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Supporting Information

Chiral Brønsted Acid-Catalyzed Enantioselective Addition of Indoles to Ketimine

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General Information: Infrared (IR) spectra were recorded on a Thermo SCIENTIFIC Nicolet iS5 spectrometer. ^{1}H NMR spectra were measured on JEOL JNM-FX400 (400 MHz) and JEOL JNM-ECA500 (500 MHz) spectrometers. Chemical shifts were reported in ppm from tetramethylsilane (in the case of $CDCl_3$) as an internal standard. Data were reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, and app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on JEOL JNM-FX400 (100 MHz) and JEOL JNM-ECA500 (125 MHz) spectrometes with complete proton decoupling. Chemical shifts were reported in ppm from the residual solvent as an internal standard. High performance liquid chromatography (HPLC) was performed on Shimadzu 20A instruments using Daicel CHIRALPAK IC 4.6 mm × 25 cm column. The high-resolution mass spectra (HRMS) were performed on Bruker microTOF. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. For thin layer chromatography (TLC) analysis throughout this work, Merck precoated TLC plates (silica gel 60 GF_{254}, 0.25 mm) were used. The products were purified by flash column chromatography on neutral silica gel 60N (Kanto Chemical Co. Inc., 40-50μm). For purification with preparative thin layer chromatography (PLC), Merck precoated PLC plates (silica gel 60 GF_{254}, 0.5 mm) were used. 1,4-Dioxane, methanol, ethanol, pyridine, acetonitrile and toluene were purchased from Wako Pure Chemistry Co. Inc. 1,4-Dioxane and acetonitrile were stored over molecular sieve 4A. Toluene was further purified by passing through neutral alumina under nitrogen atmosphere. Tetrahydrofuran was purchased from Kanto Chemical Co. Inc. as "Dehydrated". Ethyl 2-oxo-2H-benzo[*b*][1,4]oxazine-3-carboxylate (**1**),[1] bistriflamide (*R*)-**4**[2] and various phosphoric acids (*S*)-**5**[3] were synthesized according to the literature procedures and used after purification by column chromatography. Molecular sieve 4A was purchased from Sigma-Aldrich Co. LLC. Other simple chemicals were purchased and used as such.

Synthesis of Ethyl 5-Methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (2)

To a stirred solution of 2-amino-3-methylphenol (370 mg, 3.0 mmol) in toluene (15 mL) were added MS 4A (2.5 g) and diethyl ketomalonate (310 μL, 2.0 mmol) at room temperature. After stirring for 12 h under reflux with a Dean-Stark apparatus, the mixture was cooled to room temperature and then concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 8/1)

to give ketimine **2** (406 mg, 1.7 mmol, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (1H, dd, J = 8.8, 8.0 Hz, Ar-H), 7.25 (1H, d, J = 8.0 Hz, Ar-H), 7.15 (1H, d, J = 8.8 Hz, Ar-H), 4.49 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.64 (3H, s, Ar-CH_3), 1.44 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 149.9, 147.5, 143.7, 140.3, 133.3, 129.1, 127.1, 114.2, 62.8, 16.8, 14.0; IR (neat) 2984, 1759, 1739, 1481, 1309, 1269, 1247, 1180, 1031 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{12}H_{11}NNaO_4$: 256.0580 ([M + Na]$^+$), Found: 256.0575 ([M + Na]$^+$).

General Procedure for the Asymmetric Addition of Indoles 6 to Ketimines

To a stirred solution of a ketimine (0.05 mmol) and catalyst (*S*)-**5d** (0.005 mmol) in toluene (1.0 mL) was added indole **6a** (7.1 mg, 0.06 mmol) at –78 °C. After stirring for the time indicated in Table 1 and 2, the reaction mixture was directly purified by flash column chromatography on silica gel to afford the corresponding addition products **7a** or **8**.

Ethyl (*R*)-3-(1H-Indol-3-yl)-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (7a) (Table 1, entry 6)

$[\alpha]_D^{33}$ 151.6 (*c* 1.0, $CHCl_3$; 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s, NH), 7.76 (1H, d, J = 8.0 Hz, Ar-H), 7.35 (1H, d, J = 8.4 Hz, Ar-H), 7.22 (1H, app t, J = 8.0 Hz, Ar-H), 7.16-7.10 (3H, m, Ar-H), 7.05 (1H, app td, J = 8.0, 1.2 Hz, Ar-H), 6.93 (1H, app td, J = 8.0, 1.2 Hz, Ar-H), 6.89 (1H, dd, J = 8.0, 1.2 Hz, Ar-H), 4.91 (1H, s, NH), 4.24 (2H, qd, J = 7.2, 1.6 Hz, $OC\underline{H}_2CH_3$), 1.15 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 163.1, 141.3, 136.6, 131.9, 125.1, 125.0, 124.0, 122.9, 121.4, 120.5, 120.4 (two peaks are overlapped), 116.9, 116.1, 111.6, 65.8, 62.9, 14.0; IR (neat) 3397, 2981, 1774, 1734, 1500, 1459, 1292, 1237, 1196 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{19}H_{16}N_2NaO_4$: 359.1002 ([M + Na]$^+$), Found: 359.1010 ([M + Na]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 212 nm, retention time: 20.6 min (major) and 24.1 min (minor).

Ethyl (*R*)-3-(1H-Indol-3-yl)-5-methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8a) (Table 1, entry 8, Table 2, entry 1)

$[\alpha]_D^{30}$ 71.6 (*c* 1.0, $CHCl_3$; 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (1H, s, NH), 7.80 (1H, d, J = 7.6 Hz, Ar-H), 7.31 (1H, d, J = 8.0 Hz, Ar-H), 7.21 (1H, app t, J = 8.0 Hz, Ar-H), 7.14 (1H, app t, J = 8.0 Hz, Ar-H), 7.02-6.99 (2H, m, Ar-H), 6.94 (1H, d, J = 7.6 Hz, Ar-H), 6.86 (1H, dd, J = 7.6 Hz, Ar-H), 4.83 (1H, s, NH), 4.22 (2H, q, J = 6.8 Hz, $OC\underline{H}_2CH_3$), 2.25 (3H, s, Ar-CH_3), 1.14 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.8, 141.1, 136.6, 130.6, 126.3, 124.9, 124.5, 124.3, 122.7, 120.8, 120.3 (two peaks are overlapped), 114.7, 111.8, 109.9, 66.1, 62.9, 16.4, 13.9; IR (neat) 3393, 2981, 1774, 1743, 1481, 1459, 1287, 1249, 1192 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{18}N_2NaO_4$: 373.1159 ([M + Na]$^+$), Found: 373.1152 ([M + Na]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 213 nm,

retention time: 20.9 min (major) and 29.6 min (minor).

Ethyl (*R*)-5-Methyl-3-(5-methyl-1H-indol-3-yl)-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8b) (Table 2, entry 3)

$[\alpha]_D^{31}$ 54.2 (*c* 1.0, $CHCl_3$; 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (1H, s, NH), 7.55 (1H, s, Ar-H), 7.21 (1H, d, *J* = 8.8 Hz, Ar-H), 7.10 (1H, d, *J* = 3.2 Hz, Ar-H), 7.04 (1H, d, *J* = 8.4 Hz, Ar-H), 6.99 (1H, d, *J* = 8.4 Hz, Ar-H), 6.94 (1H, d, *J* = 7.6 Hz, Ar-H), 6.85 (1H, dd, *J* = 8.4, 7.6 Hz, Ar-H), 4.81 (1H, s, NH), 4.23 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.43 (3H, s, Ar-CH_3), 2.26 (3H, s, Ar-CH_3), 1.15 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 163.5, 141.2, 134.9, 130.6, 129.7, 126.3, 125.2, 124.54, 124.51, 124.1, 120.7, 120.0, 114.7, 111.3, 109.9, 66.0, 62.8, 21.6, 16.5, 13.9; IR (neat) 3395, 1773, 1742, 1481, 1287, 1191, 731 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{21}N_2O_4$: 365.1496 ($[M + H]^+$), Found: 365.1493 ($[M + H]^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 213 nm, retention time: 18.1 min (major) and 26.7 min (minor).

Ethyl (*R*)-3-(5-Methoxy-1H-indol-3-yl)-5-methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8c) (Table 2, entry 4)

$[\alpha]_D^{32}$ 100.3 (*c* 0.9, $CHCl_3$; 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (1H, s, NH), 7.20 (1H, d, *J* = 2.4 Hz, Ar-H), 7.18 (1H, d, *J* = 8.8 Hz, Ar-H), 7.09 (1H, d, *J* = 2.0 Hz, Ar-H), 6.99 (1H, d, *J* = 8.0 Hz, Ar-H), 6.94 (1H, d, *J* = 6.8 Hz, Ar-H), 6.88-6.84 (2H, m, Ar-H), 4.83 (1H, s, NH), 4.22 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 3.81 (3H, s, Ar-OCH_3), 2.27 (3H, s, Ar-CH_3), 1.14 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.4, 154.4, 141.2, 131.7, 130.6, 126.3, 125.5, 124.7, 124.6, 120.9, 114.7, 113.3, 112.4, 109.8, 102.0, 66.0, 62.9, 55.9, 16.5, 13.9; IR (neat) 3392, 2935, 1772, 1742, 1585, 1482, 1286, 1213, 1190 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{20}N_2NaO_5$: 403.1264 ($[M + Na]^+$), Found: 403.1263 ($[M + Na]^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 211 nm, retention time: 24.3 min (major) and 39.0 min (minor).

Ethyl (*R*)-3-(5-Bromo-1H-indol-3-yl)-5-methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8d) (Table 2, entry 5)

$[\alpha]_D^{28}$ 94.4 (*c* 1.0, $CHCl_3$; 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (1H, s, NH), 7.91 (1H, d, *J* = 2.0 Hz, Ar-H), 7.25 (1H, dd, *J* = 8.8, 2.0 Hz, Ar-H), 7.09 (1H, d, *J* = 8.8 Hz, Ar-H), 7.06 (1H, d, *J* = 2.8 Hz, Ar-H), 7.00 (1H, d, *J* = 8.0 Hz, Ar-H), 6.95 (1H, d, *J* = 7.6 Hz, Ar-H), 6.87 (1H, dd, *J* = 8.0, 7.6 Hz, Ar-H), 4.78 (1H, s, NH), 4.23 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.27 (3H, s, Ar-CH_3), 1.15 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 163.6, 141.2, 135.3, 130.3, 126.6, 126.5, 125.8, 125.2, 124.7, 122.9, 121.1, 114.8, 113.8, 113.1, 109.9, 65.9, 63.1, 16.5, 13.9; IR (neat) 3381, 2925, 1769, 1743, 1480, 1286, 1193, 1102 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{18}BrN_2O_4$: 429.0444 ($[M + H]^+$), Found: 429.0434 ($[M + H]^+$);

Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 280 nm, retention time: 12.9 min (major) and 16.0 min (minor).

Ethyl (*R*)-5-Methyl-3-(6-methyl-1H-indol-3-yl)-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8e) (Table 2, entry 6)

$[\alpha]_D^{31}$ 57.7 (*c* 0.6, $CHCl_3$; 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (1H, s, NH), 7.66 (1H, d, *J* = 8.4 Hz, Ar-H), 7.08 (1H, s, Ar-H), 7.02-6.97 (3H, m, Ar-H), 6.93 (1H, d, *J* = 7.6 Hz, Ar-H), 6.84 (1H, dd, *J* = 8.0, 7.6 Hz, Ar-H), 4.82 (1H, s, NH), 4.21 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.43 (3H, s, Ar-CH_3), 2.25 (3H, s, Ar-CH_3), 1.13 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.5, 141.2, 137.1, 132.7, 130.6, 126.3, 124.5, 123.5, 122.8, 122.2, 120.7, 119.9, 114.7, 111.6, 110.0, 66.0, 62.8, 21.6, 16.4, 13.9; IR (neat) 3395, 1772, 1742, 1480, 1287, 1191, 730 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{20}N_2NaO_4$: 387.1315 ($[M + Na]^+$), Found: 387.1304 ($[M + Na]^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 216 nm, retention time: 29.7 min (major) and 34.1 min (minor).

Ethyl (*R*)-3-(6-Methoxy-1H-indol-3-yl)-5-methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8f) (Table 2, entry 7)

$[\alpha]_D^{30}$ 66.0 (*c* 1.0, $CHCl_3$; 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (1H, s, NH), 7.63 (1H, d, *J* = 8.8 Hz, Ar-H), 6.99 (1H, d, *J* = 8.0 Hz, Ar-H), 6.95-6.92 (2H, m, Ar-H), 6.85 (1H, dd, *J* = 8.0, 8.0 Hz, Ar-H), 6.78 (1H, dd, *J* = 8.8, 2.0 Hz, Ar-H), 6.65-6.63 (1H, m, Ar-H), 4.81 (1H, s, NH), 4.22 (2H, qd, *J* = 7.2, 1.2 Hz, $OC\underline{H}_2CH_3$), 3.77 (3H, s, Ar-OCH_3), 2.25 (3H, s, Ar-CH_3), 1.14 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.8, 156.8, 141.1, 137.6, 130.6, 126.3, 124.5, 123.1, 120.9, 120.83, 120.78, 119.1, 114.7, 110.6, 94.6, 66.1, 62.8, 55.4, 16.4, 13.9; IR (neat) 3395, 2930, 1772, 1743, 1631, 1481, 1456, 1287, 1245, 1197 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{20}N_2NaO_5$: 403.1264 ($[M + Na]^+$), Found: 403.1250 ($[M + Na]^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 200 nm, retention time: 33.3 min (major) and 43.1 min (minor).

Ethyl (*R*)-3-(6-Bromo-1H-indol-3-yl)-5-methyl-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8g) (Table 2, entry 8)

$[\alpha]_D^{29}$ 95.3 (*c* 0.8, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (1H, s, NH), 7.64 (1H, d, *J* = 8.8 Hz, Ar-H), 7.39-7.38 (1H, br, Ar-H), 7.24 (1H, dd, *J* = 8.4, 1.6 Hz, Ar-H), 7.09-7.06 (1H, br, Ar-H), 6.99 (1H, d, *J* = 8.0 Hz, Ar-H), 6.94 (1H, d, *J* = 7.6 Hz, Ar-H), 6.86 (1H, dd, *J* = 8.0, 7.6 Hz, Ar-H), 4.79 (1H, s, NH), 4.23 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.26 (3H, s, Ar-CH_3), 1.13 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 163.5, 141.2, 137.4, 130.3, 126.4, 124.7, 124.6, 123.9, 123.8, 121.6, 121.0, 116.6, 114.7, 114.5, 110.6, 65.8, 63.1, 16.5, 13.9; IR (neat) 3382, 2925, 2854, 1770, 1743, 1481, 1287, 1246, 1194 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{17}BrN_2NaO_4$: 451.0264 ($[M + Na]^+$), Found: 451.0260 ([M +

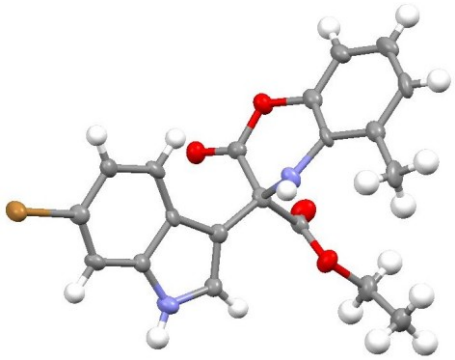
Na]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 219 nm, retention time: 14.4 min (major) and 16.3 min (minor).

Ethyl (*R*)-5-Methyl-3-(7-methyl-1H-indol-3-yl)-2-oxo-3,4-dihydro-2H-benzo[*b*][1,4]oxazine-3-carboxylate (8h) (Table 2, entry 9)

$[\alpha]_D^{34}$ 57.4 (*c* 1.0, $CHCl_3$; 94% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (1H, s, NH), 7.63 (1H, d, *J* = 7.6 Hz, Ar-H), 7.15 (1H, d, *J* = 2.8 Hz, Ar-H), 7.06 (1H, dd, *J* = 7.6, 7.6 Hz, Ar-H), 6.98-6.99 (2H, m, Ar-H), 6.93 (1H, d, *J* = 7.2 Hz, Ar-H), 6.85 (1H, dd, *J* = 8.4, 7.2 Hz, Ar-H), 4.84 (1H, s, NH), 4.23 (2H, q, *J* = 7.2 Hz, $OC\underline{H}_2CH_3$), 2.30 (3H, s, Ar-CH_3), 2.25 (3H, s, Ar-CH_3), 1.14 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 163.6, 141.2, 136.2, 130.6, 126.3, 124.52, 124.50, 124.1, 123.3, 121.0, 120.8, 120.6, 118.0, 114.7, 110.6, 66.1, 62.8, 16.4, 16.3, 13.9; IR (neat) 3388, 2980, 1772, 1743, 1481, 1444, 1286, 1245, 1191 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{21}H_{21}N_2O_4$: 365.1496 ([M + H]$^+$), Found: 365.1483 ([M + H]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 22.6 min (major) and 25.7 min (minor).

Crystal Structure Analysis of 8g

Single crystals of **8g** for X-ray diffraction experiments were grown from $CHCl_3$ and hexane at room temperature. The data were collected at –150 °C on a Rigaku R-AXIS RAPID IP diffractometer with graphite-monochromated Cu Kα radiation (λ = 1.5419 Å). The crystal structure was solved by direct methods using SIR97[4] and refined in SHELXL-97[5] by full matrix least-squares using anisotropic thermal displacement parameters for all non-hydrogen atoms. Crystallographic data for **8g**: $C_{20}H_{17}BrN_2O_4$, colorless prisms, 0.2×0.1×0.03 mm^3, monoclinic, *P*1 2_1 1, *a* = 9.24936(19), *b* = 10.4306(2), *c* = 9.62893(18) Å, *V* = 916.59(4) Å^3, ρ_{calcd} = 1.555 gcm^{-3}, *Z* = 2, $2\theta_{max}$ = 68.34°, μ = 3.314 mm^{-1}. A total of 8128 reflections were measured. *R* = 0.0535, and *Rw* = 0.1429 for 3005 observed reflections with $I > 2.0\sigma(I)$. Flack parameter = –0.01(3). CCDC-933242 (**8g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.



ORTEP diagram of **8g**

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Asymmetric Addition of Pyrrole to Ketimine 2

To a stirred solution of ketimine **2** (11 mg, 0.05 mmol) and (*S*)-**5d** (3 mg, 0.005 mmol) in toluene (1.0 mL) was added pyrrole (7 μL, 0.1 mmol) at –78 °C. After stirring for 1 h, the reaction mixture was directly purified by flash column chromatography on silica gel to afford the corresponding addition product **9** (14 mg, 99% yield); $[\alpha]_D^{31}$ –60.6 (*c* 1.0, $CHCl_3$; 75% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.05 (1H, s, NH), 6.94 (1H, d, *J* = 7.6 Hz, Ar-H), 6.93 (1H, d, *J* = 8.0 Hz, Ar-H), 6.91-6.89 (1H, m, Ar-H), 6.84 (1H, dd, *J* = 8.0, 7.6 Hz, Ar-H), 6.34-6.32 (1H, m, Ar-H), 6.24 (1H, dd, *J* = 6.4, 2.4 Hz, Ar-H), 4.81 (1H, s, NH), 4.24-4.12 (2H, m, $OC\underline{H}_2CH_3$), 2.32 (3H, s, Ar-CH_3), 1.14 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9, 162.7, 140.7, 130.0, 126.5, 124.6, 124.1, 121.1, 119.9, 114.7, 108.7, 108.1, 64.9, 63.3, 16.4, 13.8; IR (neat) 3388, 2982, 1777, 1743, 1482, 1447, 1283, 1241, 1191 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{16}H_{16}N_2NaO_4$: 323.1002 ([M + Na]$^+$), Found: 323.0994 ([M + Na]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 210 nm, retention time: 18.0 min (minor) and 22.6 min (major).

Protection of 8a by Tosylation

To a solution of **8a** (560 mg, 1.6 mmol) in 1,4-dioxane (10 mL) were added triethylamine (1.1 mL, 8.0 mmol), 4-dimethylaminopyridine (40 mg, 0.32 mmol) and *p*-toluenesulfonyl chloride (920 mg, 4.8 mmol) at room temperature. After stirring for 12 h at 95 °C, the mixture was cooled to room temperature. The reaction mixture was quenched with aq. NH_4Cl (10 mL) and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 4/1) to give **10** (789 mg, 1.6 mmol, 99% yield); $[\alpha]_D^{33}$ 48.2 (*c* 0.9, $CHCl_3$; 99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (1H, d, *J* = 8.5 Hz, Ar-H), 7.72 (2H, d, *J* = 8.5 Hz, Ar-H), 7.73-7.70 (1H, m, Ar-H), 7.65 (1H, s, Ar-H), 7.33 (1H, app t, *J* = 8.0 Hz, Ar-H), 7.24 (2H, d, *J* = 8.0 Hz, Ar-H), 7.22-7.25 (1H, m, Ar-H), 6.954 (1H, d, *J* = 8.0 Hz, Ar-H), 6.949 (1H, d, *J* = 8.0 Hz, Ar-H), 6.87 (1H, dd, *J* = 8.0 Hz, Ar-H), 4.79 (1H, s, NH), 4.26 (2H, qd, *J* = 7.0, 1.0 Hz, $OC\underline{H}_2CH_3$), 2.36 (3H, s, Ar-CH_3), 2.28 (3H, s, Ar-CH_3), 1.15 (3H, t, *J* = 7.0 Hz, $OCH_2C\underline{H}_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 161.9, 145.4, 141.4, 135.3, 134.8, 130.1, 129.4, 128.0, 127.0, 126.5, 125.6, 125.2, 125.1, 123.6, 121.5, 121.4, 116.6, 114.7, 113.5, 65.2, 63.4, 21.6, 16.5, 13.9; IR (neat) 3363, 2981, 1780, 1743, 1482, 1447, 1372, 1285, 1189, 1175 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{27}H_{24}N_2NaO_6S$: 527.1247 ([M + Na]$^+$), Found: 527.1248 ([M + Na]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 23.5 min (major) and 33.5 min (minor).

Synthesis of Lactol 11 by Chemoselective Reduction

To a solution of **10** (30 mg, 0.06 mmol) in THF (0.5 mL) were added MS 4A (150 mg) and DIBAL (1.0 M in CH_2Cl_2, 360 μL, 0.36 mmol) at 0 °C. After stirring for 1 h at room temperature, the mixture was cooled to 0 °C. The reaction mixture was then quenched with aq. NH_4Cl (2 mL) and insoluble materials were filtrated. The filtrate was extracted with ethyl acetate twice. The combined organic layers were washed with brine,

dried over Na_2SO_4 and then concentrated. The residue was purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 2/1) to give **11** as diastereomeric mixtures (17 mg, 0.036 mmol, 60% yield); ^{1}H NMR (500 MHz, CD_3CN) major isomer: δ 7.88 (1H, d, J = 8.0 Hz, Ar-H), 7.83 (1H, d, J = 8.0 Hz, Ar-H), 7.39 (2H, d, J = 9.0 Hz, Ar-H), 7.34 (1H, s, Ar-H), 7.28 (1H, app t, J = 7.5 Hz, Ar-H), 7.22 (1H, app t, J = 7.5 Hz, Ar-H), 7.18 (2H, d, J = 8.0 Hz, Ar-H), 6.75 (1H, d, J = 7.5 Hz, Ar-H), 6.65 (1H, app t, J = 8.0 Hz, Ar-H), 6.51 (1H, d, J = 8.0 Hz, Ar-H), 5.90 (1H, d, J = 7.5 Hz, Ar-OC<u>H</u>(OH)), 4.93 (1H, d, J = 7.5 Hz, Ar-OCH(O<u>H</u>)), 4.59 (1H, s, N<u>H</u>), 4.04 (1H, dd, J = 11.5, 6.5 Hz, C<u>H</u>$_2$OH), 3.96 (1H, dd, J = 11.5, 6.5 Hz, C<u>H</u>$_2$OH), 3.13 (1H, app t, J = 6.5 Hz, CH$_2$O<u>H</u>), 2.29 (3H, s, Ar-CH_3), 2.27 (3H, s, Ar-CH_3); minor isomer: δ 7.95 (1H, d, J = 8.0 Hz, Ar-H), 7.92 (1H, d, J = 9.0 Hz, Ar-H), 7.699 (2H, d, J = 8.5 Hz, Ar-H), 7.695 (1H, s, Ar-H), 7.31-7.20 (4H, m, Ar-H), 6.76-6.73 (1H, m, Ar-H), 6.66-6.63 (2H, m, Ar-H), 5.59 (1H, d, J = 6.5 Hz, Ar-OC<u>H</u>(OH)), 4.83 (1H, d, J = 6.5 Hz, Ar-OCH(O<u>H</u>)), 4.50 (1H, s, N<u>H</u>), 3.98-3.95 (1H, m, C<u>H</u>$_2$OH), 3.82 (1H, dd, J = 11.5, 7.0 Hz, C<u>H</u>$_2$OH), 3.04 (1H, app t, J = 6.5 Hz, CH$_2$O<u>H</u>), 2.32 (3H, s, Ar-CH_3), 2.23 (3H, s, Ar-CH_3); ^{13}C NMR (100 MHz, CD_3CN) major isomer: δ 146.6, 141.4, 136.6, 135.0, 131.0, 130.4, 129.8, 127.52, 127.48, 125.6, 125.5, 124.4, 123.9, 123.8, 122.5, 119.9, 115.7, 114.7, 91.2, 65.5, 59.9, 21.5, 17.1; minor isomer: δ 146.8, 142.0, 136.2, 135.5, 131.0, 130.8, 130.4, 127.8, 127.3, 125.7, 125.5, 124.12, 124.06, 123.6, 122.7, 119.8, 115.6, 114.3, 92.6, 64.6, 60.7, 21.5, 17.2; IR (neat) 3359, 1595, 1479, 1446, 1370, 1275, 1175, 1139, 1102 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{25}H_{25}N_2O_5S$: 465.1479 ([M + H]$^+$), Found: 465.1471 ([M + H]$^+$).

Synthesis of Diol 12 by MOM-protection and Reductive Ring Open

To a stirred solution of **11** (45 mg, 0.097 mmol) in THF (0.5 mL) and MeOH (0.5 mL) was added $NaBH_4$ (15 mg, 0.39 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 1 h. The mixture was then quenched with aq. NH_4Cl (3 mL) and extracted with ethyl acetate twice. The combined organic layers were washed with brine, and dried over Na_2SO_4 and then concentrated. The residue was dissolved in THF (1 mL) and added DBU (22 μL, 0.15 mmol) and MOMCl (9 μL, 0.12 mmol) at room temperature. After stirring for 1 h at room temperature, the mixture was cooled to 0 °C. The reaction mixture was then quenched with aq. NH_4Cl (1 mL) and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated. The residue was roughly purified by flash column chromatography on silica gel (eluting with hexane/ethyl acetate = 3/1) to afford the MOM protected lactol (30 mg), which was used for next step without further purification

To a solution of the MOM protected lactol (30 mg) in EtOH (0.6 mL) was added $NaBH_4$ (22 mg, 0.58 mmol) at room temperature. After stirring for 2 h under reflux, the mixture was cooled to 0 °C. The reaction mixture was then quenched with aq. NH_4Cl (3 mL) and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by preparative TLC ($CHCl_3$/MeOH = 10/1) to afford **12** (21 mg, 0.041 mmol, 42% yield); $[\alpha]_D^{30}$ 4.5 (c 1.0, $CHCl_3$, 99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (1H, d, J = 8.5 Hz, Ar-H), 7.74 (2H, d, J = 8.5 Hz, Ar-H), 7.67 (1H, s, Ar-H), 7.59 (1H, d, J = 8.5 Hz), 7.28 (1H, app t, J = 7.5 Hz, Ar-H), 7.24 (2H, d, J = 8.0

Hz, Ar-H), 7.14 (1H, app t, *J* = 7.5 Hz, Ar-H), 6.86 (1H, dd, *J* = 8.0, 7.5 Hz, Ar-H), 6.66 (1H, d, *J* = 8.0 Hz, Ar-H), 6.48 (1H, d, *J* = 7.5 Hz, Ar-H), 4.66 (1H, d, *J* = 6.5 Hz, OC<u>H</u>HOCH$_3$), 4.60 (1H, d, *J* = 6.5 Hz, OCH<u>H</u>OCH$_3$), 4.15 (1H, d, *J* =11.5 Hz, C<u>H</u>HO), 4.05 (1H, d, *J* = 10.5 Hz, C<u>H</u>HO), 3.99 (1H, d, *J* = 11.5 Hz, CH<u>H</u>O), 3.93 (1H, d, *J* = 10.0 Hz, CH<u>H</u>O), 3.34 (3H, s, OCH$_3$), 2.37 (3H, s, Ar-CH$_3$), 1.73 (3H, s, Ar-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 154.0, 145.0, 135.6, 135.4, 135.2, 129.9, 129.2, 128.6, 126.8, 125.7, 124.8, 124.7, 123.2, 122.9, 121.7, 121.6, 113.9, 113.2, 97.2, 71.0, 65.8, 62.2, 56.0, 21.6, 18.2; IR (neat) 3348, 2945, 1595, 1473, 1446, 1368, 1280, 1173 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{27}H_{30}N_2NaO_6S$: 533.1717 ([M + Na]$^+$), Found: 533.1700 ([M + Na]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 3/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 40.1 min (minor) and 59.1 min (major).

Synthesis of Amino Alcohol 13 by Oxidative Carbon-nitrogen Bond Clevage

To a stirred solution of **12** (8.8 mg, 0.017 mmol) in pyridine (100 μL) was added acetic anhydride (100 μL) at room temperature. After stirring for 1 h at room temperature, the mixture was quenched with H_2O (1 mL) and extracted with ethyl acetate twice. The combined organic layers were washed with 0.5 M aq. HCl, aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and then concentrated to afford crude diacetate, which was used for next step without further purification.

To a solution of crude diacetate (10 mg) in CH_3CN (200 μL) and H_2O (70 μL) was added CAN (28 mg, 0.051 mmol) at –15 °C. After stirring for 15 min at –15 °C, the reaction mixture was added 5 M aq. KOH (100 μL) and stirred at 80 °C for 2 h. The mixture was then cooled to 0 °C, quenched with aq. NH_4Cl (1 mL) and extracted with ethyl acetate twice. The combined organic layers were washed with brine, dried over Na_2SO_4 and then concentrated. The residue was purified by preparative TLC (eluting with $CHCl_3$/MeOH = 10/1) to afford **13** (4.3 mg, 0.011 mmol, 63% yield); $[\alpha]_D^{32}$ 7.4 (*c* 0.4, $CHCl_3$, 99% ee); ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.98 (1H, d, *J* = 8.5 Hz, Ar-H), 7.81 (1H, d, *J* = 8.0 Hz, Ar-H), 7.76 (2H, d, *J* = 8.5 Hz, Ar-H), 7.60 (1H, s, Ar-H), 7.30 (1H, app t, *J* = 8.5 Hz, Ar-H), 7.21 (2H, d, *J* = 8.0 Hz, Ar-H), 7.20-7.23 (1H, m, Ar-H), 4.61 (1H, d, *J* = 7.0 Hz, OC<u>H</u>HOCH$_3$), 4.60 (1H, d, *J* = 6.5 Hz, OCH<u>H</u>OCH$_3$), 3.94 (1H, d, *J* = 11.0 Hz, C<u>H</u>HO), 3.93 (1H, d, *J* = 9.5 Hz, C<u>H</u>HO), 3.822 (1H, d, *J* = 9.0 Hz, CH<u>H</u>O), 3.820 (1H, d, *J* = 11.5 Hz, CH<u>H</u>O), 3.24 (3H, s, Ar-CH$_3$), 2.34 (1H, s, Ar-CH$_3$); ^{13}C NMR (100 MHz, CDCl$_3$) δ 145.0, 135.7, 135.2, 129.9, 128.6, 126.9, 124.6, 124.1 (two peaks are overlapped), 123.0, 121.7, 113.8, 96.8, 72.7, 67.4, 57.2, 55.4, 21.5; IR (neat) 3357, 2924, 2852, 1597, 1447, 1369, 1271, 1174, 1042 cm^{-1}; HRMS (ESI-TOF) Calcd. for $C_{20}H_{25}N_2O_5S$: 405.1479 ([M + H]$^+$), Found: 405.1464 ([M + H]$^+$); Daicel Chiralpak IC, hexane/2-propanol = 1/1, flow rate 0.5 mL/min, λ = 254 nm, retention time: 39.6 min (minor) and 47.0 min (major).

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References

1. a) H. Miyabe, Y. Yamaoka, Y. Takemoto, *J. Org. Chem.* **2006**, *71*, 2099; b) T. Kano, S. Song, Y. Kubota, K. Maruoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 1191.
2. T. Kano, Y. Tanaka, K. Osawa, T. Yurino, K. Maruoka, *J. Org. Chem.* **2008,** *73,* 7387.
3. a) M. Hatano, T. Ikeno, T. Matsumura, S. Torii, K. Ishihara, *Adv. Synth. Catal.* **2008**, *350*, 1776; b) M. Terada, S. Yokoyama, K. Sorimachi, D. Uraguchi, *Adv. Synth. Catal.* **2007**, *349*, 1863; c) S. E. Larson, J. C. Baso, G. Li, J. C. Antilla, *Org. Lett.* **2009**, *11*, 5186; d) M. Yamanaka, J. Itoh, K. Fuchibe, T. Akiyama, *J. Am. Chem. Soc.* **2007**, *129*, 6756; e) M. Sickert, F. Abels, M. Lang, J. Sieler, C. Birkemeyer, C. Schneider, *Chem. Eur. J.* **2010**, *16*, 2806.
4. SIR97, Program for the solution of crystal structures: A. Altomare, M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32*, 115.
5. G. M. Sheldrick, *SHELXL-97*, Program for Crystal Structure Refinement; University of Göttingen: Göttingen, Germany, **1997**.

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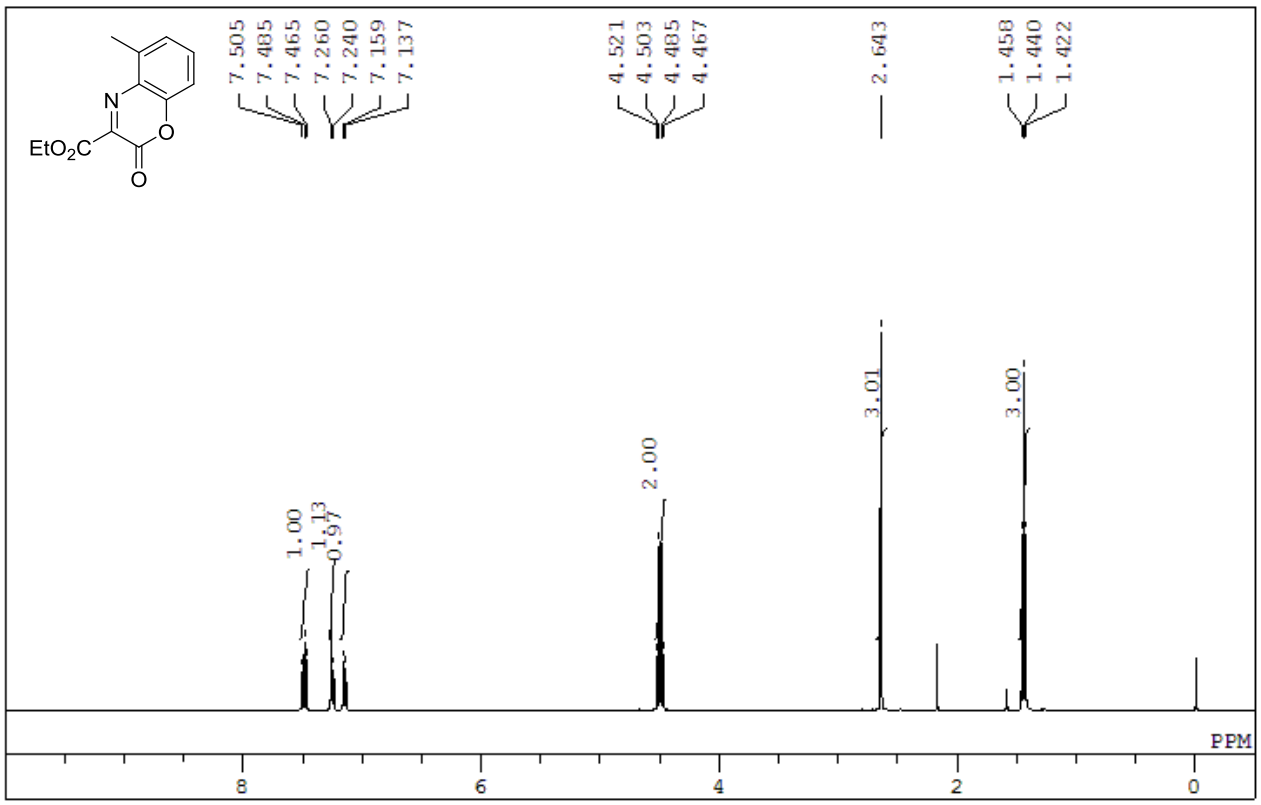

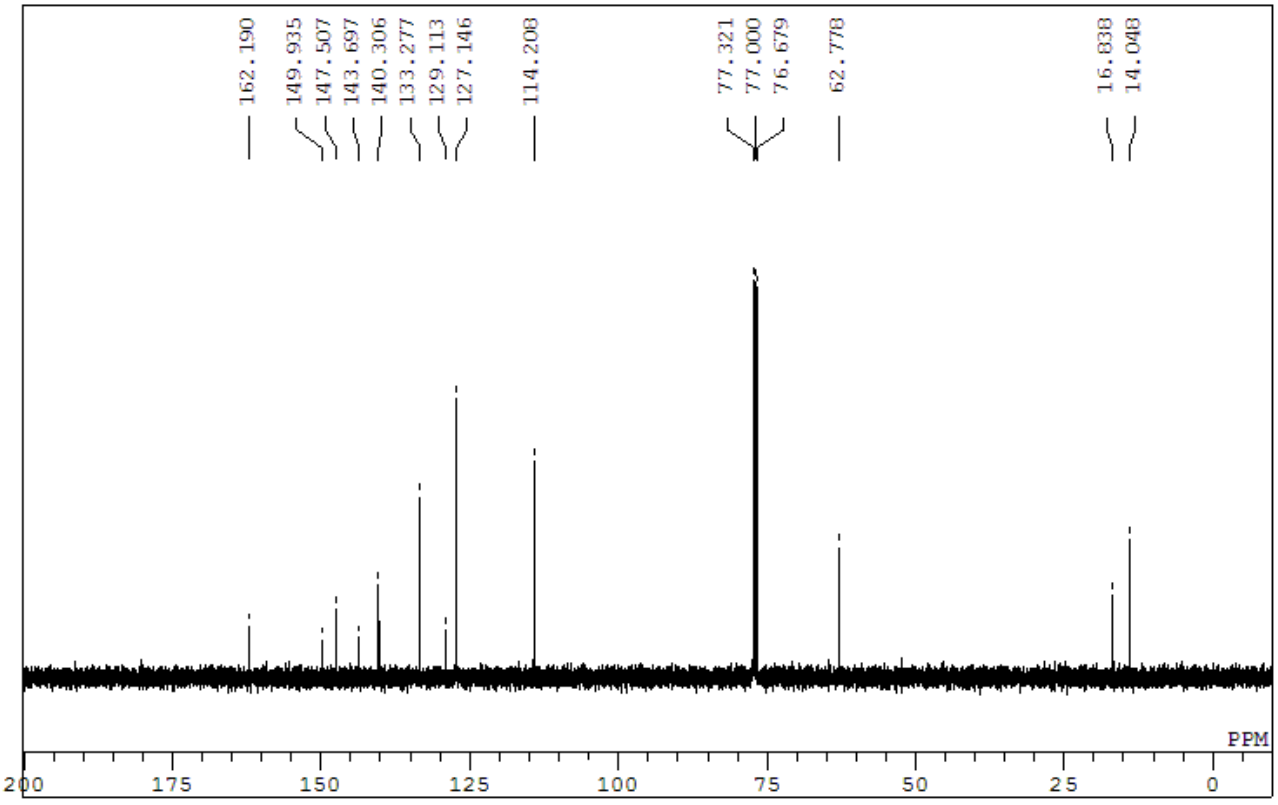

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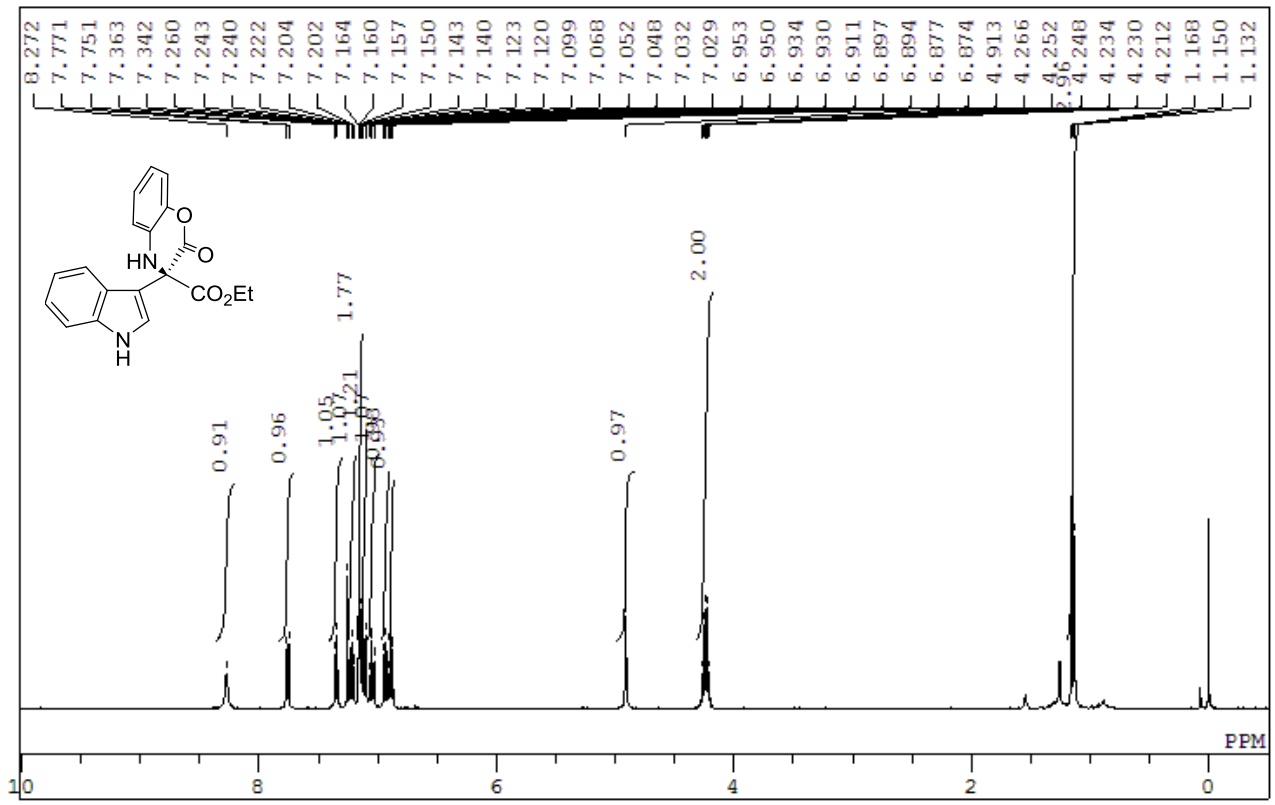

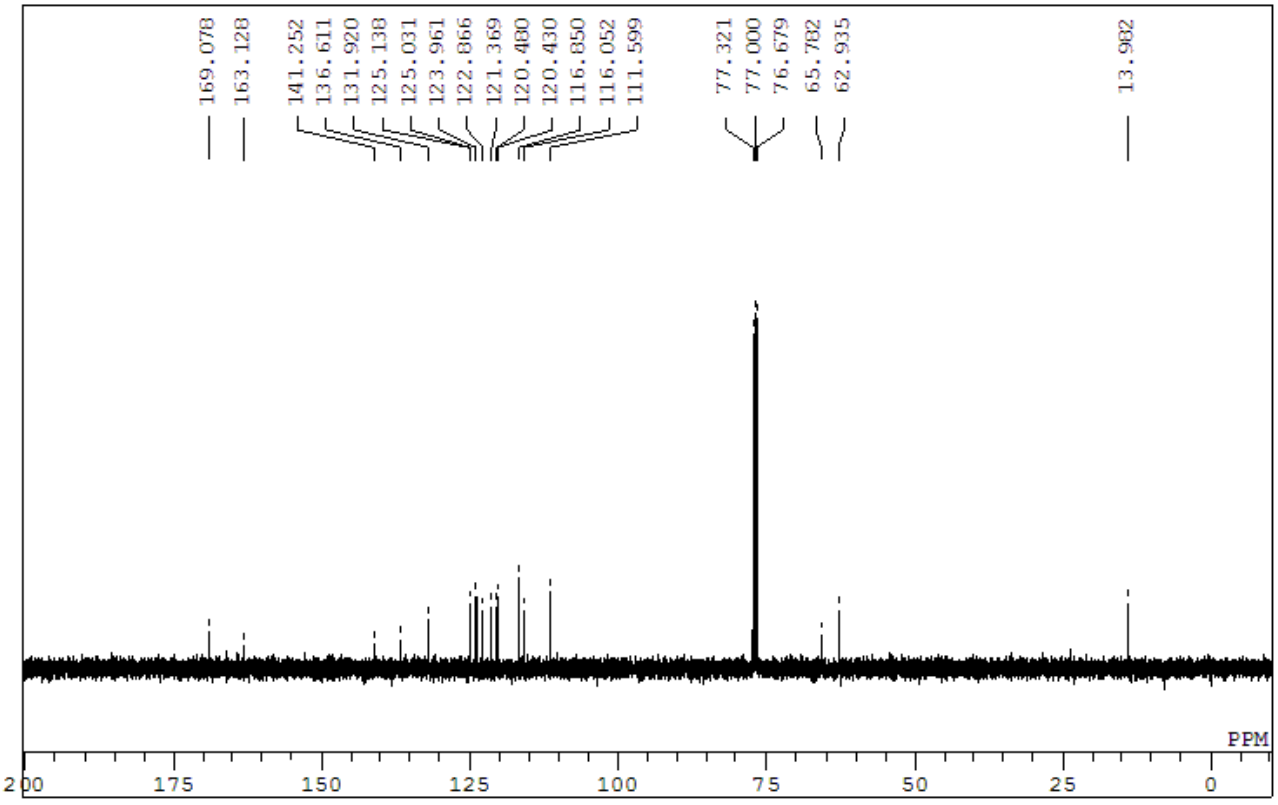

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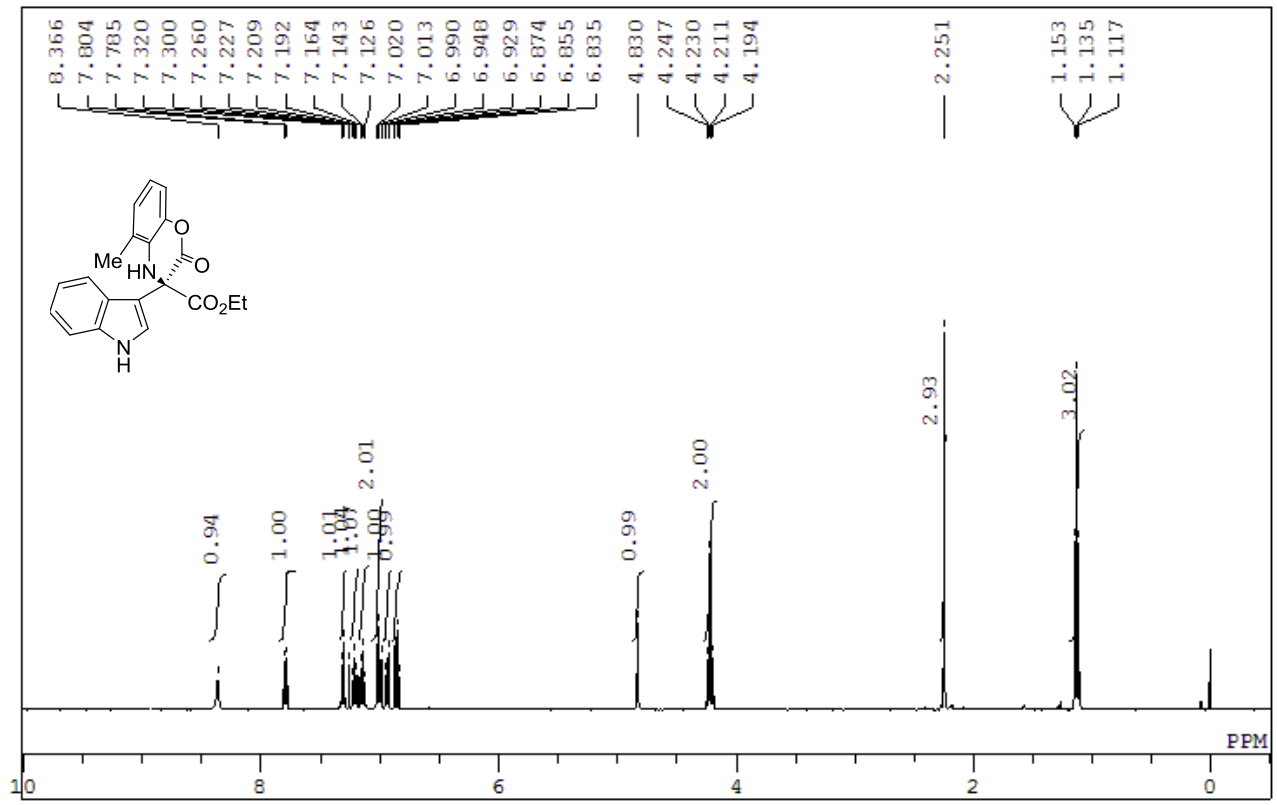

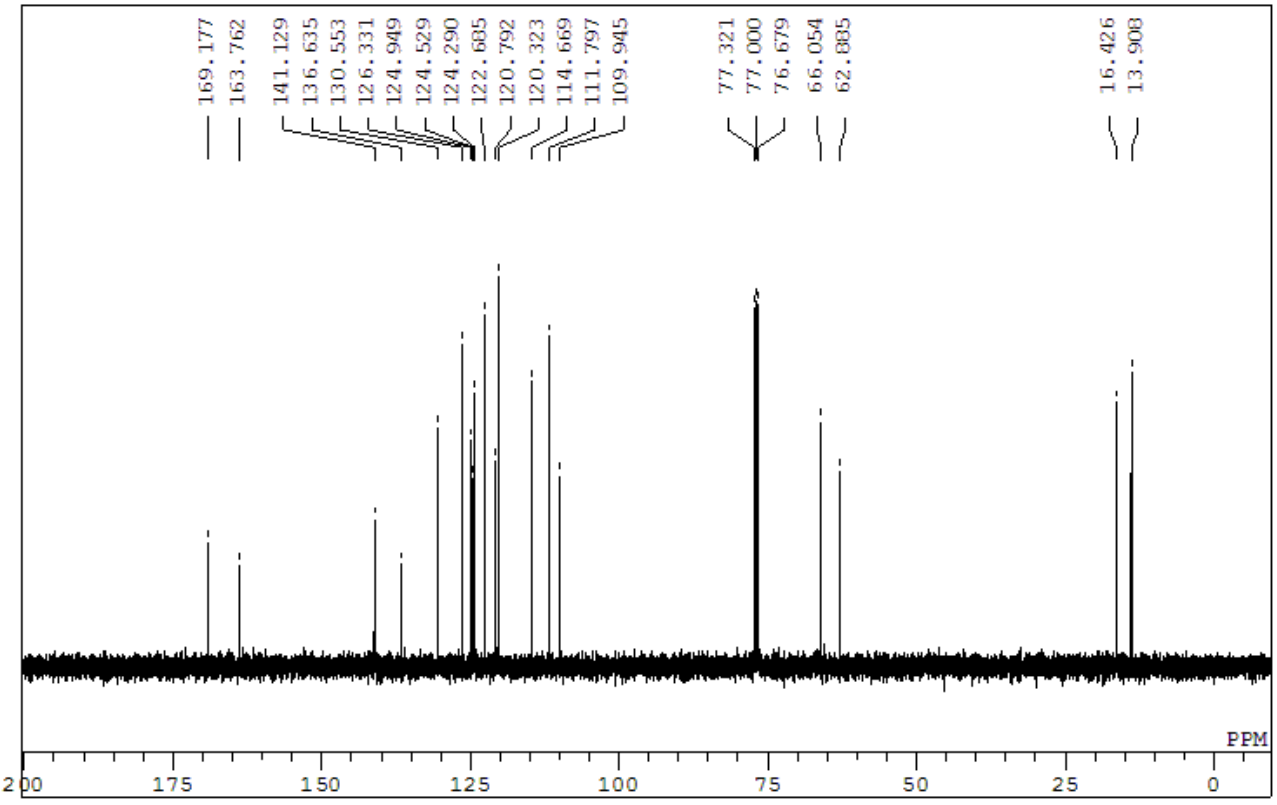

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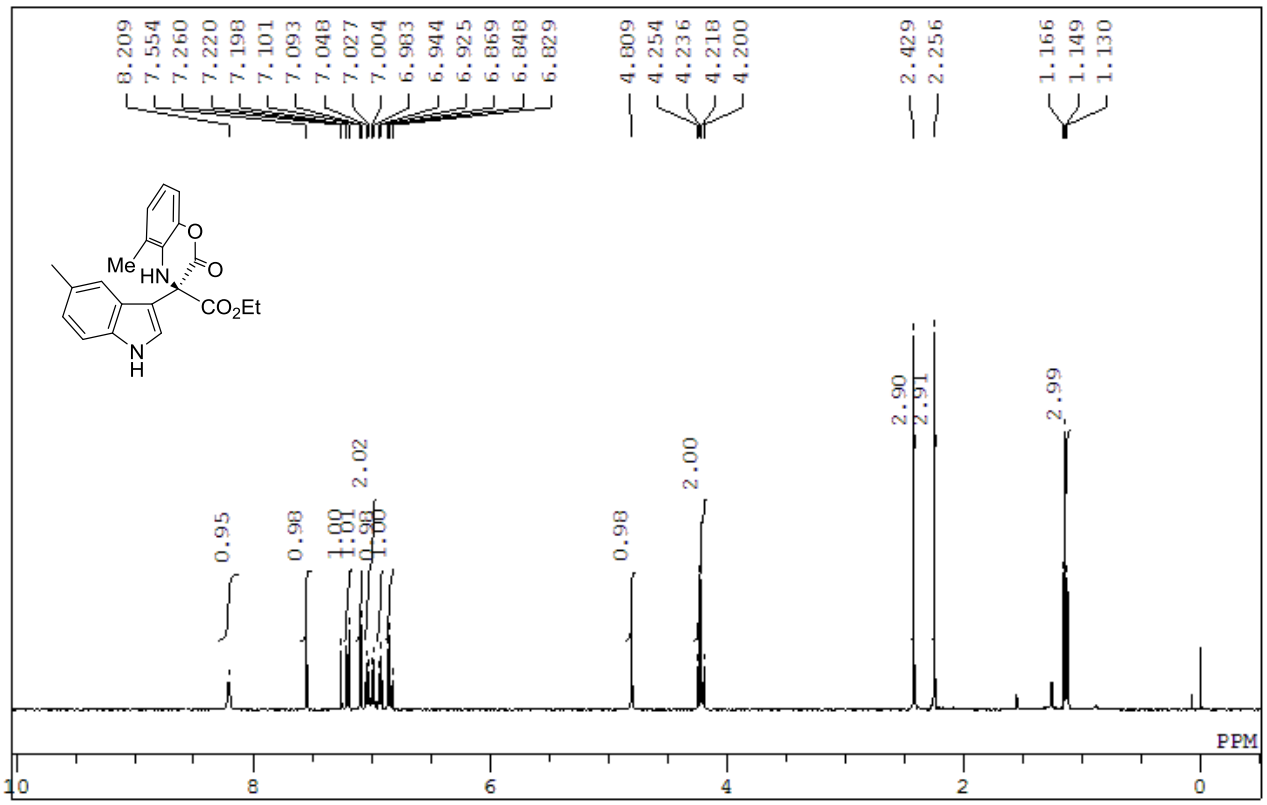

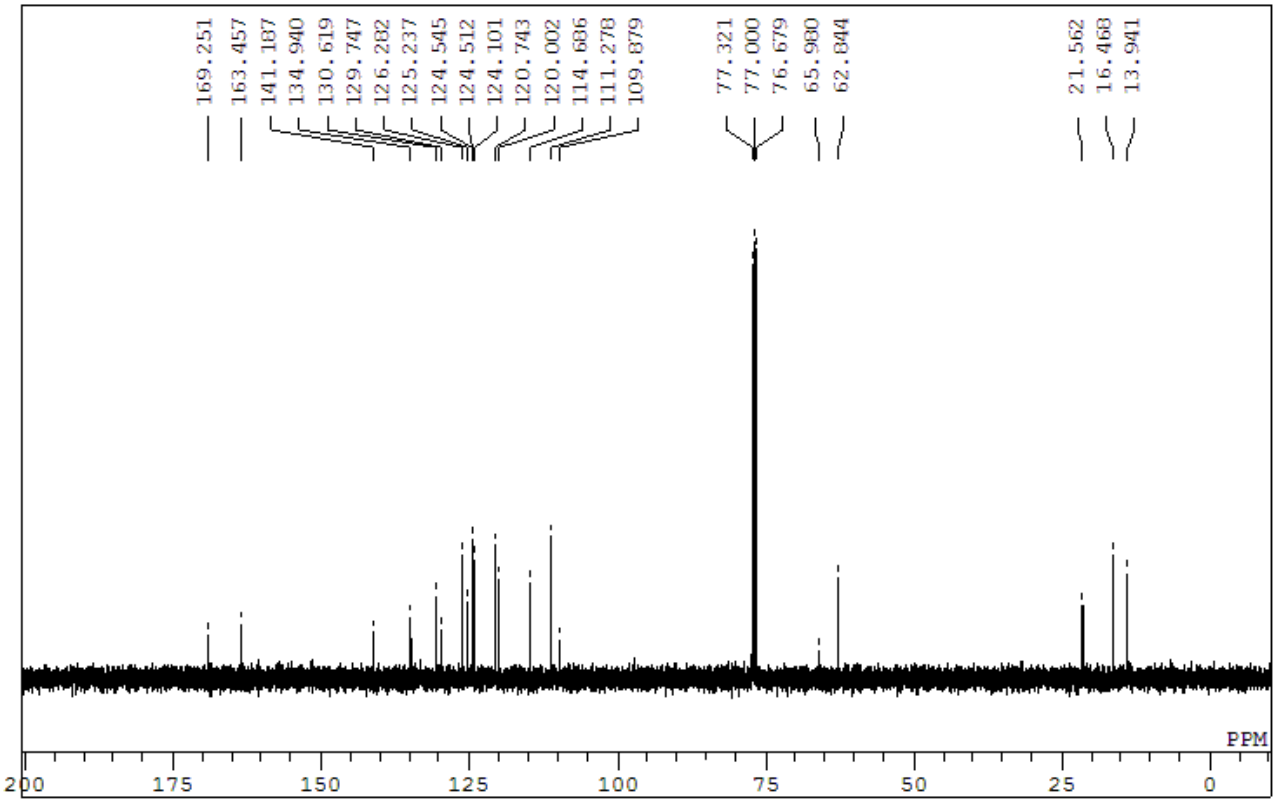

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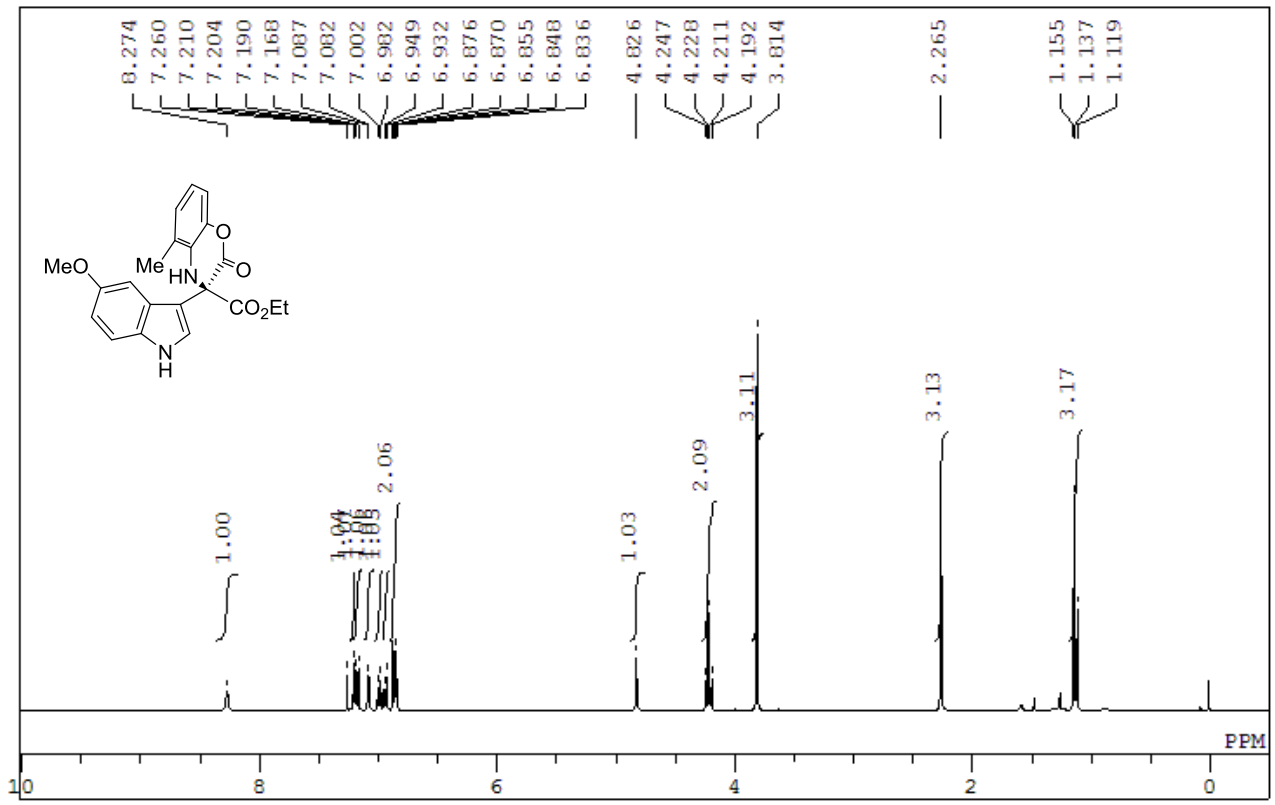

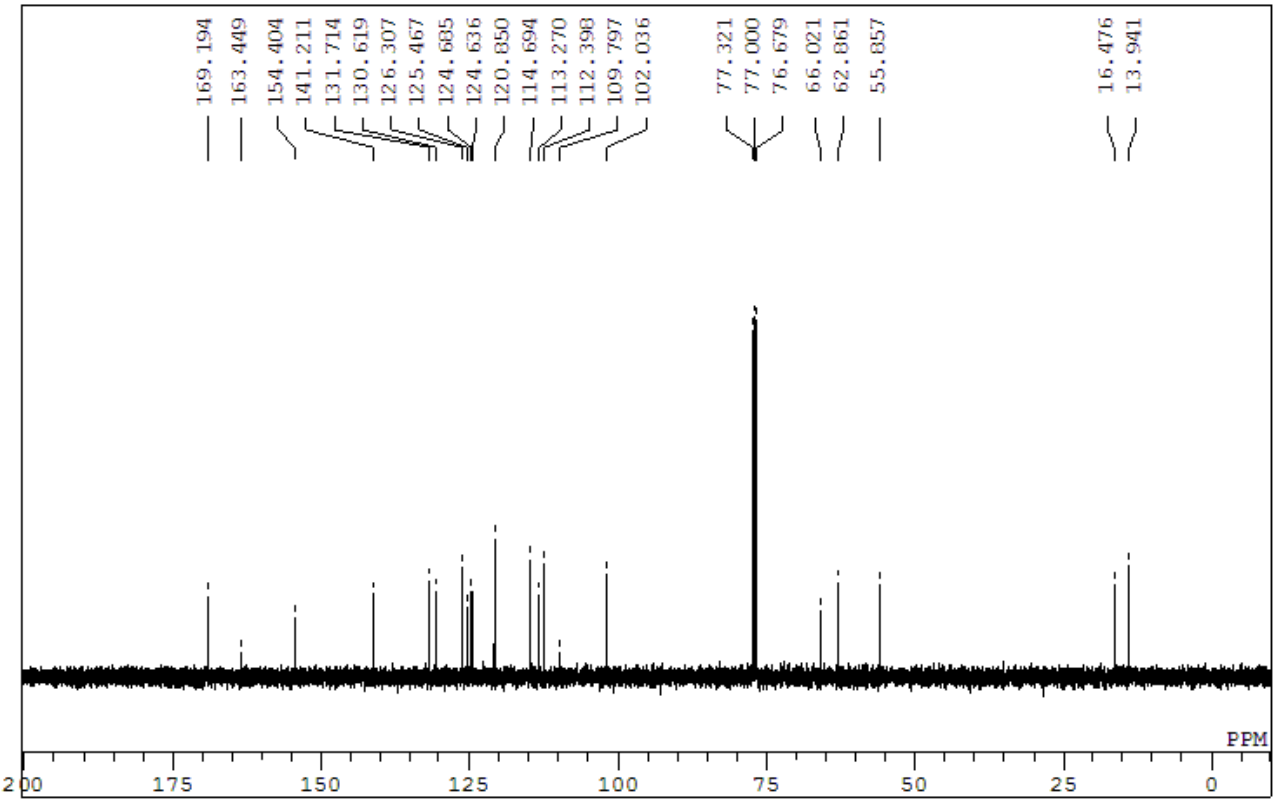

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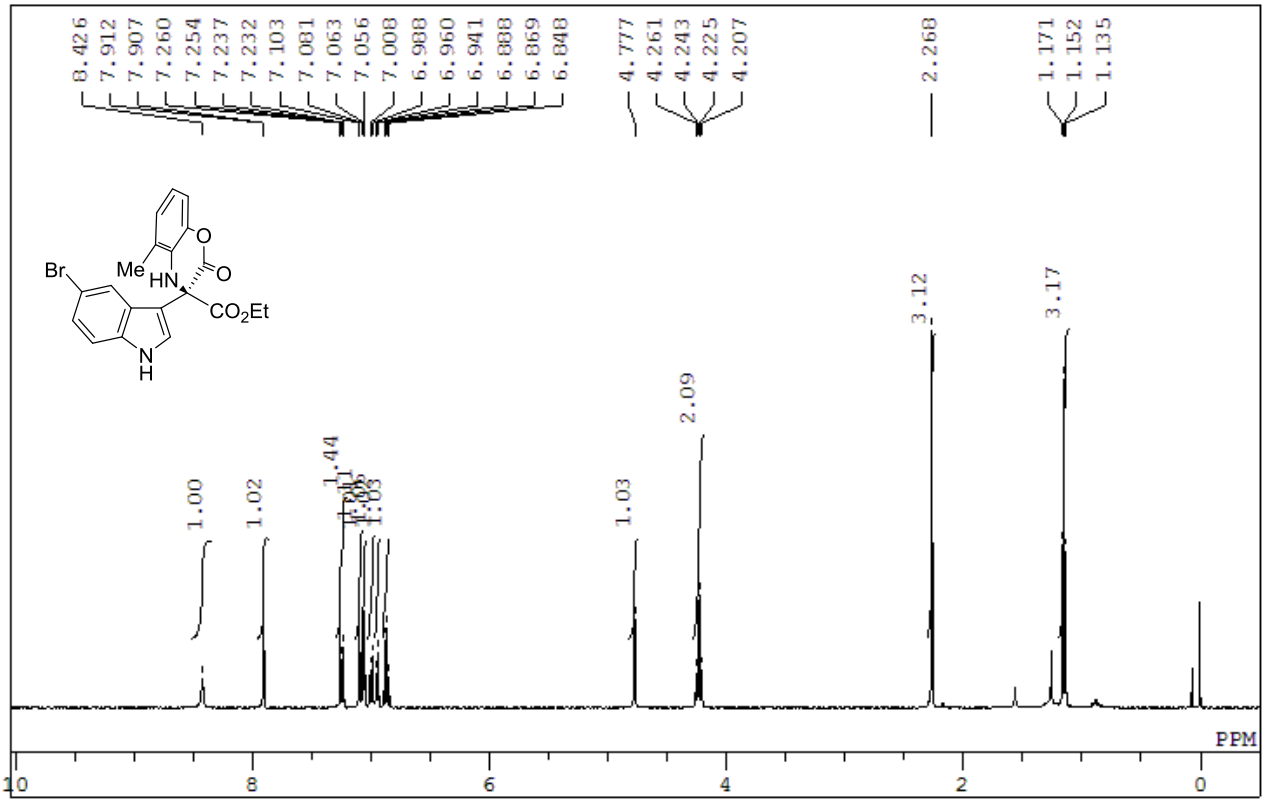

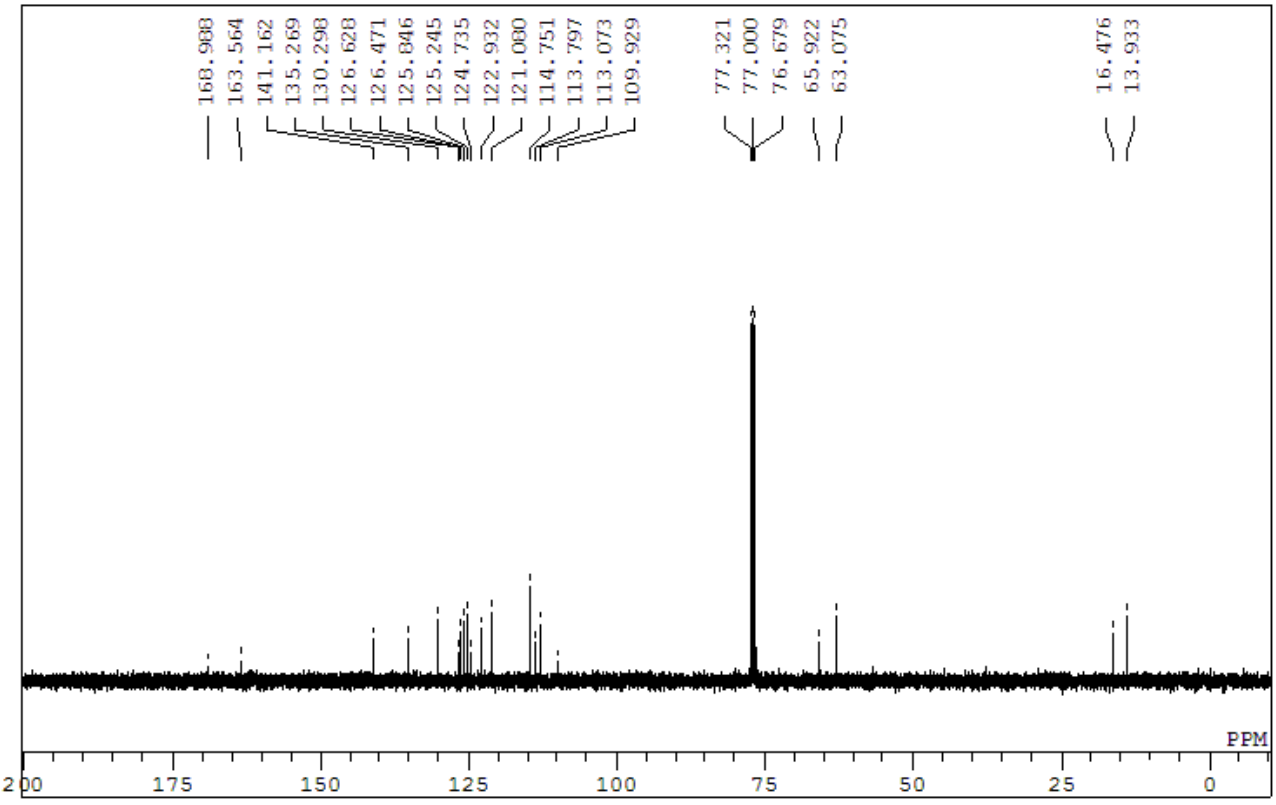

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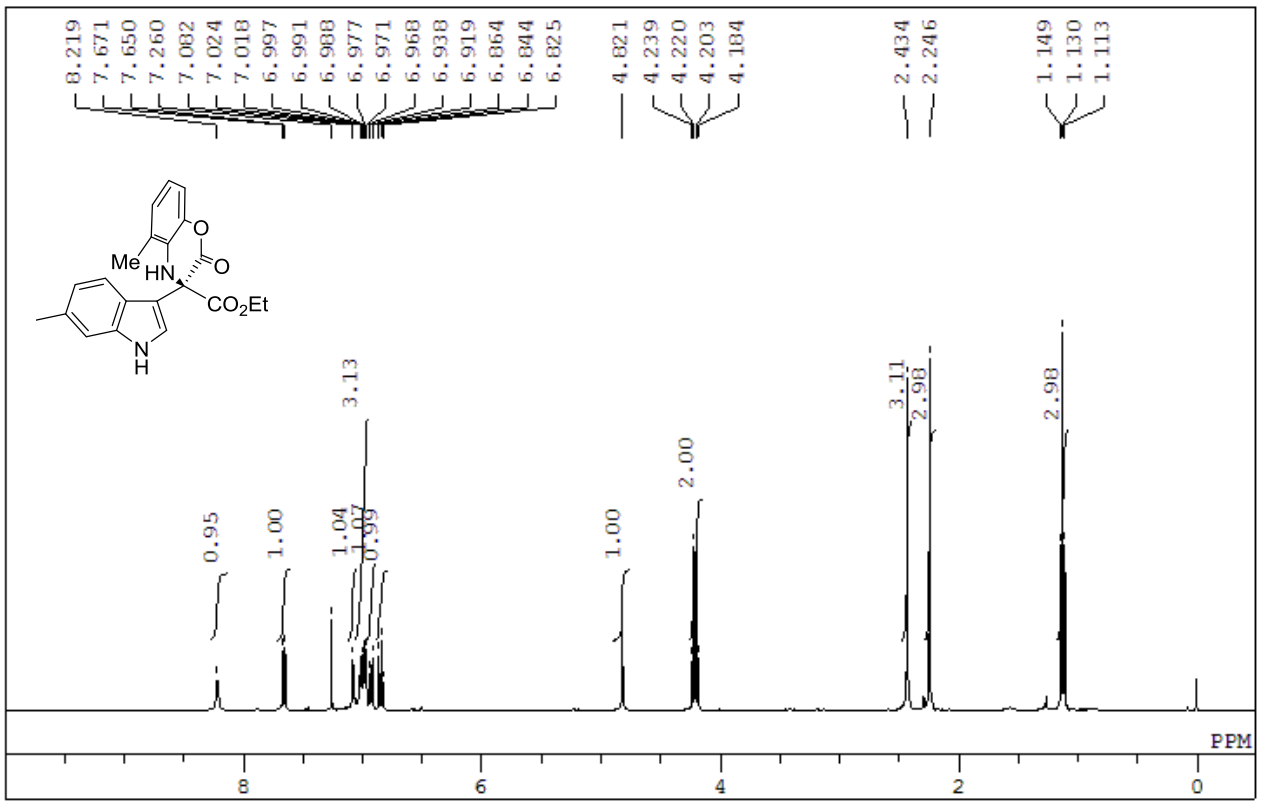

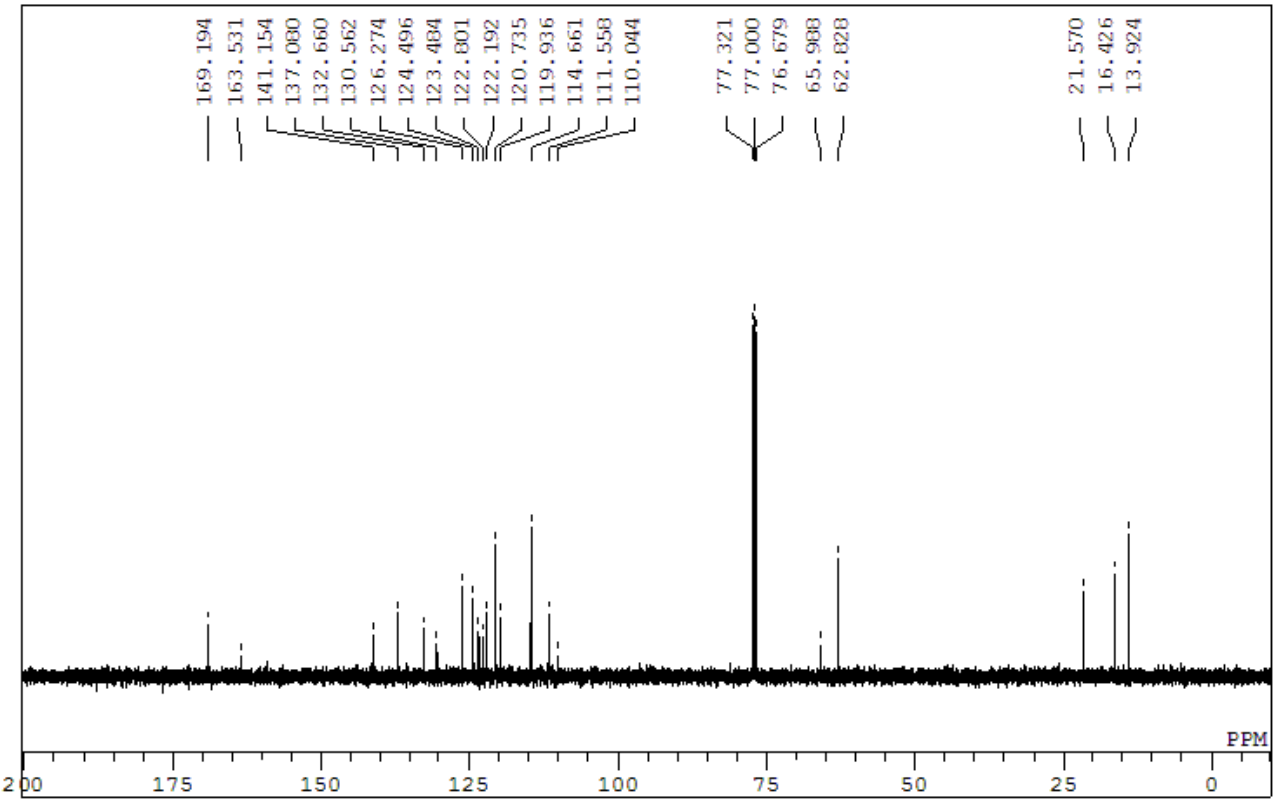

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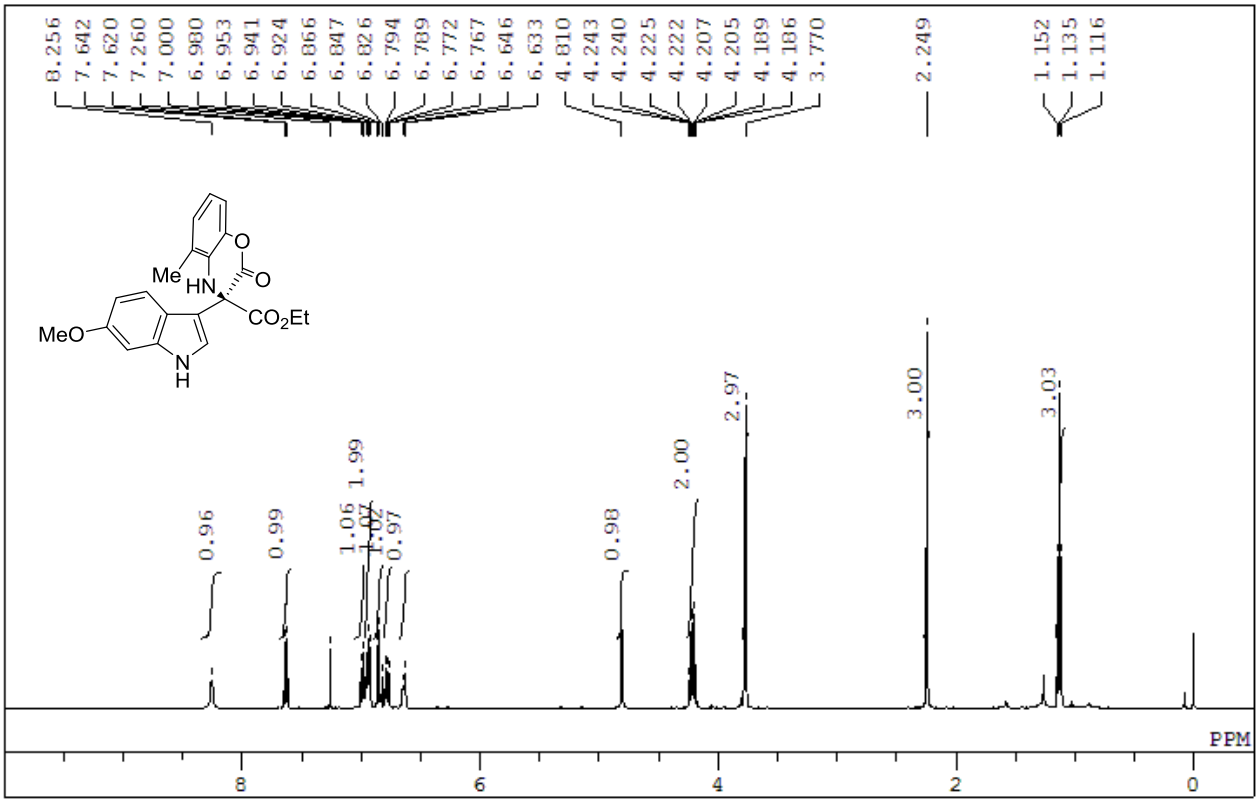

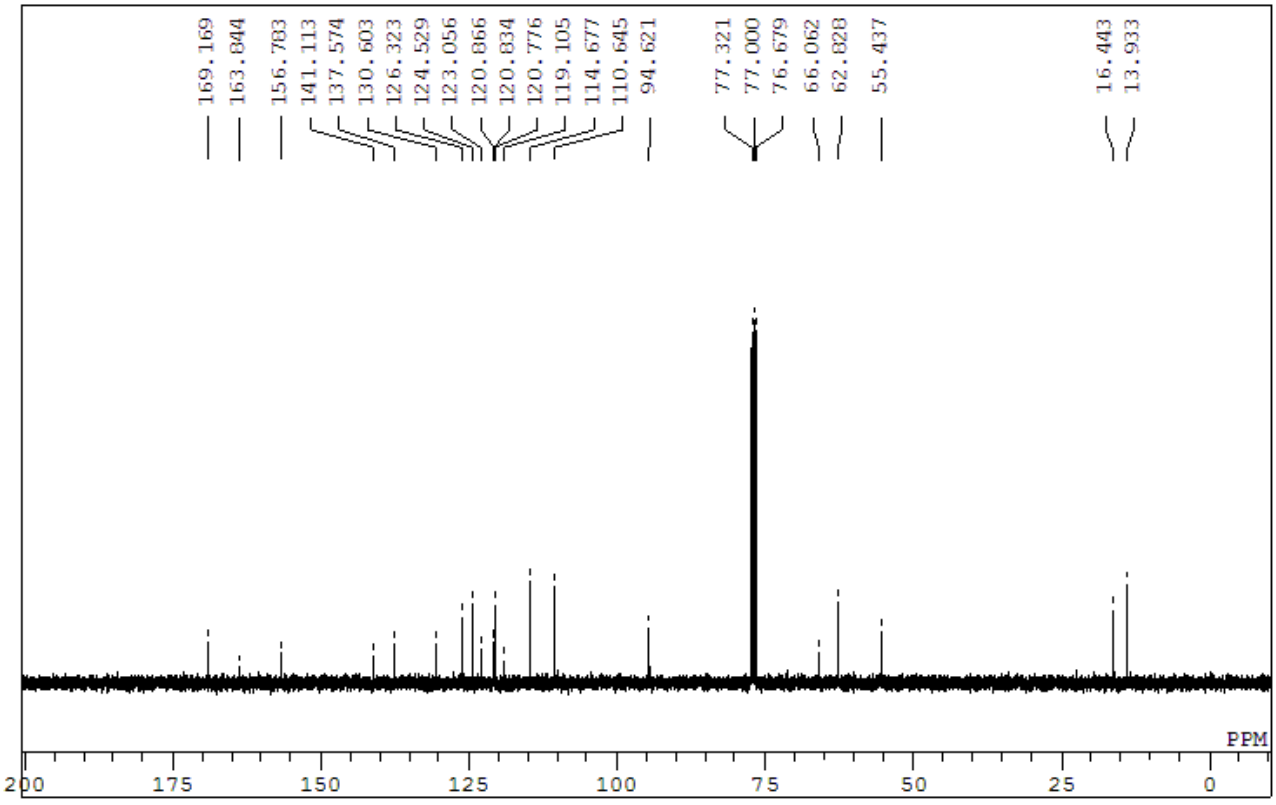

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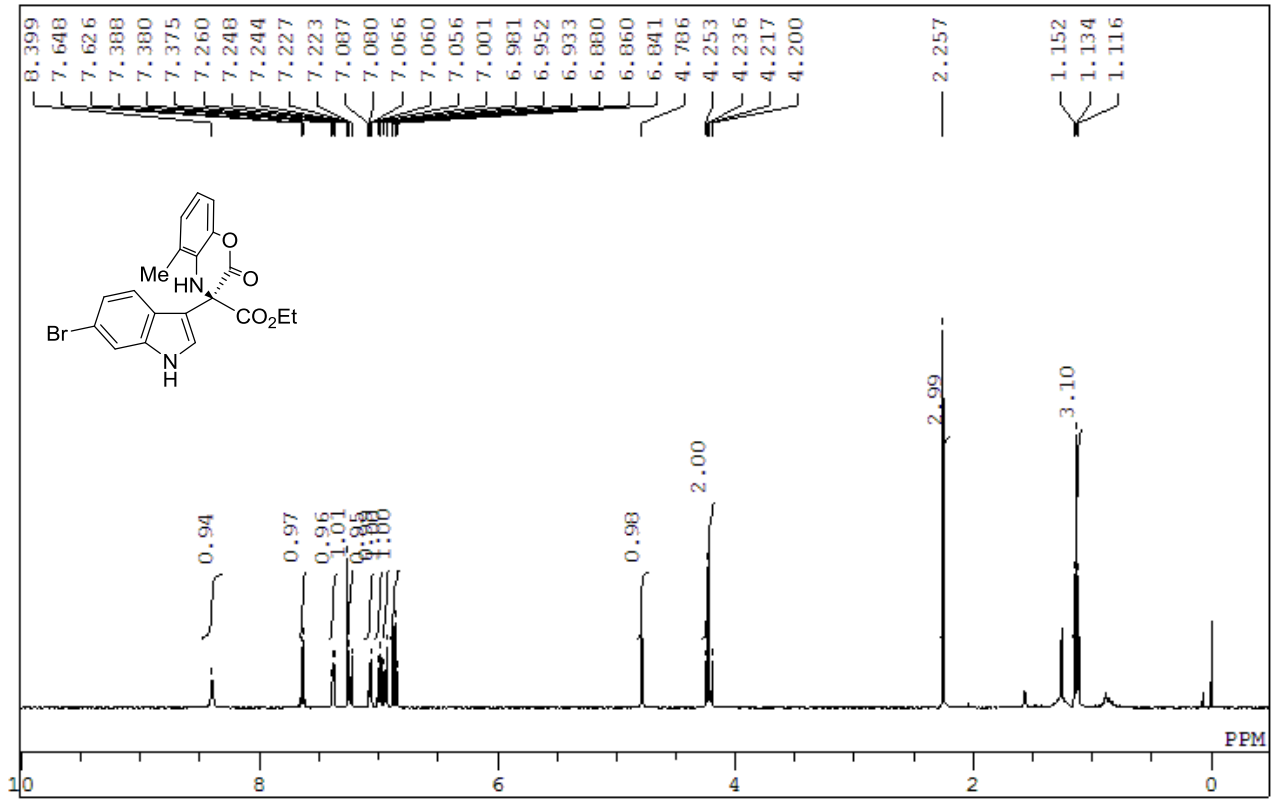

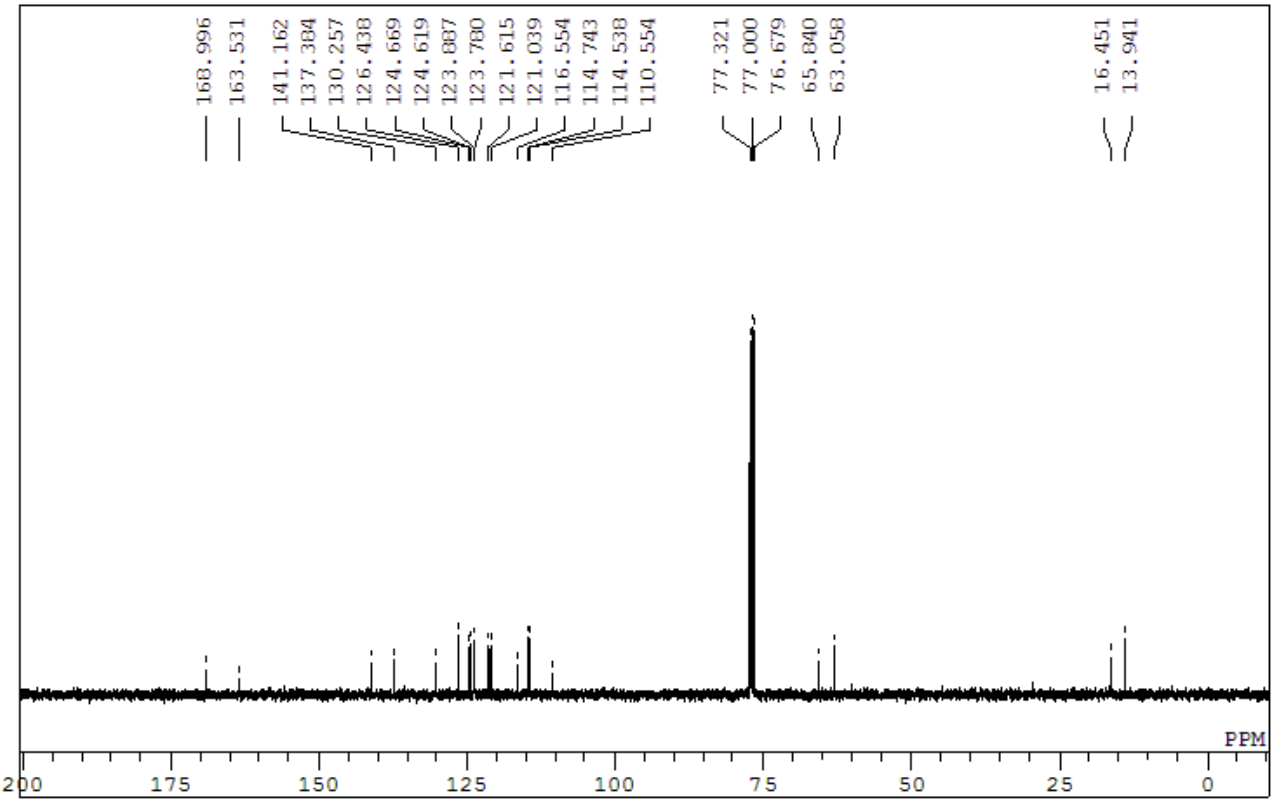

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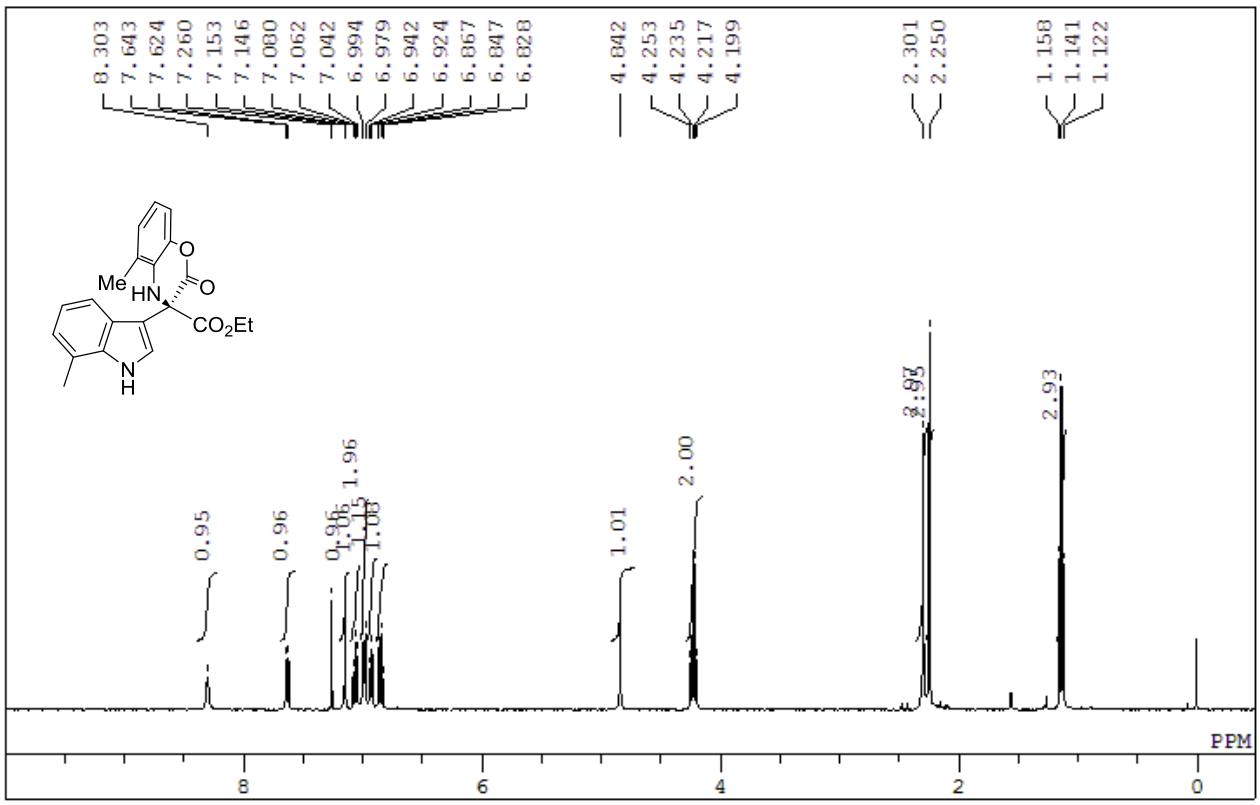

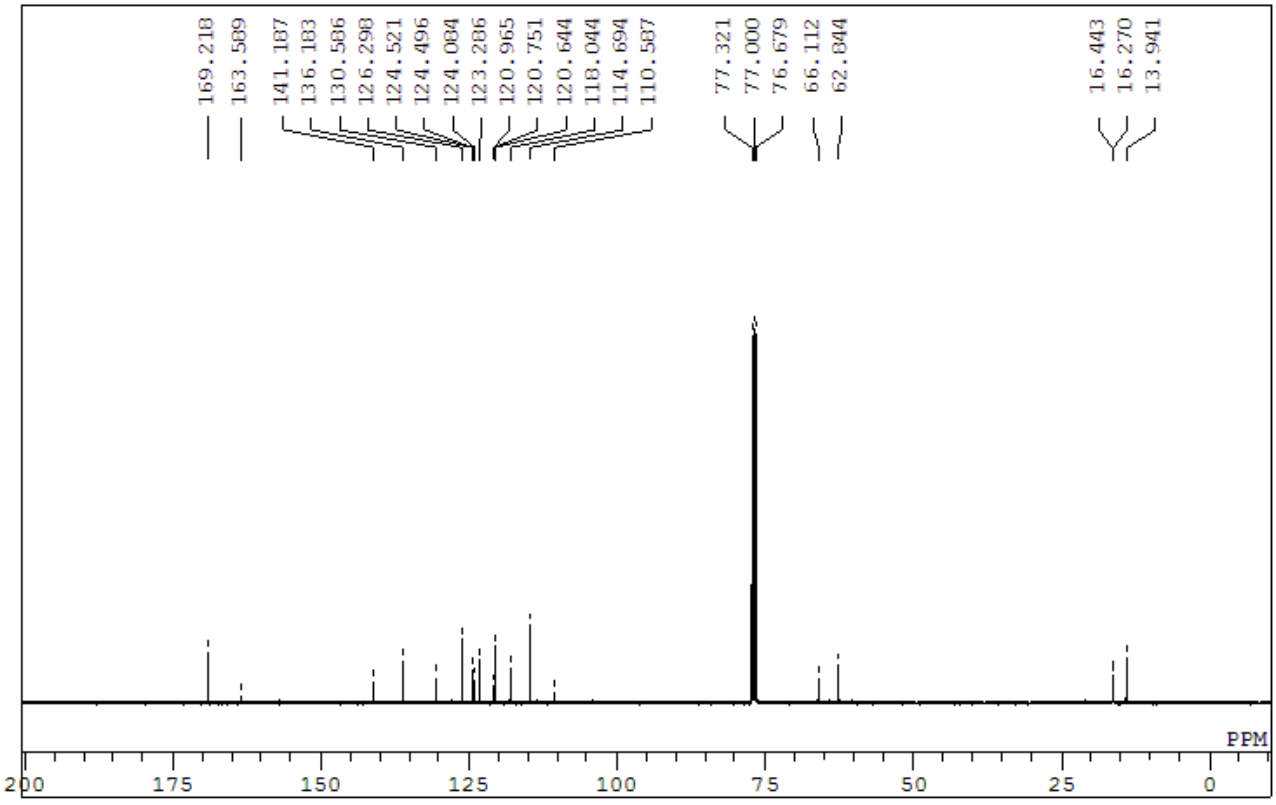

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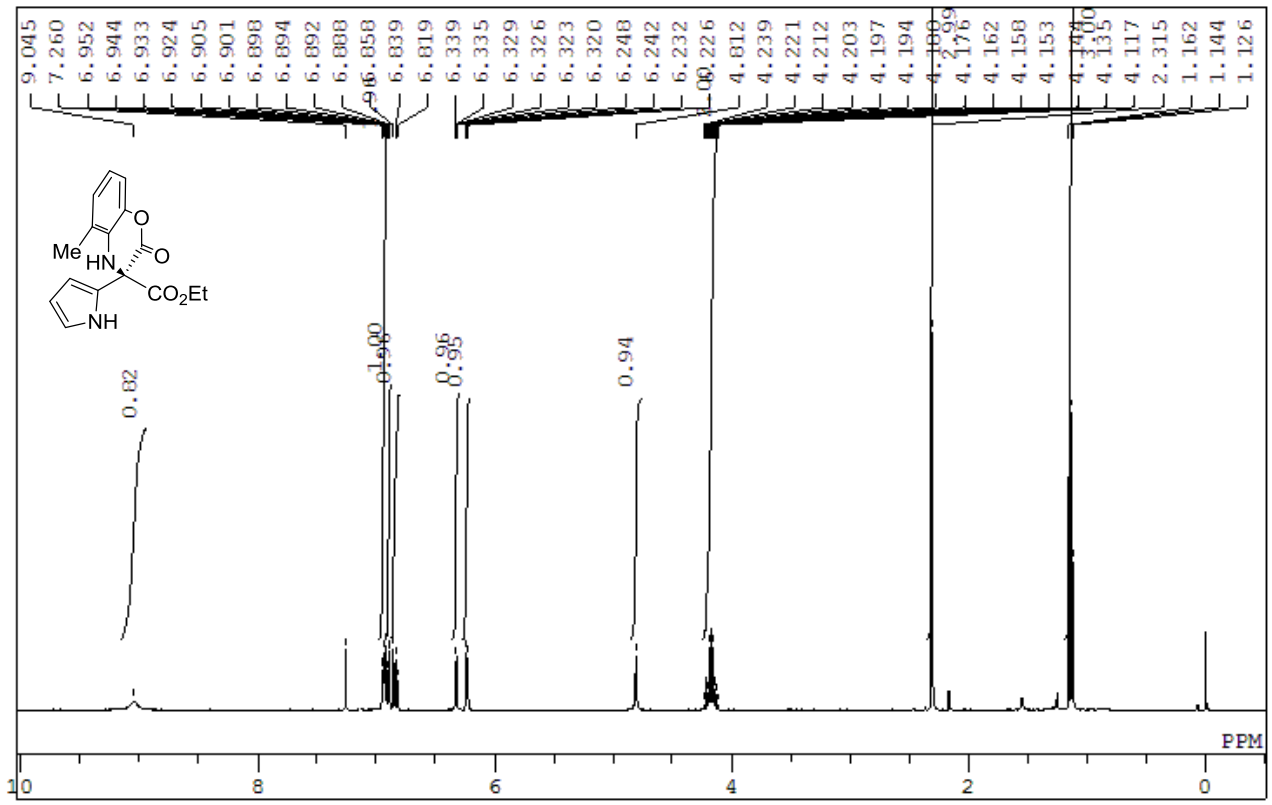

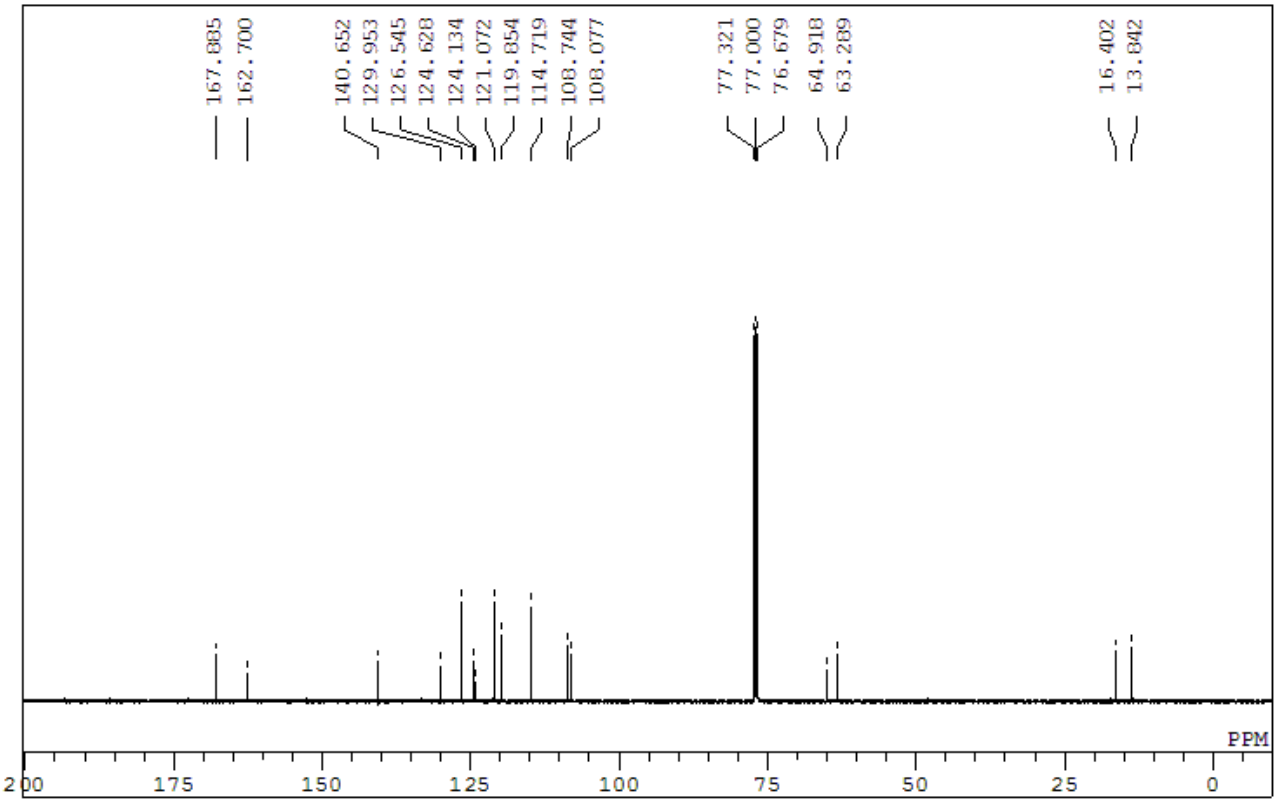

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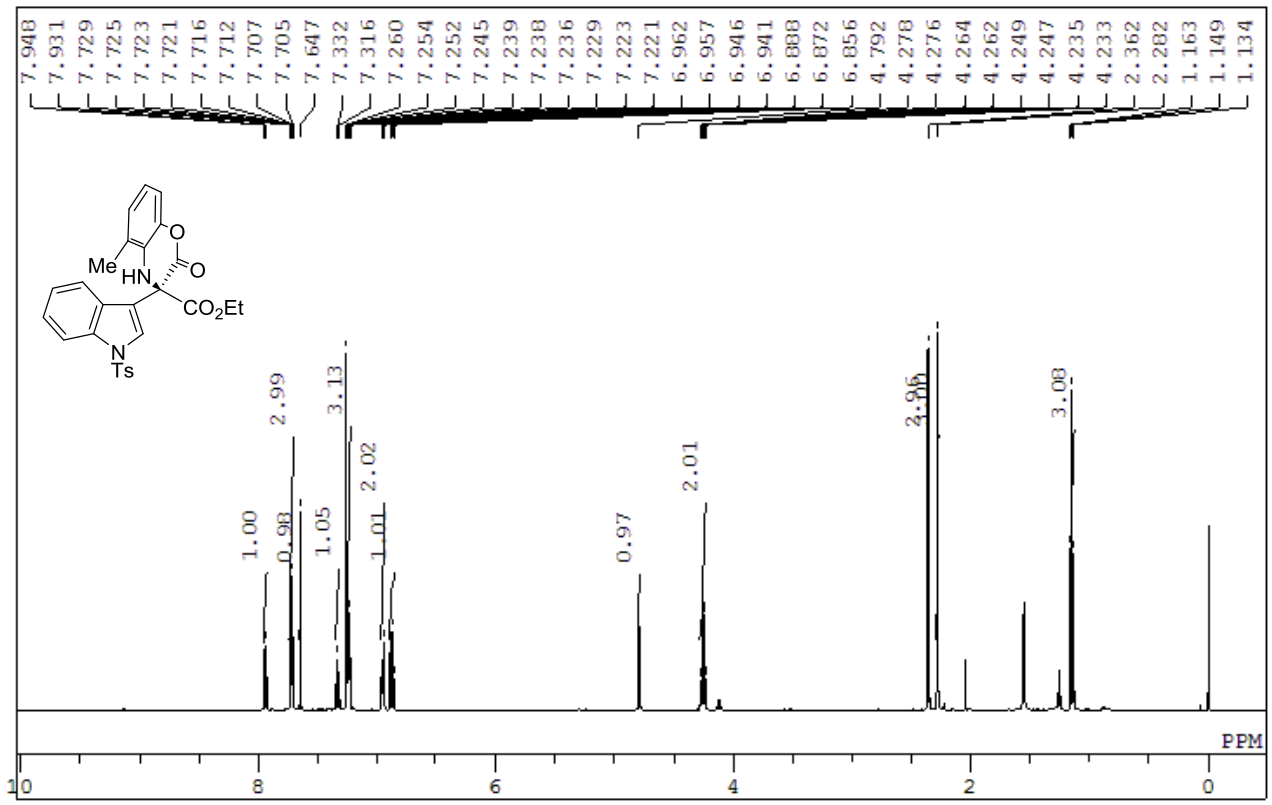

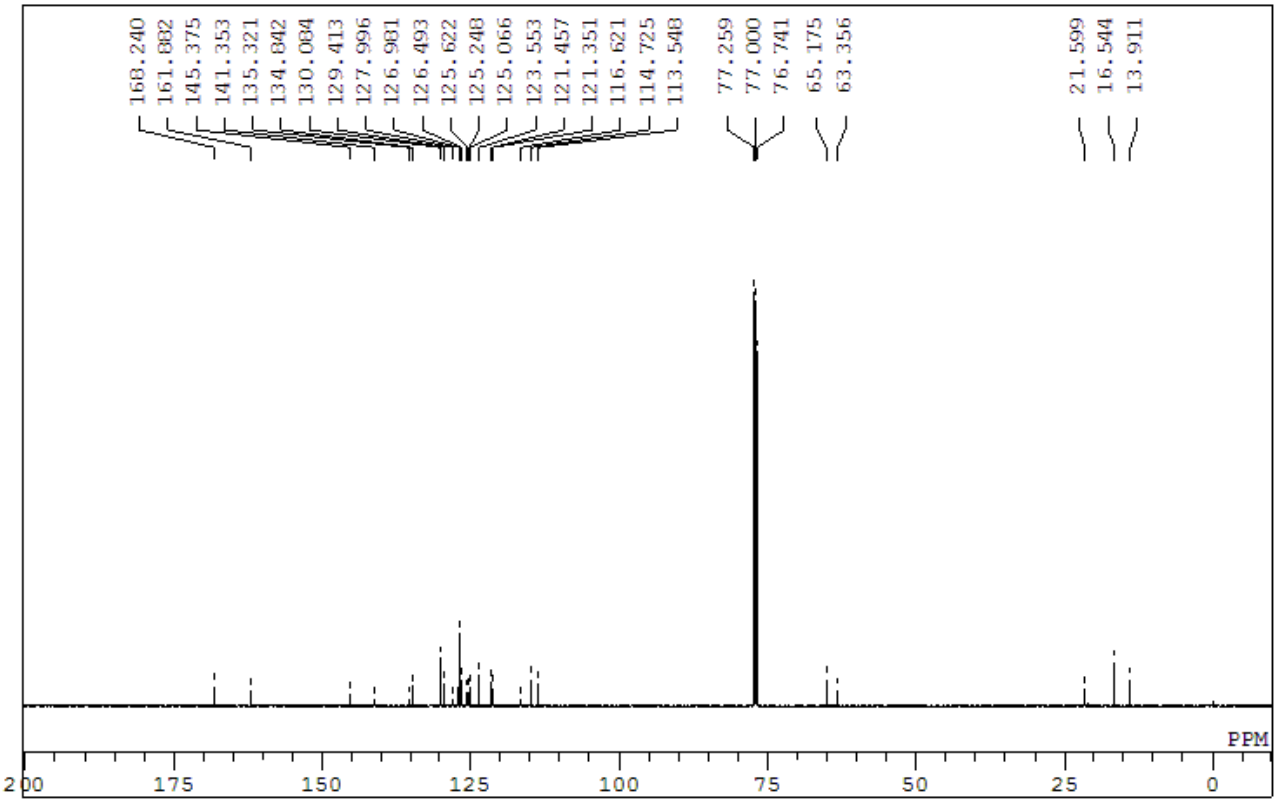

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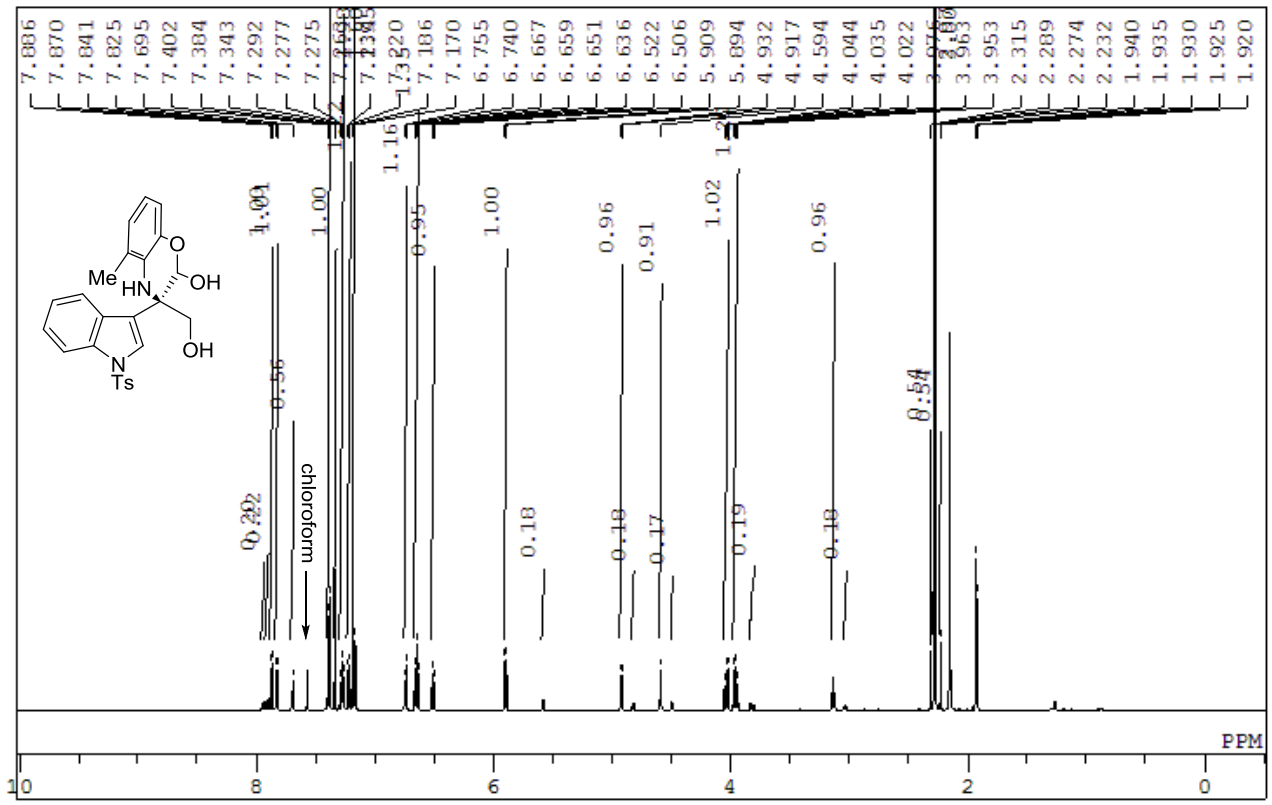

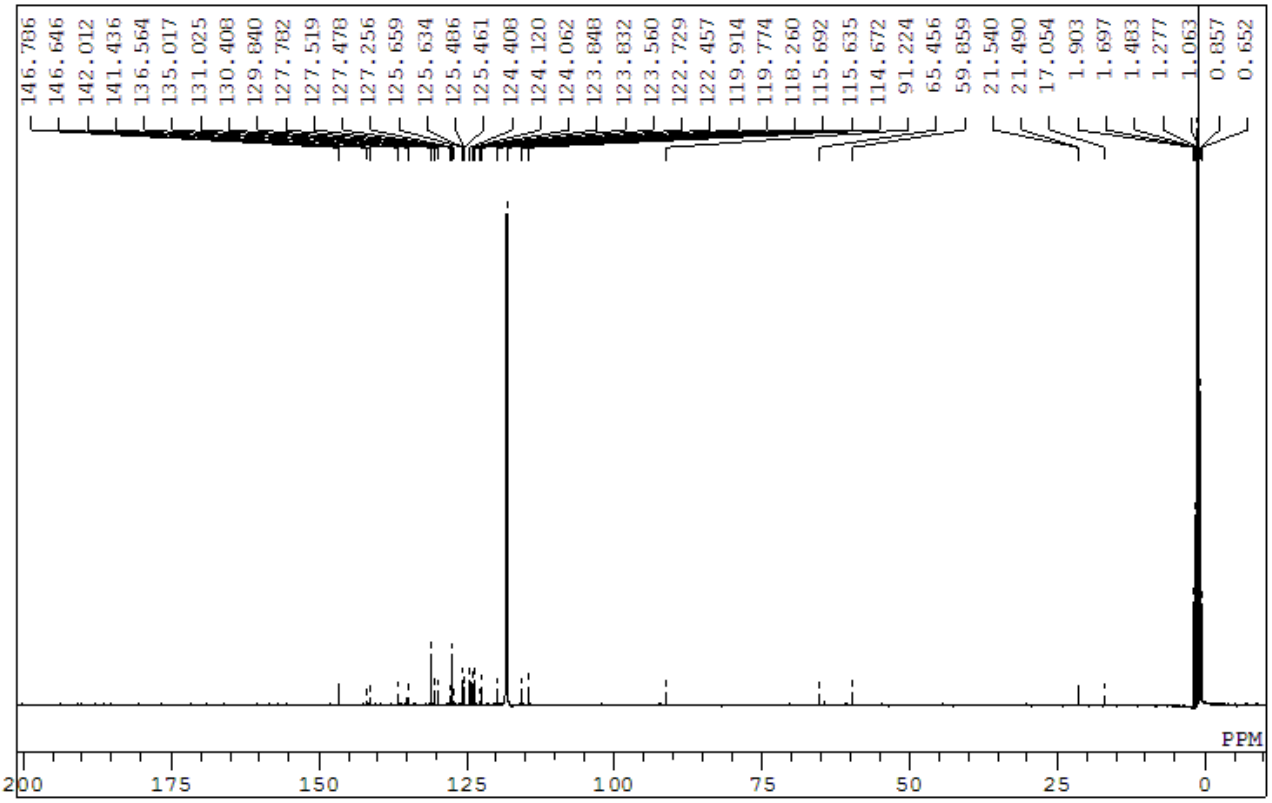

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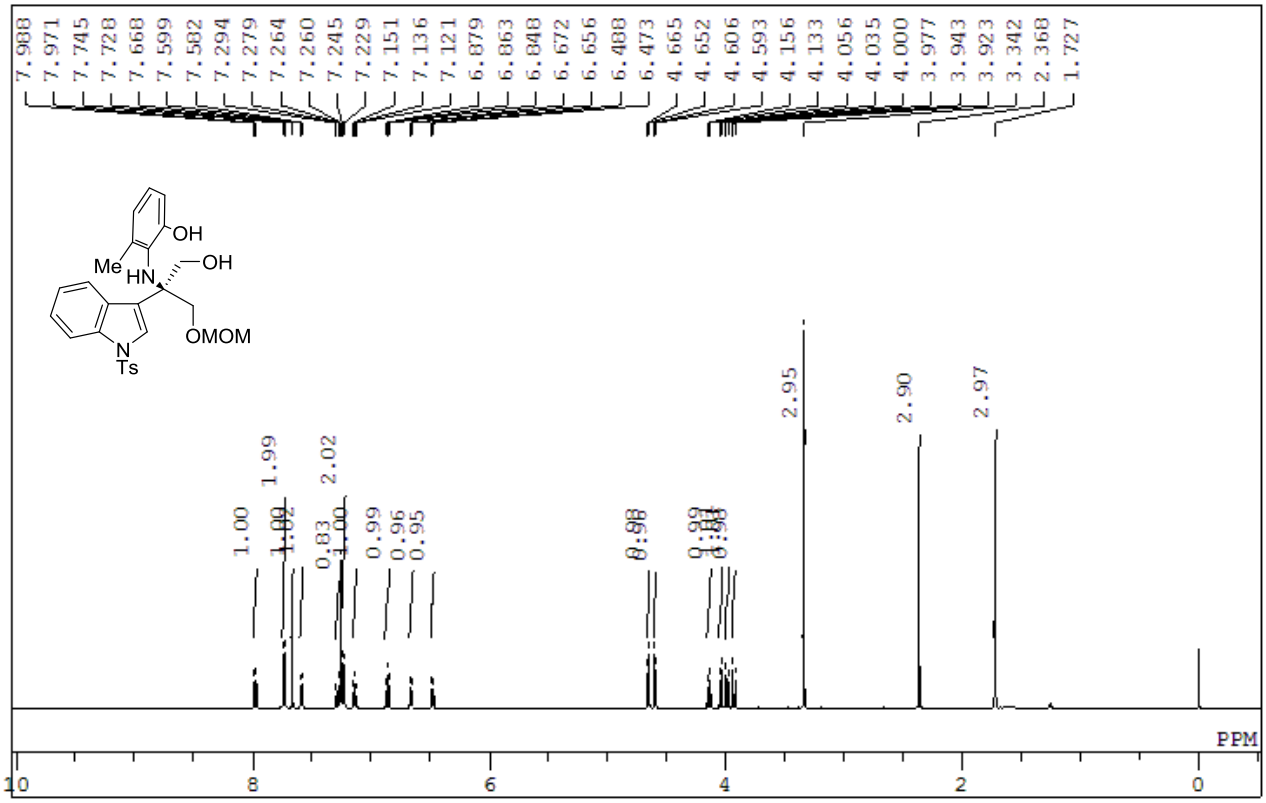

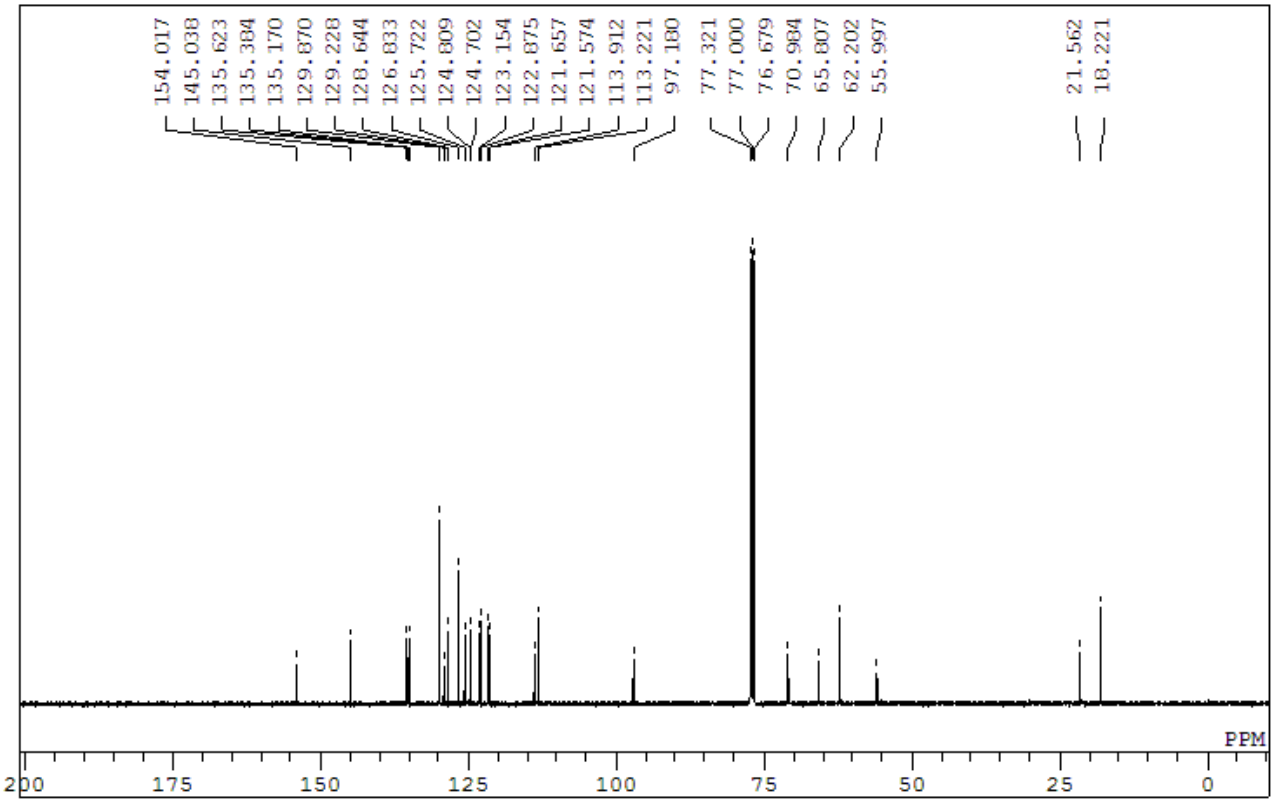

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