Enantioselective Formal Synthesis of (+)-Cycloclavine and Total Synthesis of (+)-5-*epi*-Cycloclavine

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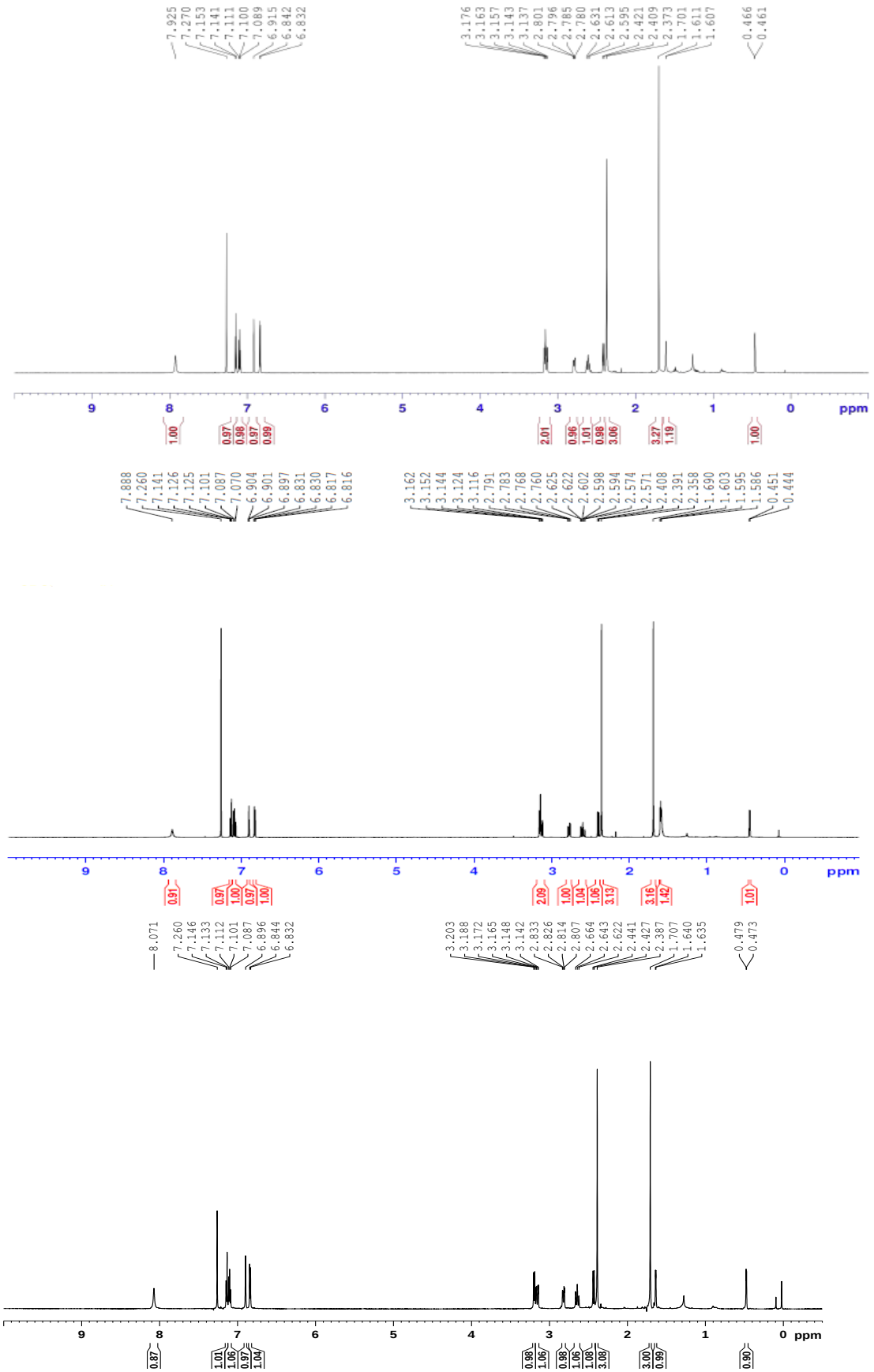
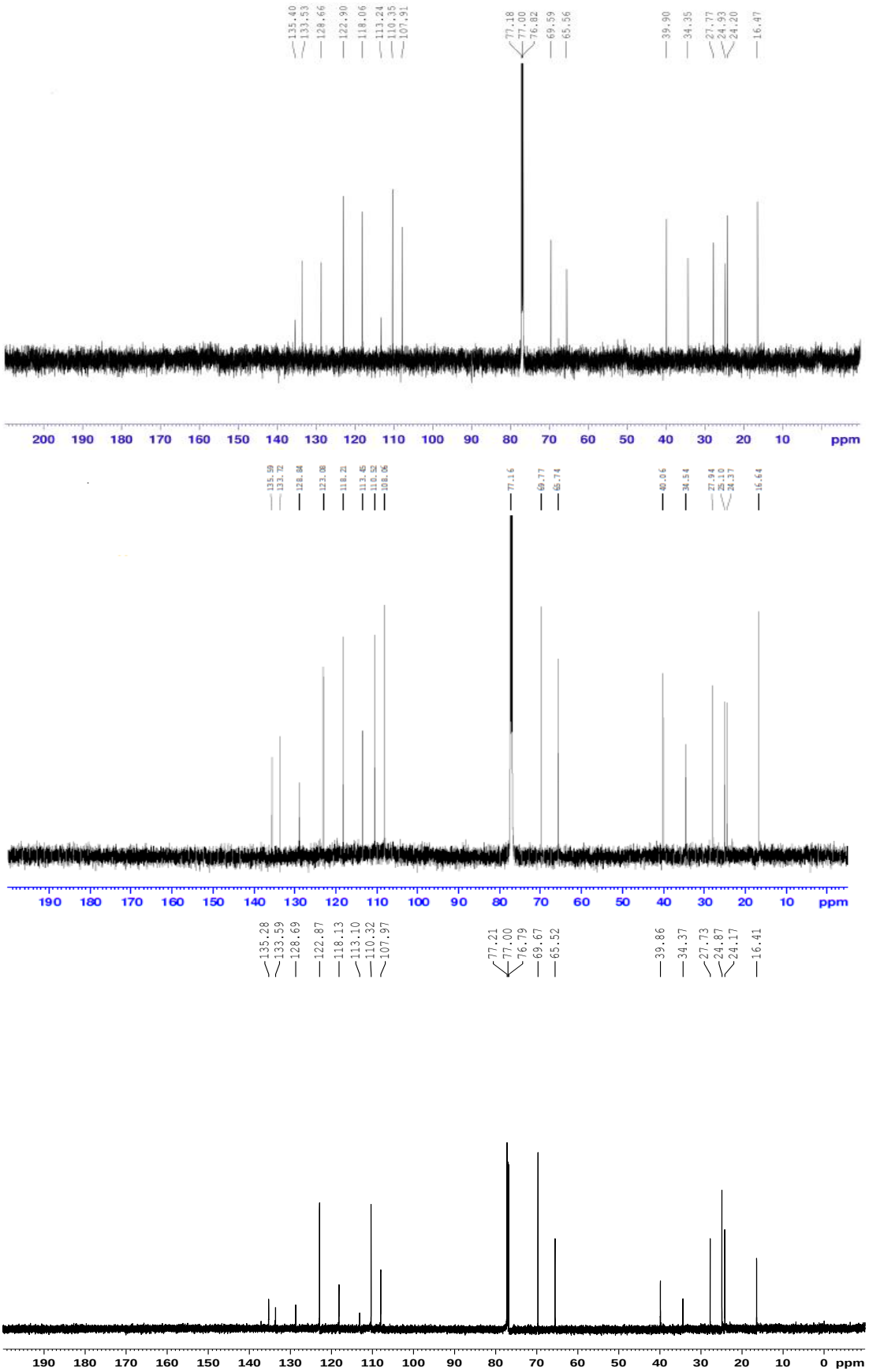
1. Comparison of ^{1}H and ^{13}C NMR data of (±)-cyclocla vine (in the ref. 4c), (+)-cyclocla vine (in the ref. 4a), and (+)-cyclocla vine [(**1**) in this work]

(±)-cyclocla vine (in the ref. 4c) (700 MHz, $CDCl_3$) δ (ppm)	(+)-cyclocla vine (in the ref. 4a) (500 MHz, $CDCl_3$) δ (ppm)	(+)-cyclocla vine [(**1**) in this work] (600 MHz, $CDCl_3$) δ (ppm)
7.92 (br s, 1H)	7.89 (br s, 1H)	8.07 (br s, 1H)
7.15 (d, *J* = 8.4 Hz, 1H)	7.13 (dd, *J* = 8.0, 0.5 Hz, 1H)	7.14 (d, *J* = 7.8 Hz, 1H)
7.10 (app t, *J* = 7.7 Hz, 1H)	7.09 (app t, *J* = 7.8 Hz, 1H)	7.10 (app t, *J* = 8.4 Hz, 1H)
7.91 (s, 1H)	7.90 (app t, *J* = 1.8 Hz, 1H)	7.90 (s, 1H)
6.84 (d, *J* = 7.0 Hz, 1H)	6.82 (dd, *J* = 7.0, 0.5 Hz, 1H)	6.84 (d, *J* = 7.2 Hz, 1H)
3.17 (d, *J* = 9.1 Hz, 1H)	3.15 (d, *J* = 9.0 Hz, 1H)	3.20 (d, *J* = 9.0 Hz, 1H)
3.15 (dd, *J* = 14.0, 4.2 Hz, 1H)	3.13 (dd, *J* = 13.8, 3.8 Hz, 1H)	3.16 (dd, J = 14.4, 4.2 Hz, 1H)
2.79 (dd, *J* = 11.2, 3.5 Hz, 1H)	2.78 (dd, *J* = 11.5, 4.0 Hz, 1H)	2.82 (dd, J = 11.4, 4.2 Hz, 1H)
2.61 (t, *J* = 12.6 Hz, 1H)	2.63-2.57 (m, 1H)	2.64 (t, J = 12.6 Hz, 1H)
2.42 (d, *J* = 8.4 Hz, 1H)	2.40 (d, *J* = 8.5 Hz, 1H)	2.43 (d, J = 8.4 Hz, 1H)
2.37 (s, 3H)	2.36 (s, 3H)	2.39 (s, 3H)
1.70 (s, 3H)	1.69 (s, 3H)	1.71 (s, 3H)
1.61 (d, *J* = 2.8 Hz, 1H)	1.60 (d, *J* = 3.5 Hz, 1H)	1.64 (d, J = 3.0 Hz, 1H)
0.46 (d, *J* = 3.5 Hz, 1H)	0.45 (d, *J* = 3.5 Hz, 1H)	0.48 (d, J = 3.6 Hz, 1H)

(±)-cyclocla vine (in the ref. 4c) (125 MHz, $CDCl_3$)	(+)-cyclocla vine (in the ref. 4a) (150 MHz, $CDCl_3$)	(+)-cyclocla vine [(**1**) in this work] (150 MHz, $CDCl_3$)		
δ^1 (ppm)	δ^2 (ppm)	δ^3 (ppm)	$\delta^3-\delta^1$ (ppm)	$\delta^3-\delta^2$ (ppm)
135.4	135.6	135.3	–0.1	–0.3
133.5	133.7	133.6	–0.1	–0.1
128.7	128.8	128.7	0.0	–0.1
122.9	123.1	122.9	0.0	–0.2
118.1	118.2	118.1	0.0	–0.1
113.2	113.5	113.1	–0.1	–0.4
110.3	110.5	110.3	0.0	–0.2
107.9	108.1	108.0	0.1	–0.1
69.6	69.8	69.7	0.1	–0.1
65.6	65.7	65.5	–0.1	–0.2
39.9	40.1	39.9	0.0	–0.2
34.3	34.5	34.4	0.1	–0.1
27.8	27.9	27.7	–0.1	–0.2
24.9	25.1	24.9	0.0	–0.2
24.2	24.4	24.2	0.0	–0.2
16.5	16.6	16.4	–0.1	–0.2



2. Comparison of ^{1}H NMR spectra of (±)-cycloclavine (in the ref. 4c), (+)-cycloclavine (in the ref. 4a), and (+)-cycloclavine [(**1**) in this work]

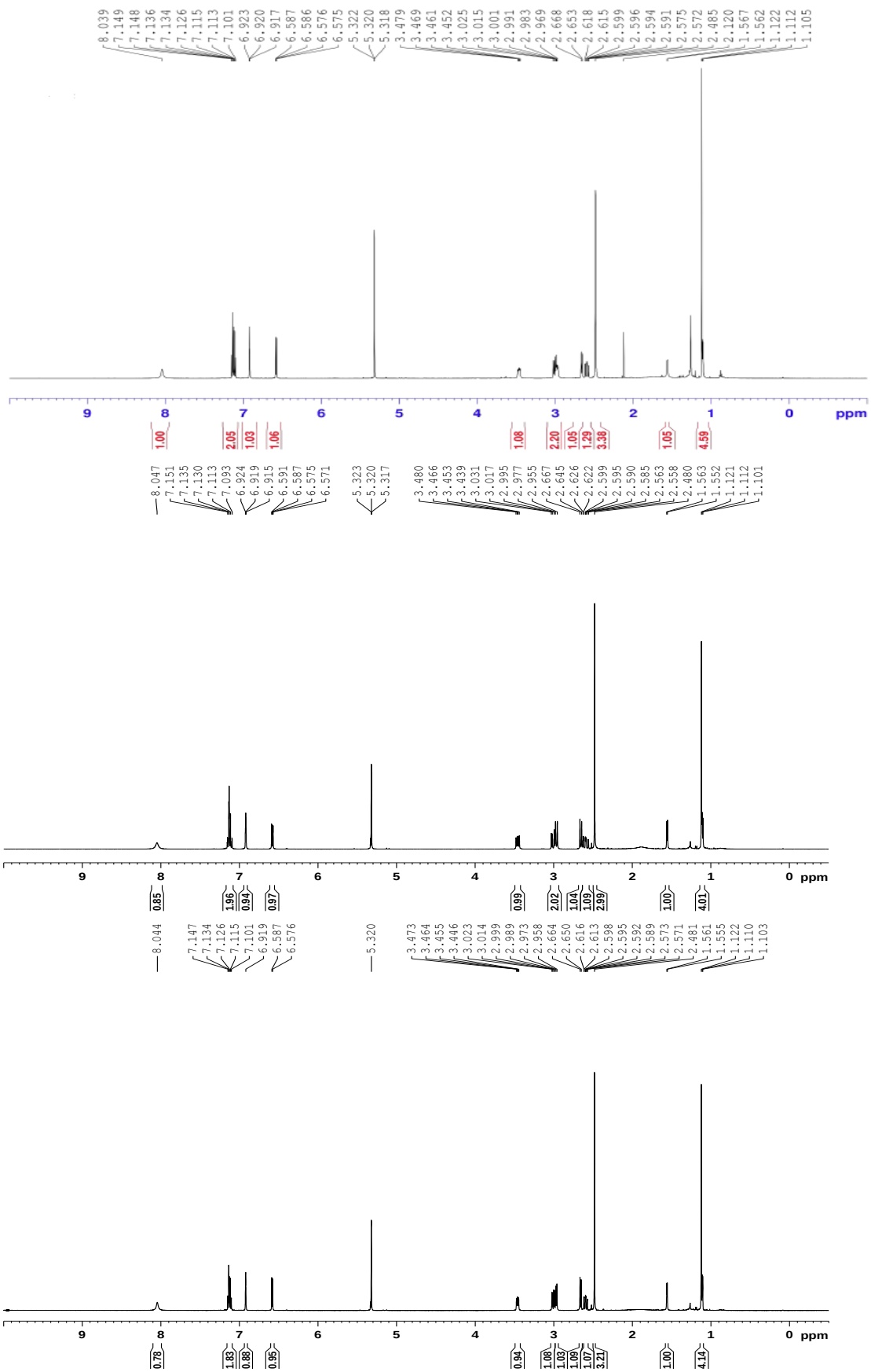


3. Comparison of ^{13}C NMR spectra of (±)-cycloclavine (in the ref. 4c), (+)-cycloclavine (in the ref. 4a), and (+)-cycloclavine [(**1**) in this work]

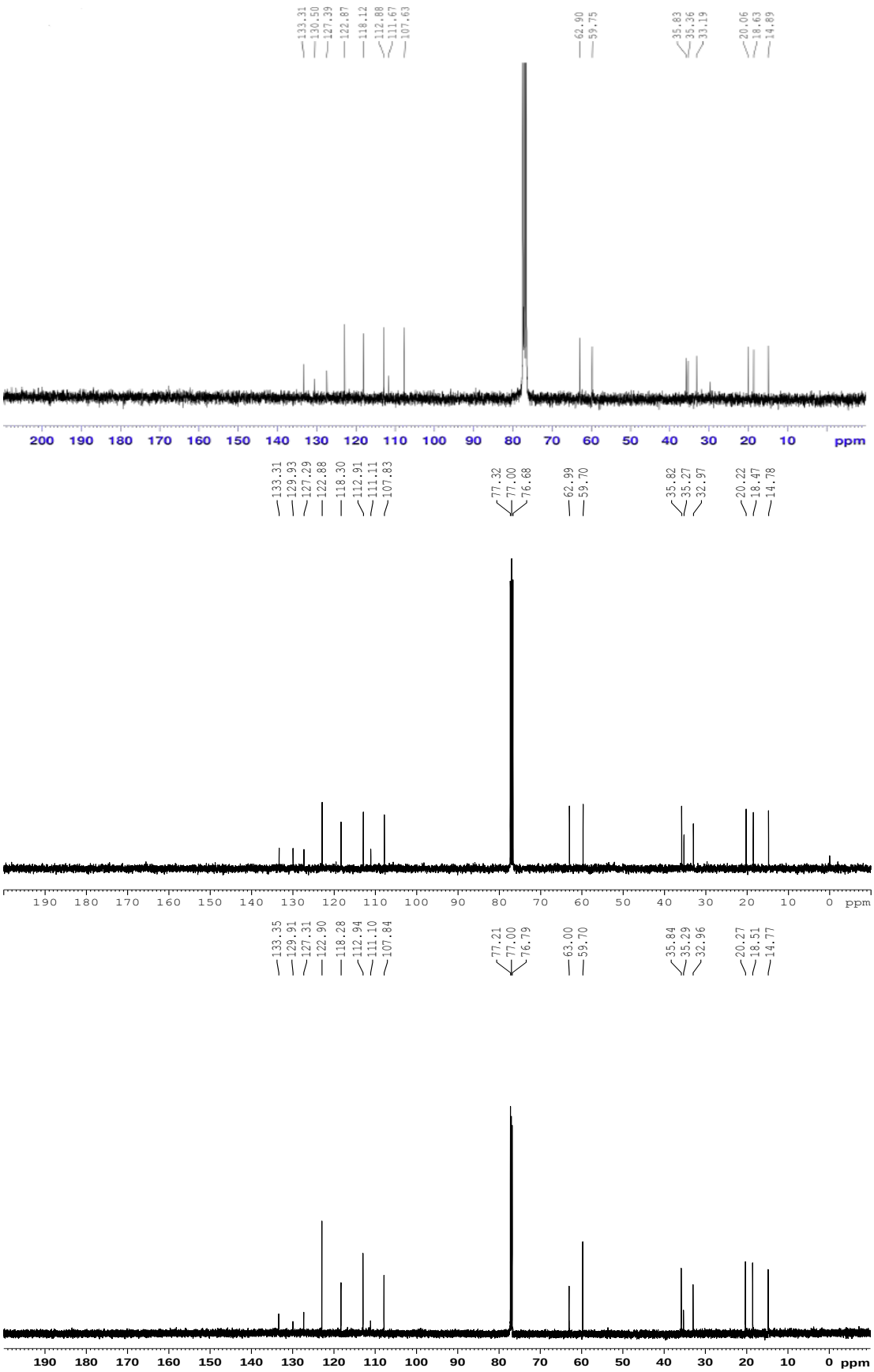
4. Comparison of ^{1}H and ^{13}C NMR data of (±)-5-*epi*-cycloclavine (in the ref. 4c) and (+)-5-*epi*-cycloclavine [(**2**) in this work]

(±)-5-*epi*-cycloclavine (in the ref. 4c) (600 MHz, CD_2Cl_2) δ (ppm)	(+)-5-*epi*-cycloclavine [(**2**) in this work] (400 MHz, CD_2Cl_2) δ (ppm)	(+)-5-*epi*-cycloclavine [(**2**) in this work] (600 MHz, CD_2Cl_2) δ (ppm)
8.04 (br s, 1H)	8.05 (br s, 1H)	8.04 (br s, 1H)
7.15–7.10 (m, 2H)	7.15–7.09 (m, 2H)	7.15–7.10 (m, 2H)
6.92 (dd, *J* = 1.8 Hz, 1H)	6.92 (t, *J* = 2.0 Hz, 1H)	6.92 (s, 1H)
6.58 (dd, *J* = 6.6, 0.6 Hz, 1H)	6.58 (dd, *J* = 6.4, 1.6 Hz, 1H)	6.58 (d, *J* = 6.6 Hz, 1H)
3.47 (dd, *J* = 10.8, 6.0 Hz, 1H)	3.46 (dd, *J* = 10.8, 5.6 Hz, 1H)	3.46 (dd, *J* = 10.8, 5.4 Hz, 1H)
3.01 (dd, *J* = 14.4, 6.0 Hz, 1H)	3.02 (dd, *J* = 14.4, 5.6 Hz, 1H)	3.01 (dd, *J* = 14.4, 5.4 Hz, 1H)
2.98 (d, *J* = 8.4 Hz, 1H)	2.97 (d, *J* = 8.8 Hz, 1H)	2.97 (d, *J* = 9.0 Hz, 1H)
2.66 (d, *J* = 9.0 Hz, 1H)	2.66 (d, *J* = 8.8 Hz, 1H)	2.66 (d, *J* = 8.4 Hz, 1H)
2.59 (ddd, *J* = 16.2, 11.4, 1.8 Hz, 1H)	2.59 (ddd, *J* = 16.4, 10.8, 1.6 Hz, 1H)	2.59 (ddd, *J* = 16.2, 10.8, 1.8 Hz, 1H)
2.48 (s, 3H)	2.48 (s, 3H)	2.48 (s, 3H)
1.57 (d, *J* = 3.0 Hz, 1H)	1.56 (d, *J* = 4.4 Hz, 1H)	1.56 (d, *J* = 3.6 Hz, 1H)
1.12 (s, 3H)	1.12 (s, 3H)	1.12 (s, 3H)
1.11 (d, *J* = 4.2 Hz, 1H)	1.11 (d, *J* = 4.4 Hz, 1H)	1.11 (d, *J* = 4.2 Hz, 1H)

(±)-5-*epi*-cycloclavine (in the ref. 4c) (75 MHz, $CDCl_3$)	(+)-5-*epi*-cycloclavine [(**2**) in this work] (100 MHz, $CDCl_3$)		(+)-5-*epi*-cycloclavine [(**2**) in this work] (150 MHz, $CDCl_3$)	
δ^1 (ppm)	δ^2 (ppm)	$\delta^2 - \delta^1$ (ppm)	δ^3 (ppm)	$\delta^3 - \delta^1$ (ppm)
133.3	133.3	0.0	133.4	0.0
130.5	129.9	–0.6	129.9	–0.6
127.4	127.3	–0.1	127.3	–0.1
122.9	122.9	0.0	122.9	0.0
118.1	118.3	0.2	118.3	0.2
112.9	112.9	0.0	112.9	0.0
111.7	111.1	–0.6	111.1	–0.6
107.6	107.8	0.2	107.8	0.2
62.9	63.0	0.1	63.0	0.1
59.8	59.7	–0.1	59.7	–0.1
35.8	35.8	0.0	35.8	0.0
35.4	35.3	–0.1	35.3	–0.1
33.2	33.0	–0.2	33.0	–0.2
20.1	20.2	0.1	20.3	0.2
18.6	18.5	–0.1	18.5	–0.1
14.9	14.8	–0.1	14.8	–0.1



5. Comparison of ^{1}H NMR spectra of (±)-5-*epi*-cycloclavine (in the ref. 4c) and (+)-5-*epi*-cycloclavine [(**2**) in this work, 400 MHz and 600 MHz]



6. Comparison of ^{13}C NMR spectra of (±)-5-*epi*-cycloclavine (in the ref. 4c) and (+)-5-*epi*-cycloclavine [(**2**) in this work, 100 MHz and 150 MHz]

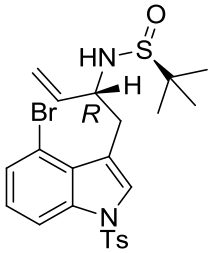
7. Tabulated summary of synthesis of cycloclavine, 5-*epi*-cycloclavine, Szántay's amine, and Wipf's lactam

main author	starting material and key features	optical rotation	compound	Ref.
Szánty (2008)	[a]Uhle's ketone derivative [b]cyclopropanation with diazomethane	(±)	cycloclavine 8 steps, 1.1% overall yield	4b
Wipf (2011)	[a]*β*-methallyl alcohol [b]intramolecular Diels-Alder cycloaddition	(±)	cycloclavine 14 steps, 1.2% overall yield	4c
		(±)	5-*epi*-cycloclavine 17 steps, 2.3% overall yield	4c
(2017)	[a]allene [b]asymmetric cyclopropanation of allene	(–)	cycloclavine 8 steps, 7.1% overall yield	4a, 4h
(2019)	[b]intermolecular [4 + 2] cycloaddition	(+) chiral	cycloclavine 8 steps, 4.2% overall yield Wipf's lactam 7 steps, 4.8% overall yield	
Brewer (2014)	[a]Uhle's ketone [b]ring fragmentation [b]1,3-dipolar cycloaddition	(±)	cycloclavine 14 steps, 2.1% overall yield	4d
Cao (2014)	[a]indole aldehyde [b]aza-Cope–Mannich cyclization [b]radical-alkene cyclization	(±)	Szántay's amine 7 steps, 27.4% overall yield	4e
(2017)	[a]4-bromoindole [b]asymmetric induction by Ellman's sulinimine [b]Ru-catalyzed isomerization C=C bond	(+)	Szántay's amine 11 steps, 19.7% overall yield	4g
Opatz (2016)	[a]4-bromoindole [b]intermolecular Heck coupling	(±)	Szántay's amine 7 steps, 16.8% overall yield	4f
Basai (2018)	[a]4-bromoindole [b]Heck cyclization, [b]late-stage ester-aminolysis	(+)	Szántay's amine 18 steps, 25.5% overall yield	4i
Dong (2018)	[a]2-iodoresorcinol [b]tandem C–N bond coupling/allylic alkylation [b] C–C activation, [b]cyclopropanation	(–)	cycloclavine 10 steps, 30% overall yield	4j
Cao	[a]4-bromoindole [b]Grignard addition, [b]Hecking couping [b]cyclopropanation, [b]ester-aminolysis reaction [b]formal [3 + 2] cycloaddition	(+) (+)	cycloclavine 13 steps, 2.0% overall yield 5-*epi*-cycloclavine 14 steps, 3.3% overall yield	

[a]starting material: known compound or commercially available. [b]key features

8. Experimental section

General Information. All reactions that required anhydrous conditions were carried out by standard procedures under argon atmosphere. Commercially available reagents were used without further purification. The solvents were dried by distillation over appropriate drying reagents. The petroleum ether (PE) used had a boiling range of 60−90 °C. Reactions were monitored by thin-layer chromatography (TLC) on silica gel GF 254 plates. Column chromatography was performed through silica gel (200−300 mesh). IR spectra were recorded on an FT-IR spectrophotometer and reported in wavenumbers (cm^{-1}). ^{1}H, ^{13}C NMR, and DEPT 135 spectra were recorded on a Bruker Avance−400 MHz (^{1}H: 400 MHz; ^{13}C: 100 MHz) or a Varian Inova−600 MHz (^{1}H: 600 MHz; ^{13}C: 150 MHz). Chemical shift values (δ) are given in ppm and coupling constants (J) in Hertz (Hz). Residual solvent signals in the ^{1}H and ^{13}C NMR spectra were used as an internal reference ($CDCl_3$: δ H 7.26, δ C 77.0 ppm; acetone-d_6: δ H 2.05, δ C 206.26, ppm). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), br (broad), dd (doublet of doublets), q (quartet) and m (multiplet). Melting points were determined by use of a microscope apparatus and are uncorrected. High resolution mass spectra were obtained on a Thermo Fisher Scientific LTQ-Orbitrap-EDT instrument using electrospray ionization (ESI) technique. Analytical chiral high performance liquid chromatography (HPLC) was conducted on a Waters 1525/2998 instrument. Optical rotations were measured using a 0.1 mL cell with a 1 cm path length on automatic polarmeter and concentrations (c) were reported in mg/mL. The X-ray single-crystal determination was performed with a diffractometer working with graphite monochromated Mo Kα radiation.



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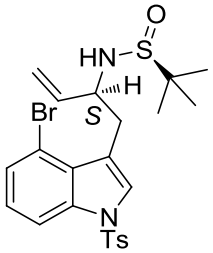
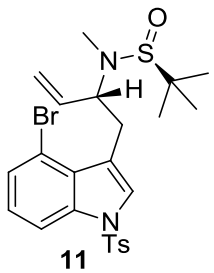


8

(S)-N-((R)-1-*(4-Bromo*-1-*tosyl*-1*H-indol*-3-*yl)but*-3-*en*-2-*yl)*-2-*methylpropane*-2-*sulfinamide [**7**] and (S)-N-((S)*-1-*(*4-*Bromo*-1-*tosyl*-1*H-indol*-3-*yl)but*-3-*en*-2-*yl)*-2-*methylpropane*-2-*sulfinamide [**8**]*. To a degassed solution of compound **9** (20.0 g, 40.5 mmol) in CH_2Cl_2 (200 mL) at −78 ℃ was added vinylmagnesium bromide (1.0 M solution in THF, 81 mL, 81 mmol). The reaction mixture was stirred at −78 ℃ for 8 h as monitored by TLC. After completion of the reaction, a saturated aqueous solution of NH_4Cl (30 mL) was slowly added dropwise with vigorous stirring. Stirring was continued for 10 min until all solid particles were dissolved. The reaction mixture

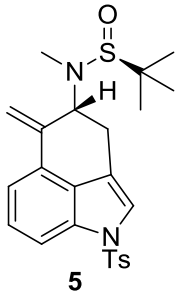
was concentrated under reduced pressure and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layer was washed with brine (70 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 1/1) afforded compound **7** (8.5 g, 40%) as a yellow solid and compound **8** (10.5 g, 50%) as a yellow solid. Data for compound **7**: R_f = 0.23 (petroleum ether/EtOAc = 3/1); Mp 60–62 ℃; $[\alpha]^{25}_D$ +85.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ 7.96 (d, *J* = 8.4 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.49 (s, 1H), 7.39 (d, *J* = 7.6 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.13 (t, *J* = 8.0 Hz, 1H), 5.73 (ddd, *J* = 16.8, 10.4, 8.0 Hz 1H), 5.18 (d, *J* = 17.6 Hz, 1H), 5.16 (d, *J* = 9.6 Hz, 1H), 4.26–4.20 (m, 1H), 3.35 (d, *J* = 2.8 Hz, 1H), 3.29–3.18 (m, 2H), 2.34 (s, 3H), 1.18 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 145.2 (C), 137.9 (CH), 136.3 (C), 134.6 (C), 129.8 (CH), 128.3 (C), 127.8 (CH), 126.7 (CH), 126.2 (CH), 125.5 (CH), 118.0 (C), 117.7 (CH_2), 114.2 (C), 112.7 (CH), 57.5 (CH), 55.4 (C), 32.9 (CH_2), 22.4 (CH_3), 21.4 (CH_3); IR (KBr, neat): 3421, 2958, 1641, 1373, 1174, 1057, 925, 813, 703, 672, 616 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{28}BrN_2O_3S_2$ 523.0719; Found 523.0730. Data for compound **8**: R_f = 0.10 (petroleum ether/EtOAc = 3/1); Mp 61–64 ℃; $[\alpha]^{25}_D$ –37.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ 7.96 (d, *J* = 8.3 Hz, 1H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.46 (s, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.23 (d, *J* = 8.1 Hz, 2H), 7.12 (t, *J* = 8.1 Hz, 1H), 5.95 (ddd, *J* = 17.2, 10.4, 6.4 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.17 (d, *J* = 10.4 Hz, 1H), 4.27–4.21 (m, 1H), 3.39–3.33 (m, 2H), 3.11 (dd, *J* = 14.5, 6.7 Hz, 1H), 2.35 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 145.1 (C), 138.9 (CH), 136.1 (C), 134.7 (C), 129.7 (CH), 128.5 (C), 127.7 (CH), 126.6 (CH), 125.2 (CH), 118.7 (C), 116.8 (CH_2), 114.1 (C), 112.7 (CH), 59.6 (CH), 55.7 (C), 31.9 (CH_2), 22.2 (CH_3), 21.4 (CH_3), one aromatic CH signal was not recognized due to overlapping. IR (KBr, neat): 3420, 2960, 1641, 1372, 1175, 1057, 926, 813, 702, 672, 615 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{23}H_{28}BrN_2O_3S_2$ 523.0719; Found 523.0728.



11

(S)-N-((R)-1-*(*4-*Bromo*-1-*tosyl*-1*H*-*indol*-3-*yl)but*-3-*en*-2-*yl)-N*,2-*dimethylpropane*-2-*sulfinamide [**11**]*. To a degassed solution of sulfinamine **7** (2.4 g, 4.6 mmol) in dry THF (50 mL) at 0 ℃ was added a solution of KHMDS in THF (1.0 M, 6.9 mL, 6.9 mmol). After stirring for 5 min, MeI (0.86 mL, 13.8 mmol) was added to the solution.

The reaction mixture was allowed to react for 1 h at 0 ℃ as monitored by TLC. After completion of the reaction, a saturated aqueous solution of NH_4Cl (10 mL) was added. The reaction mixture was concentrated under reduced pressure and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 3/1) afforded compound **11** (2.0 g, 80%) as a colorless solid. R_f = 0.20 (petroleum ether/EtOAc = 3/1); Mp 154–157 ℃; $[\alpha]^{25}_{D}$ –3.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ 7.89 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.41 (s, 1H), 7.34 (dd, *J* = 8.4, 0.8 Hz, 1H), 7.18 (d, *J* = 8.0 Hz, 2H), 7.07 (t, *J* = 8.0 Hz, 1H), 5.87 (ddd, *J* = 17.6, 10.4, 7.2 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 4.96 (d, *J* = 17.2 Hz, 1H), 3.97 (q, *J* = 7.2 Hz, 1H), 3.33 (dd, *J* = 14.8, 6.0 Hz, 1H), 3.22 (dd, *J* = 14.8, 8.4 Hz, 1H), 2.61 (s, 3H), 2.30 (s, 3H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 145.0 (C), 136.2 (C), 136.0 (CH), 134.7 (C), 129.7 (CH), 128.5 (C), 127.7 (CH), 126.9 (CH), 126.6 (CH), 125.2 (CH), 118.5 (C), 118.1 (CH_2), 114.1 (C), 112.8 (CH), 66.4 (CH), 58.2 (C), 28.9 (CH_2), 28.0 (CH_3), 23.6 (CH_3), 21.4 (CH_3); IR (KBr, neat): 3420, 2955, 1641, 1466, 1413, 1372, 1174, 1132, 927, 703, 616 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{29}BrN_2NaO_3S_2$ 559.0695; Found 559.0706.



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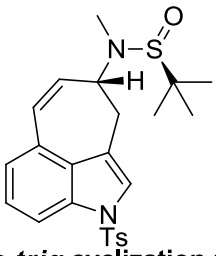
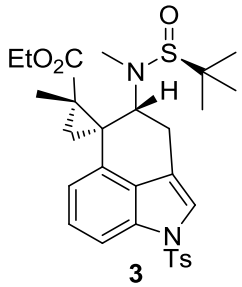


7-*endo-trig* cyclization product

*(S)-N,2-Dimethyl-N-((R)-*5*-methylene-1-tosyl-*1,3,4,5*-tetrahydrobenzo[cd]indol-*4*-yl) propane-*2*-sulfinamide [**5**] and (S)-N,2-Dimethyl-N-((S)-1-tosyl-*3,4*-dihydro-1H-cyclohepta[cd]indol-*4*-yl)propane-*2*-sulfinamide [**7-endo-trig cyclization product**]*. To a degassed solution of **11** (700 mg, 1.3 mmol), K_2CO_3 (1.1 g, 7.8 mmol) and PPh_3 (138 mg, 0.52 mmol) in CH_3CN (100 mL) was added $Pd(OAc)_2$ (30 mg, 0.13 mmol) under an argon atmosphere. The reaction mixture was stirred under reflux for 20 h as monitored by TLC. After completion of the reaction, the mixture was concentrated and passed through a short column of silica gel (eluent: ethyl acetate) to remove the catalyst and inorganic salts. The combined eluent was concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 1/1) afforded compound **5** (190 mg, 32%) as a yellow liquid and **7-*endo-trig* cyclization product** (380 mg, 64%) as a yellow liquid. Data for compound **5**: R_f = 0.23 (petroleum ether/EtOAc = 1/1); $[\alpha]^{25}_{D}$ –31.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, acetone-d_6,

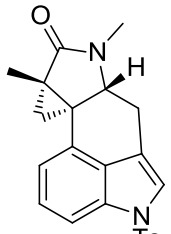
25 ℃): δ 7.84 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 7.6 Hz, 1H), 7.44–7.42 (m, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.4 Hz, 2H), 5.87 (s, 1H), 5.52 (d, J = 0.8 Hz, 1H), 4.27–4.23 (m, 1H), 3.19 (ddd, J = 10.8, 9.2, 1.6 Hz, 1H), 3.03 (dd, J = 16.0, 4.8 Hz, 1H), 2.59 (s, 3H), 2.31 (s, 3H), 0.94 (s, 9H); ^{13}C NMR (100 MHz, acetone-d_6, 25 ℃): δ 146.3 (C), 141.4 (C), 136.4 (C), 134.6 (C), 131.0 (CH), 130.8 (C), 129.8 (C), 127.8 (CH), 126.9 (CH), 121.9 (CH), 119.1 (C), 118.5 (CH), 113.9 (CH), 113.0 (CH_2), 66.1 (CH), 58.6 (C), 28.5 (CH_3), 27.1 (CH_2), 23.8 (CH_3), 21.6 (CH_3); IR (KBr, neat): 3421, 2925, 1597, 1361, 1169, 1090, 1032, 911, 814, 734, 669 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{29}N_2O_3S_2$ 457.1614; Found 457.1622. Data for compound **7-*endo-trig* cyclization product**: R_f = 0.5 (petroleum ether/EtOAc = 1/1); $[\alpha]^{24}_D$ –6.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ 7.83 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.4 Hz, 2H), 7.30 (s, 1H), 7.22 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 7.6 Hz, 2H), 6.98 (d, J = 7.6 Hz, 1H), 6.48 (d, J = 12.0 Hz, 1H), 6.04 (dd, J = 12.0 Hz, 3.2 Hz, 1H), 4.11–4.09 (m, 1H), 3.18–3.09 (m, 2H), 2.64 (s, 3H), 2.26 (s, 3H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 144.7 (C), 135.2 (C), 135.0 (C), 134.1 (CH), 130.3 (C), 129.7 (CH), 129.3 (CH), 128.3 (C), 126.6 (CH), 124.7 (CH), 124.3 (CH), 122.3 (CH), 119.7 (C), 112.6 (CH), 62.5 (CH), 58.1 (C), 32.4 (CH_2), 27.8 (CH_3), 23.3 (CH_3), 21.3 (CH_3); IR (KBr, neat): 3447, 2925, 1597, 1364, 1177, 1090, 1018, 925, 800, 734, 669 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{24}H_{29}N_2O_3S_2$ 457.1614; Found 457.1618.



3

*(1'S,2'S,4R)-Ethyl-4-((S)-N,2-dimethylpropan-2-ylsulfinamido)-2'-methyl-1-tosyl-3,4-dihydro-1H-spiro[benzo[cd]indole-5,1'-cyclopropane]-2'-carboxylate [**3**]*. To a degassed solution of *p*-acetamidobenzenesulfonyl azide (2.5 g, 10.4 mmol) and ethyl 2-methyl-3-oxobutanoate (1.0 g, 6.9 mmol) in MeCN (15 mL) at 0 ℃ was added DBU (1.6 mL, 10.4 mmol). The reaction mixture was stirred at room temperature for 24 h as monitored by TLC. After completion of the reaction, the reaction mixture was quenched with 1 N HCl (10 ml) and extracted with hexane (3 × 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ (50 mL), brine (50 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (pentane/Et_2O = 1/50) afforded ethyl 2-diazopropanoate (631 mg, 71%) as a yellow oil. To a degassed solution of $Rh_2(TPA)_4$ (0.8 mg, 0.00059mmol)

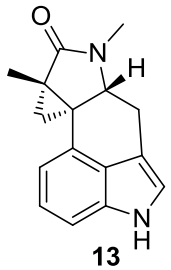
and compound **5** (270 mg, 0.59 mmol) in CH_2Cl_2 (20 mL) at room temperature was added ethyl 2-diazopropanoate (227 mg, 1.77 mmol) dissolved in CH_2Cl_2 (10 mL) at a rate of 1 mL/h as monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 1/1) afforded compound **3** (180 mg, 55%) as a colorless foam. R_f = 0.23 (petroleum ether/EtOAc = 1/1); Mp 70–72 ℃; $[\alpha]^{18}_{D}$ +84.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ 7.79 (d, *J* = 8.4 Hz, 2H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.29–7.23 (m, 4H), 6.78 (d, *J* = 7.2 Hz, 1H), 4.19 (dq, *J* = 7.2, 1.6 Hz, 2H), 3.42 (t, *J* = 2.8 Hz, 1H), 3.07 (dd, *J* = 16.4, 2.4 Hz, 1H), 3.05 (dt, *J* = 16.0, 2.8 Hz, 1H), 2.39 (s, 3H), 2.36 (s, 3H), 2.27 (d, *J* = 6.4, 1H), 1.80 (d, *J* = 6.0, 1H), 1.27 (t, *J* = 7.2 Hz, 3H),1.06 (s, 3H), 0.35 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 173.0 (C), 144.7 (C), 135.4 (C), 133.2 (C), 131.1 (C), 129.8 (CH), 129.0 (C), 126.8 (CH), 125.0 (CH), 120.5 (CH), 119.9 (CH), 117.2 (C), 111.8 (CH), 64.5 (CH), 61.2 (CH_2), 57.6 (C), 34.9 (C), 33.1 (C), 30.7 (CH_3), 25.9 (CH_2), 23.4 (CH_3), 22.9 (CH_2), 21.5 (CH_3), 16.6 (CH_3), 14.3 (CH_3). IR (KBr, neat): 3280, 2920, 2851, 1715, 1597, 1443, 1364, 1177, 1115, 1032, 667 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + K]^+$ Calcd for $C_{29}H_{36}KN_2O_5S_2$ 595.1697; Found 595.1698.



12

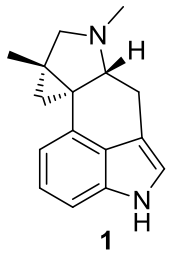
*(*1*aS*,3*aR*,9*bS)*-1*a*,3-*Dimethyl*-6-*tosyl*-3,3*a*,4,6-*tetrahydro*-1*H*-*cyclopropa[c]indolo[*4,3-*ef]indol*-2*(*1*aH)-one [**12**]*. To a solution of **3** (180 mg, 0.32 mmol) in CH_2Cl_2 (20 mL) was added 4 N HCl/MeOH (0.65 mL) and stirred for 1 h at room temperature as monitored by TLC. After completion of the reaction, a saturated $NaHCO_3$ (20 mL)was added and extracted by CH_2Cl_2 (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. The crude product was dissolved in anhydrous methanol (10 mL). Then NaOH (130 mg, 3.2 mmol) was added and stirred for another 1 h as monitored by TLC. After completion of the reaction, the mixture was quenched with water and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (petroleum ether/ EtOAc = 2/1) afforded the lactam **12** (94 mg, 72% yield) as a colorless foam. R_f = 0.12 (petroleum ether/EtOAc = 2/1); Mp 105–107 ℃; $[\alpha]^{25}_{D}$ –43.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400

MHz, $CDCl_3$, 25 ℃): δ 7.80 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.4 Hz, 1H), 7.32 (d, J = 1.6 Hz, 1H), 7.26–7.22 (m, 3H), 6.92 (d, J = 7.6 Hz, 1H), 3.70 (dd, J = 12.0, 4.0 Hz, 1H), 3.23 (dd, J = 14.4, 4.0 Hz, 1H), 2.81 (s, 3H), 2.59 (ddd, J = 14.0, 12.0, 2.0 Hz, 1H), 2.36 (s, 3H), 1.80 (s, 3H), 1.14 (d, J = 3.6 Hz, 1H), 0.83 (d, J = 4.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 178.3 (C), 144.9 (C), 135.3 (C), 133.7 (C), 133.1 (C), 130.6 (C), 129.9 (CH), 126.8 (CH), 125.7 (CH), 120.7 (CH), 117.3 (C), 114.3 (CH), 111.6 (CH), 60.6 (CH), 32.3 (C), 31.9 (C), 28.7 (CH_2), 27.4 (CH_3), 25.1 (CH_2), 21.6 (CH_3), 12.2 (CH_3). IR (KBr, neat): 3364, 2918, 1640, 1595, 1369, 1115, 1091, 991, 773, 753, 666 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{23}H_{23}N_2O_3S$ 407.1424; Found 407.1429.



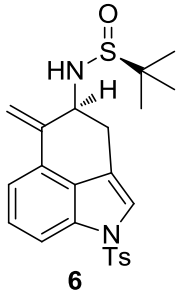
13

*(*1*aS*,3*aR*,9*bS)*-1a,3-*Dimethyl*-3,3*a*,4,6-*tetrahydro*-1*H-cyclopropa[c]indolo[*4,3-*ef]indol*-2*(*1*aH)-one [**13**]*. To a solution of naphthalene (104 mg, 0.81 mmol) in previously degassed THF (5 ml) was added sodium (22.4 mg, 0.97 mmol). The mixture was stirred at room temperature for 2 h in order to obtain a dark green. Then to a degassed solution of compound **12** (33 mg, 0.081 mmol) in THF (10 mL) at –78 ℃ was added the freshly prepared solution of sodium naphthalenide (5 ml). The mixture was stirred for 10 min at this temperature as monitored by TLC. After completion of the reaction, a saturated NH_4Cl (10 mL) was added. The mixture was made basic with saturated $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2/MeOH = 15/1) afforded compound **13** (20 mg, 98%) as a colorless foam. R_f = 0.50 (CH_2Cl_2/MeOH = 15/1); Mp 203–205 ℃; $[\alpha]^{18}_D$ –81.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ 8.46 (br s, 1H), 7.22 (d, J = 8.4 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 7.01 (s, 1H), 6.81 (d, J = 6.8 Hz, 1H), 3.84 (dd, J = 12.0, 8.0 Hz, 1H), 3.30 (dd, J = 13.6, 8.0 Hz, 1H), 2.85 (s, 3H), 2.74–2.67 (m, 1H), 1.87 (s, 3H), 1.16 (d, J = 3.6 Hz, 1H), 0.90 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 178.9 (C), 133.5 (C), 132.7 (C), 128.1 (C), 122.9 (CH), 119.2 (CH), 110.7 (C), 110.1 (CH), 109.1 (CH), 61.5 (CH), 32.6 (C), 32.2 (C), 28.8 (CH_2), 27.4 (CH_3), 25.2 (CH_2), 12.3 (CH_3). IR (KBr, neat): 3278, 2926, 1671, 1593, 1457, 1161, 1092, 1032, 775, 748, 659 cm^{-1}; HRMS (ESI-TOF) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{17}N_2O$ 253.1335; Found 253.1337.

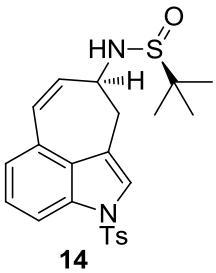


1

*(*1*aS*,3*aR*,9*bS)*-1*a*,3-*dimethyl*-1*a*,2,3,3*a*,4,6-*hexahydro*-1*H*-*cyclopropa[c]indolo[*4,3-*ef]indole [**1**]*. To a solution of **13** (25.0 mg, 0.10 mmol) in THF (2.0 mL) under an argon atmosphere was cooled to 0 ℃ and treated with $LiAlH_4$ (0.50 mL, 1.0 M solution in Et_2O, 0.240 mmol). The reaction mixture was stirred at reflux in a sealed tube for 16 h, diluted with Et_2O, cooled to 0 ℃ and treated sequentially with H_2O (0.019 mL), aq 15% NaOH (0.019 mL) and H_2O (0.057 mL), warmed to r.t. and stirred for 15 min. $MgSO_4$ was added and the solution was stirred rigorously for 15 min, and filtered through a pad of Celite. The mixture was concentrated under reduced pressure and afforded compound **1** (21 mg, 89%) as a white soild. R_f = 0.40 (CH_2Cl_2/MeOH = 10/1); Mp 160−162 ℃ (dec.); $[\alpha]^{25}_D$ + 63.0 (c 1.0, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$, 25 ℃): 8.07 (br s, 1H), 7.14 (d, *J* = 7.8 Hz, 1H), 7.10 (app t, *J* = 8.4 Hz, 1H), 7.90 (s, 1H), 6.84 (d, *J* = 7.2 Hz, 1H), 3.20 (d, *J* = 9.0 Hz, 1H), 3.16 (dd, *J* = 14.4, 4.2 Hz, 1H), 2.82 (dd, *J* = 11.4, 4.2 Hz, 1H), 2.64 (t, *J* = 12.6 Hz, 1H), 2.43 (d, *J* = 8.4 Hz, 1H), 2.39 (s, 3H), 1.71 (s, 3H), 1.64 (d, *J* = 3.0 Hz, 1H), 0.48 (d, *J* = 3.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$, 25 °C): δ135.3 (C), 133.6 (C), 128.7 (C), 122.9 (CH), 118.1 (CH), 113.1 (C), 110.3 (CH), 108.0 (CH), 69.7 (CH), 65.5 (CH_2), 39.9 (CH_3), 34.4 (C), 27.7 (C), 24.9 (CH_2), 24.2 (CH_2), 16.4 (CH_3). IR (KBr, neat): 3395, 2940, 2925, 1591, 1443, 1091, 780, 738 cm; HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2$ 239.1549; Found 239.1547.



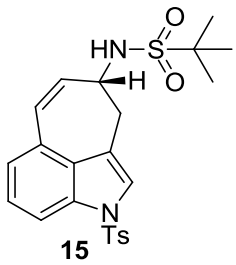
6



14

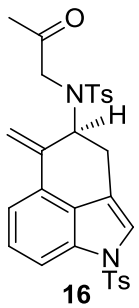
(S)-2-*Methyl*-*N*-*((S)*-5-*methylene*-1-*tosyl*-1,3,4,5-*tetrahydrobenzo[cd]indol*-4-*yl)propane*-2-*sulfinamide [**6**] and (S)*-2-*methyl*-*N*-*((S)*-1-*tosyl*-3,4-*dihydro*-1*H*-*cyclohepta[cd] indol*-4-*yl)propane*-2-*sulfinamide [**14**]*. To a degassed solution of **8** (12.0 g, 23 mmol), K_2CO_3 (19.0 g, 138 mmol) and PPh_3 (2.4 g, 9.2 mmol) in CH_3CN (1500 mL) was added $Pd(OAc)_2$ (0.52 g, 2.3 mmol) under an argon atmosphere. The reaction mixture was stirred under reflux for 20 h as monitored by TLC. After completion of the reaction, the residue was passed through a short column of silica gel (eluent: ethyl acetate) to remove the catalyst and inorganic salts. The combined eluent was concentrated under reduced pressure. Flash column chromatography (petroleum

ether/EtOAc = 1/1) afforded crude compounds **6** and **14** (quantitative). According to the characteristic integral of ^{1}H NMR spectrum for crude products, compounds **6** and **14** were in proportion to 3 : 5. The mixture was used the next step without further purification.



15

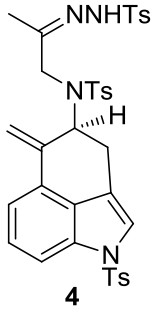
*(R)-2-Methyl-N-(1-tosyl-3,4-dihydro-1H-cyclohepta[cd]indol-4-yl)propane-2-sulfonamide [**15**]*. To a solution of sulfinamine **7** (100 mg, 0.19 mmol) in dry CH_2Cl_2 (50 mL) at 0 ℃ was added *m*-CPBA (66 mg, 0.38 mmol). The mixture was allowed to react for 1 h at room temperature as monitored by TLC. After completion of the reaction, the mixture was slowly added a mixture of saturated aqueous solution of Na_2SO_3 (5 mL) and saturated aqueous solution of Na_2CO_3 (5 mL). The organic layer was separated and washed with saturated aqueous solution of Na_2SO_3 (5 mL), water (10 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 5/1) afforded crude intermediate, which was used the next step without further purification. To a degassed solution of the above crude intermediate and (*o*-tol)$_3$P (12 mg, 0.038 mmol) in Et_3N (15 mL) was added $Pd(OAc)_2$ (4.3 mg, 0.019 mmol) under an argon atmosphere. The reaction mixture was stirred under reflux for 2 h as monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 3/1) afforded compound **15** (61 mg, 69%) as a yellow solid; R_f = 0.50 (petroleum ether/EtOAc = 2/1); Mp 183–186 ℃; $[\alpha]^{25}_D$ +100.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$, 25 ℃): δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.77 (d, *J* = 8.4 Hz, 2H), 7.43 (s, 1H), 7.29 (t, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 7.6 Hz, 1H), 6.53 (d, *J* = 12.0 Hz, 1H), 6.04 (dd, *J* = 12.0, 6.0 Hz, 1H), 4.44–4.38 (m, 1H), 4.21 (d, *J* = 10.0 Hz, 1H), 3.23–3.13 (m, 2H), 2.33 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 145.0 (C), 135.3 (C), 135.0 (C), 133.3 (CH), 130.2 (C), 129.9 (CH), 128.2 (CH), 126.8 (C), 124.9 (CH), 124.8 (CH), 123.9 (CH), 118.5 (C), 113.1 (CH), 59.8 (CH), 52.6 (C), 34.8 (CH_2), 24.2 (CH_3), 21.5 (CH_3); one aromatic CH signal was not recognized due to overlapping. IR (KBr, neat): 3444, 2959, 2925, 1639, 1363, 1305, 1177, 1027, 916, 800, 675 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{23}H_{26}N_2NaO_4S_2$ 481.1226; Found 481.1234.



16

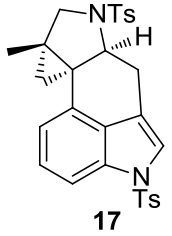
(S)-4-*Methyl*-*N*-*(*5-*methylene*-1-*tosyl*-1,3,4,5-*tetrahydrobenzo[cd]indol*-4-*yl)*-*N*-*(*2-*oxopropyl)benzenesulfonamide [**16**]*. To a solution of crude mixture **6** and **14** (10.2 g) in CH_2Cl_2 (100 mL) was added 4 N HCl/dioxane (23.0 mL, 92.3 mmol). The mixture was stirred at room temperature for 1 h as monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure. The mixture was dissolved in water and neutralized with 4 N NaOH solution to PH ~ 13. The resulting aqueous solution is extracted with EtOAc (3 × 60 mL). The combined organic layer was washed with brine (60 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The residue was used the next step without further purification. The above crude intermediate and TsCl (5.2 g, 27.6 mmol) was dissolved in CH_2Cl_2 (150 mL), which was added Et_3N (6.5 mL, 46 mmol). The reaction mixture was stirred at room temperature for 16 h as monitored by TLC. After completion of the reaction, water (100 mL) was added to the mixture and extracted with CH_2Cl_2 (3 × 70 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 3/1) afforded the crude compound (8.8 g) as a brown solid. The above crude intermediate was dissolved in acetone (100 mL), which was added Cs_2CO_3 (11.7 g, 35.8 mmol). The mixture was stirred at room temperature for 1 h and was added bromoacetone (3 mL, 35.8 mmol). The reaction was stirred at room temperature for 8 h as monitored by TLC. After completion of the reaction, the residue was passed through a short column of silica gel (eluent: ethyl acetate) to remove inorganic salts and concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 4/1) afforded compound **16** (3.3 g, 27% for four steps) as a white solid. R_f = 0.10 (petroleum ether/EtOAc = 3/1); Mp 88–91 ℃; $[\alpha]^{25}_{D}$ +34.0 (*c* 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, acetone-d_6, 25 ℃): δ 7.85–7.80 (m, 5H), 7.38–7.32 (m, 7H), 5.72 (d, *J* = 1.6 Hz, 1H), 5.04 (d, *J* = 1.6 Hz, 1H), 4.81–4.77 (m, 1H), 4.43 (d, *J* = 18.8 Hz, 1H), 4.09 (d, *J* = 18.8 Hz, 1H), 3.13 (dd, *J* = 16.0, 5.6 Hz, 1H), 2.83–2.78 (m, 1H), 2.40 (s, 3H), 2.32 (s, 3H), 2.03 (s, 3H); ^{13}C NMR (100 MHz, acetone-d_6, 25 ℃): δ 203.7 (C), 146.3 (C), 144.4 (C), 139.1 (C), 139.0 (C), 136.3 (C), 134.5 (C), 131.0 (CH), 130.4 (CH), 130.1 (C), 129.0 (C), 128.6 (CH), 127.8 (CH), 126.9 (CH), 121.7 (CH), 118.6 (C), 118.3 (CH), 113.9 (CH), 112.2 (CH_2), 58.9 (CH), 54.3 (CH_2), 27.8 (CH_2), 26.8 (CH_3), 21.54 (CH_3), 21.50 (CH_3); IR

(KBr, neat): 3110, 3061, 1737, 1636, 1597, 1359, 1157, 917, 703, 667, 609 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{29}N_2O_5S_2$ 549.1512; Found 549.1526.

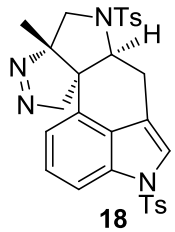


4

*(S)-4-Methyl-N-(5-methylene-1-tosyl-1,3,4,5-tetrahydrobenzo[cd]indol-4-yl)-N-(2-(2-tosylhydrazono)propyl)benzenesulfonamide [**4**]*. To a solution of compound **16** (100 mg, 0.18 mmol) in 10 mL ($MeOH/CH_2Cl_2$ = 4/1) was added tosylhydrazine (41 mg, 0.22 mmol) and one drop HCl. The resulting solution was stirred for 24 h at room temperature as monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure and used the next step without further purification.



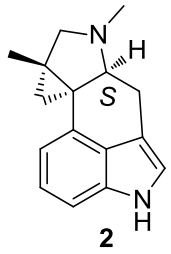
17



18

(1aS,3aS,9bS)-1a-*Methyl*-3,6-*ditosyl*-1a,2,3,3a,4,6-*hexahydro*-1*H*-*cyclopropa[c]indolo[4,3-ef]indole [**17**] and (*3a*S,11*b*S)-3*a*-*Methyl*-5,8-*ditosyl*-3*a*,4,5,5*a*,6,8-*hexahydro*-1*H*-*indolo[*4,3-*ef]pyrazolo[*3,4-*c]indole [**18**]*. To a solution of the above crude product **4** in tolune (10 mL) was added K_2CO_3 (31 mg, 0.22 mmol). The resulting mixture was heated at 120 ℃ for 10 h as monitored by TLC. After completion of the reaction, the mixture was concentrated under reduced pressure. Flash column chromatography (petroleum ether/EtOAc = 10/1) afforded compound **17** (58 mg, 60%) as a white solid and compound **18** (8 mg, 8%) as a white solid. Compound **17** was used the next step with further purification. Data for compound **17**: R_f = 0.60 (petroleum ether/EtOAc = 3/1); Mp 117–119 ℃. $[\alpha]^{25}_D$ +213.0 (*c* 1.0, CH_2Cl_2); HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{29}N_4O_4S_2$ 533.1563; Found 533.1575. Data for compound **18**: R_f = 0.24 (petroleum ether/EtOAc = 3/1); Mp 98–101 ℃; $[\alpha]^{25}_D$ +36.0 (*c* 1.0, CH_2Cl_2); ^1H NMR (600 MHz, $CDCl_3$, 25 ℃): δ 7.79–7.76 (m, 3H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.8 Hz, 1H), 7.25–7.24 (m, 3H), 6.55 (d, *J* = 7.8 Hz,

1H), 5.13 (d, *J* = 18.6 Hz, 1H), 4.47 (d, *J* = 18.6 Hz, 1H), 4.25 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.76 (d, *J* = 11.4 Hz, 1H), 3.43 (d, *J* = 12.0 Hz, 1H), 3.29 (dd, *J* = 16.2, 6.6 Hz, 1H), 2.72 (ddd, *J* = 12.0, 10.8, 1.2 Hz, 1H), 2.44 (s, 3H), 2.36 (s, 3H), 1.16 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): δ 145.0 (C), 144.2 (C), 136.6 (C), 135.5 (C), 133.0 (C), 130.7 (C), 130.0 (CH), 129.9 (CH), 128.1 (C), 127.1 (CH), 126.8 (CH), 126.2 (CH), 120.9 (CH), 120.1 (CH), 115.2 (C), 112.3 (CH), 99.0 (C), 93.9 (CH_2), 64.3 (CH), 54.6 (CH_2), 52.7 (C), 23.3 (CH_2), 21.6 (CH_3), 20.2 (CH_3), one CH_3 signal was not recognized due to overlapping. IR (KBr, neat): 3426, 2964, 2920, 1644, 1430, 1362, 1166, 1092, 1030, 798, 667 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{29}H_{29}N_4O_4S_2$ 561.1625; Found 561.1631.



2

(1aS,3aS,9bS)-1a,3-Dimethyl-1a,2,3,3a,4,6-hexahydro-1H-cyclopropa[c]indolo[4,3-ef] indole [2]. To a solution of naphthalene (245 mg, 1.9 mmol) in previously degassed THF (10 ml) was added sodium (37 mg, 1.6 mmol). The mixture was stirred at room temperature for 2 h in order to obtain a dark green. To a degassed solution of compound **17** (80 mg, 0.15 mmol) in THF (10 mL) at −78 ℃ was added the freshly prepared solution of sodium naphthalenide (10 ml). The resultant mixture was stirred for 10 min at this temperature as monitored by TLC. After completion of the reaction, a saturated NH_4Cl (10 mL) was added. The mixture was made basic with saturated aqueous solution of $NaHCO_3$ (10 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure to give a crude amine, which was used the next step without further purification. To a solution of this amine in MeOH (15 mL) were added AcOH (0.17 mL), $NaBH_3CN$ (69 mg, 1.08 mmol), and formalin (0.098 mL, 1.2 mmol) at room temperature. The mixture was stirred for 2 h as monitored by TLC. After completion of the reaction, the mixture was quenched with saturated aqueous solution of $NaHCO_3$ (10 mL), concentrated under reduced pressure, and extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with saturated $NaHCO_3$ (10 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, filtrated and concentrated under reduced pressure. Flash column chromatography (CH_2Cl_2/MeOH = 15/1) afforded compound **2** (25 mg, 71%) as a colorless foam. R_f = 0.50 (CH_2Cl_2/MeOH = 10/1); Mp 151–154 ℃; $[\alpha]^{25}_D$ +44.3 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, CD_2Cl_2,

25 ℃): δ 8.05 (br s, 1H), 7.15–7.09 (m, 2H), 6.92 (t, *J* = 2.0 Hz, 1H), 6.58 (dd, *J* = 6.4, 1.6 Hz, 1H), 3.46 (dd, *J* = 10.8, 5.6 Hz, 1H), 3.02 (dd, *J* = 14.4, 5.6 Hz, 1H), 2.97 (d, *J* = 8.8 Hz, 1H), 2.66 (d, *J* = 8.8 Hz, 1H), 2.59 (ddd, *J* = 16.4, 10.8, 1.6 Hz, 1H), 2.48 (s, 3H), 1.56 (d, *J* = 4.4 Hz, 1H), 1.12 (s, 3H), 1.11 (d, *J* = 4.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 ℃): *δ* 133.3 (C), 129.9 (C), 127.3 (C), 122.9 (CH), 118.3 (CH), 112.9 (CH), 111.1 (C), 107.8 (CH), 63.0 (CH), 59.7 (CH_2), 35.8 (CH_3), 35.3 (C), 33.0 (C), 20.2 (CH_2), 18.5 (CH_2), 14.8 (CH_3). IR (KBr, neat): 3407, 2926, 1602, 1444, 1316, 1281, 1026, 799, 784, 744, 659 cm^{-1}; HRMS (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{19}N_2$ 239.1549; Found 239.1549.

9. ^{1}H and ^{13}C NMR spectra of compounds: **7**, **8**, **11**, **5**, NOE spectra of **5**, **7-*endo-trig* cyclization product**, **3**, NOE spectra of **3**, **12**, **13**, **1**, **15**, **16**, **18**, and **2**

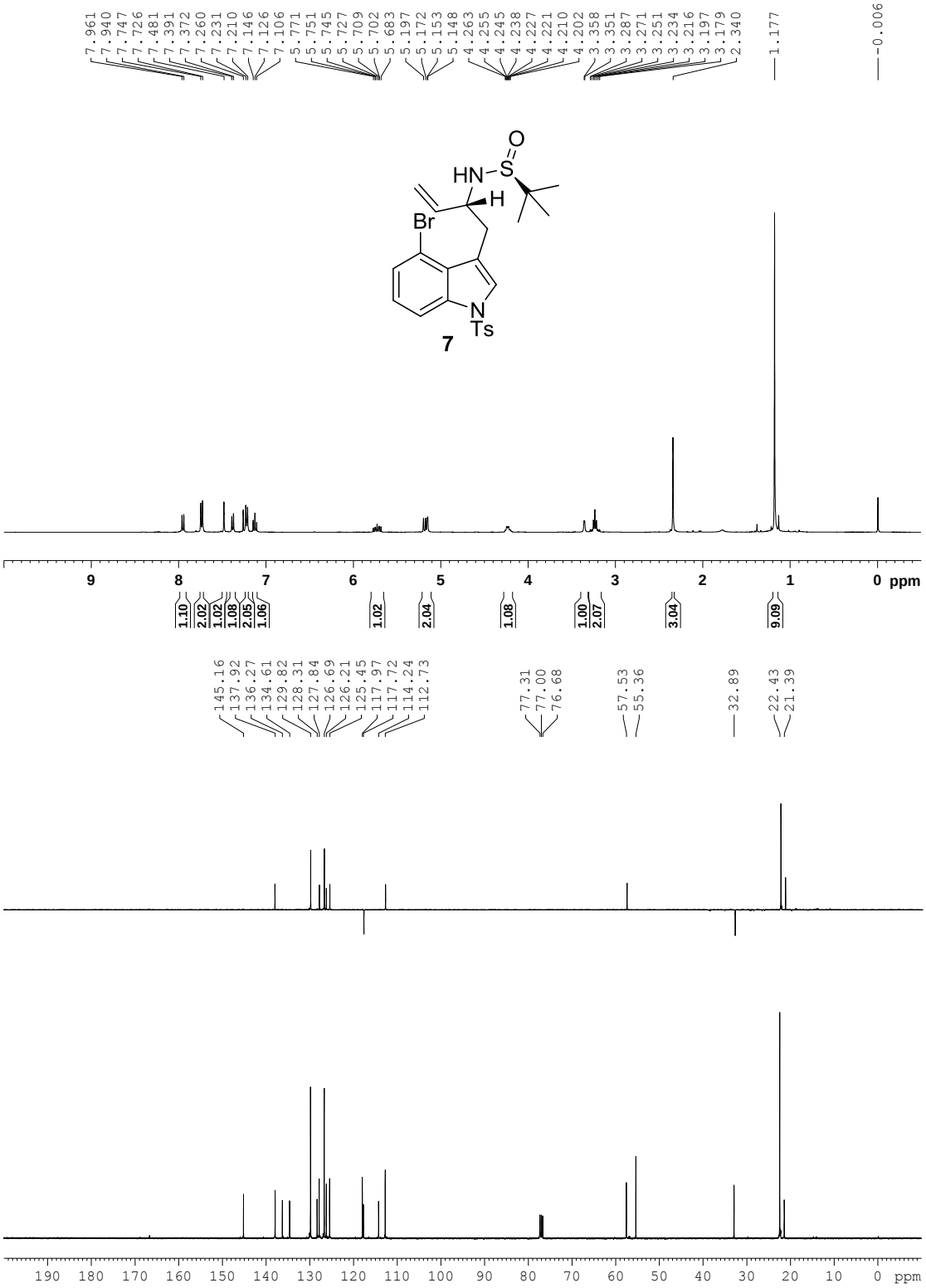


Figure S1. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **7**.

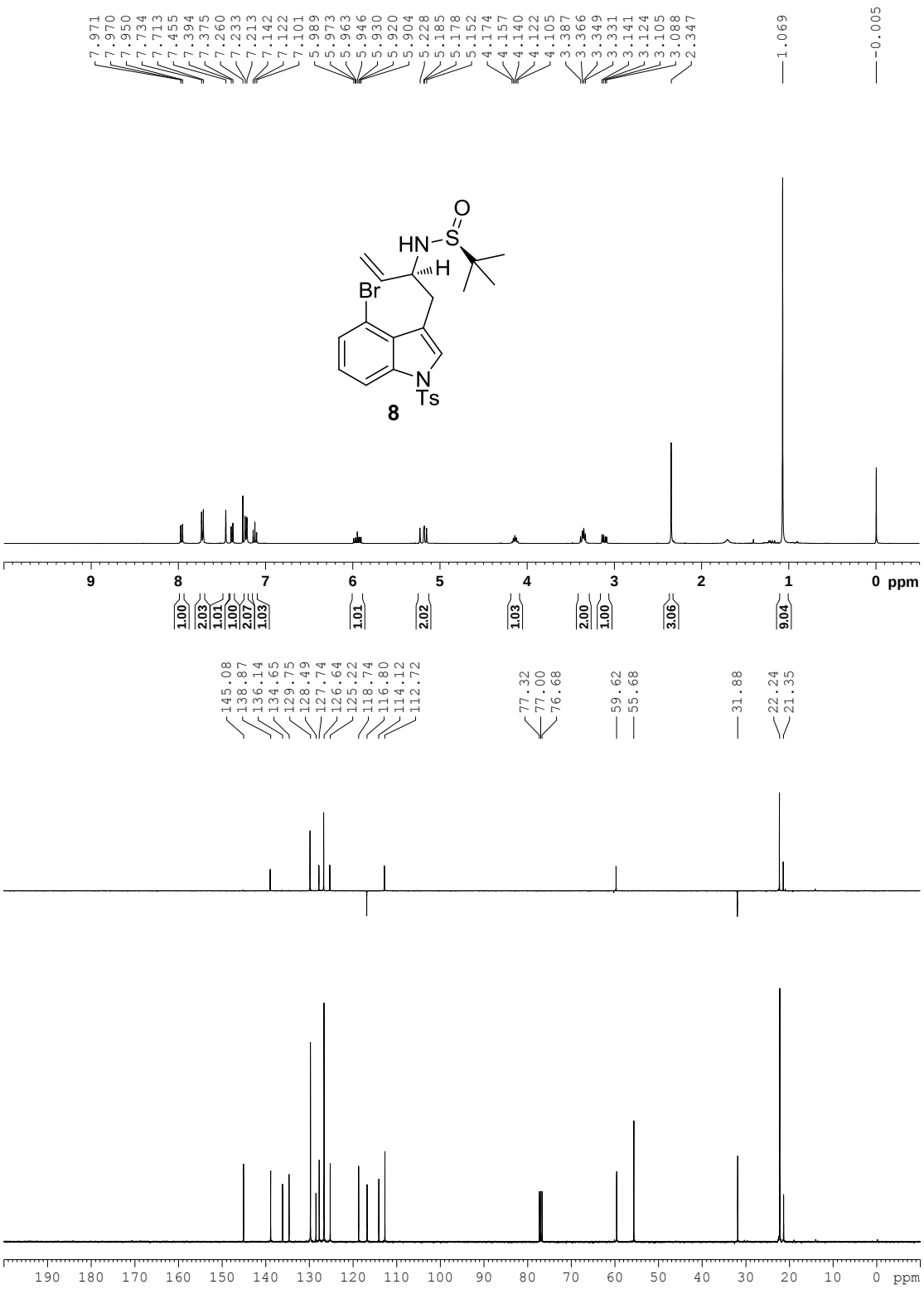


Figure S2. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **8.**

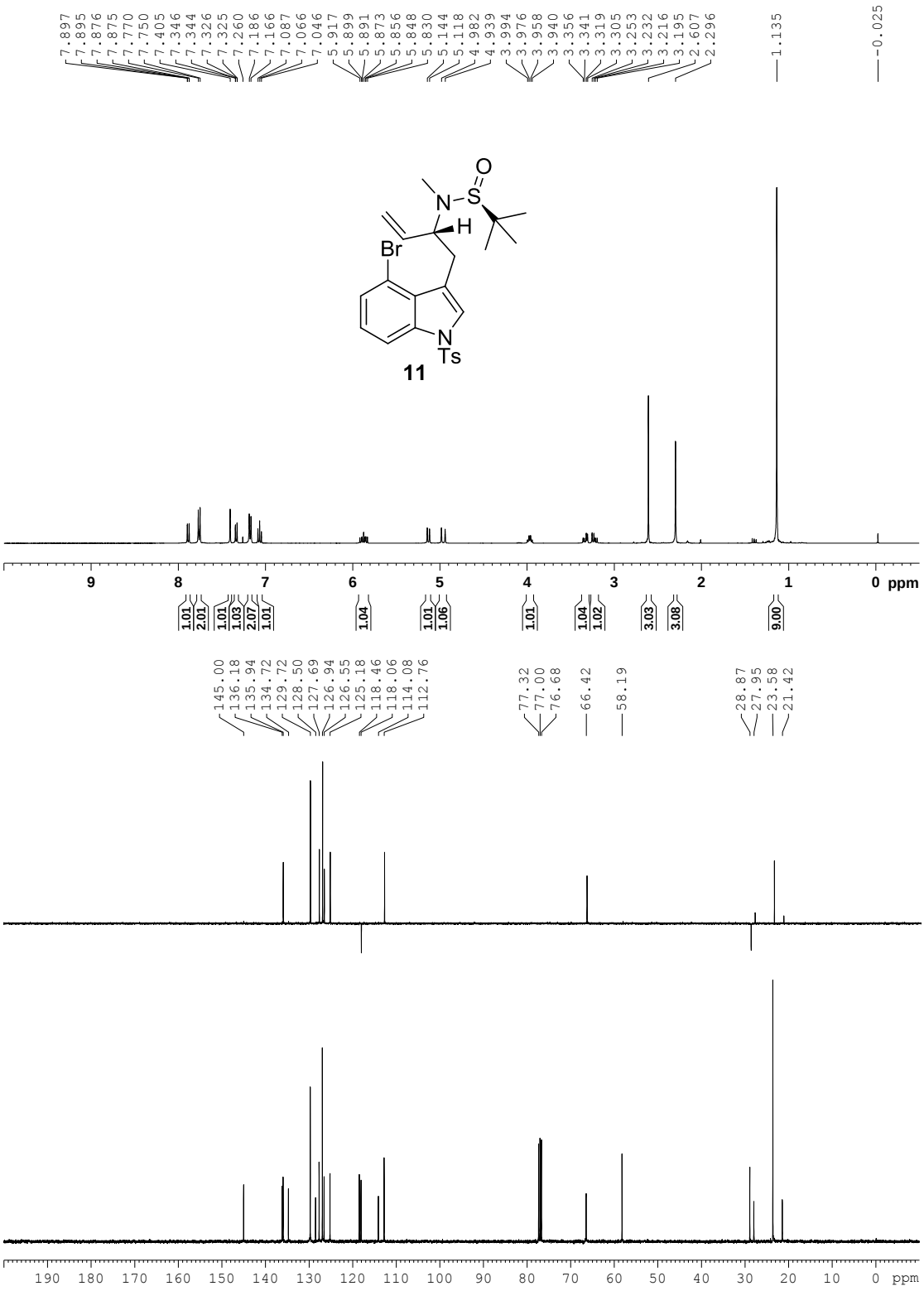


Figure S3. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **11**.

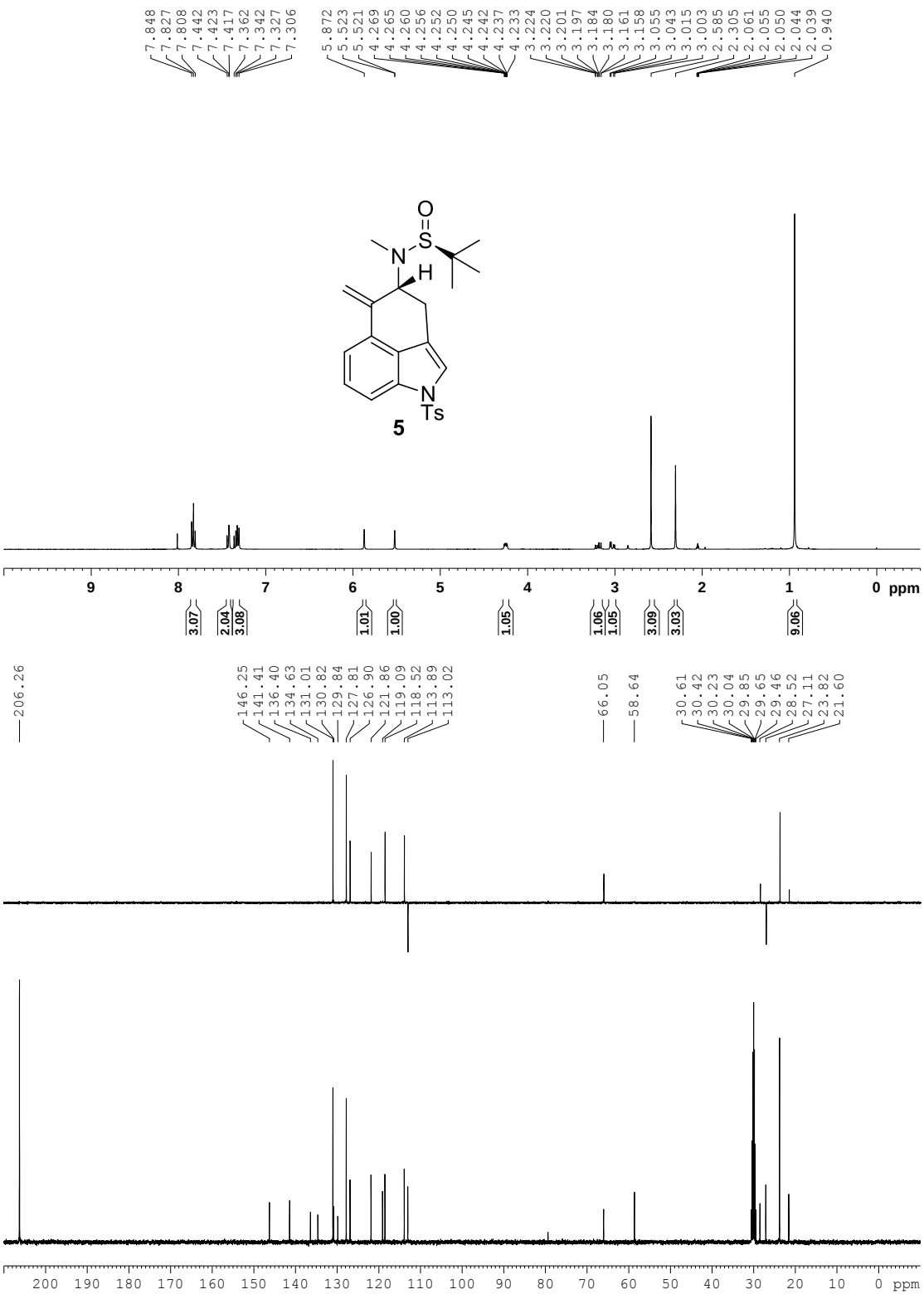


Figure S4. ^{1}H NMR spectrum (acetone-d_6, 400 MHz) and ^{13}C NMR spectrum (acetone-d_6, 100 MHz) of **5**.

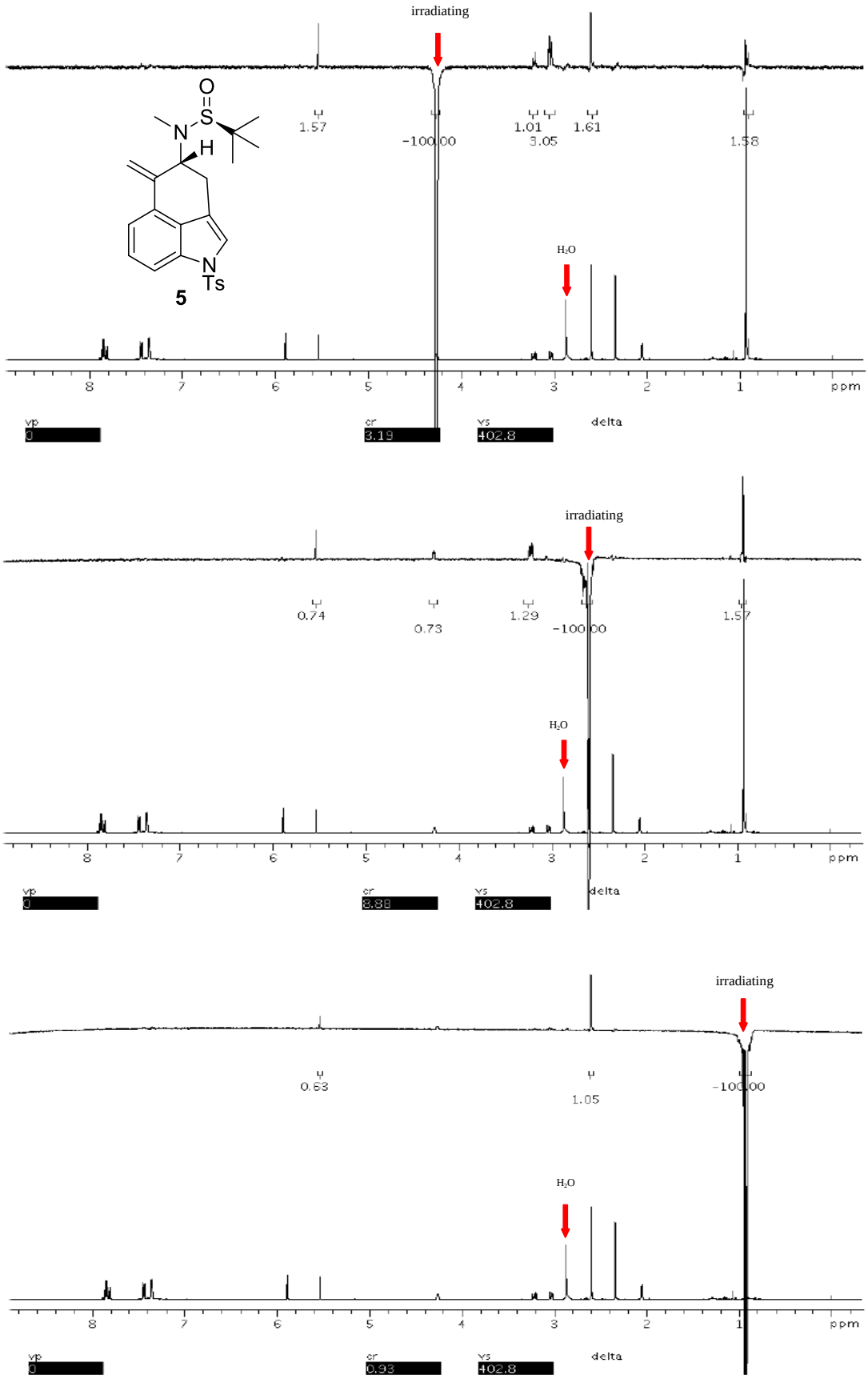


Figure S5. Difference NOE spectra of **5** irradiating (acetone-d_6, 600 MHz).

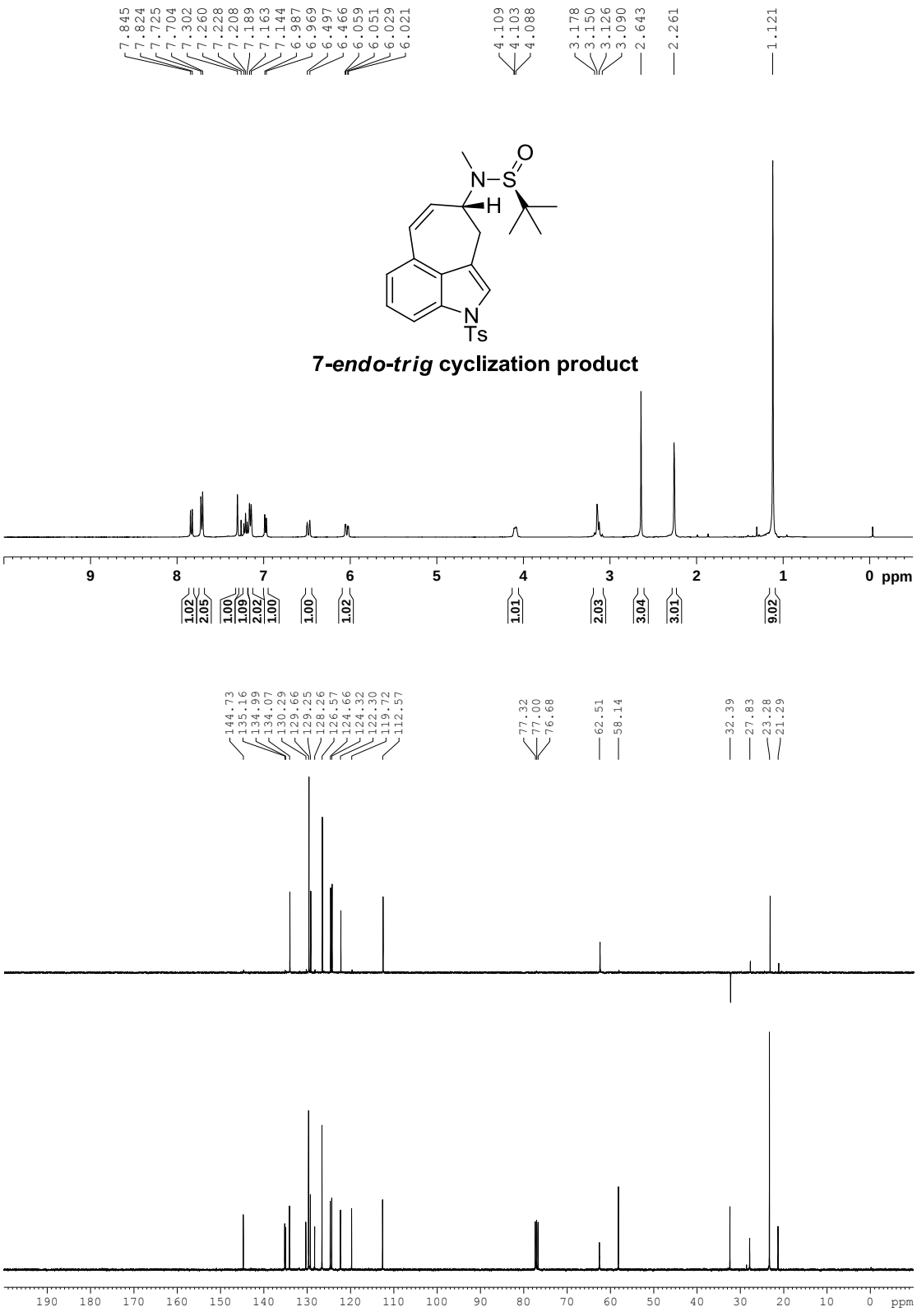


Figure S6. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **7-*endo-trig* cyclization product**.

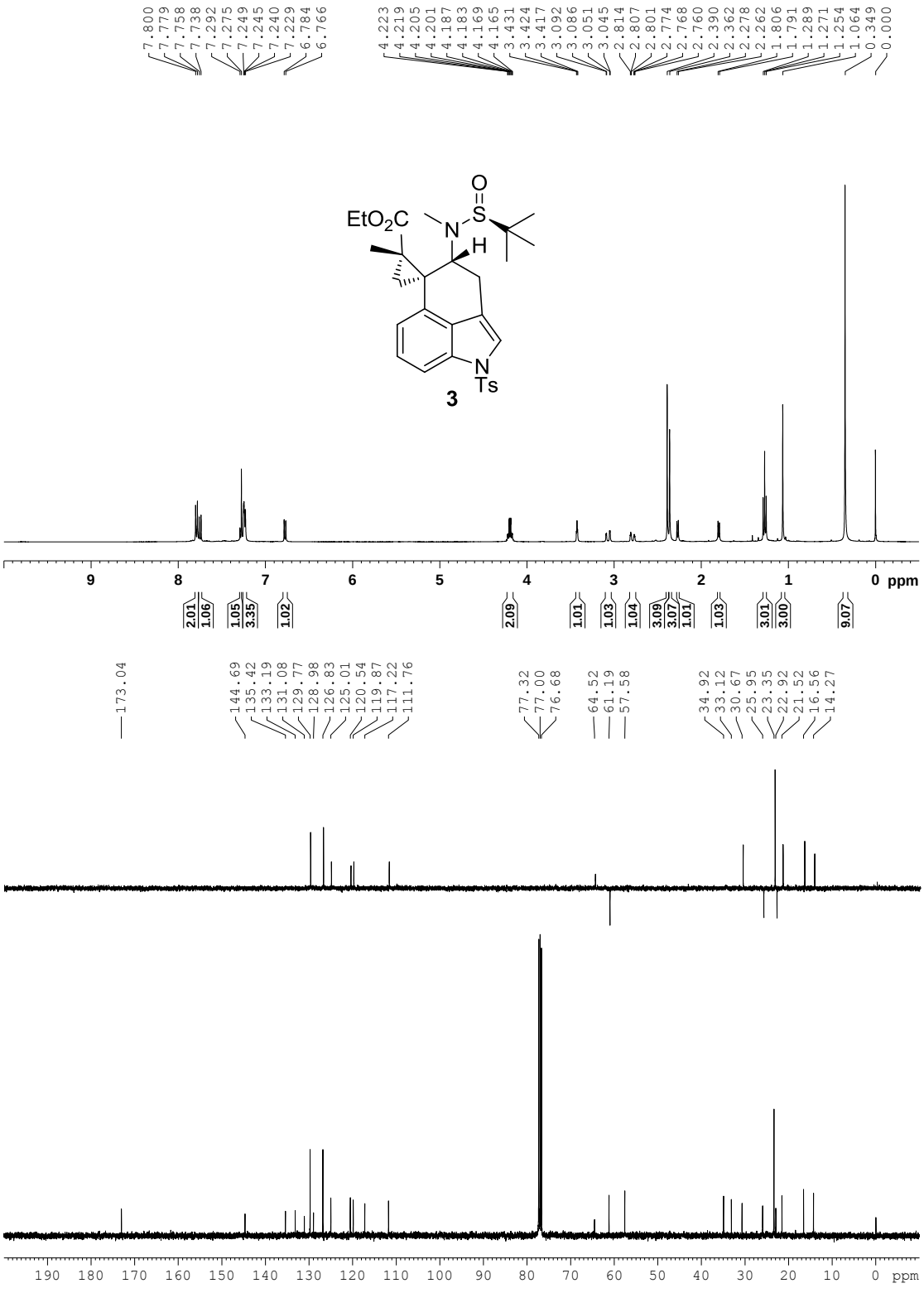


Figure S7. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **3**.

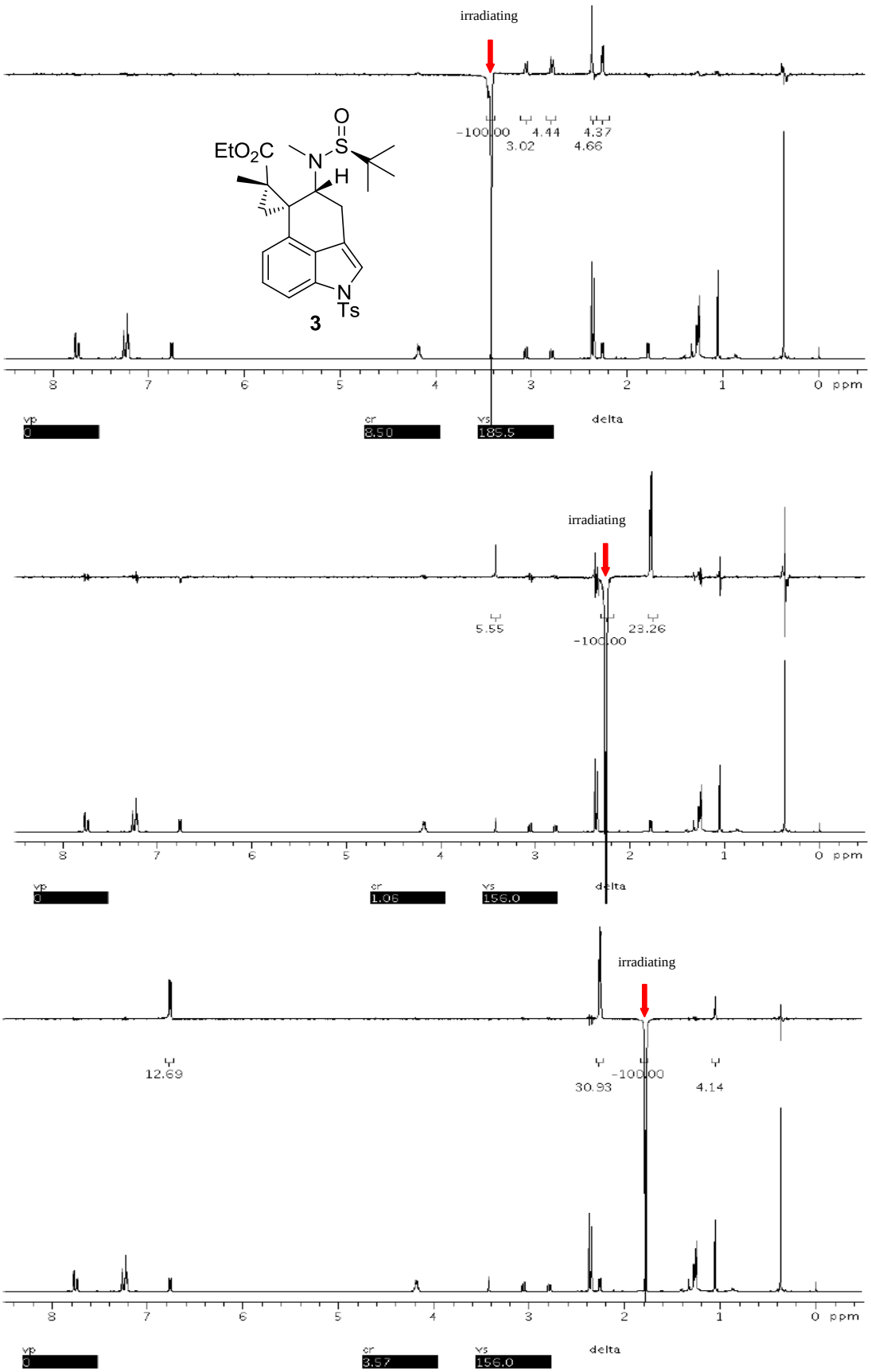


Figure S8. Difference NOE spectra of **3** irradiating ($CDCl_3$, 600 MHz).

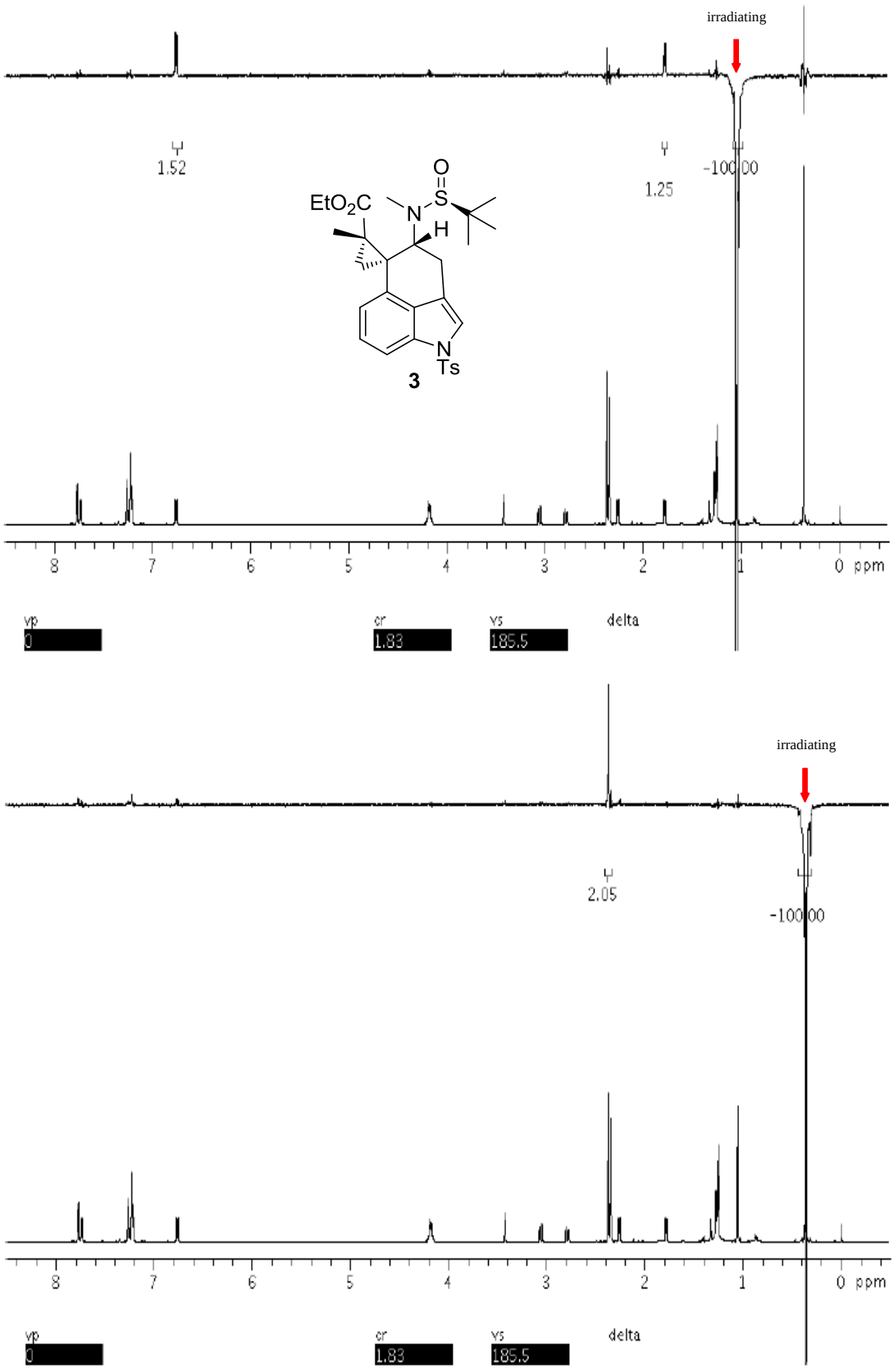


Figure S8. Difference NOE spectra of **3** irradiating ($CDCl_3$, 600 MHz).

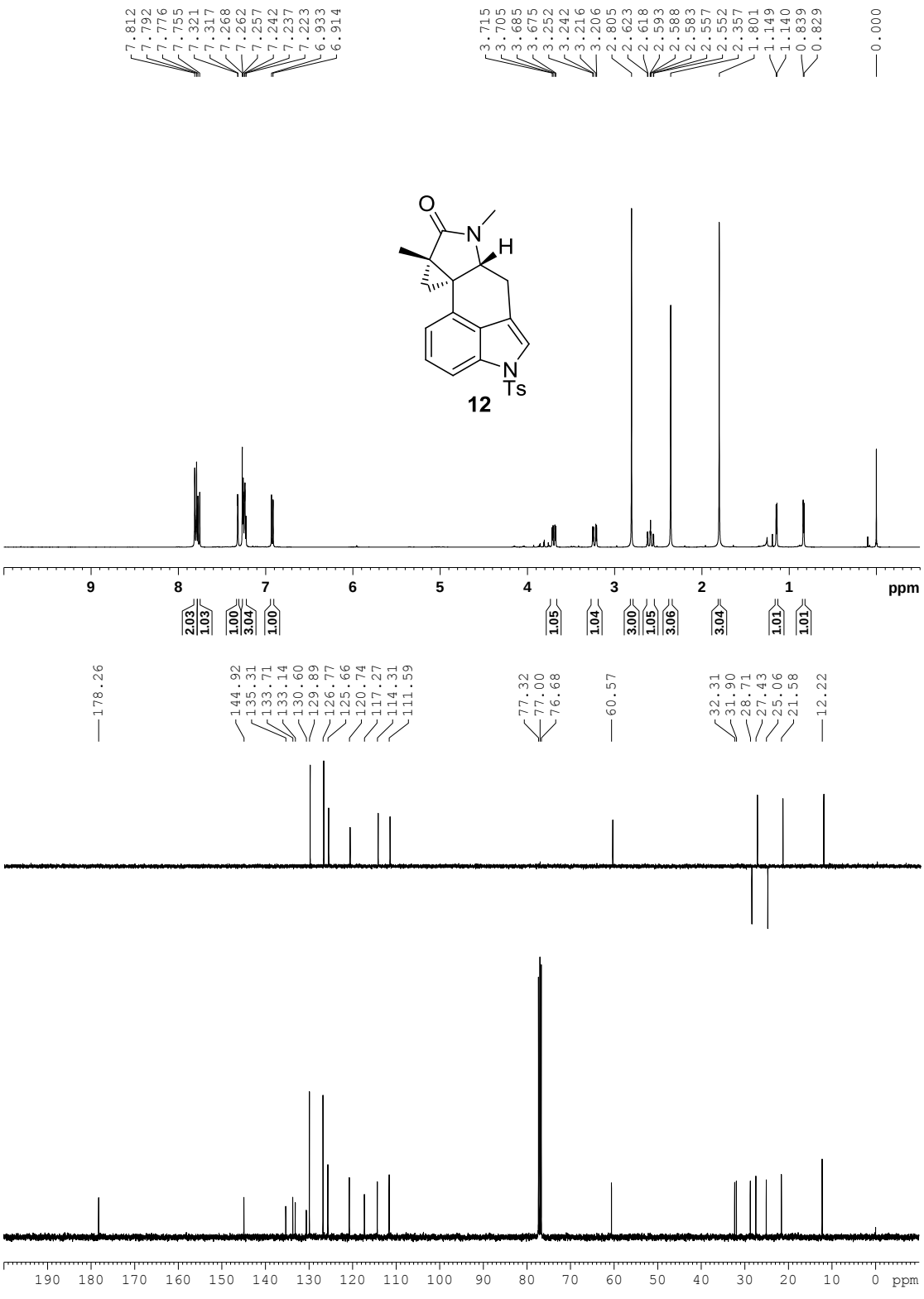


Figure S9. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **12**.

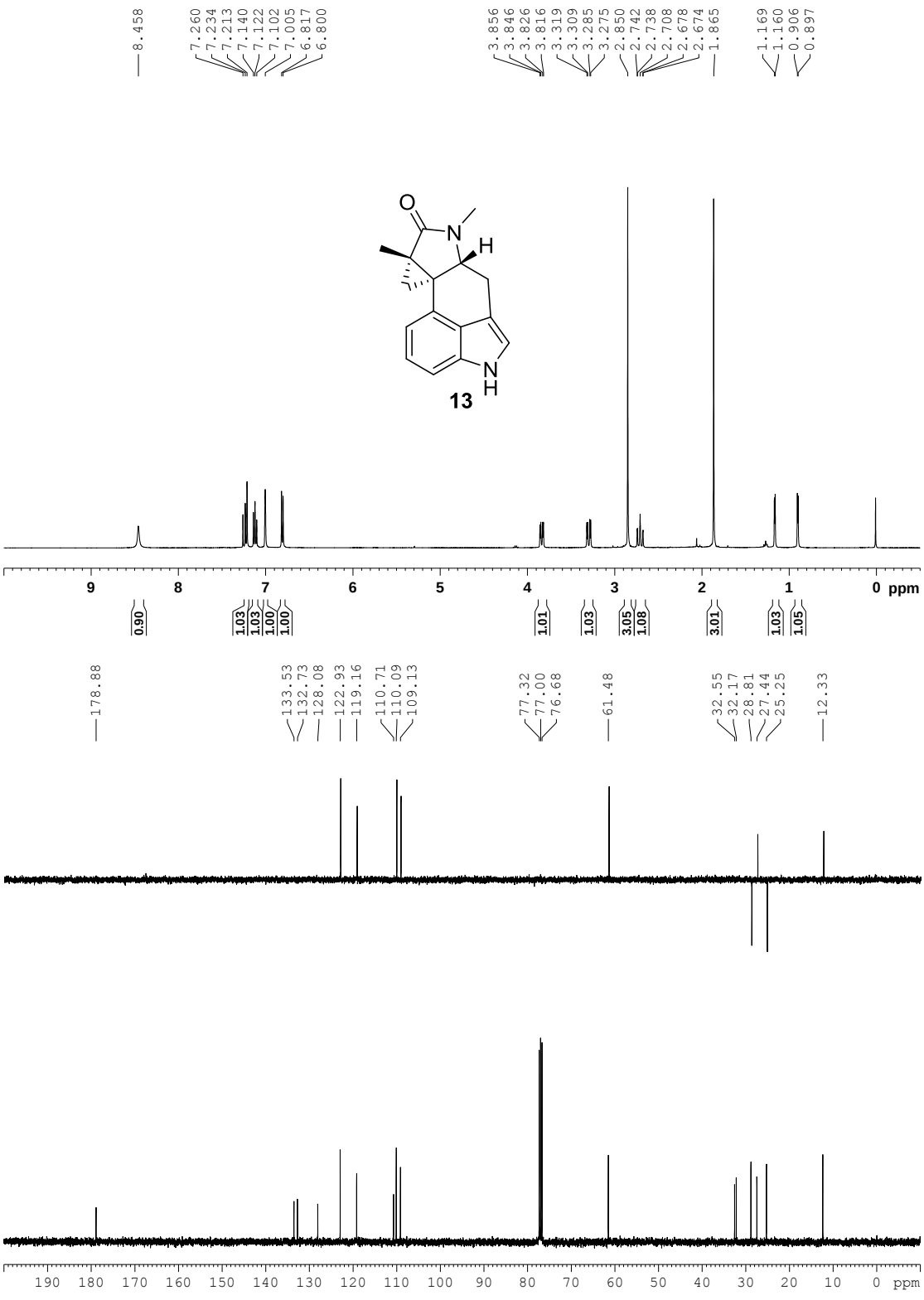


Figure S10. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **13**.

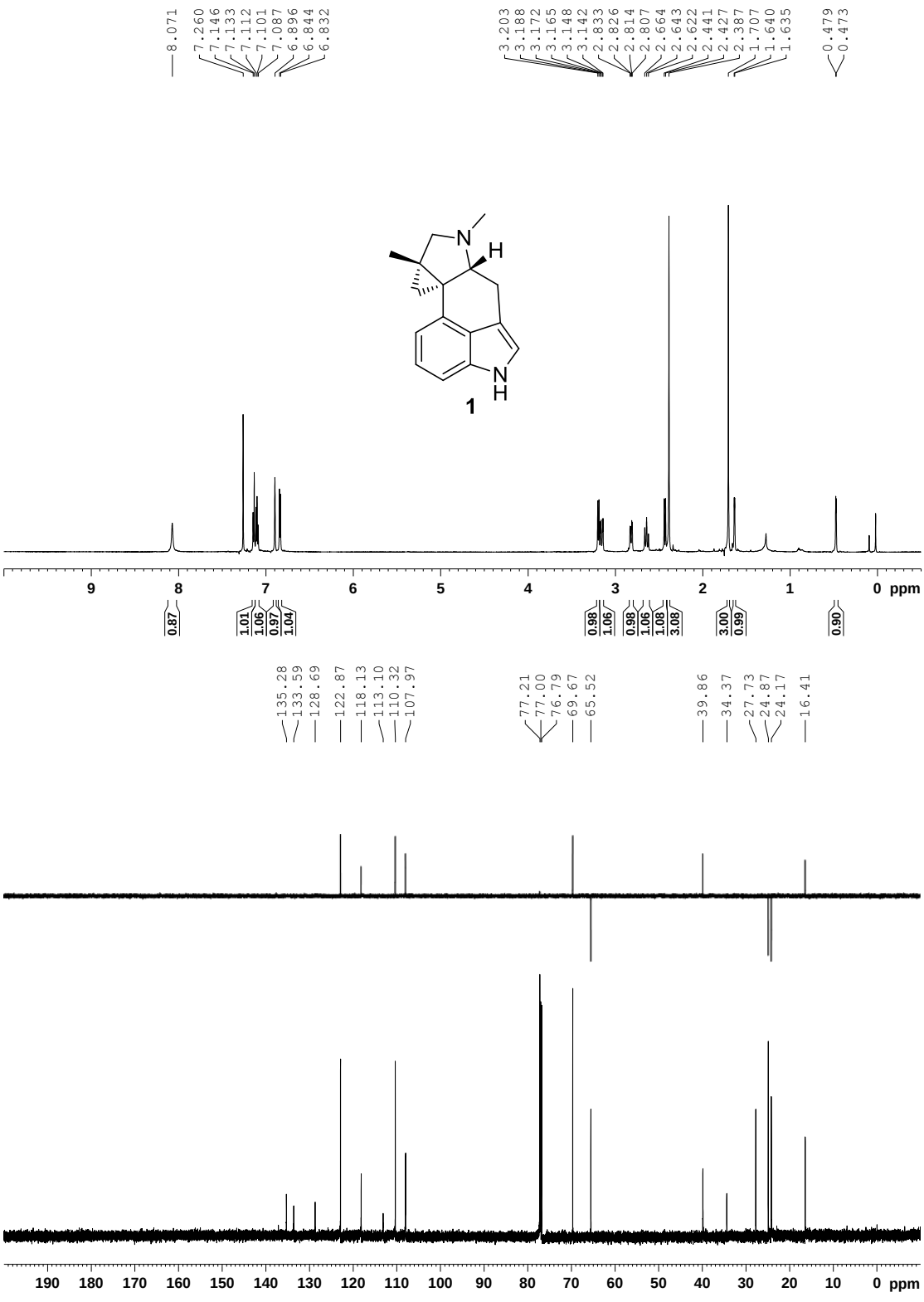


Figure S11. ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) of **1**.

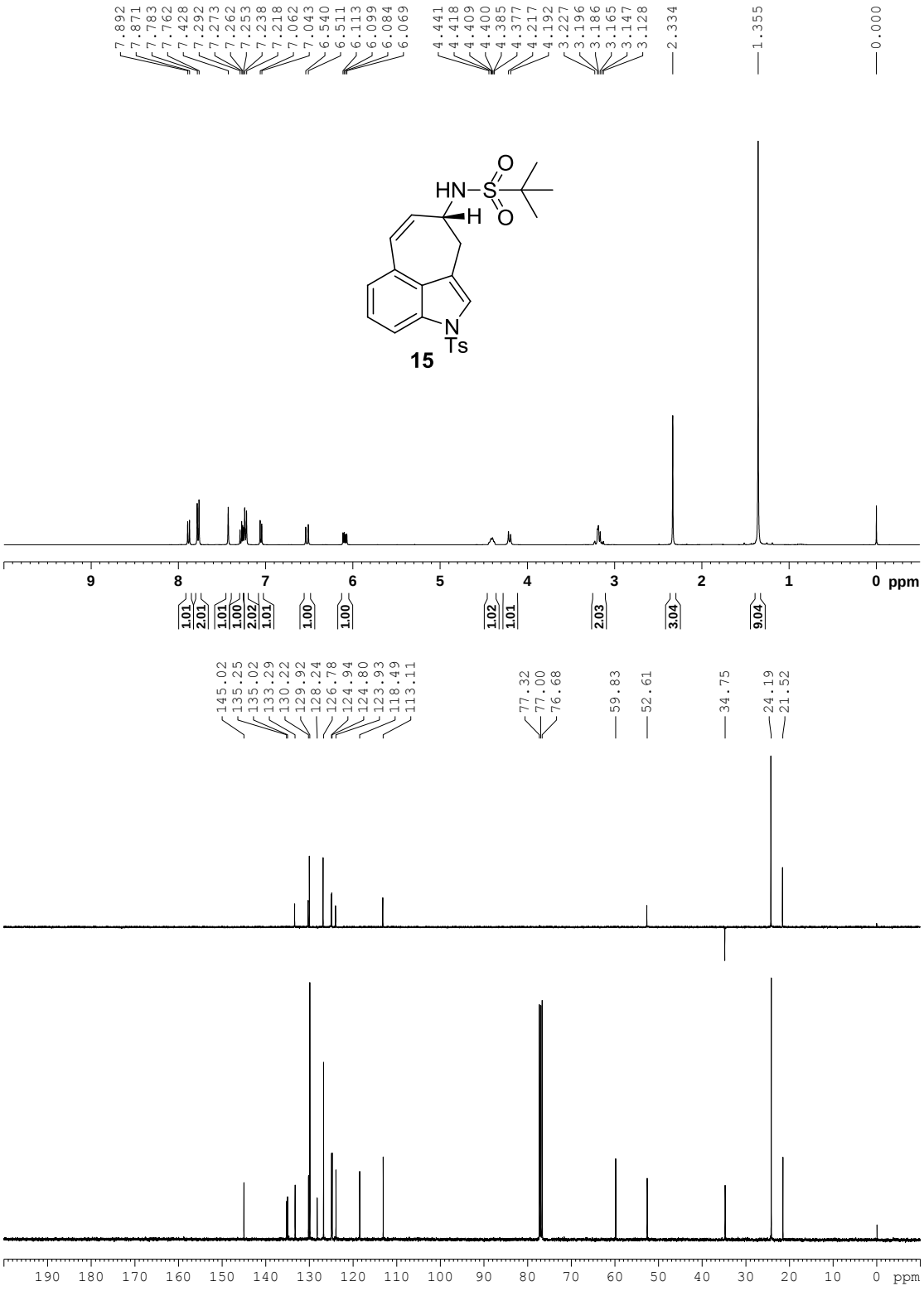


Figure S12. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **15**.

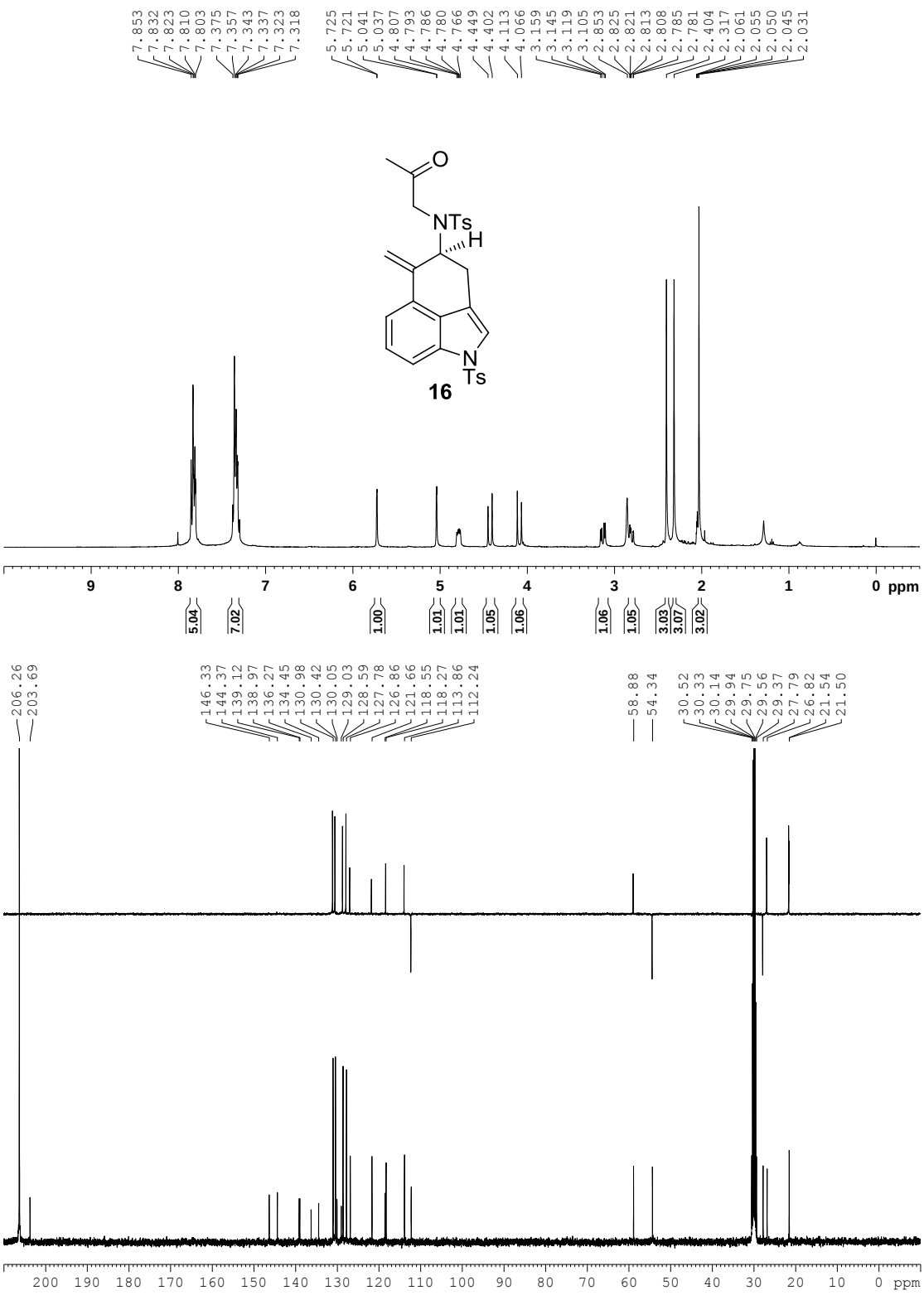


Figure S13. ^{1}H NMR spectrum (acetone-d_6, 400 MHz) and ^{13}C NMR spectrum (acetone-d_6, 100 MHz) of **16**.

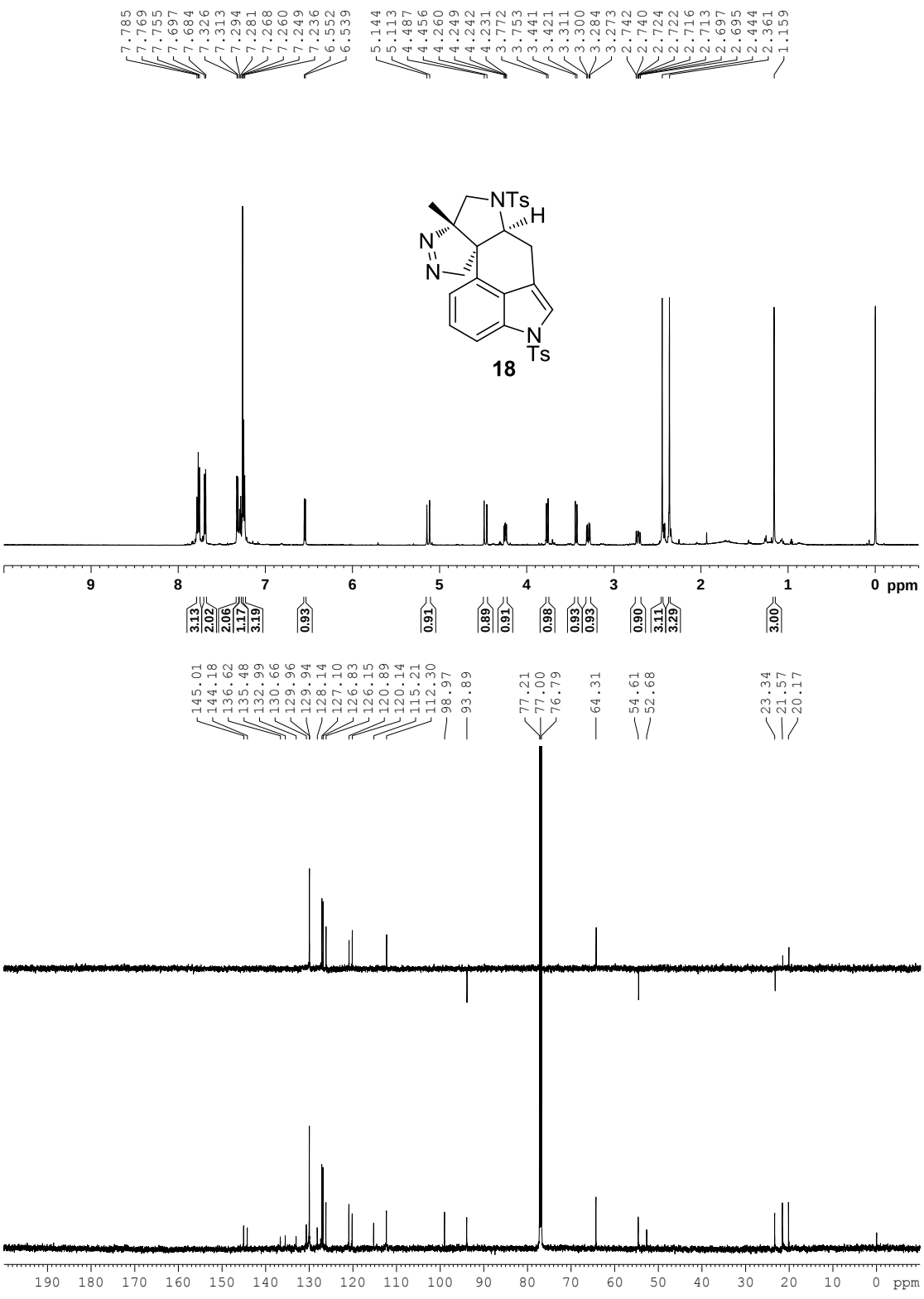


Figure S14. ^{1}H NMR spectrum ($CDCl_3$, 600 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) of **18**.

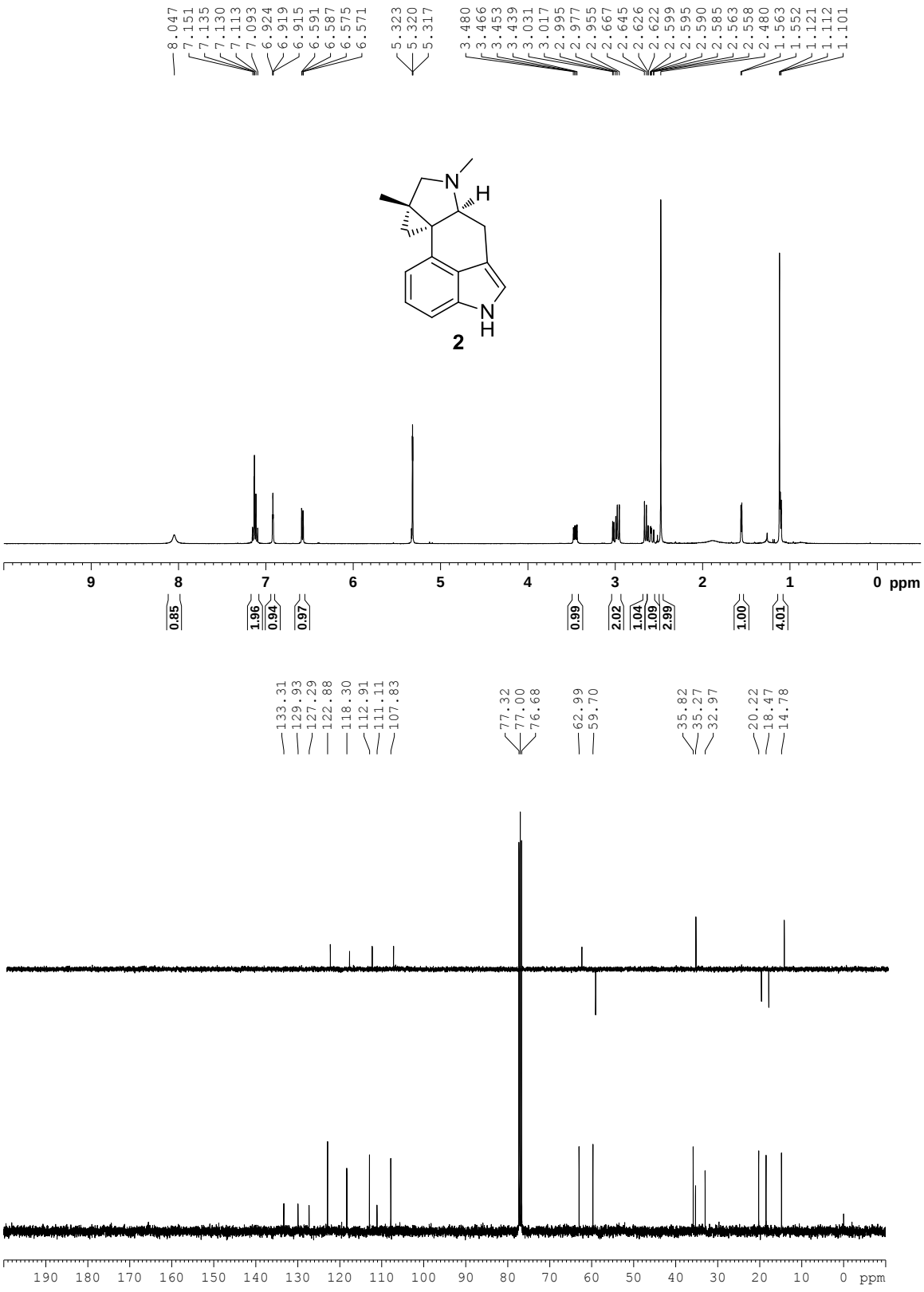


Figure S15. ^{1}H NMR spectrum (CD_2Cl_2, 400 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 100 MHz) of **2**.

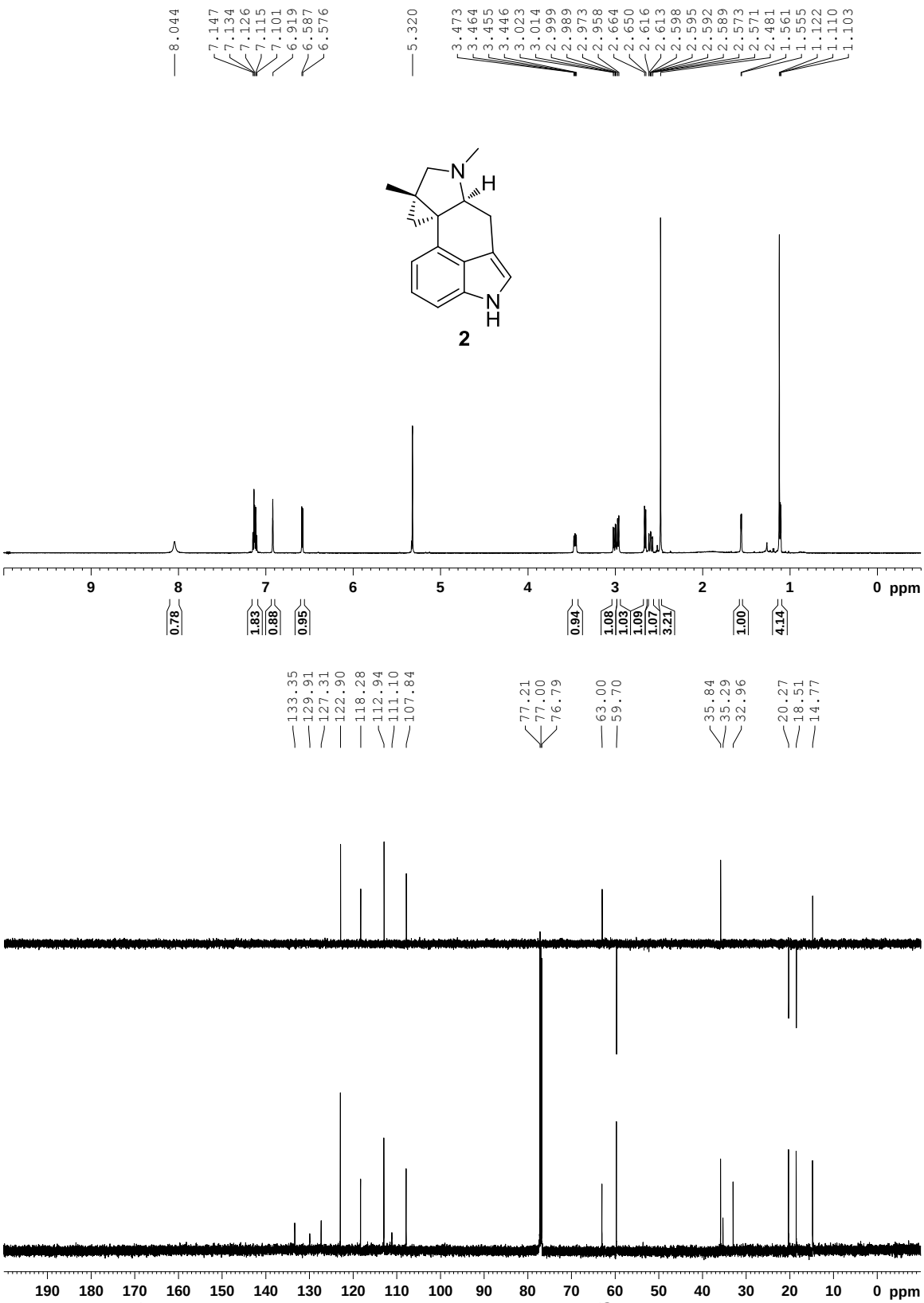
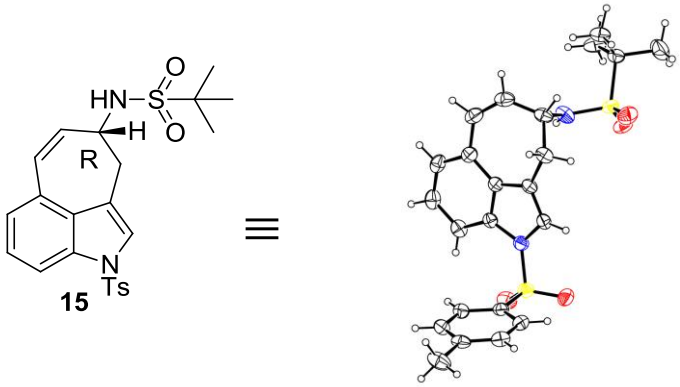
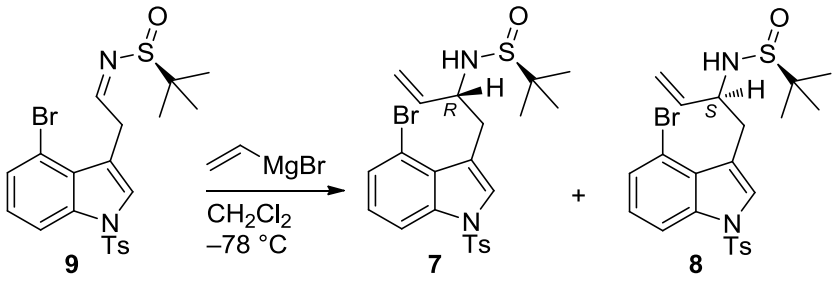


Figure S16. ^{1}H NMR spectrum (CD_2Cl_2, 600 MHz) and ^{13}C NMR spectrum ($CDCl_3$, 150 MHz) of **2**.

10. X-ray structure of compound **15** (CCDC 1882003)

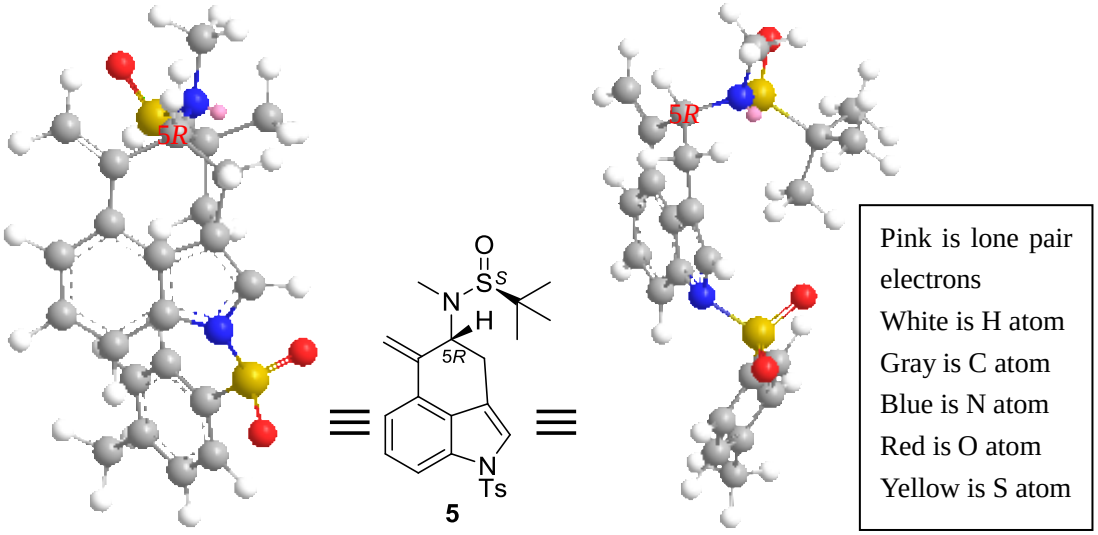


11. Grignard addition on reaction scale

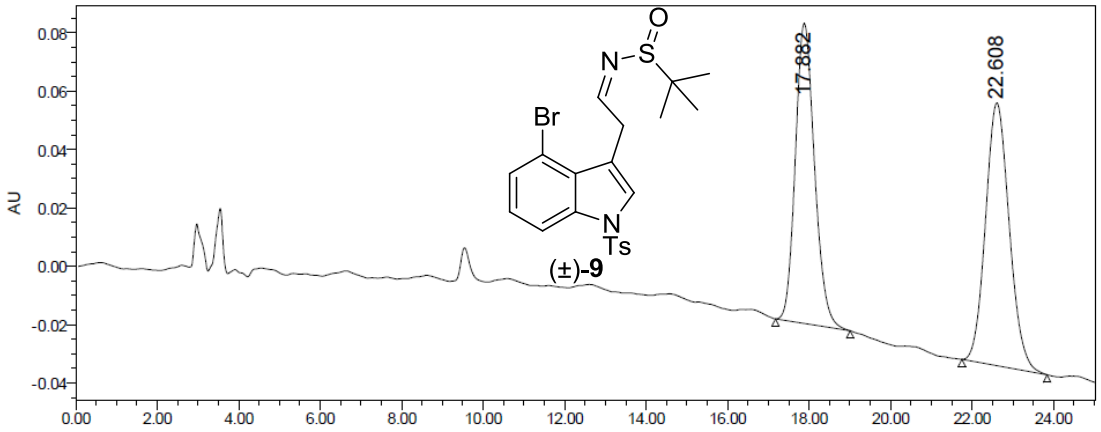


entry	reaction scale	dr
1	0.20 g	1.38 : 1
2	0.50 g	1.50 : 1
3	5.40 g	1.23 : 1
4	20.0 g	1.25 : 1

12. ChemBio 3D of compound **5**



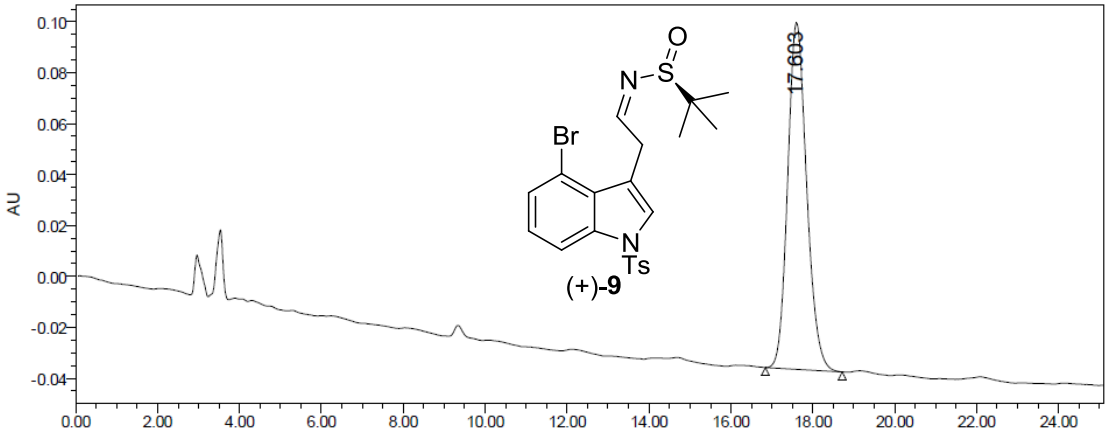
13. HPLC spectra of (±)-**9** and (+)-**9**



min

Channel: 2998; Channel Desc.: 2998 (210-400)nm; Processing Method: weiwang2014

	Channel	Retention Time (time)	Area (μv.s)	% Area	Height (μv)
1	2998 (210-400)nm	17.882	3363954	48.00	102785
2	2998 (210-400)nm	22.608	3644668	52.00	89962



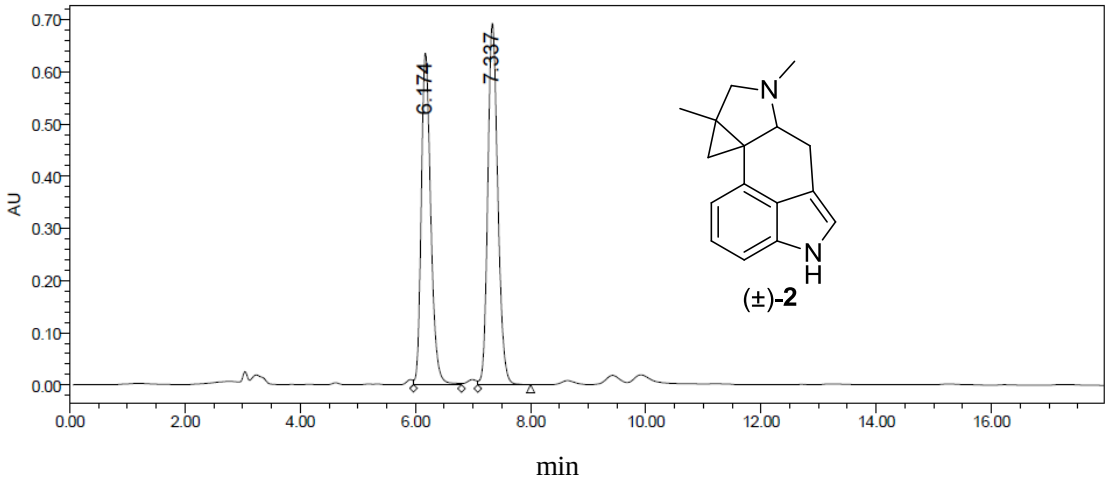
min

Channel: 2998; Channel Desc.: 2998 (210-400)nm; Processing Method: weiwang2014

	Channel	Retention Time (time)	Area (μv.s)	% Area	Height (μv)
1	2998 (210-400)nm	17.603	4388898	100.00	136108

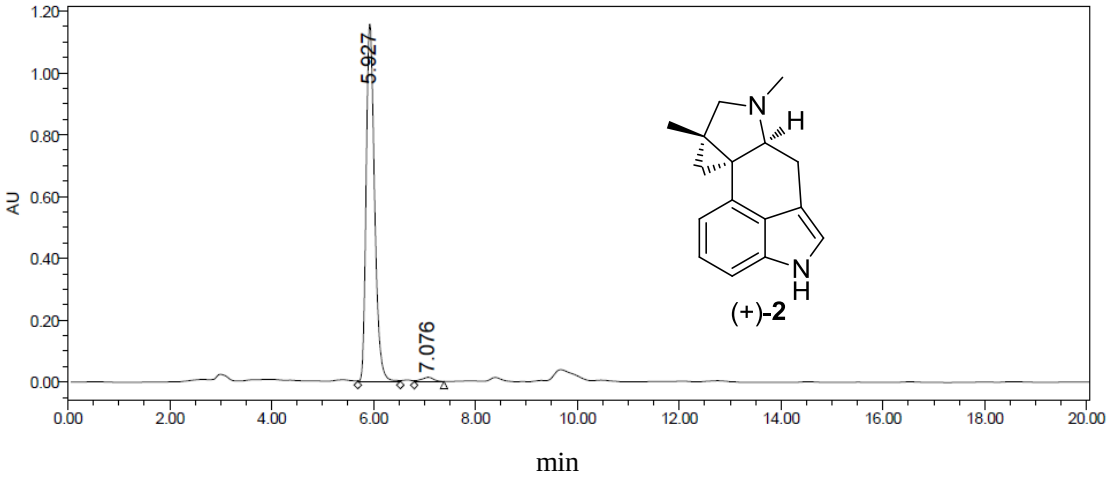
The enantiomeric excess of (+)-**9** was determined using a chiral HPLC (AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1 mL/min). Compound (±)-**9** was prepared as the similar procedure of (+)-**9**.

14. HPLC spectra of (±)-**2** and (+)-**2**



Channel: 2998; Channel Desc.: 2998 (210-400)nm; Processing Method: weiwang2014

	Channel	Retention Time (time)	Area (μv.s)	% Area	Height (μv)
1	2998 (210-400)	6.174	7289839	46.55	635026
2	2998 (210-400)	7.337	8370376	53.45	693045



Channel: 2998; Channel Desc.: 2998 (210-400)nm; Processing Method: weiwang2014

	Channel	Retention Time (time)	Area (μv.s)	% Area	Height (μv)
1	2998 (210-400)	5.927	13238574	98.44	1156576
2	2998 (210-400)	7.076	210050	1.56	13280

The enantiomeric excess of (+)-**2** was determined using a chiral HPLC (AD-H column, *n*-hexane/*i*-PrOH = 90:10, 1 mL/min). Compound (±)-**2** was prepared as the similar procedure of (+)-**2**.