2-diamine (Aldrich; 98%, optical purity *ee*: 99% by GLC). The optical antipode, (1*S*,2*S*)-*N*¹,*N*¹-dipentylcyclohexane-1,2-diamine (**ent-14**), was prepared in the same manner from commercially available (1*S*,2*S*)-cyclohexane-1,2-diamine D-tartrate (Aldrich; 99%).

3-(((1*R*,2*R*)-2-(Dipentylamino)cyclohexyl)amino)-4-((4-(trifluoromethyl)benzyl)amino)cyclobut-3-ene-1,2-dione (5a).



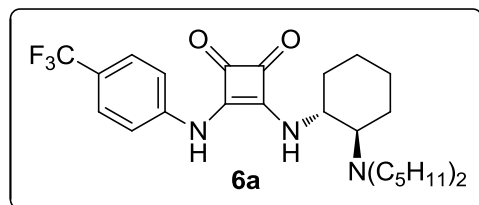
Prepared according to the general procedure by reacting 3-methoxy-4-((4-(trifluoromethyl)benzyl)amino)-cyclobut-3-ene-1,2-dione (**12a**) (0.250 g, 0.88 mmol) with (1*R*,2*R*)-*N*¹,*N*¹-dipentylcyclohexane-1,2-diamine (**14**) (0.223 g, 0.88 mmol) to afford the title compound **5a** after recrystallization from pentane. Yield: 0.211 g (48%), colourless solid; M.p.: 204 – 205 °C, decomp.; TLC (hexanes/EtOAc 1:1): *R*_f = 0.06; $[\alpha]_D^{20} = -634.9$ (*c* = 0.04, CHCl₃); ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.85 (bs, 1H), 7.70 (d, *J* = 8.0 Hz, 2H), 7.53 (d, *J* = 8.0 Hz, 2H), 7.16 (bs, 1H), 4.80 (s, 2H), 4.00 – 3.57 (m, 1H), 2.43 – 2.28 (m, 3H), 2.28 – 2.16 (m, 2H), 2.05 – 1.90 (m, 1H), 1.84 – 1.73 (m, 1H), 1.73 – 1.53 (m, 2H), 1.39 – 0.97 (m, 16H), 0.76 (t, *J* = 6.7 Hz, 6H); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 182.6, 181.9, 168.1, 166.9, 144.0, 128.2 (2C), 124.4 – 126.4 (m, 3C), 124.2 (q, ¹*J*_{CF} = 272.0 Hz, 1C), 63.8, 54.1, 49.4 (2C), 46.1, 34.6, 29.0 (2C), 28.5 (2C), 25.0, 24.6, 24.0, 22.1 (2C), 13.9 (2C); HRMS (EI): Exact mass calculated for C₂₈H₄₀F₃N₃O₂ [*M*]⁺: 507.3073, found 507.3066.

3-((3,5-Bis(trifluoromethyl)benzyl)amino)-4-(((1*R*,2*R*)-2-(dipentylamino)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (5b).



Prepared according to the general procedure by reacting 3-((3,5-bis(trifluoromethyl)benzyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**12b**) (1.050 g, 2.97 mmol) with (1*R*,2*R*)-*N*¹,*N*¹-dipentylcyclohexane-1,2-diamine (**14**) (0.756 g, 2.97 mmol) to afford the title compound **5b**. Yield: 1.045 g (85%), colourless solid; M.p.: 216 – 218 °C, decomp.; TLC (hexanes/EtOAc 1:1): *R*_f = 0.06; $[\alpha]_D^{20} = -86.0$ (*c* = 0.05, CHCl₃); ¹H NMR (300 MHz, DMSO-*d*₆) δ 8.02 (s, 3H), 7.87 (bs, 1H), 7.24 (bs, 1H), 5.08 – 4.67 (m, 2H), 4.05 – 3.57 (m, 1H), 2.41 – 2.26 (m, 3H), 2.26 – 2.12 (m, 2H), 2.04 – 1.85 (m, 1H), 1.83 – 1.72 (m, 1H), 1.72 – 1.54 (m, 2H), 1.41 – 0.87 (m, 16H), 0.70 (t, *J* = 6.4 Hz, 6H); ¹³C NMR (101 MHz, DMSO-*d*₆ + DCl) δ 183.0, 182.4, 169.3, 167.9, 142.8, 130.9 (q, ²*J*_{CF} = 32.9 Hz, 2C), 129.0 (2C), 123.8 (q, ¹*J*_{CF} = 272.9 Hz, 2C), 121.6, 64.1, 52.4, 52.0, 51.3, 46.3, 34.4, 28.8, 28.7, 24.7, 24.3 (2C), 24.1, 24.0, 22.1, 21.9, 14.2, 14.0; HRMS (EI): Exact mass calculated for C₂₉H₃₉F₆N₃O₂ [*M*]⁺: 575.2946, found 575.2937.

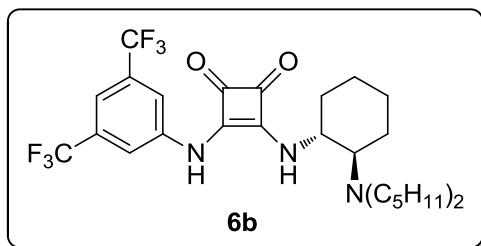
3-(((1*R*,2*R*)-2-(Dipentylamino)cyclohexyl)amino)-4-((4-(trifluoromethyl)phenyl)amino)cyclobut-3-ene-1,2-dione (6a).



Prepared according to the general procedure by reacting 3-methoxy-4-((4-(trifluoromethyl)phenyl)amino)-cyclobut-3-ene-1,2-dione (**13a**) (0.763 g, 2.81 mmol) with (1*R*,2*R*)-*N*¹,*N*¹-dipentylcyclohexane-1,2-diamine (**14**) (0.715 g, 2.81 mmol) to afford the title compound **6a**. Yield: 0.905 g (66%), colourless solid; M.p.: 200 – 201 °C, decomp.; TLC (hexanes/EtOAc 1:1): *R*_f = 0.10; $[\alpha]_D^{20} = -141.7$ (*c* = 0.13, CHCl₃); ¹H NMR (300 MHz, TFA) δ

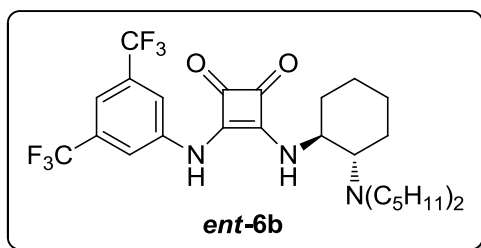
7.59 (d, $J = 8.2$ Hz, 2H), 7.36 (d, $J = 8.2$ Hz, 2H), 4.75 – 4.52 (m, 1H), 3.76 – 3.45 (m, 2H), 3.33 (td, $J = 12.6$, 4.3 Hz, 1H), 3.14 (td, $J = 12.3$, 5.2 Hz, 1H), 2.89 (td, $J = 12.2$, 4.6 Hz, 1H), 2.36 – 2.21 (m, 1H), 2.21 – 2.06 (m, 1H), 2.04 – 1.50 (m, 8H), 1.50 – 1.35 (m, 2H), 1.35 – 1.14 (m, 8H), 0.94 – 0.68 (m, 6H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 184.5, 179.6, 169.7, 162.0, 142.8, 126.6 (2C), 124.5 (q, $^1J_{\text{CF}} = 271.0$ Hz), 122.1 (q, $^2J_{\text{CF}} = 32.1$ Hz), 117.6 (2C), 64.1 (2C), 54.6, 49.2, 34.2, 29.2 (2C), 28.5 (2C), 24.9, 24.6, 23.6, 22.2 (2C), 14.0 (2C); HRMS (EI): Exact mass calculated for $\text{C}_{27}\text{H}_{38}\text{F}_3\text{N}_3\text{O}_2$ [M] $^+$: 493.2916, found 493.2921.

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*R*,2*R*)-2-(dipentylamino)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (6b**).**



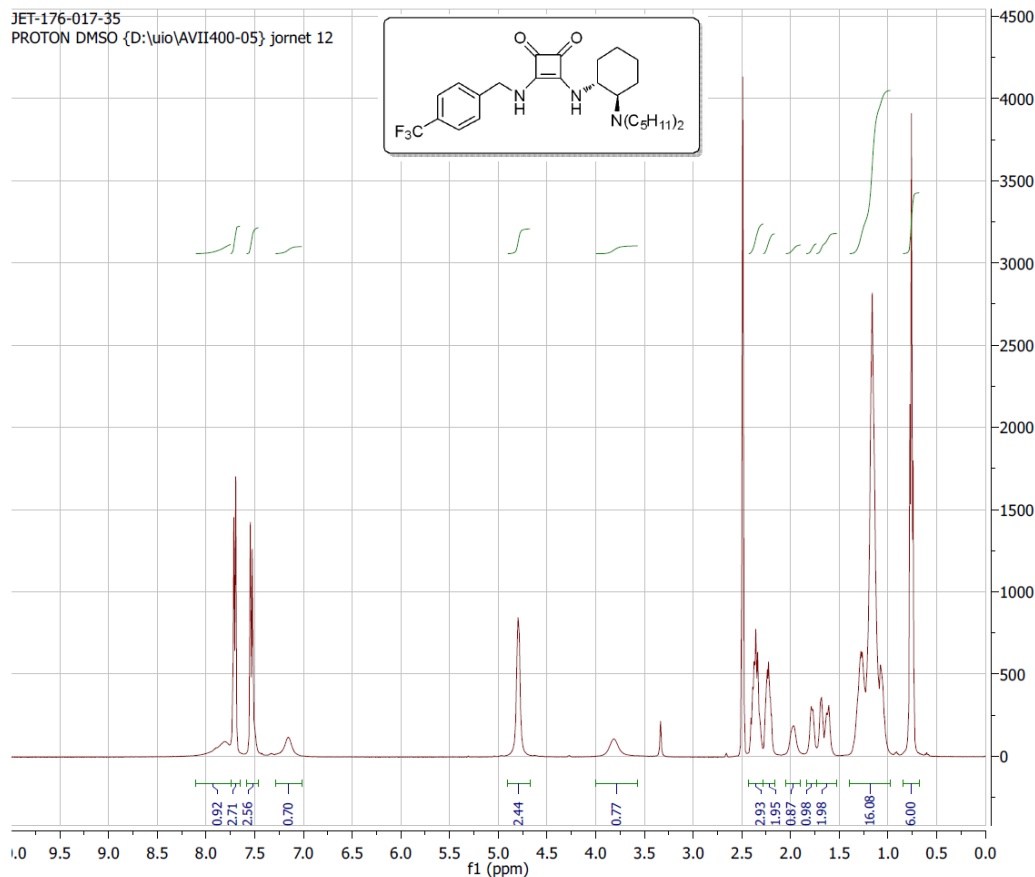
Prepared according to the general procedure by reacting 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**13b**) (1.000 g, 2.94 mmol) with (1*R*,2*R*)- N^1,N^1 -dipentylcyclohexane-1,2-diamine (**14**) (0.748 g, 2.94 mmol) to afford the title compound **6b**. Yield: 1.050 g (64%), colourless solid; M.p.: 195 – 196 °C, decomp.; TLC (hexanes/EtOAc 1:1): $R_f = 0.12$; $[\alpha]_D^{20} = -107.6$ ($c = 0.10$, CHCl_3); ^1H NMR (300 MHz, TFA) δ 7.87 (s, 2H), 7.79 (s, 1H), 4.74 (td, $J = 11.2$, 4.2 Hz, 1H), 3.89 – 3.54 (m, 2H), 3.44 (td, $J = 12.5$, 6.3 Hz, 1H), 3.25 (td, $J = 12.4$, 5.2 Hz, 1H), 2.99 (td, $J = 12.2$, 4.5 Hz, 1H), 2.47 – 2.32 (m, 1H), 2.32 – 2.17 (m, 1H), 2.16 – 1.46 (m, 10H), 1.46 – 1.26 (m, 8H), 1.02 – 0.81 (m, 6H); ^{13}C NMR (101 MHz, DMSO- d_6) δ 184.5, 179.7, 170.0, 161.4, 141.3, 131.4 (q, $^2J_{\text{CF}} = 32.9$, 31.6 Hz, 2C), 123.1 (q, $^1J_{\text{CF}} = 273.0$ Hz, 2C), 117.5 (2C), 114.3, 64.2 (2C), 54.7, 49.2, 34.1, 29.2 (2C), 28.5 (2C), 24.8, 24.6, 23.7, 22.2 (2C), 13.9 (2C); HRMS (EI): Exact mass calculated for $\text{C}_{28}\text{H}_{37}\text{F}_6\text{N}_3\text{O}_2$ [M] $^+$: 561.2790, found 561.2799.

3-((3,5-Bis(trifluoromethyl)phenyl)amino)-4-(((1*S*,2*S*)-2-(dipentylamino)cyclohexyl)amino)cyclobut-3-ene-1,2-dione (*ent*-6b**).**



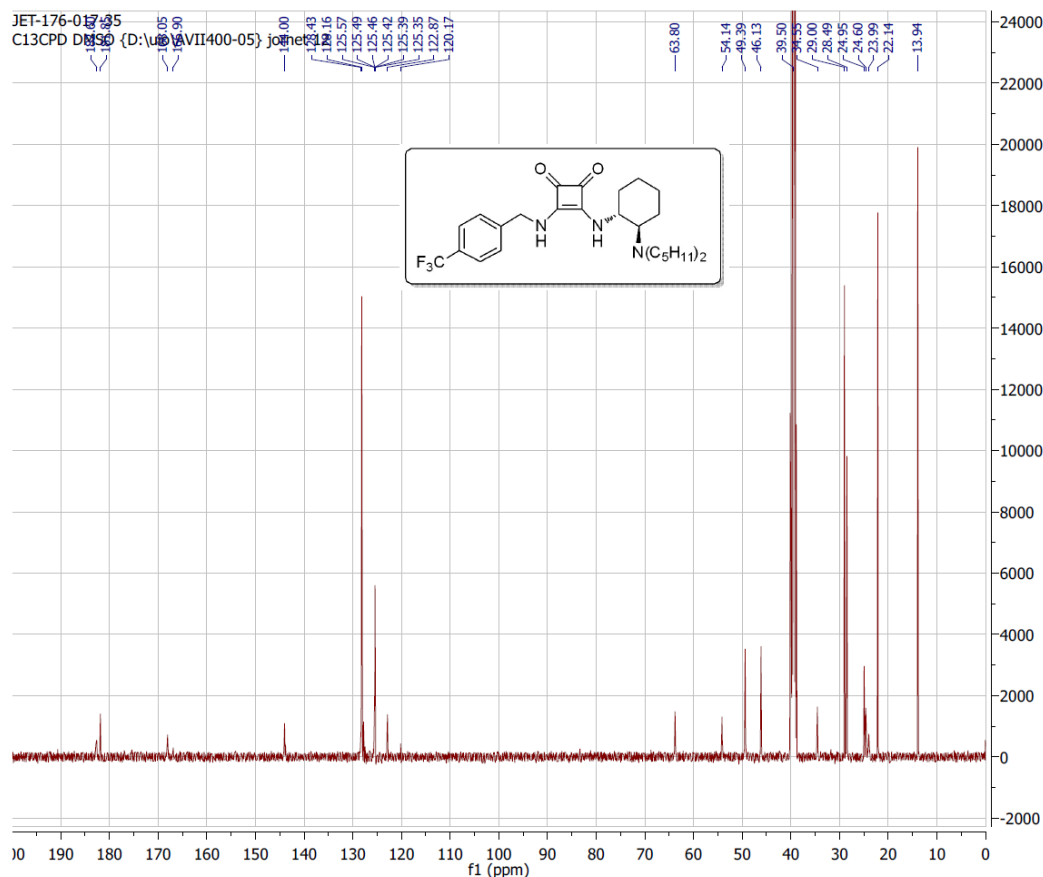
Prepared according to the general procedure by reacting 3-((3,5-bis(trifluoromethyl)phenyl)amino)-4-methoxycyclobut-3-ene-1,2-dione (**13b**) (0.240 g, 0.71 mmol) with (1*S*,2*S*)- N^1,N^1 -dipentylcyclohexane-1,2-diamine (*ent*-**14**) (0.180 g, 0.71 mmol) to afford the title compound *ent*-**6b**. Yield: 0.164 g (41%), colourless solid; TLC (hexanes/EtOAc 1:1): $R_f = 0.12$; $[\alpha]_D^{20} = 110.6$ ($c = 0.11$, CHCl_3).

JET-176-017-35
PROTON DMSO {D:\uio\AVII400-05} jorinet 12



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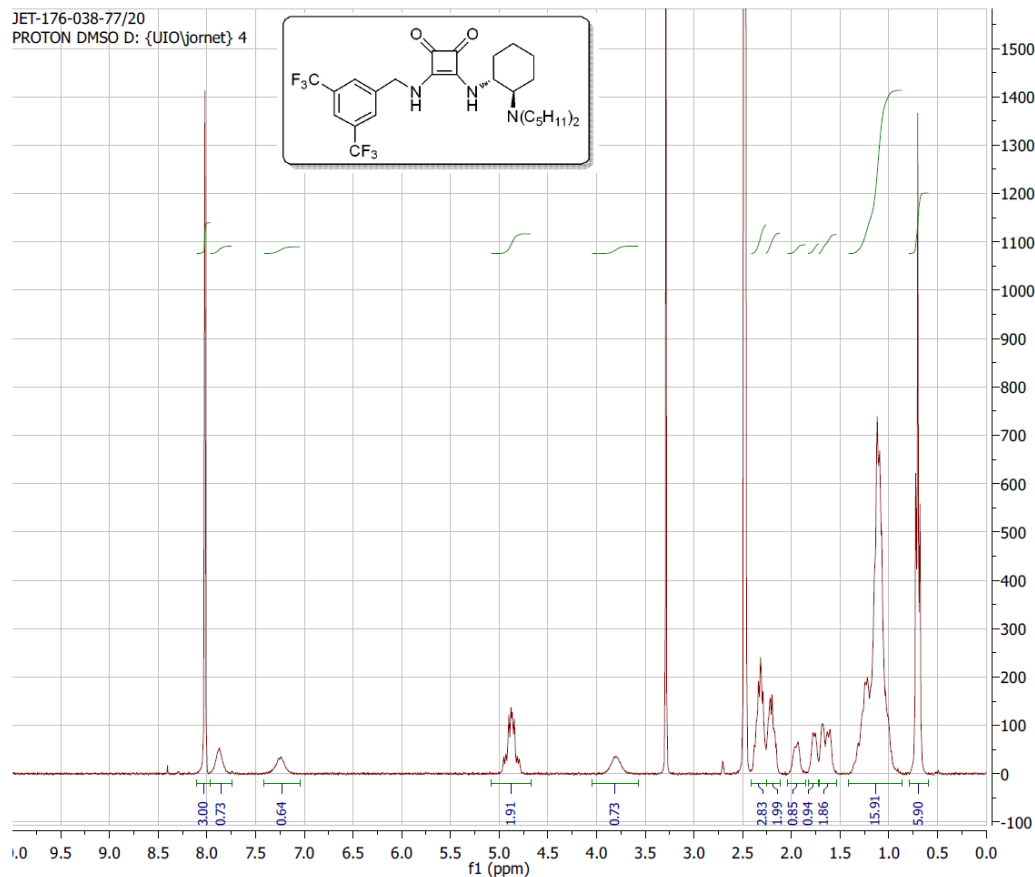
Figure S-1 ¹H-NMR spectrum of compound 5a.



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9 Solvent	DMSO
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20 Spectrometer Frequency	100.64
21 Spectral Width	25252.5
22 Lowest Frequency	-1102.0
23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	65536

Figure S-2 ¹³C-NMR spectrum of compound 5a.

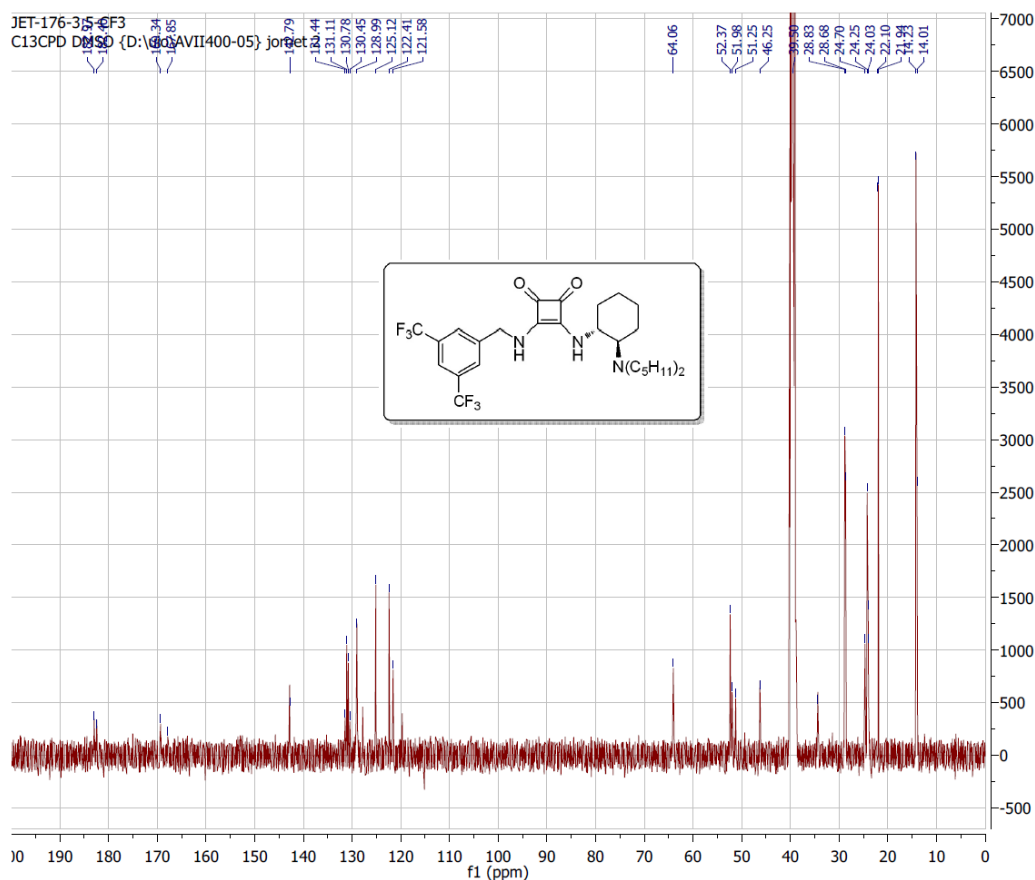
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4 Origin	Bruker BioSpin GmbH
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8 Author	
9 Solvent	DMSO
10 Temperature	298.2
11 Pulse Sequence	zg30
12 Experiment	1D
13 Number of Scans	64
14 Receiver Gain	1149
15 Relaxation Delay	1.0000
16 Pulse Width	10.0000
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18 Acquisition Date	2012-01-10T18:53:29
19 Modification Date	2012-01-10T17:53:34
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24 Acquired Size	32768
25 Spectral Size	65536

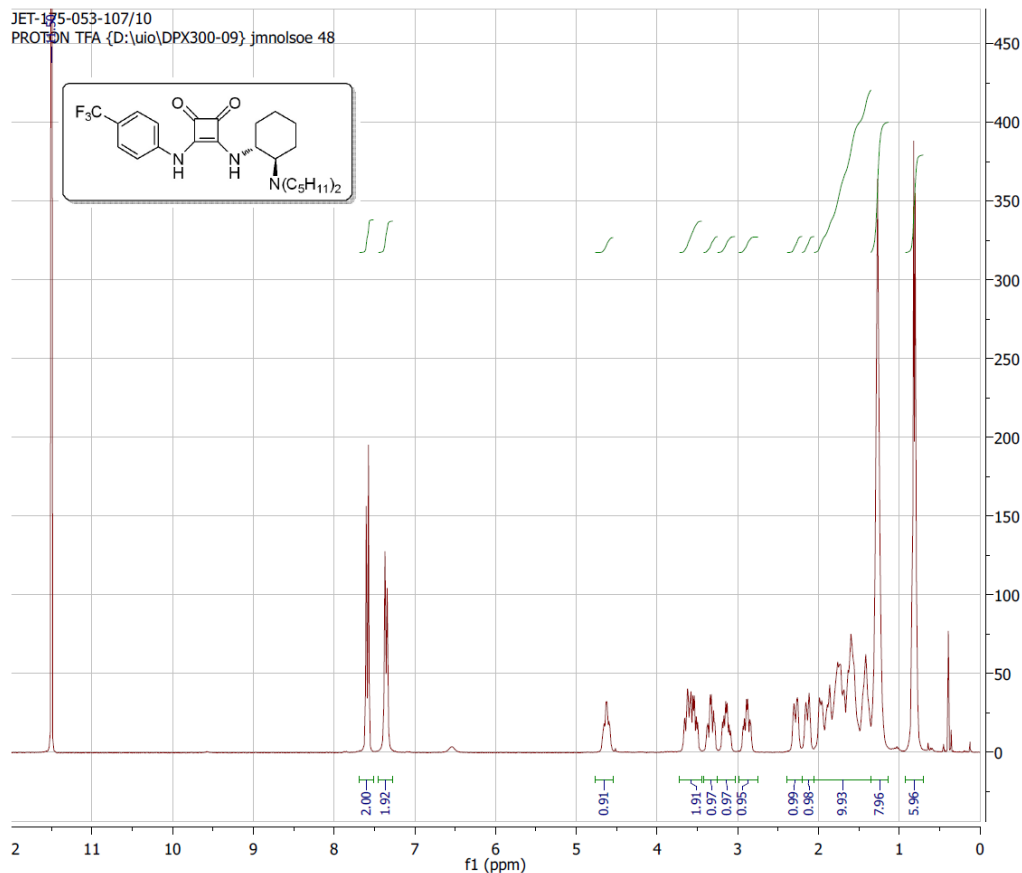
Figure S-3 ¹H-NMR spectrum of compound 5b.

JET-176-315-CF3
 C13CPD DMSO {D:\G05\AVII400-05} joriet

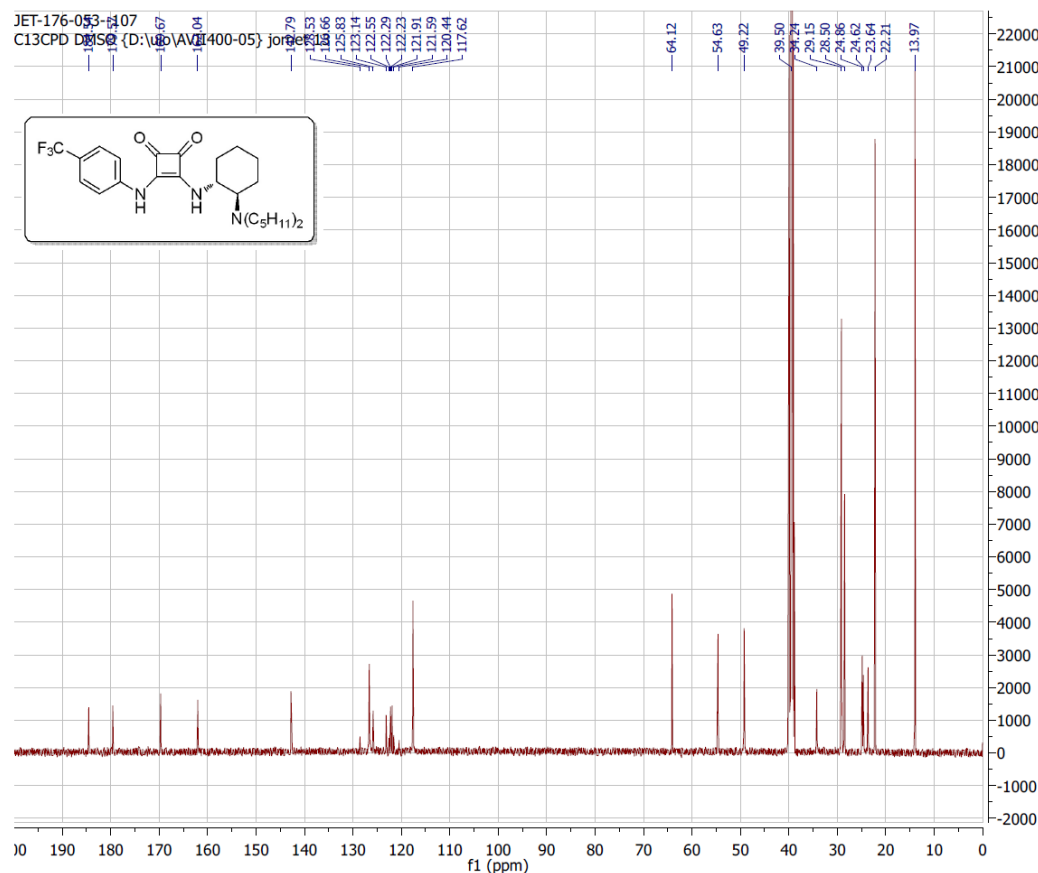


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6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	DMSO
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11 Pulse Sequence	zgpg30
12 Experiment	1D
13 Number of Scans	1024
14 Receiver Gain	2050
15 Relaxation Delay	5.0000
16 Pulse Width	7.0000
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18 Acquisition Date	2012-11-05T09:59:00
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20 Spectrometer Frequency	100.64
21 Spectral Width	25252.5
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23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	65536

Figure S-4 ¹³C-NMR spectrum of compound 5b.

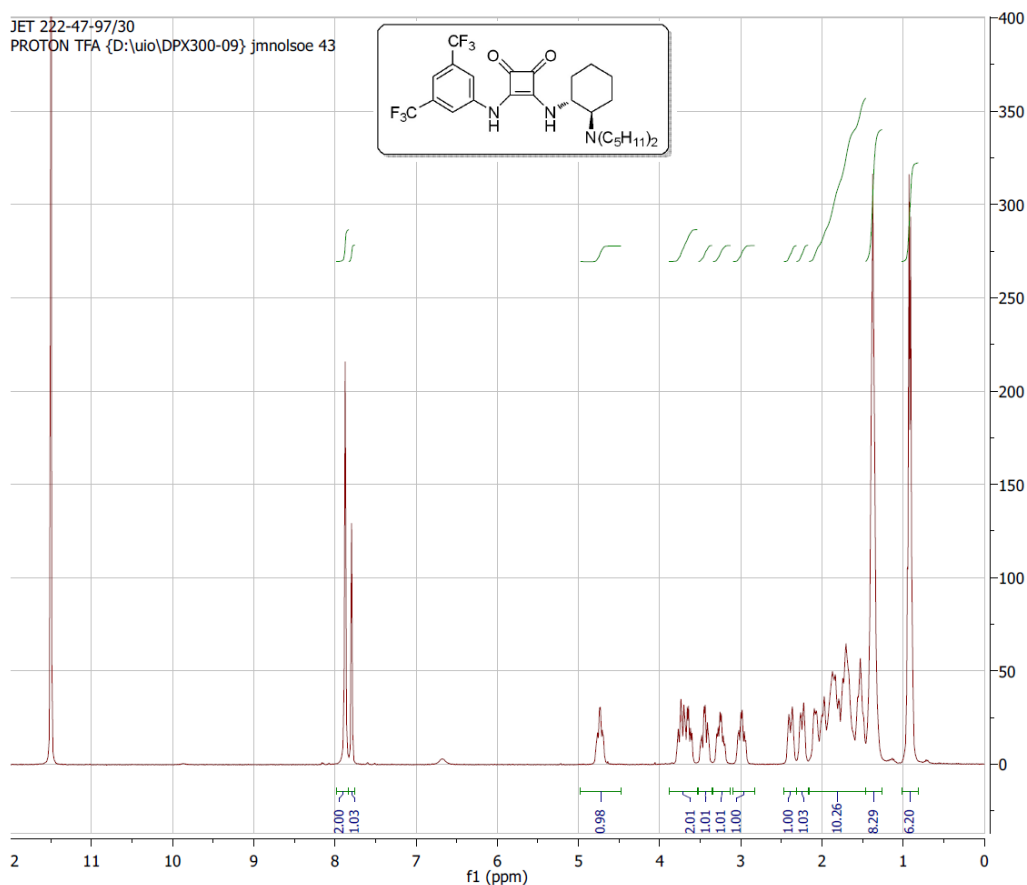


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6 Site	
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8 Author	
9 Solvent	TFA
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11 Pulse Sequence	zg30
12 Experiment	1D
13 Number of Scans	16
14 Receiver Gain	161
15 Relaxation Delay	1.0000
16 Pulse Width	10.0000
17 Acquisition Time	5.3084
18 Acquisition Date	2012-09-18T16:39:52
19 Modification Date	2012-09-18T16:39:57
20 Spectrometer Frequency	300.13
21 Spectral Width	6172.8
22 Lowest Frequency	-1277.1
23 Nucleus	^1H
24 Acquired Size	32768
25 Spectral Size	65536



Parameter	Value
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6 Site	
7 Spectrometer	spect
8 Author	
9 Solvent	DMSO
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11 Pulse Sequence	zgpg30
12 Experiment	1D
13 Number of Scans	2048
14 Receiver Gain	1150
15 Relaxation Delay	2.0000
16 Pulse Width	7.0000
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23 Nucleus	^{13}C
24 Acquired Size	32768
25 Spectral Size	65536

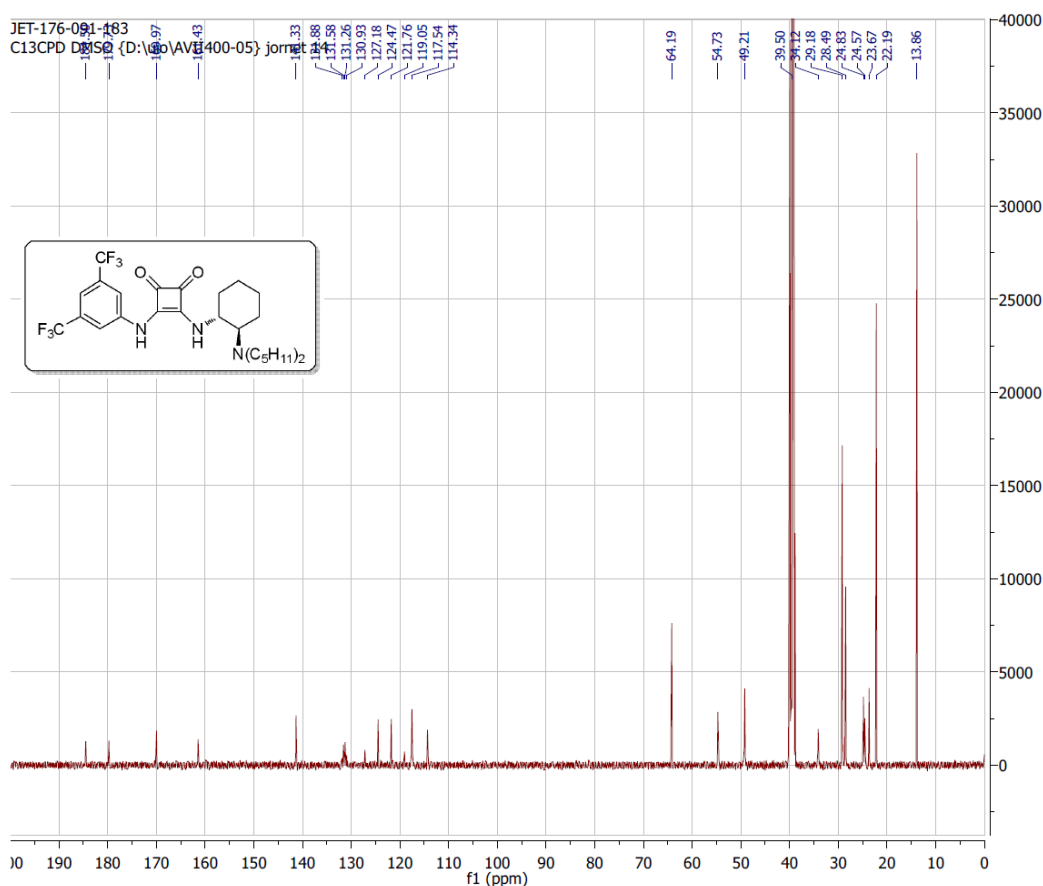
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5 Owner	tnnr
6 Site	
7 Spectrometer	DPX300
8 Author	
9 Solvent	TFA
10 Temperature	298.2
11 Pulse Sequence	zg30
12 Experiment	1D
13 Number of Scans	16
14 Receiver Gain	203
15 Relaxation Delay	1.0000
16 Pulse Width	10.0000
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18 Acquisition Date	2012-09-05T18:17:27
19 Modification Date	2012-09-05T18:17:34
20 Spectrometer Frequency	300.13
21 Spectral Width	6172.8
22 Lowest Frequency	-1275.9
23 Nucleus	1H
24 Acquired Size	32768
25 Spectral Size	65536

Figure S-7 ¹H-NMR spectrum of compound 6b.

JET-176-091-183
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9 Solvent	DMSO
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13 Number of Scans	2048
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21 Spectral Width	25252.5
22 Lowest Frequency	-1101.2
23 Nucleus	13C
24 Acquired Size	32768
25 Spectral Size	65536

Figure S-8 ¹³C-NMR spectrum of compound 6b.

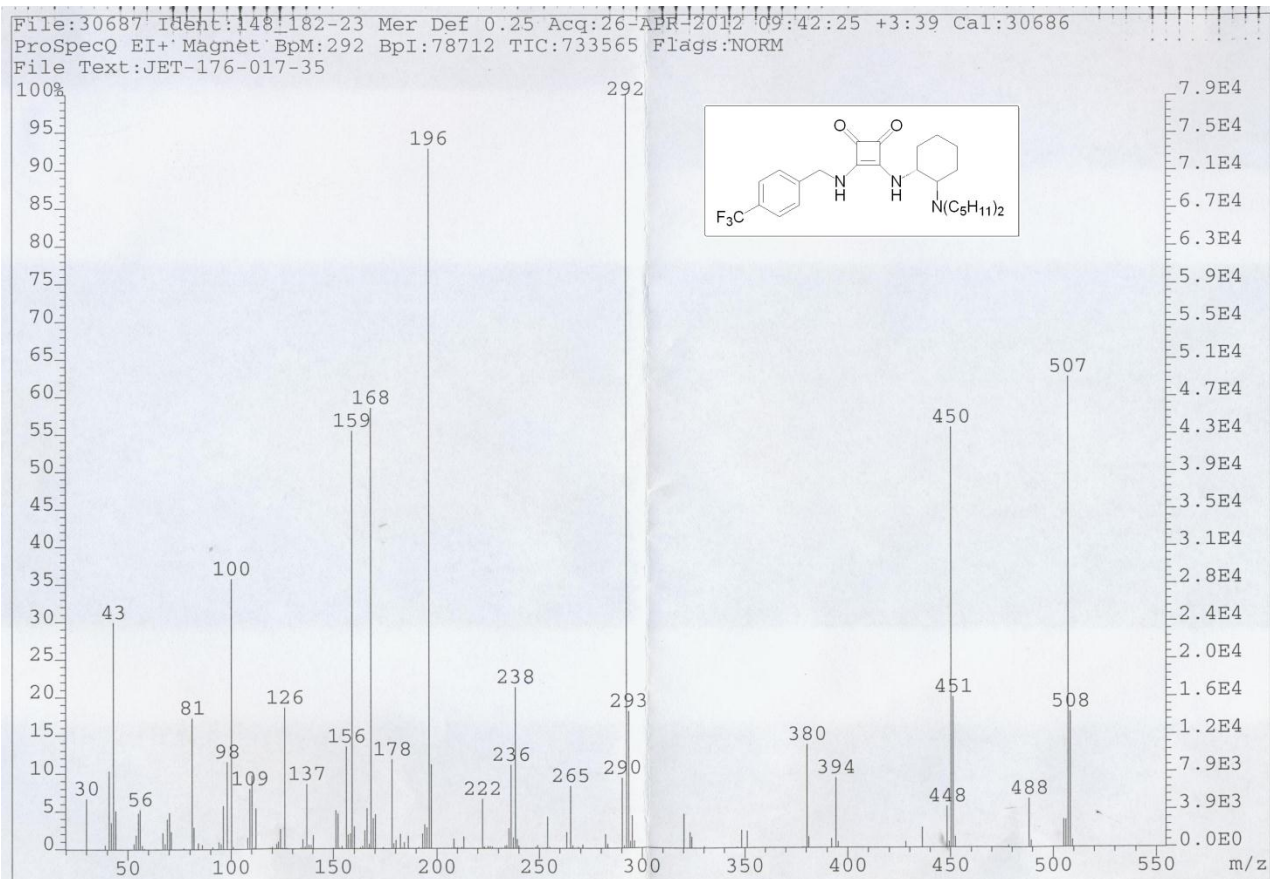


Figure S-9 MS spectrum of compound 5a.

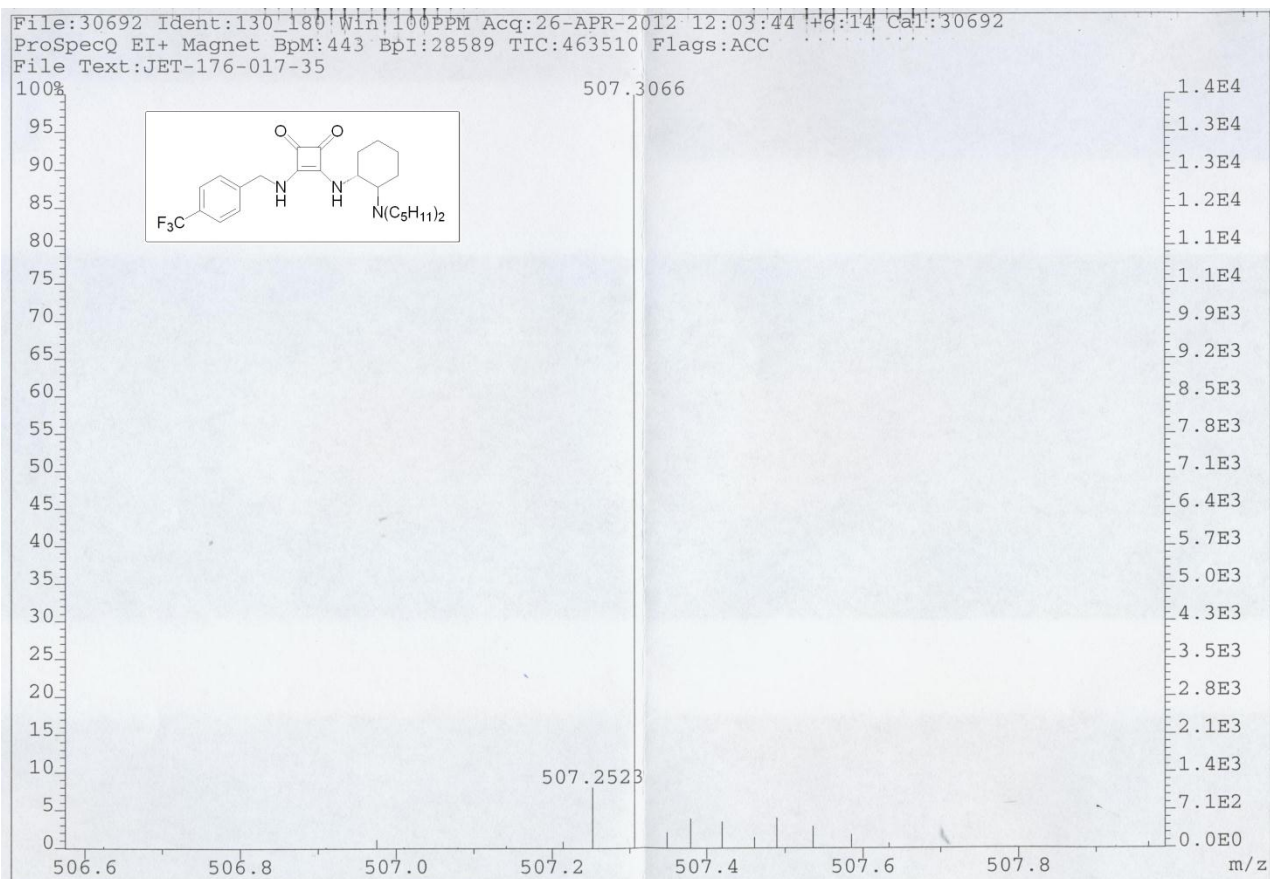


Figure S-10 HRMS spectrum of compound 5a.

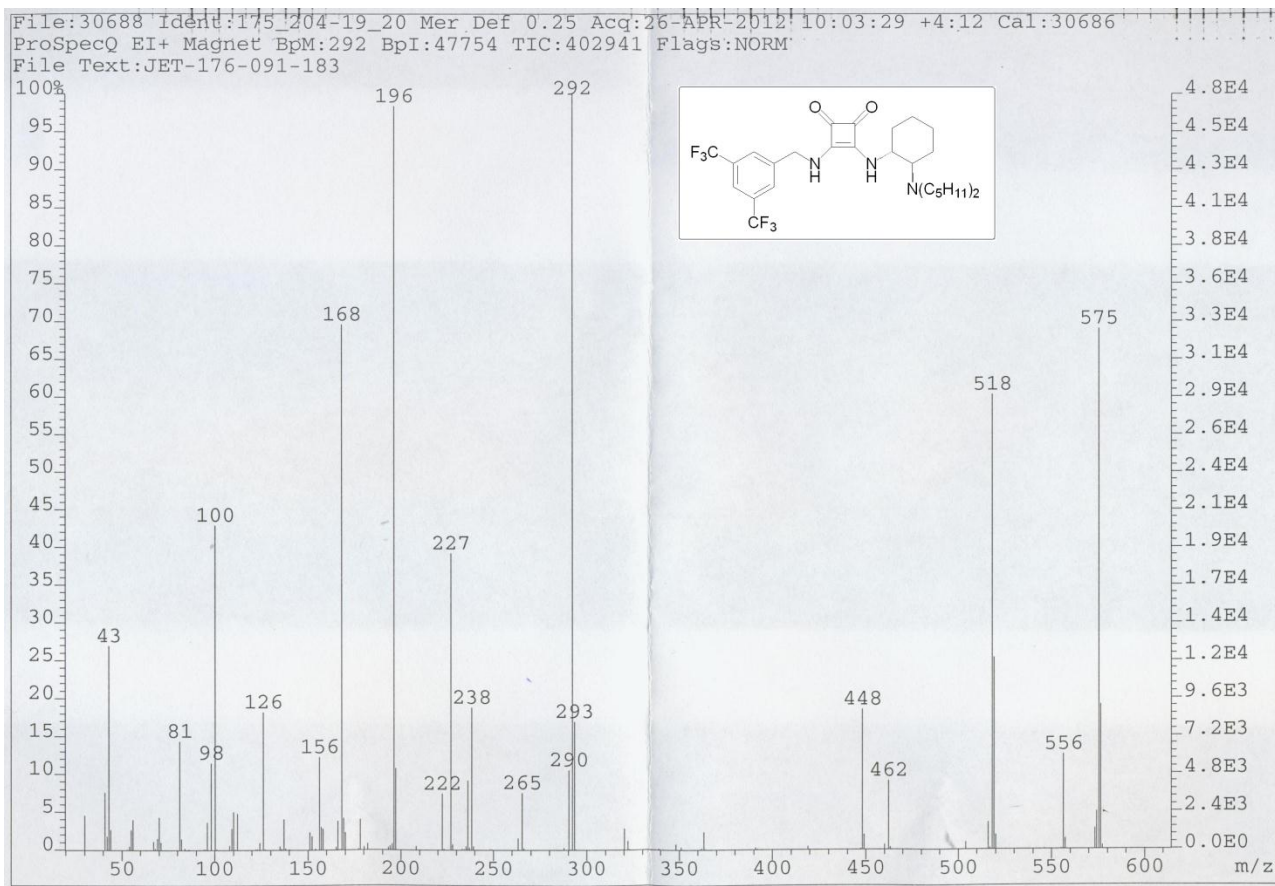


Figure S-11 MS spectrum of compound 5b.

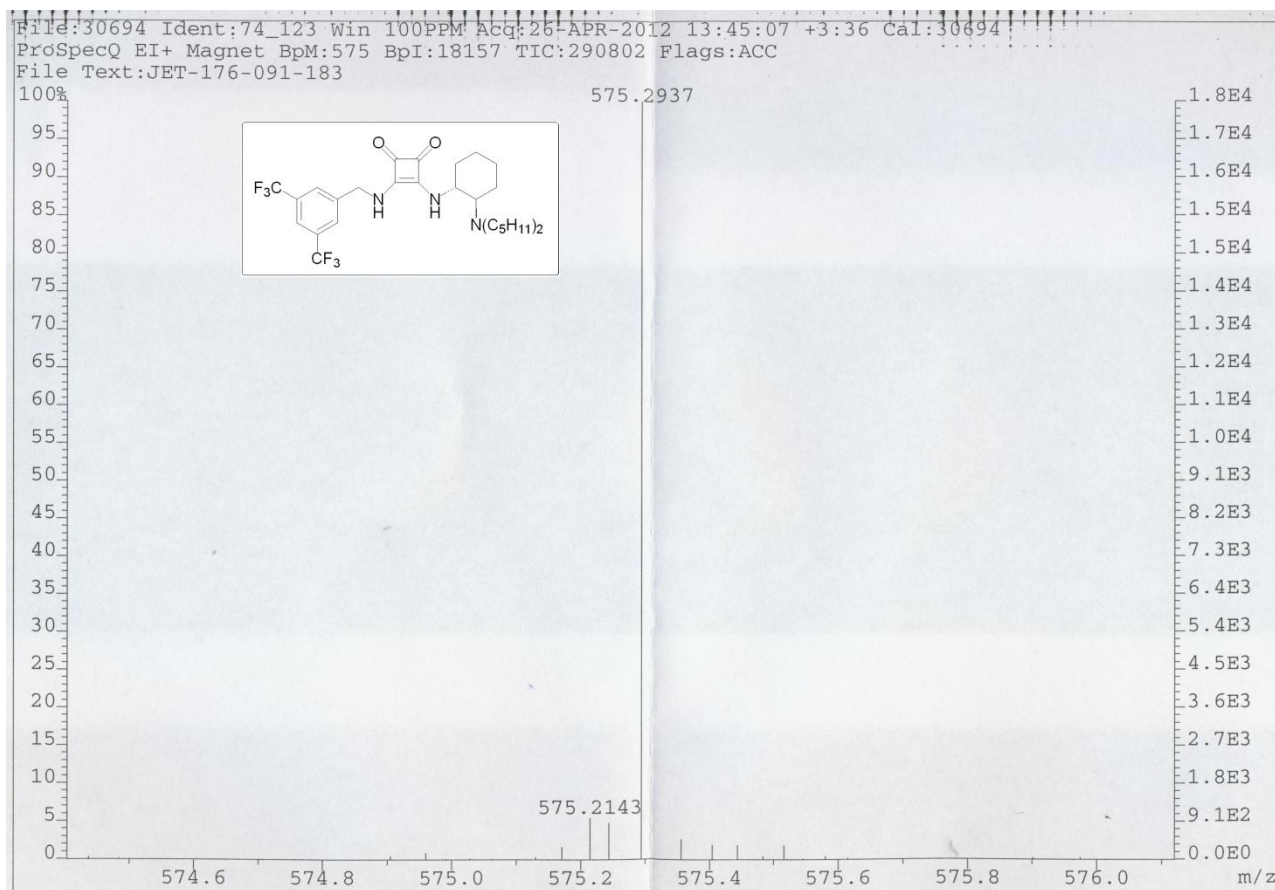


Figure S-12 HRMS spectrum of compound 5b.

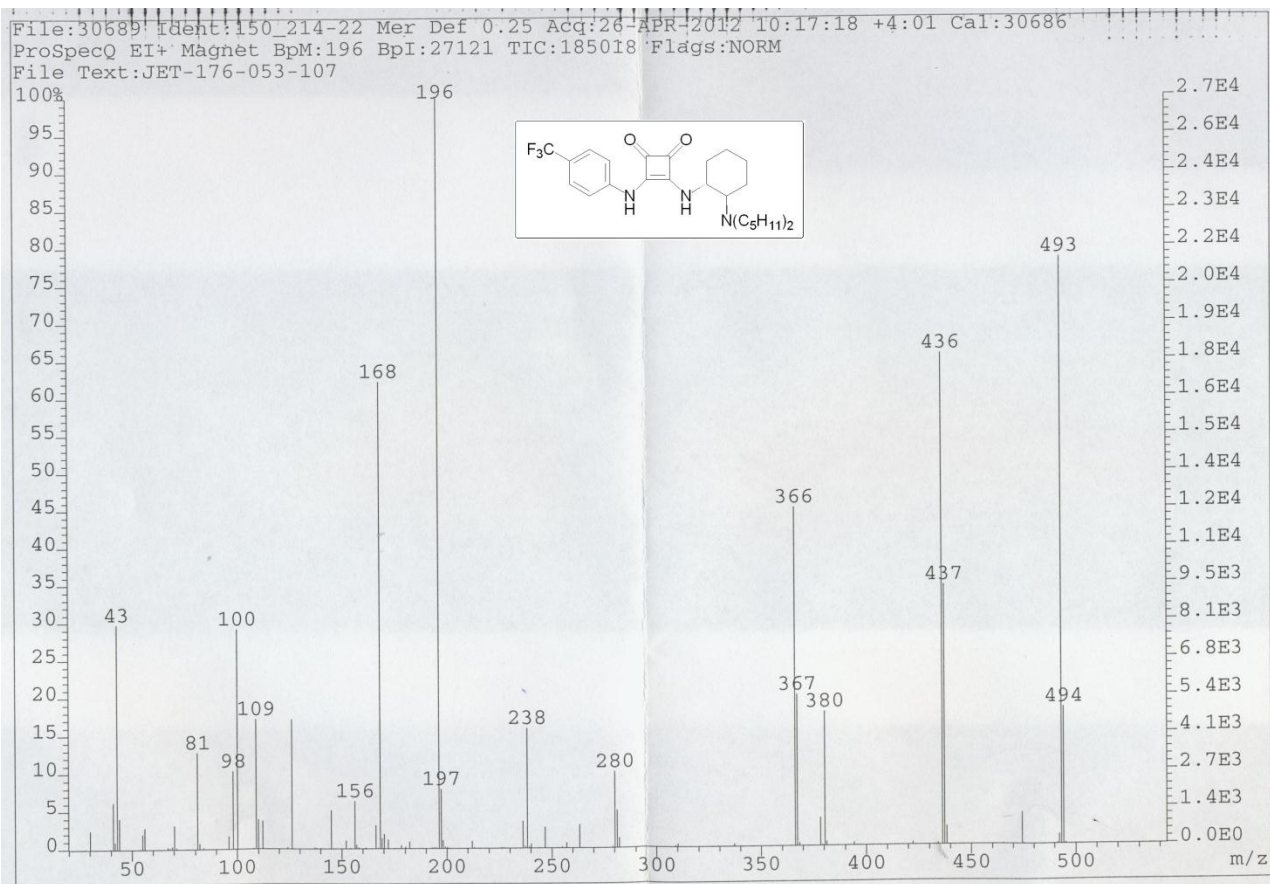


Figure S-13 MS spectrum of compound 6a.

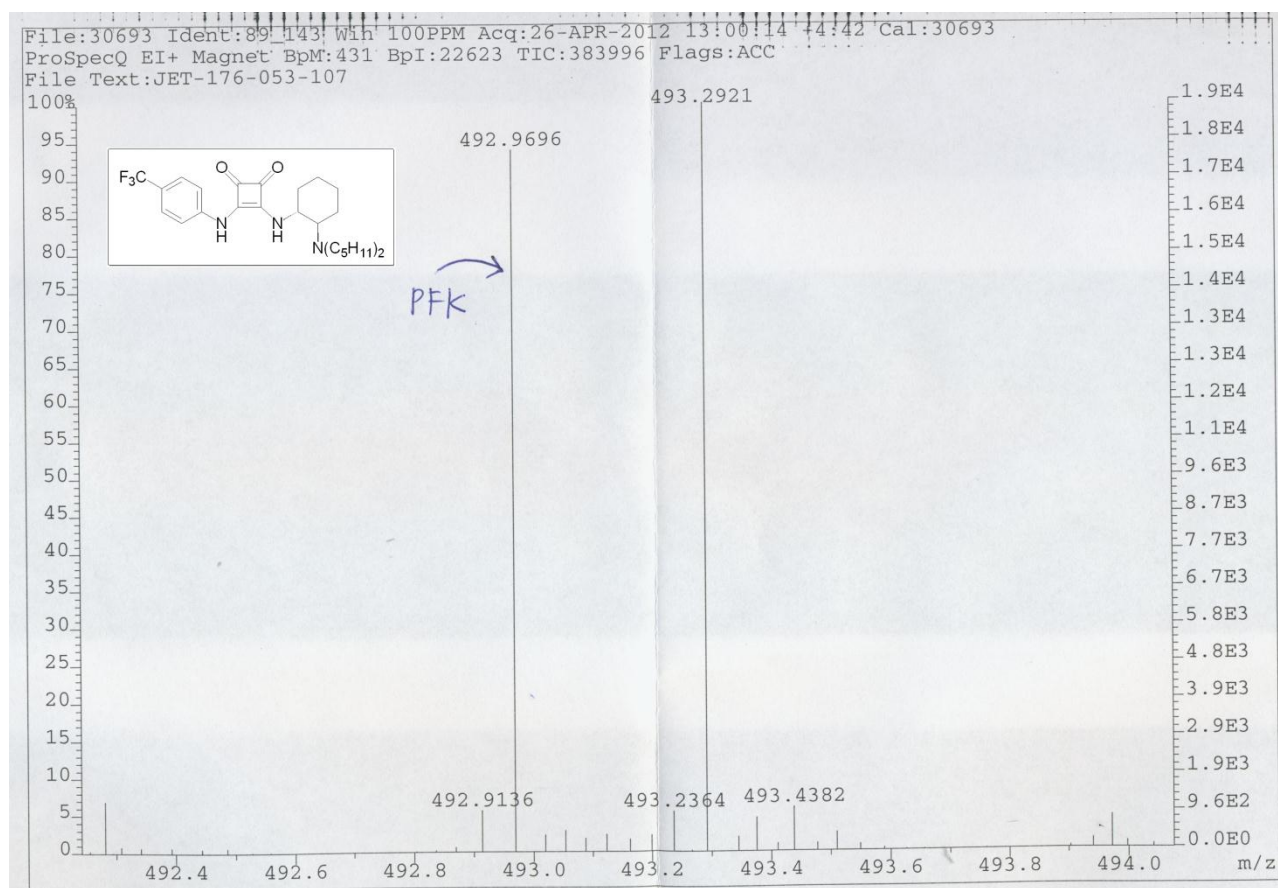


Figure S-14 HRMS spectrum of compound 6a.

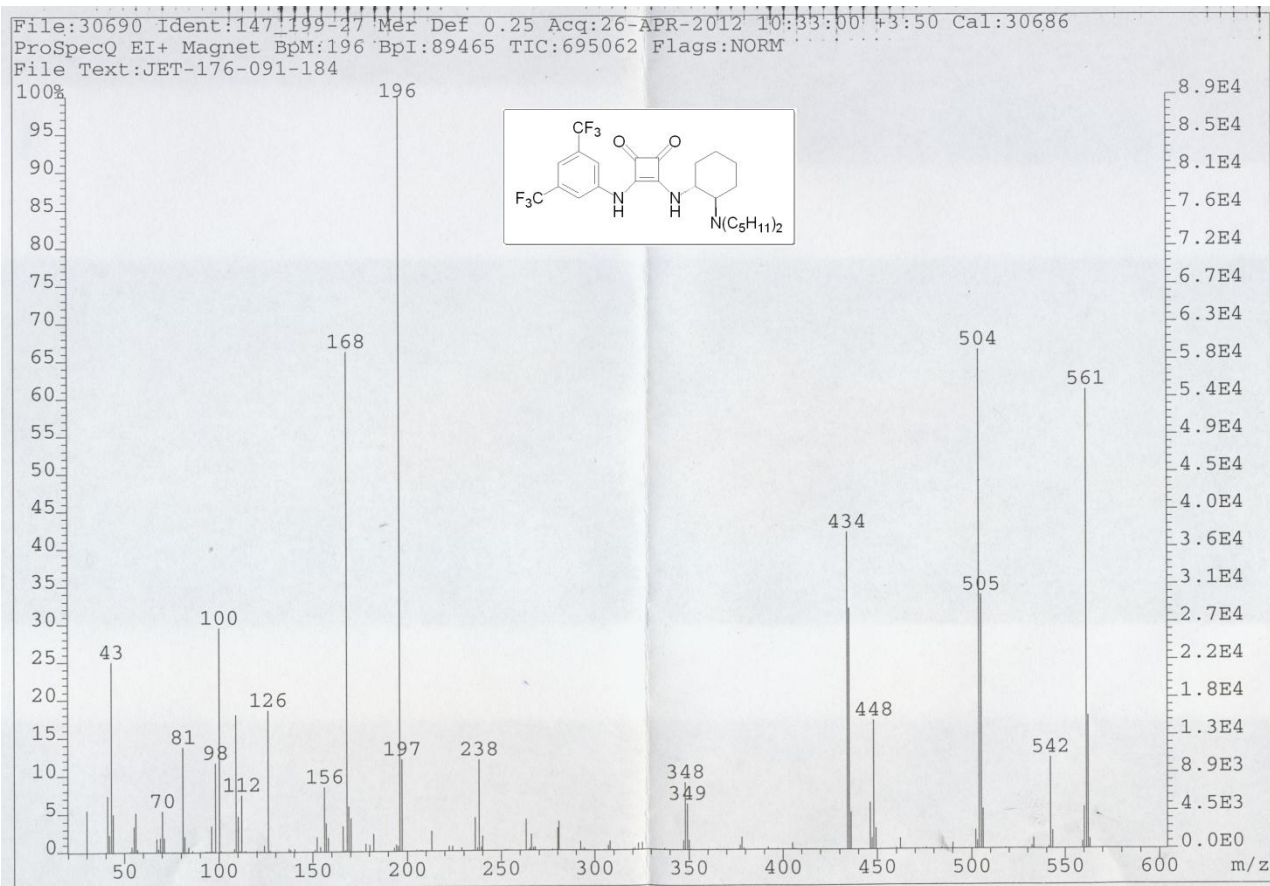


Figure S-15 MS spectrum of compound 6b.

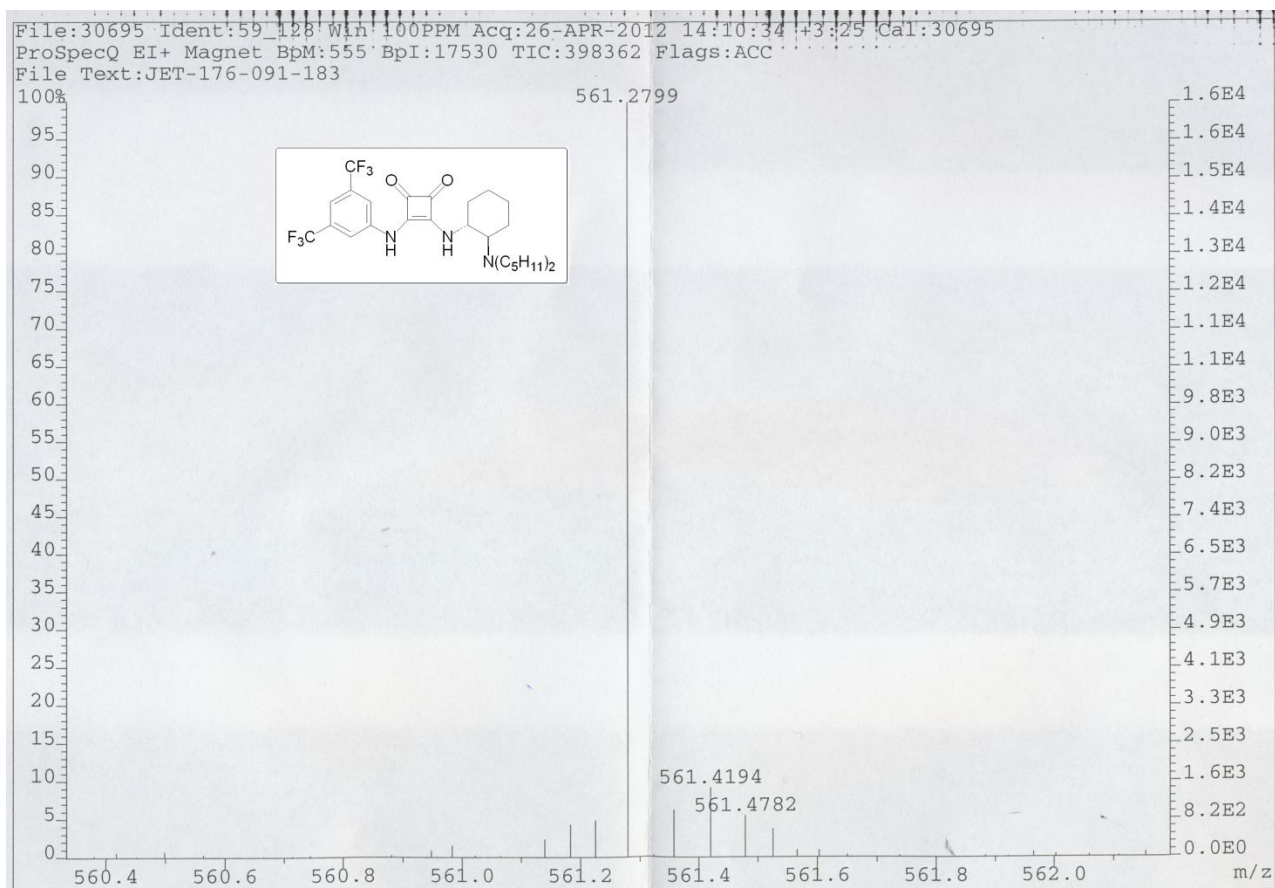


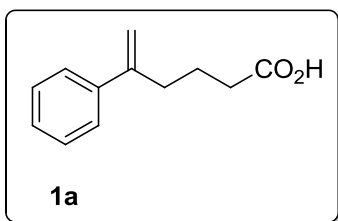
Figure S-16 HRMS spectrum of compound 6b.

Preparation of Starting Materials

General procedure for the preparation of γ - and δ -unsaturated acids: **Step 1.** 4-Aryl-4-oxobutanoic acid (1.0 equiv.) or 5-aryl-5-oxopentanoic acid (1.0 equiv.) was suspended in MeOH (0.25 M), the suspension was cooled to 0 °C and acetyl chloride (1.2 equiv.) was added. Cooling was discontinued and the resulting homogeneous mixture was stirred overnight at ambient temperature. The mixture was diluted with CH₂Cl₂ and washed in succession with satd. aq. NaHCO₃, brine and water. The organic phase was dried over MgSO₄, filtered and the solvent was evaporated *in vacuo* to afford the corresponding 4-aryl-4-oxobutanoic acid methyl ester or 5-aryl-5-oxopentanoic acid methyl ester. **Step 2.** Triphenylphosphonium bromide (1.3 equiv.) was suspended in THF (0.75 M) and cooled to 0 °C, whereupon KHMDs (0.5 M in toluene, 1.3 equiv.) was added in one go. The resulting mixture was stirred for 1 hour then cooled to -78 °C and a solution of the 4-aryl-4-oxobutanoic acid methyl ester or 5-aryl-5-oxopentanoic acid methyl ester (1.0 equiv.) in THF (~0.25 M) was added in a dropwise manner. Cooling was discontinued and the resulting mixture was stirred at ambient temperature until TLC indicated full conversion of the starting material. The mixture was treated with satd. aq. NH₄Cl and extracted with EtOAc. The combined organic extracts were dried over MgSO₄, filtered and the solvent was evaporated *in vacuo*. The residue was purified by flash chromatography on silica (hexanes, followed by hexanes/EtOAc in various proportions) to afford the corresponding 4-aryl-4-oxobutanoic acid methyl ester or 5-arylhex-5-enoic acid methyl ester. **Step 3.** 4-Arylpent-4-enoic methyl ester or 5-arylhex-5-enoic acid methyl ester (1.0 equiv.) was dissolved in THF and water was added (8:1 THF/water, ~0.10 M), followed by LiOH·H₂O (1.5 equiv.). The resulting biphasic mixture was stirred vigorously overnight at ambient temperature, whereupon the solvent was evaporated *in vacuo*. The residue was dissolved in 1 M aq. NaOH and washed with CH₂Cl₂. The pH was adjusted to approx. 2 and the aq. phase was extracted twice with CH₂Cl₂. The combined organic extracts were dried over MgSO₄, filtered and evaporated *in vacuo* to afford the corresponding 4-arylpent-4-enoic acid or 5-arylhex-5-enoic acid, respectively.

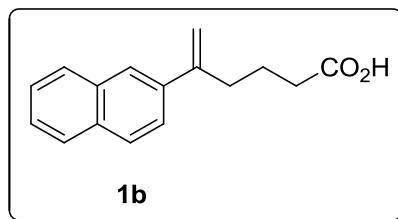
Alternatively, some of the γ - and δ -unsaturated acids were prepared directly from the corresponding 4-aryl-4-oxobutanoic acids or 5-aryl-5-oxopentanoic acids according to the procedure of Takemiya *et al.*⁵

5-Phenylhex-5-enoic acid (**1a**).⁴



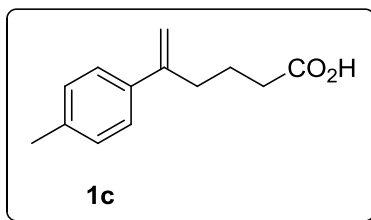
Prepared from commercially available 5-oxo-5-phenylpentanoic acid (**15a**) by a Wittig reaction according to the procedure of Takemiya *et al.*⁵ All physical data were in full agreement with those reported in the literature. ¹H NMR (400 MHz, CDCl₃) δ 11.82 (s, 1H), 7.15 – 7.63 (m, 5H), 5.34 (s, 1H), 5.11 (s, 1H), 2.61 (t, J = 7.5 Hz, 2H), 2.41 (t, J = 7.4 Hz, 2H), 1.83 (p, J = 7.4 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 180.2, 147.3, 140.7, 128.3 (2C), 127.5, 126.1 (2C), 113.1, 34.4, 33.3, 23.0.

5-(Naphthalen-2-yl)hex-5-enoic acid (**1b**).⁴



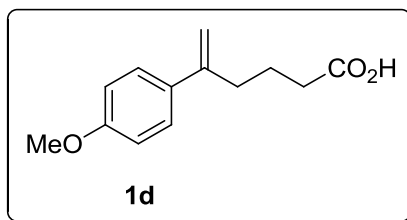
Prepared according to the general procedure using 5-(naphthalen-2-yl)-5-oxopentanoic acid (**15b**). All physical data were in full agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃) δ 11.23 (bs, 1H), 7.77–7.96 (m, 4H), 7.61 (dd, J = 8.6, 1.8 Hz, 1H), 7.42 – 7.56 (m, 2H), 5.51 (d, J = 1.3 Hz, 1H), 5.23 (d, J = 1.5 Hz, 1H), 2.73 (t, J = 7.5 Hz, 2H), 2.45 (t, J = 7.4 Hz, 2H), 1.89 (p, J = 7.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 180.1, 147.1, 137.9, 133.4, 132.8, 128.1, 127.9, 127.5, 126.1, 125.8, 124.7, 124.5, 113.6, 34.4, 33.3, 23.1.

5-(*p*-Tolyl)hex-5-enoic acid (**1c**).⁴



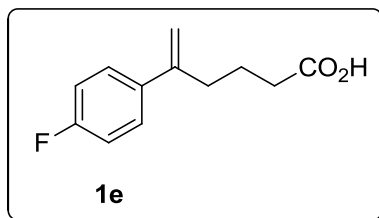
Prepared according to the general procedure using 5-oxo-5-(*p*-tolyl)pentanoic acid (**15c**). All physical data were in full agreement with those reported in the literature. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.34 (d, *J* = 8.0 Hz, 2H), 7.15 (d, *J* = 7.9 Hz, 2H), 5.29 (d, *J* = 2.0 Hz, 1H), 5.01 (d, *J* = 1.9 Hz, 1H), 2.48 (t, *J* = 7.4 Hz, 2H), 2.29 (s, 3H), 2.22 (t, *J* = 7.4 Hz, 2H), 1.60 (p, *J* = 7.4 Hz, 2H). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 174.3, 147.0, 137.2, 136.8, 129.0 (2C), 125.7 (2C), 111.8, 33.8, 33.0, 23.2, 20.7.

5-(4-Methoxyphenyl)hex-5-enoic acid (**1d**).⁴



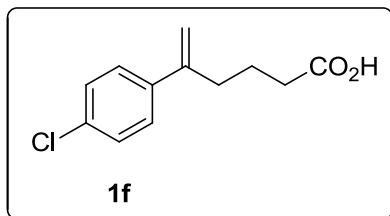
Prepared according to the general procedure using 5-(4-methoxyphenyl)-5-oxopentanoic acid (**15d**). All physical data were in full agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃) δ 7.31 – 7.41 (m, 2H), 6.84 – 6.91 (m, 2H), 5.25 (d, *J* = 1.4 Hz, 1H), 5.01 (d, *J* = 1.4 Hz, 1H), 3.82 (s, 3H), 2.56 (t, *J* = 7.4 Hz, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.81 (p, *J* = 7.5 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃) δ 179.5, 159.1, 146.5, 133.1, 127.2 (2C), 113.7 (2C), 111.5, 55.3, 34.5, 33.2, 23.1.

5-(4-Fluorophenyl)hex-5-enoic acid (**1e**).⁴



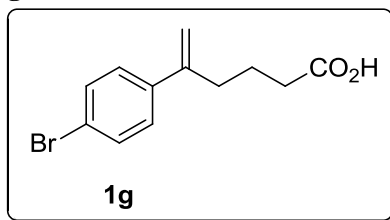
Prepared according to the general procedure using 5-(4-fluorophenyl)-5-oxopentanoic acid (**15e**). All physical data were in full agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃) δ 11.35 (bs, 1H), 7.32 – 7.45 (m, 2H), 6.97 – 7.08 (m, 2H), 5.24 – 5.30 (m, 1H), 5.04 – 5.11 (m, 1H), 2.56 (t, *J* = 7.5 Hz, 1H), 2.39 (t, *J* = 7.5 Hz, 1H), 1.80 (p, *J* = 7.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 180.0, 162.3 (d, ¹*J*_{CF} = 246 Hz), 146.3, 136.7 (d, ⁴*J*_{CF} = 3.3 Hz), 127.7 (d, ³*J*_{CF} = 7.9 Hz, 2C), 115.2 (d, ²*J*_{CF} = 21.3 Hz, 2C), 113.0, 34.5, 33.2, 22.9.

5-(4-Chlorophenyl)hex-5-enoic acid (**1f**).⁴



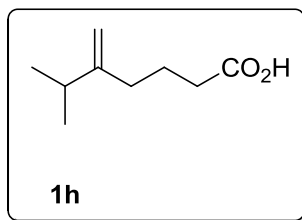
Prepared from 5-(4-chlorophenyl)-5-oxopentanoic acid (**15f**) by a Wittig reaction according to the procedure of Takemiya *et al.*⁵ All physical data were in full agreement with those reported in the literature. ¹H NMR (400 MHz, CDCl₃) δ 9.76 (bs, 1H), 7.28 – 7.38 (m, 4H), 5.31 (d, *J* = 1.3 Hz, 1H), 5.11 (d, *J* = 2.0 Hz, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 1.79 (p, *J* = 7.4 Hz, 2H); ¹³C NMR (101 MHz, CDCl₃) δ 179.6, 146.2, 139.1, 133.3, 128.5 (2C), 127.4 (2C), 113.6, 34.3, 33.2, 22.9.

5-(4-Bromophenyl)hex-5-enoic acid (**1g**).⁴



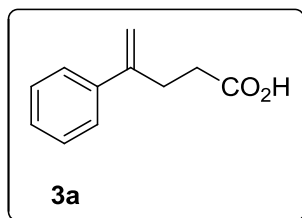
Prepared according to the general procedure using 5-(4-bromophenyl)-5-oxopentanoic acid (**15g**). All physical data were in full agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃) δ 11.44 (bs, 1H), 7.42–7.52 (m, 2H), 7.24–7.33 (m, 2H), 5.33 (s, 1H), 5.12 (s, 1H), 2.56 (t, *J* = 7.5 Hz, 2H), 2.40 (t, *J* = 7.4 Hz, 2H), 1.80 (p, *J* = 7.4 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 180.0, 146.2, 139.5, 131.4 (2C), 127.7 (2C), 121.4, 113.6, 34.2, 33.2, 22.9.

6-Methyl-5-methyleneheptanoic acid (**1h**).^{4,5}



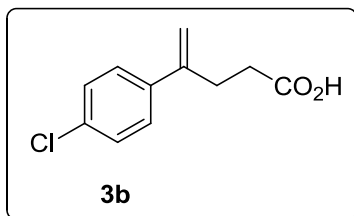
Prepared from commercially available 6-methyl-5-methyleneheptanoic acid (**15h**) by a Wittig reaction according to the procedure of Takemiya *et al.*⁵ All physical data were in full agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃) δ 11.09 (bs, 1H), 4.76–4.83 (m, 1H), 4.67–4.74 (m, 1H), 2.38 (t, *J* = 7.5 Hz, 2H), 2.24 (hept, *J* = 7.0 Hz, 1H), 2.09 (t, *J* = 7.5 Hz, 2H), 1.80 (p, *J* = 7.5 Hz, 2H), 1.03 (d, *J* = 7.0 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 180.3, 154.6, 107.1, 33.6 (3C), 23.0, 21.8 (2C).

4-Phenylpent-4-enoic acid (**3a**).⁴



Prepared according to the general procedure using 4-oxo-4-phenylbutanoic acid (**16a**). All physical data were in full agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃) δ 10.56 (bs, 1H), 7.23–7.48 (m, 5H), 5.35 (s, 1H), 5.14 (s, 1H), 2.88 (t, *J* = 7.7 Hz, 2H), 2.56 (t, *J* = 7.7 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 179.5, 146.5, 140.4, 128.4 (2C), 127.7, 126.1 (2C), 112.9, 33.0, 30.1.

4-(4-Chlorophenyl)pent-4-enoic acid (**3b**).⁶



Prepared according to the general procedure using 4-(4-chlorophenyl)-4-oxobutanoic acid (**16b**). All physical data were in full agreement with those reported in the literature. ¹H NMR (300 MHz, CDCl₃) δ 10.60 (bs, 1H), 7.28–7.38 (m, 4H), 5.32 (s, 1H), 5.14 (s, 1H), 2.83 (t, *J* = 7.7 Hz, 1H), 2.54 (t, *J* = 7.7 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 179.3, 145.4, 138.8, 133.5, 128.6 (2C), 127.4 (2C), 113.5, 32.8, 30.0.

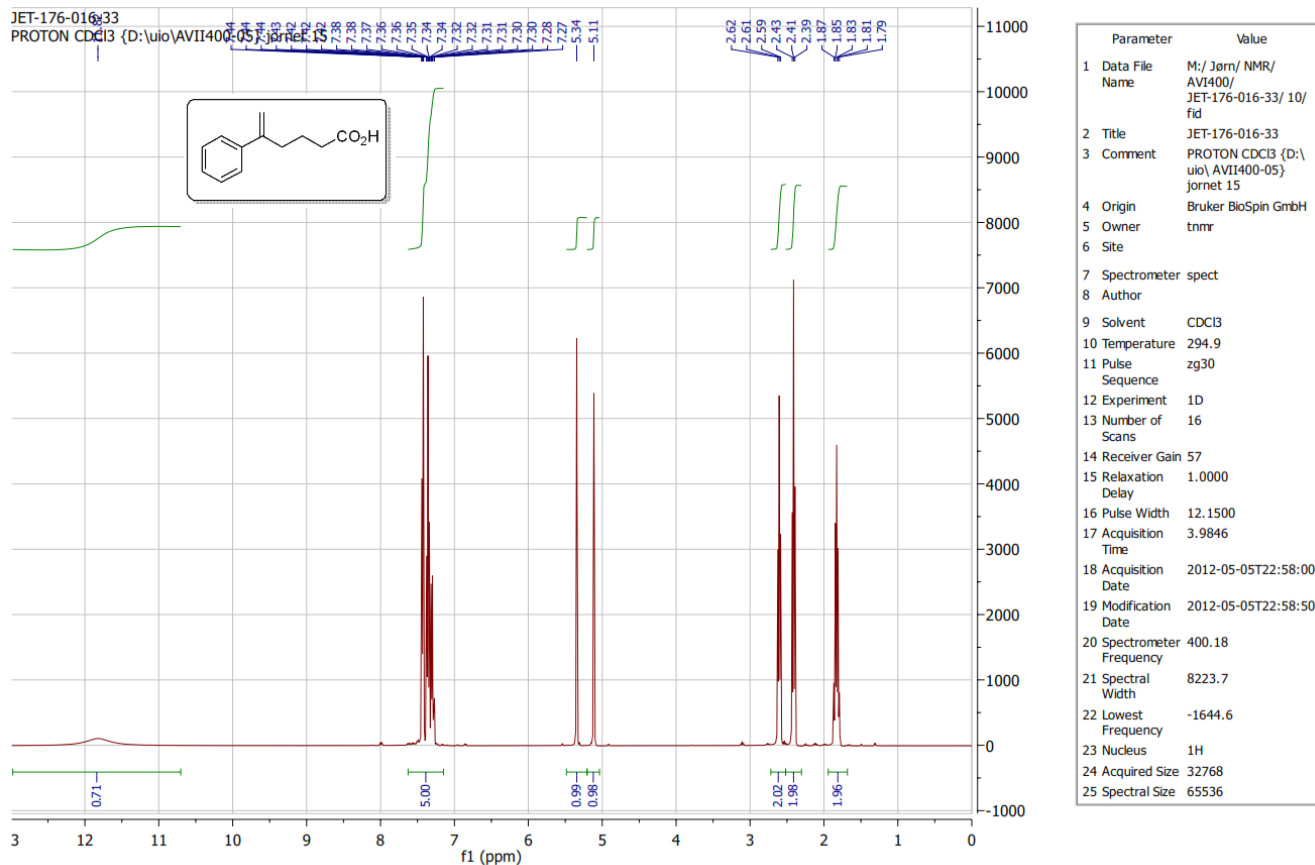


Figure S-17 ¹H-NMR spectrum of compound 1a.

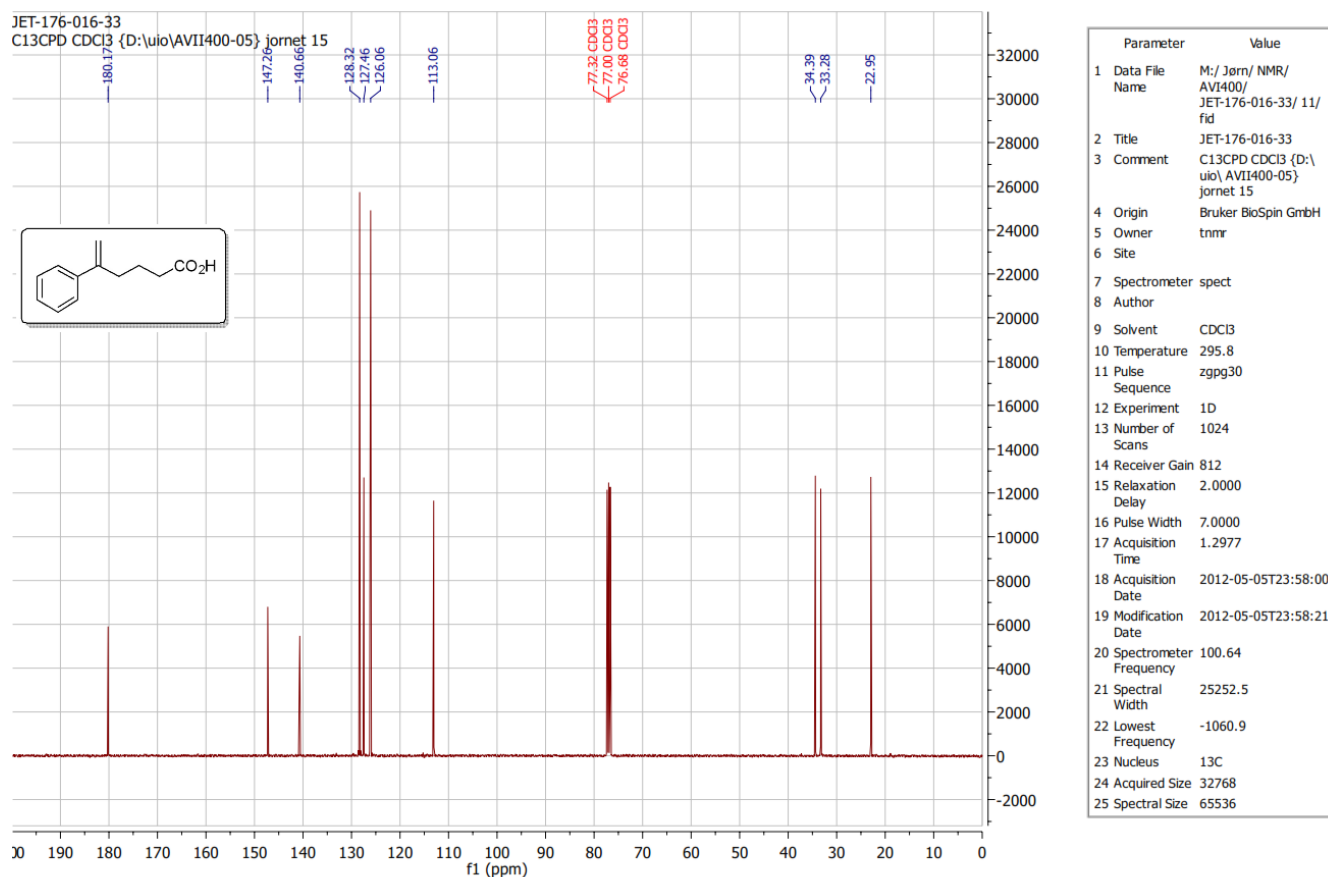


Figure S-18 ¹³C-NMR spectrum of compound 1a.

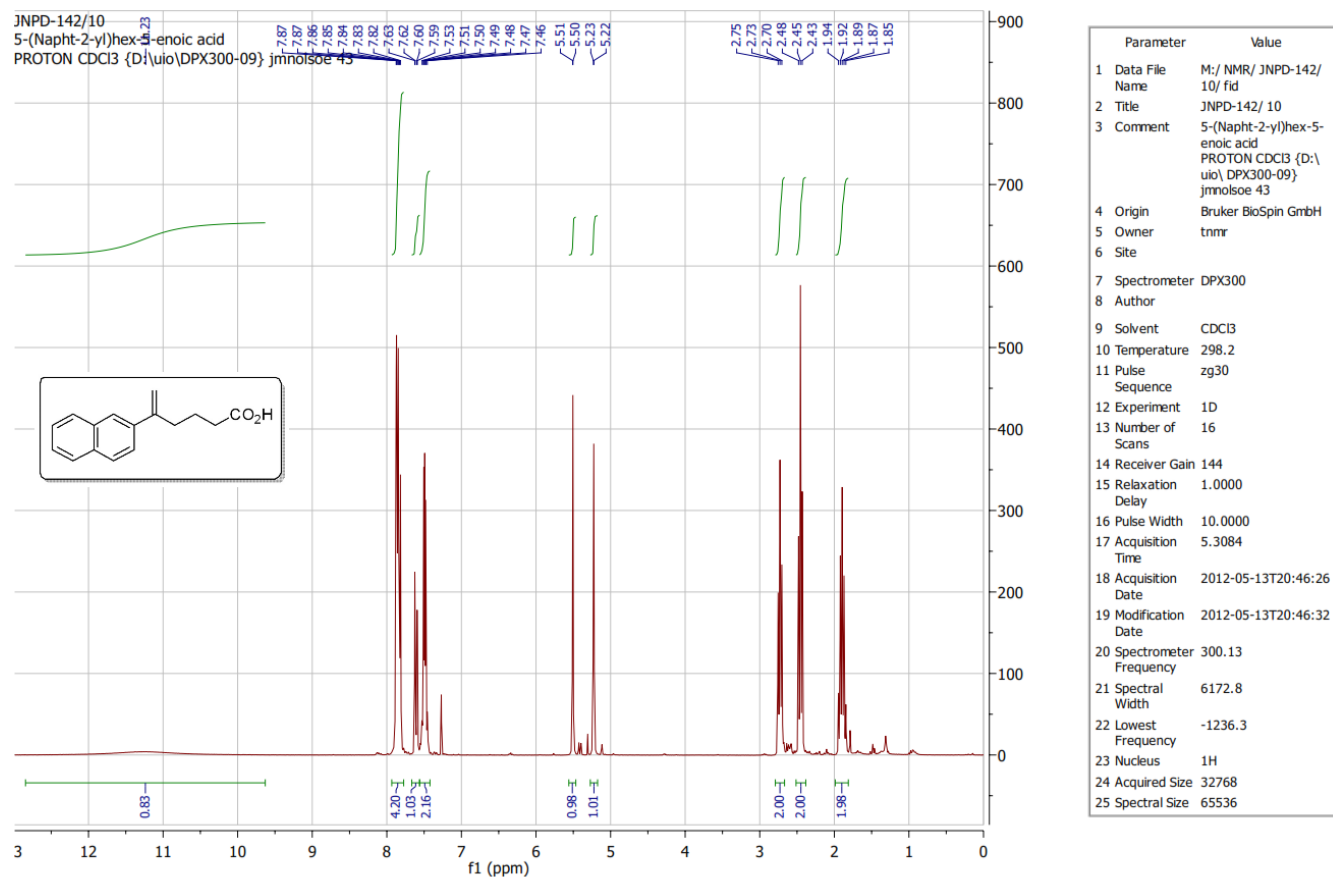


Figure S-19 ¹H-NMR spectrum of compound 1b.

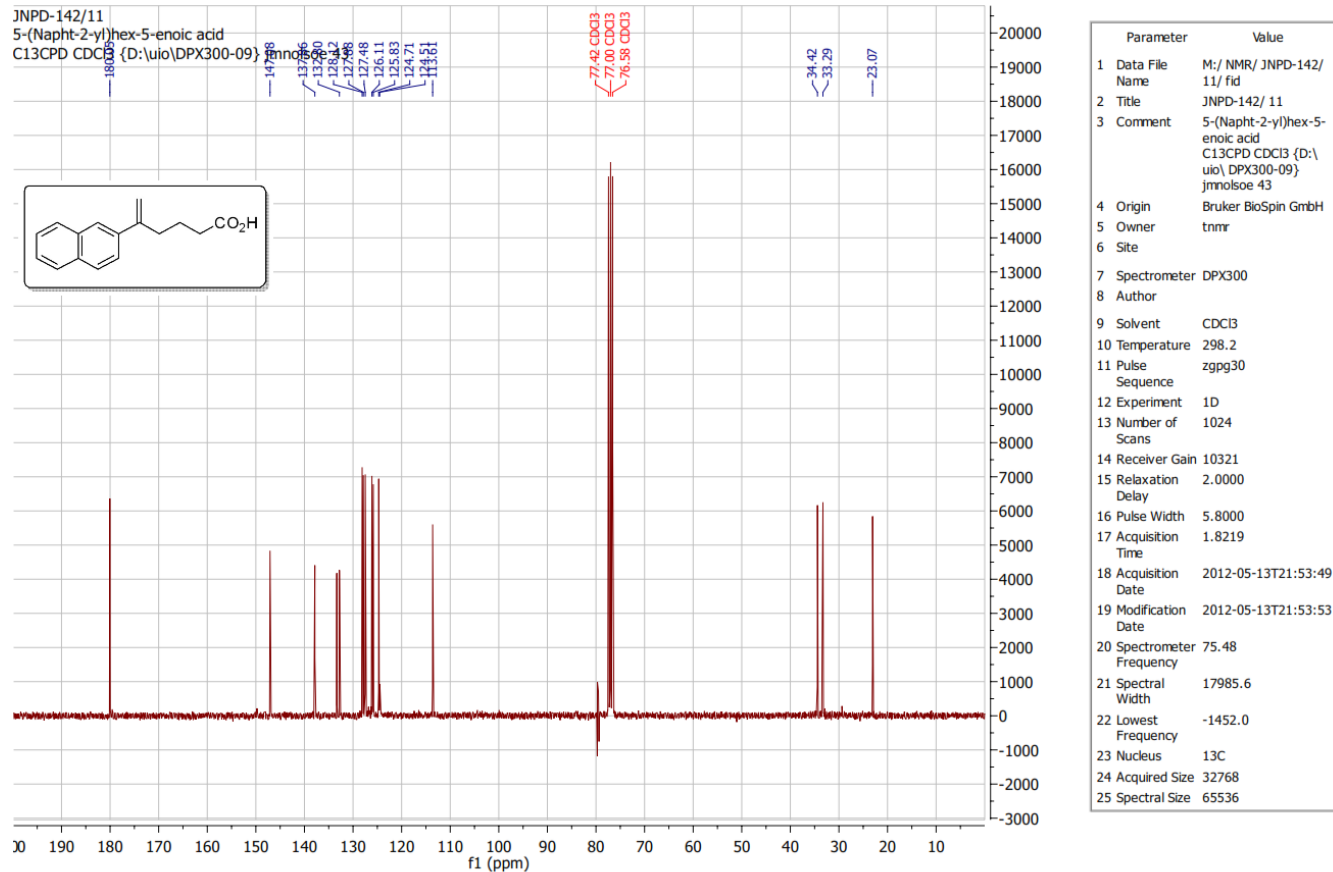


Figure S-20 ¹³C-NMR spectrum of compound 1b.

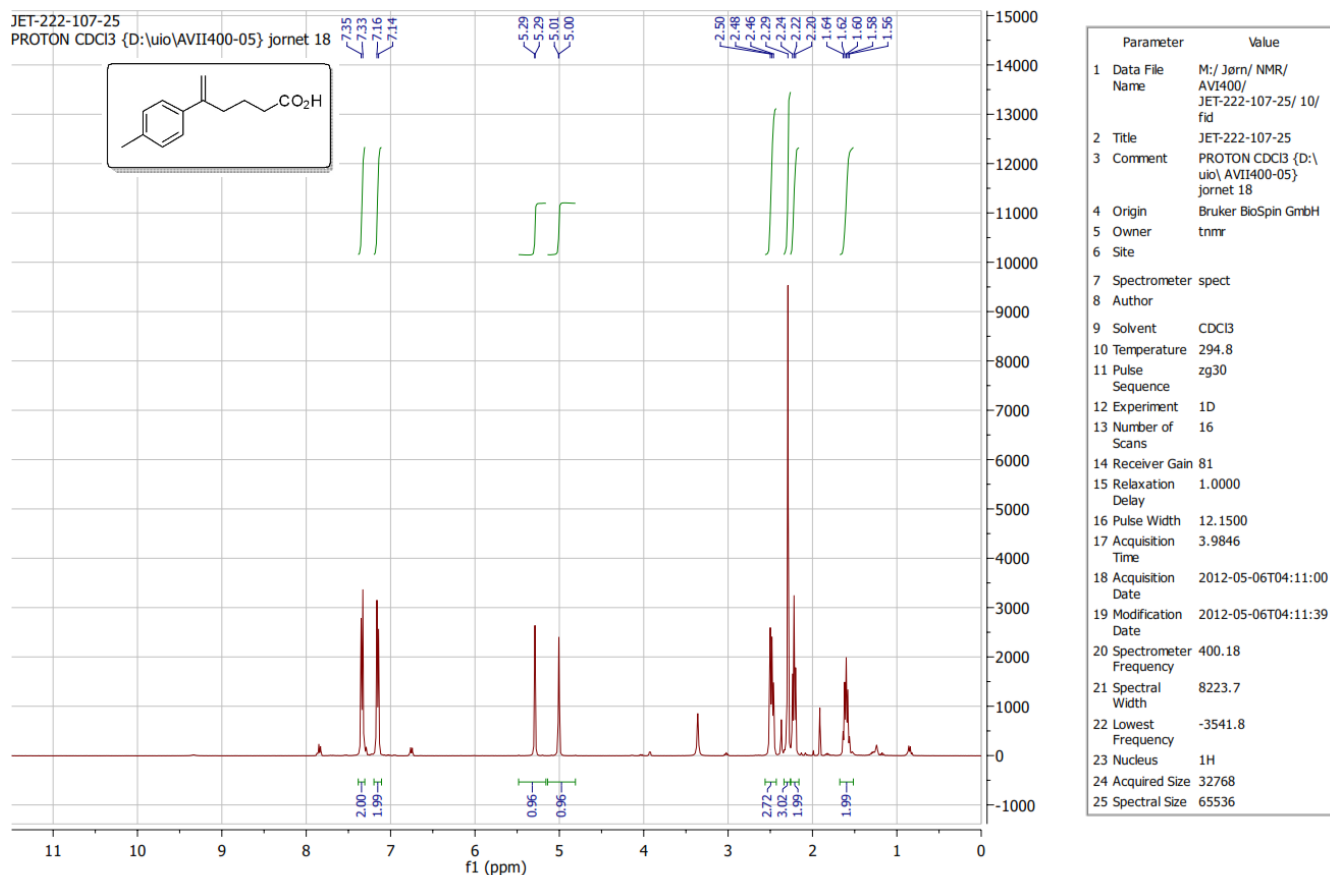


Figure S-21 ¹H-NMR spectrum of compound 1c.

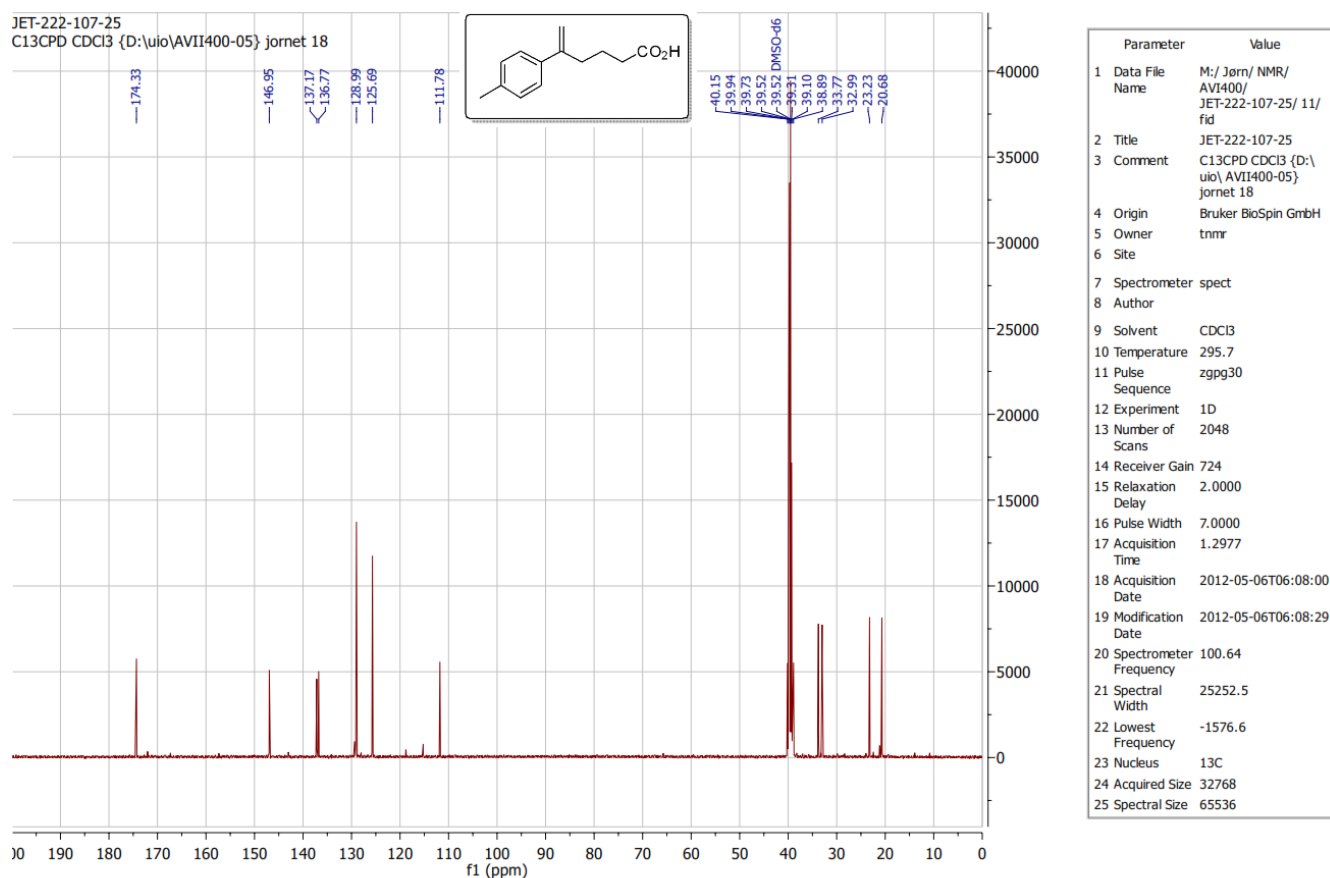


Figure S-22 ¹³C-NMR spectrum of compound 1c.

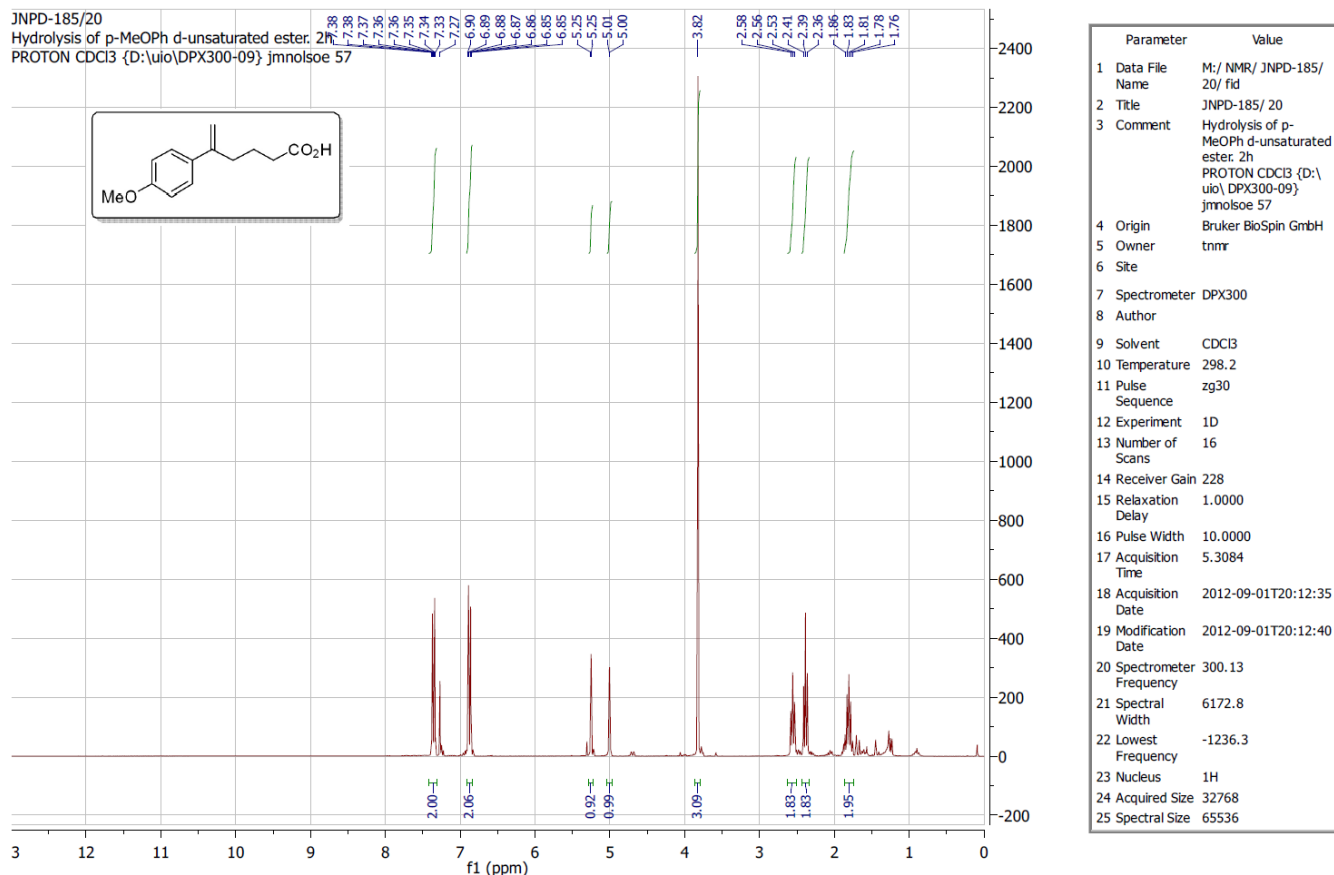


Figure S-23 ¹H-NMR spectrum of compound 1d.

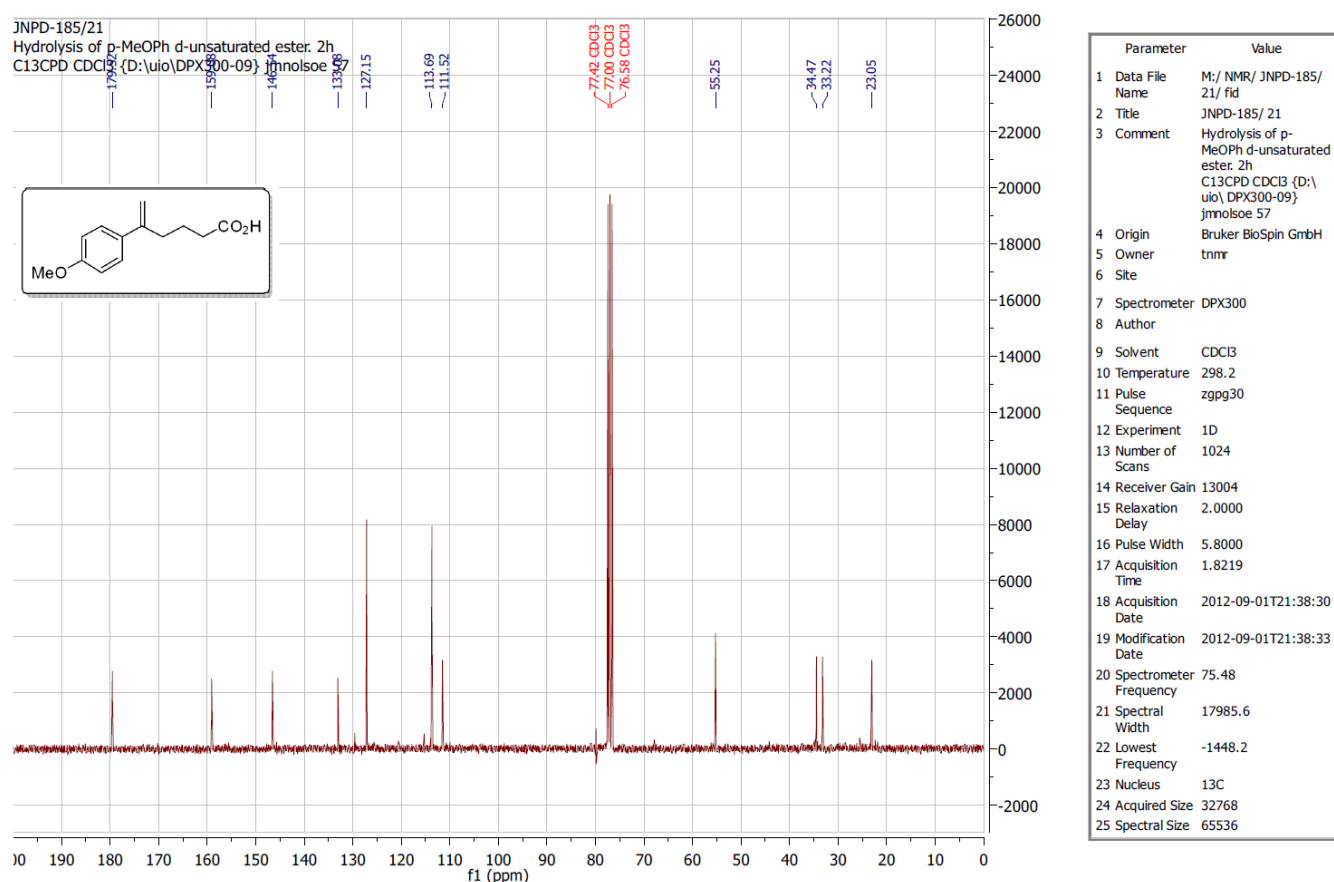


Figure S-24 ¹³C-NMR spectrum of compound 1d.

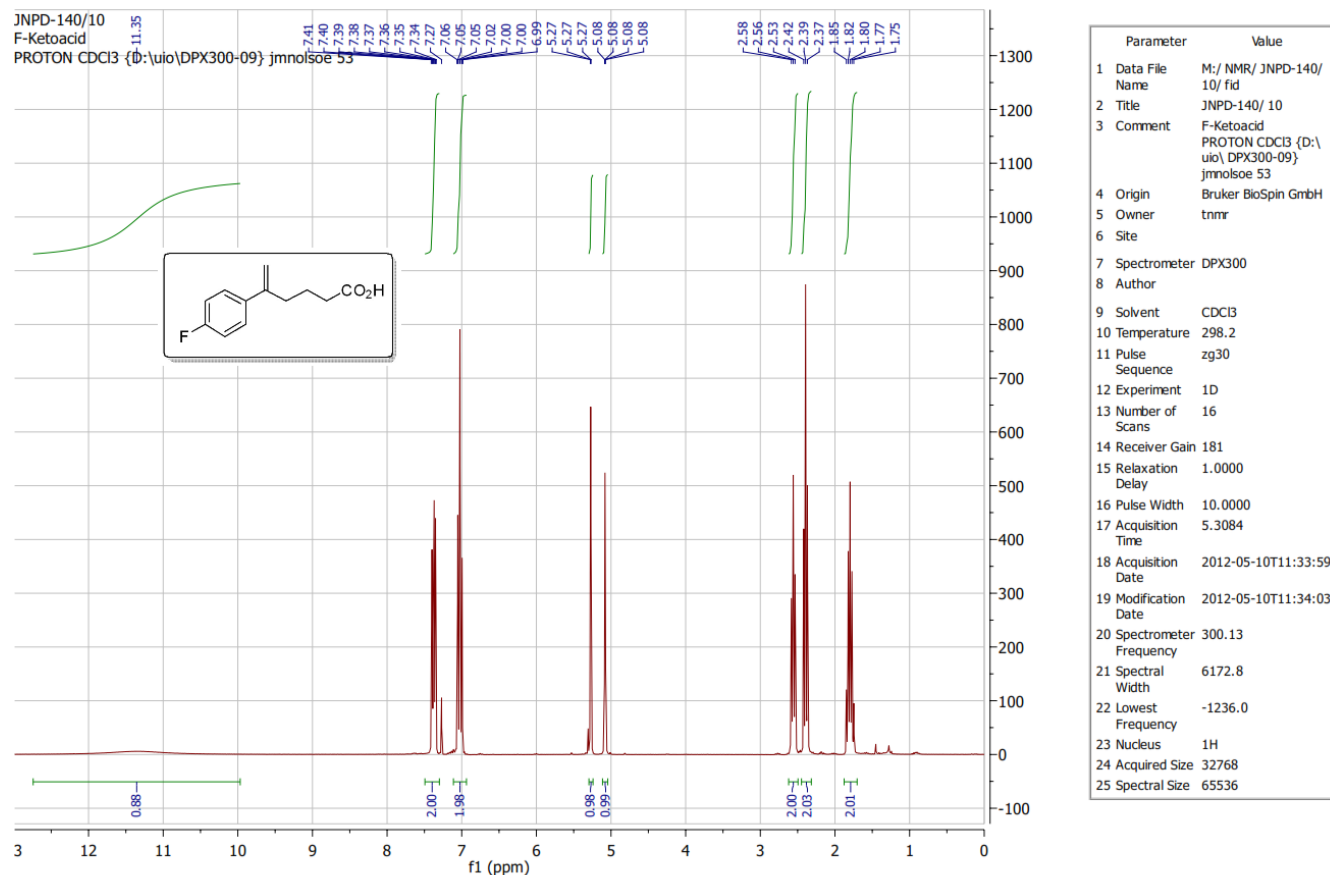


Figure S-25 ¹H-NMR spectrum of compound **1e**.

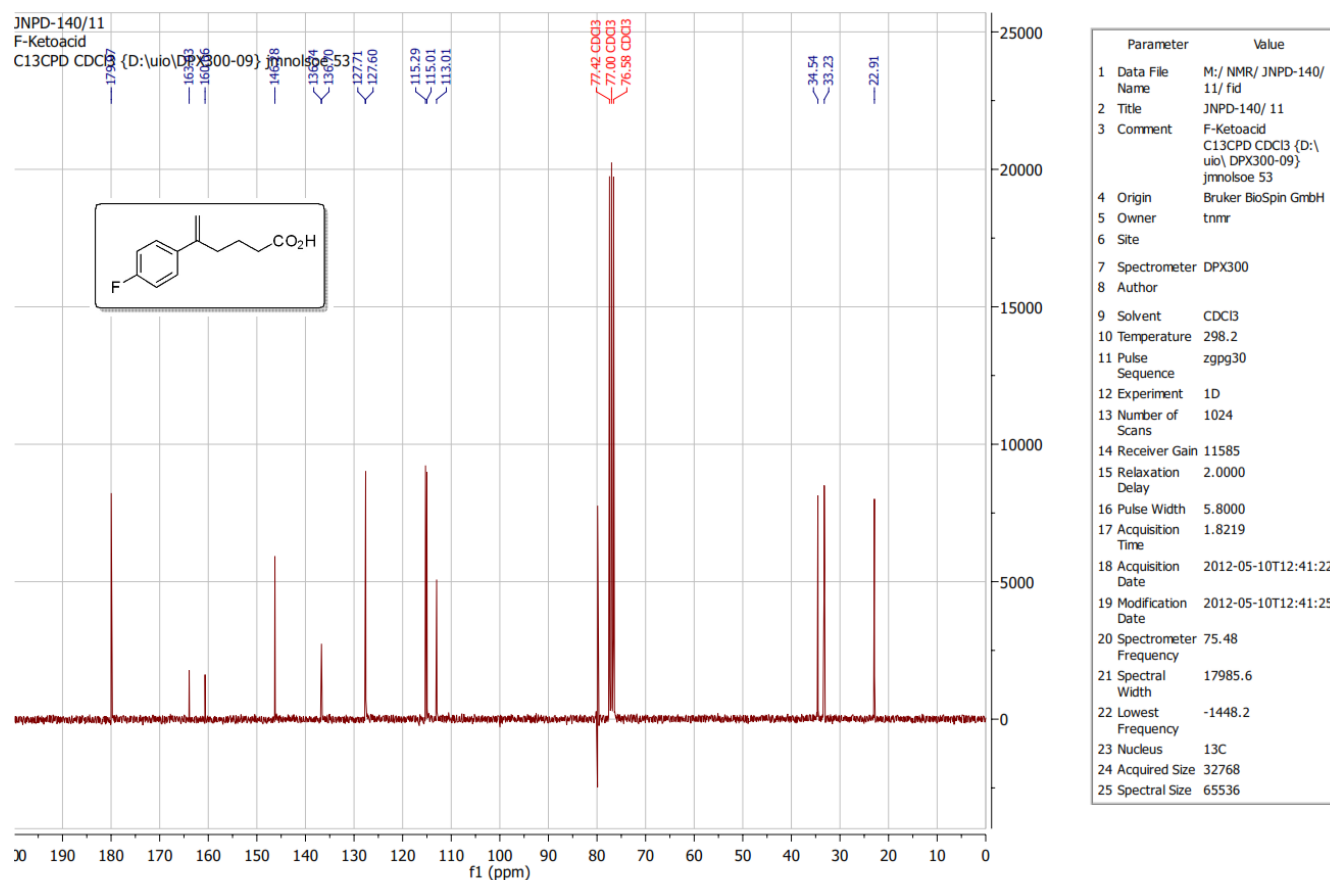


Figure S-26 ¹³C-NMR spectrum of compound **1e**.

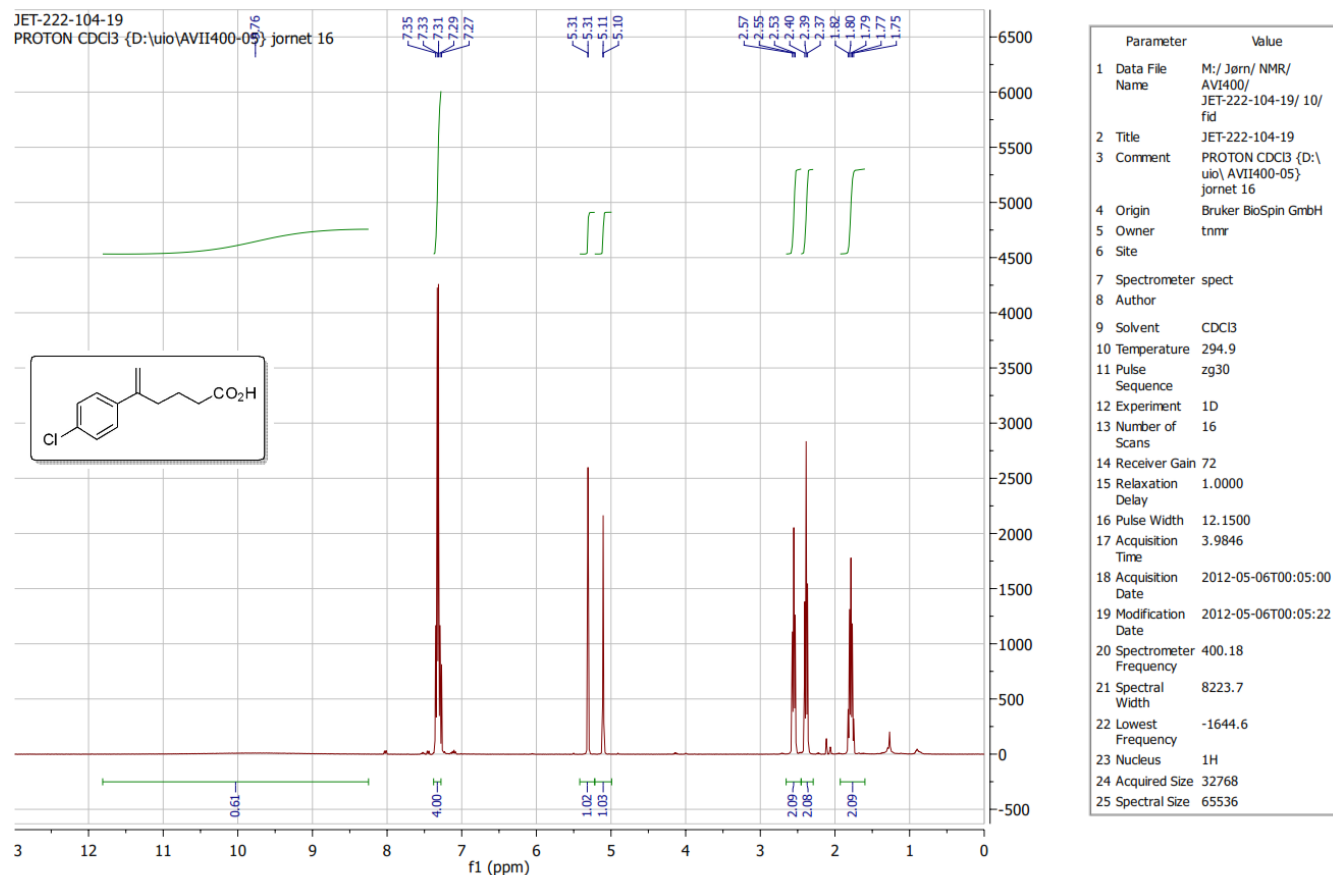


Figure S-27 ^1H -NMR spectrum of compound 1f.

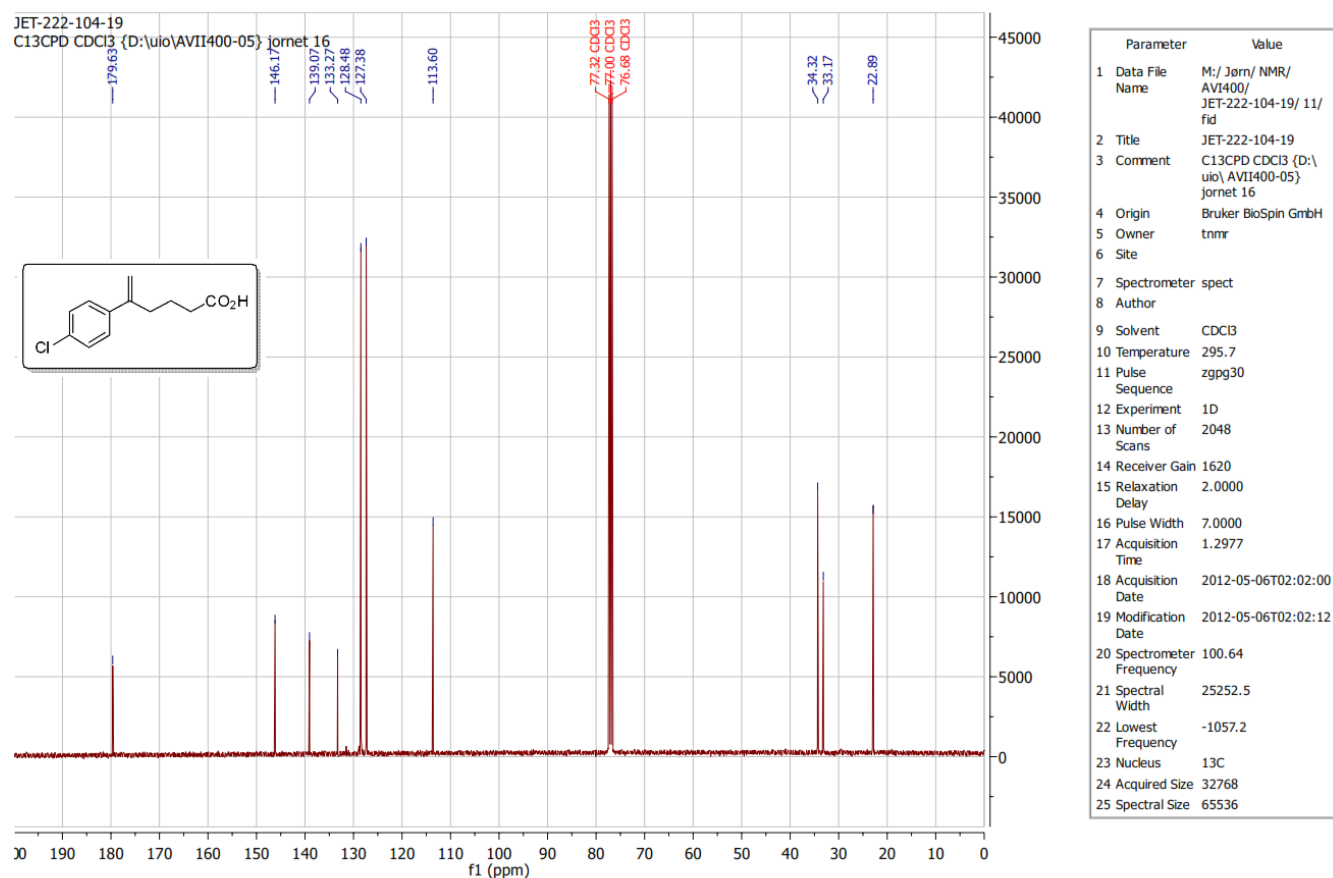


Figure S-28 ^{13}C -NMR spectrum of compound 1f.

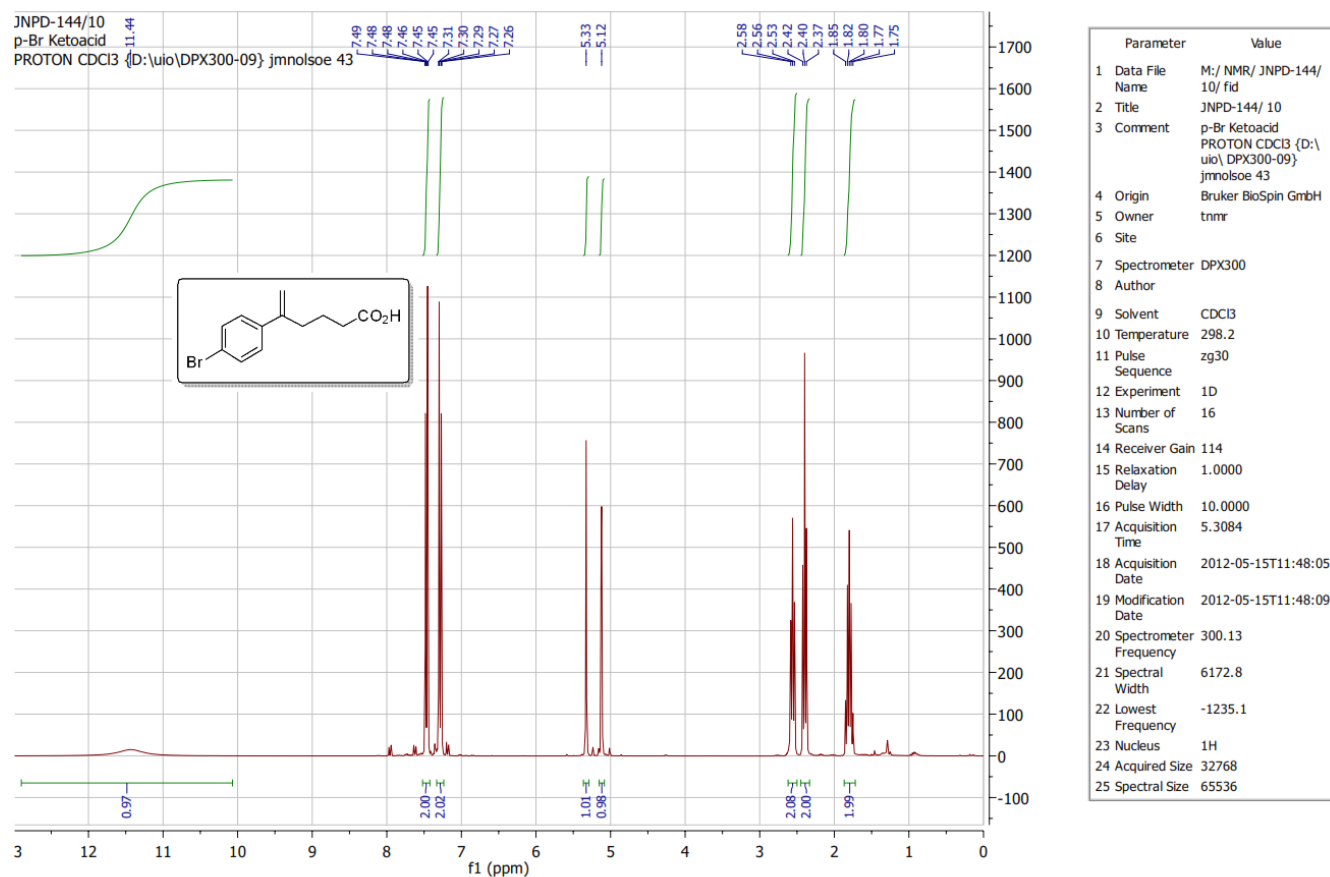


Figure S-29 ¹H-NMR spectrum of compound **1g**.

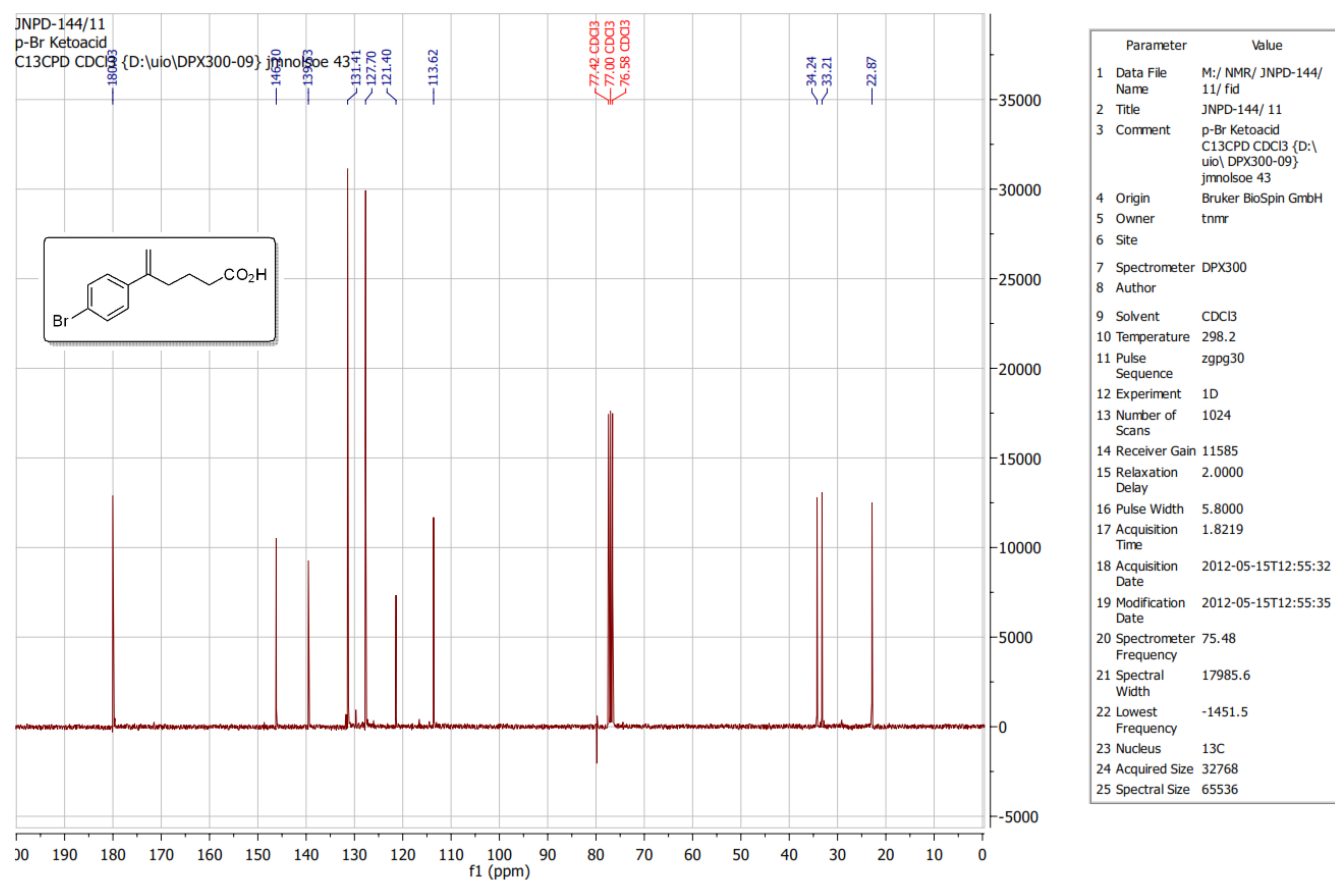


Figure S-30 ¹³C-NMR spectrum of compound **1g**.

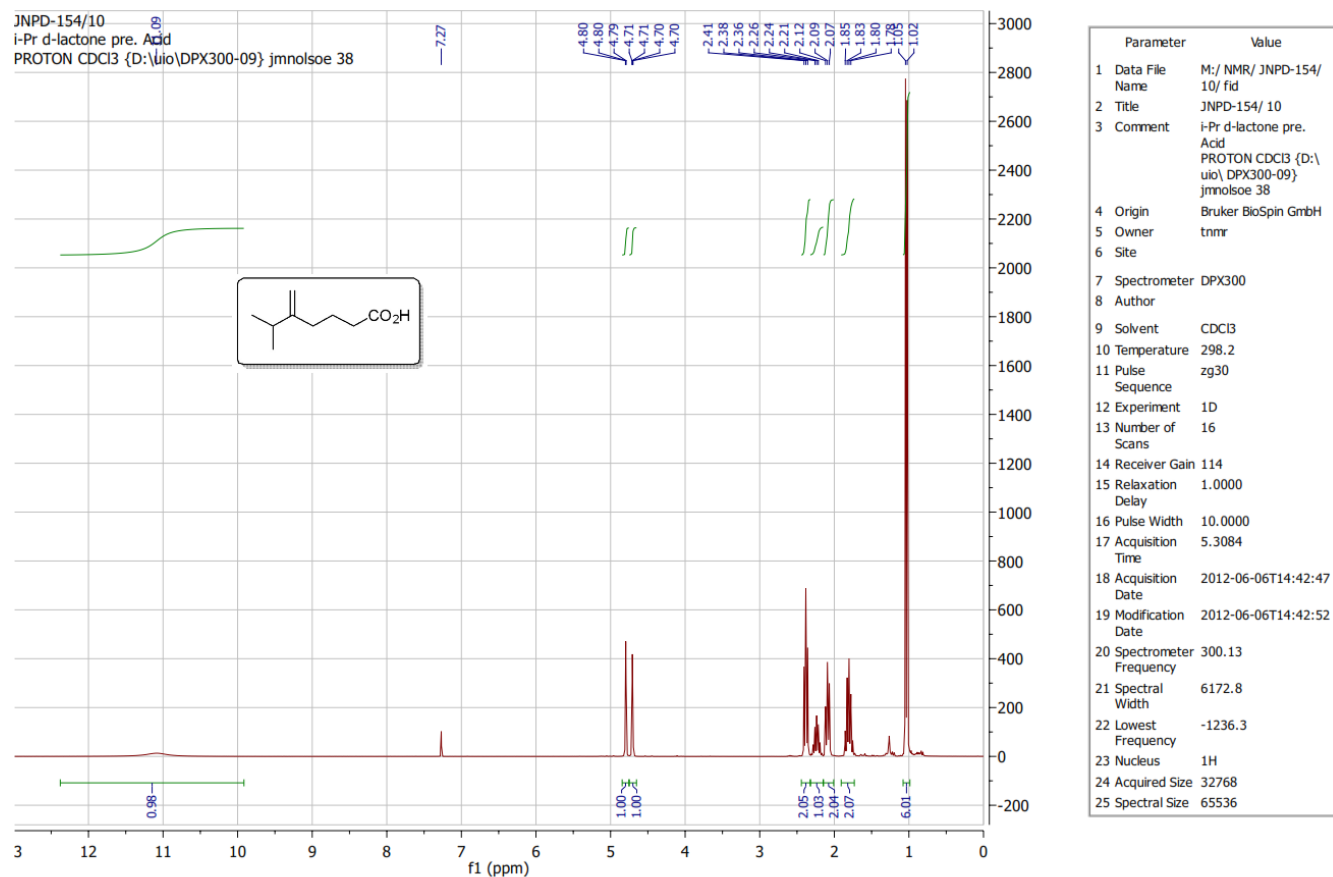


Figure S-31 ¹H-NMR spectrum of compound **1h**.

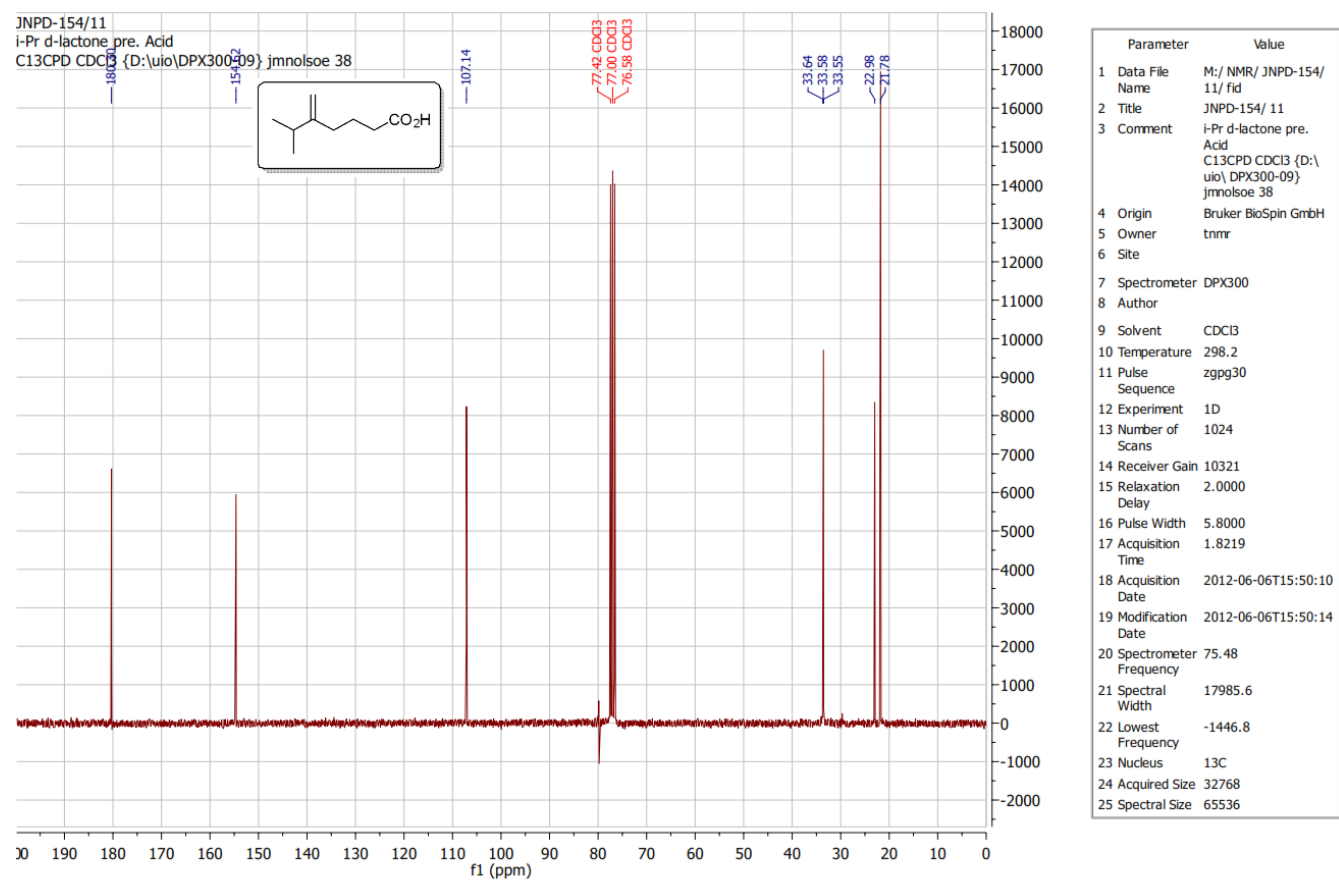


Figure S-32 ¹³C-NMR spectrum of compound **1h**.

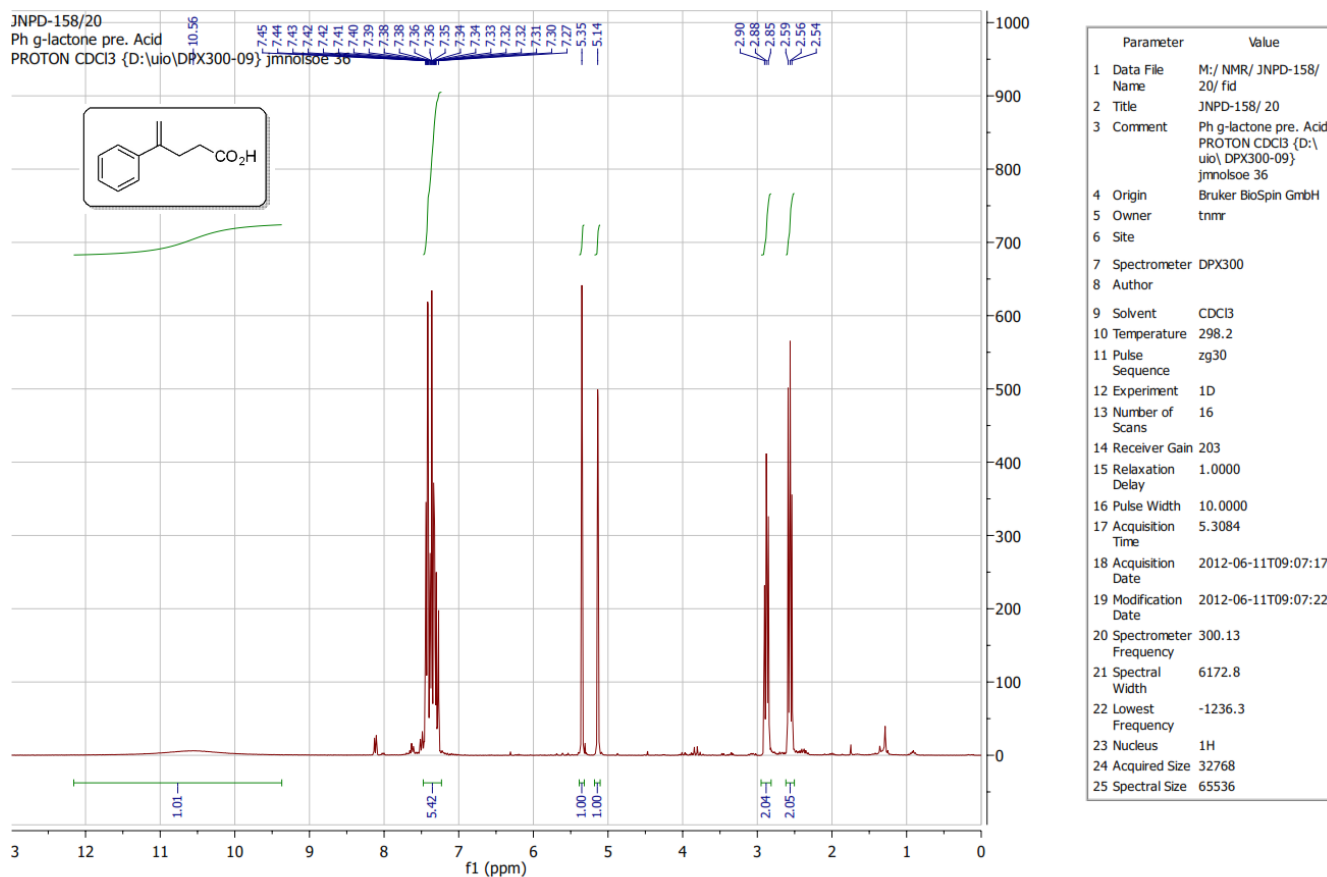


Figure S-33 ^1H -NMR spectrum of compound 3a.

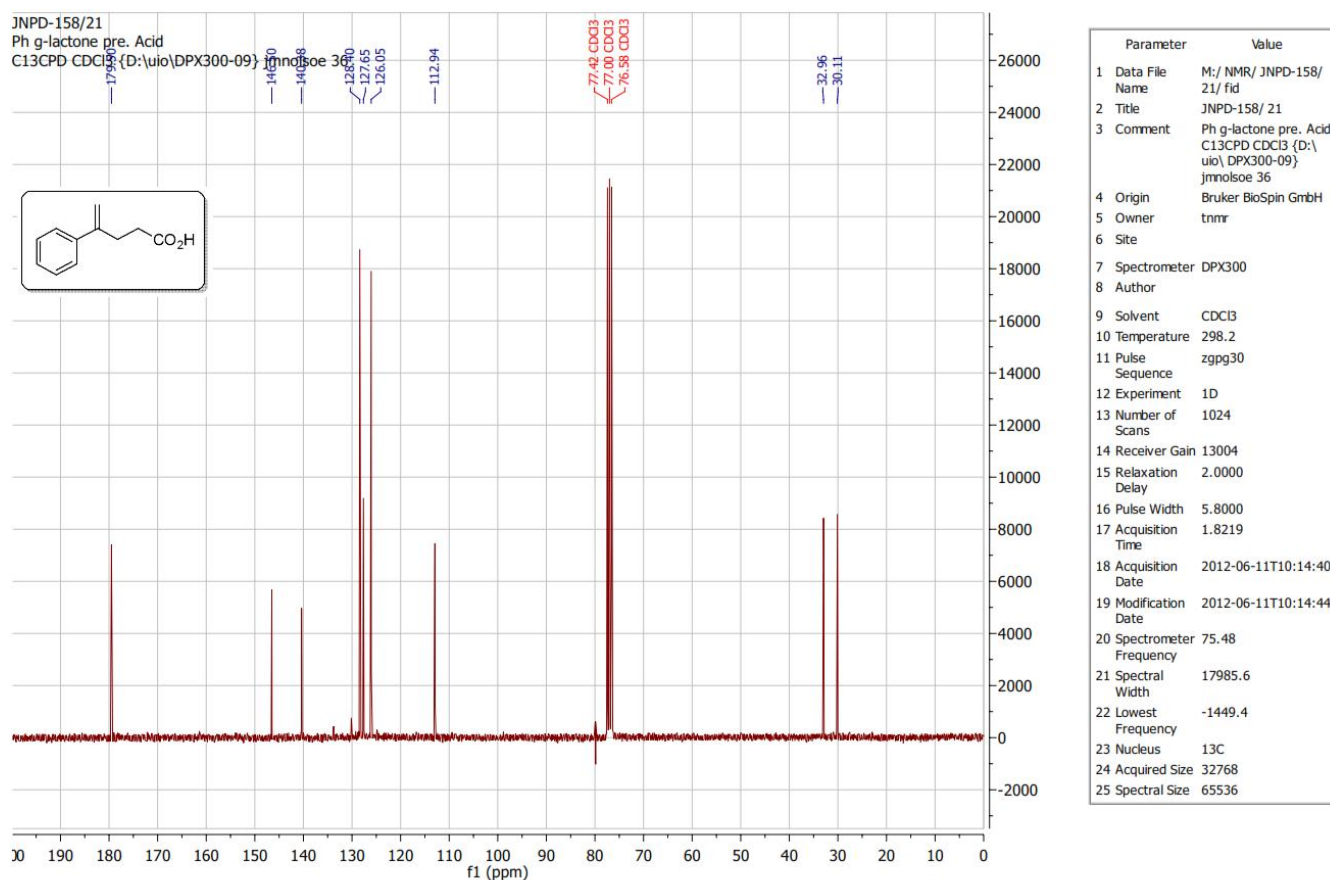


Figure S-34 ^{13}C -NMR spectrum of compound 3a.

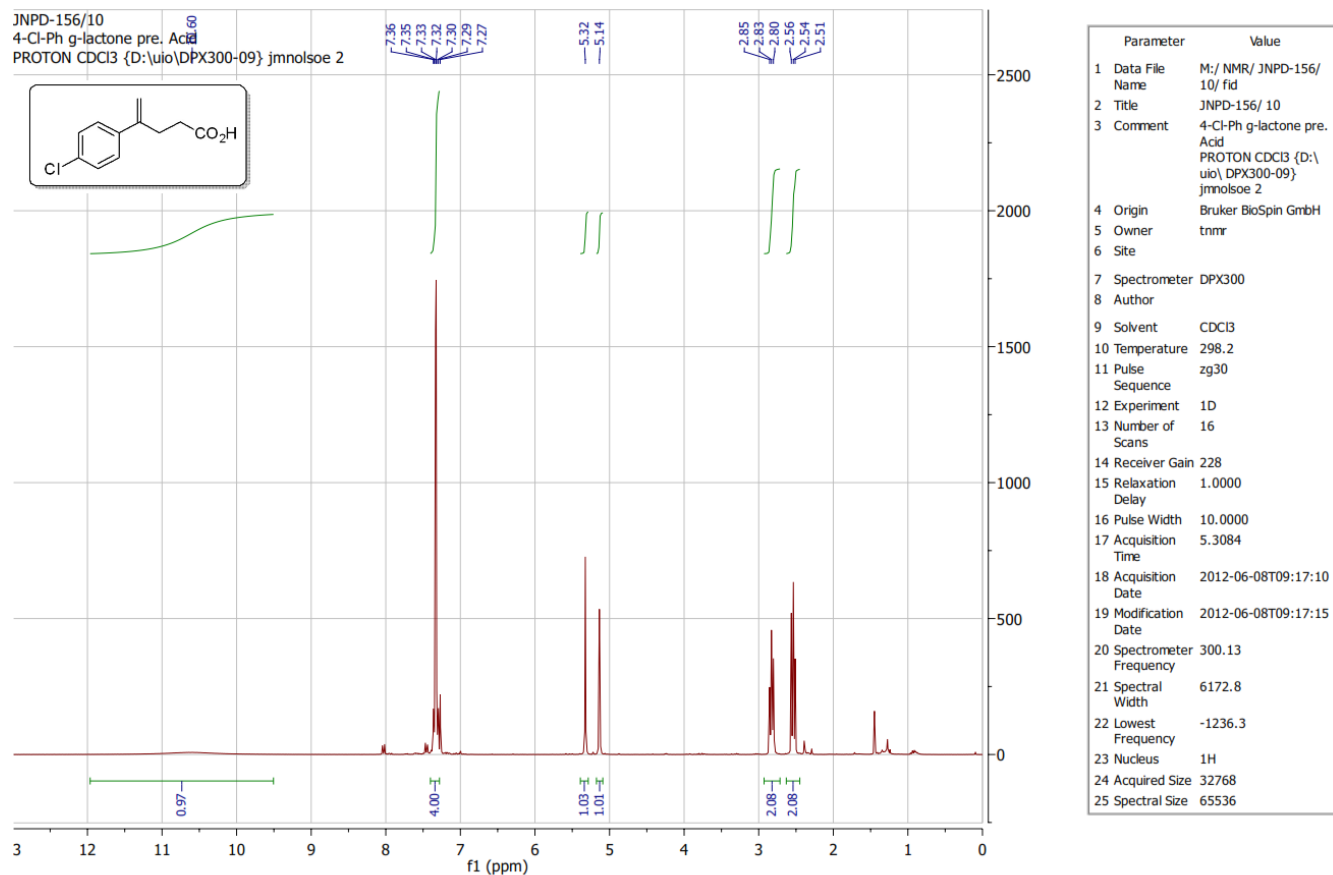


Figure S-35 ¹H-NMR spectrum of compound **3b**.

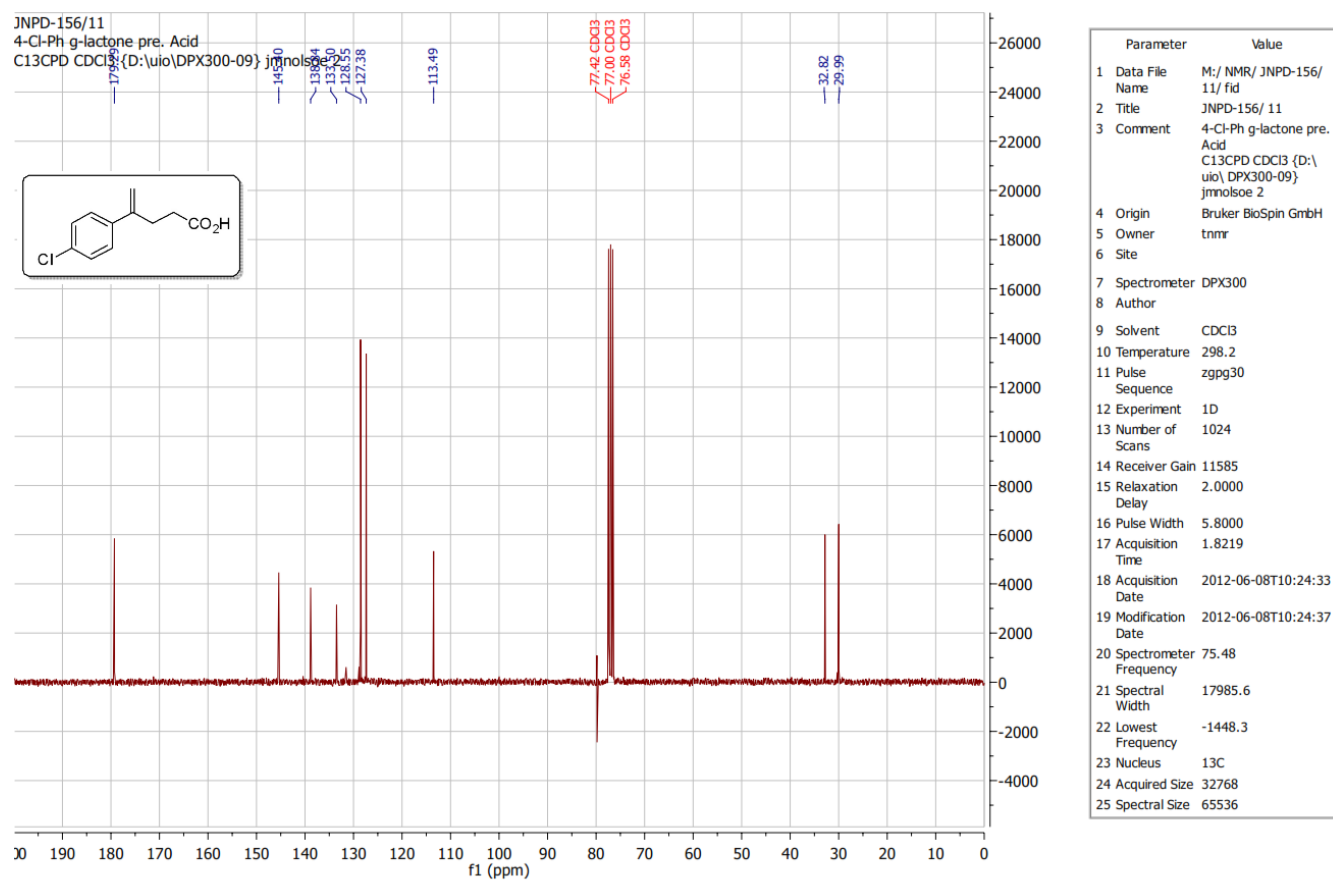


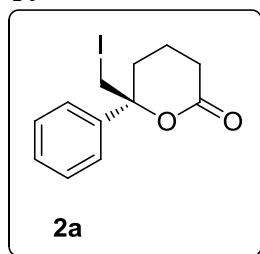
Figure S-36 ¹³C-NMR spectrum of compound **3b**.

Enantioselective Iodolactonization Utilizing Chiral Squaramides

General procedure for asymmetric iodolactonization with chiral squaramides: Iodine (0.15 equiv.) and *N*-iodosuccinimide (1.0 equiv.) was dissolved in a combination of acetone/ CH_2Cl_2 (1:1, 0.20 M). Subsequently, the squaramide **5-8** (0.15 equiv.) was added and the resulting mixture was cooled to -78°C . A solution of unsaturated acid **1** or **3** (1.0 equiv.) in a combination of acetone/ CH_2Cl_2 (1:1, 0.20 M) was added and the resulting mixture was stirred at -78°C for 24 hours. The reaction mixture was treated with satd. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 ml) while still in the cold, allowed to equilibrate to ambient temperature and then EtOAc (30 ml) was added. The phases were separated and the organic phase was washed with aq. NaOH (2 x 20 ml, 1.0 M) and brine (20 ml). The organic phase was dried over MgSO_4 , filtered and evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexanes/EtOAc 4:1) to afford the corresponding iodolactone **2** or **4**.

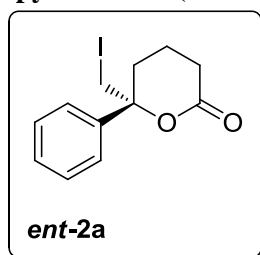
Notice! The iodolactones were observed to be very labile in the condensed state under vacuum. Thus, to avoid decomposition, great care had to be taken when evaporating the solvent *in vacuo* after isolation by flash chromatography. Once all visible traces of solvent had been removed it was of paramount importance to equilibrate back to ambient pressure immediately. Without this precaution, the isolated iodolactone would turn black spontaneously. Due to the instability of the iodolactones they were stored under argon and refrigerated.

(*S*)-6-(Iodomethyl)-6-phenyltetrahydro-2*H*-pyran-2-one (**2a**).⁴



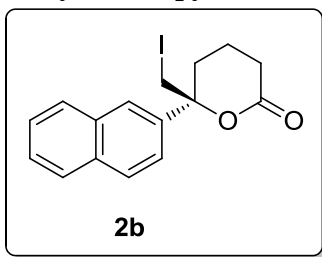
Prepared according to the general procedure using 5-phenylhex-5-enoic acid (**1a**) (40 mg, 210 μmol), squaramide **6b** (17 mg, 31 μmol), iodine (8 mg, 31 μmol) and *N*-iodosuccinimide (47 mg, 210 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*-PrOH 98:2, 1 mL/min): $t_r(e_1, \text{major}) = 24.04$ min and $t_r(e_2, \text{minor}) = 27.20$ min. Yield: 55 mg (83%) of colourless oil; *ee*: 87%; TLC (hexanes/EtOAc 1:1): $R_f = 0.48$, visualized with anisaldehyde; $[\alpha]_D^{20} = 27.2$ ($c = 0.06$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.54 (m, 5H), 3.57 (d, $J = 1.4$ Hz, 2H), 2.28 – 2.59 (m, 4H), 1.69 – 1.98 (m, 1H), 1.45 – 1.69 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.4, 140.1, 128.9 (2C), 128.3, 125.1 (2C), 84.3, 32.0, 28.9, 17.7, 16.5; HRMS (EI): Exact mass calculated for $\text{C}_{12}\text{H}_{13}\text{IO}_2$ [M]⁺: 315.9960, found 315.9972.

(*R*)-6-(Iodomethyl)-6-phenyltetrahydro-2*H*-pyran-2-one (*ent*-**2a**).⁴



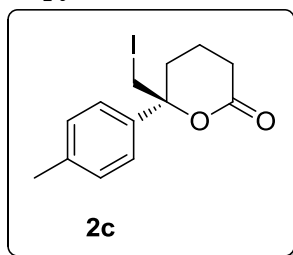
Prepared according to the general procedure using 5-phenylhex-5-enoic acid (**1a**) (40 mg, 210 μmol), squaramide *ent*-**6b** (17 mg, 31 μmol), iodine (8 mg, 31 μmol) and *N*-iodosuccinimide (47 mg, 210 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*-PrOH 98:2, 1 mL/min): $t_r(e_1, \text{minor}) = 27.00$ min and $t_r(e_2, \text{major}) = 31.00$ min. Yield: 52 mg (79%) of colourless oil; *ee*: 82%; TLC (hexanes/EtOAc 1:1): $R_f = 0.48$, visualized with anisaldehyde; $[\alpha]_D^{20} = -26.0$ ($c = 0.07$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.30 – 7.54 (m, 5H), 3.57 (d, $J = 1.4$ Hz, 2H), 2.28 – 2.59 (m, 4H), 1.69 – 1.98 (m, 1H), 1.45 – 1.69 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.4, 140.1, 128.9 (2C), 128.3, 125.1 (2C), 84.3, 32.0, 28.9, 17.7, 16.5.

(S)-6-(Iodomethyl)-6-(naphthalen-2-yl)tetrahydro-2H-pyran-2-one (2b).⁴



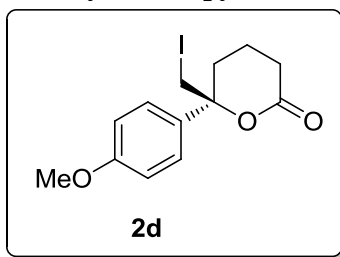
Prepared according to the general procedure using 5-(naphthalen-2-yl)hex-5-enoic acid (**1b**) (40 mg, 166 μ mol), squaramide **6b** (14 mg, 25 μ mol), iodine (7 mg, 25 μ mol) and *N*-iodosuccinimide (37 mg, 166 μ mol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 99:1, 1 mL/min): $t_r(e_1, \text{major}) = 66.14$ min and $t_r(e_2, \text{minor}) = 82.74$ min. Yield: 55 mg (91%) of colourless oil; *ee*: 92%; TLC (hexanes/EtOAc 1:1): $R_f = 0.56$, visualized with anisaldehyde; $[\alpha]_D^{20} = 22.0$ ($c = 0.13$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.81 – 7.97 (m, 4H), 7.48 – 7.62 (m, 2H), 7.41 (dd, $J = 8.6, 2.0$ Hz, 1H), 3.67 (d, $J = 2.8$ Hz, 2H), 2.29 – 2.77 (m, 4H), 1.78 – 1.93 (m, 1H), 1.52 – 1.69 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.5, 137.4, 133.0, 132.8, 129.0, 128.3, 127.5, 126.8 (2C), 125.0, 122.3, 84.6, 32.1, 29.0, 17.4, 16.6; HRMS (EI): Exact mass calculated for $\text{C}_{16}\text{H}_{15}\text{IO}_2$ $[M]^+$: 366.0117, found 366.0109.

(S)-6-(Iodomethyl)-6-(*p*-tolyl)tetrahydro-2H-pyran-2-one (2c).⁴



Prepared according to the general procedure using 5-(*p*-tolyl)hex-5-enoic acid (**1c**) (40 mg, 196 μ mol), squaramide **6b** (17 mg, 29 μ mol), iodine (7 mg, 29 μ mol) and *N*-iodosuccinimide (44 mg, 196 μ mol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 98:2, 1 mL/min): $t_r(e_1, \text{major}) = 25.32$ min and $t_r(e_2, \text{minor}) = 34.16$ min. Yield: 51 mg (80%) of colourless oil; *ee*: 86%; TLC (hexanes/EtOAc 1:1): $R_f = 0.56$, visualized with anisaldehyde; $[\alpha]_D^{20} = 24.6$ ($c = 0.10$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.25 (d, $J = 8.4$ Hz, 2H), 7.20 (d, $J = 8.2$ Hz, 2H), 3.55 (s, 2H), 2.40 – 2.54 (m, 2H), 2.35 (s, 3H), 2.27 – 2.40 (m, 2H), 1.74 – 1.89 (m, 1H), 1.66 – 1.49 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.5, 138.2, 137.1, 129.6 (2C), 125.1 (2C), 84.3, 31.9, 28.9, 21.0, 17.9, 16.5; HRMS (EI): Exact mass calculated for $\text{C}_{13}\text{H}_{15}\text{IO}_2$ $[M]^+$: 330.0117, found 330.0108.

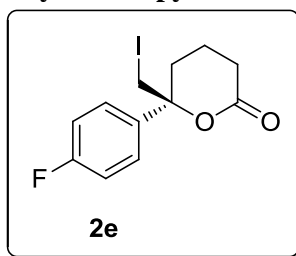
(S)-6-(Iodomethyl)-6-(4-methoxyphenyl)tetrahydro-2H-pyran-2-one (2d).⁴



Prepared according to the general procedure using 5-(4-methoxyphenyl)hex-5-enoic acid (**1d**) (48 mg, 218 μ mol), squaramide **6b** (18 mg, 33 μ mol), iodine (8 mg, 33 μ mol) and *N*-iodosuccinimide (49 mg, 218 μ mol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*PrOH 90:10, 1 mL/min): $t_r(e_1, \text{major}) = 12.91$ min and $t_r(e_2, \text{minor}) = 15.56$ min. Yield: 65 mg (87%) of colourless oil; *ee*: 12%; TLC (hexanes/EtOAc 1:1): $R_f = 0.53$, visualized with anisaldehyde; $[\alpha]_D^{20} = 1.6$ ($c = 0.06$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.24 – 7.33 (m, 2H), 6.86 – 6.95 (m, 2H), 3.81 (s, 3H), 3.50 – 3.58 (m, 2H), 2.39 – 2.55 (m, 2H), 2.25 – 2.39 (m, 2H), 1.75 – 1.90 (m, 1H), 1.48 – 1.70

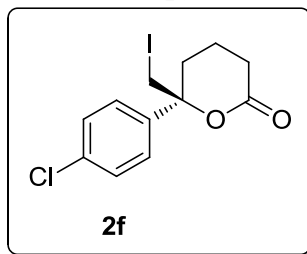
(m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 170.5, 159.4, 132.0, 126.5 (2C), 114.2 (2C), 84.2, 55.3, 31.8, 28.9, 18.1, 16.5; HRMS (EI): Exact mass calculated for $\text{C}_{13}\text{H}_{15}\text{IO}_3$ $[M]^+$: 346.0066, found 346.0064.

(S)-6-(4-Fluorophenyl)-6-(iodomethyl)tetrahydro-2H-pyran-2-one (2e).⁴



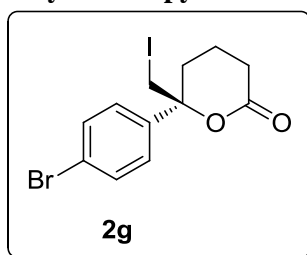
Prepared according to the general procedure using 5-(4-fluorophenyl)hex-5-enoic acid (**1e**) (42 mg, 200 μmol), squaramide **6b** (17 mg, 30 μmol), iodine (8 mg, 30 μmol) and *N*-iodosuccinimide (45 mg, 200 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*-PrOH 90:10, 1 mL/min): $t_r(e_1, \text{major}) = 10.70$ min and $t_r(e_2, \text{minor}) = 12.17$ min. Yield: 55 mg (83%) of colourless oil; *ee*: 90%; TLC (hexanes/EtOAc 1:1): $R_f = 0.49$, visualized with anisaldehyde; $[\alpha]_D^{20} = 26.0$ ($c = 0.10$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.29 – 7.47 (m, 2H), 7.02 – 7.17 (m, 2H), 3.54 (s, 1H), 2.41 – 2.58 (m, 2H), 2.41 – 2.26 (m, 2H), 1.76 – 1.93 (m, 1H), 1.48 – 1.71 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.1, 162.4 (d, $^1J_{\text{CF}} = 248$ Hz), 136.0 (d, $^4J_{\text{CF}} = 3.2$ Hz), 127.1 (d, $^3J_{\text{CF}} = 8.3$ Hz, 2C), 115.9 (d, $^2J_{\text{CF}} = 21.5$ Hz, 2C), 84.1, 31.9, 28.9, 17.5, 16.5; HRMS (EI): Exact mass calculated for $\text{C}_{12}\text{H}_{12}\text{FIO}_2$ $[M]^+$: 333.9866, found 333.9867.

(S)-6-(4-Chlorophenyl)-6-(iodomethyl)tetrahydro-2H-pyran-2-one (2f).⁴



Prepared according to the general procedure using 5-(4-chlorophenyl)hex-5-enoic acid (**1f**) (40 mg, 178 μmol), squaramide **6b** (15 mg, 27 μmol), iodine (7 mg, 27 μmol) and *N*-iodosuccinimide (40 mg, 178 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*-PrOH 98:2, 1 mL/min): $t_r(e_1, \text{major}) = 31.58$ min and $t_r(e_2, \text{minor}) = 46.09$ min. Yield: 49 mg (78%) of colourless oil; *ee*: 96%; TLC (hexanes/EtOAc 1:1): $R_f = 0.46$, visualized with anisaldehyde; $[\alpha]_D^{20} = 27.2$ ($c = 0.20$, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.38 (d, $J = 8.8$ Hz, 2H), 7.32 (d, $J = 8.8$ Hz, 2H), 2.42 – 2.59 (m, 2H), 2.27 – 2.41 (m, 2H), 1.78 – 1.93 (m, 1H), 1.50 – 1.66 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.0, 138.8, 134.5, 129.1 (2C), 126.7 (2C), 84.1, 32.0, 29.0, 17.1, 16.5; HRMS (EI): Exact mass calculated for $\text{C}_{12}\text{H}_{12}\text{ClIO}_2$ $[M]^+$: 349.9571, found 349.9577.

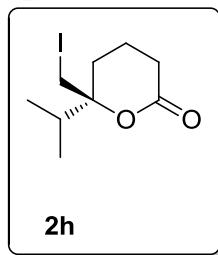
(S)-6-(4-Bromophenyl)-6-(iodomethyl)tetrahydro-2H-pyran-2-one (2g).⁴



Prepared according to the general procedure using 5-(4-bromophenyl)hex-5-enoic acid (**1g**) (22 mg, 80 μmol), squaramide **6b** (7 mg, 12 μmol), iodine (3 mg, 27 μmol) and *N*-iodosuccinimide (18 mg, 178 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*-PrOH 90:10, 1 mL/min): $t_r(e_1, \text{major}) = 11.83$ min and $t_r(e_2, \text{minor}) = 15.15$ min.

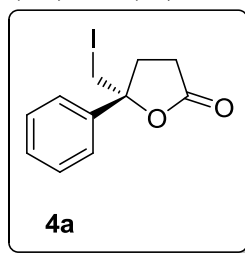
min. Yield: 23 mg (73%) of colourless oil; *ee*: 91%; TLC (hexanes/EtOAc 1:1): R_f = 0.50, visualized with anisaldehyde; $[\alpha]_D^{20}$ = 23.3 (c = 0.15, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 7.54 (d, J = 8.6 Hz, 2H), 7.26 (d, J = 8.7 Hz, 2H), 3.54 (s, 2H), 2.42 – 2.57 (m, 2H), 2.28 – 2.42 (m, 2H), 1.78 – 1.92 (m, 1H), 1.50 – 1.70 (m, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.0, 139.4, 132.1 (2C), 127.0 (2C), 122.6, 84.1, 31.9, 29.0, 16.9, 16.5; HRMS (EI): Exact mass calculated for $\text{C}_{12}\text{H}_{12}\text{BrIO}_2$ $[M]^+$: 393.9065, found 393.9070.

(S)-6-(Iodomethyl)-6-isopropyltetrahydro-2H-pyran-2-one (2h).⁴



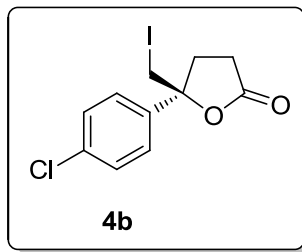
Prepared according to the general procedure using 6-methyl-5-methyleneheptanoic acid (**1h**) (29 mg, 186 μmol), squaramide **6b** (16 mg, 28 μmol), iodine (7 mg, 28 μmol) and *N*-iodosuccinimide (42 mg, 186 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral GLC analysis (Chiraldex G-TA, 170 °C isothermal): $t_r(e_1, \text{major})$ = 22.56 min and $t_r(e_2, \text{minor})$ = 22.91 min. Yield: 40 mg (77%) of colourless oil; *ee*: 16%; TLC (hexanes/EtOAc 1:1): R_f = 0.57, visualized with anisaldehyde; $[\alpha]_D^{20}$ = 1.50 (c = 0.07, CHCl_3); ^1H NMR (400 MHz, CDCl_3) δ 3.42 (s, 2H), 2.45 – 2.59 (m, 1H), 2.31 – 2.45 (m, 1H), 2.09 – 2.25 (m, 1H), 1.95 – 2.06 (m, 1H), 1.76 – 1.95 (m, 3H), 0.97 (d, J = 7.0 Hz, 6H); ^{13}C NMR (101 MHz, CDCl_3) δ 170.4, 84.8, 35.2, 29.5, 26.7, 16.7, 16.6, 16.4, 13.0; HRMS (EI): Exact mass calculated for $\text{C}_9\text{H}_{15}\text{IO}_2$ $[M]^+$: 282.0119, found 282.0124.

(R)-5-(Iodomethyl)-5-phenyldihydrofuran-2(3H)-one (4a).^{4, 6}



Prepared according to the general procedure using 4-phenylpent-4-enoic acid (**3a**) (40 mg, 227 μmol), squaramide **6b** (19 mg, 34 μmol), iodine (9 mg, 34 μmol) and *N*-iodosuccinimide (51 mg, 227 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC analysis (Chiralpak AD-H, hexanes/*i*-PrOH 98:2, 1 mL/min): $t_r(e_1, \text{minor})$ = 20.69 min and $t_r(e_2, \text{major})$ = 23.69 min. Yield: 59 mg (86%) of colourless oil; *ee*: 7%; TLC (hexanes/EtOAc 1:1): R_f = 0.55, visualized with anisaldehyde; $[\alpha]_D^{20}$ = 5.70 (c = 0.02, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.31 – 7.49 (m, 5H), 3.64 (d, J = 0.9 Hz, 2H), 2.41 – 2.88 (m, 4H); ^{13}C NMR (101 MHz, CDCl_3) δ 175.3, 140.5, 128.8 (2C), 128.5, 124.8 (2C), 86.0, 33.9, 29.2, 16.3; HRMS (EI): Exact mass calculated for $\text{C}_{11}\text{H}_{11}\text{IO}_2$ $[M]^+$: 301.9804, found 301.9793.

(S)-5-(4-Chlorophenyl)-5-(iodomethyl)dihydrofuran-2(3H)-one (4b).⁷



Prepared according to the general procedure using 4-(4-chlorophenyl)pent-4-enoic acid (**3b**) (42 mg, 200 μmol), squaramide **6b** (17 mg, 30 μmol), iodine (8 mg, 30 μmol) and *N*-iodosuccinimide (45 mg, 200 μmol). Purified by column chromatography on silica (hexanes/EtOAc 4:1). The enantiomeric excess was determined by chiral HPLC

analysis (Chiralpak AD-H, hexanes/*i*PrOH 98:2, 1 mL/min): $t_r(e_1, \text{major}) = 25.97$ min and $t_r(e_2, \text{minor}) = 27.98$ min. Yield: 57 mg (85%) of colourless oil; *ee*: 14%; TLC (hexanes/EtOAc 1:1): $R_f = 0.52$, visualized with anisaldehyde; $[\alpha]_D = 0.0$ ($c = 0.21$, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 7.30 – 7.43 (m, 4H), 3.59 (s, 2H), 2.65 – 2.88 (m, 2H), 2.43 – 2.65 (m, 2H); ^{13}C NMR (101 MHz, CDCl_3) δ 174.9, 139.1, 134.6, 129.0 (2C), 126.3 (2C), 85.6, 33.8, 29.1, 15.7; HRMS (EI): Exact mass calculated for $\text{C}_{11}\text{H}_{10}\text{ClIO}_2$ $[M]^+$: 335.9414, found 335.9407.

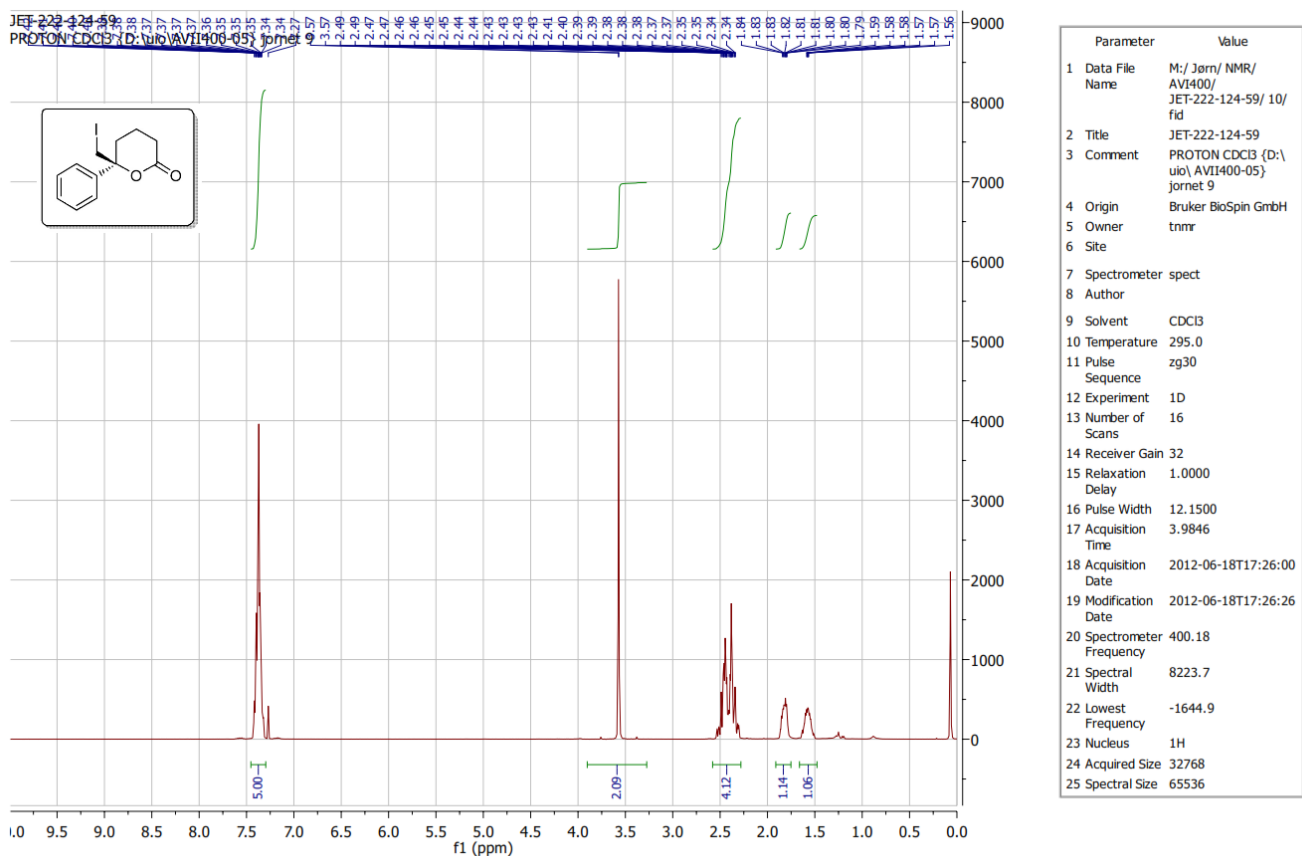


Figure S-37 ^1H -NMR spectrum of compound 2a.

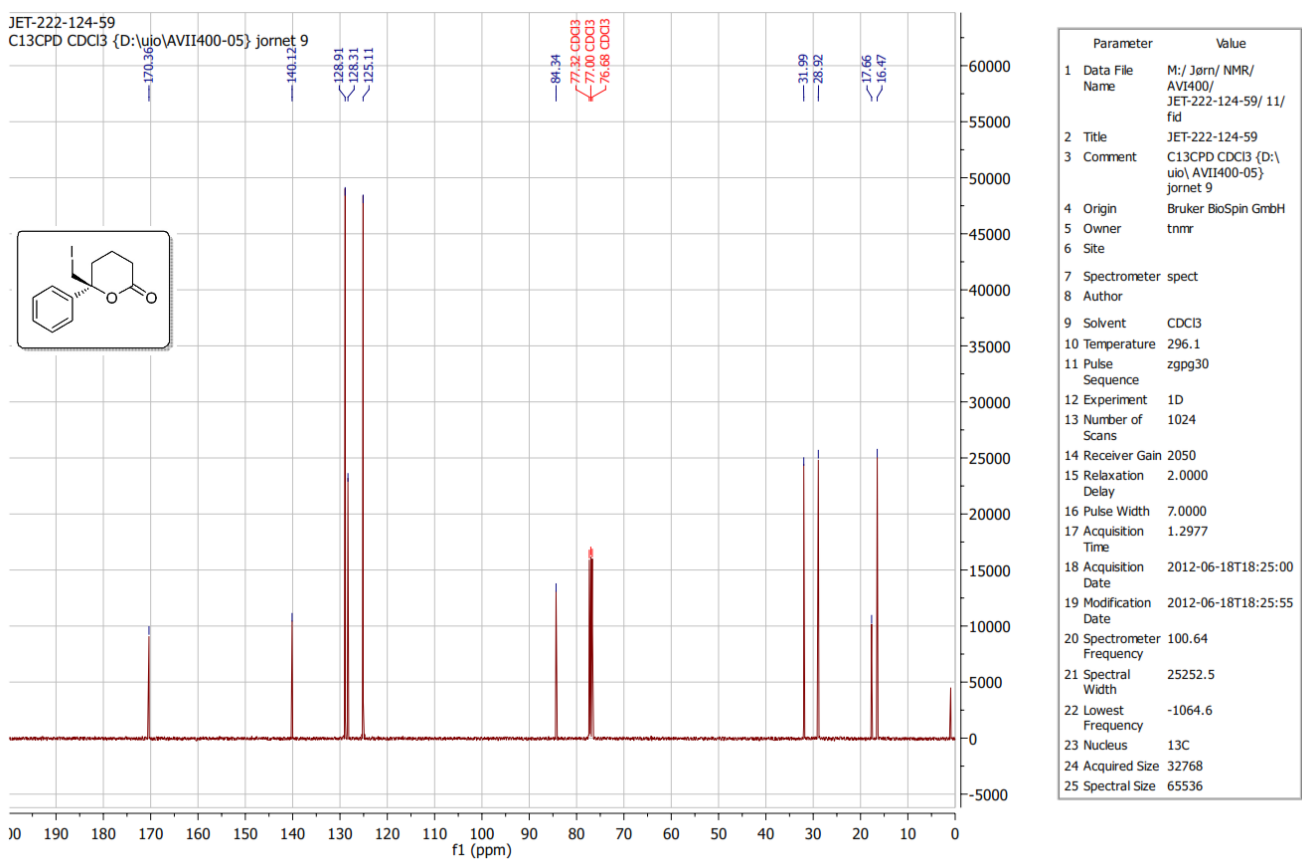


Figure S-38 ^{13}C -NMR spectrum of compound 2a.

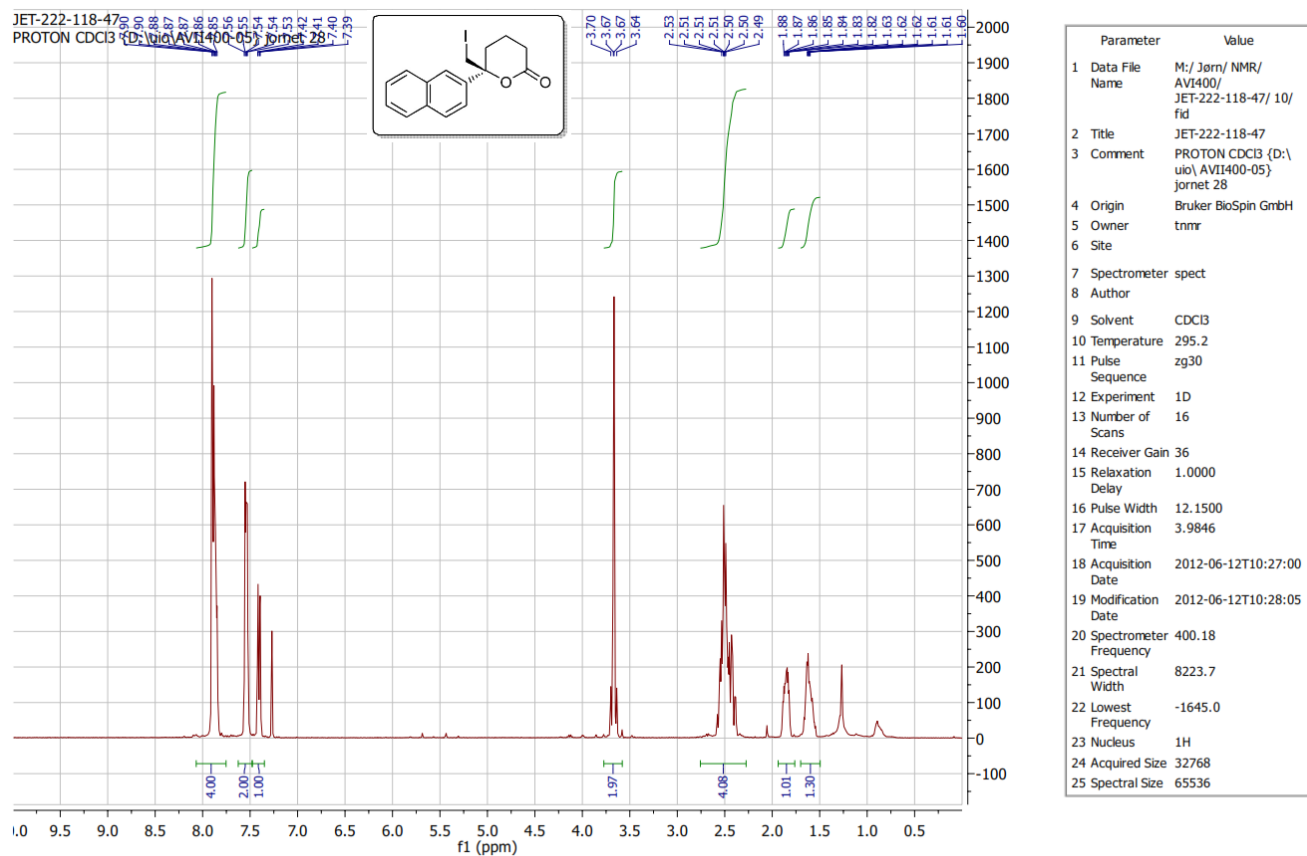


Figure S-39 ¹H-NMR spectrum of compound 2b.

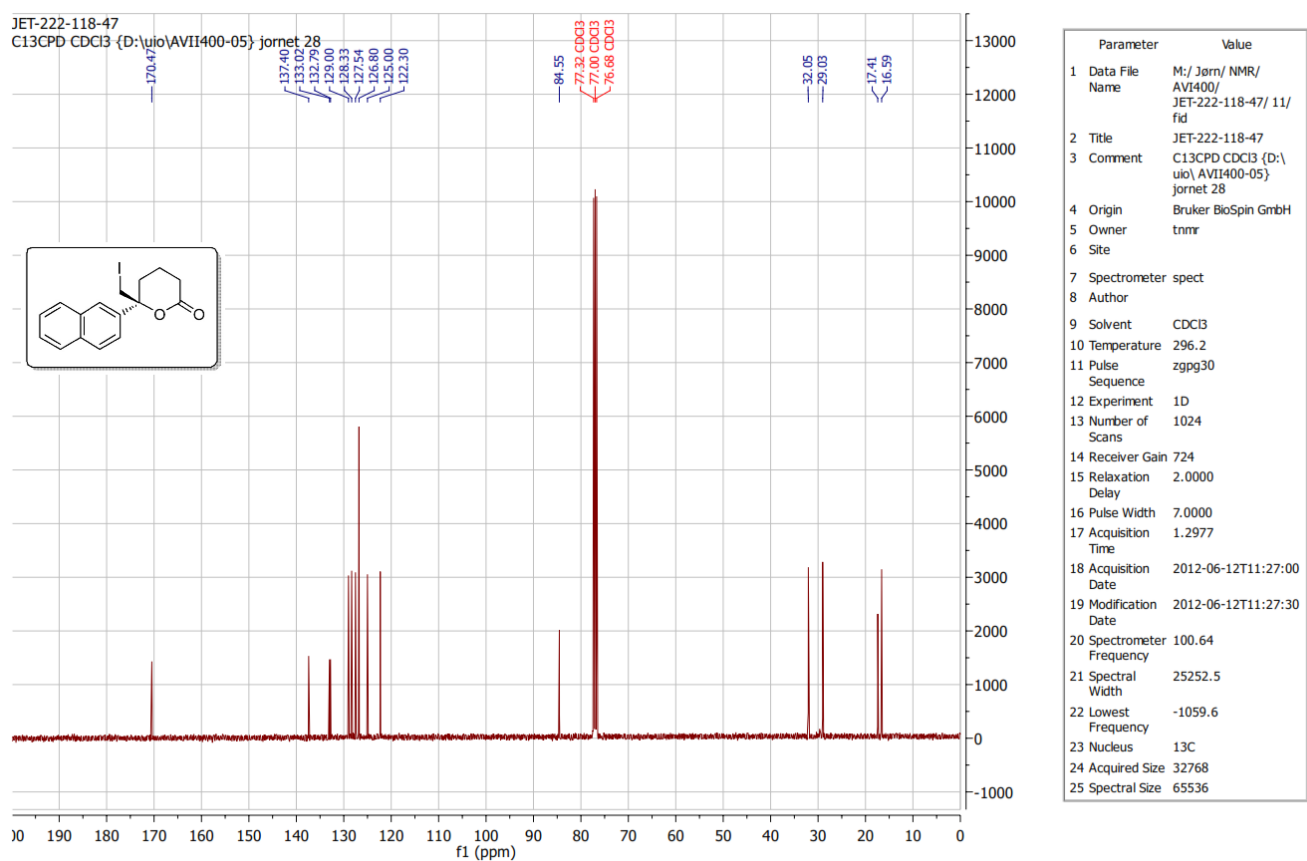


Figure S-40 ¹³C-NMR spectrum of compound 2b.

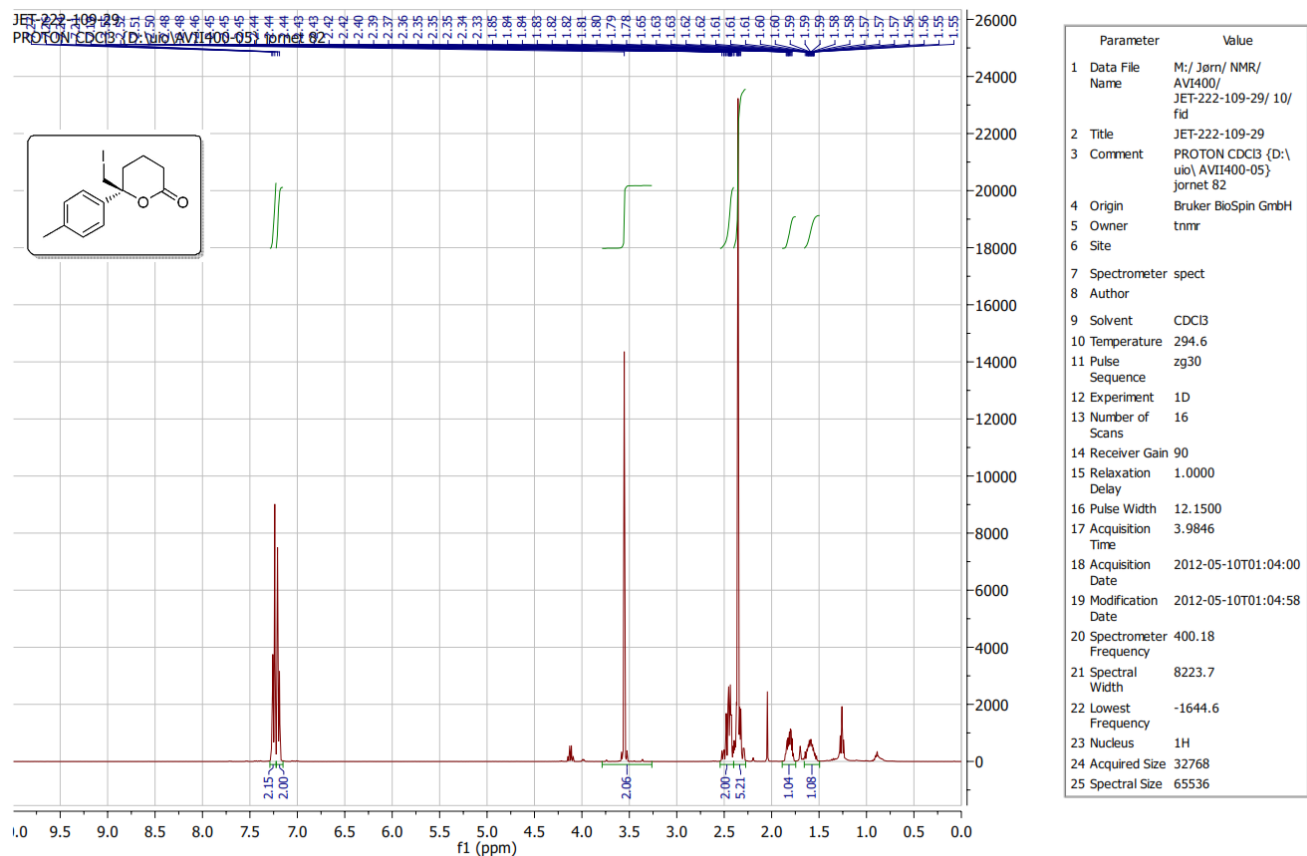


Figure S-41 ^1H -NMR spectrum of compound 2c.

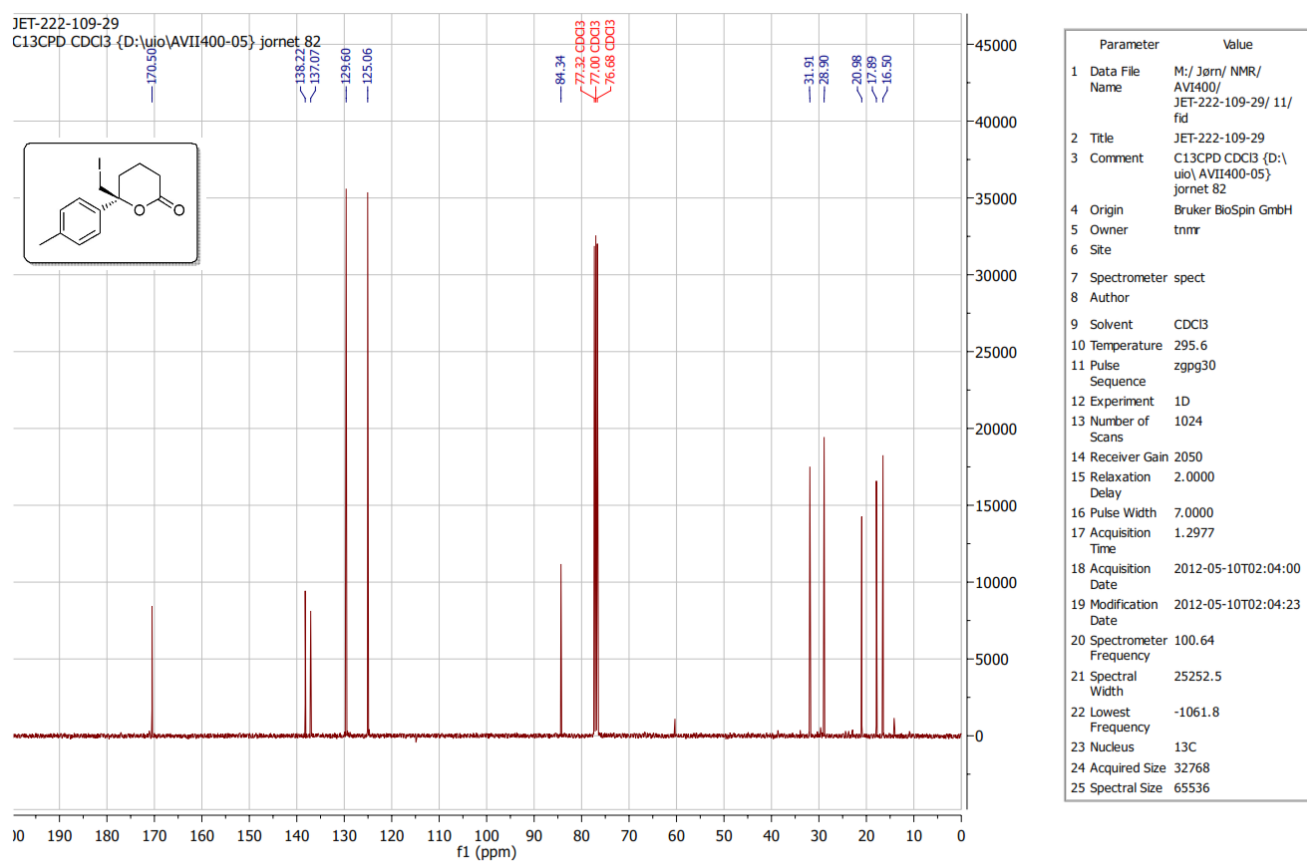


Figure S-42 ^{13}C -NMR spectrum of compound 2c.

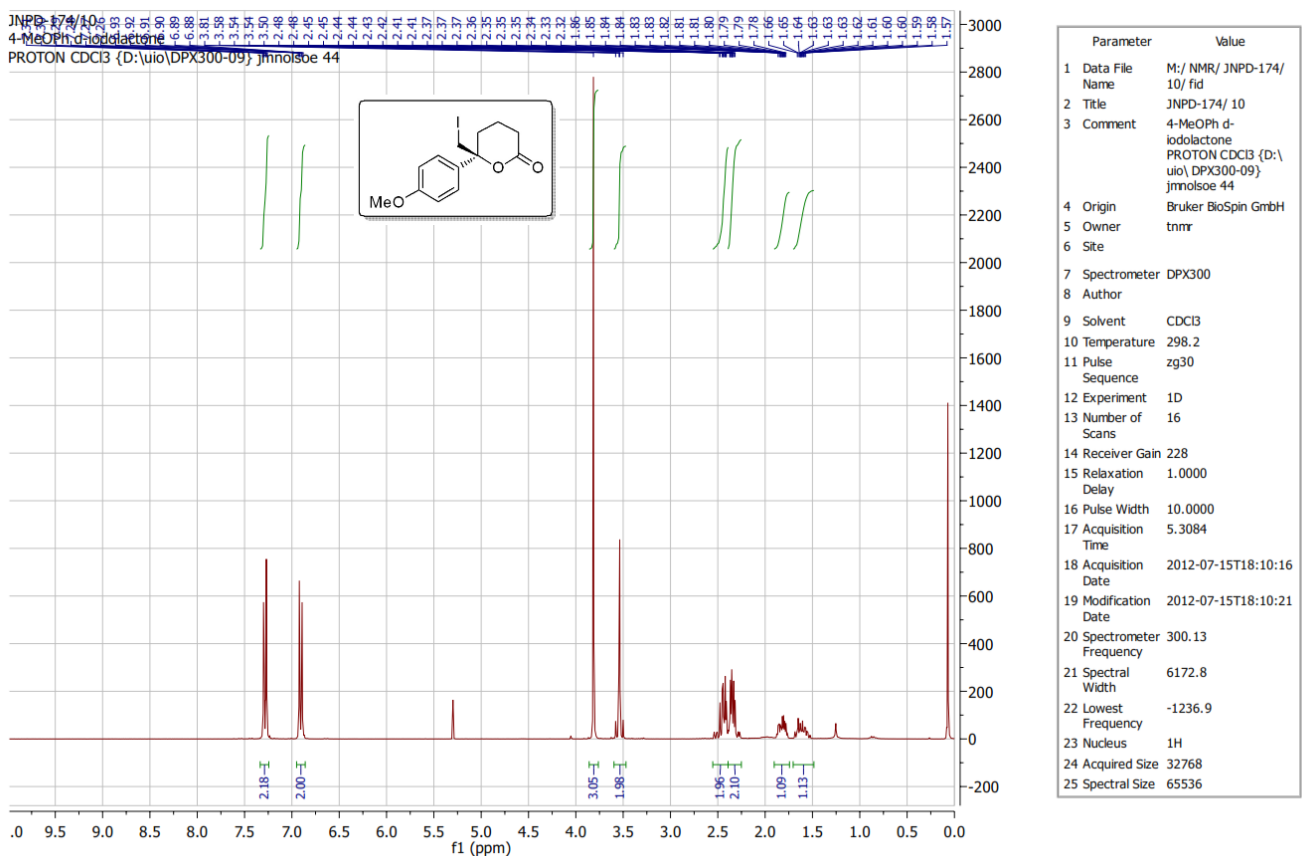


Figure S-43 ^1H -NMR spectrum of compound **2d**.

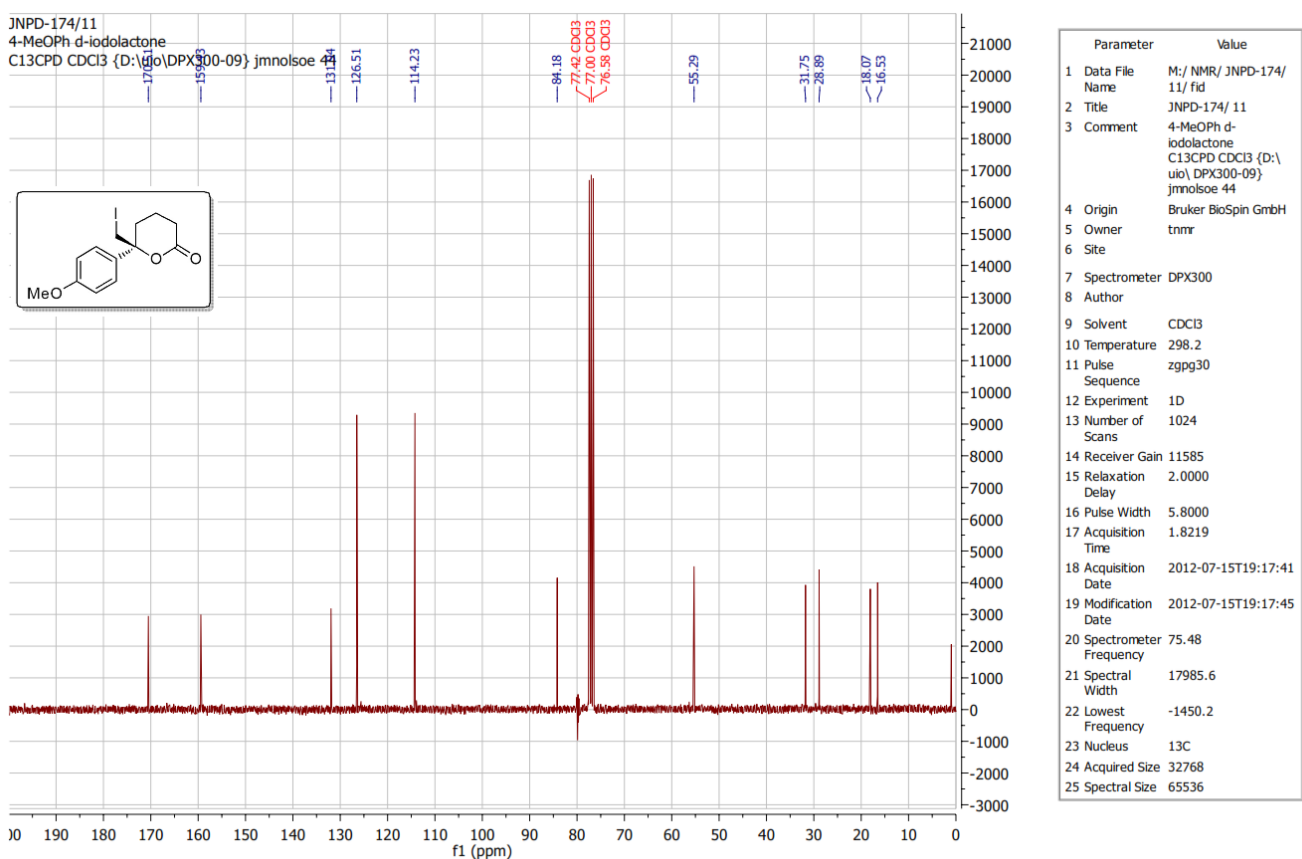


Figure S-44 ^{13}C -NMR spectrum of compound **2d**.

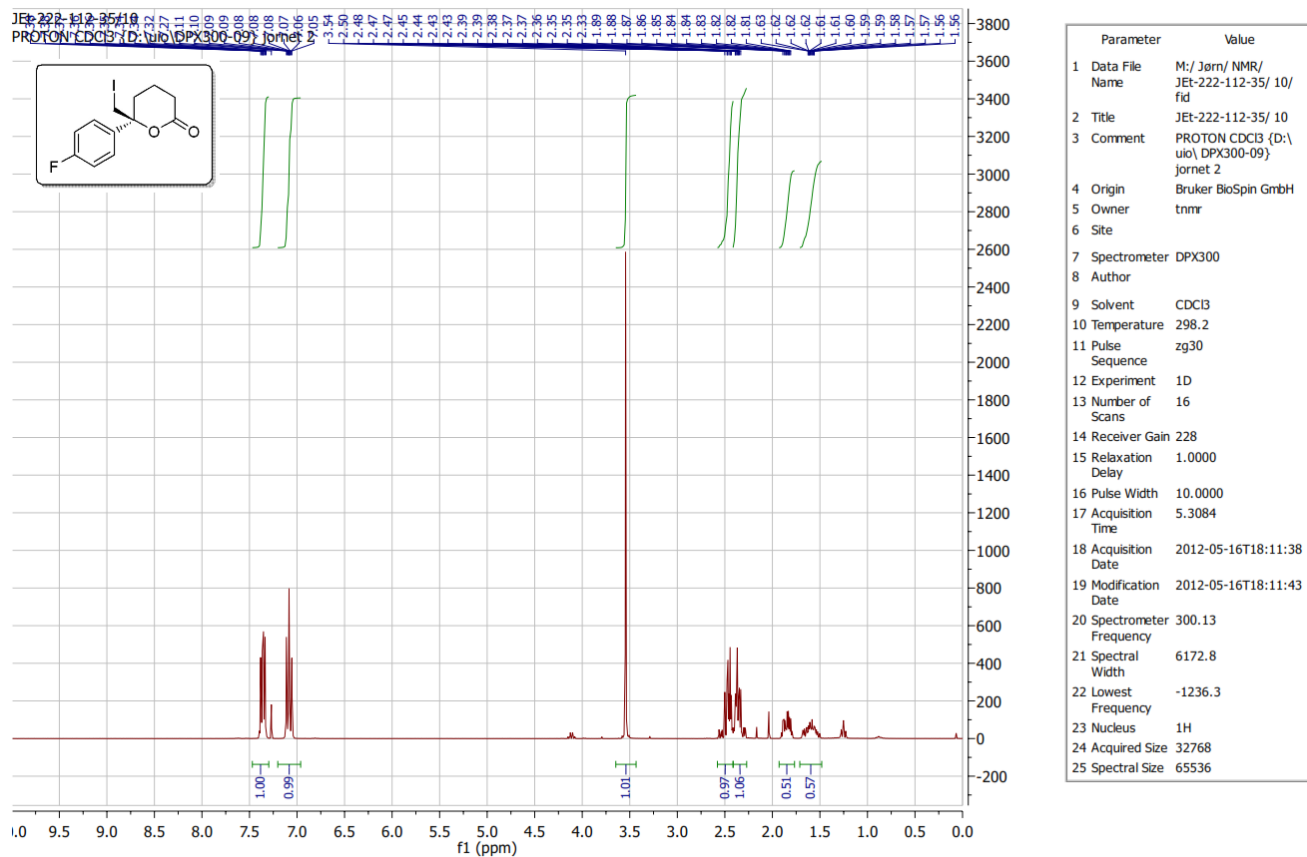


Figure S-45 ^1H -NMR spectrum of compound 2e.

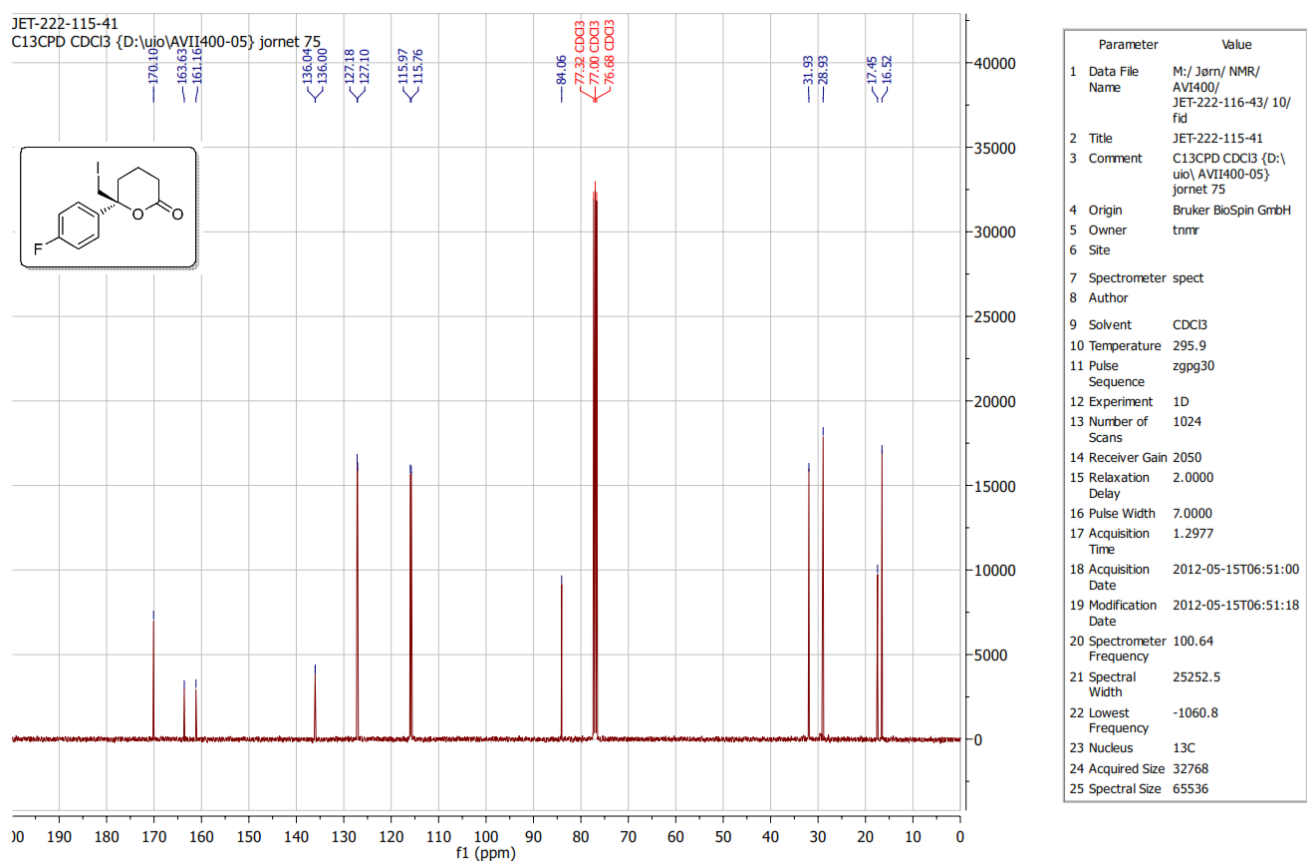


Figure S-46 ^{13}C -NMR spectrum of compound 2e.

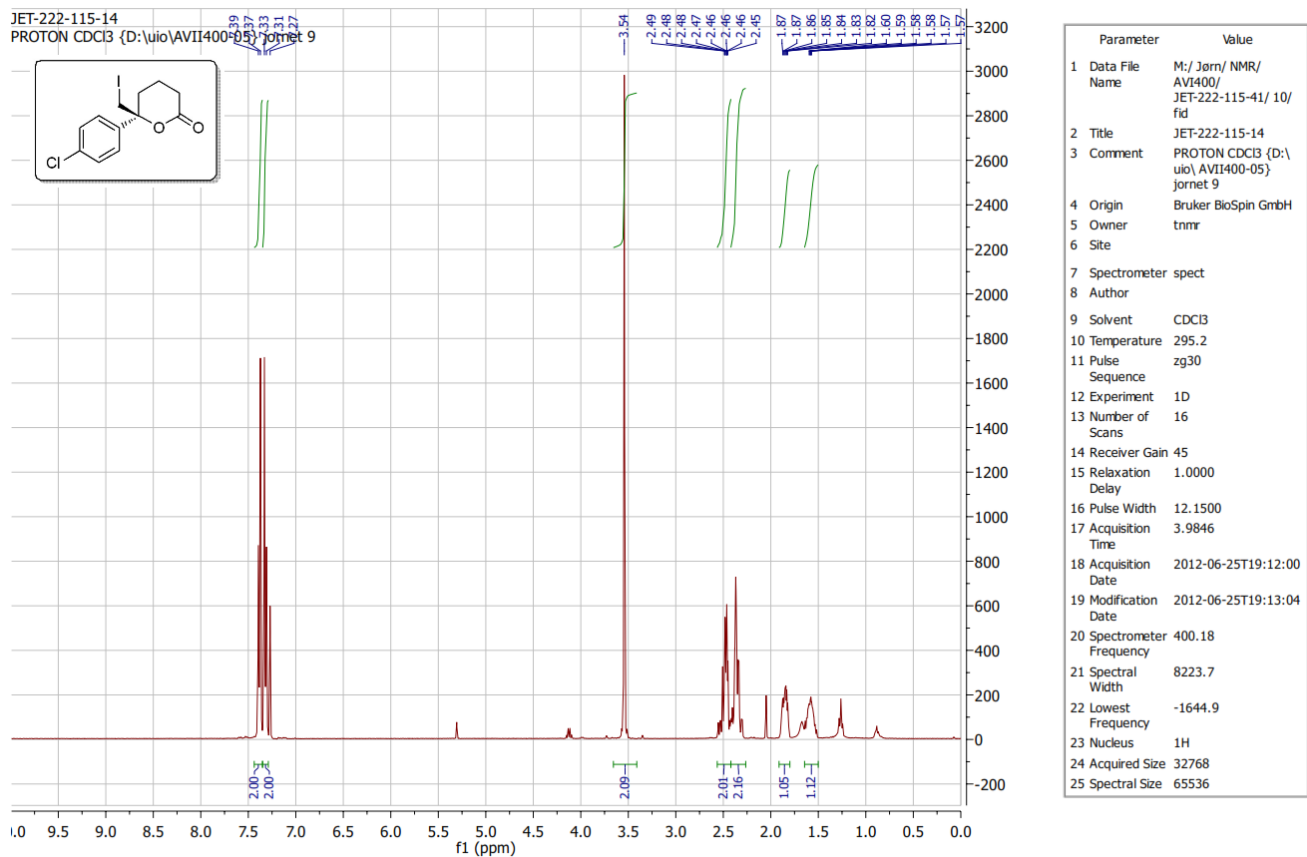


Figure S-47 ^1H -NMR spectrum of compound 2f.

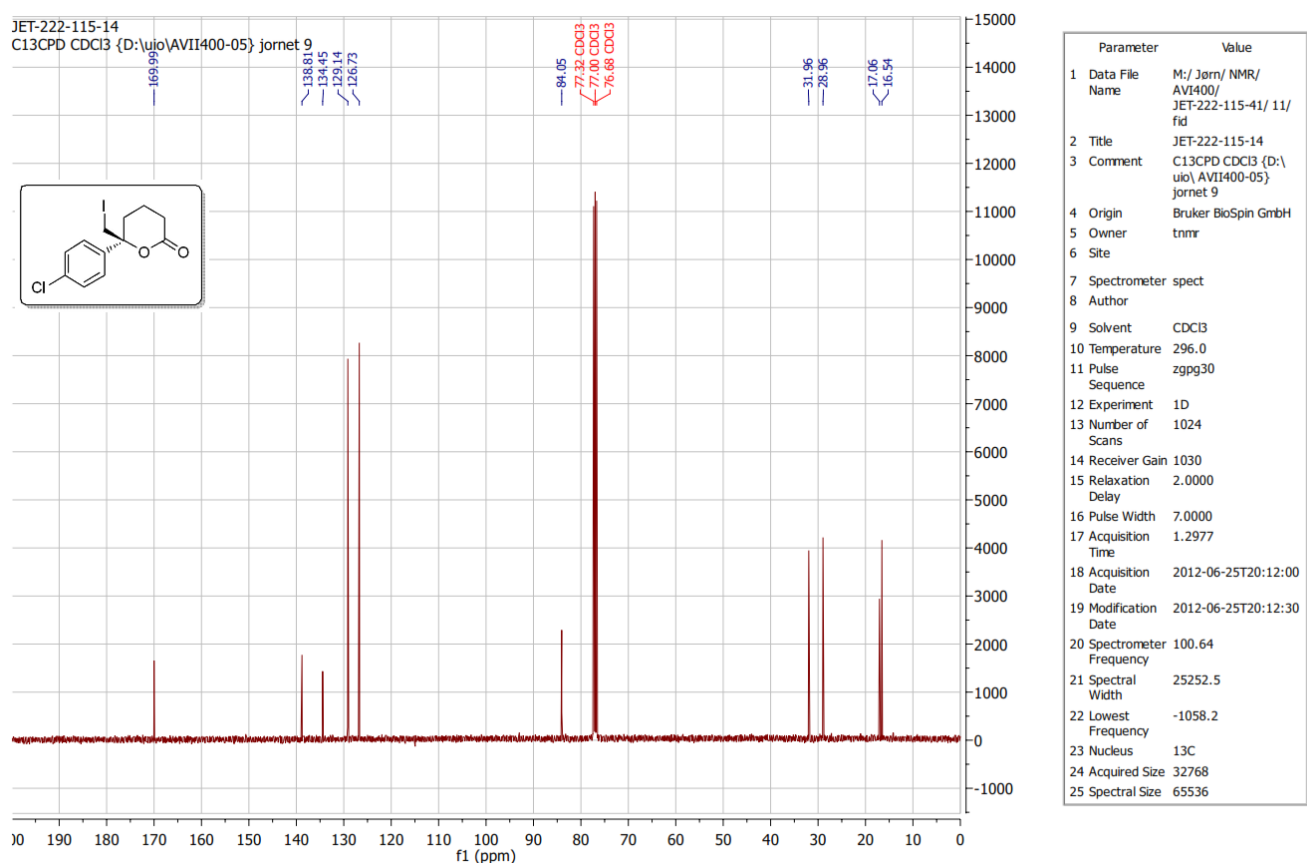


Figure S-48 ^{13}C -NMR spectrum of compound 2f.

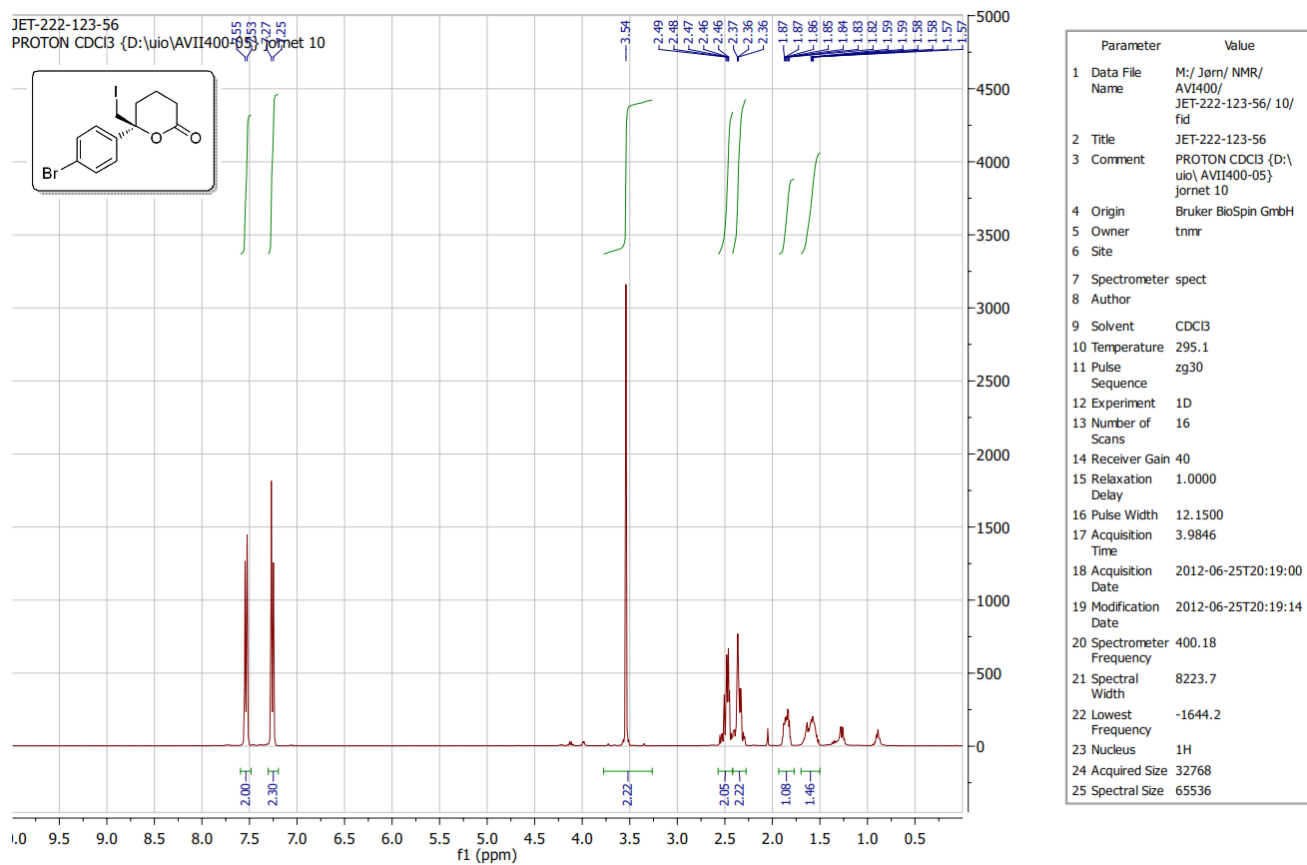


Figure S-49 ¹H-NMR spectrum of compound 2g.

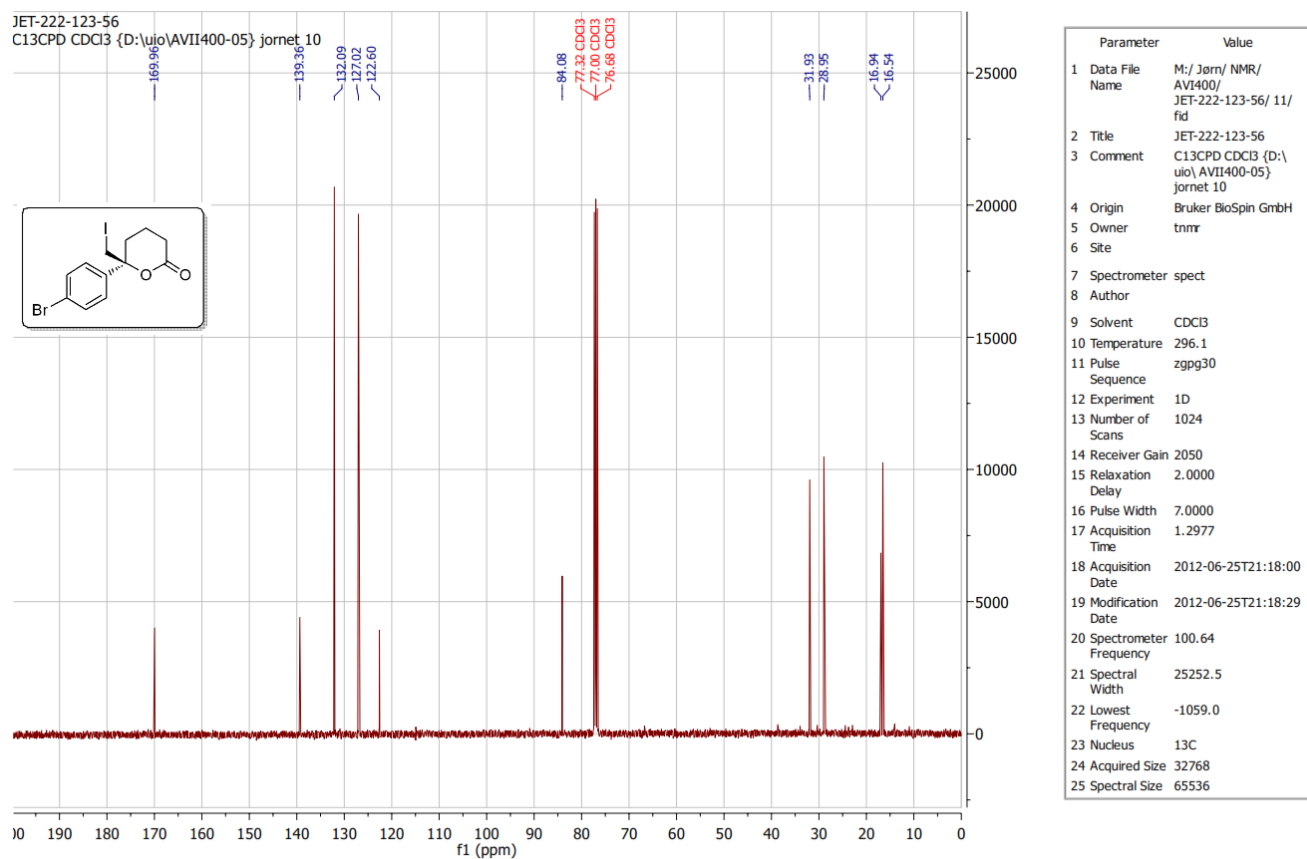


Figure S-50 ¹³C-NMR spectrum of compound 2g.

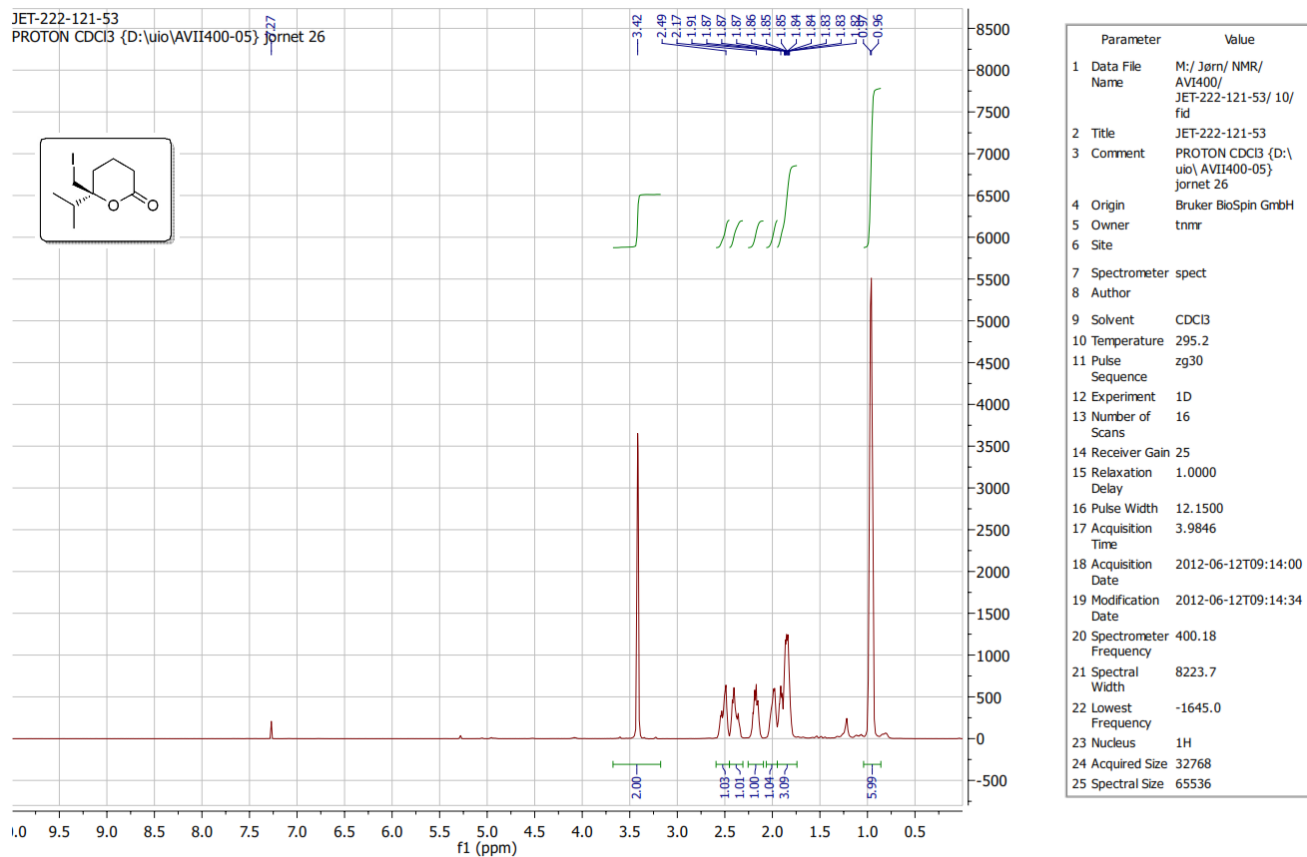


Figure S-51 ^1H -NMR spectrum of compound 2h.

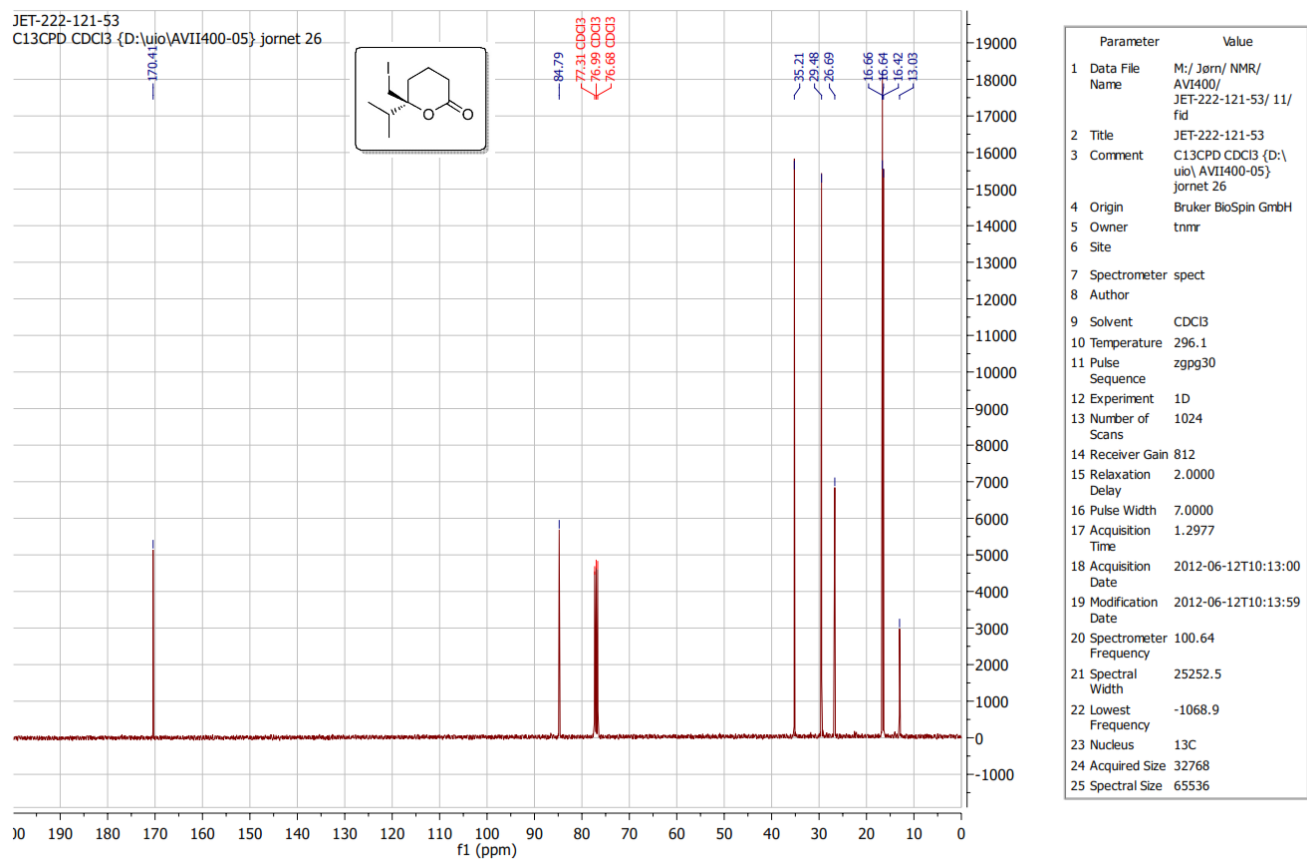


Figure S-52 ^{13}C -NMR spectrum of compound 2h.

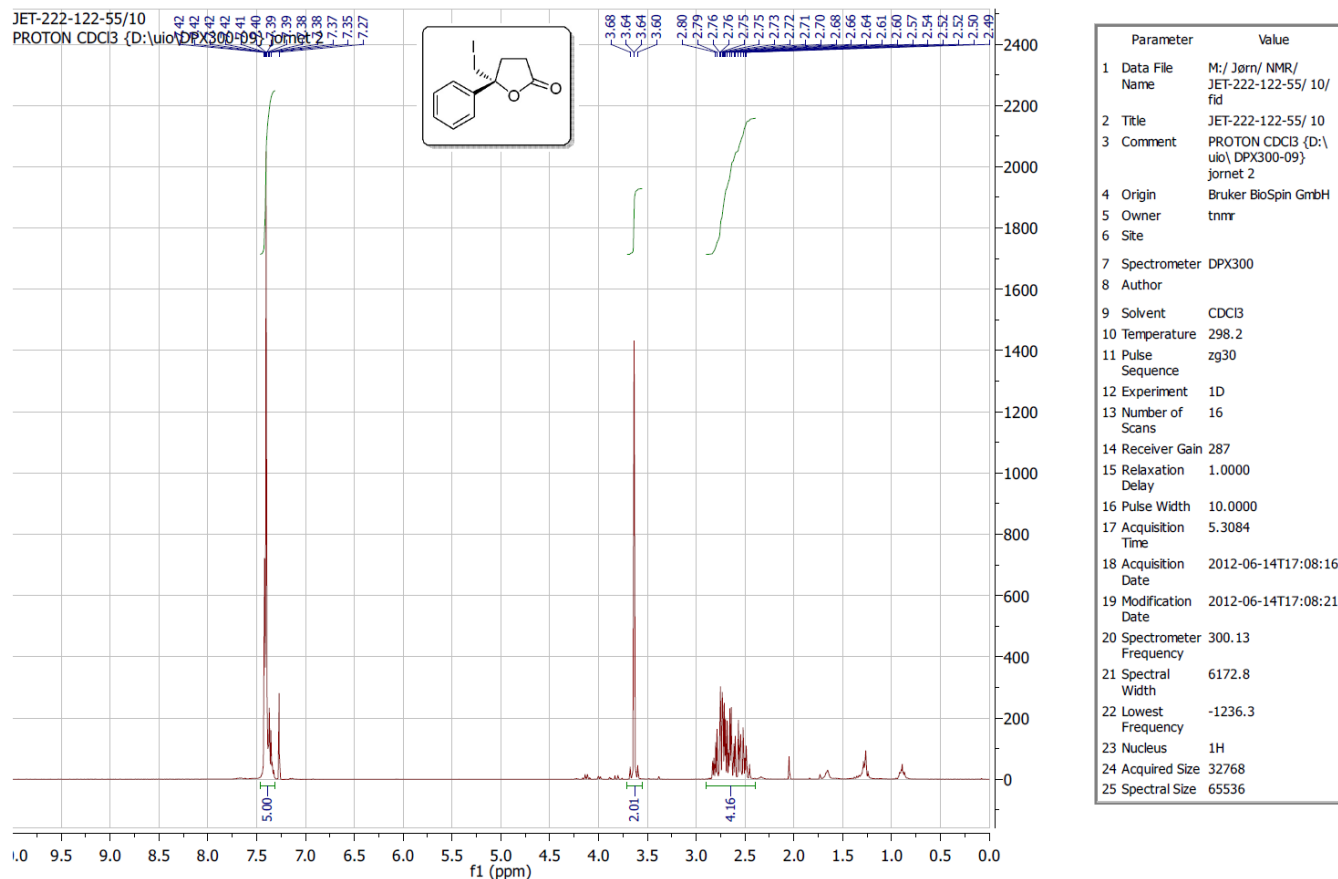


Figure S-53 ^1H -NMR spectrum of compound 4a.

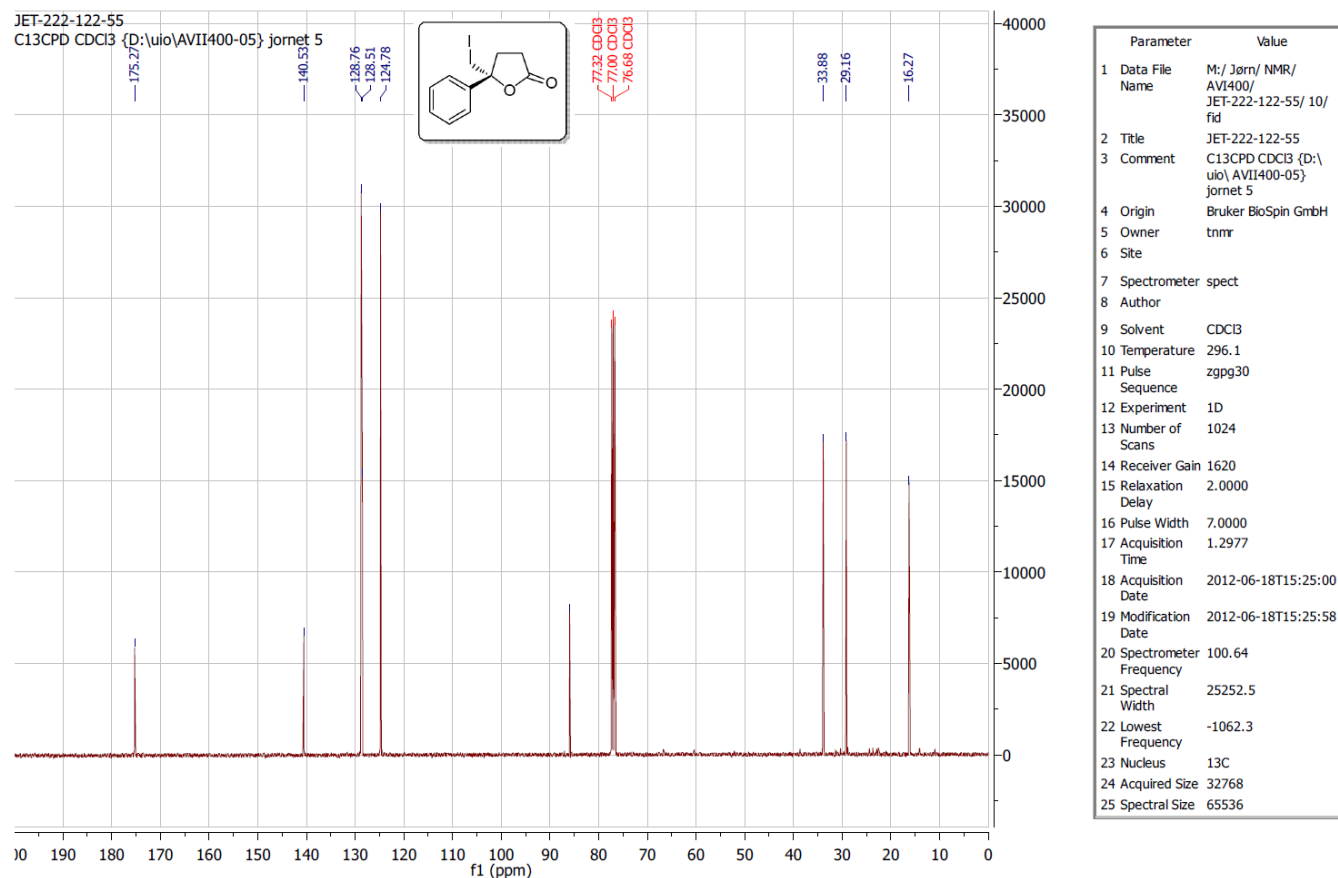


Figure S-54 ^{13}C -NMR spectrum of compound 4a.

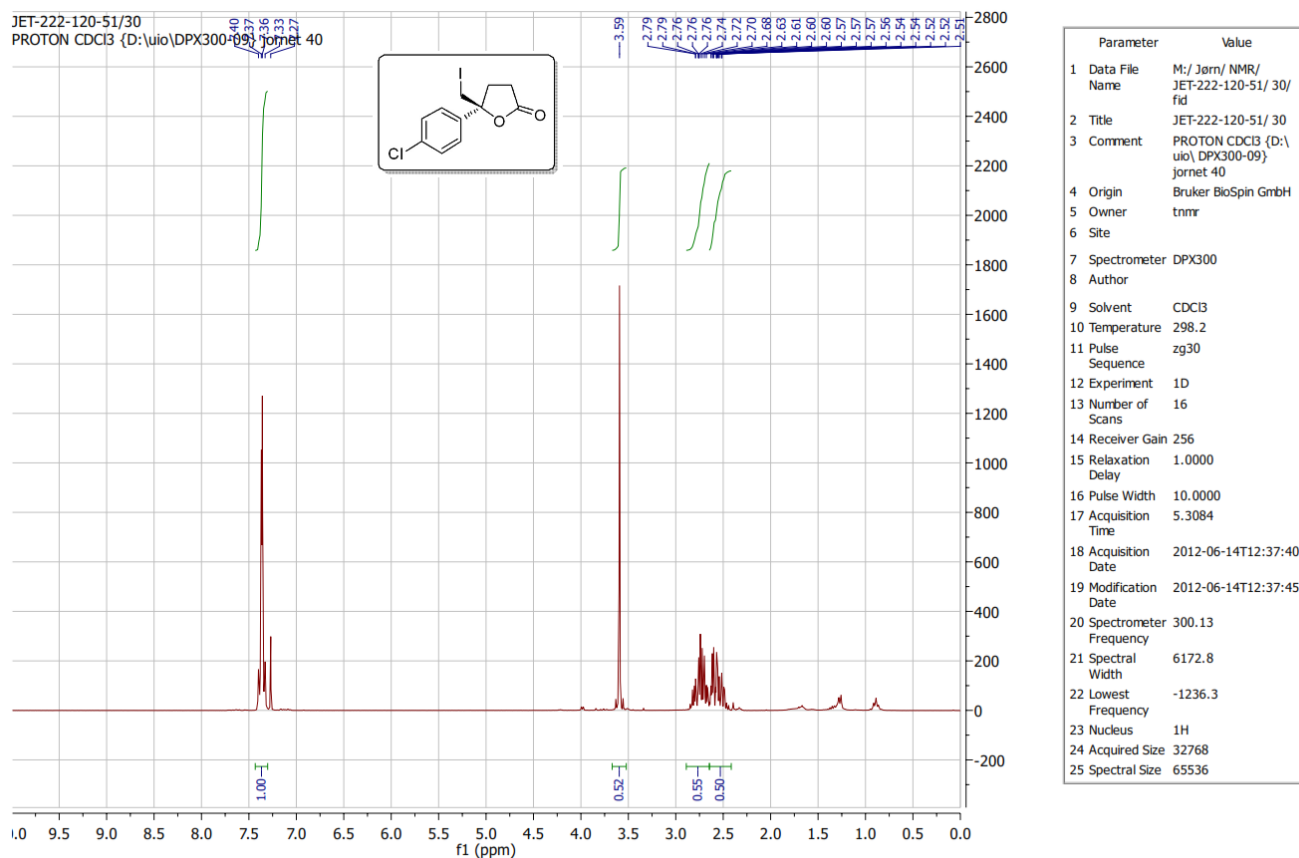


Figure S-55 ¹H-NMR spectrum of compound 4b.

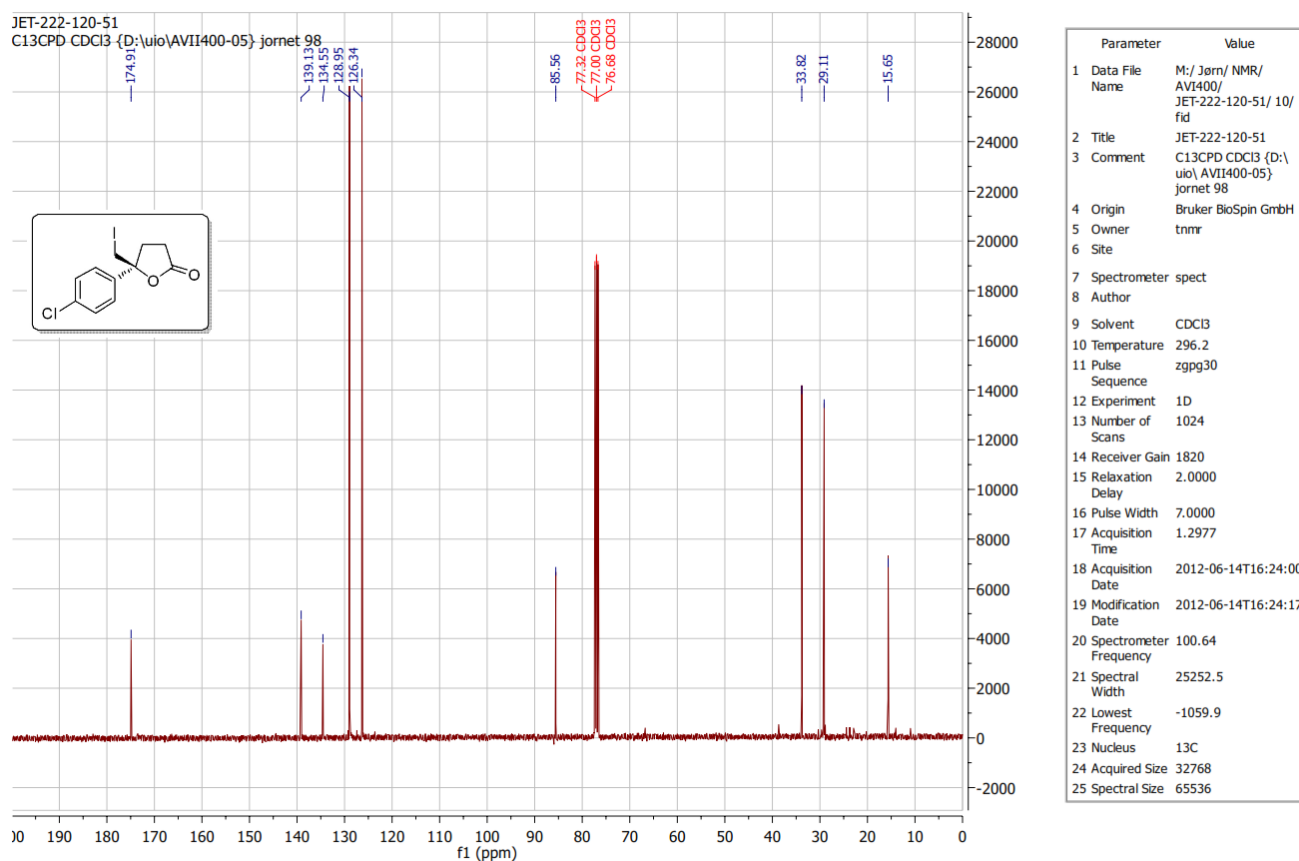


Figure S-56 ¹³C-NMR spectrum of compound 4b.

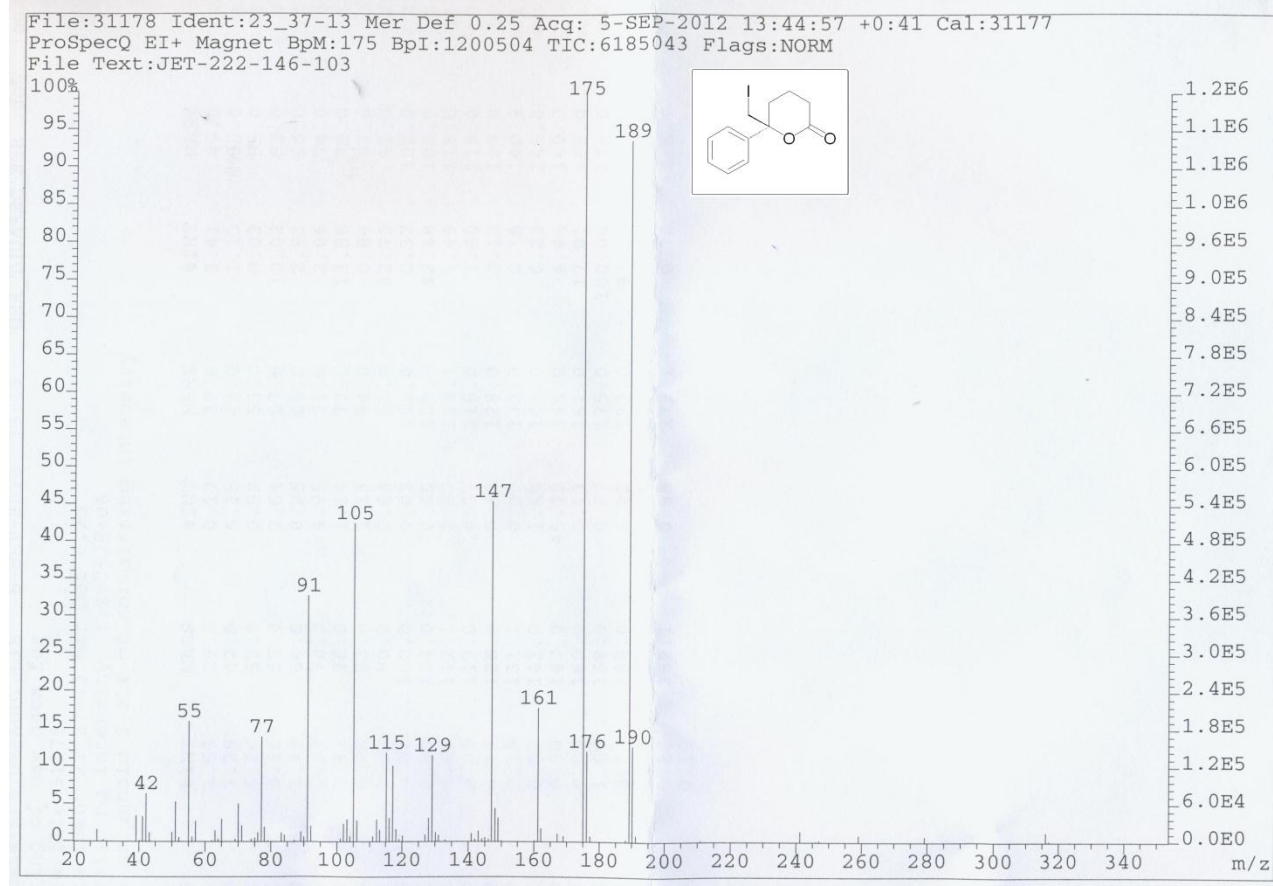


Figure S-57 MS spectrum of compound 2a.

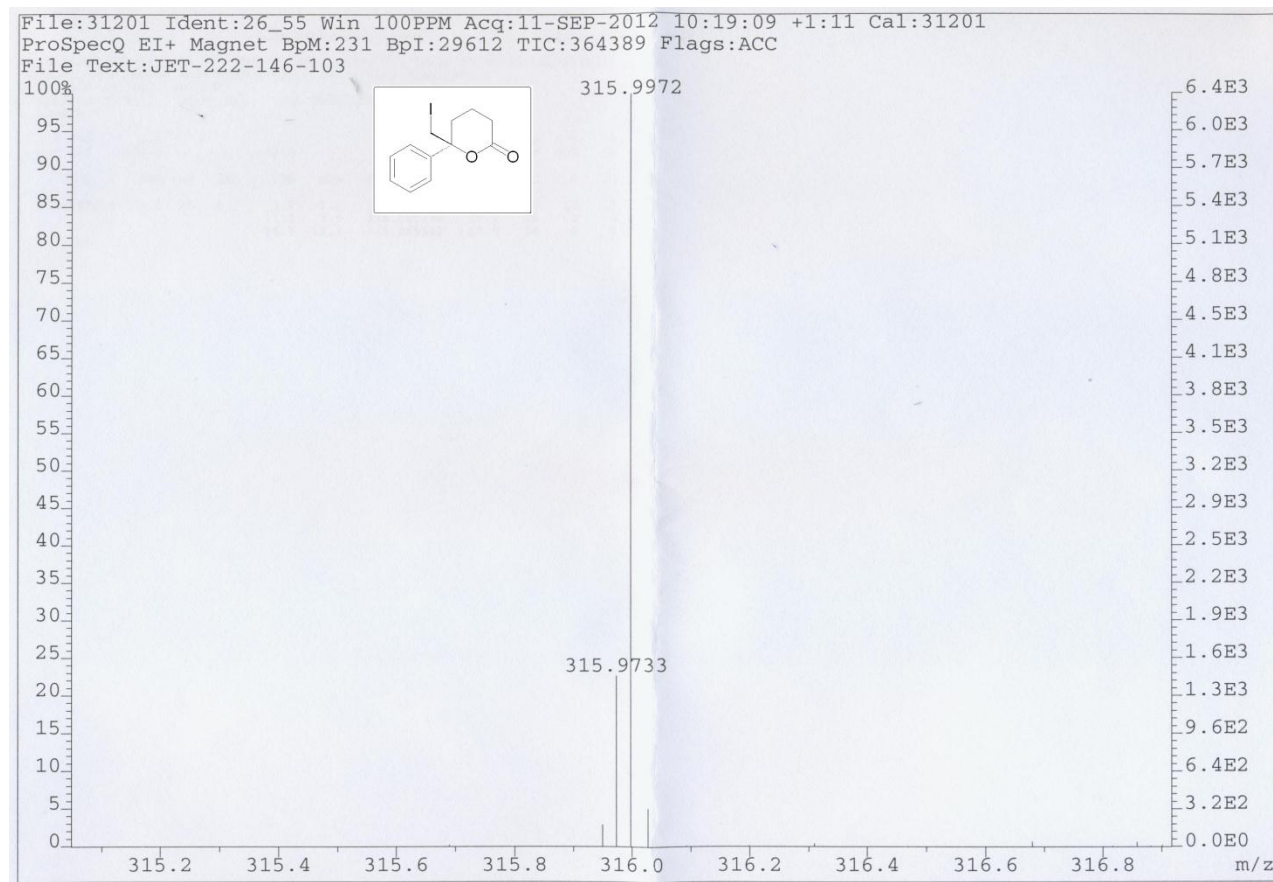


Figure S-58 HRMS spectrum of compound 2a.

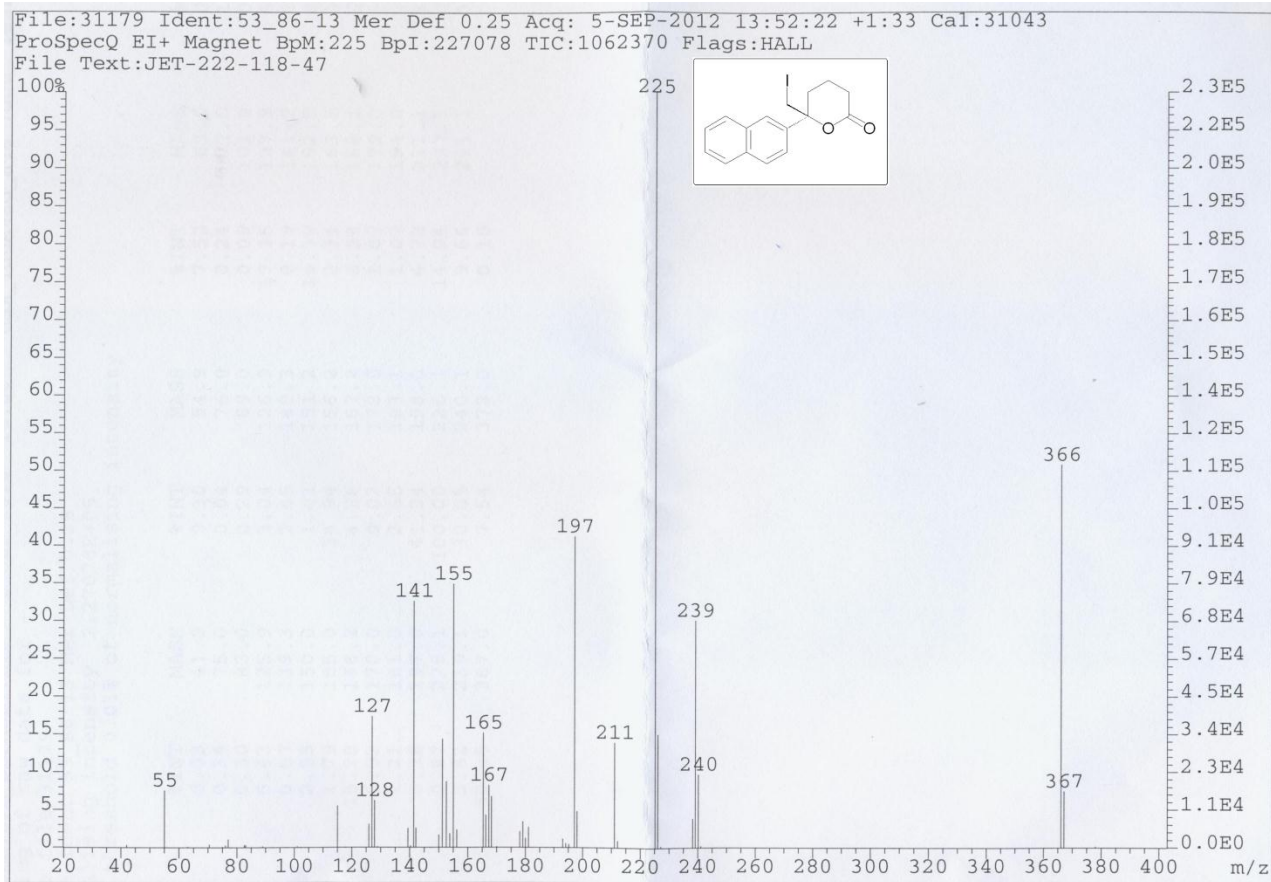


Figure S-59 MS spectrum of compound 2b.

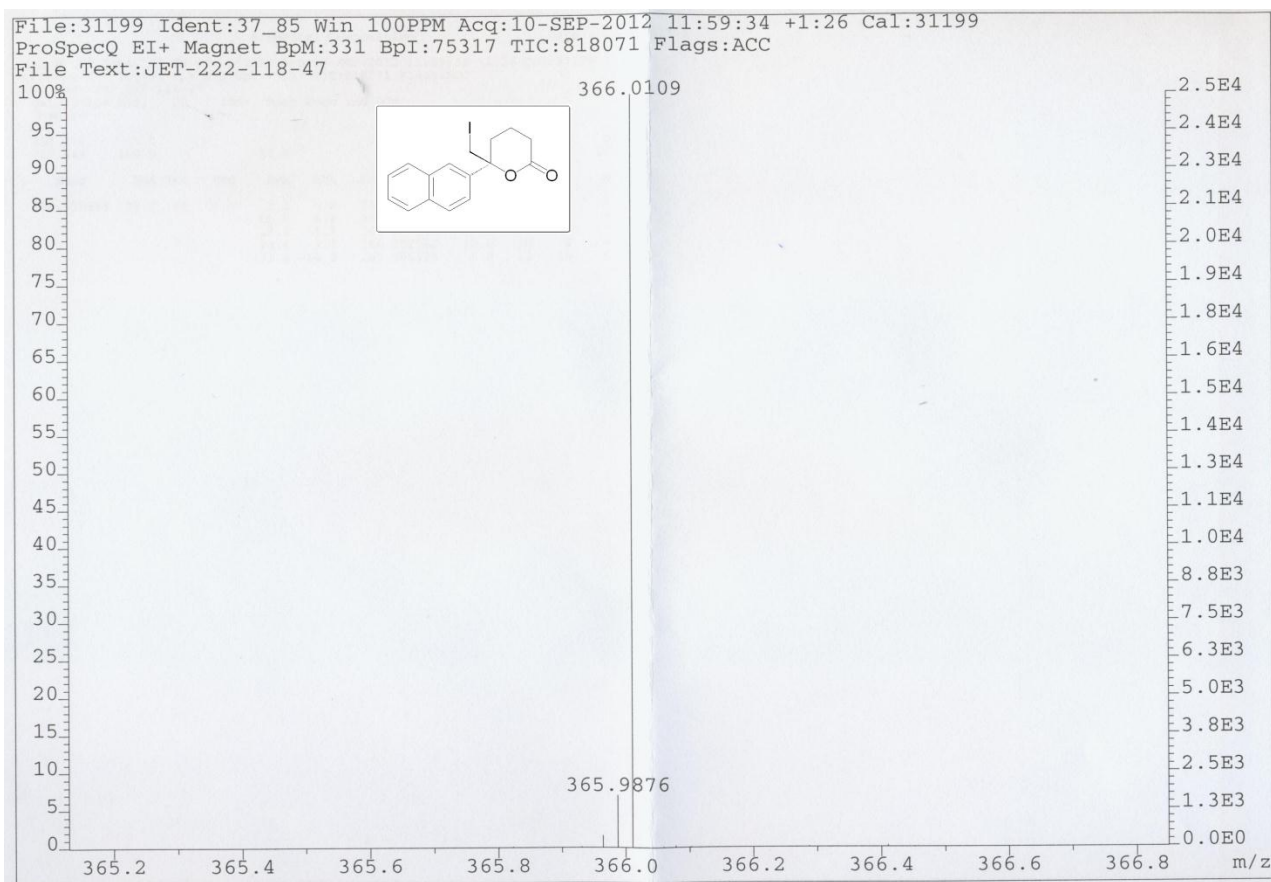


Figure S-60 HRMS spectrum of compound 2b.

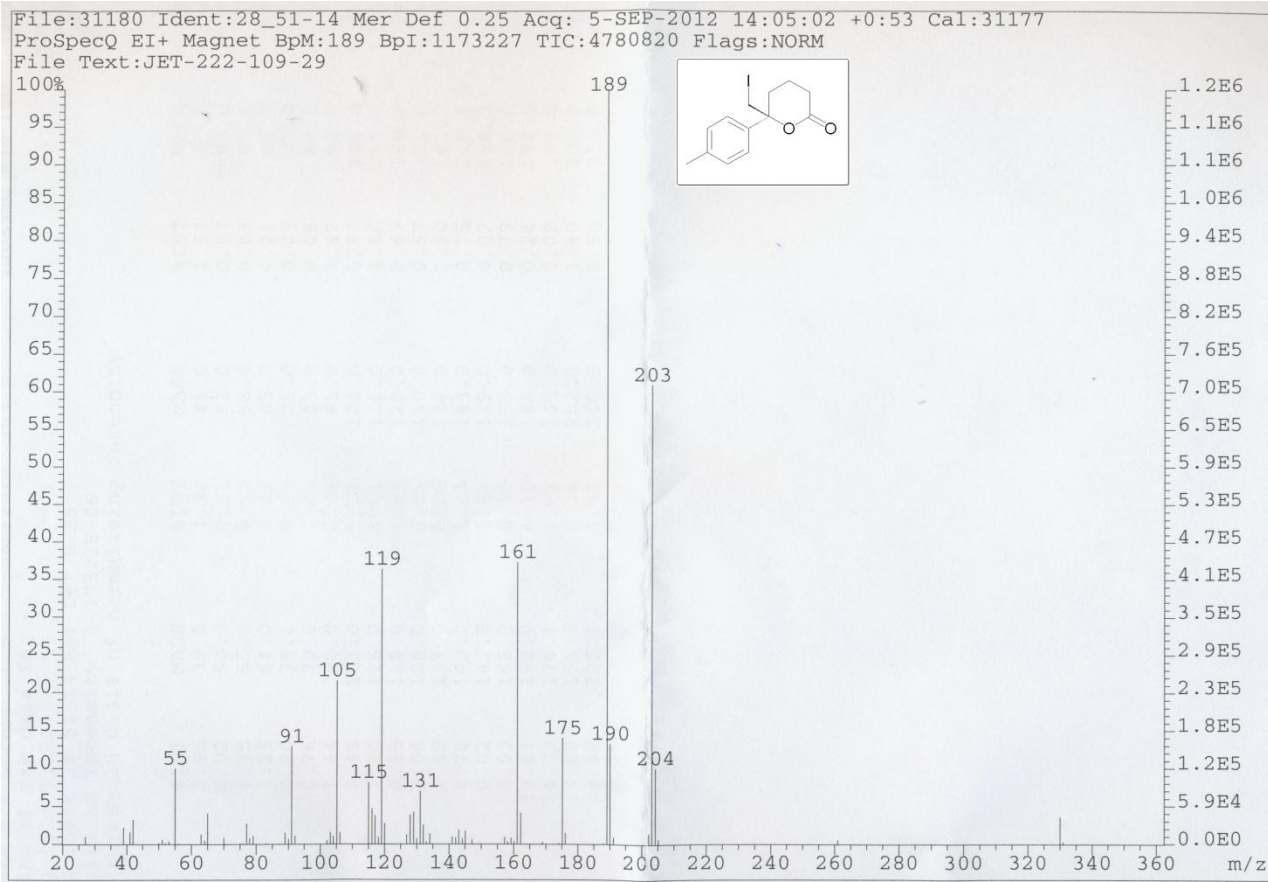


Figure S-61 MS spectrum of compound 2c.

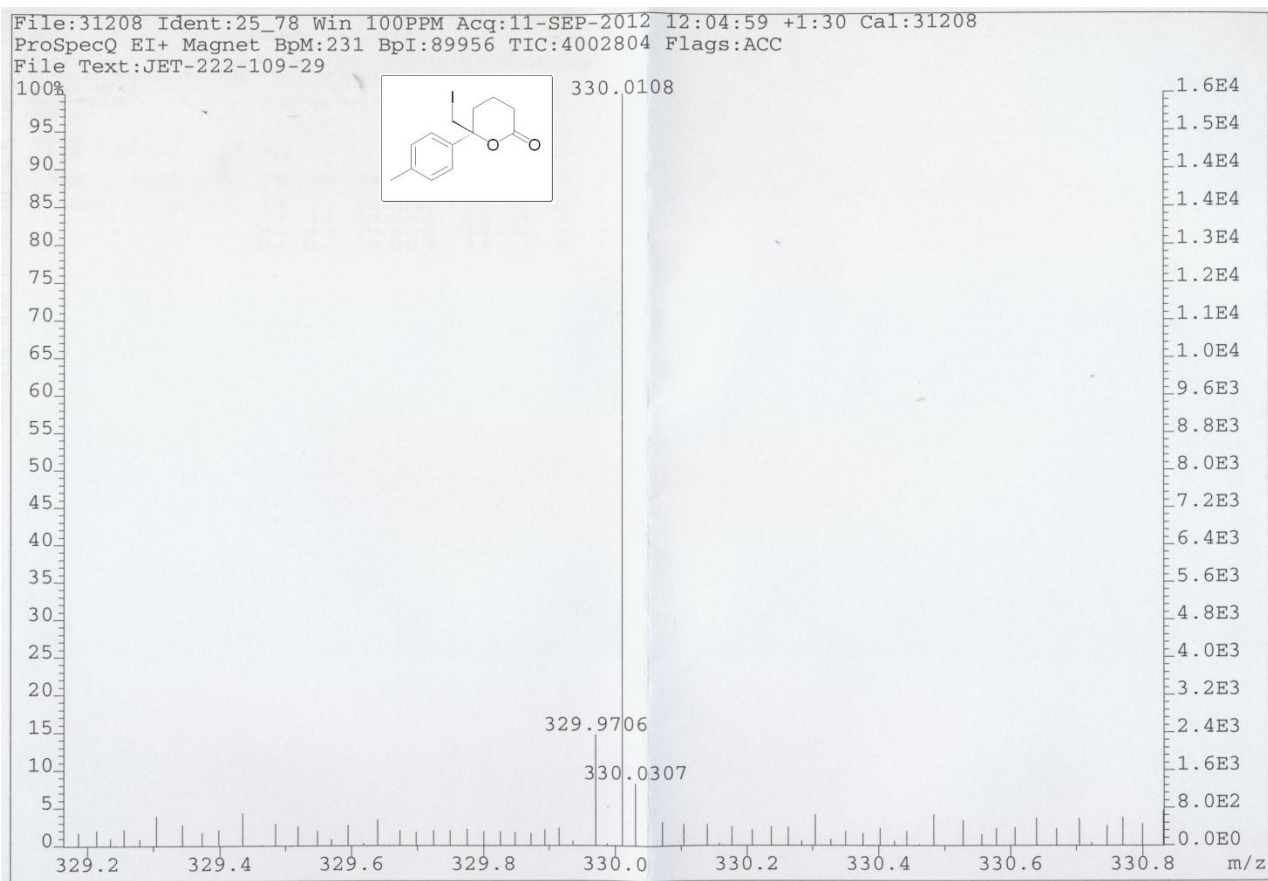


Figure S-62 HRMS spectrum of compound 2c.

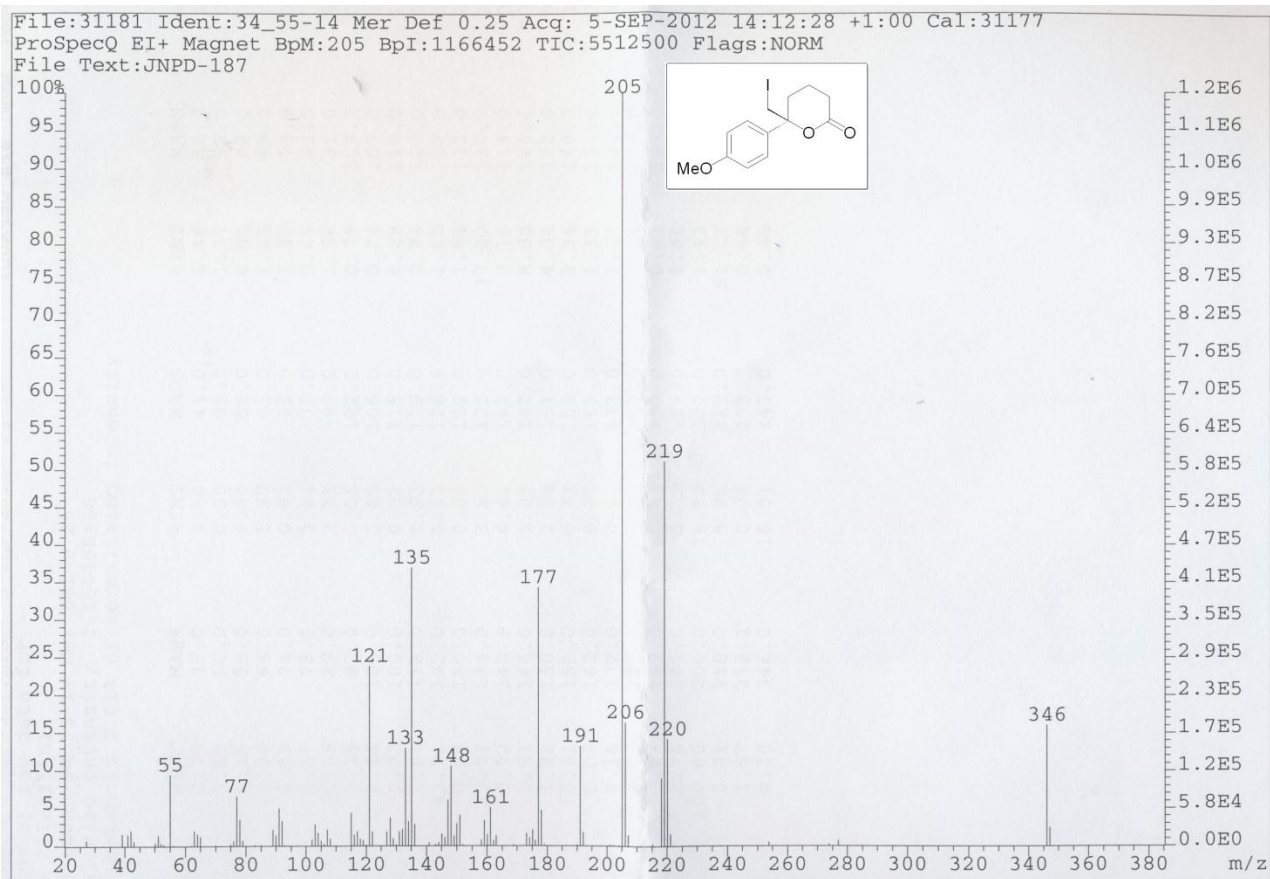


Figure S-63 MS spectrum of compound 2d.

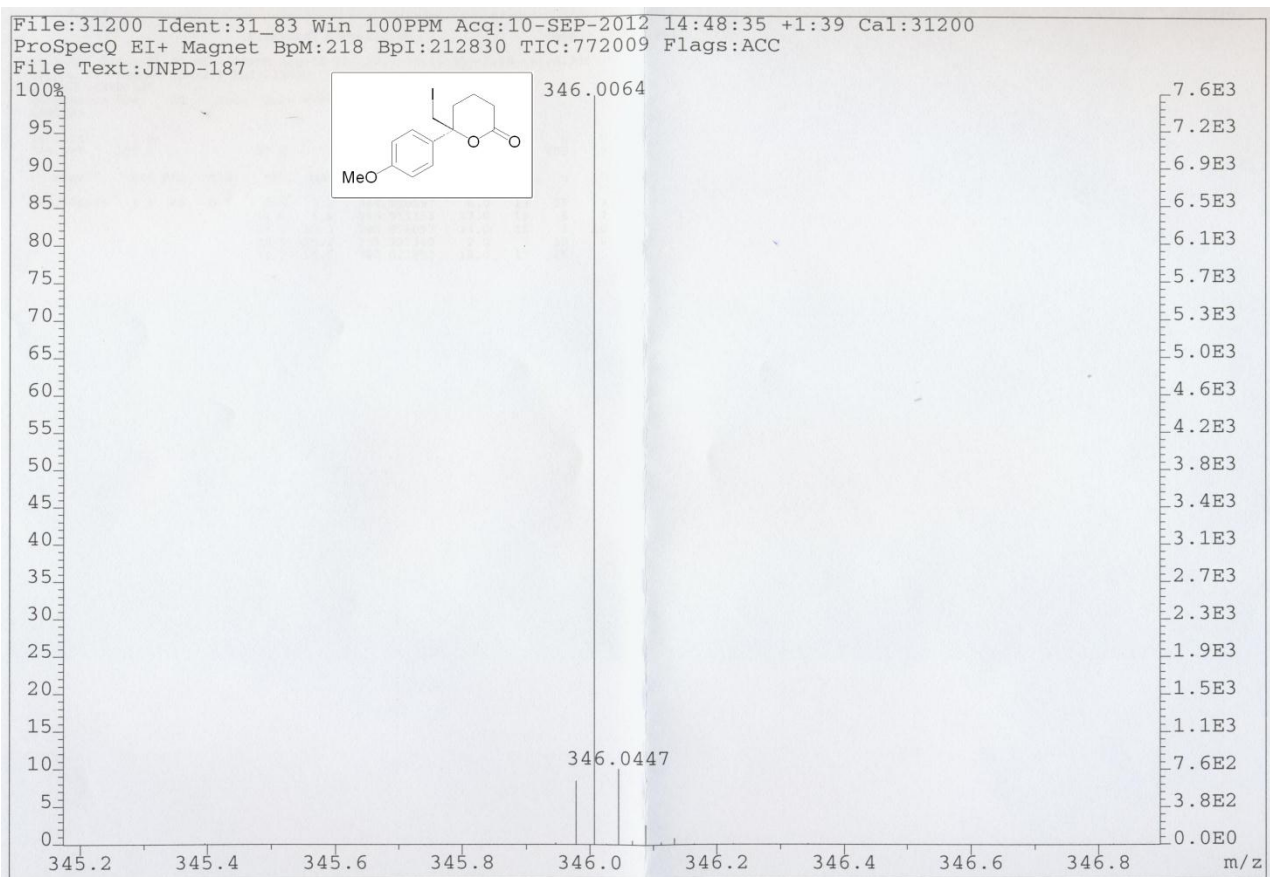


Figure S-64 HRMS spectrum of compound 2d.

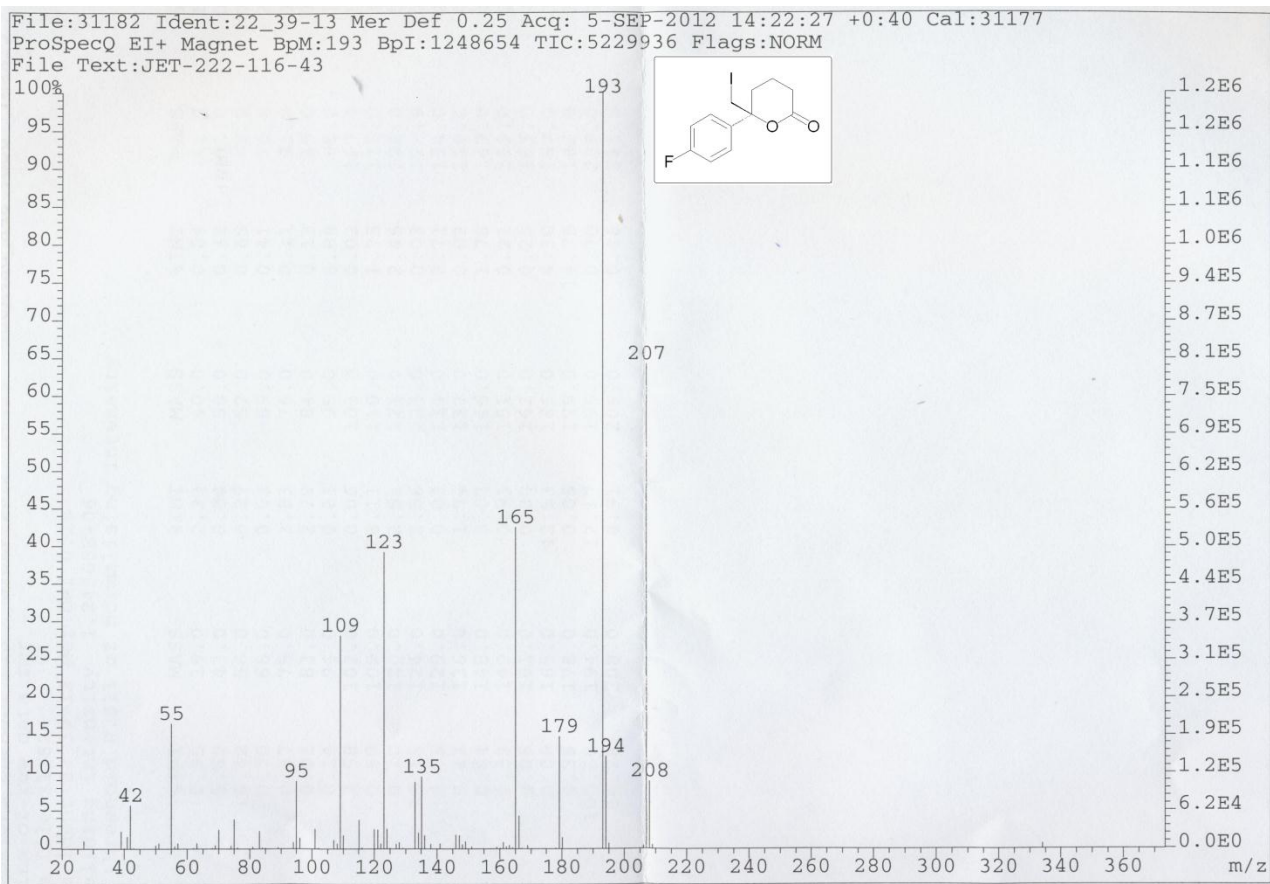


Figure S-65 MS spectrum of compound 2e.

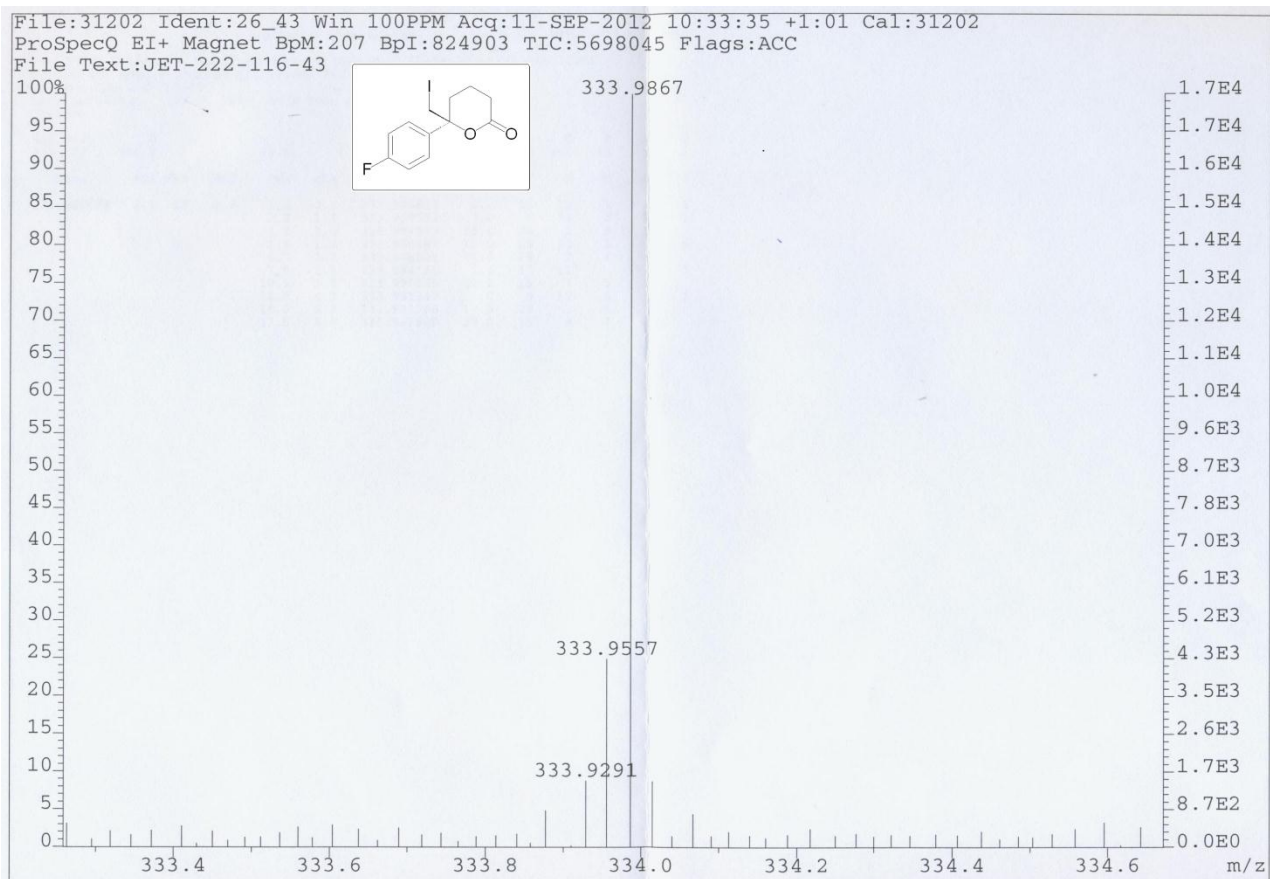


Figure S-66 HRMS spectrum of compound 2e.

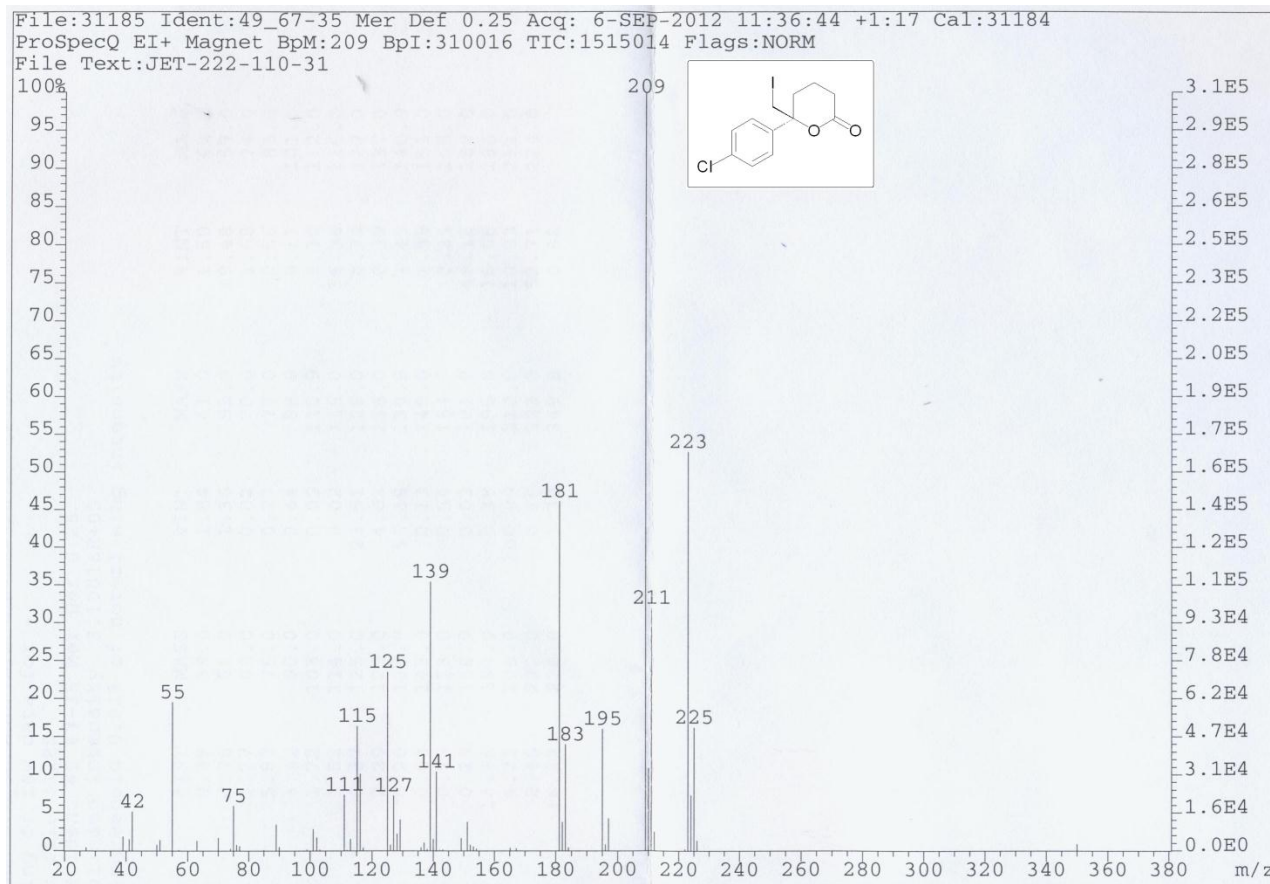


Figure S-67 MS spectrum of compound 2f.

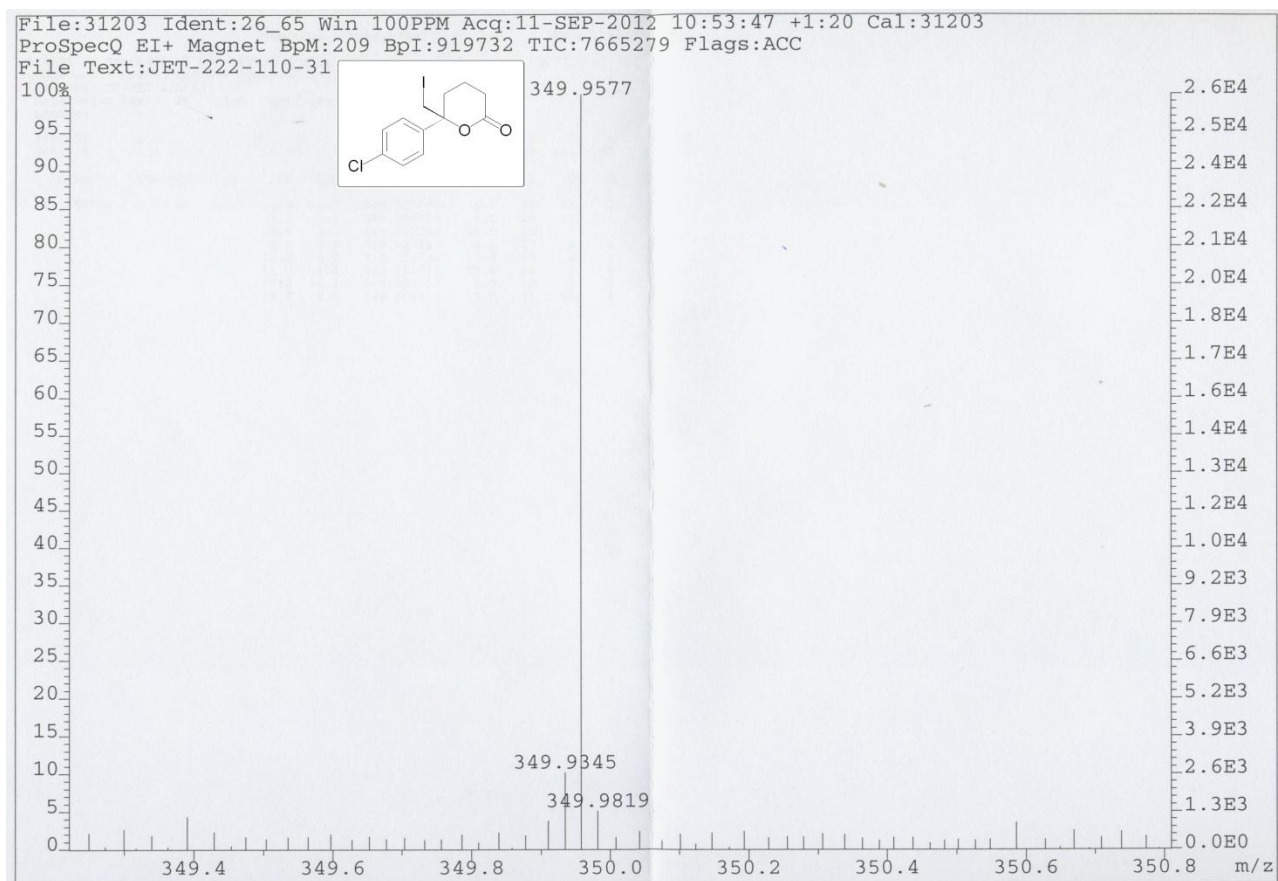


Figure S-68 HRMS spectrum of compound 2f.

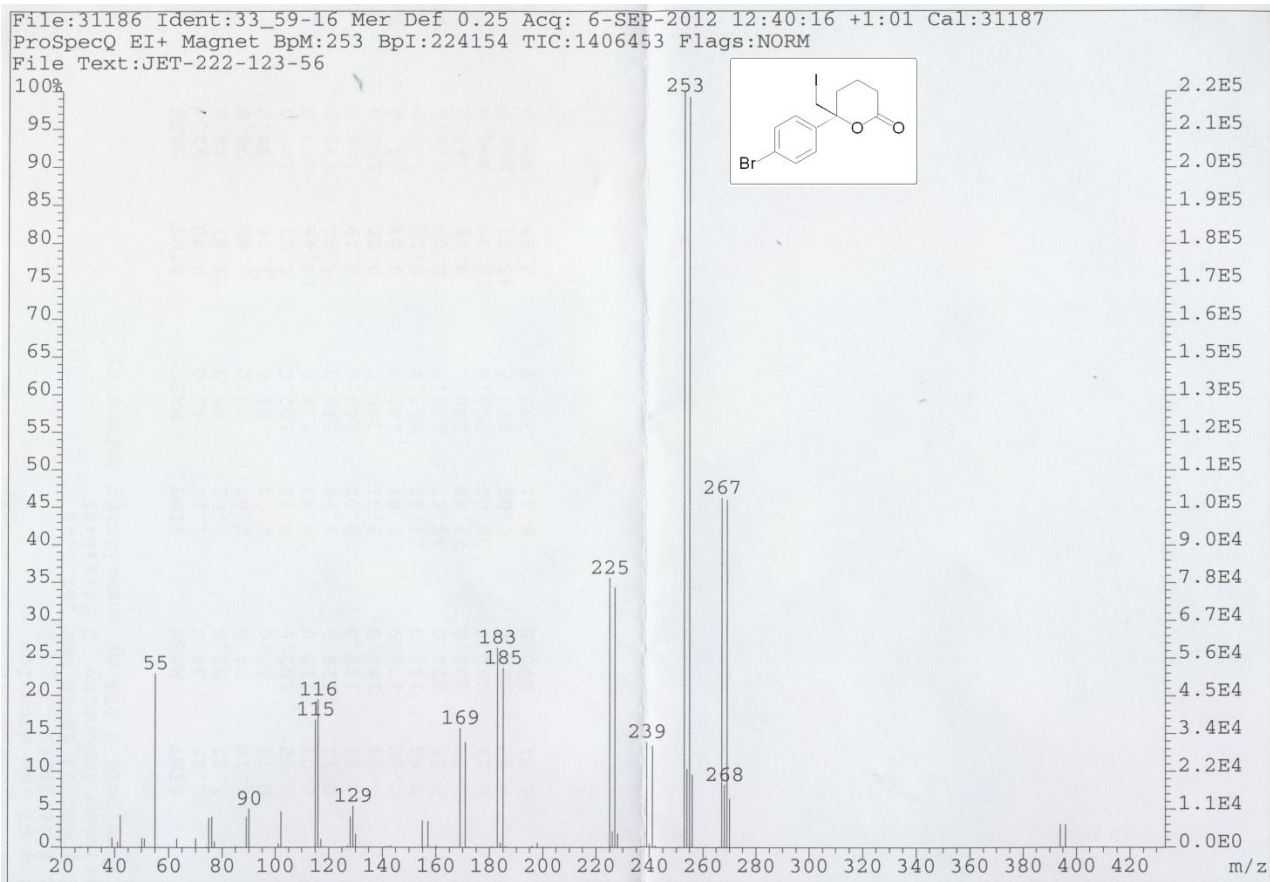


Figure S-69 MS spectrum of compound 2g.

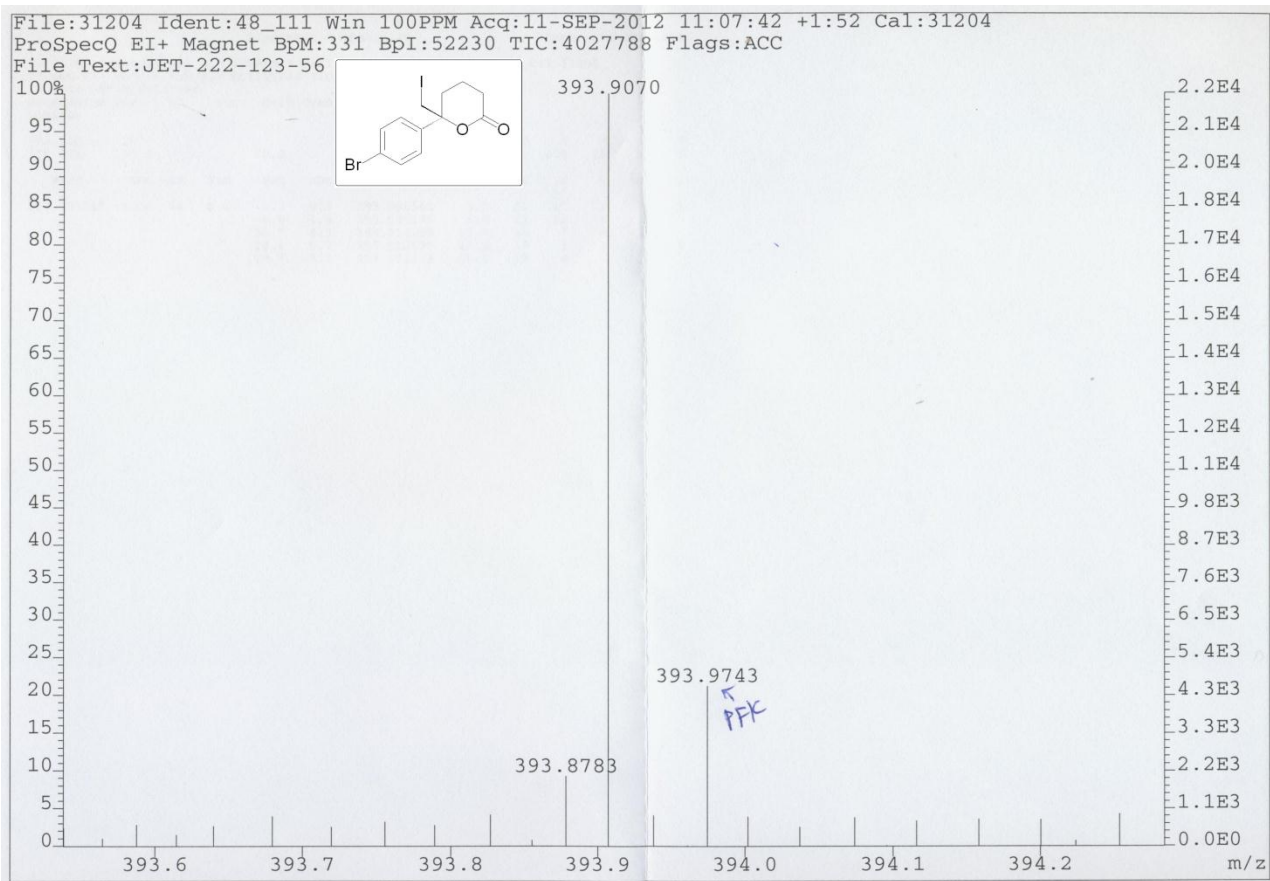


Figure S-70 HRMS spectrum of compound 2g.

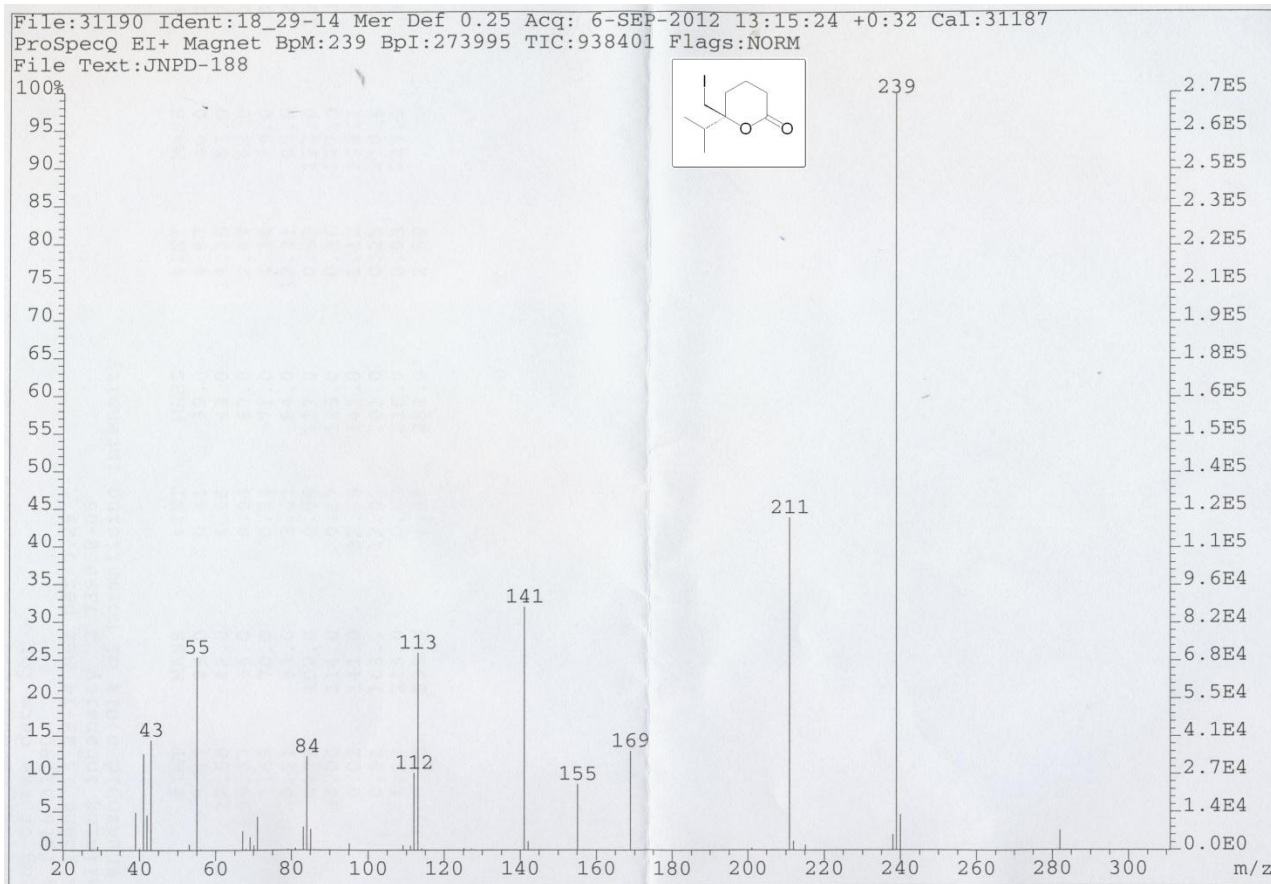


Figure S-71 MS spectrum of compound **2h**.

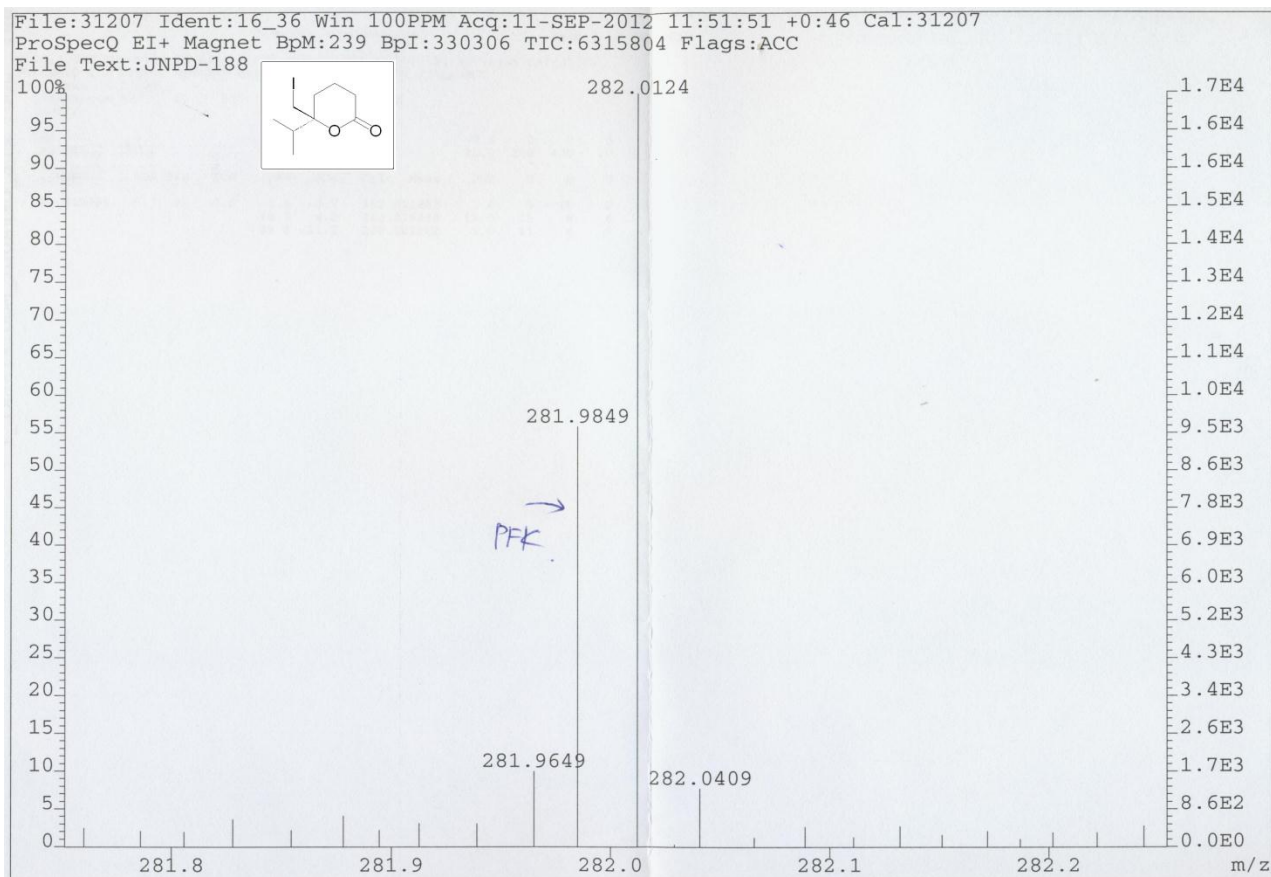


Figure S-72 HRMS spectrum of compound **2h**.

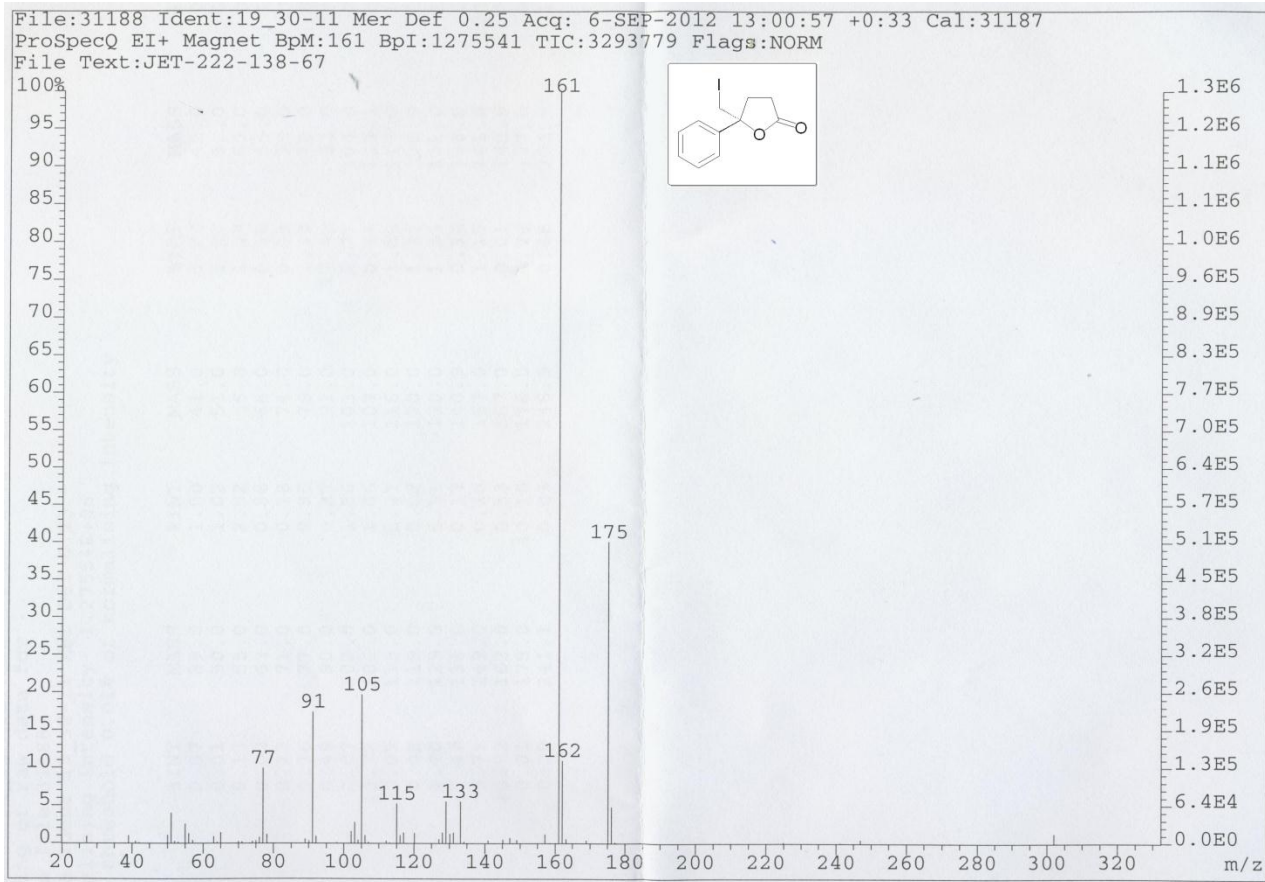


Figure S-73 MS spectrum of compound 4a.

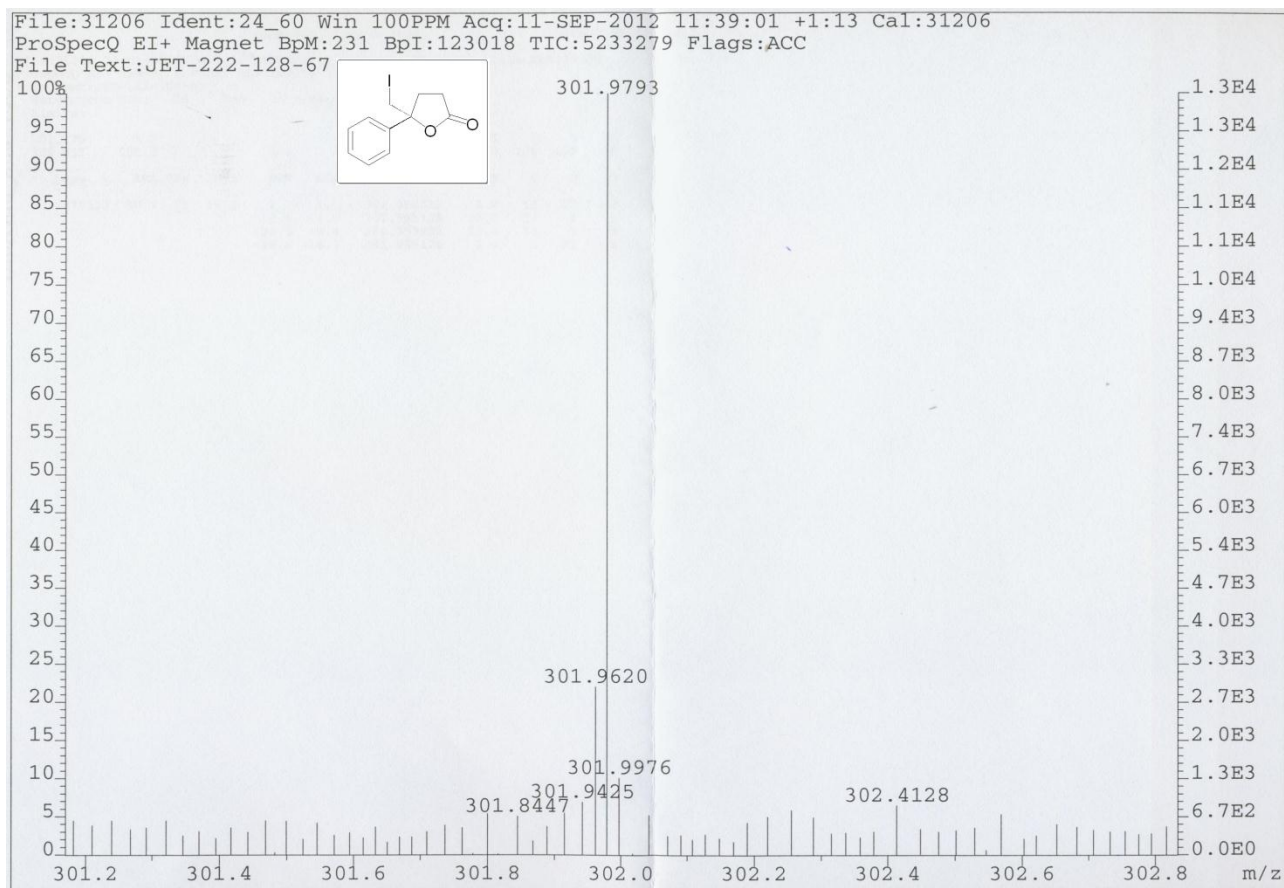


Figure S-74 HRMS spectrum of compound 4a.

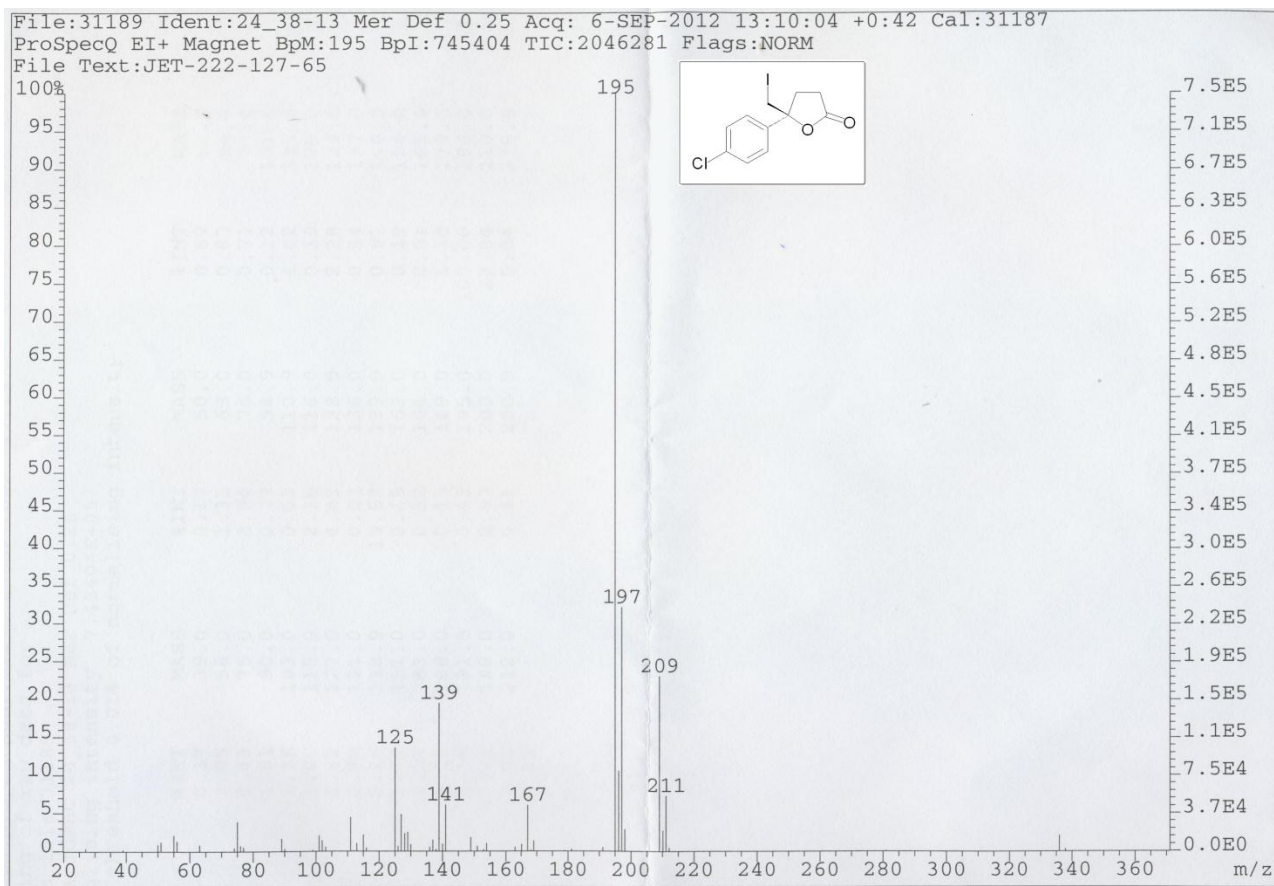


Figure S-75 MS spectrum of compound 4b.

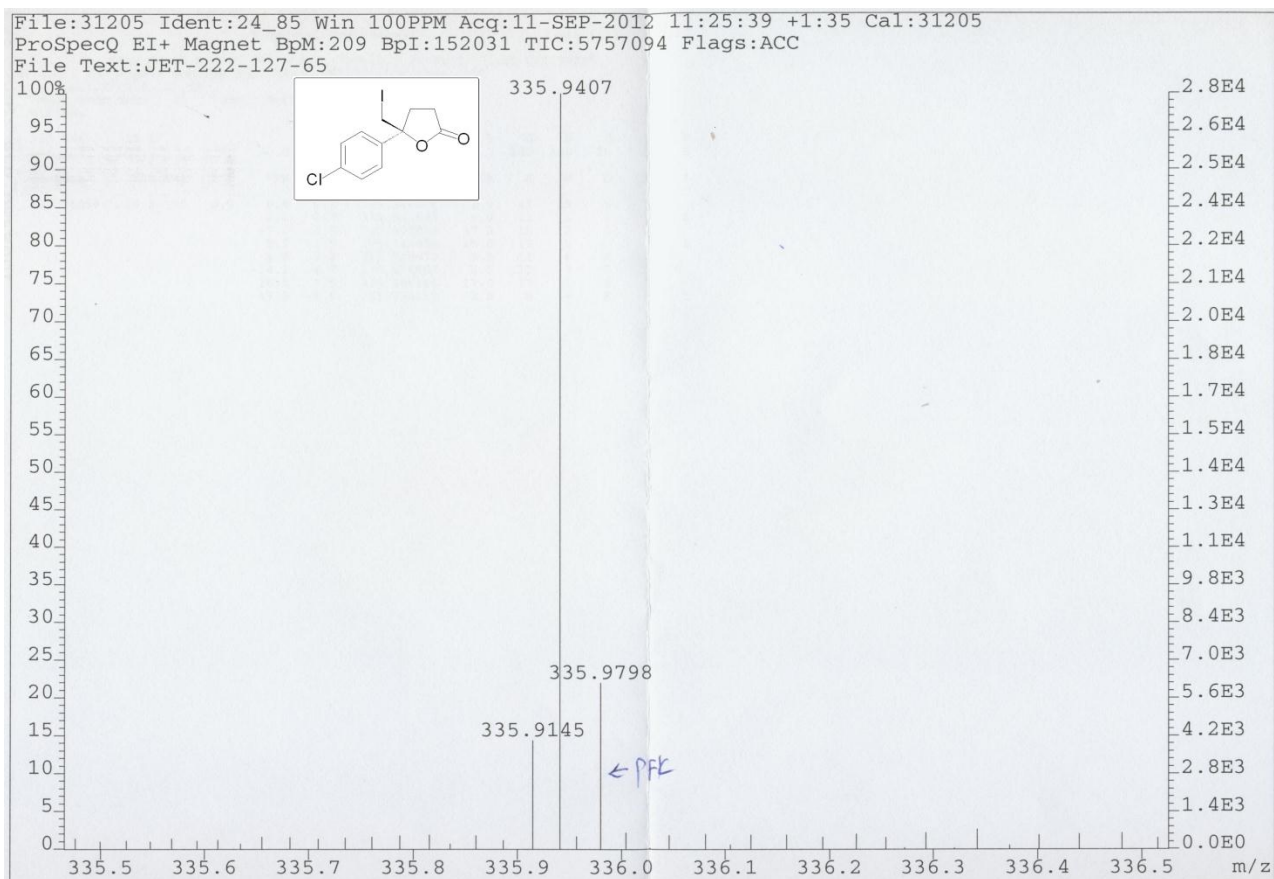


Figure S-76 HRMS spectrum of compound 4b.

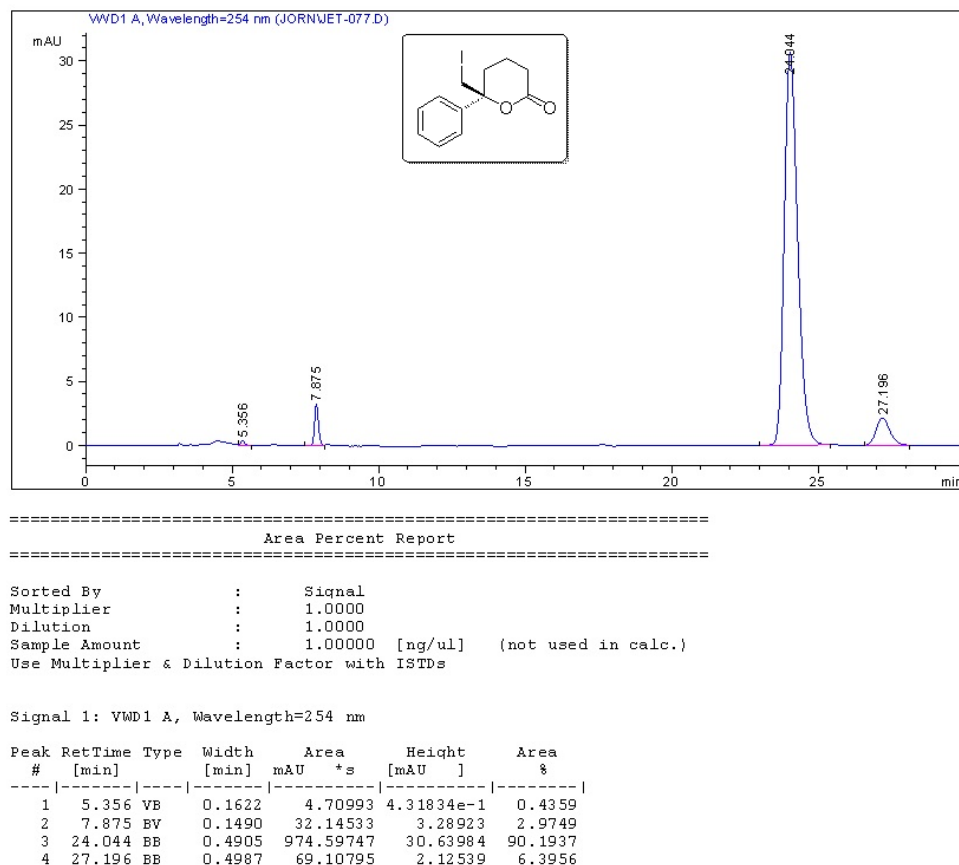


Figure S-77 HPLC chromatogram of chiral compound **2a**.

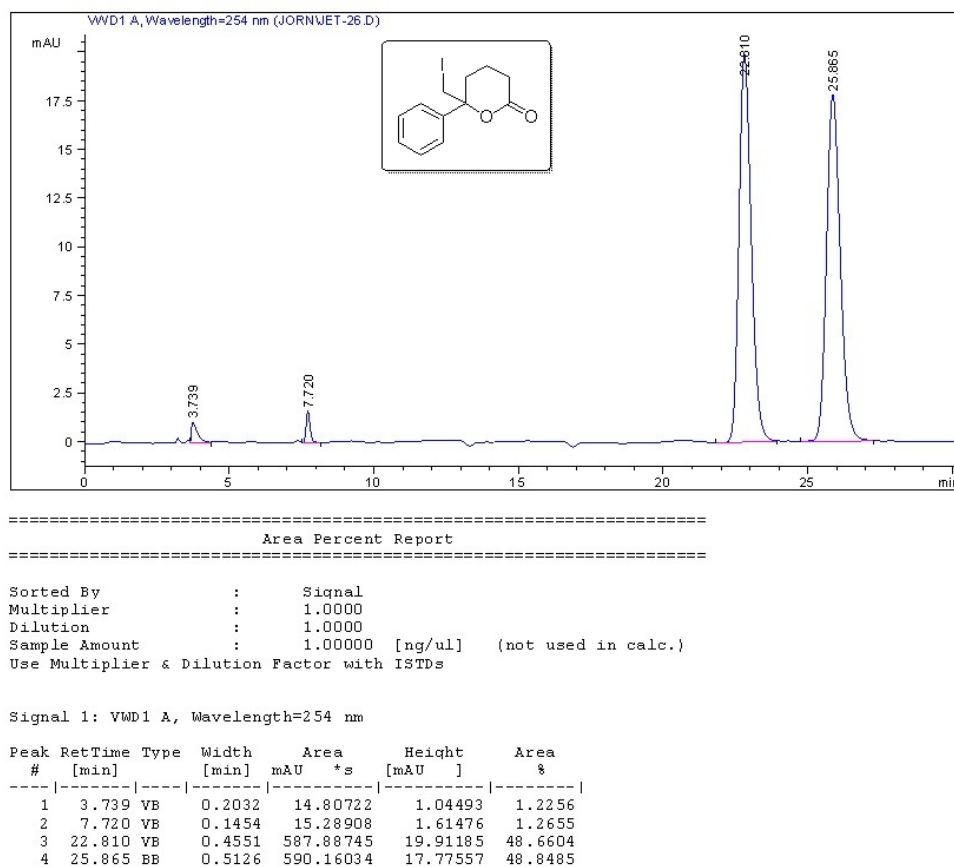


Figure S-78 HPLC chromatogram of racemic compound **2a**.

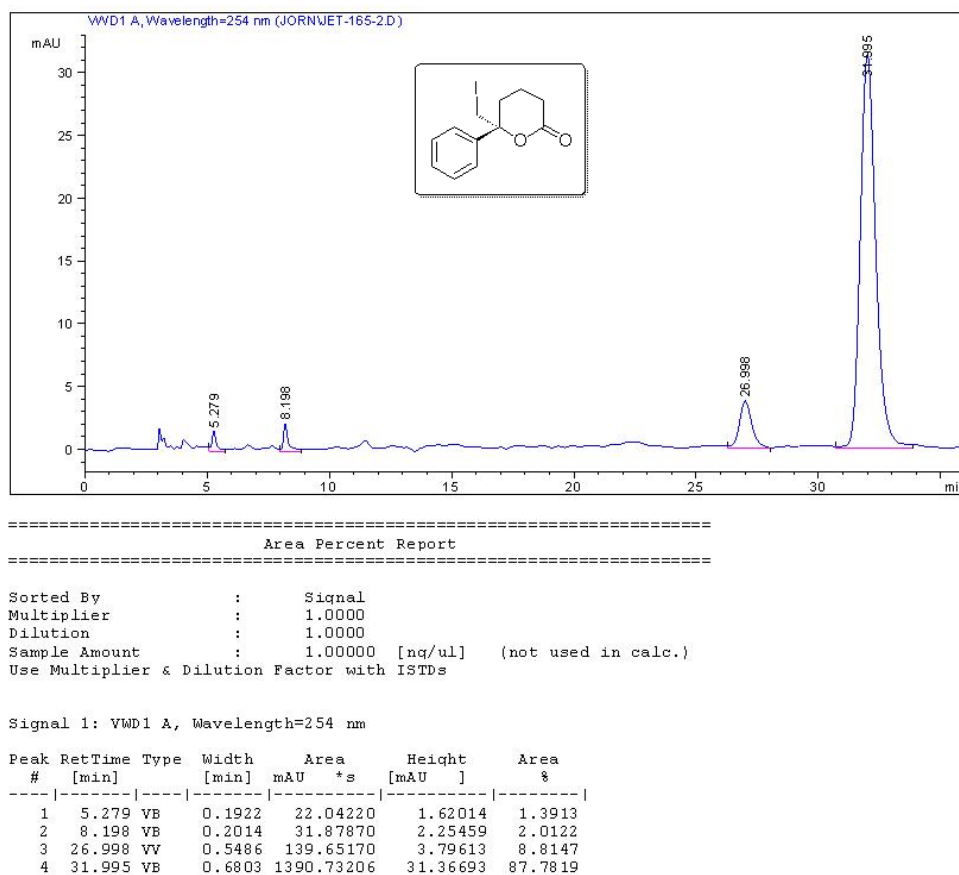


Figure S-79 HPLC chromatogram of chiral compound *ent*-2a.

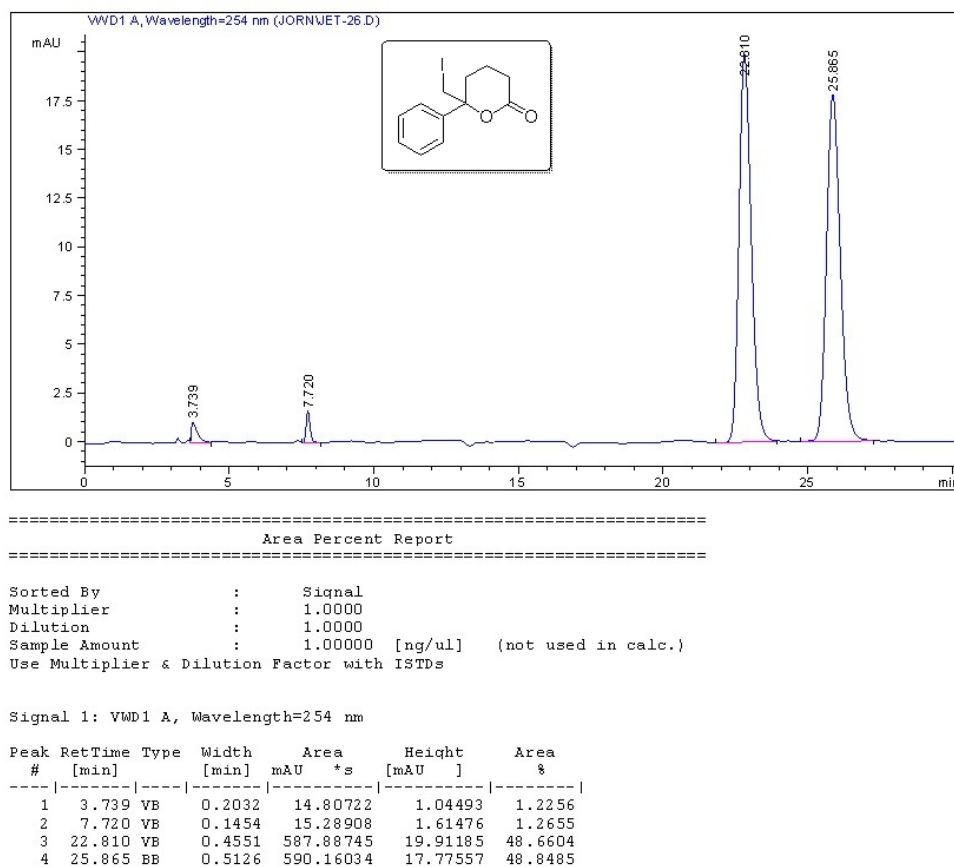
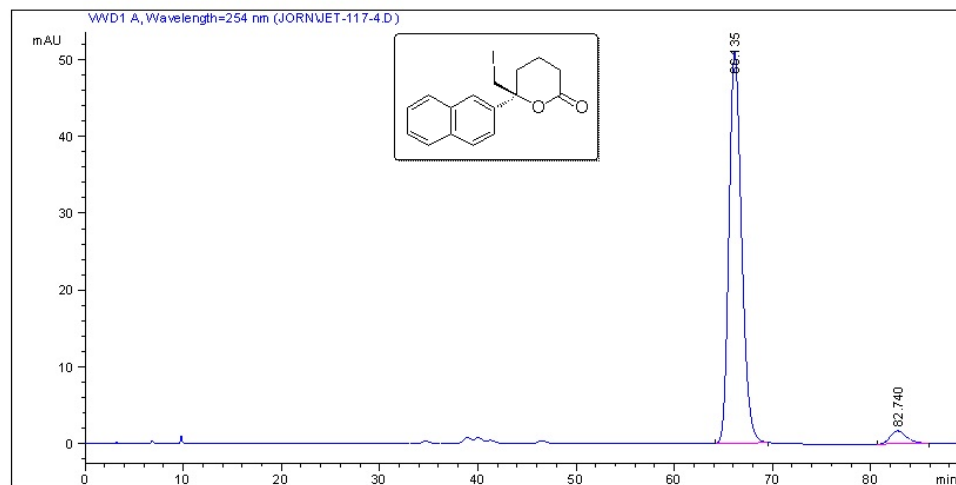


Figure S-80 HPLC chromatogram of racemic compound 2a.



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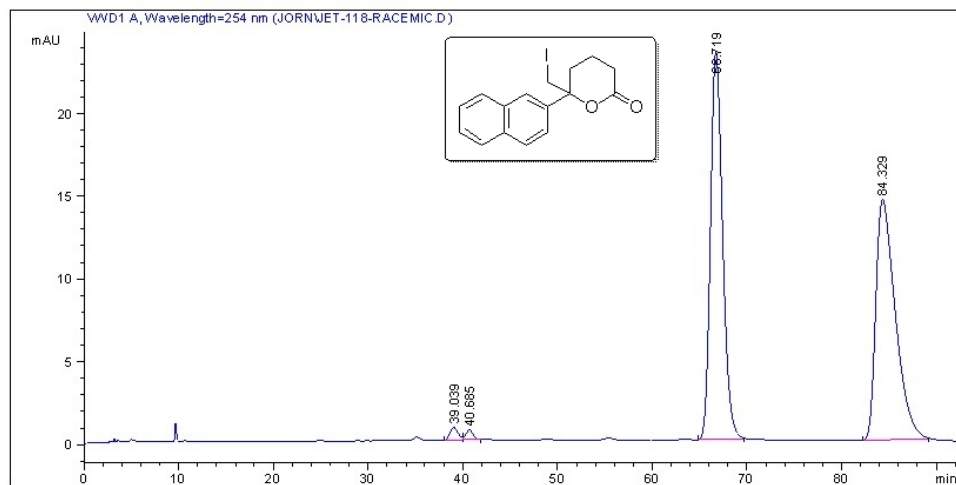
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                        Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Sample Amount  :      1.00000 [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

```

Signal 1: VMD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	66.135	BB	1.3795	4541.92334	51.01031	95.8606	
2	82.740	BB	1.3748	196.12740	1.68219	4.1394	

Figure S-81 HPLC chromatogram of chiral compound **2b**.



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                        Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Sample Amount  :      1.00000 [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

```

Signal 1: VMD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	39.039	BV	0.7115	44.73745	7.60013e-1	1.0564	
2	40.685	VB	0.6518	31.29905	5.93316e-1	0.7391	
3	66.719	BB	1.3373	2082.88916	23.42559	49.1862	
4	84.329	BB	1.9874	2075.78003	14.51388	49.0183	

Figure S-82 HPLC chromatogram of racemic compound **2b**.

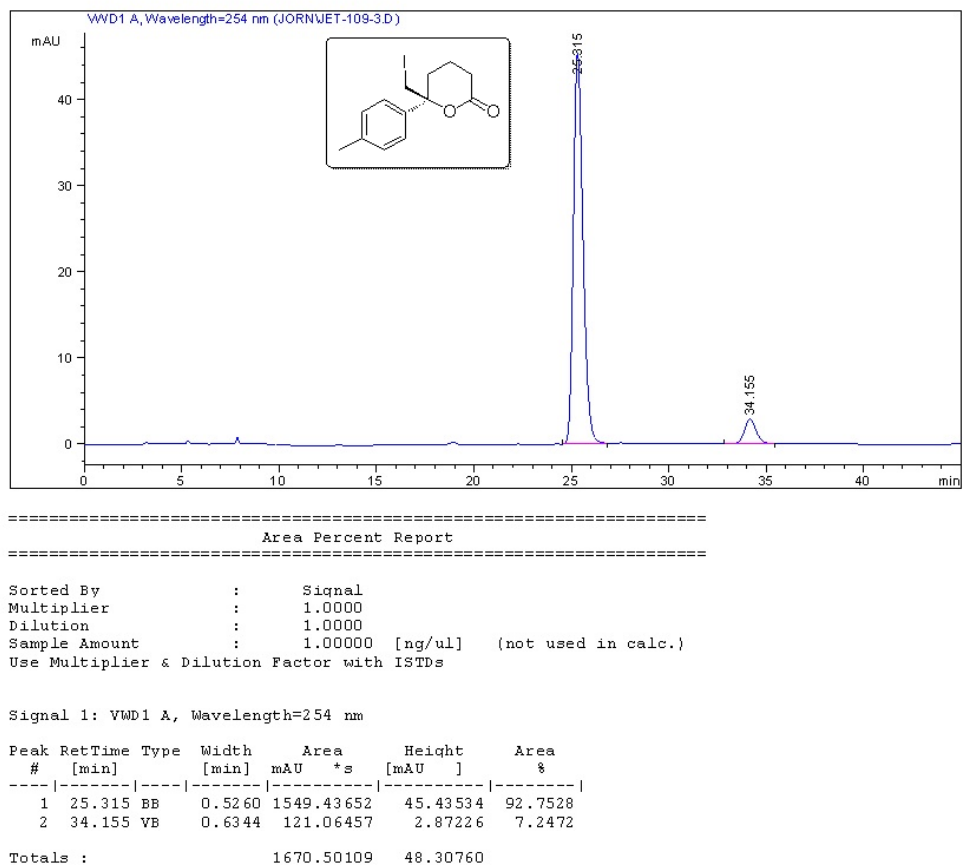


Figure S-83 HPLC chromatogram of chiral compound 2c.

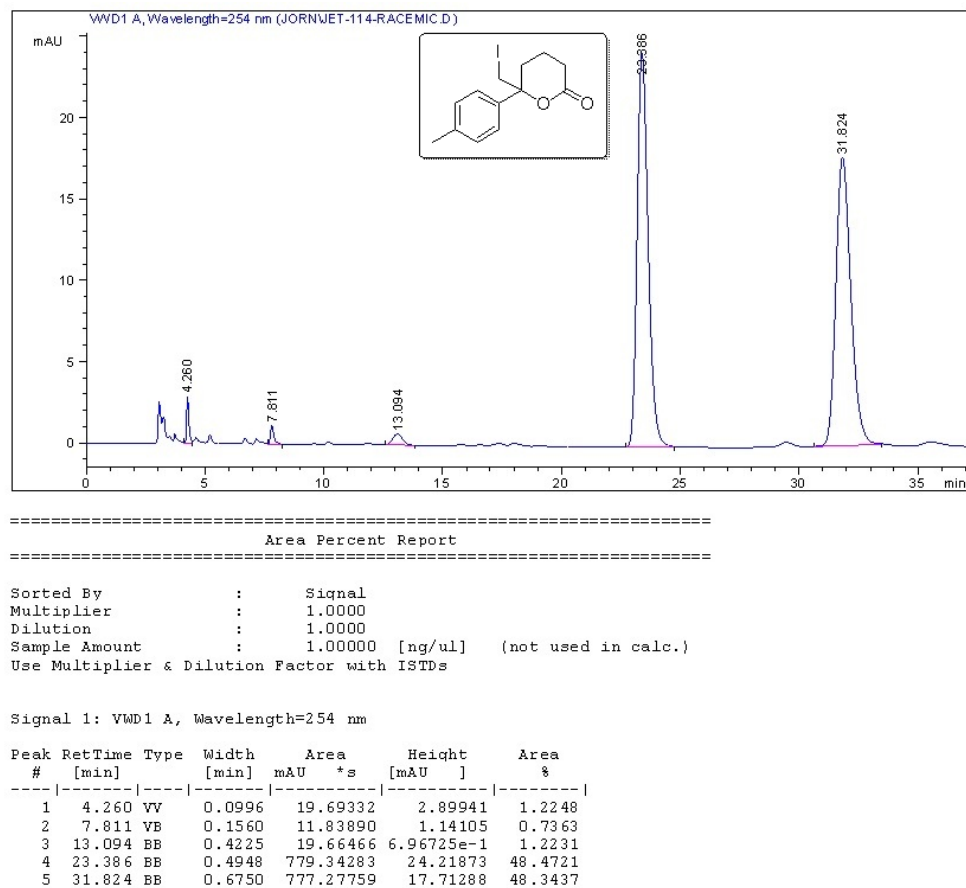
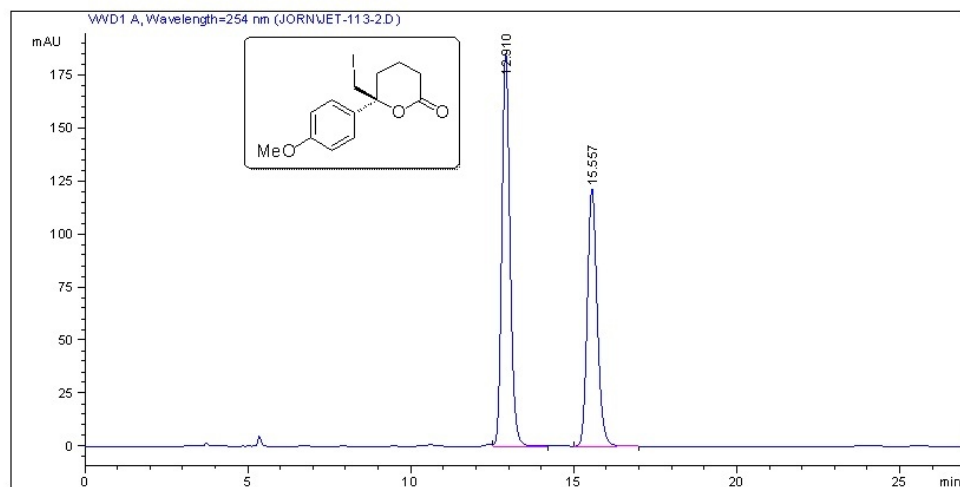


Figure S-84 HPLC chromatogram of racemic compound 2c.



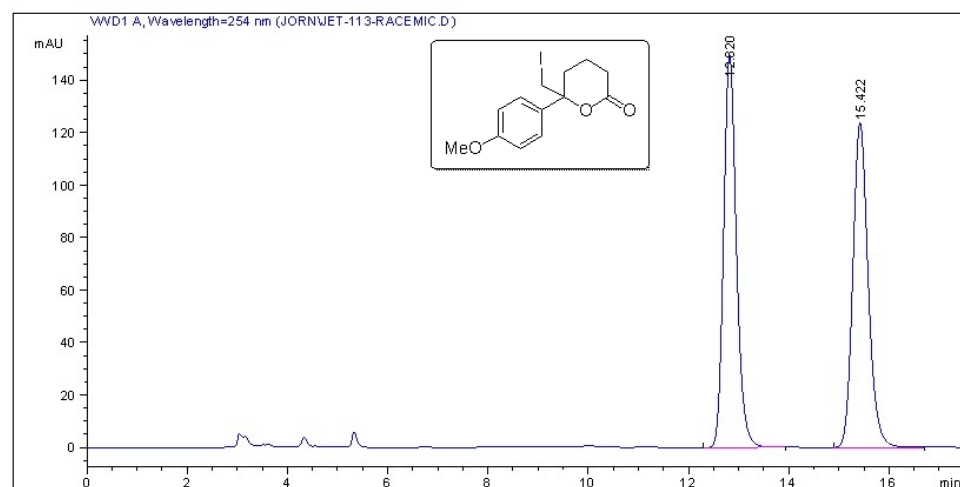
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 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000
 Sample Amount : 1.00000 [ng/ul] (not used in calc.)
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	12.910	VB	0.2723	3259.94897	185.27579	55.9150	
2	15.557	VB	0.3259	2570.23486	121.28237	44.0850	

Figure S-85 HPLC chromatogram of chiral compound **2d**.



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 Area Percent Report
 =====

Sorted By : Signal
 Multiplier : 1.0000
 Dilution : 1.0000
 Sample Amount : 1.00000 [ng/ul] (not used in calc.)
 Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Area *s	Height [mAU]	Area %
1	12.820	VB	0.2717	2645.92920	149.69565	50.1674	
2	15.422	BB	0.3265	2628.27539	123.70401	49.8326	

Figure S-86 HPLC chromatogram of racemic compound **2d**.

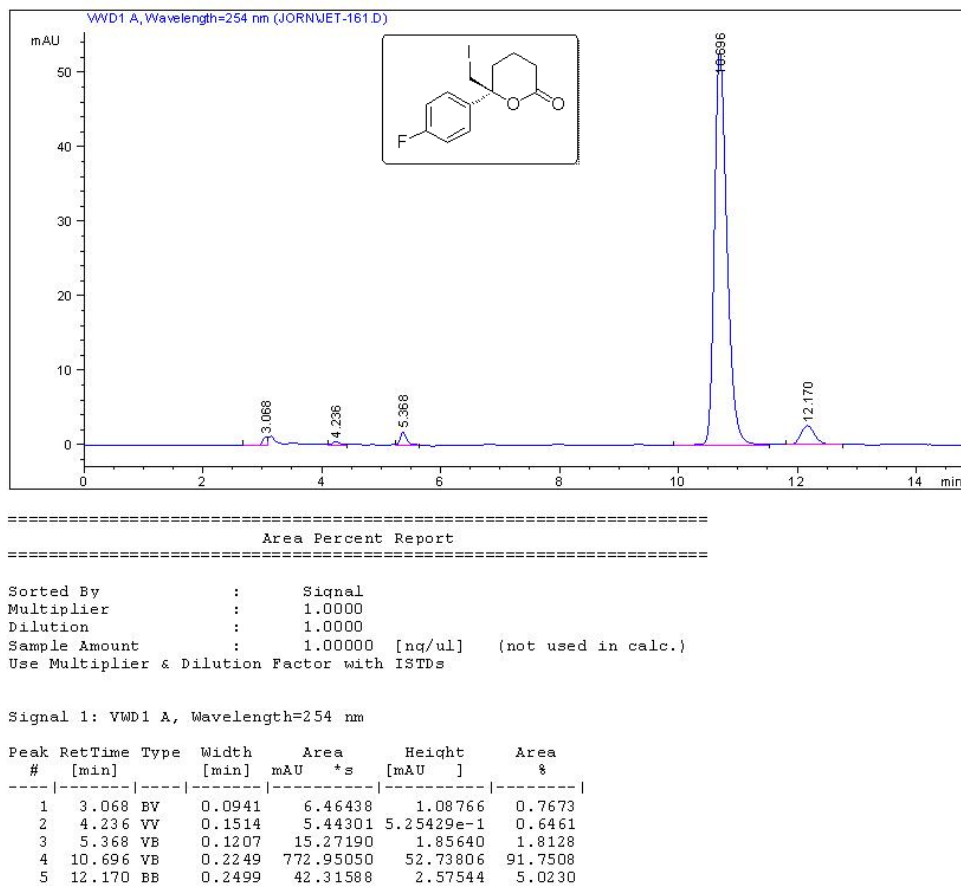


Figure S-87 HPLC chromatogram of chiral compound **2e**.

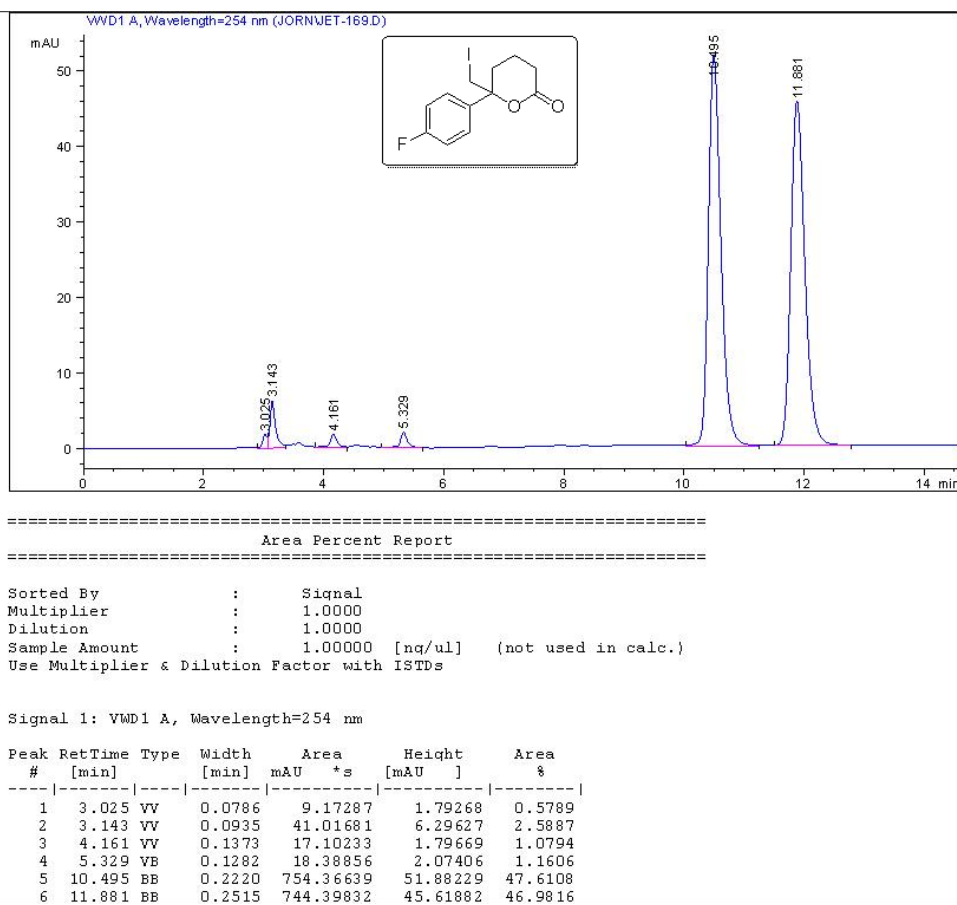
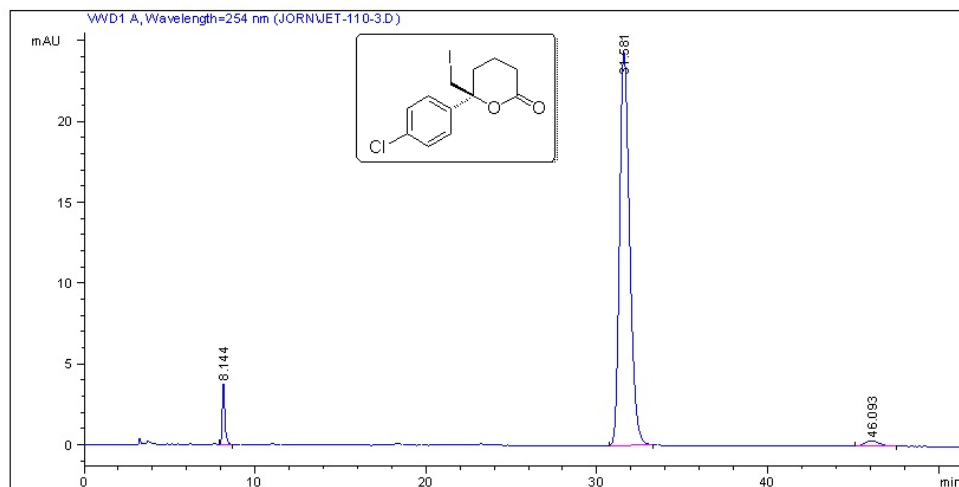


Figure S-88 HPLC chromatogram of racemic compound **2e**.



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                        Area Percent Report
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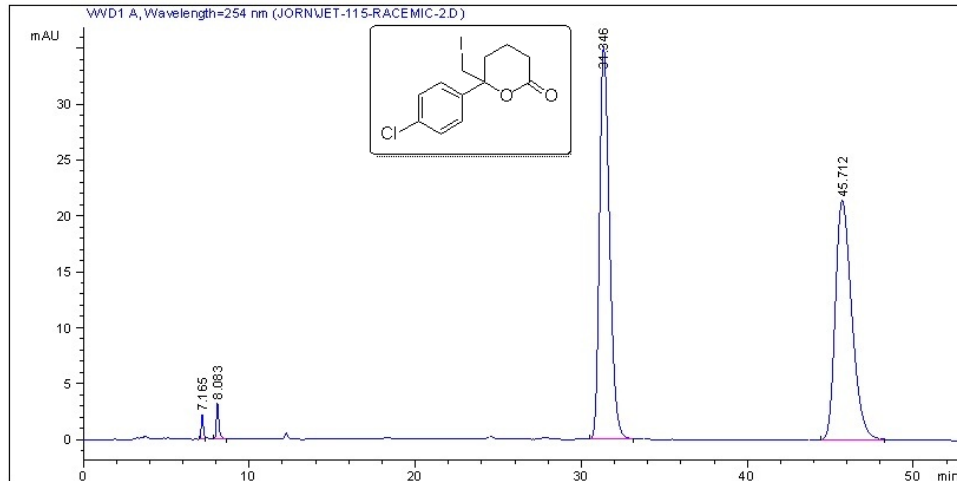
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Sample Amount   :      1.00000 [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	8.144	BB	0.1656	41.03710	3.74670	3.8829
2	31.581	BB	0.6337	995.85950	24.30956	94.2282
3	46.093	BB	0.7059	19.96289	3.35492e-1	1.8889

Totals : 1056.85949 28.39175

Figure S-89 HPLC chromatogram of chiral compound 2f.



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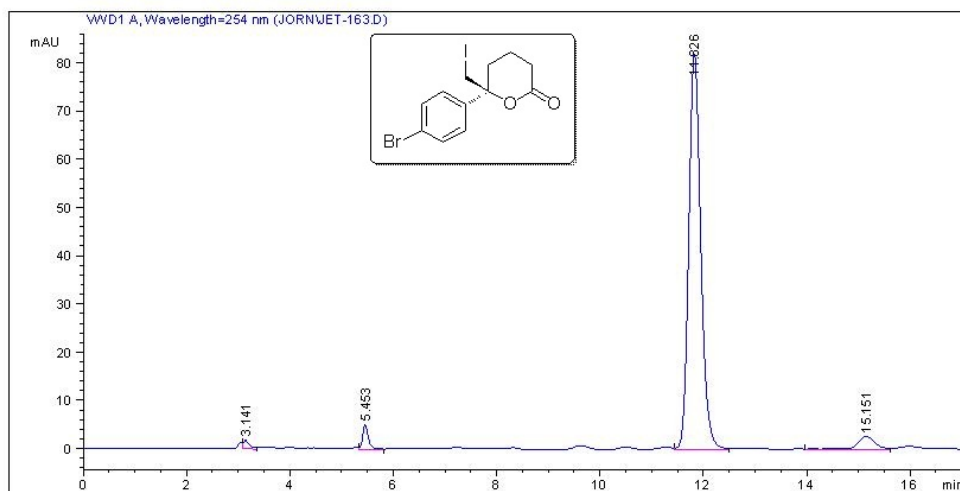
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                        Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Sample Amount   :      1.00000 [ng/ul]   (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs
  
```

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.165	BV	0.1352	19.76059	2.23410	0.6601
2	8.083	VB	0.1659	35.50255	3.23448	1.1859
3	31.346	BB	0.6430	1468.44702	35.05751	49.0527
4	45.712	BB	1.0581	1469.89929	21.38708	49.1012

Figure S-90 HPLC chromatogram of racemic compound 2f.



Area Percent Report

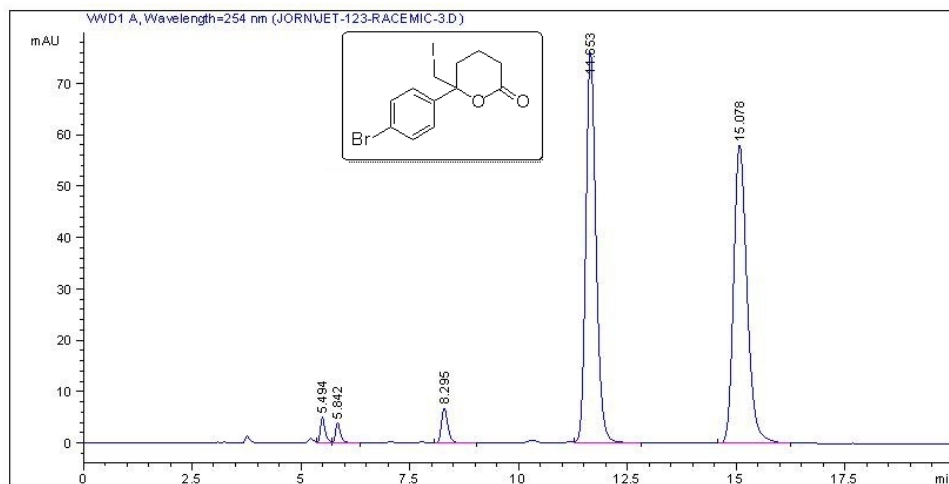
Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	3.141	VV	0.1089	14.83858	1.83550	1.0290
2	5.453	VV	0.1161	39.32522	5.10360	2.7271
3	11.826	VV	0.2480	1324.15820	82.04984	91.8253
4	15.151	VV	0.3620	63.71920	2.65011	4.4187

Totals : 1442.04120 91.63906

Figure S-91 HPLC chromatogram of chiral compound **2g**.



Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	5.494	VV	0.1187	39.89697	5.03377	1.5198
2	5.842	VB	0.1267	34.77424	4.03581	1.3247
3	8.295	VB	0.1602	72.90378	6.87111	2.7771
4	11.653	VB	0.2497	1239.67615	76.10136	47.2232
5	15.078	VB	0.3273	1237.89148	58.07527	47.1552

Figure S-92 HPLC chromatogram of racemic compound **2g**.

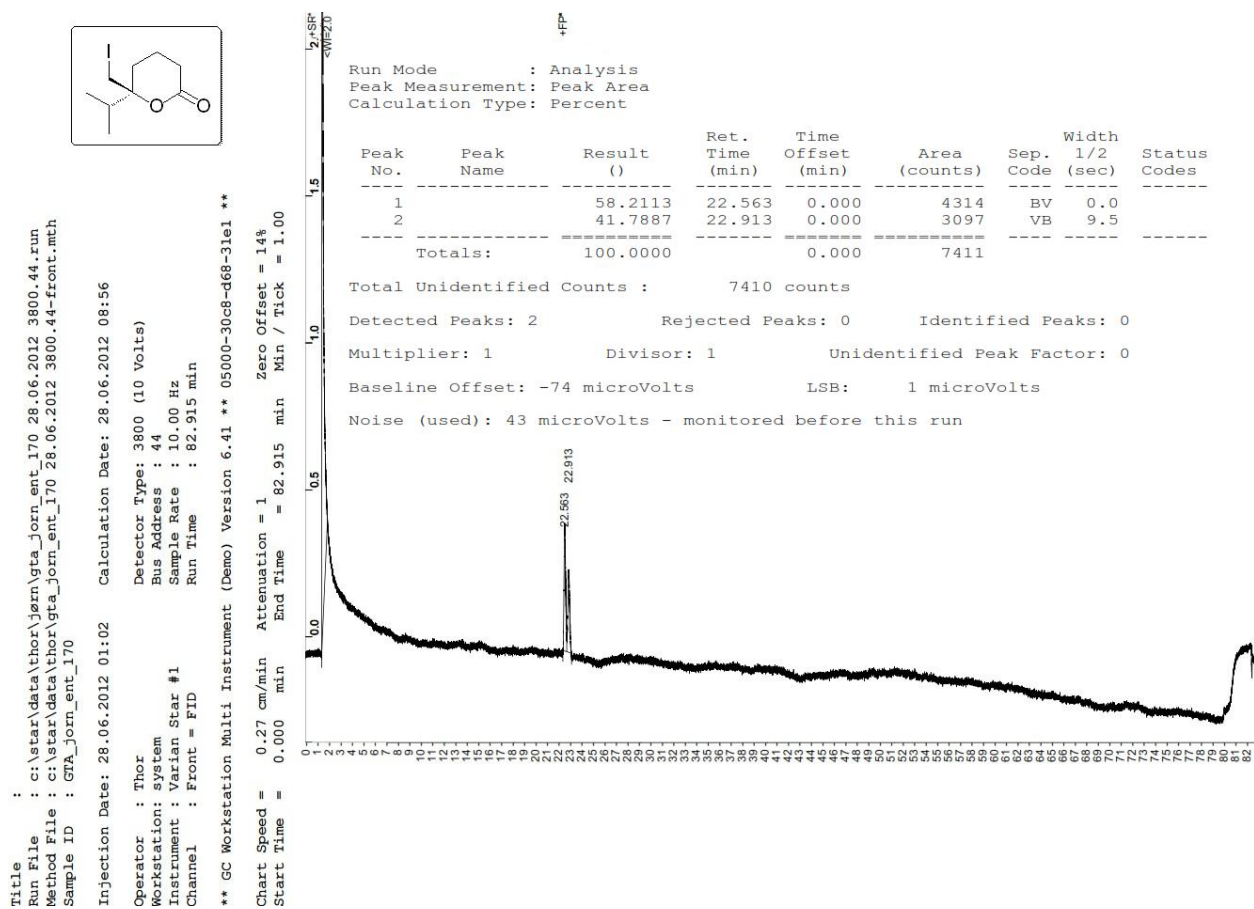


Figure S-93 GLC chromatogram of chiral compound 2h.

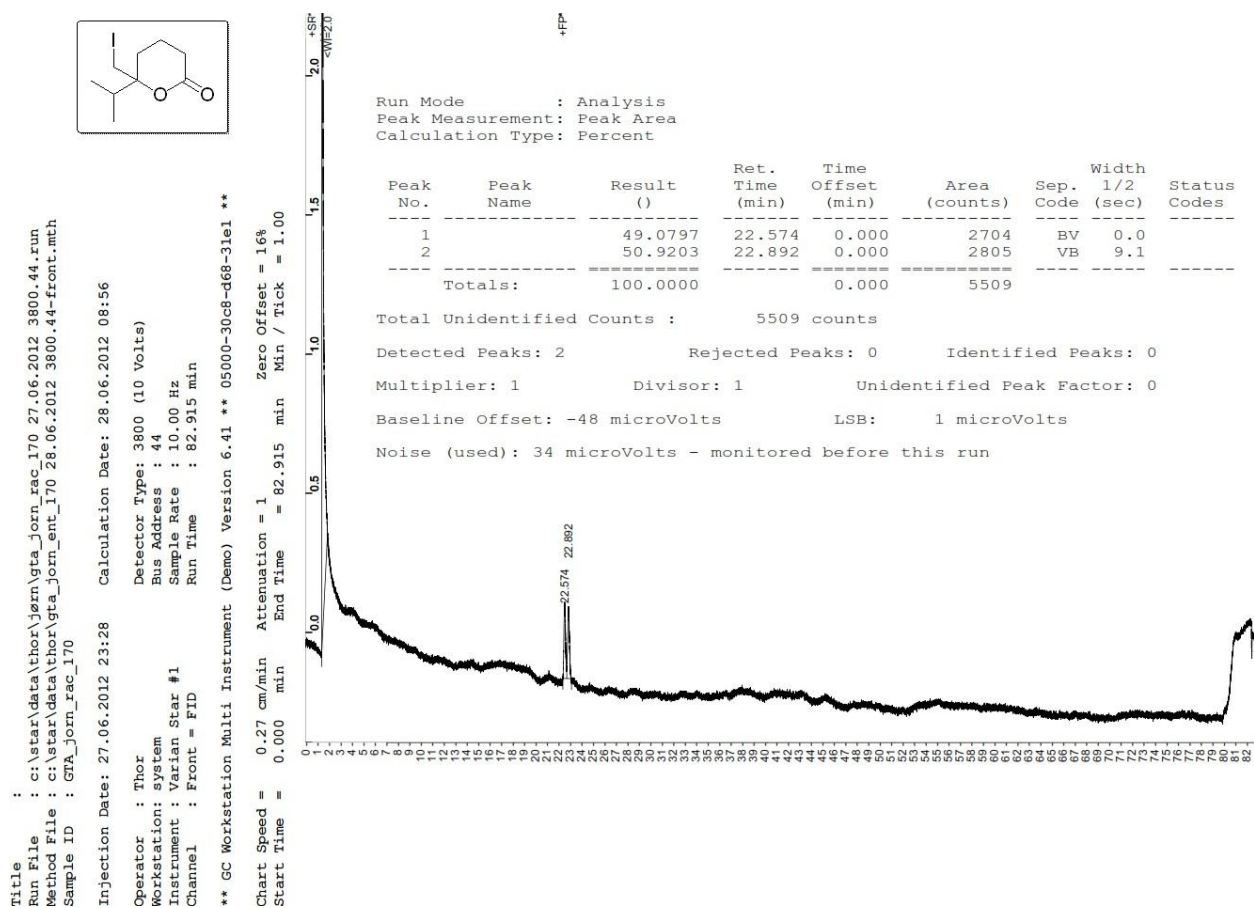


Figure S-94 GLC chromatogram of racemic compound 2h.

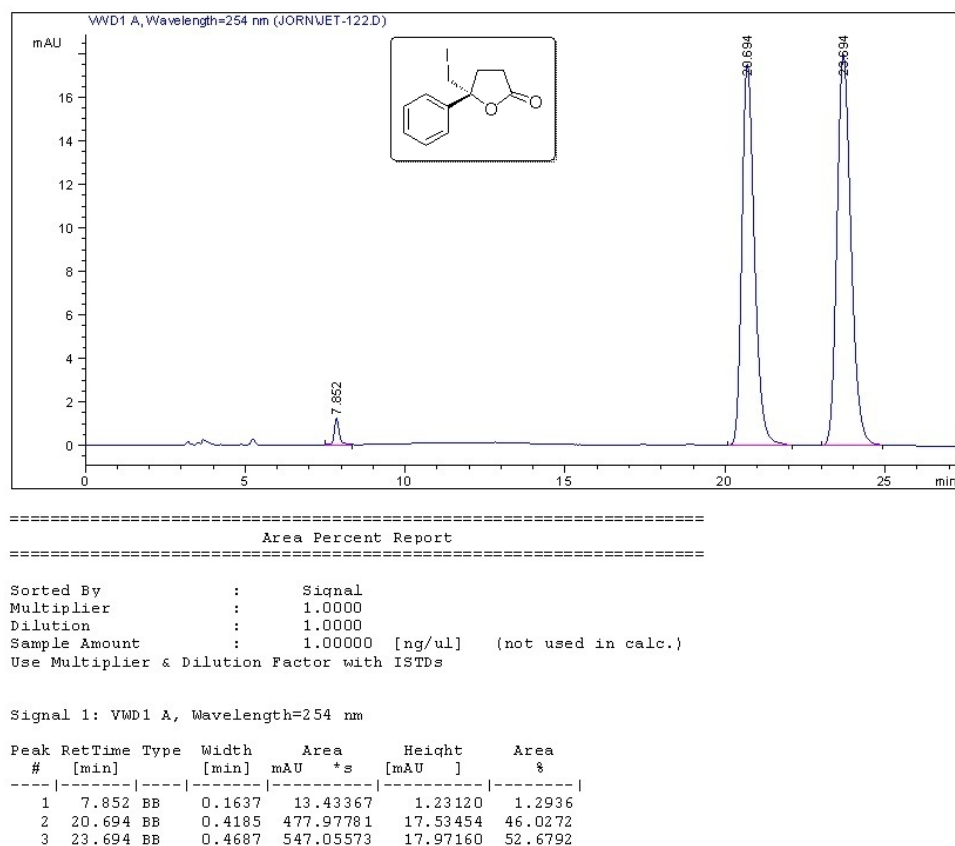


Figure S-95 HPLC chromatogram of chiral compound **4a**.

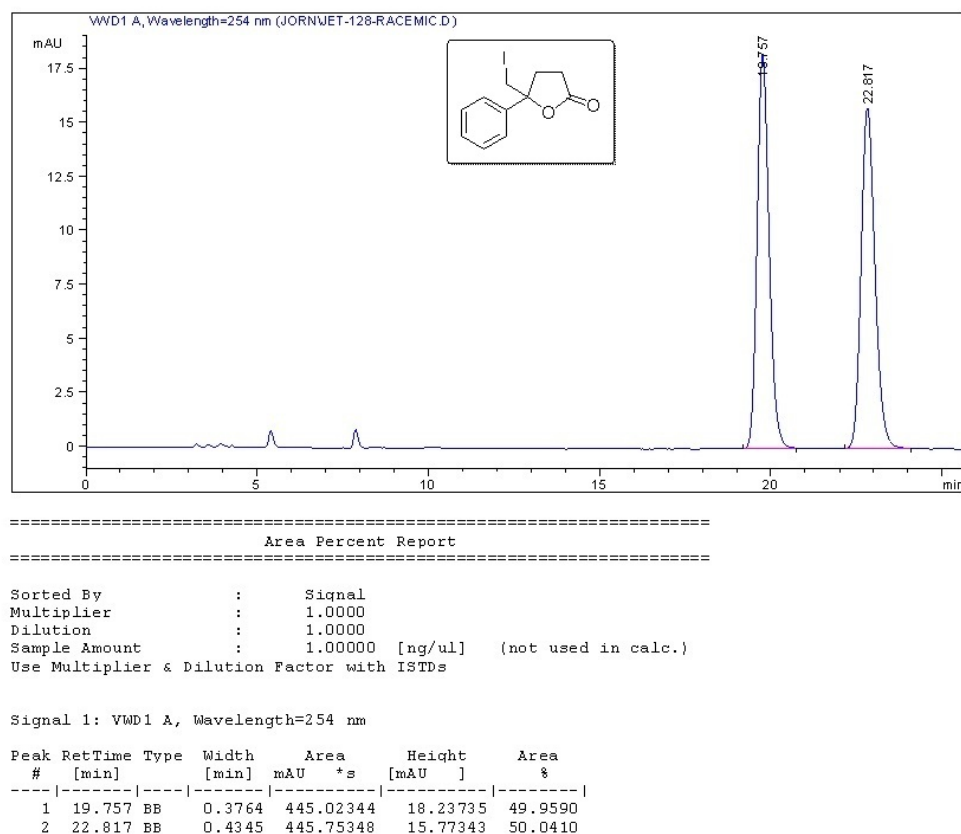
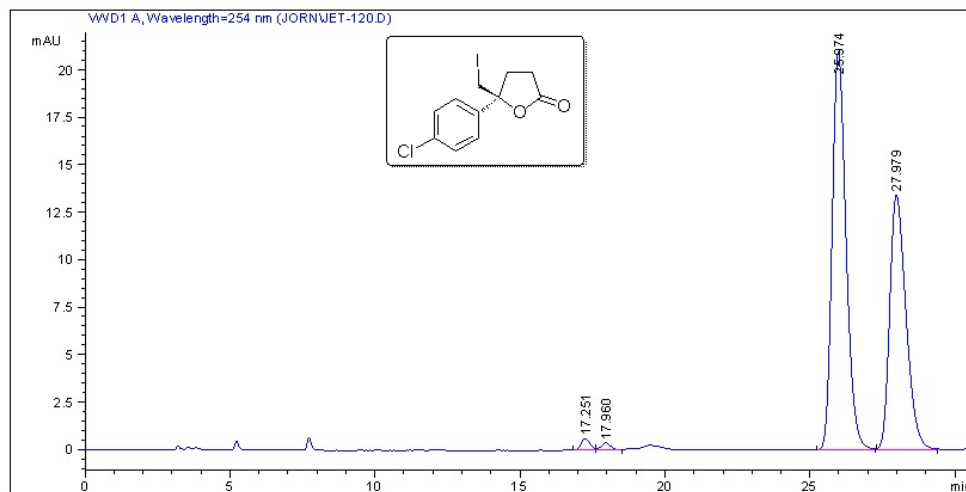


Figure S-96 HPLC chromatogram of racemic compound **4a**.



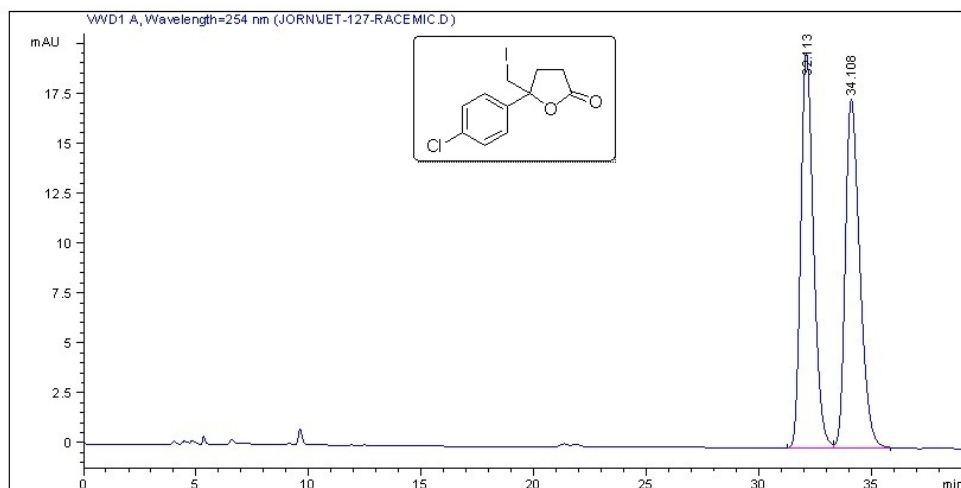
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Area Percent Report
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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Height [mAU]	Area %
1	17.251	BV	0.3300	13.05685	6.16798e-1	1.0500
2	17.960	VV	0.3514	8.60201	3.69826e-1	0.6918
3	25.974	BB	0.5148	699.29700	20.94307	56.2366
4	27.979	BB	0.6003	522.53461	13.40707	42.0216

Figure S-97 HPLC chromatogram of chiral compound **4b**.



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Area Percent Report
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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Sample Amount : 1.00000 [ng/ul] (not used in calc.)
Use Multiplier & Dilution Factor with ISTDs

Signal 1: VWD1 A, Wavelength=254 nm

Peak #	RetTime [min]	Type	Width [min]	Area mAU	Height [mAU]	Area %
1	32.113	BV	0.6062	777.20465	19.74822	49.8885
2	34.108	VB	0.6869	780.67926	17.43519	50.1115

Figure S-98 HPLC chromatogram of racemic compound **4b**.

References

- (1) Malerich, J. P.; Hagihara, K.; Rawal, V. H. *J. Am. Chem. Soc.* **2008**, *130*, 14416.
- (2) Konishi, H.; Lam, T. Y.; Malerich, J. P.; Rawal, V. H. *Org. Lett.* **2010**, *12*, 2028.
- (3) Zhu, Y.; Malerich, J. P.; Rawal, V. H. *Angew. Chem. Int. Ed.* **2010**, *49*, 153.
- (4) Veitch, G. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2010**, *49*, 7332.
- (5) A. Takemiya, J. F. Hartwig, *J. Am. Chem. Soc.* **2006**, *128*, 6042.
- (6) Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* **2002**, *4*, 297.
- (7) For the antipodal (*R*)-enantiomer, see ref. 6.