Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Discovery of Temperature-dependent, Autoinductive Reversal of Enantioselectivity: Palladium-mediated [3+3]-Annulation of 4-Hydroxycoumarins

Shasha Wang,[a] Junan Xiao,[a] Jun Li,[a] Haoyue Xiang,[a] Chaoming Wang,[a] Rich G. Carter,[b] Xiaoqing Chen,[a] Hua Yang[a]

[a] College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, P. R. China

[b] Department of Chemistry, Oregon State University, Corvallis, Oregon 97331 (USA)

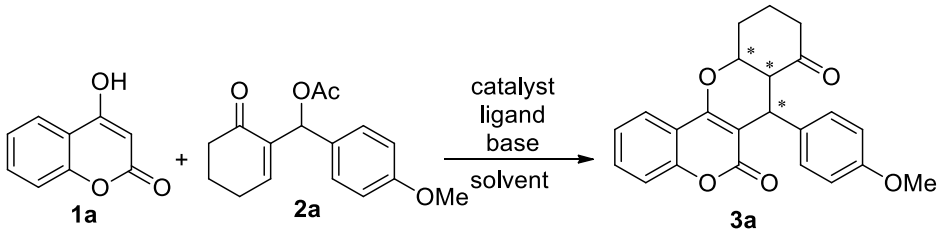
Contents

1. General Information

Unless otherwise noted, all the reagents were purchased from commercial suppliers and used without further purification. ^{1}H NMR spectra were recorded at 400 MHz. The chemical shifts were recorded in ppm relative to tetramethylsilane and with the solvent resonance as the internal standard. Data were reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), integration. ^{13}C NMR data were collected at 100 MHz with complete proton decoupling. Chemical shifts were reported in ppm from the tetramethylsilane with the solvent resonance as internal standard. Infrared spectra (IR) were measured by FT-IR apparatus. High resolution mass spectroscopy (HRMS) was recorded on TOF MS mass spectrometer and acetonitrile was used to dissolve the sample. Chiral HPLC was performed with chiral columns (chirapak AD, OD, OJ columns).

Column chromatography was carried out on silica gel (200-300 mesh). All solvents and commercially available reagents were either purified via literature procedures or used without further purification.

2. Optimization of Reaction Conditions



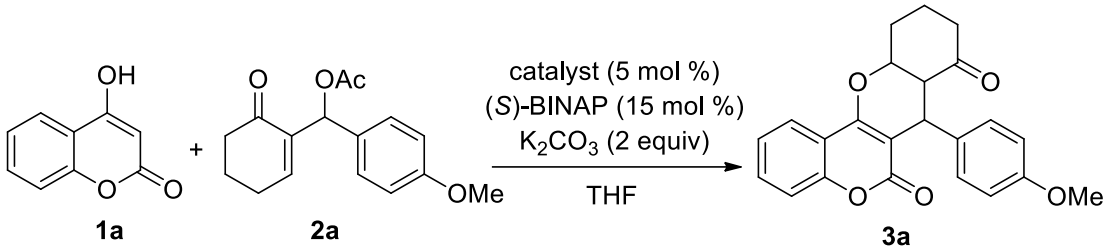
Typical experimental procedure

To a solution of 4-hydroxycoumarin **1a** (0.20 mmol), and MBHA **2a** (0.40 mmol, 2.0 equiv) in dry solvent (2 mL) was added catalyst (0.01 mmol, 5 mol %), and ligand (0.03 mmol, 15 mol %), and base. The resulting mixture was then stirred at the designated temperature. After completion of the reaction (monitored by TLC), organic solvent was removed *in vacuo*. Then the residue was purified *via* silica gel

chromatography (ethyl acetate / petroleum ether = 10% - 20%) to yield the corresponding product **3a**.

-- Screening of Pd catalyst is presented in Table 1S. We carefully examined the effect of Pd catalyst on enantioselectivity and chemical yield by employing (*S*)-binap as the ligand at room temperature and 60 °C respectively. It was found that $Pd(OAc)_2$ afforded the best ee value and yield (entry 2).

Table 1S. Screening of Catalysts for [3+3]-Annulation of **1a** and **2a**

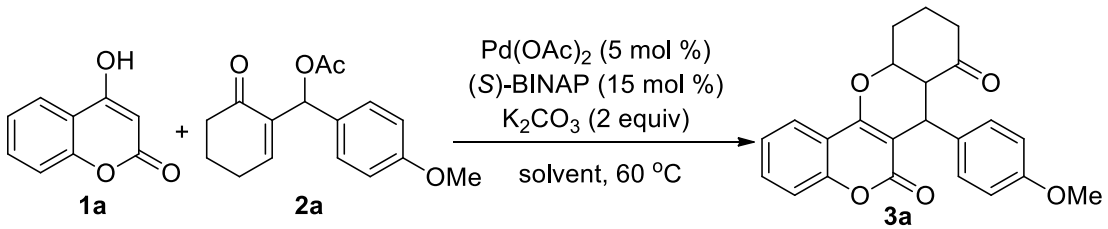


Entry[a]	Cat.	Ligand	T (°C)	Time (h)	Yield (%)	ee (%)
1	$Pd(OAc)_2$	(*S*)-binap	rt	48	85	-31
2	**$Pd(OAc)_2$**	**(*S*)-binap**	**60**	**12**	**97**	**+56**
3	$Pd_2(dba)_3$	(*S*)-binap	rt	48	Trace	-
4	$Pd_2(dba)_3$	(*S*)-binap	60	12	50	+2
5	$PdCl_2$	(*S*)-binap	rt	48	NR	-
6	$PdCl_2$	(*S*)-binap	60	12	NR	-

[a] The reactions were carried out with **1a** (0.2 mmol) and **2a** (0.4 mmol) in dry THF (2 mL).

-- The model reaction was carried out in a variety of solvents while the other reaction parameters remained unchanged (Table 2s). It can be clearly seen that toluene gave a superior enantioselectivity.

Table 2S. Effect of Solvent on the Model Reaction[a]



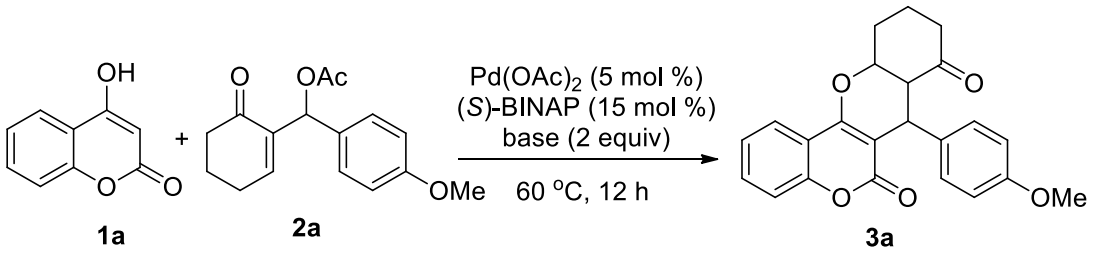
Entry[a]	Solvent	Time (h)	Yield (%)	ee (%)
1	DMSO	12	NR	-
2	MeCN	12	55	2

3	DMF	12	87	44
4	Dioxane	12	81	18
5	THF	12	89	59
6	Et_2O	12	85	54
7	MeOH	12	Trace	-
8	DCM	12	92	41
9	DEM	12	87	-23
10	**Toluene**	**12**	**91**	**61**
11	*p*-Xylene	12	97	39
12	Trifluorotoluene	12	84	2
13	Hexane	12	NR	-

[a] The reactions were carried out with **1a** (0.2 mmol) and **2a** (0.4 mmol) in dry solvent (2 mL).

-- Various bases were examined in this model reaction. Generally, inorganic bases such as K_2CO_3, Na_2CO_3, and Cs_2CO_3 gave better ee's than organic bases. And K_2CO_3 was proven the optimum base for this annulation (Table 3S).

Table 3S. Screening of Different Bases[a]



Entry[a]	Base[b]	Yield (%)	ee (%)
1	**K_2CO_3**	**99**	**65**
2	Na_2CO_3	98	59
3	Cs_2CO_3	77	59
4	K_3PO_4	76	43
5	NaOAc	NR	-
6	AgOAc	Trace	-
7	$NaHCO_3$	Trace	-
8	*t*-BuOK	81	45
9	AgOTf	96	4
10	Et_3N	47	18
11	DMAP	36	0
12	DABCO	77	26
13	Quinine	83	12
14	TMEDA	NR	-

[a] The reactions were carried out with **1a** (0.2 mmol) and **2a** (0.4 mmol) in dry solvent (2 mL); [b] Base (2 equiv) in reaction.

-- The loading of base was also examined as shown in Table 4S. Using 2 equivalents of K_2CO_3 afforded the highest ee (65% ee) and the best yield (96%).

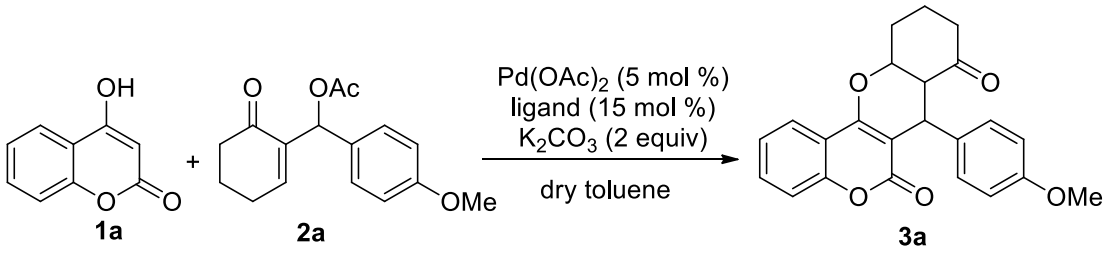
Table 4S. Effect of Loading of K_2CO_3[a]

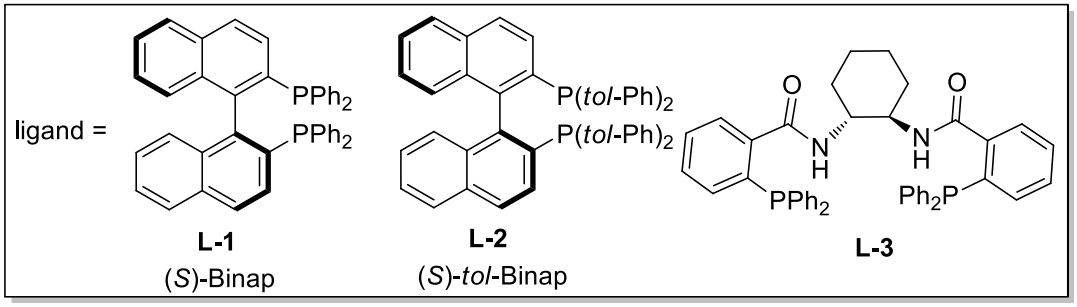
Entry	Equiv	Yield (%)	ee (%)
1	0.5	80	19
2	1.0	84	35
3	**2.0**	**96**	**65**
4	3.0	95	41
5	5.0	94	45

[a]The reactions were carried out with **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (5 mol %), and (*S*)-BINAP in dry toluene (2 mL) at 60 °C for 12 h.

--The phosphine ligands were also investigated for the annulation process. BINAP was effective in promoting the model reaction (Table 5S) and only medium enantioselectivity and yield were obtained (entries 1 and 2). Notably, TARE was observed by using this ligand. Obviously, (*S*)-*tol*-BINAP gave better ee's and yields. Unfortunately, Trost's ligand (**L3**) was ineffective in this reaction. As a result, (*S*)-*tol*-BINAP was employed in the following reactions.

Table 5S. Screening of Ligand in the Model Reaction[a]



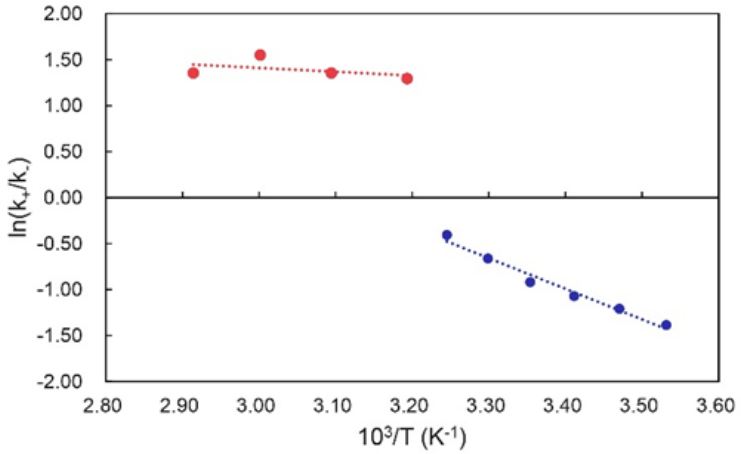


Entry	Ligand	T (°C)	Time (h)	Yield (%)	ee (%)
1	L-1	rt	48	90	-31
2	L-1	60	12	97	+61
3	**L-2**	**rt**	**48**	**95**	**-50**

4	**L-2**	**60**	**12**	**99**	**+65**
5	L-3	rt	48	NR	-
6	L-3	60	12	NR	-

[a] The reactions were carried out with **1a** (0.2 mmol) and **2a** (0.4 mmol) in dry tolene (2 mL).

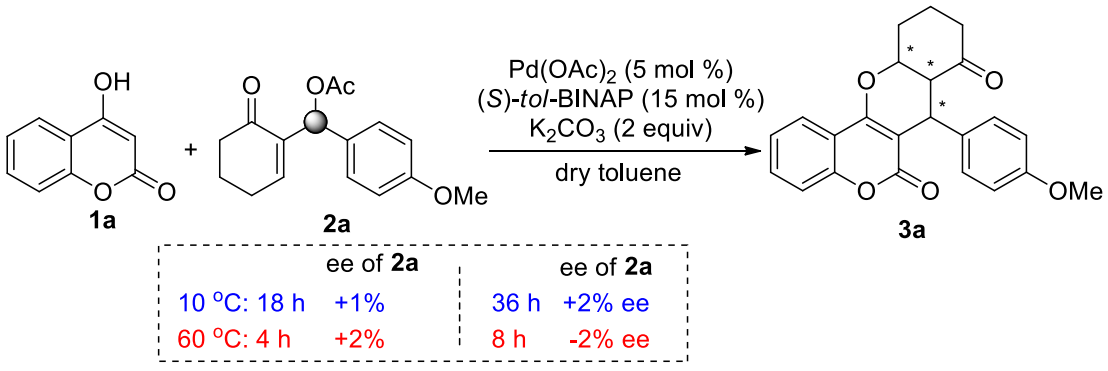
Figure 1S. Correlation of temperature and enantioselectivity of the reaction as represented by a plot of ln(k+/k-) vs 1/T



3. Control Experiments for the Mechanistic Studies

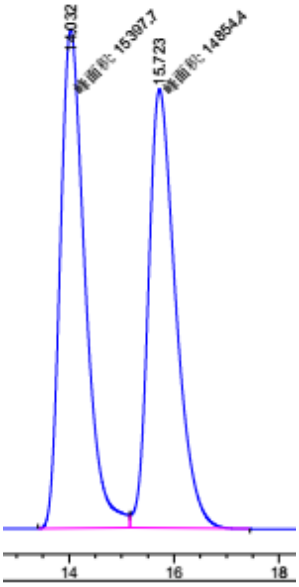
-- In order to elaborate the effect of the chiral center in MBHA **2** on the reversal of enantioselectivity, the model reaction was intentionally stopped at given points, where the enantiopurity of **2a** was determined. The results and the corresponding HPLC traces are shown in the following Table and spectra. As we can see, the enantiopurity of **2a** is always close to racemic regardless of reaction temperature and reaction time, which can essentially rule out the possibility of TARE induced by the kinetic resolution of **2.**

Table 6S. Monitoring the Change of Enantiopurity of **2a**



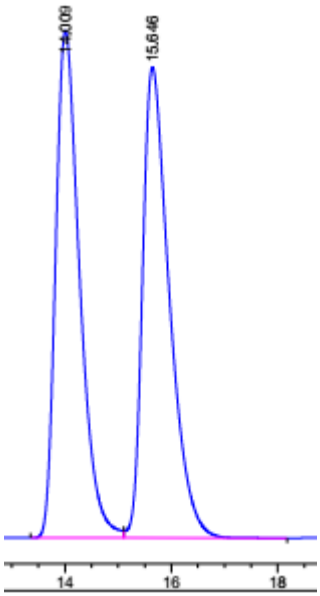
HPLC Spectra of 2a

HPLC chromatogram of racemic 2a



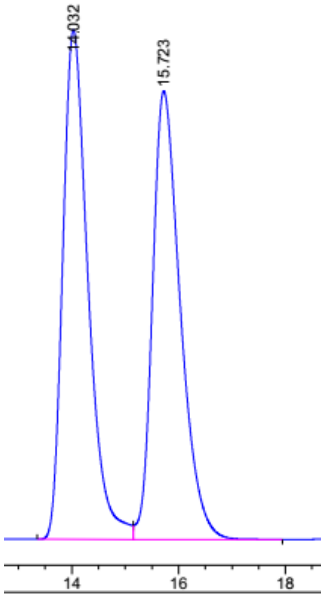
	RT [min]	Type	Width [min]	Area	Height	Area%
1	14.032	MM	0.5457	1.53977e4	470.26639	50.8980
2	15.723	MM	0.5991	1.48544e4	413.26068	49.1020

MBHA 2a (after 18 h at 10 °C)



	RT [min]	Type	Width [min]	Area	Height	Area%
1	14.009	BV	0.4776	4.88452e4	1556.59595	49.1518
2	15.646	VB	0.5234	5.05311e4	1445.12915	50.8482

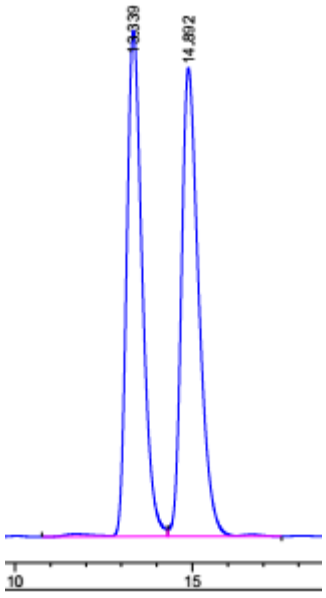
MBHA 2a (after 36 h at 10 °C)

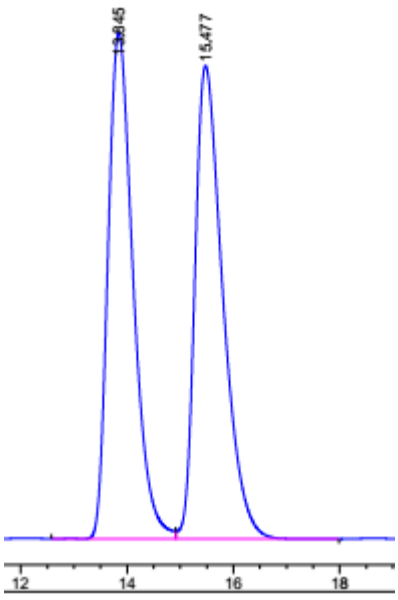


	RT [min]	Type	Width [min]	Area	Height	Area%
1	14.032	BV	0.4988	1.54397e4	470.59622	50.8088
2	15.723	VB	0.5471	1.49481e4	414.14090	49.1912

MBHA 2a (after 4 h at 60 °C)

MBHA 2a (after 8 h at 60 °C)



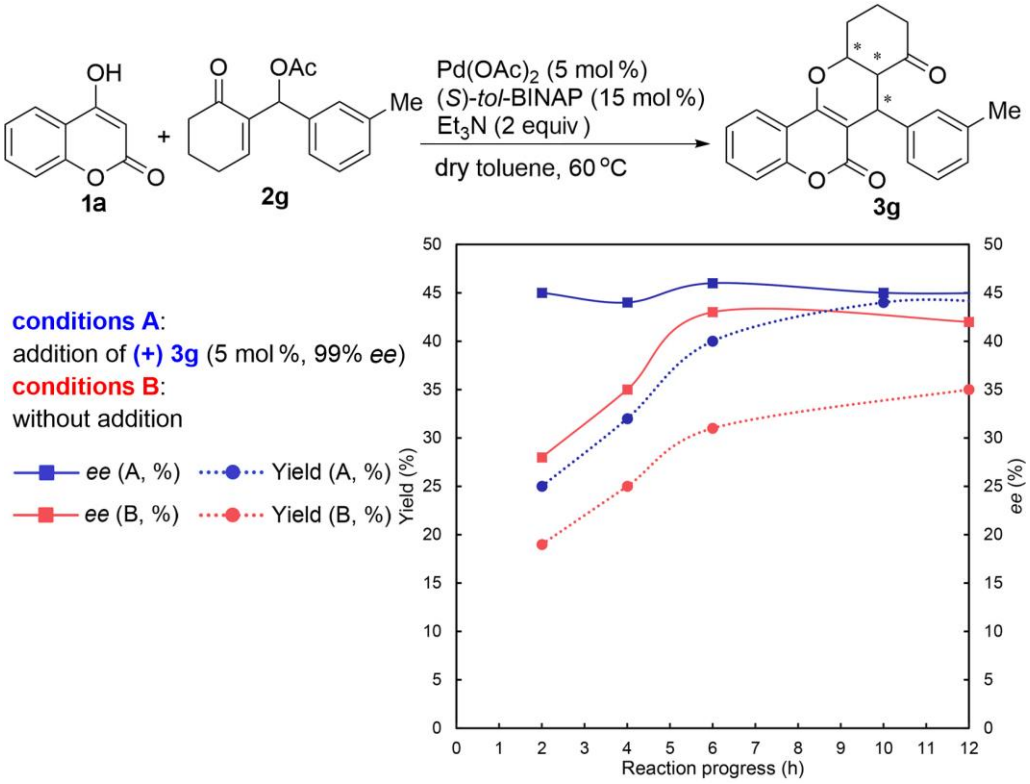


RT [min]	Type	Width [min]	Area	Height	Area%
1 13.339	VV R	0.4646	2.81722e4	914.74237	49.4654
2 14.892	VV R	0.5132	2.87812e4	847.36871	50.5346

RT [min]	Type	Width [min]	Area	Height	Area%
1 13.845	VV R	0.5043	5.71021e4	1742.46265	49.0722
2 15.477	VB	0.5493	5.92614e4	1629.40173	50.9278

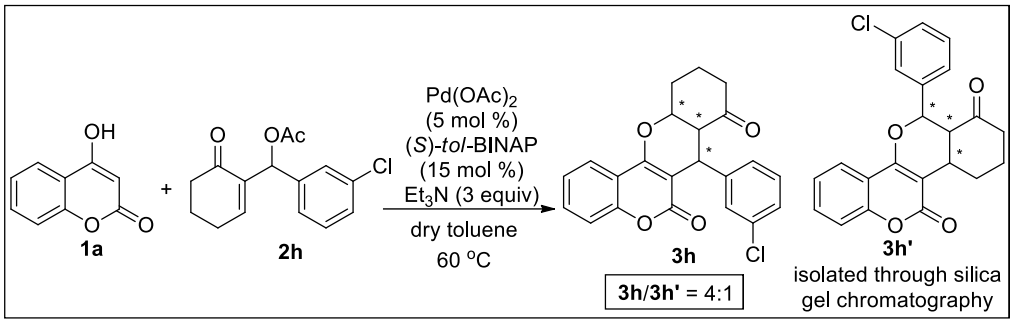
-- Given the poor solubility of K_2CO_3 in organic solvent, the role of base in the seeding experiments as shown in Figure 4 (main text) needs to be clarified. As the added product might increase the solubility of K_2CO_3 in toluene, the observed acceleration in the seeding experiments could be affected by the improved solubility of base. Therefore, we employed organic base – Et_3N to proceed the seeding experiments, which is miscible with toluene. The obtained ee and yield of the seeded and unseeded reactions were monitored in the process of reaction (as shown in Figure 1S). As a result, the exact same trend was observed in this control experiment. The addition of the matched product (+)-**3g** significantly promoted the reaction in the sense of yield and ee. After 2 hours, the seeded reaction already gave 45% ee while only 28% ee was obtained in the unseeded reaction. On the other hand, the addition of product also clearly accelerated the reaction and the seeded reaction consistently gave higher yields as compared to the unseeded reaction. *Accordingly, the hypothesis that the observed acceleration was induced by the change of solubility of K_2CO_3 can be completely ruled out. The corresponding product affected the reaction pathway and the stereochemical outcome in an autoinductive manner.*

Figure 2S. Model Validation of TARE by Using Et_3N at 60 °C

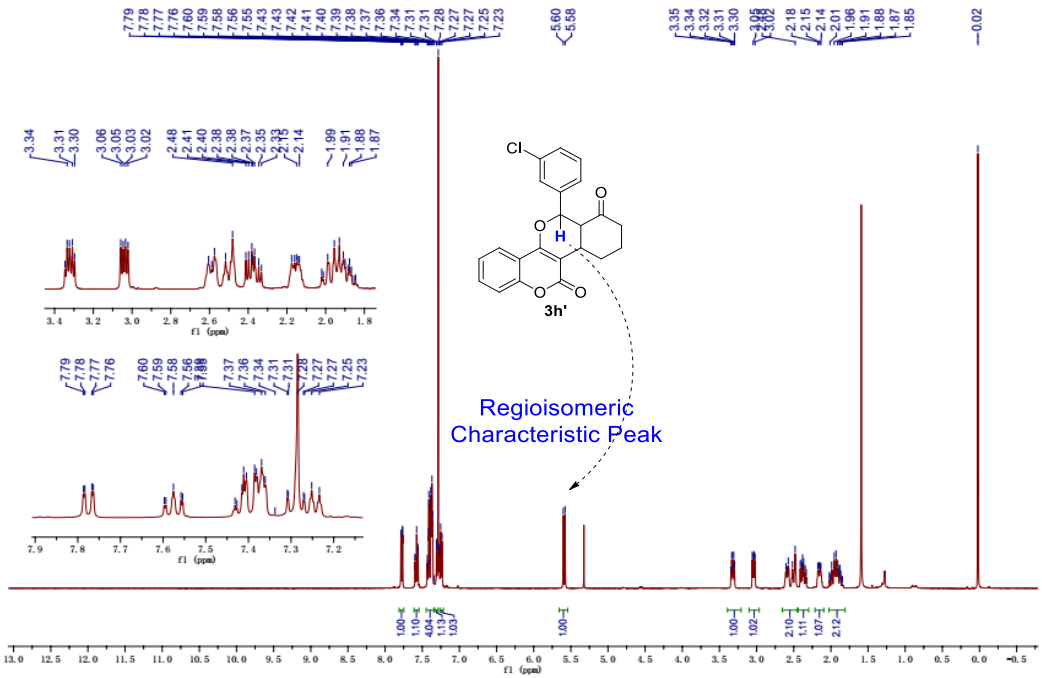


-- In some cases, the other regioisomer was obtained as the minor product (**3c** *regioisomeric ratio: 18:1;* **3k** *regioisomeric ratio: 8:1;* **3l** *regioisomeric ratio: 7:1*) at 60 °C. However, it was extremely difficult to isolate the pure minor regioisomer since only small amount of the minor product was present in the product mixture and silica gel chromatography was ineffective in separating these two regioisomers. Extensive efforts were made to achieve the minor regioisomer on the other substrates. Ultimately, a minor regioisomer **3h'**, whose structure was confirmed by NMR spectroscopy, was isolated under modified reaction conditions as shown in Scheme 1S. A characteristic doublet can be found at 5.60 ppm for the minor regioisomer **3h'**, which also can be observed in the NMR spectra of the product mixtures of **3c**, **3k**, and **3l**, respectively. Finally, the regioisomeric ratios can be calculated based on the ratios of peak areas in their HPLC spectra, which are specified in Table 2 of main text.

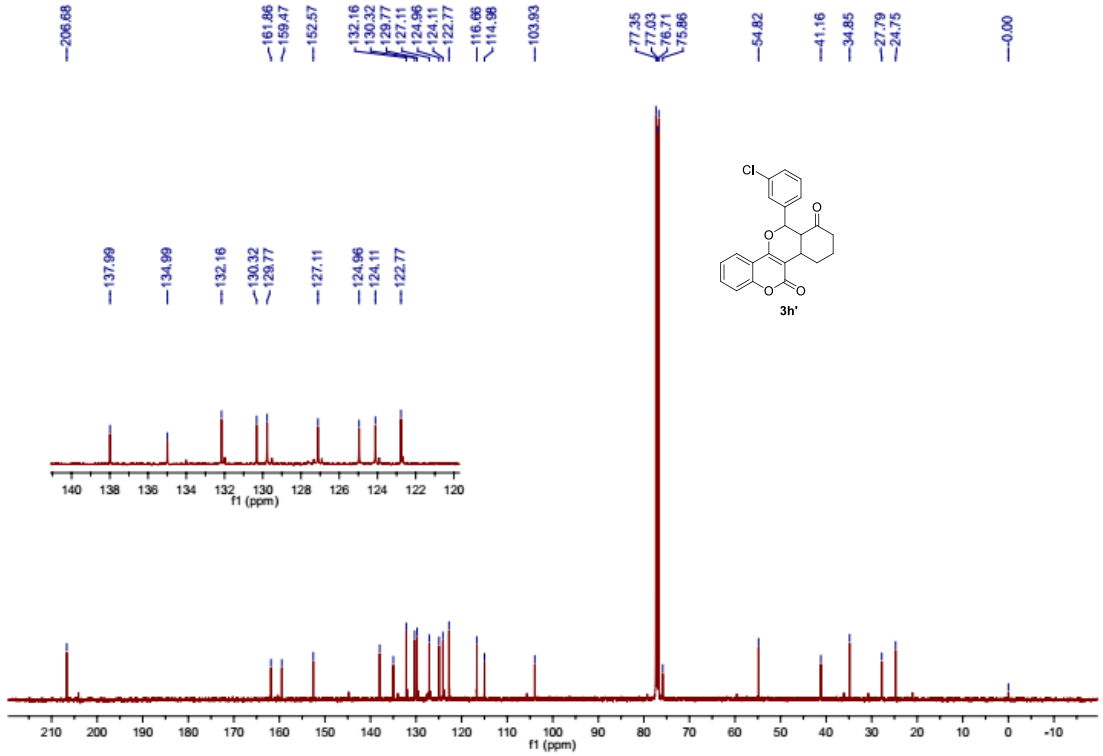
Scheme 1S. Regioisomeric Studies under Modified Reaction Conditions



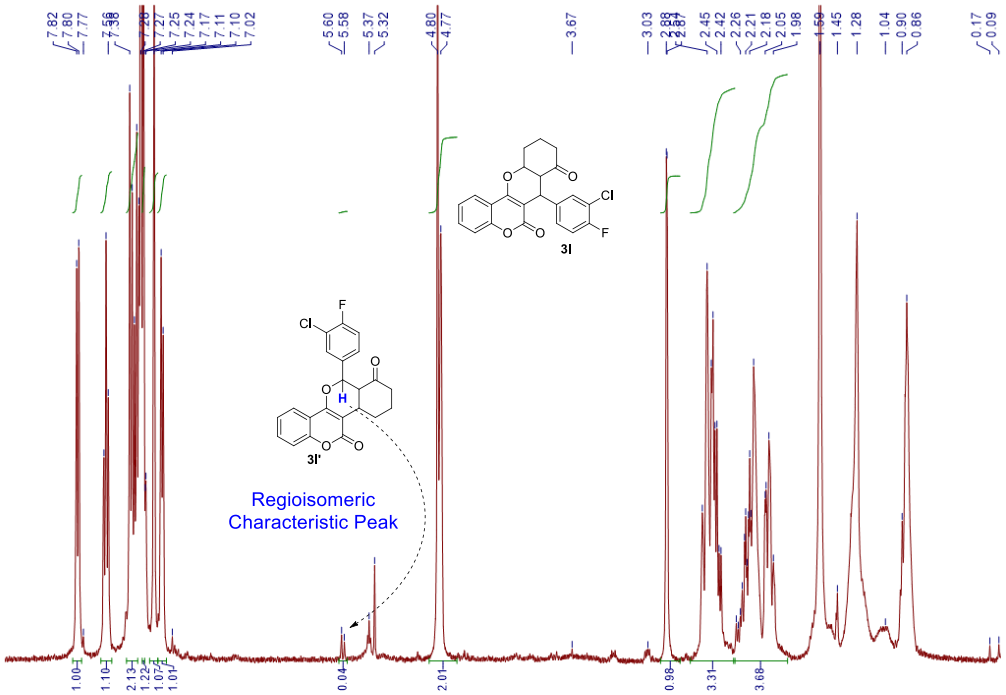
^{1}H NMR Spectrum for Minor Regioisomer **3h'**



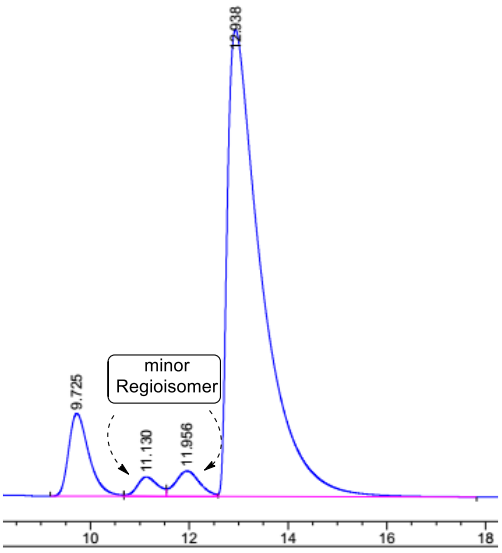
^{13}C NMR Spectrum for Minor Regioisomer **3h'**



^{1}H NMR Spectrum for the product mixture of **3l** and **3l'**

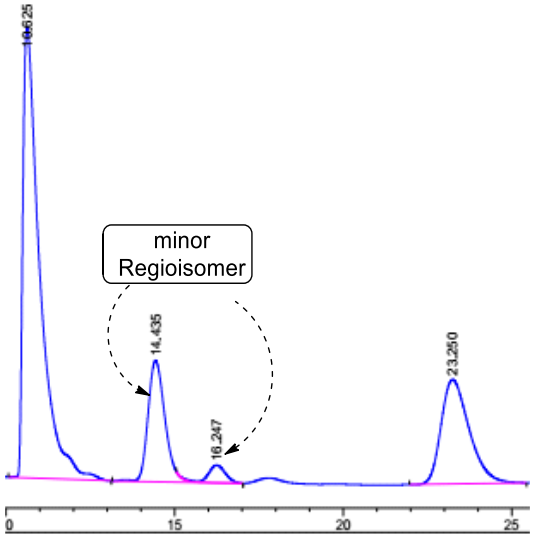


Product mixture of **3c** and **3c'** from 60 ° Product mixture of **3h** and **3h'** from 60 °C



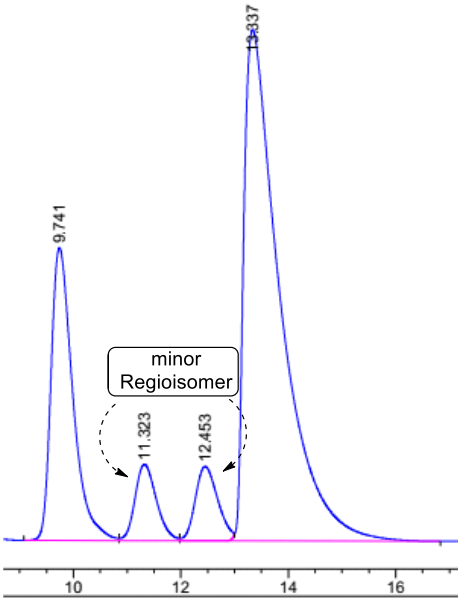
RT [min]	Type	Width [min]	Area	Height	Area%
1	9.725	BV	0.4361	2360.36499	82.42591	8.9997
2	11.130	VV	E	0.4310	558.26044	19.44283	2.1286
3	11.956	VV	E	0.5134	857.31293	25.33034	3.2688
4	12.938	VB	R	0.6983	2.24512e4	464.18182	85.6029

Product mixture of **3k** and **3k'** from 60 °C

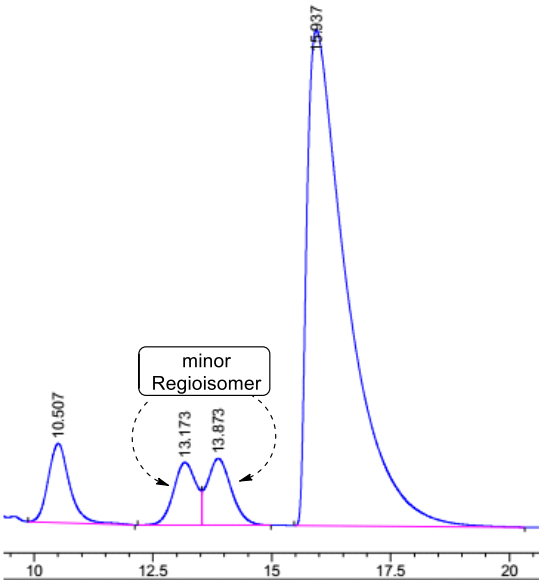


RT [min]	Type	Width [min]	Area	Height	Area%
1	10.625	BB	0.5037	1.36331e4	389.60834	59.1446
2	14.435	VV	R	0.5397	3665.01880	104.62477	15.9000
3	16.247	VB	E	0.5438	534.29694	15.17453	2.3179
4	23.250	BB	0.8820	5218.02539	90.18288	22.6374

Product mixture of **3l** and **3l'** from 60 °C



RT [min]	Type	Width [min]	Area	Height	Area%
1	9.741	BV	0.4307	8626.78809	306.16614	22.5265
2	11.323	VV	0.4296	2211.65991	79.86983	5.7751
3	12.453	VV	E	0.4491	2257.19043	77.77489	5.8940
4	13.337	VB	R	0.6811	2.52006e4	534.42200	65.8044

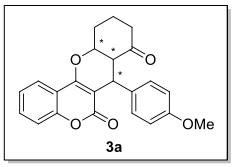


RT [min]	Type	Width [min]	Area	Height	Area%
1	10.507	BB	0.4734	879.60944	28.27873	6.7871
2	13.173	BV	0.5005	740.38031	22.40889	5.7128
3	13.873	VB	0.5257	838.65149	23.82165	6.4711
4	15.937	BB	0.8510	1.05013e4	177.29396	81.0289

4. Experimental Procedures and Characterization Data of 3a-3q, and 4.

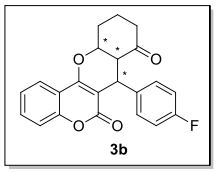
Typical experimental procedure for 3

To a solution of 4-hydroxycoumarin **1** (0.20 mmol), and MBHA **2** (0.40 mmol, 2.0 equiv) in dry toluene (2 mL) was added $Pd(OAc)_2$ (0.01 mmol, 5 mol %), and (*S*)-*tol*-BINAP (0.03 mmol, 15 mol %), and K_2CO_3 (0.40 mmol, 2.0 equiv). The resulting mixture was stirred at 10 °C or 60 °C for the designated reaction time. After completion of the reaction (monitored by TLC), organic solvent was removed *in vacuo*. Then the residue was purified *via* silica gel chromatography (ethyl acetate / petroleum ether = 10% - 20%) to yield the corresponding product.



3a

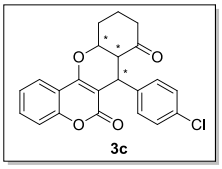
3a: white solid (**10 °C**: 50.0 mg, 0.13 mmol, yield 67%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -60% ee, $[\alpha]_D^{20}$ = -110.1 (c = 0.5 in CH_2Cl_2); **60 °C**: 65.1 mg, 0.20 mmol, quantitive yield, *regioisomeric ratio* >20:1, > 20:1 *dr*, +65% ee, $[\alpha]_D^{20}$ = +120.4 (c = 0.5 in CH_2Cl_2)) m.p. 176-178 °C; IR (KBr) ν 3413, 2956, 1704, 1627, 1510, 1251, 1033 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.28-7.33 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.84 (d, *J* = 8.4 Hz, 2H), 4.76-4.79 (m, 1H), 4.73 (s, 1H), 3.77 (s, 3H), 2.84 (s, 1H), 2.38-2.53 (m, 3H), 2.10-2.21 (m, 2H), 1.93-2.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.2, 161.8, 159.9, 158.6, 152.7, 134.8, 131.7, 128.8, 123.8, 122.4, 116.7, 115.2, 114.3, 101.5, 74.3, 55.3, 54.7, 41.1, 33.7, 29.4, 21.8; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{23}H_{20}O_5Na$ 399.1208, found 399.1204; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 11.2 min (major), 17.8 min (minor); 60 °C: t_R = 11.7 min (minor), 17.4 min (major).



3b

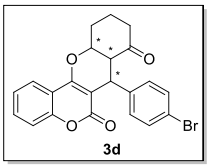
3b: white solid (**10 °C**: 48.1 mg, 0.12 mmol, yield 62%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -66% ee, $[\alpha]_D^{20}$ = -197.0 (c = 0.4 in CH_2Cl_2); **60 °C**: 60.5 mg, 0.16 mmol, yield 82%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +73% ee, $[\alpha]_D^{20}$ = +216.2 (c = 0.3 in CH_2Cl_2)); m.p. 231-233 °C; IR (KBr) ν 3404, 2943, 1708, 1629, 1506, 1311,

1013, 751 ; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.54 (td, *J* = 8.4, 1.6 Hz, 1H), 7.27-7.34 (m, 2H), 7.13-7.16 (m, 2H), 6.98-7.02 (m, 2H), 4.77 (s, 1H), 4.75 (d, *J* = 2.8 Hz, 1H), 2.83 (d, *J* = 2.8 Hz, 1H), 2.41-2.54 (m, 3H), 2.10-2.19 (m, 2H), 1.94-2.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.8, 161.9 (d, $^{1}J_{C-F}$ = 244 Hz), 161.7, 160.0, 152.7, 138.49, 138.46, 131.9, 129.3 (d, $^{3}J_{C-F}$ = 8 Hz), 123.8, 122.4, 116.8 , 115.8 (d, $^{2}J_{C-F}$ = 21 Hz) , 115.1, 101.1, 74.1, 54.6, 41.1, 33.9, 29.4, 21.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -115.9; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{17}O_4NaF$ calcd for 387.1009, found 387.1002; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 9.4 min (major), 12.9 min (minor); 60 °C: t_R = 9.5 min (minor), 12.5 min (major).



3c

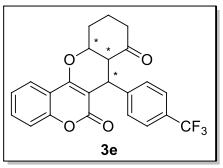
3c: white solid (**10 °C**: 50.3 mg, 0.13 mmol, yield 66%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -84% ee, $[\alpha]_D^{20}$ = -190.5 (c = 0.5 in CH_2Cl_2); **60 °C**: 65.8 mg, 0.17 mmol, yield 86%, *regioisomeric ratio* 18:1, > 20:1 *dr*, +82% ee, $[\alpha]_D^{20}$ = +275.0 (c = 0.5 in CH_2Cl_2)); m.p. 240-242 °C; IR (KBr) ν 3388, 2951, 2887, 1698, 1630, 1403, 1307, 1086, 755; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.27-7.35 (m, 4H), 7.12 (d, *J* = 7.6 Hz, 2H), 4.76 (s, 1H), 4.71-4.74 (m, 1H), 2.83 (s, 1H), 2.43-2.55 (m, 3H), 2.12-2.19 (m, 2H), 1.95-2.02 (m, 1H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 205.6, 161.7, 160.1, 152.7, 141.4, 132.9, 132.0, 129.2, 129.0, 123.9, 122.4, 116.8, 115.0, 100.8, 74.2, 54.5, 41.1, 34.1, 29.4, 21.7; HRMS (TOF-ES+) m/z: $[M+H]^+$ calcd for $C_{22}H_{18}O_4Cl$ calcd for 381.0894, found 381.0908; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 9.6 min (major), 13.7 min (minor); 60 °C: t_R = 9.7 min (minor), 12.9 min (major).



3d

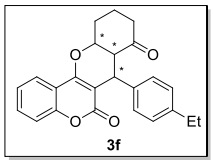
3d: white solid (**10 °C**: 550.3 mg, 0.13 mmol, yield 65%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -77% ee, $[\alpha]_D^{20}$ = -90.5 (c = 0.5 in CH_2Cl_2); **60 °C**: 82.5 mg, 0.19 mmol, yield 97%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +51% ee, $[\alpha]_D^{20}$ = +148.6 (c = 0.7 in CH_2Cl_2)); m.p. 240-242 °C; IR (KBr) ν 3423, 2917, 1702, 1625, 1489, 1407, 1310, 1011, 761; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54

(td, *J* = 8.4, 1.6 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 2H), 7.29-7.35 (m, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 4.75 (s, 1H), 4.73 (d, *J* = 1.6 Hz, 1H), 2.82 (d, *J* = 2.4 Hz, 1H), 2.39-2.55 (m, 3H), 2.11-2.22 (m, 2H), 1.94-2.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.5, 161.6, 160.1, 152.8, 141.9, 131.98, 131.95, 0129.5, 123.8, 122.4, 121.0, 116.8, 115.0, 100.7, 74.2, 54.5, 41.0, 34.2, 29.4, 21.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{17}O_4NaBr$ calcd for 447.0208, found 447.0191; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 9.9 min (major), 14.3 min (minor), 60 °C: t_R = 9.9 min (minor), 12.7 min (major).



3e

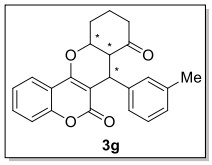
3e: white solid (**10 °C**: 20.2 mg, 0.05 mmol, yield 24%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -54% ee, $[\alpha]_D^{20}$ = -213.6 (c = 0.2 in CH_2Cl_2); **60 °C**: 50 mg, 0.12 mmol, yield 60%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +37% ee, $[\alpha]_D^{20}$ = +199.5 (c = 0.5 in CH_2Cl_2)); m.p. 232-234 °C; IR (KBr) ν 3414, 2964, 1706, 1629, 1323, 1209, 1111, 759; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54-7.59 (m, 3H), 7.28-7.35 (m, 4H), 4.85 (s, 1H), 4.72 (d, *J* = 2.8 Hz, 1H), 2.86 (d, *J* = 2.8 Hz, 1H), 2.41-2.57 (m, 3H), 2.11-2.24 (m, 2H), 1.95-2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.4, 161.7, 160.4, 152.8, 147.0, 132.1, 128.2, 125.89, 125.85, 123.9, 122.5, 116.8, 115.0, 100.4, 74.2, 54.3, 41.0, 34.6, 29.3, 21.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -62.5; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{23}H_{17}O_4NaF_3$ calcd for 437.0977, found 437.0965; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 11.9 min (minor), 23.6 min (major); 60 °C: t_R = 11.5 min (major), 24.4 min (minor).



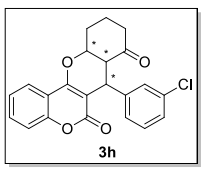
3f

3f: white solid (**10 °C**: 71.0 mg, 0.19 mmol, yield 94%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -51% ee, $[\alpha]_D^{20}$ = -140.3 (c = 0.5 in CH_2Cl_2); **60 °C**: 73.8 mg, 0.20 mmol, yield 99%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +60% ee, $[\alpha]_D^{20}$ = +176.4 (c = 0.5 in CH_2Cl_2)); m.p. 143-145 °C; IR (KBr) ν 3411, 2962, 2931, 1712, 1627, 1399, 1310, 1190, 1110, 1009, 763; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (d, *J* = 8.0 Hz, 1H), 7.53 (td, *J* = 8.1, 1.2 Hz, 1H), 7.28-7.33 (m, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 7.80 (d, *J* = 8.0 Hz, 2H), 4.78 (d, *J* = 0.8 Hz,1H), 4.76 (s, 1H), 2.86 (d, *J* = 2.8 Hz, 1H), 2.61 (q, *J*

= 7.6 Hz, 2H), 2.42-2.53 (m, 3H), 2.10-2.21 (m, 2H); 1.93-1.99 (m, 1H),1.21 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.2, 161.8, 159.8, 152.7, 142.9, 139.9, 131.7, 128.4, 127.7, 123.7, 122.4, 116.7, 115.2, 101.4, 74.3, 54.6, 41.1, 34.2, 29.4, 28.4, 21.8, 15.5; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{24}H_{22}O_4Na$ calcd for 397.1416, found 397.1404; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 7.8 min (major), 10.5 min (minor); 60 °C: t_R = 7.8 min (minor), 10.0 min (major).

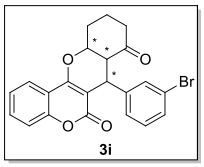


3g: White solid (**10 °C**: 34.6 mg, 0.10 mmol, yield 48%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -99% ee, $[\alpha]_D^{20}$ = -185.2 (c = 0.3 in CH_2Cl_2); **60 °C**: 50.5 mg, 0.14 mmol, yield 70%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +99% ee, $[\alpha]_D^{20}$ = +184.4 (c = 0.5 in CH_2Cl_2)); m.p. 264-266 °C; IR (KBr) *v* 3404, 2938, 1711, 1628, 1311, 1086, 1010, 766 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.53 (td, *J* = 7.6, 1.6 Hz,, 1H), 7.28-7.34 (m, 2H), 7.20 (t, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.95-6.98 (m, 2H), 4.78 (d, *J* = 2.8 Hz, 1H), 4.75 (s, 1H), 2.86 (d, *J* = 3.2 Hz, 1H), 2.38-2.50 (m, 3H), 2.31 (s, 3H), 2.08-2.21 (m, 2H), 1.92-2.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.0, 161.8, 159.9, 152.7, 142.8, 138.5, 131.7, 128.7, 128.5, 127.8, 124.8, 123.7, 122.4, 116.8, 115.2, 101.3, 74.3, 54.6, 41.1, 34.5, 29.4, 21.7, 21.5; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{23}H_{20}O_4Na$ 383.1259, found 383.1253; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 11.8 min (minor), 14.4 min (major); 60 °C: t_R = 11.0 min (major), 14.7 min (minor).

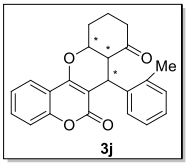


3h: White solid (**10 °C**: 38.1 mg, 0.10 mmol, yield 50%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -96% ee, $[\alpha]_D^{20}$ = -82.4 (c = 0.3 in $CHCl_3$); **60 °C**: 53.3 mg, 0.14 mmol, yield 70%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +99% ee, $[\alpha]_D^{20}$ = +110.5 (c = 0.3 in $CHCl_3$)); m.p. 261-263 °C; IR (KBr) *v* 3397, 2949, 1704, 1628, 1401, 1311, 1014, 762 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.55 (td, *J* = 6.8, 1.6 Hz, 1H), 7.26-7.35 (m, 2H), 7.21-7.24 (m, 2H), 7.14-7.16 (m, 1H), 7.07-7.09 (m, 1H), 4.77 (s, 1H), 4.75 (d, *J* = 2.8 Hz, 1H), 2.85 (d, *J* = 2.8 Hz, 1H),

2.43-2.55 (m, 3H), 2.10-2.19 (m, 2H), 1.98-2.03 (m, 1H); ^{13}C NMR ($CDCl_3$ 100 MHz) δ 205.5, 161.7, 160.2, 152.8, 145.0, 134.8, 132.0, 130.2, 127.9, 127.3, 126.1, 123.9, 122.4, 116.8, 115.0, 100.5, 74.2, 54.4, 41.1, 34.4, 29.3, 21.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{17}O_4NaCl$ 403.0713, found 403.0695; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 11.6 min (minor), 23.3 min (major); 60 °C: t_R = 10.6 min (major), 24.0 min (minor).

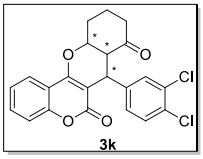


3i: white solid (**10 °C**: 35.4 mg, 0.08 mmol, yield 41%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -55% ee, $[\alpha]_D^{20}$ = -92.6 (c = 0.3 in CH_2Cl_2); **60 °C**: 53.0 mg, 0.12 mmol, yield 62%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +36% ee, $[\alpha]_D^{20}$ = +62.5 (c = 0.5 in CH_2Cl_2)); m.p. 246-248 °C; IR (KBr) ν 3406, 2949, 1711, 1629, 1527, 1350, 1308, 1017, 767; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.12 (dd, *J* = 8.0, 1.2 Hz, 1H), 8.02-8.04 (m, 1H), 7.81 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.49-7.61 (m, 3H), 7.35 (d, *J* = 8.8 Hz, 1H), 7.32 (t, *J* = 8.4 Hz, 1H), 4.90 (s, 1H), 4.73 (d, *J* = 2.8 Hz, 1H) 2.89 (d, *J* = 2.8 Hz, 1H), 2.43-2.59 (m, 3H), 2.14-2.26 (m, 2H), 1.96-2.05 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.0, 161.7, 160.7, 152.8, 148.7, 145.2, 134.2, 132.3, 129.9, 124.1, 122.9, 122.6, 122.3, 116.9, 114.9, 99.9, 74.2, 54.2, 41.0, 34.5, 29.3, 21.6; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{17}O_4NaBr$ calcd for 447.0208, found 447.0191; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 11.9 min (minor), 23.6 min (major); 60 °C: t_R = 11.5 min (major), 24.4 min (minor).

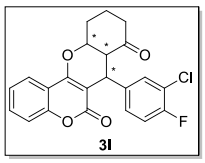


3j: White solid (**10 °C**: 30.3 mg, 0.08 mmol, yield 42%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -39% ee, $[\alpha]_D^{20}$ = -100.1 (c = 0.3 in CH_2Cl_2); **60 °C**: 46.9 mg, 0.13 mmol, yield 65%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +8% ee, $[\alpha]_D^{20}$ = +15.8 (c = 0.4 in CH_2Cl_2)); m.p. 265-267 °C; IR (KBr) *v* 3402, 2946, 1707, 1629, 1399, 1312, 1012, 767; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.53 (td, *J* = 8.4, 1.6 Hz, 1H), 7.28-7.33 (m, 2H), 7.22 (d, *J* = 7.2 Hz,1H), 7.15 (td, *J* = 7.2, 0.8 Hz, 1H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 1H), 4.97 (s, 1H), 4.80 (d, *J* = 2.4 Hz,

1H), 2.69 (d, *J* = 3.2 Hz, 1H), 2.38-2.55 (m, 6H), 2.07-2.15 (m, 1H), 2.15-2.21 (m, 1H), 1.91-2.00 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.9, 161.5, 160.0, 152.7, 140.7, 135.51, 131.7, 131.2, 127.4, 127.0, 126.0, 123.7, 122.3, 116.7, 115.2, 101.6, 74.1, 52.3, 41.0, 31.3, 29.4, 21.6, 19.2; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{23}H_{20}O_4Na$ 383.1259, found 383.1271; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 12.0 min (minor), 24.9 min (major), 60 °C: t_R = 12.0 min (major), 25.0 min (minor).

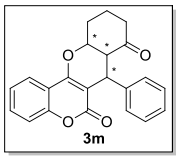


3k: White solid (**10 °C**: 19.1 mg, 0.05 mmol, yield 23%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -75% ee, $[\alpha]_D^{20}$ = -156.9 (c = 0.2 in CH_2Cl_2); **60 °C**: 34.1 mg, 0.08 mmol, yield 41%, *regioisomeric ratio* 8:1, > 20:1 *dr*, +49% ee, $[\alpha]_D^{20}$ = +25.7 (c = 0.3 in CH_2Cl_2)); m.p. 271-273 °C; IR (KBr) *v* 3422, 2918, 1703, 1629, 1310, 1017, 761; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 8.0 Hz, 1H), 7.28-7.40 (m, 4H), 7.04 (dd, *J* = 8.0, 1.2 Hz, 1H), 4.75 (s, 1H), 4.71-4.73 (m, 1H), 2.83 (d, *J* = 1.6 Hz, 1H), 2.40-2.56 (m, 3H), 2.13-2.22 (m, 2H), 1.94-2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.3, 161.6, 160.4, 152.8, 143.2, 133.0, 132.2, 131.3, 130.8, 129.7, 127.2, 124.0, 122.5, 116.9, 114.9, 100.2, 74.2, 54.3, 41.0, 34.0, 29.3, 21.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{16}O_4NaCl_2$ 437.0323, found 437.0338; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 9.6 min (major), 13.8 min (minor); 60 °C: t_R = 9.7 min (minor), 13.3 min (major).

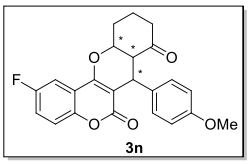


3l: White solid (**10 °C**: 19.9 mg, 0.05 mmol, yield 25%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -97% ee, $[\alpha]_D^{20}$ = -95.3 (c = 0.2 in CH_2Cl_2); **60 °C**: 35.9 mg, 0.09 mmol, yield 45%, *regioisomeric ratio* 7:1, > 20:1 *dr*, +84% ee, $[\alpha]_D^{20}$ = +55.7 (c = 0.3 in CH_2Cl_2)); m.p. 248-250 °C; IR (KBr) *v* 3394, 2944, 1706, 1631, 1356, 1314, 1016, 755; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.54 (td, *J* = 6.8, 1.2 Hz, 1H), 7.28-7.35 (m ,2H), 7.20 (dd, *J* = 6.8, 2.0 Hz, 1H), 7.04-7.12 (m, 2H), 4.75 (s, 1H), 4.73 (d, *J* = 2.8 Hz, 1H), 2.83 (d, *J* = 2.8 Hz, 1H), 2.40-2.56 (m, 3H), 2.11-2.20 (m, 2H), 1.96-2.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.4, 161.6, 160.3, 157.2 (d,

$^{1}J_{C\text{-}F}$ = 247 Hz) 152.8, 139.9, 132.1, 129.8, 127.5 (d, $^{3}J_{C\text{-}F}$ = 8 Hz) 123.9, 122.5, 121.5, 121.4, 117.0 (d, $^{2}J_{C\text{-}F}$ = 21 Hz), 114.9, 100.4, 74.1, 54.4, 41.0, 33.8, 29.3, 21.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -117.9; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{16}O_4NaClF$ 421.0619, found 421.0632; HPLC analysis: (CHIRALCEL OD-H, 20% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), 10 °C: t_R = 10.1 min (major), 17.1 min (minor); 60 °C: t_R = 10.5 min (minor), 16.0 min (major).

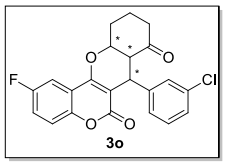


3m: White solid (**10 °C**: 49.8 mg, 0.14 mmol, yield 72%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -88% ee, $[\alpha]_D^{20}$ = -60.3 (c = 0.5 in CH_2Cl_2); **60 °C**: 65.2 mg, 0.19 mmol, yield 94%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +76% ee, $[\alpha]_D^{20}$ = +154.0 (c = 0.5 in CH_2Cl_2)); m.p. 276-278 °C; IR (KBr) ν 3402, 2950, 2909, 1709, 1626, 1311, 1013; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.51-7.56 (m, 1H), 7.28-7.32 (m, 4H), 7.23-7.25 (m, 1H), 7.17-7.18 (m, 2H), 4.80 (s, 1H), 4.78 (d, *J* = 2.8 Hz, 1H), 2.87 (d, *J* = 2.8 Hz, 1H), 2.39-2.51 (m, 3H), 2.09-2.19 (m, 2H), 1.92-1.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.0, 161.8, 159.9, 152.7, 142.8, 131.8, 128.9, 127.8, 127.0, 123.8, 122.4, 116.8, 115.2, 101.2, 74.2, 54.6, 41.1, 34.5, 29.4, 21.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{18}O_4Na$ calcd for 369.1103, found 369.1117; *Due to the problematic solubility of **3m**, the determination of ee for **3m** was conducted on the corresponding reduced product of **3m** – alcohol **4** (HPLC analysis: please see the HPLC data of **4**).*

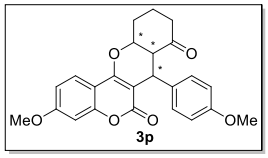


3n: White solid (**10 °C**: 75.7 mg, 0.19 mmol, yield 96%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -46% ee, $[\alpha]_D^{20}$ = -131.2 (c = 0.5 in CH_2Cl_2); **60 °C**: 78.9 mg, 0.20 mmol, yield 99%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +56% ee, $[\alpha]_D^{20}$ = +91.5 (c = 0.5 in CH_2Cl_2)); m.p. 157-159 °C; IR (KBr) *v* 3406, 2940, 1712, 1631, 1506, 1240, 1004, 831; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.28-7.32 (m, 1H), 7.21-7.25 (m, 1H), 7.07 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.78 (d, *J* = 2.4 Hz, 1H), 4.72 (s, 1H), 3.77 (s, 3H), 2.84 (d, *J* = 2.8 Hz, 1H), 2.39-2.54 (m, 3H), 2.09-2.18 (m, 2H), 1.93-2.02 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.1 161.4, 158.9, 158.7, 158.6 (d, $^{1}J_{C\text{-}F}$ = 242 Hz), 148.8, 134.5, 128.8,

119.2 (d, $^{2}J_{C\text{-}F}$ = 25 Hz), 118.4 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 116.0 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 114.4, 108.3, 108.1, 102.4, 74.6, 55.3, 54.6, 41.1, 33.8, 29.3, 21.8; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -117.6; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{23}H_{19}O_5NaF$ 417.1114, found 417.1104; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 11.7 min (minor), 19.5 min (major); 60 °C: t_R = 11.7 min (major), 20.0 min (minor).

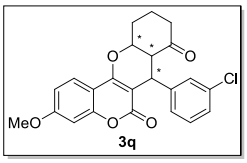


3o: White solid (**10 °C**: 30.3 mg, 0.08 mmol, yield 38%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -98% ee, $[\alpha]_D^{20}$ = -128.1 (c = 0.3 in CH_2Cl_2); **60 °C**: 44.7 mg, 0.11 mmol, yield 56%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +94% ee, $[\alpha]_D^{20}$ = +80.5 (c = 0.3 in CH_2Cl_2)); m.p. 277-279 °C; IR (KBr) *v* 3406, 2947, 1709, 1629, 1580, 1303, 834; ^{1}H NMR ($CDCl_3$, 400 Hz) δ 7.44 (dd, *J* = 8.4, 2.8 Hz, 1H), 7.23-7.34 (m, 4H), 7.11-7.13 (m, 1H), 7.06 (d, *J* = 6.8 Hz, 1H), 4.75-4.77 (m, 2H), 2.86-2.87 (m, 1H), 2.40-2.56 (m, 3H), 2.09-2.18 (m, 2H), 1.96-2.03 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.4, 161.3, 159.4, 158.7 (d, $^{1}J_{C\text{-}F}$ = 242 Hz), 148.9, 144. 7, 134.9, 130.2, 127.9, 127.4, 126.0, 119.4 (d, $^{2}J_{C\text{-}F}$ = 25 Hz), 118.5 (d, $^{3}J_{C\text{-}F}$ = 8 Hz), 115.9 (d, $^{3}J_{C\text{-}F}$ = 9 Hz), 108.3 (d, $^{2}J_{C\text{-}F}$ = 25 Hz), 101.4, 74.5, 54.3, 41.0, 34.4, 29.3, 21.7; ^{19}F NMR ($CDCl_3$, 376 MHz) δ -117.3; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{16}O_4NaClF$ 421.0619, found 421.0617; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 13.3 min (minor), 29.7 min (major); 60 °C: t_R = 12.7 min (major), 31.1 min (minor).



3p: White solid (**10 °C**: 52.8 mg, 0.13 mmol, yield 65%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -65% ee, $[\alpha]_D^{20}$ = -152.5 (c = 0.5 in CH_2Cl_2); **60 °C**: 65.0 mg, 0.16 mmol, yield 80%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +62% ee, $[\alpha]_D^{20}$ = +130.9 (c = 0.5 in CH_2Cl_2)); m.p. 235-237 °C; IR (KBr) *v* 3415, 2928, 1701, 1619, 1509, 1438, 1246, 1157, 830; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.66 (d, *J* = 8.8 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 2H), 6.81-6.86 (m, 4H), 4.74-4.76 (m, 1H), 4.70 (s, 1H), 3.86 (s, 3H), 3.77 (s, 3H), 2.80-2.82 (m, 1H), 2.38-2.52 (m, 3H), 2.09-2.20 (m, 2H), 1.92-1.99 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.3, 162.7, 162.2, 160.2, 158.55, 154.5,

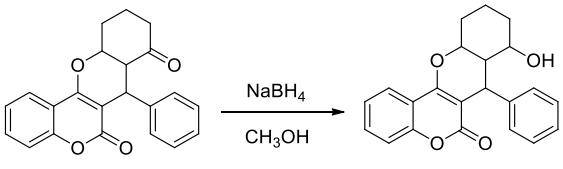
135.0, 128.8, 123.4, 114.3, 112.1, 108.4, 100.4, 98.7, 74.1, 55.8, 55.3, 54.8, 41.1, 33.6, 29.4, 21.7; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{24}H_{22}O_6Na$ 429.1314, found 429.1298; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 13.0 min (major), 25.4 min (minor); 60 °C: t_R = 14.0 min (minor), 25.5 min (major).



3q

3q: White solid (**10 °C:** 24.7 mg, 0.06 mmol, yield 37%, *regioisomeric ratio* >20:1, > 20:1 *dr*, -65% ee, $[\alpha]_D^{20}$ = -135.2 (c = 0.2 in CH_2Cl_2); **60 °C**: 45.2 mg, 0.11 mmol, yield 55%, *regioisomeric ratio* >20:1, > 20:1 *dr*, +48% ee, $[\alpha]_D^{20}$ = +80.5 (c = 0.6 in CH_2Cl_2)); m.p. 238-240 °C; IR (KBr) *v* 3426, 2935, 1686, 1622, 1402, 1157, 1028, 775; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.67 (d, *J* = 8.8 Hz, 1H), 7.20-7.25 (m, 2H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.08 (td, *J* = 7.2, 1.6 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 4.74 (s, 1H), 4.71 (d, *J* = 2.8 Hz, 1H), 3.87 (s, 3H), 2.82 (d, *J* = 2.8 Hz, 1H), 2.38-2.55 (m, 3H), 2.09-2.22 (m, 2H), 1.92-2.01 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 205.6, 162.9, 162.1, 160.7, 154.6, 145.3, 134.7, 130.1, 127.9, 127.2, 126.1, 123.5, 112.3, 108.3, 100.7, 97.8, 74.0, 55.6, 54.5, 41.0, 34.2, 29.4, 21.6; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{23}H_{19}O_5NaCl$ 433.0819, found 433.0838; HPLC analysis: (CHIRALCEL OD-H, 30% *i*-propanol/hexanes, 0.8 mL/min, UV: 254 nm), 10 °C: t_R = 15.7 min (minor), 22.4 min (major); 60 °C: t_R = 15.2 min (major), 23.6 min (minor).

Preparation of 4 *via* the reduction of 3m

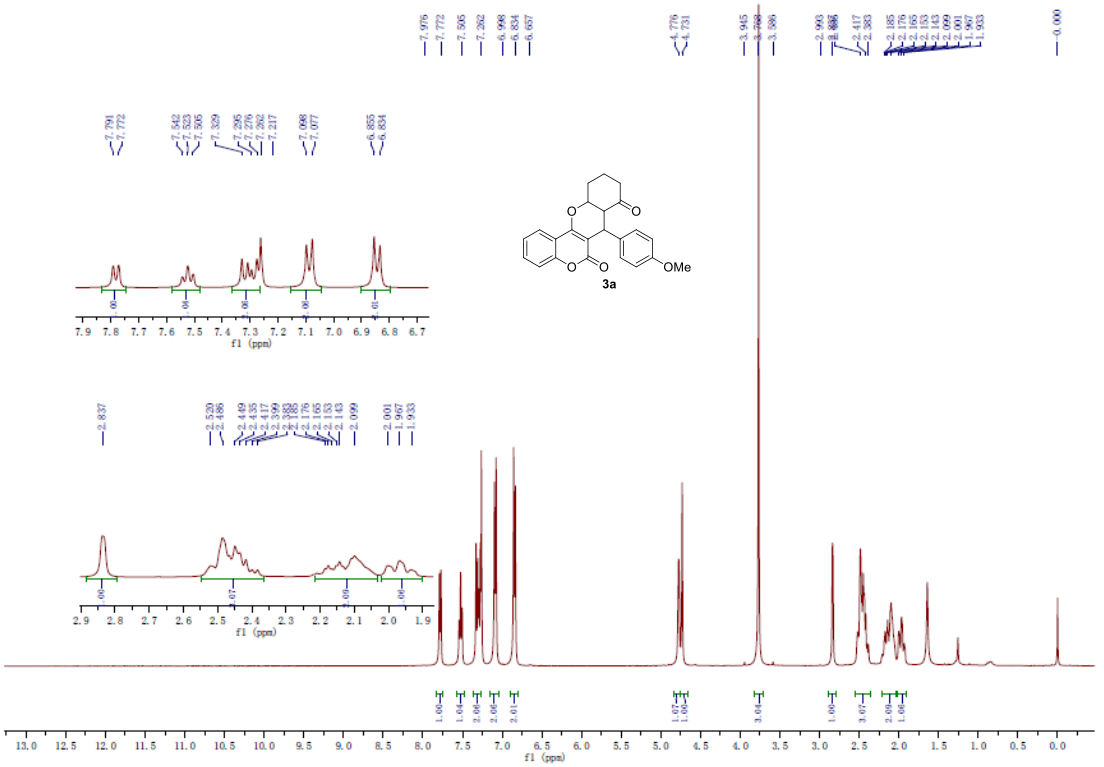


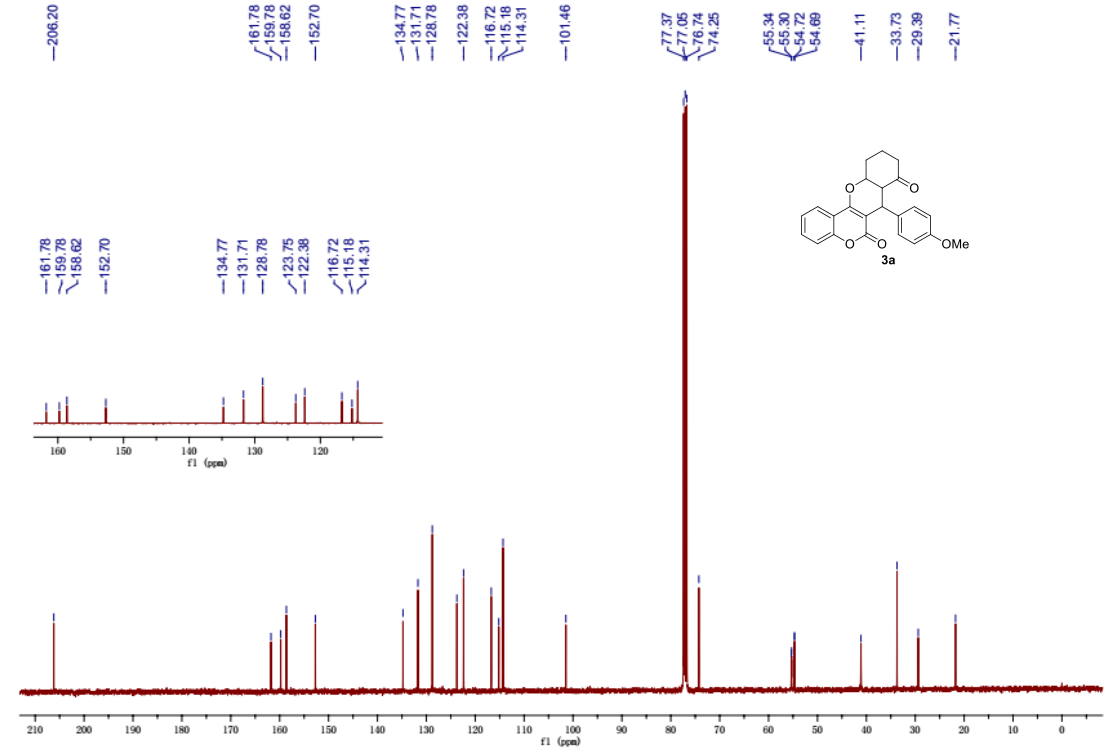
3m 4

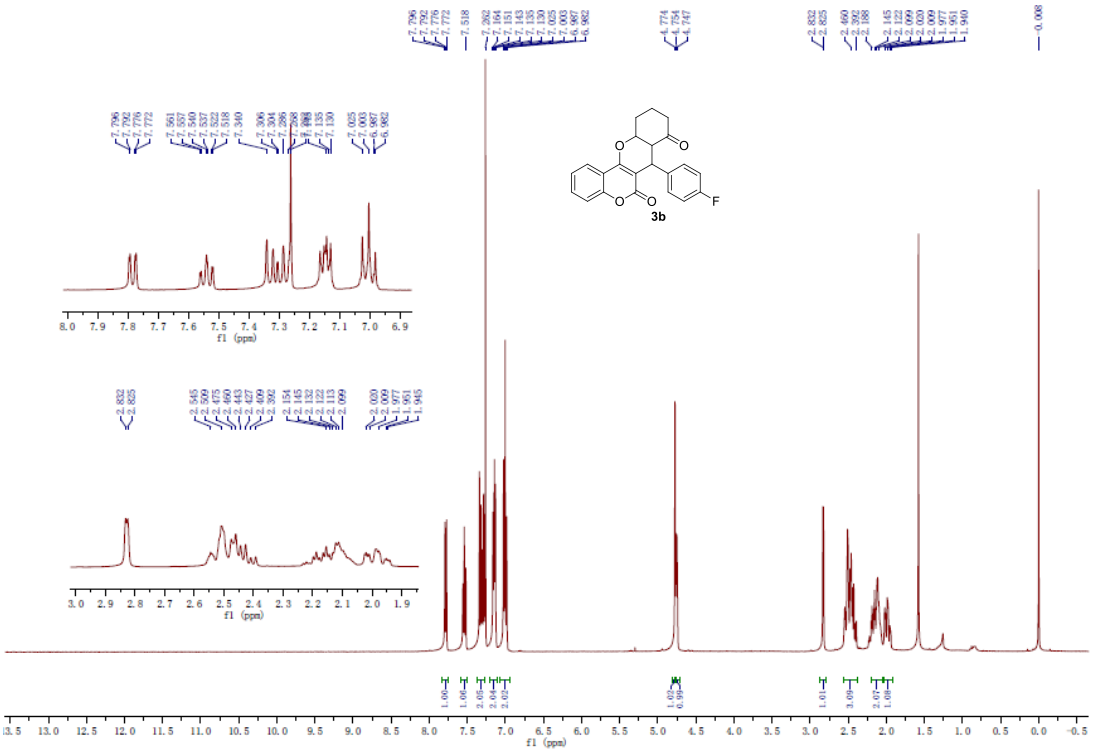
To a solution of **3m** (0.2 mmol) in methanol (5 mL) was added $NaBH_4$ (0.30 mmol) under argon atmosphere at 0°C. Then, the resulting mixture was stirred for 2 h at room temperature before it was quenched with saturated NH_4Cl aqueous solution. Methanol was removed under reduced pressure and the corresponding aqueous solution was extracted with ethyl acetate (3×10 mL). The combined organic layer was

washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. After filtration through a short pad of silica gel, alcohol **4** was obtained as a **w**hite solid. (from **(-)-3m**: 5.1:1 *dr*, -88% ee, $[\alpha]_D^{20}$ = -110.8 (c = 0.5 in CH_2Cl_2); from **(+)-3m**: 6.0:1 *dr*, +79% ee, $[\alpha]_D^{20}$ = +165.7 (c = 0.5 in CH_2Cl_2); m.p. 277-279 °C; IR (KBr) *v* 3385, 2911, 1681, 1622, 1410, 1324, 1112, 759; ^{1}H NMR ($CDCl_3$, 400 Hz, *mixture of two diastereomers, ratio = 6:1, major isomer*) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.50-7.54 (m, 1H), 7.29-7.32 (m, 4H), 7.19-7.24 (m, 3H), 4.45-4.47 (m, 1H), 4.28 (d, *J* = 2.0 Hz, 1H), 4.11 (s, 1H), 2.36 (d, *J* = 14.0 Hz, 1H), 1.85-2.06 (m, 2H), 1.40-1.66 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz, *mixture of two diastereomers, ratio = 6:1, major isomer*) δ 162.4, 161.9, 152.7, 144.8, 143.7, 131.8，131.5, 128.7, 128.6, 127.9, 127.4, 126.7, 123.7, 123.8, 122.8, 122.6, 116.8, 116.6, 115.5, 101.8, 100.0, 90.3, 72.5, 70.9, 70.5, 67.9, 49.1, 44.5, 40.7, 36.6, 34.8, 33.3, 30.0, 29.8, 19.0, 14.1; HRMS (TOF-ES+) m/z: $[M+Na]^+$ calcd for $C_{22}H_{20}O_4Na$ 371.1259, found 371.1264; HPLC analysis: (CHIRALCEL OD-H, 10% *i*-propanol/hexanes, 1.0 mL/min, UV: 254 nm), from **(-)-3m**: t_R = 10.9 min (minor), 24.5 min (major); from **(+)-3m**: t_R = 10.8 min (major), 25.5 min (minor).

5. NMR Spectra of All New Compounds



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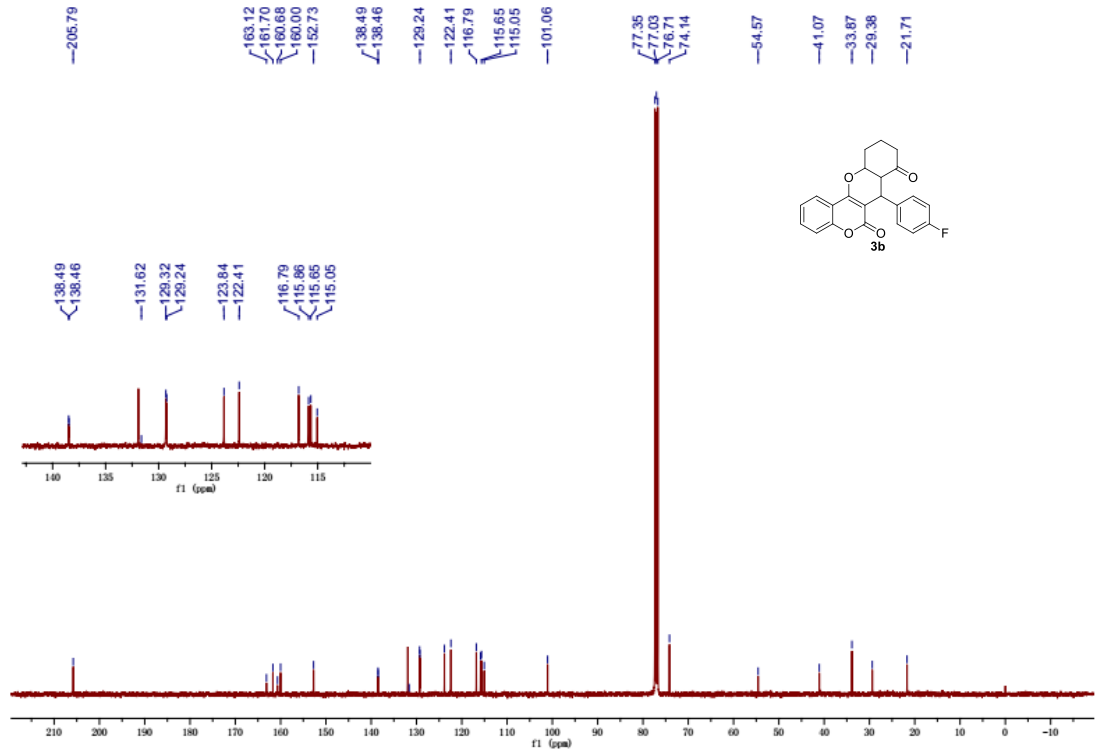
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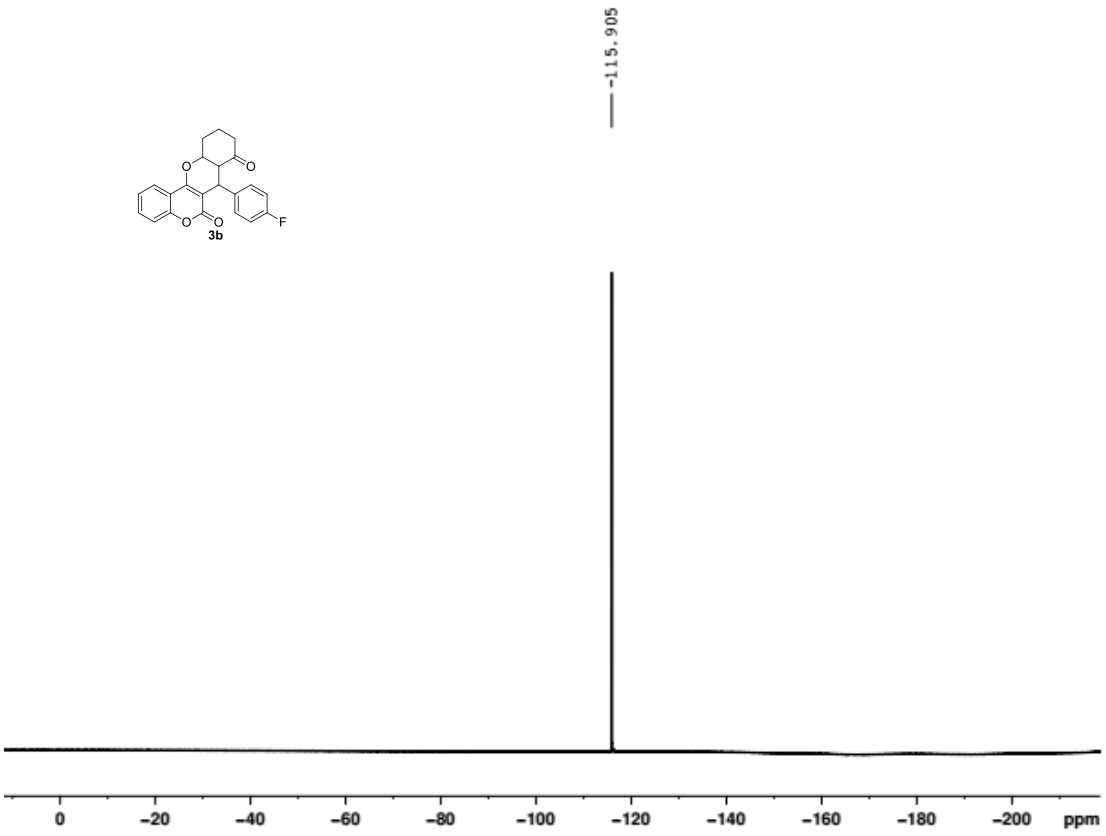
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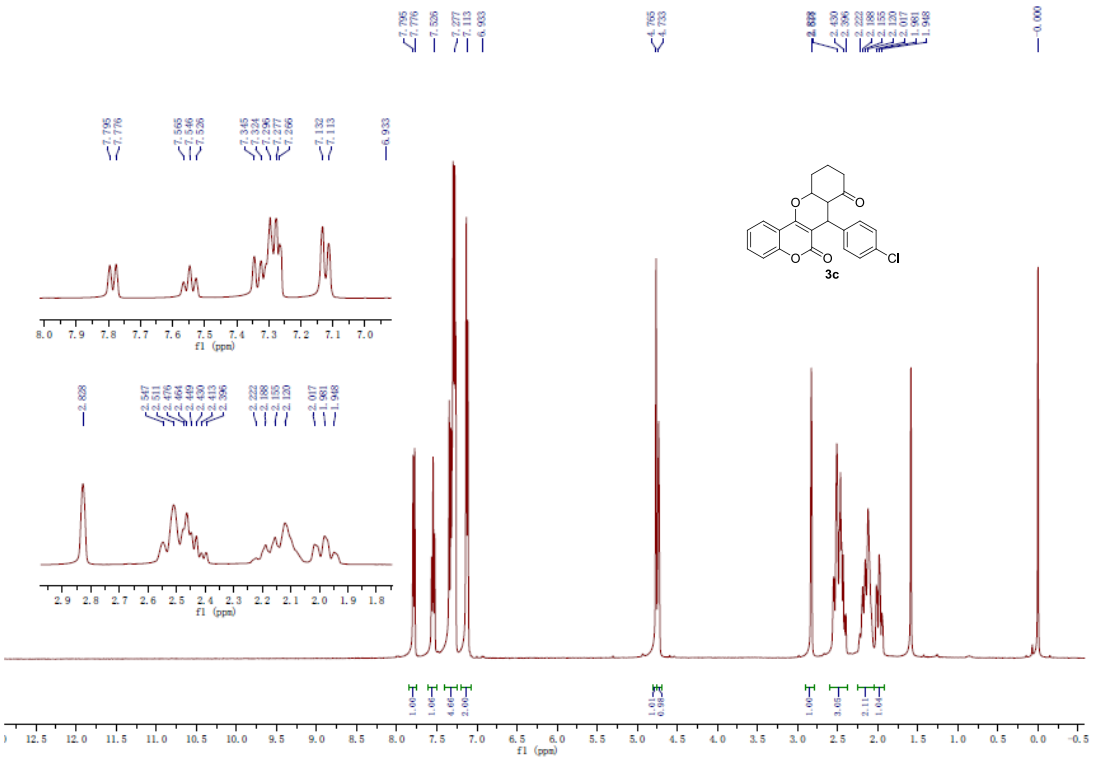
ppm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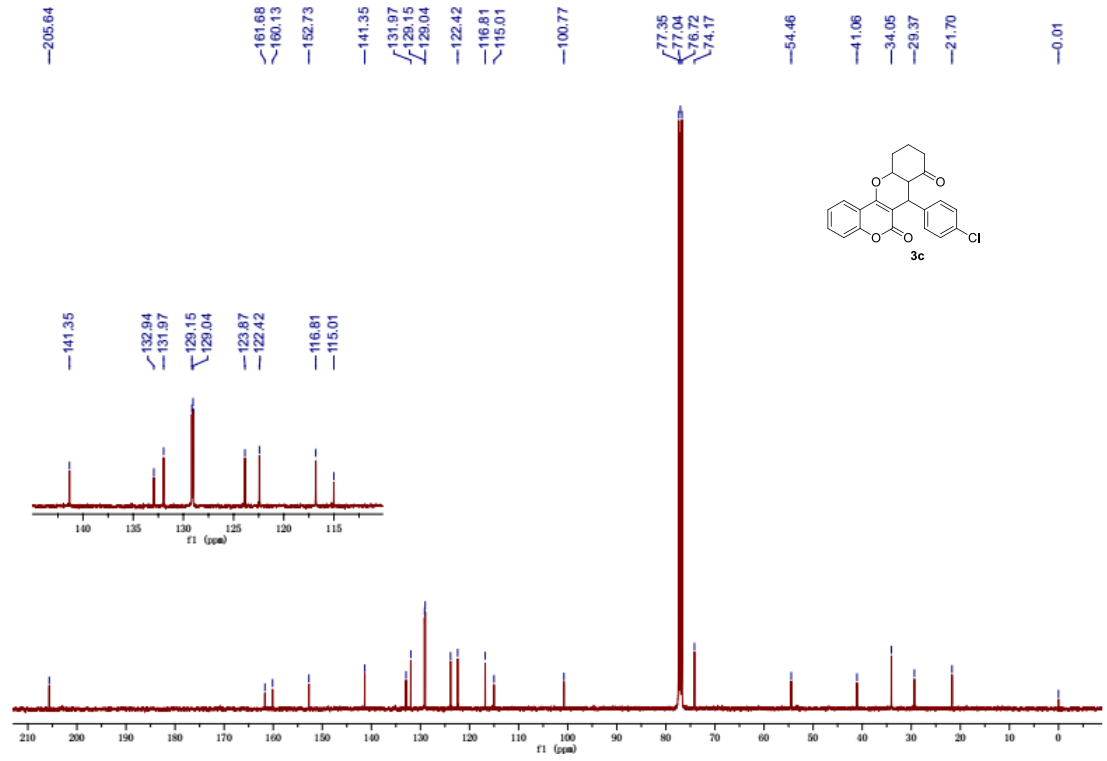
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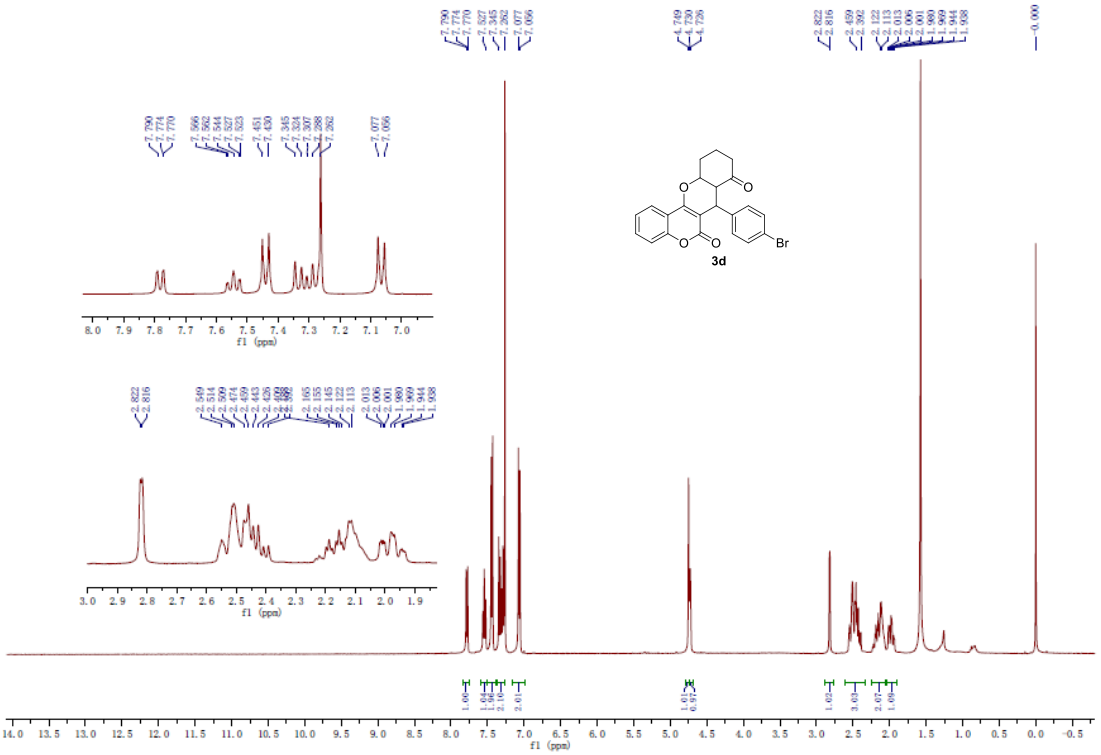
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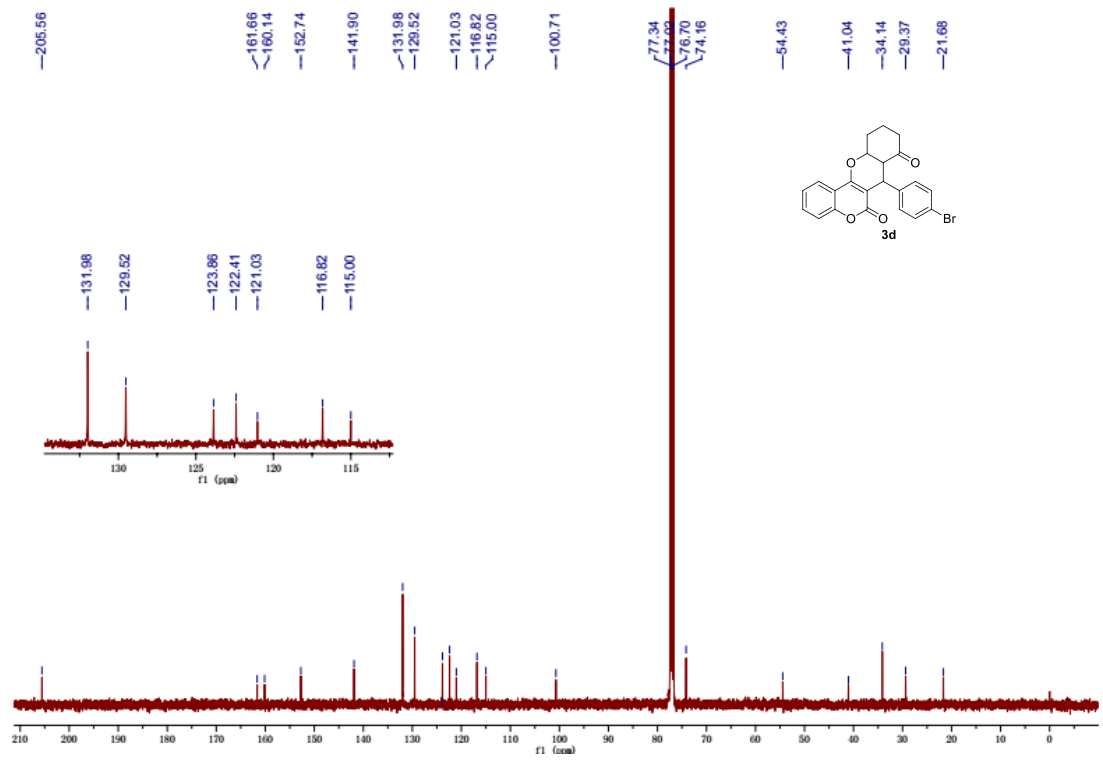
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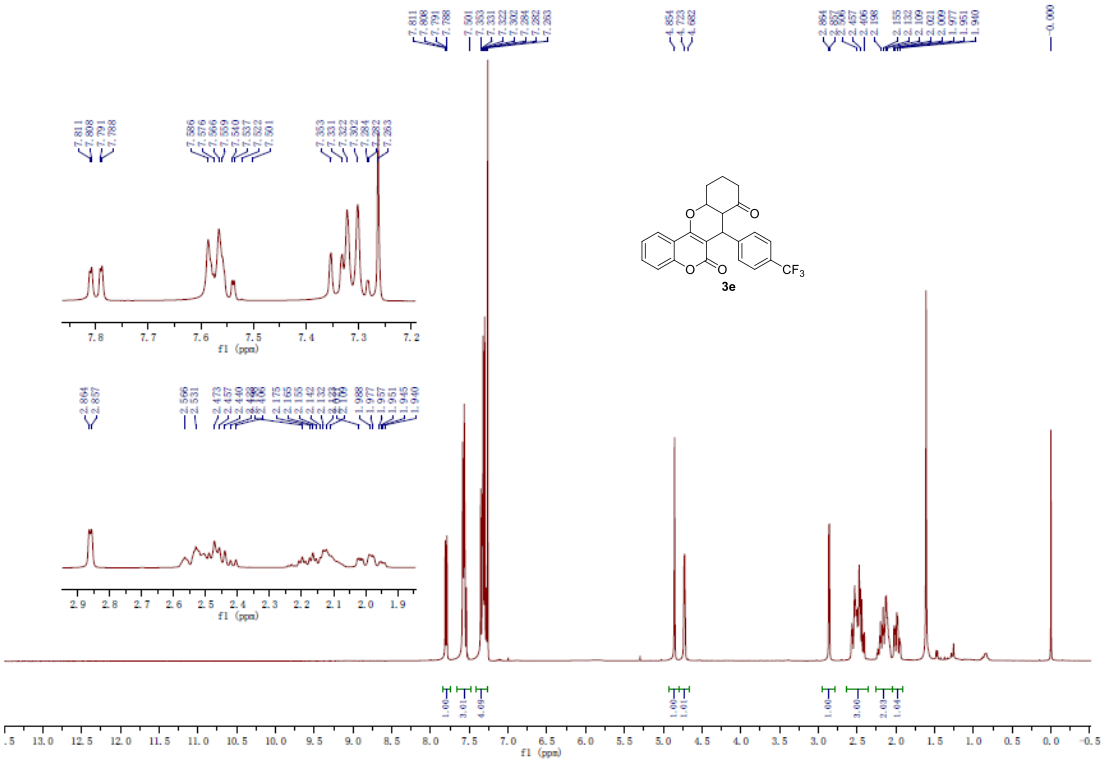
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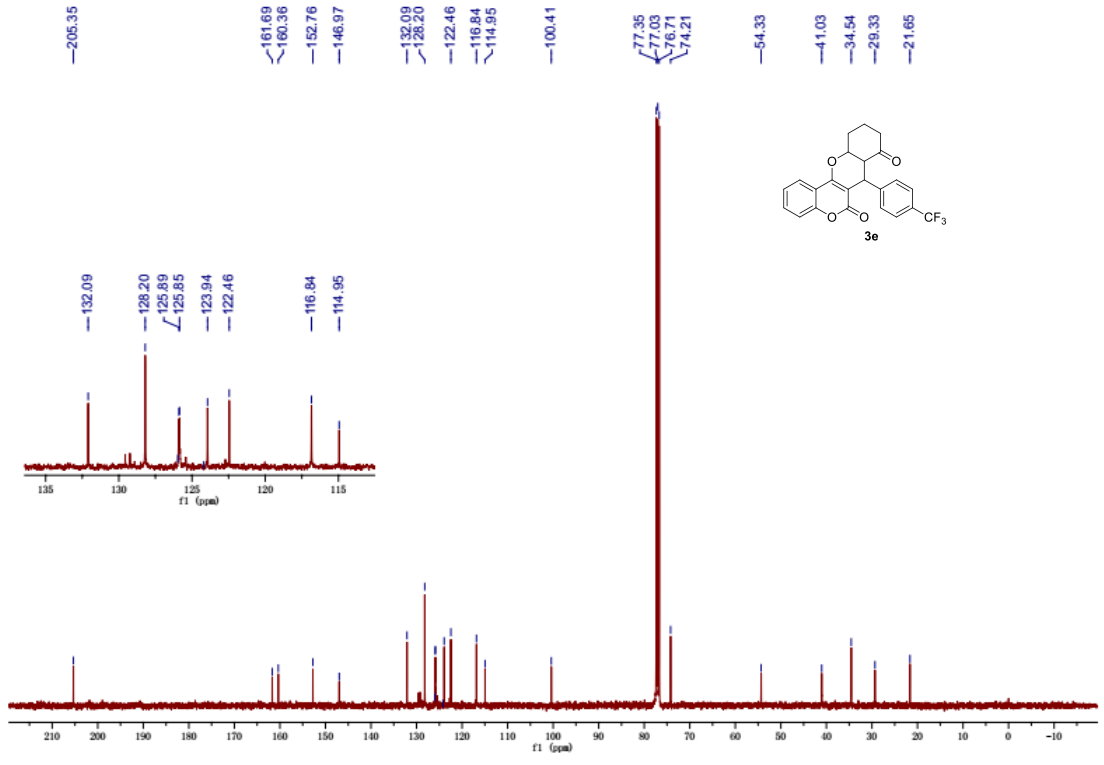
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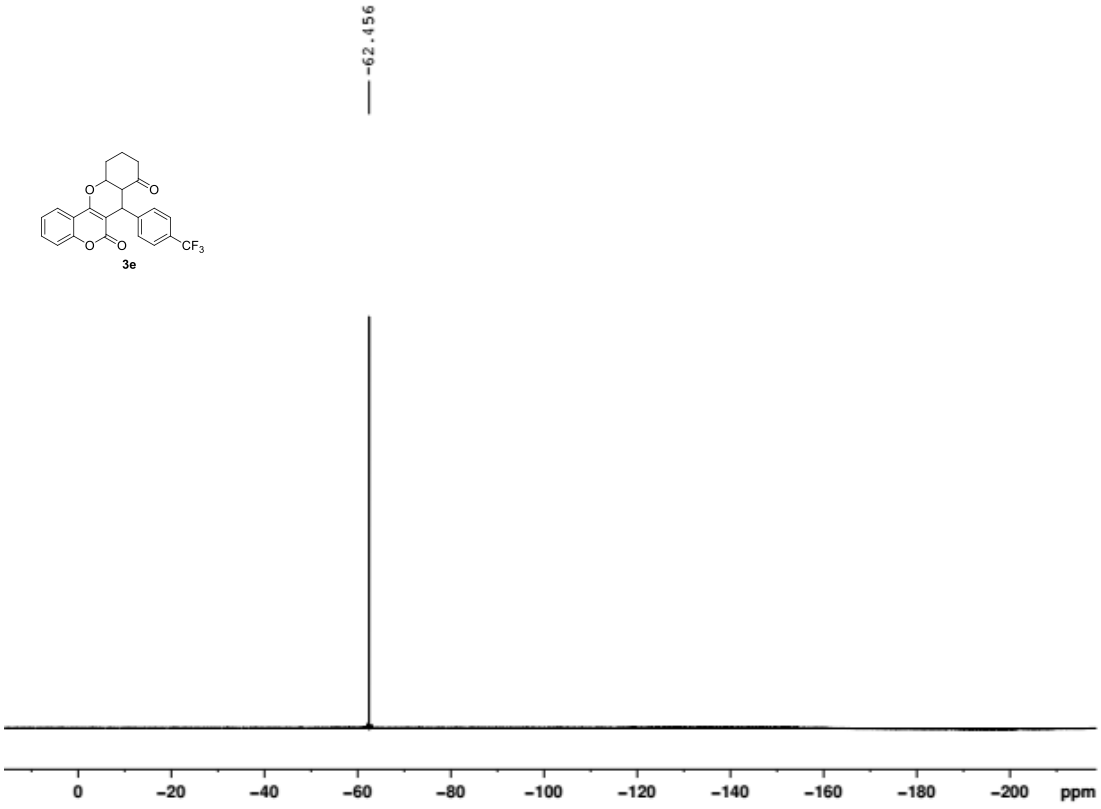
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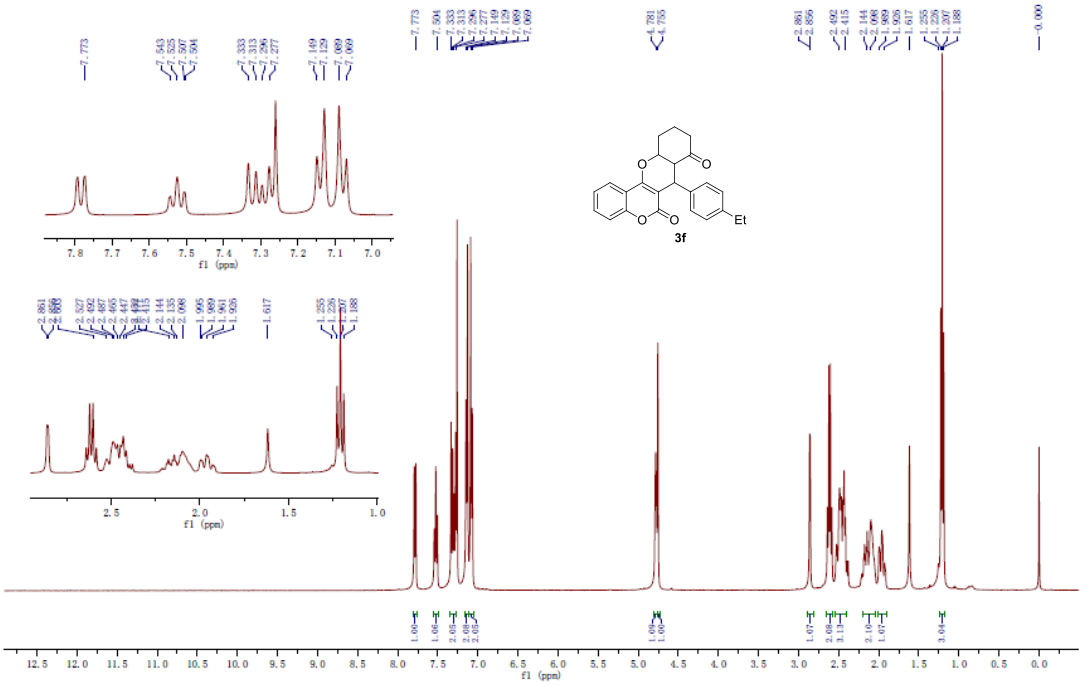
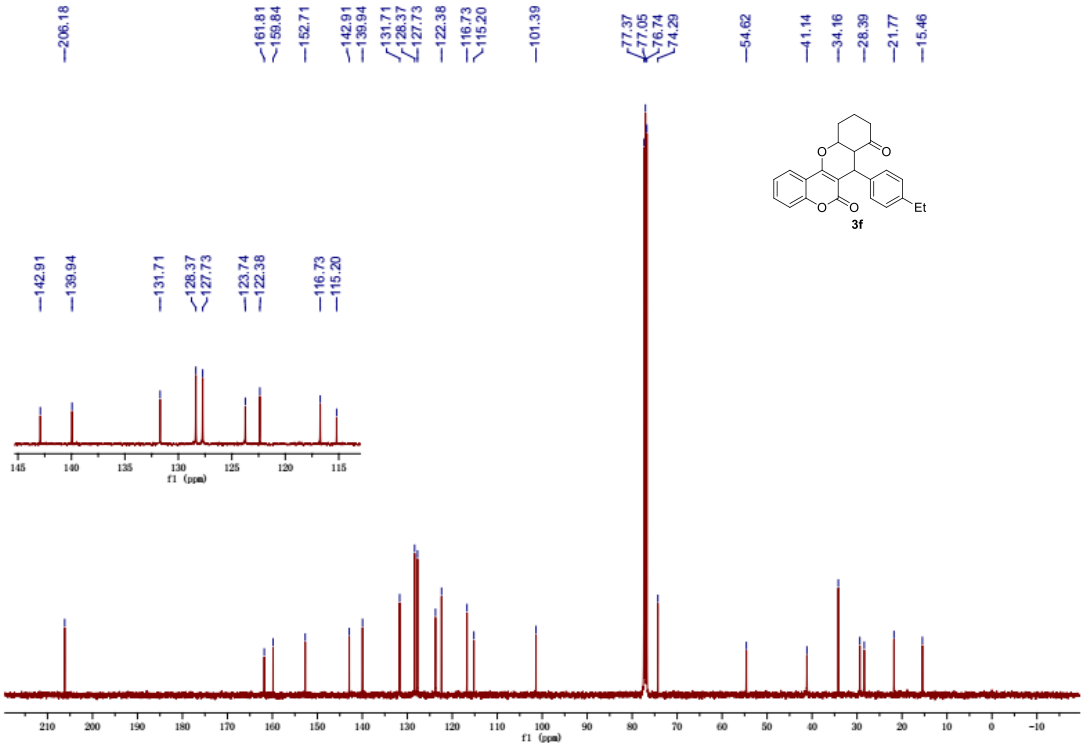
ppm


3f
Et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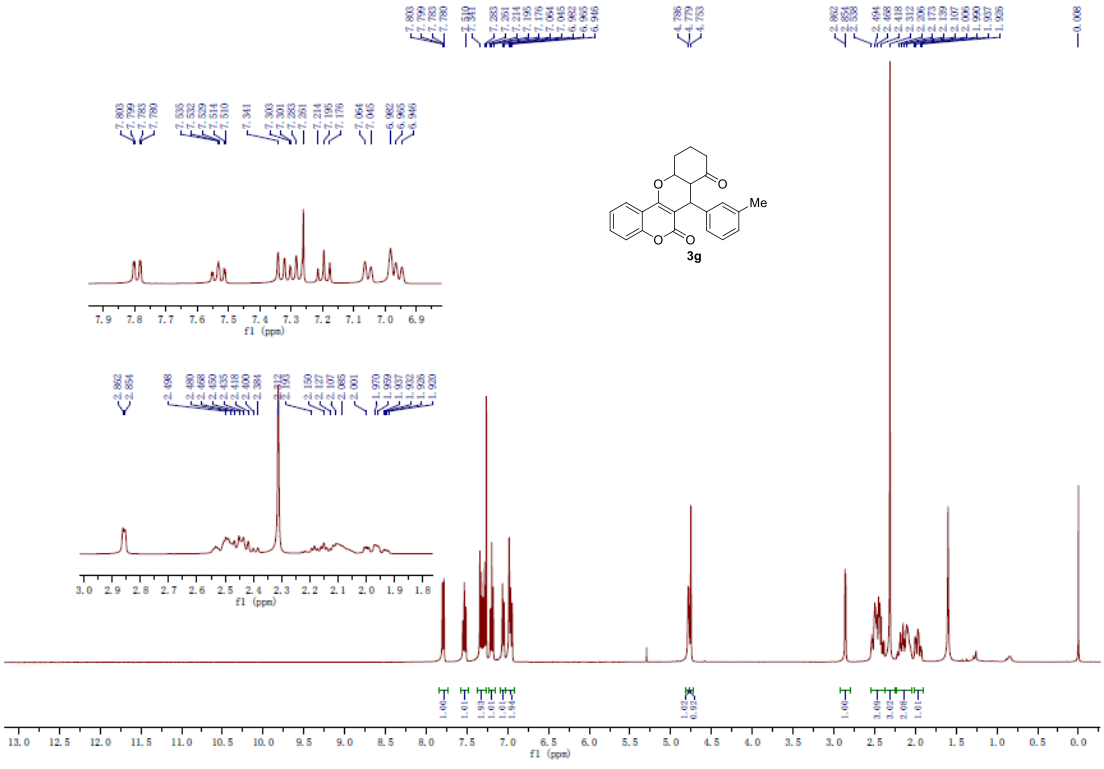
Et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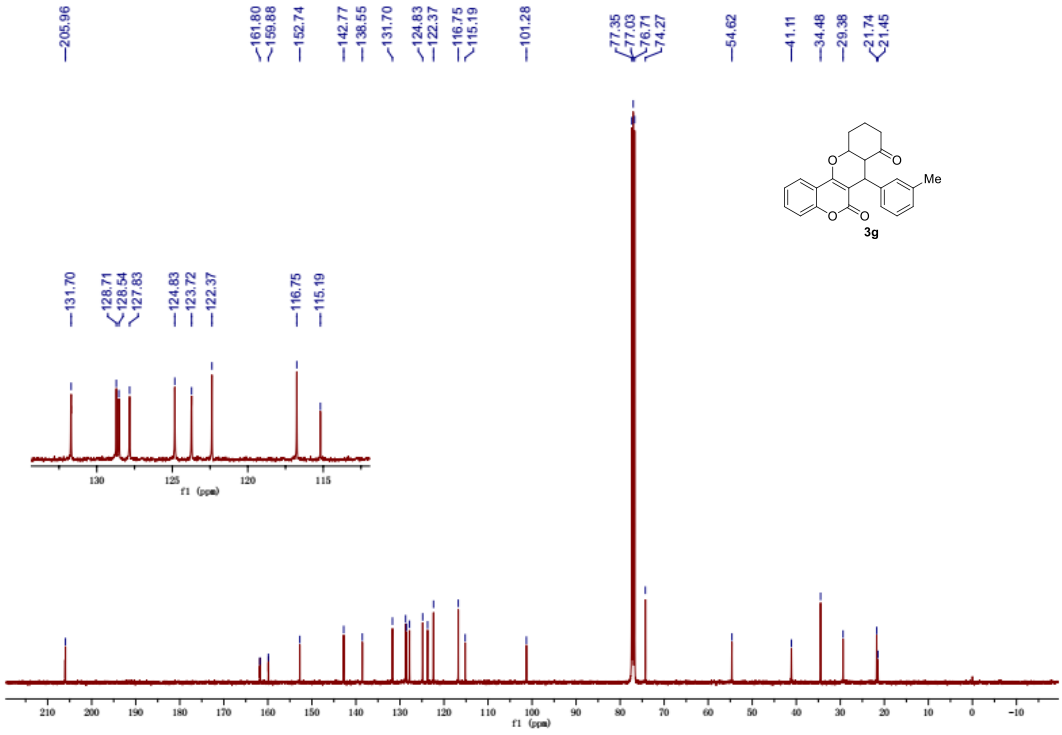
f1 (ppm)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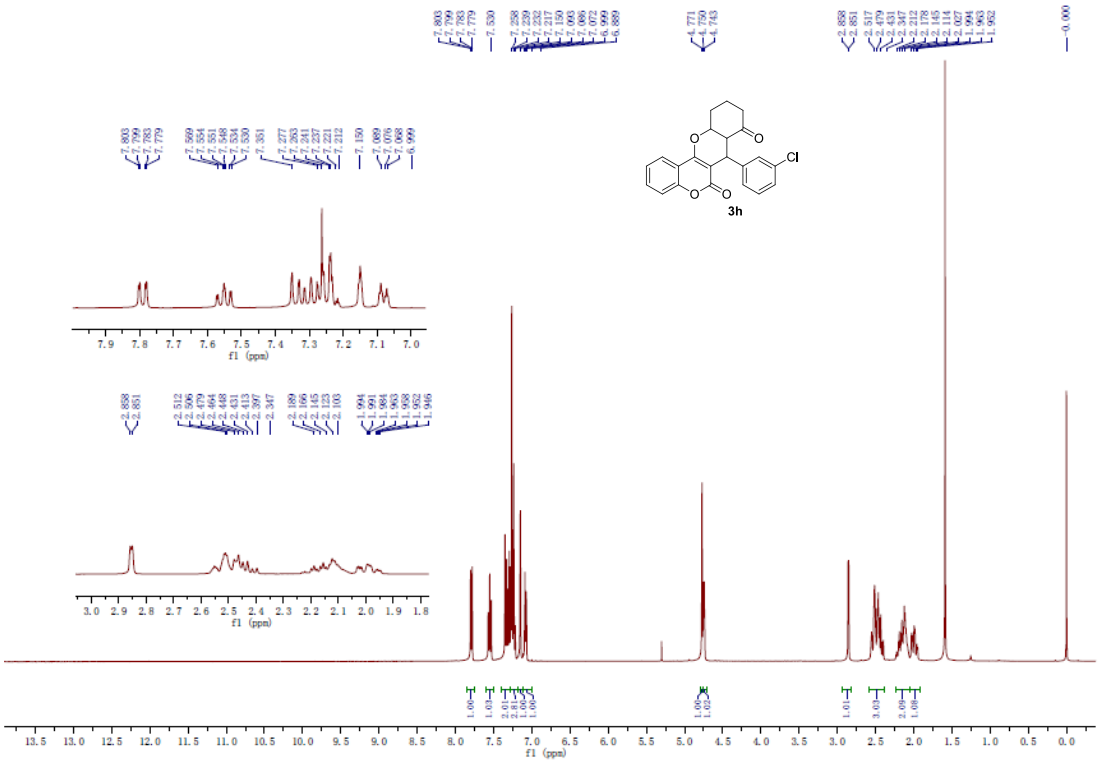
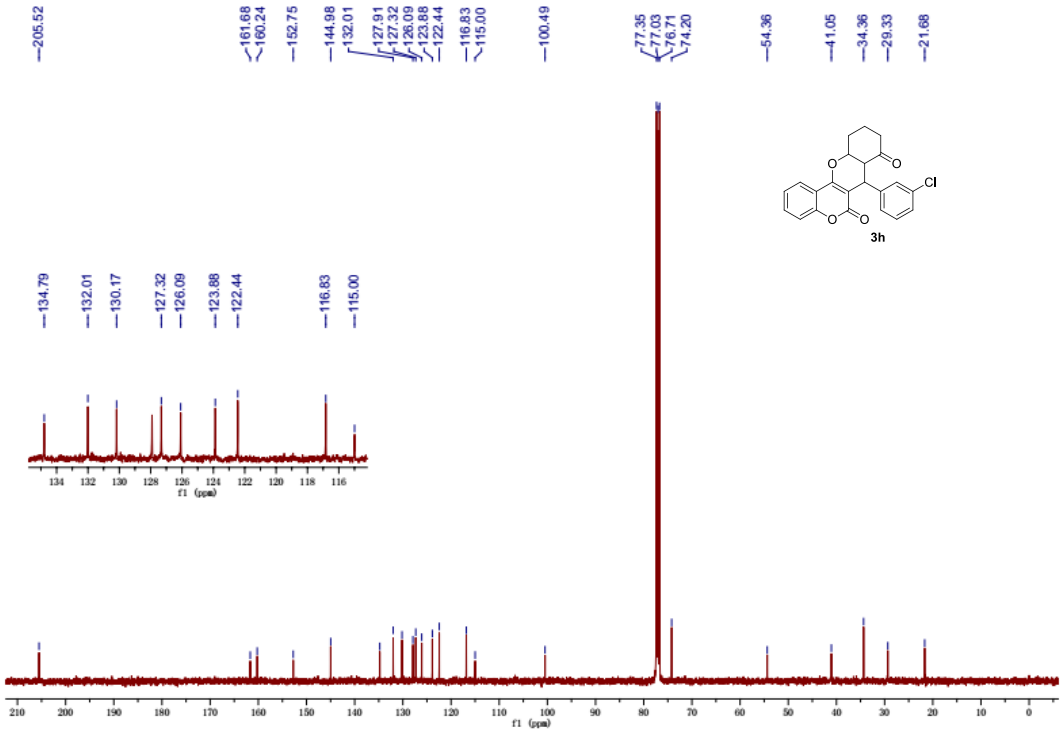
f1 (ppm)


3h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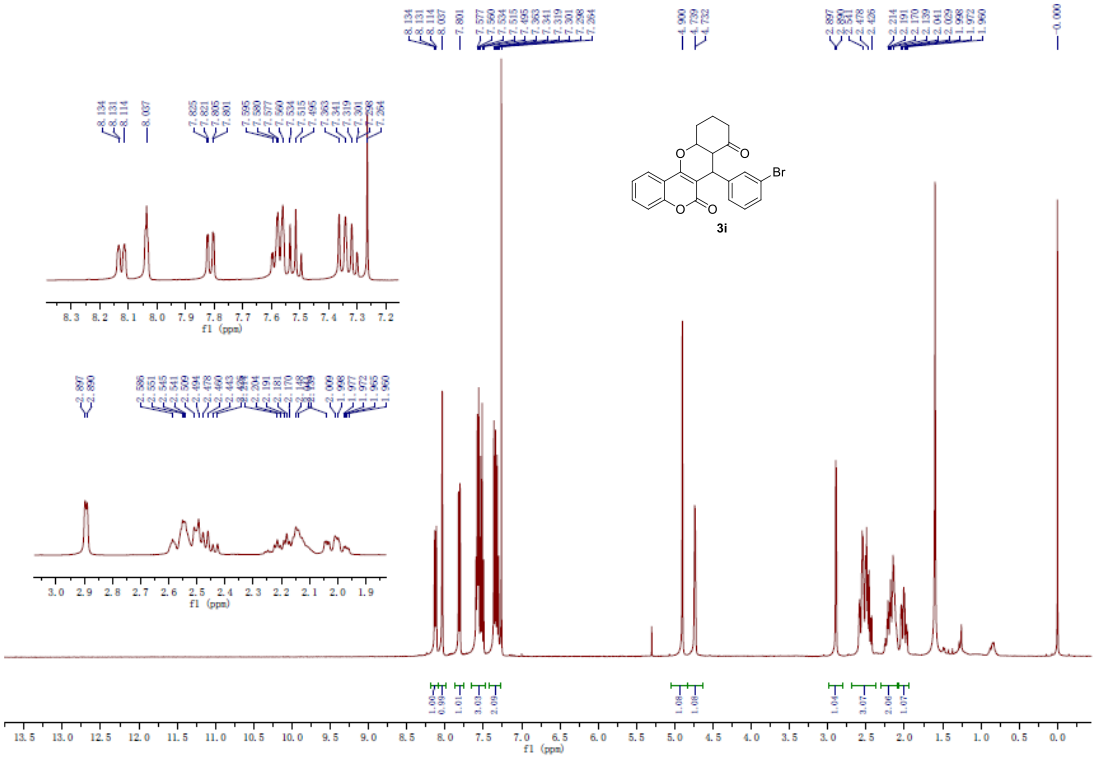
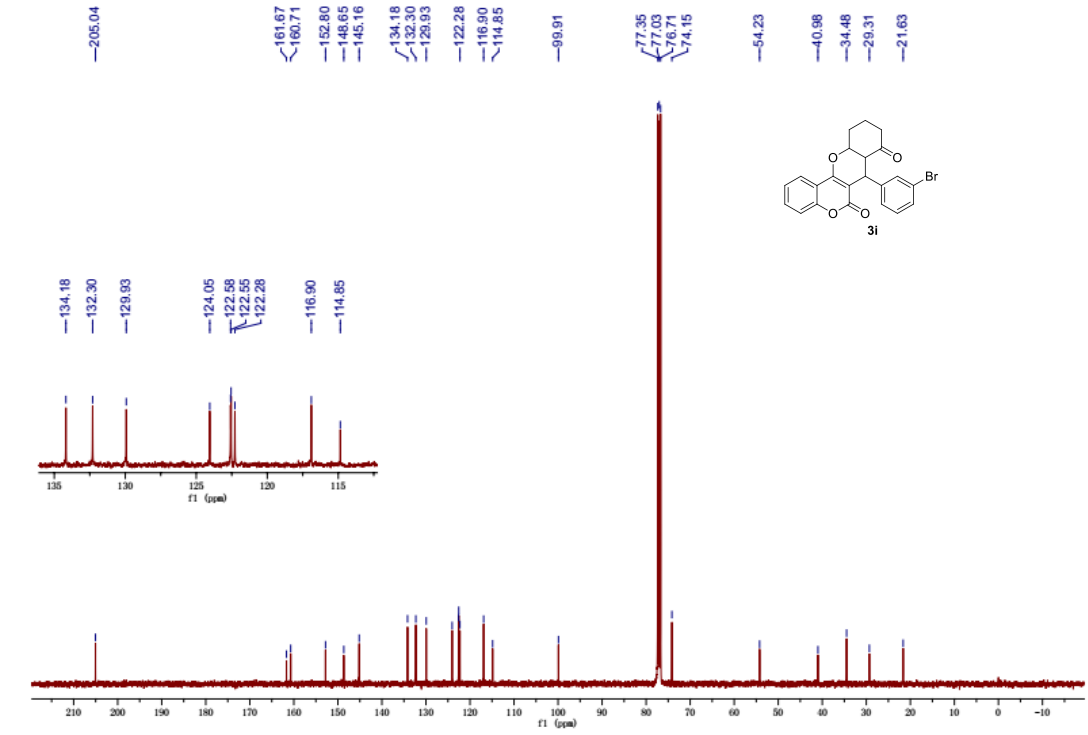
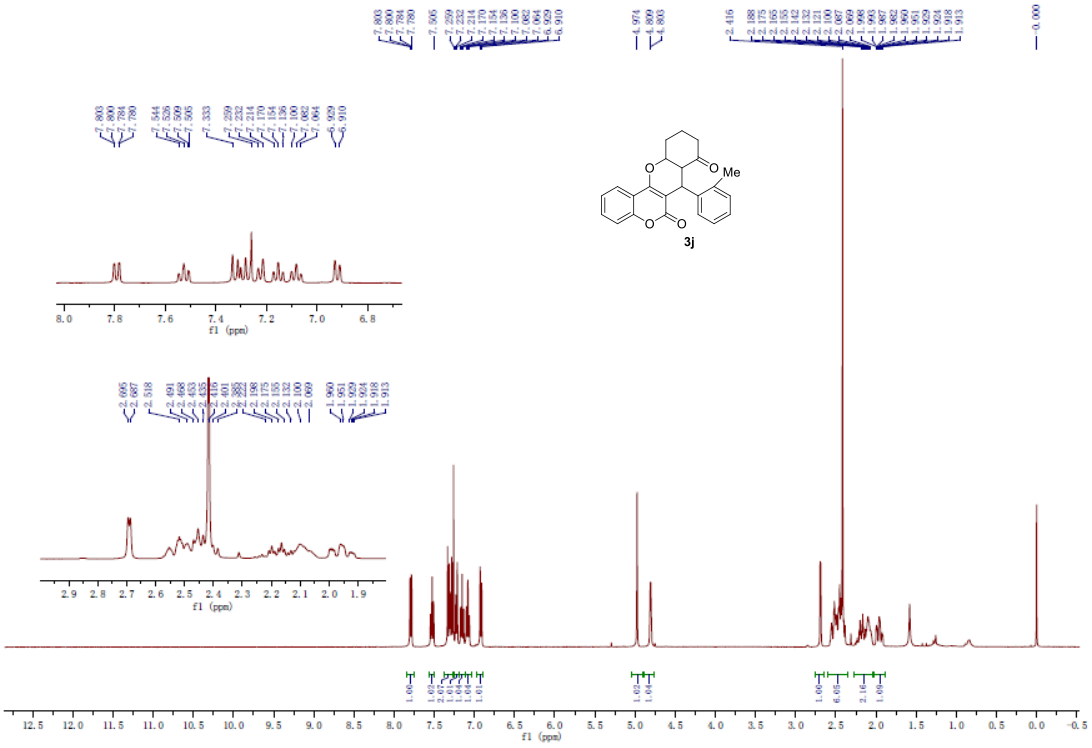
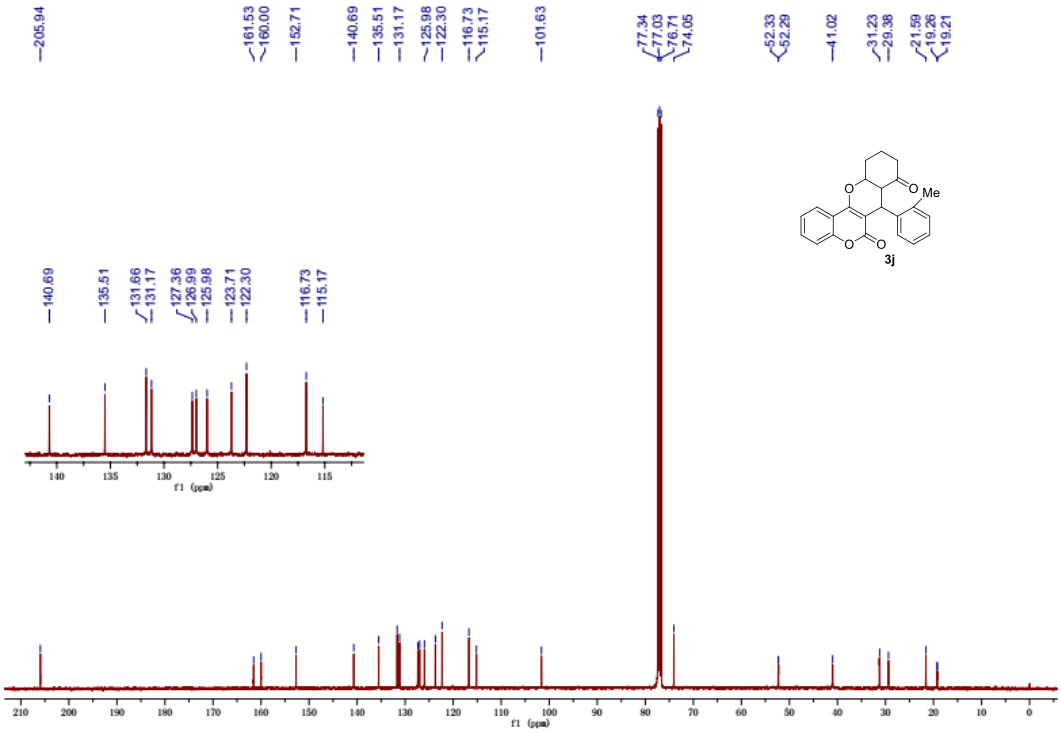
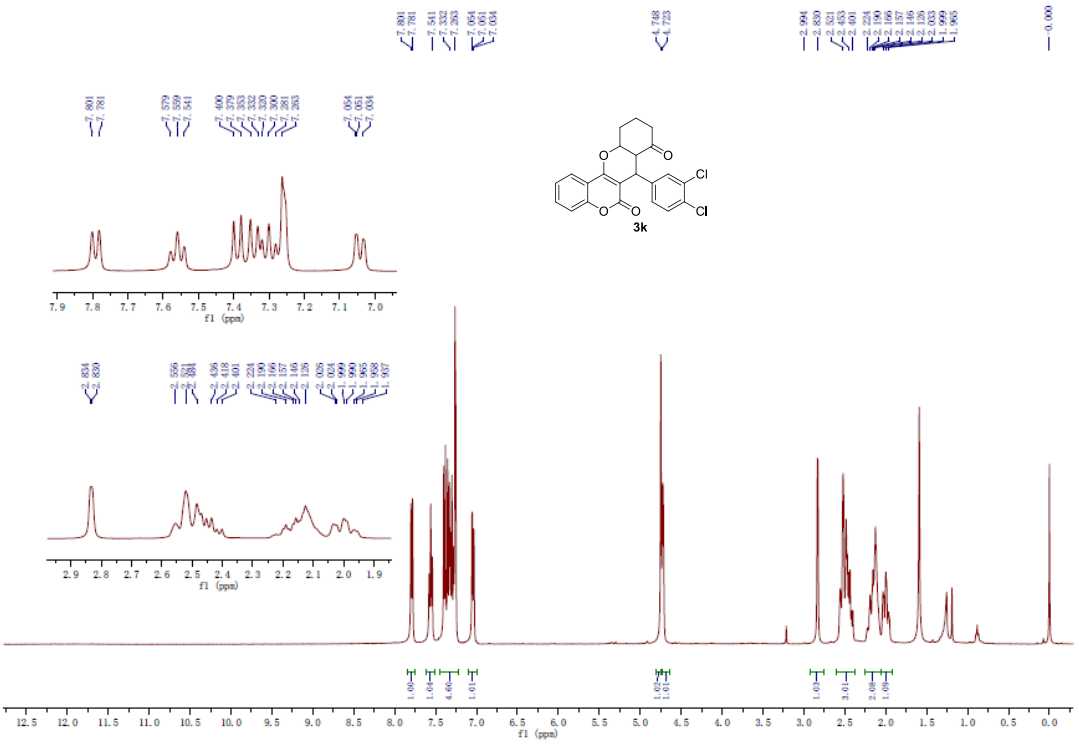
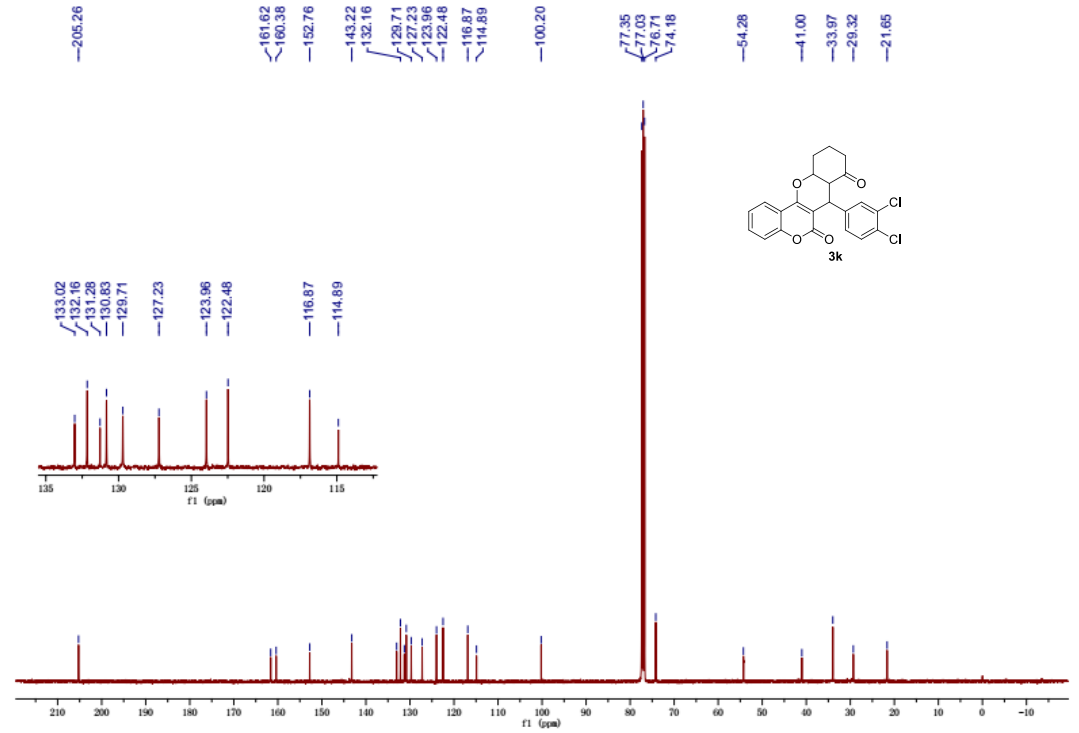

3i

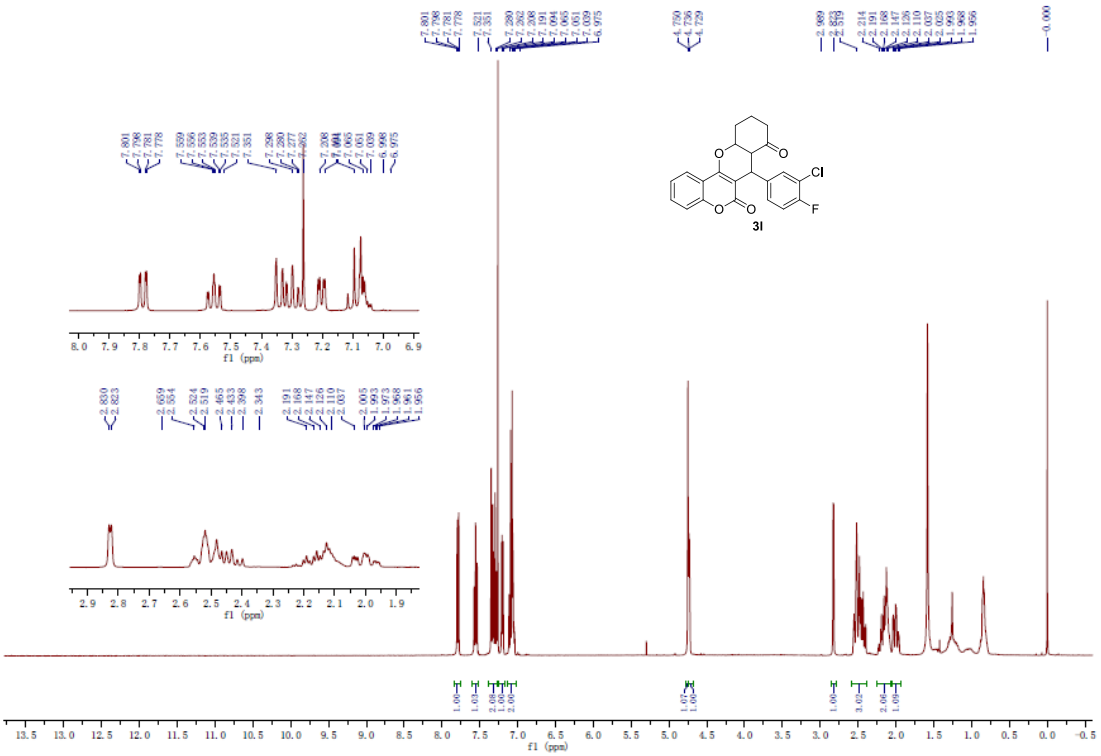

3i


Me
3j
f1 (ppm)


Me
3j
f1 (ppm)


3k


3k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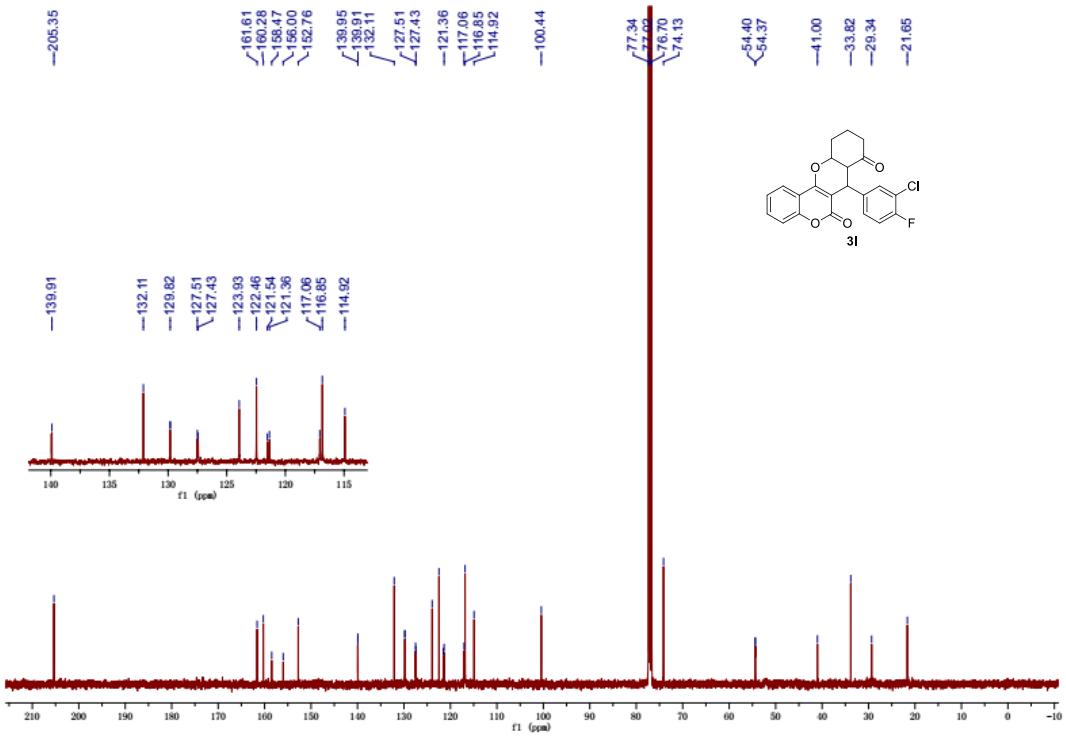
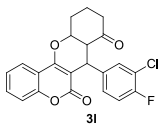
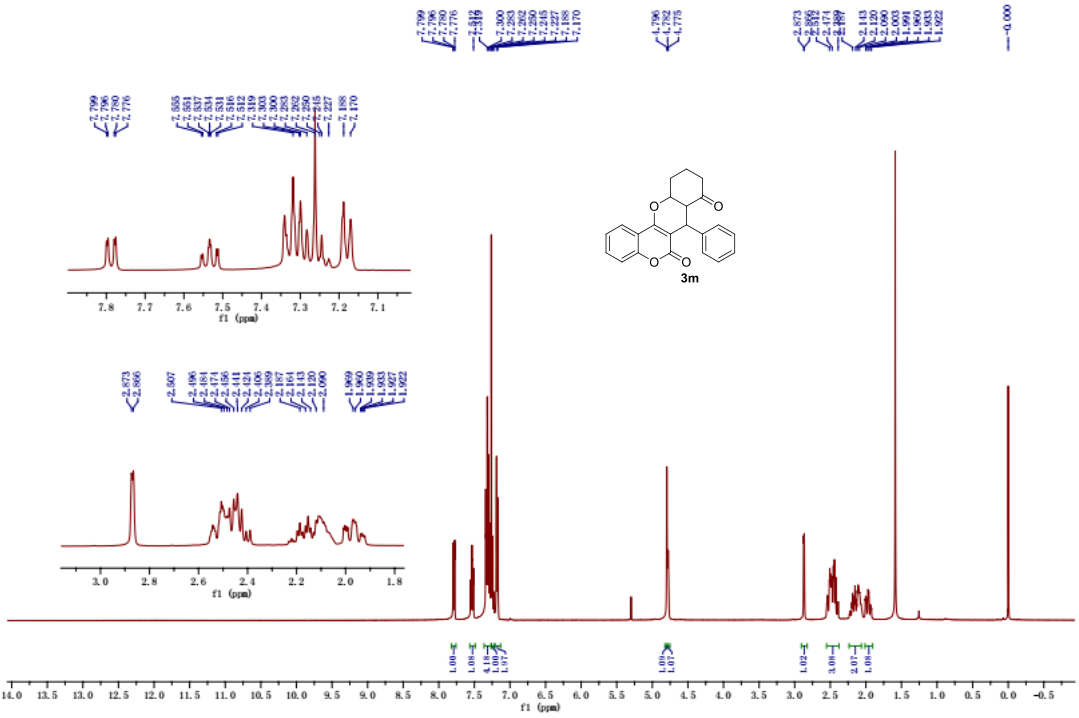
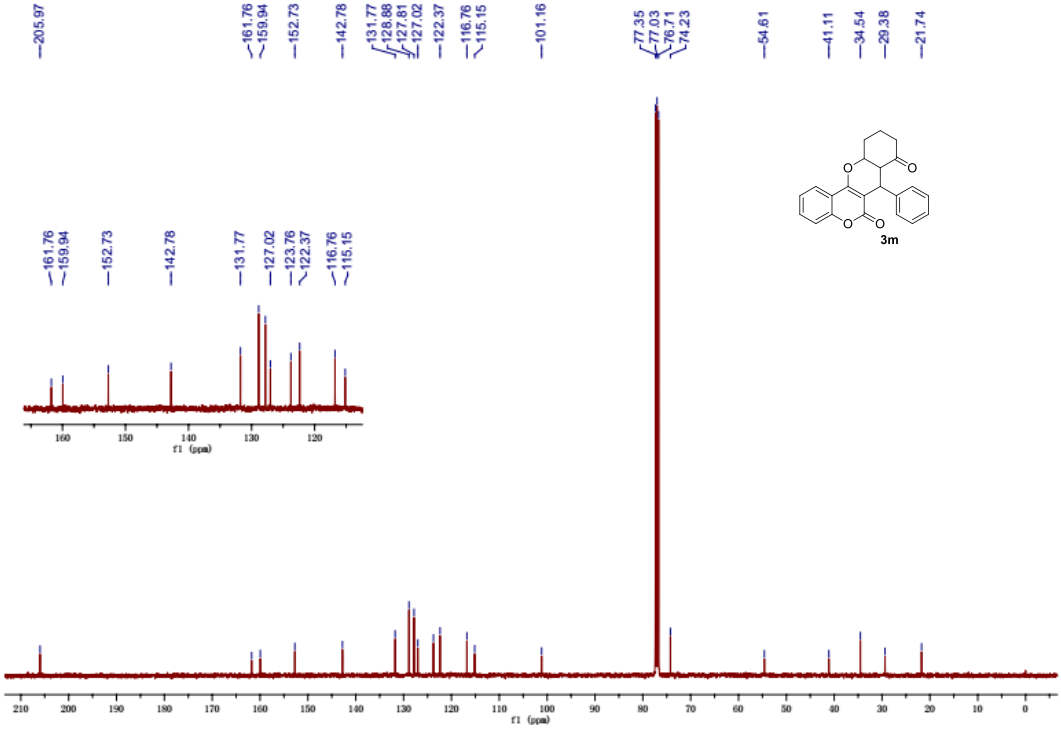
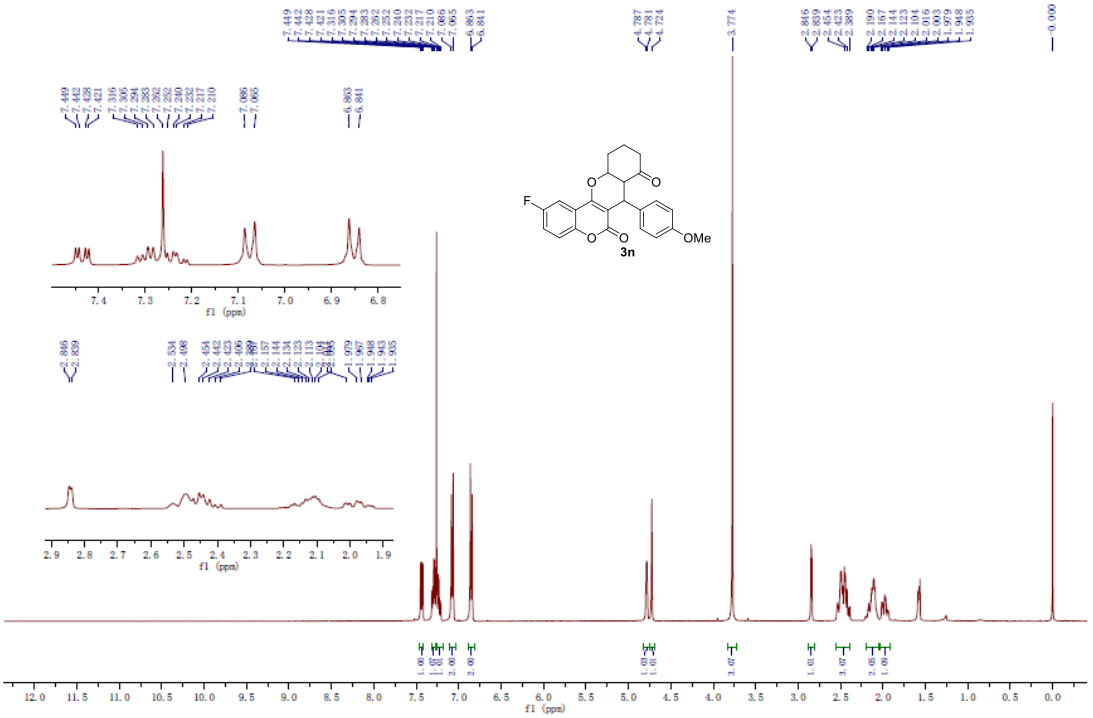

3l

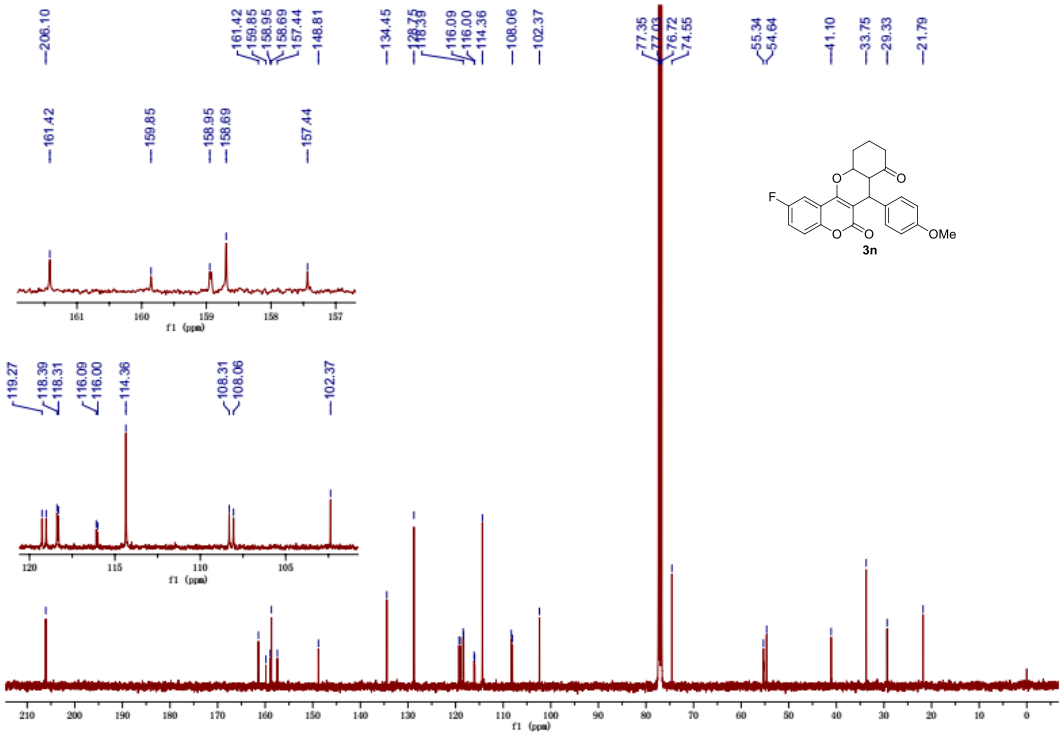


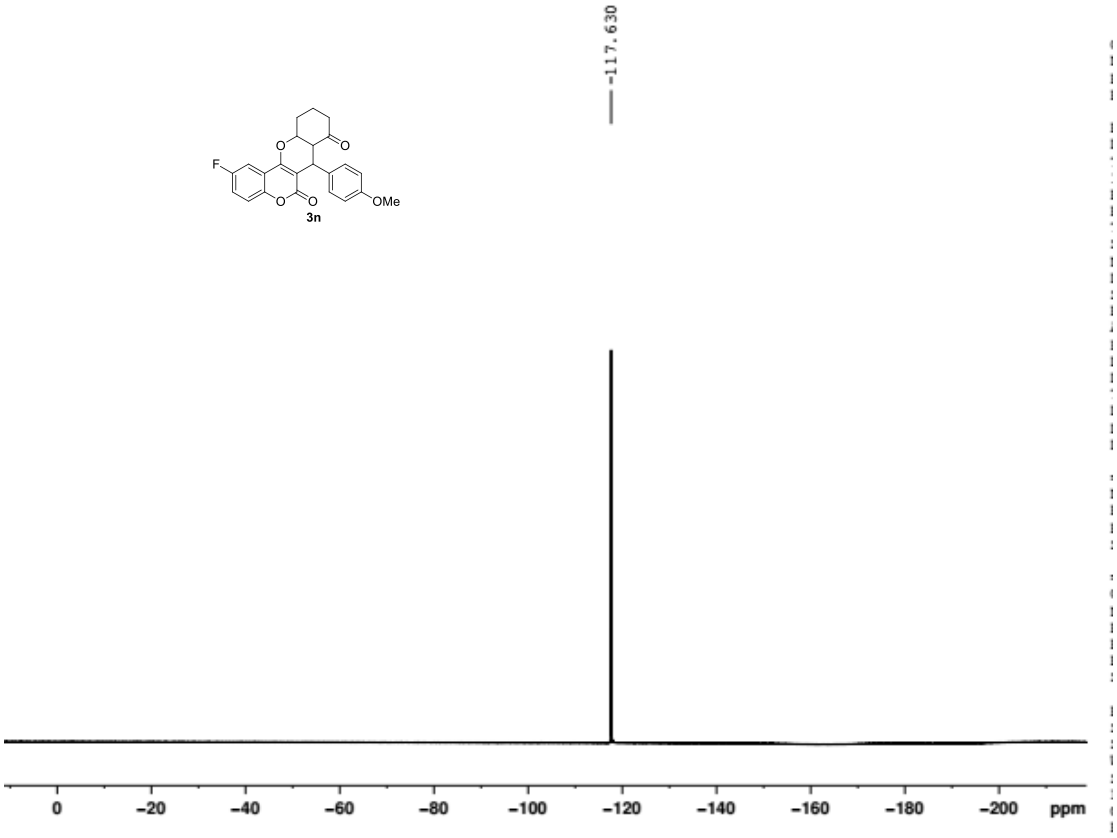
3l

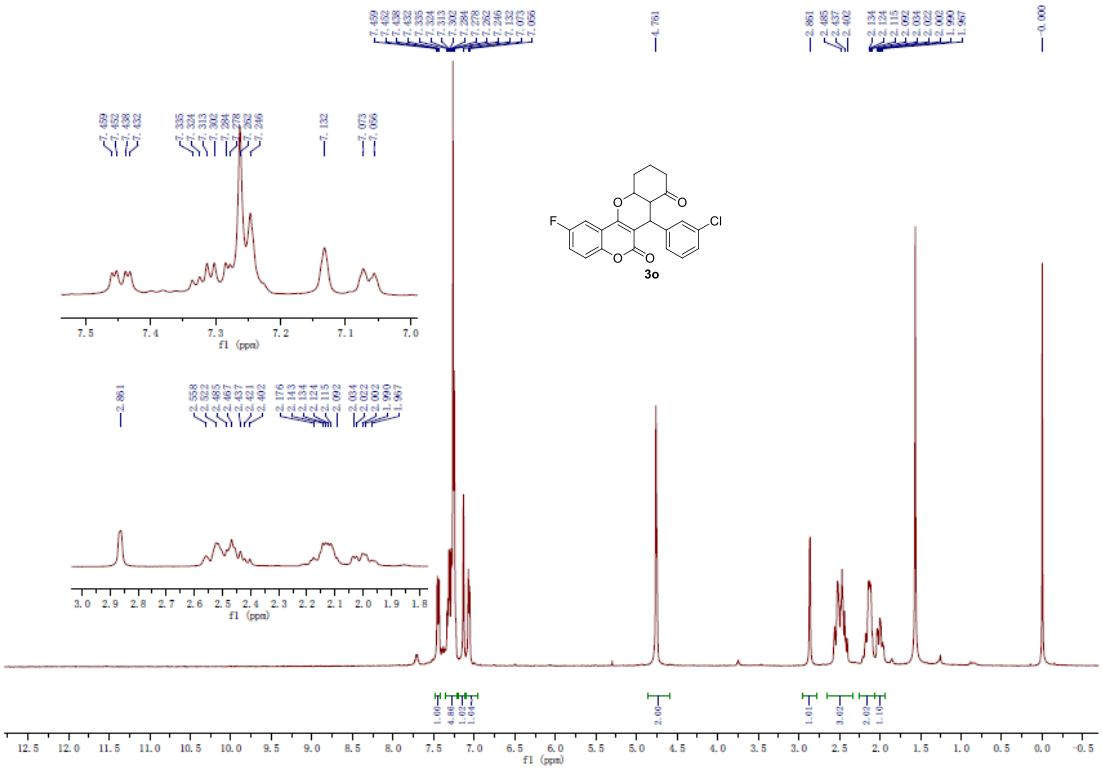

3m

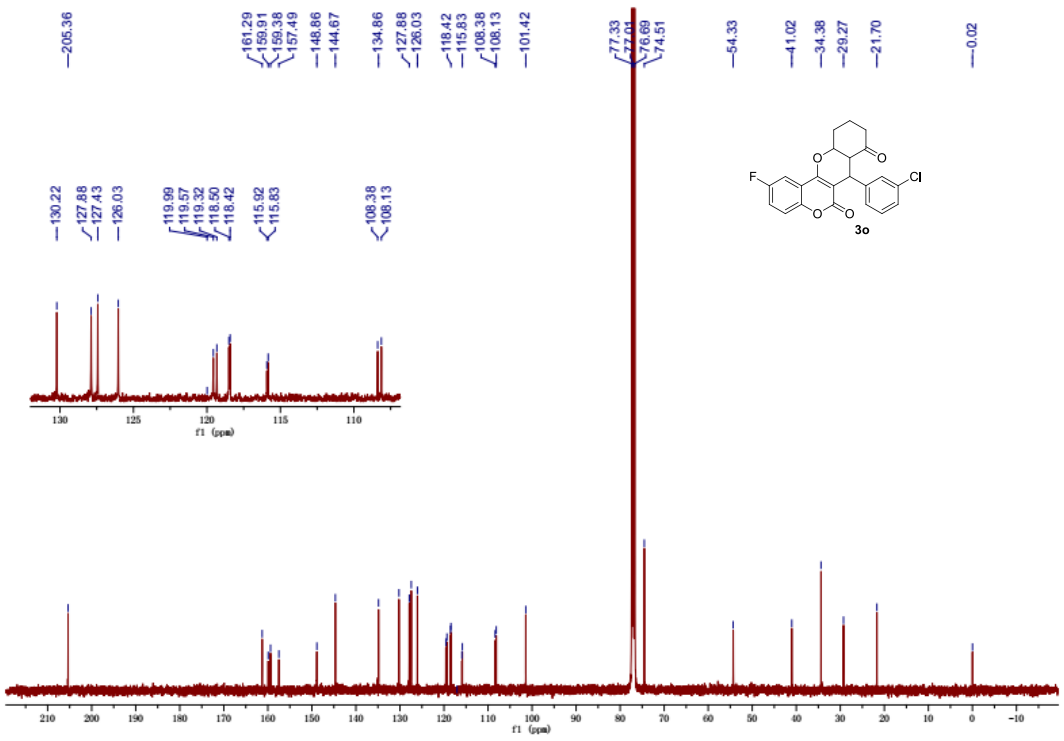

3m

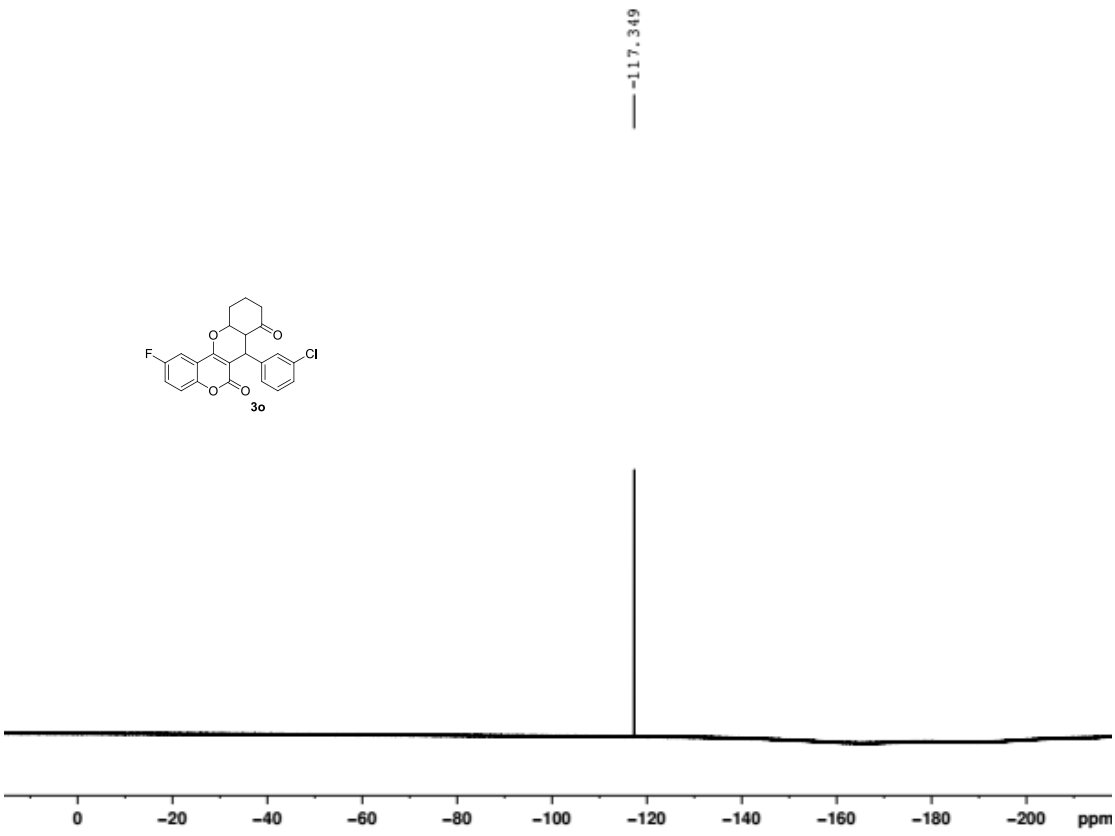

3n

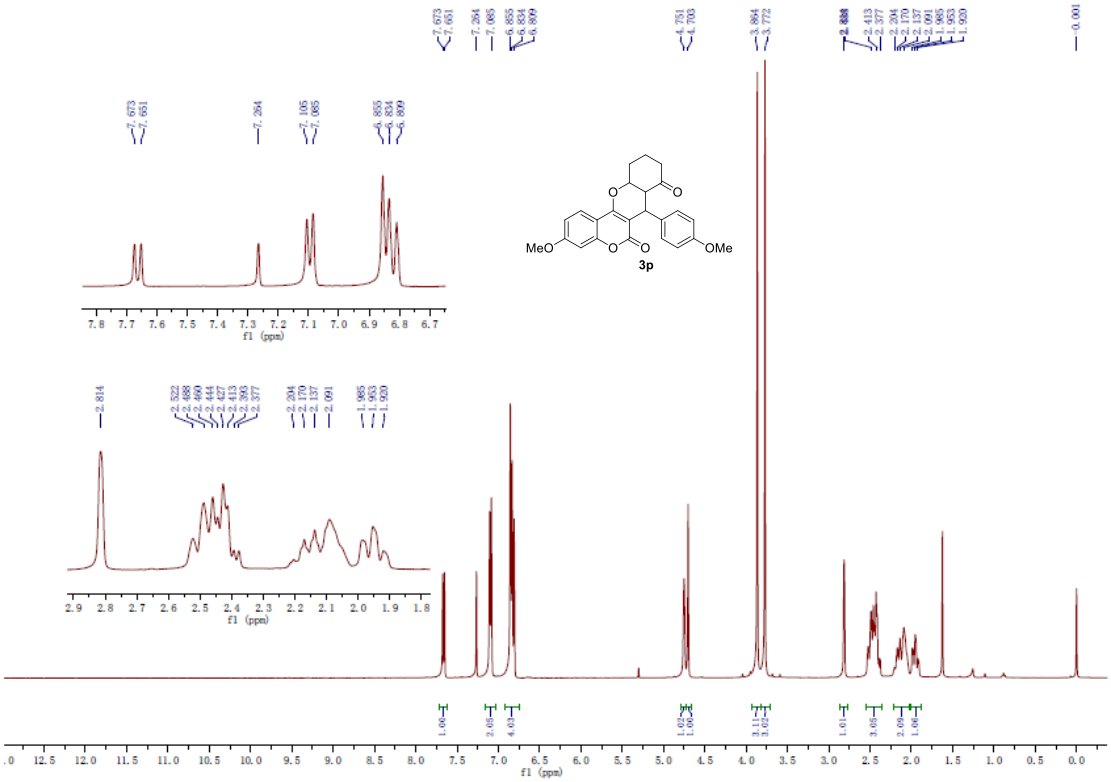

3n

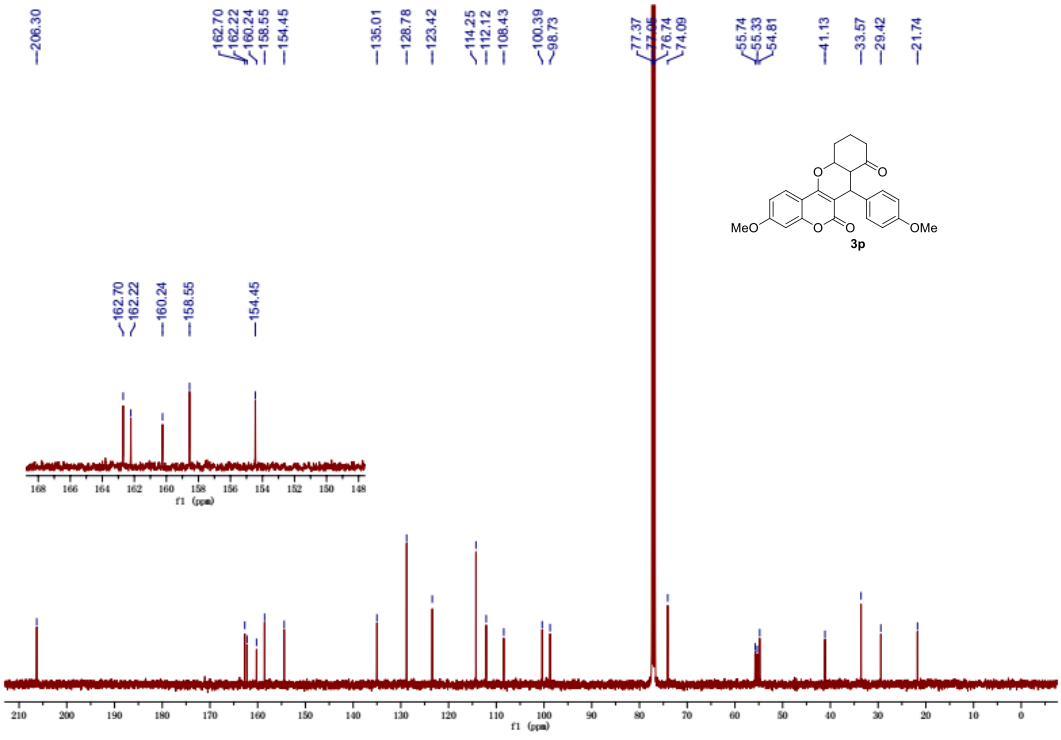

-117.630
F
O
O
O
O
OMe
3n
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

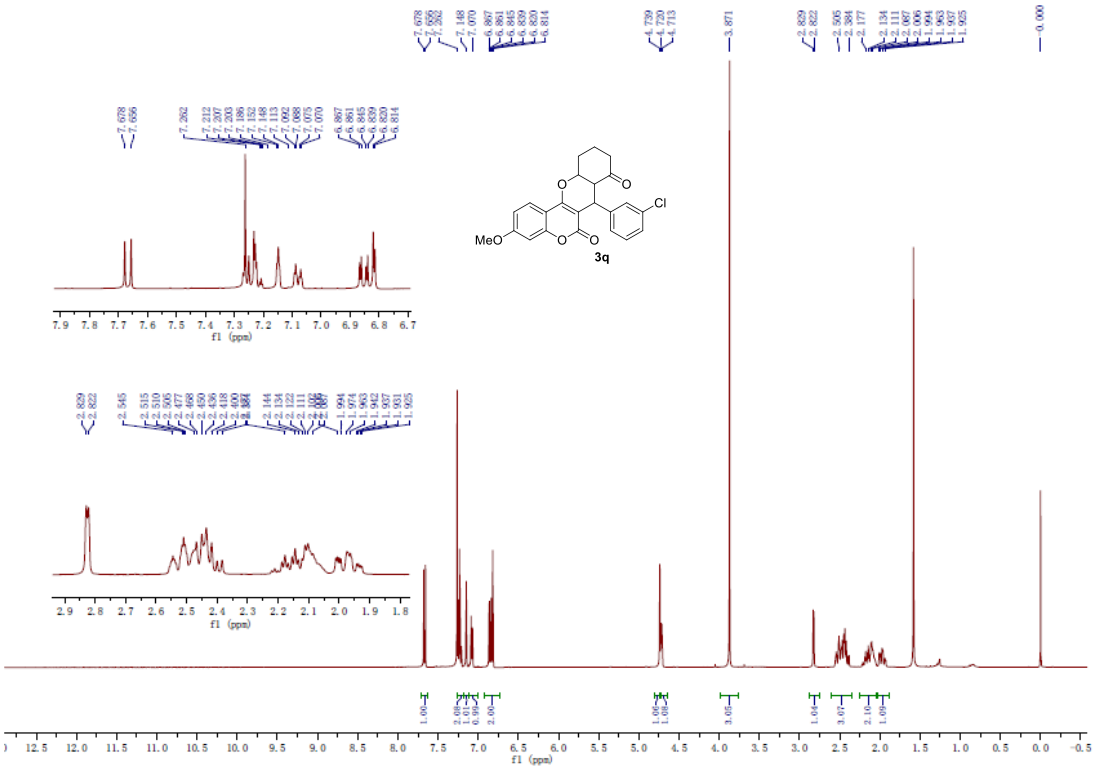

3o

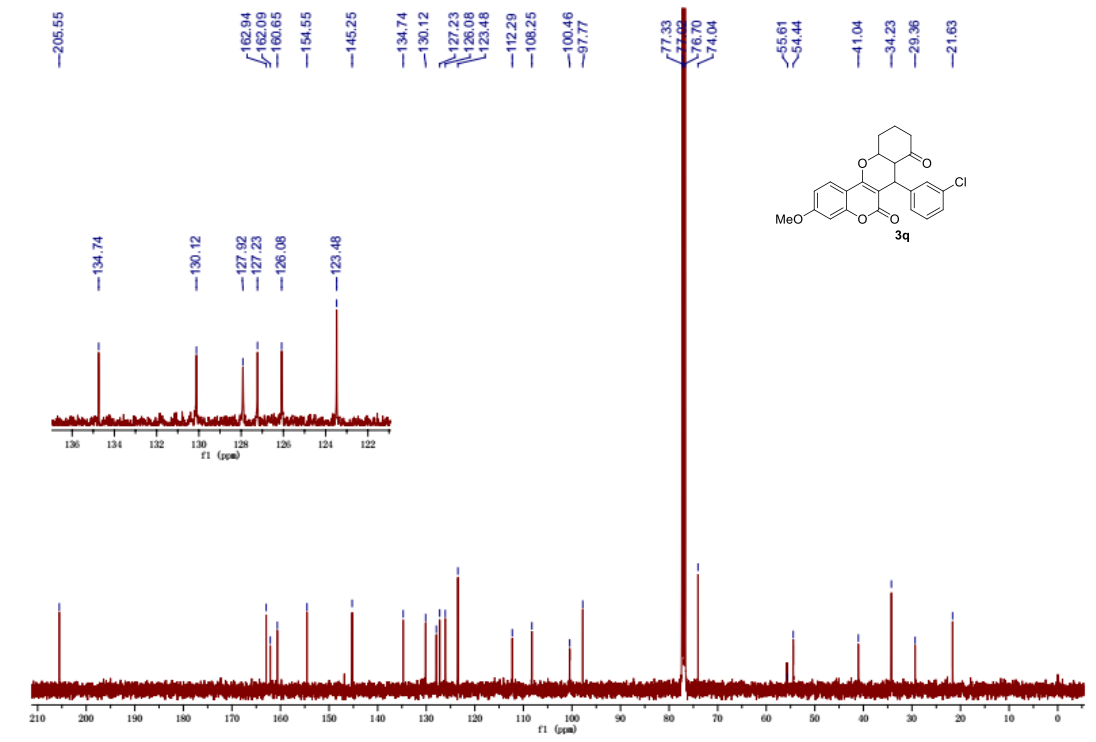

3o

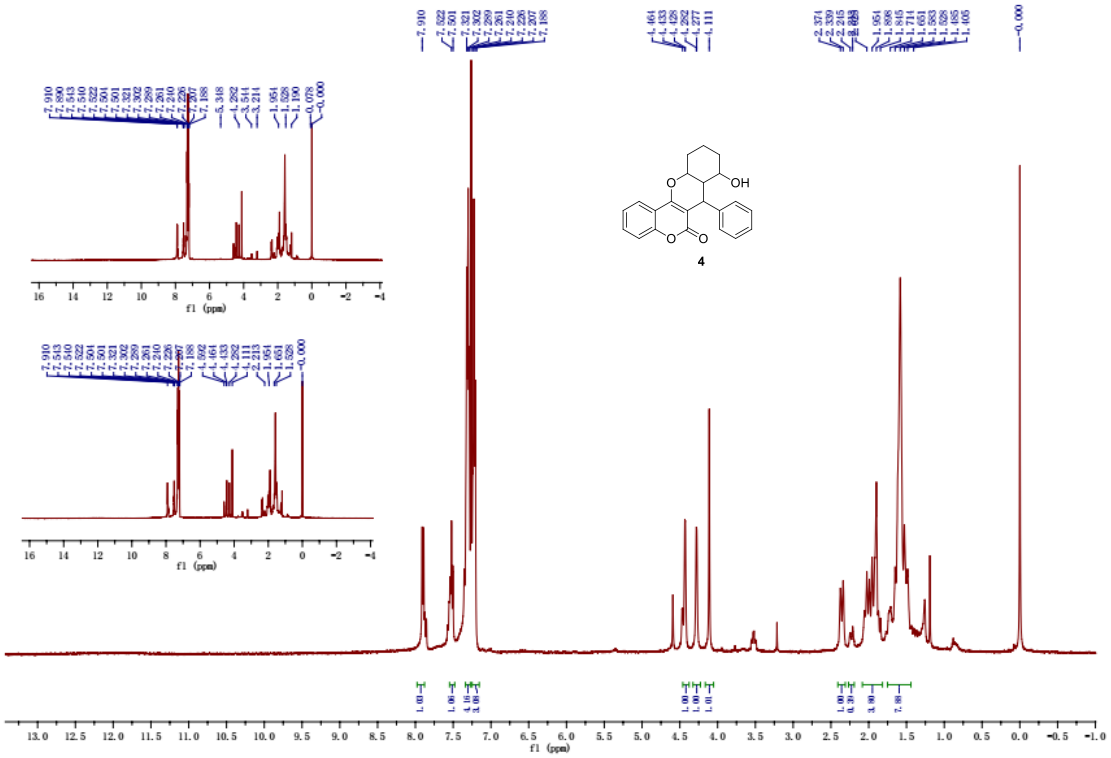

-117.349
F
O
O
O
O
Cl
3o
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
-200
ppm

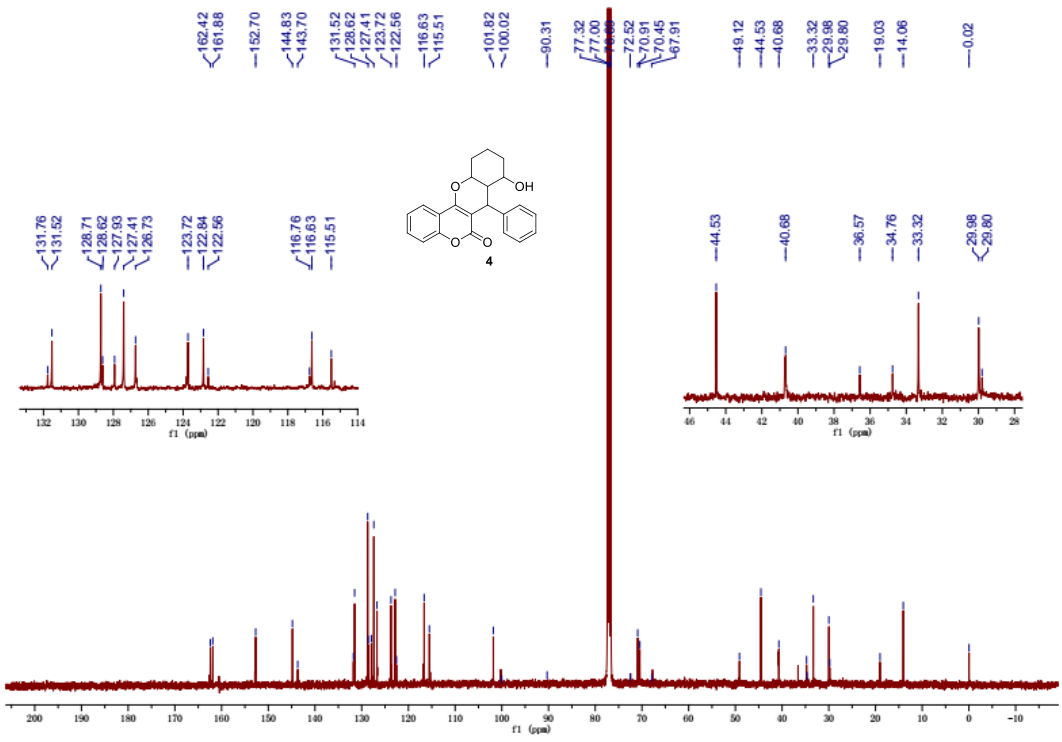

MeO
OMe
3p


MeO
OMe
3p


MeO
Cl
O
3q
f1 (ppm)

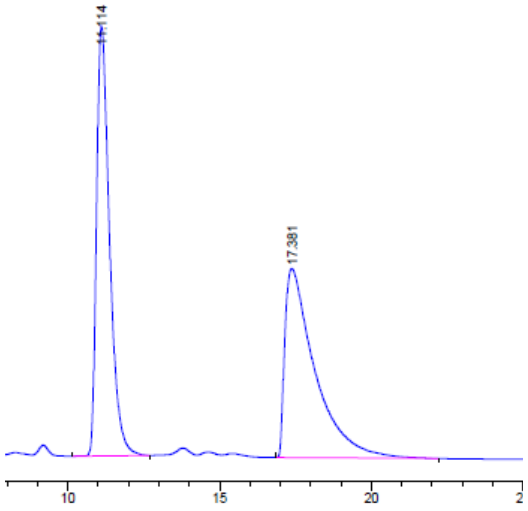

MeO
Cl
O
3q
f1 (ppm)


4


4

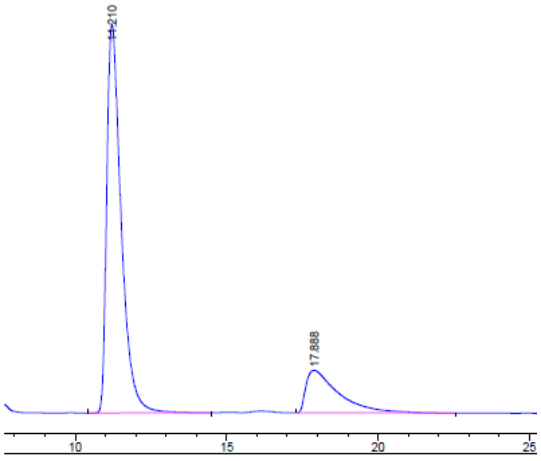
6. Chiral HPLC Spectra of Products

HPLC chromatogram of racemic **3a**



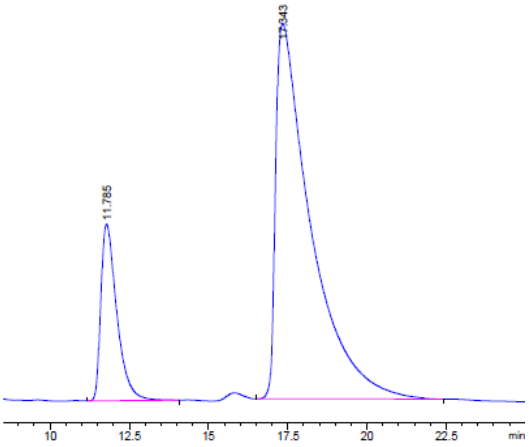
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.114	BB	0.4543	8298.62207	278.76825	49.4974
2	17.381	BB	0.9817	8467.13770	122.67794	50.5026

enantioenriched **3a** from 10 °C



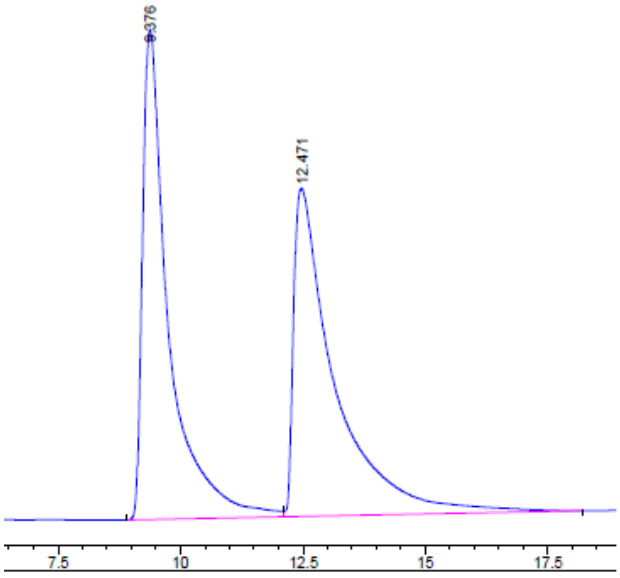
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.210	BB	0.5000	1.05452e4	318.32419	80.2171
2	17.888	BB	1.0388	2600.62476	34.70420	19.7829

enantioenriched **3a** from 60 °C



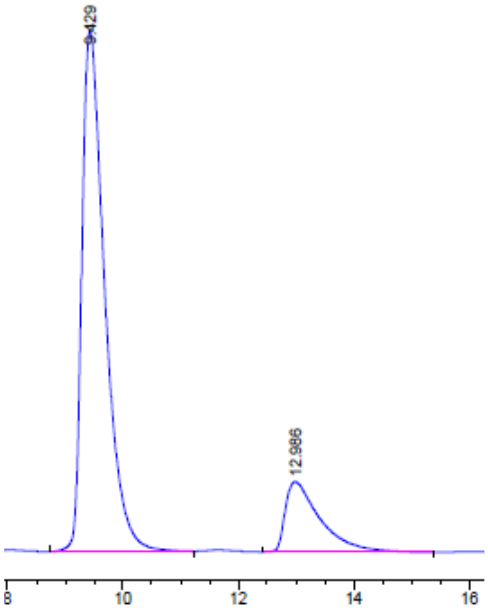
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.785	BB	0.5310	9520.75391	272.26218	17.6088
2	17.343	BB	1.0665	4.45473e4	579.06000	82.3912

HPLC chromatogram of racemic **3b**



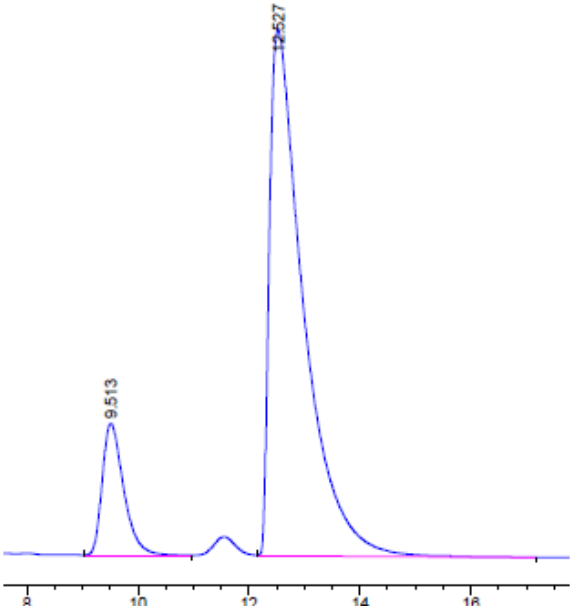
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.376	BV	0.5344	2.71407e4	729.83002	48.6557
2	12.471	VB	0.8054	2.86404e4	489.27054	51.3443

enantioenriched **3b** from 10 °C



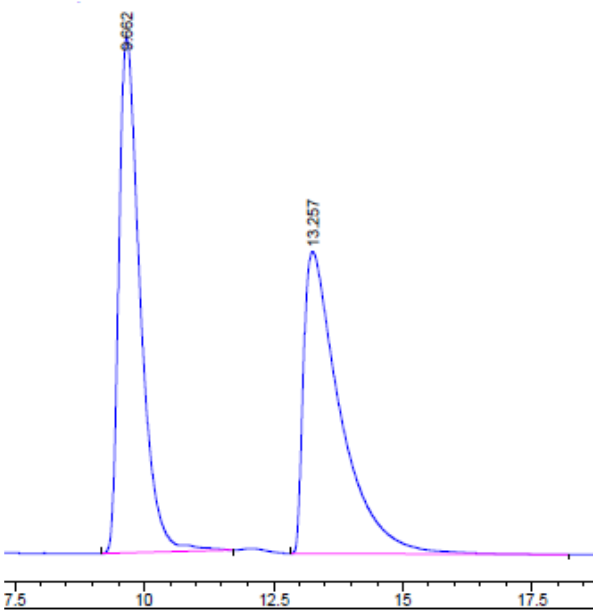
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.513	BB	0.4102	2529.80396	93.79897	13.6269
2	12.527	VB	0.6262	1.60349e4	374.35944	86.3731

enantioenriched **3b** from 60 °C



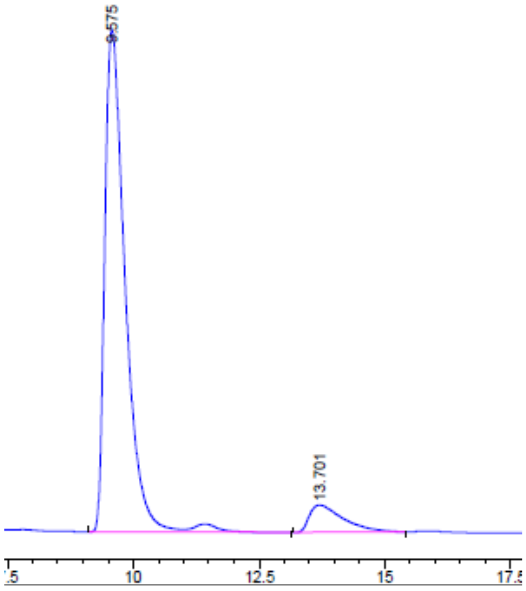
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.429	BB	0.4157	2.19105e4	797.01630	82.9423
2	12.986	BB	0.6122	4506.05225	107.25294	17.0577

HPLC chromatogram of racemic **3c**



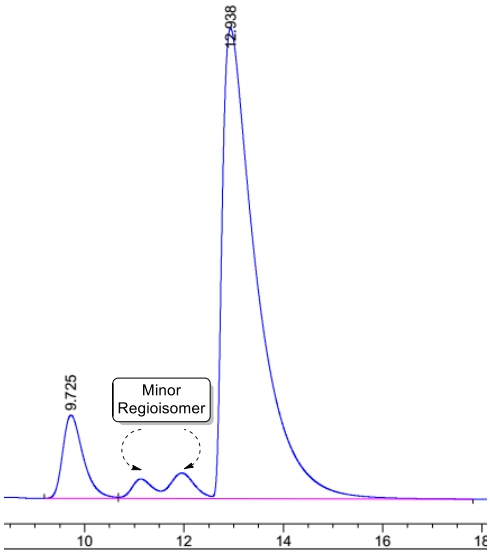
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.662	BV R	0.4334	1.10456e4	384.14923	49.8189
2	13.257	BB	0.7159	1.11259e4	224.98959	50.1811

enantioenriched **3c** from 10 °C



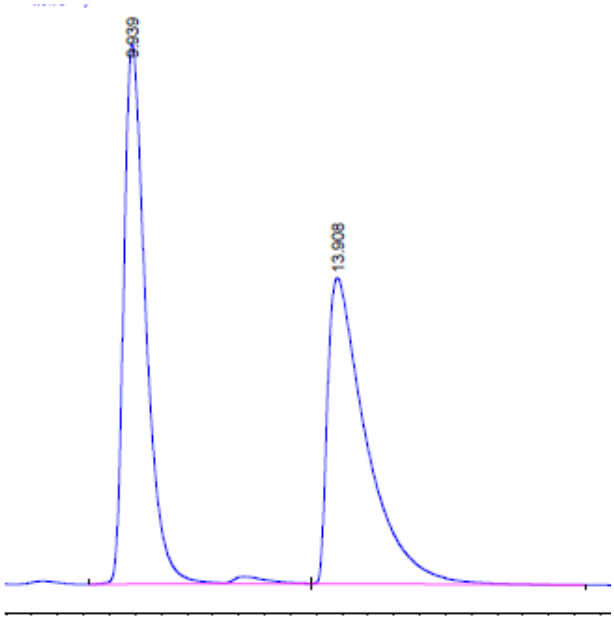
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.575	BV R	0.4270	2.14575e4	752.88885	91.8318
2	13.701	BB	0.6932	1908.58044	40.84161	8.1682

enantioenriched **3c** from 60 °C



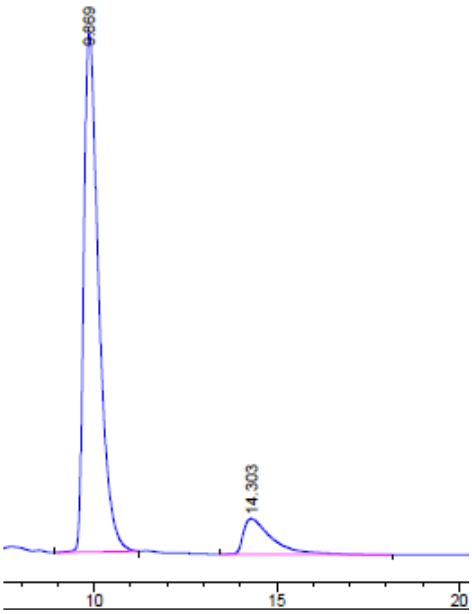
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.725	BV	0.4361	2360.36499	82.42591	8.9997
2	12.938	VB R	0.6983	2.38668e4	464.18182	91.0003

HPLC chromatogram of racemic **3d**



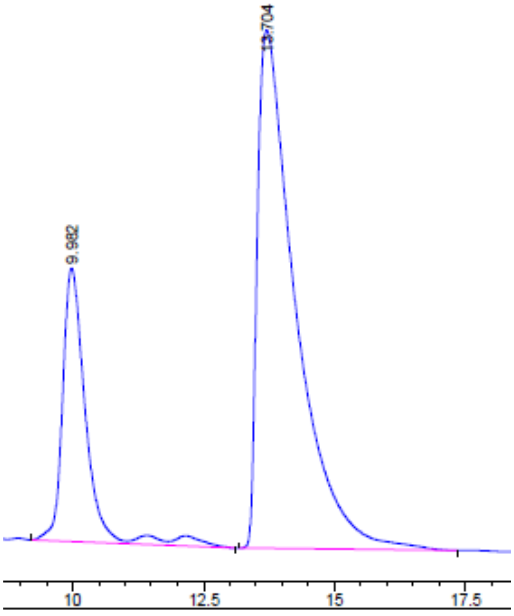
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.939	BV R	0.4482	1.14224e4	380.06781	50.4611
2	13.908	BB	0.7518	1.12137e4	215.07857	49.5389

enantioenriched **3d** from 10 °C



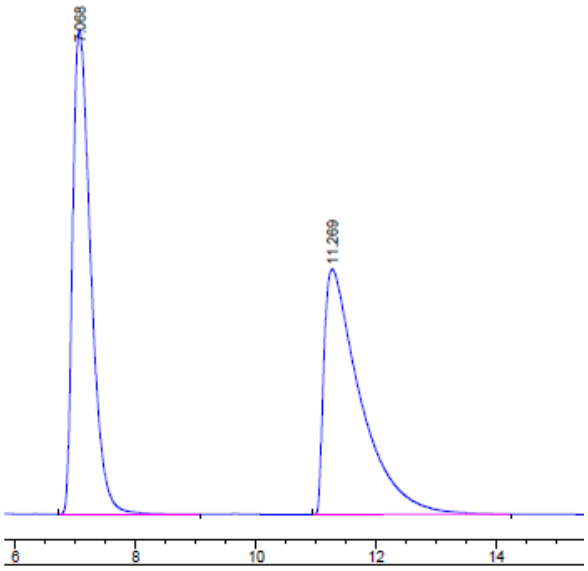
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.869	BB	0.4331	2.59863e4	914.14038	88.6082
2	14.303	BB	0.7694	3340.88135	62.52182	11.3918

enantioenriched **3d** from 60 °C



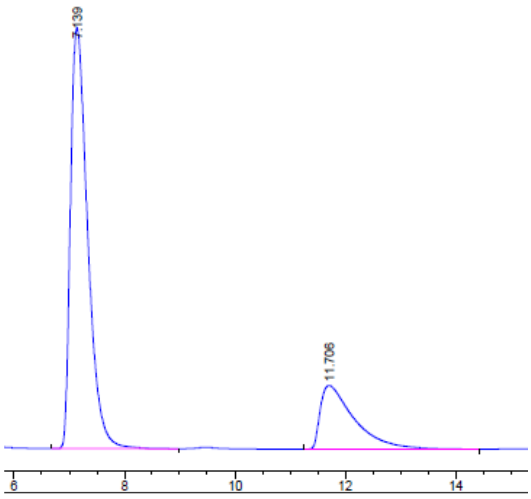
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.982	BV R	0.4452	5892.84814	186.19588	24.7522
2	13.704	BB	0.7292	1.79145e4	353.52075	75.2478

HPLC chromatogram of racemic **3e**



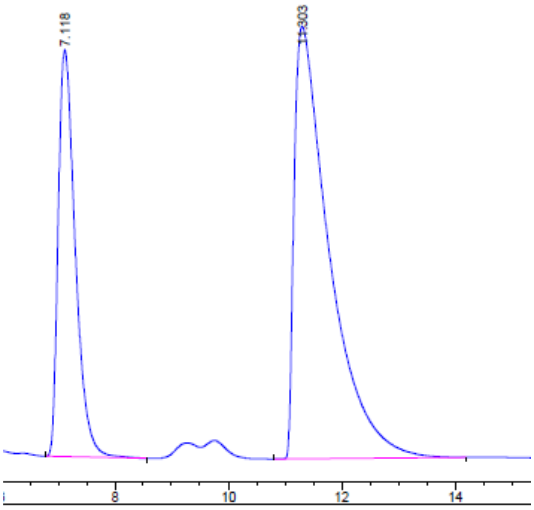
	RT [min]	Type	Width [min]	Area	Height	Area%
1	7.068	BB	0.3232	4.31287e4	2065.02710	49.5028
2	11.269	BB	0.6087	4.39951e4	1045.03577	50.4972

enantioenriched **3e** from 10 °C



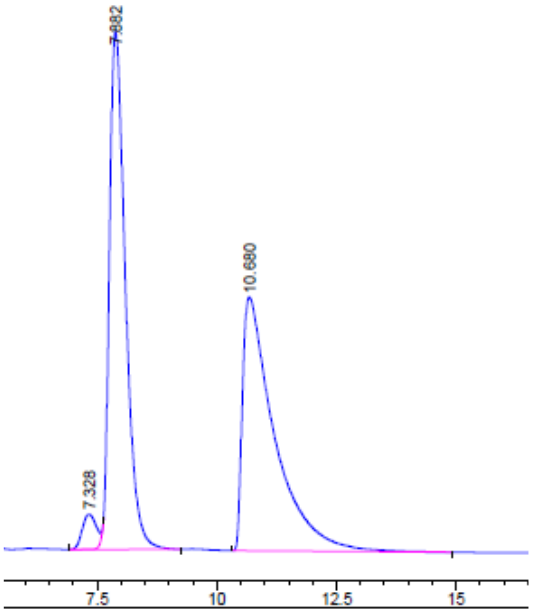
	RT [min]	Type	Width [min]	Area	Height	Area%
1	7.139	BB	0.3341	3.09626e4	1435.82019	77.0064
2	11.706	BB	0.6240	9245.22949	217.02707	22.9936

enantioenriched **3e** from 60 °C



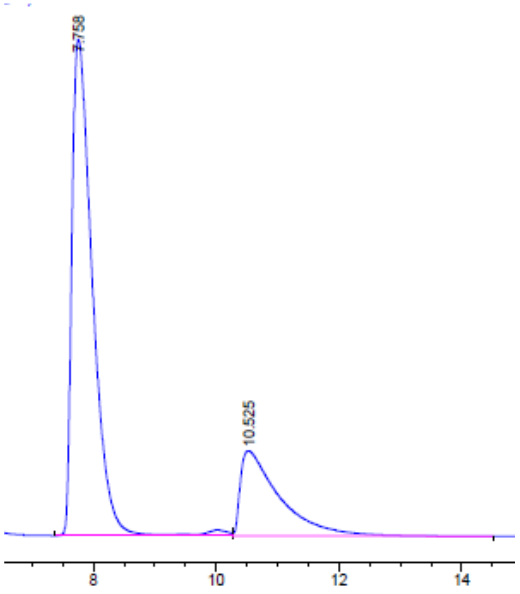
	RT [min]	Type	Width [min]	Area	Height	Area%
1	7.118	BB	0.3220	2.07286e4	991.17999	31.3816
2	11.303	BB	0.6262	4.53247e4	1052.96619	68.6184

HPLC chromatogram of racemic **3f**



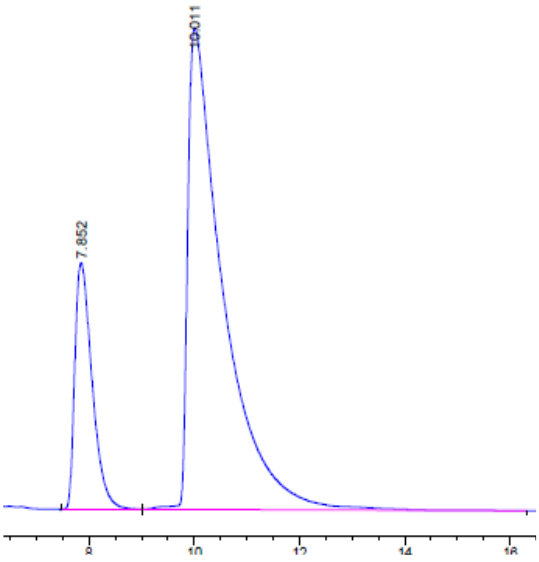
	RT [min]	Type	Width [min]	Area	Height	Area%
1	7.328	BV E	0.3252	903.35999	44.52401	2.8898
2	7.882	VB R	0.3596	1.53118e4	658.85986	48.9808
3	10.680	BB	0.6666	1.50456e4	322.59534	48.1295

enantioenriched **3f** from 10 °C



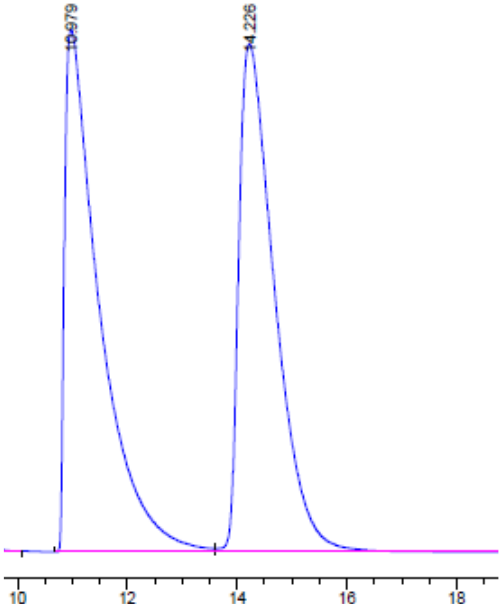
	RT [min]	Type	Width [min]	Area	Height	Area%
1	7.758	BV R	0.3499	6.26278e4	2687.37939	75.3684
2	10.525	VB	0.6261	2.04678e4	461.37109	24.6316

enantioenriched **3f** from 60 °C



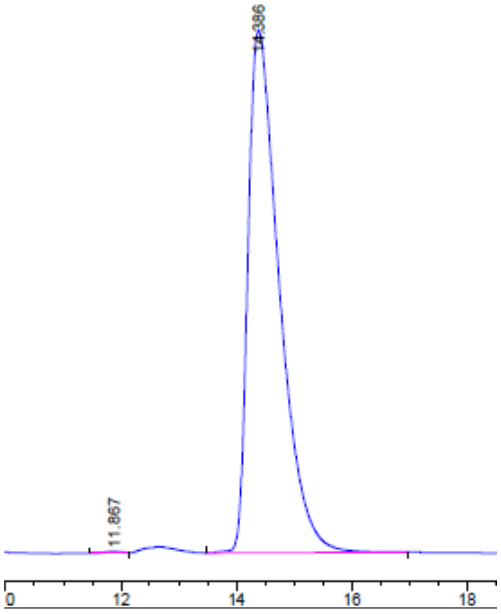
	RT [min]	Type	Width [min]	Area	Height	Area%
1	7.852	BB	0.3529	2.28337e4	999.87079	20.0157
2	10.011	BB	0.6530	9.12454e4	1947.91235	79.9843

HPLC chromatogram of racemic **3g**



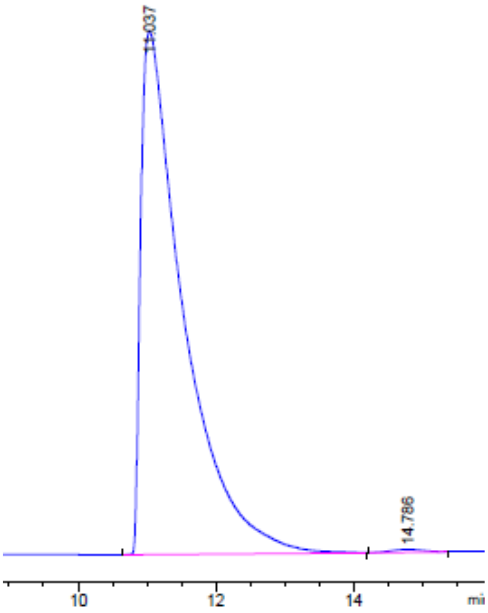
RT [min]	Type	Width [min]	Area	Height	Area%
10.979	BV	0.6176	8.01522e4	1813.61926	49.8508
14.226	VB	0.6845	8.00662e4	1764.00476	49.7973

enantioenriched **3g** from 10 °C



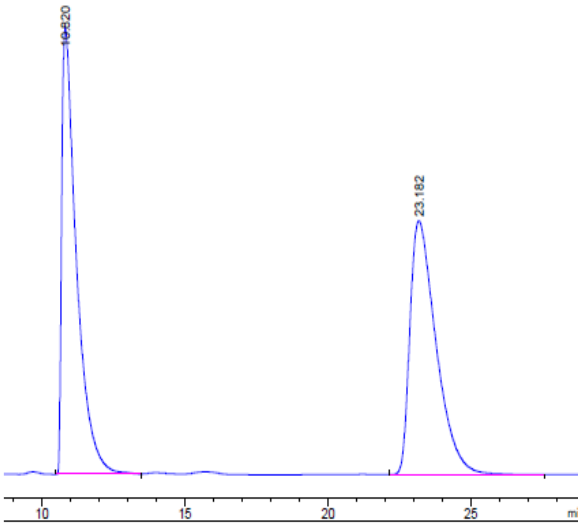
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.867	BV	0.3214	50.35434	2.32248	0.1576
2	14.386	VB	0.5770	3.18996e4	846.74261	99.8424

enantioenriched **3g** from 60 °C



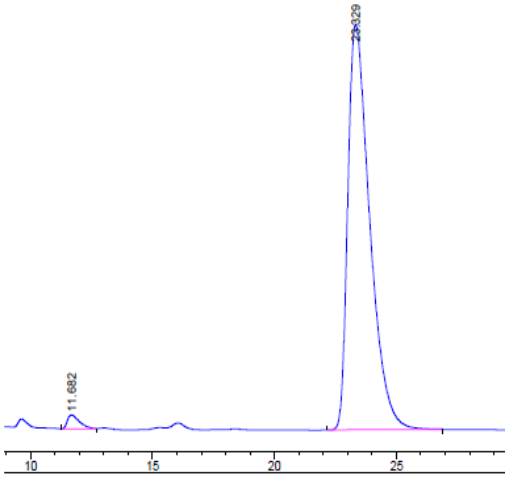
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.037	BB	0.6141	6.13654e4	1422.91821	99.5779
2	14.786	BB	0.4817	260.11621	8.14296	0.4221

HPLC chromatogram of racemic **3h**



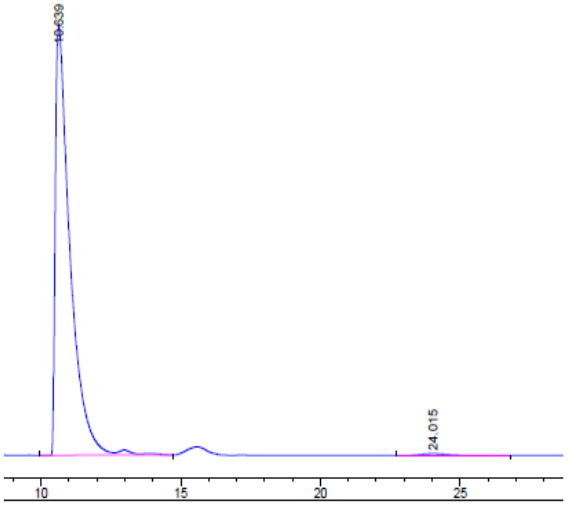
	RT [min]	Type	Width [min]	Area	Height	Area%
1	10.820	BB	0.5216	2.79232e4	779.11823	49.7970
2	23.182	BB	0.9546	2.81509e4	442.88602	50.2030

enantioenriched **3h** from 10 °C



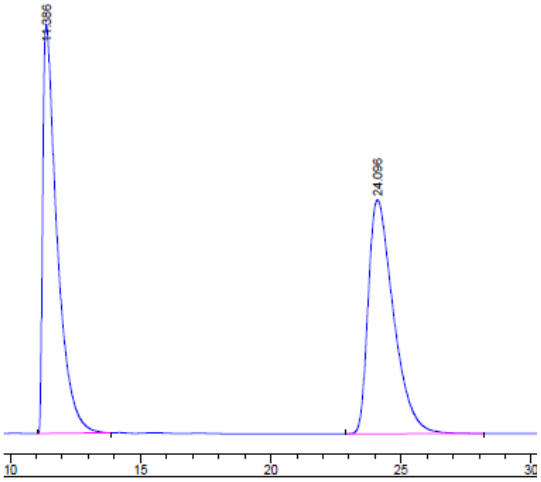
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.682	BB	0.5113	398.49265	11.71786	1.8433
2	23.329	BB	0.9398	2.12194e4	340.38669	98.1567

enantioenriched **3h** from 60 °C



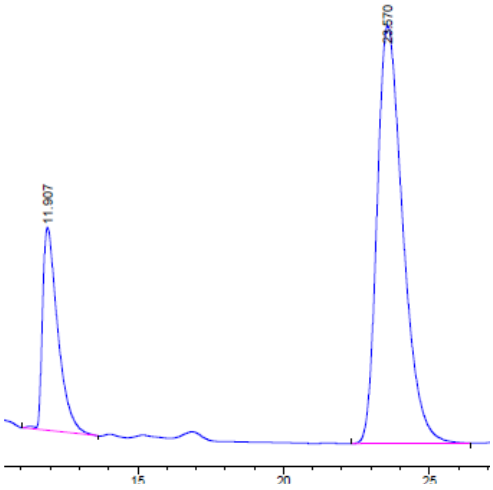
	RT [min]	Type	Width [min]	Area	Height	Area%
1	10.639	BV R	0.5214	6.52498e4	1771.35010	99.3439
2	24.015	BB	0.7940	430.91010	6.44490	0.6561

HPLC chromatogram of racemic **3i**



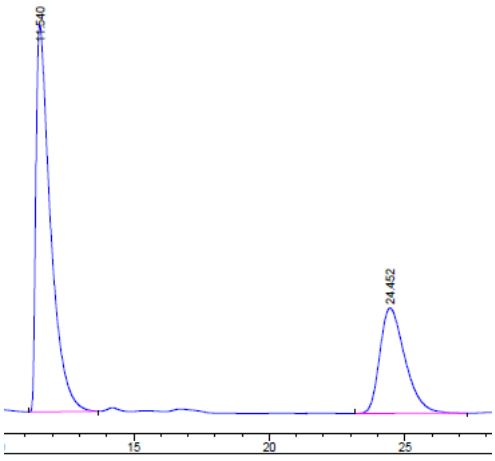
RT [min]	Type	Width [min]	Area	Height	Area%
11.386	BB	0.5548	2.13180e4	559.76349	49.6835
24.096	BB	1.0068	2.14662e4	319.94095	50.0290

enantioenriched **3i** from 10 °C



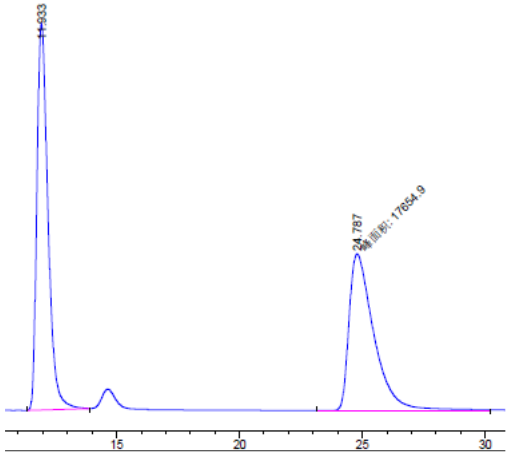
RT [min]	Type	Width [min]	Area	Height	Area%
11.907	VB R	0.5384	1494.99670	41.19356	22.3307
23.570	BB	0.9368	5199.80029	84.69267	77.6693

enantioenriched **3i** from 60 °C



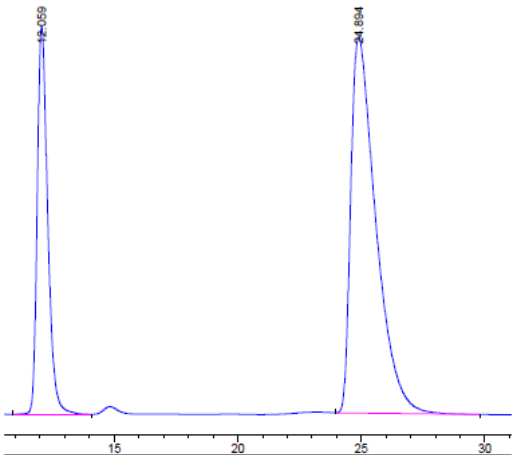
RT [min]	Type	Width [min]	Area	Height	Area%
11.540	BB	0.5516	1.16737e4	310.88513	68.0969
24.452	BB	0.9887	5469.08887	84.66055	31.9031

HPLC chromatogram of racemic **3j**



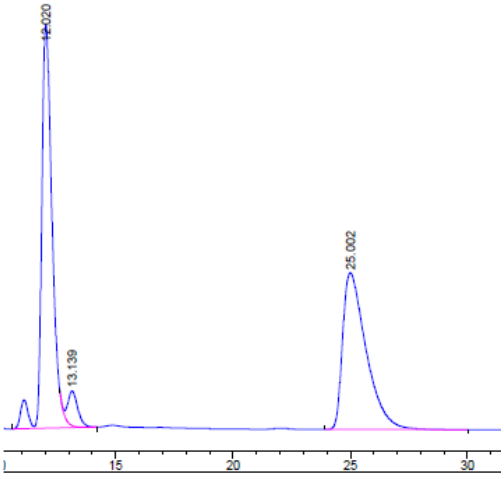
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.933	BB	0.4798	1.90557e4	608.66315	51.9079
2	24.787	MM	1.1916	1.76549e4	246.93097	48.0921

enantioenriched **3j** from 10 °C



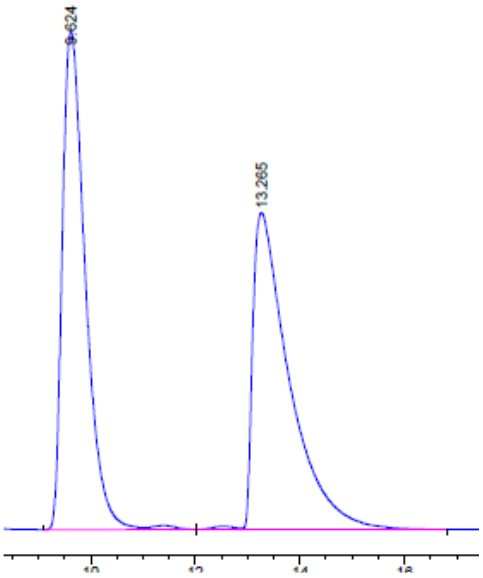
	RT [min]	Type	Width [min]	Area	Height	Area%
1	12.059	BB	0.4508	1.02110e4	346.04269	30.1549
2	24.894	BB	1.0474	2.36508e4	335.32468	69.8451

enantioenriched **3j** from 60 °C



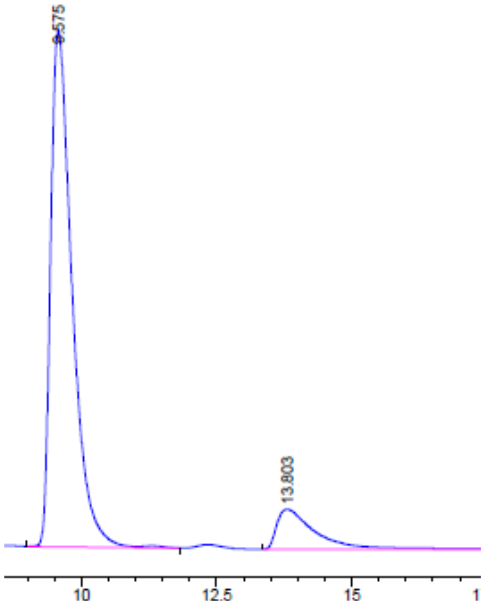
	RT [min]	Type	Width [min]	Area	Height	Area%
1	12.020	VV R	0.4654	2.34351e4	734.81024	51.9333
2	13.139	VB E	0.4516	1877.15283	62.90704	4.1598
3	25.002	BB	1.0439	1.98132e4	284.71979	43.9069

HPLC chromatogram of racemic **3k**



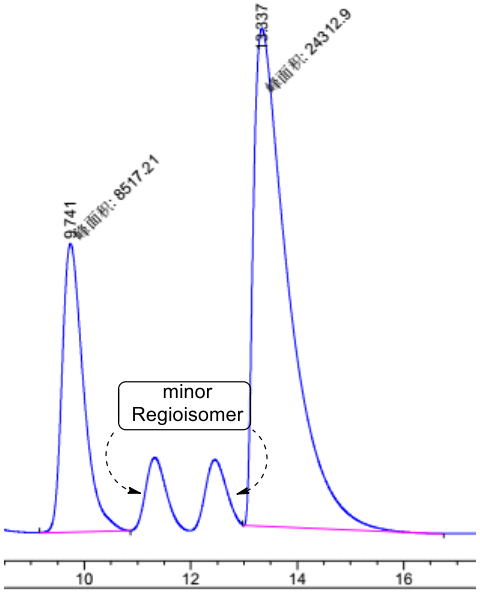
RT [min]	Type	Width [min]	Area	Height	Area%
1	9.624	BV R	0.4685	3.41953e4	1117.18884	49.8074
2	13.265	VB R	0.7023	3.44597e4	709.22925	50.1926

enantioenriched **3k** from 10 °C



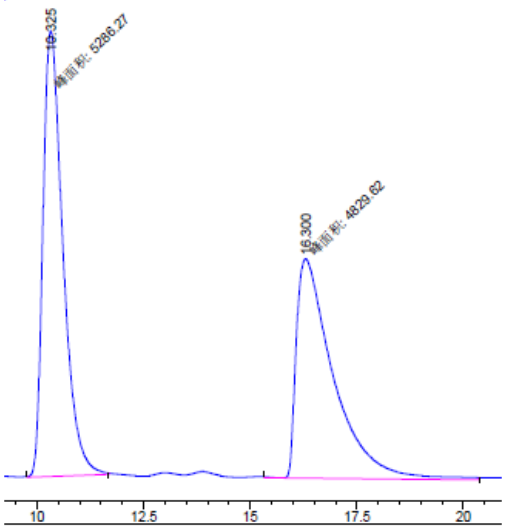
RT [min]	Type	Width [min]	Area	Height	Area%
1	9.575	BV R	0.4164	2.92688e4	1060.67517	87.4423
2	13.803	BBA	0.7371	4203.33154	81.99293	12.5577

enantioenriched **3k** from 60 °C



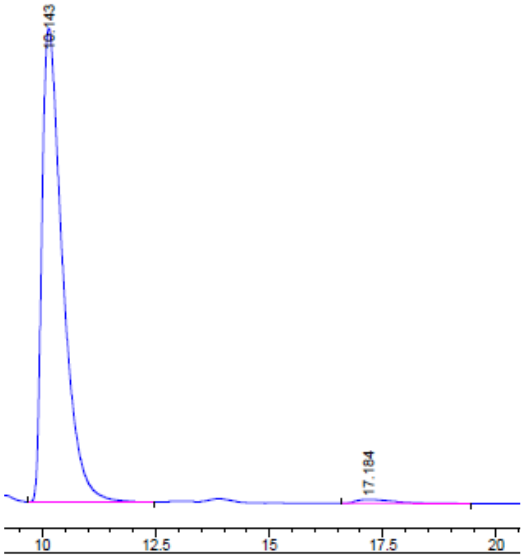
RT [min]	Type	Width [min]	Area	Height	Area%
1	9.741	MM	0.4646	8517.20605	305.53580	25.9433
2	13.337	MM	0.7689	2.43129e4	526.99005	74.0567

HPLC chromatogram of racemic **3l**



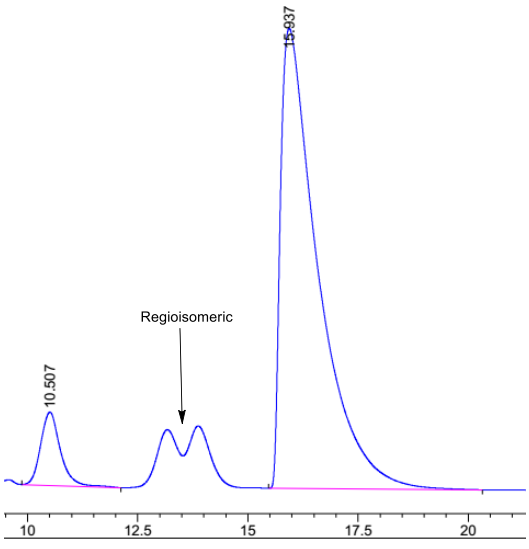
	RT [min]	Type	Width [min]	Area	Height	Area%
1	10.325	MM	0.5434	5286.27393	162.14830	52.2571
2	16.300	MM	1.0096	4829.62354	79.73052	47.7429

enantioenriched **3l** from 10 °C



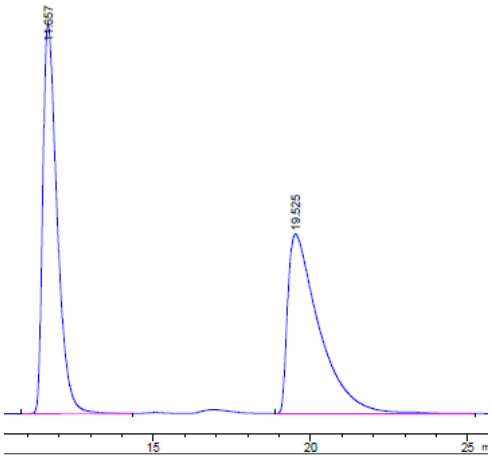
	RT [min]	Type	Width [min]	Area	Height	Area%
1	10.143	BB	0.4783	2.58056e4	815.30371	98.5693
2	17.184	BB	0.7654	374.55237	6.70275	1.4307

enantioenriched **3l** from 60 °C



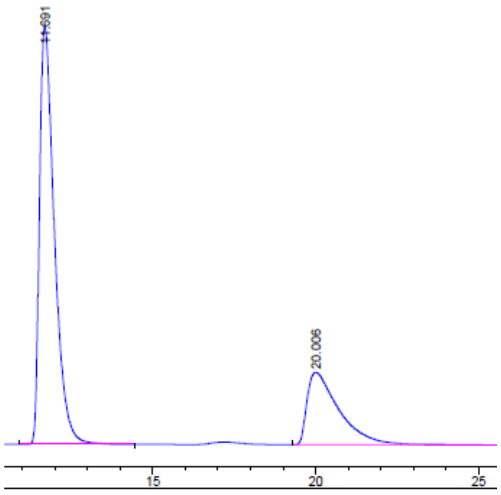
	RT [min]	Type	Width [min]	Area	Height	Area%
1	10.507	BB	0.4734	879.60944	28.27873	7.7288
2	15.937	BB	0.8510	1.05013e4	177.29396	92.2712

HPLC chromatogram of racemic **3n**



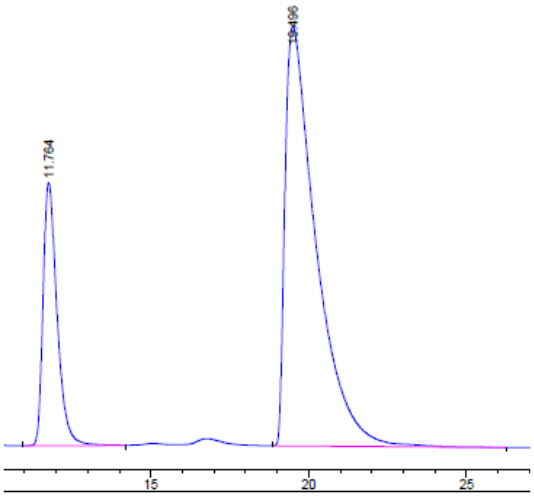
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.657	BB	0.4821	2.88279e4	907.61591	49.7968
2	19.525	BB	0.9970	2.90632e4	418.34332	50.2032

enantioenriched **3n** from 10 °C



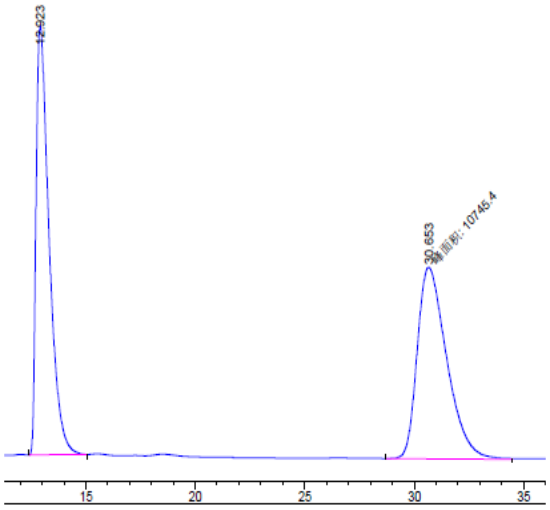
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.691	BB	0.4799	3.58653e4	1132.65918	72.8638
2	20.006	BB	0.9838	1.33571e4	196.19766	27.1362

enantioenriched **3n** from 60 °C



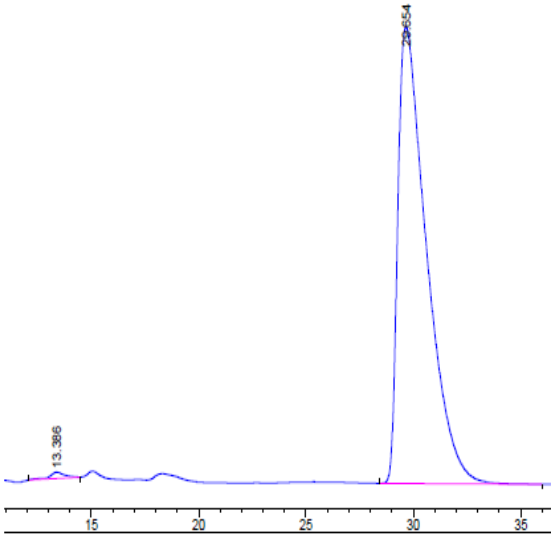
	RT [min]	Type	Width [min]	Area	Height	Area%
1	11.764	BB	0.4669	6988.29053	227.18742	22.0435
2	19.496	BB	0.9818	2.47141e4	362.31577	77.9565

HPLC chromatogram of racemic **3o**



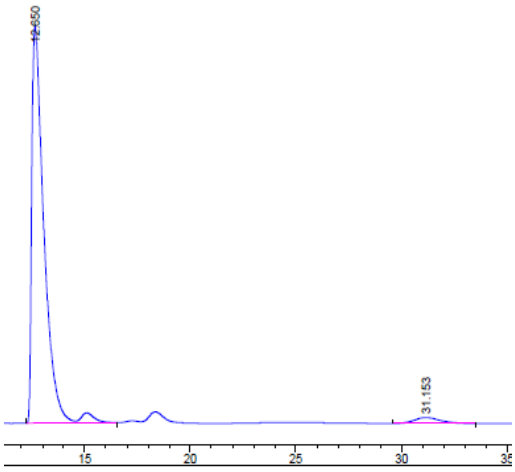
	RT [min]	Type	Width [min]	Area	Height	Area%
1	12.923	BB	0.6277	1.05901e4	255.98097	49.6362
2	30.653	MM	1.5639	1.07454e4	114.51707	50.3638

enantioenriched **3o** from 10 °C



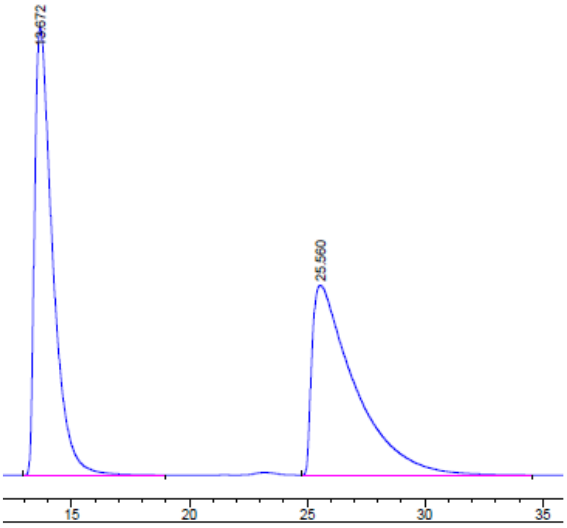
	RT [min]	Type	Width [min]	Area	Height	Area%
1	13.386	BB	0.6605	344.24796	6.88938	0.7257
2	29.654	BB	1.3547	4.70897e4	507.43292	99.2743

enantioenriched **3o** from 60 °C



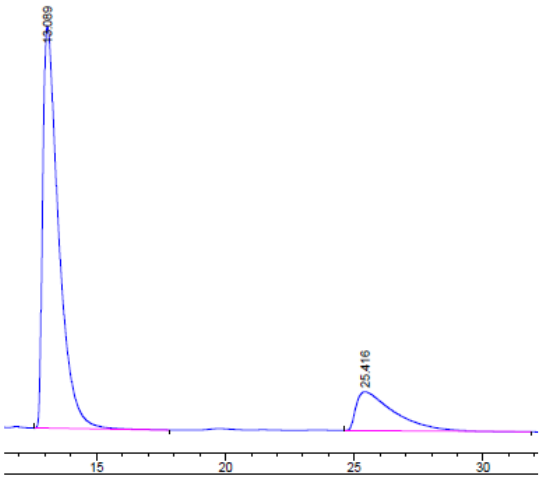
	RT [min]	Type	Width [min]	Area	Height	Area%
1	12.650	BV R	0.5832	3.00389e4	740.71155	97.0867
2	31.153	BB	1.0057	901.37122	10.67976	2.9133

HPLC chromatogram of racemic **3p**



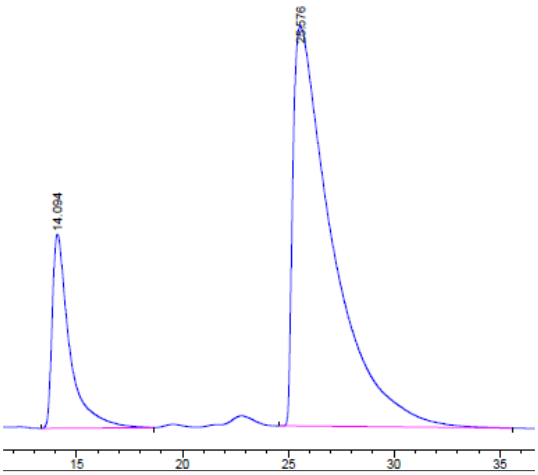
	RT [min]	Type	Width [min]	Area	Height	Area%
1	13.672	BB	0.7985	1.72447e4	323.73431	49.8890
2	25.560	BB	1.7103	1.73214e4	136.88574	50.1110

enantioenriched **3p** from 10 °C



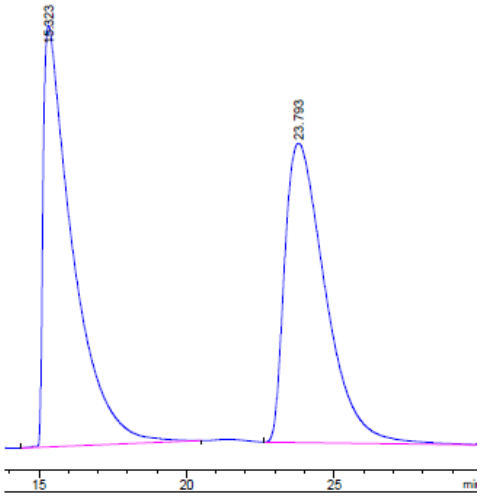
	RT [min]	Type	Width [min]	Area	Height	Area%
1	14.094	BB	0.8278	3858.60693	67.31400	17.6315
2	25.576	BB	1.7743	1.80262e4	138.92110	82.3685

enantioenriched **3p** from 60 °C



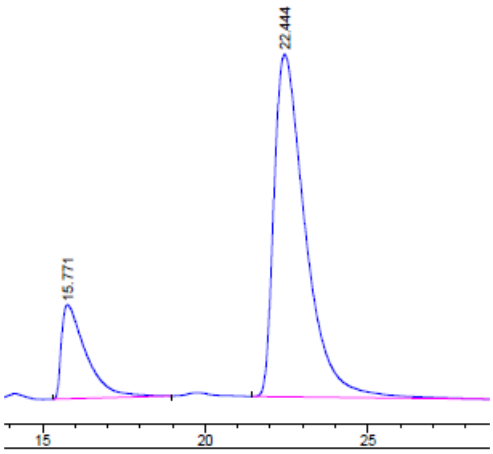
	RT [min]	Type	Width [min]	Area	Height	Area%
1	13.089	BB	0.6385	3.13823e4	729.99127	81.1415
2	25.416	BB	1.4253	7293.70605	70.71930	18.8585

HPLC chromatogram of racemic **3q**



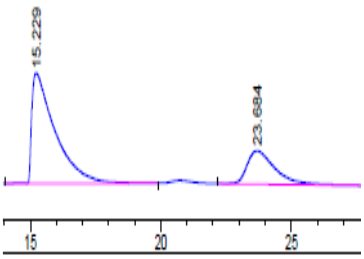
	RT [min]	Type	Width [min]	Area	Height	Area%
1	15.323	BB	0.9516	5.10150e4	737.87396	50.4099
2	23.793	BBA	1.4793	5.01853e4	524.73767	49.5901

enantioenriched **3q** from 10 °C



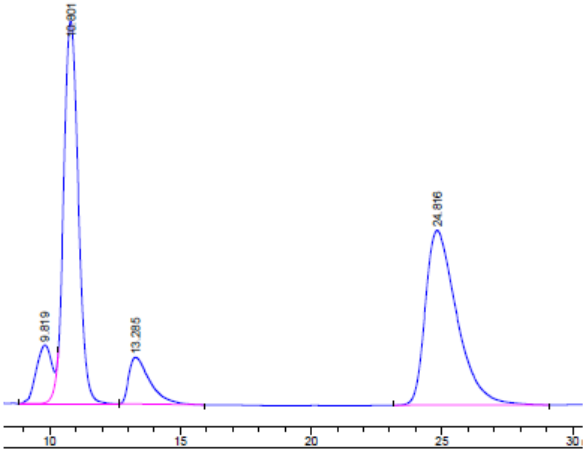
	RT [min]	Type	Width [min]	Area	Height	Area%
1	15.771	BB	0.7604	5008.19287	95.02427	17.7091
2	22.444	BBA	1.0040	2.32721e4	346.29694	82.2909

enantioenriched **3q** from 60 °C



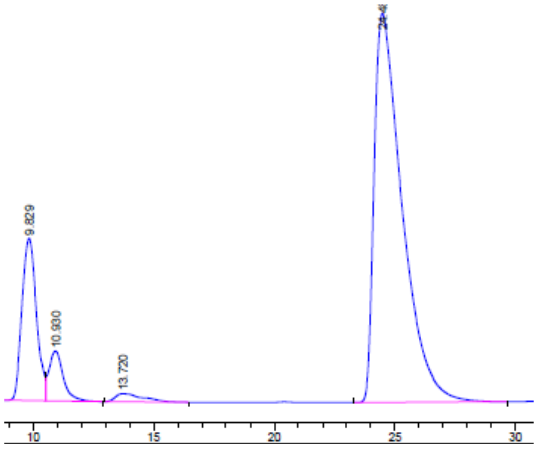
	RT [min]	Type	Width [min]	Area	Height	Area%
1	15.229	VB R	0.8589	3.74359e4	600.12408	73.7573
2	23.684	BBA	1.1050	1.33196e4	180.47701	26.2427

HPLC chromatogram of racemic **4**



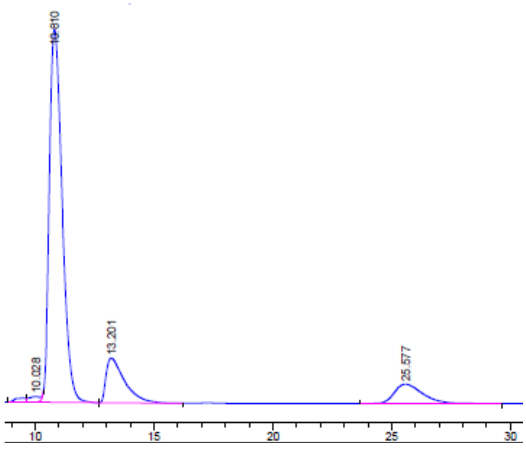
	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.819	BV E	0.6235	762.61139	19.23539	6.5984
2	10.801	VB R	0.6198	5025.77539	127.94446	43.4849
3	13.285	BB	0.8170	875.40460	15.53421	7.5743
4	24.816	BB	1.2465	4893.73584	58.37514	42.3424

enantioenriched **4** from (-)-**3m**



	RT [min]	Type	Width [min]	Area	Height	Area%
1	9.829	BV	0.6619	3111.75073	74.55902	16.5455
2	10.930	VB	0.6203	944.41174	22.96232	5.0215
3	13.720	BB	0.9515	292.45987	3.60877	1.5550
4	24.485	BB	1.2133	1.44586e4	179.19699	76.8779

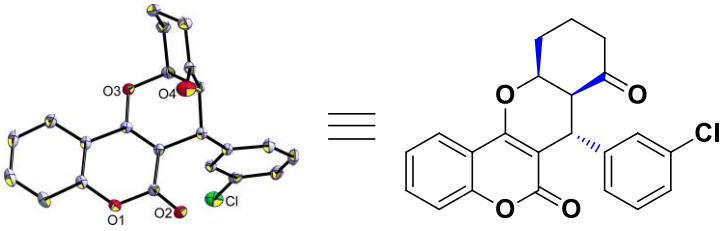
enantioenriched **4** from (+)-**3m**



	RT [min]	Type	Width [min]	Area	Height	Area%
1	10.028	VV E	0.4478	221.64622	6.85300	0.9925
2	10.810	VB R	0.5855	1.70892e4	454.74857	76.5194
3	13.201	BB	0.8023	2973.65552	54.48104	13.3150
4	25.577	BB	1.1872	2048.66064	24.04023	9.1732

7. X-ray crystallographic data of compound 3h

i. X-ray crystallographic data of compound **(-)-3h** **(CCDC 1508097)**



Bond precision: C-C = 0.0030 A Wavelength=0.71073

Cell: a=9.3404(10) b=11.2518(11) c=16.982(2)
alpha=90 beta=90 gamma=90
Temperature: 293 K

	Calculated	Reported
Volume	1784.8(3)	1784.7(3)
Space group	P 21 21 21	P2(1)2(1)2(
Hall group	P 2ac 2ab	?
Moiety formula	C22 H17 Cl O4	?
Sum formula	C22 H17 Cl O4	C22 H17 Cl O4
Mr	380.81	380.81
Dx,g cm-3	1.417	1.417
Z	4	4
Mu (mm-1)	0.240	0.240
F000	792.0	792.0
F000'	792.97	
h,k,lmax	11,13,20	11,13,20
Nref	3138[1810]	3132
Tmin,Tmax	0.944,0.953	
Tmin'	0.931	

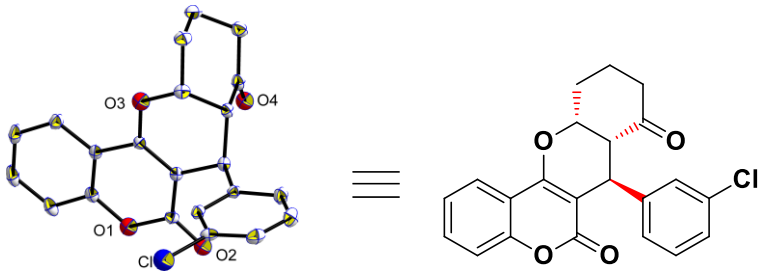
Correction method= Not given

Data completeness= 1.73/1.00 Theta(max)= 25.010

R(reflections)= 0.0305(2753) wR2(reflections)= 0.0723(3132)

S = 1.022 Npar= 244

ii. X-ray crystallographic data of compound **(+)-3h (CCDC 1508098)**



Bond precision: C-C = 0.0025 A Wavelength=0.71073

Cell: a=9.3379(2) b=11.2530(3) c=17.0022(4)
alpha=90 beta=90 gamma=90
Temperature: 296 K

	Calculated	Reported
Volume	1786.58(7)	1786.58(7)
Space group	P 21 21 21	P2(1)2(1)2(
Hall group	P 2ac 2ab	?
Moiety formula	C22 H17 Cl O4	?
Sum formula	C22 H17 Cl O4	C88 H68 C14 O16
Mr	380.81	1523.22
Dx,g cm-3	1.416	1.416
Z	4	1
Mu (mm-1)	0.240	0.240
F000	792.0	792.0
F000'	792.97	
h,k,lmax	11,13,20	11,13,20
Nref	3273[1886]	3239
Tmin,Tmax	0.944,0.953	
Tmin'	0.931	

Correction method= Not given

Data completeness= 1.72/0.99 Theta(max)= 25.340

R(reflections)= 0.0279(2984) wR2(reflections)= 0.0730(3239)

S = 0.983 Npar= 244