

## Supporting Information

### **Stereodivergent Synthesis of Chiral Spiropyrazolones through Pd-Catalyzed Asymmetric Sequential Hydroalkylation of 1,3-Enynes: Unusual Solvent Effect on the Enantioselectivity**

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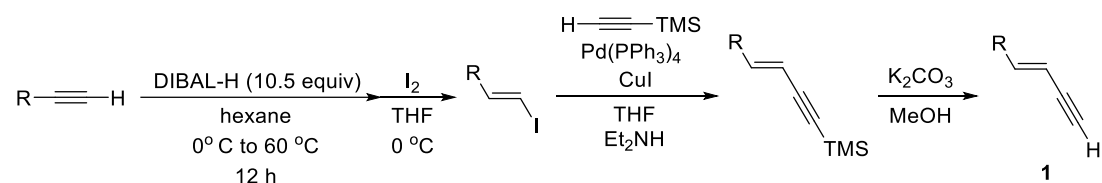
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## 1. General Information

Unless otherwise noted, all reactions in standard conditions were carried out under an argon atmosphere. Solvents were dried by standard methods under argon atmosphere.  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR,  $^{19}\text{F}$  NMR and  $^{31}\text{P}$  NMR spectra were recorded on 400 MHz, 600 MHz instruments using  $\text{CDCl}_3$  as solvent. Chemical shifts of  $^1\text{H}$  NMR were recorded in parts per million (ppm,  $\delta$ ) relative to tetramethylsilane ( $\delta = 0.00$  ppm) with the solvent resonance as an internal standard ( $\text{CDCl}_3$ :  $\delta = 7.26$  ppm). NMR multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, sept = septet, m = multiplet, br = broad signal. High-resolution mass spectral analysis (HRMS) data were measured on a spectrometer by means of the ESI technique. The enantiomeric excess was determined by chiral HPLC with *n*-hexane and *i*-propanol as eluents. Optical rotations were measured on a polarimeter. Column chromatography was performed on silica gel (200–300 mesh).

## 2. General Procedures for the Synthesis of Substrates

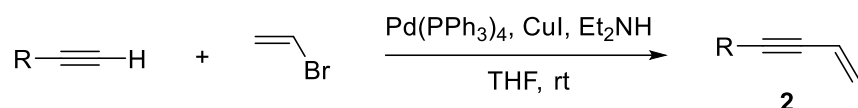
### Synthesis of the 1,3-enynes **1**<sup>1</sup>



Terminal alkyne (40 mmol) was stirred in hexane (40 mL) at room temperature in 200 mL two-necked flask Under an Ar atmosphere. To the solution was added diisobutylaluminum hydride (DIBAL-H, 1.0 M in hexane, 42 mmol, 42 mL) at  $0\text{ }^\circ\text{C}$ . The mixture was stirred at  $0\text{ }^\circ\text{C}$  to room temperature for 2 h and then at  $60\text{ }^\circ\text{C}$  for 10 h. The mixture was checked with TLC (*n*-hexane). Then to the mixture was added  $\text{I}_2/\text{THF}$  at  $0\text{ }^\circ\text{C}$  and the mixture was stirred at room temperature for 6 h. The reaction mixture was quenched with water at  $0\text{ }^\circ\text{C}$ . The aqueous mixture was extracted with hexane. The organic layer was dried over  $\text{Na}_2\text{SO}_4$  and concentrated. The residue was purified with silica gel column chromatography (*n*-hexane).  $\text{Pd}(\text{PPh}_3)_4$  (2 mol %, 0.668 mmol, 771.9 mg) and  $\text{CuI}$  (2 mol %, 0.668 mmol, 127.2 mg) were placed in a 100 mL two-necked flask Under an Ar atmosphere. To the flask was added  $\text{Et}_2\text{NH}$  (30 mL) and then iodine compounds (33.4 mmol) in THF (30 mL) via syringe. Then trimethylsilyl acetylene (36.7 mmol, 5.2 mL) was added. After stirring for 17 h, the

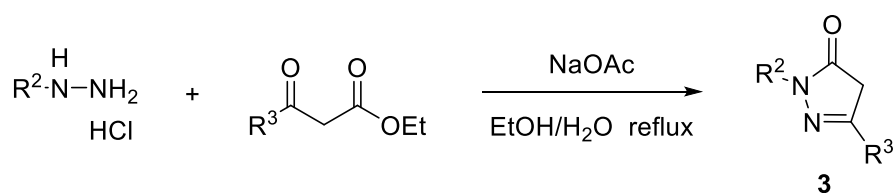
reaction mixture was checked with TLC (hexane). The mixture was poured into water at 0 °C. The aqueous mixture was extracted with Et<sub>2</sub>O. The organic layer was washed with 2 M aq. HCl and then washed with saturated aq. NaHCO<sub>3</sub>. The organic layer was dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated. The residue was purified with silica gel column (hexane) and then distilled.

### Synthesis of the 1,3-enynes **2**<sup>2</sup>



Copper (I) iodide (152.4 mg, 0.8 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (231.1 mg, 0.2 mmol) were dissolved in diethylamine (20 mL, 0.5 mL/1.0 mmol alkyne) under an Ar atmosphere which was then cooled to 0 °C. Terminal alkyne (4.1 g, 40 mmol, 1 equiv) and vinyl bromide (52 mL, 52 mmol, 1.3 equiv, 1.0 M in THF) were added and the resulting mixture was left to stir and warmed up to room temperature until complete conversion of the starting material was observed from TLC. The reaction mixture was washed with water followed by extraction with *n*-pentane:diethyl ether (1:1). The combined organic layers were washed with 1 M HCl and dried over magnesium sulfate. The crude product was afforded after evaporation of the solvent in vacuo and ready to be purified by column chromatography to afford 1,3-enynes **2**.

### Synthesis of pyrazolones **3**<sup>3,4</sup>

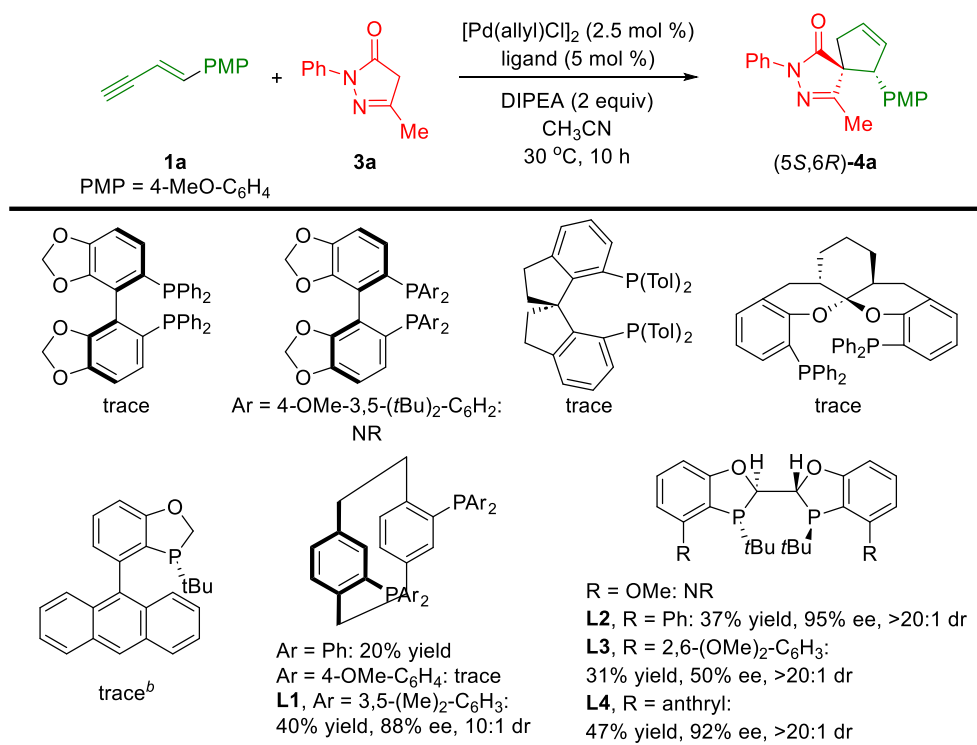


Sodium acetate (328 mg, 4 mmol) was added to the solvent of aromatic hydrazine hydrochloride derivatives (4 mmol) in 5 mL of EtOH and 1 mL of water, and the mixture was stirred at room temperature for 5 min. Then, ethyl acetoacetate (521 mg, 4 mmol) was added, and the mixture reaction was heated to reflux for 3 h. After that, the mixture was poured dropwisely into crushed ice (50 g) with vigorous stirring, and the resulting precipitate was then filtered and crystallized with EtOH. These pyrazolone derivatives were directly employed for the synthesis of pyrazolonethioethers without further purification.



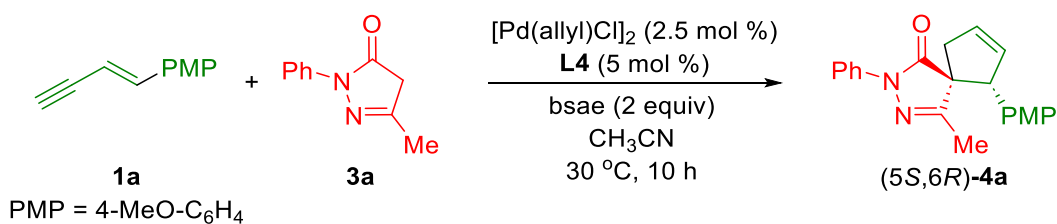
### 3. Optimization for Asymmetric Sequential Hydroalkylation with 1,3-Enynes

Table S1. Screening chiral ligands for Pd-catalyzed asymmetric sequential hydroalkylation of 1,3-enyne **1a** with pyrazolone **3a**<sup>a</sup>



<sup>a</sup>Reactions were performed with **1a** (0.1 mmol), **3a** (0.12 mmol), [Pd(allyl)Cl]<sub>2</sub> (2.5 mol %), ligand (5 mol %) and DIPEA (2 equiv) in 0.5 mL of CH<sub>3</sub>CN at 30 °C for 10 h. Yield of isolated product, dr was determined by <sup>1</sup>H NMR, ee was determined by chiral HPLC. <sup>b</sup>Ligand (10 mol %). DIPEA = *N,N*-diisopropylethylamine. NR = no reaction.

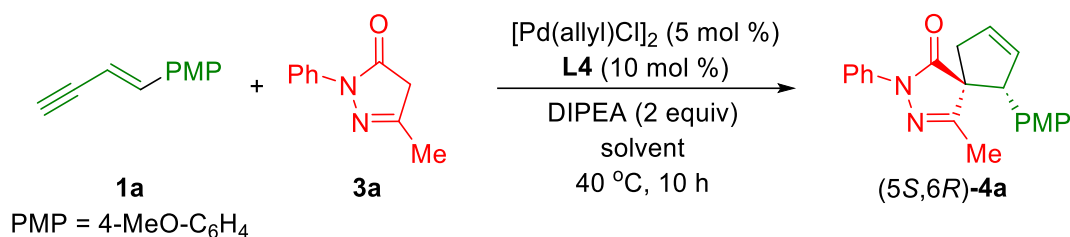
**Table S2. Screening base for Pd-catalyzed asymmetric sequential hydroalkylation of 1,3-enyne **1a** with pyrazolone **3a**<sup>a</sup>**



entry	base	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	dr <sup>d</sup>
1	DIPEA	47	92	>20:1
2	Et <sub>3</sub> N	46	92	5:1
3	Cy <sub>2</sub> NMe	56	92	6:1
4	K <sub>2</sub> CO <sub>3</sub>	55	91	4:1

<sup>a</sup>Reactions were performed with **1a** (0.1 mmol), **3a** (0.12 mmol), [Pd(allyl)Cl]<sub>2</sub> (2.5 mol %), **L4** (5 mol %), base (2 equiv) in 0.5 mL of CH<sub>3</sub>CN at 30 °C for 10 h. <sup>b</sup>Isolated yield. <sup>c</sup>ee was determined by chiral HPLC. <sup>d</sup>dr was determined by <sup>1</sup>H NMR.

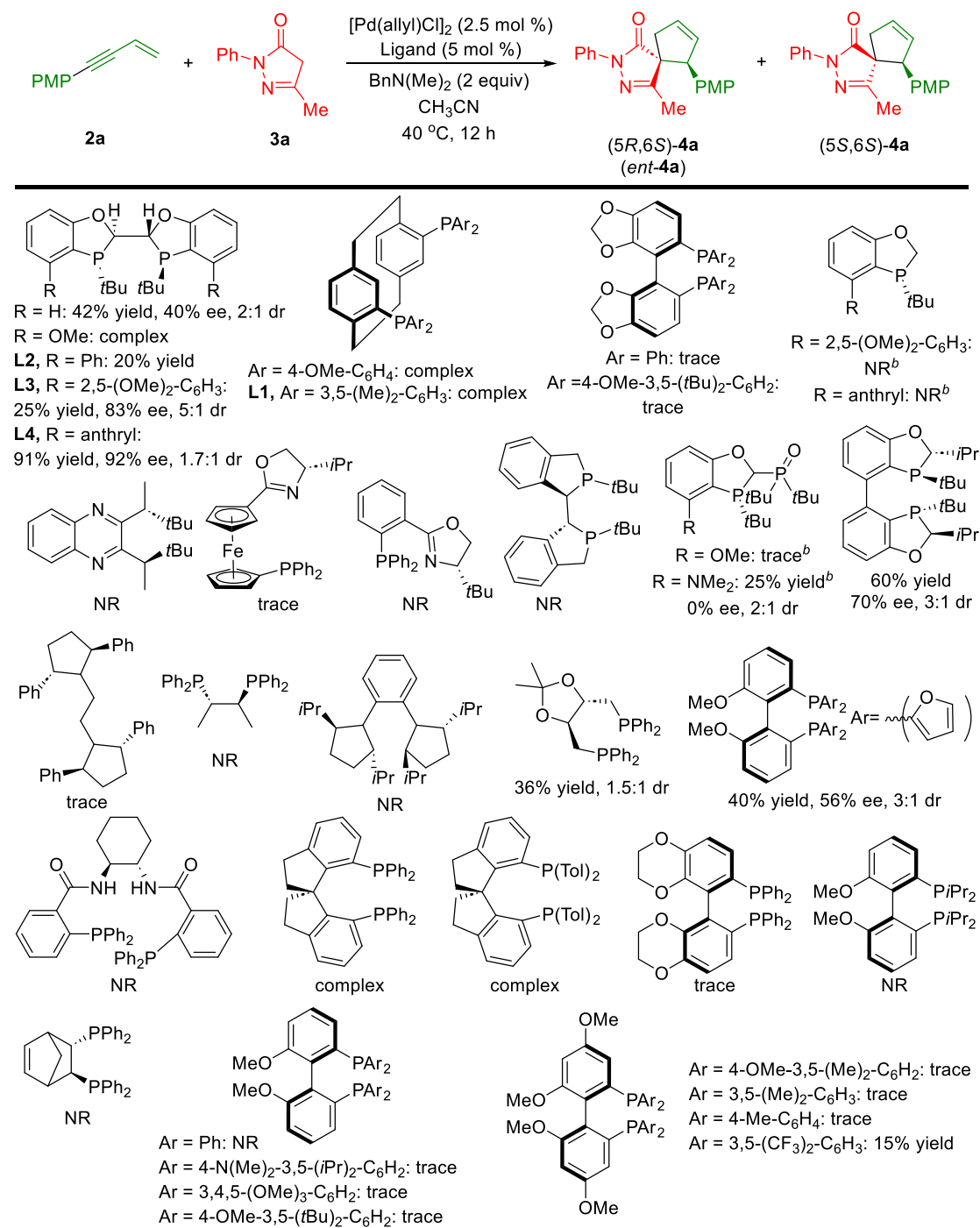
**Table S3. Further investigation of solvent effect on the enantioselectivity<sup>a</sup>**



entry	solvent (C <sub>6</sub> HF <sub>5</sub> + CH <sub>3</sub> CN)	yield (%) <sup>b</sup>	ee (%) <sup>c</sup>	dr <sup>d</sup>
1	0.5 mL + 0 mL	54	0	10:1
2	0.49 mL + 0.01 mL	51	4	10:1
3	0.45 mL + 0.05 mL	63	45	10:1
4	0.40 mL + 0.10 mL	71	70	10:1
5	0.30 mL + 0.20 mL	68	82	10:1
6	0.20 mL + 0.30 mL	77	93	10:1
7	0.10 mL + 0.40 mL	71	92	10:1
8	0 mL + 0.5 mL	69	94	8:1

<sup>a</sup>Reactions were performed with **1a** (0.1 mmol), **3a** (0.12 mmol), [Pd(allyl)Cl]<sub>2</sub> (5 mol %), **L4** (10 mol %), DIPEA (2 equiv) in 0.5 mL of solvent at 40 °C for 10 h. <sup>b</sup>Isolated yield. <sup>c</sup>ee was determined by chiral HPLC. <sup>d</sup>dr was determined by <sup>1</sup>H NMR.

**Table S4. Screening chiral ligands for Pd-catalyzed asymmetric sequential hydroalkylation of 1,3-enyne **2a** with pyrazolone **3a**<sup>a</sup>**



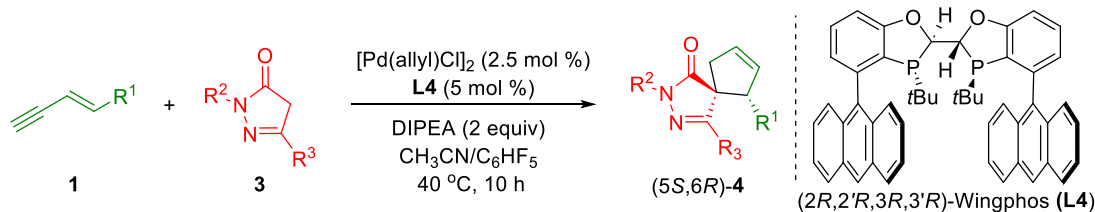
<sup>a</sup>Reactions were performed with **2a** (0.12 mmol), **3a** (0.1 mmol), [Pd(allyl)Cl]<sub>2</sub> (2.5 mol %), ligand (5 mol %) and BnN(Me)<sub>2</sub> (2 equiv) in 0.5 mL of CH<sub>3</sub>CN at 40 °C for 12 h. Yield of isolated product, ee was determined by chiral HPLC, dr was determined by <sup>1</sup>H NMR. <sup>b</sup>Ligand (10.0 mol %).

**Table S5. Screening base for Pd-catalyzed asymmetric sequential hydroalkylation of internal 1,3-enyne **2a** with pyrazolone **3a**<sup>a</sup>**

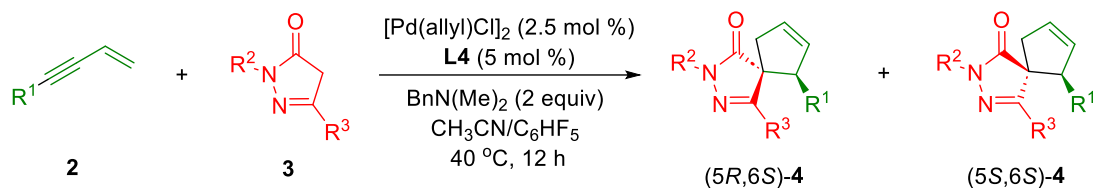
entry	base	yield (%) <sup>b</sup>	ee of (5 <i>R</i> ,6 <i>S</i> )- <b>4a</b> (%) <sup>c</sup>	dr <sup>c</sup>
1	DMAP	trace		
2	Et <sub>3</sub> N	48	92	1:1
3	DIPEA	20	85	1:1
4	BnN(Me) <sub>2</sub>	91	92	1.7:1
5	BnN(Et) <sub>2</sub>	78	-	1.5:1
6	BnN(Me)(Et)	74		1.5:1
7	Bn <sub>2</sub> NMe	trace	-	-
8	Bn <sub>3</sub> N	trace	-	-
9		trace	-	-
10		trace	-	-
11		33	-	-
12	PMP	20	-	-
13	DBU	trace	-	-
14	DABCO	15	-	-
15	quinuclidine	trace	-	-

<sup>a</sup>Reactions were performed with **2a** (0.12 mmol), **3a** (0.1mmol), [Pd(allyl)Cl]<sub>2</sub> (2.5 mol %), **L4** (5 mol %), base (2 equiv) in 0.5 mL of CH<sub>3</sub>CN at 40 °C for 12 h. <sup>b</sup>Isolated yield. <sup>c</sup>ee was determined by chiral HPLC. <sup>d</sup>dr was determined by <sup>1</sup>H-NMR. DMAP = 4-Dimethylaminopyridine. PMP = 1,2,2,6,6-Pentamethylenepiperidine. DBU = 1,8-Diazabicyclo[5.4.0]undec-7-ene. DABCO = 1,4-Diazabicyclo[2.2.2]octane.

## 4. General Procedure for Asymmetric Sequential Hydroalkylation with 1,3-Enynes

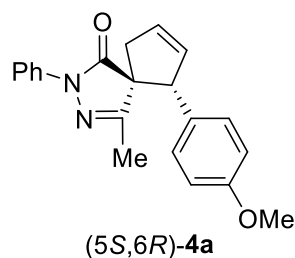


Dissolving the [Pd(allyl)Cl]<sub>2</sub> (0.9 mg, 2.5 mol %), and **L4** (3.7 mg, 5 mol %) in a mixed solvent of CH<sub>3</sub>CN/C<sub>6</sub>HF<sub>5</sub> (3:2, 0.5 mL, 0.2 M) was stirred for 15 min at room temperature. Subsequently, 1,3-enynes **1** (0.1 mmol, 1 equiv), pyrazolones **3** (0.12 mmol, 1.2 equiv), and DIPEA (2 equiv, 32 μL) were added. The reaction mixture was stirred at 40 °C for 10 h under an Ar atmosphere. The solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 95:5 to 90:10) to afford the spiropyrazolones (5*S*, 5*R*)-**4**.



In an Ar-filled glovebox, dissolving the [Pd(allyl)Cl]<sub>2</sub> (0.9 mg, 2.5 mol %), and **L4** (3.7 mg, 5 mol %) in a mixed solvent of CH<sub>3</sub>CN/C<sub>6</sub>HF<sub>5</sub> (3:2, 0.5 mL, 0.2 M) was stirred for 15 min at room temperature. Subsequently, 1,3-enynes **2** (0.2 mmol, 1.2 equiv), pyrazolones **3** (0.1 mmol, 1 equiv), and BnN(Me)<sub>2</sub> (2 equiv, 30 μL) were added. The reaction mixture was stirred at 40 °C for 12 h outside the glove box. The solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 95:5 to 90:10) to afford the spiropyrazolones (5*R*, 6*S*)-**4** and (5*S*, 6*S*)-**4**.

**(5*S*,6*R*)-6-(4-methoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 26.2 mg, 79% yield, 93% ee, 10:1 dr.  $R_f = 0.40$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +19.87$  (*c* 1.0, CHCl<sub>3</sub>).

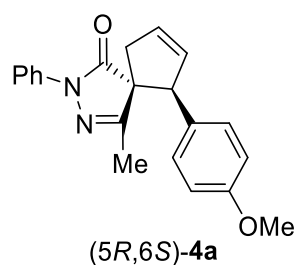
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.91 (d, *J* = 8.2 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.19 (t, *J* = 7.6 Hz, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.08-6.03 (m, 1H), 6.01-5.96 (m, 1H), 4.67 (s, 1H), 3.75 (s, 3H), 3.05-2.96 (m, 1H), 2.75-2.67 (m, 1H), 1.68 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.9, 163.0, 159.0, 138.3, 131.7, 130.0, 129.4, 129.0, 128.1, 125.0, 119.0, 114.0, 64.5, 59.3, 55.3, 40.7, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 9.5$  min,  $t_{\text{major}} = 11.2$  min.

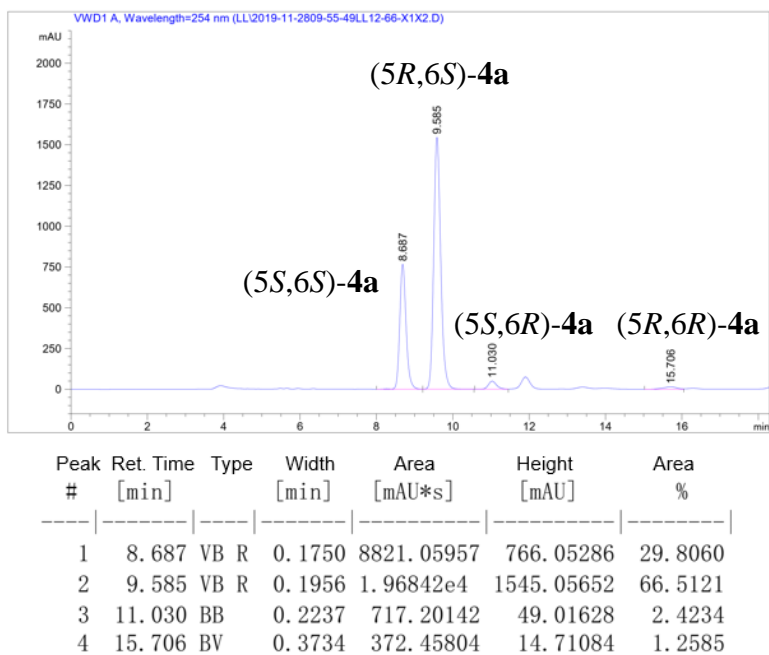
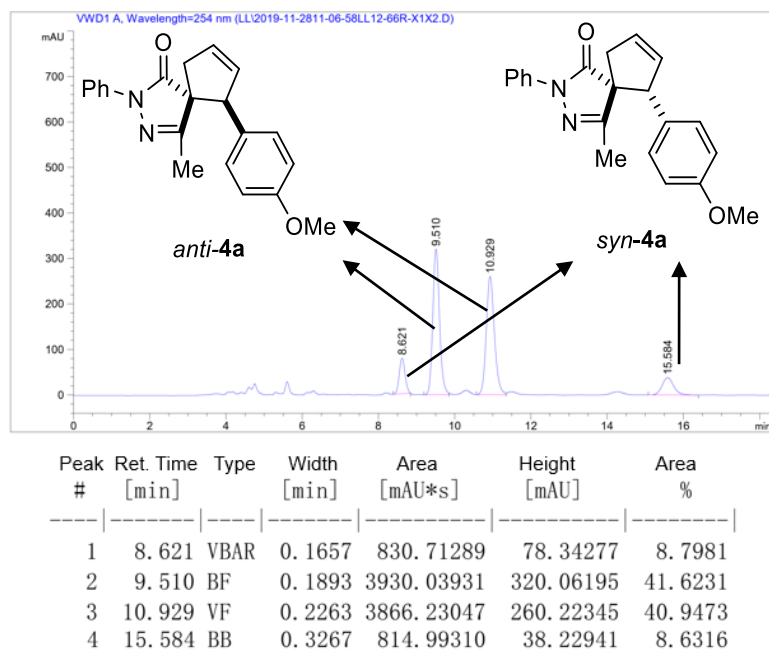
**HRMS** (ESI) calcd for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 333.1598, found 333.1598.

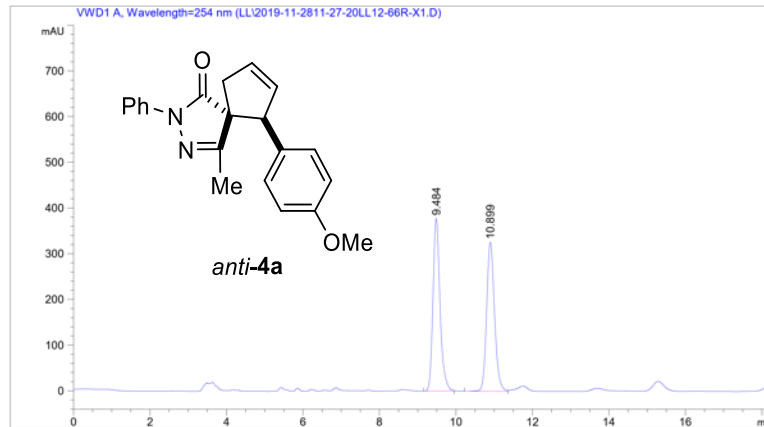
**(5*R*,6*S*)-6-(4-methoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



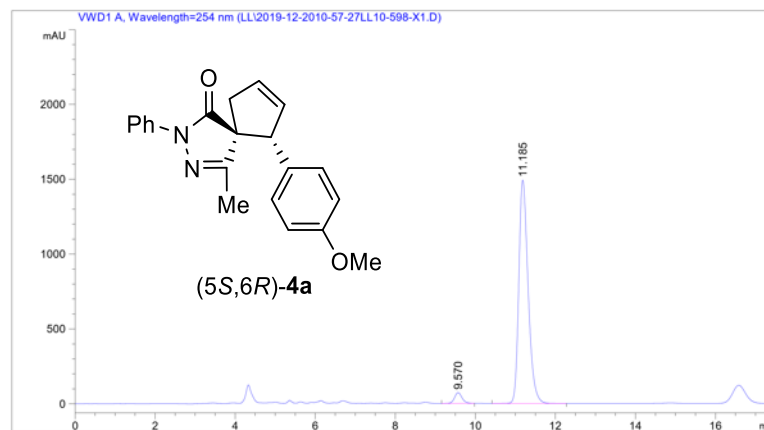
Yellow oil, 21.2 mg, 64% yield, 91% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 9.5$  min,  $t_{\text{minor}} = 11.0$  min.

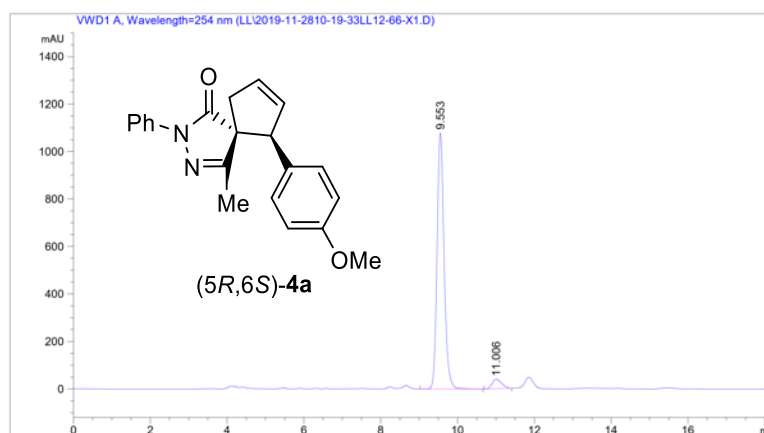




Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.484	BBA	0.1935	4800.84180	377.13745	50.6649
2	10.899	BF	0.2192	4674.84180	326.15051	49.3351



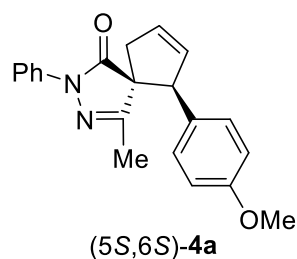
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.570	BBA	0.1999	938.16968	72.03567	3.7535
2	11.185	BB	0.2470	2.40561e4	1492.87915	96.2465



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.553	VB R	0.1934	1.36298e4	1078.74915	95.2512
2	11.006	BB	0.2587	679.51477	40.09328	4.7488



**(5*S*,6*S*)-6-(4-methoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



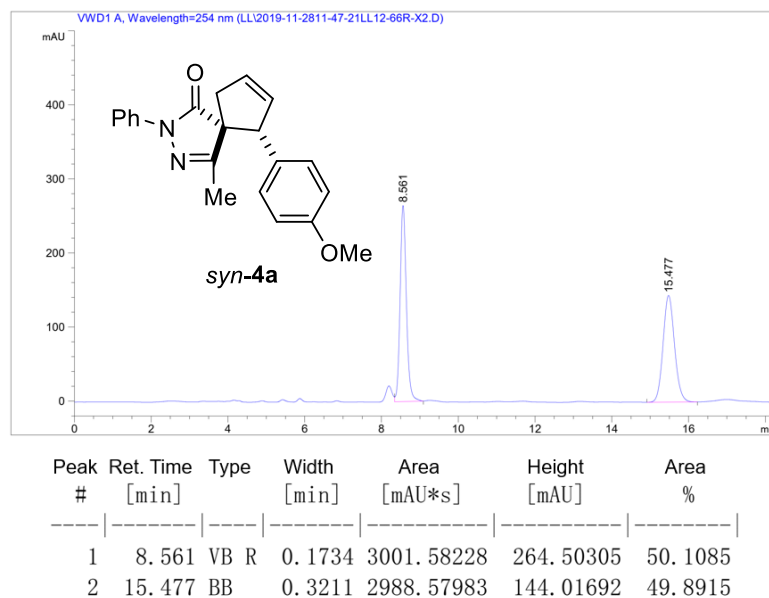
Yellow oil, 9.6 mg, 29% yield, 94% ee.  $R_f = 0.35$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -22.82$  (*c* 1.0, CHCl<sub>3</sub>).

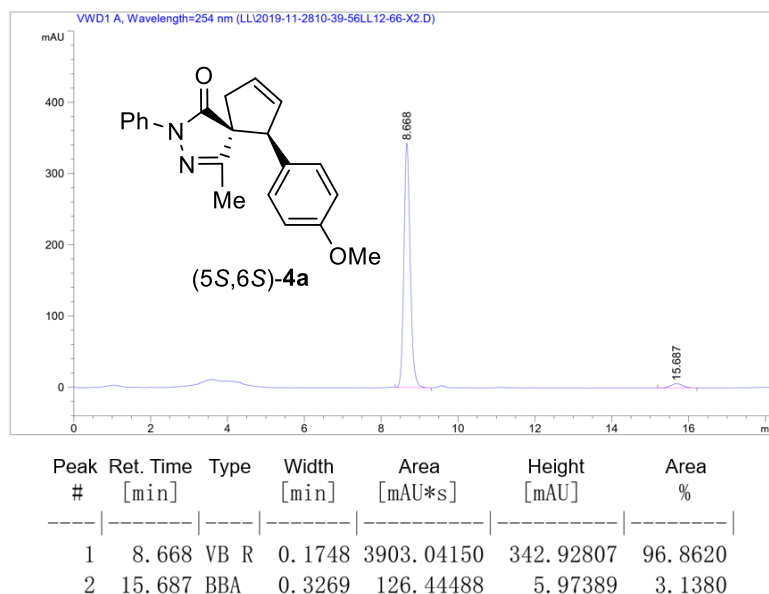
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.43 (d,  $J = 7.8$  Hz, 2H), 7.28-7.19 (m, 5H), 7.12 (d,  $J = 7.2$  Hz, 2H), 7.07 (t,  $J = 7.2$  Hz, 1H), 6.12-6.08 (m, 1H), 5.92-5.88 (m, 1H), 4.34 (t,  $J = 1.8$  Hz, 1H), 2.98-2.92 (m, 1H), 2.75-2.69 (m, 1H), 2.26 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.1, 162.9, 159.2, 137.9, 131.7, 130.6, 129.4, 129.3, 128.7, 124.8, 119.2, 113.7, 63.0, 58.4, 55.3, 39.4, 13.8.

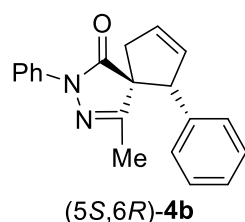
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 8.7$  min,  $t_{\text{minor}} = 15.7$  min.

**HRMS (ESI)** calcd for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 333.1598, found 333.1598.





**(5S,6R)-4-methyl-2,6-diphenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 21.1 mg, 70% yield, 94% ee, 10:1 dr.  $R_f = 0.45$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +24.08$  (*c* 1.0, CHCl<sub>3</sub>).

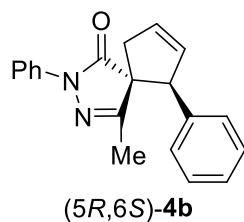
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.91 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.27-7.17 (m, 4H), 7.13-7.07 (m, 2H), 6.12-6.06 (m, 1H), 6.04-5.97 (m, 1H), 6.01-5.96 (m, 1H), 4.71 (s, 1H), 3.07-2.97 (m, 1H), 2.75-2.67 (m, 1H), 2.76-2.67 (m, 1H), 1.65 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.8, 162.8, 138.2, 138.1, 131.3, 129.7, 129.0, 128.7, 127.7, 127.1, 125.1, 119.0, 64.4, 59.8, 40.8, 15.1.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 7.1$  min,  $t_{\text{major}} = 10.6$  min.

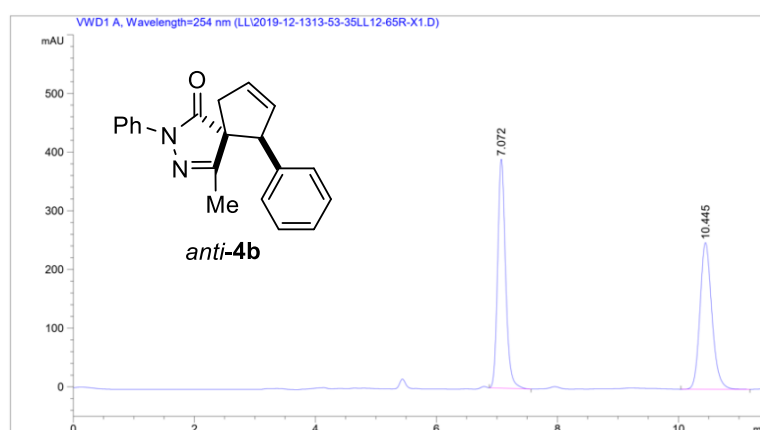
**HRMS (ESI)** calcd for C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 303.1492, found 303.1491.

**(5R,6S)-4-methyl-2,6-diphenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**

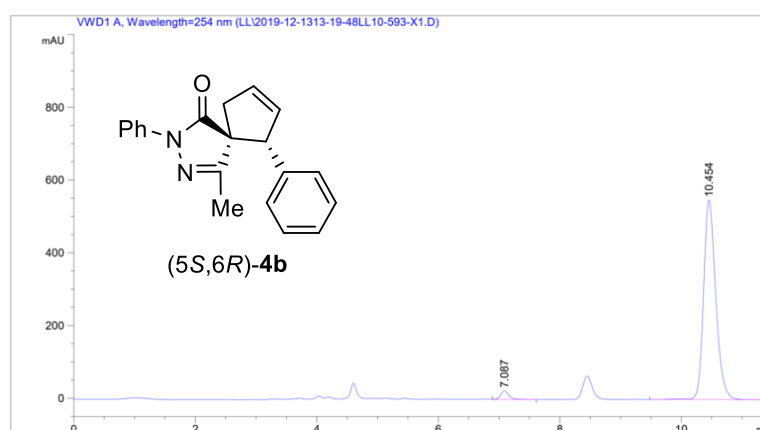


Yellow solid, 21.2 mg, 70% yield, 90% ee.

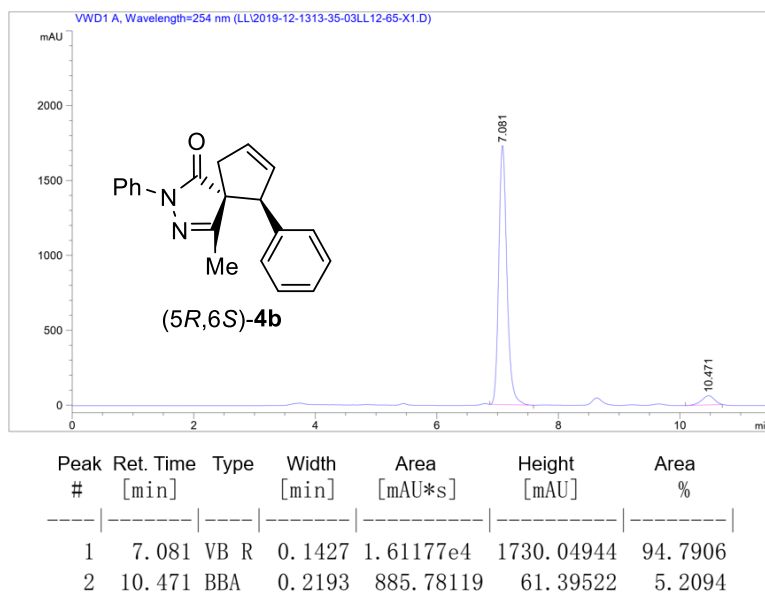
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda$  = 254 nm, retention time:  $t_{\text{major}}$  = 7.1 min,  $t_{\text{minor}}$  = 10.5 min.



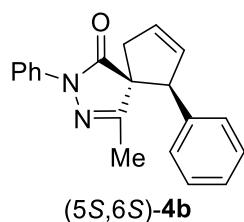
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.072	BB	0.1388	3538.88135	390.26102	50.8174
2	10.445	BB	0.2100	3425.03931	249.70245	49.1826



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.087	VB S	0.1438	226.00227	23.80328	2.8735
2	10.454	VB R	0.2104	7638.99854	548.74799	97.1265



**(5S,6S)-4-methyl-2,6-diphenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



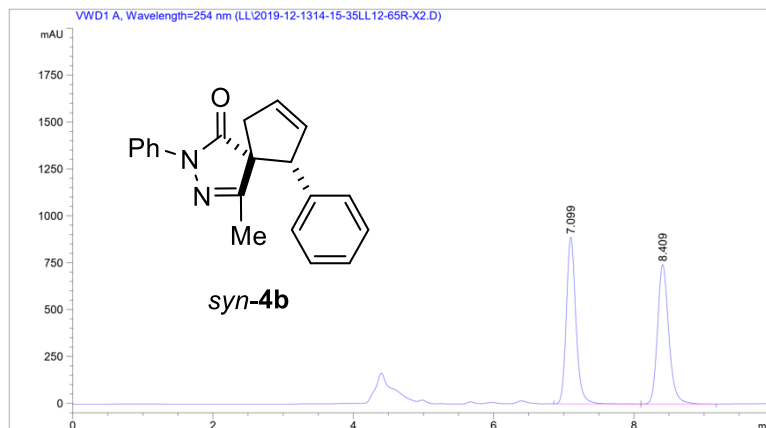
White solid, 7.8 mg, 26% yield, 95% ee.  $R_f = 0.40$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -16.31$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.43 (d, *J* = 7.8 Hz, 2H), 7.28-7.19 (m, 5H), 7.12 (d, *J* = 7.2 Hz, 2H), 7.07 (t, *J* = 7.2 Hz, 1H), 6.12-6.08 (m, 1H), 5.92-5.88 (m, 1H), 4.34 (t, *J* = 1.8 Hz, 1H), 2.98-2.92 (m, 1H), 2.75-2.69 (m, 1H), 2.26 (s, 3H).

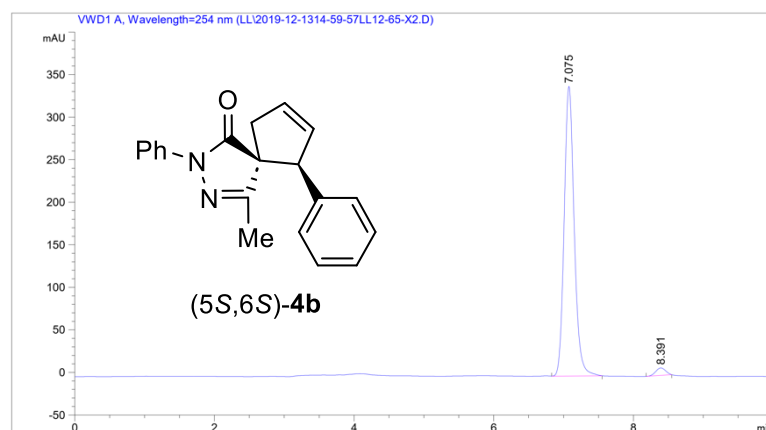
<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.9, 162.8, 137.8, 137.2, 131.3, 131.0, 128.7, 128.3, 128.3, 127.8, 124.8, 119.2, 63.0, 58.9, 39.4, 13.9.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 7.1$  min,  $t_{\text{minor}} = 8.4$  min.

**HRMS** (ESI) calcd for C<sub>20</sub>H<sub>19</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 303.1492, found 303.1492.

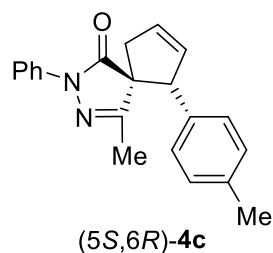


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.099	BV R	0.1446	8432.69922	889.37305	50.3384
2	8.409	BB	0.1705	8319.33301	743.60504	49.6616



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.075	BBA	0.1523	3391.32300	340.28882	97.5233
2	8.391	BBA	0.1563	86.12506	8.79254	2.4767

**(5S,6R)- 4-methyl-2-phenyl-6-(p-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 24.2 mg, 77% yield, 94% ee, 9:1 dr.  $R_f = 0.46$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +34.99$  (*c* 1.0, CHCl<sub>3</sub>).

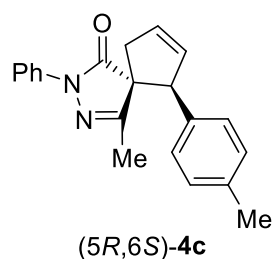
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.91 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.2 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 2H), 7.00 (d, *J* = 8.0 Hz, 2H), 6.11-6.05 (m, 1H), 6.02-5.96 (m, 1H), 4.67 (s, 1H), 3.75 (s, 3H), 3.05-2.96 (m, 1H), 2.75-2.67 (m, 1H), 1.68 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.9, 163.0, 159.0, 138.3, 131.7, 130.0, 129.4, 129.0, 128.1, 125.0, 119.0, 114.0, 64.5, 59.3, 55.3, 40.7, 15.2.

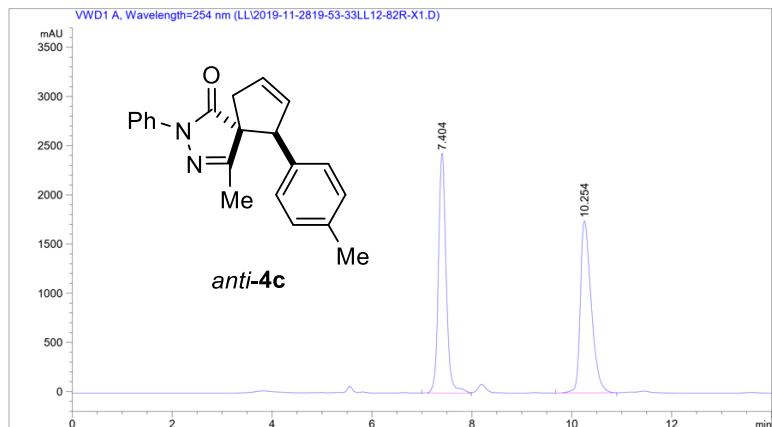
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 7.3$  min,  $t_{\text{major}} = 10.1$  min.

**HRMS** (ESI) calcd for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 317.1648, found 317.1645.

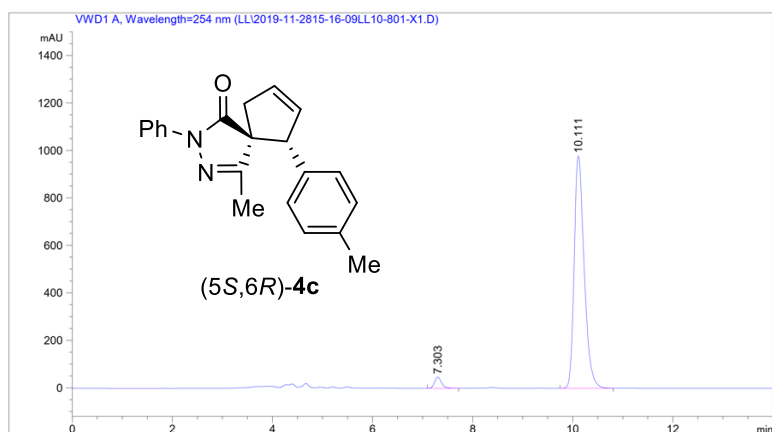
**(5R,6S)- 4-methyl-2-phenyl-6-(p-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



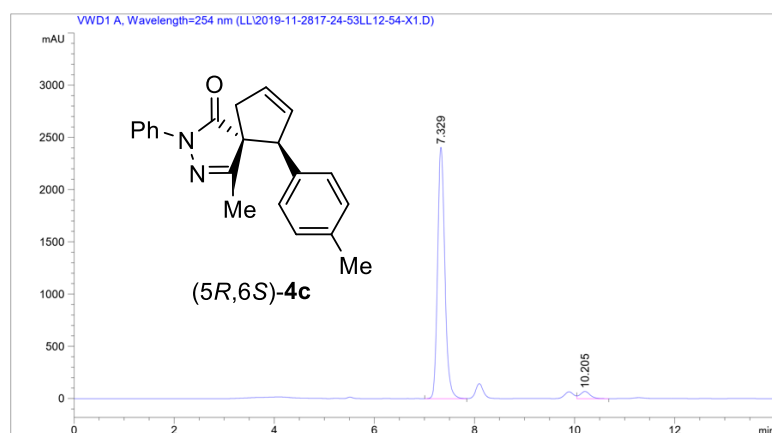
Yellow oil, 22.2 mg, 70% yield, 93% ee. **HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 7.3$  min,  $t_{\text{minor}} = 10.2$  min.



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.404	BF	0.1643	2.61771e4	2437.52490	49.7000
2	10.254	BF	0.2296	2.64932e4	1750.05737	50.3000

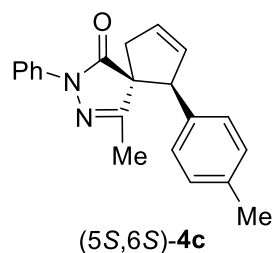


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.303	FF	0.1457	447.06006	47.09787	3.1881
2	10.111	FF	0.2118	1.35757e4	979.00830	96.8119



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.329	BV	0.1555	2.42266e4	2406.49438	96.2539
2	10.205	VF	0.2079	942.86719	68.78529	3.7461

**(5*S*,6*S*)- 4-methyl-2-phenyl-6-(*p*-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



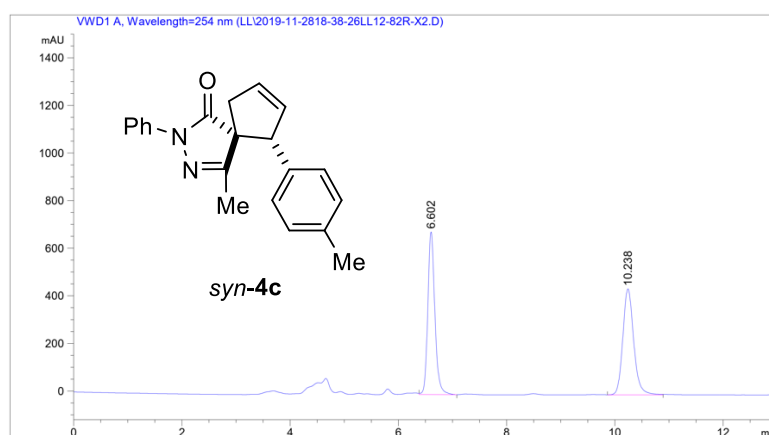
Yellow oil, 8.2 mg, 26% yield, 89% ee.  $R_f = 0.42$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -22.26$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.48 (d,  $J = 7.2$  Hz, 2H), 7.26 (t,  $J = 7.2$  Hz, 2H), 7.07 (q,  $J = 4.8$  Hz, 3H), 7.01 (d,  $J = 7.8$  Hz, 2H), 6.10-6.06 (m, 1H), 5.91-5.86 (m, 1H), 4.30 (s, 1H), 2.99-2.92 (m, 1H), 2.74-2.67 (m, 1H), 2.28 (s, 3H), 2.25 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.0, 162.9, 137.9, 137.4, 134.2, 131.6, 130.6, 129.0, 128.7, 128.3, 124.8, 119.2, 62.9, 58.6, 39.5, 21.2, 13.8.

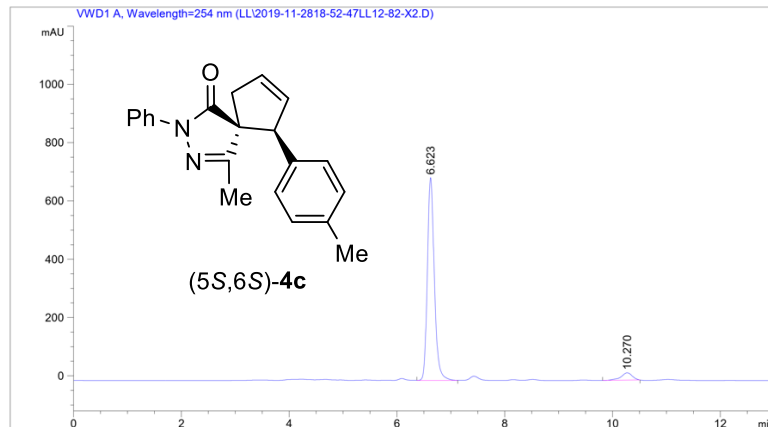
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 6.6$  min,  $t_{\text{minor}} = 10.3$  min.

**HRMS (ESI) calcd for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 317.1648, found 317.1650.**



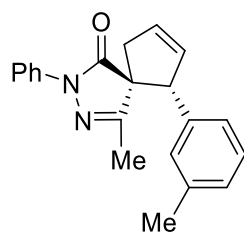
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.602	VB R	0.1386	6182.14307	683.11212	49.8540
2	10.238	FFA	0.2128	6218.35596	445.52859	50.1460





Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.623	VV	0.1380	6256.38184	695.35980	94.4857
2	10.270	BBA	0.2187	365.12720	25.10624	5.5143

**(5S,6R)-4-methyl-2-phenyl-6-(m-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



**(5S,6R)-4d**

Yellow oil, 20.1 mg, 67% yield, 93% ee, 10:1 dr.  $R_f = 0.46$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +19.85$  (c 1.0, CHCl<sub>3</sub>).

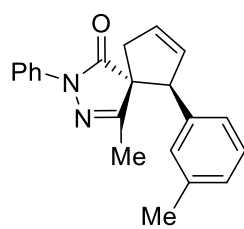
**<sup>1</sup>H NMR** (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.88 (d,  $J = 8.4$  Hz, 2H), 7.41 (t,  $J = 7.6$  Hz, 2H), 7.20 (t,  $J = 7.2$  Hz, 1H), 7.13 (t,  $J = 7.6$  Hz, 1H), 7.03 (d,  $J = 7.6$  Hz, 1H), 6.90 (d,  $J = 7.6$  Hz, 2H), 6.11-6.05 (m, 1H), 6.03-5.96 (m, 1H), 4.67 (s, 1H), 3.06-2.97 (m, 1H), 2.76-2.67 (m, 1H), 2.23 (s, 3H), 1.68 (s, 3H).

**<sup>13</sup>C NMR** (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.9, 163.0, 159.0, 138.3, 138.2, 137.9, 131.5, 129.5, 129.0, 128.6, 128.4, 127.8, 125.2, 124.1, 119.2, 64.5, 59.9, 40.7, 21.5, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 10.3$  min,  $t_{\text{major}} = 14.5$  min.

**HRMS** (ESI) calcd for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 317.1648, found 317.1650.

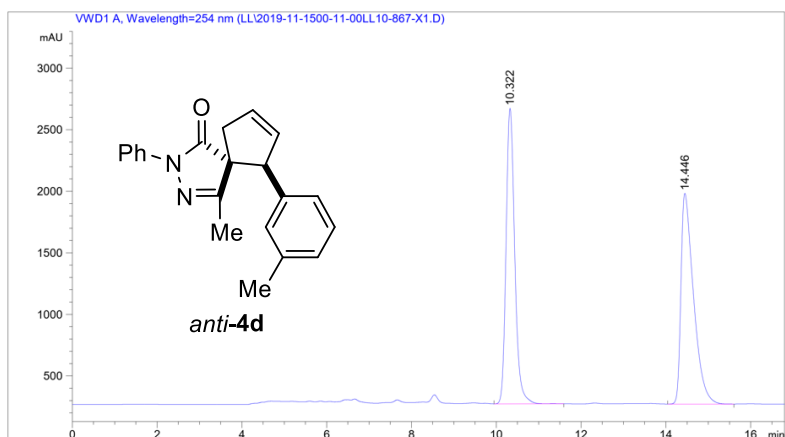
**(5R,6S)-4-methyl-2-phenyl-6-(m-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



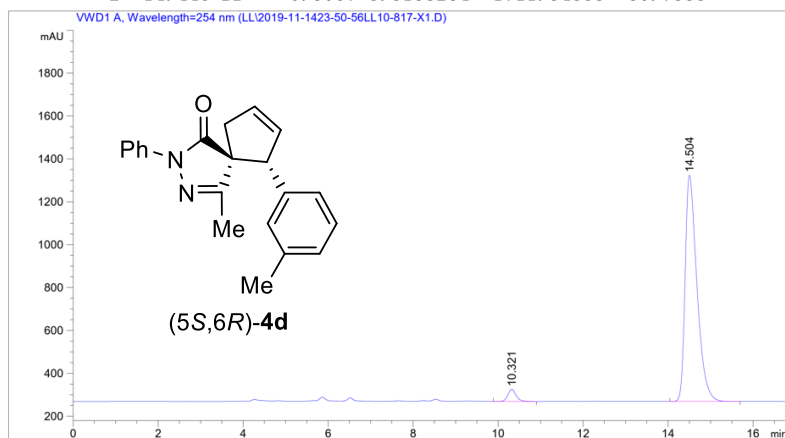
**(5R,6S)-4d**

Yellow oil, 21.5mg, 68% yield, 92% ee.

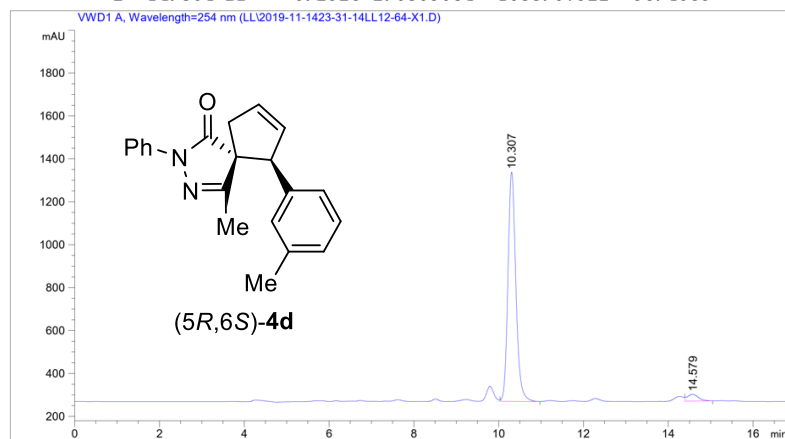
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 10.3$  min,  $t_{\text{minor}} = 14.6$  min.



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.322	BV R	0.2187	3.41070e4	2399.59253	49.2412
2	14.446	BB	0.3067	3.51582e4	1711.34888	50.7588

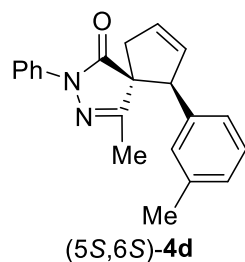


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.321	BB	0.2054	756.91199	56.11644	3.5931
2	14.504	BB	0.2926	2.03090e4	1055.07922	96.4069



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.307	VB	0.1987	1.38041e4	1068.85925	96.0067
2	14.579	VBA	0.2699	574.16425	31.61188	3.9933

**(5S,6S)-4-methyl-2-phenyl-6-(m-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



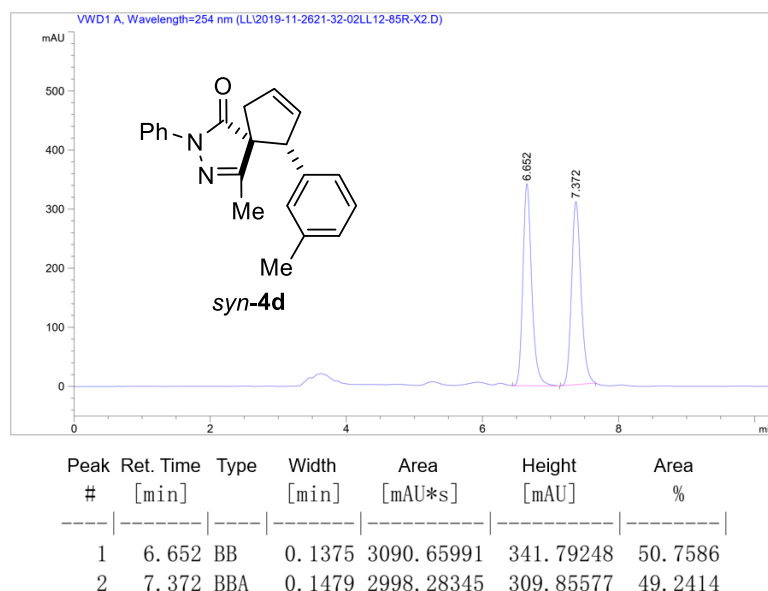
Yellow oil, 7.7 mg, 24% yield, 93% ee.  $R_f = 0.42$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -19.13$  (*c* 1.0, CHCl<sub>3</sub>).

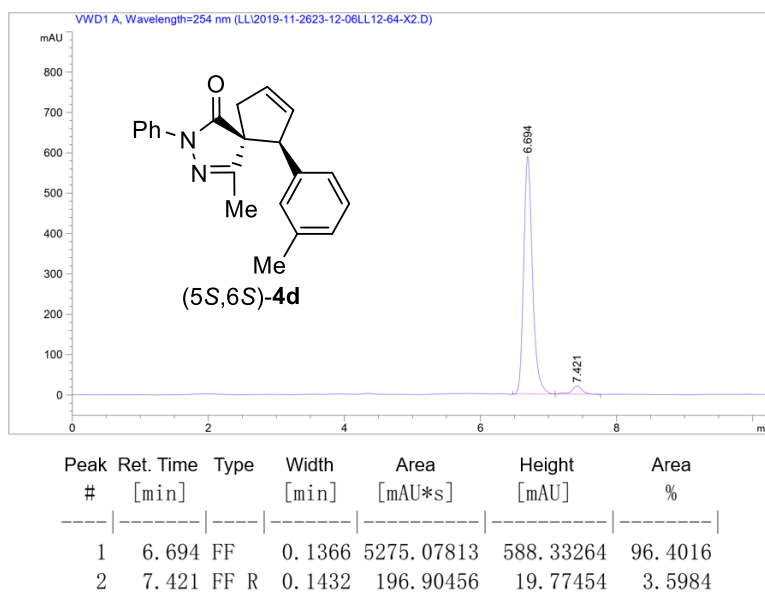
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.45 (d, *J* = 7.8 Hz, 2H), 7.27-7.22 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 7.06 (t, *J* = 7.2 Hz, 1H), 7.01 (d, *J* = 7.8 Hz, 1H), 6.94-6.89 (m, 2H), 6.10-6.06 (m, 1H), 5.90-5.86 (m, 1H), 4.29 (t, *J* = 1.8 Hz, 1H), 2.97-2.90 (m, 1H), 2.73-2.66 (m, 1H), 2.25 (s, 3H), 2.24 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.0, 162.9, 137.9, 137.8, 137.2, 131.4, 130.8, 129.0, 128.7, 128.5, 128.2, 125.4, 124.8, 119.2, 62.9, 58.8, 39.4, 21.5, 13.8.

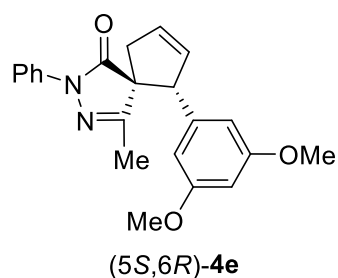
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 6.7$  min,  $t_{\text{minor}} = 7.4$  min.

**HRMS (ESI)** calcd for C<sub>21</sub>H<sub>21</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 317.1648, found 317.1648.





**(5S,6R)-6-(3,5-dimethoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



White solid, 22.1 mg, 61% yield, 93% ee, 10:1 dr.  $R_f = 0.35$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +36.37$  (*c* 1.0, CHCl<sub>3</sub>).

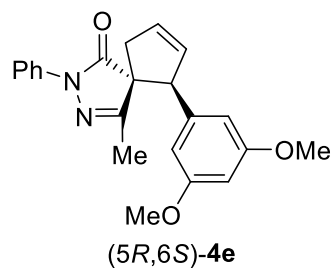
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.91 (d, *J* = 8.4 Hz, 2H), 7.39 (t, *J* = 7.6 Hz, 2H), 7.18 (t, *J* = 7.2 Hz, 1H), 6.30 (s, 1H), 6.23 (s, 2H), 6.08-6.01 (m, 1H), 6.01-5.96 (m, 1H), 4.64 (s, 1H), 3.59 (s, 6H), 3.06-2.97 (m, 1H), 2.74-2.65 (m, 1H), 1.74 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.8, 163.0, 161.0, 140.4, 138.2, 131.2, 129.7, 129.0, 118.9, 104.9, 99.8, 64.5, 60.0, 55.3, 40.6, 15.3.

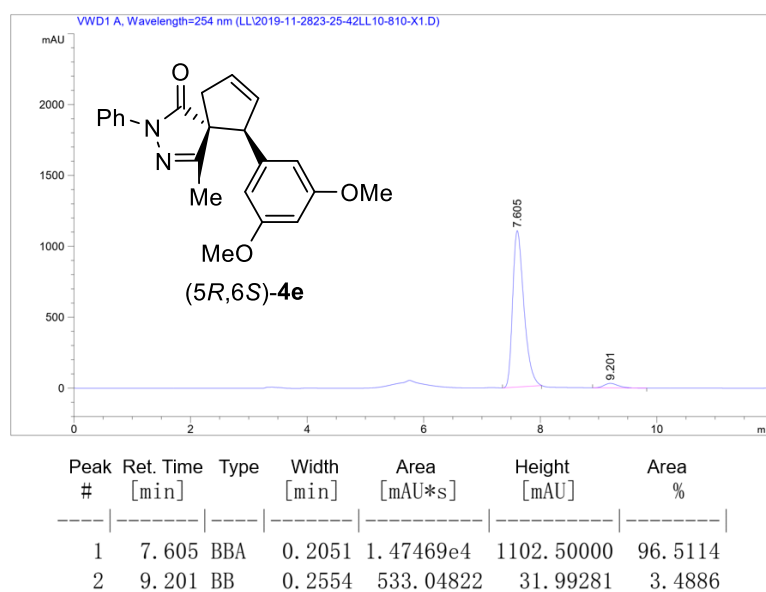
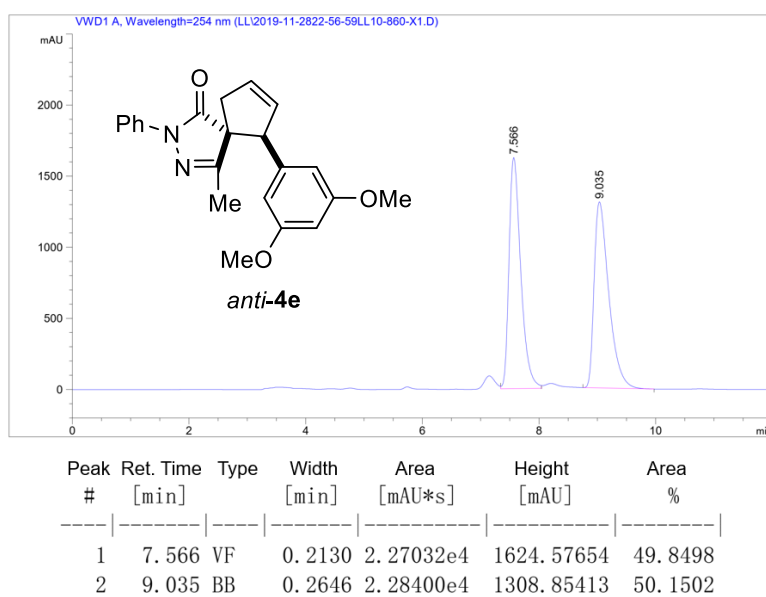
**HPLC analysis:** Daicel CHIRALPAK OD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 7.6$  min,  $t_{\text{minor}} = 9.2$  min.

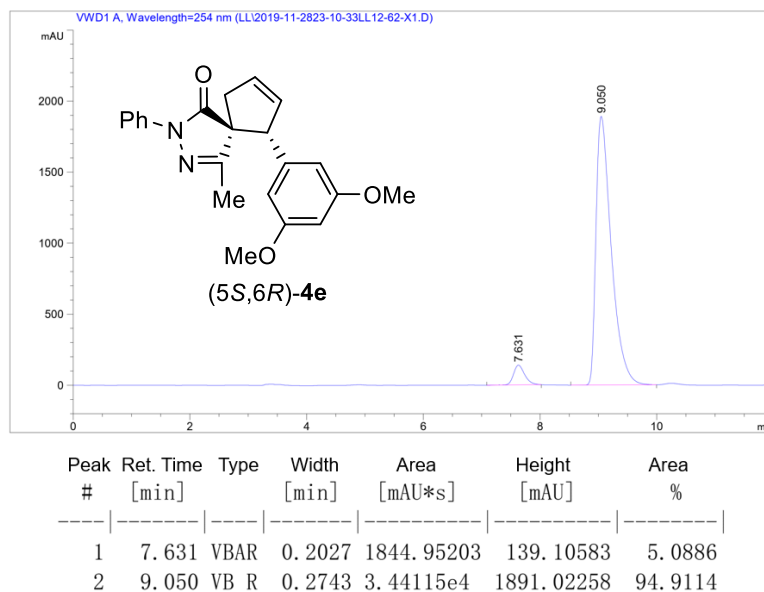
**HRMS** (ESI) calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 363.1703, found 363.1703.

**(5R,6S)-6-(3,5-dimethoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**

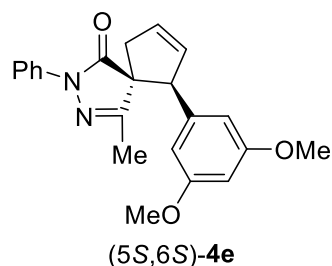


White solid, 19.2 mg, 53% yield, 90% ee. **HPLC analysis:** Daicel CHIRALPAK OD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda$  = 254 nm, retention time:  $t_{\text{minor}} = 7.6$  min,  $t_{\text{major}} = 9.1$  min.





**(5S,6S)-6-(3,5-dimethoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



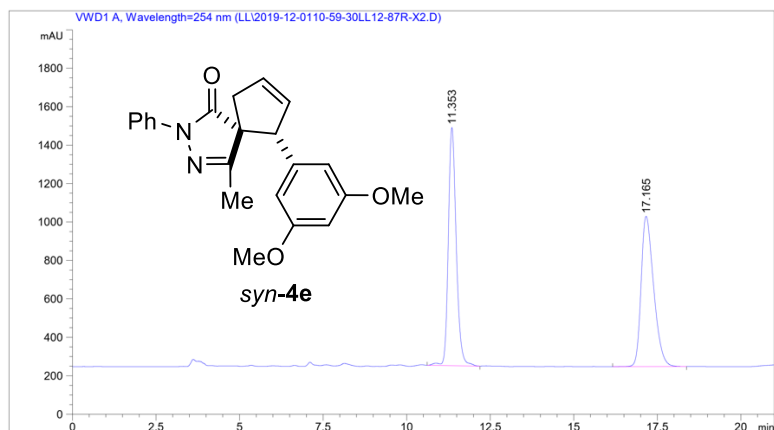
Yellow oil, 6.6 mg, 18% yield, 90% ee.  $R_f = 0.32$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -10.21$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.54 (d, *J* = 7.8 Hz, 2H), 7.31-7.24 (m, 3H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.31 (s, 1H), 6.27 (s, 1H), 6.11-6.07 (m, 1H), 5.89-5.86 (m, 1H), 4.25 (s, 1H), 3.67 (s, 6H), 2.94 (d, *J* = 17.4Hz, 1H), 2.69 (d, *J* = 17.4Hz, 1H), 2.23 (s, 3H).

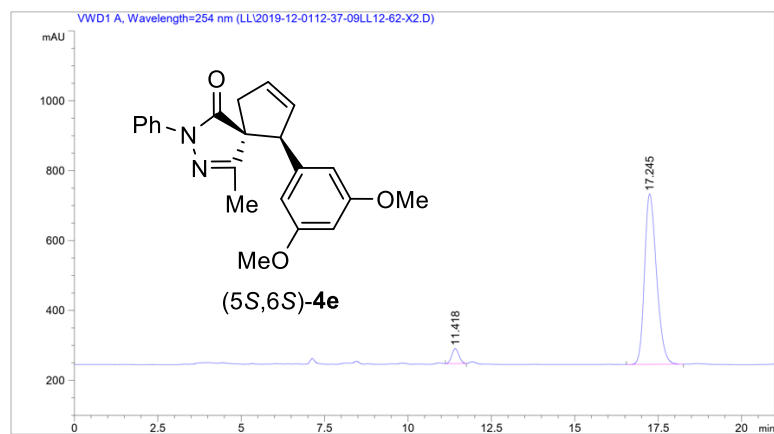
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.8, 162.8, 160.7, 139.7, 138.0, 131.1, 128.7, 124.8, 119.0, 106.5, 100.0, 62.8, 58.9, 55.4, 39.4, 13.8.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 11.4$  min,  $t_{\text{major}} = 17.2$  min.

**HRMS** (ESI) calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 363.1703, found 363.1704.



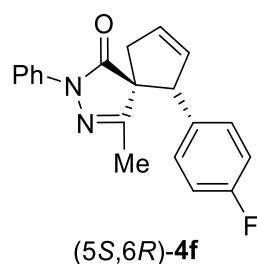
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.353	VB R	0.2505	2.03908e4	1238.80237	50.0209
2	17.165	BB	0.3979	2.03737e4	782.01758	49.9791



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.418	BB	0.2317	635.02228	42.89882	4.9461
2	17.245	BB	0.3819	1.22037e4	487.72076	95.0539



**(5*S*,6*R*)-6-(4-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 21.1 mg, 66% yield, 94% ee, 8:1 dr.  $R_f = 0.45$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +24.74$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.89 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.07 (t, *J* = 7.2 Hz, 2H), 6.94 (t, *J* = 8.4 Hz, 2H), 6.07-5.99 (m, 2H), 4.67 (s, 1H), 3.06-2.98 (m, 1H), 2.76-2.67 (m, 1H), 1.67 (s, 3H).

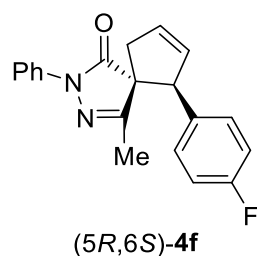
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.6, 162.6, 162.3 (d, <sup>1</sup>*J*<sub>C-F</sub> = 244.7 Hz), 138.2, 133.8 (d, <sup>3</sup>*J*<sub>C-F</sub> = 3.2 Hz), 131.2, 130.0, 129.0, 128.6, 128.6, 125.2, 119.0, 115.7 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.3 Hz), 64.5, 59.2, 40.7, 15.2.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  -114.6 (s, 1F, CF).

**HPLC analysis:** Daicel CHIRALPAK OD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 7.7$  min,  $t_{\text{minor}} = 7.6$  min.

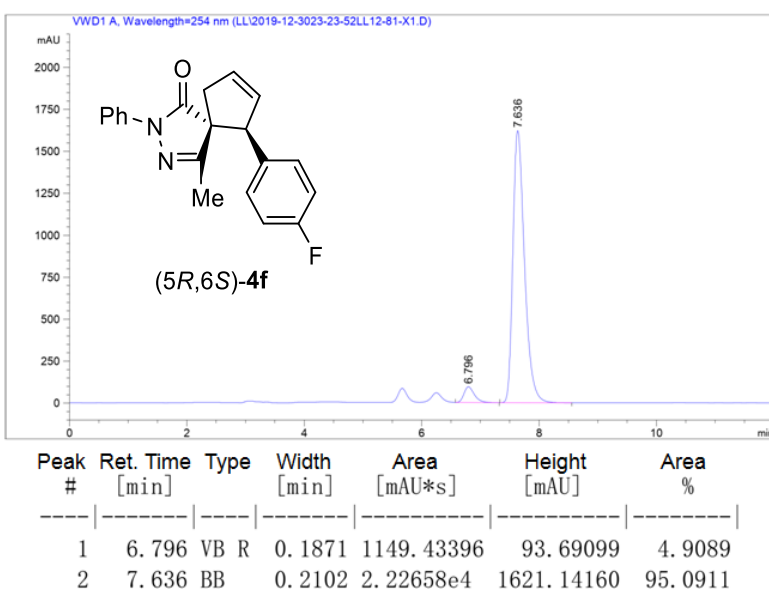
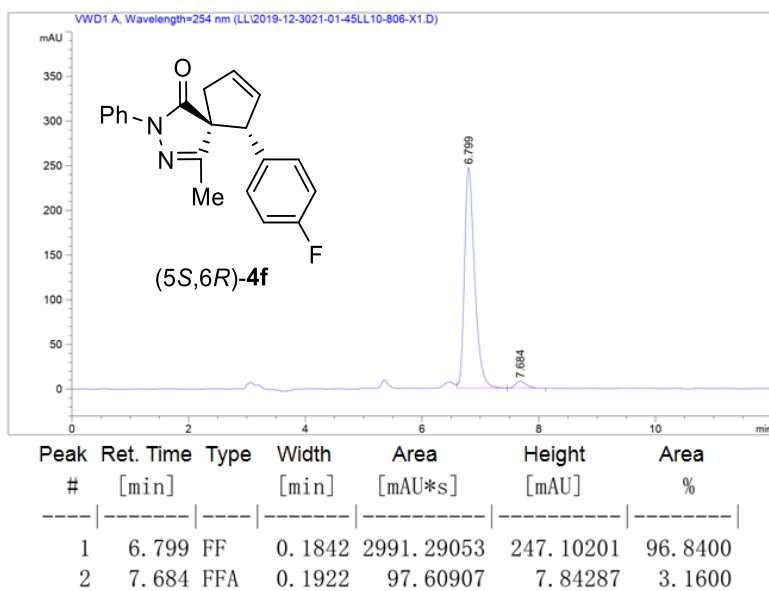
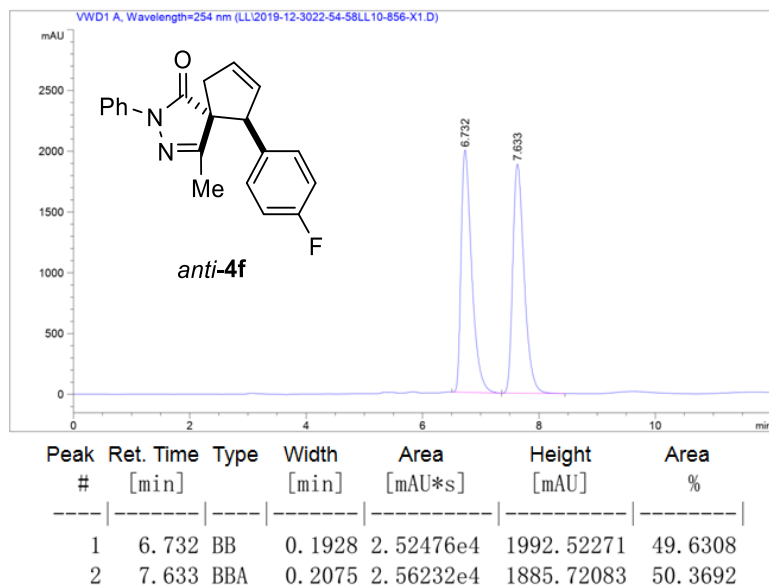
**HRMS** (ESI) calcd for C<sub>20</sub>H<sub>18</sub>FN<sub>2</sub>O [M + H]<sup>+</sup>: 321.1398, found 321.1401.

**(5*R*,6*S*)-6-(4-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**

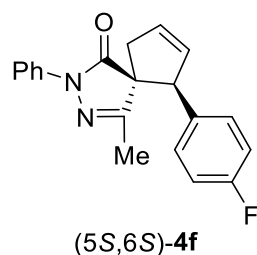


Yellow oil, 17.3 mg, 54% yield, 90% ee.

**HPLC analysis:** Daicel CHIRALPAK OD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 6.8$  min,  $t_{\text{major}} = 7.6$  min.



**(5S,6S)-6-(4-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 8.7 mg, 27% yield, 92% ee.  $R_f = 0.42$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -11.51$  (*c* 1.0, CHCl<sub>3</sub>).

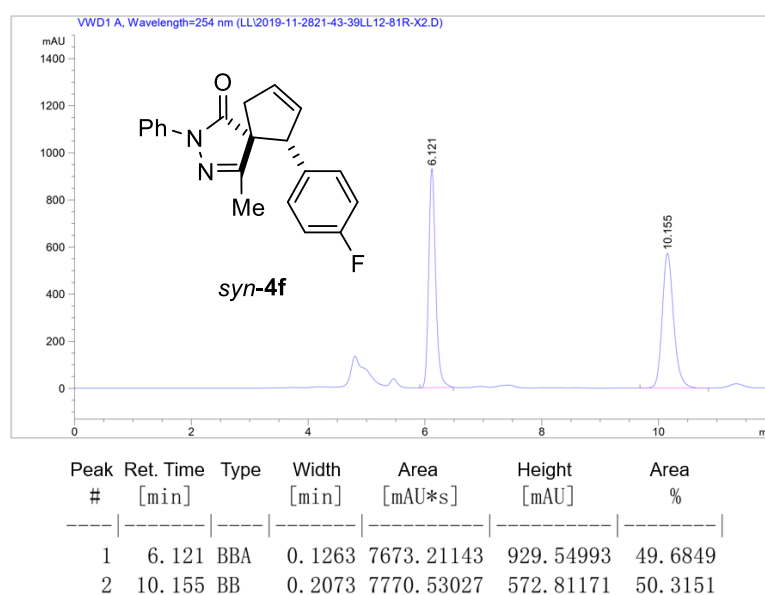
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.48 (d, *J* = 7.8 Hz, 2H), 7.27 (t, *J* = 7.8 Hz, 2H), 7.11-7.06 (m, 3H), 6.97-6.91 (m, 2H), 6.12-6.08 (m, 1H), 5.87-5.84 (m, 1H), 4.30 (s, 1H), 2.98-2.92 (m, 1H), 2.74-2.68 (m, 1H), 2.25 (s, 3H), 2.25 (s, 3H).

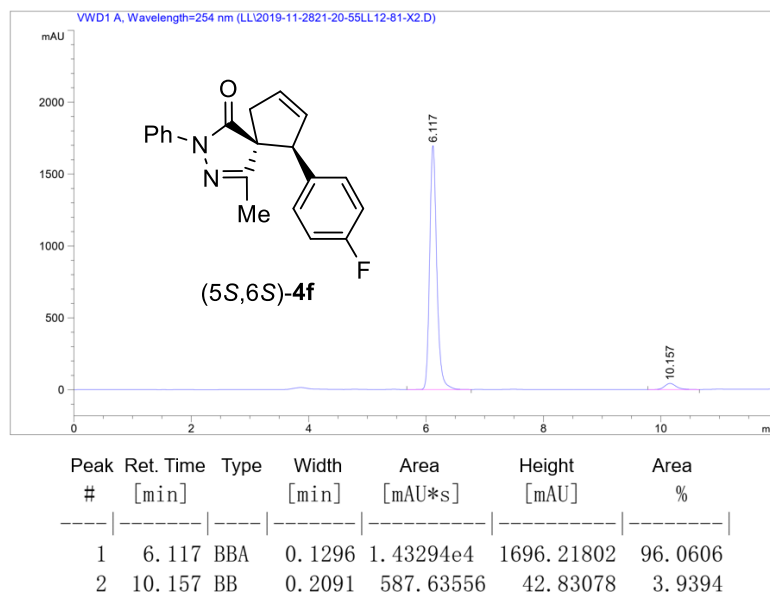
<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.8, 162.8, 162.4 (d, <sup>1</sup>*J*<sub>C-F</sub> = 244.8 Hz), 137.8, 133.0 (d, <sup>3</sup>*J*<sub>C-F</sub> = 3.2 Hz), 131.2, 131.2, 130.0, 129.9, 128.8, 124.9, 119.0, 151.2 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.7 Hz), 62.8, 58.2, 39.4, 13.8.

<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  -114.7 (s, 1F, CF).

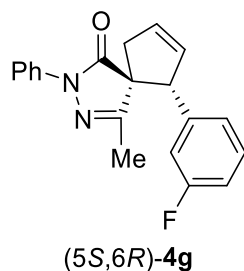
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 6.1$  min,  $t_{\text{minor}} = 10.2$  min.

**HRMS (ESI)** calcd for C<sub>20</sub>H<sub>18</sub>FN<sub>2</sub>O [M + H]<sup>+</sup>: 321.1398, found 321.1395.





**(5S,6R)-6-(3-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 19.3 mg, 60% yield, 91% ee, 7:1 dr.  $R_f = 0.46$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +25.62$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.89 (d, *J* = 8.0 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 2H), 7.25-7.17 (m, 2H), 6.97-6.90 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.07-6.00 (m, 2H), 4.69 (s, 1H), 3.07-2.98 (m, 1H), 2.76-2.68 (m, 1H), 1.68 (s, 3H).

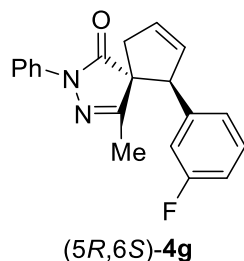
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.5, 163.0 (d, <sup>1</sup>*J*<sub>C-F</sub> = 245.6 Hz), 162.4, 140.7 (d, <sup>3</sup>*J*<sub>C-F</sub> = 6.9 Hz), 138.1, 130.7, 130.4, 130.3, 130.3, 129.0, 125.3, 122.9, 119.1, 114.7 (d, <sup>2</sup>*J*<sub>C-F</sub> = 21.0 Hz), 114.0 (d, <sup>2</sup>*J*<sub>C-F</sub> = 22.2 Hz), 64.3, 59.3, 59.3, 40.9, 15.2.

<sup>19</sup>F NMR (376 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  -112.3 (s, 1F, CF).

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 11.7$  min,  $t_{\text{major}} = 17.8$  min.

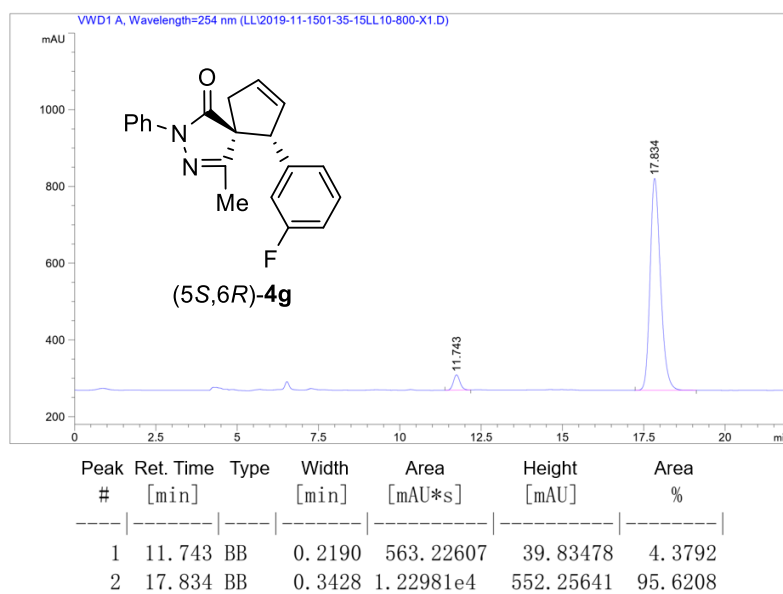
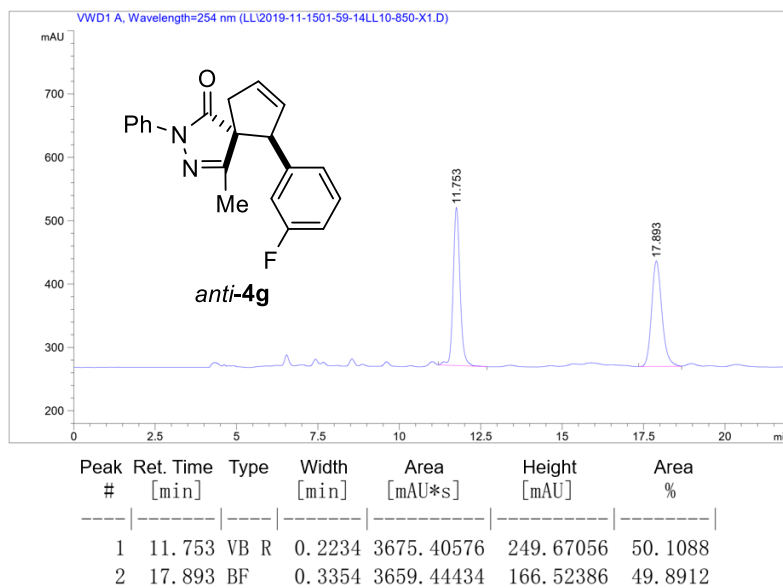
**HRMS** (ESI) calcd for C<sub>20</sub>H<sub>18</sub>FN<sub>2</sub>O [M + H]<sup>+</sup>: 321.1398, found 321.1400.

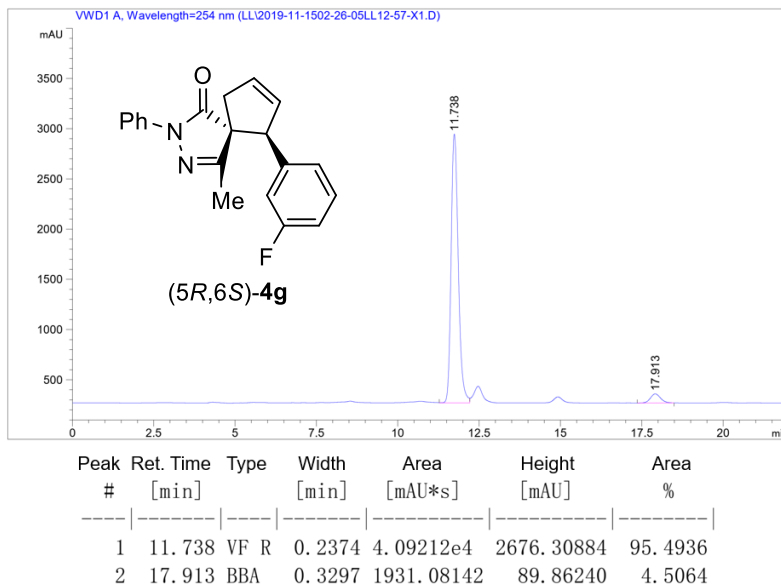
**(5*R*,6*S*)-6-(3-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**  
**-one**



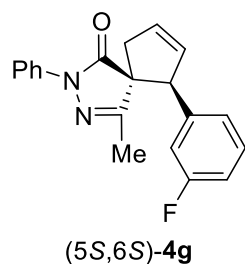
Yellow oil, 15.7 mg, 49% yield, 91% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda$  = 254 nm, retention time:  $t_{\text{major}}$  = 11.7 min,  $t_{\text{minor}}$  = 17.9 min.





**(5S,6S)-6-(3-fluorophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 7.8mg, 24% yield, 93% ee.  $R_f = 0.42$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -14.03$  (*c* 1.0, CHCl<sub>3</sub>).

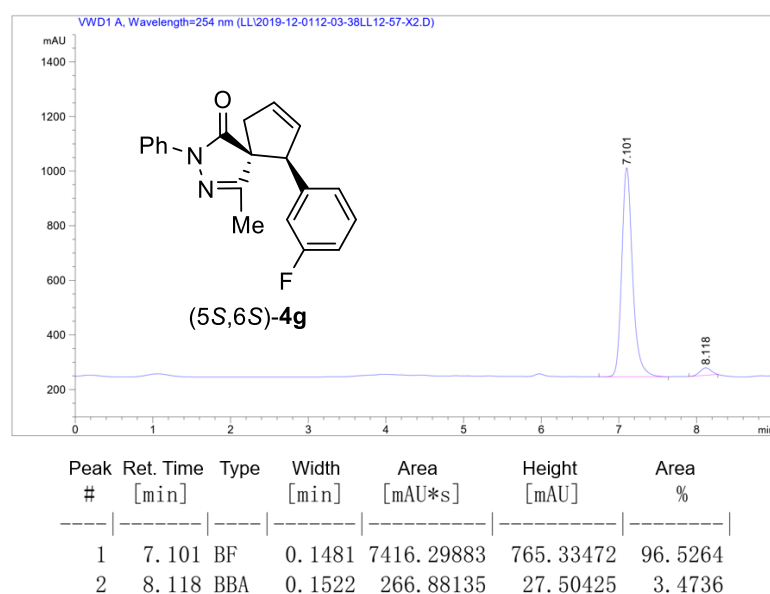
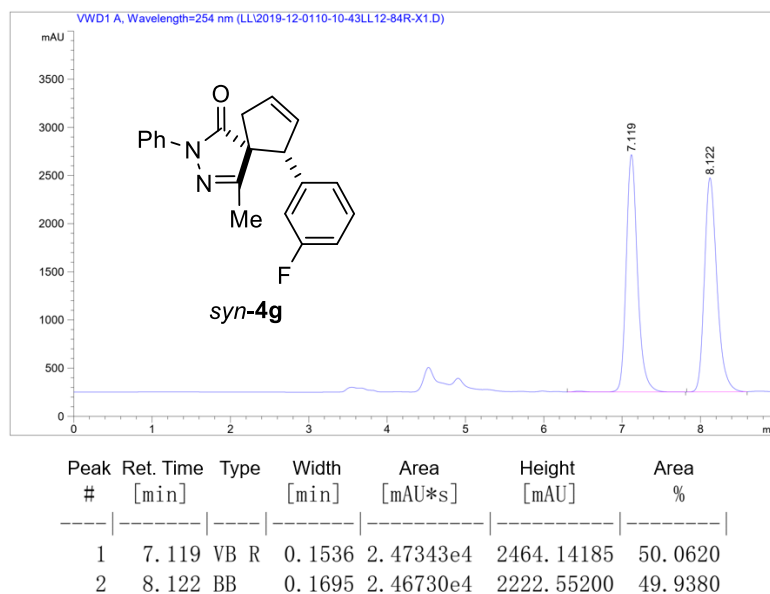
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.50 (d,  $J = 7.8$  Hz, 2H), 7.27 (t,  $J = 7.2$  Hz, 2H), 7.23-7.17 (m, 1H), 7.09 (t,  $J = 7.8$  Hz, 1H), 6.94-6.84 (m, 3H), 6.15-6.11 (m, 1H), 5.89-5.85 (m, 1H), 4.30 (t,  $J = 1.8$  Hz, 1H), 2.99-2.92 (m, 1H), 2.75-2.68 (m, 1H), 2.25 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.6, 162.8 (d,  $^1J_{C-F} = 244.9$  Hz), 162.6, 139.9, 139.9 (d,  $^3J_{C-F} = 7.2$  Hz), 137.8, 131.6, 130.8, 129.7, 129.7, 128.8, 124.9, 124.1, 124.0, 119.1, 115.4 (d,  $^2J_{C-F} = 21.9$  Hz), 114.7 (d,  $^2J_{C-F} = 20.9$  Hz), 62.7, 58.3, 39.5, 13.8.

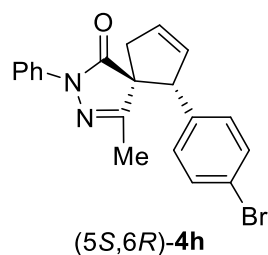
<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  -113.2 (s, 1F, CF).

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 7.1$  min,  $t_{\text{minor}} = 8.1$  min.

HRMS (ESI) calcd for C<sub>20</sub>H<sub>18</sub>FN<sub>2</sub>O [M + H]<sup>+</sup>: 321.1398, found 321.1396.



**(5S,6R)-6-(4-bromophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



White solid, 27.2 mg, 71% yield, 91% ee, 8:1 dr.  $R_f = 0.44$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +32.3750$  (*c* 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.89 (d, *J* =

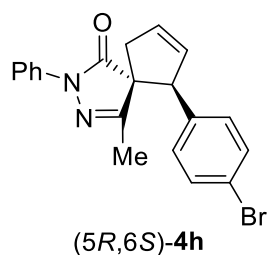
7.8 Hz, 2H), 7.41 (t,  $J = 7.6$  Hz, 2H), 7.37 (d,  $J = 8.4$  Hz, 2H), 7.20 (t,  $J = 7.4$  Hz, 2H), 6.97 (d,  $J = 8.4$  Hz, 2H), 6.08-5.98 (m, 2H), 4.70-4.60 (m, 1H), 3.10-2.97 (m, 1H), 2.78-2.66 (m, 1H), 1.68 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  176.5, 162.4, 138.1, 137.1, 131.9, 130.8, 130.2, 129.0, 128.7, 125.3, 121.6, 119.0, 64.4, 59.2, 40.8, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 9.5$  min,  $t_{\text{major}} = 11.0$  min.

**HRMS** (ESI) calcd for  $\text{C}_{20}\text{H}_{18}\text{BrN}_2\text{O}$  [ $\text{M} + \text{H}$ ] $^+$ : 381.0597, found 381.0599.

**(5*R*,6*S*)-6-(4-bromophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**

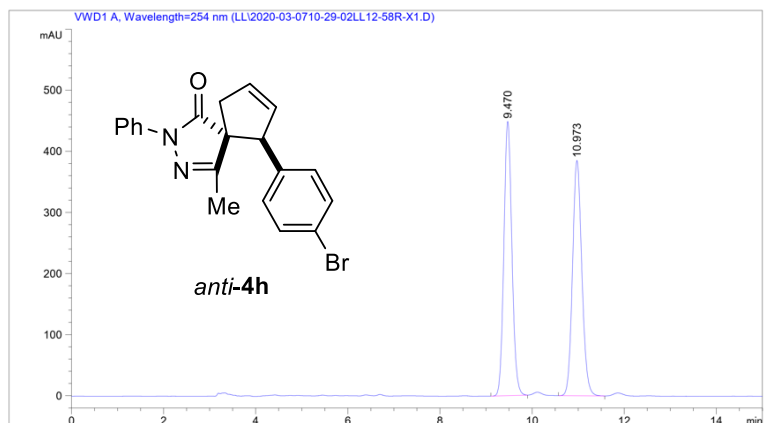


Yellow solid, 16.9 mg, 44% yield, 86% ee.

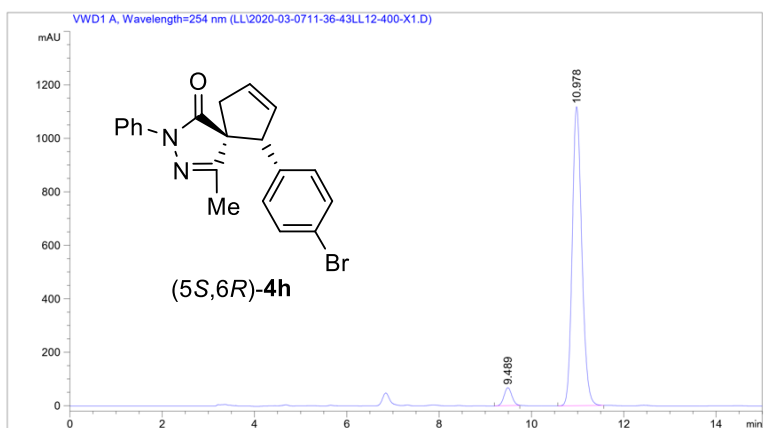
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 9.5$  min,  $t_{\text{minor}} = 11.0$  min.

**HRMS** (ESI) calcd for  $\text{C}_{20}\text{H}_{18}\text{BrN}_2\text{O}$  [ $\text{M} + \text{H}$ ] $^+$ : 381.0597, found 381.0598.

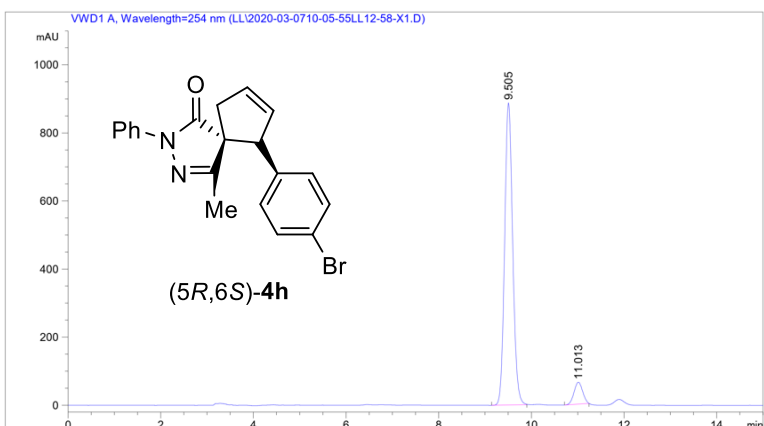




Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.470	BB	0.1876	5449.04736	448.93063	50.1503
2	10.973	BB	0.2171	5416.38037	385.18298	49.8497



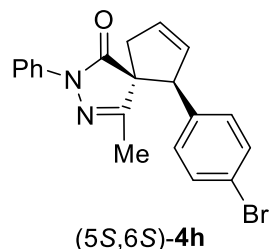
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.489	BBA	0.1831	789.82263	67.22457	4.6729
2	10.978	BB	0.2222	1.61125e4	1117.92102	95.3271



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.505	BF	0.1864	1.06840e4	887.69507	92.8009
2	11.013	BBA	0.2024	828.81818	64.27758	7.1991

**(5S,6S)-6-(4-bromophenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1**

**-one**



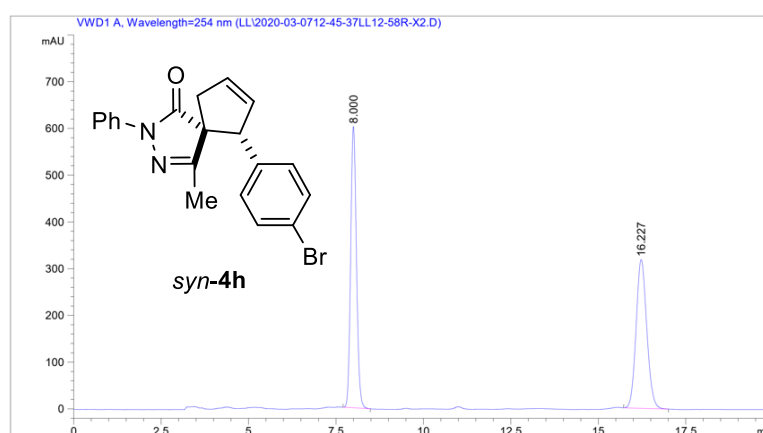
Yellow solid, 11.3 mg, 32% yield, 88% ee.  $R_f = 0.42$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -29.7555$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.47 (d, *J* = 7.8 Hz, 2H), 7.37 (d, *J* = 8.4 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.09 (t, *J* = 7.4 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.16-6.09 (m, 1H), 5.88-5.80 (m, 1H), 4.30-4.23 (m, 1H), 2.78-2.66 (m, 1H), 2.24 (s, 3H).

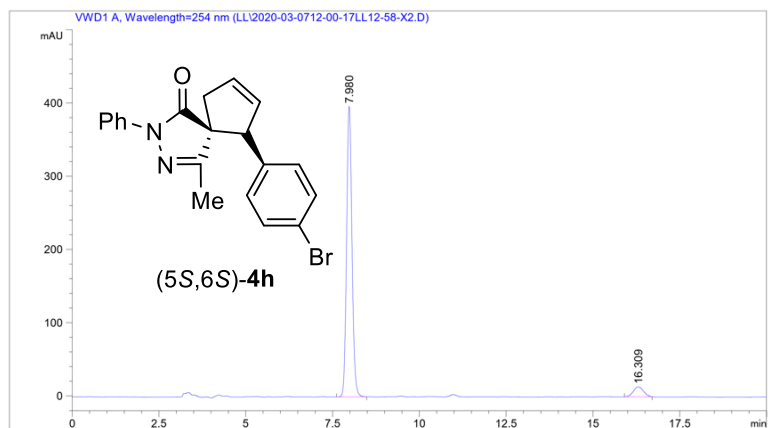
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.6, 162.6, 137.6, 136.2, 131.4, 130.8, 130.0, 128.7, 124.9, 121.7, 119.0, 62.5, 58.0, 39.4, 13.7.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 8.0$  min,  $t_{\text{minor}} = 16.3$  min.

**HRMS (ESI)** calcd for C<sub>20</sub>H<sub>18</sub>BrN<sub>2</sub>O [M + H]<sup>+</sup>: 381.0597, found 381.0597.

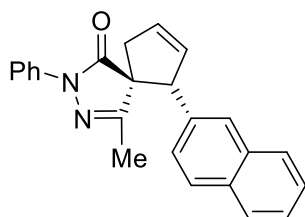


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.000	BBA	0.1777	6895.62549	601.78424	50.5476
2	16.227	BBA	0.3264	6746.22412	318.12531	49.4524



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.980	BBA	0.1654	4259.99951	396.47430	93.9745
2	16.309	BBAS	0.3179	273.14420	13.51094	6.0255

**(5*S*,6*R*)-4-methyl-6-(naphthalen-2-yl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



**(5*S*,6*R*)-4i**

Yellow oil, 24.0 mg, 68% yield, 94% ee, 8:1 dr.  $R_f = 0.37$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +14.00$  (*c* 1.0, CHCl<sub>3</sub>).

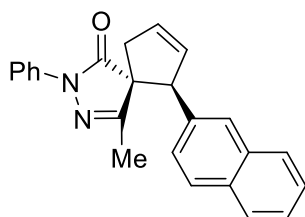
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.91 (d, *J* = 8.4 Hz, 2H), 7.81-6.8 (m, 3H), 7.62 (s, 1H), 7.48-7.39 (m, 4H), 7.21 (t, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 6.23 (s, 1H), 6.08 (s, 1H), 4.88 (s, 1H), 3.09 (d, *J* = 16.8 Hz, 1H), 2.77 (d, *J* = 16.8 Hz, 1H), 1.64 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.9, 162.8, 138.2, 135.7, 133.3, 132.9, 131.4, 129.8, 128.6, 127.9, 126.4, 125.5, 119.1, 64.4, 60.0, 41.0, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 9.5$  min,  $t_{\text{major}} = 15.6$  min.

**HRMS (ESI)** calcd for C<sub>24</sub>H<sub>21</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 353.1648, found 353.1651.

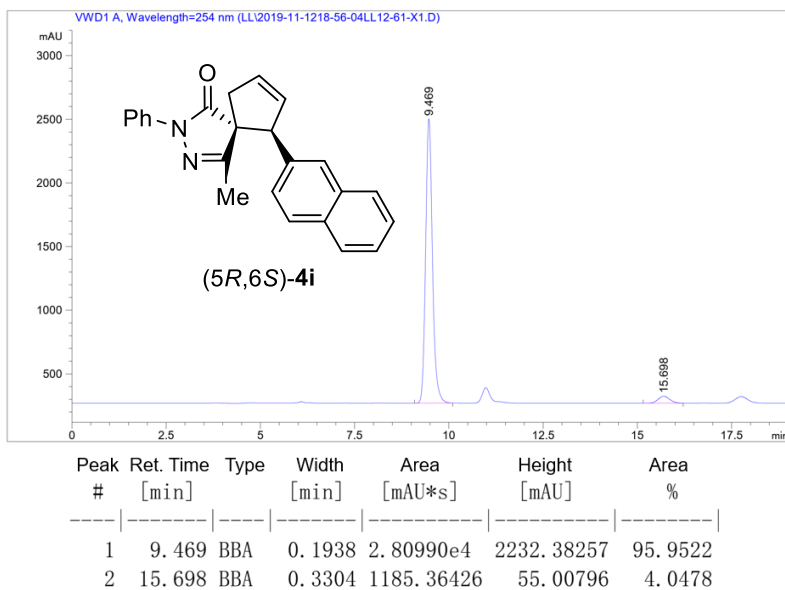
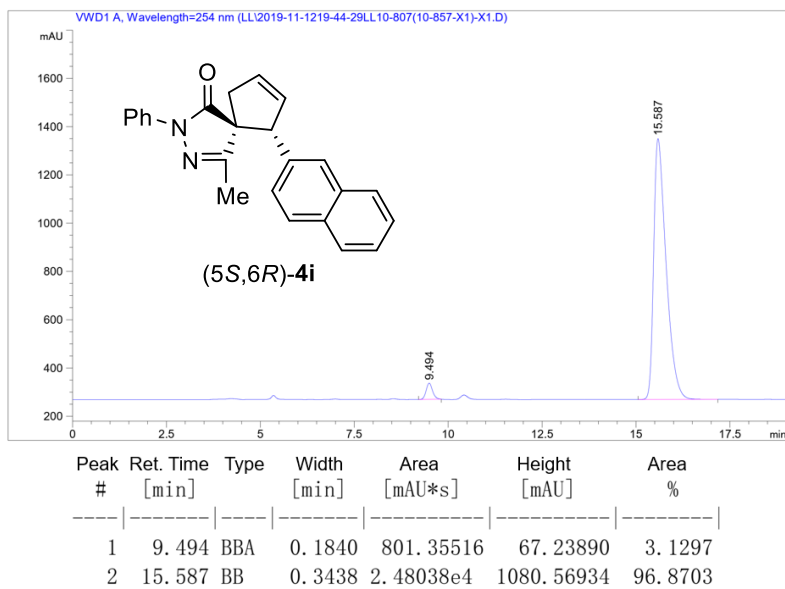
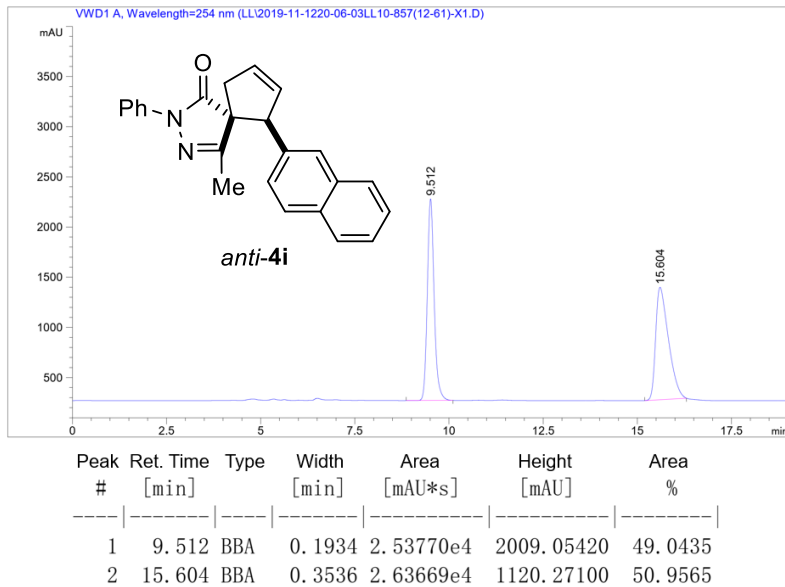
**(5*R*,6*S*)-4-methyl-6-(naphthalen-2-yl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



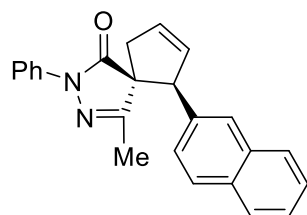
**(5*R*,6*S*)-4i**

Yellow oil, 23.0 mg, 65% yield, 92% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 9.5$  min,  $t_{\text{minor}} = 15.7$  min.



**(5*S*,6*S*)-4-methyl-6-(naphthalen-2-yl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



**(5*S*,6*S*)-4*i***

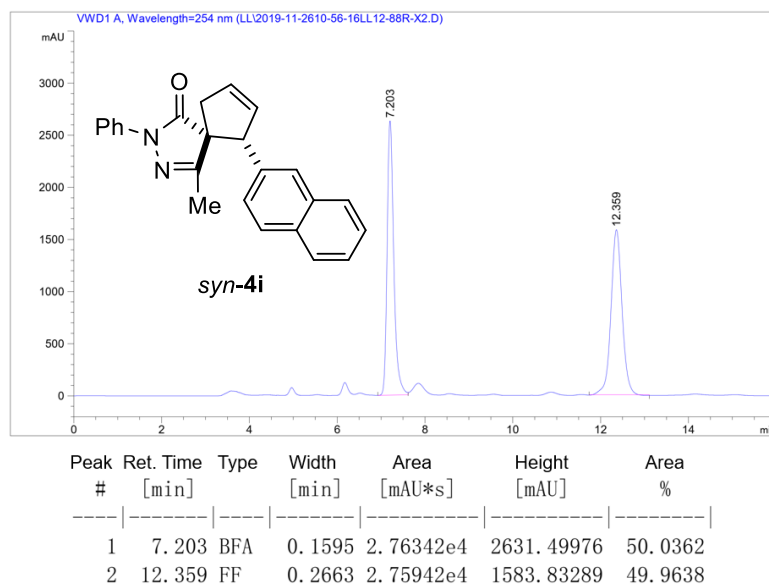
Yellow oil, 7.7 mg, 22% yield, 93% ee.  $R_f = 0.35$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -8.69$  (*c* 1.0, CHCl<sub>3</sub>).

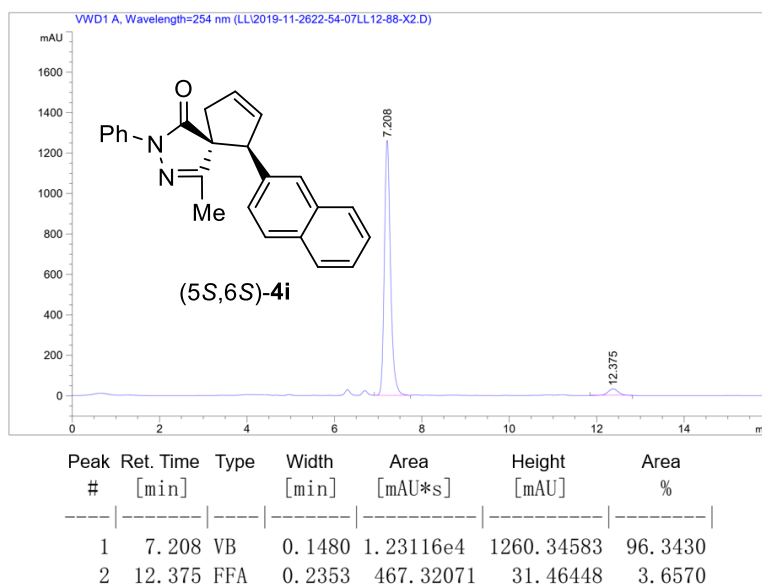
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.79-7.74 (m, 2H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.62 (s, 1H), 7.45-7.38 (m, 4H), 7.25-7.21 (m, 1H), 7.18 (t, *J* = 8.4 Hz, 2H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.39-6.15 (m, 1H), 6.01-5.97 (m, 1H), 4.49 (s, 1H), 3.05-3.00 (m, 1H), 2.79-2.73 (m, 1H), 2.30 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.8, 163.0, 137.8, 134.9, 133.3, 133.0, 131.5, 131.0, 128.7, 128.1, 127.9, 127.7, 127.2, 126.6, 125.9, 124.7, 119.1, 62.8, 59.0, 39.7, 13.8.

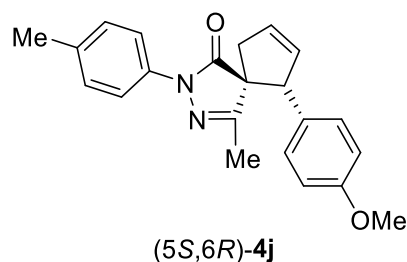
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 7.2$  min,  $t_{\text{minor}} = 12.4$  min.

**HRMS (ESI)** calcd for C<sub>24</sub>H<sub>21</sub>N<sub>2</sub>O [M + H]<sup>+</sup>: 353.1648, found 353.1647.





**(5S,6R)-6-(4-methoxyphenyl)-4-methyl-2-(p-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 20.4 mg, 60% yield, 90% ee, 12:1 dr.  $R_f = 0.44$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +24.74$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.77 (d, *J* = 8.4 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.08-6.02 (m, 1H), 6.01-5.95 (m, 1H), 4.65 (s, 1H), 3.09 (s, 3H), 3.04-2.95 (m, 1H), 2.74-2.66 (m, 1H), 2.36 (s, 3H), 1.67 (s, 3H).

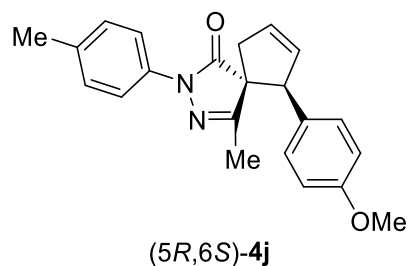
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.7, 162.9, 159.0, 135.9, 134.7, 131.7, 130.1, 129.5, 129.4, 28.1, 119.1, 114.0, 64.5, 59.3, 55.3, 40.6, 21.1, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 12.1$  min,  $t_{\text{major}} = 20.7$  min.

**HRMS (ESI)** calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 347.1754, found 347.1756.

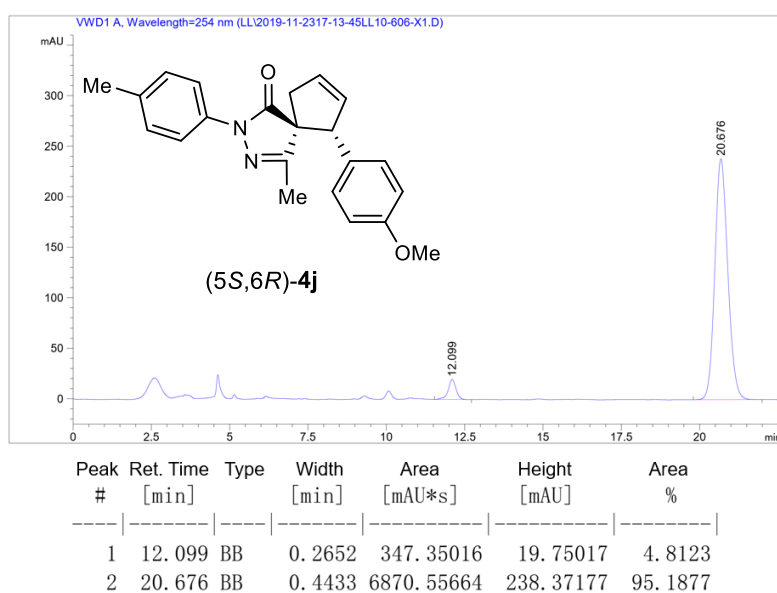
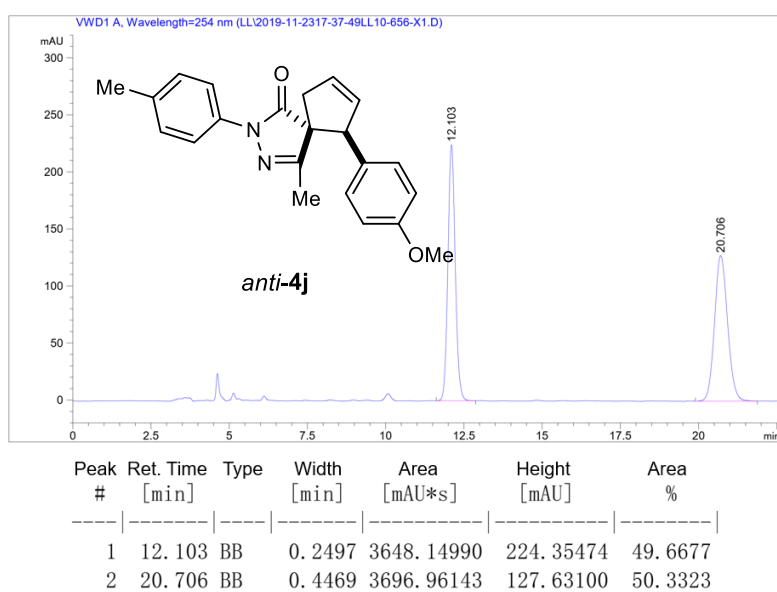
**(5R,6S)-6-(4-methoxyphenyl)-4-methyl-2-(p-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**

### en-1-one

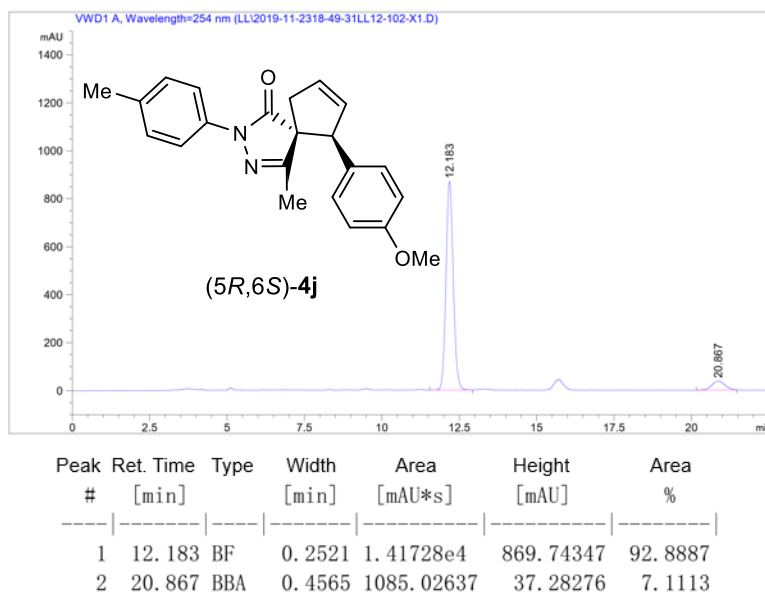


Yellow oil, 18.7 mg, 54% yield, 86% ee.

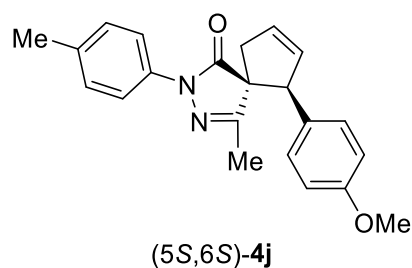
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 12.2$  min,  $t_{\text{minor}} = 20.9$  min.







**(5S,6S)-6-(4-methoxyphenyl)-4-methyl-2-(p-tolyl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



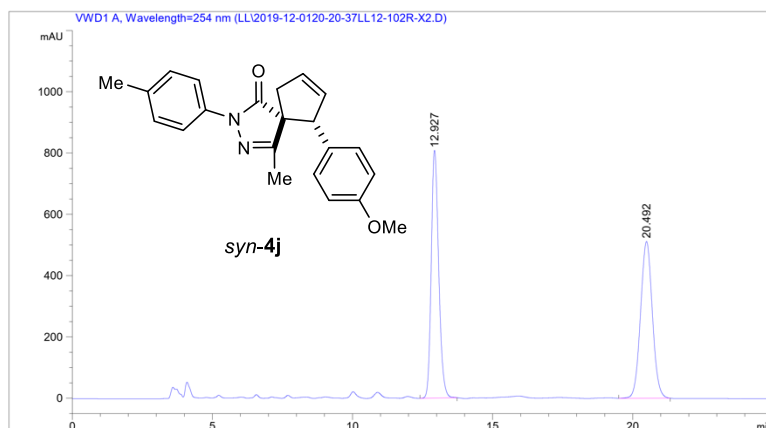
Yellow oil, 8.9 mg, 26% yield, 93% ee.  $R_f = 0.42$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -13.19$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.34 (d, *J* = 8.4 Hz, 2H), 7.08-7.02 (m, 4H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.08-6.04 (m, 1H), 5.87-5.83 (m, 1H), 4.28 (s, 1H), 3.74 (s, 3H), 2.97-2.90 (m, 1H), 2.72-2.66 (m, 1H), 2.28 (s, 3H), 2.23 (s, 3H).

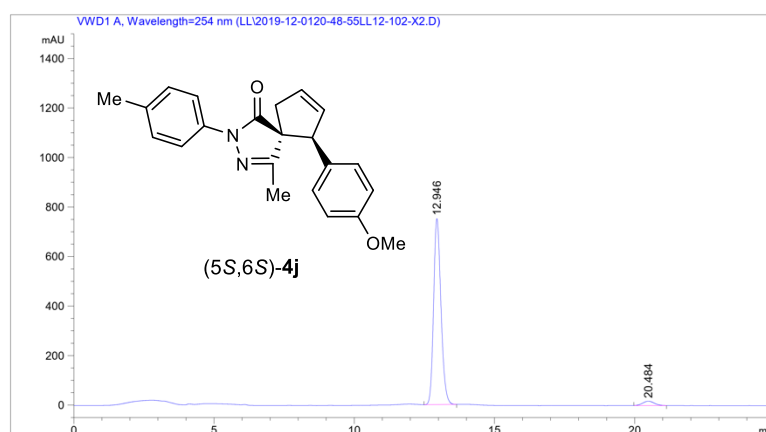
<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.9, 162.8, 159.1, 135.5, 134.4, 131.7, 130.6, 129.4, 129.3, 129.2, 119.2, 113.7, 62.9, 58.3, 55.3, 39.3, 21.0, 13.8.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 12.9$  min,  $t_{\text{minor}} = 20.5$  min.

**HRMS (ESI)** calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 347.1754, found 347.1756.

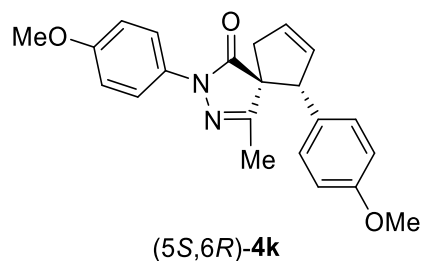


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.927	VBAS	0.2842	1.49058e4	808.03247	49.8482
2	20.492	VBAS	0.4568	1.49966e4	511.90067	50.1518



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.946	BBA	0.2815	1.36852e4	751.21710	96.4446
2	20.484	VBAS	0.4481	504.50131	17.56474	3.5554

**(5S,6R)-2,6-bis(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow solid, 30.7 mg, 85% yield, 91% ee, 10:1 dr.  $R_f = 0.36$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = +28.50$  (*c* 1.0, CHCl<sub>3</sub>). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.78 (d, *J* = 8.8 Hz, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H),

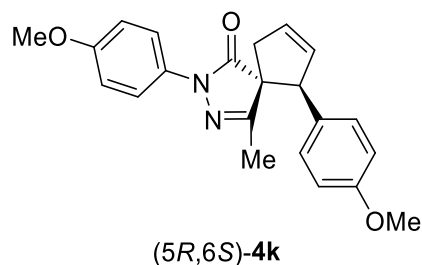
6.07-6.02 (m, 1H), 6.01-5.95 (m, 1H), 4.65 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.03-2.95 (m, 1H), 2.74-2.65 (m, 1H), 1.66 (s, 3H).

$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  176.5, 162.9, 159.0, 157.1, 131.7, 130.1, 129.5, 128.1, 120.8, 114.1, 114.0, 64.4, 59.3, 55.6, 55.3, 40.5, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda$  = 254 nm, retention time:  $t_{\text{minor}}$  = 16.1 min,  $t_{\text{major}}$  = 30.1 min.

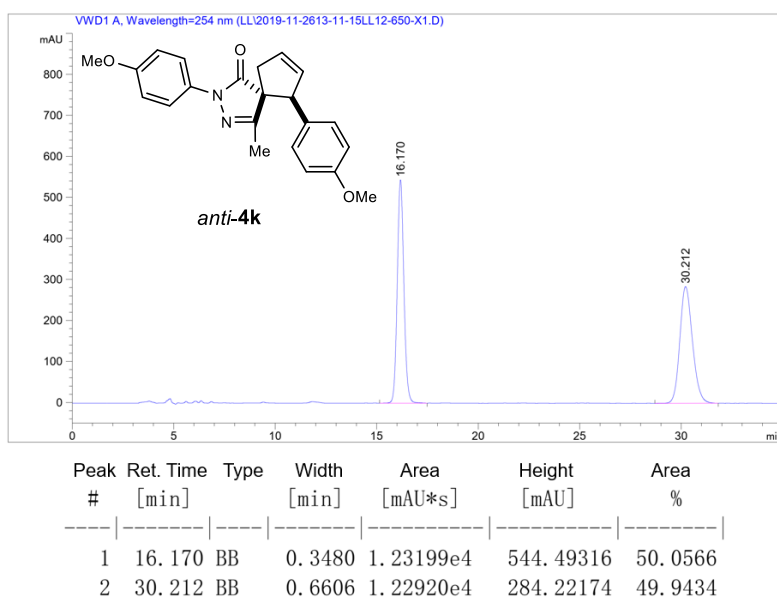
**HRMS** (ESI) calcd for  $\text{C}_{22}\text{H}_{23}\text{N}_2\text{O}_3$  [ $\text{M} + \text{H}$ ] $^+$ : 363.1703, found 363.1706.

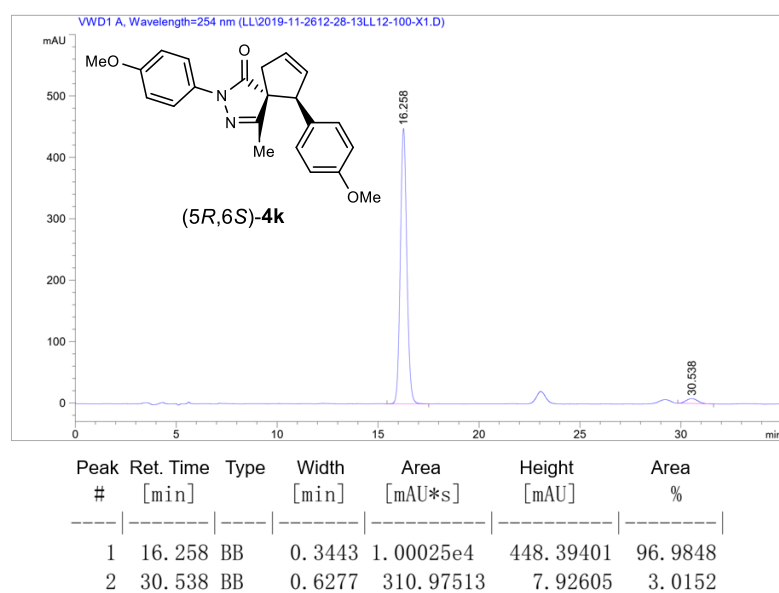
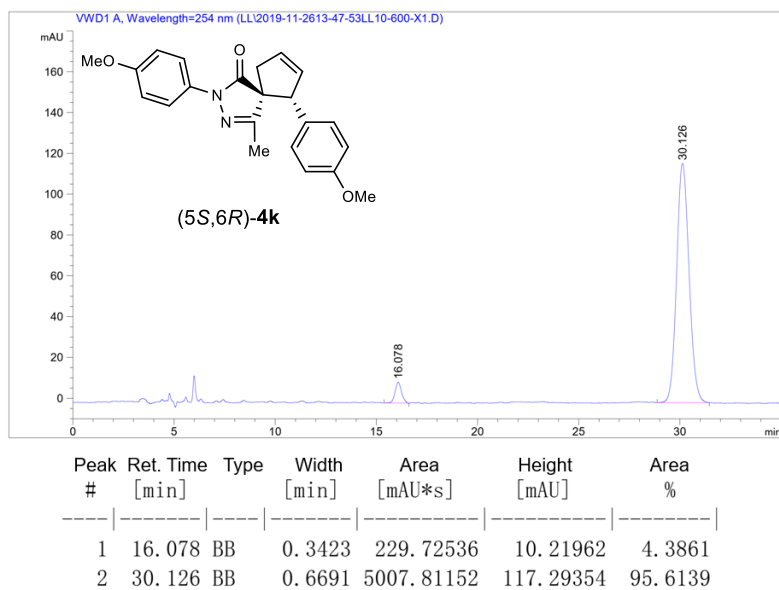
**(5*R*,6*S*)-2,6-bis(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



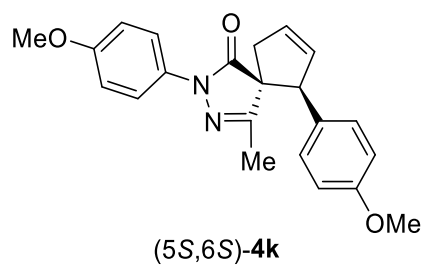
Yellow solid, 20.4 mg, 56% yield, 94% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda$  = 254 nm, retention time:  $t_{\text{major}}$  = 16.3 min,  $t_{\text{minor}}$  = 30.5 min.





**(5S,6S)-2,6-bis(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



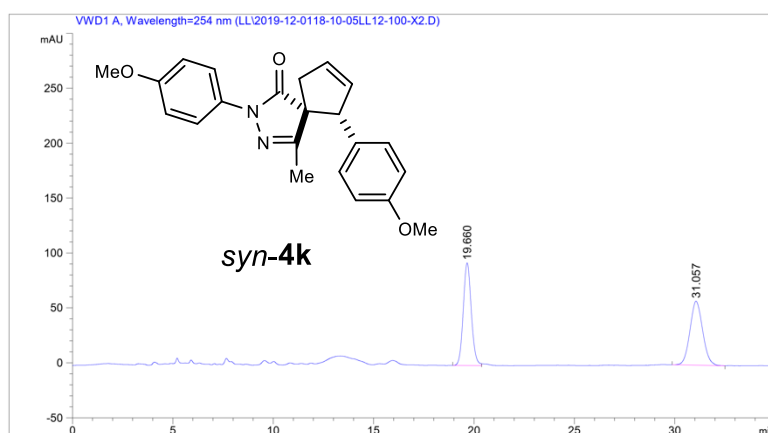
Yellow oil, 9.3 mg, 26% yield, 92% ee.  $R_f = 0.33$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -7.50$  (*c* 1.0, CHCl<sub>3</sub>).

**<sup>1</sup>H NMR** (600 MHz, CDCl<sub>3</sub>, ppm): δ 7.32 (d, *J* = 9.0 Hz, 2H), 7.05 (d, *J* = 12.0 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 4H), 6.08-6.04 (m, 1H), 5.87-5.83 (m, 1H), 4.28 (s, 1H), 3.75 (s, 3H), 3.75 (s, 3H), 2.97-2.90 (m, 1H), 2.73-2.66 (m, 1H), 2.23 (s, 3H).

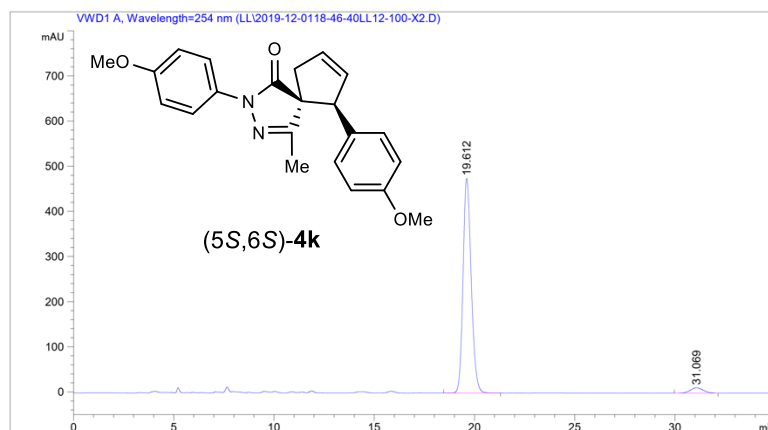
**<sup>13</sup>C NMR** (150 MHz, CDCl<sub>3</sub>, ppm): δ 173.9, 162.8, 159.3, 157.0, 131.8, 131.4, 130.7, 129.5, 129.4, 121.2, 114.0, 113.8, 63.0, 58.4, 55.7, 55.4, 39.4, 13.9.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 254 nm, retention time: *t*<sub>major</sub> = 19.6 min, *t*<sub>minor</sub> = 31.1 min.

**HRMS** (ESI) calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 363.1703, found 363.1702.

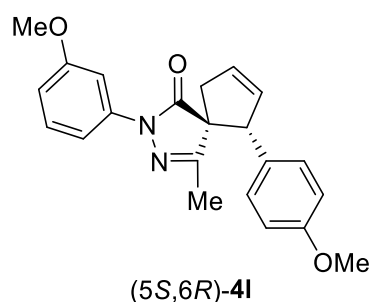


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.660	BF	0.4309	2598.66138	93.32137	50.4271
2	31.057	BB	0.6797	2554.64380	58.24865	49.5729



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.612	BB	0.4376	1.35084e4	475.23856	96.2275
2	31.069	BB	0.6775	529.58569	11.91637	3.7725

**(5*S*,6*R*)-2-(3-methoxyphenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 31.1 mg, 86% yield, 91% ee, 10:1 dr.  $R_f = 0.35$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = +28.25$  (*c* 1.0, CHCl<sub>3</sub>).

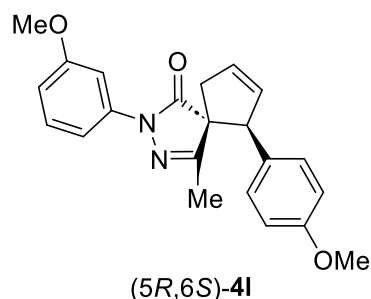
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.55 (s, 1H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.79-6.73 (m, 3H), 6.07-6.02 (m, 1H), 6.00-5.96 (m, 1H), 4.65 (s, 1H), 3.84 (s, 3H), 3.75 (s, 3H), 3.02-2.95 (m, 1H), 2.74-2.67 (m, 1H), 1.66 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  177.0, 162.9, 160.2, 159.1, 139.4, 131.7, 130.0, 129.8, 128.1, 114.1, 111.2, 111.2, 104.3, 64.6, 59.3, 55.5, 55.3, 40.7, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 9.3$  min,  $t_{\text{major}} = 10.9$  min.

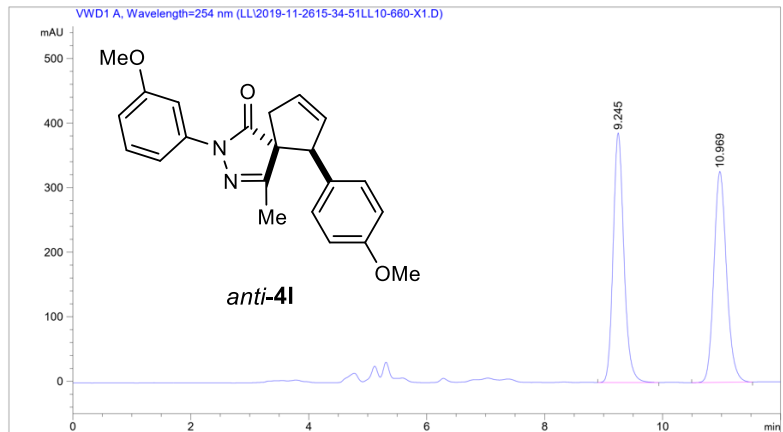
**HRMS** (ESI) calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 363.1703, found 363.1704.

**(5*R*,6*S*)-2-(3-methoxyphenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**

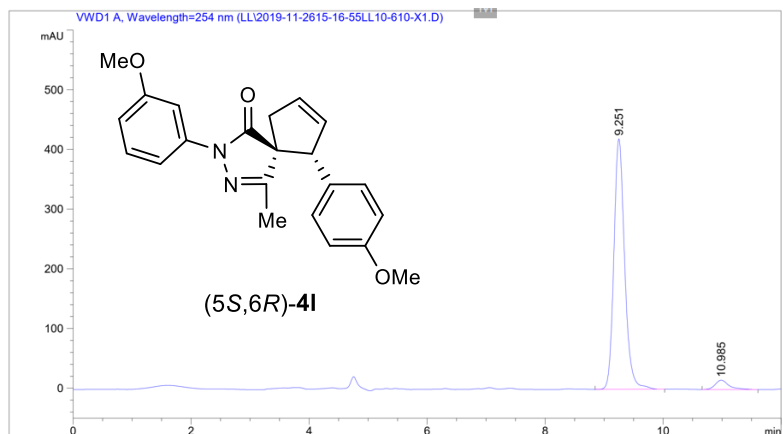


Yellow oil, 20.8 mg, 57% yield, 92% ee.

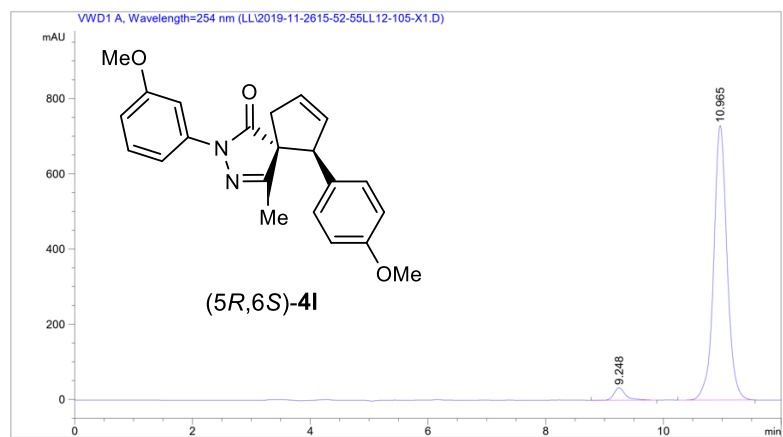
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 9.2$  min,  $t_{\text{minor}} = 10.9$  min.



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.245	BB	0.1939	4901.65186	386.55356	50.1856
2	10.969	BB	0.2288	4865.38965	326.65305	49.8144

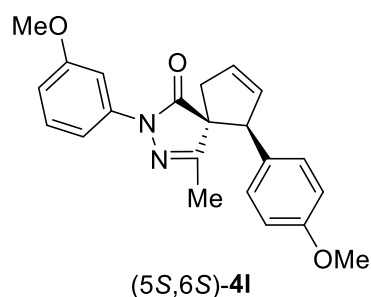


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.251	BB	0.1930	5323.90771	419.63129	95.4940
2	10.985	BB	0.2421	251.21257	15.58515	4.5060



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.248	BB	0.2032	445.82706	32.88392	3.7332
2	10.965	BBA	0.2398	1.14964e4	729.67804	96.2668

**(5*S*,6*S*)-2-(3-methoxyphenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



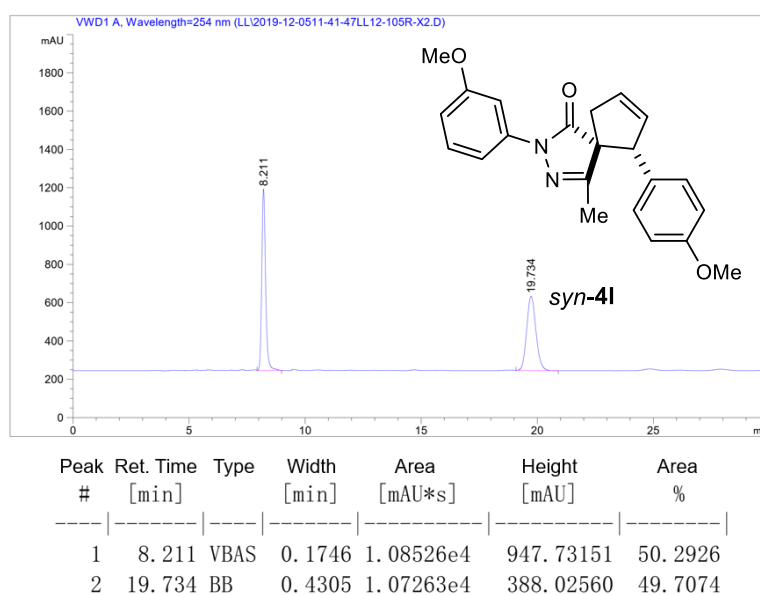
Yellow oil, 8.9 mg, 25% yield, 93% ee.  $R_f = 0.32$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -10.89$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.16 (t,  $J = 8.4$  Hz, 1H), 7.10 (d,  $J = 7.8$  Hz, 1H), 7.07 (t,  $J = 2.4$  Hz, 1H), 7.04 (d,  $J = 8.4$  Hz, 2H), 6.78 (d,  $J = 9.0$  Hz, 2H), 6.65-6.61 (m, 1H), 6.09-6.04 (m, 1H), 5.88-5.83 (m, 1H), 4.29 (s, 1H), 3.74 (s, 3H), 3.73 (s, 3H), 2.97-2.90 (m, 1H), 2.73-2.66 (m, 1H), 2.24 (s, 3H).

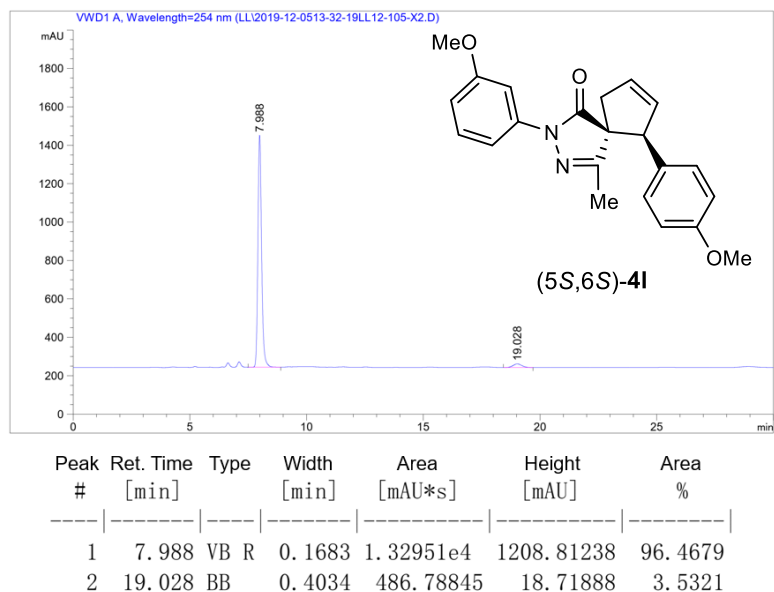
<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.1, 162.8, 159.9, 159.2, 139.0, 131.6, 130.6, 129.5, 129.4, 129.2, 113.7, 111.5, 111.2, 104.5, 63.2, 58.4, 55.4, 55.3, 39.3, 13.8.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 7.9$  min,  $t_{\text{minor}} = 19.0$  min.

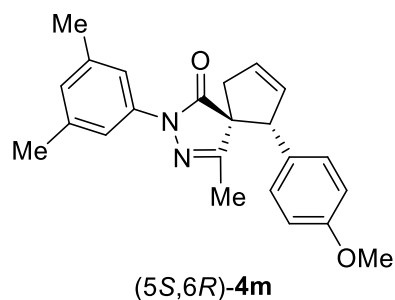
**HRMS (ESI)** calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>3</sub> [M + H]<sup>+</sup>: 363.1703, found 363.1705.







**(5S,6R)-2-(3,5-dimethylphenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 31.2 mg, 87% yield, 93% ee, 10:1 dr.  $R_f = 0.46$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = +28.12$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.54 (s, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 6.84 (s, 1H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.08-6.03 (m, 1H), 6.01-5.95 (m, 1H), 4.65 (s, 1H), 3.76 (s, 3H), 3.03-2.94 (m, 1H), 2.73-2.65 (m, 1H), 2.35 (s, 6H), 1.67 (s, 3H).

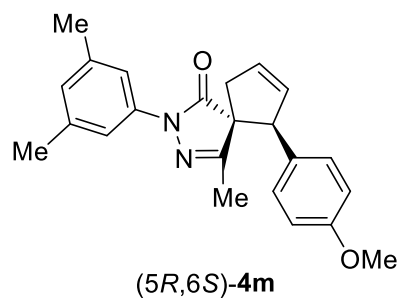
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.9, 162.9, 159.0, 138.7, 138.1, 131.7, 130.1, 129.4, 128.1, 126.9, 116.8, 114.1, 64.5, 59.3, 55.3, 40.7, 21.6, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 5.7$  min,  $t_{\text{minor}} = 7.7$  min.

**HRMS (ESI)** calcd for C<sub>23</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 361.1911, found 361.1912.

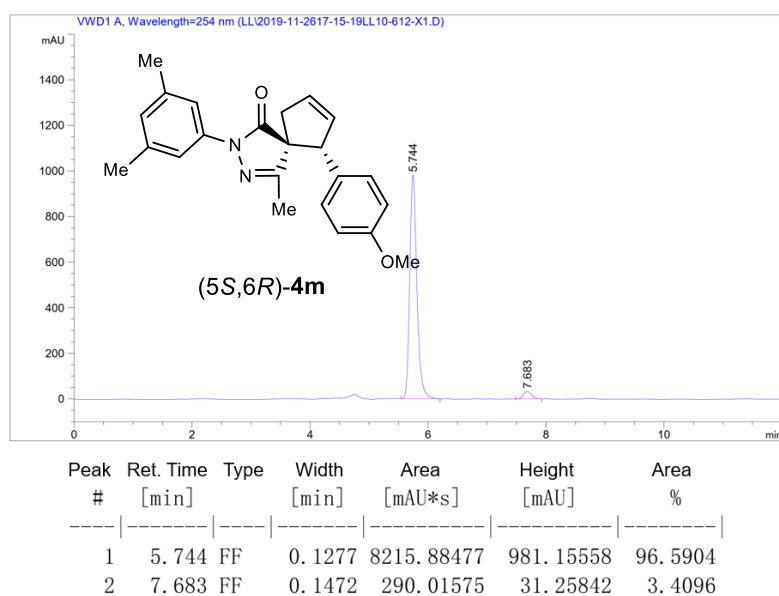
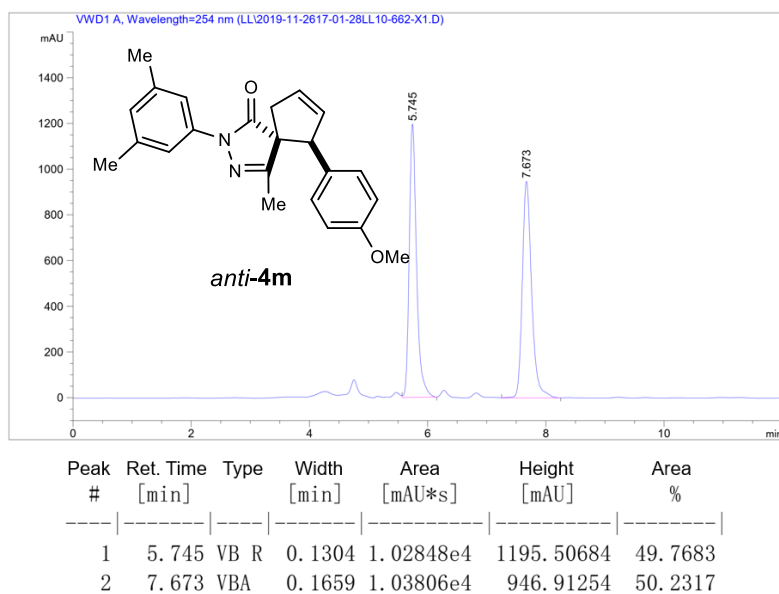
**(5R,6S)-2-(3,5-dimethylphenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]**

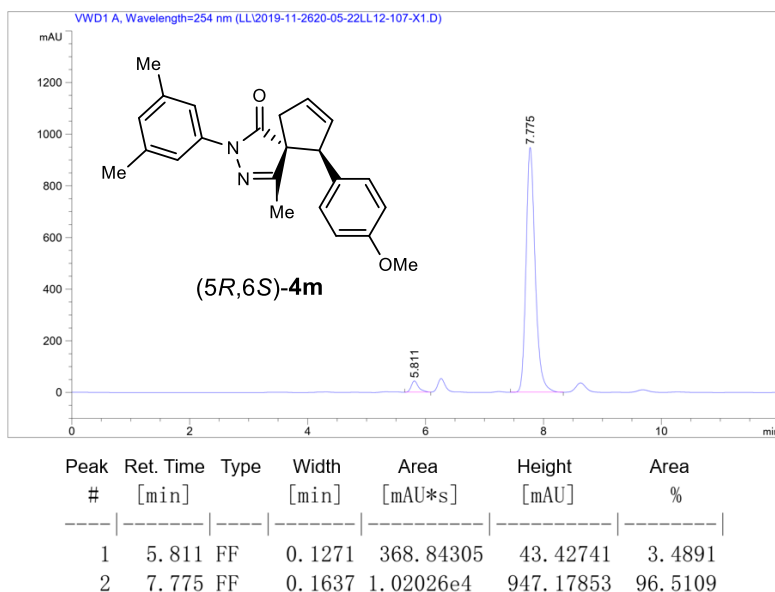
## nona-3,7-dien-1-one



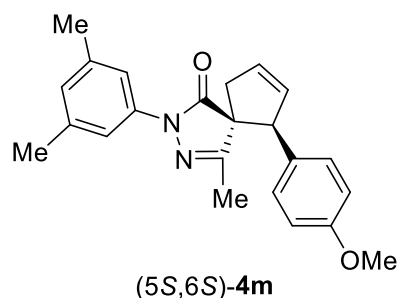
Yellow oil, 23.9 mg, 66% yield, 93% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 5.8$  min,  $t_{\text{major}} = 7.8$  min.





**(5S,6S)-2-(3,5-dimethylphenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



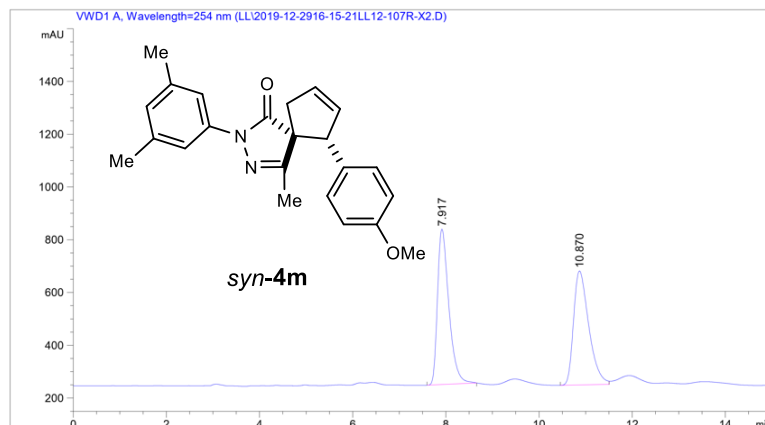
Yellow oil, 11.4 mg, 32% yield, 93% ee.  $R_f = 0.46$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -18.57$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.08 (s, 2H), 7.05 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 6.73 (s, 1H), 6.08-6.04 (m, 1H), 5.87-5.83 (m, 1H), 4.28 (s, 1H), 3.75 (s, 3H), 2.97-2.90 (m, 1H), 2.72-2.66 (m, 1H), 2.24 (s, 6H), 2.24 (s, 3H).

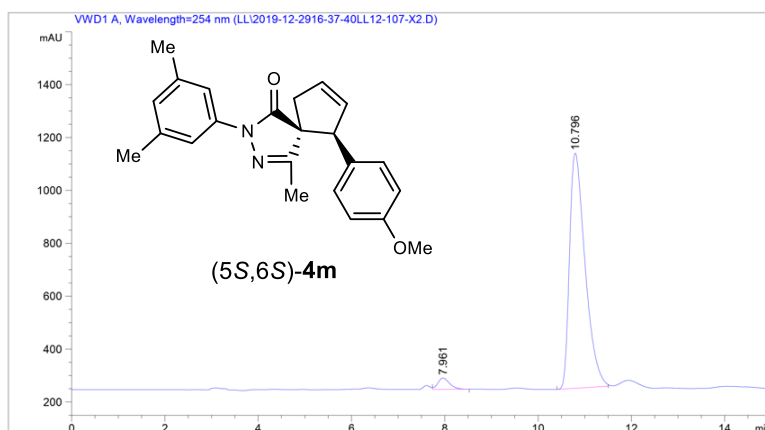
<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.0, 162.7, 159.2, 138.4, 137.7, 131.7, 130.5, 129.5, 129.3, 126.7, 117.2, 113.7, 63.0, 58.3, 55.3, 39.4, 21.5, 13.8.

**HPLC analysis:** Daicel CHIRALPAK OD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 7.9$  min,  $t_{\text{major}} = 10.8$  min.

**HRMS (ESI)** calcd for C<sub>23</sub>H<sub>25</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 361.1911, found 361.1909.

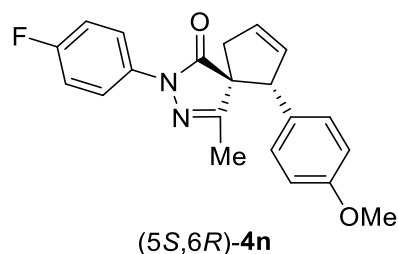


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.917	BBA	0.2572	9955.71387	588.92969	50.3976
2	10.870	BF	0.3457	9798.61816	431.86929	49.6024



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.961	VB	0.2640	739.30566	42.69846	3.4622
2	10.796	BF	0.3546	2.06143e4	888.92120	96.5378

**(5S,6R)-2-(4-fluorophenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 24.9 mg, 71% yield, 90% ee, 10:1 dr.  $R_f = 0.42$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +23.61$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.90-7.84 (m, 2H), 7.09 (t, *J* = 8.4 Hz, 2H), 7.00

(d,  $J = 8.4$  Hz, 2H), 6.08-6.02 (m, 1H), 6.01-5.95 (m, 1H), 4.65 (s, 1H), 3.82 (s, 3H), 3.76 (s, 3H), 3.04-2.95 (m, 1H), 2.75-2.66 (m, 1H), 1.67 (s, 3H).

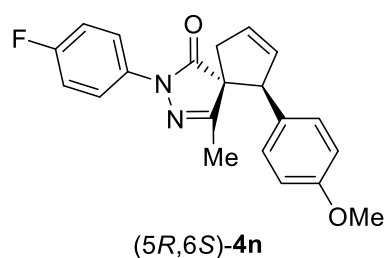
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  176.7, 163.2, 160.0 (d,  $^1J_{\text{C-F}} = 242.7$  Hz), 159.1, 134.5, 134.4, 131.7, 129.9, 129.4, 128.1, 120.7 (d,  $^3J_{\text{C-F}} = 7.8$  Hz), 115.6 (d,  $^2J_{\text{C-F}} = 22.3$  Hz), 114.1, 64.5, 59.4, 55.3, 40.6, 15.2.

$^{19}\text{F}$  NMR (565 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  -111.3 (s, 1F, CF).

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 8.9$  min,  $t_{\text{major}} = 9.9$  min.

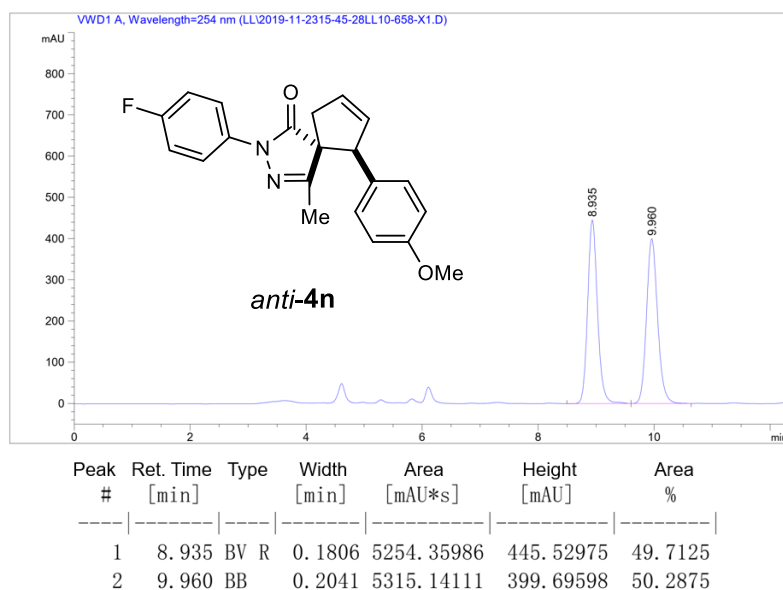
**HRMS** (ESI) calcd for  $\text{C}_{21}\text{H}_{20}\text{FN}_2\text{O}_2$  [ $\text{M} + \text{H}$ ] $^+$ : 351.1503, found 351.1502.

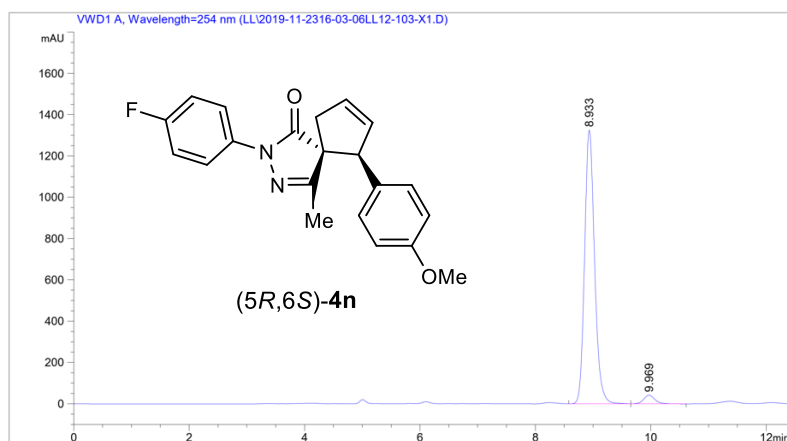
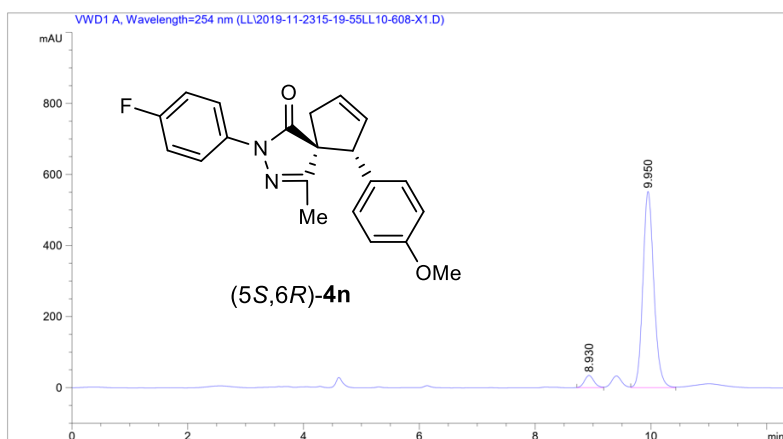
**(5*R*,6*S*)-2-(4-fluorophenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



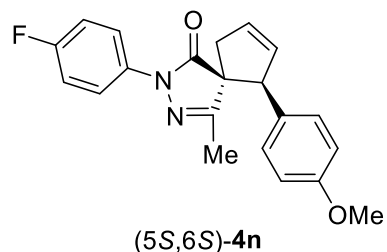
Yellow oil, 17.6 mg, 50% yield, 93% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 8.9$  min,  $t_{\text{minor}} = 9.9$  min.





**(5S,6S)-2-(4-fluorophenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 8.0 mg, 23% yield, 94% ee.  $R_f = 0.39$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -32.92$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.45-7.40 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.94 (t, *J* = 9.0 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.09-6.05 (m, 1H), 5.87-5.84 (m,

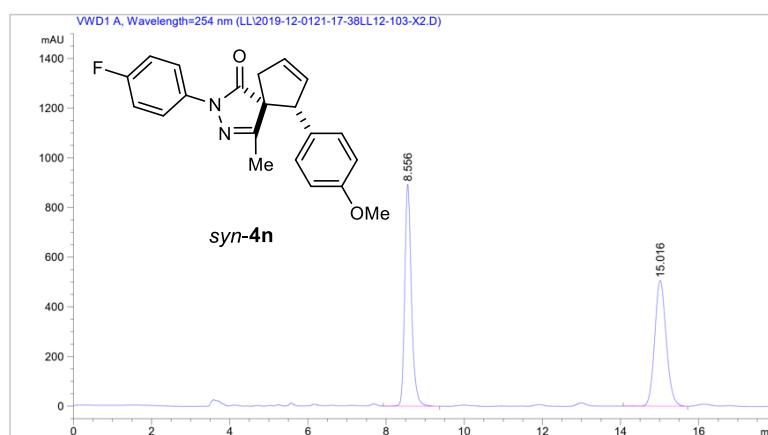
1H), 4.29 (s, 1H), 3.74 (s, 3H), 2.97-2.90 (m, 1H), 2.73-2.67 (m, 1H), 2.24 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm): δ 173.9, 163.1, 159.8 (d, <sup>1</sup>J<sub>C-F</sub> = 161.8 Hz), 159.2, 134.0, 131.6, 130.6, 129.4, 129.1, 120.9 (d, <sup>3</sup>J<sub>C-F</sub> = 5.3 Hz), 115.4 (d, <sup>2</sup>J<sub>C-F</sub> = 14.9 Hz), 113.7, 63.0, 58.4, 55.3, 39.2, 13.8.

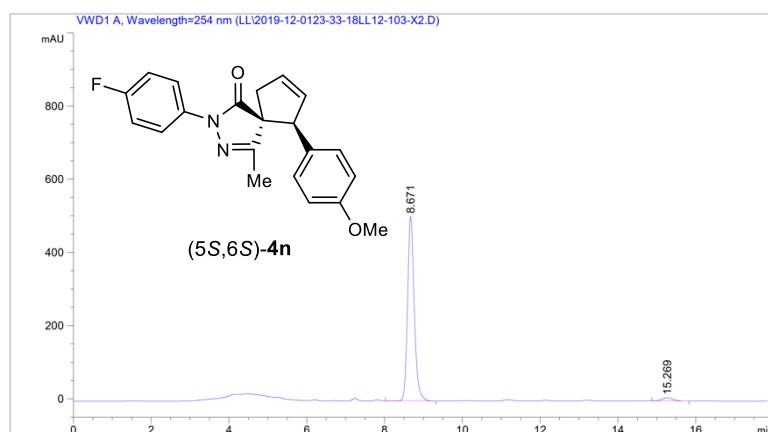
<sup>19</sup>F NMR (565 MHz, CDCl<sub>3</sub>, ppm): δ -117.7 (s, 1F, CF).

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min, λ = 254 nm, retention time: *t*<sub>major</sub> = 8.7 min, *t*<sub>minor</sub> = 15.3 min.

**HRMS (ESI) calcd for C<sub>21</sub>H<sub>20</sub>FN<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 351.1503, found 351.1504.**

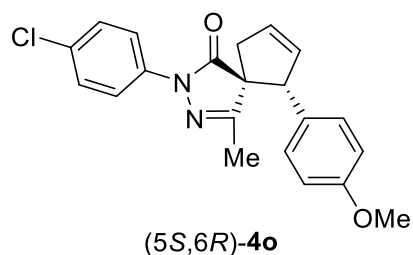


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.556	VB R	0.1813	1.06665e4	893.50482	50.6873
2	15.016	VV R	0.3163	1.03773e4	506.02167	49.3127



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.671	BB S	0.1811	6006.37158	503.79129	97.1454
2	15.269	BB	0.3141	176.49692	8.79476	2.8546

**(5*S*,6*R*)-2-(4-chlorophenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 25.8 mg, 70% yield, 87% ee, 9:1 dr.  $R_f = 0.45$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +25.13$  (*c* 1.0, CHCl<sub>3</sub>).

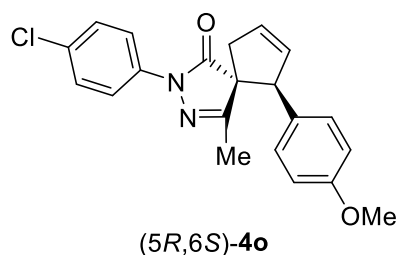
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.88 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.8 Hz, 2H), 6.07-6.02 (m, 1H), 6.01-5.95 (m, 1H), 4.64 (s, 1H), 3.76 (s, 3H), 3.03-2.95 (m, 1H), 2.75-2.66 (m, 1H), 1.67 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.9, 163.3, 159.1, 136.9, 131.7, 130.1, 129.9, 129.4, 129.0, 128.1, 120.0, 114.1, 64.6, 59.5, 55.3, 40.6, 15.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 9.4$  min,  $t_{\text{major}} = 13.0$  min.

**HRMS (ESI)** calcd for C<sub>21</sub>H<sub>20</sub>ClN<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 367.1208, found 367.1209.

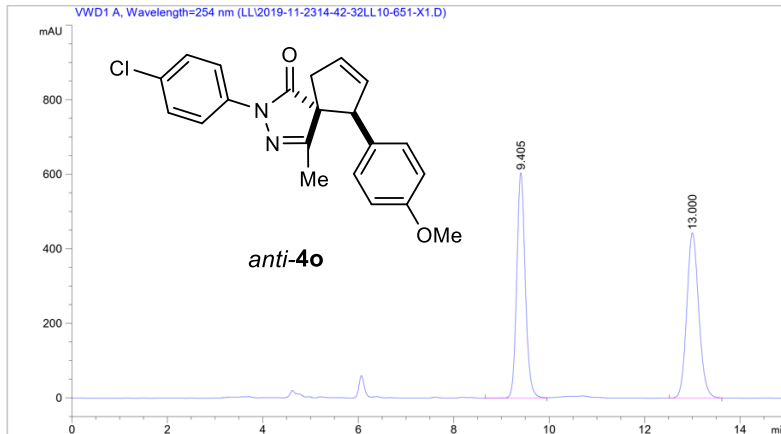
**(5*R*,6*S*)-2-(4-chlorophenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one (101-X1)**



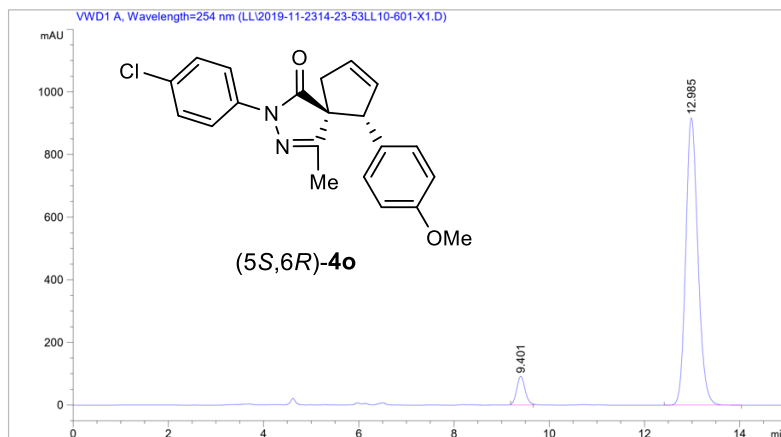
Yellow oil, 24.0 mg, 66% yield, 88% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 9.4$  min,  $t_{\text{minor}} = 13.1$  min.

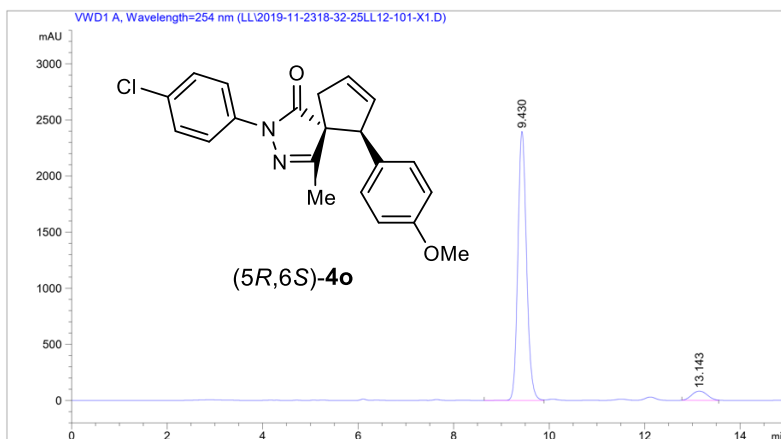




Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.405	BF	0.1910	7511.94092	604.43817	49.2778
2	13.000	FFA	0.2686	7732.13623	443.10541	50.7222

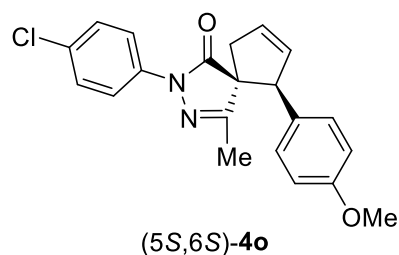


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.401	FFA	0.1895	1120.90771	91.77544	6.4642
2	12.985	FF	0.2712	1.62193e4	917.46088	93.5358



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.430	VF R	0.1950	3.02498e4	2398.56909	94.1339
2	13.143	FFA	0.3696	1885.06970	82.48037	5.8661

**(5*S*,6*S*)-2-(4-chlorophenyl)-6-(4-methoxyphenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



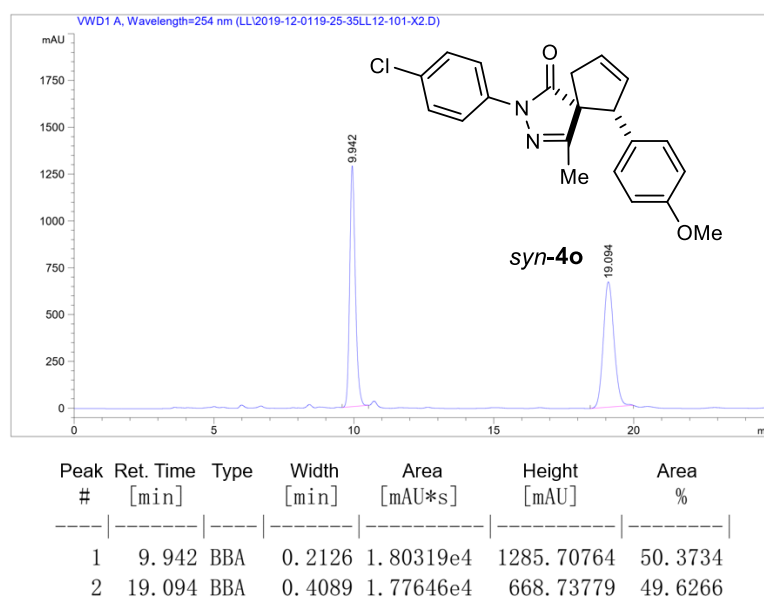
Yellow oil, 11.7 mg, 32% yield, 93% ee.  $R_f = 0.33$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -40.46$  (*c* 1.0, CHCl<sub>3</sub>).

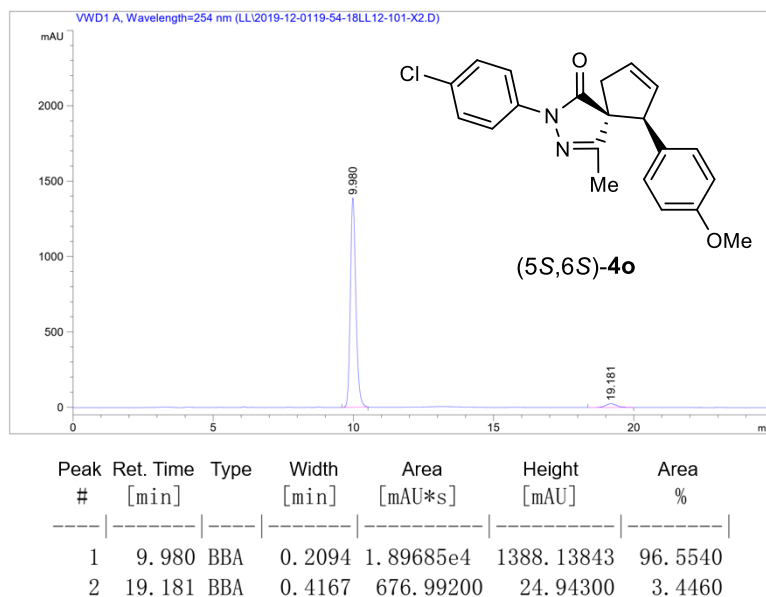
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.47 (d, *J* = 9.0 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.09-6.04 (m, 1H), 5.87-5.83 (m, 1H), 4.28 (s, 1H), 3.74 (s, 3H), 2.97-2.90 (m, 1H), 2.73-2.67 (m, 1H), 2.24 (s, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.0, 163.3, 159.2, 136.5, 131.6, 130.5, 129.7, 129.4, 129.1, 128.7, 120.1, 113.7, 63.1, 58.5, 55.3, 39.3, 13.8.

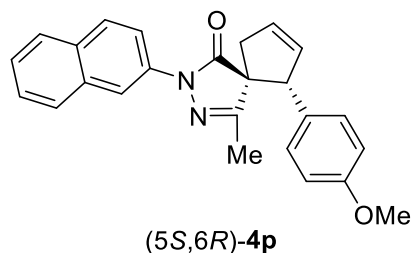
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 9.9$  min,  $t_{\text{minor}} = 19.2$  min.

**HRMS (ESI)** calcd for C<sub>21</sub>H<sub>20</sub>ClN<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 367.1208, found 367.1206.





**(5S,6R)-6-(4-methoxyphenyl)-4-methyl-2-(naphthalen-2-yl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 32.1 mg, 84% yield, 90% ee, 10:1 dr.  $R_f = 0.34$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +30.55$  (*c* 1.0, CHCl<sub>3</sub>).

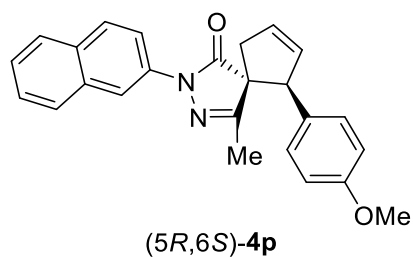
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  8.40 (s, 1H), 8.15-8.10 (m, 1H), 7.91-7.80 (m, 3H), 7.52-7.41 (m, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.10-6.05 (m, 1H), 6.04-5.98 (m, 1H), 4.71 (s, 1H), 3.75 (s, 3H), 3.09-3.01 (m, 1H), 2.79-2.71 (m, 1H), 1.73 (s, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  177.1, 163.2, 159.1, 135.9, 133.7, 131.7, 131.1, 130.0, 129.5, 128.8, 128.1, 127.7, 126.6, 125.4, 118.6, 116.0, 114.1, 64.7, 59.5, 55.3, 40.7, 15.3.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 19.0$  min,  $t_{\text{major}} = 24.4$  min.

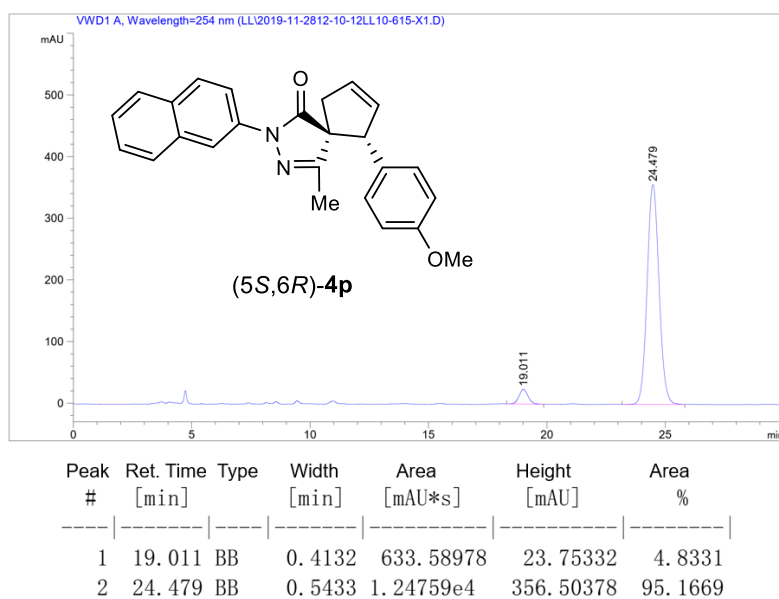
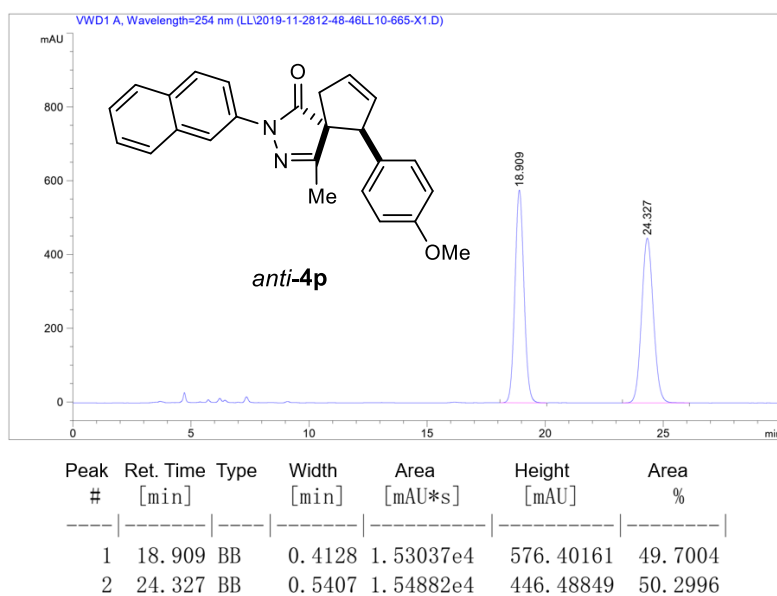
**HRMS (ESI)** calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 383.1754, found 383.1751.

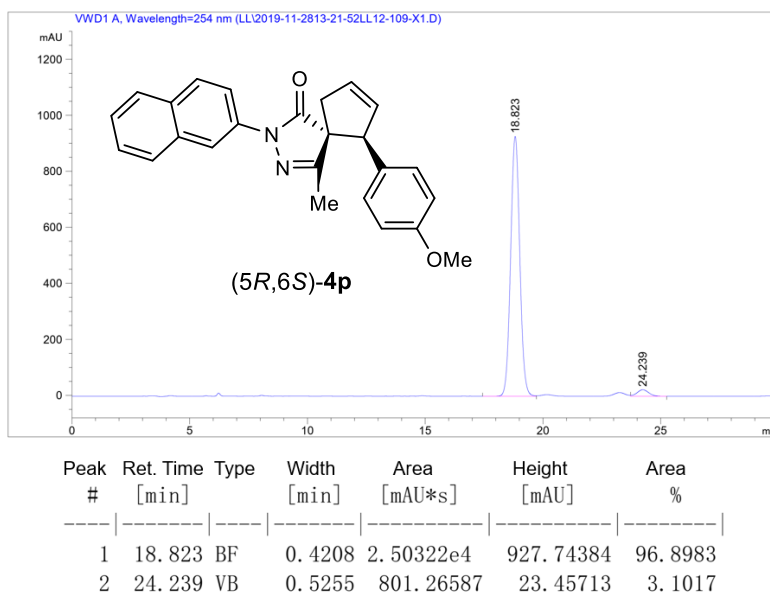
**(5*R*,6*S*)-6-(4-methoxyphenyl)-4-methyl-2-(naphthalen-2-yl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



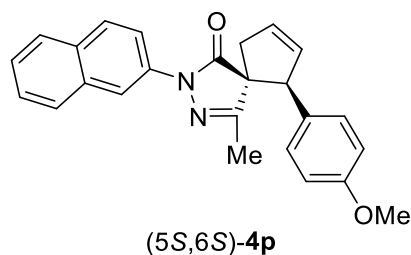
Yellow oil, 22.6 mg, 59% yield, 94% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 18.8$  min,  $t_{\text{minor}} = 24.2$  min.





**(5S,6S)-6-(4-methoxyphenyl)-4-methyl-2-(naphthalen-2-yl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



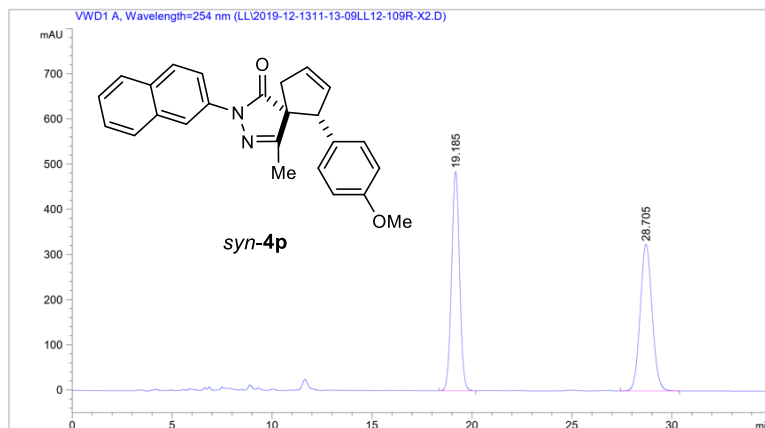
Yellow oil, 9.1 mg, 24% yield, 91% ee.  $R_f = 0.31$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -23.82$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.94 (s, 1H), 7.77-7.68 (m, 4H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 7.04 (d, *J* = 8.4 Hz, 2H), 6.78 (d, *J* = 9.0 Hz, 2H), 6.11-6.09 (m, 1H), 5.90-5.86 (m, 1H), 4.33 (s, 1H), 3.72 (s, 3H), 3.03-2.95 (m, 1H), 2.77-2.70 (m, 1H), 2.29 (s, 3H).

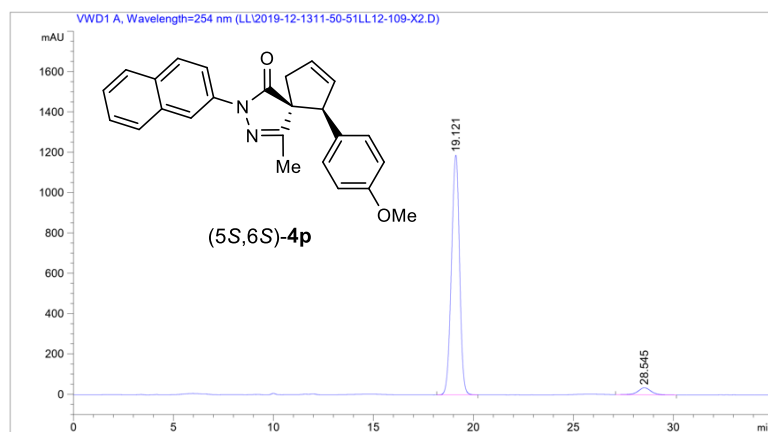
<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.3, 163.3, 159.3, 135.7, 133.7, 131.8, 131.1, 130.7, 129.6, 129.3, 128.6, 128.1, 127.7, 126.4, 125.3, 118.9, 116.2, 113.9, 63.3, 58.6, 55.4, 39.5, 14.0.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{major} = 19.1$  min,  $t_{minor} = 28.5$  min.

**HRMS** (ESI) calcd for C<sub>25</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 383.1754, found 383.1752.

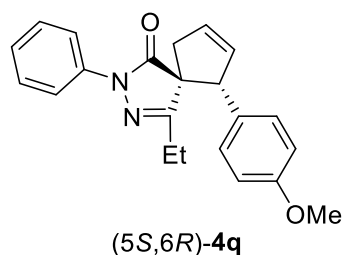


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.185	BB	0.4317	1.34769e4	485.73447	50.0248
2	28.705	BB	0.6398	1.34635e4	324.66049	49.9752



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	19.121	BB	0.4445	3.34564e4	1188.21973	95.5364
2	28.545	BB	0.6808	1563.13367	34.74764	4.4636

**(5*S*,6*R*)-4-ethyl-6-(4-methoxyphenyl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 23.6 mg, 68% yield, 90% ee, 4:1 dr.  $R_f = 0.41$  (*n*-hexane:EtOAc = 5:1).

$[\alpha]_D^{20} = +29.82$  (*c* 1.0, CHCl<sub>3</sub>).

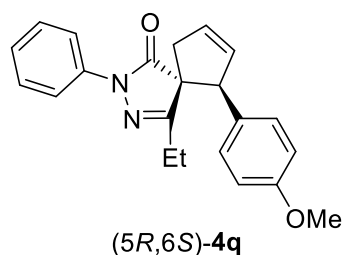
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.94 (d,  $J = 8.4$  Hz, 2H), 7.41 (t,  $J = 7.6$  Hz, 2H), 7.19 (t,  $J = 7.2$  Hz, 1H), 6.99 (d,  $J = 8.4$  Hz, 2H), 6.76 (d,  $J = 8.8$  Hz, 2H), 6.07-6.02 (m, 1H), 6.01-5.96 (m, 1H), 4.65 (s, 1H), 3.76 (s, 3H), 3.03-2.95 (m, 1H), 2.76-2.68 (m, 1H), 2.18-2.06 (m, 1H), 1.94-1.82 (m, 1H), 0.88 (t,  $J = 7.2$  Hz, 3H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  177.1, 166.9, 159.0, 138.5, 131.6, 130.2, 129.7, 129.0, 128.1, 125.0, 119.0, 114.0, 64.6, 59.6, 55.3, 40.8, 22.4, 9.5.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 8.4$  min,  $t_{\text{major}} = 10.9$  min.

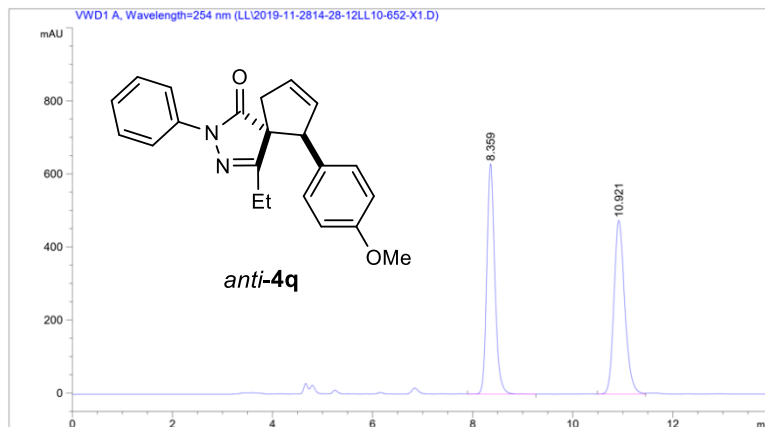
**HRMS (ESI)** calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 347.1754, found 347.1756.

**(5*R*,6*S*)-4-ethyl-6-(4-methoxyphenyl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**

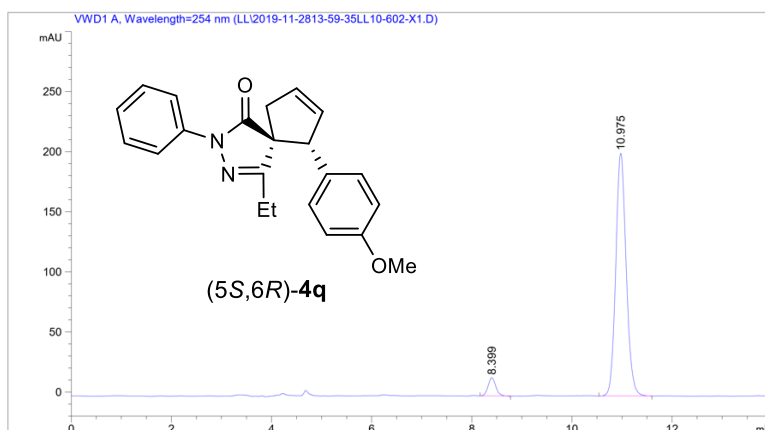


Yellow oil, 21.8 mg, 63% yield, 90% ee.

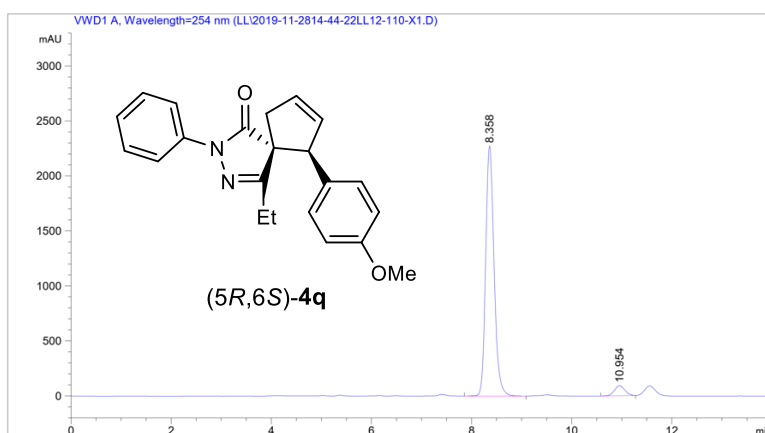
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 8.4$  min,  $t_{\text{minor}} = 10.9$  min.



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.359	VB R	0.1704	6989.54883	630.07062	49.4116
2	10.921	VF	0.2306	7156.02100	475.46106	50.5884



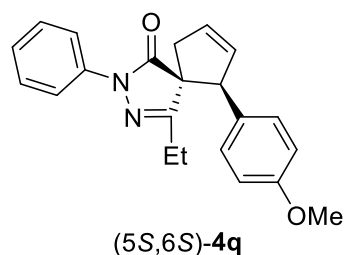
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.399	FF	0.1640	160.09607	15.06440	5.2021
2	10.975	FF	0.2216	2917.44922	201.91856	94.7979



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.358	VV	0.1800	2.65094e4	2273.87134	95.2212
2	10.954	VBAR	0.2243	1330.40735	91.68713	4.7788



**(5S,6S)-4-ethyl-6-(4-methoxyphenyl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**  
**-one**



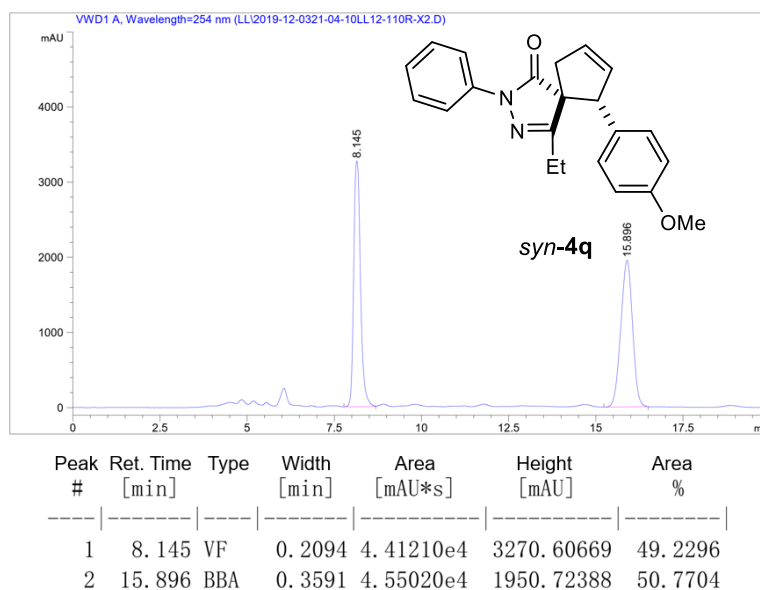
Yellow oil, 9.0 mg, 26% yield, 92% ee.  $R_f = 0.38$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -30.09$  (*c* 1.0, CHCl<sub>3</sub>).

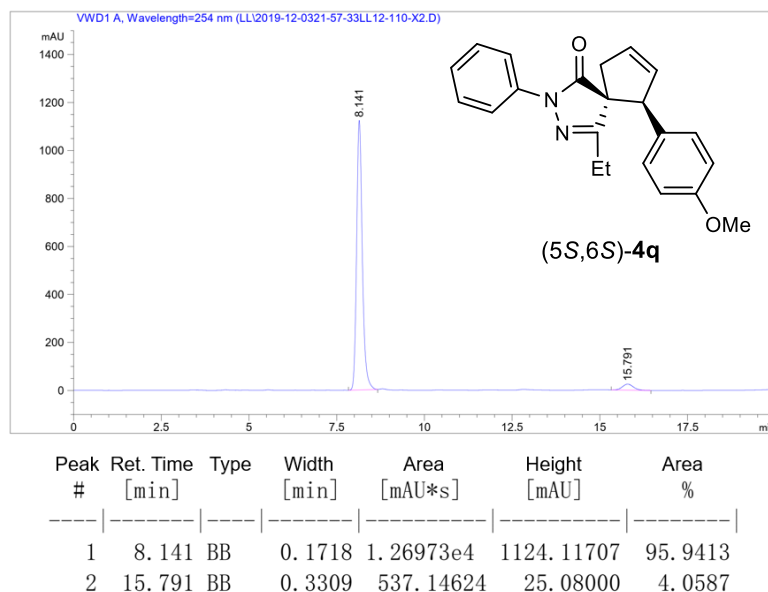
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.52 (d,  $J = 7.8$  Hz, 2H), 7.26 (t,  $J = 7.2$  Hz, 2H), 7.07 (t,  $J = 7.2$  Hz, 1H), 7.04 (d,  $J = 9.0$  Hz, 2H), 6.78 (d,  $J = 8.4$  Hz, 2H), 7.04 (d,  $J = 8.4$  Hz, 2H), 6.78 (d,  $J = 9.0$  Hz, 2H), 6.09-6.05 (m, 1H), 5.87-5.83 (m, 1H), 4.30 (s, 1H), 3.74 (s, 3H), 2.98-2.90 (m, 1H), 2.74-2.68 (m, 1H), 2.68-2.59 (m, 1H), 2.56-2.48 (m, 1H), 1.40 (t,  $J = 7.2$  Hz, 3H).

<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.3, 166.7, 159.1, 138.1, 131.7, 130.6, 129.4, 129.4, 128.7, 124.7, 119.1, 113.7, 63.1, 58.6, 55.3, 39.5, 21.1, 9.9.

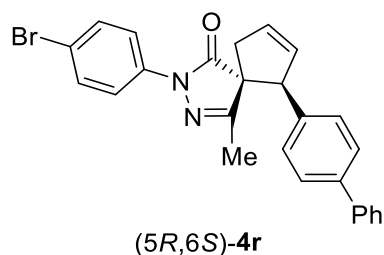
**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 8.1$  min,  $t_{\text{minor}} = 15.8$  min.

**HRMS (ESI)** calcd for C<sub>22</sub>H<sub>23</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 347.1754, found 347.1755.





**(5R,6S)-6-([1,1'-biphenyl]-4-yl)-2-(4-bromophenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



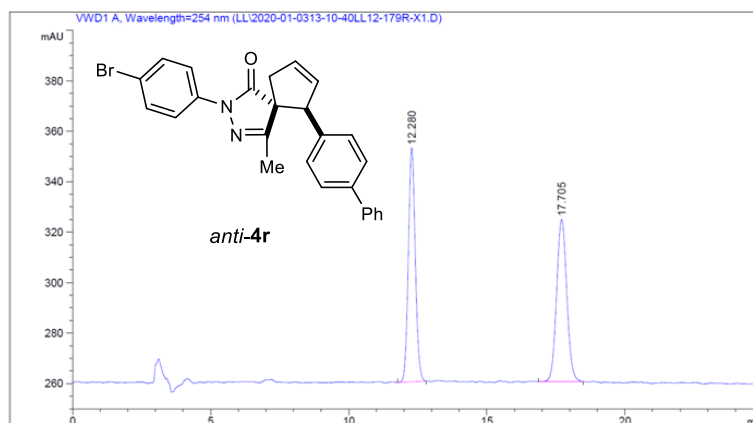
White solid, *m.p.*: 228.0-289.9 mg, 50% yield, 97% ee.  $R_f = 0.33$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -57.5455$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.85 (d, *J* = 7.7 Hz, 2H), 7.55 (d, *J* = 8.8 Hz, 2H), 7.52 (d, *J* = 8.8 Hz, 2H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 8.1 Hz, 2H), 6.15-6.09 (m, 1H), 6.06-5.99 (m, 1H), 4.77-4.71 (m, 1H), 3.08-2.99 (m, 1H), 2.78-2.69 (m, 1H), 1.71 (s, 3H).

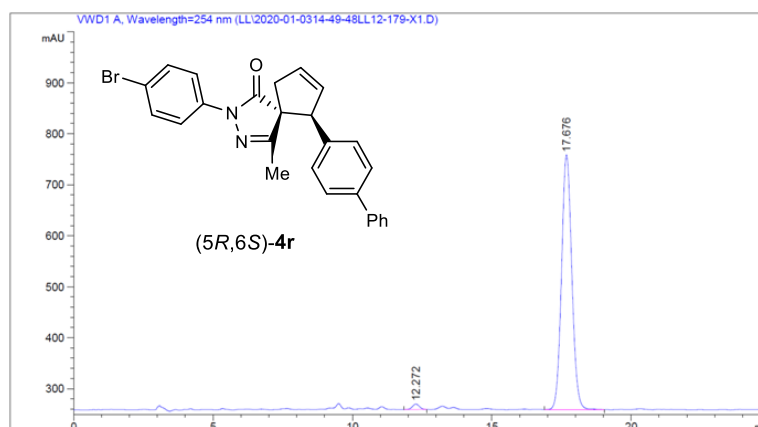
<sup>13</sup>C NMR (150 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.8, 163.1, 140.6, 140.5, 137.3, 137.0, 132.0, 131.0, 129.7, 128.9, 127.6, 127.5, 127.4, 127.1, 120.4, 117.9, 64.6, 59.7, 40.8, 15.3.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 12.3$  min,  $t_{\text{major}} = 17.7$  min.

**HRMS** (ESI) calcd for C<sub>26</sub>H<sub>22</sub>BrN<sub>2</sub>O [M + H]<sup>+</sup>: 457.0910, found 457.0906.

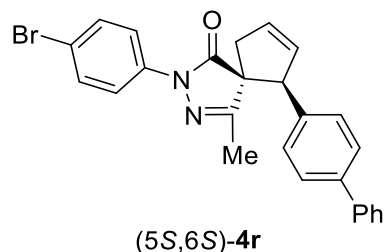


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.280	BB	0.2698	1620.88660	92.77139	49.5889
2	17.705	BB	0.3990	1647.76001	64.29202	50.4111



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.272	BBA	0.2655	184.90880	10.75889	1.4263
2	17.676	BV R	0.3955	1.27798e4	499.49805	98.5737

**(5*S*,6*S*)-6-([1,1'-biphenyl]-4-yl)-2-(4-bromophenyl)-4-methyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



White solid, *m.p.*:188.5-189.4 °C, 14.2 mg, 31% yield, 91% ee.  $R_f = 0.30$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -9.0$  (*c* 1.0, CHCl<sub>3</sub>).

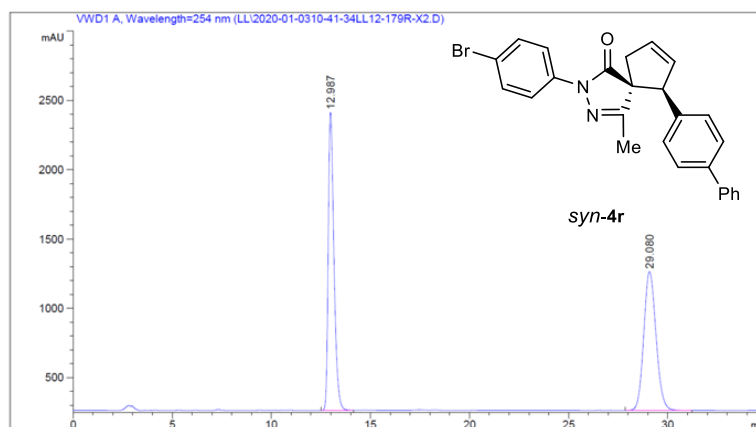
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ppm): δ 7.52 (d, *J* = 7.3 Hz, 2H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 7.5 Hz, 2H), 7.40-7.36 (m, 2H), 7.36-7.31 (m, 3H), 7.17 (d, *J* = 8.1

Hz, 2H), 6.15-6.09 (m, 1H), 5.95-5.89 (m, 1H), 4.41-4.35 (m, 1H), 3.01-2.94 (m, 1H), 2.79-2.71 (m, 1H), 2.28 (s, 3H).

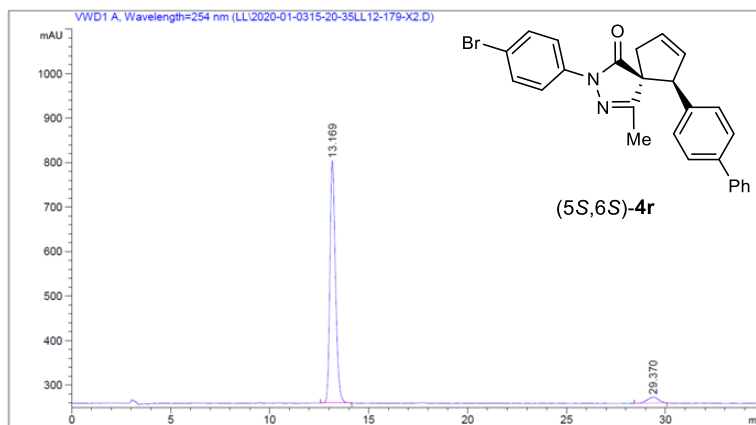
$^{13}\text{C}$  NMR (150 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  173.9, 163.2, 140.8, 140.7, 136.9, 136.2, 131.7, 131.2, 131.0, 128.9, 128.7, 127.4, 127.2, 127.0, 120.5, 117.6, 63.2, 58.8, 39.4, 13.9.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 90:10, flow rate = 1.0 mL/min,  $\lambda$  = 254 nm, retention time:  $t_{\text{major}}$  = 13.2 min,  $t_{\text{minor}}$  = 29.4 min.

**HRMS (ESI) calcd for  $\text{C}_{26}\text{H}_{22}\text{BrN}_2\text{O}$  [ $\text{M} + \text{H}$ ] $^+$ :** 457.0910, found 457.0910.

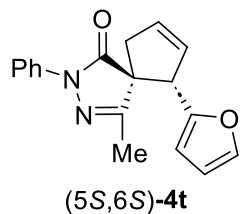


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.987	BB	0.3032	4.28209e4	2151.14282	49.8414
2	29.080	BV R	0.6647	4.30934e4	1002.05591	50.1586



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.169	BBA	0.2983	1.06025e4	544.12396	95.4512
2	29.370	BBA	0.6336	505.26678	13.02350	4.5488

**(5*S*,6*S*)-6-(furan-2-yl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



Yellow oil, 19.9 mg, 68% yield, 93% ee, 10:1 dr.  $R_f = 0.30$  (*n*-hexane:EtOAc = 10:1).

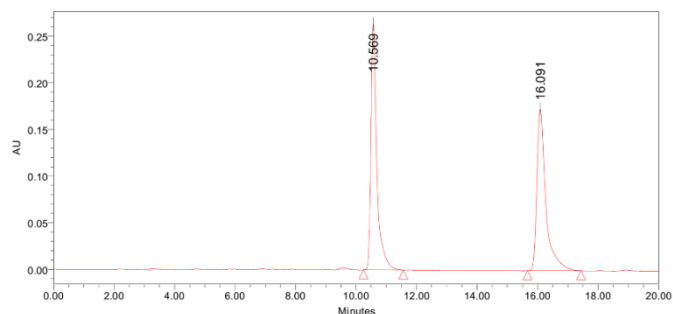
$[\alpha]_D^{20} = 33.7$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.93 (dd,  $J = 8.8$  Hz,  $J = 1.1$  Hz, 2H), 7.43-7.38 (m, 2H), 7.26 (s, 1H), 7.21-7.16 (m, 1H), 6.26 (dd,  $J = 3.1$  Hz,  $J = 1.9$  Hz, 1H), 6.10 (d,  $J = 3.2$  Hz, 1H), 5.99-5.95 (m, 2H), 6.64 (s, 1H), 3.02-2.96 (m, 1H), 2.74-2.67 (m, 1H), 1.77 (s, 3H).

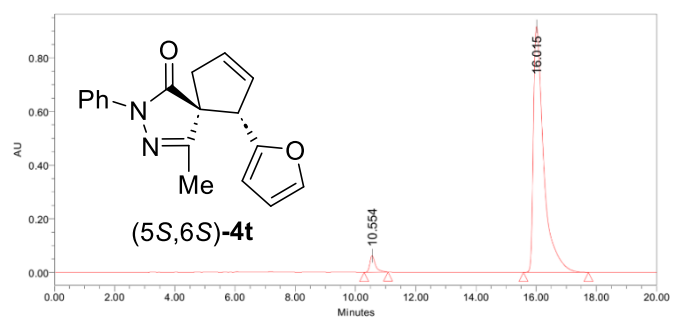
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.0, 162.5, 152.0, 142.3, 138.3, 129.9, 129.4, 1219.0, 125.0, 119.0, 110.4, 106.7, 62.8, 53.4, 40.8, 14.5.

**HPLC analysis:** Daicel CHIRALPAK IA-3, *n*-hexane:*i*-PrOH = 95:5, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 10.6$  min,  $t_{\text{major}} = 16.0$  min.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>O<sub>2</sub> [M + H]<sup>+</sup>: 293.1285, found 293.1283.

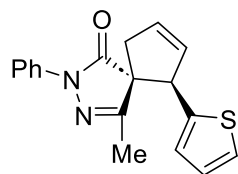


Name	RT	Area	Height	% Area	Peak Width (sec)
1	10.569	3581430	263708	50.24	30.00
2	16.091	3547017	173183	49.76	30.00



Name	RT	Area	Height	% Area	Peak Width (sec)
1	10.554	803556	62084	3.57	30.00
2	16.015	2171728	916816	96.43	30.00

**(5*R*,6*R*)-4-methyl-2-phenyl-6-(thiophen-2-yl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



**(5*R*,6*R*)-4u**

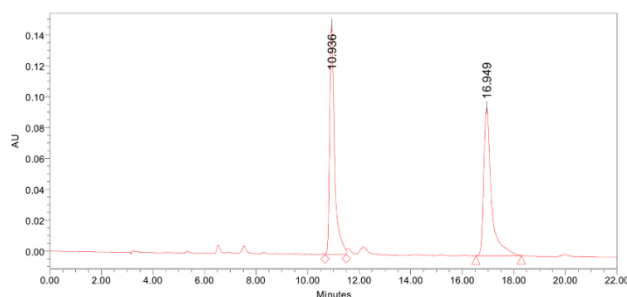
White solid, 19.3 mg, 62% yield, 95% ee.  $R_f = 0.31$  (*n*-hexane:EtOAc = 10:1).  $[\alpha]_D^{20} = -46.3$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.92 (d, *J* = 8.2 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.24-7.15 (m, 2H), 7.00 (s, 1H), 6.72 (d, *J* = 4.8 Hz, 1H), 6.00 (m, 2H), 4.67 (s, 1H), 3.07-2.94 (m, 1H), 2.75-2.65 (m, 1H), 1.68 (s, 3H).

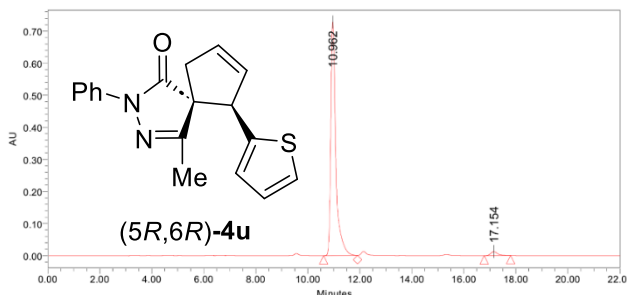
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  176.5, 163.0, 138.9, 138.2, 131.5, 129.3, 129.0, 126.6, 126.6, 125.1, 121.0, 118.9, 63.8, 55.3, 40.8, 14.9.

**HPLC analysis:** Daicel CHIRALPAK IA-3, *n*-hexane:*i*-PrOH = 95:5, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 10.9$  min,  $t_{\text{minor}} = 17.1$  min.

**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>OS [M + H]<sup>+</sup>: 309.1056, found 309.1052.

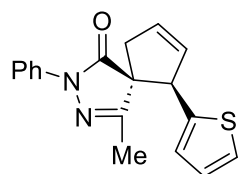


Name	RT	Area	Height	% Area	Peak Width (sec)
1	10.936	1949750	148558	49.52	30.00
2	16.949	1987420	96031	50.48	30.00



Name	RT	Area	Height	% Area	Peak Width (sec)
1	10.962	9805810	728774	97.70	30.00
2	17.154	231239	12233	2.30	30.00

**(5*S*,6*R*)-4-methyl-2-phenyl-6-(thiophen-2-yl)-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



**(5*S*,6*R*)-4u**

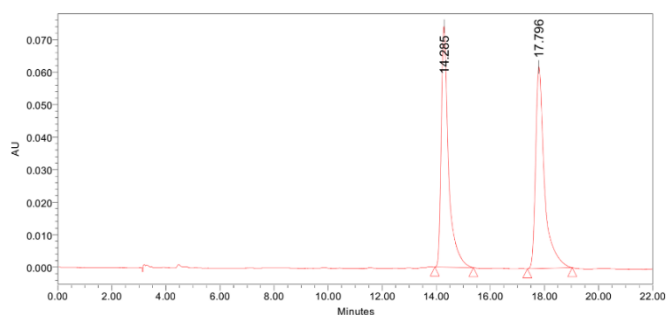
White solid, 6.8mg, 22% yield, 96% ee.  $R_f = 0.28$  (*n*-hexane:EtOAc = 10:1).  $[\alpha]_D^{20} = -40.1$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.58-7.50 (m, 2H), 7.32-7.26 (m, 2H), 7.22-7.18 (m, 1H), 7.13-7.07 (m, 1H), 7.06-7.03 (m, 1H), 6.09-6.03 (m, 1H), 5.95-5.87 (m, 1H), 4.42-4.37 (m, 1H), 2.99-2.92 (m, 1H), 2.75-2.67 (m, 1H), 2.23 (s, 3H).

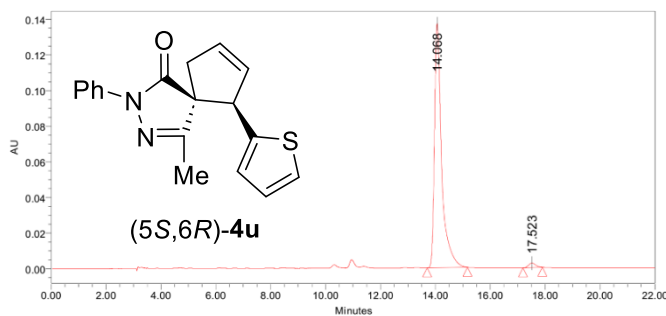
<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  173.9, 162.7, 138.2, 137.9, 131.3, 130.5, 128.8, 127.6, 125.6, 124.9, 122.6, 119.1, 62.6, 54.0, 39.3, 13.9.

**HPLC analysis:** Daicel CHIRALPAK IA-3, *n*-hexane:*i*-PrOH = 95:5, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 14.1$  min,  $t_{\text{minor}} = 17.5$  min.

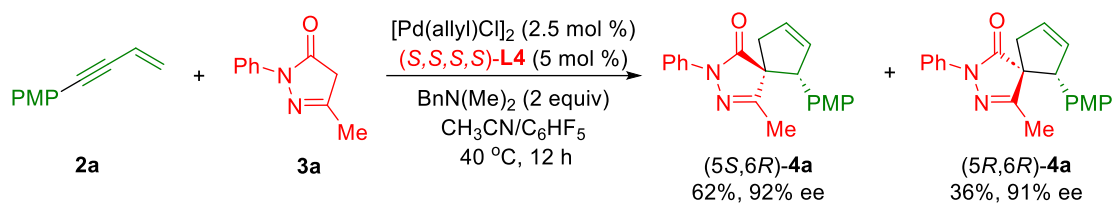
**HRMS (ESI)** calcd for C<sub>18</sub>H<sub>17</sub>N<sub>2</sub>OS [M + H]<sup>+</sup>: 309.1056, found 309.1053.



Name	RT	Area	Height	% Area	Peak Width (sec)
1	14.285	1373095	74161	49.37	30.00
2	17.796	1408312	62002	50.63	30.00

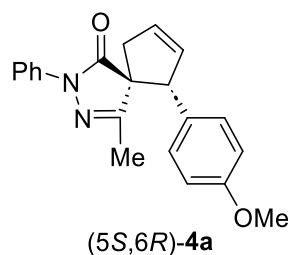


Name	RT	Area	Height	% Area	Peak Width (sec)
1	14.068	2496370	137044	98.27	30.00
2	17.523	44024	2512	1.73	30.00



**(5*S*,6*R*)-6-(4-methoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-die**

**n-1-one**

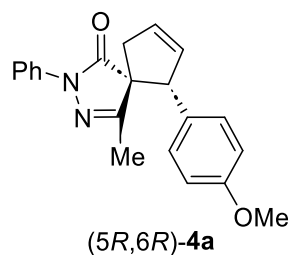


Yellow oil, 20.6 mg, 62% yield, 92% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.1 mL/min,  $\lambda = 254\text{ nm}$ , retention time:  $t_{\text{minor}} = 8.7\text{ min}$ .  $t_{\text{major}} = 10.1\text{ min}$ ,

**(5*R*,6*R*)-6-(4-methoxyphenyl)-4-methyl-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-die**

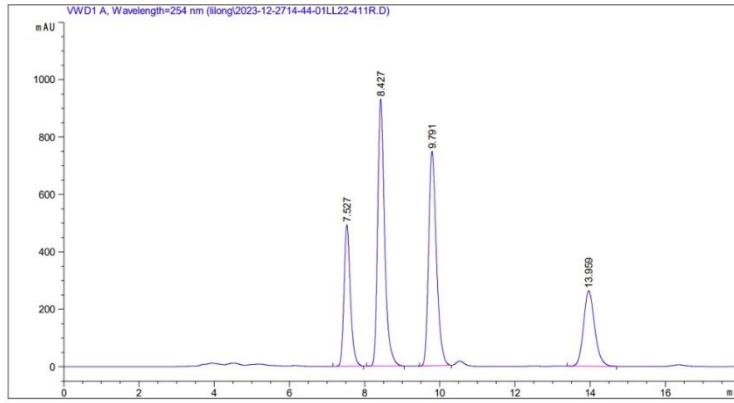
**n-1-one**



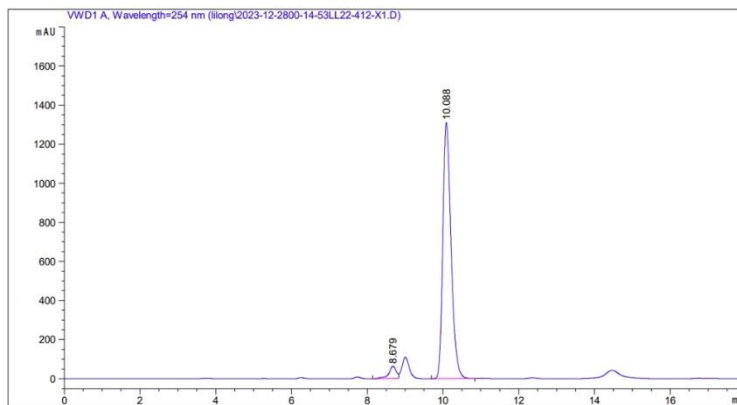
Yellow oil, 12 mg, 36% yield, 91% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.1 mL/min,  $\lambda = 254\text{ nm}$ , retention time:  $t_{\text{minor}} = 7.5\text{ min}$ ,  $t_{\text{major}} = 14.9\text{ min}$ .

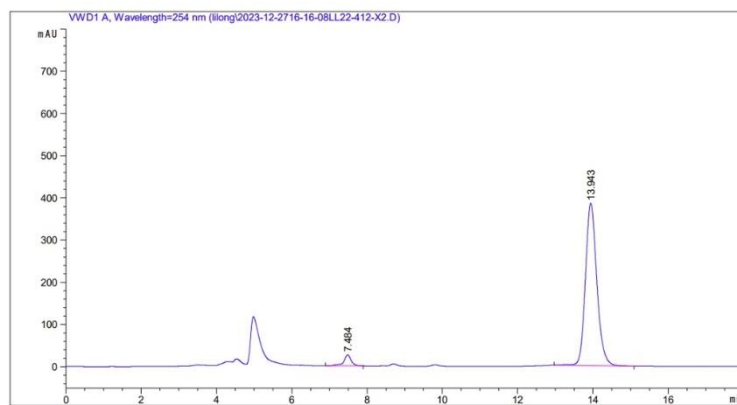




Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.527	BBA	0.1785	5764.97803	492.58981	17.0577
2	8.427	BBA	0.1924	1.18396e4	930.53345	33.0316
3	9.791	BB	0.2201	1.07698e4	747.29089	33.8663
4	13.959	BBA	0.3165	5422.50635	263.01965	16.0444

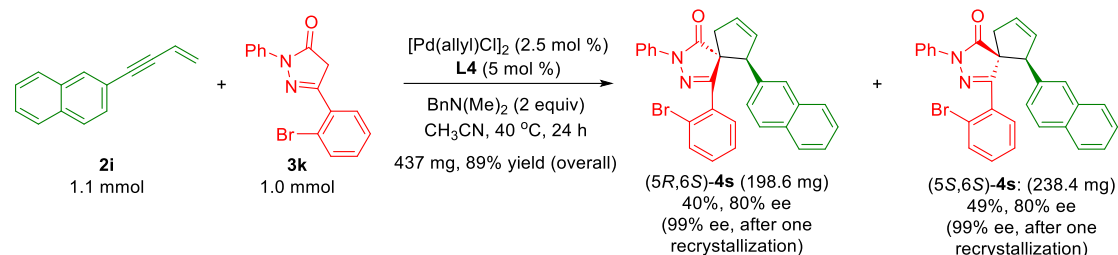


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.679	BV	0.2018	863.50537	63.05351	4.2044
2	10.088	BB	0.2293	1.96746e4	1309.56519	95.7956



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.484	BBA	0.2029	368.17786	26.37399	4.3365
2	13.943	HB	0.3240	8121.97949	385.18732	95.6635

## 5. Application in Asymmetric Catalysis

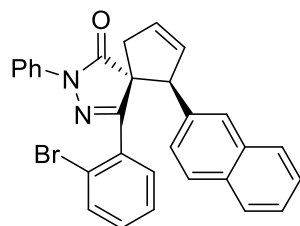


In an Ar-filled glovebox, dissolving the [Pd(allyl)Cl]<sub>2</sub> (9.1 mg, 2.5 mol %), and **L4** (37 mg, 5 mol %) in CH<sub>3</sub>CN (5 mL, 0.2 M) was stirred for 15 min at room temperature. Subsequently, conjugated enyne **2i** (1.1 mmol, 1.1 equiv), **3k** (1 mmol, 1 equiv), and BnN(Me)<sub>2</sub> (2 equiv, 300 μL) were added. The reaction mixture was stirred at 40 °C for 24 h outside the glove box. The solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 20:1 to 5:1) to afford the pyrazolone-derived spiro product (*5R,6S*)-**4s** (199.6 mg) and (*5S,6S*)-**4s** (238.4 mg).

The above-obtained product (*5R,6S*)-**4s** (199.6 mg, 80% ee) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL), followed by addition of *n*-hexane (9 mL). The mixed solution was stood at room temperature (about 3 days), until the enantiomeric excess of mother liquor reached 99% upon inspection by chiral HPLC analysis. Then the racemic crystal was separated from the solution by filtration, the mother liquor was collected to afford the enantioenriched product (*5R,6S*)-**4s** (158mg, 99% ee).

The above-obtained product (*5S,6S*)-**4s** (238.4 mg, 80% ee) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3 mL), followed by addition of *n*-hexane (9 mL). The mixed solution was stood at 0 °C (about 5 days), until the enantiomeric excess of mother liquor reached 99% upon inspection by chiral HPLC analysis. Then the racemic crystal was separated from the solution by filtration, the mother liquor was collected to afford the enantioenriched product (*5S,6S*)-**4s** (155mg, 99% ee).

**(5R,6S)-4-(2-bromophenyl)-6-(naphthalen-2-yl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



(5R,6S)-4s

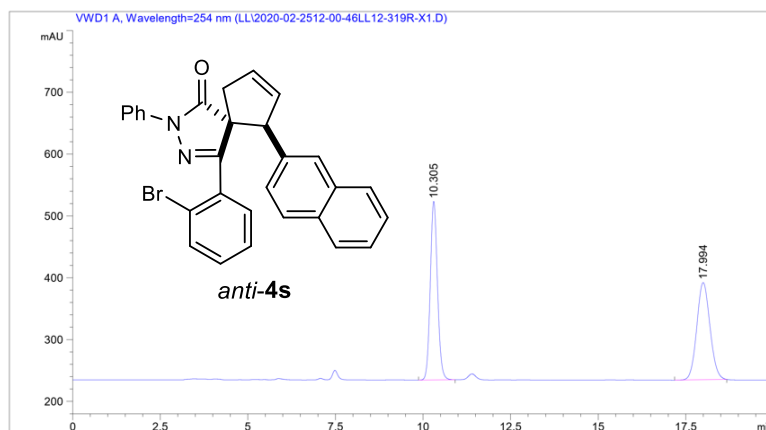
White solid, 198.6 mg, 40% yield, 80% ee, 99% ee after one recrystallization.  $R_f = 0.32$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -35.3$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  8.04 (d, *J* = 7.7 Hz, 2H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 8.4 Hz, 1H), 7.48-7.31 (m, 5H), 7.27-7.17 (m, 2H), 7.14 (s, 1H), 7.12-7.01 (m, 2H), 7.00-6.93 (m, 1H), 6.92-6.86 (m, 1H), 6.15-6.02 (m, 2H), 4.98-4.87 (m, 1H), 3.48-3.17 (m, 2H).

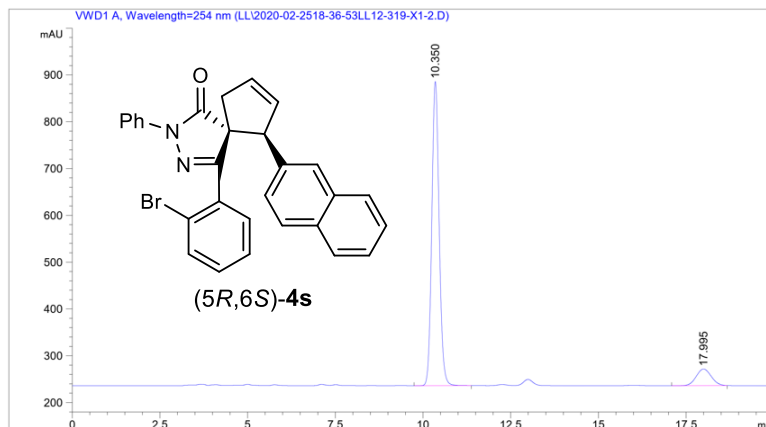
<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  177.0, 159.4, 138.2, 134.7, 133.3, 132.9, 131.9, 130.1, 129.6, 129.1, 128.4, 127.7, 127.5, 126.5, 126.3, 126.0, 125.8, 125.8, 125.5, 123.5, 119.3, 64.8, 60.3, 44.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 10.4$  min,  $t_{\text{minor}} = 18.0$  min.

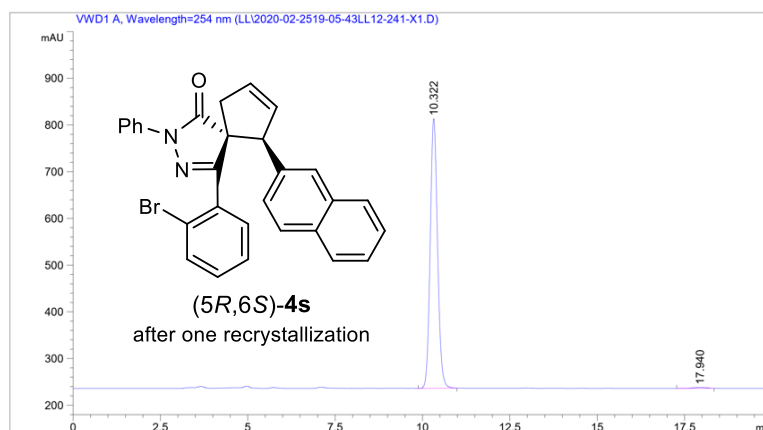
**HRMS (ESI)** calcd for C<sub>29</sub>H<sub>21</sub>BrN<sub>2</sub>O [M + H]<sup>+</sup>: 493.0910, found 493.0911.



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.305	BB	0.2210	4133.73242	288.82712	50.1628
2	17.994	BBA	0.4055	4106.89990	157.32948	49.8372



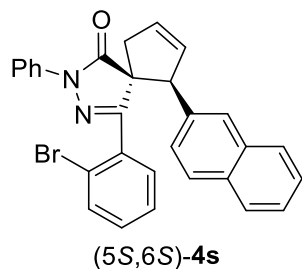
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.350	BB	0.2248	9457.68945	649.76111	89.9866
2	17.995	BBA	0.4656	1052.42029	35.42489	10.0134



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.322	BBA	0.2239	8409.06348	577.47101	99.3739
2	17.940	BBA	0.4244	52.97989	1.91697	0.6261

**(5S,6S)-4-(2-bromophenyl)-6-(naphthalen-2-yl)-2-phenyl-2,3-diazaspiro[4.4]**

**nona-3,7-dien-1-one**



White solid, 238.4 mg, 49% yield, 80% ee, 99% ee after one recrystallization.  $R_f = 0.30$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -27.3$  (*c* 1.0, CHCl<sub>3</sub>).

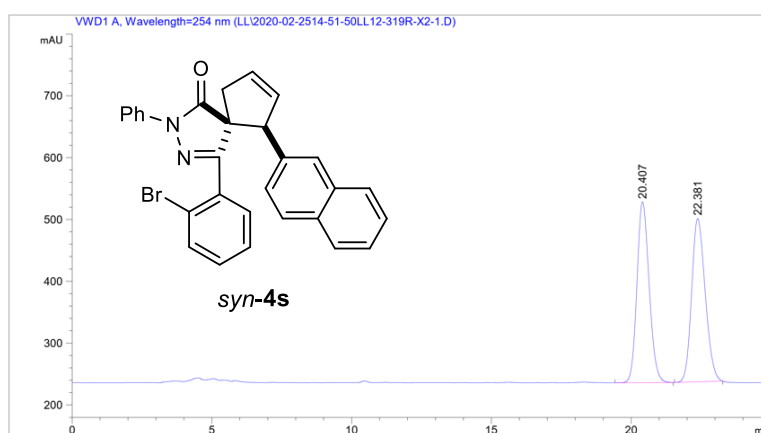
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.82-7.69 (m, 5H), 7.66-7.59 (m, 2H), 7.47-7.37

(m, 5H), 7.37-7.29 (m, 2H), 7.17 (t,  $J = 7.6$  Hz, 2H), 7.02 (t,  $J = 7.4$  Hz, 1H), 6.14-6.00 (m, 1H), 5.93-5.79 (m, 1H), 4.94-4.81 (m, 1H), 3.23-3.00 (m, 2H).

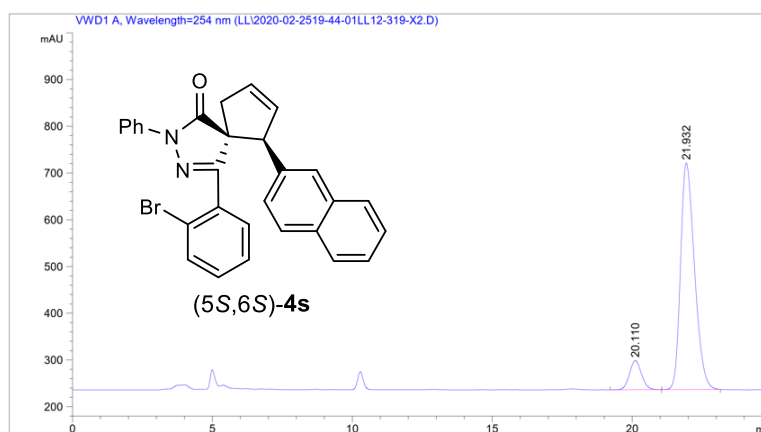
$^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  173.7, 161.0, 137.5, 135.0, 134.7, 133.2, 133.0, 131.9, 131.2, 131.1, 130.4, 128.7, 128.1, 127.9, 127.7, 127.5, 127.4, 126.6, 126.1, 125.9, 125.5, 123.8, 119.5, 63.9, 58.7, 40.8.

**HPLC analysis:** Daicel CHIRALPAK AD-H,  $n$ -hexane: $i$ -PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 20.1$  min,  $t_{\text{major}} = 21.9$  min.

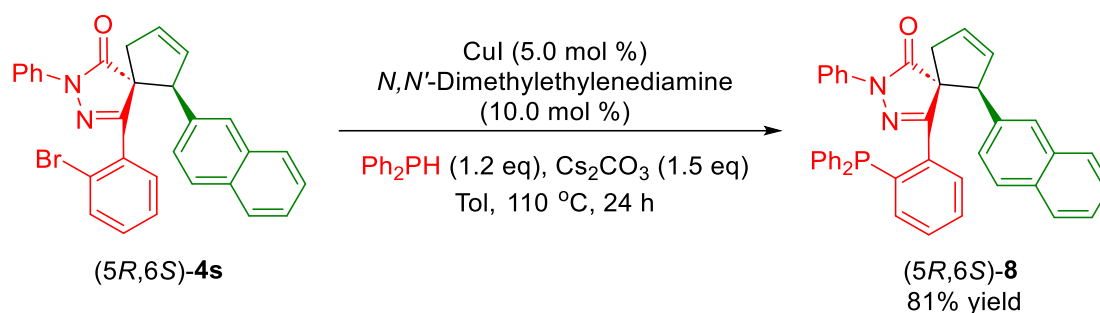
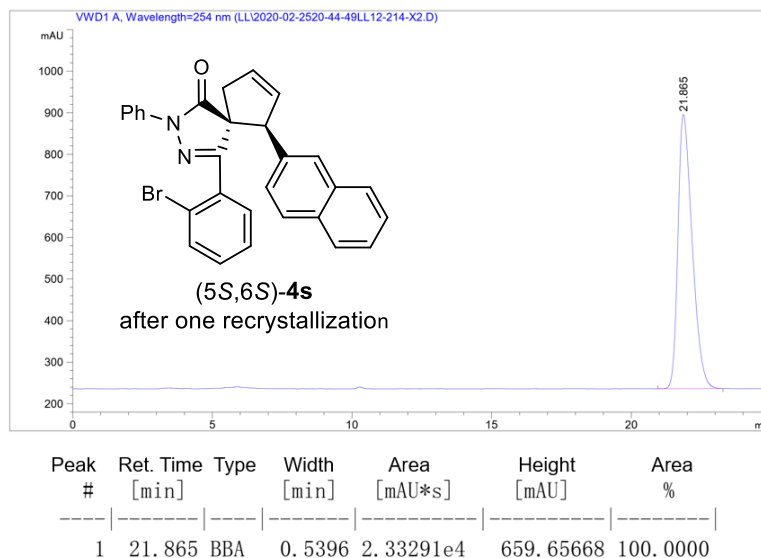
**HRMS (ESI)** calcd for  $\text{C}_{29}\text{H}_{21}\text{BrN}_2\text{O}$  [ $\text{M} + \text{H}$ ] $^+$ : 493.0910, found 493.0913.



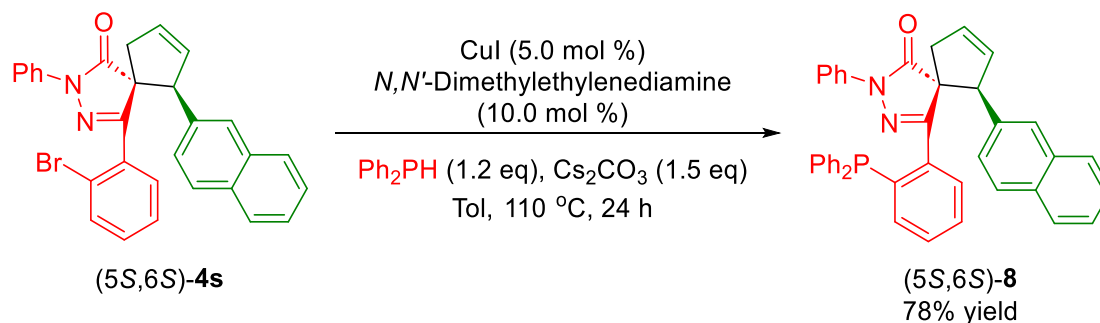
Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.407	BB	0.4705	8857.78809	292.33295	49.8070
2	22.381	BBA	0.5216	8926.43652	263.91544	50.1930



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.110	BB	0.4599	1855.79846	62.41451	9.9577
2	21.932	BBA	0.5350	1.67810e4	484.60211	90.0423



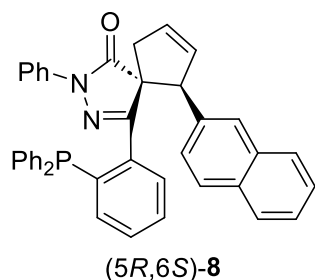
A solution of CuI (3.8 mg, 0.02 mmol), *N,N'*-dimethylethylenediamine (3.5  $\mu\text{L}$ , 0.04 mmol) and diphenylphosphane (83.5  $\mu\text{L}$ , 0.58 mmol) in 2 mL dry toluene was stirred at room temperature for 20 min.  $\text{Cs}_2\text{CO}_3$  (196 mg, 0.6 mmol) and  $(5R,6S)\text{-4s}$  (199 mg, 0.40 mmol; 0.1 M in dry toluene) were added and the mixture was heated to 110  $^\circ\text{C}$  for 24 h under an Ar atmosphere. The reaction mixture was cooled to room temperature, filtered and concentrated. Column chromatography of the residue (n-hexanes:EtOAc = 10:1) provided  $(5R,6S)\text{-8}$  (194 mg) as white solid.



A solution of CuI (4.6 mg, 0.024 mmol), *N,N'*-dimethylethylenediamine (4.2  $\mu\text{L}$ , 0.048 mmol) and diphenylphosphane (107  $\mu\text{L}$ , 1.31 mmol) in 2 mL dry toluene was

stirred at room temperature for 20 min. Cs<sub>2</sub>CO<sub>3</sub> (235 mg, 0.72 mmol) and (5*S*,6*S*)-**4s** (238 mg, 0.48 mmol; 0.1 M in dry toluene) were added and the mixture was heated to 110 °C for 24 h under an Ar atmosphere. The reaction mixture was cooled to room temperature, filtered and concentrated. Column chromatography of the residue (*n*-hexane:EtOAc = 10:1 to 5:1) provided (5*S*,6*S*)-**8** (224mg) as white solid.

**(5*R*,6*S*)-4-(2-bromophenyl)-6-(naphthalen-2-yl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



White solid, 81% yield.  $R_f = 0.34$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -40.2$  ( $c$  1.0, CHCl<sub>3</sub>).

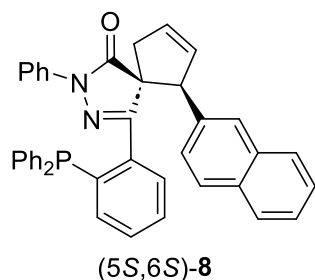
<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.82-7.71 (m, 2H), 7.57-7.51 (m, 1H), 7.48-7.41 (m, 4H), 7.38-7.06 (m, 12H), 7.05-6.92 (m, 6H), 6.57-6.48 (m, 1H), 6.32-6.13 (m, 4H), 5.06-5.00 (m, 1H), 3.52-3.23 (m, 2H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  178.1, 159.6, 138.1, 137.5, 137.3, 136.1, 135.9, 135.8, 135.1, 133.9, 133.7, 133.6, 133.5, 133.3, 133.0, 128.9, 128.8, 128.8, 128.7, 128.4, 128.2, 128.12, 128.0, 127.9, 127.9, 127.8, 127.6, 127.4, 126.7, 126.3, 126.1, 125.7, 125.0, 119.1, 63.5, 63.5, 61.5, 61.5, 45.2.

<sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  6.4 (s, 1P, C<sub>3</sub>P).

HRMS (ESI) calcd for C<sub>41</sub>H<sub>31</sub>N<sub>2</sub>OP [M + H]<sup>+</sup>: 599.2247, found 599.2244.

**(5*S*,6*S*)-4-(2-bromophenyl)-6-(naphthalen-2-yl)-2-phenyl-2,3-diazaspiro[4.4]nona-3,7-dien-1-one**



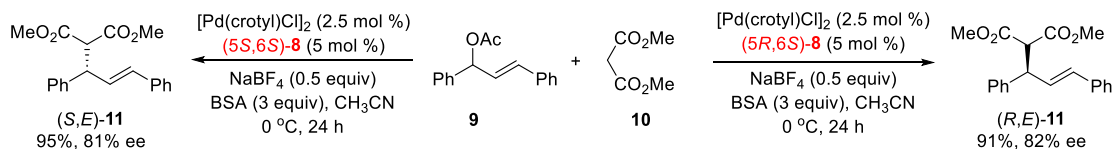
White solid, 78% yield.  $R_f = 0.32$  (*n*-hexane:EtOAc = 5:1).  $[\alpha]_D^{20} = -39.8$  (*c* 1.0, CHCl<sub>3</sub>).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  7.81-7.62 (m, 4H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.41 (t, *J* = 7.4 Hz, 1H), 7.38-7.24 (m, 13H), 7.21-7.13 (m, 2H), 6.98-6.82 (m, 5H), 6.23-6.11 (m, 1H), 6.08-5.96 (m, 1H), 4.99-4.89 (m, 1H), 3.32-3.15 (m, 2H).

<sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  174.3, 160.1, 138.8, 138.7, 138.7, 138.6, 137.3, 136.2, 135.4, 135.0, 134.8, 134.1, 134.1, 133.9, 133.9, 133.1, 132.7, 131.5, 131.3, 129.5, 128.6, 128.5, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 127.7, 127.5, 127.0, 126.4, 125.9, 125.7, 124.6, 119.0, 62.3, 60.2, 42.8.

<sup>31</sup>P NMR (162 MHz, CDCl<sub>3</sub>, ppm):  $\delta$  4.8 (s, 1P, C<sub>3</sub>P).

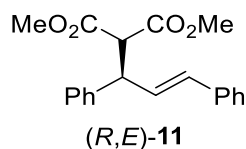
HRMS (ESI) calcd for C<sub>41</sub>H<sub>31</sub>N<sub>2</sub>OP [M + H]<sup>+</sup>: 599.2247, found 599.2249.



Dissolving the [Pd(crotyl)Cl]<sub>2</sub> (0.5 mg, 2.5 mol %), and (5*R*,6*S*)-**8** or (5*S*,6*S*)-**8** (3.0 mg, 5 mol %) in CH<sub>3</sub>CN (0.5 mL) was stirred for 15 min at room temperature. Subsequently, NaBF<sub>4</sub> (2.7 mg, 0.5 equiv), malonate **10** (0.15 mmol, 3 equiv) were added and cooled to 0 °C before allylic ester **9** (0.05 mmol, 1 equiv) were added. The reaction mixture was stirred at at 0 °C for 24 h. The solution was concentrated in vacuo and the crude product was purified by column chromatography on silica gel (*n*-hexane:EtOAc = 95:5) to afford product (*R*)-**11** or (*S*)-**11**.

### Dimethyl (*R,E*)-2-(1,3-diphenylallyl)malonate





Colorless oil, 91% yield, 82% ee.  $R_f = 0.50$  (*n*-hexane:EtOAc = 20:1).

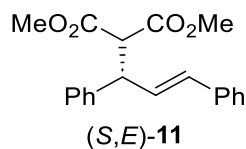
$^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  7.36-7.16 (m, 10H), 6.48 (d,  $J = 15.8$  Hz, 1H), 6.33 (dd,  $^1J = 8.6$  Hz,  $^2J = 15.7$  Hz, 1H), 4.26 (t,  $J = 8.7$  Hz, 1H), 3.96 (d,  $J = 10.9$  Hz, 1H), 3.70 (s, 3H), 3.52 (s, 3H).

$^{13}\text{C NMR}$  (100 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  168.2, 167.8, 140.2, 136.8, 131.9, 129.1, 128.7, 128.5, 127.9, 127.6, 127.2, 126.4, 57.7, 52.6, 52.5, 49.2.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{minor}} = 9.1$  min,  $t_{\text{major}} = 12.3$  min.

**HRMS** (ESI) calcd for  $\text{C}_{20}\text{H}_{20}\text{O}_4\text{Na}$   $[\text{M} + \text{Na}]^+$ : 347.1254, found 347.1253.

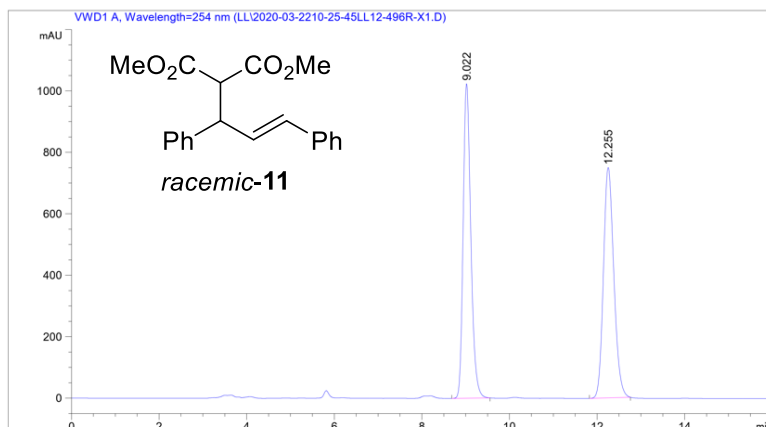
#### Dimethyl (*S,E*)-2-(1,3-diphenylallyl)malonate



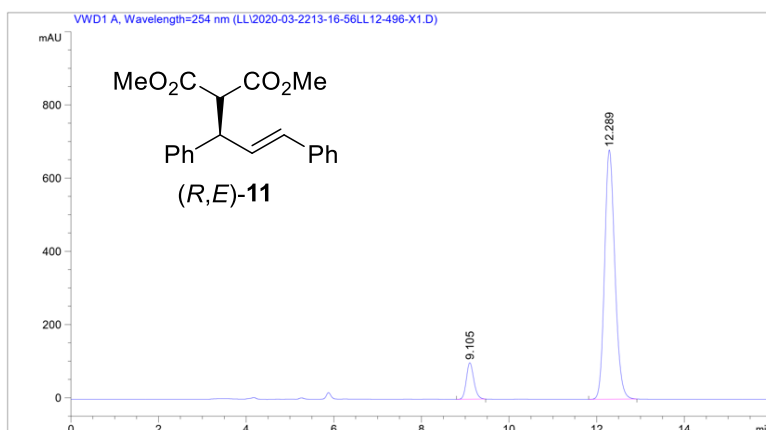
Colorless oil, 95% yield, 81% ee.

**HPLC analysis:** Daicel CHIRALPAK AD-H, *n*-hexane:*i*-PrOH = 80:20, flow rate = 1.0 mL/min,  $\lambda = 254$  nm, retention time:  $t_{\text{major}} = 9.1$  min,  $t_{\text{minor}} = 12.3$  min.

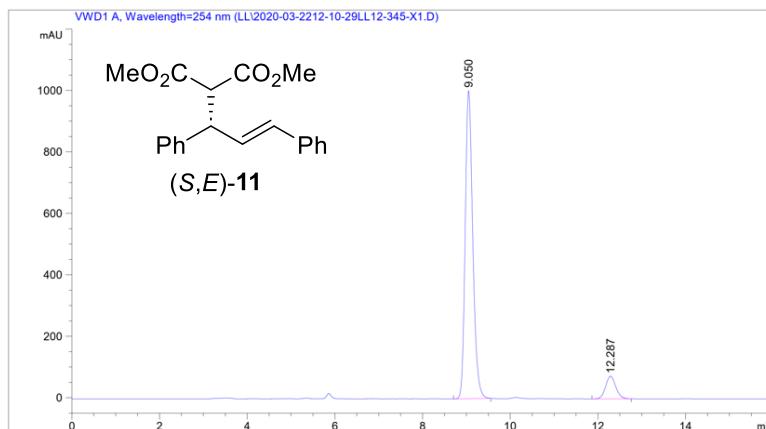
**HRMS** (ESI) calcd for  $\text{C}_{20}\text{H}_{20}\text{O}_4\text{Na}$   $[\text{M} + \text{Na}]^+$ : 347.1253, found 347.1254.



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.022	BBA	0.1869	1.24522e4	1023.56781	50.1915
2	12.255	BBA	0.2542	1.23572e4	749.99780	49.8085



Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.105	BBA	0.1822	1179.24683	99.52358	9.6039
2	12.289	BBA	0.2512	1.10996e4	680.73932	90.3961

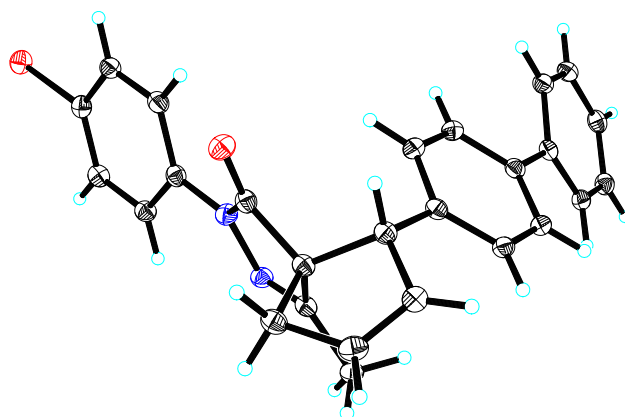


Peak #	Ret. Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.050	BBA	0.1836	1.19911e4	1002.01477	91.0151
2	12.287	BBA	0.2491	1183.74219	73.42167	8.9849

## 6. The Assignment of Structure and Configuration

### 5.1 Assignment of Absolute Configuration for Product (5*R*,6*S*)-4r

Crystal data for (5*R*,6*S*)-4r: C<sub>26</sub>H<sub>21</sub>BrN<sub>2</sub>O,  $M = 457.36$ ,  $a = 8.6954(2) \text{ \AA}$ ,  $b = 14.0748(3) \text{ \AA}$ ,  $c = 16.9937(4) \text{ \AA}$ ,  $\alpha = 90^\circ$ ,  $\beta = 90^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 2079.79(8) \text{ \AA}^3$ ,  $T = 100.(2) \text{ K}$ , space group  $P2_12_12_1$ ,  $Z = 4$ ,  $\mu(\text{Cu K}\alpha) = 2.847 \text{ mm}^{-1}$ , 21873 reflections measured, 4446 independent reflections ( $R_{int} = 0.0367$ ). The final  $R_I$  values were 0.0224 ( $I > 2\sigma(I)$ ). The final  $wR(F^2)$  values were 0.0563 ( $I > 2\sigma(I)$ ). The final  $R_I$  values were 0.0225 (all data). The final  $wR(F^2)$  values were 0.0564 (all data). The goodness of fit on  $F^2$  was 1.127. Flack parameter = 0.032(5).



(30% ellipsoid probability)

**Figure S2.** Crystal Structure of (5*R*,6*S*)-4r (CCDC 2012367).

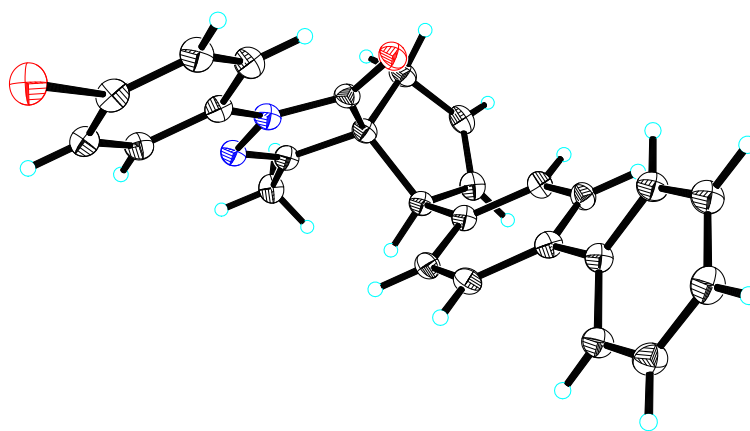
**Table S6.** Crystal data and structure refinement for (5*R*,6*S*)-4r.

Identification code	global
Empirical formula	C <sub>26</sub> H <sub>21</sub> BrN <sub>2</sub> O
Formula weight	457.36
Temperature	100(2) K
Wavelength	1.54178 \AA
Crystal system	Orthorhombic
Space group	P2 <sub>1</sub> 2 <sub>1</sub> 2 <sub>1</sub>
Unit cell dimensions	$a = 8.6954(2) \text{ \AA}$ $b = 14.0748(3) \text{ \AA}$ $c = 16.9937(4) \text{ \AA}$ $\alpha = \beta = \gamma = 90^\circ$

	$b = 14.0748(3) \text{ \AA}$	$= 90^\circ.$
	$c = 16.9937(4) \text{ \AA}$	$= 90^\circ.$
Volume	2079.79(8) $\text{\AA}^3$	
Z	4	
Density (calculated)	1.461 $\text{Mg/m}^3$	
Absorption coefficient	2.847 $\text{mm}^{-1}$	
F(000)	936	
Crystal size	0.380 x 0.300 x 0.200 $\text{mm}^3$	
Theta range for data collection	4.08 to 80.23°.	
Index ranges	-11<=h<=10, -17<=k<=14, -21<=l<=21	
Reflections collected	21873	
Independent reflections	4446 [R(int) = 0.0367]	
Completeness to theta = 80.23°	99.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.60 and 0.20	
Refinement method	Full-matrix least-squares on $F^2$	
Data / restraints / parameters	4446 / 0 / 272	
Goodness-of-fit on $F^2$	1.127	
Final R indices [I>2sigma(I)]	R1 = 0.0224, wR2 = 0.0563	
R indices (all data)	R1 = 0.0225, wR2 = 0.0564	
Absolute structure parameter	0.032(5)	
Largest diff. peak and hole	0.231 and -0.296 $\text{e.\AA}^{-3}$	

## 5.2 Assignment of Absolute Configuration for Product (5*S*,6*S*)-4r

Crystal data for (5*S*,6*S*)-4r: C<sub>26</sub>H<sub>21</sub>BrN<sub>2</sub>O,  $M = 457.36$ ,  $a = 6.08550(10)$  Å,  $b = 15.9623(4)$  Å,  $c = 21.2691(5)$  Å,  $\alpha = 90^\circ$ ,  $\beta = 90^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 2066.05(8)$  Å<sup>3</sup>,  $T = 100.(2)$  K, space group  $P2_12_12_1$ ,  $Z = 4$ ,  $\mu(\text{Cu K}\alpha) = 2.866$  mm<sup>-1</sup>, 14666 reflections measured, 3980 independent reflections ( $R_{int} = 0.0503$ ). The final  $R_I$  values were 0.0277 ( $I > 2\sigma(I)$ ). The final  $wR(F^2)$  values were 0.0729 ( $I > 2\sigma(I)$ ). The final  $R_I$  values were 0.0281 (all data). The final  $wR(F^2)$  values were 0.0734 (all data). The goodness of fit on  $F^2$  was 1.029. Flack parameter = 0.039(7).



(30% ellipsoid probability)

**Figure S3.** Crystal Structure of (5*S*,6*S*)-4r (CCDC 2012368).

**Table S7.** Crystal data and structure refinement for (5*S*,6*S*)-4r.

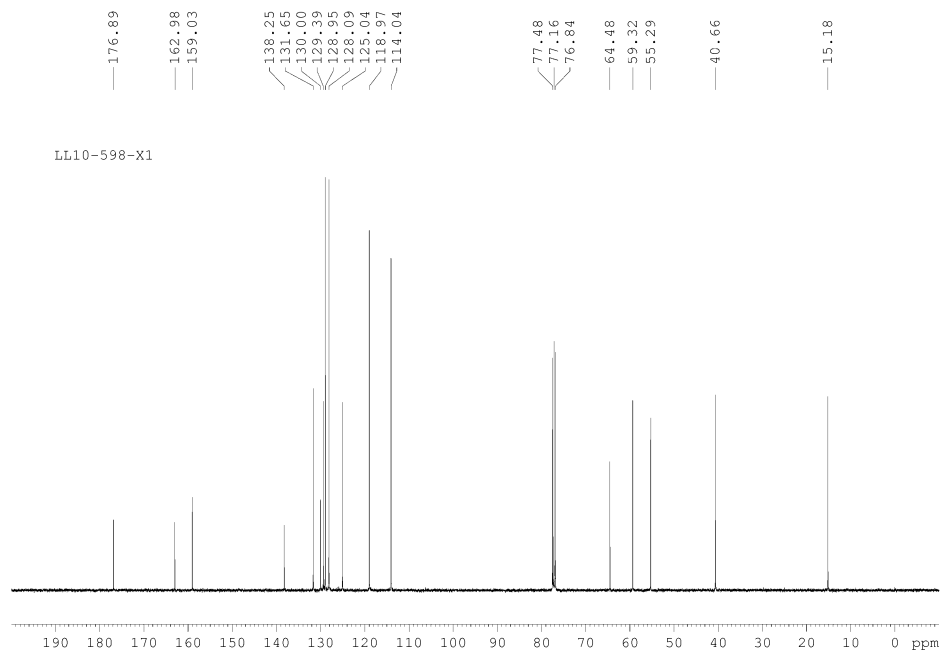
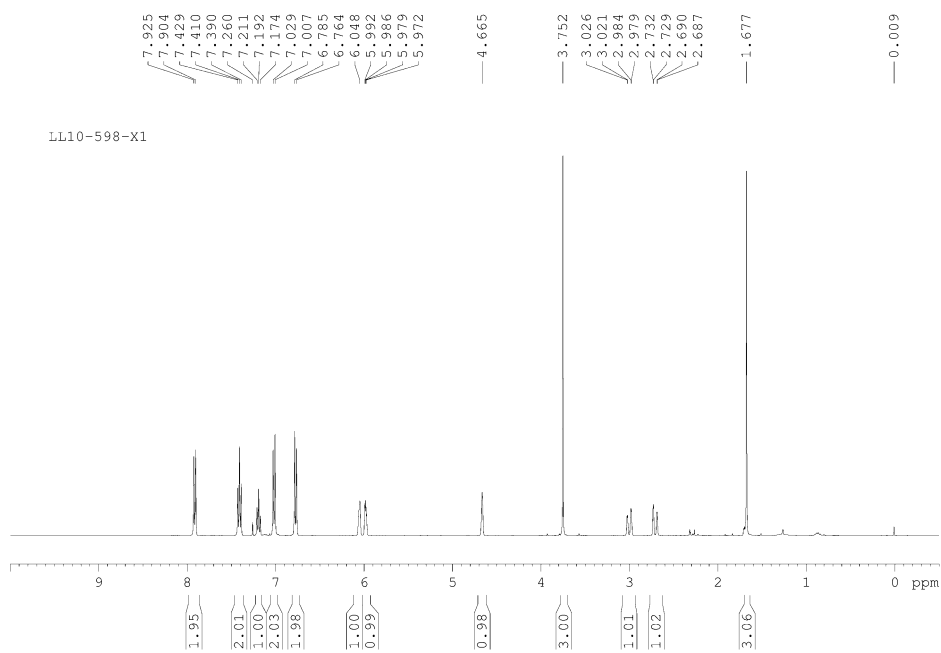
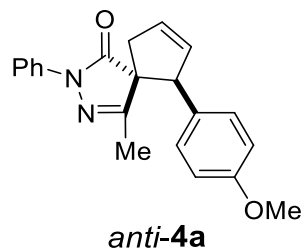
Identification code	global
Empirical formula	C <sub>26</sub> H <sub>21</sub> Br N <sub>2</sub> O
Formula weight	457.36
Temperature	100(2) K
Wavelength	1.54178 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 6.08550(10)$ Å = 90°. $b = 15.9623(4)$ Å = 90°. $c = 21.2691(5)$ Å = 90°.
Volume	2066.05(8) Å <sup>3</sup>

Z	4
Density (calculated)	1.470 Mg/m <sup>3</sup>
Absorption coefficient	2.866 mm <sup>-1</sup>
F(000)	936
Crystal size	0.550 x 0.450 x 0.070 mm <sup>3</sup>
Theta range for data collection	3.46 to 72.38°.
Index ranges	-7<=h<=5, -19<=k<=19, -26<=l<=26
Reflections collected	14666
Independent reflections	3980 [R(int) = 0.0503]
Completeness to theta = 72.38°	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.82 and 0.20
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3980 / 0 / 272
Goodness-of-fit on F <sup>2</sup>	1.029
Final R indices [I>2sigma(I)]	R1 = 0.0277, wR2 = 0.0729
R indices (all data)	R1 = 0.0281, wR2 = 0.0734
Absolute structure parameter	0.039(7)
Largest diff. peak and hole	0.435 and -0.491 e.Å <sup>-3</sup>

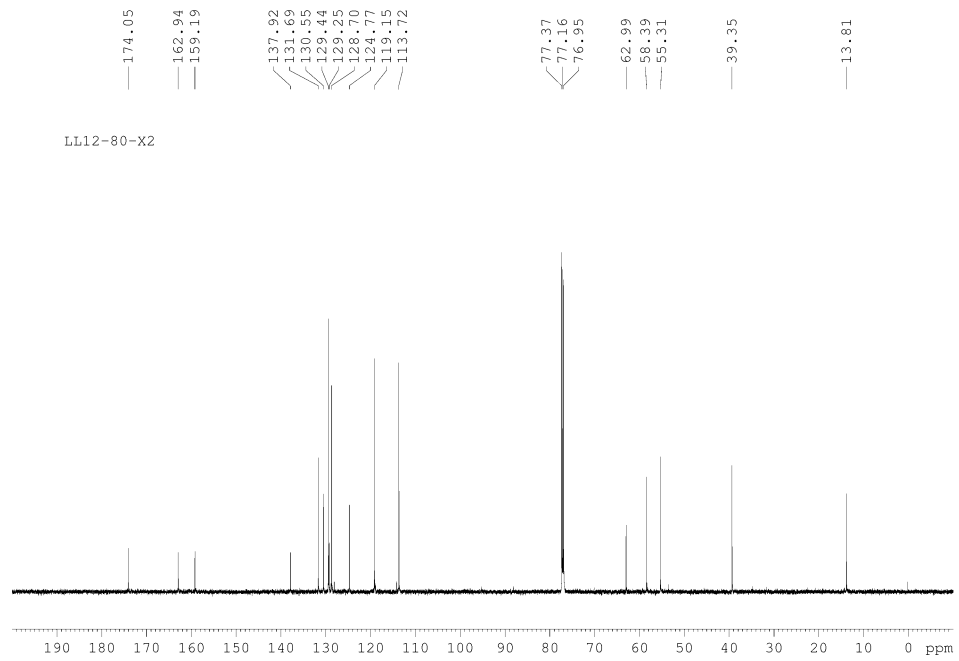
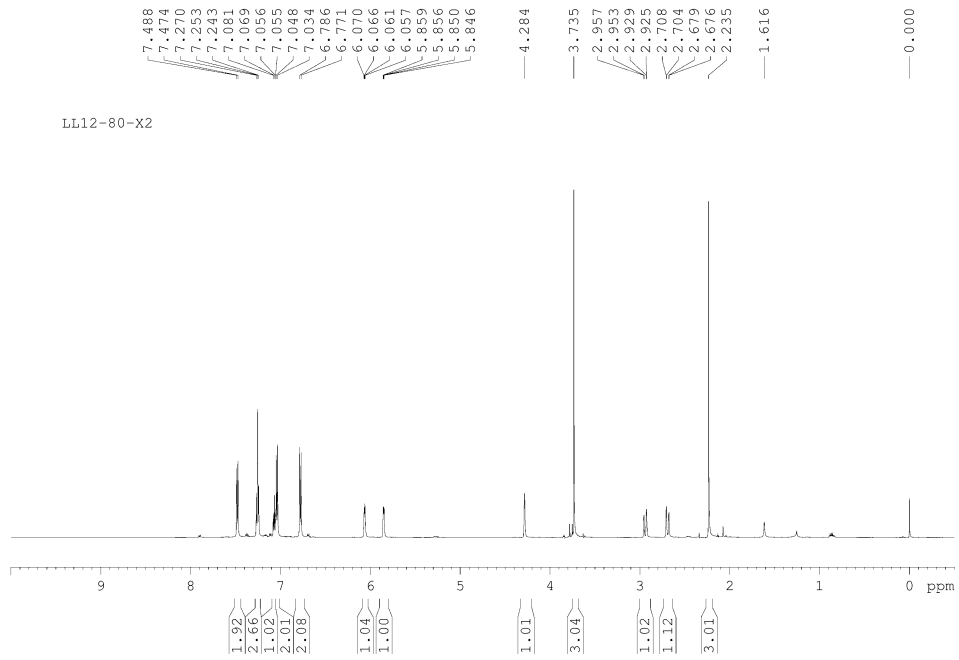
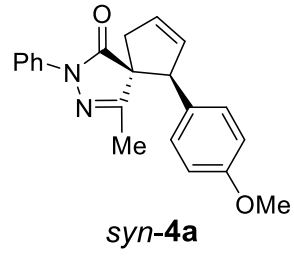
## 7. Reference

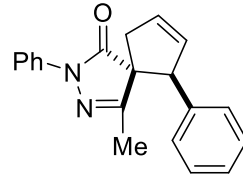
- (1) Kinoshita, H.; Ishikawa, T.; Miura, K. Dialkylaluminum Hydride-Promoted Cyclodimerization of Silylated 1,3-Enynes via Skeletal Rearrangement. *Org. Lett.* **2011**, *13*, 6192–6195.
- (2) Zhang, Y.-C.; Yu, B.-K.; Gao, B.-J.; Zhang, T.-Z.; Huang, H.-M. Triple-Bond Insertion Triggers Highly Regioselective 1,4-Aminomethylation of 1,3-Enynes with Aminals Enabled by Pd-Catalyzed C–N Bond Activation. *Org. Lett.* **2019**, *21*, 535–539.
- (3) Lehmann, F.; Holm, M.; Laufer, S. Three-Component Combinatorial Synthesis of Novel Dihydropyrano[2,3-*c*]pyrazoles. *J. Comb. Chem.* **2008**, *10*, 364–367.
- (4) Mukherjee, P.; Das, A. R. One-Flask Synthesis of Pyrazolone Thioethers Involving Catalyzed and Uncatalyzed Thioetherification Pathways of Pyrazolones. *Org. Biomol. Chem.* **2017**, *15*, 7267–7271.

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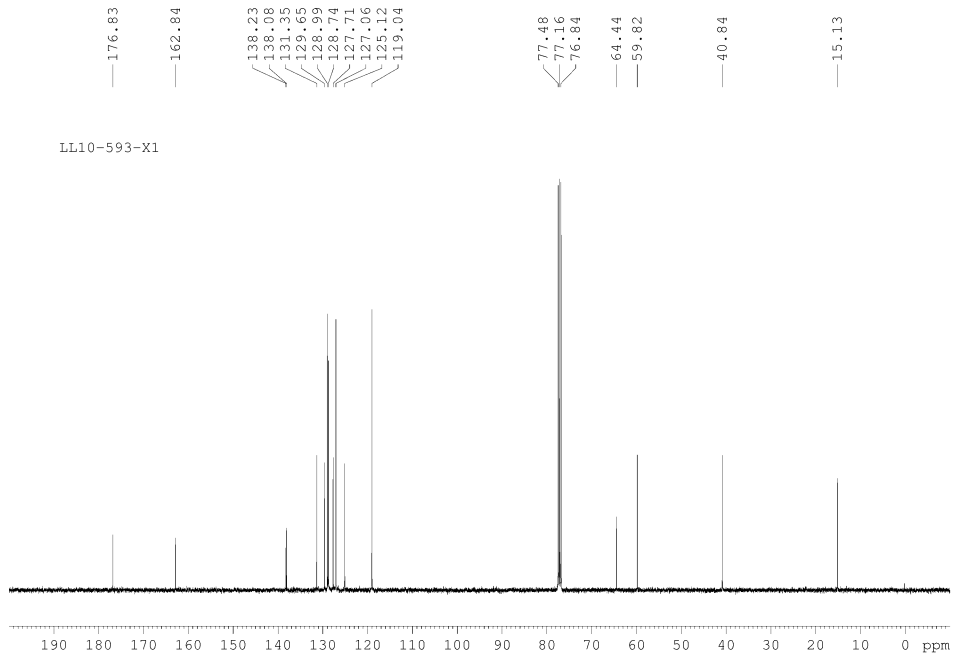
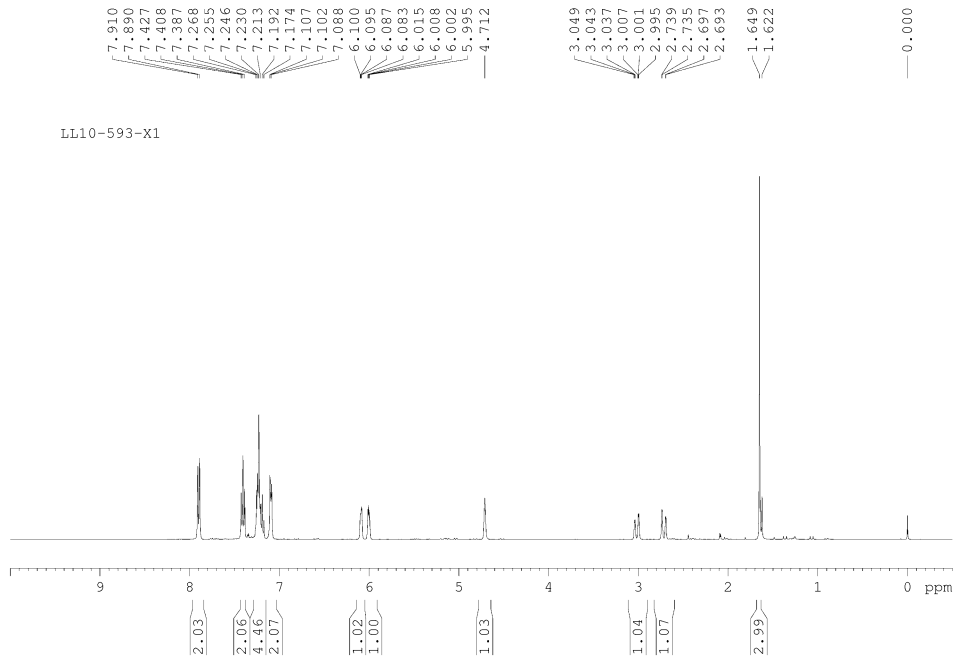


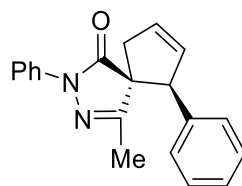




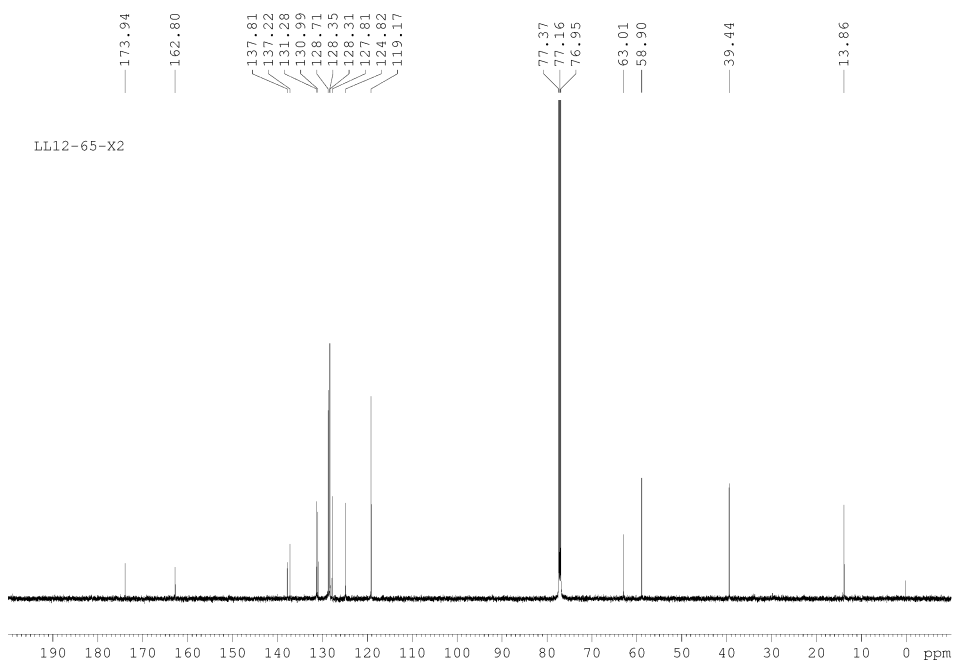
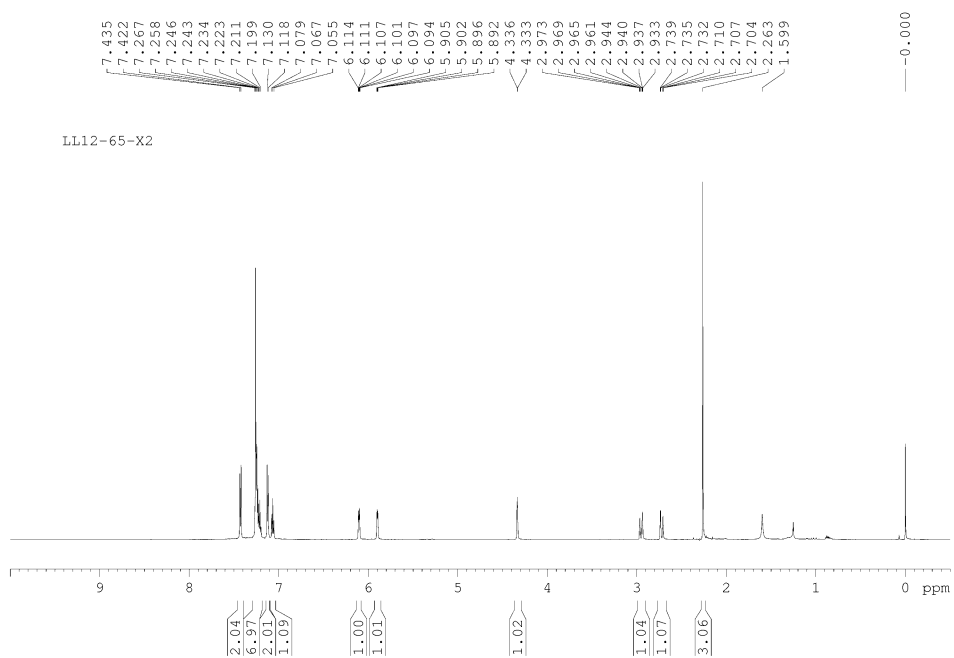


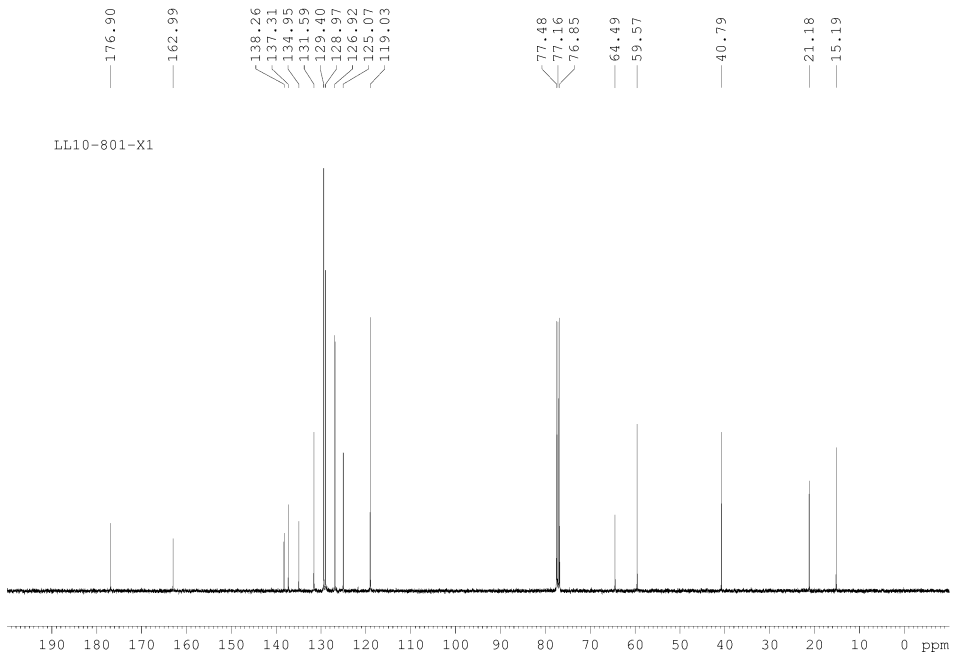
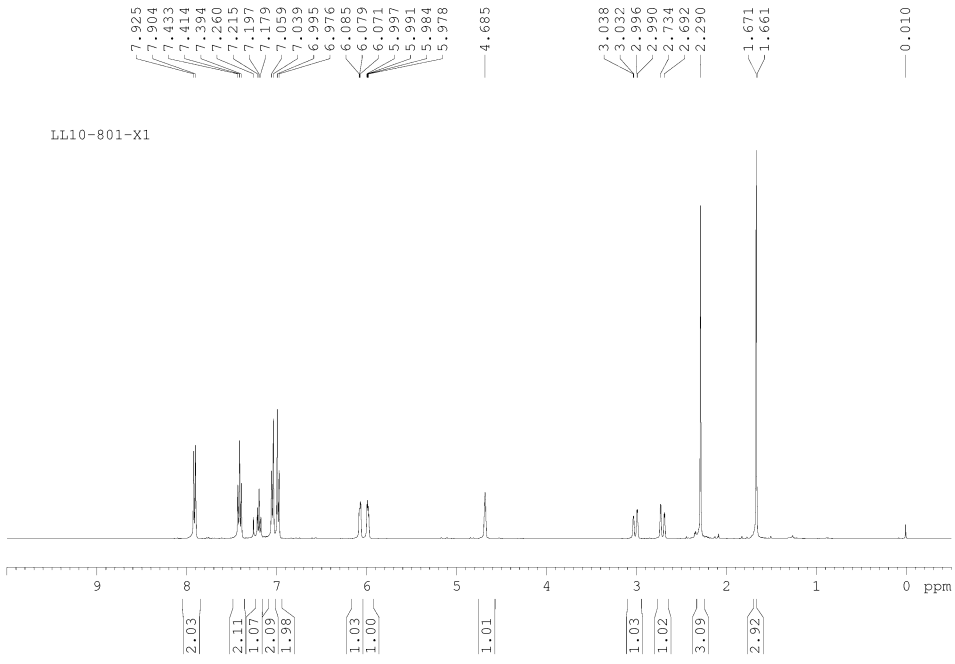
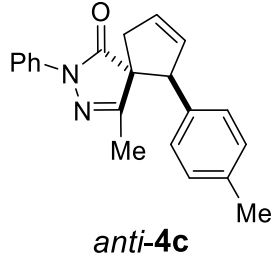
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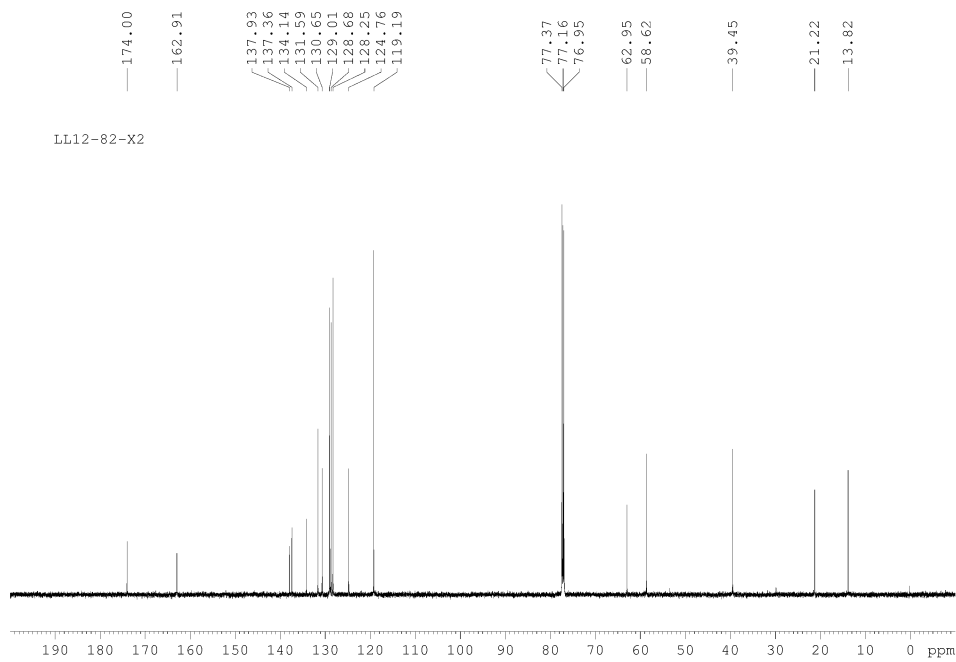
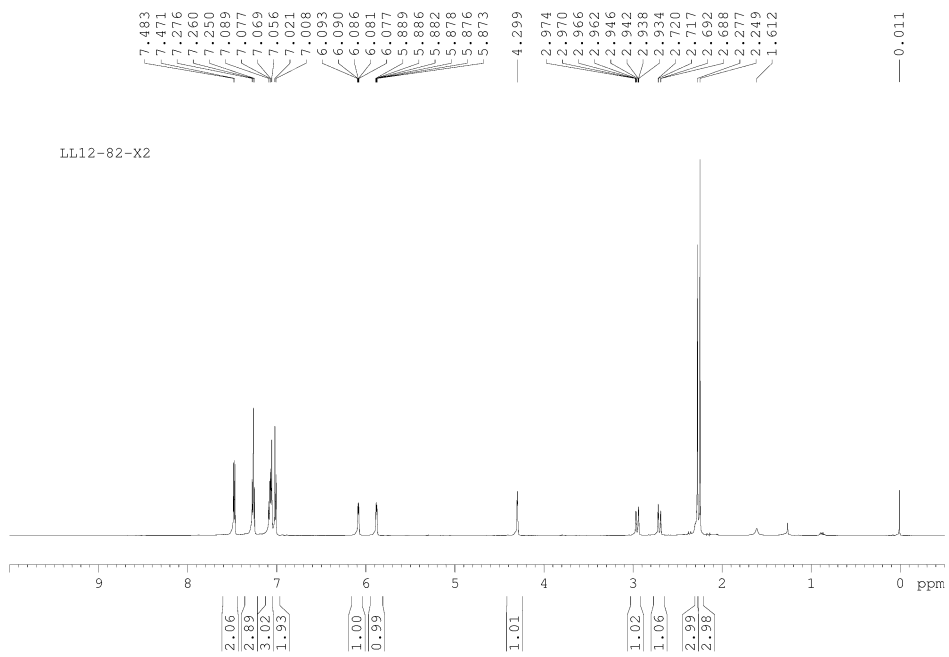
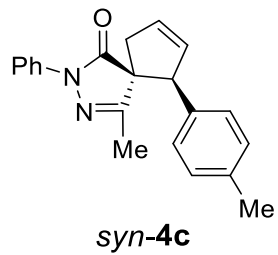


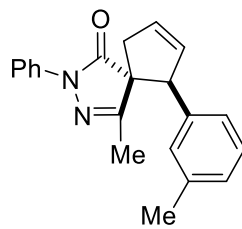


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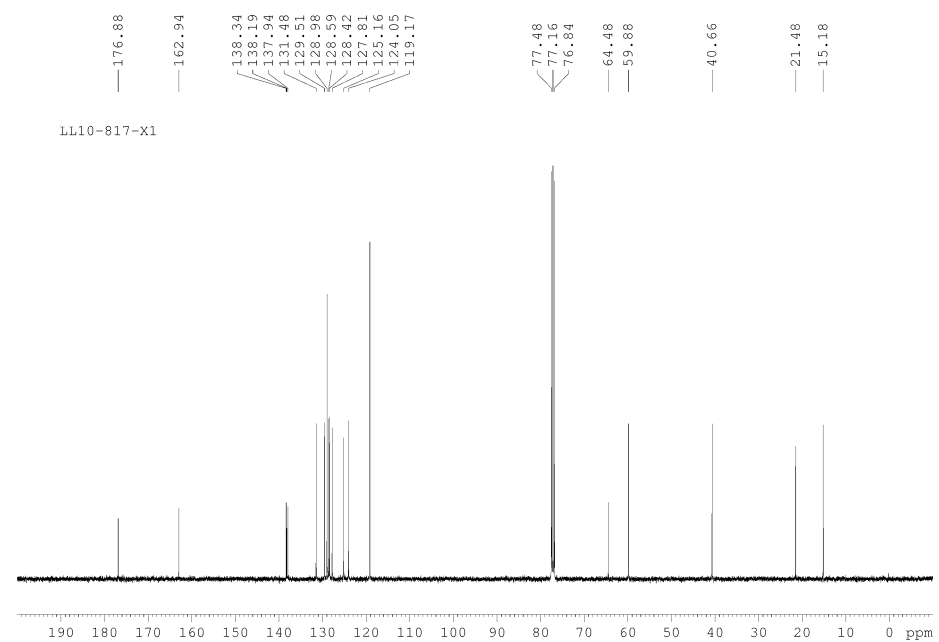
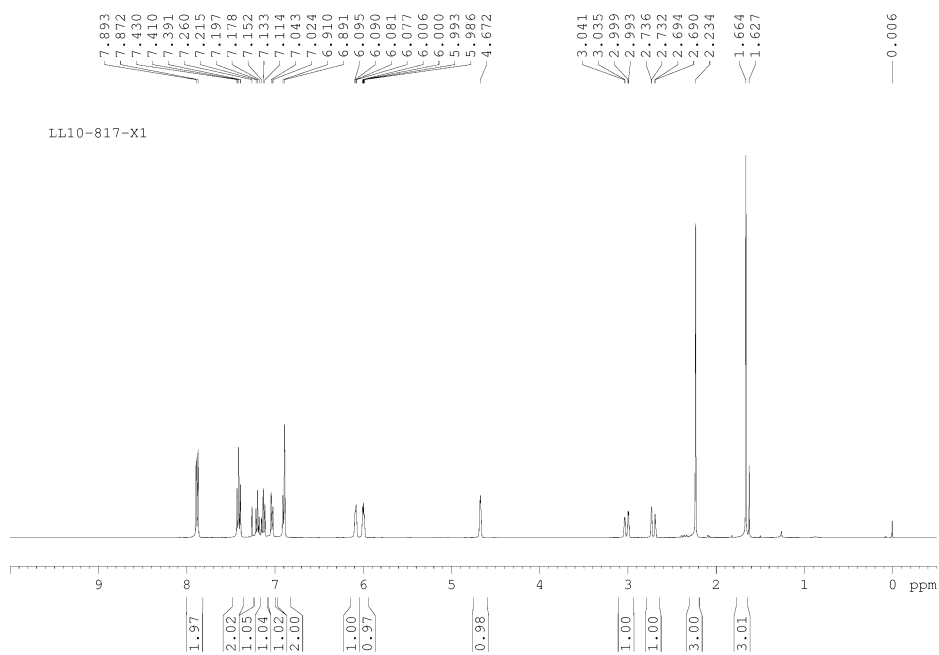


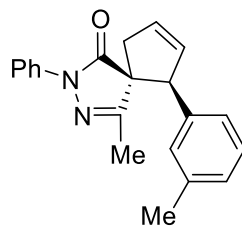






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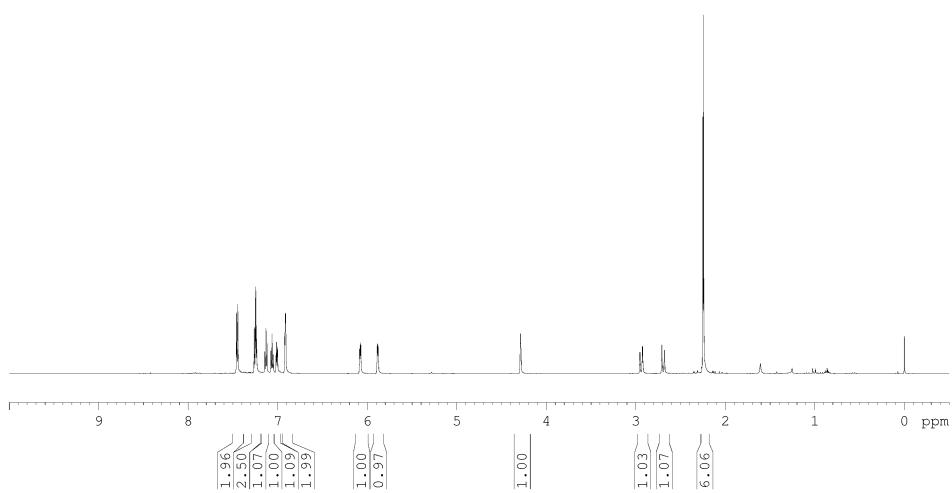




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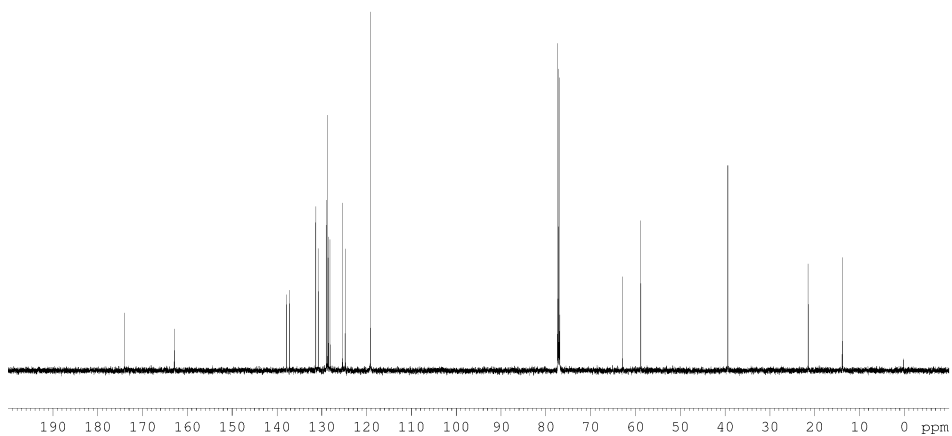
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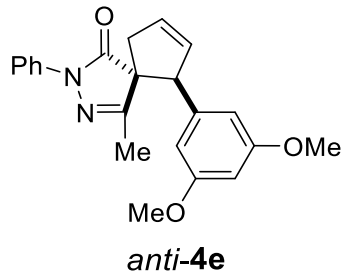
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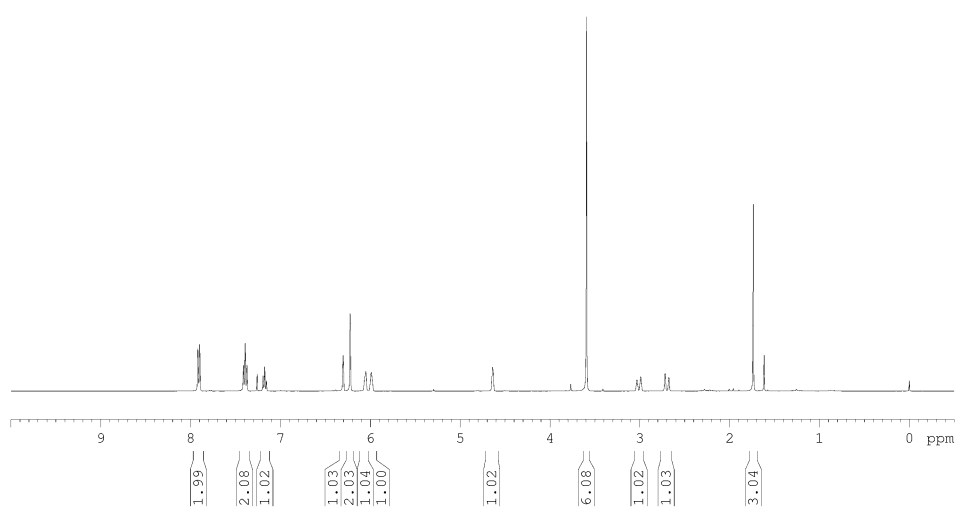
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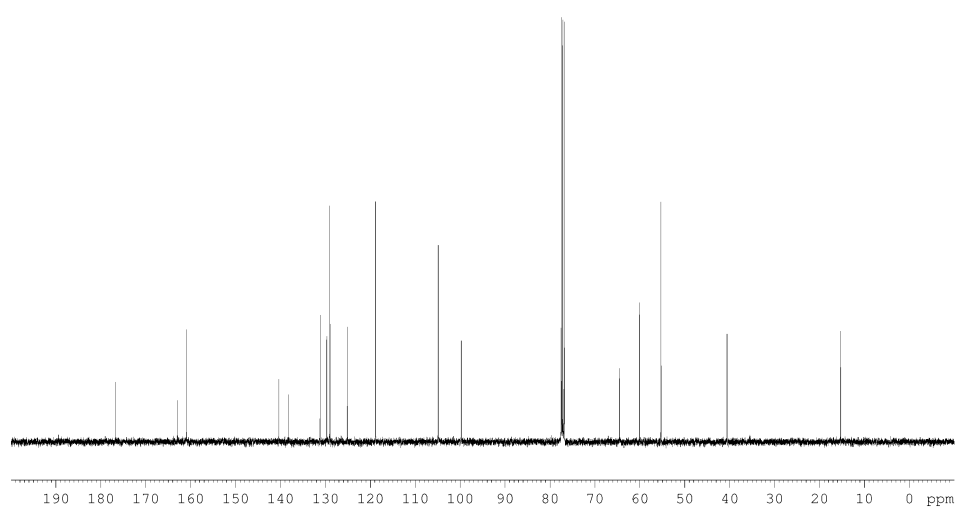
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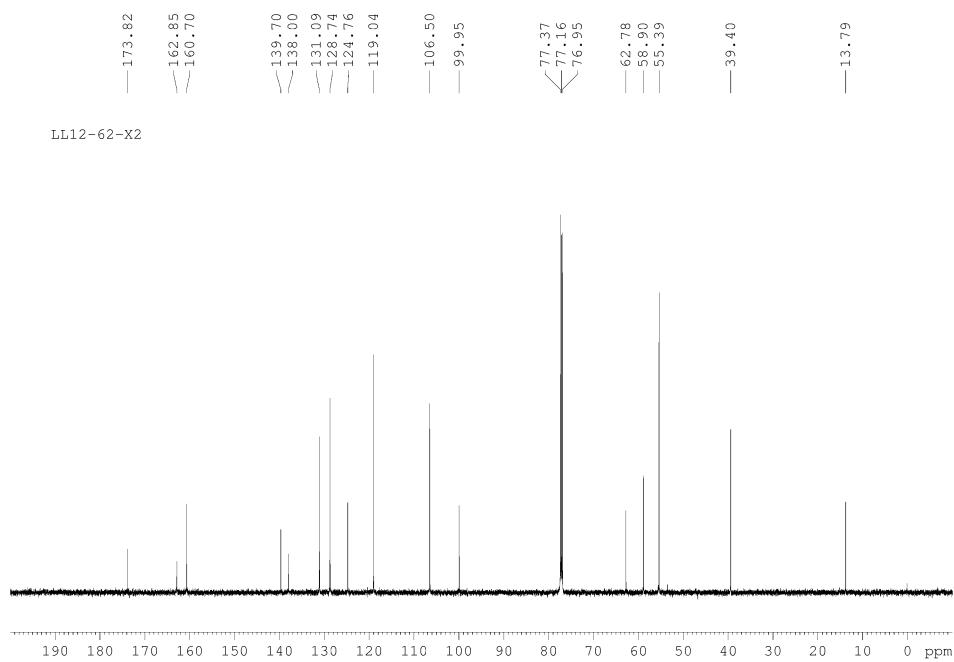
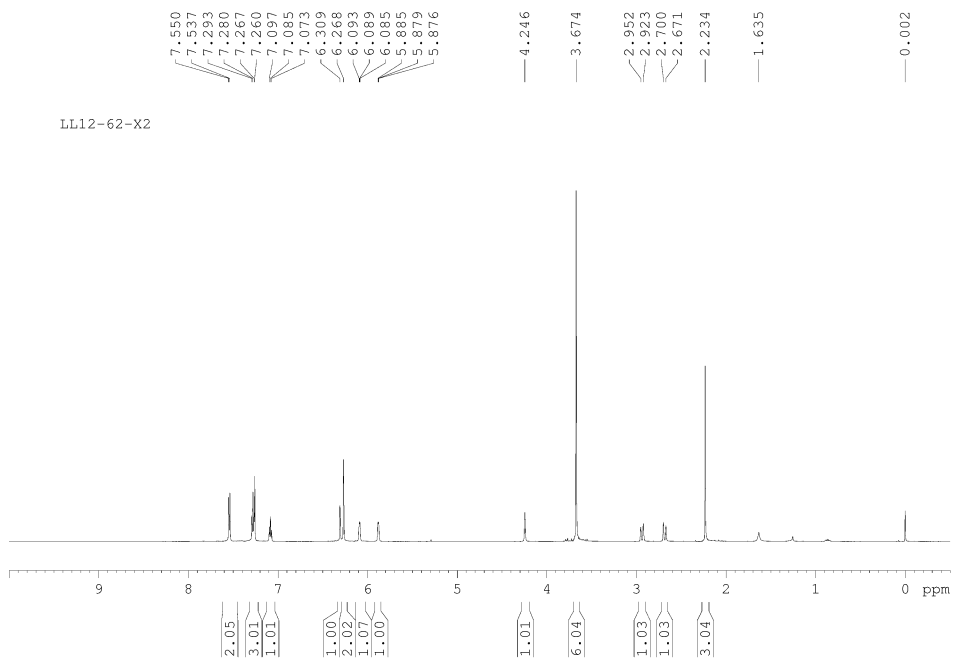
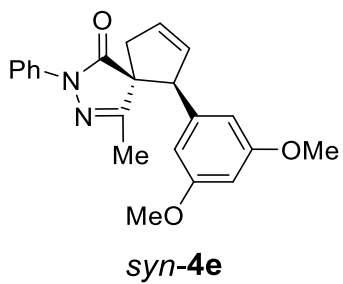


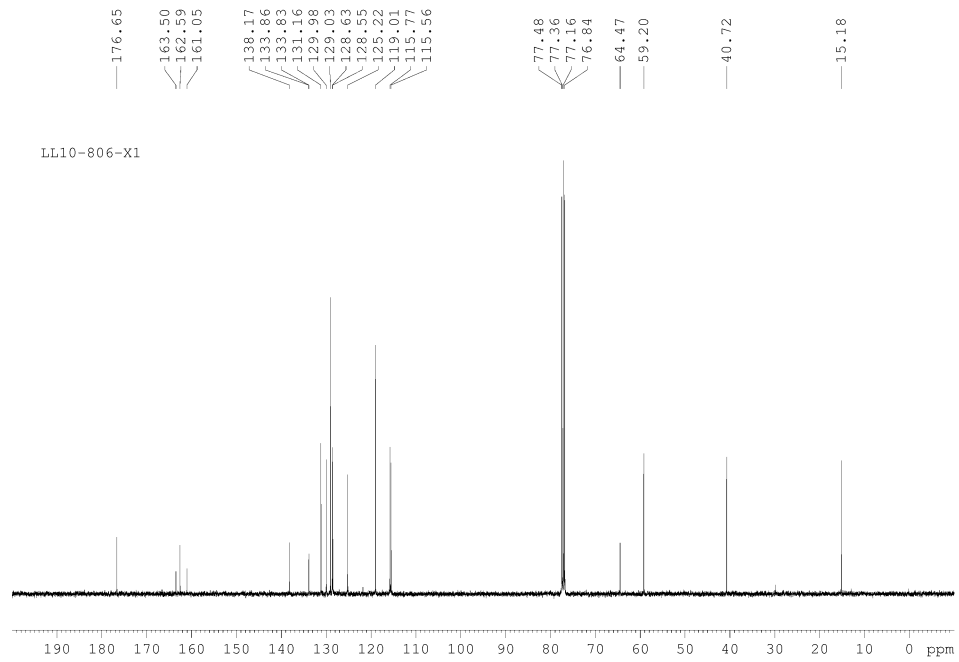
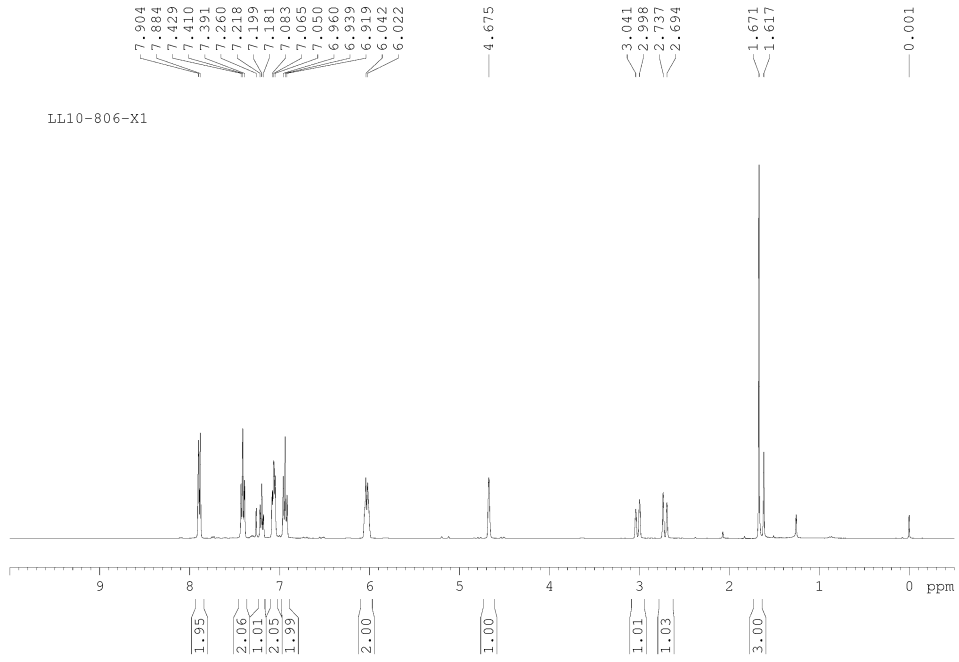
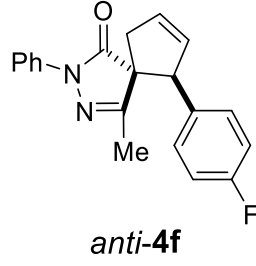
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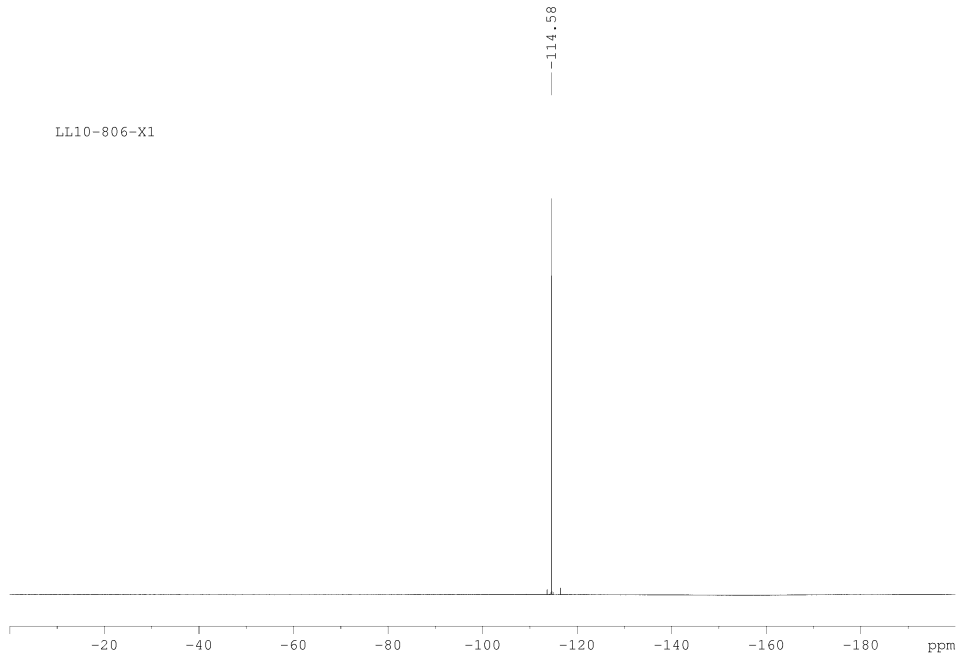


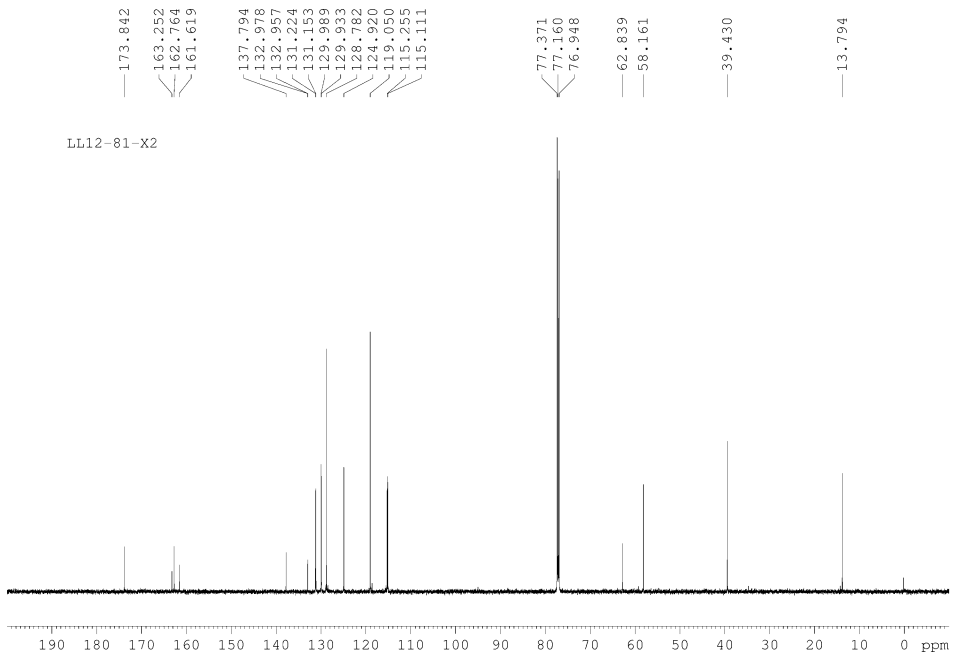
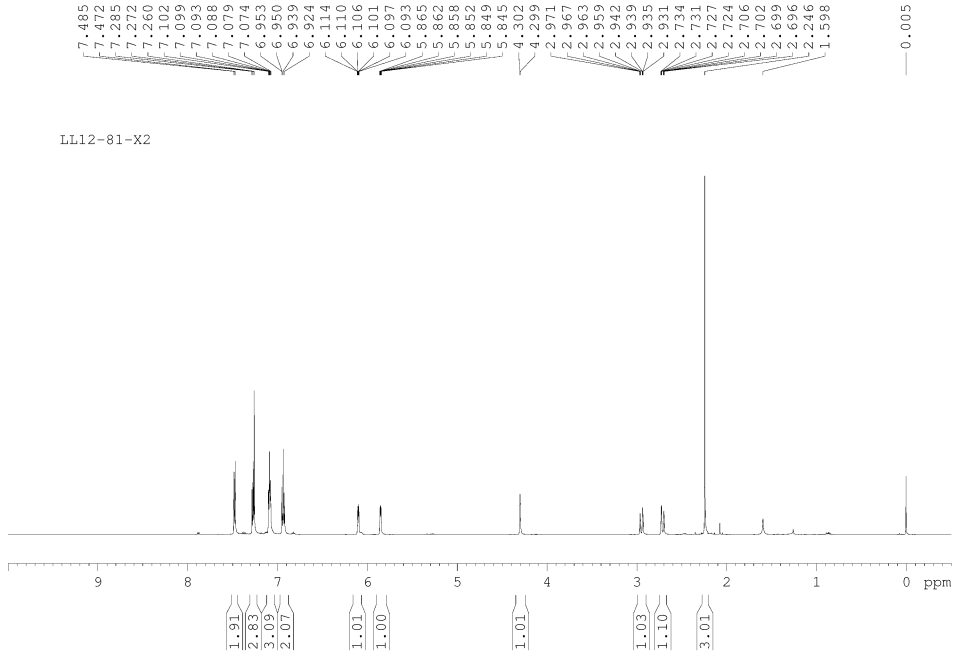
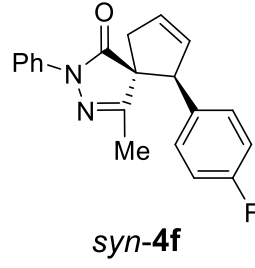




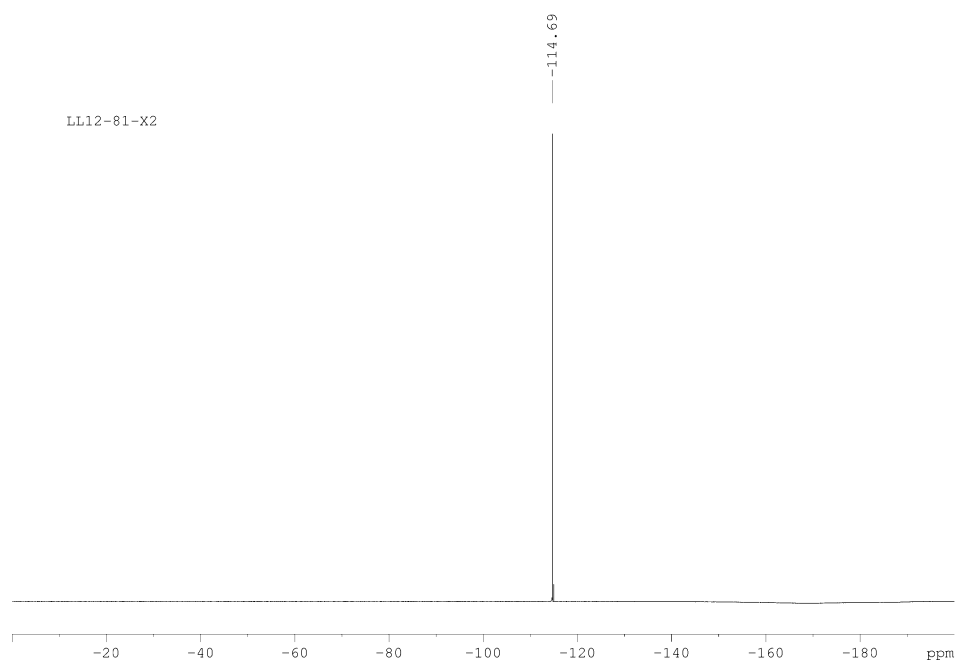


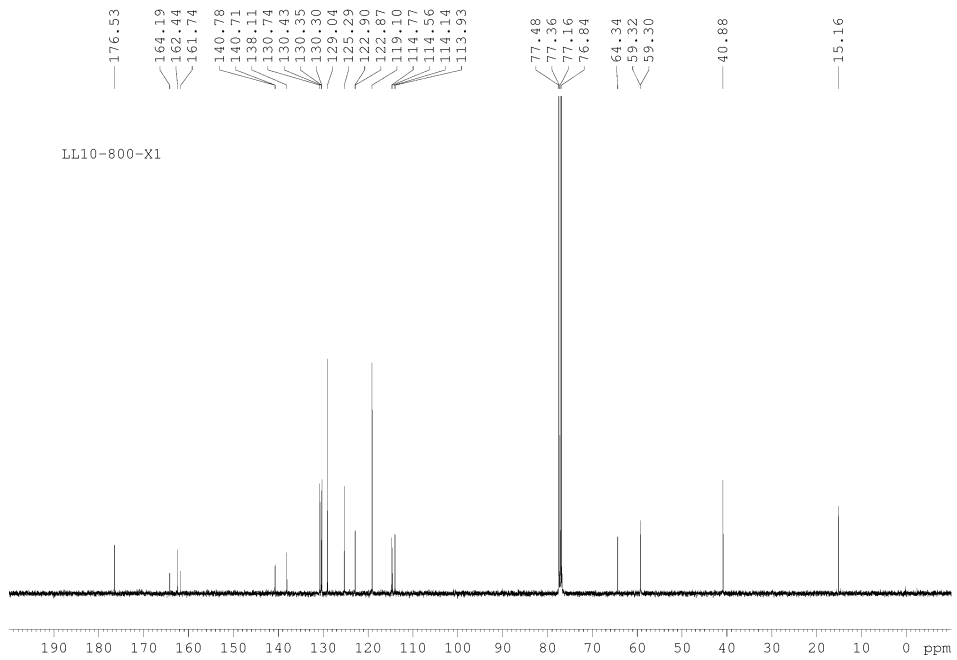
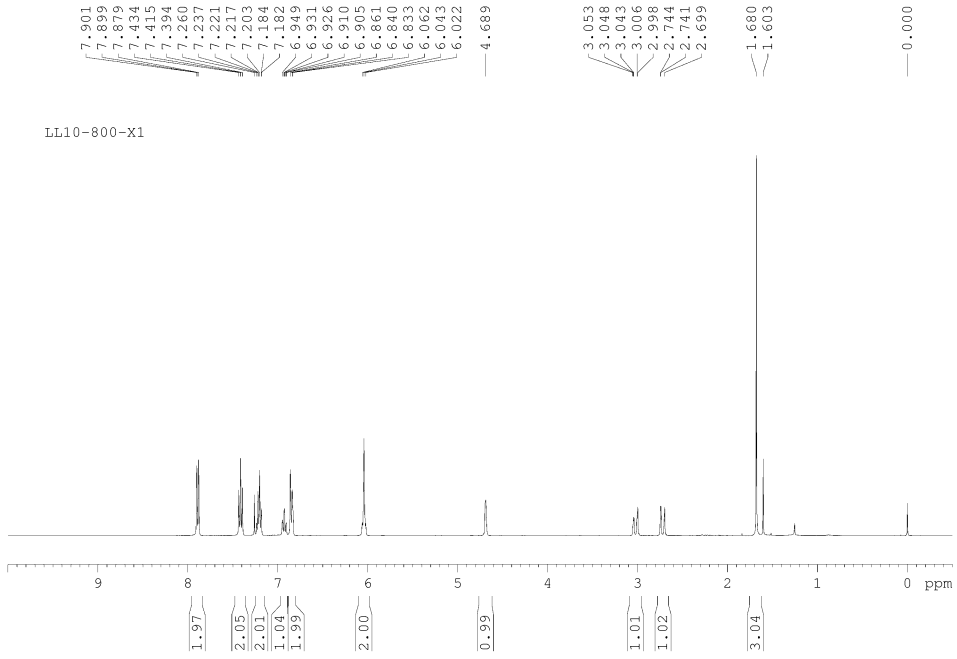
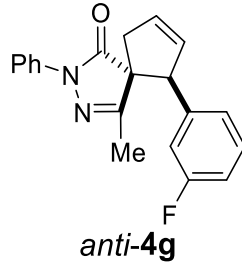
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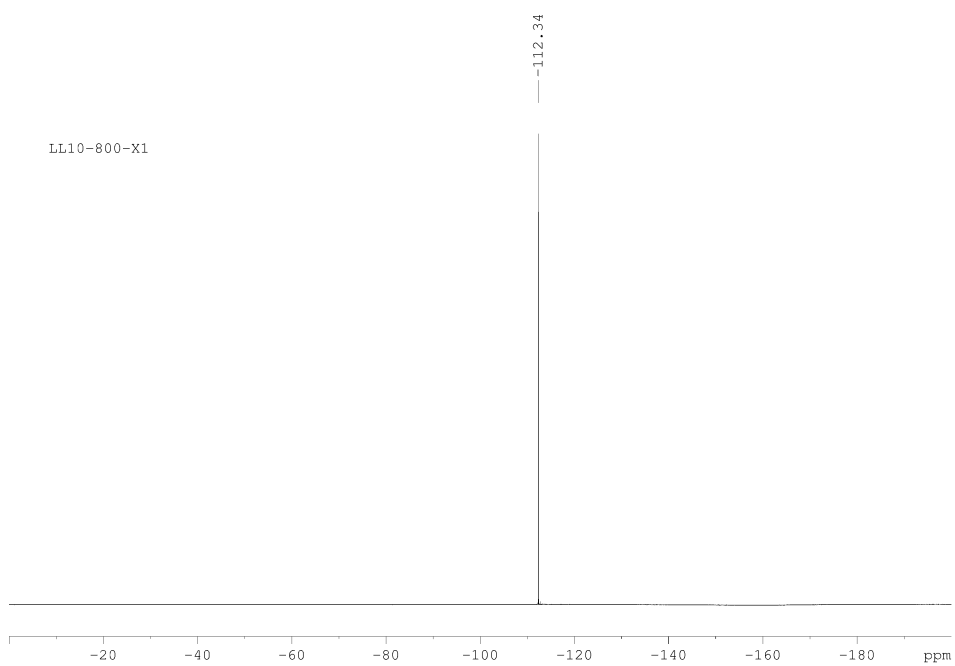


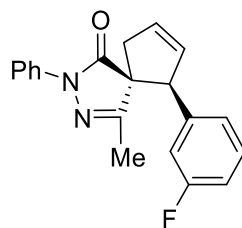


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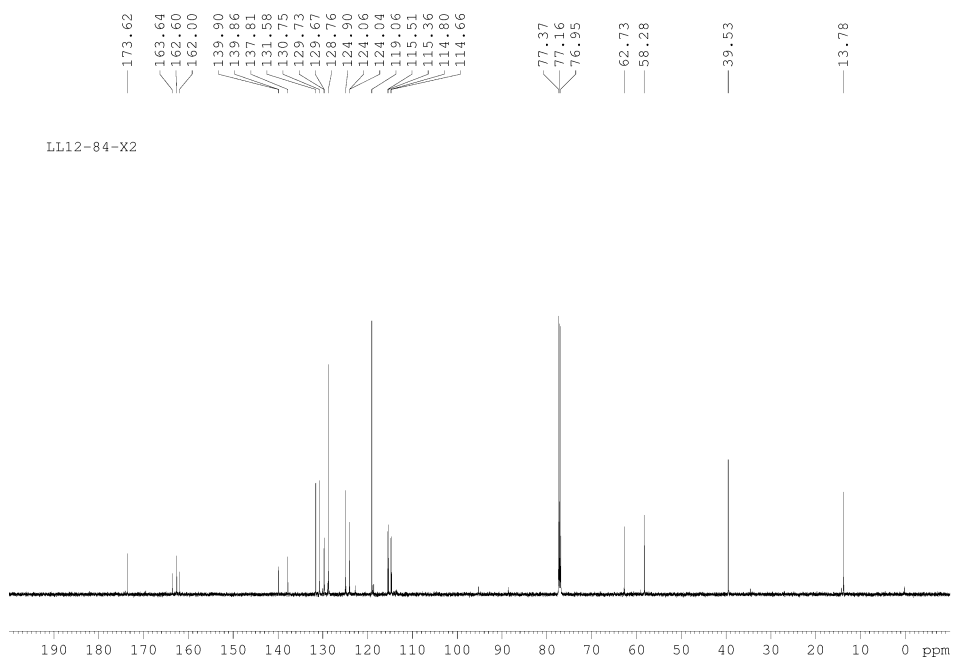
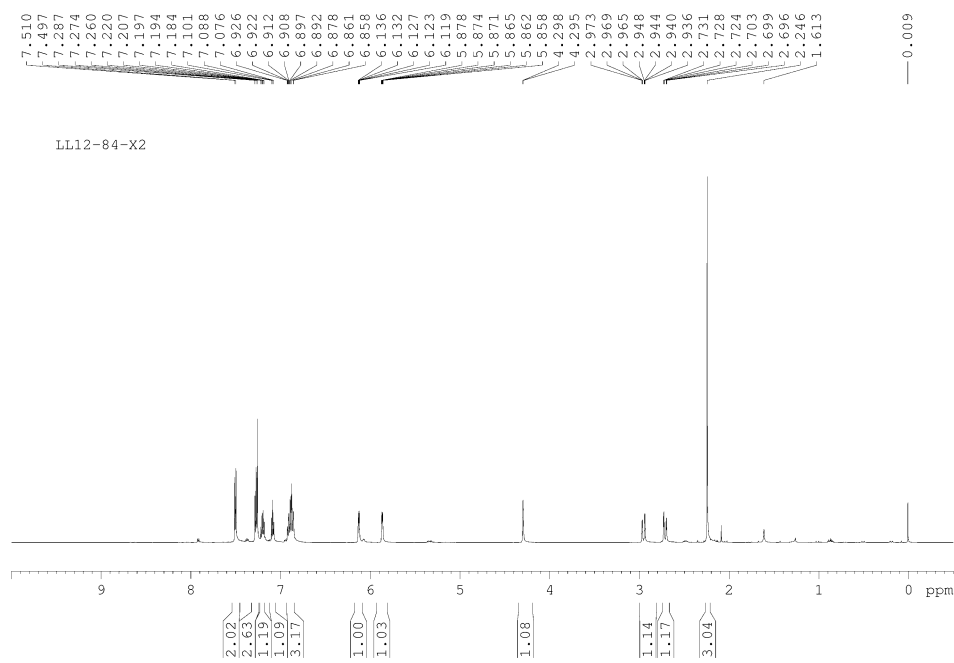




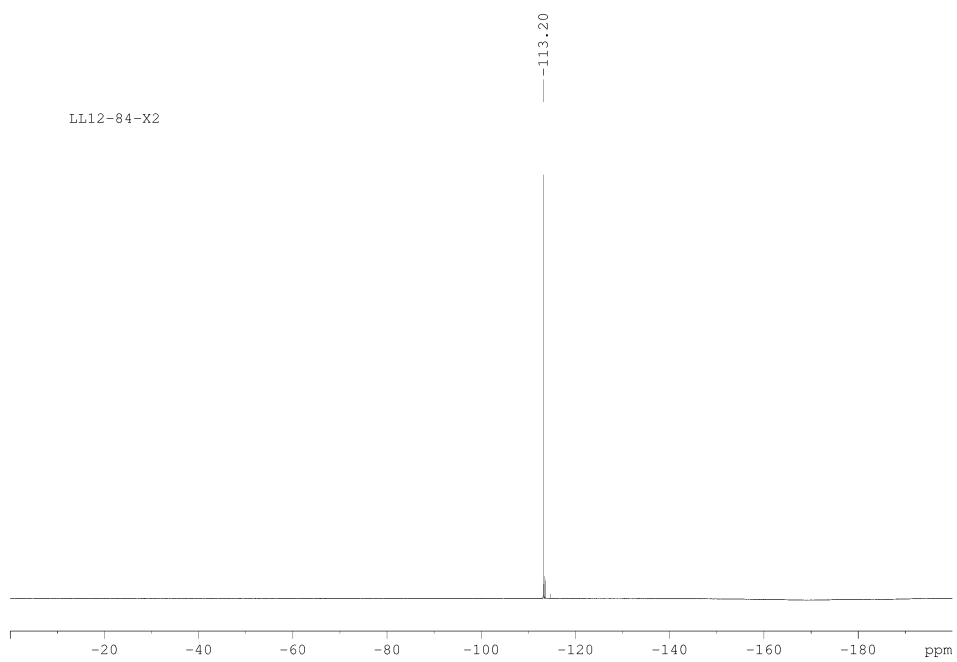


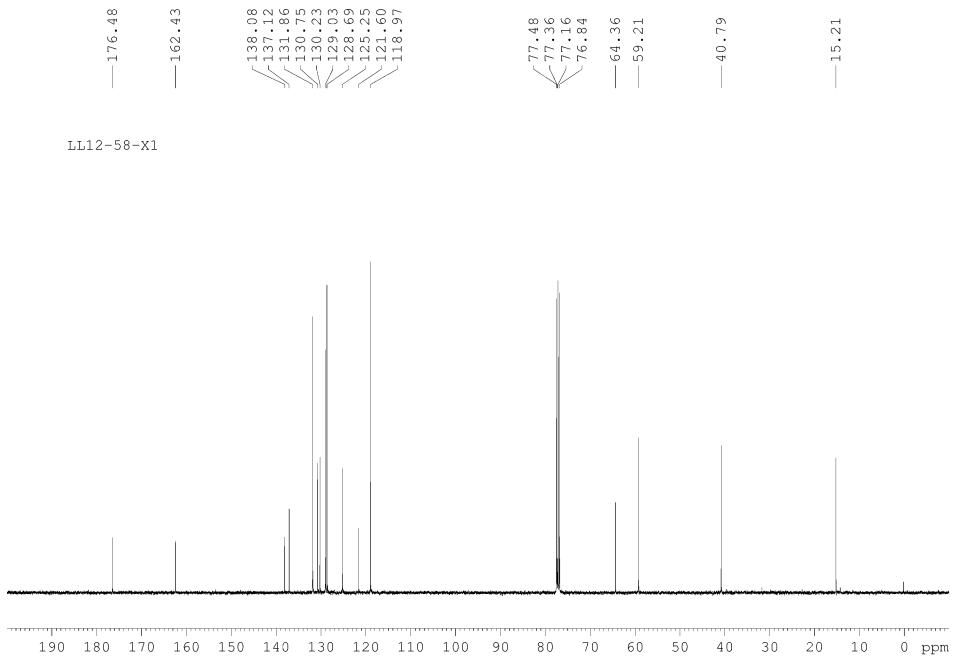
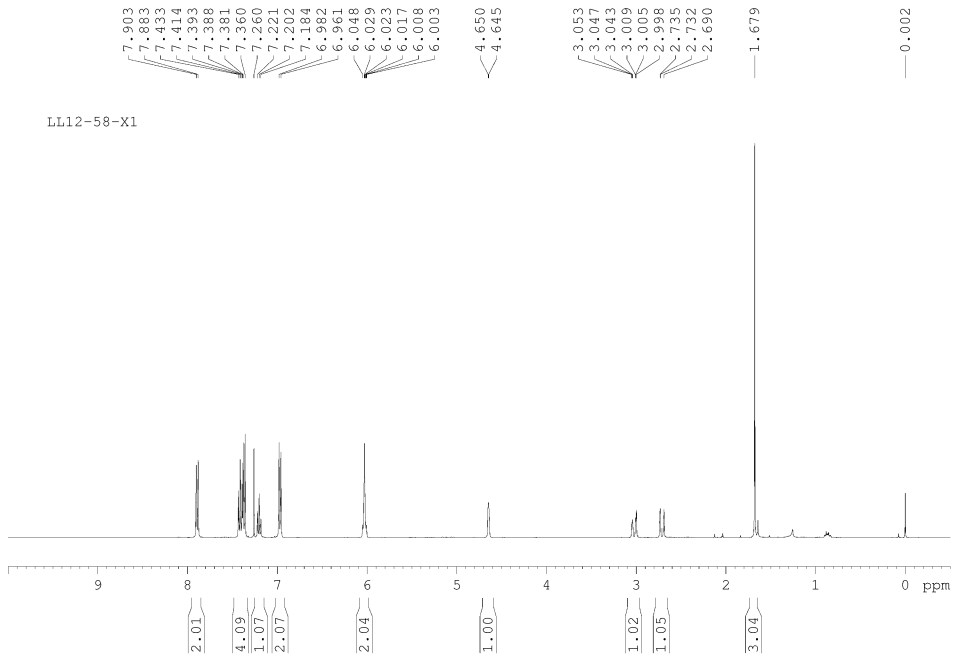
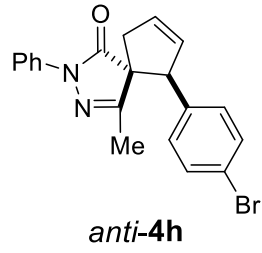


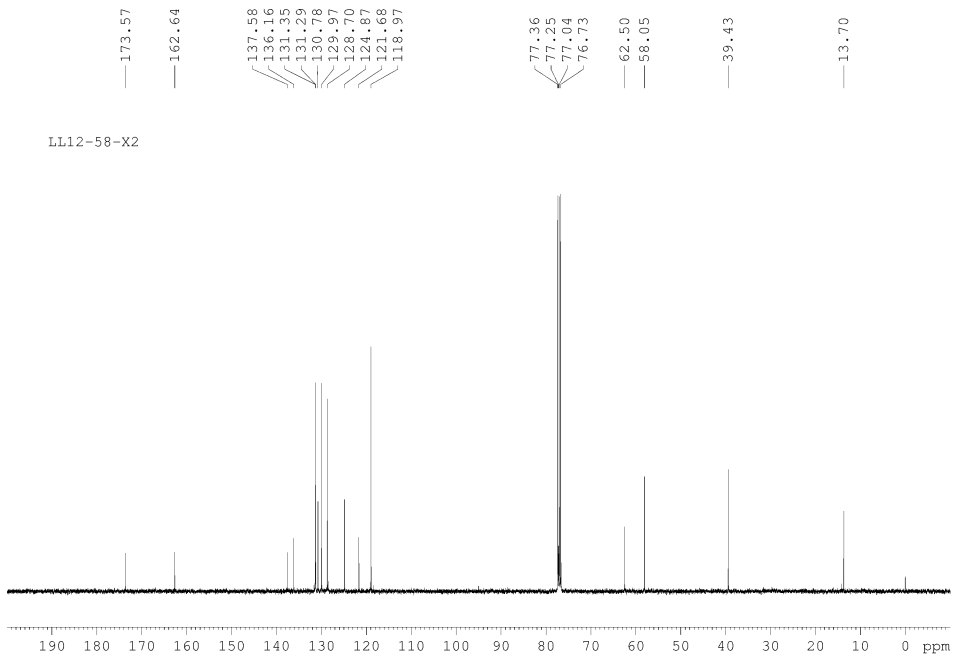
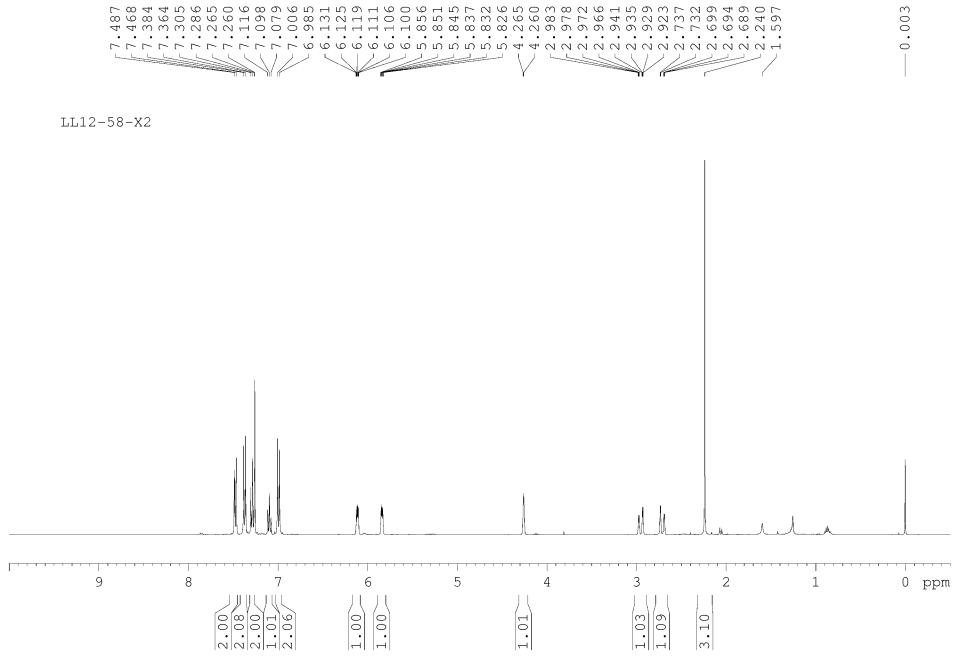
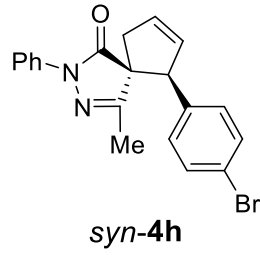
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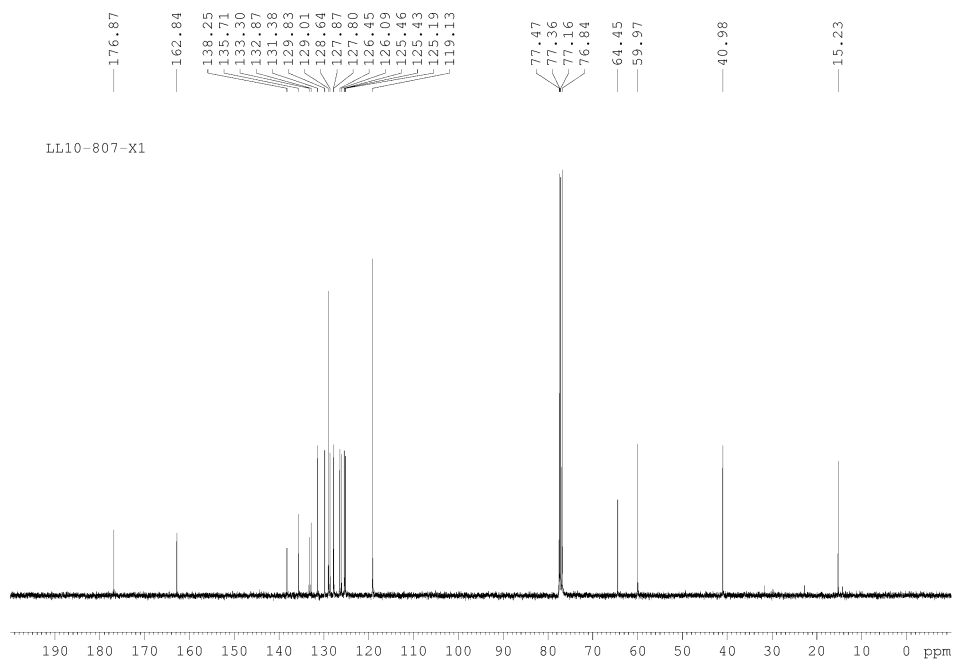
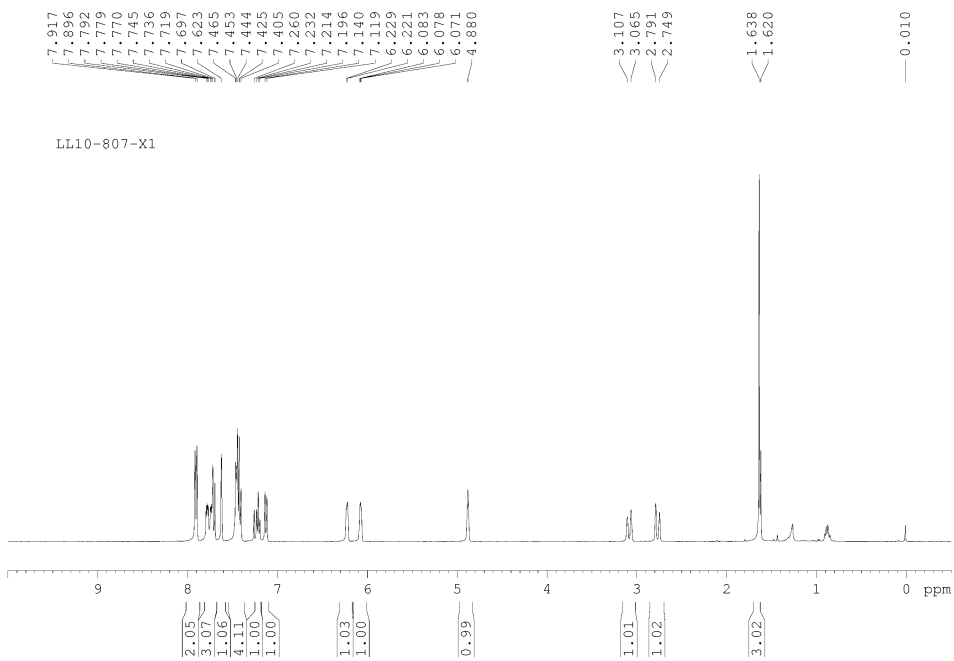
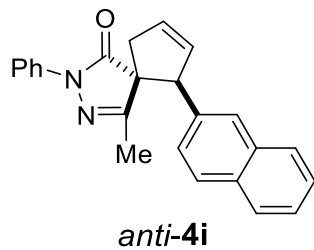


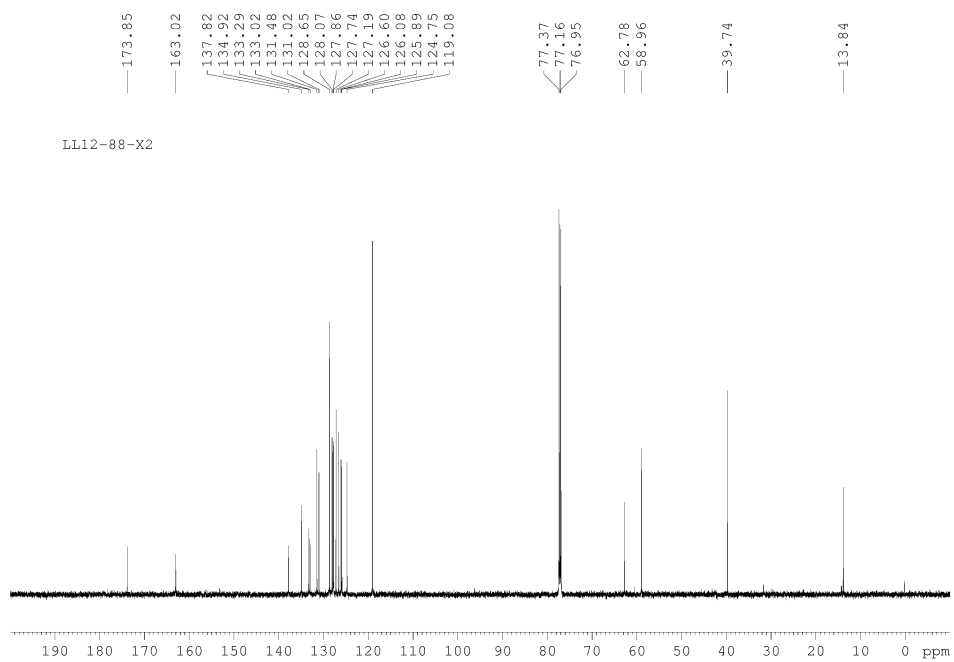
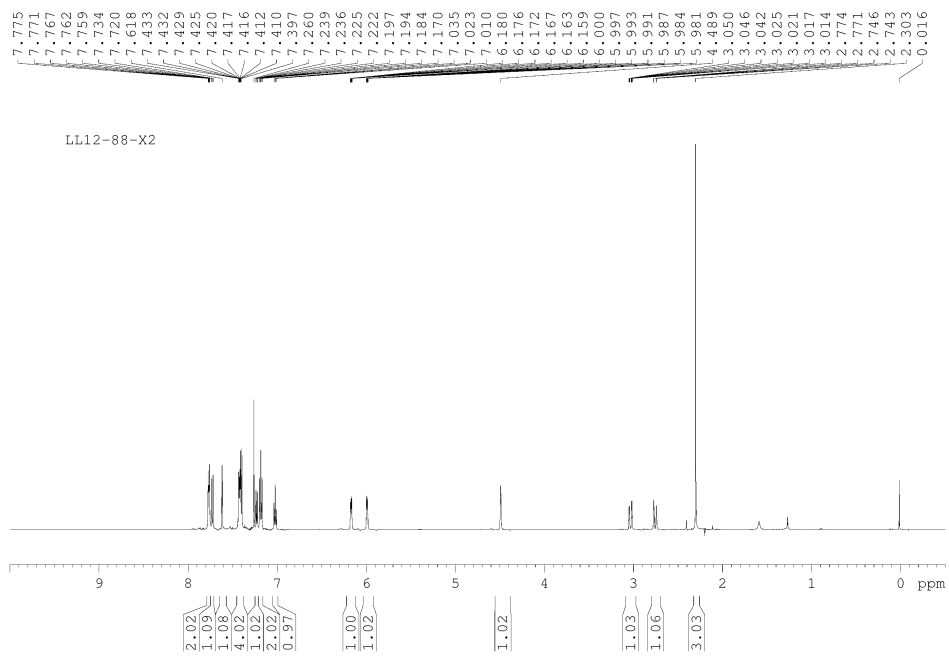
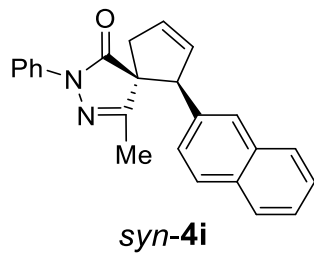


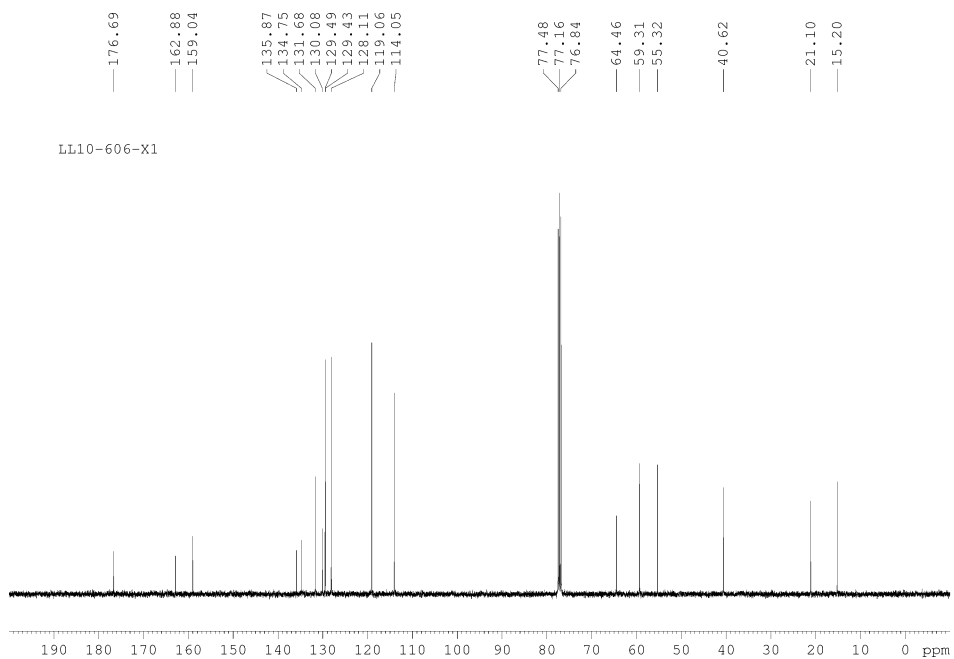
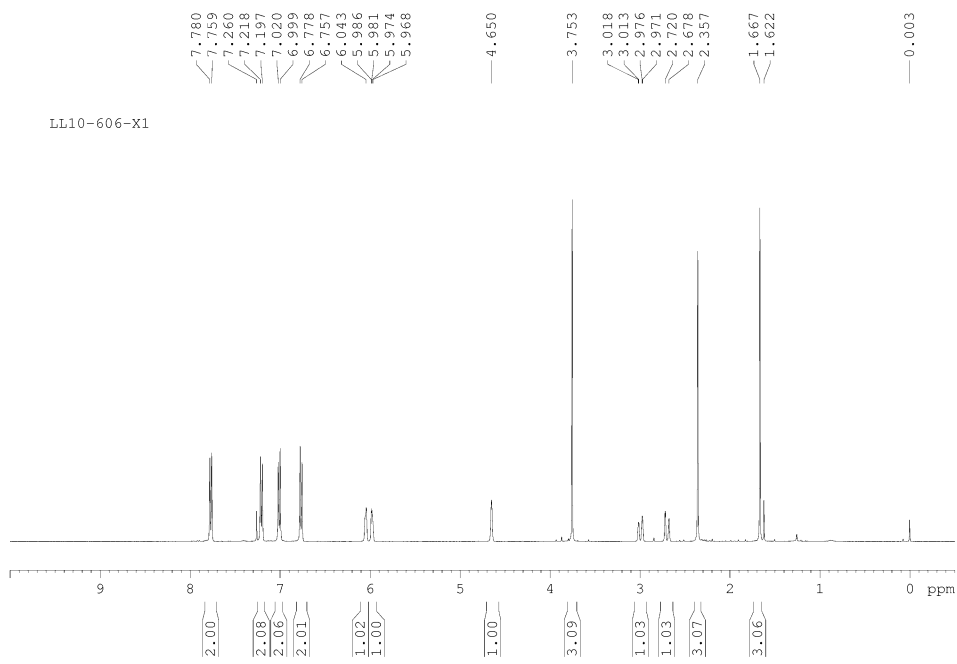
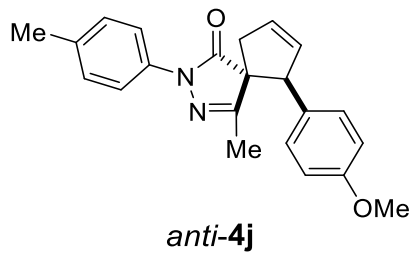


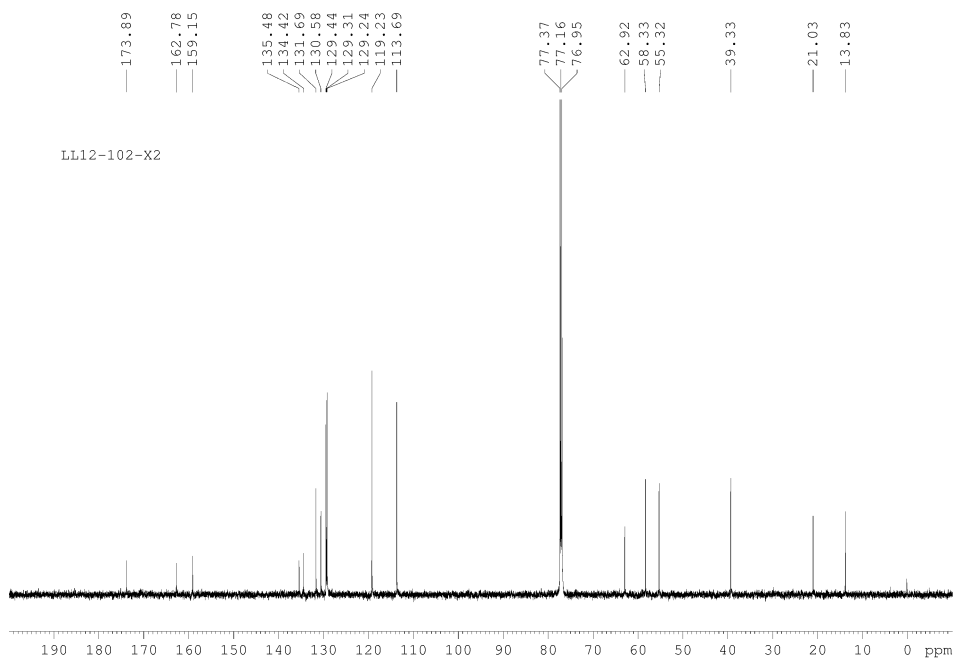
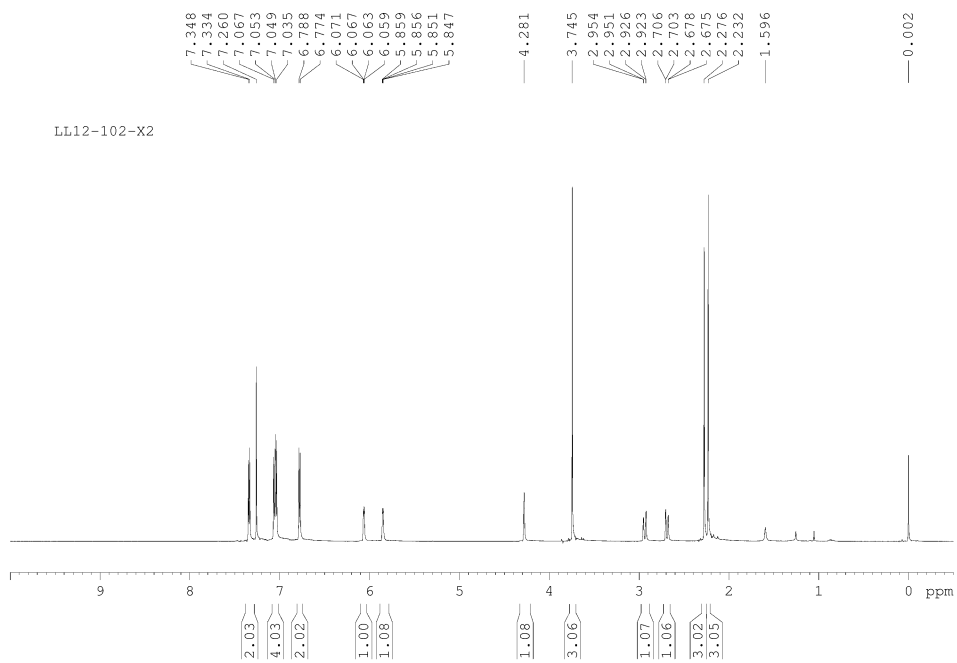
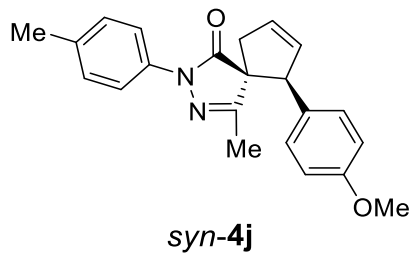


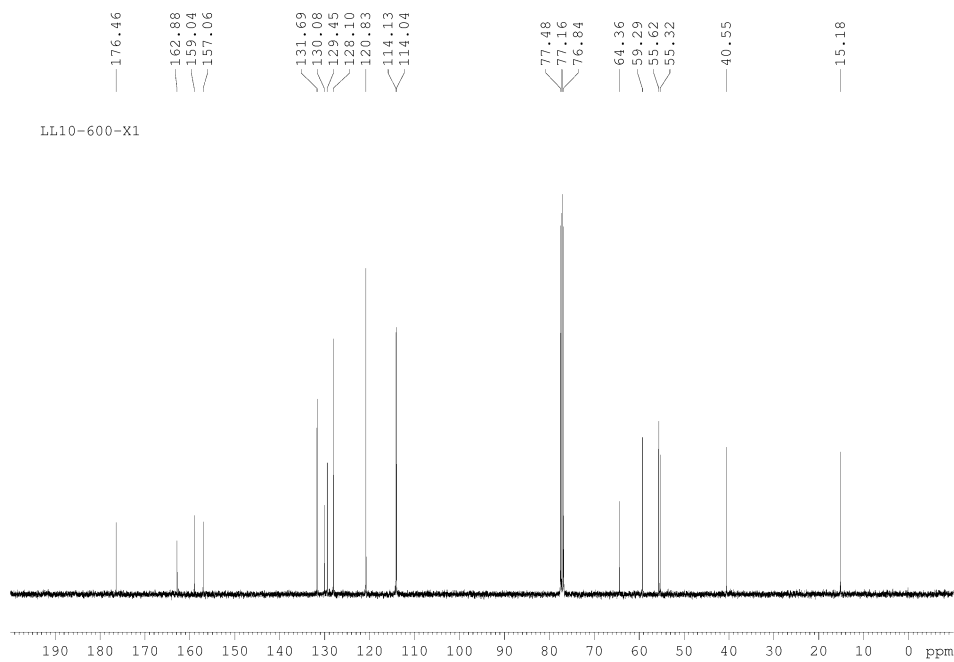
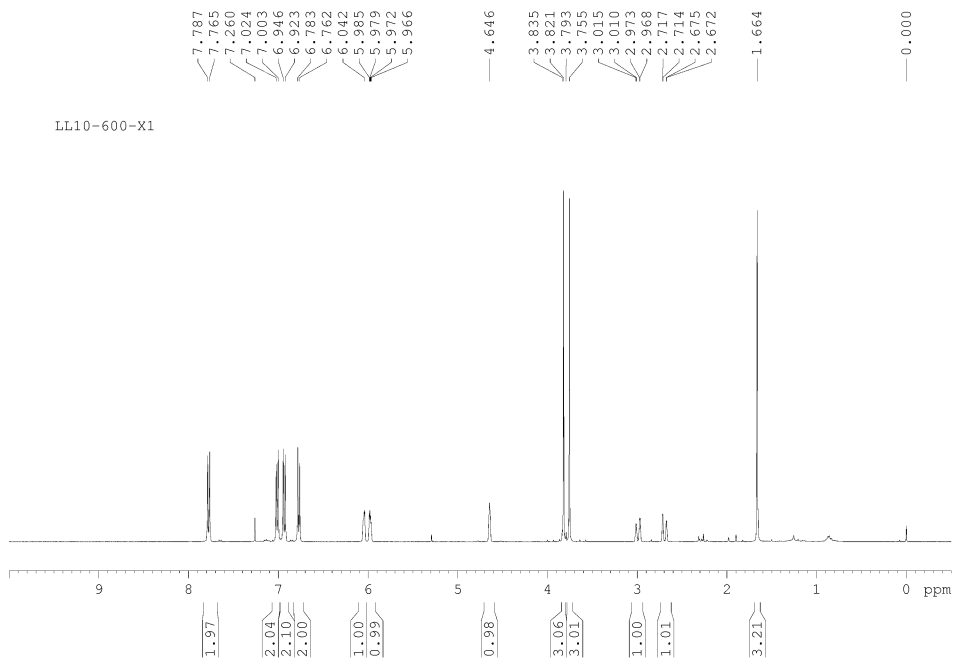
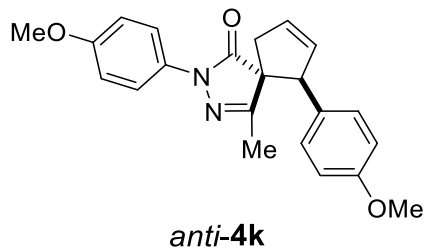




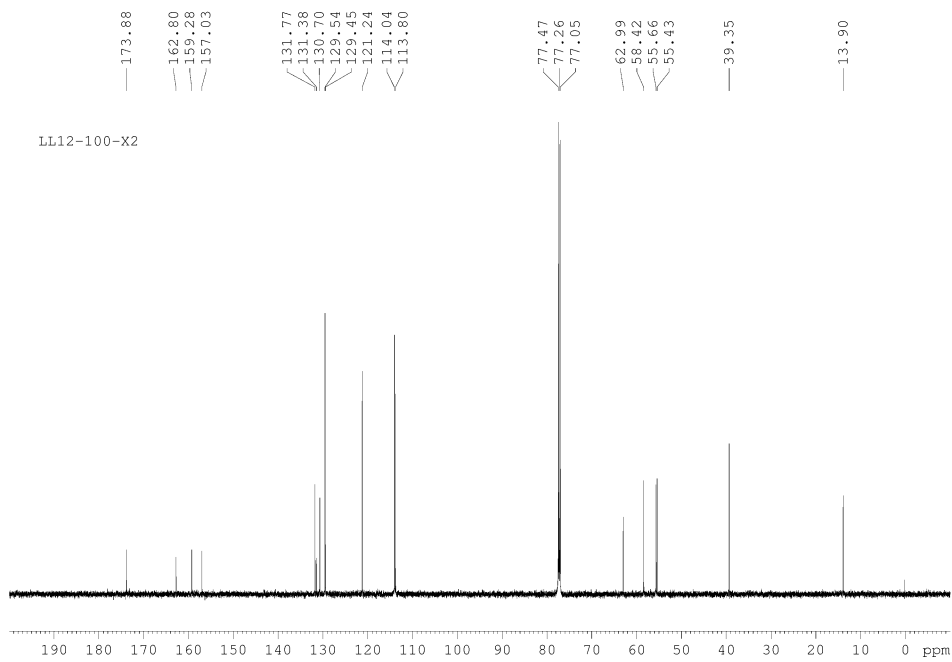
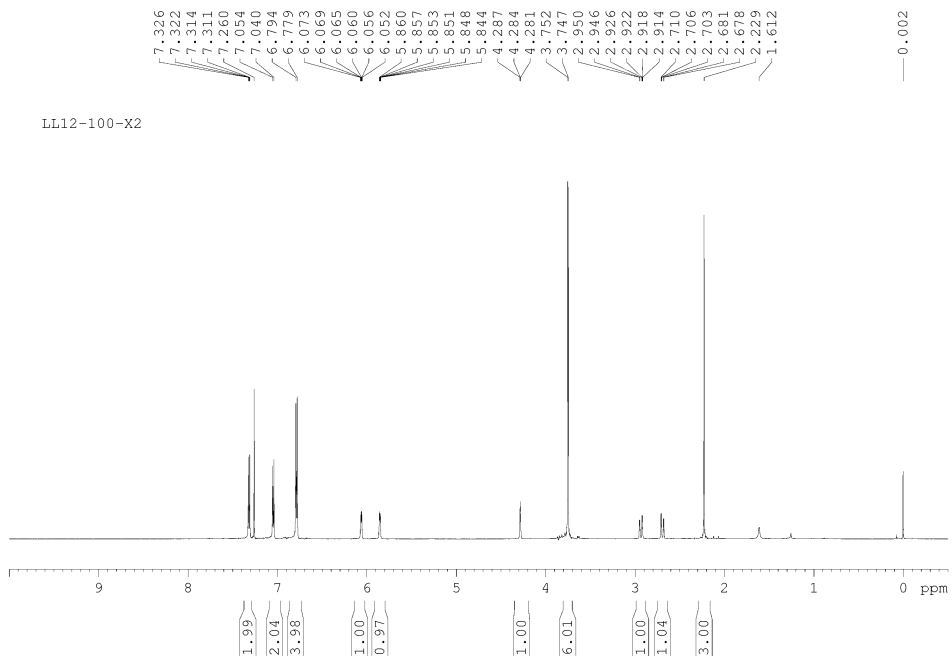
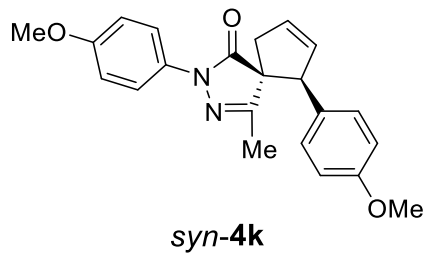


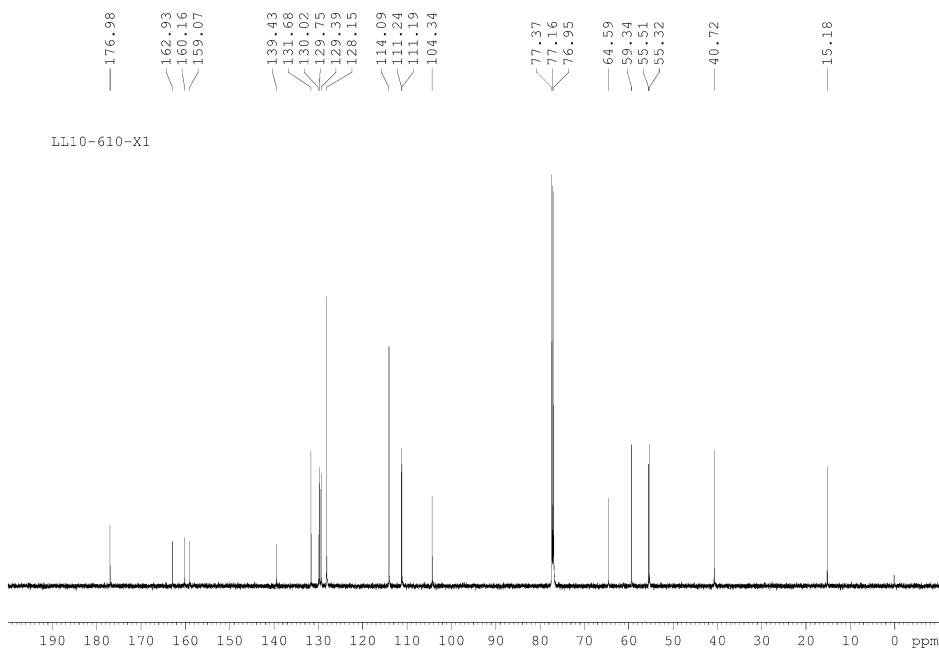
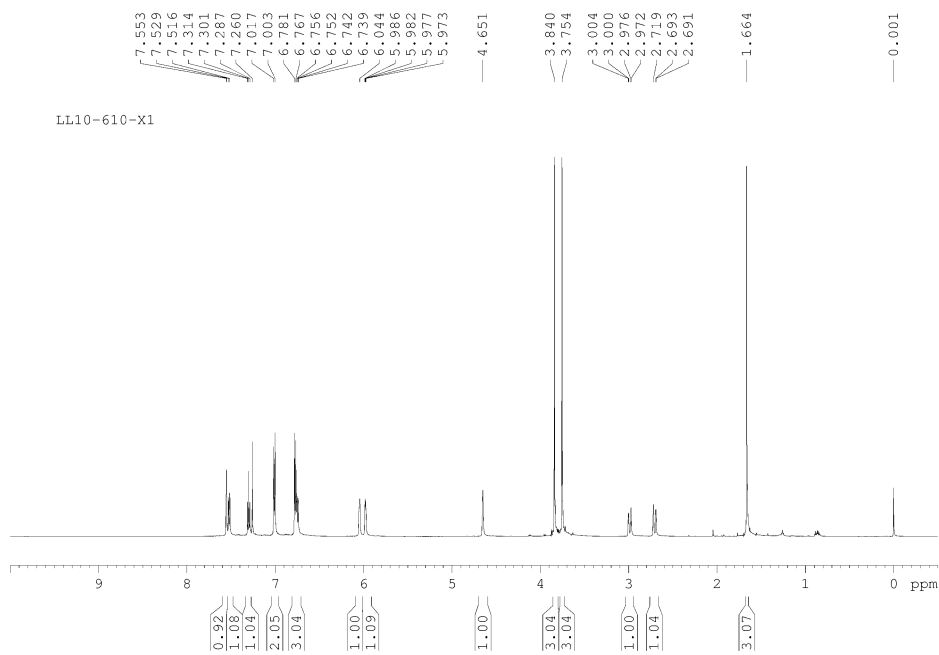
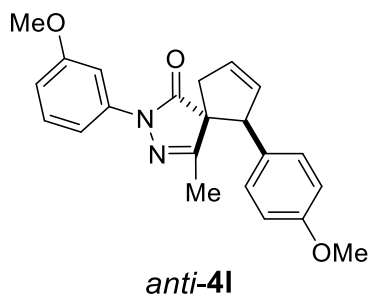


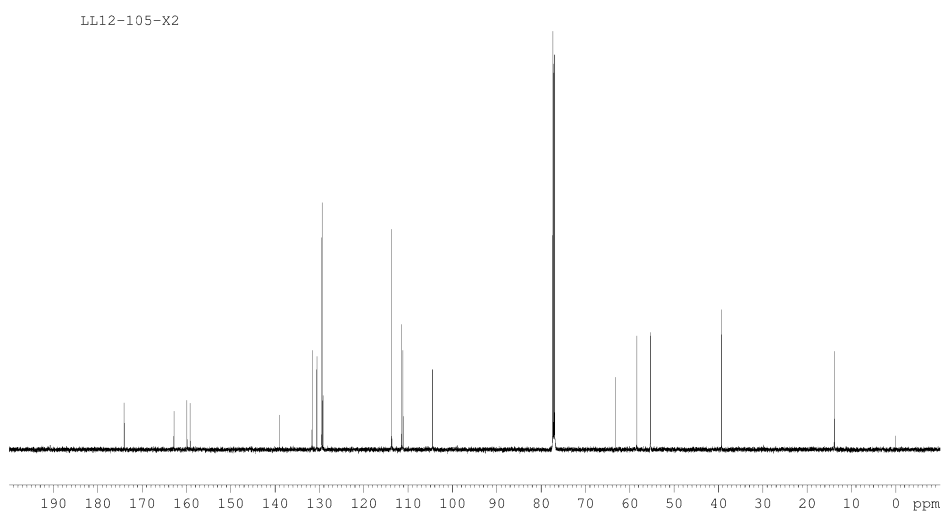
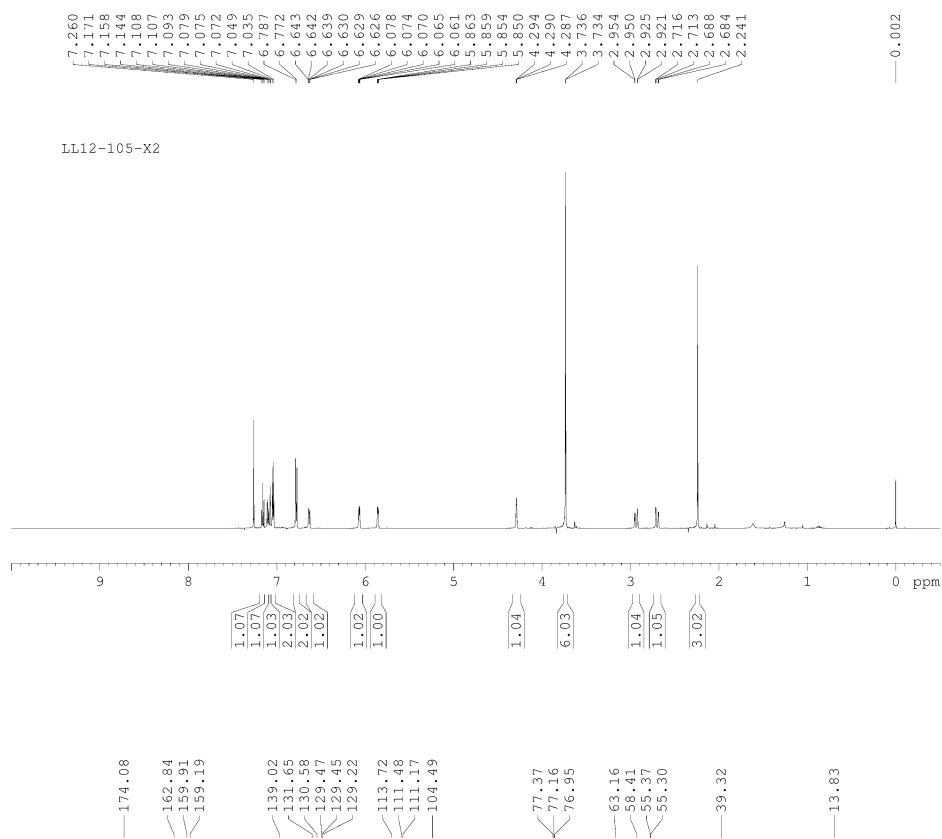
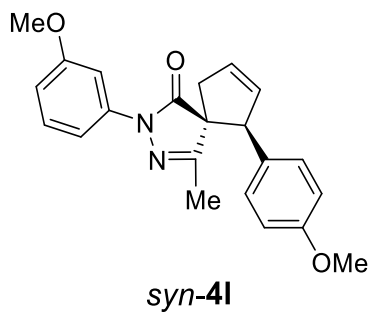


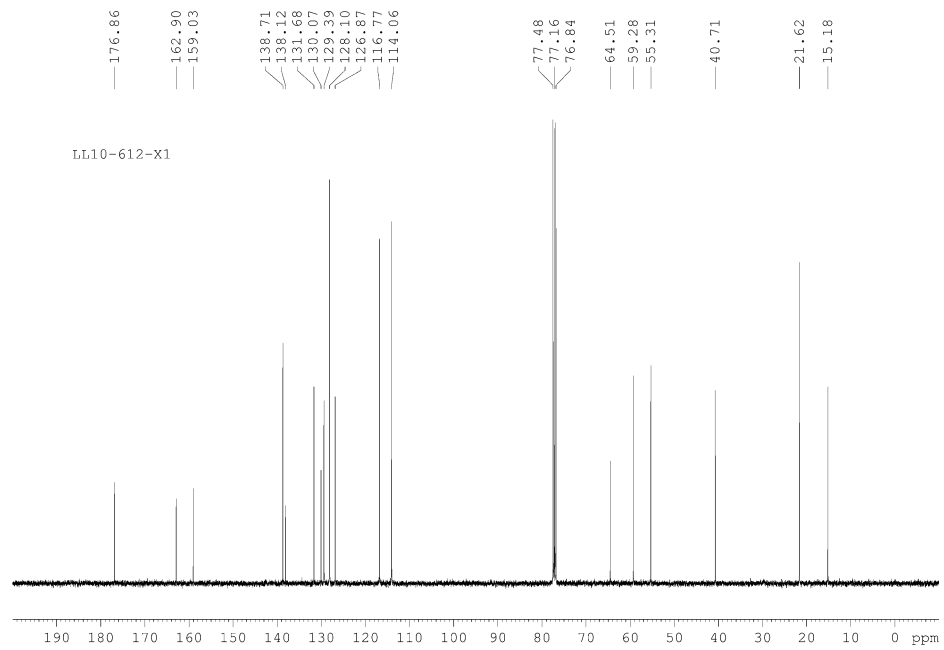
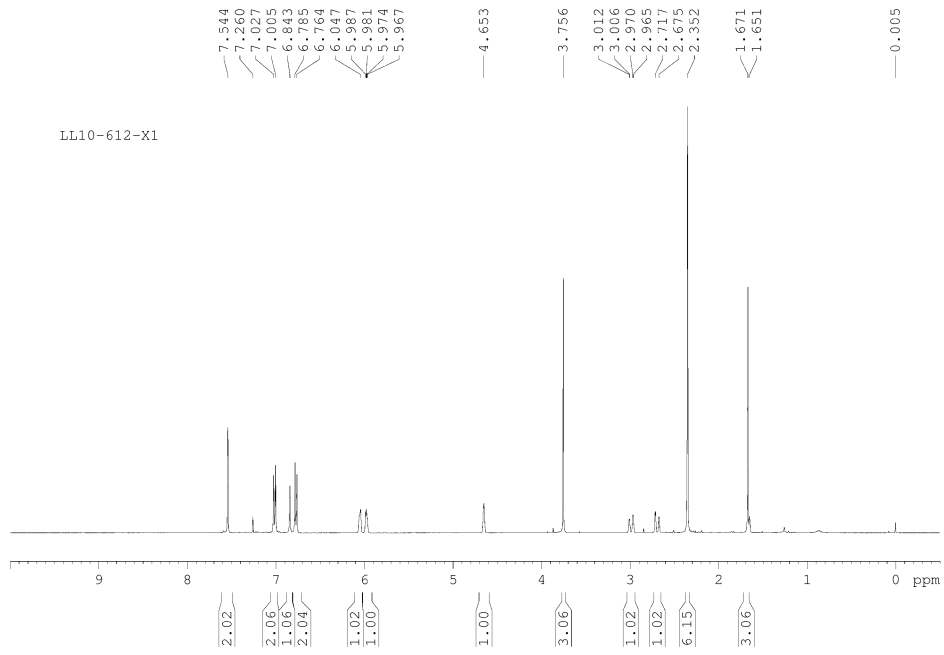
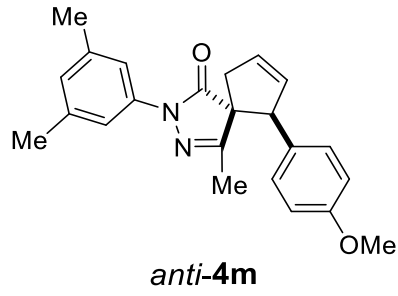


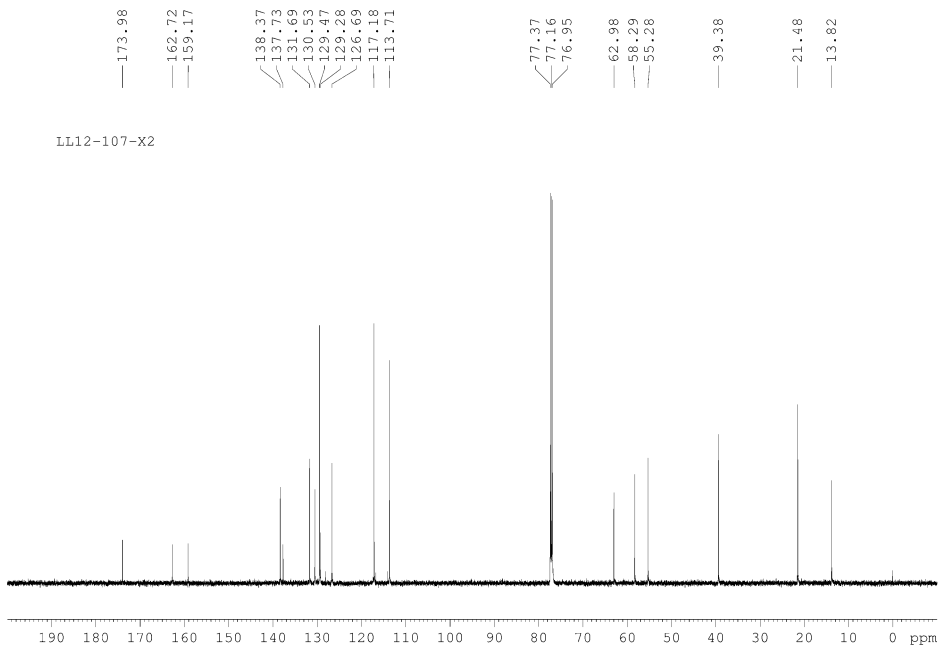
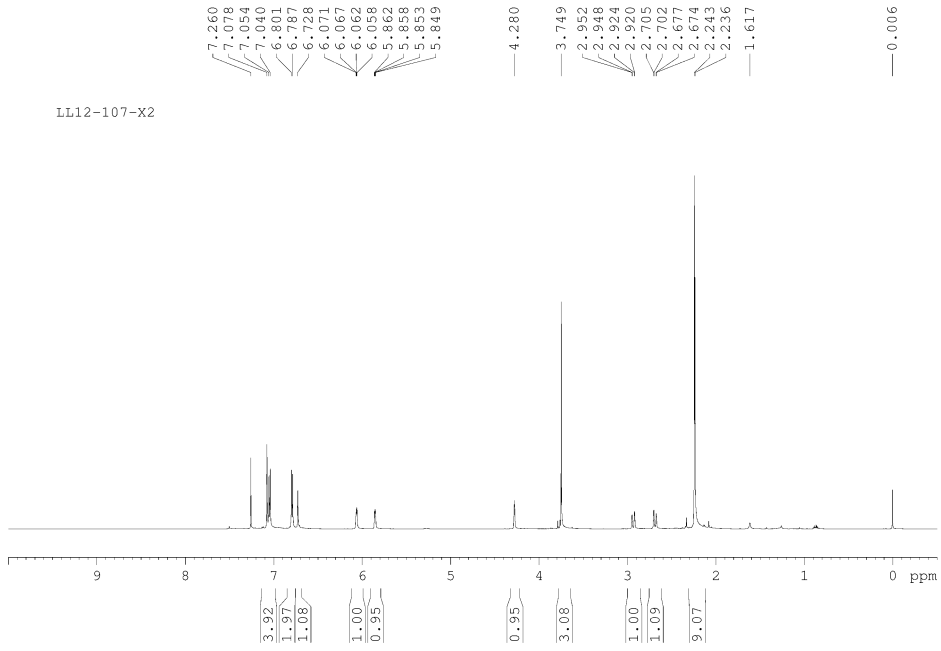
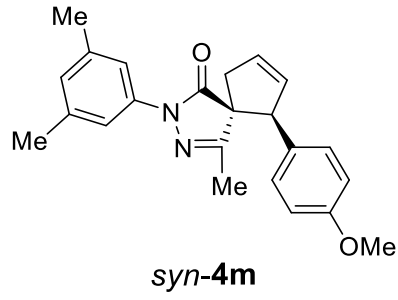


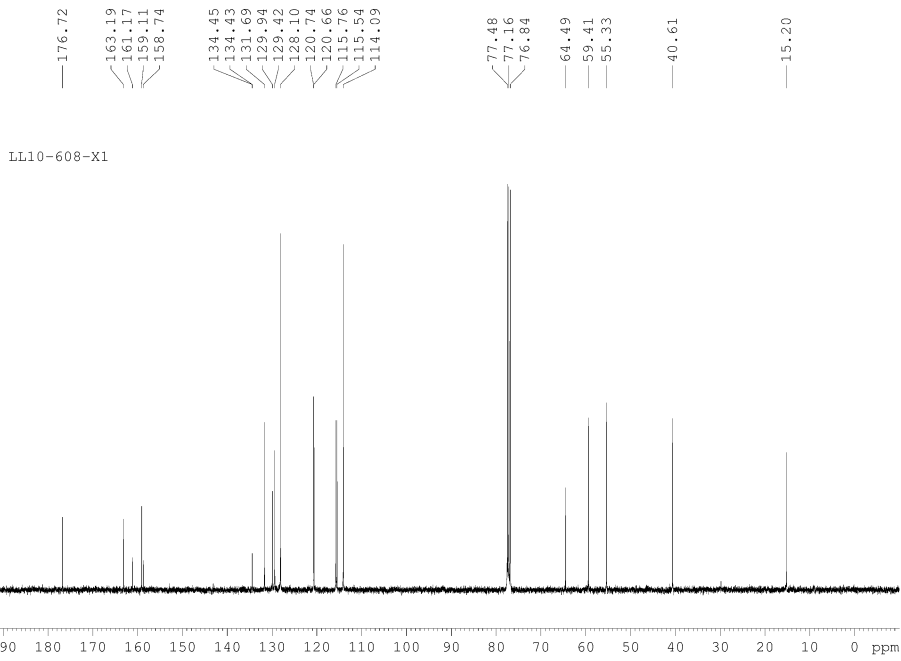
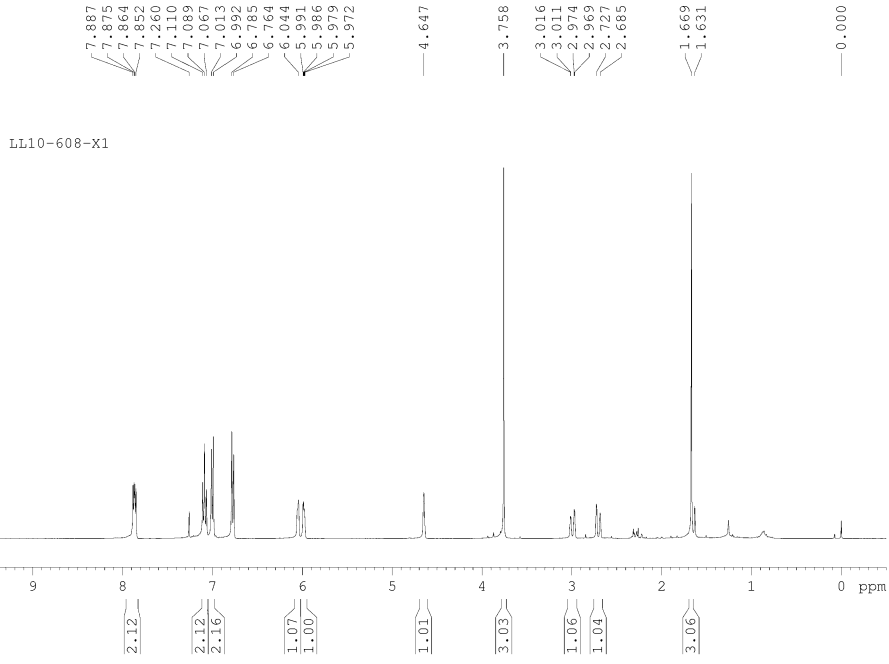
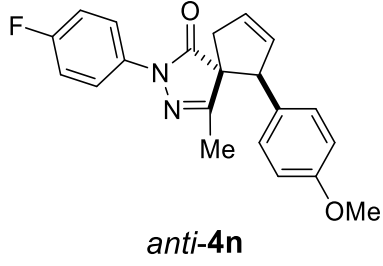




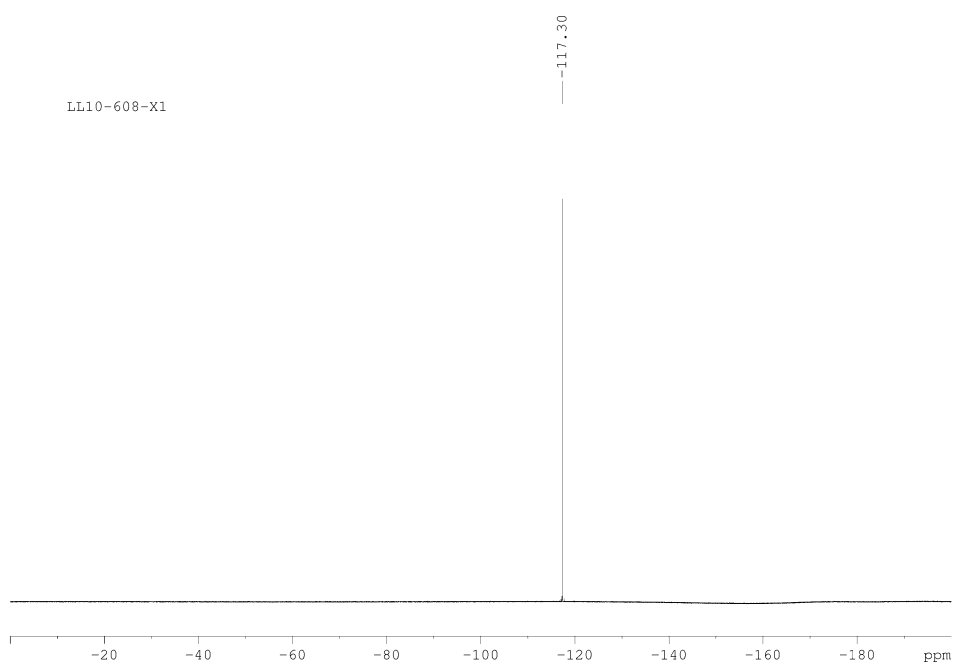


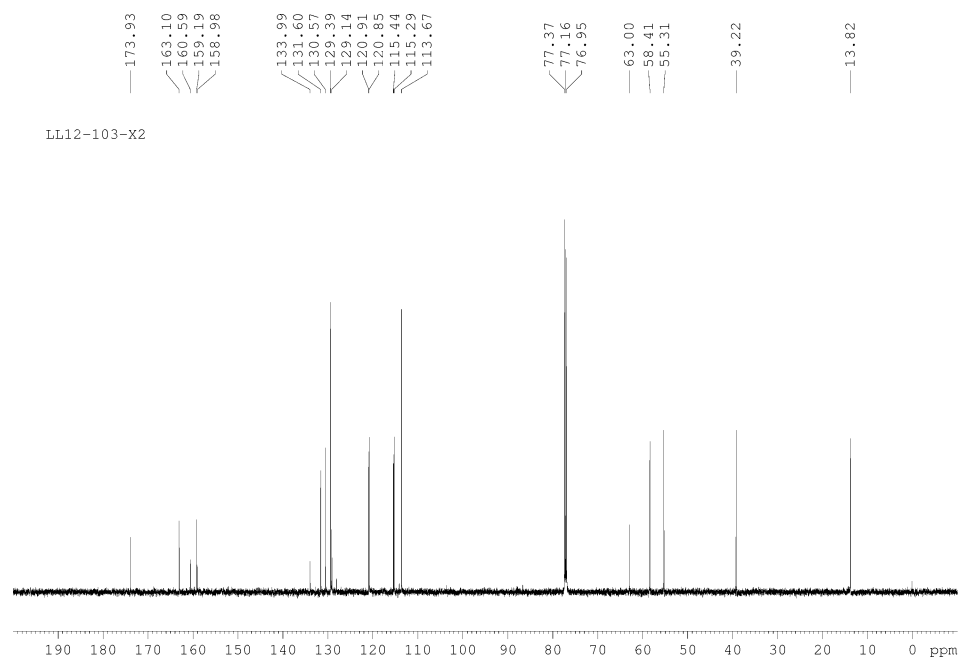
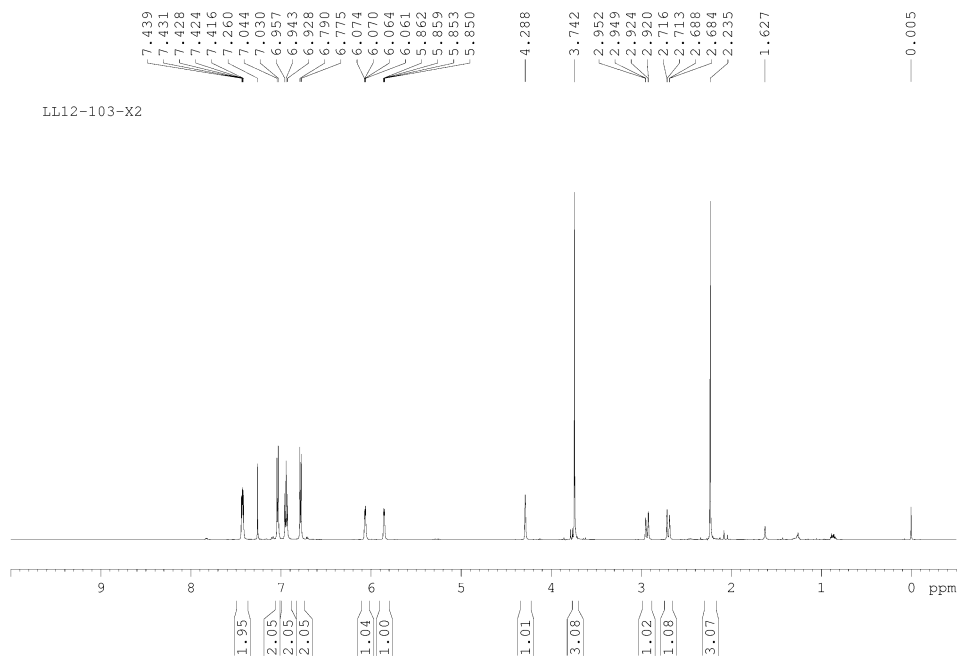
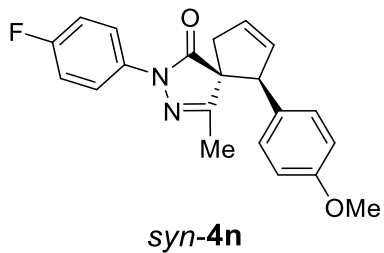






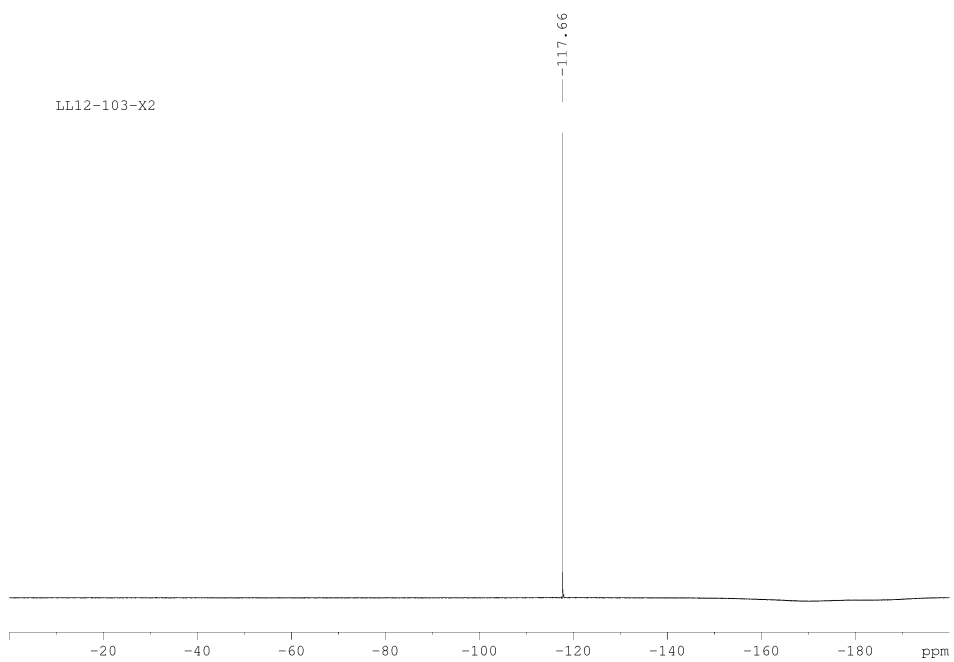
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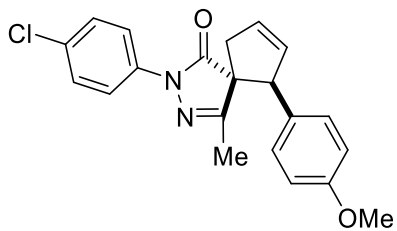




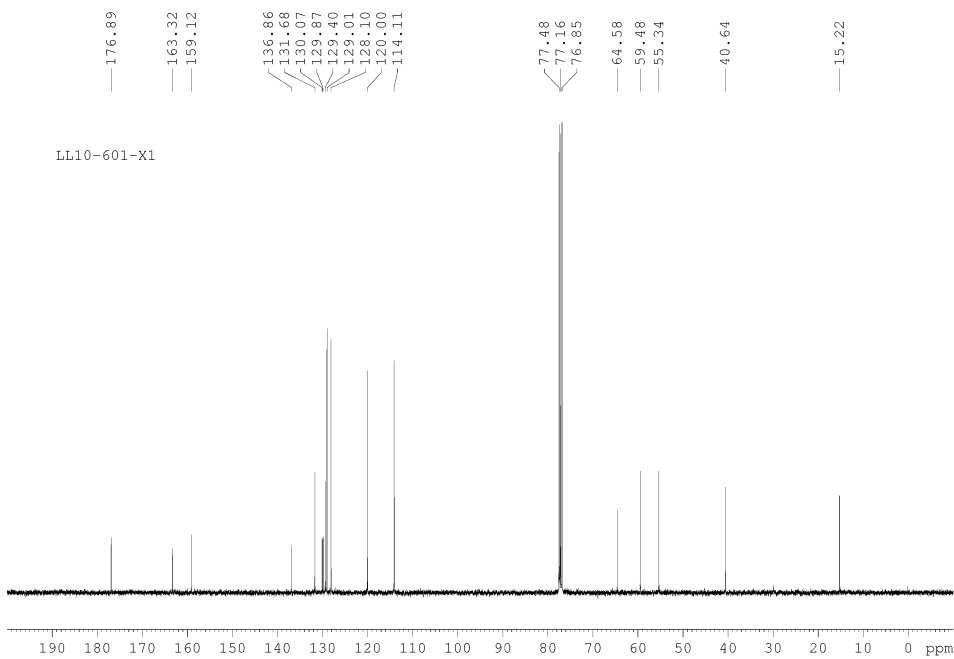
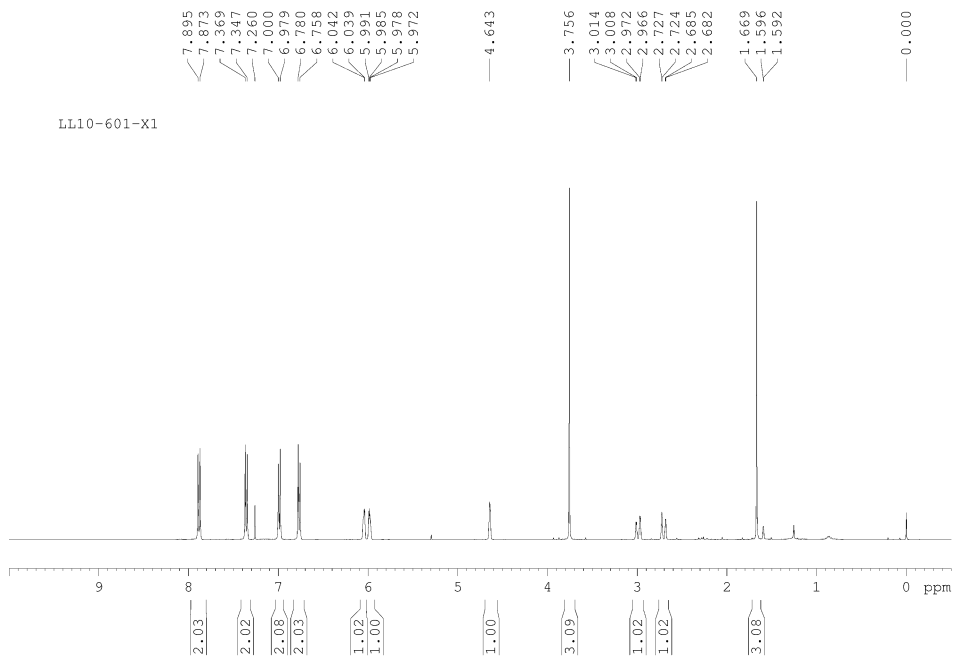


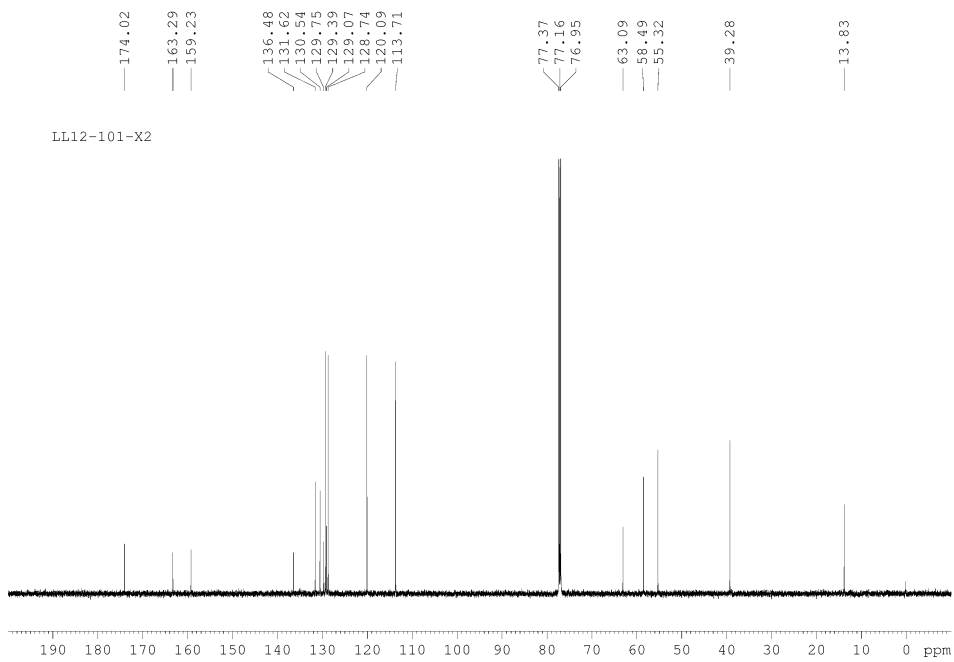
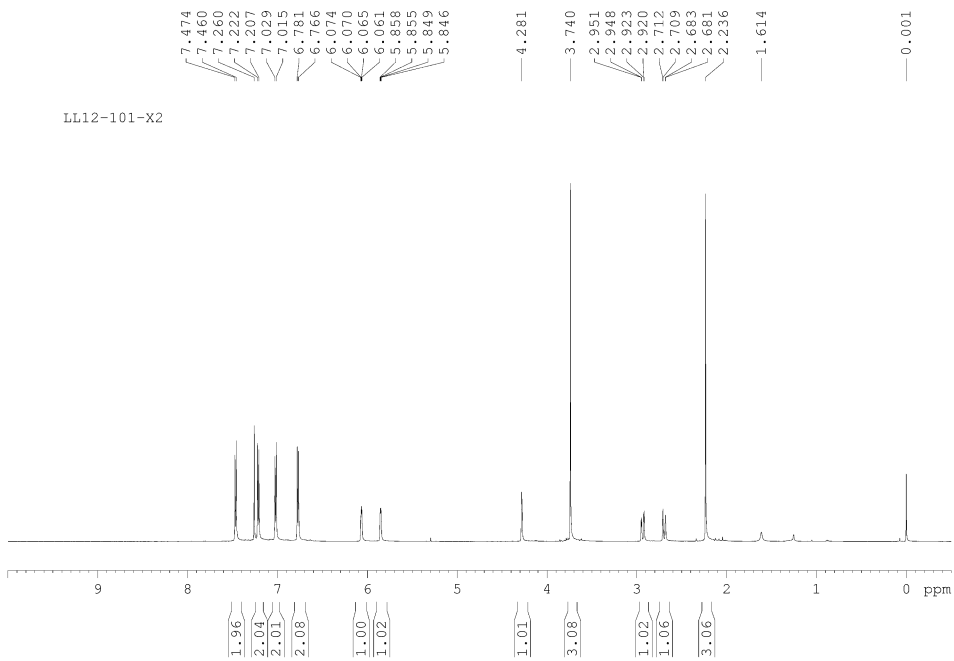
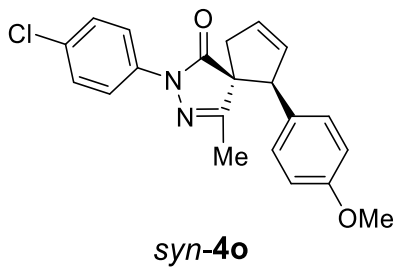
LL12-103-X2

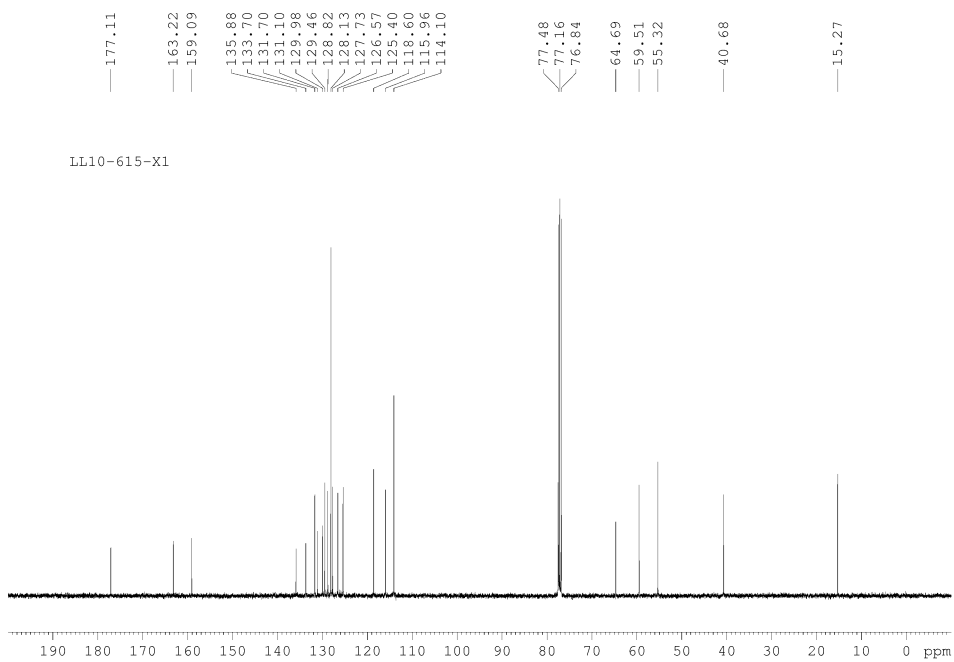
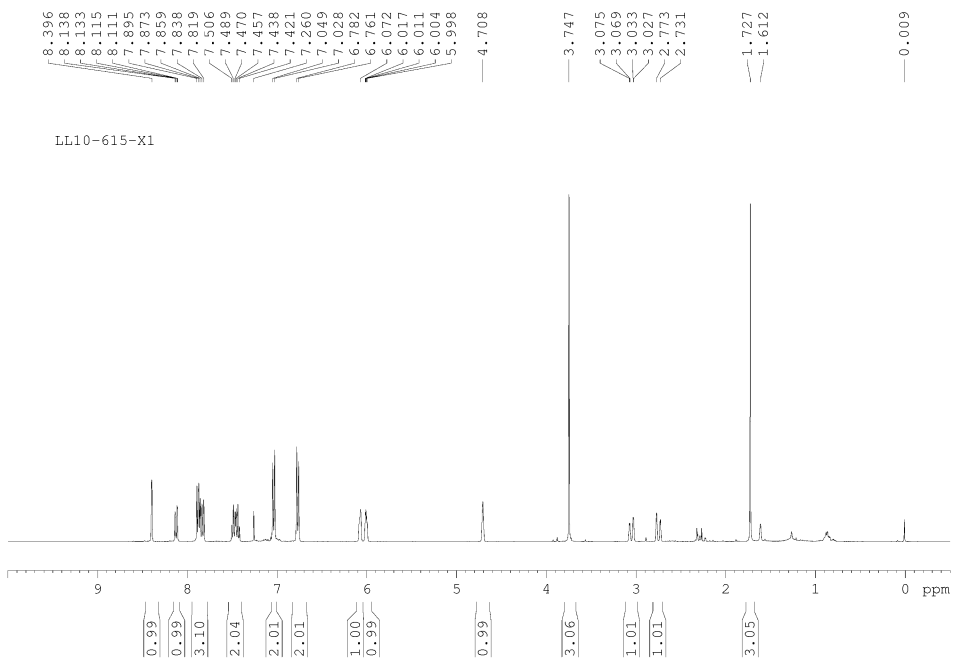
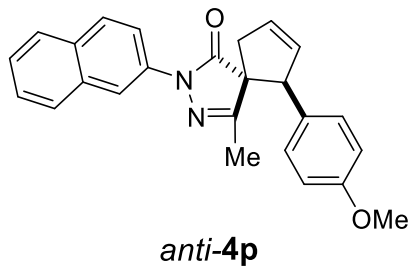


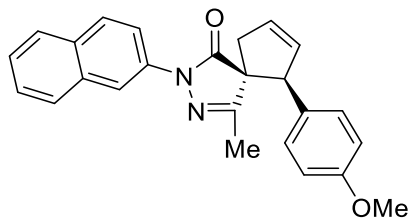


*anti-4o*

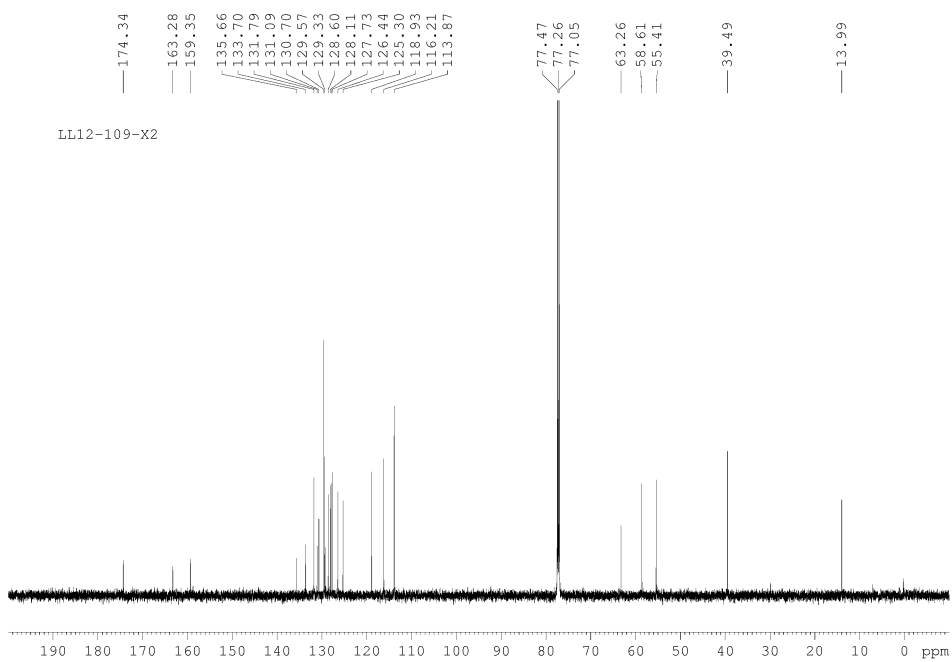
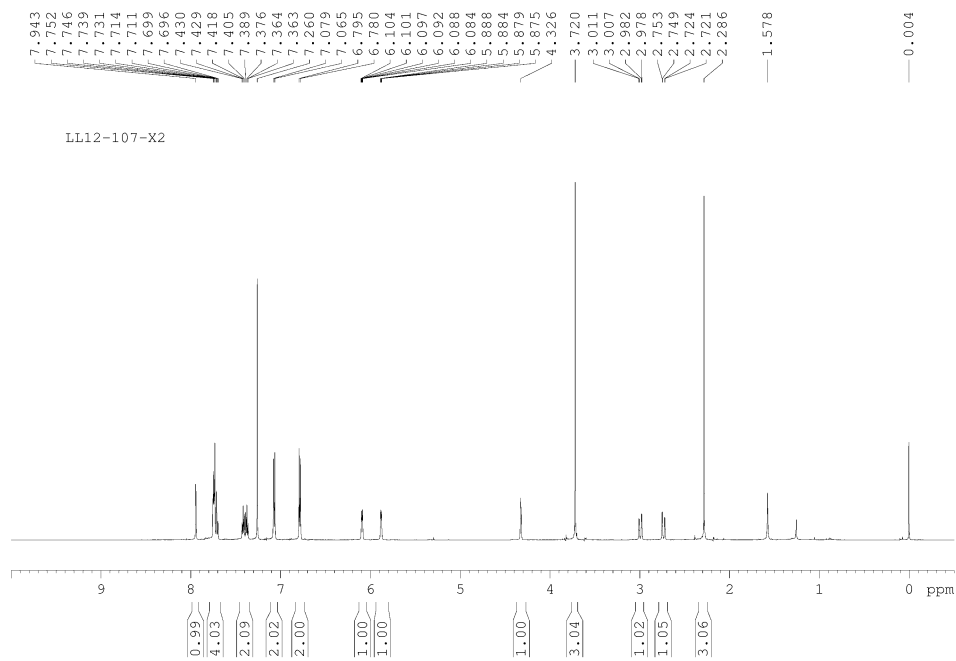


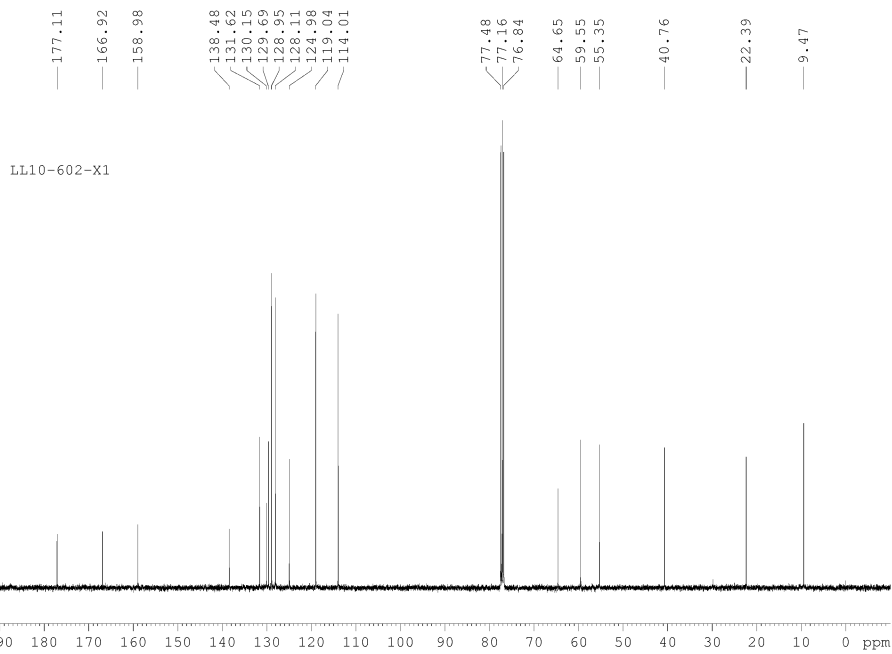
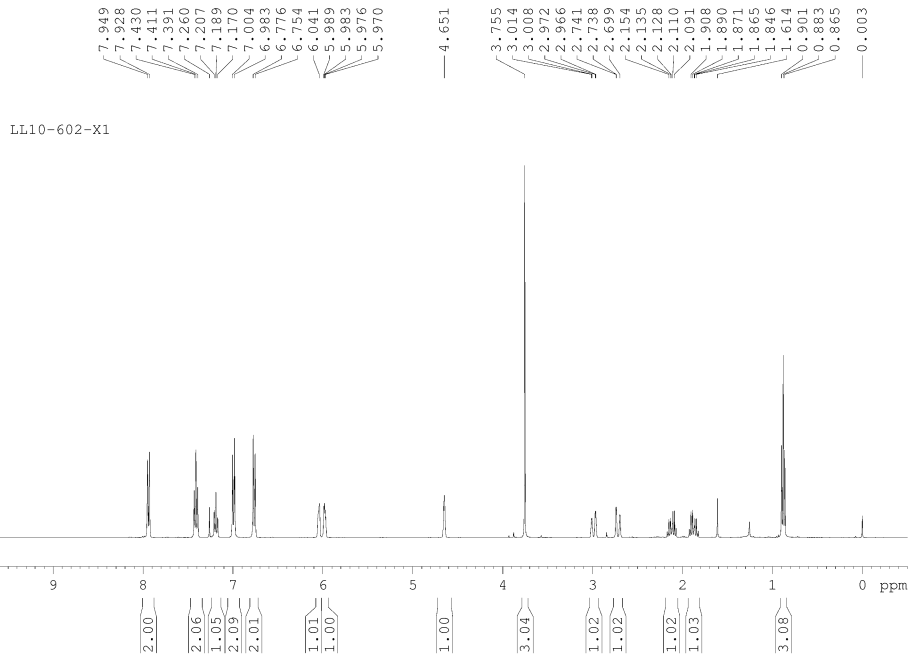
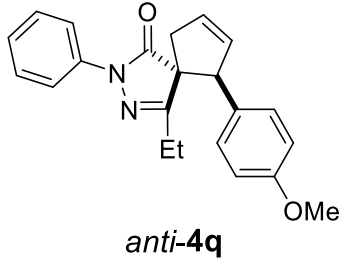


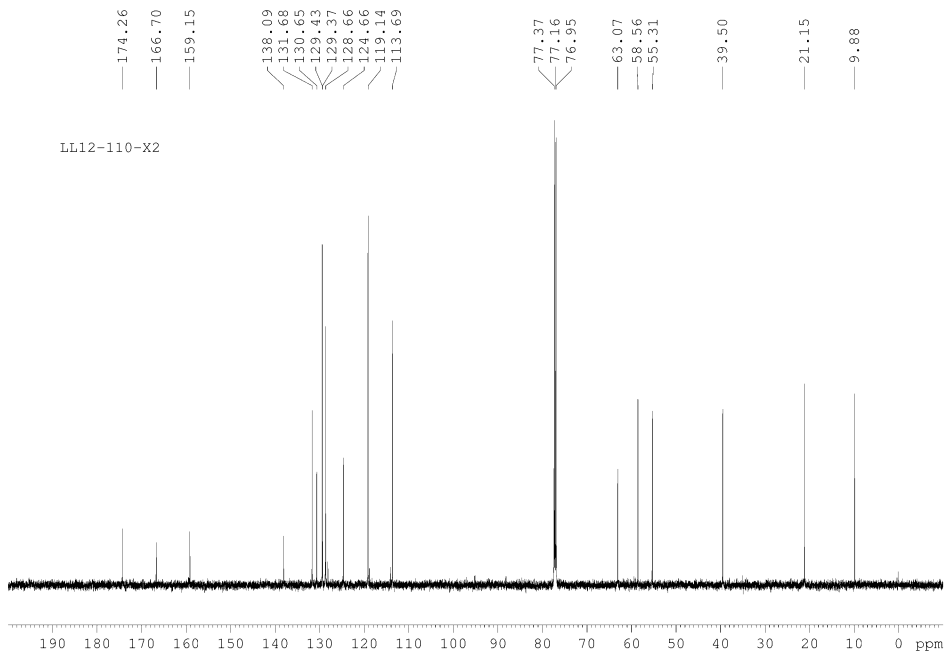
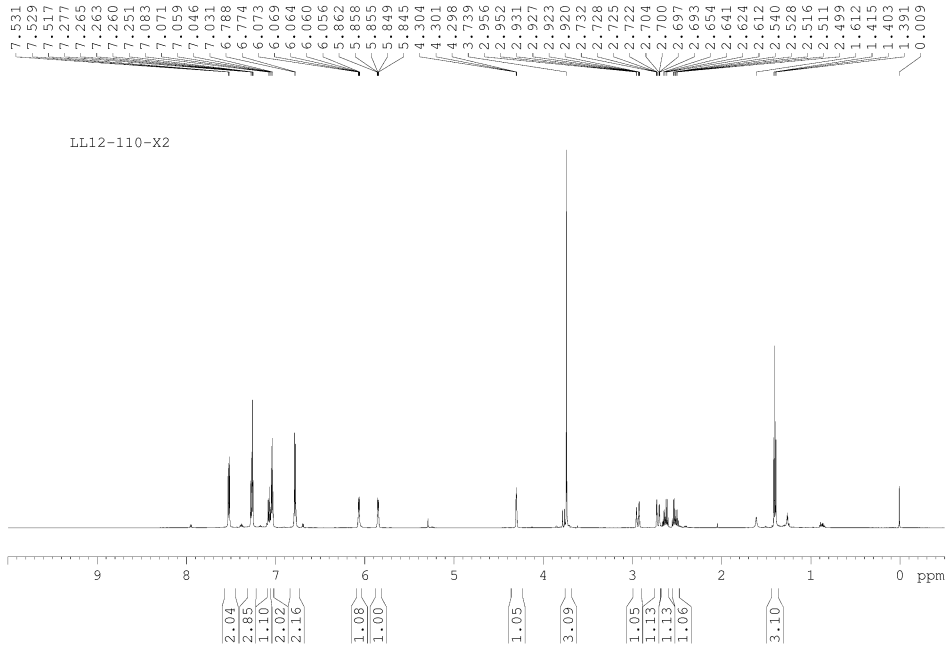
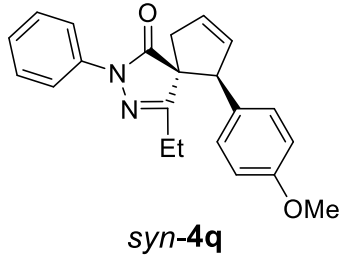


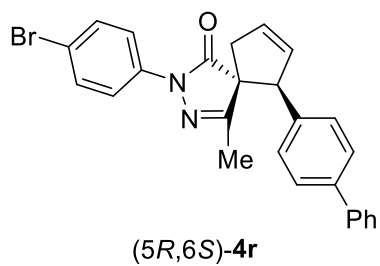


**syn-4p**



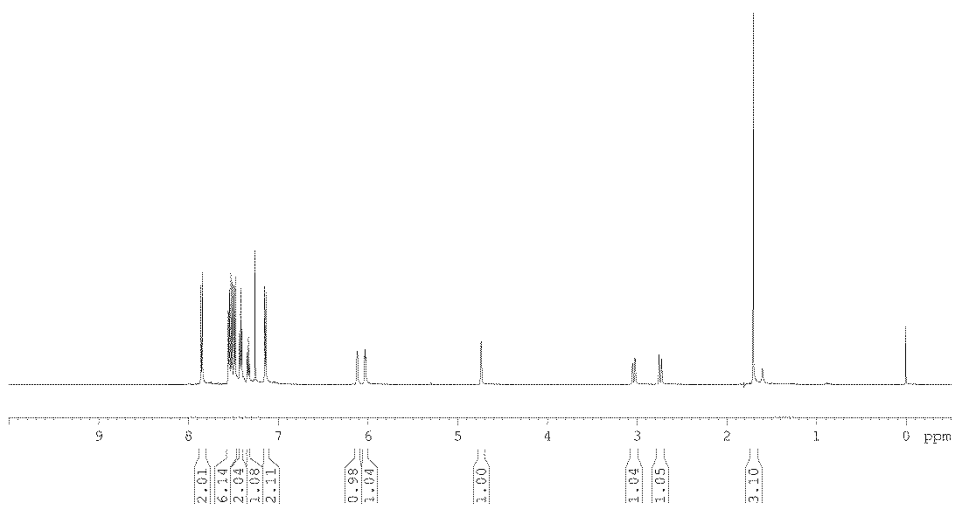






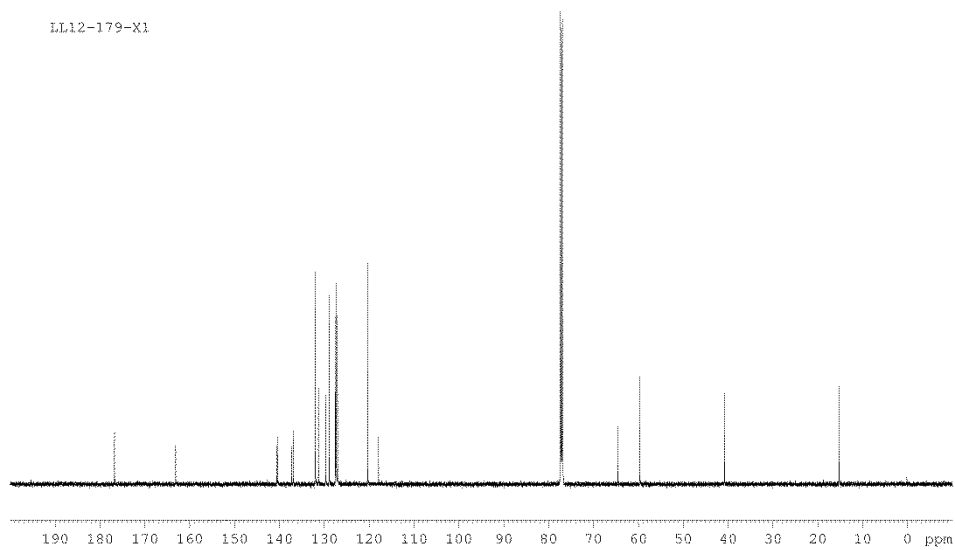
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7.391  
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7.334  
7.322  
7.260  
7.152  
7.139  
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6.118  
6.039  
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6.030  
6.026  
4.740  
3.054  
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3.022  
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0.006

LL12-179-X1

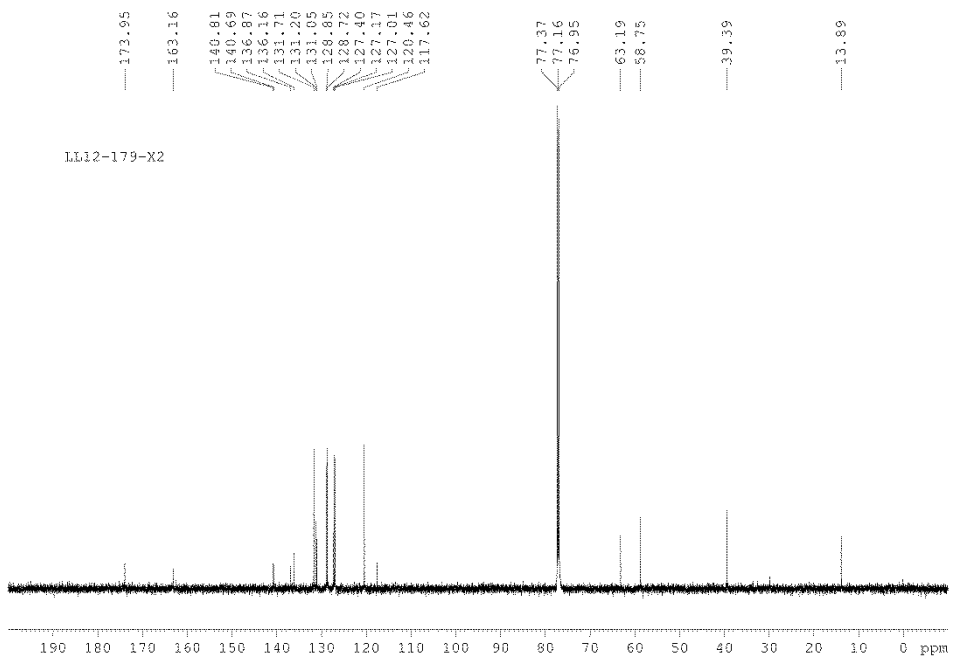
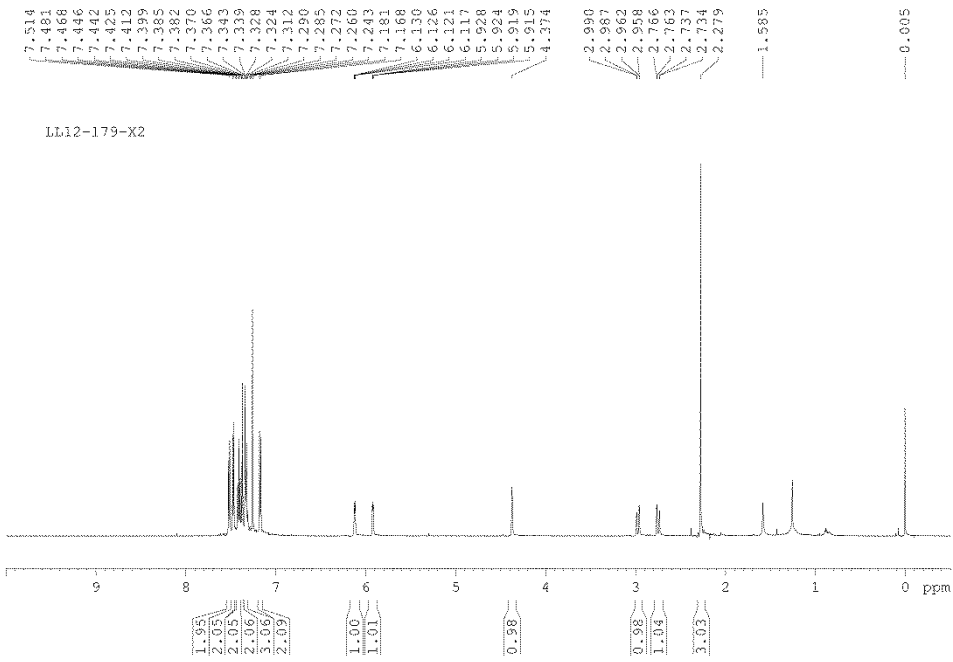
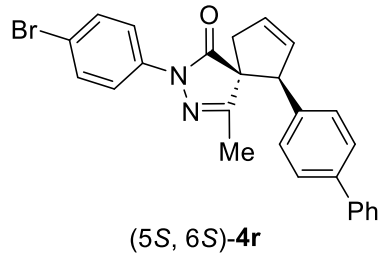


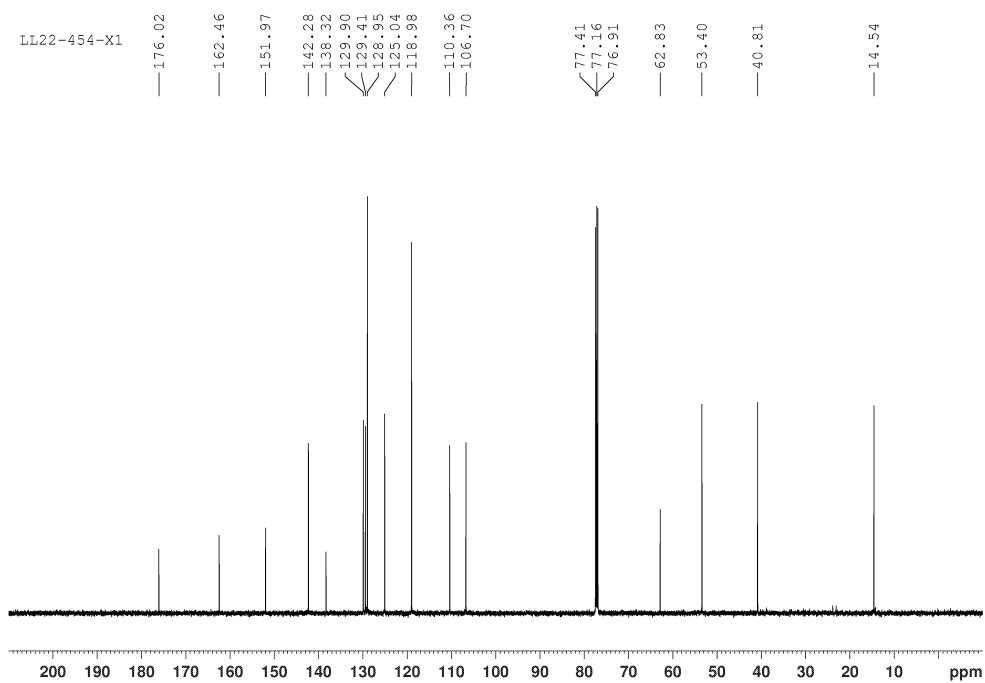
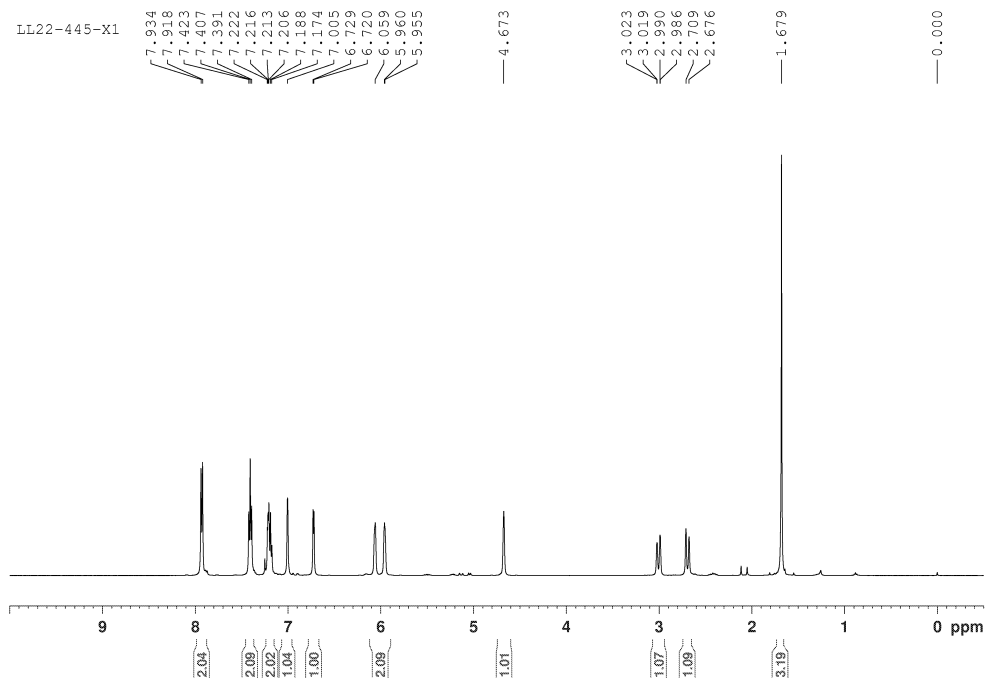
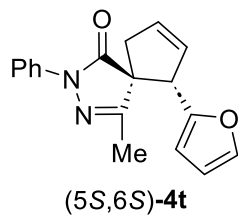
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132.00  
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127.47  
127.38  
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76.95  
64.60  
59.67  
40.62  
15.26

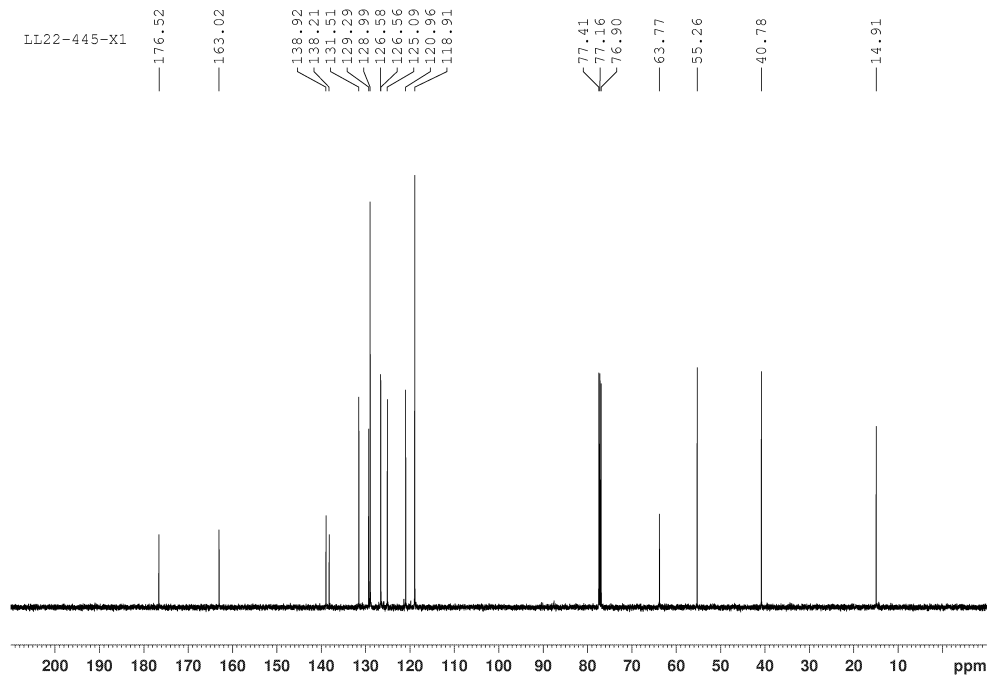
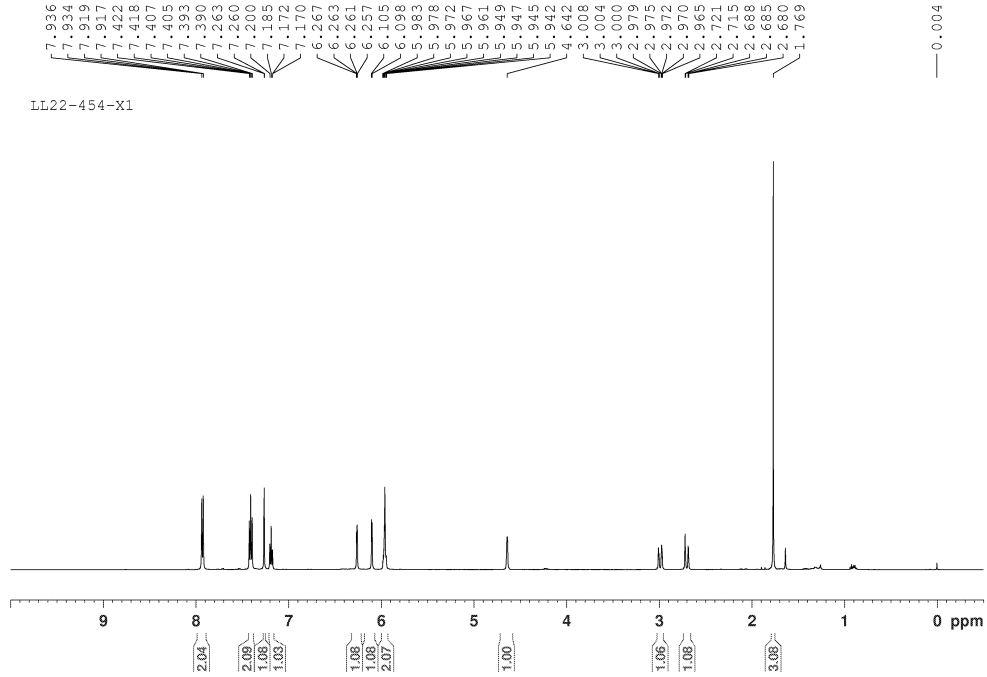
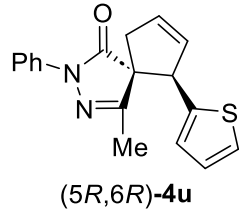
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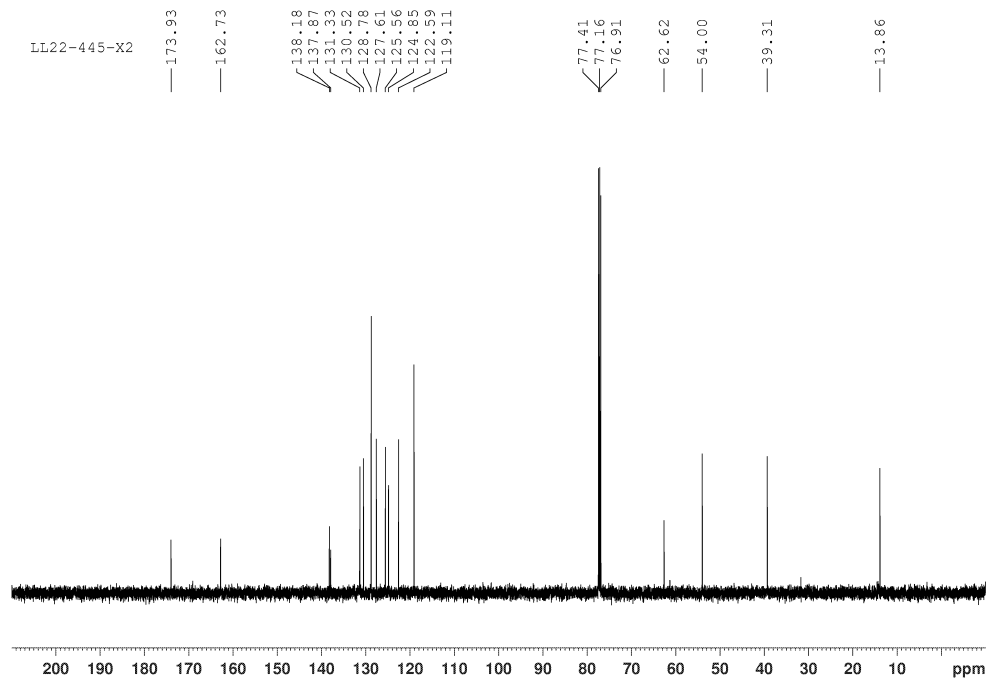
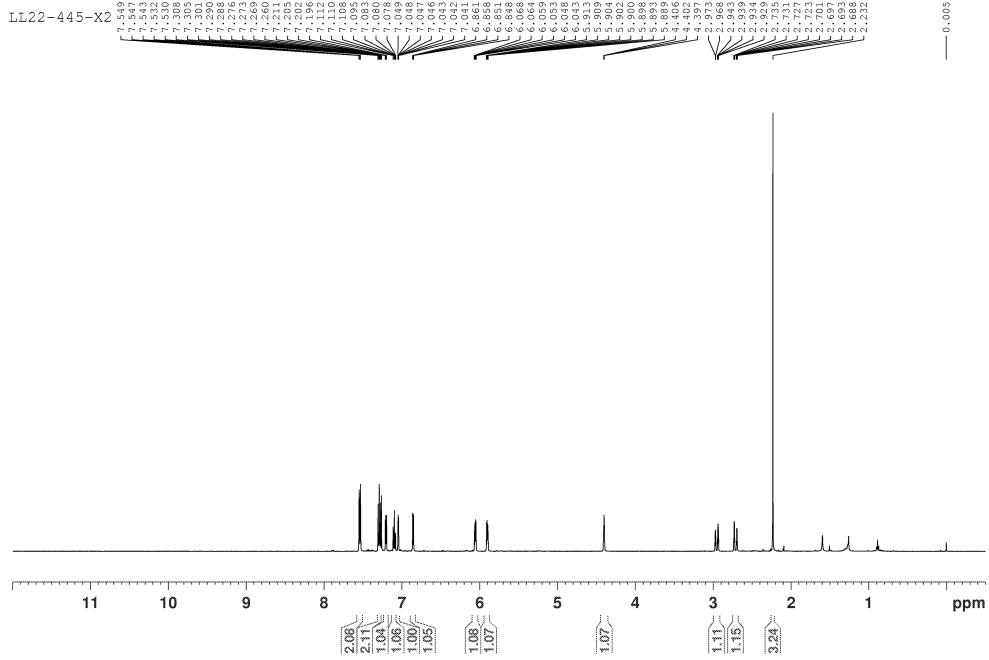
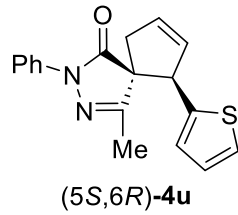


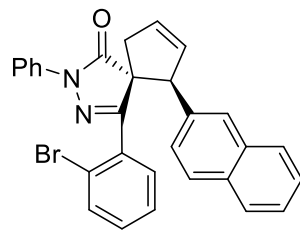








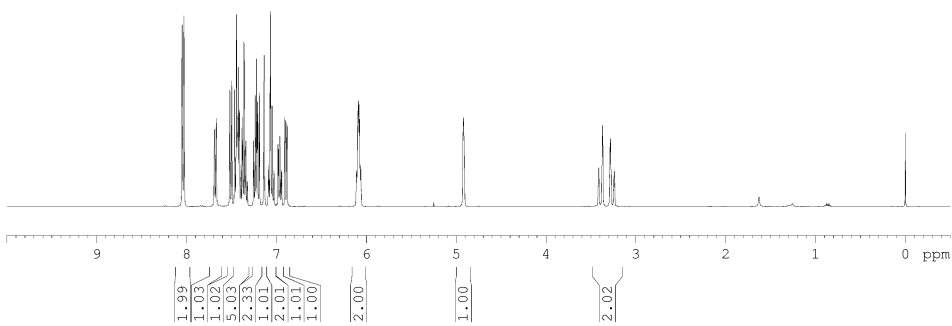




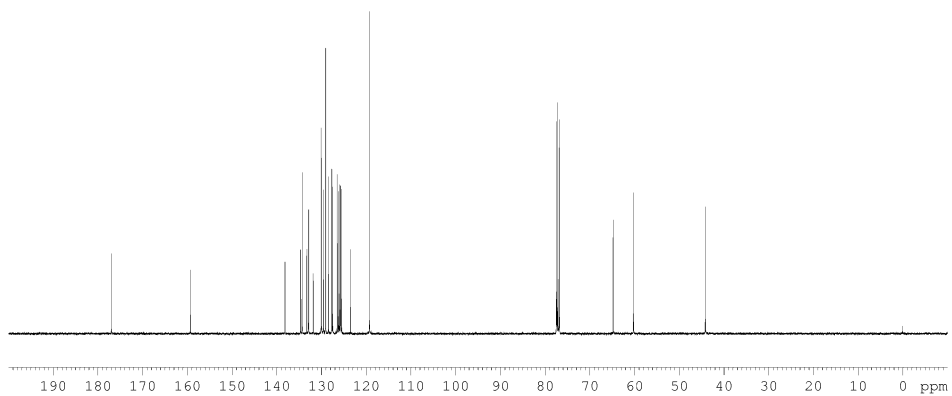
(5R,6S)-4s

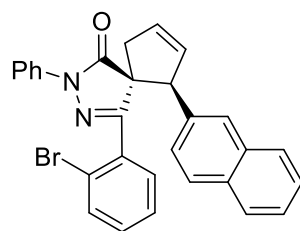


LL12-241-X1

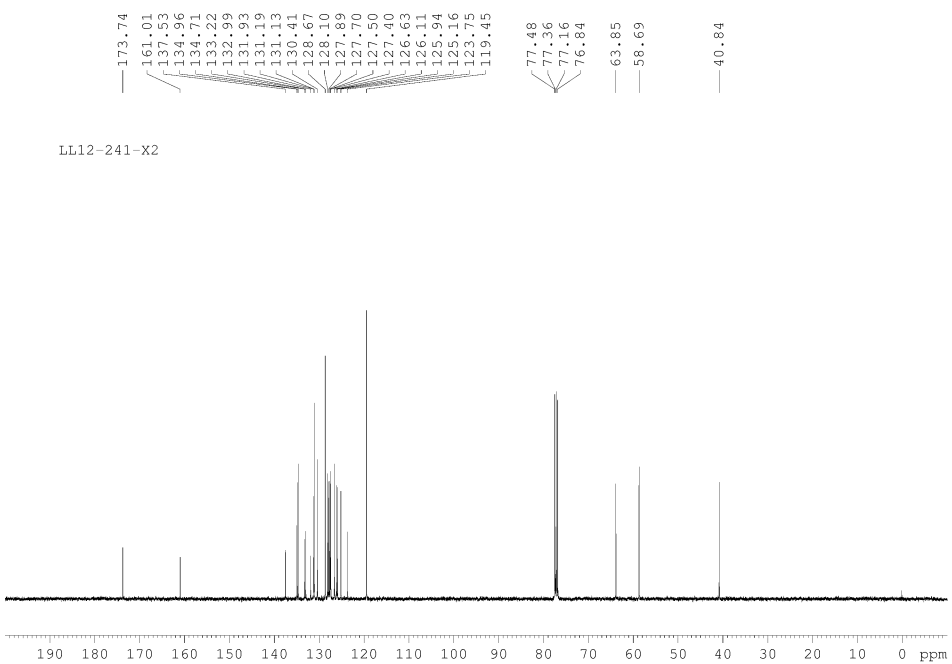
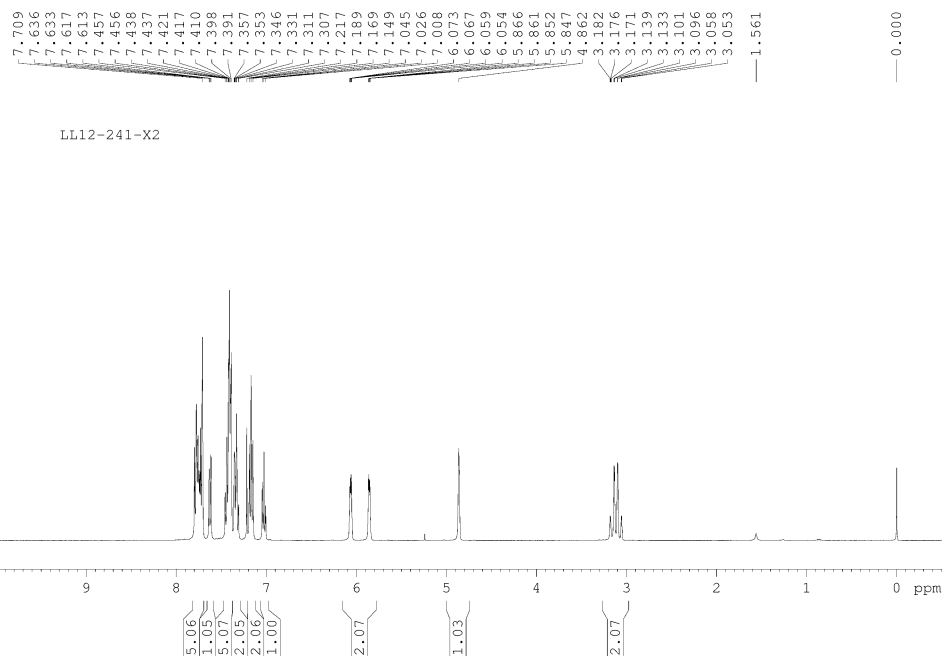


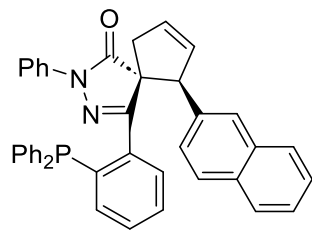
LL12-241-X1



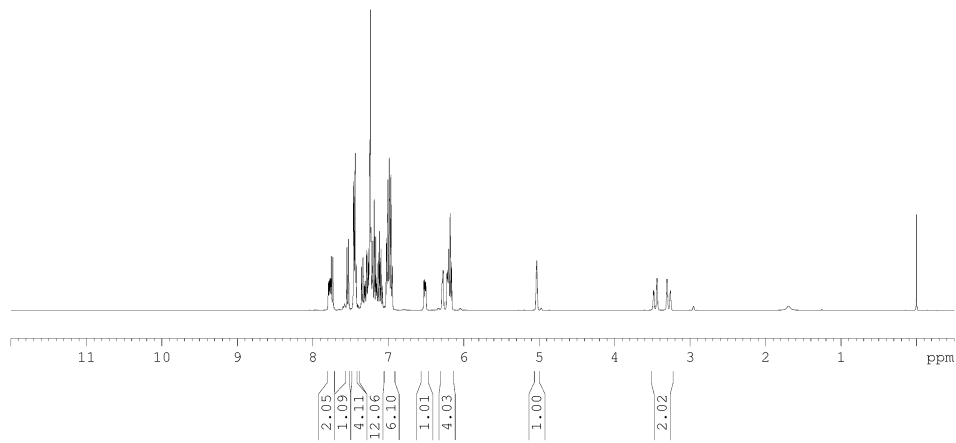
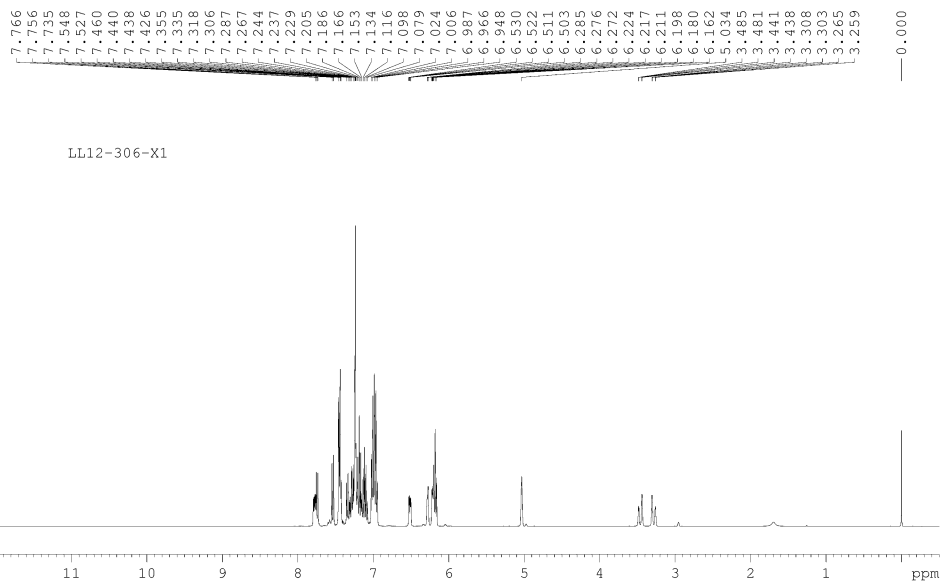


(5S,6S)-4s





(5R,6S)-8



LL12-306-X1

