

Asymmetric 1,3-dipolar cycloaddition of 4-aminopyrazolone-based azomethine ylides: a straightforward approach to spiropyrazolones

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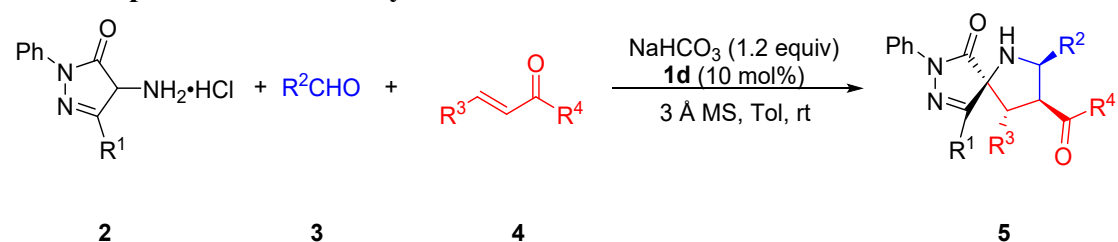
1. General information

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: $[\alpha]_D^T$ (c g/100 mL, solvent). All ^1H 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 ^1H 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 **5aea** 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: X. Bao, S. Wei, X. Qian, J. Qu, B. Wang, L. Zou and G. Ge, Asymmetric construction of a multi-pharmacophore-containing dispirotriheterocyclic scaffold and identification of a human carboxylesterase 1 inhibitor, *Org. Lett.*, 2018, **20**, 3394-3398.

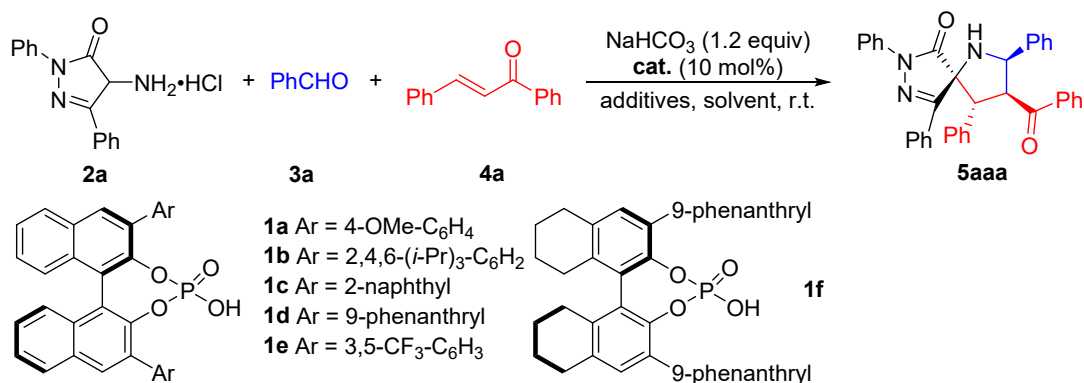
2. Experimental sections

General procedure for the synthesis of **5**



In a reaction tube, 4-amino pyrazolone **2** (0.24 mmol), α,β -enone **4** (0.20 mmol), catalyst (0.02 mmol) and 3 Å MS (200 mg) were added into toluene (2 mL). Then aldehyde **3** (0.24 mmol) and NaHCO_3 (0.24 mmol) were 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 **5**.

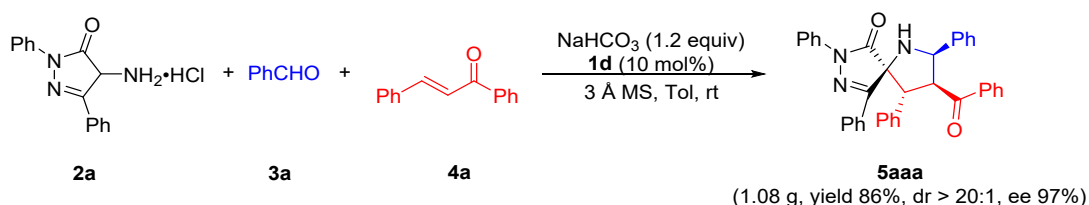
Table 1: Optimization of reaction conditions.^a CPA=chiral phosphoric acid.



Entry	Cat.	Additives	Solvent	Yield [%] ^b	dr ^c	ee [%] ^d
1	1a	3 Å	Tol.	94	>20:1	88
2	1b	3 Å	Tol.	70	>20:1	79
3	1c	3 Å	Tol.	92	>20:1	95
4	1d	3 Å	Tol.	87	>20:1	97
5	1e	3 Å	Tol.	78	>20:1	63
6	1f	3 Å	Tol.	82	>20:1	98
7	1d	3 Å	DCM	92	>20:1	90
8	1d	3 Å	Et ₂ O	97	>20:1	93
9	1d	3 Å	THF	58	>20:1	0
10	1d	3 Å	CHCl ₃	81	>20:1	88
11 ^e	1d	3 Å	Tol	45	>20:1	98
12 ^{ef}	1d	3 Å	Tol	68	>20:1	98
13	1d	4 Å	Tol	85	>20:1	98
14	1d	5 Å	Tol	64	>20:1	83
15	1d	MgSO ₄	Tol	60	>20:1	98

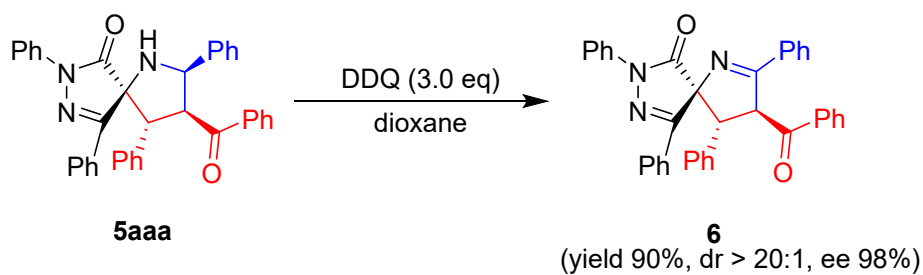
^aThe reaction was conducted with **2a** (0.12 mmol), **3a** (0.12 mmol), **4a** (0.10 mmol) and **cat.** (0.01 mmol), additives (100 mg) in solvent (1.0 mL) at room temperature. ^bIsolated yield. ^cThe dr was determined by ¹H NMR of crude product. ^dDetected by chiral HPLC analysis. ^eWithout NaHCO₃. ^fBy using Na₂CO₃.

Gram-scale reaction



In a reaction tube, 4-amino pyrazolone **2a** (2.76 mmol), **4a** (2.3 mmol), **1d** (0.23 mmol) and 3 Å MS (2300 mg) were added into toluene (23 mL). Then aldehyde **3a** (2.76 mmol) and NaHCO₃ (2.76 mmol) were 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 **5aaa** with 86% yield, >20:1 dr and 97% ee.

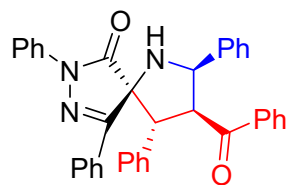
Procedure for the Synthesis of **6**



A reaction tube was charged with **5aaa** (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 **6** as a white solid.

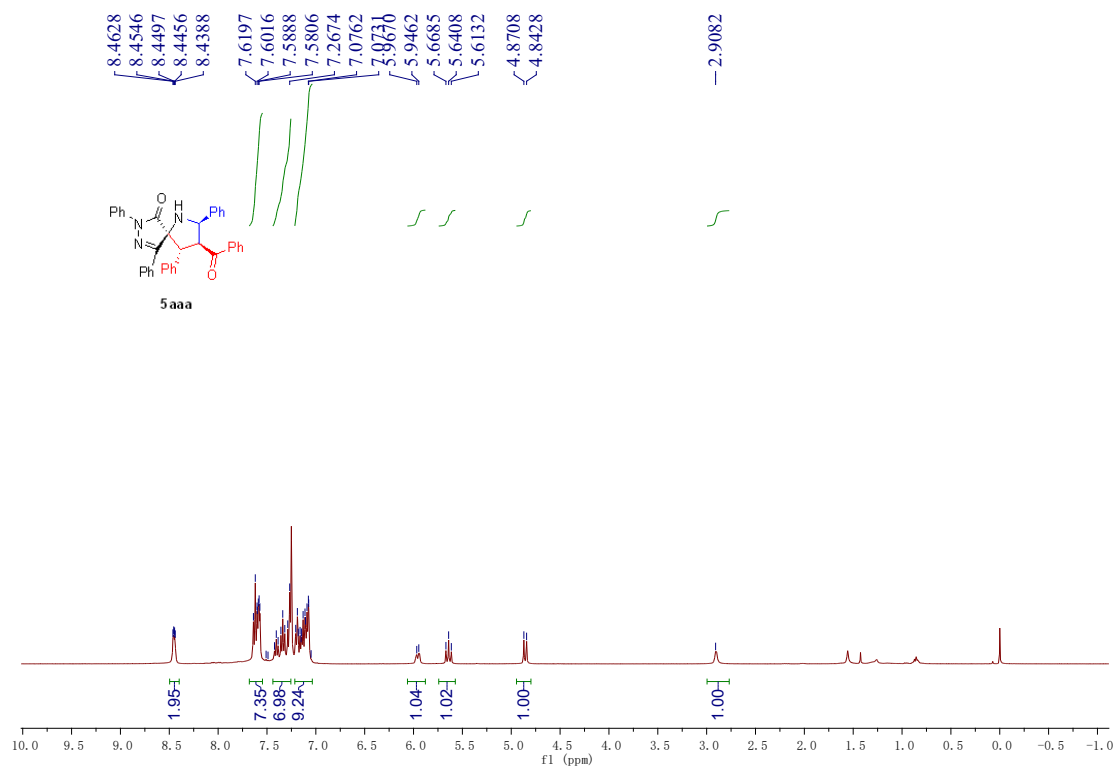
Copies of ^1H NMR and ^{13}C NMR spectra

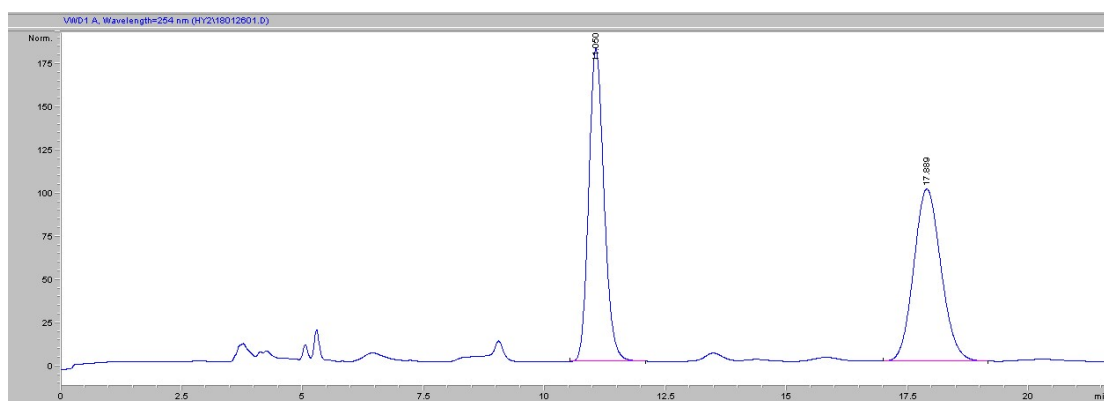
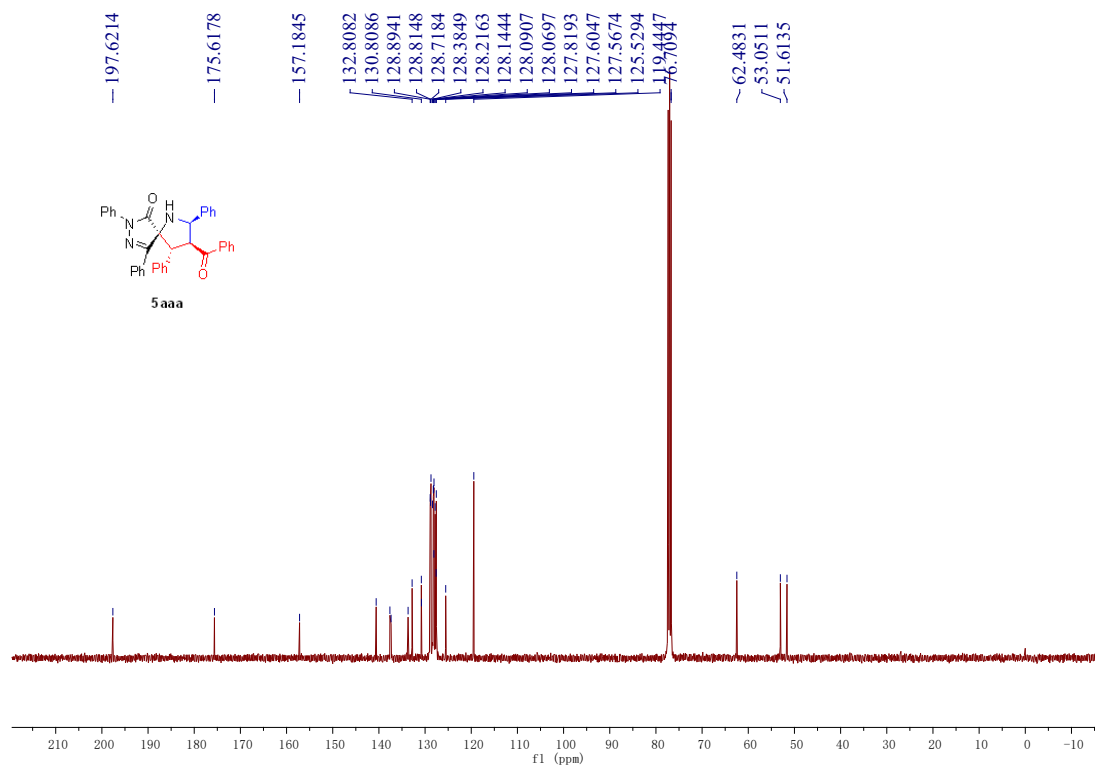
5aaa



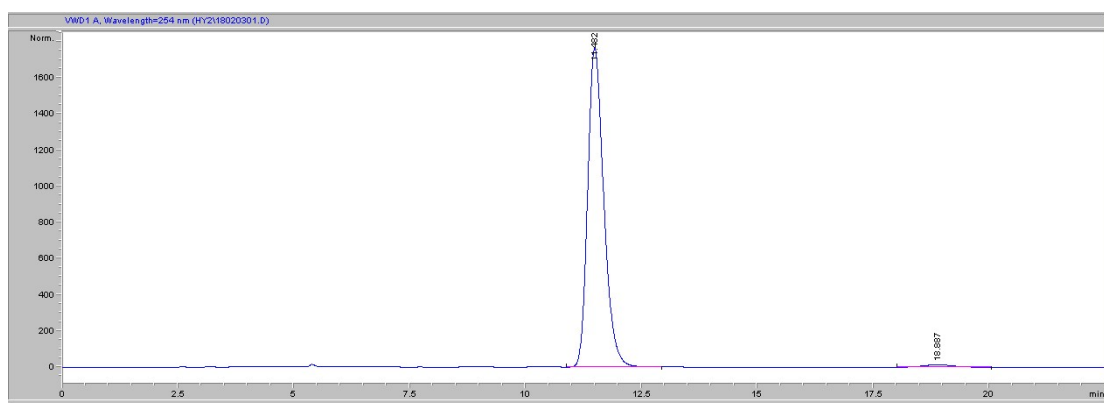
Prepared according to the procedure within 48 h as White solid

(95.2 mg, 87% yield, dr > 20:1). mp 125.1 – 126.9 °C; $[\alpha]_D^{19} = -70.408$ (c 0.49, CH_2Cl_2); ^1H NMR (400 MHz, CDCl_3) δ 8.50 – 8.40 (m, 2H), 7.68 – 7.55 (m, 7H), 7.44 – 7.26 (m, 7H), 7.22 – 7.04 (m, 9H), 5.96 (d, $J = 8.3$ Hz, 1H), 5.64 (t, $J = 11.1$ Hz, 1H), 4.86 (d, $J = 11.2$ Hz, 1H), 2.91 (s, 1H); ^{13}C NMR (101 MHz, CDCl_3) δ 197.62, 175.62, 157.18, 140.59, 137.62, 137.36, 133.68, 132.81, 130.81, 130.78, 128.89, 128.81, 128.72, 128.38, 128.22, 128.14, 128.09, 128.07, 127.82, 127.60, 127.57, 125.53, 119.44, 76.71, 62.48, 53.05, 51.61; HRMS (ESI) m/z Calcd. for $\text{C}_{37}\text{H}_{29}\text{N}_3\text{O}_2^+$ ($[\text{M}+\text{H}]^+$) 548.2333, Found 548.2315; Enantiomeric excess was determined to be 97% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, $\lambda = 254$ nm, 30 °C, 0.8 mL/min, $t_{\text{major}} = 11.5$ min, $t_{\text{minor}} = 18.9$ min).



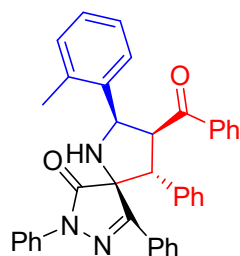


#	Time	Area	Height	Width	Area%	Symmetry
1	11.05	3991.3	181	0.3402	50.494	0.826
2	17.889	3913.1	99.8	0.6105	49.506	0.877



#	Time	Area	Height	Width	Area%	Symmetry
1	11.482	42673.6	1762.2	0.3728	98.650	0.722
2	18.887	583.9	13.4	0.6817	1.350	0.937

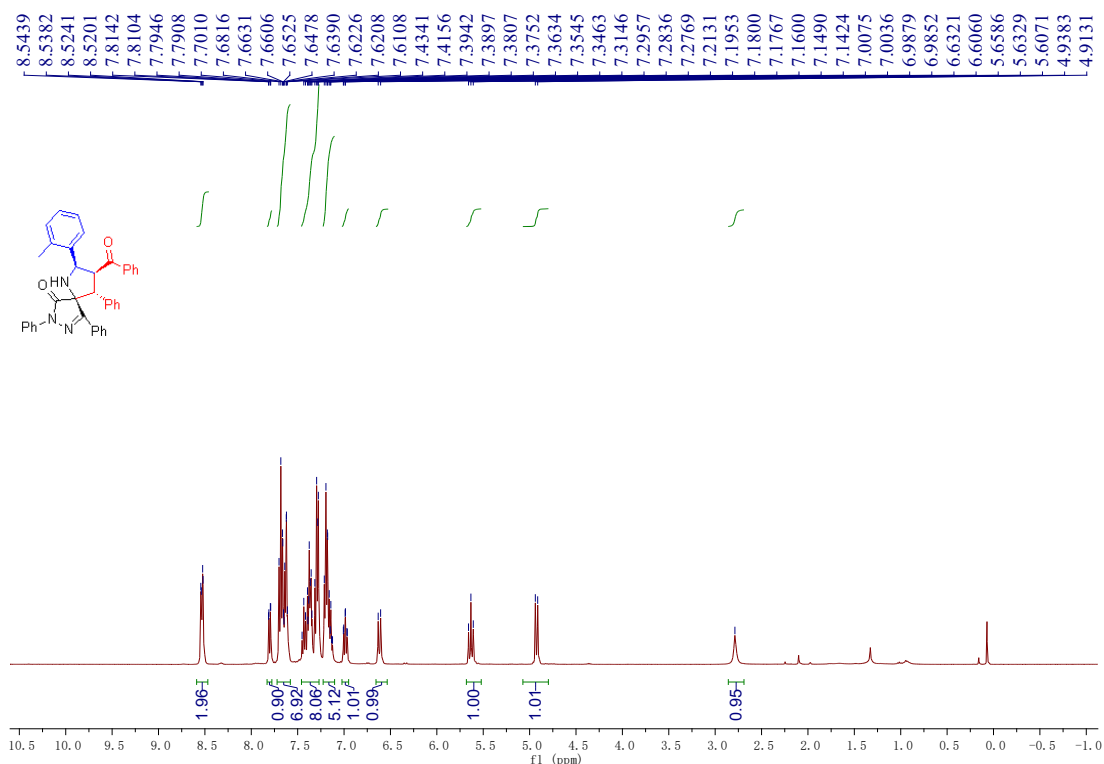
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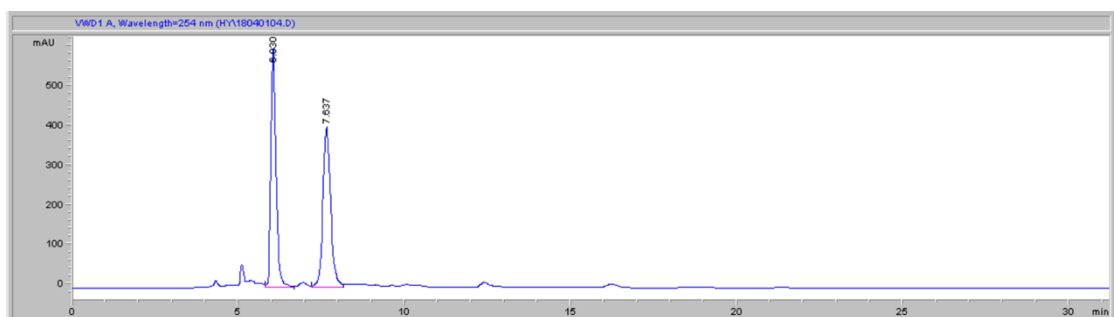
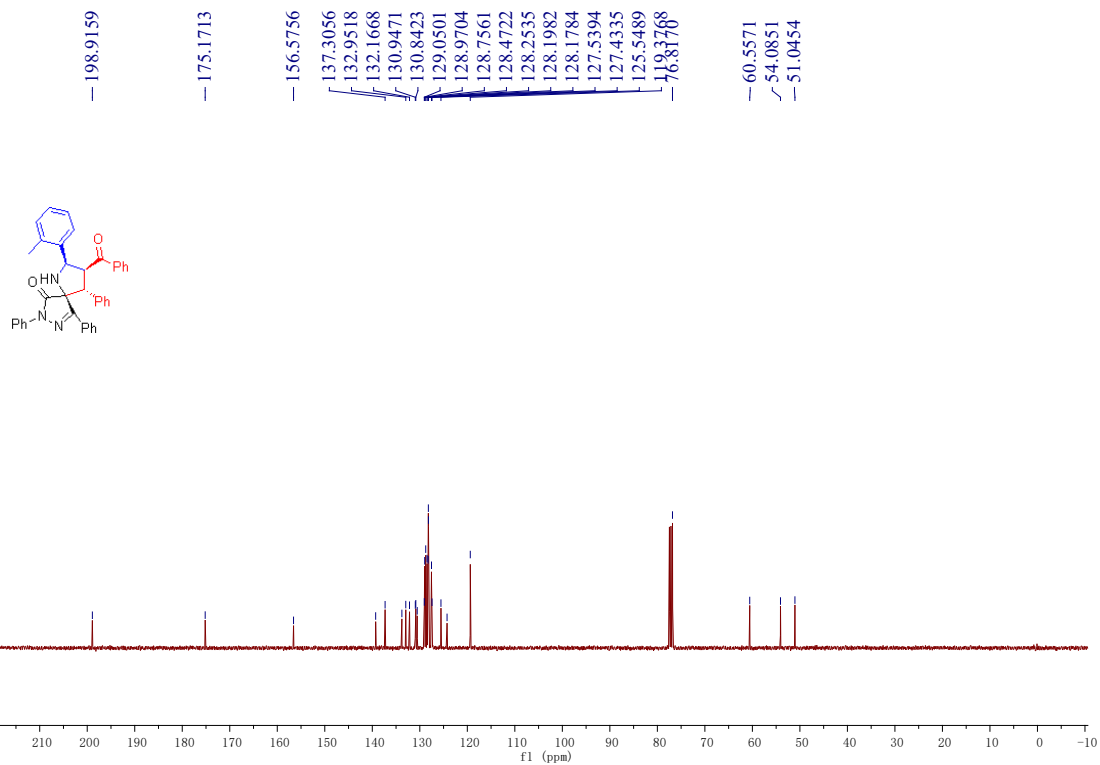


Prepared according to the procedure within 48 h as White solid

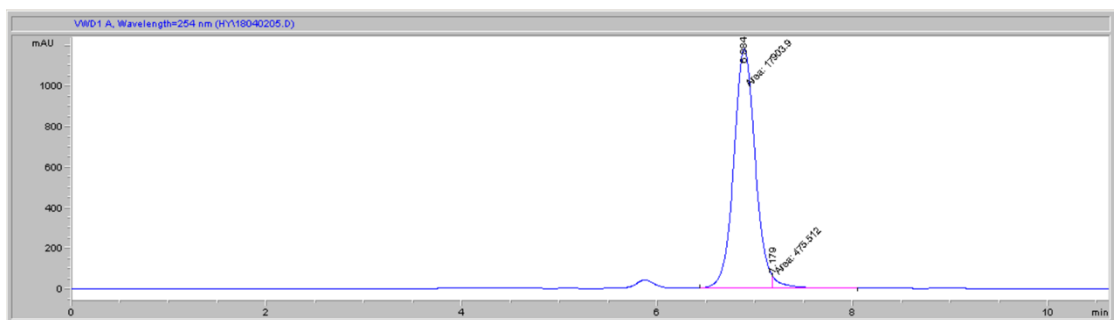
(101.0 mg, 90% yield, dr > 20:1). mp 117.5 – 116.9 °C; $[\alpha]_D^{19} = -$

43.496 (c 0.98, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.53 (dd, *J* = 7.6, 2.0 Hz, 2H), 7.80 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.72 – 7.58 (m, 7H), 7.46 – 7.27 (m, 8H), 7.23 – 7.10 (m, 5H), 6.99 (td, *J* = 7.9, 1.6 Hz, 1H), 6.62 (d, *J* = 10.4 Hz, 1H), 5.63 (t, *J* = 10.3 Hz, 1H), 4.93 (d, *J* = 10.1 Hz, 1H), 2.79 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 198.92, 175.17, 156.58, 139.29, 137.31, 133.77, 132.95, 132.17, 130.95, 130.84, 130.55, 129.05, 128.97, 128.76, 128.47, 128.25, 128.20, 128.18, 127.54, 127.43, 125.55, 124.26, 119.38, 76.82, 60.56, 54.09, 51.05; HRMS (ESI) *m/z* Calcd. for C₃₈H₃₂N₃O₃⁺ ([M+H]⁺) 562.2489, Found 562.2485; Enantiomeric excess was determined to be 94% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, *t*_{major} = 6.9 min, *t*_{minor} = 7.2 min).



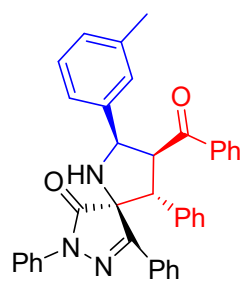


#	Time	Area	Height	Width	Area%	Symmetry
1	6.03	6536.3	601.3	0.1647	49.655	0.701
2	7.637	6627	402.9	0.253	50.345	0.838



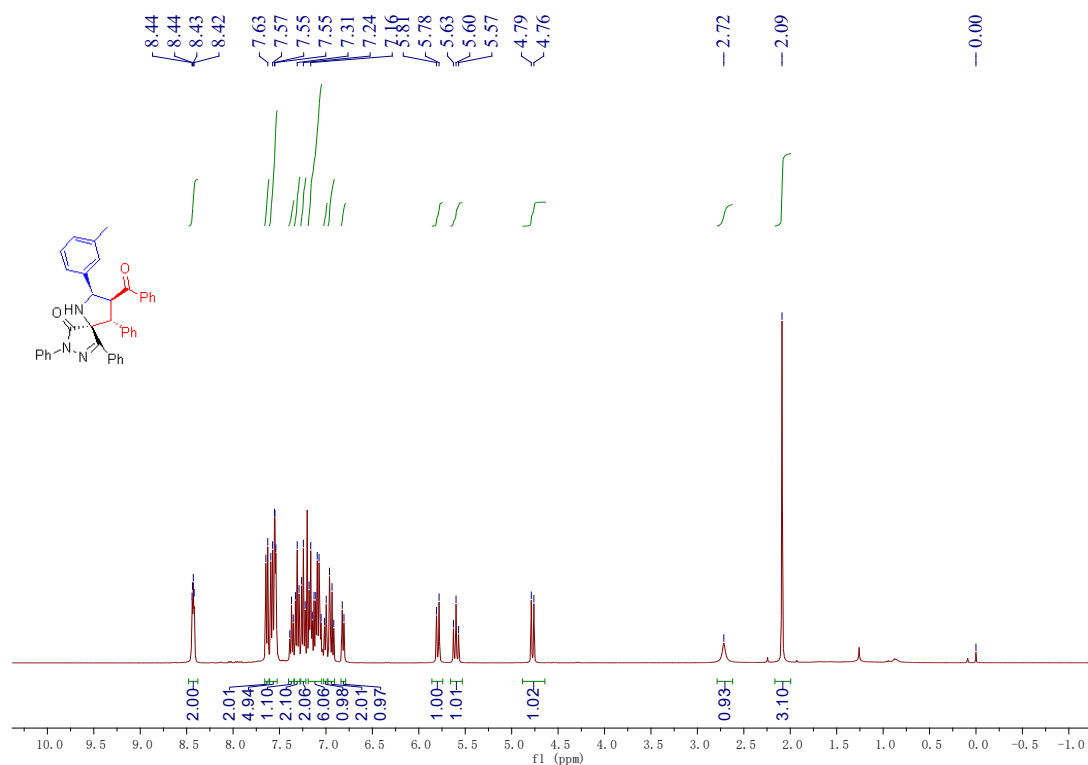
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1	6.884	17903.9	1179.9	0.2529	97.413	0.936
2	7.179	475.5	57.2	0.2712	2.587	0

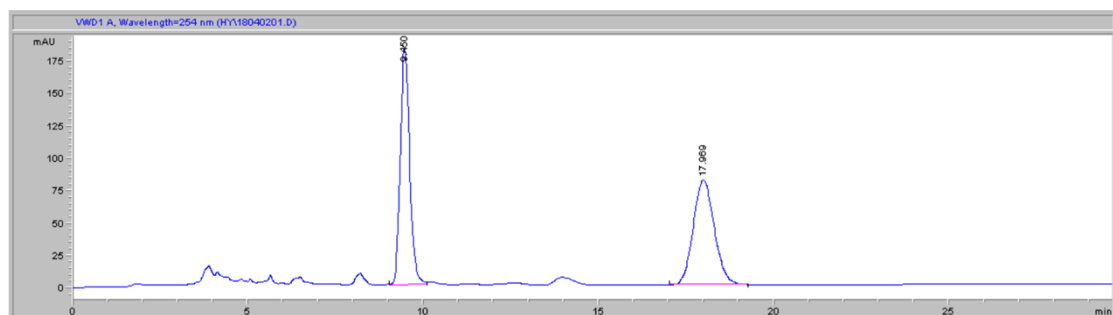
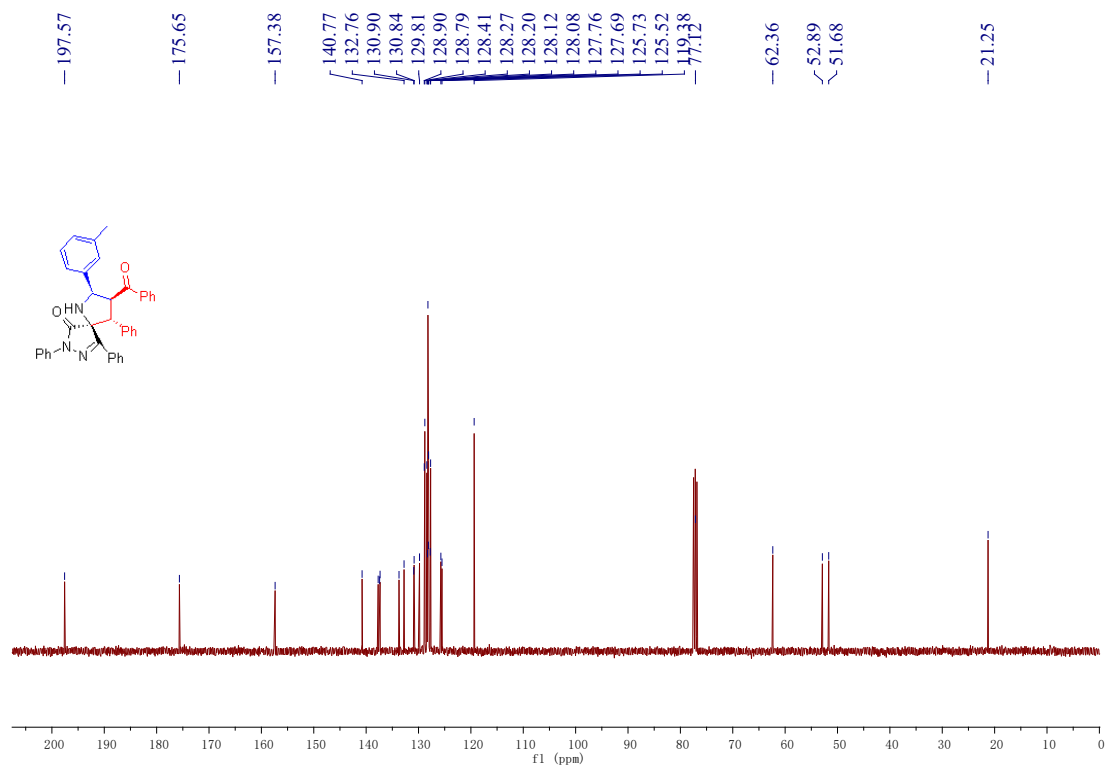
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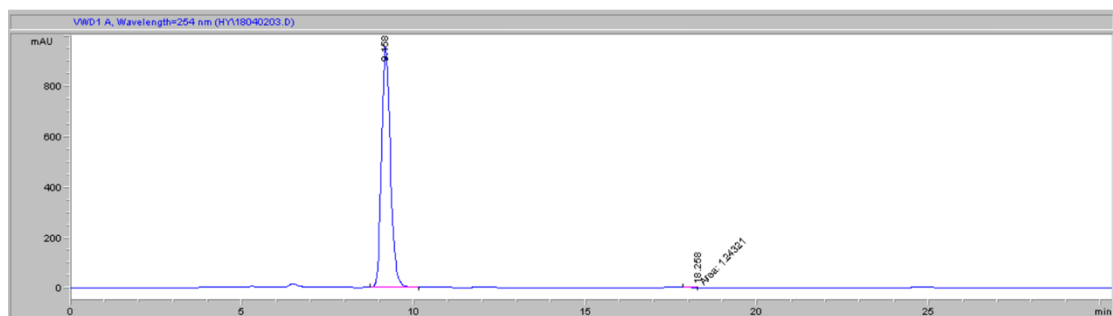
Prepared according to the procedure within 48 h as White solid

(103.2 mg, 92% yield, dr > 20:1). mp 104.2 – 104.9 °C; $[\alpha]_D^{19} = -62.280$ (*c* 0.94, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.41 – 8.45 (m, 2H), 7.64 (d, *J* = 8.1 Hz, 2H), 7.61 – 7.53 (m, 5H), 7.37 (dd, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.04 – 7.19 (m, 6H), 7.01 (d, *J* = 7.6 Hz, 1H), 6.98 – 6.91 (m, 2H), 6.82 (d, *J* = 7.4 Hz, 1H), 5.80 (d, *J* = 10.9 Hz, 1H), 5.60 (t, *J* = 11.1 Hz, 1H), 4.77 (d, *J* = 11.3 Hz, 1H), 2.72 (s, 1H), 2.09 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.57, 175.65, 157.38, 140.77, 137.70, 137.43, 137.34, 133.72, 132.76, 130.90, 130.84, 129.81, 128.90, 128.79, 128.41, 128.27, 128.20, 128.12, 128.08, 127.76, 127.69, 125.73, 125.52, 119.38, 77.12, 62.36, 52.89, 51.68, 21.25; HRMS (ESI) *m/z* Calcd. for C₃₈H₃₂N₃O₂⁺ ([M+H]⁺) 562.2489, Found 562.2484; 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} = 9.2 min, *t*_{minor} = 18.3 min).



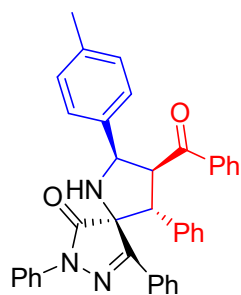


#	Time	Area	Height	Width	Area%	Symmetry
1	9.45	3423.9	182.8	0.2869	50.441	0.809
2	17.969	3364	80.8	0.6447	49.559	0.872



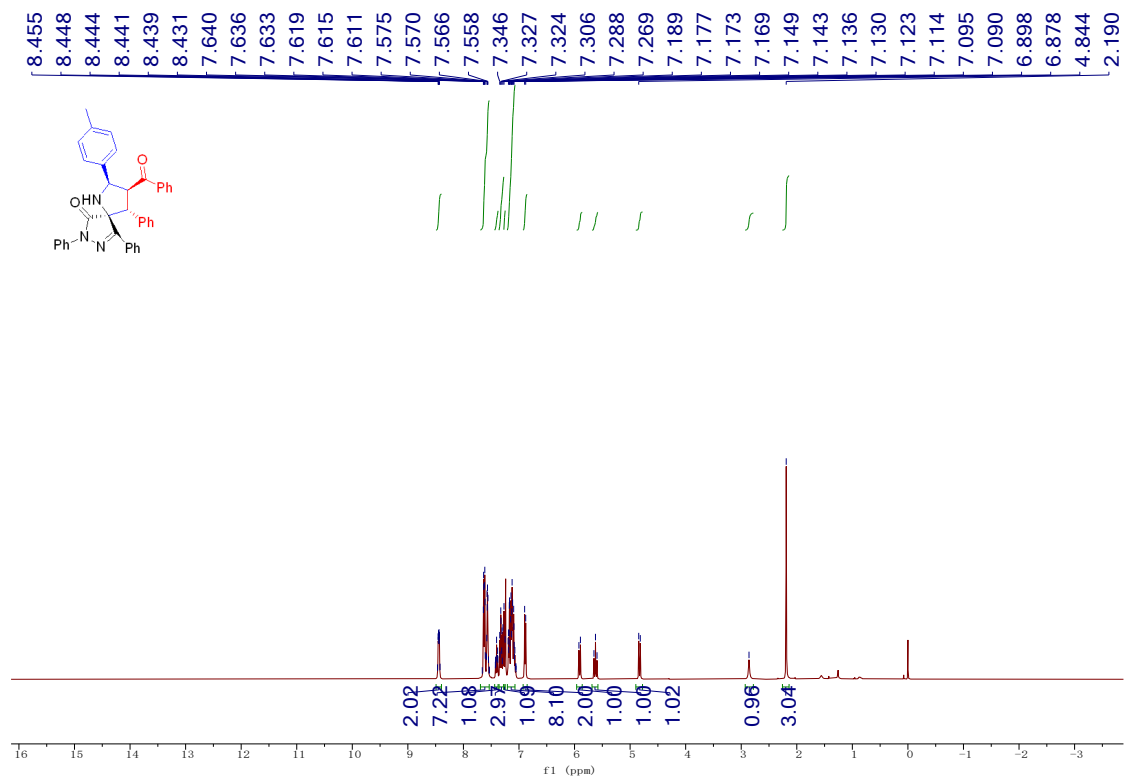
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1	9.158	17173.7	951.2	0.2791	99.993	0.788
2	18.258	1.2	2.8E-1	0.0736	0.007	0

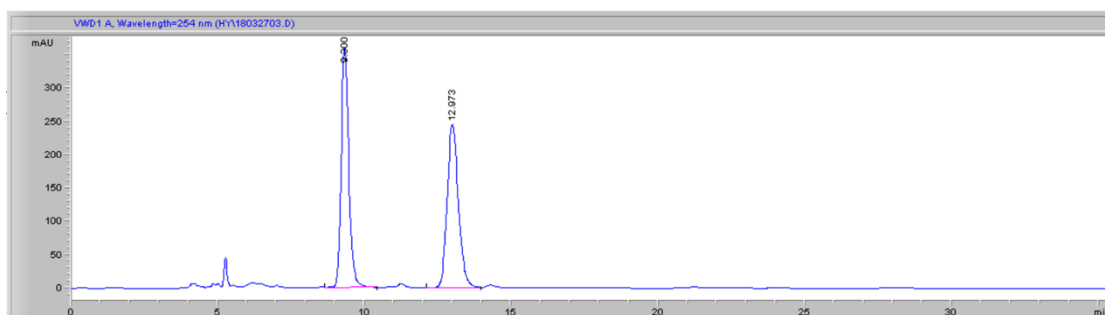
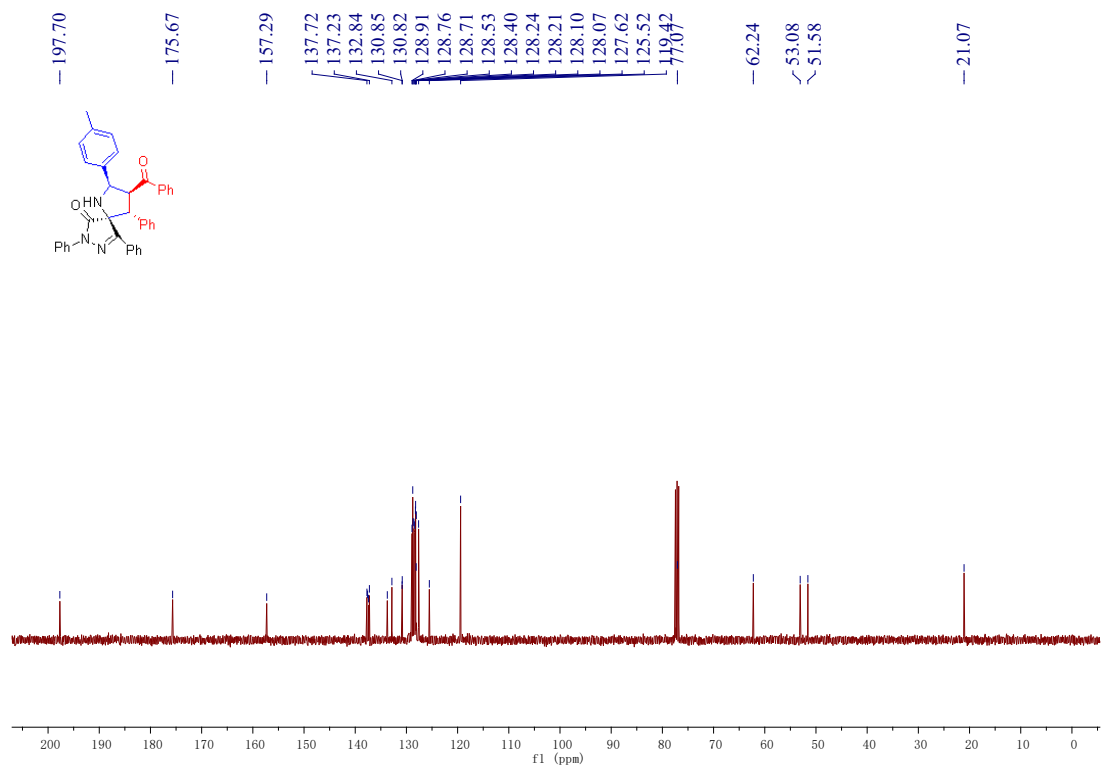
5ada



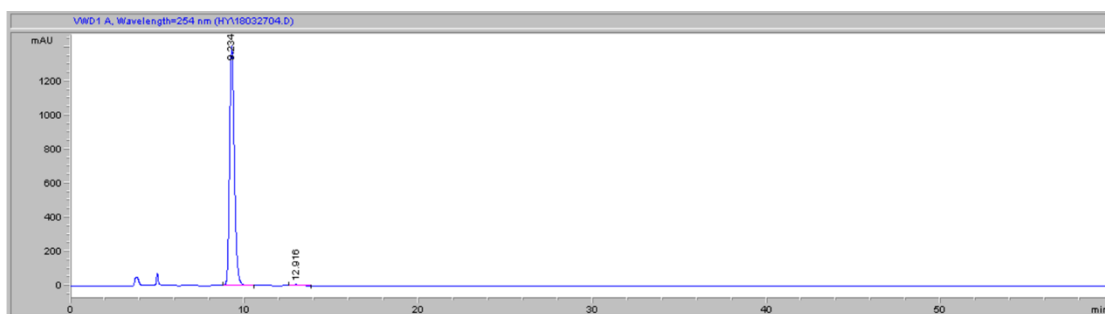
Prepared according to the procedure within 48 h as White solid

(79.7 mg, 71% yield, dr > 20:1). mp 161.7 – 162.9 °C; $[\alpha]_D^{18} = -82.848$ (c 0.65, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.50 – 8.35 (m, 2H), 7.64 – 7.53 (m, 7H), 7.38 (dd, J = 7.4 Hz, 1H), 7.26 – 7.34 (m, 3H), 7.23 (d, J = 7.1 Hz, 1H), 7.18 – 7.06 (m, 8H), 6.87 (d, J = 7.9 Hz, 2H), 5.88 (d, J = 10.9 Hz, 1H), 5.61 (t, J = 11.1 Hz, 1H), 4.82 (d, J = 11.3 Hz, 1H), 2.85 (s, 1H), 2.17 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.70, 175.67, 157.29, 137.72, 137.59, 137.40, 137.23, 133.73, 132.84, 130.85, 130.82, 128.91, 128.76, 128.71, 128.53, 128.40, 128.24, 128.21, 128.10, 128.07, 127.62, 125.52, 119.42, 77.07, 62.24, 53.08, 51.58, 21.07; HRMS (ESI) m/z Calcd. for C₃₈H₃₂N₃O₂⁺ ([M+H]⁺) 562.2489, Found 562.2484; 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} = 9.2 min, *t*_{minor} = 12.9 min).



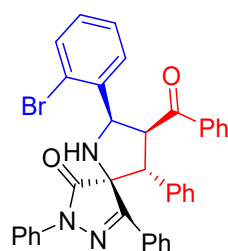


#	Time	Area	Height	Width	Area%	Symmetry
1	9.3	6530.6	358.9	0.2778	49.894	0.77
2	12.973	6558.3	244.7	0.4131	50.106	0.825



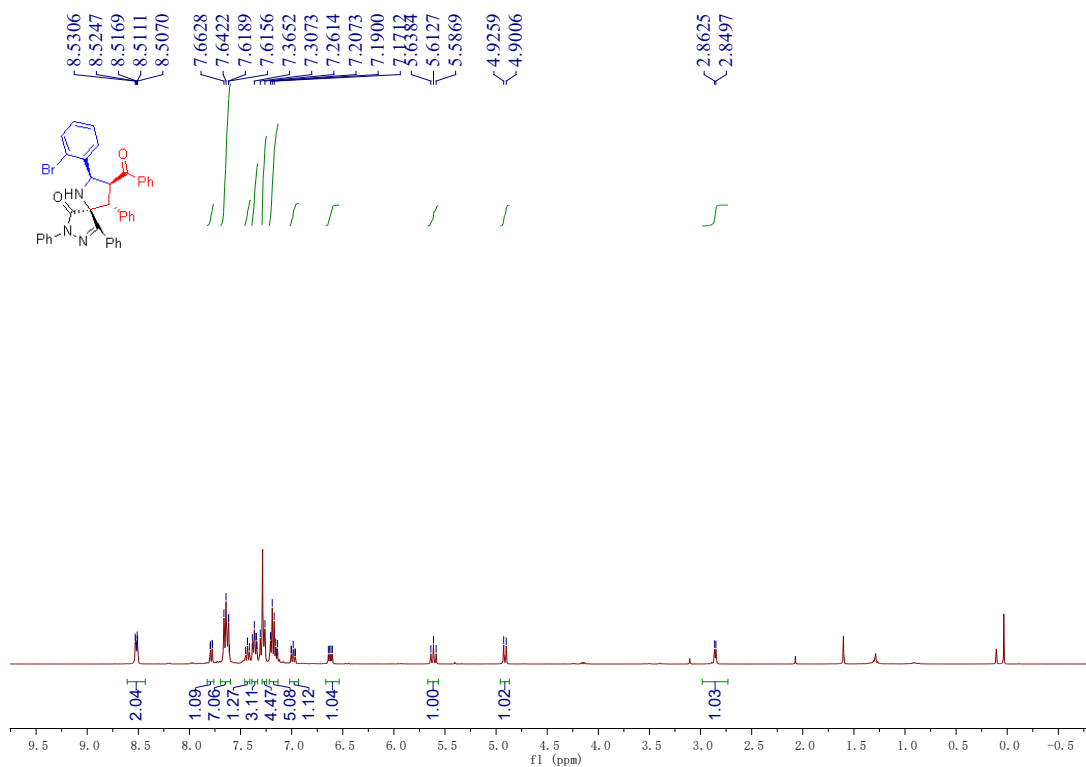
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1	9.234	25896.7	1406.7	0.2818	99.297	0.753
2	12.916	183.3	6.6	0.4206	0.703	0.896

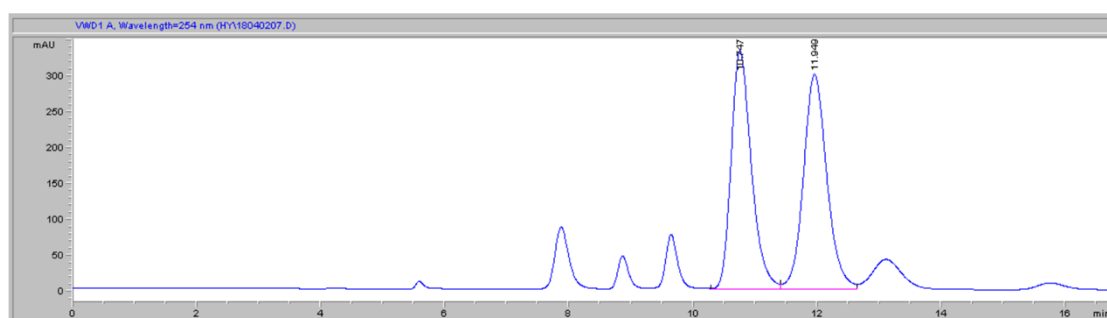
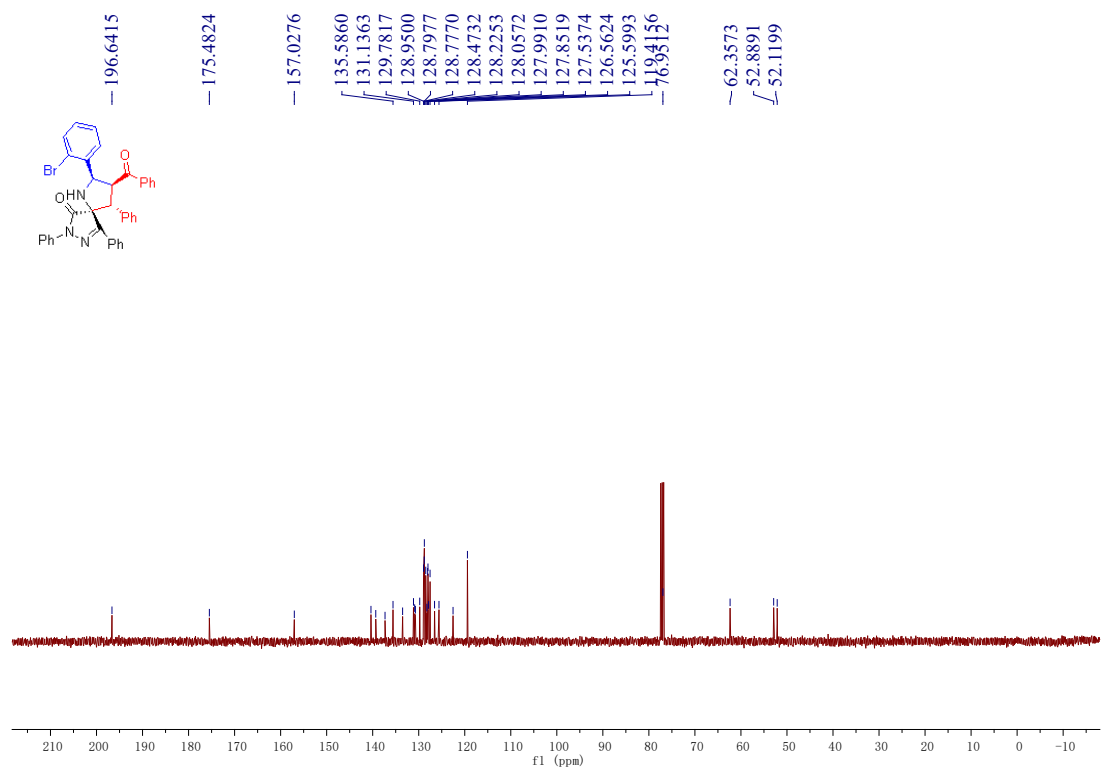
5aea



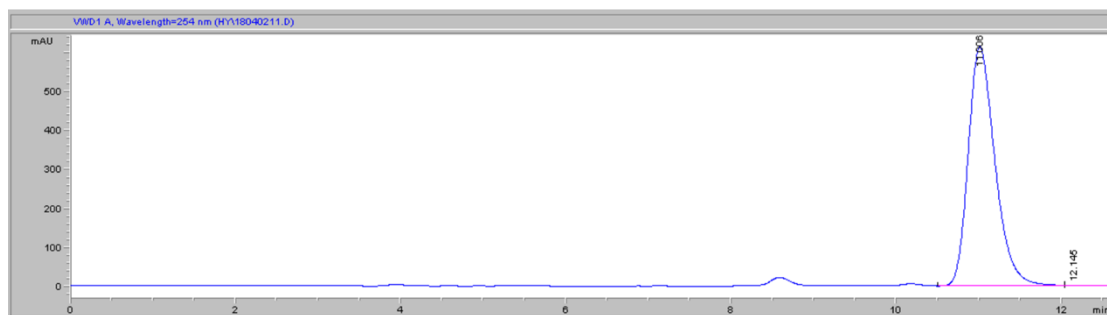
Prepared according to the procedure within 60 h as White solid

(101.3 mg, 81% yield, dr > 20:1). mp 136.9 – 137.8 °C; $[\alpha]_D^{19} = -39.024$ (c 0.04, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.61 – 8.43 (m, 2H), 7.79 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.70 – 7.60 (m, 7H), 7.43 (dd, *J* = 7.3 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.29 – 7.24 (m, 4H), 7.22 – 7.13 (m, 5H), 7.02 – 6.93 (m, 1H), 6.62 (dd, *J* = 10.5, 5.2 Hz, 1H), 5.61 (t, *J* = 10.3 Hz, 1H), 4.91 (d, *J* = 10.1 Hz, 1H), 2.86 (d, *J* = 5.1 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 196.64, 175.48, 157.03, 140.38, 139.33, 137.32, 135.59, 133.50, 131.14, 130.88, 130.73, 129.78, 128.95, 128.80, 128.78, 128.47, 128.23, 128.06, 127.99, 127.85, 127.54, 126.56, 125.60, 122.54, 119.42, 76.95, 62.36, 52.89, 52.12; HRMS (ESI) *m/z* Calcd. for C₃₇H₂₉BrN₃O₂⁺ ([M+H]⁺) 626.1438, Found 626.1428; 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} = 11.0 min, *t*_{minor} = 12.1 min).



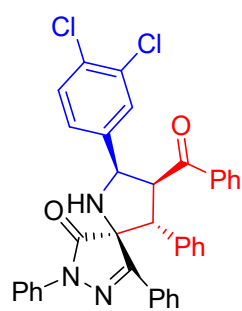


#	Time	Area	Height	Width	Area%	Symmetry
1	10.747	7529.9	332	0.3462	48.926	0.726
2	11.949	7860.5	299.5	0.4008	51.074	0.856



#	Time	Area	Height	Width	Area%	Symmetry
1	11.006	13886.6	612.4	0.3475	99.586	0.707
2	12.145	57.7	2.6	0.3373	0.414	0.36

5afa

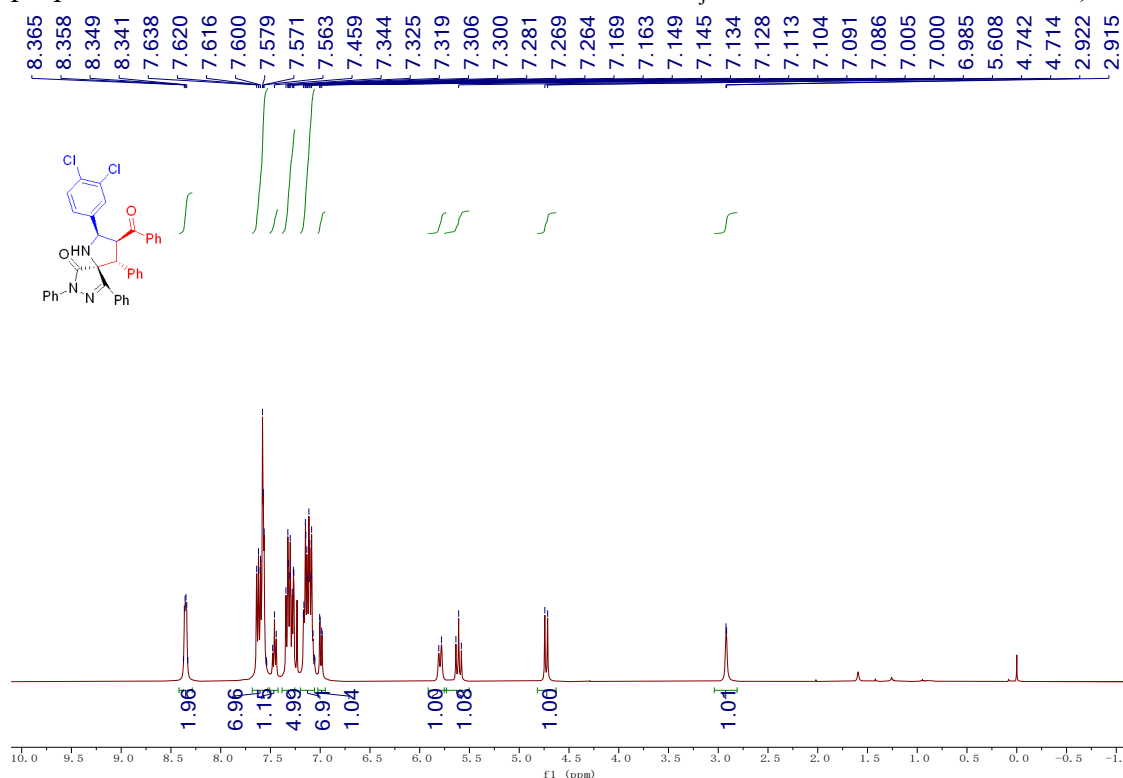


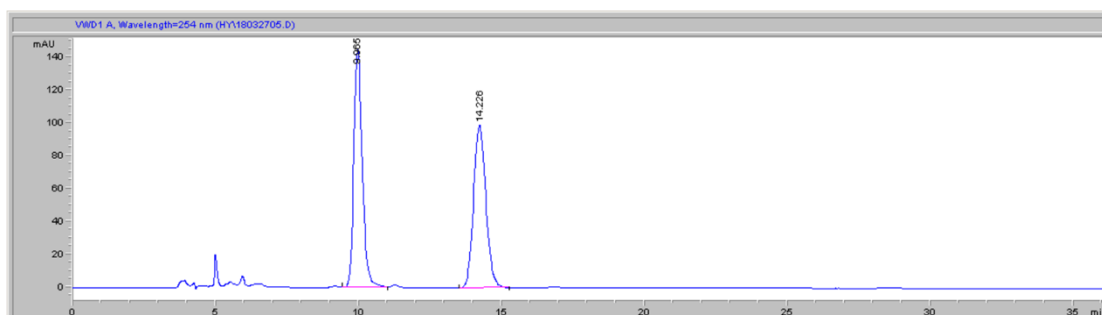
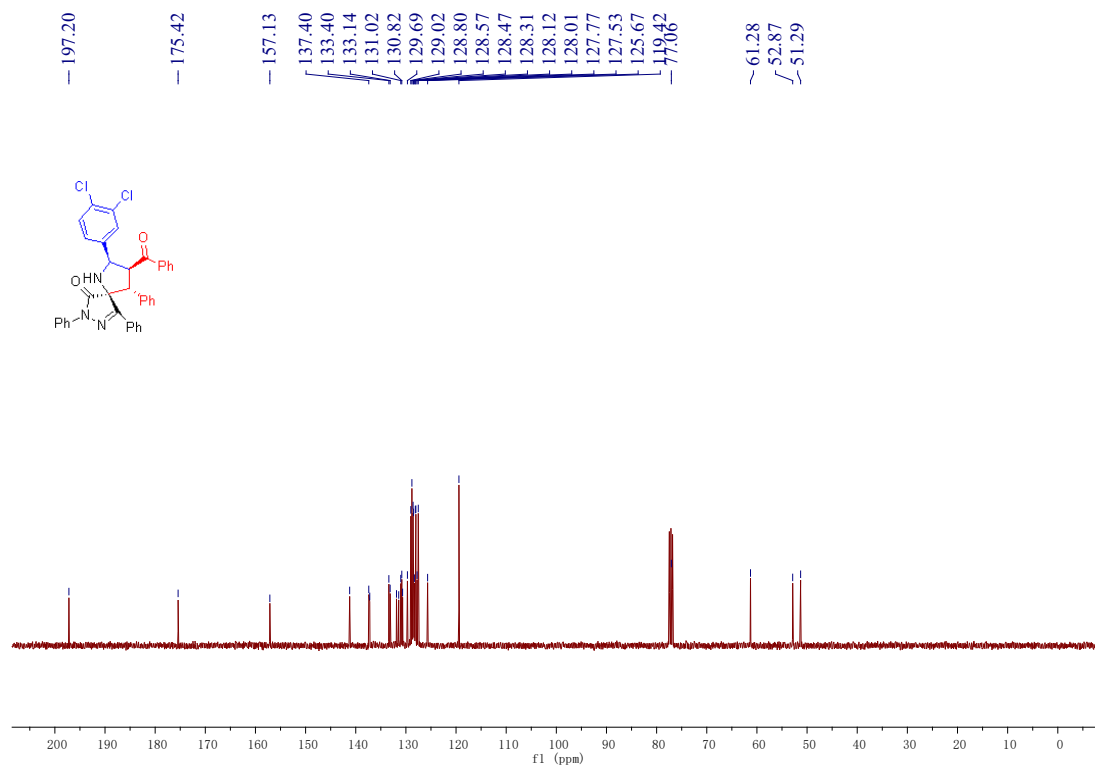
Prepared according to the procedure within 36 h as White solid

(113.2 mg, 92% yield, dr > 20:1). mp 115.9 – 116.8 °C; $[\alpha]_D^{18} =$

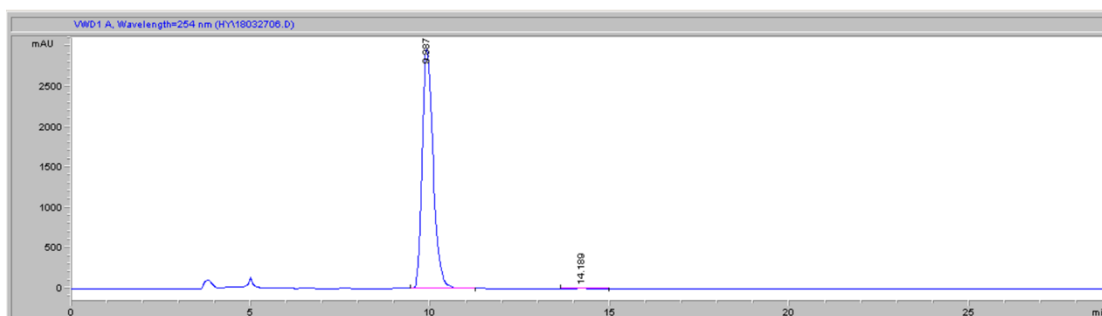
104.14 (*c* 0.94, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.39 – 8.31 (m, 2H), 7.67 – 7.54 (m, 7H), 7.45 (dd, *J* = 7.4 Hz, 1H), 7.34 – 7.22 (m, 5H), 7.17 – 7.04 (m, 7H), 6.96 (dd, *J* = 8.3, 1.9 Hz, 1H), 5.76 (d, *J* = 10.8 Hz, 1H), 5.60 (t, *J* = 11.0 Hz, 1H), 4.71 (d, *J* = 11.2 Hz, 1H), 2.94 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 197.20,

175.42, 157.13, 141.21, 137.40, 137.21, 133.40, 133.14, 131.87, 131.43, 131.02, 130.82, 130.66, 129.69, 129.02, 128.80, 128.57, 128.47, 128.31, 128.12, 128.01, 127.77, 127.53, 125.67, 119.42, 77.06, 61.28, 52.87, 51.29; HRMS (ESI) *m/z* Calcd. for C₃₇H₂₈Cl₂N₃O₂⁺ ([*M*+*H*]⁺) 616.1553, Found 616.1532; 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} = 9.9 min, *t*_{minor} = 14.2 min).



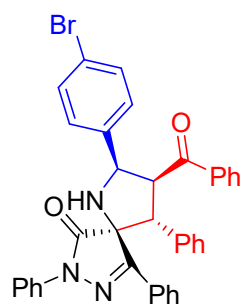


#	Time	Area	Height	Width	Area%	Symmetry
1	9.965	2999.9	144.9	0.3158	50.324	0.761
2	14.226	2961.2	99	0.4624	49.676	0.875



#	Time	Area	Height	Width	Area%	Symmetry
1	9.887	62919.2	2956.7	0.3284	99.895	0.682
2	14.189	65.9	2.2	0.4547	0.105	0.905

5aga



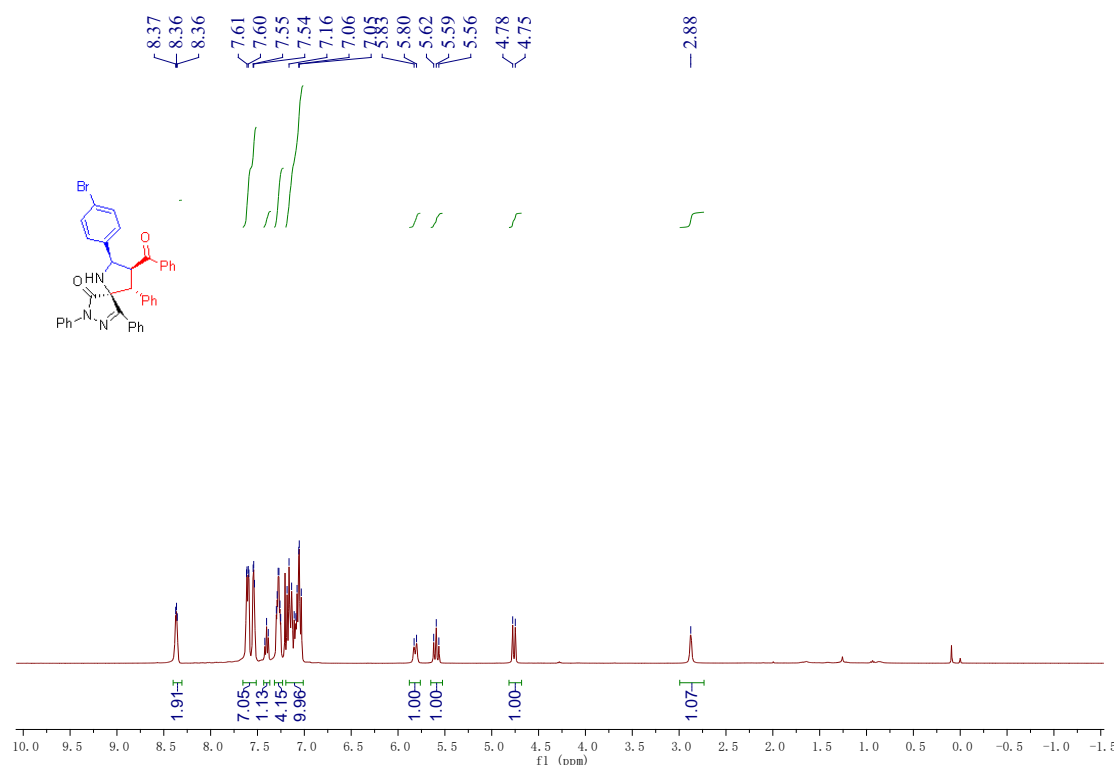
Prepared according to the procedure within 60 h as White solid

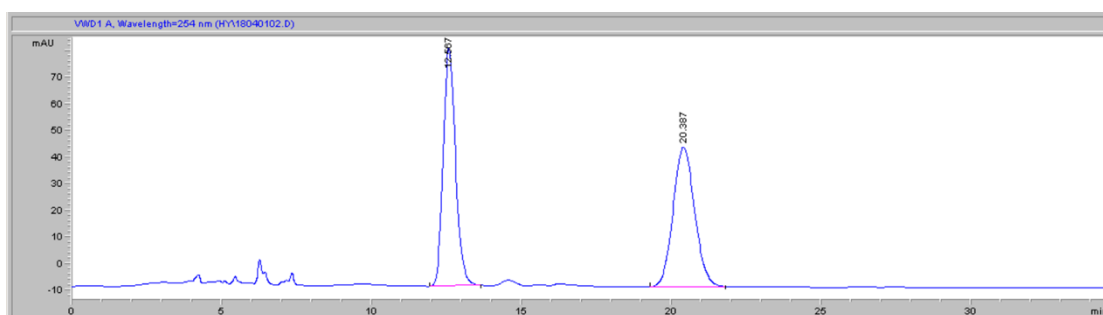
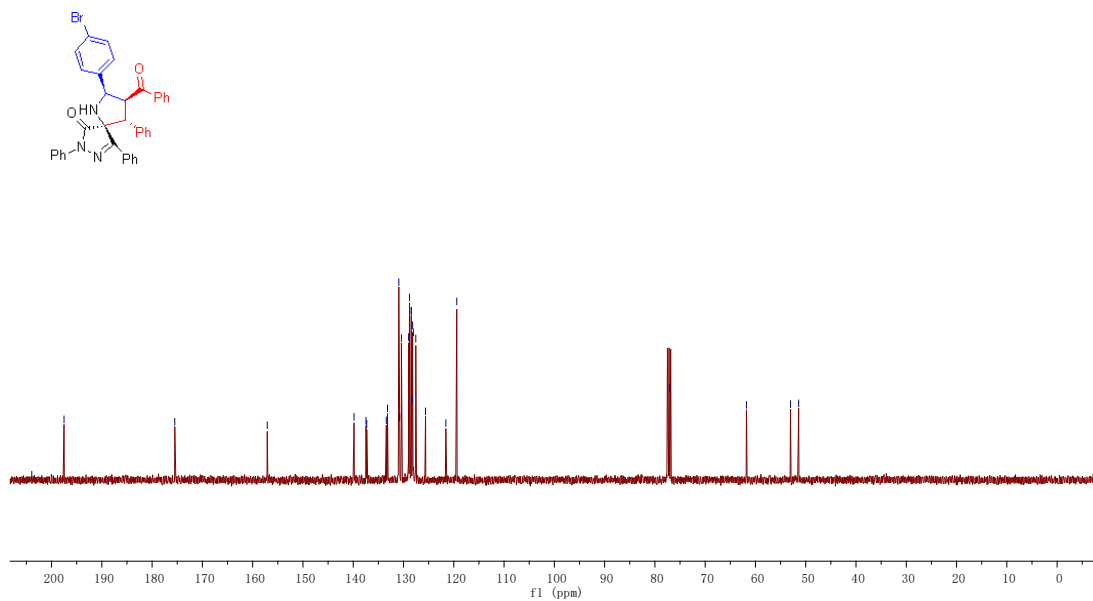
(114.0 mg, 91% yield, dr > 20:1). mp 109.5 – 110.2 °C; $[\alpha]_D^{19} =$

60.728 (c 0.97, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.31 (m, 2H), 7.66 – 7.51 (m, 7H), 7.40 (dd, J = 7.3 Hz, 1H), 7.23 – 7.32 (m, 4H), 7.20 – 7.01 (m, 10H), 5.82 (d, J = 10.4 Hz, 1H), 5.59 (t, J = 11.0 Hz, 1H), 4.76 (d, J = 11.2 Hz, 1H), 2.88 (s, 1H);

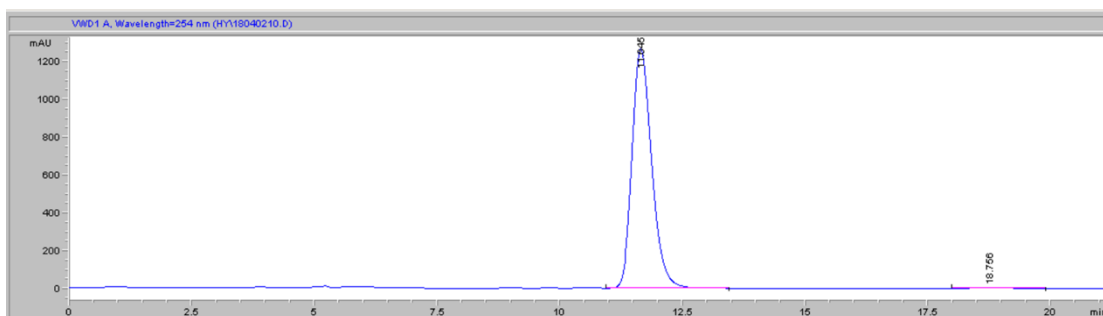
¹³C NMR (101 MHz, CDCl₃) δ 203.93, 197.52, 175.49, 157.10,

139.84, 137.46, 137.30, 133.42, 133.18, 130.93, 130.76, 130.42, 128.98, 128.81, 128.46, 128.44, 128.24, 128.19, 128.04, 127.55, 125.62, 121.58, 119.41, 77.05, 61.79, 53.02, 51.41; HRMS (ESI) m/z Calcd. for C₃₇H₂₉BrN₃O₂⁺ ([M+H]⁺) 626.1438, Found 626.1424; 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} = 11.6 min, *t*_{minor} = 18.8 min).



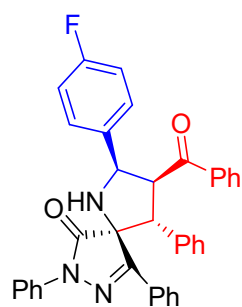


#	Time	Area	Height	Width	Area%	Symmetry
1	12.567	2566.8	88.9	0.446	49.421	0.815
2	20.387	2626.9	52.5	0.7789	50.579	0.89



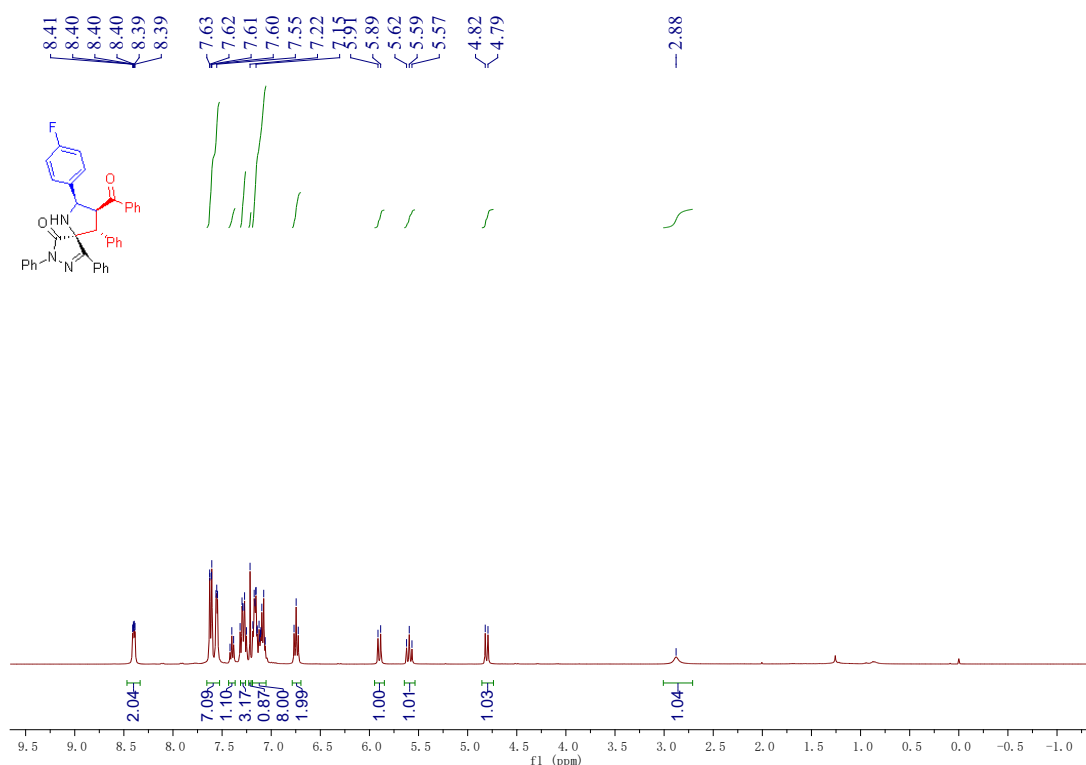
#	Time	Area	Height	Width	Area%	Symmetry
1	11.645	34971.8	1263.5	0.4248	99.662	0.764
2	18.756	118.6	2.7	0.6097	0.338	0.863

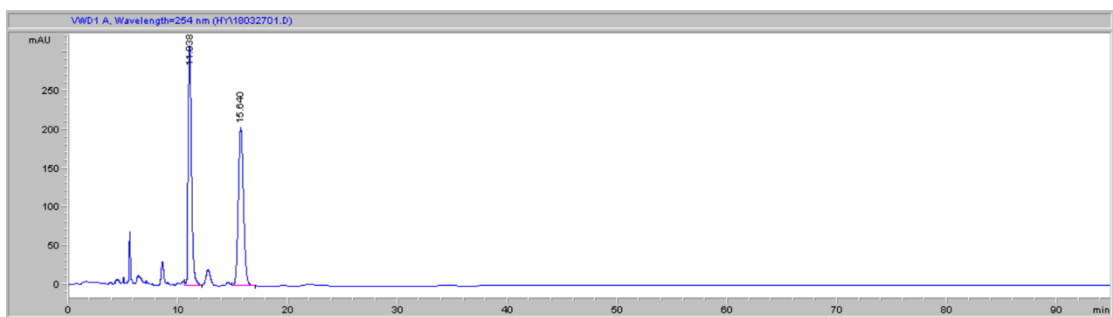
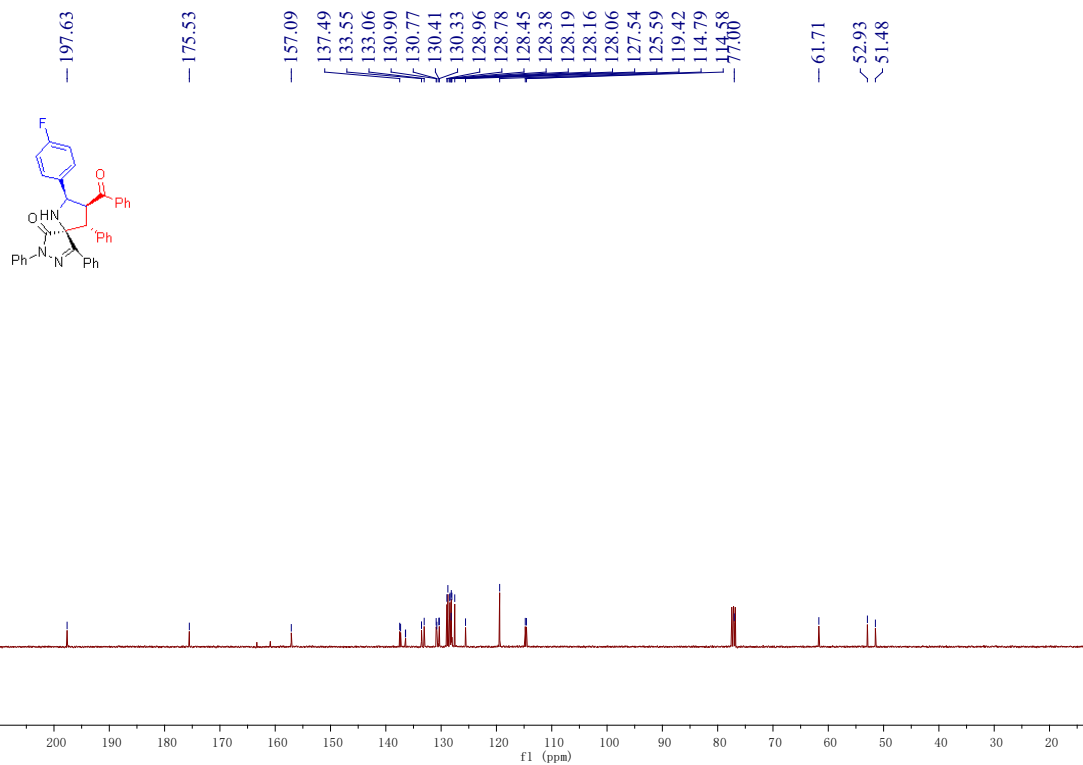
Saha



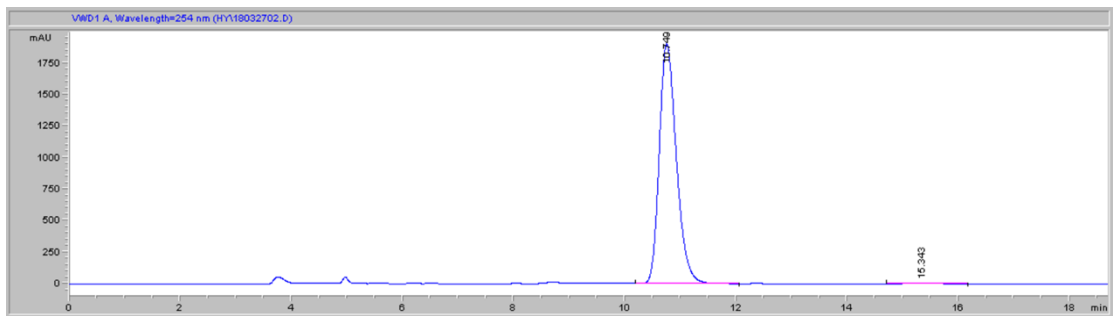
Prepared according to the procedure within 48 h as White solid

(99.6 mg, 88% yield, dr > 20:1). mp 117.6 – 118.9 °C; $[\alpha]_D^{19} = -55.268$ (c 0.54, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.47 – 8.33 (m, 2H), 7.66 – 7.53 (m, 7H), 7.40 (dd, J = 7.4 Hz, 1H), 7.28 (dd, J = 8.1, 2.3 Hz, 3H), 7.22 (s, 1H), 7.19 – 7.05 (m, 8H), 6.80 – 6.70 (m, 2H), 5.90 (d, J = 10.9 Hz, 1H), 5.59 (t, J = 11.0 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 2.88 (s, 1H); ¹⁹F NMR (377 MHz, CDCl₃) δ -114.52; ¹³C NMR (101 MHz, CDCl₃) δ 197.63, 175.53, 157.09, 137.49, 137.33, 136.45 (J = 3.0 Hz), 133.55, 133.06, 130.90, 130.77, 130.41, 130.33, 128.96, 128.78, 128.45, 128.38, 128.19, 128.16, 128.06, 127.54, 125.59, 119.42, 114.68, 77.00, 61.71, 52.93, 51.48; HRMS (ESI) m/z Calcd. for C₃₇H₂₉FN₃O₂⁺ ([M+H]⁺) 566.2238, Found 566.2234; 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} = 10.7 min, t_{minor} = 15.3 min).



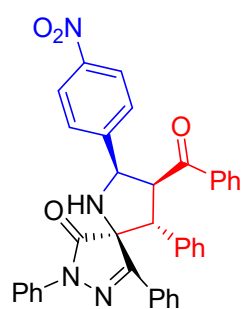


#	Time	Area	Height	Width	Area%	Symmetry
1	11.038	6685.6	308.3	0.3302	50.490	0.759
2	15.64	6555.9	204.3	0.4967	49.510	0.867



#	Time	Area	Height	Width	Area%	Symmetry
1	10.749	40719.3	1903.3	0.3297	99.508	0.73
2	15.343	201.2	6.5	0.4854	0.492	0.903

5aia

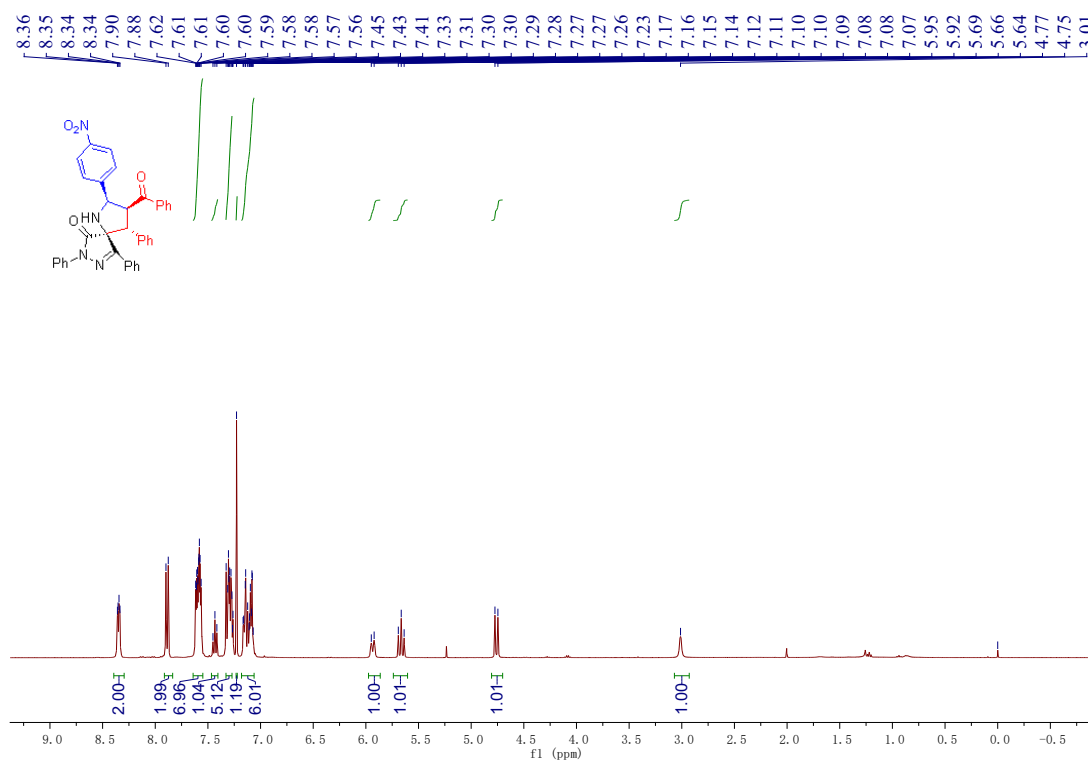


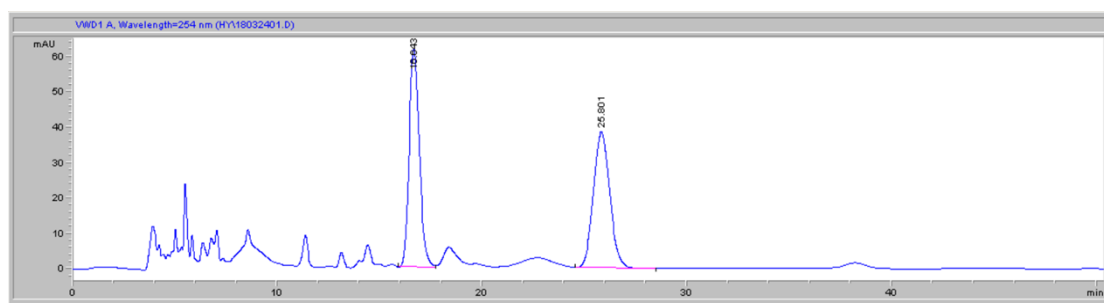
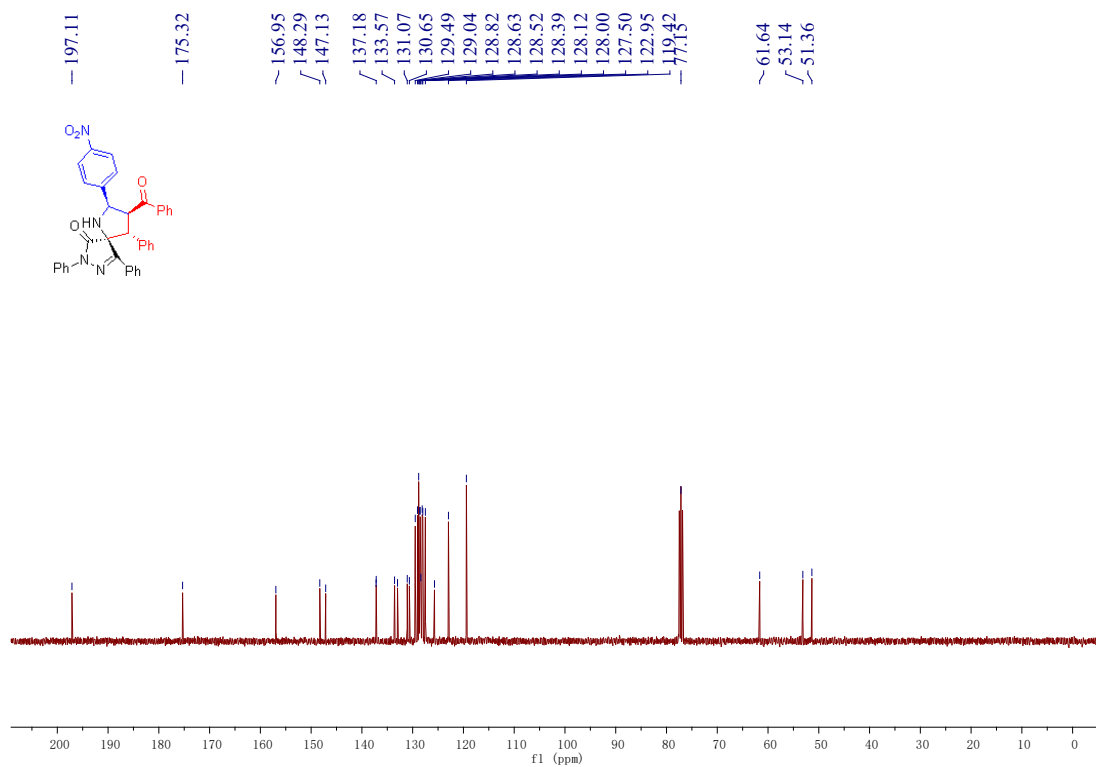
Prepared according to the procedure within 60 h as White solid

(104.3 mg, 88% yield, dr > 20:1). mp 132.1 – 132.9 °C; $[\alpha]_D^{19} = -$

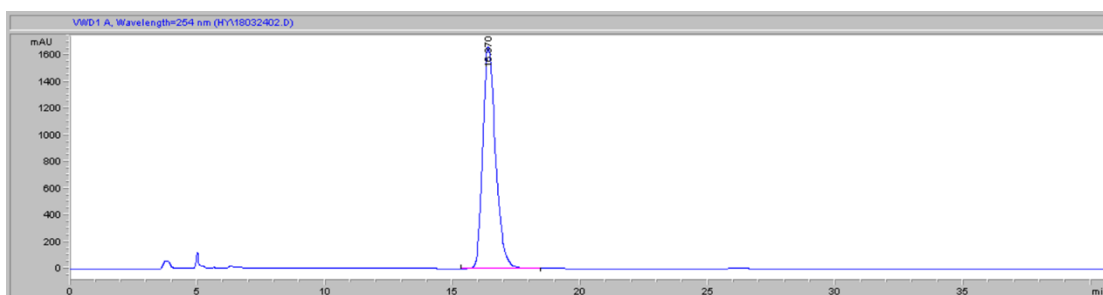
126.16 (*c* 0.88, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.33 – 8.38 (m, 2H), 7.86 – 7.91 (m, 2H), 7.64 – 7.55 (m, 7H), 7.43 (dd, *J* = 7.4 Hz, 1H), 7.33 – 7.27 (m, 5H), 7.23 (s, 1H), 7.18 – 7.06 (m, 6H), 5.93 (d, *J* = 10.8 Hz, 1H), 5.66 (t, *J* = 11.1 Hz, 1H), 4.76 (d, *J* = 11.2 Hz, 1H), 3.01 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ

197.11, 175.32, 156.95, 148.29, 147.13, 137.20, 137.18, 133.57, 132.98, 131.07, 130.65, 129.49, 129.04, 128.82, 128.63, 128.52, 128.39, 128.12, 128.00, 127.50, 125.70, 122.95, 119.42, 77.15, 61.64, 53.14, 51.36; HRMS (ESI) *m/z* Calcd. for C₃₇H₂₉N₄O₄⁺ ([*M*+*H*]⁺) 593.2183, Found 593.2175; 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} = 16.4 min, *t*_{minor} = 25.8 min).

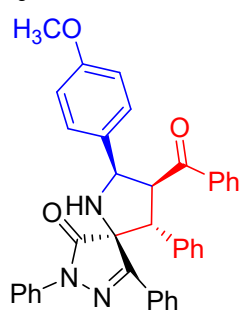




#	Time	Area	Height	Width	Area%	Symmetry
1	16.643	2144.2	61.7	0.5366	49.780	0.815
2	25.801	2163.2	38.7	0.8678	50.220	0.911



#	Time	Area	Height	Width	Area%	Symmetry
1	16.37	58237.4	1661.6	0.5385	100.000	0.712

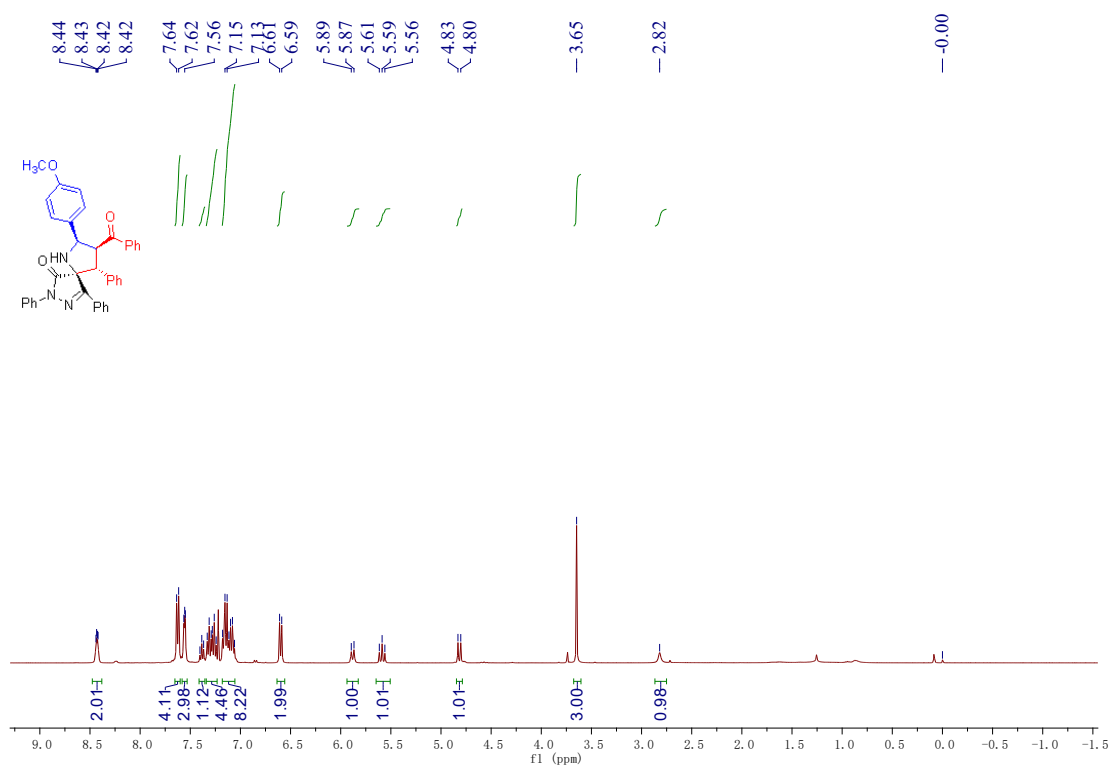
5aja

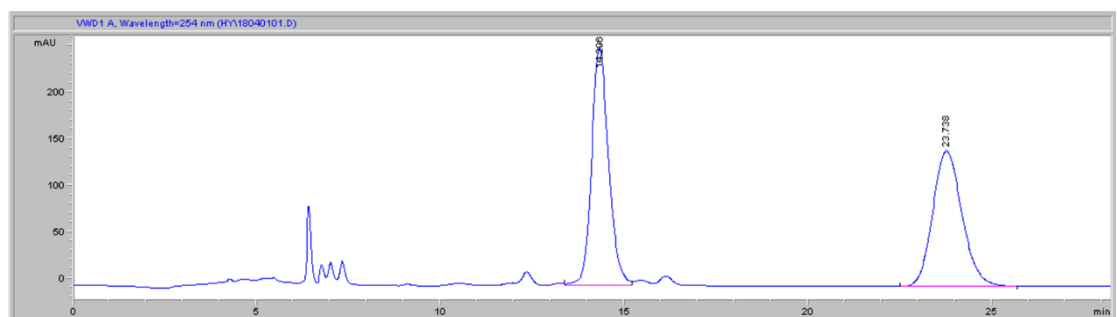
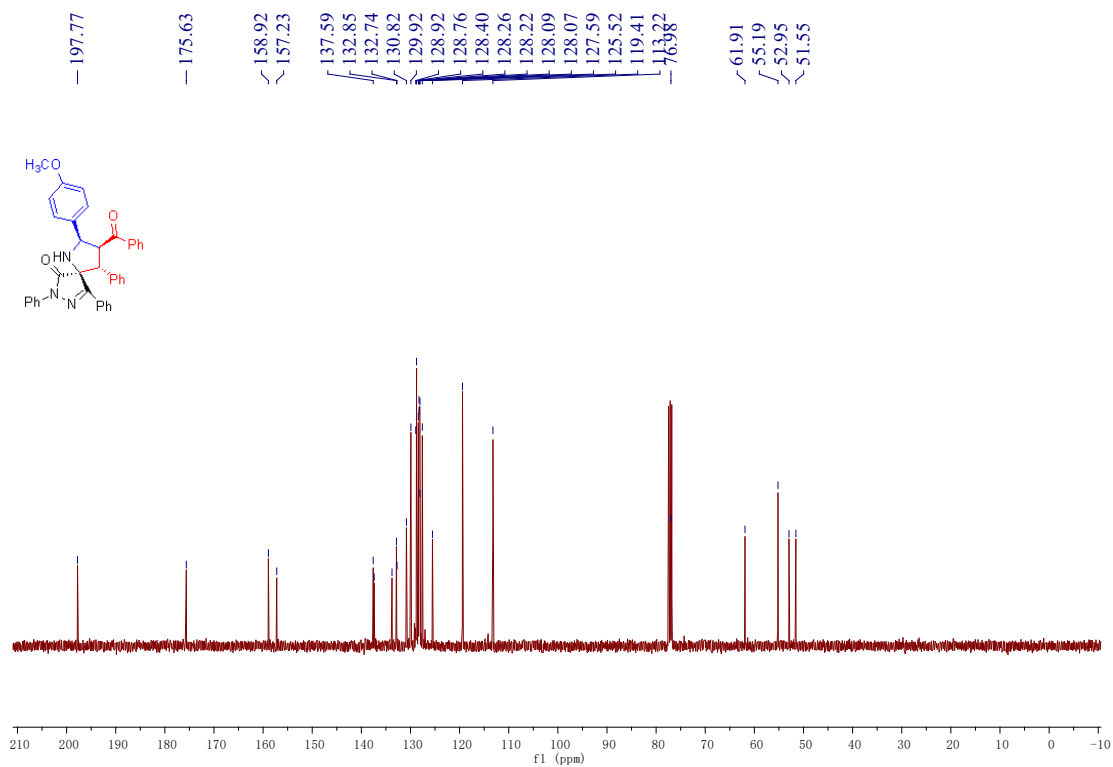
Prepared according to the procedure within 36 h as White solid

(99.4 mg, 86% yield, dr > 20:1). mp 107.5 – 108.9 °C; $[\alpha]_D^{19} = -$

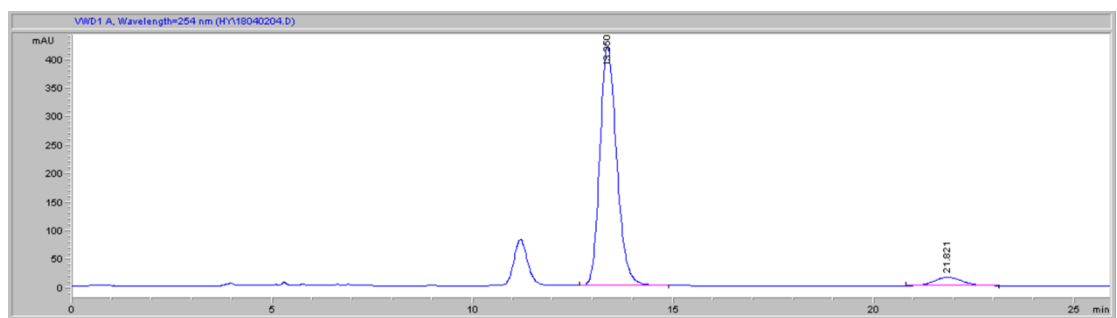
59.784 (*c* 0.60, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.46 (m, 2H), 7.63 (d, *J* = 8.1 Hz, 4H), 7.58 – 7.53 (m, 3H), 7.39 (dd, *J* = 7.4 Hz, 1H), 7.23 – 7.34 (m, 4H), 7.18 – 7.06 (m, 8H), 6.60 (d, *J* = 8.6 Hz, 2H), 5.88 (d, *J* = 10.8 Hz, 1H), 5.59 (t, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 3.65 (s, 3H), 2.82 (s,

1H); ¹³C NMR (101 MHz, CDCl₃) δ 197.77, 175.63, 158.92, 157.23, 137.59, 137.39, 133.76, 132.85, 132.74, 130.82, 129.92, 128.92, 128.76, 128.40, 128.26, 128.22, 128.09, 128.07, 127.59, 125.52, 119.41, 113.22, 76.98, 61.91, 55.19, 52.95, 51.55; HRMS (ESI) *m/z* Calcd. for C₃₈H₃₂N₃O₃⁺ ([M+H]⁺) 578.2438, Found 578.2434; Enantiomeric excess was determined to be 90% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, *t*_{major} = 13.4 min, *t*_{minor} = 21.8 min).



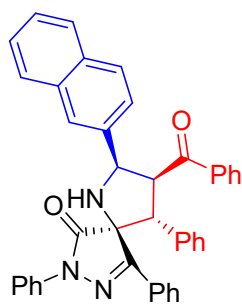


#	Time	Area	Height	Width	Area%	Symmetry
1	14.296	8258	254.7	0.4947	50.619	0.821
2	23.738	8055.9	145.8	0.8541	49.381	0.837



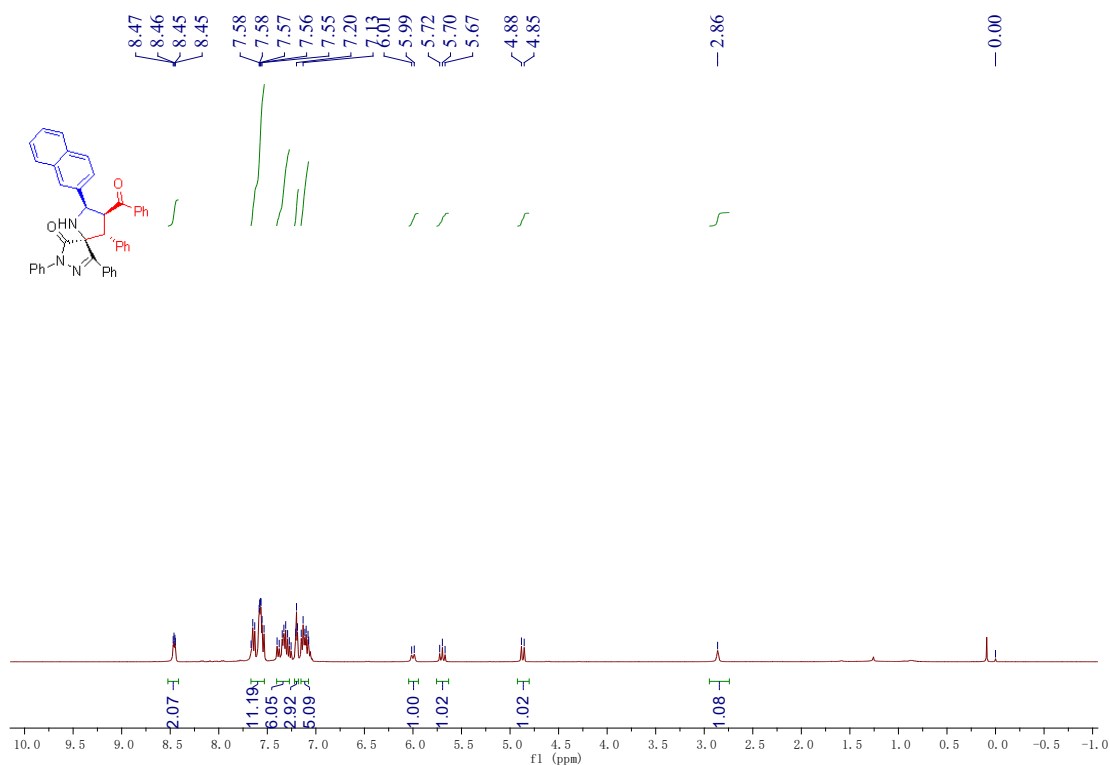
#	Time	Area	Height	Width	Area%	Symmetry
1	13.35	12177.7	418.7	0.4471	94.383	0.788
2	21.821	724.7	14.7	0.7687	5.617	0.875

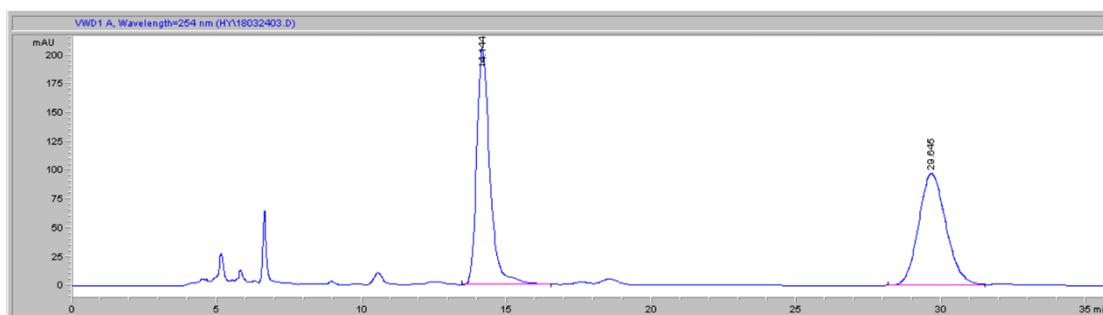
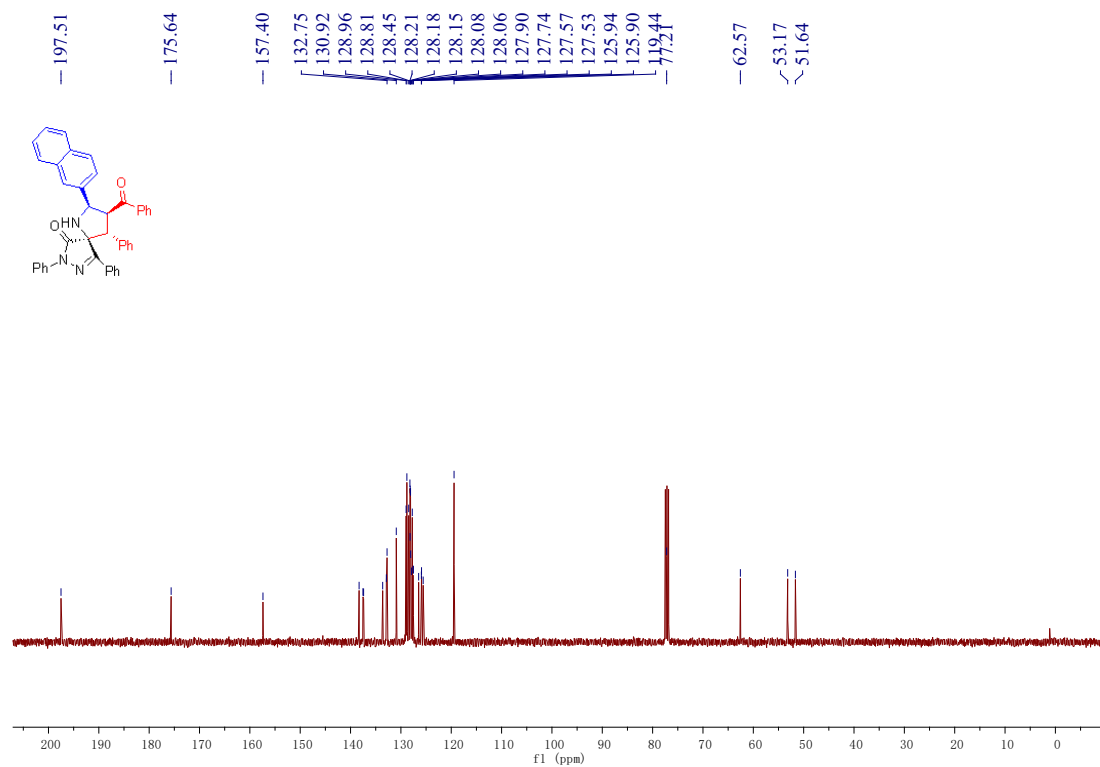
5aka



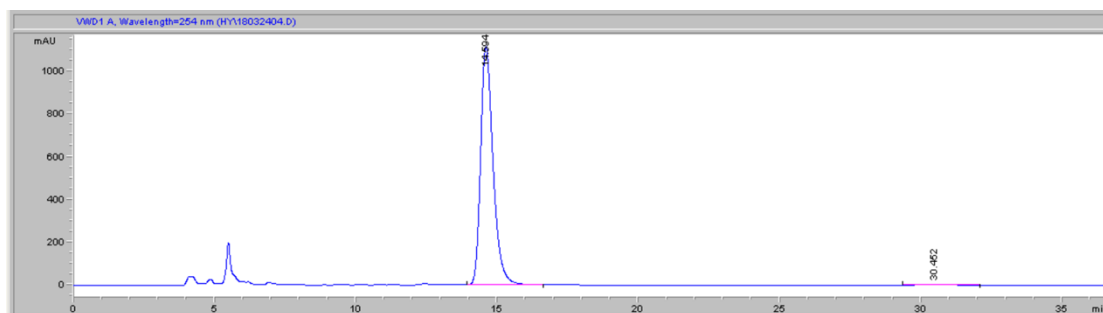
Prepared according to the procedure within 72 h as White solid

(83.6 mg, 70% yield, dr > 20:1). mp 124.9 – 125.6 °C; $[\alpha]_D^{19} = -94.760$ (c 0.67, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.46 (dd, J = 6.3, 2.6 Hz, 2H), 7.67 – 7.53 (m, 11H), 7.40 – 7.27 (m, 6H), 7.18 – 7.22 (m, 3H), 7.15 – 7.08 (m, 5H), 6.00 (d, J = 10.8 Hz, 1H), 5.70 (t, J = 11.1 Hz, 1H), 4.87 (d, J = 11.4 Hz, 1H), 2.86 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 197.51, 175.64, 157.40, 138.30, 137.54, 137.41, 133.62, 132.89, 132.75, 130.92, 128.96, 128.81, 128.45, 128.21, 128.18, 128.15, 128.08, 128.06, 127.90, 127.74, 127.57, 127.53, 126.47, 125.94, 125.90, 125.58, 119.44, 77.21, 62.57, 53.17, 51.64; HRMS (ESI) m/z Calcd. for C₄₁H₃₂N₃O₂⁺ ([M+H]⁺) 598.2489, Found 598.2474; 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} = 14.6 min, *t*_{minor} = 30.5 min).



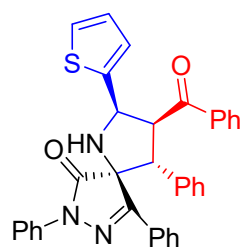


#	Time	Area	Height	Width	Area%	Symmetry
1	14.144	6510.2	204.8	0.48	50.554	0.68
2	29.645	6367.4	97	1.0137	49.446	0.845



#	Time	Area	Height	Width	Area%	Symmetry
1	14.594	33806	1113	0.4606	99.372	0.692
2	30.452	213.5	3.3	0.8399	0.628	0.818

5ala

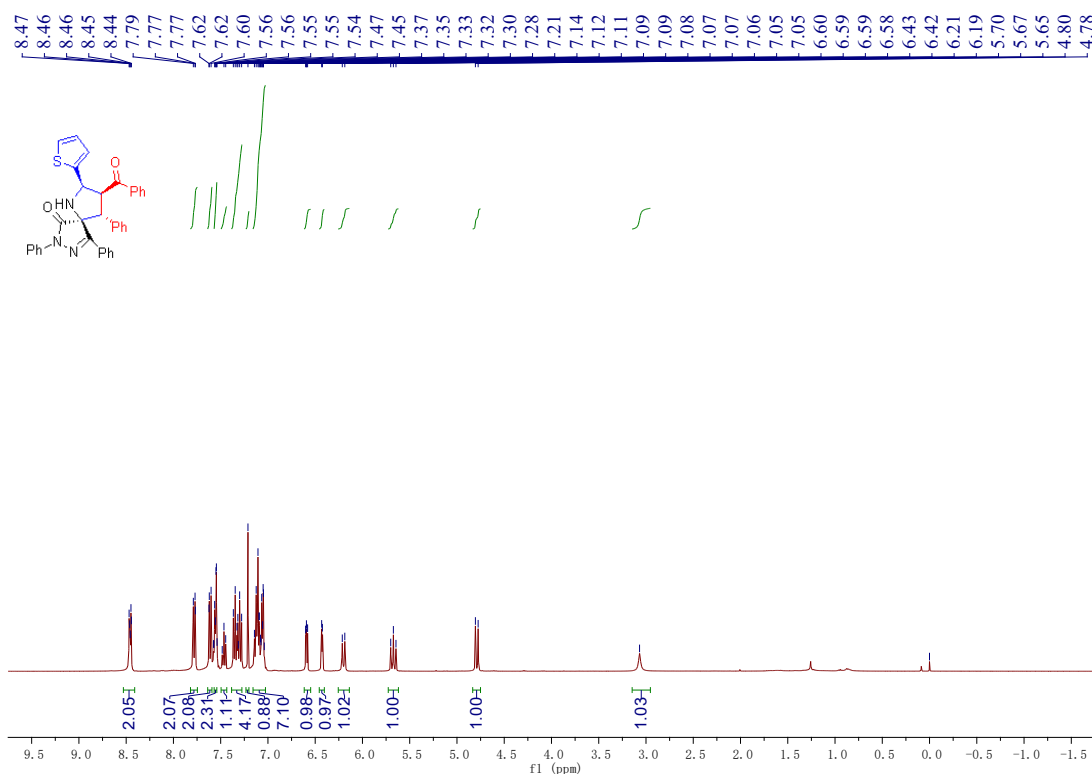


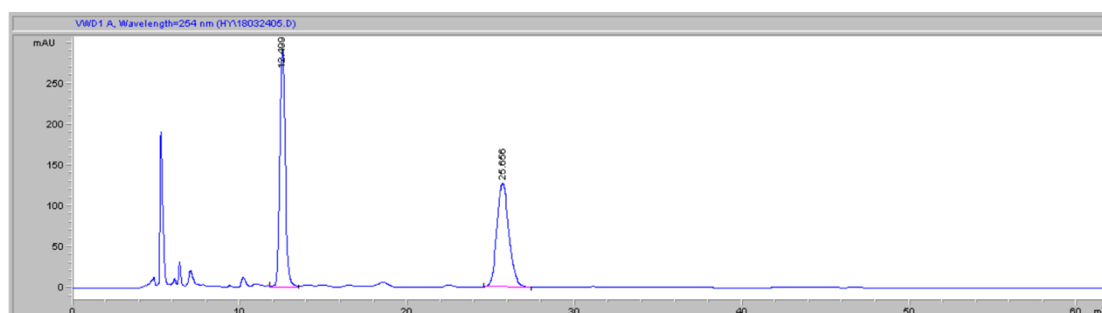
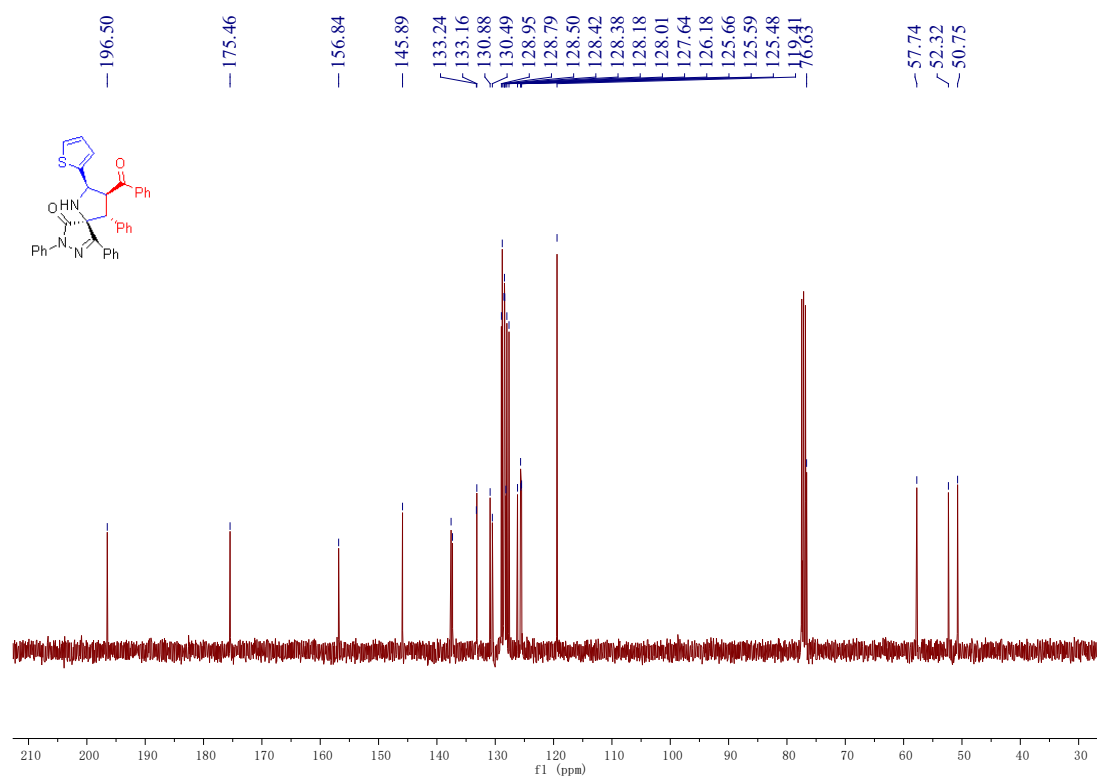
Prepared according to the procedure within 36 h as White solid

(85.3 mg, 77% yield, dr > 20:1). mp 117.5 – 118.1 °C; $[\alpha]_D^{19} = -$

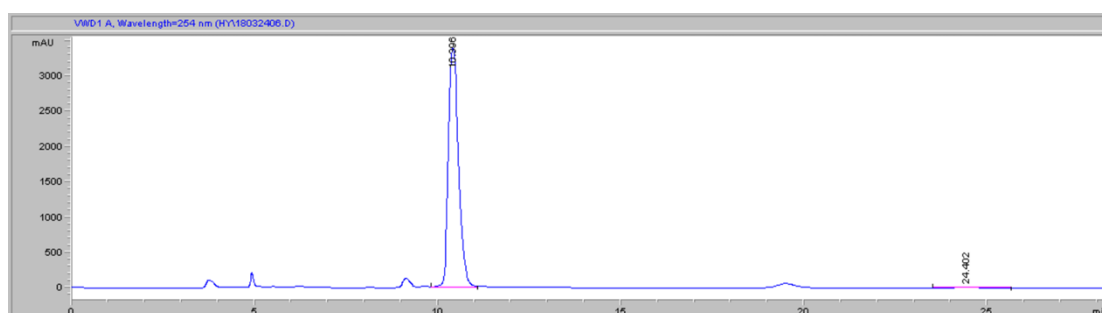
77.815 (c 0.60, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.53 – 8.41 (m, 2H), 7.82 – 7.75 (m, 2H), 7.64 – 7.59 (m, 2H), 7.54 – 7.57 (m, 2H), 7.44 – 7.49 (m, 1H), 7.38 – 7.28 (m, 4H), 7.21 (s, 1H), 7.16 – 7.03 (m, 7H), 6.59 (dd, J = 5.0, 3.5 Hz, 1H), 6.43 (d, J = 3.1

Hz, 1H), 6.20 (d, J = 10.6 Hz, 1H), 5.67 (t, J = 11.1 Hz, 1H), 4.79 (d, J = 11.6 Hz, 1H), 3.07 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 196.50, 175.46, 156.84, 145.89, 137.57, 137.32, 133.24, 133.16, 130.88, 130.49, 128.95, 128.79, 128.50, 128.42, 128.38, 128.18, 128.01, 127.64, 126.18, 125.66, 125.59, 125.48, 119.41, 76.63, 57.74, 52.32, 50.75; HRMS (ESI) m/z Calcd. for C₃₅H₂₈N₃O₂S⁺ ([M+H]⁺) 554.1897, Found 554.1890; Enantiomeric excess was determined to be 94% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, *t*_{major} = 10.4 min, *t*_{minor} = 24.4 min).



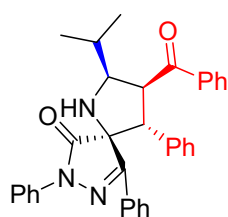


#	Time	Area	Height	Width	Area%	Symmetry
1	12.499	6552.3	292.2	0.3431	50.888	0.799
2	25.656	6323.6	126.7	0.7745	49.112	0.833



#	Time	Area	Height	Width	Area%	Symmetry
1	10.396	65936.4	3387.5	0.3028	99.672	0.709
2	24.402	217.1	4.5	0.7069	0.328	0.922

5ama

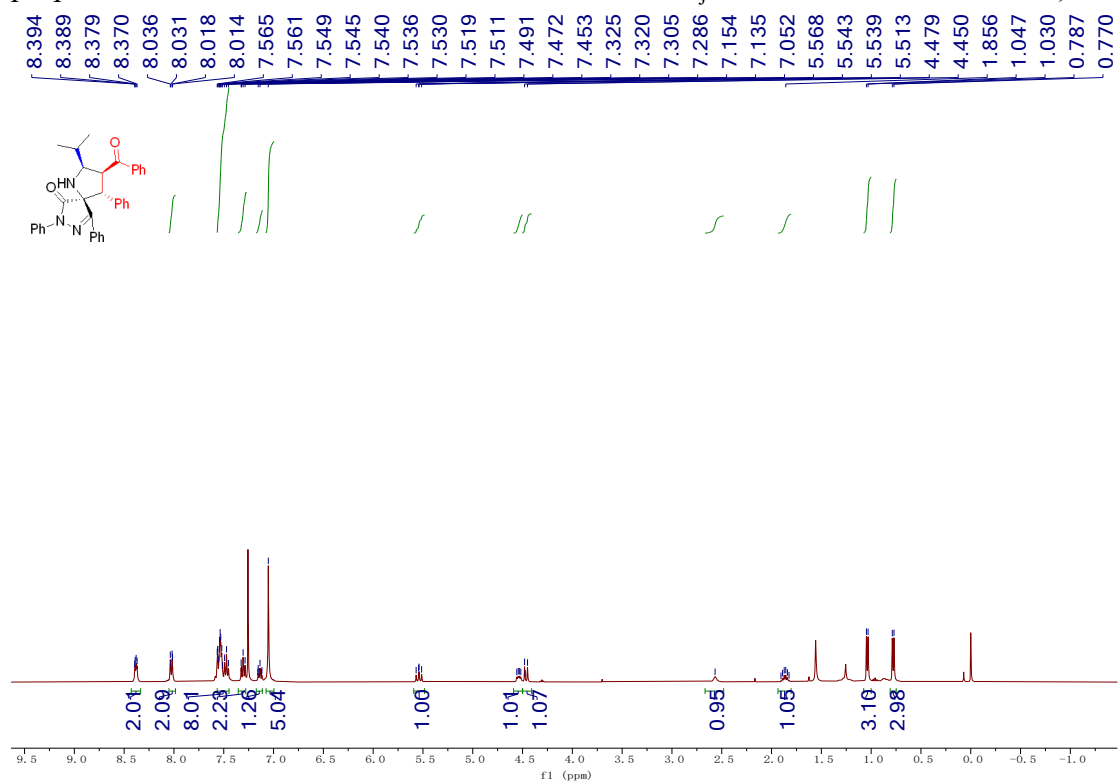


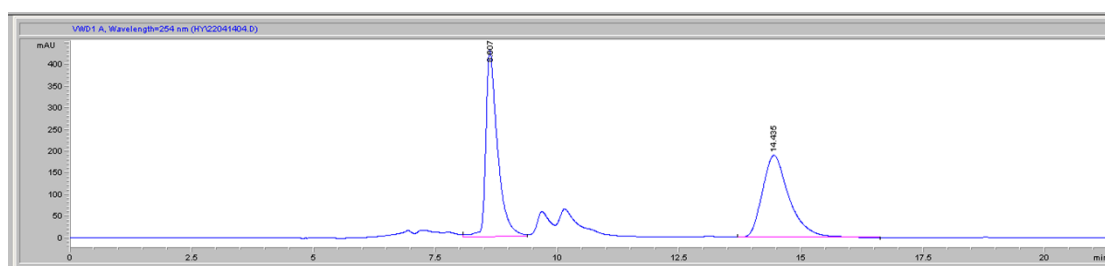
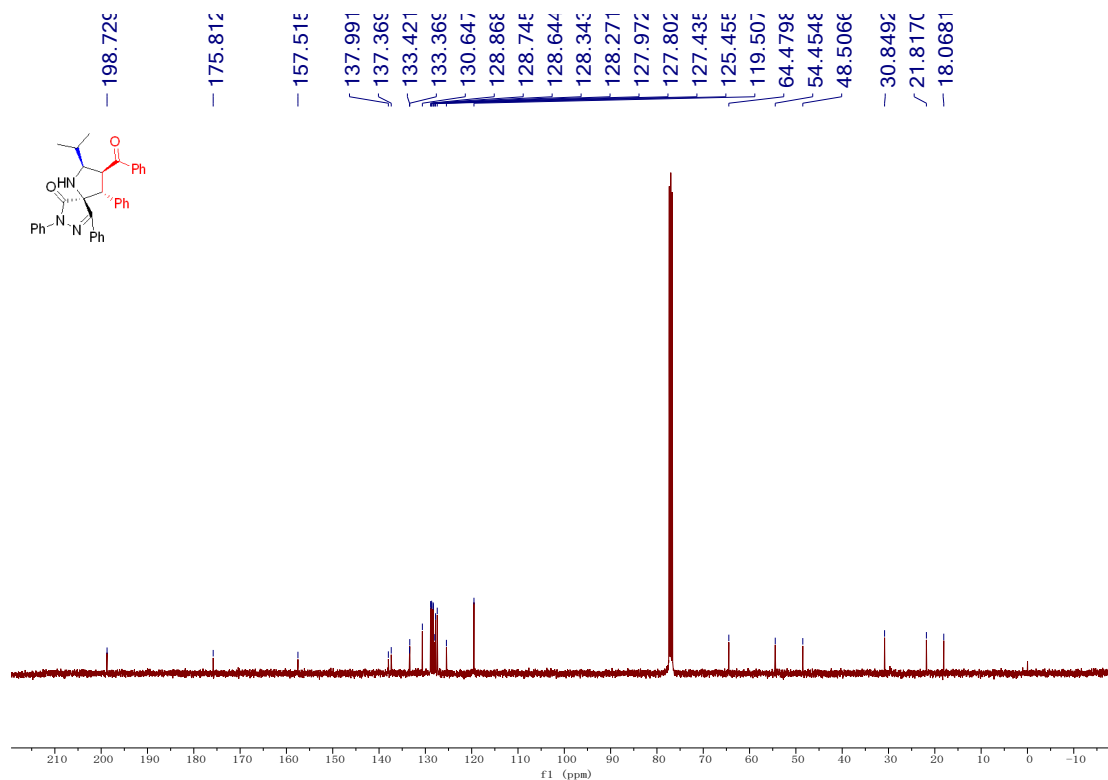
Prepared according to the procedure within 48 h as White solid

(73.9 mg, 72% yield, dr > 20:1). mp 81.6.9 – 82.4 °C; $[\alpha]_D^{13} = -$

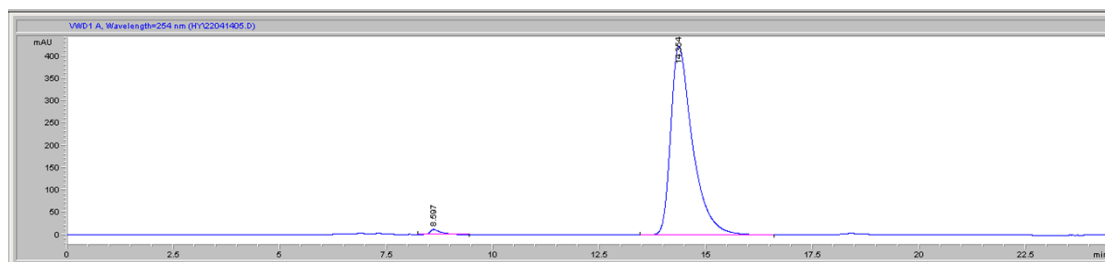
46.000 (*c* 0.11, CH₂Cl₂); ¹H NMR (400 MHz, Chloroform-*d*) δ 8.38 (dd, *J* = 6.8, 3.0 Hz, 2H), 8.05 – 7.98 (m, 2H), 7.57 – 7.45 (m, 8H), 7.35 – 7.28 (m, 2H), 7.17 – 7.11 (m, 1H), 7.08 – 7.00 (m, 5H),

5.54 (dd, *J* = 11.9, 10.2 Hz, 1H), 4.54 (dd, *J* = 10.3, 5.8 Hz, 1H), 4.46 (d, *J* = 11.9 Hz, 1H), 2.57 (s, 1H), 1.94 – 1.80 (m, 1H), 1.04 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.6 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 198.73, 175.81, 157.52, 137.99, 137.37, 133.42, 133.37, 130.65, 128.87, 128.75, 128.64, 128.34, 128.27, 127.97, 127.80, 127.44, 125.46, 119.51, 64.48, 54.45, 48.51, 30.85, 21.82, 18.07; HRMS (ESI) *m/z* Calcd. for C₃₄H₃₂N₃O₂⁺ ([M+H]⁺) 514.2489, Found 514.2473; 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, 0.5 mL/min, *t*_{major} = 14.3 min, *t*_{minor} = 8.6 min).

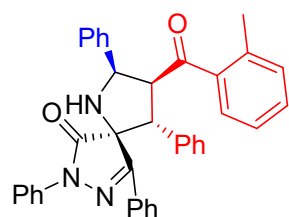




#	Time	Area	Height	Width	Area%	Symmetry
1	8.607	7308.8	432.8	0.2436	50.260	0.505
2	14.435	7233.3	189.3	0.5768	49.740	0.699

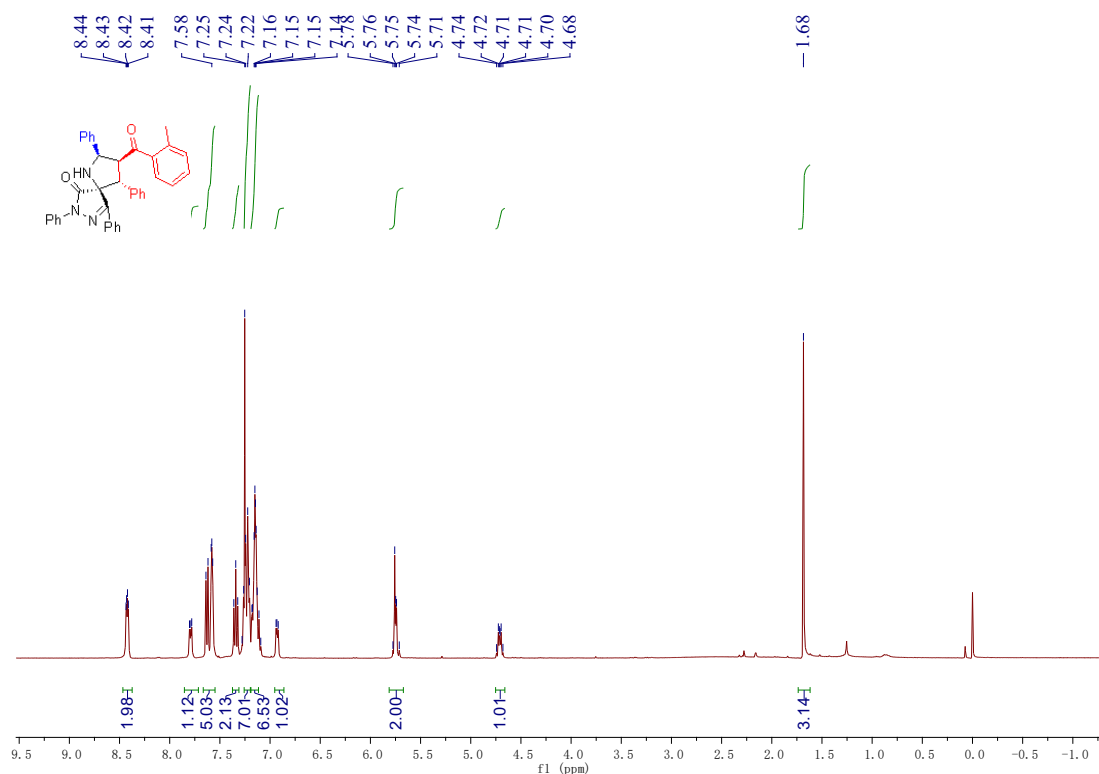


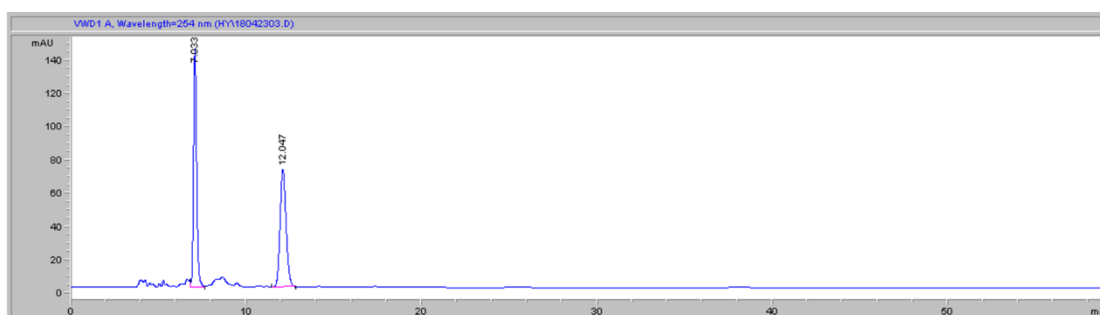
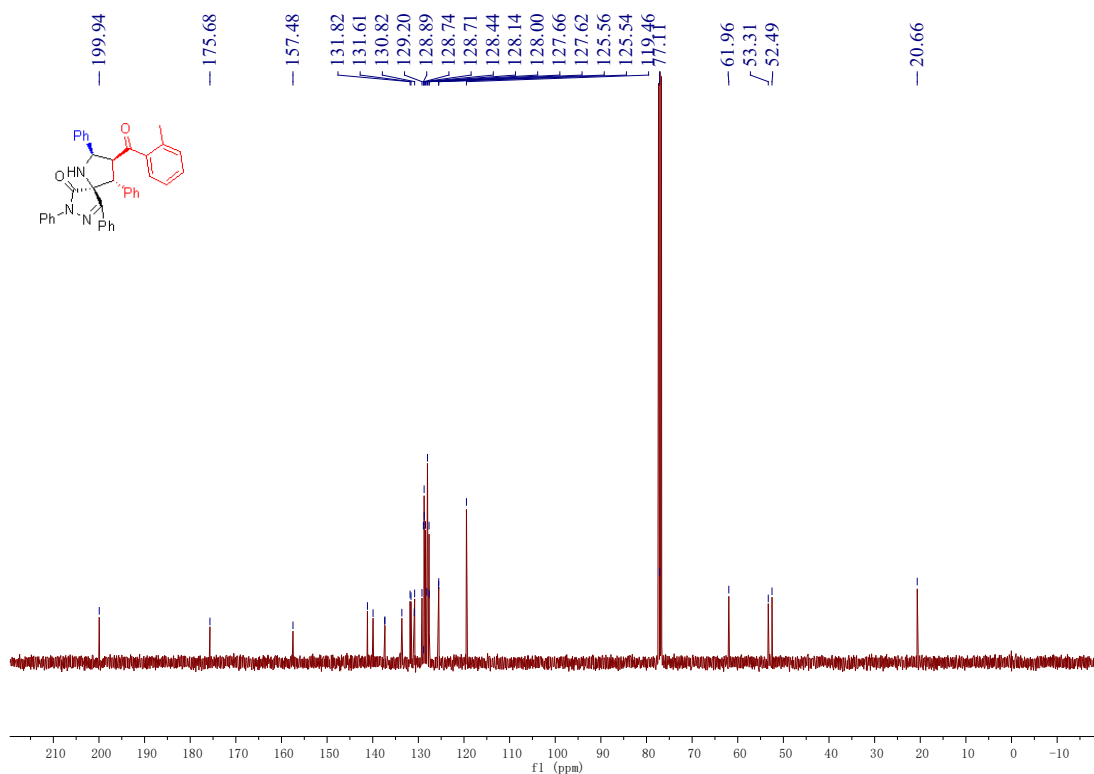
#	Time	Area	Height	Width	Area%	Symmetry
1	8.597	211.2	11.5	0.2577	1.384	0.421
2	14.354	15053.9	421.5	0.5317	98.616	0.551

5aab

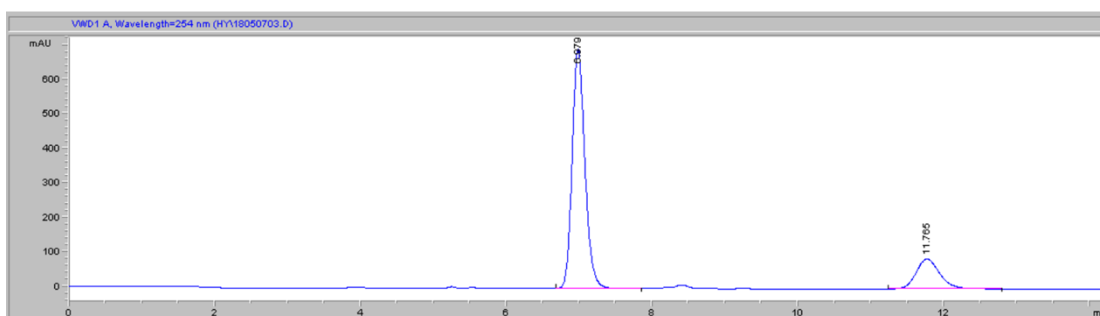
Prepared according to the procedure within 96 h as White solid

(44.9 mg, 40% yield, dr > 20:1). mp 157.6 – 158.3 °C; $[\alpha]_D^{19} = -36.449$ (c 0.11, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.46 (m, 2H), 7.85 – 7.71 (m, 1H), 7.67 – 7.55 (m, 5H), 7.45 – 7.28 (m, 2H), 7.20 – 7.26 (m, 7H), 7.19 – 7.12 (m, 6H), 6.95 – 6.86 (m, 1H), 5.81 – 5.67 (m, 2H), 4.75 – 4.66 (m, 1H), 1.68 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 199.94, 175.68, 157.48, 141.16, 139.93, 137.38, 137.32, 133.62, 131.82, 131.61, 130.89, 130.82, 129.20, 128.89, 128.83, 128.74, 128.71, 128.44, 128.14, 128.00, 127.66, 127.62, 125.56, 125.54, 119.46, 77.11, 61.96, 53.31, 52.49, 20.66; HRMS (ESI) m/z Calcd. for C₃₈H₃₂N₃O₂⁺ ([M+H]⁺) 562.2489, Found 562.2492; Enantiomeric excess was determined to be 63% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, *t*_{major} = 7.0 min, *t*_{minor} = 11.8 min).

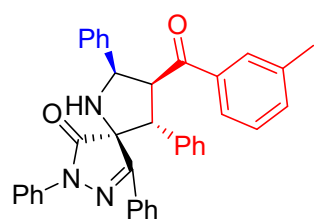




#	Time	Area	Height	Width	Area%	Symmetry
1	7.033	1684.2	143.1	0.1796	50.843	0.771
2	12.047	1628.4	70.7	0.3548	49.157	0.853



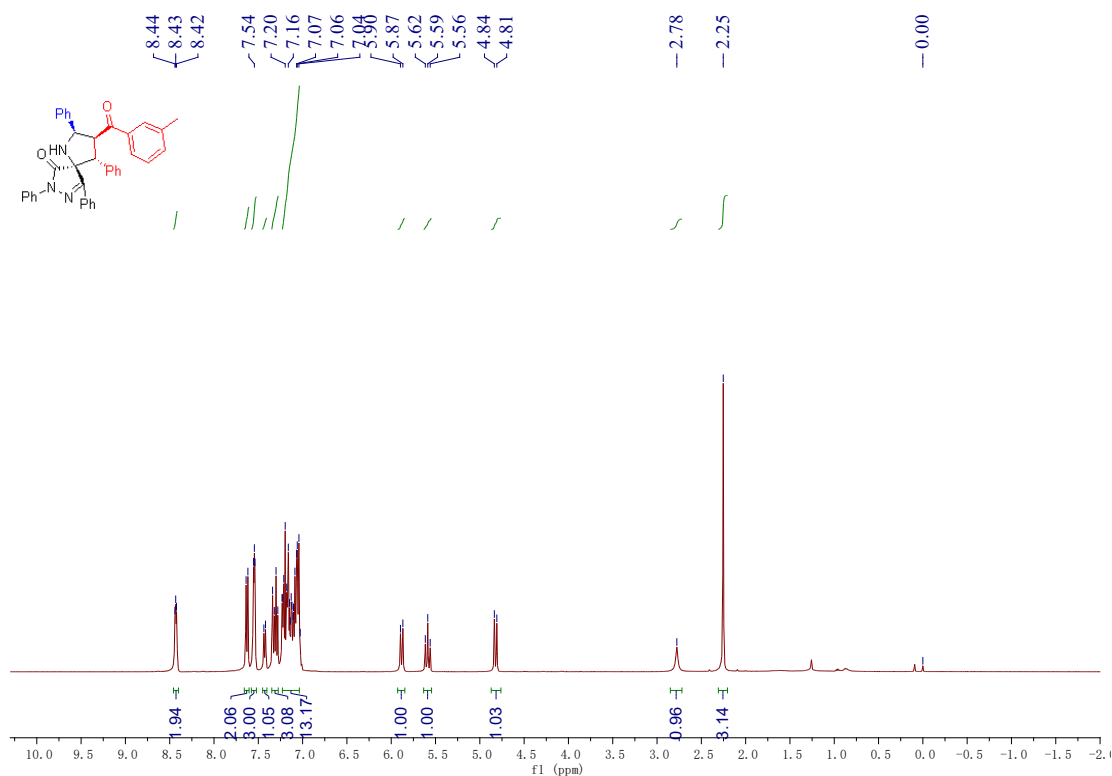
#	Time	Area	Height	Width	Area%	Symmetry
1	6.979	8478	694.9	0.1875	81.356	0.802
2	11.765	1942.9	86.5	0.3451	18.644	0.813

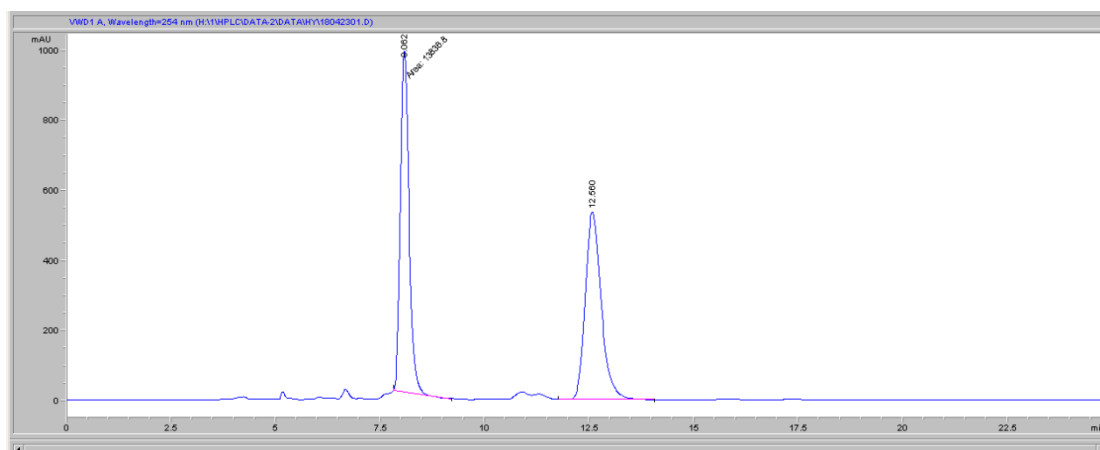
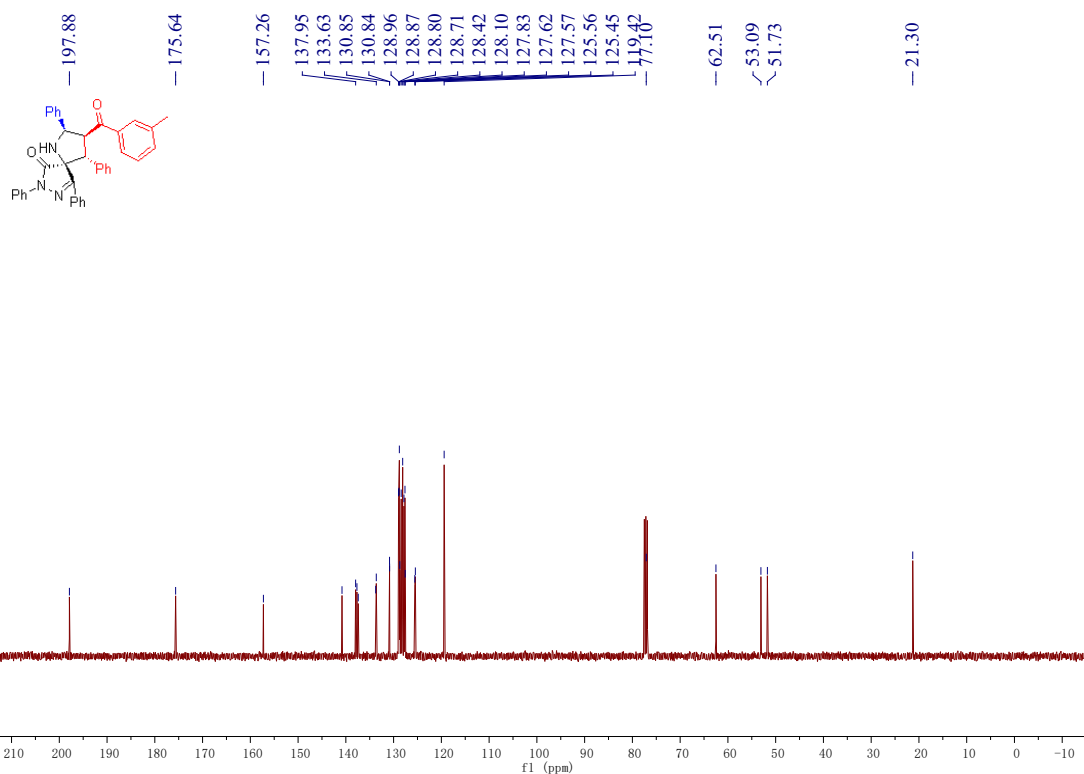
5aac

Prepared according to the procedure within 96 h has White solid (100.0 mg, 89% yield, dr > 20:1). mp 132.6 – 133.3 °C;

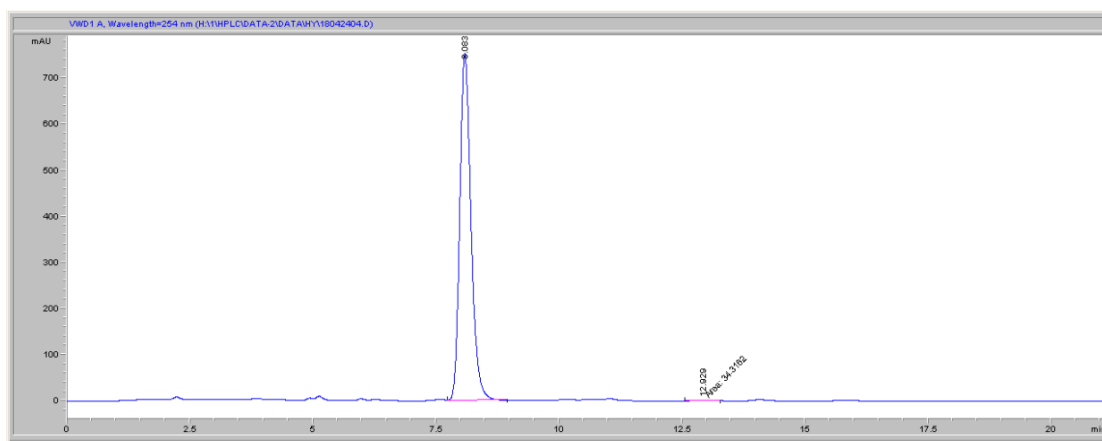
$[\alpha]_D^{19} = -63.567$ (*c* 0.91, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.46 – 8.40 (m, 2H), 7.63 (d, *J* = 8.2 Hz, 2H), 7.58 – 7.52 (m, 3H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.28 – 7.35 (m, 3H),

7.23 – 7.04 (m, 13H), 5.88 (d, *J* = 10.9 Hz, 1H), 5.59 (t, *J* = 11.0 Hz, 1H), 4.82 (d, *J* = 11.2 Hz, 1H), 2.78 (s, 1H), 2.25 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.88, 175.64, 157.26, 140.80, 137.95, 137.68, 137.40, 133.75, 133.63, 130.85, 130.84, 128.96, 128.87, 128.80, 128.71, 128.42, 128.10, 127.83, 127.62, 127.57, 125.56, 125.45, 119.42, 77.10, 62.51, 53.09, 51.73, 21.30; HRMS (ESI) *m/z* Calcd. for C₃₈H₃₂N₃O₂⁺ ([M+H]⁺) 562.2489, Found 562.2485; 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} = 8.1 min, *t*_{minor} = 12.9 min).



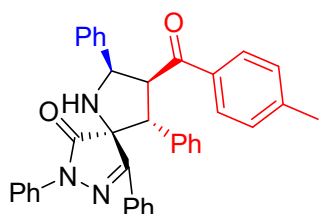


#	Time	Area	Height	Width	Area%	Symmetry
1	8.062	13836.8	971.5	0.2374	49.220	0.776
2	12.56	14275.2	535.3	0.4087	50.780	0.762

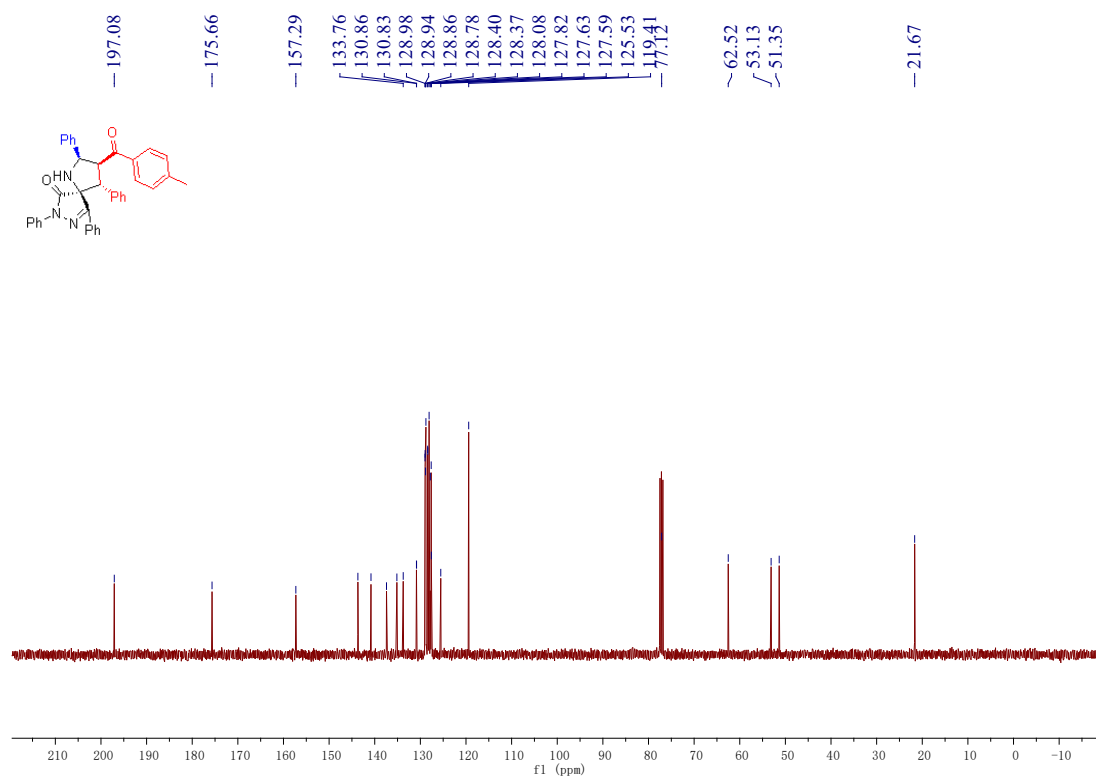


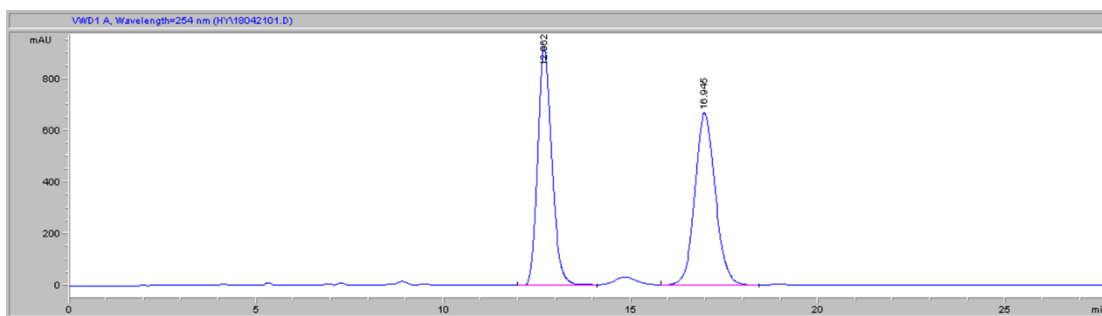
#	Time	Area	Height	Width	Area%	Symmetry
1	8.083	11917.4	753.4	0.2413	99.713	0.761
2	12.929	34.3	1.4	0.4223	0.287	1.606

5aad

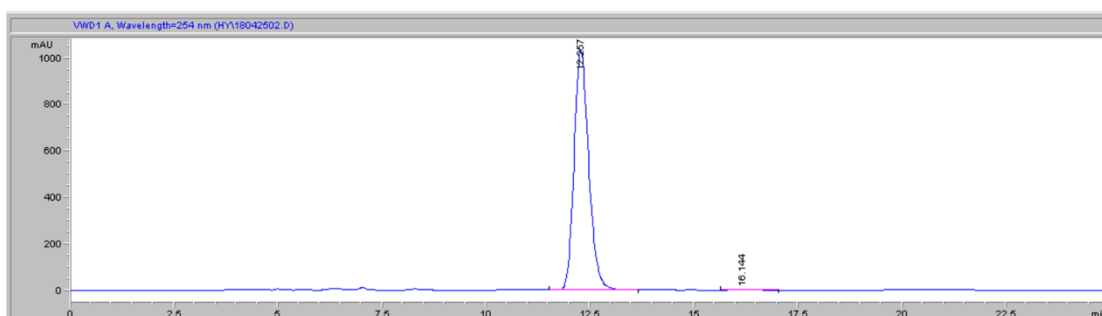


Prepared according to the procedure within 72 h as White solid (101.1 mg, 90% yield, dr > 20:1). mp 121.9 – 122.6 °C; $[\alpha]_D^{19} = -67.684$ (c 0.95, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.40 – 8.46 (m, 2H), 7.61 – 7.65 (m, 2H), 7.50 – 7.57 (m, 5H), 7.32 – 7.23 (m, 4H), 7.20 (s, 1H), 7.17 – 7.03 (m, 10H), 5.88 (d, J = 10.9 Hz, 1H), 5.60 (t, J = 11.1 Hz, 1H), 4.82 (d, J = 11.3 Hz, 1H), 2.80 (s, 1H), 2.28 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.08, 175.66, 157.29, 143.69, 140.82, 137.42, 135.14, 133.76, 130.86, 130.83, 128.98, 128.94, 128.86, 128.78, 128.40, 128.37, 128.08, 127.82, 127.63, 127.59, 125.53, 119.41, 77.12, 62.52, 53.13, 51.35, 21.67; HRMS (ESI) m/z Calcd. for C₃₈H₃₂N₃O₂⁺ ([M+H]⁺) 562.2489, Found 562.2485; 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} = 12.3 min, *t*_{minor} = 16.1 min).



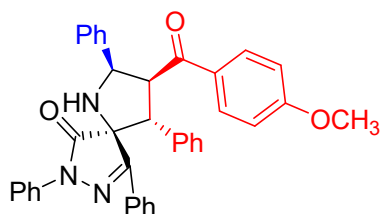


#	Time	Area	Height	Width	Area%	Symmetry
1	12.662	24357	926.4	0.4043	49.026	0.777
2	16.945	25324.6	666.5	0.5845	50.974	0.86

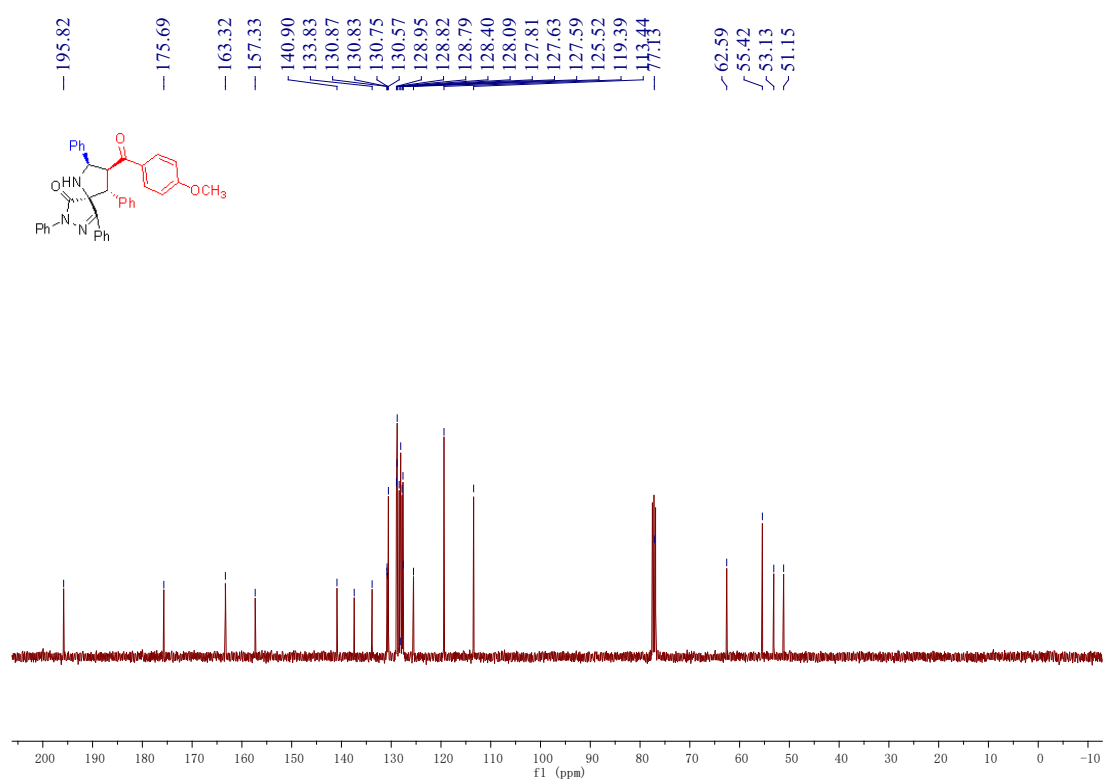
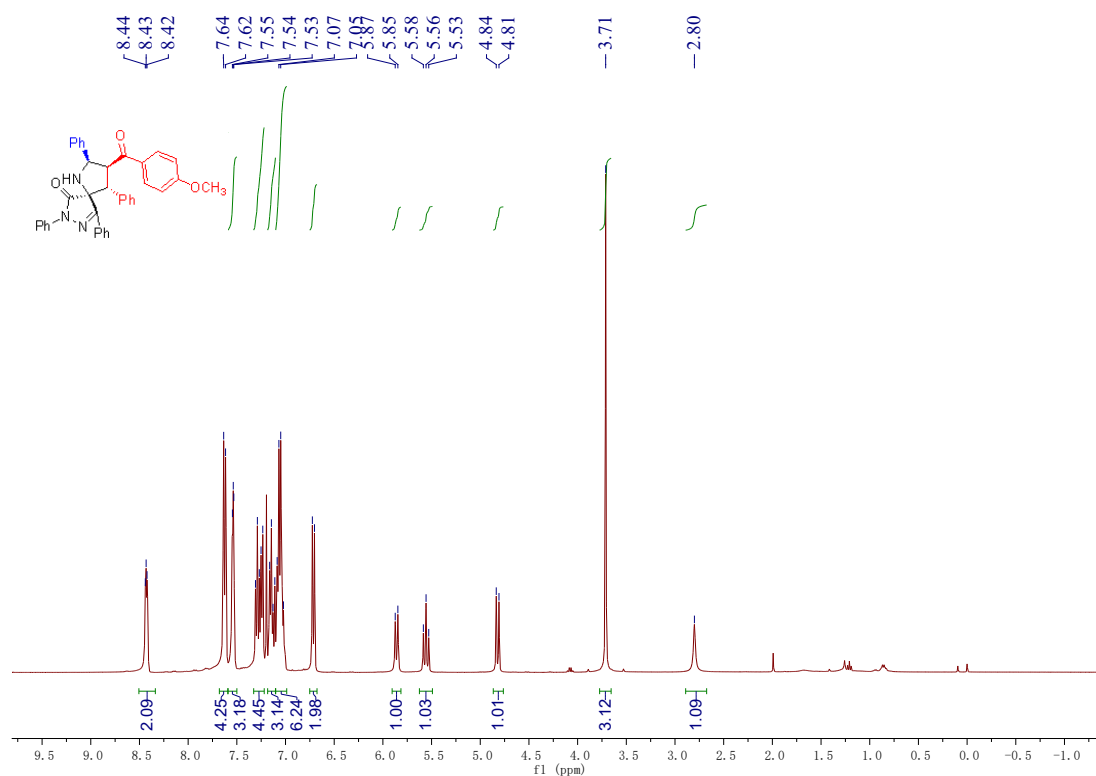


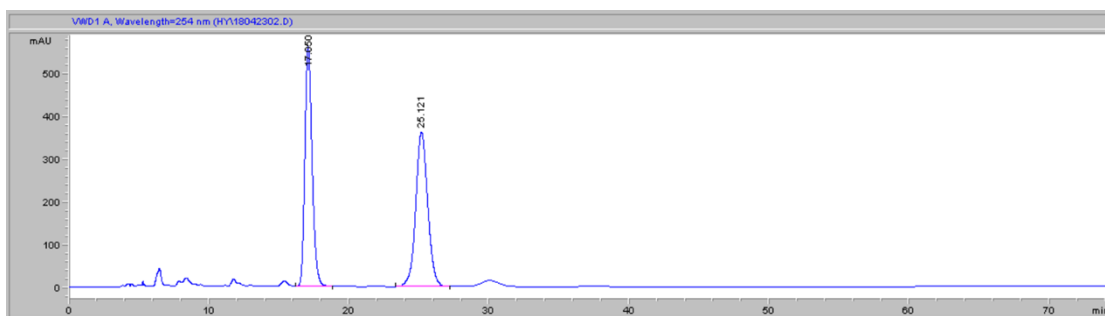
#	Time	Area	Height	Width	Area%	Symmetry
1	12.257	25295.4	1029.3	0.3799	99.741	0.785
2	16.144	65.6	2	0.4848	0.259	0.742

5aae

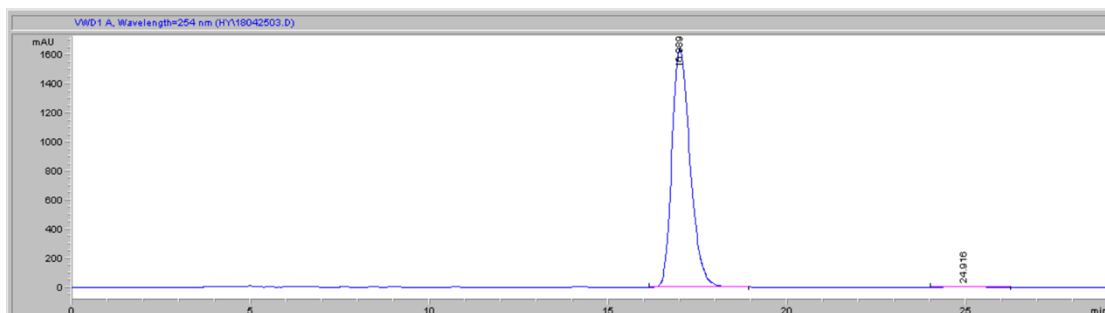


Prepared according to the procedure within 72 h as White solid (105.1 mg, 91% yield, dr > 20:1). mp 125.4 – 126.3 °C; $[\alpha]_D^{19} = -55.237$ (c 0.70, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.51 – 8.34 (m, 2H), 7.63 (d, J = 7.7 Hz, 4H), 7.59 – 7.50 (m, 3H), 7.33 – 7.22 (m, 4H), 7.10 – 7.18 (m, 3H), 7.10 – 6.99 (m, 6H), 6.71 (d, J = 8.7 Hz, 2H), 5.86 (d, J = 10.9 Hz, 1H), 5.56 (t, J = 11.1 Hz, 1H), 4.82 (d, J = 11.2 Hz, 1H), 3.71 (s, 3H), 2.80 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 195.82, 175.69, 163.32, 157.33, 140.90, 137.43, 133.83, 130.87, 130.83, 130.75, 130.57, 128.95, 128.82, 128.79, 128.40, 128.17, 128.09, 127.81, 127.63, 127.59, 125.52, 119.39, 113.44, 77.13, 62.59, 55.42, 53.13, 51.15; HRMS (ESI) m/z Calcd. for C₃₈H₃₂N₃O₃⁺ ([M+H]⁺) 578.2438, Found 578.2419; 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} = 17.0 min, *t*_{minor} = 24.9 min).



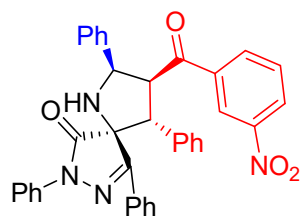


#	Time	Area	Height	Width	Area%	Symmetry
1	17.05	19808.5	560.2	0.545	48.437	0.771
2	25.121	21086.9	361.2	0.8921	51.563	0.895

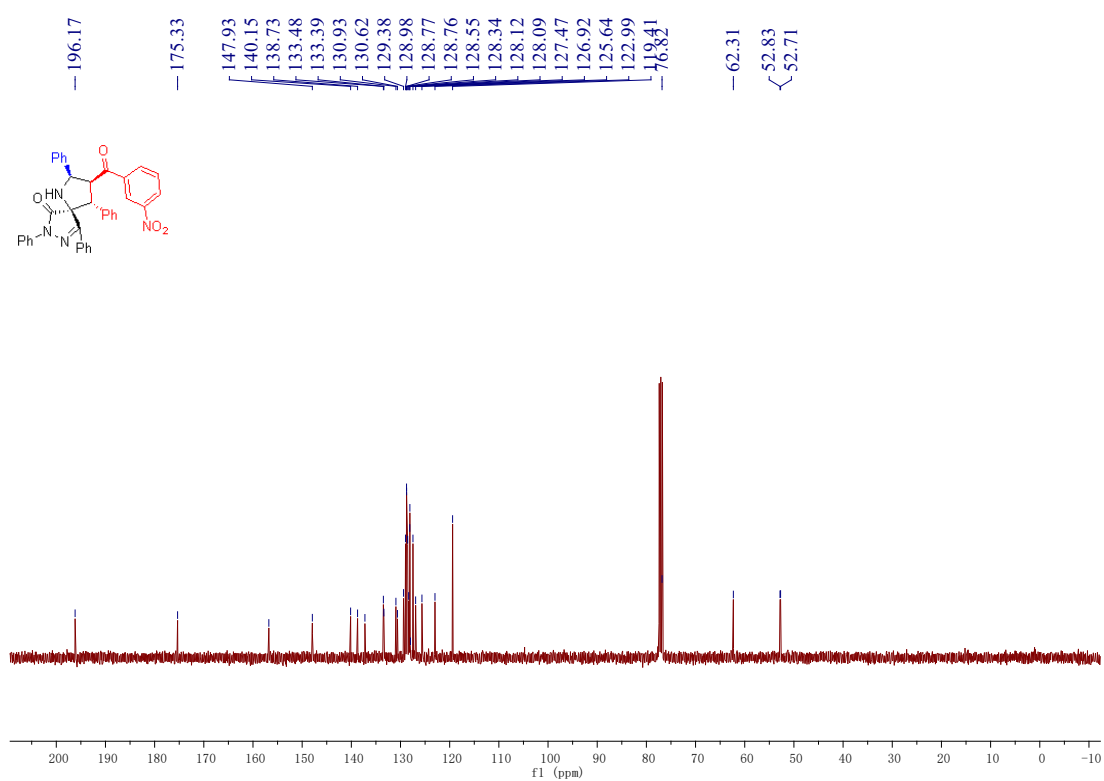
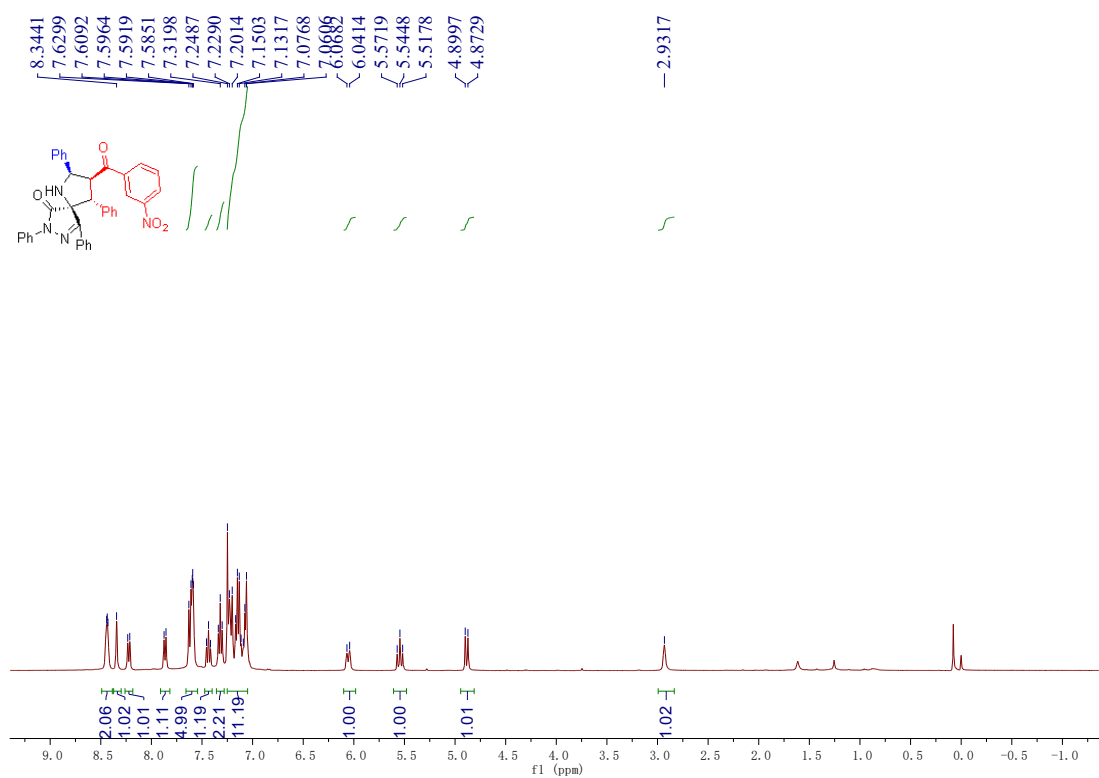


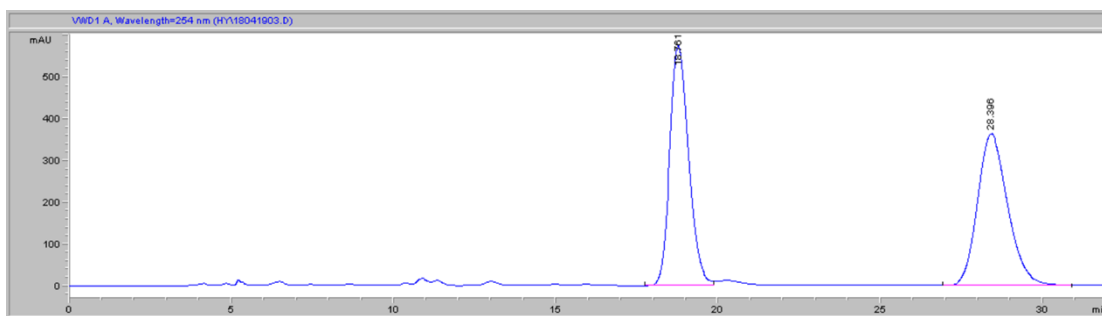
#	Time	Area	Height	Width	Area%	Symmetry
1	16.989	57924.5	1646.9	0.5414	99.655	0.718
2	24.916	200.6	3.9	0.7074	0.345	0.871

5aaf

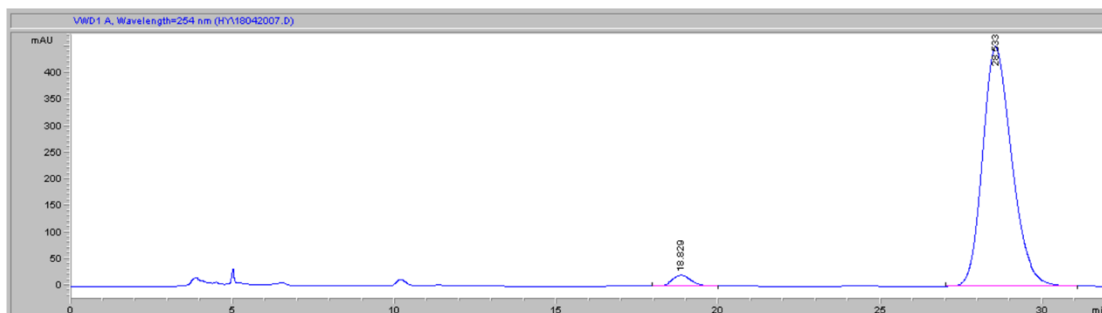


Prepared according to the procedure within 96 h as White solid (54.5 mg, 46% yield, dr > 20:1). mp 181.3 – 182.8 °C; $[\alpha]_D^{19} = -39.640$ (c 0.22, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.49 – 8.39 (m, 2H), 8.34 (s, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.7 Hz, 1H), 7.66 – 7.54 (m, 5H), 7.44 (dd, J = 7.9 Hz, 1H), 7.36 – 7.28 (m, 2H), 7.25 – 7.05 (m, 11H), 6.05 (d, J = 10.7 Hz, 1H), 5.54 (t, J = 10.8 Hz, 1H), 4.89 (d, J = 10.7 Hz, 1H), 2.93 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 196.17, 175.33, 156.77, 147.93, 140.15, 138.73, 137.24, 133.48, 133.39, 130.93, 130.62, 129.38, 128.98, 128.77, 128.76, 128.55, 128.34, 128.12, 128.09, 127.97, 127.47, 126.92, 125.64, 122.99, 119.41, 76.82, 62.31, 52.83, 52.71; HRMS (ESI) m/z Calcd. for C₃₇H₂₉N₄O₄⁺ ([M+H]⁺) 593.2183, Found 593.2166 Enantiomeric excess was determined to be 94% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, *t*_{major} = 28.5 min, *t*_{minor} = 18.8 min).



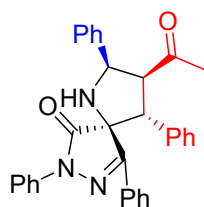


#	Time	Area	Height	Width	Area%	Symmetry
1	18.761	23179.3	574	0.624	49.740	0.791
2	28.396	23421.6	363.2	0.997	50.260	0.777

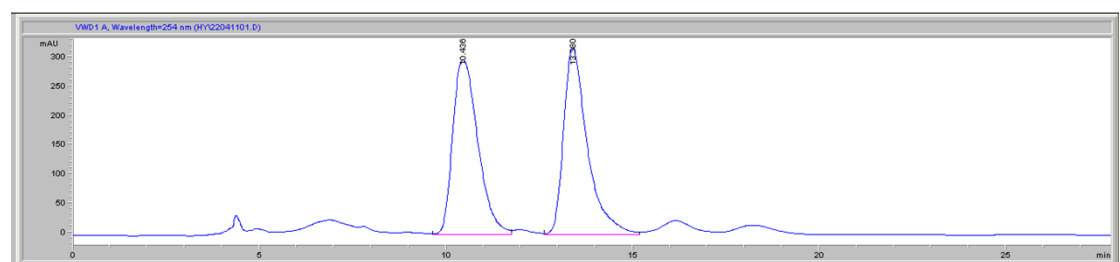
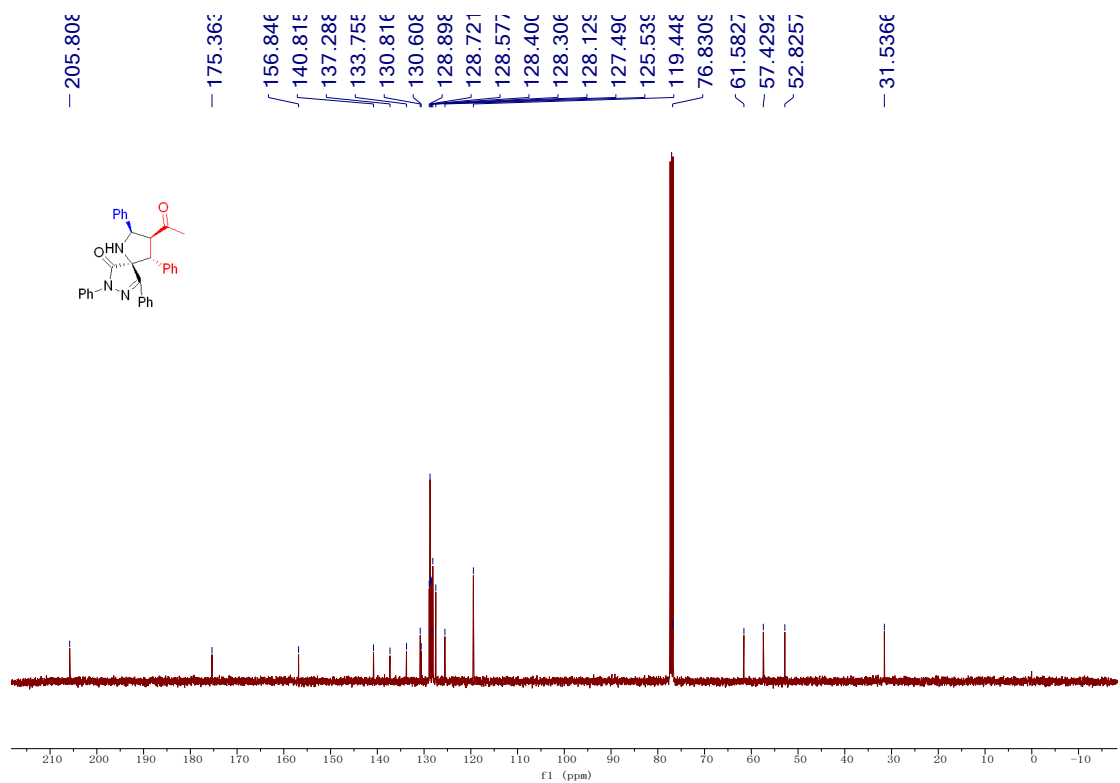
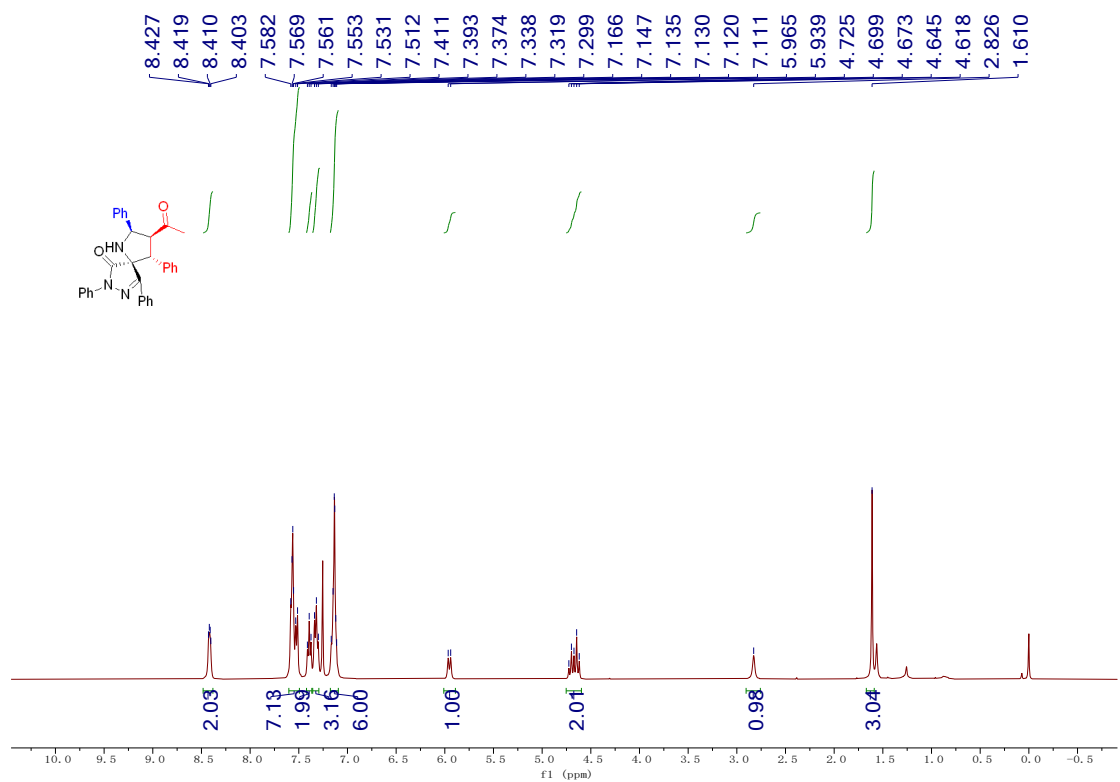


#	Time	Area	Height	Width	Area%	Symmetry
1	18.829	808.9	20.4	0.6157	2.783	0.893
2	28.533	28253.9	452.2	0.9693	97.217	0.755

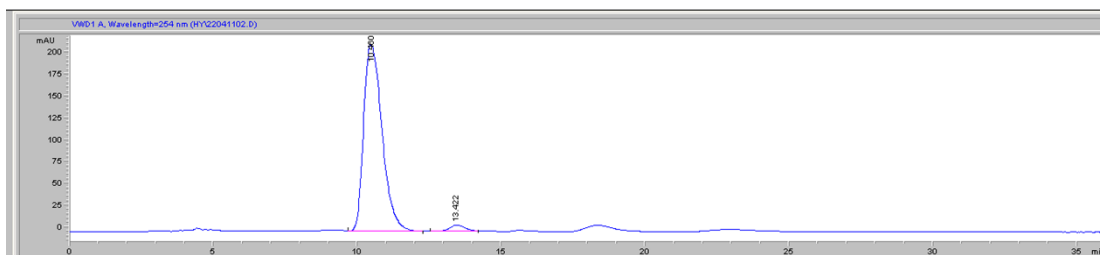
5aag



Prepared according to the procedure within 60 h as White solid (83.4 mg, 86% yield, dr > 20:1). mp 106.2 – 107.3 °C; $[\alpha]_D^{13} = -83.628$ (c 0.23, CH₂Cl₂); ¹H NMR (400 MHz, Chloroform-*d*) δ 8.42 (dd, J = 6.6, 3.1 Hz, 2H), 7.60 – 7.49 (m, 7H), 7.39 (dd, J = 7.4 Hz, 2H), 7.36 – 7.29 (m, 3H), 7.18 – 7.09 (m, 6H), 5.95 (d, J = 10.2 Hz, 1H), 4.75 – 4.60 (m, 2H), 2.83 (s, 1H), 1.61 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 205.81, 175.36, 156.85, 140.82, 137.29, 133.76, 130.82, 130.61, 128.90, 128.72, 128.58, 128.40, 128.31, 128.13, 127.49, 125.54, 119.45, 76.83, 61.58, 57.43, 52.83, 31.54; HRMS (ESI) m/z Calcd. for C₃₂H₂₈N₃O₂⁺ ([M+H]⁺) 486.2176, Found 486.2158 Enantiomeric excess was determined to be 94% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, t_{major} = 10.4 min, t_{minor} = 13.4 min).

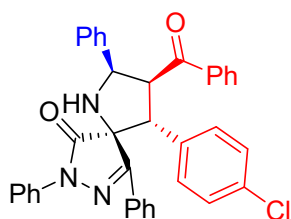


#	Time	Area	Height	Width	Area%	Symmetry
1	10.436	14211.3	301.3	0.7293	49.752	0.644
2	13.38	14353.1	320.6	0.6679	50.248	0.584



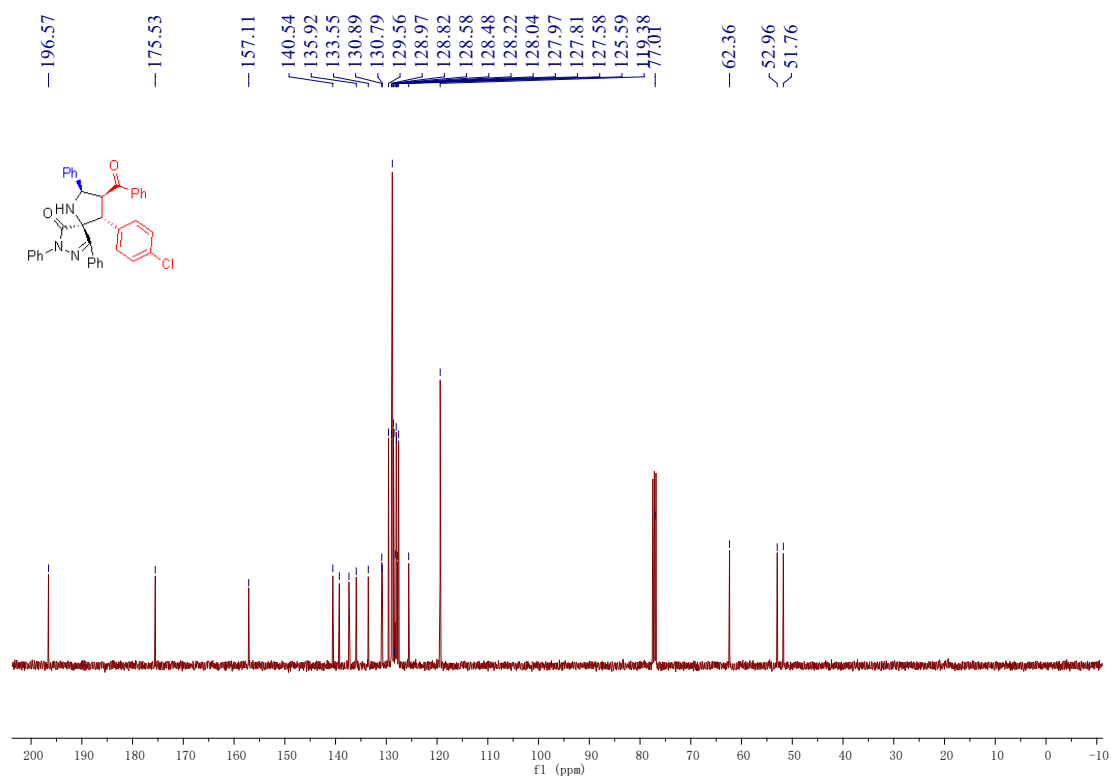
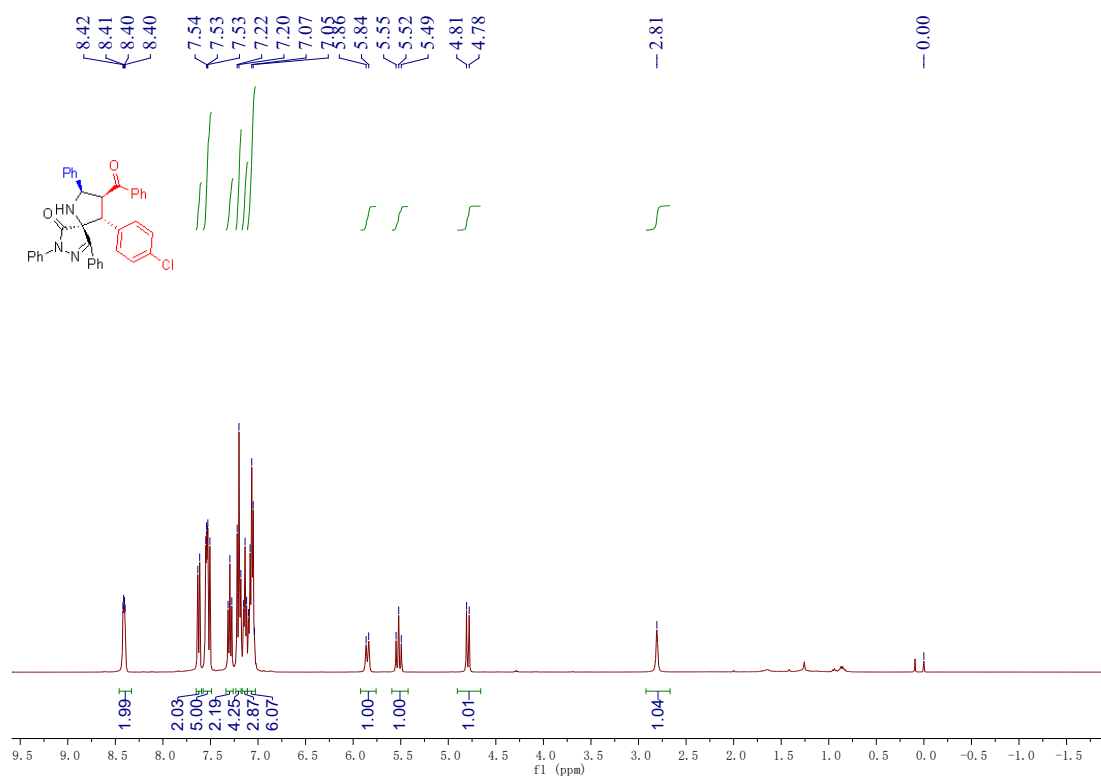
#	Time	Area	Height	Width	Area%	Symmetry
1	10.46	9473.8	213.4	0.6986	97.094	0.632
2	13.422	283.5	7.2	0.5909	2.906	0.769

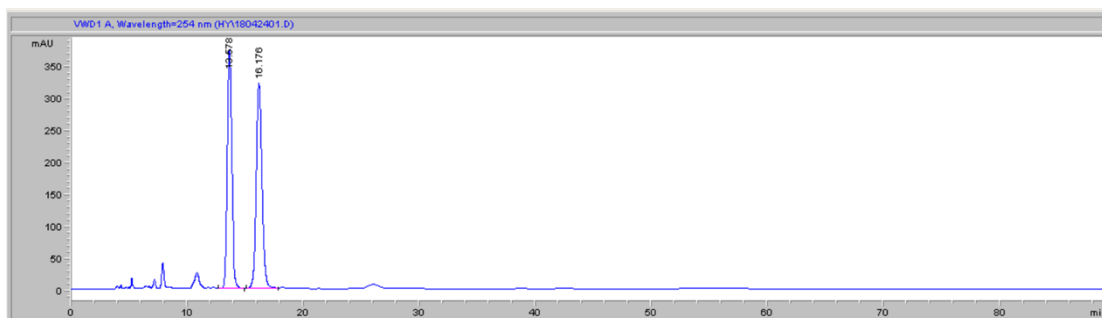
5aah



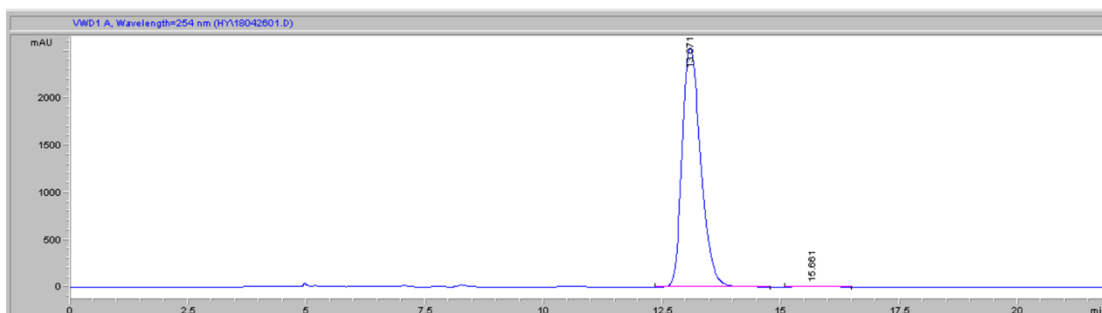
Prepared according to the procedure within 96 h as White solid

(104.5 mg, 90% yield, dr > 20:1). mp 119.6 – 119.3 °C; $[\alpha]_D^{19} = -57.382$ (c 0.62, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.41 (dd, J = 6.5, 2.9 Hz, 2H), 7.62 (d, J = 7.9 Hz, 2H), 7.58 – 7.49 (m, 5H), 7.38 – 7.25 (m, 2H), 7.17 – 7.23 (m, 4H), 7.25 – 7.12 (m, 3H), 7.11 – 7.03 (m, 6H), 5.85 (d, J = 10.9 Hz, 1H), 5.52 (t, J = 11.0 Hz, 1H), 4.79 (d, J = 11.1 Hz, 1H), 2.81 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 196.57, 175.53, 157.11, 140.54, 139.26, 137.36, 135.92, 133.55, 130.89, 130.79, 129.56, 128.97, 128.82, 128.58, 128.48, 128.41, 128.22, 128.04, 127.97, 127.81, 127.58, 125.59, 119.38, 77.01, 62.36, 52.96, 51.76; HRMS (ESI) m/z Calcd. for C₃₇H₂₉ClN₃O₂⁺ ([M+H]⁺) 582.1943, Found 582.1932 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} = 13.1 min, *t*_{minor} = 15.7 min)



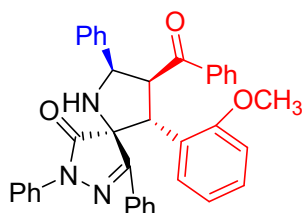


#	Time	Area	Height	Width	Area%	Symmetry
1	13.578	10590.8	373.5	0.4357	49.238	0.824
2	16.176	10918.4	320.9	0.5222	50.762	0.849



#	Time	Area	Height	Width	Area%	Symmetry
1	13.071	68951.1	2526.4	0.4218	99.612	0.698
2	15.661	268.7	8.7	0.4754	0.388	0.845

5aai

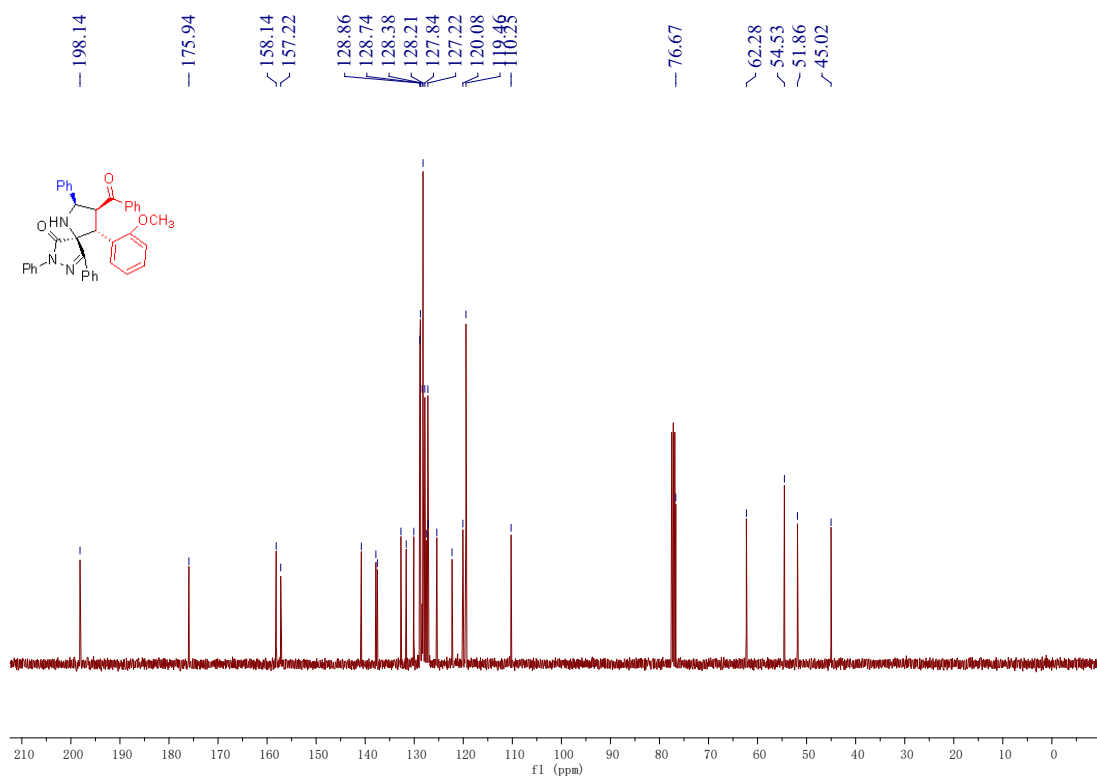
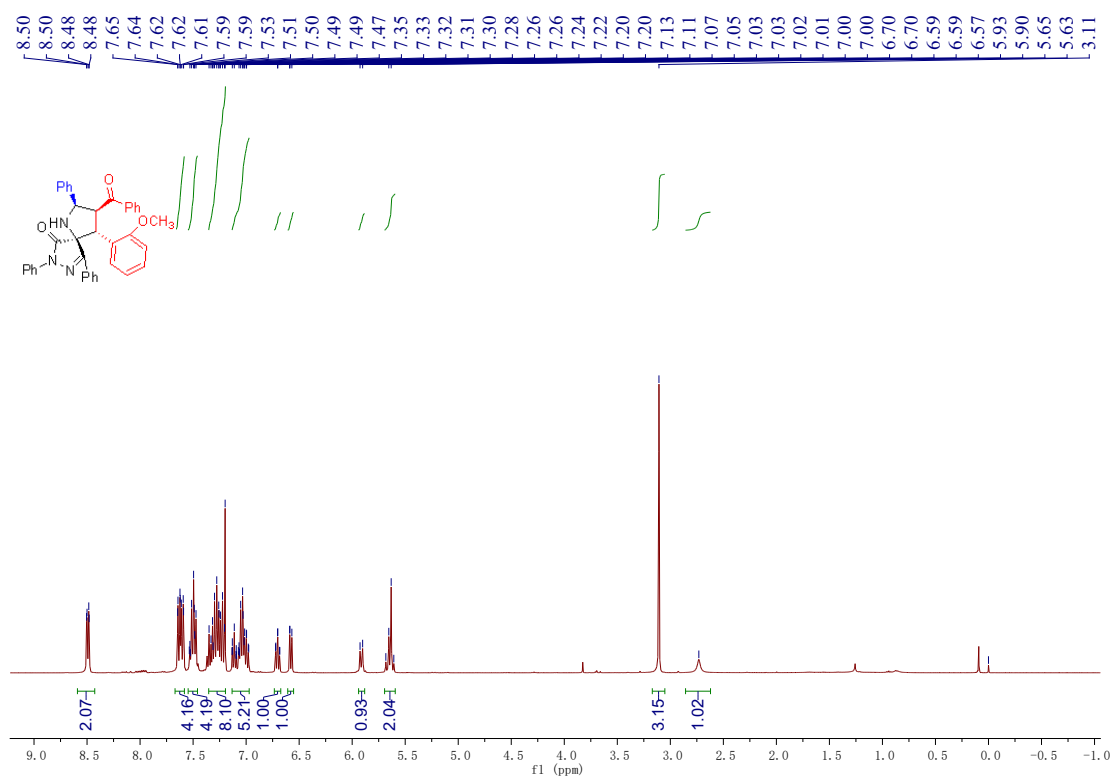


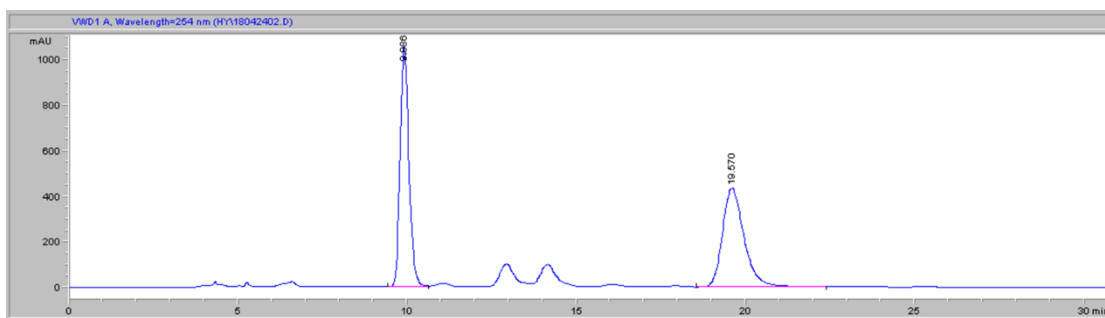
Prepared according to the procedure within 48 h as White solid (109.8 mg, 95% yield, dr > 20:1). mp 116.3 – 117.5 °C;

$[\alpha]_D^{19} = -29.087$ (*c* 1.00, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃)

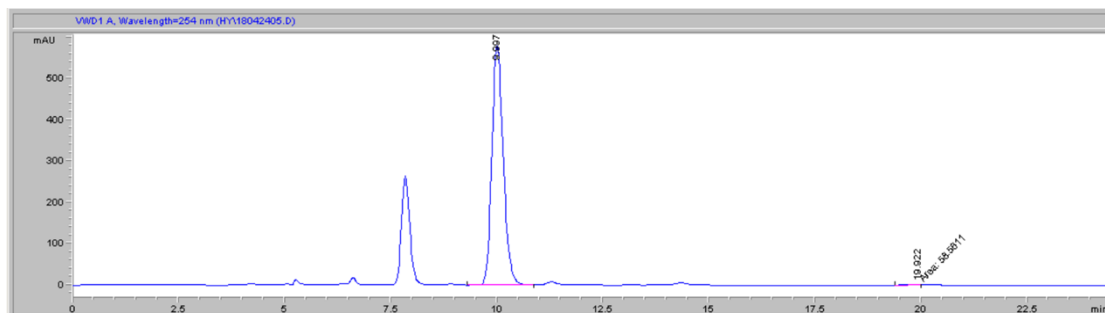
δ 8.47 – 8.52 (m, 2H), 7.67 – 7.58 (m, 4H), 7.46 – 7.54 (m, 4H), 7.35 – 7.19 (m, 8H), 7.13 – 6.97 (m, 5H), 6.70 (td, *J* =

7.6, 0.8 Hz, 1H), 6.61 – 6.55 (m, 1H), 5.91 (d, *J* = 9.8 Hz, 1H), 5.69 – 5.59 (m, 2H), 3.11 (s, 3H), 2.73 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 198.14, 175.94, 158.14, 157.22, 140.79, 137.82, 137.51, 132.71, 131.63, 130.08, 128.86, 128.74, 128.38, 128.21, 127.84, 127.54, 127.22, 127.10, 125.40, 122.29, 120.08, 119.46, 110.25, 76.67, 62.28, 54.53, 51.86, 45.02; HRMS (ESI) *m/z* Calcd. for C₃₈H₃₂N₃O₃⁺ ([M+H]⁺) 578.2438, Found 578.2424; 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} = 10.0 min, *t*_{minor} = 19.9 min).



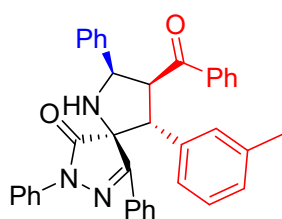


#	Time	Area	Height	Width	Area%	Symmetry
1	9.886	19269.3	1052.3	0.2821	50.161	0.782
2	19.57	19146	433.3	0.6727	49.839	0.715



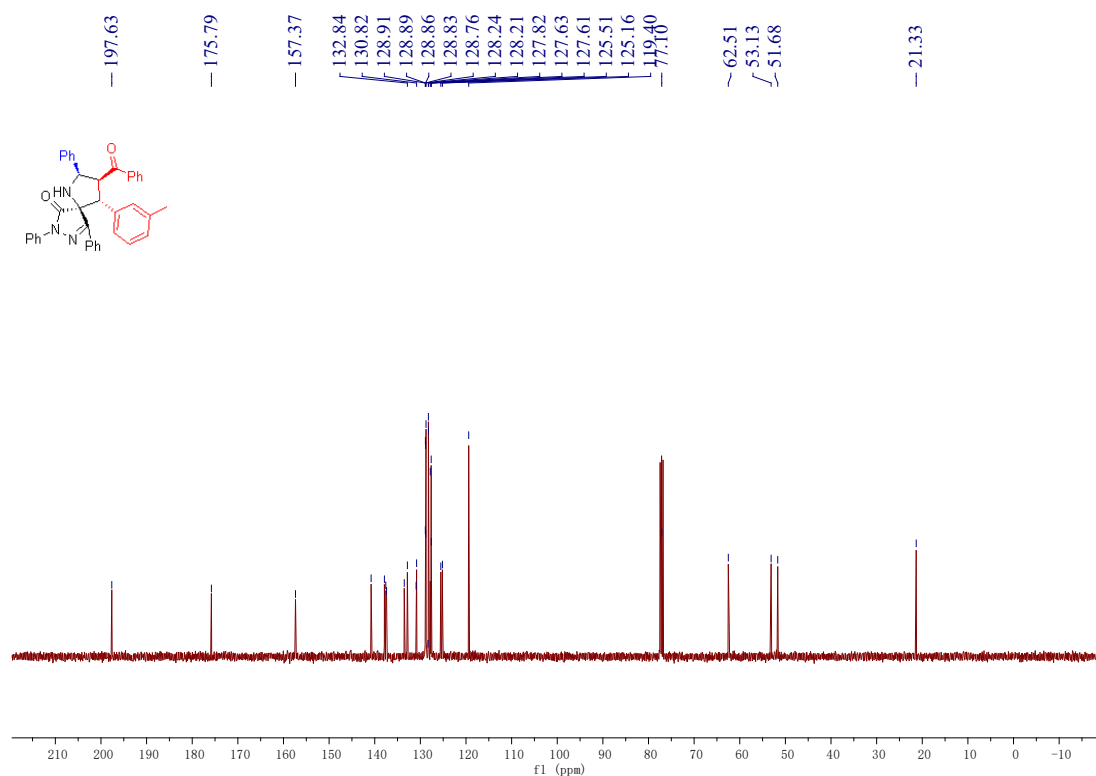
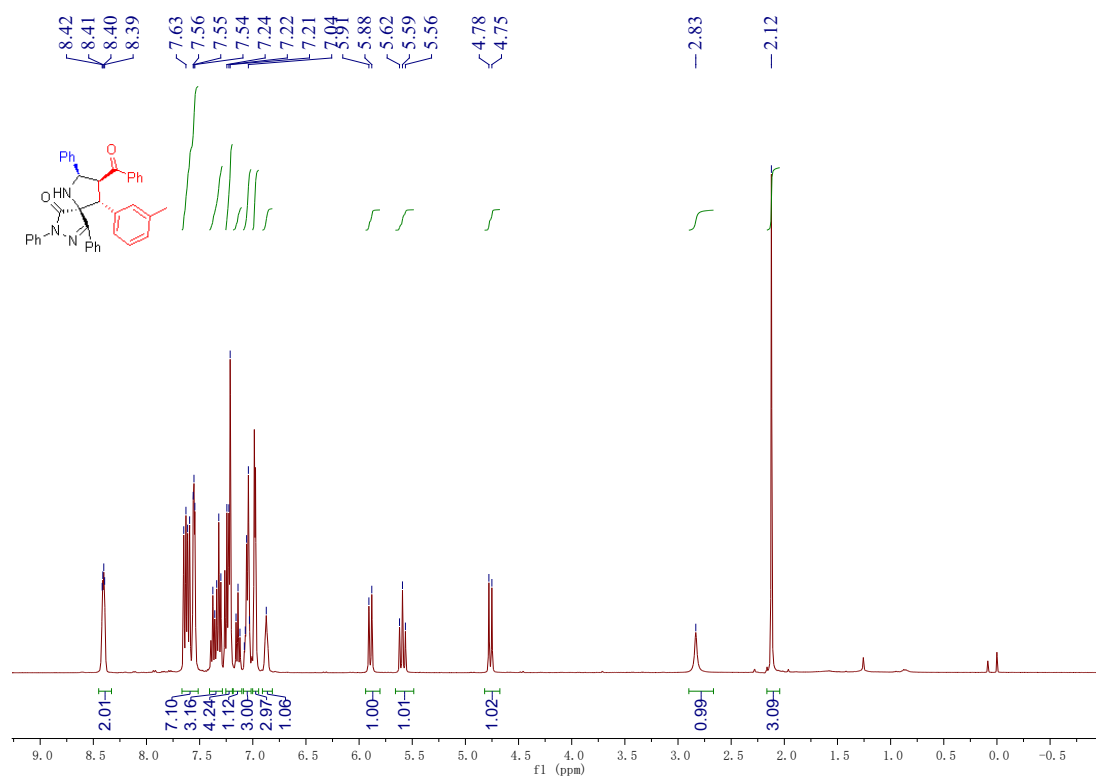
#	Time	Area	Height	Width	Area%	Symmetry
1	9.997	10896.1	578.5	0.2896	99.465	0.81
2	19.922	58.6	1.8	0.539	0.535	5.517

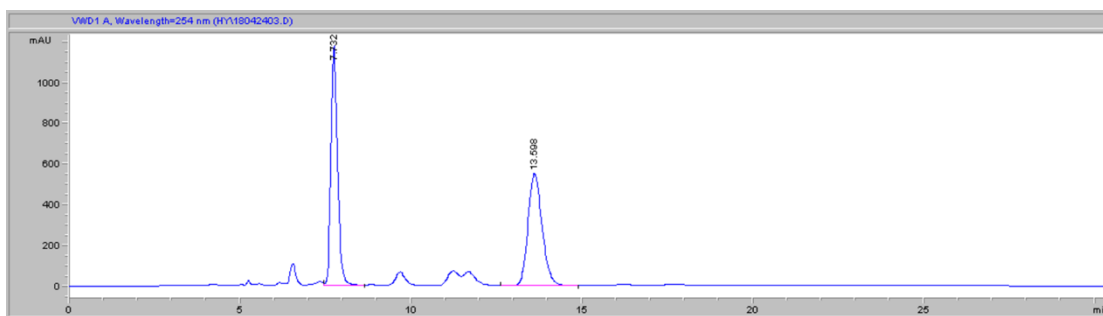
5aaj



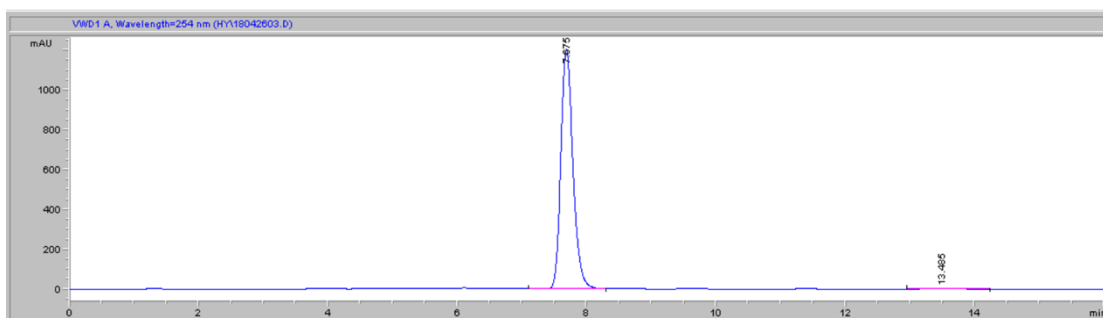
Prepared according to the procedure within 82 h as White solid

(92.1 mg, 82% yield, dr > 20:1). mp 108.7 – 109.5 °C; $[\alpha]_D^{19} = -60.873$ (*c* 0.87, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.41 (dd, *J* = 6.4, 2.8 Hz, 2H), 7.67 – 7.51 (m, 7H), 7.41 – 7.29 (m, 3H), 7.25 – 7.19 (m, 4H), 7.14 (dd, *J* = 7.4 Hz, 1H), 7.09 – 7.02 (m, 3H), 6.98 (d, *J* = 4.4 Hz, 3H), 6.82 – 6.91 (m, 1H), 5.89 (d, *J* = 10.9 Hz, 1H), 5.59 (t, *J* = 11.1 Hz, 1H), 4.76 (d, *J* = 11.3 Hz, 1H), 2.83 (s, 1H), 2.12 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.63, 175.79, 157.37, 140.79, 137.88, 137.58, 137.41, 133.53, 132.84, 130.93, 130.82, 128.91, 128.89, 128.86, 128.83, 128.76, 128.32, 128.24, 128.21, 127.82, 127.63, 127.61, 125.51, 125.16, 119.40, 77.10, 62.51, 53.13, 51.68, 21.33; HRMS (ESI) *m/z* Calcd. for C₃₈H₃₂N₃O₂⁺ ([M+H]⁺) 562.2489, Found 562.2485; 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} = 7.7 min, *t*_{minor} = 13.5 min).



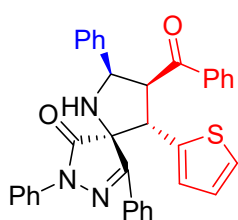


#	Time	Area	Height	Width	Area%	Symmetry
1	7.732	15991.2	1174.9	0.2068	50.456	0.75
2	13.598	15701.9	550.6	0.439	49.544	0.805



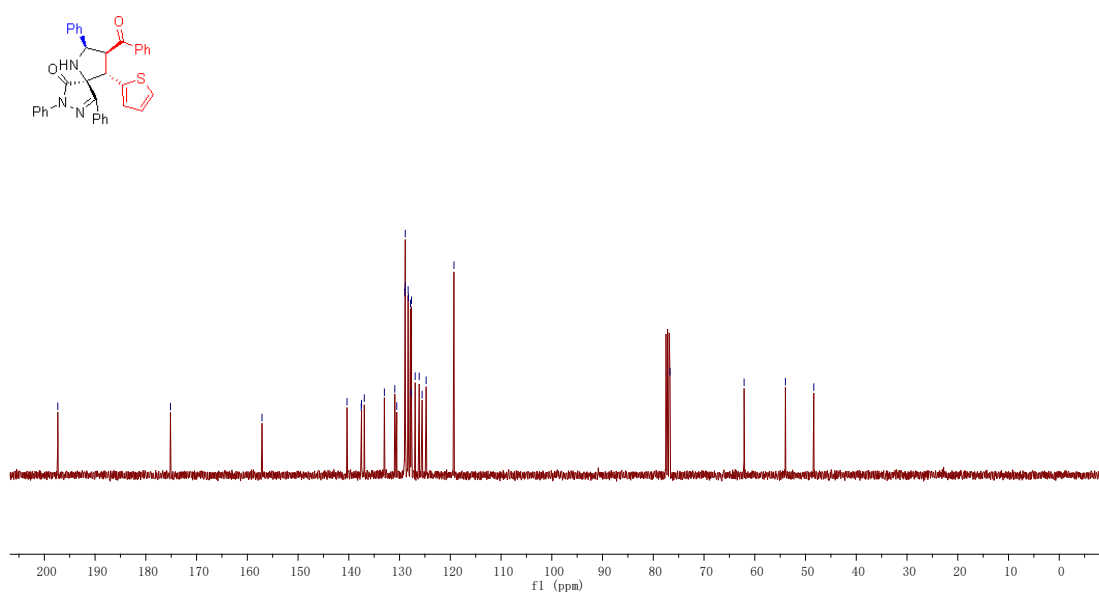
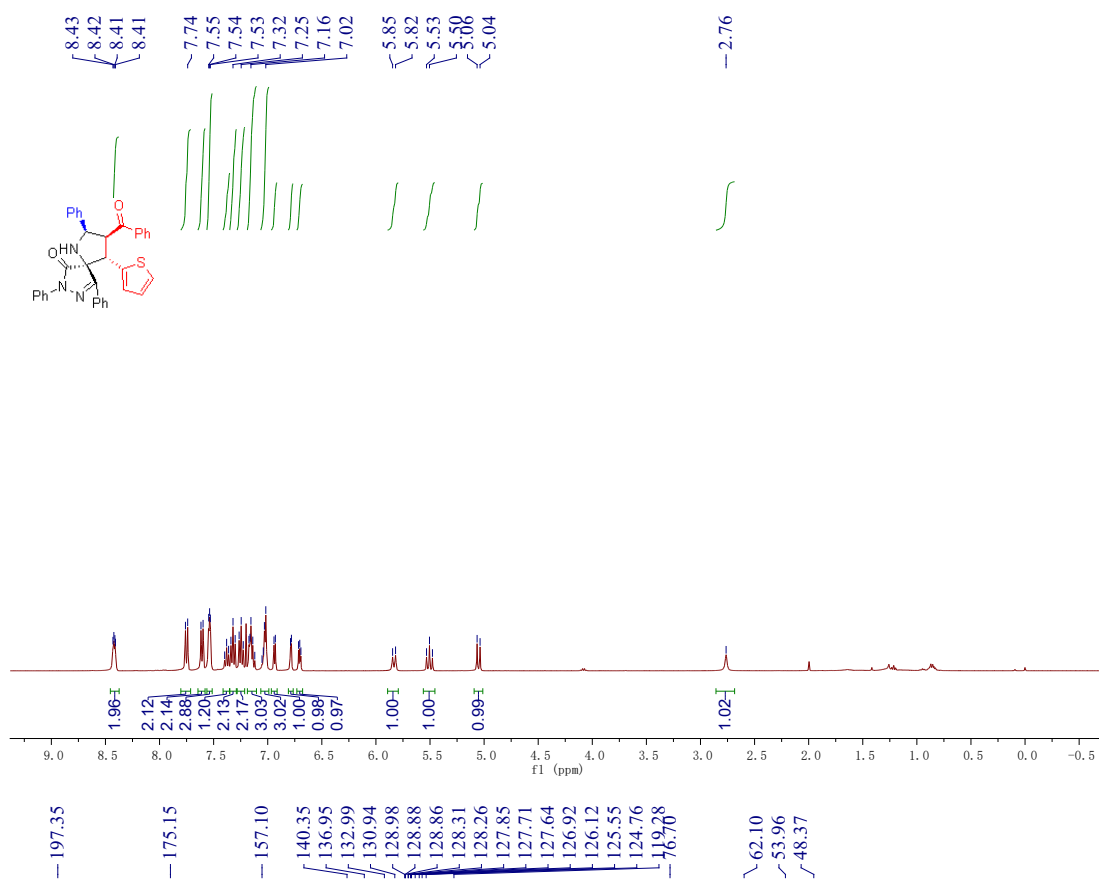
#	Time	Area	Height	Width	Area%	Symmetry
1	7.675	15703.2	1204.5	0.2002	99.465	0.776
2	13.485	84.4	2.9	0.4306	0.535	0.917

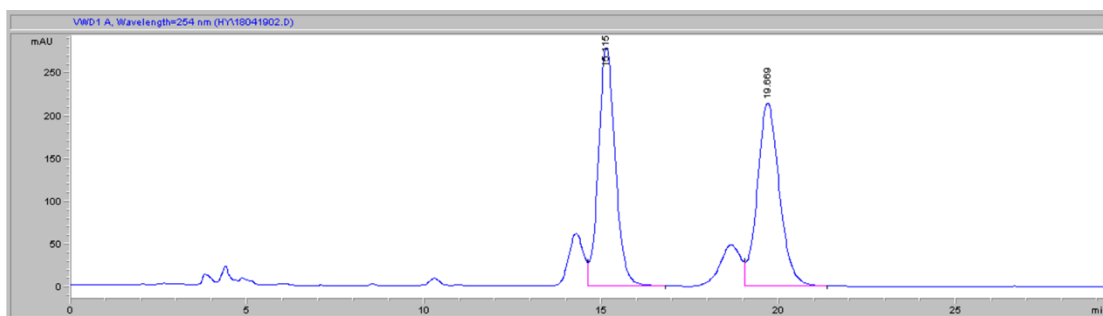
5aak



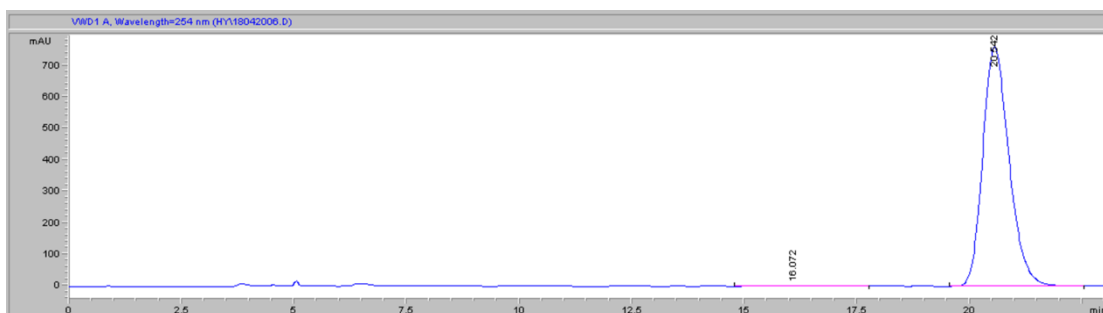
Prepared according to the procedure within 48 h as White solid

(100.8 mg, 91% yield, dr > 20:1). mp 116.5 – 117.9 °C; $[\alpha]_D^{19} = -100.71$ (c 0.84, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.42 (dd, J = 6.5, 2.8 Hz, 2H), 7.75 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 7.7 Hz, 2H), 7.56 – 7.51 (m, 3H), 7.38 (dd, J = 7.3 Hz, 1H), 7.36 – 7.30 (m, J = 7.8 Hz, 2H), 7.28 – 7.23 (m, 2H), 7.19 – 7.10 (m, 3H), 6.99 – 7.06 (m, 3H), 6.94 (d, J = 5.0 Hz, 1H), 6.79 (d, J = 3.4 Hz, 1H), 6.73 – 6.68 (m, 1H), 5.83 (d, J = 10.9 Hz, 1H), 5.50 (t, J = 10.9 Hz, 1H), 5.05 (d, J = 11.0 Hz, 1H), 2.76 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 197.35, 175.15, 157.10, 140.35, 137.55, 137.49, 136.95, 132.99, 130.94, 130.55, 128.98, 128.88, 128.86, 128.31, 128.26, 127.85, 127.71, 127.64, 126.92, 126.12, 125.55, 124.76, 119.28, 76.70, 62.10, 53.96, 48.37; HRMS (ESI) m/z Calcd. for C₃₅H₂₈N₃O₂S⁺ ([M+H]⁺) 554.1897, Found 554.1880; 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} = 20.5 min, t_{minor} = 16.1 min).



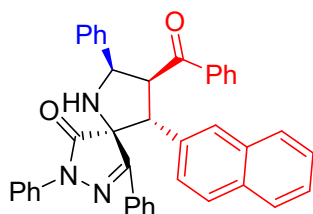


#	Time	Area	Height	Width	Area%	Symmetry
1	15.115	9221.8	278.5	0.5086	49.885	0.844
2	19.669	9264.4	213.5	0.6635	50.115	0.846



#	Time	Area	Height	Width	Area%	Symmetry
1	16.072	138.6	2.1	0.842	0.446	0.939
2	20.542	30949	759.6	0.6282	99.554	0.752

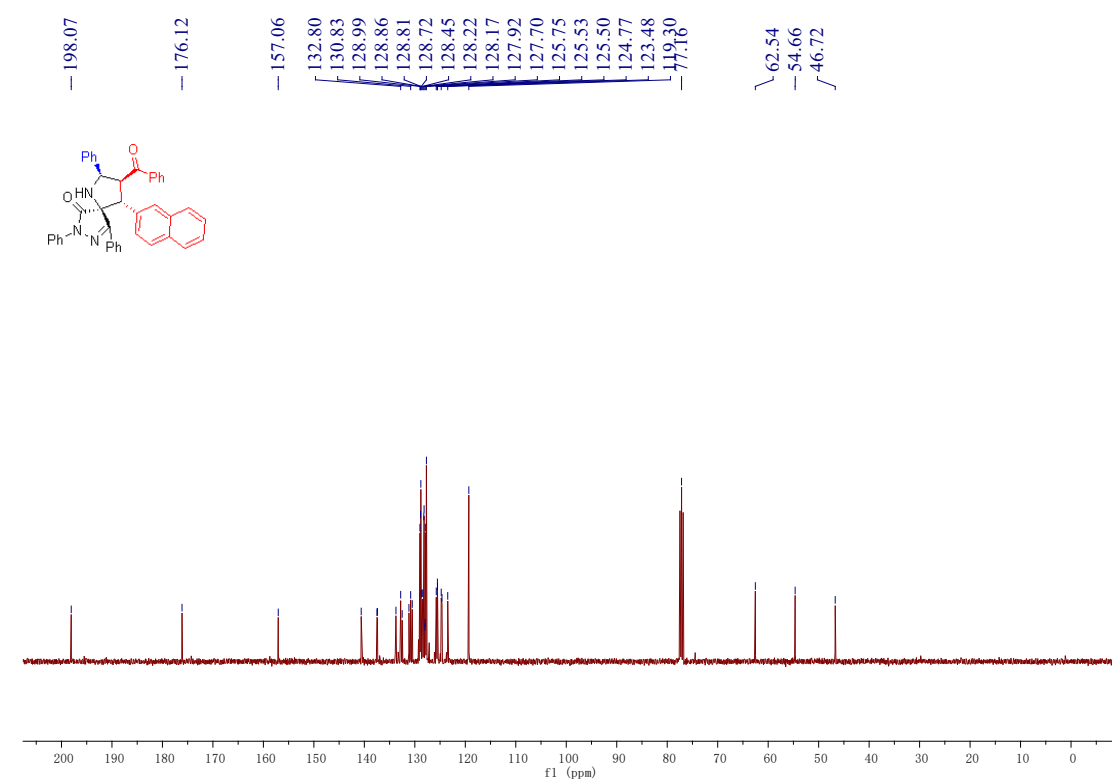
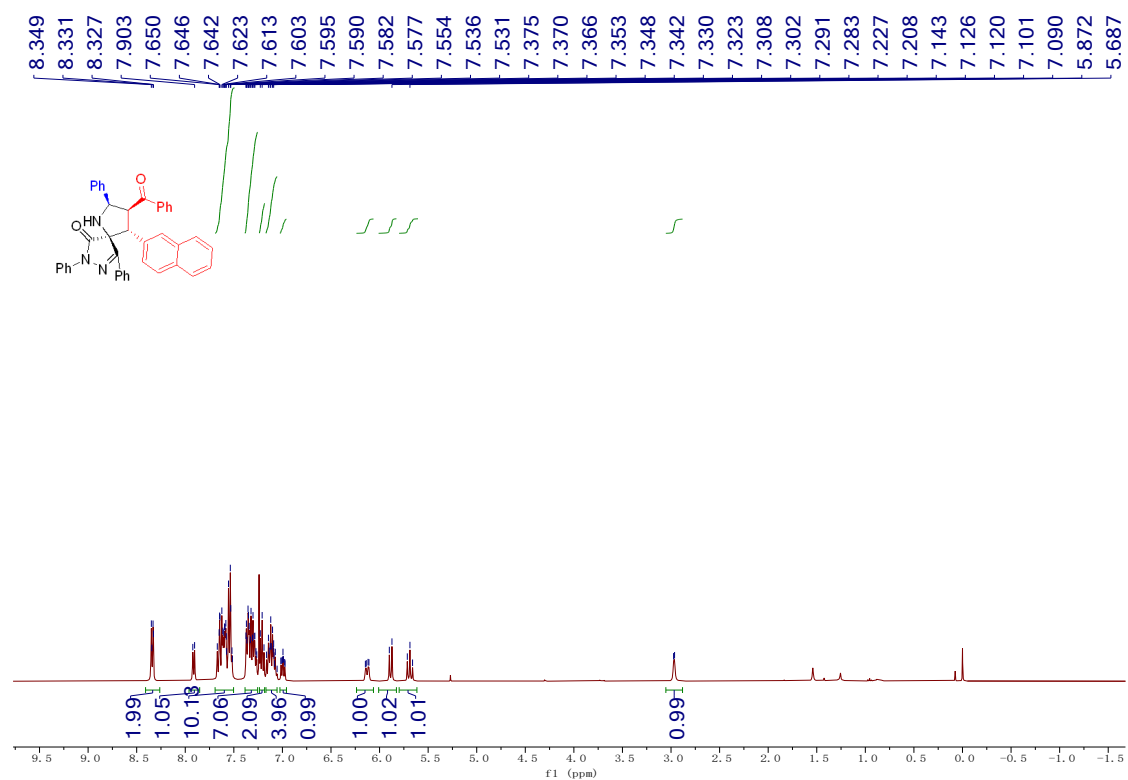
5aai

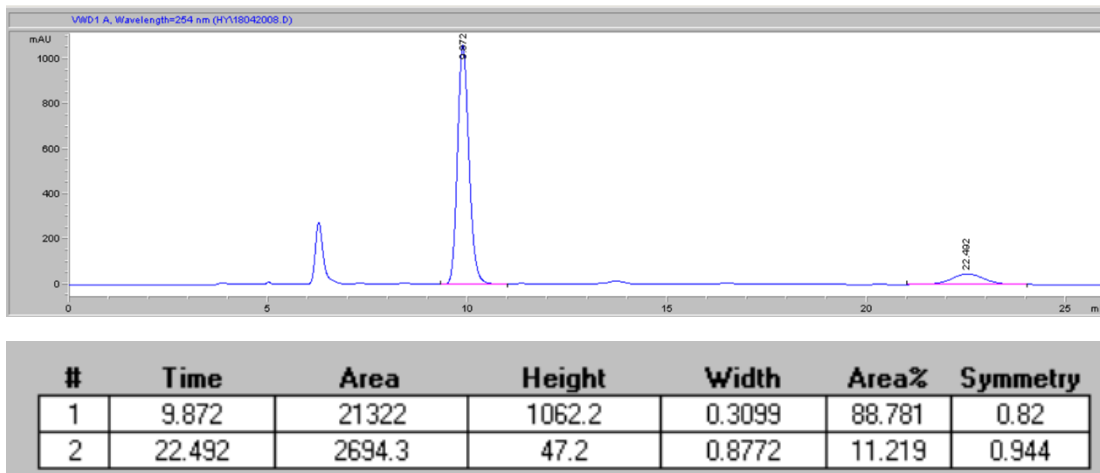
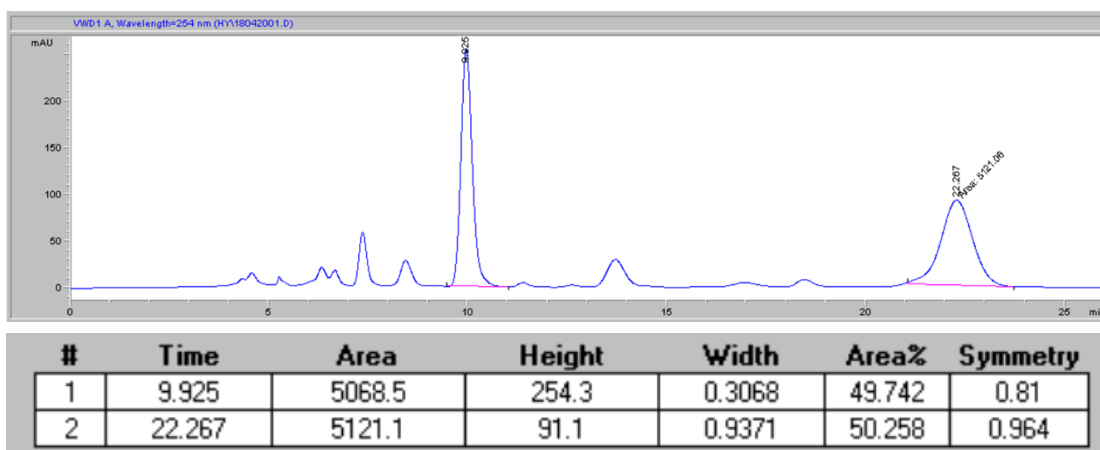


Prepared according to the procedure within 86 h as White solid (89.7 mg, 75% yield, dr > 20:1). mp 118.9 – 119.6 °C;

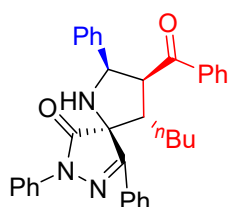
$[\alpha]_D^{19} = -45.224$ (c 0.67, CH₂Cl₂); ¹H NMR (400 MHz,

Chloroform-*d*) δ 8.41 – 8.26 (m, 2H), 7.91 (d, *J* = 7.4 Hz, 1H), 7.69 – 7.50 (m, 10H), 7.38 – 7.26 (m, 7H), 7.21 (dd, *J* = 7.6 Hz, 2H), 7.17 – 7.06 (m, 4H), 7.03 – 6.96 (m, 1H), 6.13 (dd, *J* = 10.9, 3.7 Hz, 1H), 5.89 (d, *J* = 10.8 Hz, 1H), 5.69 (t, *J* = 10.8 Hz, 1H), 2.97 (d, *J* = 4.1 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 198.07, 176.12, 157.06, 140.62, 137.50, 137.40, 133.74, 132.80, 132.50, 131.17, 130.83, 130.51, 128.99, 128.86, 128.81, 128.72, 128.45, 128.22, 128.17, 128.00, 127.97, 127.92, 127.70, 125.75, 125.53, 125.50, 124.77, 124.62, 123.48, 119.30, 77.16, 62.54, 54.66, 46.72; HRMS (ESI) *m/z* Calcd. for C₄₁H₃₂N₃O₂⁺ ([M+H]⁺) 598.2489, Found 598.2469; Enantiomeric excess was determined to be 78% (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} = 22.5 min).

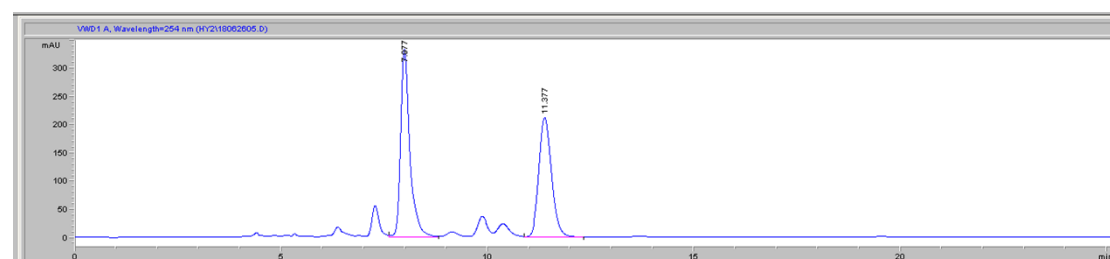
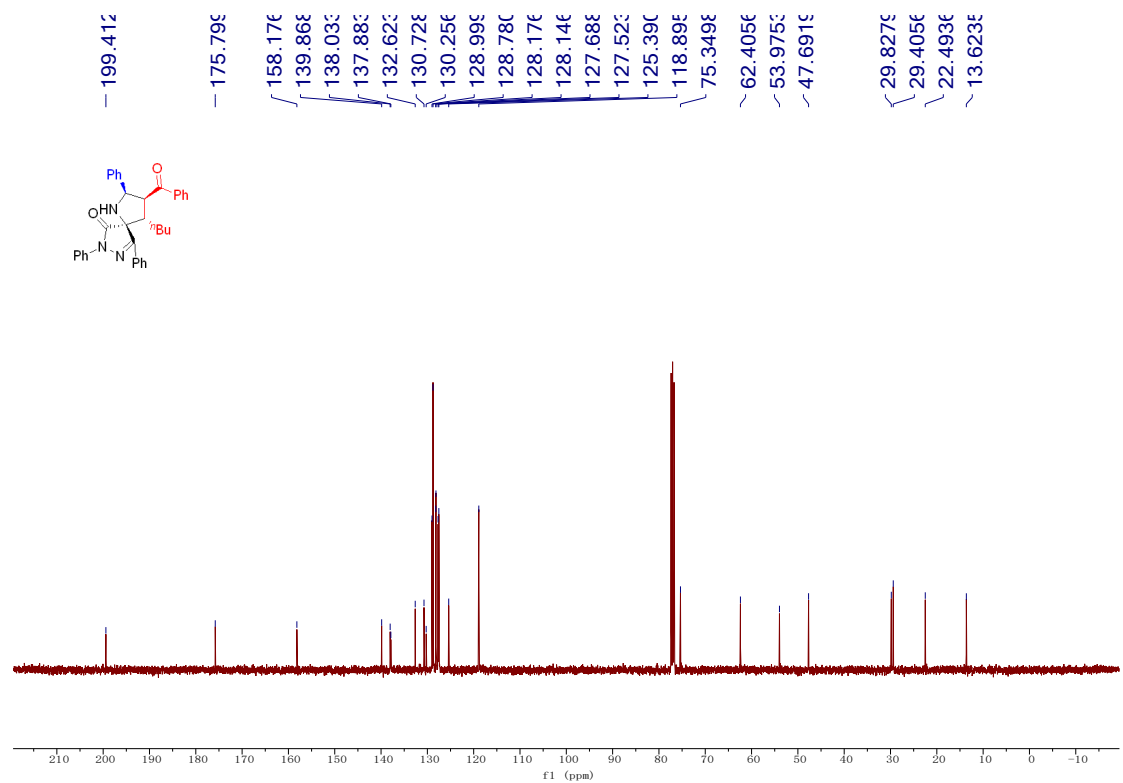
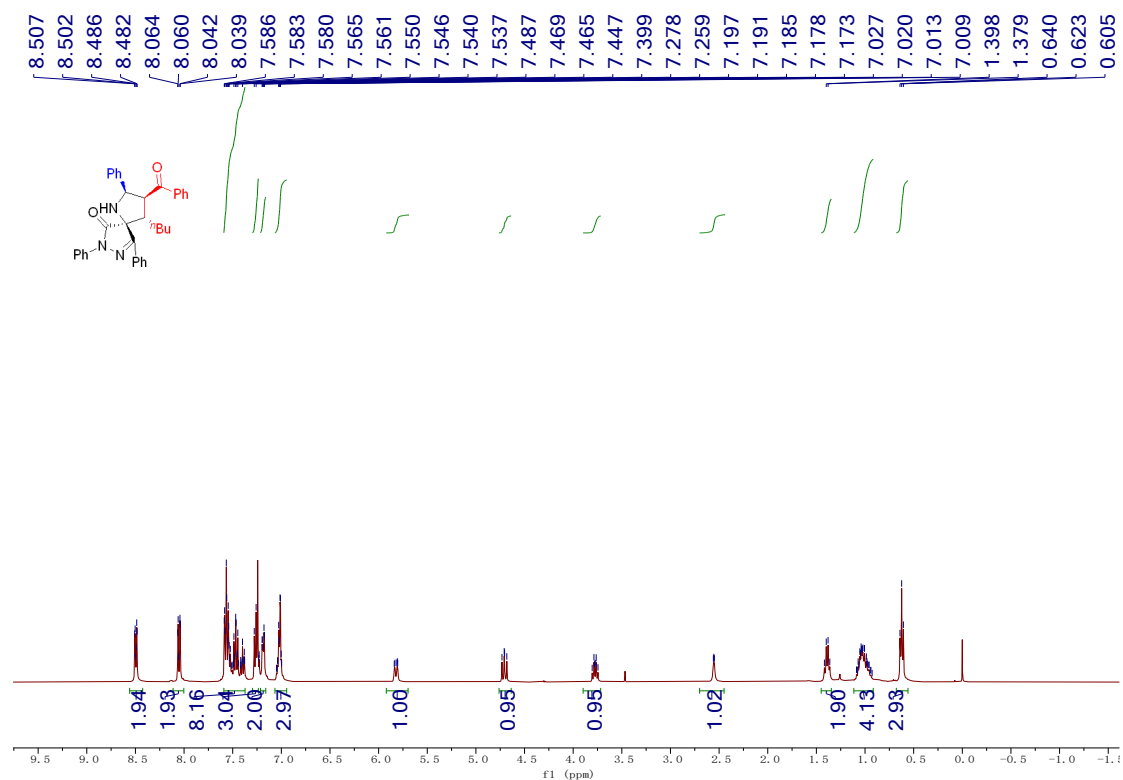




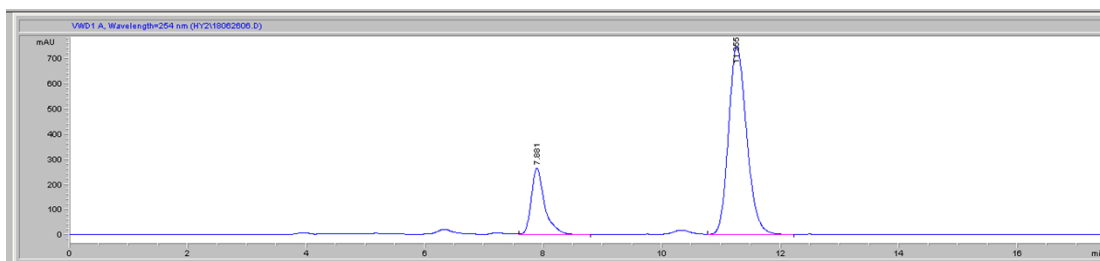
5aam



Prepared according to the procedure within 60 h as White solid (65.3 mg, 62% yield, dr > 20:1). mp 176.1 – 177.3 °C; $[\alpha]_D^{13} = -53.360$ (*c* 0.51, CH₂Cl₂); ¹H NMR (400 MHz, Chloroform-*d*) δ 8.56 – 8.43 (m, 2H), 8.11 – 8.00 (m, 2H), 7.59 – 7.37 (m, 8H), 7.30 – 7.24 (m, 3H), 7.21 – 7.16 (m, 2H), 7.07 – 6.95 (m, 3H), 5.92 – 5.70 (m, 1H), 4.71 (dd, *J* = 10.8, 9.2 Hz, 1H), 3.77 (dt, *J* = 9.3, 7.3 Hz, 1H), 2.70 – 2.45 (m, 1H), 1.39 (q, *J* = 7.3 Hz, 2H), 1.11 – 0.92 (m, 4H), 0.62 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 199.41, 175.80, 158.18, 139.87, 138.03, 137.88, 132.62, 130.73, 130.26, 129.00, 128.78, 128.18, 128.15, 127.69, 127.52, 125.39, 118.90, 75.35, 62.41, 53.98, 47.69, 29.83, 29.41, 22.49, 13.62; HRMS (ESI) *m/z* Calcd. for C₃₅H₃₄N₃O₂⁺ ([M+H]⁺) 528.2646, Found 528.2631; Enantiomeric excess was determined to be 59% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, *t*_{major} = 11.3 min, *t*_{minor} = 7.9 min).

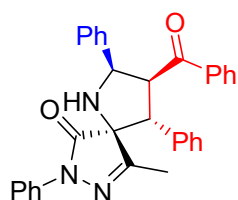


#	Time	Area	Height	Width	Area%	Symmetry
1	7.977	5099.1	332.7	0.2268	52.948	0.649
2	11.377	4531.4	212.2	0.3292	47.052	0.828



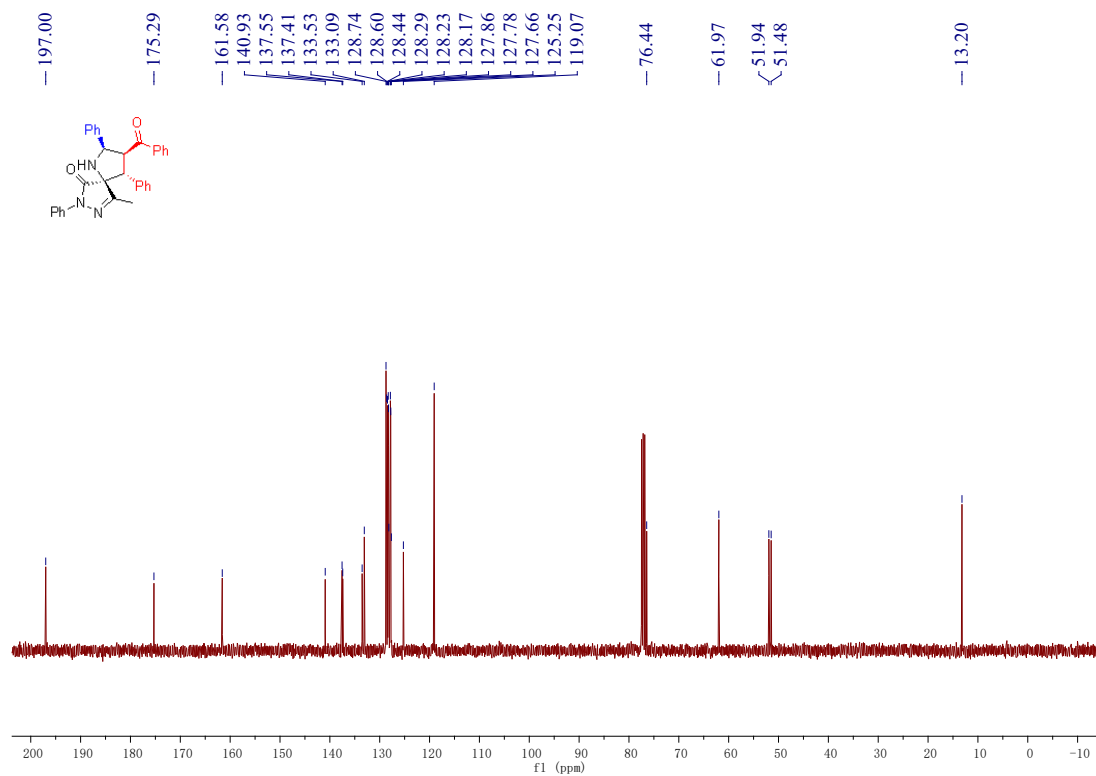
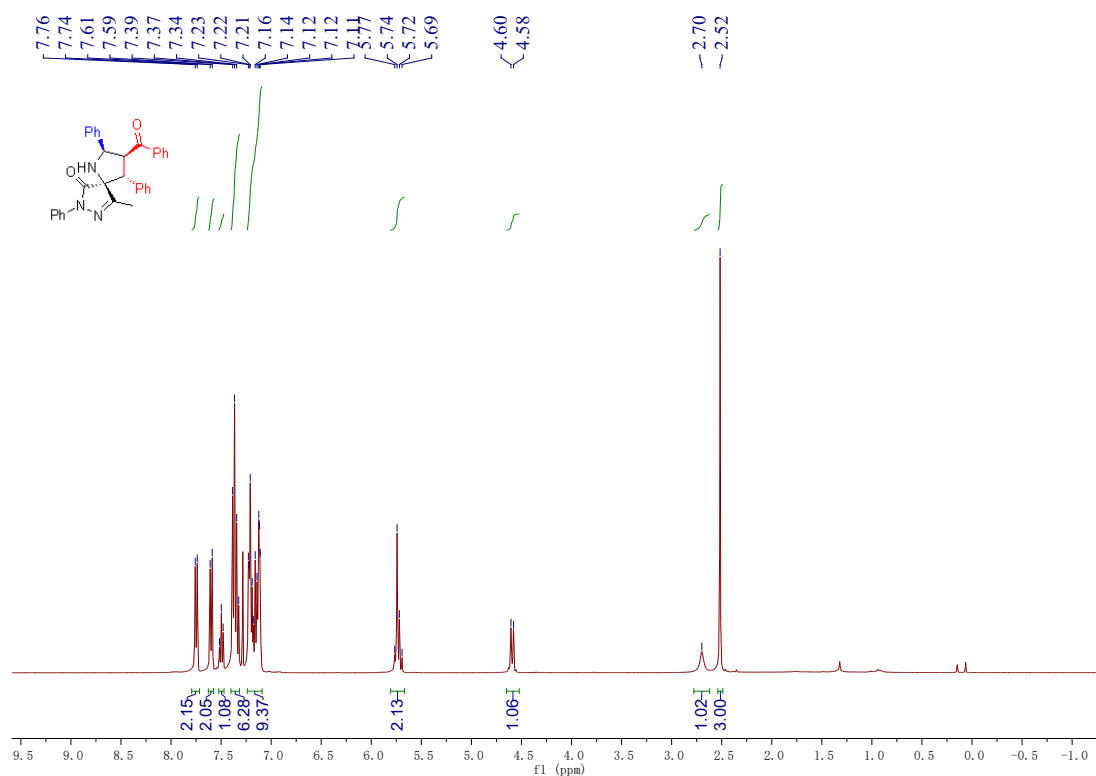
#	Time	Area	Height	Width	Area%	Symmetry
1	7.881	4203	264.2	0.238	20.786	0.652
2	11.255	16017.7	748.6	0.3312	79.214	0.792

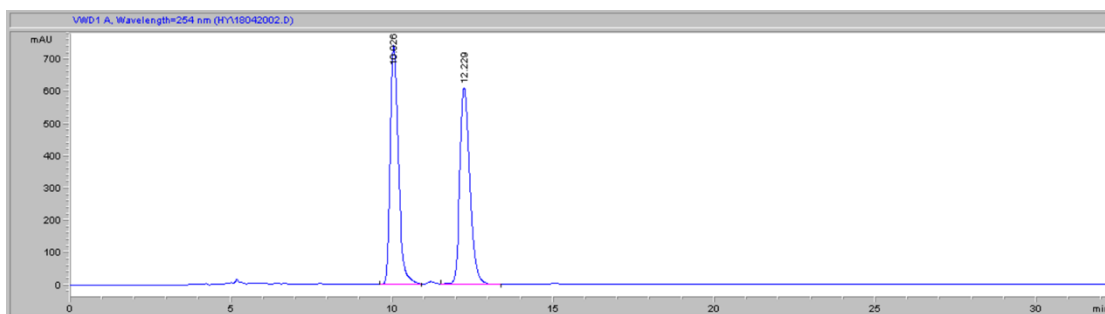
5baa



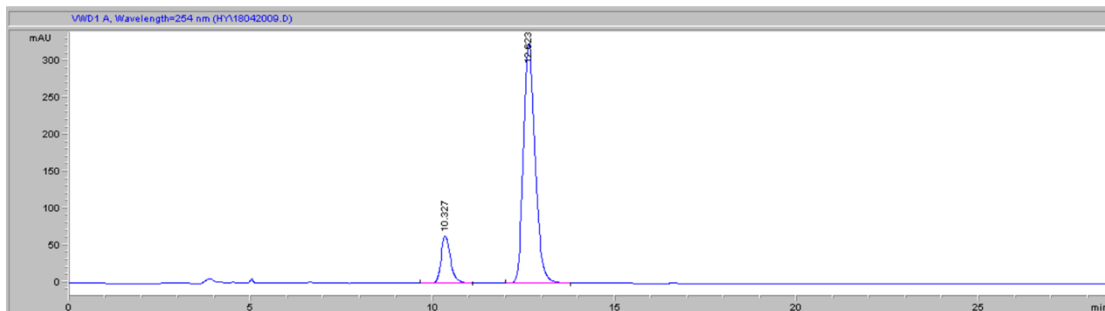
Prepared according to the procedure within 72 h as White solid

(78.7 mg, 81% yield, dr > 20:1). mp 177.0 – 177.8 °C; $[\alpha]_D^{19} = -91.441$ (*c* 0.67, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 7.75 (d, *J* = 8.0 Hz, 2H), 7.60 (d, *J* = 8.4 Hz, 2H), 7.50 (dd, *J* = 7.3 Hz, 1H), 7.32 – 7.40 (m, 6H), 7.24 – 7.09 (m, 9H), 5.81 – 5.67 (m, 2H), 4.59 (d, *J* = 10.2 Hz, 1H), 2.70 (s, 1H), 2.52 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.00, 175.29, 161.58, 140.93, 137.55, 137.41, 133.53, 133.09, 128.74, 128.60, 128.44, 128.29, 128.23, 128.17, 127.86, 127.78, 127.66, 125.25, 119.07, 76.44, 61.97, 51.94, 51.48, 13.20; HRMS (ESI) *m/z* Calcd. for C₃₂H₂₈N₃O₂⁺ ([M+H]⁺) 486.2176, Found 486.2172; Enantiomeric excess was determined to be 72% (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} = 10.3 min).



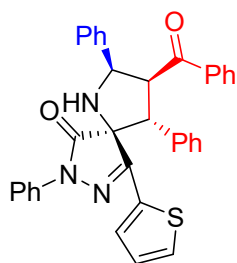


#	Time	Area	Height	Width	Area%	Symmetry
1	10.026	13146.2	741.2	0.2695	49.931	0.644
2	12.229	13182.6	610.2	0.3321	50.069	0.766

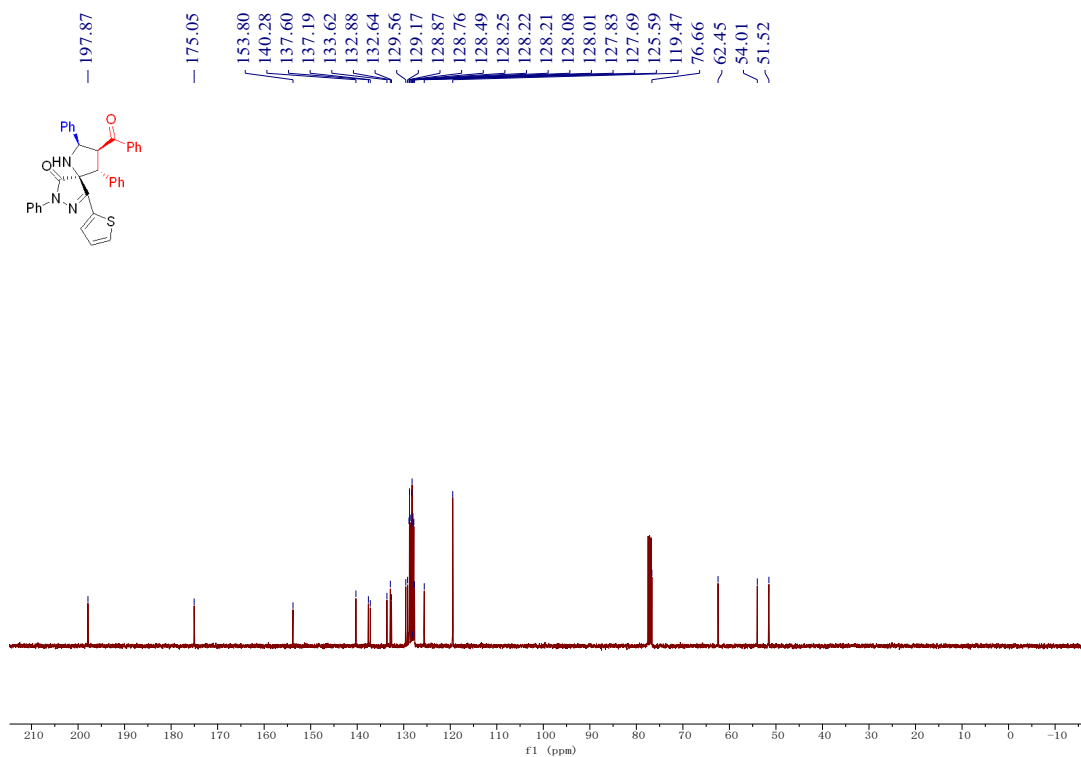
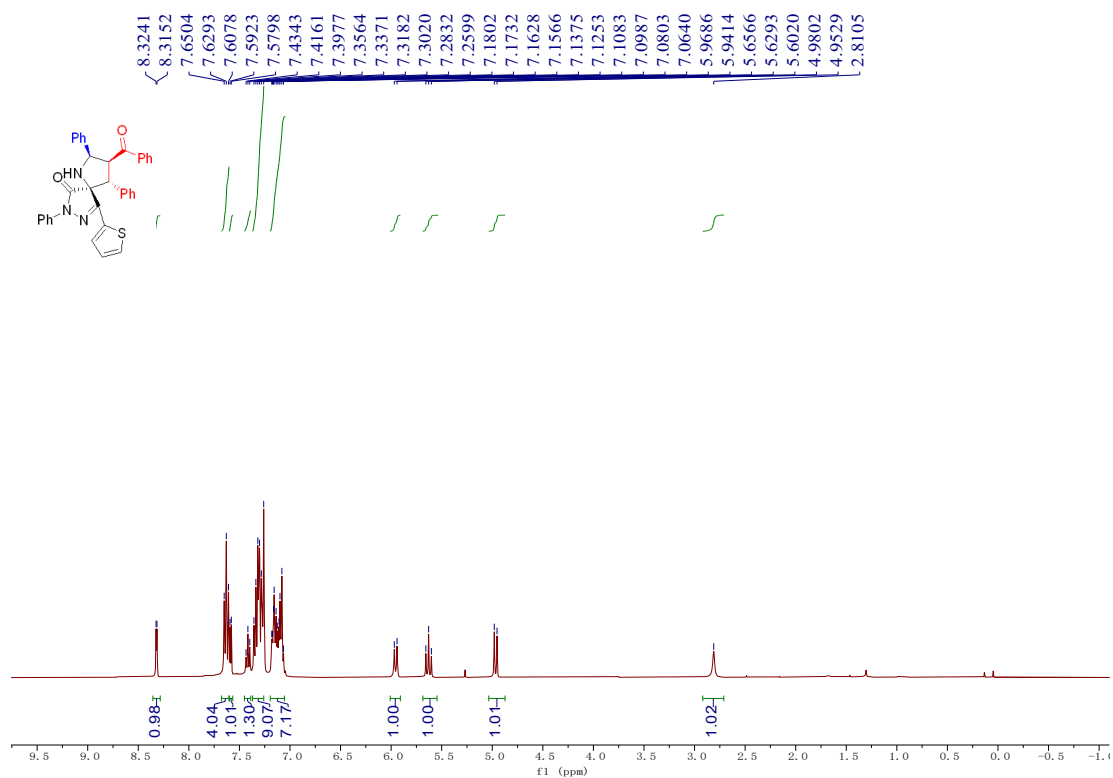


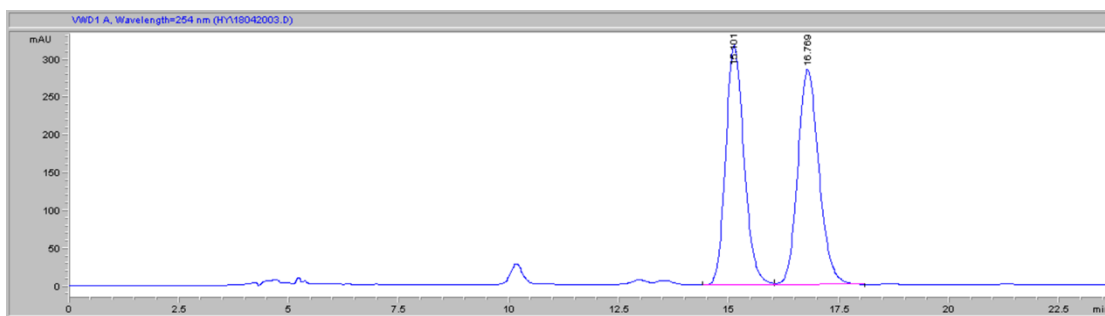
#	Time	Area	Height	Width	Area%	Symmetry
1	10.327	1164.4	64	0.2779	13.858	0.76
2	12.623	7237.9	324.7	0.343	86.142	0.785

5caa

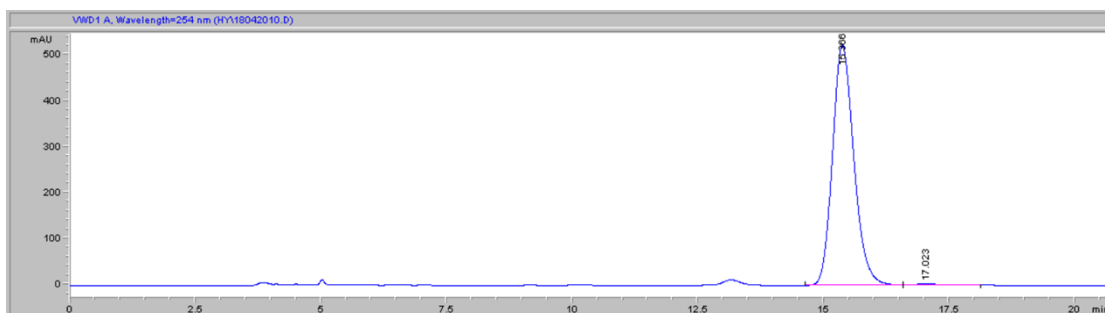


Prepared according to the procedure within 48 h as White solid (78.6 mg, 71% yield, dr > 20:1). mp 125.1 – 126.5 °C; $[\alpha]_D^{19} = -29.025$ (*c* 0.44, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.32 (d, *J* = 3.6 Hz, 1H), 7.69 – 7.60 (m, 4H), 7.59 (d, *J* = 5.0 Hz, 1H), 7.42 (dd, *J* = 7.3 Hz, 1H), 7.37 – 7.26 (m, 9H), 7.19 – 7.05 (m, 7H), 5.95 (d, *J* = 10.9 Hz, 1H), 5.63 (t, *J* = 10.9 Hz, 1H), 4.97 (d, *J* = 10.9 Hz, 1H), 2.81 (s, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 197.87, 175.05, 153.80, 140.28, 137.60, 137.19, 133.62, 132.88, 132.64, 129.56, 129.17, 128.87, 128.76, 128.49, 128.25, 128.22, 128.21, 128.08, 128.01, 127.83, 127.69, 125.59, 119.47, 76.66, 62.45, 54.01, 51.52; HRMS (ESI) *m/z* Calcd. for: C₃₅H₂₈N₃O₂S⁺ ([M+H]⁺) 554.1897, Found 554.1892; 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} = 15.4 min, *t*_{minor} = 17.0 min).



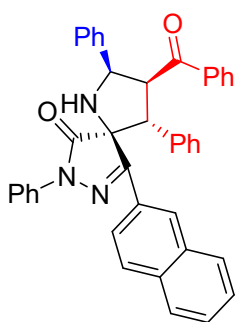


#	Time	Area	Height	Width	Area%	Symmetry
1	15.101	9168	316.4	0.4473	49.133	0.82
2	16.769	9491.7	284.1	0.5149	50.867	0.823

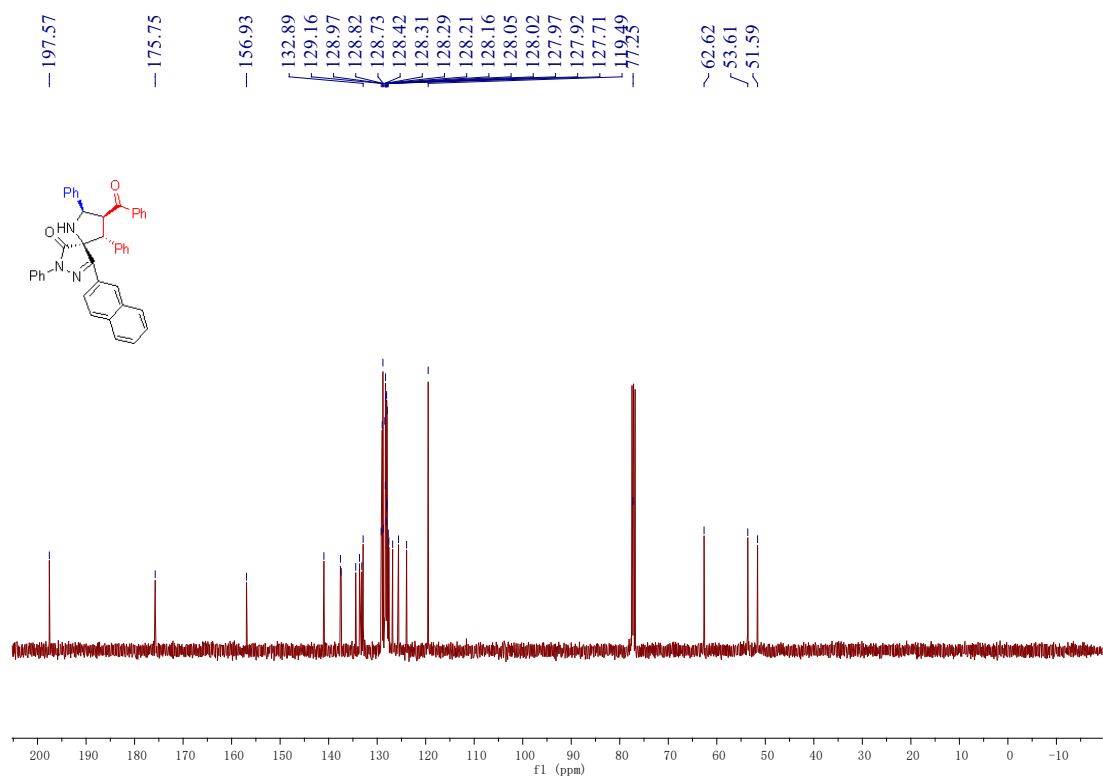
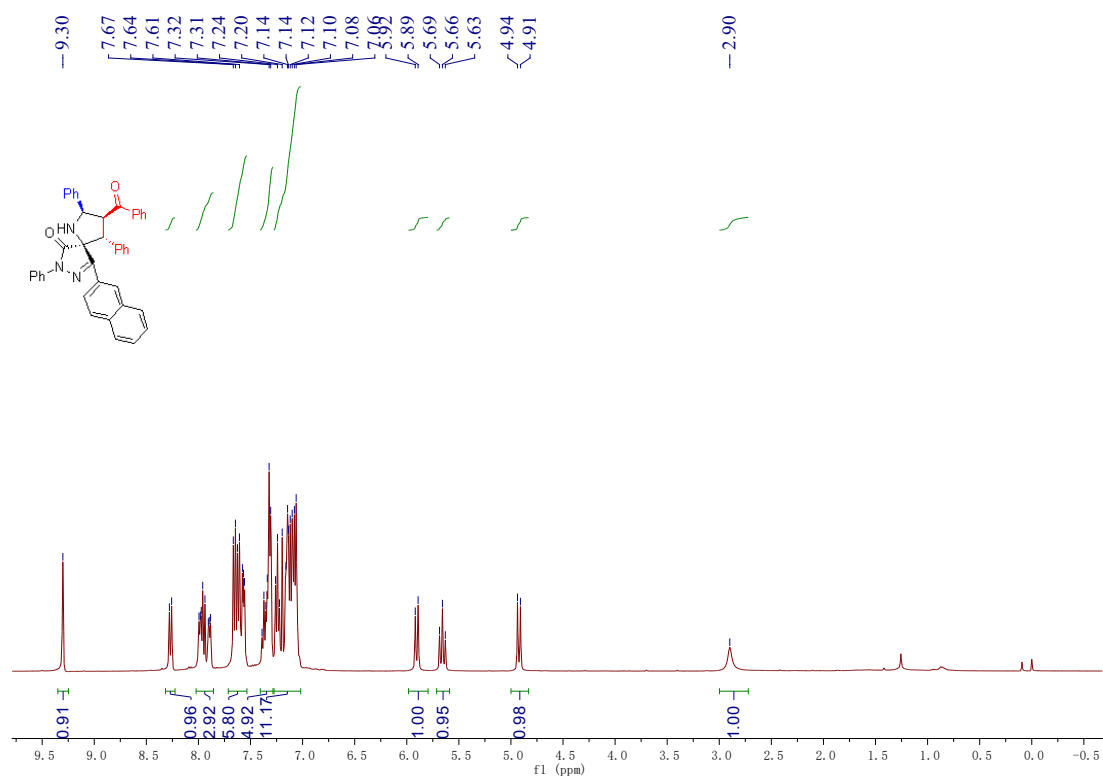


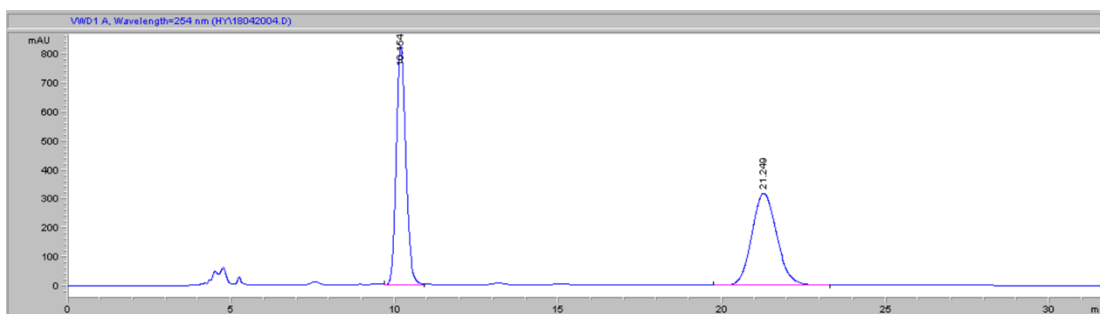
#	Time	Area	Height	Width	Area%	Symmetry
1	15.366	15515.2	522.4	0.4572	99.237	0.8
2	17.023	119.2	2.9	0.5796	0.763	0.729

5daa

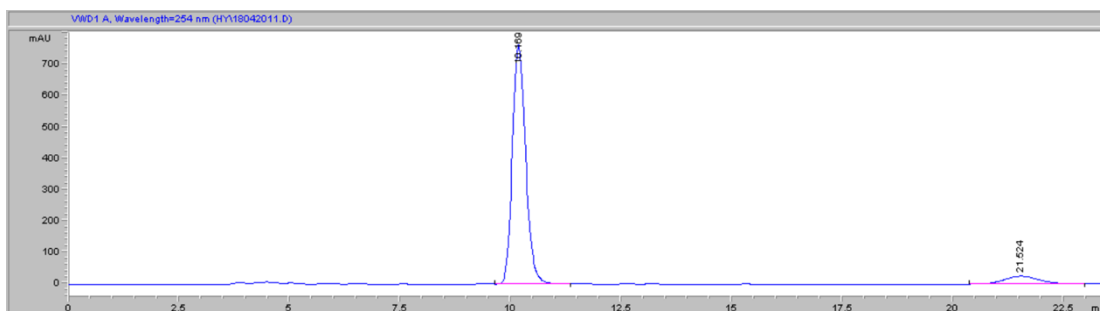


Prepared according to the procedure within 60 h as White solid (78.9 mg, 66% yield, dr > 20:1). mp 179.3 – 180.9 °C; $[\alpha]_D^{19} = 24.795$ (*c* 0.61, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 9.30 (s, 1H), 8.27 (d, *J* = 8.6 Hz, 1H), 8.06–7.86 (m, 3H), 7.71 – 7.53 (m, 6H), 7.41 – 7.28 (m, 5H), 7.27 – 7.02 (m, 11H), 5.90 (d, *J* = 10.9 Hz, 1H), 5.66 (t, *J* = 11.1 Hz, 1H), 4.92 (d, *J* = 11.2 Hz, 1H), 2.90 (s, 1H.); ¹³C NMR (101 MHz, CDCl₃) δ 197.57, 175.75, 156.93, 140.98, 137.57, 137.42, 134.42, 133.64, 133.17, 132.89, 129.16, 128.97, 128.82, 128.73, 128.42, 128.31, 128.29, 128.21, 128.16, 128.05, 128.02, 127.97, 127.92, 127.71, 127.59, 126.81, 125.61, 123.93, 119.49, 77.25, 62.62, 53.61, 51.59; HRMS (ESI) *m/z* Calcd. for C₄₁H₃₂N₃O₂⁺ (*[M+H]*⁺) 598.2489, Found 598.2488; Enantiomeric excess was determined to be 84% (determined by HPLC using chiral AD-H column, hexane/2-propanol = 70/30, λ = 254 nm, 30 °C, 0.8 mL/min, *t*_{major} = 10.2 min, *t*_{minor} = 21.5 min)



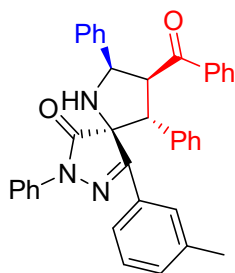


#	Time	Area	Height	Width	Area%	Symmetry
1	10.154	16682	824.7	0.3117	50.039	0.805
2	21.249	16655.7	317.7	0.811	49.961	0.854

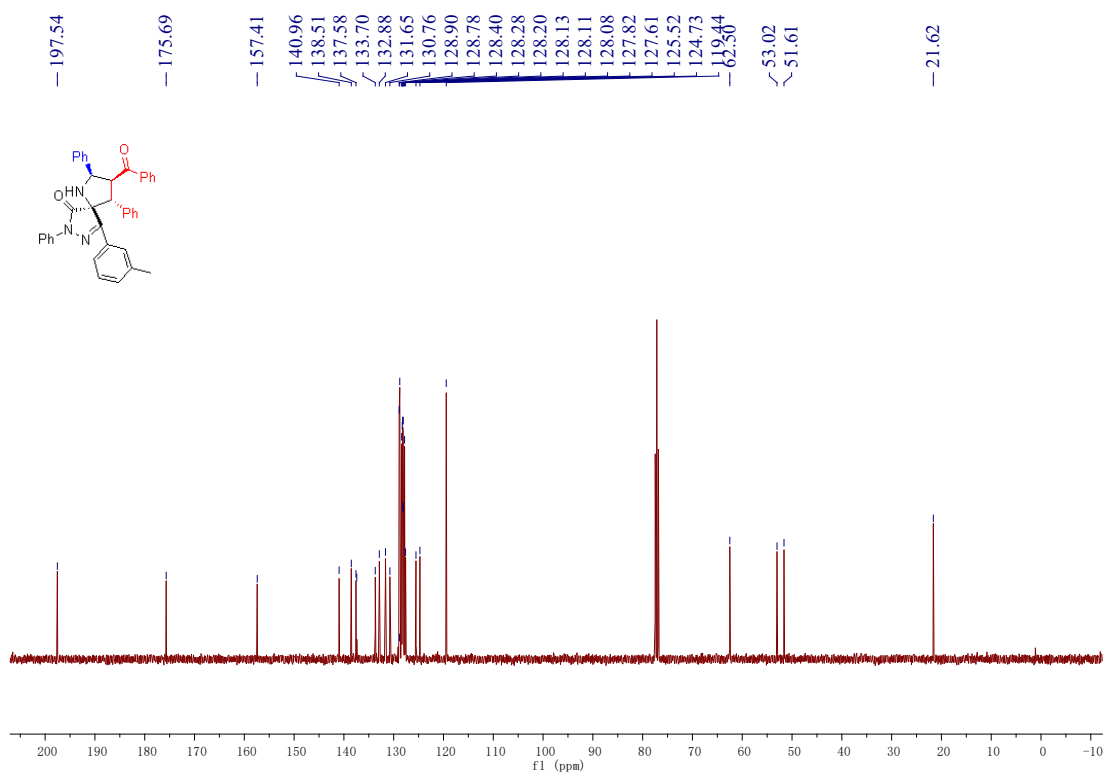
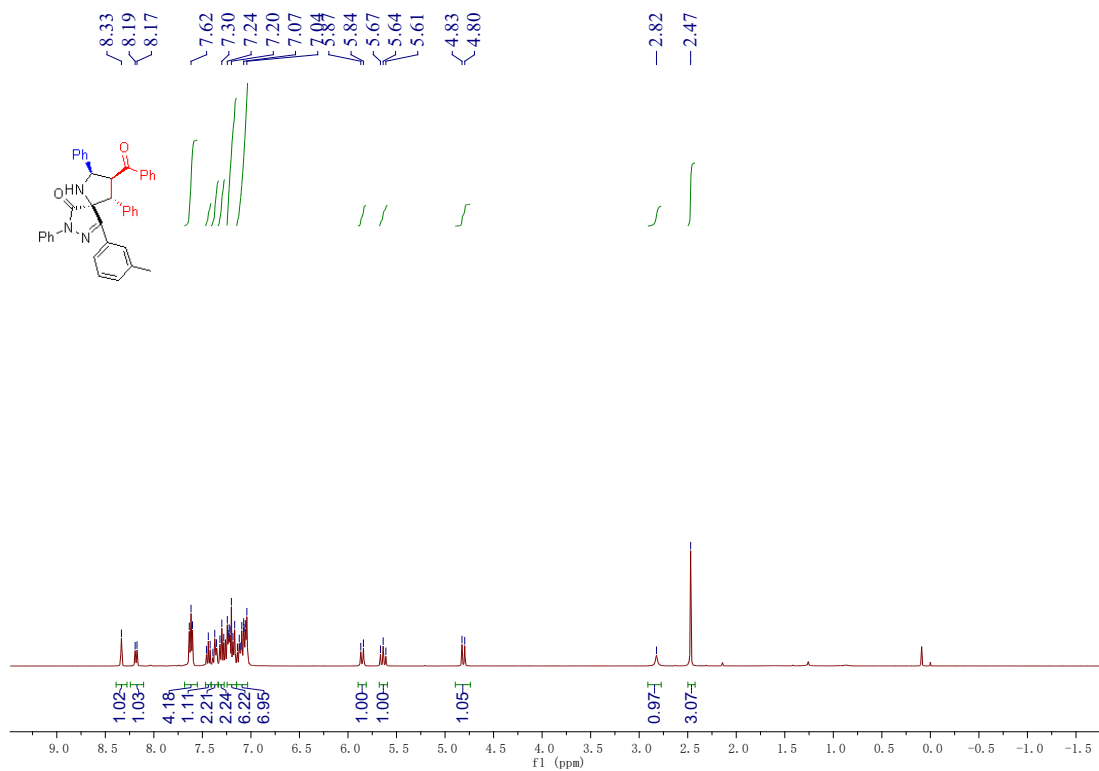


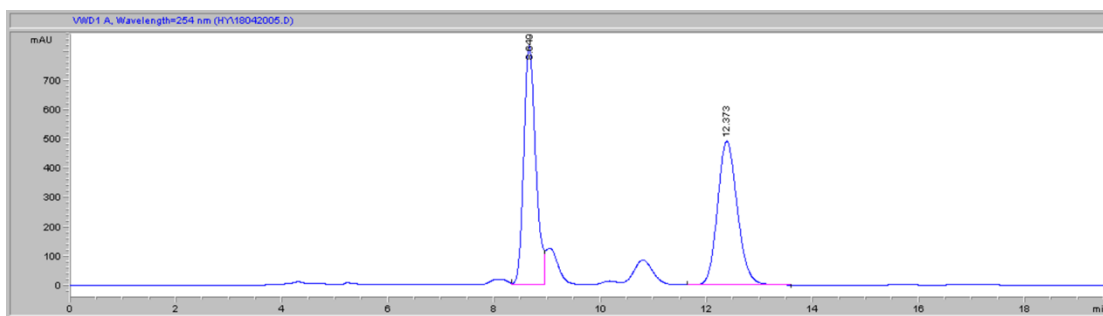
#	Time	Area	Height	Width	Area%	Symmetry
1	10.169	15928.8	765	0.3201	92.121	0.808
2	21.524	1362.4	24.8	0.8484	7.879	0.877

5eaa

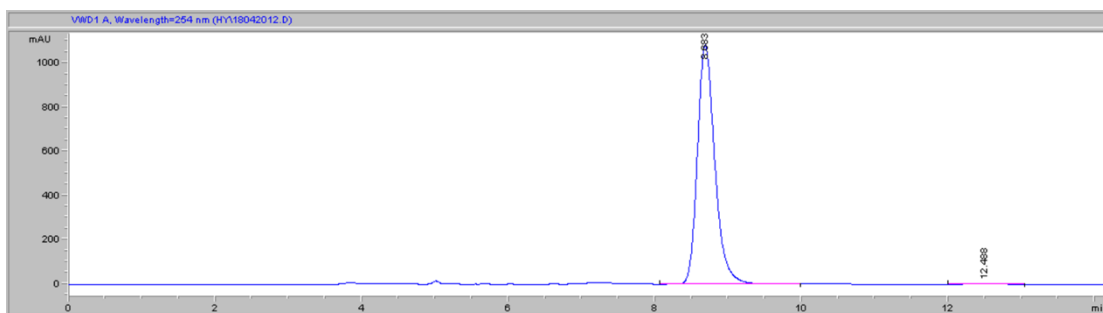


Prepared according to the procedure within 48 h as White solid (100.0 mg, 89% yield, dr > 20:1). mp 109.1 – 110.3 °C; $[\alpha]_D^{19} = -43.758$ (c 0.81, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.33 (s, 1H), 8.18 (d, J = 7.7 Hz, 1H), 7.68 – 7.55 (m, 4H), 7.44 (dd, J = 7.6 Hz, 1H), 7.34 – 7.40 (m, 2H), 7.36 – 7.28 (m, 2H), 7.25 – 7.15 (m, 6H), 7.03 – 7.15 (m, 7H), 5.85 (d, J = 10.9 Hz, 1H), 5.64 (t, J = 11.1 Hz, 1H), 4.81 (d, J = 11.3 Hz, 1H), 2.82 (s, 1H), 2.47 (s, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 197.54, 175.69, 157.41, 140.96, 138.51, 137.58, 137.41, 133.70, 132.88, 131.65, 130.76, 128.90, 128.83, 128.78, 128.40, 128.28, 128.20, 128.13, 128.11, 128.08, 127.82, 127.61, 125.52, 124.73, 119.44, 62.50, 53.02, 51.61, 21.62; HRMS (ESI) m/z Calcd. for C₃₈H₃₂N₃O₂⁺ ([M+H]⁺) 562.2489, Found 562.2490; 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} = 8.7 min, *t*_{minor} = 12.5 min).



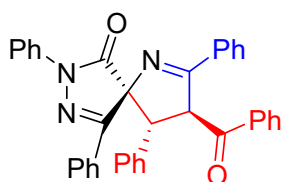


#	Time	Area	Height	Width	Area%	Symmetry
1	8.649	12880.2	816.7	0.2408	50.271	0.776
2	12.373	12741.1	491.2	0.4016	49.729	0.835



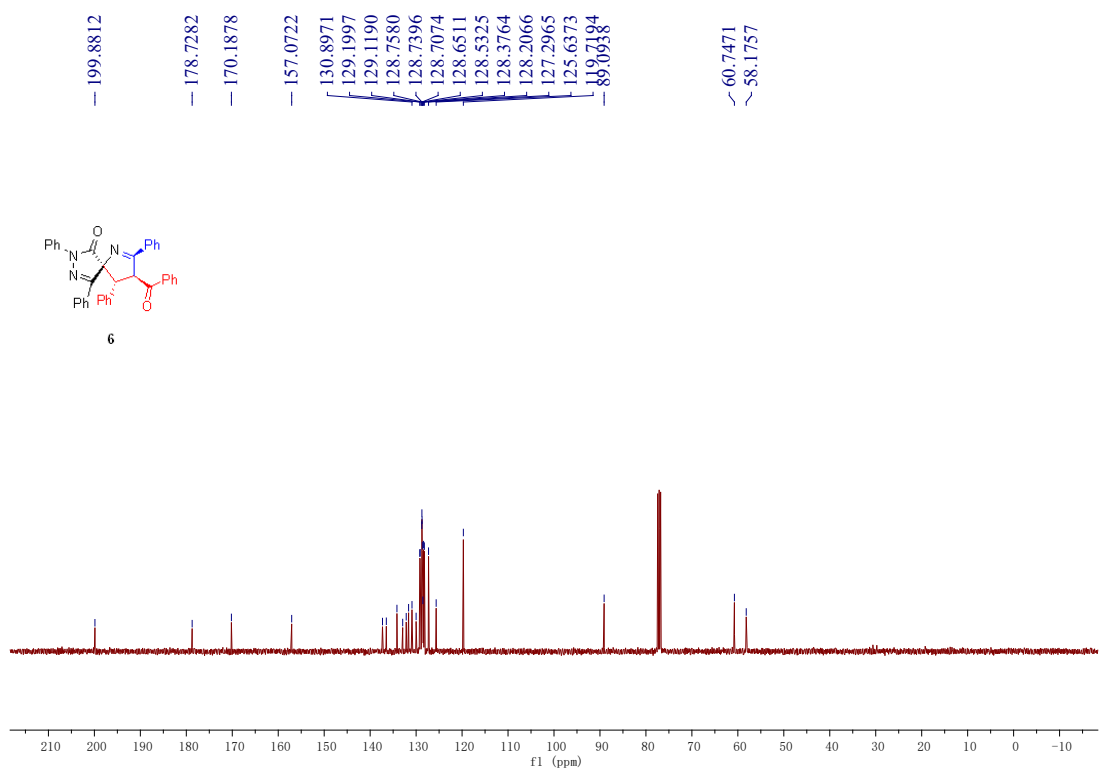
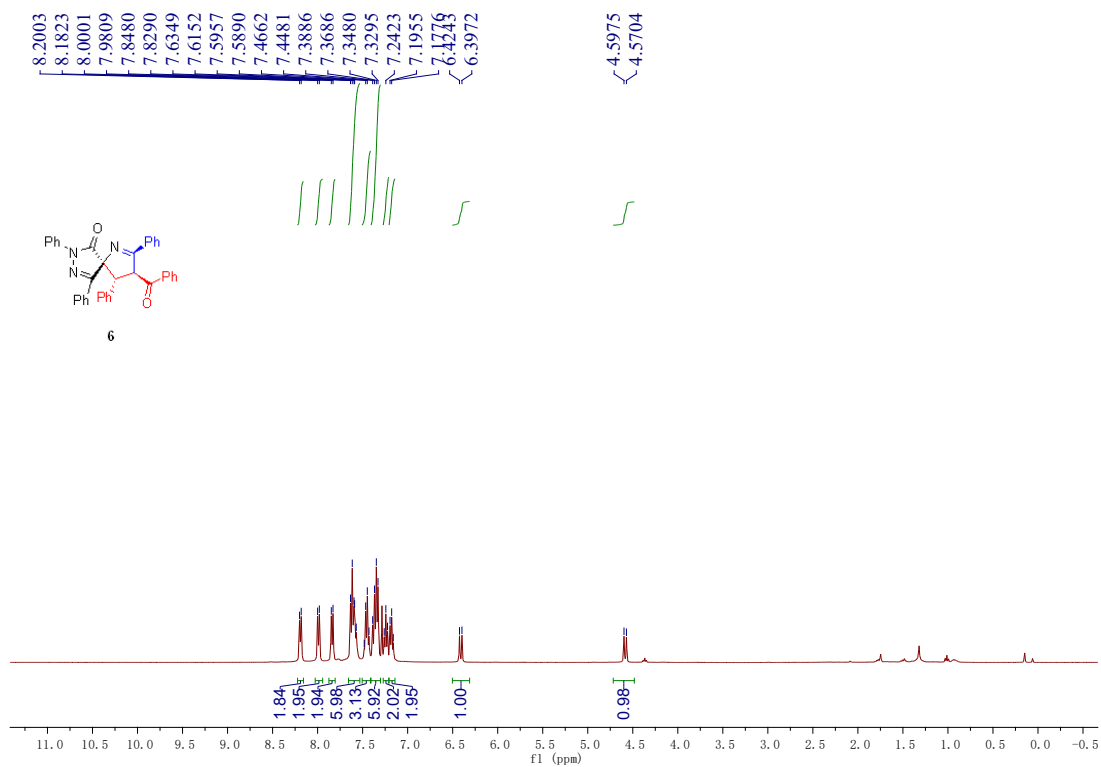
#	Time	Area	Height	Width	Area%	Symmetry
1	8.683	17959.6	1082.8	0.2532	99.497	0.753
2	12.488	90.7	3.4	0.4166	0.503	0.89

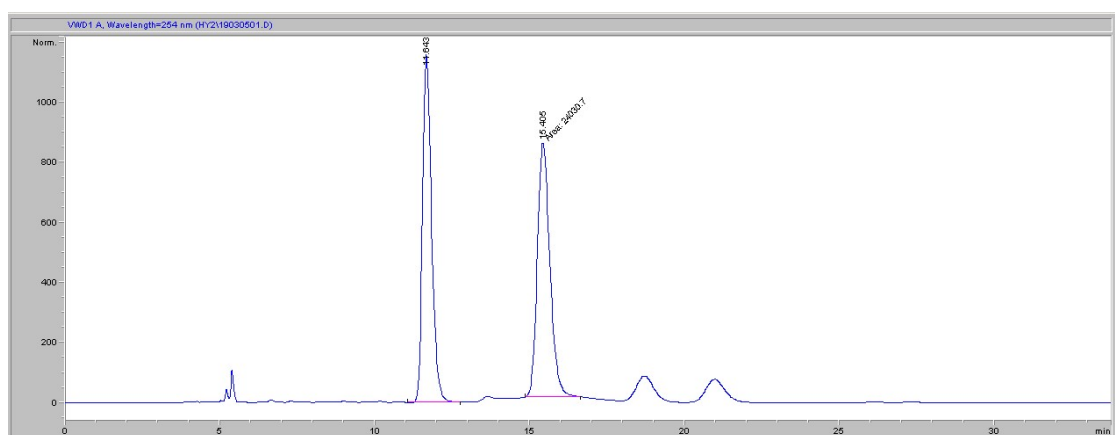
6



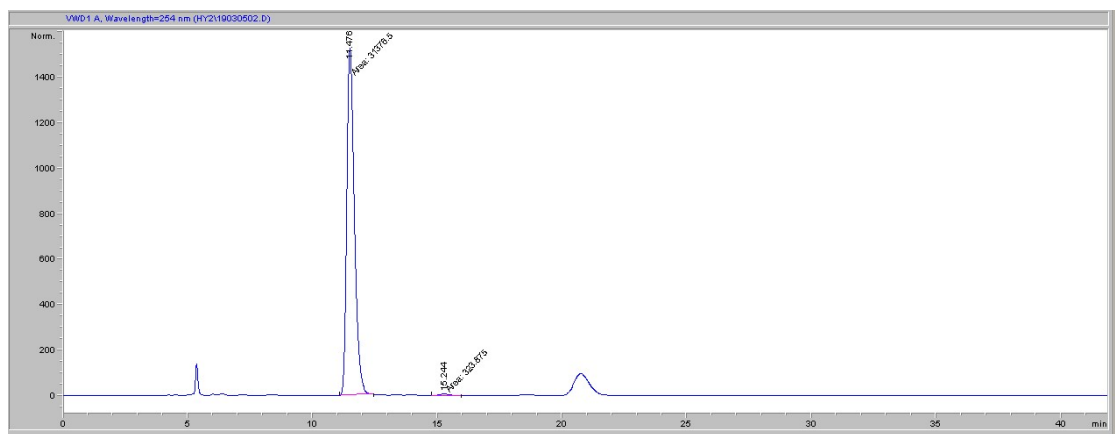
6

Prepared according to the procedure within 36 h as White solid (98.2 mg, 90% yield, dr > 20:1). mp 224.1 – 225.3 °C; $[\alpha]_D^{19} = -591.32$ (c 0.44, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 8.19 (d, *J* = 7.2 Hz, 2H), 7.99 (d, *J* = 7.7 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.66 – 7.53 (m, 6H), 7.51 – 7.41 (m, 3H), 7.41 – 7.30 (m, *J* = 16.0, 7.7 Hz, 6H), 7.28 – 7.20 (m, 2H), 7.19 – 7.15 (m, 2H), 6.41 (d, *J* = 10.8 Hz, 1H), 4.58 (d, *J* = 10.8 Hz, 1H); ¹³C NMR (101 MHz, CDCl₃) δ 199.88, 178.73, 170.19, 157.07, 137.31, 136.48, 134.17, 132.92, 132.15, 131.64, 130.90, 130.00, 129.20, 129.12, 128.76, 128.74, 128.71, 128.65, 128.53, 128.38, 128.21, 127.30, 125.64, 119.72, 89.09, 60.75, 58.18; HRMS (ESI) *m/z* Calcd. for C₃₇H₂₈N₃O₂⁺ ([M+H]⁺) 546.2176, Found 546.2170; 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} = 11.5 min, *t*_{minor} = 15.2 min).



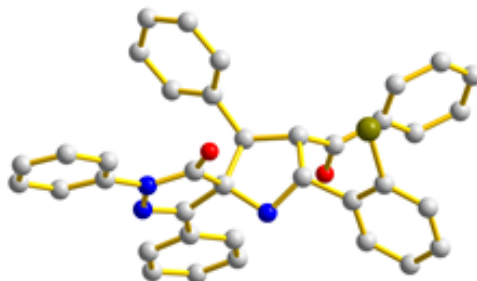


#	Time	Area	Height	Width	Area%	Symmetry
1	11.643	23672.3	1159.6	0.3124	49.624	0.692
2	15.405	24030.7	847.6	0.4725	50.376	0.765



#	Time	Area	Height	Width	Area%	Symmetry
1	11.476	31376.5	1526.8	0.3425	98.978	0.679
2	15.244	323.9	9	0.6015	1.022	0.7

3. X-ray crystal structure of 5aea



X-ray crystal structure of **5aea** CCDC: 2089345

Bond precision: C-C = 0.0088 Å Wavelength=0.71073

Cell: a=12.3671 (7) b=12.3671 (7) c=16.8393 (10)
 alpha=90 beta=90 gamma=120

Temperature: 296 K

	Calculated	Reported
Volume	2230.4 (3)	2230.4 (3)
Space group	P 31	P 31
Hall group	P 31	P 31
Moiety formula	C37 H28 Br N3 O2	C37 H28 Br N3 O2
Sum formula	C37 H28 Br N3 O2	C37 H28 Br N3 O2
Mr	626.52	626.53
Dx, g cm ⁻³	1.399	1.399
Z	3	3
Mu (mm ⁻¹)	1.421	1.421
F000	966.0	966.0
F000'	965.48	
h,k,lmax	14,14,20	14,14,20
Nref	5426 [2713]	5424
Tmin,Tmax	0.749,0.808	0.602,0.746
Tmin'	0.735	

Correction method= # Reported T Limits: Tmin=0.602 Tmax=0.746
AbsCorr = NONE

Data completeness= 2.00/1.00 Theta(max)= 25.329

R(reflections)= 0.0395 (4385) wR2(reflections)= 0.0862 (5424)

S = 1.050 Npar= 393