

Stereoselective assembly of multifunctional spirocyclohexene pyrazolones that induce autophagy-dependent apoptosis in colorectal cancer cells

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Supporting Information

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1. Crystal data of **4m** and **4k'**

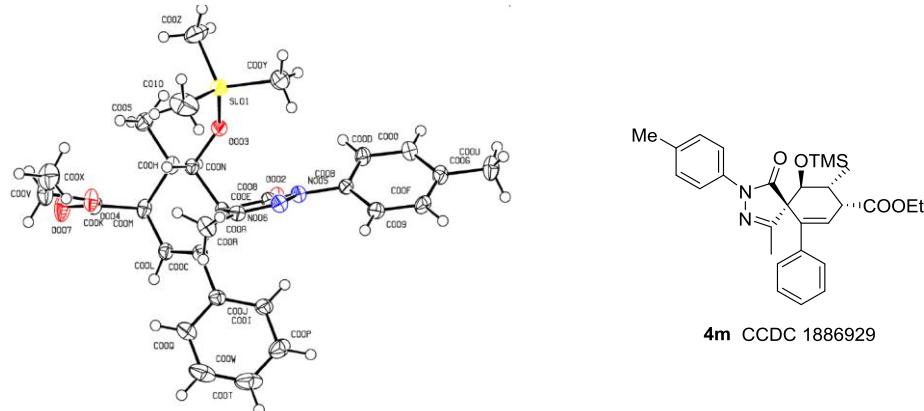


Figure S1 X-ray crystal structure of **4m**. The thermal ellipsoids are drawn at a 50% probability level.

Single crystals suitable for XRD were obtained by vapor diffusion experiment: compound **4m** (*5S,8R,9R,10S*, 50 mg,) was dissolved in 0.5 mL dichloromethane and 1.0 mL methanol in a glass vial, which was then placed in sealed glass container. Crystals were obtained in about 4-5 days.

Identification code	lq-18012702-139k
Empirical formula	C ₂₉ H ₃₆ N ₂ O ₄ Si
Formula weight	504.69
Temperature/K	139.1(2)
Crystal system	orthorhombic
Space group	P2 ₁ 2 ₁ 2 ₁
a/Å	8.96693(9)
b/Å	16.8380(2)
c/Å	18.4036(3)
α/°	90
β/°	90
γ/°	90
Volume/Å ³	2778.68(6)
Z	4
ρ _{calc} g/cm ³	1.206
μ/mm ⁻¹	1.031
F(000)	1080.0
Crystal size/mm ³	0.6 × 0.4 × 0.25
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.116 to 145.916
Index ranges	-8 ≤ h ≤ 11, -19 ≤ k ≤ 20, -21 ≤ l ≤ 22
Reflections collected	12506
Independent reflections	5418 [R _{int} = 0.0368, R _{sigma} = 0.0471]
Data/restraints/parameters	5418/0/332

Goodness-of-fit on F ²	1.054
Final R indexes [$I >= 2\sigma(I)$]	R ₁ = 0.0552, wR ₂ = 0.1337
Final R indexes [all data]	R ₁ = 0.0582, wR ₂ = 0.1371
Largest diff. peak/hole / e Å ⁻³	0.43/-0.42
Flack parameter	-0.007(19)

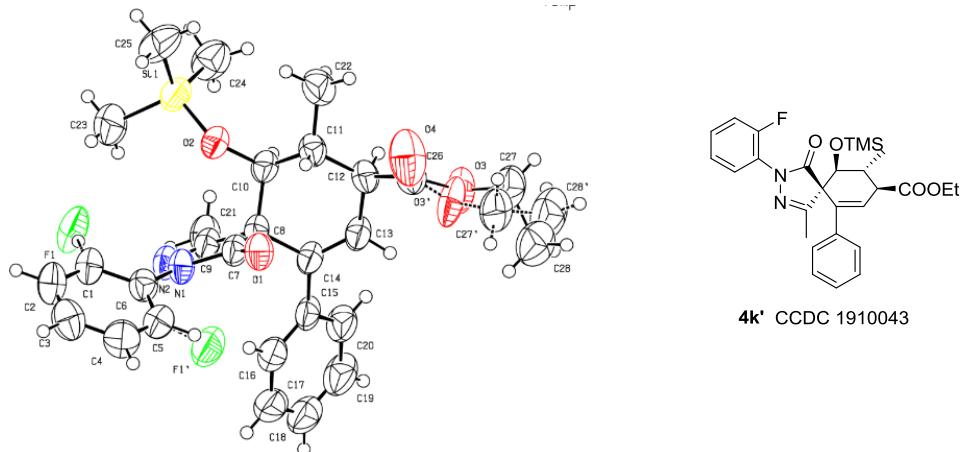


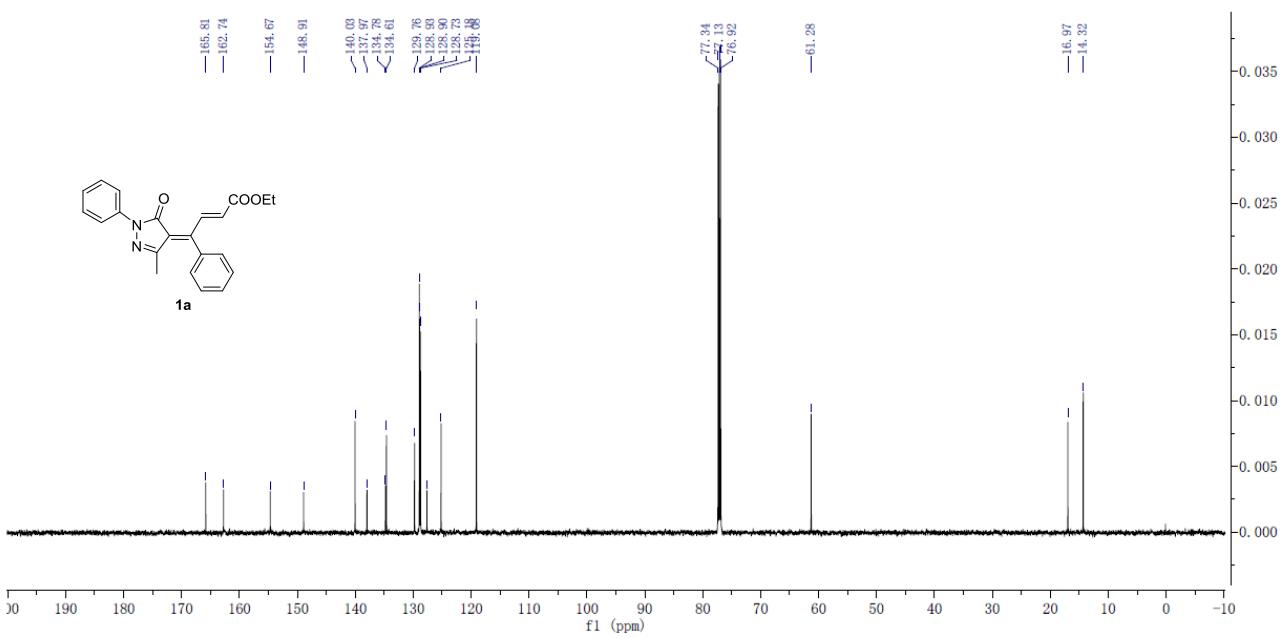
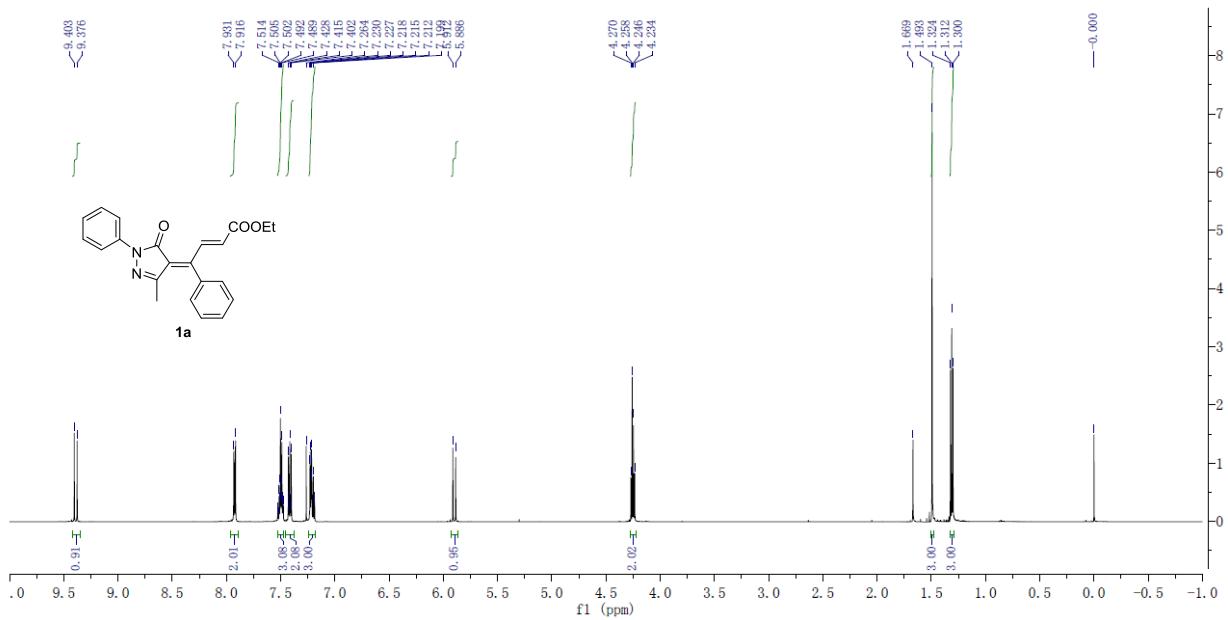
Figure S2 X-ray crystal structure of **4k'**. The thermal ellipsoids are drawn at a 50% probability level.

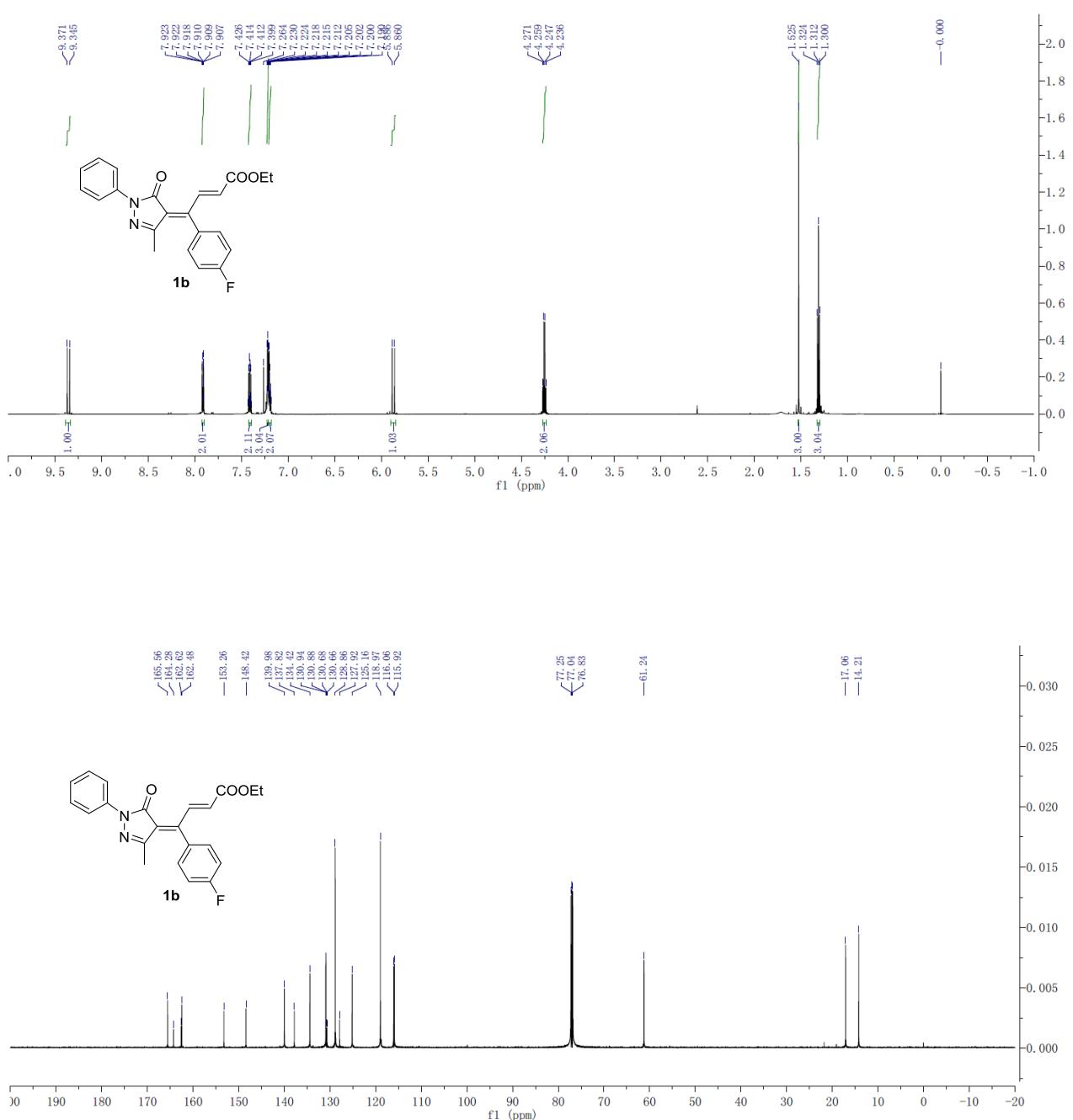
Single crystals suitable for XRD were obtained by vapor diffusion experiment: compound **4k'** (50 mg) was dissolved in 2.0 mL methanol in a glass vial, which was then placed in sealed glass container. Crystals were obtained in about 5-6 days.

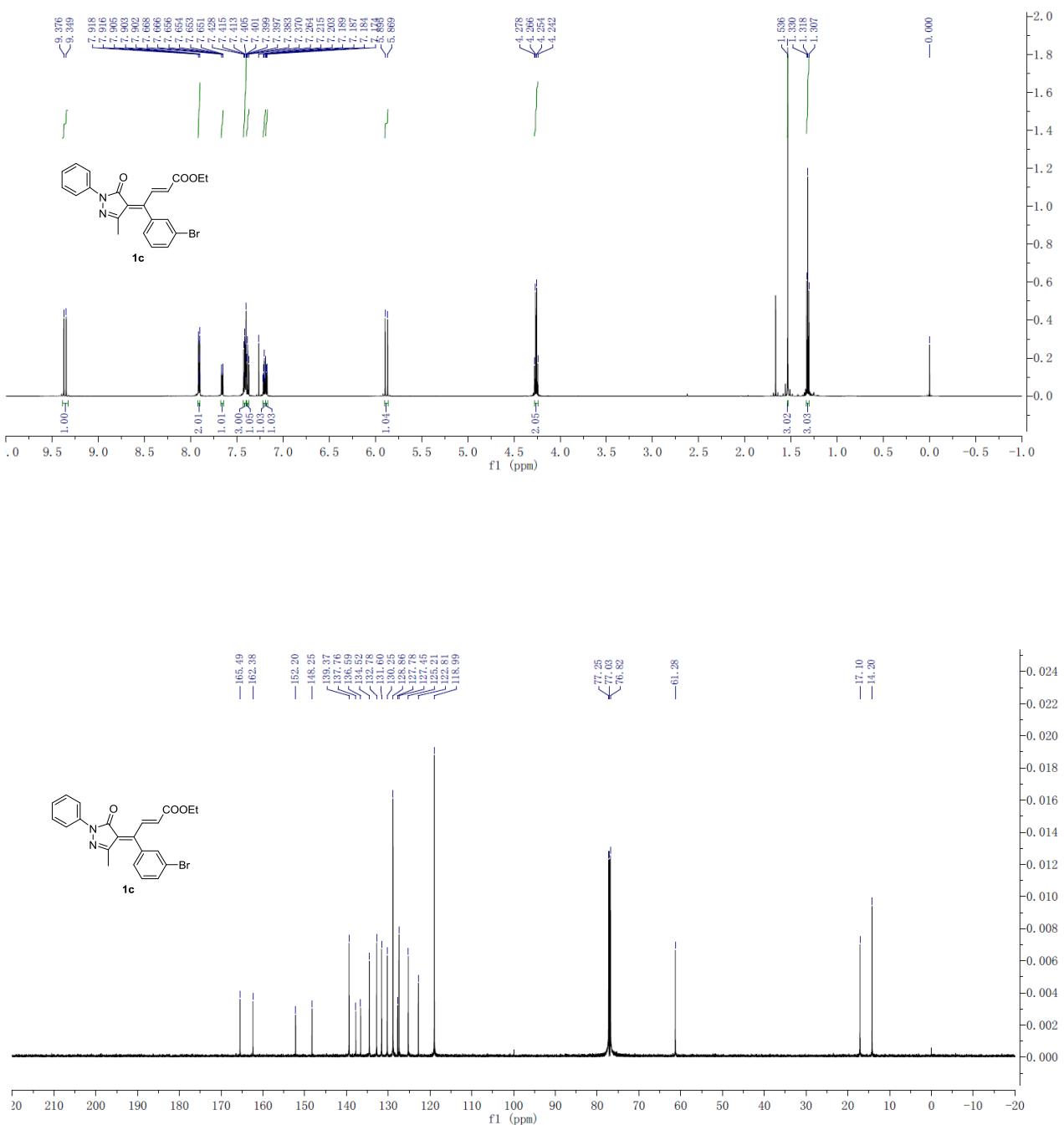
Identification code	exp_10192
Empirical formula	C ₂₈ H ₃₃ FN ₂ O ₄ Si
Formula weight	508.65
Temperature/K	293(2)
Crystal system	N/A
Space group	P2 ₁ /c
a/Å	18.8993(18)
b/Å	14.9288(11)
c/Å	9.7511(8)
α/°	90.00
β/°	97.082(9)
γ/°	90.00
Volume/Å ³	2730.2(4)
Z	4
ρ _{calcg/cm³}	1.237
μ/mm ⁻¹	1.109
F(000)	1080.0
Crystal size/mm ³	0.08 × 0.08 × 0.07
Radiation	CuKα (λ = 1.54184)
2θ range for data collection/°	7.56 to 134.5
Index ranges	-22 ≤ h ≤ 18, -13 ≤ k ≤ 17, -9 ≤ l ≤ 11
Reflections collected	9790
Independent reflections	4891 [R _{int} = 0.0609, R _{sigma} = N/A]
Data/restraints/parameters	4891/2/331
Goodness-of-fit on F ²	1.215

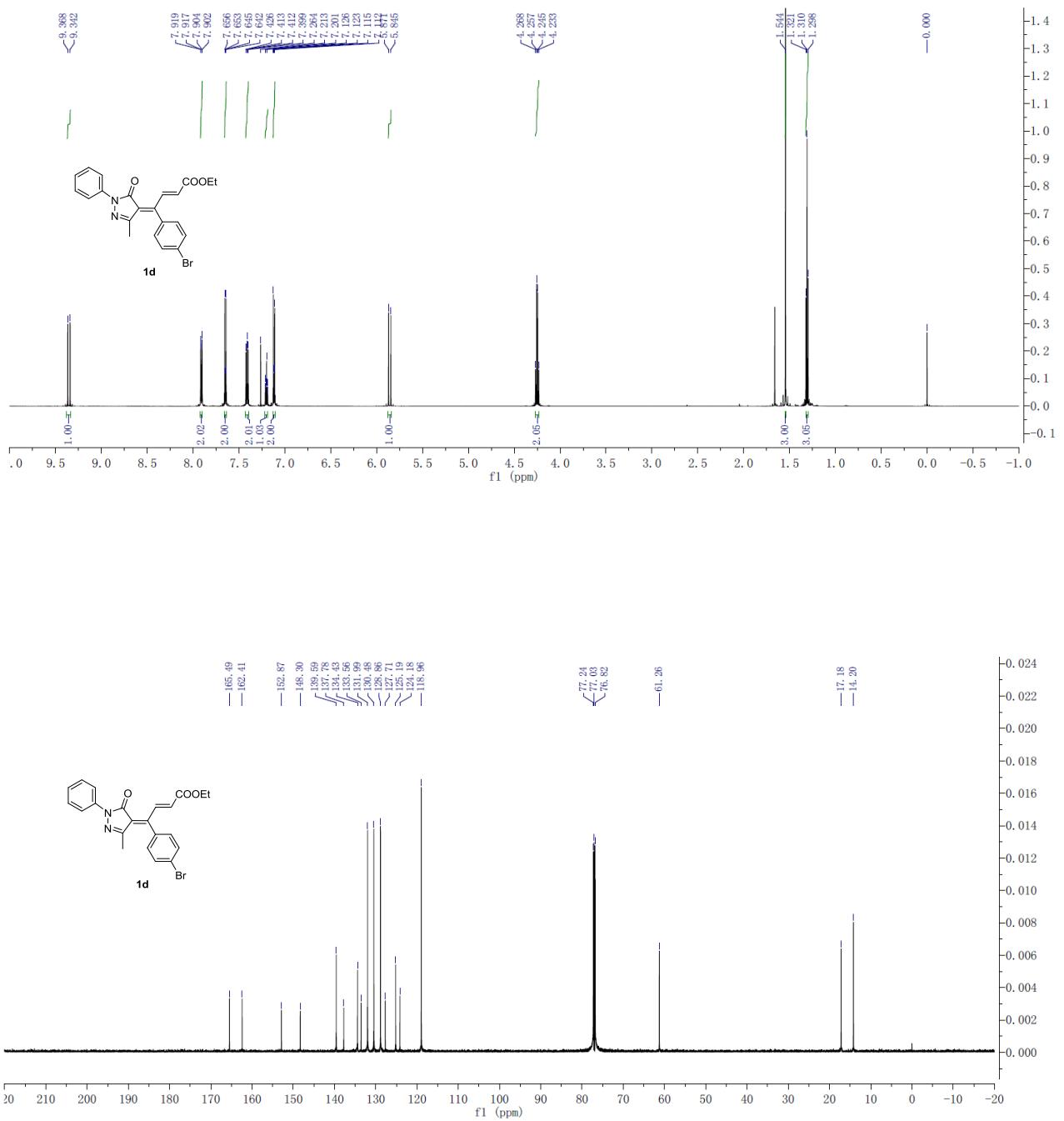
Final R indexes [$I \geq 2\sigma$ (I)] $R_1 = 0.0860$, $wR_2 = 0.1880$
Final R indexes [all data] $R_1 = 0.1485$, $wR_2 = 0.2256$
Largest diff. peak/hole / e Å⁻³ 1.10/-0.32

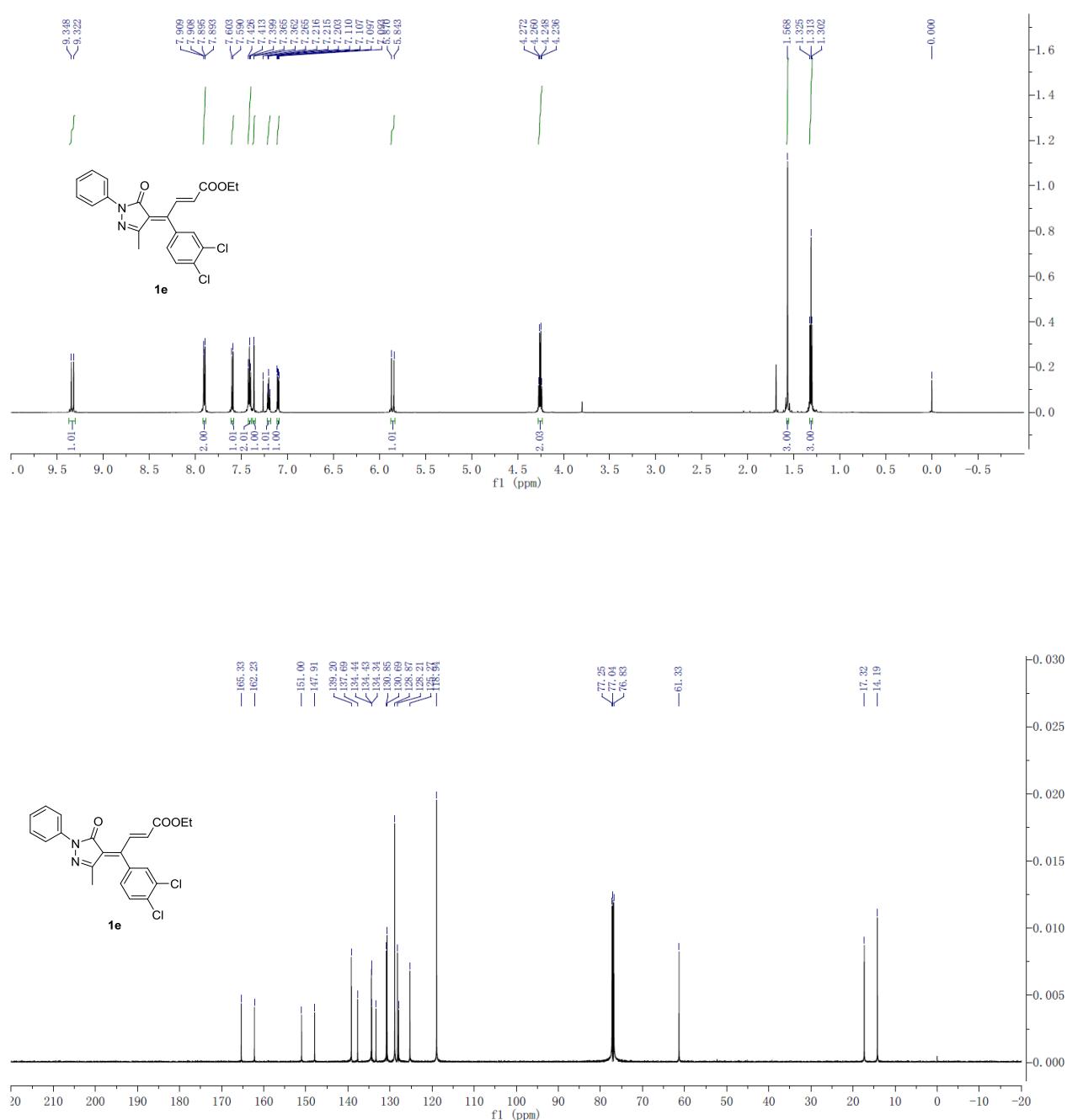
2. NMR spectra and HPLC chromatograms

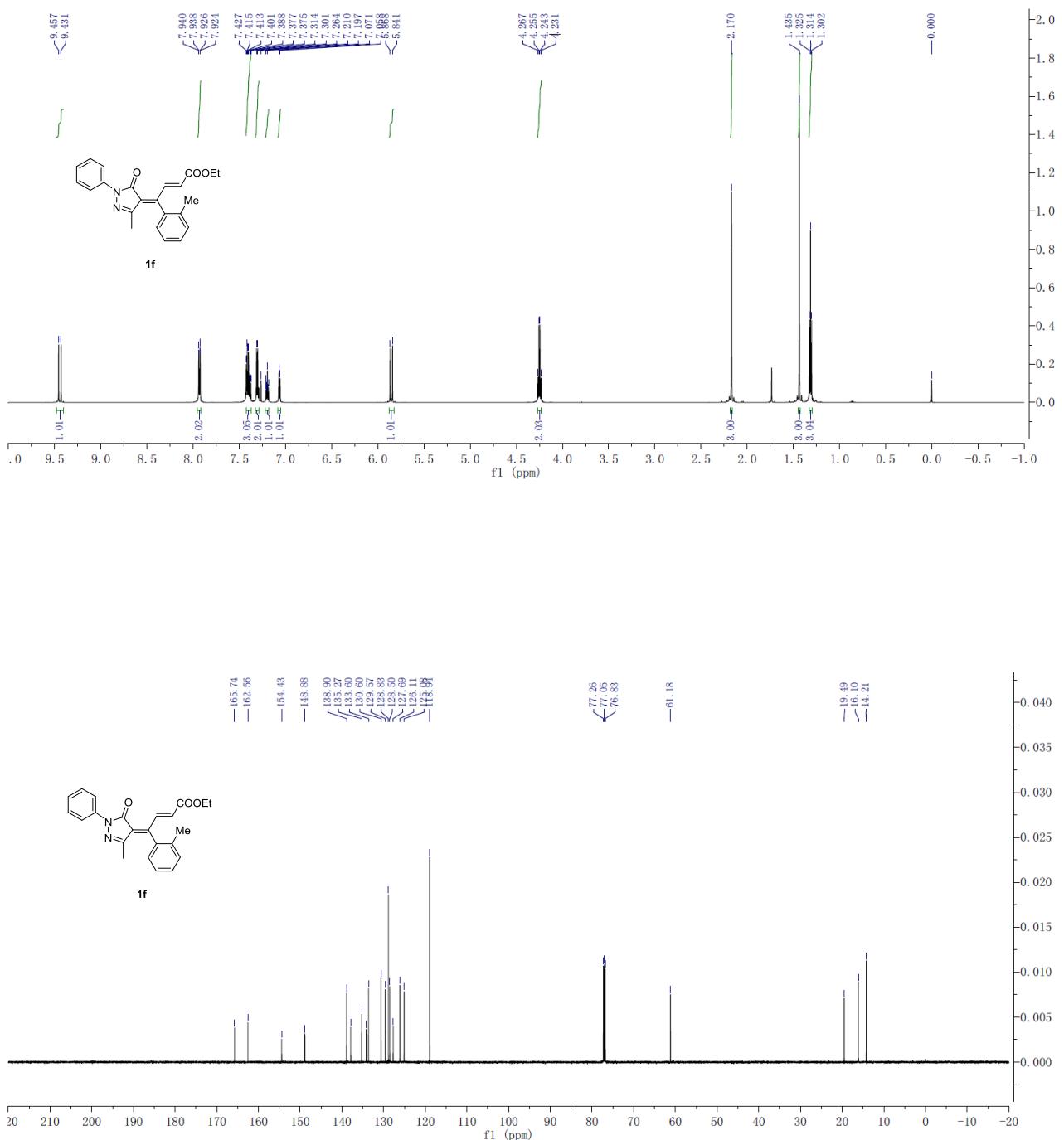


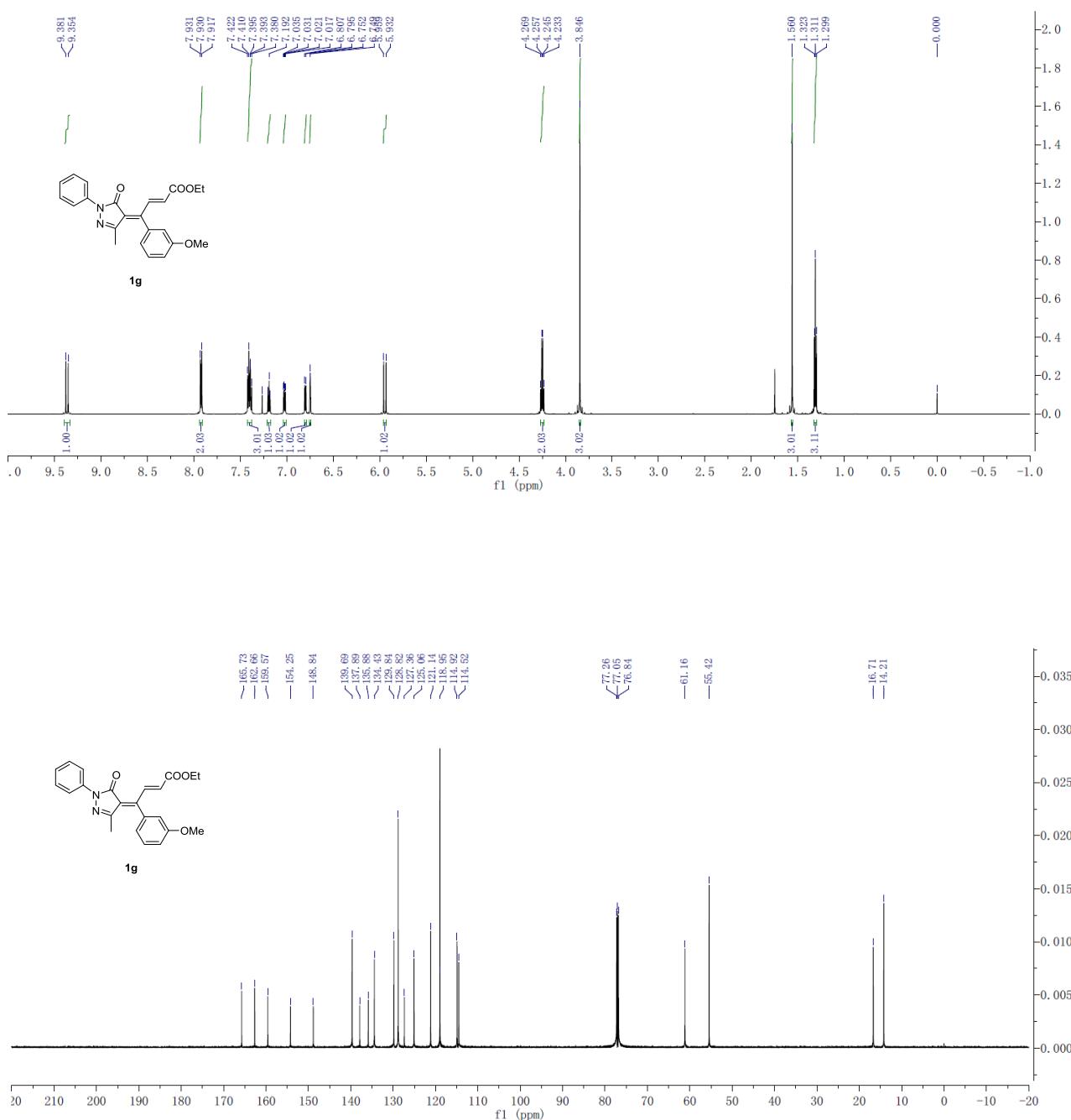


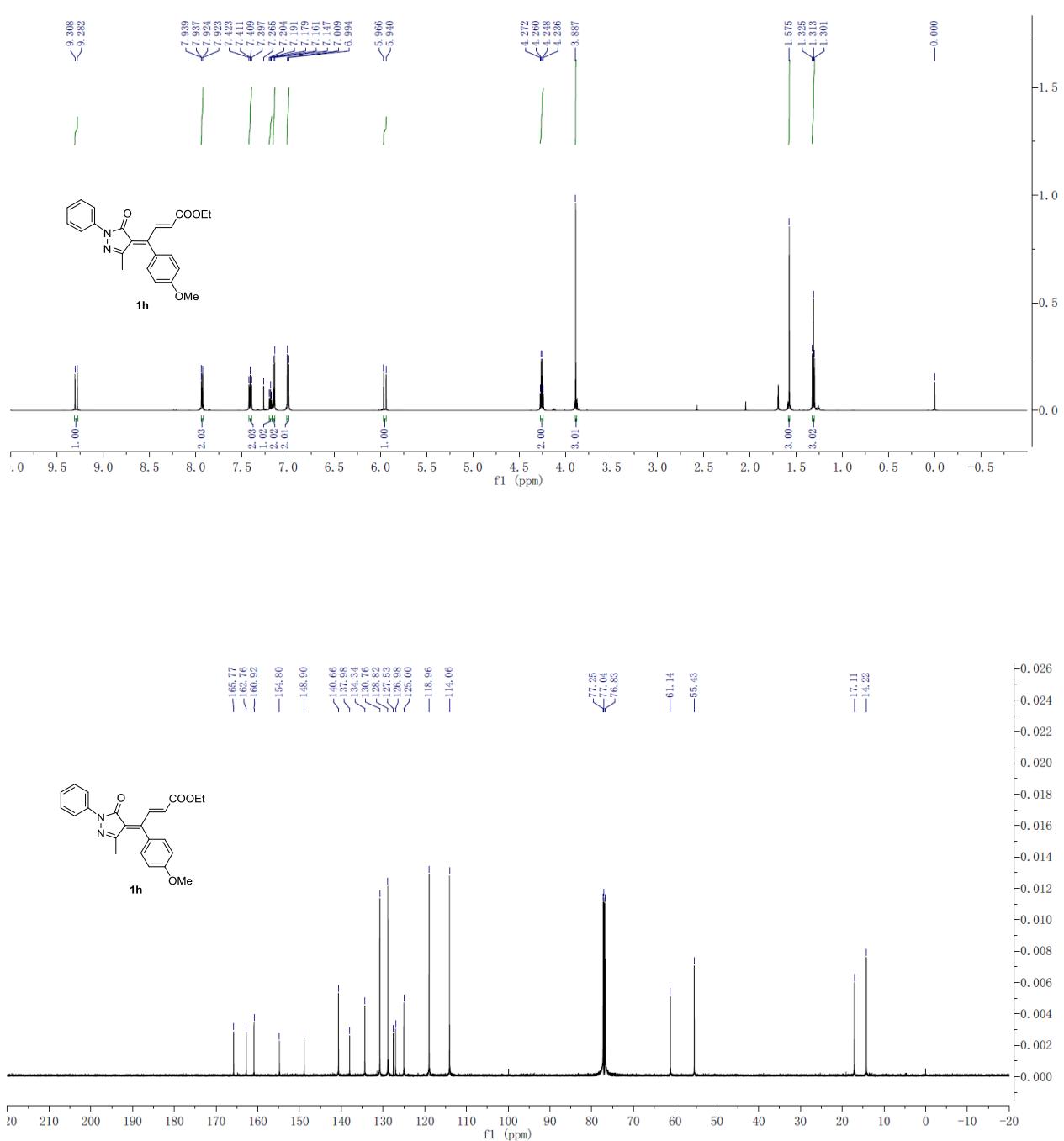


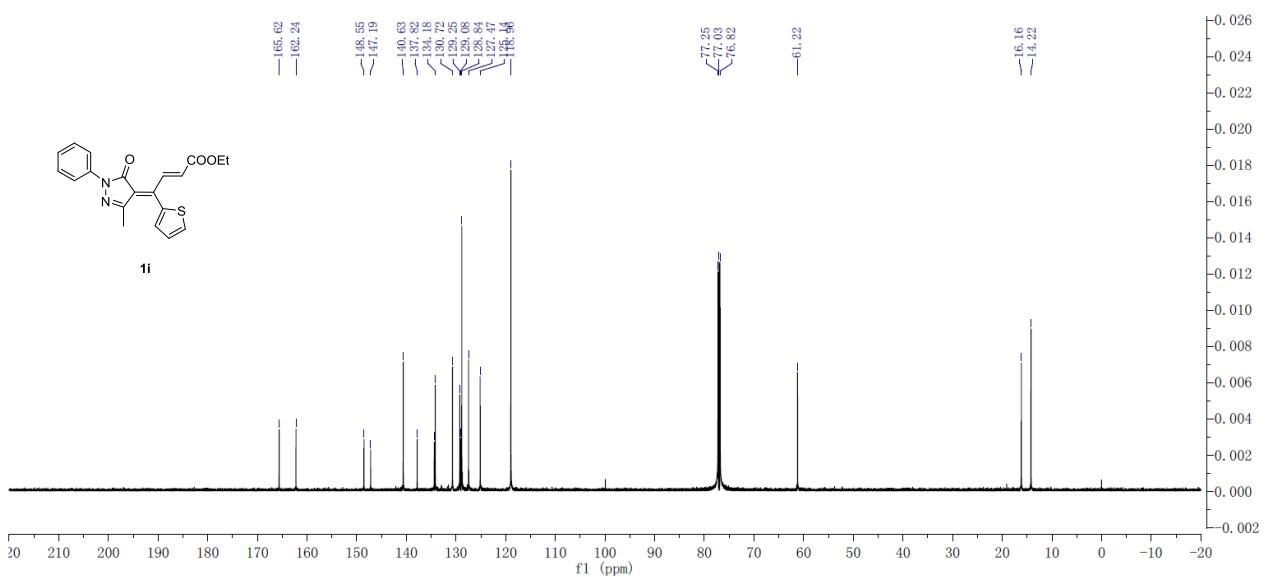
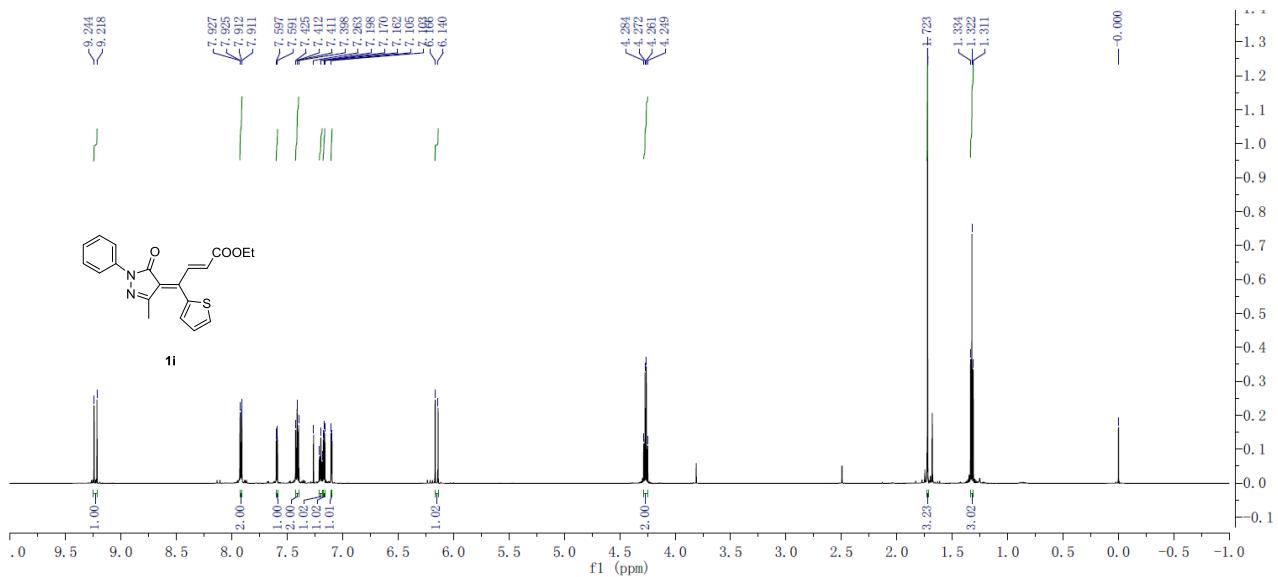


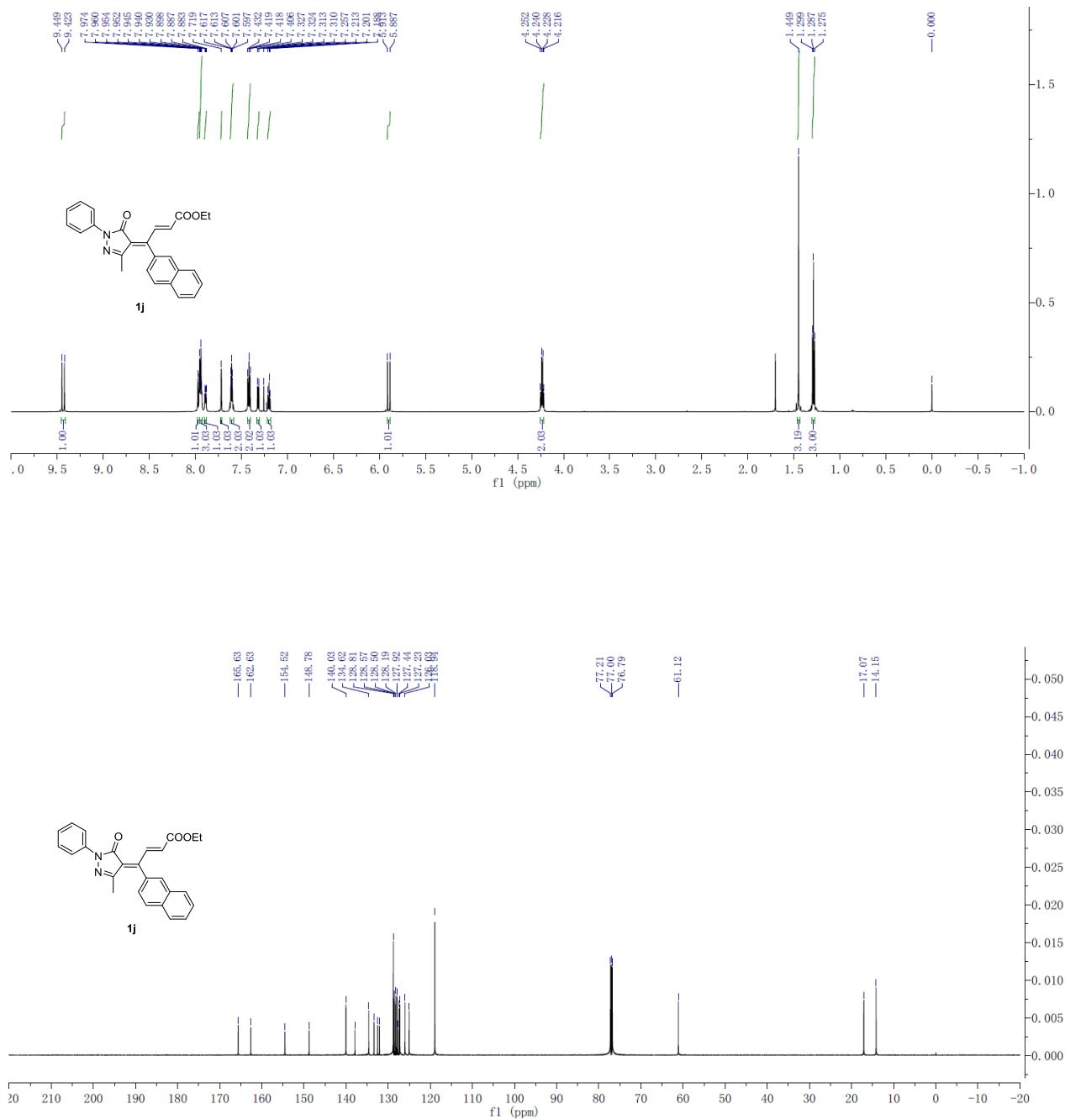


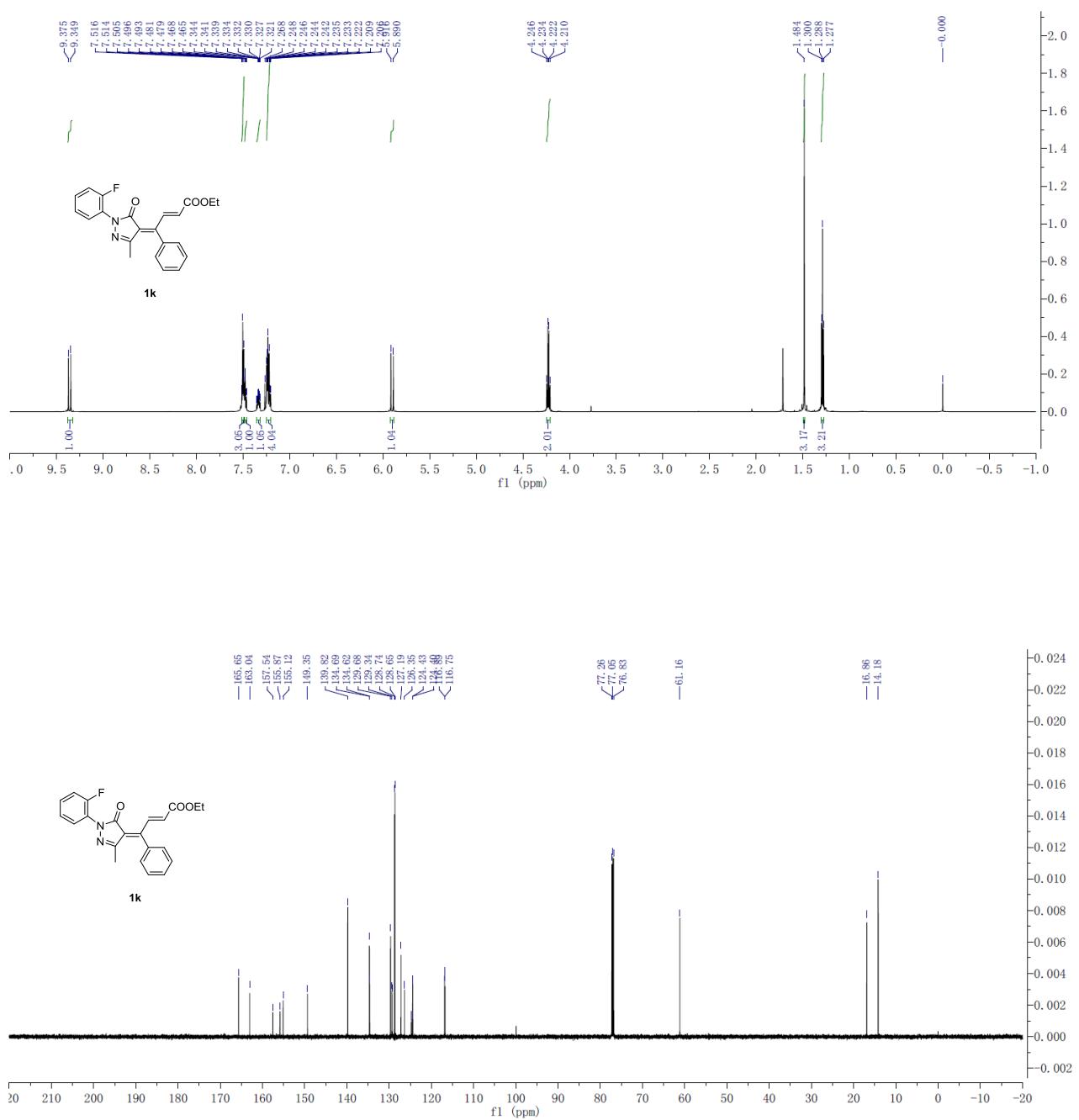


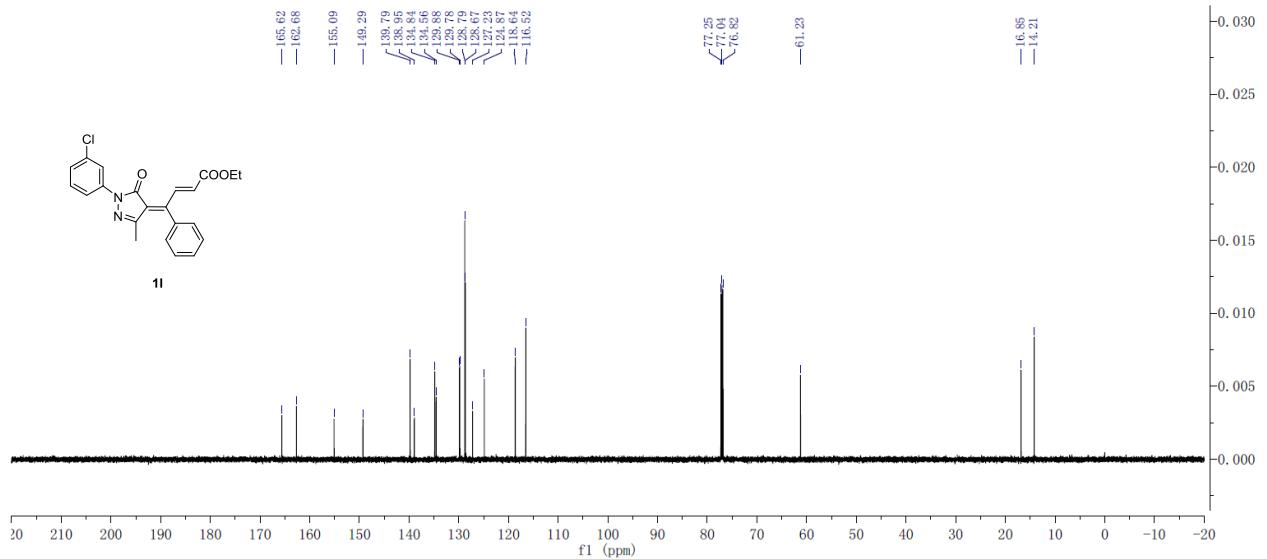
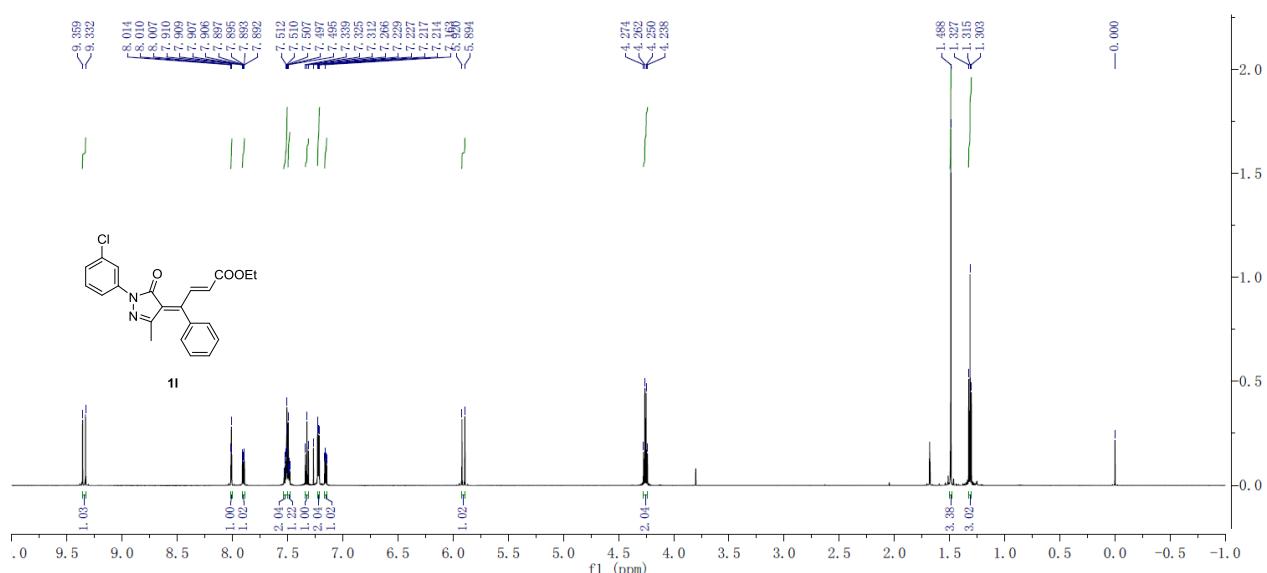


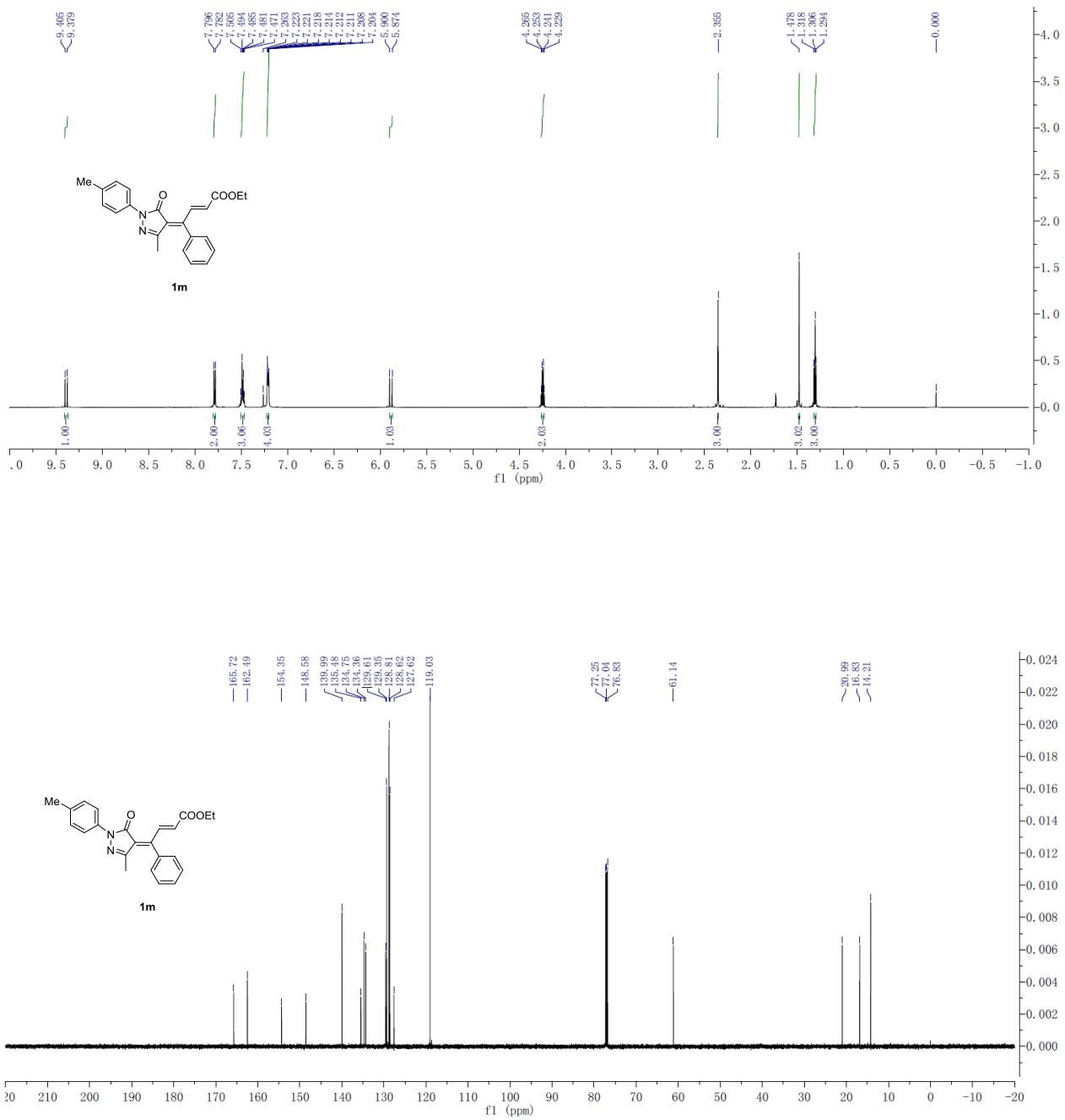


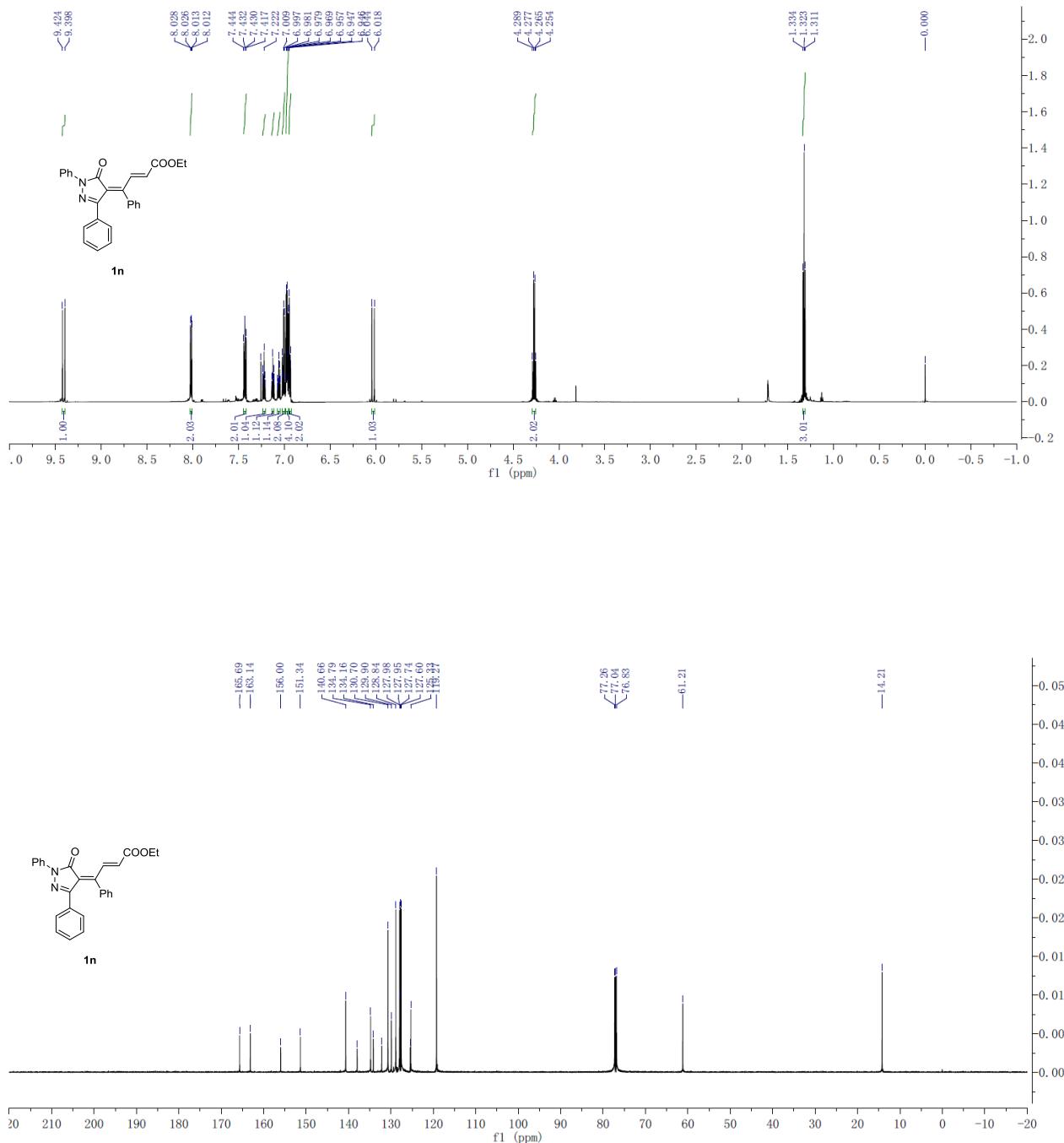


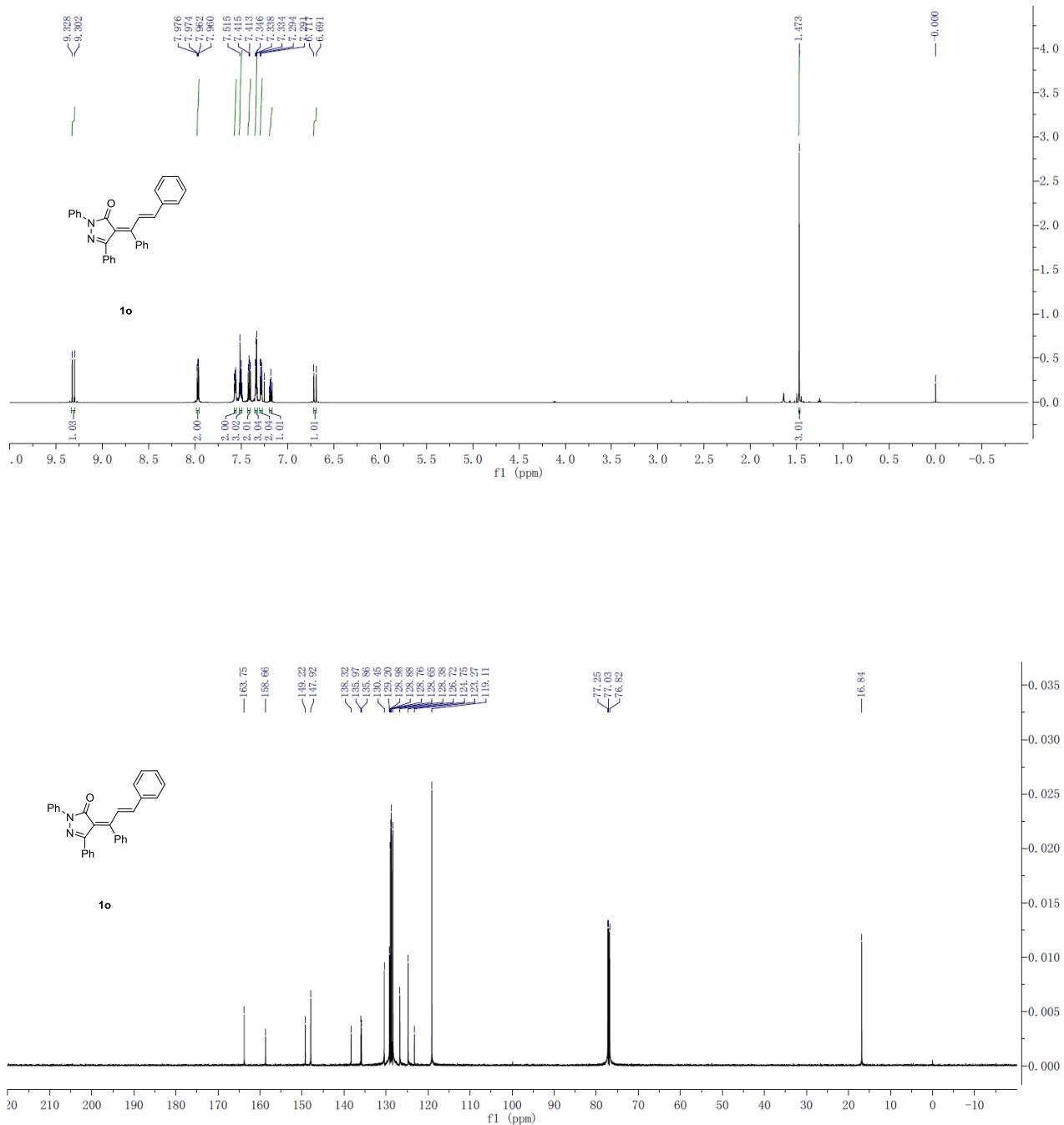


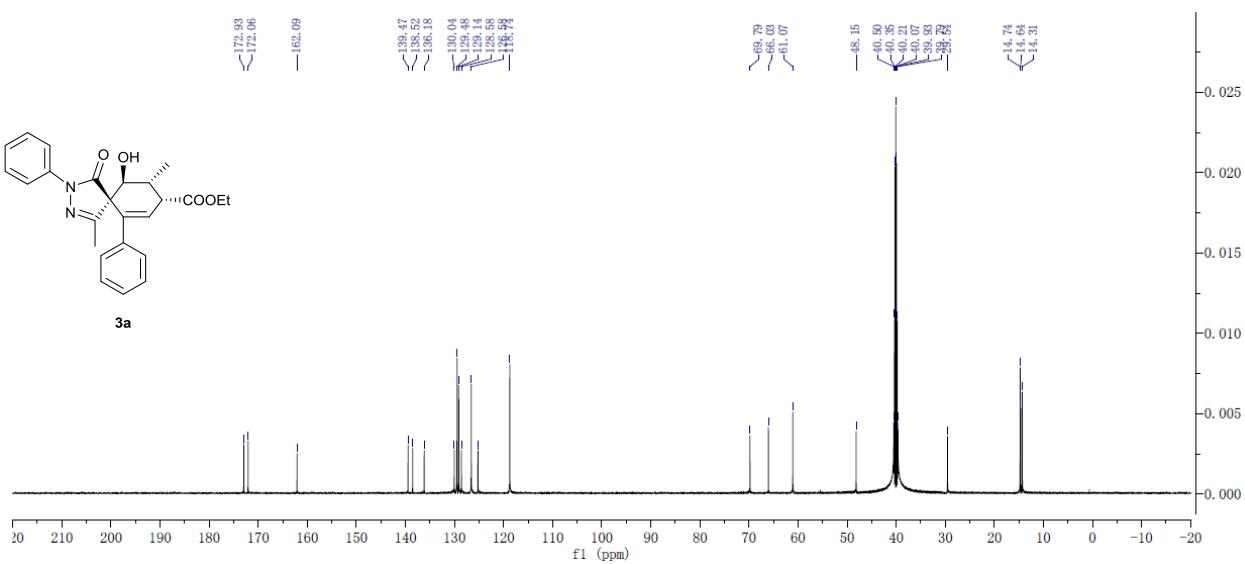
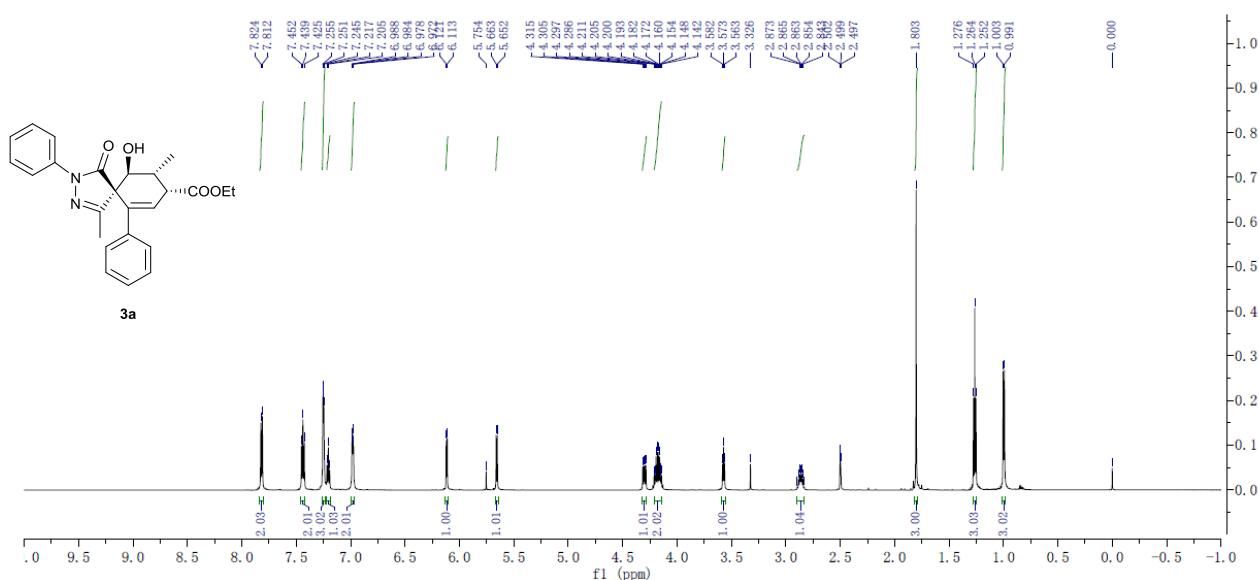


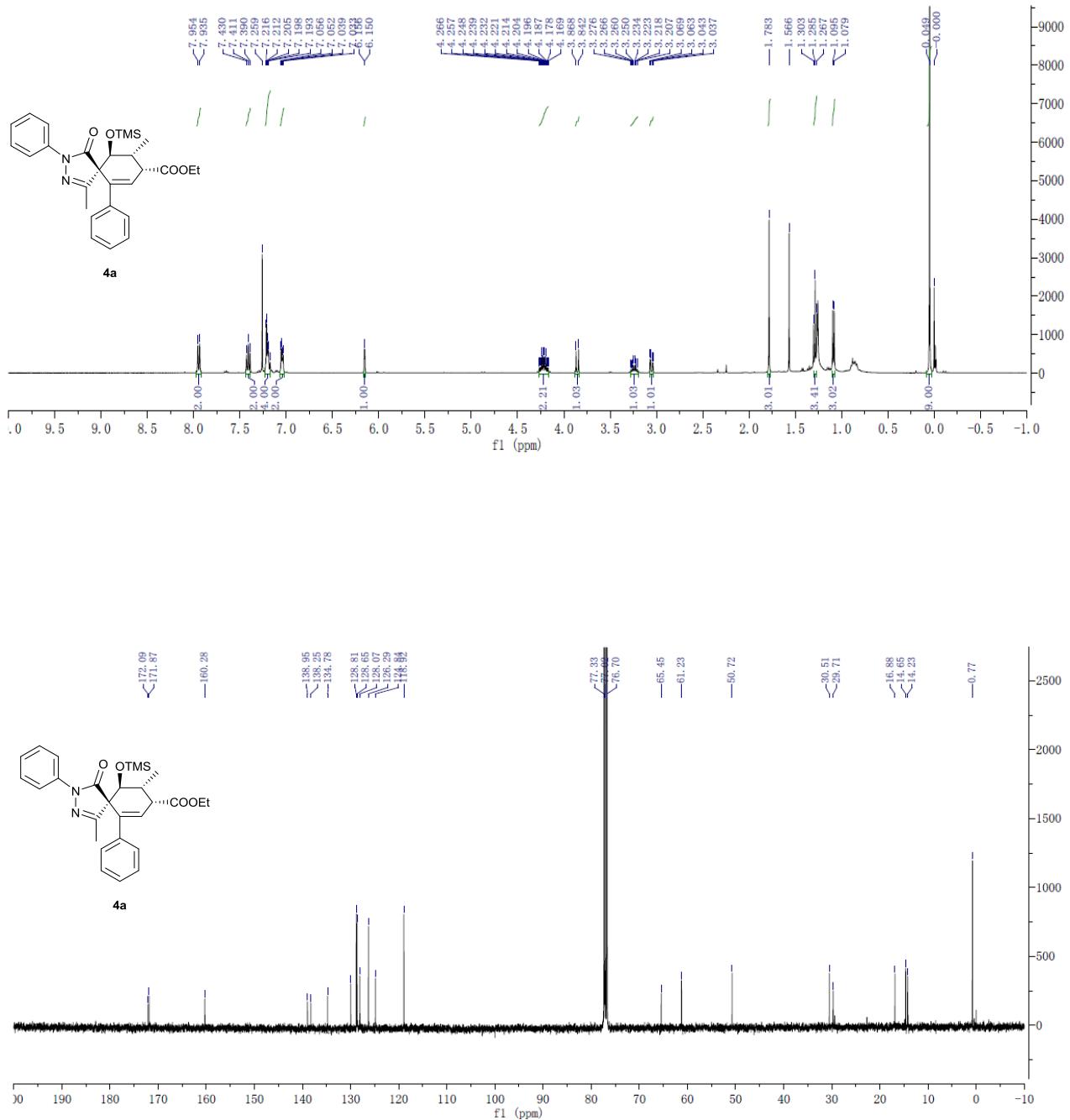








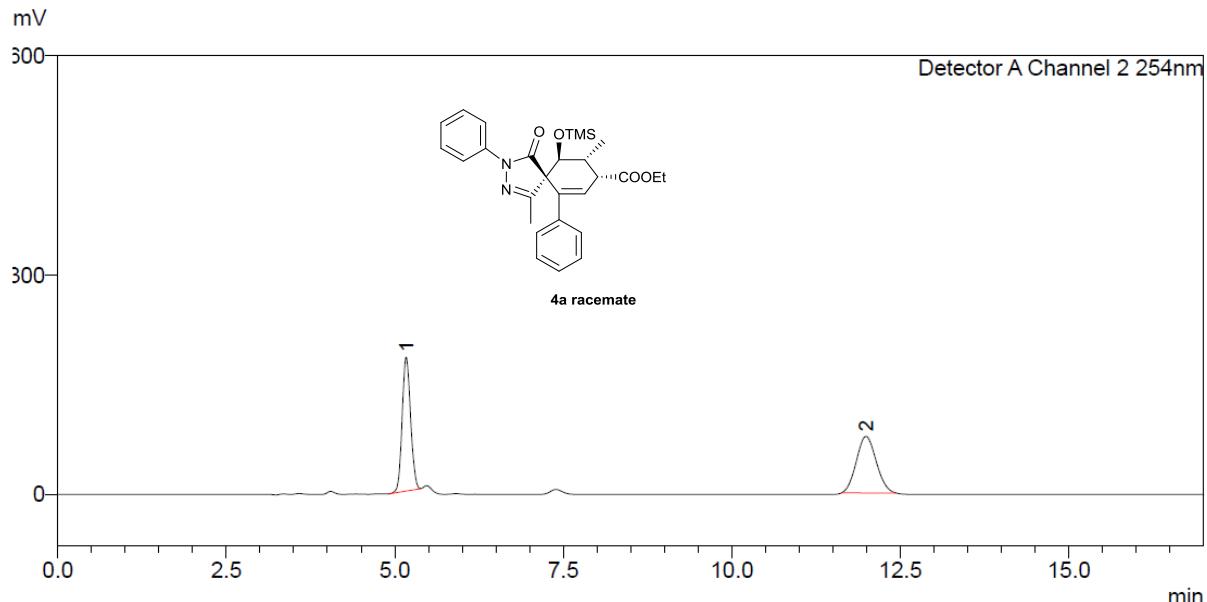




Peak Analysis Report

Detector A Channel 2 254nm

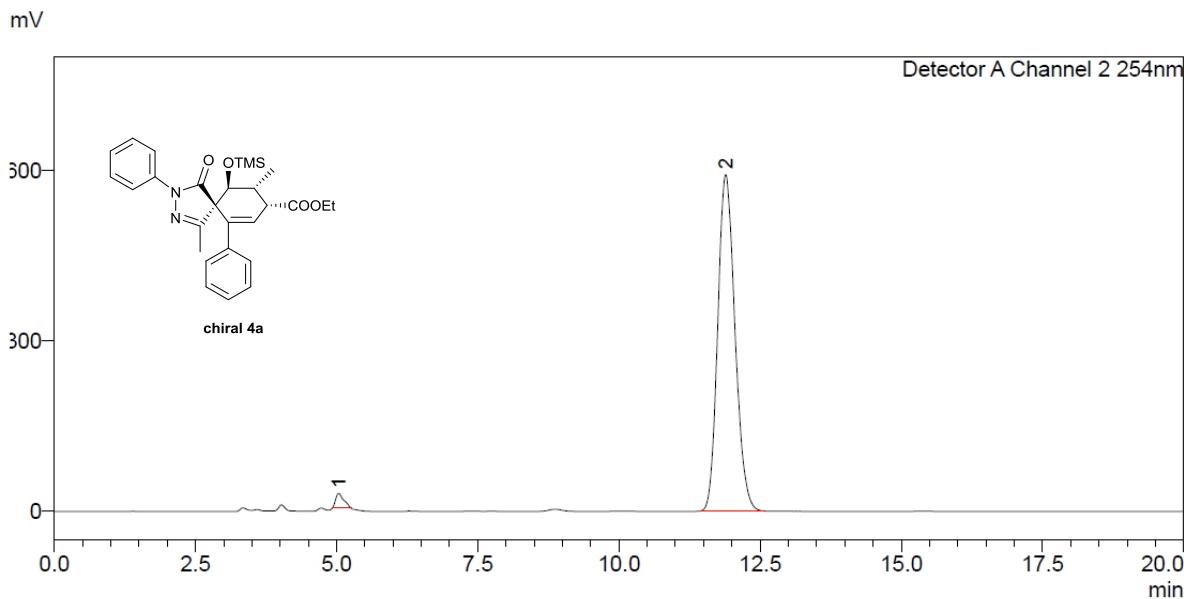
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	5.169	182987	1593958	50.123
2	11.990	77391	1586105	49.877
Total		260378	3180063	100.000

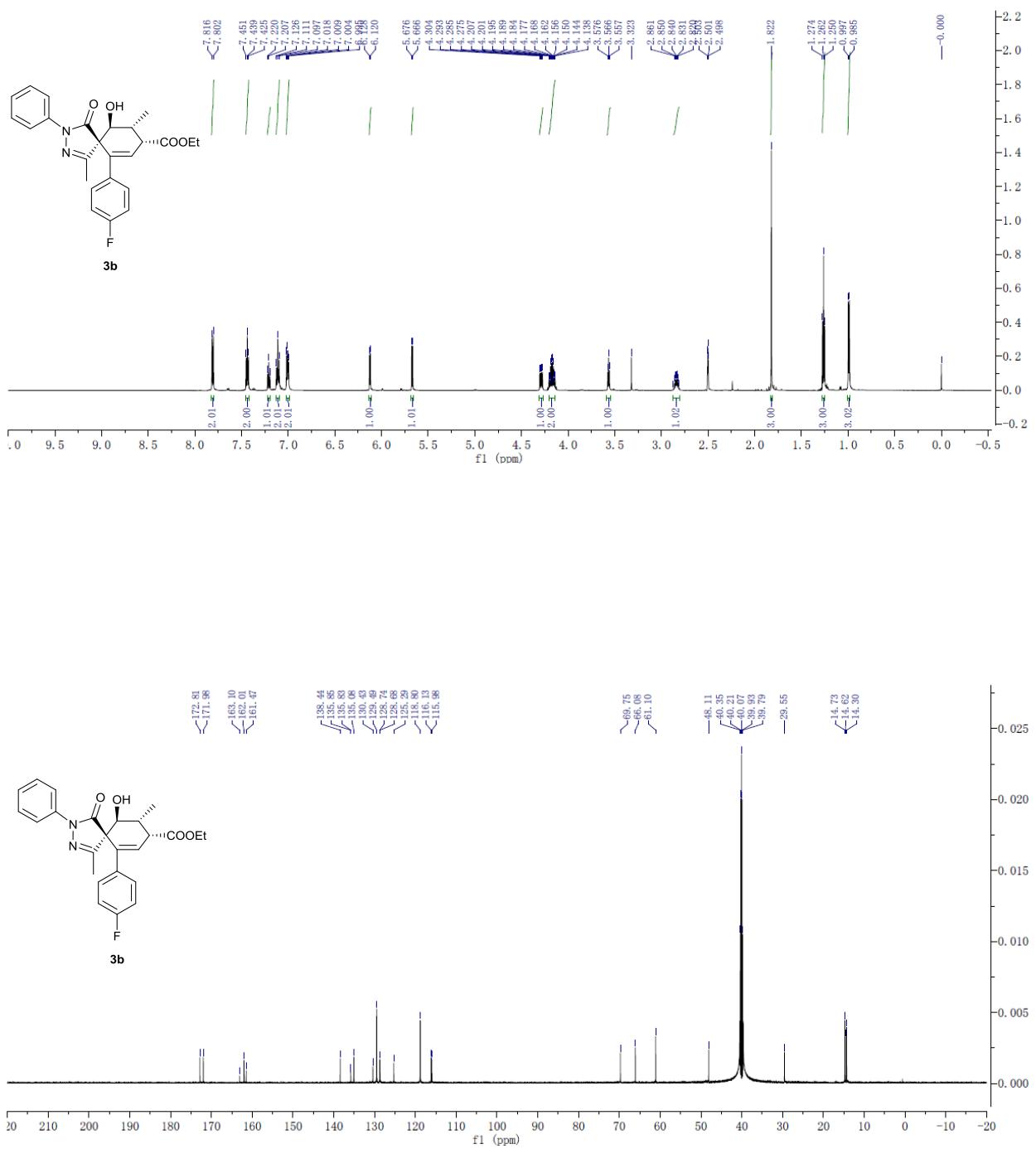


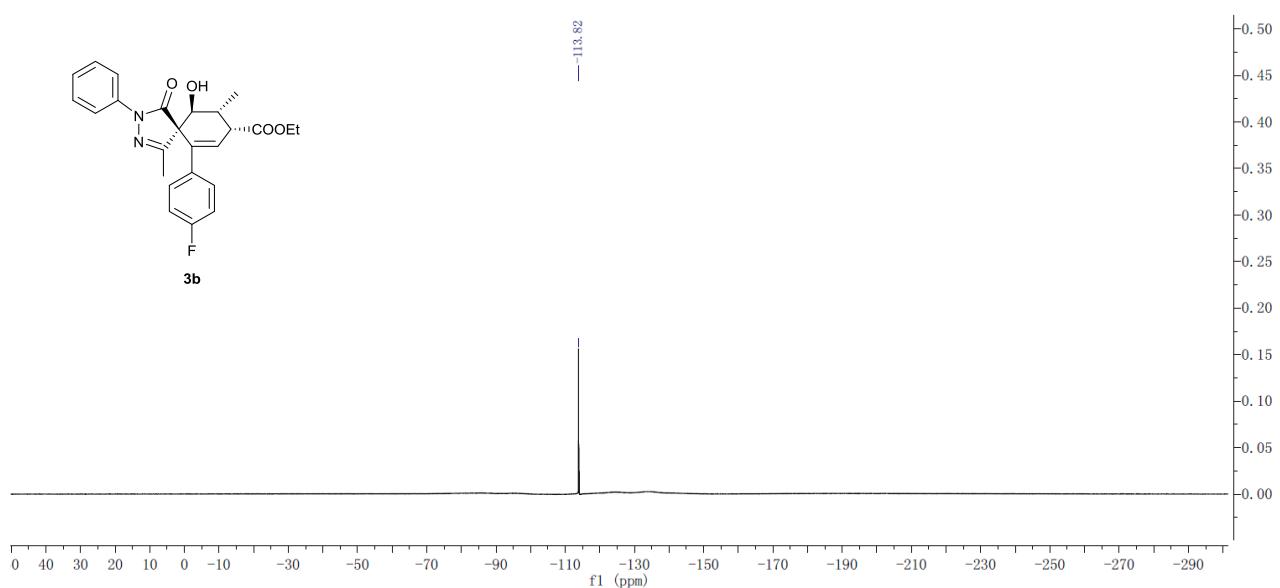
Peak Analysis Report

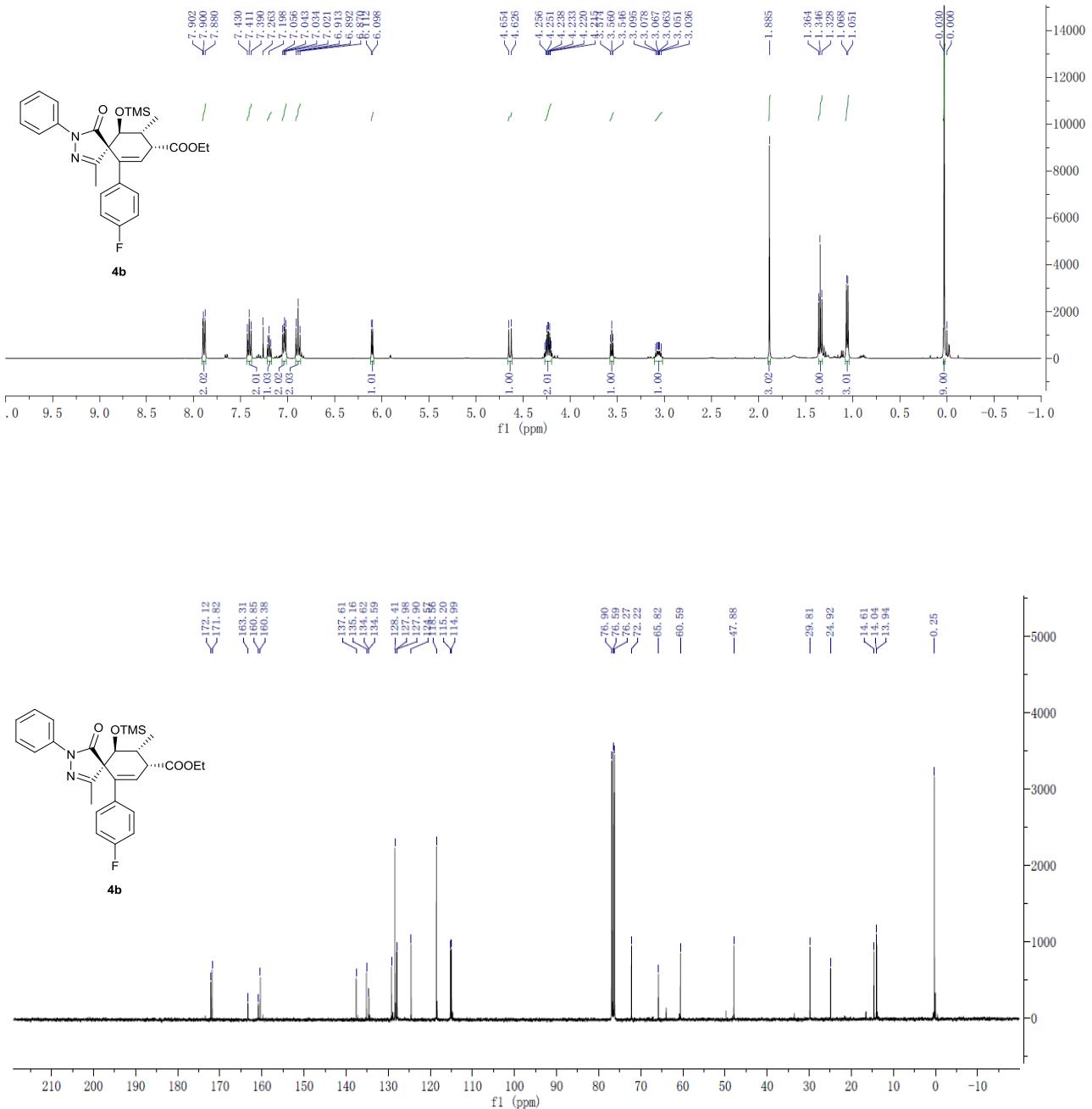
Detector A Channel 2 254nm

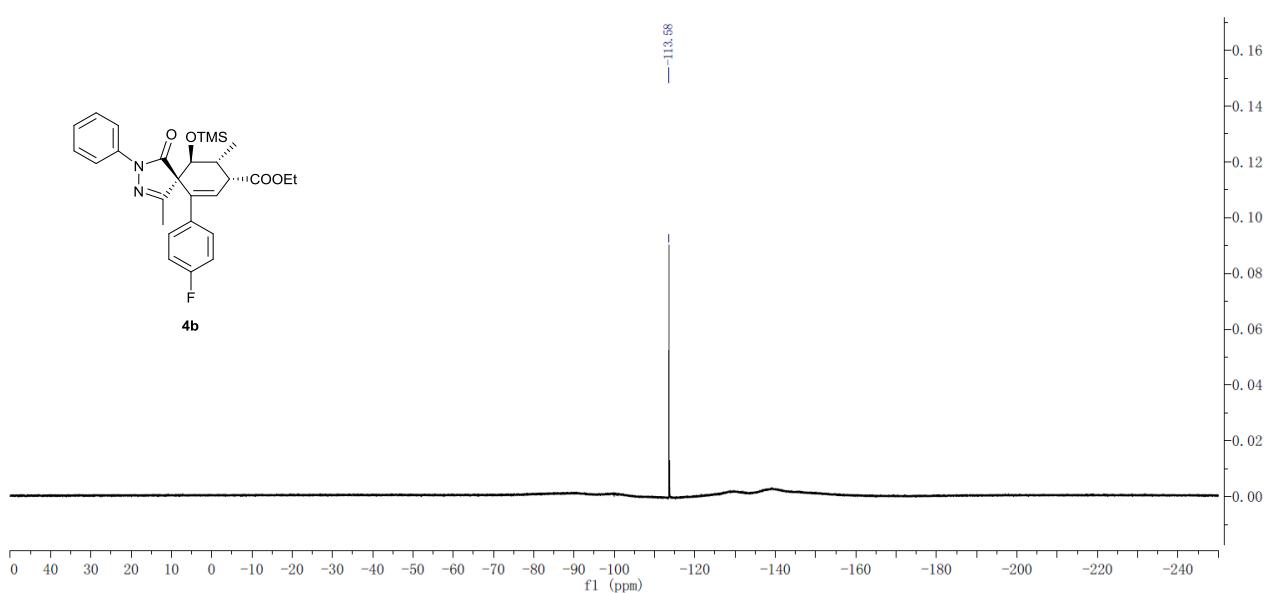
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	5.037	25982	263104	2.050
2	11.889	592176	12572471	97.950
Total		618158	12835575	100.000









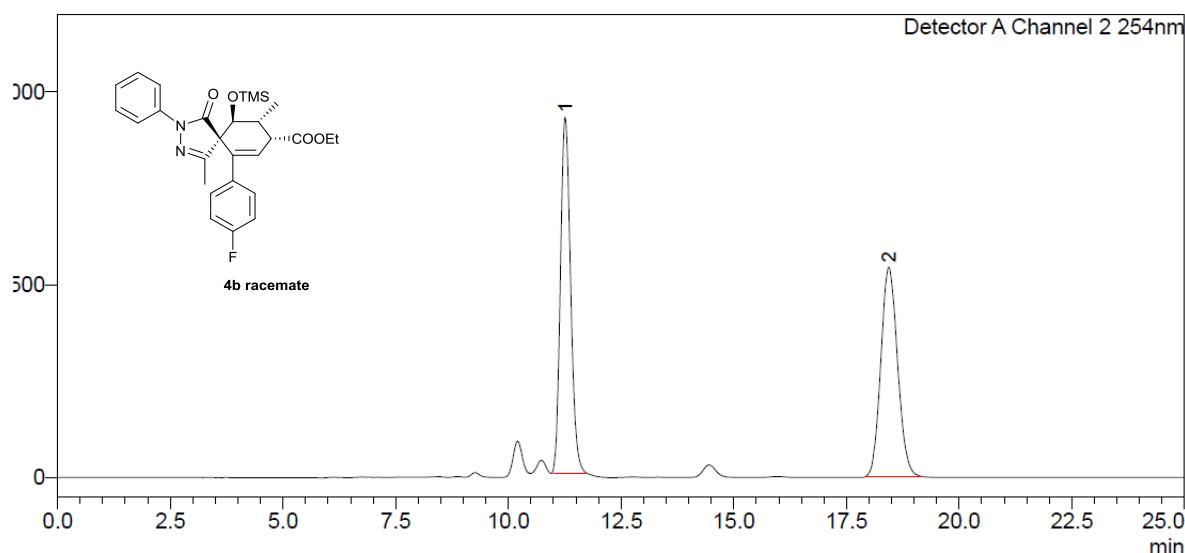


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	11.260	923154	14454926	50.763
2	18.440	542922	14020556	49.237
Total		1466076	28475482	100.000

mV

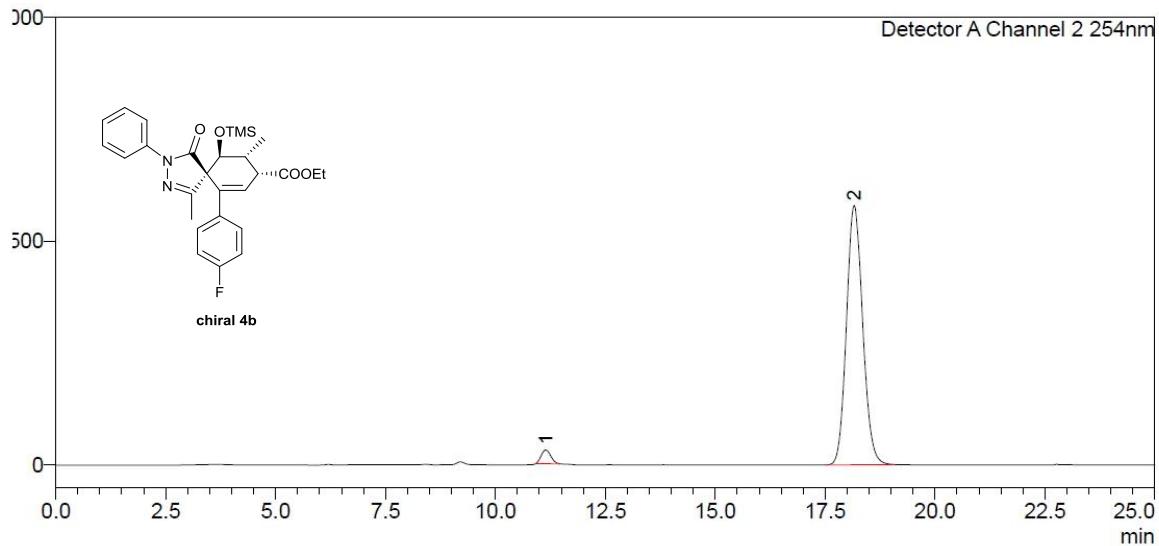


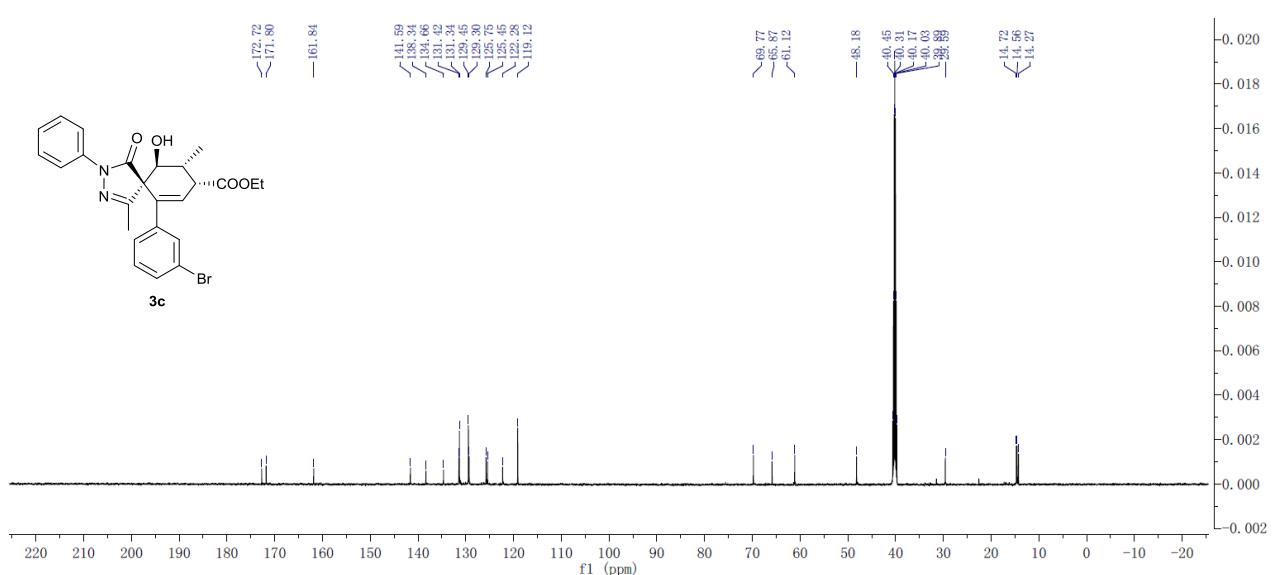
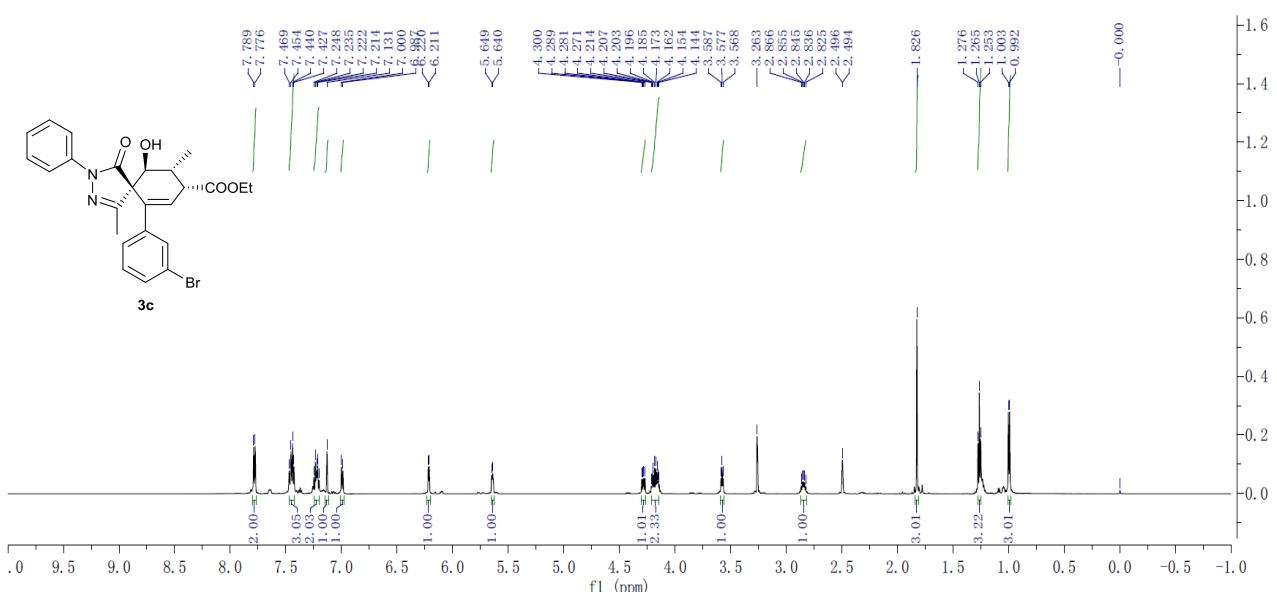
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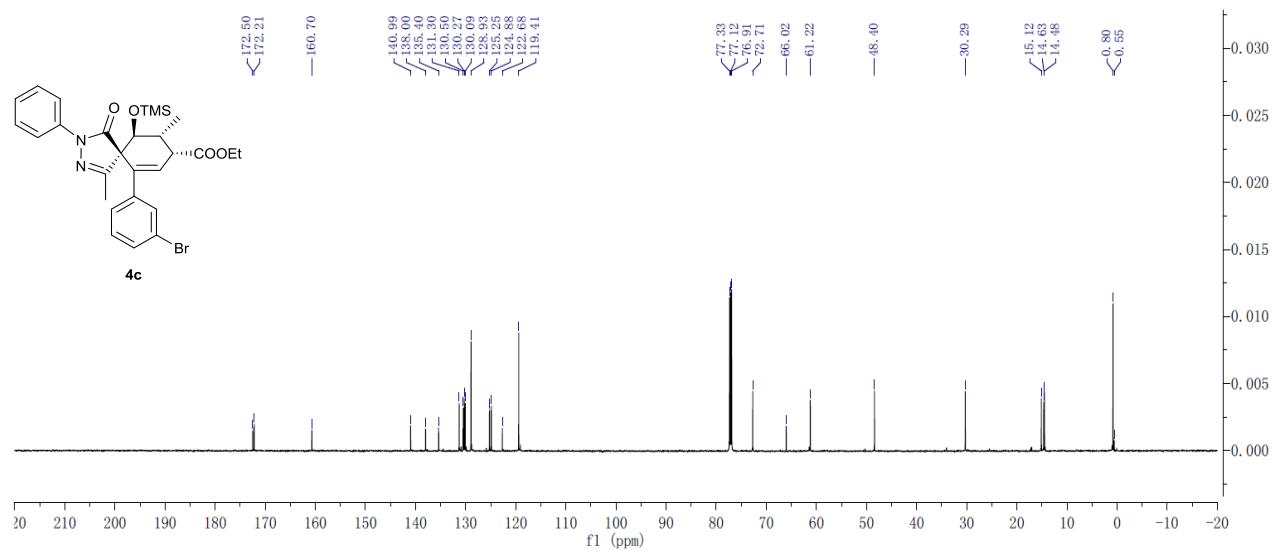
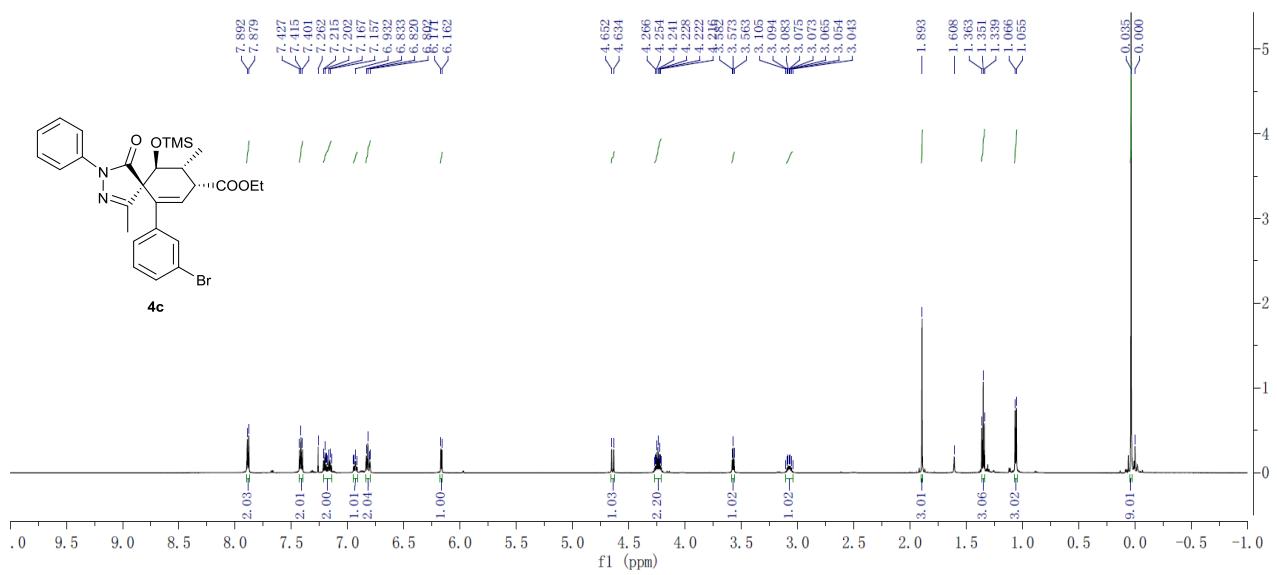
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	11.146	30780	465526	3.027
2	18.162	579049	14916062	96.973
Total		609828	15381588	100.000

mV





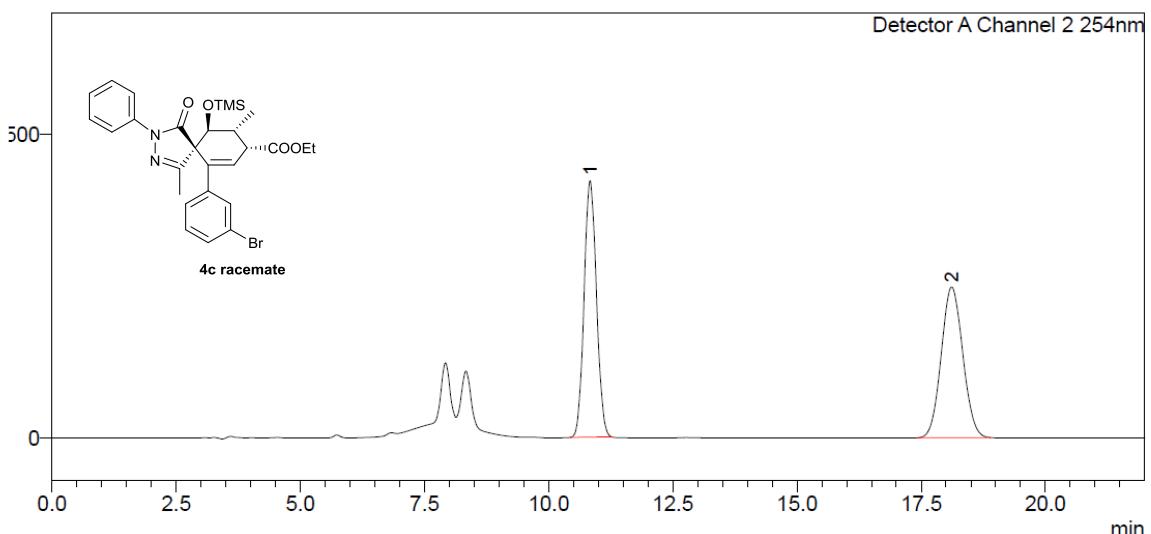


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.835	422545	7307583	49.405
2	18.114	248226	7483612	50.595
Total		670771	14791195	100.000

mV

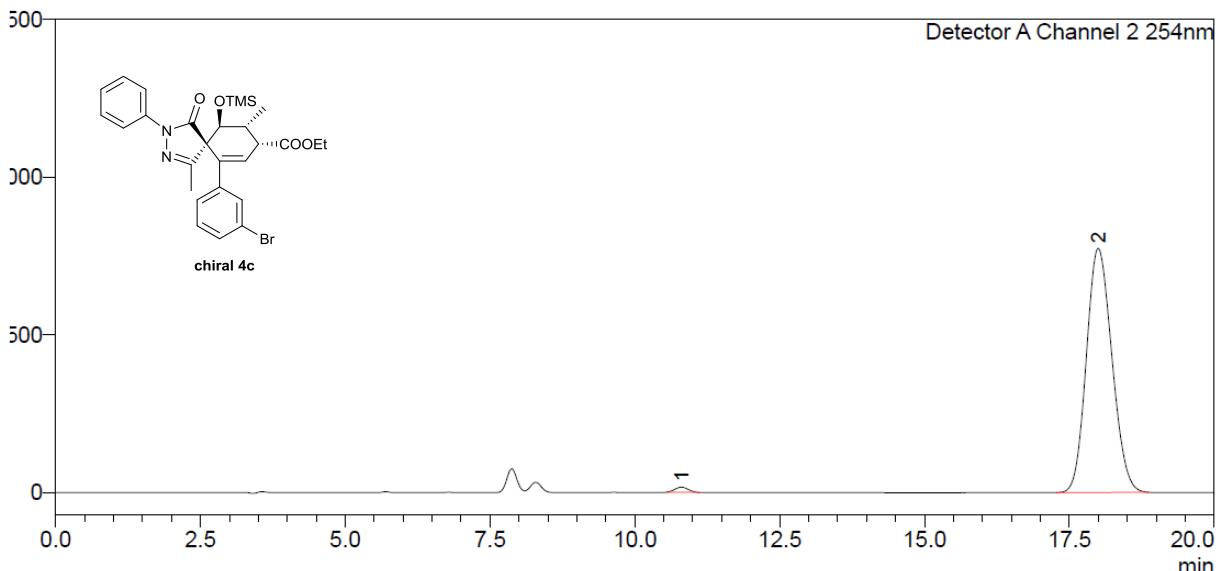


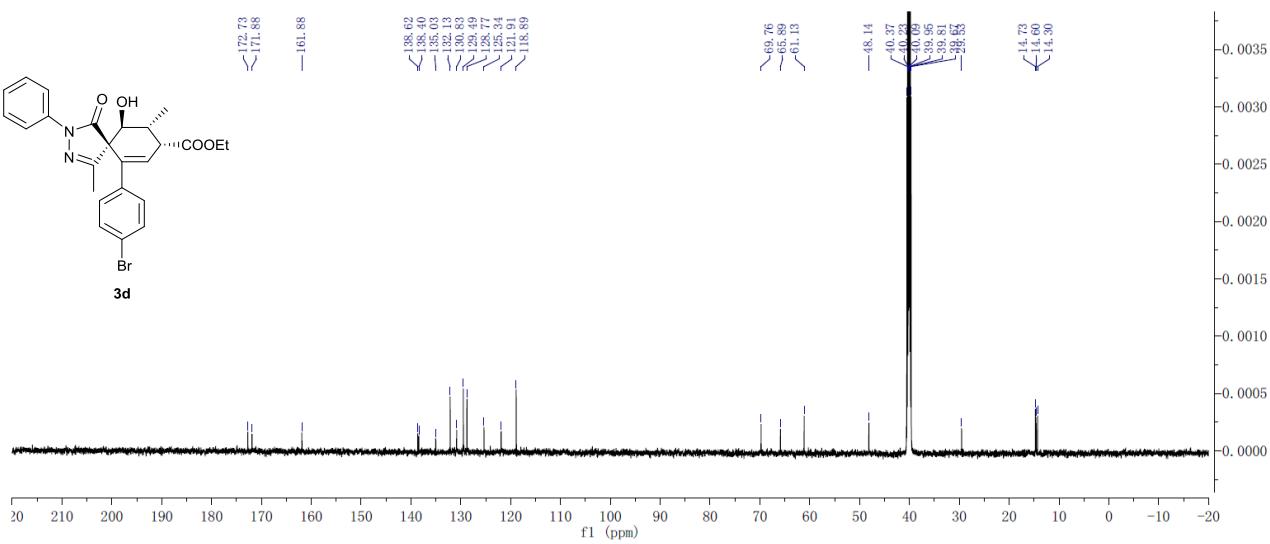
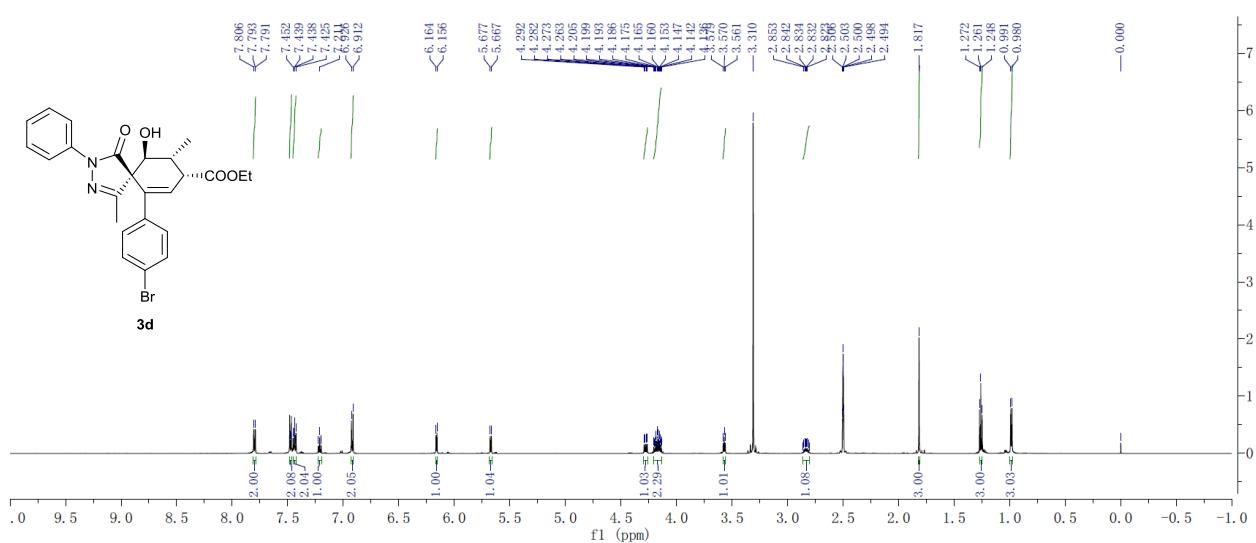
Peak Analysis Report

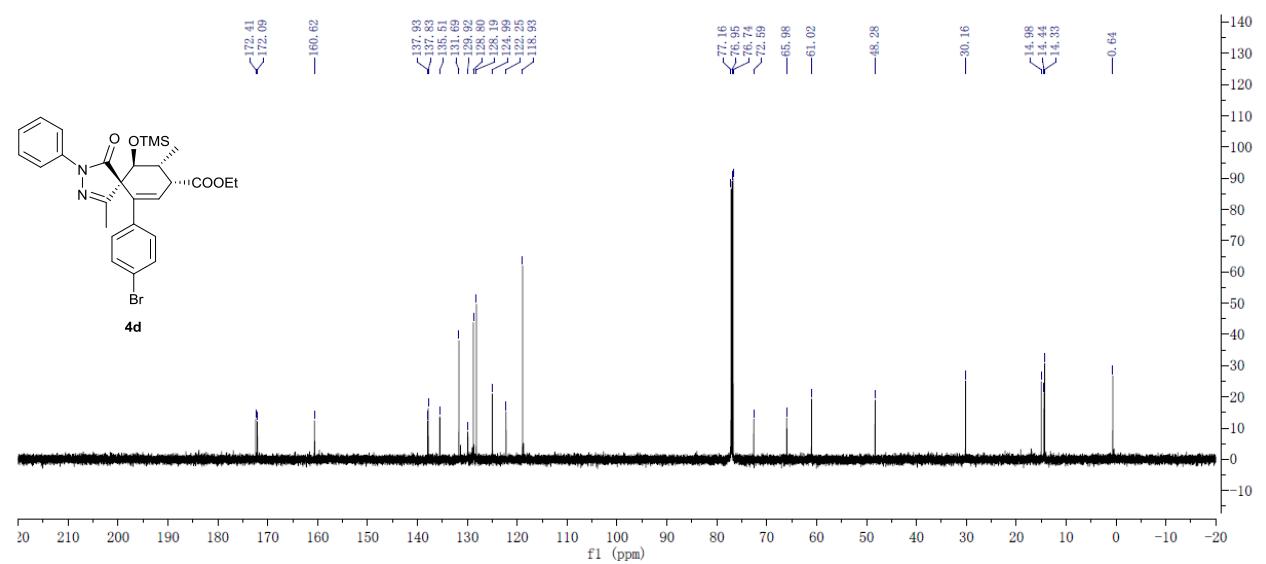
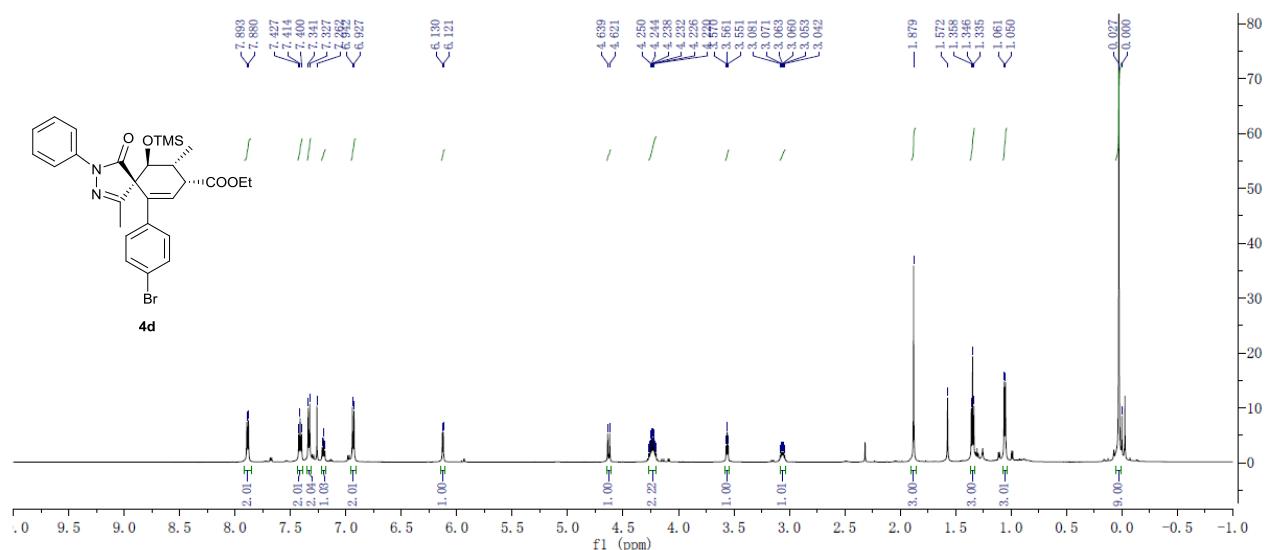
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.803	16125	256815	1.071
2	17.997	773577	23717599	98.929
Total		789702	23974414	100.000

mV



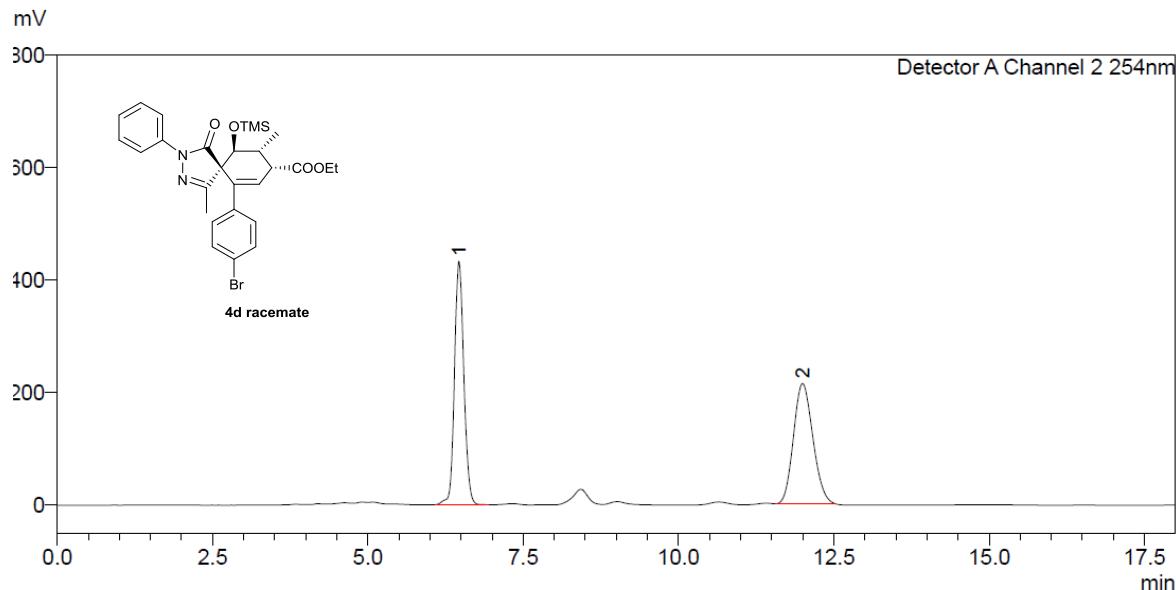




Peak Analysis Report

Detector A Channel 2 254nm

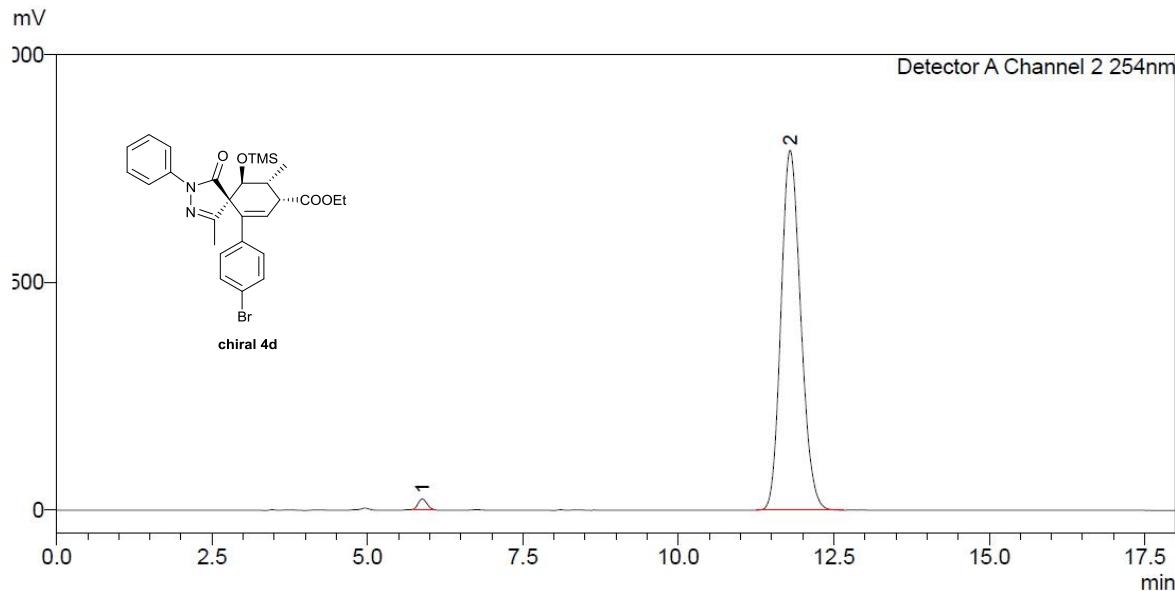
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	6.465	432807	4551080	49.532
2	11.997	213552	4637124	50.468
Total		646359	9188204	100.000

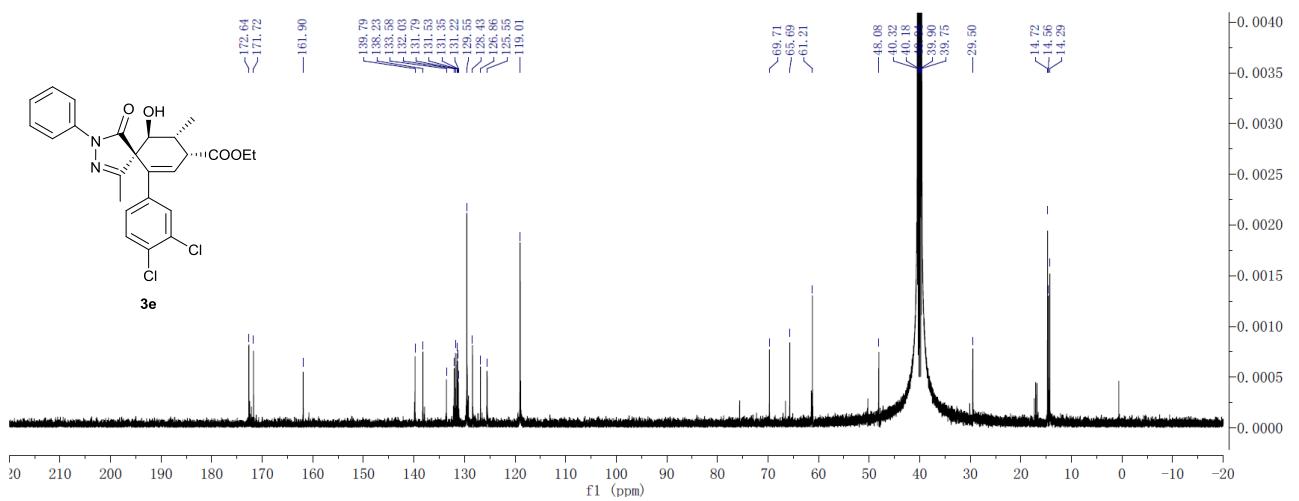
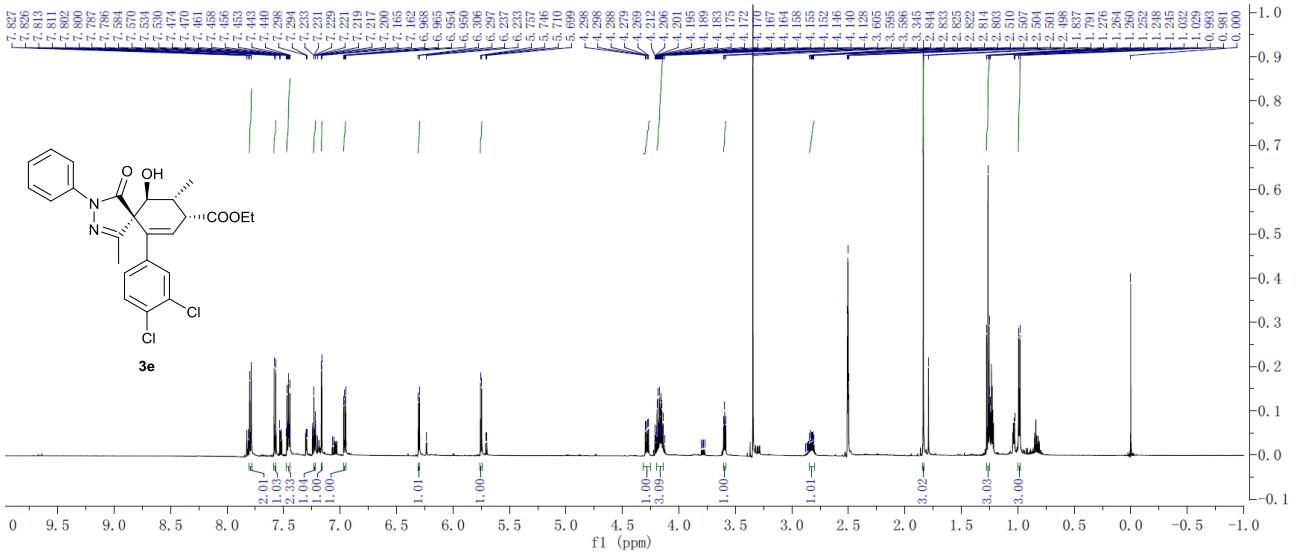


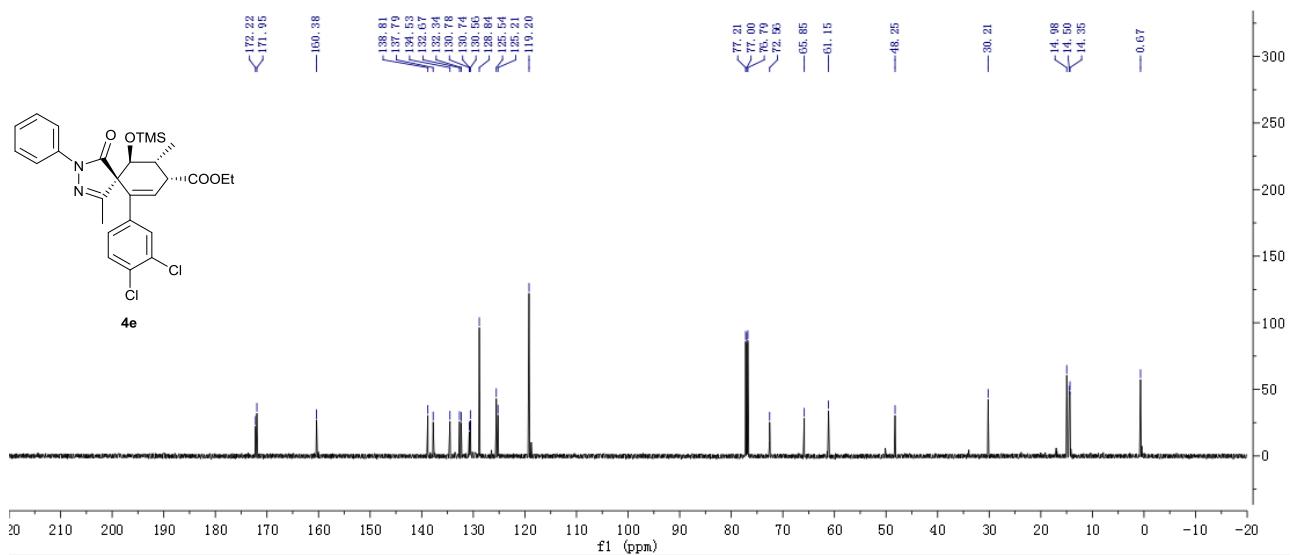
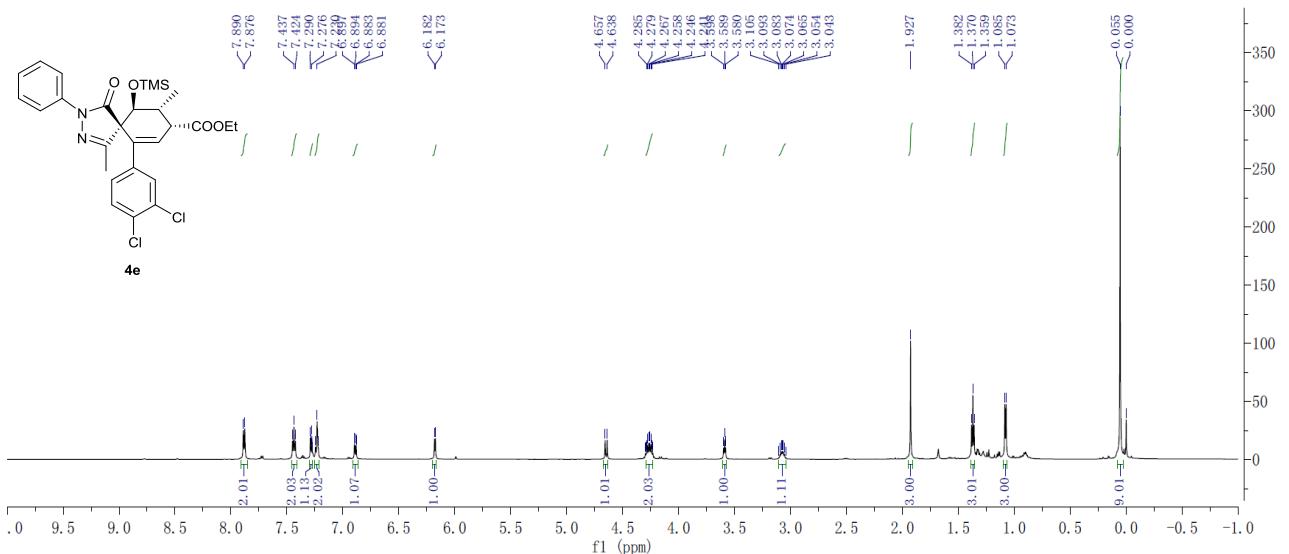
Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	5.882	23599	229069	1.294
2	11.798	790342	17470673	98.706
Total		813941	17699743	100.000



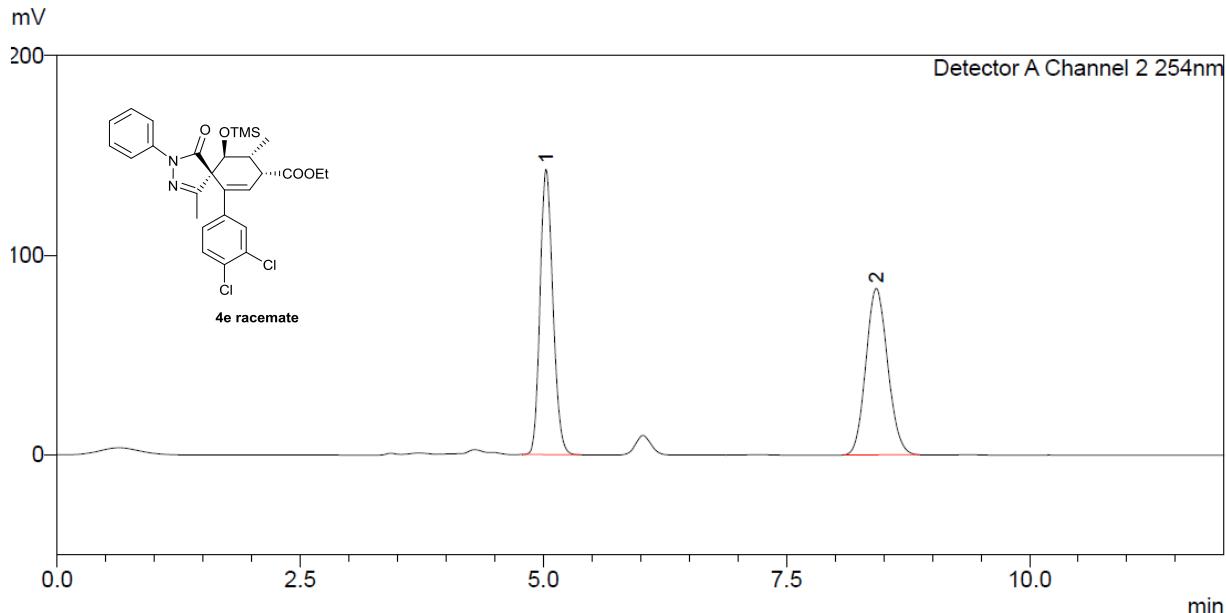




Peak Analysis Report

Detector A Channel 2 254nm

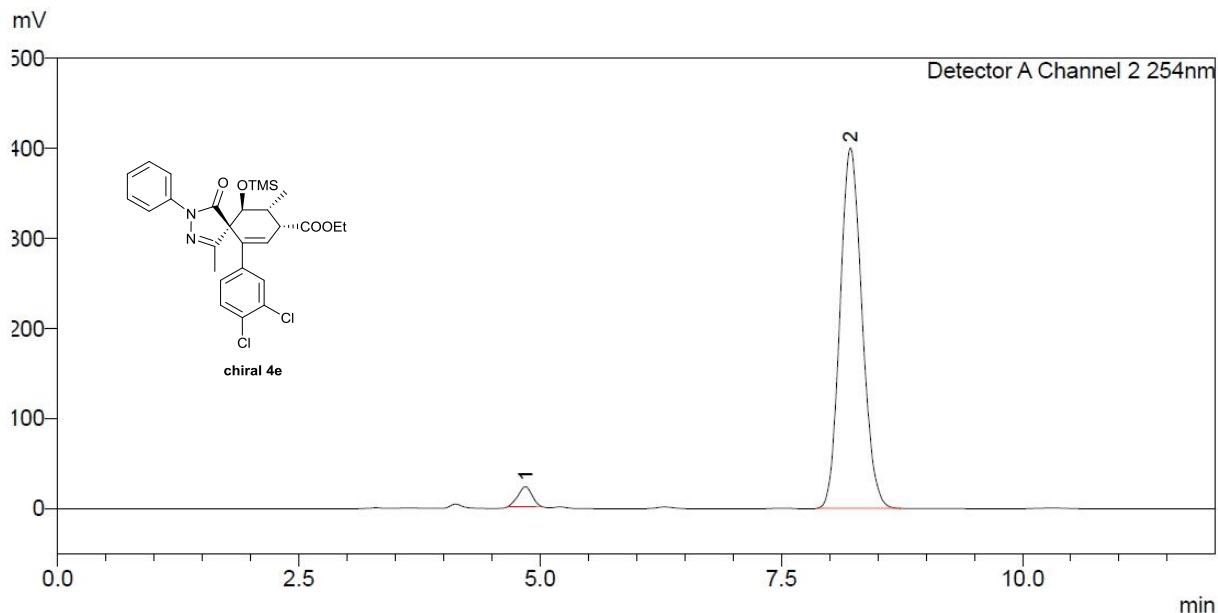
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	5.028	142930	1316670	50.298
2	8.424	83373	1301045	49.702
Total		226303	2617715	100.000

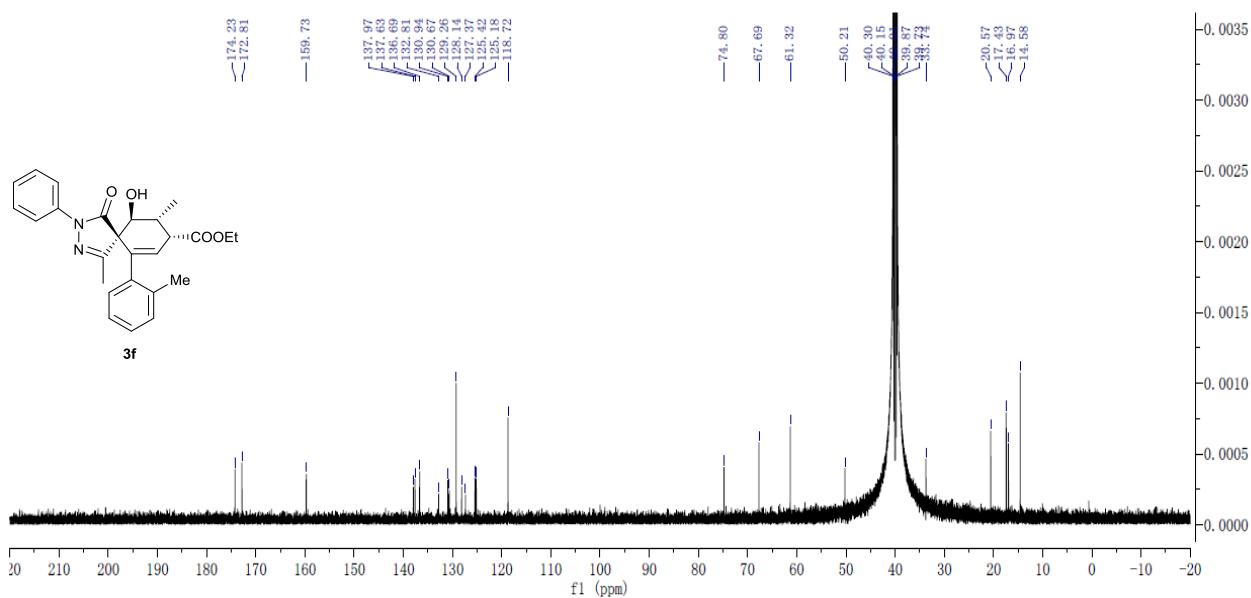
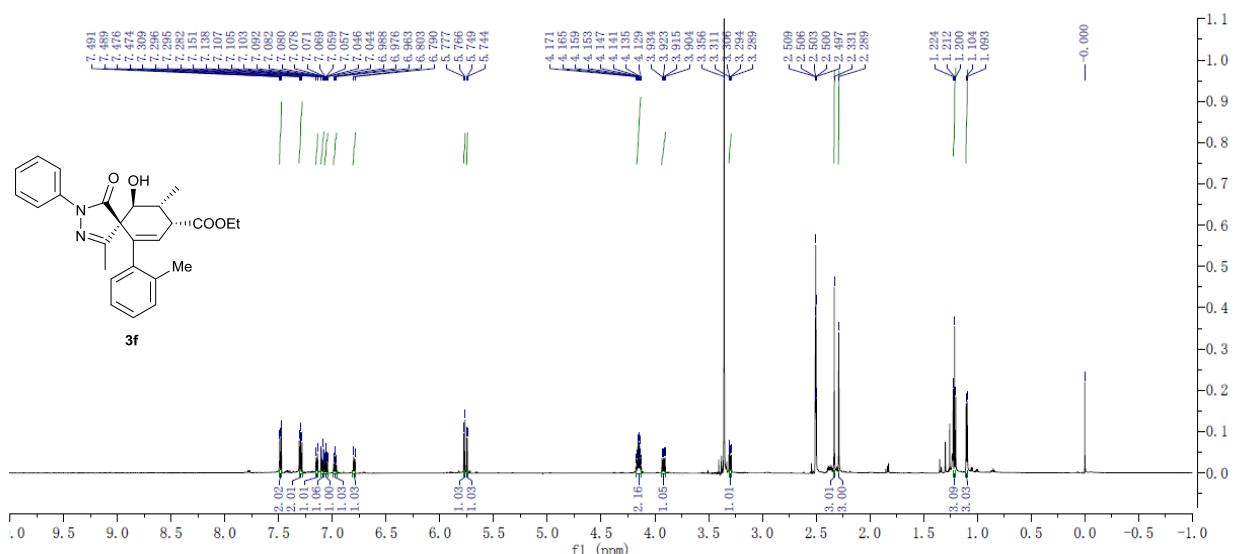


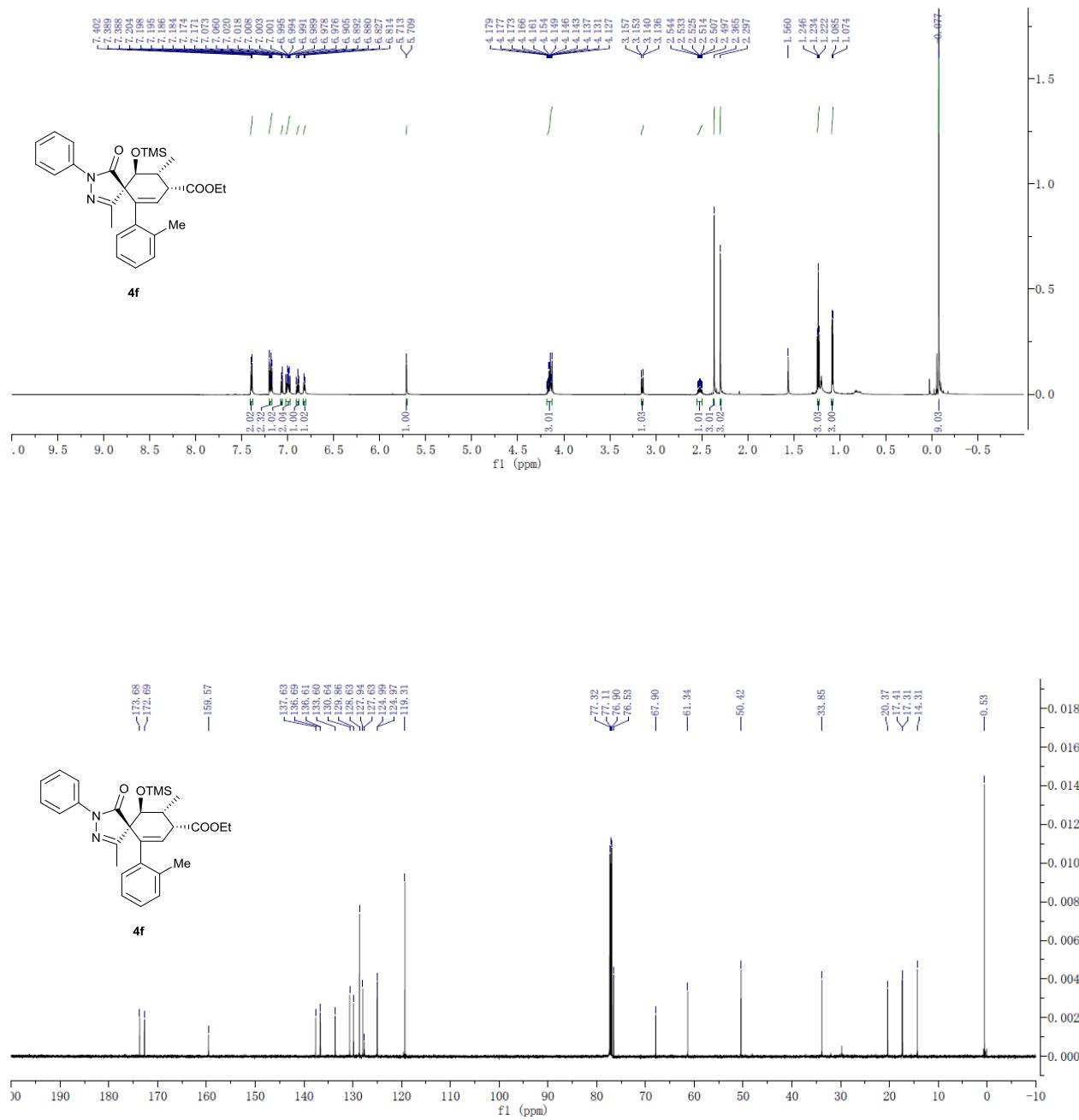
Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.849	22149	222490	3.399
2	8.217	400135	6323732	96.601
Total		422284	6546222	100.000





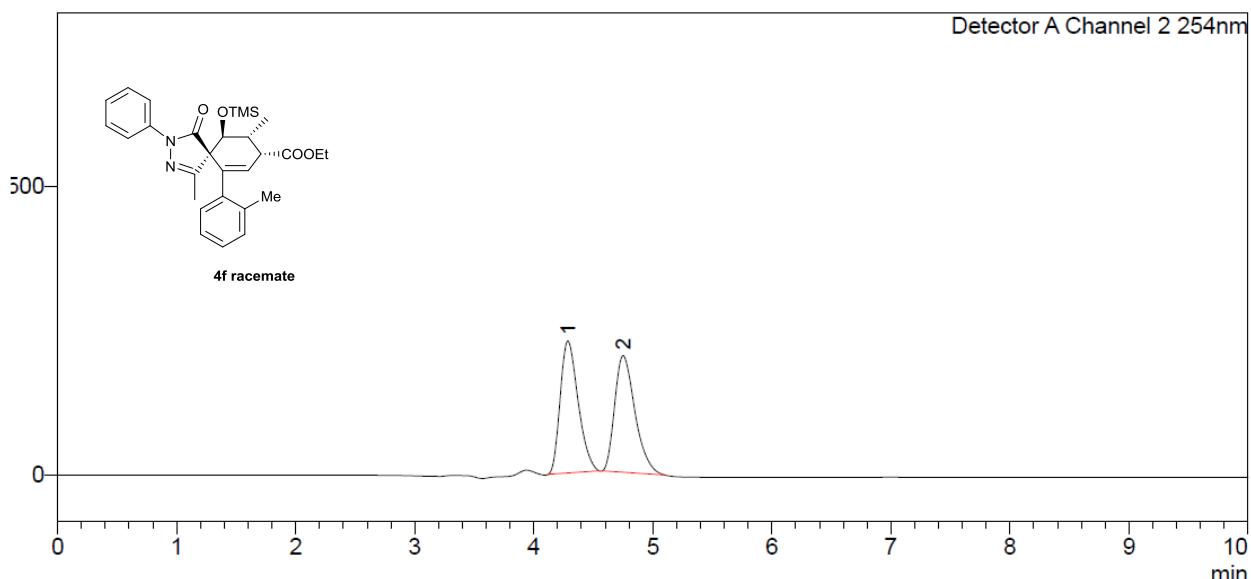


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.286	228493	2398705	50.014
2	4.751	202427	2397380	49.986
Total		430920	4796086	100.000

mV

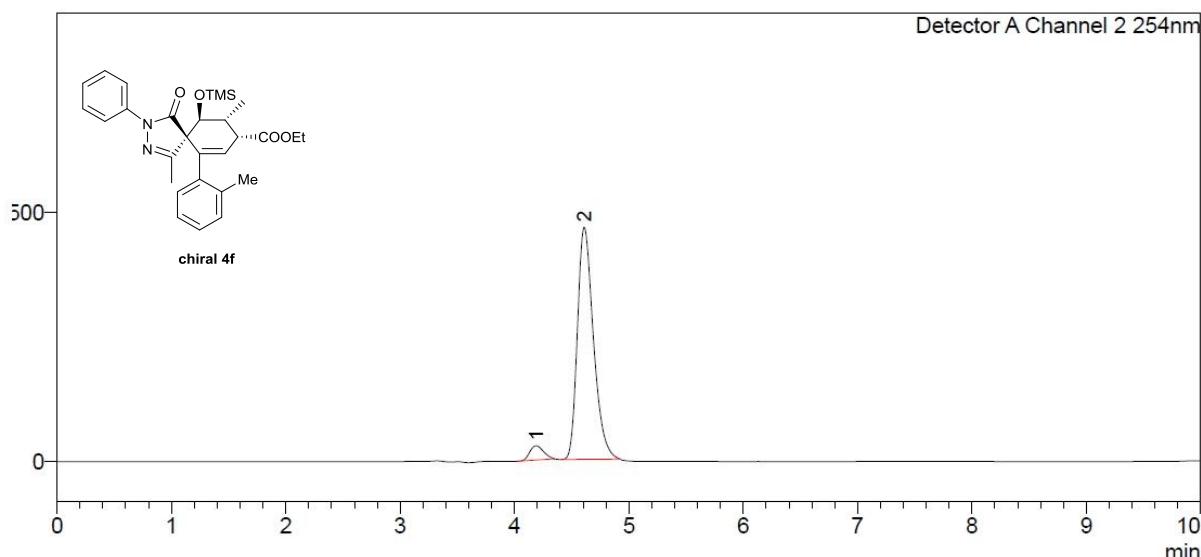


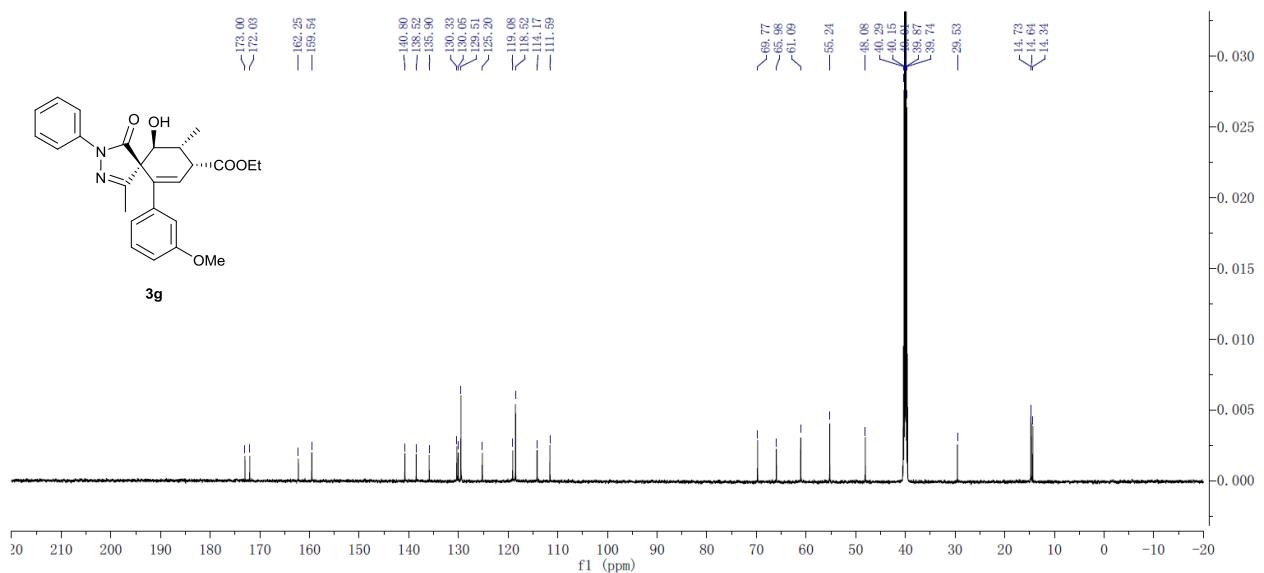
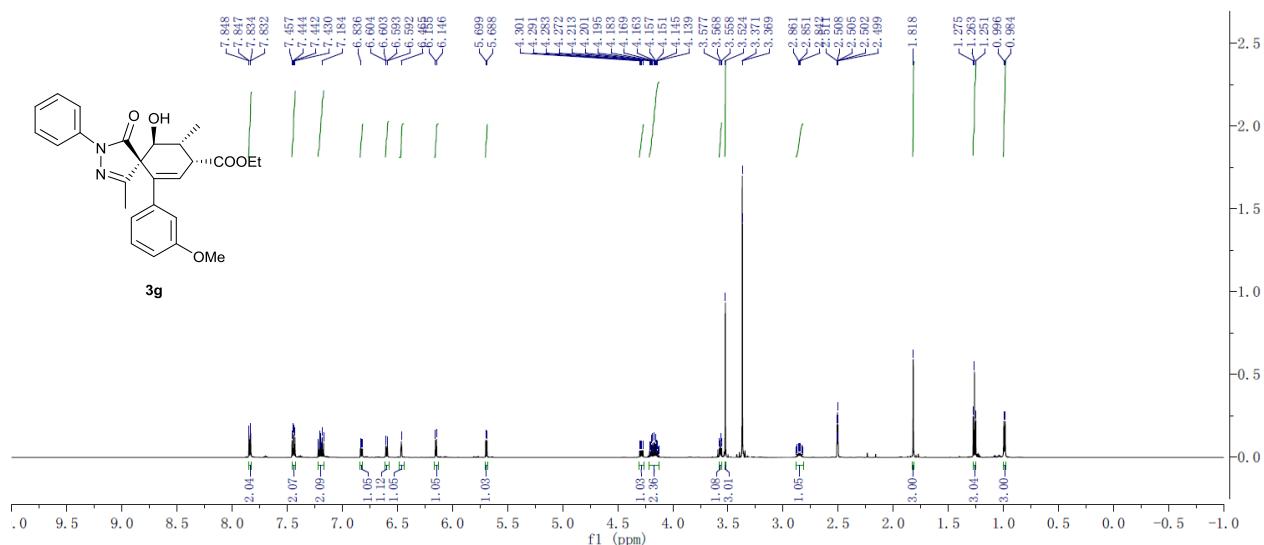
Peak Analysis Report

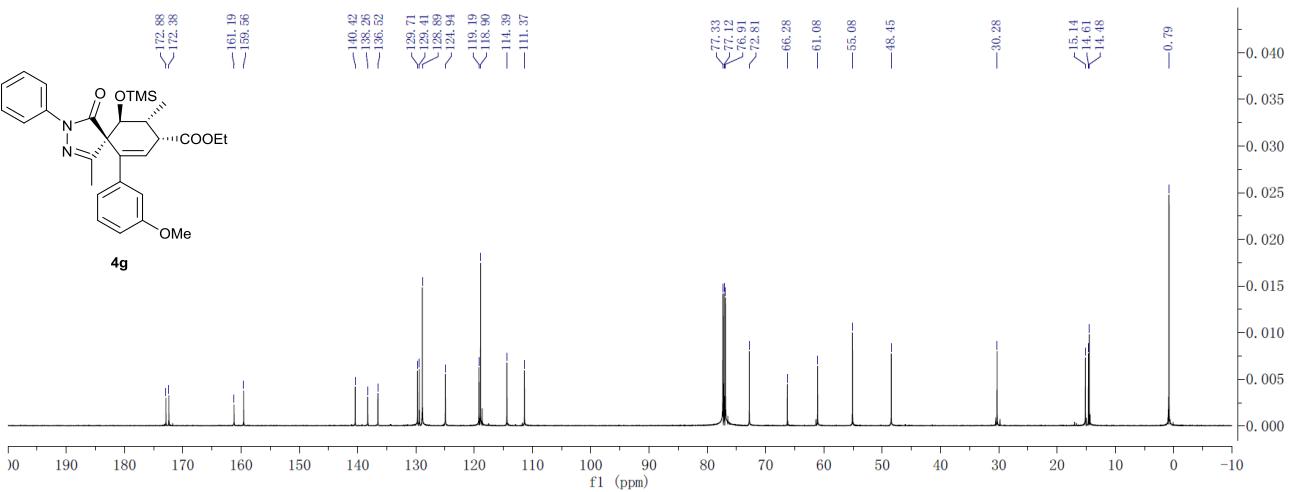
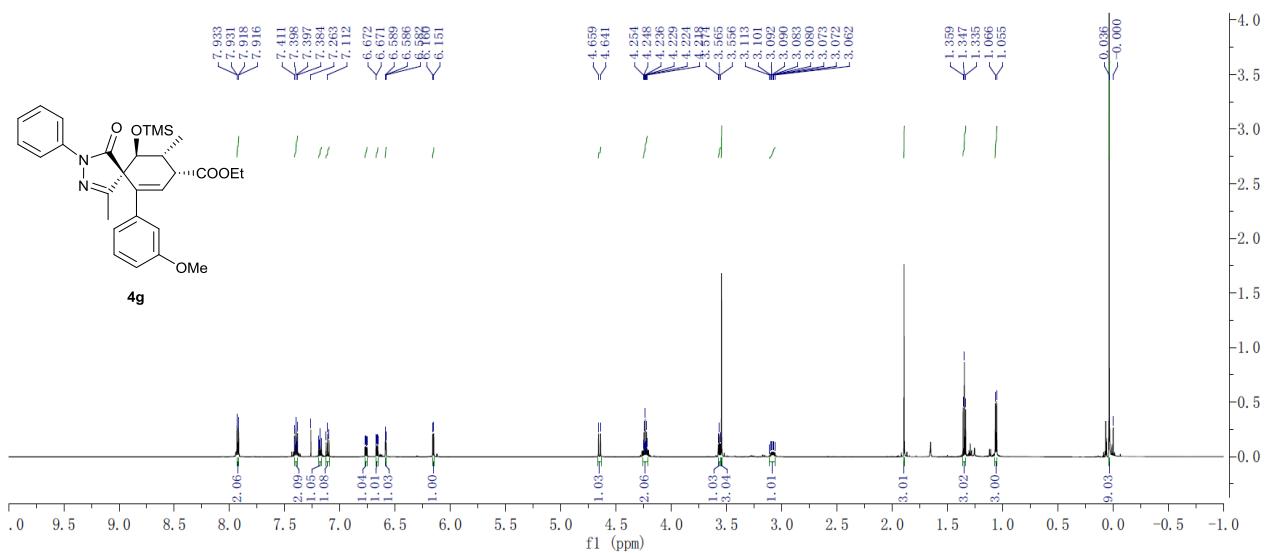
Detector A Channel 2 254nm

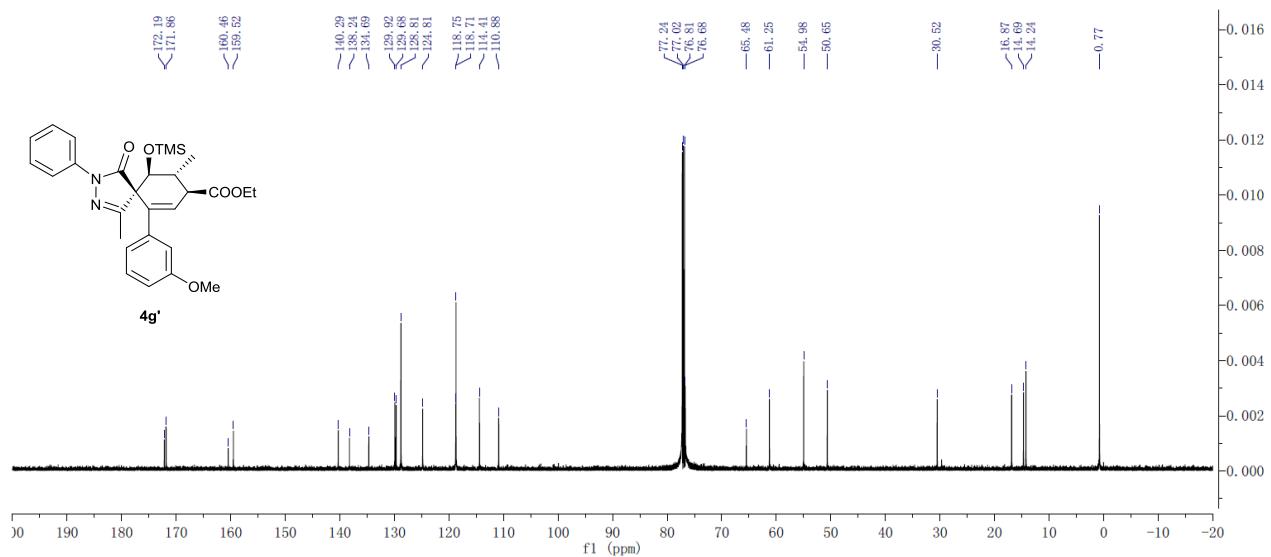
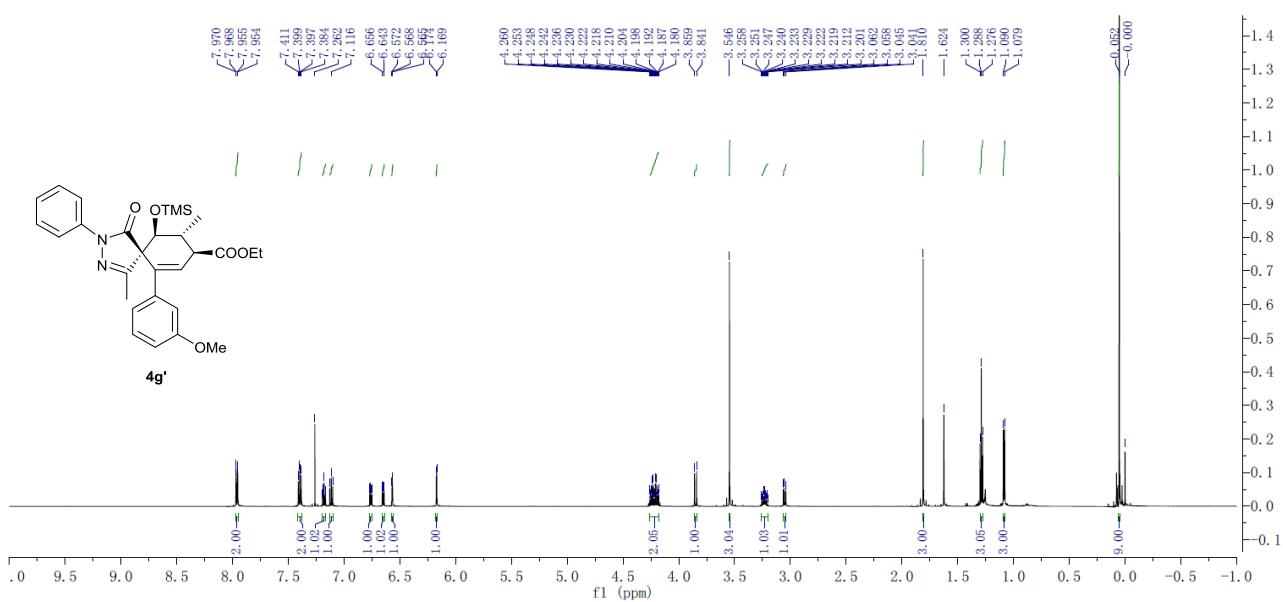
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.188	28581	238881	5.003
2	4.610	466693	4536091	94.997
Total		495273	4774972	100.000

mV







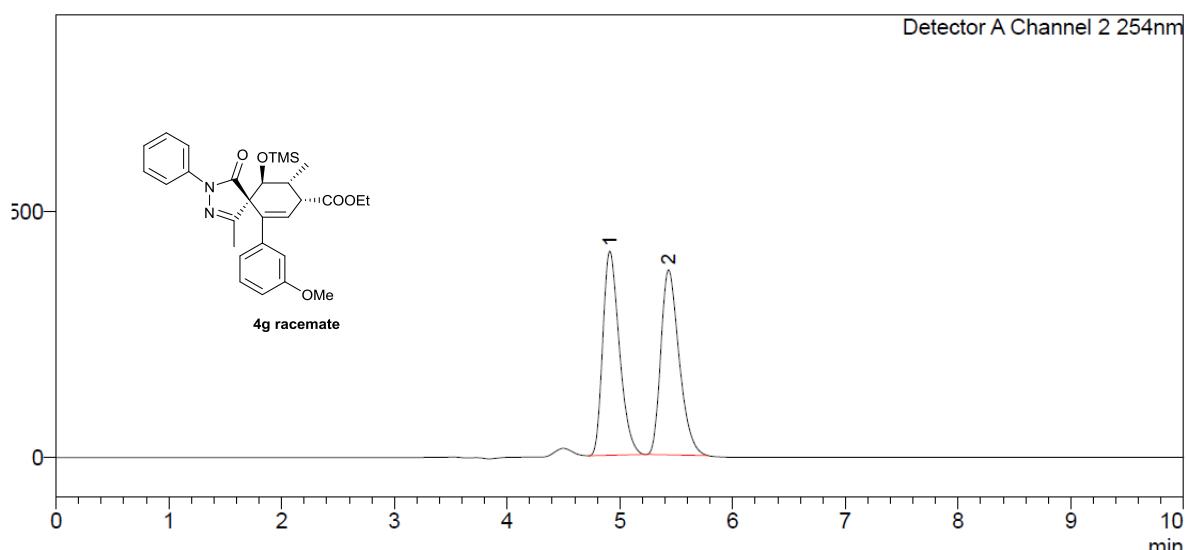


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.911	415317	4244522	49.970
2	5.432	376813	4249558	50.030
Total		792130	8494080	100.000

mV

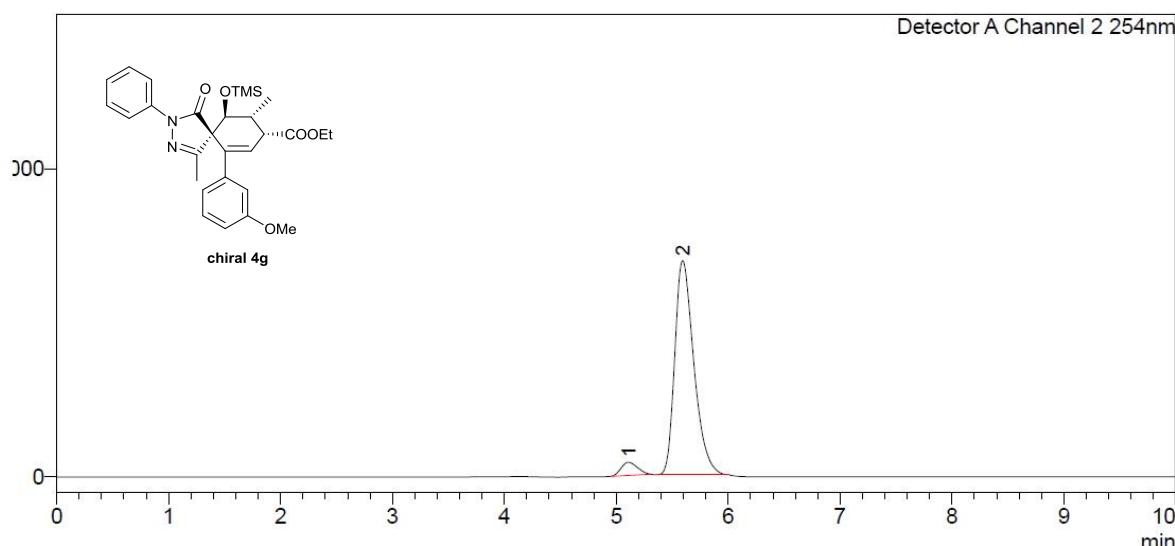


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	5.109	84941	864336	4.995
2	5.594	1389232	16438144	95.005
Total		1474172	17302480	100.000

mV

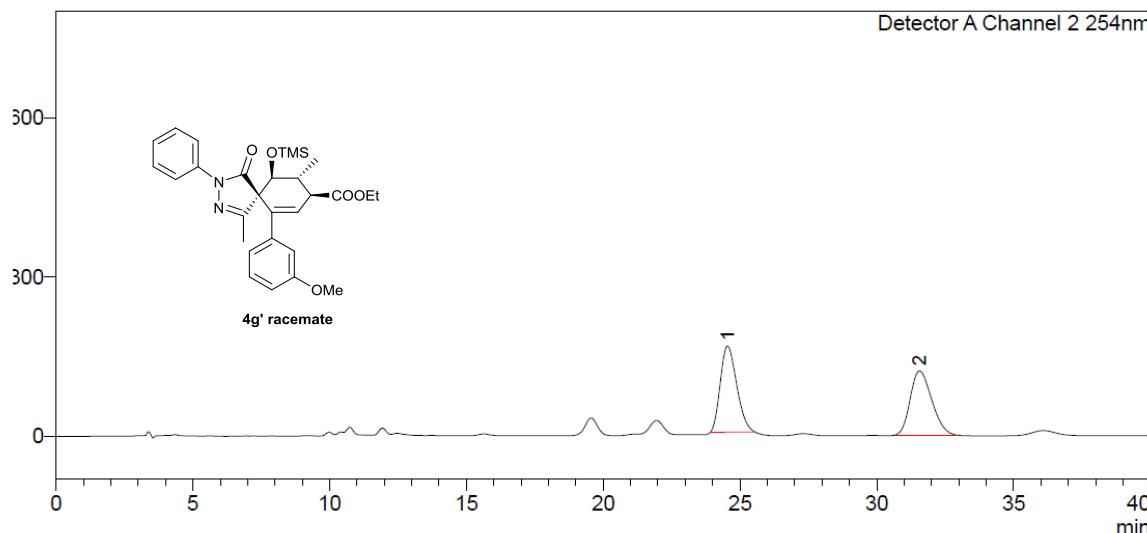


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	24.542	162009	6763921	50.822
2	31.560	120818	6545108	49.178
Total		282827	13309029	100.000

mV

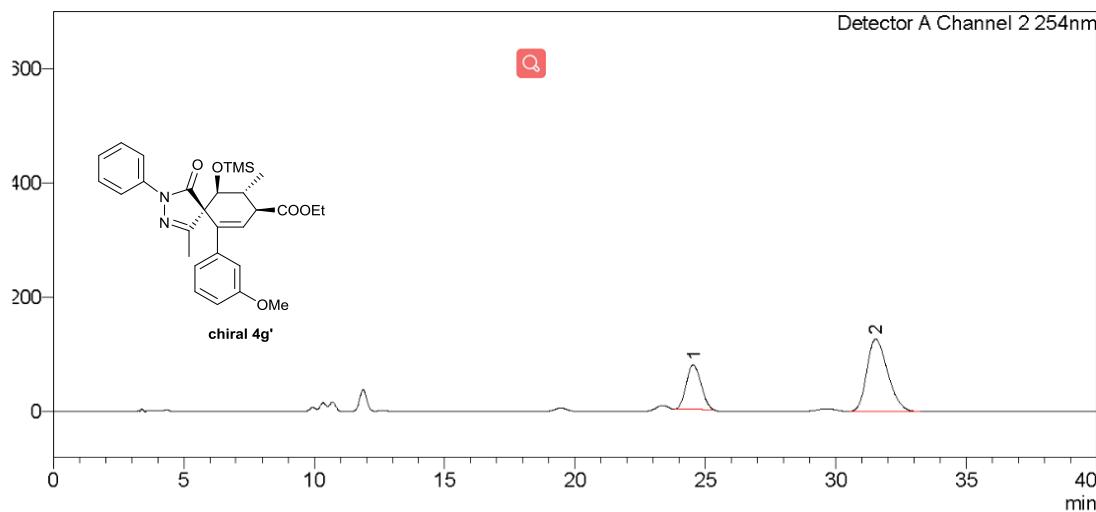


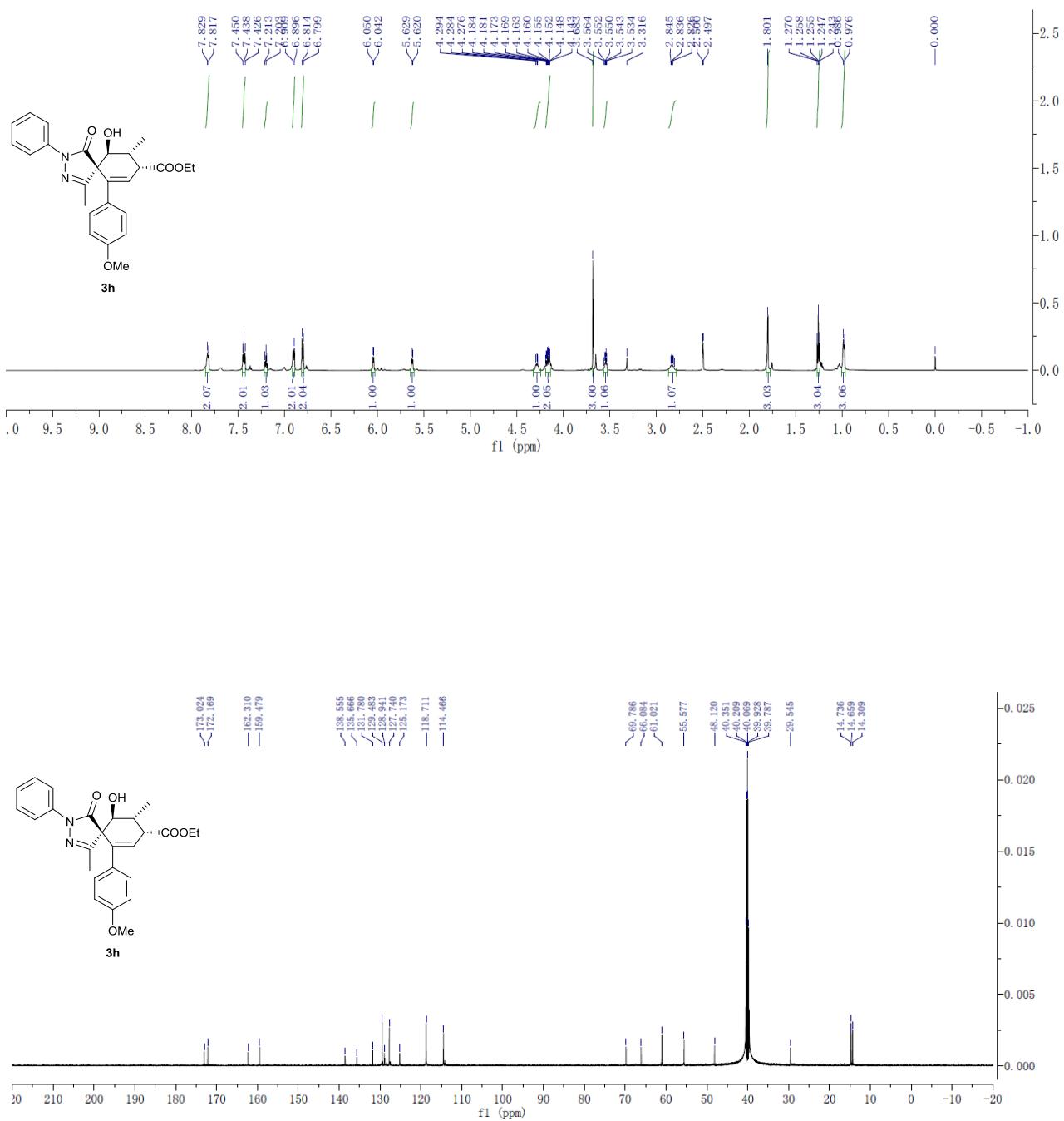
Peak Analysis Report

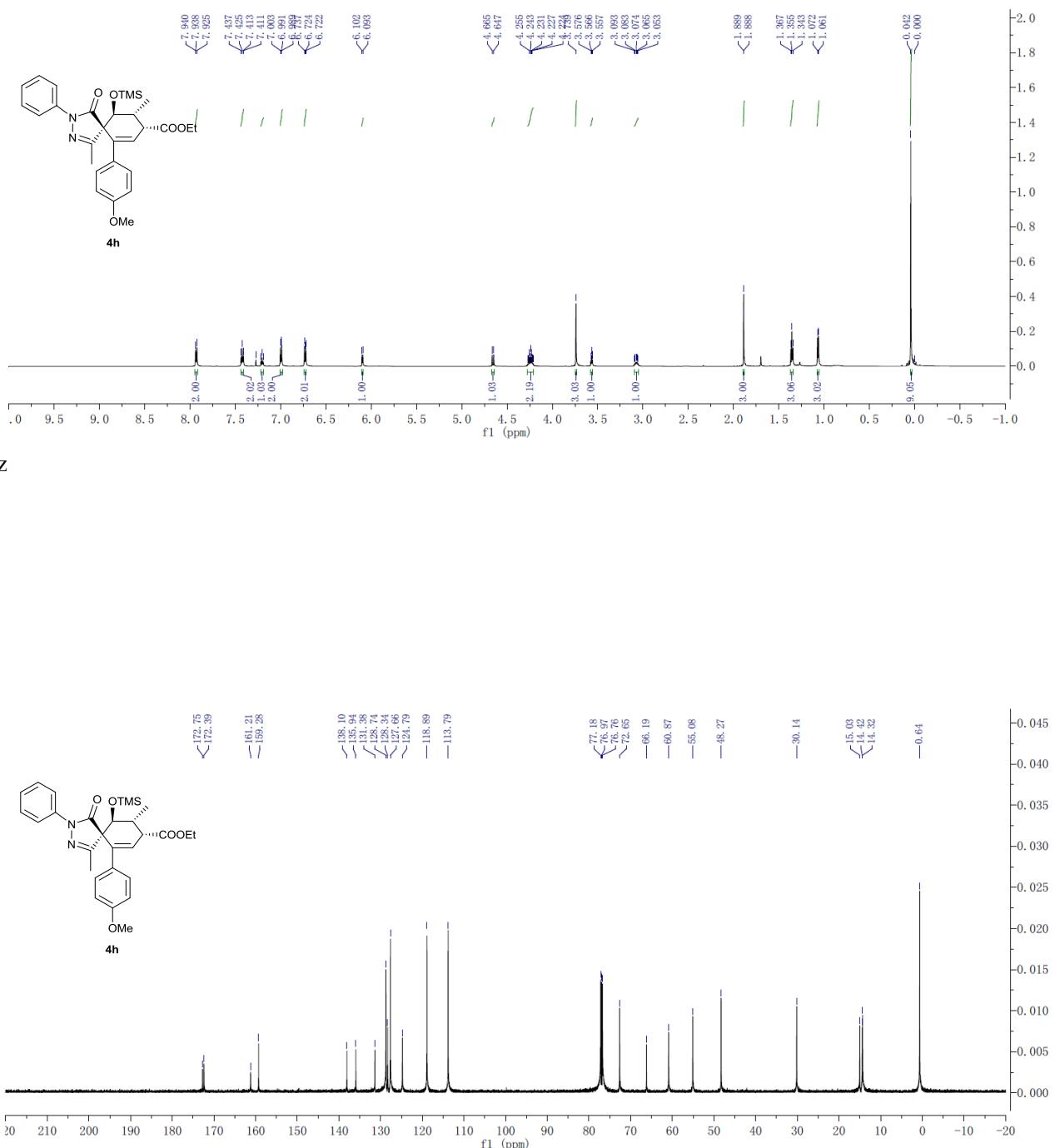
Detector A Channel 2 254nm

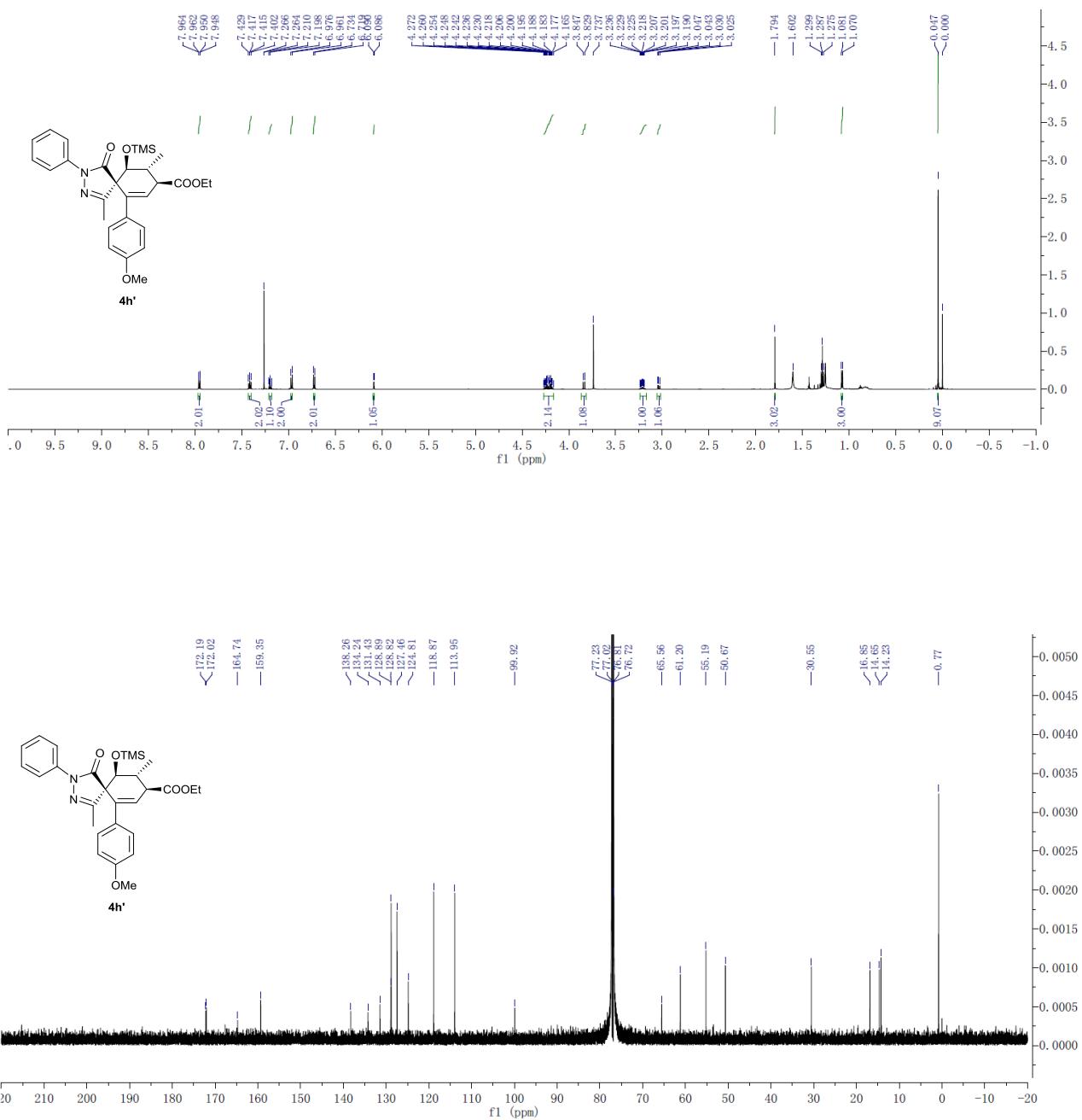
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	24.530	77693	3016918	30.290
2	31.519	126322	6943252	69.710
Total		204015	9960170	100.000

mV







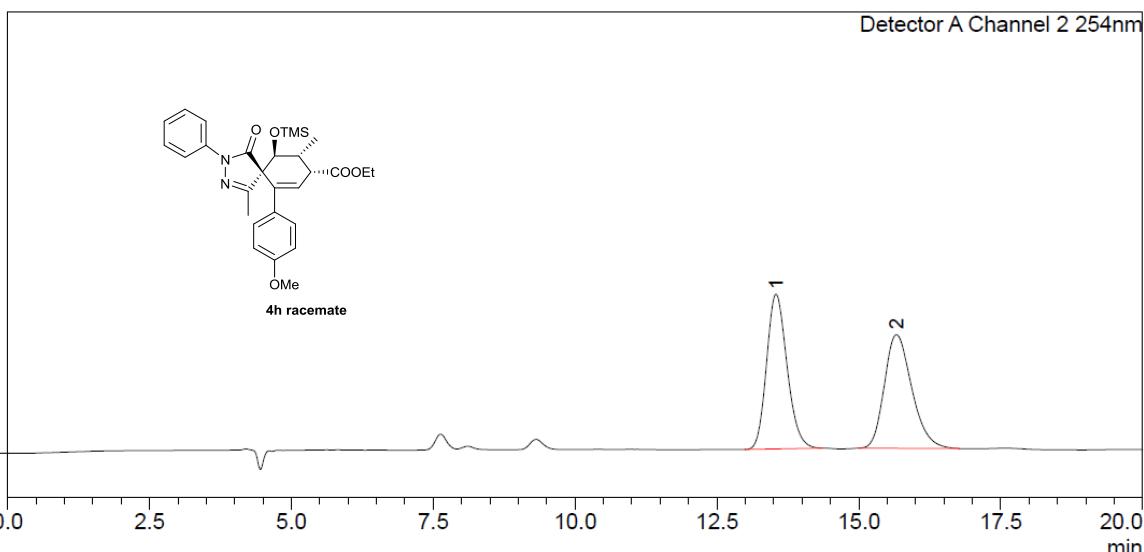


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.540	70167	1763772	50.442
2	15.662	51559	1732891	49.558
Total		121725	3496662	100.000

mV

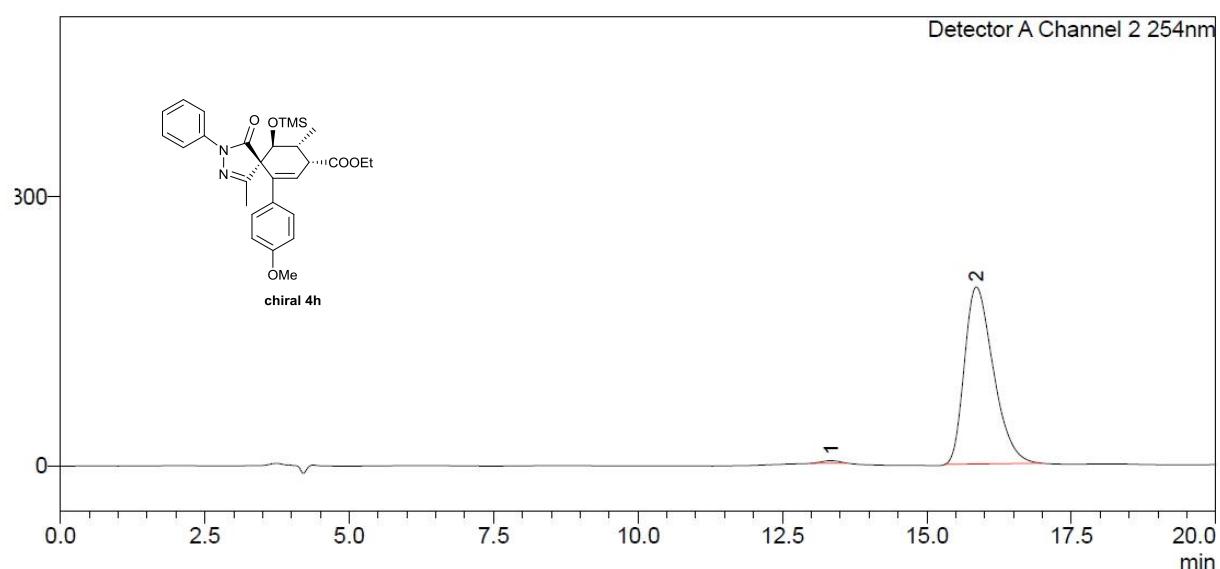


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	13.335	2806	56971	0.822
2	15.856	197172	6869698	99.178
Total		199978	6926669	100.000

mV

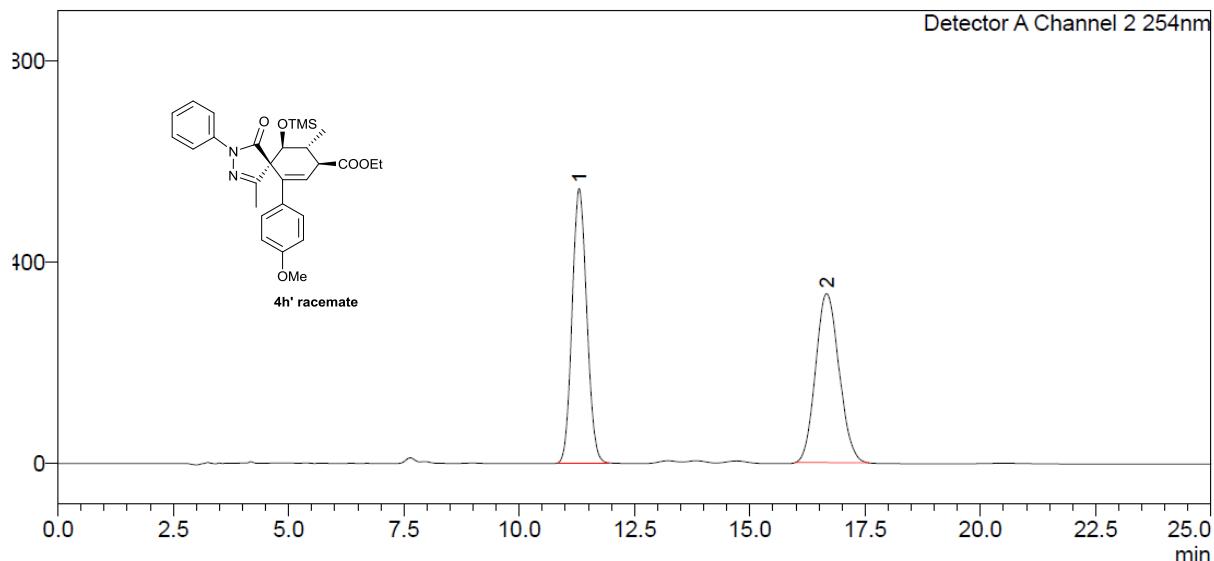


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	11.299	545143	12026203	50.239
2	16.667	336309	11911989	49.761
Total		881452	23938192	100.000

mV

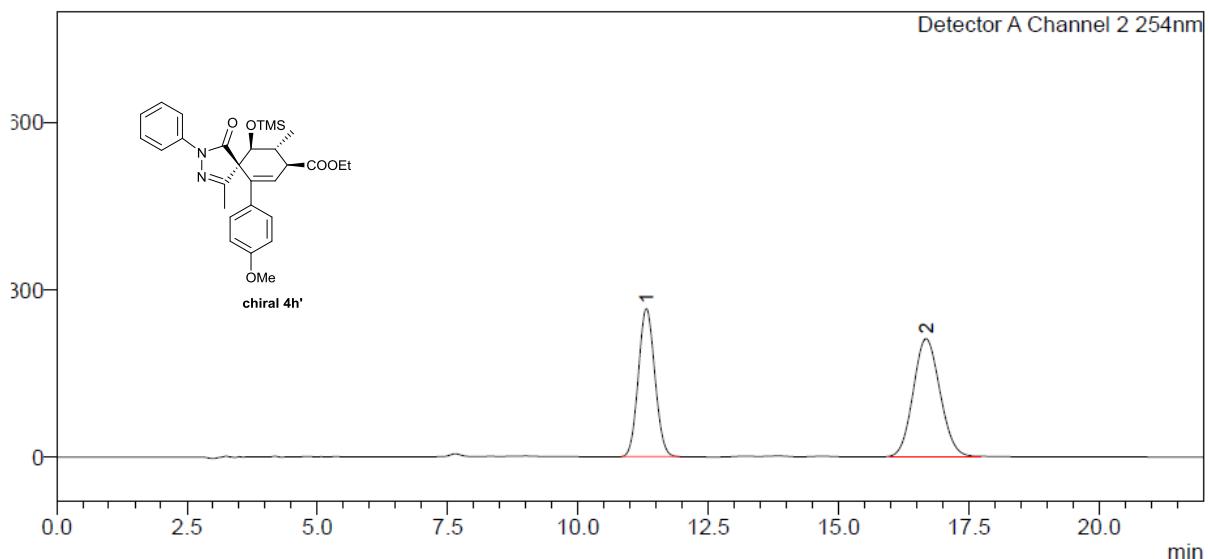


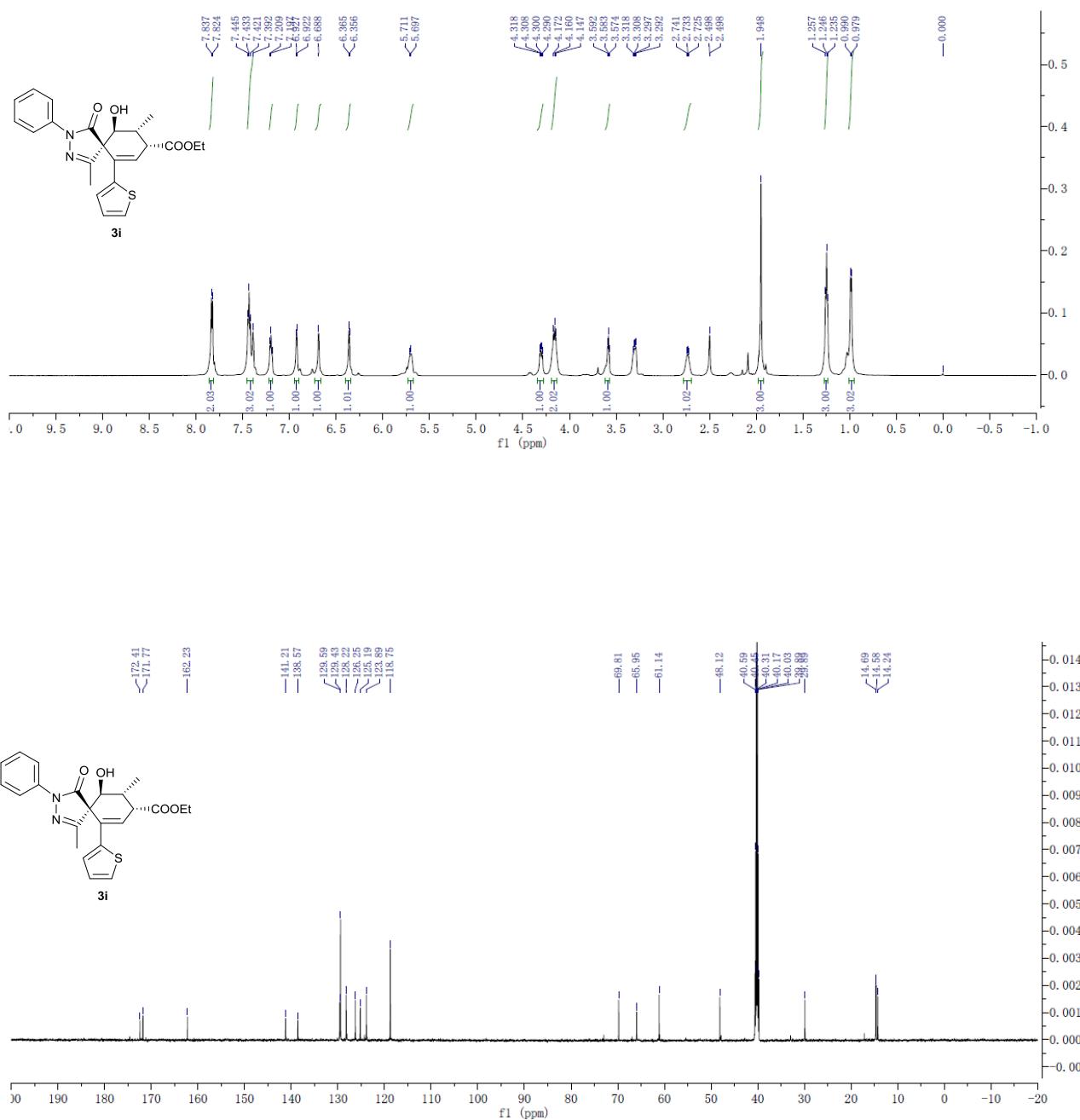
Peak Analysis Report

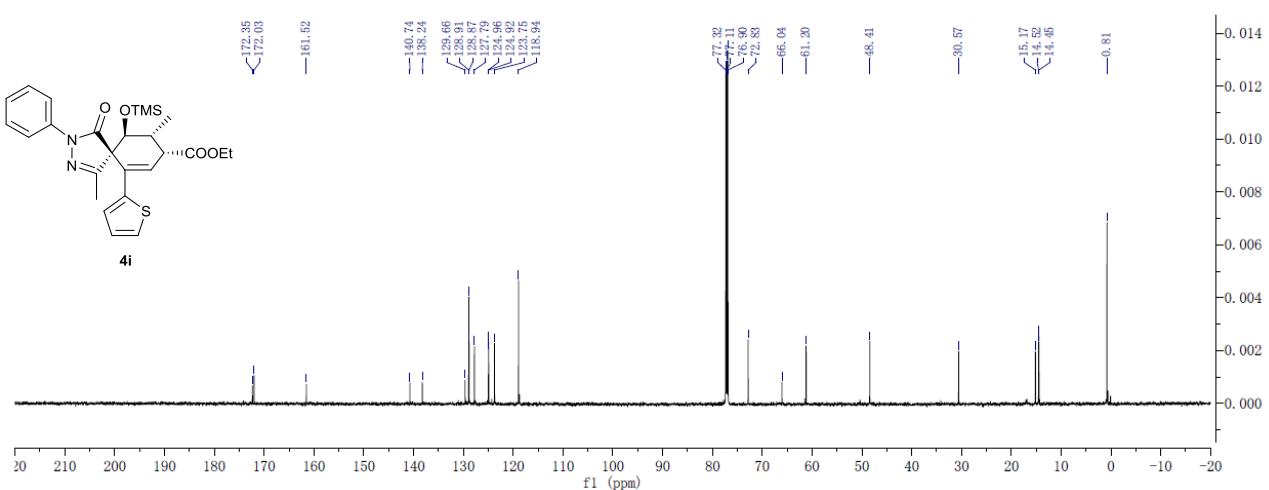
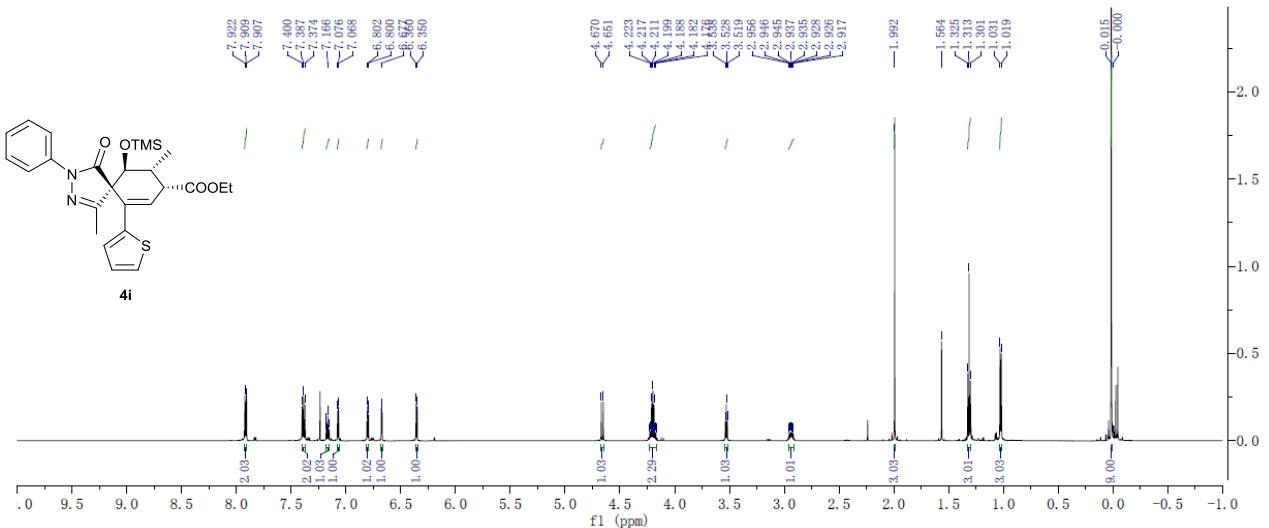
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	11.312	265796	5843447	43.780
2	16.677	211337	7503835	56.220
Total		477133	13347282	100.000

mV





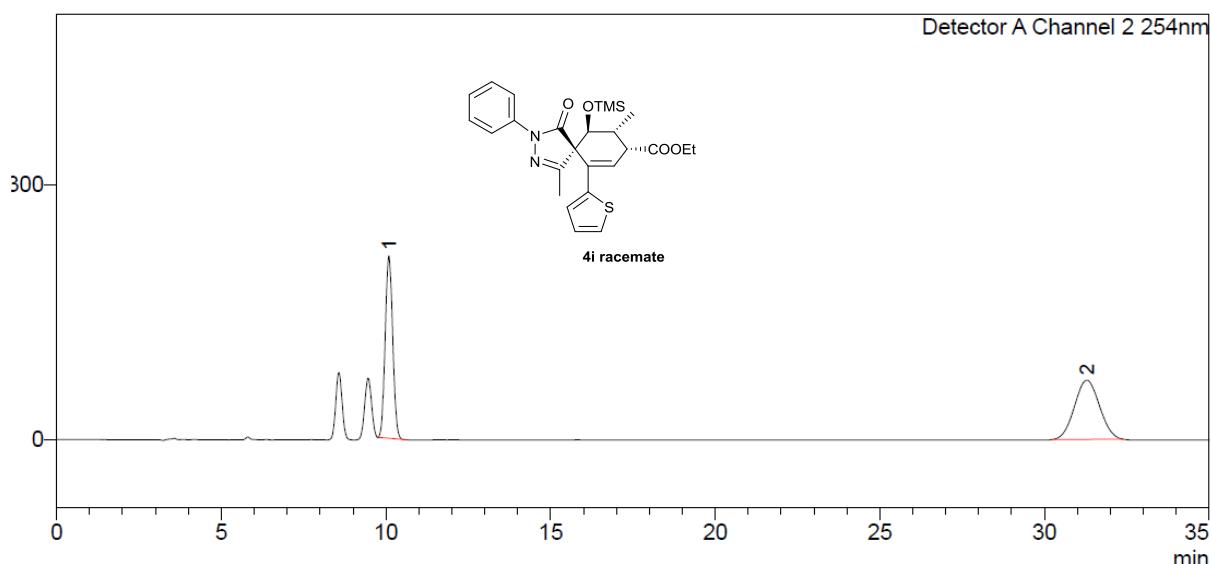


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.090	214501	3408081	48.067
2	31.284	69681	3682251	51.933
Total		284182	7090332	100.000

mV

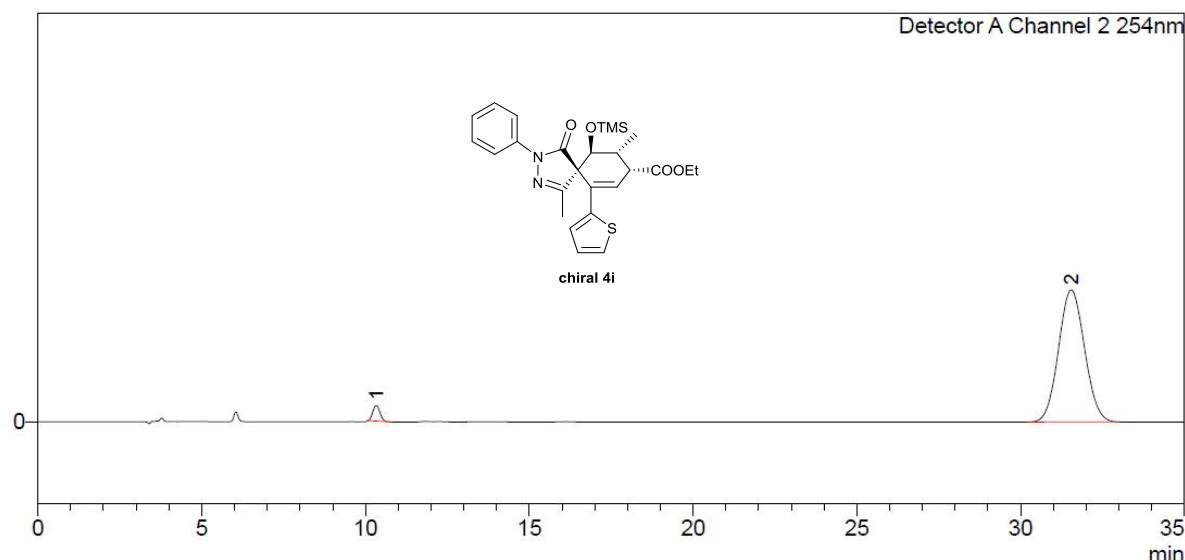


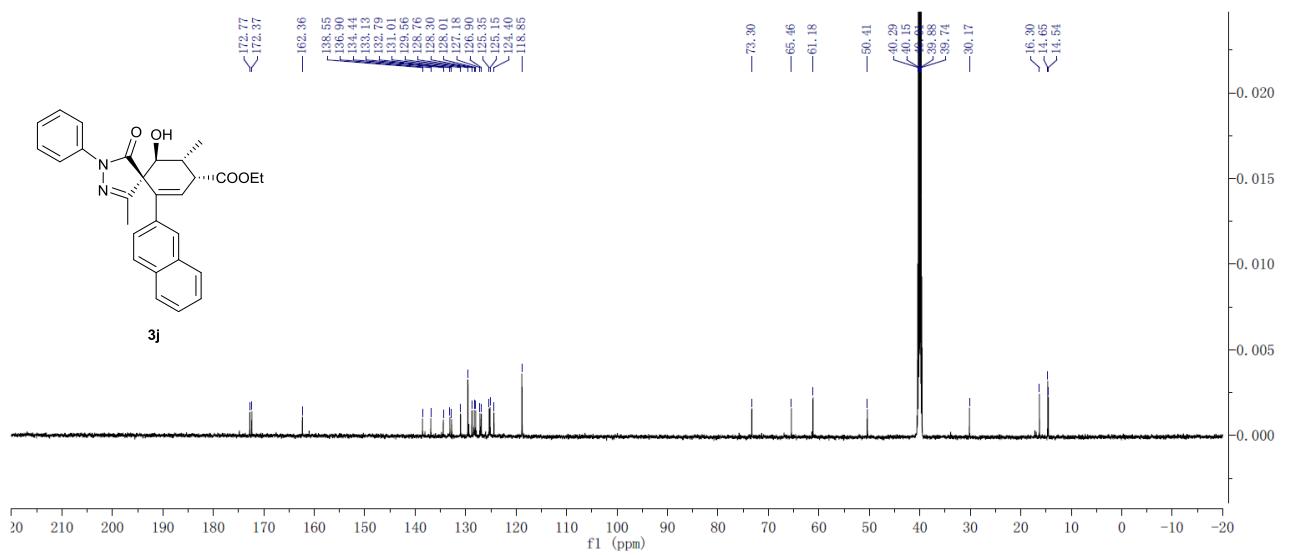
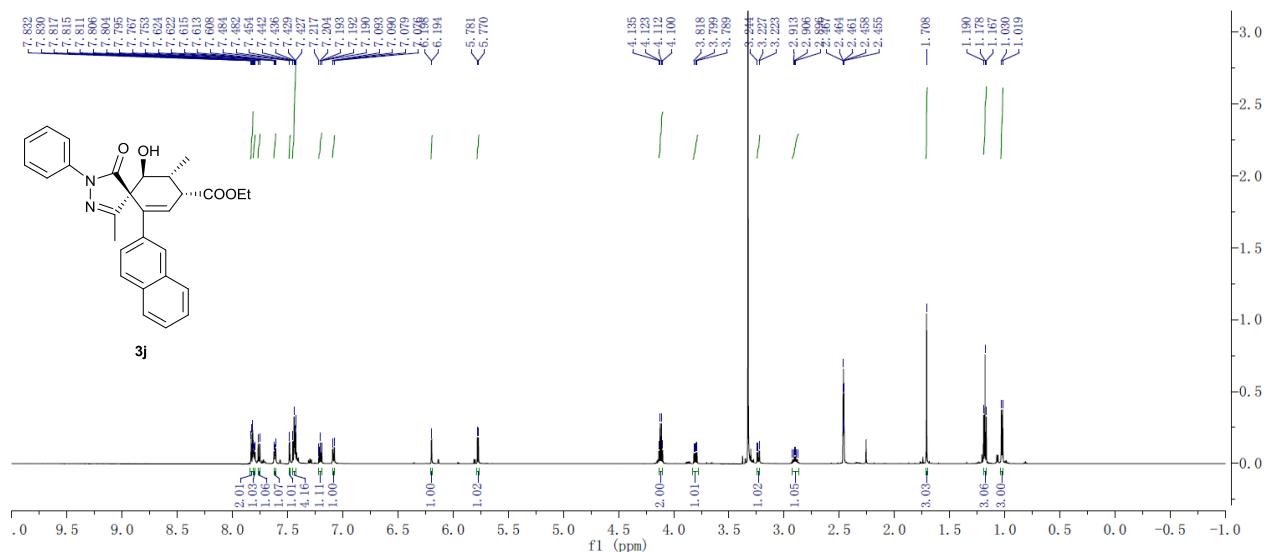
Peak Analysis Report

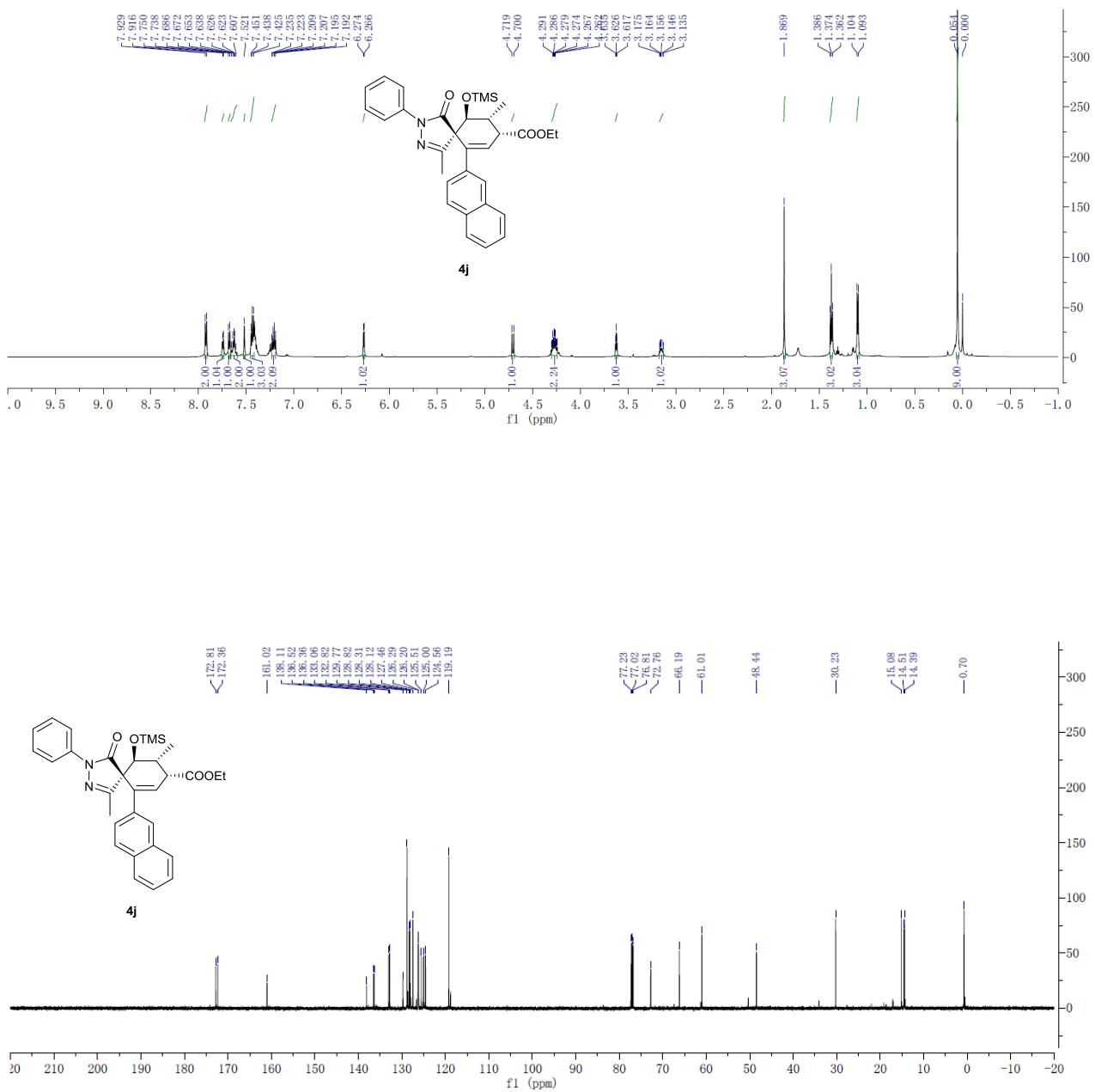
Detector A Channel 2 254nm

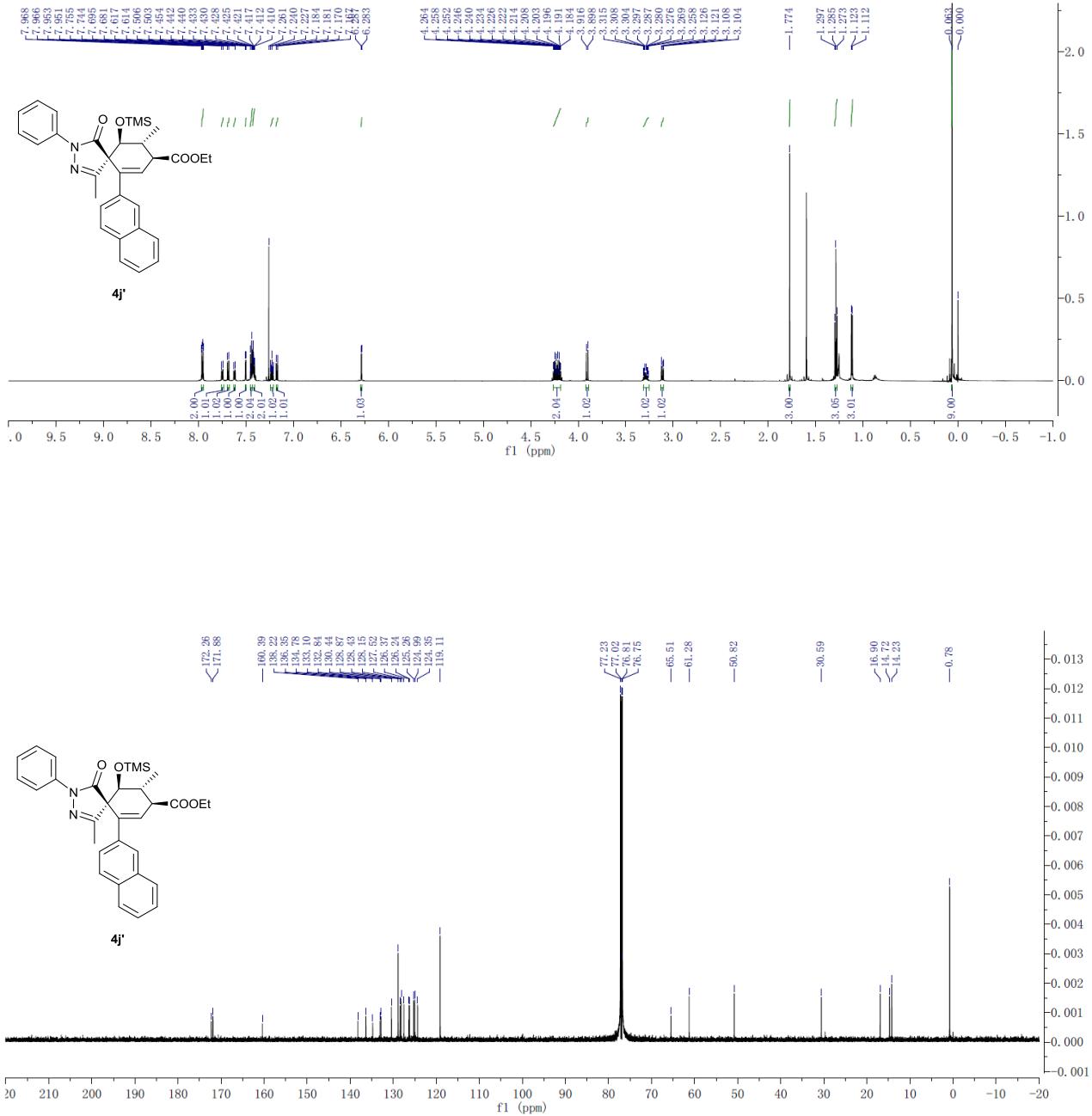
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.328	7698	113697	3.091
2	31.543	64669	3565011	96.909
Total		72368	3678708	100.000

mV







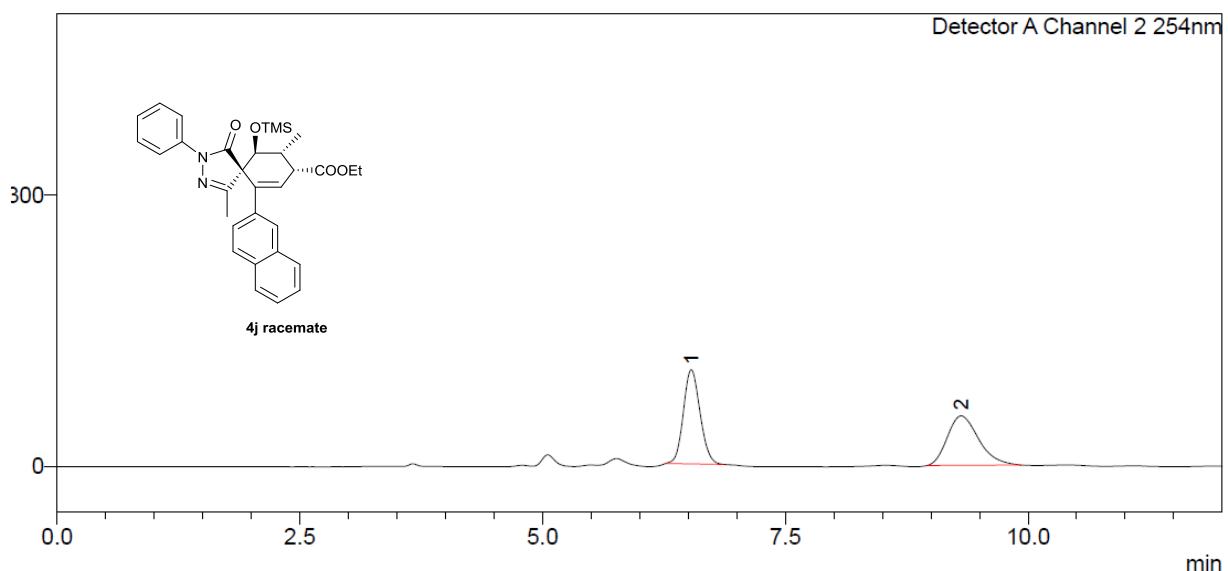


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	6.531	104174	1245797	50.450
2	9.312	54595	1223566	49.550
Total		158770	2469363	100.000

mV

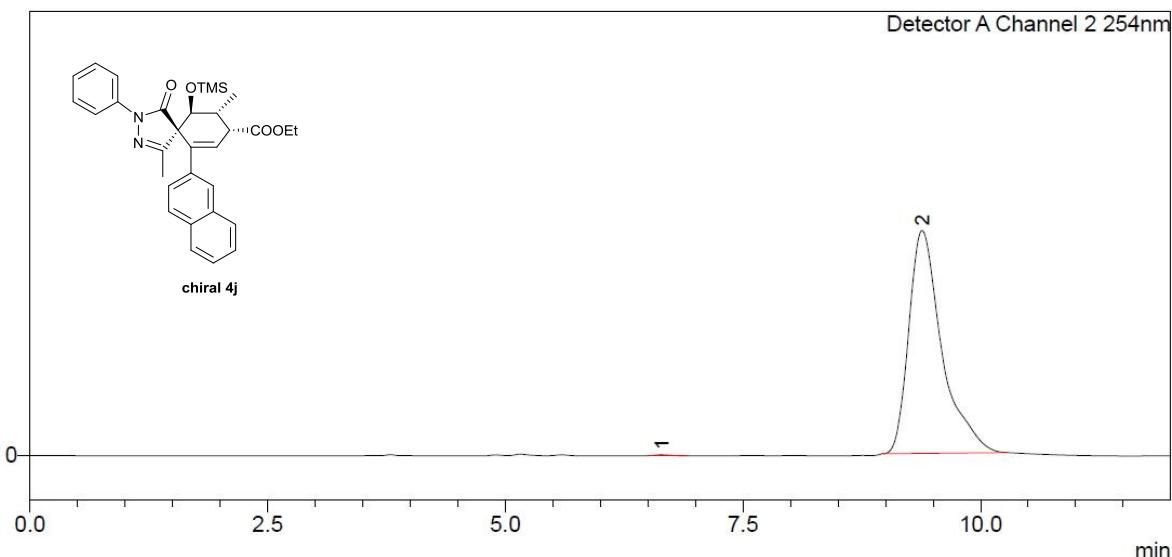


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	6.647	384	4116	0.170
2	9.385	100440	2422975	99.830
Total		100824	2427091	100.000

mV

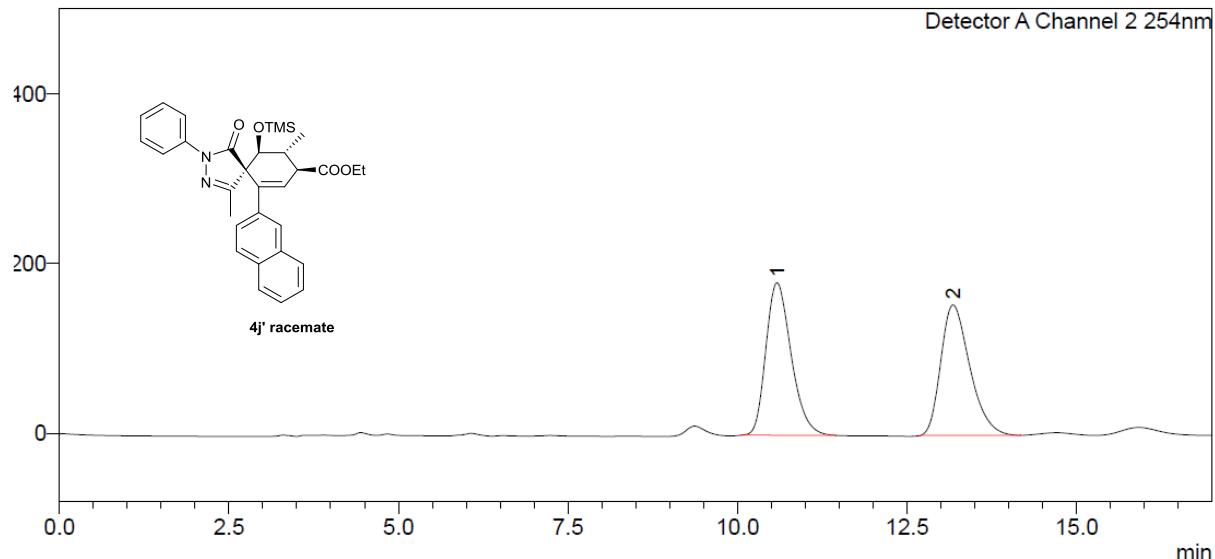


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.582	179470	4656010	50.480
2	13.178	153608	4567379	49.520
Total		333078	9223389	100.000

mV

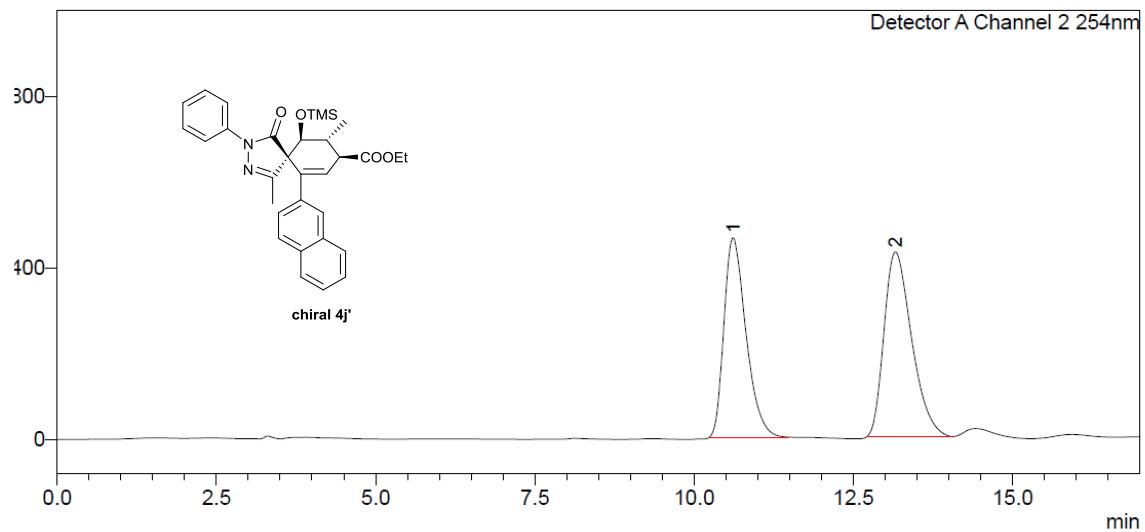


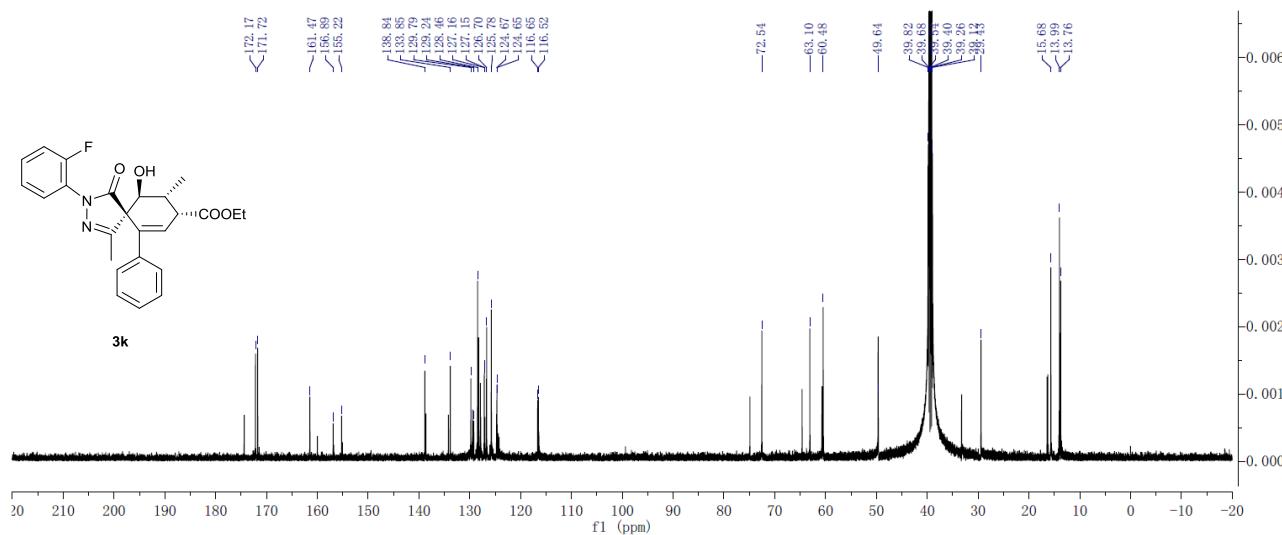
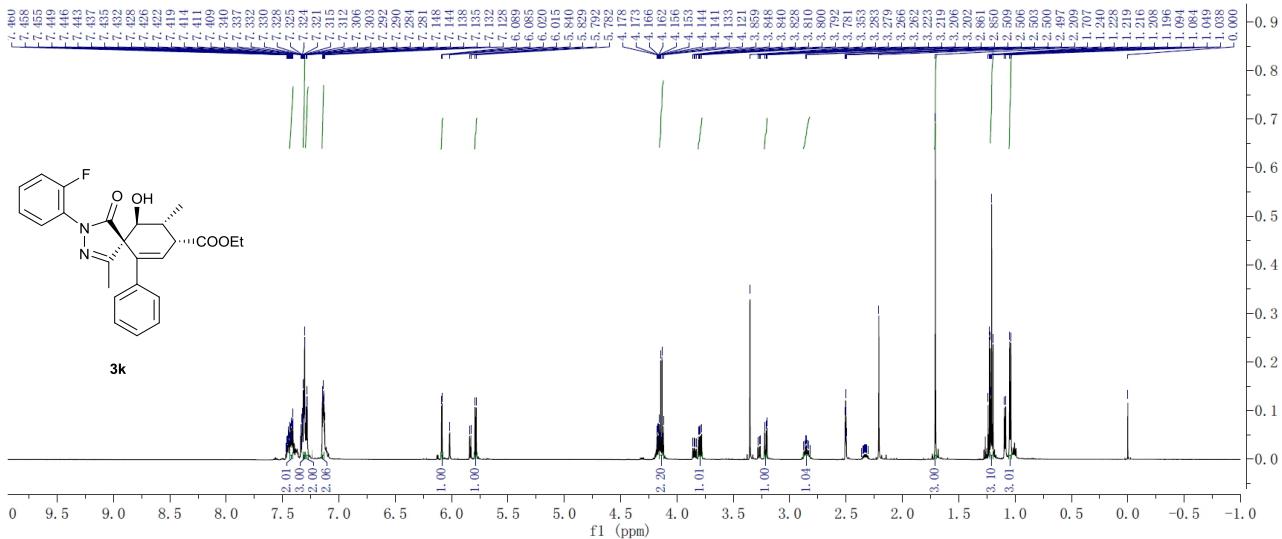
Peak Analysis Report

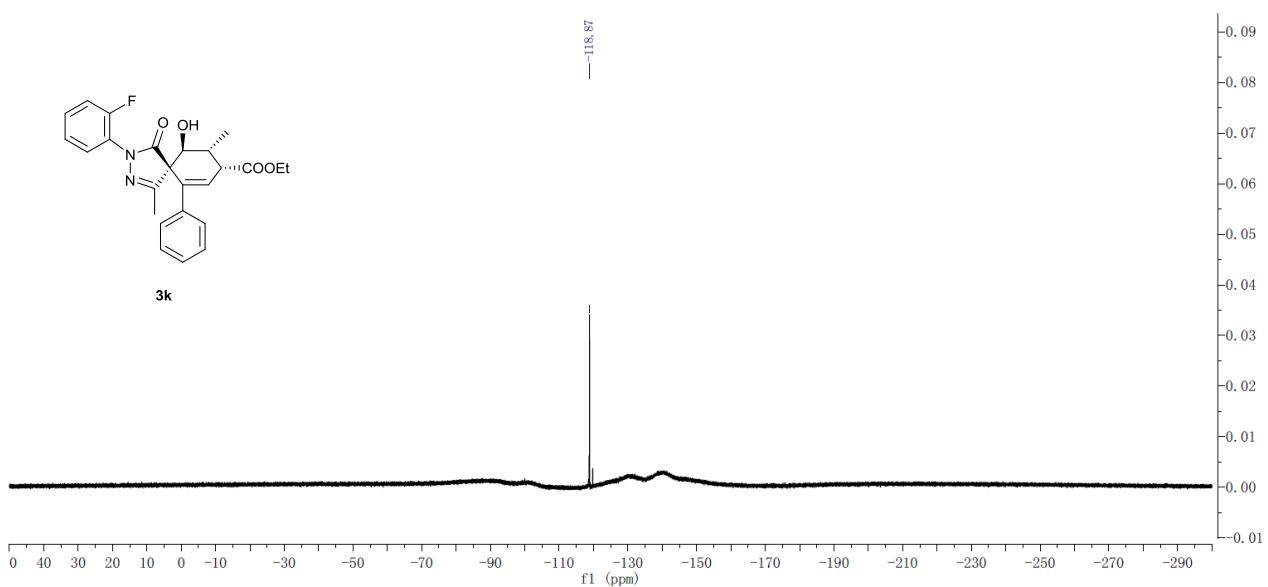
Detector A Channel 2 254nm

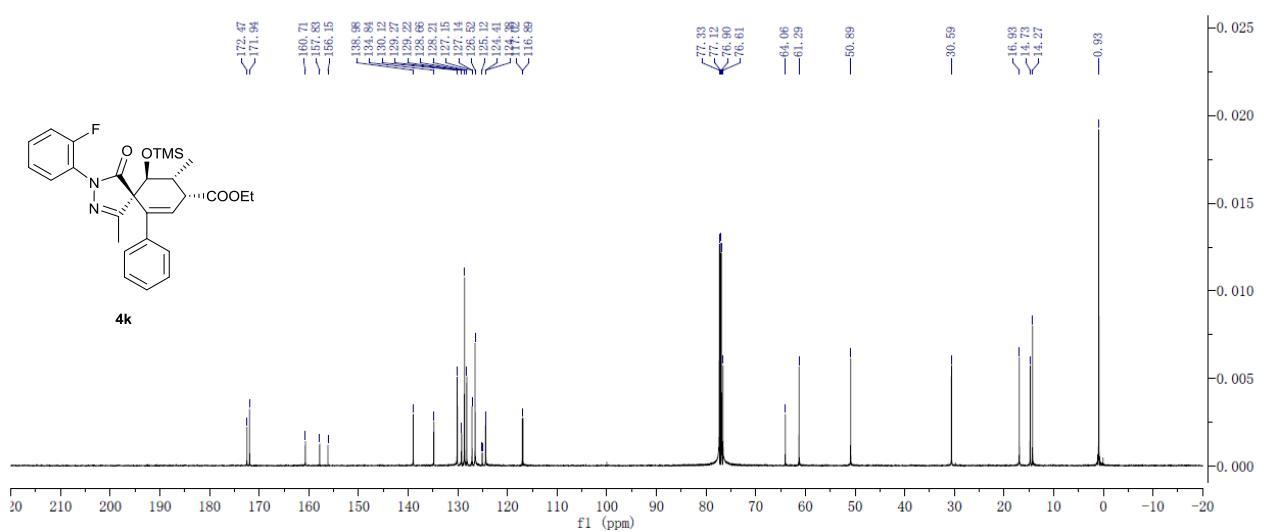
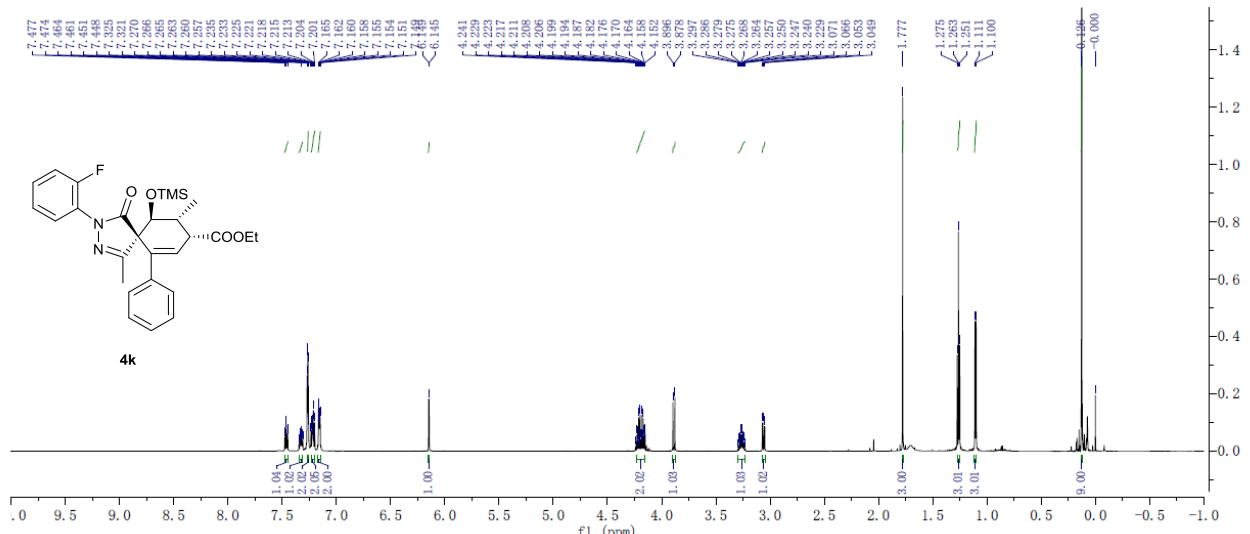
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	10.611	465273	11202278	46.374
2	13.160	430456	12954251	53.626
Total		895728	24156529	100.000

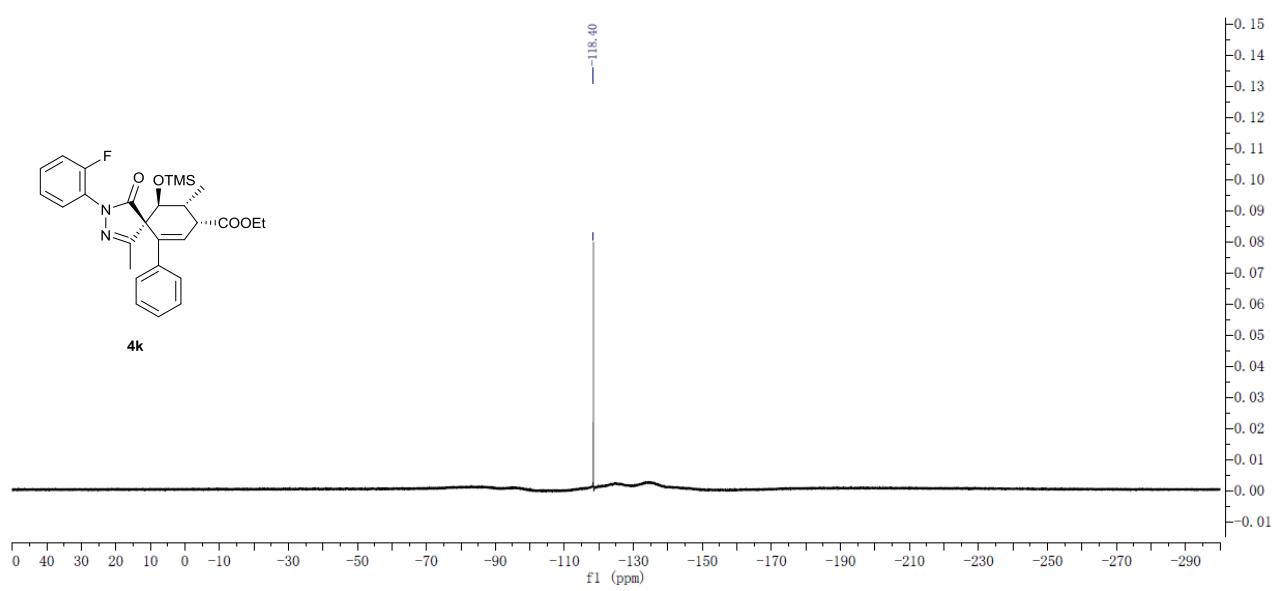
mV

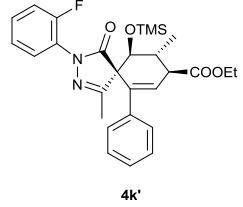
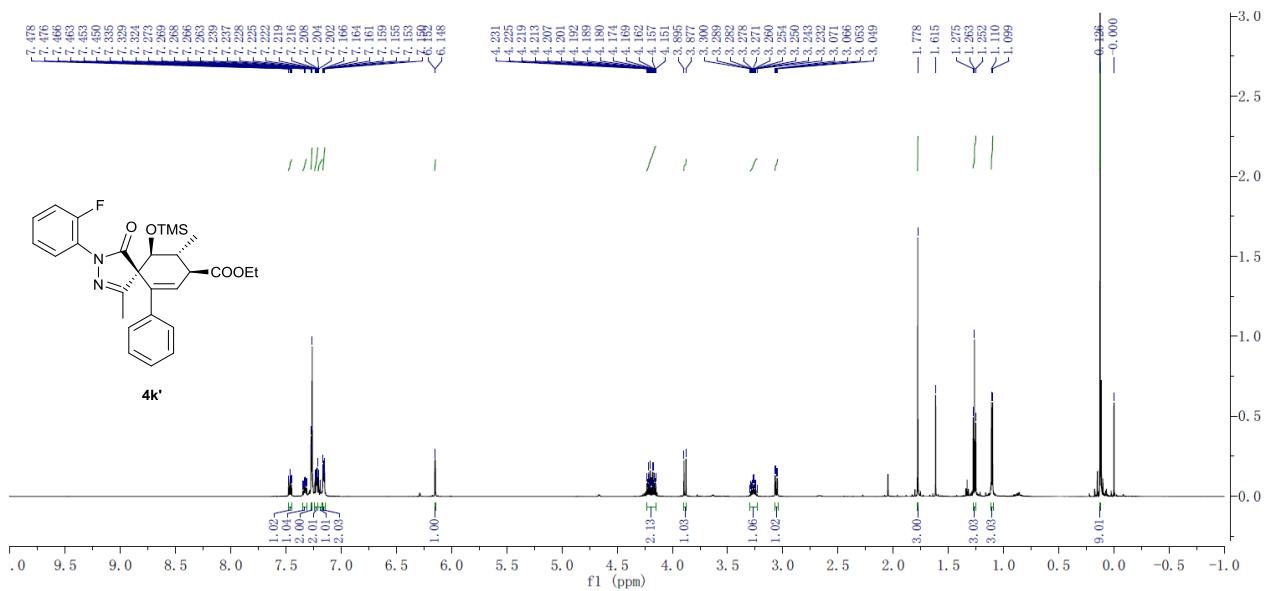




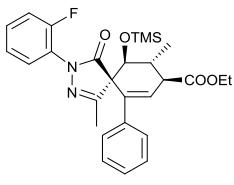
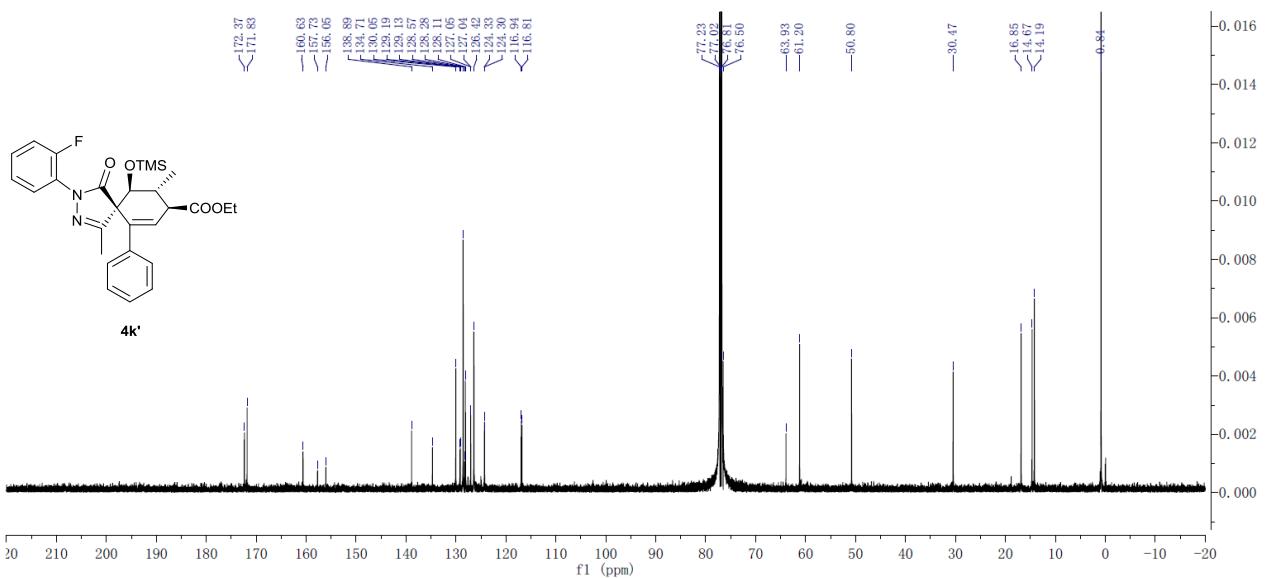




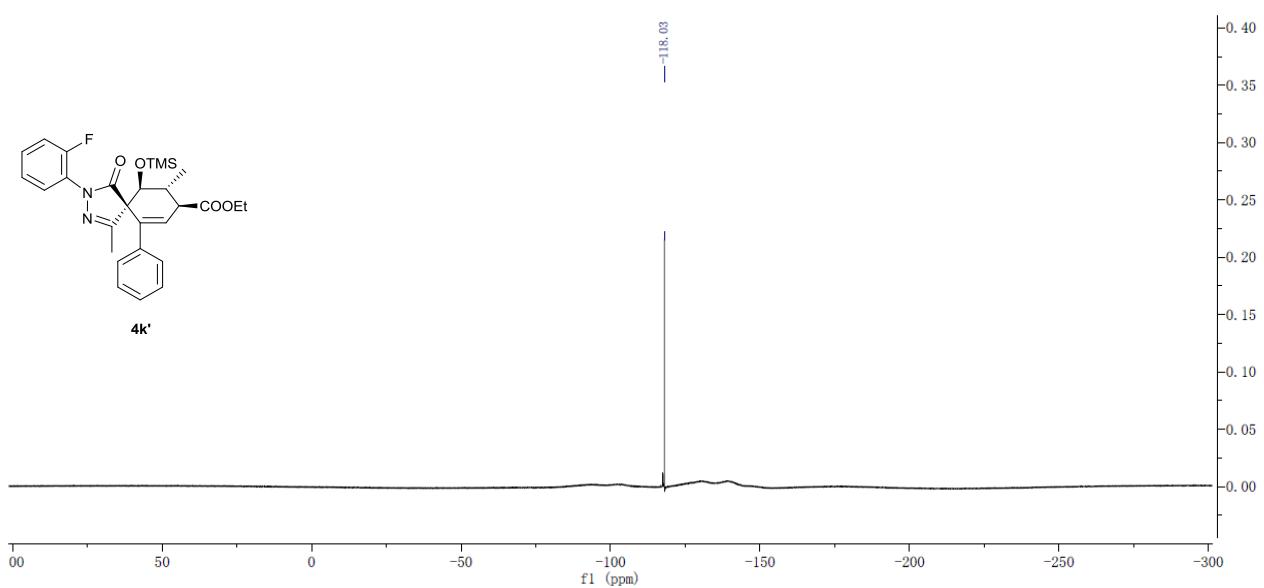




4k'



4k'

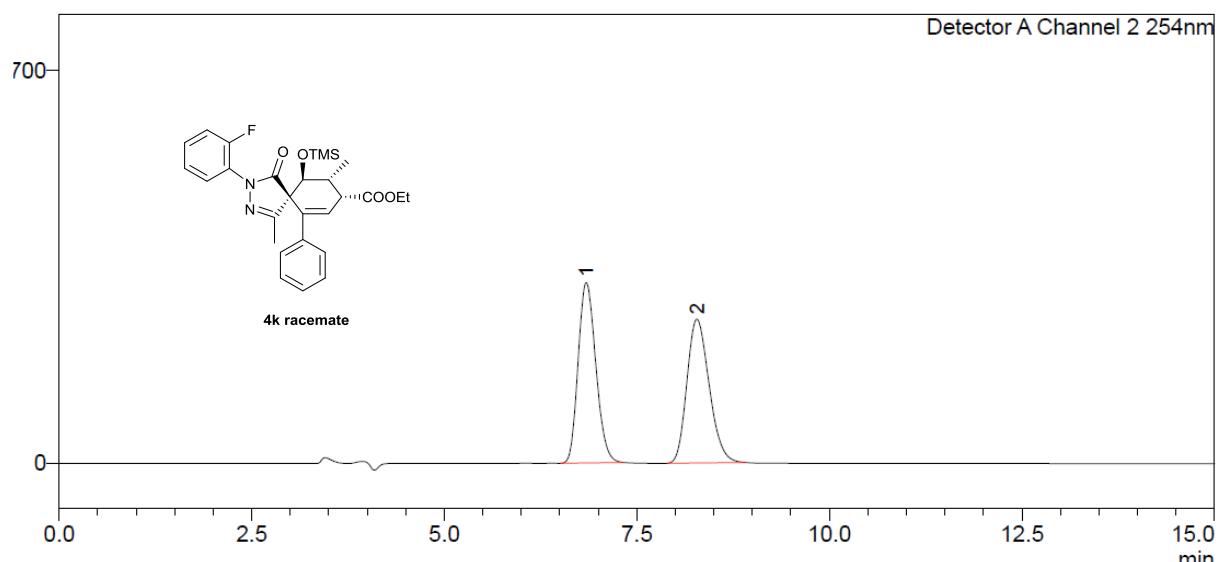


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	6.844	321519	5129132	49.907
2	8.280	256323	5148347	50.093
Total		577842	10277479	100.000

mV

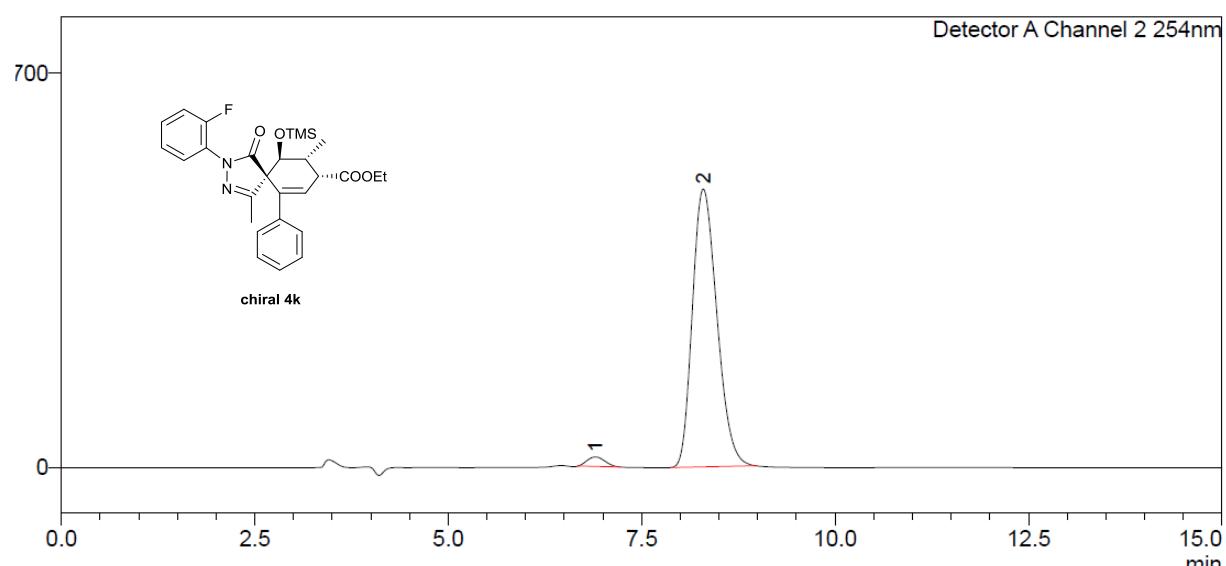


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	6.902	16738	265967	2.389
2	8.297	493190	10864988	97.611
Total		509927	11130954	100.000

mV

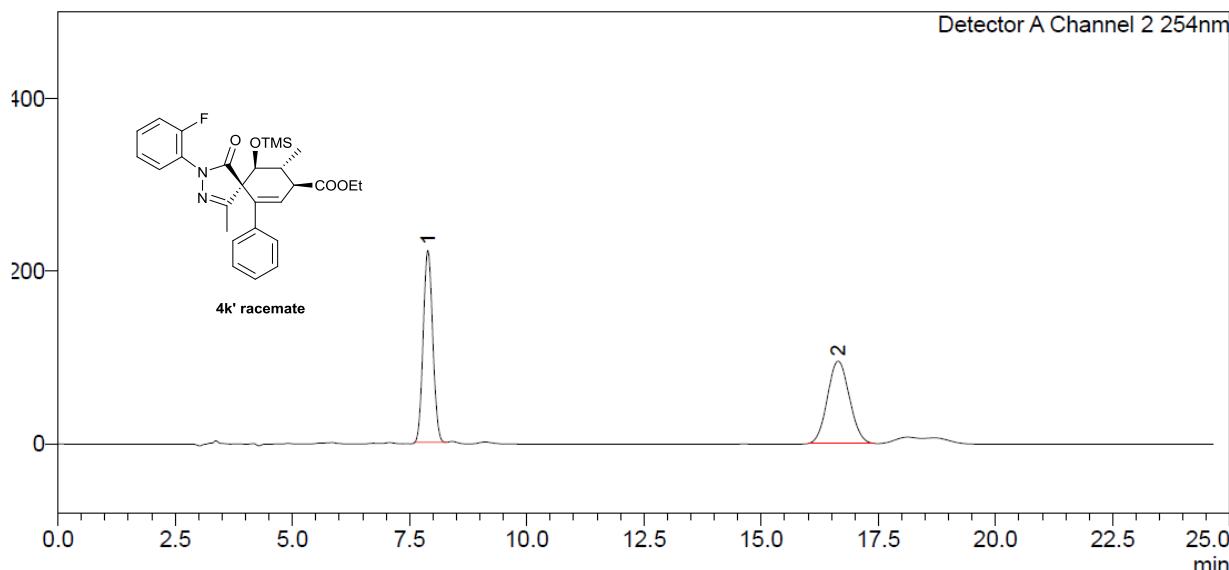


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	7.889	222055	3137631	50.302
2	16.643	95187	3099950	49.698
Total		317242	6237581	100.000

mV

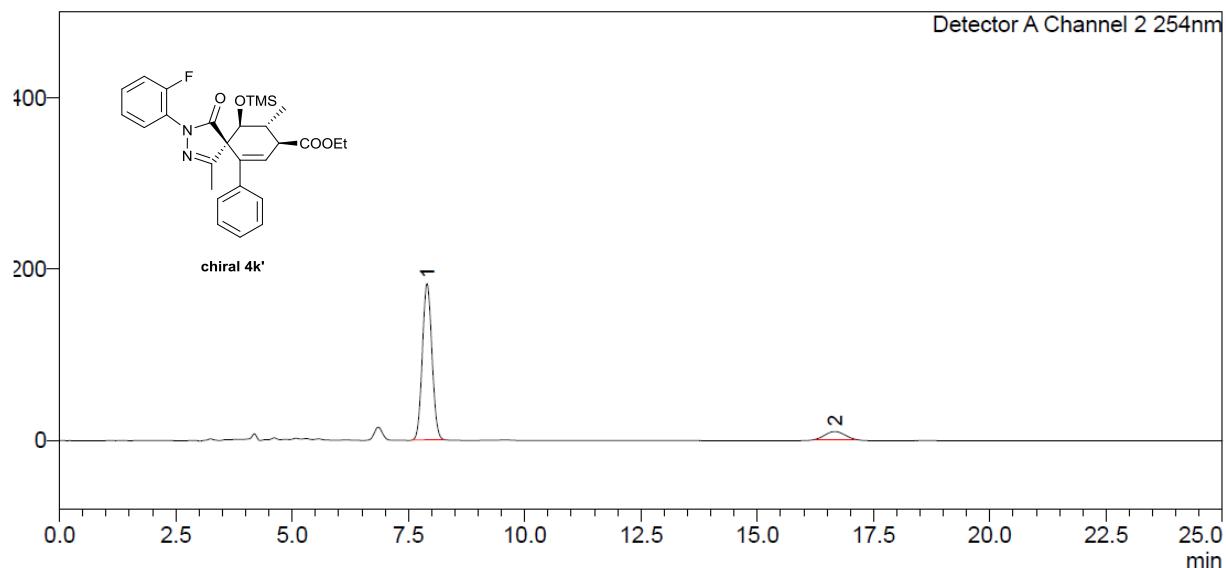


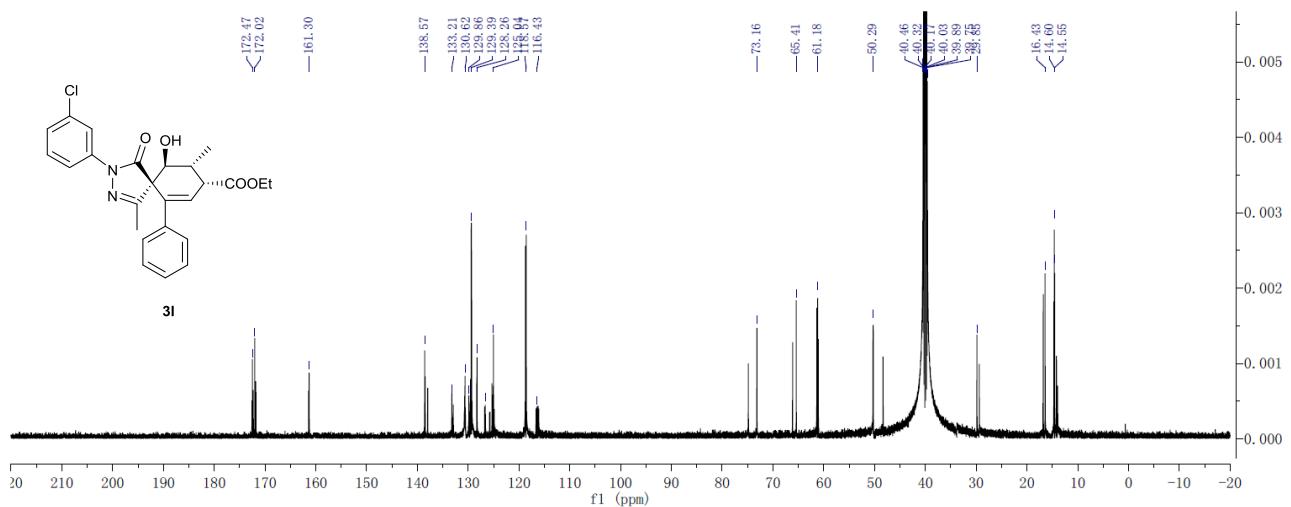
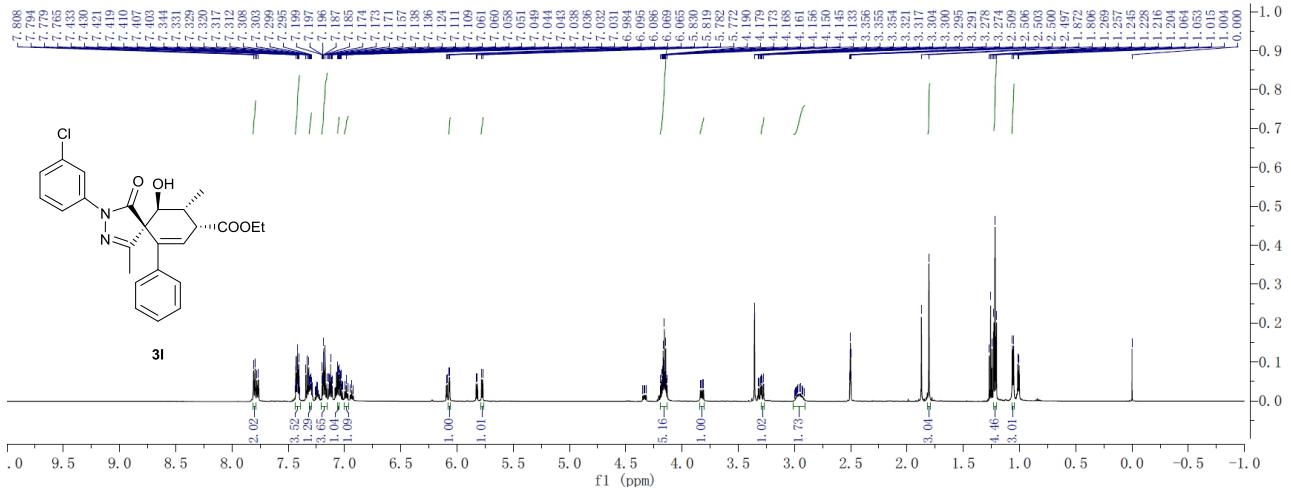
Peak Analysis Report

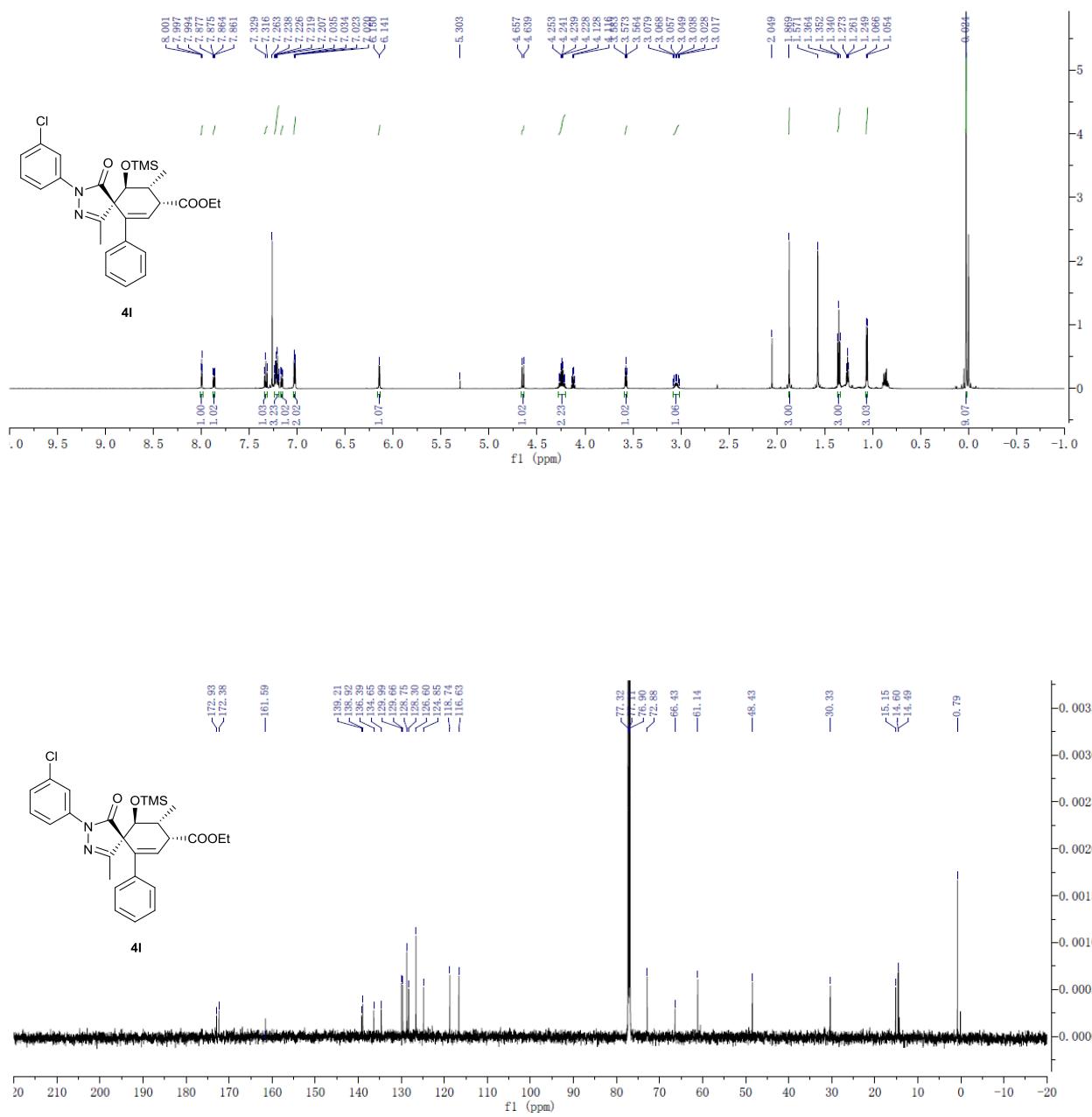
Detector A Channel 2 254nm

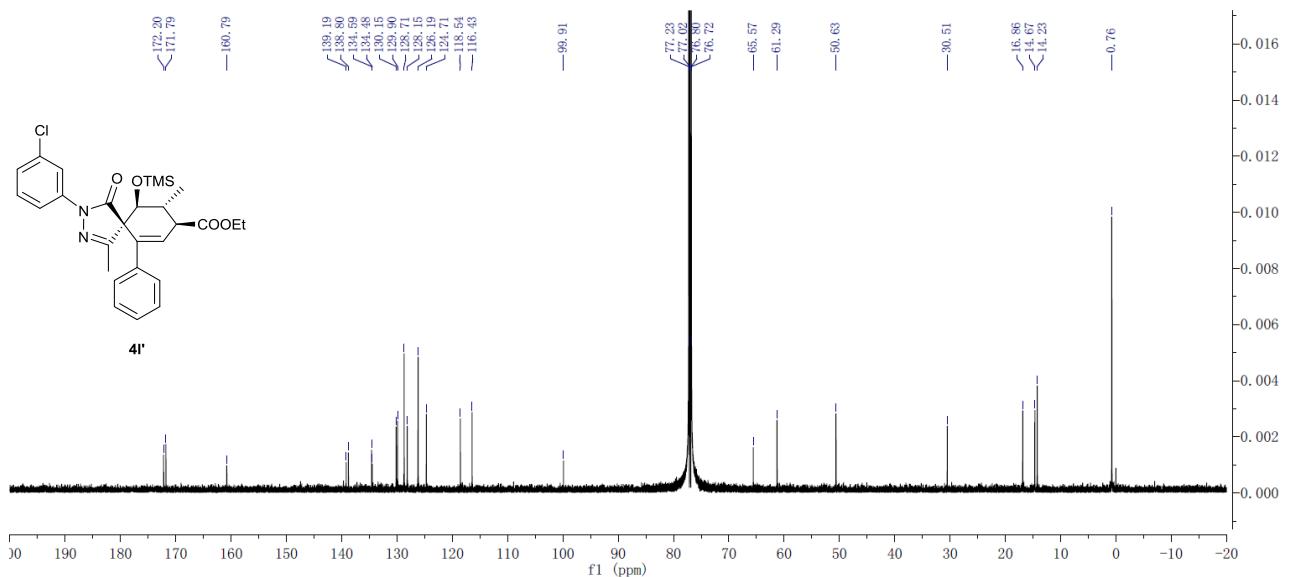
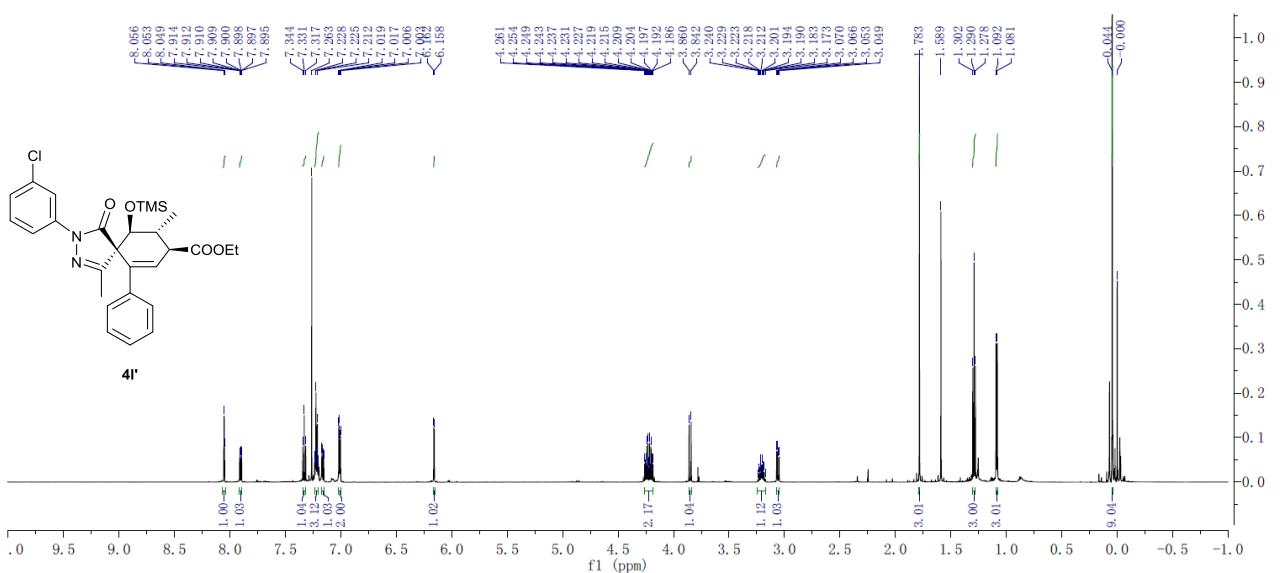
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	7.900	182282	2618672	91.075
2	16.667	9138	256605	8.925
Total		191420	2875277	100.000

mV







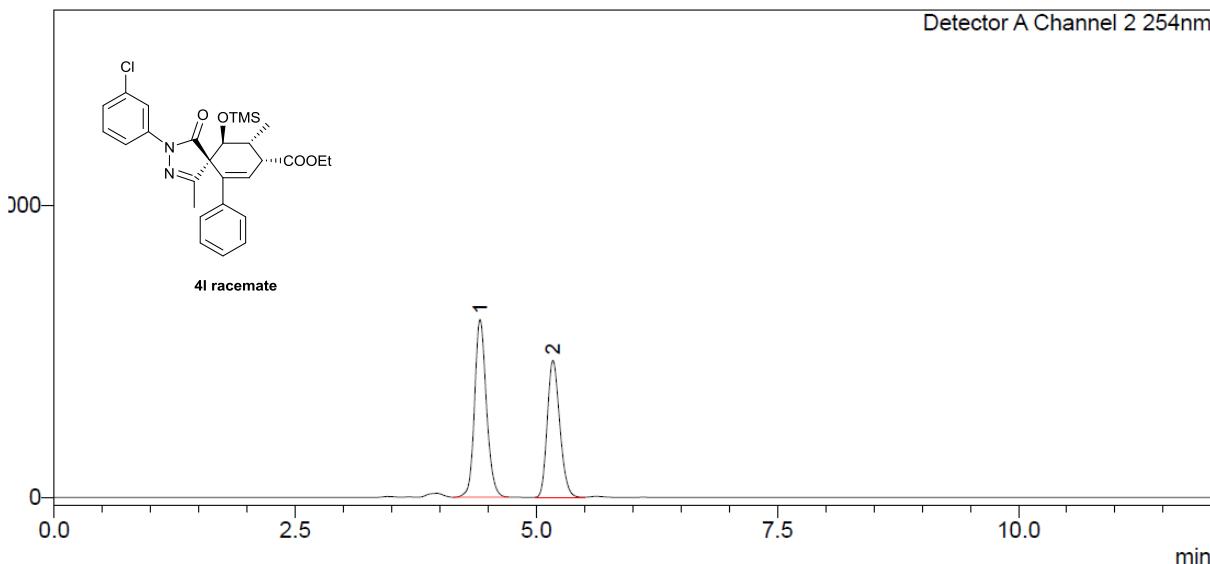


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.417	1826016	15596972	55.234
2	5.173	1404990	12640997	44.766
Total		3231006	28237969	100.000

mV

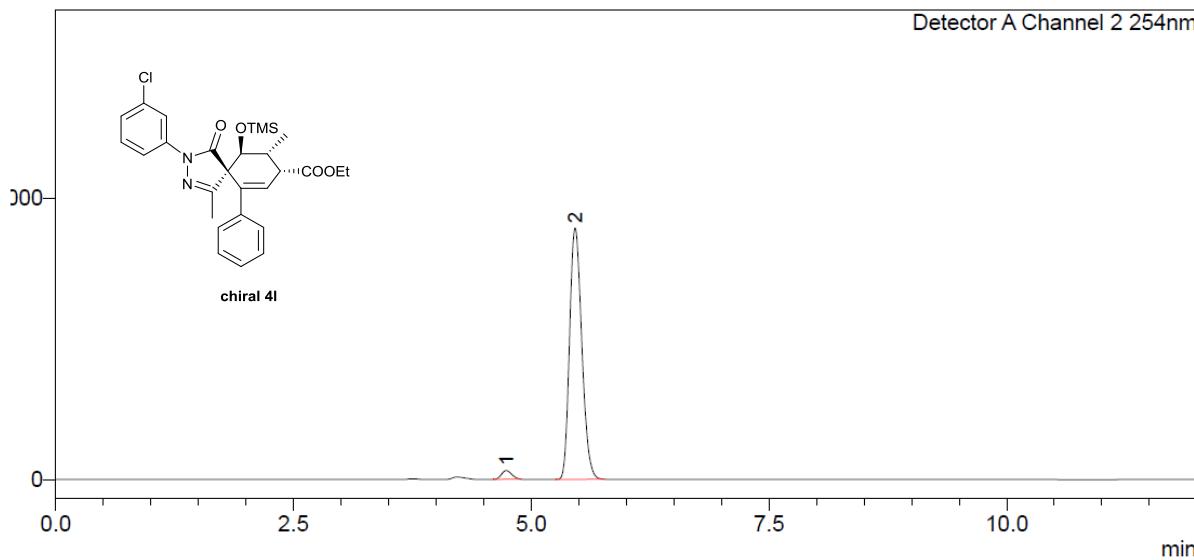


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.739	93550	702610	2.854
2	5.462	2676671	23918558	97.146
Total		2770221	24621168	100.000

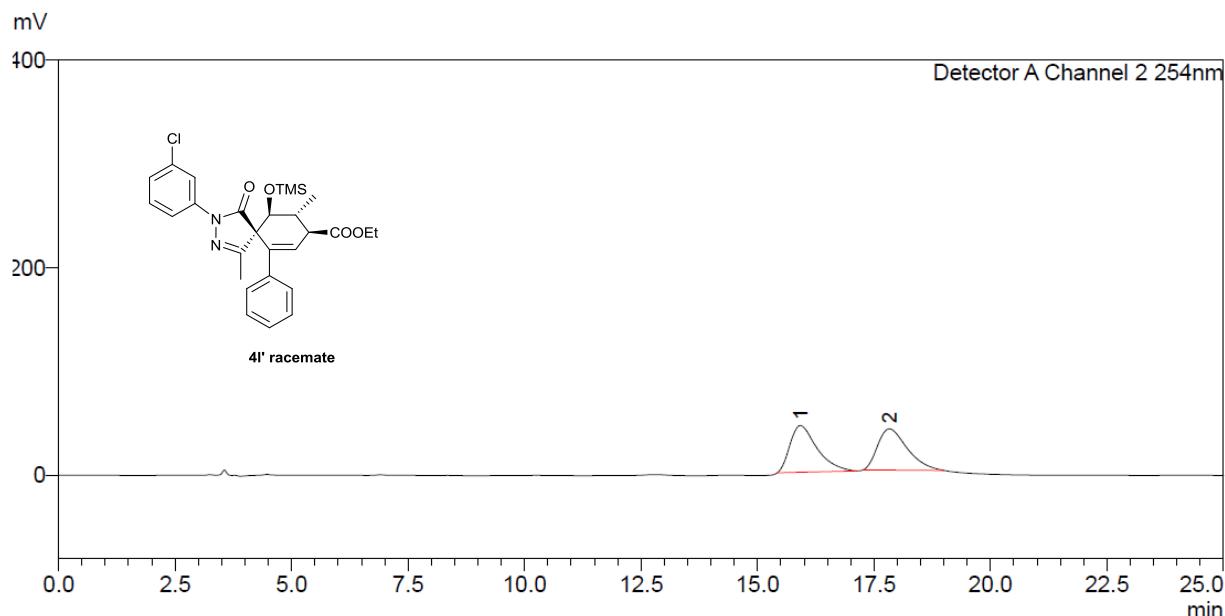
mV



Peak Analysis Report

Detector A Channel 2 254nm

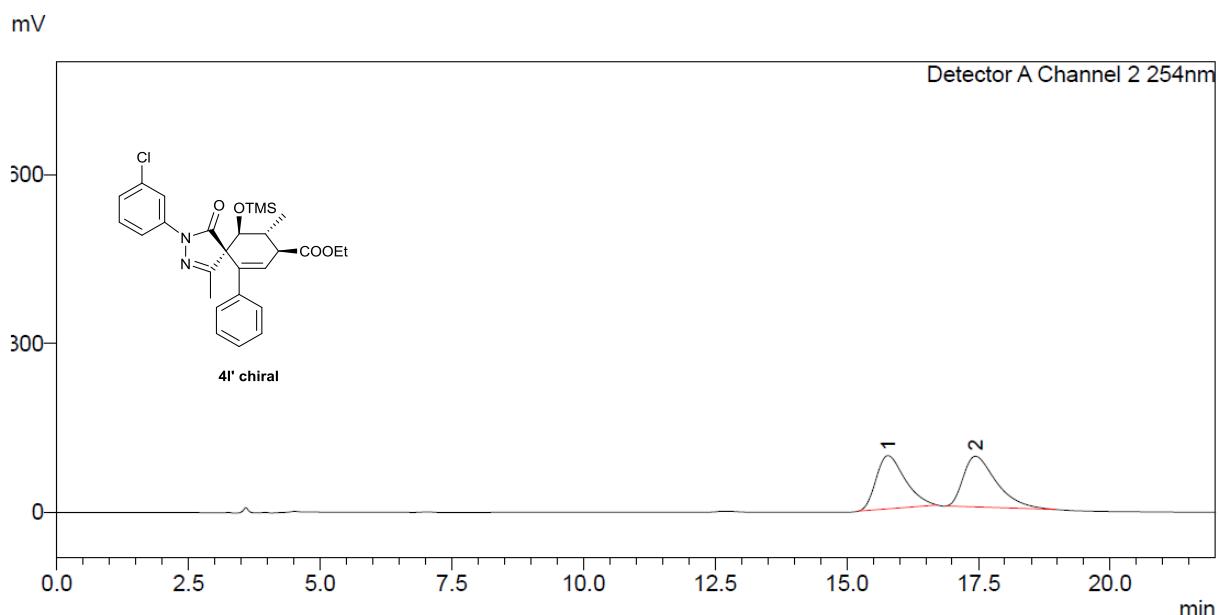
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	15.920	44994	1821774	50.818
2	17.830	39744	1763146	49.182
Total		84738	3584920	100.000

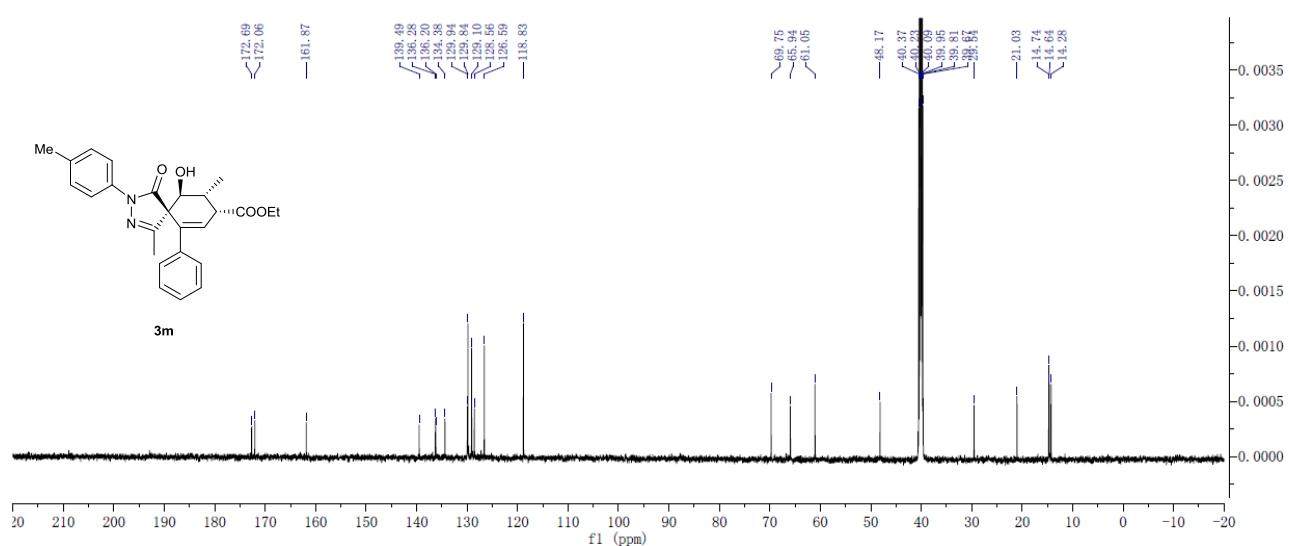
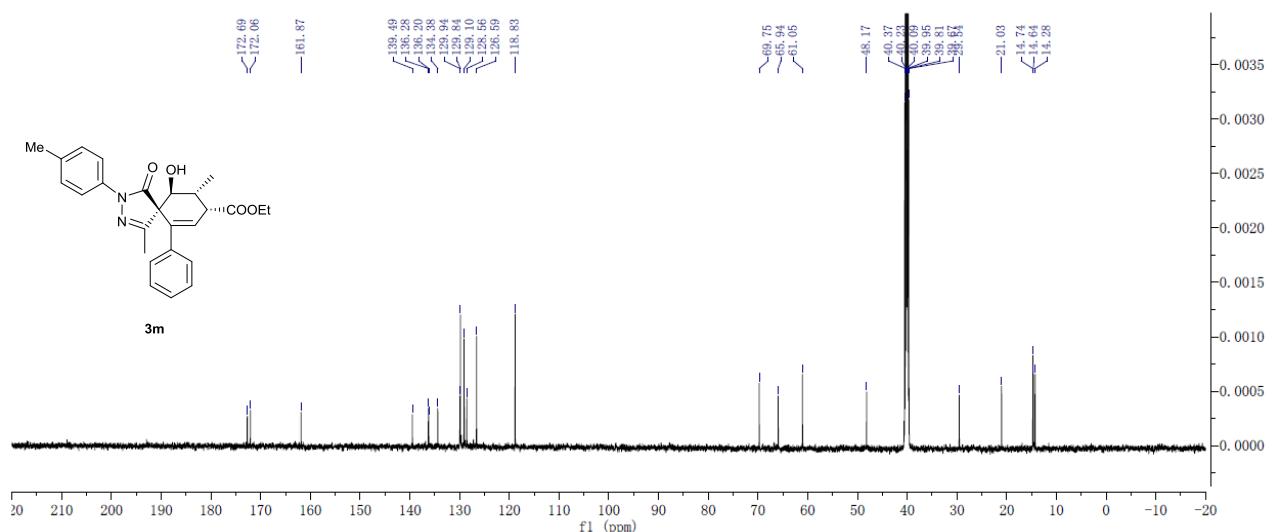


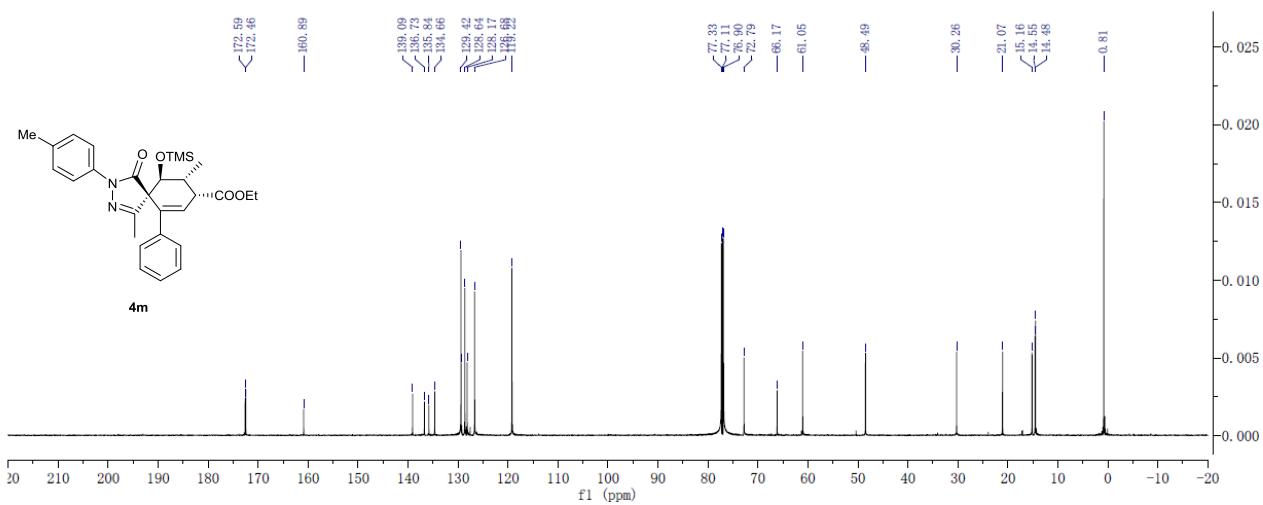
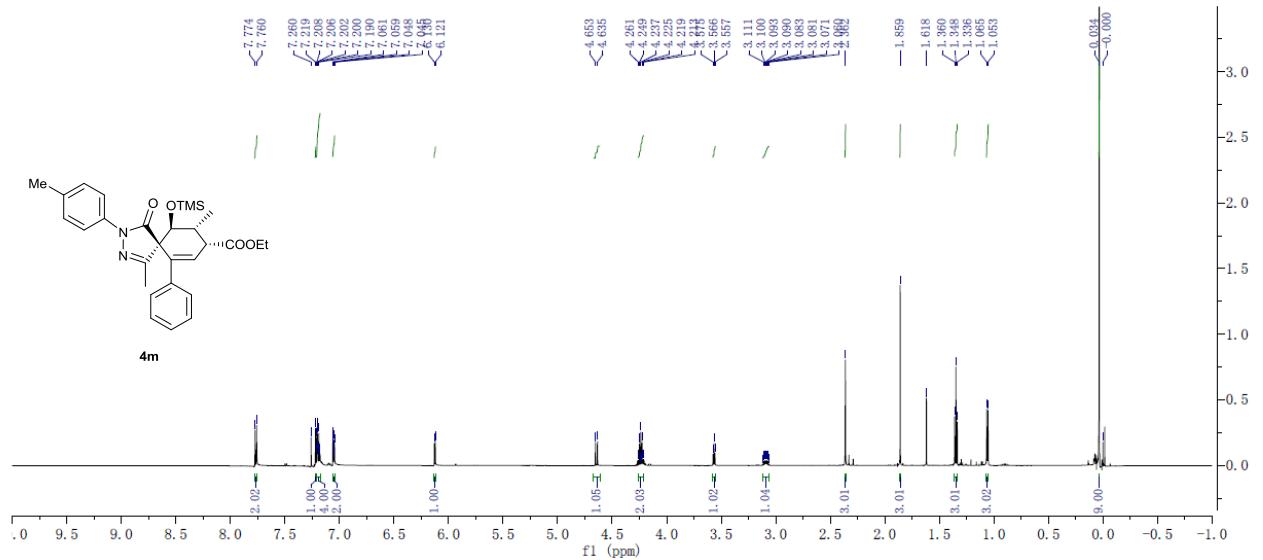
Peak Analysis Report

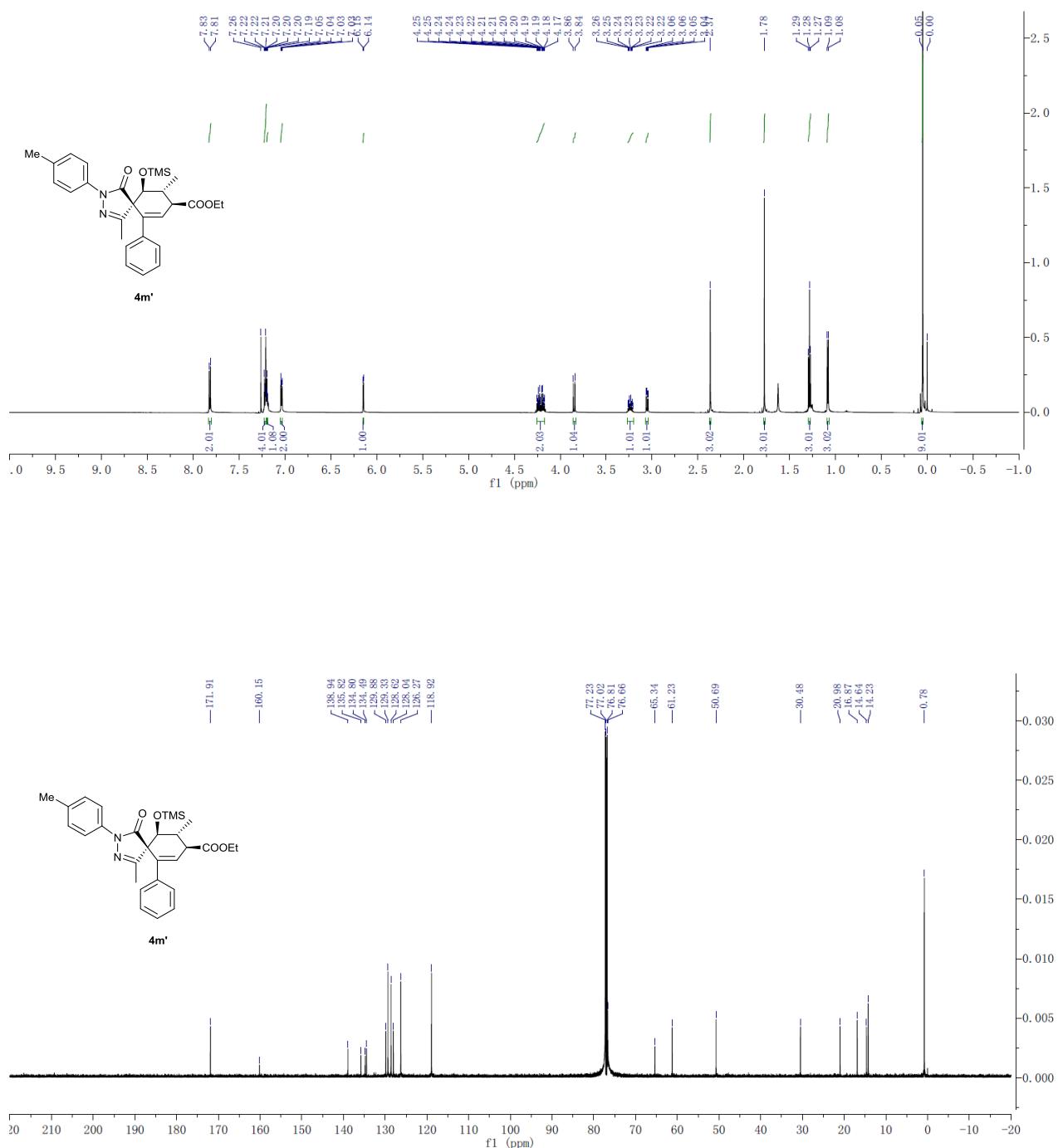
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	15.782	94466	3614296	47.936
2	17.444	89865	3925536	52.064
Total		184331	7539832	100.000





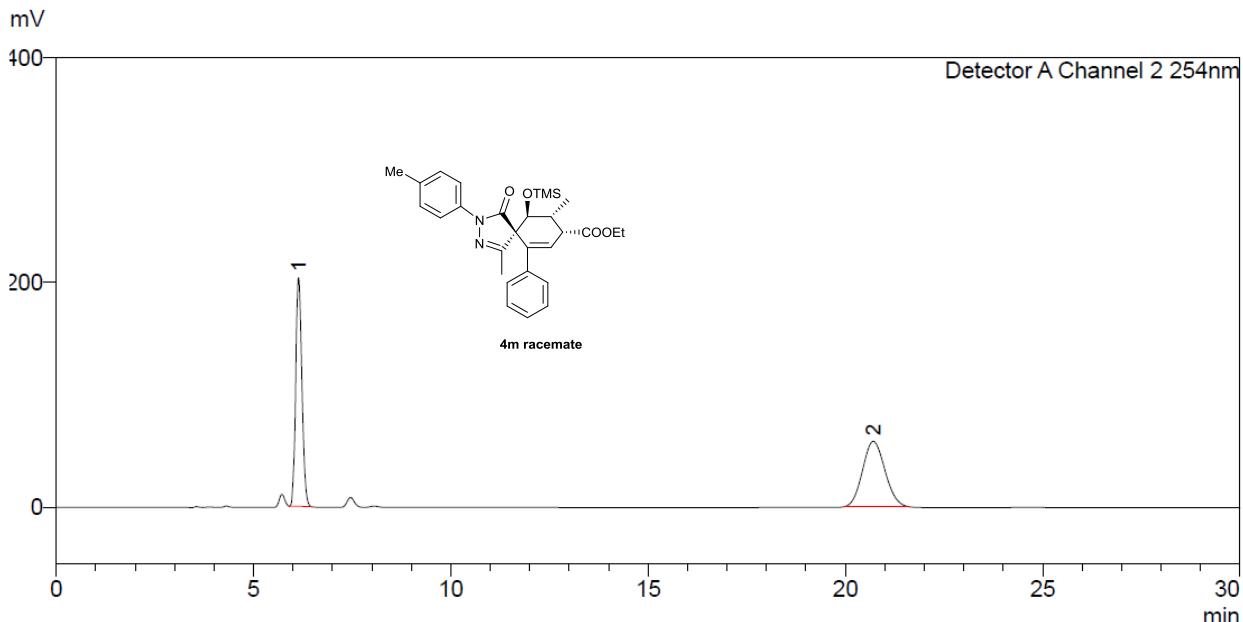




Peak Analysis Report

Detector A Channel 2 254nm

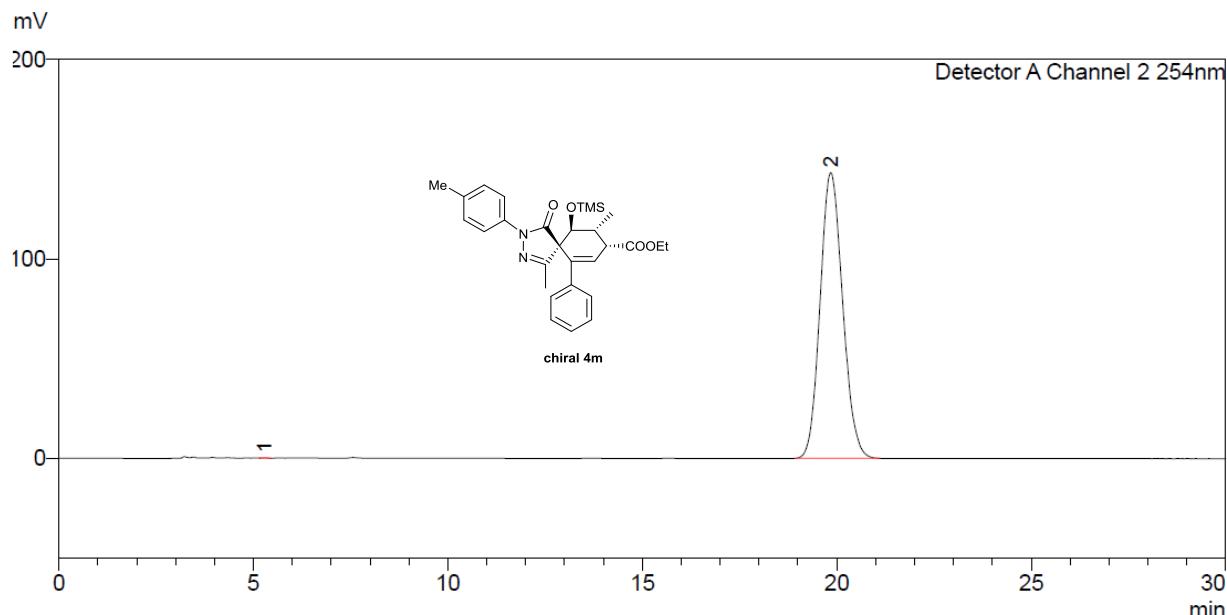
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	6.142	203440	2226360	49.338
2	20.709	58122	2286117	50.662
Total		261562	4512477	100.000



Peak Analysis Report

Detector A Channel 2 254nm

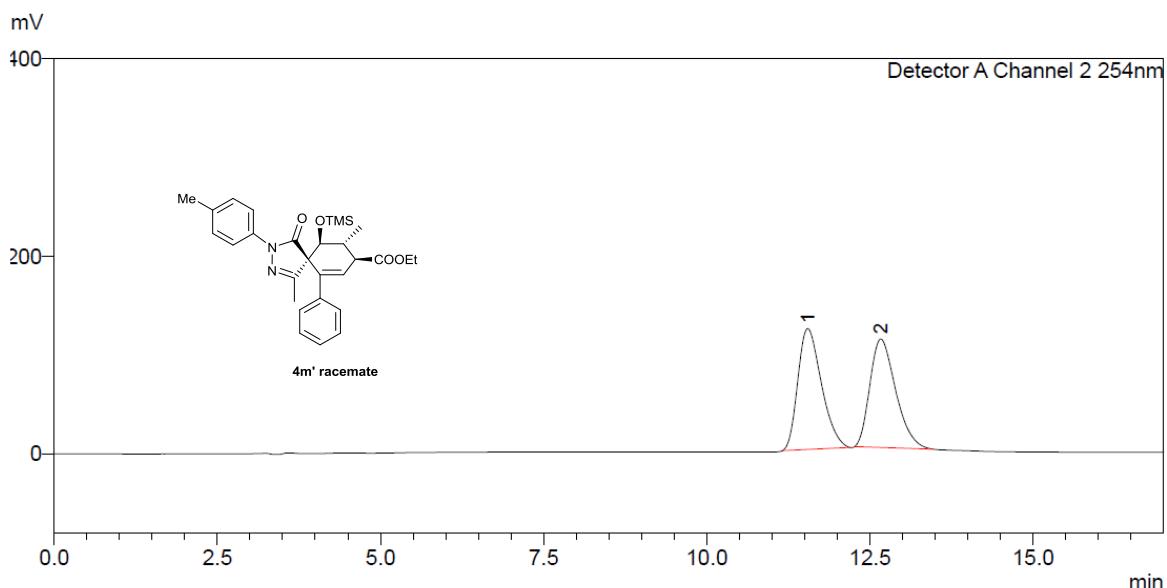
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	5.279	140	1295	0.022
2	19.847	143170	5758541	99.978
Total		143310	5759835	100.000



Peak Analysis Report

Detector A Channel 2 254nm

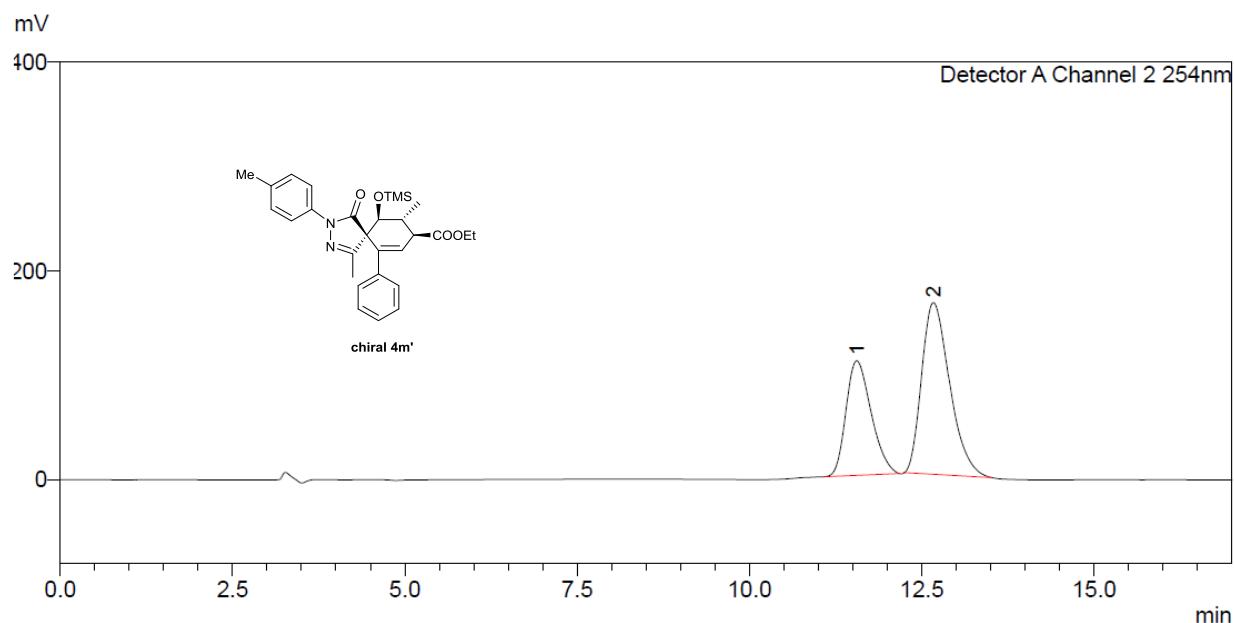
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	11.547	122424	3082190	50.583
2	12.667	109713	3011187	49.417
Total		232137	6093378	100.000

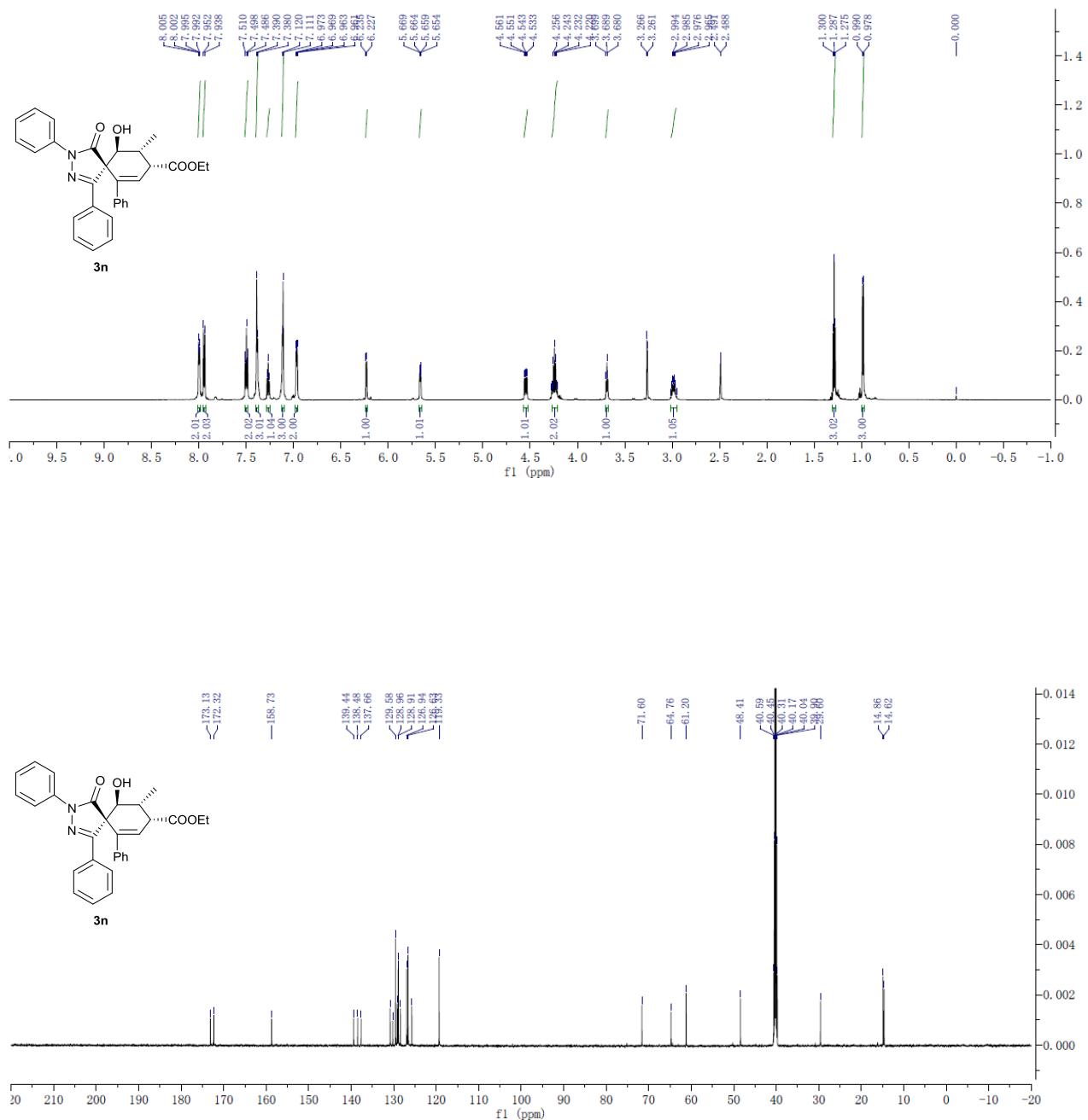


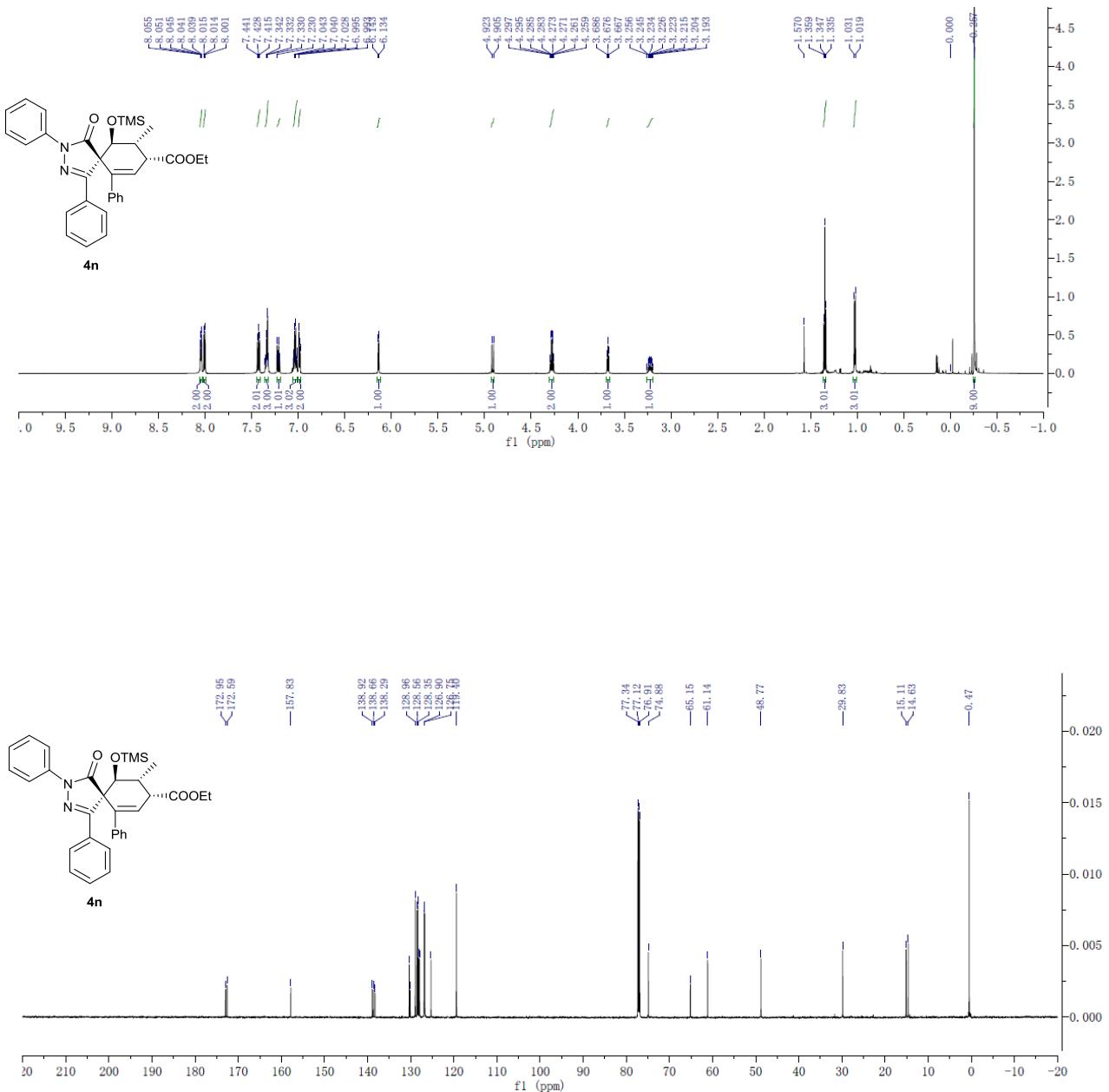
Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	11.556	109795	2784940	37.424
2	12.669	164418	4656606	62.576
Total		274213	7441545	100.000





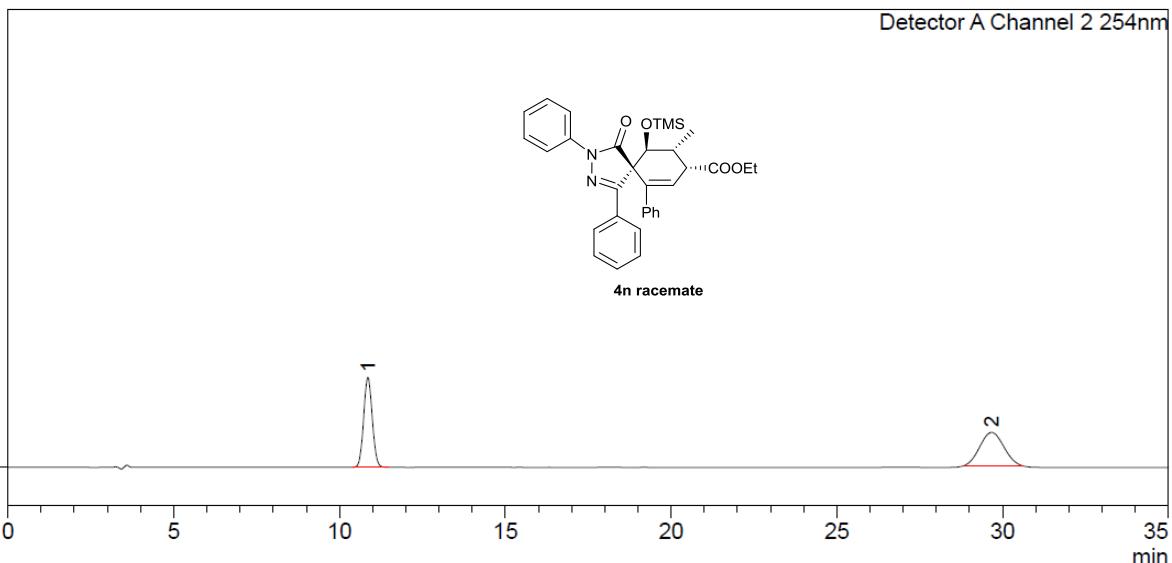


Peak Analysis Report

Detector A Channel 2 254nm

Detector A Channel 2 254nm				
No.	Ret. Time	Height (mAU)	Area (mAU*min)	Rel. Area (%)
1	10.855	117729	2131981	49.265
2	29.665	43883	2195605	50.735
Total		161612	4327587	100.000

mV

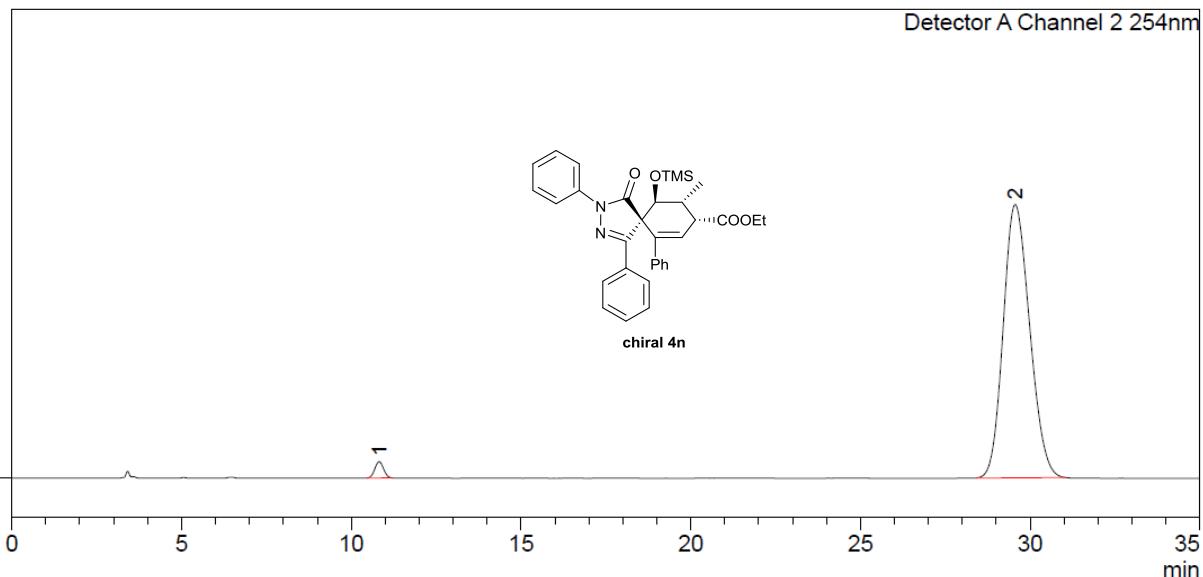


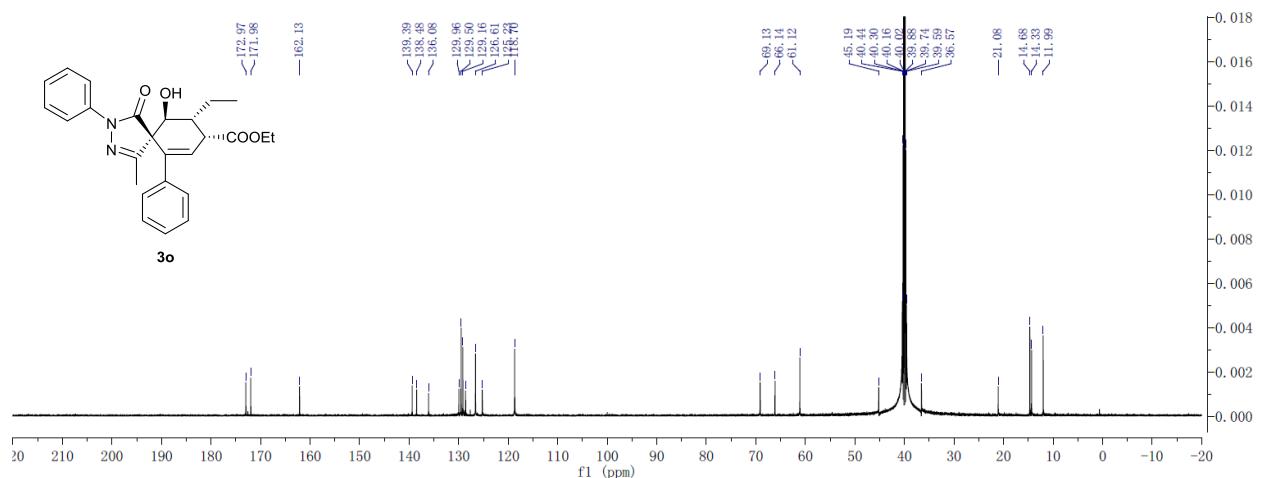
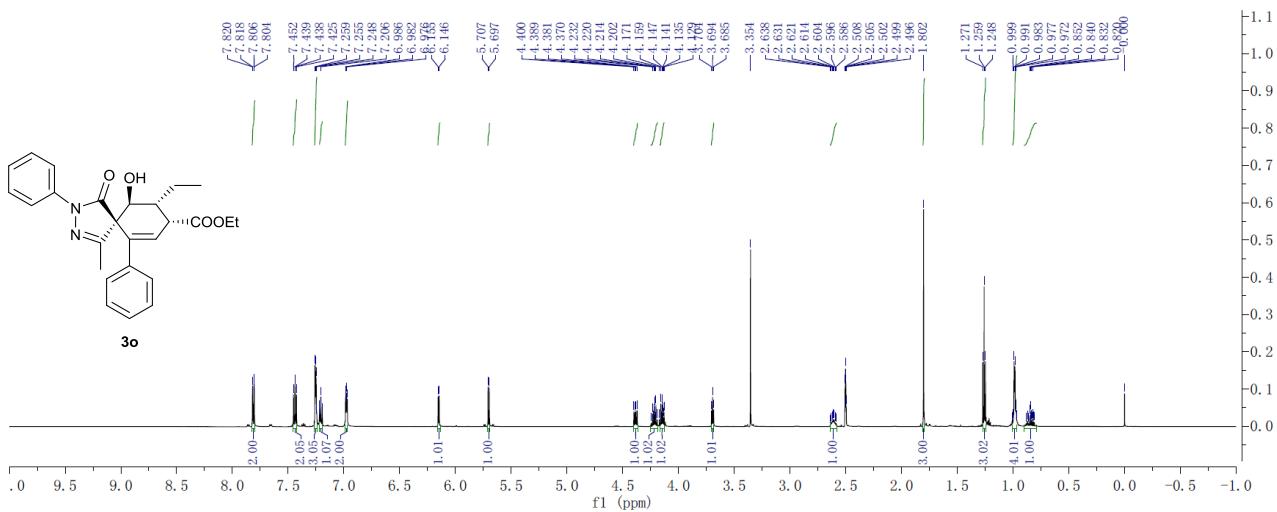
Peak Analysis Report

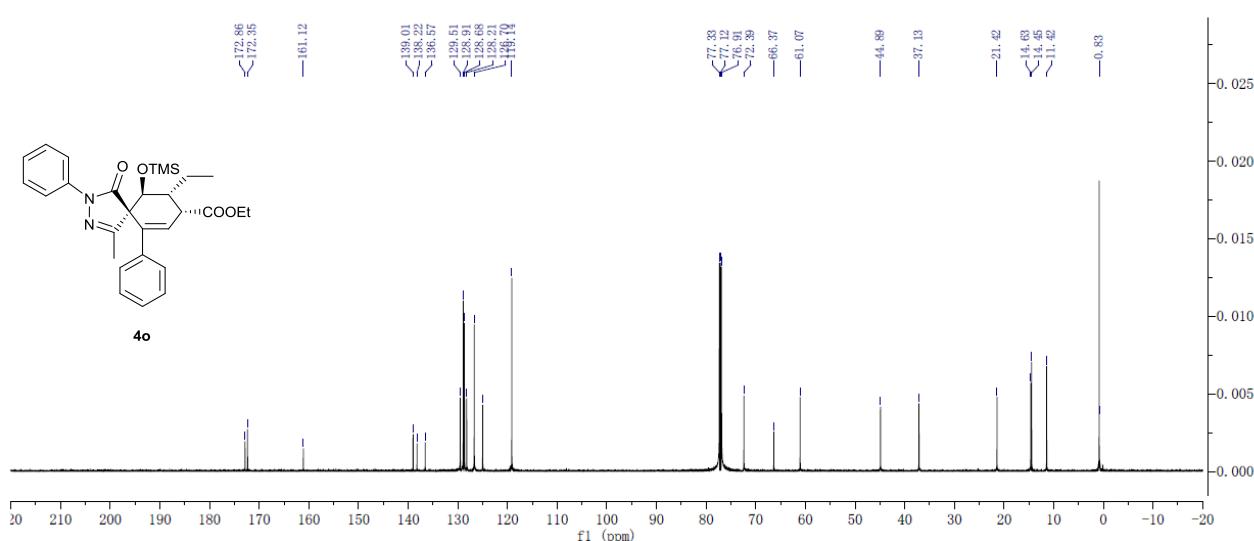
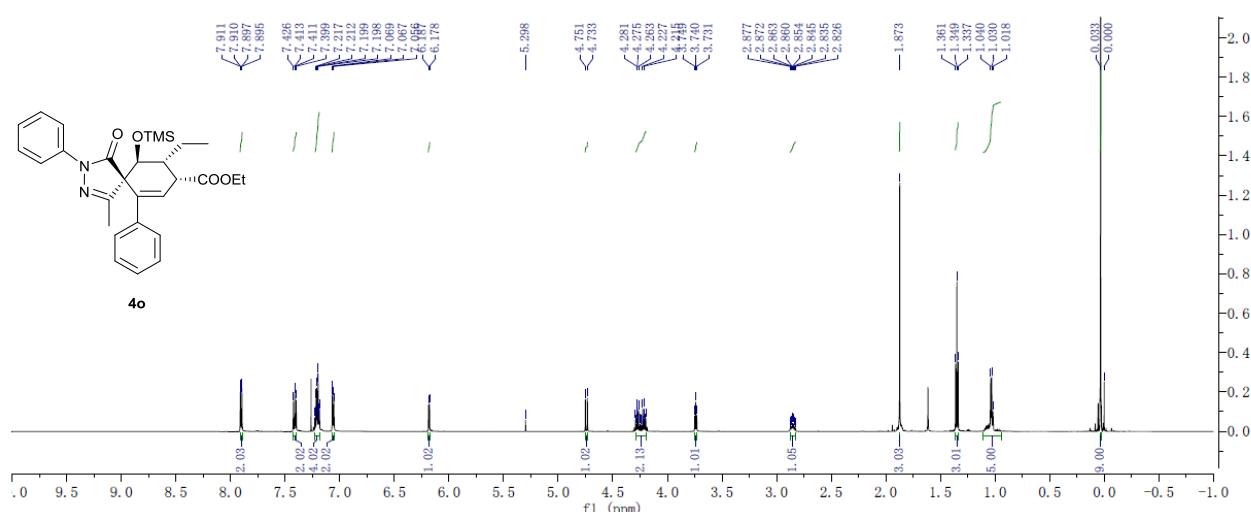
Detector A Channel 2 254nm

Detector A Channel 2 254nm				
No.	Ret. Time	Height (mAU)	Area (mAU*min)	Rel. Area (%)
1	10.821	20953	372893	1.927
2	29.557	350222	18976900	98.073
Total		371175	19349792	100.000

mV





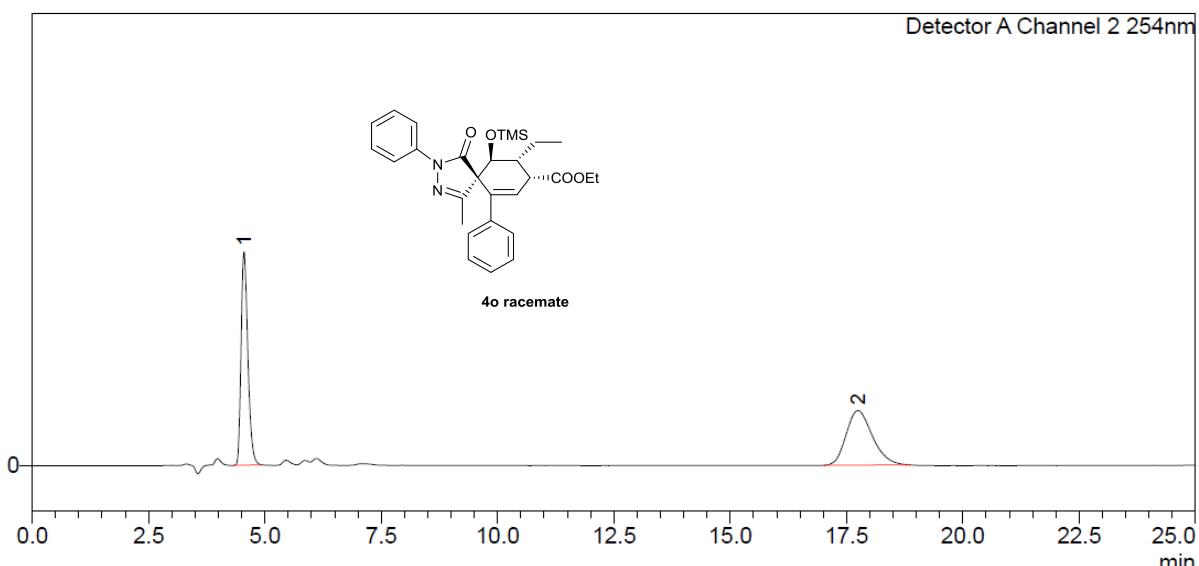


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.551	141622	1426179	50.089
2	17.744	36281	1421103	49.911
Total		177903	2847283	100.000

mV

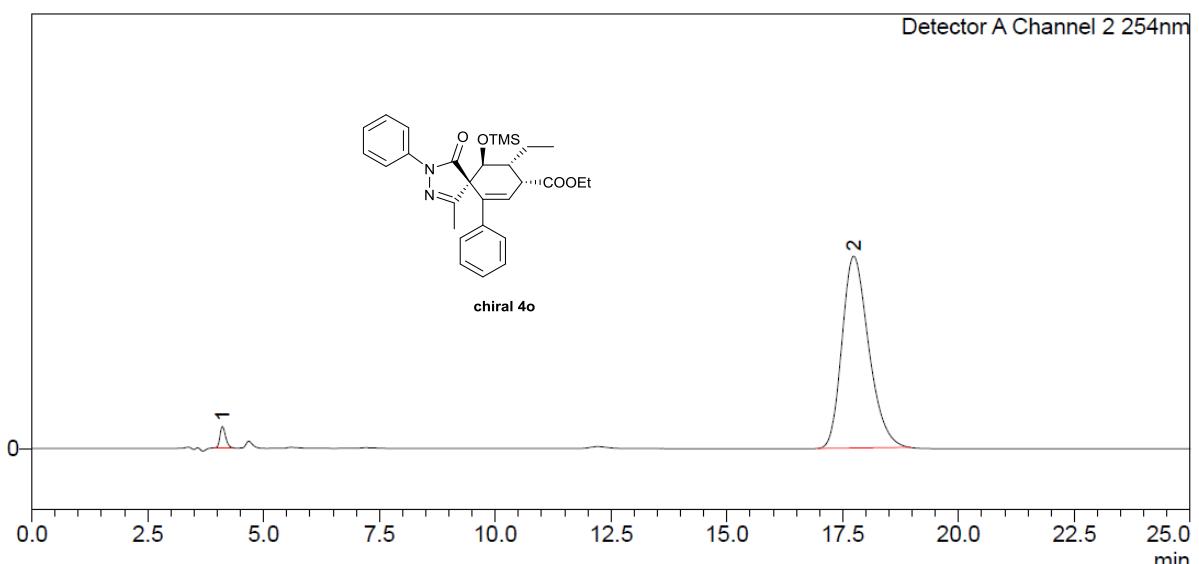


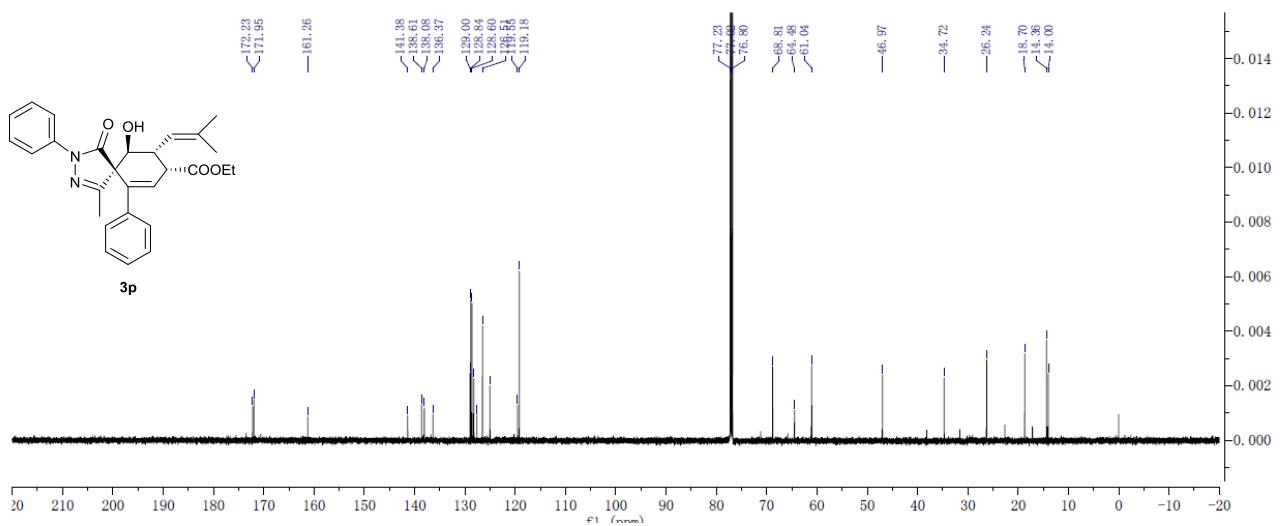
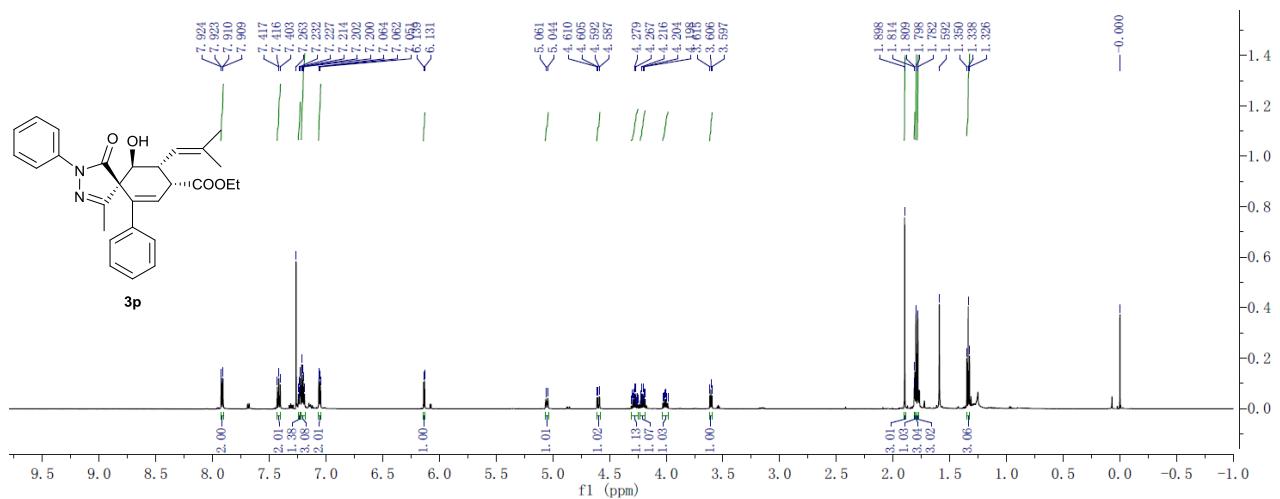
Peak Analysis Report

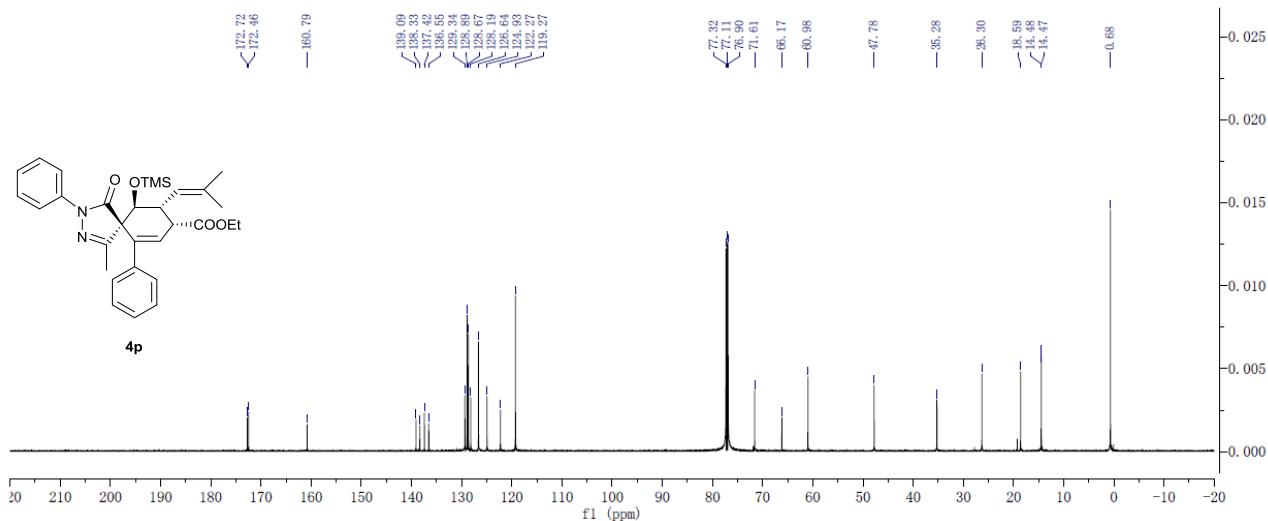
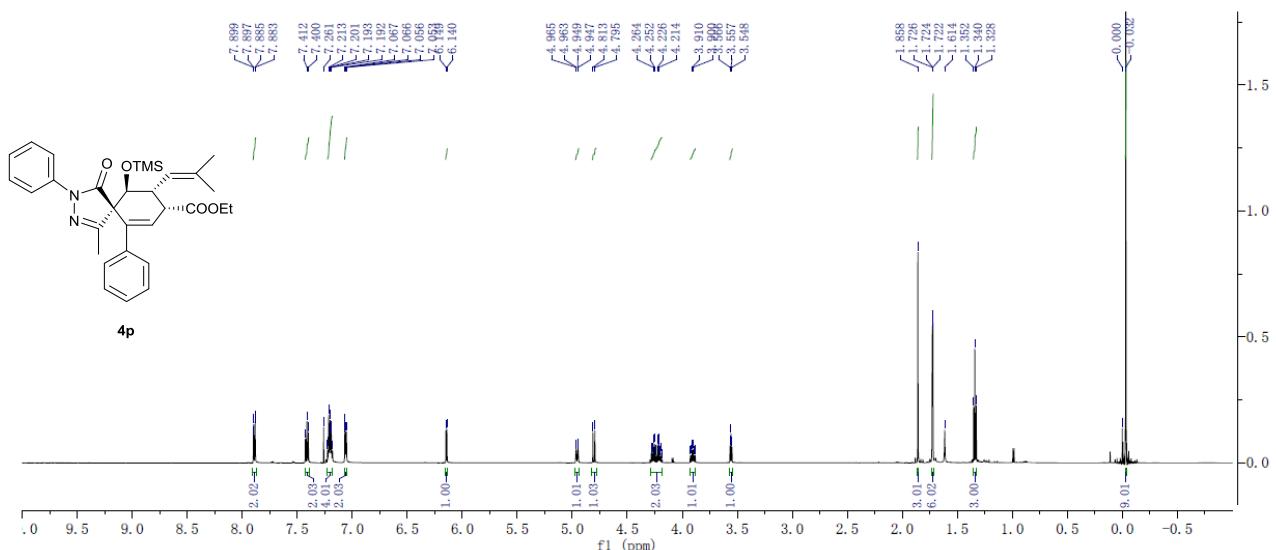
Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	4.110	24487	205447	2.266
2	17.738	220804	8862887	97.734
Total		245292	9068334	100.000

mV





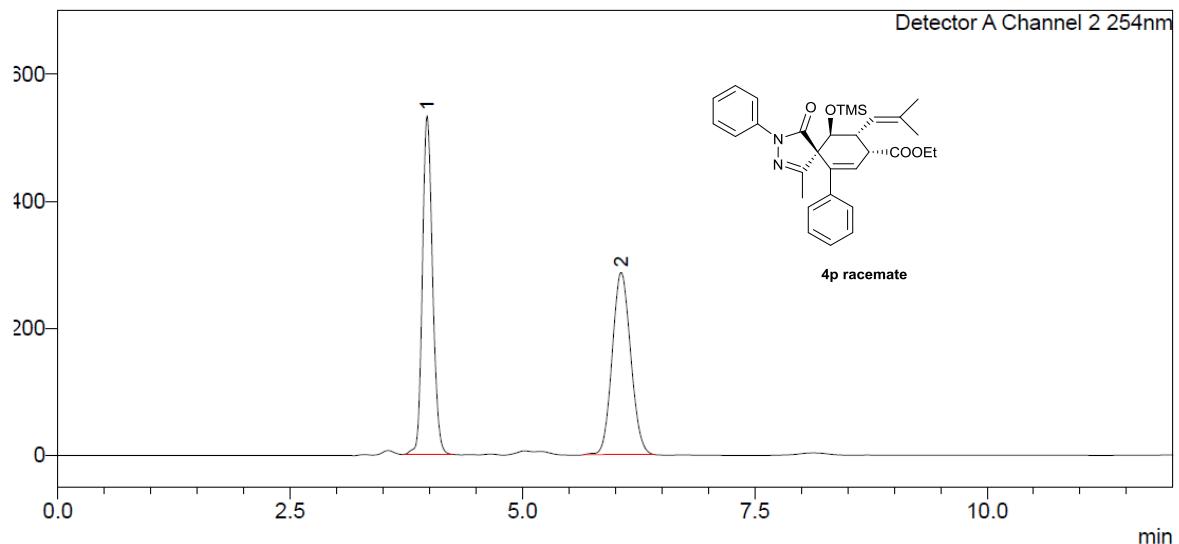


Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	3.974	533358	4047084	50.532
2	6.062	286359	3961905	49.468
Total		819717	8008989	100.000

mV

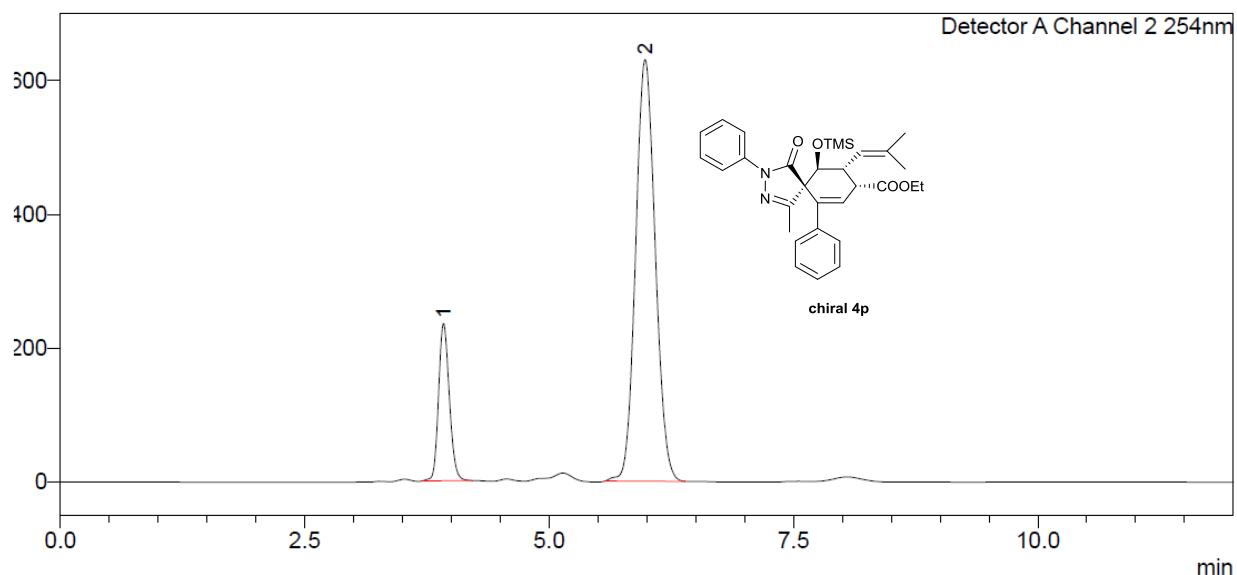


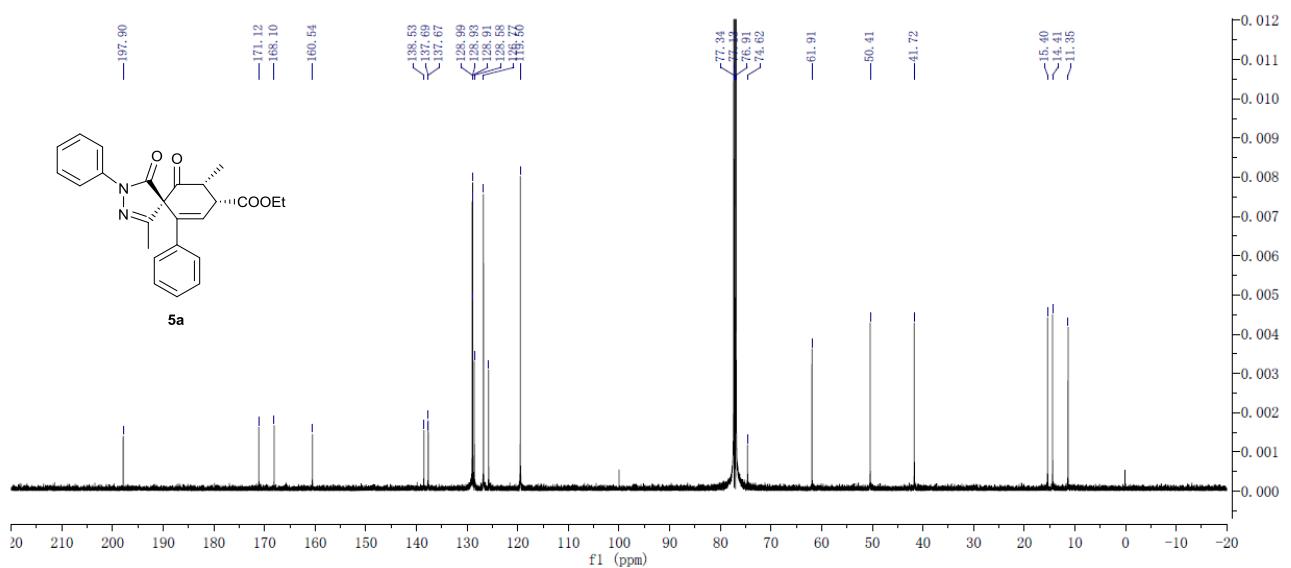
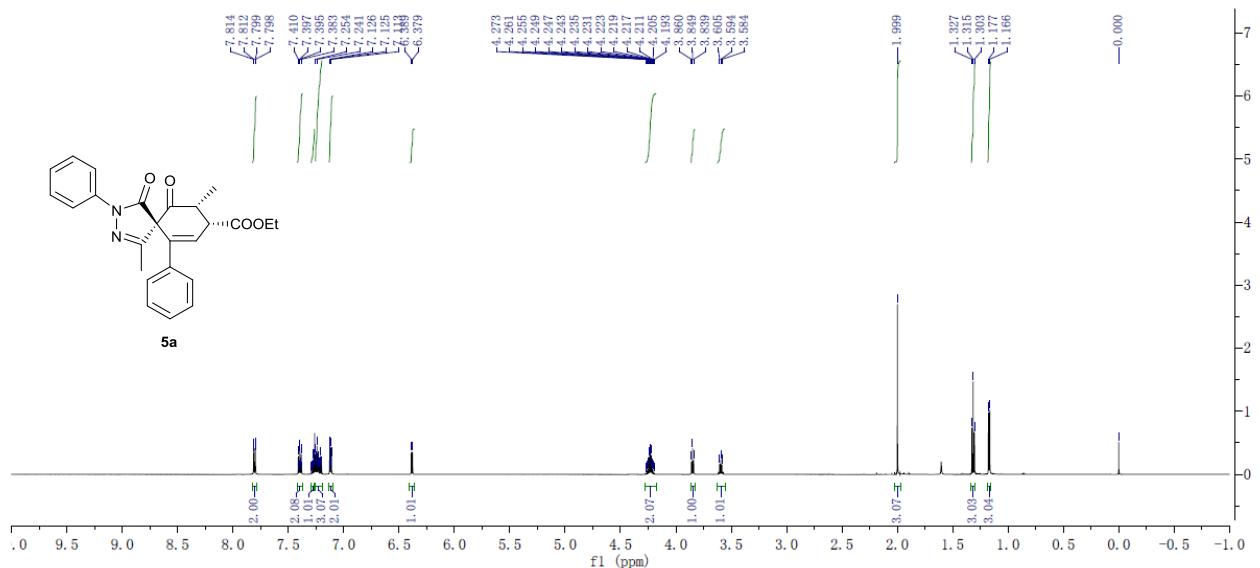
Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	3.920	234880	1800661	16.918
2	5.982	630427	8842937	83.082
Total		865307	10643598	100.000

mV

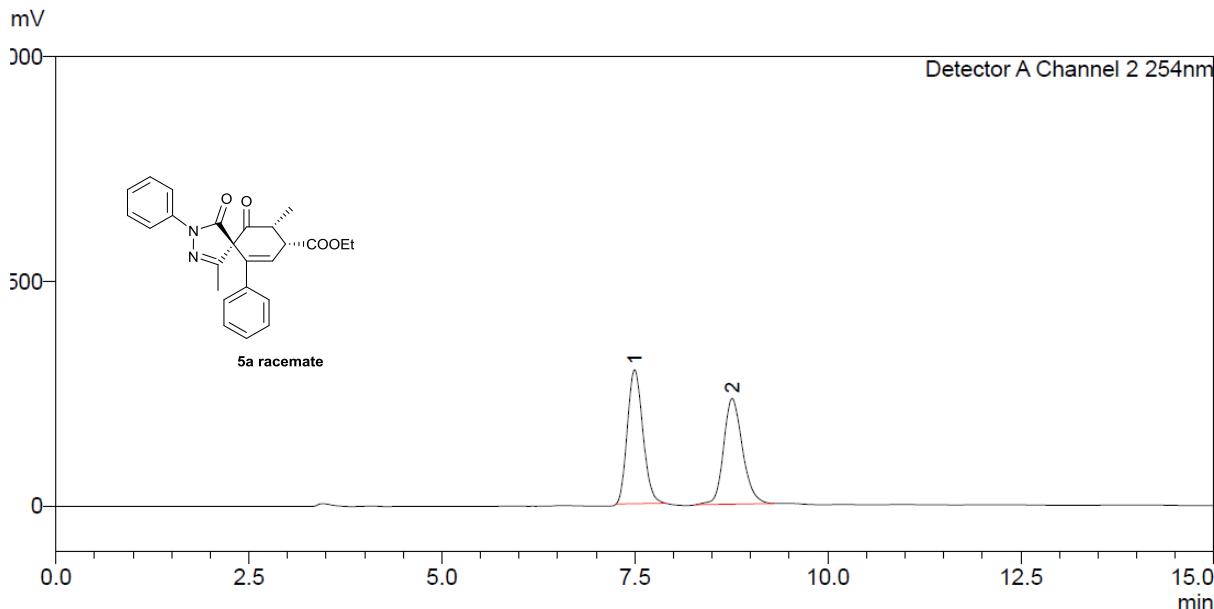




Peak Analysis Report

Detector A Channel 2 254nm

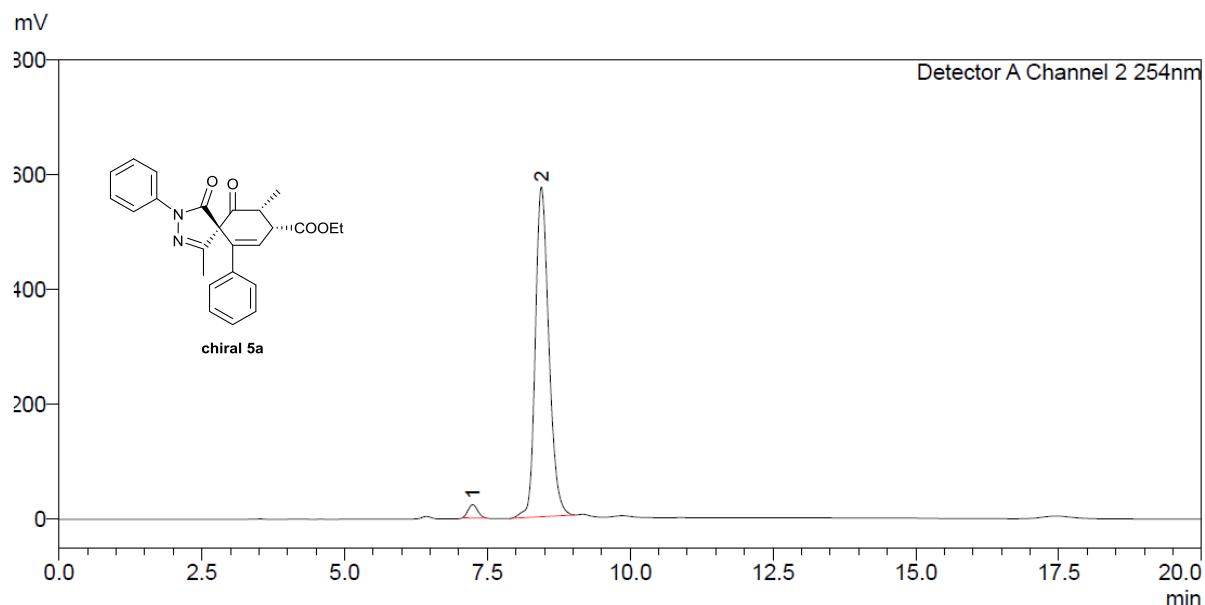
No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	7.497	297698	4166768	50.929
2	8.760	234955	4014760	49.071
Total		532653	8181528	100.000



Peak Analysis Report

Detector A Channel 2 254nm

No.	Ret. Time	Height (mAu)	Area (mAu*min)	Rel. Area (%)
1	7.241	23075	269161	2.757
2	8.444	574399	9492657	97.243
Total		597474	9761818	100.000



3. The anti-proliferative IC₅₀ values against a panel of cancer cell lines (Table S1)^a

Compound	IC ₅₀ (μ M)					
	BEAS-2B	A549	MCF-7	PANC-1	786O	HCT116
3a	27.40	4.88	3.23	5.86	8.97	2.10
3b	12.30	3.02	2.16	4.65	6.56	1.66
3c	14.82	2.99	2.10	3.57	4.58	1.57
3d	11.78	2.57	1.96	3.67	5.39	1.36
3e	15.43	2.97	2.34	4.58	5.86	1.53
3f	39.35	8.73	5.86	12.56	18.34	4.80
3g	25.99	1.13	0.81	1.54	2.16	0.56
3h	23.07	0.77	0.52	1.17	2.44	0.37
3i	14.79	3.12	2.17	3.96	6.26	1.68
3j	45.06	25.14	20.44	39.97	61.16	15.14
3k	42.28	8.29	6.74	10.53	14.21	4.68
3l	37.87	6.52	4.18	8.21	11.50	3.37
3m	26.15	5.62	4.61	7.42	11.80	3.81
3n	25.79	50.05	40.69	62.06	>50.00	27.31
3o	26.79	20.11	14.37	25.14	35.95	9.15
3p	41.41	40.78	27.93	59.54	>50.00	17.79
4a	54.50	>50.00	46.50	>50.00	37.80	>50.00
5a	36.82	6.35	4.41	10.03	13.44	2.79

^a Each compound was tested in triplicate; the data are presented as the mean values.