Supporting information

Simple Organocatalysts Component System for Asymmetric Hetero Diels-Alder Reaction of Isatins with Enones

Perumalsamy Parasuraman,[a] Zubeda Begum,[a] Madhu Chennapuram,[a] Chigusa Seki,[a] Yuko Okuyama,[b] Eunsang Kwon,[c] Koji Uwai,[a] Michio Tokiwa,[d] Suguru Tokiwa,[d] Mitsuhiro Takeshita,[d] and Hiroto Nakano*[a]

[a]Division of Sustainable and Environmental Engineering, Graduate school of engineering, Muroran Institute of Technology, 27-1 Mizumoto-cho, Muroran 050-8585, E-mail: catanaka@mmm.muroran-it.ac.jp.

[b]Tohoku Medicinal and Pharmaceutical University, 4-4-1 Komastsushima, Aoba-Ku, Sendai 981-8558, Japan.

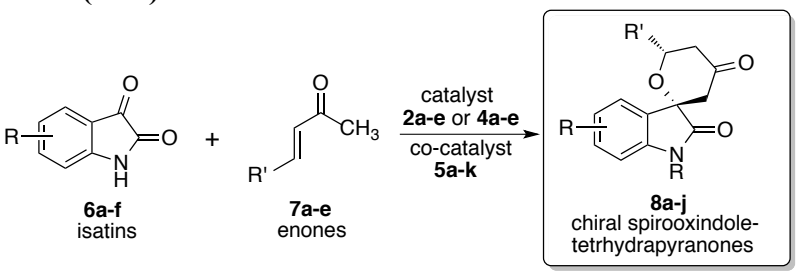
[c]Research and Analytical center for Giant molecules, Graduate School of Sciences, Tohoku University, 6-3 Aoba, Aramaki, Aoba-Ku, Sendai 980-8578, Japan.

[d]Tokiwakai Group, 62 Numajiri Tsuduri-Chou Uchigo, Iwaki 973-8053, Japan.

1. General information:

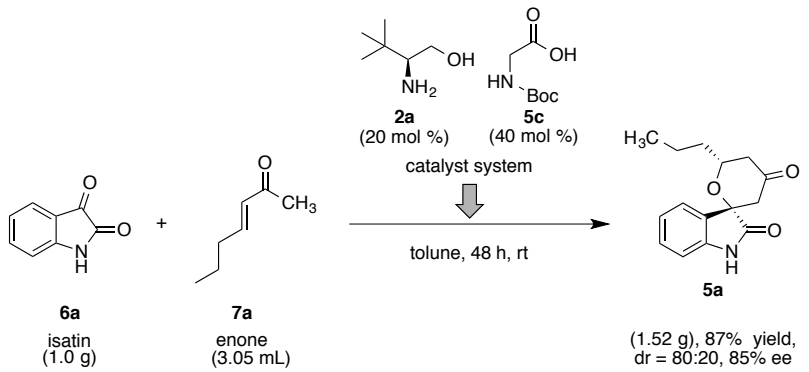
All reagents and dry solvents were purchased from commercial vendors and used directly without further purification. All reactions were placed in dried sample vials inserted with magnetic beads. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F_{254} plates and the analytes were identified under UV light. Flash column chromatography was performed using silica gel pore size 60_N (40-100 μm). Melting points were recorded with a micro-melting point apparatus. IR spectra were recorded with a JASCO-4100 Fourier transform infrared spectrophotometer. ^1H and ^{13}C NMR spectroscopic data were recorded using a JEOL JNM-ECA500 instrument with tetramethyl silane as the internal standard. HPLC data were collected using the TOSOH instrument equipped with (UV-8020, DP-8020, and SD-8022) detectors using CHIRALPAK IB column. Optical rotations were recorded using a JASCO DIP-360 digital polarimeter. High-resolution mass spectrometry (HRMS) data were collected by electron impact (EI) modes using Hitachi RMG-GMG and JEOL JNX-DX303 sector instruments.

2. General procedure for the Hetero Diels-Alder (HAD) reaction of isatins (6a-f) with enones (7a-e)



To a solution of the corresponding isatins **6a-f** (0.2 mmol, 1 eq.) and enones **7a-e** (0.8 mmol, 4 eq.) in anhydrous toluene (0.3 mL) were added catalysts **2a-e** or **4a-e** (0.04 mmol, 20 mol%) and co-catalysts **5a-k** (0.08 mmol, 40 mol%) at room temperature and the mixture were stirred at that temperature for 48 h. The mixture was purified by flash column chromatography (SiO_2: hexane/ethyl acetate, 7:3) to afford the corresponding major HDA adducts **8a-j**[9]. The diastereoselectivity (*dr*) of the obtained HDA adducts were determined by the crude reaction mixture by ^1H-NMR.[9] The enantiomeric excess (ee) of **8a-j** were determined by HPLC (CHIRALPAK-IB, hexane/*i*-PrOH = 70:30, 90:10 and 95:5, 1.0mL and 0.6mL/min, λ = 245 nm).[9]

3. Large scale synthesis of 8a using Hetero Diels-Alder (HAD) reaction of isatins (6a) with enones (7a)

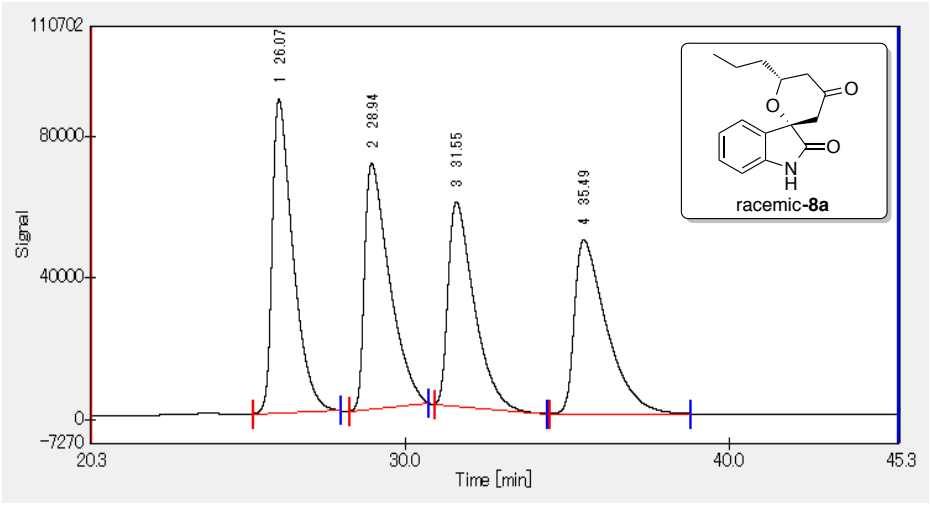


To a solution of the corresponding isatins **6a** (6.79 mmol, 1 eq.) and enones **7a** (27.1 mmol, 4 eq.) in anhydrous toluene (15 mL) were added catalysts **2a** and (1.35 mmol, 20 mol%) and co-catalysts **5c** (2.71 mmol, 40 mol%) at room temperature and the mixture were stirred at that temperature for 48 h. The mixture was purified by column chromatography (SiO_2: hexane/ethyl acetate, 7:3) to afford the corresponding major HDA adducts **8a**[9] as a pale yellow amorphous solid (1.52g, 87% yield, dr= 80:20 and major diastereomer 85% ee). The diastereoselectivity (*dr*) of the obtained HDA adducts were determined by the crude reaction mixture by ^{1}H NMR. The enantiomeric excess (ee) of **8a** were determined by HPLC (CHIRALPAK-IB, hexane/*i*-PrOH = 90:10 1.0mL /min, λ = 245 nm).[9]

4. High Performance Liquid Chromatography (HPLC) data of HDA adducts (8a-i)

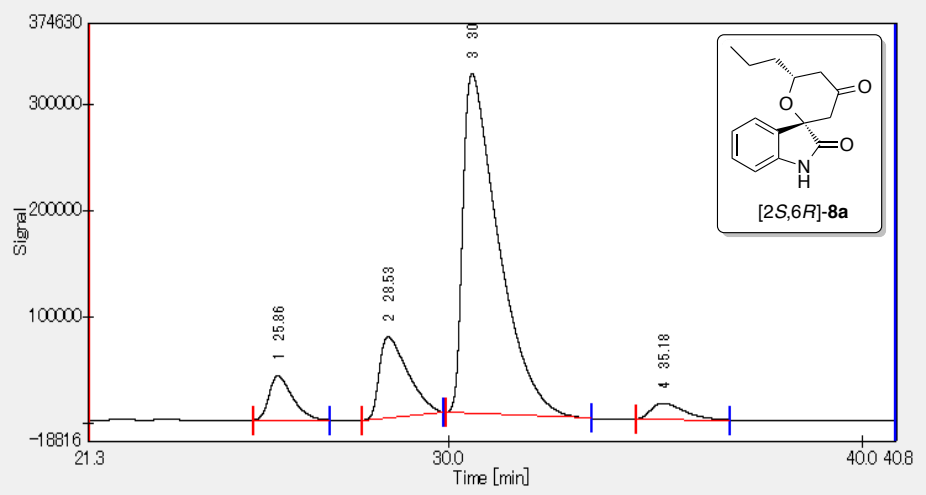
(2*S*,6*R*)- 6'-propyl-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8a): Daicel chiralpak IB, hexane/*i*-PrOH = 70/30, 1.0ml/min, λ=254 nm).

Racemic 8a + diastereomer



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	26.07	3969172.8	27.73	88773	7046.8	1.867	2.08
2	28.94	3728728.6	26.0502	69566	5842.6	2.175	1.706
3	31.55	3214591.4	22.4583	57734	6635.2	1.939	2.26
4	35.49	3401132.4	23.7615	49149	5368.5	2.113	*****
		14313625.2	100	265222			

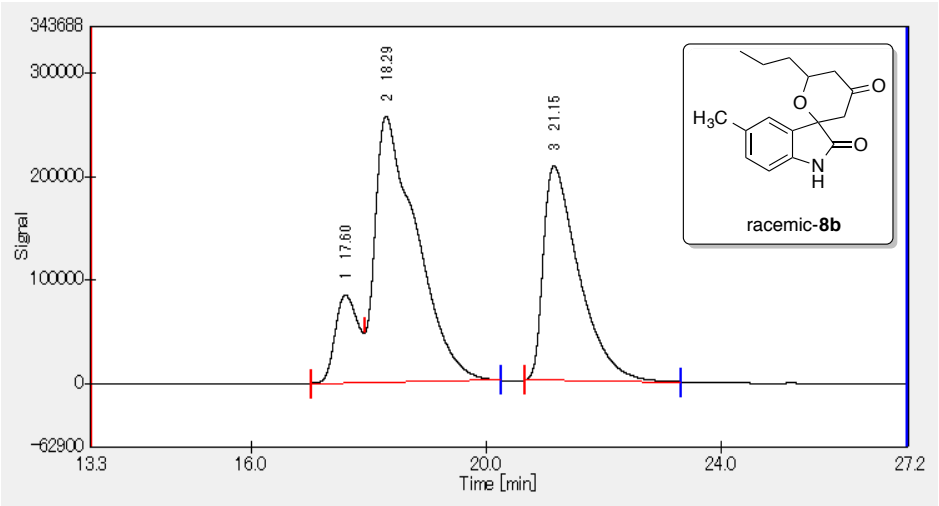
Chiral 8a + diastereomer



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	25.86	1632598.8	6.4164	41464	9074.1	1.513	2.21
2	28.53	3670713.8	14.4265	76315	7354.8	1.897	1.34
3	30.56	19307107.2	75.8803	319917	5173.9	2.536	2.877
4	35.18	833745	3.2768	15120	8610	1.61	*****
		25444164.8	100	452816			

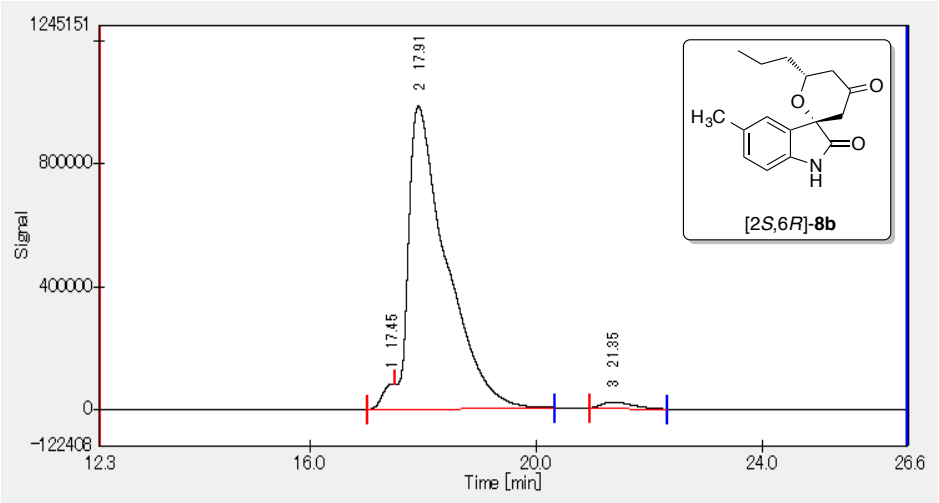
(2*S*,6*R*)- (5-methyl-6'-propyl-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8b): HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 90/10, 0.6ml/min, λ=254 nm)

Racemic 8b + diastereomer



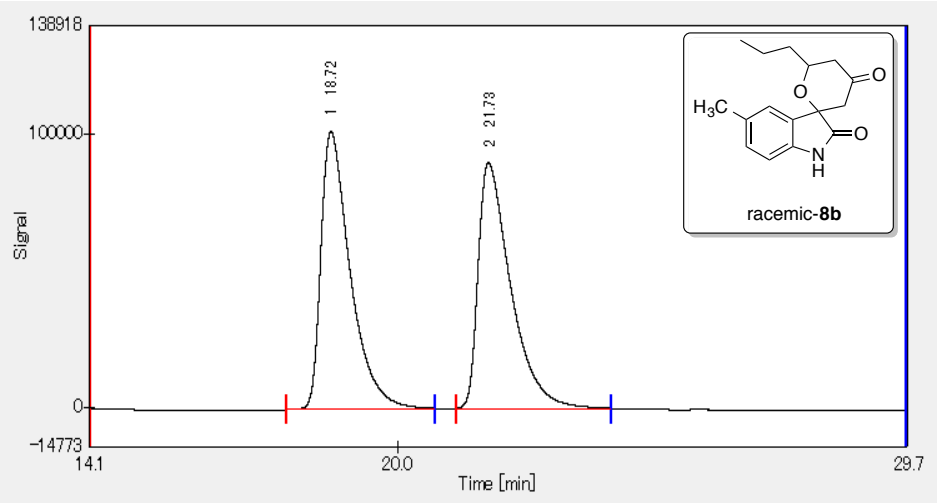
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	17.6	2342131	9.8417	84785	9178.2	*****	0.677
2	18.29	12701307	53.3711	257164	3101.9	*****	2.347
3	21.15	8754651	36.7872	207209	5168.4	2.108	*****
		23798089	100	549158			

Chiral 8b + distereomer



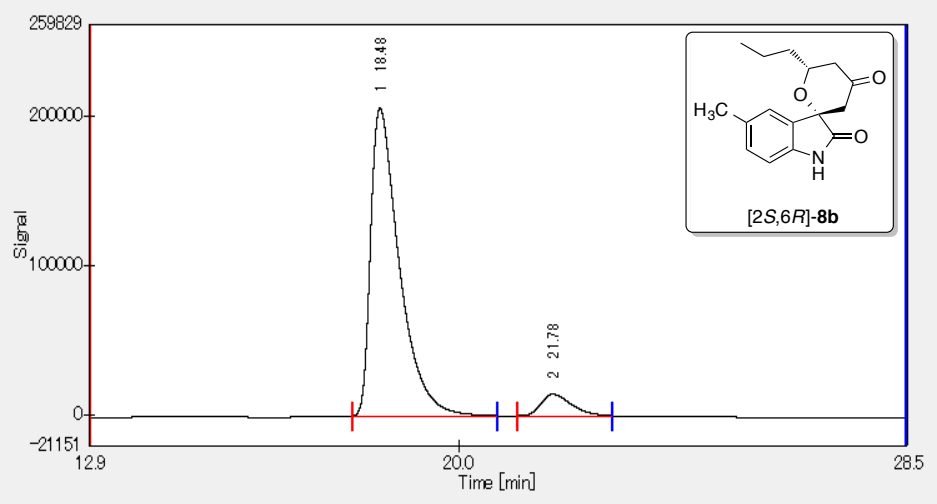
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	17.45	1213559	2.5552	83185	32350	*****	0.577
2	17.91	45497860	95.7991	984894	3401.2	*****	3.11
3	21.35	781560.9	1.6456	21130	7342.4	1.559	*****
		47492979	100	1089209			

Racemic 8b: after separation of minor diastereomer



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	18.72	3941972	50.4765	101149	4813.2	1.81	2.648
2	21.73	3867546	49.5235	89525	5296.2	1.948	*****
		7809518	100	190674			

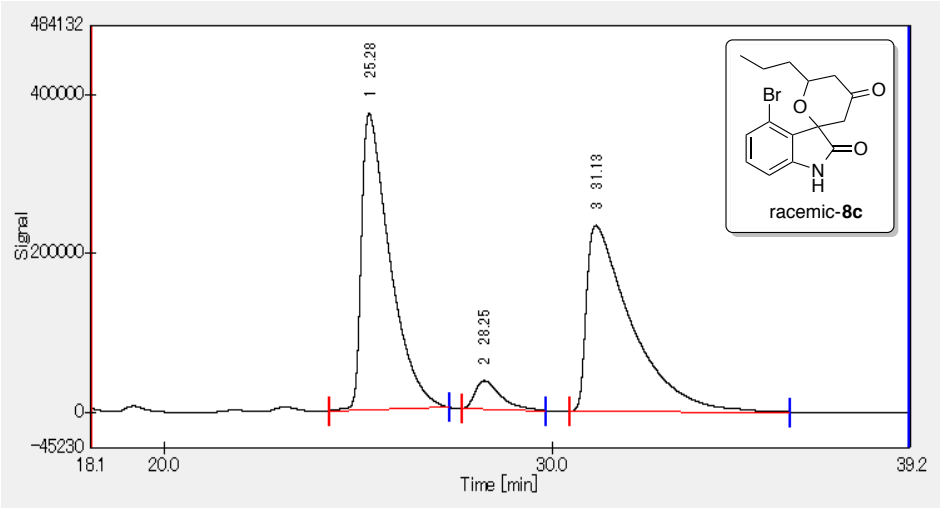
Chiral 8b



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	18.48	7832636	93.0814	205808	4918.3	1.972	3.04
2	21.78	582190.6	6.9186	14366	6102.4	1.444	*****
		8414826	100	220174			

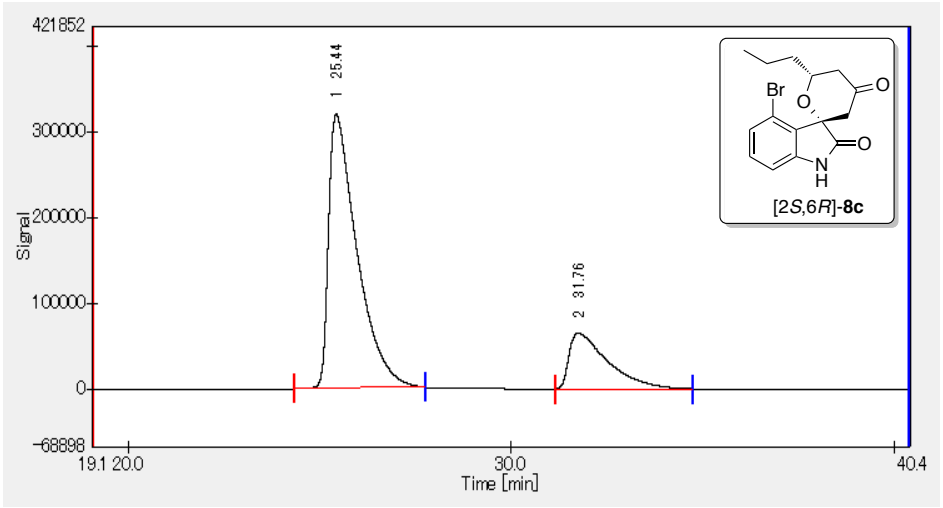
(2*S*,6*R*)-4-bromo-6'-propyl-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8c): HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 90/10, 0.6ml/min, λ=254 nm)

Racemic 8c



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	25.28	19003631	48.0353	370874	4911.4	2.412	2.145
2	28.25	1655904	4.1856	35498	7287.2	1.825	1.572
3	31.13	18902308	47.7791	233267	2822	3.504	*****
		39561843	100	639639			

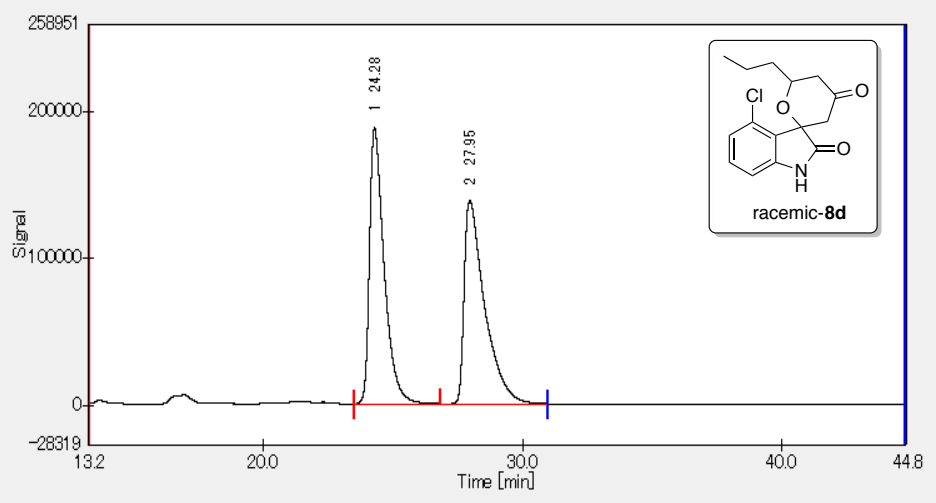
Chiral 8c



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	25.44	16507190	78.1396	319586	4889.8	2.415	3.633
2	31.76	4618058	21.8604	65520	3927.1	2.861	*****
		21125248	100	385106			

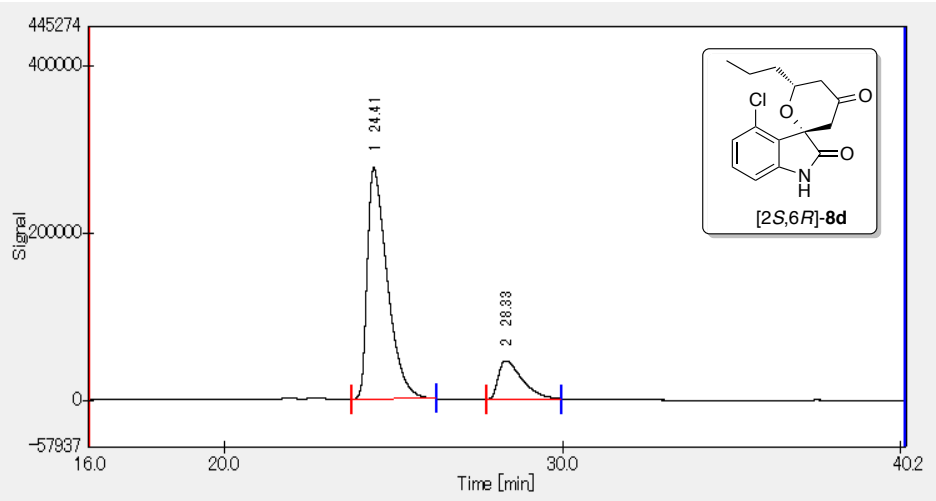
(2*S*,6*R*)-4-chloro-6'-propyl-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8d): HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 90/10, 0.6ml/min, λ=254 nm)

Racemic 8d



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmety	Resolution
1	24.28	7438325	49.4096	188809	8589.3	1.751	2.93
2	27.95	7616076	50.5904	138589	5852.5	2.427	*****
		15054401	100	327398			

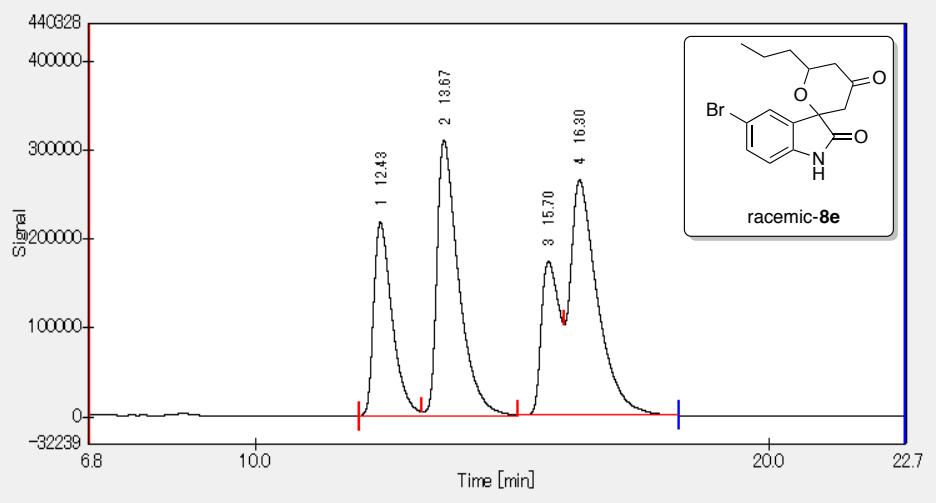
Chiral 8d



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	24.41	1144227	834758	277134	7440.3	1.869	3.13
2	28.33	2265008	16.5242	46062	6837.5	1.952	*****
		1370725	100	323196			

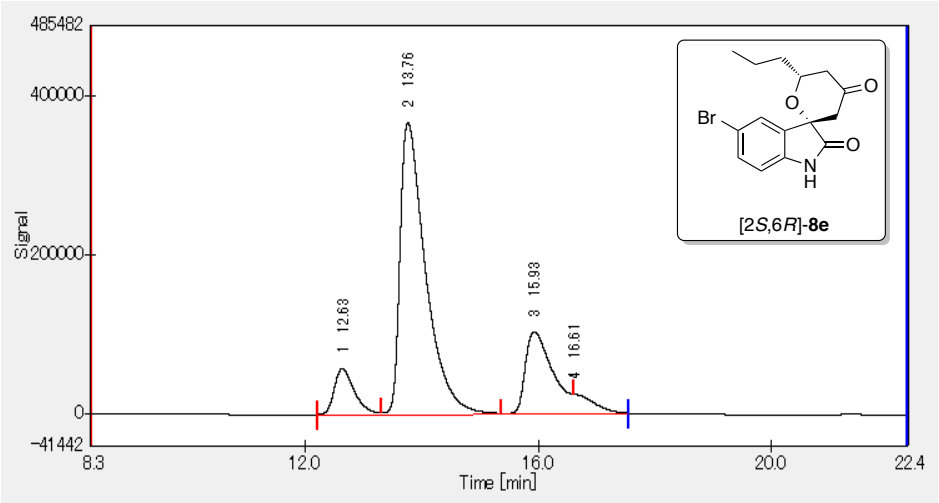
(2*S*,6*R*)- (5-Bromo-6'-propyl-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8e): HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 90/10, 1.0ml/min, λ=254 nm)

Racemic 8e + diastereomer



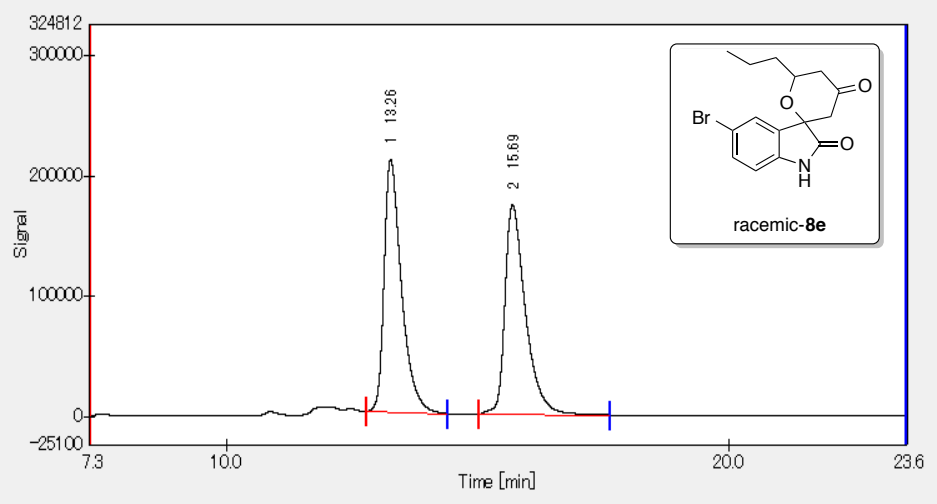
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmety	Resolution
1	12.43	5455406	19.0679	217857	5576.3	1.705	1.707
2	13.67	9126375	31.8988	310044	4878.3	1.928	2.836
3	15.7	4214367	14.7302	173433	9438.3	*****	0.743
4	16.3	9814227	34.303	264477	4366.2	*****	*****
		28610375	100	965811			

Chiral 8e + diastereomer



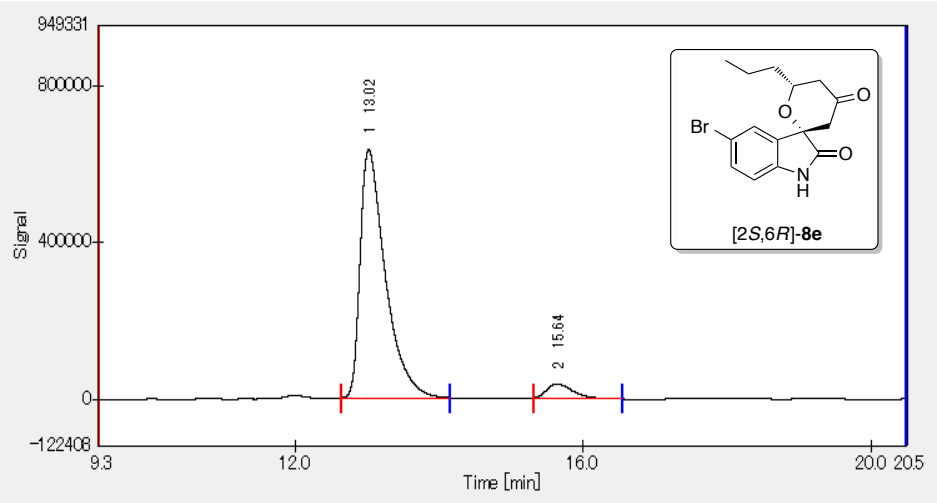
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmety	Resolution
1	12.63	1383292	8.4274	57945	6331.3	1.494	1.562
2	13.76	11117674	67.7321	365975	4638.6	2.114	2.597
3	15.93	3337446	20.3327	102534	5417.8	*****	0.905
4	16.61	575775.4	3.5078	24008	10849.9	*****	*****
		16414187	100	550462			

Racemic 8e after separation of minor diastereomer



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.26	5060467	50.5643	210447	6360.9	1.563	3.379
2	15.69	4947526	49.4357	174190	6589.6	1.582	*****
		1000792	100	384637			

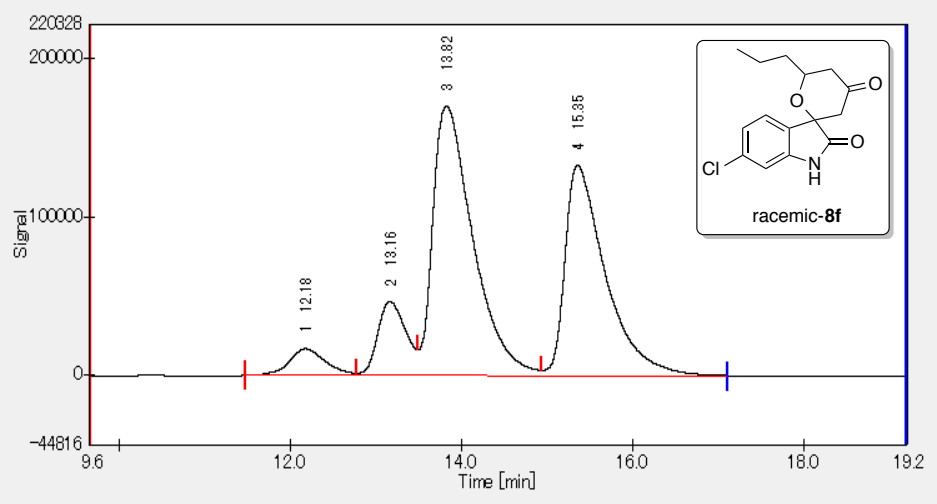
Chiral 8e



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.02	1540325	94.4043	632995	5868.6	1.859	3.826
2	15.64	913011.5	5.5957	36401	8225.6	1.493	*****
		16316262	100	669396			

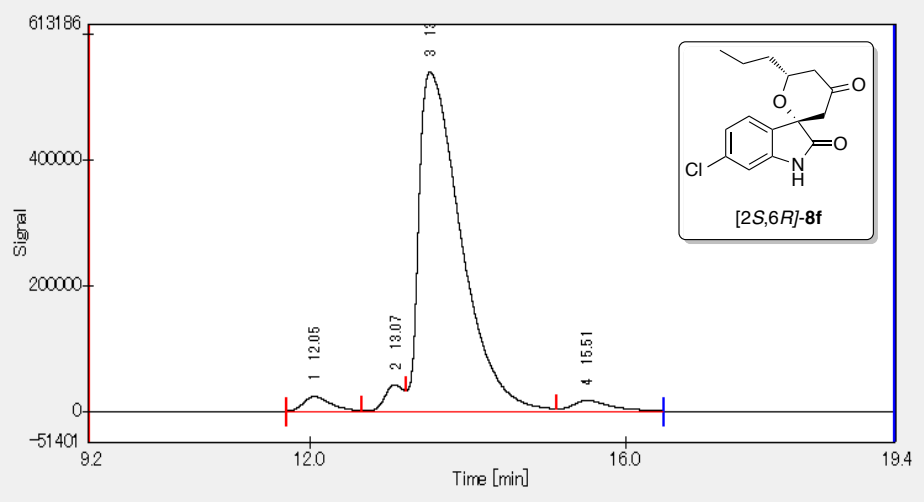
(2*S*,6*R*)- 6-chloro-6'-propyl-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8f): HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 90/10, 1.0ml/min, λ=254 nm)

Racemic 8f + diastereomer



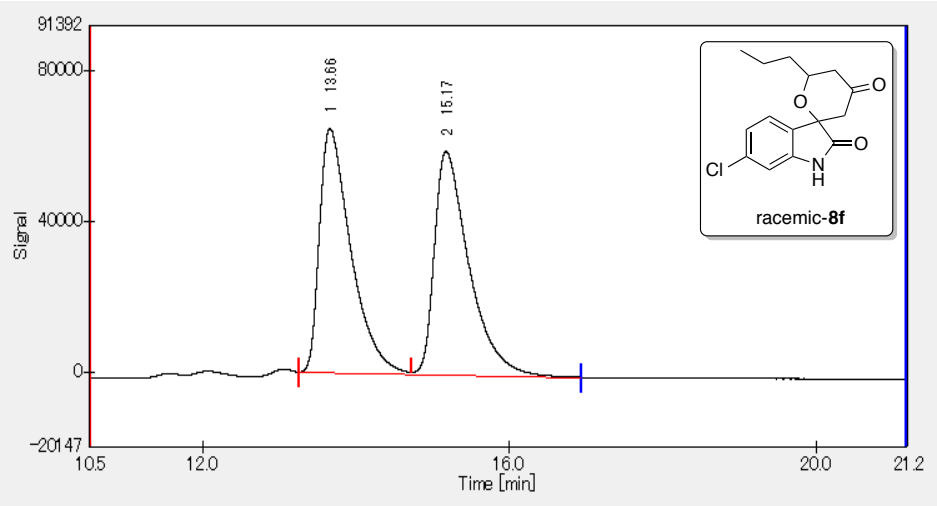
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	12.18	493221.5	4.3038	16763	3874	*****	1.415
2	13.16	1066845	9.3091	46753	7523.3	*****	0.894
3	13.82	5544759	48.3828	169718	4047.5	*****	1.761
4	15.35	4355363	38.0043	132738	4952.6	2.012	*****
		11460188	100	365972			

Chiral 8f + diastereomer



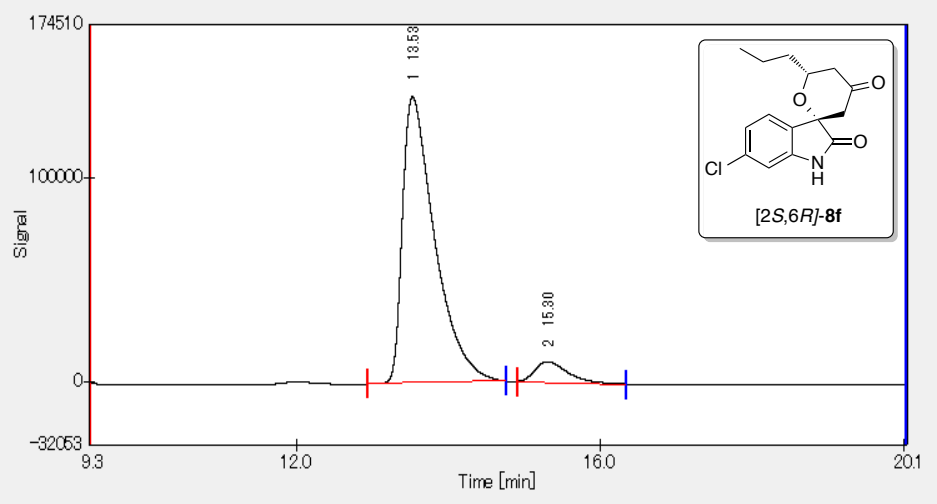
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	12.05	558248	2.5635	23169	5660.5	1.495	1.892
2	13.07	684906.6	3.1451	41667	14307.9	*****	0.623
3	13.52	19957025	91.6425	538712	3011.2	*****	2.108
4	15.51	576851.2	2.6489	16987	4716.6	*****	*****
		21777031	100	620535			

Racemic 8f after separation of minor diastereomer



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.66	1841968	49.7642	64527	5179.7	1.856	1.897
2	15.17	1859426	50.2358	59161	5271.8	1.827	*****
		3701394	100	123688			

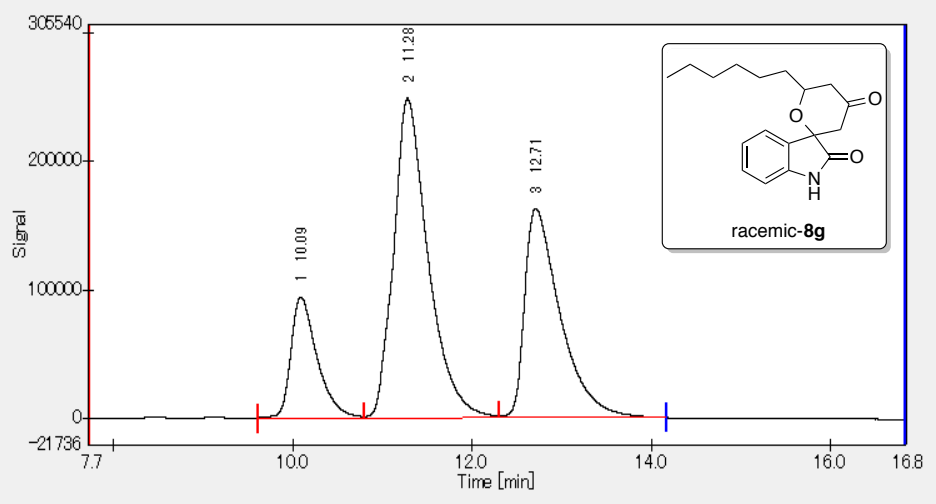
Chiral 8f



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.53	4161655	93.2789	140767	4257.3	2.051	2.156
2	15.3	299865.2	6.7211	10129	5630.9	1.553	*****
		4461520	100	150896			

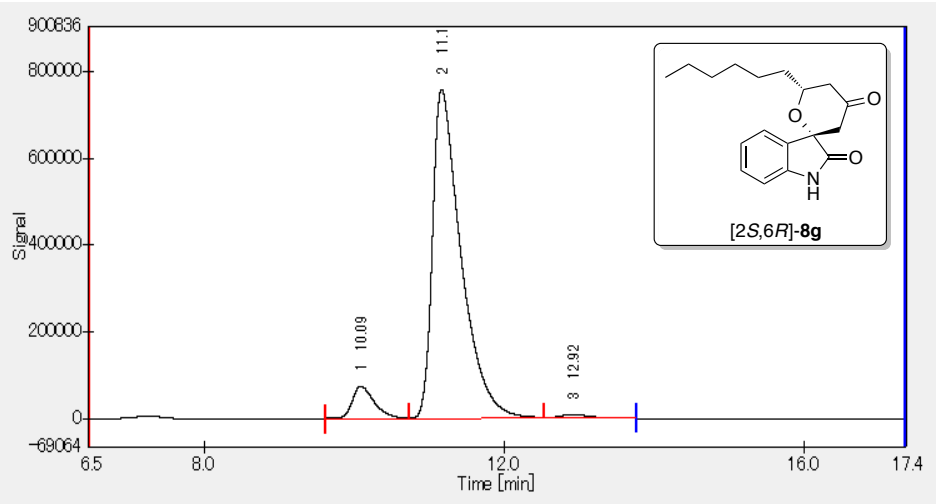
(2*S*,6*R*)- 6'-hexyl-5',6'-dihydrospiro(indoline-3,2'-pyran-2,4')(3'*H*)-dione (8g): HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 90/10, 1.0ml/min, λ=254 nm)

Racemic 8g + diastereomer



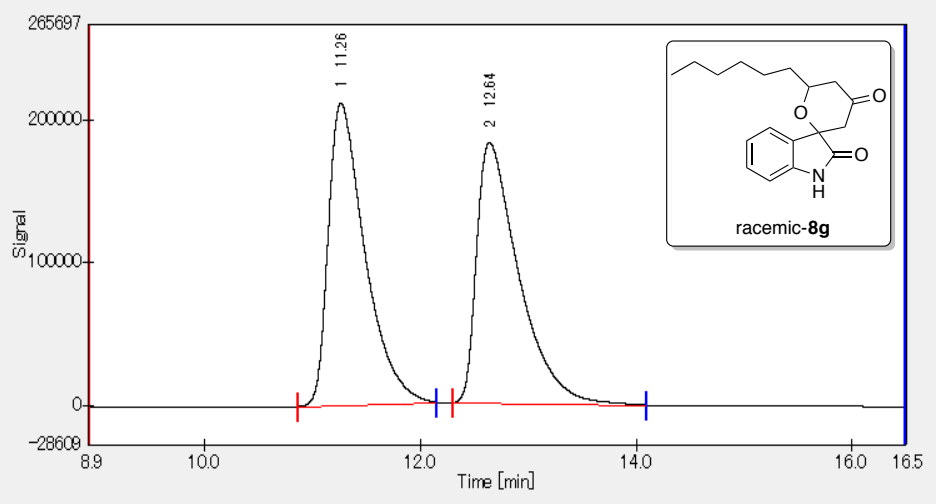
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	10.09	1903566	14.5692	93937	5604.2	1.545	1.902
2	11.28	6654146	50.9282	248510	4011.9	1.429	1.974
3	12.71	4508016	34.5026	162691	4756.7	2.04	*****
		13065728	100	505138			

Chiral 8g + diastereomer



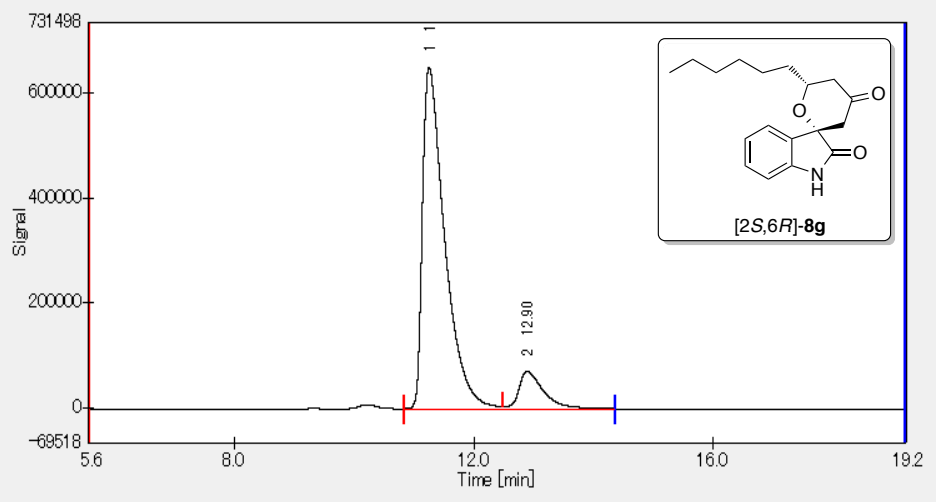
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	10.09	1511949	6.9328	74487	5592.9	1.455	1.734
2	11.17	20029190	91.8406	758895	4051.6	1.872	2.378
3	12.92	267500.6	1.2266	9244	4509	*****	*****
		21808640	100	842626			

Racemic 8g after separation of minor diastereomer



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	11.26	4992970	50.1257	211282	4683.9	1.763	1.945
2	12.64	4967923	49.8743	182595	4458.7	2.062	*****
		9960893	100	393877			

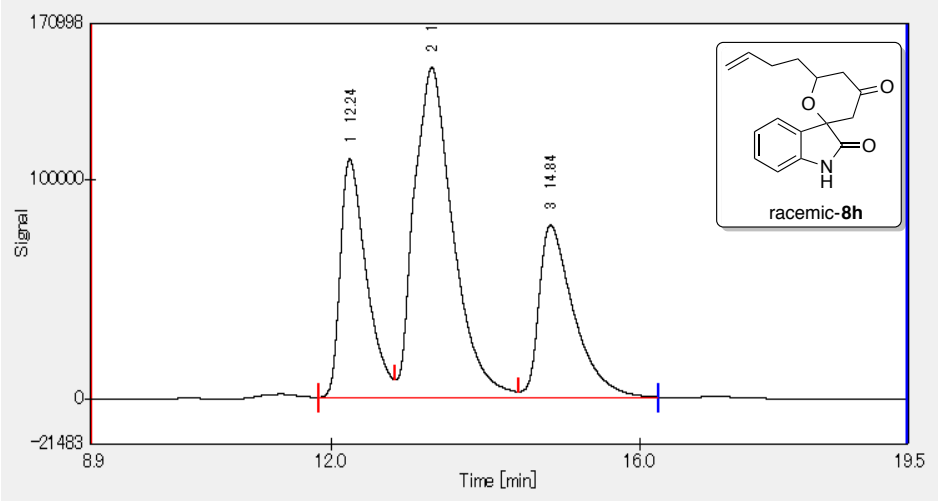
Chiral 8g



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	11.26	16816346	89.0849	650461	4288.3	2.172	2.252
2	12.9	2060416	10.9151	71255	4499.4	*****	*****
		18876762	100	721716			

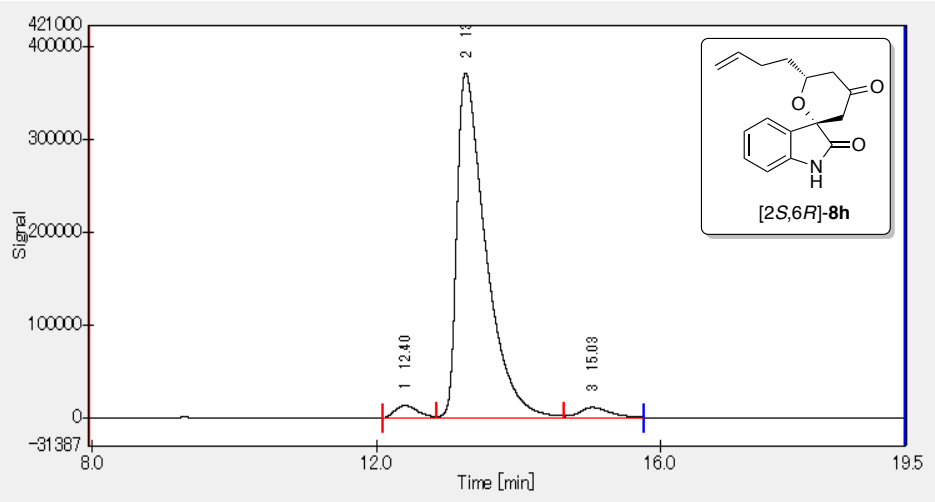
(2*S*,6*R*)- 6'-(but-3-en-1-yl)-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8h):
HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 90/10, 1.0ml/min, λ=254 nm)

Racemic 8h + diastereomer



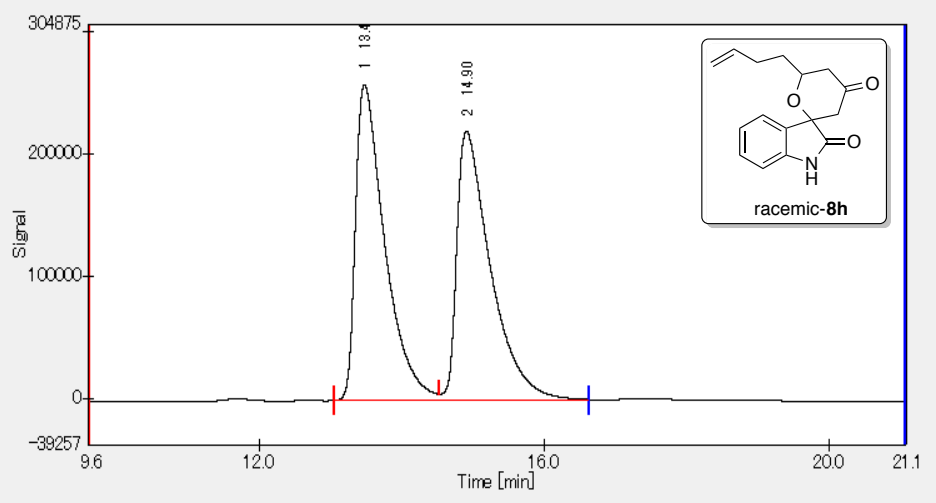
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	12.24	2564291	24.8408	109123	6140.2	*****	1.367
2	13.31	5284556	51.1925	150953	3268	*****	1.74
3	14.84	2474071	23.9668	78750	5049.2	1.819	*****
		10322918	100	338826			

Chiral 8h + diastereomer



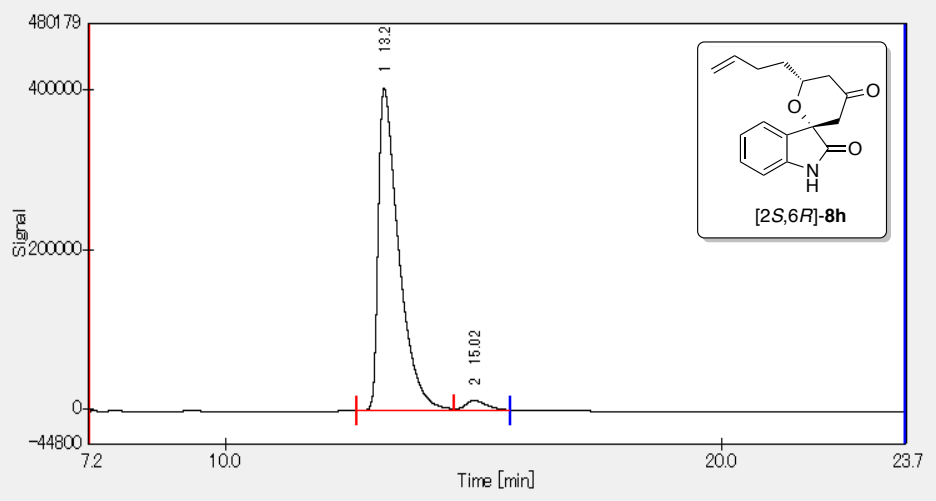
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	12.4	296696.6	2.6784	13464	7162.2	*****	1.277
2	13.25	10456903	94.4004	370662	4992.1	2.145	2.314
3	15.03	323586.2	2.9212	10964	5866.2	*****	*****
		11077186	100	395090			

Racemic 8h after separation of minor diastereomer



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.47	7383695	50.4758	258352	5024.5	2.129	1.753
2	14.9	7244482	49.5242	220250	4643.7	2.24	*****
		14628177	100	478602			

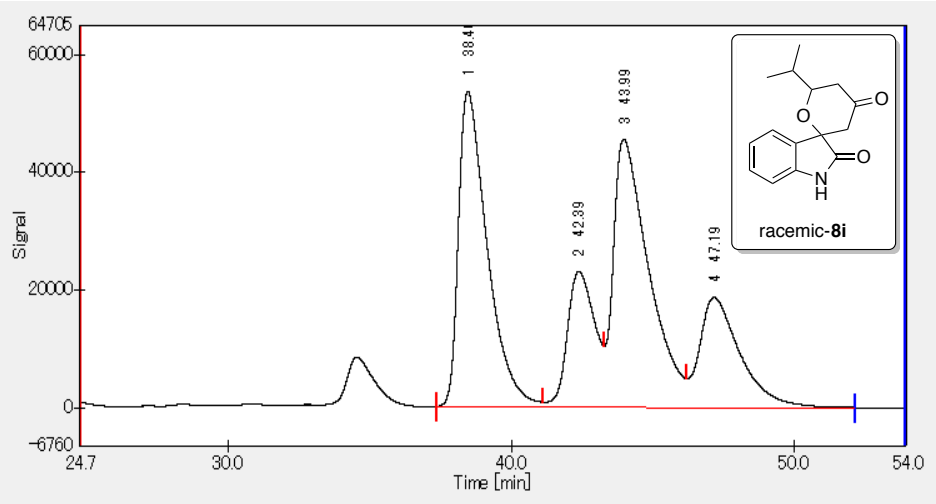
Chiral 8h



S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	13.2	11612010	96.9259	403276	4751.2	2.24	2.316
2	1 5.02	368284.1	3.0741	12152	5553.4	*****	*****
		11980294	100	415428			

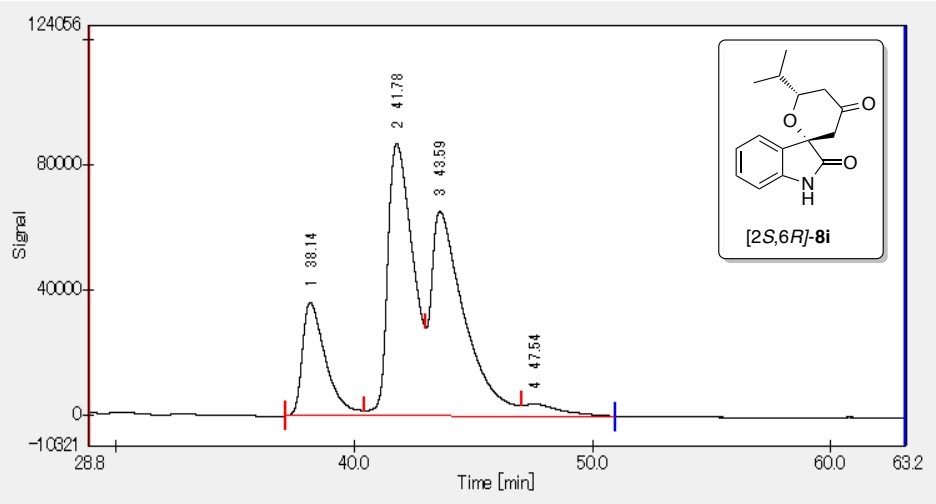
(2*S*,6*R*)- 6'-(isopropyl)-5',6'-dihydrospiro(indoline-3,2'-pyran)-2,4'(3'*H*)-dione (8i):
HPLC (Daicel chiralpak IB, hexane/*i*-PrOH = 95/5, 0.6ml/min, λ=254 nm)

Racemic 8i + diastereomer



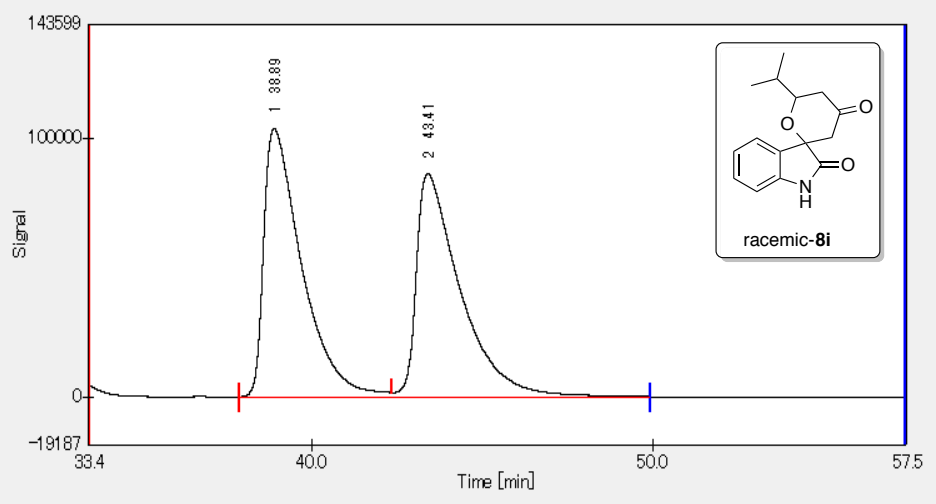
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmety	Resolution
1	38.46	3787346	33.86	53568	6693.3	1.894	2.14
2	42.39	1548167	13.8411	23017	8982.6	*****	0.778
3	43.99	3981689	35.5974	45532	5723	*****	1.283
4	47.19	1868121	16.7015	18667	5028.8	*****	*****
		11185322	100	140784			

Chiral 8i + diastereomer



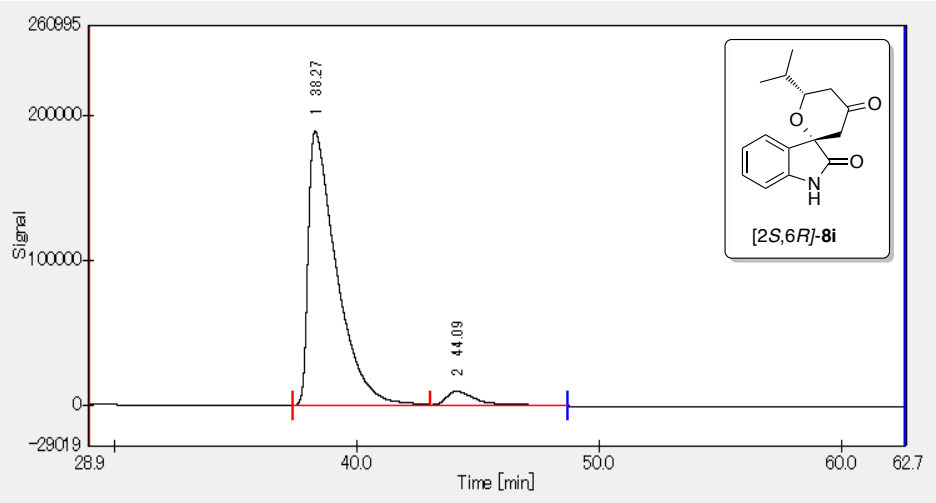
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmety	Resolution
1	38.14	2486018	15.8015	36262	7000.7	2.053	1.926
2	41.78	6392030	40.6287	87086	7327.7	*****	0.792
3	43.59	6440601	40.9374	65435	4435.6	*****	1.436
4	47.54	414153.8	2.6324	3808	4322.5	*****	*****
		15732803	100	192591			

Racemic 8i after separation of minor diastereomer



O	S.N	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
	1	38.89	8051751	50.9401	103938	5701.7	2.376	2.03
	2	43.41	7754572	49.0599	86449	5296.6	2.404	*****
			15806323	100	190387			

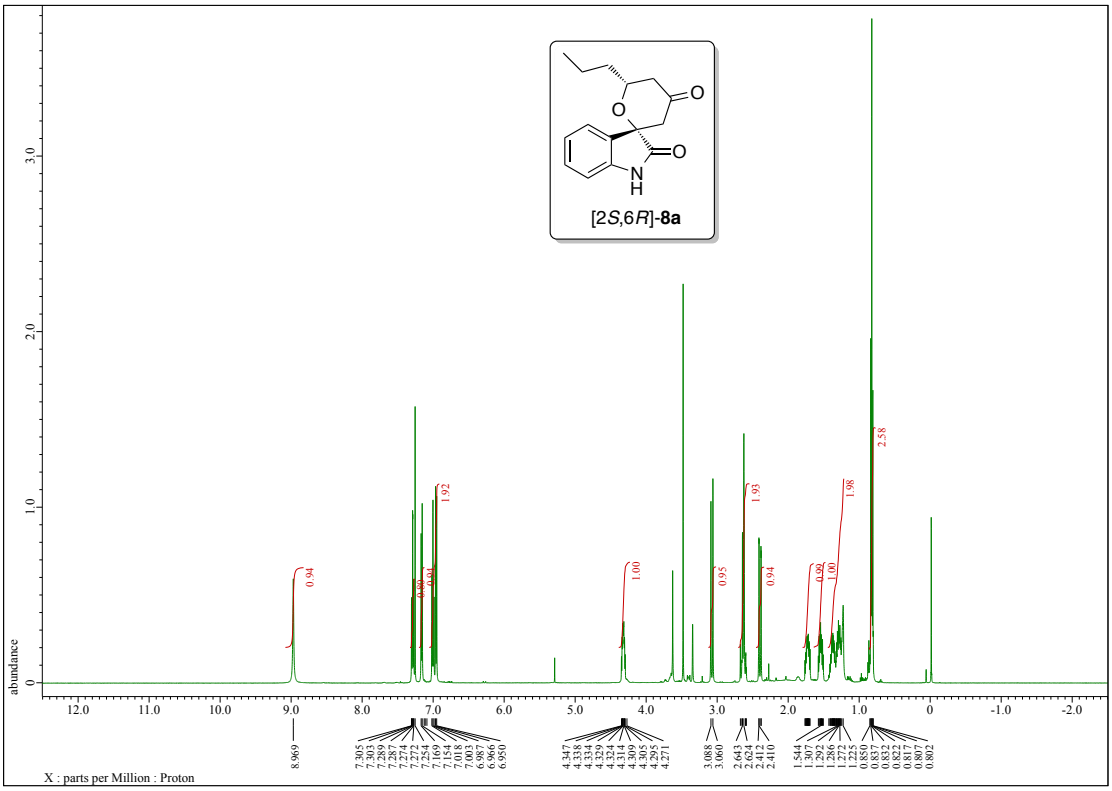
Chiral 8i



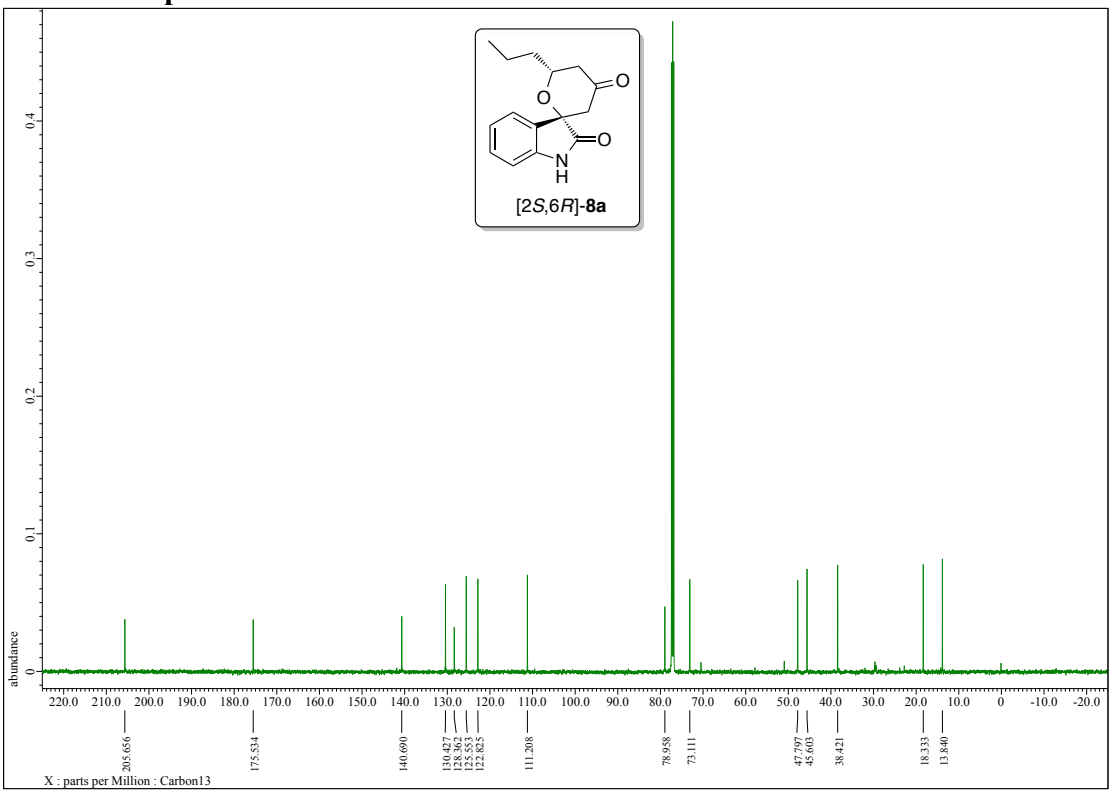
S.NO	Rt(min)	Area	Area %	Height	NTP	Symmetry	Resolution
1	38.27	15433990	94.1491	189474	4992.8	2.707	2.459
2	44.09	959145.3	5.8509	9929	4712.7	*****	*****
		16393135	100	199403			

5. ^{1}H NMR and ^{13}C NMR spectrum of compounds 8a-i

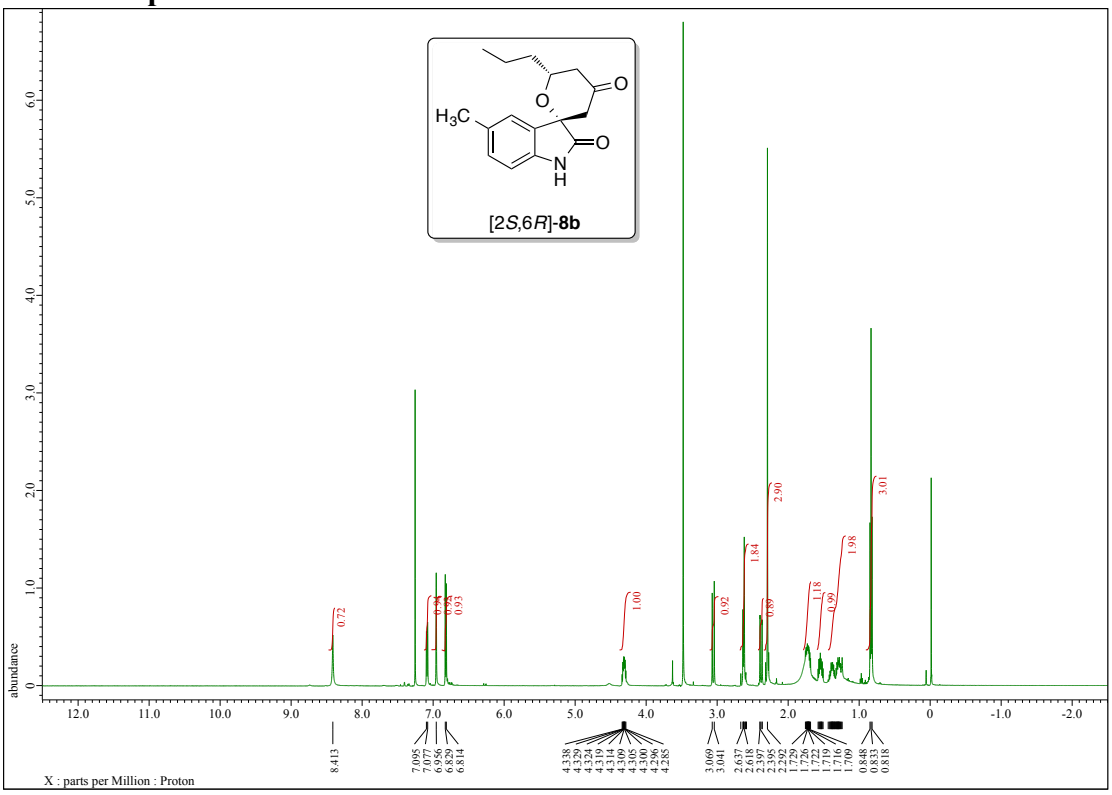
^{1}H NMR Spectra of 8a



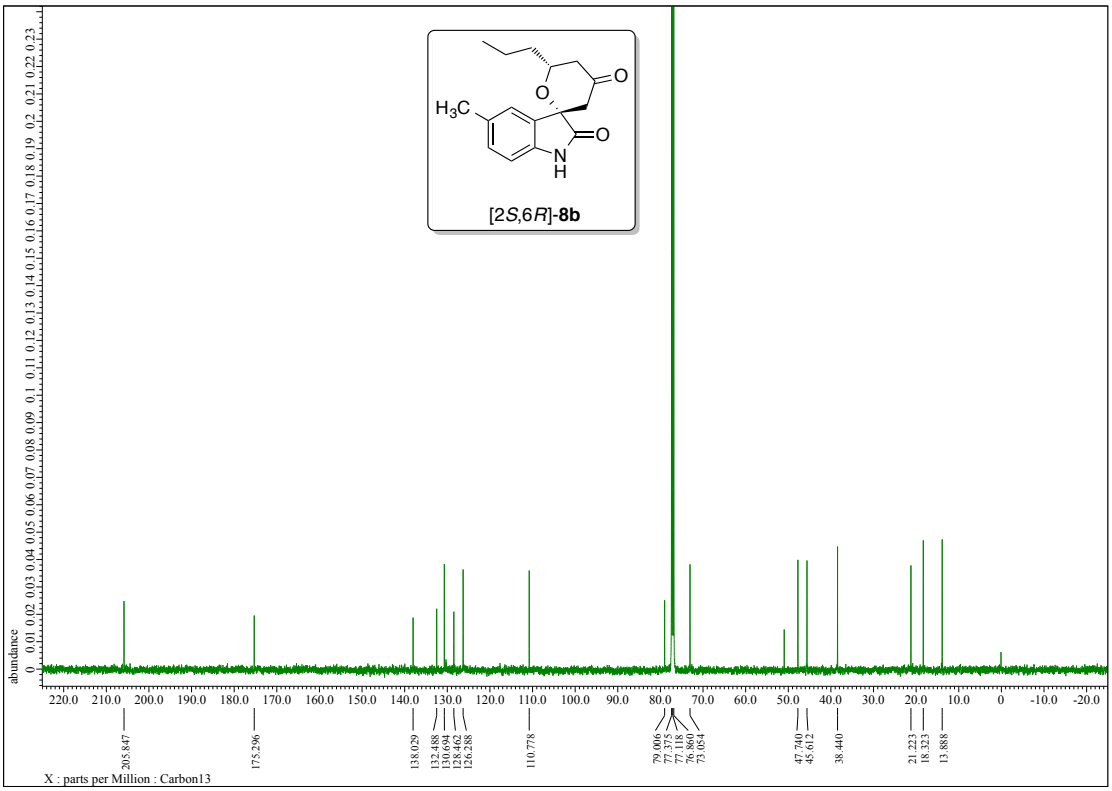
^{13}C NMR Spectra of 8a



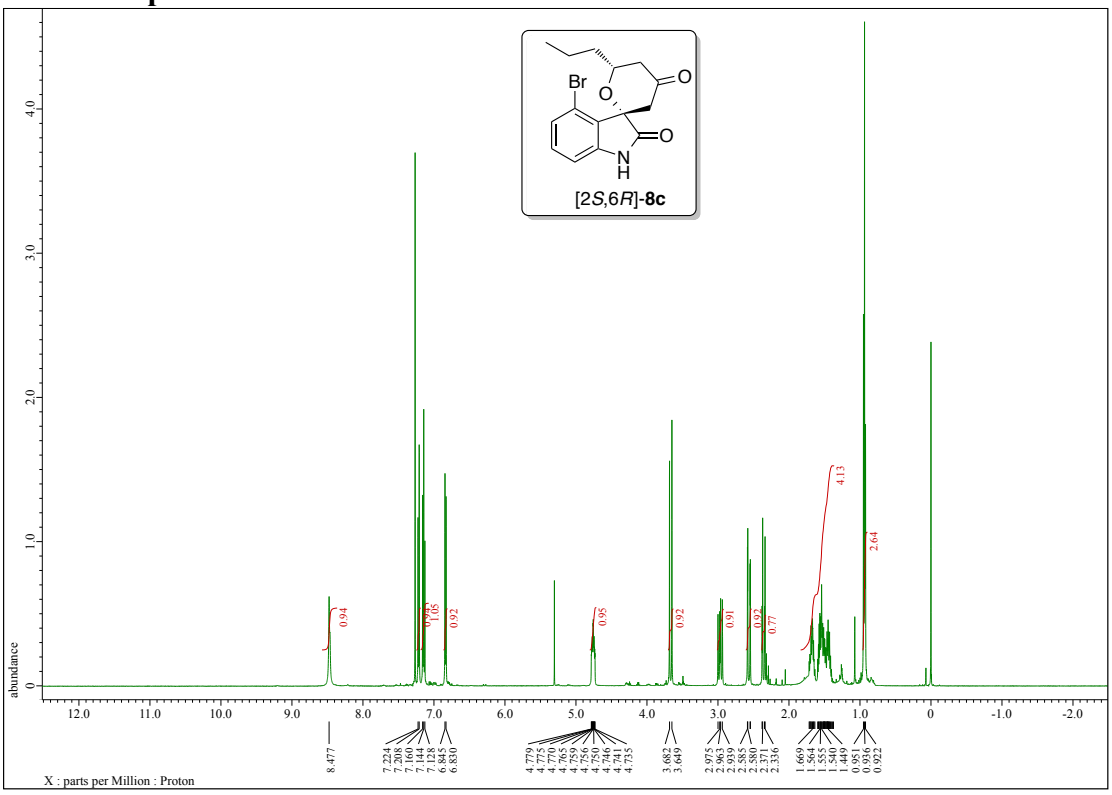
^{1}H NMR Spectra of 8b



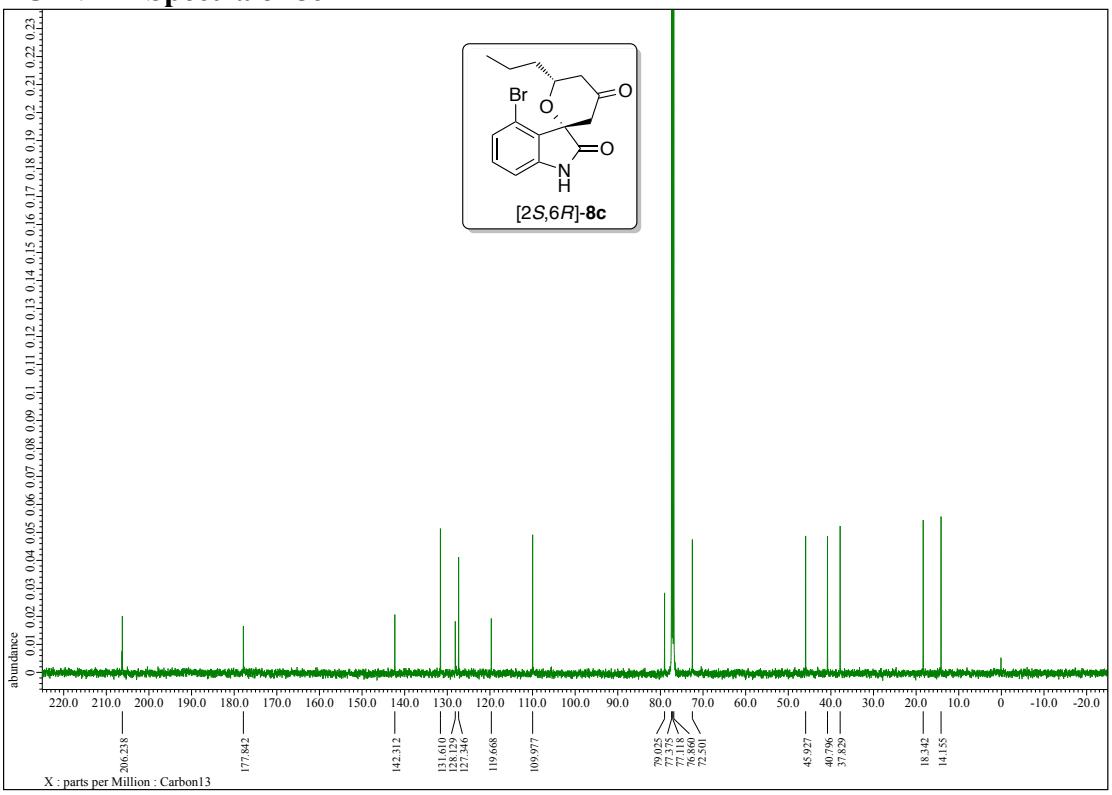
^{13}C NMR Spectra of 8b



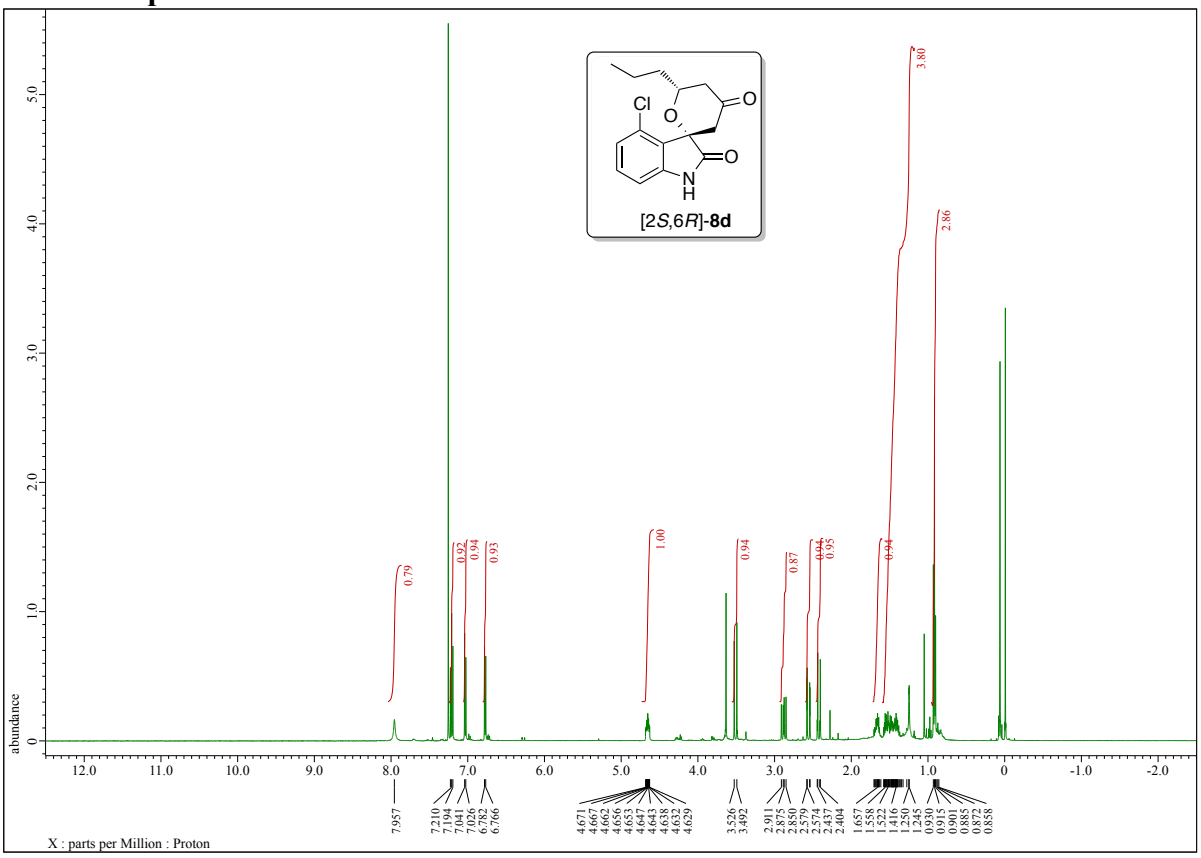
^{1}H NMR Spectra of 8c



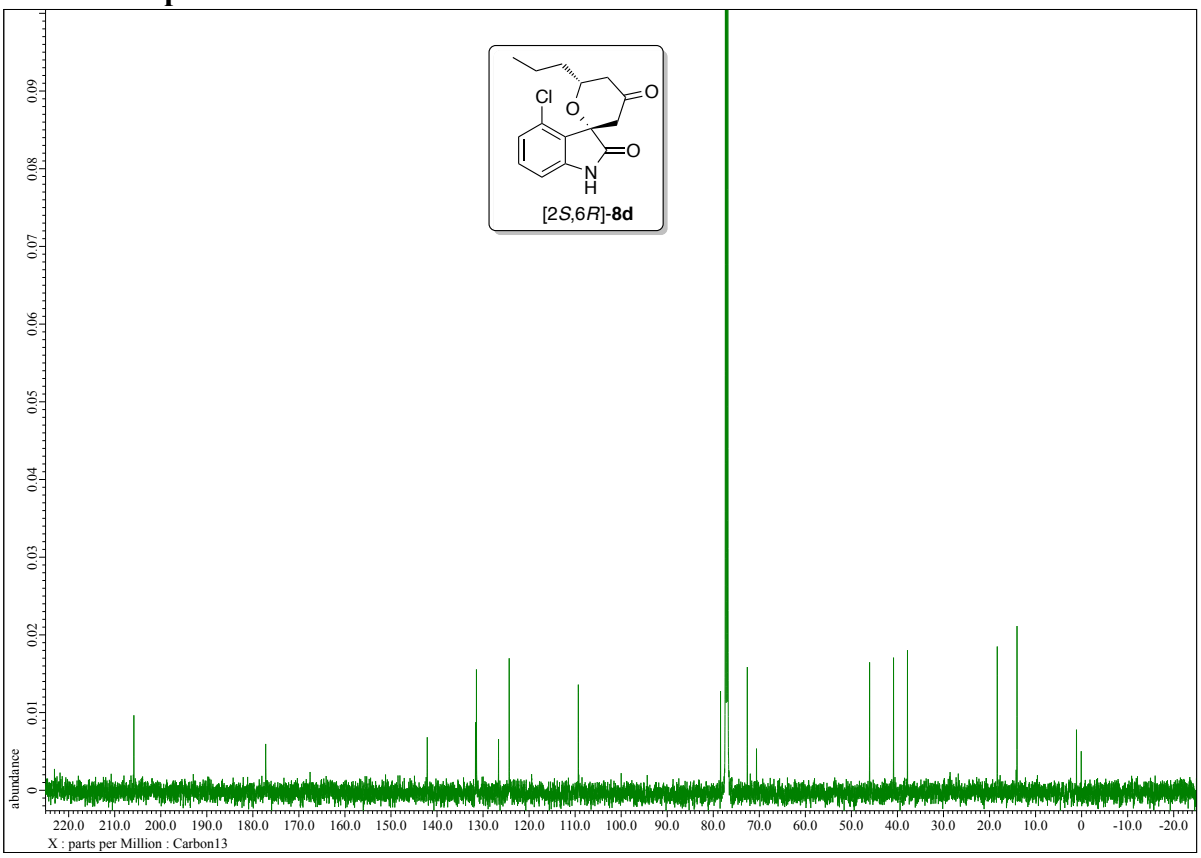
^{13}C NMR Spectra of 8c



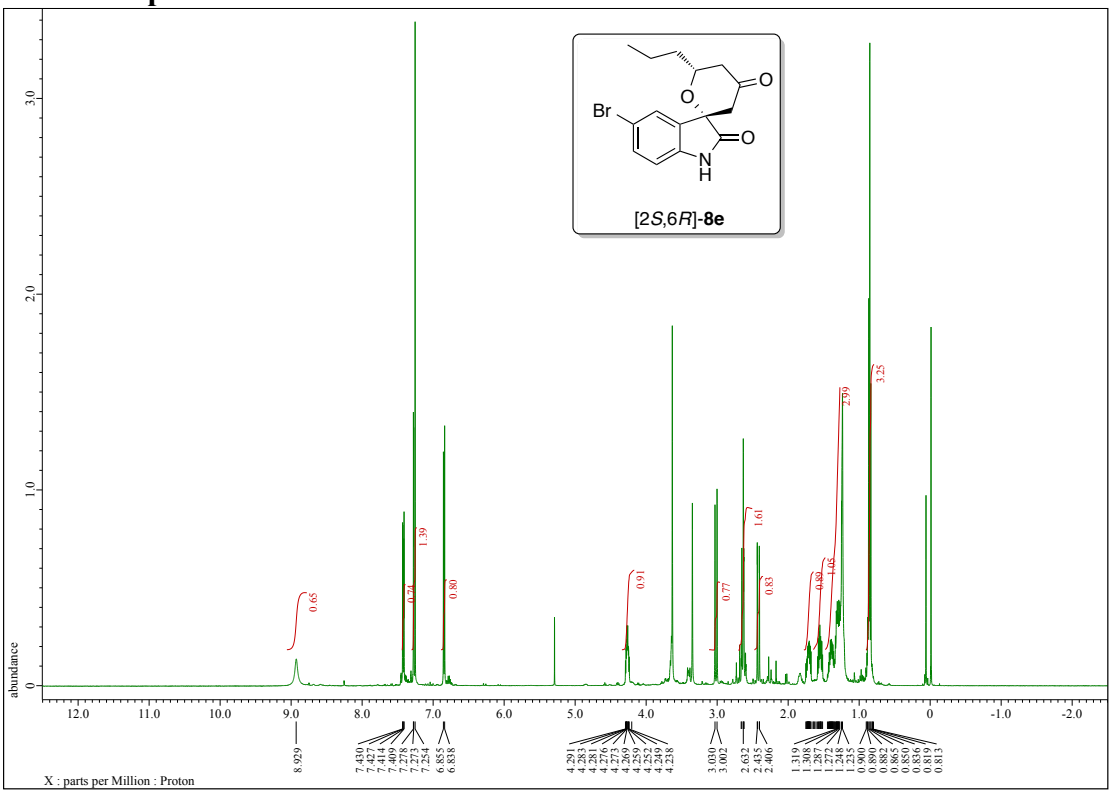
^{1}H NMR Spectra of 8d



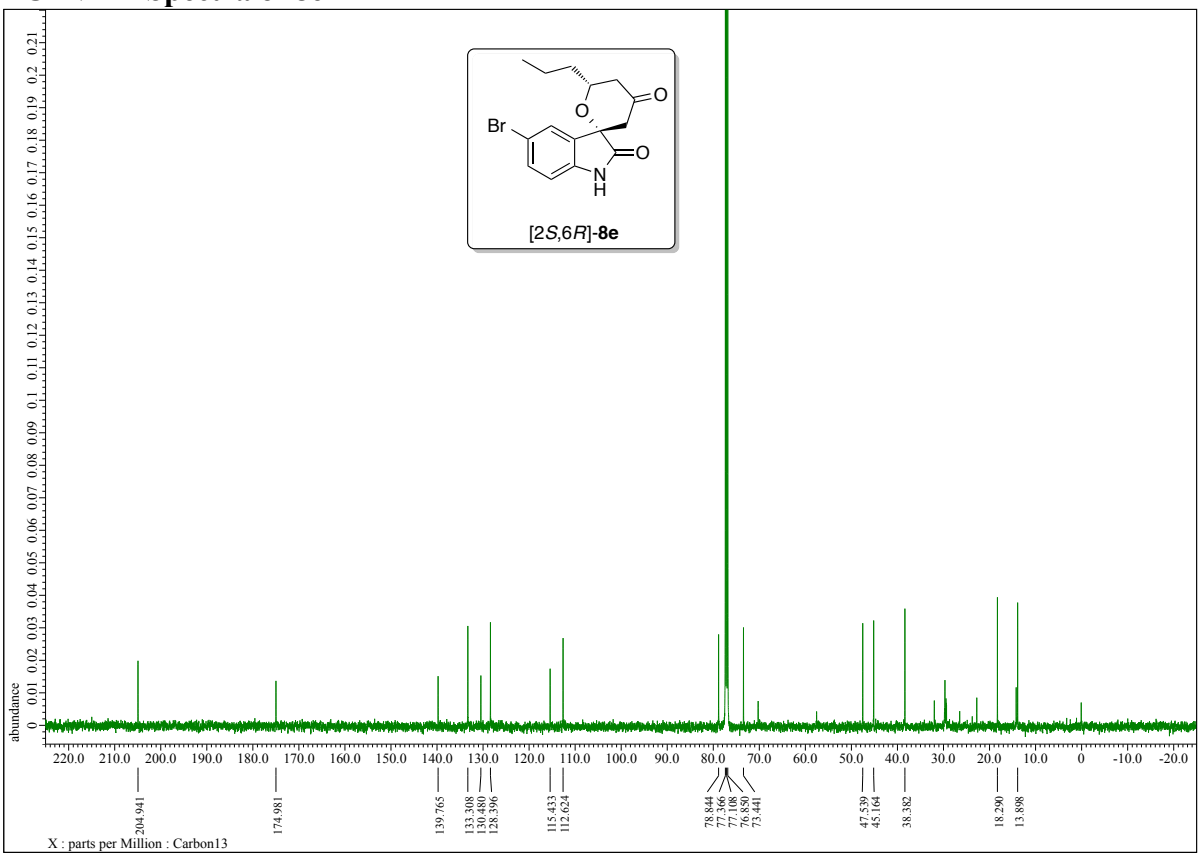
^{13}C NMR Spectra of 8d



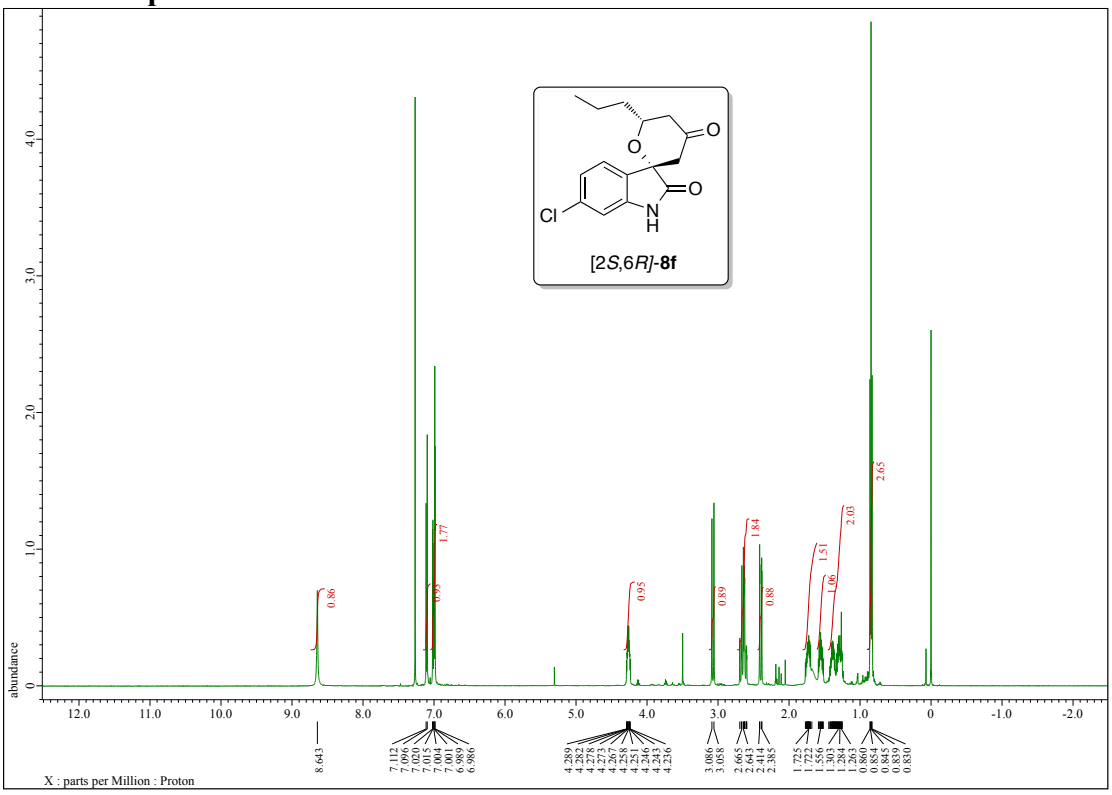
^{1}H NMR Spectra of 8e



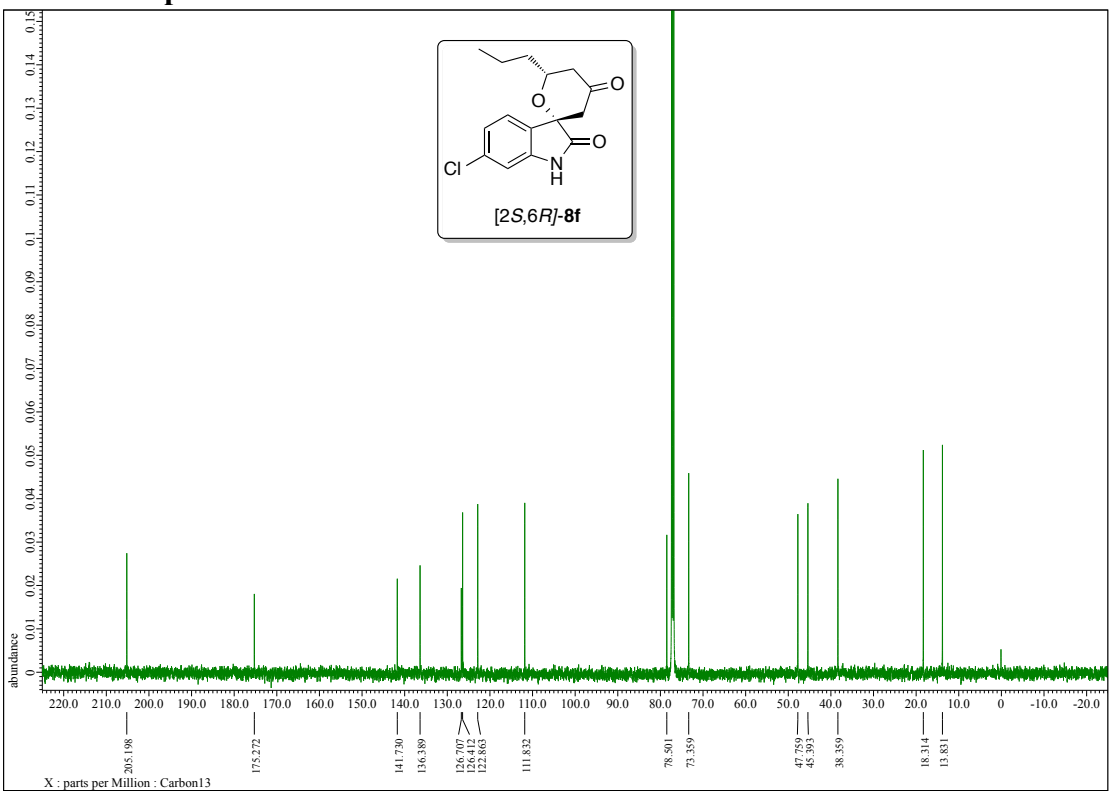
^{13}C NMR Spectra of 8e



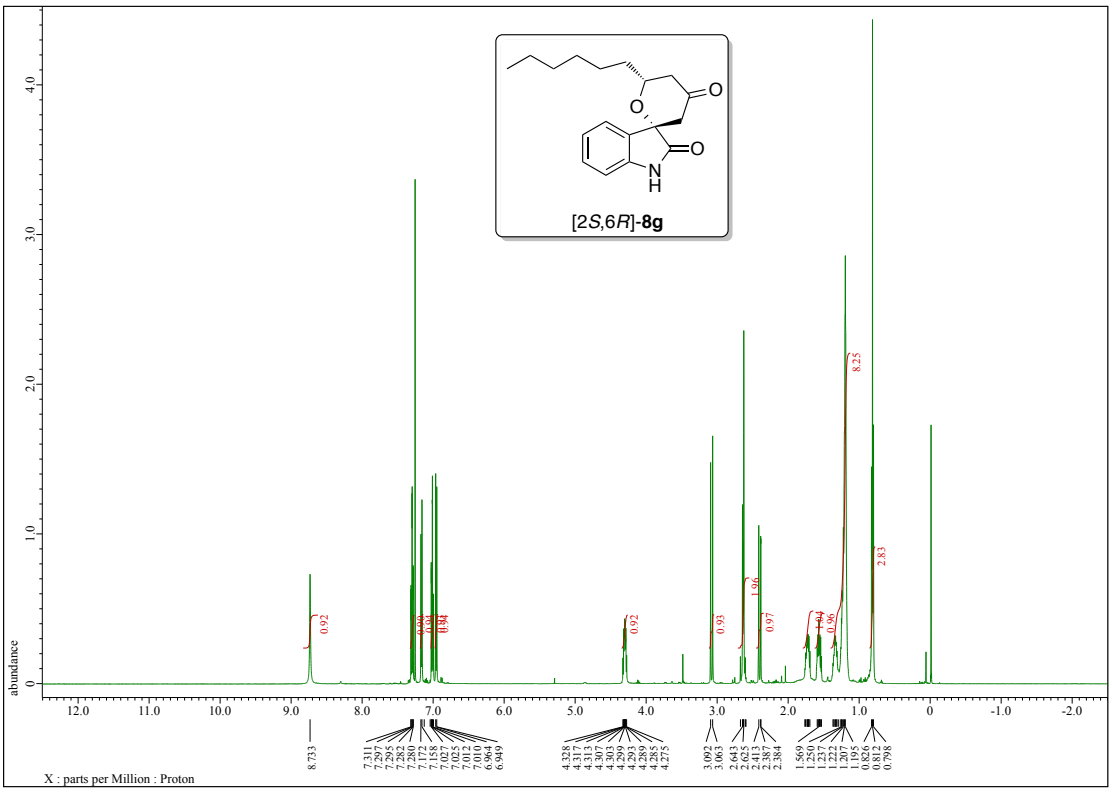
^{1}H NMR Spectra of 8f



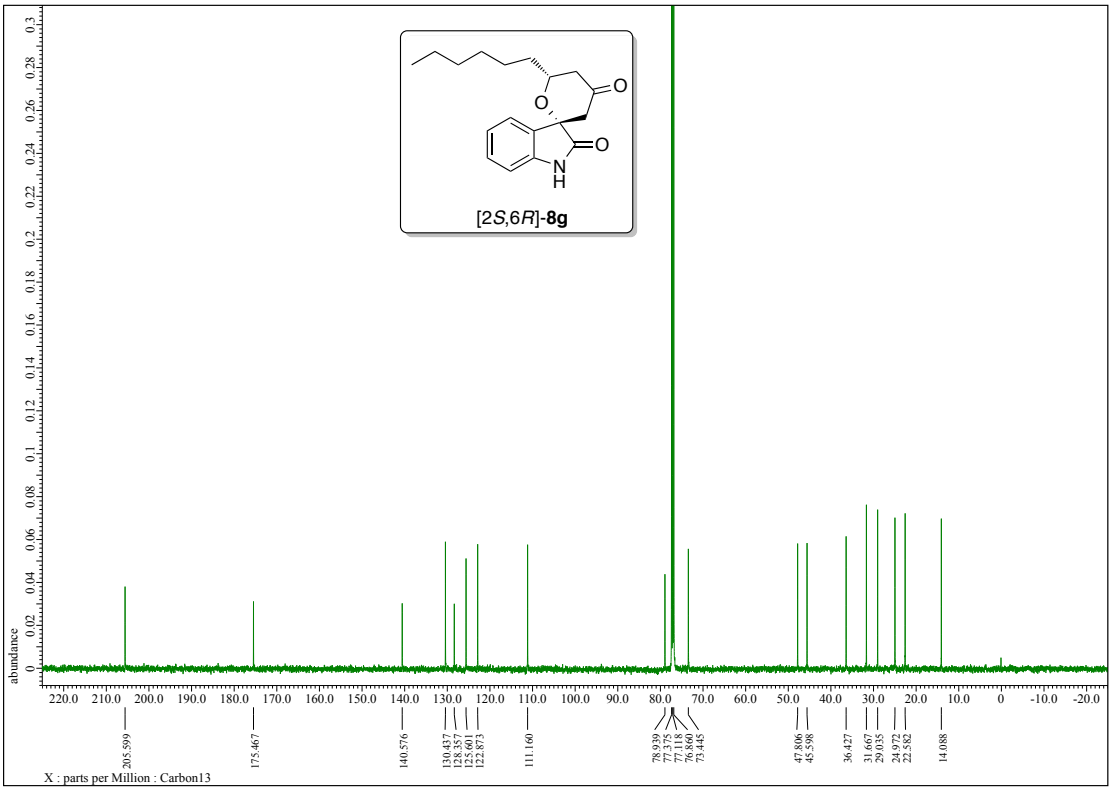
^{13}C NMR Spectra of 8f



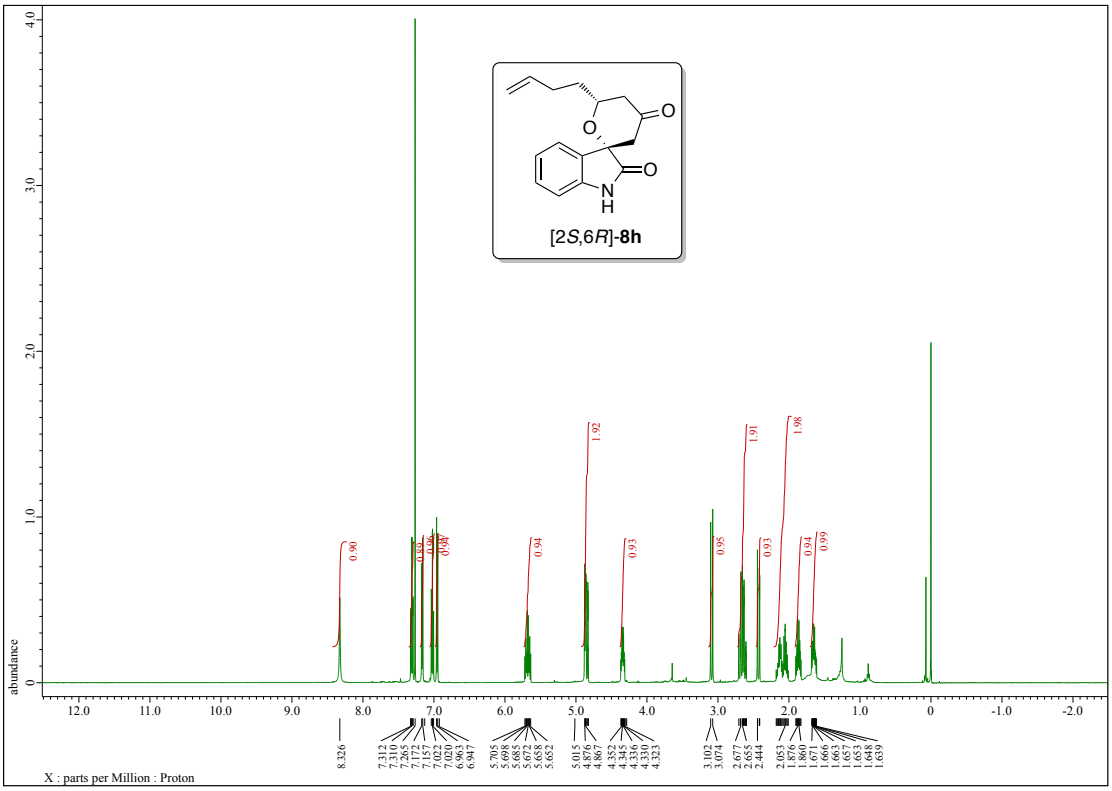
^{1}H NMR Spectra of 8g



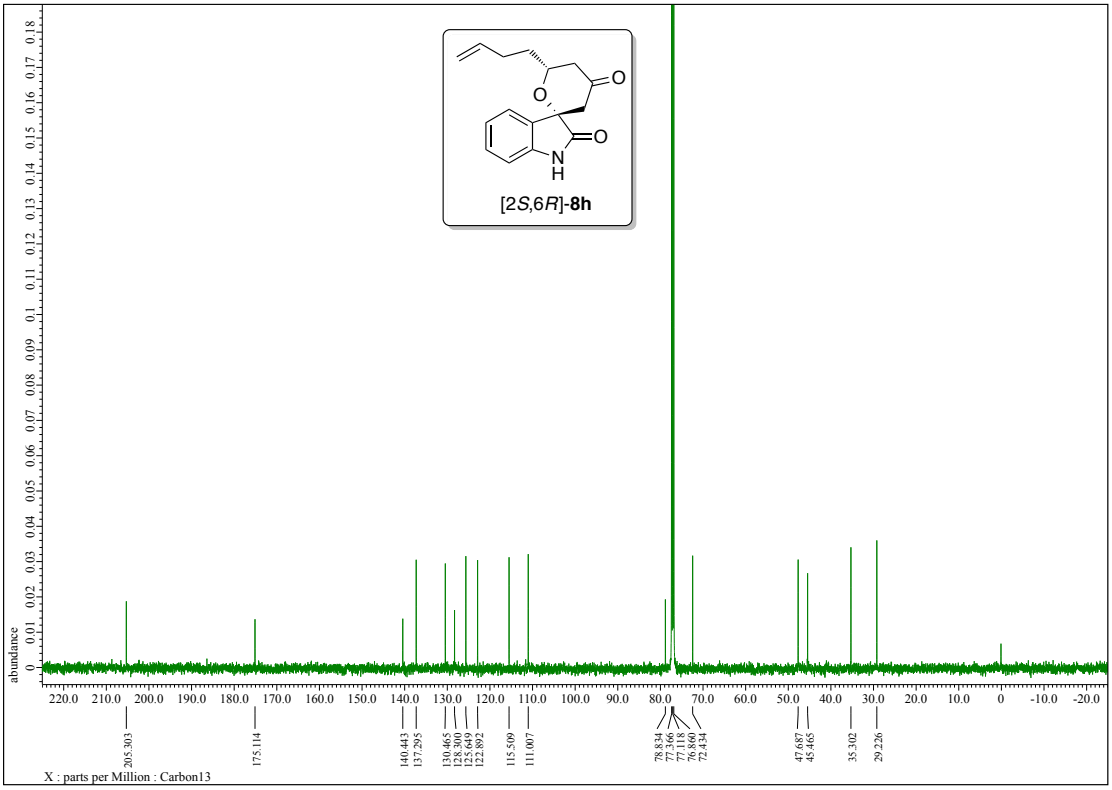
^{13}C NMR Spectra of 8g



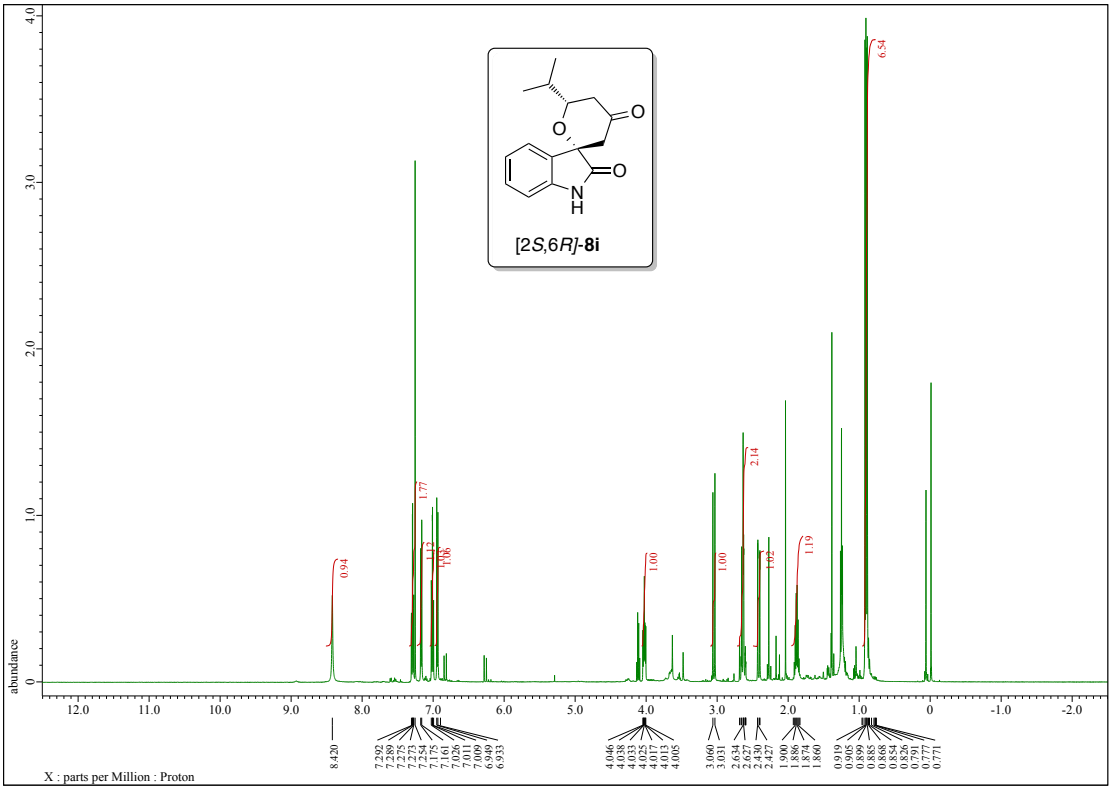
^{1}H NMR Spectra of 8h



^{13}C NMR Spectra of 8h



^{1}H NMR Spectra of 8i



^{13}C NMR Spectra of 8i