Supporting Information

The Exocyclic Olefin Geometry Control via Ireland-Claisen Rearrangement: Stereoselective Total Syntheses of Barmumycin and Limazepine E

Gints Smits and Ronalds Zemribo*

Latvian Institute of Organic Synthesis, Aizkraukles 21, LV-1006, Riga, Latvia

ronalds@osi.lv

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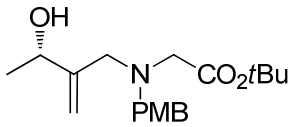
General Experimental Methods

Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use; petroleum ether of boiling range 60–80 °C was used. Flash chromatography was carried out using Merck Kieselgel (230–400 mesh). Thin-layer chromatography was performed on Merck Kieselgel 60F254. NMR spectra were recorded on Varian Mercury (400 MHz) and Varian Unity Inova (600 MHz) spectrometers. Chemical shift values are referenced against residual proton in the deuterated solvents, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad). Infrared spectra were recorded in the range 4000-600 cm^{-1} as a film. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer. Optical rotations were measured using a Perkin Elmer 141 polarimeter. Melting points were determined using a Stanford Research System MPA100 Automated Melting Point Apparatus and were uncorrected.

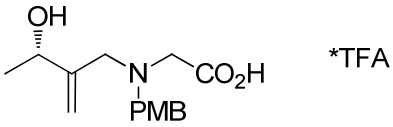
Experimental Procedures

(*S*)-*Tert*-Butyl 2-((3-hydroxy-2-methylenebutyl) (4-methoxybenzyl)amino)acetate 10



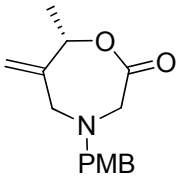
To a stirred solution of *tert*-butyl 2-((4-methoxybenzyl)amino)acetate (18.627 g, 0.074 mmol, 1.5 eq) and DIPEA (12.772 g, 0.099 mmol, 2 eq) in 50 mL of THF was dropwise added a solution of **9** (8.154 g, 0.049 mmol, 1 eq) in 20 mL of THF and the obtained solution was stirred for 16 h. The reaction mixture was diluted with DCM and saturated aqueous sodium bicarbonate solution, and twice extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Pet:EtOAc 9:1 – 2:1). The title compound was isolated as a yellow oil (11.270 g, 68%). **^{1}H NMR** (400MHz; $CDCl_3$): δ 7.24 (2H, d, *J*=8.6 Hz), 6.86 (2H, d, *J*=8.6 Hz), 5.23 (1H, br s), 5.07 (1H, s), 4.94 (1H, s), 4.35 (1H, q, *J*=6.2 Hz), 3.79 (3H, s), 3.64 (2H, AB m), 3.42 (1H, d, *J*=12.5 Hz), 3.16 (1H, d, *J*=12.5 Hz), 3.15 (2H, AB m), 1.45 (9H, s), 1.24 (3H, d, *J*=6.2 Hz). **^{13}C NMR** (100MHz, CDCl3): δ 170.35, 158.98, 147.81, 130.46, 129.63, 114.30, 113.82, 81.38, 70.50, 58.33, 57.57, 55.22, 54.49, 28.11, 21.68. **HRMS-ESI** (m/z): [M + H] calculated for $C_{19}H_{30}NO_4$, 336.2175; found 336.2182. **IR** (ν_{max}, film): 3442, 2977, 2933, 2836, 1733, 1612, 1513, 1301, 1157 cm^{-1}. **$[\alpha]_D^{25}$**= -0.07^o (c = 1, $CHCl_3$).

(S)-2-((3-Hydroxy-2-methylenebutyl)(4-methoxybenzyl)amino)acetic acid 2,2,2-trifluoroacetic acid salt SI-1



To a stirred solution of **10** (4.000 g, 9.534 mmol) in 30 mL of DCM was added 10 mL of TFA. The mixture was stirred for 4 h, as color changed to black. The volatiles were removed *in vacuo* and the residue was used in the next step without further purification.

(*S*)-4-(4-Methoxybenzyl)-7-methyl-6-methylene-1,4-oxazepan-2-one 11



To a stirred solution of **SI-1** (8.654 g, 22.000 mmol, 1 eq) in 170 mL of DCM were added 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (10.544 g, 191.71 mmol, 2.5 eq), 1-hydroxybenzotriazole hydrate (7.432 g, 55.000 mmol, 2.5 eq) and *N*,*N*-diisopropylethylamine (11.374 g, 88.000 mmol, 4 eq). The obtained slurry was stirred for 15 h. The reaction mixture was diluted with saturated aqueous sodium bicarbonate solution, and extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Pet:EtOAc 2:1). The title compound was isolated as a yellow solid (4.320 g, 75%). **^{1}H NMR** (400MHz; $CDCl_3$): δ 7.20 (2H, d, *J*=8,2 Hz), 6.85 (2H, d, *J*=8,2 Hz), 5.39 (1H, s), 5.12 (1H, s), 5.02 (1H, q, *J*=6.6 Hz), 3.81 (1H, d, *J*=16.0 Hz), 3.79 (3H, s), 3.58 (1H, d, *J*=16.0 Hz), 3.55 (2H, AB m), 3.40 (2H, AB m), 1.54 (3H, d, *J*=6.6 Hz). **^{13}C NMR** (100MHz, CDCl3): δ 172.19, 158.94, 141.46, 130.09, 129.37, 116.80, 113.79, 75.54, 60.30, 57.51, 56.72, 55.21, 18.40. **HRMS-ESI** (m/z): [M + H] calculated for $C_{15}H_{20}NO_3$, 262.1443; found 262.1438. **IR** ($\nu_{max,}$ film): 2985, 2943, 1729, 1611, 1513, 1246, 1028 cm^{-1}. **$[\alpha]_D^{25}$**= -64.32^o (c = 0.82, CH_2Cl_2). **m.p.** 88 – 90^{o}C.

General procedure for Ireland – Claisen rearrangement of 11

a) Generation of Si and B enolates

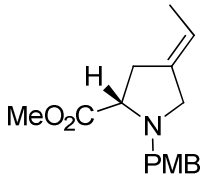
To a stirred solution of **11** (50 mg, 0.191 mmol, 1 eq) in 1 mL of dry DCM was added *N*,*N*-diisopropylethylamine (296 mg, 0.383 mmol, 12 eq, 0.761 mL, freshly distilled form sodium). The mixture was then cooled to -78^{o}C and treated with appropriate triflate. After 0.5h, the reaction mixture was allowed to warm to ambient temperature and stirred for 3h. Dry methanol (492 mg, 15.383 mmol, 6 eq, 0.623 mL) was added followed by O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (2.917 g, 7.692 mmol, 3 eq) and 1-hydroxybenzotriazole hydrate (1.177 g, 7.692 mmol, 3 eq). The obtained mixture was stirred for 16 h, then diluted with saturated aqueous sodium bicarbonate solution, and extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and

concentrated *in vacuo*. The residue was purified by preparative HPLC/MS (MeOH : H_2O +1% HCOOH). The obtained results are shown in Table 1.

b) Generation of Zn enolate

A solution of **11** (60 mg, 0.230 mmol, 1 eq) was dropwise added to 1M LiHMDS solution in THF/ethylbenzene (77mg, 0.459 mmol, 2 eq, 0.459 mL). After stirring for 0.5h at -78°C, 1M $ZnCl_2$ in Et_2O (47 mg, 0.344 mmol, 1.5 eq, 0.344 mL) was added and the reaction mixture turned red. After 0.5h, the reaction mixture was allowed to warm to ambient temperature and was stirred for 3h. Formation of the intermediate carboxylic acid was not observed by LC/MS.

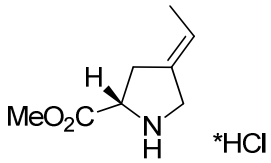
(*S*,*E*)-Methyl 4-ethylidene-1-(4-methoxybenzyl)pyrrolidine-2-carboxylate 14



To a stirred solution of **11** (670 mg, 2.564 mmol, 1 eq) in 3 mL of dry DCM was added *N*,*N*-diisopropylethylamine (3.976 g, 30.767 mmol, 12 eq, 5.098 mL, freshly distilled form sodium). The mixture was then cooled to -78°C and 1M solution of dibutylboranylium trifluoromethanesulfonate (2.108 g, 7.692 mmol, 3 eq, 7.69 mL) in DCM was added dropwise. After 15 min the mixture was warmed to 10°C and stirred for 1h. Dry methanol (492 mg, 15.383 mmol, 6 eq, 0.623 mL) was then added, followed by O-benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate (2.917 g, 7.692 mmol, 3 eq) and 1-hydroxybenzotriazole hydrate (1.177 g, 7.692 mmol, 3 eq). The obtained mixture was stirred for 16 h and then diluted with saturated aqueous sodium bicarbonate solution, and extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (Pet:EtOAc 9:1 + 2% Et_3N). The title compound was isolated as a yellow oil (540 mg, 85%). **^{1}H NMR** (400MHz; $CDCl_3$): δ 7.24 (2H, d, *J*=8.2), 6.83 (2H, d, *J*=8.2), 5.28 (1H, m), 3.84 (1H, d, *J*=12.5 Hz), 3.78 (3H, s), 3.69 (3H, s), 3.51 (1H, d, *J*=12.5 Hz), 3.41 (1H, d, *J*=12.5 Hz), 3.36 (1H, t, *J*=8,2 Hz), 2.98 (1H, d, *J*=12.5 Hz), 2.73 (1H, dd, *J*=16.3, 7.8 Hz), 2.53 (1H, dd, *J*=16.3, 7.8 Hz), 1.54 (3H, d, *J*=7.0 Hz). **^{13}C NMR** (100MHz, $CDCl_3$): δ 173.79, 158.77, 135.92, 130.31, 130.03, 115.53, 113.55, 65.44, 57.95, 57.91, 55.21, 51.78, 33.03, 14.30.

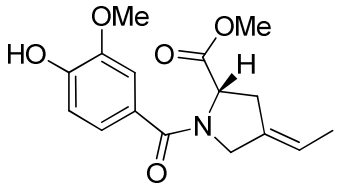
HRMS-ESI (m/z): [M + H] calculated for $C_{16}H_{22}NO_3$, 276.1660; found 276.1664. **IR** (ν_{max}, film): 2951, 2832, 1748, 1612, 1513, 1248, 1172. **$[\alpha]_D^{25}$**= -56.29° (c = 0.75, CH_2Cl_2).

(*S,E*)-Methyl 4-ethylidenepyrrolidine-2-carboxylate hydrochloride SI-2



To a solution of **14** (250 mg, 0.908 mmol, 1 eq) in dry DCM (0.6 mL) was slowly added 1-chloroethyl chloroformate (259 mg, 1.816 mmol, 2 eq) slowly at 0ºC. The reaction mixture was stirred for 20 min at 0ºC. After removal of the solvent, the residue was disolved in MeOH (1 mL) and refluxed for 40 min. Removal of the solvent and trituration with ether afforded a dark red oil wich was used in the next step without further purification.

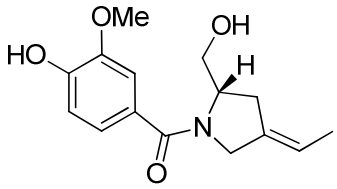
(*S,E*)-Methyl 4-ethylidene-1-(4-hydroxy-3-methoxybenzoyl)pyrrolidine-2-carboxylate SI-3



To a stirred slurry of vanilic acid (91 mg, 0.545 mmol, 1.5 eq) and benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (240 mg, 0.545 mmol, 1.5 eq) in 3 mL of dry THF was added DIPEA (140 mg, 1.089 mmol, 3 eq). After stirring for 0.5h at ambient temperature, a solution of **SI-2** (69 mg, 0.363 mmol, 1 eq) in 1mL of dry THF was added. The obtained mixture was stirred for 16 h, then diluted with saturated aqueous sodium bicarbonate solution, and extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preperative HPLC/MS (MeOH : H_2O +1% HCOOH). The title compound was isolated as a yellow solid (46 mg, 41%). **^{1}H NMR** (400MHz; $CDCl_3$): δ 7,01 (1H, bm), 6.89 (1H, d, *J*=7.8 Hz), 5.98 (1H, s), 5.37 (0.5H, bs), 4.95 (0.5H, bs), 4.11 – 4.31 (2H, m), 3.89 (3H, s), 3.76 (3H, bs), 2.85 – 2.93 (1H, m), 2.64 – 2.69 (1H, m), 1.61 (3H, d, *J*=6.65 Hz). **^{13}C NMR** (100MHz,

$CDCl_3$): δ 172.61, 169.76, 147.70, 146.45, 134.15, 127.52, 120.96, 117.78, 113.79, 110.64, 58.58, 55.97, 54.05, 52.32, 30.91, 14.34. **HRMS-ESI** (m/z): [M + Na] calculated for $C_{16}H_{19}NO_5Na$, 328.1161; found 328.1184. $[\alpha]_D^{25}$=-19.44°(c = 0.25, CH_2Cl_2).

Barmumycin 1

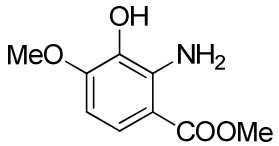


A solution of ester **SI-3** (10 mg, 0.033 mmol, 1 eq) in dry THF (0.5 mL) was cooled to 0ºC and treated portion-wise with $LiBH_4$ (2 mg, 0.098 mmol, 3 eq). The stirred reaction mixture was allowed to warm to room temperature over 2.5 h, after which the TLC revealed complete consumption of the starting material. The mixture was cooled to 0ºC, treated with water and extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preperative HPLC/MS (MeOH : H_2O +1% HCOOH). The title compound was isolated as a yellow solid (6.1 mg, 71%). **^{1}H NMR** (400MHz; $CDCl_3$): δ 7.09 (1H, s), 7.04 (1H, d, *J*=7.82 Hz), 6.91 (1H, d, *J*=7.82 Hz), 5.92 (1H, bs), 5.36 (1H, bs), 4.66 (1H, bs), 4.06 – 4.20 (2H, m), 3.91 (3H, s), 3.74 (2H, bs), 2.68 – 2.76 (1H, m); 2.22 – 2.32 (1H, m), 1.62 (3H, d, *J*=6.65 Hz). **^{13}C NMR** (100MHz, $CDCl_3$): δ171.71, 147.53, 146.43, 134.44, 128.07, 120.76, 117.39, 113.81, 110.35, 67.01, 60.41, 56.07, 54.96, 30.04, 14.33. **HRMS-ESI** (m/z): [M + H] calculated for $C_{15}H_{20}NO_4$, 278.1387; found 278.1386. $[\alpha]_D^{25}$ Lit. -51.2° (c = 0.25, CH_2Cl_2); found -49.6° (c = 0.25, CH_2Cl_2).

Comparison of Barmumycin to the literature NMR data

δ_H, (400MHz; $CDCl_3$)	Lit. δ_H, (400MHz; $CDCl_3$)	δ_C	Lit. δ_C
1.62 (3H, d, *J*=6.65 Hz)	1.62 (3H, d, *J* =6.8 Hz)	14.33	14.5
2.22 – 2.32 (1H, m)	2.20-2.35 (1H, m)	30.04	30.1
2.68 – 2.76 (1H, m)	2.67-2.77 (1H, m)	54.96	55.1
3.74 (2H, bs)	3.75 (2H, bs)	56.07	56.3
3.91 (3H, s)	3.90 (3H, s)	60.41	60.6
4.02 – 4.20 (2H, m)	4.00-4.22 (2H, m)	67.01	67.1
4.66 (1H, bs)	4.67 (1H, bs)	110.35	110.6
5.36 (1H, bs)	5.34 (1H, bs)	113.81	114.1
5.92 (1H, bs)	-	117.39	117.6
6.91 (1H, d, *J*=7.82 Hz)	6.91 (1H, d, *J*=7.8 Hz)	120.76	121.0
7.04 (1H, d, *J*=7.82 Hz)	7.04 (1H, d, *J*=7.82 Hz)	128.07	128.3
7.09 (1H, s)	7.09 (1H, s)	134.44	134.7
		146.43	146.7
		147.53	147.8
		171.71	172.0

Methyl 2-amino-3-hydroxy-4-methoxybenzoate SI-4



To a stirred solution of methyl 3-hydroxy-4-methoxy-2-nitrobenzoate[1] (6.60 mmol, 1.500 g) in 20 mL of EtOH was added 50 mg of 10% Pd on carbon and the reaction flask was then purged with hydrogen (balloon) three times and the reaction was stirred for 14 h at room temperature. The catalyst was filtred off, the solvent was evaporated and the residue was purified by flash column chromatography (Pet:EtOAc 3:1). The title compound was isolated as a yellow solid (1.350 g, 90%). **^{1}H NMR** (400MHz; $CDCl_3$): δ 7.47 (1H, d, *J*=8.9 Hz), 6.28 (1H, d, *J*=8.9 Hz), 5.77 (2H br s), 5.44 (1H, br s), 3.89 (3H, s), 3.84 (3H, s). **^{13}C NMR**

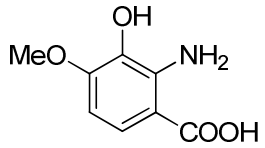
[1] WO 2008/006050

(100MHz, CDCl3): δ 168.28, 148.86, 139.63, 131.47, 123.04, 105.85, 99.509, 55.946, 51.31. **HRMS-ESI** (m/z): [M + H] calculated for $C_9H_{12}NO_4$, 198.0766; found 198.0775. **IR**: (ν_{max}, film): 3425, 3333, 2902, 1658, 1464, 1377, 1278, 1214, 1088 cm^{-1}. **M.p.** 70–72°C. Characterization Data matches that reported in the literature[2].

Comparison of SI-4 to the literature NMR data

δ_H, (400MHz; $CDCl_3$)	Lit. δ_H, (300MHz; $CDCl_3$)	δ_C	Lit. δ_C
3.84 (3H, s)	3.85 (3H, s)	51.31	51.6
3.89 (3H, s)	3.91 (3H, s)	55.946	56.2
5.44 (1H, br s)	-	99.509	99.7
5.77 (2H br s)	5.72 (2H br s, H/D)	105.85	106.1
6,28 (1H, d, *J*=8.9 Hz)	6,29 (1H, d, *J*=9.0 Hz)	123.04	123.3
7.47 (1H, d, *J*=8.9 Hz)	7.47 (1H, d, *J*=9.0 Hz)	131.47	131.7
		139.63	139.9
		148.86	149.1
		168.28	168.6

2-Amino-3-hydroxy-4-methoxybenzoic acid SI-5



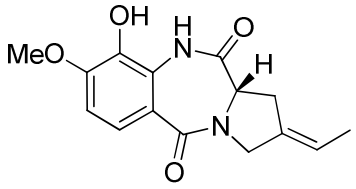
To a stirred solution of **SI-4** (380 mg, 1.927 mmol, 1 eq) was dropwise added 2.89 mL of 1M boron tribromide solution (724 mg, 2.891 mmol, 1.5 eq) at -78°C. The mixture was warmed to ambient temperature overnight. Water (~1 mL) was then added and after 0.5 h of stirring, the mixture was evaporated to dryness. The residue was purified on reversed phase flash chromatography (MeOH:H_2O + 1% AcOH). The title compound was isolated as a grey solid (200 mg, 57%).

^{1}H NMR (400MHz; $(CH_3)_2SO$): δ 8.48 (1H br s), 7.28 (1H, d, *J*=8.9 Hz), 6.31 (1H, d, *J*=8.9 Hz), 3.79 (3H, s), 3.33 (2H, br s). **^{13}C NMR** (100MHz, $(CH_3)_2SO$): δ 169.42, 149.91, 141.54,

[2] Fotso, S.; Zabriskie, T., M.; Proteau, P., J.; Flatt, P., M.; Santosa, D., A.; Mahmud, S.; Mahmud, T. *J. Nat. Prod.* **2009**, *72,* 690-695

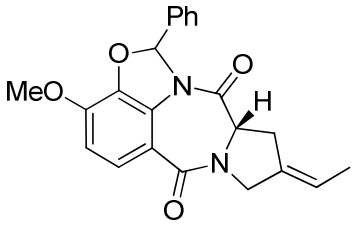
131.31, 122.51, 104.80, 99.79, 55.56. **HRMS-ESI** (m/z): [M + H] calculated for $C_8H_{10}NO_4$, 184.0610; found 184.0636. **IR**: (ν_{max}, film) 3491, 3378, 2951, 1683, 1625, 1272, 1120 cm^{-1}. **M.p.** 190°C (dec.).

(*S*,*E*)-2-Ethylidene-9-hydroxy-8-methoxy-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione 17



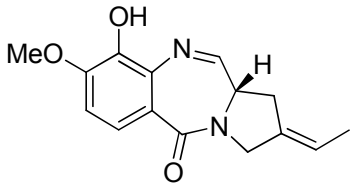
To a stirred solution of **SI-2** (208 mg, 1.090 mmol, 1 eq), **SI-5** (400 mg, 2.180 mmol, 2 eq), benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate (965 mg, 2.180 mmol, 2 eq) and 1-hydroxybenzotriazole hydrate (334 mg, 2.180 mmol, 2 eq) in 10 mL of *N*,*N*-dimethylformamide was added triethylamine (550 mg, 5.45 mmol, 5 eq) and the obtained solution was stirred for 16 h. The volatiles were removed *in vacuo* and the residue was partitioned between DCM and brine. The organic phase was dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography (MeOH:$CHCl_3$ 1:20). The collected product was recrystallized form acetonitrile. The title compound was isolated as a white solid (200 mg, 64%). **^{1}H NMR** (400MHz; CD_3OD): δ 7.39 (1H, d, *J*=8.9 Hz), 6.91 (1H, d, *J*=8.9 Hz), 5.55 (1H, m), 4.33 (2H, d, *J*=11.3 Hz), 4.11 (1H, d, *J*=16.4 Hz), 3.94 (3H, s), 3,46 (1H, d, *J*=16.4 Hz), 2.69 (1H, dd, *J*=16.4, 9.7 Hz), 1.74 (3H, d, *J*=6.6 Hz). **^{13}C NMR** (100MHz, CD_3OD + few drops of $CDCl_3$): δ 170.39, 166.49, 150.17, 136.08, 132.88, 124.51, 120.71, 119.58, 117.79, 107.63, 57.20, 55.50, 51.21, 27.00, 13.43. **HRMS-ESI** (m/z): [M + H] calculated for $C_{15}H_{17}N_2O_4$, 289.1188; found 289.1198. **IR** (ν_{max}, film): 3373, 3244, 2928, 2840, 1699, 1626, 1585, 1435, 1383, 1259, 1177. **$[\alpha]_D^{25}$**=280.83°(c = 0.1, MeOH); **M.p.** 230°C (dec.).

(9a*S*,*E*)-8-Ethylidene-3-methoxy-1-phenyl-7,8,9,9a-tetrahydro-1*H*-2-oxa-6a,10a-diazabenzo[*cd*]cyclopenta[*g*]azulene-6,10-dione 18



To solid **17** (100 mg, 0.347 mmol, 1 eq) was added 1mL of benzaldehyde dimethyl acetal and *p*-toluenesulfonic acid hydrate (6 mg, 0.035 mmol, 0.1 eq) and the obtained mixture was heated to reflux at 150°C for 8 h. After that the mixture was directly purified by flash column chromatography (Pet:EtOAc 2:1). The title compound was isolated as a yellow solid (80 mg, 61%). **^{1}H NMR** (400MHz; $CDCl_3$): δ 7.59 (1H, d, *J*=8.9 Hz), 7.43 (2H, m), 7.35 (3H, m), 7.32 (1H, s), 6.84 (1H, d, *J*=8.9 Hz), 5.51 (1H, m), 4.51 (1H, d, *J*=15.6 Hz), 4.32 (1H, d, *J*=15.6 Hz), 4.06 (1H, d, *J*=15.6 Hz)3.97 (3H, s), 3.56 (1H, d, *J*=15.6 Hz), 2.73 (1H, dd, *J*=15.6, 9.7 Hz), 1.72 (3H, d, *J*=7.0 Hz). **^{13}C NMR** (100MHz, CDCl3): δ 169.33, 165.20, 146.46, 137,59, 136.41, 132.20, 129.85, 128.76, 128.34, 125.84, 123.47, 118.44, 114.41, 110.67, 95.20, 59.00, 56.63, 52.11, 28.14, 14.48. **HRMS-ESI** (m/z): [M + H] calculated for $C_{22}H_{21}N_2O_4$, 377.1501; found 377.1505.

Limazepine E 4



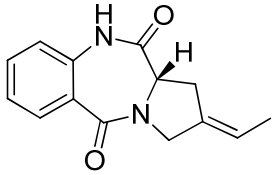
To a stirred solution of **18** (65 mg, 0.173 mmol, 1 eq) in 3 mL of dry methanol was added sodium borohydride (20 mg, 0.518 mmol, 3 eq) at 0°C. The mixture was then warmed to ambient temperature and stirred for 3h, then diluted with saturated aqueous sodium bicarbonate solution, and extracted twice with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by preperative HPLC/MS (MeOH : H_2O +1% HCOOH). The collected aqueous fractions were basified with saturated aqueous sodium bicarbonate solution, and extracted with DCM. The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The title compound was isolated as a yellow solid. (6 mg, 13%). **^{1}H NMR** (600MHz; $CDCl_3$): δ 7.78 (1H, d, *J*=4.2 Hz), 7.61 (1H, d, *J*=9.0 Hz), 6.94 (1H, d, *J*=9.0 Hz), 5.60 (1H,

m), 4.25 (2H, AB m), 3.96 (3H, s), 3.96 (1H, m), 2.98 (2H, d, *J*=5.5 Hz), 1.74 (3H, d, *J*=6.8 Hz). **^{13}C NMR** (125MHz, $CDCl_3$): 165.48, 164.63, 148.84, 140.18, 132.77, 132.57, 121.65, 120.80, 119.01, 110.81, 56.22, 54.25, 51.69, 31.22, 14.60. **HRMS-ESI** (m/z): [M + H] calculated for $C_{15}H_{17}N_2O_3$, 273.1239; found 243.1256. **$[\alpha]_D^{25}$**= 232.41^o (c = 0.58, $CHCl_3$). Characterization Data matches that reported in the literature.

Comparison of natural and synthetic Limazepine E NMR data

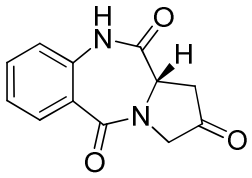
δ_H, (600MHz; $CDCl_3$)	Lit. δ_H, (400MHz; $CDCl_3$)	δ_C	Lit. δ_C
1.74 (3H, d, *J*=6.8 Hz)	1.76 (3H, d, *J*=6.8 Hz)	14.60	14.8
2.98 (2H, d, *J*=5.5 Hz)	3.00 (2H, br d, *J*=5.8 Hz)	31.22	31.5
3.96 (1H, m)	3.98 (1H, m)	51.69	51.9
3.96 (3H, s)	3.98 (3H, s)	54.25	54.5
4.25 (2H, AB m)	4.28 (2H, br s)	56.22	56.5
5.60 (1H, m)	5.62 (1H, m)	110.81	111.1
6.94 (1H, d, *J*=9.0 Hz)	6.97 (1H, d, *J*=8.9 Hz)	119.01	119.2
7.61 (1H, d, *J*=9.0 Hz)	7.63 (1H, d, *J*=8.9 Hz)	120.80	121.0
7.78 (1H, d, *J*=4.2 Hz)	7.80 (1H, d, *J*=4.3 Hz)	121.65	121.9
		132.57	132.0
		132.77	132.8
		140.18	140.4
		148.84	149.1
		164.63	164.9
		165.48	165.7

(*S*,*E*)-2-Ethylidene-2,3-dihydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,11(10*H*,11a*H*)-dione 19



The title compound was obtained similarly as described for preparation of **17**. White solid (70mg, 41%) was obtained. **^{1}H NMR** (400MHz; CD_3OD): δ 7.86 (1H, d, *J*=7.82 Hz), 7.54 (1H, t, *J*=7.82 Hz), 7.28 (1H, t, *J*=7.82 Hz), 7.13 (1H, d, *J*=7.82 Hz), 5.56 (1H, m), 4.35 (1H, dd, *J*=9.39, 2.35 Hz), 4.31 (1H, m), 4.12 (1H, d, *J*=16.04Hz), 3.44 (1H, d, *J*=16.04Hz), 2.69 (1H, m), 1.74 (3H, d, *J*=6.65). **^{13}C NMR** (100MHz, CD_3OD): δ 170.76, 166.27, 136.35, 133.04, 132.44, 129.92, 126.27, 124.35, 121.09, 117.61, 56.94, 51.07, 26.80, 13.09. **IR** (ν_{max}, film): 3292, 2923, 2854, 1694, 1668, 1637, 1629, 1603, 1591, 1476, 1413, 1249, 1167. **HRMS-ESI** (m/z): [M + H] calculated for $C_{14}H_{15}N_2O_2$, 243.1134; found 243.1135. **$[\alpha]_D^{25}$**= 553.60^o (c = 0.1, MeOH). **M.p.** 245^{o}C (dec.).

(*S*)-1*H*-Benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepine-2,5,11(3*H*,10*H*,11a*H*)-trione 20



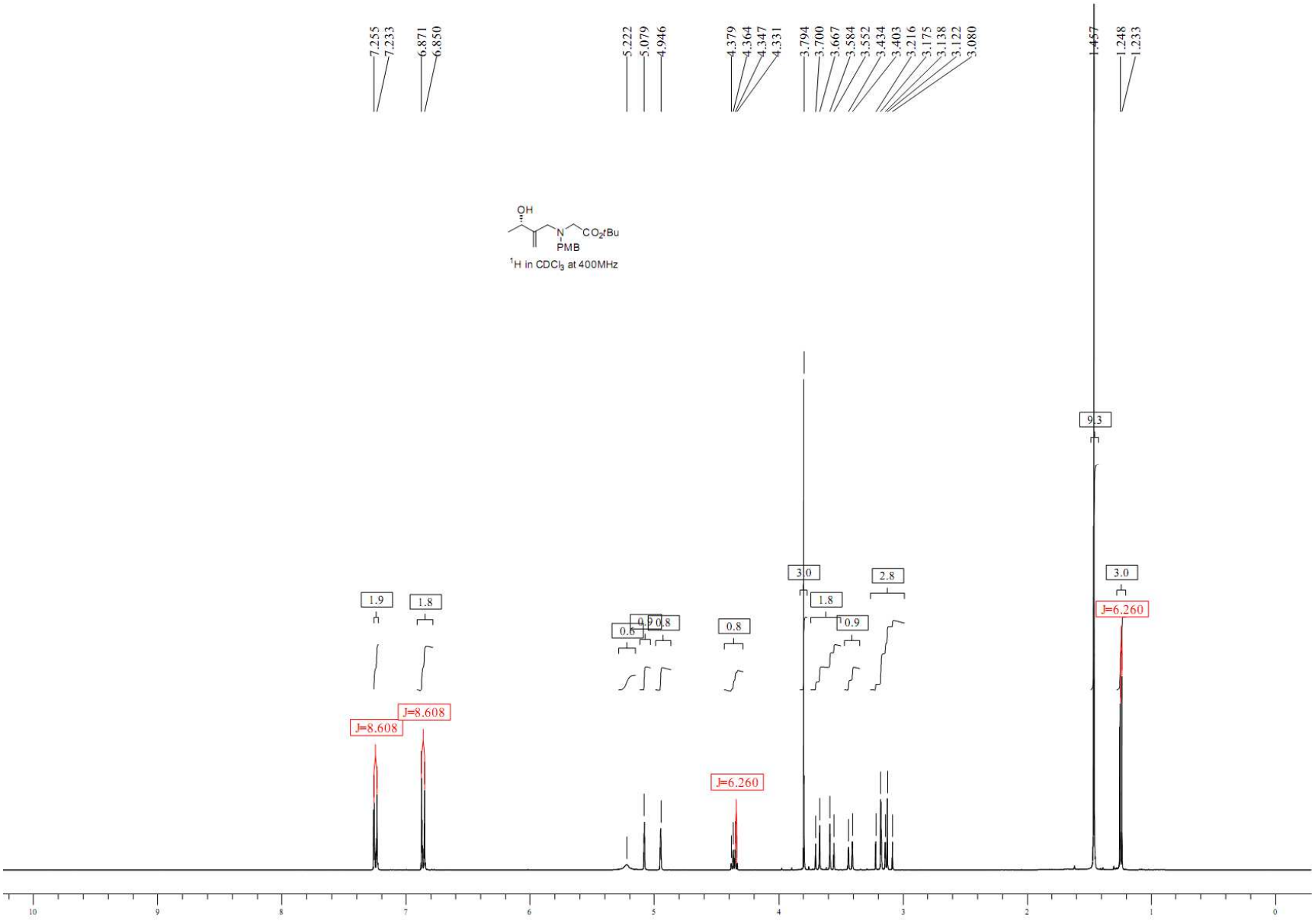
Ozone was bubbled through a solution of **19** (50 mg, 0.206 mmol, 1 eq) in dry dicloromethane at -78^{o}C untill the mixture remained blue. Then oxygen was bubbled through the mixture to remove the excess of ozone, after witch polymer-supported triphenylphosphine (1.4-2.0 mmol/g, 370 mg, ~0.6 mmol, ~3 eq) was added. The mixture was then warmed to ambient temperature overnight. The resin was filtered off, the mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography (MeOH:$CHCl_3$ 1:20). The title compound was isolated as a white solid (35 mg, 74%). Characterization Data matches that reported in the literature. **^{1}H NMR** (400MHz; $CDCl_3$): δ 8.12 (1H, s), 8.00 (1H, d, *J*=7.8 Hz), 7.55 (1H, t, *J*=7.8 Hz), 7.33 (1H, t, *J*=7.8 Hz), 7.04 (1H, d, *J*=7.8 Hz), 4.59 (1H, dd, *J*=13.7, 3.5 Hz), 4.30 (1H, d, *J*=19.9 Hz), 3.95 (1H, d, *J*=19.9 Hz), 3.60 (1H, d, *J*=19.9 Hz), 2.82 (1H, dd, *J*=19.6, 10.2 Hz). **^{13}C NMR** (100MHz, CDCl3): δ 206.46, 169.31, 166.02, 134.82, 133.20, 131.44, 125.90, 121.23, 53.98, 52.76, 36.64. **IR** (ν_{max}, film): 3229, 2920, 1772, 1696, 1616, 1483, 1454, 1384, 1254, 1165. **HRMS-ESI** (m/z): [M + H] calculated for $C_{12}H_{13}N_2O_3$, 233.0926; found 233.0931. **$[\alpha]_D^{25}$** Lit. 548^o (c = 0.124, MeOH); found 550.81^o (c = 0.124, MeOH). **M.p.** 202-204^{o}C.

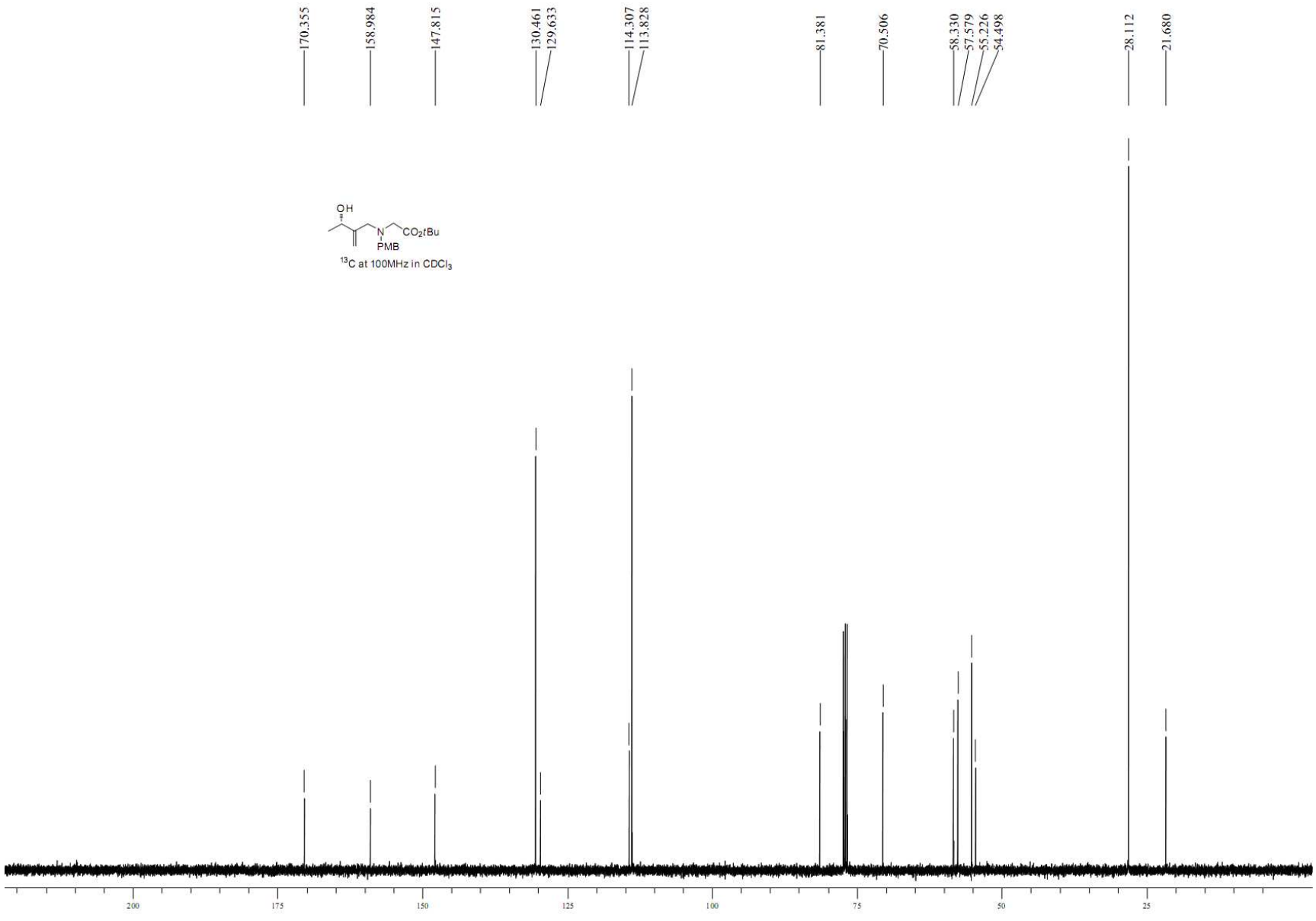
Comparison of 20 to the literature NMR data

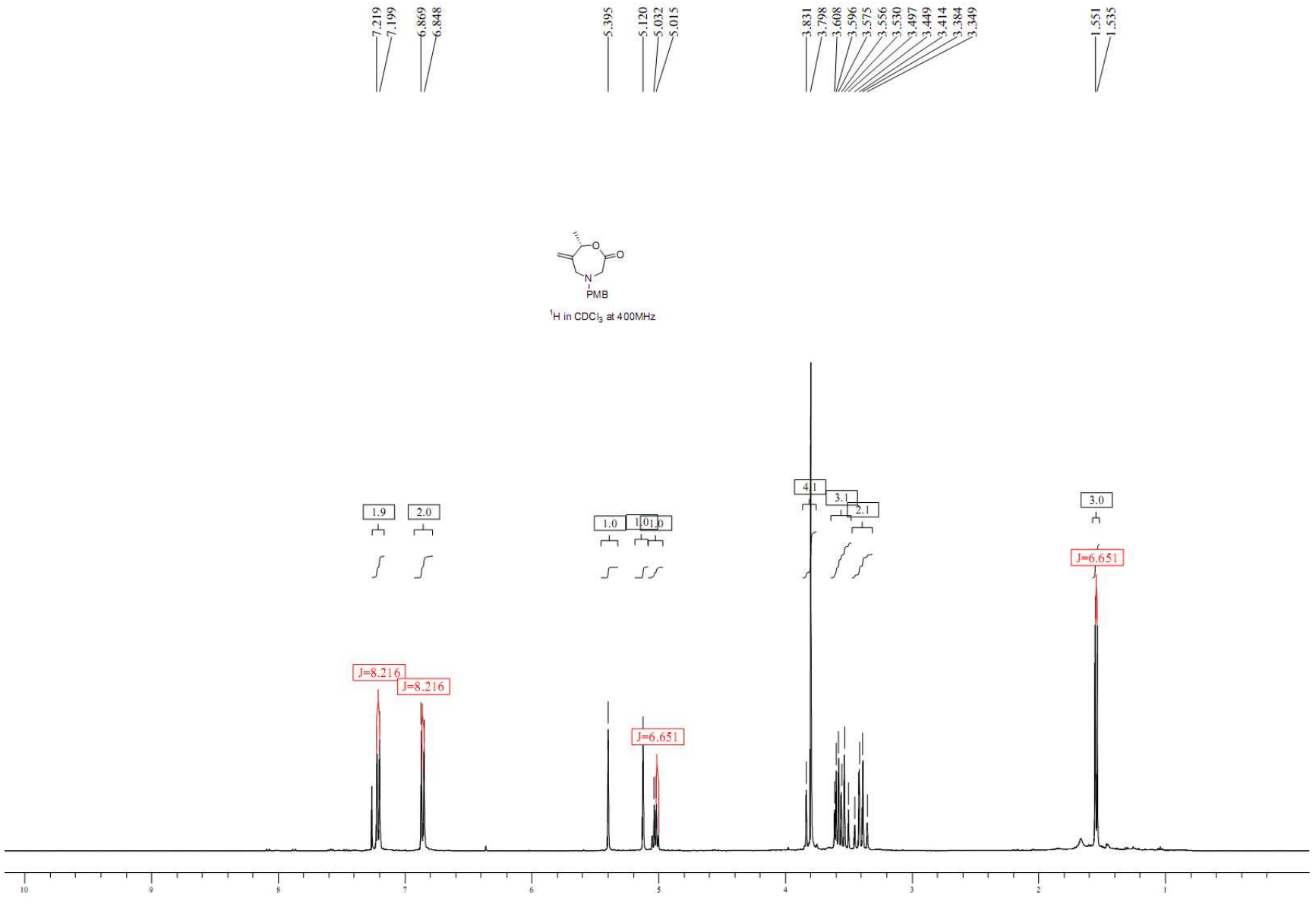
δ_H, (400MHz; $CDCl_3$)	Lit. δ_H, (400MHz; $CDCl_3$)	δ_C	Lit. δ_C
2.84 (1H, dd, *J*=19.4, 10.2 Hz)	2.82 (1H, dd, *J*=19.6, 10.2 Hz)	36.64	36.6
3.62 (1H, dd, *J*=19.5, 3.5 Hz)	3.60 (1H, dd, *J*=19.9, 3.5 Hz)	52.76	52.8
3.95 (1H, d, *J*=20.2 Hz)	3.95 (1H, d, *J*=19.9 Hz)	53.98	54.0
4.30 (1H, d, *J*=20.2 Hz)	4.30 (1H, d, *J*=19.9 Hz)	121.23	121.3
4.61 (1H, dd, *J*=10.2, 3.5 Hz)	4.59 (1H, dd, *J*=13.7, 3.5 Hz)	125.90	125.88
7.08 (1H, d, *J*=8.1 Hz)	7.04 (1H, d, *J*=7.8 Hz)		125.90
7.34 (1H, t, *J*=7.8 Hz)	7.33 (1H, t, *J*=7.8 Hz)	131.44	131.4
7.56 (1H, t, *J*=8.0 Hz)	7.55 (1H, t, *J*=7.8 Hz)	133.20	133.2
8.01 (1H, d, *J*=7.9 Hz)	8.00 (1H, d, *J*=7.8 Hz)	134.82	134.9
8.60 (1H, br s)	8.12 (1H, s)	166.02	166.1
		169.31	169.5
		206.46	206.5

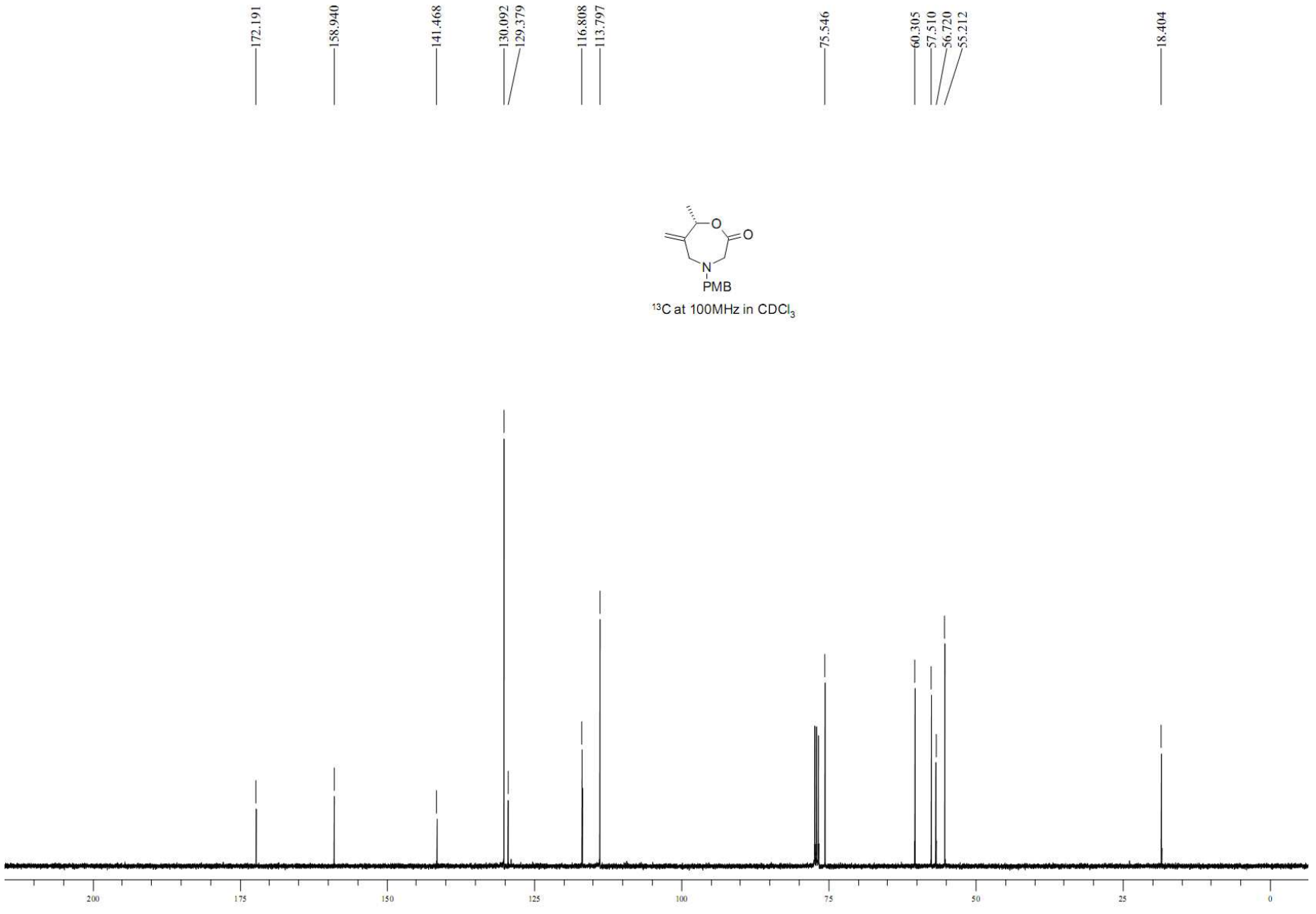
.

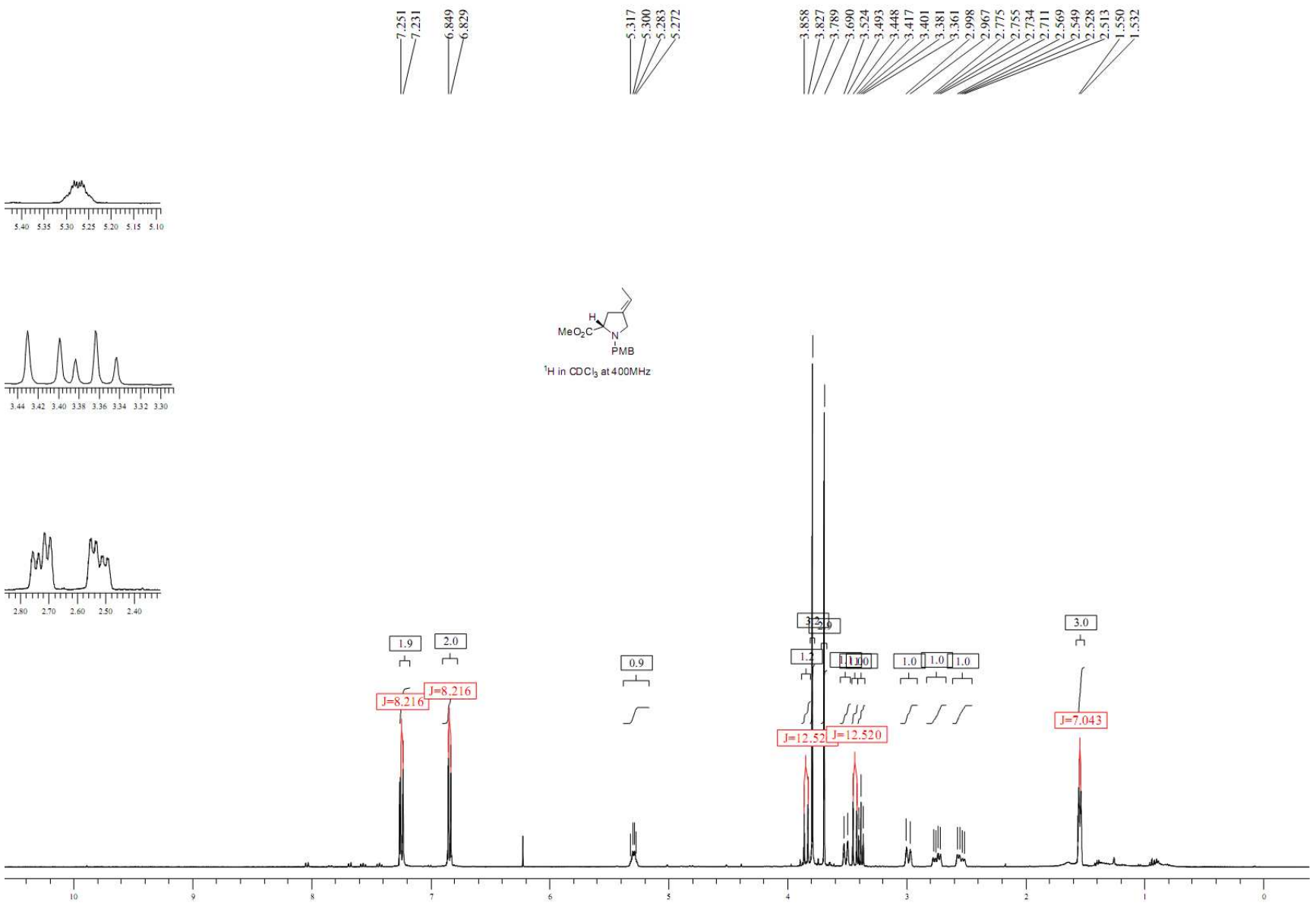
NMR spectra

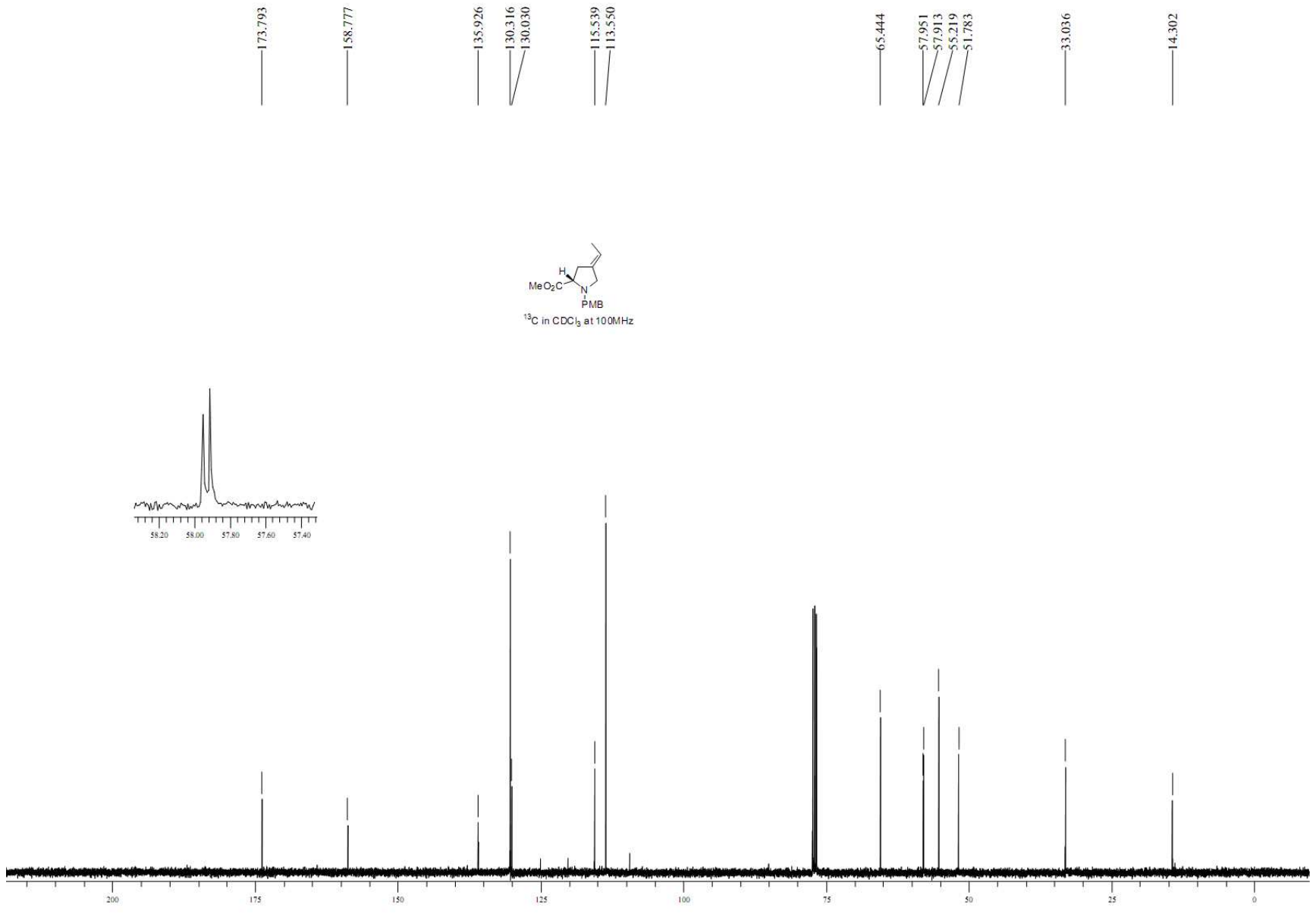

7.255
7.233
6.871
6.850
5.222
5.079
4.946
4.379
4.364
4.347
4.331
3.794
3.700
3.667
3.584
3.552
3.434
3.403
3.216
3.175
3.138
3.122
3.080
1.457
1.248
1.233
OH
N
CO2tBu
PMB
1H in CDCl3 at 400MHz
1.9
1.8
0.6
0.8
0.8
3.0
1.8
0.9
2.8
9.3
3.0
J=8.608
J=8.608
J=6.260
J=6.260

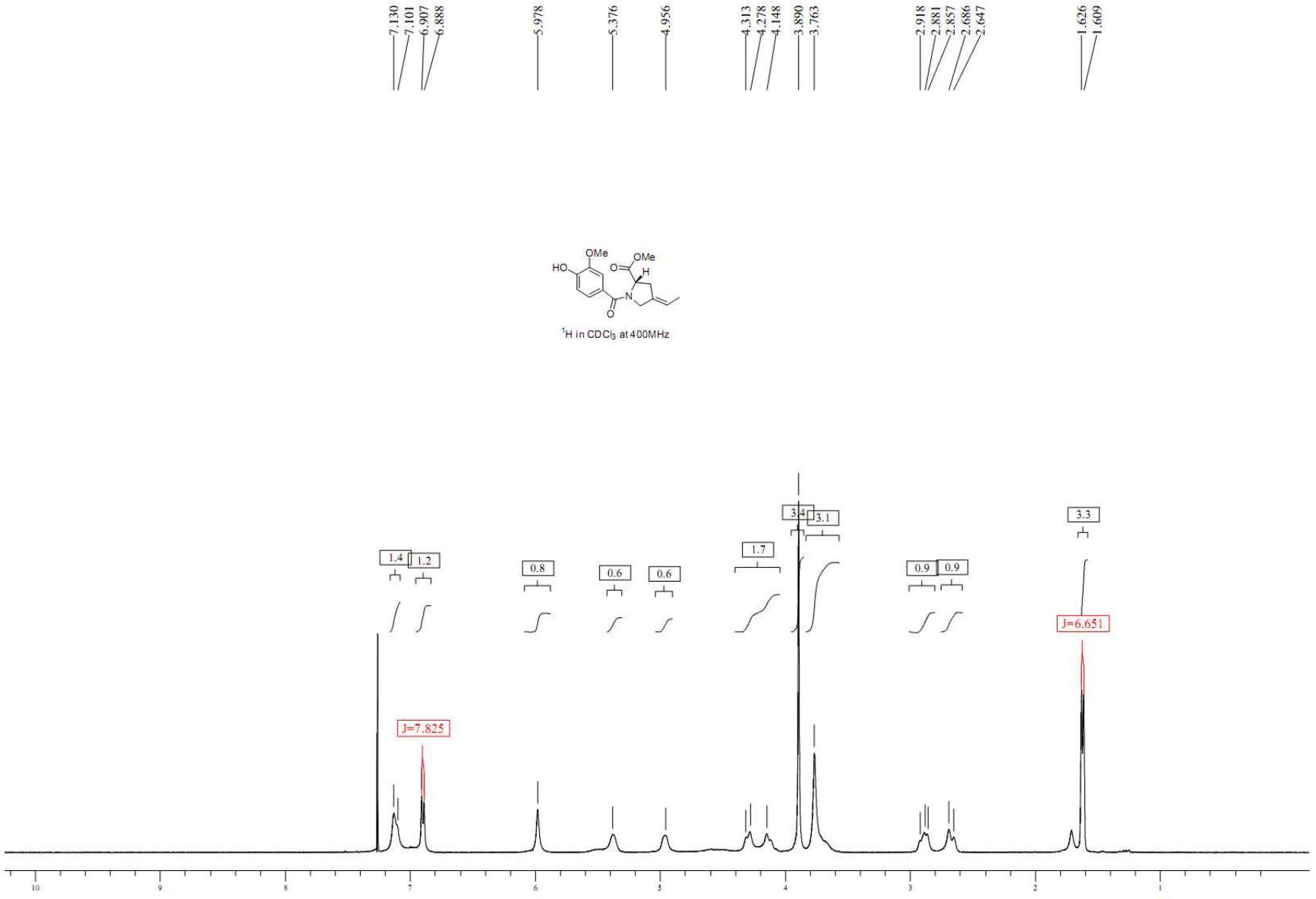

170.355
158.984
147.815
130.461
129.633
114.307
113.828
81.381
70.506
58.330
57.579
55.226
54.498
28.112
21.680
OH
N
CO2tBu
PMB
13C at 100MHz in CDCl3
200
175
150
125
100
75
50
25

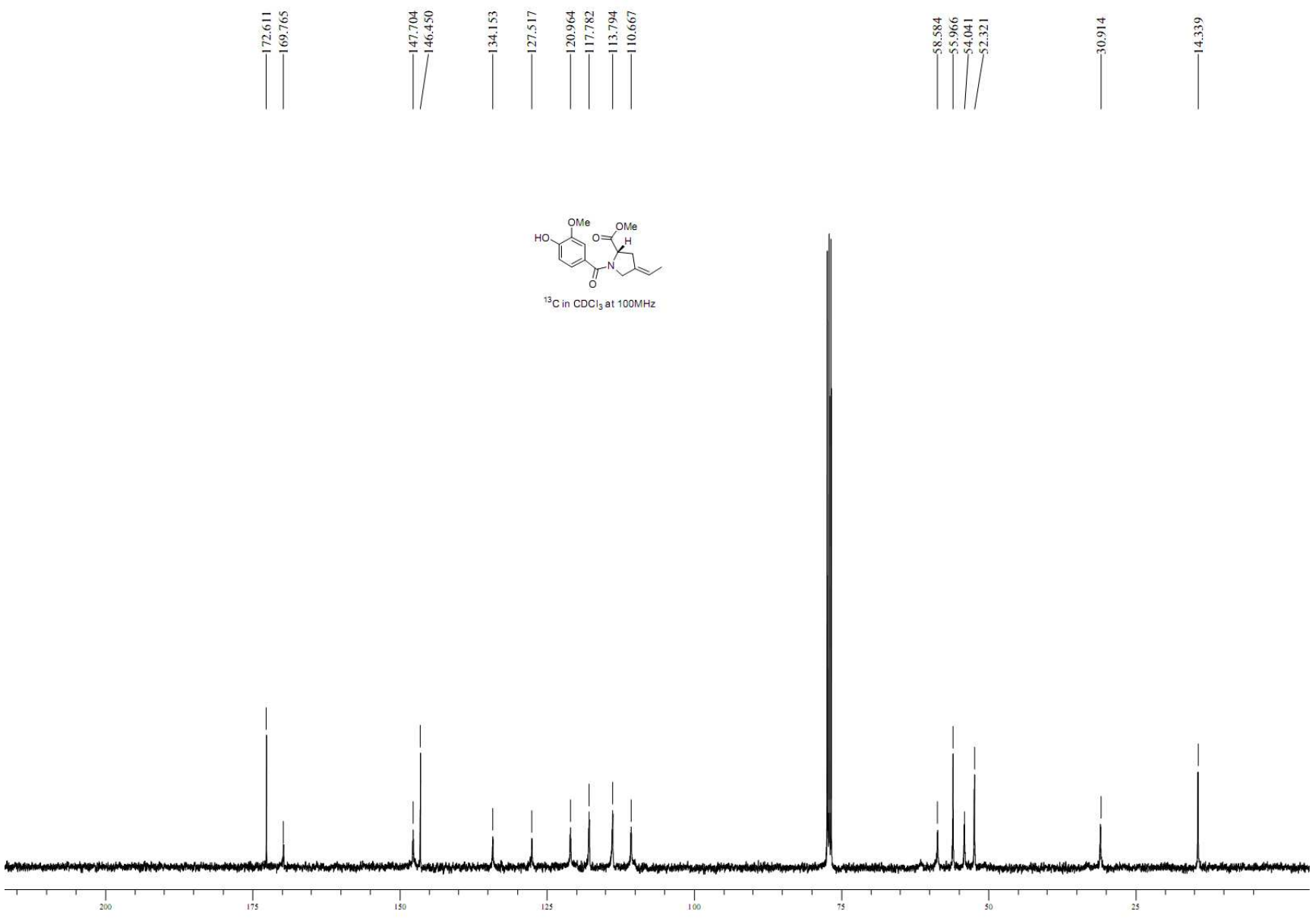

7.219
7.199
6.869
6.848
5.395
5.120
5.032
5.015
3.831
3.798
3.608
3.596
3.575
3.556
3.530
3.497
3.449
3.414
3.384
3.349
1.551
1.535
PMB
1H in CDCl3 at 400MHz
1.9
2.0
1.0
1.0
1.0
4.1
3.1
2.1
3.0
J=8.216
J=8.216
J=6.651
J=6.651
10
9
8
7
6
5
4
3
2
1

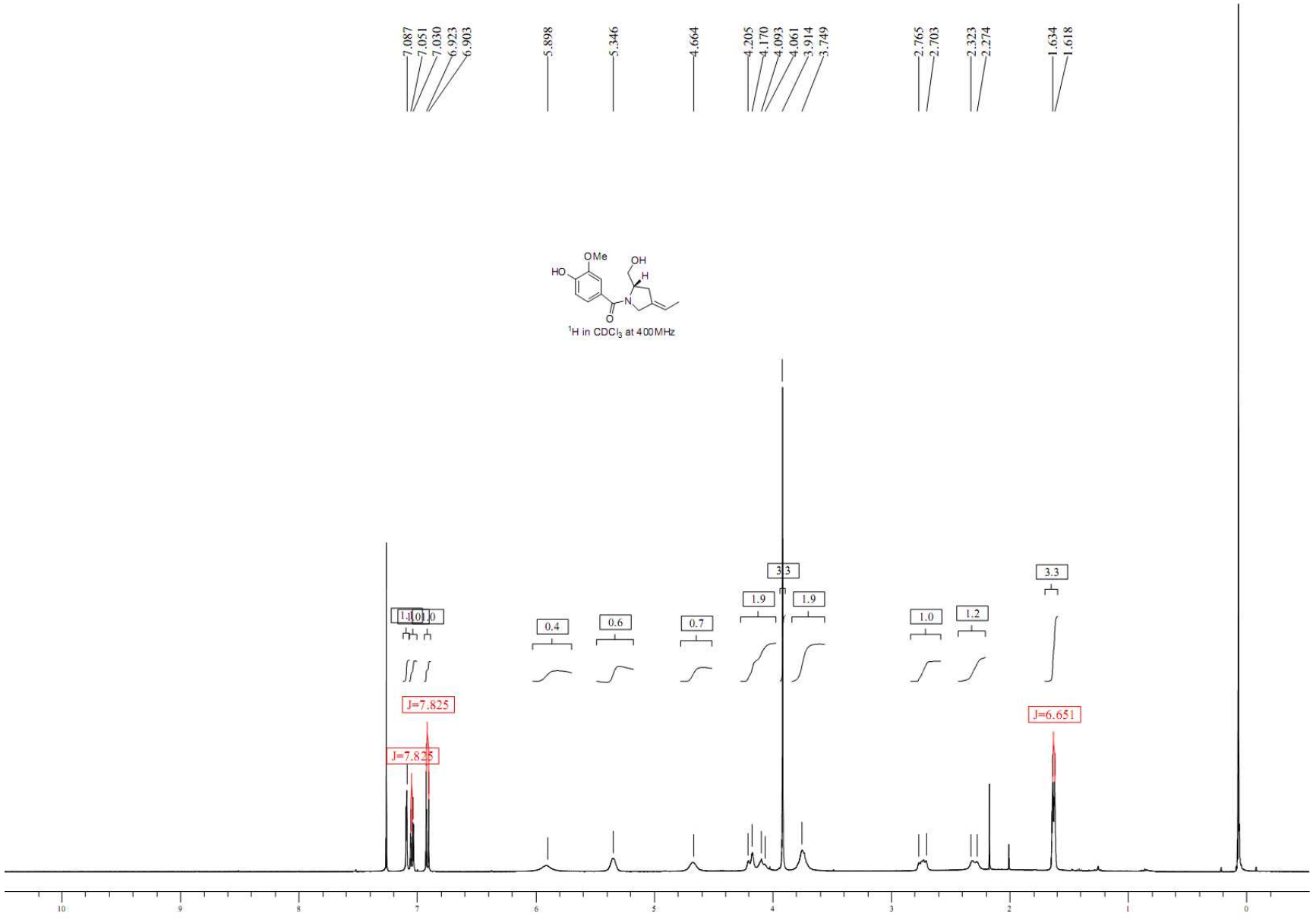

172.191
158.940
141.468
130.092
129.379
116.808
113.797
75.546
60.305
57.510
56.720
55.212
18.404
O
O
N
PMB
13C at 100MHz in CDCl3
200
175
150
125
100
75
50
25
0

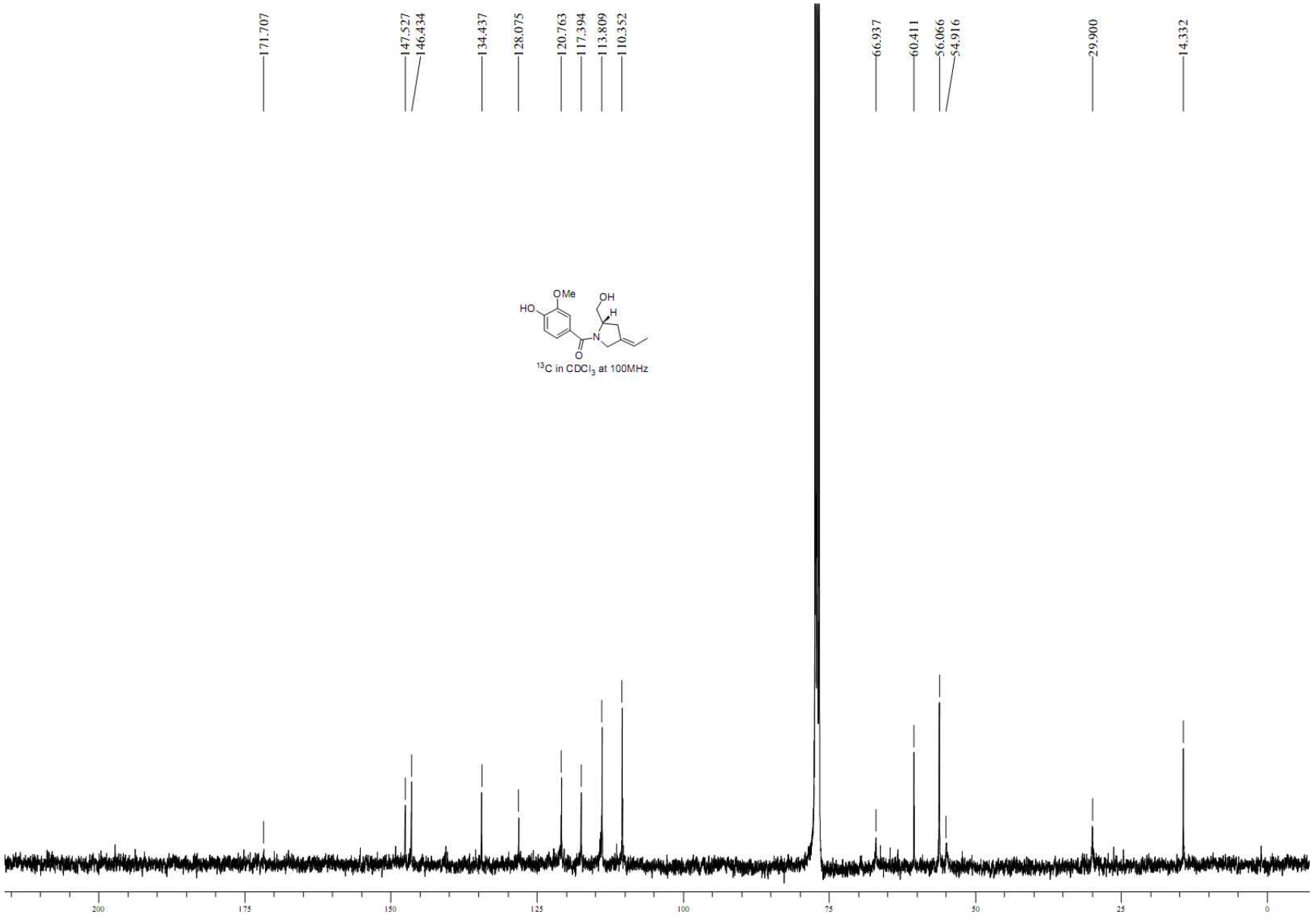

7.251
7.231
6.849
6.829
5.317
5.300
5.283
5.272
3.858
3.827
3.789
3.690
3.524
3.493
3.448
3.417
3.401
3.381
3.361
2.998
2.967
2.775
2.755
2.734
2.711
2.569
2.549
2.528
2.513
1.550
1.532
MeO2C
H
N
PMB
1H in CDCl3 at 400MHz
J=8.216
J=8.216
J=12.52
J=12.520
J=7.043

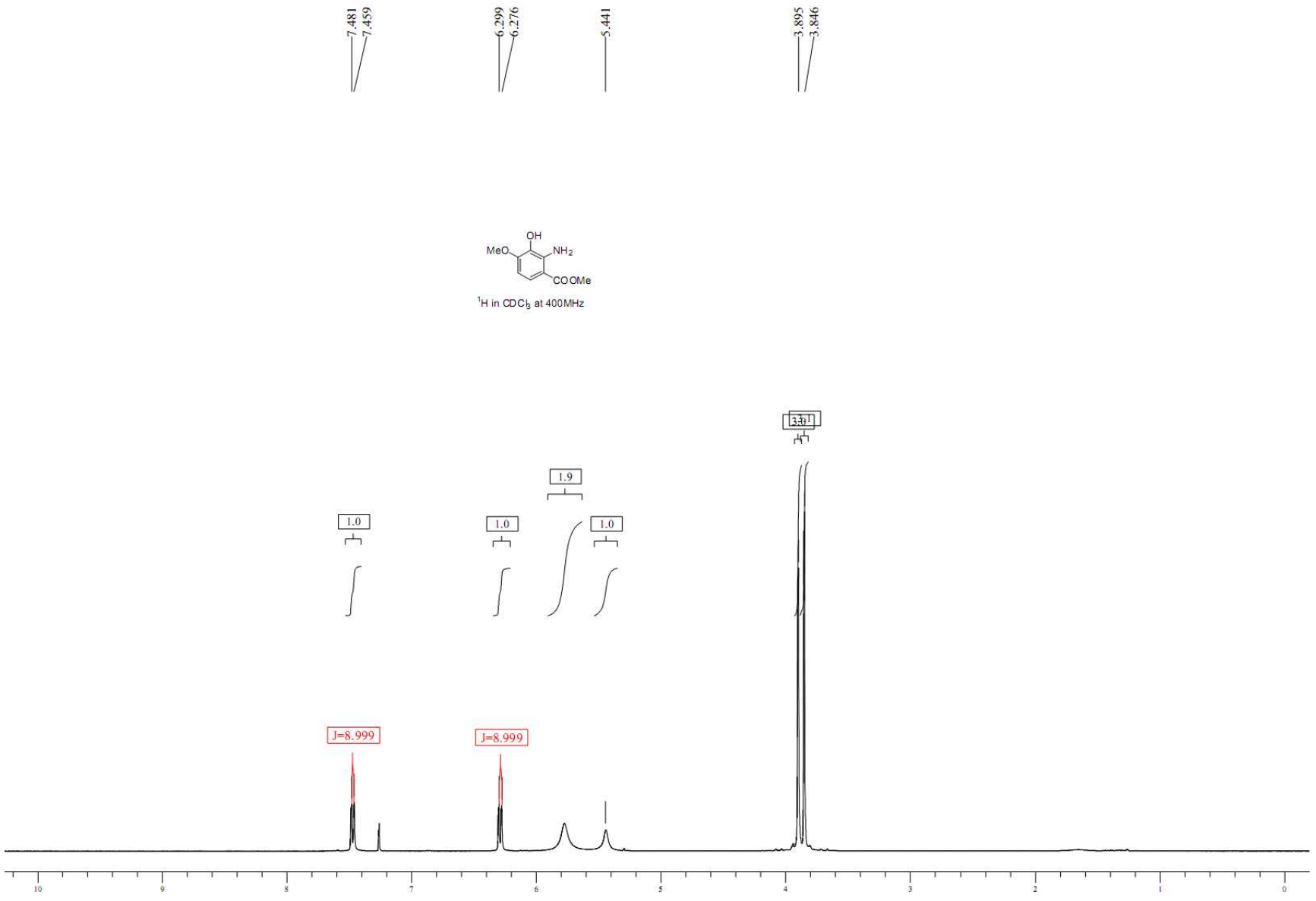

173.793
158.777
135.926
130.316
130.030
115.539
113.550
65.444
57.951
57.913
55.219
51.783
33.036
14.302
MeO2C
H
N
PMB
13C in CDCl3 at 100MHz
58.20
58.00
57.80
57.60
57.40
200
175
150
125
100
75
50
25
0

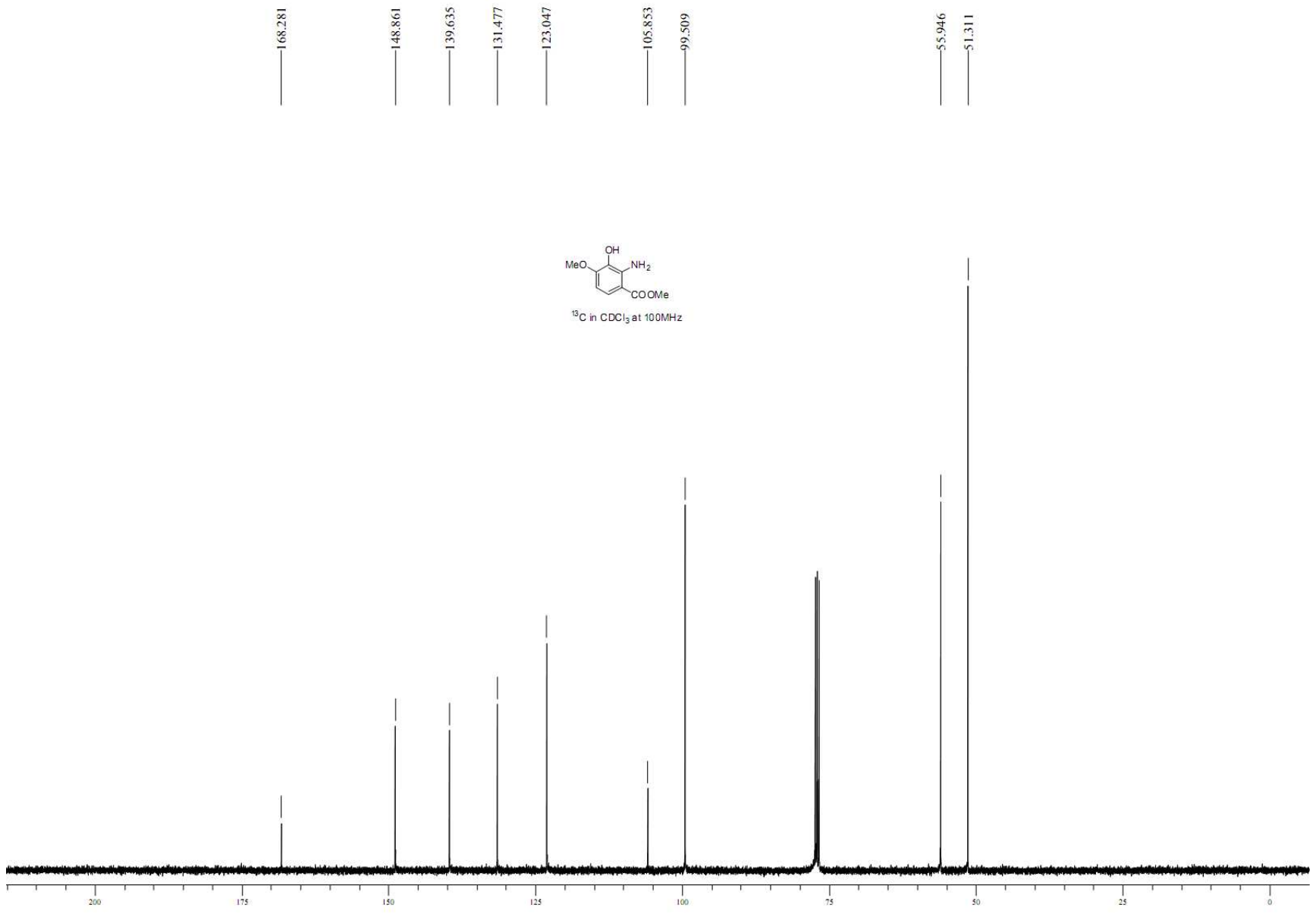

7.130
7.101
6.907
6.888
5.978
5.376
4.956
4.313
4.278
4.148
3.890
3.763
2.918
2.881
2.857
2.686
2.647
1.626
1.609
OMe
OMe
HO
O
H
N
O
^{1}H in CDCl$_3$ at 400MHz
1.4
1.2
0.8
0.6
0.6
1.7
3.4
3.1
0.9
0.9
3.3
J=7.825
J=6.651
10
9
8
7
6
5
4
3
2
1

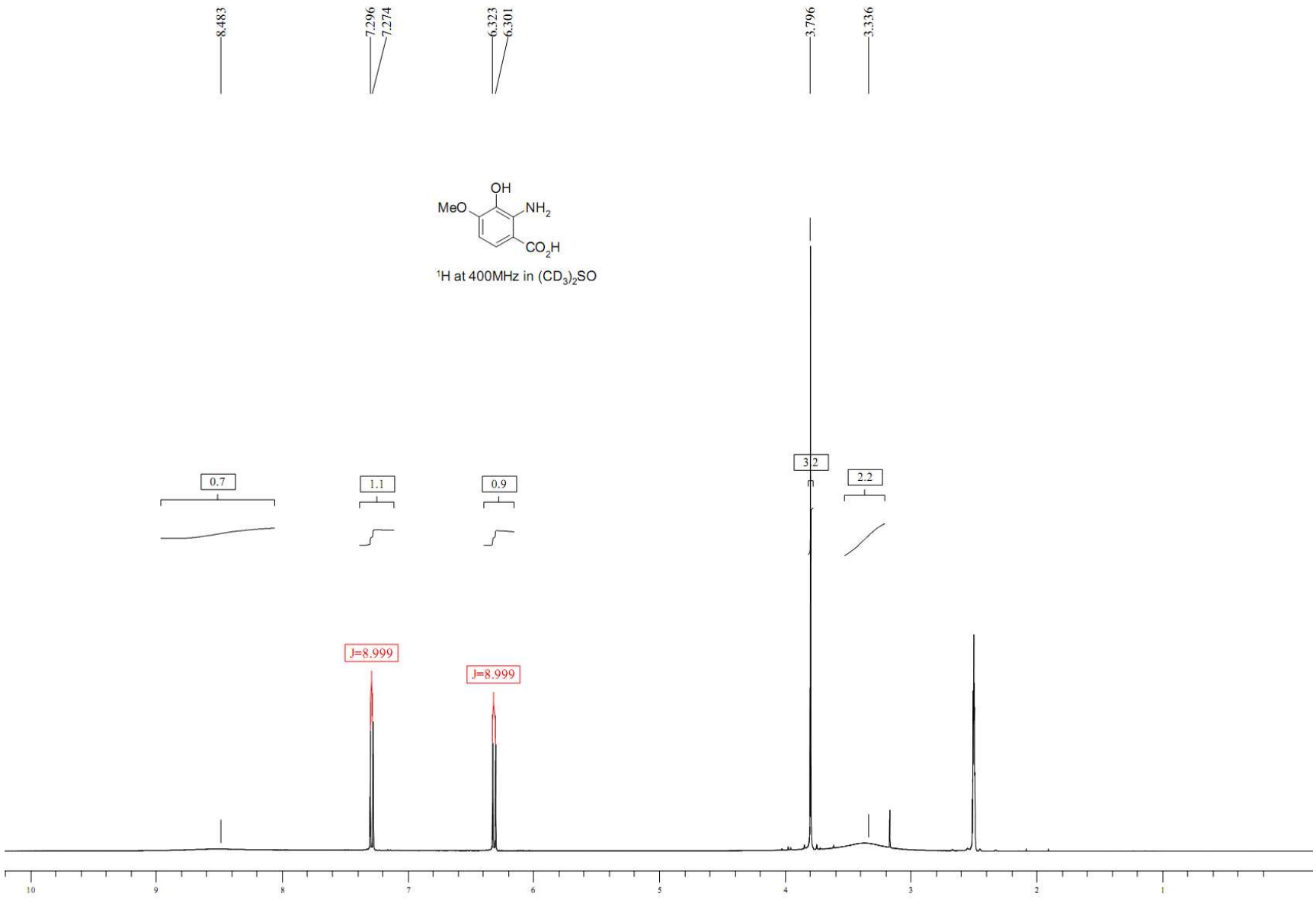

172.611
169.765
147.704
146.450
134.153
127.517
120.964
117.782
113.794
110.667
58.584
55.966
54.041
52.321
30.914
14.339
OMe
OMe
HO
O
H
N
O
^{13}C in CDCl$_3$ at 100MHz
200
175
150
125
100
75
50
25

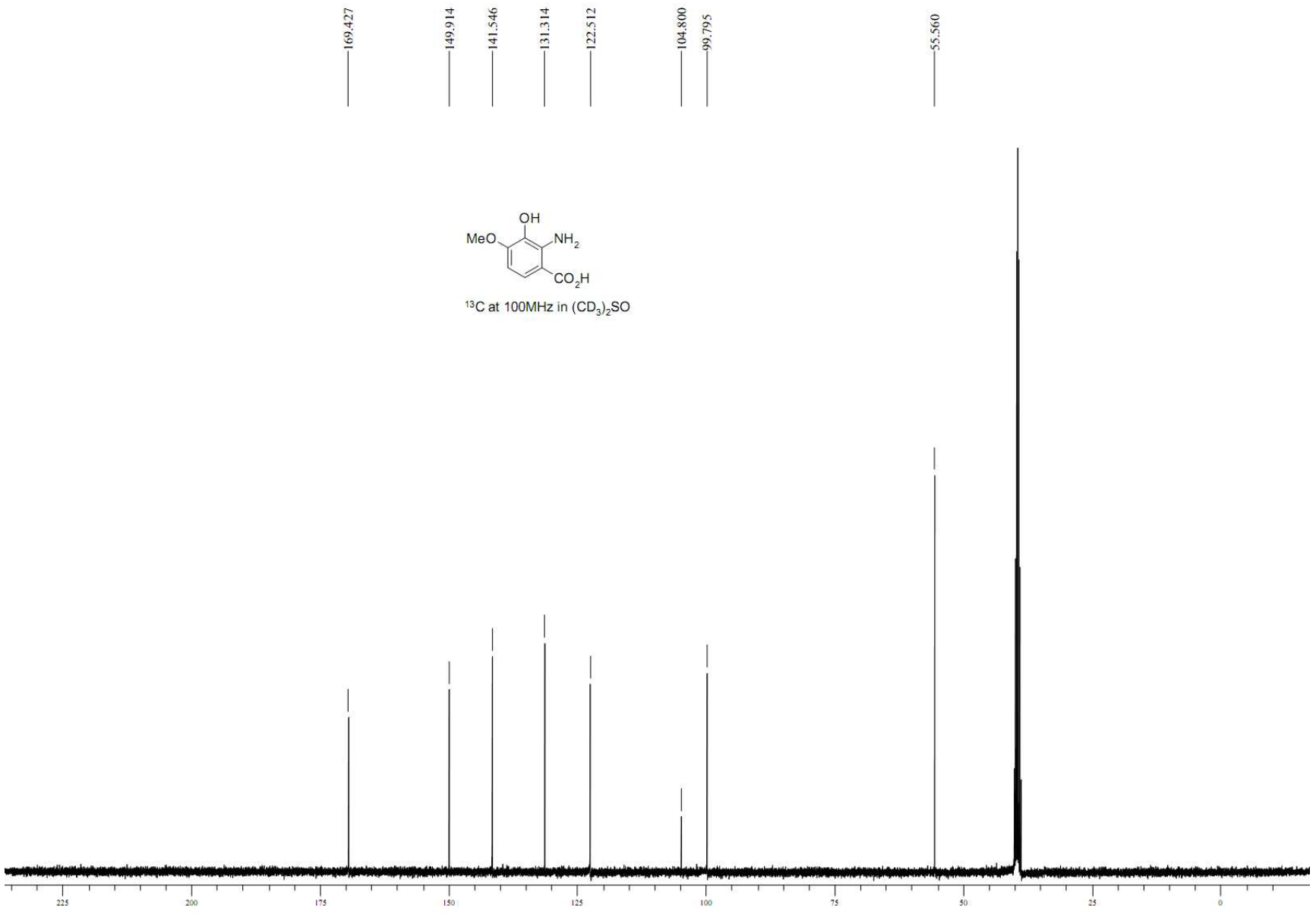

7.087
7.051
7.030
6.923
6.903
5.898
5.346
4.664
4.205
4.170
4.093
4.061
3.914
3.749
2.765
2.703
2.323
2.274
1.634
1.618
OMe
OH
HO
H
N
O
^{1}H in CDCl$_3$ at 400MHz
1.0
0.4
0.6
0.7
1.9
3.3
1.9
1.0
1.2
3.3
J=7.825
J=7.825
J=6.651

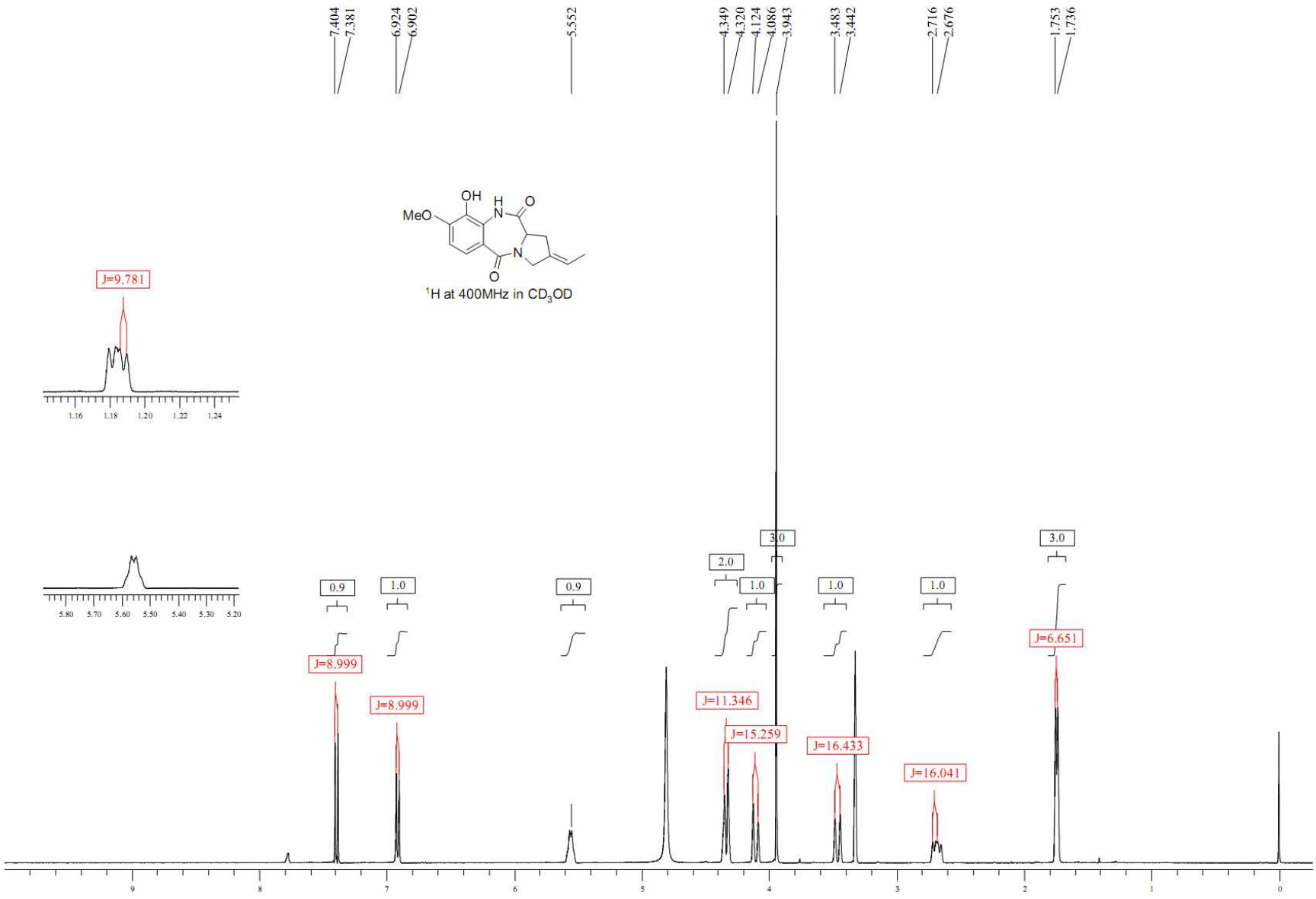

171.707
147.527
146.434
134.437
128.075
120.763
117.394
113.809
110.352
66.937
60.411
56.066
54.916
29.900
14.332
OMe
OH
HO
H
N
O
^{13}C in CDCl$_3$ at 100MHz
200
175
150
125
100
75
50
25
0

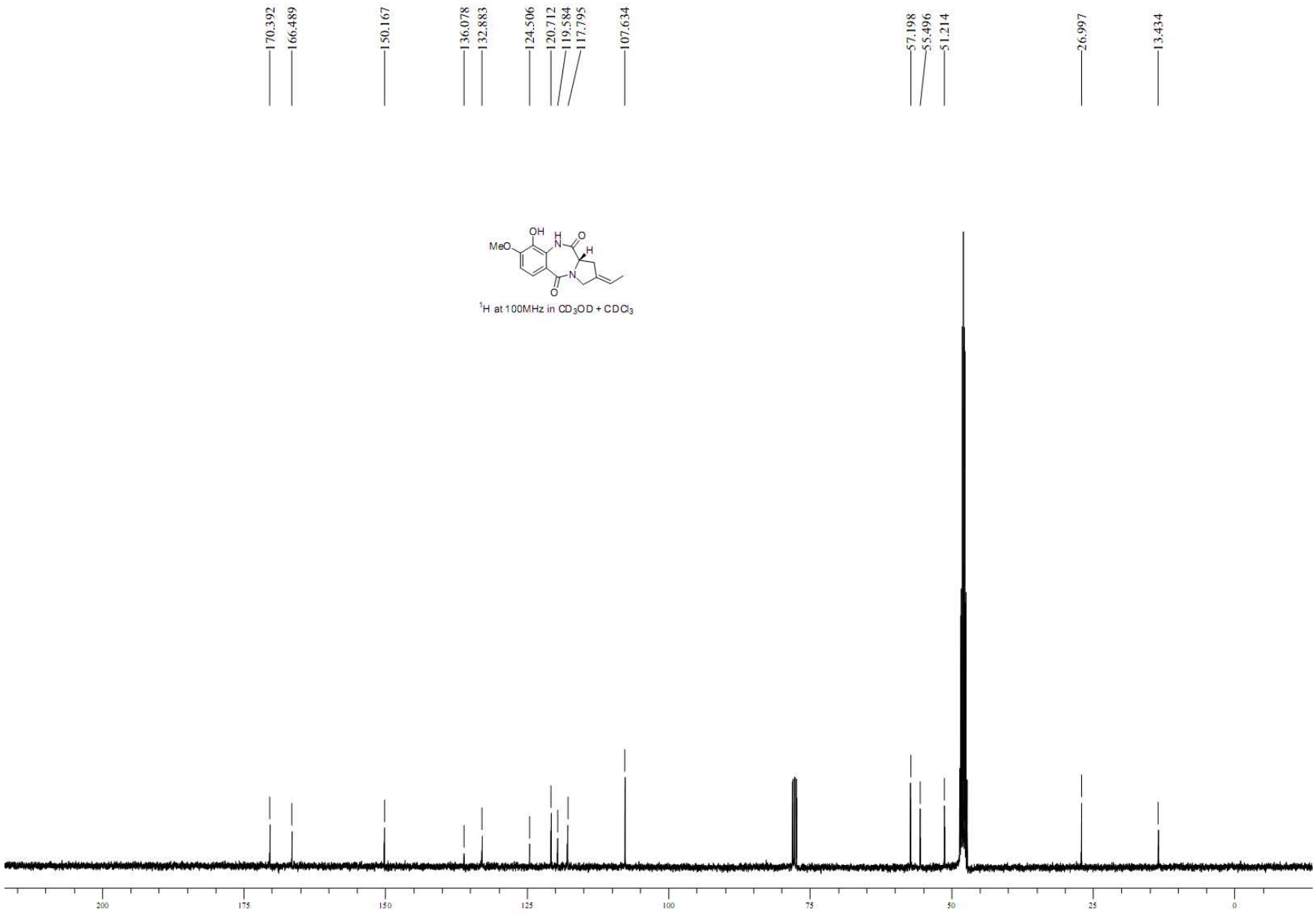

7.481
7.459
6.299
6.276
5.441
3.895
3.846
OH
MeO
NH2
COOMe
1H in CDCl3 at 400MHz
1.0
1.0
1.9
1.0
J=8.999
J=8.999

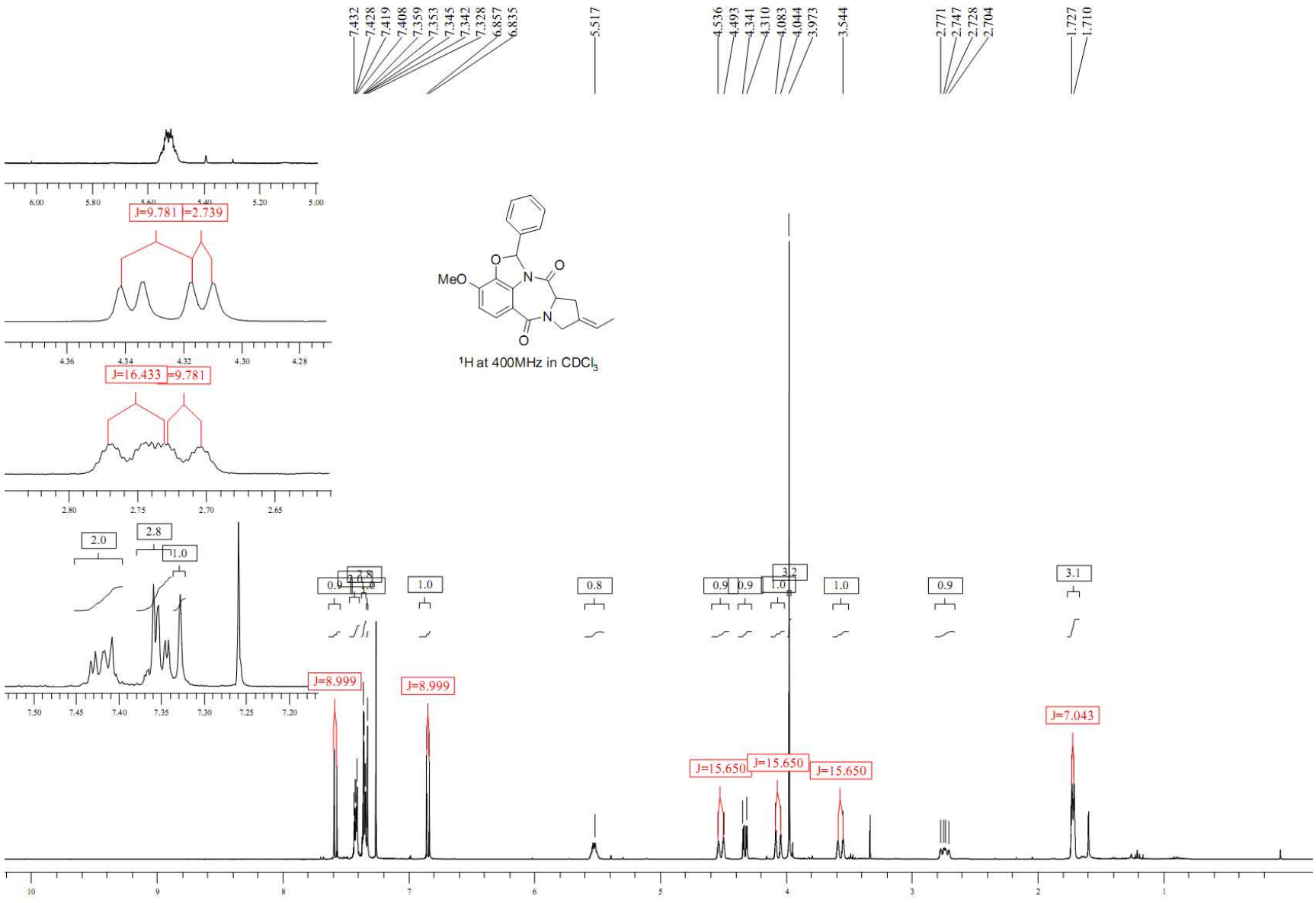

168.281
148.861
139.635
131.477
123.047
105.853
99.509
55.946
51.311
OH
MeO
NH2
COOMe
13C in CDCl3 at 100MHz
200
175
150
125
100
75
50
25
0

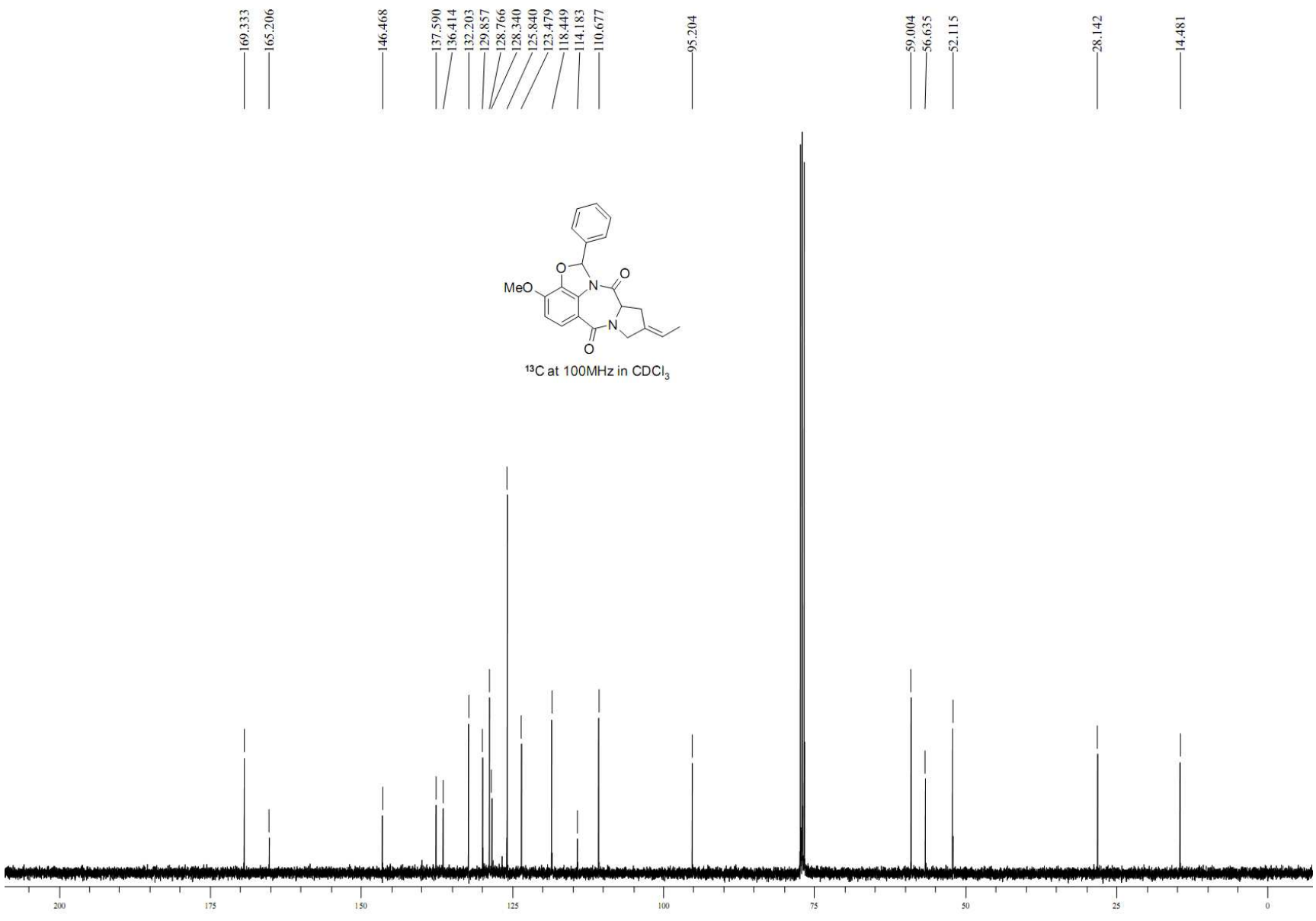

8.483
7.296
7.274
6.323
6.301
3.796
3.336
OH
MeO
NH2
CO2H
1H at 400MHz in (CD3)2SO
0.7
1.1
0.9
3.2
2.2
J=8.999
J=8.999
10
9
8
7
6
5
4
3
2
1

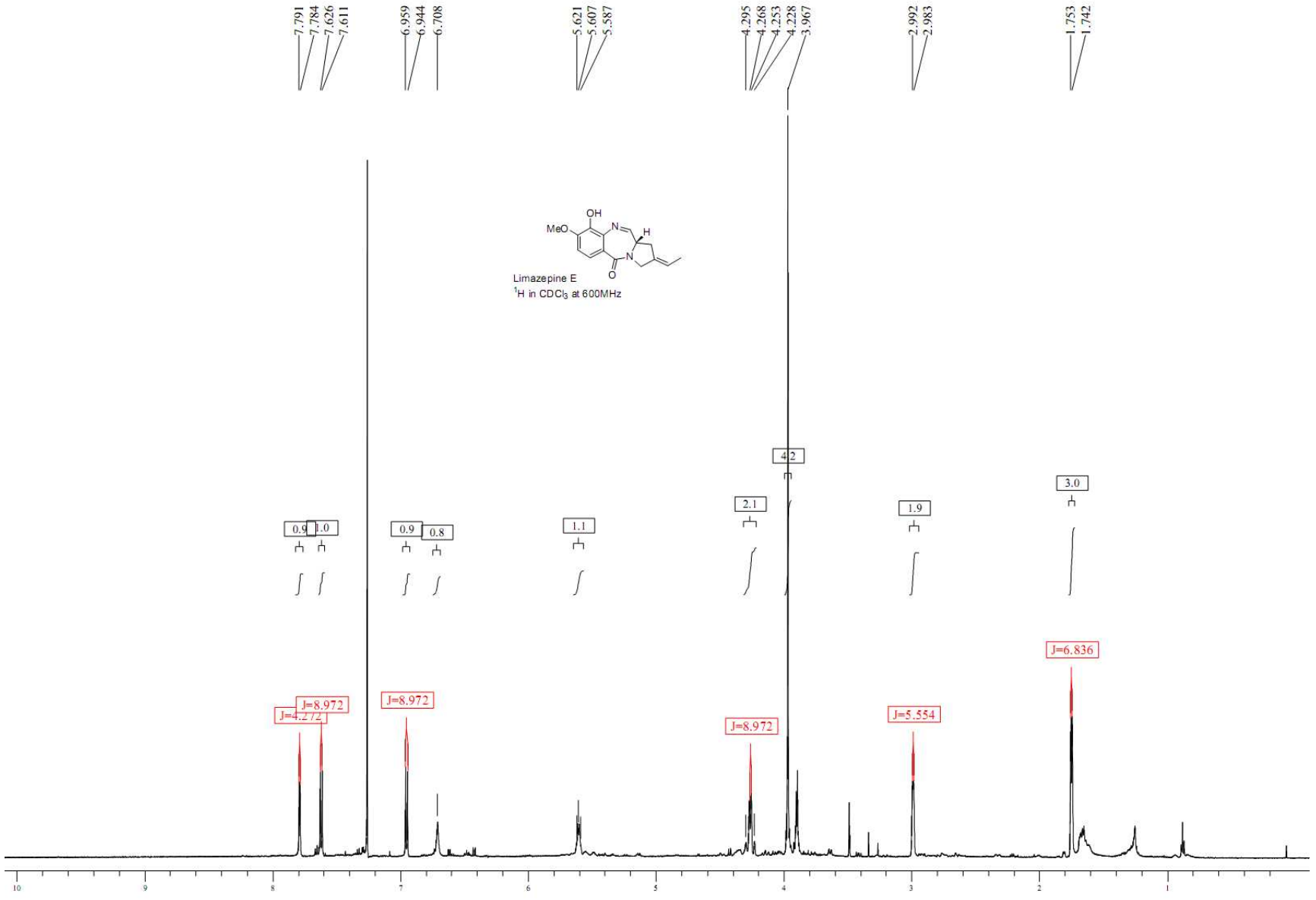

169.427
149.914
141.546
131.314
122.512
104.800
99.795
55.560
OH
MeO
NH2
CO2H
13C at 100MHz in (CD3)2SO
225
200
175
150
125
100
75
50
25
0

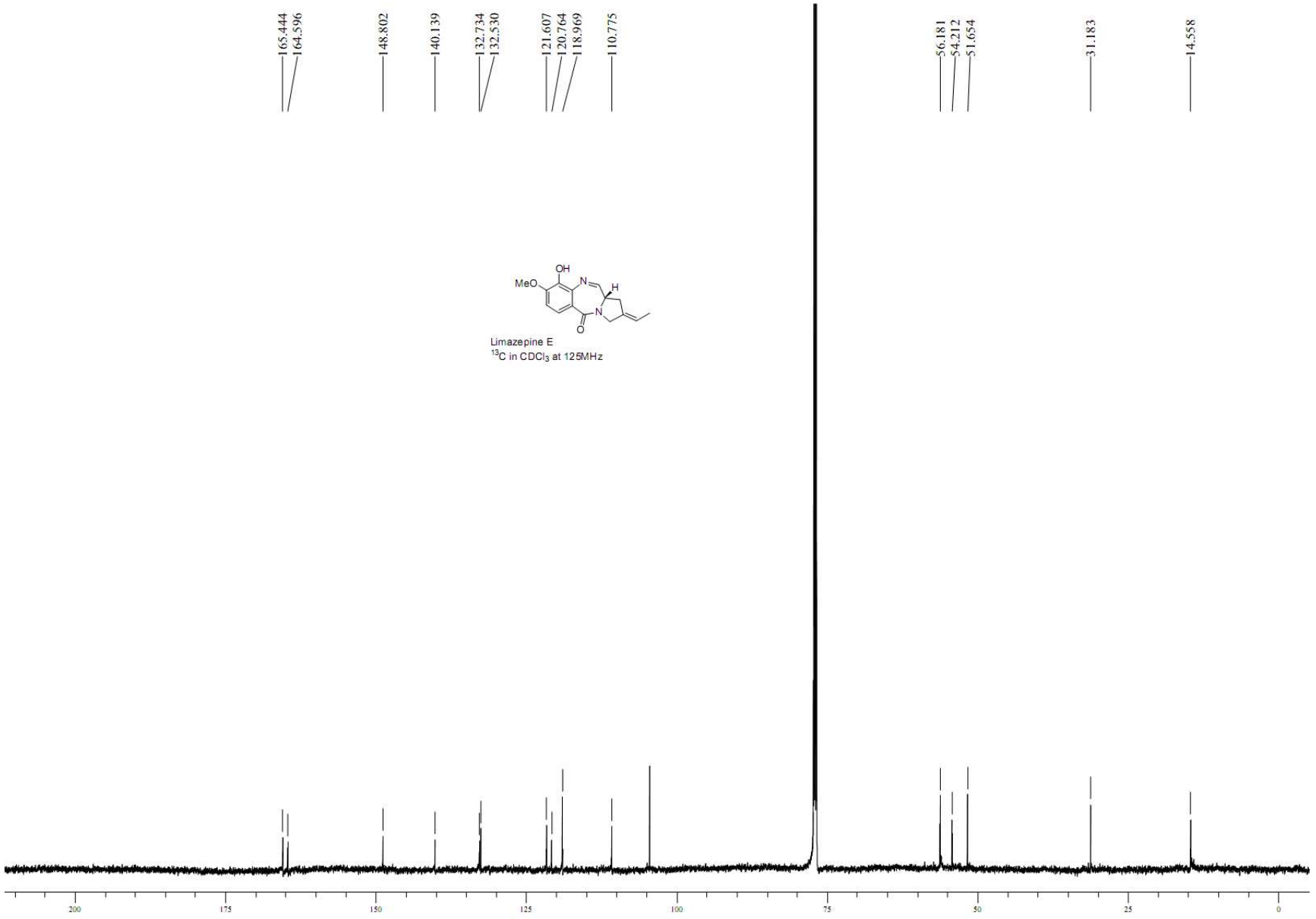

7.404
7.381
6.924
6.902
5.552
4.349
4.320
4.124
4.086
3.943
3.483
3.442
2.716
2.676
1.753
1.736
OH
H
N
O
MeO
N
O
1H at 400MHz in CD3OD
J=9.781
1.16
1.18
1.20
1.22
1.24
5.80
5.70
5.60
5.50
5.40
5.30
5.20
0.9
1.0
0.9
2.0
1.0
3.0
1.0
1.0
3.0
J=8.999
J=8.999
J=11.346
J=15.259
J=16.433
J=16.041
J=6.651
9
8
7
6
5
4
3
2
1
0


170.392
166.489
150.167
136.078
132.883
124.506
120.712
119.584
117.795
107.634
57.198
55.496
51.214
26.997
13.434
OH
MeO
H
N
O
H
N
O
^{1}H at 100MHz in CD_3OD + $CDCl_3$
200
175
150
125
100
75
50
25
0

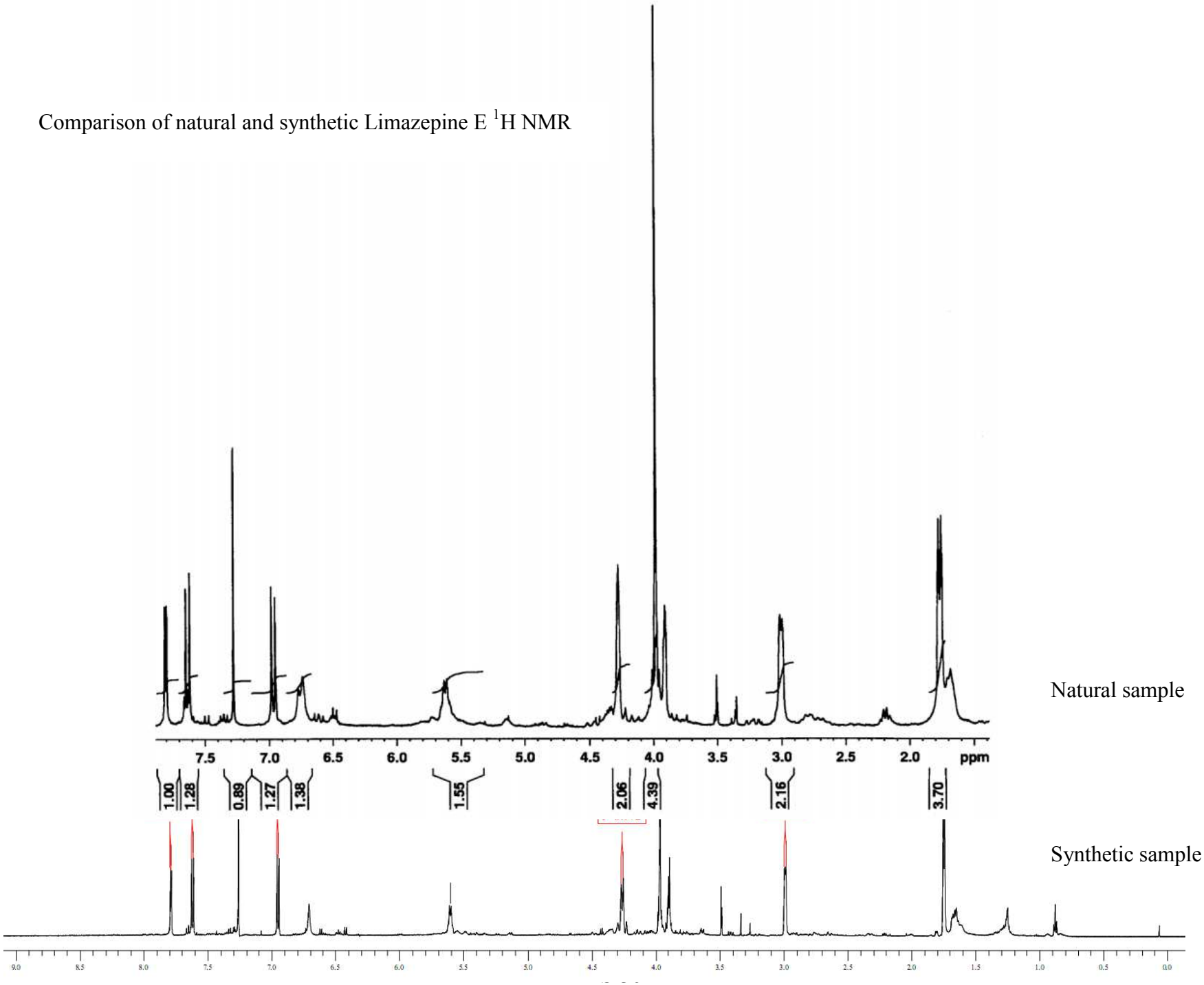

7.432
7.428
7.419
7.408
7.359
7.353
7.345
7.342
7.328
6.857
6.835
5.517
4.536
4.493
4.341
4.310
4.083
4.044
3.973
3.544
2.771
2.747
2.728
2.704
1.727
1.710
MeO
O
N
O
N
O
1H at 400MHz in CDCl3
J=9.781
J=2.739
J=16.433
J=9.781
2.0
2.8
1.0
2.8
0.9
1.0
0.8
0.9
0.9
3.2
1.0
1.0
0.9
3.1
J=8.999
J=8.999
J=15.650
J=15.650
J=15.650
J=7.043


169.333
165.206
146.468
137.590
136.414
132.203
129.857
128.766
128.340
125.840
123.479
118.449
114.183
110.677
95.204
59.004
56.635
52.115
28.142
14.481
MeO
O
N
O
N
O
13C at 100MHz in CDCl3
200
175
150
125
100
75
50
25
0


7.791
7.784
7.626
7.611
6.959
6.944
6.708
5.621
5.607
5.587
4.295
4.268
4.253
4.228
3.967
2.992
2.983
1.753
1.742
OH
MeO
N
H
N
O
Limazepine E
1H in CDCl3 at 600MHz
0.9
1.0
0.9
0.8
1.1
2.1
4.2
1.9
3.0
J=8.972
J=4.272
J=8.972
J=8.972
J=5.554
J=6.836
10
9
8
7
6
5
4
3
2
1


165.444
164.596
148.802
140.139
132.734
132.530
121.607
120.764
118.969
110.775
56.181
54.212
51.654
31.183
14.558
OH
MeO
N
H
N
O
Limazepine E
13C in CDCl3 at 125MHz
200
175
150
125
100
75
50
25
0

Comparison of natural and synthetic Limazepine E ^{1}H NMR



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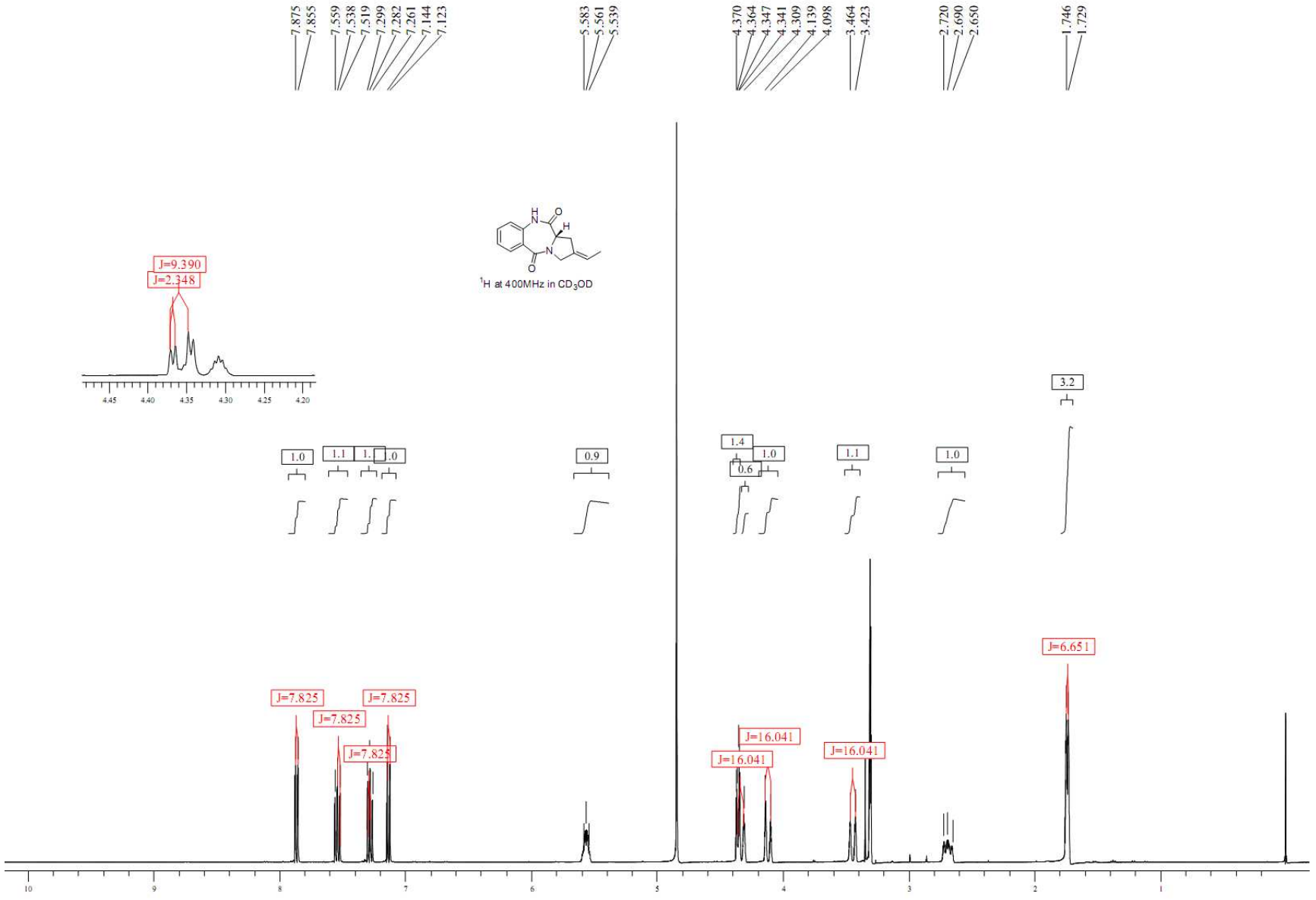
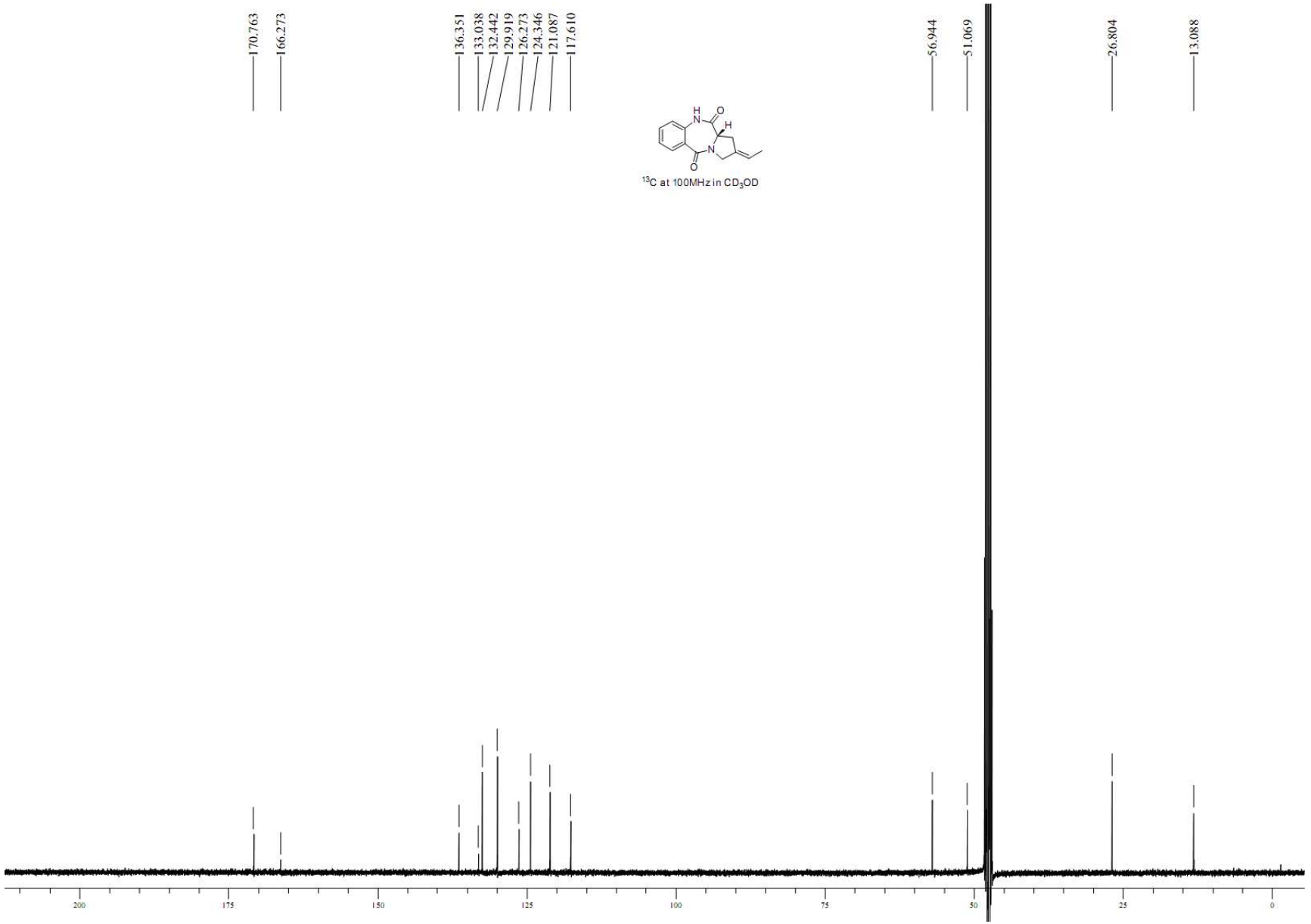
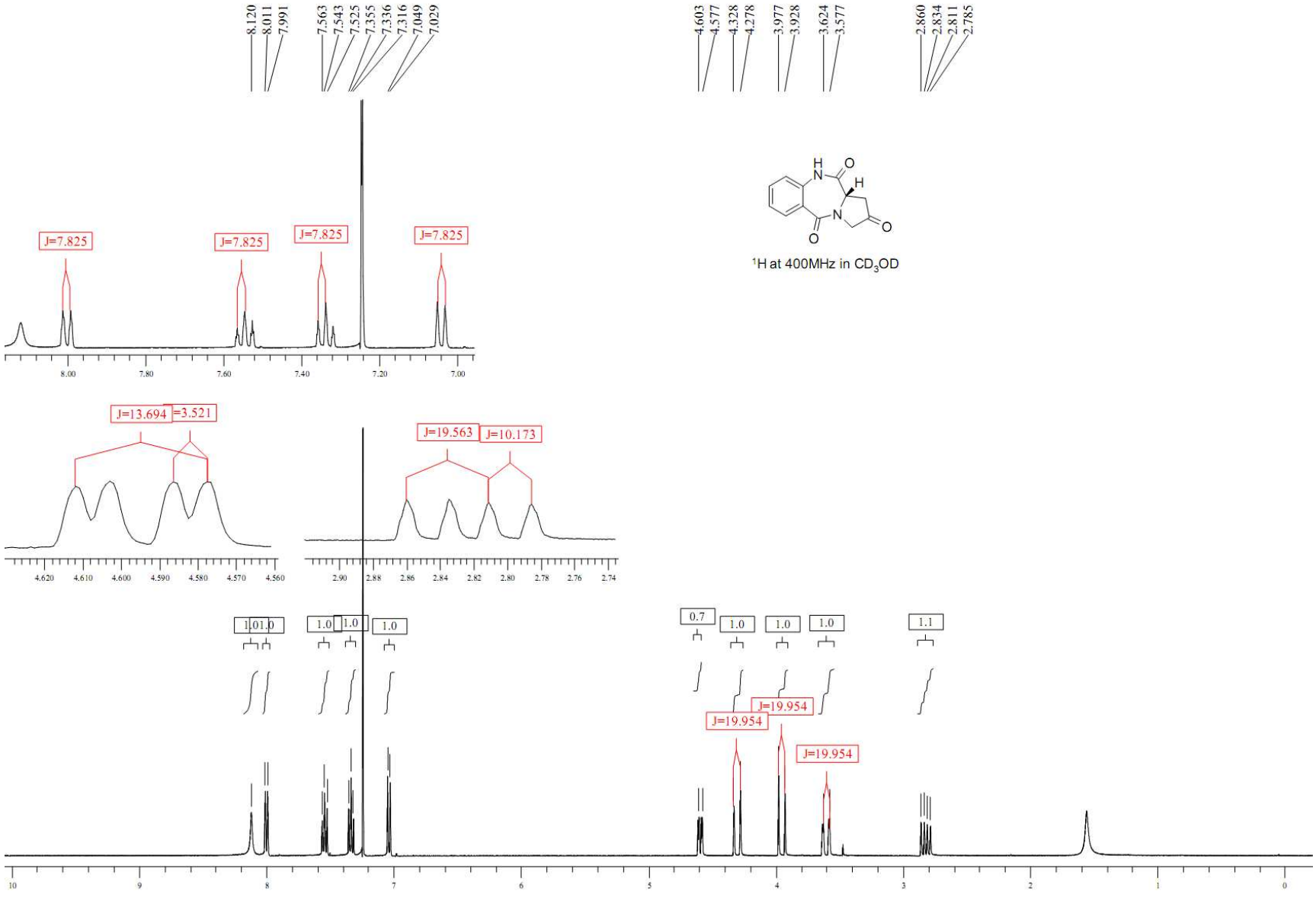
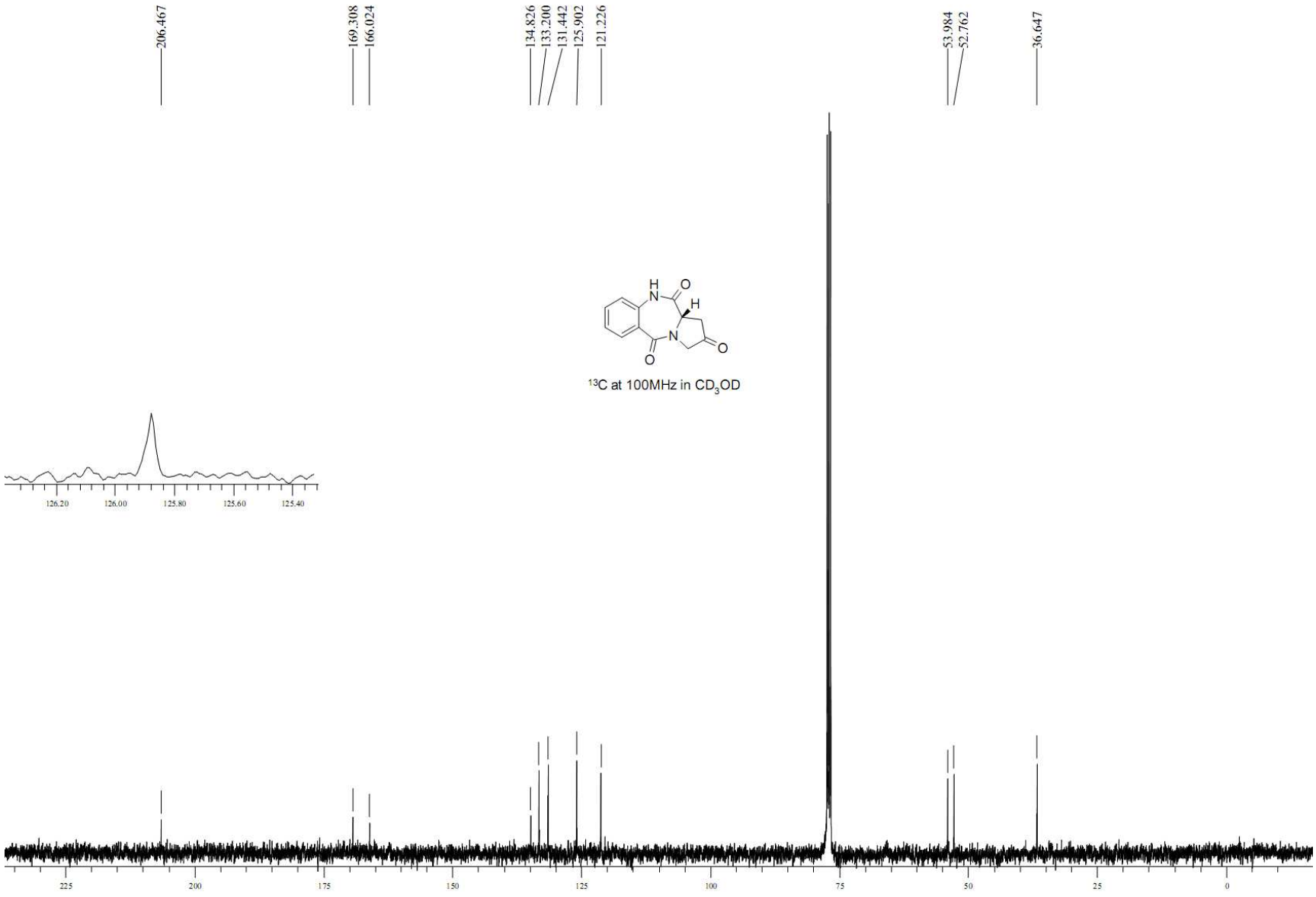

7.875
7.855
7.559
7.538
7.519
7.299
7.282
7.261
7.144
7.123
5.583
5.561
5.539
4.370
4.364
4.347
4.341
4.309
4.139
4.098
3.464
3.423
2.720
2.690
2.650
1.746
1.729
J=9.390
J=2.348
1H at 400MHz in CD3OD
1.0
1.1
1.
.0
0.9
1.4
1.0
0.6
1.1
1.0
3.2
J=7.825
J=7.825
J=7.825
J=7.825
J=16.041
J=16.041
J=16.041
J=6.651


170.763
166.273
136.351
133.038
132.442
129.919
126.273
124.346
121.087
117.610
56.944
51.069
26.804
13.088
^{13}C at 100MHz in CD_3OD
200
175
150
125
100
75
50
25
0



^{1}H at 400MHz in CD_3OD


206.467
169.308
166.024
134.826
133.200
131.442
125.902
121.226
53.984
52.762
36.647
^{13}C at 100MHz in CD_3OD