

Supporting Information

Indole Synthesis via Cyclative Formation of 2,3-Dizincindoles and Regioselective Electrophilic Trapping

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1. General Information

All reactions dealing with air- or moisture-sensitive compounds were conducted in a dry reaction vessel under an atmosphere of nitrogen. Air- and moisture-sensitive liquids and solutions were transferred *via* syringe or Teflon cannula. Analytical thin-layer chromatography was performed on glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (Merck). Thin layer chromatography plates were visualized by exposure to ultraviolet light (UV) and/or iodine. Organic solutions were concentrated by rotary evaporation at *ca.* 40 Torr (evacuated with a diaphragm pump). Flash column chromatography was performed as described by Still et al.,¹ employing Kanto Silica gel 60 N (spherical, neutral, 40–50 μm).

2. Instrumentation

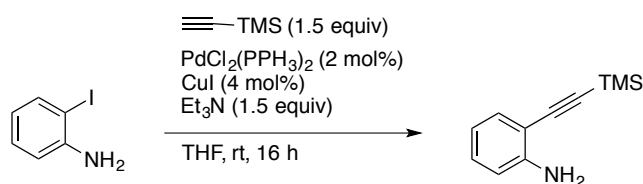
The water content of the solvent was confirmed with a Karl-Fischer Moisture Titrator (CA-21, Mitsubishi Chemical Analytech Company) to be less than 20 ppm. Proton nuclear magnetic resonance (^1H NMR) was recorded with JEOL ECX-400 (400 MHz) NMR, JEOL ECA-500 (500 MHz), JEOL ECZ-500 (500 MHz), and Bruker US500 (500 MHz) spectrometer. Chemical data for protons are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane (0.0 ppm) and are referenced to residual proton in the NMR solvent (CDCl_3 : δ 7.26, $\text{THF-}d_8$: δ 3.58). Carbon nuclear magnetic resonance (^{13}C NMR) was recorded at 125 MHz: chemical data for carbons are referenced to the carbon resonance of the solvent (CDCl_3 : δ 77.0). NOE experiments were conducted using the Delta noe_1d_dpfgse pulse sequence and detailed experimental parameters are listed at the spectroscopic data section for each compound. The data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, m = multiplet and/or multiplet resonances, br = broad), coupling constant in Hertz (Hz), and integration. Gas chromatographic (GC) analyses were performed on Shimadzu GC-2025 instruments equipped with an FID detector and a capillary column, HR-1 (25 m \times 0.25 mm i.d., 0.25 μm film). Gel permeation column chromatography was performed on a Japan Analytical Industry LC-92XX II NEXT SERIES (eluent: chloroform) with 1HH and 2HH polystyrene column, and Japan Analytical Industry LC-908 (eluent: toluene) with JAIGEL 1H and 2H polystyrene columns. Mass spectra were acquired by Shimadzu Parvum 2 gas chromatograph mass spectrometer (GC-MS) or by atmospheric

pressure ionization (APCI) using a time-of-flight mass analyzer on Bruker micrOTF II with a calibration standard of polyethylene glycol (MW 600), JEOL JMS-700P (FAB) with a calibration standard of polyethylene glycol (MW 600), and JEOL JMS-T100LC (AccuTOF) spectrometer with a calibration standard of polyethylene glycol (MW 400) or Reserpine (MW 609). Melting points were determined by METTER TOLEDO MP70 Melting Point System or MEL-TEMP II.

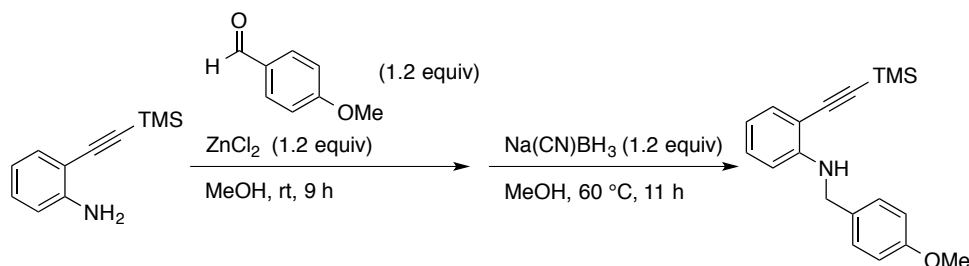
3. Materials

Unless otherwise noted, materials were purchased from Tokyo Kasei Co., Aldrich Inc., KANTO Chemical Co., Inc., or WAKO Pure Chemical and used after appropriate purification before use. Anhydrous ether, THF, and toluene (stabilizer-free) were purchased from WAKO Pure Chemical and purified by a solvent purification system (Glass Contour)² equipped with columns of activated alumina and supported copper catalyst (Q-5) prior to use. Butyllithium was purchased from KANTO Chemical Co., Inc., passed over a pad of Celite under nitrogen and the concentration was determined by titration with menthol in the presence of 2,2'-bipyridyl. Organozinc reagents were purchased from Aldrich Inc., and concentration was determined by titration with methylorange. A solution of $\text{CuCN} \cdot 2\text{LiCl}$ in THF (1.0 mol/L) was prepared by mixing CuCN (0.62 g, 7.0 mmol) and LiCl (0.59 g, 14.0 mmol), drying under vacuo at 160 °C for 3.5 h in a Schlenk-flask, then adding 80 mL of dry THF and stirring until all salts were dissolved. A solution of ZnCl_2 in THF (1 mol/L) was prepared by melting pure ZnCl_2 (beads, 99.99%) with a heat gun, then adding dry THF and stirring until all ZnCl_2 were dissolved.

4. Preparation of Starting Materials

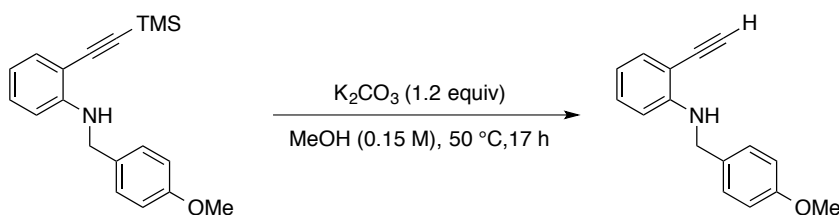


2-((Trimethylsilyl)ethynyl)aniline : In a 200 mL oven-dried two-necked round bottom flask, 2-iodoaniline (5.2 g, 23.9 mmol) was dissolved in THF (30 mL), and triethylamine (16.0 mL, 34.2 mmol) was added. Trimethylsilylacetylene (5.1 mL, 36.0 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (337 mg, 0.48 mmol, 2 mol%), and CuI (183 mg, 0.96 mmol, 4 mol%) were added to this solution and the reaction mixture was stirred for 16 h at room temperature. Volatiles were removed by rotary evaporation (evacuated with a diaphragm pump) to obtain a brown residue (6.11 g). The residue was dissolved in EtOAc (30 mL) and filtrated. After the concentration of the filtrate *in vacuo*, purification by silica gel column chromatography (150 g, eluent: 20% ethyl acetate, 1% triethylamine/hexane) afforded the title compound (4.28 g, 94%) as a brown oil. The compound data was in agreement with the literature.³ ^1H NMR (400 MHz, CDCl_3): δ 0.26 (s, 9H), 4.22 (br, 2H), 6.64–6.69 (m, 2H), 7.11 (t, 1H), 7.30 (d, $J = 7.6$ Hz, 1H). (400 MHz, CDCl_3): δ 0.27 (s, 9H), 4.23 (br, 2H), 6.64–6.69 (m, 2H), 7.11 (t, 1H), 7.28 (d, $J = 7.6$ Hz, 1H); HRMS (APCI+) Calcd. for $\text{C}_{11}\text{H}_{15}\text{NSi}$ (M): 189.0968; Found: 189.0964.

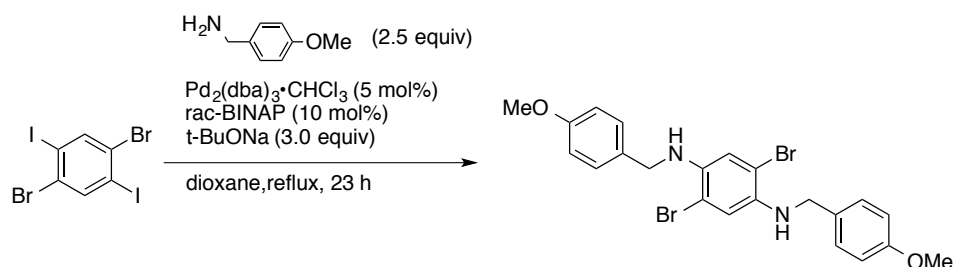


2-((Trimethylsilyl)ethynyl)-N-(4-methoxybenzyl)aniline : In a 300 mL oven-dried two-necked round bottom flask 2-((trimethylsilyl)ethynyl)aniline (4.02 g, 22.4 mmol) was dissolved in methanol (42.0 mL). A solution of anhydrous ZnCl_2 (3.68 g, 26.8 mmol) in methanol (30.0 mL), and *p*-anisaldehyde (3.26 mL, 26.8 mmol) were added. After stirring for 9 h, sodium cyanoborohydride

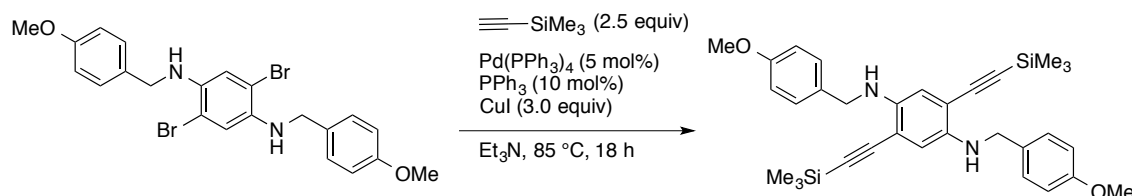
(1.78 g, 26.8 mmol) was added at 0 °C. After refluxing for 11 h at 70 °C, the reaction mixture was cooled to room temperature and methanol was removed *in vacuo* (evacuated with a diaphragm pump). The organic layer was extracted twice with Et₂O and then three times with CH₂Cl₂ and the combined organic extracts were washed with water. Drying over MgSO₄ and concentration *in vacuo* afforded a brown oily product (7.50 g). The crude material was purified by silica gel column chromatography (225 g, eluent: 5% ethyl acetate, 1% triethylamine/hexane) to give the title compound (4.60 g, 70%) as a yellow oil. The compound data was in agreement with the literature.⁴ ¹H NMR (400 MHz, CDCl₃): δ 0.21 (s, 9H), 3.81 (s, 3H), 4.33 (d, *J* = 5.3 Hz, 2H), 4.98 (br, 1H), 6.56 (d, *J* = 8.2 Hz, 1H), 6.60 (t, *J* = 7.7 Hz, 1H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.15 (t, *J* = 7.6 Hz, 1H), 7.28–7.31 (m, 3H); HRMS (APCI+) Calcd. for C₁₉H₂₃NOSi (M): 309.1543; Found: 309.1550.



2-Ethynyl-*N*-(4-methoxybenzyl)aniline (1): In a 200 mL oven-dried two-necked round bottom flask *N*-(4-methoxybenzyl)-2-((trimethylsilyl)ethynyl)aniline (4.60 g, 14.9 mmol) was dissolved in methanol (100 mL). K₂CO₃ (2.48 g, 17.8 mmol) was added to this solution. The yellow solution was warmed to 50 °C and stirred for 17 h. Methanol was removed *in vacuo* (evacuated with a diaphragm pump) and the reaction mixture was quenched with aqueous NaOH (10 %). The organic layer was extracted four times with Et₂O (50 mL). Drying over MgSO₄ and concentration *in vacuo* afforded a sticky yellow solid (3.10 g). The crude material was purified by silica gel column chromatography (90 g, eluent: 13% ethyl acetate, 1% triethylamine/hexane) to obtain the title compound (2.27 g, 64%) as a white yellow solid. The compound data was in agreement with the literature.³ ¹H NMR (400 MHz, CDCl₃): δ 3.37 (s, 1H), 3.78 (s, 3H), 4.31 (d, *J* = 5.5 Hz, 2H), 4.99 (br, 1H), 6.56–6.62 (m, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 7.16–7.35 (m, 4H); Melting Point: 86–87 °C; HRMS (APCI+) Calcd. for C₁₆H₁₅NO (M): 237.1148; Found: 237.1140.

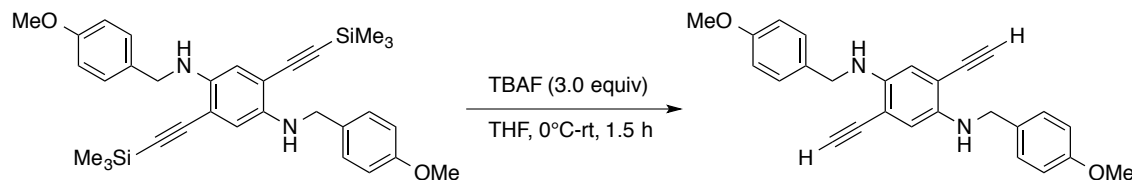


2,5-Dibromo-*N*¹,*N*⁴-bis(4-methoxybenzyl)benzene-1,4-diamine: In a 300 mL oven-dried two-necked round bottom flask, 1,4-dibromo-2,5-diiodobenzene (24.38 g, 50.0 mmol) was dissolved in dioxane (110 mL). To this mixture, 4-(methoxyphenyl)methanamine (16.0 mL, 121 mmol), tBuONa (14.4 g, 150 mmol), *rac*-BINAP (3.11 g, 5.0 mmol), and Pd₂(dba)₃•CHCl₃ (2.61 g, 2.5 mmol) were added. The solution was heated to 110 °C and stirred for 23 h. The reaction mixture was quenched with H₂O and the organic layer was extracted four times with dichloromethane (50 mL). After drying over MgSO₄, the extract was filtrated through celite and washed with DCM. Concentration *in vacuo* afforded a dark brown oil (34.43 g). The crude material was purified by silica gel column chromatography (eluent: DCM/hexane = 3/1, 1% triethylamine) to obtain the mixture (21.19 g). The mixture was used without further purification for the next reaction. ¹H NMR (500 MHz, CDCl₃): δ 3.80 (s, 6H), 4.11 (br, 2H), 4.22 (br, 4H), 6.83 (s, 2H), 6.88-6.90 (m, 4H), 7.28 (s, 4H).



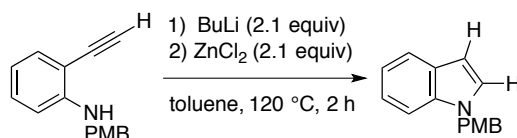
***N*¹,*N*⁴-bis(4-Methoxybenzyl)-2,5-bis((trimethylsilyl)ethynyl)benzene-1,4-diamine:** In a 100 mL oven-dried two-necked round bottom flask, 2-iodoaniline (2.25 g, 4.44 mmol) was dissolved in triethylamine (40 mL) was added. Trimethylsilylacetylene (1.58 mL, 11.18 mmol), Pd(PPh₃)₂ (103.6 mg, 0.09 mmol, 2 mol%), PPh₃ (46.5 mg, 0.18 mmol) and CuI (33.2 mg, 0.17 mmol) were added to this solution and the reaction mixture was stirred for 18 h at 85°C. Volatiles were removed by rotary evaporation (evacuated with a diaphragm pump), and dissolved in MeOH. The solution was filtrated to obtain a brown filtrate (2.137 g). After the concentration of the filtrate *in vacuo*, purification by silica gel column chromatography (eluent: DCM/hexane = 2/1, 1% triethylamine) afforded the title compound, containing a small amount of byproduct (1.99 g, 83%). The mixture was used without

further purification for the next reaction. ^1H NMR (500 MHz, CDCl_3): δ 0.25 (s, 18H), 3.26 (s, 2H), 4.68 (br, 2H), 6.71-6.74 (d, J = 8.8 Hz, 4H), 6.96 (s, 2H), 7.09 (d, J = 8.8 Hz, 4H).



2,5-Diethynyl- N^1,N^4 -bis(4-methoxybenzyl)benzene-1,4-diamine (3): In a 200 mL oven-dried two-necked round bottom flask N^1,N^4 -bis(4-methoxybenzyl)-2,5-bis(trimethylsilyl)ethynylbenzene-1,4-diamine (1.83 g, 3.38 mmol) was dissolved in THF (40 mL). TBAF (1.0 M, 8.5 mL, 8.5 mmol) was added to this solution at 0 °C. The yellow brown solution was warmed to room temperature and stirred for 1.5 h. THF was removed *in vacuo* (evacuated with a diaphragm pump). The organic layer was extracted four times with DCM. Drying over MgSO_4 and concentration *in vacuo* afforded a yellow solid (1.30 g). The crude material was purified by silica gel column chromatography (eluent: DCM, 1% triethylamine) to obtain the title compound (1.50 g, 97%) as a yellow solid. ^1H NMR (400 MHz, CDCl_3): δ 3.40 (s, 2H), 3.80 (s, 6H), 4.25 (s, 4H), 4.48 (br, 1H), 6.68 (s, 2H), 6.87 (d, J = 8.7 Hz, 4H), 7.28 (d, J = 8.7 Hz, 4H). ^{13}C NMR (100MHz, CDCl_3): δ 48.0, 55.2, 80.8, 83.9, 109.0, 114.0, 114.5, 128.6, 131.1, 141.3, 158.8; Melting Point: 173-174 °C; HRMS (APCI+) Calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_2$ (M): 396.1832; Found: 396.1839.

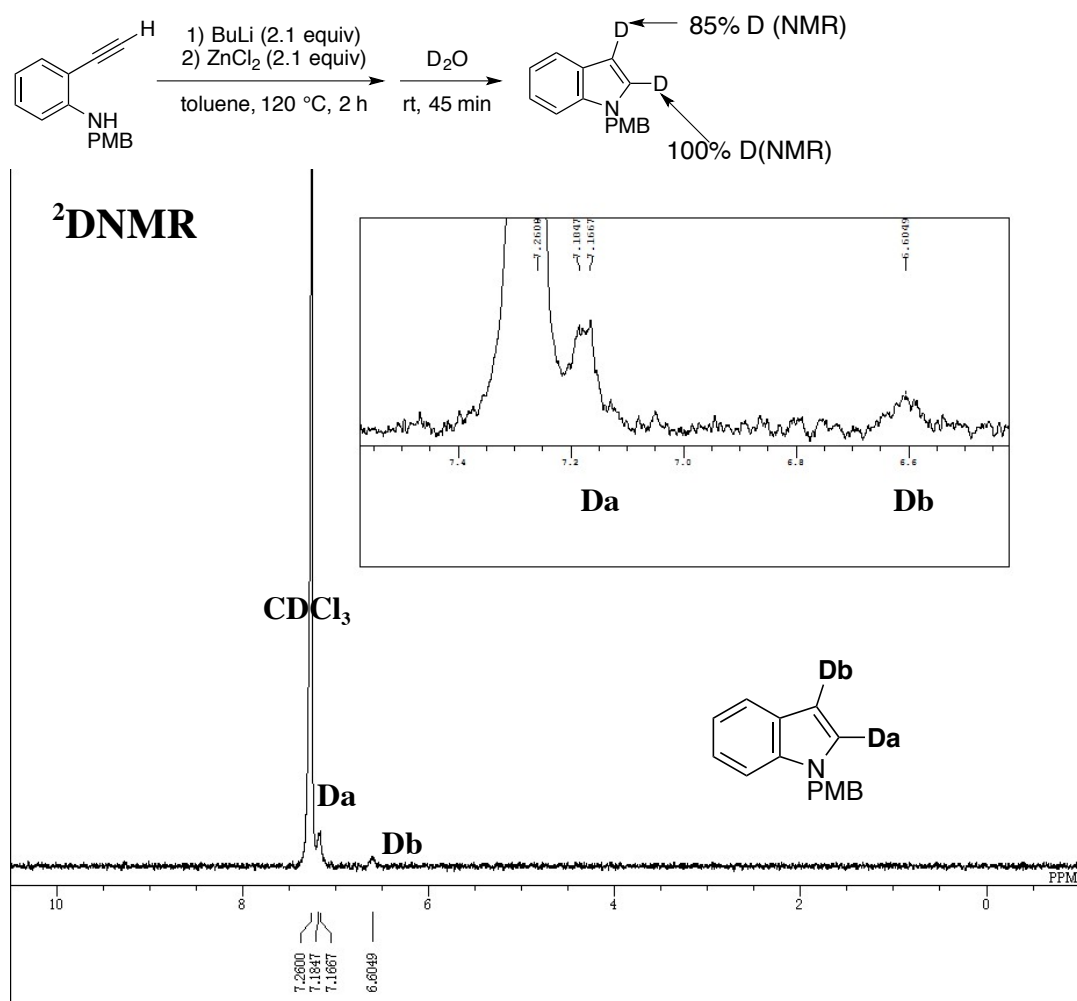
5. Typical Procedure for the Cyclization Reaction



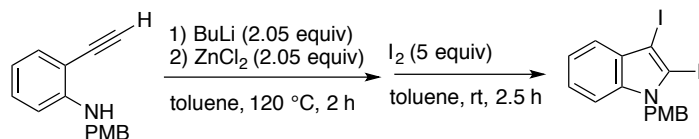
N -(4-methoxybenzyl)indole : In an oven-dried Schlenk tube, 2-ethynyl- N -(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et_2O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of ZnCl_2 in THF (1.0 mol/L, 0.82mL, 0.82 mmol) was added dropwise at room temperature. Volatiles were removed *in vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to afford a yellow suspension. The reaction was quenched with aq. NH_4Cl . The reaction mixture was extracted with ethyl acetate (3×5

mL), and the solvent was removed in *vacuo*, to afford a dark yellow oily product (136 mg). The product was passed by over a pad of silica gel to give the title compound (114 mg, 96%) as a yellow oil. The compound data was in agreement with the literature.³ ¹H NMR (400 MHz, CDCl₃): δ 3.77 (s, 3H), 5.26 (s, 2H), 6.53 (d, *J* = 3.0 Hz, 1H), 6.82 (d, *J* = 8.5 Hz, 2H), 7.16 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.30 (d, *J* = 10 Hz, 1H). ¹H NMR (500 MHz, THF-*d*₈): δ 3.70 (s, 3H), 5.28 (s, 2H), 6.41 (d, *J* = 5.0 Hz, 1H), 6.78-6.81 (m, 2H), 6.95 (t, *J* = 5.0 Hz, 1H), 7.02 (t, *J* = 5.0 Hz, 1H), 7.06-7.08 (m, 2H), 7.18-7.19 (m, 1H), 7.30 (d, *J* = 5.0 Hz, 1H), 7.50 (d, *J* = 5.0 Hz, 1H). ¹³C NMR (100MHz, CDCl₃): δ 49.5, 55.2, 101.8, 109.7, 114.1 (2C), 119.4, 120.9, 121.6, 128.0, 128.2 (2C), 128.7, 129.5, 136.2, 159.0; HRMS (APCI+) Calcd. for C₁₆H₁₅NO (M): 237.1148; Found: 237.1158.

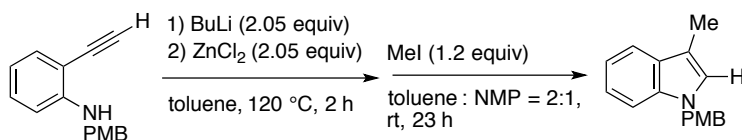
2,3-*d*₂-*N*-(4-methoxybenzyl)indole (2a) : Using the same procedure, following by quenching with D₂O instead of water, produced 2,3-dideuterioindole. The degree of deuterium incorporation was determined by NMR (solvent THF-*d*₈) by comparison with the spectrum of *N*-(4-methoxybenzyl)indole **2a'**. ²D NMR (77 MHz, CHCl₃) δ 6.60, 7.17.



6. Reaction of Dimetalloindole with Various Electrophiles

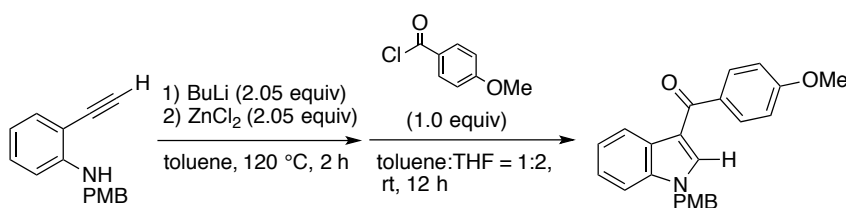


2,3-Diiodo-1-(4-methoxybenzyl)indole (Table 1, entry 1): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et₂O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of ZnCl₂ in THF (1.0 mol/L, 0.82 mL, 0.82 mmol) was added dropwise at room temperature. Volatiles were removed in *vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give a yellow suspension. After cooling the reaction mixture at 0 °C, a solution of iodine (508 mg, 2.0 mmol) in toluene (2 mL) was added. The reaction mixture was stirred at room temperature for 2.5 h, and was quenched with aq. Na₂S₂O₃. The reaction mixture was extracted with ethyl acetate (3×5 mL), and the solvent was removed in *vacuo*, to afford a brown oily product (224 mg). The product was purified by silica gel column chromatography (eluent: 2% ethyl acetate in hexane) to give the title compound (145 mg, 74%) as a white solid. Monoiodoindole formed in 7% (NMR). Melting Point: 85-86 °C; ¹H NMR (500 MHz, CDCl₃): δ 3.76 (s, 3H), 5.47 (s, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 7.11-7.16 (m, 2H), 7.22-7.25 (m, 1H), 7.42-7.44 (m, 1H); ¹³C NMR (125 MHz): 52.0, 55.2, 95.9, 110.4, 114.1 (2C), 121.0, 121.4, 123.1, 127.7 (2C), 128.6, 131.9, 137.7, 159.1; Anal. Calcd. for C₁₆H₁₃I₂NO: C, 39.29; H, 2.68; N, 2.86. Found: C, 39.21; H, 2.76; N, 2.51.



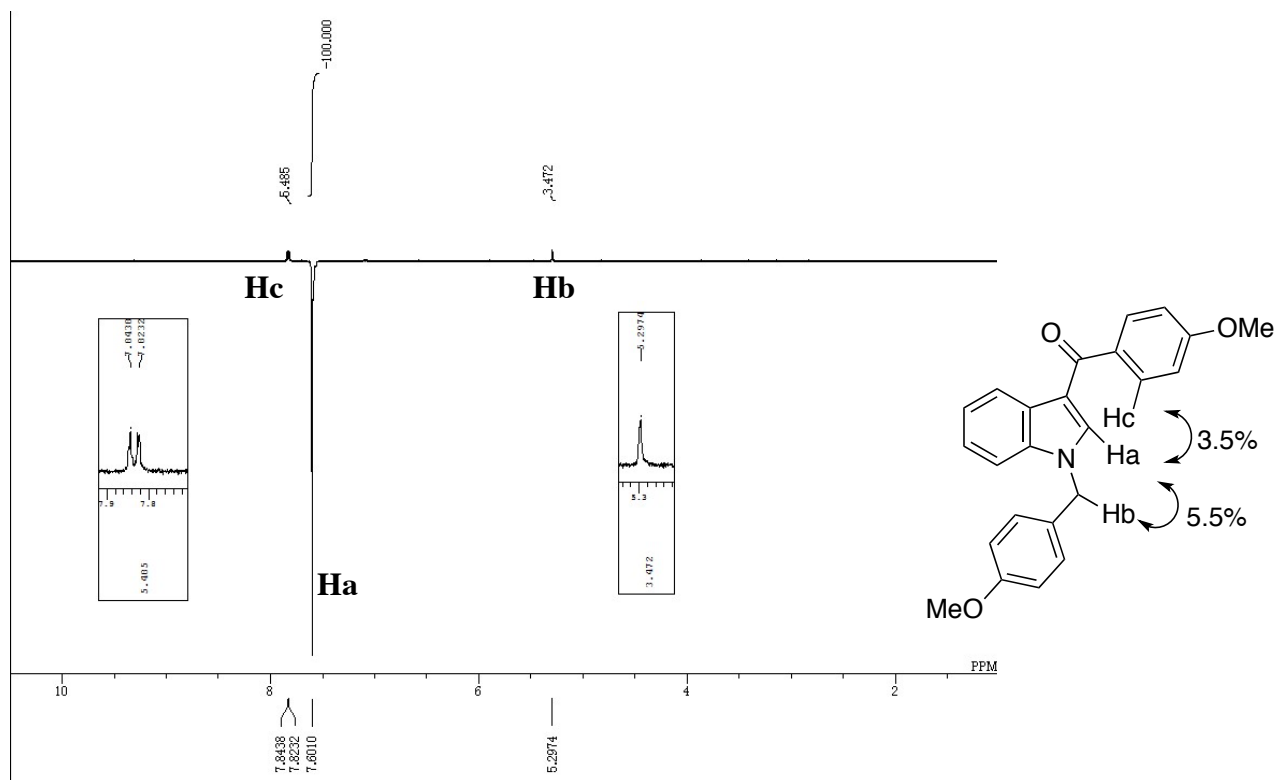
1-(4-Methoxybenzyl)-3-methylindole (Table 1, entry 2): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et₂O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of ZnCl₂ in THF (1.0 mol/L, 0.82 mL, 0.82 mmol) was added dropwise at room temperature. Volatiles were removed in *vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give a yellow suspension. After cooling the reaction mixture at 0 °C, NMP (0.4 mL) and

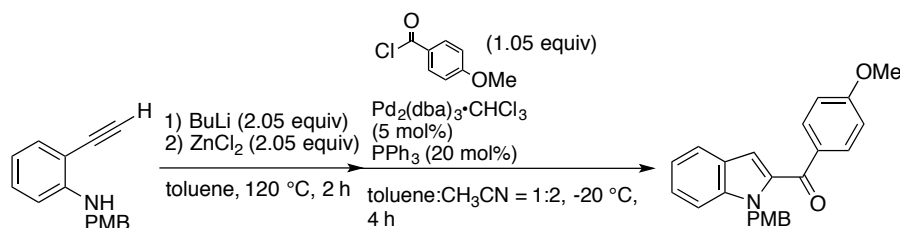
iodomethane (29.8 mL, 0.48 mmol) was added. The reaction mixture was stirred at room temperature for 16 h, and was quenched with aq. NH_4Cl . The reaction mixture was extracted with ethyl acetate (3×5 mL), and the solvent was removed in *vacuo*, to afford a yellow oily product. The product was purified by silica gel column chromatography (eluent: 1.5% ethyl acetate and 0.2% triethylamine in hexane) to give the mixture of the title compound as a yellow oil (NMR yield, 73%) with inseparable byproducts: 7% of unsubstituted indole **2** and 6% of 2,3-dimethylindole (yield determined by NMR). 2-Methylindole was not observed at all by GC or NMR. GPC using chloroform as an eluent to afford the title compound as a yellow oil. Deuterium incorporation was determined by using the same procedure, following by quenching with D_2O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ^1H NMR (400 MHz, CDCl_3): δ 2.32 (s, 3H), 3.75 (s, 3H), 5.19 (s, 2H), 6.81 (d, $J = 9.0$ Hz, 2H), 6.87 (s, 1H), 7.06-7.11 (m, 3H), 7.17 (t, 1H), 7.27 (s, 1H), 7.57 (d, $J = 7.5$ Hz, 1H); C^{13} NMR (100 MHz): δ 9.63, 49.2, 55.3, 109.4, 110.7, 114.0 (2C), 118.7, 119.0, 121.5, 125.6, 128.2 (2C), 128.9, 129.9, 136.5, 158.9; HRMS (APCI+) Calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}$ (M): 251.1305; Found: 251.1315.



3-(4-Methoxybenzoyl)-1-(4-methoxybenzyl)indole (Table 1, entry 3): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (47 mg, 0.20 mmol) was dissolved in Et_2O (0.4 mL), and a solution of BuLi in hexane (1.59 mol/L, 0.26 mL, 0.41 mmol) was added at 0 °C. ZnCl_2 in THF (1 mol/L, 0.41 mL, 0.41 mmol) was added at room temperature. Solvents were removed in *vacuo*, and then toluene (0.4 mL) was added. The resulting mixture was stirred at 120 °C for 2 h. After cooling the reaction mixture at room temperature, THF (0.8 mL) was added. *p*-Methoxybenzoyl chloride (27 mL, 0.20 mmol) was added to resulting clear orange solution. The reaction mixture was stirred at room temperature for 12 h, and then it was quenched with aq. NH_4Cl . The reaction mixture was extracted with AcOEt, and the solvent was removed in *vacuo* to afford a dark yellow oily product. The product was purified by silica gel column chromatography (eluent: 40% ethyl acetate in hexane) to give the title compound (54.1 mg, 73%) as a white solid. 2-Aroylindole and 2,3-diaroylindole were not observed at all (NMR). Unsubstituted indole **2** was

recovered in 20% (GC). Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ¹H NMR (500 MHz, CDCl₃): δ 3.75 (s, 3H), 3.85 (s, 3H), 5.26 (s, 2H), 6.83 (td, *J* = 8.5 Hz, 2.0 Hz, 2H), 6.95 (td, *J* = 8.5 Hz, 2.0 Hz, 2H), 7.07 (d, *J* = 8.5 Hz, 2H), 7.24-7.33 (m, 3H), 7.60 (s, 1H), 7.83 (td, *J* = 9.0 Hz, 2.5 Hz, 2H), 8.38 (dd, *J* = 6.8 Hz, 1.3 Hz, 1H), ¹³C NMR (125 MHz): δ 50.2 (2C), 55.2 (2C), 55.3, 110.13, 113.5 (2C), 114.3 (2C), 116.0, 122.5, 122.6, 123.5, 127.5, 127.8, 128.3 (2C), 130.9 (2C), 133.3, 136.2, 136.9, 159.4, 162.2, 189.7; Melting Point: 122-123 °C; HRMS (APCI+) Calcd. for C₂₄H₂₁NO₃ (M): 371.1516; Found: 371.1529. The structure of the compound was confirmed by NOE experiments in CDCl₃. When signal Ha at δ = 7.60 (s, 1H) was irradiated, Hb at δ = 7.83 (td, *J* = 9.0 Hz, 2.5 Hz, 2H) exhibited an enhancement by 5.5%, and 5.30 (s, 2H) exhibited an enhancement by 3.5%.

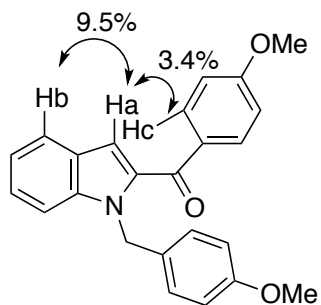
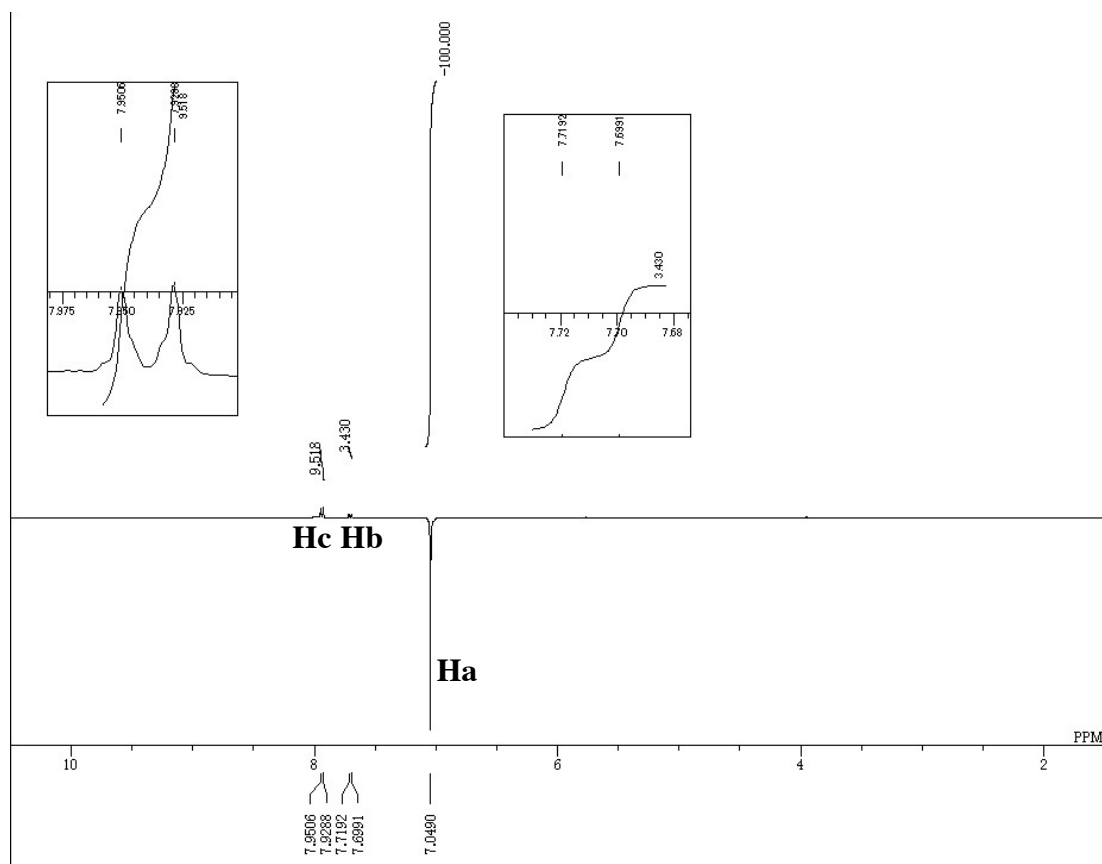




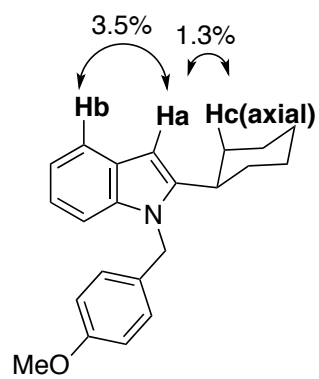
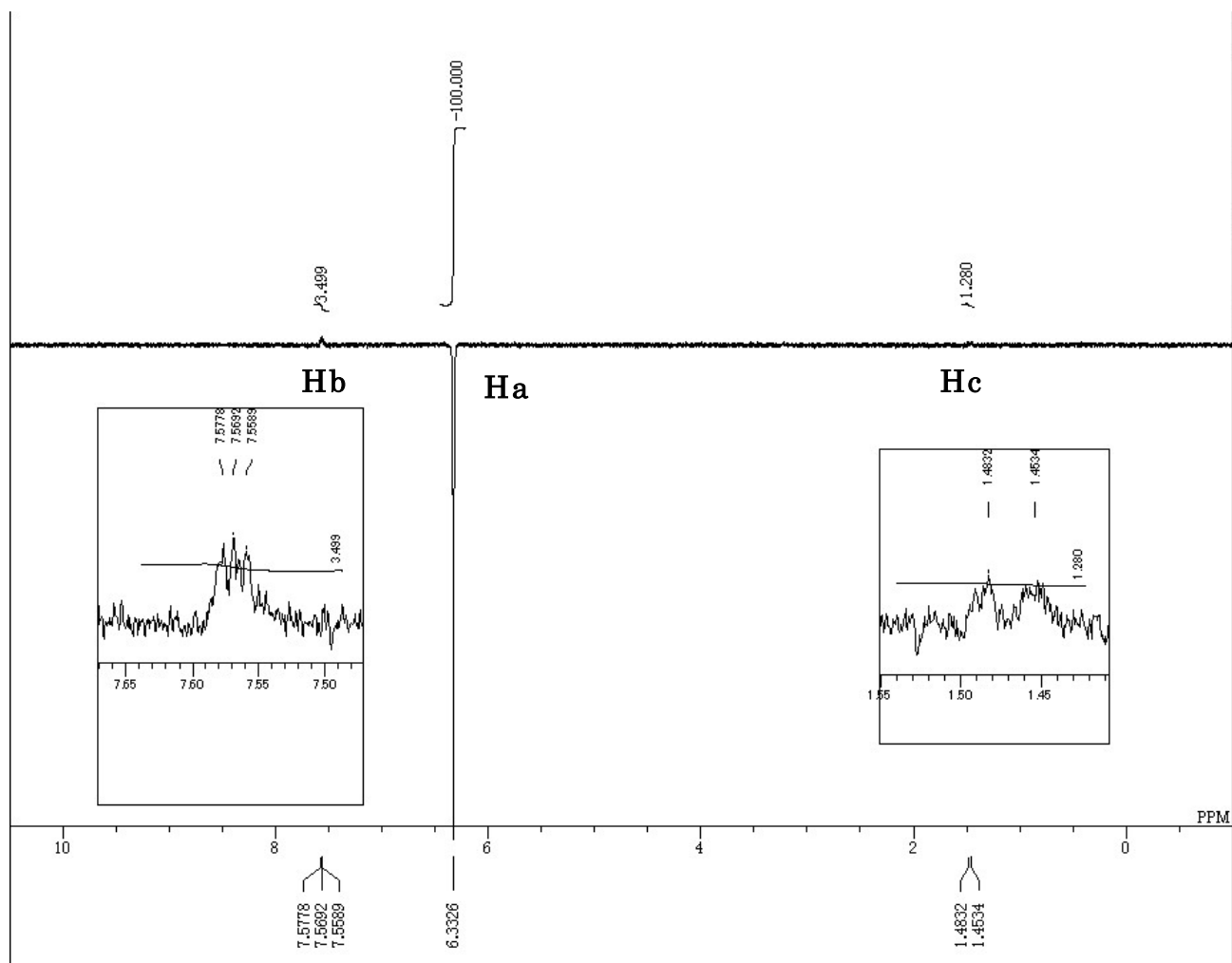
3-(4-Methoxybenzoyl)-1-(4-methoxybenzyl)indole (Table 1, entry 4): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (47 mg, 0.20 mmol) was dissolved in Et₂O (0.4 mL), and a solution of BuLi in hexane (1.59 mol/L, 0.26 mL, 0.41 mmol) was added at 0 °C. ZnCl₂ in THF (1 mol/L, 0.41 mL, 0.41 mmol) was added at room temperature. Solvents were removed *in vacuo*, and then toluene (0.4 mL) was added. The resulting mixture was stirred at 120 °C for 2 h. After cooling the reaction mixture at rt, half of the toluene was removed *in vacuo* and THF (0.8 mL) was added, then the reaction mixture was cooled to -20 °C. A solution of triphenylphosphine (10.5 mg, 0.04 mmol) and Pd₂(dba)₃•CHCl₃ (10.4 mg, 0.01 mmol) in THF (0.2 mL) was added, then *p*-methoxybenzoylchloride (28 uL, 0.21 mmol) were sequentially added. The reaction mixture was stirred at -20 °C for 4 h, and then it was quenched with aq. NH₄Cl. The reaction mixture was extracted with AcOEt, and the solvent was removed *in vacuo* to afford a dark brown oily product. The product was purified by silica gel column chromatography (eluent: 25% ethyl acetate in hexane) to give the title compound as a white solid (38 mg, 51%). 3-Aroylindole formed in 1% (GC) and 2,3-diaroylindole formed in 14% (NMR). Unsubstituted indole **2** was recovered in 13% (GC). Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ¹H NMR (500 MHz, CDCl₃): δ 3.73 (s, 3H), 3.90 (s, 3H), 5.76 (s, 2H), 6.75-6.77 (m, 2H), 6.96-6.98 (m, 2H), 7.03 (s, 1H), 7.07-7.08 (m, 2H), 7.16 (t, *J* = 1.0 Hz, 1H), 7.34 (t, *J* = 1.0 Hz, 1H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.91-7.93 (m, 1H); C¹³ NMR (100 MHz): δ 47.4, 55.2, 55.5, 111.0, 113.5 (2C), 113.9 (2C), 114.4, 120.9, 122.8, 125.7, 126.1, 127.9 (2C), 130.5, 131.9 (2C), 132.1, 135.0, 139.8, 158.6, 163.1, 187.3; HRMS (APCI+) Calcd. for C₂₄H₂₁NO₃ (M): 371.1516; Found: 371.1518. The regiochemistry of the compound was determined by NOE experiments in CDCl₃. When signal Ha at δ = 7.03 (s, 2H) was irradiated, Hb at δ = 7.69 (d, *J* = 8.0 Hz, 1H) exhibited an enhancement by 9.5%, and Hc at δ = 7.93 (m, 2H) exhibited an enhancement by 3.4%.

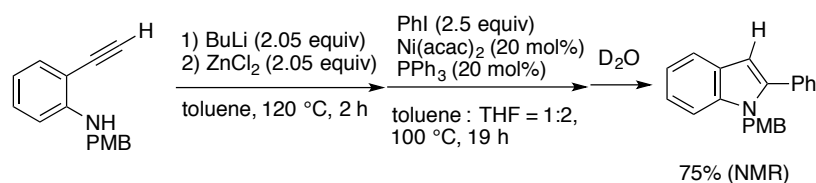
When signal Ha at δ = 5.75 (s, 2H) was irradiated, Hb at δ = 7.42 (d, *J* = 8.0 Hz, 1H) exhibited an

enhancement by 15%, and Hc at $\delta = 7.08$ (m, 2H) exhibited an enhancement by 10%.

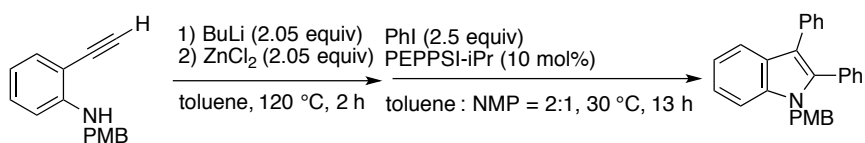


give a yellow suspension. After cooling the reaction mixture to 0 °C, THF (0.4 mL) was added to give a clear yellow solution. (Trimethylsilyl)methylmagnesium chloride (0.93 mol/L, 0.44 mL, 0.41 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 1 h. After raising the temperature to room temperature, iodocyclohexane (0.18 mL, 294 mg, 1.40 mmol), *N,N,N',N'*-Tetramethylethylenediamine (TMEDA) (61 µL, 48 mg, 0.41 mmol), and iron(II)chloride (2.5 mg, 0.02 mmol) were sequentially added. The reaction mixture was stirred at 30 °C for 17 h, and then it was quenched with aq. D₂O. The organic phase was extracted with ethyl acetate (3×5 mL). Then the reaction mixture was passed over a pad of Florisil and the solvent was removed in *vacuo*. The product was purified by silica gel column chromatography (eluent: 40% chloroform and 1% triethylamine in hexane), and then GPC using chloroform as an eluent to afford the title compound as a white solid (30 mg, 47%). Dicyclohexylindole formed in a trace amount (GC), 3-cyclohexylindole formed in 13% (NMR), and protonated indole **2** was recovered in 19% (NMR). Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. Melting point: 135-136 °C; ¹H NMR (500 MHz, CDCl₃): δ 1.25-1.35 (m, 3H), 1.43-1.48 (q, *J* = 12 Hz, 2H), 1.73 (d, *J* = 10 Hz, 1H), 1.80 (d, *J* = 10 Hz, 2H), 1.92 (d, *J* = 11 Hz, 2H), 2.62 (m, 1H), 3.75 (s, 3H), 5.28 (s, 2H), 6.33 (s, 1H), 6.78 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 7.06 (m, 2H), 7.15 (m, 1H), 7.57 (m, 1H); C¹³ NMR (100 MHz): δ 26.1, 26.7, 33.7, 26.0, 45.9, 55.2, 97.3, 109.5, 114.1 (2C), 119.4, 119.8, 120.7, 127.0, 128.2, 130.2, 136.8, 146.9, 158.7; HRMS (APCI+) Calcd. for C₂₂H₂₅NO(M): 319.1931 Found: 319.1932. The regiochemistry of the compound was determined by NOE experiments in CDCl₃. When signal Ha at δ = 6.33 (s, 1H) was irradiated, Hb at δ = 7.57 (m, 1H) exhibited an enhancement by 3.5%, and Hc at δ = 1.45-1.48 (m, 2H) exhibited an enhancement by 1.3%.



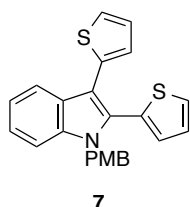


1-(4-Methoxybenzyl)-2-phenylindole (Table 1, entry 6): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (47 mg, 0.20 mmol) was dissolved in Et₂O (0.4 mL), and BuLi in hexane (1.59 mol/L, 0.26 mL, 0.41 mmol) was added dropwise at 0 °C. A solution of ZnCl₂ in THF (1 mol/L, 0.41 mL, 0.41 mmol) was added at room temperature. Volatiles were removed in *vacuo*, and then toluene (0.4 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give a yellow suspension. After cooling the reaction mixture to room temperature, THF (0.8 mL) was added to give a clear yellow solution. Iodobenzene (55.8 μL, 102 mg, 0.50 mmol), triphenylphosphine (10.5 mg, 0.04 mmol), and nickel(II) acetylacetonate (Ni(acac)₂) (10.3 mg, 0.04 mmol) were sequentially added. The reaction mixture was stirred at 100 °C for 19 h, and then it was quenched with aq. D₂O. The organic phase was extracted with ethyl acetate (3×5 mL). The yield of the title compound was determined by NMR (75%). Diphenylindole formed 4% (GC), and protonated indole **2** was recovered in 18%. Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. The compound data was in good agreement with the literature.⁵



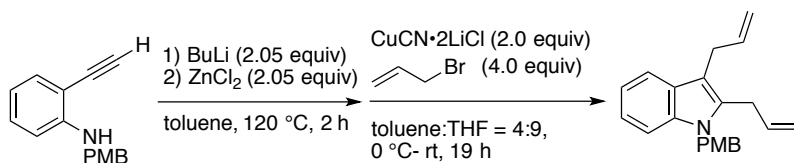
1-(4-Methoxybenzyl)-2,3-diphenylindole (Table 1, entry 7): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et₂O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added dropwise at 0 °C. A solution of ZnCl₂ in THF (1.0 mol/L, 0.82 mL, 0.82 mmol) was added at room temperature. Volatiles were removed in *vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give a yellow suspension. After cooling the reaction mixture to room temperature, NMP (0.4 mL) was added to give a clear yellow solution. Iodobenzene (0.11 mL, 204 mg, 1.00 mmol) and bis[(diisopropylphenyl)imidazolylidene]-(3-chloropyridyl)palladium(II) (PEPPSI-iPr) (27 mg, 0.04 mmol) were sequentially added. The reaction mixture was stirred at 30 °C for 13 h, and then it was

quenched with aq. NH_4Cl . The organic phase was extracted with ethyl acetate (3×5 mL). Then the reaction mixture was passed over a pad of Florisil and the solvent was removed in *vacuo* to afford a dark brown oily product. The product was purified by silica gel column chromatography (eluent: 7% ethyl acetate and 1% triethylamine in hexane) to give the title compound (136 mg, 87%) as a white solid. Monophenylindole formed in 9% (GC). Deuterium incorporation was determined by using the same procedure, following by quenching with D_2O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. Melting point: 121-122 °C; ^1H NMR (500 MHz, CDCl_3): δ 3.80 (s, 3H), 5.28 (s, 2H), 6.82 (d, J = 8.0 Hz, 2H), 6.97 (d, J = 8.0 Hz, 2H), 7.20-7.38 (m, 13H), 7.85 (d, J = 7.0 Hz, 1H); ^{13}C NMR (125 MHz): δ 47.0, 55.2, 110.5, 114.0 (2C), 115.5, 119.6, 120.3, 122.3, 125.5, 127.3 (3C), 128.1, 128.1 (2C), 128.3 (2C), 129.9, 130.0 (2C), 130.1, 131.1 (2C), 131.8, 135.1, 136.9, 137.8; HRMS (APCI+) Calcd. for $\text{C}_{28}\text{H}_{23}\text{NO}$ (M): 389.1774; Found: 389.1774.



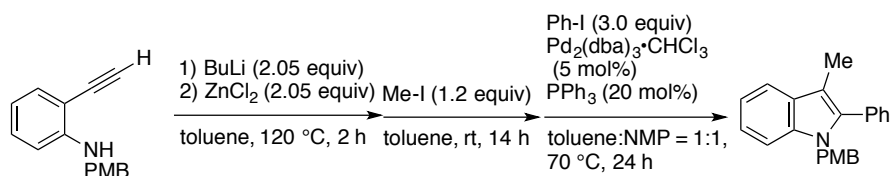
1-(4-Methoxybenzyl)-2,3-di(thien-2-yl)indole (Table 1, entry 8): Obtained in 67% yield as a white solid. Monothienylindole formed in 15%, and protonated indole **2** was recovered in 6% (GC). Deuterium incorporation was determined by using the same procedure, following by quenching with D_2O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. Melting Point: 131-132 °C; ^1H NMR (500 MHz, CDCl_3): δ 3.76 (s, 3H), 5.26 (s, 2H), 6.79 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 8.0 Hz, 2H), 7.02-7.09 (m, 4H), 7.11-7.27 (m, 4H), 7.45 (d, J = 5.0 Hz, 1H), 7.95 (d, J = 7.5 Hz, 1H); ^{13}C NMR (125 MHz): 47.0, 55.2, 110.4, 114.0 (2C), 114.1, 112.1, 120.7, 123.1, 123.8, 125.1, 126.6, 126.8, 127.2, 127.3 (2C), 128.4, 129.8, 130.1, 130.7, 131.5, 136.6, 136.7, 158.7; HRMS (APCI+) Calcd. for $\text{C}_{24}\text{H}_{19}\text{NOS}_2$ (M): 401.0903; Found: 401.0908.

Gram-Scale Reaction



2,3-Diallyl-1-(4-methoxybenzyl)indole (Scheme 2 and Table 1, entry 9): In an oven-dried Schlenk

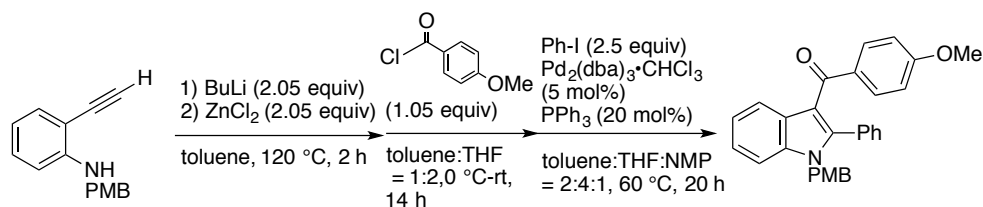
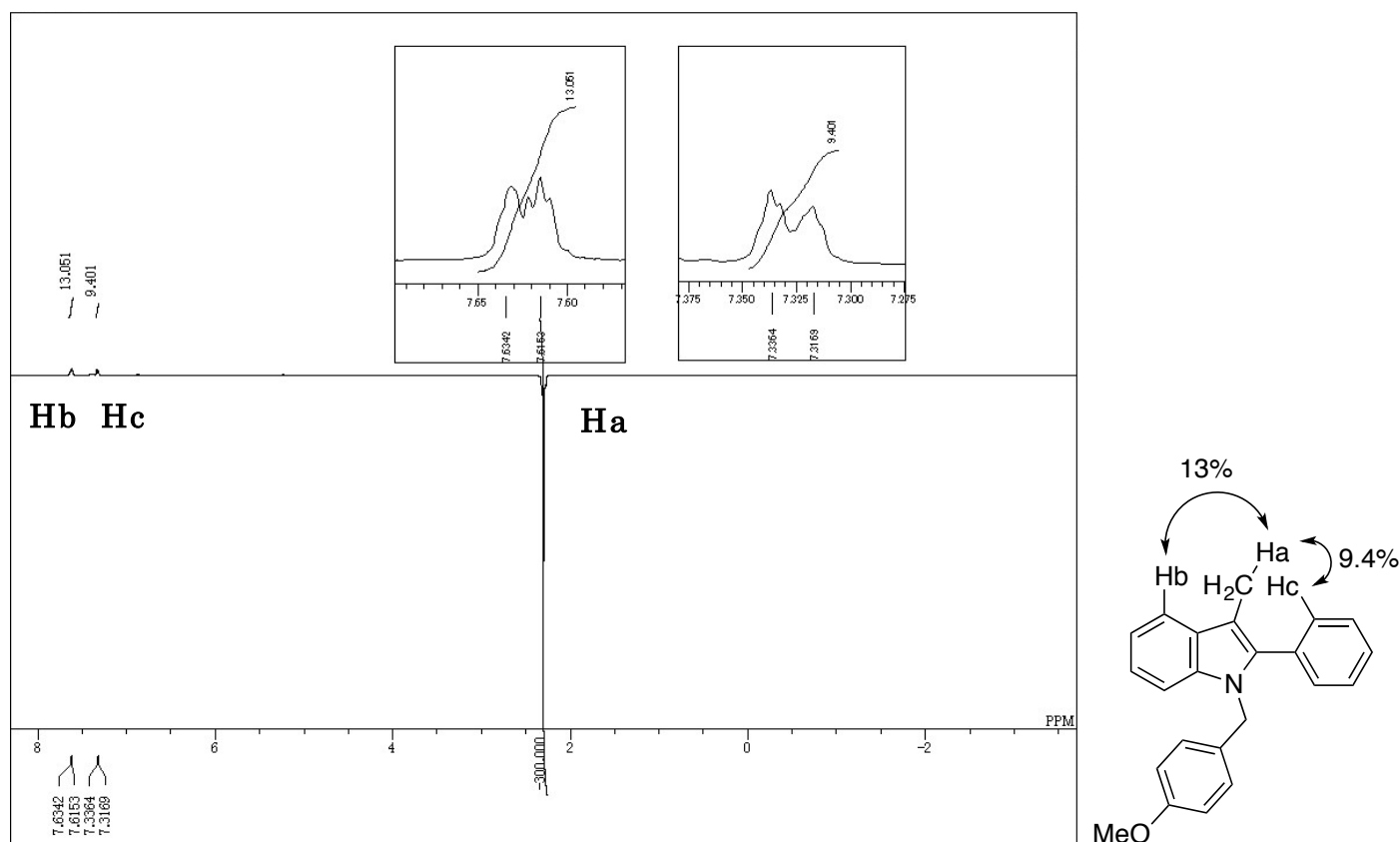
tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (1.00 g, 4.22 mmol) was dissolved in Et₂O (4.0 mL), and BuLi in hexane (1.64 mol/L, 5.27 mL, 8.65 mmol) was added at 0 °C. A solution of ZnCl₂ in THF (1.0 mol/L, 8.65 mL, 8.65 mmol) was added dropwise at room temperature. Volatiles were removed in *vacuo*, and then toluene (4.22 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give a yellow suspension. After cooling the reaction mixture at 0 °C, CuCN•2LiCl in THF (1 mol/L, 9.28 mL, 9.28 mmol), then allyl bromide (1.46 mL, 2.04 g, 16.88 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 19 h, and then it was quenched with aq. NH₄Cl. The reaction mixture was extracted with ethyl acetate (5×5 mL), and the solvent was removed in *vacuo* to afford a yellow oily product. The product was purified by silica gel column chromatography (eluent: 7% ethyl acetate and 1% triethylamine in hexane) to give the of title compound (1.20 mg, 89%). Monoallylindole formed in 8% (GC). ¹H NMR (500 MHz, CDCl₃): δ 3.43 (d, *J* = 3.5 Hz, 2H), 3.50 (d, *J* = 4.0 Hz, 2H), 3.71 (s, 3H), 4.93-5.08 (m, 4H), 5.22 (s, 2H), 5.79-5.87 (m, 1H), 5.95-6.02 (m, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 7.5 Hz, 2H), 7.06-7.12 (m, 2H), 7.18-7.19 (m, 1H), 7.57 (d, *J* = 6.5 Hz, 1H). ¹³C NMR (125 MHz): δ 28.8 (2C), 45.9, 55.2, 109.3, 110.1, 114.0 (2C), 114.4, 116.1, 118, 121.1, 127.1(2C), 127.9, 130.2, 134.0, 135.1, 136.6, 137.6, 158.7; HRMS (APCI+) Calcd. for C₂₂H₂₃NO (M): 317.1774; Found: 317.1784.



1-(4-Methoxybenzyl)-3-methyl-2-phenylindole (Table 1, entry 10): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et₂O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of ZnCl₂ in THF (1.0 mol/L, 0.82 mL, 0.82 mmol) was added dropwise at room temperature. Volatiles were removed *in vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give a yellow suspension product. After cooling the reaction mixture to 0 °C, NMP (0.4 mL) and iodomethane (29.8 mL, 0.48 mmol) was added. The reaction mixture was stirred at room temperature for 14 h, then a solution of triphenylphosphine (21 mg, 0.08 mmol) and Pd₂(dba)₃•CHCl₃ (21 mg, 0.02 mmol) in NMP (0.4 mL), and iodobenzene (0.13 mL, 245 mg, 1.20 mmol) were sequentially added. The reaction mixture was stirred at 70 °C for 24 h, and then it was quenched with

aq. NH_4Cl . The reaction mixture was extracted with ethyl acetate (3×5 mL), and the solvent was removed in *vacuo*, to afford a yellow oily product. The product was purified by silica gel column chromatography (eluent: 1% ethyl acetate and 0.2% triethylamine in hexane), and then GPC using toluene as an eluent to afford the title compound as a yellow oil (83 mg, 64%). 3-Methylindole formed in 7%, 2,3-dimethylindole formed in 4%, 2-phenylindole formed in 6%, 2,3-diphenylindole formed in a trace amount, and unsubstituted indole **2** was recovered in 5% (GC). Deuterium incorporation was determined by using the same procedure, following by quenching with D_2O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ^1H NMR (500 MHz, CDCl_3): δ 2.30 (s, 3H), 3.70 (s, 3H), 5.15 (s, 2H), 6.73 (d, J = 8.0 Hz, 2H), 6.85 (d, J = 7.5 Hz, 2H), 7.15-7.18 (m, 3H), 7.31-7.38 (m, 5H), 7.61 (d, J = 6.0 Hz, 1H). ^{13}C NMR (125 MHz): δ 9.4, 47.0, 55.1, 109.0, 110.2, 113.9 (2C), 118.8, 119.3, 121.8, 127.2 (2C), 127.8, 128.3 (2C), 128.8, 130.5 (3C), 132.1, 136.7, 137.8, 158.5; HRMS (APCI+) Calcd. for $\text{C}_{23}\text{H}_{21}\text{NO}$ (M): 327.1618; Found: 327.1615.

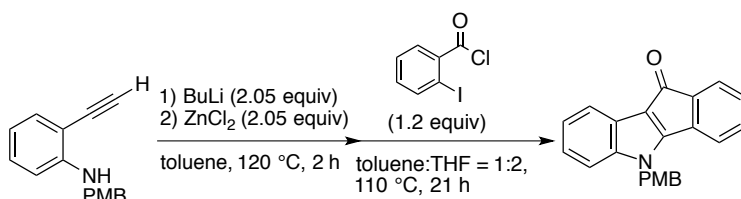
The regiochemistry of the compound was determined by NOE experiments in CDCl_3 . When signal Ha at δ = 2.30 (s, 3H) was irradiated, Hb at δ = 7.61 (d, J = 8.0 Hz, 1H) exhibited an enhancement by 13%, and Hc at δ = 7.32 (m, 2H) exhibited an enhancement by 9.4%.



3-(4-Methoxybenzoyl)-1-(4-methoxybenzyl)indole (Table 1, entry 11): In an oven-dried Schlenk tube, 2-ethynyl-N-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et₂O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of ZnCl₂ in THF (1.0 mol/L, 0.82 mL, 0.82 mmol) was added dropwise at room temperature. Volatiles were removed *in vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give a yellow suspension. After cooling the reaction mixture at room temperature, THF (1.6 mL) was added. To resulting clear orange solution, *p*-methoxybenzoyl chloride (57 μL, 0.42 mmol) was added. The reaction mixture was stirred at room temperature for 14 h, then a solution of triphenylphosphine (21 mg, 0.08 mmol) and Pd₂(dba)₃•CHCl₃ (21 mg, 0.02 mmol) in NMP (0.8 mL), and iodobenzene (0.11 mL, 204 mg, 1.00 mmol) were sequentially added. The reaction mixture was stirred at 60 °C for 20 h, and then it was quenched with aq. NH₄Cl. The

product was purified by silica gel column chromatography (eluent: 30% ethyl acetate and 1% triethylamine in hexane) to give the title compound (134.8 mg, 76%) as a white solid. 3-Aroylindole formed in 5%, 2-phenylindole formed in 12%, 2,3-diphenylindole formed in 5%, and unsubstituted indole **2** was recovered in 5% (GC). Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ¹H NMR (500 MHz, CDCl₃): δ 3.75 (s, 6H), 5.25 (s, 2H), 6.65 (d, *J* = 7.0 Hz, 2H), 6.78 (d, *J* = 7.5 Hz, 2H), 6.90 (d, *J* = 8.0 Hz, 2H), 7.18-7.25 (m, 7H), 7.27-7.29 (m, 1H), 7.61 (d, *J* = 7.0 Hz, 2H), 7.91-7.93 (m, 1H), C¹³ NMR (125 MHz): δ 47.2, 55.2 (2C), 110.8, 112.8 (2C), 114.1 (2C), 115.3, 121.6, 122.1, 123.1, 127.2 (2C), 127.8, 128.1 (2C), 128.7, 129.0, 130.7, 130.8 (2C), 131.6 (2C), 132.5, 136.7, 145.5, 158.8, 162.1, 191.5; Melting Point: 104-105 °C; HRMS (APCI+) Calcd. for C₃₀H₂₅NO₃ (M): 447.1829; Found: 447.1845.

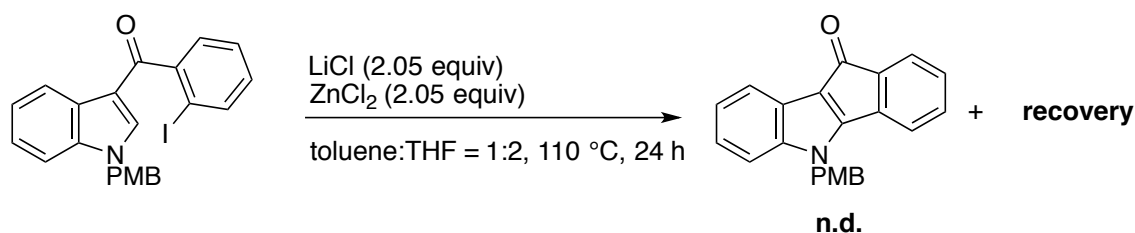
7. One Pot Synthesis of Indenoindolone



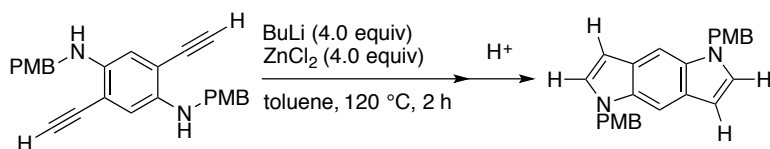
5-(4-Methoxybenzyl)indeno[1,2-*b*]indol-10-one (Table 1, entry 12): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (94 mg, 0.40 mmol) was dissolved in Et₂O (0.8 mL), and a solution of BuLi in hexane (1.59 mol/L, 0.52 mL, 0.81 mmol) was added at 0 °C. ZnCl₂ in THF (1 mol/L, 0.82 mL, 0.82 mmol) was added at room temperature. Solvents were removed *in vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2 h. After cooling the reaction mixture to rt, half of the toluene was removed and THF (0.8 mL) was added. To the resulting clear orange solution, *o*-iodobenzoyl chloride (66 mL, 0.48 mmol) was added. The reaction mixture was stirred 110 °C for 21 h, and then it was quenched with aq. NH₄Cl. The reaction mixture was extracted with chloroform, and the solvent was removed *in vacuo* to afford a dark orange solid product. The product was purified by silica gel column chromatography (eluent: 20% ethyl acetate in hexane), and then GPC using chloroform as an eluent to afford the title compound as an orange solid (79 mg, 58%). ¹H NMR (500 MHz, CDCl₃): δ 3.77 (s, 3H), 5.46 (s, 2H), 6.85-6.87 (d, *J* = 8.5 Hz, 2H), 7.05-7.07 (m, 1H), 7.11-7.21 (m, 7H), 7.46-7.47 (m, 1H), 7.82 (d,

$J = 8.5$ Hz, 1H), C^{13} NMR (125 MHz): δ 48.3, 55.3, 110.1, 114.5 (2C), 115.5, 118.5, 120.8, 123.1 (2C), 123.2, 123.6, 127.5, 127.6 (2C), 129.6, 132.0, 134.7, 141.2, 142.6, 158.6, 159.4, 185.1. GCMS $C_{24}H_{21}NO$ $m/z = 339.2$. FAB⁺ $C_{24}H_{21}NO$ $m/z = 339.1258$; Melting Point: 191-192 °C; HRMS (APCI+) Calcd. for $C_{23}H_{17}NO_2$ (M): 339.1254; Found: 339.1269.

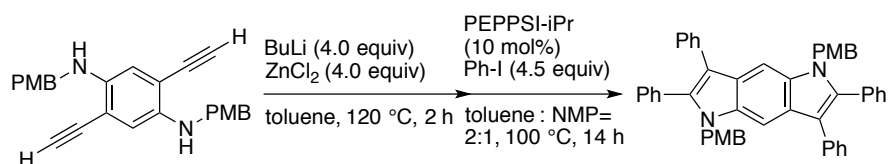
Control Experiment



8. Synthesis of Benzodipyrrole

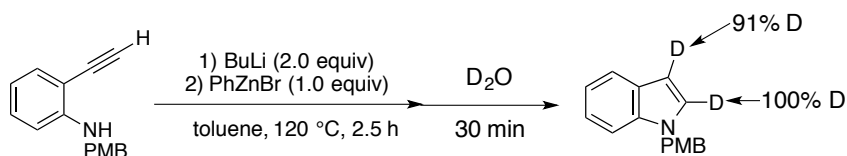


1,5-bis(4-Methoxybenzyl)benzo[1,2-*b*:4,5-*b'*]dipyrrole (4a): In an oven-dried Schlenk tube, 2,5-diethynyl-*N*¹,*N*⁴-bis(4-methoxybenzyl)benzene-1,4-diamine (79 mg, 0.20 mmol) was dissolved in Et₂O (1.6 mL), and BuLi in hexane (1.61 mol/L, 0.50 mL, 0.80 mmol) was added at 0 °C. A solution of ZnCl₂ in THF (1.0 mol/L, 0.80 mL, 0.80 mmol) was added at room temperature. Volatiles were removed in *vacuo*, and then toluene (1.6 mL) was added. The resulting mixture was stirred at 120 °C for 2 h, to give an orange suspension. The reaction was quenched with aq. NH₄Cl. The reaction mixture was extracted with DCM (3×5 mL), and the solvent was removed in *vacuo*, to afford a dark green product. The product was passed over a pad of silica gel (eluent: ethylacetate) to give the title compound (73 mg, 92%) as a white solid. ¹H NMR (400 MHz, CDCl₃): δ 3.75 (s, 6H), 5.27 (s, 4H), 6.50 (d, $J = 3.0$ Hz, 2H), 6.81 (d, $J = 8.5$ Hz, 4H), 7.07-7.12 (m, 6H), 7.44 (d, $J = 7.8$ Hz, 2H). ¹³C NMR (100MHz, CDCl₃): δ 49.7 (2C), 55.2 (2C), 99.1 (2C), 100.1 (2C), 114.0 (4C), 126.5 (2C), 128.1 (4C), 128.9 (2C), 130.0 (2C), 133.5 (2C), 158.9 (2C); Melting Point: 186-187 °C; HRMS (APCI+) Calcd. for $C_{26}H_{24}N_2O_2$ (M): 396.1832; Found: 396.1850.



1,5-bis(4-Methoxybenzyl)-2,3,6,7-tetraphenylbenzo[1,2-*b*:4,5-*b'*]dipyrrole (4b): After the cyclization reaction, NMP (0.4 mL) was added. Iodobenzene (0.10 mL, 184 mg, 0.90 mmol) and bis[(diisopropylphenyl)imidazolyldiene]-(3-chloropyridyl)palladium(II) (PEPPSI-*i*Pr) (14 mg, 0.02 mmol) were sequentially added. The reaction mixture was stirred at 100 °C for 14 h, and then it was quenched with aq. NH_4Cl . The organic phase was extracted with chloroform (3×5 mL). Then the reaction mixture was passed over a pad of Florisil and the solvent was removed in *vacuo* to afford a dark black oily product. The yield (40%) was determined by ^1H NMR using tetrachloroethane (δ 7.26, singlet, 2H) as an internal standard. A sample of pure product was obtained as a white solid after purification by GPC using chloroform as an eluent. ^1H NMR (500 MHz, CDCl_3): δ 3.76 (s, 6H), 5.24 (s, 4H), 6.77 (d, J = 6.3 Hz, 4H), 6.96 (d, J = 6.9 Hz, 4H), 7.12-7.17 (m, 2H), 7.26-7.29 (m, 18H), 7.62 (s, 2H). ^{13}C NMR (125 MHz, CDCl_3): δ 47.3 (2C), 55.2 (2C), 98.9 (2C), 113.9 (4C), 114.4 (2C), 125.2 (2C), 124.5 (2C), 127.6 (4C), 127.9 (2C), 128.1 (4C), 128.2 (4C), 129.8 (4C), 130.6 (2C), 131.1 (4C), 132.3 (2C), 134.8 (2C), 135.7 (2C), 138.7 (2C), 158.5 (2C); Melting Point: 280-281 °C; HRMS (APCI+) Calcd. for $\text{C}_{50}\text{H}_{40}\text{N}_2\text{O}_2$ ($\text{M}+\text{H}$): 701.3168; Found: 701.3178.

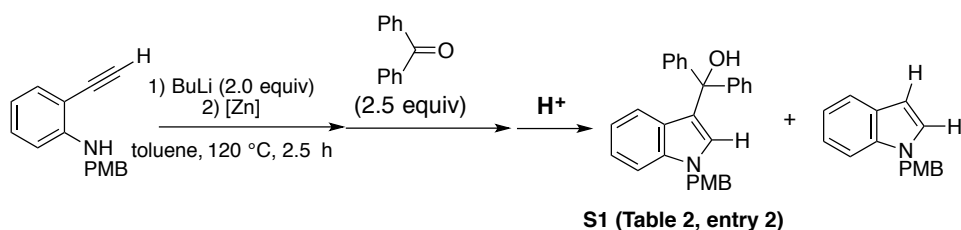
9. Cyclization with One Equivalent of Phenylzinc Bromide



2,3- d_2 -*N*-(4-Methoxybenzyl)indole (Table 2, entry 1): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et_2O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of PhZnBr in THF (0.43 mol/L, 0.93 mL, 0.40 mmol) was added. After the heating the mixture to room temperature, volatiles were removed in *vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2.5 h, to give a gray suspension product. The reaction was quenched with aq. NH_4Cl . The reaction mixture was extracted with ethyl acetate (3×5 mL), and the solvent was

removed in *vacuo*, which afforded a dark yellow oily product. The product was passed by over a pad of silica gel (eluent: 10% ethylacetate, 1% triethylamine in hexane) to give the title compound (94 mg, 98%) as a yellow oil. Deuterium incorporation was determined by ^1H NMR (solvent: $\text{THF-}d_8$), by comparison with the signals of *N*-(4-methoxybenzyl)indole (**2**).

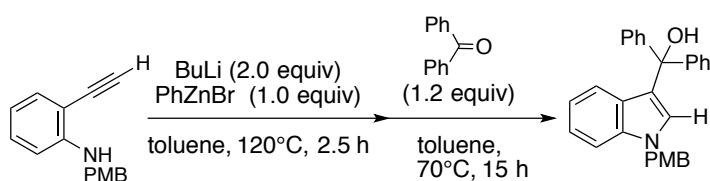
10. Reactivity of Dimetallic Intermediates



[Zn]	yield of S1 (%) ^a
ZnCl ₂ (2.0 equiv)	2
ZnCl ₂ (1.0 equiv)	18
PhZnBr (1.0 equiv)	63

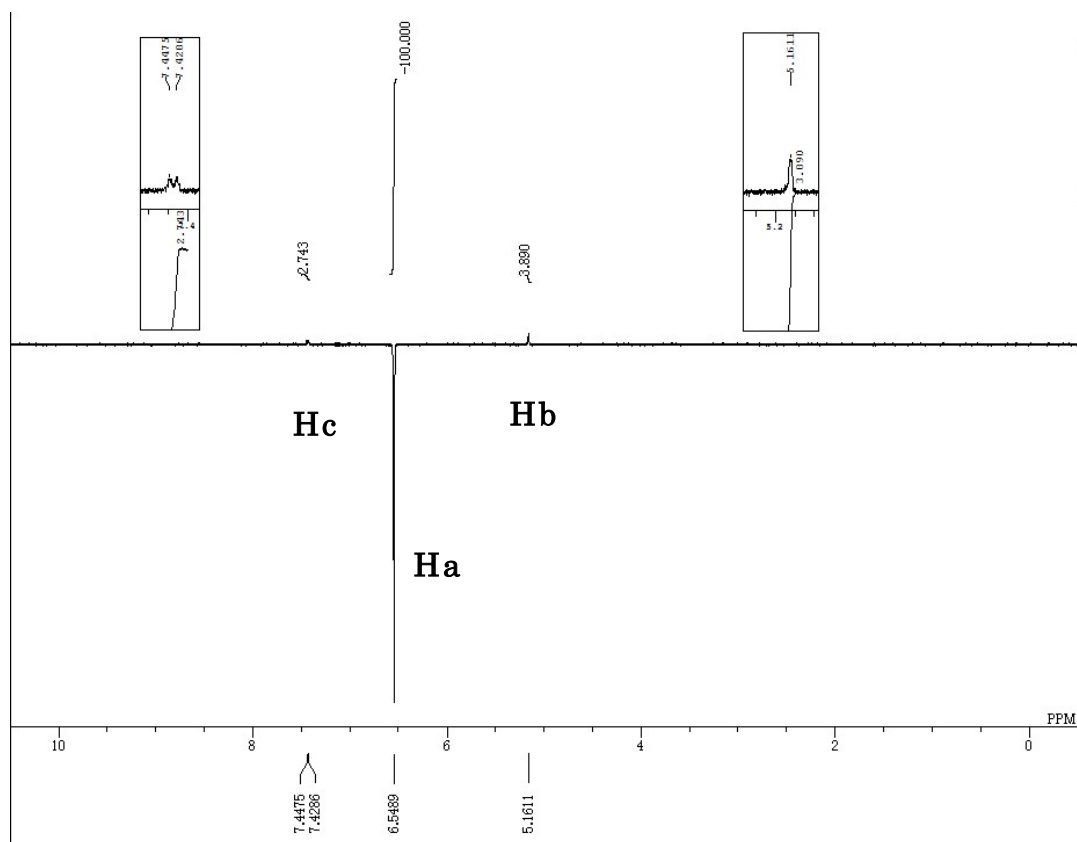
^a NMR yield, (tetrachloroethane as an internal standard)

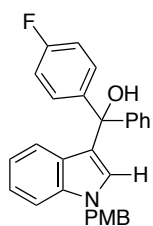
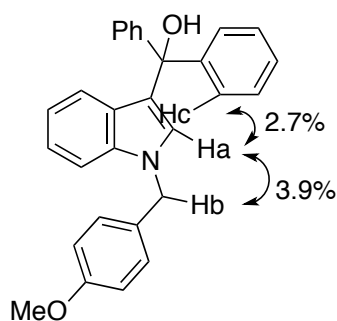
11. Reaction of Intermediate B² with Electrophiles



(1-(4-Methoxybenzyl)-1H-indol-3-yl)diphenylmethanol (Table 2, entry 2): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et_2O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of PhZnBr in THF (0.43 mol/L, 0.93 mL, 0.40 mmol) was added. After the heating the mixture to room temperature, volatiles were removed in *vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2.5 h, which afforded a gray suspension product. After cooling the reaction mixture at room temperature, benzophenone (88 mg, 0.48 mmol) was added. The reaction mixture was stirred at 70 °C for 15 h, and was quenched with NH_4Cl . The reaction mixture was

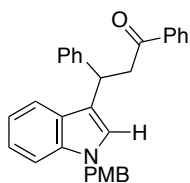
extracted with AcOEt, and the solvent was removed in *vacuo* to afford a dark yellow oily product. The product was purified by silica gel column chromatography (eluent: 20% ethyl acetate, 1% triethylamine in hexane) to give the title compound (127 mg, 76%) as a white solid. 2-Substituted and 2,3-disubstituted product was not observed at all. Unsubstituted indole **2** was recovered in 18% (NMR). Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ¹H NMR (400 MHz, CDCl₃): δ 2.92 (s, 1H), 3.77 (s, 3H), 5.17 (s, 2 H), 6.55 (s, 1H), 6.81(d, *J* = 8.7 Hz, 2H), 6.96 (t, *J* = 8.0 Hz, 1H), 7.01 (d, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.24-7.33 (m, 8H), 7.43-7.45 (m, 4H) ¹³C NMR (100MHz, CDCl₃): δ 49.5, 55.2, 78.4, 110.0, 114.0 (2C), 119.5, 121.6, 121.9, 122.0, 126.4, 126.8 (2C), 127.2 (4C), 127.8 (5C), 128.2, 128.9, 129.2, 130.0, 137.2, 146.5, 158.9; HRMS (APCI+) Calcd. for C₂₉H₂₅NO₂ (M): 419.1880; Found: 419.1888. The regiochemistry of the compound was determined by NOE experiments in CDCl₃. When signal Ha at δ = 6.54 (s, 1H) was irradiated, Hb at δ = 5.16 (s, 2 H), exhibited an enhancement by 3.9%, and Hc at δ = 7.44 (m, 4H) exhibited an enhancement by 2.7%.





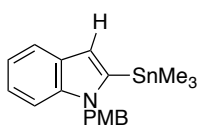
(4-Fluorophenyl)(1-(4-methoxybenzyl)-1*H*-indol-3-yl)(phenyl)methanol (Table 2, entry 3):

Obtained in 77% yield as a colorless oil. 2-Substituted and 2,3-disubstituted product was not observed at all. Unsubstituted indole **2** was recovered in 18% (NMR). Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ¹H NMR (400 MHz, CDCl₃): δ 2.97 (s, 1H), 3.71 (s, 3H), 5.10 (s, 2 H), 6.52 (s, 1H), 6.78(d, *J* = 8.7 Hz, 2H), 6.93-6.99 (m, 5H), 7.14 (t, *J* = 8.0 Hz, 1H), 7.22-7.30 (m, 5H), 7.37-7.41 (m, 4H) ¹³C NMR (100MHz, CDCl₃): δ 49.6, 55.2, 78.1, 110.1, 114.1 (2C), 114.4, 114.6, 119.6, 121.5, 121.9, 122.0, 126.2, 127.0 (2C), 127.1, 127.8 (2C), 127.9, 128.8, 128.9, 129.0, 129.1, 137.3, 142.4, 146.4, 159.0, 160.5, 163.0; HRMS (APCI+) Calcd. for C₂₉H₂₄FNO₂ (M): 437.1786; Found: 437.1797.



3-(1-(4-Methoxybenzyl)-1*H*-indol-3-yl)-1,3-diphenylpropan-1-one (Table 2, entry 4): Obtained in 83% yield as a white solid. 3-Substituted and 2,3-disubstituted product was not observed at all. Unsubstituted indole **2** was recovered in 5% (NMR). Deuterium incorporation was determined by using the same procedure, following by quenching with D₂O and GC MS analysis by comparison

with the isotope pattern of the corresponding protio compound. ^1H NMR (400 MHz, CDCl_3): δ 3.71-3.79 (m, 2H), 3.76 (s, 3H), 5.05 (t, $J=7.0$ Hz, 1H), 5.18 (s, 2H), 6.79 (d, $J=8.7$ Hz, 2H), 6.91 (s, 1H), 6.96-7.00 (m, 3H), 7.08-7.16 (m, 2H), 7.19-7.27 (m, 3H), 7.34 (d, $J=7.3$ Hz, 2H), 7.38-7.43 (m, 3H), 7.51 (t $J=7.3$ Hz, 1H), 7.89 (d, $J=7.8$ Hz, 2H) ^{13}C NMR (100MHz, CDCl_3): δ 38.2, 45.1, 49.3, 55.1, 109.6, 114.0 (2C), 118.2, 119.0, 119.6, 121.7, 125.4, 126.2, 127.2, 127.7 (2C), 127.9 (2C), 128.0 (2C), 128.3 (2C), 128.4 (2C), 129.5, 132.9, 136.8, 137.0, 144.2, 158.8, 198.5; HRMS (APCI+) Calcd. for $\text{C}_{31}\text{H}_{27}\text{NO}_2$ (M): 445.2036; Found: 445.2038.

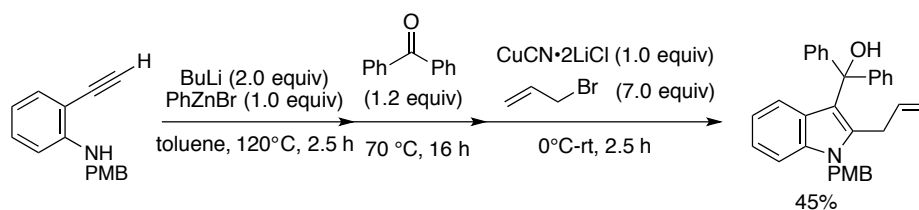
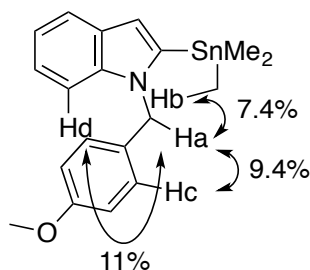
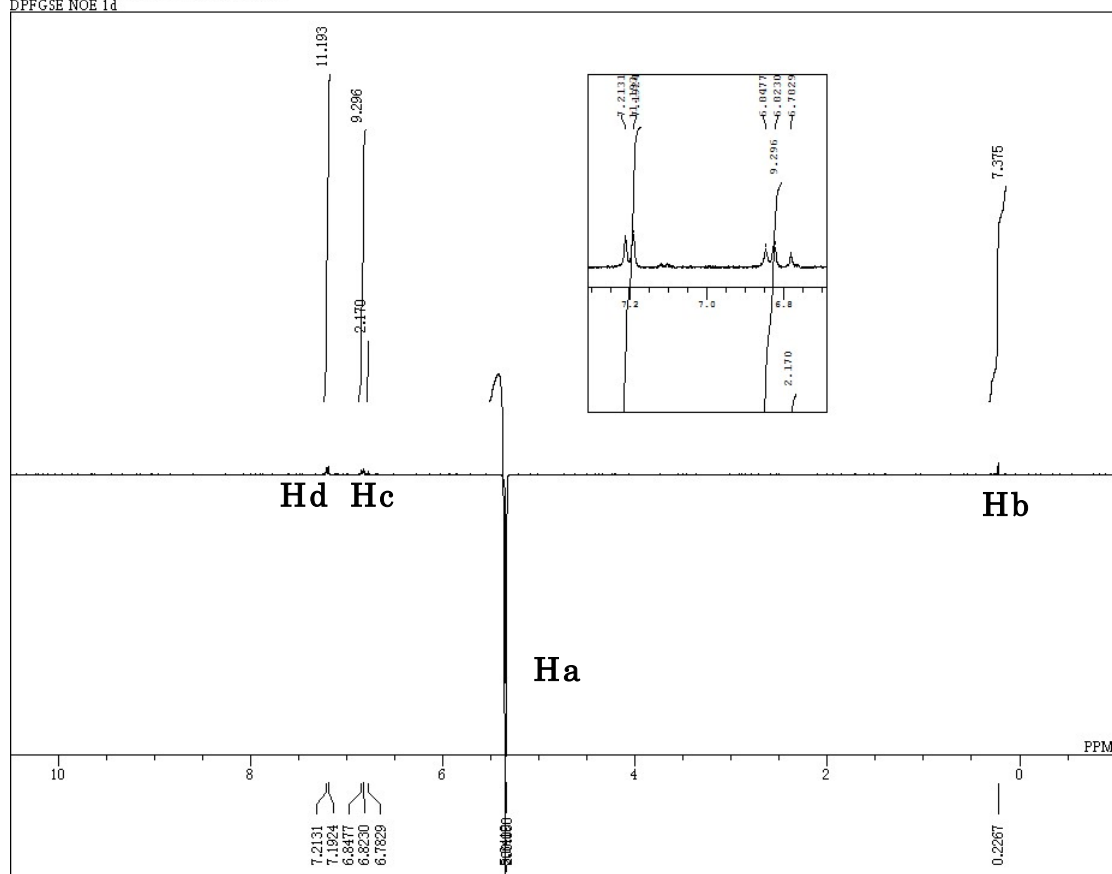


1-(4-Methoxybenzyl)-2-(trimethylstannyl)-1H-indole (Table 2, entry 5): After the cyclization reaction, trimethyltin chloride in THF (1 mol/L, 0.24 mL, 0.24 mmol) was added and the reaction mixture was stirred at room temperature. The title compound was obtained in 55% yield as a yellow oil after purification by GPC using chloroform as an eluent. 3-Substituted and 2,3-disubstituted product was not observed at all. Unsubstituted indole **2** was recovered in 40% (NMR). Deuterium incorporation was determined by using the same procedure, following by quenching with D_2O and GC MS analysis by comparison with the isotope pattern of the corresponding protio compound. ^1H NMR (400 MHz, CDCl_3): δ 0.23 (s, 9H), 3.73 (s, 3H), 5.34 (s, 2H), 6.69 (s, 1 H), 6.77 (d, $J=8.9$ Hz, 2H), 6.84 (d, $J=8.7$ Hz, 2H), 7.04-7.12 (m, 2H), 7.19 (m, 1H), 7.61 (m, 1H) ^{13}C NMR (100MHz, CDCl_3): δ -8.7 (3C), 50.3, 55.2, 109.45, 111.9, 114.1 (2C), 119.1, 120.0, 121.4, 127.0 (2C), 129.1, 130.3, 139.5, 142.5, 158.8; HRMS (APCI+) Calcd. for $\text{C}_{19}\text{H}_{23}\text{NOSn}$ (M): 401.0796; Found: 401.0798. The regiochemistry of the compound was determined by NOE experiments in CDCl_3 . When signal Ha at $\delta=5.34$ (s, 2H) was irradiated, Hb at $\delta=0.23$ (s, 9H) exhibited an enhancement by 7.4%, Hc at $\delta=6.84$ (d, $J=8.7$ Hz, 2H) exhibited an enhancement by 9.4%, and Hd at $\delta=7.19$ (m, 1H) exhibited an enhancement by 11%.

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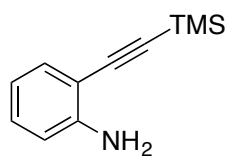
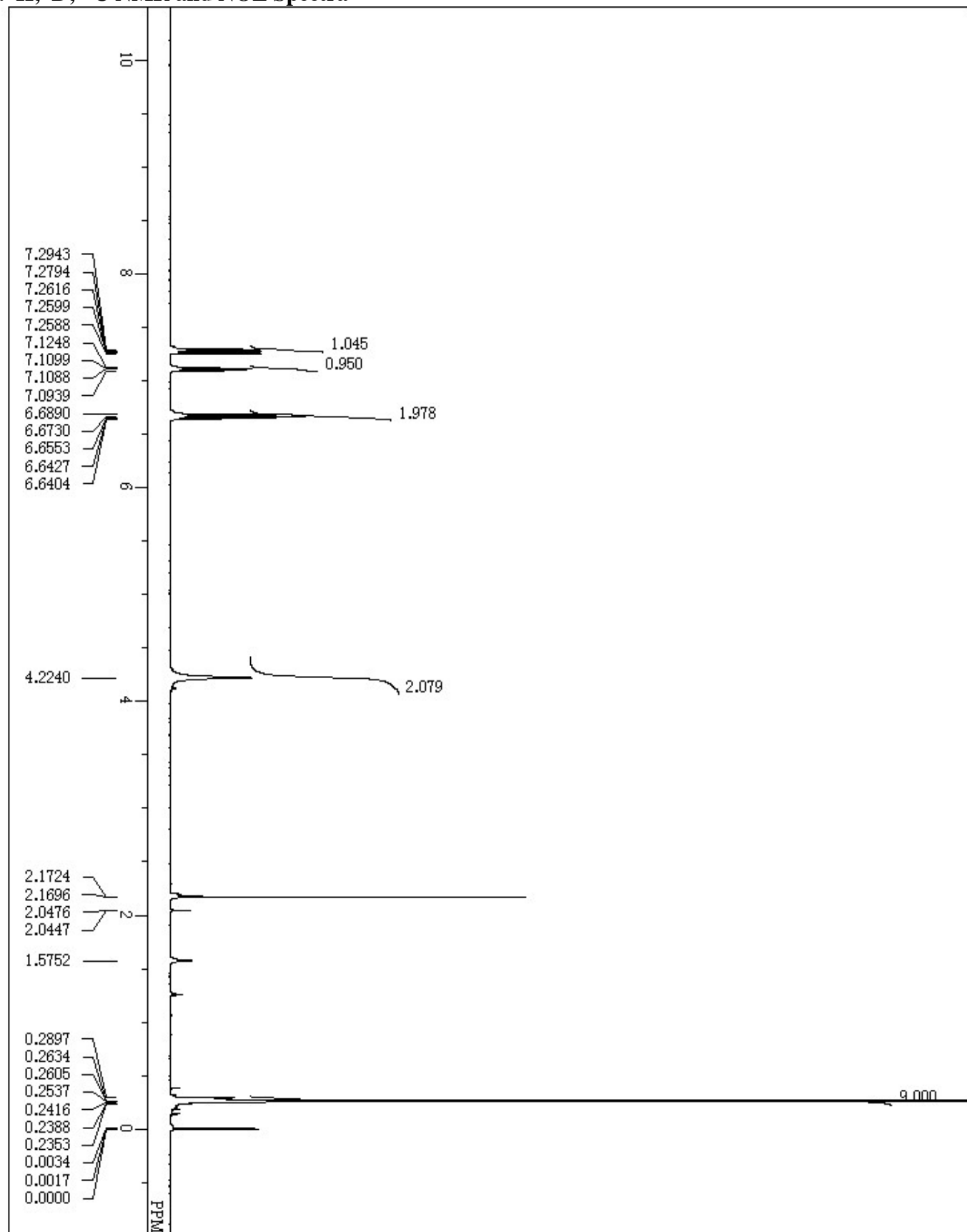
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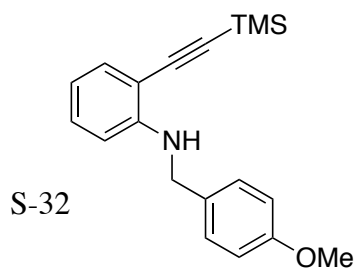
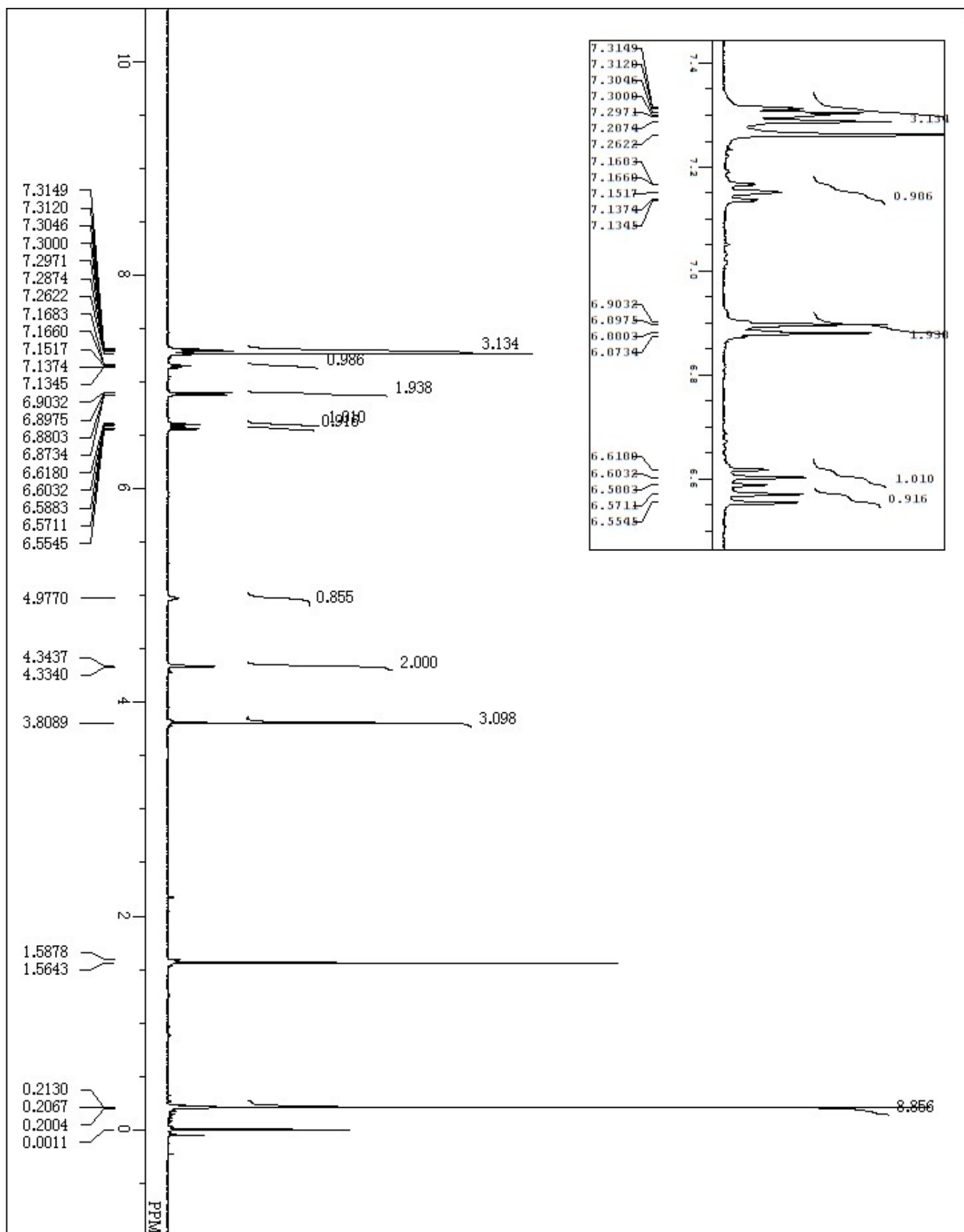


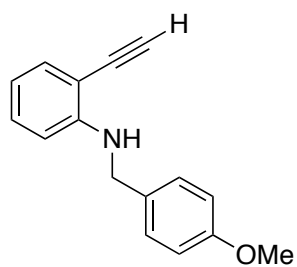
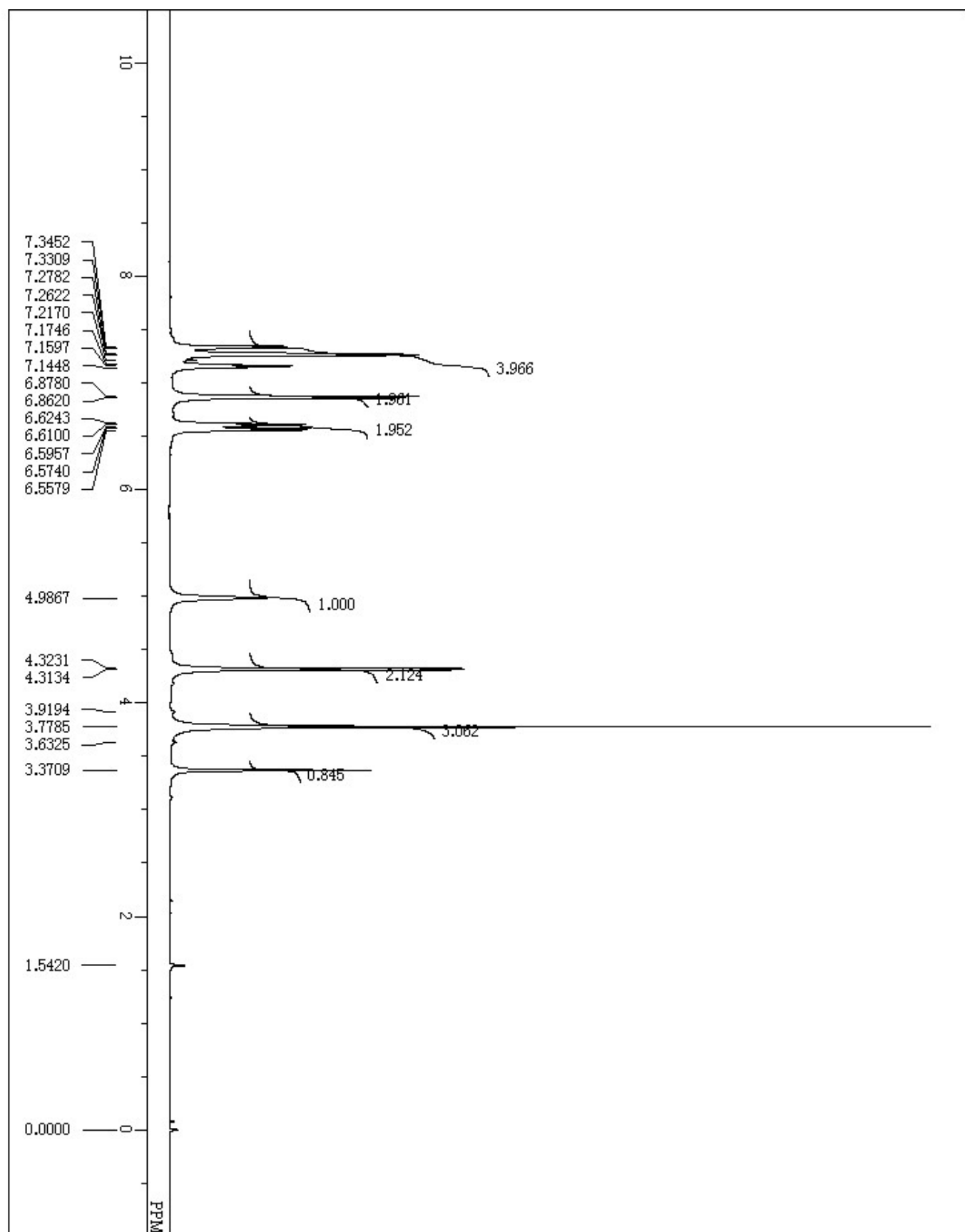
(1-(4-Methoxybenzyl)(2-allyl)-1*H*-indol-3-yl)diphenylmethanol (Table 2, entry 6): In an oven-dried Schlenk tube, 2-ethynyl-*N*-(4-methoxybenzyl)aniline **1** (95 mg, 0.40 mmol) was dissolved in Et₂O (0.8 mL), and BuLi in hexane (1.59 mol/L, 0.52 mL, 0.82 mmol) was added at 0 °C. A solution of PhZnBr in THF (0.43 mol/L, 0.93 mL, 0.40 mmol) was added. After the heating

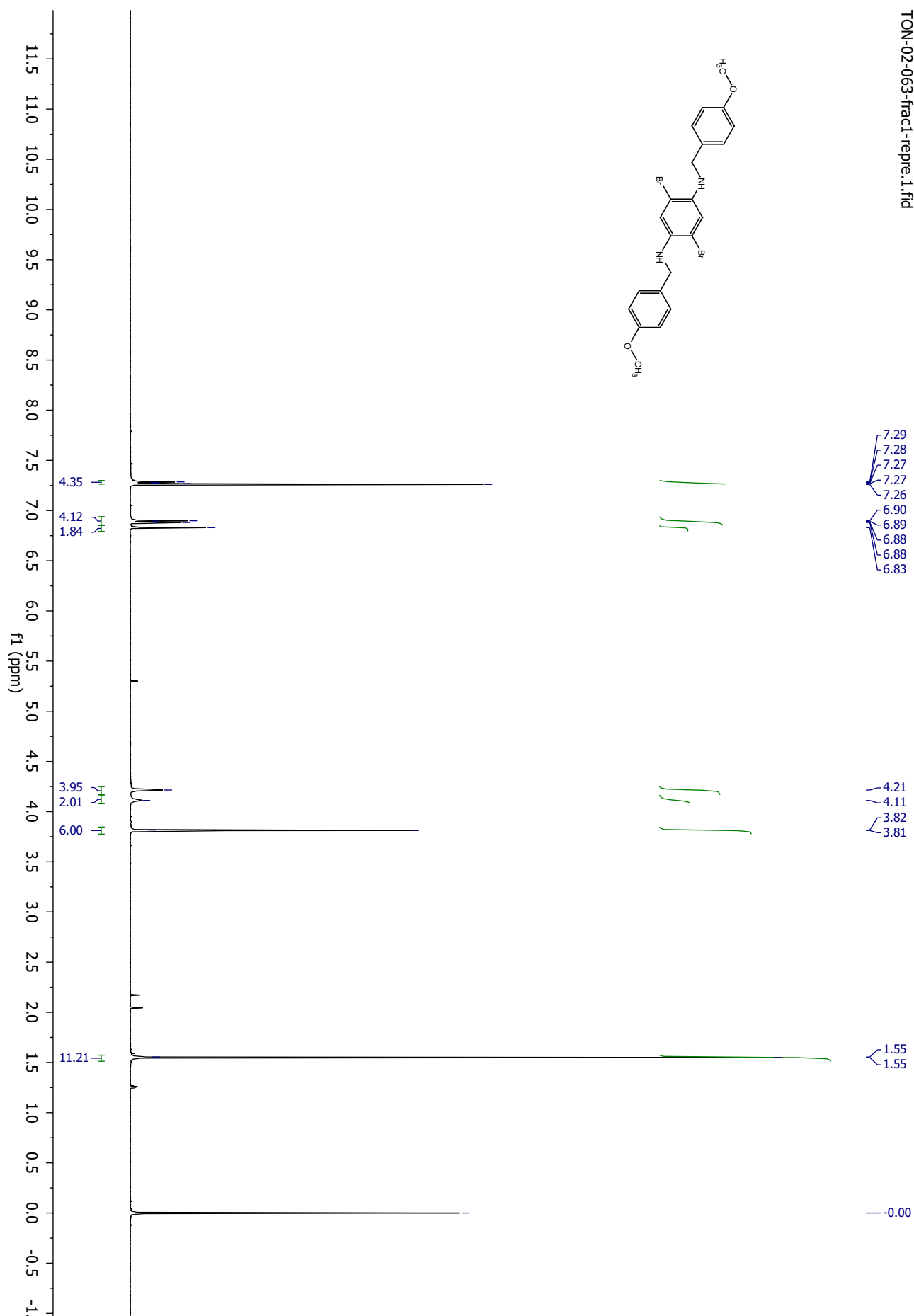
the mixture to room temperature, volatiles were removed in *vacuo*, and then toluene (0.8 mL) was added. The resulting mixture was stirred at 120 °C for 2.5 h, which afforded a gray suspension product. After cooling the reaction mixture at room temperature, benzophenone (88 mg, 0.48 mmol) was added. The reaction mixture was stirred at 70 °C for 16 h. After cooling the reaction mixture at 0 °C, CuCN•2LiCl in THF (1 mol/L, 0.40 mL, 0.40 mmol), then allyl bromide (0.24 mL, 0.34 g, 2.8 mmol) were sequentially added. The reaction mixture was stirred at room temperature for 2.5 h, and was quenched with aq. NH₄Cl. The reaction mixture was extracted with ethyl acetate (5×2 mL), and the solvent was removed in *vacuo*. The product was purified by silica gel column chromatography (eluent: 15% ethyl acetate and 1% triethylamine in hexane) to give the title compound (82 mg, 45%) as an orange oil. Other byproducts detected were monoallylindole (38%), diallylindole (6%), and a trace amount of (indol-3-yl)diphenylmethanol. ¹H NMR (400 MHz, CDCl₃): δ 3.03 (s, 1H), 3.13-3.14 (m, 2 H), 3.75 (s, 3H), 4.80 (dd, *J* = 17 Hz, 1.5 Hz, 1H), 4.97 (dd, *J* = 17 Hz, 1.5 Hz, 1H), 5.24 (s, 2H), 5.70 (m, 1 H), 6.42 (d, *J* = 8.2 Hz, 1H), 6.77-6.85 (m, 5 H), 7.03 (m, 1H), 7.20 (d, *J* = 8.2 Hz, 1H), 7.27-7.40 (m, 10H); ¹³C NMR(100MHz,CDCl₃):δ 29.7, 45.7, 55.2, 79.6, 109.3, 114.1 (2C), 115.7, 118.1, 119.4, 121.1, 126.5, 126.9 (2C), 127.1 (2C), 127.6 (4C), 127.7 (4C), 127.9, 128.5, 129.7, 136.2, 136.6, 147.2 (2C), 158.7 ; HRMS (APCI+) Calcd. for C₃₂H₂₉NO₂ (M): 459.2193; Found: 459.216

12. ^1H , ^2D , ^{13}C NMR and NOE Spectra

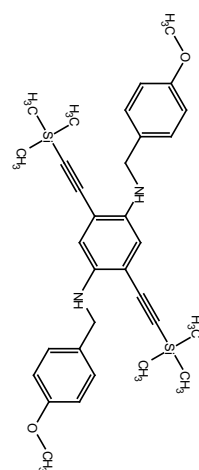








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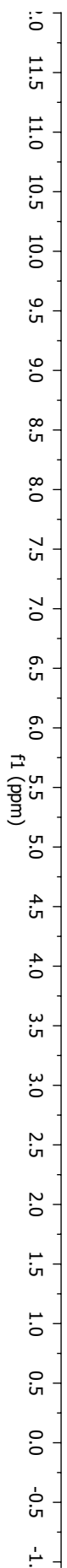
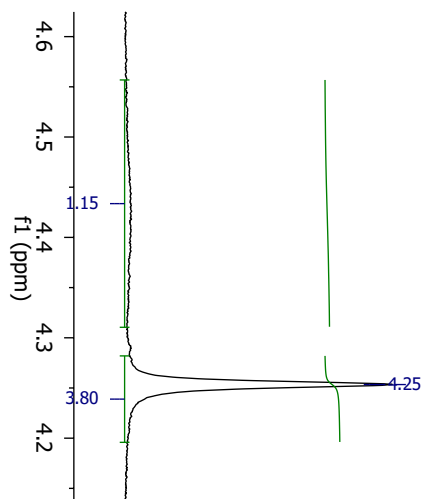
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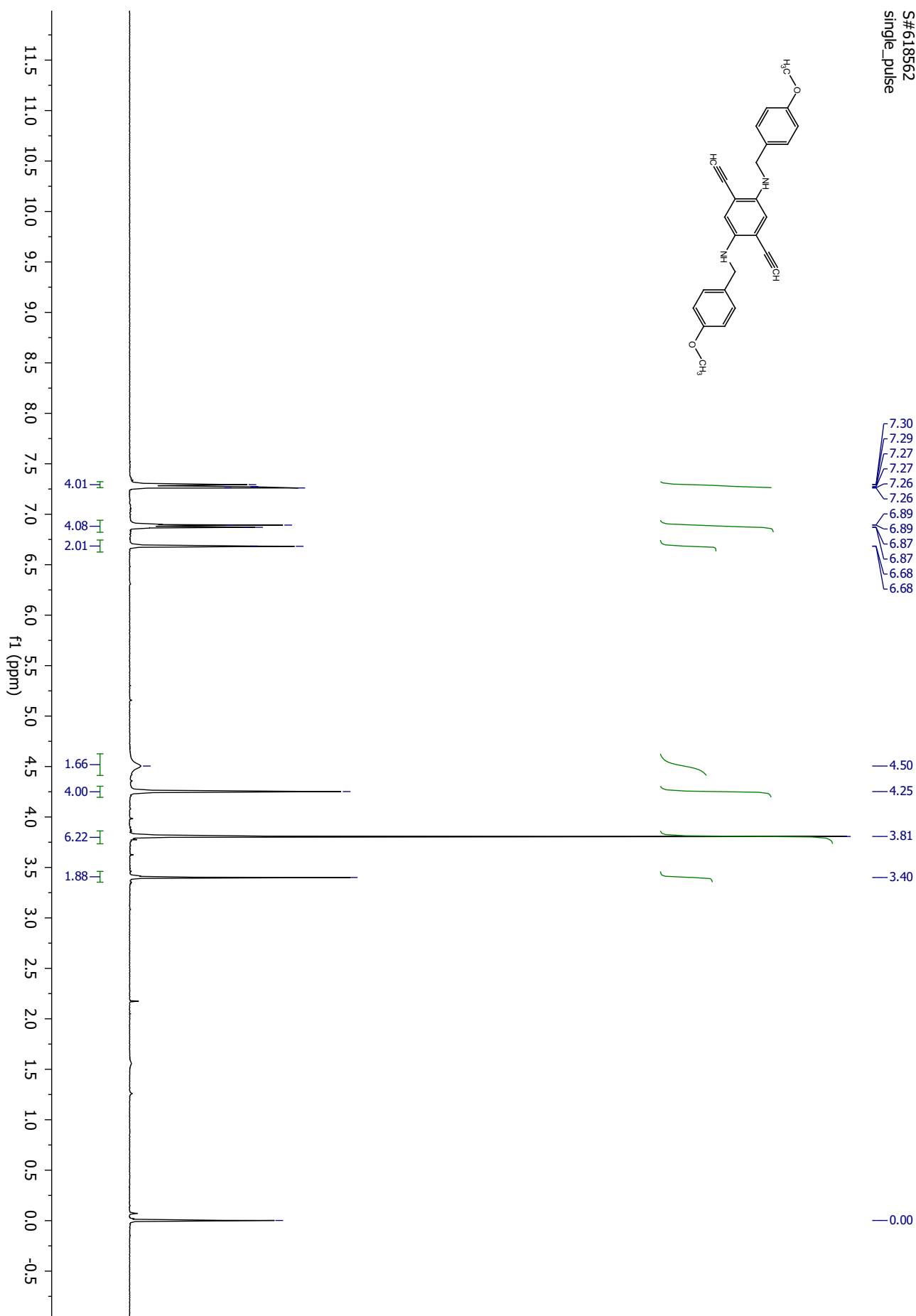
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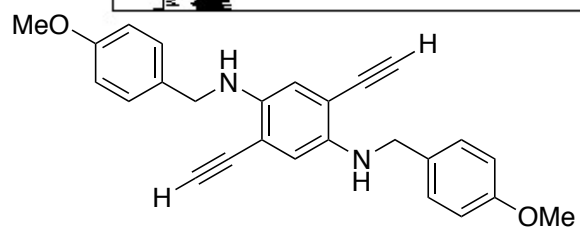
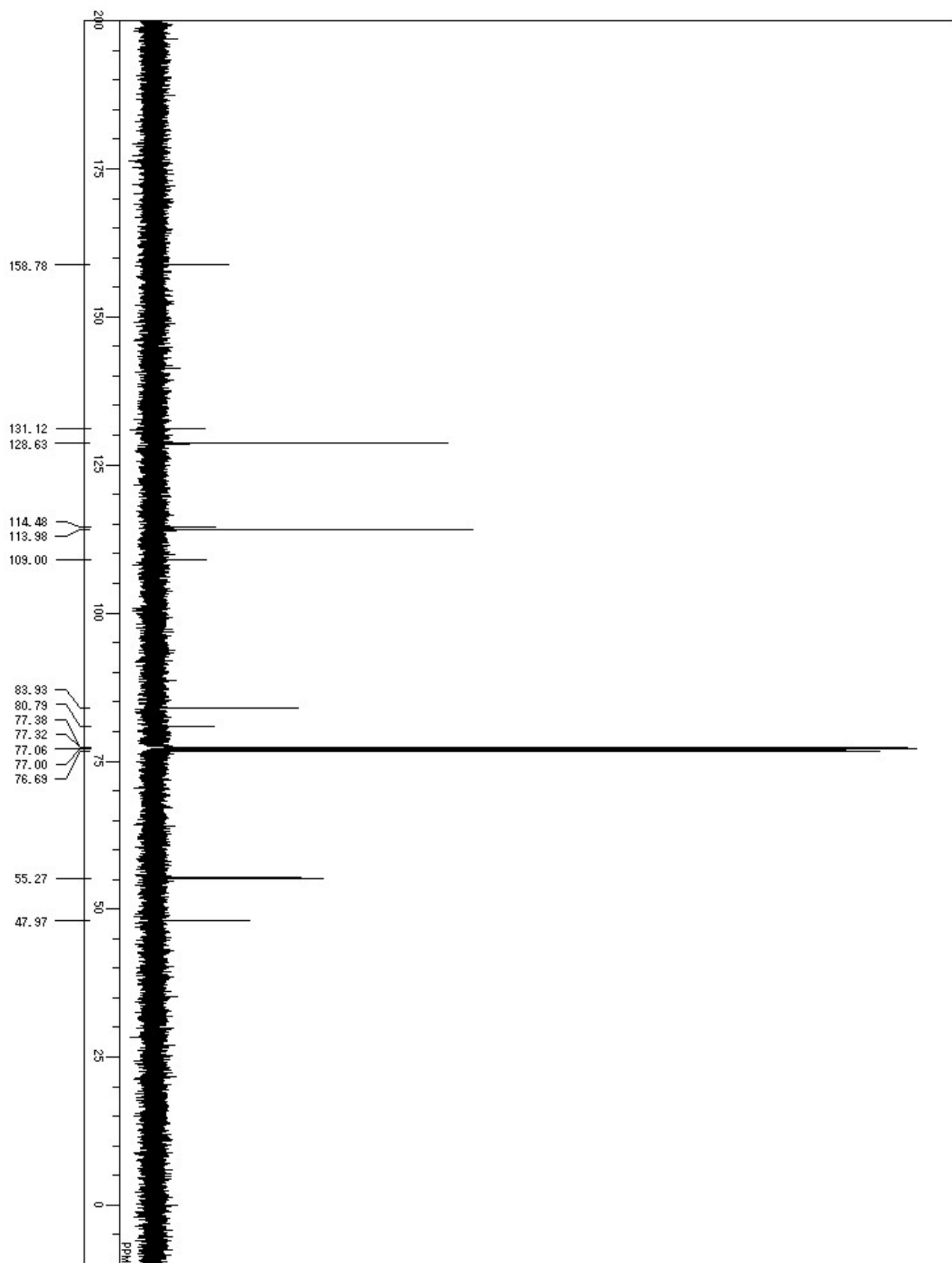
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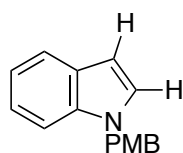
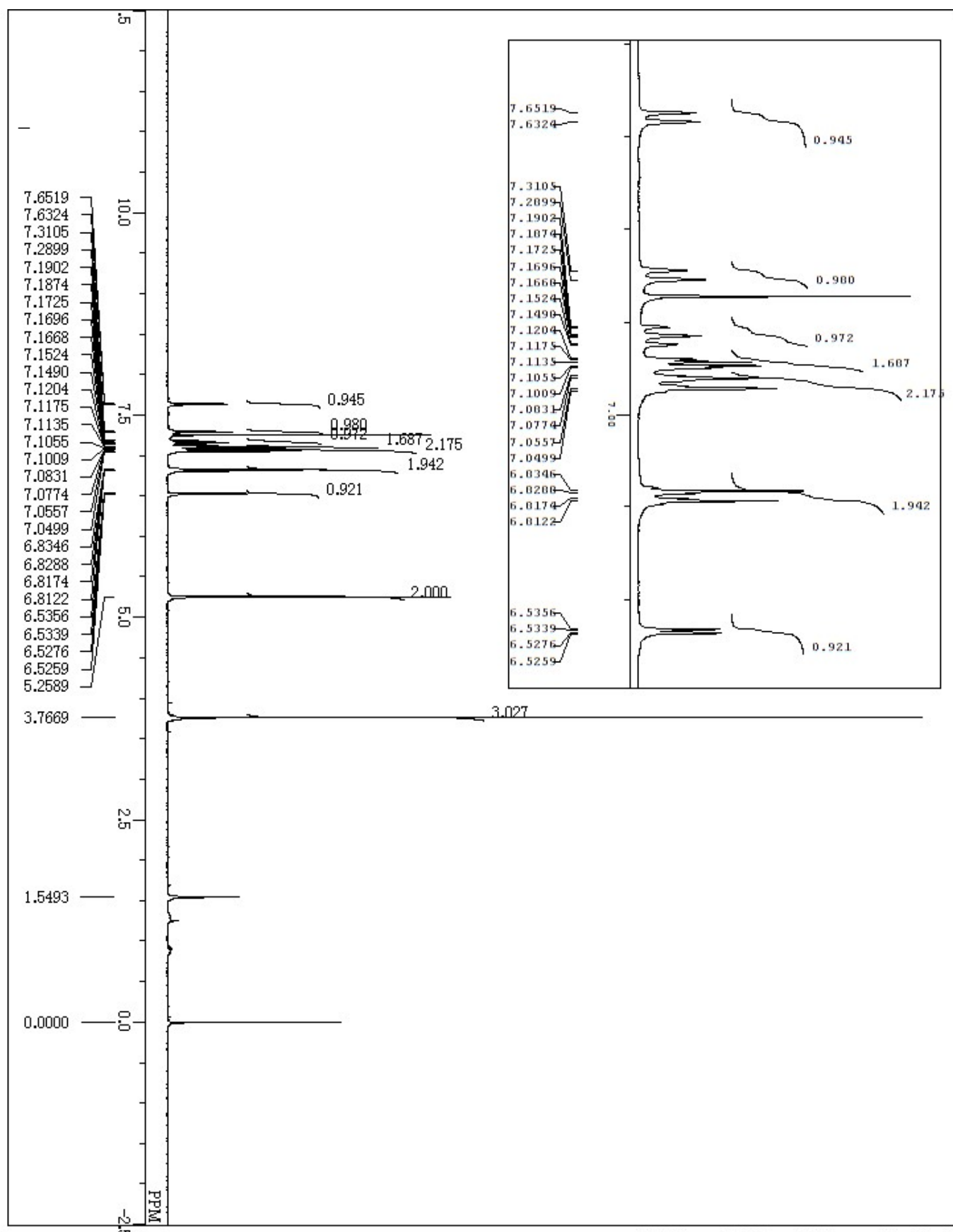
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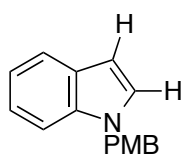
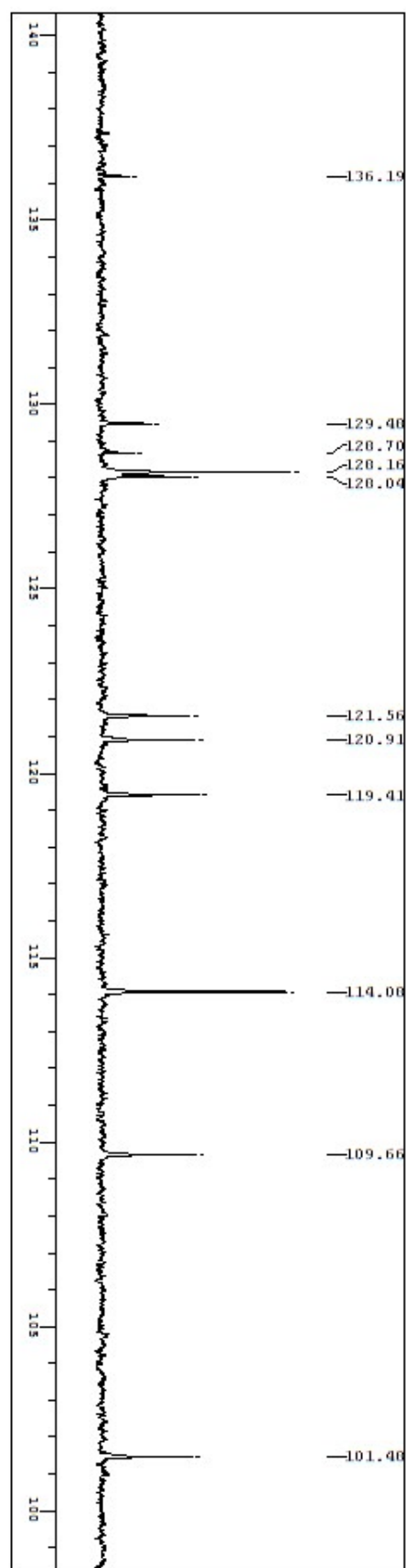
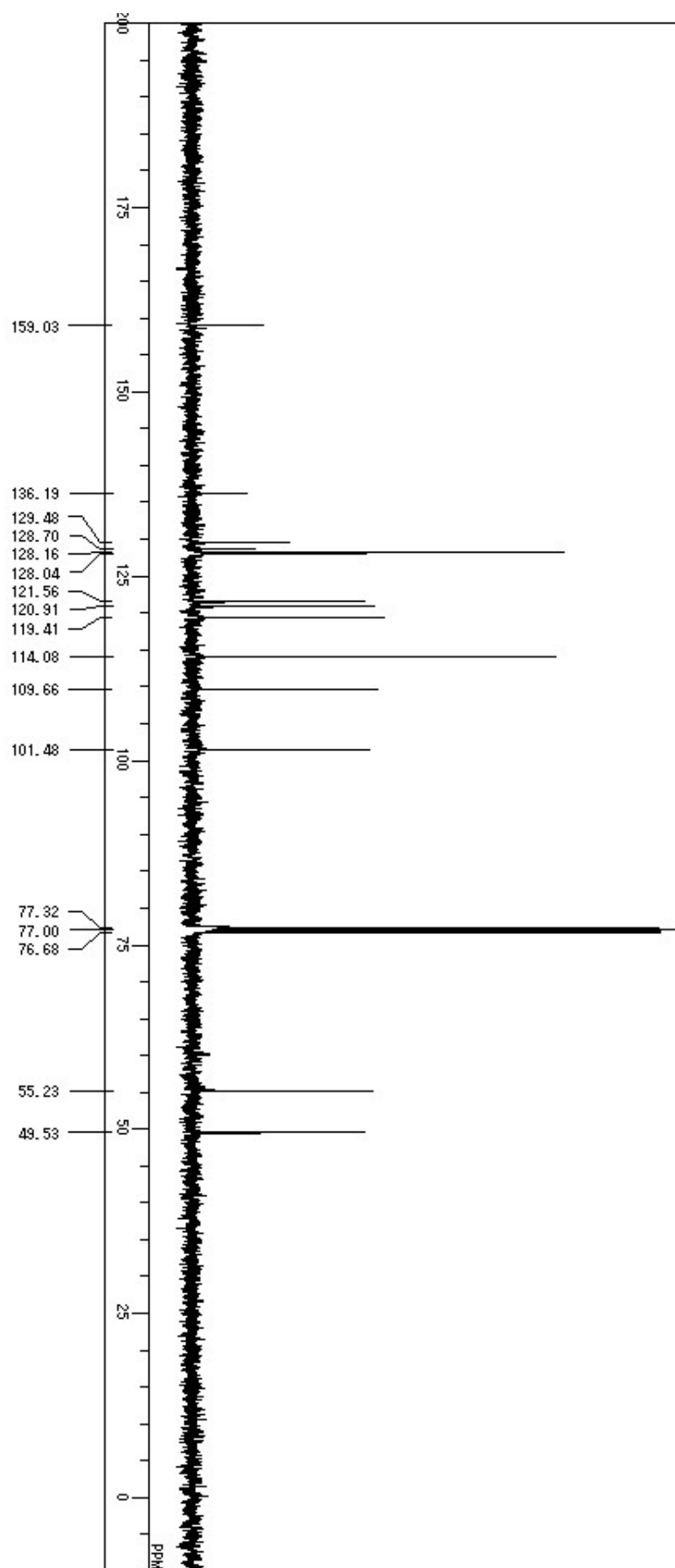


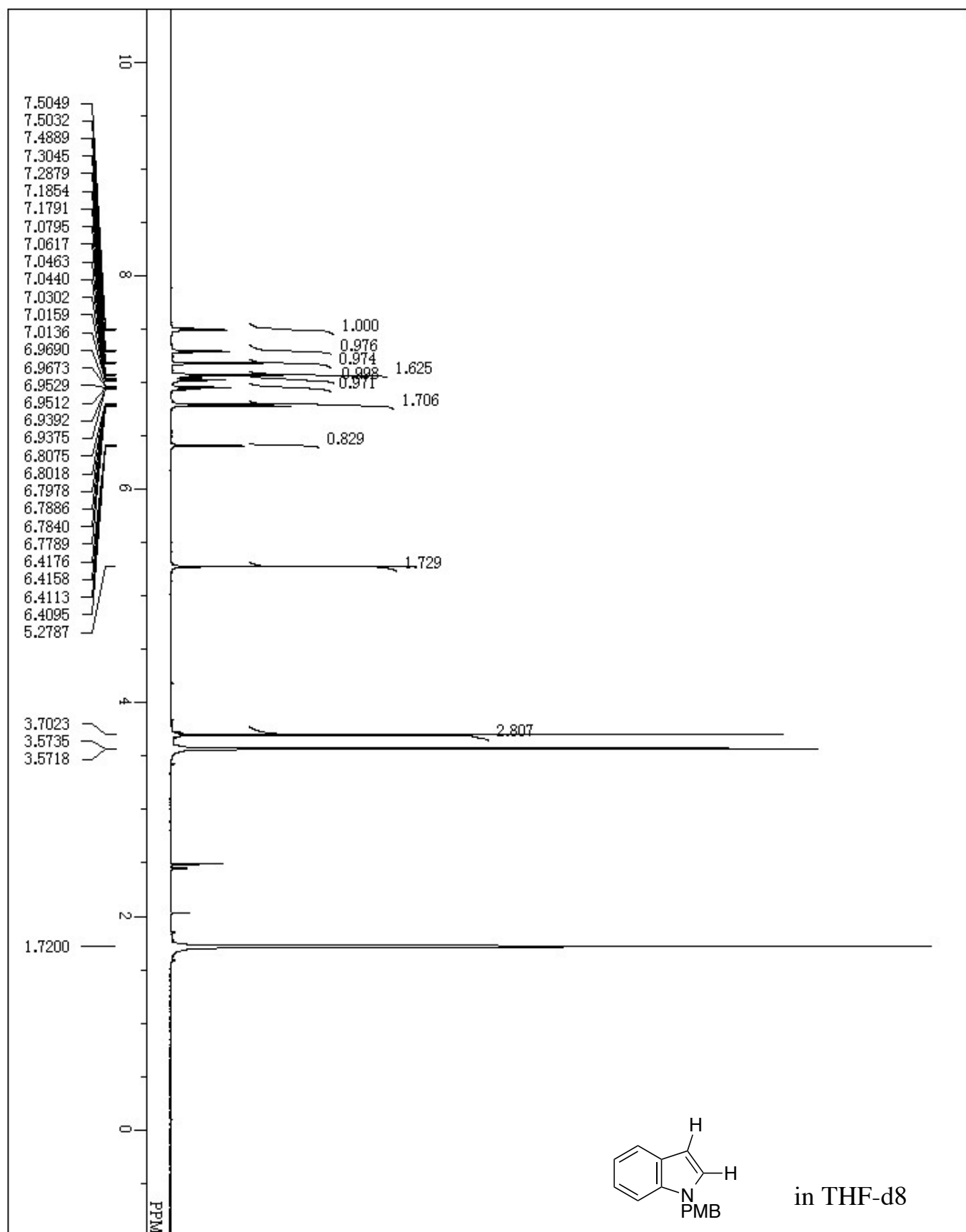
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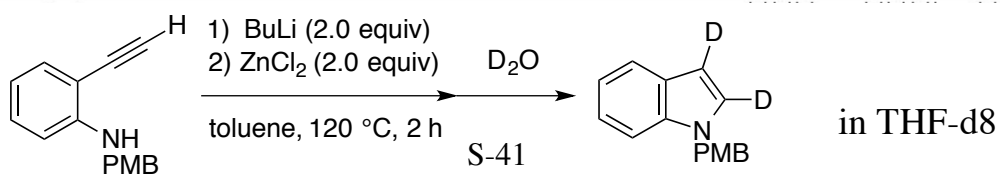
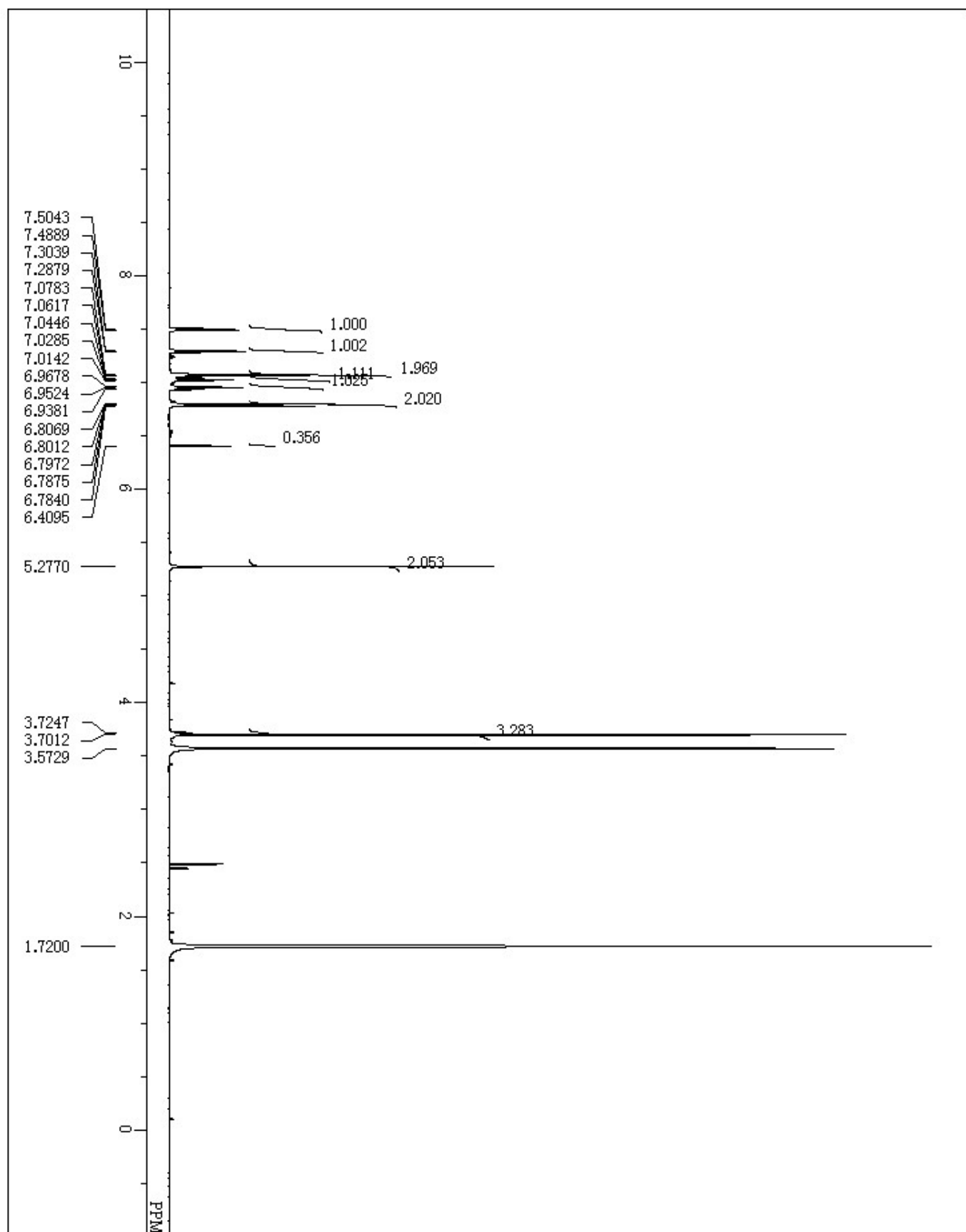


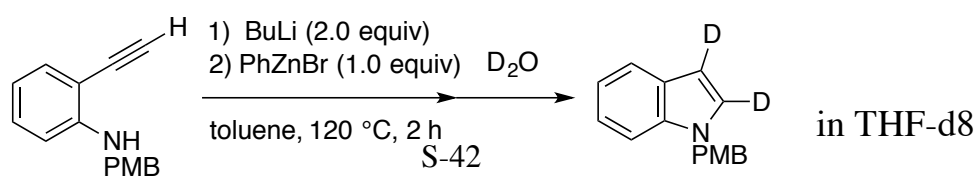
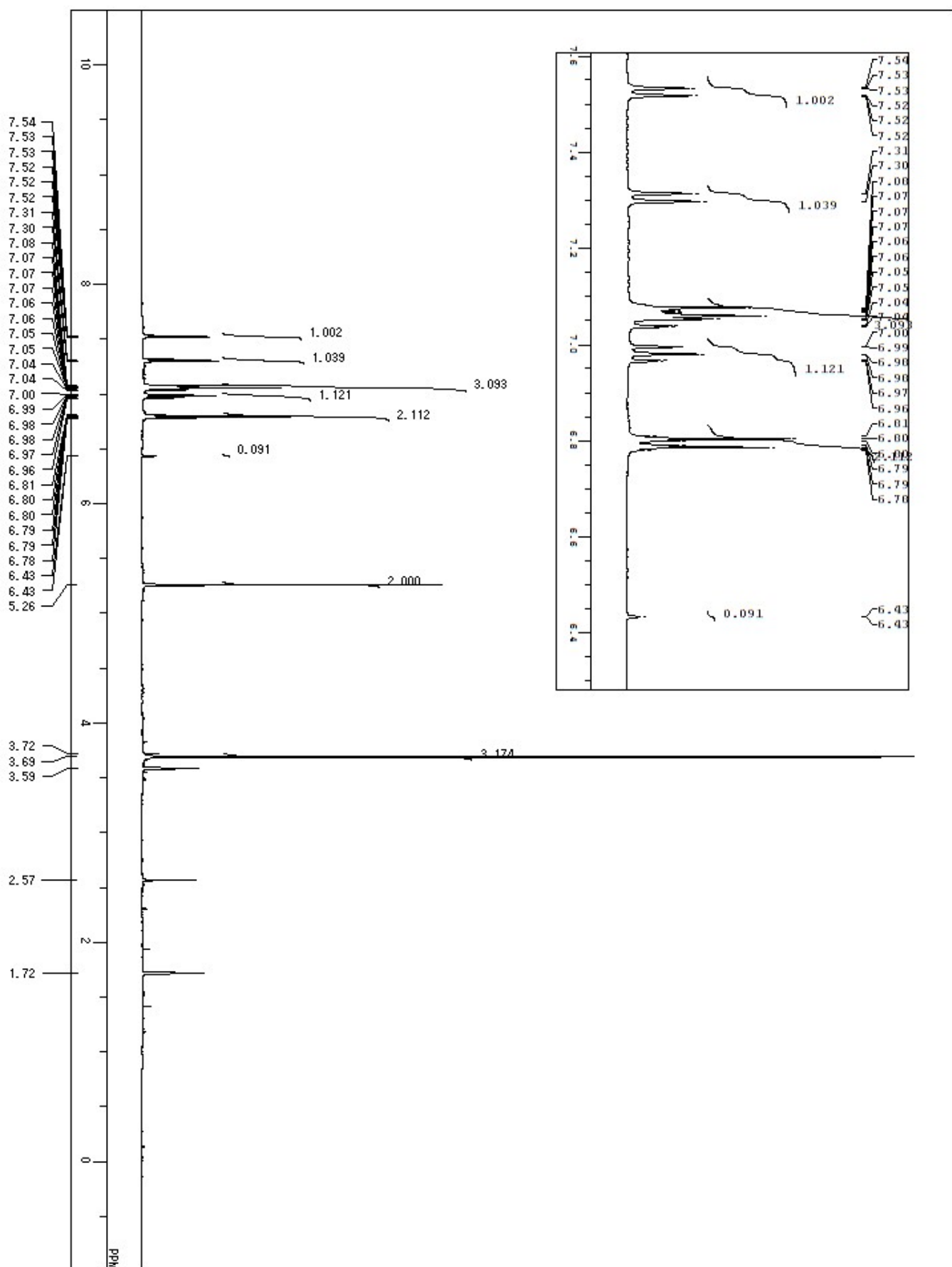


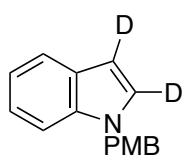
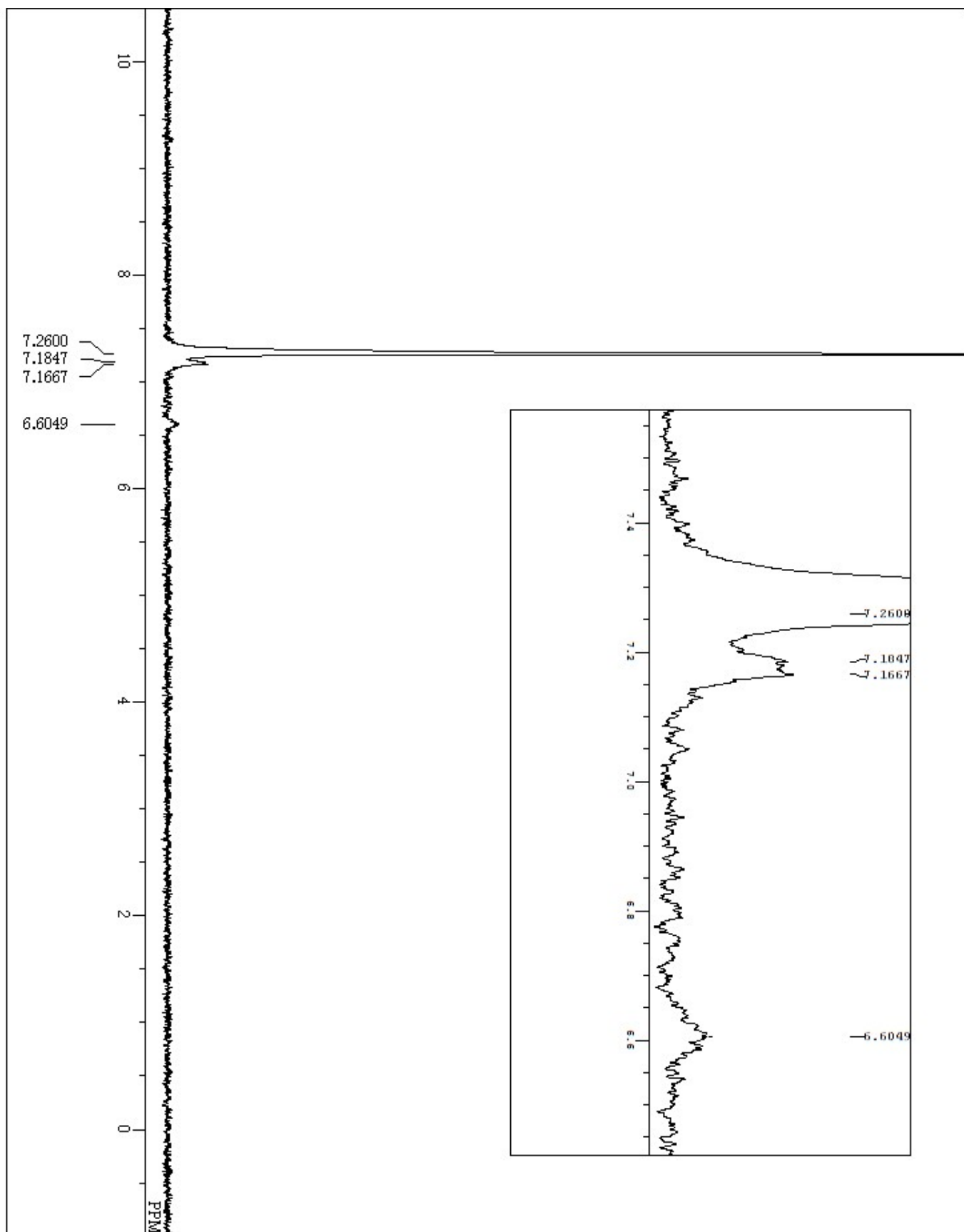




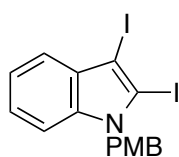
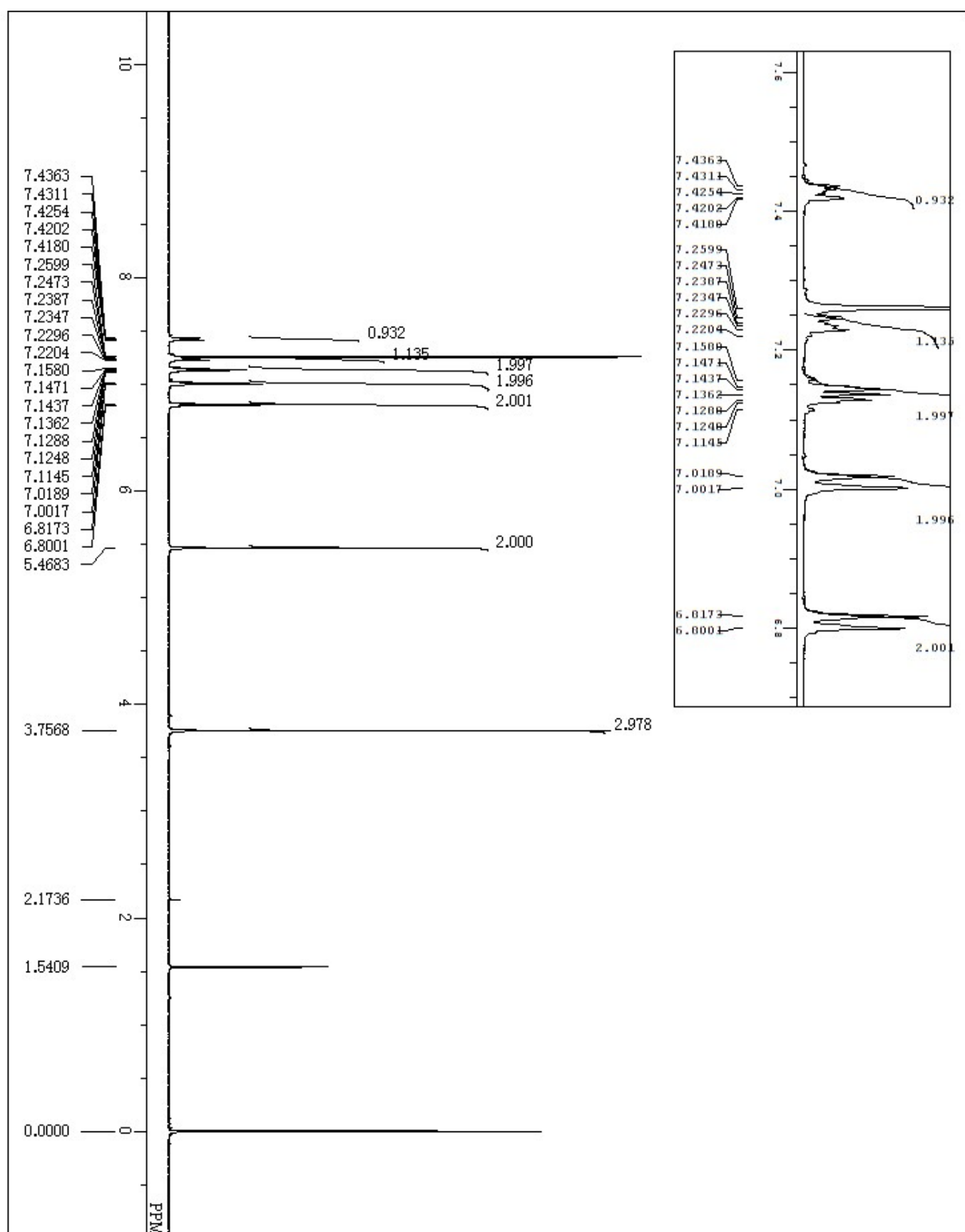


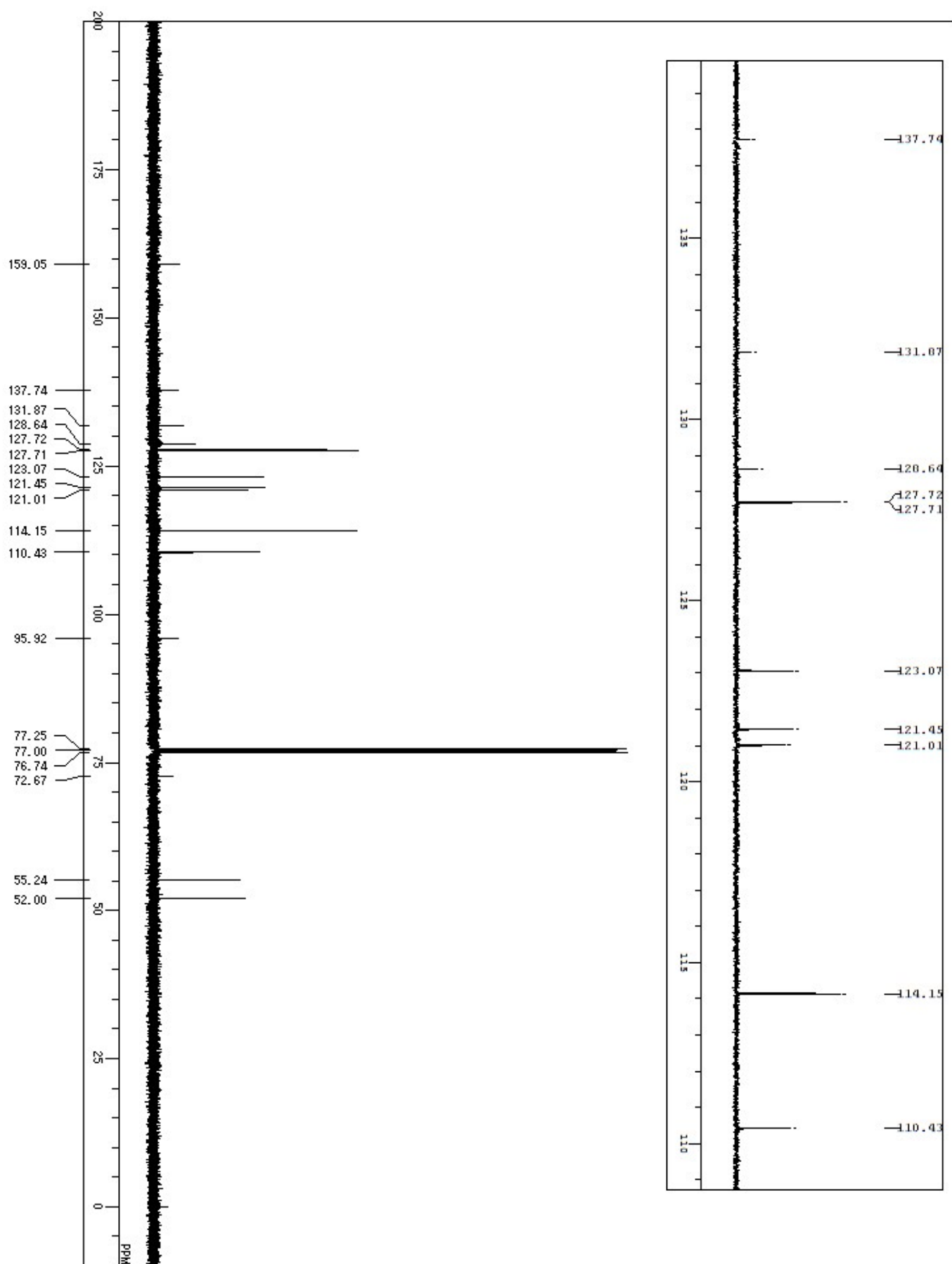


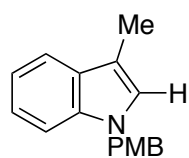
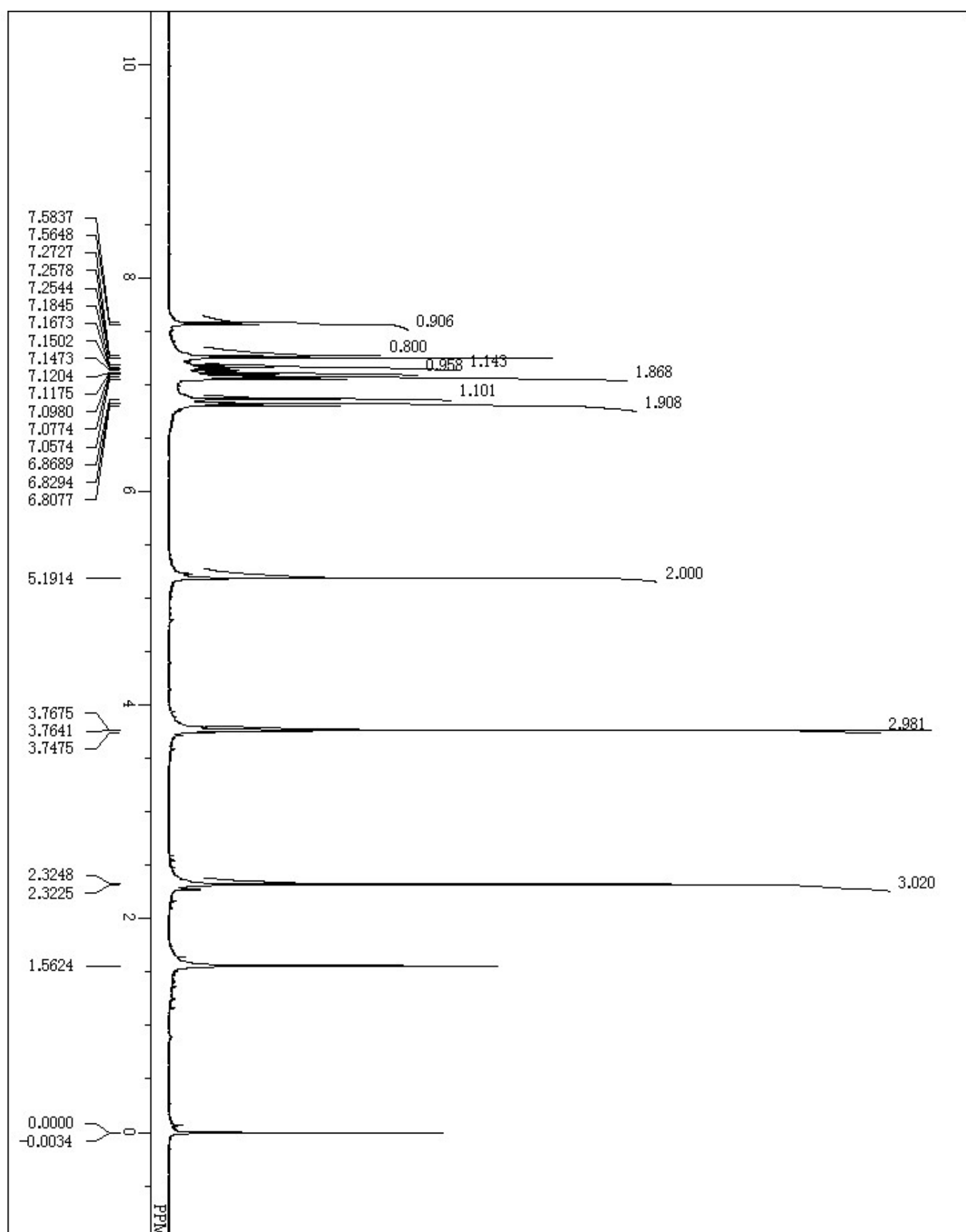


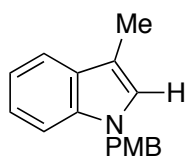
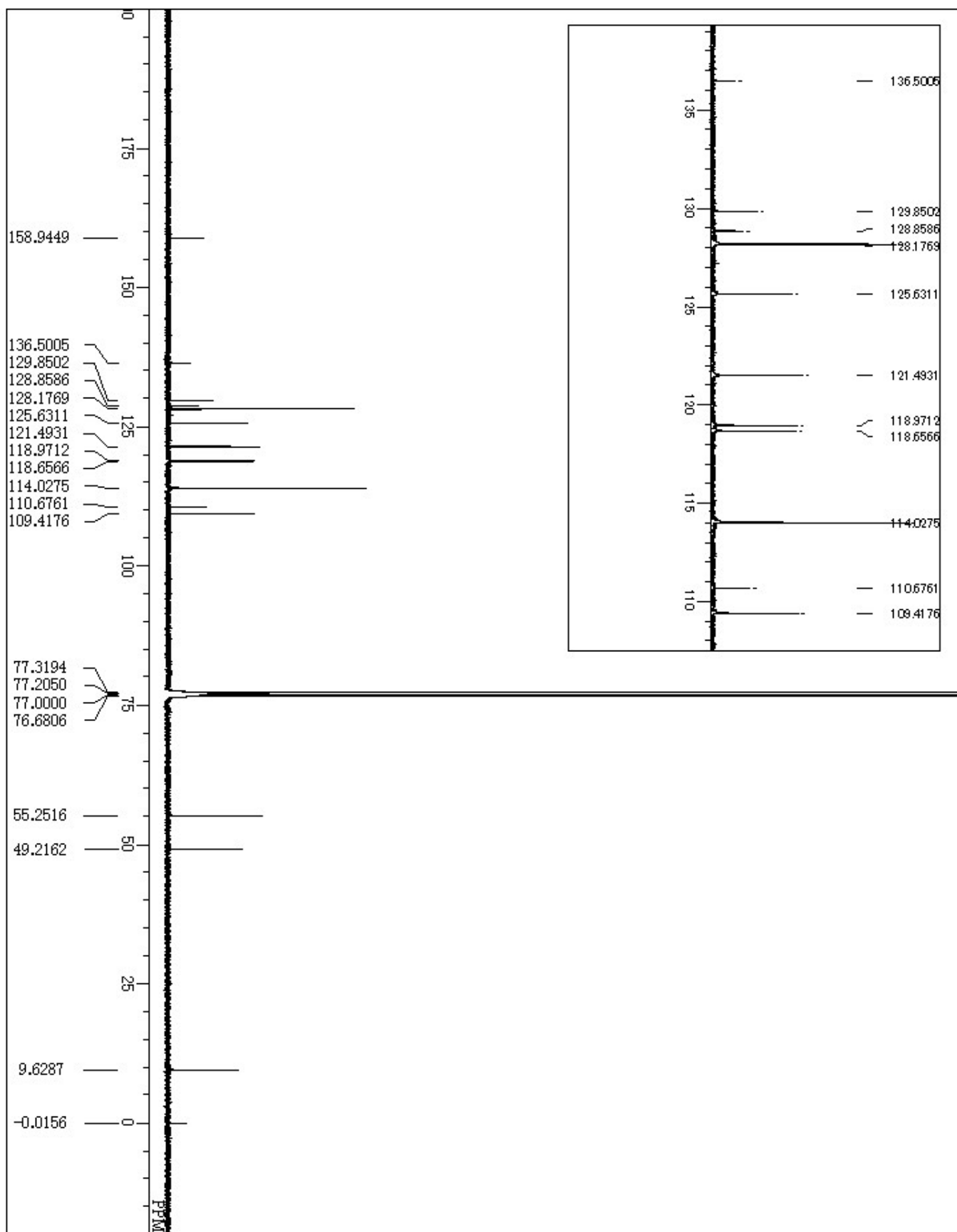


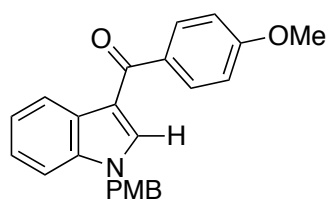
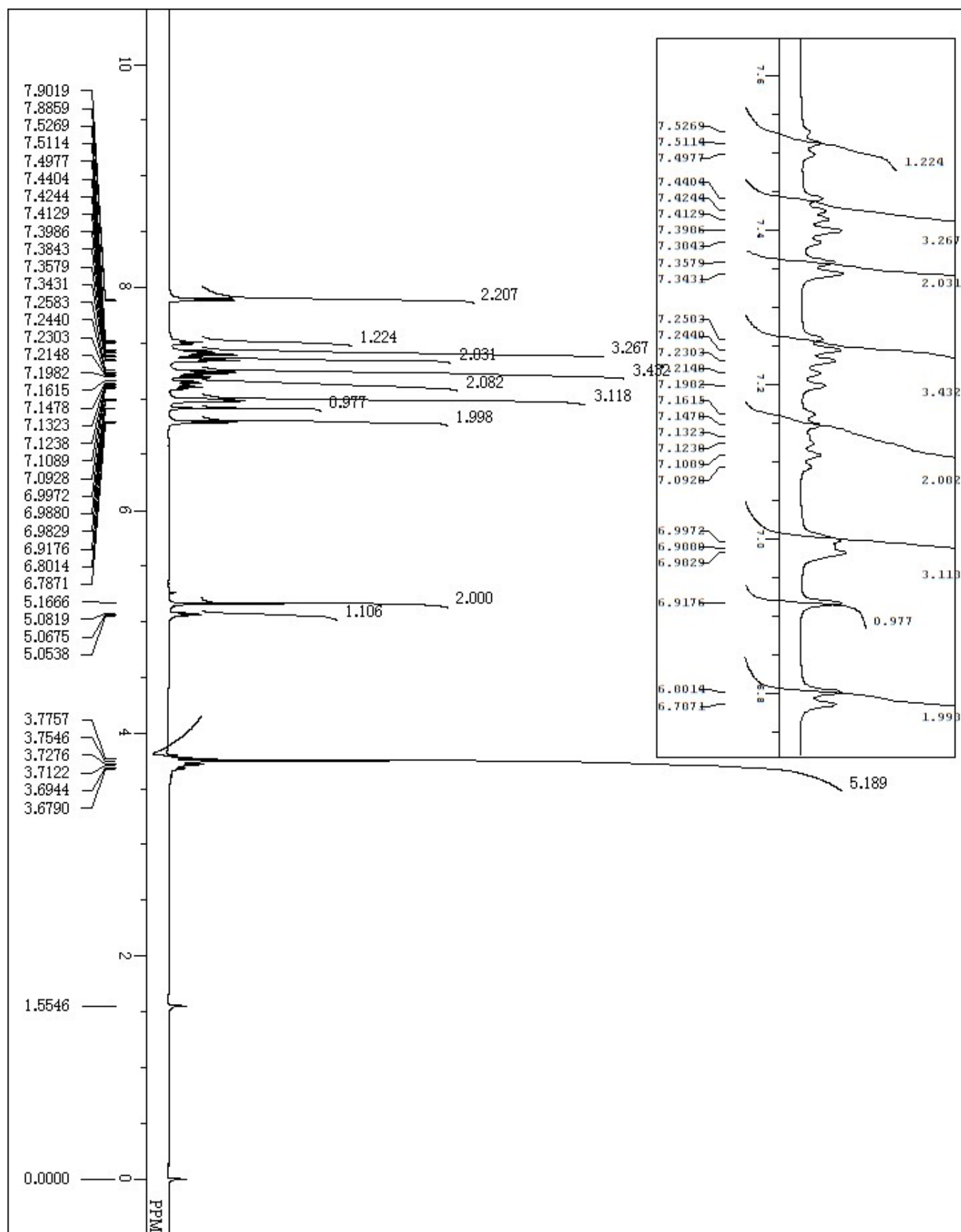
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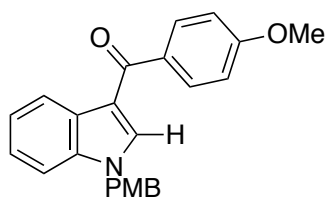
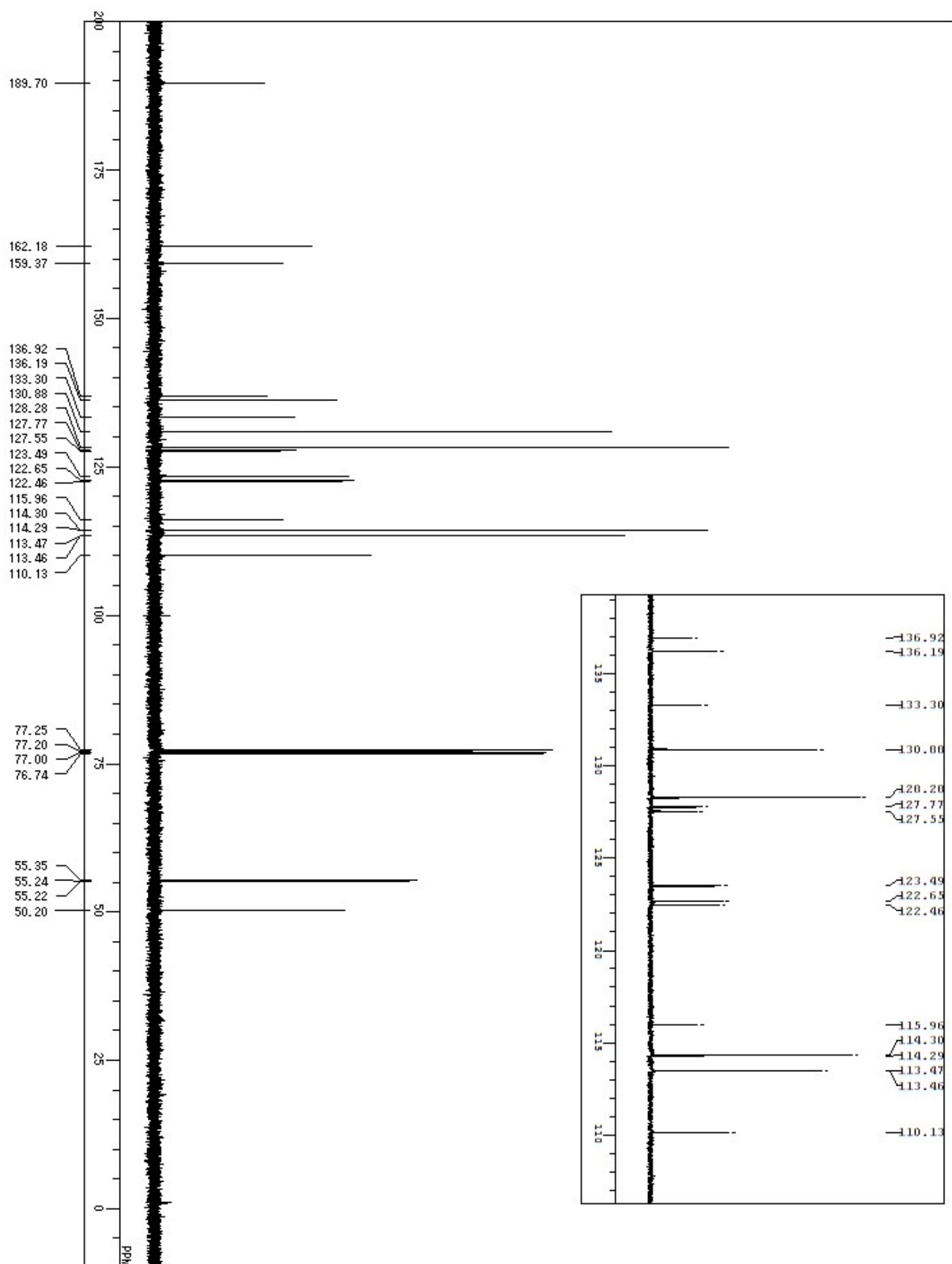




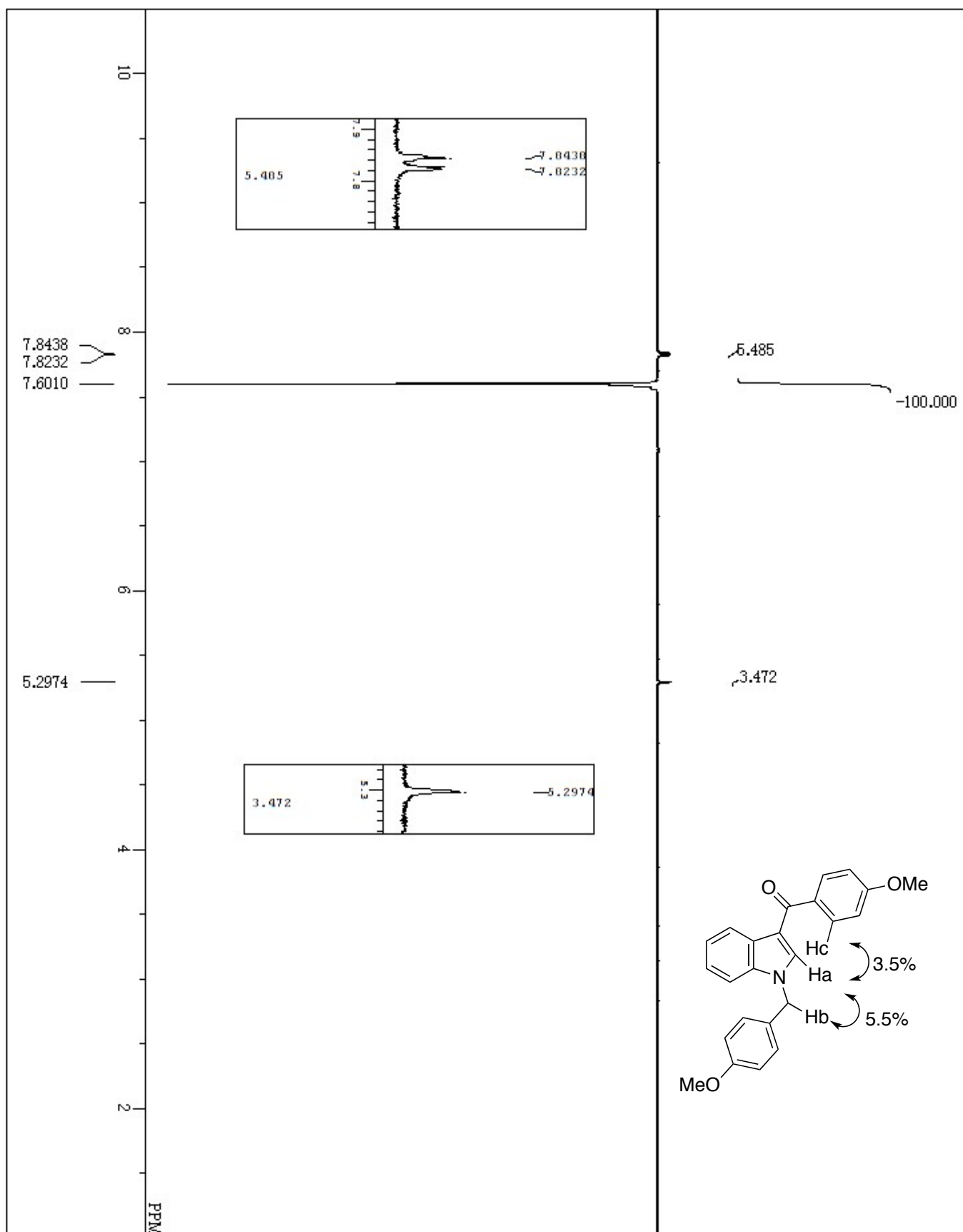


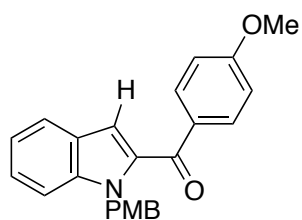
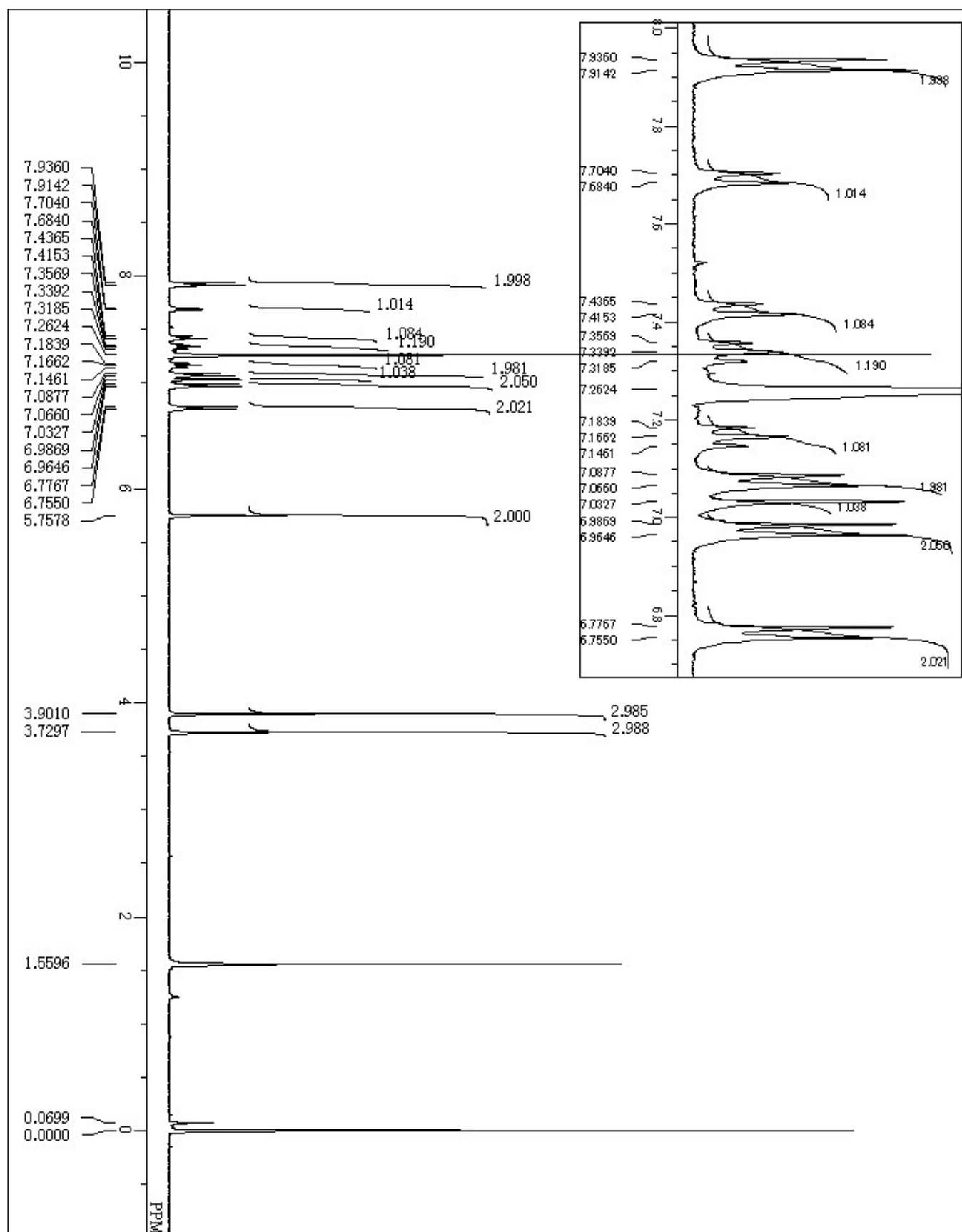


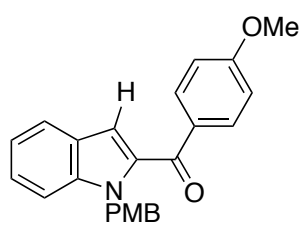
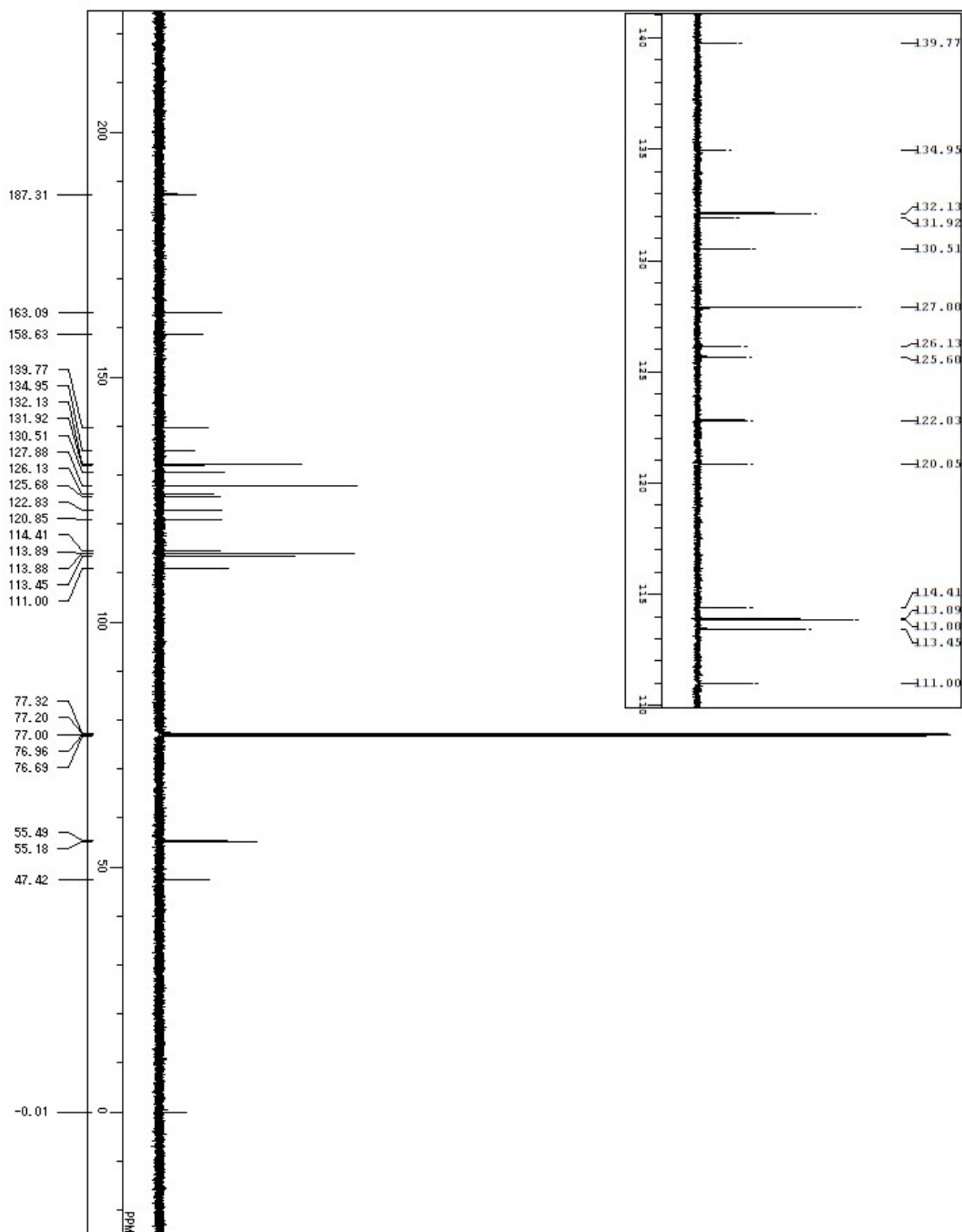




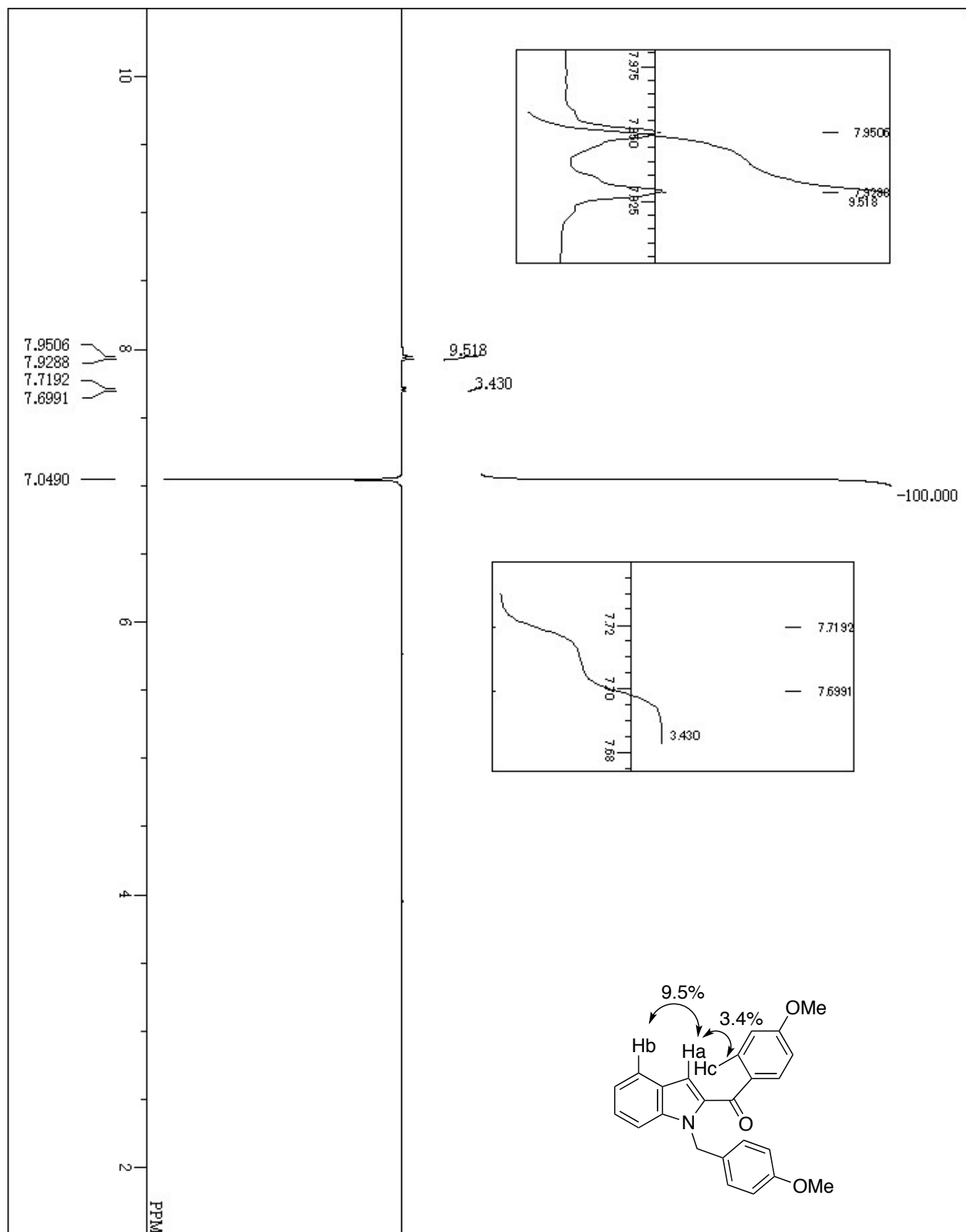
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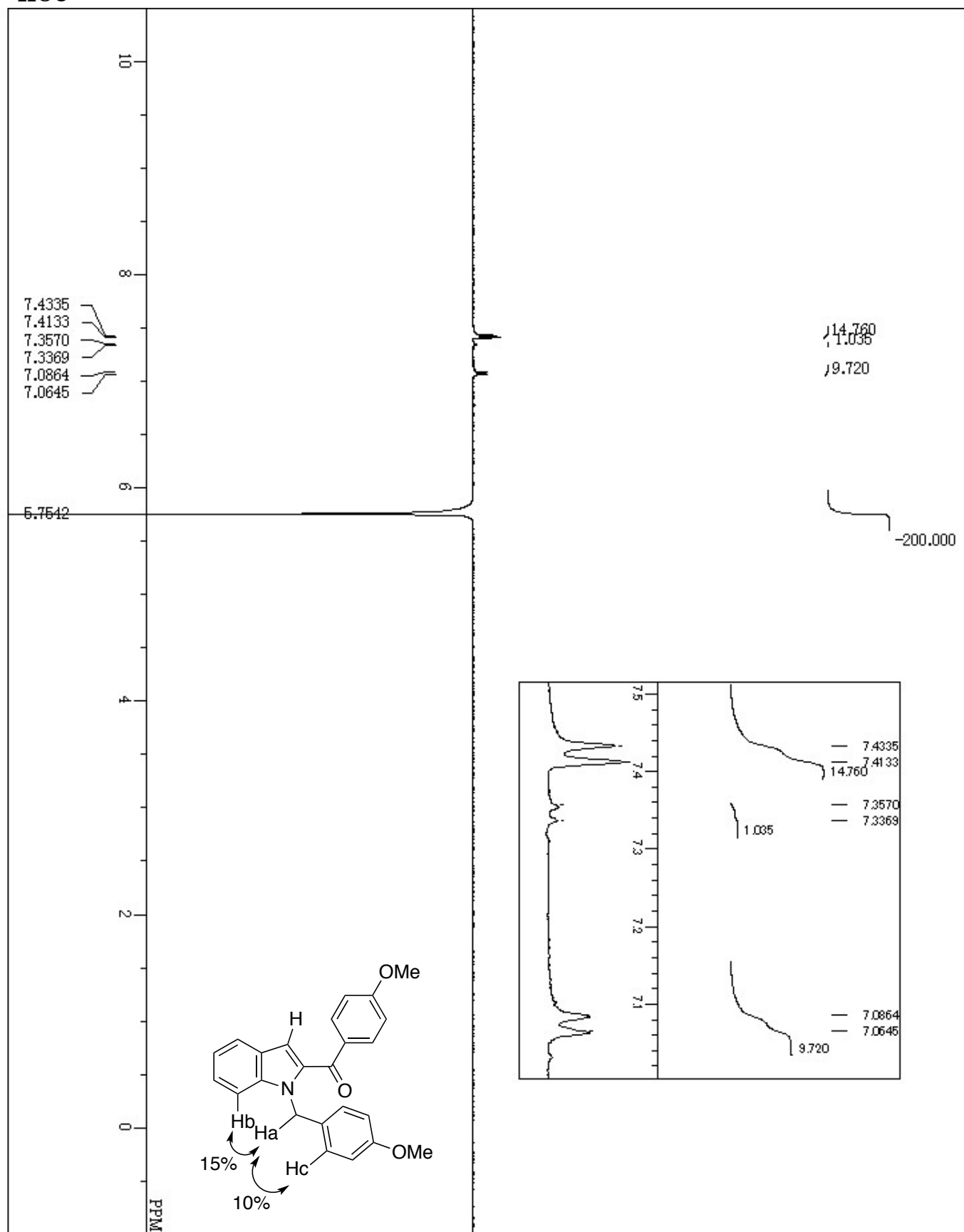


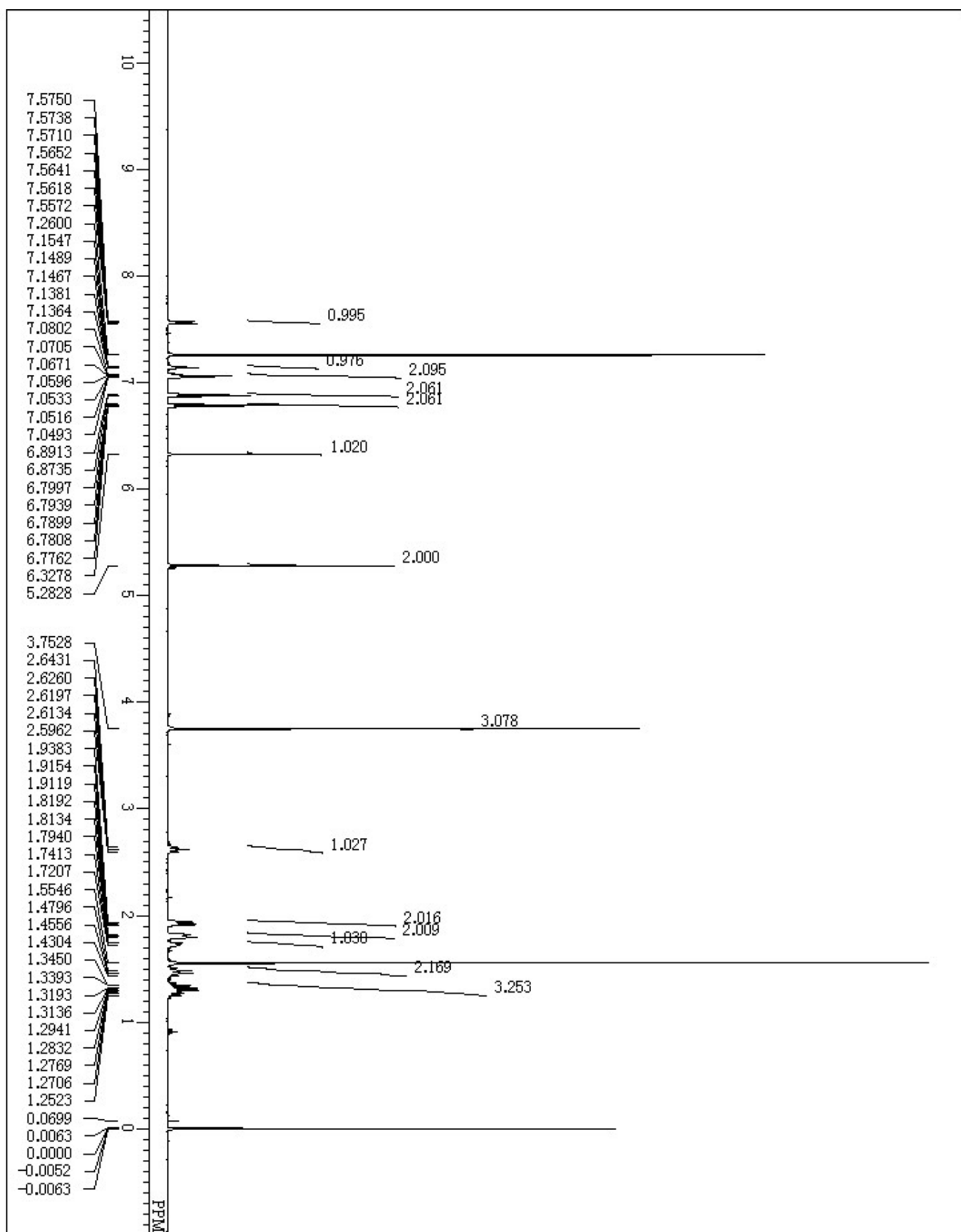


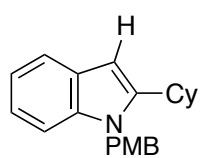
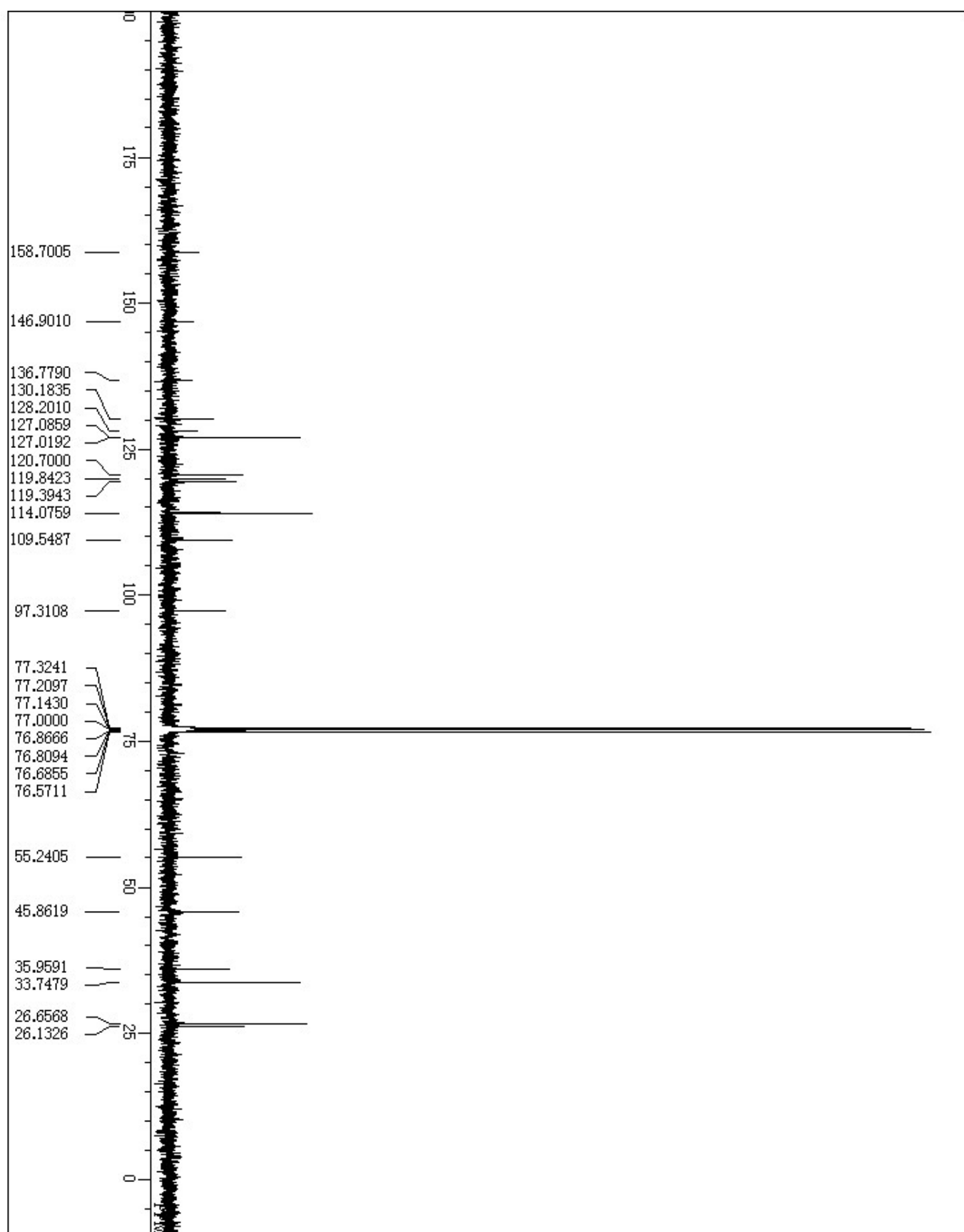
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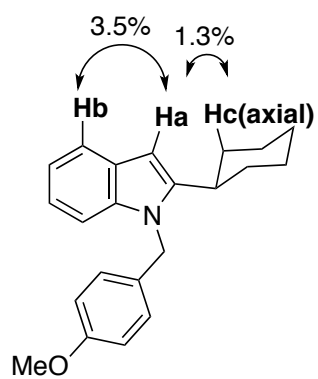
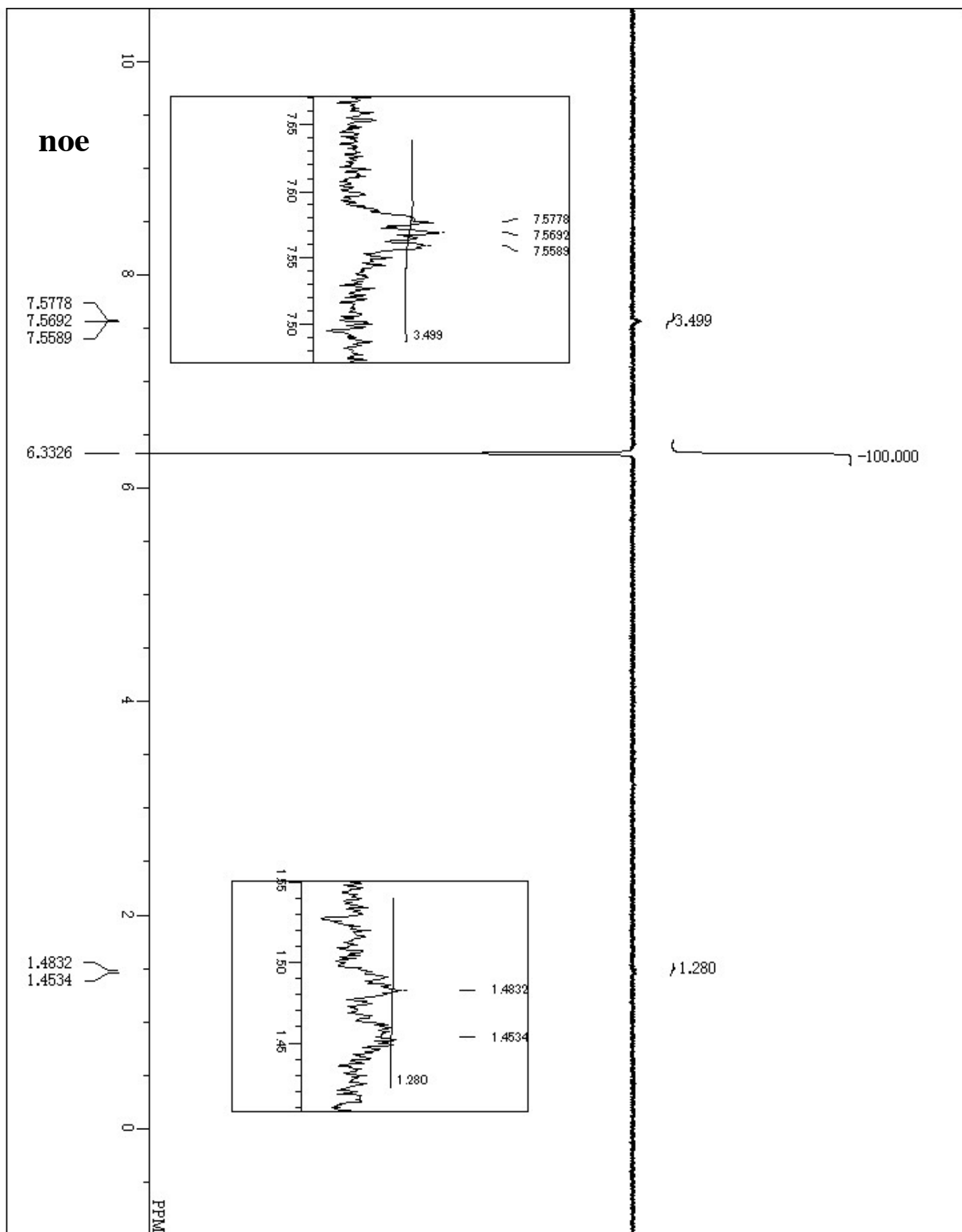


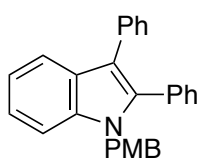
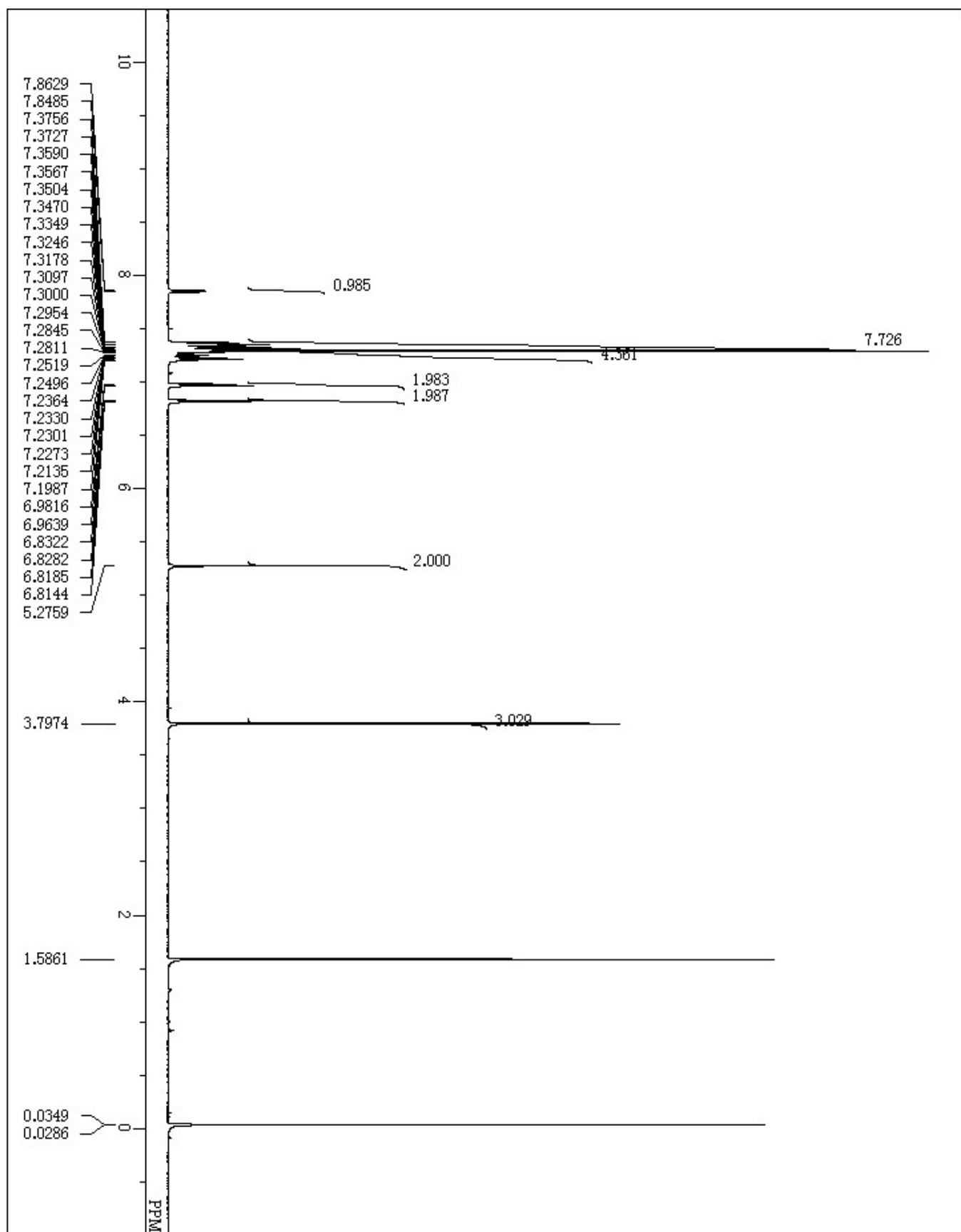
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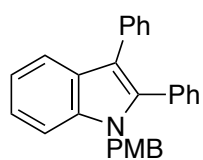
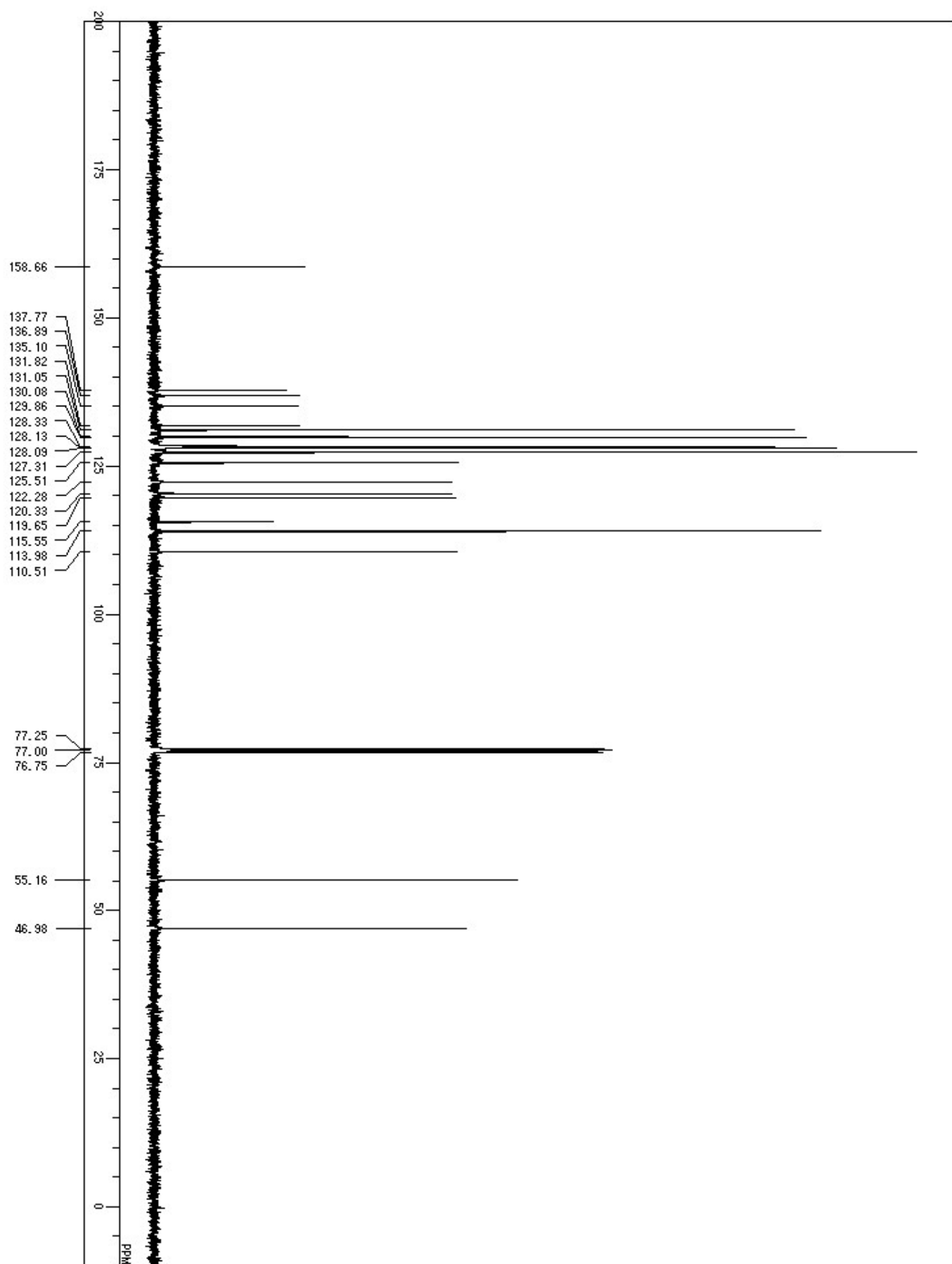


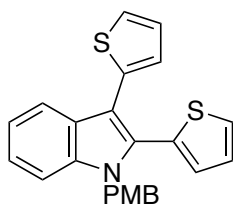
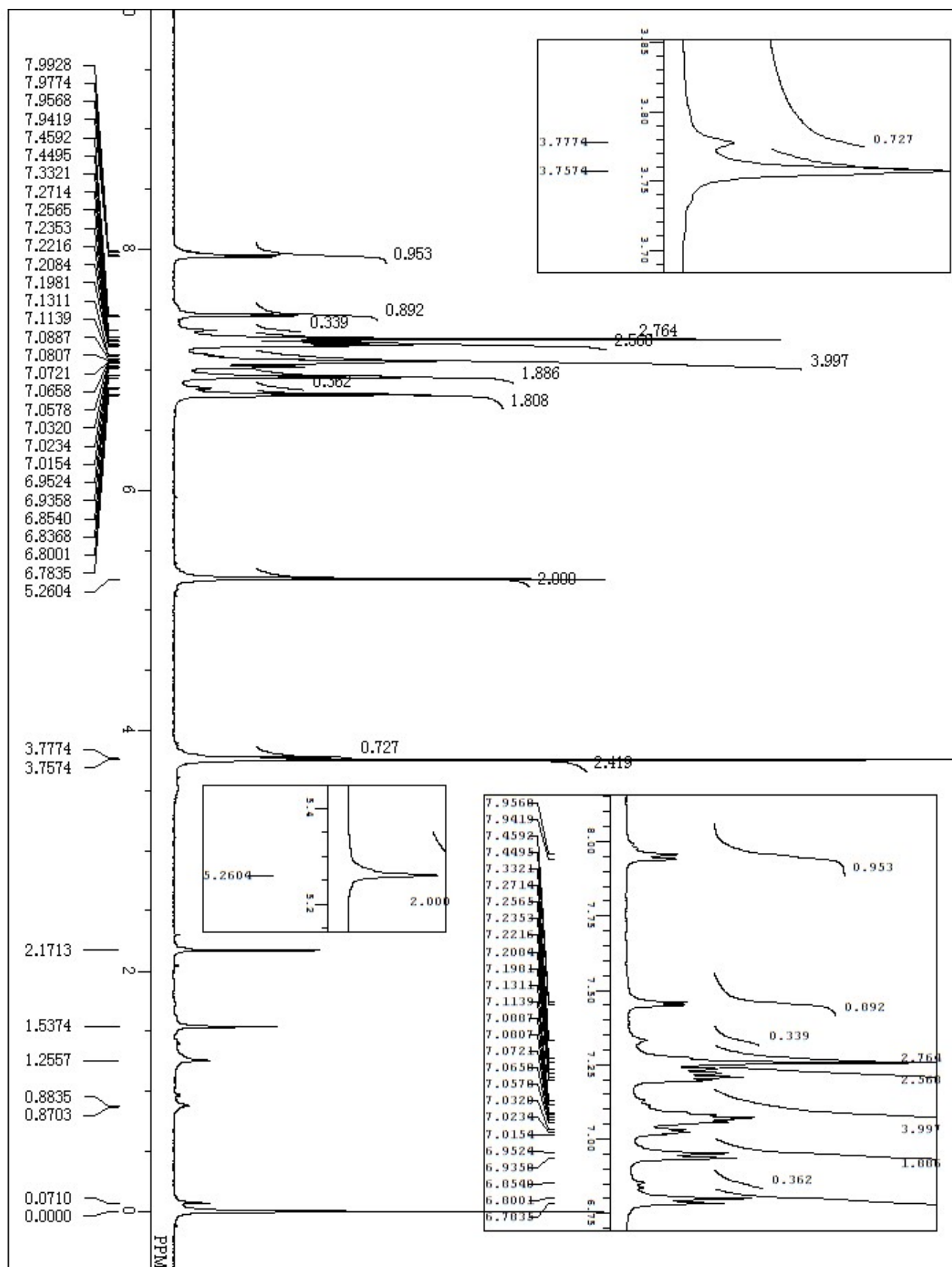


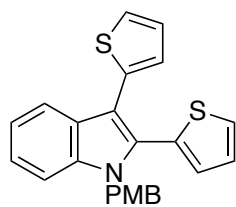
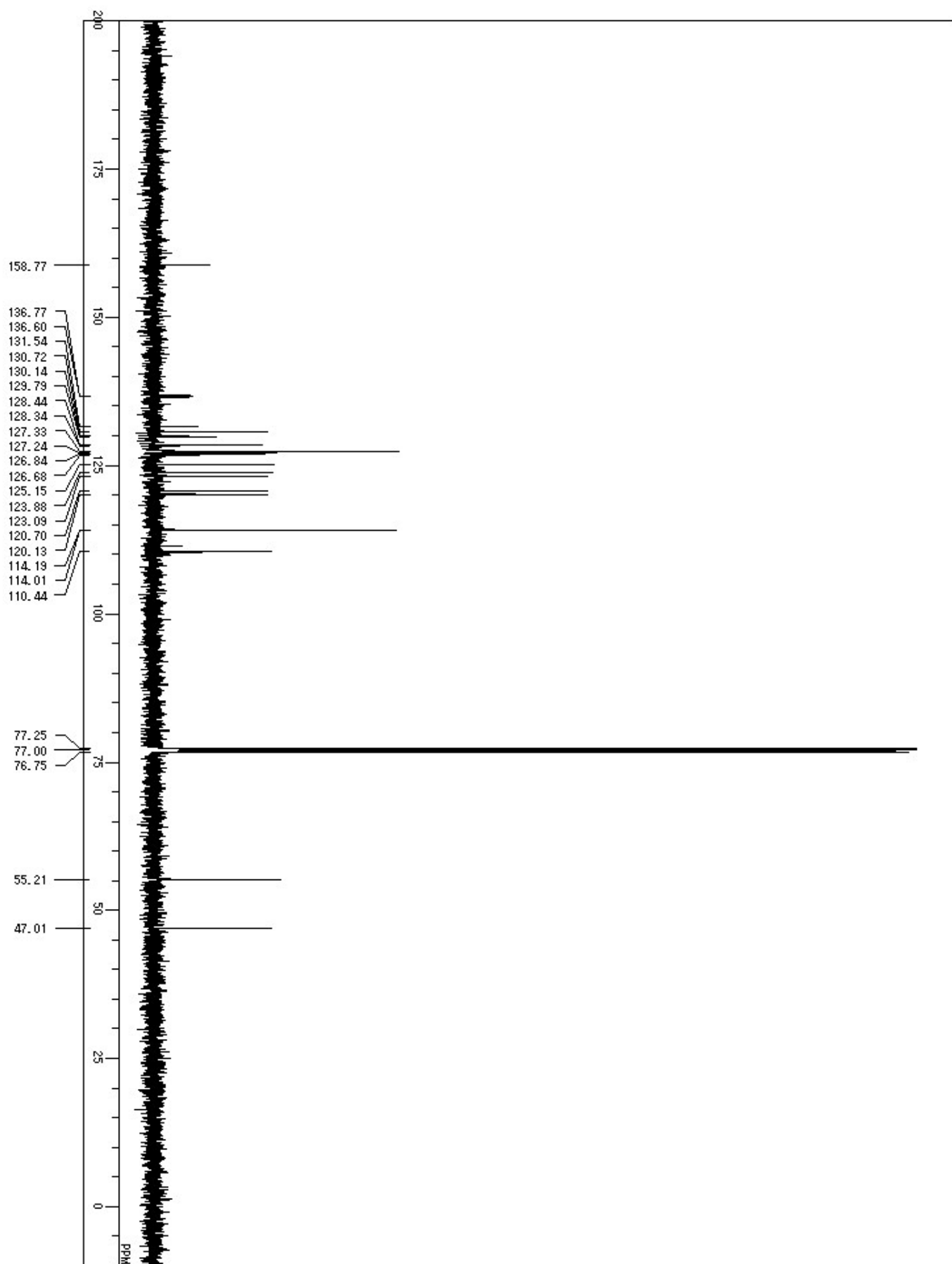


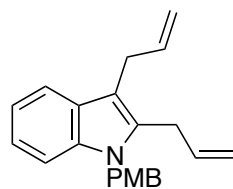
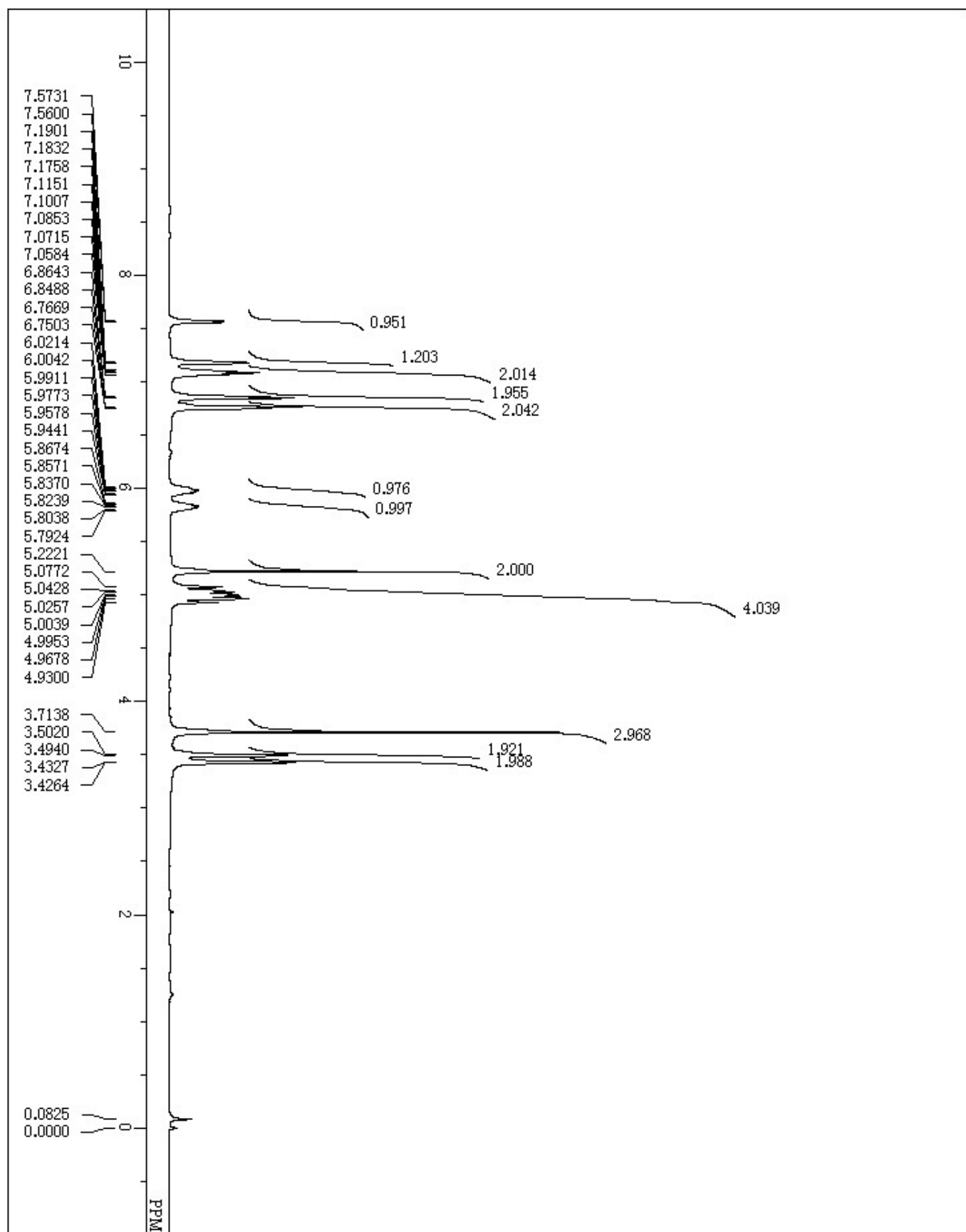


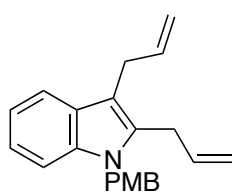
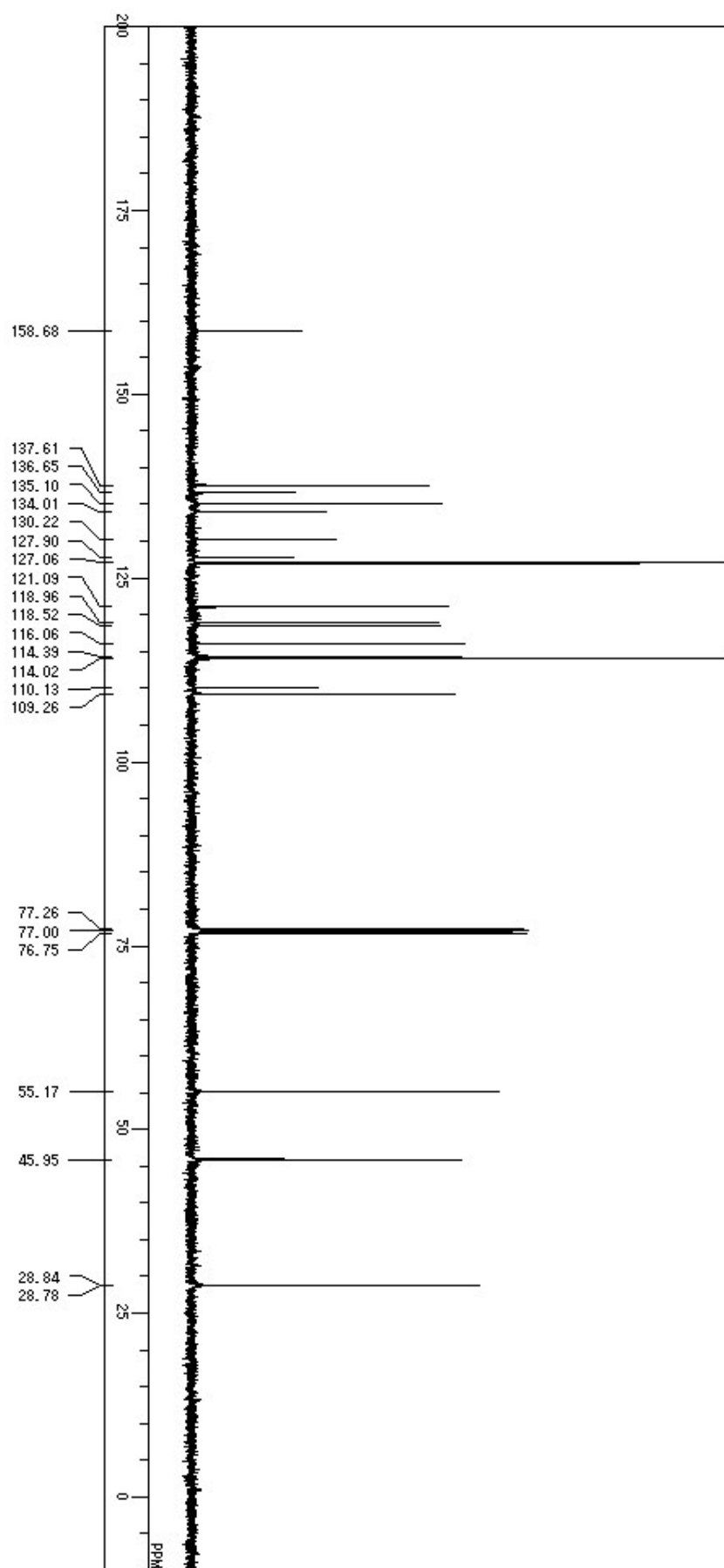
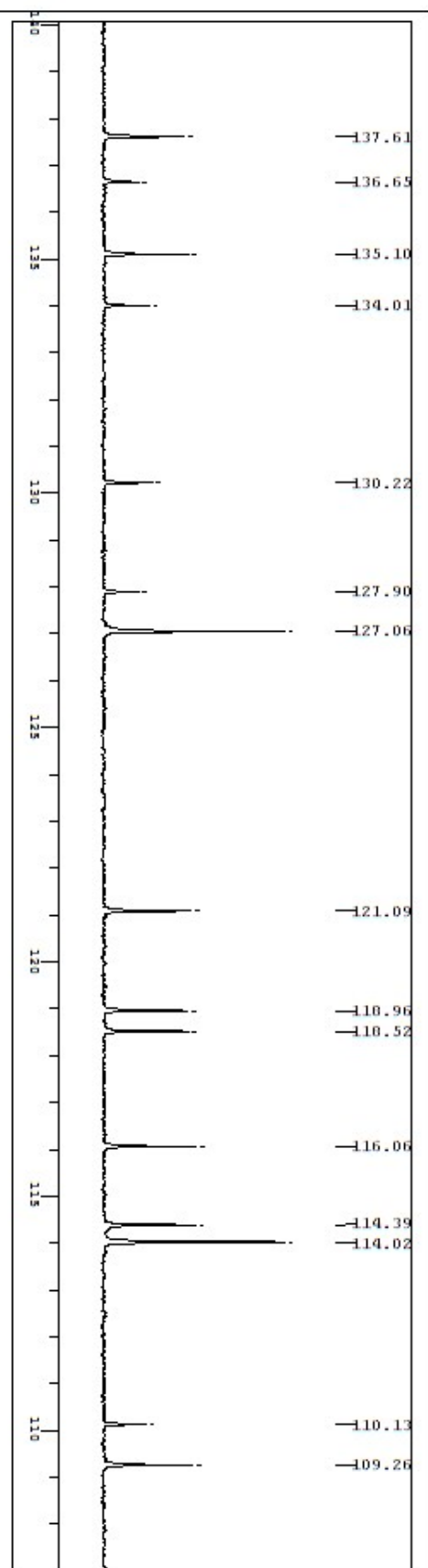


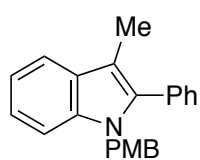
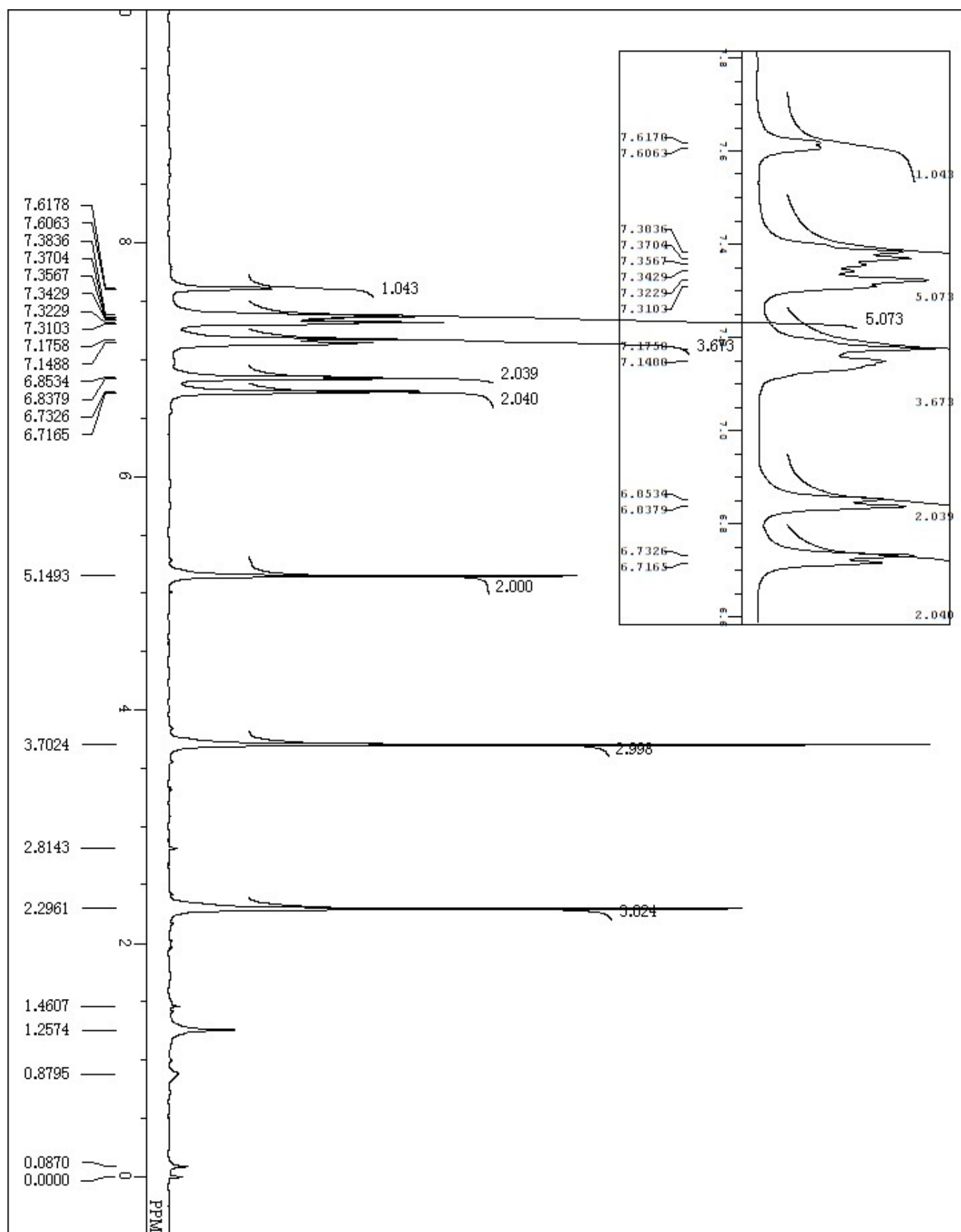


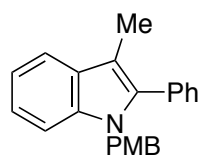
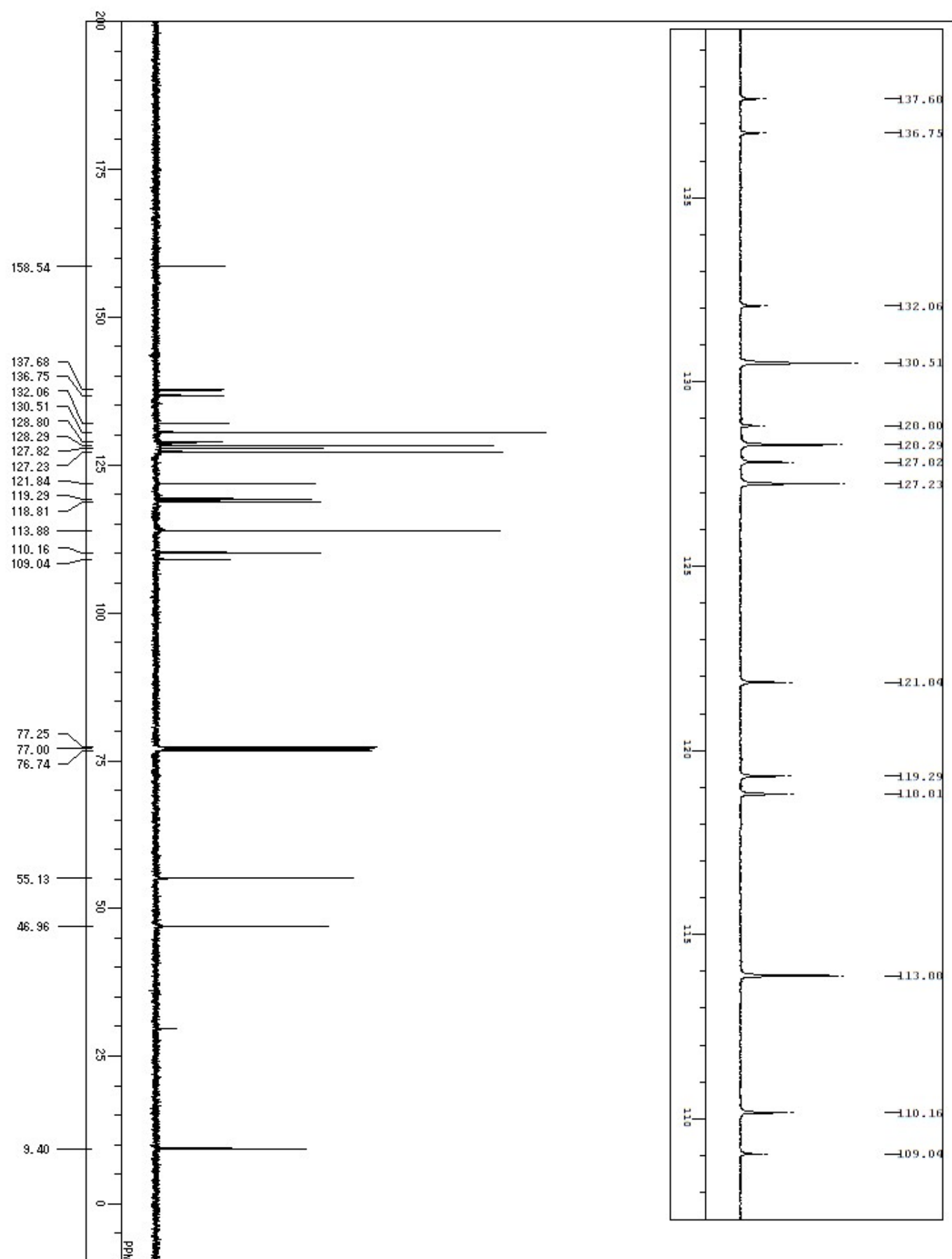


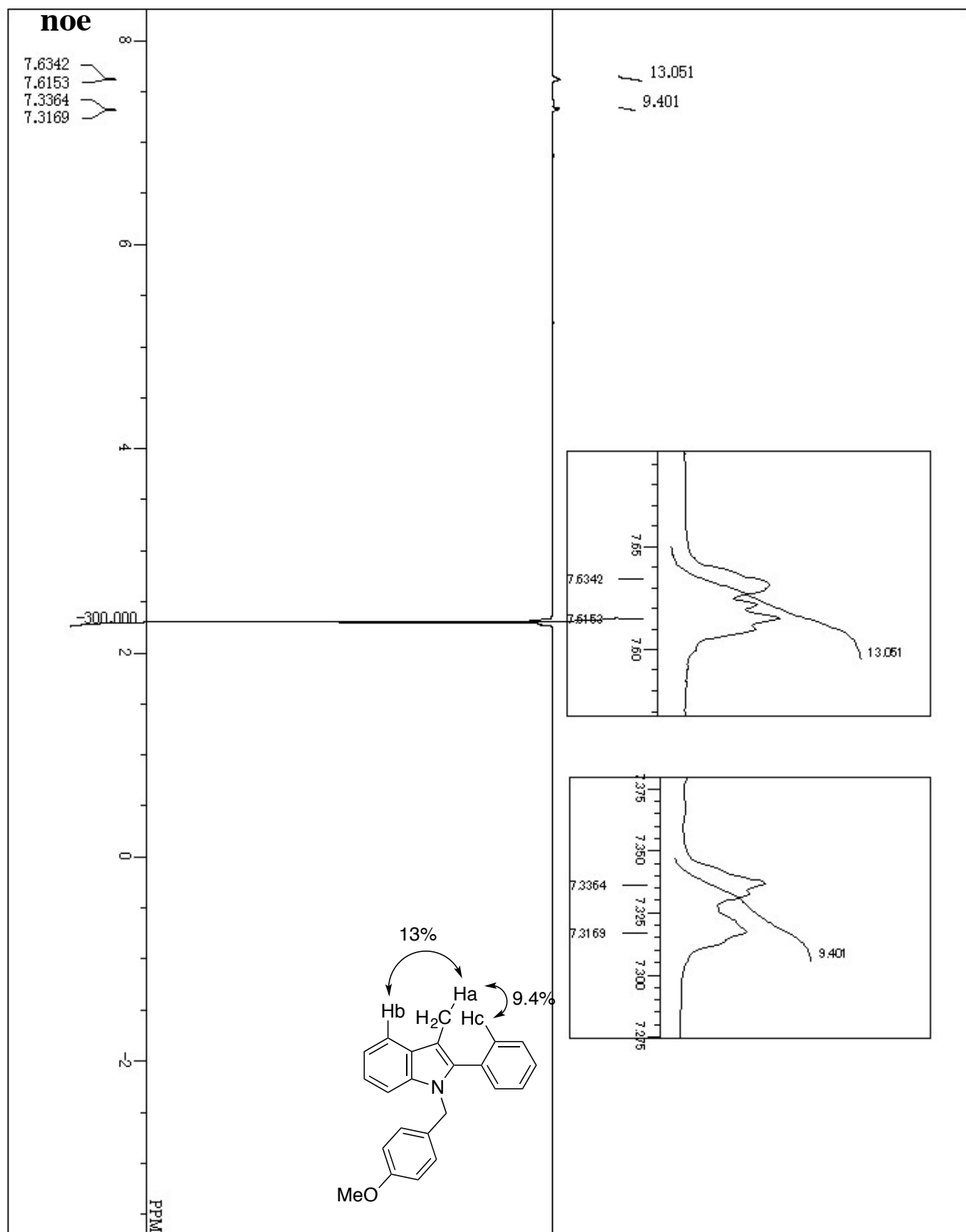


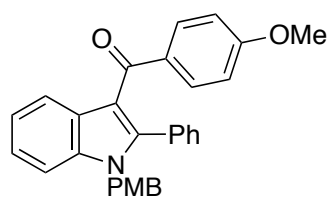
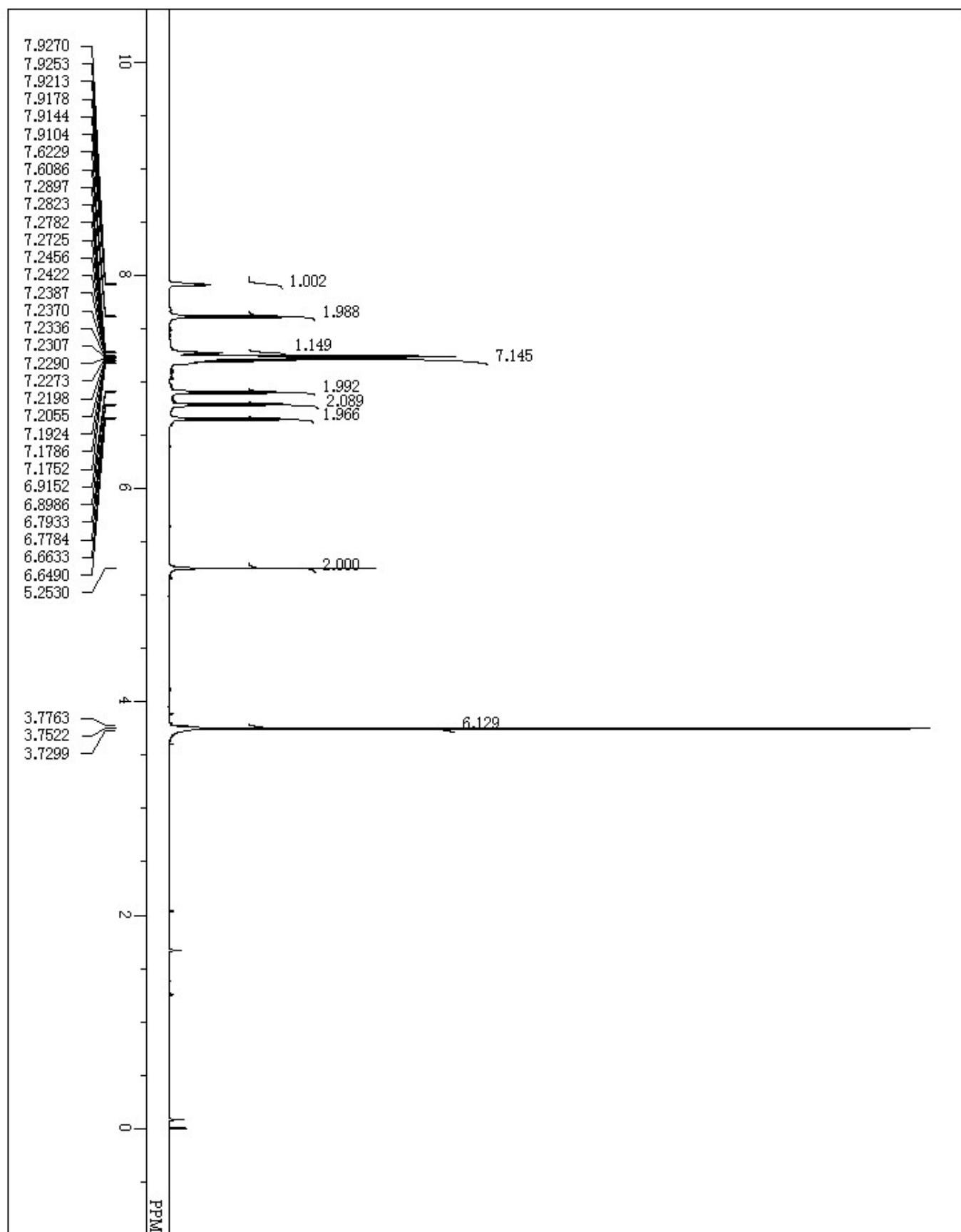


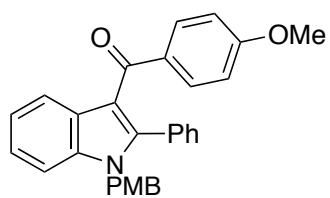
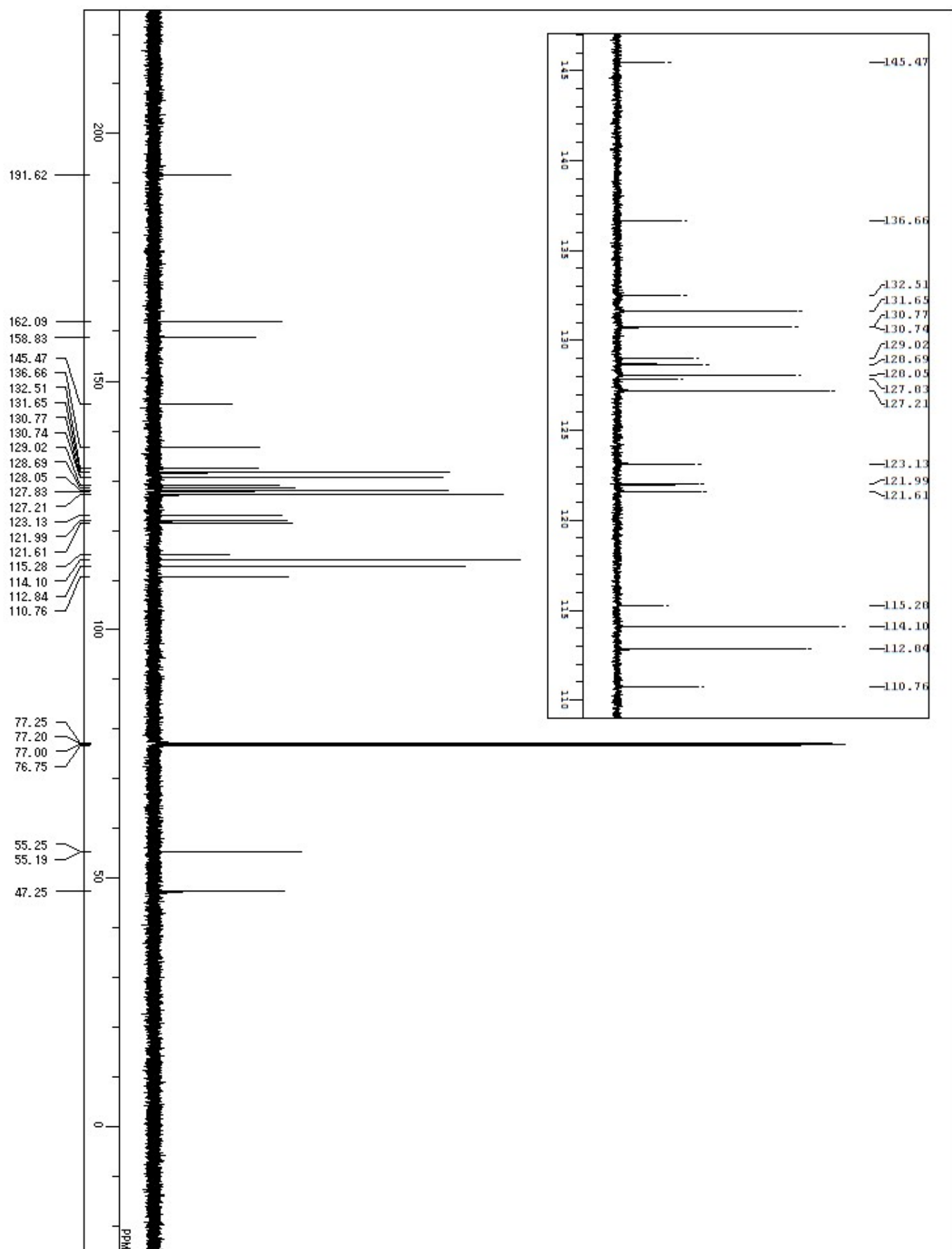


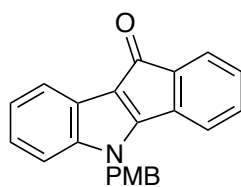
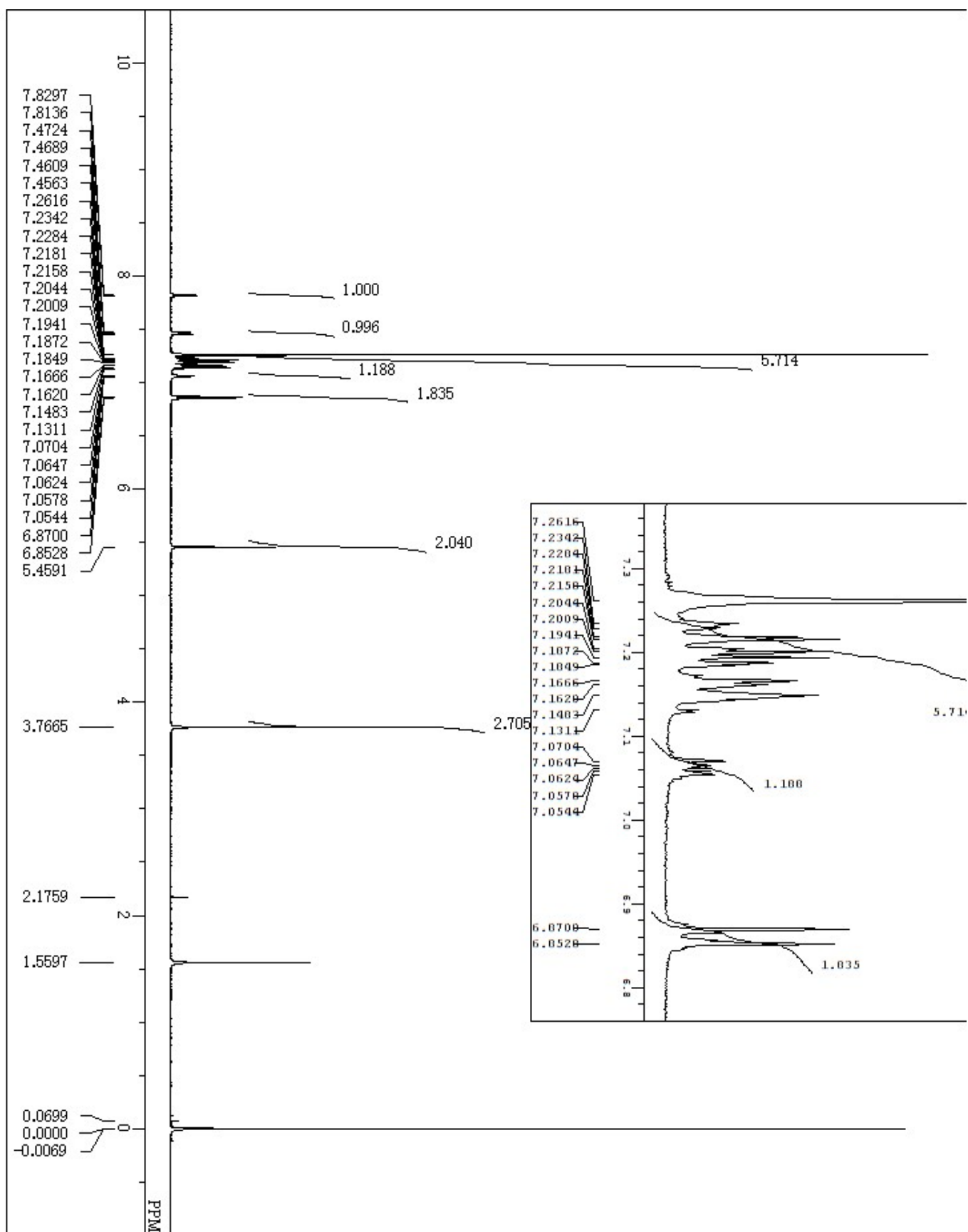


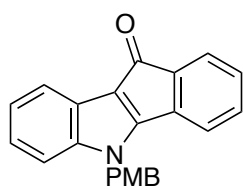
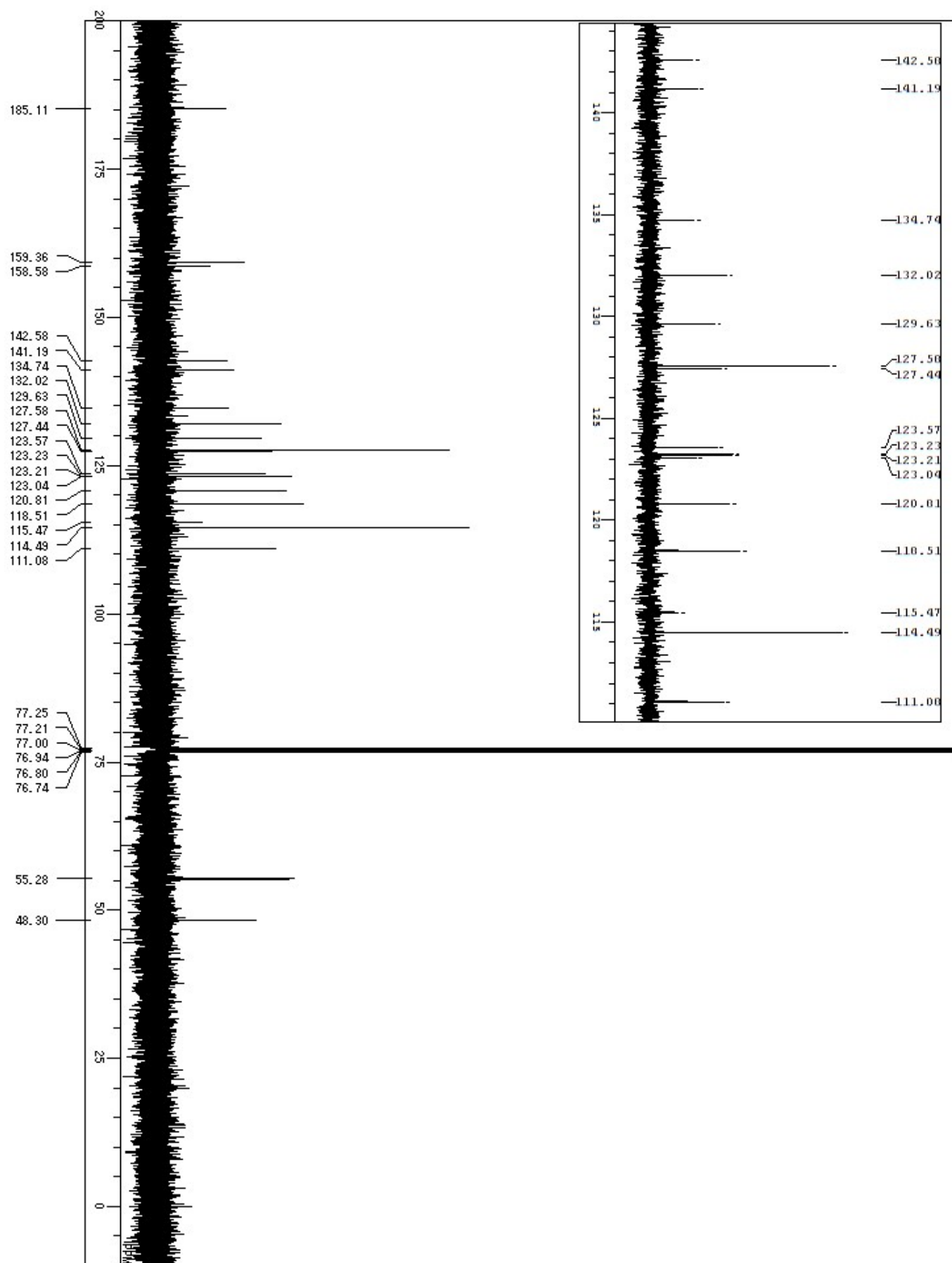


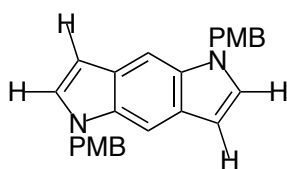
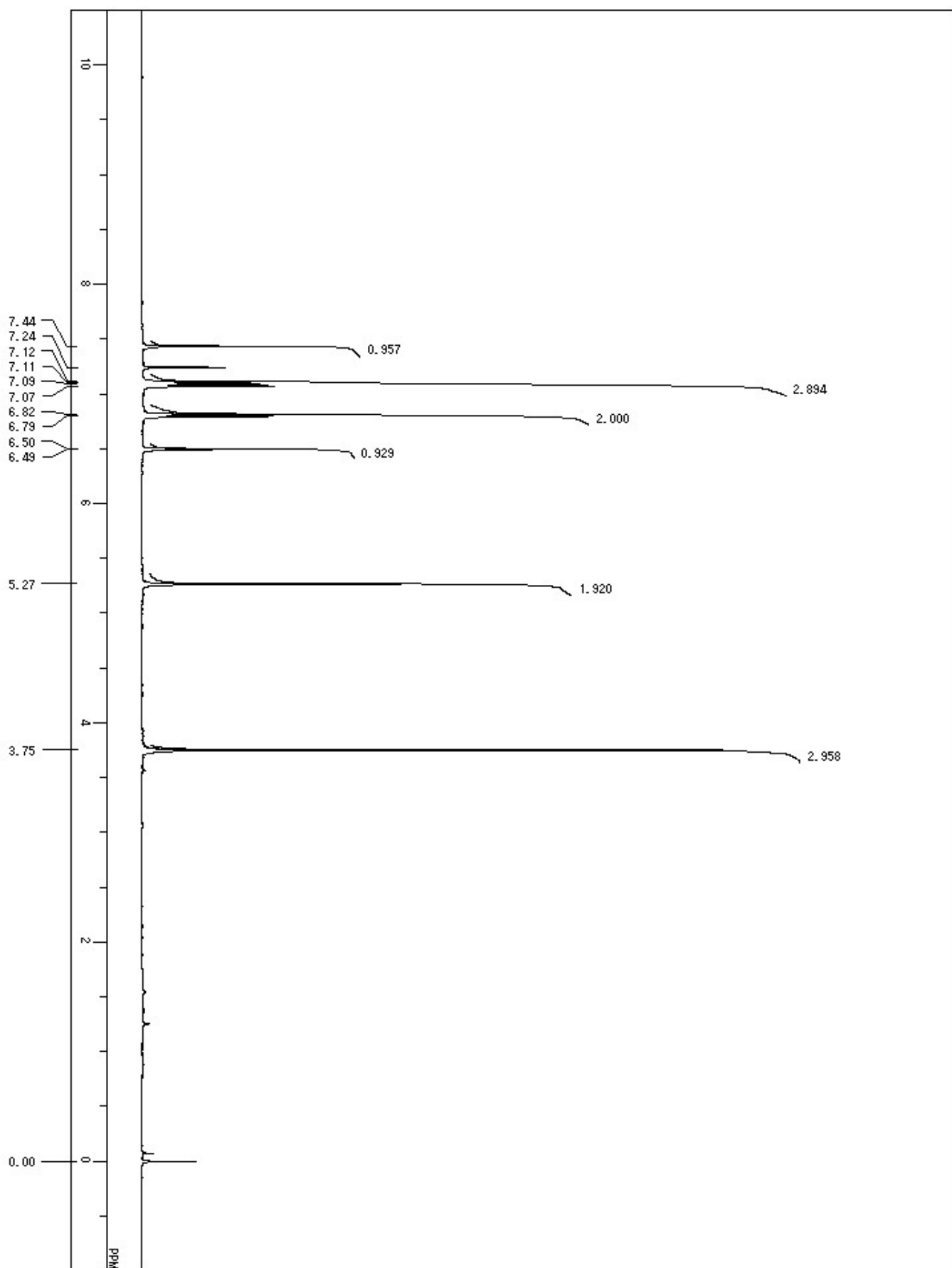


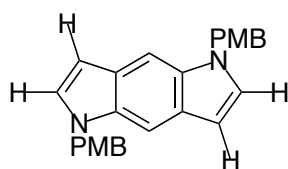
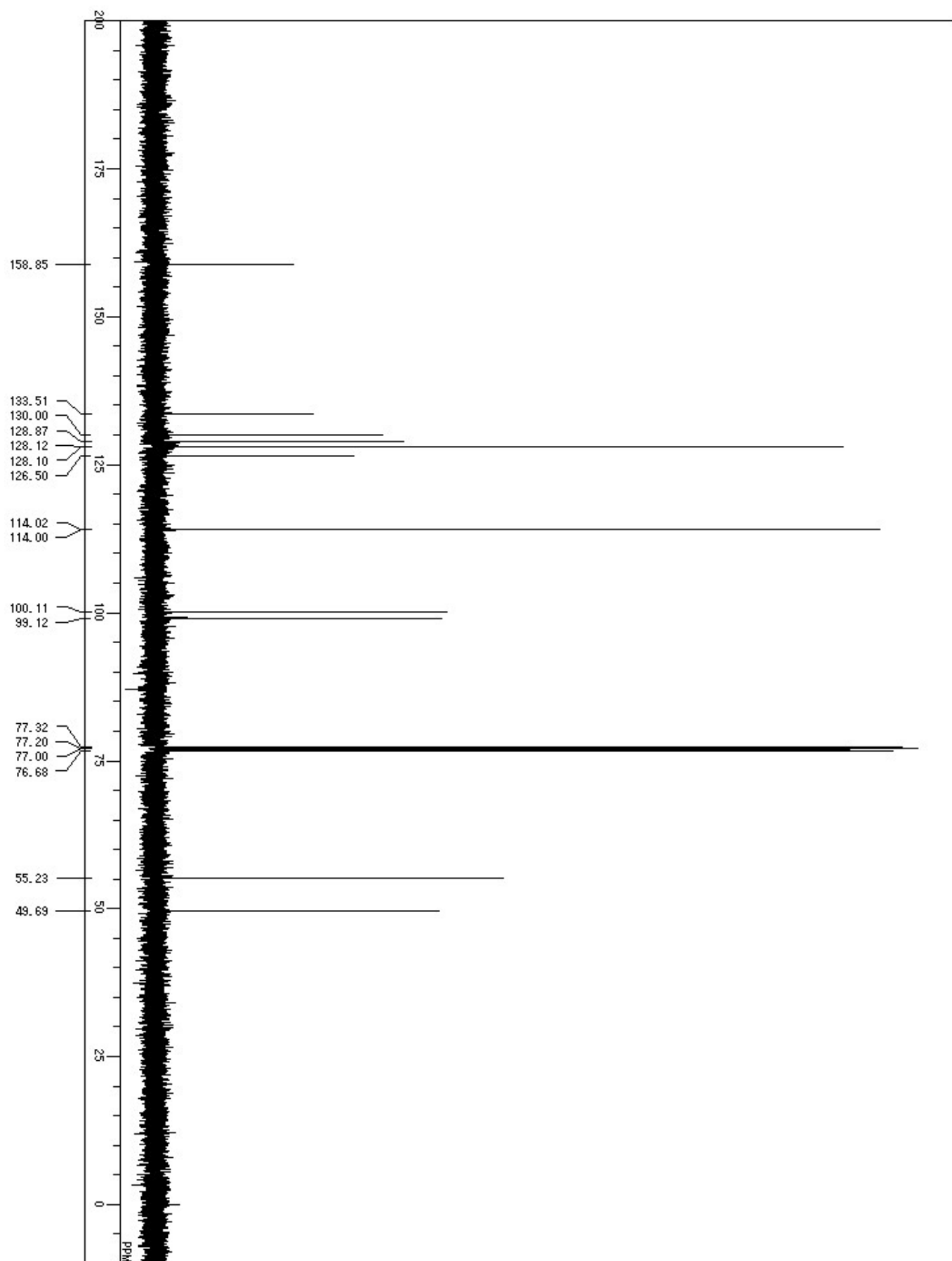


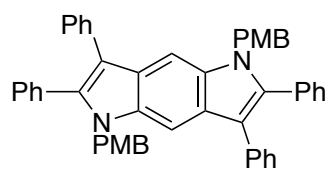
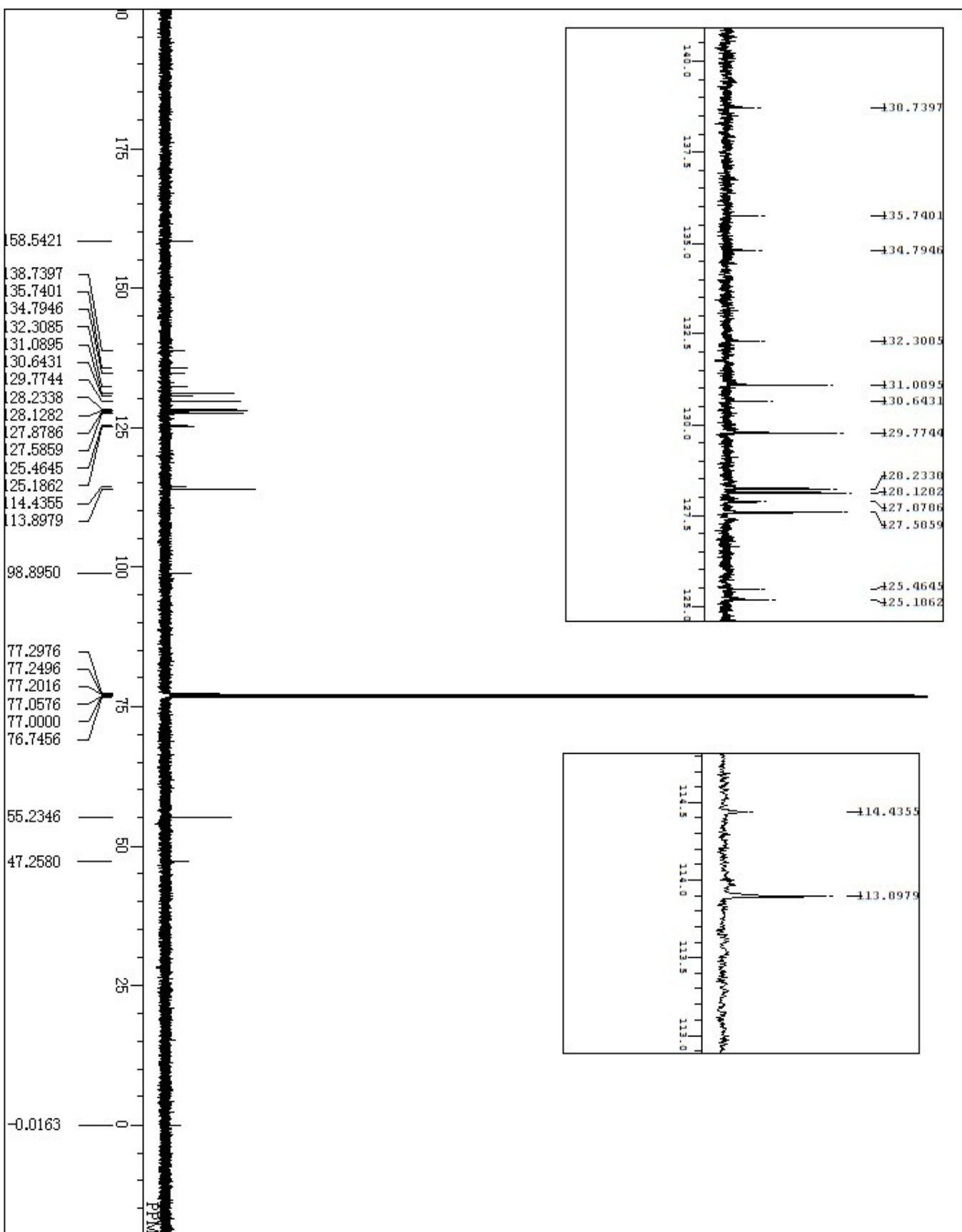


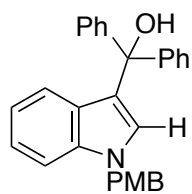
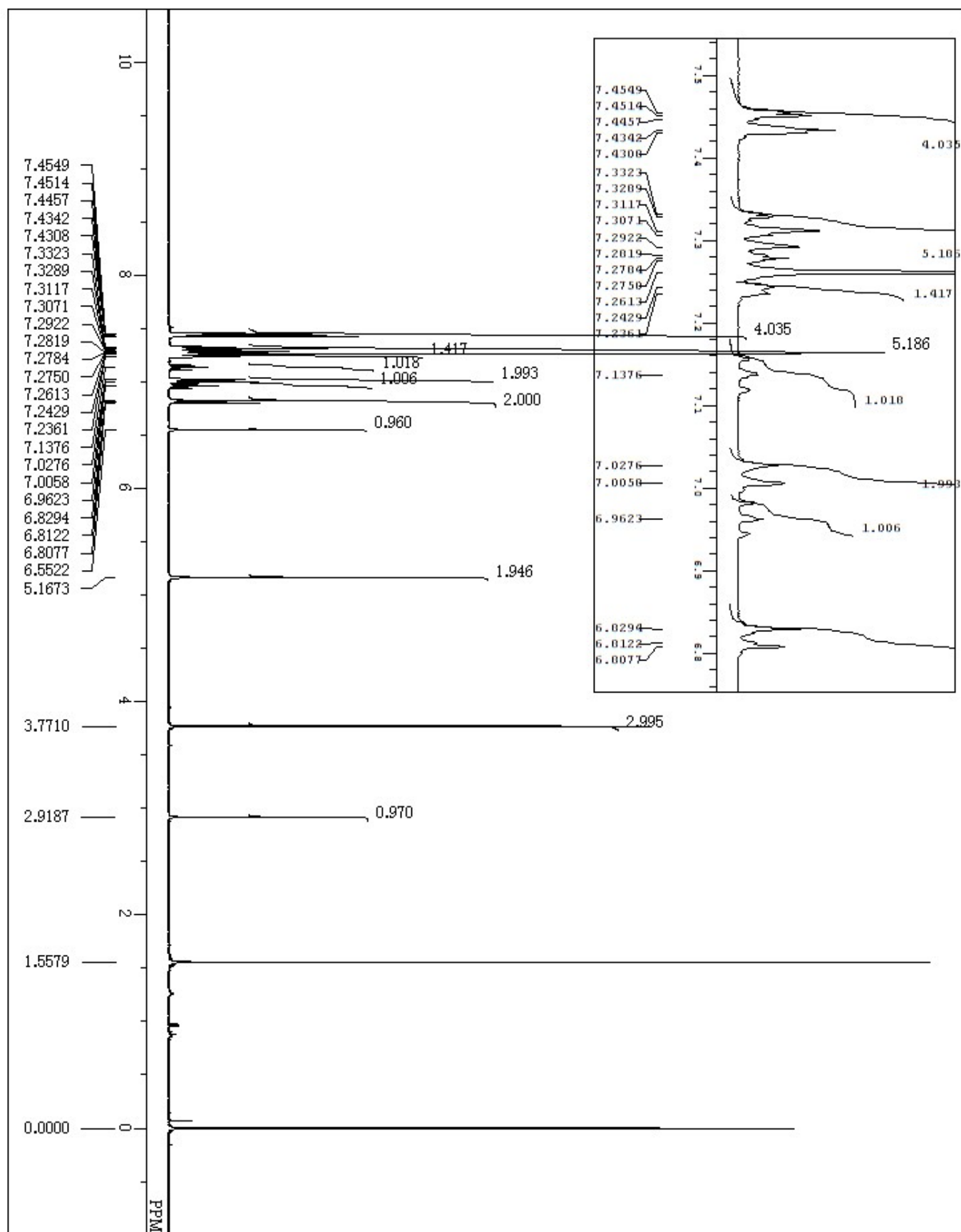


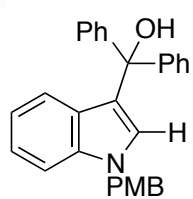
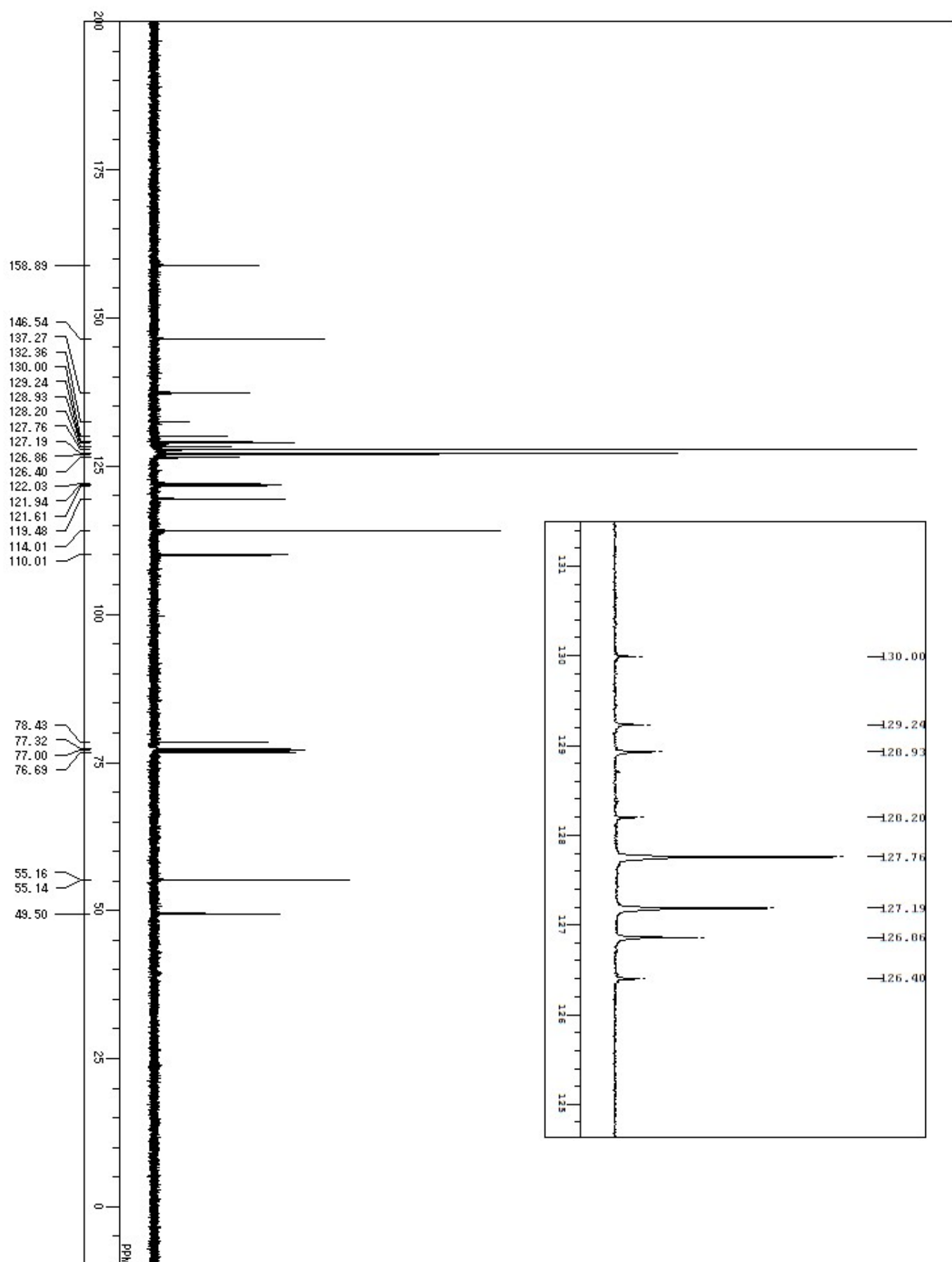




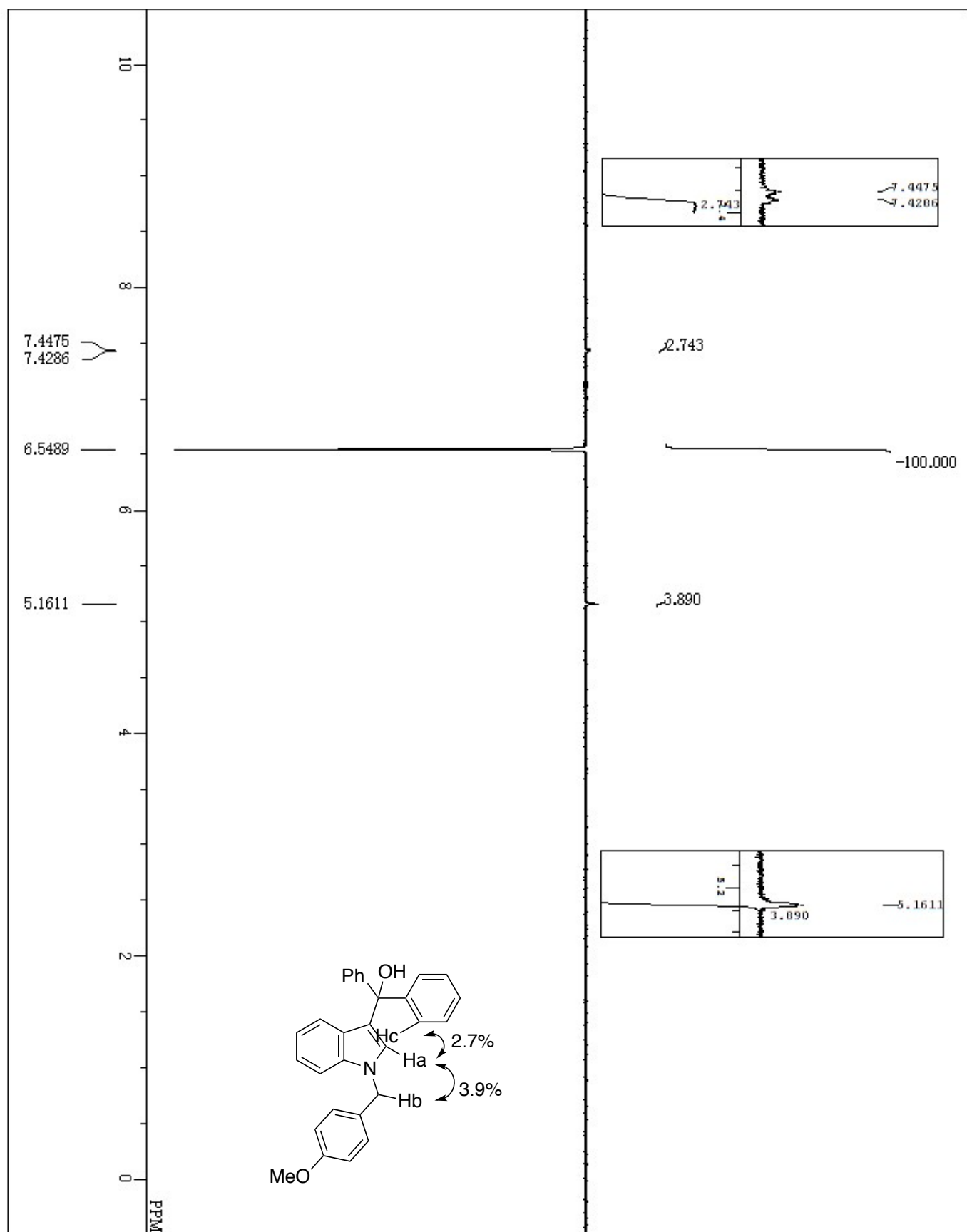


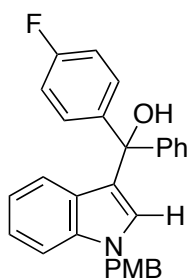
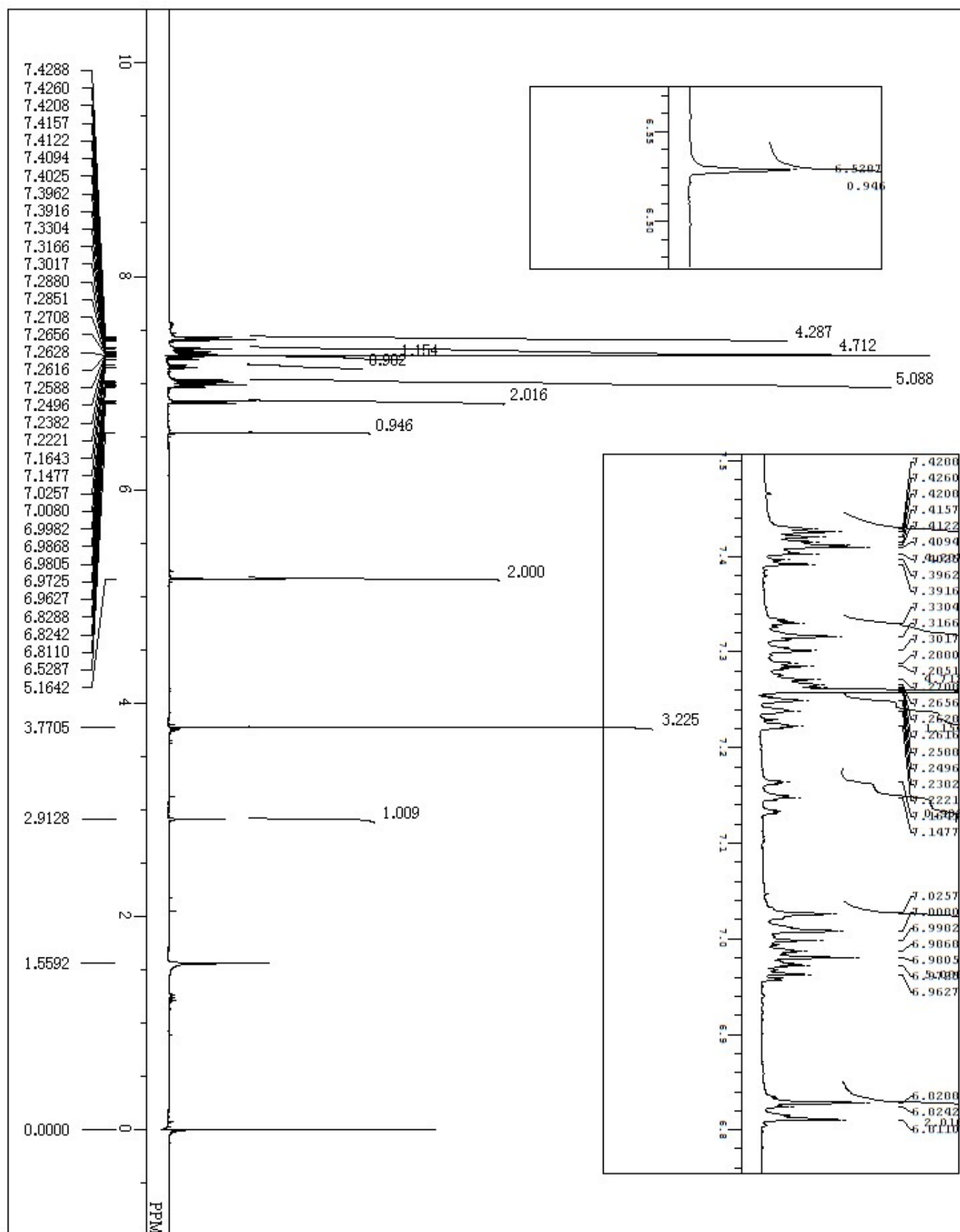


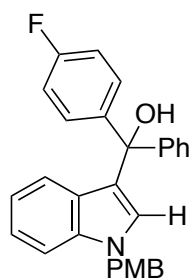


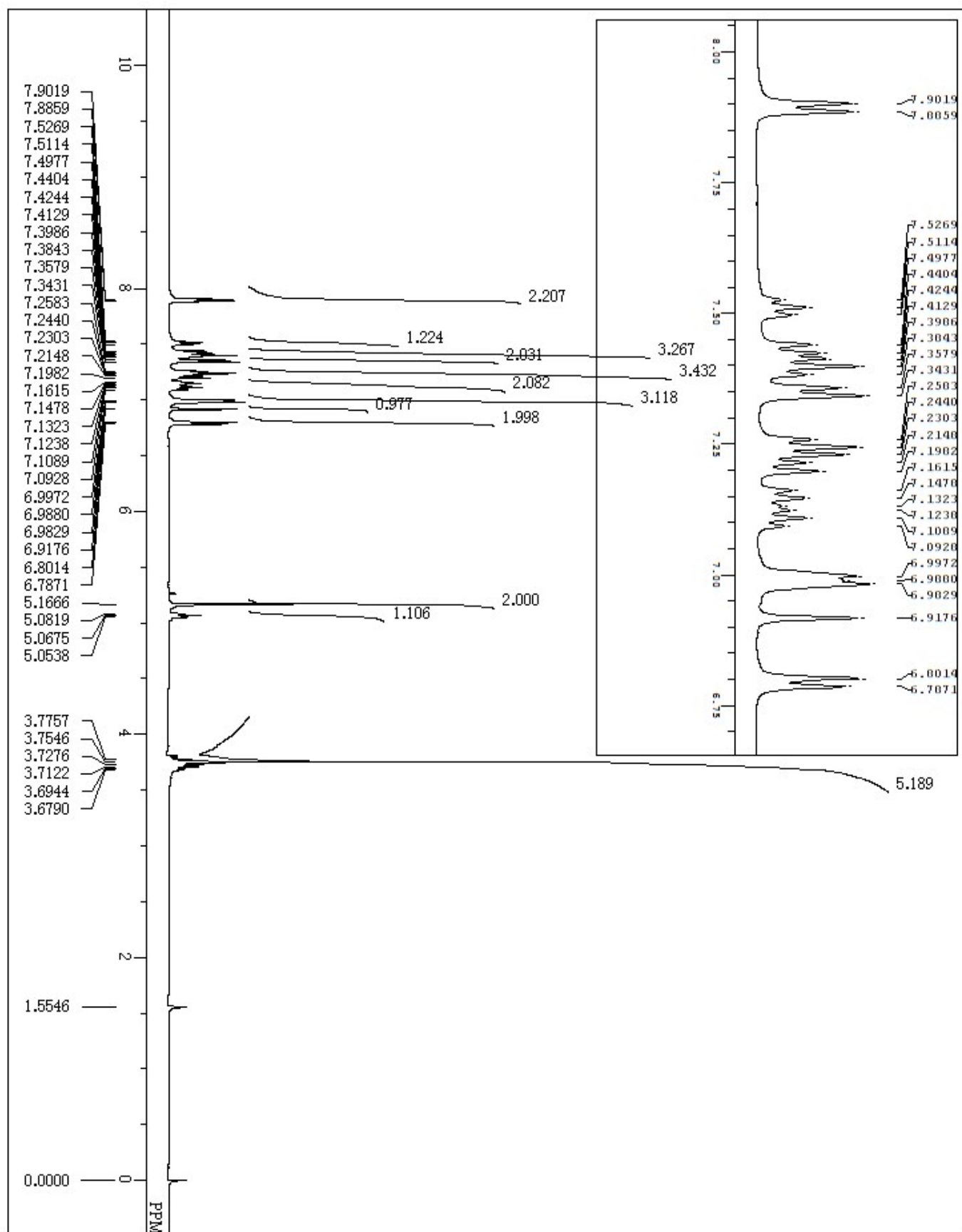


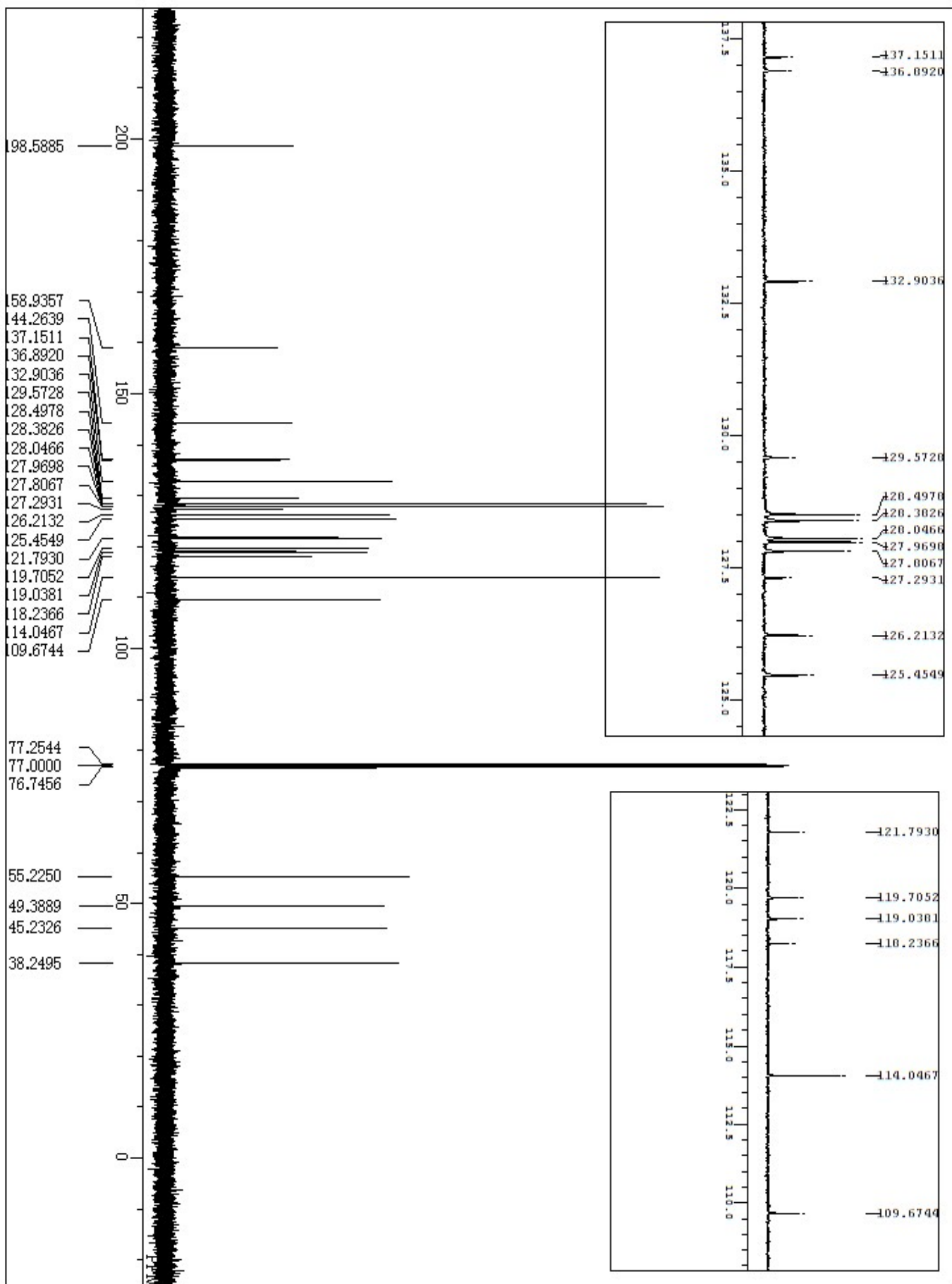
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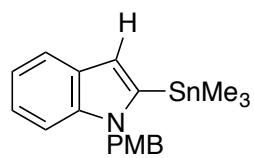
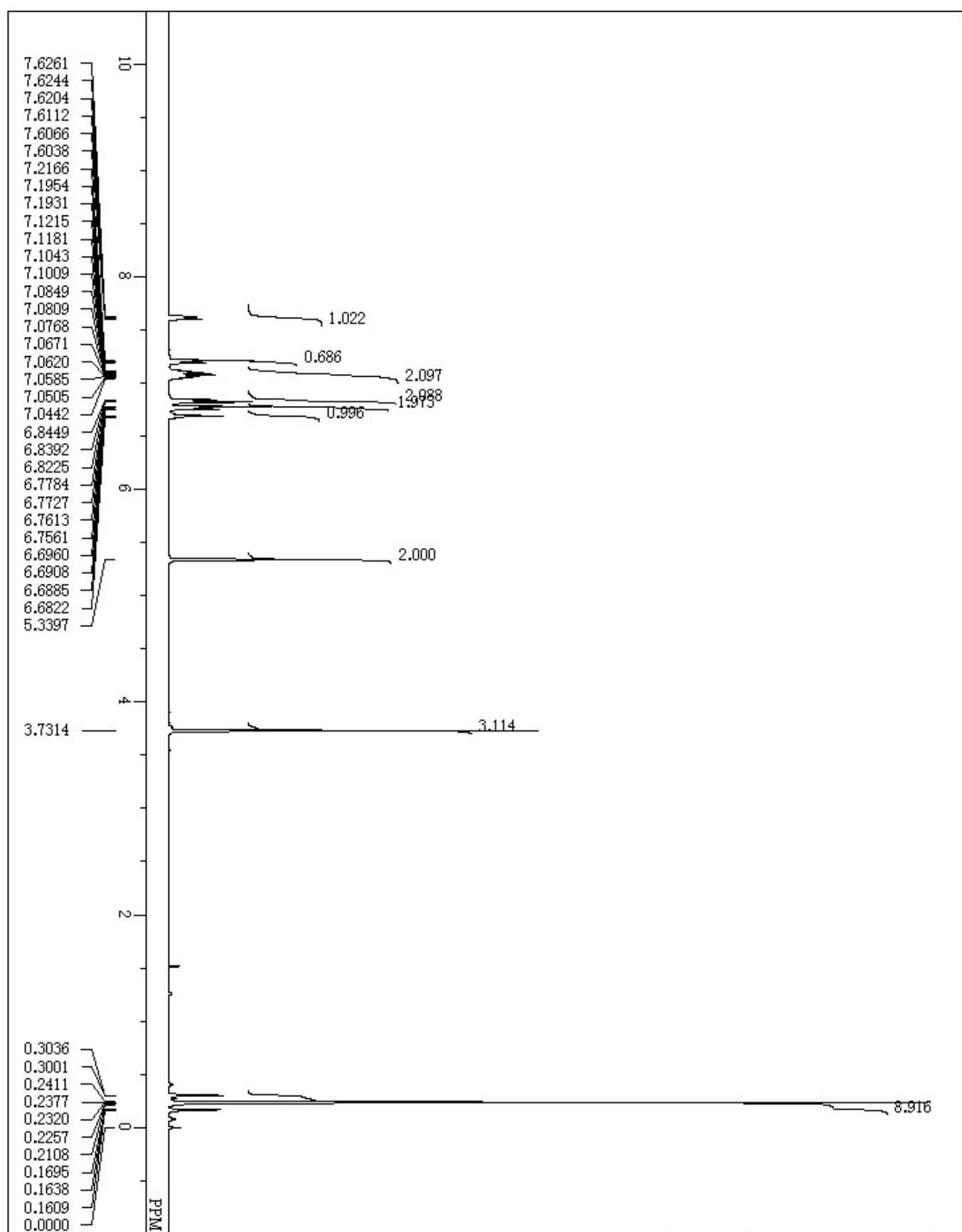


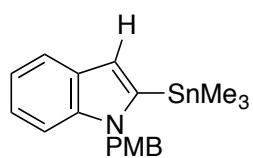
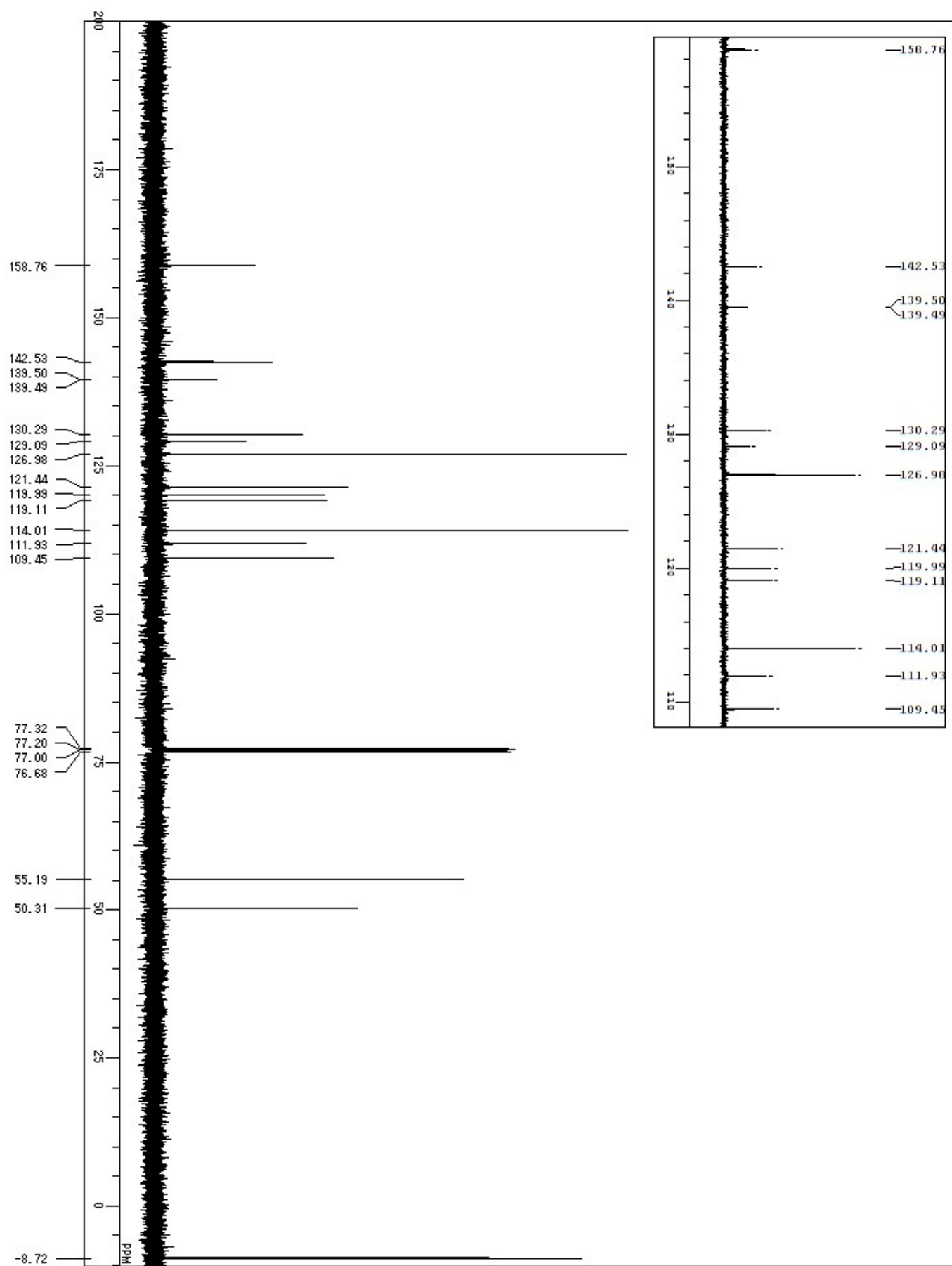




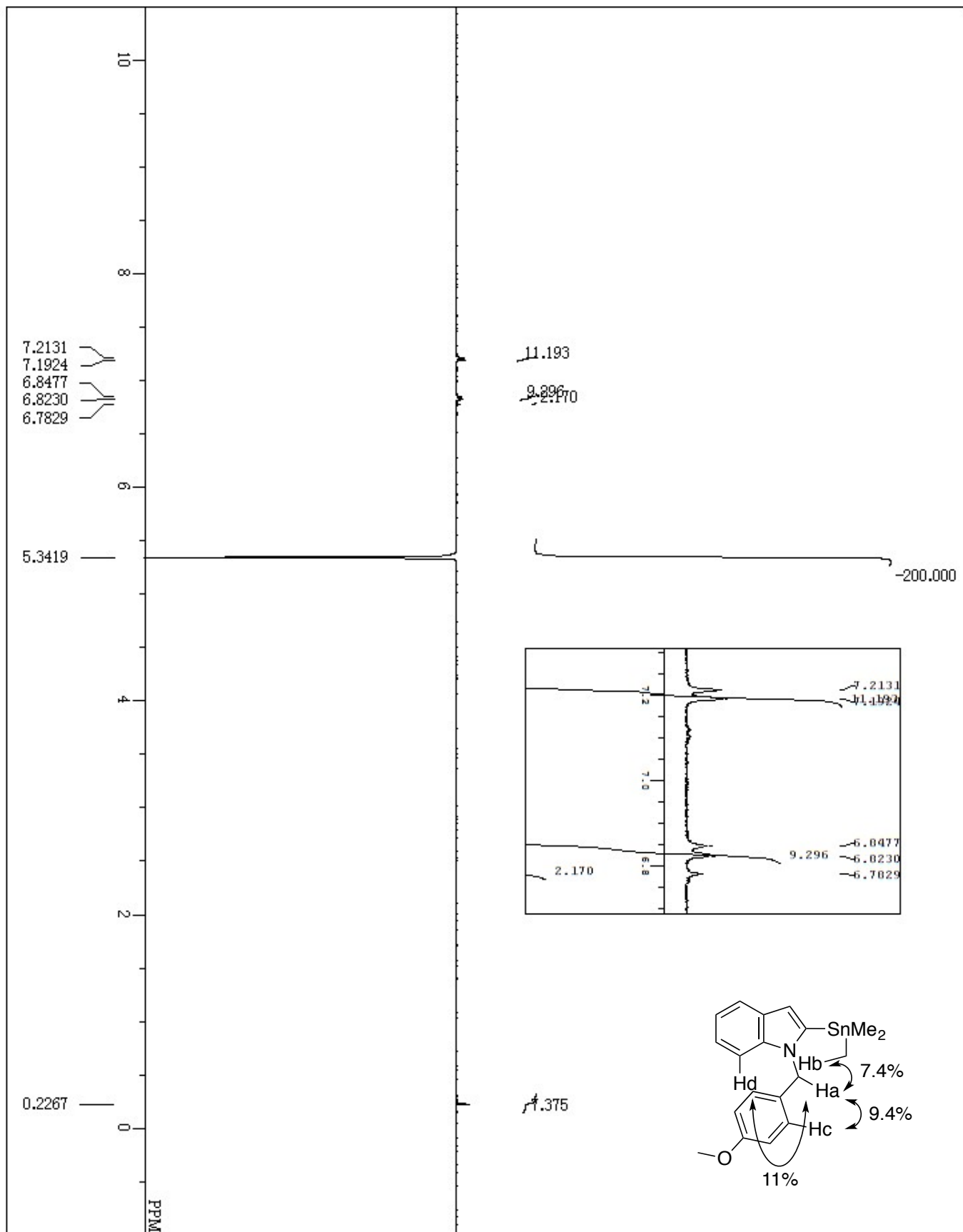


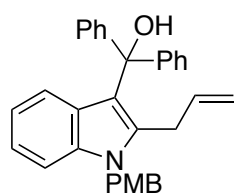
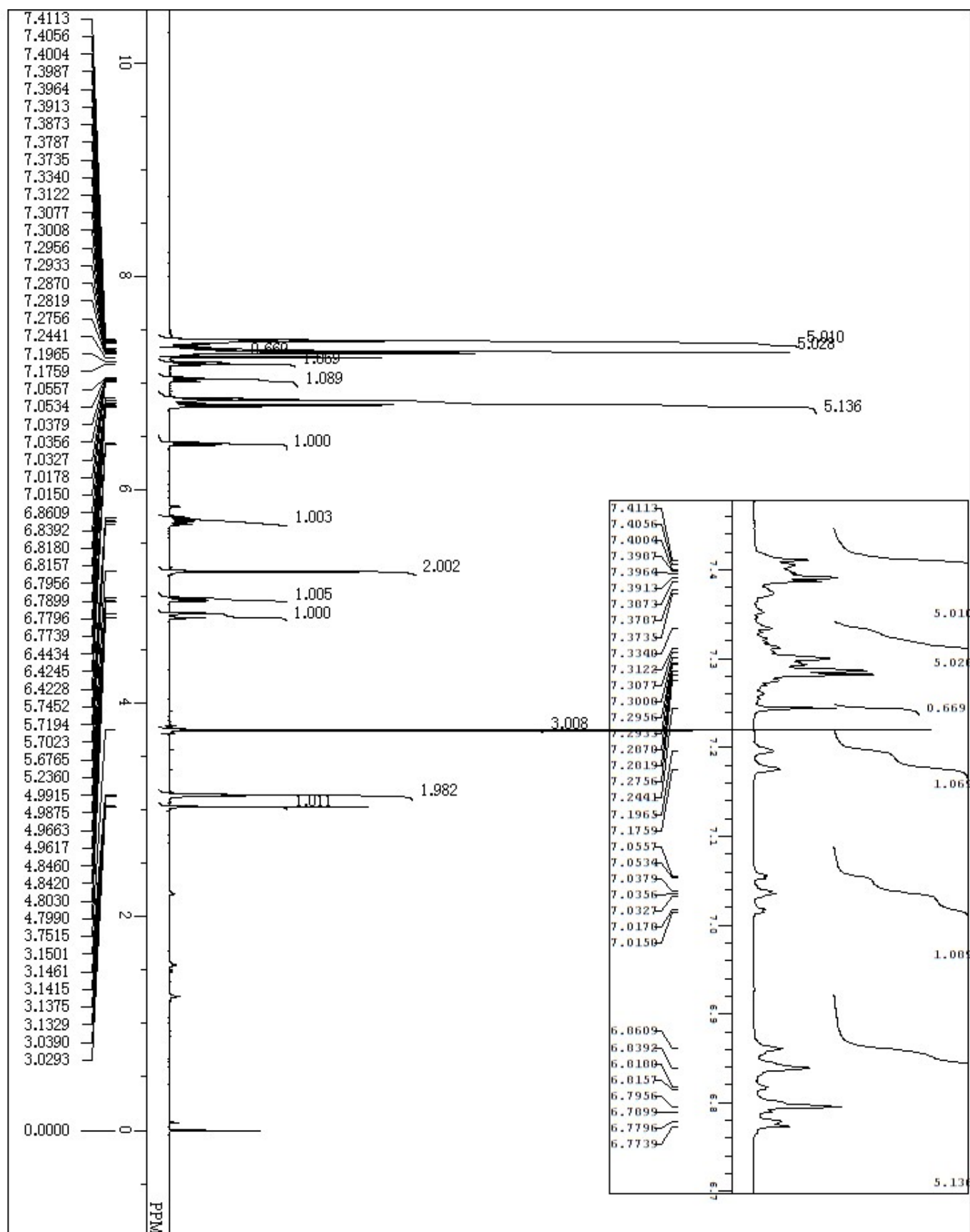


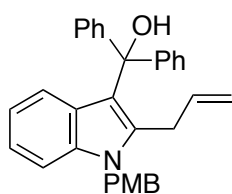
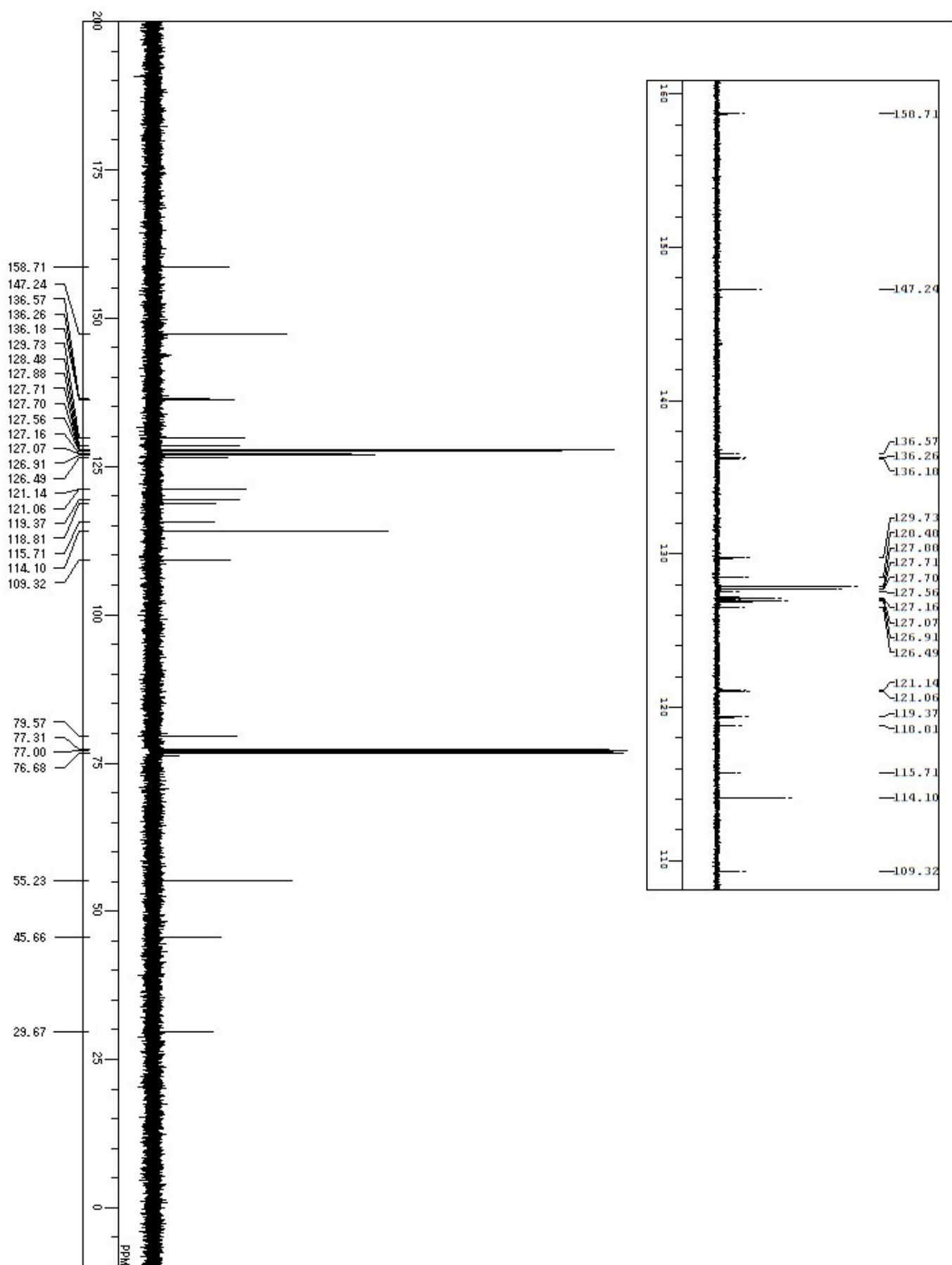




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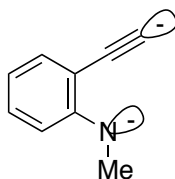






13. DFT Calculations

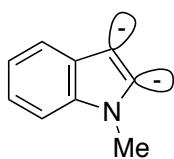
Calculations were performed with the GAUSSIAN 09 program package. All calculations were performed with the B3LYP method using the split valence basis set with polarization. 6-31G*+ basis set was used for all atoms. Energy difference was calculated using Sum of electronic and thermal Energies.



(Scheme 1, A) B3LYP/6-31+g(d)

Energy = -401.621612 (Hartree)

Atom	X	Y	Z
C	-0.9009	-1.307126	0.000151
C	-0.597258	0.107887	0.000015
C	0.840491	0.453321	0.000201
C	1.777133	-0.59299	-0.000063
C	1.437632	-1.965704	-0.000091
C	0.08144	-2.306269	-0.000021
H	-1.944232	-1.61671	-0.000002
H	2.828503	-0.305078	-0.000108
H	2.216795	-2.730645	-0.000229
H	-0.225054	-3.357953	-0.000052
C	1.326048	1.806055	0.000277
N	-1.516883	1.079611	-0.000146
C	-2.884149	0.665006	-0.000027
H	-3.189558	0.048528	0.888108
H	-3.539429	1.553667	-0.000228
H	-3.189639	0.048107	-0.887889
C	1.86303	2.940286	-0.000205



(Scheme 1, B) B3LYP/6-31+g(d)

Energy = -401.572927 (Hartree)

Atom	X	Y	Z
C	-0.56896	-1.442416	-0.000008
C	0.218146	-0.288284	-0.000018
C	-0.340728	1.06064	0.000004
C	-1.751415	1.1421	0.000006
C	-2.551636	-0.011911	0.000008
C	-1.974255	-1.303544	-0.000003
H	-0.121158	-2.443839	-0.000013
H	-2.215761	2.132916	0.000029
H	-3.642136	0.084679	0.000021
H	-2.610803	-2.193029	-0.000001
C	0.727179	2.032034	0.000012
C	1.940964	1.305325	-0.000009
N	1.577209	-0.117835	-0.000048
C	2.506607	-1.205599	0.000029
H	2.400866	-1.859742	-0.890745
H	3.512274	-0.766561	0.000035
H	2.40085	-1.859645	0.890881

14. References

- ¹ Still, W.C. et al. *J. Org. Chem*, **1978**, *43*, 2923.
- ² Pingborn, A.B.; Giardello, M.A.; Grubbs, R.H.; Rosen R.K.; Timmers F.J. *Organometallics* **1996**, *15*, 1518-1520.
- ³ Mohammed I. et al., *ACS Med. Chem. Lett.*, **2012**, *3*, 465.
- ⁴ Hiroya et al., *J. Org. Chem.*, **2004**, *69*, 1126-1136.
- ⁵ Higuchi, K.; Sato, Y.; Kojima, S.; Tsuchimochi, M.; Sugiura, K.; Hatori, M.; Kawasaki, T. *Tetrahedron* **2010**, *66*, 1236.