Catalytic asymmetric construction of dispirotriheterocyclic structures through [3+2] cycloadditions of 4-amino pyrazolone-based azomethine ylides

Yue Huang, Xiaoze Bao, Xingfu Wei, Jianfang Zhang, Shah Nawaz, Jingping Qu and Baomin Wang*

State Key Laboratory of Fine Chemicals, Department of Pharmaceutical Sciences, School of Chemical Engineering, Dalian University of Technology, Dalian 116024, P. R. China
bmwang@dlut.edu.cn

Contents:

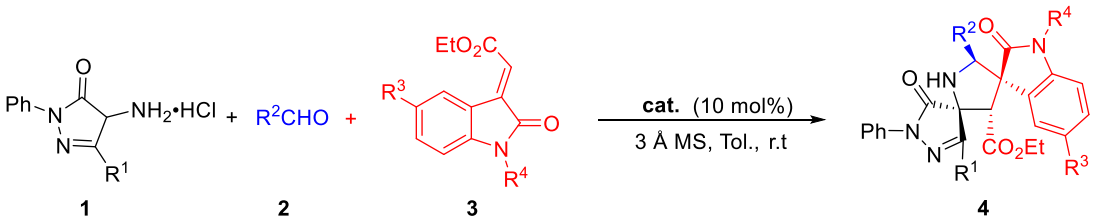
1. General information

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Column chromatography was performed on silica gel (200~300 mesh). Enantiomeric excesses (*ee*) were determined by HPLC using corresponding commercial chiral columns as stated at 30 °C with UV detector at 254 nm. Optical rotations were reported as follows: $[a]_D^T$ (c g/100 mL, solvent). All ^{1}H NMR and ^{19}F NMR spectra were recorded on a Bruker Avance Ⅱ 400 MHz and Bruker Avance Ⅲ 471 MHz respectively, ^{13}C NMR spectra were recorded on a Bruker Avance Ⅱ 101 MHz or Bruker Avance Ⅲ 126 MHz with chemical shifts reported as ppm (in $CDCl_3$, TMS as an internal standard). Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, br = broad singlet, dd = double doublet, coupling constants in Hz, integration). HRMS (ESI) was obtained with an HRMS/MS instrument (LTQ Orbitrap XL TM). The absolute configuration of **4ad** was assigned by the X-ray analysis.

Starting materials: All the aldehydes were commercially obtained and recrystallized or distilled prior to use. (1) 4-Amino pyrazolones were prepared following the reported procedures: 5 X. Bao, S. Wei, X. Qian, J. Qu, B. Wang, L. Zou and G. Ge, *Org. Lett.*, 2018, **20**, 3394. (2) Methyleneindolinones were synthesized according to following literature procedures: (a) K. Suman, L. Srinu and S. Thennarasu, *Org. Lett.*, 2014, **16**, 3732; (b) A. Huang, J. J. Kodanko and L. E. Overman, *J. Am. Chem. Soc.*, **2004**, *126*, 14043.

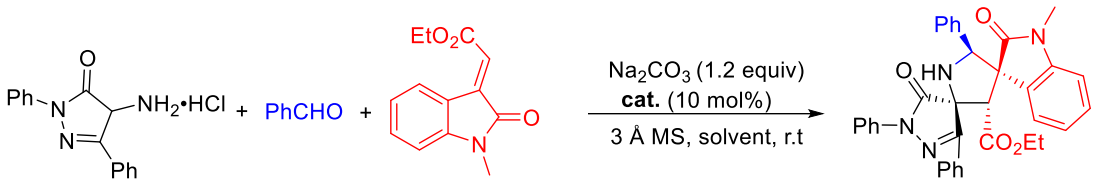
2. Experimental sections

General procedure for the synthesis of 4

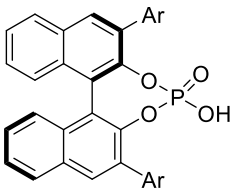


In a reaction tube, 4-amino pyrazolone **1** (0.24 mmol), methyleneindolinone **3** (0.2 mmol), catalyst (0.02 mmol) and 3 Å MS (200 mg) were added into toluene (2 mL). Then aldehyde **2** (0.24 mmol) was added and the reaction solution was stirred at 25 °C. After the reaction was complete (monitored by TLC), the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/20 to 1/4) on silica gel to give the product **4**.

Table 1: Optimization of reaction conditions. [a] BPA=chiral phosphoric acid.



1a **2a** **3a** **4aa**



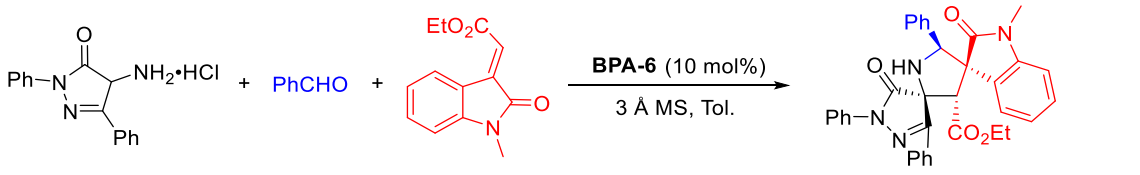
BPA

BPA-1 Ar = 2,4,6-(*i*-Pr)$_3$-C$_6$H$_2$
BPA-2 Ar = 2-naphthyl
BPA-3 Ar = Ph
BPA-4 Ar = 3-Ph-C$_6$H$_4$
BPA-5 Ar = SiPh$_3$
BPA-6 Ar = 9-phenanthryl
BPA-7 Ar = 9-anthryl

entry	**Cat.**	Additives	Solvent	t[h]	Yield[%][b]	dr[c]	ee[%][d]
1	**BPA-1**	3 Å	DCM	59	74	>20:1	35
2	**BPA-2**	3 Å	DCM	59	94	>20:1	65
3	**BPA-3**	3 Å	DCM	59	53	>20:1	25
4	**BPA-4**	3 Å	DCM	59	70	>20:1	25
5	**BPA-5**	3 Å	DCM	59	64	>20:1	0
6	**BPA-6**	3 Å	DCM	59	83	>20:1	93
7	**BPA-7**	3 Å	DCM	59	65	>20:1	90
8	**BPA-6**	3 Å	$CHCl_3$	43	78	>20:1	78
9	**BPA-6**	3 Å	THF	13	73	>20:1	40
10	**BPA-6**	3 Å	Et_2O	13	85	>20:1	76
11	**BPA-6**	3 Å	Tol	24	85	>20:1	96
12[e]	**BPA-6**	3 Å	Tol	67	96	>20:1	95
13[e]	**BPA-6**	4 Å	Tol	60	88	>20:1	95
14[e]	**BPA-6**	5 Å	Tol	36	85	>20:1	96
15[e]	**BPA-6**	$MgSO_4$	Tol	36	82	>20:1	95
16[e]	**BPA-6**	-	Tol	84	72	>20:1	95
17[e,f]	**BPA-6**	3 Å	Tol	60	86	>20:1	95
18[e,f,g]	**BPA-6**	3 Å	Tol	60	97	>20:1	95

[a]The reaction was conducted with **1a** (0.1 mmol), **2a** (0.12 mmol), **3a** (0.12 mmol) and **cat.** (0.01 mmol), MS (100 mg) in solvent (1.0 mL) at room temperature under argon. [b]Isolated yield. [c]Detected by ^{1}HNMR of the crude product. [d]Detected by chiral HPLC analysis. [e]Without Na_2CO_3 [f]No protection. [g]A the ratio of **1a**/**2a**/**3a** was 1.2/1.2/1.

Gram-scale reaction

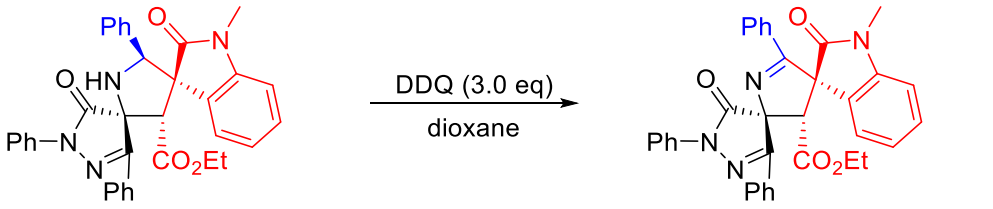


1a **2a** **3a** **4aa**

(1.02 g, 81% yield, >20:1 dr, 95% ee)

In a reaction tube, 4-amino pyrazolone **1a** (0.264 mmol), **3a** (0.22 mmol), **BPA-6** (0.022 mmol) and 3 Å MS (220 mg) were added into toluene (2.2 mL). Then aldehyde **2a** (0.264 mmol) was added and the reaction solution was stirred at 25 ℃. After the reaction was complete (monitored by TLC), the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/20 to 1/4) on silica gel to give the product **4aa** with 81% yield, >20:1 dr and 95% ee.

Procedure for the Synthesis of 5



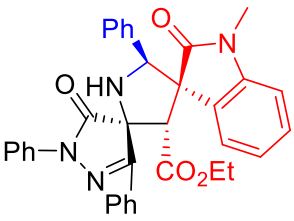
4aa **5**

(yield 96%, dr >20:1, ee 95%)

A reaction tube was charged with **4aa** (0.2 mmol) and dioxane (2 mL), then DDQ (0.6 mmol) was added. The reaction was stirred at room temperature until it was complete (monitored by TLC), then the crude product was purified by column chromatography (ethyl acetate/petroleum ether = 1/10) on silica gel to give the product **5** as a white solid.

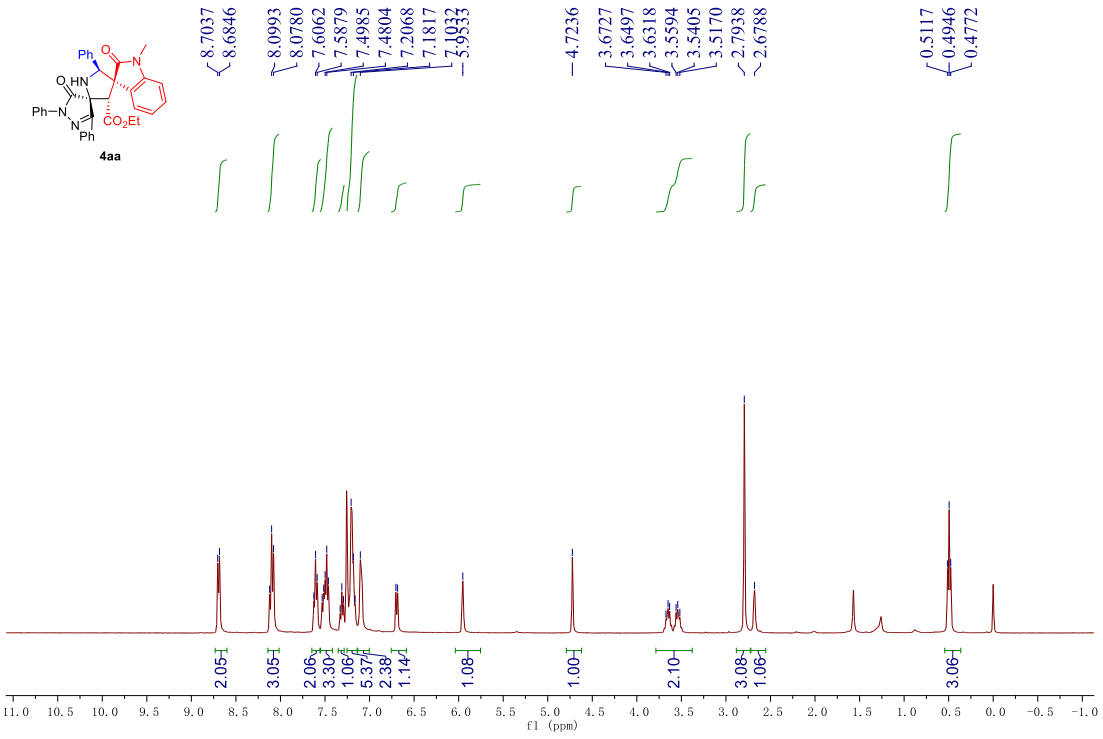
Copies of ^{1}H NMR and ^{13}C NMR spectra

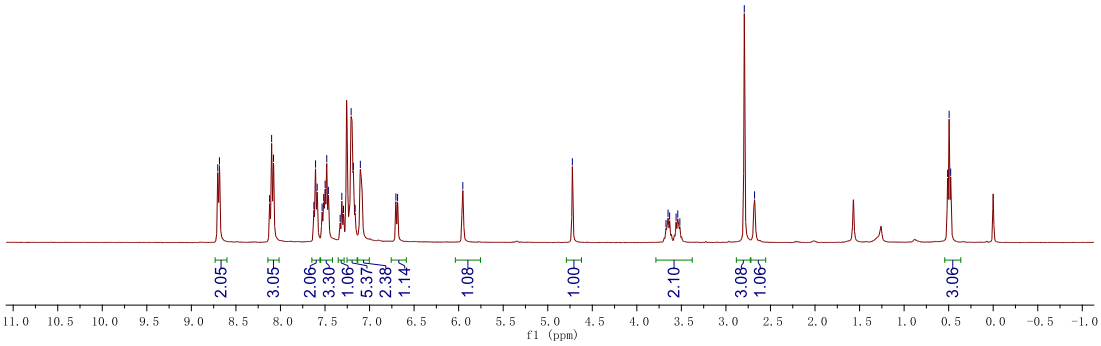
4aa

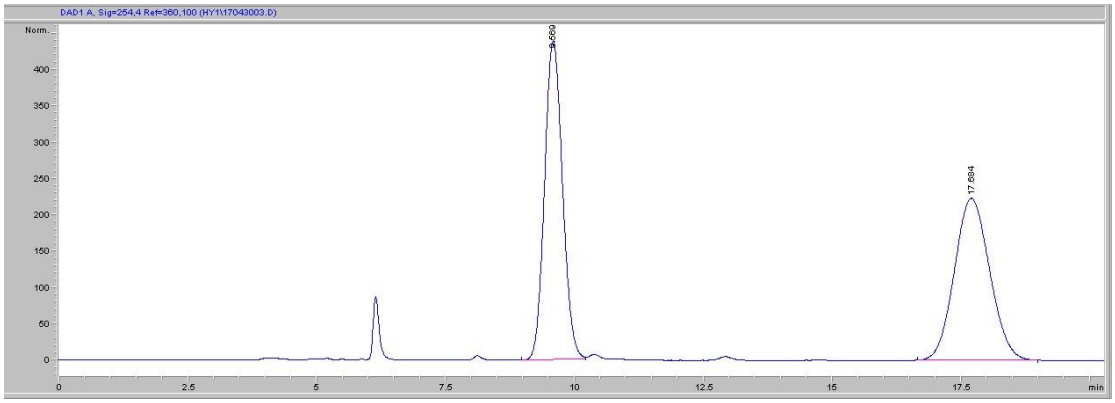


4aa

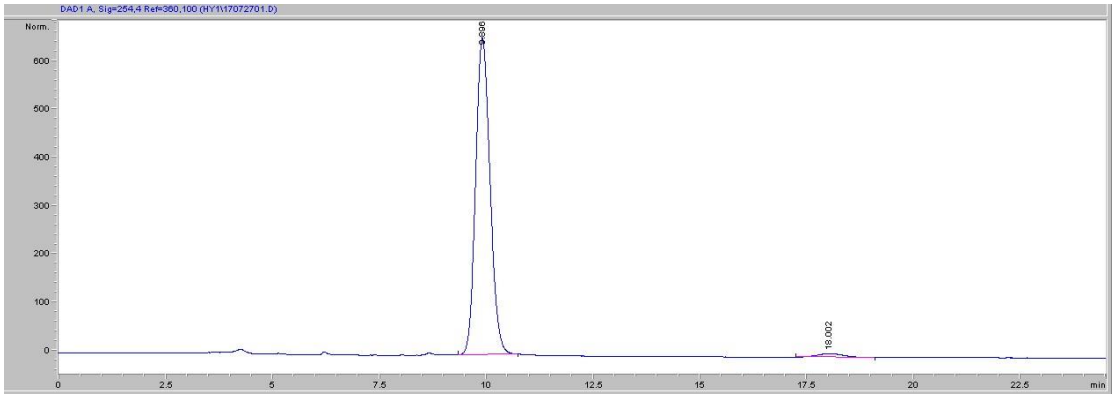
Prepared according to the procedure within 72 h as White solid (110.6 mg, 97% yield, dr > 20:1). mp 176.2 – 177.5 ºC; $[\alpha]_D^{19}$ = -385.22 (*c* 0.46, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 7.7 Hz, 2H), 8.05 – 8.11 (m, 3H), 7.58 – 7.65 (m, 2H), 7.56 – 7.42 (m, 3H), 7.31 (dd, *J* = 7.6 Hz, 1H), 7.25 – 7.14 (m, 5H), 7.13 – 7.00 (m, 2H), 6.69 (d, *J* = 7.5 Hz, 1H), 5.95 (s, 1H), 4.72 (s, 1H), 3.79 – 3.38 (m, 2H), 2.79 (s, 3H), 2.68 (s, 1H), 0.49 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.43, 175.08, 167.67, 155.14, 143.88, 138.18, 136.45, 130.73, 129.70, 129.59, 129.00, 128.90, 128.65, 128.16, 127.92, 127.64, 126.71, 125.67, 125.32, 123.43, 119.28, 107.42, 70.87, 69.21, 60.85, 60.41, 58.44, 26.02, 13.17; HRMS (ESI) m/z Calcd. for $C_{35}H_{31}N_4O_4^+$ ([M+H]$^+$) 571.2340, Found 571.2323; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ℃, 0.8 mL/min, t_{major} = 9.9 min, t_{minor} = 18.0 min).





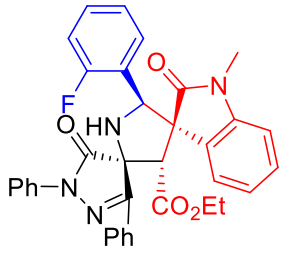


#	Time	Area	Height	Width	Area%	Symmetry
1	9.569	10640.8	439	0.3788	50.075	0.869
2	17.684	10608.7	222.9	0.7352	49.925	0.888



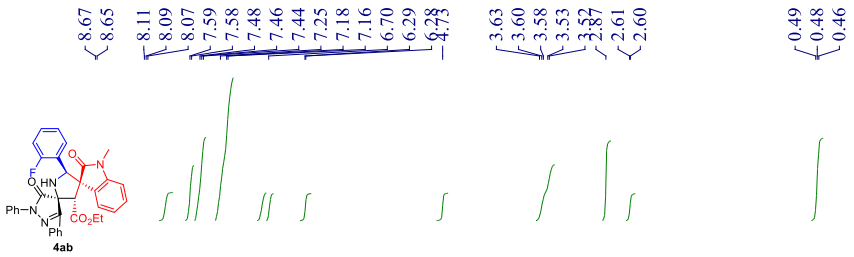
#	Time	Area	Height	Width	Area%	Symmetry
1	9.896	15444.4	658.2	0.3658	97.894	0.829
2	18.002	332.2	7.7	0.5161	2.106	0.805

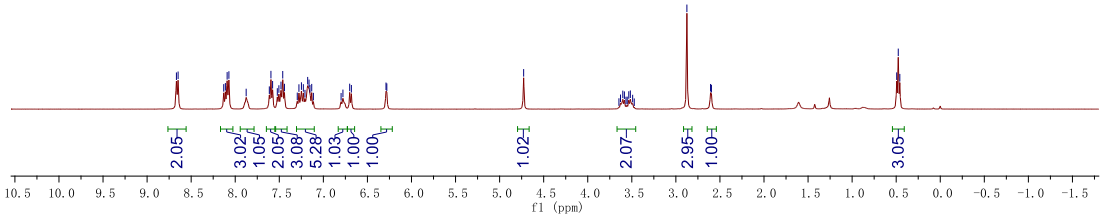
4ab

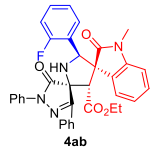


4ab

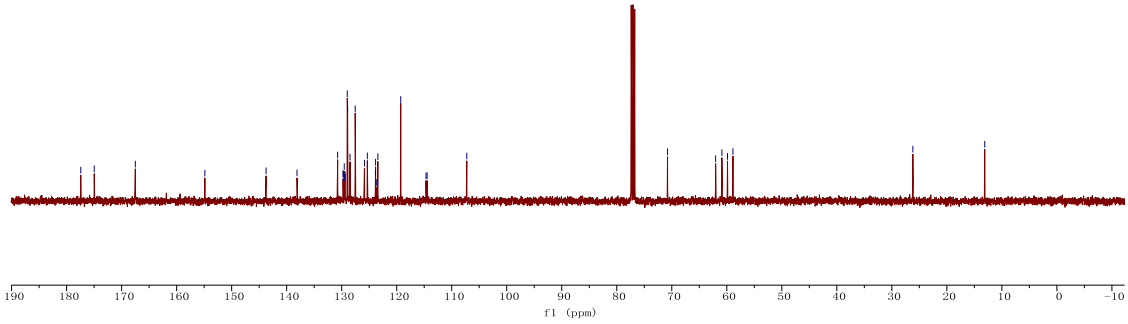
Prepared according to the procedure within 72 h as White solid (93.0 mg, 79% yield, dr > 20:1). mp 110.0 – 110.5 ºC; $[\alpha]_D^{18}$ = -341.31 (*c* 0.49, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 7.6 Hz, 2H), 8.16 – 8.15 (m, 3H), 7.82 – 7.91 (m, 1H), 7.70 – 7.50 (m, 2H), 7.54 – 7.43 (m, 3H), 7.29 – 7.09 (m, 5H), 6.74 - 6.82 (m, 1H), 6.69 (d, *J* = 7.6 Hz, 1H), 6.28 (d, *J* = 3.8 Hz, 1H), 4.73 (s, 1H), 3.46 - 3.66 (m, 2H), 2.87 (s, 3H), 2.60 (d, *J* = 3.8 Hz, 1H), 0.48 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -116.57; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.42, 174.97, 167.51, 154.87, 143.74, 138.12, 130.73, 129.73 （J = 3.6 Hz）, 129.53, 129.42 (J = 3.8 Hz), 129.41, 128.99, 128.92, 128.49, 127.54, 125.86, 125.34, 123.87, 123.84, 123.71, 123.42, 119.27, 114.57 (J = 21.5 Hz), 107.26, 70.77, 62.03, 60.89, 59.87, 58.88, 26.18, 13.12; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}FN_4O_4^+$ ($[M+H]^+$) 589.2246, Found 589.2234; Enantiomeric excess was determined to be 90% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ℃, 0.8 mL/min, t_{major} = 9.2 min, t_{minor} = 14.0 min).

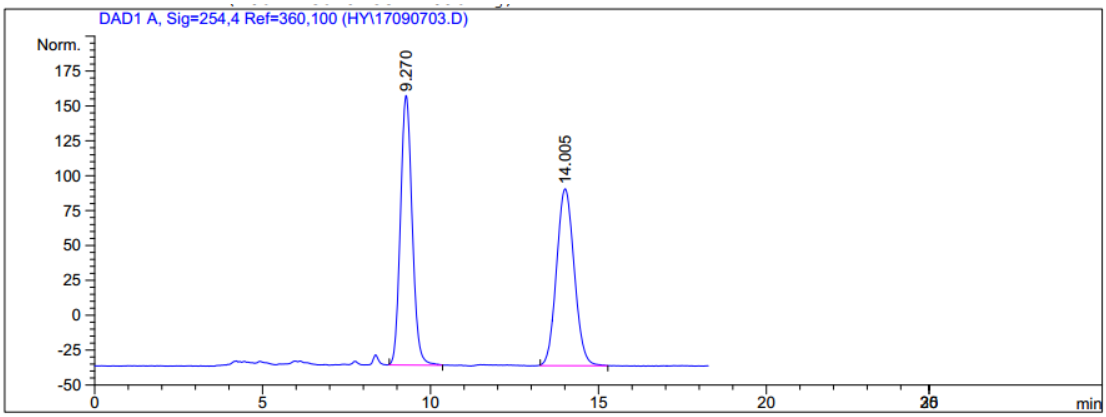




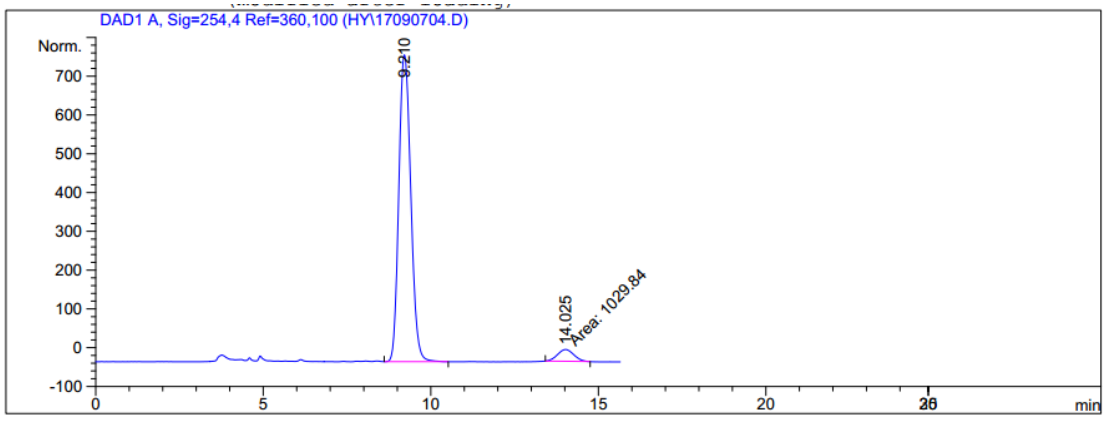


4ab



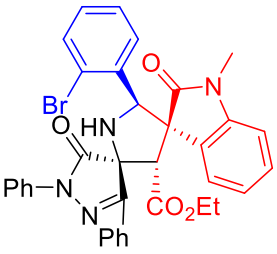


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.270	BB	0.3749	4685.85059	193.23424	50.2373
2	14.005	BB	0.5753	4641.58154	126.73827	49.7627



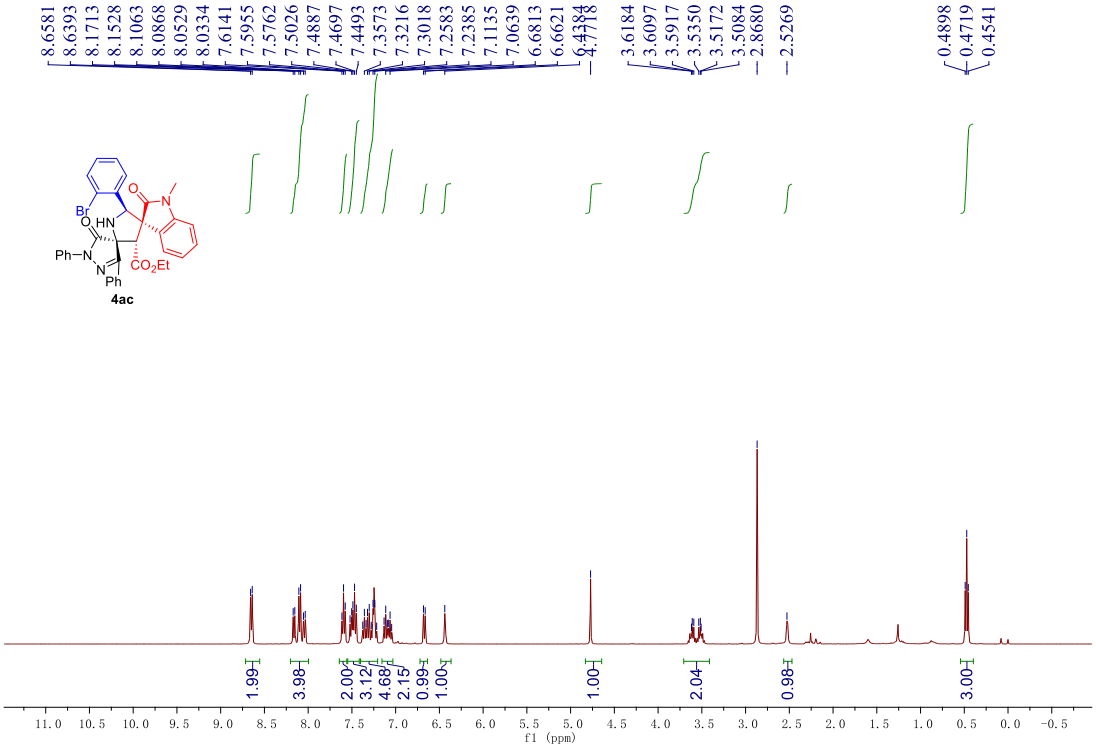
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.210	VP	0.3891	1.96098e4	791.26025	95.0104
2	14.025	MM	0.5644	1029.83936	30.41260	4.9896

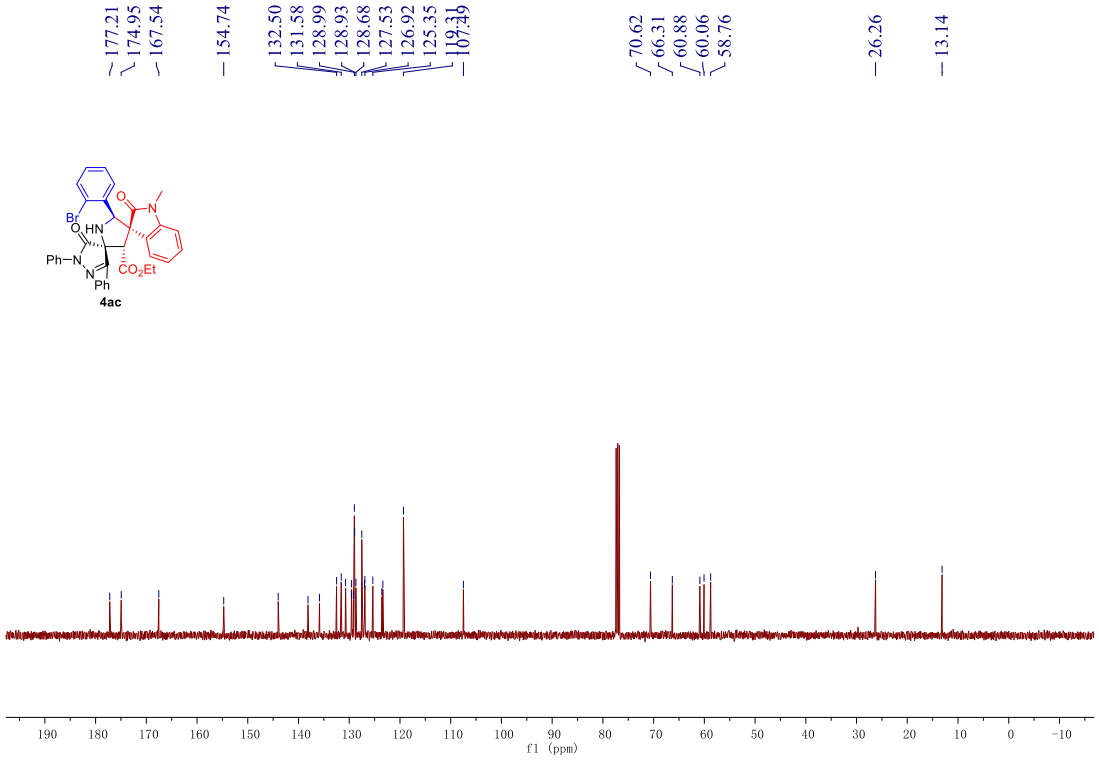
4ac

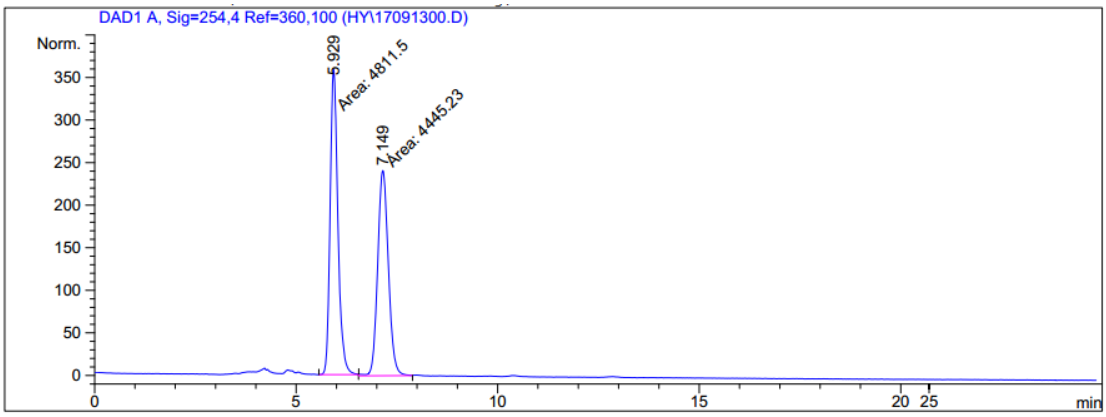


4ac

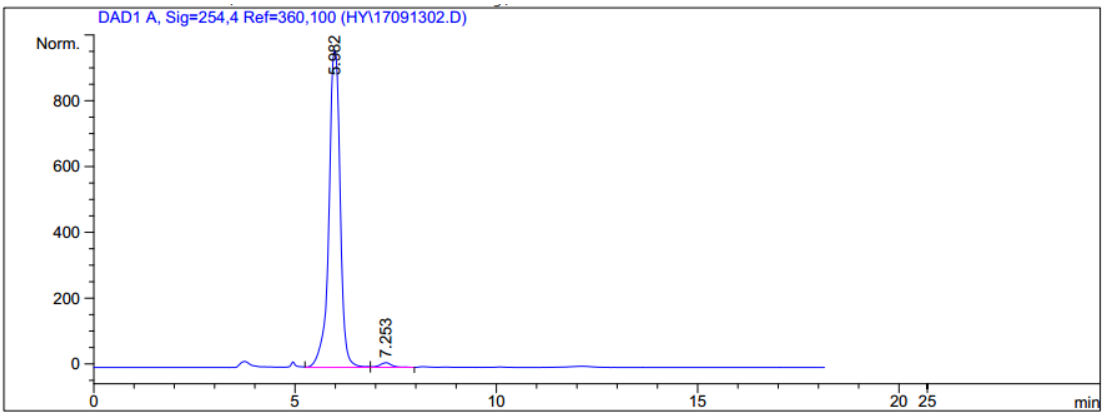
Prepared according to the procedure within 72 h as White solid (125.7 mg, 97% yield, dr > 20:1). mp 133.3 – 134.0 °C; $[\alpha]_D^{17}$ = -285.85 (*c* 0.83, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.5 Hz, 2H), 8.21 – 8.00 (m, 4H), 7.56 – 7.65 (m, 2H), 7.55 – 7.42 (m, 3H), 7.40 – 7.20 (m, 4H), 7.15 – 7.03 (m, 2H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.44 (d, *J* = 1.8 Hz, 1H), 4.77 (s, 1H), 3.73 – 3.42 (m, 2H), 2.87 (s, 3H), 2.52 (d, *J* = 2.2 Hz, 1H), 0.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.21, 174.95, 167.54, 154.74, 144.00, 138.13, 135.86, 132.50, 131.58, 130.72, 129.57, 129.54, 129.15, 128.99, 128.93, 128.68, 127.53, 127.00, 126.92, 125.35, 123.58, 123.38, 119.31, 107.49, 70.62, 66.31, 60.88, 60.06, 58.76, 26.26, 13.14; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}BrN_4O_4^+$ ($[M+H]^+$) 649.1445, Found 649.1436; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 6.0 min, t_{minor} = 7.3 min).





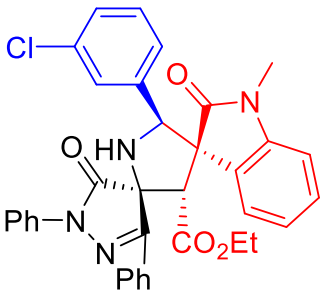


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.929	MM	0.2236	4811.49805	358.63751	51.9784
2	7.149	MM	0.3071	4445.23096	241.24675	48.0216



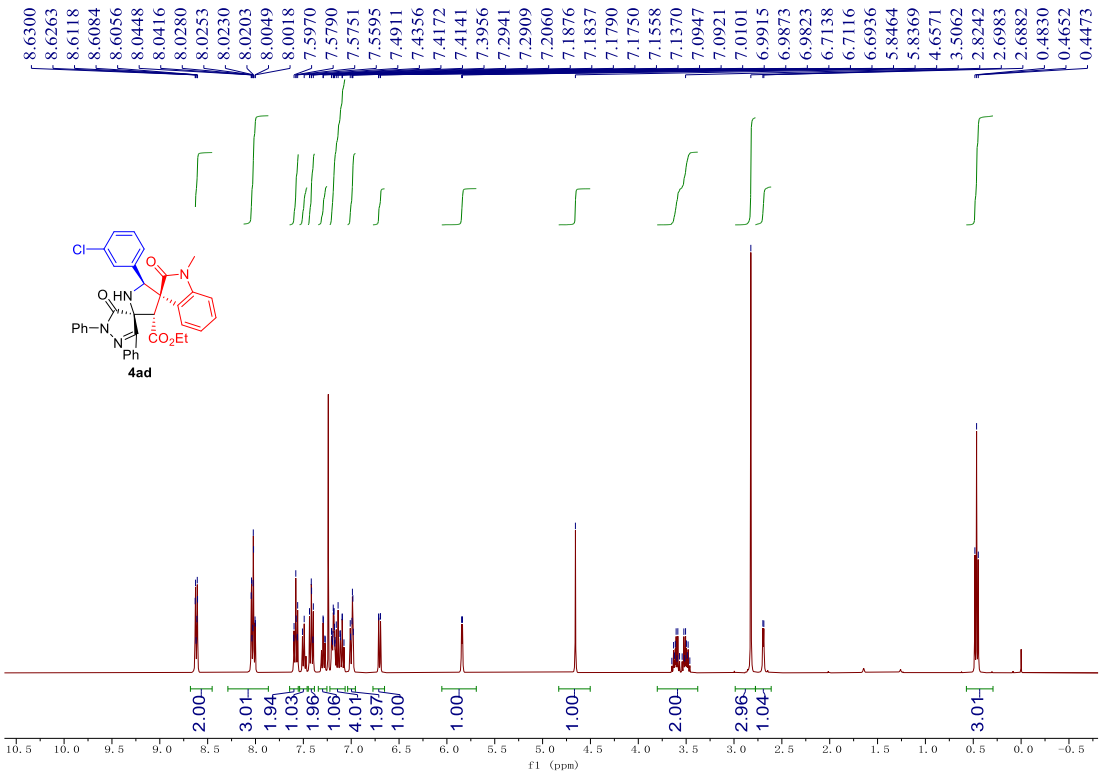
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.982	VV	0.3031	1.87300e4	962.18994	98.4062
2	7.253	VB	0.3152	303.34732	14.31570	1.5938

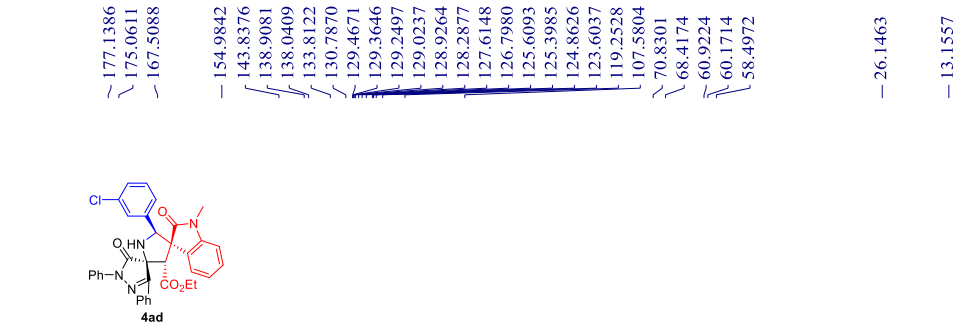
4ad



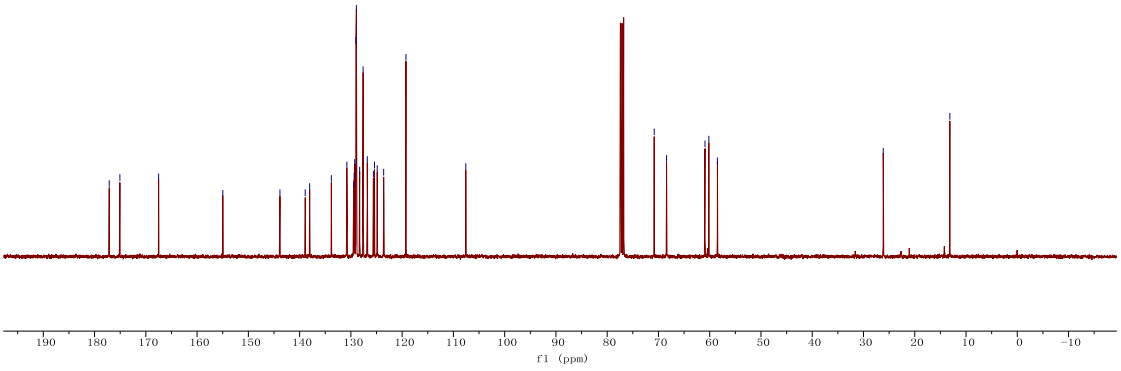
4ad

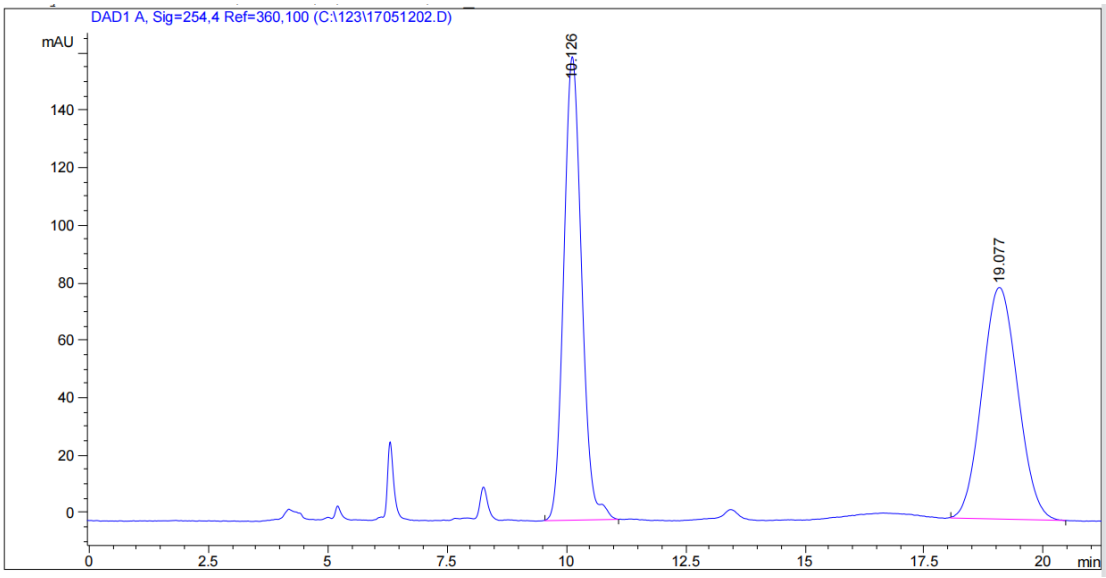
Prepared according to the procedure within 84 h as White solid (108.7 mg, 90% yield, dr > 20:1). mp 143.8 – 144.5 °C; $[\alpha]_D^{19}$ = -402.59 (*c* 0.42, CH_2Cl_2); ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.68 – 8.45 (m, 2H), 8.29 – 7.87 (m, 3H), 7.64 – 7.55 (m, 2H), 7.54 – 7.46 (m, 1H), 7.45 – 7.38 (m, 2H), 7.34 – 7.25 (m, 1H), 7.22 – 7.06 (m, 4H), 7.04 – 6.96 (m, 2H), 6.77 – 6.65 (m, 1H), 5.84 (d, *J* = 3.8 Hz, 1H), 4.66 (s, 1H), 3.56 (ddq, *J* = 43.0, 10.7, 7.1 Hz, 2H), 2.82 (s, 3H), 2.69 (d, *J* = 4.0 Hz, 1H), 0.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.14, 175.06, 167.51, 154.98, 143.84, 138.91, 138.04, 133.81, 130.79, 129.47, 129.36, 129.25, 129.02, 128.93, 128.29, 127.61, 126.80, 125.61, 125.40, 124.86, 123.60, 119.25, 107.58, 70.83, 68.42, 60.92, 60.17, 58.50, 26.15, 13.16; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}ClN_4O_4$ ($[M+H]^+$) 605.1950, Found 605.1947; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 11.6 min, t_{minor} = 20.4 min).



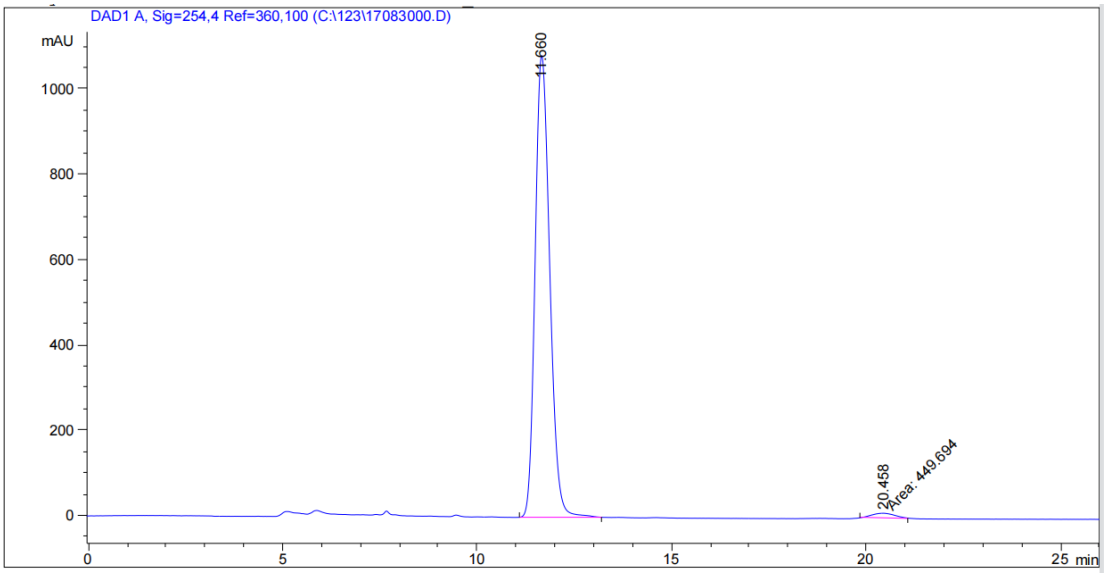


4ad



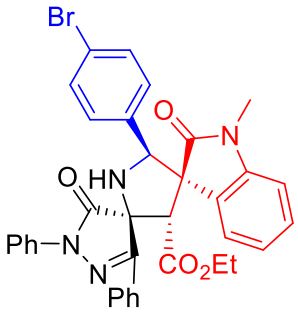


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.126	BB	0.4078	4198.37402	161.24039	49.9935
2	19.077	BB	0.7902	4199.46533	80.55557	50.0065



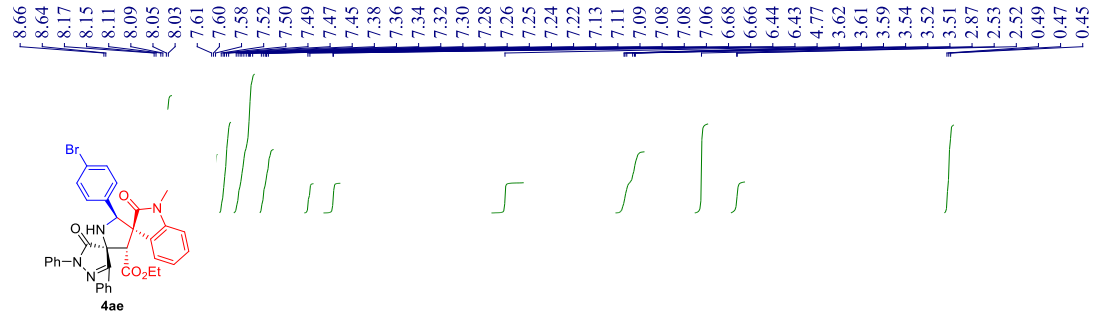
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.660	BB	0.4052	2.83101e4	1082.30286	98.4364
2	20.458	MM	0.6780	449.69357	11.05484	1.5636

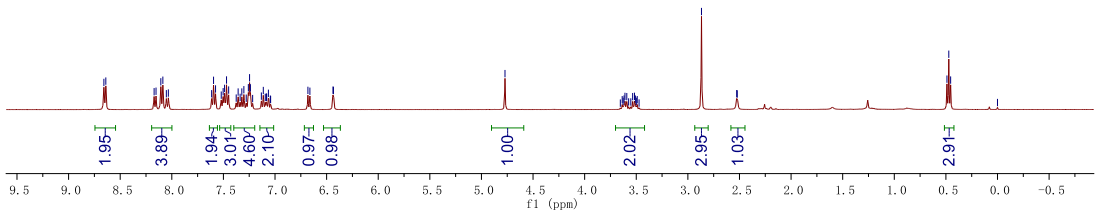
4ae

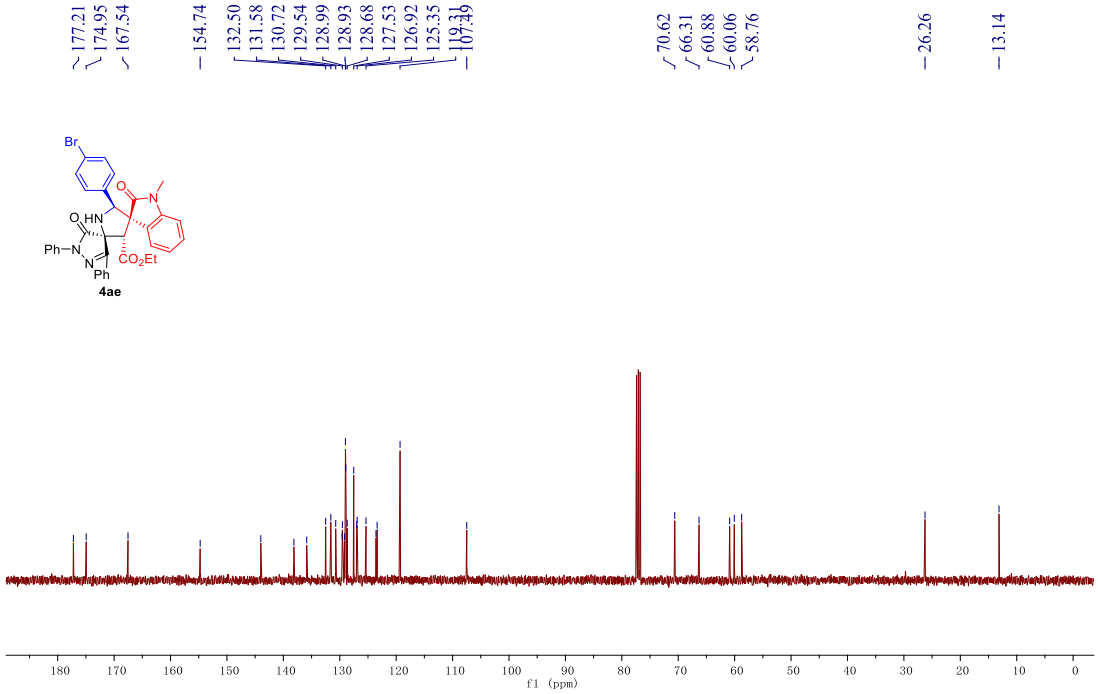


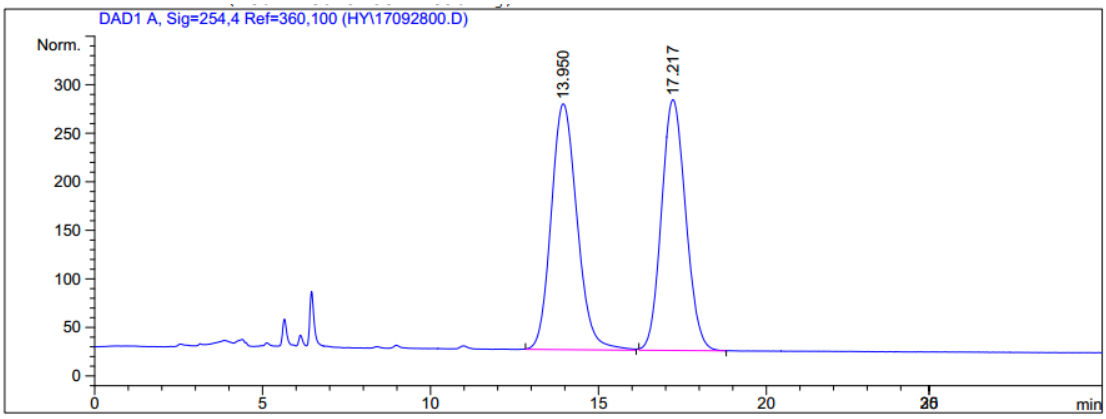
4ae

Prepared according to the procedure within 84 h as White solid (116.6 mg, 90% yield, dr > 20:1). mp 135.0 – 135.5 °C; $[\alpha]_D^{20}$ = -333.38 (*c* 0.71, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.5 Hz, 2H), 8.20 – 8.00 (m, 4H), 7.56 – 7.80 (m, 2H), 7.54 – 7.43 (m, 3H), 7.40 – 7.20 (m, 4H), 7.15 – 7.03 (m, 2H), 6.67 (d, *J* = 7.7 Hz, 1H), 6.44 (d, *J* = 1.8 Hz, 1H), 4.77 (s, 1H), 3.70 – 3.42 (m, 2H), 2.87 (s, 3H), 2.52 (d, *J* = 2.2 Hz, 1H), 0.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.21, 174.95, 167.54, 154.74, 144.00, 138.13, 135.86, 132.50, 131.58, 130.72, 129.57, 129.54, 129.15, 128.99, 128.93, 128.68, 127.53, 127.00, 126.92, 125.35, 123.58, 123.38, 119.31, 107.49, 70.62, 66.31, 60.88, 60.06, 58.76, 26.26, 13.14; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}BrN_4O_4^+$ ($[M+H]^+$) 649.1445, Found 649.1438; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 13.8 min, t_{minor} = 17.1 min).

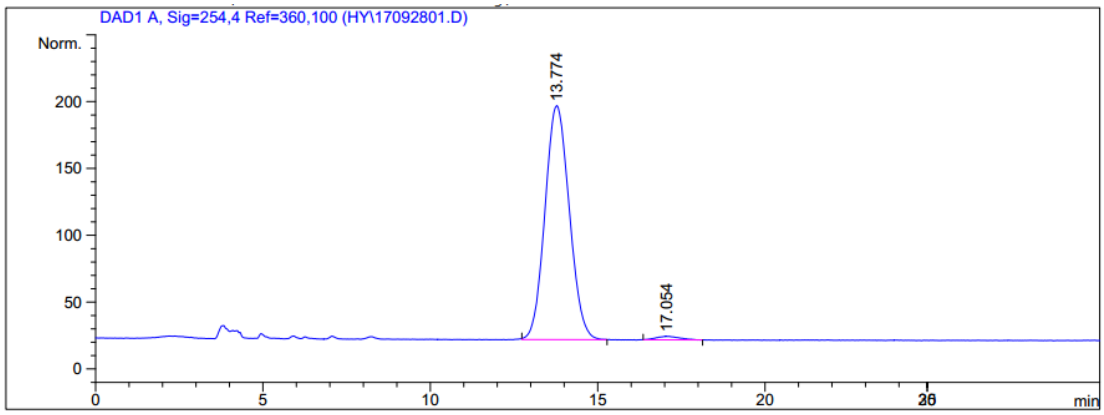

8.66
8.64
8.17
8.15
8.11
8.09
8.05
8.03
7.61
7.60
7.58
7.52
7.50
7.49
7.47
7.45
7.38
7.36
7.34
7.32
7.30
7.28
7.26
7.25
7.24
7.22
7.13
7.11
7.09
7.08
7.08
7.06
6.68
6.66
6.44
6.43
4.77
3.62
3.61
3.59
3.54
3.52
3.51
2.87
2.53
2.52
0.49
0.47
0.45
Br
O
N
O
HN
Ph–N
N
Ph
CO2Et
4ae


1.95
3.89
1.94
3.01
4.60
2.10
0.97
0.98
1.00
2.02
2.95
1.03
2.91
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
f1 (ppm)


177.21
174.95
167.54
154.74
132.50
131.58
130.72
129.54
128.99
128.93
128.68
127.53
126.92
125.35
119.31
107.39
70.62
66.31
60.88
60.06
58.76
26.26
13.14
Br
O
N
O
HN
Ph–N
N
Ph
CO2Et
4ae
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

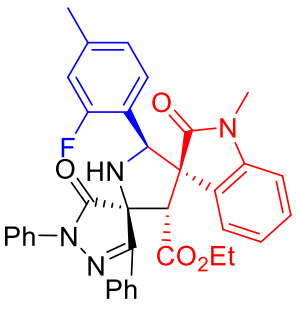


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.950	BB	0.8378	1.35765e4	253.11127	51.1867
2	17.217	BB	0.7808	1.29470e4	258.30658	48.8133



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	13.774	BB	0.7935	8843.50977	175.01552	98.5319
2	17.054	BB	0.6200	131.76395	2.63205	1.4681

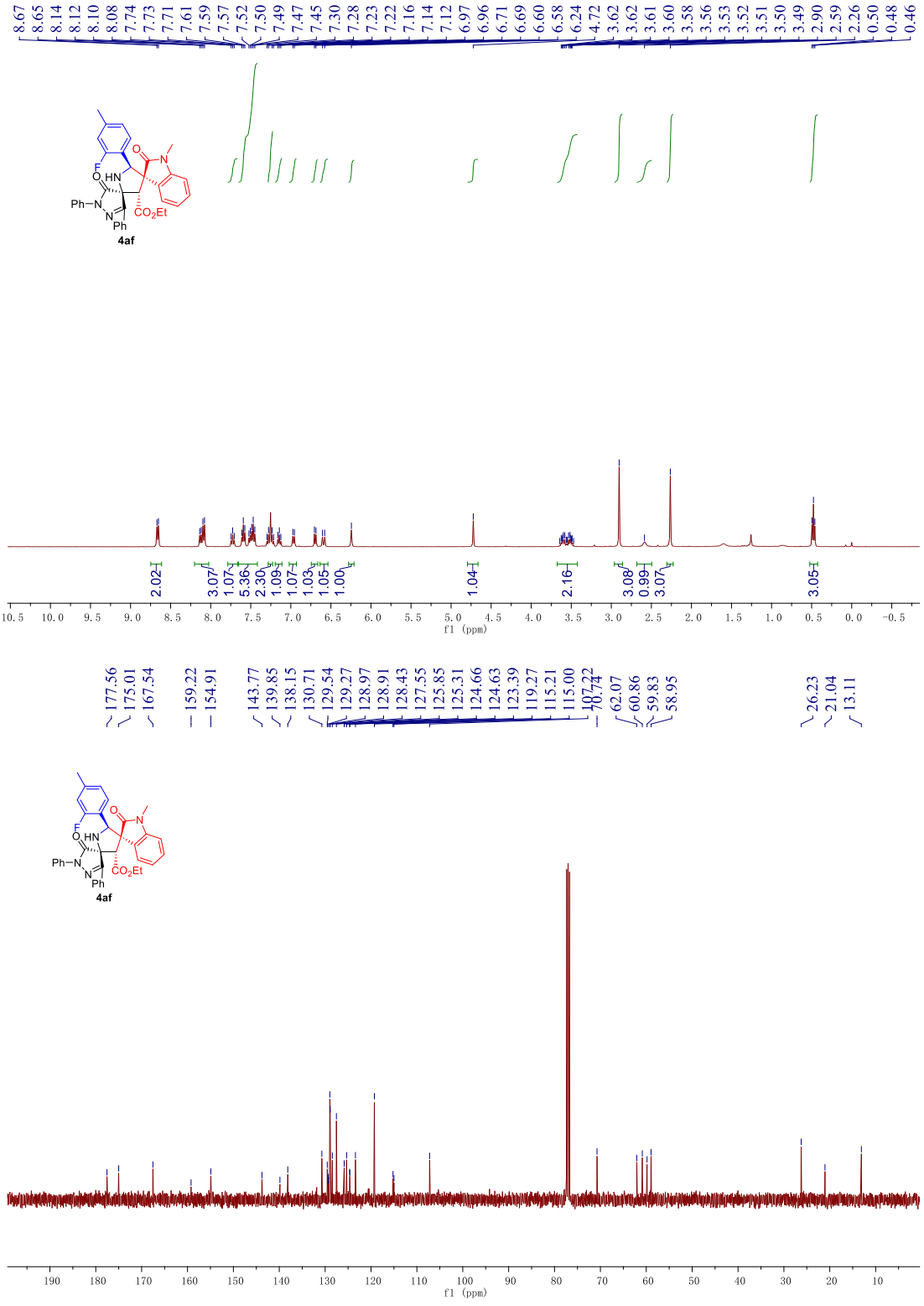
4af

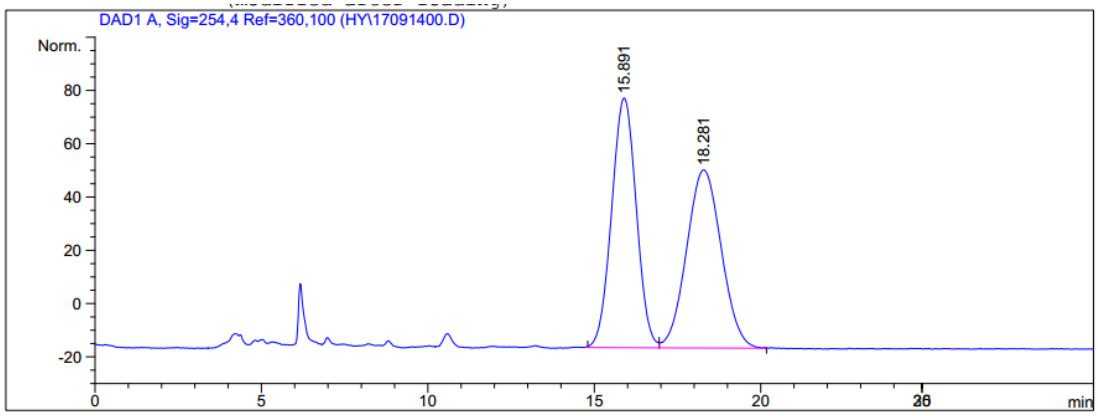


4af

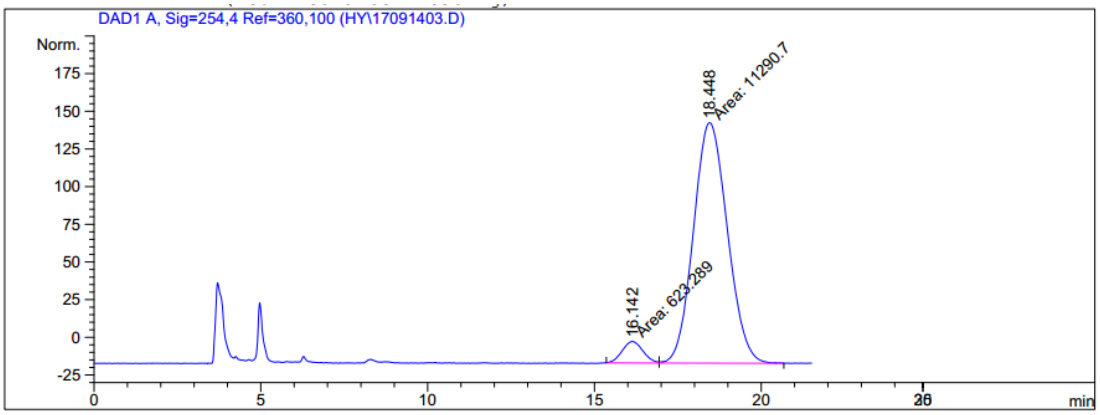
Prepared according to the procedure within 94 h as White solid (108.5 mg, 90% yield, dr > 20:1). mp 126.3 – 126.7 ºC; $[\alpha]_D^{20}$ = -328.93 (*c* 0.76, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 7.6 Hz, 2H), 8.03 – 8.18 (m, 3H), 7.73 (dd, *J* = 7.7 Hz, 1H), 7.40 – 7.64 (m, 5H), 7.21 – 7.30(m, 2H), 7.14 (m, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 7.7 Hz, 1H), 6.59 (d, *J* = 11.1 Hz, 1H), 6.24 (s, 1H), 4.72 (s, 1H), 3.67 – 3.42 (m, 2H), 2.90 (s, 3H), 2.59 (s, 1H), 2.26 (s, 3H), 0.48 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (470 MHz, $CDCl_3$) δ -117.64; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.56, 175.01, 167.54, 159.22, 154.91, 143.77, 139.85, 138.15, 130.71, 129.54, 129.28 (J = 2.8 Hz), 128.97, 128.91, 128.43, 127.55,

125.85, 125.31, 124.64 (J = 2.6 Hz), 123.39, 119.27, 115.10 (J = 21.1 Hz), 107.22, 70.74, 62.07, 60.86, 59.83, 58.95, 26.23, 21.04, 13.11; HRMS (ESI) m/z Calcd. for $C_{36}H_{32}FN_4O_4^+$ ($[M+H]^+$) 603.2402, Found 603.2390; Enantiomeric excess was determined to be 90 % (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 18.4 min, t_{minor} = 16.1 min).



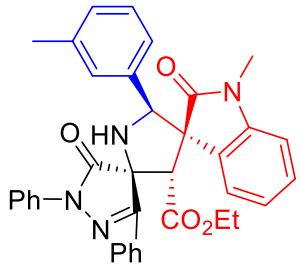


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.891	BV	0.8036	4817.09082	93.72789	49.8363
2	18.281	VB	1.0983	4848.74561	66.83953	50.1637



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.142	MM	0.7214	623.28943	14.39915	5.2316
2	18.448	MM	1.1794	1.12907e4	159.55942	94.7684

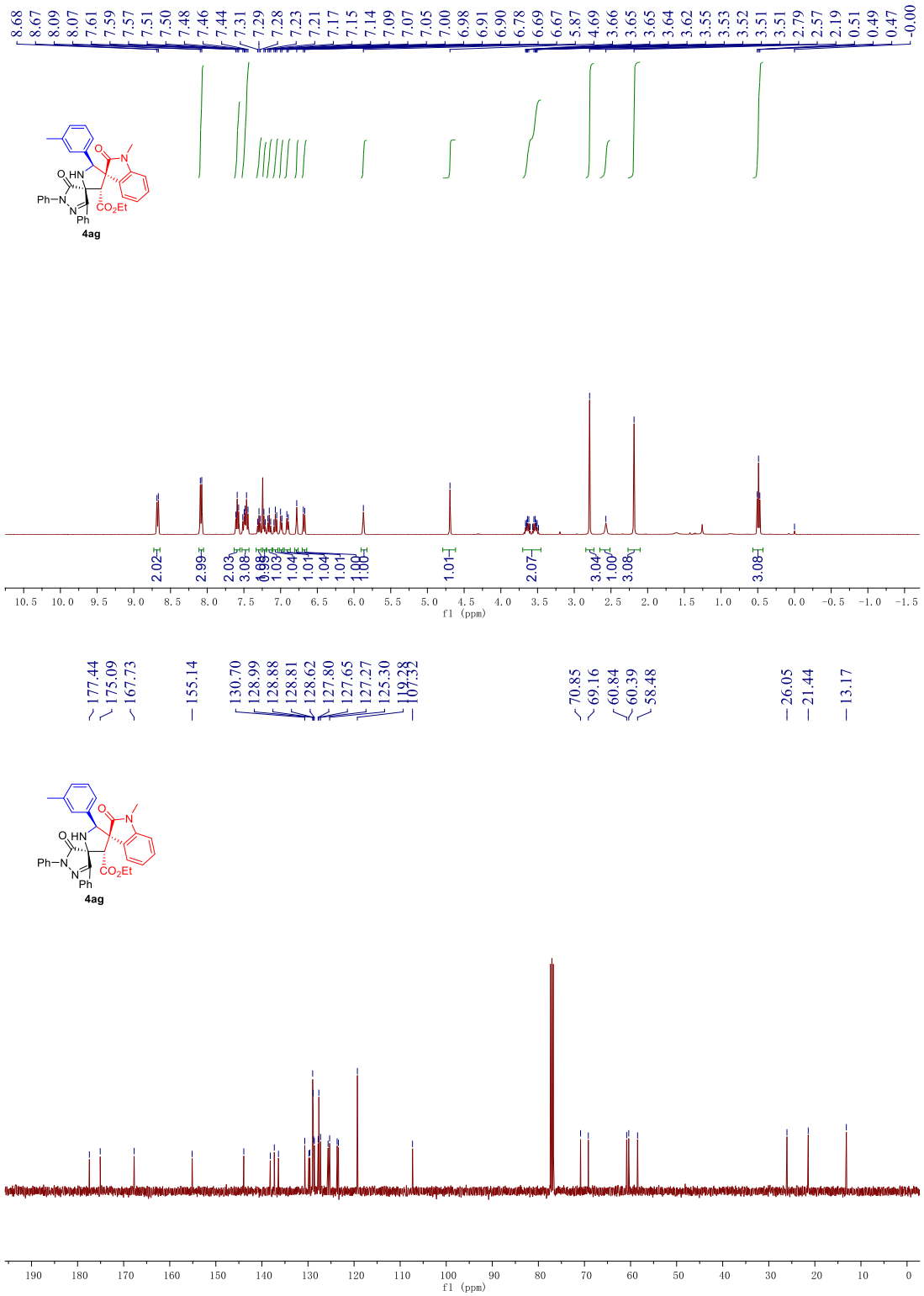
4ag

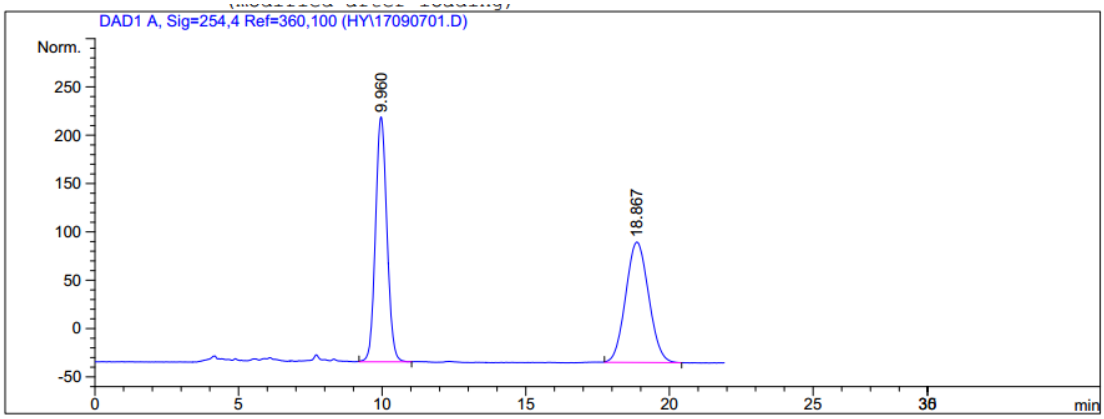


4ag

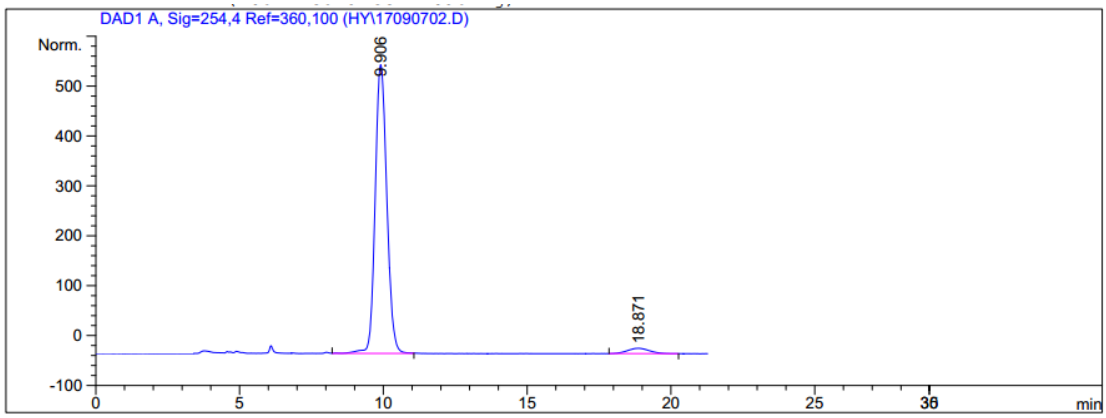
Prepared according to the procedure within 108 h as White solid (113.4 mg, 97% yield, dr > 20:1). mp 130.2 – 131.1 °C; $[\alpha]_D^{19}$ = -303.20 (*c* 0.44, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 7.6 Hz, 2H), 8.08 (d, *J* = 7.7 Hz, 3H), 7.70 – 7.59 (m, 2H), 7.53 – 7.43 (m, 3H), 7.29 (dd, *J* = 7.5 Hz, 1H), 7.22 (d, *J* = 7.4 Hz, 1H), 7.15 (dd, *J* = 7.5 Hz, 1H), 7.07 (dd, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.78 (s, 1H), 6.68 (d, *J* = 7.7 Hz, 1H), 5.87 (s, 1H), 4.69 (s, 1H), 3.70 – 3.45 (m, 2H), 2.79 (s, 3H), 2.57 (s, 1H), 2.19 (s, 3H), 0.49 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.44, 175.09, 167.73, 155.14, 143.93, 138.18,

137.31, 136.40, 130.70, 129.82, 129.59, 128.99, 128.88, 128.81, 128.62, 127.80, 127.65, 127.27, 125.64, 125.30, 123.68, 123.40, 119.28, 107.32, 70.85, 69.16, 60.84, 60.39, 58.48, 26.05, 21.44, 13.17; HRMS (ESI) m/z Calcd. for $C_{36}H_{33}N_4O_4^+$ ([M+H]$^+$) 585.2496, Found 585.2506; Enantiomeric excess was determined to be 93% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 9.9 min, t_{minor} = 18.9 min).



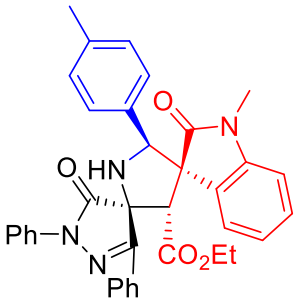


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.960	BB	0.4303	6999.81592	253.41316	50.2397
2	18.867	BB	0.8731	6933.03271	124.60486	49.7603



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.906	VB	0.4406	1.62986e4	578.75165	96.6105
2	18.871	PB	0.8114	571.81323	10.77078	3.3895

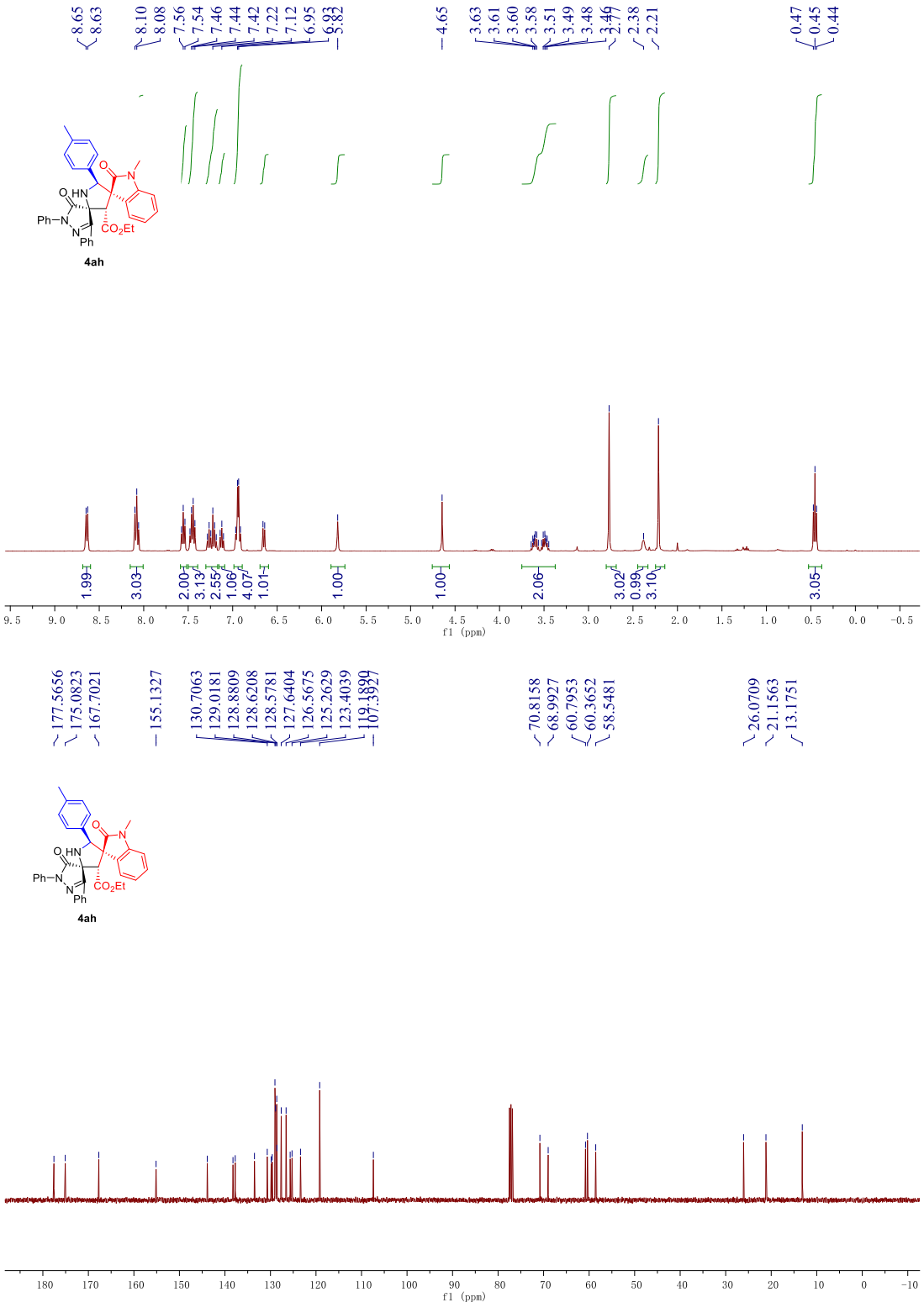
4ah

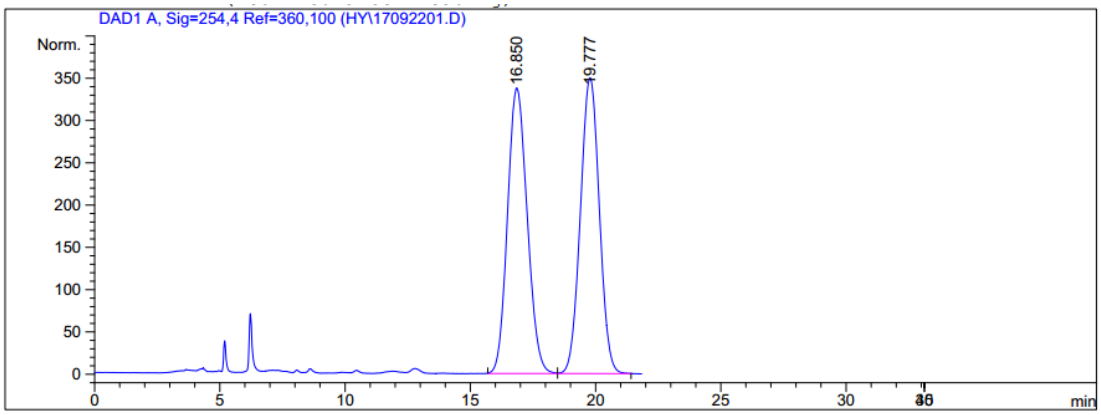


4ah

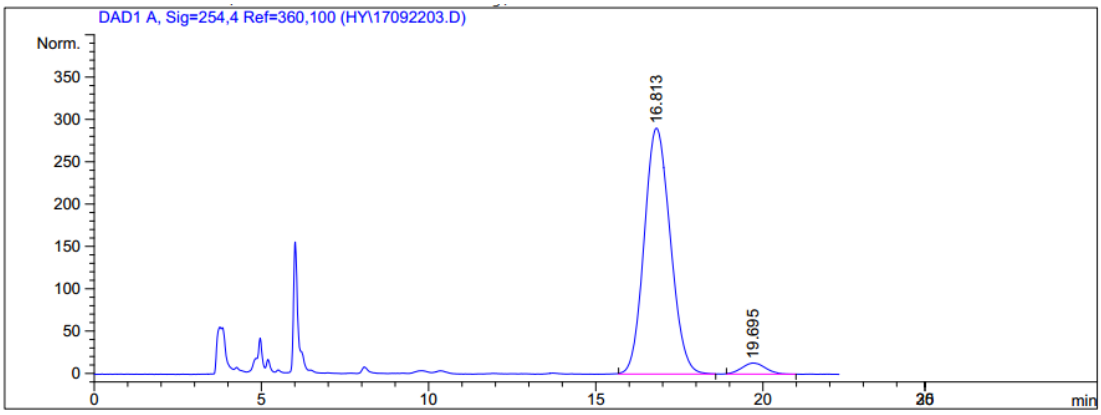
Prepared according to the procedure within 96 h as White solid (114.5 mg, 98% yield, dr > 20:1). mp 126.3 – 127.0 °C; $[\alpha]_D^{20}$ = -281.98 (*c* 1.09, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 7.5 Hz, 2H), 8.12 – 8.05 (m, 3H), 7.60 – 7.50 (m, 2H), 7.45 (dd, *J* = 14.8, 7.3 Hz, 3H), 7.30 – 7.17 (m, 2H), 7.12 (dd, *J* = 7.5 Hz, 1H), 6.94 (q, *J* = 8.2 Hz, 4H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.82 (s, 1H), 4.65 (s, 1H), 3.75 – 3.37 (m, 2H), 2.77 (s, 3H), 2.38 (s, 1H), 2.21 (s, 3H), 0.45 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.57, 175.08, 167.70, 155.13, 143.88, 138.23, 137.74, 133.52, 130.71,

129.84, 129.60, 129.02, 128.88, 128.62, 128.58, 127.64, 126.57, 125.67, 125.26, 123.40, 119.19, 107.39, 70.82, 68.99, 60.80, 60.37, 58.55, 26.07, 21.16, 13.18; HRMS (ESI) m/z Calcd. for $C_{36}H_{33}N_4O_4^+$ ($[M+H]^+$) 585.2496, Found 585.2487; Enantiomeric excess was determined to be 92% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 16.8 min, t_{minor} = 19.7 min).



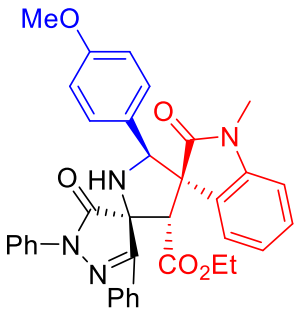


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.850	BV	0.8485	1.84287e4	337.79550	50.1113
2	19.777	VB	0.8279	1.83468e4	349.82687	49.8887



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.813	BB	0.8401	1.57387e4	290.47037	96.0302
2	19.695	BB	0.7483	650.62445	13.08059	3.9698

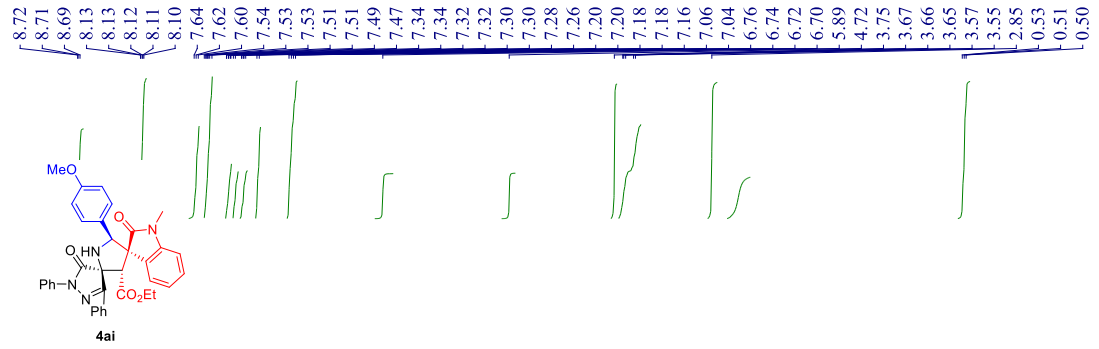
4ai



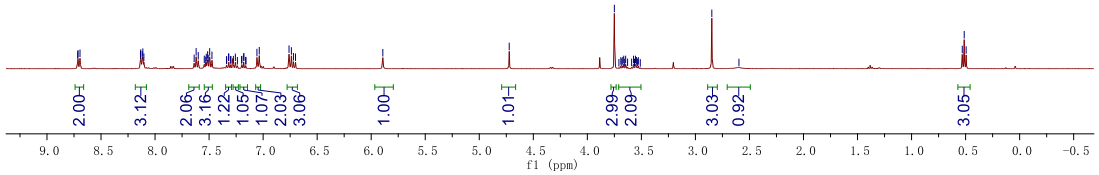
4ai

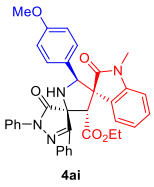
Prepared according to the procedure within 84 h as White solid (91.2 mg, 76% yield, dr > 20:1). mp 122.2 – 123.5 °C; $[\alpha]_D^{19}$ = -221.5 (*c* 0.53, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.74 – 8.66 (m, 2H), 8.18 – 8.08 (m, 3H), 7.70 – 7.58 (m, 2H), 7.54 – 7.47 (m, 3H), 7.32 (td, *J* = 7.7, 0.9 Hz, 1H), 7.26 (dd, *J* = 7.4 Hz, 1H), 7.18 (td, *J* = 7.6, 0.7 Hz, 1H), 7.05 (d, *J* = 8.6 Hz, 2H), 6.69 – 6.78 (m, 3H), 5.89 (s, 1H), 4.72 (s, 1H), 3.75 (s, 3H), 3.71 – 3.50 (m, 2H), 2.85 (s, 3H), 2.60 (s, 1H), 0.51 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.61, 175.09, 167.73, 159.42, 155.15, 143.83, 138.19, 130.71, 129.78, 129.61, 128.99, 128.87, 128.58, 128.41, 127.98, 127.64, 125.62, 125.29, 123.39, 119.24, 113.26, 107.40, 70.77, 68.90, 60.82, 60.36, 58.39, 55.13, 26.12,

13.17; HRMS (ESI) m/z Calcd. for $C_{36}H_{33}N_4O_5^+$ ([M+H]$^+$) 601.2445, Found 601.2441; Enantiomeric excess was determined to be 81% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 29.4 min, t_{minor} = 25.4 min).

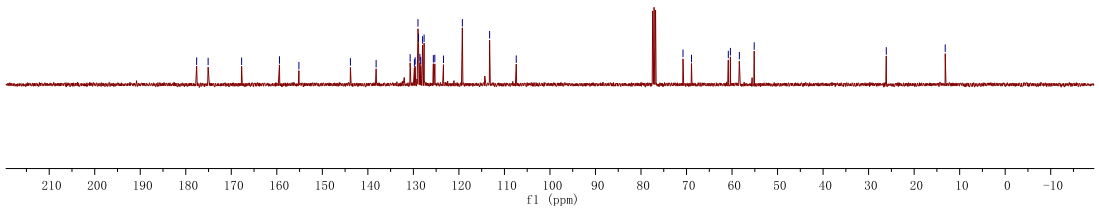


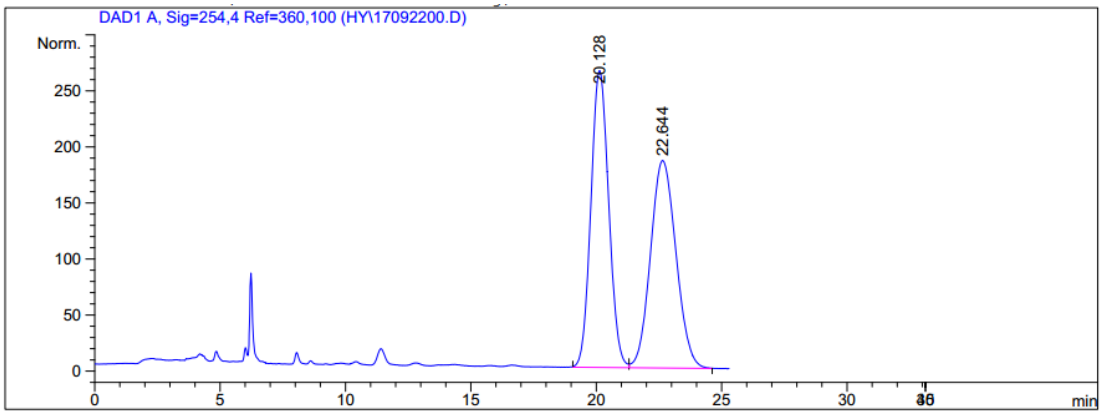
4ai



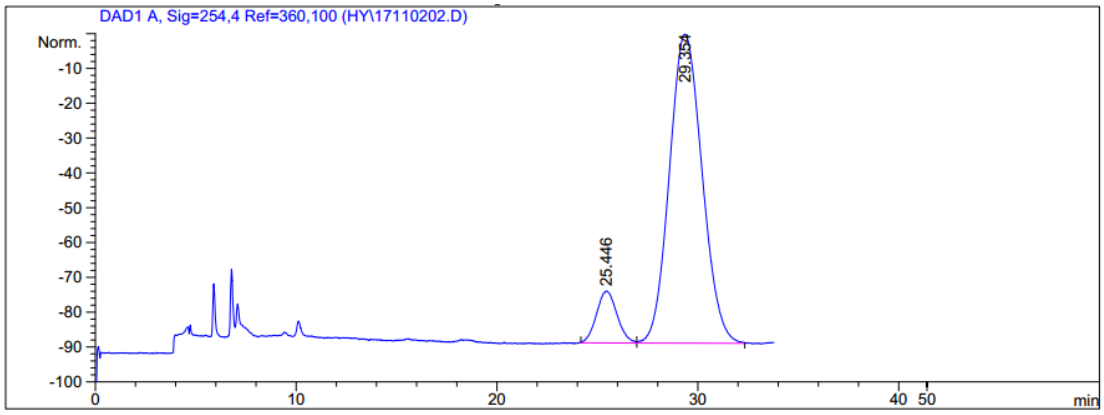


4ai



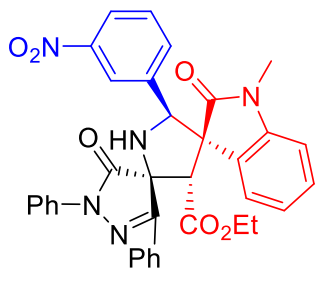


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.128	BV	0.7713	1.30542e4	264.73181	49.9903
2	22.644	VB	1.0988	1.30593e4	185.17702	50.0097



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	25.446	BV	0.8697	1058.59338	14.88562	9.5434
2	29.354	VB	1.5112	1.00338e4	88.73840	90.4566

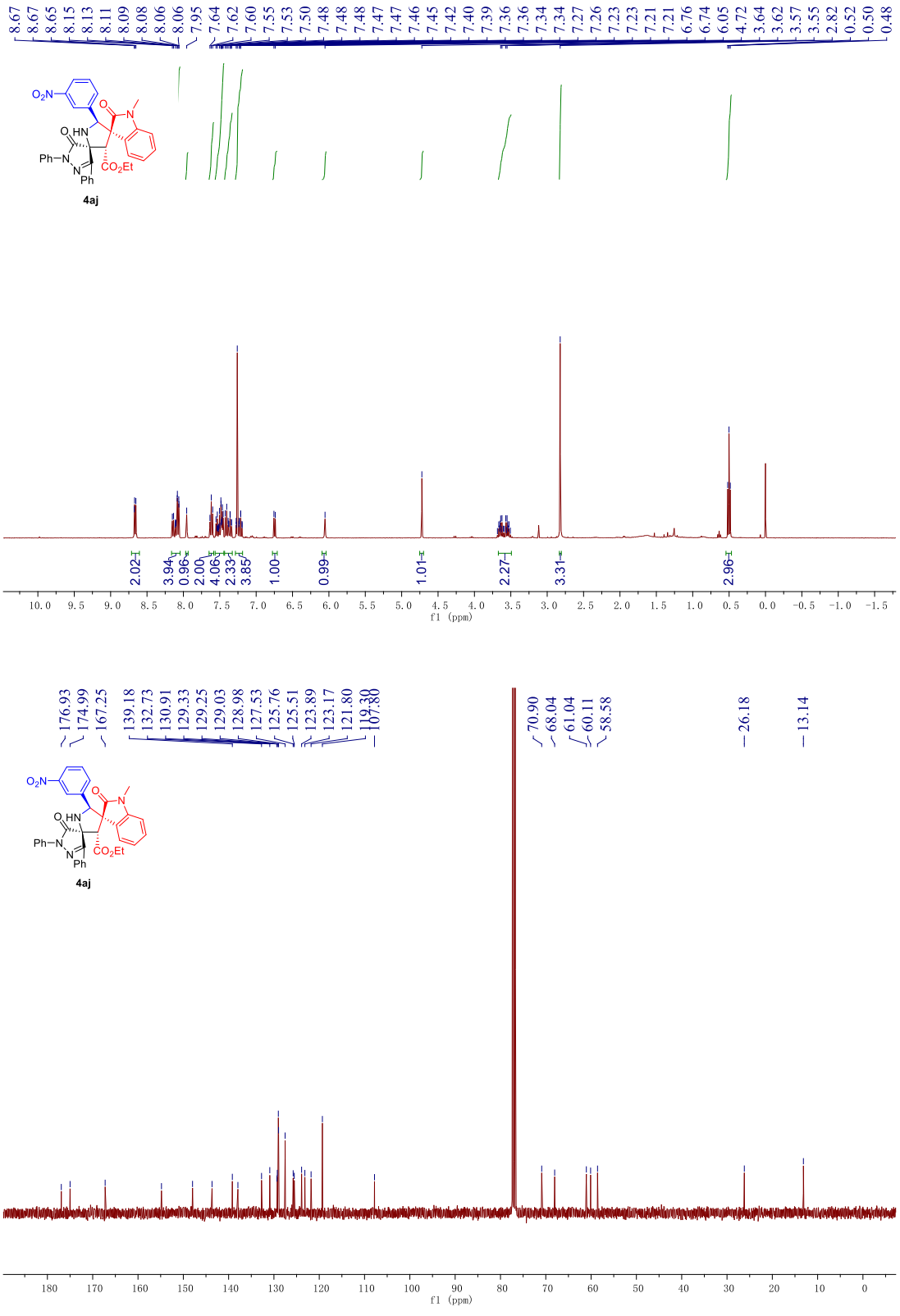
4aj

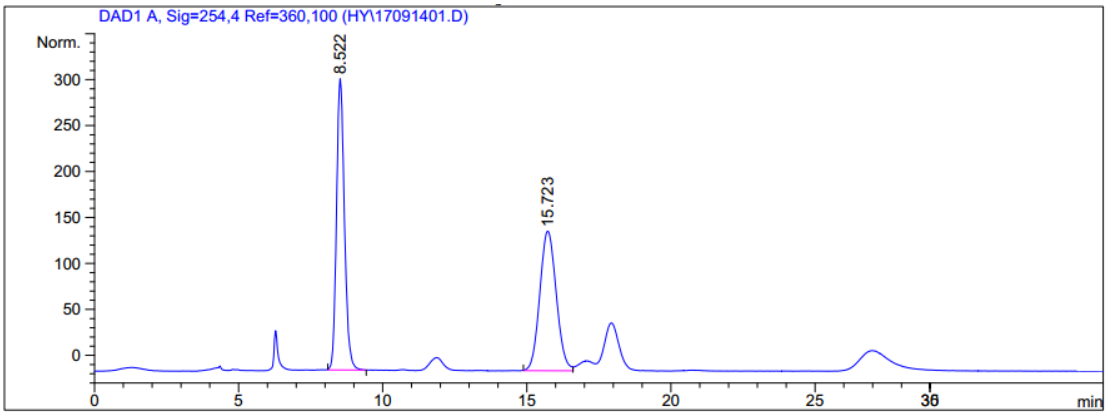


4aj

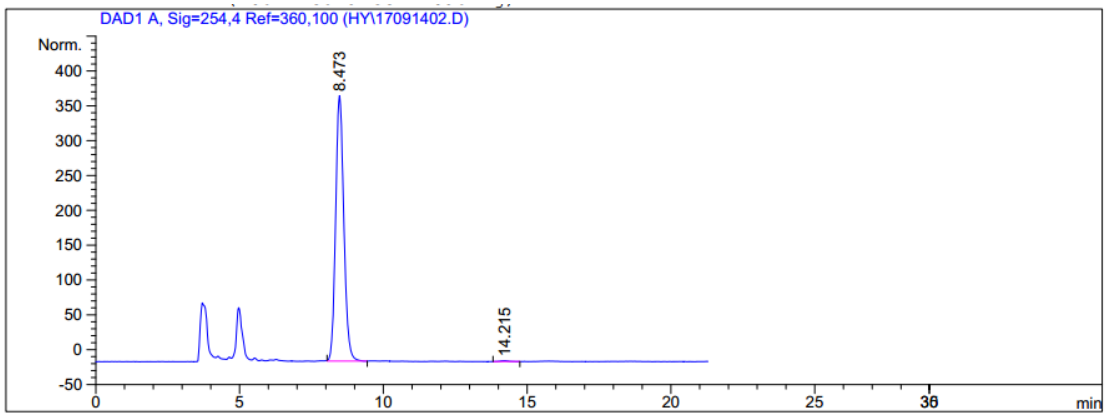
Prepared according to the procedure within 72 h as White solid (81.2 mg, 66% yield, dr > 20:1). mp 192.6 – 193.5 °C; $[\alpha]_D^{20}$ = -340.00 (*c* 0.29, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 – 8.60 (m, 2H), 8.17 – 8.05 (m, 1H), 7.97 – 7.94 (m, 1H), 7.65 – 7.58 (m, 2H), 7.56 – 7.44 (m, 4H), 7.43 – 7.33 (m, 2H), 7.28 – 7.19 (m, 3H), 6.75 (d, *J* = 7.6 Hz, 1H), 6.05 (s, 1H), 4.72 (s, 1H), 3.67 – 3.49 (m, 2H), 2.82 (s, 3H), 0.50 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.93, 174.99, 167.25, 154.82, 147.96, 143.66, 139.18, 137.95, 132.73, 130.91, 129.33, 129.25, 129.03, 128.98, 127.53, 125.76, 125.51, 123.89, 123.17, 121.80, 119.30, 107.80, 70.90, 68.04, 61.04, 60.11, 58.58, 26.18, 13.14; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}N_5O_6^+$ ([M+H]$^+$) 616.2191, Found 616.2185;

Enantiomeric excess was determined to be 99% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 8.5 min, t_{minor} = 14.2 min).



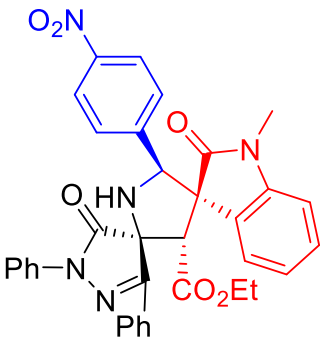


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.522	BB	0.2990	6057.80615	316.97592	50.1204
2	15.723	BV	0.6190	6028.70068	151.89487	49.8796



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.473	BP	0.3068	7535.39404	380.92163	99.6496
2	14.215	PP	0.3106	26.50032	1.23373	0.3504

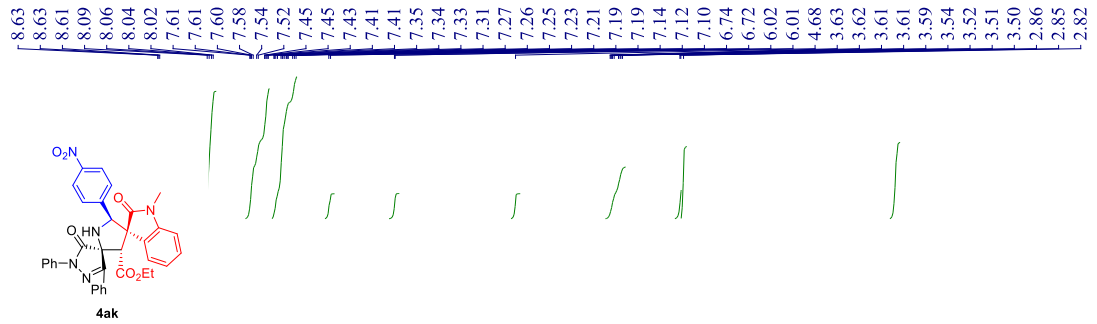
4ak

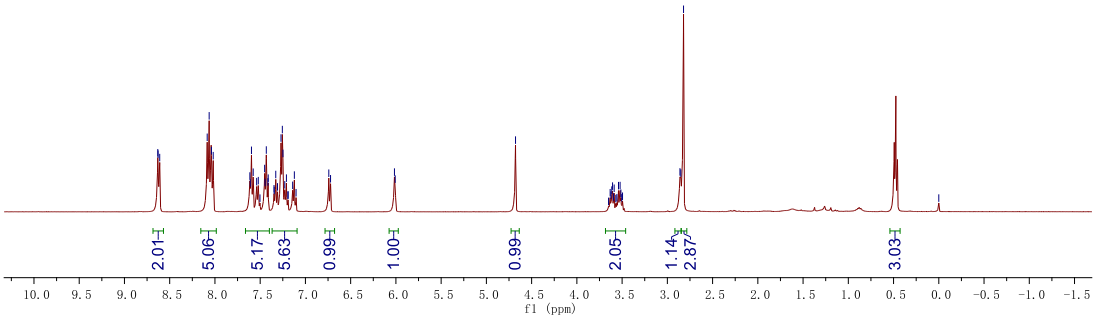


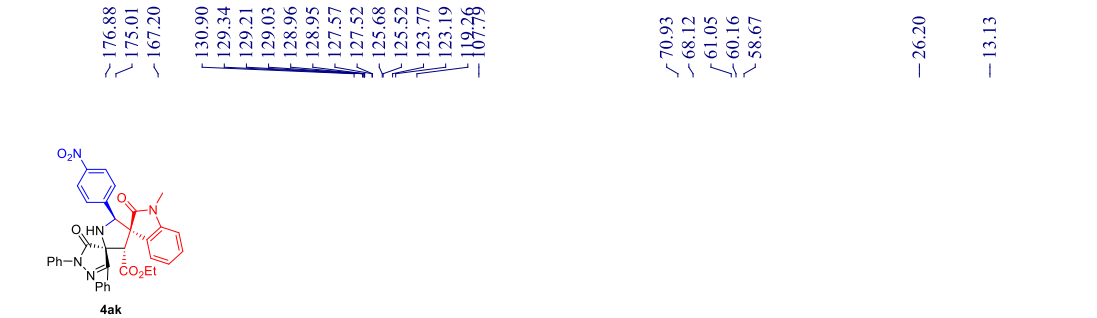
4ak

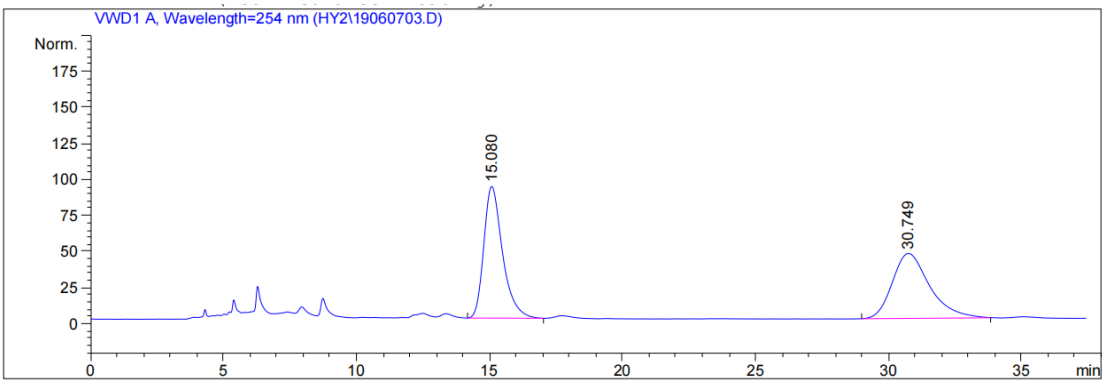
Prepared according to the procedure within 94 h as White solid (107.0 mg, 87% yield, dr > 20:1). mp 144.2 – 144.9 °C; $[\alpha]_D^{17}$ = -376.20 (*c* 0.84, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.68 – 8.57 (m, 2H), 8.15 – 8.00 (m, 5H), 7.66 – 7.40 (m, 5H), 7.37 – 7.09 (m, 5H), 6.73 (d, *J* = 7.7 Hz, 1H), 6.01 (d, *J* = 3.3 Hz, 1H), 4.68 (s, 1H), 3.68 – 3.46 (m, 2H), 2.86 (d, *J* = 3.9 Hz, 1H), 2.82 (s, 3H), 0.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.88, 175.01, 167.20, 154.78, 147.77, 144.27, 143.75, 137.89, 130.90, 129.34, 129.21, 129.03, 128.96, 128.95, 127.57, 127.52, 125.68, 125.52, 123.77, 123.19, 119.26, 107.79, 70.93, 68.12, 61.05,

60.16, 58.67, 26.20, 13.13; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}N_5O_6^+$ ($[M+H]^+$) 616.2191, Found 616.2181; Enantiomeric excess was determined to be 99% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 15.9 min, t_{minor} = 31.7 min).

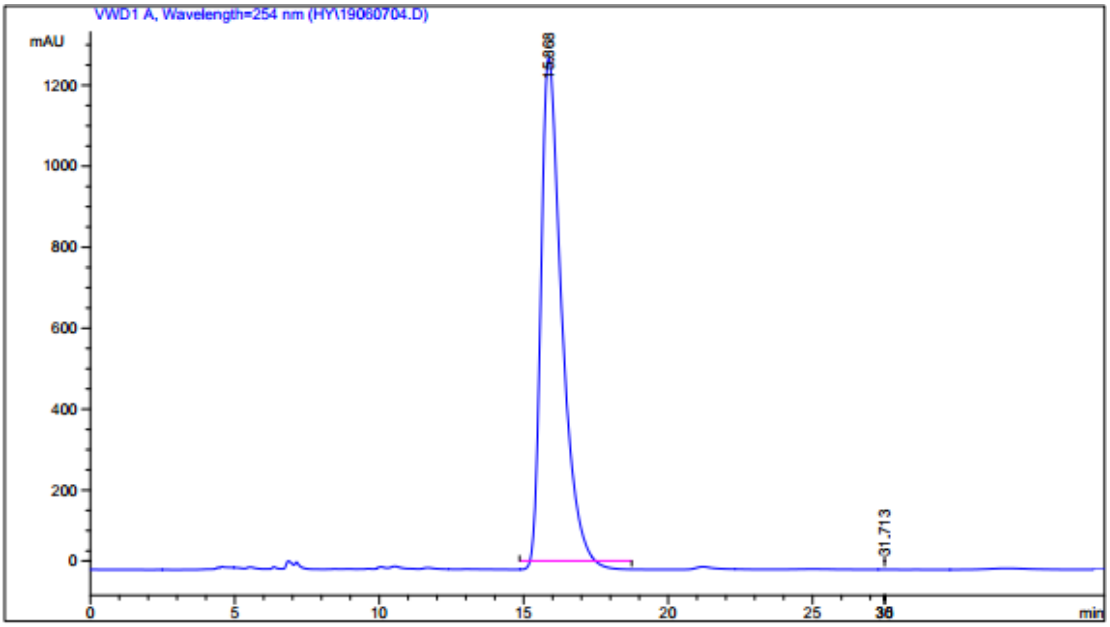








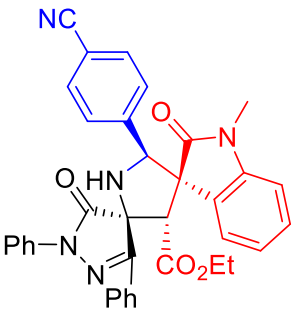
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.080	BB	0.7405	4489.63232	91.40505	50.4835
2	30.749	BB	1.4505	4403.63184	45.05145	49.5165



Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	15.868	BB	0.7582	6.40252e4	1264.48511	99.5630
2	31.713	BB	1.0869	281.02573	3.04089	0.4370

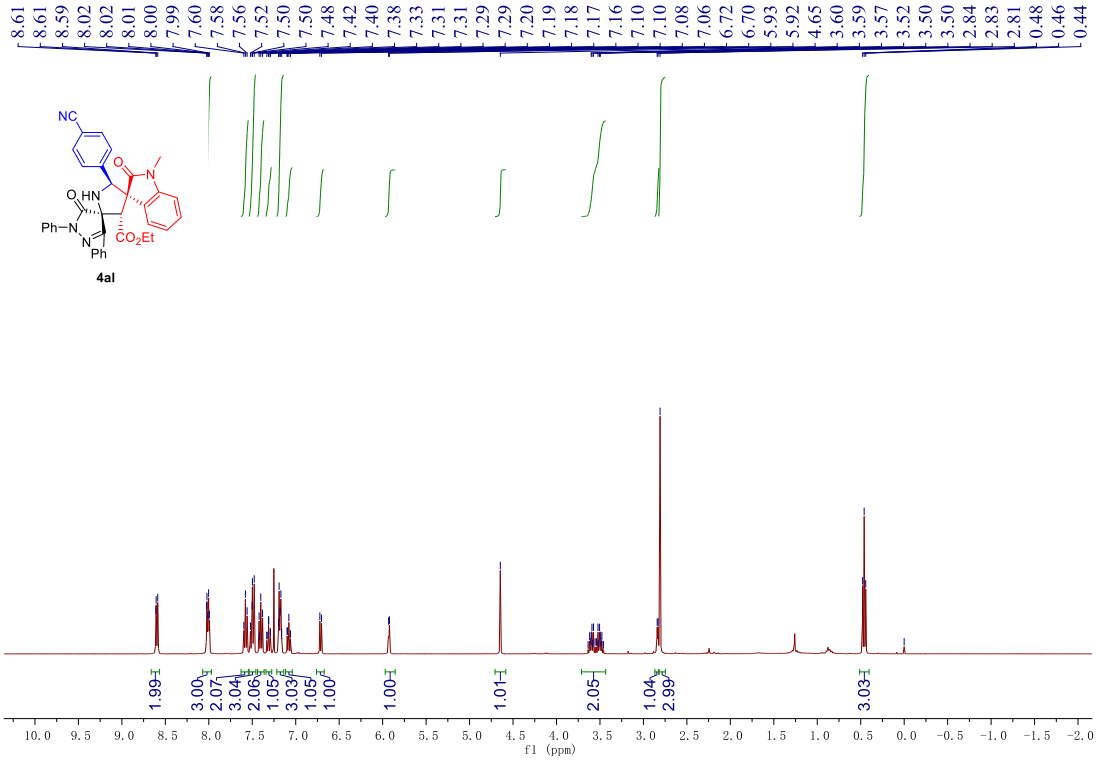
4al

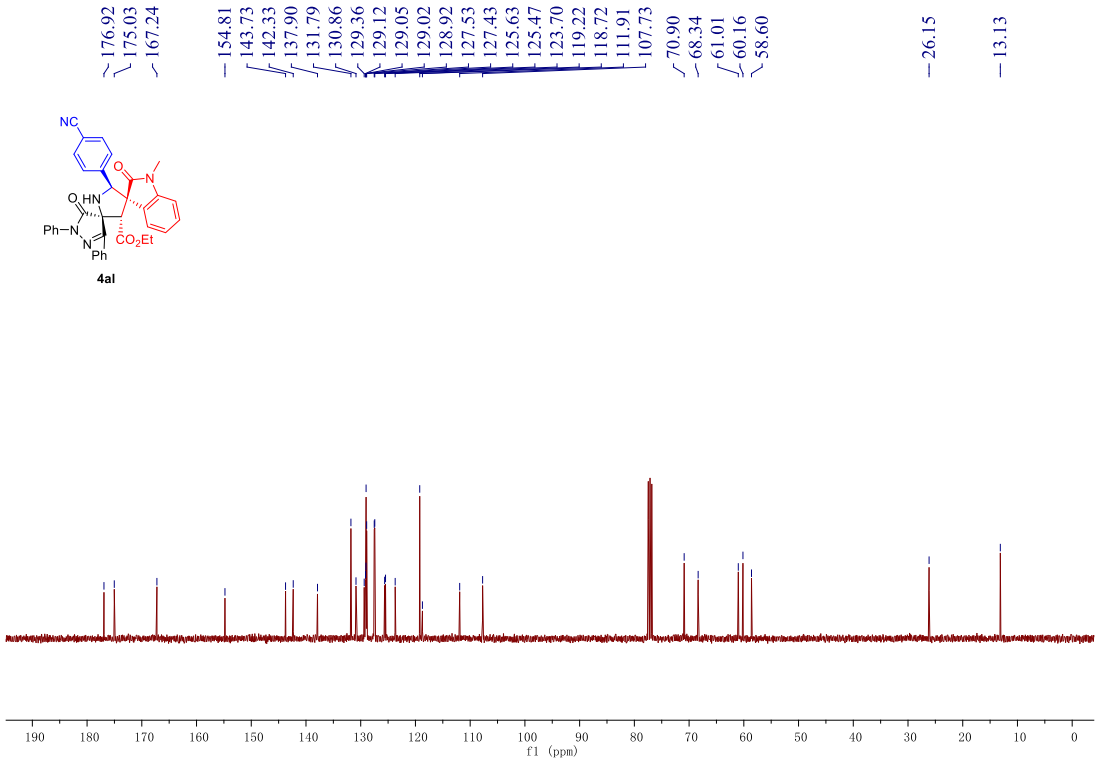
Prepared according to the procedure within 94 h as White solid (107.1 mg, 90% yield, dr > 20:1). mp 145.4 – 145.9 °C; $[\alpha]_D^{21}$ = -380.61 (*c* 0.89, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 – 8.57 (m, 2H), 8.07 – 7.97 (m, 3H), 7.62 – 7.55 (m, 2H), 7.54 – 7.46 (m, 3H), 7.44 – 7.37 (m, 2H), 7.31 (td, *J* = 7.7, 1.0 Hz, 1H), 7.22 – 7.14 (m, 3H),

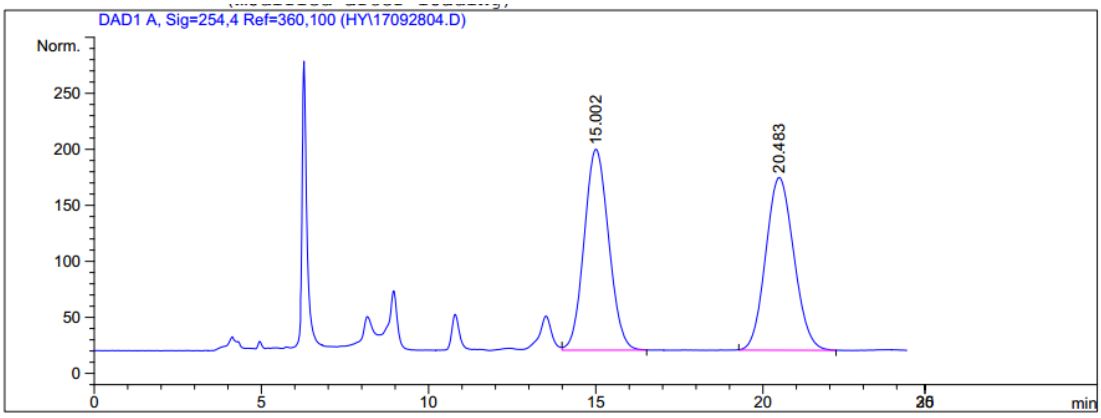


4al

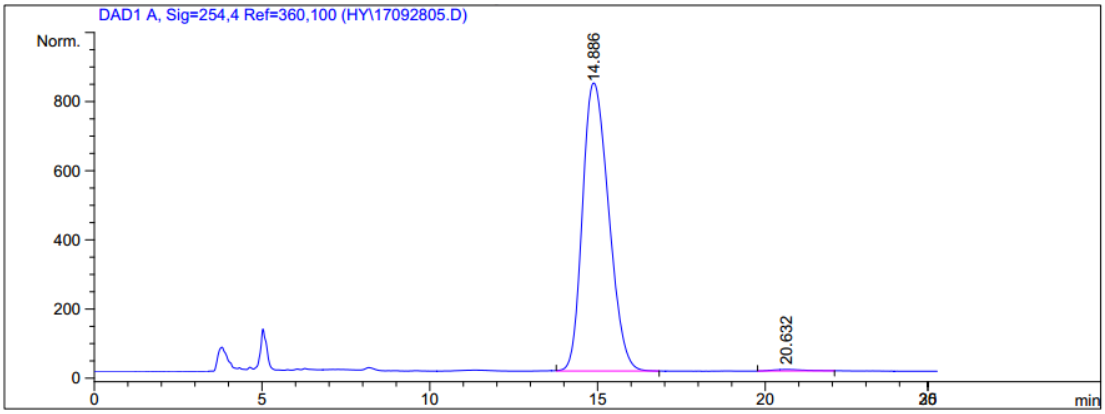
7.10 – 7.04 (m, 1H), 6.71 (d, J = 7.7 Hz, 1H), 5.93 (d, J = 3.8 Hz, 1H), 4.65 (s, 1H), 3.71 – 3.43 (m, 2H), 2.84 (d, J = 4.0 Hz, 1H), 2.81 (s, 3H), 0.46 (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.92, 175.03, 167.24, 154.81, 143.73, 142.33, 137.90, 131.79, 130.86, 129.36, 129.12, 129.05, 129.02, 128.92, 127.53, 127.43, 125.63, 125.47, 123.70, 119.22, 118.72, 111.91, 107.73, 70.90, 68.34, 61.01, 60.16, 58.60, 26.15, 13.13; HRMS (ESI) m/z Calcd. for $C_{36}H_{30}N_5O_4^+$ ($[M+H]^+$) 596.2292, Found 596.2285; Enantiomeric excess was determined to be 99% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 14.9 min, t_{minor} = 20.6 min).





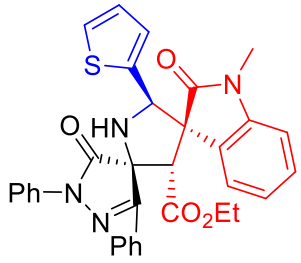


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	15.002	VB	0.7993	9156.83984	179.46423	50.3280
2	20.483	BB	0.9240	9037.46973	154.14279	49.6720



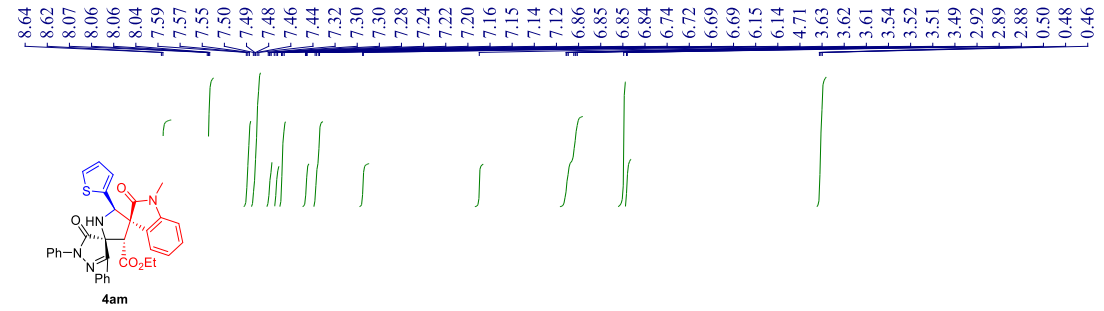
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	14.886	BB	0.8574	4.52224e4	832.99689	99.3262
2	20.632	BB	0.8470	306.78772	4.41326	0.6738

4am



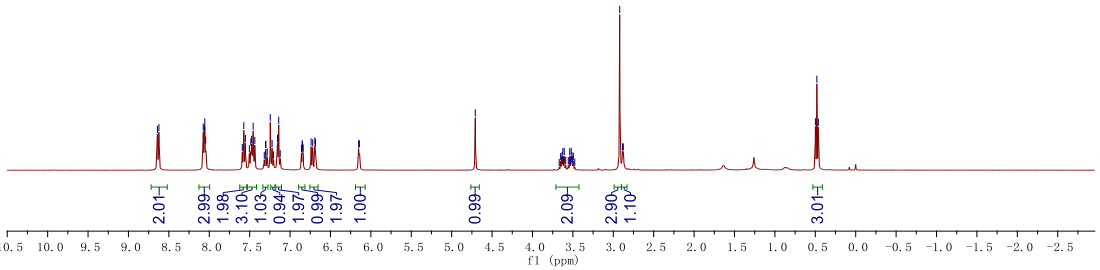
4am

Prepared according to the procedure within 84 h as White solid (109.4 mg, 95% yield, dr > 20:1). mp 145.3 – 146.9 °C; $[\alpha]_D^{20}$ = -289.30 (*c* 0.94, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 7.4 Hz, 2H), 8.02 – 8.10 (m, 3H), 7.60 – 7.54 (m, 2H), 7.53 – 7.42 (m, 3H), 7.27 – 7.33 (m, 1H), 7.19 – 7.24 (m, 1H), 7.11 – 7.17 (m, 2H), 6.85 (dd, *J* = 4.9, 3.6 Hz, 1H), 6.66 – 6.76 (m, 2H), 6.15 (d, *J* = 3.7 Hz, 1H), 4.71 (s, 1H), 3.71 – 3.43 (m, 2H), 2.92 (s, 3H), 2.88 (d, *J* = 4.1 Hz, 1H)., 0.48 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.22, 174.94, 167.49, 154.94, 144.04, 140.00, 138.09, 130.79, 129.47, 129.34, 129.00, 128.88, 128.78, 127.66, 126.50, 125.67, 125.38, 125.06, 124.45, 123.48, 119.28, 107.52, 70.69, 65.90, 60.90, 60.20, 58.45, 26.26, 13.15; HRMS (ESI) m/z Calcd. for $C_{33}H_{29}N_4O_4S^+$ ([M+H]$^+$) 577.1904, Found 577.1902; Enantiomeric excess was determined to be 96% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 12.6 min, t_{minor} = 32.9 min).

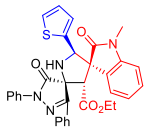

8.64
8.62
8.07
8.06
8.06
8.04
7.59
7.57
7.55
7.50
7.49
7.48
7.46
7.44
7.32
7.30
7.30
7.28
7.24
7.22
7.20
7.16
7.15
7.14
7.12
6.86
6.85
6.85
6.84
6.74
6.72
6.69
6.69
6.15
6.14
4.71
3.63
3.62
3.61
3.54
3.52
3.51
3.49
2.92
2.89
2.88
0.50
0.48
0.46

S
O
N
O
HN
Ph–N
N
Ph
CO2Et

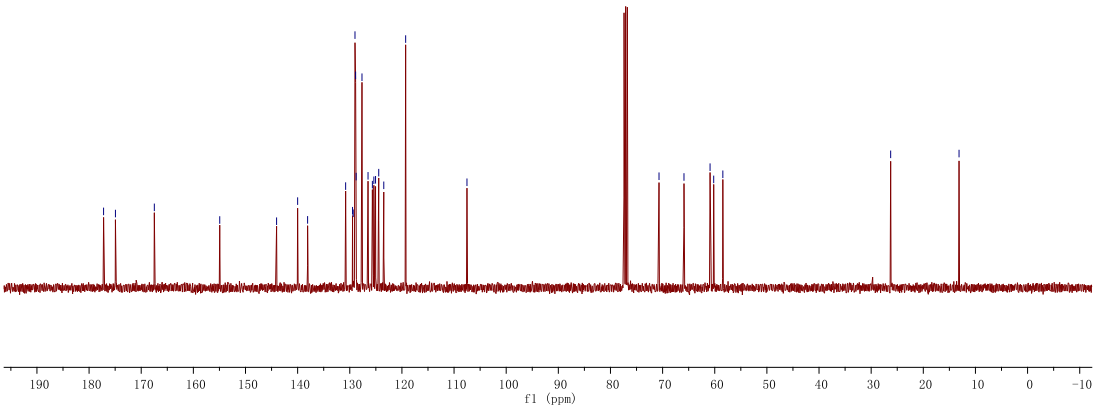
4am

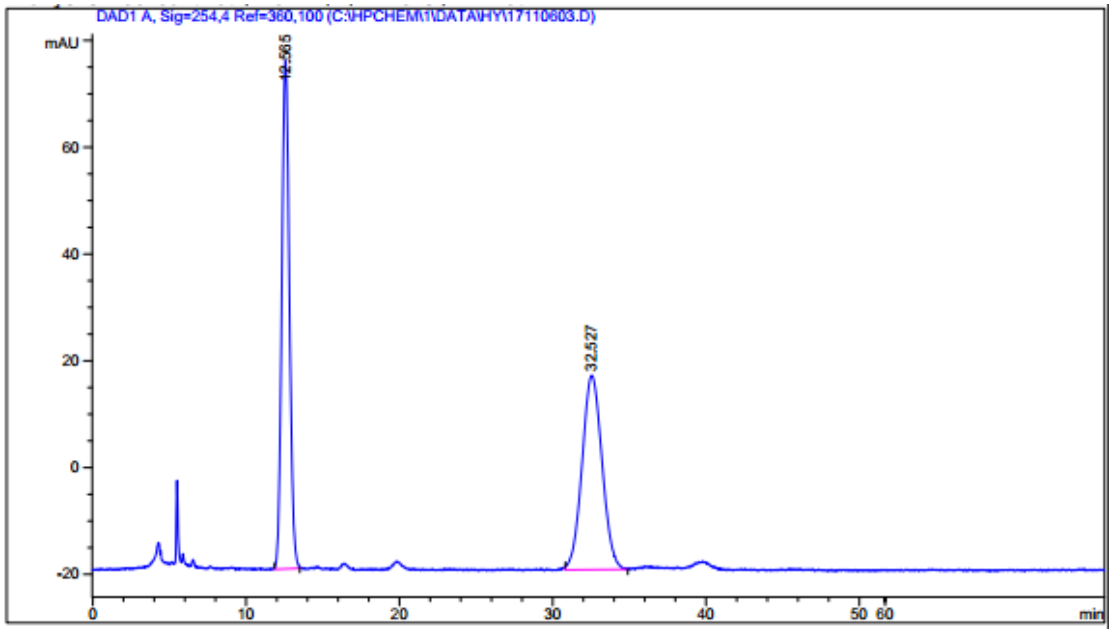

2.01
2.99
1.98
3.10
1.03
0.94
1.97
0.99
1.97
1.00
0.99
2.09
2.90
1.10
3.01
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 −0.5 −1.0 −1.5 −2.0 −2.5
f1 (ppm)


177.22
174.94
167.49
154.94
129.00
128.88
128.78
127.66
126.50
125.67
125.38
125.06
124.45
119.28
107.32
70.69
65.90
60.90
60.20
58.45
26.26
13.15

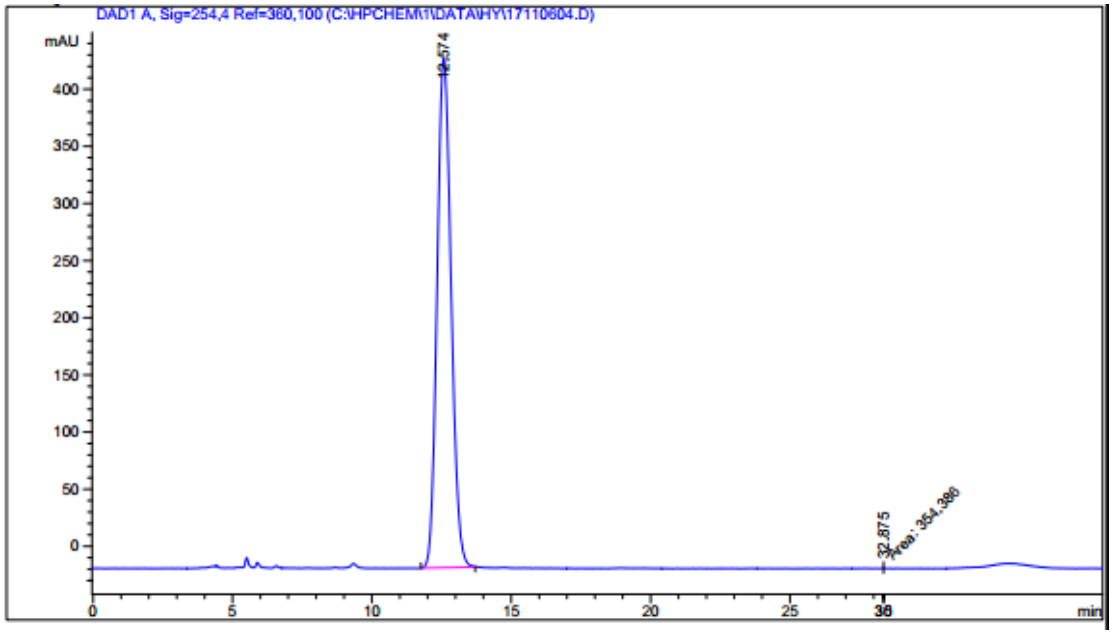

S
O
N
O
HN
Ph–N
N
Ph
CO2Et

4am


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 −10
f1 (ppm)

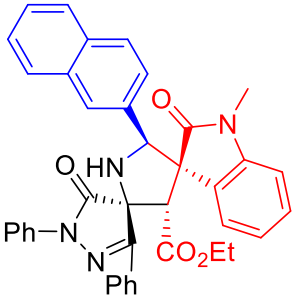


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.565	BB	0.5222	3269.94019	95.32548	49.7426
2	32.527	BP	1.0768	3303.77979	36.40379	50.2574



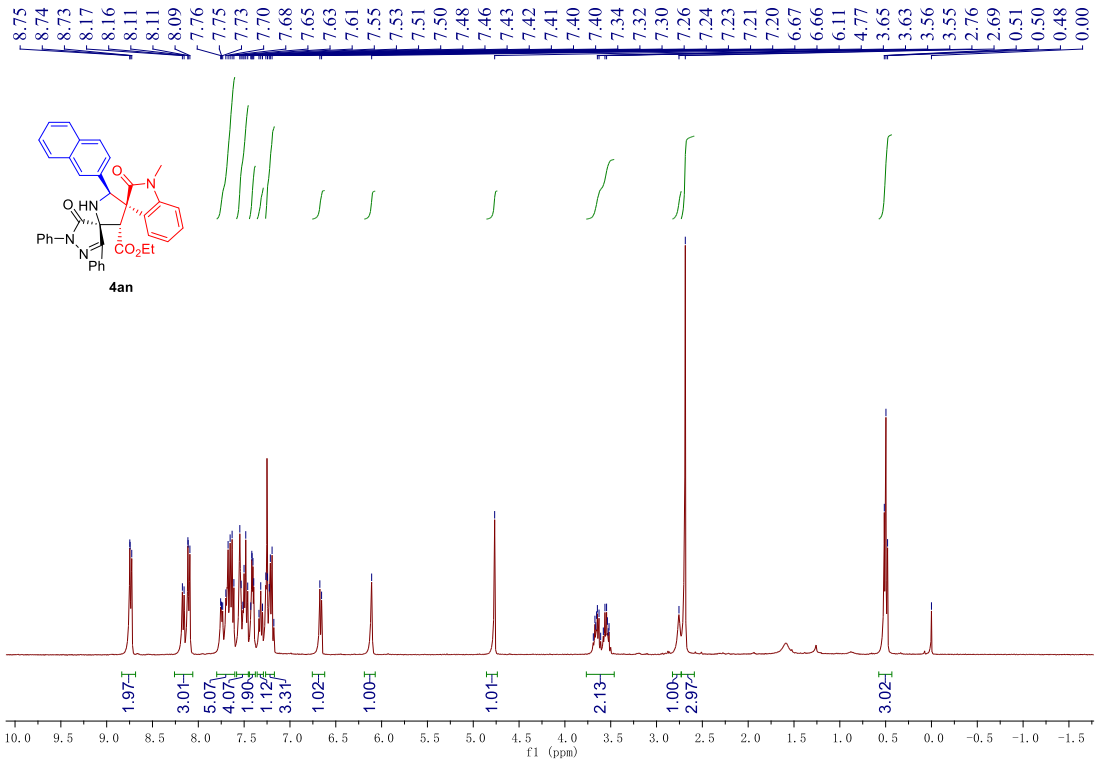
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.574	PB	0.5411	1.55627e4	446.01660	97.7735
2	32.875	MM	1.4676	354.38586	4.02450	2.2265

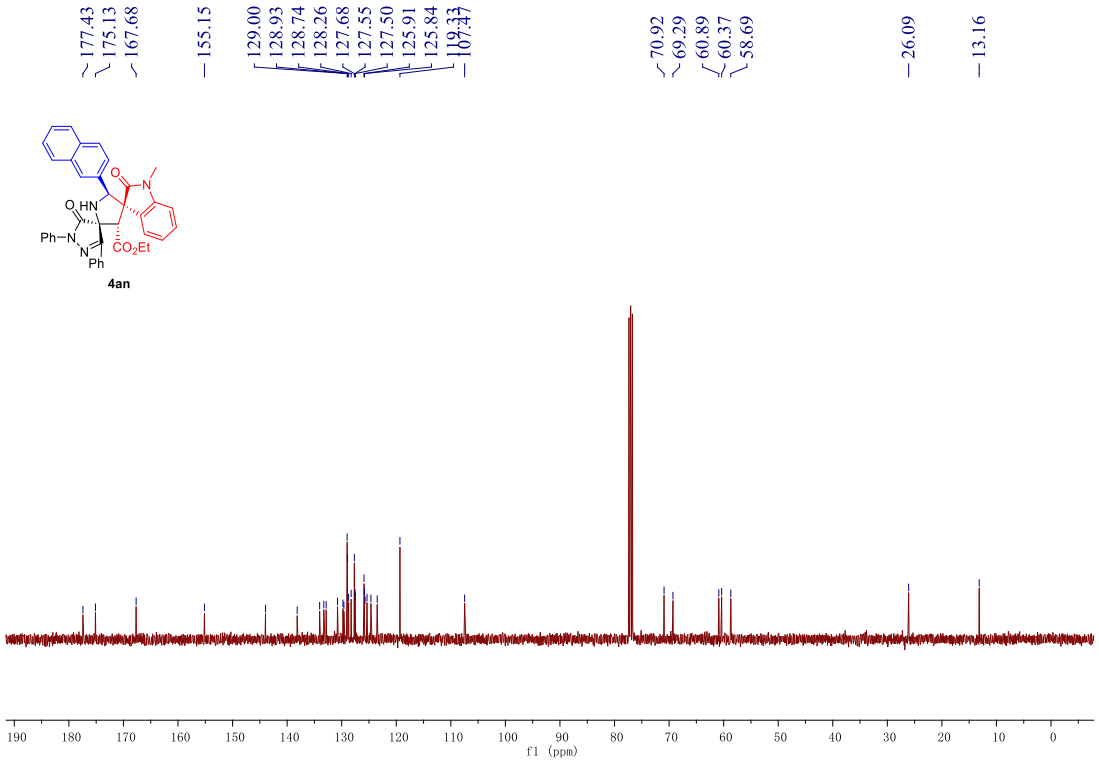
4an

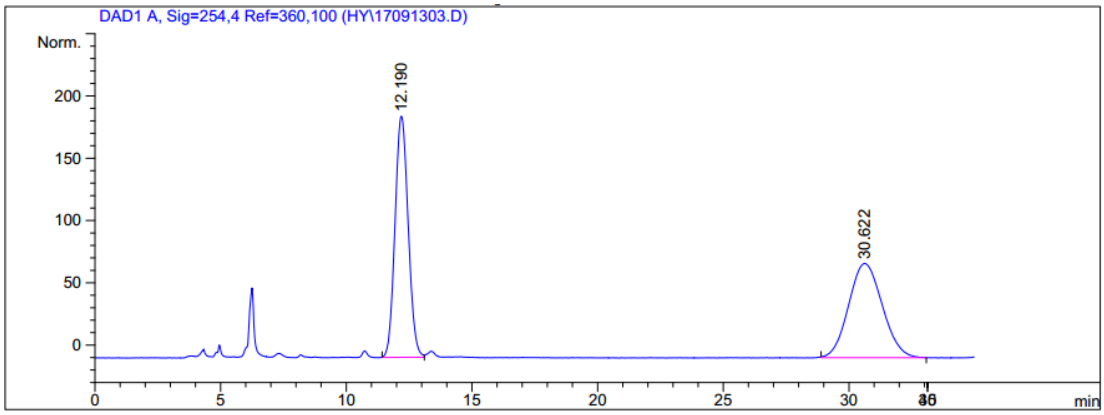


4an

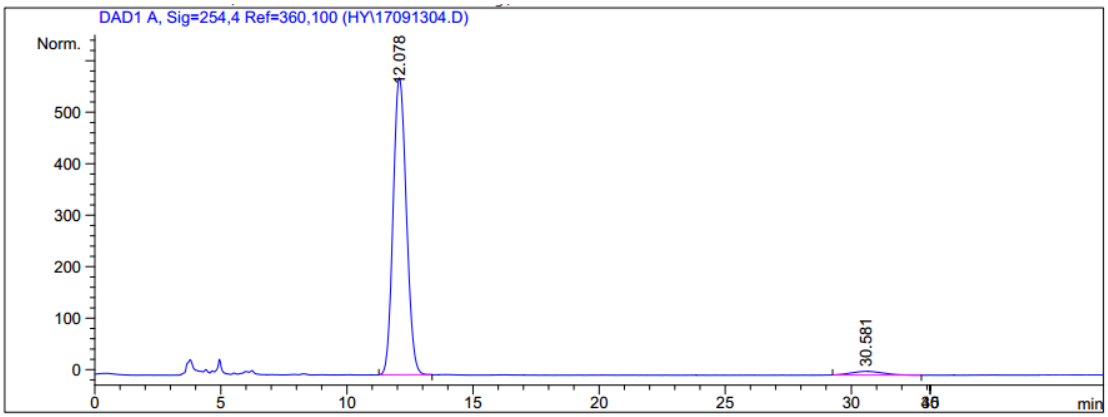
Prepared according to the procedure within 72 h as White solid (119.1 mg, 96% yield, dr > 20:1). mp 126.0 – 126.9 ºC; $[\alpha]_D^{19}$ = -364.95 (*c* 0.43, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.84 – 8.68 (m, 2H), 8.26 – 8.06 (m, 3H), 7.60 – 7.80 m, 5H), 7.58 – 7.45 (m, 4H), 7.44 – 7.38 (m, 2H), 7.29 – 7..36 (m, 1H), 7.17 – 7.28 (m, 3H), 6.66 (d, *J* = 7.6 Hz, 1H), 6.11 (s, 1H), 4.77 (s, 1H), 3.77 – 3.46 (m, 2H), 2.67 – 2.82 (m, 3H), 0.50 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.43, 175.13, 167.68, 155.15, 143.96, 138.16, 134.04, 133.28, 132.84, 130.77, 129.77, 129.60, 129.00, 128.93, 128.74, 128.26, 127.68, 127.55, 127.50, 125.91, 125.84, 125.72, 125.36, 124.65, 123.49, 119.33, 107.47, 70.92, 69.29, 60.89, 60.37, 58.69, 26.09, 13.16; HRMS (ESI) m/z Calcd. for $C_{39}H_{33}N_4O_4^+$ ($[M+H]^+$) 621.2496, Found 621.2494; Enantiomeric excess was determined to be 94% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 12.1 min, t_{minor} = 30.6 min).





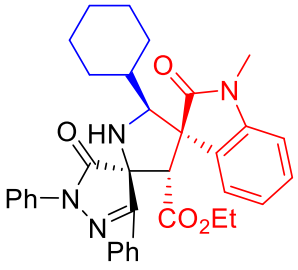


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.190	BV	0.5673	7024.87256	193.59529	49.9189
2	30.622	BB	1.3742	7047.68555	75.70037	50.0811



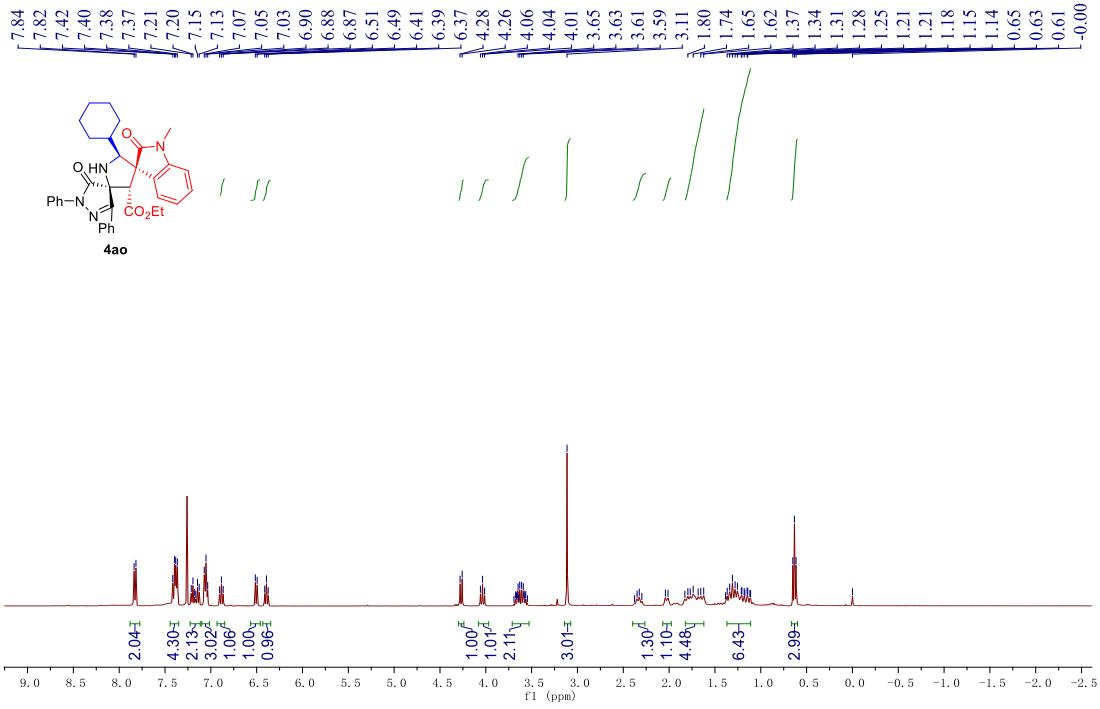
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.078	BP	0.5721	2.09724e4	576.92859	97.0048
2	30.581	BP	1.0708	647.56854	7.32914	2.9952

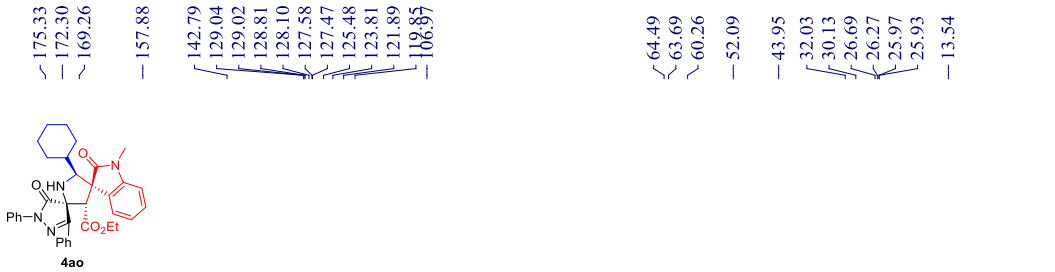
4ao

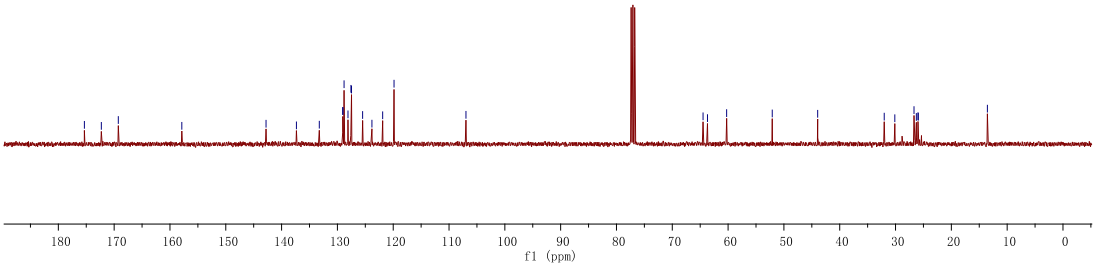


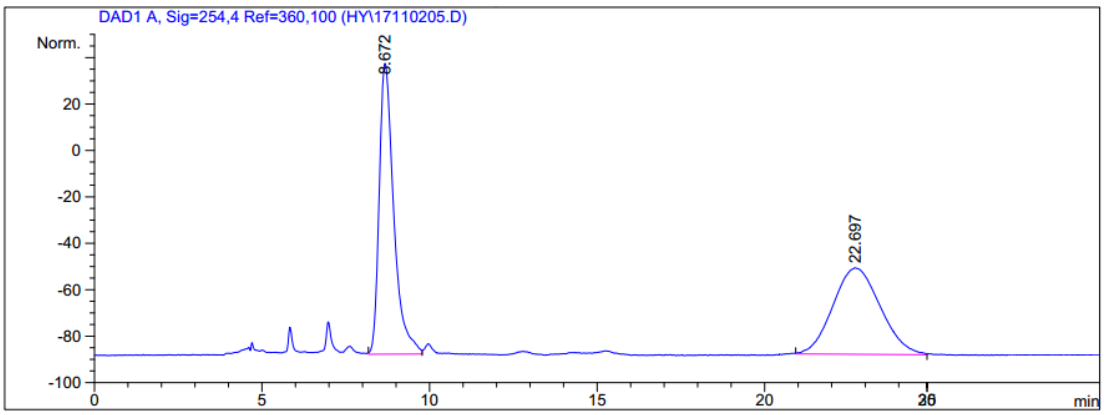
4ao

Prepared according to the procedure within 96 h as White solid (80.7 mg, 70% yield, dr > 20:1). mp 105.6 – 105.2 ºC; $[\alpha]_D^{20}$ = -128.36 (*c* 0.40, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.1 Hz, 2H), 7.43 – 7.35 (m, 4H), 7.23 – 7.12 (m, 2H), 7.08 – 7.02 (m, 3H), 6.88 (dd, *J* = 7.8 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 6.39 (dd, *J* = 7.6 Hz, 1H), 4.27 (d, *J* = 9.0 Hz, 1H), 4.04 (t, *J* = 9.1 Hz, 1H), 3.71 – 3.53 (m, 2H), 3.11 (s, 3H), 2.40 - 2.28 (m, 1H), 2.03 (d, *J* = 11.4 Hz, 1H), 1.82 – 1.62 (m, 4H), 1.37 – 1.11 (m, 6H), 0.63 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.33, 172.30, 169.26, 157.88, 142.79, 137.34, 133.24, 129.04, 129.02, 128.81, 128.10, 127.58, 127.47, 125.48, 123.81, 121.89, 119.85, 106.97, 64.49, 63.69, 60.26, 52.09, 43.95, 32.03, 30.13, 26.69, 26.27, 25.97, 25.93, 13.54; HRMS (ESI) m/z Calcd. for $C_{35}H_{37}N_4O_4^+$ ([M+H]$^+$) 577.2809, Found 577.2811; Enantiomeric excess was determined to be 33% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 22.8 min, t_{minor} = 8.7 min).

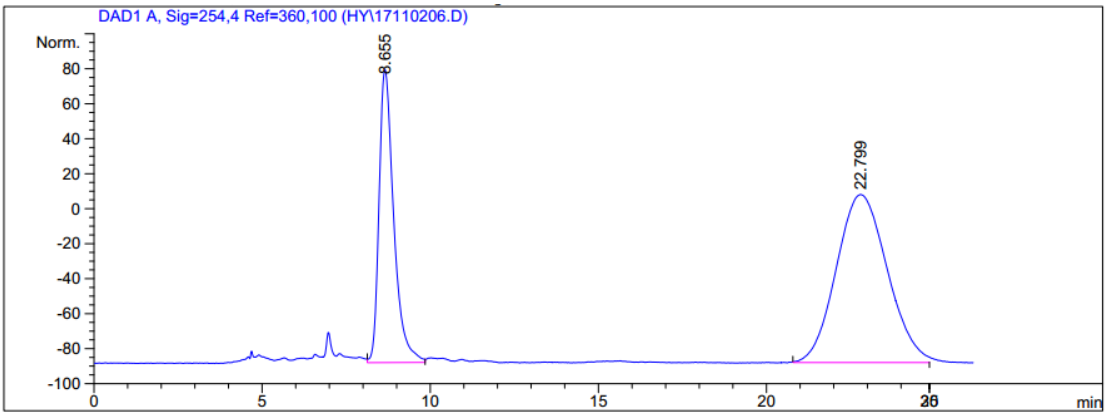






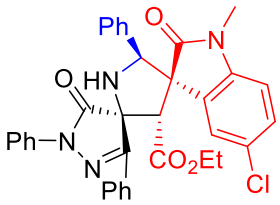


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.672	BV	0.4555	3776.38086	125.35869	50.8044
2	22.697	BB	1.1783	3656.80151	37.21746	49.1956



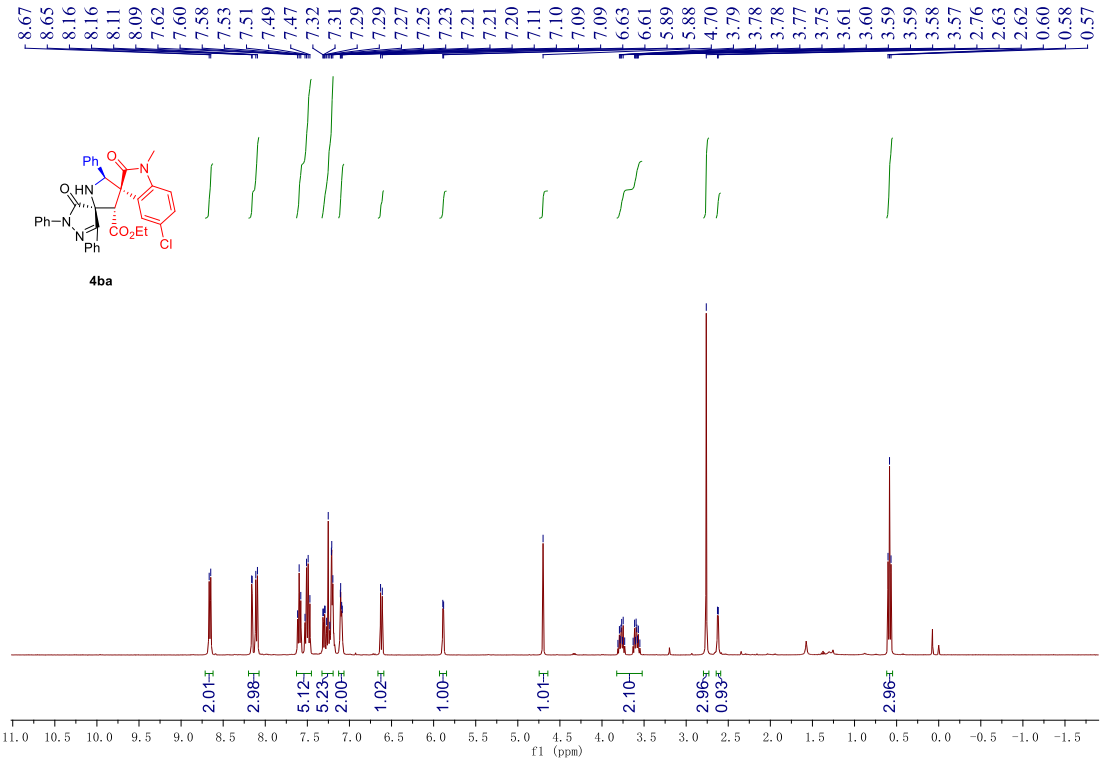
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.655	BV	0.4618	5079.09961	167.46519	33.3441
2	22.799	BB	1.5288	1.01533e4	96.08777	66.6559

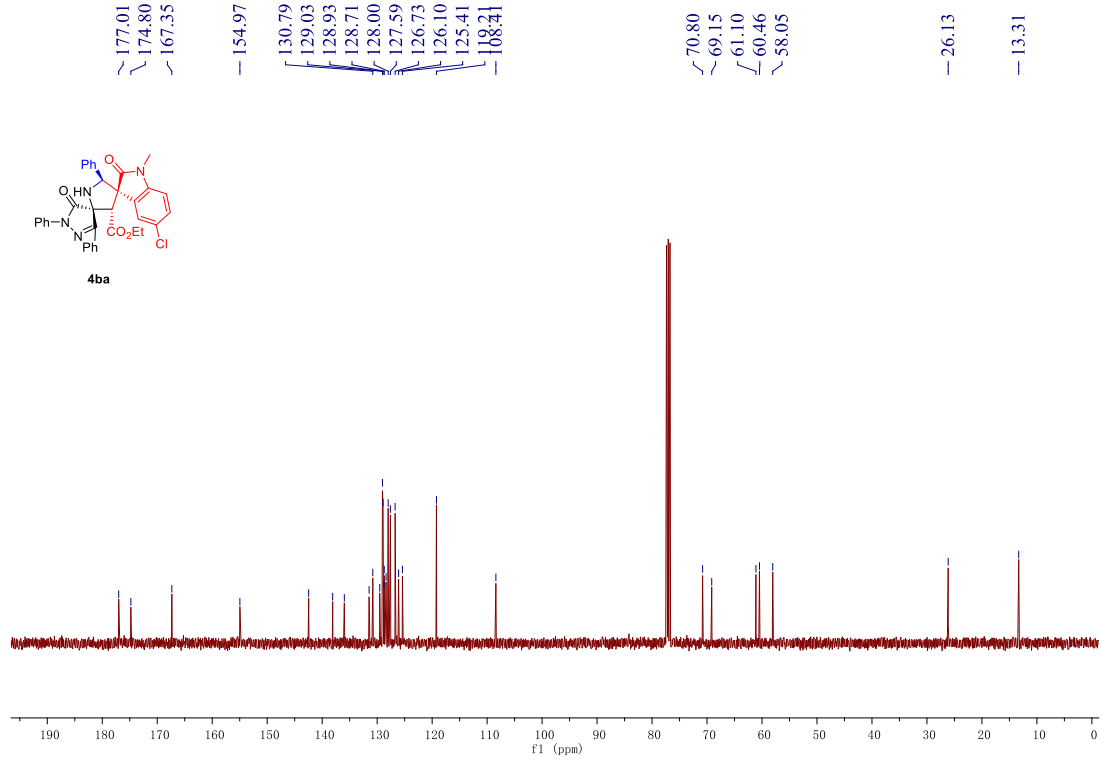
4ba

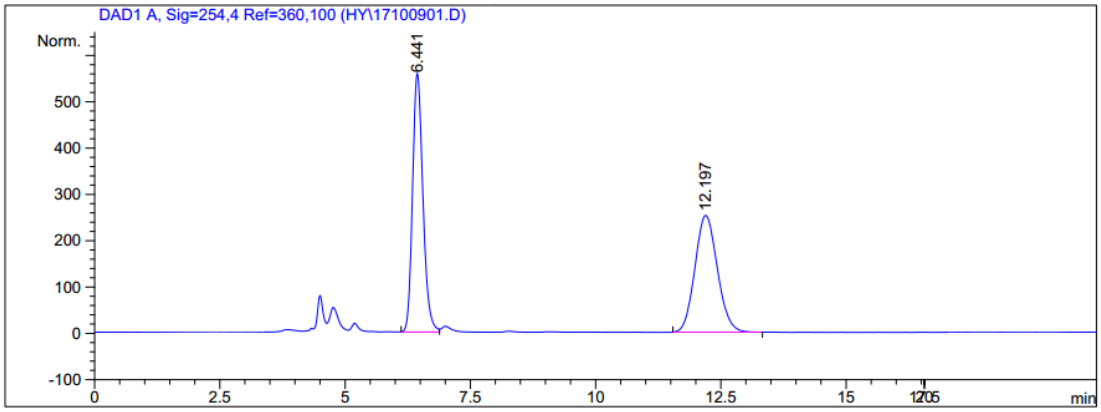


4ba

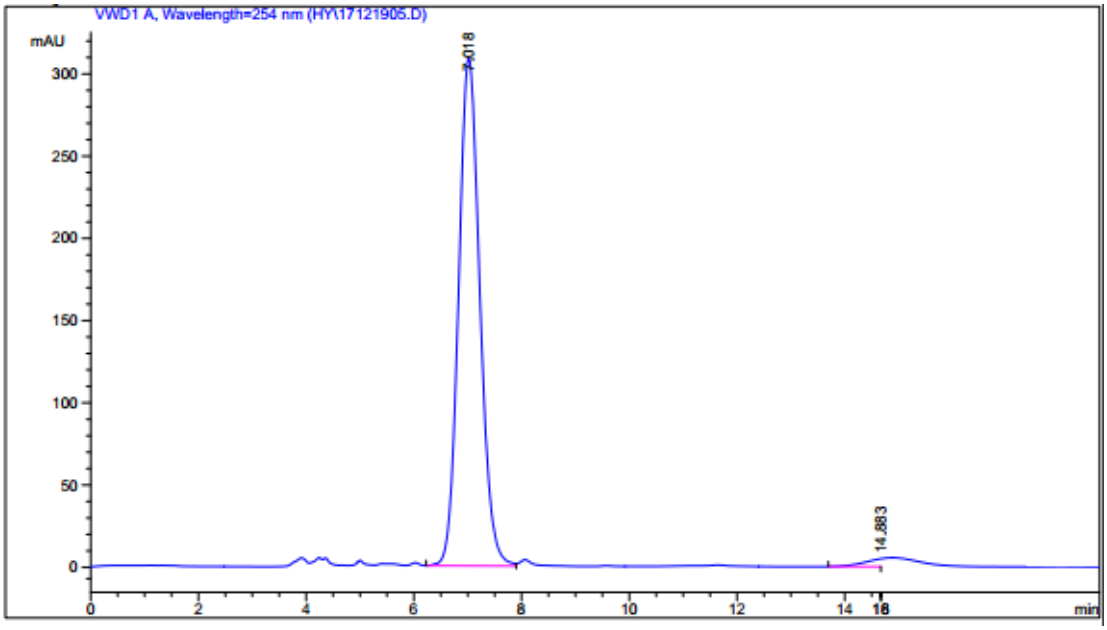
Prepared according to the procedure within 84 h as White solid (114.7 mg, 95% yield, dr > 20:1). mp 138.9 – 139.5 ºC; $[\alpha]_D^{19}$ = -276.16 (*c* 0.58, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 7.4 Hz, 2H), 8.08 – 8.18 (m, 3H), 7.63 – 7.45 (m, 5H), 7.33 – 7.19 (m, 5H), 7.06 – 7.13 (m, 2H), 6.62 (d, *J* = 8.3 Hz, 1H), 5.89 (d, *J* = 3.8 Hz, 1H), 4.70 (s, 1H), 3.53 – 3.64(m, 2H), 2.76 (s, 3H), 2.62 (d, *J* = 3.9 Hz, 1H), 0.58 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.01, 174.80, 167.35, 154.97, 142.46, 138.09, 135.97, 131.46, 130.79, 129.53, 129.03, 128.93, 128.76, 128.71, 128.39, 128.00, 127.59, 126.73, 126.10, 125.41, 119.21, 108.41, 70.80, 69.15, 61.10, 60.46, 58.05, 26.13, 13.31; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}ClN_4O_4^+$ ([M+H]$^+$) 605.1950, Found 605.1953; Enantiomeric excess was determined to be 92% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 7.0 min, t_{minor} = 14.9 min).


8.67
8.65
8.16
8.16
8.11
8.09
7.62
7.60
7.58
7.53
7.51
7.49
7.47
7.32
7.31
7.29
7.29
7.27
7.25
7.23
7.21
7.21
7.20
7.11
7.10
7.09
7.09
6.63
6.61
5.89
5.88
4.70
3.79
3.78
3.78
3.77
3.75
3.61
3.60
3.59
3.59
3.58
3.57
2.76
2.63
2.62
0.60
0.58
0.57
Ph
O
HN
Ph–N
N
Ph
CO2Et
Cl
N
4ba
2.01
2.98
5.12
5.23
2.00
1.02
1.00
1.01
2.10
2.96
0.93
2.96
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


177.01
174.80
167.35
154.97
130.79
129.03
128.93
128.71
128.00
127.59
126.73
126.10
125.41
119.21
108.41
70.80
69.15
61.10
60.46
58.05
26.13
13.31
Ph
O
HN
Ph–N
N
Ph
CO2Et
Cl
N
4ba
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

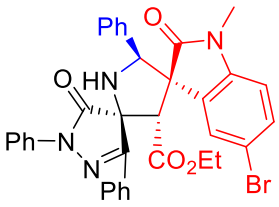


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.441	BV	0.2240	8040.66992	558.33801	50.5012
2	12.197	BB	0.4883	7881.06104	252.38983	49.4988



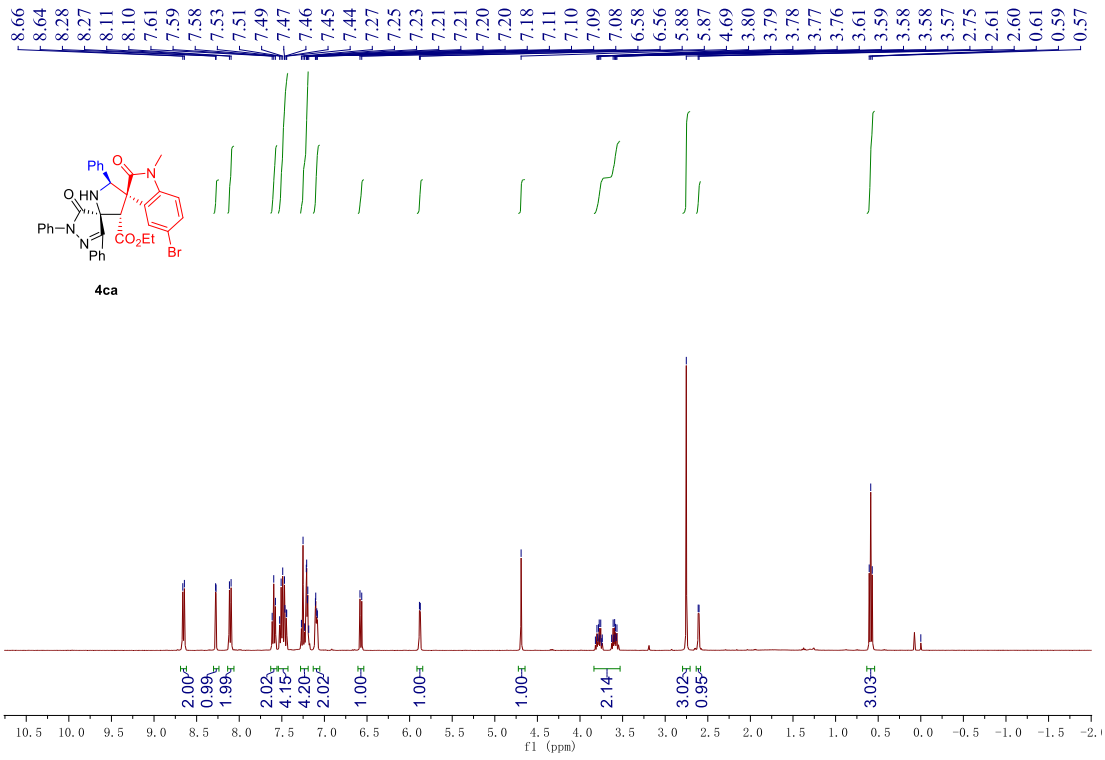
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	7.018	VV	0.4228	8459.22949	308.94608	95.8527
2	14.883	BB	0.9571	366.00558	5.40769	4.1473

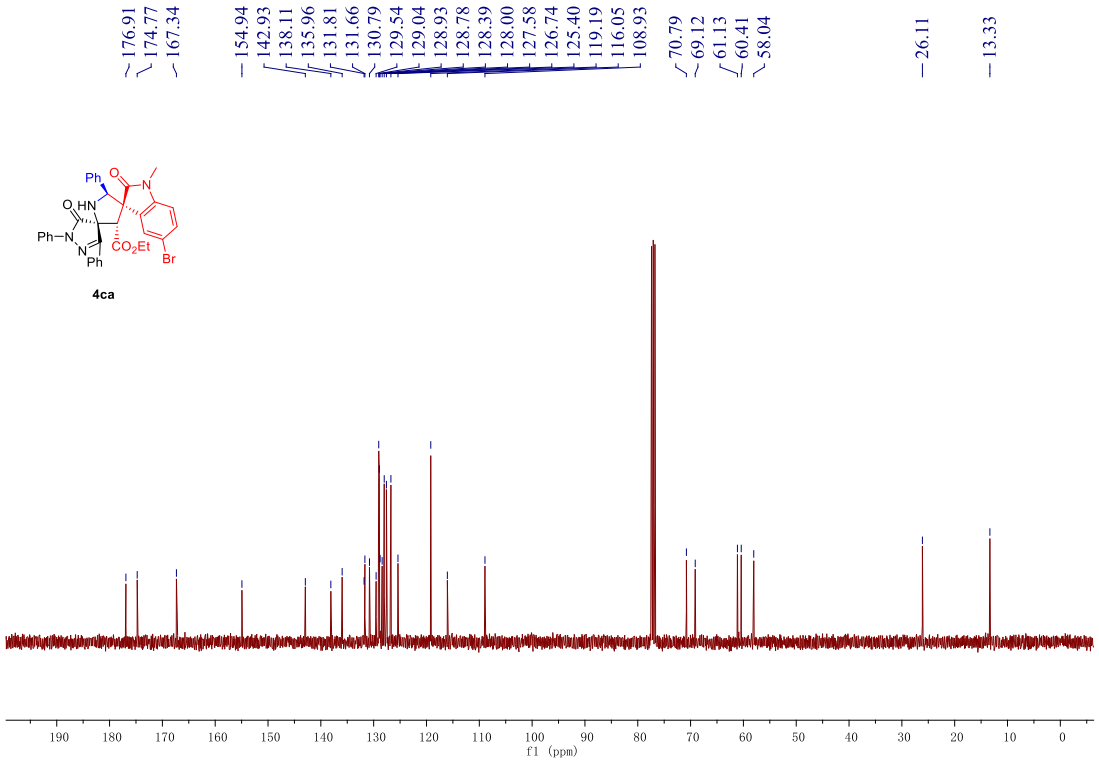
4ca

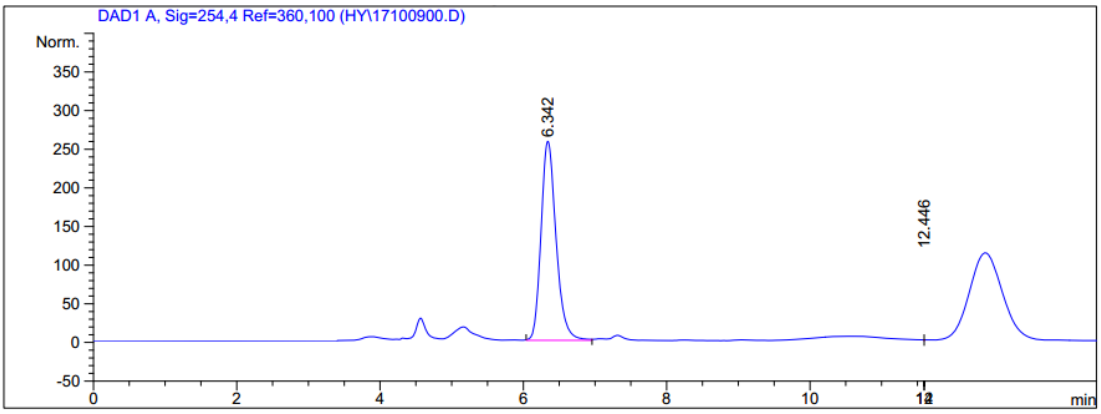


4ca

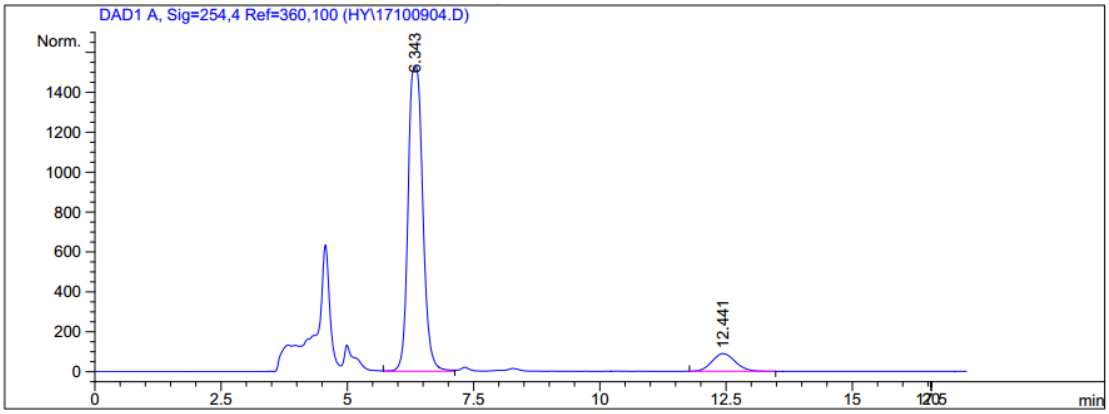
Prepared according to the procedure within 84 h as White solid (103.7 mg, 80% yield, dr > 20:1). mp 134.0 – 134.6 ºC; $[\alpha]_D^{18}$ = 254.18 (*c* 0.69, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 7.4 Hz, 2H), 8.27 (d, *J* = 1.9 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 2H), 7.65 – 7.55 (m, 2H), 7.54 – 7.43 (m, 4H), 7.28 – 7.19 (m, 4H), 7.13 – 7.06 (m, 2H), 6.57 (d, *J* = 8.2 Hz, 1H), 5.88 (d, *J* = 4.0 Hz, 1H), 4.69 (s, 1H), 3.84 – 3.53 (m, 2H), 2.75 (s, 3H), 2.61 (d, *J* = 4.1 Hz, 1H), 0.59 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.91, 174.77, 167.34, 154.94, 142.93, 138.11, 135.96, 131.81, 131.66, 130.79, 129.54, 129.04, 128.93, 128.78, 128.39, 128.00, 127.58, 126.74, 125.40, 119.19, 116.05, 108.93, 70.79, 69.12, 61.13, 60.41, 58.04, 26.11, 13.33; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}BrN_4O_4^+$ ($[M+H]^+$) 649.1445, Found 649.1444; Enantiomeric excess was determined to be 83% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 6.3 min, t_{minor} = 12.4 min).





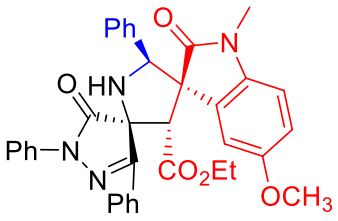


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.342	BV	0.2261	3754.68188	257.46786	50.6777
2	12.446	VB	0.5039	3654.26245	113.42494	49.3223



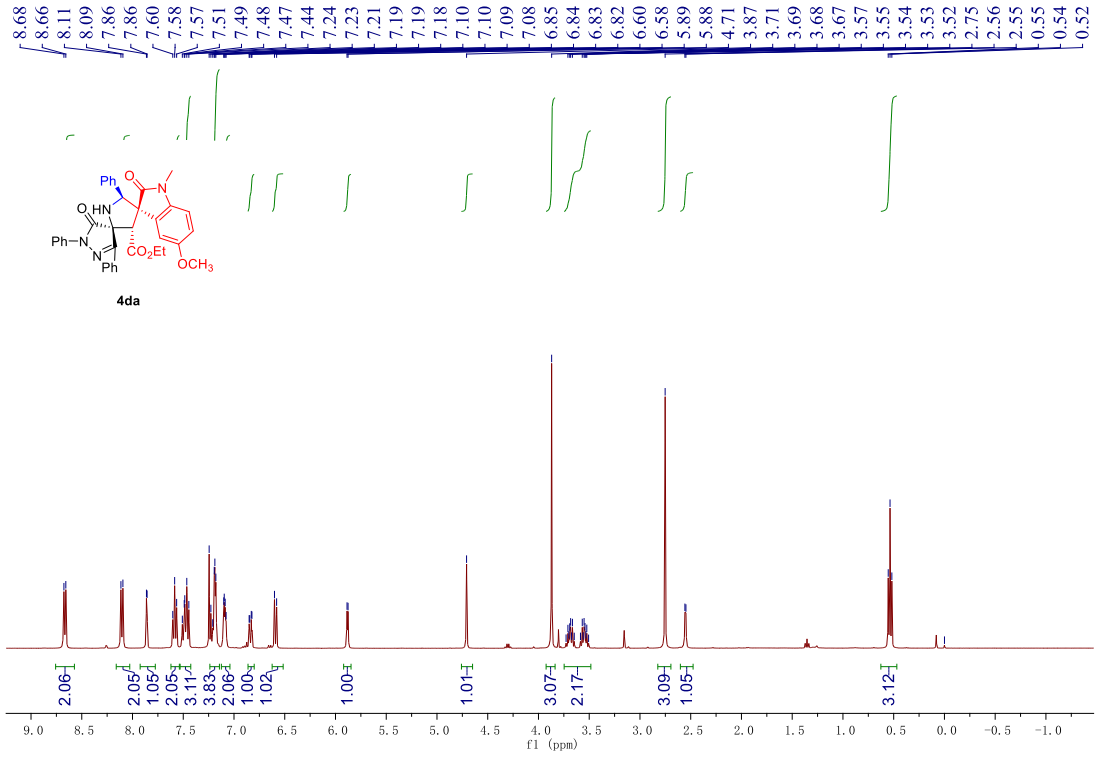
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.343	VV	0.3153	3.07090e4	1522.47791	91.4570
2	12.441	BB	0.5036	2868.52686	89.10049	8.5430

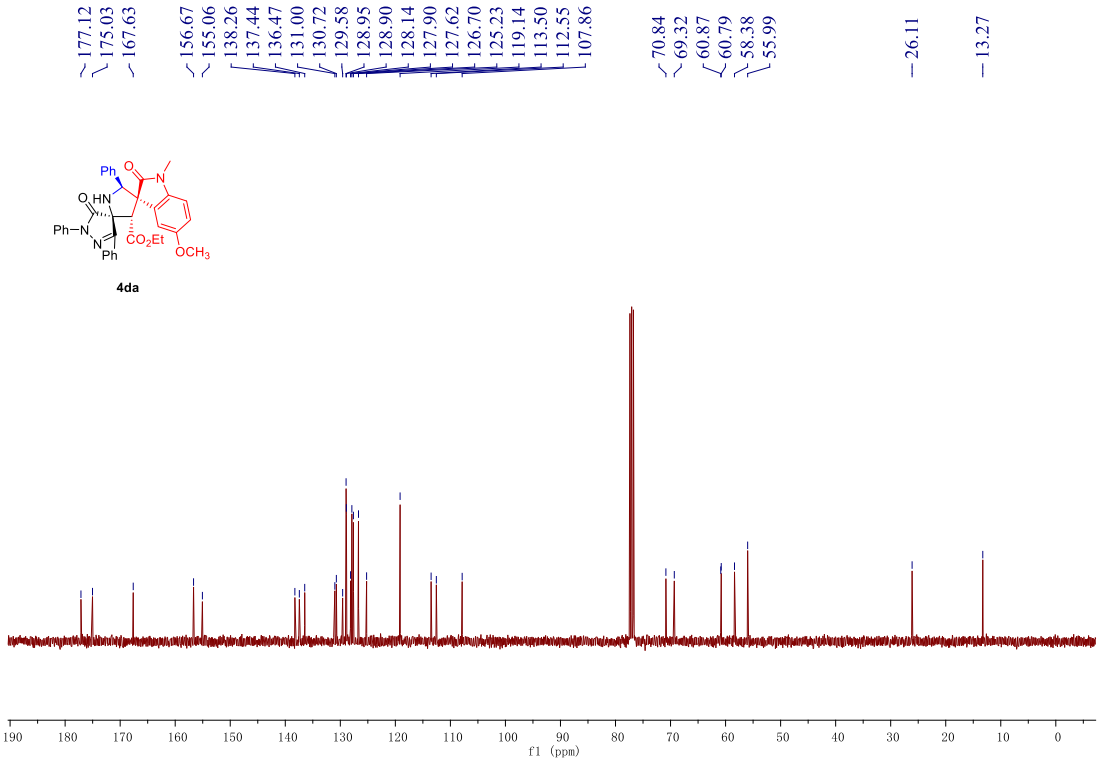
4da

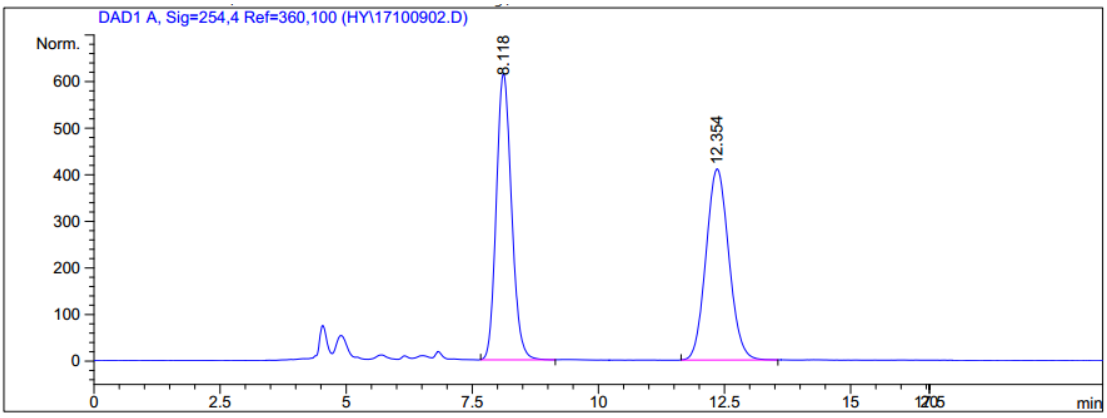


4da

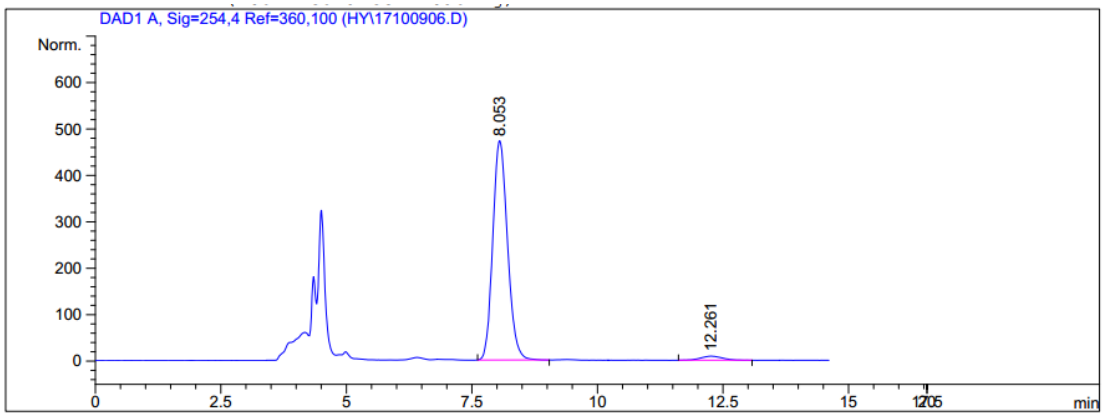
Prepared according to the procedure within 96 h as White solid (97.2 mg, 81% yield, dr > 20:1). mp 129.3 – 130.7 °C; $[\alpha]_D^{15}$ = -289.96 (*c* 0.76, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.70 – 8.63 (d, *J* = 7.5 Hz, 2H), 8.15 – 8.07 (d, *J* = 7.8 Hz, 2H), 7.86 (d, *J* = 2.5 Hz, 1H), 7.62 – 7.55 (m, 2H), 7.53 – 7.43 (m, 3H), 7.24 – 7.14 (m, 4H), 7.13 – 7.05 (m, 2H), 6.84 (dd, *J* = 8.4, 2.5 Hz, 1H), 6.59 (d, *J* = 8.4 Hz, 1H), 5.88 (d, *J* = 4.1 Hz, 1H), 4.71 (s, 1H), 3.87 (s, 3H), 3.75 – 3.49 (m, 2H), 2.75 (s, 3H), 2.55 (d, *J* = 4.1 Hz, 1H), 0.54 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.12, 175.03, 167.63, 156.67, 155.06, 138.26, 137.44, 136.47, 131.00, 130.72, 129.58, 128.95, 128.90, 128.14, 127.90, 127.62, 126.70, 125.23, 119.14, 113.50, 112.55, 107.86, 70.84, 69.32, 60.87, 60.79, 58.38, 55.99, 26.11, 13.27; HRMS (ESI) m/z Calcd. for $C_{36}H_{33}N_4O_5^+$ ($[M+H]^+$) 601.2445, Found 601.2439; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 8.1 min, t_{minor} = 12.3 min).





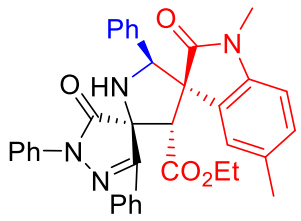


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.118	BB	0.3290	1.29060e4	614.63336	49.9738
2	12.354	BB	0.4955	1.29196e4	410.17297	50.0262



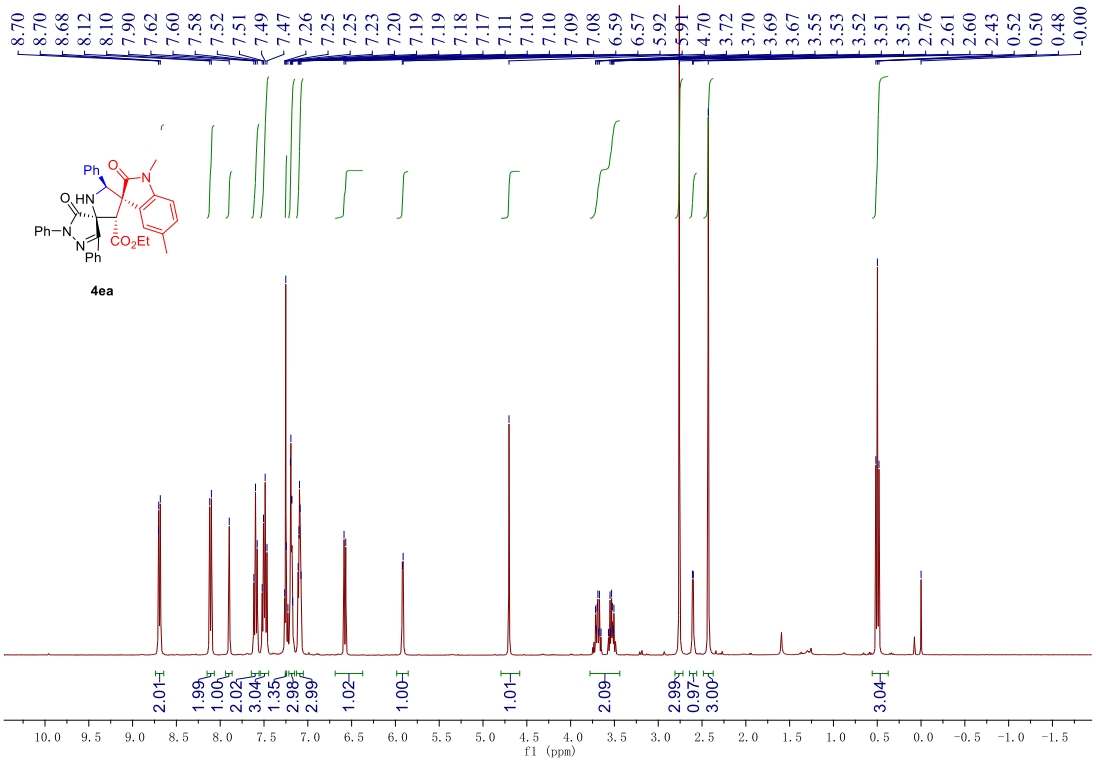
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.053	BP	0.3175	9614.10156	472.31683	97.2807
2	12.261	BB	0.4777	268.74646	8.76637	2.7193

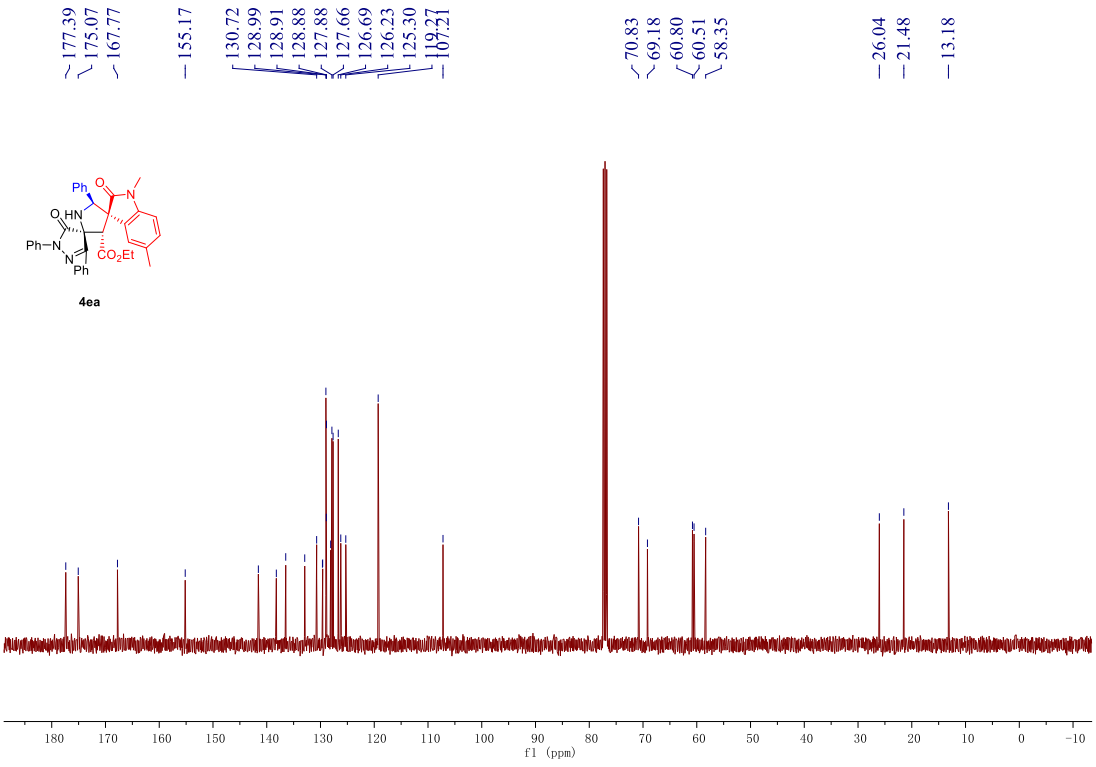
4ea

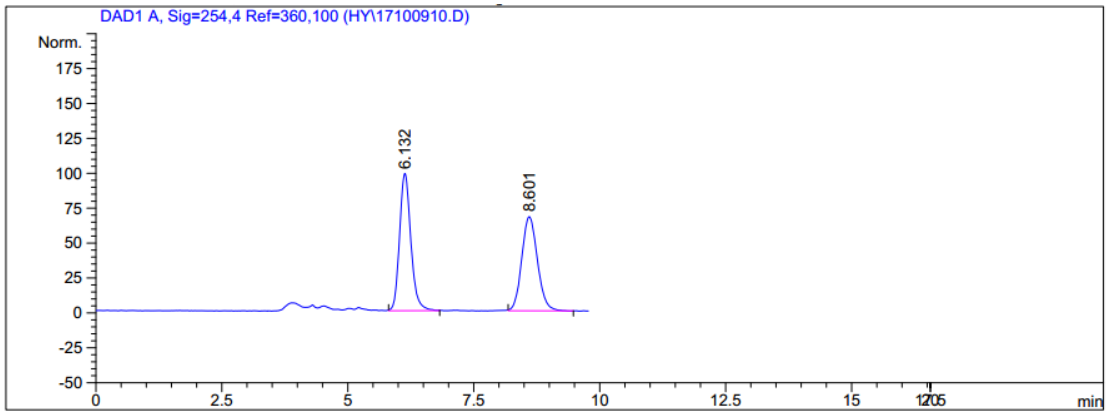


4ea

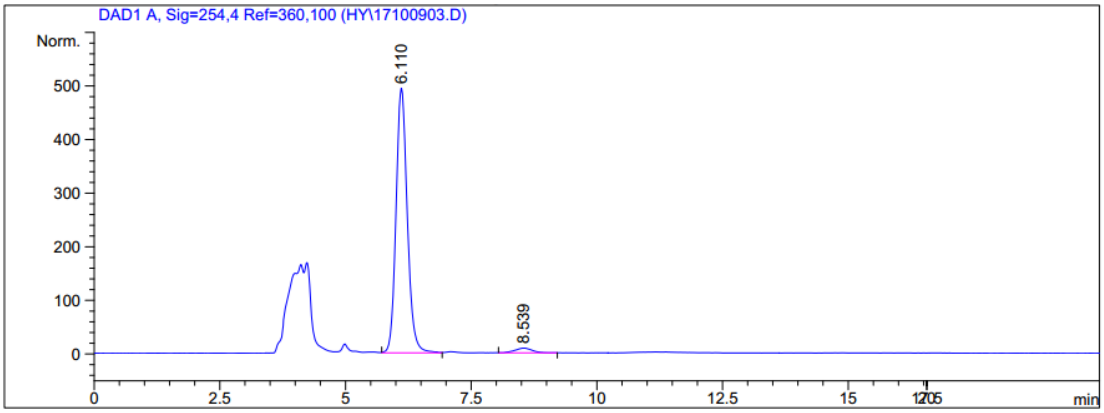
Prepared according to the procedure within 96 has White solid (97.0 mg, 83% yield, dr > 20:1). mp 129.0 – 129.6 ºC; $[\alpha]_D^{14}$ = -318.26 (*c* 0.56, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.75 – 8.65 (m, 2H), 8.16 – 8.09 (m, 2H), 7.91 (s, 1H), 7.65 – 7.59 (m, 2H), 7.55 – 7.46 (m, 3H), 7.28 – 7.24 (m, 2H), 7.23 – 7.16 (m, 3H), 7.14 – 7.06 (m, 3H), 6.59 (d, *J* = 7.8 Hz, 1H), 5.93 (d, *J* = 3.8 Hz, 1H), 4.71 (s, 1H), 3.79 – 3.45 (m, 2H), 2.77 (s, 3H), 2.61 (d, *J* = 4.0 Hz, 1H), 2.44 (s, 3H), 0.51 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.39, 175.07, 167.77, 155.17, 141.56, 138.21, 136.47, 132.93, 130.72, 129.64, 129.59, 128.99, 128.91, 128.88, 128.11, 127.88, 127.66, 126.69, 126.23, 125.30, 119.27, 107.21, 70.83, 69.18, 60.80, 60.51, 58.35, 26.04, 21.48, 13.18; HRMS (ESI) m/z Calcd. for $C_{36}H_{33}N_4O_4^+$ ([M+H]$^+$) 585.2496, Found 585.2489; Enantiomeric excess was determined to be 94% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 6.1 min, t_{minor} = 8.5 min).


8.70 8.70 8.68 8.12 8.10 7.90 7.62 7.60 7.58 7.52 7.51 7.49 7.47 7.26 7.25 7.25 7.23 7.20 7.19 7.19 7.18 7.17 7.11 7.10 7.10 7.09 7.08 6.59 6.57 5.92 5.91 4.70 3.72 3.70 3.69 3.67 3.55 3.53 3.52 3.51 3.51 2.76 2.61 2.60 2.43 0.52 0.50 0.48 -0.00
Ph
O
N
HN
Ph–N
N
Ph
CO2Et
4ea
2.01 1.99 1.00 2.02 3.04 1.35 2.98 2.99 1.02 1.00 1.01 2.09 2.99 0.97 3.00 3.04
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0 -1.5
f1 (ppm)


177.39 175.07 167.77 155.17 130.72 128.99 128.91 128.88 127.88 127.66 126.69 126.23 125.30 119.27 107.21 70.83 69.18 60.80 60.51 58.35 26.04 21.48 13.18
Ph
O
N
HN
Ph–N
N
Ph
CO2Et
4ea
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

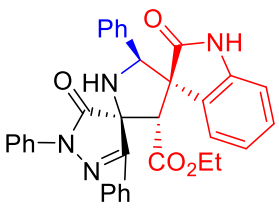


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.132	BB	0.2419	1532.95886	98.29766	51.2463
2	8.601	BB	0.3365	1458.39343	67.39500	48.7537



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.110	BV	0.2421	7709.37842	493.82007	97.2407
2	8.539	BB	0.3718	218.76387	8.74604	2.7593

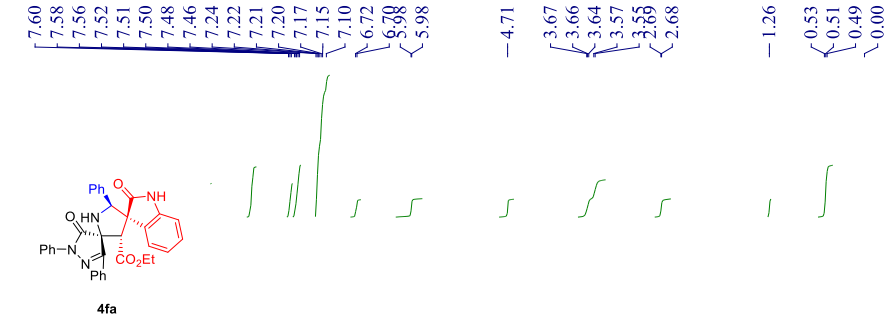
4fa

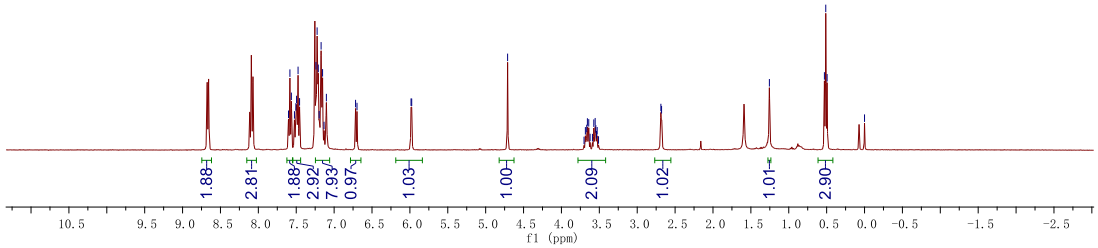


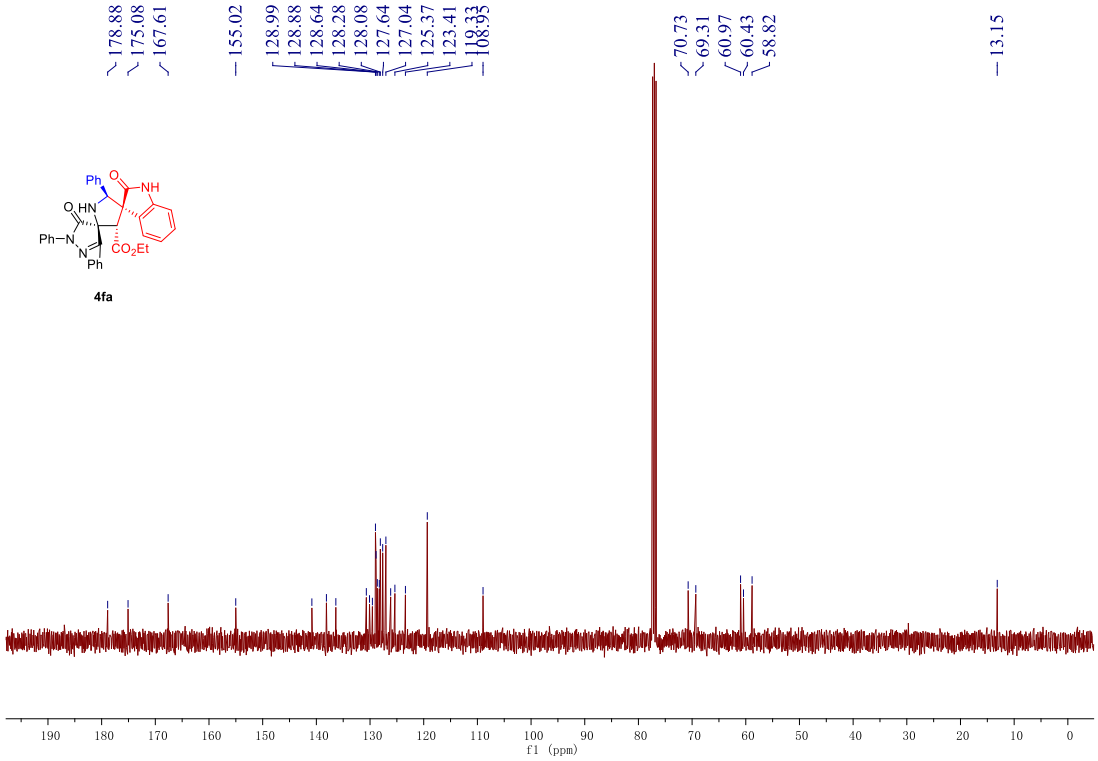
4fa

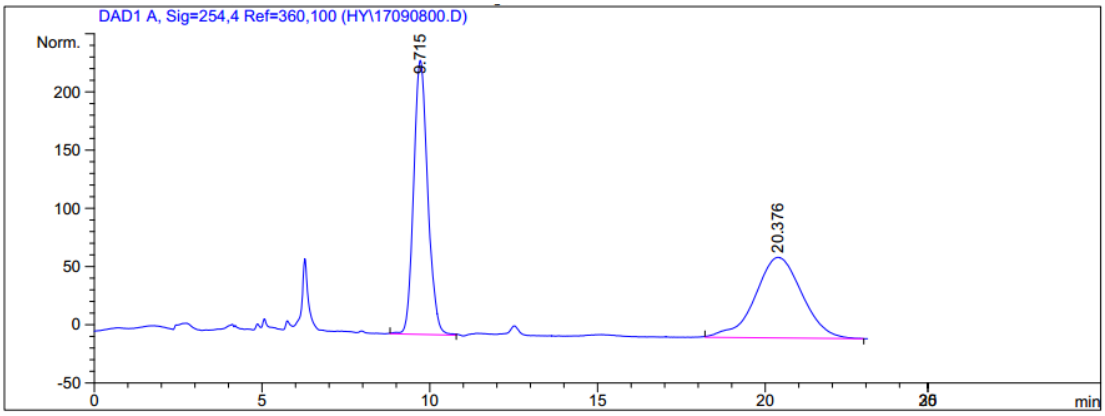
Prepared according to the procedure within 72 h as White solid (104.5 mg, 94% yield, dr > 20:1). mp 214.6 – 215.6 ºC; $[\alpha]_D^{20}$ = -261.28 (*c* 0.36, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 7.5 Hz, 2H), 8.12 – 8.05 (m, 3H), 7.62 – 7.55 (m, 2H), 7.54 – 7.44 (m, 3H), 7.25 – 7.07(m, 8H), 6.71 (d, *J* = 7.6 Hz, 1H), 5.98 (d, *J* = 3.5 Hz, 1H), 4.71 (s, 1H), 3.78 – 3.42 (m, 2H), 2.68 (d, *J* = 3.7 Hz, 1H), 1.26 (s, 1H), 0.51 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.88, 175.08, 167.61, 155.02, 140.83, 138.12, 136.37, 130.69, 130.10, 129.56, 128.99, 128.88, 128.64, 128.28, 128.08, 127.64, 127.04, 126.16, 125.37, 123.41, 119.33, 108.95, 70.73, 69.31, 60.97, 60.43, 58.82, 13.15; HRMS (ESI) m/z Calcd. for $C_{34}H_{29}N_4O_4^+$ ([M+H]$^+$) 557.2183, Found 557.2175;

Enantiomeric excess was determined to be 73% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 20.2 min, t_{minor} = 9.6 min).

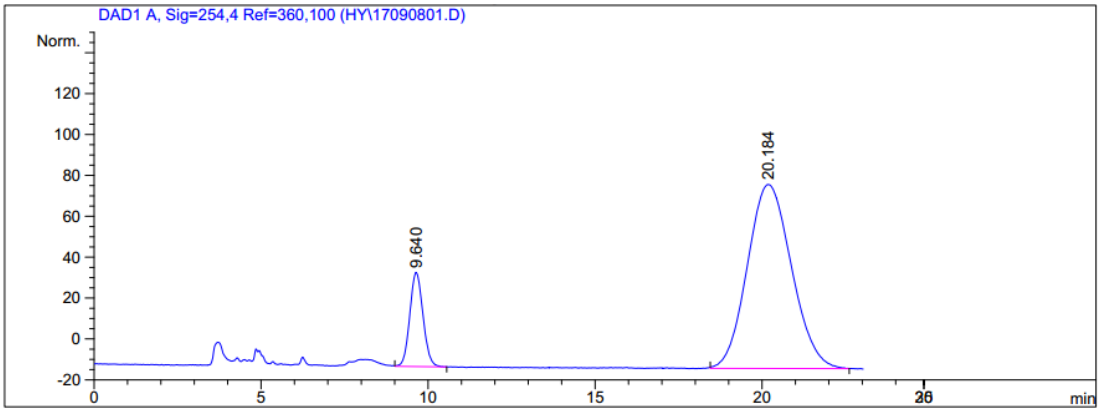






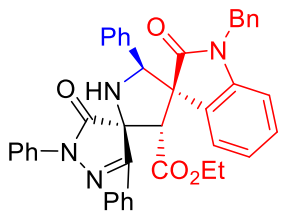


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.715	BB	0.4484	6867.38623	235.36469	50.5093
2	20.376	BP	1.3657	6728.90723	69.24541	49.4907



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.640	VB	0.4289	1267.18005	46.06562	13.2824
2	20.184	BB	1.3886	8273.10742	89.98389	86.7176

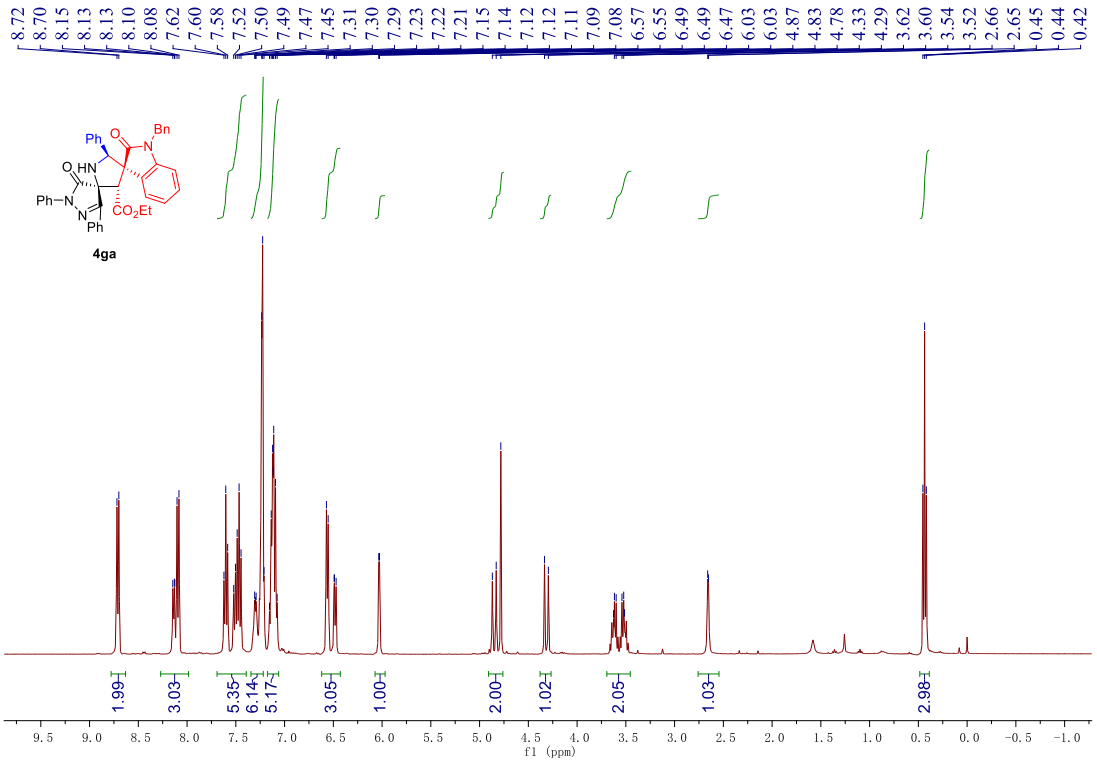
4ga

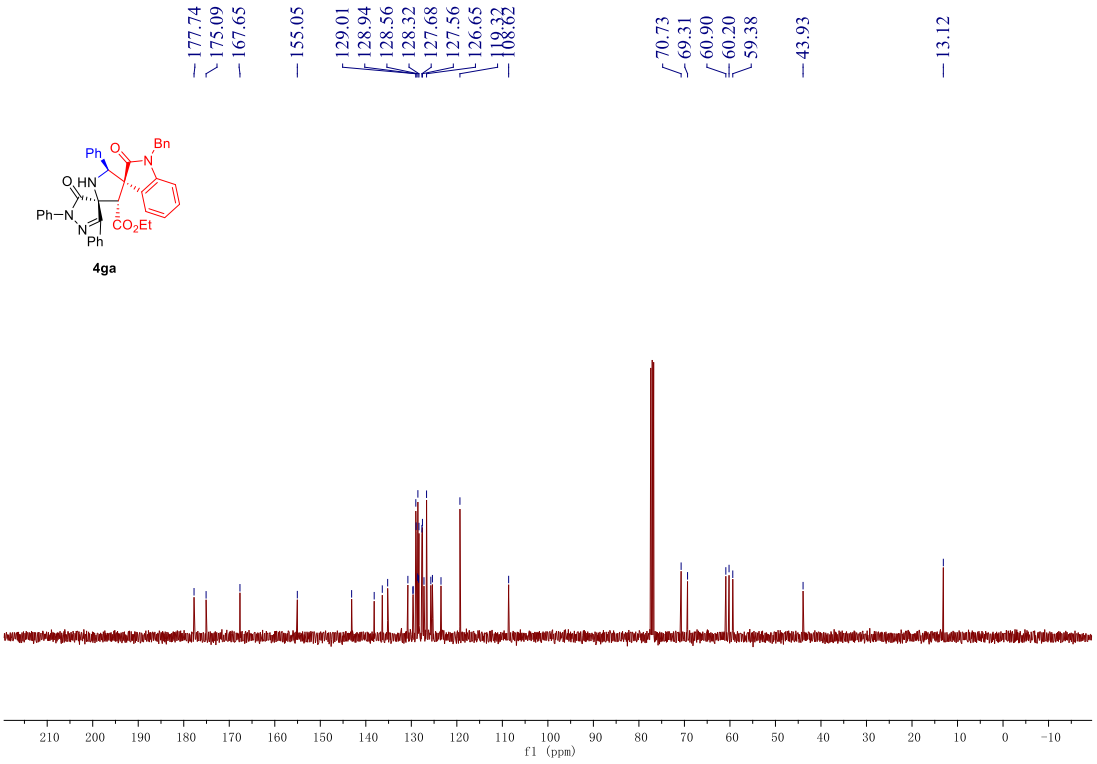


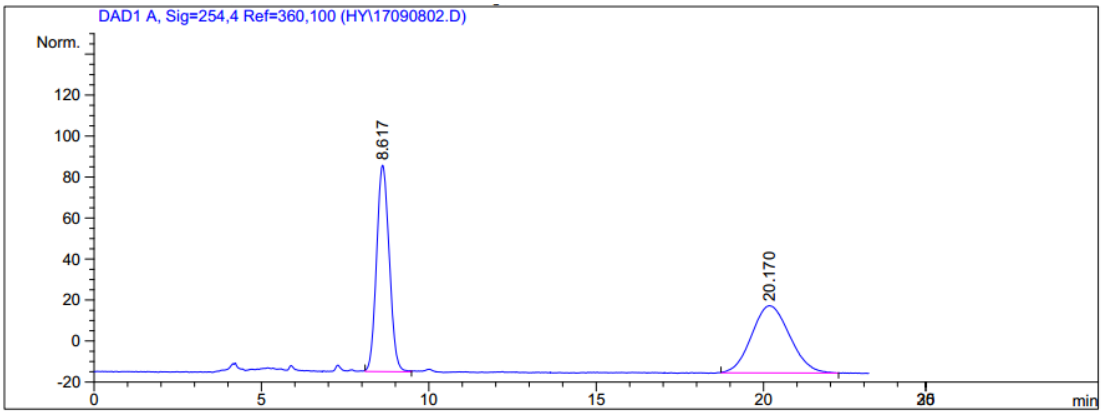
4ga

Prepared according to the procedure within 72 h as White solid (125.3 mg, 97% yield, dr > 20:1). mp 132.6 – 133.2 ºC; $[\alpha]_D^{15}$ = 308.12 (*c* 0.52, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 7.6 Hz, 2H), 8.27 – 7.98 (m, 3H), 7.40 – 7.65 (m 5H), 7.34 – 7.22 (m, 6H), 7.06 – 7.17 (m, 5H), 6.62 – 6.43 (m, 3H), 6.03 (d, *J* = 3.2 Hz, 1H), 4.85 (dd, *J* = 31.6, 15.8 Hz, 2H), 4.31 (d, *J* = 15.9 Hz, 1H), 3.70 – 3.45 (m, 2H), 2.66 (d, *J* = 3.5 Hz, 1H), 0.44 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.74, 175.09, 167.65, 155.05, 143.12, 138.16, 136.38, 135.20, 130.76, 129.64, 129.61, 129.01, 128.94, 128.61, 128.56, 128.41, 128.32, 127.68, 127.56, 127.22, 126.65, 125.72, 125.37, 123.48, 119.32, 108.62, 70.73, 69.31, 60.90, 60.20, 59.38, 43.93, 13.12; HRMS (ESI)

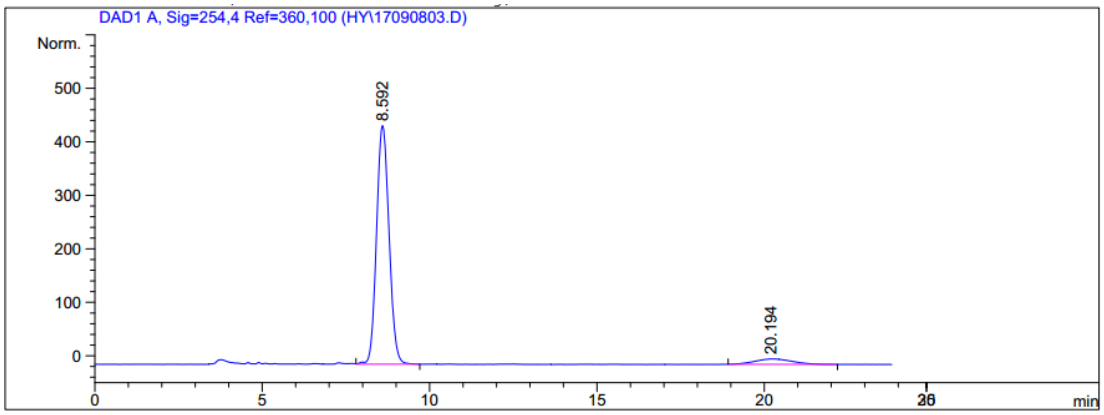
m/z Calcd. for $C_{41}H_{35}N_4O_4^+$ ([M+H]$^+$) 647.2653, Found 647.2642; Enantiomeric excess was determined to be 87% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 8.6 min, t_{minor} = 20.2 min).





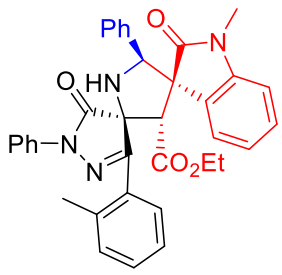


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.617	BB	0.4153	2653.98486	100.75963	50.5429
2	20.170	BB	1.0840	2596.96558	32.78823	49.4571



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.592	VB	0.4060	1.15393e4	445.73947	93.6033
2	20.194	BB	0.9335	788.57892	10.15983	6.3967

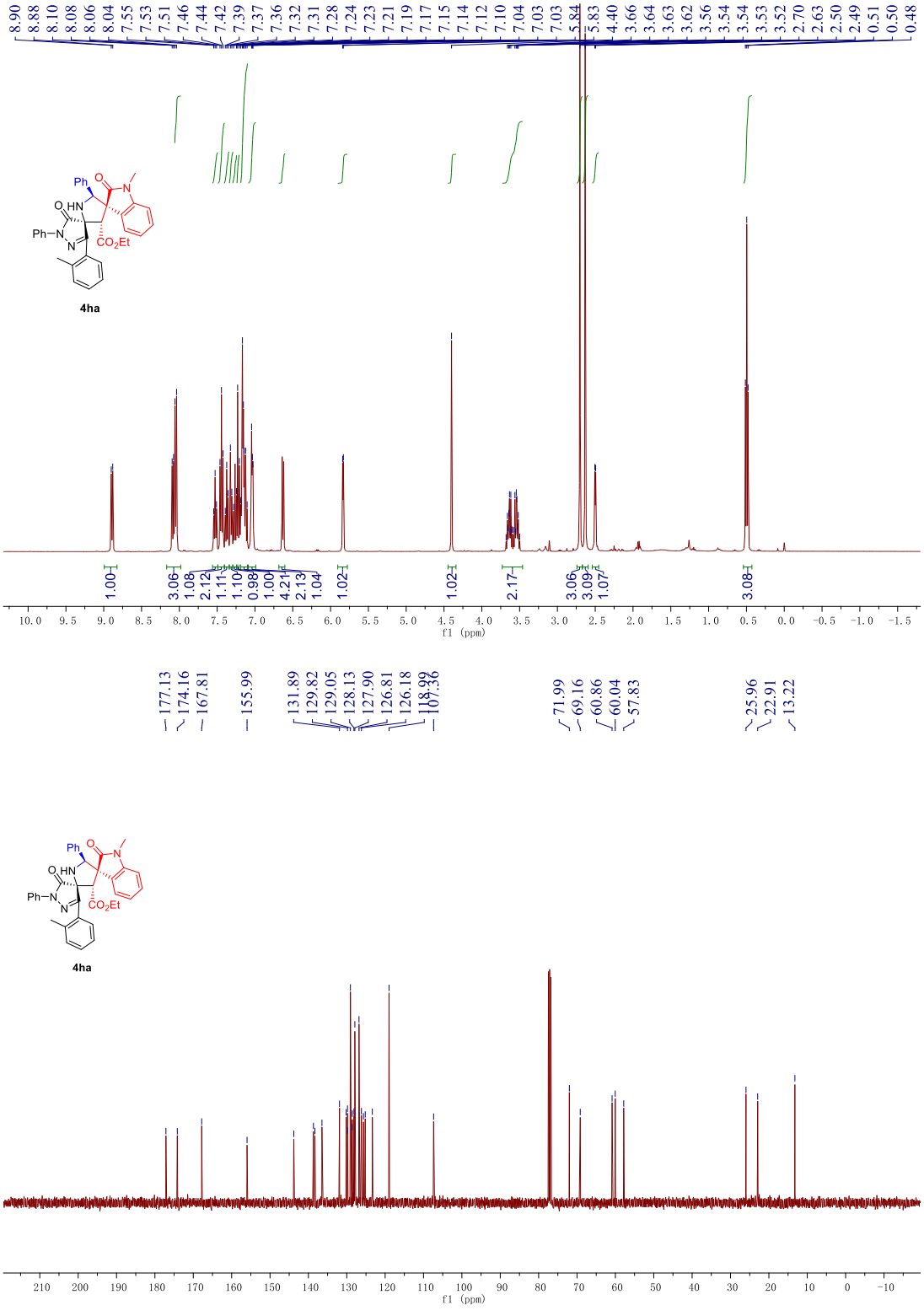
4ha

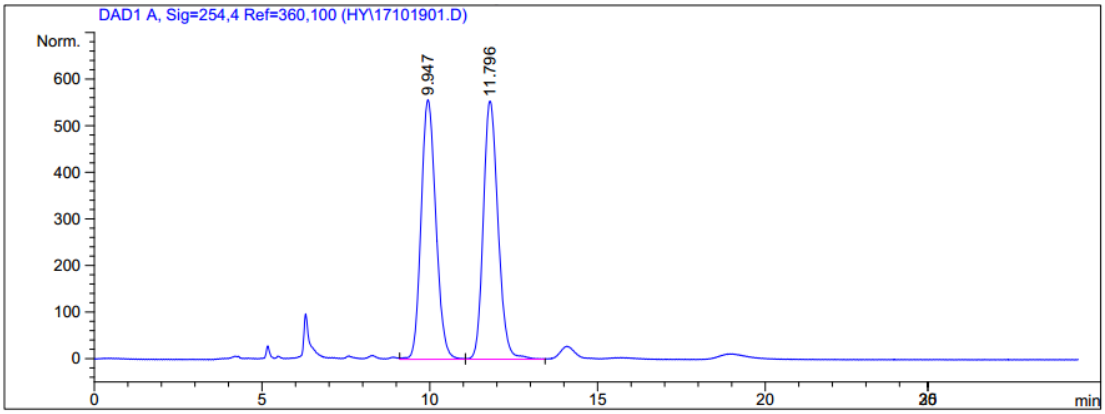


4ha

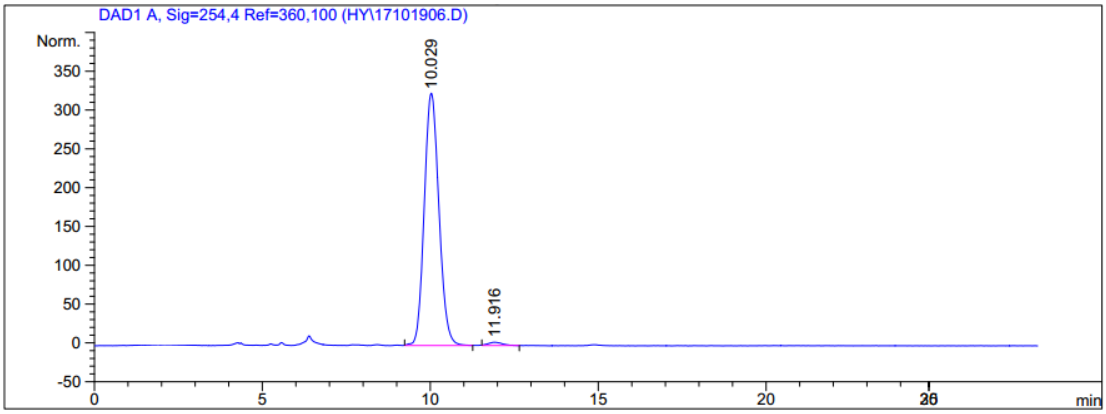
Prepared according to the procedure within 96 h as White solid (108.6 mg, 93% yield, dr > 20:1). mp 115.2 – 116.2 ºC; $[\alpha]_D^{19}$ = -333.70 (*c* 0.86, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, *J* = 7.8 Hz, 1H), 8.07 (dd, *J* = 15.5, 7.8 Hz, 3H), 7.53 (dd, *J* = 7.5 Hz, 1H), 7.52 – 7.41 (m, 2H), 7.37 (dd, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 7.26 (dd, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 9.5 Hz, 1H), 7.19 – 7.11 (m, 4H), 7.07 – 7.00 (m, 2H), 6.63 (d, *J* = 7.7 Hz, 1H), 5.84 (d, *J* = 4.1 Hz, 1H), 4.40 (s, 1H),3.68 – 3.50 (m, 2H), 2.70 (s, 3H), 2.63 (s, 3H), 2.50 (d, *J* = 4.2 Hz, 1H), 0.50 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.13, 174.16, 167.81, 155.99, 143.81, 138.69, 138.30, 136.47, 131.89, 130.16, 129.82, 129.75, 129.05,

128.60, 128.56, 128.13, 127.90, 126.81, 126.18, 125.66, 125.19, 123.34, 118.99, 107.36, 71.99, 69.16, 60.86, 60.04, 57.83, 25.96, 22.91, 13.22; HRMS (ESI) m/z Calcd. for $C_{36}H_{33}N_4O_4^+$ ($[M+H]^+$) 585.2496, Found 585.2485; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 10.0 min, t_{minor} = 11.9 min).



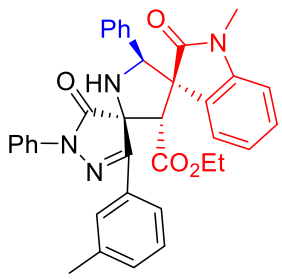


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	9.947	VV	0.4798	1.69987e4	557.46118	50.1127
2	11.796	VB	0.4722	1.69223e4	554.29669	49.8873



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	10.029	BB	0.4741	9868.39551	325.17874	98.7389
2	11.916	BB	0.4241	126.04471	4.22391	1.2611

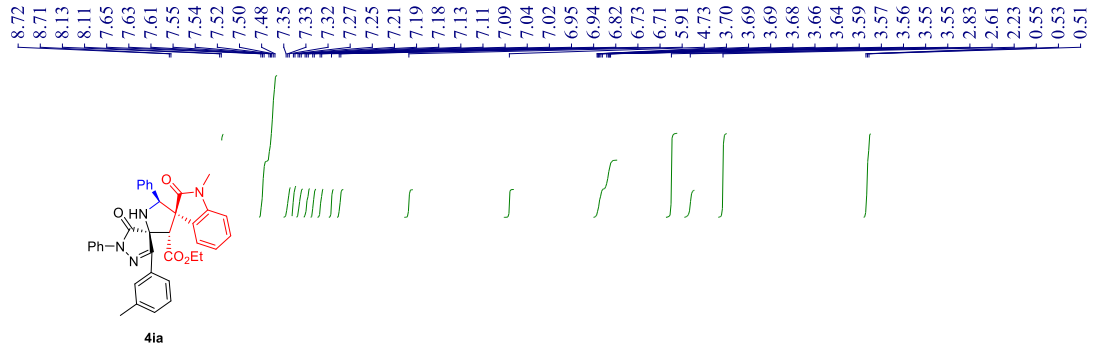
4ia

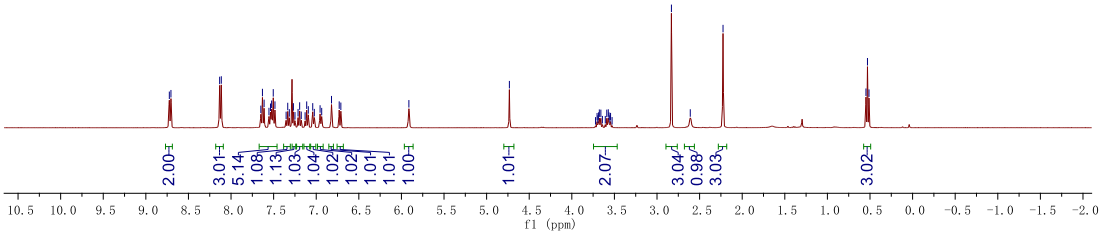


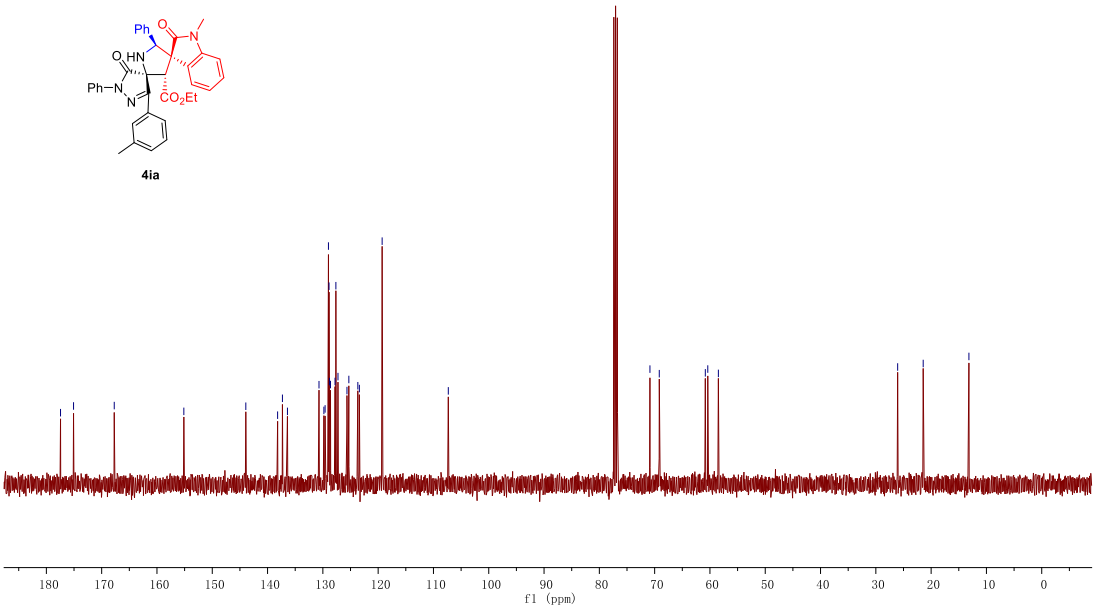
4ia

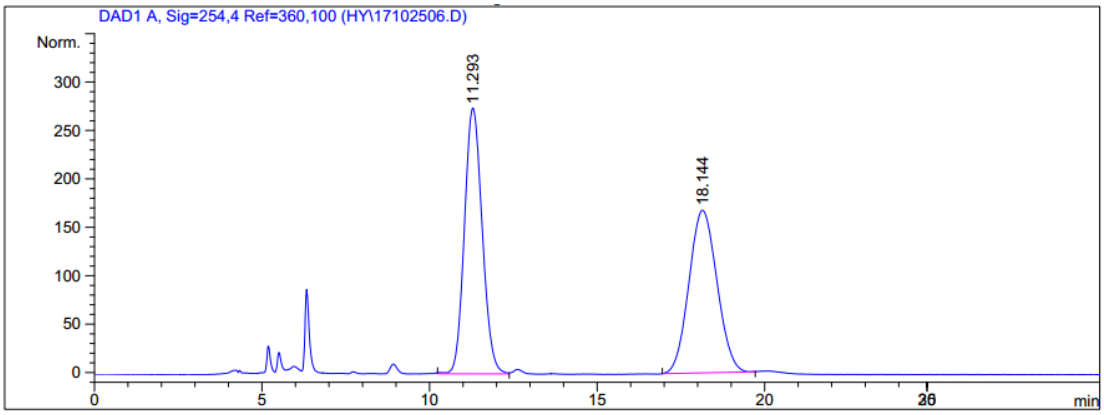
Prepared according to the procedure within 96 h as White solid (99.3 mg, 85% yield, dr > 20:1). mp 123.2 – 124.3 ºC; $[\alpha]_D^{17}$ = -239.93 (*c* 0.57, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71 (d, *J* = 7.6 Hz, 2H), 8.12 (d, *J* = 7.7 Hz, 3H), 7.46 – 7.56 (m, 5H), 7.33 (dd, *J* = 7.5 Hz, 1H), 7.26 (d, *J* = 7.4 Hz, 1H), 7.19 (dd, *J* = 7.5 Hz, 1H), 7.11 (dd, *J* = 7.5 Hz, 1H), 7.03 (d, *J* = 7.5 Hz, 1H), 6.95 (d, *J* = 7.6 Hz, 1H), 6.82 (s, 1H), 6.72 (d, *J* = 7.7 Hz, 1H), 5.91 (s, 1H), 4.73 (s, 1H), 3.75 – 3.47 (m, 2H), 2.83 (s, 3H), 2.63 (d, *J* = 17.8 Hz, 1H), 2.23 (s, 3H), 0.53 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.44, 175.09, 167.73, 155.14, 143.93, 138.18, 137.31, 136.40, 130.70, 129.82, 129.59, 128.99, 128.88, 128.81, 128.62,

127.80, 127.65, 127.27, 125.64, 125.30, 123.68, 123.40, 119.28, 107.32, 70.85, 69.16, 60.84, 60.39, 58.48, 26.05, 21.44, 13.17; HRMS (ESI) m/z Calcd. for $C_{36}H_{33}N_4O_4^+$ ($[M+H]^+$) 585.2496, Found 585.2494; Enantiomeric excess was determined to be 99% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 11.1 min, t_{minor} = 18.1 min).

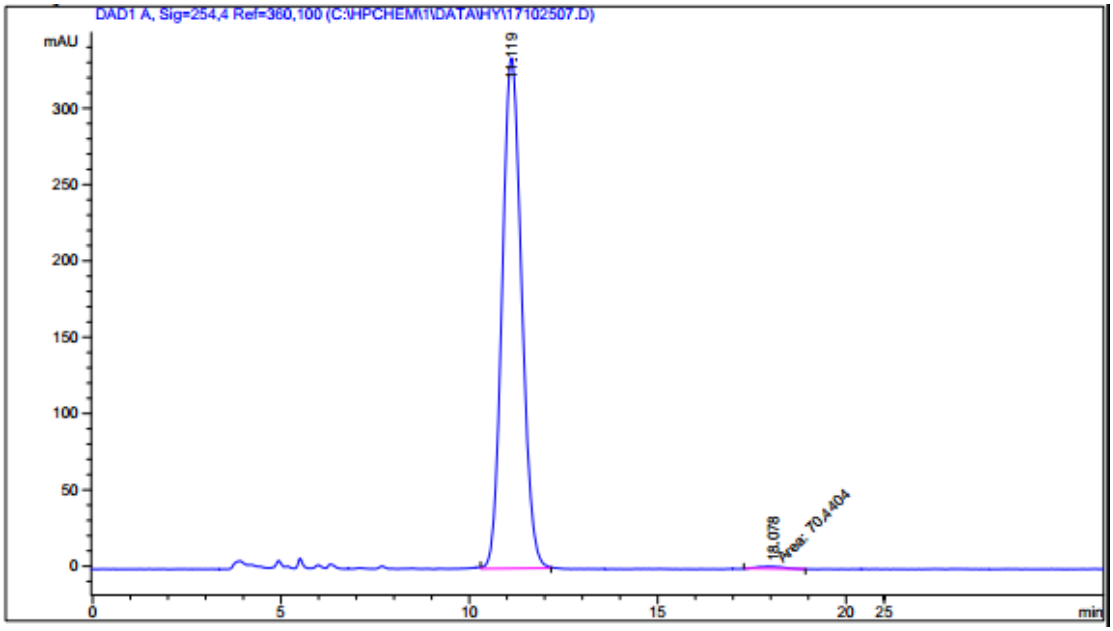






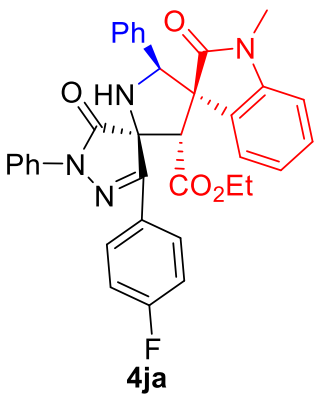


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.293	BV	0.5745	1.01308e4	274.53659	50.8869
2	18.144	BB	0.9068	9777.69531	168.04346	49.1131



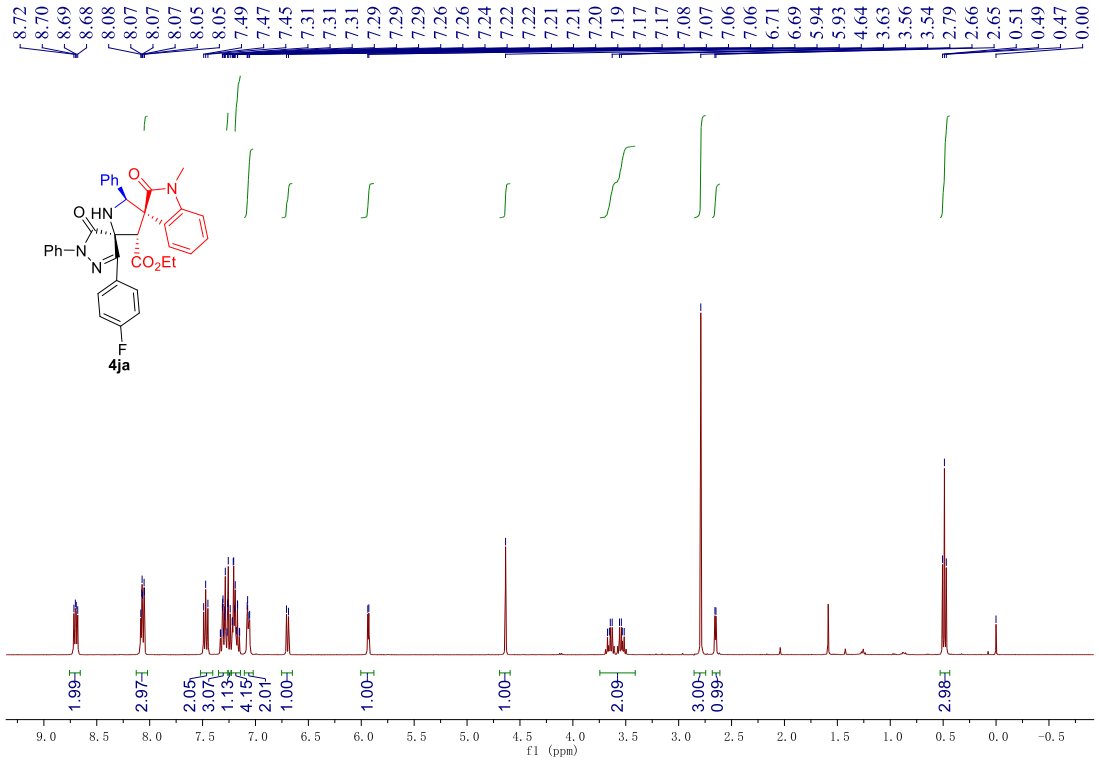
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	11.119	BB	0.5539	1.19781e4	334.40463	99.4154
2	18.078	MM	0.7875	70.44043	1.49080	0.5846

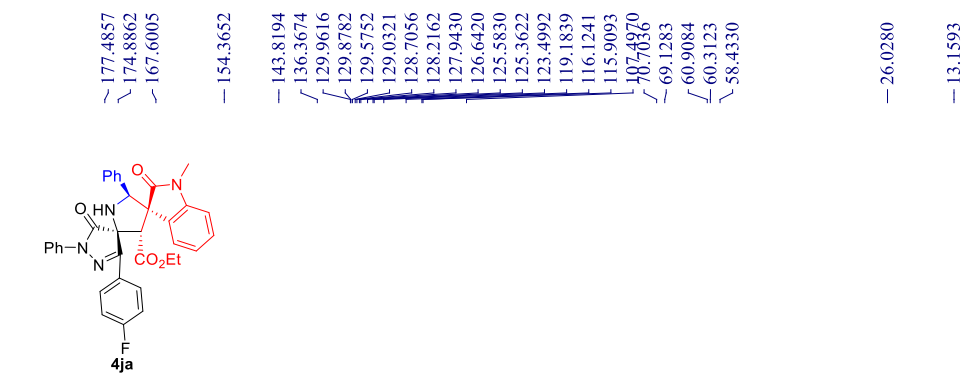
4ja

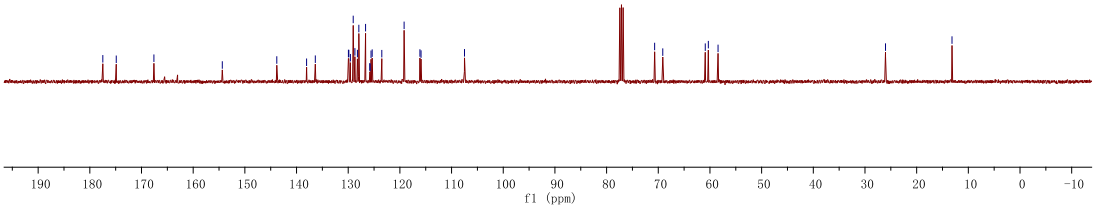


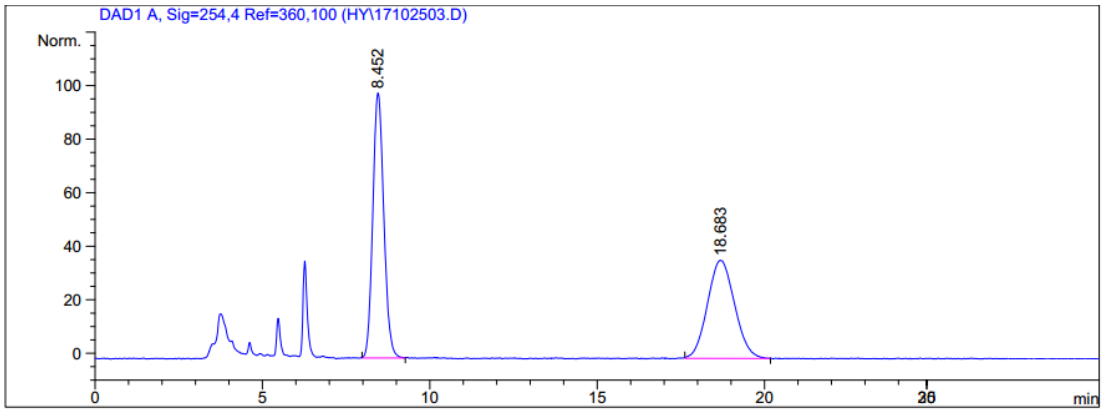
4ja

Prepared according to the procedure within 84 h as White solid (96.5 mg, 82% yield, dr > 20:1). mp 128.5.0 – 129.2 °C; $[\alpha]_D^{18}$ = -328.99 (*c* 0.75.9, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.76 – 8.66 (m, 2H), 8.13 – 8.02 (m, 3H), 7.50 – 7.44 (m, 2H), 7.35 – 7.26 (m, 3H), 7.25 (d, *J* = 7.4 Hz, 1H), 7.23 – 7.14 (m, 4H), 7.10 – 7.05 (m, 2H), 6.70 (d, *J* = 7.6 Hz, 1H), 5.93 (d, *J* = 7.4 Hz, 1H), 4.64 (s, 1H), 3.74 – 3.41 (m, 2H), 2.79 (s, 3H), 2.64 (t, *J* = 8.6 Hz, 1H), 0.49 (t, *J* = 7.1 Hz, 3H); ^{19}F NMR (376 MHz, $CDCl_3$) δ -108.68; ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.49, 174.89, 167.60, 154.37, 143.82, 138.05, 136.37, 129.96, 129.88, 129.58, 129.03, 128.71, 128.22, 127.94, 126.64, 125.80 (d, *J* = 3.2 Hz), 125.58, 125.36, 123.50, 119.18, 116.02 (d, *J* = 21.6 Hz), 107.50, 70.70, 69.13, 60.91, 60.31, 58.43, 26.03, 13.16; HRMS (ESI) m/z Calcd. for $C_{35}H_{30}FN_4O_4^+$ ($[M+H]^+$) 589.2246, Found 589.2228; Enantiomeric excess was determined to be 99%(determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 8.4 min t_{minor} = 18.7 min).

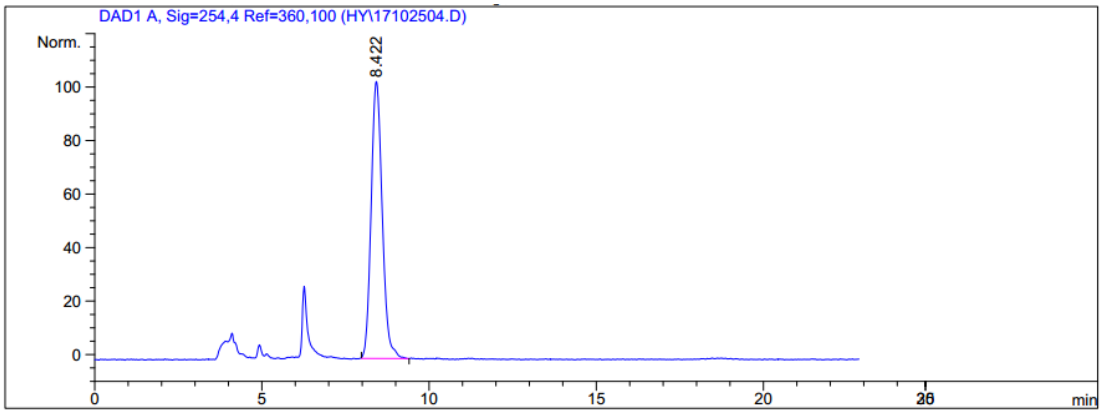






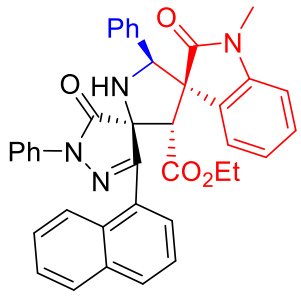


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.452	BB	0.3543	2260.18335	99.02084	52.3003
2	18.683	BB	0.8436	2061.36646	36.68541	47.6997



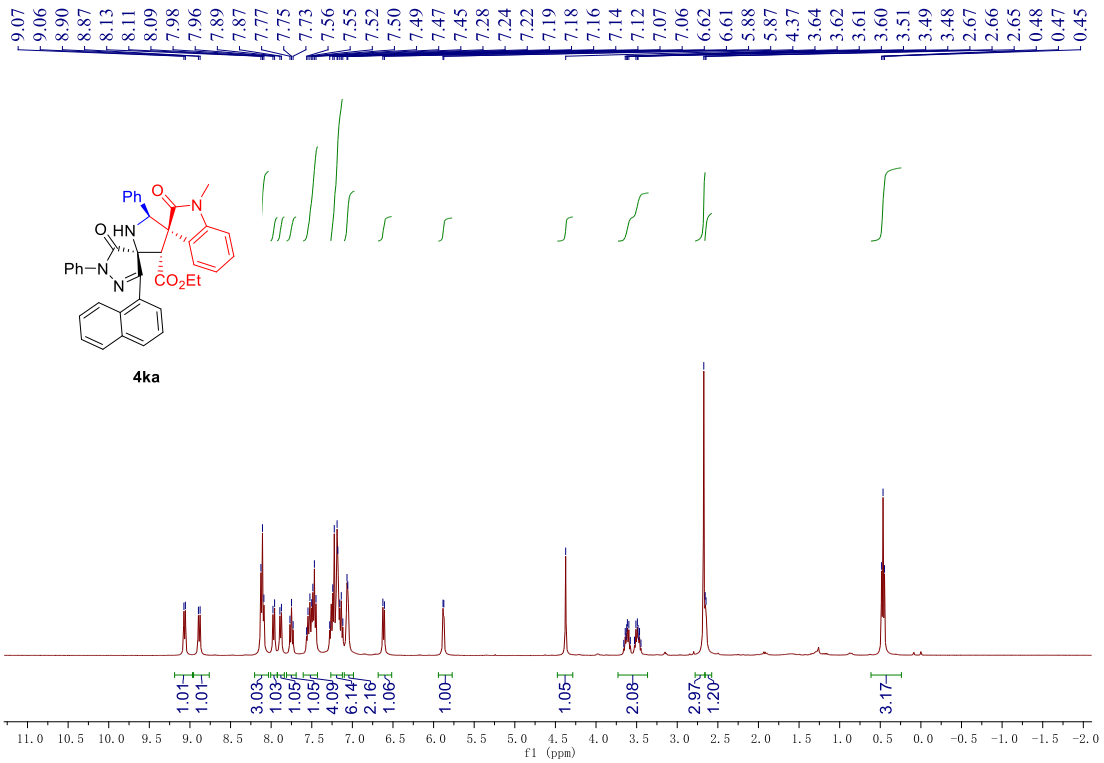
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.422	BP	0.3567	2385.19214	103.55997	100.0000

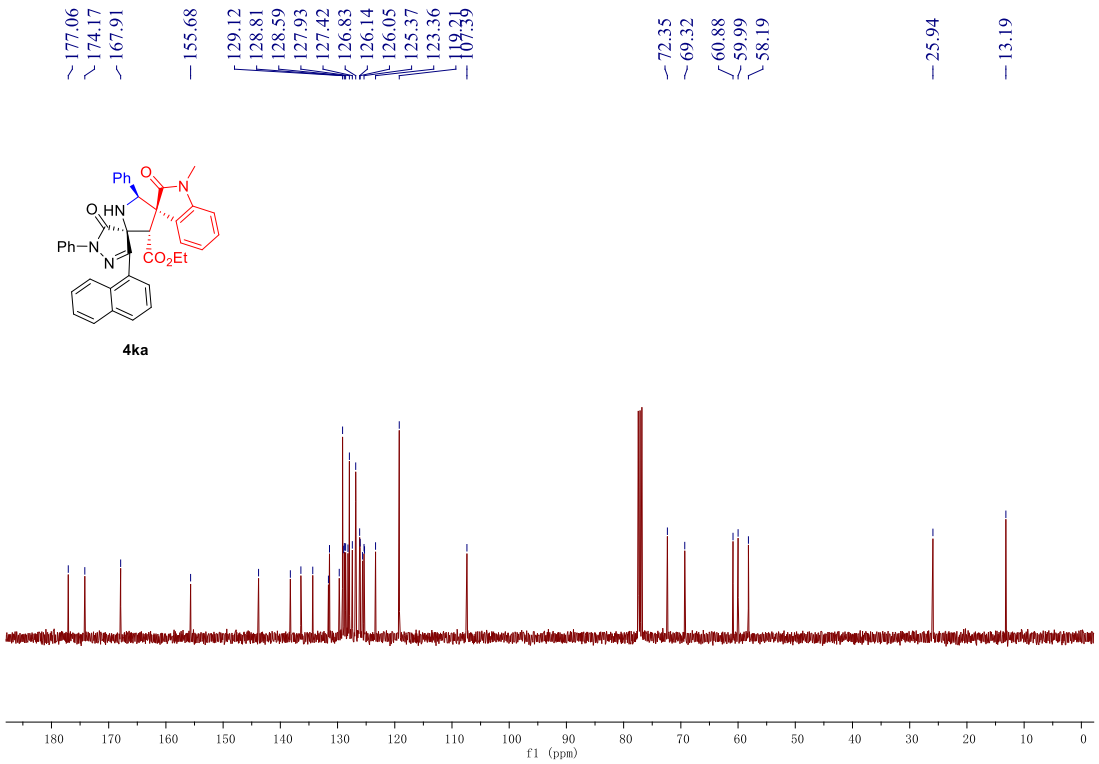
4ka

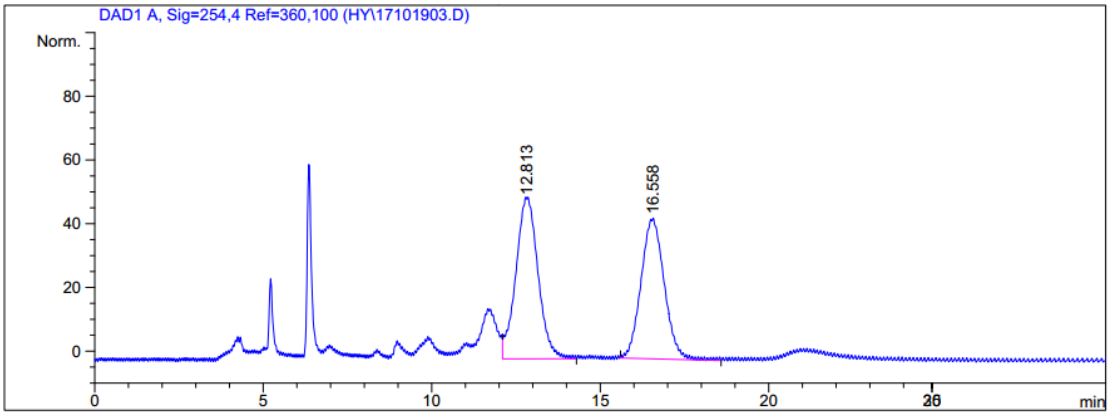


4ka

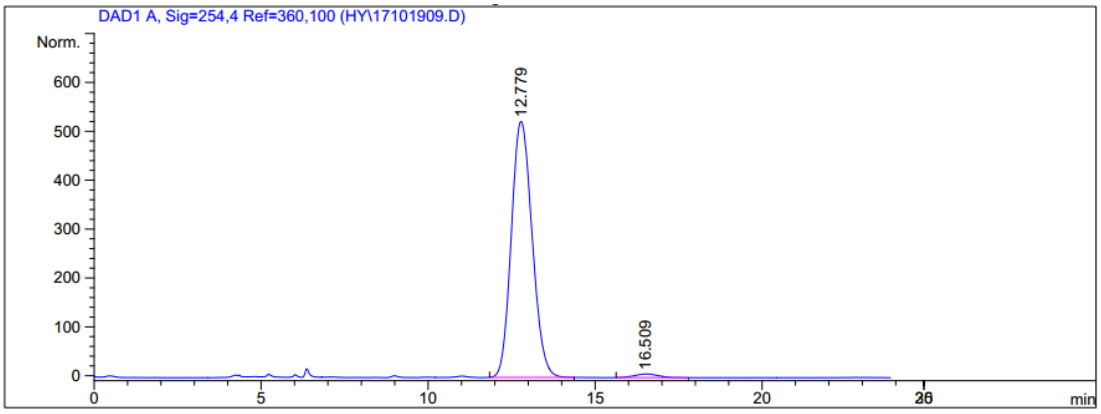
Prepared according to the procedure within 82 h as White solid (90.5 mg, 73% yield, dr > 20:1). mp 126.8 – 127.9 °C; $[\alpha]_D^{16}$ = -221.73 (*c* 0.65, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (d, *J* = 7.3 Hz, 1H), 8.89 (d, *J* = 8.3 Hz, 1H), 8.15 – 8.05 (m, 3H), 7.97 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.7 Hz, 1H), 7.75 (dd, *J* = 7.8 Hz, 1H), 7.59 – 7.41 (m, 4H), 7.30 – 7.11 (m, 6H), 7.09 – 7.01 (m, 2H), 6.61 (d, *J* = 7.6 Hz, 1H), 5.88 (d, *J* = 3.8 Hz, 1H), 4.37 (s, 1H), 3.69 – 3.40 (m, 2H), 2.66 (s, 3H), 2.65 (s, 1H), 0.47 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.06, 174.17, 167.91, 155.68, 143.80, 138.25, 136.41, 134.33, 131.59, 131.41, 129.70, 129.12, 128.92, 128.81, 128.59, 128.18, 127.93, 127.42, 126.83, 126.14, 126.05, 125.63, 125.37, 125.28, 123.36, 119.21, 107.39, 72.35, 69.32, 60.88, 59.99, 58.19, 25.94, 13.19; HRMS (ESI) m/z Calcd. for $C_{39}H_{33}N_4O_4^+$ ($[M+H]^+$) 621.2496, Found 621.2493; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 12.8 min, t_{minor} = 16.5 min).





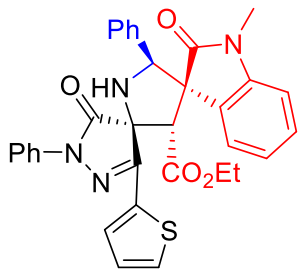


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.813	VP	0.5851	2325.48999	50.13725	52.2698
2	16.558	BP	0.5818	2123.52197	44.10070	47.7302



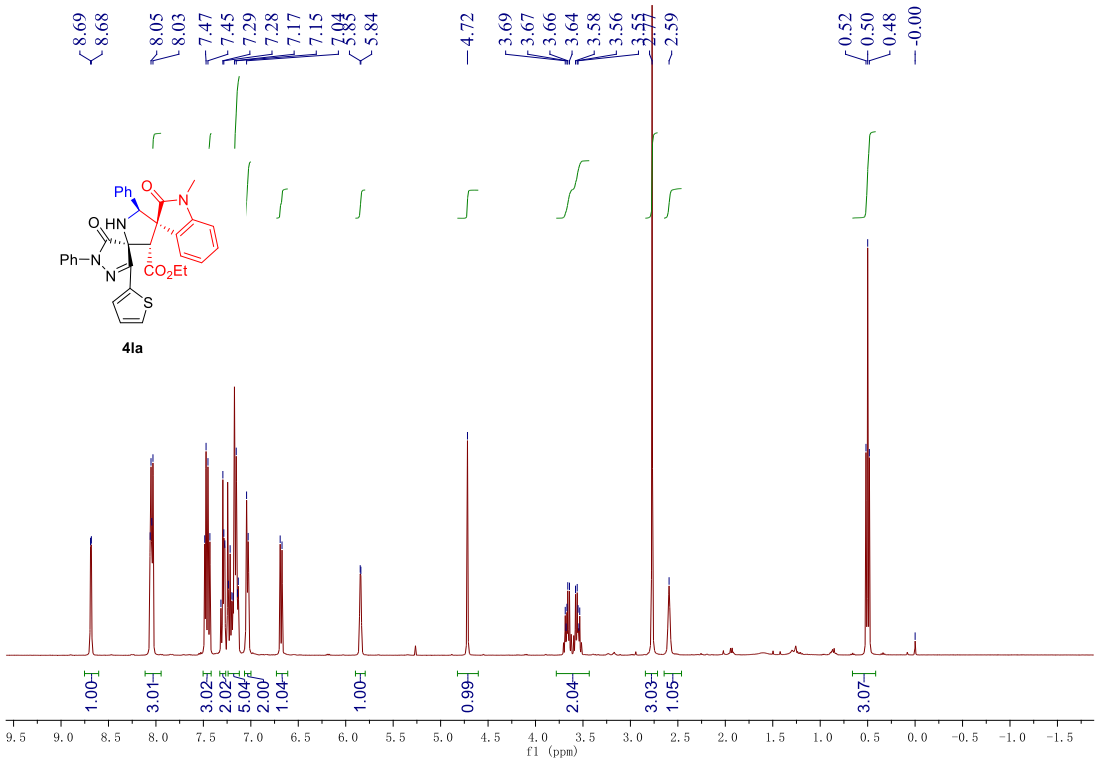
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.779	BB	0.6815	2.27002e4	523.90503	98.4278
2	16.509	BP	0.6173	362.58969	7.37825	1.5722

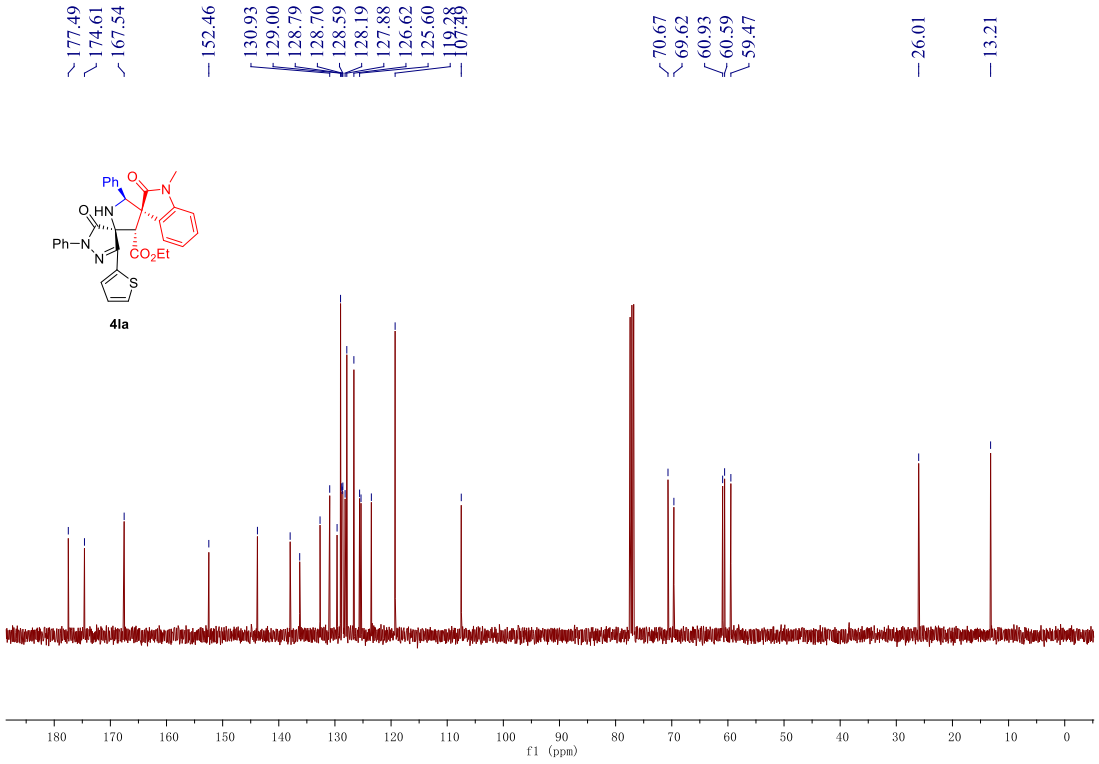
4la

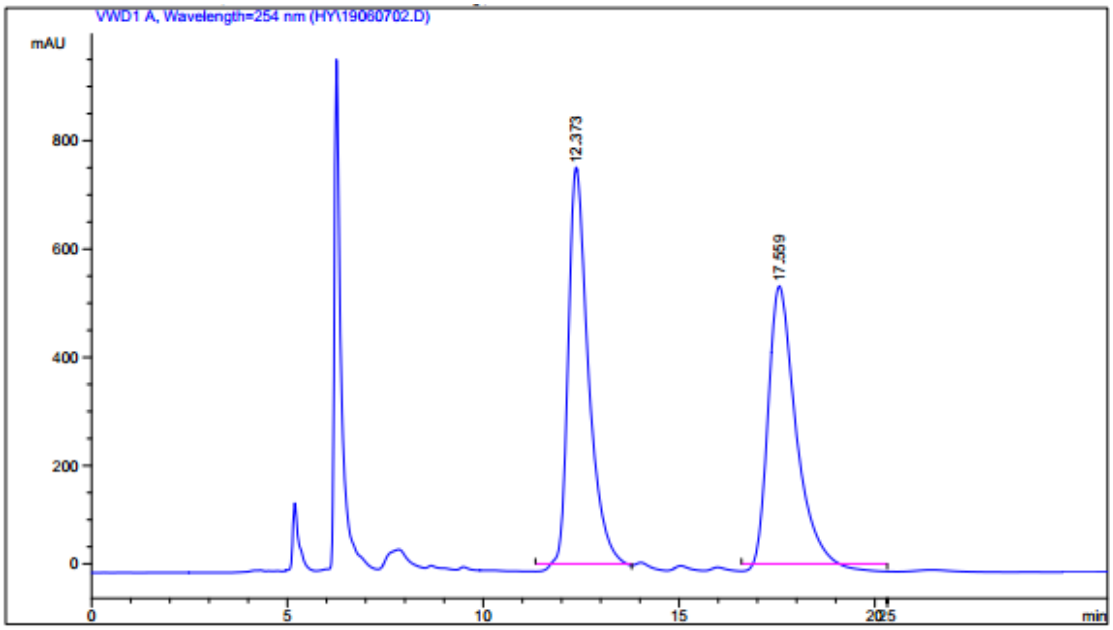


4la

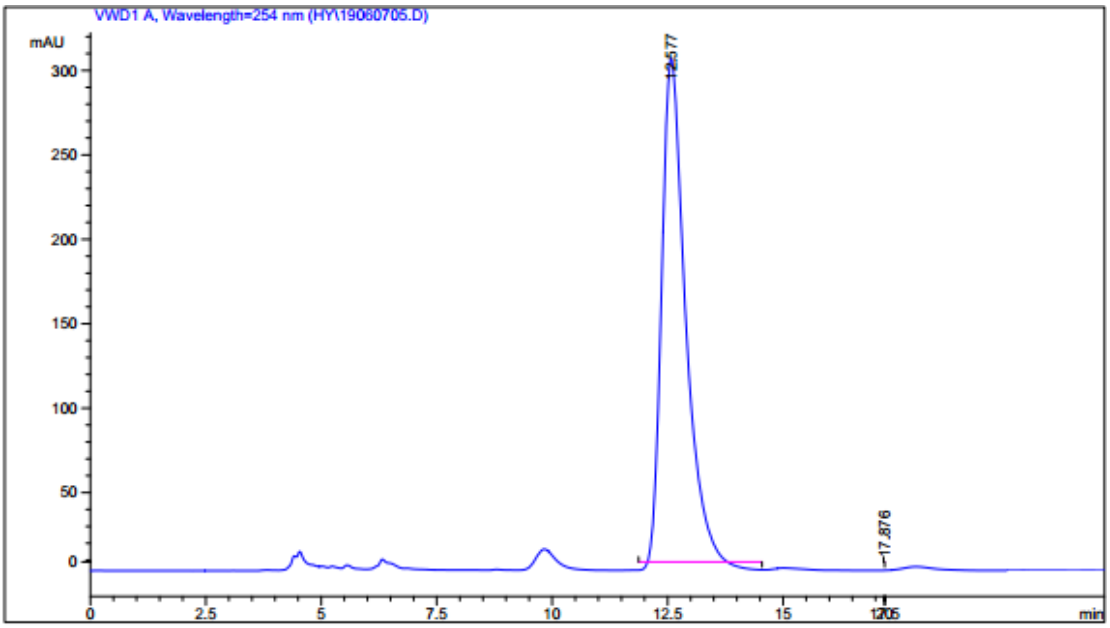
Prepared according to the procedure within 96 h as White solid (92.2 mg, 80% yield, dr > 20:1). mp 133.6.8 – 134.1 °C; $[\alpha]_D^{14}$ = -331.90 (*c* 0.72, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 3.6 Hz, 1H), 8.07 – 8.01 (m, 3H), 7.46 (dd, *J* = 14.9, 6.9 Hz, 3H), 7.33 – 7.26 (m, 2H), 7.24 – 7.11(m, 5H), 7.04 (d, *J* = 6.7 Hz, 2H), 6.68 (d, *J* = 7.7 Hz, 1H), 5.84 (d, *J* = 2.7 Hz, 1H), 4.72 (s, 1H), 3.71 – 3.51 (m, 2H), 2.77 (s, 3H), 2.59 (s, 1H), 0.50 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.49, 174.61, 167.54, 152.46, 143.80, 137.98, 136.28, 132.65, 130.93, 129.62, 129.00, 128.79, 128.70, 128.59, 128.19, 127.88, 126.62, 125.60, 125.35, 123.51, 119.28, 107.49, 70.67, 69.62, 60.93, 60.59, 59.47, 26.01, 13.21; HRMS (ESI) m/z Calcd. for $C_{33}H_{29}N_4O_4S^+$ ([M+H]$^+$) 577.1904, Found 577.1902; Enantiomeric excess was determined to be 98% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 12.6 min, t_{minor} = 17.9 min).


8.69
8.68
8.05
8.03
7.47
7.45
7.29
7.28
7.17
7.15
7.04
5.85
5.84
4.72
3.69
3.67
3.66
3.64
3.58
3.56
3.55
2.59
0.52
0.50
0.48
-0.00
Ph
O
N
HN
Ph–N
N
CO2Et
S
4la
1.00
3.01
3.02
2.02
5.04
2.00
1.04
1.00
0.99
2.04
3.03
1.05
3.07
f1 (ppm)


177.49
174.61
167.54
152.46
130.93
129.00
128.79
128.70
128.59
128.19
127.88
126.62
125.60
119.28
107.49
70.67
69.62
60.93
60.59
59.47
26.01
13.21
Ph
O
N
HN
Ph–N
N
CO2Et
S
4la
f1 (ppm)

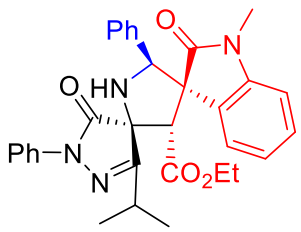


Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.373	VV	0.5513	2.79710e4	747.93073	50.6356
2	17.559	VB	0.7669	2.72688e4	528.17114	49.3644



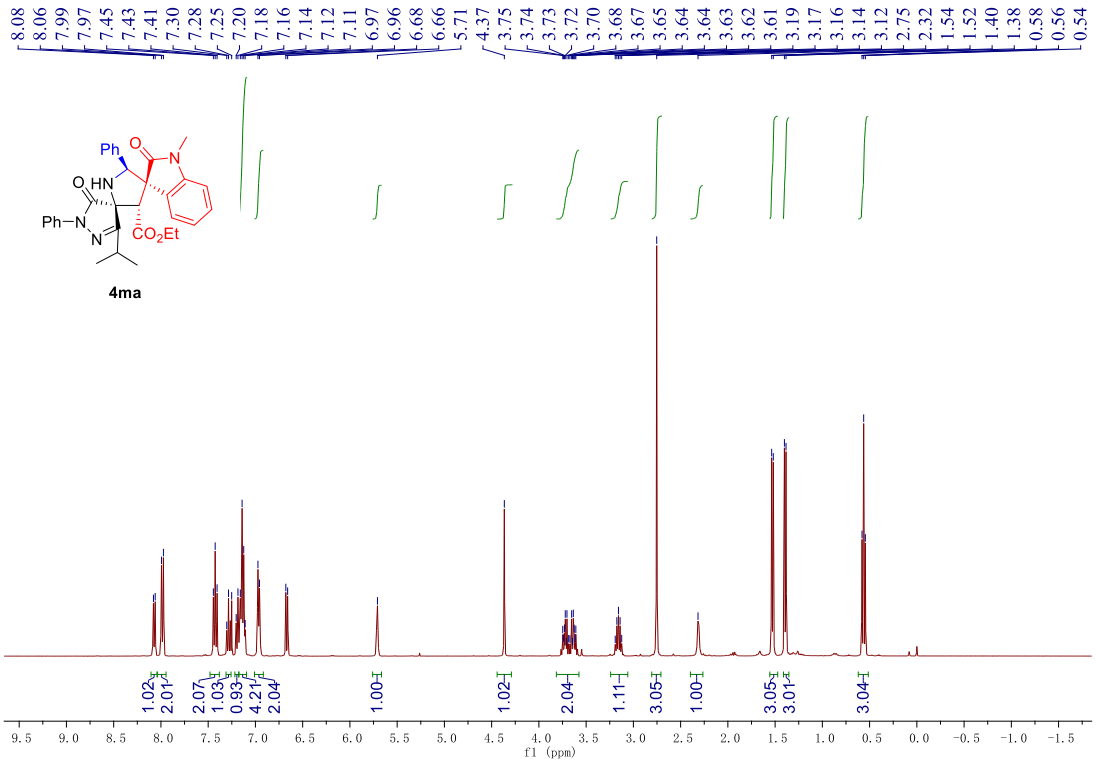
Peak #	RetTime [min]	Type	Width [min]	Area mAU *s	Height [mAU]	Area %
1	12.577	BB	0.5440	1.11789e4	303.01846	99.1009
2	17.876	BB	0.6082	101.42113	2.21016	0.8991

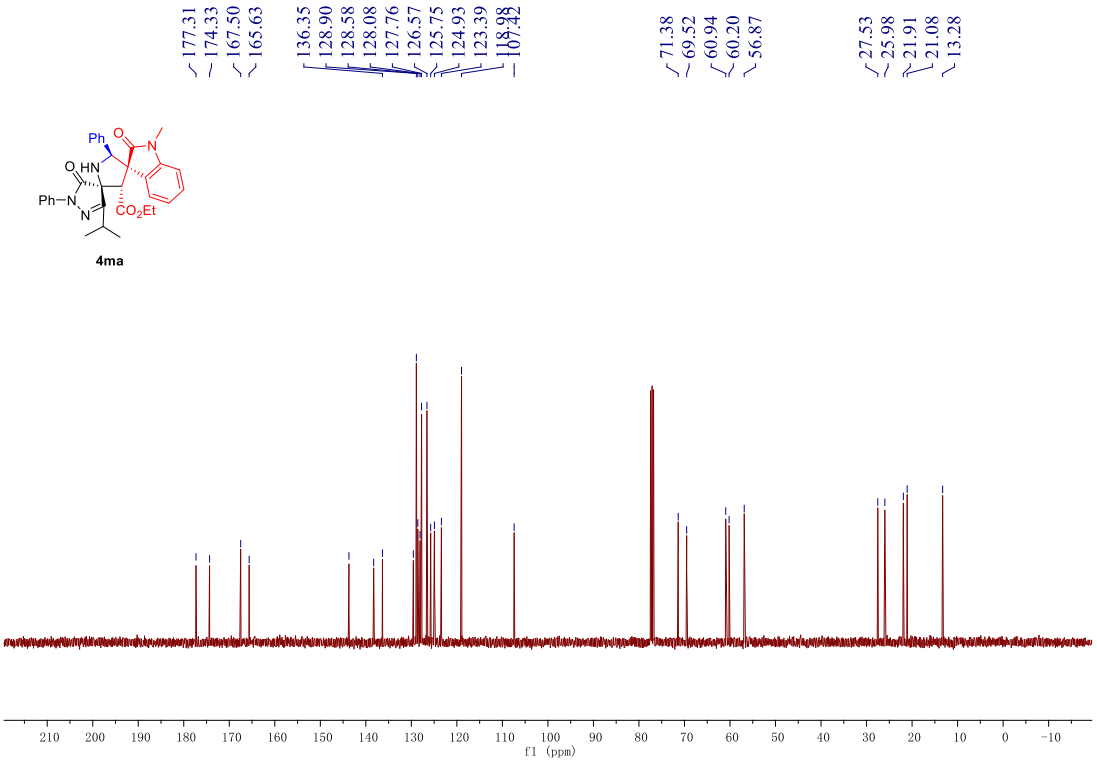
4ma

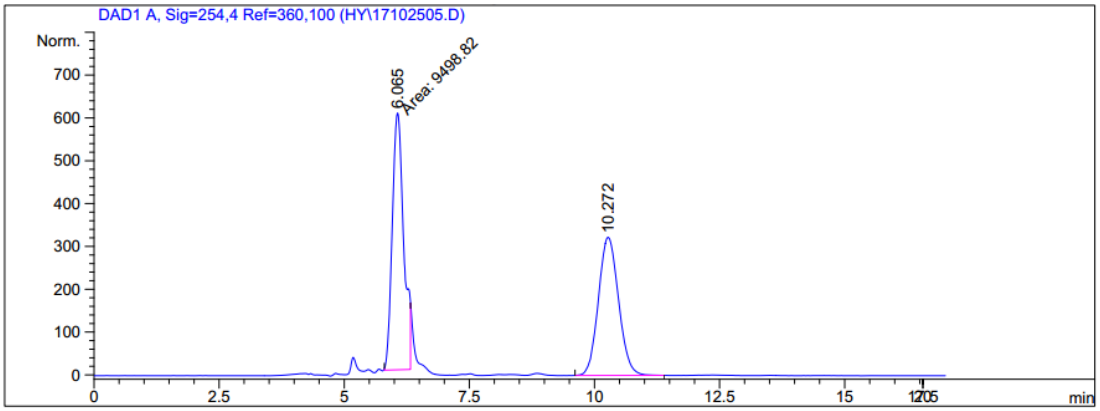


4ma

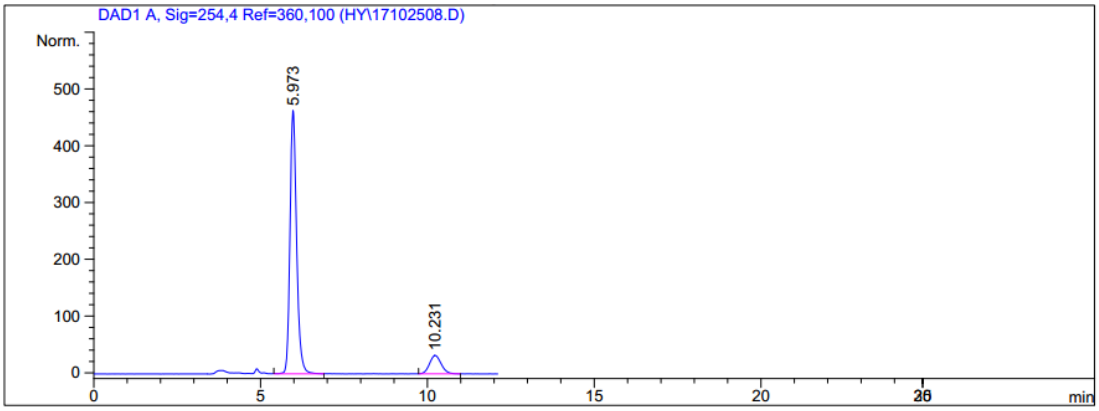
Prepared according to the procedure within 86 h as White solid (93.3 mg, 87% yield, dr > 20:1). mp 94.6 – 95.3 ºC; $[\alpha]_D^{18}$ = -220.77 (*c* 0.80, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 7.4 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.47 – 7.40 (m, 2H), 7.28 (dd, *J* = 7.6 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.17 – 7.10 (m, 4H), 6.96 (d, *J* = 6.6 Hz, 2H), 6.67 (d, *J* = 7.7 Hz, 1H), 5.71 (s, 1H), 4.37 (s, 1H), 3.75 – 3.61 (m, 2H), 3.16 (dt, *J* = 13.6, 6.8 Hz, 1H), 2.75 (s, 3H), 2.32 (s, 1H), 1.53 (d, *J* = 6.9 Hz, 3H), 1.39 (d, *J* = 6.8 Hz, 3H), 0.56 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.31, 174.33, 167.50, 165.63, 143.71, 138.28, 136.35, 129.56, 128.90, 128.58, 128.08, 127.76, 126.57, 125.75, 124.93, 123.39, 118.98, 107.42, 71.38, 69.52, 60.94, 60.20, 56.87, 27.53, 25.98, 21.91, 21.08, 13.28; HRMS (ESI) m/z Calcd. for $C_{32}H_{33}N_4O_4^+$ ($[M+H]^+$) 537.2496, Found 537.2499; Enantiomeric excess was determined to be 78% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 6.0 min, t_{minor} = 10.2 min).





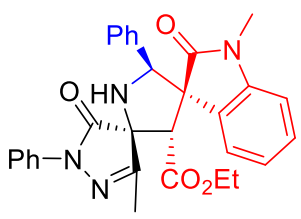


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.065	MM	0.2637	9498.81738	600.31177	51.2526
2	10.272	BB	0.4386	9034.53027	322.76035	48.7474



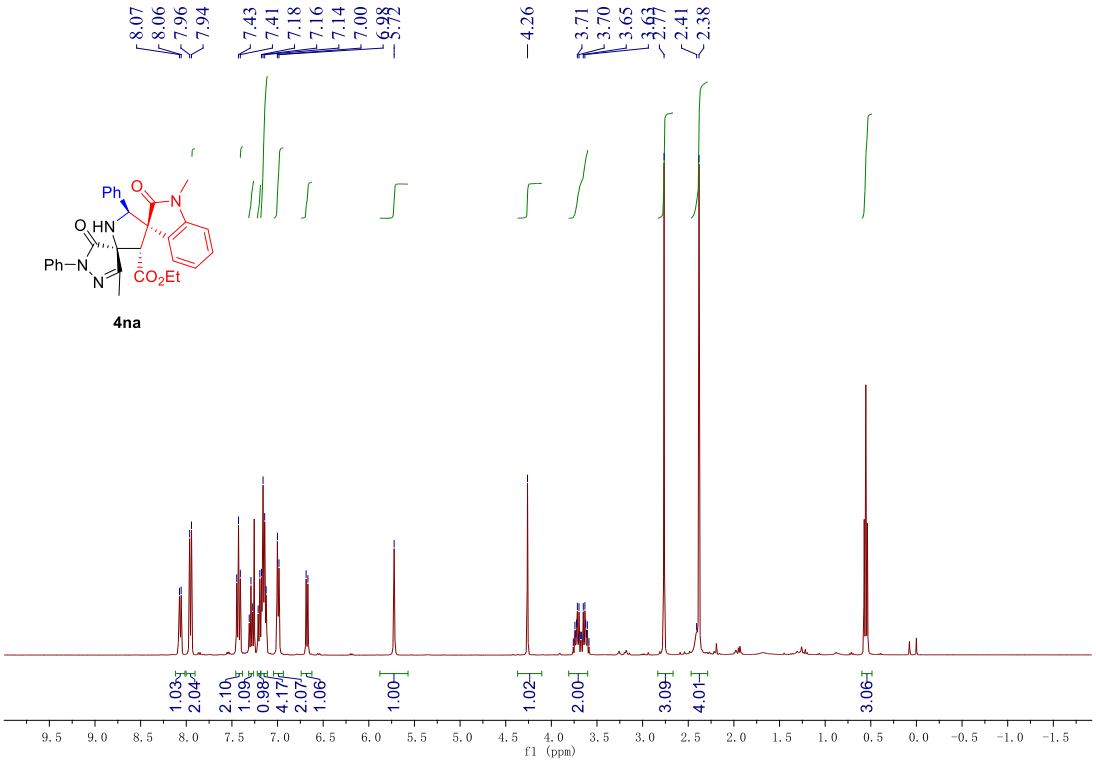
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.973	BB	0.2132	6408.82764	463.72354	89.0192
2	10.231	BB	0.3835	790.54883	32.53530	10.9808

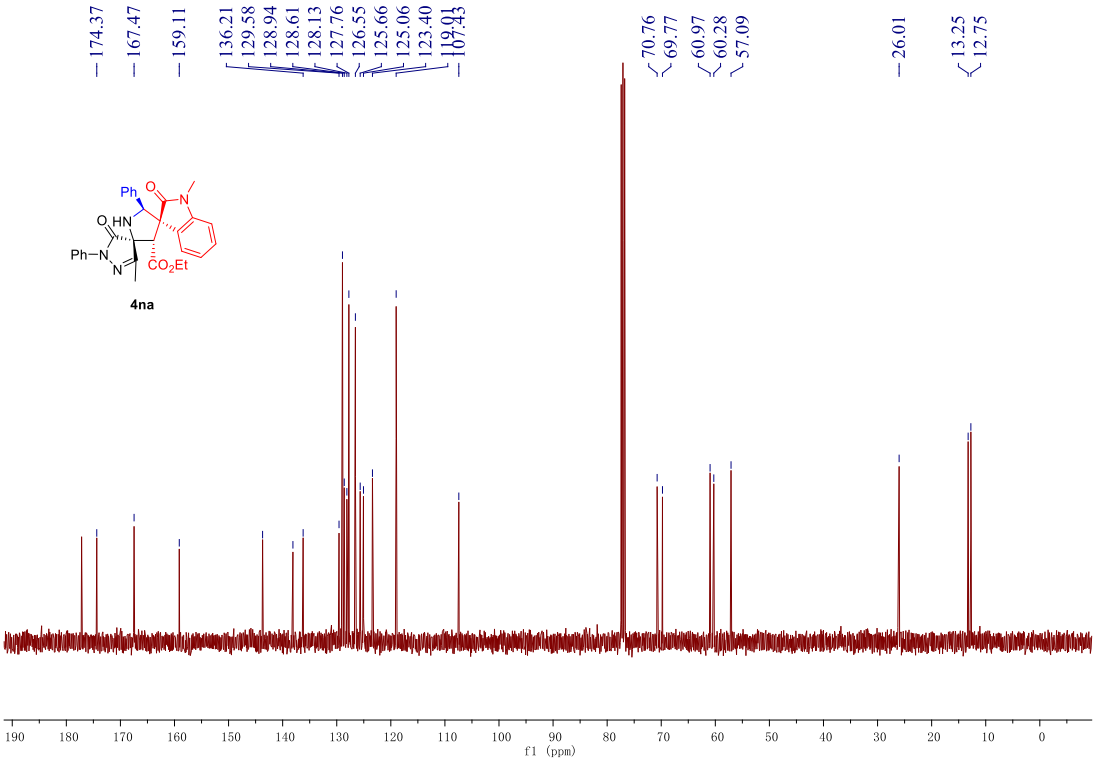
4na

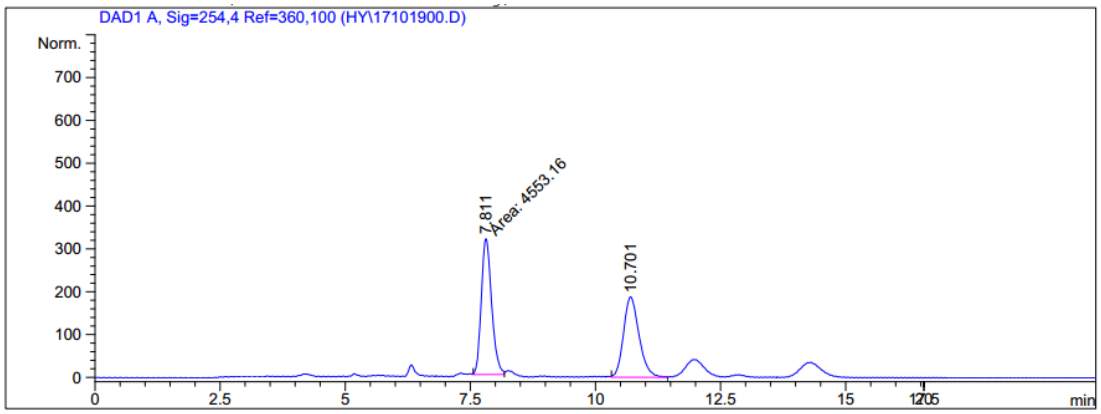


4na

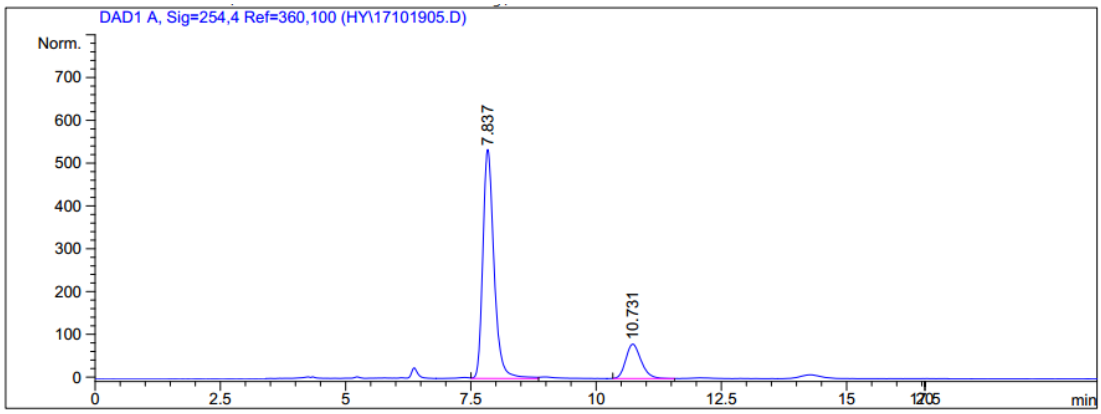
Prepared according to the procedure within 72 h as White solid (82.3 mg, 81% yield, dr > 20:1). mp 112.3 – 113.6 °C; $[\alpha]_D^{18}$ = -168.71 (*c* 0.47, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.4 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 2H), 7.46 – 7.40 (m, 2H), 7.32 (dd, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 7.3 Hz, 1H), 7.18 (dd, *J* = 13.6, 6.6 Hz, 4H), 7.02 (d, *J* = 6.8 Hz, 2H), 6.71 (d, *J* = 7.7 Hz, 1H), 5.75 (s, 1H), 4.29 (s, 1H), 3.80 – 3.59 (m, 2H), 2.79 (s, 3H), 2.44 (s, 1H), 2.41 (s, 3H), 0.58 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.18, 174.37, 167.47, 159.11, 143.71, 138.10, 136.21, 129.58, 128.94, 128.61, 128.13, 127.76, 126.55, 125.66, 125.06, 123.40, 119.01, 107.43, 70.76, 69.77, 60.97, 60.28, 57.09, 26.01, 13.25, 12.75; HRMS (ESI) m/z Calcd. for $C_{30}H_{29}N_4O_4^+$ ($[M+H]^+$) 509.2183, Found 509.2178; Enantiomeric excess was determined to be 66% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 7.8 min, t_{minor} = 10.7 min).


8.07
8.06
7.96
7.94
7.43
7.41
7.18
7.16
7.14
7.00
6.98
6.72
4.26
3.71
3.70
3.65
3.63
2.41
2.38
Ph
O
N
O
HN
Ph–N
N
CO2Et
4na
1.03
2.04
2.10
1.09
0.98
4.17
2.07
1.06
1.00
1.02
2.00
3.09
4.01
3.06
f1 (ppm)


174.37
167.47
159.11
136.21
129.58
128.94
128.61
128.13
127.76
126.55
125.66
125.06
123.40
119.01
107.43
70.76
69.77
60.97
60.28
57.09
26.01
13.25
12.75
Ph
O
N
O
HN
Ph–N
N
CO2Et
4na
f1 (ppm)

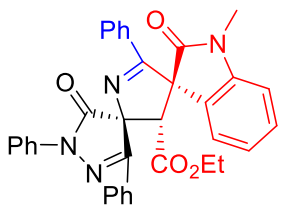


Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.811	MM	0.2390	4553.16455	317.55609	52.8711
2	10.701	BV	0.3240	4058.66113	187.88934	47.1289



Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.837	VB	0.2375	8316.05469	534.64166	82.9083
2	10.731	BB	0.3284	1714.37305	80.53384	17.0917

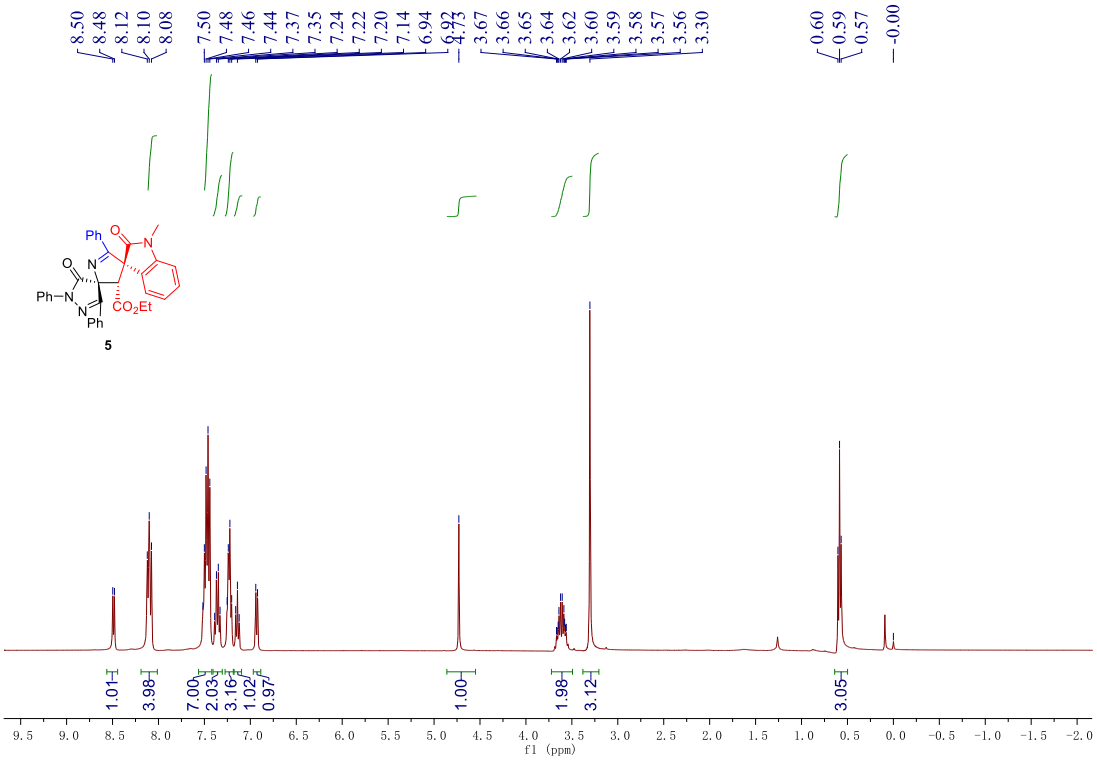
5

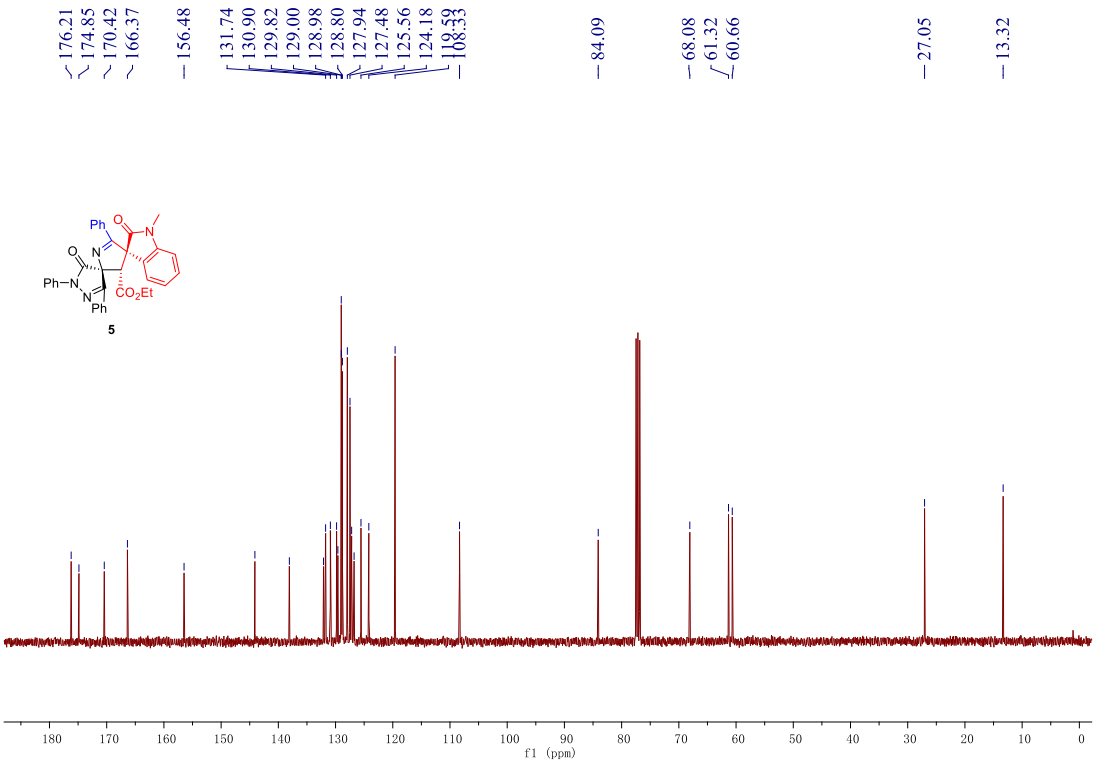


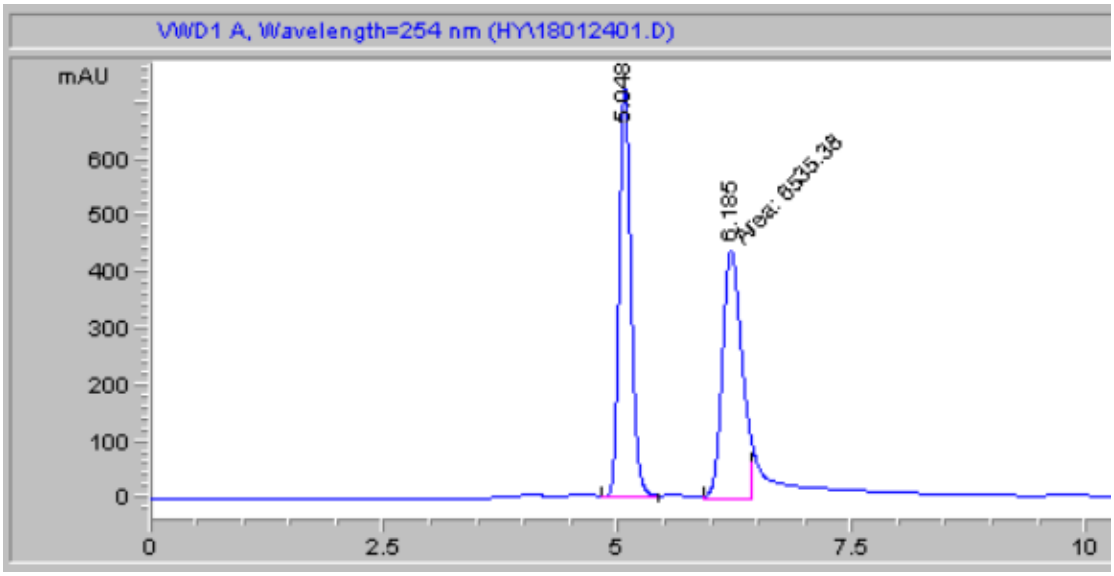
5

Prepared according to the procedure within 48 h as White solid (109.1 mg, 96% yield, dr > 20:1). mp 209.8 – 210.3 °C; $[\alpha]_D^{14}$ = -70.82 (*c* 0.83, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 7.5 Hz, 1H), 8.19 – 8.01 (m, 4H), 7.56 – 7.42 (m, 7H), 7.40 – 7.32 (m, 2H), 7.28 – 7.19 (m, 3H), 7.14 (dd, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 7.7 Hz, 1H), 4.73 (s, 1H), 3.69 – 3.53 (m, 2H), 3.30 (s, 3H), 0.59 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.21, 174.85, 170.42, 166.37, 156.48, 144.10, 138.07, 132.10, 131.74, 130.90, 129.82, 129.59, 129.00, 128.98, 128.80, 127.94, 127.48, 127.19, 126.76, 125.56, 124.18, 119.59, 108.33, 84.09, 68.08, 61.32, 60.66, 27.05, 13.32; HRMS (ESI) m/z Calcd. for $C_{35}H_{29}N_4O_4^+$ ($[M+H]^+$) 569.2183, Found 569.2179; Enantiomeric excess was determined to be 95% (determined by HPLC using chiral AD-H column,

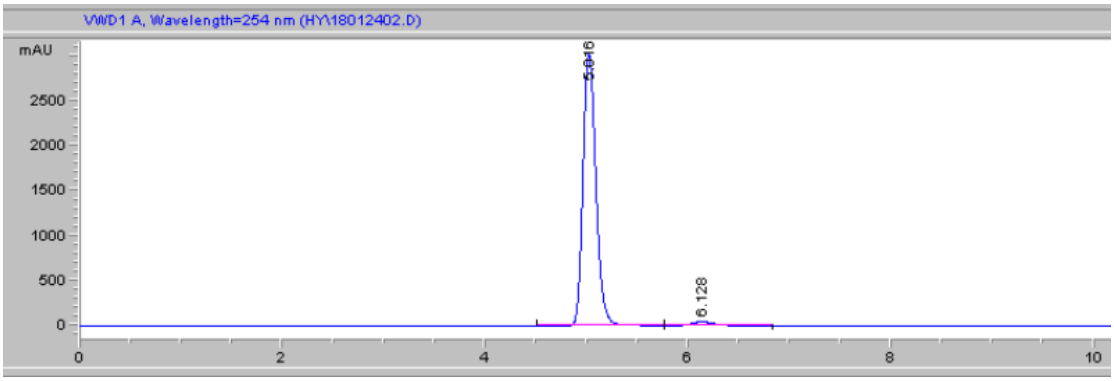
hexane/2-propanol = 70/30, λ = 254 nm, 30 ºC, 0.8 mL/min, t_{major} = 5.0 min, t_{minor} = 6.1 min).





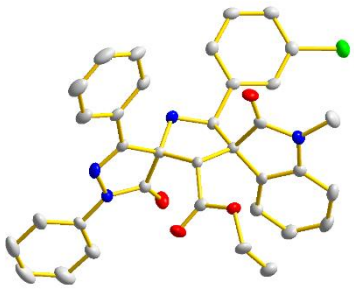


#	Time	Area	Height	Width	Area%	Symmetry
1	5.048	6494.5	735.4	0.1365	49.843	0.801
2	6.185	6535.4	440.8	0.2471	50.157	0.75



#	Time	Area	Height	Width	Area%	Symmetry
1	5.016	26732.8	3019.7	0.1382	97.457	0.781
2	6.128	697.7	44	0.2372	2.543	0.794

3. X-ray crystal structure of 4ad.



X-ray crystal structure of **4ad**.

Bond precision: C-C = 0.0049 A Wavelength=0.71073

Cell: a=6.4132(4) b=10.9919(7) c=40.683(2)
alpha=90 beta=90 gamma=90
Temperature: 173 K

	Calculated	Reported
Volume	2867.9(3)	2867.9(3)
Space group	P 21 21 21	P 21 21 21
Hall group	P 2ac 2ab	P 2ac 2ab
Moiety formula	C35 H30 Cl N4 O4	C35 H30 Cl N4 O4
Sum formula	C35 H30 Cl N4 O4	C35 H30 Cl N4 O4
Mr	606.08	606.08
Dx,g cm-3	1.404	1.404
Z	4	4
Mu (mm-1)	0.182	0.182
F000	1268.0	1268.0
F000'	1269.11	
h,k,lmax	8,13,50	8,13,50
Nref	5831[3372]	5813
Tmin,Tmax	0.974,0.982	0.638,0.746
Tmin'	0.964	

Correction method= # Reported T Limits: Tmin=0.638 Tmax=0.746
AbsCorr = NONE

Data completeness= 1.72/1.00 Theta(max)= 26.372

R(reflections)= 0.0435(4754) wR2(reflections)= 0.0979(5813)

S = 1.048 Npar= 403