

Total Synthesis of (+)-Raputindole A: An Iridium-catalyzed Cyclization Approach

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Supporting Information

Table of Contents

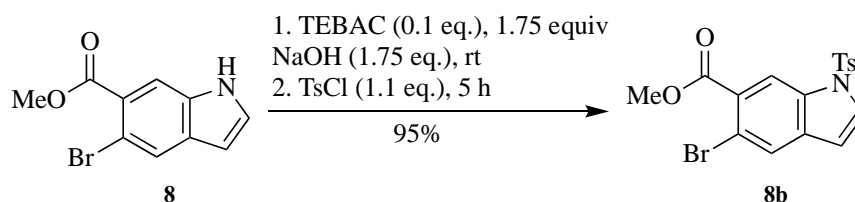
General Experimental	SI2
Synthetic procedures	SI3
References	SI22
NMR Spectra	SI23

General Experimental

All the solvents were kept under a nitrogen atmosphere. Dimethylformamide (DMF) and TMEDA were distilled after 12 hours under 4 Å molecular sieves. Tetrahydrofuran (THF) was distilled under sodium-benzophenone immediately prior to use.¹ Dichloroethane (DCE), dichloromethane (DCM) and trimethylamine (Et₃N) were distilled from calcium hydride under a nitrogen atmosphere prior to use. The other anhydrous solvents were used without further purification, unless otherwise specified. The commercial reagents were used without further purification, unless otherwise stated. Oven-dried syringes were used to transfer the anhydrous solvents. The progress of the reactions was monitored by thin chromatography (TLC) using 0.25 mm E. Merck silica plates 60-F254 or neutral alumina. The visualizing agents were UV light (254 nm), *p*-anisaldehyde, curcumin and/or phosphomolybdic acid stain solutions and heat as developing agents. The purifications of the crude reaction mixtures were carried out using flash silica gel chromatography (Merck, 40-63 µm) under positive pressure. NMR spectra were recorded on Bruker AIII 300 or 500 MHz, Varian Gemini 400 MHz and Bruker AIII 800 MHz equipped with cryoprobe. Chemical shifts (δ) are in parts per million (ppm) and the calibration was performed with reference to residual non-deuterated solvent (CHCl₃ ¹H NMR δ 7.26 ppm, ¹³C NMR 77.0 ppm). The following descriptors were used to describe the NMR data: chemical shift (ppm), multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hertz) and integration. Infrared spectra were recorded on a Thermo Scientific iD3 spectrometer. High resolution mass spectra (HRMS) were recorded in a MicroToF Bruker Daltonics and in an Agilent Technologies 6530 Accurate-Mass Q-TOF LC-MS. The specific optical rotations were measured on a Perkin Elmer 341 polarimeter (sodium line = 589.3 nm).

Synthetic procedures

Methyl 5-bromo-1-tosyl-1*H*-indole-6-carboxylate (**8b**)



To a soln. of indole **8** (1.00 g, 3.94 mmol, 1.0 eq.) in DCM (150 mL) was added TEBAC (0.092 g, 0.39 mmol, 0.1 eq.). Then NaOH (0.276 g, 6.89 mmol, 1.75 eq.) and TsCl (0.826 g, 4.33 mmol, 1.1 eq.) were successively added. The reaction flask was stirred at room temperature for 5 hours. The reaction mixture was quenched with H₂O (50 mL) and 1 M hydrochloric acid (30 mL) and the resulting mixture was stirred for 10 min. The aqueous layer was separated and extracted with 3% methanol/chloroform soln. (3 x 100 mL). The combined organic layer was washed with brine, dried over MgSO₄ and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, 10-20% AcOEt/hexanes) to provide **8b** in 95% yield (1.53 g, 3.75 mmol) as a white solid.

¹H NMR (800 MHz, CDCl₃): δ 8.46 (s, 1 H); 7.81 (s, 1 H); 7.76 (d, J = 8.0 Hz; 2 H); 7.67 (d, J = 4.0 Hz; 1 H); 7.25 (d, J = 8.0 Hz; 2 H); 6.61 (dd, J = 0.8 and 3.2 Hz; 1 H); 3.98 (s, 3 H); 2.36 (s, 3 H).

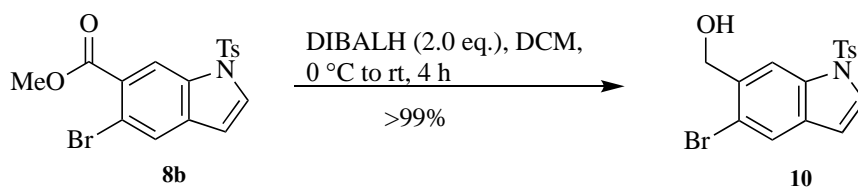
¹³C NMR (200 MHz, CDCl₃): δ 166.7; 145.6; 134.8; 134.3; 133.1; 130.2; 130.0; 127.6; 126.8; 126.7; 116.6; 115.6; 108.0; 52.7; 21.6.

IR (cm⁻¹) 1727; 1593; 1452; 1425; 1403; 1374; 1279; 1222; 1169; 1101; 1010; 982; 930; 889; 864; 815; 768; 727; 708.

HRMS (ESI) m/z [M+H]⁺ Calcd for C₁₇H₁₅NO₄SBr 407.9905; Found 407.9887.

Mp: 155.0-155.8 °C.

(5-Bromo-1-tosyl-1*H*-indol-6-yl)methanol (**10**)



To a flame dried Schlenk flask was added **8b** (0.520 g, 1.28 mmol, 1.0 eq.) and DCM (10 mL). The soln. was cooled to 0 °C and then DIBALH (1M in toluene, 2.54 mL, 2.54 mmol, 2.0 eq.) was slowly added. The reaction mixture was stirred for 1 hour and the temperature was let to reach room temperature. After 3 hours, the reaction was completed by TLC and the reaction temperature was decreased to 0 °C. AcOEt (8 mL) was slowly added, followed by the addition of Rochelle's salt soln. (1M soln., 8 mL, 8 mmol) and Et₂O (40 mL). The reaction mixture was stirred overnight and then the aqueous layer was separated and extracted with 3% MeOH in chloroform soln. (3 x 15 mL). The combined organic layer was washed with brine, dried (MgSO₄) and the solvent was removed under reduced pressure. The product **10** was obtained in >99% yield (0.484 g, 1.27 mmol) as a white solid.

¹H NMR (300MHz, CDCl₃) δ 8.10 (s, 1H); 7.77 (s, 1H); 7.73 (d, J = 9.0 Hz, 2H), 7.57 (d, J = 6.0 Hz, 1H); 7.24 (d, J = 9.0 Hz, 2H); 6.59 (dd, J = 0.3 and 3.6 Hz, 1H); 4.83 (s, 2H); 2.35 (s, 3H).

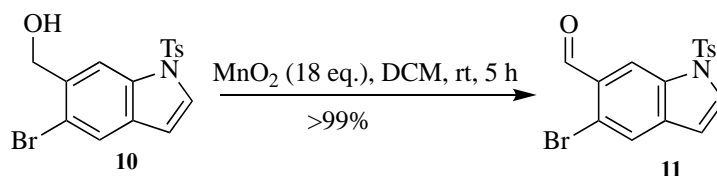
¹³C NMR (126 MHz, d6-(CD₃)₂CO): δ 146.3, 138.0, 135.7, 135.0, 131.8, 130.7, 128.4, 127.5, 125.2, 116.7, 113.4, 108.9, 64.3, 21.2.

HRMS (ESI) *m/z* [M-H₂O+ H]⁺ Calcd for C₁₆H₁₂NO₂SBr 361.9850; Found= 361.9863.

Mp: 136,7 – 139,2 °C.

IR (cm⁻¹): 1411; 1367; 1164; 1123; 1057; 812; 688.

5-Bromo-1-tosyl-1H-indole-6-carbaldehyde (**11**)



In a round bottom flask was added a solution of **10** (1.164 g, 3.063 mmol, 1.0 eq.) in DCM (100 mL). MnO₂ (5.205 g, 55.10 mmol, 18 eq.) was then added and the mixture was stirred for at rt 5 h. The suspension was filtered in a Celite pad and washed with AcOEt (400 mL) After

evaporation under reduced pressure, aldehyde **11** was obtained in >99% yield (1.15 g, 3.06 mmol) as an off-white solid.

¹H NMR (300MHz, CDCl₃): δ 10.42 (s, 1 H); 8.53 (s, 1 H); 7.82-7.76 (m, 4 H); 7.27 (m, 1 H); 7.25 (m, 1 H); 6.64-6.63 (dd, *J*=0.87 and 3.7 Hz; 1 H); 2.35 (s, 3 H).

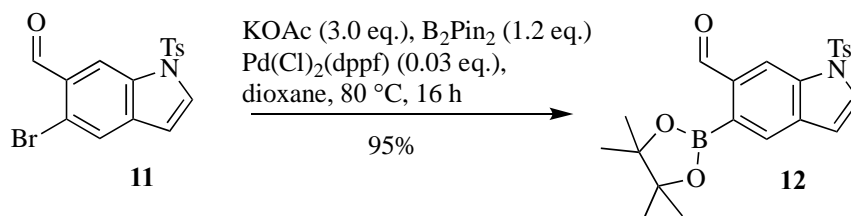
¹³C NMR (75 MHz, CDCl₃): δ 191.7, 145.7, 136.5, 134.6, 133.6, 131.3, 130.2, 129.2, 127.0, 125.9, 120.5, 115.1, 107.7, 21.6.

IR (cm⁻¹): 1686, 1598, 1417, 1276, 1167, 1090, 815, 765, 664.

Mp = 191.0 – 191.3 °C

HRMS (ESI-TOF) *m/z* [M+H]⁺ Calcd for C₁₆H₁₃NO₃SBr 377.9799; Found 377.9779.

5-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)-1-tosyl-1*H*-indole-6-carbaldehyde (12**)**



In a Schlenk flask charged with aldehyde **11** (1.014 g, 2.69 mmol, 1.0 eq.), bis(pinacolato)diboron (0.842 g, 3.22 mmol, 1.2 eq.), KOAc (0.790 g, 8.04 mmol, 3.0 eq.) and Pd(Cl)₂(dppf) (0.059 g, 0.080 mmol, 0.03 eq.) under nitrogen atmosphere was added degassed dioxane (36 mL). The reaction mixture was stirred at 80 °C using an oil bath for 16 hours. After this time, the reaction mixture was cooled to rt and the crude mixture was filtered in a Celite/SiO₂ pad and washed with AcOEt (300 mL). The solvent was removed under reduced pressure and the crude product was purified by flash column chromatography (SiO₂, 10-20% AcOEt/hexanes) to provide **12** in 95% yield (1.05 g, 2.55 mmol) as an off-white thick oil.

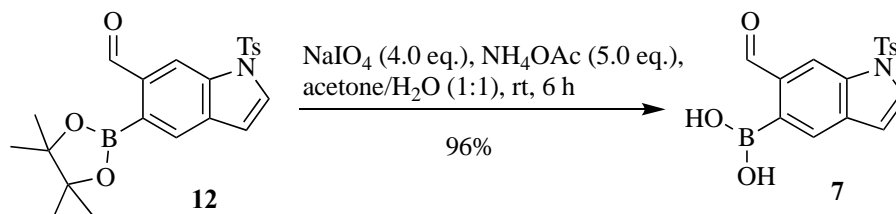
¹H NMR (400MHz, CDCl₃): δ 10.57 (s, 1 H); 8.56 (t, *J* = 0.8 and 1.2 Hz, 1 H); 8.02 (s, 1 H); 7.78 (d, *J* = 8.4 Hz; 2 H); 7.74 (d, *J* = 3.6 Hz; 1 H); 7.22 (d, *J* = 8.4 Hz, 2 H); 6.71 (dd, *J* = 1.2 and 3.6 Hz; 1 H); 2.32 (s, 3 H); 1.39 (s, 12 H).

¹³C NMR (75 MHz, CDCl₃): δ 194.0, 145.4, 137.8, 135.7, 134.8, 134.4, 130.0, 130.0, 129.0, 126.8, 114.0, 108.9, 84.3, 25.0, 24.8, 21.5.

HRMS (ESI) m/z [M+H]⁺ Calcd for C₂₂H₂₅BNO₅S⁺ 426.1541; Found 426.1570.

IR (cm⁻¹): 2978, 1680, 1477, 1455, 1414, 1373, 1331, 1279, 1169, 1120, 974, 853, 675.

(6-Formyl-1-tosyl-1*H*-indol-5-yl)boronic acid (7)



In a round bottom flask was added the aldehyde **12** (0.165 g, 0.388 mmol, 1.0 eq.) dissolved in acetone/H₂O (1:1, v/v,) 8 mL). NaIO₄ (0.333 g, 1.56 mmol, 4.0 eq.) and NH₄OAc (0.150 g, 1.94 mmol, 5.0 eq.) were added and the reaction mixture was stirred 6 h at rt. The solvent was removed under reduced pressure and the product was extracted using a mixture of 5% MeOH/DCM (3 x 10 mL). The combined organic layer was washed with brine, dried over Na₂SO₄ and the solvent was reduced under reduced pressure to provide **7** in 96% yield as an orange solid (0.128 g, 0.373 mmol).

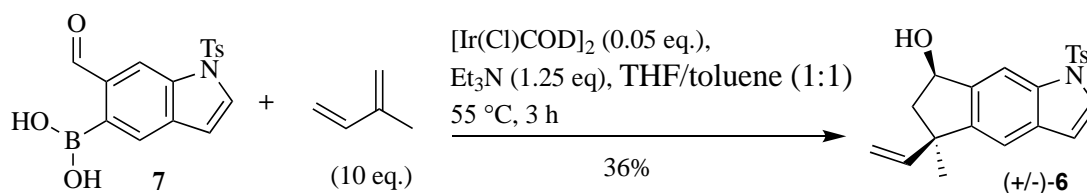
¹H NMR (300 MHz, CDCl₃): δ 9.97 (s, 1H); 8.54 (s, 1H); 8.50 (s, 1H); 7.82 (m, 2H); 7.78 (s, 1H); 7.28 (m, 1 H); 7.18 (s, 1H); 6.81 (m, 1H); 2.37 (s, 3H).

¹³C NMR (75 MHz, d₆-(CD₃)₂CO): δ 196.9, 147.6, 138.6, 136.4, 136.5, 136.3, 132.2, 131.9, 130.4, 128.7, 128.6, 120.3, 111.0, 22.2.

HRMS (ESI) m/z [M-H₂O]⁻ Calcd for C₁₆H₁₃BNO₅S 326.0658; Found 326.0655.

Mp = 135-139 °C.

(5*R*,7*R*) and (5*S*,7*S*)-5-Methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indol-7-ol ((+/-)-6)



A resealable pressured tube equipped with a magnetic stir bar was charged with $[\text{Ir}(\text{Cl})(\text{COD})]_2$ (0.001 g, 0.001 mmol, 0.05 eq.) and degassed toluene (0.3 mL). Et_3N (0.0050 mL, 0.036 mmol, 1.25 eq.) and isoprene (0.030 mL, 0.29 mmol, 10 eq.) were next added by a syringe. In another vessel, a solution of aldehyde **7** (0.010 g, 0.029 mmol, 1.0 eq.) in THF/toluene (0.7 mL, 5:2 v/v) which was cannulated to the resealable tube and the reaction mixture was protect from visible light and the temperature was increased to 55 °C using a heating block. After 3 h (monitored by ^1H NMR) the reaction mixture was allowed to cool to rt and it was concentrated under reduced pressure. The resulting brown mixture was purified by flash column chromatography (SiO_2 , 10-20% EtOAc/hexanes) to provide indole (+/-)-**6** in 36% yield (0.0038 g, 0.010 mmol) as a yellow solid.

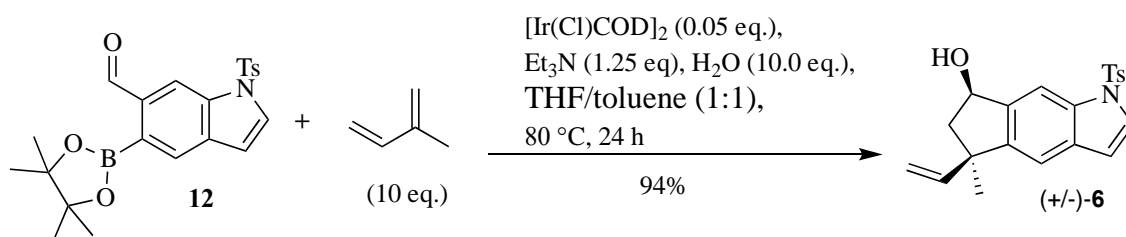
^1H NMR (300 MHz, CDCl_3): δ 8.01 (m, 1H), 7.81 (m, 2H), 7.57 (d, J = 6.0 Hz, 1H), 7.24 (m, 2H), 7.22 (m, 1H), 6.61 (dd, J = 1.5 and 6.0 Hz, 1H), 6.17 (m, 1H), 5.33 (m, 1H), 5.04 (m, 2H), 2.43 (m, 1H), 2.34 (s, 3H), 2.15 (m, 1H), 1.61 (brs, 1H), 1.32 (m, 3H).

^{13}C NMR (126 MHz, CDCl_3): δ 147.5, 144.9, 144.7, 141.7, 135.4, 134.5, 131.7, 129.9, 126.9, 126.8, 116.1, 111.7, 109.5, 108.8, 74.6, 51.0, 47.9, 26.3, 21.6.

HRMS (ESI) m/z [$\text{M}+\text{Na}$] $^+$ Calcd for $\text{C}_{21}\text{H}_{21}\text{NO}_3\text{SNa}$ 390.1134; Found 390.1150.

Mp = 84.1 – 89.9 °C.

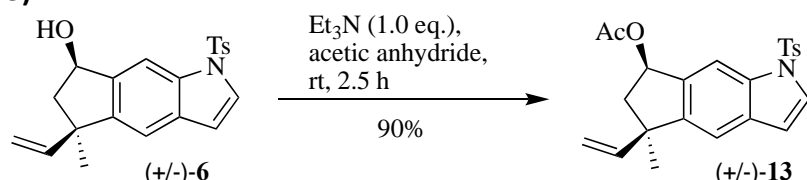
IV (cm^{-1}) = 2359, 2343, 1372, 1167, 1109, 703, 668.



A resealable pressure tube equipped with a magnetic stir bar was charged with $[\text{Ir}(\text{Cl})(\text{COD})]_2$ (0.012 g, 0.017 mmol, 0.05 eq.) and degassed toluene (0.7 mL).² Et_3N (0.060 mL, 0.42 mmol, 1.5 eq.) and isoprene (0.340 mL, 3.34 mmol, 10.0 eq.) were next added via syringe. In another vessel, a solution of pinacol ester **12** (0.142 g, 0.334 mmol, 1.0 eq.) in THF/toluene (3.5 mL, 3:2 v/v) was prepared and cannulated to the resealable reaction tube. Degassed H_2O (0.060 mL, 3.3 mmol) was added. The reaction flask was protected from visible light and the reaction temperature was increased to 80 °C using a heating block. After 24 hours (monitored by ^1H

NMR) the reaction mixture was allowed to cool to rt and concentrated under reduced pressure. The resulting brown mixture was purified by flash column chromatography (SiO₂, 10-20% EtOAc/hexanes) to provide indole (+/-)-**6** in 94% yield (0.116 g, 0.315 mmol) as a yellow solid.

(5*R*,7*R*) and (5*S*,7*S*)-5-Methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indol-7-yl acetate ((+/-)-13**)**



To a solution of indole (+/-)-**6** (0.020 g, 0.054 mmol, 1.0 eq.) in acetic anhydride (1.0 mL) in a round-bottom flask was added Et₃N (0.0080 mL, 0.054 mmol, 1.0 eq.). After 2.5 h of stirring, the mixture was diluted with diethyl ether (3 mL) and washed with saturated NaHCO₃ (2 x 3 mL). The organic layer was dried over MgSO₄ and the solvent was removed under reduced pressure to provide (+/-)-**13** as a yellow oil (0.020 g; 0.049 mmol) in 90% yield.⁴

¹H NMR (500 MHz, CDCl₃): δ 7.97 (s, 1H), 7.81 (d, *J* = 8.5 Hz, 2H), 7.58 (d, *J* = 3.5 Hz, 1H), 7.27 (m, 3H), 6.62 (dd, *J* = 0.5, 3.5 Hz, 1H), 6.31 (m, 1H), 6.12 (m, 1H), 5.08 (m, 2H), 2.50 (m, 1H), 2.37 (s, 3H), 2.24 (s, 1H), 2.13 (s, 3H) 1.38 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ (ppm): 166.38, 146.2, 145.8, 144.9, 137.3, 135.3, 134.3, 132.2, 129.9, 127.1, 127.0, 115.9, 111.2, 110.4, 108.7, 76.4, 48.1, 47.5, 26.3, 22.2, 21.4.

(5*R*,7*R*)-5-Methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indol-7-ol ((*R*,*R*)-6**) and (5*S*,7*S*)-5-methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indol-7-yl acetate ((*S*,*S*)-**13**)**

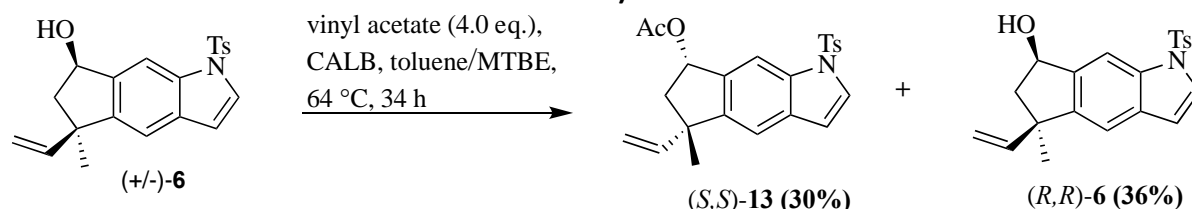


Table 1. Optimization of enzymatic resolution.

Entry	Solvent	CALB (eq.)	Time (h)	Conversion	<i>e.e.</i>
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1	Toluene	1.2	17	25	>99%
2	Toluene:MTBE (4:1)	1.2	17	37.5	>99%
3	Toluene:MTBE (4:1)	1.2	34	47.5	>99%
4	Toluene:MTBE (4:1)	2.0	17	40	>99%
5	Toluene:MTBE (4:1)	2.0	34	50	>99%
6	Toluene:MTBE (4:1)	2.0	34	50 (30/36) ^a	>99%

^a yields of (*S,S*)-**13**/*(R,R)*-**6**.

To a magnetically stirred solution of alcohol (+/-)-**6** (0.080 g, 0.22 mmol, 1.0 eq.) in a toluene/MTBE mixture (6.40 mL, 8:2 v/v) was added CALB (0.160 g, 2.0 g/g alcohol). The reaction mixture was warmed to 64 °C using a heating block and after 15 minutes, vinyl acetate (0.080 mL, 0.87 mmol, 4.0 eq.) was added. After 34 h, the reaction mixture was allowed to cool to rt. The solids were filtered off and washed with EtOAc (40 mL) and DCM (40 mL). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (SiO₂, 5-30% EtOAc/hexanes). The enantiomerically pure acetylated product (*S,S*)-**13** was isolated in 30% yield (0.0264 g, 0.064 mmol) as a colorless thick oil and the enantiomerically pure alcohol (*R,R*)-**6**, in 36% yield (0.029 g, 0.079 mmol) as a white viscous oil. The enantiomeric excess (ee) of 99% was determined by HPLC using an analytical column Chiralpak IA.

(5*R*,7*S*)-7-allyl-5-methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indole (Ia) and (5*R*,7*R*)-7-allyl-5-methyl-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indole (Ib)

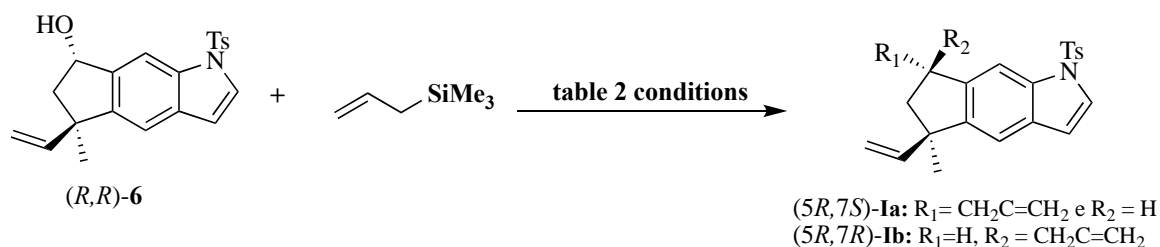


Table 2. Screening of Lewis acids in the allylation reaction.

Entry	Lewis Acid	Loading catalyst (mmol)	Time (h)	Ratio Ia:Ib	Yield (%)
1	InCl ₃	20	27	1:4	52
2	BiBr ₃	10	1.5	1:3	66
3	FeCl ₃	10	1.5	-	complex mixture

A All the reactions were carried out at rt and using DCE^b as the solvent.

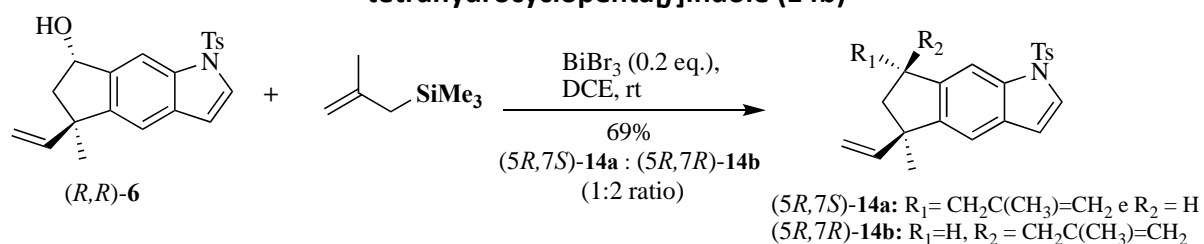
To a resealable pressure tube charged with Lewis Acid under nitrogen atmosphere was added a solution of indole (5*R*,7*R*)-**6** and allyltrimethylsilane in DCE. After 1 hour under stirring at room temperature, the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (SiO₂, 5% EtOAc/hexanes) to provide an unseparable 1:2 mixture of (5*R*,7*S*)-**1a** and (5*R*,7*R*)-**1b** in yields as indicated in table 2.

¹H NMR (CDCl₃, solvent) for (5*R*,7*S*)-1a** and (5*R*,7*R*)-**1b**:** δ 7.81 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.49 (d, *J* = 3.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.15 (s, 1H), [6.56, d, *J* = 4.0 Hz (major) and 6.59, d, *J* = 4.0 Hz (minor), 1H], 6.02 (m, 1H), 5.90 (m, 1H), 5.11 (m, 4H), [3.40, m (major) and 3.29, m (minor), 1H], 2.74 (m, 1H), 2.35 (s, 3H), 2.32 (m, 1H), 2.14 (m, 1H), 1.85 (m, 1H), 1.27 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 147.0, 146.3, 144.8, 143.2, 136.9, 135.4, 134.4, 129.8, 126.9, 125.9, 125.9, 116.2, 115.7, 111.6, 108.9, 108.6, 48.5, 47.2, 41.5, 39.2, 25.6, 21.5.

HRMS (ESI) *m/z*[M+H]⁺ Calcd for C₂₄H₂₆NO₂S 392.1679; Found 392.1676.

(5*R*,7*S*)-5-Methyl-7-(2-methylallyl)-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indole (14a**) and (5*R*,7*R*)-5-Methyl-7-(2-methylallyl)-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indole (**14b**)**



To a resealable pressure tube charged with BiBr₃ (0.031 g, 0.069 mmol, 0.2 eq.) under nitrogen atmosphere was added a solution of indole (*R,R*)-**6** (0.127 g, 0.345 mmol, 1.0 eq.)

and methallylsilane³ (0.12 mL, 0.69 mmol, 2.0 eq.) in DCE (1.7 mL). After 1 hour under stirring at room temperature the reaction mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography (SiO₂, 5% EtOAc/hexanes) to provide a 1:2 mixture of (5*R*,7*S*)-**14a** and (5*R*,7*R*)-**14b** in 69% yield (0.096 g, 0.24 mmol) as a colorless viscous oil.

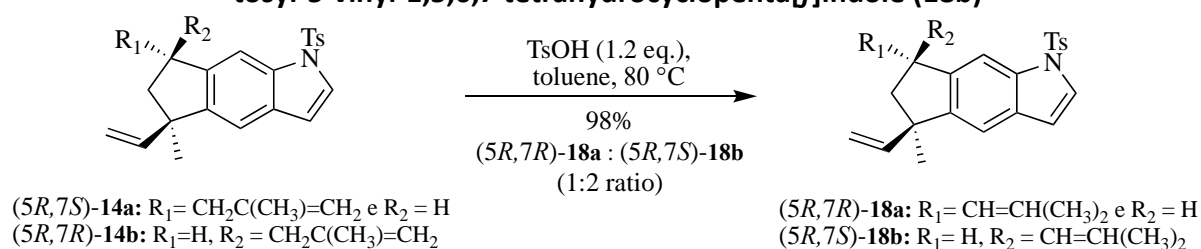
¹H NMR (5*R*,7*S*)-14a** and (5*R*,7*R*)-**14b**:** δ 7.82 (s, 1 H), 7.78 (d, *J* = 8.5 Hz, 2 H), 7.50 (m, 1 H), 7.24 (m, 3 H), [6.57, m (major) and 6.59, m (minor), 1H], [6.05, m (major) and 5.97 m (minor), 1H], 5.11 (m, 2H), 4.88 (m, 2 H), [3.50 m (major) and 3.38 m (minor), 1H], 2.70 (dd, *J* = 6.0 and 14.5 Hz, 1H), 2.35 (s, 3 H), 2.32 (m, 1H), 2.19 (m, 2H), 1.87 (s, 3 H), 1.28 (s, 3 H).

¹³C NMR (126 MHz, CDCl₃) δ (ppm): 147.1, 146.2, 146.2, 144.7, 144.3; 143.7, 135.5, 134.4, 129.8, 126.9, 125.9, 115.6, 111.8, 111.6, 108.9, 108.6, 48.4, 47.6, 43.9, 39.7, 25.7, 22.5, 21.5.

HRMS (ESI) *m/z*[M+H]⁺ Calcd for C₂₅H₂₈NO₂S 406.1841; Found 406.1822.

IV (cm⁻¹): 2964, 2914, 2857, 1634, 1595, 1494, 1441, 1370, 1340, 1285, 1230, 1183, 1167, 1120, 1092, 999, 919, 878, 806, 732, 702, 672

(5*R*,7*R*)-5-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-vinyl-1,5,6,7-tetrahydrocyclopenta[*f*]indole (18a**) and (5*R*,7*S*)-5-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-vinyl-1,5,6,7 tetrahydrocyclopenta[*f*]indole (**18b**)**



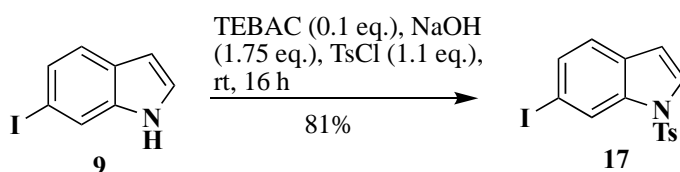
To a 1:2 mixture of indoles **14a** and **14b** (0.0960 g, 0.237 mmol, 1.0 eq.) in a resealable pressure tube was added dry toluene (8 mL). Then TsOH (0.050 g, 0.28 mmol, 1.2 eq.) was added and the temperature was increased to 80 °C using an oil bath. The reaction progress was accompanied by ¹H NMR and after 4 h, the reaction mixture was cooled to rt and concentrated under reduced pressure. The crude product was treated with satd. aq. NaHCO₃ soln. (10 mL) and extracted with EtOAc (3 x 15 mL). The mixture of products (5*R*,7*R*)-**18a** and (5*R*,7*S*)-**18b** was obtained as a brown viscous oil in 98% yield (0.0945 g, 0.233 mmol) and used in the next step without purification.

¹H NMR ((5*R*,7*R*)-18a** and (5*R*,7*S*)-**18b**):** δ 7.75 (m, 3H), 7.60 (s, 1H), 7.48 (d, J = 4.0 Hz, 1H), 7.22 (m, 2H), 7.14 (s, 1H), [6.59 m(minor) and 6.56 m (major), 1H], [6.05 m (major) and 6.00 m (minor), 1H], 5.17 (m, 1H), 5.11 (m, 1H), 4.15 m (major) and 4.02 m (minor), 1H], 2.35 (s, 3H), 2.16 (m, 1H), 1.86 (m, 1H), 1.86 (s, 6H), 1.30 (s, 3H).

¹³C NMR (126 MHz, CDCl₃) δ (ppm): 146.6, 146.1, 144.7, 143.6, 135.4, 134.4, 133.1, 130.1, 129.7, 127.7, 127.0, 125.8, 115.4, 111.7, 109.3, 108.9, 48.9, 48.7, 41.5, 25.9, 24.9, 21.5, 18.3.

IV (cm⁻¹): 2961, 2923, 2860, 1639, 1598, 1458, 1439, 1367, 1342, 1290, 1238, 1189, 1169, 1114, 1032, 996, 908, 883, 883, 809, 760, 732, 699, 669.

6-Iodo-1-tosil-1H-indol (**17**)



To a solution of indole **9** (0.854 g, 3.51 mmol, 1.00 eq.) in DCM (35 mL) was added TEBAC (0.080 g, 0.35 mmol, 0.10 eq.). Then, NaOH (0.203 g, 6.15 mmol, 1.75 eq.) and TsCl (0.734 g, 3.864 mmol, 1.10 eq.) were added. The reaction mixture was stirred at room temperature for 16 h and quenched with H₂O (50 mL) and of 1 M HCl (30 mL). After stirring for 10 min, the aqueous layer was separated and extracted with DCM (3 x 100 mL). The organic layer was washed with brine, dried over MgSO₄ and evaporated under reduced pressure. The resulting residue was purified by flash column chromatography (SiO₂, 5-10% AcOEt/hexanes) to provide **17** (1.14 g, 2.87 mmol) in 82% yield as a yellow solid.

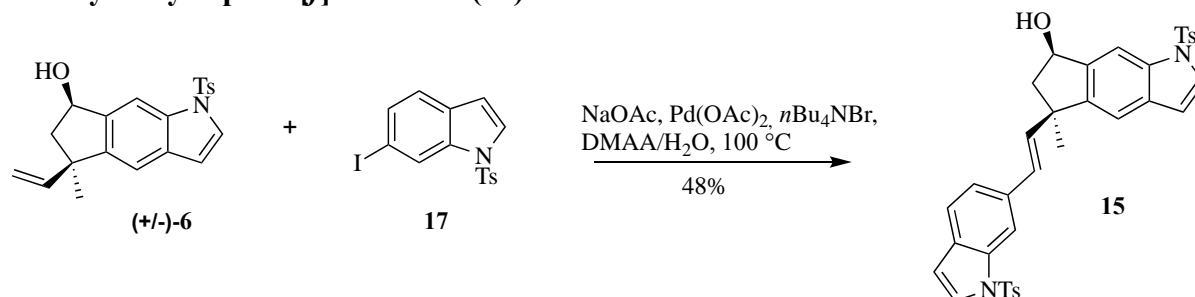
¹H NMR (300 MHz, CDCl₃): δ 8.36 (t, J = 6.6 Hz, 1 H), 7.75 (d, J = 8.4 Hz, 2 H), 7.52 – 7.47 (m, 2 H), 7.27 – 7.22 (m, 3 H), 6.61 (dd, J = 3.9 and 0.9 Hz, 1 H), 2.34 (s, 3 H).

¹³C NMR (75 MHz, CDCl₃): δ 145.2, 135.7, 135.0, 132.2, 130.0, 129.9, 126.7, 126.5, 122.8, 122.3, 108.7, 88.7, 21.5.

HRMS (ESI) m/z [M+H]⁺ Calcd for C₁₅H₁₃INO₂S 397.9707; Found 397.9708.

Mp = 124.8 - 125.3 °C.

(5*R*,7*R*)-5-Methyl-1-tosyl-5-((*E*)-2-(1-tosyl-1*H*-indol-6-yl)vinyl)-1,5,6,7-tetrahydrocyclopenta[*f*]indol-7-ol (15**)**



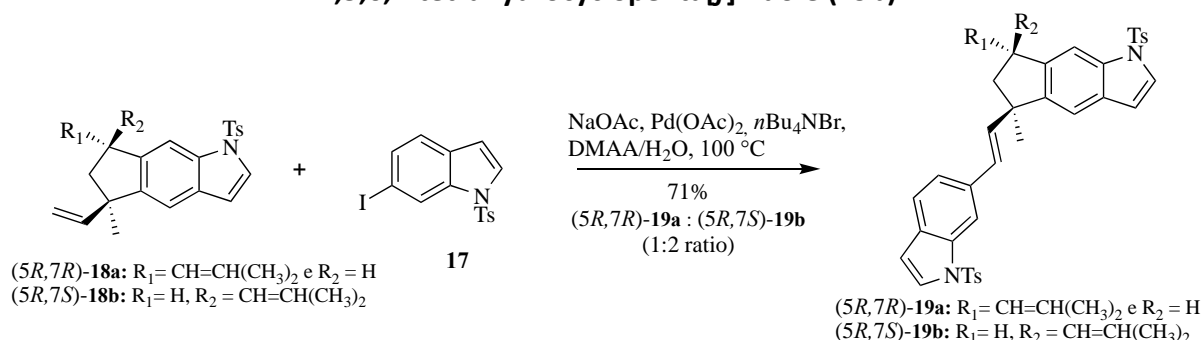
To a dried round bottom flask charged with the tricyclic indole (+/-)-**6** (0.030 g, 0.082 mmol, 1.00 eq.), *N*-tosyl 6-iodo-indole **17** (0.065 g, 0.16 mmol; 2.0 eq.), NaOAc (0.013 g, 0.16 mmol, 2.0 eq.), Pd(OAc)₂ (0.002 g, 0.008 mmol, 0.1 eq.) and *n*-Bu₄NBr (0.0060 g, 0.016 mmol, 0.20 eq.). Degassed DMAA/H₂O (0.96 mL, 9:1, v/v) was added under a nitrogen atmosphere and the reaction mixture was kept under stirring at 100 °C using an oil bath for 12 h. After that, the reaction mixture was allowed to reach rt and quenched by the addition of H₂O (2 mL), extracted with DCM (3 x 5 mL), washed with saturated solution of NaHCO₃ (30 mL) and brine (40 mL). The combined organics were dried over MgSO₄, filtered and the solvent was removed by reduced pressure. The crude product was purified by flash column chromatography (SiO₂, 5-10% AcOEt/hexanes) to furnish tosyl indole **15** (0.025 g, 0.039 mmol) in 48% yield as a yellow oil.

¹H NMR (500 MHz, CDCl₃): δ 8.05 (m, 1H), 7.91 (m, 1H), 7.82 (m, 2H), 7.73 (m, 2H), 7.59 (d, J = 3.5 Hz, 1H), 7.49 (d, J = 4.0 Hz, 1H), 7.41 (m, 1H), 7.32 (s, 1H), 7.29 (dd, J = 1.5 and 8.0 Hz, 1H), 7.25 (m, 2H), 7.21 (m, 2H), 6.63 (dd, J = 0.8 and 3.6 Hz, 1H), 6.59 (dd, J = 0.65 and 3.65 Hz, 1H), 6.56 (d, J = 16.1 Hz, 1H), 6.49 (d, J = 16.1 Hz, 1H), 5.38 (t, J = 6.2 Hz, 1H), 2.55 (m, 1H), 2.35 (s, 3H), 2.33 (s, 3H), 2.26 (m, 1H), 1.47 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 144.9, 144.9, 141.7, 139.0, 135.4, 135.4, 135.4, 134.6, 134.2, 131.8, 130.0, 130.0, 127.4, 126.9, 126.7, 126.6, 121.4, 121.3, 116.3, 111.7, 109.5, 109.1, 108.8, 75.0, 74.5, 51.7, 47.5, 27.0, 24.8, 21.6, 21.5.

HRMS (ESI-TOF) *m/z*[M+H-H₂O]⁺ Calcd for C₃₆H₃₁N₂O₄S₂ 619.1720; Found 619.1710.

(5*R*,7*R*)-5-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-((*E*)-2-(1-tosyl-1*H*-indol-6-yl)vinyl)-1,5,6,7-tetrahydrocyclopenta[*f*]indole (19a) and
(5*R*,7*S*)-5-methyl-7-(2-methylprop-1-en-1-yl)-1-tosyl-5-((*E*)-2-(1-tosyl-1*H*-indol-6-yl)vinyl)-1,5,6,7-tetrahydrocyclopenta[*f*]indole (19b)



To a dried round bottom flask charged with a 1:2 mixture of tricyclic indoles **18a** and **18b** (0.0080 g, 0.020 mmol, 1.0 eq.), iodoindole **17** (0.016 g, 0.039 mmol; 2.0 eq.), NaOAc (0.0030 g, 0.039 mmol, 2.0 eq.), Pd(OAc)₂ (0.044 g, 0.0020 mmol, 0.10 eq.) and *n*-Bu₄NBr (0.001 g, 0.004 mmol, 0.2 eq.) was added degassed DMAA/H₂O (0.5 mL, 9:1, v/v) under nitrogen atmosphere and the reaction mixture was kept under stirring at 100 °C using an oil bath for 22 h. After that, the reaction mixture was allowed to reach rt and quenched with H₂O (1 mL) extracted with DCM (3 x 5 mL), washed with saturated solution of NaHCO₃ (15 mL) and brine (20 mL), dried over MgSO₄, filtered and the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (SiO₂, 5-10% AcOEt/hexanes) to furnish a mixture of diastereomers (5*R*,7*R*)-**19a** and (5*R*,7*S*)-**19b** (0.0096 g, 0.014 mmol), in 71% yield, as a yellow solid.

The diastereoisomers were separated by preparative HPLC using a chiral column Chiralpak® IA (21 x 250 mm, 5 μm, 3:97 v/v, *i*-PrOH/hexanes, isocratic mode, flow 12.6 mL/min, UV detection at 291 nm).

Minor isomer (5*R*,7*R*)-**19a**

¹H NMR (400 MHz, CDCl₃): δ 7.83 (s, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.72 (d, *J* = 8.4 Hz, 2H), 7.65 (s, 1H), 7.54 (d, *J* = 3.6 Hz, 1H), 7.47 (d, *J* = 3.6 Hz, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.31 (s, 1H), 7.23 (m, 5H), 6.64 (dd, *J* = 0.8 and 3.6 Hz, 1H), 6.57 (dd, *J* = 0.8 and 3.6 Hz, 1H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.10 (d, *J* = 16.0 Hz, 1H), 5.18 (m, 1H), 4.09 (m, 1H), 2.47 (m, 1H), 2.35 (d, *J* = 10.4 Hz, 6H), 1.88 (s, 3H), 1.84 (s, 3H), 1.84 (m, 1H), 1.25 (s, 3H).

¹³C NMR (126 MHz, CDCl₃): δ 144.9, 144.8, 144.7, 144.4, 138.1, 135.4, 135.4, 135.4, 134.5, 134.5, 133.4, 130.1, 129.9, 129.8, 129.7, 127.7, 127.0, 126.7, 126.6, 126.4, 125.8, 121.5, 121.1, 115.8, 111.5, 109.2, 109.1, 109.0, 49.6, 48.5, 41.2, 26.9, 25.9, 21.6, 21.5, 18.4.

IV (cm⁻¹): 3896, 3849, 3838, 3747, 3742, 3497, 3494, 3472, 1450, 1433, 1367, 1169, 1117, 1090, 996, 881, 809, 732, 696.6.

HRMS (ESI) *m/z*[M+H]⁺ of 19a and 19b Calcd for C₄₀H₃₉N₂O₄S₂ 675.2351; Found 675.2313.

Mp: 106.7-109.1 °C.

Major isomer (5*R*,7*S*)-19b

¹H NMR (400 MHz, CDCl₃): δ 7.96 (s, 1H), 7.76 (m, 4H), 7.65 (s, 1H), 7.50 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 1H), 7.34 (dd, *J* = 1.6, 8.4 Hz, 1H), 7.22 (m, 5H), 6.65 (d, *J* = 16.0, 1H), 6.60 (dd, *J* = 0.8, 3.6 Hz, 1H), 6.56 (dd, *J* = 0.8, 3.6 Hz, 1H), 6.49 (d, *J* = 16, 1H), 5.22 (m, 1H), 4.23 (m, 1H), 2.36 (d, *J* = 9.6 Hz, 6H), 2.30 (m, 1H), 2.00 (m, 1H), 1.89 (d, *J* = 1.2 Hz, 6H), 1.45 (s, 3H).

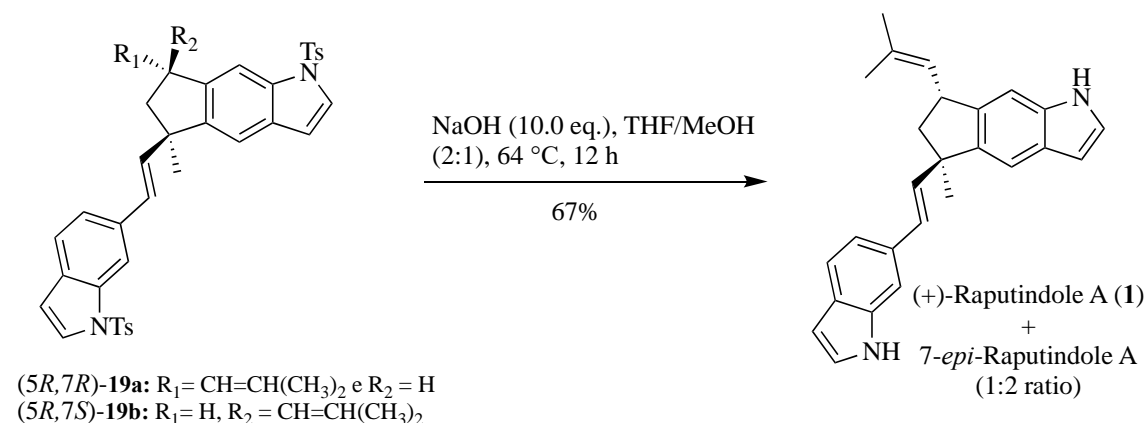
¹³C NMR (126 MHz, CDCl₃): δ 146.2, 144.9, 144.8, 143.6, 143.5, 138.6, 135.4, 135.4, 134.6, 134.5, 133.3, 130.2, 129.9, 129.9, 127.6, 127.4, 127.0, 126.7, 126.5, 125.9, 121.4, 121.3, 114.4, 115.6, 111.6, 109.4, 109.1, 108.9, 49.4, 48.5, 41.6, 25.9, 25.6, 21.6, 21.5, 18.4.

HRMS (ESI) *m/z*[M+H]⁺ of 19a and 19b Calcd for C₄₀H₃₉N₂O₄S₂ 675.2351; Found 675.2313.

Mp: 104.2-109.2 °C.

IV (cm⁻¹): 3846, 3830, 3813, 3791, 1436, 1373, 1271, 1172, 1114, 1092, 1026, 1002, 966, 848, 812, 719, 699.

(5*R*,7*R*)-5-((*E*)-2-(1*H*-Indol-6-yl)vinyl)-5-methyl-7-(2-methylprop-1-en-1-yl)-1,5,6,7-tetrahydrocyclopenta[*f*]indole (1)



To a solution of bisindole mixture **19a:19b** (0.055 g, 0.081 mmol, 1.0 eq.) dissolved in a mixture of MeOH/THF (1.2 mL, 2:1, v/v) was added NaOH (0.036 g, 0.81 mmol, 10 eq.). The reaction mixture was warmed to 64 °C using a heating block and stirred during 12 h. Upon completion of the reaction, the organic solvent was removed under reduced pressure and H₂O was added (1 mL). The mixture was extracted with EtOAc (3 x 3 mL) and the combined organic layer was washed with brine (10 mL). After drying over MgSO₄, the solvent was removed under reduced pressure and the residue was purified by column chromatography (activated neutral alumina, 5-20% EtOAc/hexanes) to provide raputindole A (**1**), as the minor isomer, together with its C-6 epimer (1:2 ratio), in 67% yield (0.020 g, 0.055 mmol) as a yellow oil. The diastereoisomers were separated by preparative HPLC using a chiral column Chiralpak® IA (21 x 250 mm, 5 µm, 12:88 v/v, *i*-PrOH/hexane, isocratic mode, flow 12.6 mL/min, UV detection at 291 nm). Pure (+)-raputindole A (**1**) {[α]²²_D = +76 (c 0.10, MeOH, 20 °C)} was isolated (R_T = 32.11 min) and its C-6 epimer (R_T = 36.73 min) both as colorless oil.

(+)-Raputindole A (**1**)

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 8.04 (br s, 1H, H-1'), 8.02 (br s, 1H, H-1''), 7.50 (d, *J* = 8.25, 1H, H-4''), 7.44 (s, 1H, H-4'), 7.26 (s, 1H, H-7''), 7.17 (t, *J* = 2.45, 1H, H-2'), 7.15 (m, 1H, H-5''), 7.13 (m, 1H, H-2''), 7.08 (s, 1H, H-7'), 6.53 (m, 1H, H-3'), 6.47 (m, 1H, H-3''), 6.45 (d, *J* = 15.9, 1H, H-2), 6.15 (d, *J* = 16.9, 1H, H-1), 5.22 (d, *J* = 9.0, 1H, H-7), 4.07 (m, 1H, H-6), 2.44 (dd, *J* = 6.85 and 12.1, 1H, H-5β), 1.82 (m, 1H, H-5α), 1.82 (d, 3H, *J* = 1.4, H-9), 1.79 (d, 3H, *J* = 1.3, H-10), 1.61 (s, 3H, H-4).

¹³C NMR (800 MHz, CDCl₃) δ (ppm) = 142.2 (C-6'), 141.5 (C-5'), 137.2 (C-2), 136.2 (C-7''a), 135.7 (C-7'a), 132.6 (C-8), 132.2 (C-6''), 128.3 (C-7), 127.2 (C-3'a), 127.0 (C-3''a), 126.8 (C-1), 124.3 (C-2''), 123.7 (C-2'), 120.5 (C-4''), 118.5 (C-5''), 115.0 (C-4'), 108.9 (C-7''), 106.2 (C-7'), 102.6 (C-3''), 102.5 (C-3'), 49.9 (C-5), 48.4 (C-3), 41.0 (C-6), 27.2 (C-4), 25.9 (C-9), 18.3 (C-10).

HRMS (ESI) *m/z* [M+H⁺] Calcd for C₂₆H₂₇N₂ 367.2174; Found 367.2166.

[α]²²_D = +76 (c 0.10, MeOH, 20 °C)

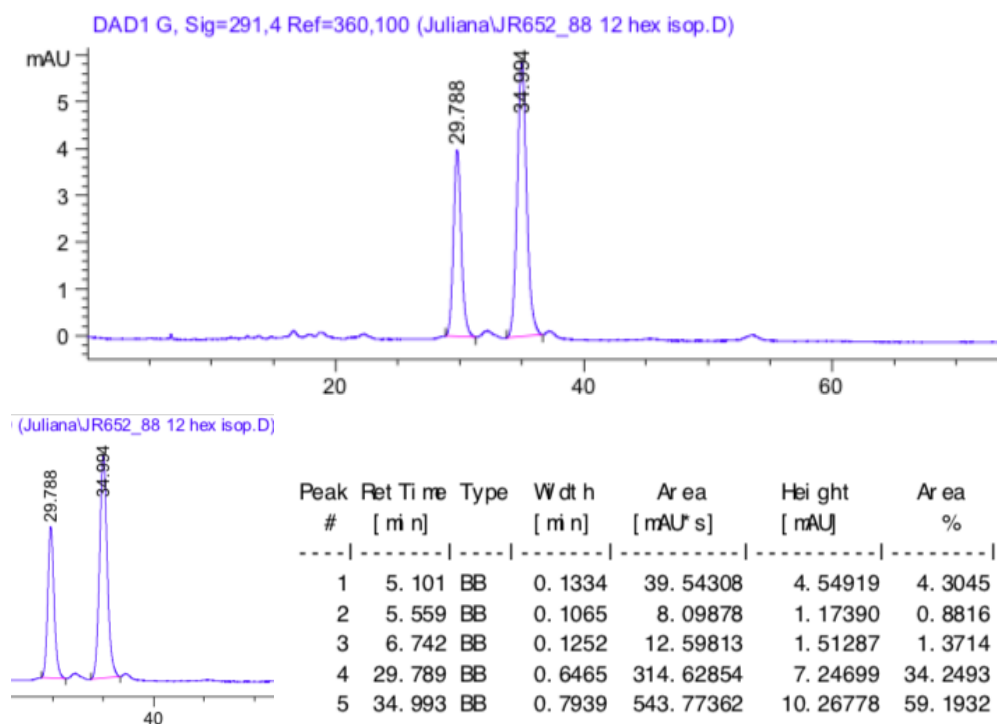


Figure 3. HPLC chromatogram of mixture (+)-raputindole A (**1**) and 7-*epi*-raputindole A. Chiral column Chiralpak® IA (4.6 x 250 mm, 5 μ m, 12:88 v/v, *i*-PrOH/hexane, isocratic mode, flow 0.6 mL/min, UV detection at 291 nm).

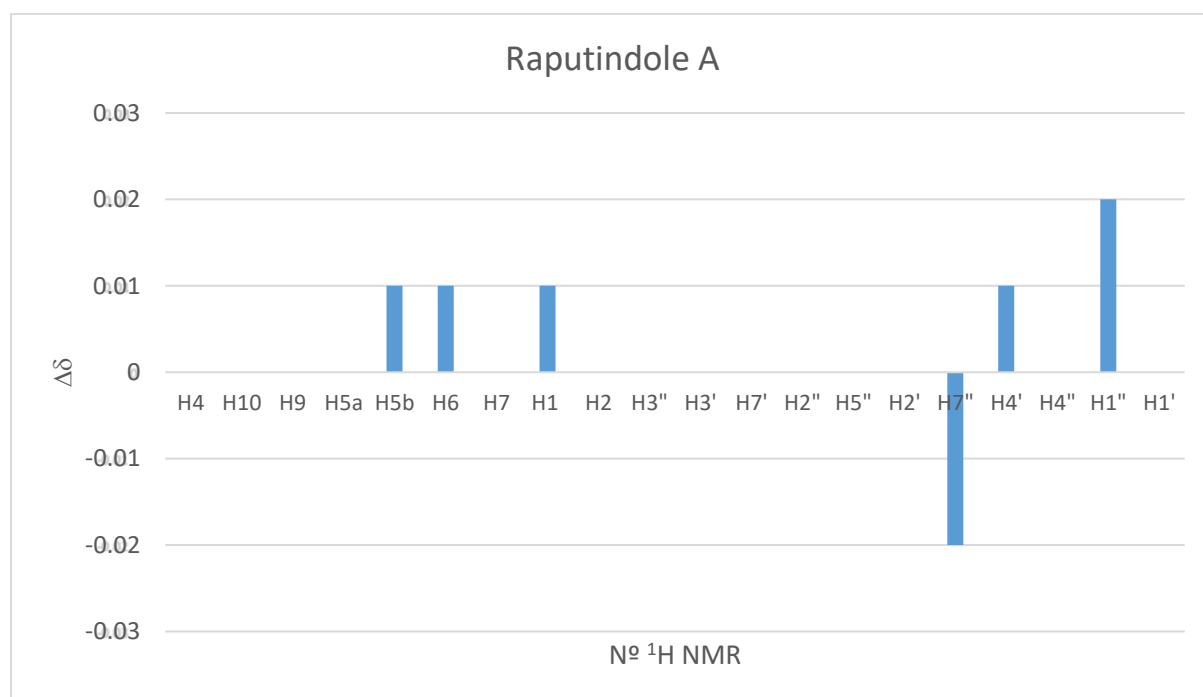


Figure 4. Differences δ (ppm) between ^1H NMR (+)-raputindole A (**1**) synthetic and natural.

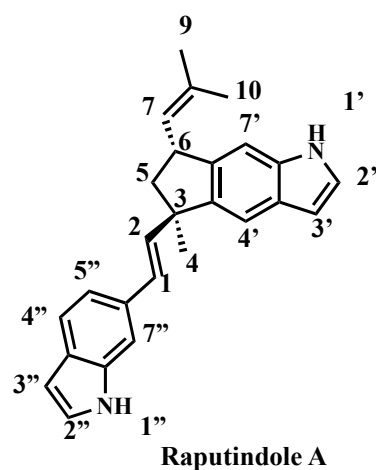


Figure 5. Numbering of Hydrogens.

Table 2. Comparison of ^1H NMR chemical shifts of synthetic and natural (+)-raputindole A (**1**), in ppm.

Hydrogen	Natural	JR670	(Nat – JR670)
H4	1,61	1,61	0
H10	1,79	1,79	0
H9	1,82	1,82	0
H5a	1,82	1,82	0
H5b	2,45	2,44	0,01
H6	4,08	4,07	0,01
H7	5,22	5,22	0
H1	6,14	6,15	0,01
H2	6,45	6,45	0
H3''	6,47	6,47	0
H3'	6,53	6,53	0
H7'	7,08	7,08	0
H2''	7,13	7,13	0
H5''	7,15	7,15	0
H2'	7,17	7,17	0
H7''	7,24	7,26	-0,02
H4'	7,45	7,44	0,01
H4''	7,5	7,5	0

H1''	8	8,02	0,02
H1'	8,04	8,04	0

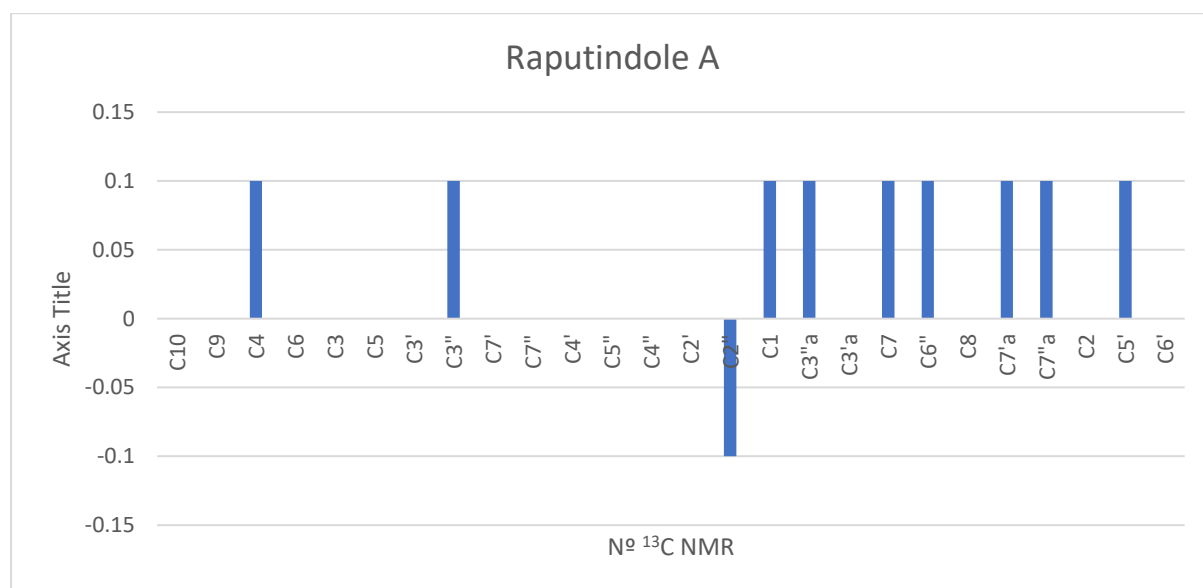


Figure 5. Differences δ (ppm) between ^{13}C NMR (+)-raputindole A (**1**) synthetic and natural.

Table 3. Comparison of ^{13}C NMR chemical shifts of (+)-raputindole A (**1**) synthetic and natural in ppm.

Carbon	Natural	JR670	(Nat – JR670)
C10	18,3	18,3	0
C9	25,9	25,9	0
C4	27,20	27,1	0,1
C6	41	41	0
C3	48,4	48,4	0
C5	50	50	0
C3'	102,6	102,5	0
C3''	102,7	102,6	0,1
C7'	106,2	106,2	0
C7''	108,9	108,9	0
C4'	115	115	0
C5''	118,5	118,5	0

C4''	120,5	120,5	0
C2'	123,7	123,7	0
C2''	124,2	124,3	-0,1
C1	126,9	126,8	0,1
C3''a	127,1	127	0,1
C3'a	127,2	127,2	0
C7	128,4	128,3	0,1
C6''	132,3	132,2	0,1
C8	132,6	132,6	0
C7'a	135,8	135,7	0,1
C7''a	136,3	136,2	0,1
C2	137,2	137,2	0
C5'	141,6	141,5	0,1
C6'	142,2	142,2	0

7-*epi*-Raputindole A (7-*epi*-1)

¹H NMR (500 MHz, CDCl₃) δ (ppm) = 8.10 (brs, 1H), 8.02 (brs, 1H), 7.56 (d, J = 8.25 Hz, 1H), 7.43 (s, 1H), 7.36 (s, 1H), 7.17 (dd, J = 2.3, 3.1, 3.3 Hz, 1H), 7.13 (dd, J = 2.45, 3.25, 3.15 Hz, 1H), 7.08 (s, 1H), 6.67 (d, J = 16.05 Hz, 1 H), 6.53 (d, J = 16.05 Hz, 1 H), 6.51 (m, 1H), 6.45 (m, 1H), 5.25 (d, J = 9.0 Hz, 1H), 4.22 (m, 1H), 2.26 (dd, J = 6.95, 12.25 Hz, 1H), 2.00 (dd, J = 10.3, 12.35 Hz, 1H), 1.85 (d, J = 1.35 Hz, 3H), 1.83 (d, J = 1.4 Hz, 3H), 1.49 (s, 3H).

¹³C NMR (800 MHz, CDCl₃) δ (ppm) = 143.27, 140.94, 137.81, 136.23, 135.61, 132.53, 132.28, 128.24, 127.38, 127.24, 127.10, 124.39, 123.86, 120.62, 118.56, 114.95, 108.72, 106.34, 102.64, 102.43, 49.78, 48.30, 41.34, 25.95, 25.57, 18.29.

HRMS (ESI) m/z [M+H⁺] Calcd for C₂₆H₂₇N₂ 367.2174; Found 367.2166.

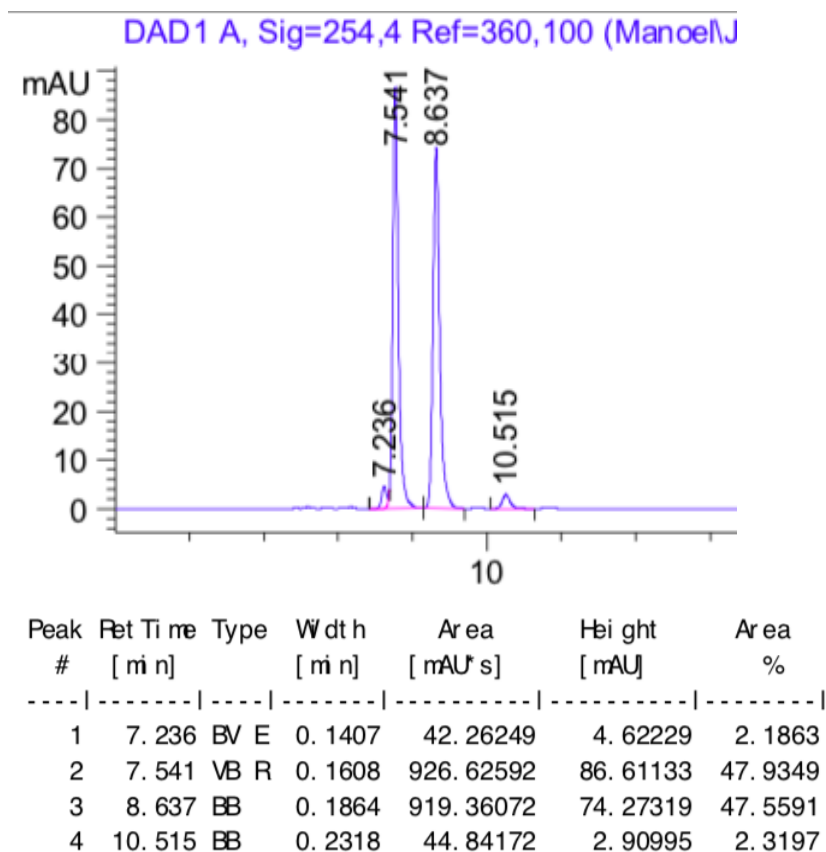
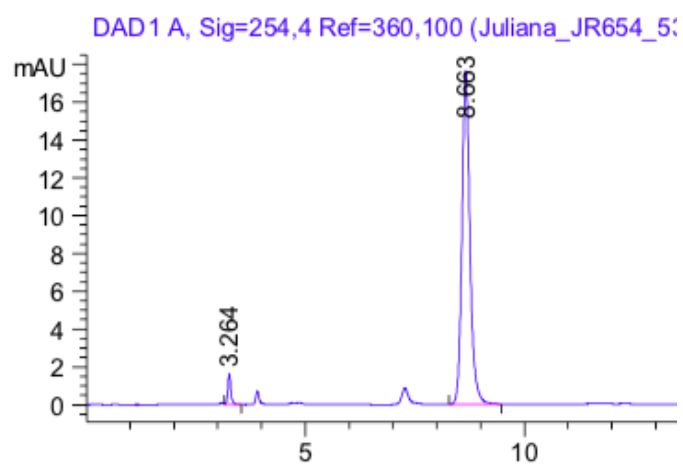


Figure 1. HPLC chromatogram of racemic acetate (+/-)-**13**. Chiral column Chiralpak® IA (4.6 x 250 mm, 5 µm, 10:90 v/v, *i*-PrOH/hexane, isocratic mode, flow 1.0 mL/min, UV detection at 254 nm).



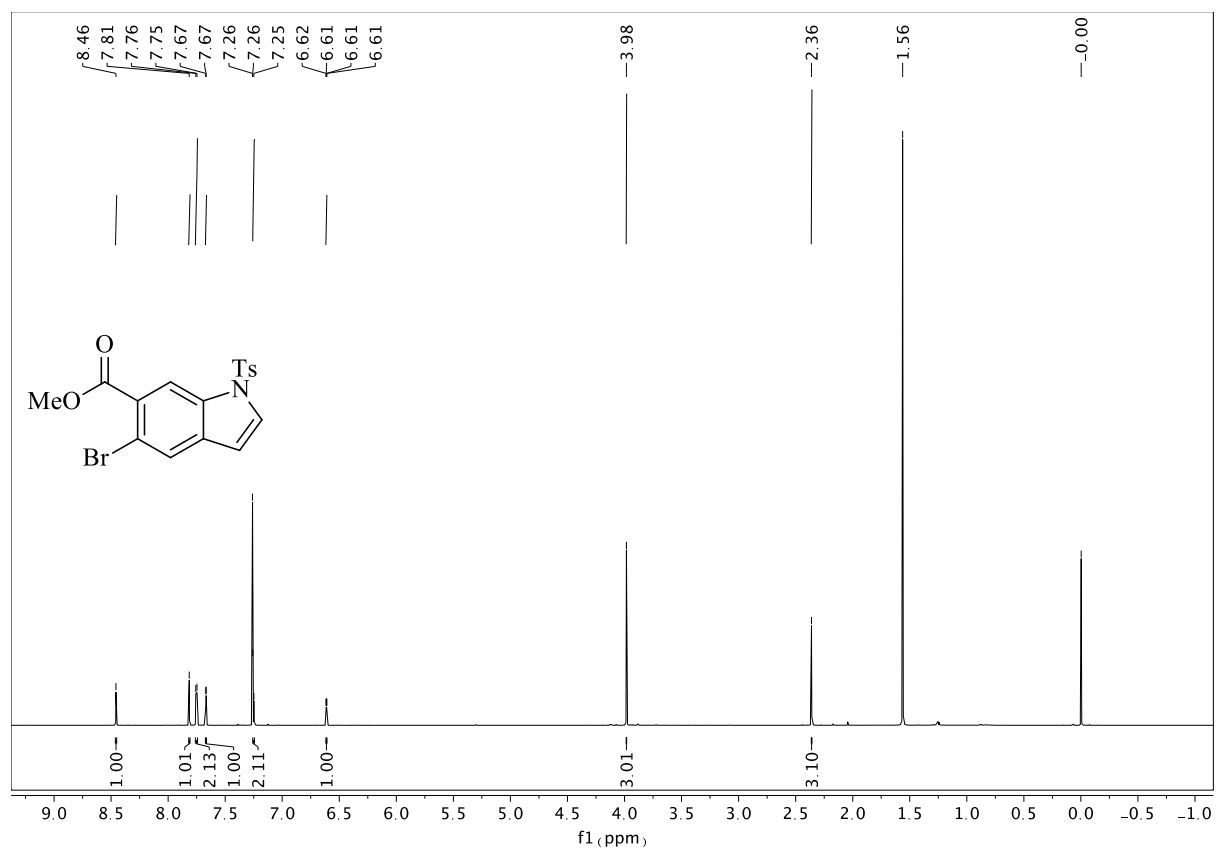
Peak #	Ret Time [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	3.264	BB	0.0698	7.37568	1.59971	1.5411
2	8.663	BB	0.1922	223.98225	17.63116	46.7990
3	19.222	BB	0.4876	247.24731	7.63991	51.6600

Figure 2. HPLC chromatogram of acetate (5S,7S)-**13**. Chiral column Chiralpak® IA (4.6 x 250 mm, 5 µm, 10:90 v/v, *i*-PrOH/hexane, isocratic mode, flow 1.0 mL/min, UV detection at 254 nm).

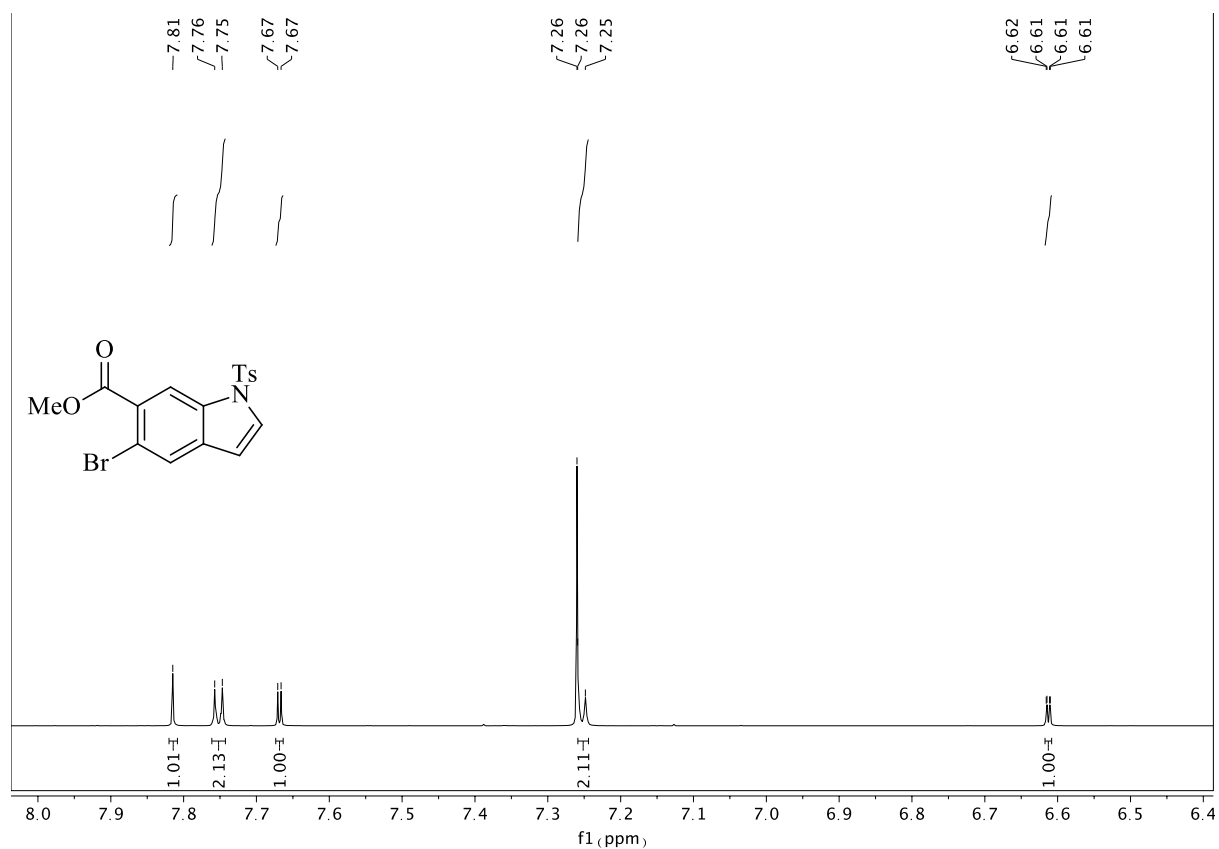
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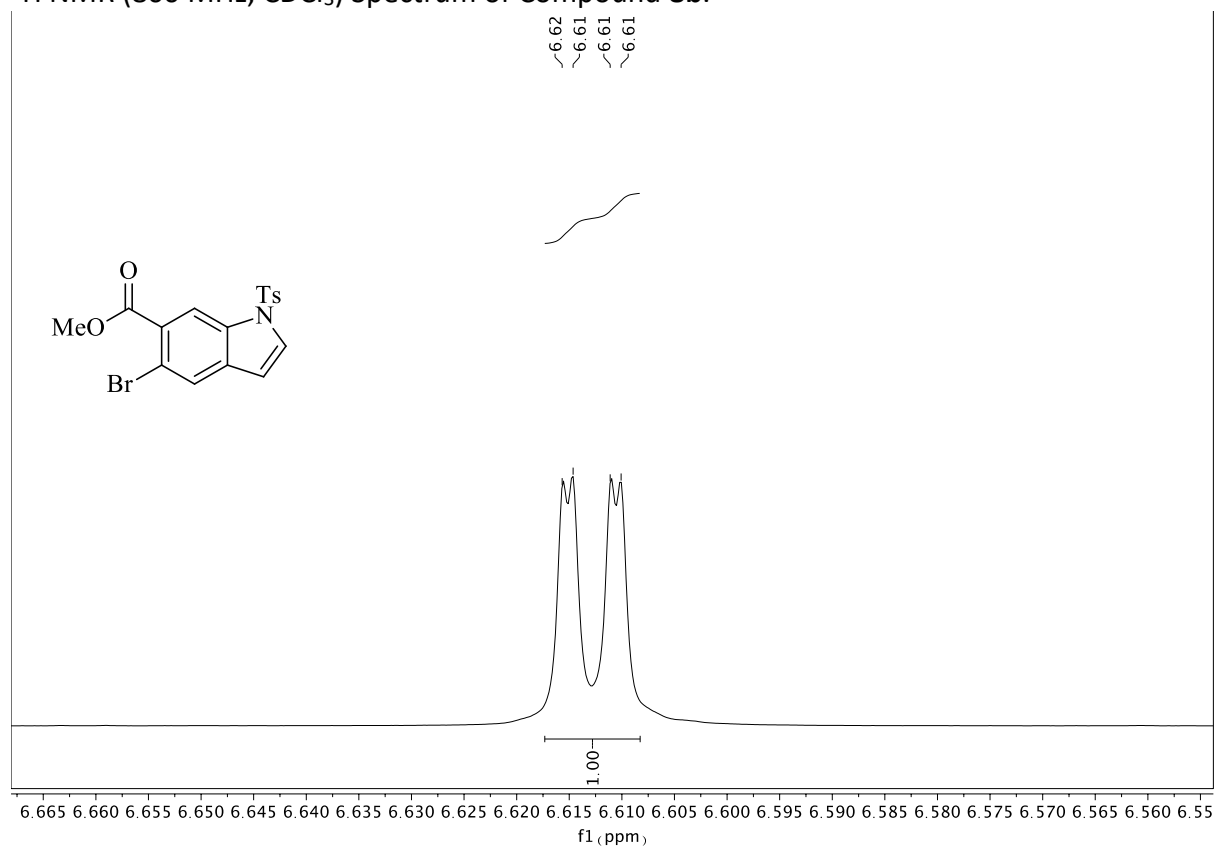
NMR Spectra



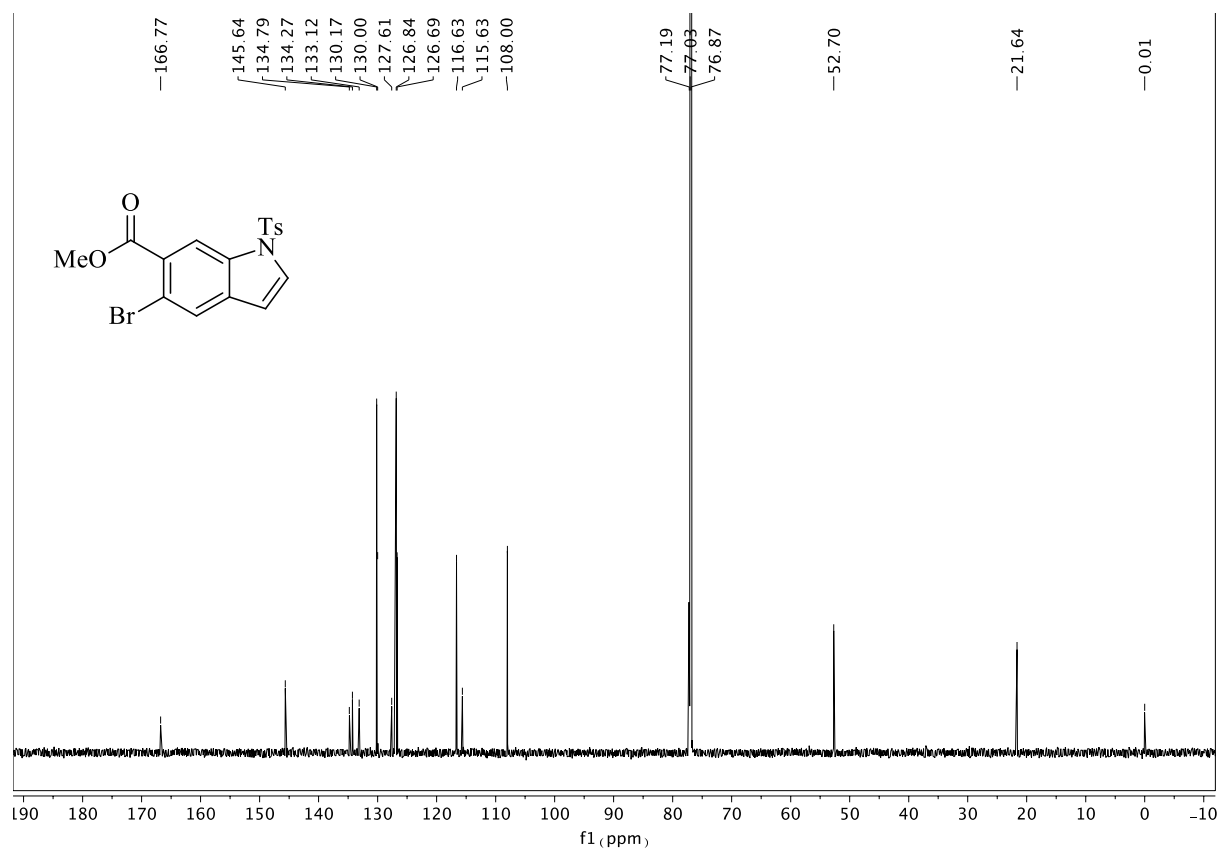
¹H NMR (800 MHz, CDCl₃) Spectrum of Compound **8b**. (residual water: in 1.55 ppm).



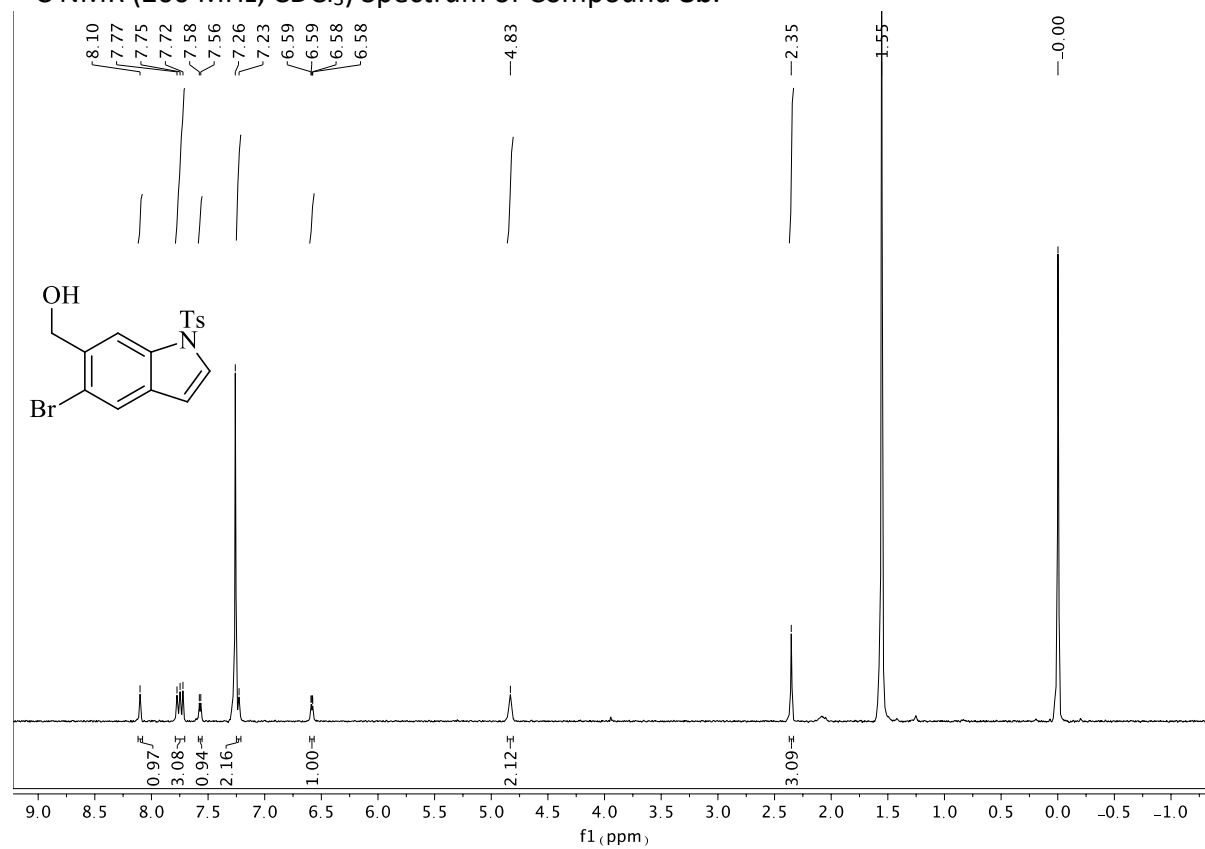
¹H NMR (800 MHz, CDCl₃) Spectrum of Compound **8b.**



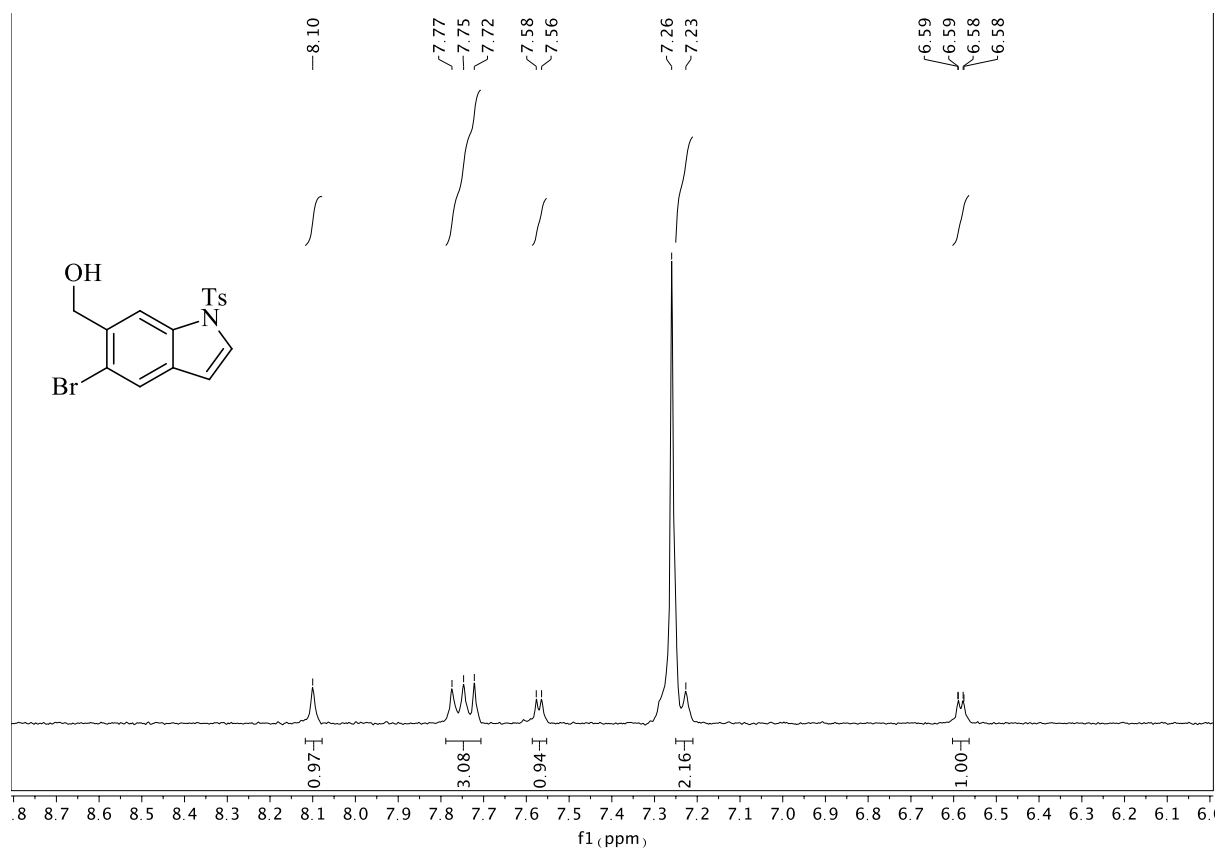
¹H NMR (800 MHz, CDCl₃) Spectrum of Compound **8b.**



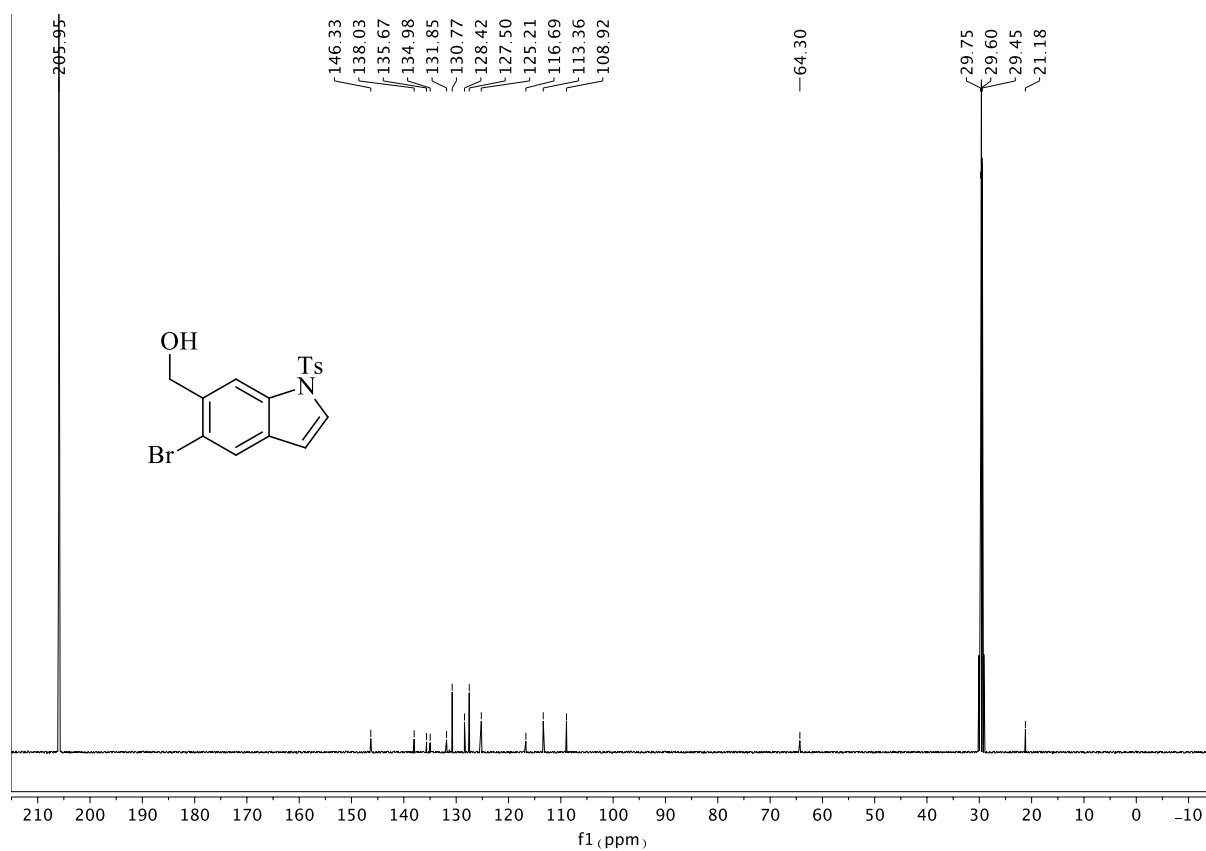
¹³C NMR (200 MHz, CDCl₃) Spectrum of Compound **8b.**



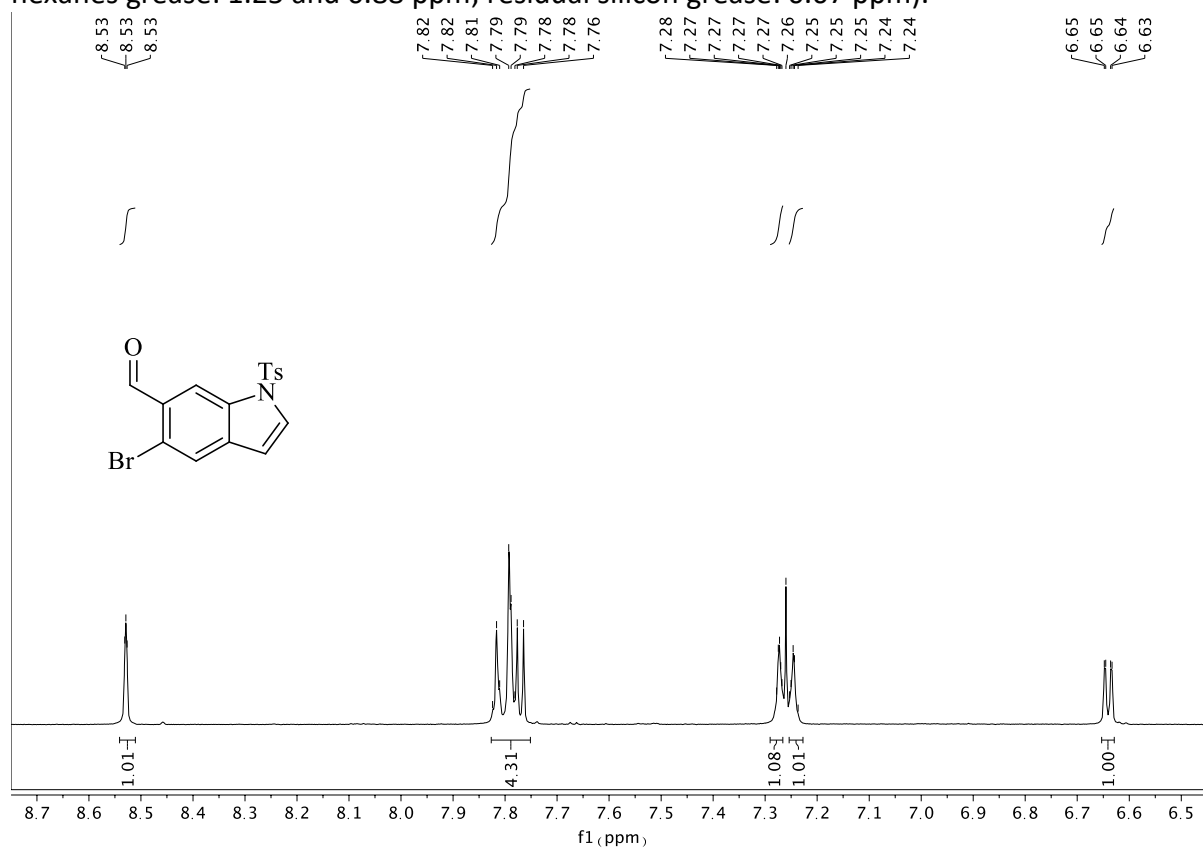
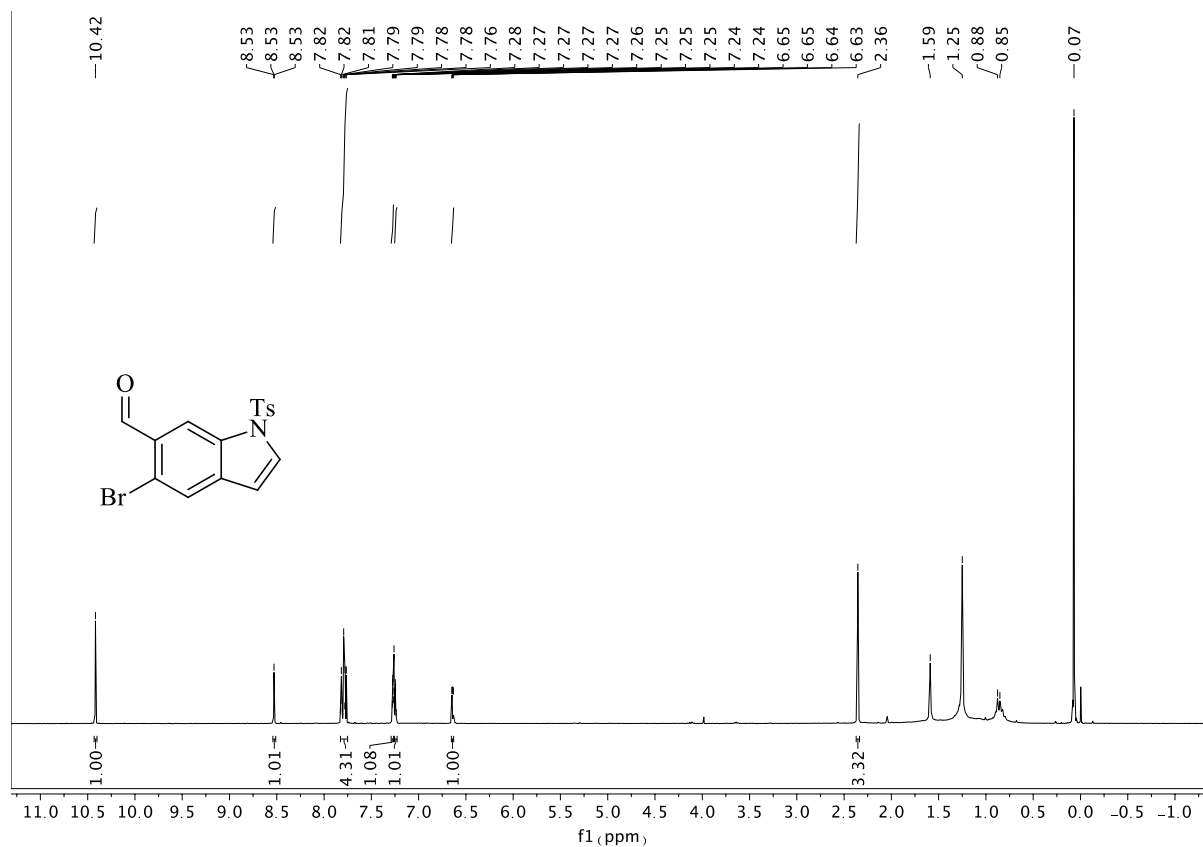
¹H NMR (300 MHz, CDCl₃) Spectrum of Compound **10. (residual water: 1.55 ppm).**



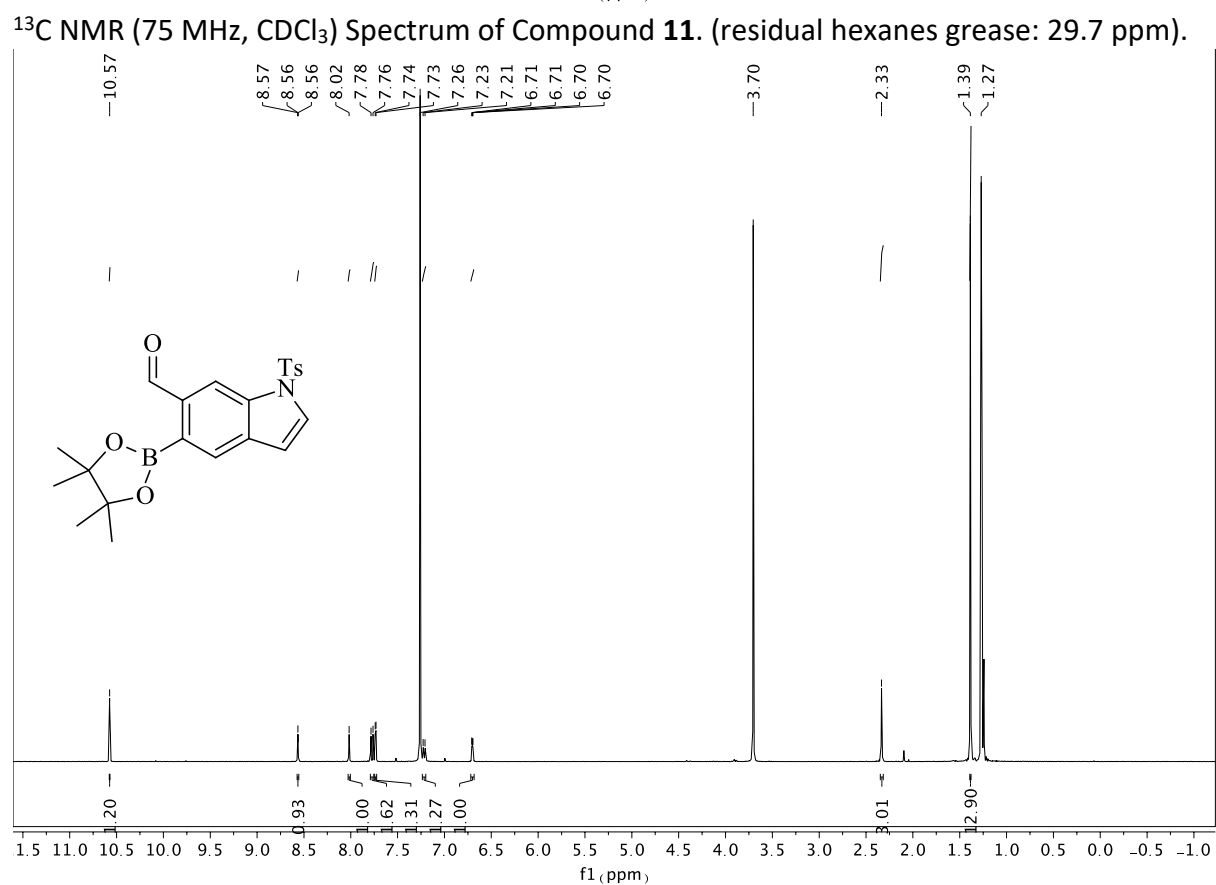
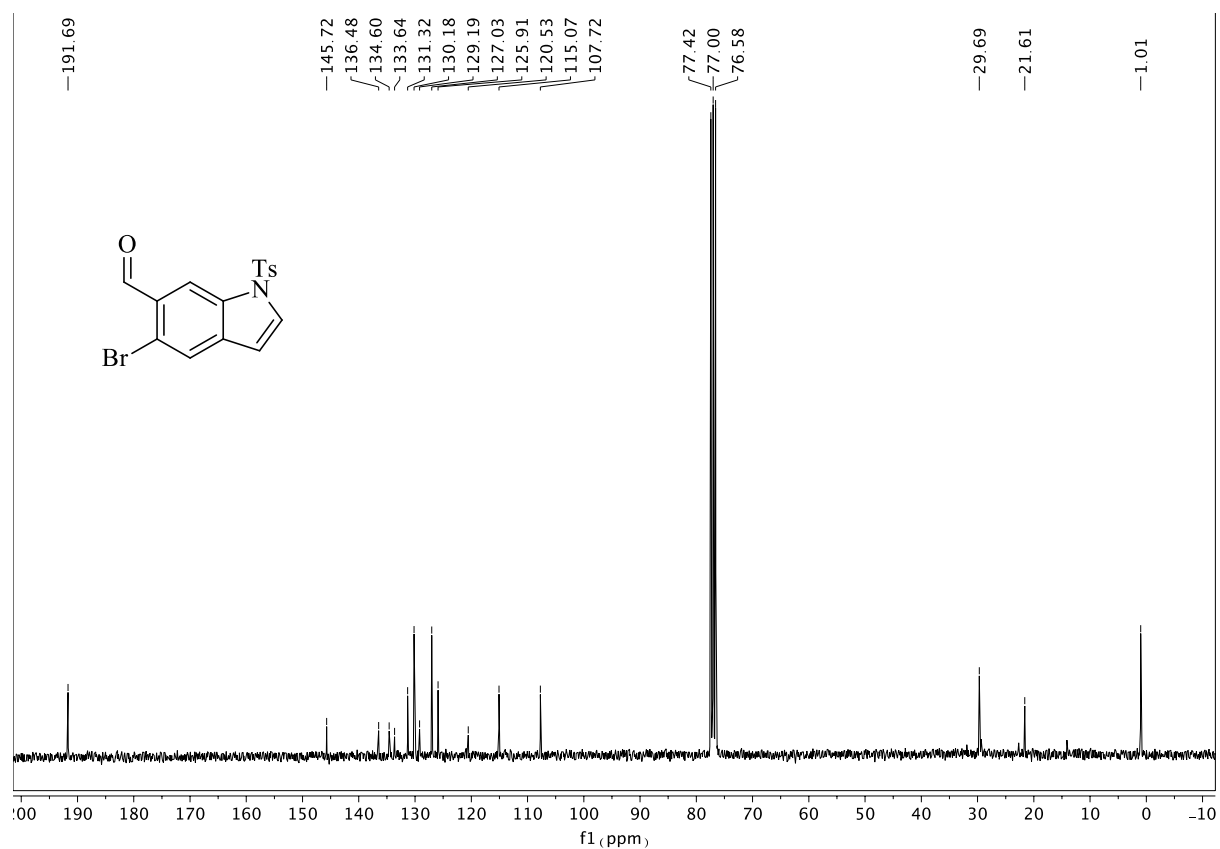
¹H NMR (300 MHz, CDCl₃) Spectrum of Compound 10.

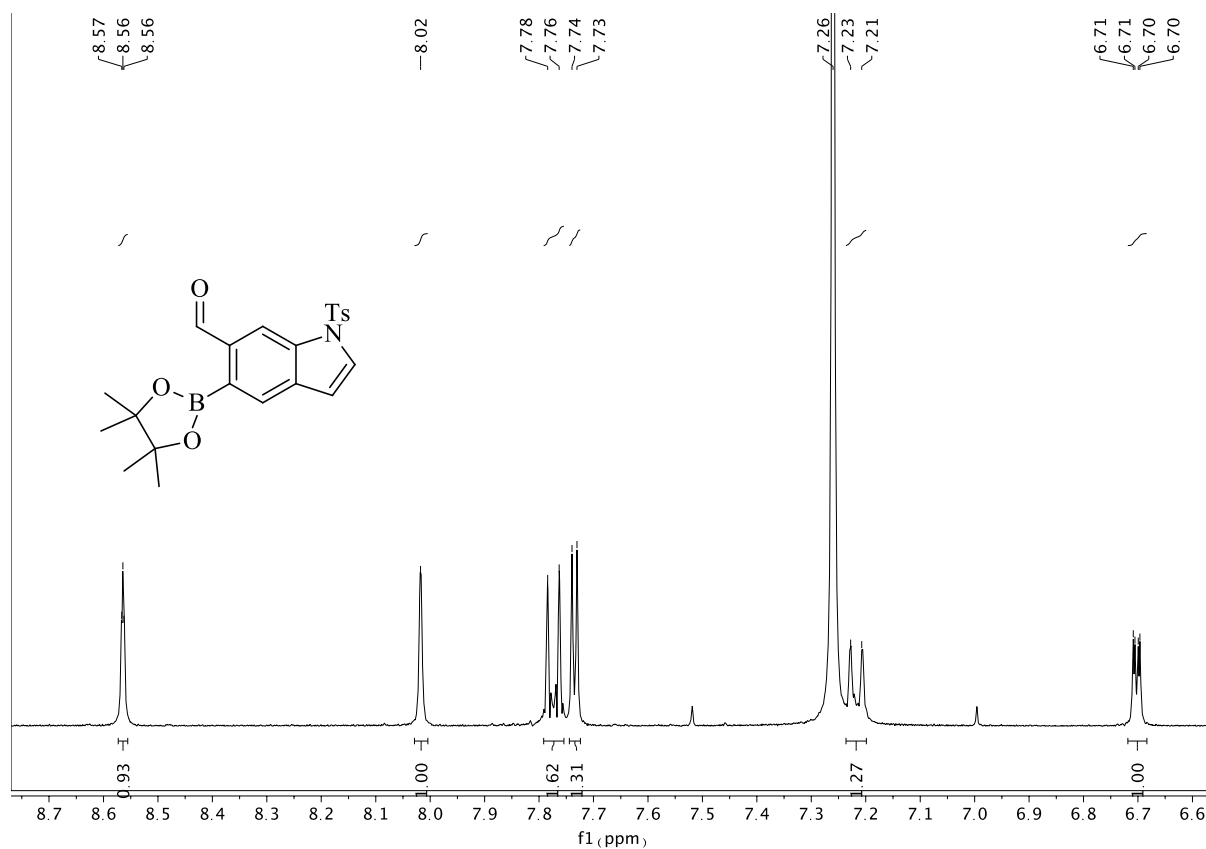


¹³C NMR (126 MHz, d₆-(CD₃)₂CO) Spectrum of Compound 10.

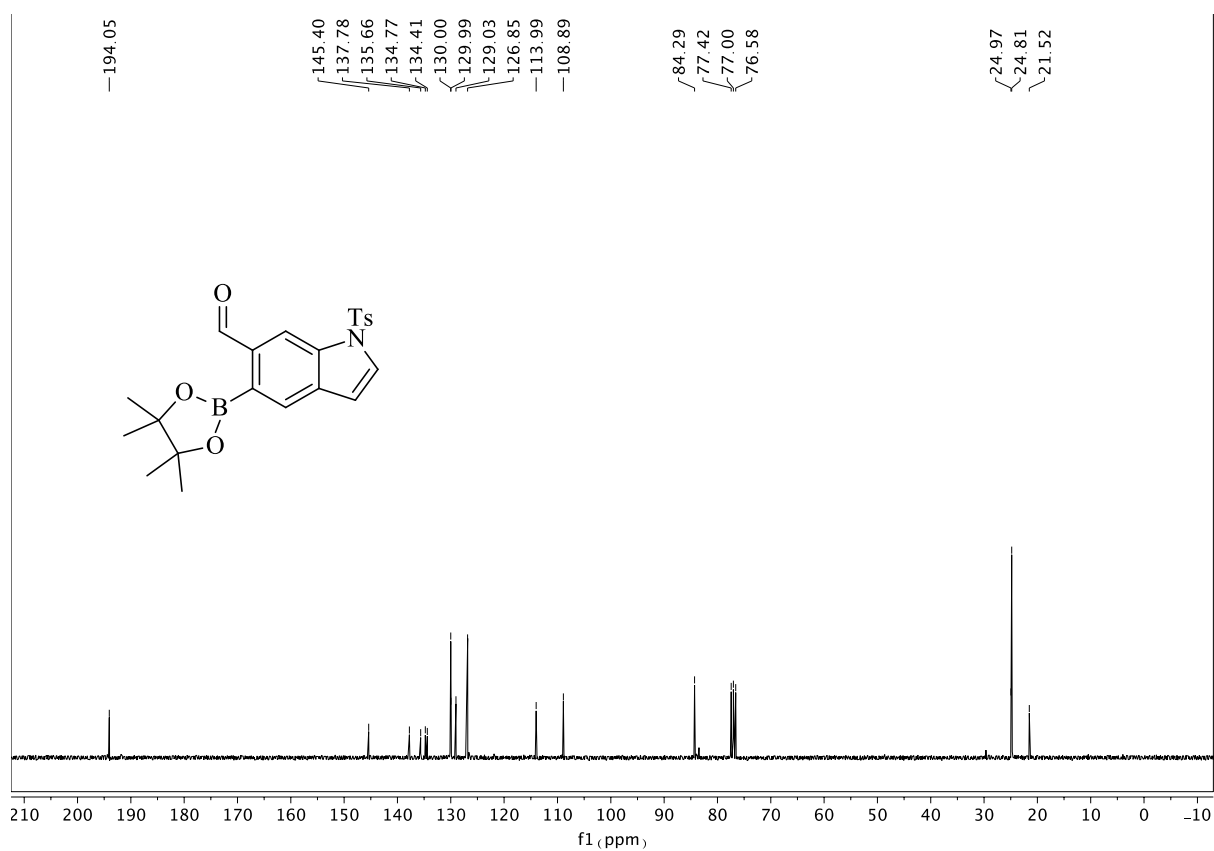


¹H NMR (300 MHz, CDCl₃) Spectrum of Compound 11.

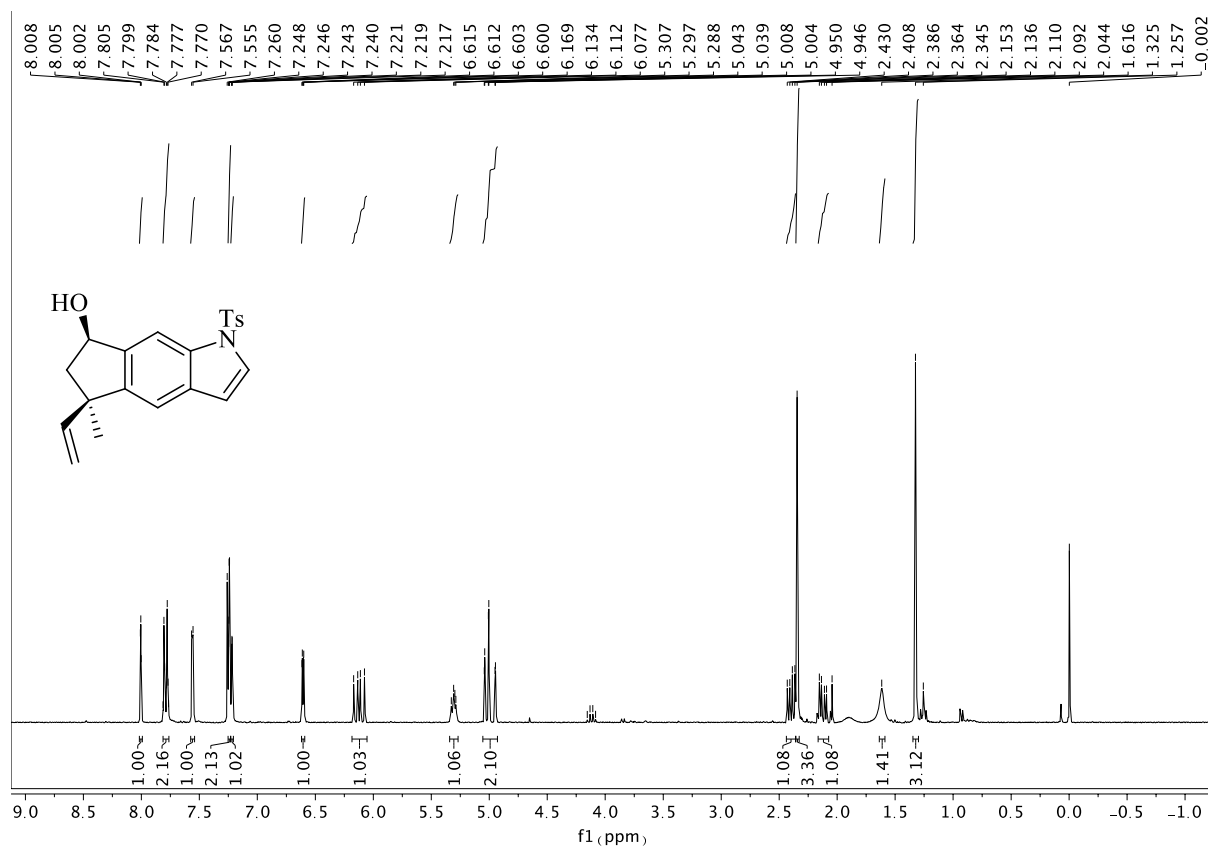




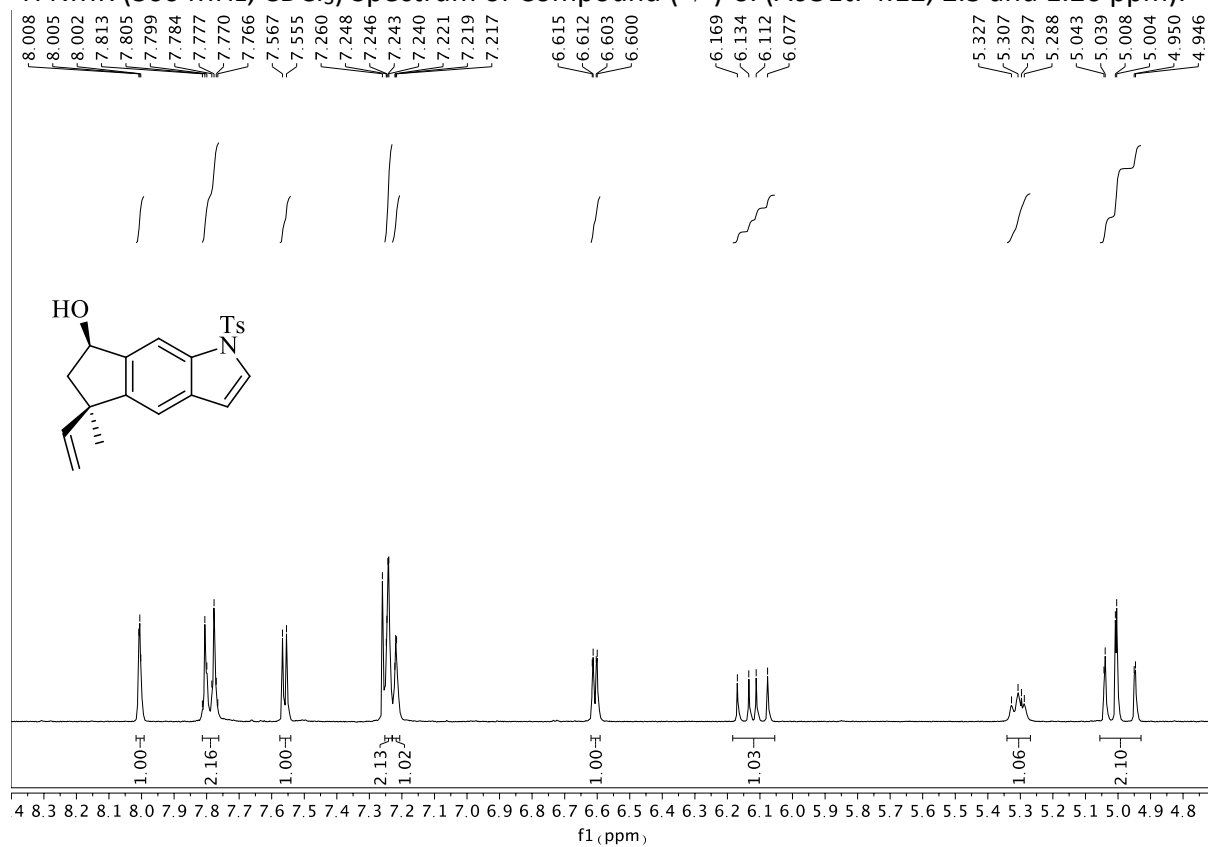
¹H NMR (400 MHz, CDCl₃) Spectrum of Compound **12**.



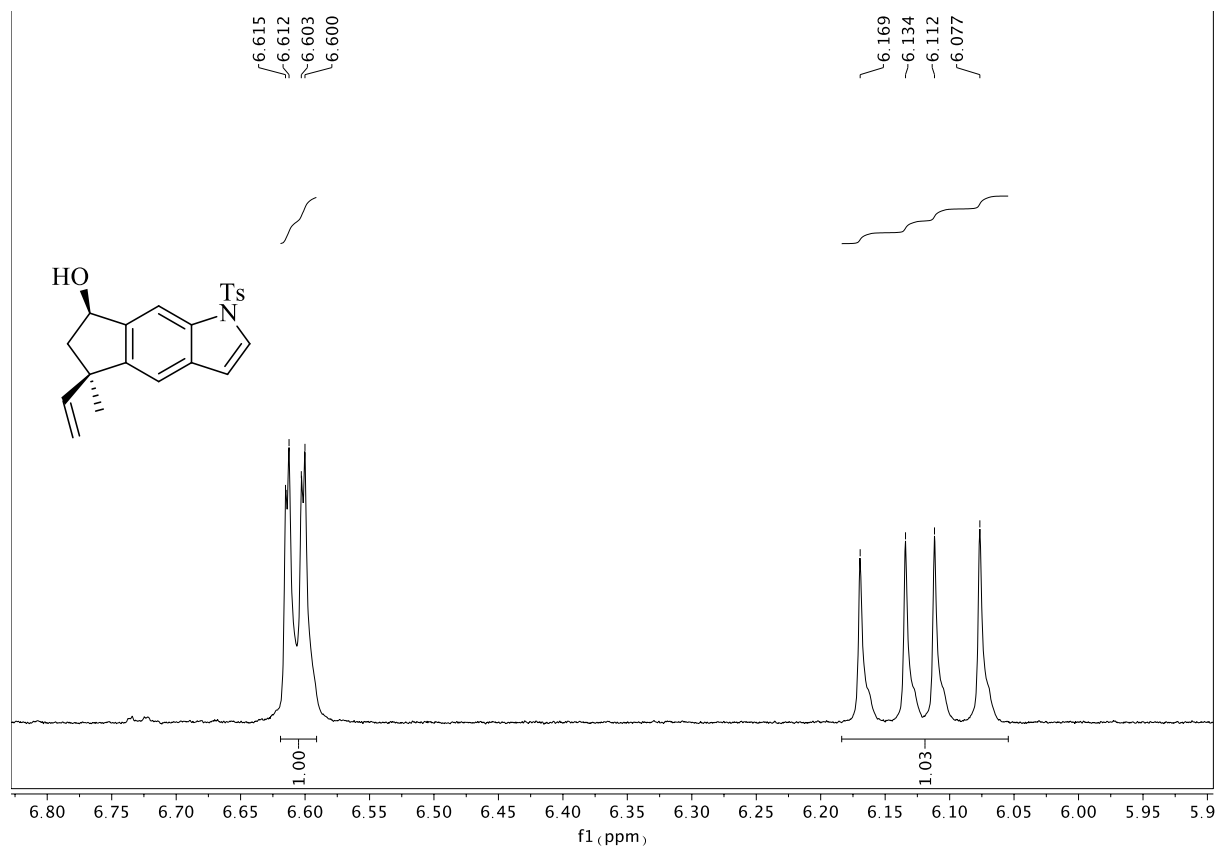
¹³C NMR (75 MHz, CDCl₃) Spectrum of Compound **12**.



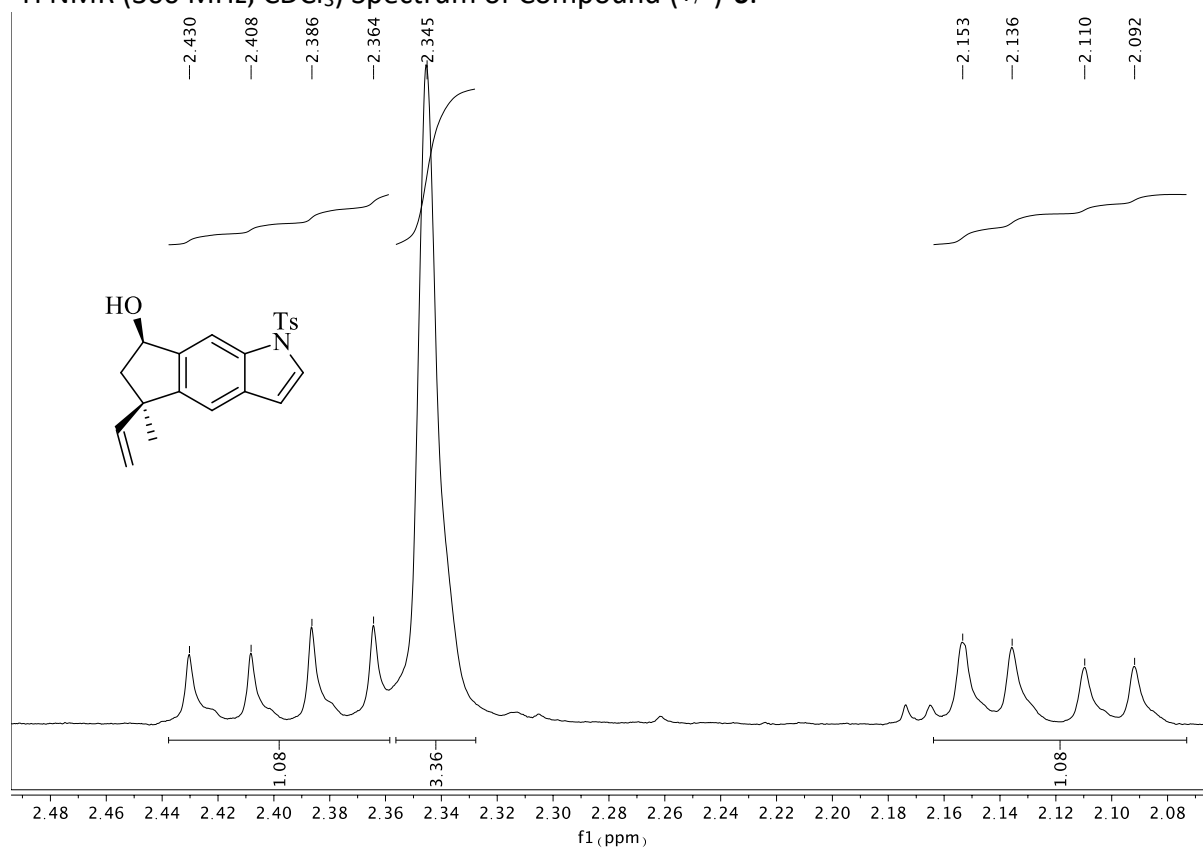
¹H NMR (300 MHz, CDCl₃) Spectrum of Compound (+/-)-6. (AcOEt: 4.12, 2.5 and 1.26 ppm).



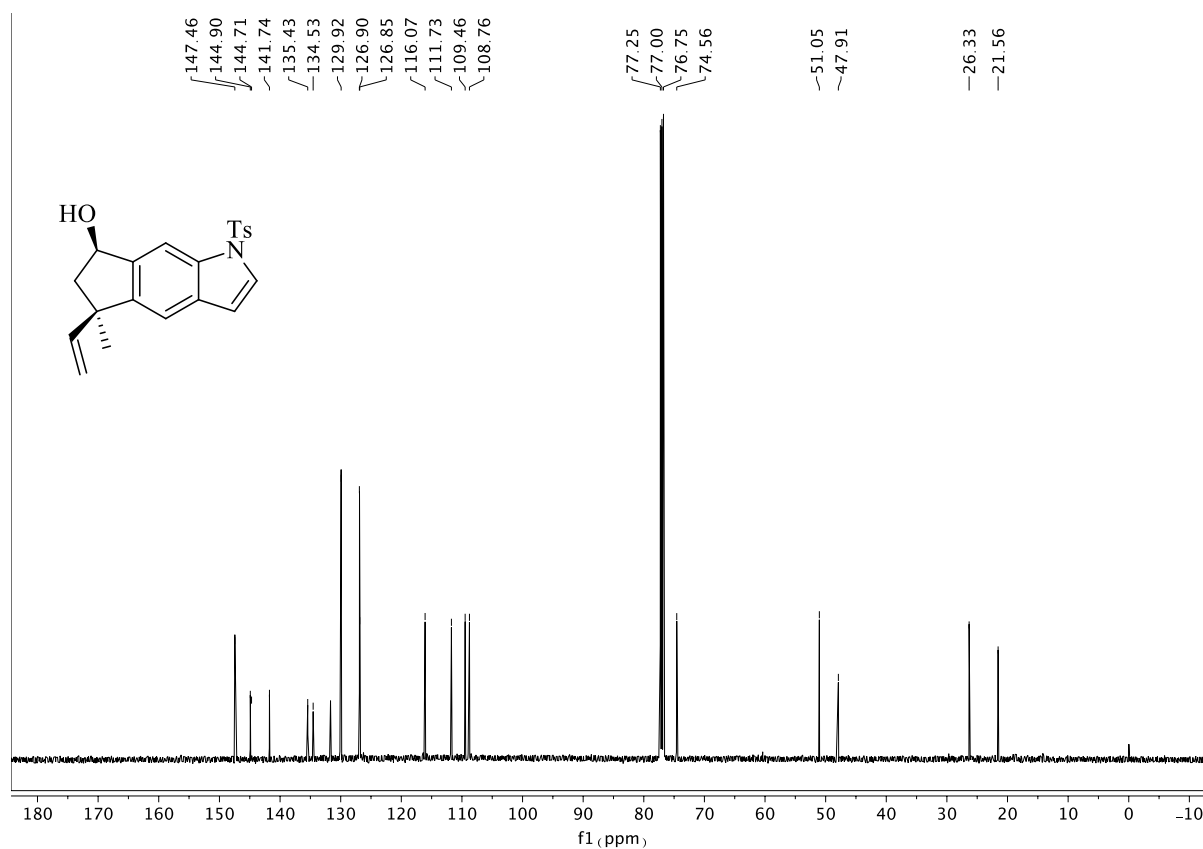
¹H NMR (300 MHz, CDCl₃) Spectrum of Compound (+/-)-6.



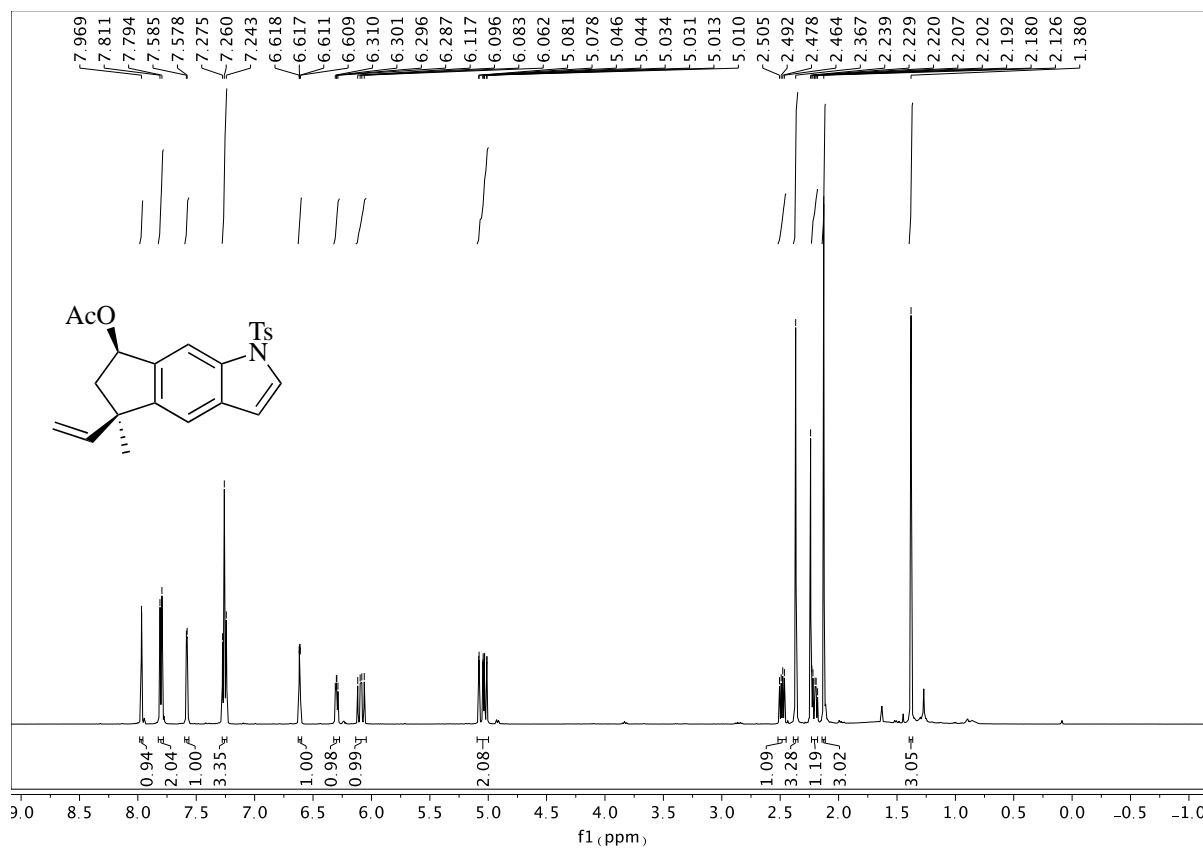
¹H NMR (300 MHz, CDCl₃) Spectrum of Compound (+/-)-6.



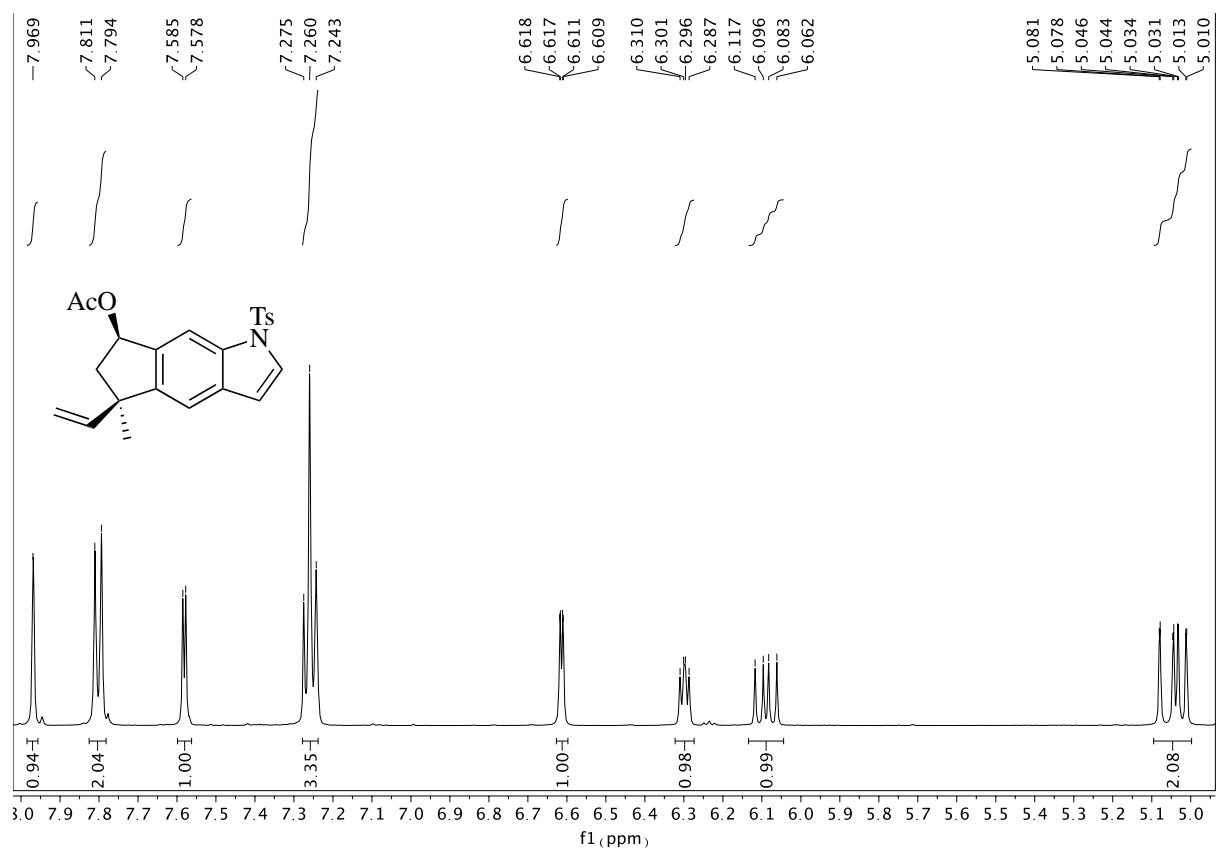
¹H NMR (300 MHz, CDCl₃) Spectrum of Compound (+/-)-6.



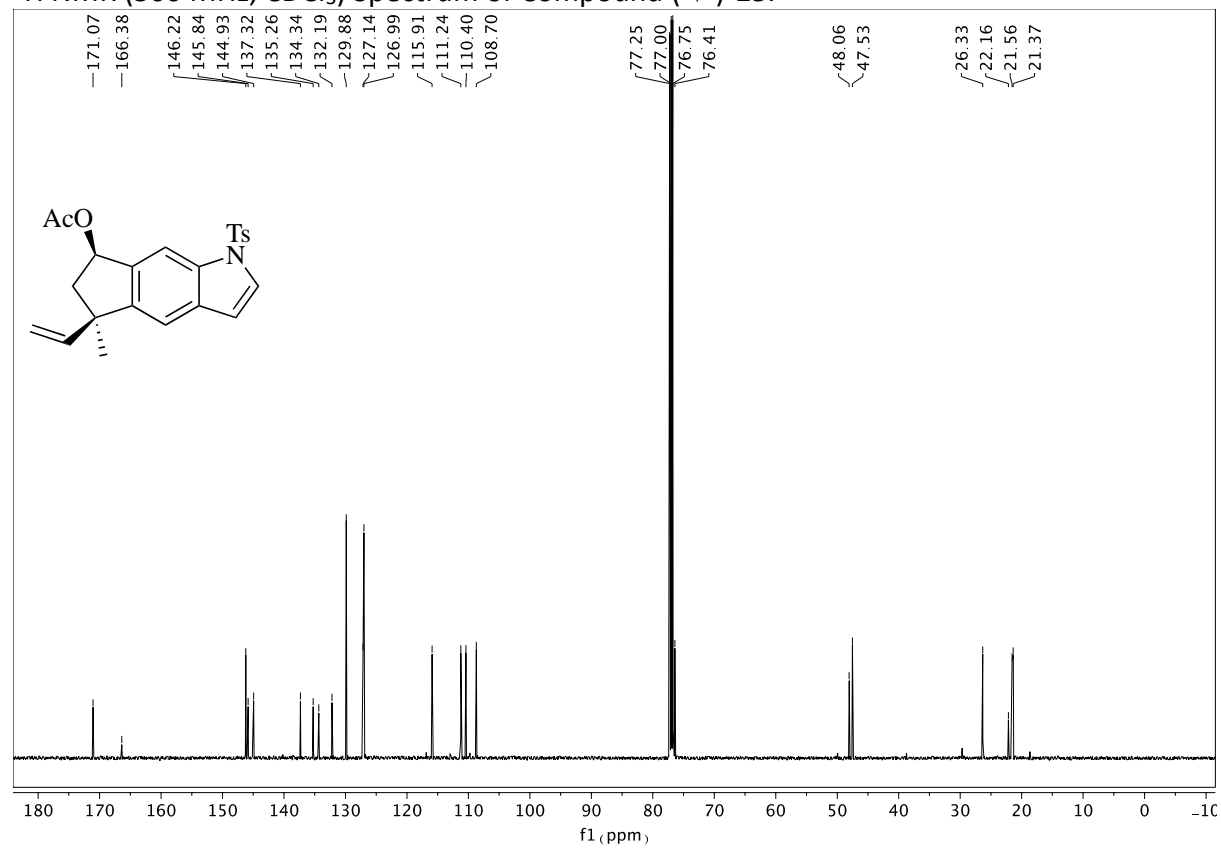
¹³C NMR (126 MHz, CDCl₃) Spectrum of Compound (+/-)-6.



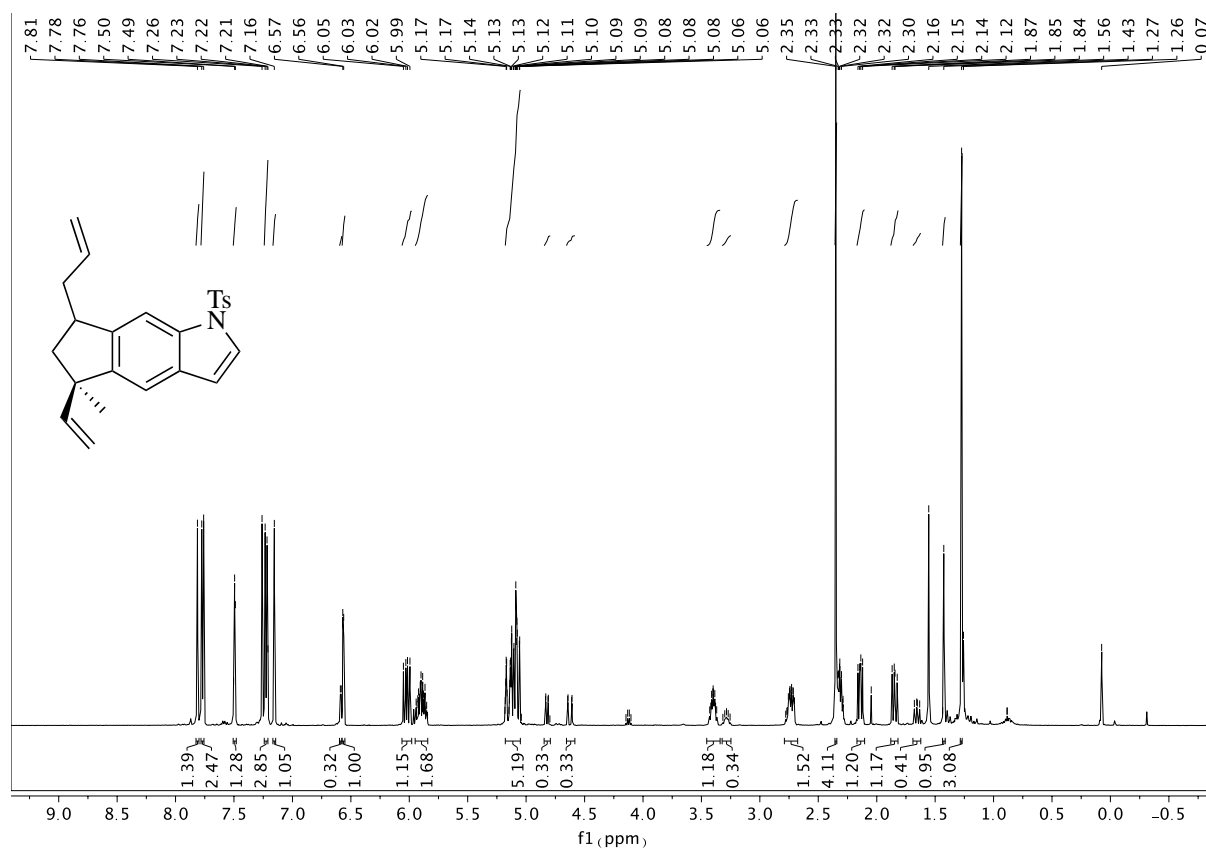
¹H NMR (500 MHz, CDCl₃) Spectrum of Compound (+/-)-13.



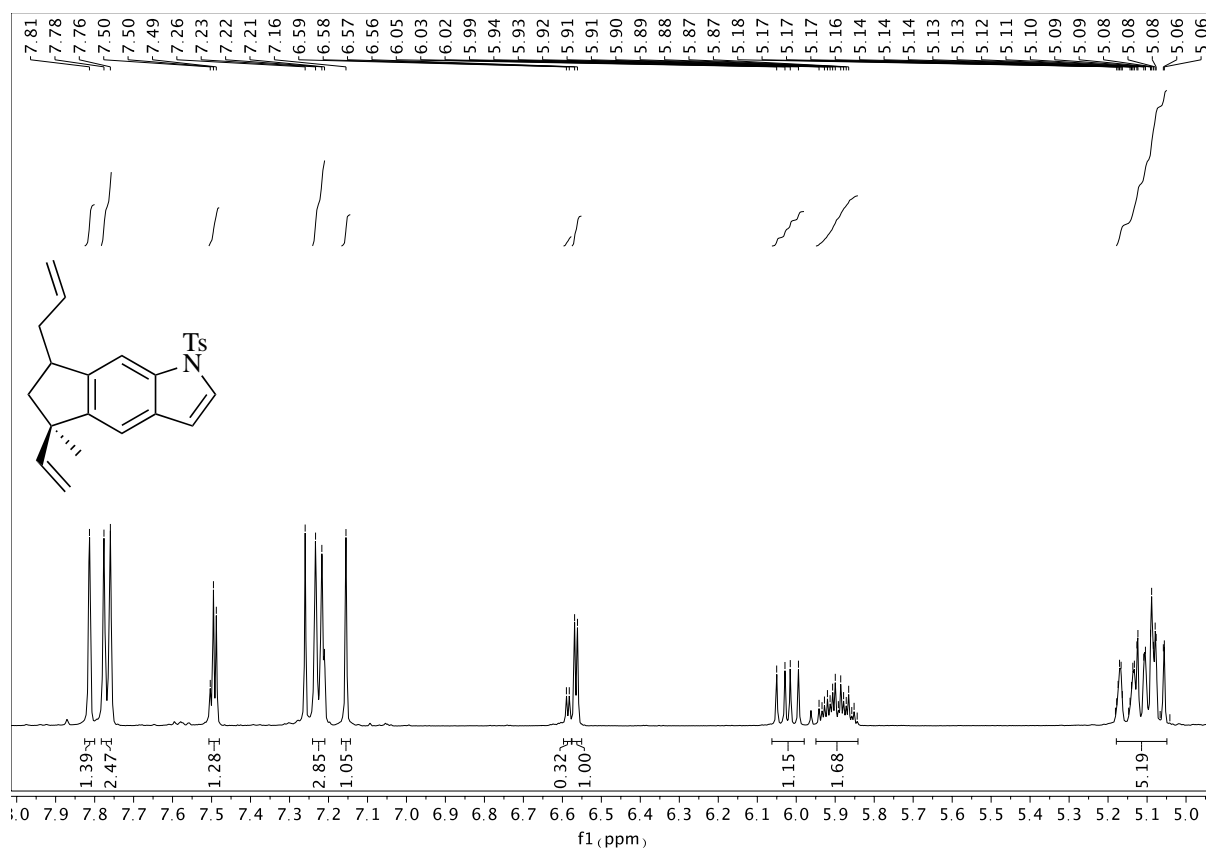
¹H NMR (500 MHz, CDCl₃) Spectrum of Compound (+/-)-13.



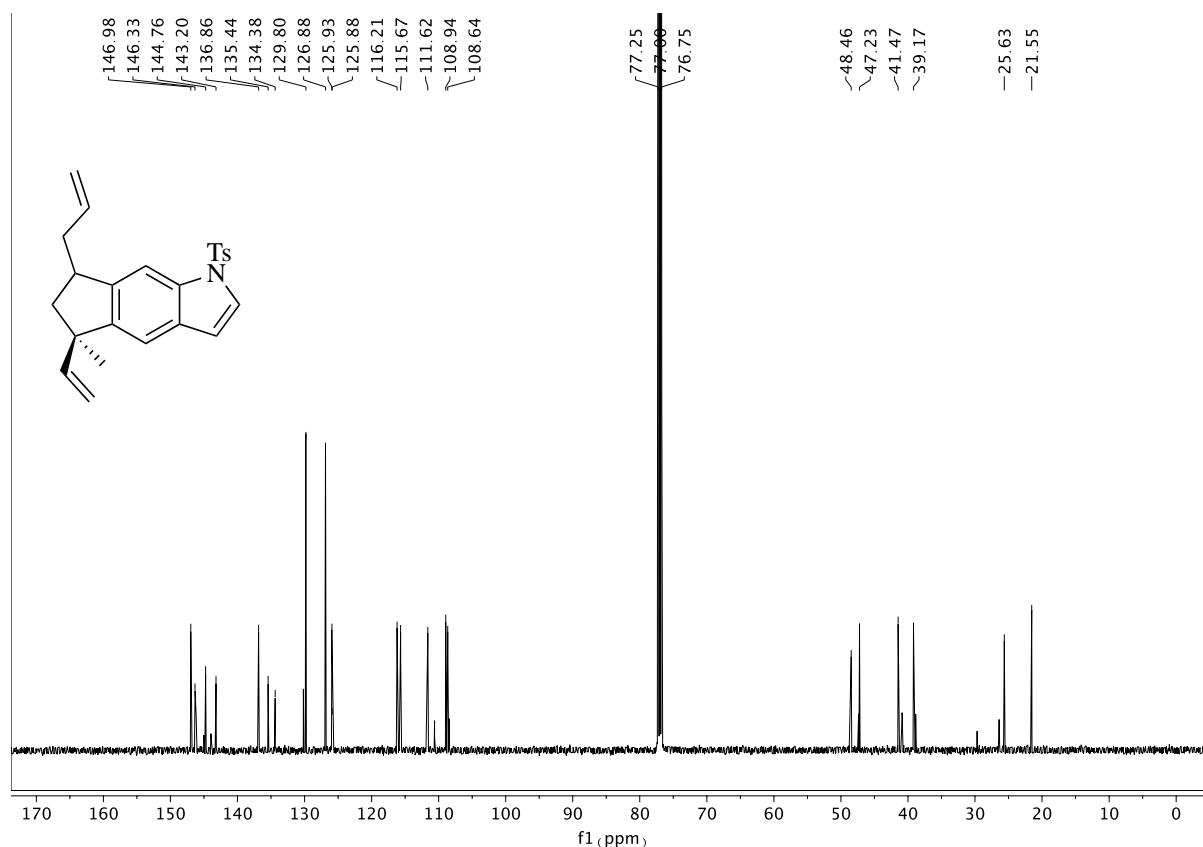
¹³C NMR (126 MHz, CDCl₃) Spectrum of Compound (+/-)-13. (*N,N*-DMA: 171.07 and 21.37).



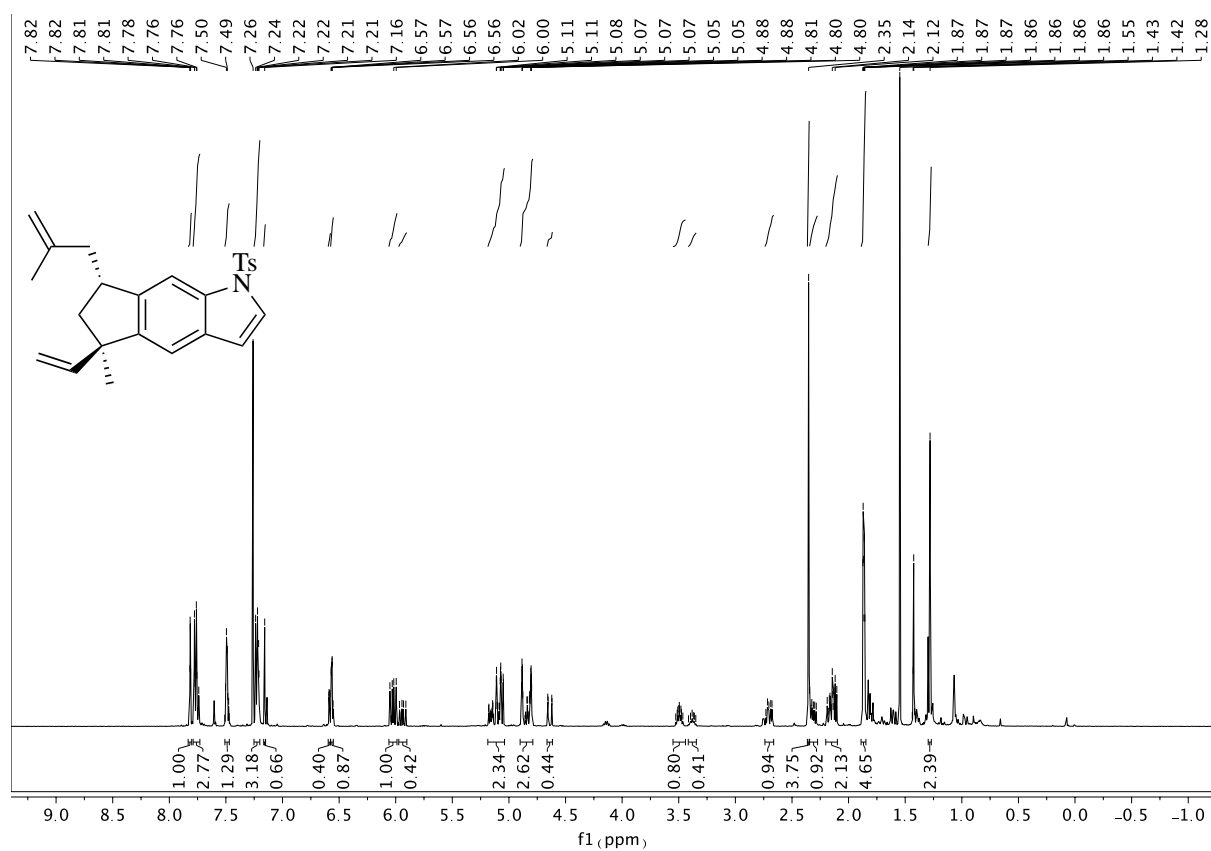
¹H NMR (500 MHz, CDCl₃) Spectrum of a mixture **1a:1b**. (AcOEt: 4.12, 2.5 and 1.26 ppm).



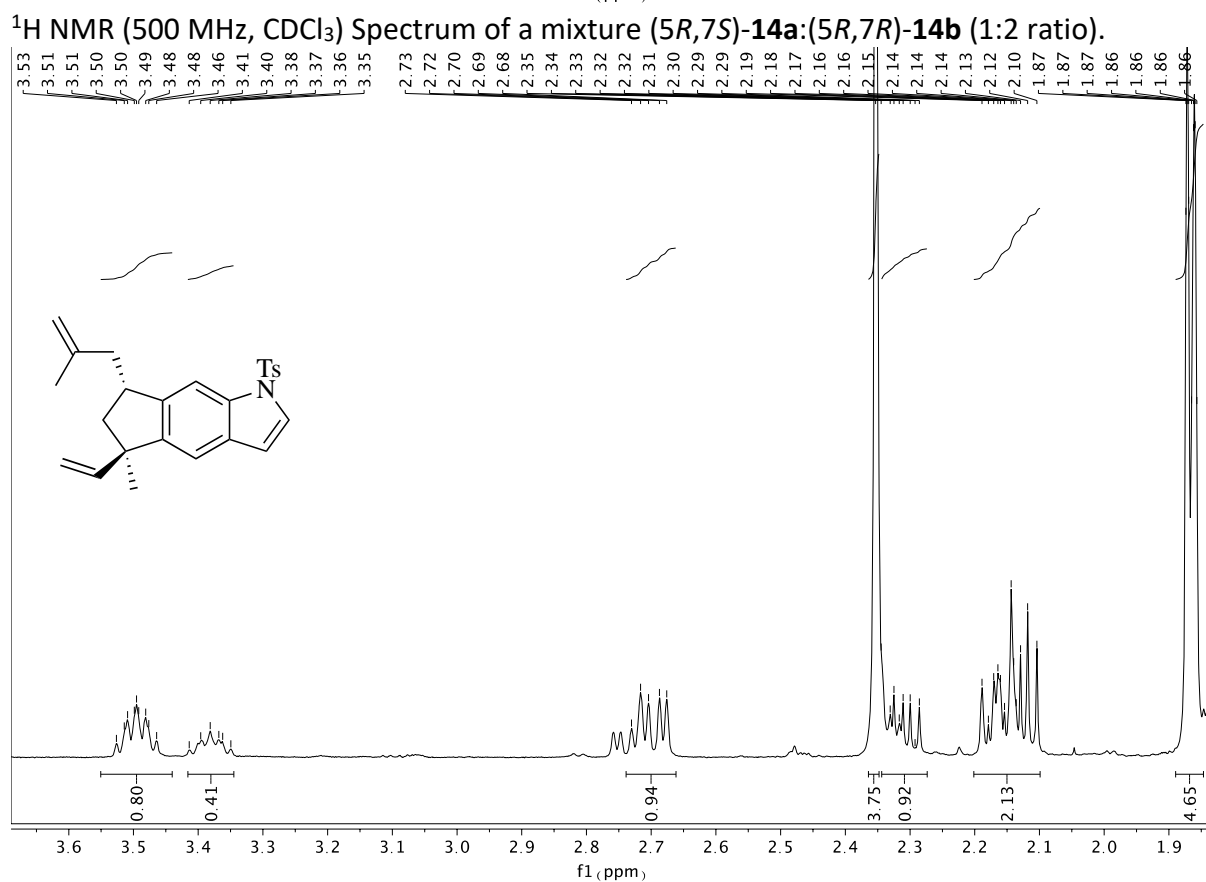
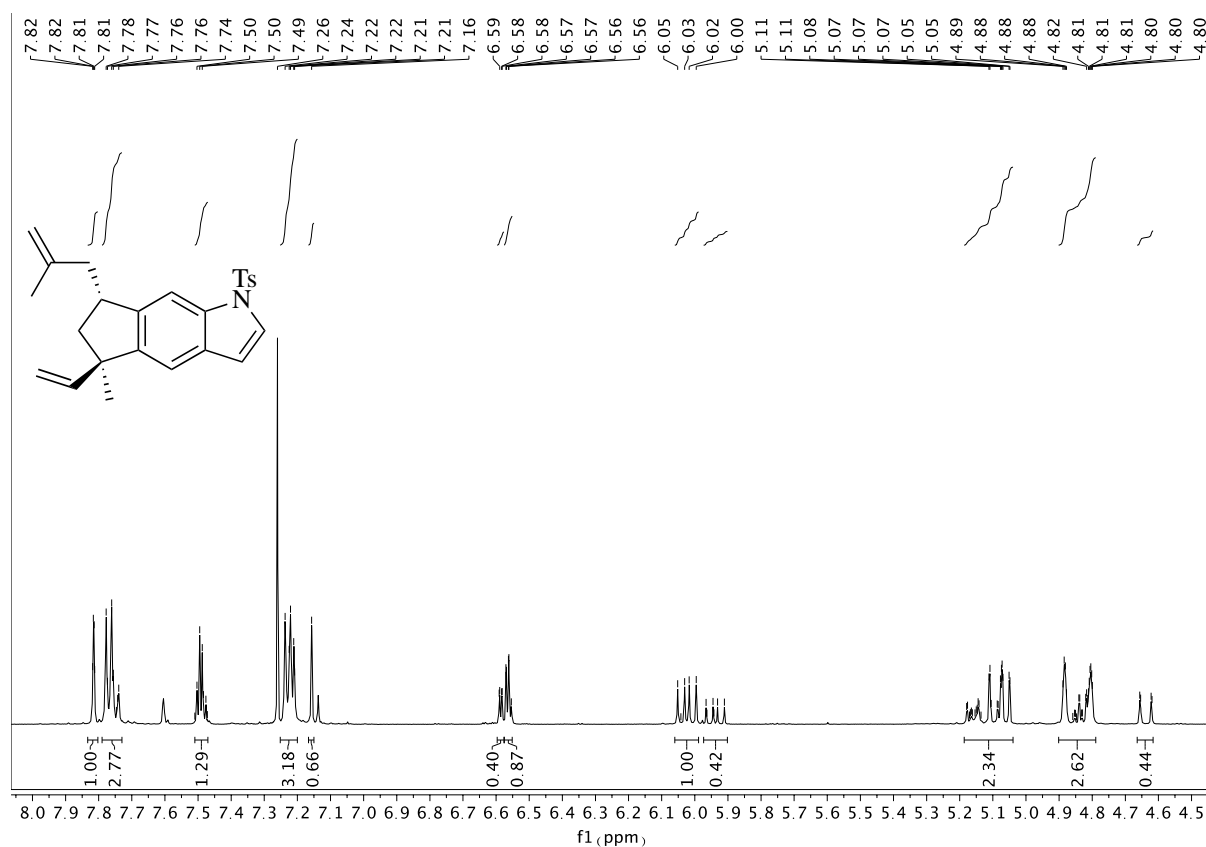
¹H NMR (500 MHz, CDCl₃) Spectrum of a mixture **1a:1b**. (AcOEt: 4.12, 2.5 and 1.26 ppm).



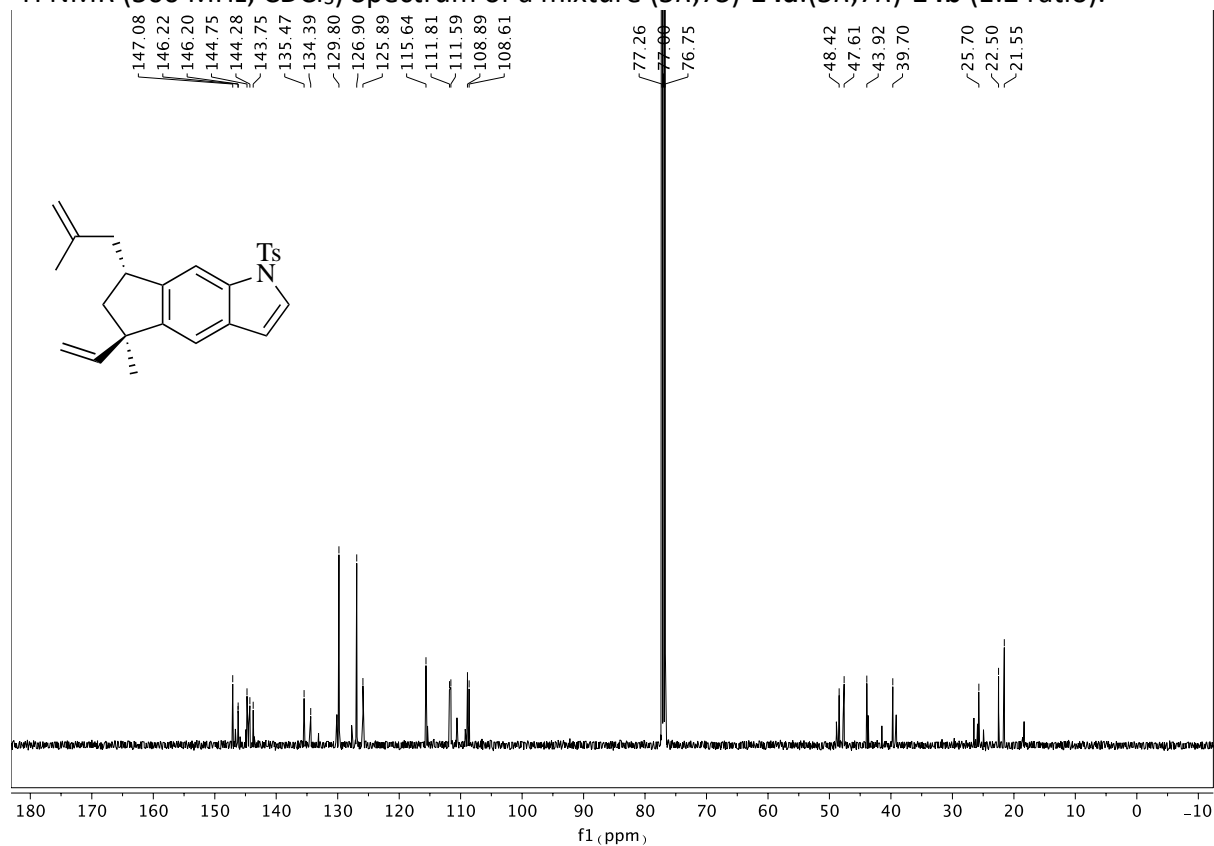
¹³C NMR (126 MHz, CDCl₃) Spectrum of a mixture **1a**:**1b**.



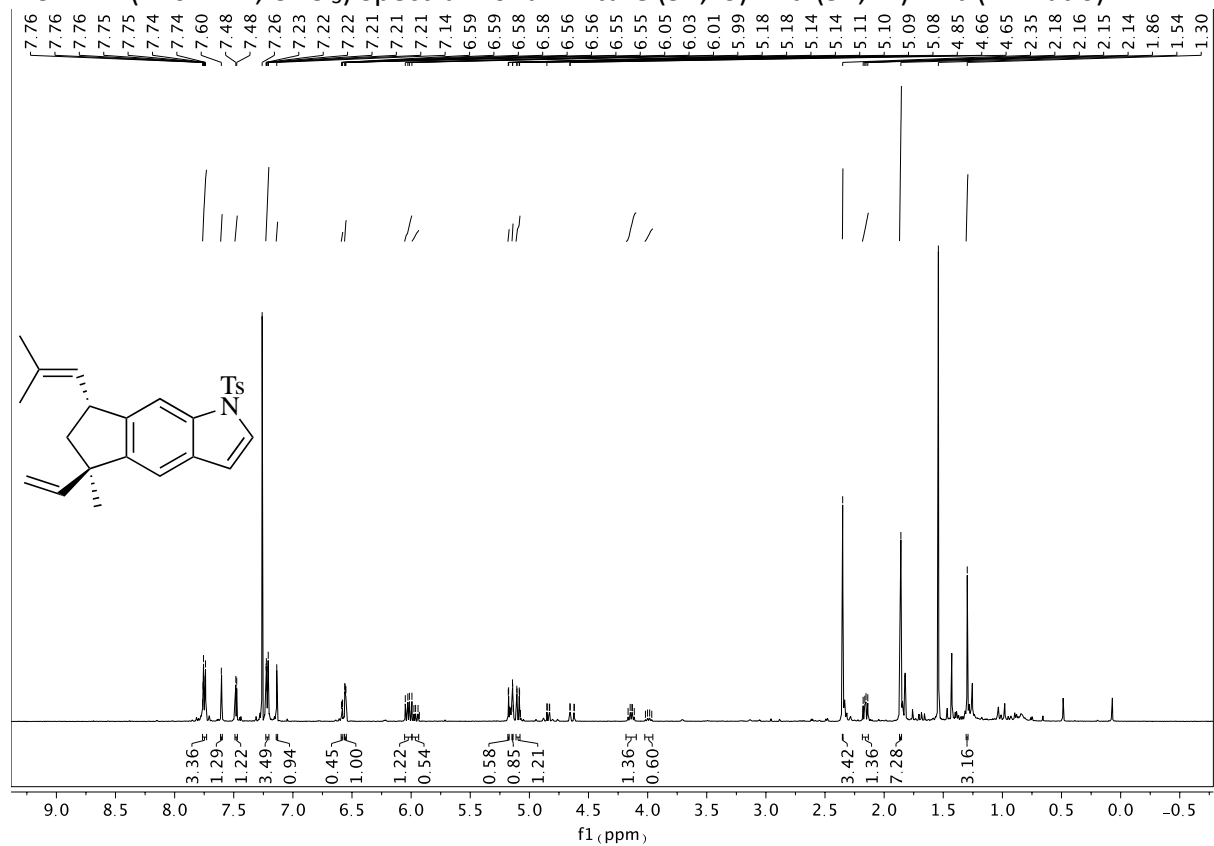
¹H NMR (500 MHz, CDCl₃) Spectrum of a mixture (5*R*,7*S*)-**1a**:(5*R*,7*R*)-**1b** (1:2 ratio).
(residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.55 ppm).



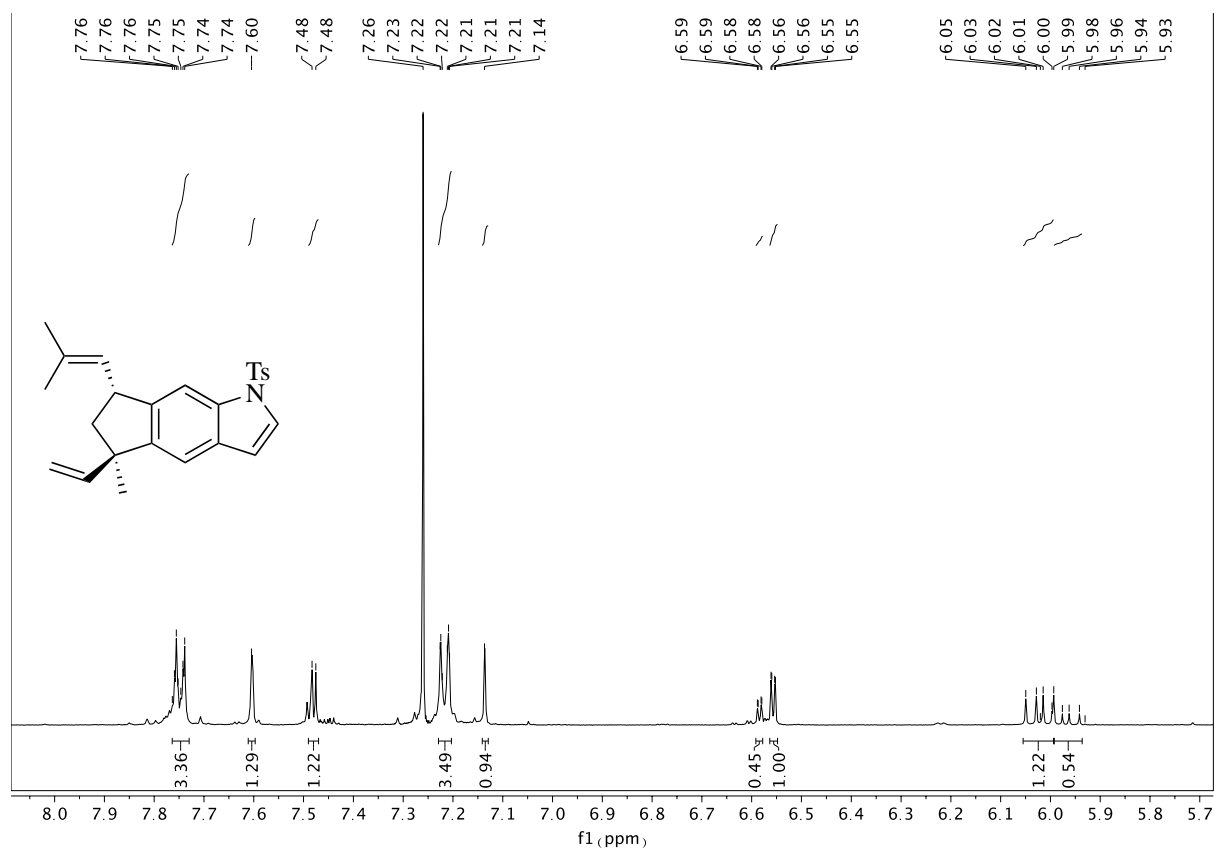
^1H NMR (500 MHz, CDCl_3) Spectrum of a mixture (5*R*,7*S*)-**14a**:(5*R*,7*R*)-**14b** (1:2 ratio).



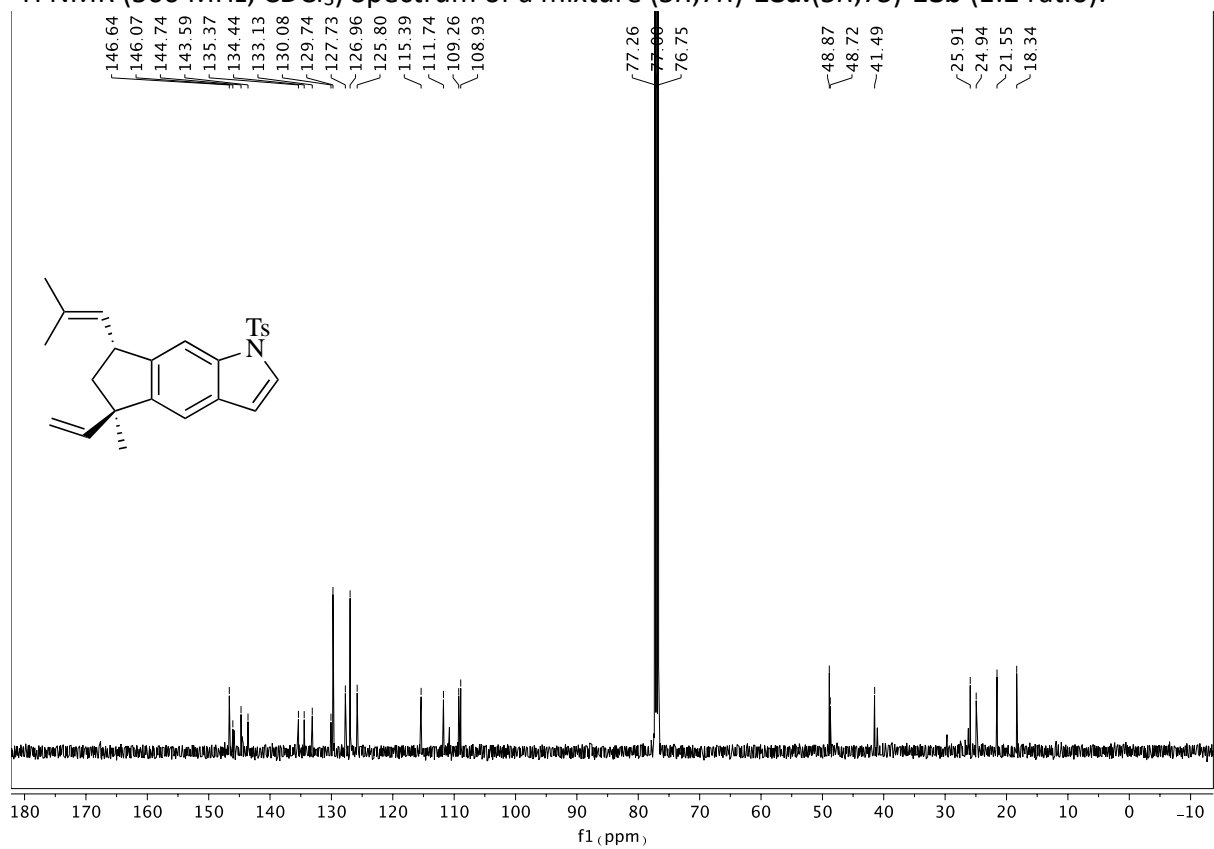
^{13}C NMR (126 MHz, CDCl_3) Spectrum of a mixture (5*R*,7*S*)-**14a**:(5*R*,7*R*)-**14b** (1:2 ratio).



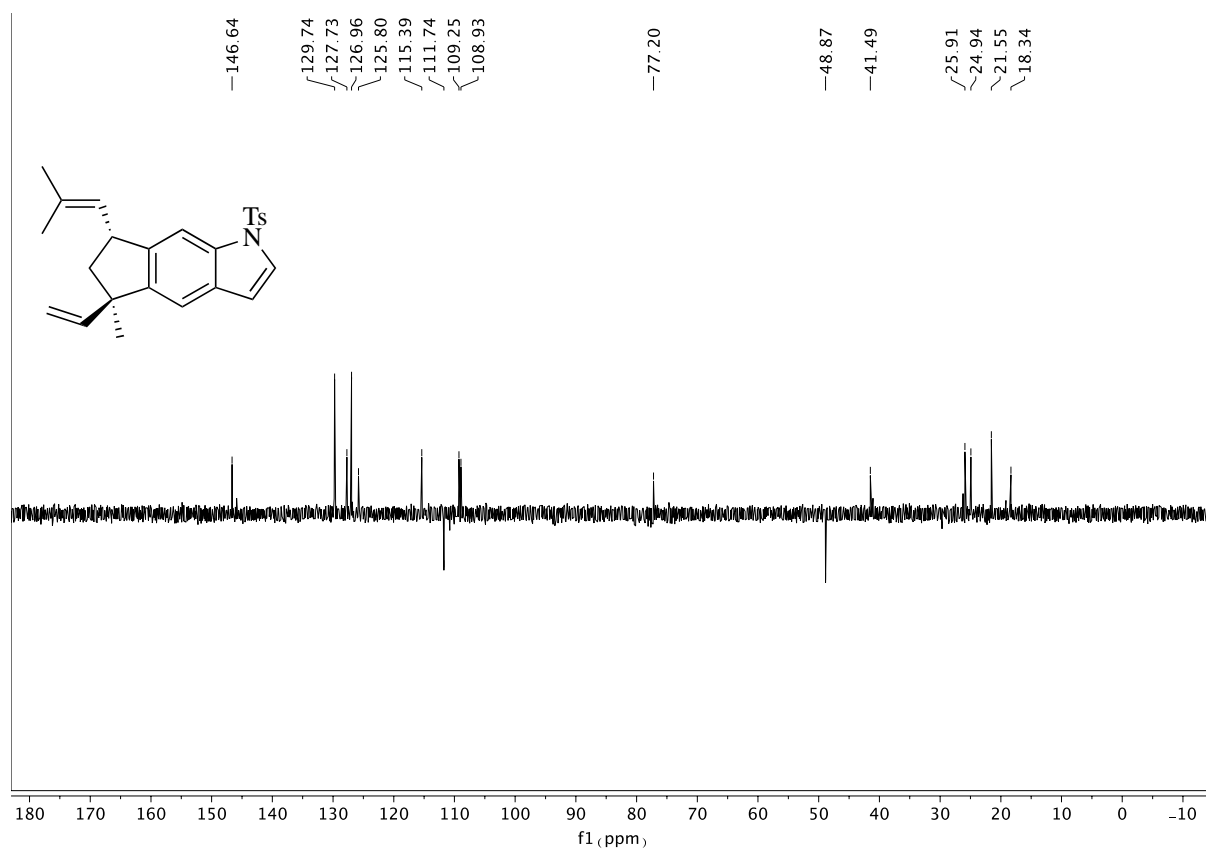
^1H NMR (500 MHz, CDCl_3) Spectrum of a mixture (5*R*,7*R*)-**18a**:(5*R*,7*S*)-**18b** (1:2 ratio). (Obs.: spectrum with traces of starting material).



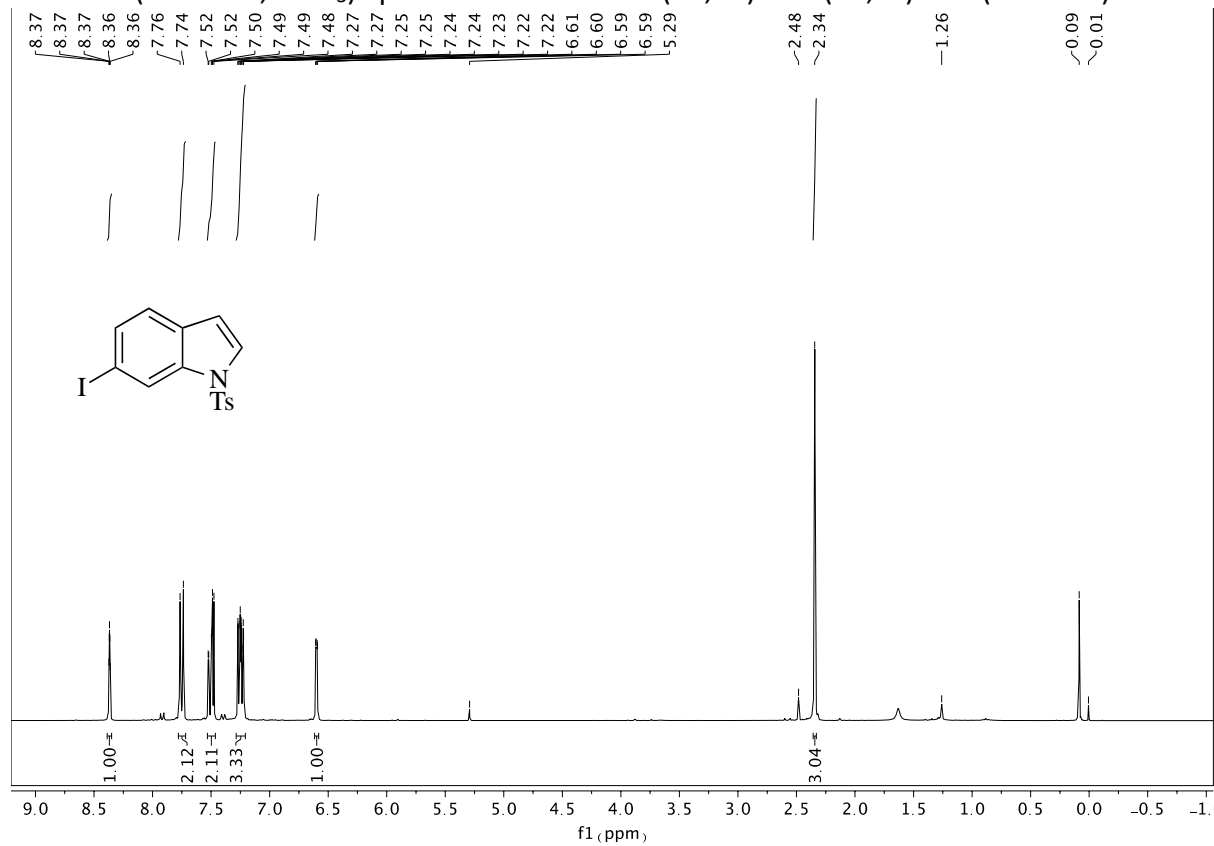
¹H NMR (500 MHz, CDCl₃) Spectrum of a mixture (5*R*,7*R*)-18a**:(5*R*,7*S*)-**18b** (1:2 ratio).**



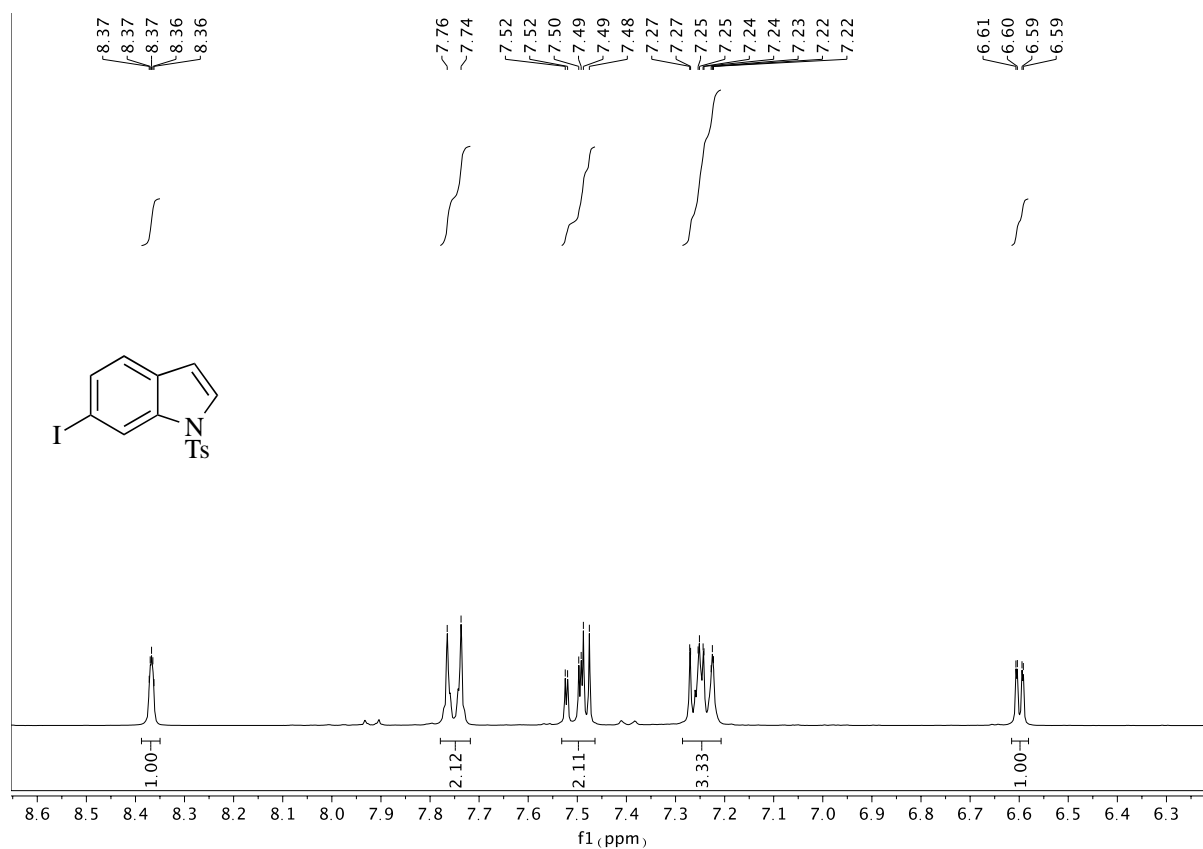
¹³C NMR (126 MHz, CDCl₃) Spectrum of a mixture (5*R*,7*R*)-18a**:(5*R*,7*S*)-**18b** (1:2 ratio).**



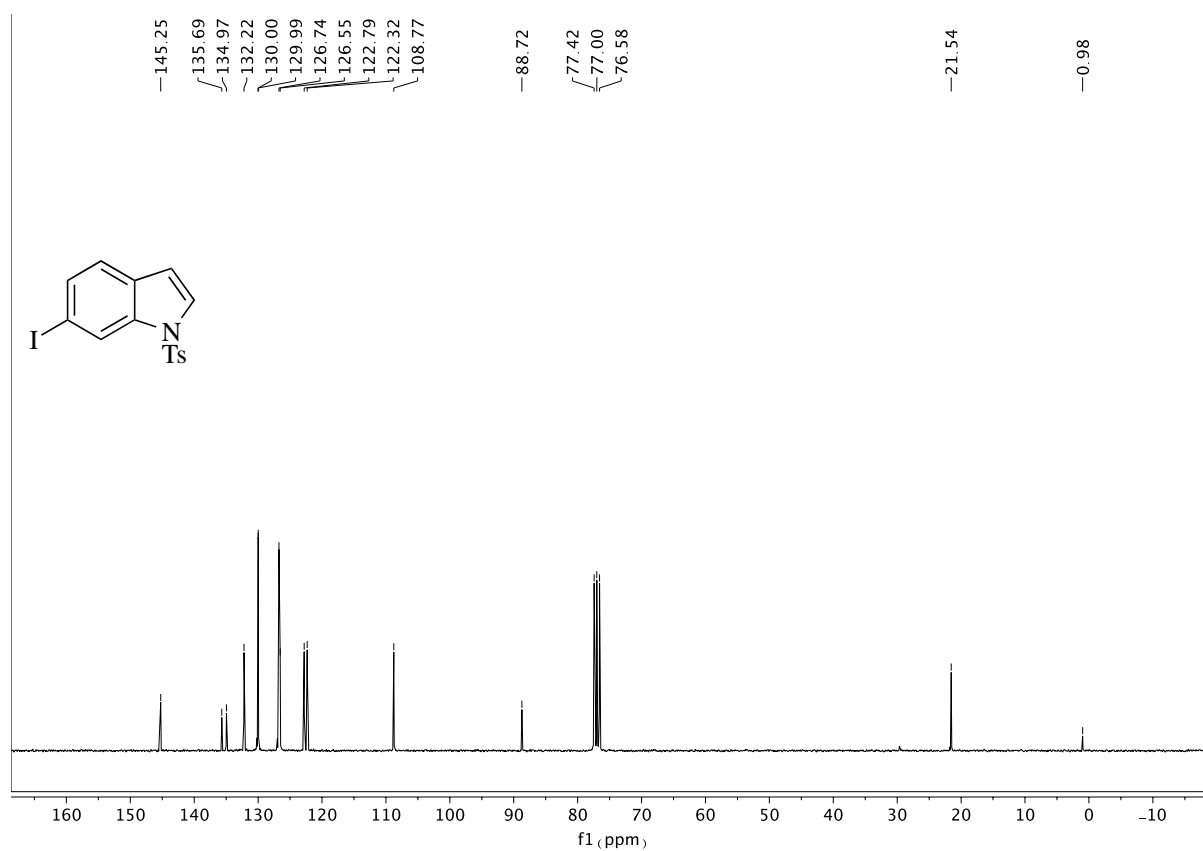
DEPT135 (126 MHz, CDCl₃) Spectrum of a mixture (5*R*,7*R*)-**18a**:(5*R*,7*S*)-**18b** (1:2 ratio).



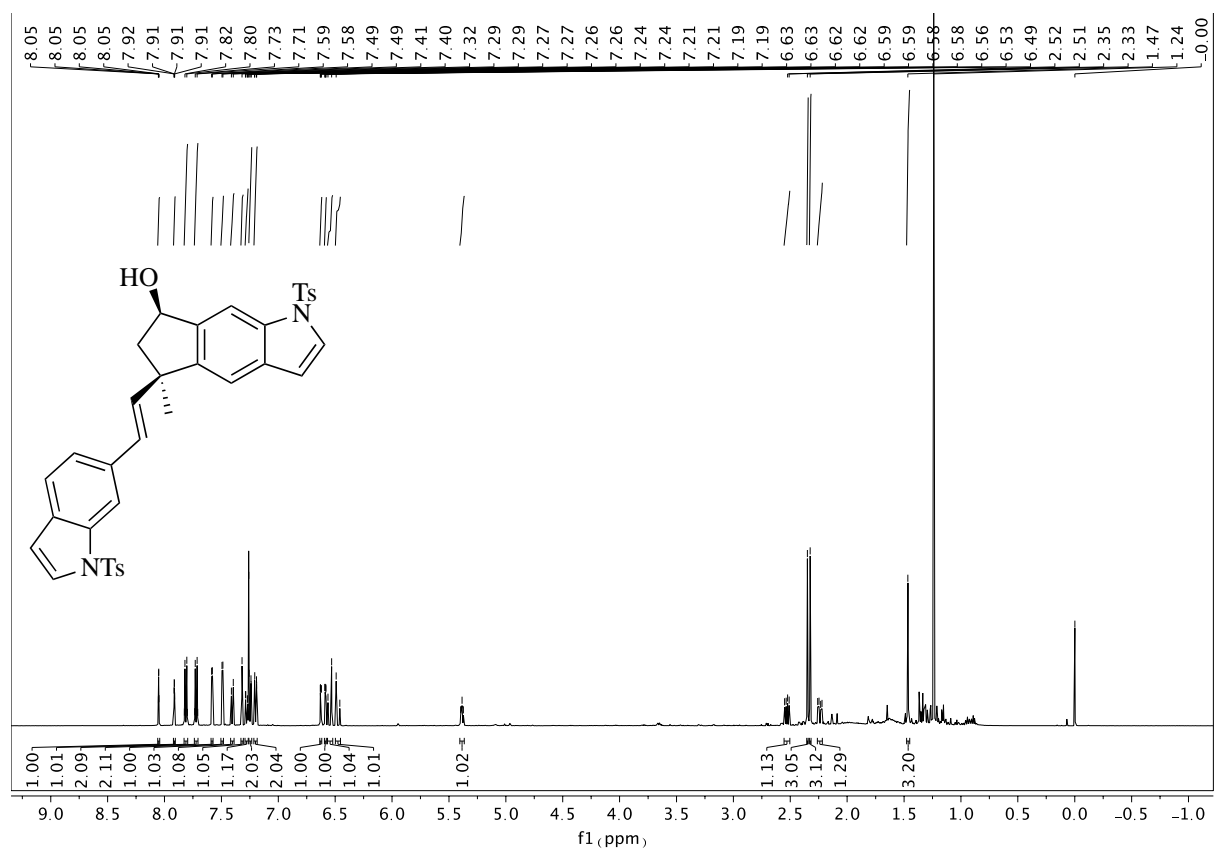
¹H NMR (300 MHz, CDCl₃) Spectrum of compound **17**. (DCM: 5.27 ppm and TsCl impurity).



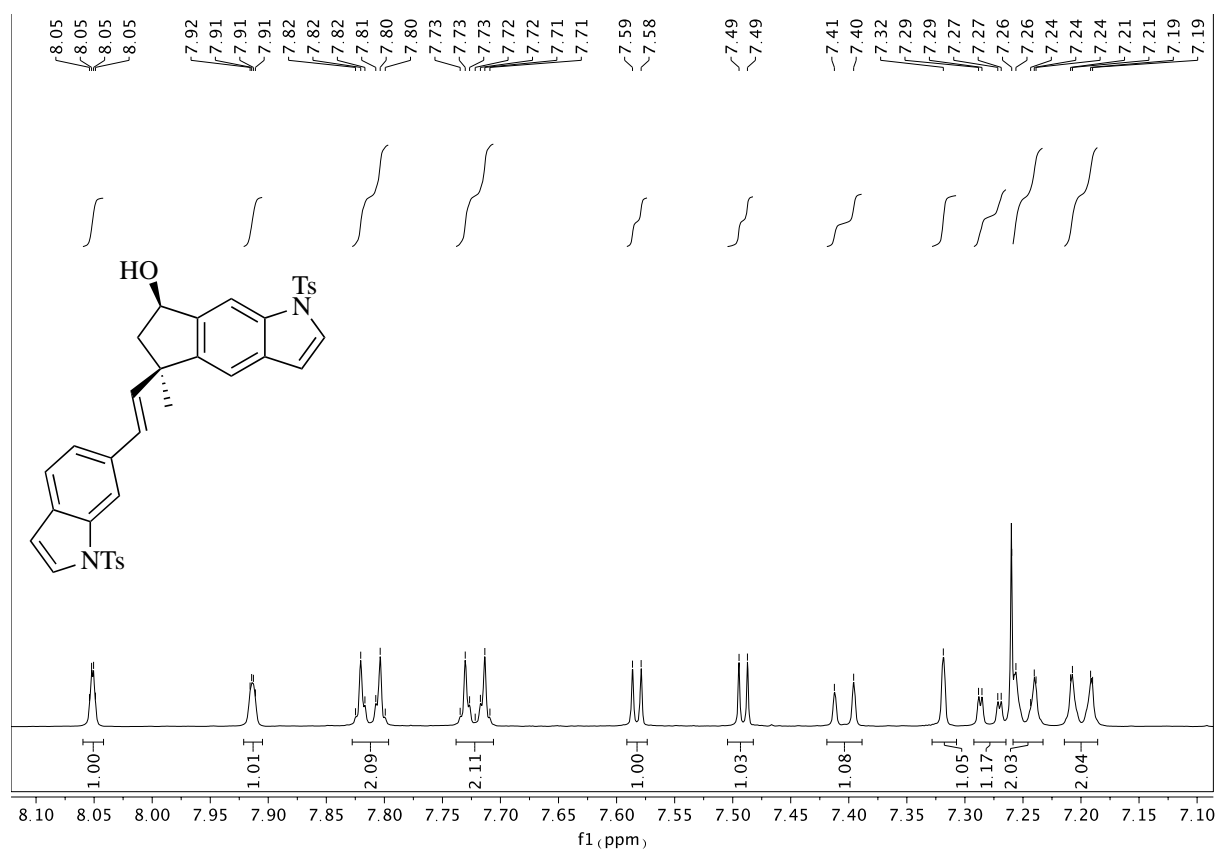
¹H NMR (300 MHz, CDCl₃) Spectrum of compound 17.



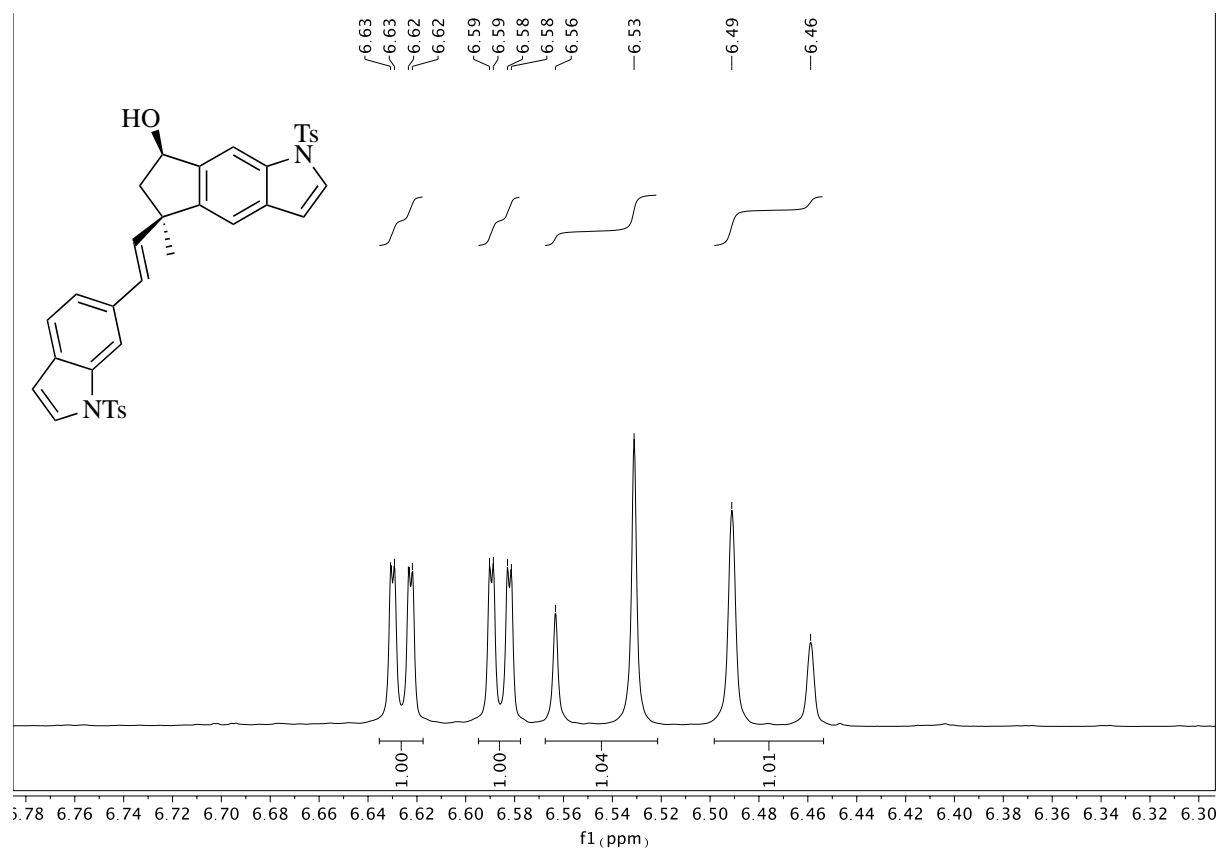
¹³C NMR (75 MHz, CDCl₃) Spectrum of Compound 17.



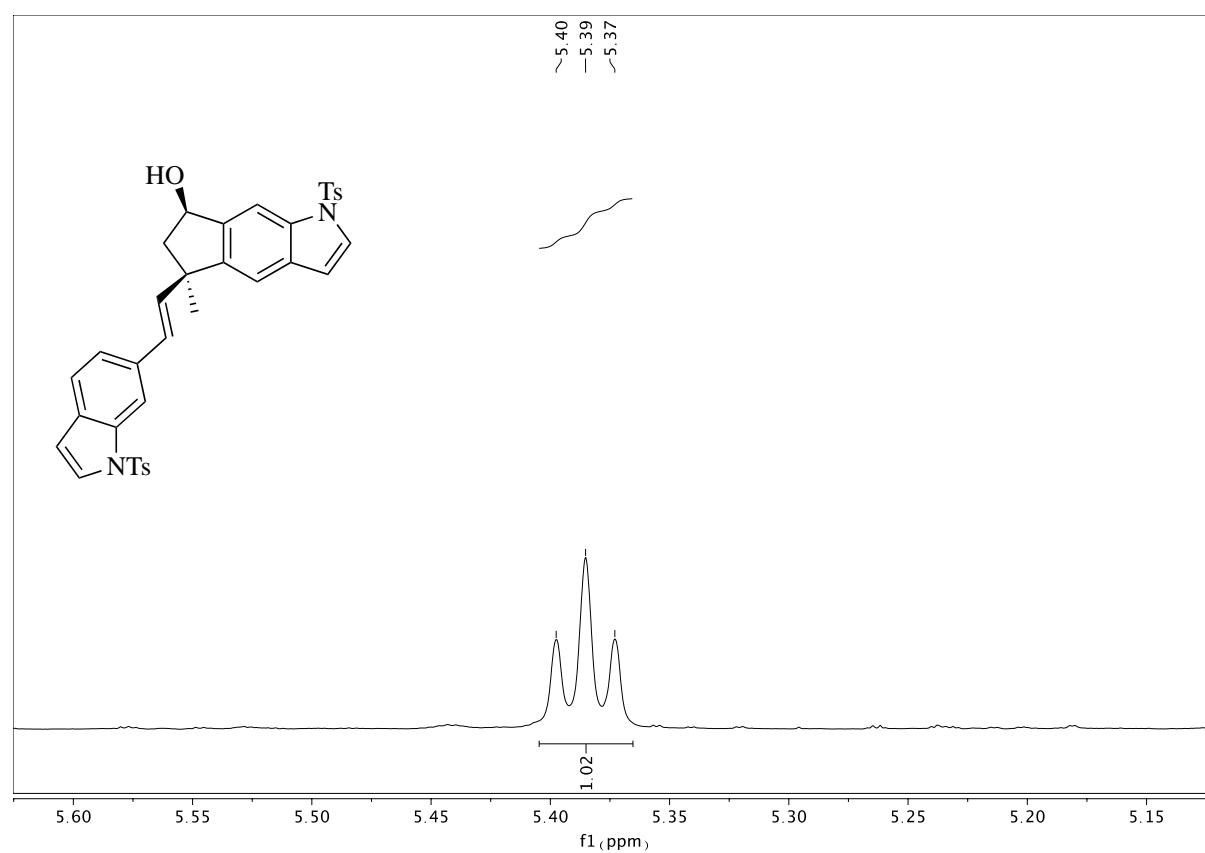
¹H NMR (500 MHz, CDCl₃) Spectrum of compound **15**.



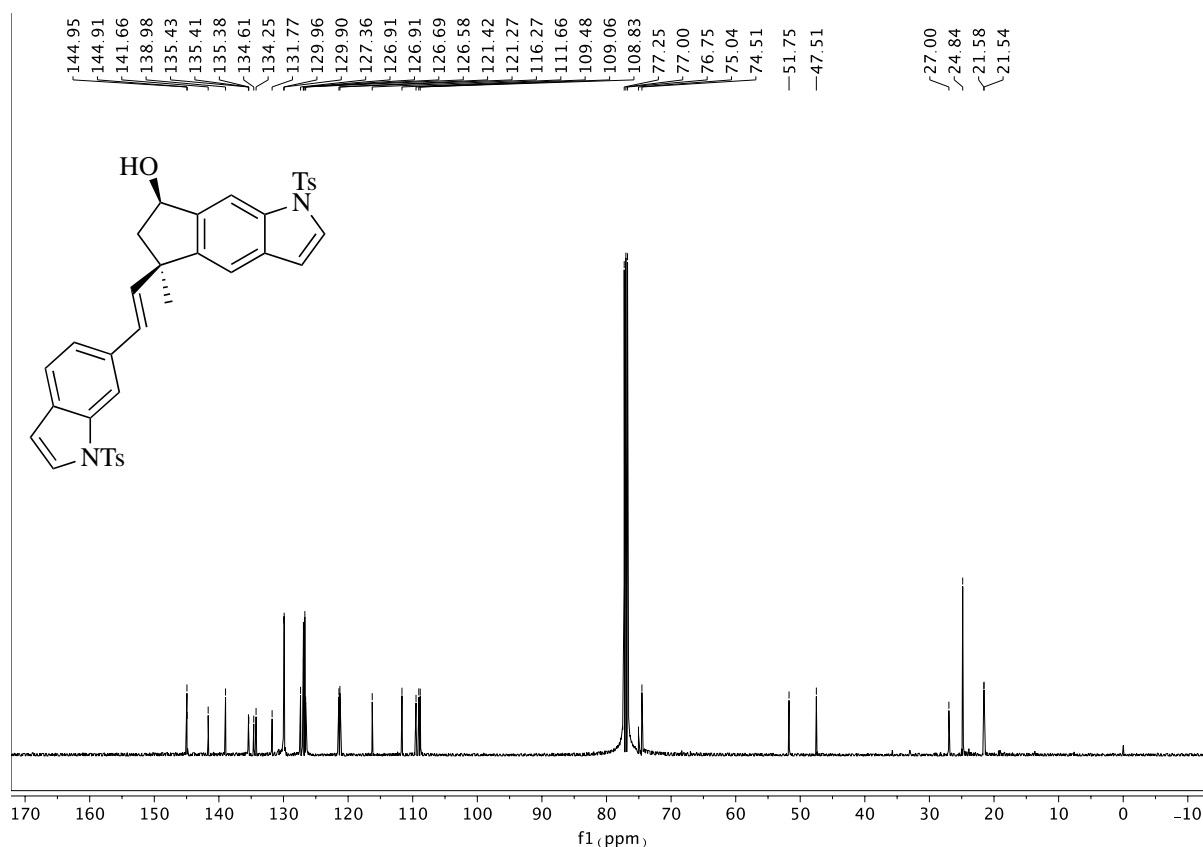
¹H NMR (500 MHz, CDCl₃) Spectrum of compound **15**.



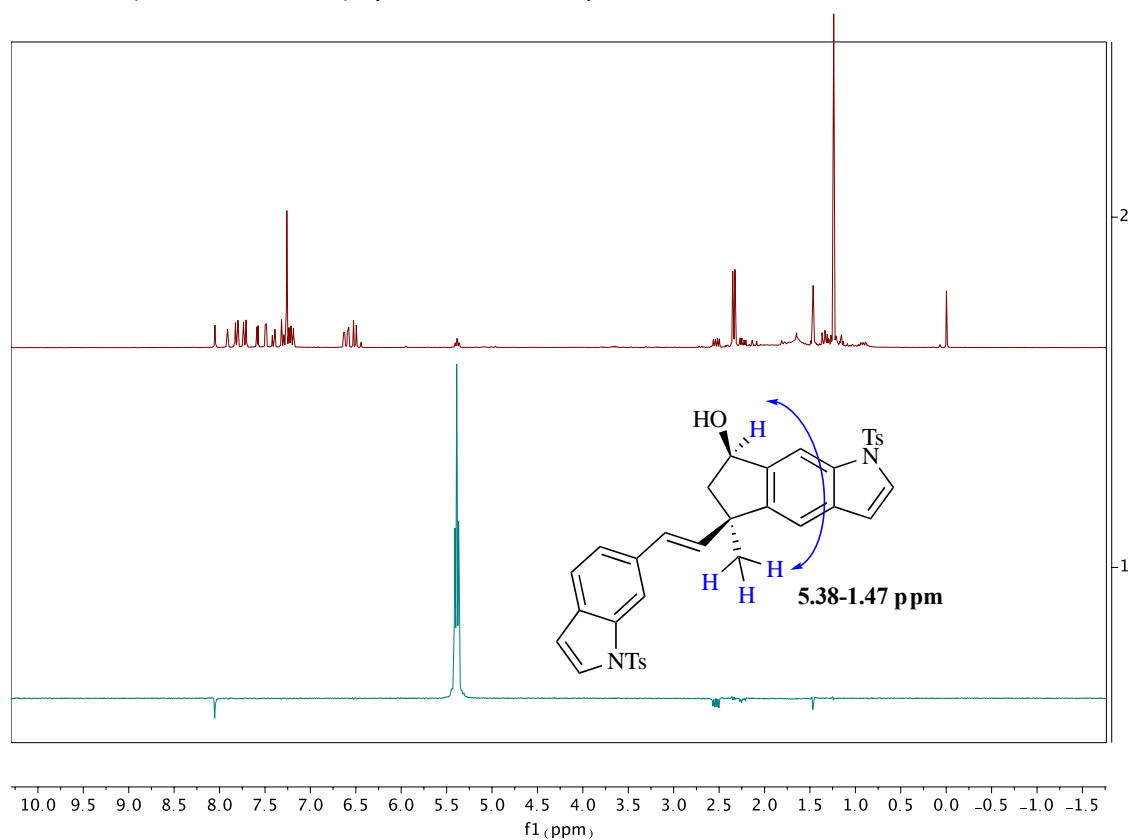
^1H NMR (500 MHz, CDCl_3) Spectrum of compound **15**.



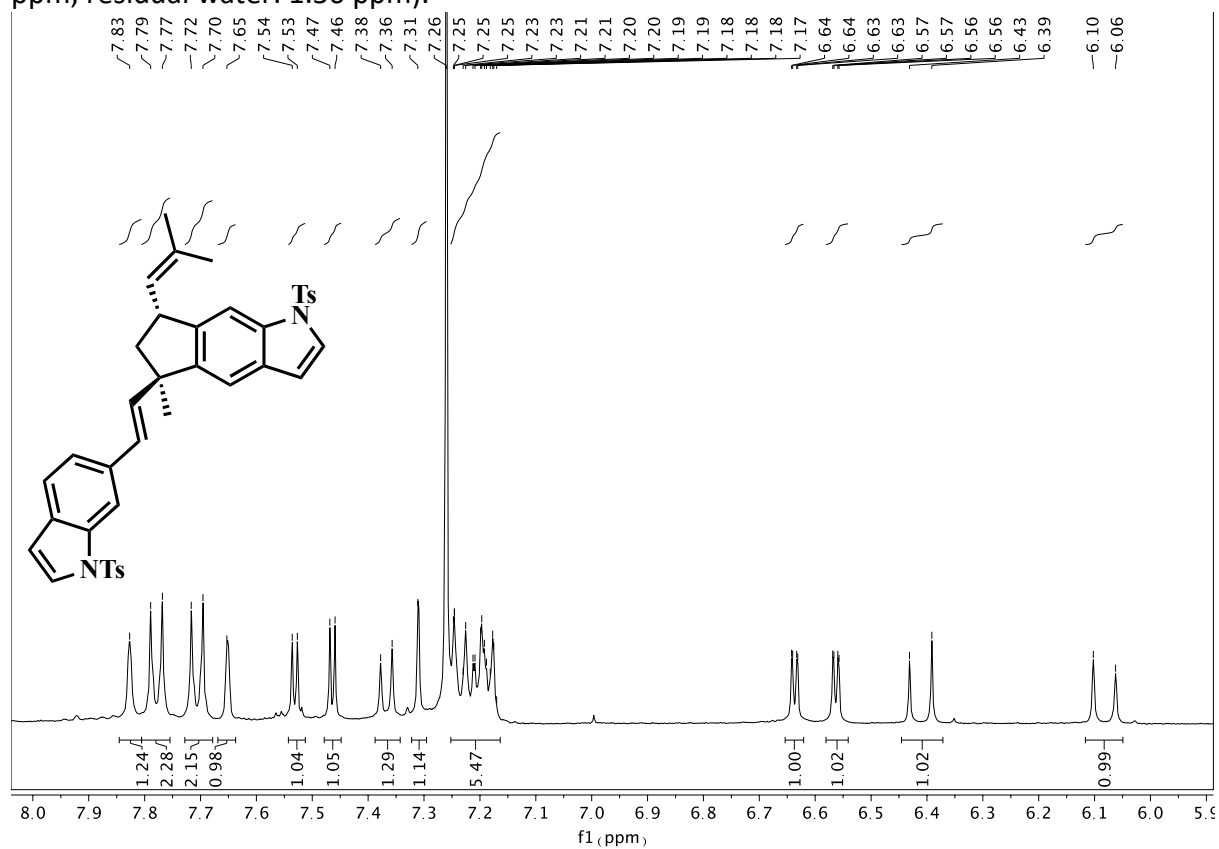
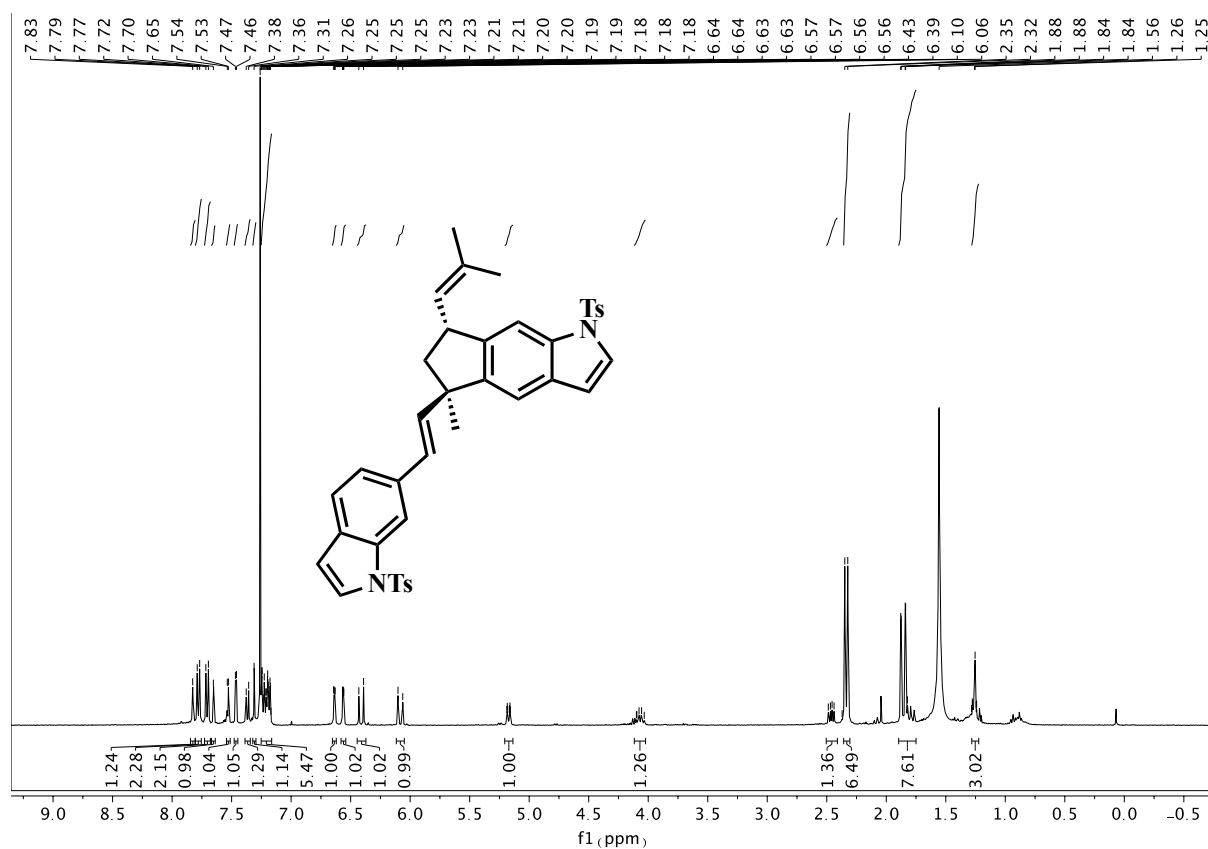
^1H NMR (500 MHz, CDCl_3) Spectrum of compound **15**.

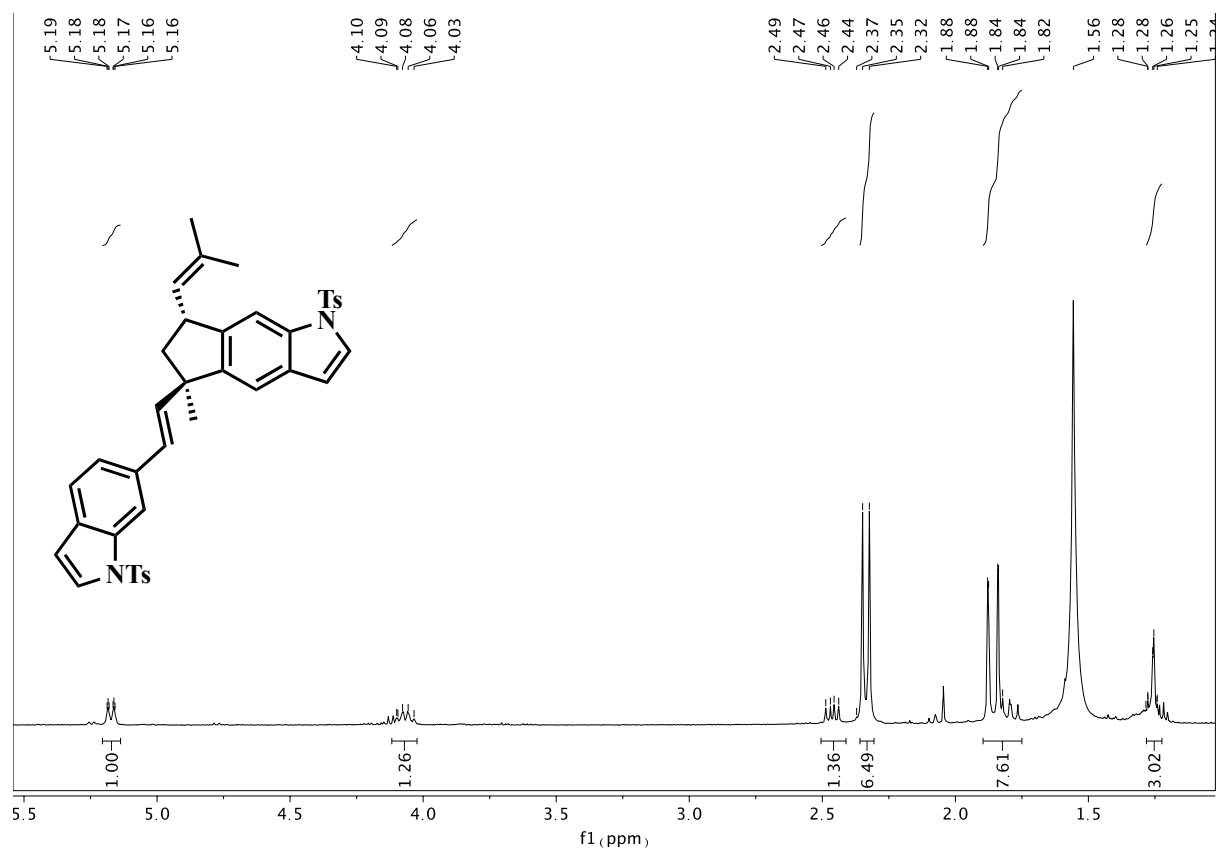


^{13}C NMR (126 MHz, CDCl_3) Spectrum of Compound 15.

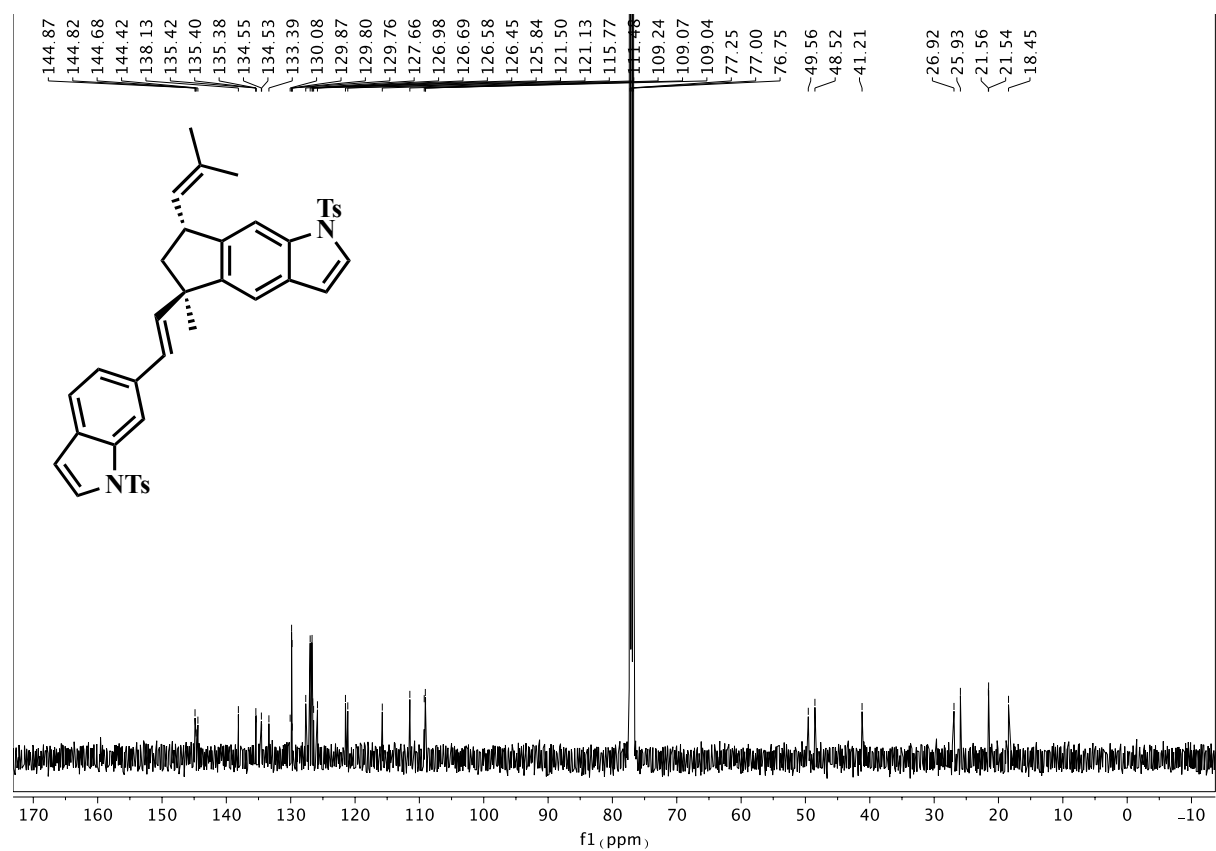


NOE 1D NMR (300 MHz, CDCl_3) Spectrum of compound 15. (irradiation: 5.38 ppm).

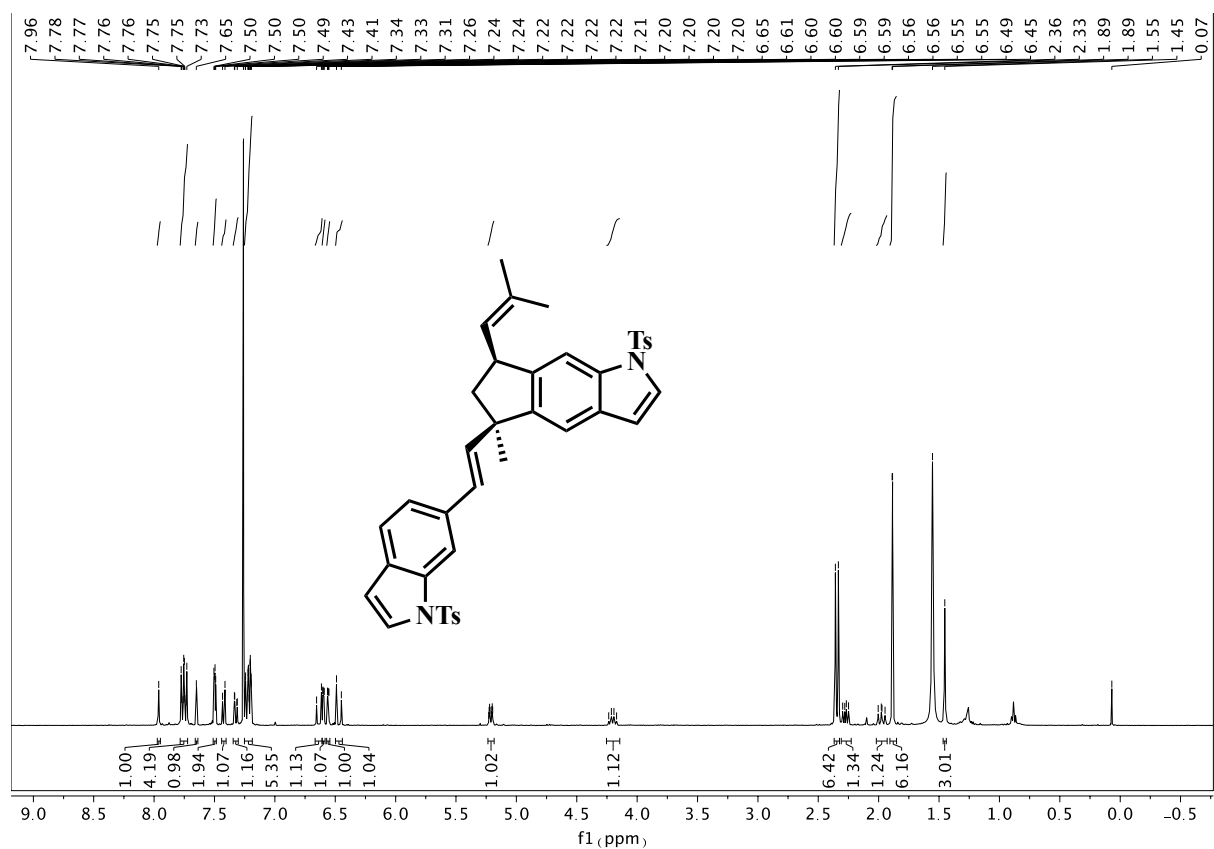




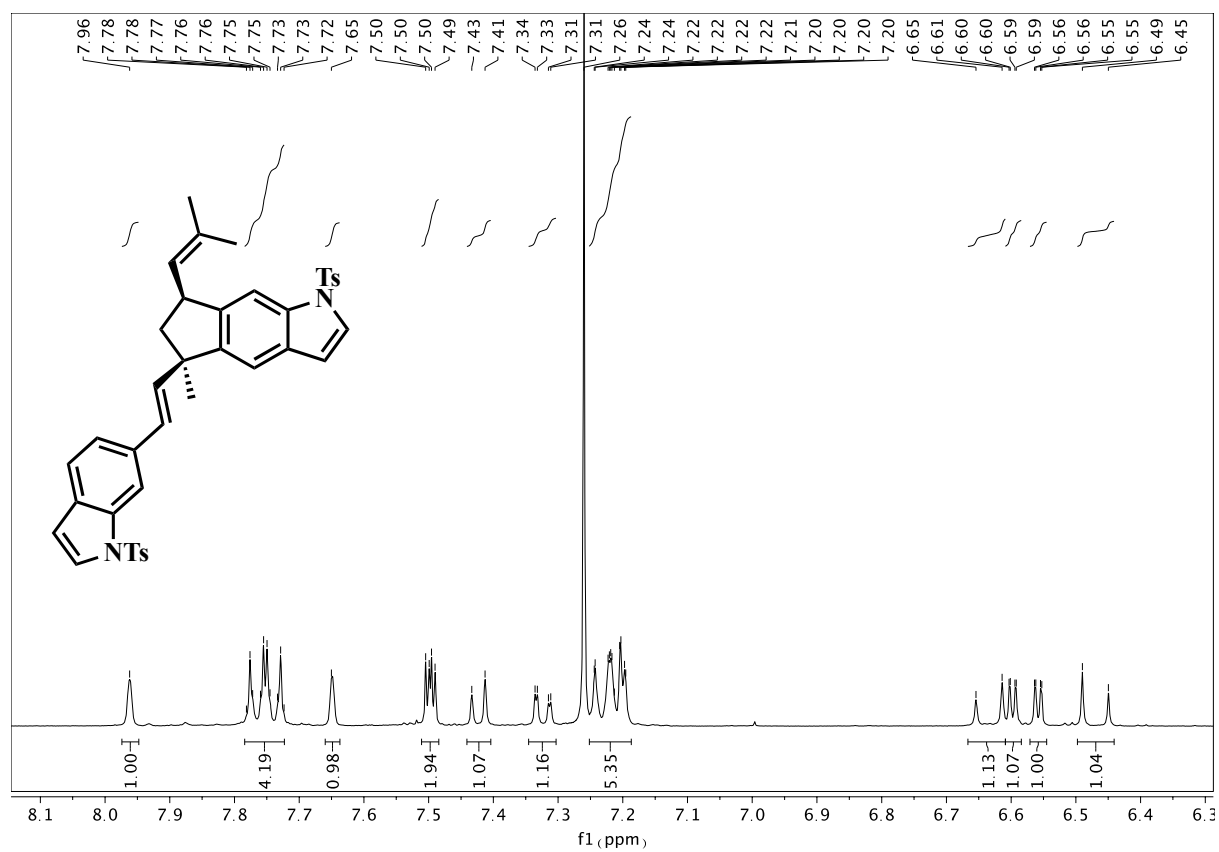
¹H NMR (400 MHz, CDCl₃) Spectrum of (5R,7R)-19a.



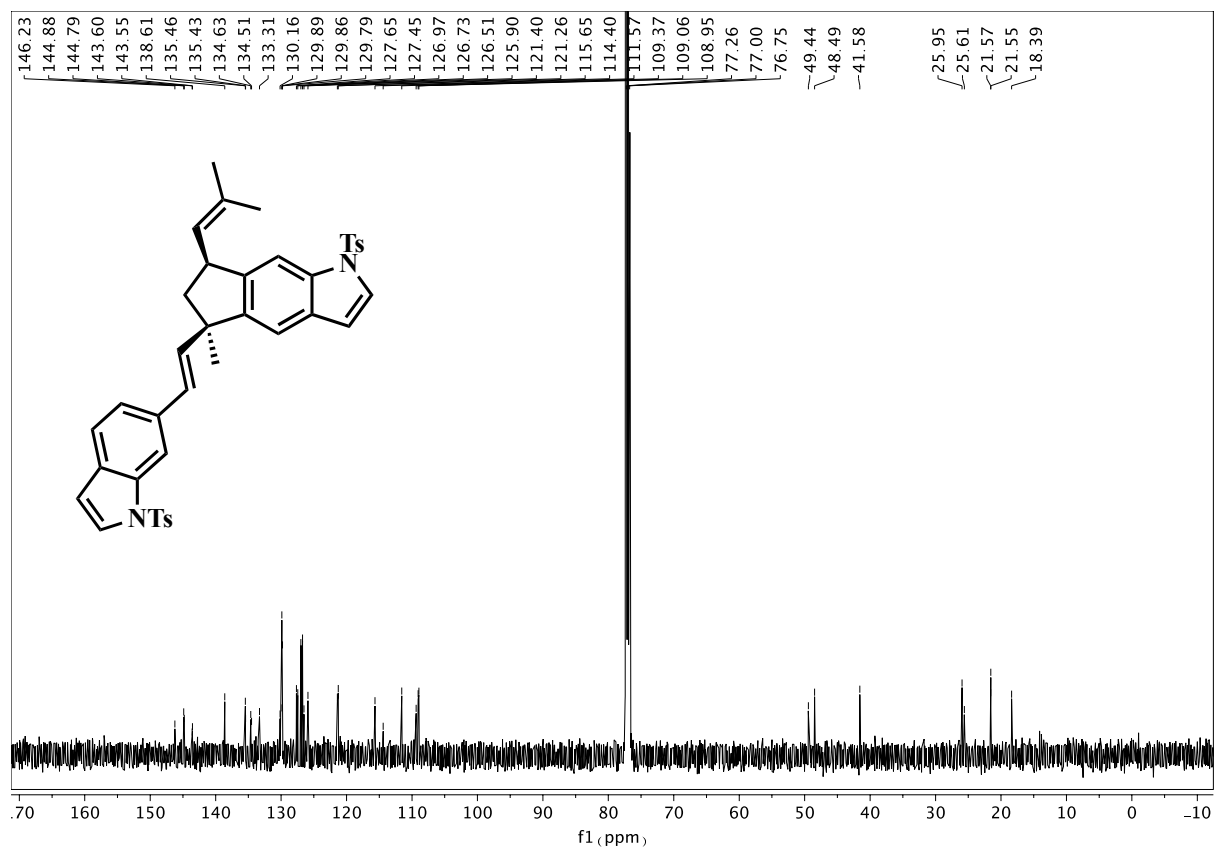
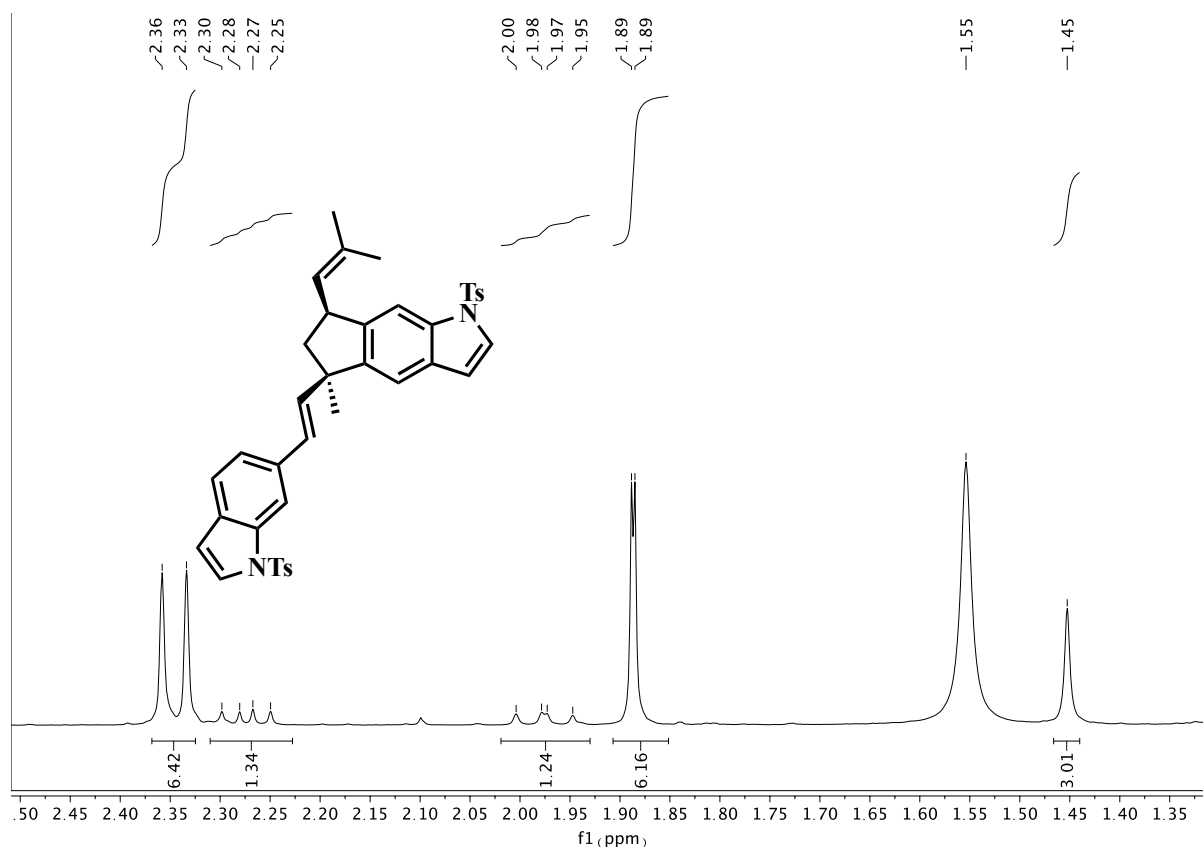
¹³C NMR (126 MHz, CDCl₃) Spectrum of (5R,7R)-19a.

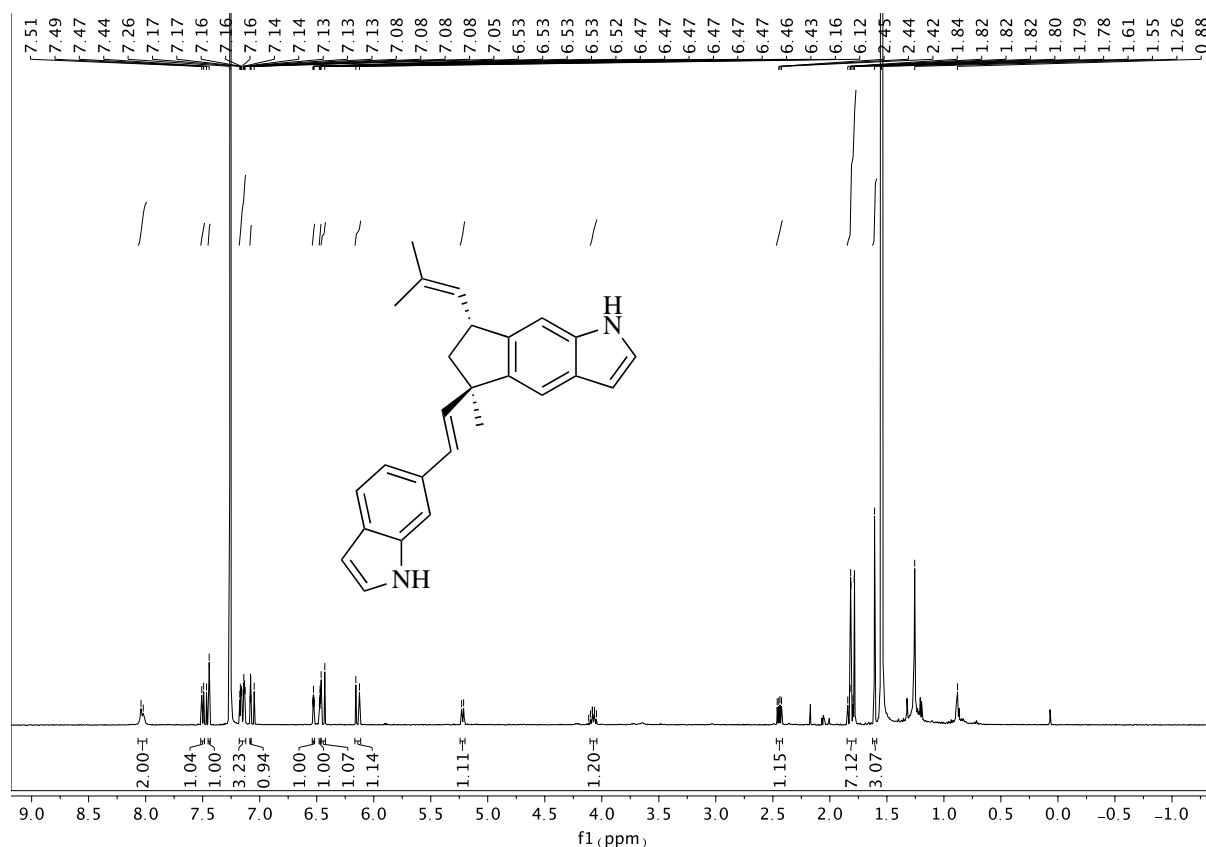


¹H NMR (400 MHz, CDCl₃) Spectrum of (5R,7S)-**19b**. (residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.56 ppm).

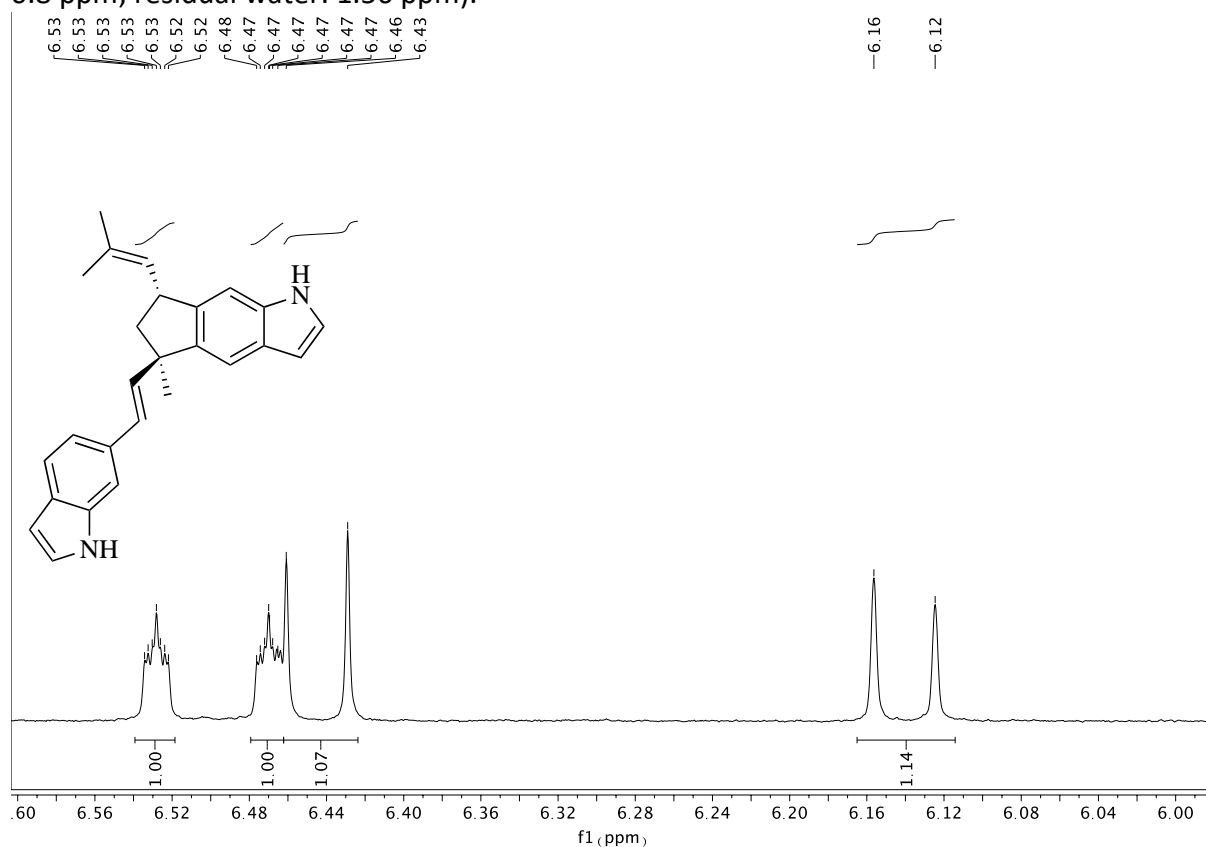


¹H NMR (400 MHz, CDCl₃) Spectrum of (5R,7S)-**19b**.

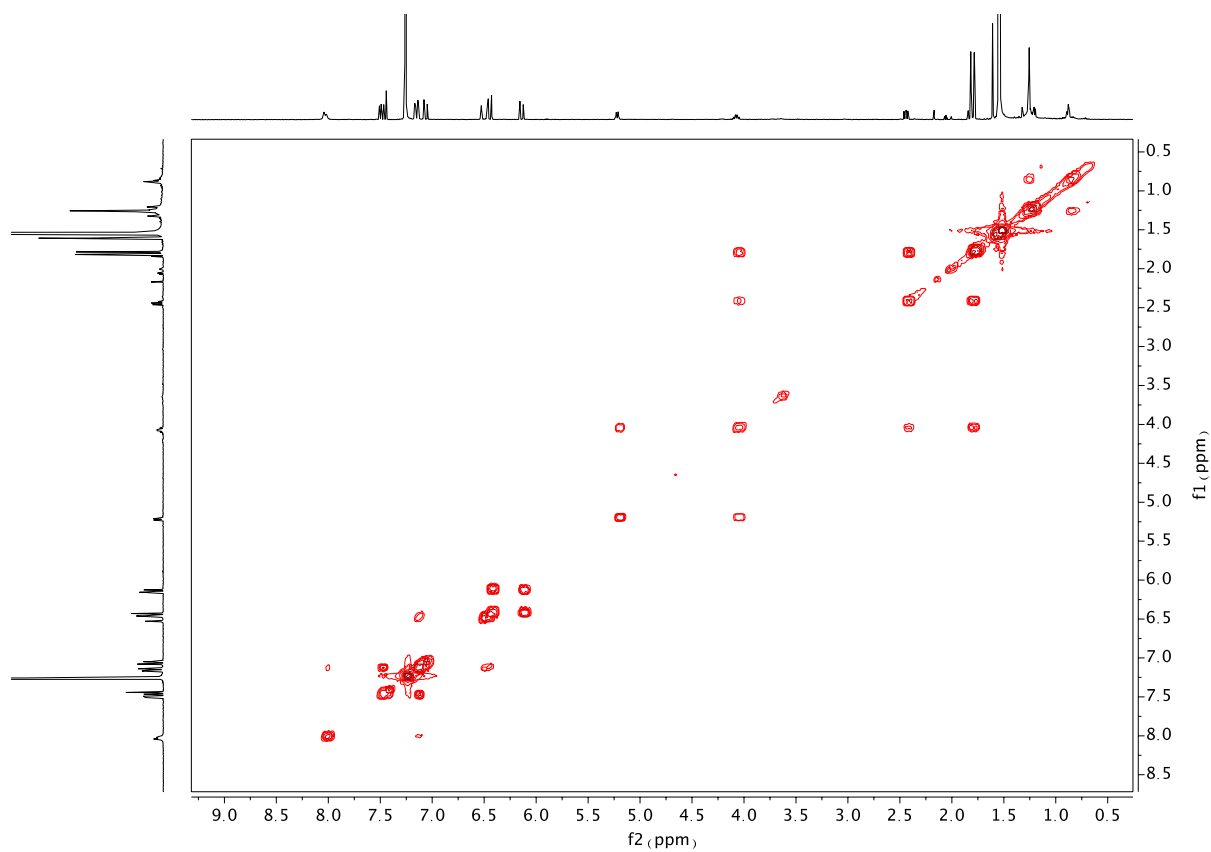
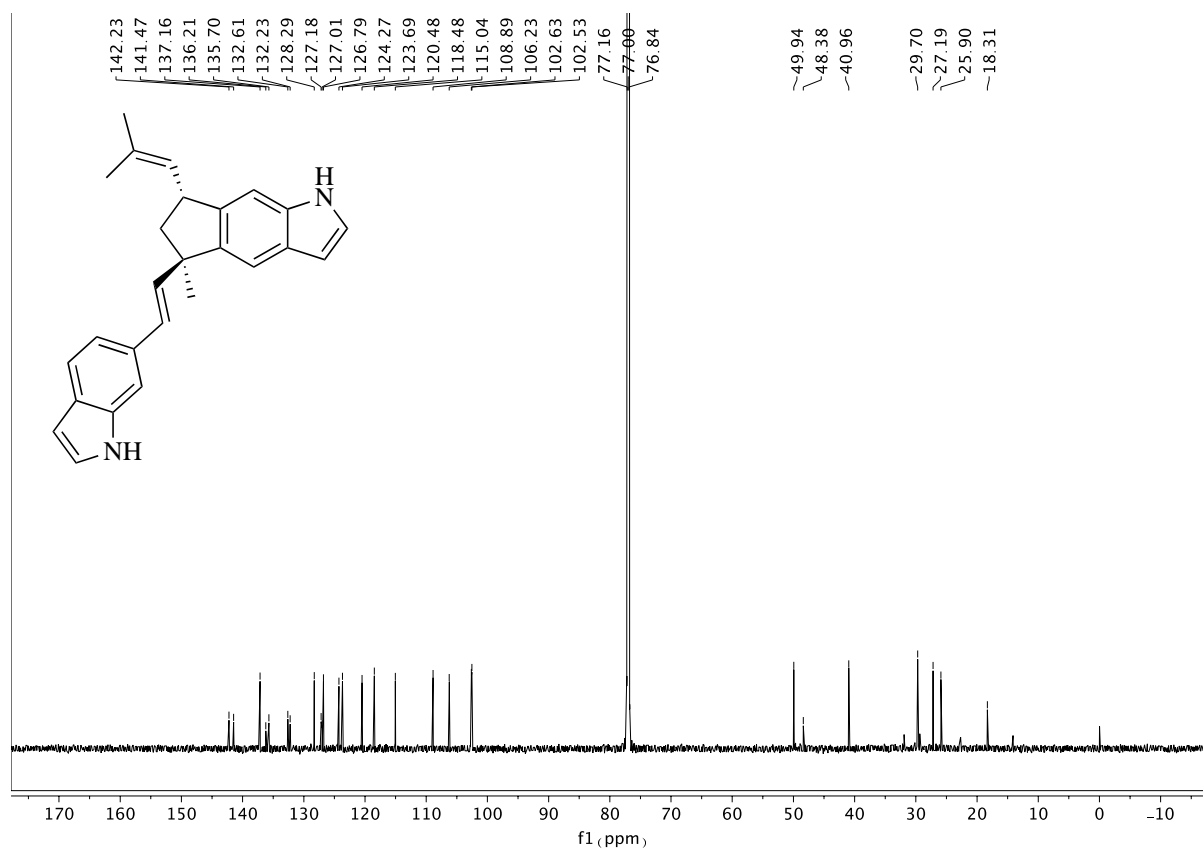


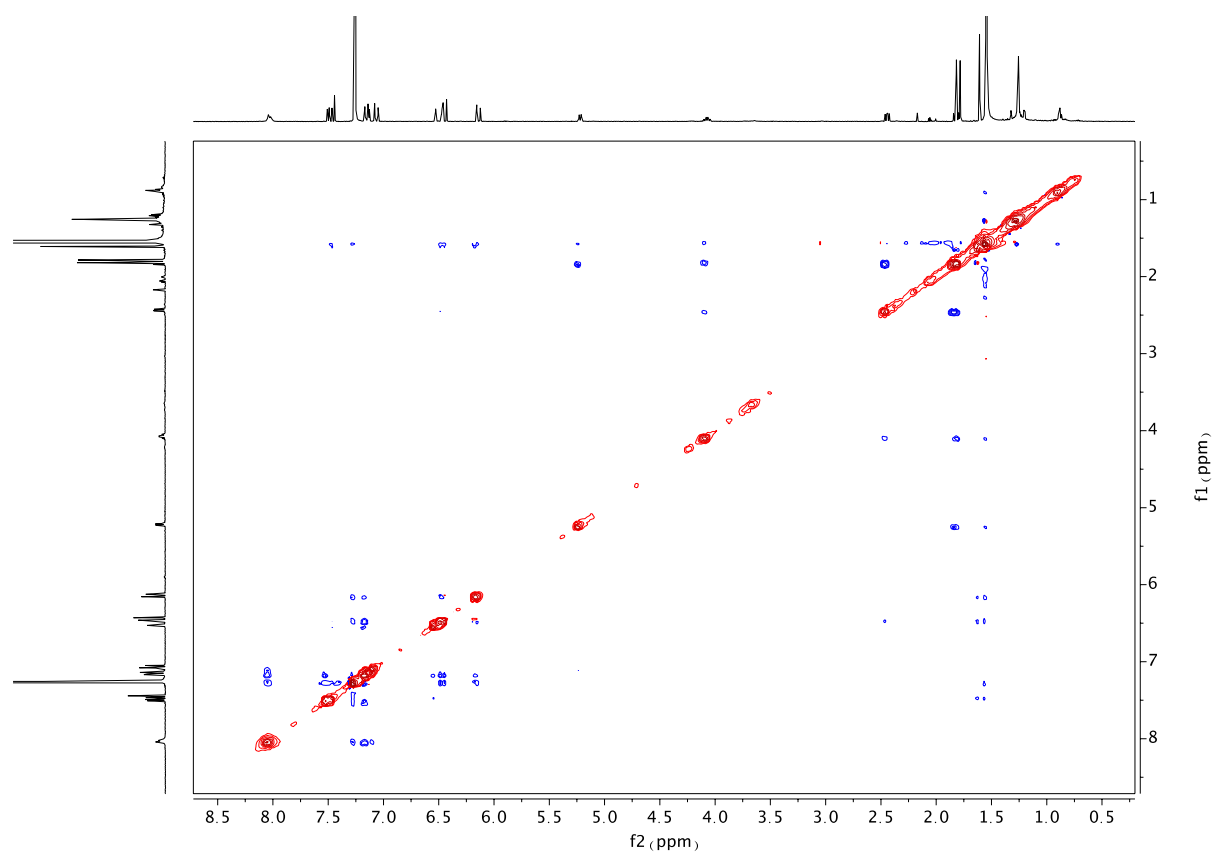


^1H NMR (500 MHz, CDCl_3) Spectrum of Raputindole A (**1**). (residual hexanes grease: 1.26 and 0.8 ppm; residual water: 1.56 ppm).

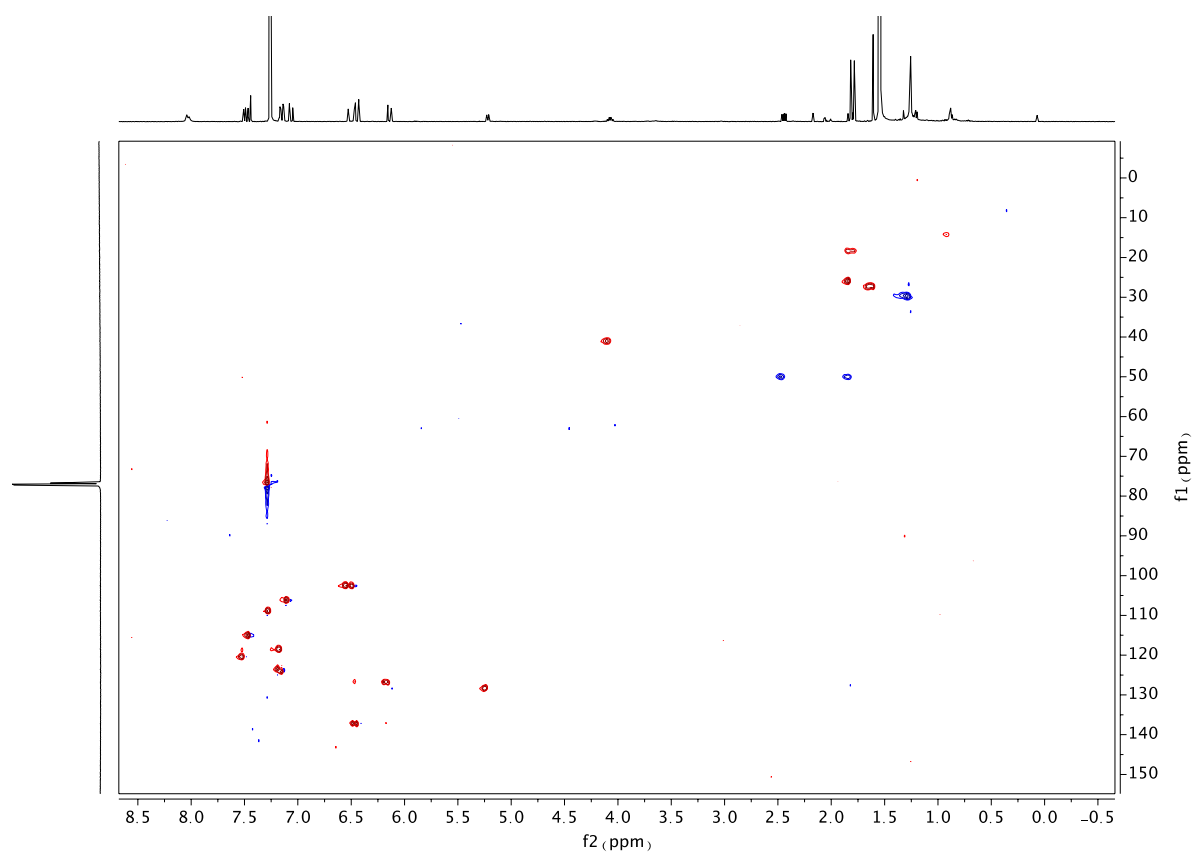


^1H NMR (500 MHz, CDCl_3) Spectrum of Raputindole A (**1**). (residual hexanes grease: 1.26 and 0.8 ppm; residual H_2O : 1.56 ppm).

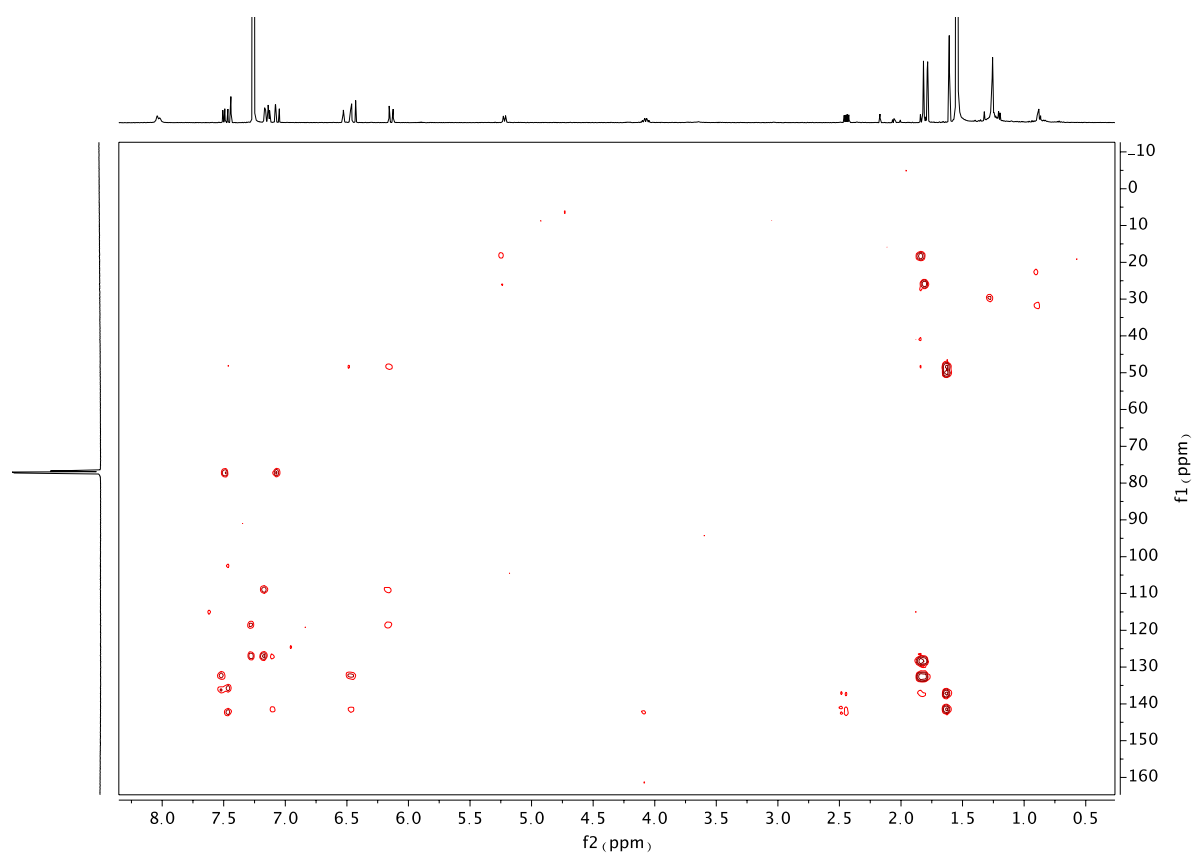




NOESY 2D (500 MHz) of Raputindole A (**1**).



HSQC (500 MHz) of Raputindole A (**1**).



HMBC (500 MHz) of Raputindole A (**1**).