Supporting Information

Enantioselective total synthesis of (+)-ibophyllidine via an asymmetric phosphine-catalyzed [3 + 2] annulation

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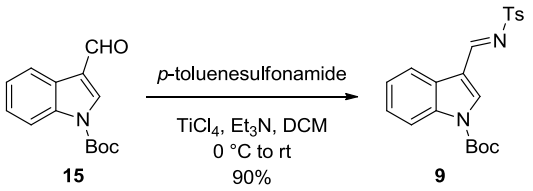
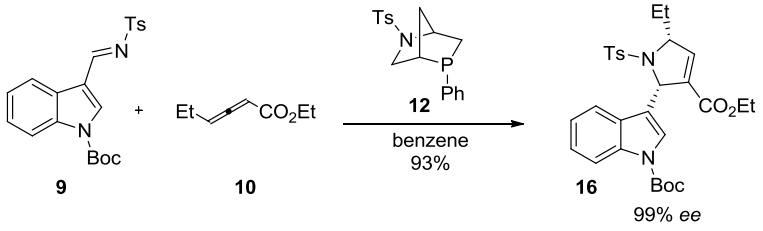
Materials and Methods

Unless otherwise stated, all reactions were performed in flame-dried glassware fitted with a rubber septum, under an Ar atmosphere, and stirred with a Teflon-coated stirrer bar. All reaction solvents were distilled immediately prior to use [dichloromethane (DCM), acetonitrile (MeCN), benzene (PhH), and toluene (PhMe) were distilled from CaH_2; tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl; methanol (MeOH) was distilled from magnesium methoxide] and transferred with an oven-dried needle and a disposable syringe using standard Schlenk techniques. Thin layer chromatography (TLC) was performed using SiliCycle silica gel 60 F-254–precoated glass-backed plates (thickness: 0.25 mm) and visualized under UV light and through anisaldehyde or permanganate staining. Flash column chromatography was performed using SiliCycle Silica-P silica gel (particle size: 40–63 μm). Melting points were measured using an Electrothermal capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using Bruker Avance-500, ARX-400, and ARX-500 MHz spectrometers, with ^{13}C operating frequencies of 125, 100, and 125 MHz respectively. Chemical shifts are reported in ppm (δ) with respect to the residual solvent ($CHCl_3$; δ = 7.26 ppm for ^{1}H; δ = 77 ppm for ^{13}C). Data for ^{1}H NMR spectra are reported as follows: chemical shift (ppm), multiplicity, coupling constant (Hz), and number of protons. The following abbreviations are used for ^{1}H NMR multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; quint = quintet; dd = doublet of doublets; dt = doublet of triplets; dq = doublet of quartets; td = triplet of doublets; tdd = triplet of doublet of doublets; m = multiplet; br = broad; app = apparent. Data for ^{13}C NMR spectra are reported with respect to chemical shift (ppm). IR spectra were recorded using a Jasco FTIR-4100 spectrometer equipped with an ATR attachment. MALDI mass spectra were recorded using an AB/PerSpective DE-STR instrument. Samples for MALDI analysis were dissolved with 2,5-dihydroxybenzoic acid as the matrix. High-resolution mass spectra were recorded using a Waters LCT Premier instrument. Optical rotations were recorded using a Rudolph Autopol IV automatic polarimeter. Enantiomeric excess was measured using a Mettler Toledo SFC (supercritical fluid chromatography) instrument and a chiral OD-H column (20% EtOAc).

Experimental Procedures



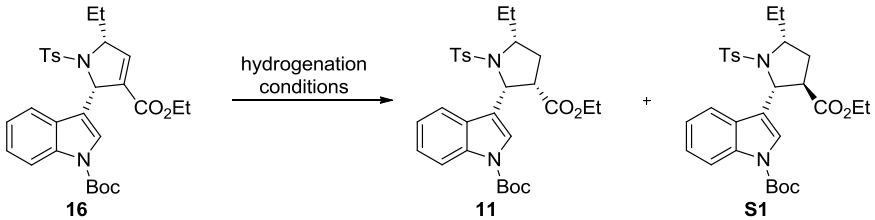
***N*-Tosyl-imine 9.** Indole-3-carboxaldehyde is commercially available or readily prepared via Vilsmeier–Haack formylation of indole, following the procedure of James and Snyder.[1] Indole-3-carboxaldehyde was then N-Boc–protected, following the procedure of Grehn and Ragnarsson, to provide **15**.[2] *N*-Boc-indole-3-aldehyde (**15**; 4.76 g, 19.4 mmol, 1 equiv) and *p*-toluenesulfonamide (3.36 g, 19.6 mmol, 1.01 equiv) were suspended in freshly distilled DCM (194 mL). The mixture was placed under a positive pressure of Ar and then freshly distilled triethylamine (8.12 mL, 58.2 mmol, 3 equiv) was introduced via syringe. The heterogeneous mixture was cooled to 0 °C and then 1 M $TiCl_4$ in DCM (9.71 mL, 9.71 mmol, 0.5 equiv) was added via syringe pump over 1 h. The mixture was then stirred until the starting material was consumed (overnight, as determined by TLC; the mixture was slowly warmed to room temperature over the course of the reaction). The mixture was cooled to 0 °C and then the reaction was quenched through the addition of saturated aqueous $NaHCO_3$. The layers were separated and the aqueous phase extracted twice with DCM. The combined organic phases were washed with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was recrystallized (DCM/hexanes) to provide a yellow crystalline solid (6.96 g, 90%). Mp: 139–140 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.29 (d, *J* = 7.9 Hz, 1H), 8.28 (s, 1H), 8.14 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.3 Hz, 2H), 7.41 (td, *J* = 7.4, 1.4 Hz, 1H), 7.36–7.30 (m, 3H), 2.42 (s, 3H), 1.69 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2, 148.3, 144.0, 137.5, 136.1, 135.9, 129.6, 127.7, 126.2, 126.2, 124.6, 122.7, 116.4, 115.1, 85.9, 27.9, 21.5; IR (film): 3132, 1575, 1329, 1235, 1083, 811, 544 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{21}H_{22}N_2O_4SH$, 399.1378, found 399.1375.



[1] P. N. James, H. R. Snyder, *Org. Synth.*, 1963, **Coll. Vol. 4**, 539.
[2] (a) L. Grehn, U. Ragnarsson, *Angew. Chem. Int. Ed.*, 1984, **23**, 296. (b) G. Bringmann, S. Tasler, H. Endress, K. Peters, E.-M. Peters, *Synthesis*, 1998, 1501.

Pyrroline 16. A flame-dried round-bottom flask was charged with the imine **9** (50.0 mg, 0.125 mmol, 1 equiv) and the phosphine **12** (4.30 mg, 0.0125 mmol, 0.1 equiv) in a glove box. The flask was capped with a rubber septum, transferred out of the glove box, and placed under a positive pressure of Ar. The solid mixture was dissolved in benzene (1 mL), followed by the addition of the allenoate **10** (23 mg, 0.163 mmol, 1.3 equiv), prepared using the method of Lang and Hansen.[3] The mixture was stirred at room temperature until the starting imine **9** was consumed (4 h, as determined by TLC). The crude reaction product was loaded directly onto a column of SiO_2 and purified through flash column chromatography (30% Et_2O/pentanes) to yield a white solid (62.4 mg, 93%, 99% *ee* as determined by SFC). Mp: 92–94 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.77 (d, *J* = 7.7 Hz, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.41 (s, 1H), 7.28 (td, *J* = 7.3, 1.1 Hz, 1H), 7.22 (td, *J* = 7.3, 1.0 Hz, 1H), 7.1 (d, *J* = 8.1 Hz, 2H), 6.79 (app t, *J* = 2.0 Hz, 1H), 5.98 (app t, *J* = 1.9 Hz, 1H), 4.66–4.60 (m, 1H), 4.00 (q, *J* = 7.1 Hz, 2H), 2.33 (s, 3H), 2.14–2.03 (m, 1H), 1.89–1.77 (m, 1H), 1.66 (s, 9H), 1.06 (t, *J* = 7.5 Hz, 3H), 1.03 (t, *J* = 7.1 Hz, 3H); ^{13}C (125 MHz, $CDCl_3$): δ 162.1, 149.4, 143.4, 139.2, 135.3, 135.2, 133.9, 129.2, 128.9, 127.4, 125.3, 124.2, 122.4, 120.0, 119.7, 114.9, 83.7, 68.6, 61.3, 60.7, 29.3, 28.1, 21.3, 13.8, 10.4; IR (film) 2978, 2932, 2879, 1722, 1449, 1368, 1254, 1156, 1087 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{29}H_{34}N_2O_6SH$, 539.2216, found 539.2208; $[\alpha]^{24.2}_D$ +83.2° (*c* = 1.000, $CHCl_3$).

Large-Scale Synthesis of the Pyrroline 16. A flame-dried 1-L-round-bottom flask was charged with the imine **9** (28.8 g, 72.4 mmol, 1 equiv) and the phosphine **12** (2.5 g, 7.2 mmol, 0.1 equiv) in a glove box. The flask was capped with a rubber septum, transferred out of the glove box, and placed under a positive pressure of Ar. Benzene (576 mL) was added to the flask and then the mixture was stirred at room temperature until it became homogeneous (ca. 10 min). The allenoate **10** (13.2 g, 94.1 mmol, 1.3 equiv) was introduced via syringe and then the reaction mixture was stirred at room temperature until the starting imine **9** had been consumed (8 h, as determined by TLC). The crude reaction product was loaded directly onto a large column of SiO_2 and purified through flash column chromatography (30% Et_2O/pentanes). The impure fractions were subjected to a second round of column chromatography. The clean fractions were combined to yield a slightly yellow solid (36.7 g, 94% yield, 97% *ee* as determined by SFC).



[3] R. Lang, H.-J. Hansen, *Org. Synth.*, 1984, **62**, 202.

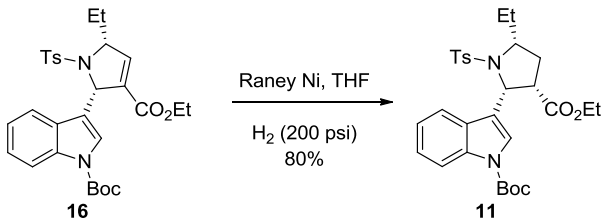
Hydrogenation of the Pyrroline 16. A summary of the results obtained for the hydrogenation of the pyrroline **16** is provided in Table S1. The study began with the hydrogenation of **16** using 5% palladium on carbon in EtOH under a balloon of H_2. Although the double bond was reduced, the hydrogenation occurred predominantly—and surprisingly—from the same face of the ring bearing the ethyl and indole groups, yielding little of the desired compound **11** (entry 1). Performing the reaction under milder conditions (room temperature) provided more of the desired diastereoisomer **11**, but still favored **S1** with a 1:8 dr (entry 2). Performing the reaction in EtOAc provided no difference in selectivity (entry 3), whereas changing the solvent to THF led to a small improvement, but still favored the undesired isomer **S1** with a 1:5 ratio (entry 4). When using benzene as the solvent, the ratio of products changed in favor of the desired isomer **11**, albeit only slightly (1.8:1 dr, entry 5). In an attempt to improve the diastereoselectivity, the reaction was performed under a greater pressure of H_2. Upon switching from a H_2-filled balloon to running the reaction in a pressure reactor at 100 psi, the selectivity increased from 1.8:1 to a tolerable 5:1 (entries 5 and 6, respectively). Increasing the pressure to 200 psi did not change

Table S1 Optimization of the hydrogenation of the pyrroline **16** to form the pyrrolidine **11**

Entry	Catalyst	Solvent	Hydrogen source	**11**:**S1**[a]
1	5% Pd/C	EtOH	H_2 balloon (50 °C)	1:37
2	5% Pd/C	MeOH	H_2 (balloon)	1:8
3	5% Pd/C	EtOAc	H_2 (balloon)	1:8
4	5% Pd/C	THF	H_2 (balloon)	1:5
5	5% Pd/C	PhH	H_2 (balloon)	1.8:1
6	5% Pd/C	PhH	H_2 (100 psi)	5:1
7	5% Pd/C	PhH	H_2 (200 psi)	5:1
8	5% Pd/C	PhH	H_2 (500 psi)	3.7:1
9	5% Pd/C	PhMe	H_2 (200 psi)	2.4:1
10	$(PPh_3)_2RhCl_2$	DCM	H_2 (balloon)	N/A[b,c]
11	$NiCl_2$	EtOH	$NaBH_4$ (2 equiv, 0 °C)	N/A[b]
12	$NiCl_2$	EtOH	$NaBH_4$ (10 equiv, 0 °C)	1:3 + **16**
13	N/A	EtOH	$NaBH_4$ (50 equiv, 3days)	N/A (see text)
14	Raney Ni	EtOH	H_2 (balloon)	8:1:0
15	Raney Ni	THF	none	N/A
16	Raney Ni	THF	H_2 (100 psi)	9:1
17	Raney Ni	THF	H_2 (200 psi)	16:1

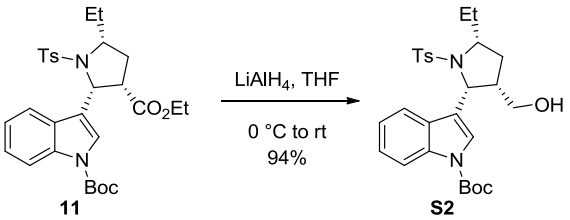
[a] The reported diastereoisomeric ratio (dr) was determined from the NMR spectrum of the crude product. [b] Mainly unreacted starting material was recovered. [c] These conditions were also tested on the allylic alcohol resulting from the DIBAL-mediated reduction of **16**. Again, no reduction was observed in the NMR spectrum of the crude product.

the ratio of **11** to **S1** (entry 7); increasing the pressure further, to 500 psi, resulted in a lower selectivity of 3.7:1 (entry 8). Using other aromatic solvents (e.g., toluene) in place of benzene, under otherwise identical conditions, provided lower selectivity (2.4:1 dr) for the desired isomer **11** (entry 9). In an attempt to identify conditions that would favor the desired diastereoisomer with higher selectivity, other hydrogenation catalysts were screened. Homogeneous conditions using Wilkinson's catalyst provided mainly recovered starting material (entry 10). *In situ*–generated nickel boride provided little, if any, reduction products when employing two equivalents of $NaBH_4$ (entry 11). Using 10 equivalents of $NaBH_4$ provided some of the desired pyrrolidine along with recovered starting material; nevertheless, the reduction again favored the undesired diastereoisomer **S1** by 1:3 (entry 12). Treating the pyrroline **16** with 50 equivalents of $NaBH_4$ in EtOH for three days cleanly provided a single diastereoisomer of a new compound, identified as the alcohol derived from reduction of the ester group of **S1**. The best reducing agent identified for this transformation was Raney Ni (entries 14–17). When treating the pyrroline **16** with Raney Ni in EtOH, the reduction favored the desired diastereoisomer with a 8:1 dr (entry 14). Performing the reaction without external H_2 led to recovered starting material (entry 15). Notably, repeated trials with Raney Ni gave variable results in terms of reaction times and conversion to the pyrrolidine products **11** and **S1** when performing the reaction without H_2 or under a balloon of H_2. In an attempt to achieve more-consistent results, the reactions with Raney Ni were performed under higher pressures of H_2. Not only did this ensure more-reliable reaction times and conversions but also, in congruence with the aforementioned outcome using high pressure, resulted in higher dr (entries 16 and 17). When employing Raney Ni at 100 psi, the desired pyrroline **11** was isolated with a 9:1 dr (entry 16). Upon increasing the pressure to 200 psi, the dr increased to a very respectable 16:1—the best selectivity obtained in this study. Under these optimized conditions (see below), the desired pyrrolidine **11** could be isolated consistently in 80% yield as a single diastereoisomer on multigram scale.



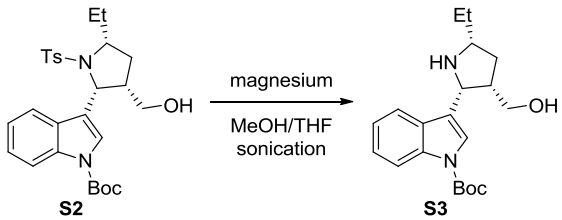
Pyrrolidine 11. The pyrroline **16** (10.0 g, 18.6 mmol) was added to a metal high-pressure reaction vessel equipped with a stirrer bar and then THF (400 mL) was added to form a solution. A suspension of Raney Ni in water [Raney Ni 4200 (Aldrich), 20 mL] was added directly to the solution without removal of the water. The reaction vessel was sealed and purged three times with H_2 gas (pressurized to 50 psi, followed

by release of the H_2 gas). The vessel was then pressurized to 200 psi with H_2 gas and the mixture left to stir vigorously (to keep Raney Ni suspended) until no starting material remained (8 h, as determined from the crude NMR spectrum of a small aliquot). The reaction mixture was decanted from the solid Raney Ni into a separatory funnel containing saturated aqueous NaCl. The solids were rinsed three times with EtOAc and the rinses were added to the separatory funnel. After separation of the layers, the aqueous phase was extracted three times with EtOAc. The combined organic phases were washed again with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude reaction product was recrystallized (by dissolving in boiling DCM and quickly diluting the mixture with a large amount of hexanes) to yield a white crystalline solid (8.3 g, 80%). Mp: 180–182 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (br s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.30–7.23 (m, 3H), 7.19 (td, *J* = 7.4, 1.0 Hz, 1H), 5.52 (d, *J* = 8.4 Hz, 1H), 3.67 (dq, *J* = 10.8, 7.1 Hz, 1H), 3.6 (tdd, *J* = 9.1, 8.9, 3.5 Hz, 1H), 3.47 (dq, 10.8, 7.1 Hz, 1H), 2.87–2.79 (m, 1H), 2.4 (s, 3H), 2.44–2.35 (m, 1H), 2.24–2.18 (m, 2H), 1.81–1.69 (m, 1H), 1.66 (s, 9H), 1.01 (t, *J* = 7.5 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.6, 149.5, 143.6, 135.1, 129.7, 128.8, 127.6, 125.0, 124.5, 122.2, 119.6, 119.2, 115.1, 83.8, 62.0, 60.9, 57.9, 47.4, 32.2, 29.5, 28.2, 21.5, 13.5, 10.6; IR (film) 2978, 2936, 2899, 2879, 1726, 1458, 1372, 1343, 1266, 1152 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{29}H_{36}N_2O_6SH$, 541.2372, found 541.2370; $[\alpha]^{24.1}_D$ +88.6° (*c* = 1.000, $CHCl_3$).



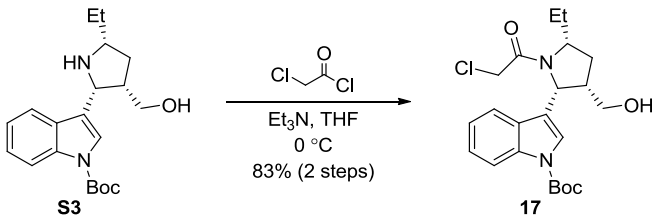
Alcohol S2. Freshly distilled THF (65 ml) was added to a flame-dried round-bottom flask charged with $LiAlH_4$ (710 mg, 18.7 mmol, 1 equiv). The flask was capped with an addition funnel and the setup was placed under a positive pressure of Ar. The heterogeneous mixture was cooled to 0 °C and then the pyrrolidine **11** (10.1 g, 18.7 mmol) was added to the addition funnel as a solution in THF (20 mL) over the course of 1 h. The mixture was then warmed to room temperature and stirred until the starting material had been consumed (2 h, as determined by TLC). Once complete, the reaction was quenched through the dropwise addition of saturated aqueous sodium potassium tartrate at 0 °C. The mixture was stirred vigorously until the two phases were distinctly visible. The layers were separated and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed once with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through

flash column chromatography (30% EtOAc/hexanes) to yield a white solid (8.7 g, 94%). Mp: 81–84 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.70 (d, *J* = 8.3 Hz, 2H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.50 (br s, 1H), 7.31–7.24 (m, 3H), 7.20 (td, *J* = 7.5, 1.04 Hz, 1H), 5.23 (d, *J* = 7.9 Hz, 1H), 3.54–3.45 (m, 1H), 3.28 (dd, *J* = 10.9, 7.0 Hz, 1H), 3.14 (dd, *J* = 10.8, 6.0 Hz, 1H), 2.53–2.42 (m, 1H), 2.40 (s, 3H), 2.13–2.00 (m, 2H), 1.81–1.70 (m, 1H), 1.67 (s, 9H), 1.58–1.45 (m, 1H), 0.99 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 143.5, 135.3, 134.8, 129.7, 129.1, 127.6, 125.0, 124.6, 122.6, 120.1, 119.0, 115.4, 83.9, 62.6, 62.1, 58.6, 44.9, 33.0, 29.7, 28.0, 21.6, 10.8; IR (film) 3547, 2978, 2916, 2875, 1722, 1453, 1372, 1254, 1152, 1087 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{27}H_{34}N_2O_5SH$, 499.2267, found 499.2273; $[\alpha]^{24.0}_D$ +123.8° (*c* = 1.000, $CHCl_3$).

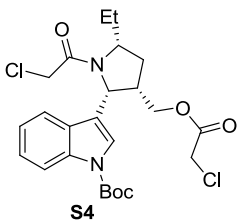


Amino Alcohol S3. The alcohol **S2** (1.0 g, 20 mmol, 1 equiv) was dissolved in freshly distilled THF (7 mL) and then the homogeneous solution was diluted with freshly distilled MeOH (63 mL). Powdered Mg (980 mg, 40 mmol, 20 equiv) was added and then the flask was capped with a reflux condenser and placed under a positive pressure of Ar. The heterogeneous reaction mixture was sonicated for 30 min and then a second aliquot of Mg powder (980 mg, 40 mmol, 20 equiv) was added and sonication continued for another 30 min. The reaction was monitored (TLC) after each period of sonication. If starting material remained, then another 20 equiv of Mg was added and then the reaction mixture was sonicated for another 30 min (typically, the reaction was complete after 2–4 additions of Mg). Once the starting material had been consumed, the mixture was cooled to 0 °C and the reaction quenched through the dropwise addition of 2 M $HCl_{(aq)}$ until all of the solid Mg had dissolved to form a homogeneous solution, which was transferred to a separatory funnel. The aqueous phase was extracted five times with EtOAc; the combined organic phases were washed once with water then once with a saturated $NaHCO_3$. The organic phase was washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the resulting brown oil (crude amino alcohol **S3**) was used in the next step without purification. Alternatively, **S3** could be purified through flash column chromatography (5% Et_3N in 35% EtOAc/hexanes) to give analytically pure material, isolated as a dark oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.59 (s, 1H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.21 (t, *J* = 7.6 Hz, 1H), 4.49 (d, *J* = 6.25 Hz, 1H), 3.33 (dd, *J* = 10.56, 3.25 Hz, 1H), 3.28 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.13 (app

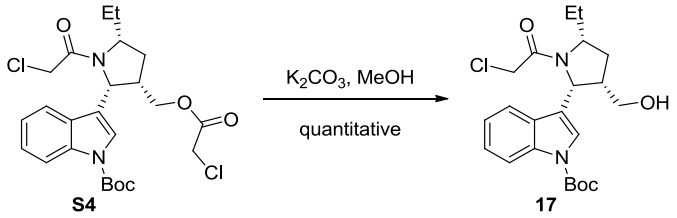
quint, J = 7.3 Hz, 1H), 2.60–2.53 (m, 1H), 2.34 (dt, J = 13.0, 8.6 Hz, 1H), 1.72–1.59 (m, 4H), 1.67 (s, 9H), 1.00 (t, J = 7.46 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 135.6, 129.2, 124.4, 122.4, 122.3, 120.0, 118.9, 115.3, 83.6, 64.5, 58.6, 58.3, 41.4, 33.6, 28.7, 28.1, 11.5; IR (film) 3393, 3324, 2969, 2928, 2875, 1731, 1453, 1372, 1250, 1152, 1087 cm^{-1}; HRMS–ESI (m/z) [M + H]$^+$ calcd $C_{20}H_{28}N_2O_3H$, 345.2178, found 345.2166; $[\alpha]^{23.9}_D$ +72.6° (c = 1.000, $CHCl_3$).



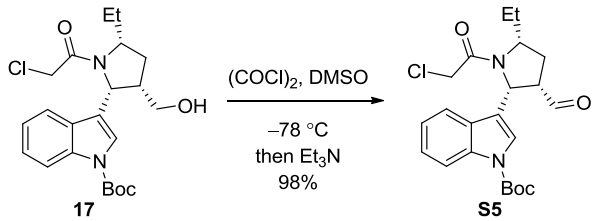
Chloroamide 17. The crude residue **S3** from the detosylation was dissolved in THF (7 mL) and placed under a positive pressure of Ar. Et_3N (279 μL, 2.00 mmol, 1 equiv) was added and then the reaction mixture was cooled to 0 °C. Chloroacetyl chloride (159 μL, 2.00 mmol, 1 equiv) was added dropwise over 5 min. The mixture was stirred at 0 °C until the starting material had been consumed (30 min, as determined by TLC) and then the reaction was quenched through the addition of saturated $NH_4Cl_{(aq)}$. The layers were separated and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (30%–50% EtOAc/hexanes) to yield a white solid (699 mg, 83% over two steps). Mp: 168–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13 (br s, 1H), 7.70 (d, J = 7.85 Hz, 1H), 7.45 (s, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.27 (t, J = 7.6 Hz, 1H), 5.46 (d, J = 7.5 Hz, 1H), 3.96–3.88 (m, 2H), 3.67 (d, J = 12.4 Hz, 1H), 3.40–3.28 (m, 2H), 2.79–2.61 (m, 2H), 2.3 (app quint, J = 6.2 Hz, 1H), 1.68 (s, 9H), 1.53 (q, J = 12.1 Hz, 1H), 1.50–1.30 (m, 1H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 149.4, 135.2, 129.0, 125.2, 124.3, 123.0, 119.1, 118.9, 115.5, 84.5, 62.1, 60.8, 56.7, 45.5, 42.7, 32.0, 28.2, 27.3, 10.9; IR (film) 3454, 2985, 2965, 2921, 2879, 1735, 1653, 1458, 1376, 1258, 1147 cm^{-1}; HRMS–ESI (m/z) [M + H]$^+$ calcd $C_{22}H_{29}ClN_2O_4H$, 421.1894, found 421.1862; $[\alpha]^{23.9}_D$ +21.0° (c = 1.000, $CHCl_3$).



Bisacylation Product S4. During some trials of the acylation reaction, the bis-acylation product **S4** was isolated as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.61 (d, *J* = 7.8 Hz, 1H), 7.48 (s, 1H), 7.37 (t, *J* = 7.6 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 5.49 (d, *J* = 7.6 Hz, 1H), 4.00–3.83 (m, 5H), 3.74 (dd, *J* = 10.9, 8.7 Hz, 1H), 3.69 (d, *J* = 12.6, 1H), 2.94–2.82 (m, 1H), 2.74–2.62 (m, 1H), 2.34 (app quint, *J* = 6.3 Hz, 1H), 1.69 (s, 9H), 1.66–1.54 (m, 1H), 1.48–1.35 (m, 1H), 1.02 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.7, 165.8, 149.3, 135.1, 128.7, 125.4, 124.4, 123.0, 118.3, 118.2, 115.8, 84.7, 65.3, 60.6, 56.2, 42.6, 41.8, 40.6, 32.1, 28.2, 27.3, 10.9; IR (film) 2978, 2932, 2879, 1735, 1661, 1453, 1368, 1258, 1152 cm^{-1}; HRMS-ESI (*m*/*z*) $[M + H]^+$ calcd $C_{24}H_{30}Cl_2N_2O_5H$, 497.1610, found 497.1601.

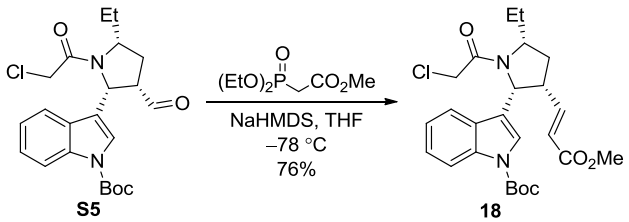


Cleavage of the O-Acetate. The bis-acylation product **S4** (50.0 mg, 0.100 mmol, 1 equiv) was dissolved in freshly distilled MeOH (1 mL) and cooled to 0 °C. K_2CO_3 (138 mg, 1.00 mmol, 10 equiv) was added and then the heterogeneous mixture was stirred at 0 °C until the starting material had been consumed (10 min, as determined by TLC). The mixture was poured into water and extracted three times with EtOAc. The combined organic phases were washed with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (50% EtOAc/hexanes) to yield **17** (42 mg, quantitative) as a white solid, with spectroscopic data consistent with those for compound **17** isolated from the selective N-acylation of **S3**.



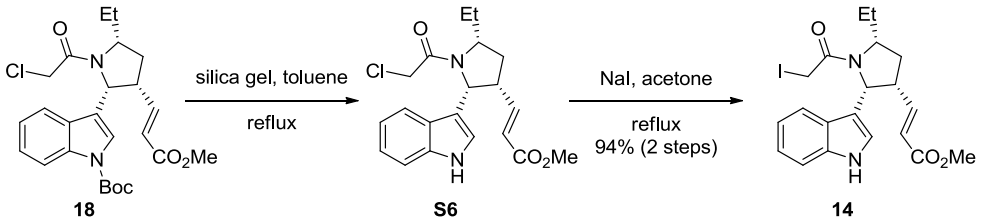
Aldehyde S5. Freshly distilled DCM (45 mL) was added to a flame-dried round-bottom flask under a positive pressure of Ar. DMSO (895 µL, 11.5 mmol, 3.5 equiv) was added and the solution cooled to –78 °C. 2 M oxalyl chloride in DCM (4.94 mL, 9.88 mmol, 3 equiv) was added dropwise and then the mixture was stirred at –78 °C for 20 min. A solution of the alcohol **17** (1.39 g, 3.29 mmol, 1 equiv) in freshly distilled DCM was then added to the mixture over 5 min. The solution was stirred at –78 °C for

20 min and then Et_3N (2.3 mL, 16.5 mmol, 5 equiv) was added. The cooling bath was removed and the reaction monitored (TLC) until the starting material had been consumed (5–10 min). The reaction was quenched through the addition of water and then the phases were separated. The aqueous phase was extracted twice with DCM. The combined organic phases were washed with brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (50% EtOAc/hexane) to yield a white solid (1.35 g, 98%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 8.12 (br s, 1H), 7.54 (s, 1H), 7.50 (br s, 1H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.29 (t, *J* = 7.5 Hz, 1H), 5.75 (br s, 1H), 4.08–4.00 (m, 1H), 3.89 (d, *J* = 11.5 Hz, 1H), 3.74 (d, *J* = 11.5 Hz, 1H), 3.40–3.31 (m, 1H), 2.61 (br s, 1H), 2.37 (app quint, *J* = 7 Hz, 1H), 2.27–2.13 (m, 1H), 1.68 (s, 9H), 1.50 (br s, 1H), 1.05 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.6, 165.7, 149.3, 135.4, 127.7, 125.6, 124.2, 123.4, 118.3, 118.0, 115.8, 84.8, 60.6, 55.4, 54.1, 42.5, 29.6, 28.1, 27.5, 10.9; IR (film) 3055, 2978, 2936, 2879, 2835, 2741, 1726, 1661, 1453, 1372, 1254, 1152 cm^{-1}; MS–MALDI-TOF (*m*/*z*) $[M + Na]^+$ calcd $C_{22}H_{27}ClN_2O_4Na$, 441.1557, found 441.0644; $[\alpha]^{23.8}_D$ +77.4° (*c* = 1.000, $CHCl_3$).



***α,β*-Unsaturated Ester 18.** Freshly distilled THF (1.5 mL) and methyl diethylphosphonoacetate (55.2 mg, 0.26 mmol, 1.1 equiv) were added to a flame-dried round-bottom flask under a positive pressure of Ar. The solution was cooled to –78 °C and then NaHMDS (239 μL, 0.240 mmol, 1 equiv) was added. The mixture was stirred at –78 °C for 30 min and then a solution of the aldehyde **S5** (100 mg, 0.240 mmol, 1 equiv) in freshly distilled THF (1 mL) was added. The mixture was stirred at –78 °C for 5 min, at which point the starting material had been consumed (TLC). The reaction was quenched through the addition of saturated $NH_4Cl_{(aq)}$; the layers were separated and the aqueous phase extracted three times with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (25% EtOAc/hexanes) to yield a white solid (86 mg, 76%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.1 (br s, 1H), 7.47 (s, 1H), 7.39–7.30 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 6.33 (dd, *J* = 15.5, 9.0 Hz, 1H), 5.92 (d, *J* = 15.5 Hz, 1H), 5.43 (d, *J* = 7.5 Hz, 1H), 4.01–3.93 (m, 1H), 3.89 (d, *J* = 12.4 Hz, 1H), 3.73 (d, *J* = 12.4 Hz, 1H), 3.55 (s, 3H), 3.33–3.21 (m, 1H), 2.76–2.63 (m, 1H), 2.29 (app quint, *J* = 6.2 Hz, 1H), 1.80 (q, *J* = 11.9 Hz, 1H), 1.68 (s, 9H), 1.51–1.40 (m, 1H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9, 165.8, 149.4, 145.6, 135.4, 128.4, 125.2, 124.3, 123.2, 122.9, 119.2, 118.6, 115.5, 84.5, 61.0, 58.6, 51.5,

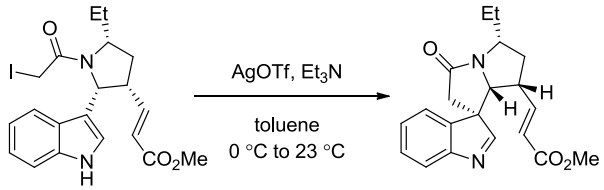
46.0, 42.5, 35.0, 28.2, 27.4, 10.9; IR (film) 2969, 2932, 2879, 1735, 1653, 1458, 1376, 1254, 1147 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{25}H_{31}ClN_2O_5H$, 475.2000, found 475.1994.



Iodoamide 14. The N-Boc–protected indole **18** (85 mg, 0.179 mmol, 1 equiv) was dissolved in freshly distilled toluene (2 mL). Silica gel (85 mg) was added and then the mixture was heated under reflux until the starting material had been consumed (TLC; typically 2–3 h). The mixture was cooled to room temperature and filtered through a glass frit. The silica gel was washed three times with EtOAc. The solution obtained was concentrated *in vacuo* to give **S6** as a dark oil, which was used in the next reaction without purification. Alternatively, the crude material could be purified through flash column chromatography (20%–40% EtOAc/hexanes) to yield analytically pure **S6** as a white solid. Mp: 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52 (br s, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.38 (dd, *J* = 15.5, 9.1 Hz, 1H), 5.93 (dd, *J* = 15.5, 0.6 Hz, 1H), 5.51 (d, *J* = 7.4 Hz, 1H), 4.02–3.96 (m, 1H), 3.96 (d, *J* = 12.7 Hz, 1H), 3.72 (d, *J* = 12.7 Hz, 1H), 3.57 (s, 3H), 3.31–3.20 (m, 1H), 2.79–2.68 (m, 1H), 2.28 (app quint, *J* = 6.2 Hz, 1H), 1.79 (q, *J* = 12.1 Hz, 1H), 1.49–1.37 (m, 1H), 1.01 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1, 166.0, 146.5, 136.4, 125.7, 122.9, 122.8, 122.7, 120.1, 118.9, 113.5, 111.6, 60.9, 59.3, 51.5, 46.4, 42.6, 35.2, 27.5, 11.0; IR (film) 3291, 3059, 2969, 2932, 2879, 1718, 1649, 1458, 1421, 1262, 1233, 137 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{23}ClN_2O_3H$, 375.1476, found 375.1472.

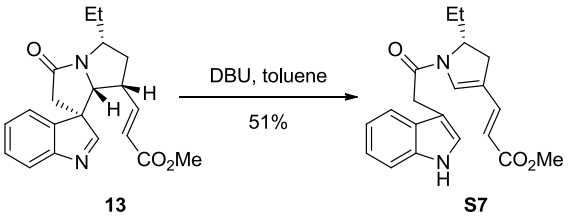
The crude material **S6** was dissolved in acetone (3 mL). NaI (255 mg, 1.79 mmol, 10 equiv) was added and then the mixture was heated under reflux for 2 h, at which point the starting material had been consumed (determined from the NMR spectrum of a removed aliquot). The mixture was poured into water and extracted three times with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (20%–40% EtOAc/hexanes) to yield the iodoamide **14** (78.6 mg, 94% over two steps) as a light-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (br s, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.2 Hz, 1H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.09 (d, *J* = 2.3 Hz, 1H), 6.40 (dd, *J* = 15.6, 9.1 Hz, 1H), 5.94 (d, *J* = 15.5 Hz, 1H), 5.49 (d, *J* = 7.5 Hz, 1H), 3.95–3.86 (m, 1H), 3.57 (s, 3H),

3.48 (s, 2H), 3.32–3.21 (m, 1H), 2.78–2.66 (m, 1H), 2.30–2.22 (m, 1H), 1.84–1.75 (m, 1H), 1.50–1.34 (m, 1H), 1.00 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 166.2, 146.6, 136.4, 125.9, 122.8, 122.8, 122.7, 120.1, 118.9, 113.6, 111.6, 61.2, 60.6, 51.5, 46.1, 35.4, 27.6, 11.0, –0.5; IR (film) 3288, 3053, 2964, 2932, 2875, 1718, 1629, 1431, 1232, 739 cm^{-1}; HRMS–ESI (m/z) [M + H]$^+$ calcd $C_{20}H_{23}IN_2O_3H$, 467.0832, found 467.0818; $[\alpha]^{23.9}_D$ +77.4° (c = 1.000, $CHCl_3$).



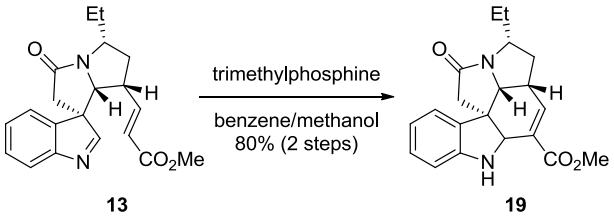
14 **13**

Spirocyclic Indolenine 13. The iodoamide **14** (20.0 mg, 0.428 mmol, 1 equiv) was dissolved in freshly distilled toluene (8 mL) and placed under a positive pressure of Ar. Et_3N (112 μL, 0.856 mmol, 2 equiv) was added and the solution cooled to 0 °C. Silver trifluoromethanesulfonate (206 mg, 0.856 mmol, 2 equiv) was added as a solid in a single portion and then the mixture was removed from the ice bath and warmed to room temperature. Once the starting material had been consumed (TLC; typically within 30 min), the mixture was filtered through a short pad of Celite, which was rinsed three times with EtOAc. The solution was transferred to a separatory funnel and washed with a 1:1 solution of saturated $NaHCO_{3(aq)}$ and saturated $Na_2S_2O_3$ and then with brine. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield the crude spirocyclic indolenine **13** as a dark oil, which was used for the next reaction without purification. Alternatively, the crude material could be purified through flash column chromatography (5% Et_3N in 35% EtOAc/hexanes) to yield the analytically pure spirocyclic indolenine **13** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (s, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.40 (d, J = 7.4 Hz, 1H), 7.37 (td, J = 7.6, 1.2 Hz, 1H), 7.30 (td, J = 7.4, 0.9 Hz, 1H), 6.52 (dd, J = 15.4, 8.9 Hz, 1H), 5.47 (dd, J = 15.6, 1.1Hz, 1H), 4.64 (d, J = 7.7 Hz, 1H), 3.64 (s, 3H), 3.57–3.49 (m, 1H), 3.04 (dd, J = 16.7, 1.2 Hz, 1H), 2.82–2.67 (m, 2H), 2.48 (d, J = 16.6 Hz, 1H), 2.43 (dt, J = 13.0, 7.2 Hz, 1H), 1.76 (app quint, J = 6.5 Hz, 1H), 1.69–1.58 (m, 1H), 0.99 (t, J = 7.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.2, 169.0, 165.7, 155.2, 144.2, 136.7, 129.1, 126.9, 122.8, 121.8, 121.3, 70.0, 61.7, 57.2, 51.7, 42.9, 39.8, 39.2, 25.1, 11.1; IR (film) 3041, 2973, 2948, 2883, 2846, 1718, 1682, 1641, 1548, 1442, 1415, 1273 cm^{-1}; HRMS–ESI (m/z) [M + H] calcd $C_{20}H_{22}N_2O_3H$, 339.1709, found 339.1718; $[\alpha]^{23.8}_D$ +245.8° (c = 1.000, $CHCl_3$).



13 S7

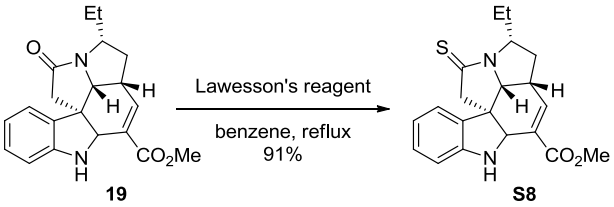
Diene S7. DBU (24.3 μL, 0.162 mmol, 1.5 equiv) was added to a solution of the spirocyclic indolenine **13** (38.0 mg, 0.112 mmol, 1 equiv) in toluene (2 mL) and then the homogeneous mixture was stirred for 60 h. The resulting mixture was diluted with EtOAc and washed with saturated aqueous NH_4Cl. The organic phase was dried (Na_2SO_4) and concentrated *in vacuo*; the crude residue was purified using preparatory TLC (EtOAc/hexanes, 1:1) to give a light-yellow solid (19.4 mg, 51%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (br s, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 15.8 Hz, 1H), 7.34 (s, 1H), 7.21 (td, *J* = 7.1, 1.1 Hz, 1H), 7.23 (dd, *J* = 7.1, 1.1 Hz, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.92 (s, 1H), 5.63 (d, *J* = 15.4 Hz, 1H), 4.56–4.47 (m, 1H), 3.89 (d, *J* = 3.5 Hz, 2H), 3.74 (s, 3H), 2.83 (dd, *J* = 15.5, 10.5 Hz, 1H), 2.32 (dd, *J* = 15.9, 3.6 Hz, 1H), 1.93–1.83 (m, 1H), 1.66–1.56 (m, 1H), 0.83 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.8, 167.6, 138.5, 136.1, 134.5, 126.9, 122.5, 122.3, 121.3, 119.7, 118.6, 115.7, 111.2, 108.2, 59.8, 51.4, 32.5, 32.0, 26.1, 8.3; IR (film) 3328, 3104, 3059, 2957, 2879, 1701, 1661, 1612, 1596, 1421, 1156, 732 cm^{-1}; MS–MALDI-TOF $[M + Na]^+$ (*m*/*z*) calcd $C_{20}H_{22}N_2O_3Na$, 361.1528, found 361.1049.



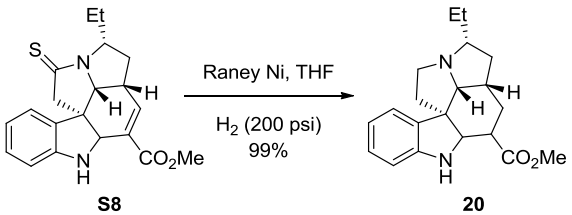
13 19

Pentacycle 19. Trimethylphosphine (55 μL, 0.536 mmol, 10 equiv) was added to a solution of the crude spirocyclic indolenine **13** (18.13 mg, 0.0536 mmol, 1 equiv) in freshly distilled benzene (700 μL) and MeOH (50 μL). The mixture was stirred at room temperature until the starting material had been consumed (2 h, as determined by TLC). Once complete, the mixture was concentrated and purified through flash column chromatography (EtOAc/hexanes, 1:1) to yield a white solid (14.6 mg, 80% over two steps). Mp: 149–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, *J* = 7.5 Hz, 1H), 7.04 (td, *J* = 7.7, 1.2 Hz, 1H), 6.86 (d, *J* = 2.8 Hz, 1H), 6.71 (td, *J* = 7.5, 1.0 Hz, 1H), 6.53 (d, *J* = 7.9 Hz, 1H), 4.65 (br s, 1H), 4.44 (d, *J* = 5.7 Hz, 1H), 4.38 (s, 1H), 3.80 (s, 3H), 3.53 (t, *J* = 9.7 Hz, 1H), 3.02 (dd, *J* = 16.5, 1.2 Hz, 1H), 2.87 (d, *J* = 16.5 Hz, 1H), 3.73–3.66 (m, 1H), 2.60 (dt, *J* = 17.4, 8.8 Hz, 1H), 2.48–2.39 (m, 1H), 2.02 (d, *J* = 13.5 Hz, 1H), 1.16–1.05 (m, 1H), 0.85 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ

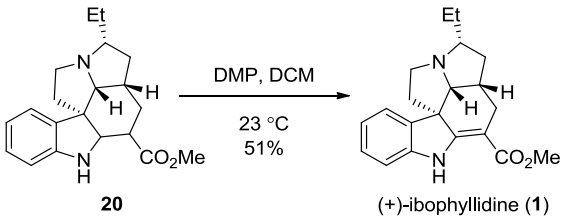
169.3, 166.7, 149.8, 141.0, 130.2, 129.1, 128.6, 122.8, 118.4, 109.1, 67.1, 60.4, 54.7, 53.5, 52.2, 49.3, 38.1, 33.3, 24.3, 10.8; IR (film) 3401, 3051, 2965, 2879, 1678, 1608, 1490, 1482, 1416, 1254, 1095, 911, 732 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{22}N_2O_3H$, 339.1709, found 339.1707; $[\alpha]^{23.9}_D$ +181.0° (*c* = 1.000, $CHCl_3$).



Thioamide S8. A solution of the pentacycle **19** (20.0 mg, 0.0590 mmol, 1 equiv) in freshly distilled benzene (2 mL) was placed under a positive pressure of Ar. Lawesson's reagent (14.3 mg, 0.0350 mmol, 0.6 equiv) was added and then the mixture was heated under reflux. The reaction was closely monitored (TLC) until the starting material had been consumed (typically 1 h; continued heating under reflux after consumption of the starting material decreased the yields). The mixture was poured into water and the phases separated. The aqueous phase was extracted three times with EtOAc. The combined organic phases were washed successively with water and brine and then dried (Na_2SO_4). After filtration and concentration *in vacuo*, the crude material was purified through flash column chromatography (25% EtOAc/hexanes) to yield a yellow solid (19.1 mg, 91%). Mp: 222–224 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, *J* = 7.5 Hz, 1H), 7.05 (td, *J* = 7.7, 1.2 Hz, 1H), 6.90–6.86 (m, 1H), 6.69 (td, *J* = 7.5, 0.8 Hz, 1H), 6.52 (d, *J* = 7.7 Hz, 1H), 4.71 (d, *J* = 5.5 Hz, 1H), 4.67 (br s, 1H), 4.35 (s, 1H), 3.81 (s, 3H), 3.78 (t, *J* = 9.6 Hz, 1H), 3.53 (d, *J* = 17.4 Hz, 1H), 3.40 (dd, *J* = 17.4, 1.5 Hz, 1H), 3.04–2.94 (m, 1H), 2.82–2.77 (m, 1H), 2.73 (dt, *J* = 13.4, 8.5 Hz, 1H), 2.19 (d, *J* = 13.5 Hz, 1H), 1.09–0.98 (m, 1H), 0.87 (t, 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.1, 166.4, 149.7, 139.5, 131.3, 129.2, 126.4, 122.5, 118.2, 109.0, 72.9, 65.8, 59.2, 57.7, 52.1, 50.8, 38.0, 32.9, 22.6, 10.6; IR (film) 3275, 3047, 2965, 2936, 2899, 2875, 2855, 1711, 1498, 1482, 1250, 1091 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{22}N_2O_2SH$, 355.1480, found 355.1486; $[\alpha]^{22.6}_D$ +235.8° (*c* = 1.000, $CHCl_3$).



Dihydroibophyllidine (20). A suspension of Raney Ni [Raney Ni 4200 (Aldrich)] in water was added to a solution of the thioamide **S8** (31.1 mg, 0.088 mmol, 1 equiv.) in freshly distilled THF (1 mL). The mixture was placed in a high-pressure reaction vessel, which was then sealed. The reactor was purged with H_2 gas (pressurized to 50 psi with H_2 gas, followed by release of the pressure) three times and then pressurized to 200 psi with H_2 gas. The mixture was stirred vigorously (to keep the Raney Ni suspended) for 2 h, at which point the starting material had been consumed (1 h, as determined by TLC). The mixture was decanted from the solid Raney Ni into a separatory funnel containing brine. The solids were rinsed three times with EtOAc; these washings were added to the separatory funnel. The layers were separated and the aqueous phase was extracted twice more with EtOAc. The combined organic phases were washed with brine and dried (Na_2SO_4). After filtration and concentration of the volatiles, dihydroibophyllidine (**20**, 28.4 mg, 99%) was isolated as a colorless oil that required no further purification. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, *J* = 7.5 Hz, 1H), 7.03 (td, *J* = 7.5, 1.2 Hz, 1H), 6.73 (td, *J* = 7.5, 0.9 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 4.37 (br s, 1H), 3.72 (s, 3H), 3.65 (d, *J* = 10.3 Hz, 1H), 3.29 (d, *J* = 6.4 Hz, 1H), 2.97–2.86 (m, 1H), 2.62–2.45 (m, 3H), 2.39–2.20 (m, 2H), 2.10–1.90 (m, 3H), 1.82–1.69 (m, 1H), 1.51–1.32 (m, 3H), 0.95 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 148.7, 134.6, 127.7, 122.6, 118.8, 109.2, 72.6, 68.0, 61.6, 51.8, 51.4, 46.4, 45.9, 45.4, 40.0, 33.6, 31.8, 26.6, 11.4; IR (film) 3389, 3051, 2957, 2928, 2868, 2782, 1726, 1462 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{26}N_2O_2H$, 327.2072, found 327.2067; $[\alpha]^{22.2}_D$ +101.6° (*c* = 1.000, $CDCl_3$).

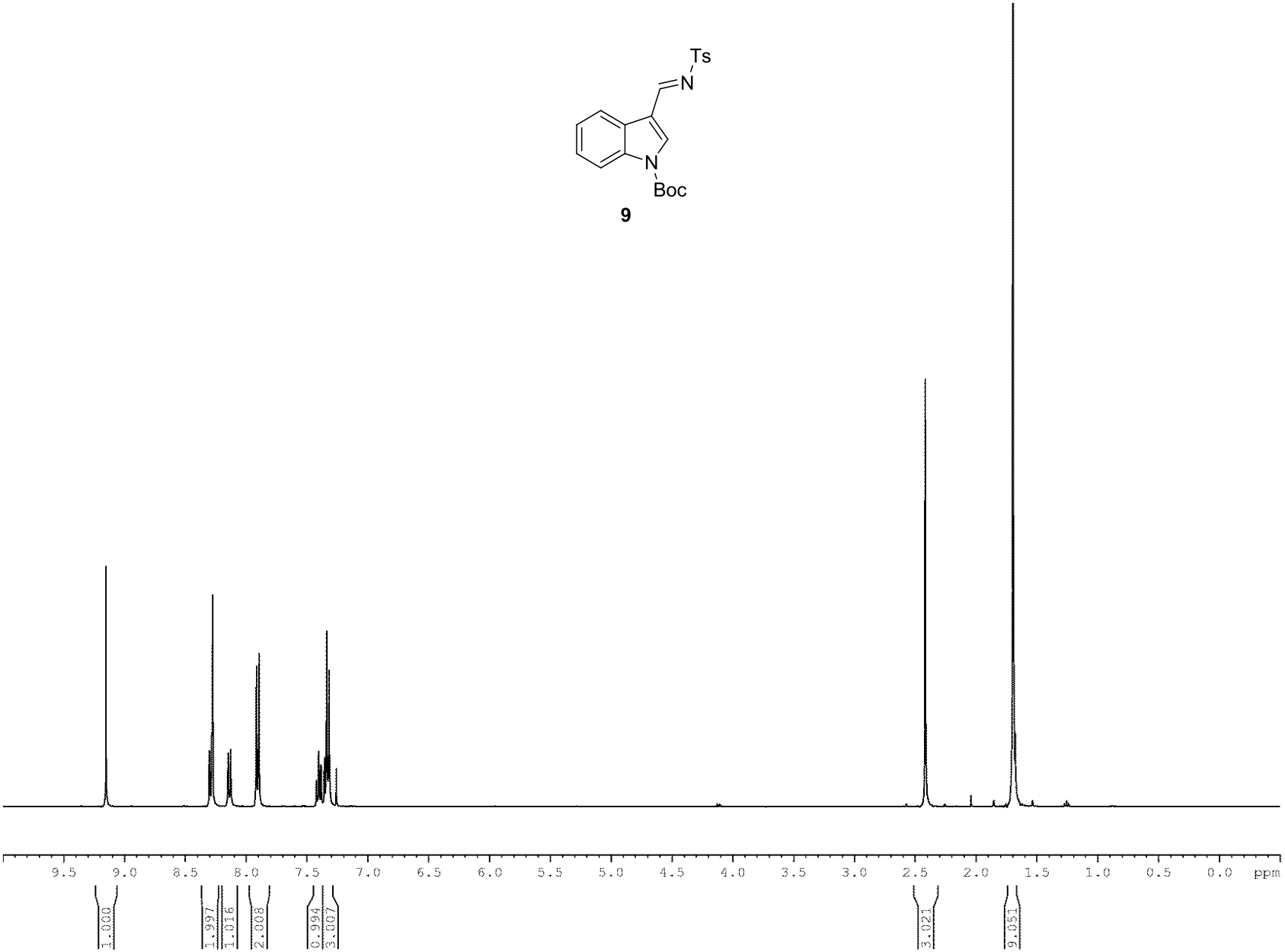


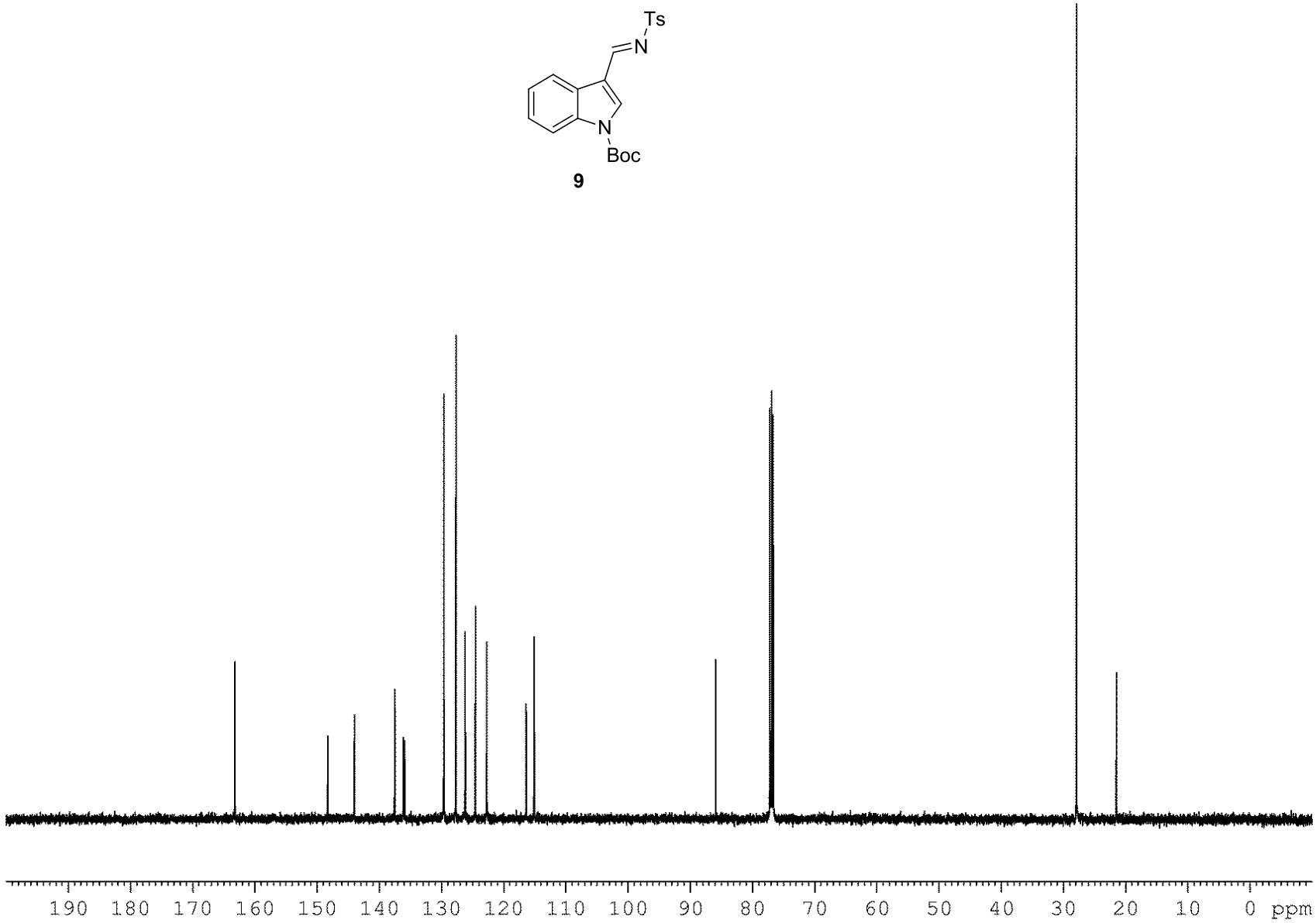
20 (+)-ibophyllidine (**1**)

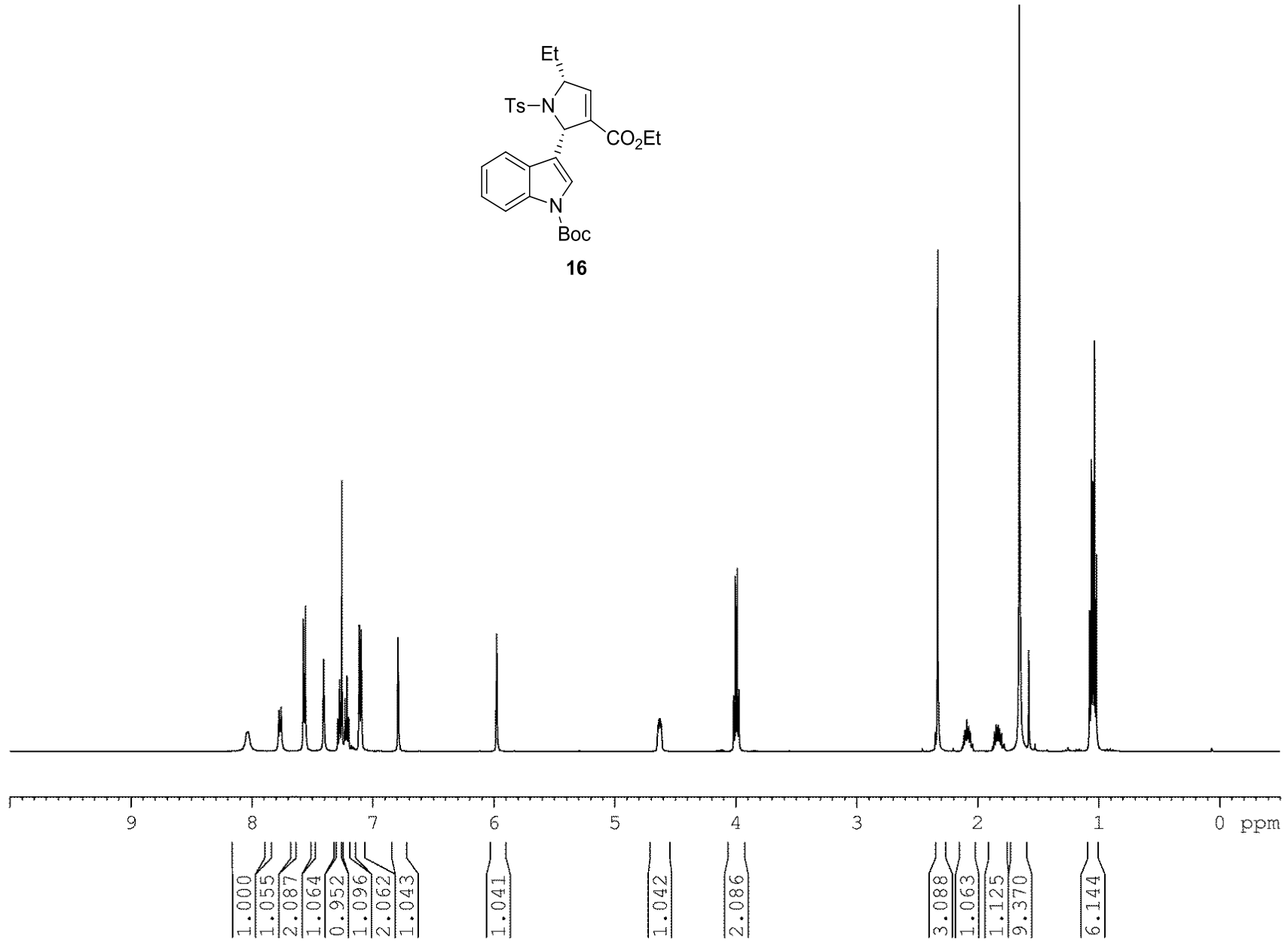
(+)-Ibophyllidine (1). The Dess–Martin periodinane (12 mg, 1.1 equiv) was added to a solution of the dihydroibophyllidine (**20**, 8.4 mg, 0.026 mmol, 1 equiv) in DCM (2 mL) and then the mixture was stirred for 5 min. The reaction was quenched through the addition of a 1:1 solution of saturated $NaHCO_{3(aq)}$ and saturated $Na_2S_2O_{3(aq)}$. The mixture was diluted with EtOAc and the phases separated. The aqueous phase was extracted twice more with EtOAc and then the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated *in vacuo*. The crude residue was passed through a short pad of basic alumina and eluted with Et_2O. The NMR spectrum of the crude product revealed that some starting material remained. The crude product was redissolved in DCM and then a second aliquot of the Dess–

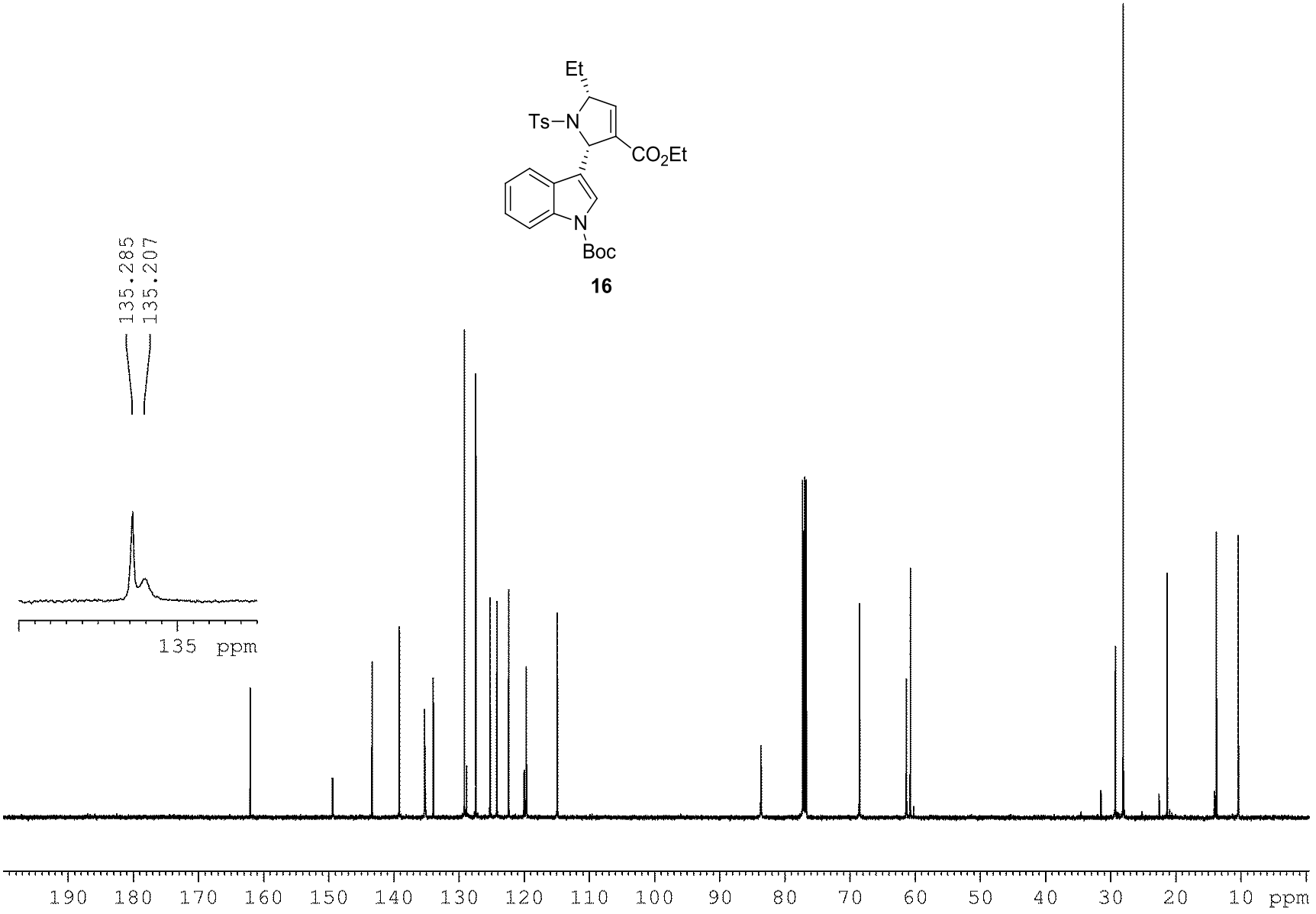
Martin periodinane (8 mg, 0.019 mmol, 0.73 equiv) was added. The mixture was stirred for 5 min and then worked up as before to yield (+)-ibophyllidine (**1**, 4.2 mg, 51%) as a thin film. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.13 (br s, 1H), 7.51 (d, *J* = 7.6 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.92 (td, *J* = 7.5, 1.0 Hz, 1H), 6.80 (d, *J* = 7.7 Hz, 1H), 3.76 (s, 3H), 3.49 (d, *J* = 8.7 Hz, 1H), 3.25–3.13 (m, 2H), 3.11 (dd, *J* = 15.5, 6.9 Hz, 1H), 2.77 (app q, *J* = 9.6 Hz, 1H), 2.29–2.22 (m, 1H), 2.21–2.11 (m, 2H), 2.07–1.96 (m, 1H), 1.94–1.85 (m, 1H), 1.81 (dd, *J* = 15.3, 11.2 Hz, 1H), 1.61–1.51 (m, 1H) 1.32–1.22 (m, 1H), 1.03 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7, 165.2, 143.2, 138.8, 127.7, 123.2, 121.3, 108.8, 92.1, 75.7, 65.8, 55.9, 51.0, 47.8, 41.4, 37.9, 34.9, 31.9, 25.7, 12.5; IR (film) 3377, 2957, 2925, 2863, 1674, 1608, 1466, 1437, 1282, 1246 cm^{-1}; HRMS–ESI (*m*/*z*) $[M + H]^+$ calcd $C_{20}H_{24}N_2O_2H$, 325.1916, found 325.1905; $[\alpha]^{24.3}_D$ +140° (*c* = 1.000, $CHCl_3$).

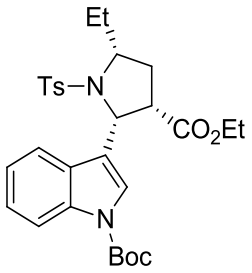
^{1}H and ^{13}C NMR spectra











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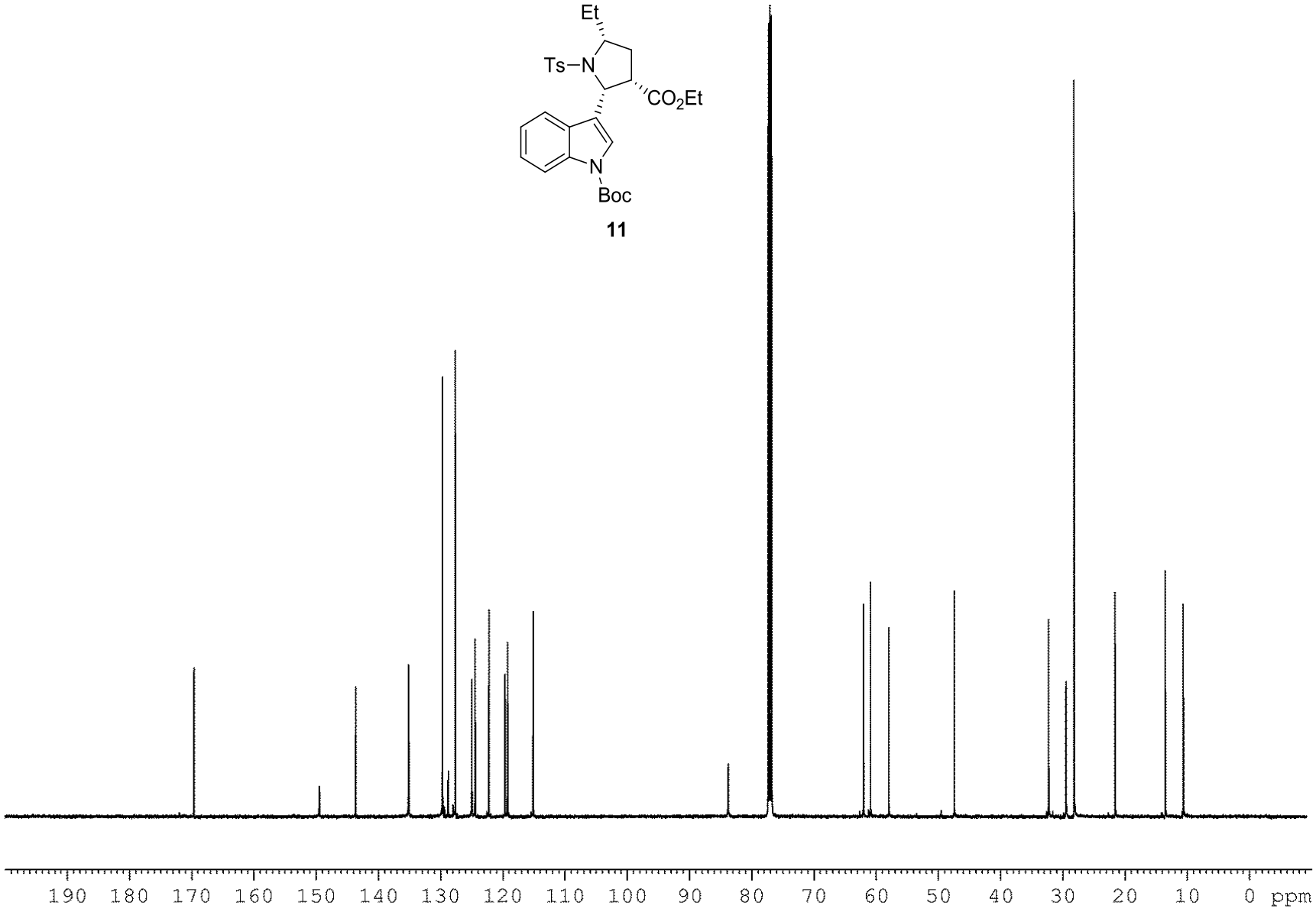

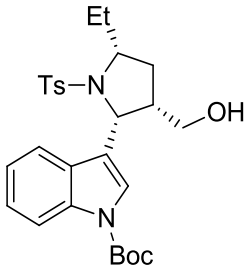

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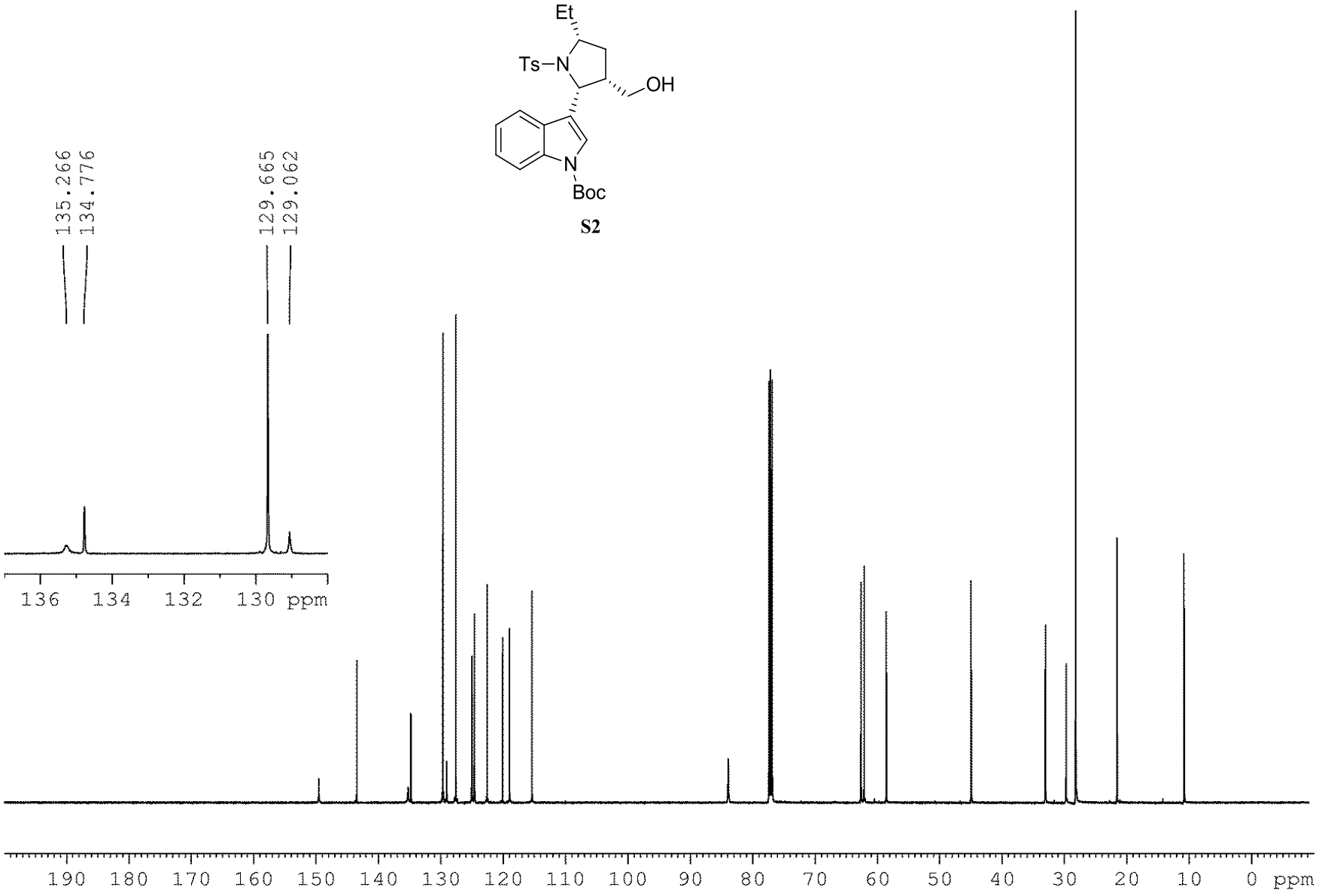

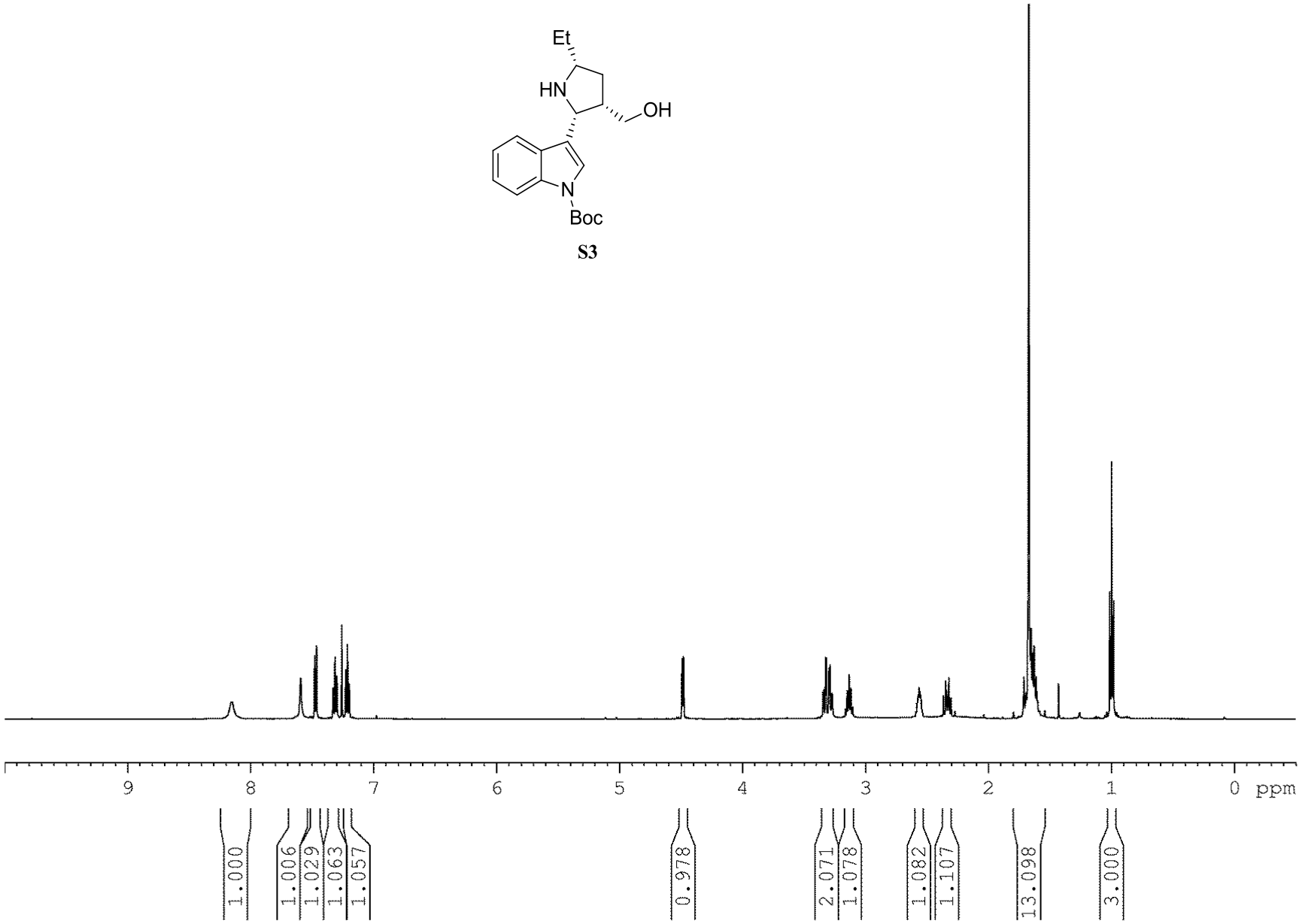

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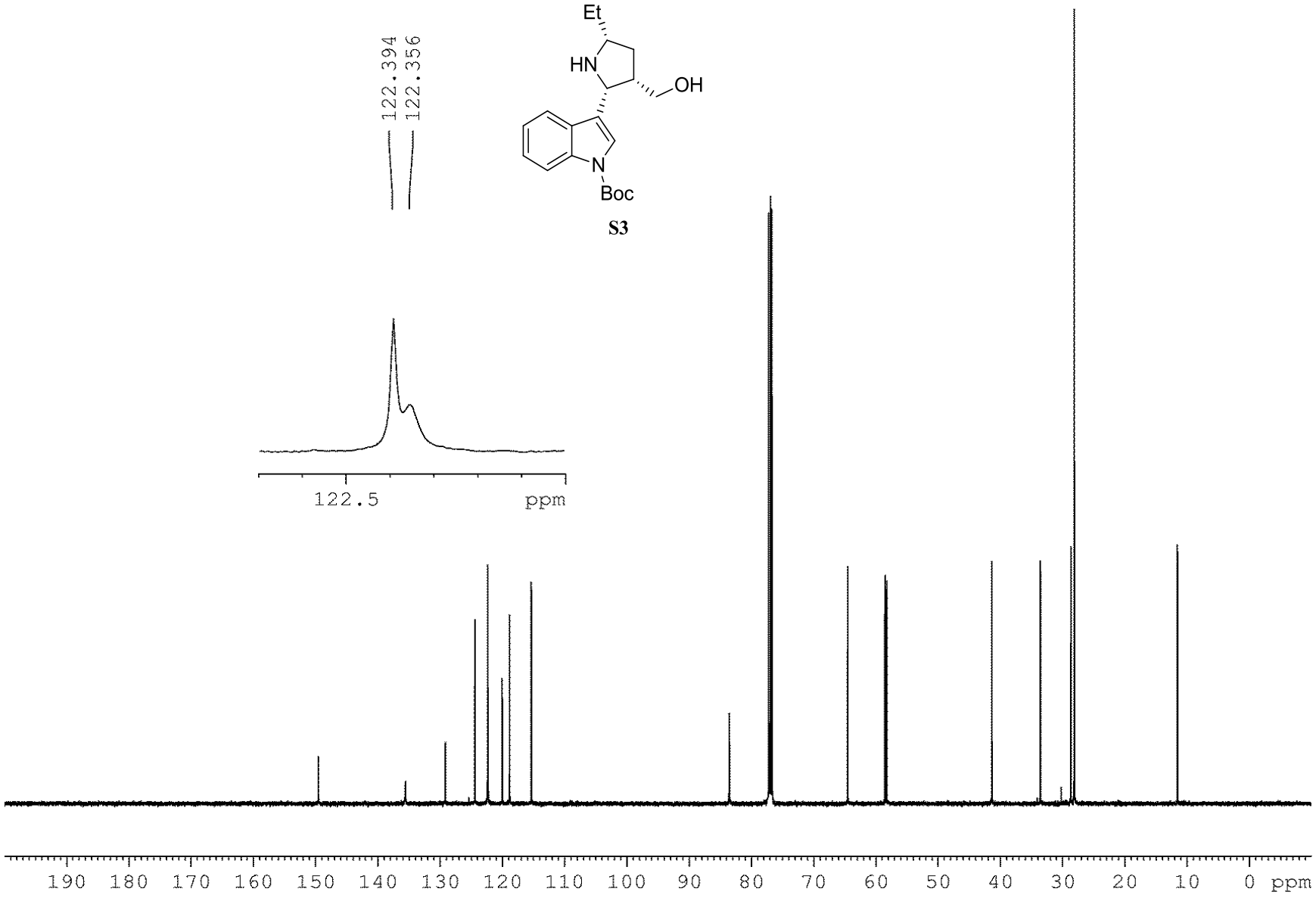

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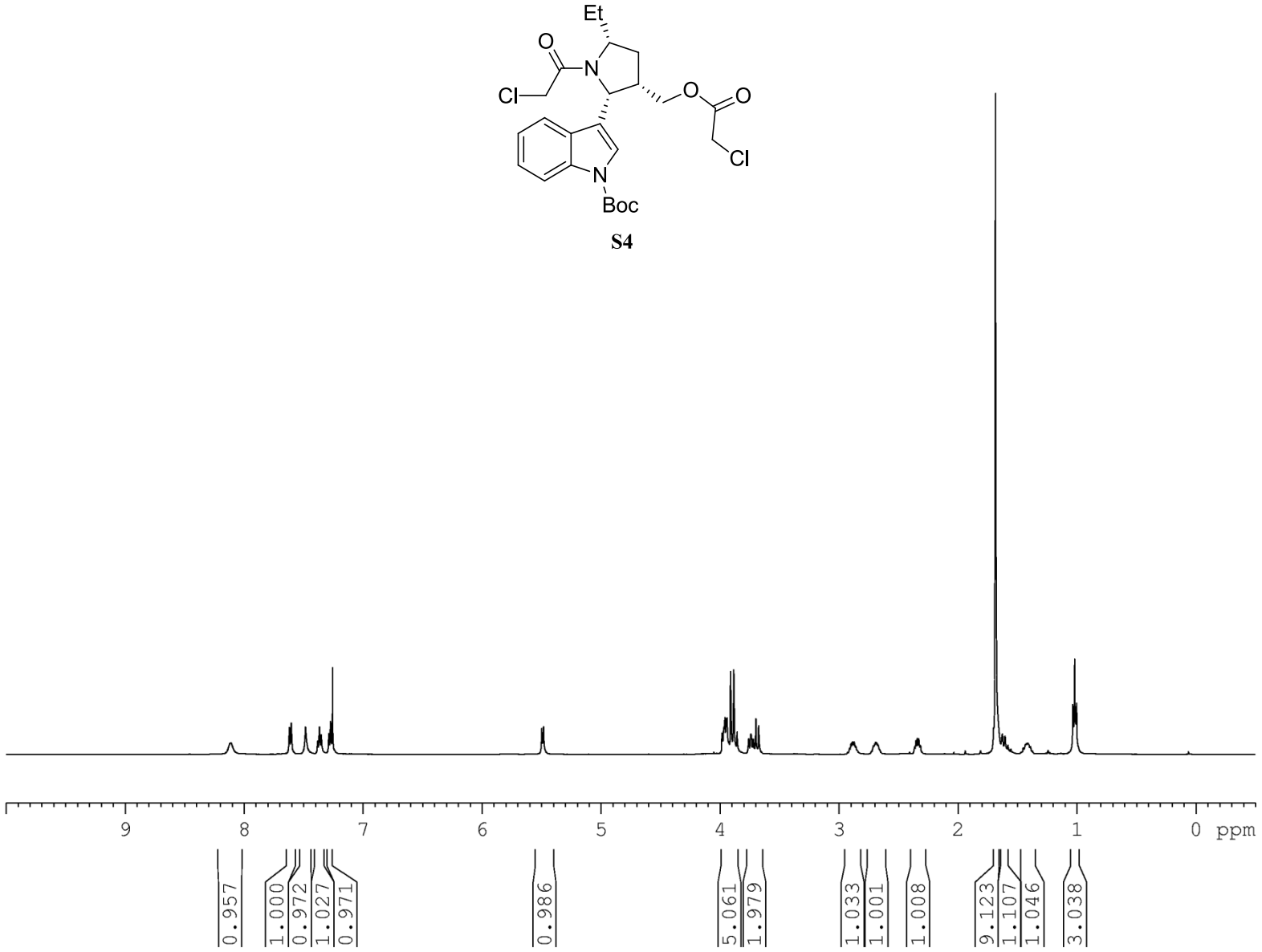
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1.000
0.972
1.027
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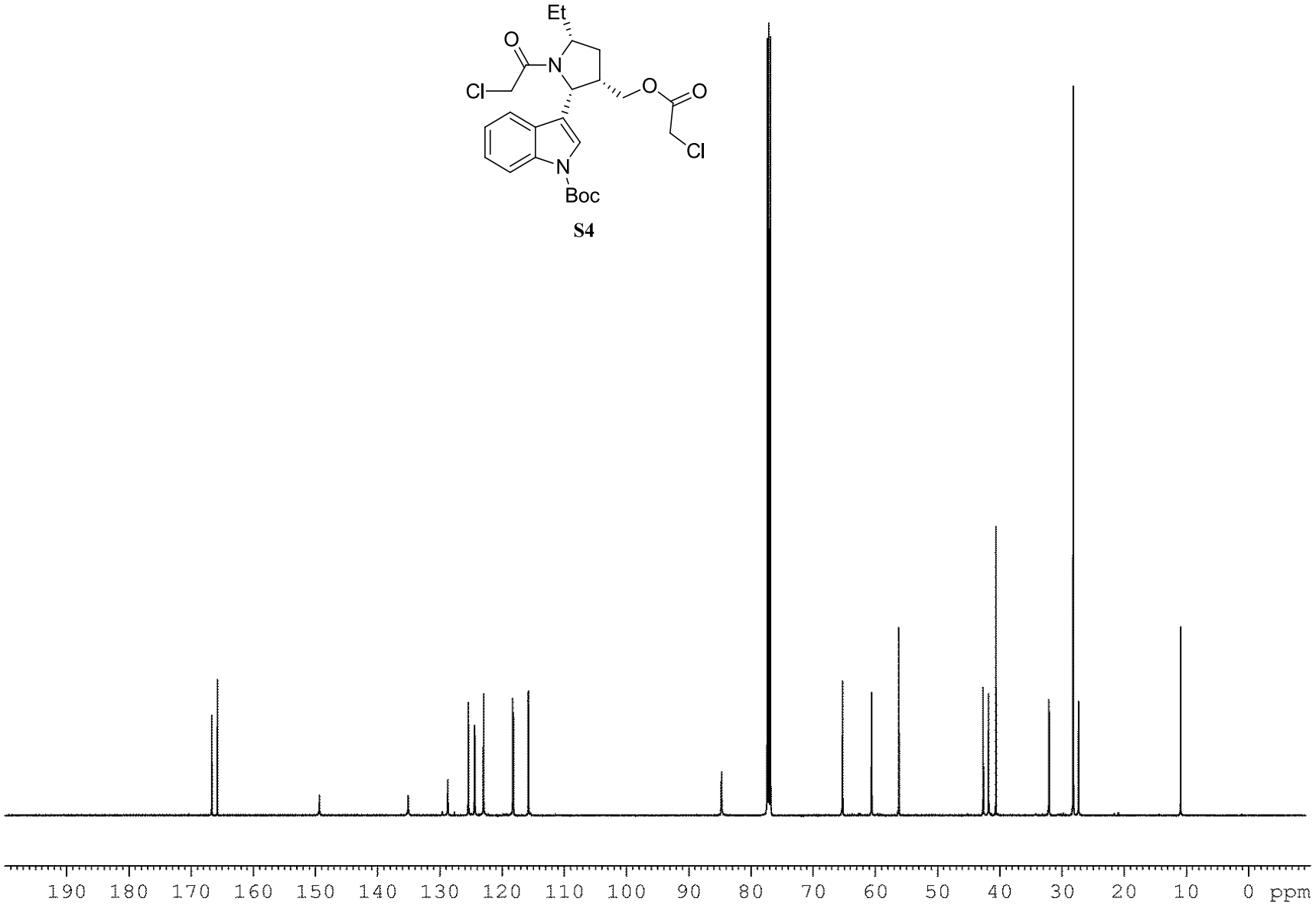
S4



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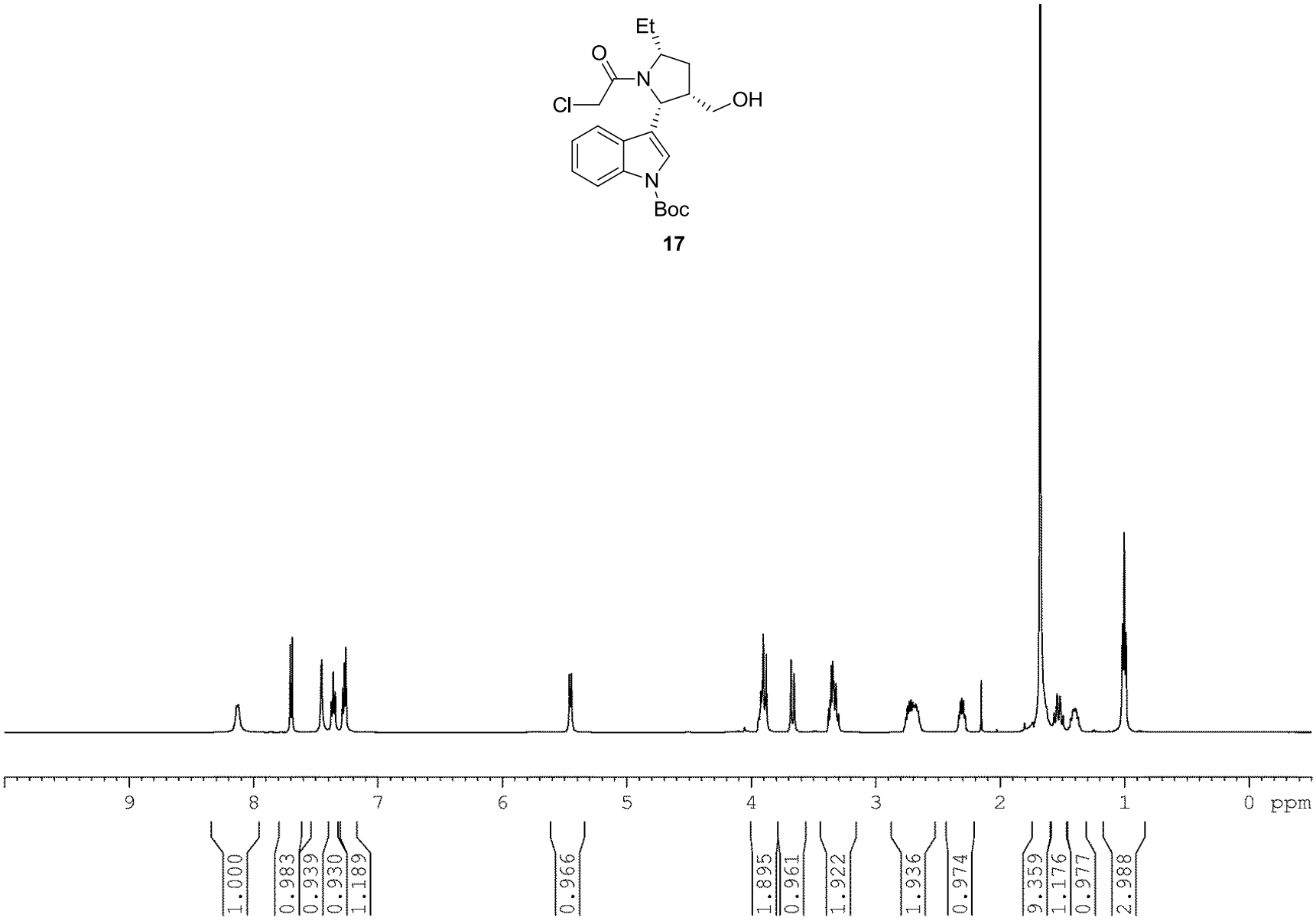

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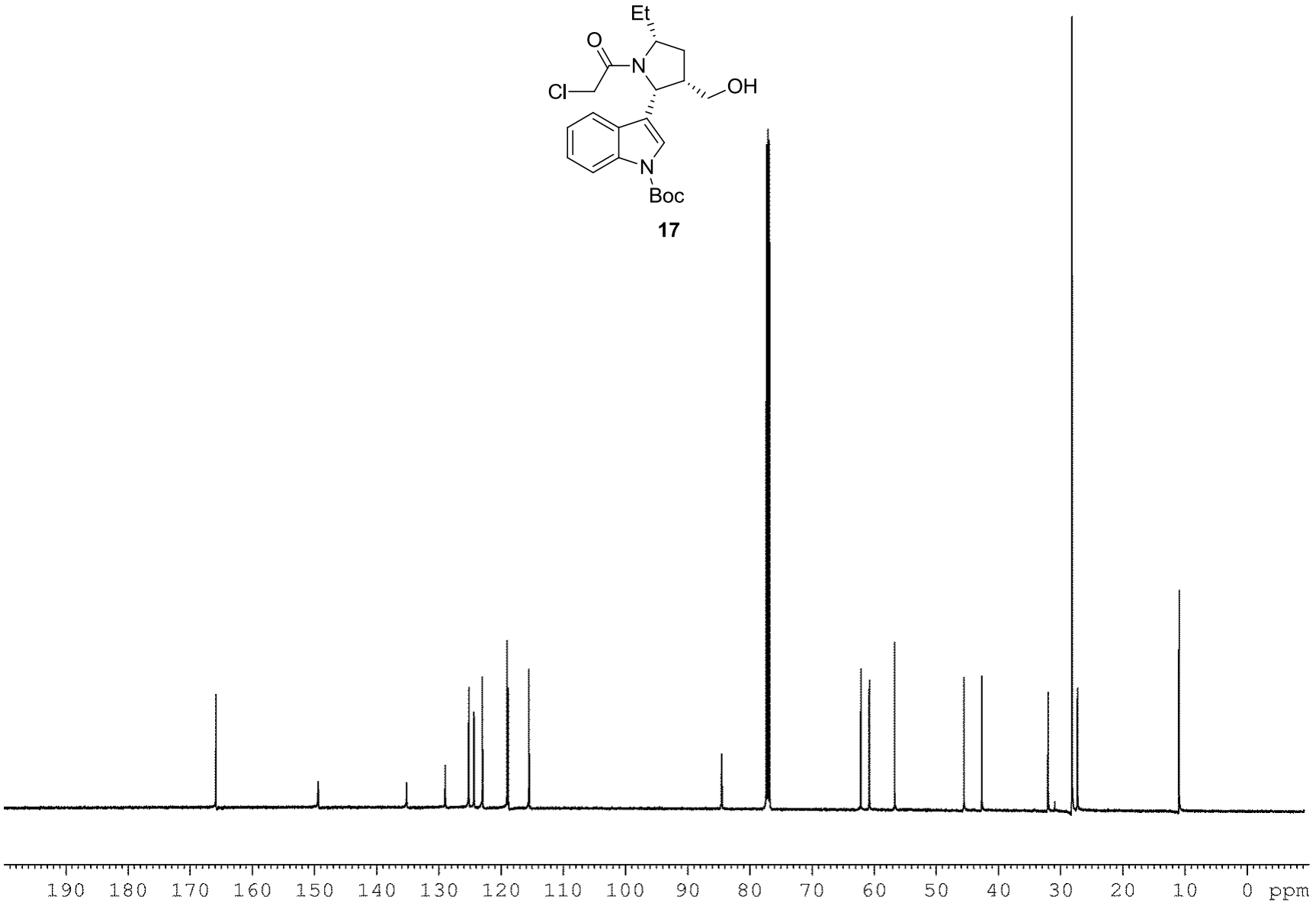

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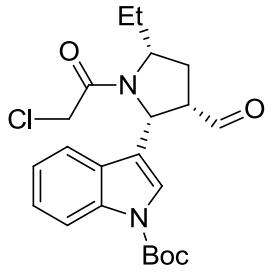

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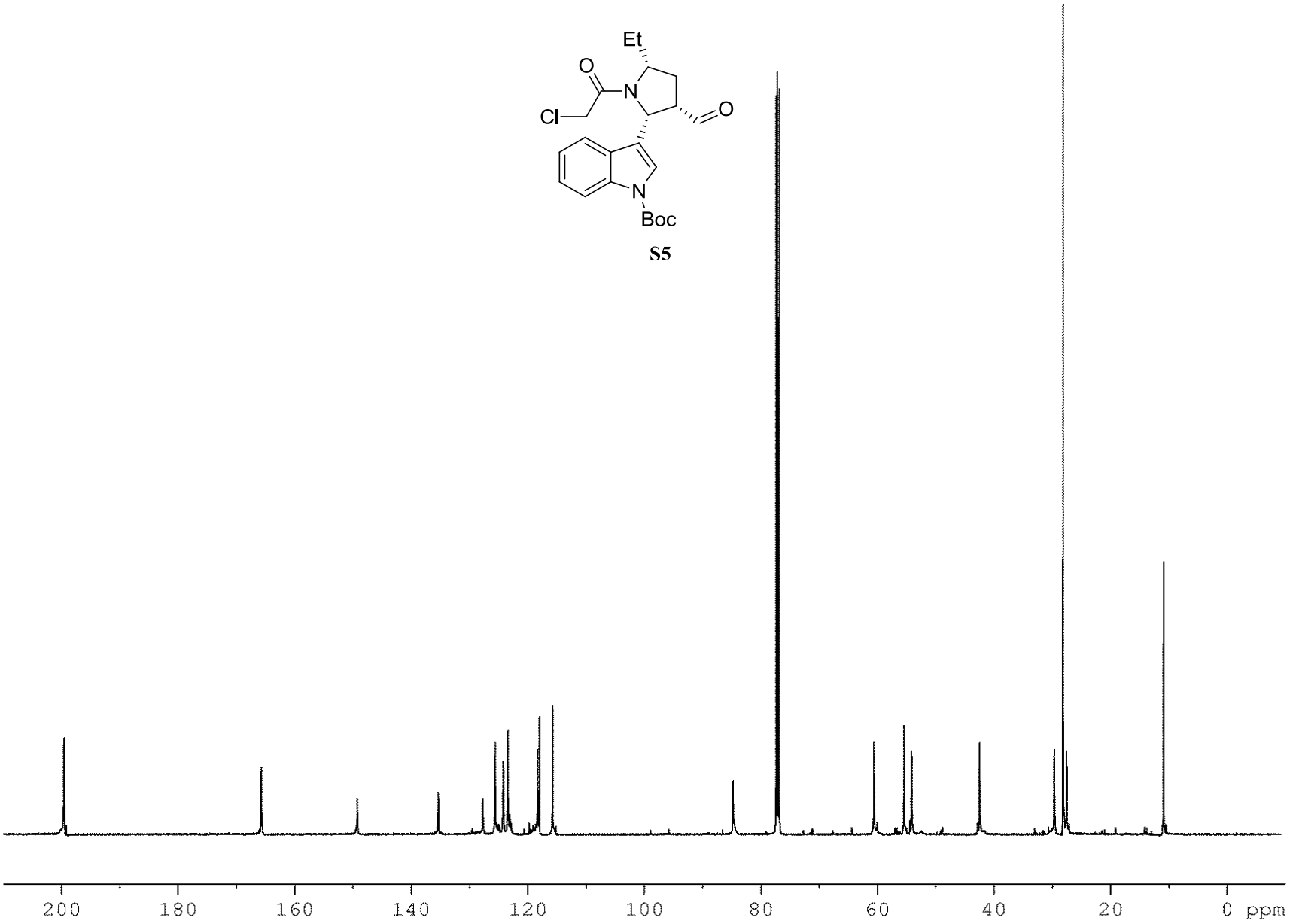

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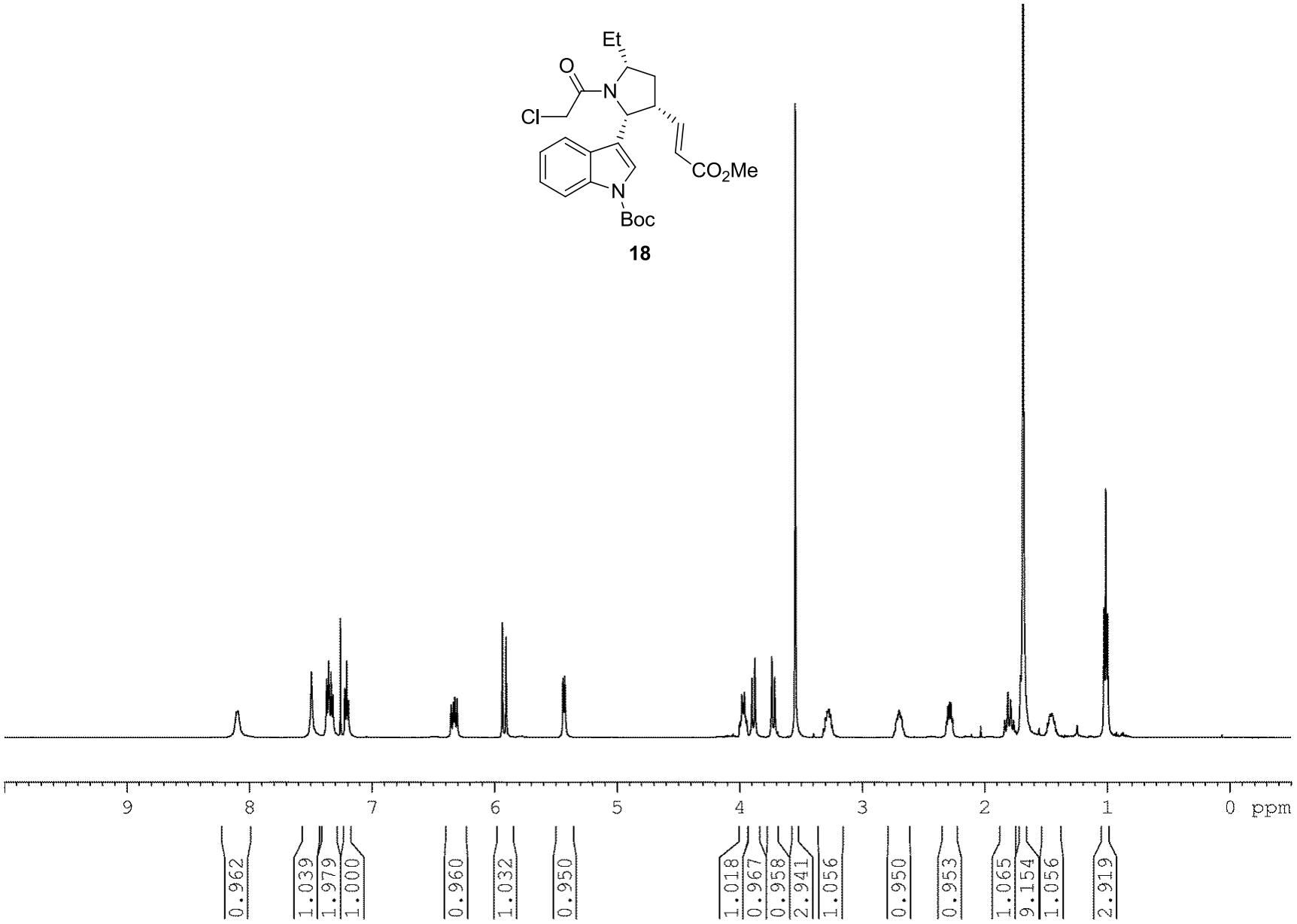

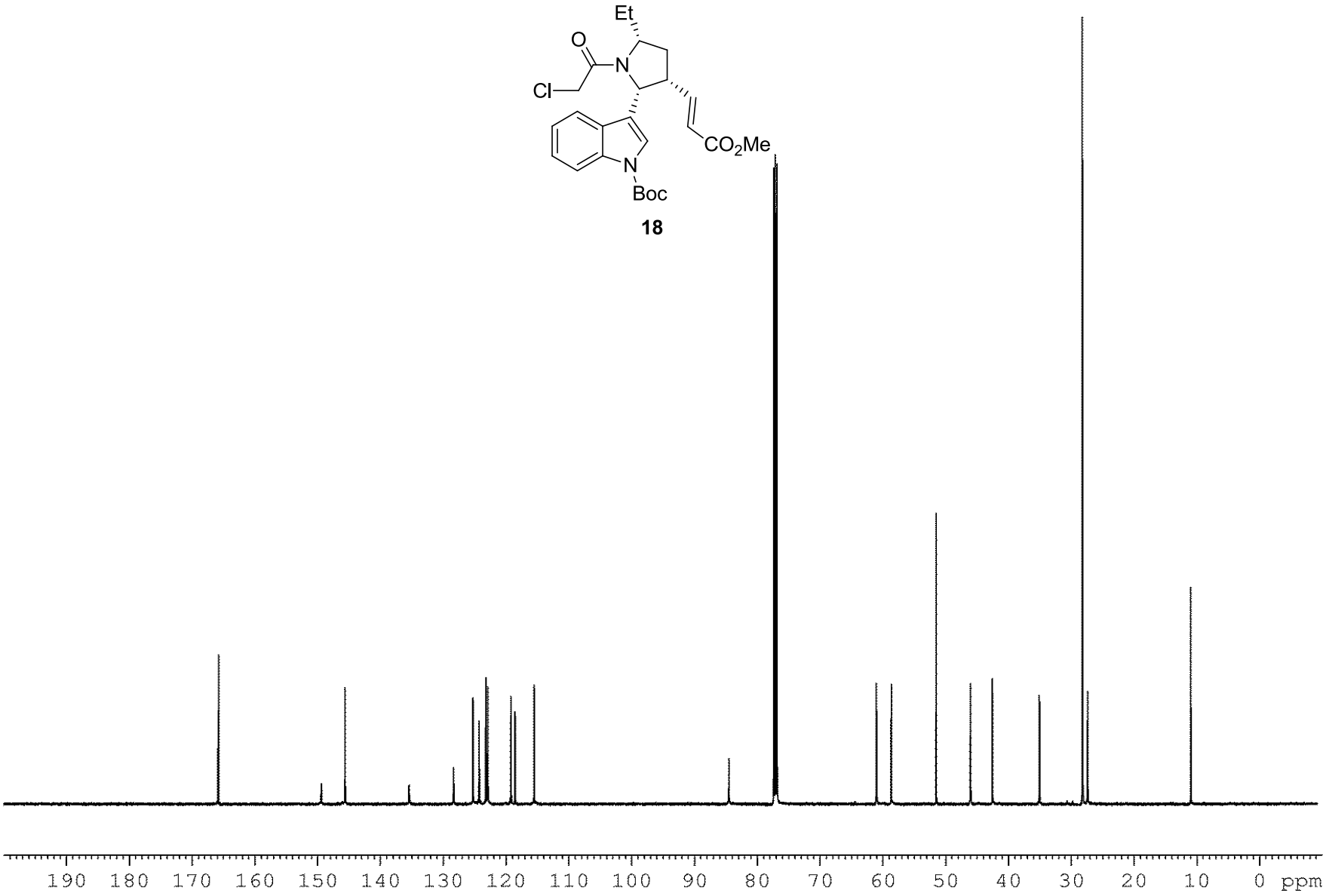

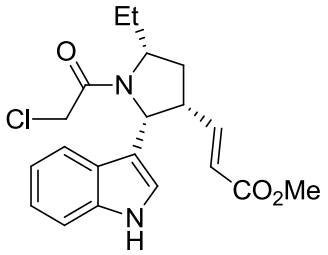

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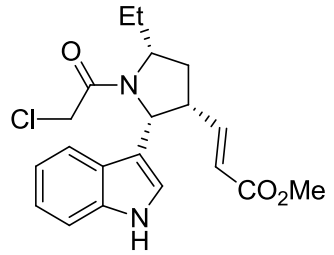

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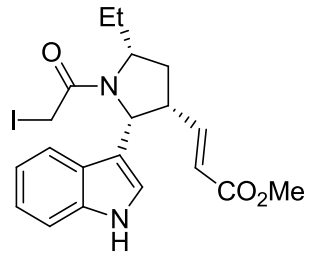

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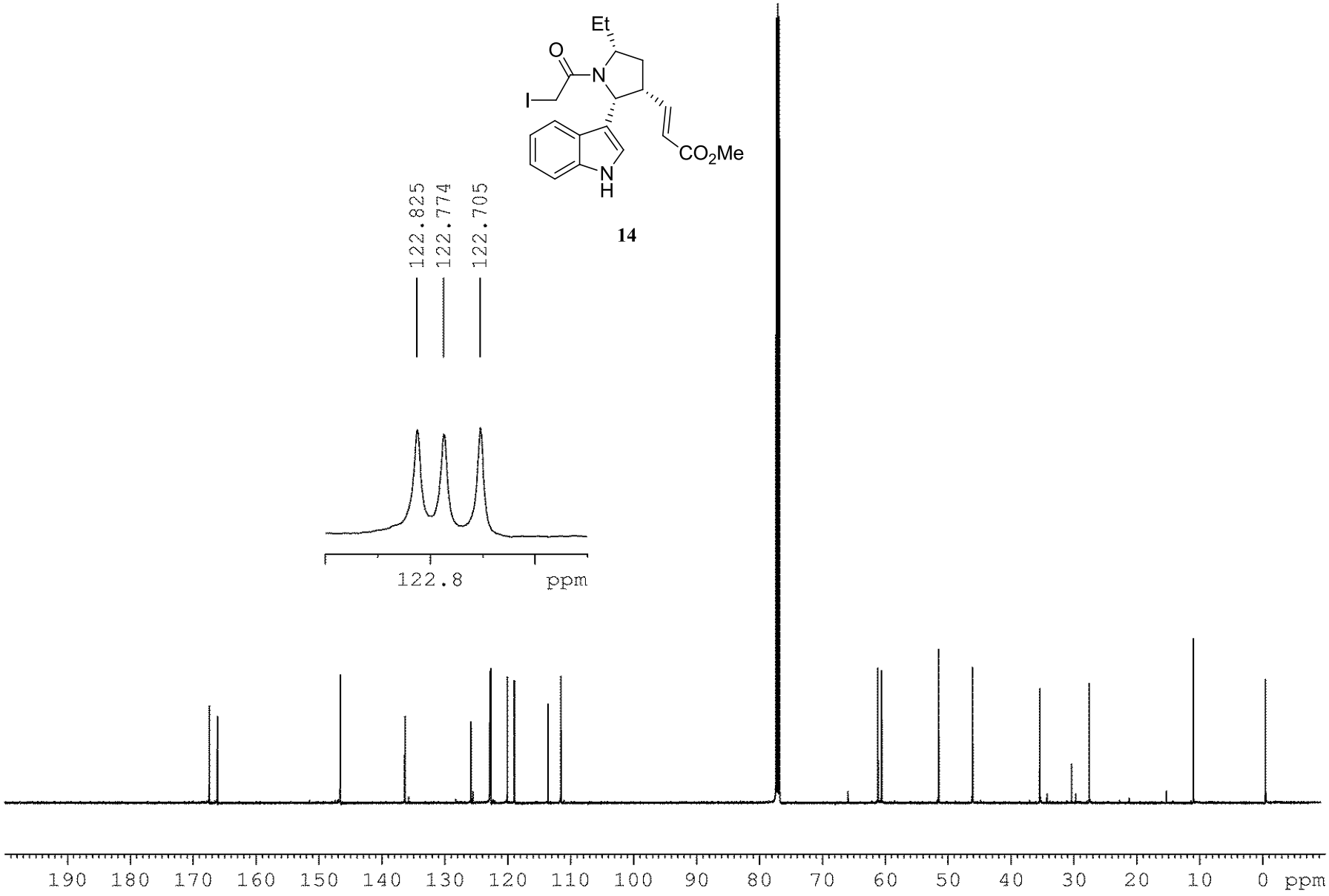

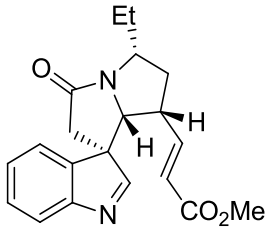

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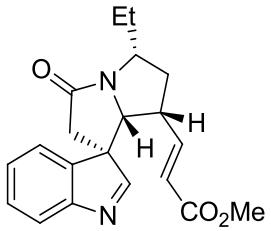

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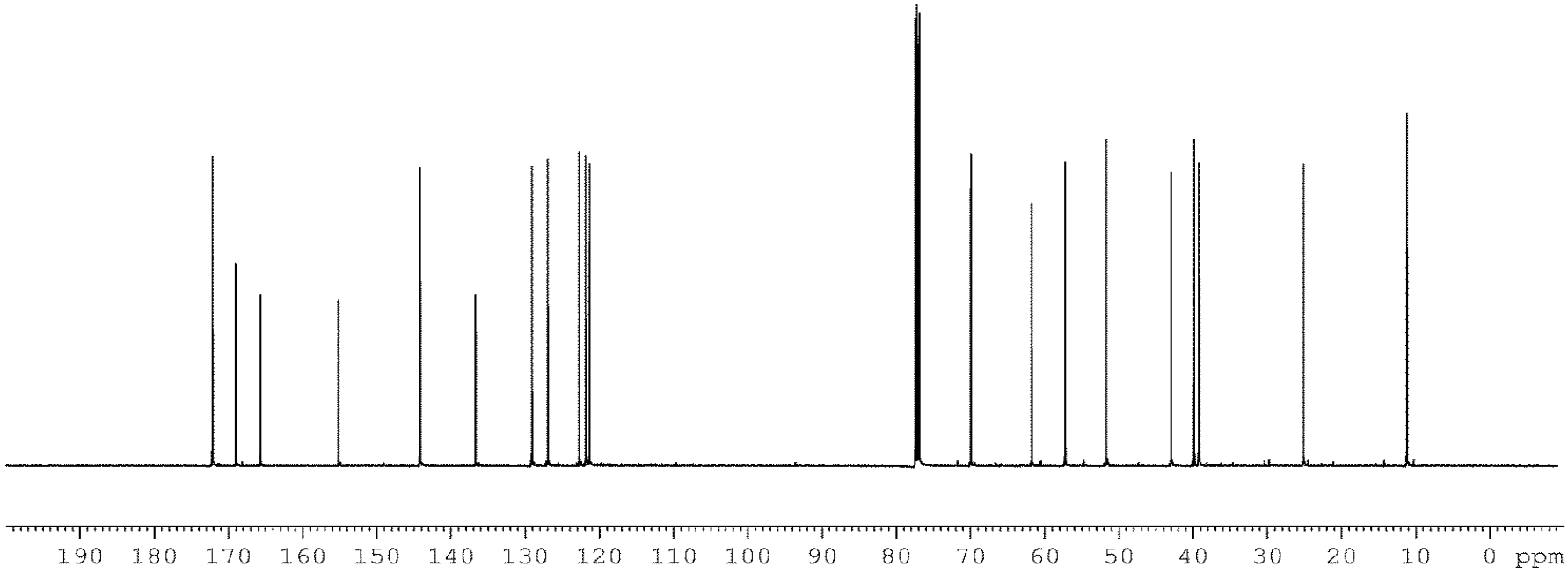

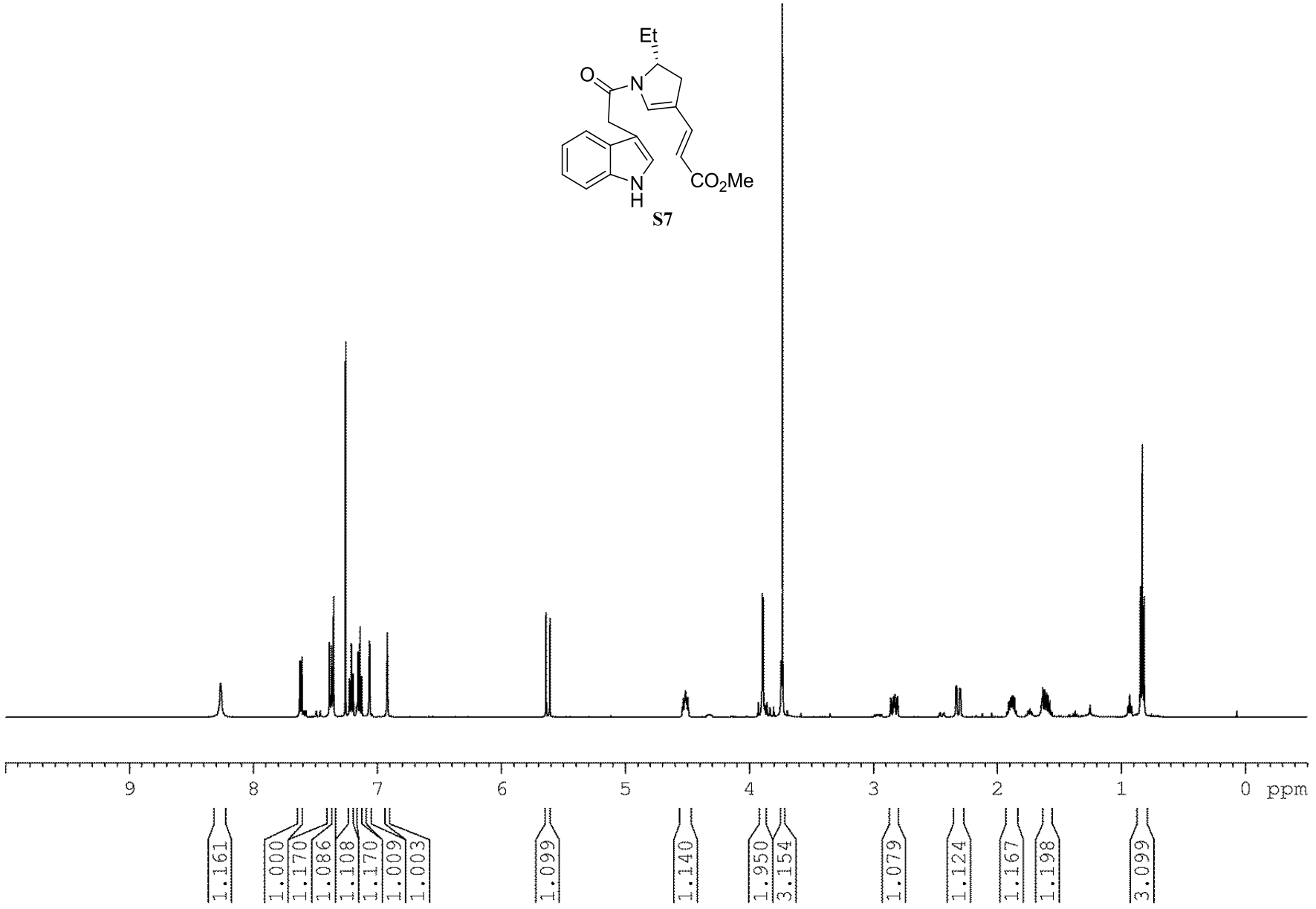

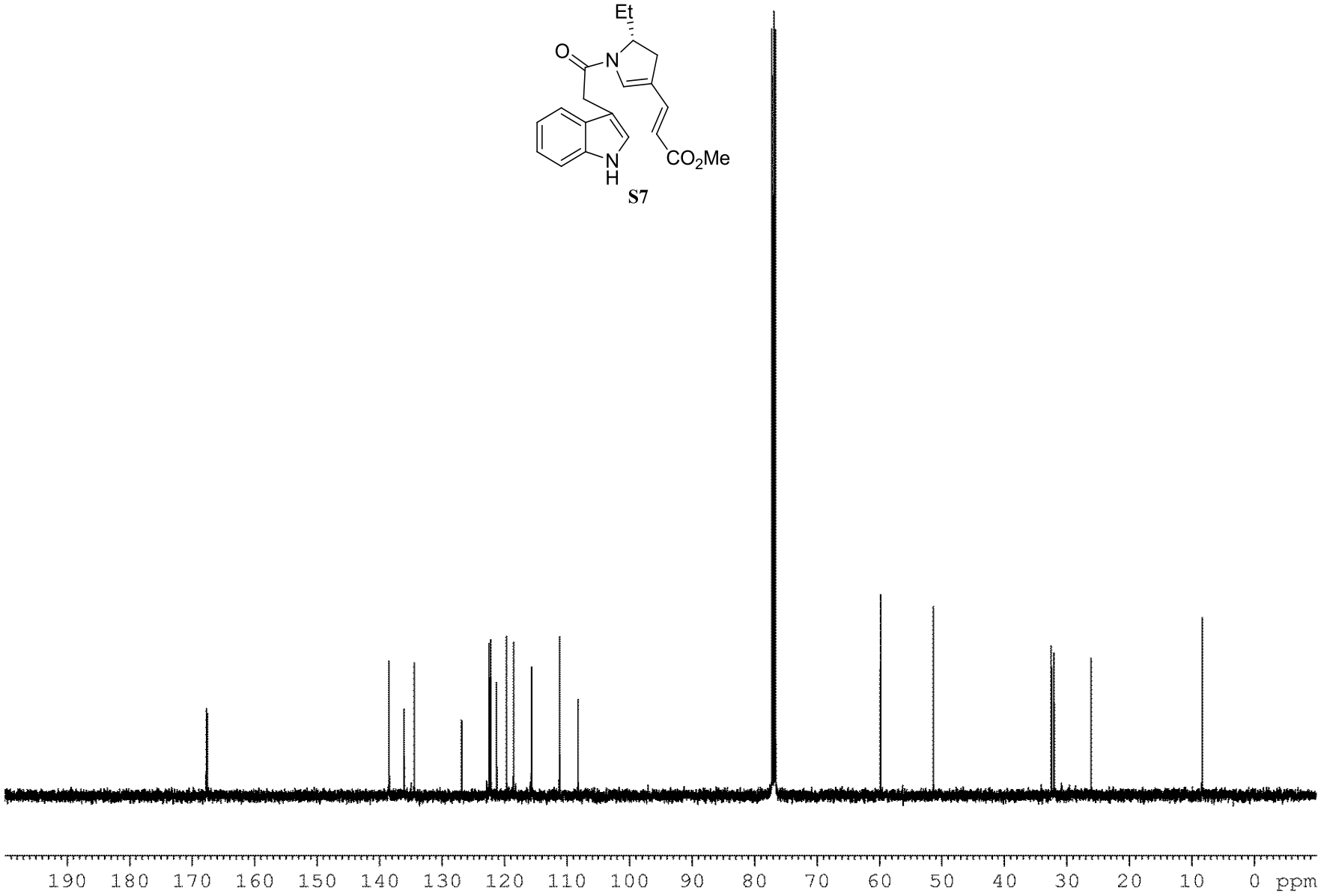

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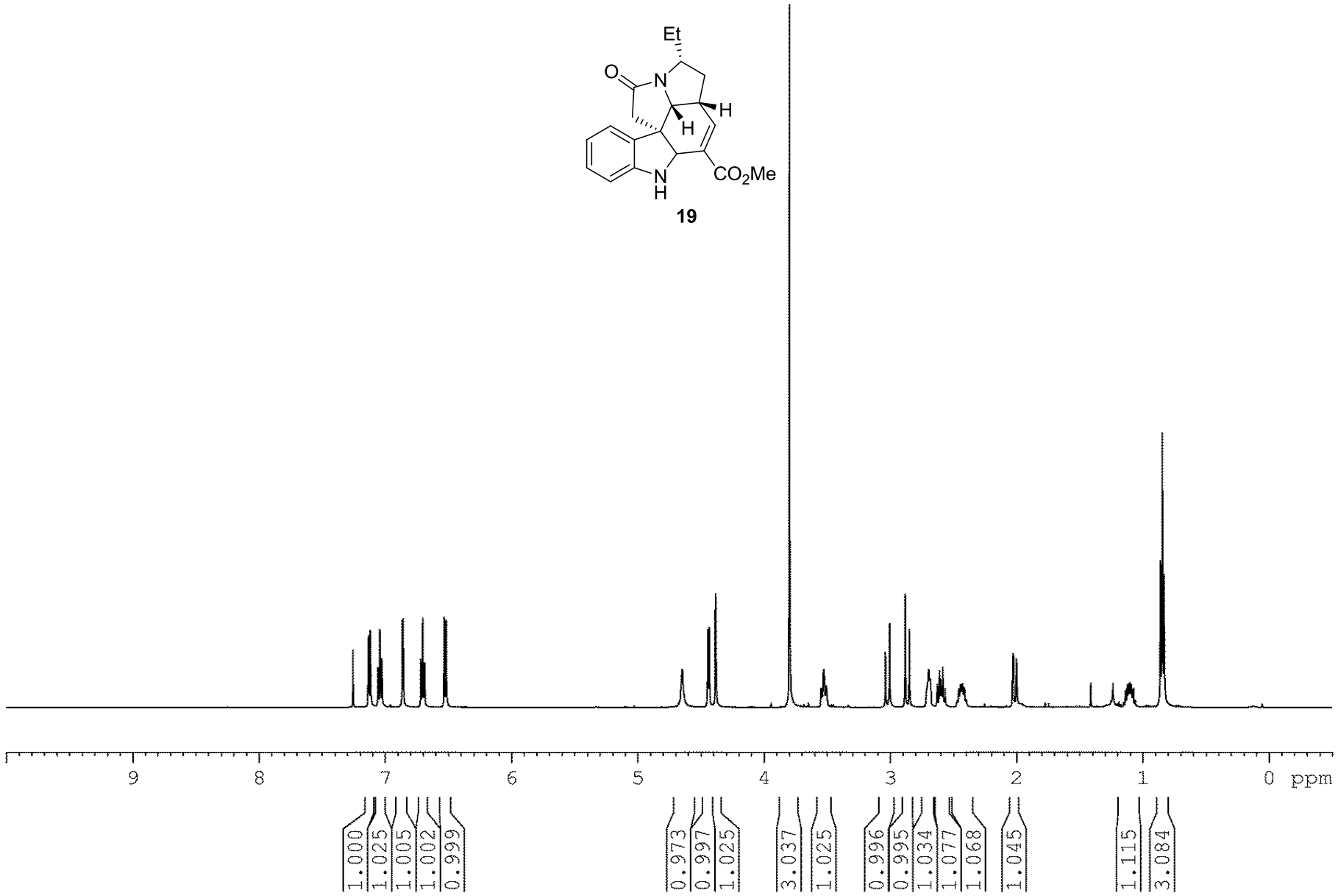

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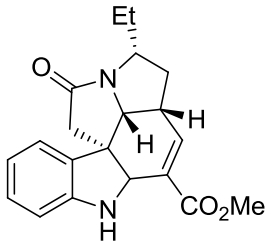

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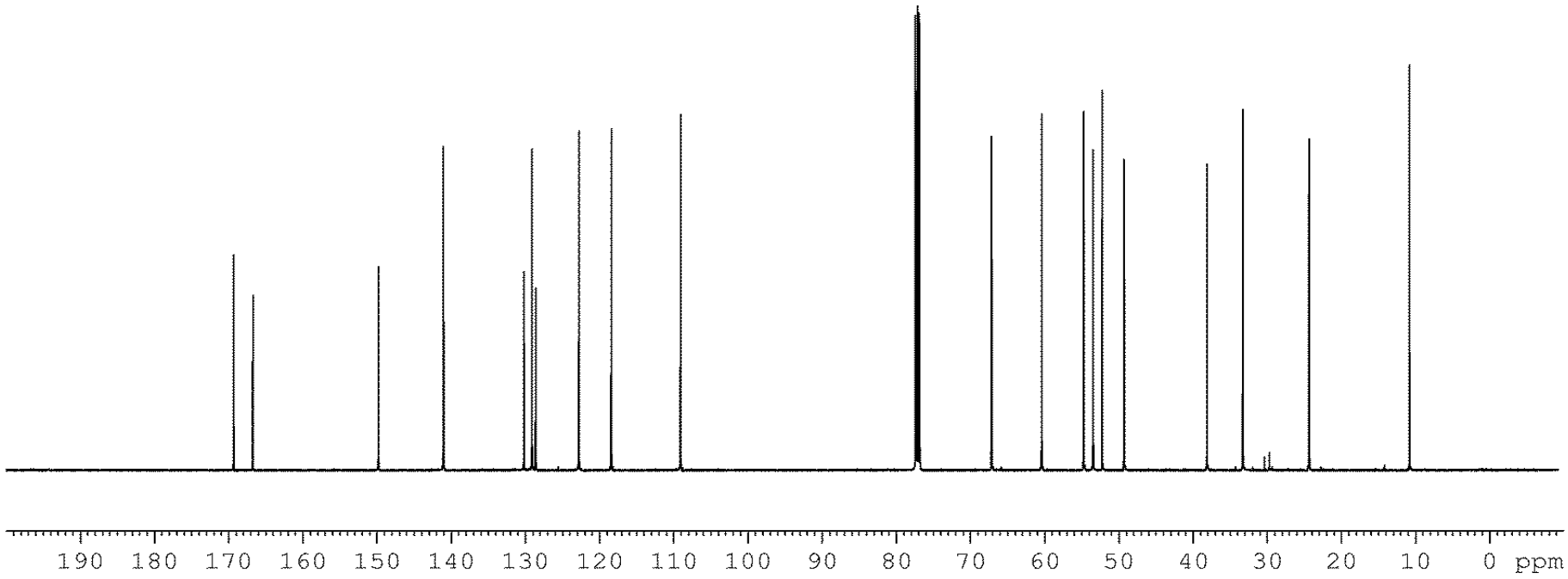
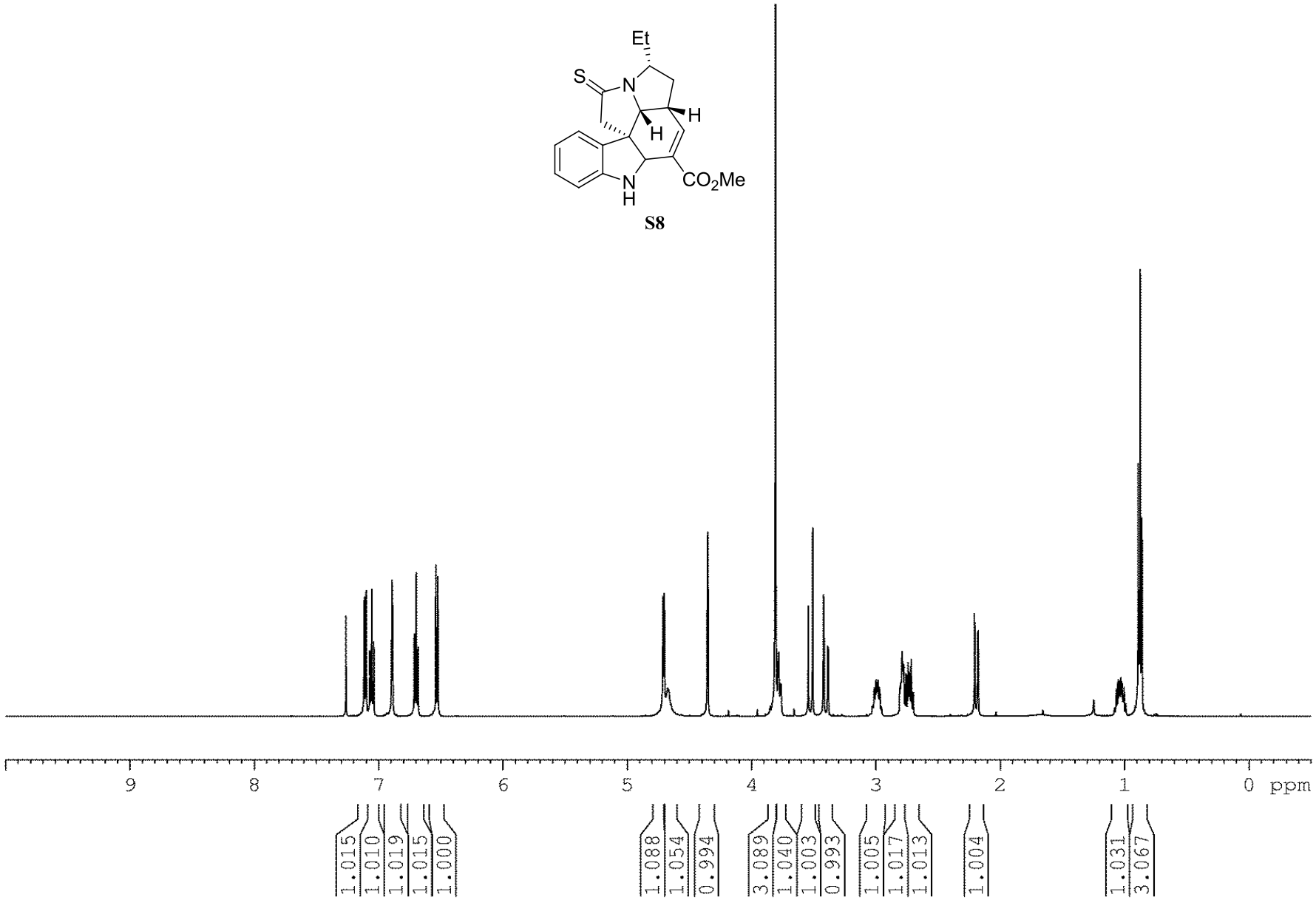
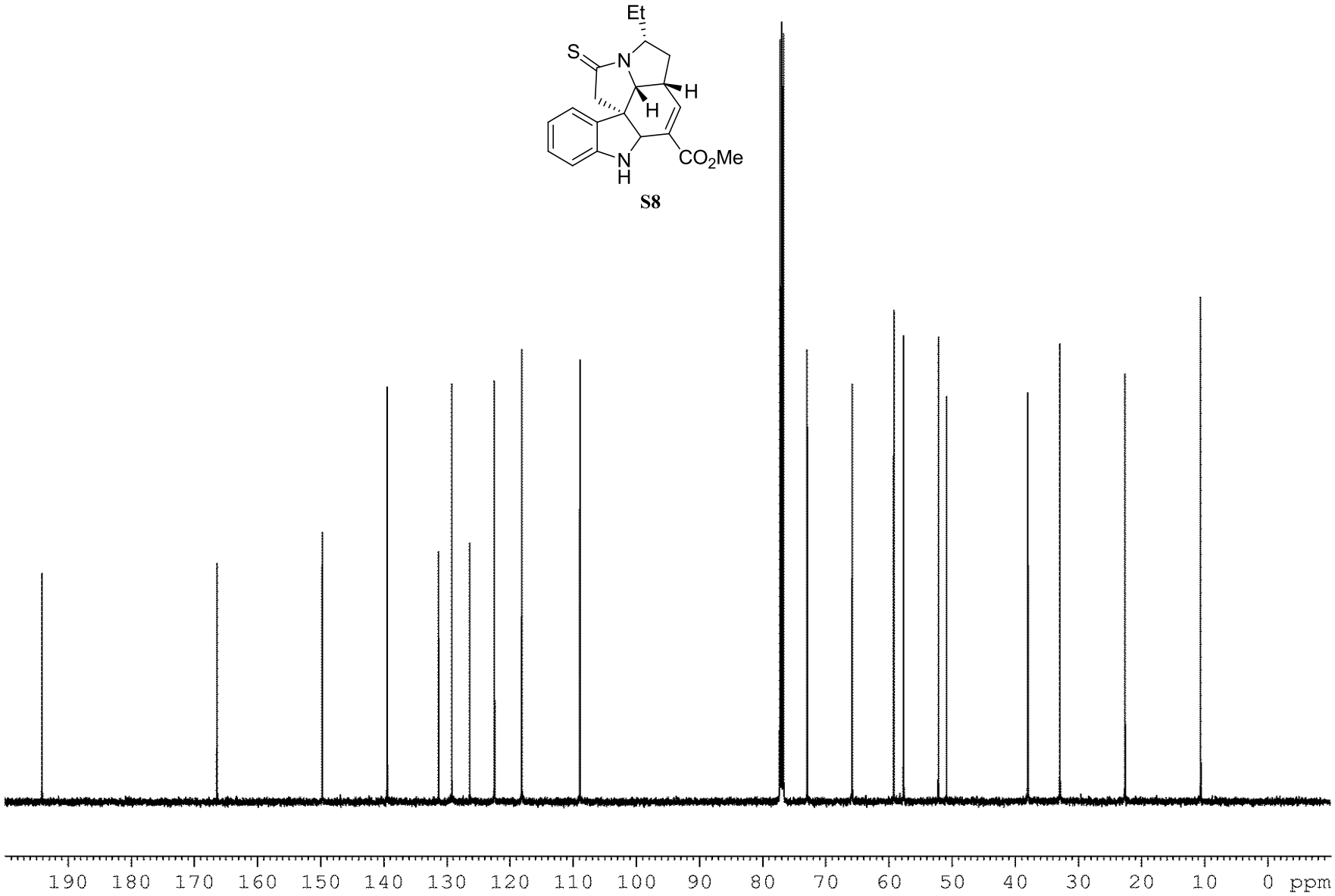




S8



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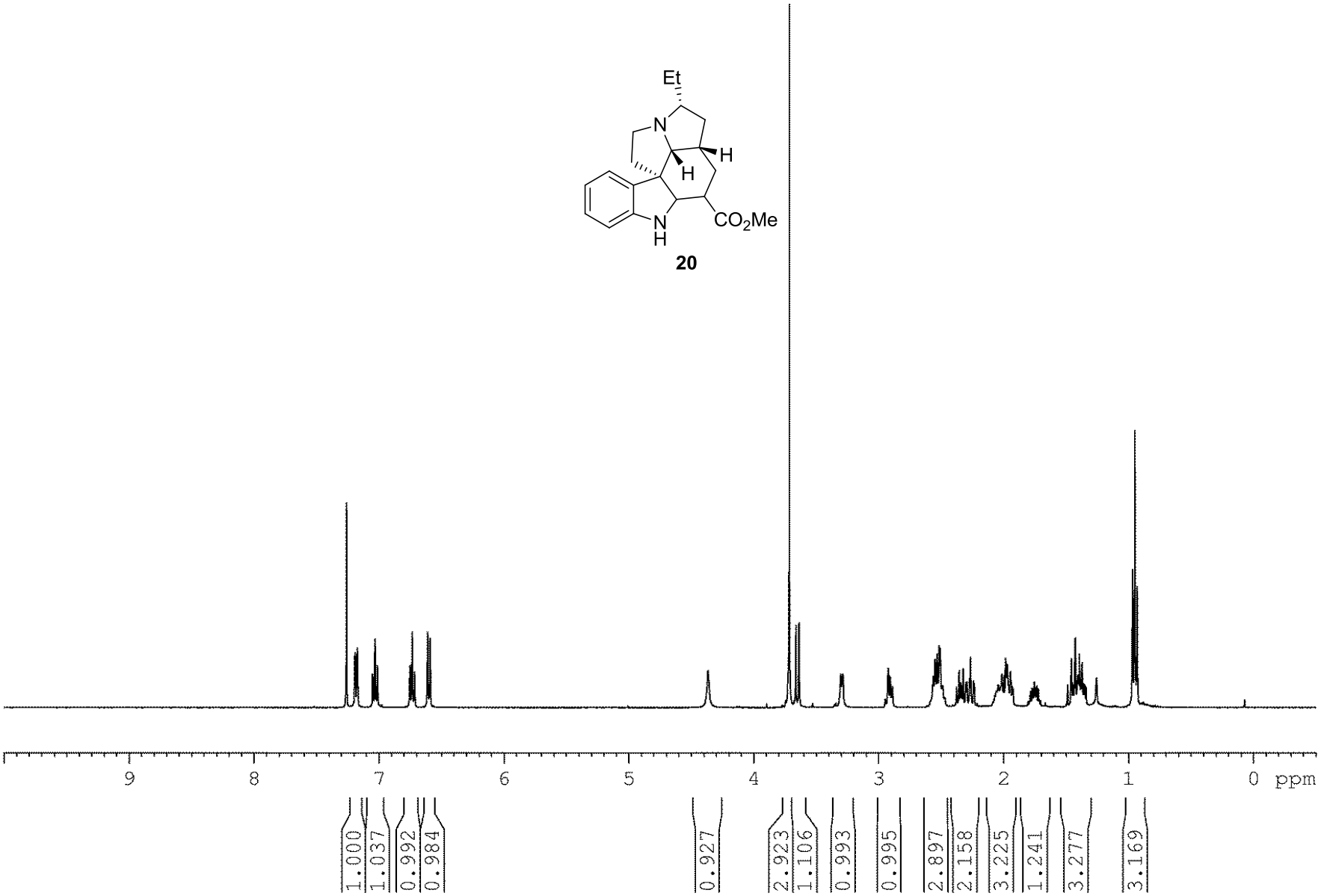
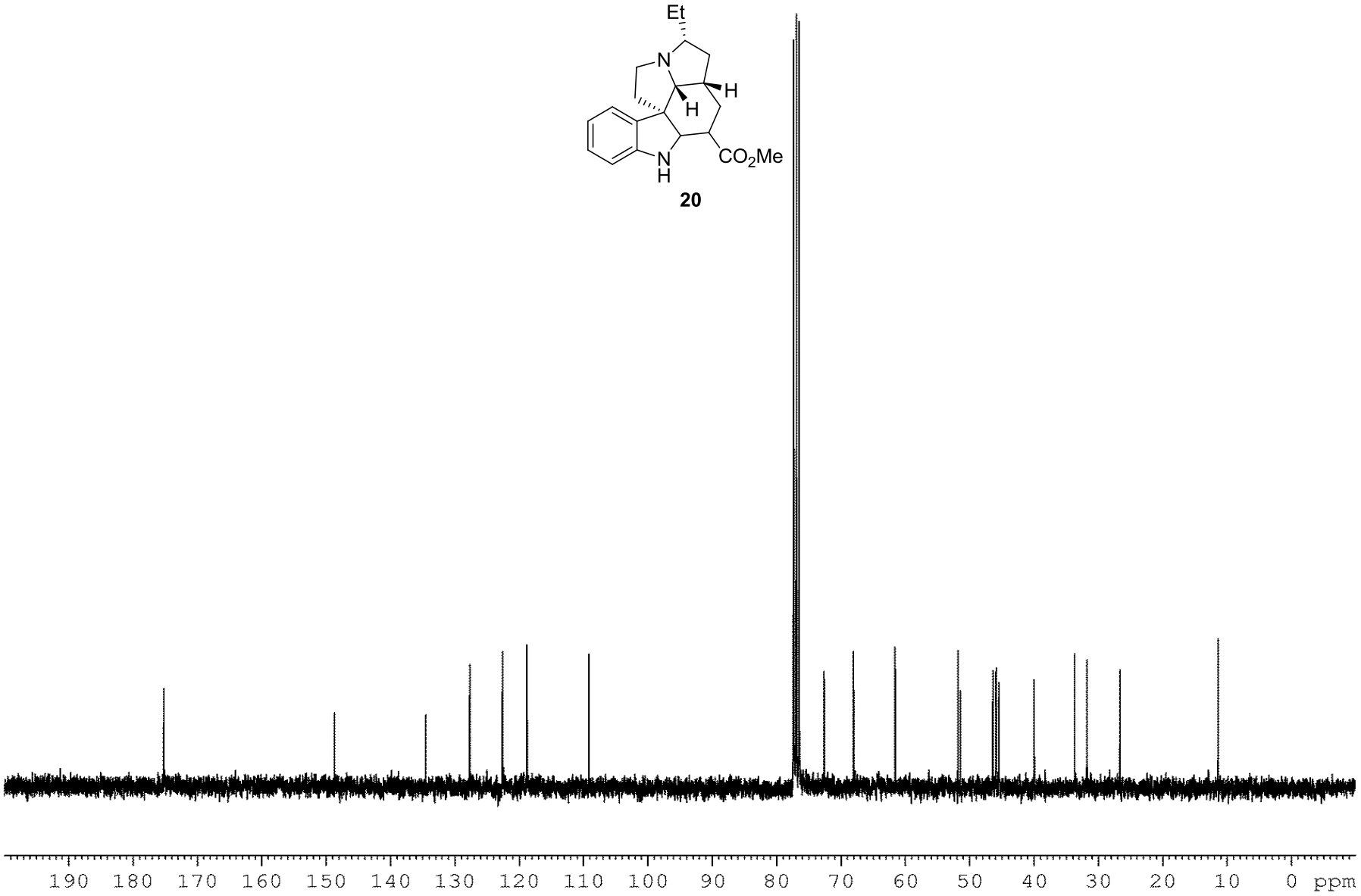
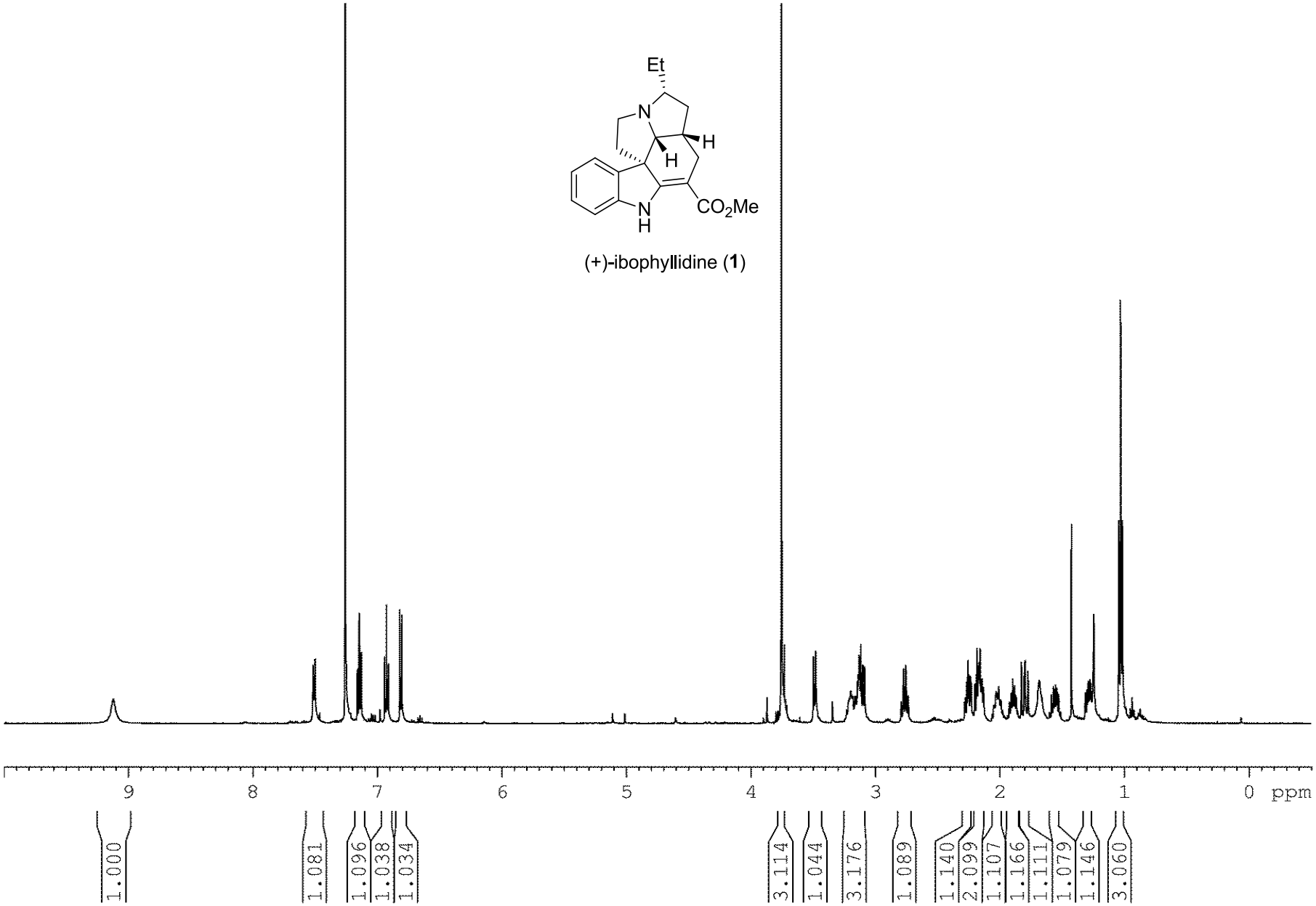
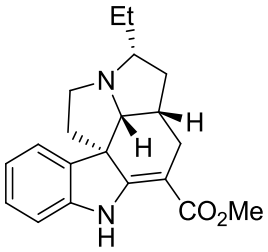




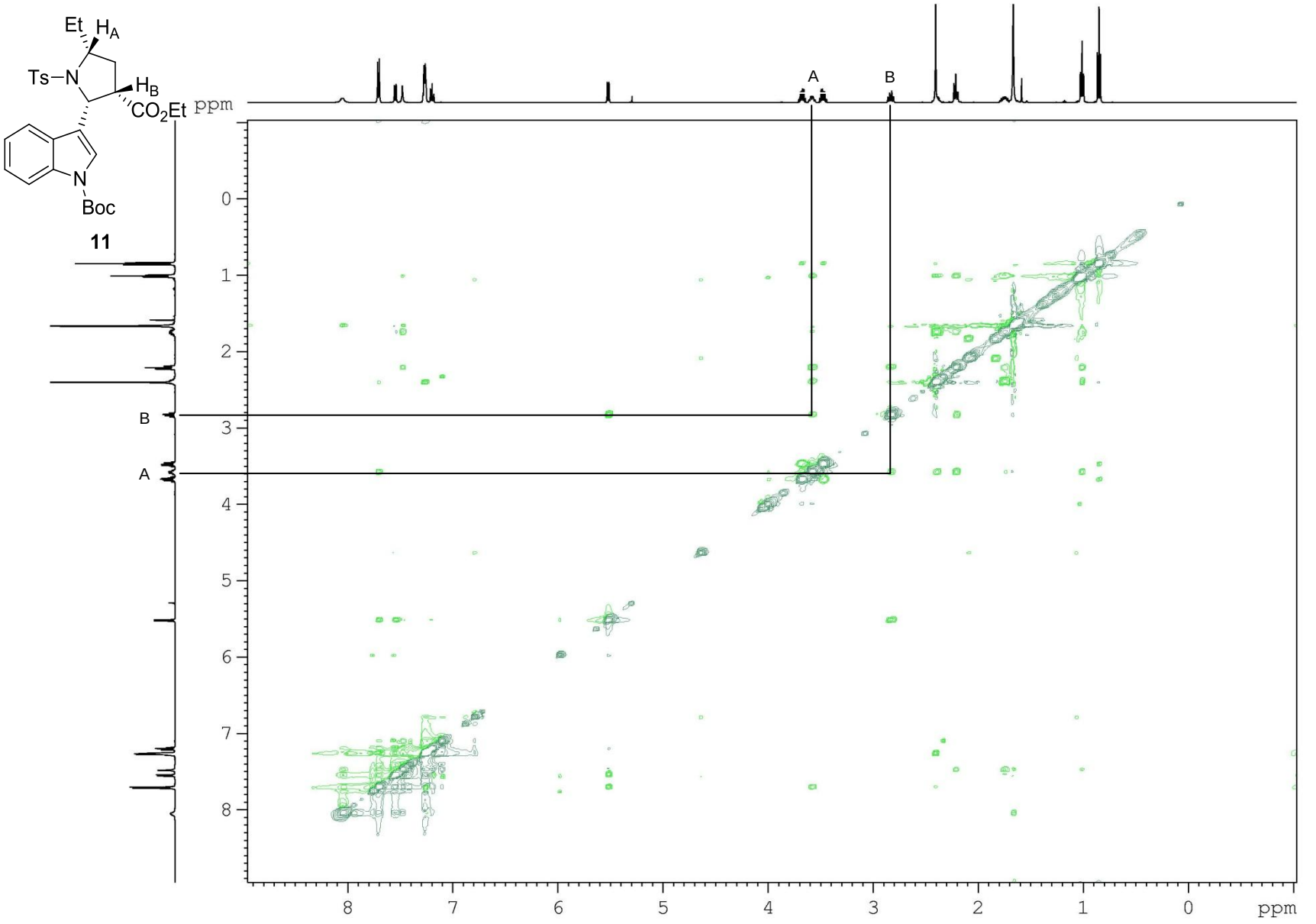


(+)-ibophyllidine (**1**)



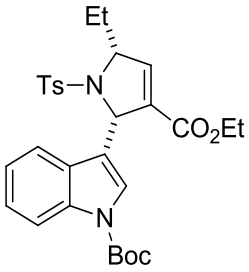
(+)-ibophyllidine (**1**)

NOESY spectrum of pyrrolidine 11

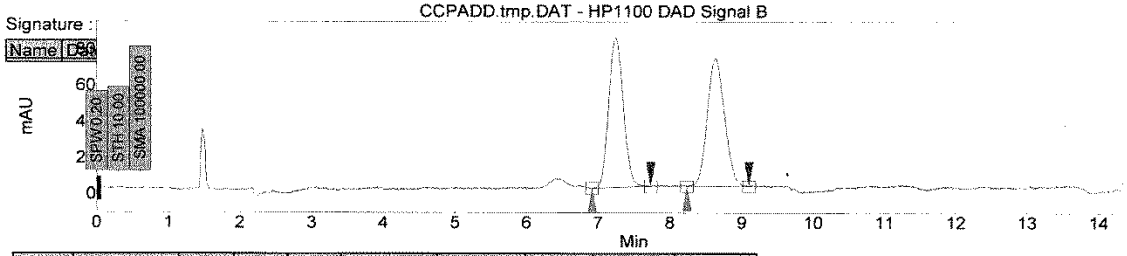


SFC traces for racemic pyrroline **16** and optically active pyrroline **16**

Racemic **16** was prepared according to the general procedure described in reference 13a of the manuscript.



16 (racemic)



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.91	7.25	7.73	0.00	49.57	82.7	19.5	49.571
2	UNKNOWN	8.24	8.65	9.10	0.00	50.43	70.7	19.9	50.429
Total						100.00	153.4	39.4	100.000

CHROMATOGRAM METHOD REPORT :

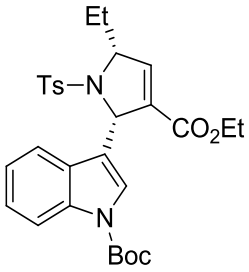
No calibration file found.

Acquisition :
System : UCLA SFC USER
Project : SFC USER
Run Name : ian racemic16_
Run Id. : 2
Run Time : 15.00
Scale :
Autoscale
Vial : 1
Rack : 0
Divisor factor : 1.00
Multipliplier factor : 1.00
Analysis : Sample
Injection volume : 5.00
Sample mass : 0.00

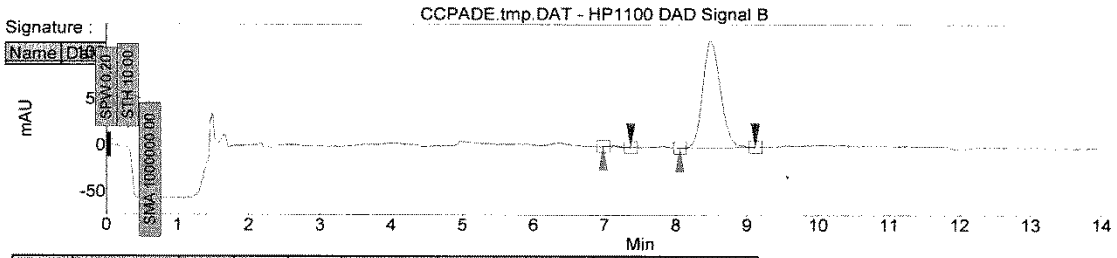
Run Log :

Injection occured at 11/14/2011 12:10:17 PM

DAD [Agilent G1315A/B Diode Array Detector]
HP1100 G1315A Events occurred
11/14/2011 12:09:07 PM Event 108 (Status change to Not Ready)
11/14/2011 12:09:07 PM Event 121 (Unknown Event)
11/14/2011 12:09:07 PM Event 122 (Unknown Event)
11/14/2011 12:09:07 PM Event 109 (Status change to Ready)
11/14/2011 12:09:12 PM Event 202 (Home parameters modified)
11/14/2011 12:09:14 PM Event 201 (Sysvar modified)
11/14/2011 12:09:26 PM Event 108 (Status change to Not Ready)
11/14/2011 12:09:26 PM Event 7200 (Balance started)
11/14/2011 12:09:33 PM Event 109 (Status change to Ready)
11/14/2011 12:09:33 PM Event 7090 (Device idle)
11/14/2011 12:10:17 PM Event 104 (Status change to Run)
11/14/2011 12:10:17 PM Event 110 (Status change to Analysis)
11/14/2011 12:11:26 PM Event 1039 (Unknown Event)



16



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.98	7.11	7.37	0.00	0.35	1.4	0.1	0.350
2	UNKNOWN	8.06	8.49	9.12	0.00	99.65	115.6	33.2	99.650
Total						100.00	117.0	33.3	100.000

CHROMATOGRAM METHOD REPORT :

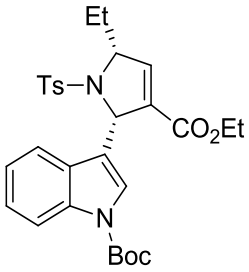
No calibration file found.

Acquisition :
System : UCLA SFC USER
Project : SFC USER
Run Name : ian 10%
Run Id. : 19
Run Time : 15.00
Scale :
Autoscale
Vial : 2
Rack : 0
Divisor factor : 1.00
Multipliplier factor : 1.00
Analysis : Sample
Injection volume : 5.00
Sample mass : 0.00

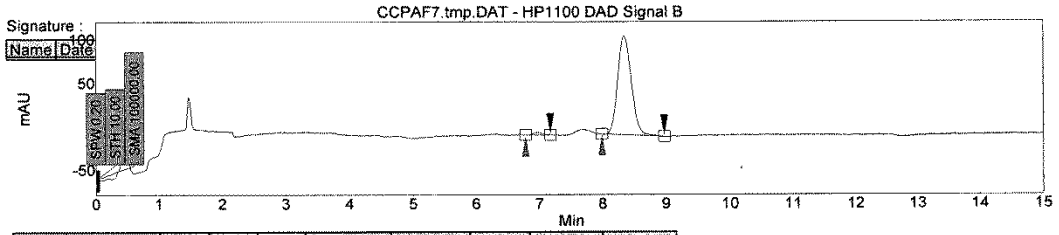
Run Log :

Injection occured at 11/14/2011 1:00:31 PM

DAD [Agilent G1315A/B Diode Array Detector]
HP1100 G1315A Events occurred
11/14/2011 12:59:21 PM Event 108 (Status change to Not Ready)
11/14/2011 12:59:21 PM Event 121 (Unknown Event)
11/14/2011 12:59:21 PM Event 122 (Unknown Event)
11/14/2011 12:59:21 PM Event 109 (Status change to Ready)
11/14/2011 12:59:27 PM Event 202 (Home parameters modified)
11/14/2011 12:59:27 PM Event 201 (Sysvar modified)
11/14/2011 12:59:40 PM Event 108 (Status change to Not Ready)
11/14/2011 12:59:40 PM Event 7200 (Balance started)
11/14/2011 12:59:47 PM Event 109 (Status change to Ready)
11/14/2011 12:59:47 PM Event 7090 (Device idle)
11/14/2011 1:00:31 PM Event 104 (Status change to Run)
11/14/2011 1:00:31 PM Event 110 (Status change to Analysis)
11/14/2011 1:01:40 PM Event 1039 (Unknown Event)



16
From large scale synthesis



Index	Name	Start	Time	End	RT Offset	Quantity	Height	Area	Area
		[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
1	UNKNOWN	6.78	6.98	7.17	0.00	1.56	2.6	0.4	1.563
2	UNKNOWN	7.99	8.35	8.97	0.00	98.44	113.7	28.2	98.437
Total						100.00	116.3	28.6	100.000

97% ee

~~38~~ 30g Scale

CHROMATOGRAM METHOD REPORT :

No calibration file found.

Acquisition :
System : UCLA SFC USER
Project : SFC USER
Run Name : ianscale5_
Run Id. : 1
Run Time : 15.00
Scale :
Autoscale
Vial : 1
Rack : 0
Divisor factor : 1.00
Multipliplier factor : 1.00
Analysis : Sample
Injection volume : 5.00
Sample mass : 0.00

Run Log :

Injection occured at 12/12/2011 6:41:26 PM

PUMP [Berger FCM-1100/1200 Fluid Control Module]
System not ready; Pressure not ready
Pressure ready Device is ready.

DAD [Agilent G1315A/B Diode Array Detector]
HP1100 G1315A Events occurred
12/12/2011 6:39:36 PM Event 108 (Status change to Not Ready)
12/12/2011 6:39:36 PM Event 121 (Unknown Event)
12/12/2011 6:39:36 PM Event 122 (Unknown Event)
12/12/2011 6:39:36 PM Event 109 (Status change to Ready)
12/12/2011 6:39:41 PM Event 202 (Home parameters modified)
12/12/2011 6:39:43 PM Event 201 (Sysvar modified)
12/12/2011 6:40:35 PM Event 108 (Status change to Not Ready)
12/12/2011 6:40:36 PM Event 7200 (Balance started)
12/12/2011 6:40:41 PM Event 109 (Status change to Ready)