Supporting Information for

Total Synthesis PDE-II by Copper-Mediated Double Amination

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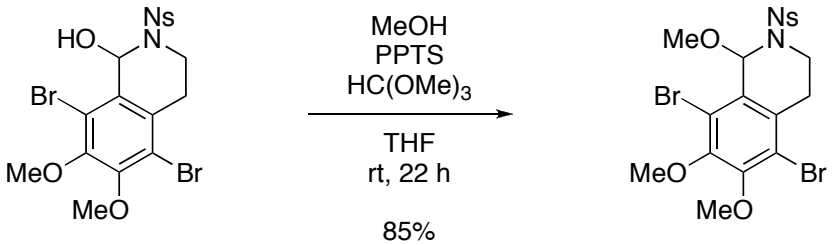
General Remarks.

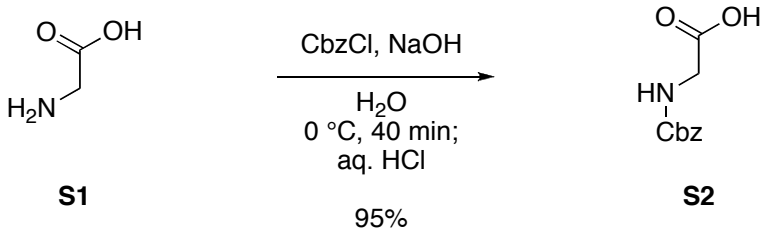
All reactions were performed in oven-dried glassware, sealed with a rubber septum under a slight positive pressure of argon unless otherwise noted. Anhydrous THF and dichloromethane were purchased from Kanto Chemical Co., Inc. Diisopropylamine and TMSCl were distilled from CaH_2. Unless otherwise mentioned, materials were obtained from commercial suppliers and were used without further purification. Chromatography was carried out using Kanto silica gel 60 (230-400 mesh). Gel permeation chromatography was carried out using a Japan Analytical Industry Co., Ltd-LC-9201. Preparative TLC was performed with precoated silica gel 60 F_{254} plates (Merck). IR spectra were measured on a JASCO IR Report-100 spectrometer or a Shimazu FTIR-8300 spectrometer. NMR spectra were measured on a Varian Gemini 2000, a JEOL AL 400, a JEOL ECP 500, or a JEOL ECA 600 spectrometer. For ^{1}H NMR spectra, chemical shifts are expressed in ppm downfield from internal tetramethylsilane (δ 0) or relative internal $CHCl_3$ (δ 7.26), or acetone (δ 2.04), or DMSO (δ 2.49). For ^{13}C NMR spectra, chemical shifts are expressed in ppm downfield from relative internal $CHCl_3$ (δ 77.0), or acetone (δ 29.8 and 206.5), or DMSO (δ 39.7). Coupling constants are in hertz. Mass spectra were recorded on a JEOL JMS-DX-303 or a JMS-AX-500 spectrometer. Elemental analyses were performed by a Yanaco CHN CORDER MT-6 spectrometer.



8 **9**

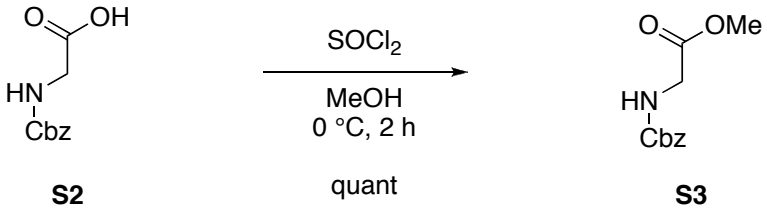
5,8-Dibromo-2-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-methoxyisoquinoline (9). A 300-mL round-bottomed flask equipped with a magnetic stirring bar was charged with **8**[1] (1.00 g, 1.92 mmol), PPTS (528.3 mg, 2.10 mmol), dry THF (4.1 mL), trimethyl orthoformate (1.0 mL), and MeOH (12.3 mL). The resulting mixture was stirred vigorously at room temperature for 21.5 h, after which time TLC (hexanes-ethyl acetate = 1:1) indicated complete consumption of the starting material. The reaction mixture was concentrated under reduced pressure. The residue was treated with saturated aqueous ammonium chloride followed by saturated aqueous sodium bicarbonate. The mixture was filtered, and the solid was washed with ethyl acetate and water to afford product **9** (20.7 mg, 36.6 μmol, 1.9%) as a colorless powder. The filtrate was separated, and the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with 1:1 mixture of saturated aqueous ammonium chloride and saturated aqueous sodium bicarbonate, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the crude **9**. Trituration with hexanes-ethyl acetate = 1:1 and the resulting solid was filtrated to afford analytically pure **9** (905.7 mg, 1.60 mmol, 83%, 85% as a combined yield) as a colorless powder. R_f = 0.30 (hexanes-ethyl acetate = 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10–8.04 (m, 1H), 7.73–7.61 (m,

3H), 6.00 (s, 1H), 3.99 (dd, 1H, J = 14.6, 7.0 Hz), 3.90 (s, 3H), 3.87 (s, 3H), 3.69 (ddd, 1H, J = 14.6, 13.6, 4.4 Hz), 3.50 (s, 3H), 2.79 (dd, 1H, J = 17.6, 4.4 Hz), 2.46 (ddd, 1H, J = 17.6, 13.6, 7.0 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.3, 150.0, 147.7, 134.0, 133.6, 131.9, 131.1, 130.72, 130.65, 124.6, 119.6, 119.3, 84.6, 60.9, 60.7, 56.2, 37.7, 28.8. IR (neat, cm^{-1}): 2939, 1541, 1458, 1404, 1396, 1339, 1313, 1302, 1173, 1080, 1026, 968, 760. HRMS-EI calcd. for $C_{18}H_{18}Br_2N_2O_7S$ (M^+) 563.9201; found 563.9209.



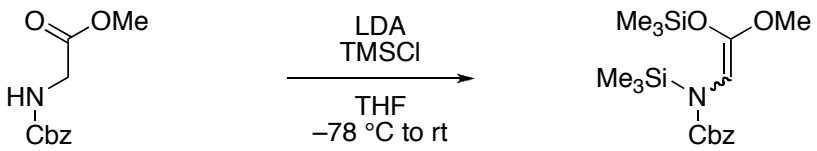
S1 **S2**

***N*-(Benzyloxycarbonyl)glycine (S2).**[2] A 300-mL three-necked round-bottomed flask equipped with a magnetic stirring bar and fitted with two dropping funnels was charged with glycine (**S1**) (10.0 g, 133 mmol) and 2 M aqueous sodium hydroxide (67.5 mL). The flask was then cooled to 0 °C. To the vigorously stirred solution were added CbzCl (22.8 mL, 160 mmol, 1.2 equiv) and 4 M sodium hydroxide (33.8 mL) simultaneously over a period of 10 min via each dropping funnel. The reaction mixture was stirred for an additional 40 min at 0 °C, after which time TLC (H_2O-AcOEt-*n*-BuOH-MeOH = 1:1:1:1) indicated complete consumption of glycine (**S1**). The aqueous solution was washed three times with diethyl ether and acidified with 6 M hydrochloric acid to pH 1. The resulting mixture was cooled at 0 °C to give a precipitate, which was collected by filtration, washed with small portions of cold water, and dried under reduced pressure to afford analytically pure **S2** (26.4 g, 126 mmol, 95%) as colorless crystals. R_f = 0.66 (H_2O-AcOEt-*n*-BuOH-MeOH = 1:1:1:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.58 (br s, 1H), 7.62-7.48 (br s, 1H), 7.44–7.25 (m, 5H), 5.05 (s, 2H), 3.70 (d, 2H, J = 5.6 Hz). ^{13}C NMR (100 MHz, DMSO-d_6): δ 171.7, 156.6, 137.1, 128.4, 127.9, 127.8, 65.6, 42.2. IR (neat, cm^{-1}): 3335, 1695, 1541, 1408, 1290, 1252, 1055. HRMS-EI calcd. for $C_{10}H_{11}NO_4$ (M^+), 209.0688; found 209.0682.



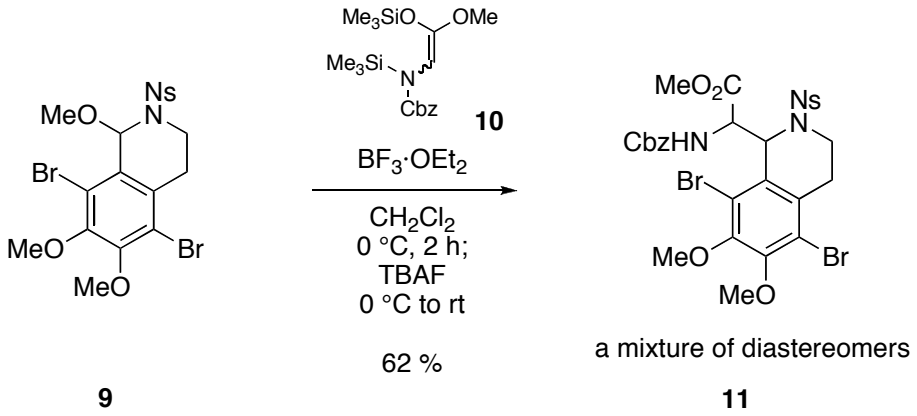
S2 **S3**

***N*-(Benzyloxycarbonyl)glycine methyl ester (S3).** A 300-mL three-necked round-bottomed flask equipped with a magnetic stirring bar and fitted with a dropping funnel was charged with **S2** (2.50 g, 12.0 mmol) and methanol (60 mL). The flask was cooled to 0 °C, and thionyl chloride (1.20 mL, 16.5 mmol, 1.4 equiv) was added to the vigorously stirred solution over a period of 10 min. The mixture was stirred for an additional 2 h, after which time TLC (ethyl acetate) indicated complete consumption of the starting acid **S2**. The reaction mixture was concentrated under reduced pressure to give a crude material, which was purified by silica gel column chromatography (ethyl acetate) to afford pure **S3** (2.66 g, 11.9 mmol, quant) as a colorless oil. R_f = 0.55 (ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32–7.18 (m, 5H), 5.58 (br s, 1H), 5.02 (s, 2H), 3.84 (d, 2H, J = 5.6 Hz), 3.62 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 156.2, 136.1, 128.2, 127.9, 127.8, 66.7, 51.9, 42.3. IR (neat, cm^{-1}): 3337, 2953, 1701, 1508, 1443, 1364, 1207, 1051, 1004. HRMS-EI calcd. for $C_{11}H_{13}NO_4$ (M^+) 223.0845; found 223.0833.



S3 **10**

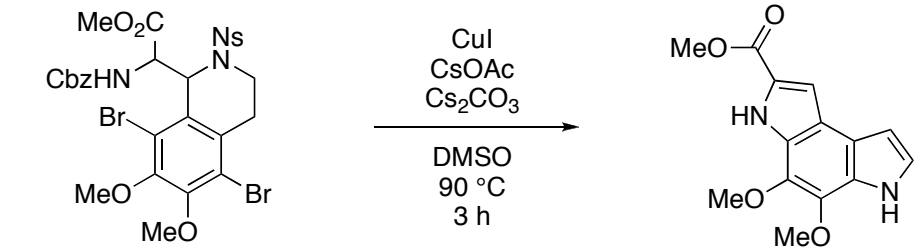
Benzyl 2-methoxy-2-(trimethylsilyl)vinyl(trimethylsilyl)carbamate (10).[3] A flame-dried 200-mL three-necked round-bottomed flask equipped with a magnetic stirring bar and fitted with dropping funnel was charged with freshly distilled diisopropylamine (2.8 mL, 20 mmol, 2.0 equiv) and dry THF (22.4 mL). The resulting solution was cooled to 0 °C. To the reaction mixture was added *n*-BuLi (1.51 M in *n*-hexane, 13.3 mL, 20 mmol, 2.0 equiv) dropwise over the period of 5 min at 0 °C. The reaction mixture was stirred at 0 °C for 20 min then cooled to –78 °C. To the reaction mixture was added dry THF (6.3 mL) solution of methyl ester **S3** (2.25 g, 10.1 mmol) and trimethylsilyl chloride (5.1 mL, 40 mmol, 4.0 equiv) slowly over the period of 15 min via a dropping funnel. After stirred for 20 min at –78 °C, the reaction mixture was then warmed to room temperature and stirred for another 2 h. The reaction mixture was concentrated under reduced pressure. The residue was diluted with dry hexanes (50 mL) and passed through Celite®, and the filter cake was washed with hexanes (50 mL). The filtrate was concentrated under reduced pressure to afford the crude ketene silyl acetal **10** (3.99 g) as a pale yellow oil, which was used to the next reaction without further purification.



9 **11**

Methyl 2-(benzyloxycarbonylamino)-2-(5,8-dibromo-6,7-dimethoxy-2-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanoate (11). An oven-dried 200-mL round-bottomed flask equipped with a magnetic stirring bar was charged with hemiaminal **9** (1.14 g, 201 mmol), ketene silyl acetal **10** (3.99 g, theoretically 5.0 equiv), and dry dichloromethane (20.0 mL). The resulting mixture was cooled to 0 °C. To the reaction mixture was added $BF_3{\cdot}OEt_2$ (745 μL, 6.04 mmol, 3.0 equiv) slowly at 0 °C over the period of 12 min. The reaction mixture was stirred at 0 °C for 2 h, after which time TLC (dichloromethane-methanol = 50:1) indicated complete consumption of the starting hemiaminal **9** (R_f = 0.72). Tetrabutylammonium fluoride (1.0 M in THF, 20 mL, 20 mmol, 10 equiv) was dropwise to the solution over the period of 3 min. After stirred for 15 min at 0 °C, the reaction mixture was warmed to room temperature and stirred for another 1 h, after which time TLC (dichloromethane-methanol = 50:1) indicated complete removal of the TMS group on nitrogen (R_f = 0.42). The reaction was quenched with saturated aqueous ammonium chloride. The mixture was concentrated under reduced pressure to remove organic solvents. The residue was extracted three times with ethyl acetate. The combined organic extracts were washed with aqueous ammonium chloride and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated

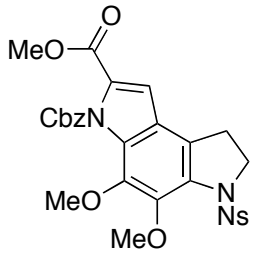
under reduced pressure. The residue was purified by silica gel column chromatography followed by GPC to provide the pure amination precursor **11** (952 mg, 1.23 mmol, 62%) as a white amorphous. R_f = 0.56 (dichloromethane-methanol = 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.00–7.90 (m, 1H), 7.69–7.46 (m, 3H), 7.40–7.15 (m, 5H), 5.78–5.54 (m, 2H), 5.08–4.85 (m, 3H), 4.15–3.54 (m, 11H), 3.10–2.80 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 155.7, 151.0, 149.4, 148.0, 136.0, 133.8, 132.2, 131.7, 131.5, 130.9, 126.4, 128.5, 128.2, 127.8, 124.2, 119.6, 118.7, 96.1, 67.2, 60.8, 58.1, 57.2, 53.0, 40.6, 27.3 (observed peaks). IR (neat, cm^{-1}): 1730, 1717, 1541, 1506, 1458, 1373, 1217, 1169, 1028, 772. Elemental analysis; calcd. (%) for $C_{28}H_{27}Br_2N_3O_{10}S$: C 44.40, H 3.59, N 5.55; found: C 44.62, H 3.66, N 5.47.



a mixture of diastereomers

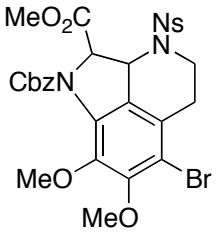
11 **15**

Methyl 3,6-dihydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (15). A 20-mL flame-dried round-bottomed flask was equipped with a magnetic stirring bar was charged with **11** (312.6 mg, 413 µmol) and copper iodide (118.0 mg, 620 µmol, 1.5 equiv). Cesium acetate (393.9 mg, 2.05 mmol, 5.0 equiv) and cesium carbonate (408.1 mg, 1.25 mmol, 3.0 equiv) were weighed and added to the flask in a glove box. The flask was then evacuated then backfilled with argon three times. To the mixture was added dry DMSO (4.1 mL). The resulting pale yellow solution was stirred at 90 °C for 3 h and was cooled to room temperature. The reaction mixture was treated with 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide. The aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide, brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography and preparative TLC to afford the pyrroloindole **15** (64.0 mg, 233 µmol, 57%) as a white solid. R_f = 0.48 (hexanes-ethyl acetate = 1:1). ^{1}H NMR (500 MHz, acetone-d_6): δ 10.59 (br s, 1H), 10.36 (br s, 1H), 7.35 (d, 1H, J = 1.5 Hz), 7.25 (dd, 1H, J = 2.4, 2.0 Hz), 6.71 (dd, 1H, J = 2.4, 1.6 Hz), 4.03 (s, 3H), 3.98 (s, 3H), 3.85 (s, 3H). ^{13}C NMR (125 MHz, acetone-d_6): δ 162.5, 138.8, 134.7, 129.3, 126.4, 126.1, 123.5, 118.4, 117.9, 108.3, 101.9, 62.0, 61.3, 51.6. IR (neat, cm^{-1}): 3335, 2939, 1693, 1518, 1443, 1379, 1288, 1265, 1202, 1169, 1148, 1053, 760. HRMS-EI calcd. for $C_{14}H_{14}N_2O_4$ (M^+) 274.0954; found 274.0942.



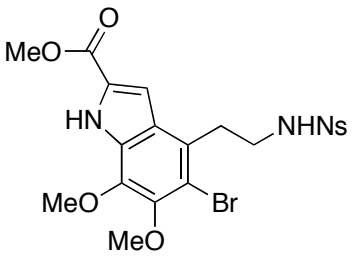
12

Methyl 4,5-dimethoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carbozylate (**12**) R_f = 0.33 (hexanes-ethyl acetate = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14–8.10 (m, 1H), 7.71–7.60 (m, 3H), 7.50–7.42 (m, 2H), 7.41–7.30 (m, 3H), 7.06 (s, 1H), 5.43 (s, 2H), 4.43 (t, 2H, *J* = 7.5 Hz), 3.83 (s, 3H), 3.70 (s, 3H), 3.38 (s, 3H), 3.14 (t, 2H, *J* = 7.5 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.8, 152.6, 147.5, 142.9, 138.2, 134.9, 134.2, 133.0, 131.8, 131.4, 130.6, 130.3, 128.9, 128.74, 128.71, 128.5, 124.0, 123.3, 119.9, 109.9, 71.0, 61.1, 59.8, 54.2, 52.2, 28.9. IR (neat, cm^{-1}): 1771, 1717, 1541, 1491, 1369, 1350, 1252, 1163, 754. HRMS-Fab calcd. for $C_{28}H_{25}N_3O_{10}S$ (M^+) 595.1261; found 595.1265.



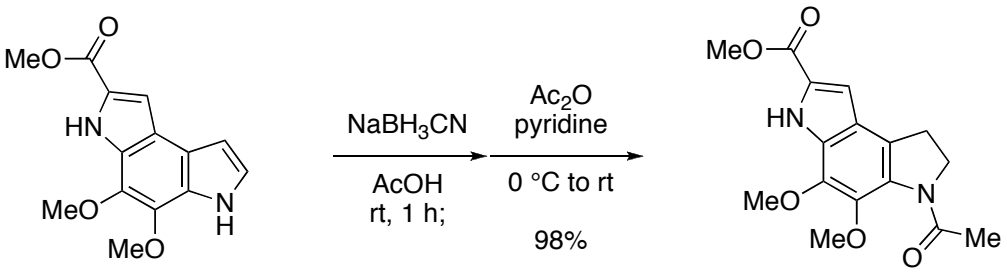
13

1-Benzyloxycarbonyl-6-bromo-7,8-dimethoxy-3-(*o*-nitrobenzenesulfonyl)-2-methoxycarbonyl-1, 2,2a,3,4,5-hexahydro-1,3-diazaacenaphthylene (13). R_f = 0.42 (hexanes-ethyl acetate = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05–8.01 (m, 1H), 7.75–7.68 (m, 2H), 7.63–7.59 (m, 1H), 7.43–7.32 (m, 5H), 5.30–5.17 (m, 3H), 4.83–4.80 (m, 1H), 4.24–4.18 (m, 1H), 3.85 (s, 3H), 3.78 (s, 3H), 3.60 (s, 3H), 3.11–3.04 (m, 1H), 2.93–2.88 (m, 1H), 2.44–2.31 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 153.0, 152.3, 148.3, 141.8, 135.1, 134.3, 131.9, 131.8, 131.6, 131.4, 130.1, 128.7, 128.5, 124.2, 122.3, 112.8, 71.8, 68.7, 60.9, 60.7, 59.0, 52.5, 45.7, 28.2. (one signal of an aromatic carbon is missing due to overlapping). IR (neat, cm^{-1}): 1695, 1539, 1435, 1416, 1337, 1259, 1207, 1161, 1080, 756. HRMS-Fab calcd. for $C_{28}H_{26}BrN_3O_{10}S$ (M^+) 675.0522; found 675.0529.



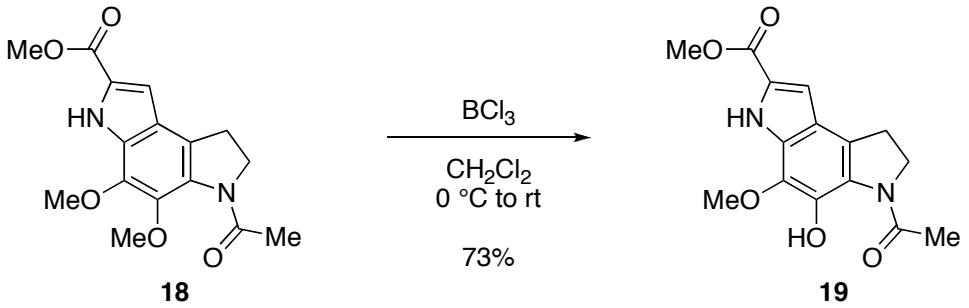
14

Methyl 5-bromo-6,7-dimethoxy-4-(2-(2-nitrophenylsulfonamido)ethyl)-1H-indole-2-carboxylate (**14**) R_f = 0.31 (hexanes-ethyl acetate = 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.01 (br s, 1H), 8.12–8.07 (m, 1H), 7.87–7.76 (m, 1H), 7.70–7.65 (m, 2H), 7.13 (d, 1H, *J* = 2.5 Hz), 5.44 (t, 1H, *J* = 6.3 Hz), 4.03 (s, 3H), 3.96 (s, 3H), 3.88 (s, 3H), 3.50-3.42 (m, 2H), 3.26 (t, 2H, *J* = 7.3 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.8, 147.7, 145.9, 138.0, 133.7, 133.4, 132.7, 130.9, 130.2, 127.7, 126.1, 125.5, 125.3, 114.0, 107.3, 61.2, 61.0, 52.2, 42.9, 33.5. IR (neat, cm^{-1}): 1747, 1545, 1468, 1435, 1362, 1296, 1271, 1169, 1016, 968, 754. HRMS-Fab calcd. for $C_{20}H_{20}BrN_3O_8S$ (M^+) 541.0154; found 541.0154.



15 **18**

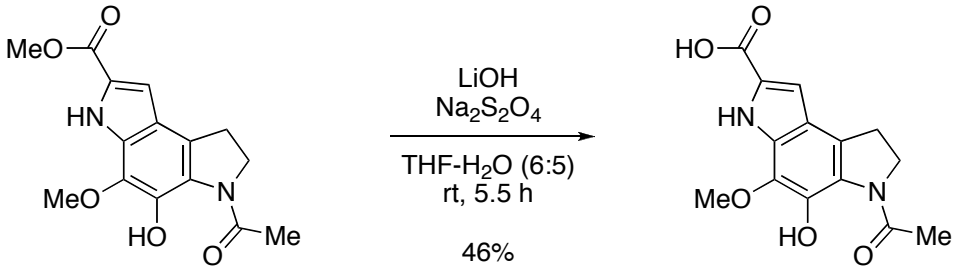
Methyl 6-acetyl-3,6,7,8-tetrahydro-4,5-dimethoxy-benzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylate (18).[4] A 50-mL round-bottomed flask equipped with a magnetic stirring bar was charged with pyrroloindole **15** (206.3 mg, 752 μmol) and acetic acid (2.1 mL, 0.36 M). $NaBH_3CN$ (ca. 1 g, excess) was added to the flask, and the resulting reaction mixture was stirred at room temperature for 1 h, after which time TLC (hexanes-ethyl acetate = 1:1) indicated complete consumption of the starting pyrroloindole **15** (R_f = 0.48). The resulting mixture was cooled to 0 °C. To the reaction mixture was added pyridine (2.1 mL, 0.36 M) and acetic anhydride (284.4 μL, 3.01 mmol, 4.0 equiv). The resulting solution was stirred at room temperature for 1.5 h, after which time TLC (hexanes-ethyl acetate = 1:1) indicated complete consumption of the dihydropyrroloindole. The reaction mixture was diluted with ethyl acetate and basified with saturated aqueous sodium bicarbonate (20 mL) and 1 M NaOH (1 mL). After separation of organic layer, the aqueous layer was extracted twice with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, 1 M HCl and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (dichloromethane-methanol = 50:1) to provide crude material **18**, which material was purified by GPC to afford pure **18** (235.3 mg, 739.2 μmol, 98%) as a yellow amorphous. R_f = 0.40 (dichloromethane-methanol = 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.04 (br s, 1H), 7.06 (s, 1H), 4.34 (t, 2H, *J* = 7.6 Hz), 4.05 (s, 3H), 3.95 (s, 3H), 3.84 (s, 3H), 3.10 (t, 2H, *J* = 7.6 Hz), 2.27 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 161.9, 141.3, 137.7, 131.2, 129.8, 128.2, 123.1, 121.1, 107.0, 61.3, 60.5, 52.04, 51.99, 28.3, 22.9. IR (neat, cm^{-1}): 3306, 3001, 2947, 2839, 1715, 1634, 1537, 1504, 1030, 995, 756. HRMS-EI calcd. for $C_{16}H_{18}N_2O_5$ (M^+) 318.1216; found 318.1219.



18 **19**

Methyl 6-acetyl-3,6,7,8-tetrahydro-5-hydroxy-4-methoxy-benzo[1,2-*b*:4,3-*b*'] dipyrrole-2-carboxylate (19, PDE-II methyl ester).[5] A 2-L oven-dried three-necked round-bottomed flask was equipped with a magnetic stirring bar was charged with dry dichloromethane (670 mL, 1.03 mM) and dry dichloromethane (30 mL) solution of **18** (219.3 mg, 689 μmol). The resulting mixture was cooled to 0 °C. To the clear solution was added BCl_3 (1.0 M in dichloromethane, 5.51 mL, 5.51 mmol, 8.0 equiv) dropwise at 0 °C over the period of 8 min. After stirred for 1 h at 0 °C, the reaction mixture was warmed to room temperature and stirred for additional 19 h, after which time TLC (dichloromethane-methanol = 20:1) indicated complete consumption of the starting material. The

reaction mixture was treated with saturated aqueous sodium bicarbonate (50 mL). The organic solvents were removed under reduced pressure. The residue was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by recrystallization (dichloromethane) to give pure **19** (131.3 mg, 431 μmol, 63%) as light brown crystals. The residue was purified by preparative TLC (dichloromethane-methanol = 50:1) to afford **19** (21.6 mg, 71.0 μmol, 10%) as a white solid. R_f = 0.46 (dichloromethane-methanol = 20:1). Mp: 248.9–252.1 °C (dichloromethane). ^{1}H NMR (600 MHz, $CDCl_3$): δ 12.03 (s, 1H), 8.85 (br s, 1H), 7.02 (d, 1H, *J* = 2.4 Hz), 4.18 (t, 2H, *J* = 7.8 Hz), 4.02 (s, 3H), 3.93 (s, 3H), 3.28 (t, 2H, *J* = 7.8 Hz), 2.34 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.8, 161.9, 139.1, 133.0, 131.3, 127.7, 127.0, 120.4, 117.3, 107.4, 60.6, 51.9, 51.3, 27.0, 23.9. IR (neat, cm^{-1}): 3323, 1688, 1452, 1437, 1298, 1261, 1097. HRMS-EI calcd. for $C_{15}H_{16}N_2O_5$ (M^+) 304.1059; found 304.1053.



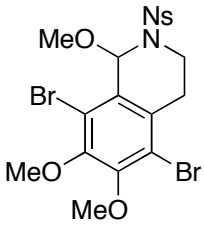
19 **2**

6-Acetyl-3,6,7,8-tetrahydro-5-hydroxy-4-methoxy-benzo[1,2-*b*:4,3-*b*']dipyrrole-2-carboxylic acid (2, PDE-II).[6] A 10-mL test tube equipped with a magnetic stirring bar was charged with PDE-II methyl ester (**19**) (15.4 mg, 50.6 μmol) and dry THF (617 μL). To the solution were added $Na_2S_2O_4$ (26.2 mg, 152 μmol, 3.0 equiv) and 1 M LiOH (506 μL, 5.0 equiv), and the resulting mixture was stirred at room temperature for 5.5 h, after which time TLC (dichloromethane-methanol = 10:1) indicated complete consumption of the starting material. THF was removed under resuced pressure, and the residue was diluted with water and then the aqueous layer was washed with dichloromethane. The aqueous layer was acidified by 1 M hydrochloric acid (541 mL, 10.7 equiv) to give PDE-II as a white precipitate. The precipitate was washed twice with 20 mM hydrochloric acid (2 mL). Benzene (2 mL) was added to the precipitate and the resulting mixture was completely dried under reduced pressure to afford analytically pure PDE-II (**2**) (6.8 mg, 23 μmol, 46%) as a white solid. The physical properties of the synthetic PDE-II (**2**) were identical in all aspects to those reported for the natural product.[4d] R_f = 0.11 (dichloromethane-methanol = 10:1). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.18 (s, 1H), 11.40 (br s, 1H), 6.94 (br s, 1H), 4.22 (t, 2H, *J* = 8.2 Hz), 3.78 (s, 3H), 3.20 (t, 2H, *J* = 8.2 Hz), 2.29 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6): δ 169.3, 162.4, 138.1, 132.6, 131.3, 128.8, 126.5, 120.7, 117.2, 106.9, 60.0, 50.8, 26.4, 23.6. IR (KBr, cm^{-1}): 3288, 2922, 2853, 1672, 1574, 1466, 1259, 1097, 1026, 799. HRMS-EI calcd. for $C_{14}H_{14}N_2O_5$ (M^+) 209.0903; found 209.0890.

References

(1) (a) K. Okano, H. Tokuyama, T. Fukuyama, *J. Am. Chem. Soc*. 2006, **128**, 7136. (b) K. Okano, H. Tokuyama, T. Fukuyama, *Chem. Asian J*. 2008, **3**, 296.
(2) H. E. Carter, R. L. Frank, H. W. Johnston, *Org. Synth., Coll. Vol. III* 1955, 167.
(3) (a) E. J. Cory and A.W. Gross, *Tetrahedron Lett*. 1984, **25**, 495. (b) K. Oisaki, Y. Suto, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc*. 2003, **125**, 5644.
(4) R. E. Bolton, C. J. Moody, C. W. Rees, G. Tojo, *J. Chem. Soc., Chem. Commun*. 1985, 1775.
(5) The demethylation required high dilution for complete consumption of the starting material.
(6) Reaction condition, see: (a) D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc*. 1988, **110**, 1321. (b)D. L. Boger and R. S. Coleman, *J. Am. Chem. Soc*. 1988, **110**, 4796. (c) K. S. MacMillan, Y. Nguyen, I. Hwang, D. L. Boger, *J. Am. Chem. Soc*. 2009, **131**, 1187. ^{1}H NMR data see: (d) Y. Enomoto, Y. Furutani, H. Naganawa, M. Hamada, T. Takeuchi, H. Umezawa, *Agric. Biol. Chem*. **1978**, *42*, 1331. (e) N. Komoto,

Y. Enomoto, M. Miyagaki, Y. Tanaka, K. Nitanai, H. Umezawa, *Agric. Biol. Chem*. **1979**, *43*, 555.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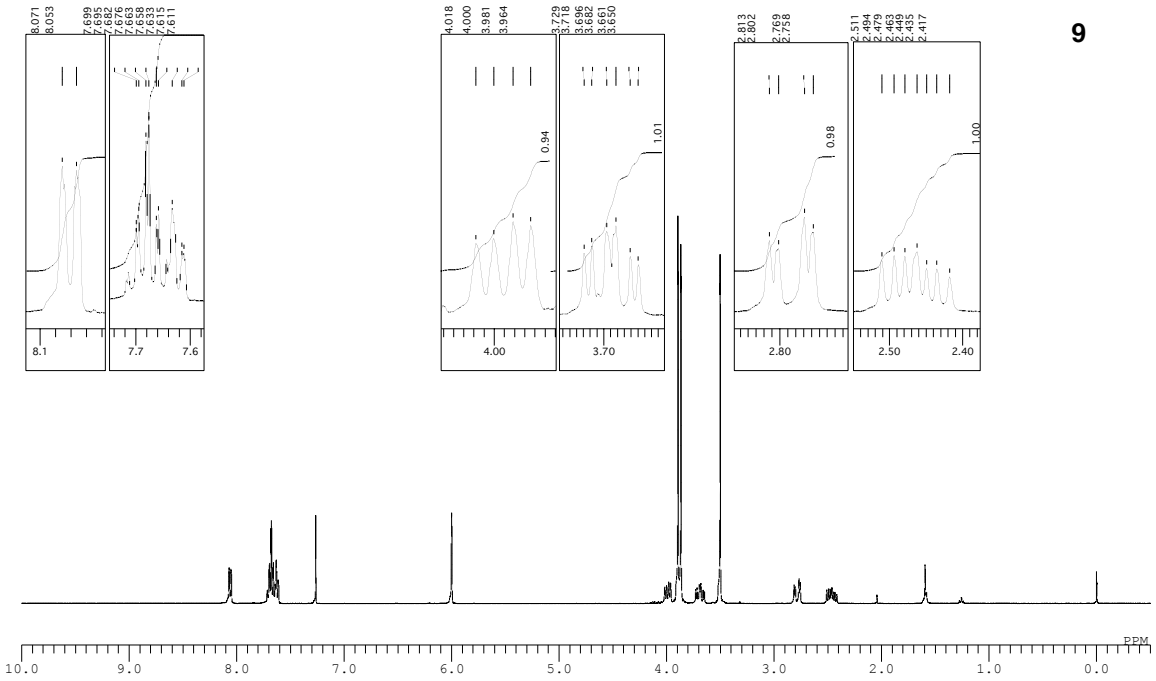
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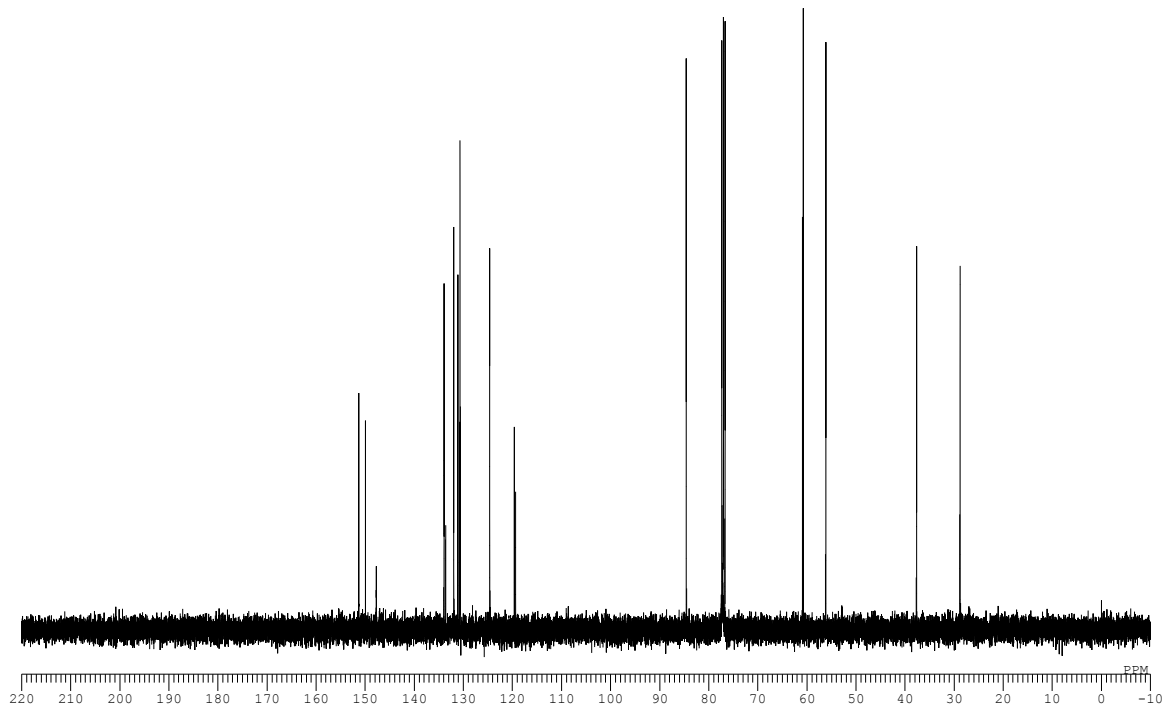
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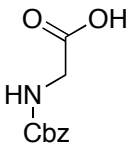
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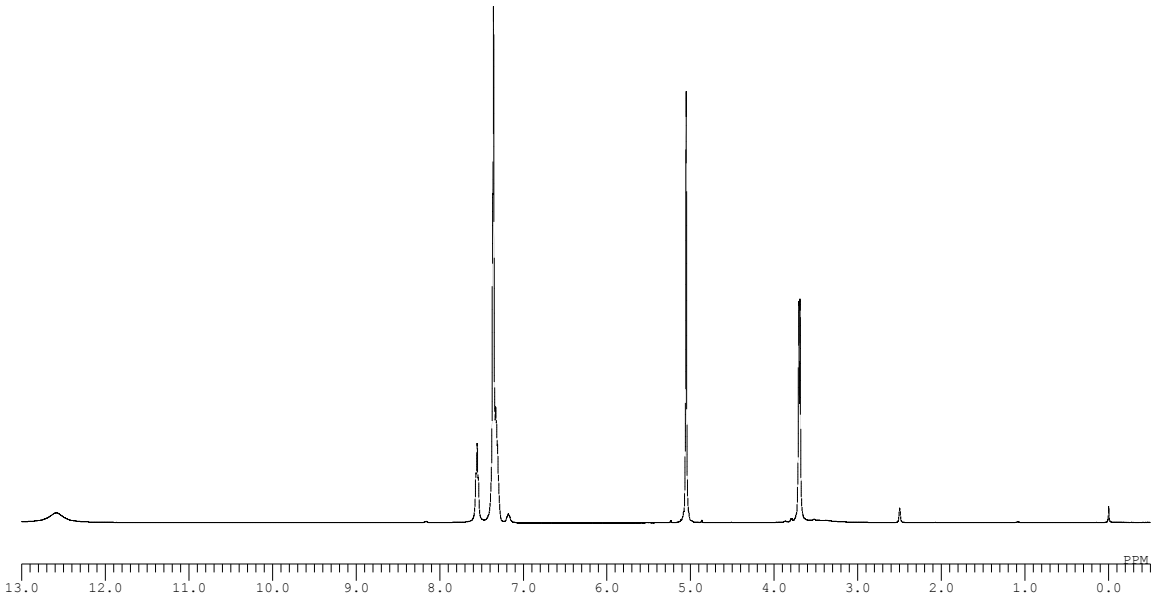
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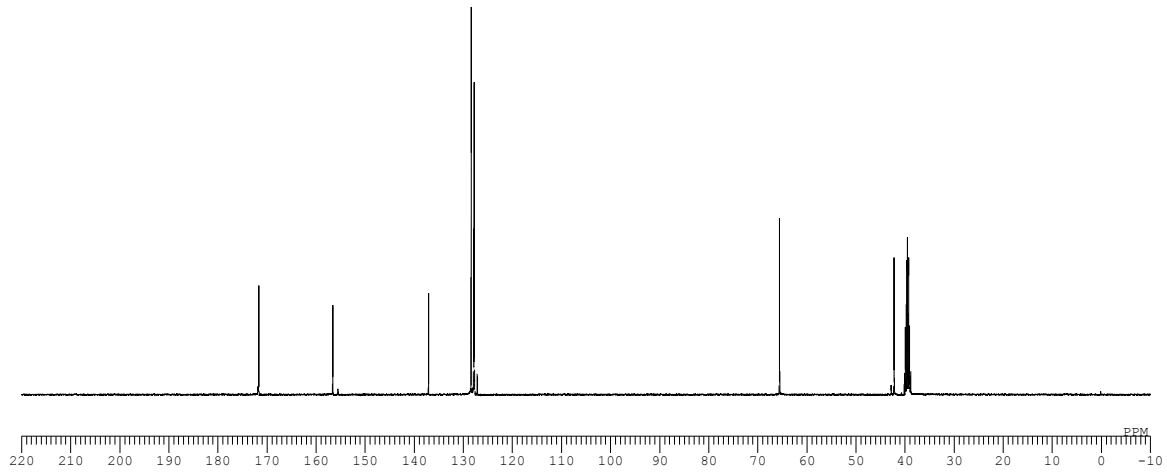
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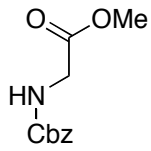
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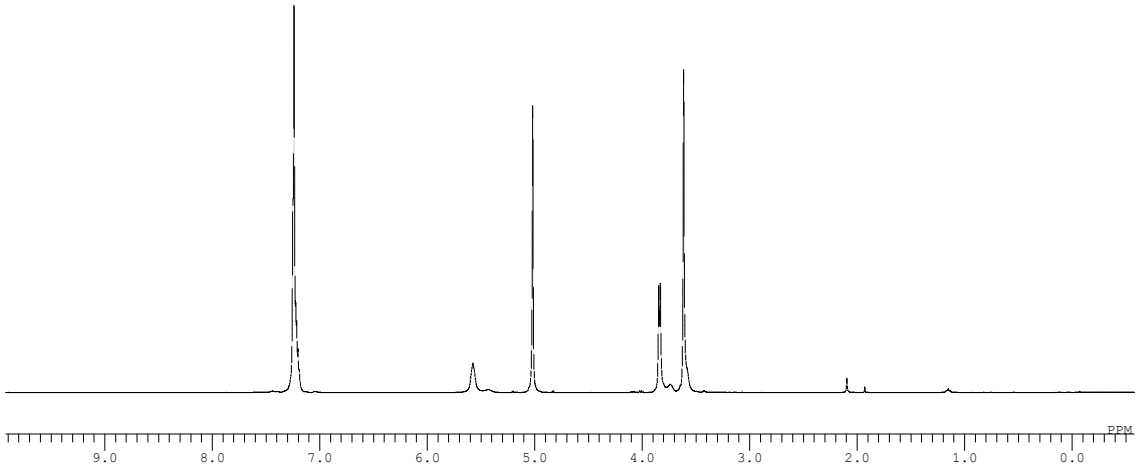
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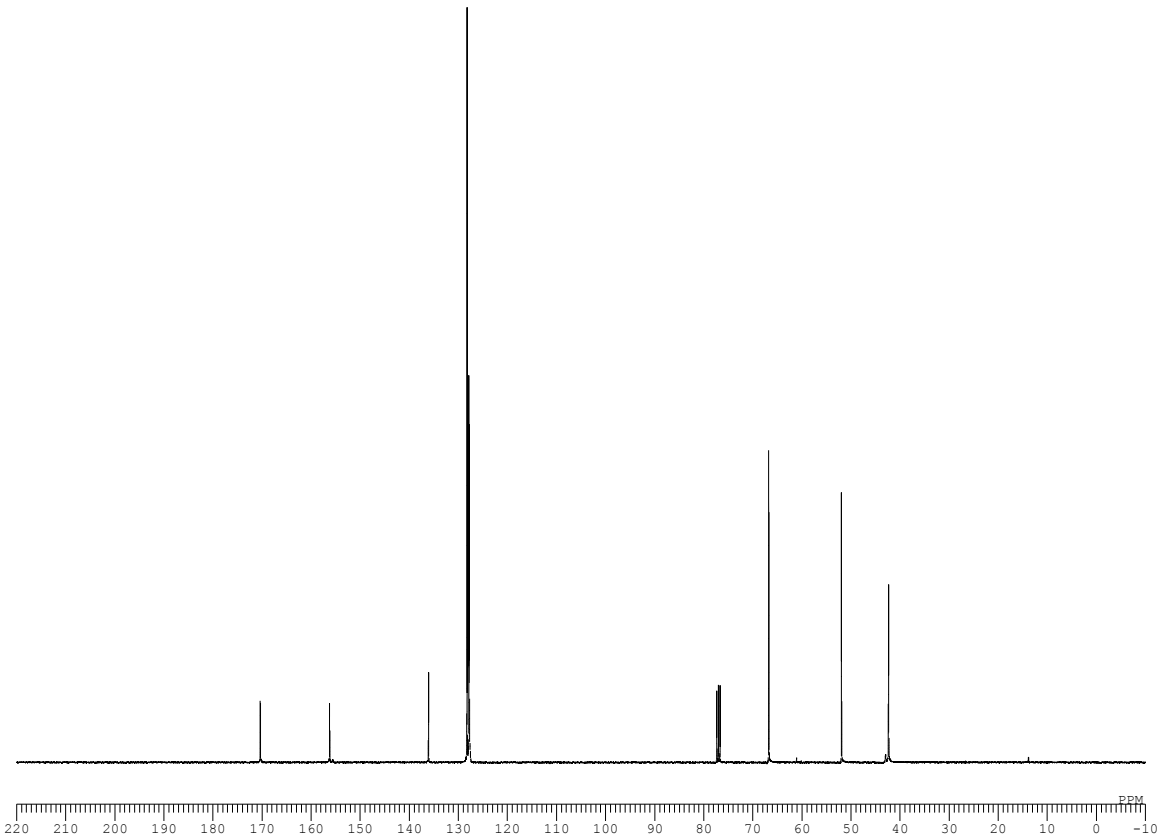
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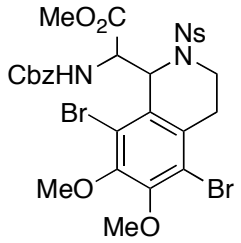
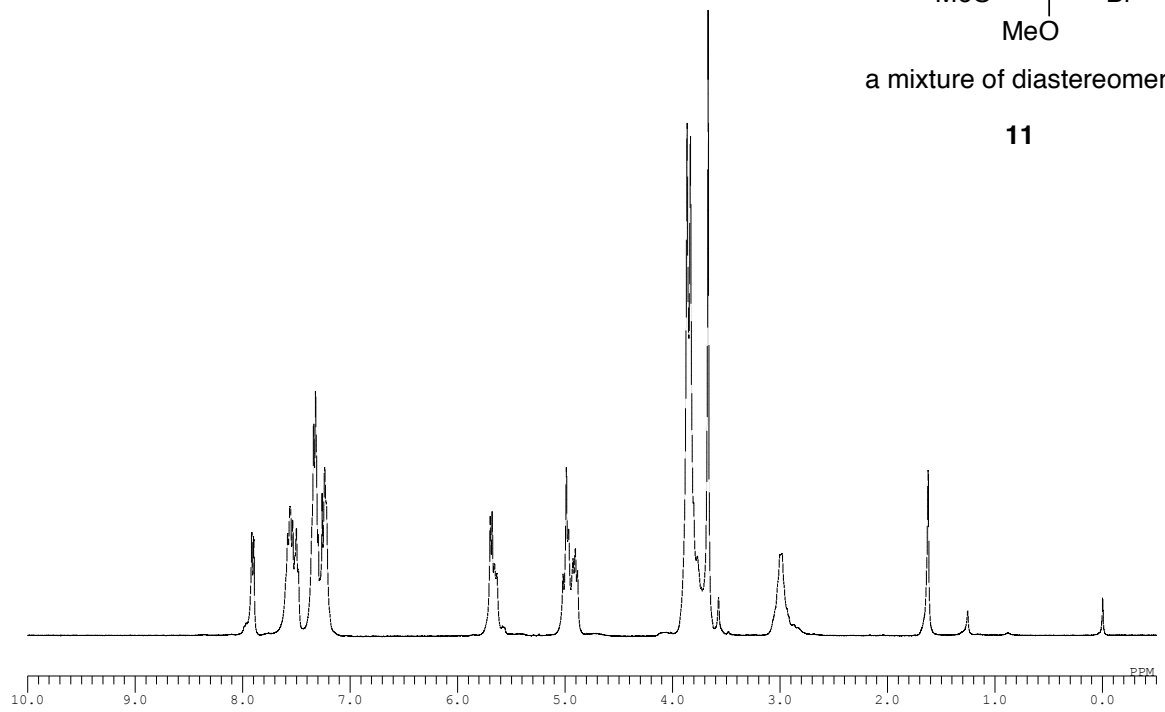
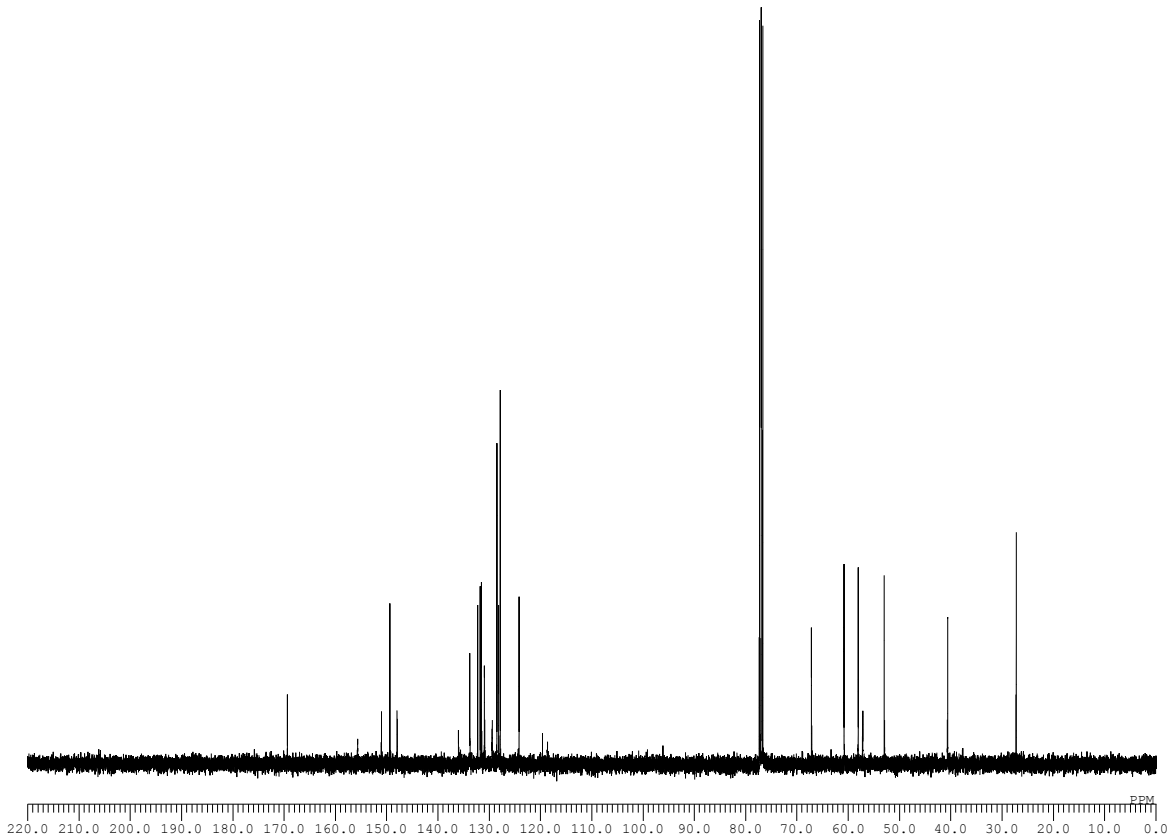
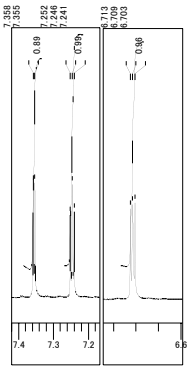


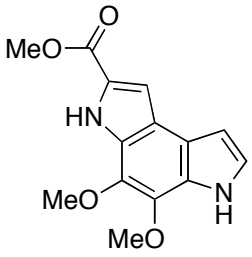
a mixture of diastereomers

11





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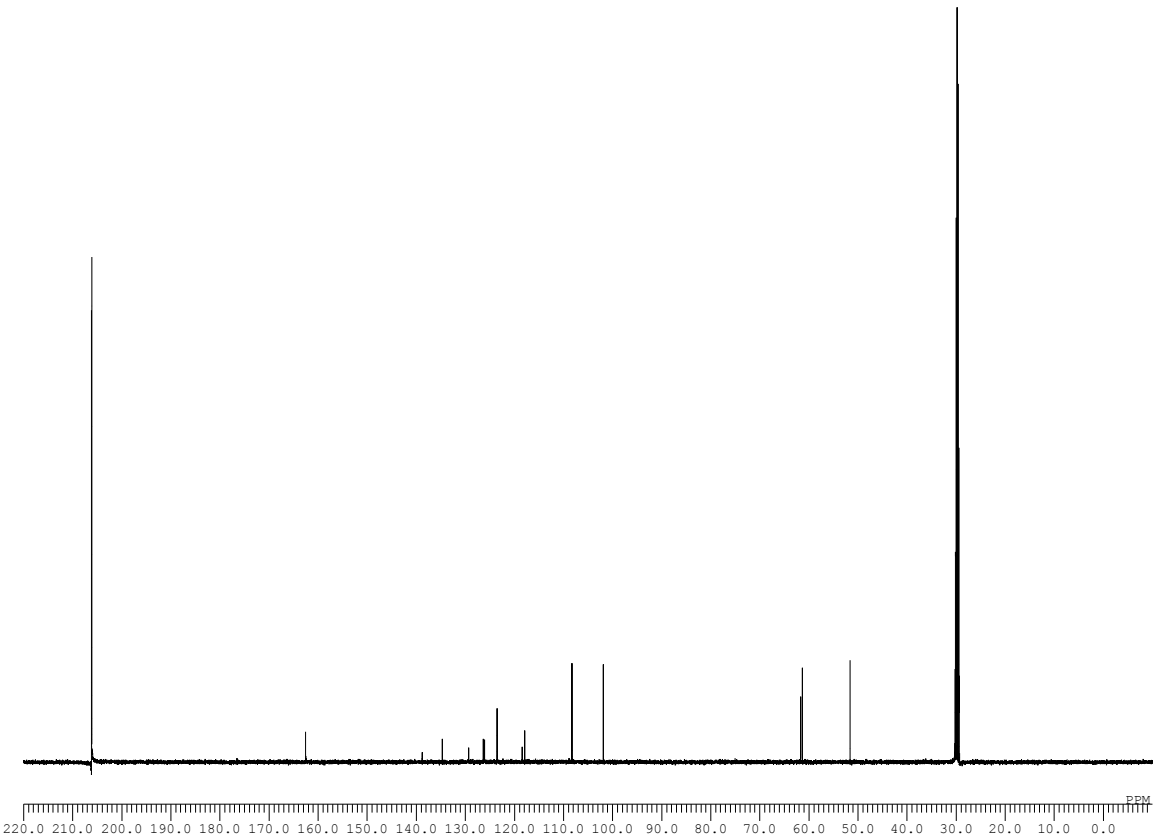
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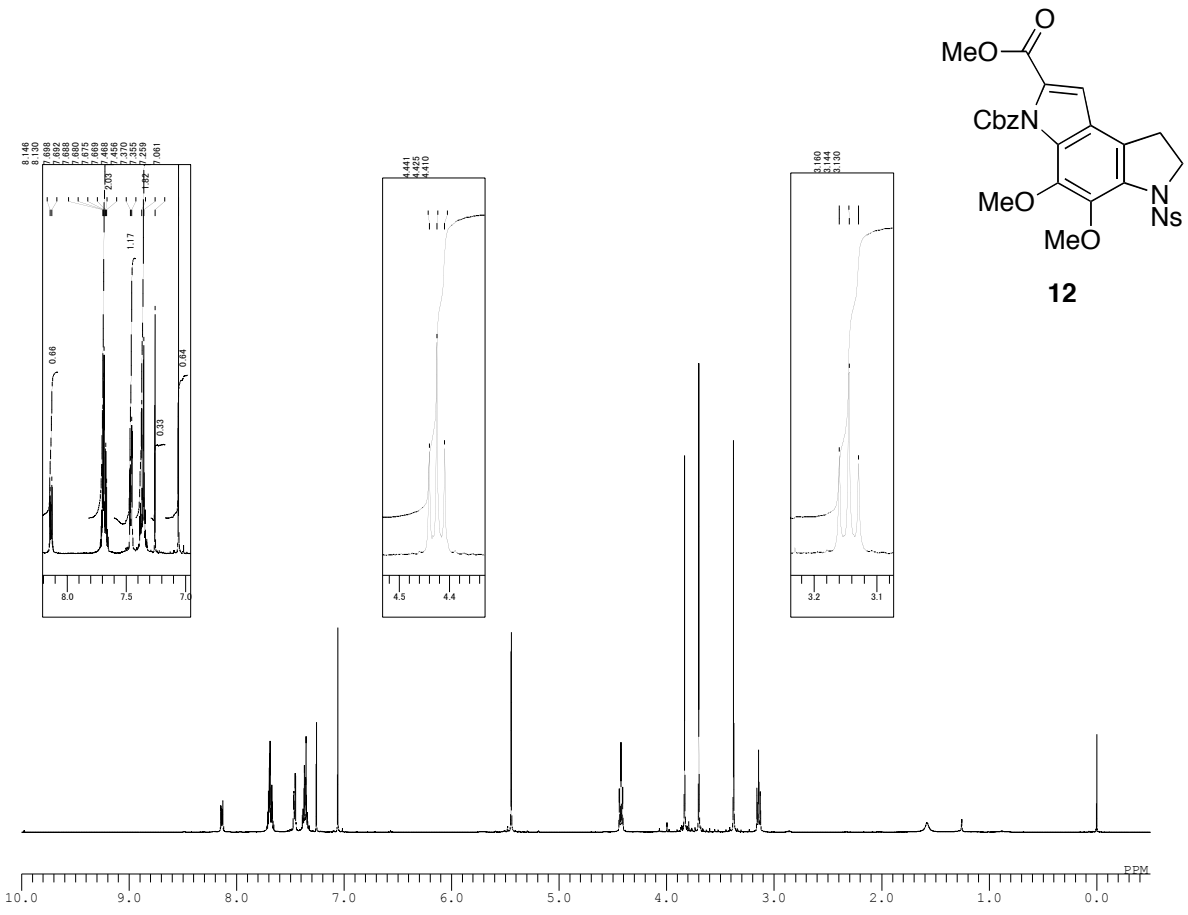
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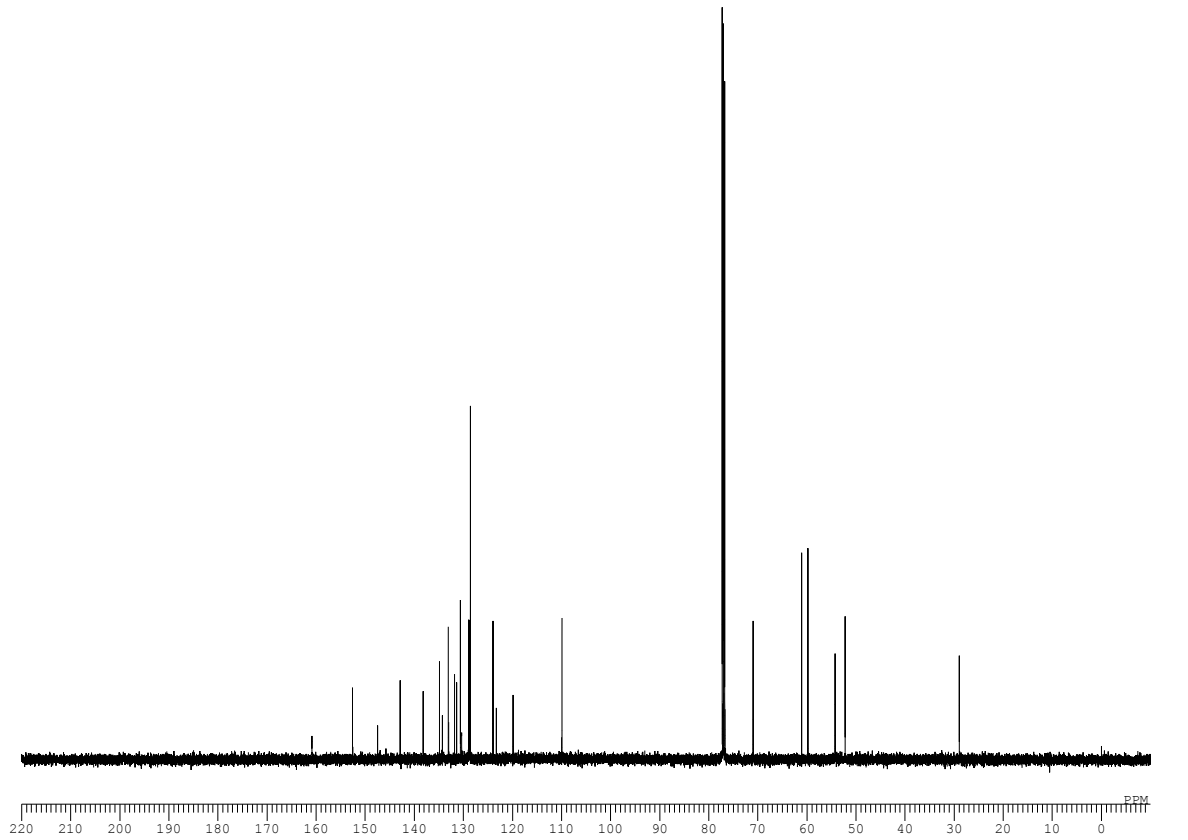
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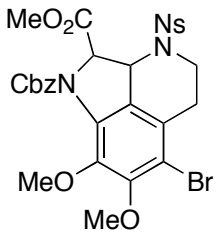
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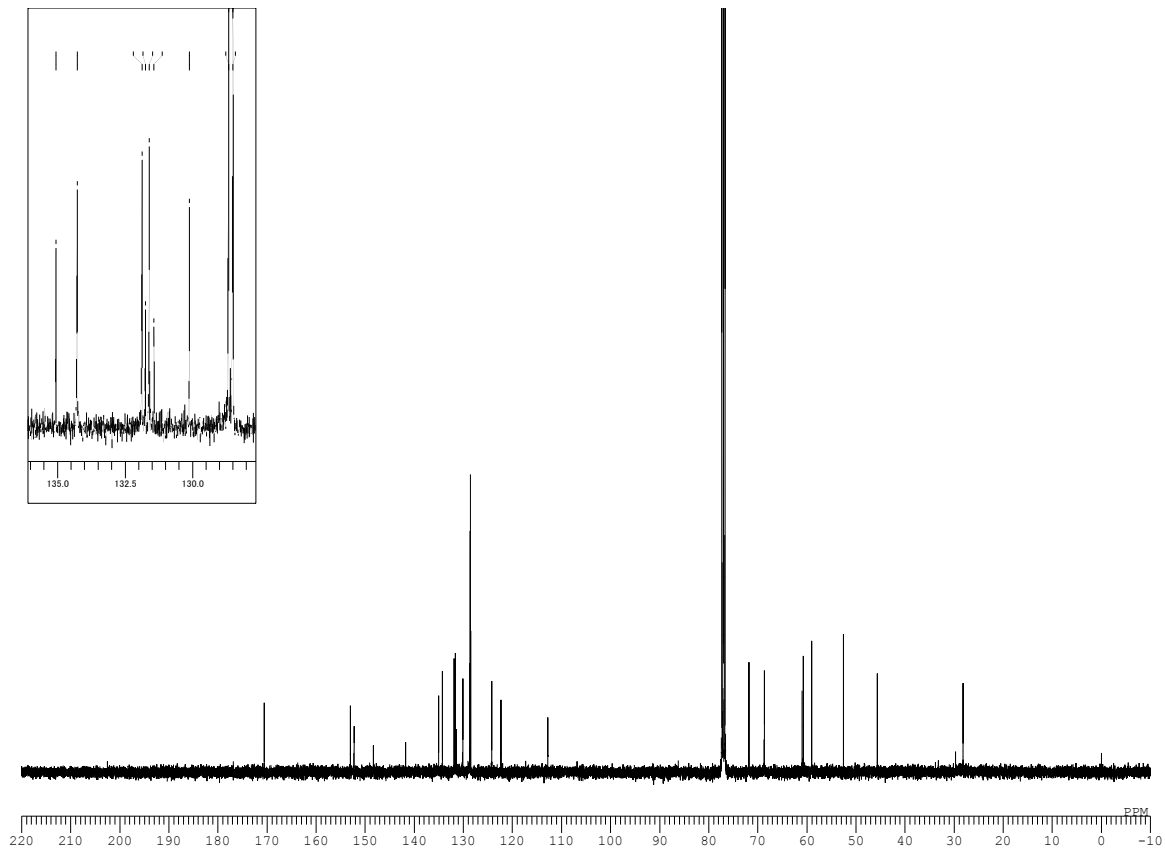
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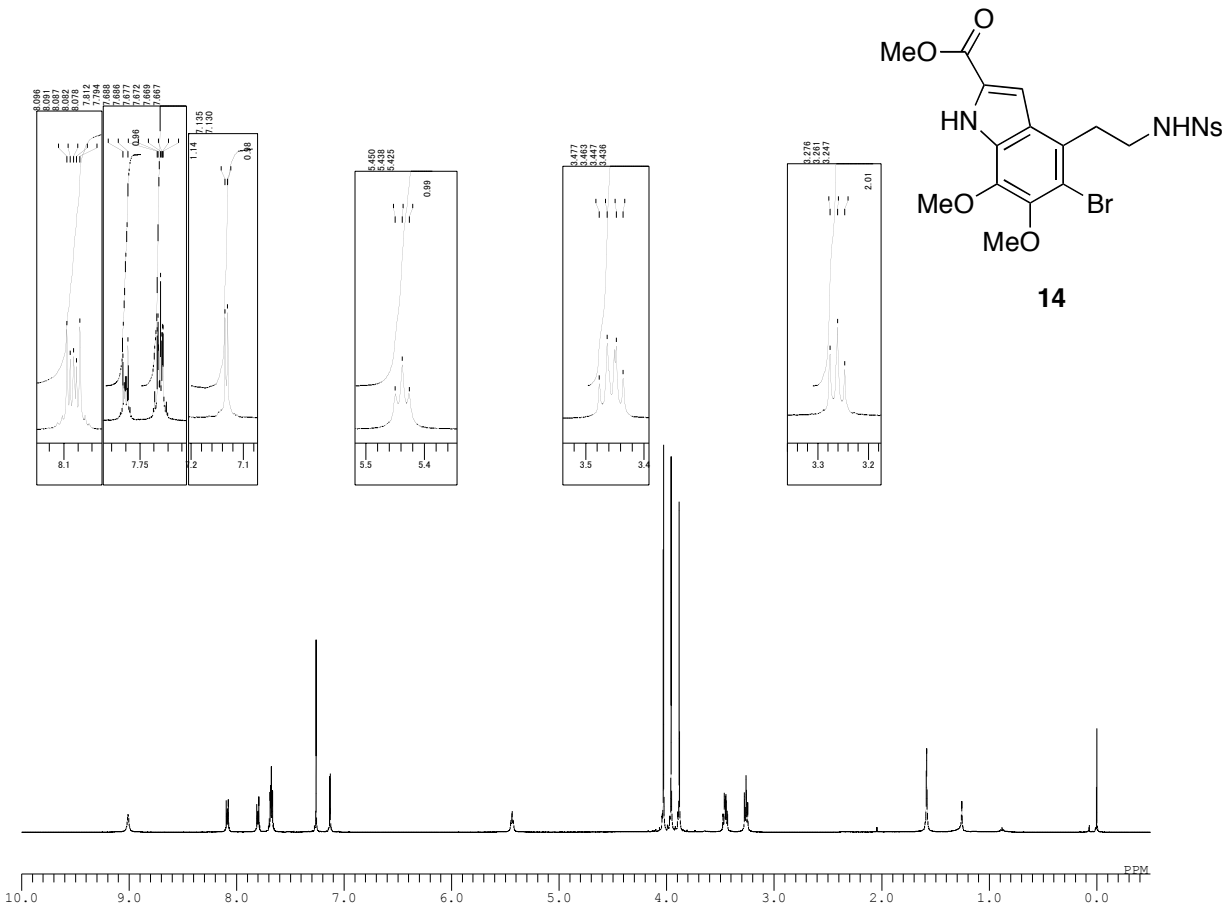
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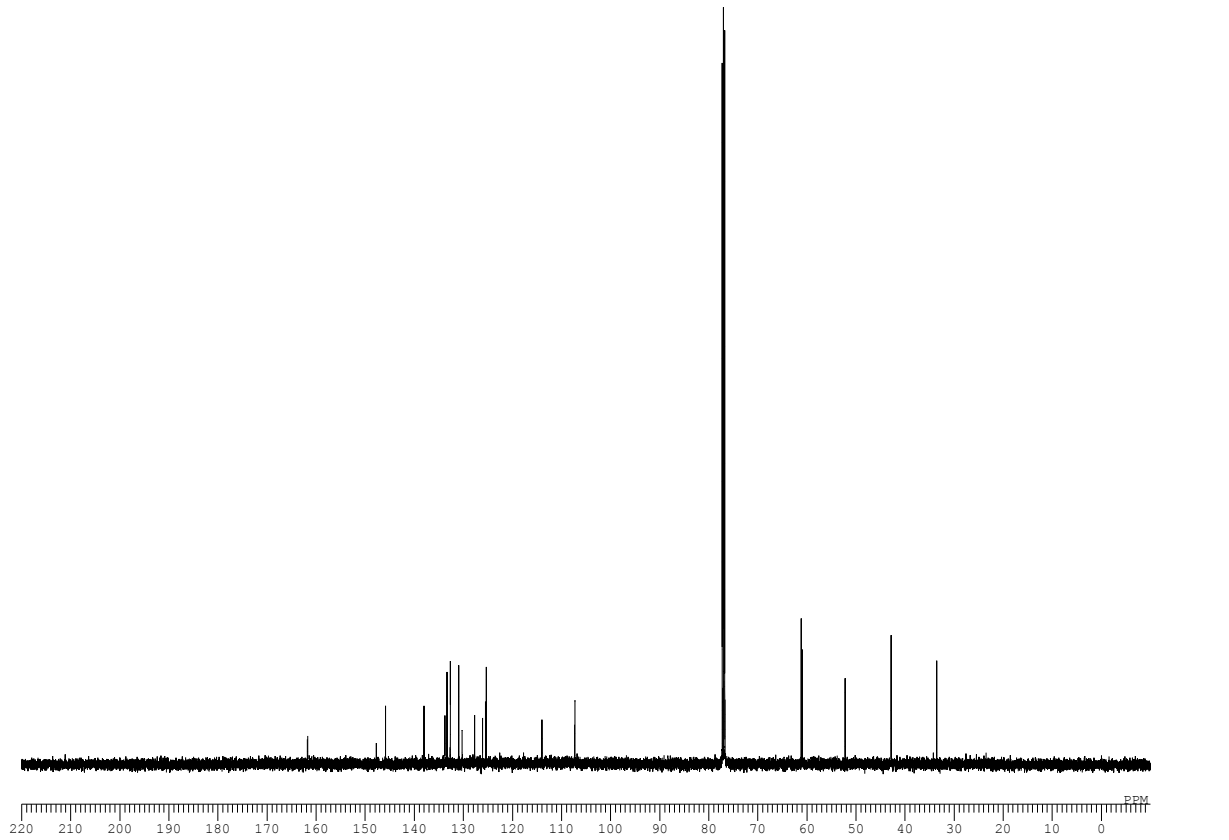
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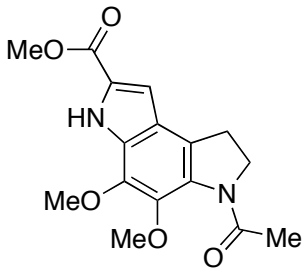
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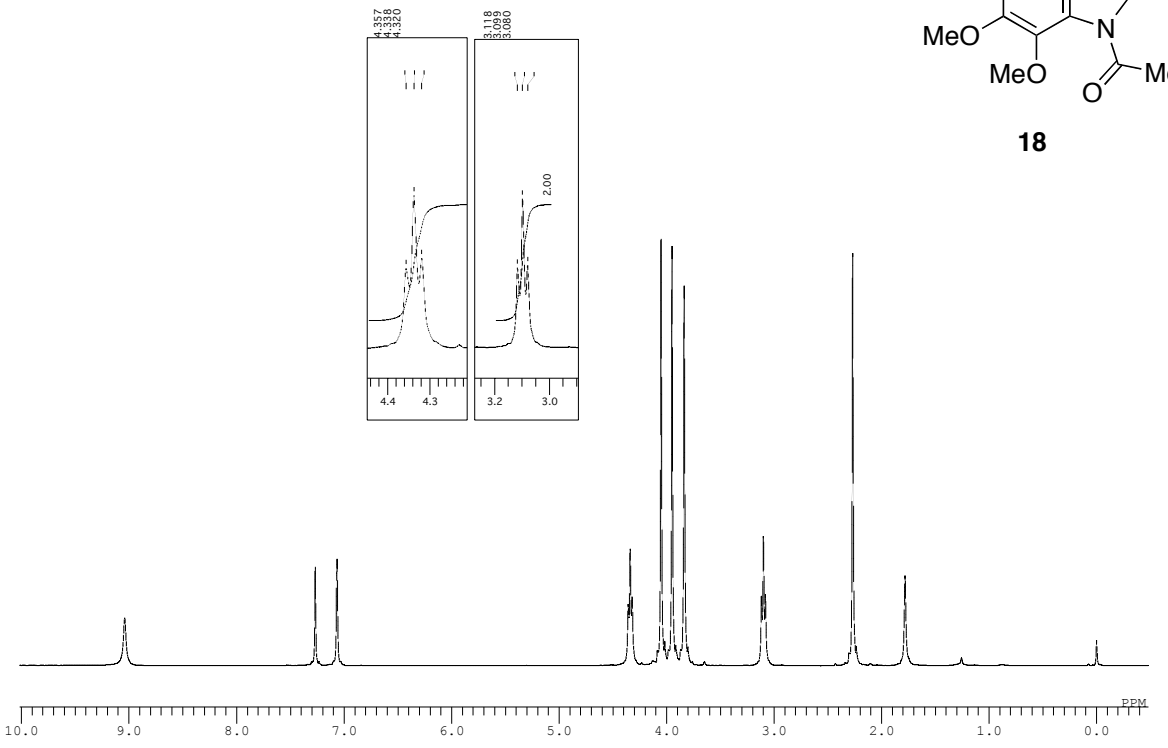
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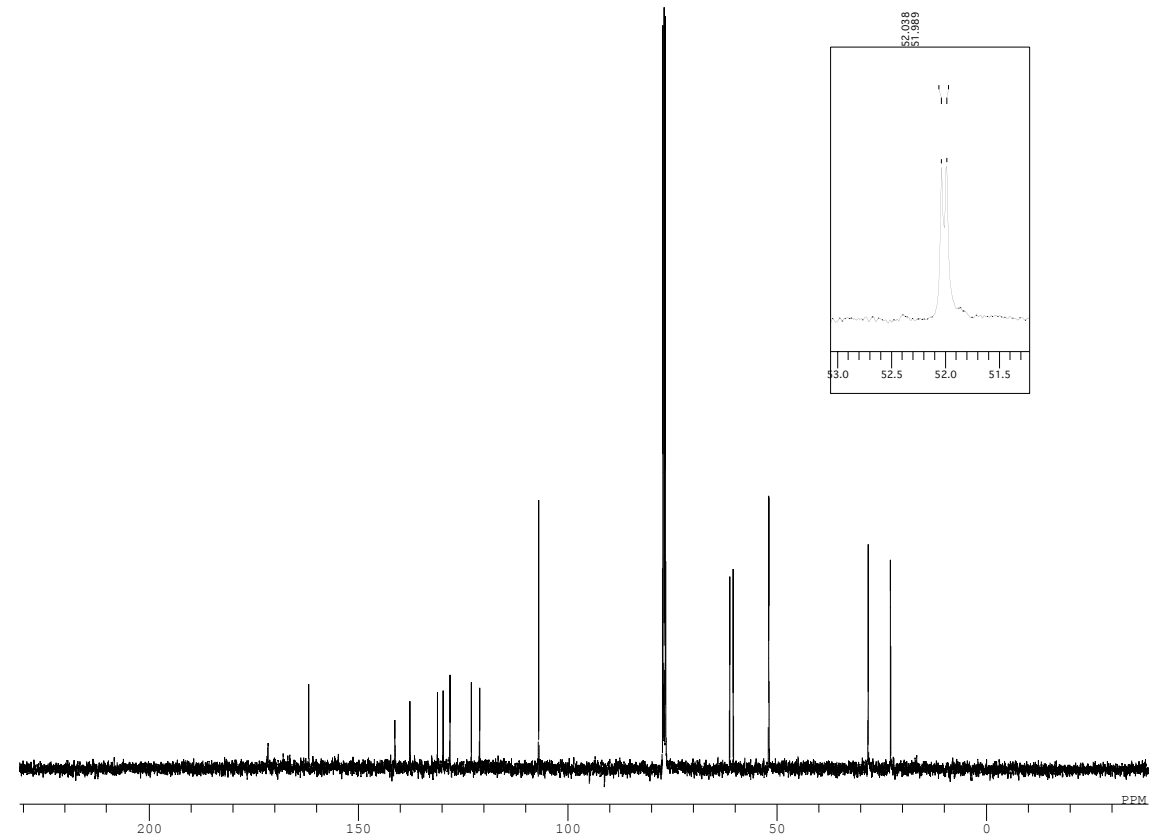
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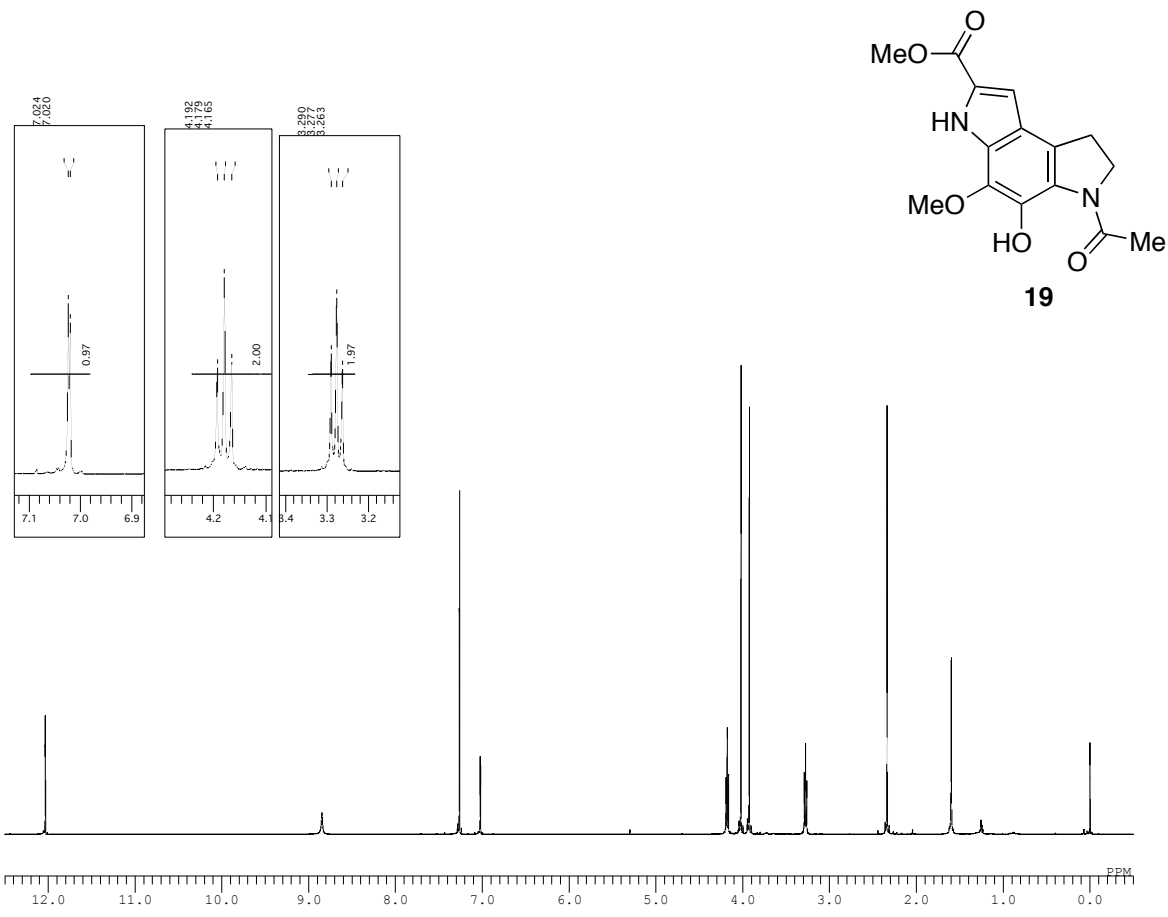
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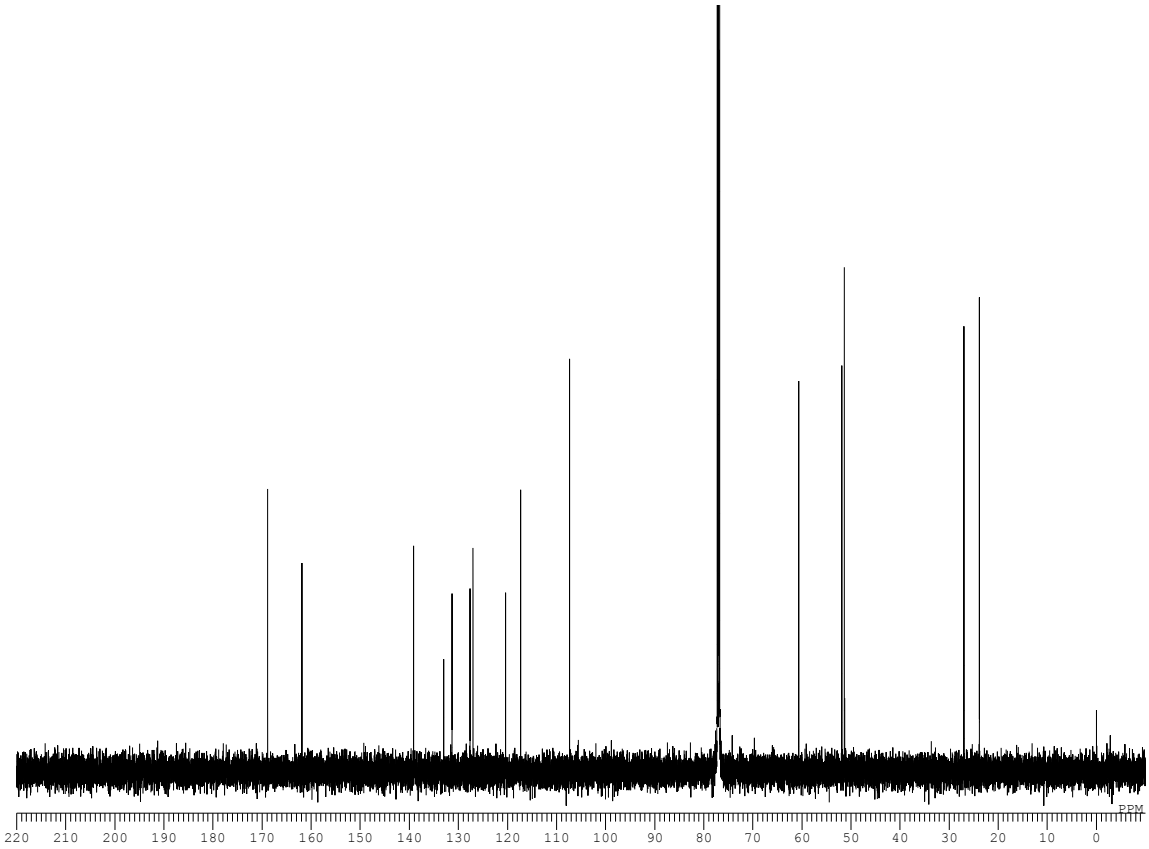
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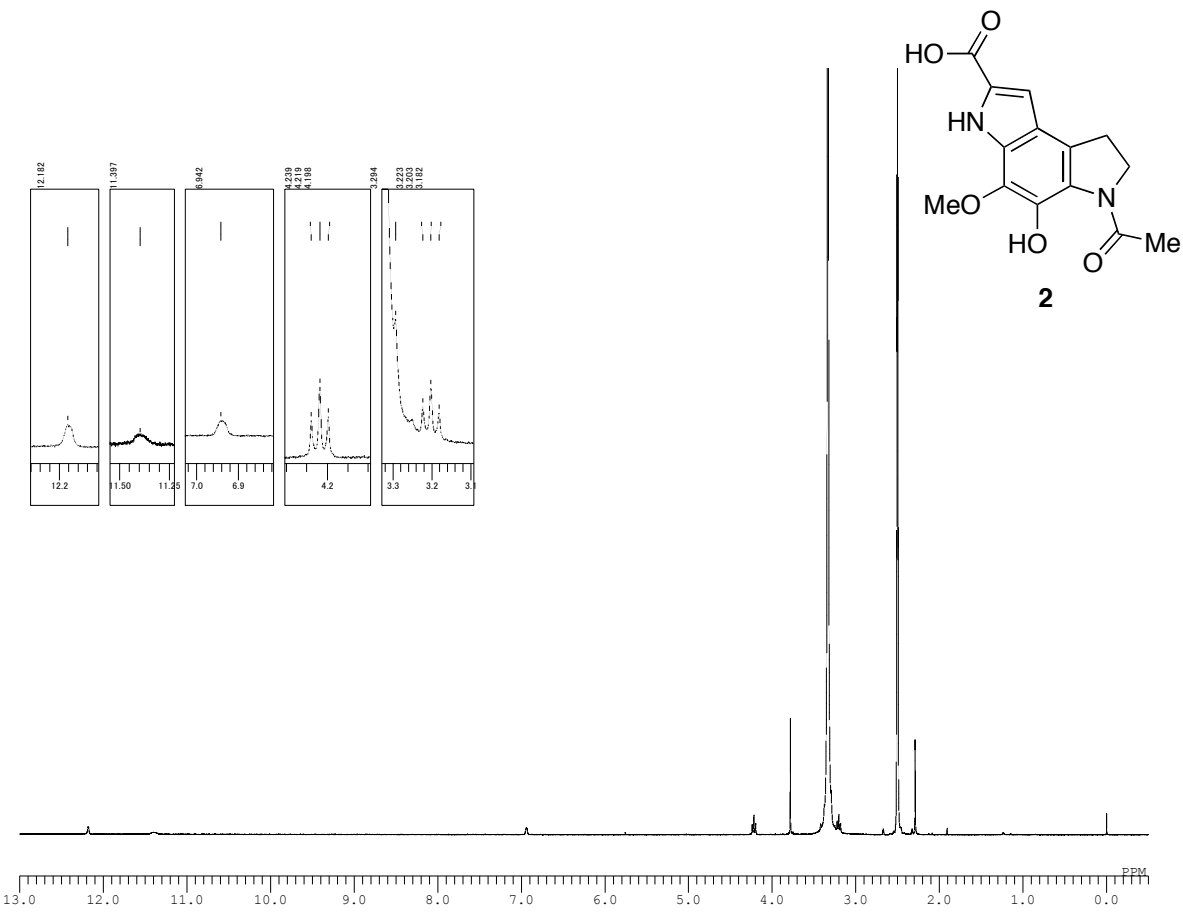
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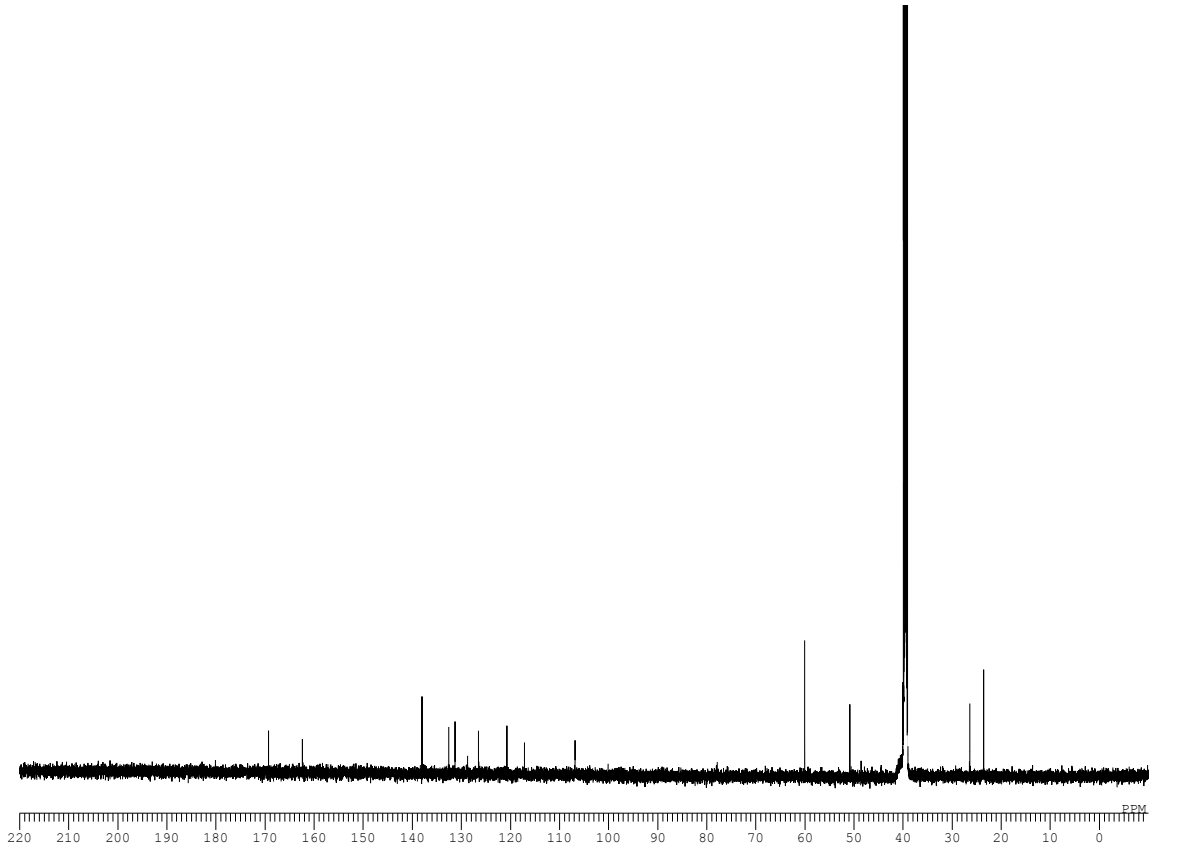
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