Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

[Supporting Information]

Stereocontrolled Synthesis of Carbocyclic Compounds with a Quaternary Carbon Atom based on S_N2' Alkylation of γ,δ-Epoxy-α,β-unsaturated Ketones

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Experimental procedure and compound characterization for 12, 13-*anti*, 14, 15, and 13-*syn*

(*E*)-2-(((2*S,3*S**)-3-((Benzyloxy)methyl)oxiran-2-yl)methylene)cyclohexanone (12)**: To a freshly prepared THF solution of lithium diisopropylamide, which was prepared from *i*-Pr_2NH (614 μL, 4.38 mmol) and *n*-BuLi (2.69 M in hexane, 1.6 mL, 4.38 mmol) in THF (12 mL) was added a solution of cyclohexanone (432 μL, 4.17 mmol) in THF (1 mL) slowly at –78 °C and the stirring was continued at this temperature for 2 h. Then, a solution of $ZnBr_2$ (freshly dried, 939 mg, 4.17 mmol) in THF (4 mL) was added, and the mixture was stirred at –78 °C for 2 h. A solution of aldehyde **10** (842 mg, 4.38 mmol) in THF (2 mL) was added at –78 °C, and the mixture was stirred at this temperature for an additional 1 h. After a saturated aqueous solution of NH_4Cl was added, the mixture was filtered through a pad of Celite by the aid of EtOAc. The organic layer was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude aldol product **11** was used for next step without further purification.

To a solution of the crude aldol product **11** in CH_2Cl_2 (14 mL) were added Et_3N (1.4 mL, 10.0 mmol) and MsCl (389 μL, 5.00 mmol) at 0 °C. After the solution was stirred at room temperature for 40 min, DBU (1.5 mL, 10.0 mmol) wad added, and the mixture was stirred at room temperature for 45 min. The reaction was quenched with saturated aqueous $NaHCO_3$ solution. After the layers were separated, the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc = 5:1) twice to give *trans*-epoxide **12** (556 mg, 2.04 mmol, 49% for 2 steps): Yellow oil; IR (neat) ν 2939, 2863, 1729, 1690, 1622, 1497, 1454, 1301, 1232, 1141, 1100, 880, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 6.09 (dt, *J* = 9.2, 1.7 Hz, 1H), 4.59 (d, *J* = 12.1 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 3.77 (dd, *J* = 11.5, 2.9 Hz, 1H), 3.58 (dd, *J* = 11.5, 5.2 Hz, 1H), 3.51 (dd, *J* = 9.2, 3.2 Hz, 1H), 3.22 (quintet, *J* = 2.3 Hz, 1H), 2.77–2.65 (m, 1H), 2.58–2.39 (m, 3H), 1.94–1.74 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 200.1, 141.3, 137.6, 133.2, 128.4, 127.8, 127.7, 73.4, 69.2, 58.6, 51.2, 40.2, 27.2, 23.4, 23.3; MS (FI) *m/z* 272 (M^+, 100%); HRHS (FI) calcd for $C_{17}H_{20}O_3$ (M^+): 272.1412, found: 272.1405.

S_N2' methylation reaction of 12: To a mixture of *trans*-epoxide **12** (38.0 mg, 0.140 mmol) and CuCN (26.3 mg, 0.294 mmol) in DMF (350 μL) was added Me_2Zn (2.0 M in toluene, 147 μL, 0.294 mmol) at –50 °C. After the reaction mixture was stirred at this temperature for 1 h, it was quenched by the addition of a mixture of saturated aqueous NH_4Cl and 35% aqueous NH_4OH (9:1) and extracted with Et_2O. The combined organic layers were washed with water and brine, dried over $MgSO_4$, and

concentrated under reduced pressure to give 48.6 mg of the crude methylation products **13-*anti*** and **14**. Yields of **13-*anti*** and **14** were determined by ^{1}H NMR using pyrazine as an internal standard. For characterization, the mixture of the crude products was purified by preparative thin layer chromatography (hexane/EtOAc = 1.2:1) to afford analytically pure samples.

(*R)-2-((3*R**,1*E*)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-2-methylcyclohexanone (13-*anti*)**: Colorless oil; IR (neat) ν 3446, 2931, 2861, 1706, 1452, 1117, 974, 907, 739, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.27 (m, 5H), 5.98 (dd, *J* = 16.1, 1.2 Hz, 1H), 5.40 (dd, *J* = 16.0, 5.7 Hz, 1H), 4.56 (s, 2H), 4.37–4.31 (m, 1H), 3.50 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.34 (dd, *J* = 9.7, 8.1 Hz, 1H), 2.53 (d, *J* = 3.5 Hz, 1H), 2.48 (ddd, *J* = 14.4, 10.9, 5.8 Hz, 1H), 2.35–2.27 (m, 1H), 2.00–1.90 (m, 2H), 1.83–1.57 (m, 4H), 1.15 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.2, 137.7, 136.7, 128.5, 128.4, 127.8, 127.7, 74.1, 73.3, 71.1, 51.1, 40.0, 39.2, 27.5, 24.0, 21.6; MS (FI) *m/z* 289 ([M+H]$^+$, 100%); HRHS (FI) calcd for $C_{18}H_{24}O_3$ (M^+): 288.1725, found: 288.1700.

(*E*)-2-(4-(Benzyloxy)-3-hydroxy-2-methylbutylidene)cyclohexanone (14): Colorless oil; IR (neat) ν 3444, 2932, 2867, 1684, 1614, 1143, 1100, 997, 817, 738, 699 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.27 (m, 5H), 6.56 (brd, *J* = 9.8 Hz, 1H), 4.56 (d, *J* = 12.0 Hz, 1H), 4.53 (d, *J* = 12.0 Hz, 1H), 3.81–3.75 (m, 1H), 3.53 (dd, *J* = 9.2, 3.5 Hz, 1H), 3.40 (dd, *J* = 9.2, 7.4 Hz, 1H) 2.68–2.41 (m, 5H), 2.33 (d, *J* = 3.4 Hz, 1H), 1.88–1.68 (m, 4H), 1.01 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 201.2, 140.0, 137.8, 136.8, 128.4, 127.8, 127.7, 73.6, 73.4, 72.3, 40.2, 35.1, 26.9, 23.3, 23.3, 15.8; MS (FI) *m/z* 288 (M^+, 100%); HRHS (FI) calcd for $C_{18}H_{24}O_3$ (M^+): 288.1725, found: 288.1730.

(*E*)-2-((2*R,3*S**)-4-(Benzyloxy)-2-chloro-3-hydroxybutylidene)cyclohexanone (15):** A mixture of *trans*-epoxide **12** (150 mg, 0.550 mmol) and $MgCl_2$ (262 mg, 2.75 mmol) in MeCN (2.8 mL) was stirred at 50 °C for 12 h. After the mixture was cooled to room temperature, water was added, and the mixture was extracted with EtOAc. The combined organic extracts were washed with water and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was quickly purified by flash column chromatography (SiO_2, hexane/EtOAc = 5:3) to afford chlorohydrin **15** (170 mg, 0.550 mmol, quant.): Yellow oil; IR (neat) ν 3434, 2939, 2866, 1686, 1618, 1454, 1114, 916, 816, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 6.59 (dt, *J* = 10.3, 2.3 Hz, 1H), 4.72 (dd, *J* = 10.3, 6.3 Hz, 1H), 4.56 (s, 2H), 3.99 (quintet, *J* = 5.5 Hz, *1*H), 3.69 (dd, *J* = 9.7, 5.7 Hz, 1H), 3.61 (dd, *J* = 9.7, 4.6 Hz, 1H), 2.71 (d, *J* = 5.2 Hz, 1H), 2.63 (dtd, *J* = 16.7, 5.7, 1.7 Hz, 1H), 2.53 (dtd, *J* = 16.1, 6.3, 1.7 Hz, 1H), 2.47 (t, *J* = 6.3 Hz, 2H), 1.93–1.73 (m, 4H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 200.6, 139.9, 137.5, 132.1, 128.5, 127.9, 127.8, 73.6, 73.2, 70.3, 55.8, 40.4, 27.2, 23.3, 23.2; MS (FD) *m/z* 308 (M^+, 60%); HRHS (FD)

calcd for $C_{17}H_{21}{}^{35}ClO_3$ (M^+): 308.1179, found: 308,1183.

(*S)-2-((3*R**,1*E*)-4-(Benzyloxy)-3-hydroxybut-1-en-1-yl)-2-methylcyclohexanone (13-*syn*):** To a mixture of chlorohydrin **15** (170 mg, 0.550 mmol) and CuCN (98.7 mmol, 1.10 mmol) in MeCN (3.7 mL) was added Me_3Al (2.0 M in hexane, 1.1 mL, 2.20 mmol) at 0 °C. After the reaction mixture was stirred at this temperature for 1 h, it was quenched by the addition of water, diluted with EtOAc, and filtered through a pad of Celite, which was rinsed with EtOAc. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc = 5:2) to afford methylation product **13-*syn*** (123 mg, 0.425 mmol, 77% for 2 steps): Colorless oil; IR (neat) ν 3443, 2929, 2861, 1707, 1497, 1453, 1117, 975, 907, 738, 699 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.32–7.27 (m, 5H), 5.96 (dd, *J* = 16.0, 1.2 Hz, 1H), 5.38 (dd, *J* = 16.1, 5.7 Hz, 1H), 4.55 (s, 2H), 4.36–4.31 (m, 1H), 3.50 (dd, *J* = 9.8, 3.5 Hz, 1H), 3.33 (dd, *J* = 9.2, 8.0 Hz, 1H), 2.55 (d, *J* = 3.5 Hz, 1H), 2.50 (ddd, *J* = 14.3, 10.9, 5.2 Hz, 1H), 2.35–2.28 (m, 1H), 1.99–1.89 (m, 2H), 1.83–1.57 (m, 4H), 1.15 (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 213.3, 137.7, 136.9, 128.5, 128.4, 127.8, 127.7, 74.0, 73.3, 71.1, 51.1, 40.0, 39.2, 27.6, 24.3, 21.6; MS (FI) *m/z* 289 ($[M+H]^+$, 100%); HRHS (FI) calcd for $C_{18}H_{24}O_3$ (M^+): 288.1725, found: 288.1722.

NOE data for structural assignments of 16a, 17a-*anti*, and 17a-*syn*

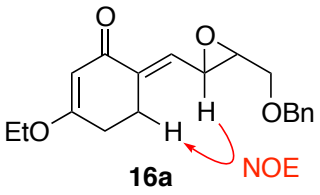
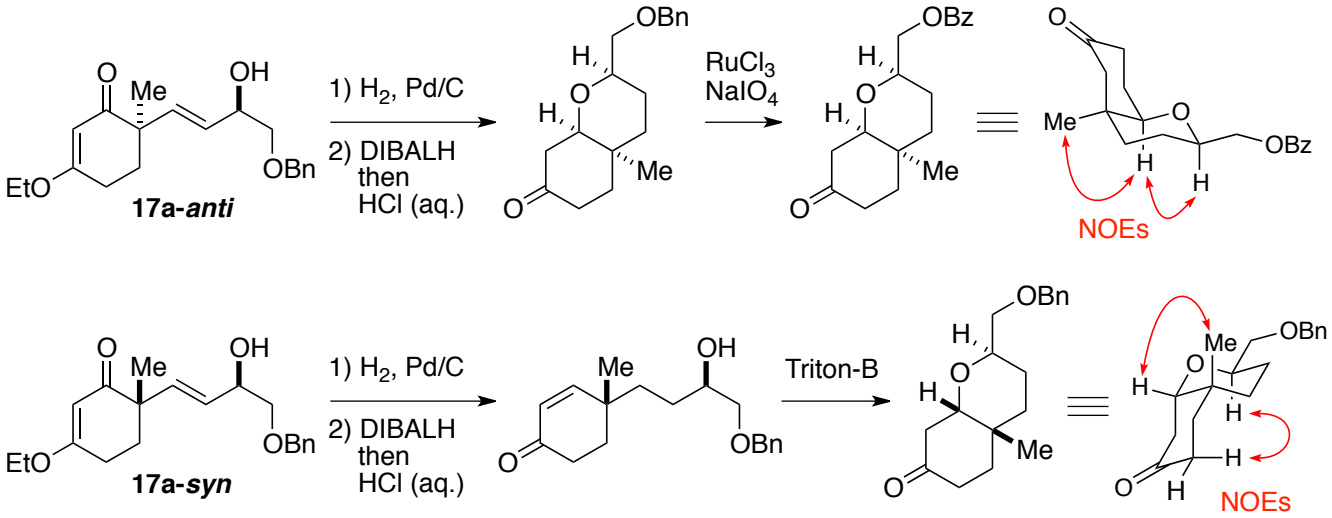
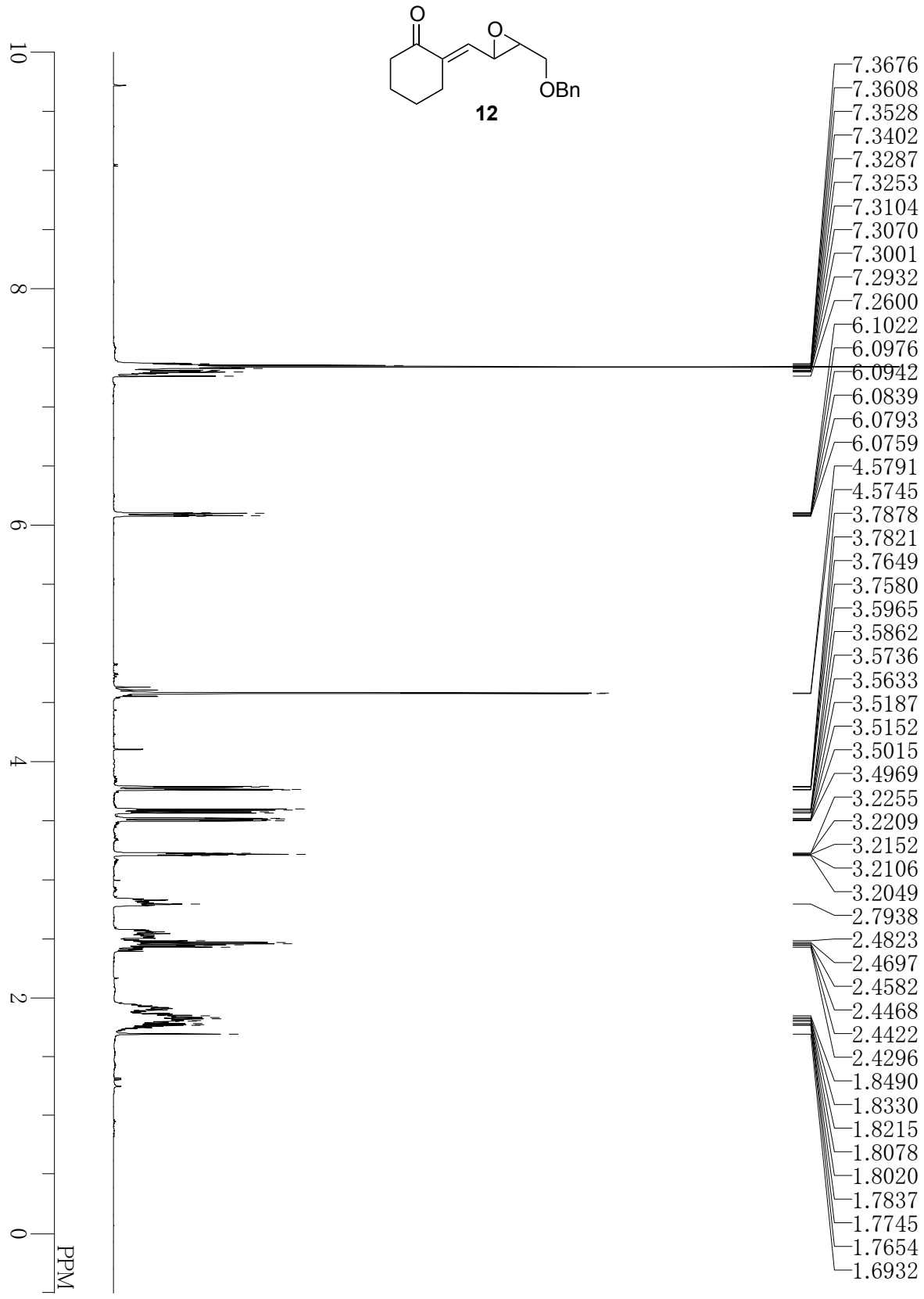
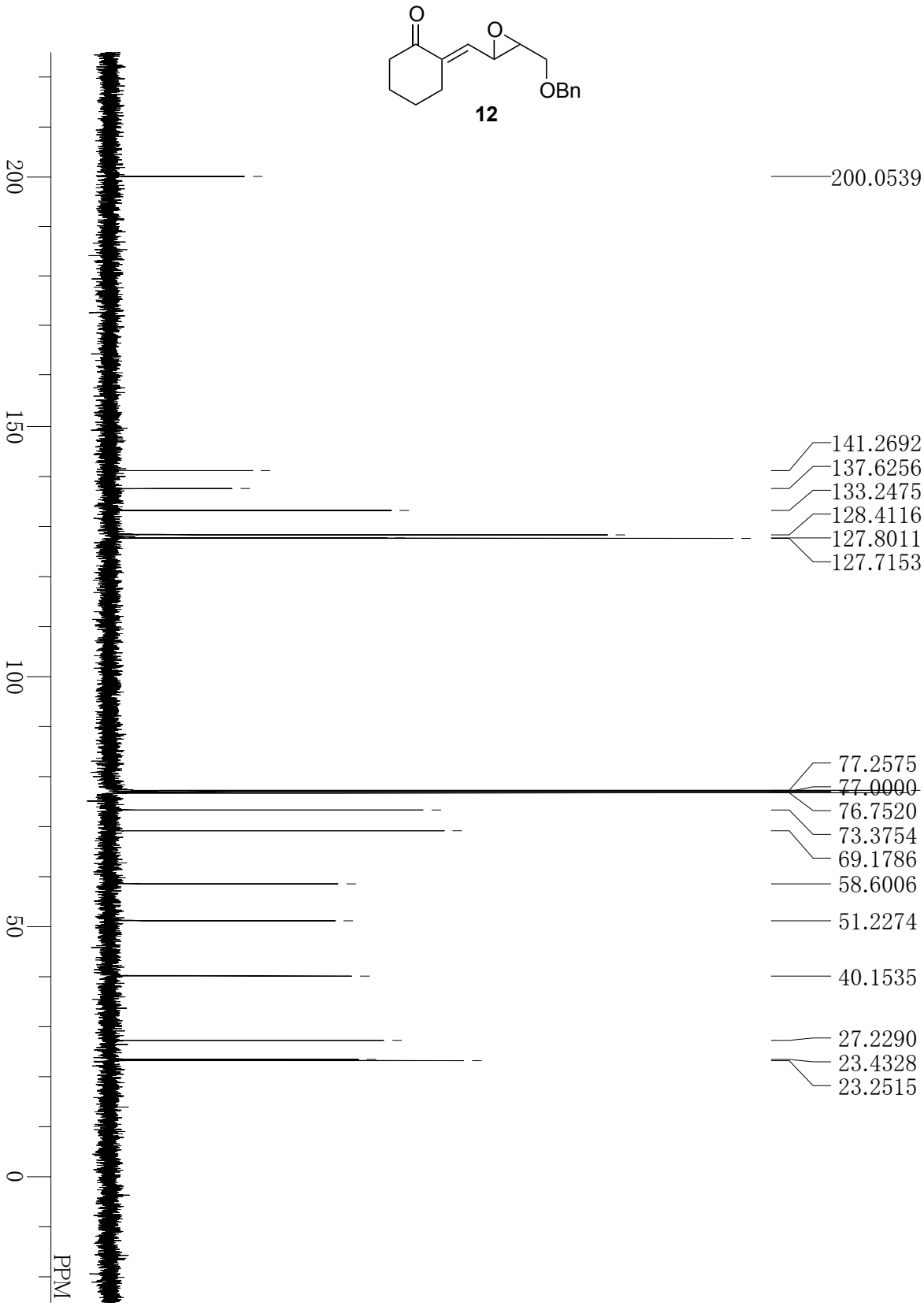


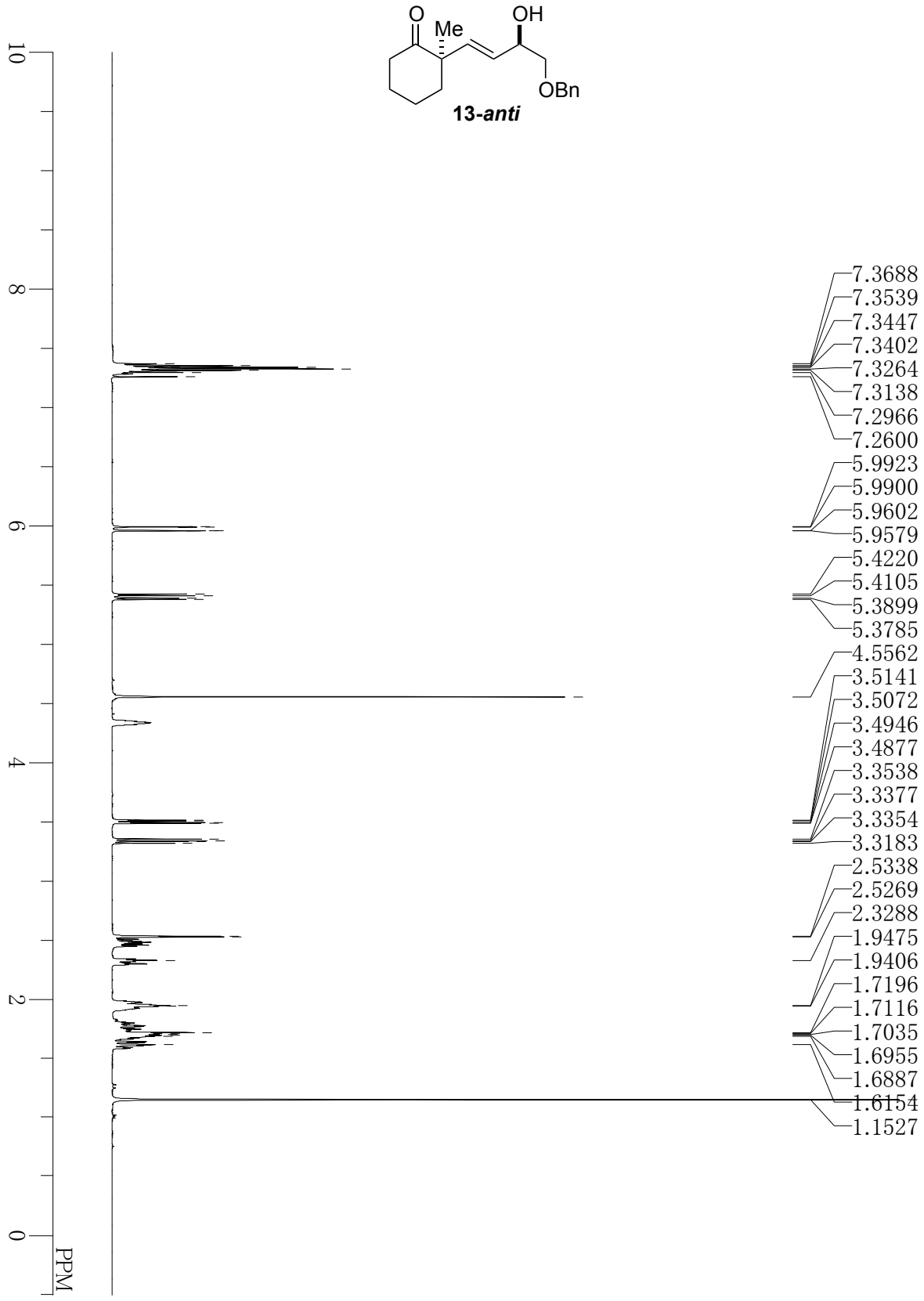
Figure S1. The key NOE for the determination of the configuration of **16a**

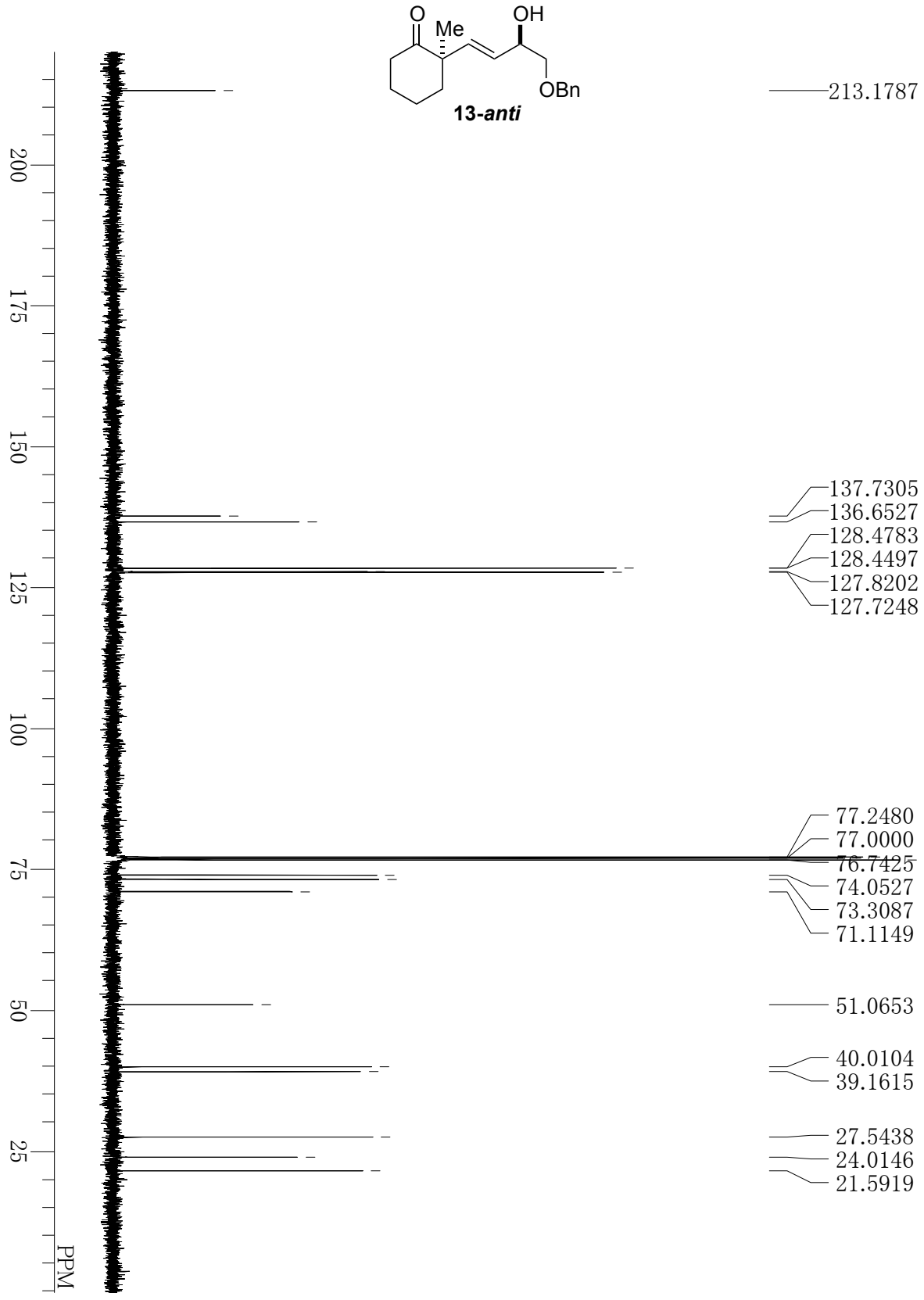
Scheme S1. Determinations of the stereochemistries of **17a-*anti*** and **17a-*syn***

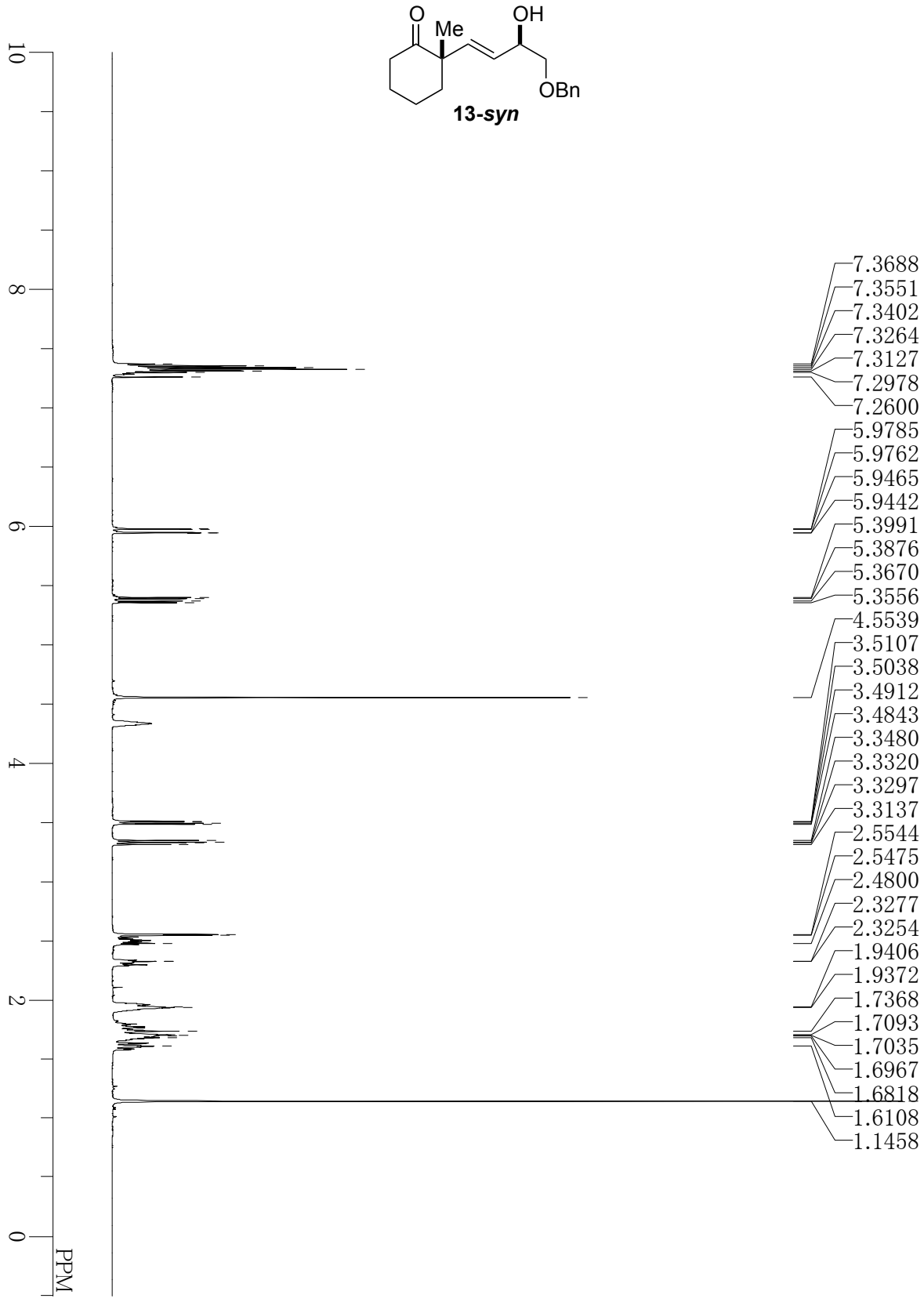


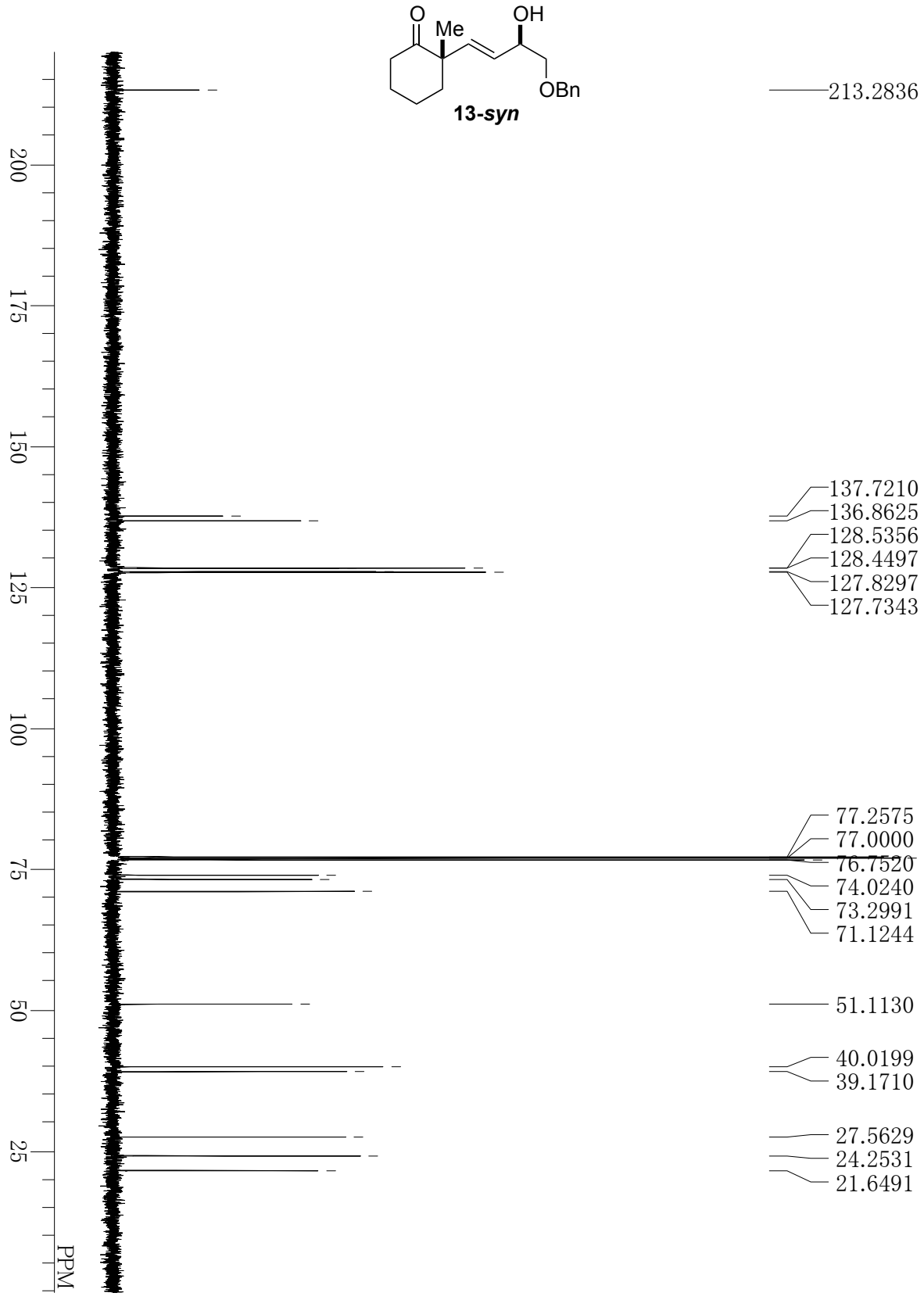


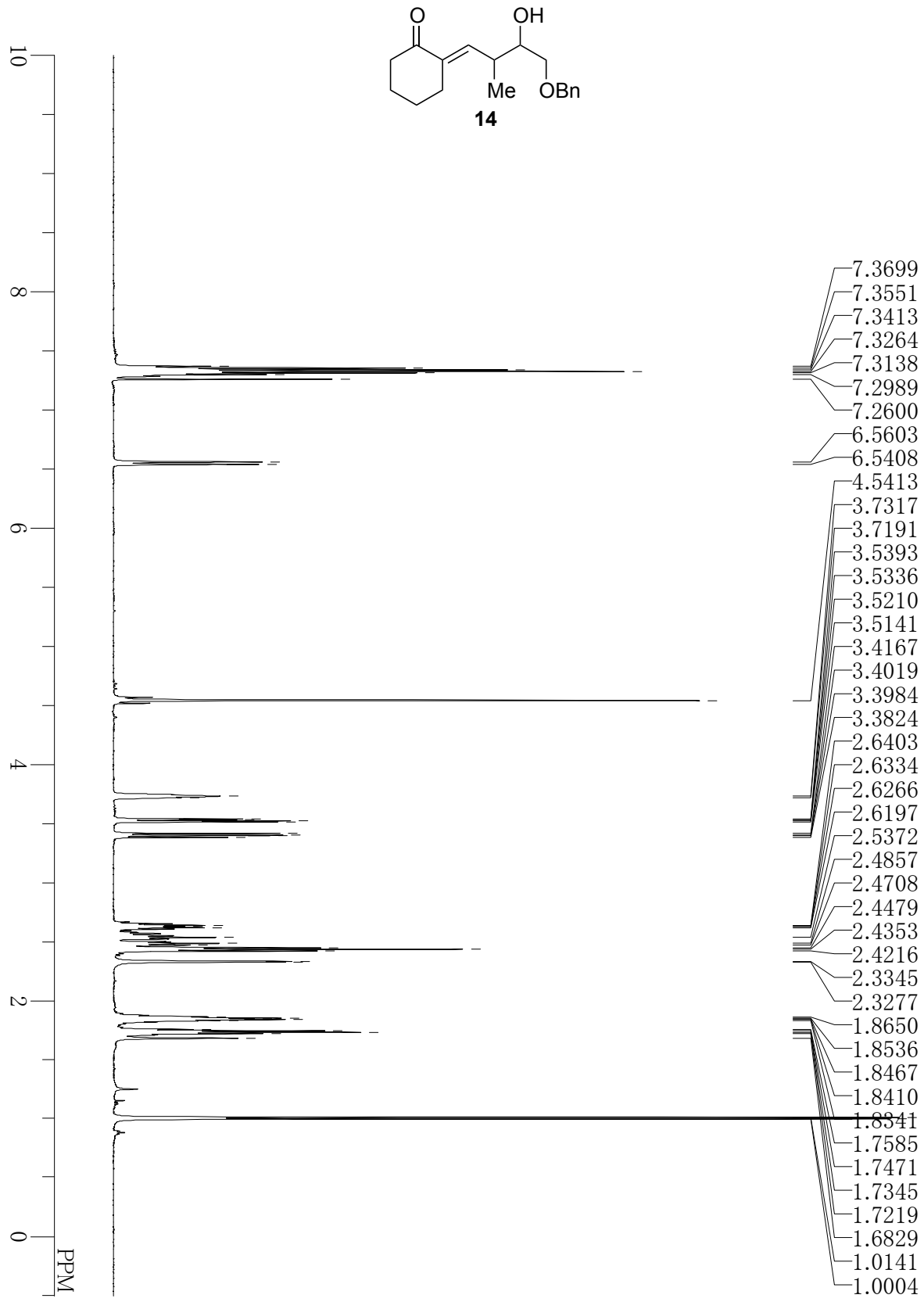


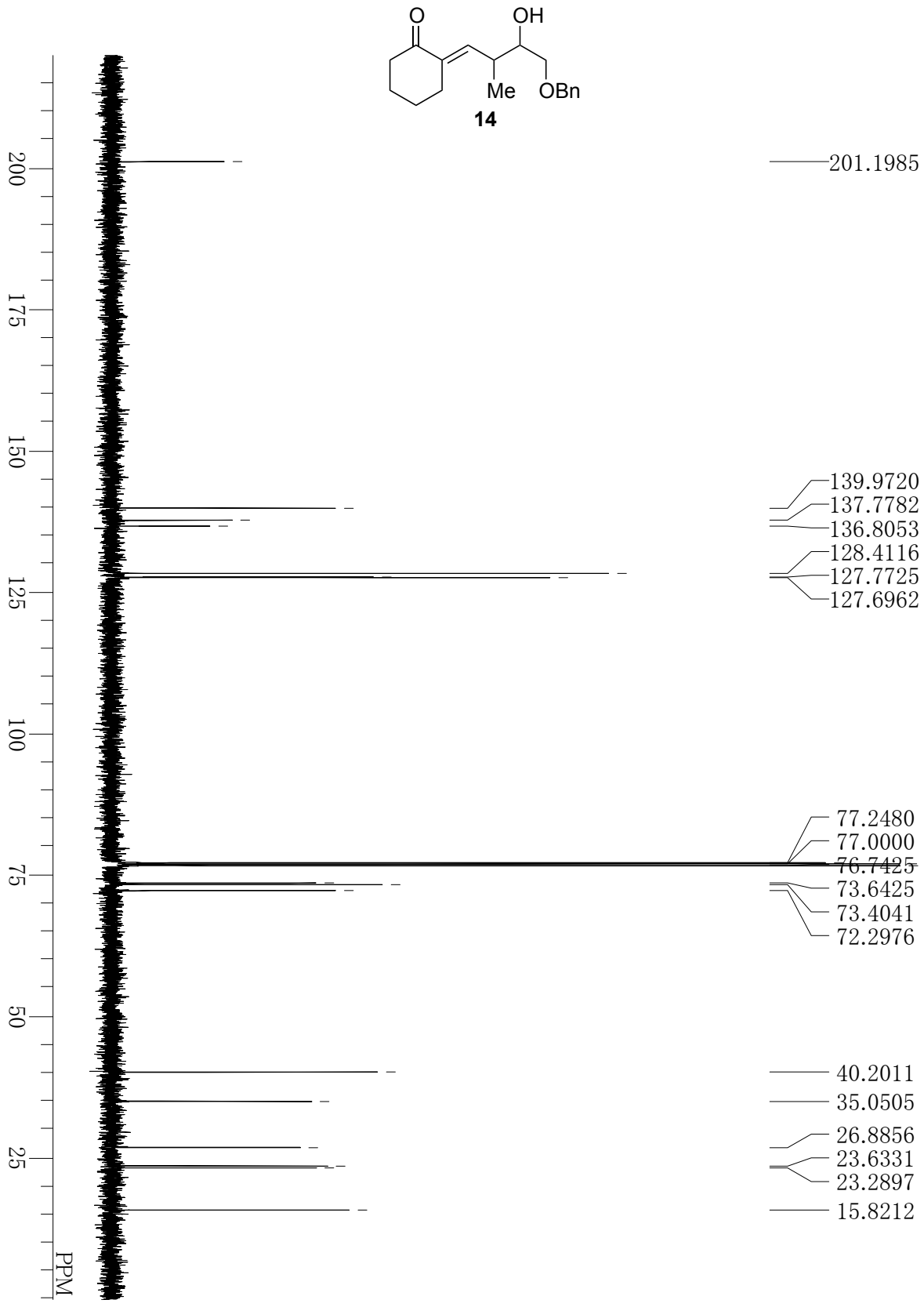


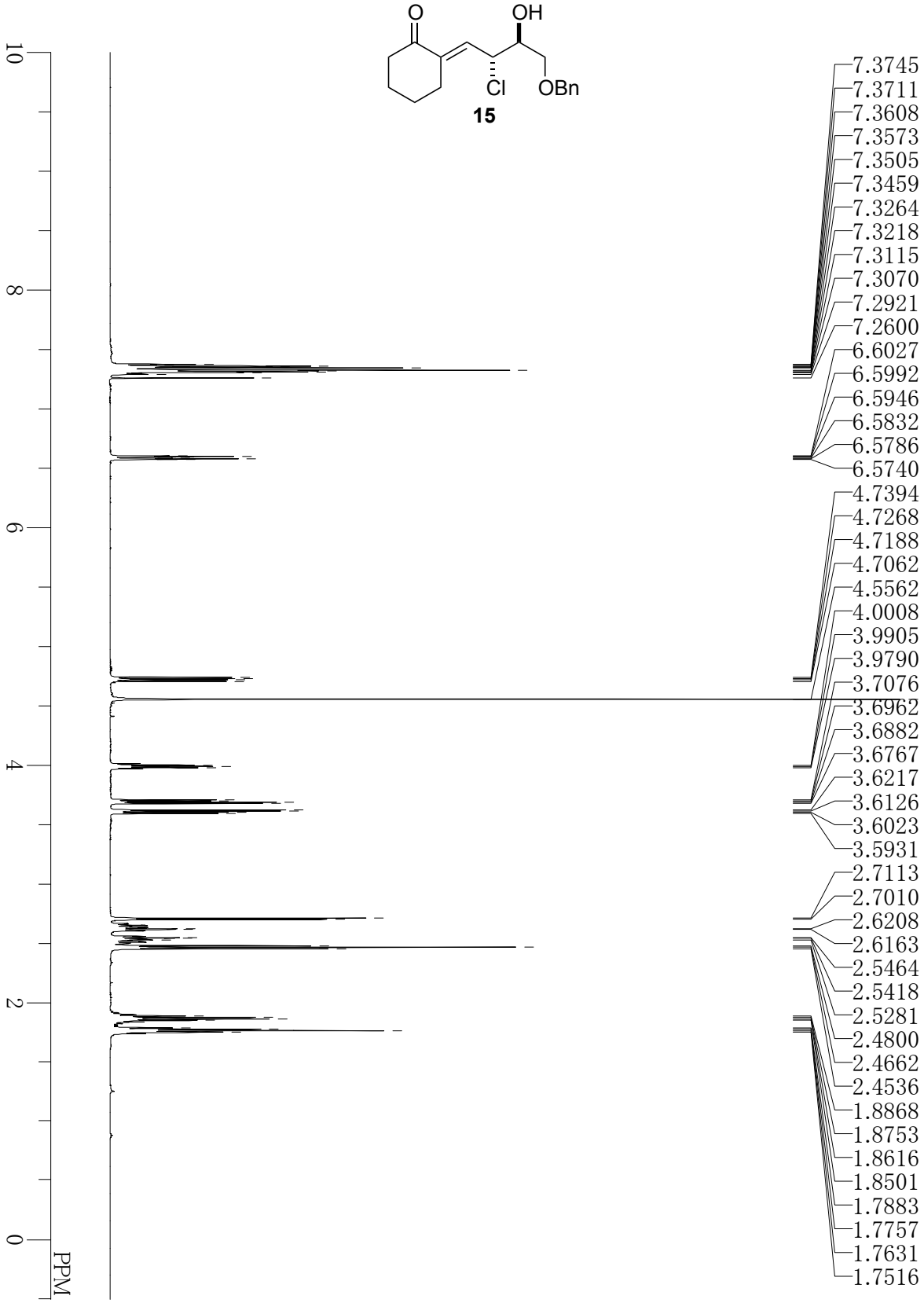


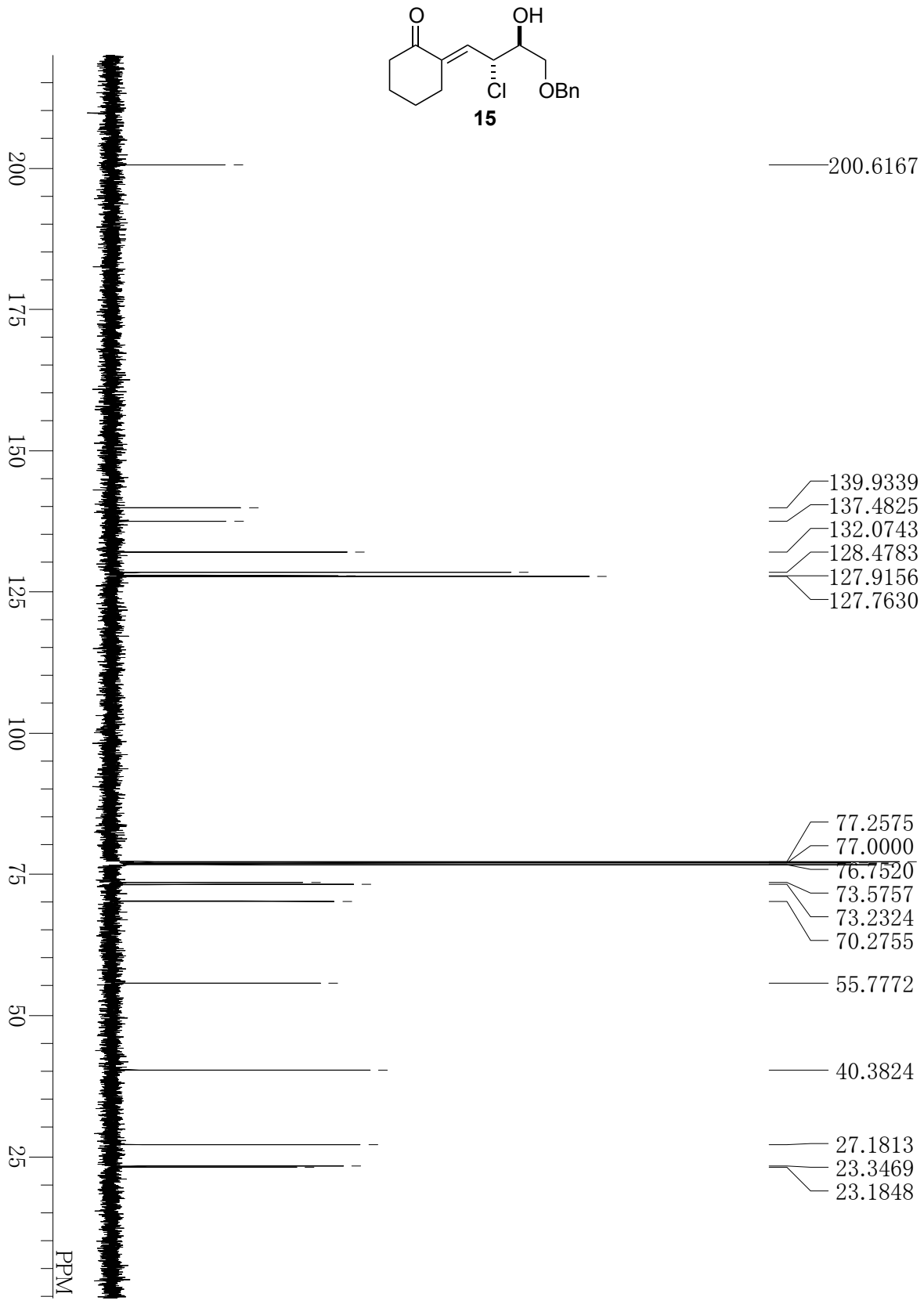


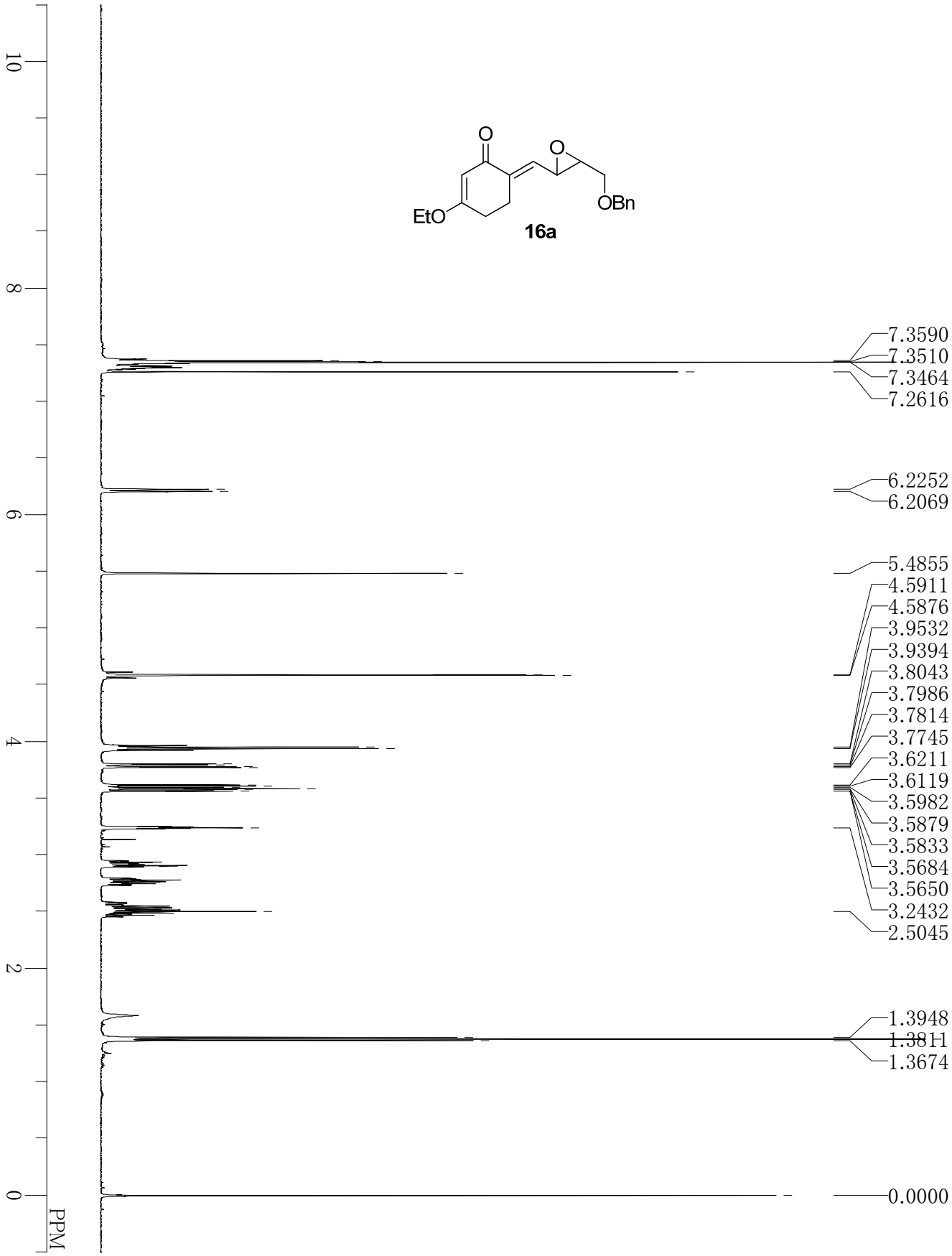


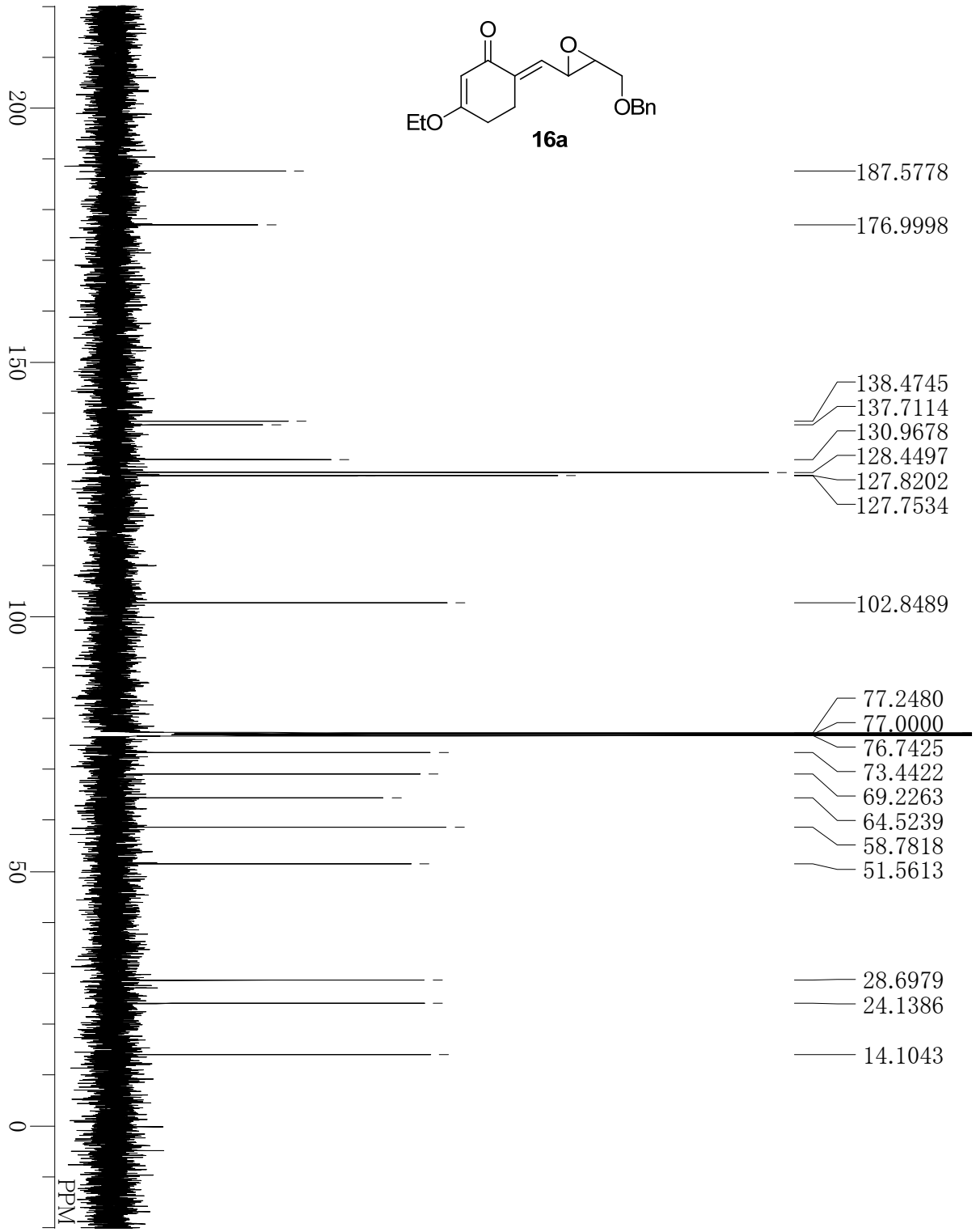


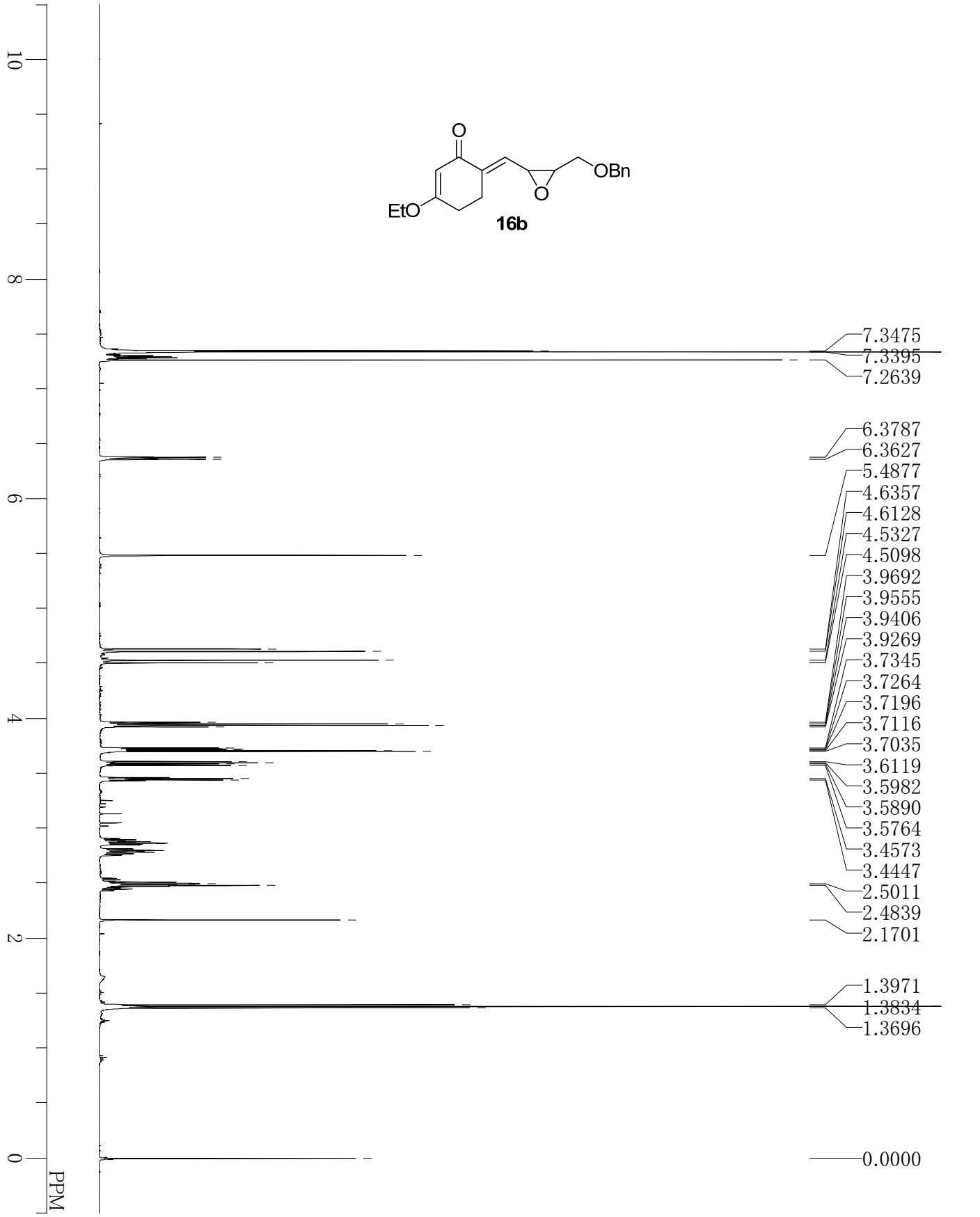


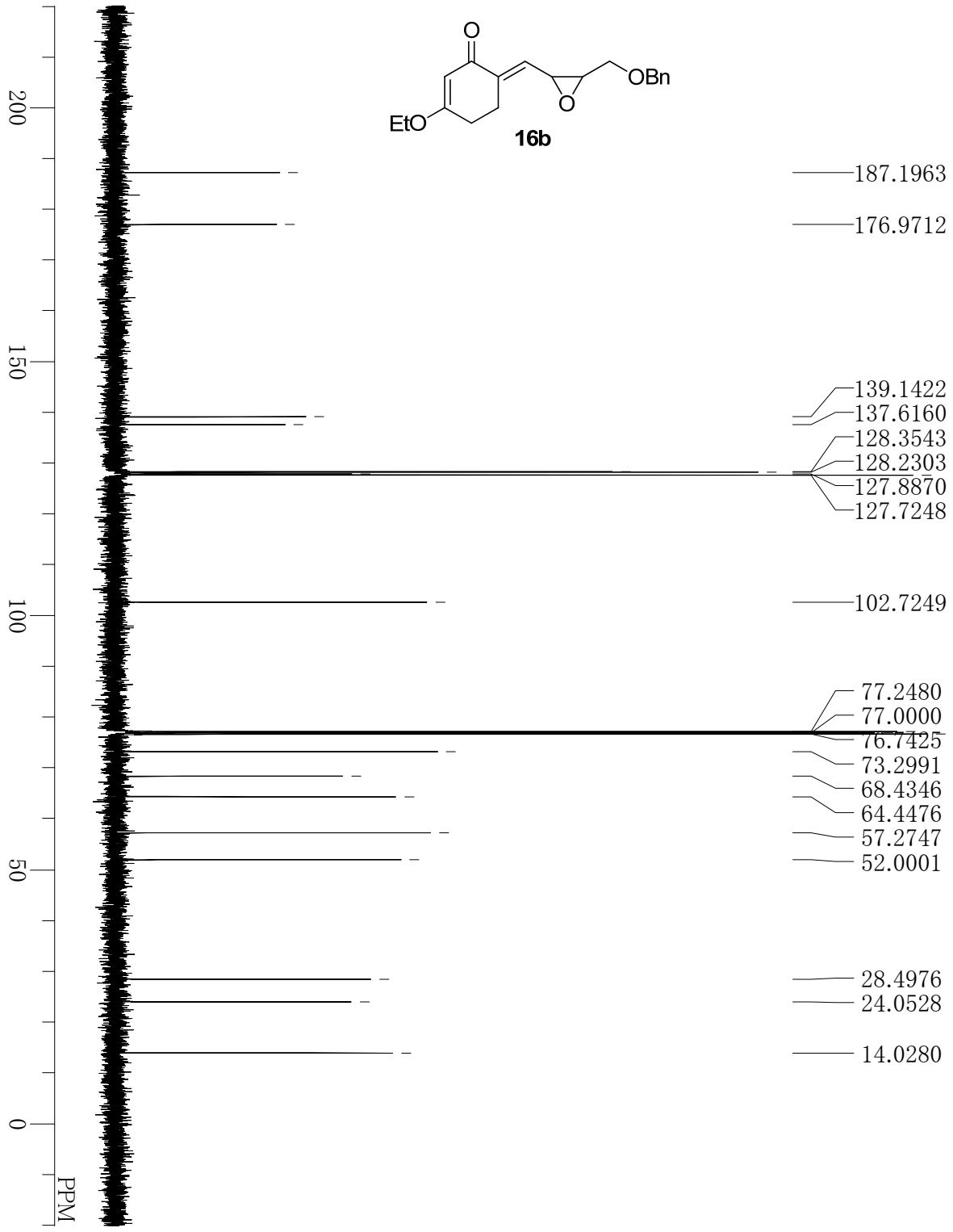


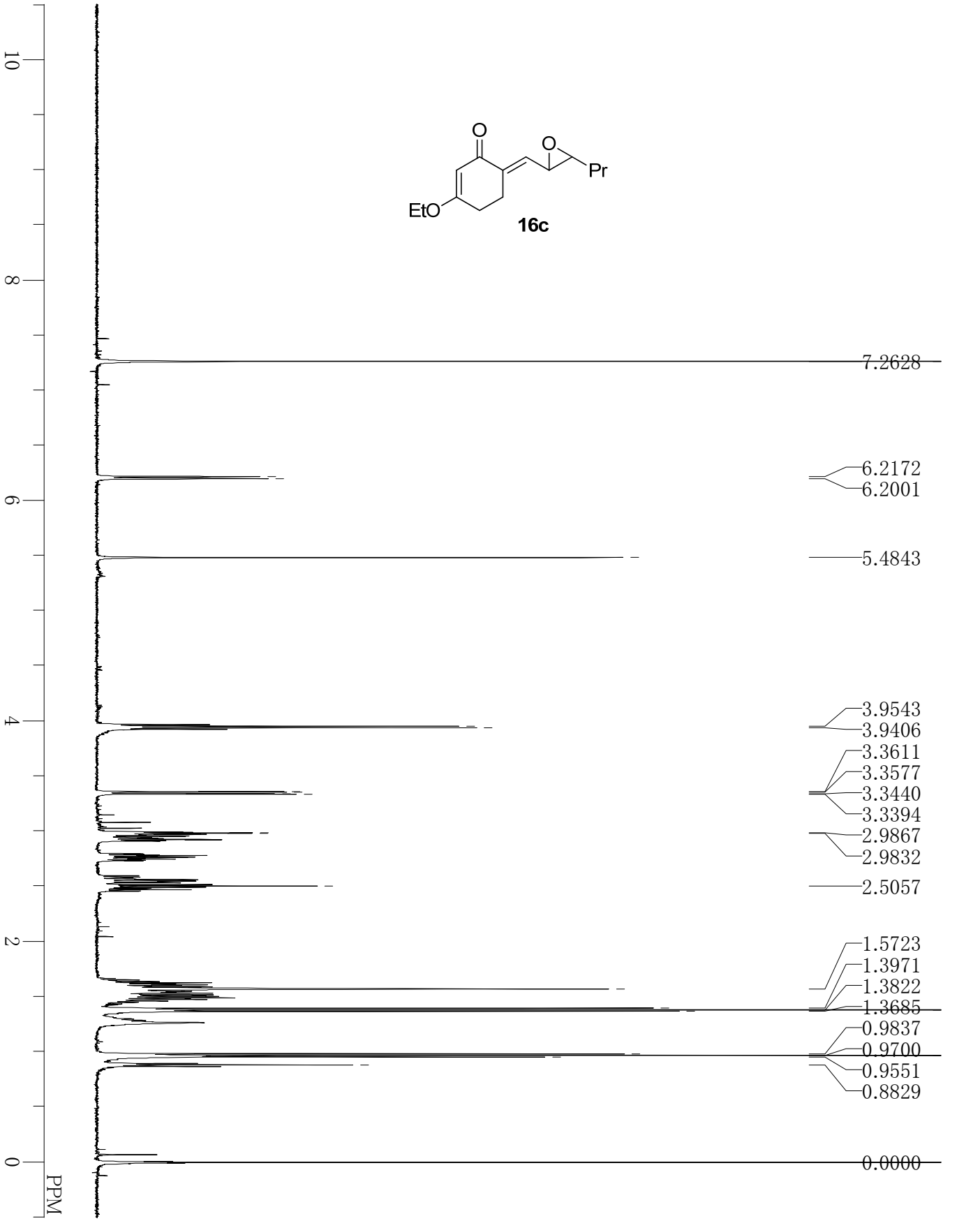


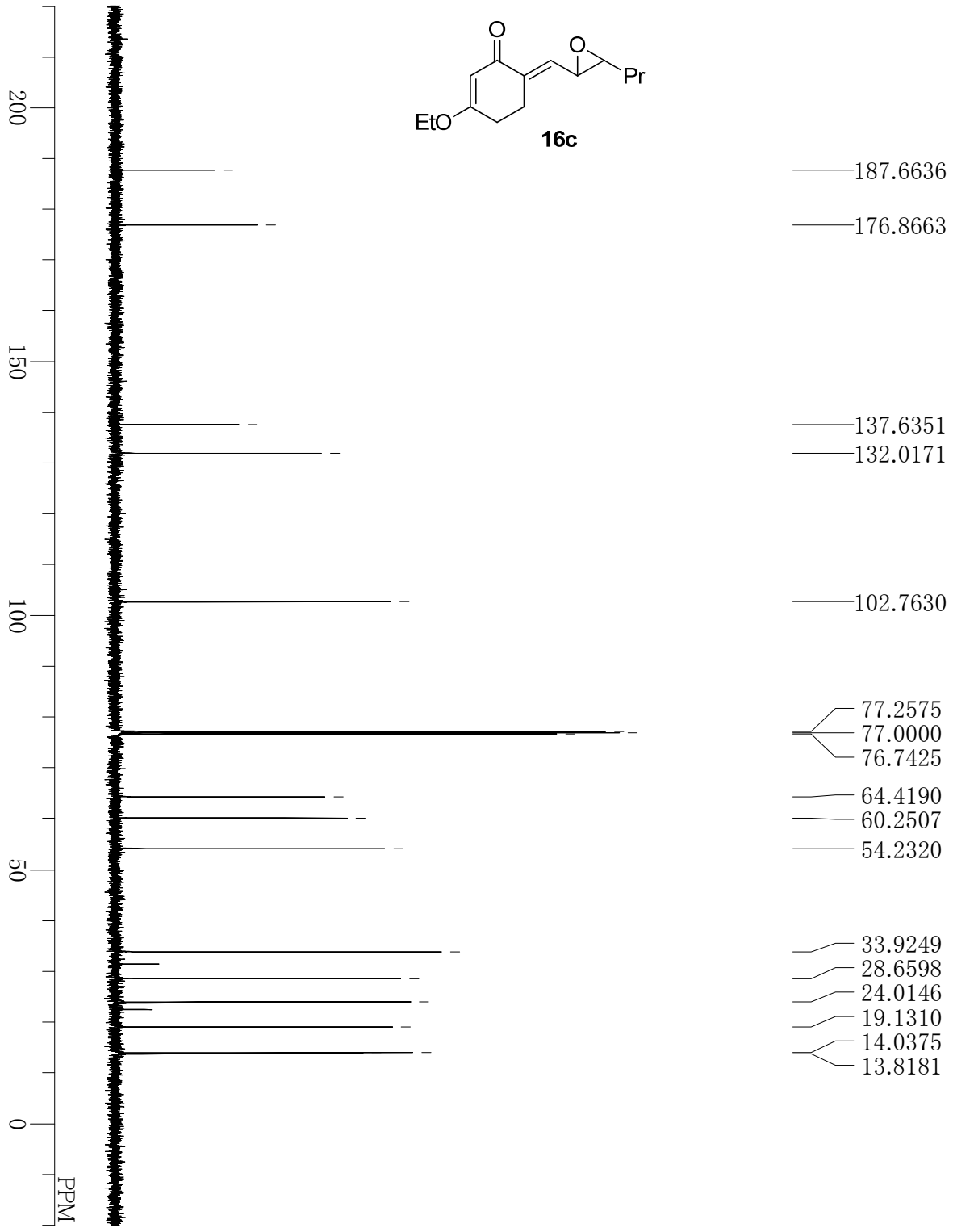


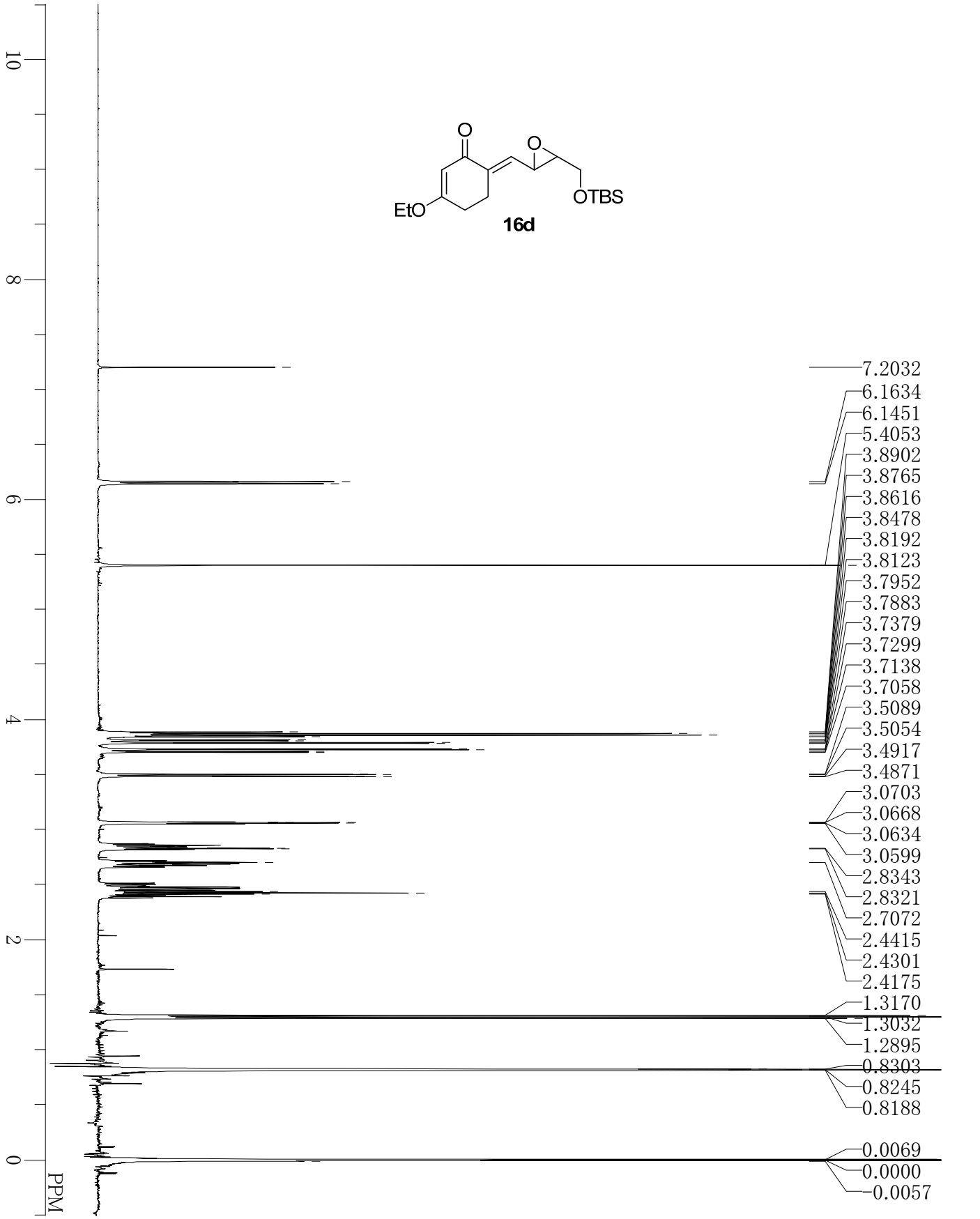


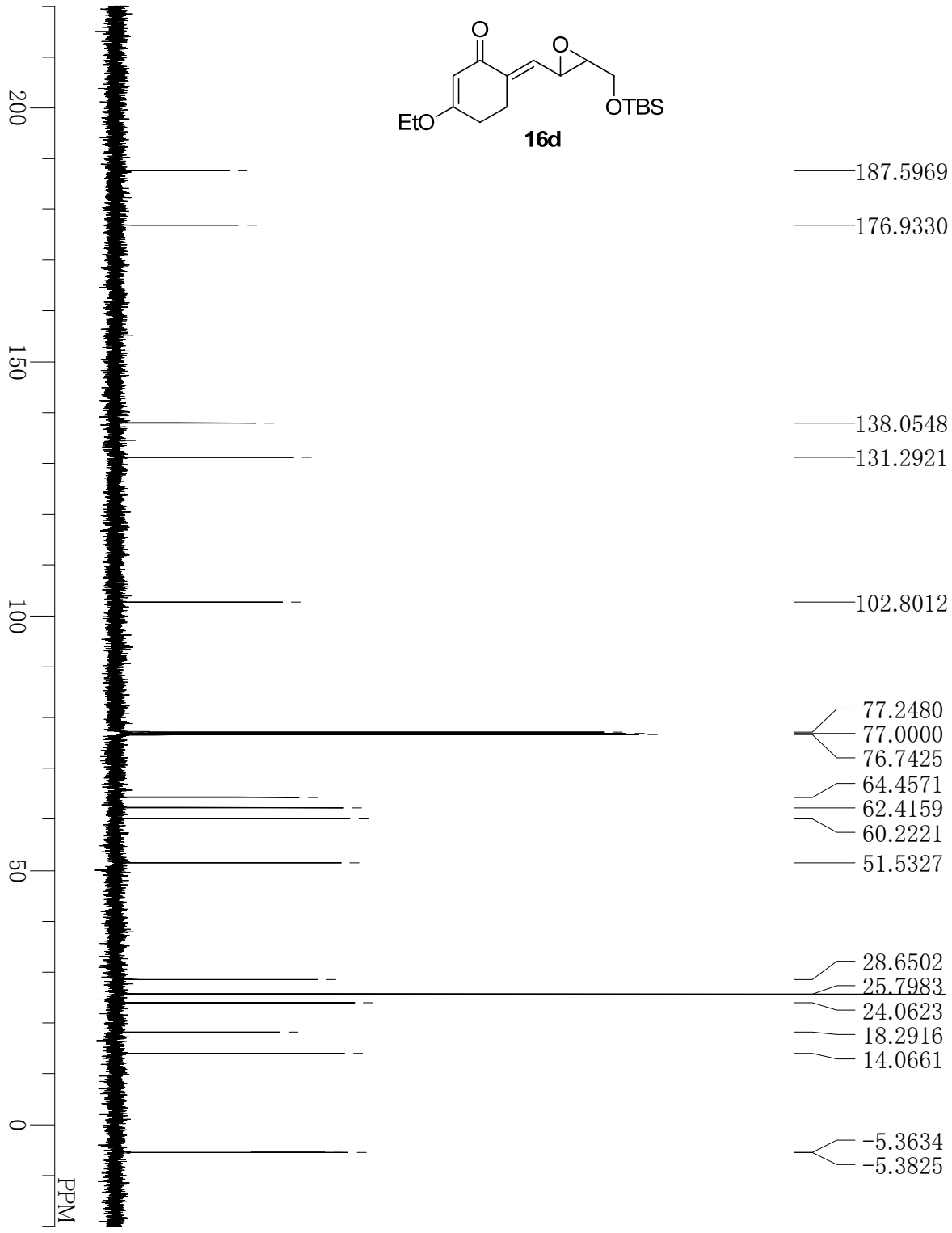


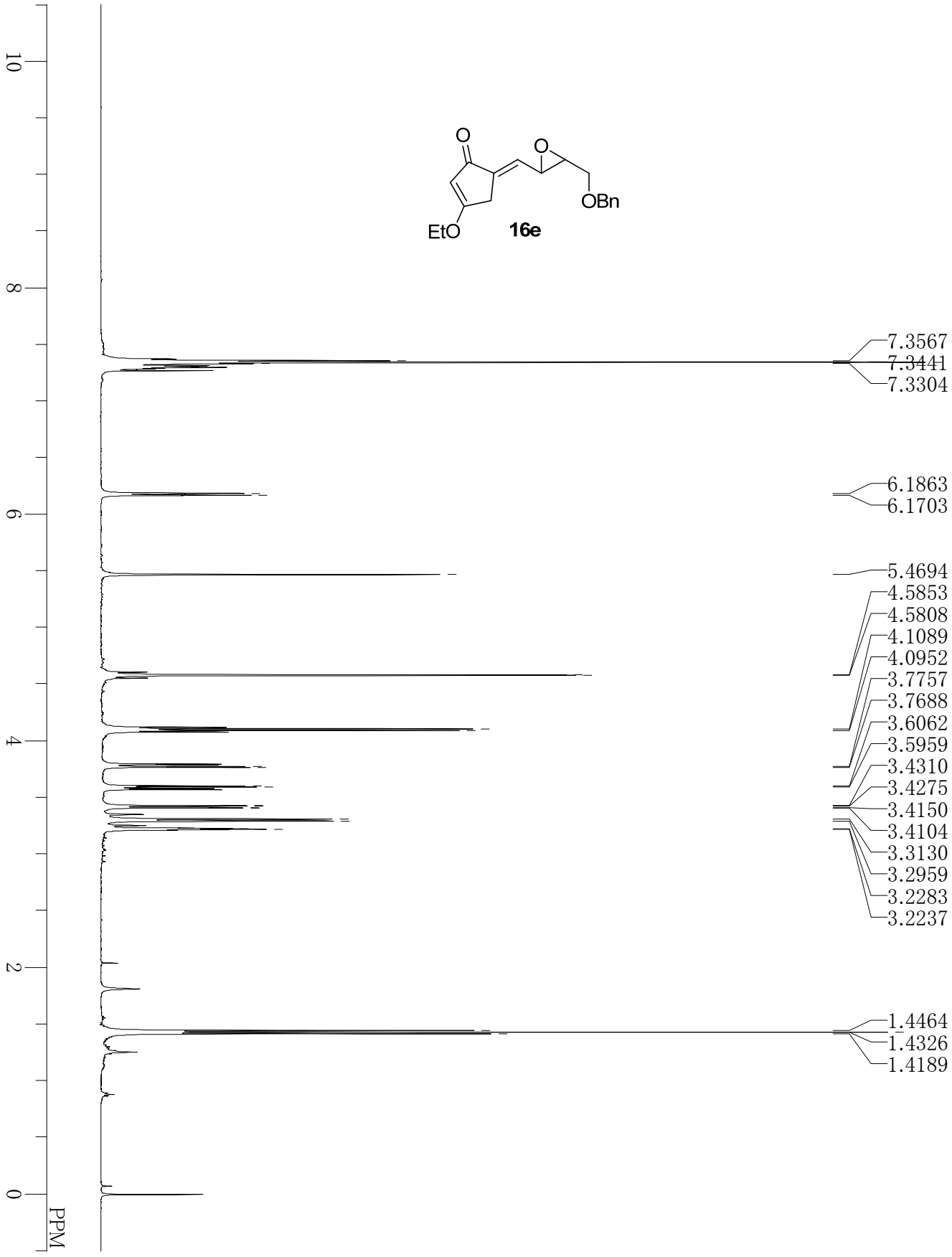


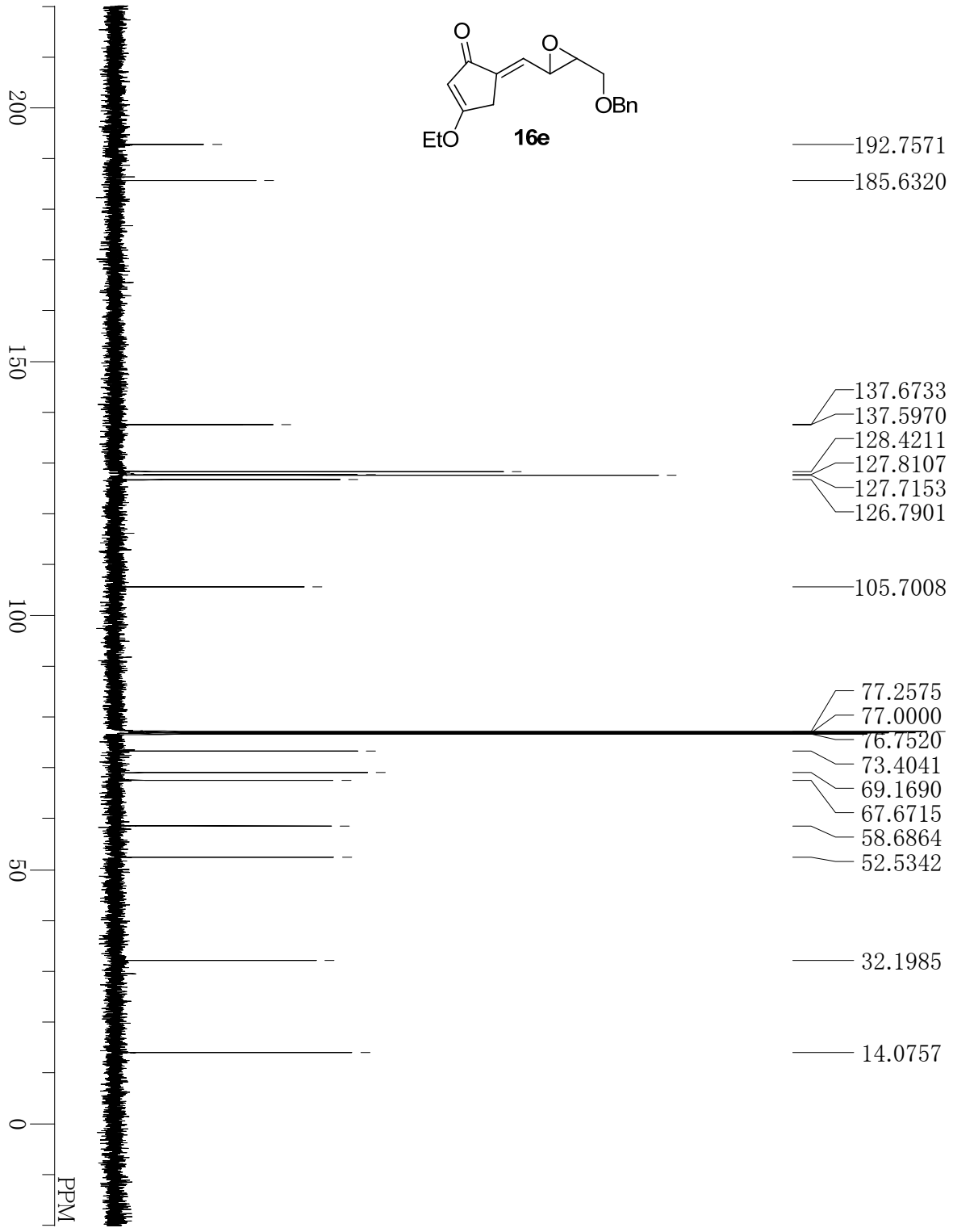


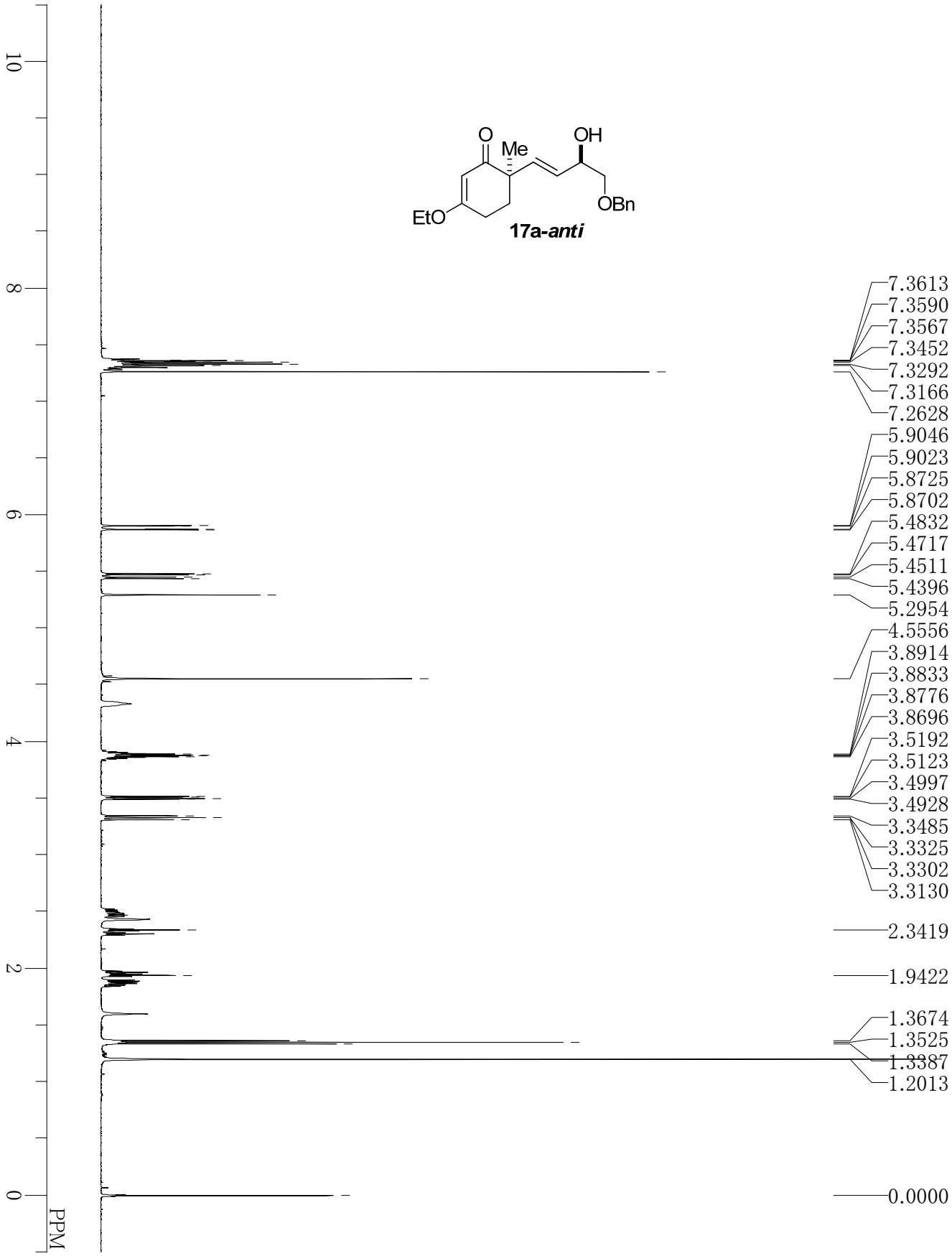


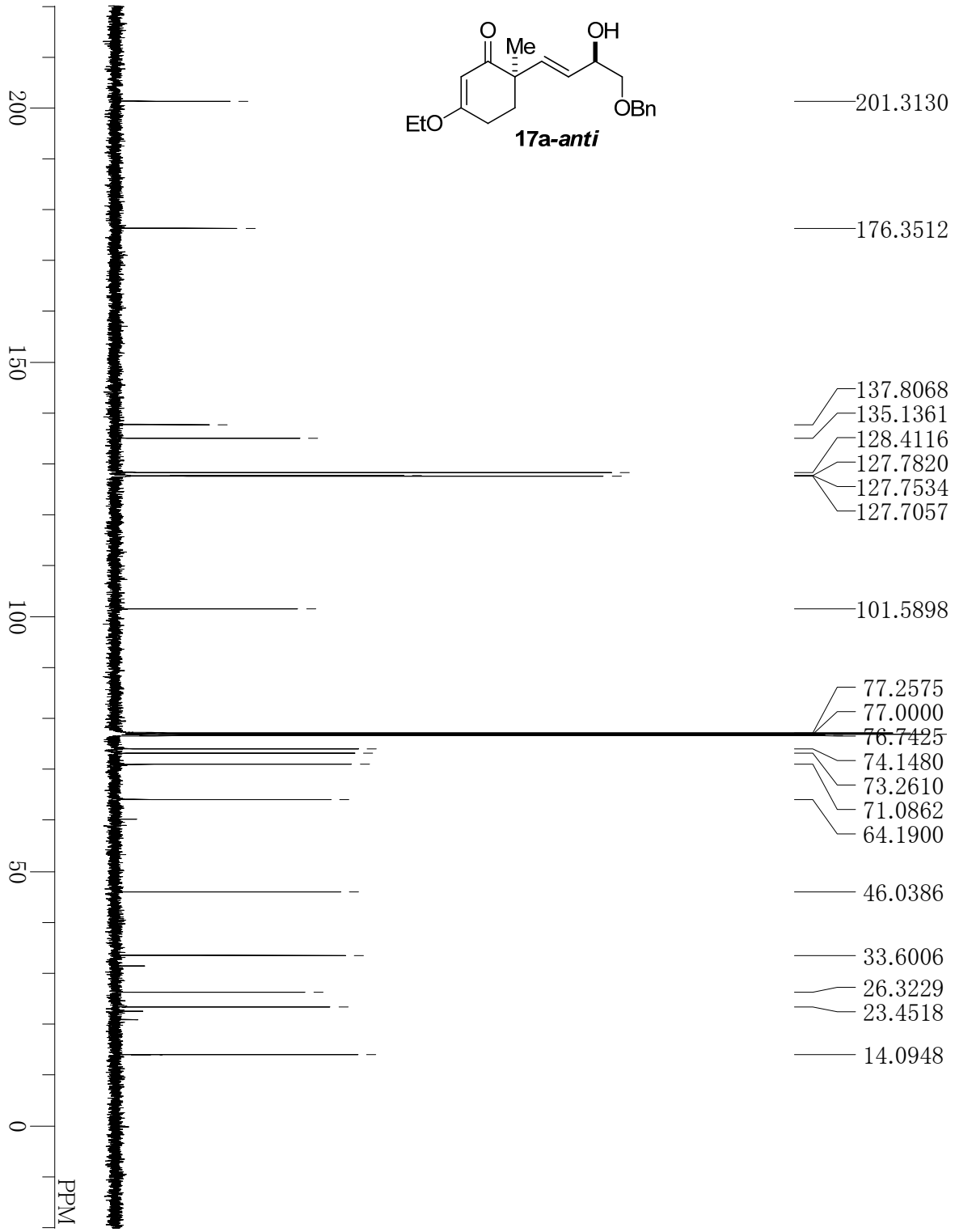


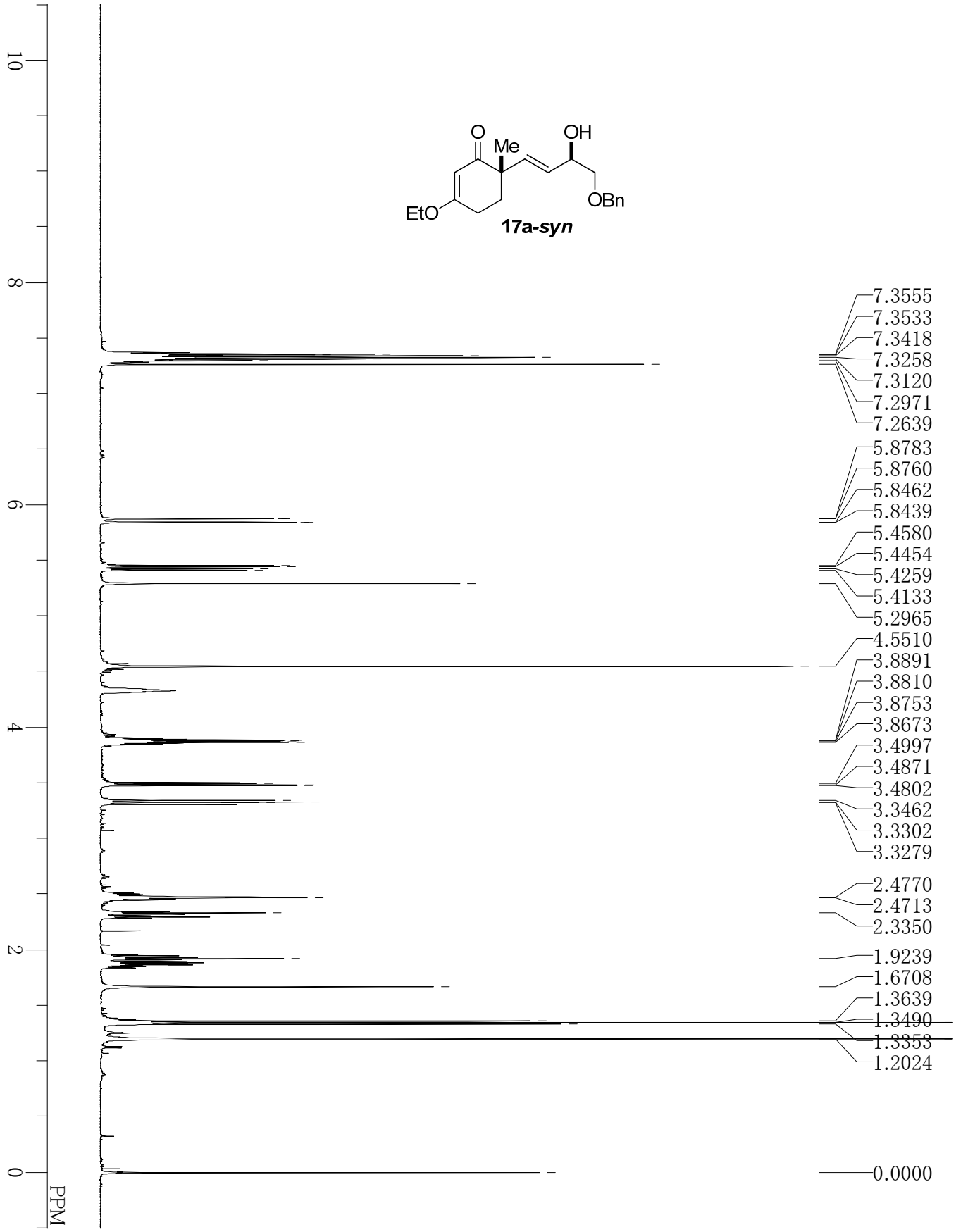


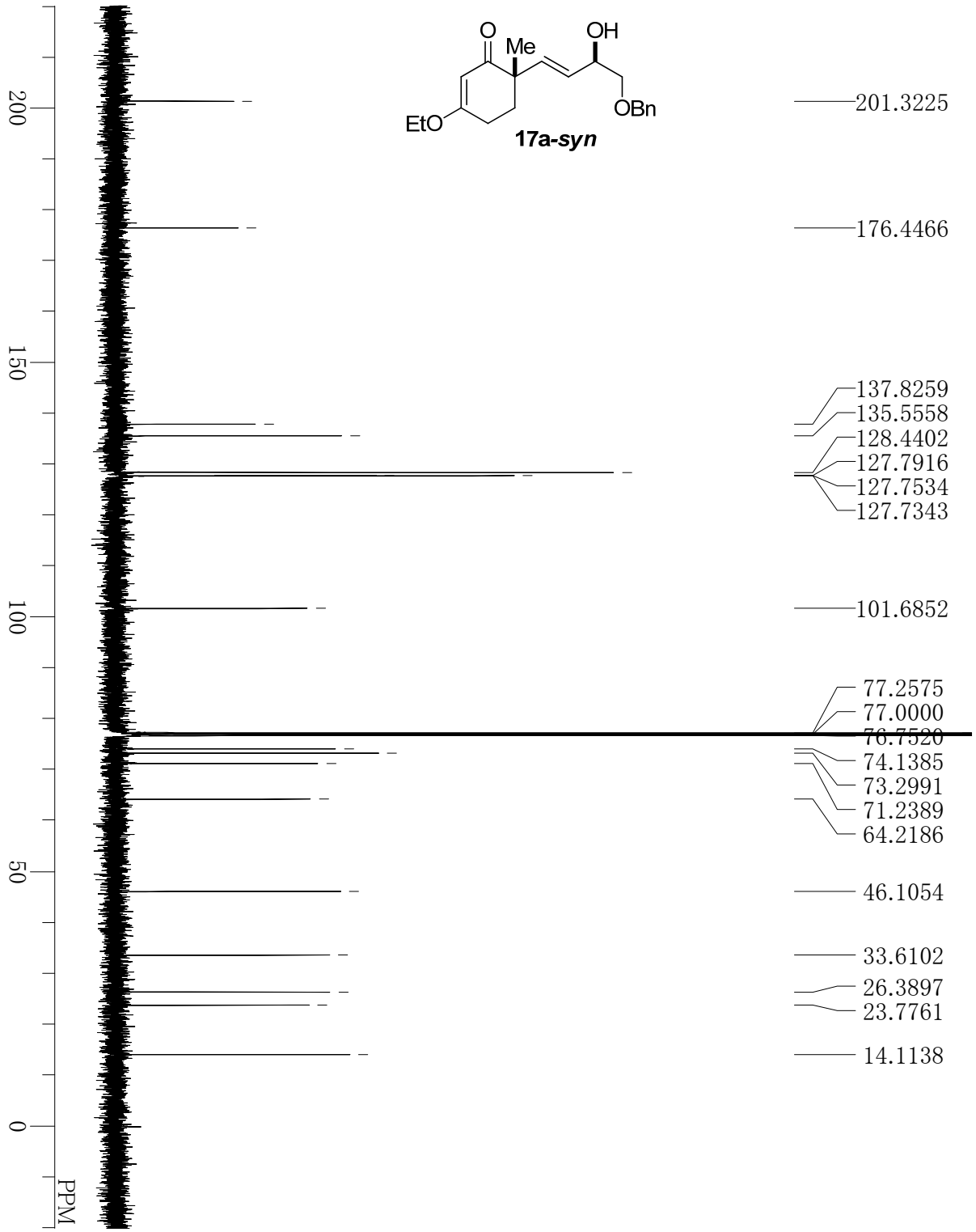


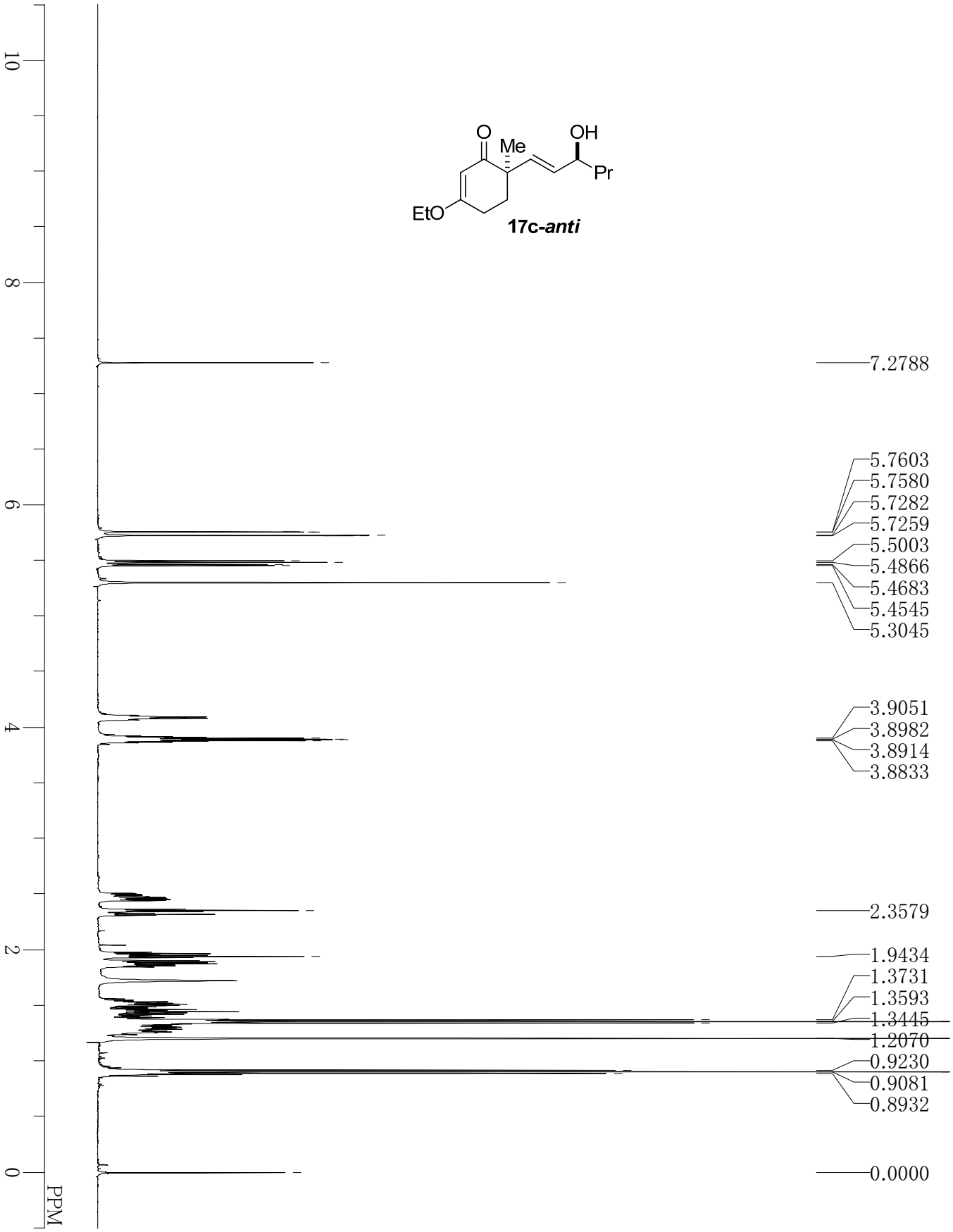


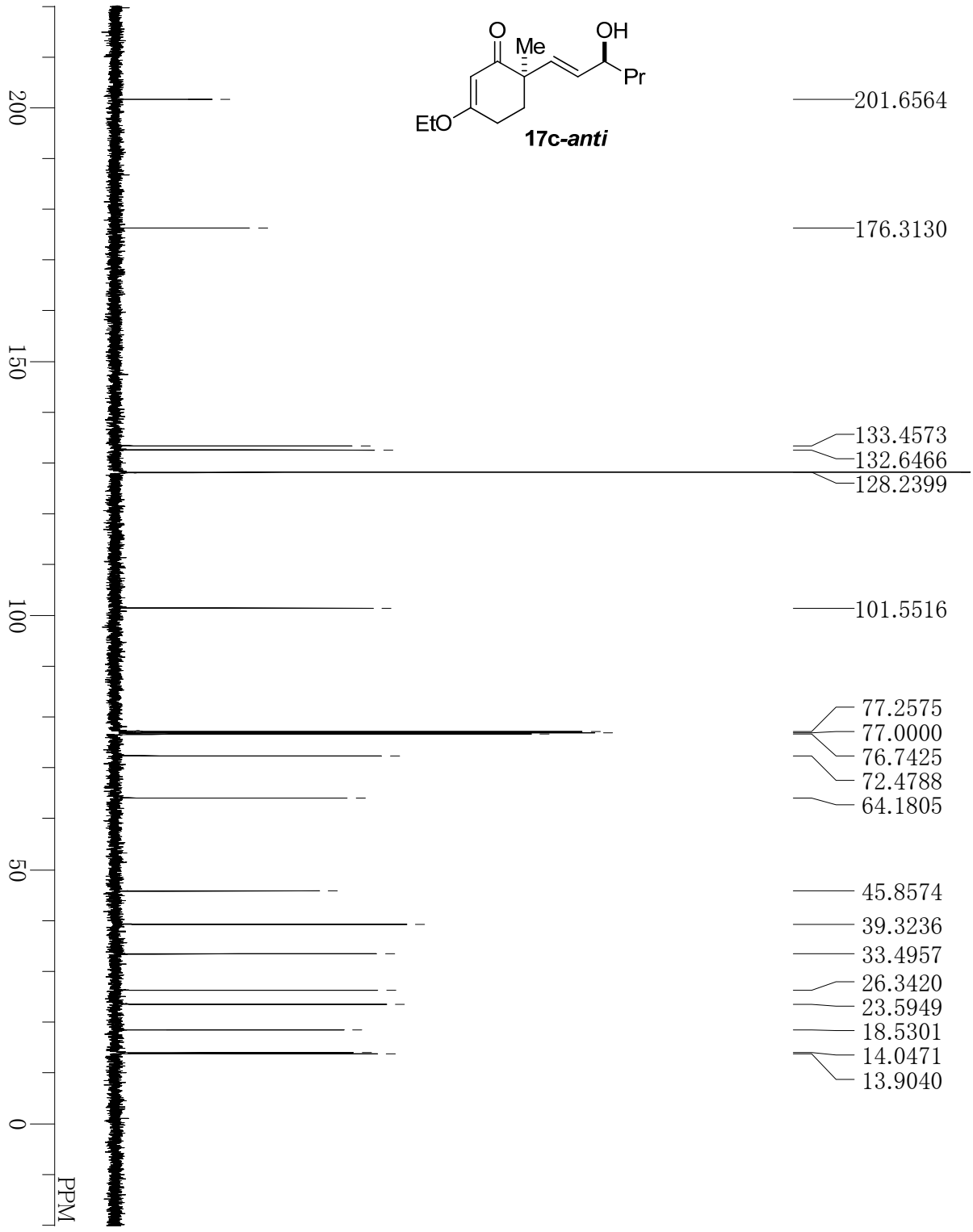


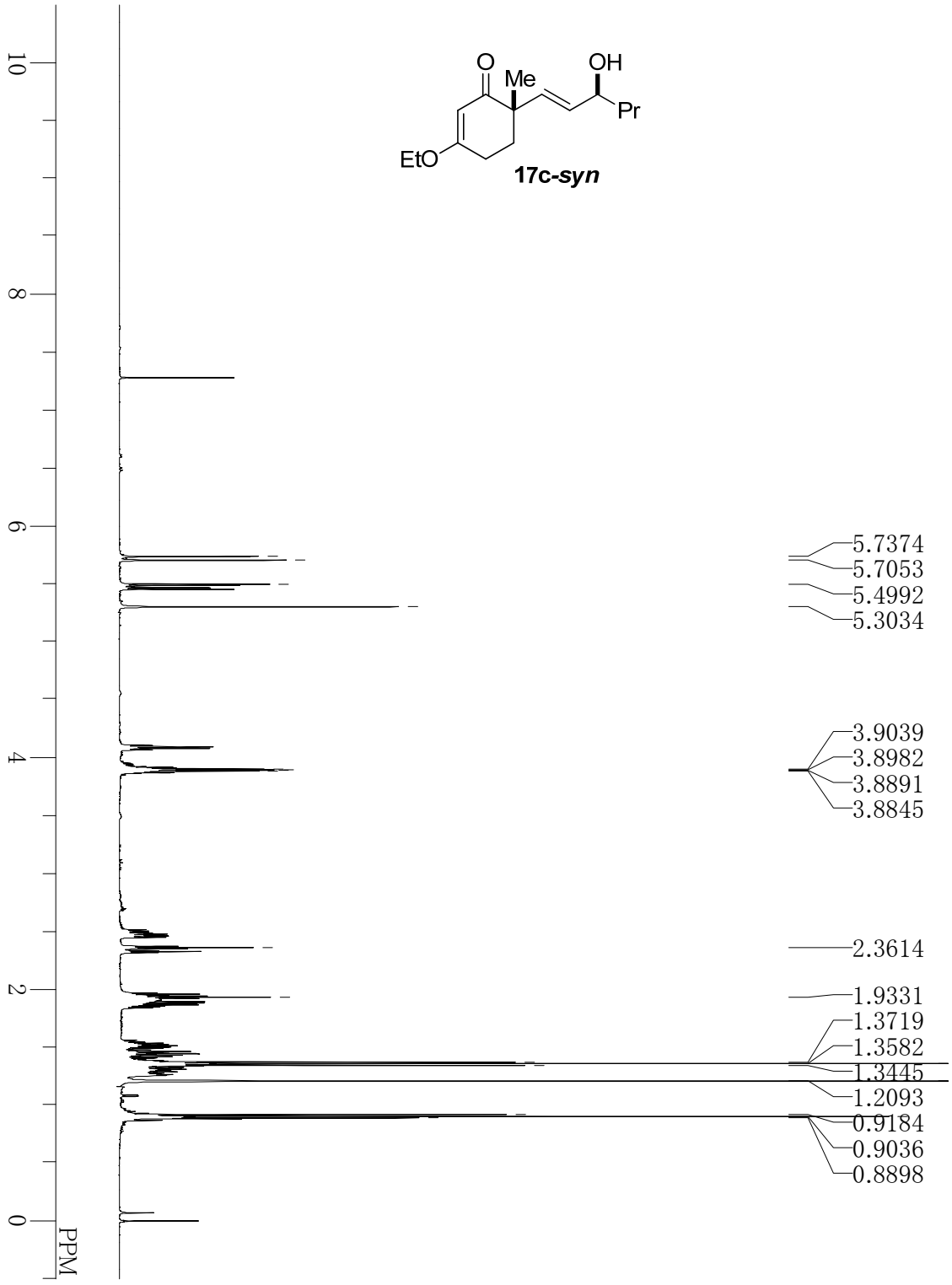


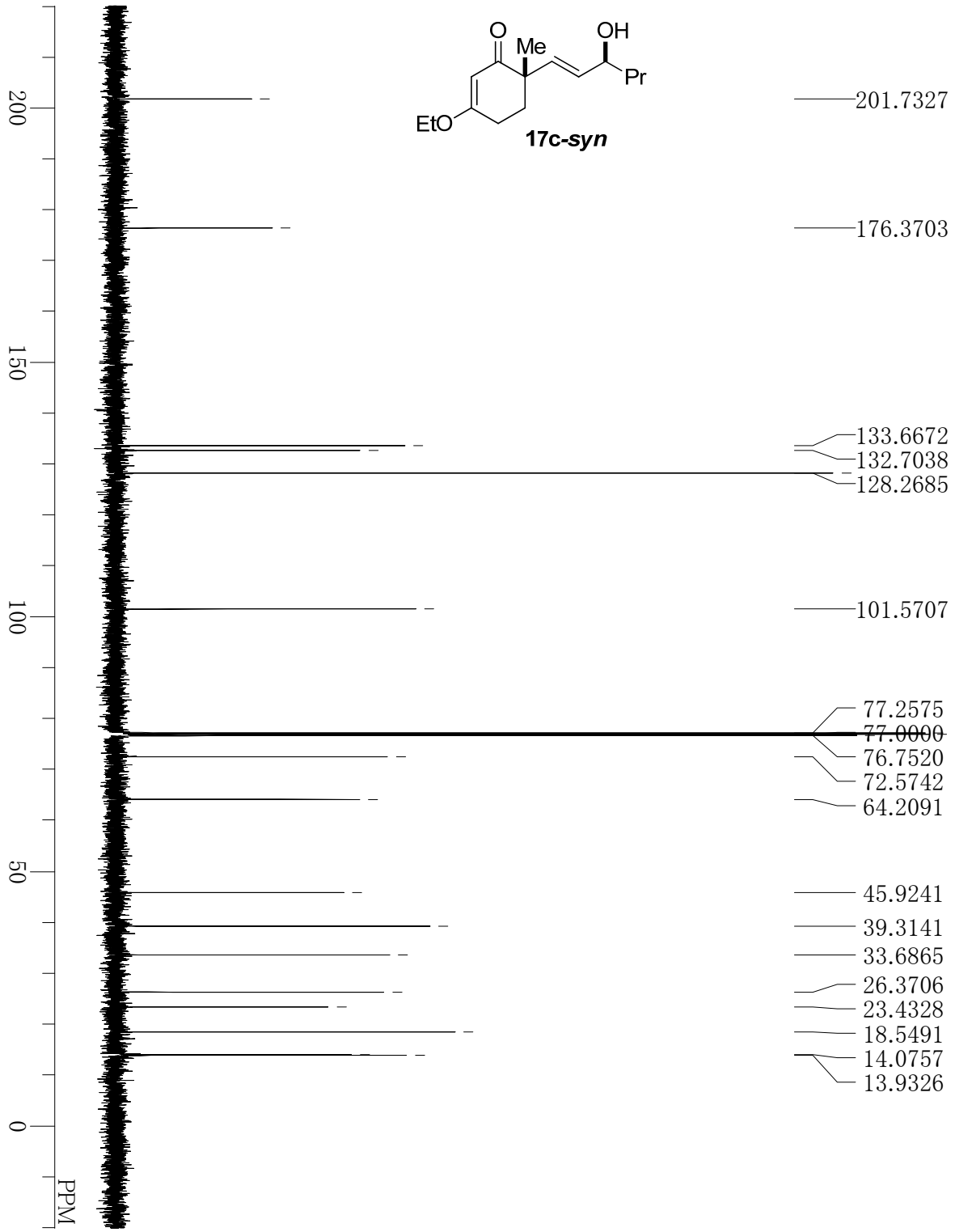


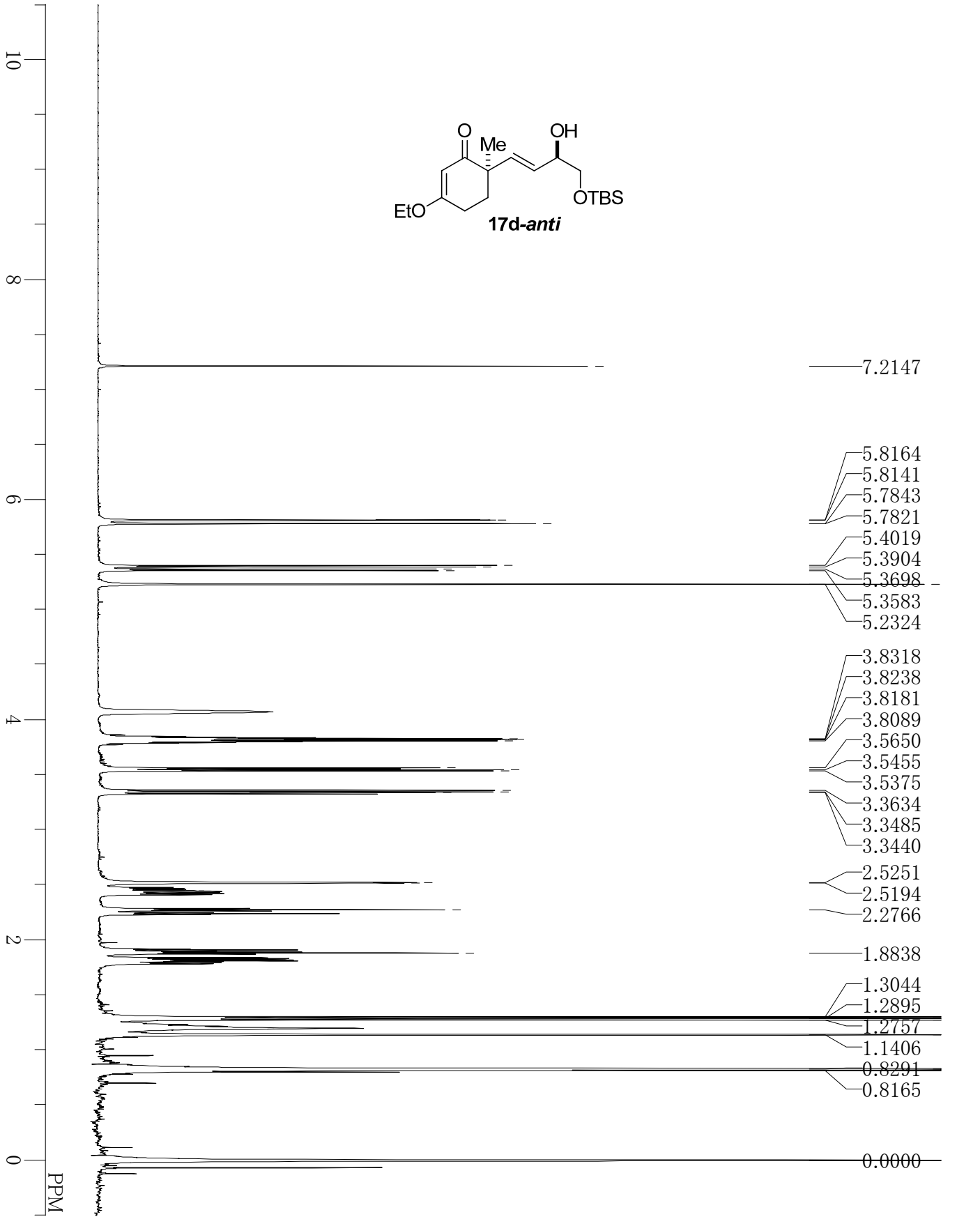


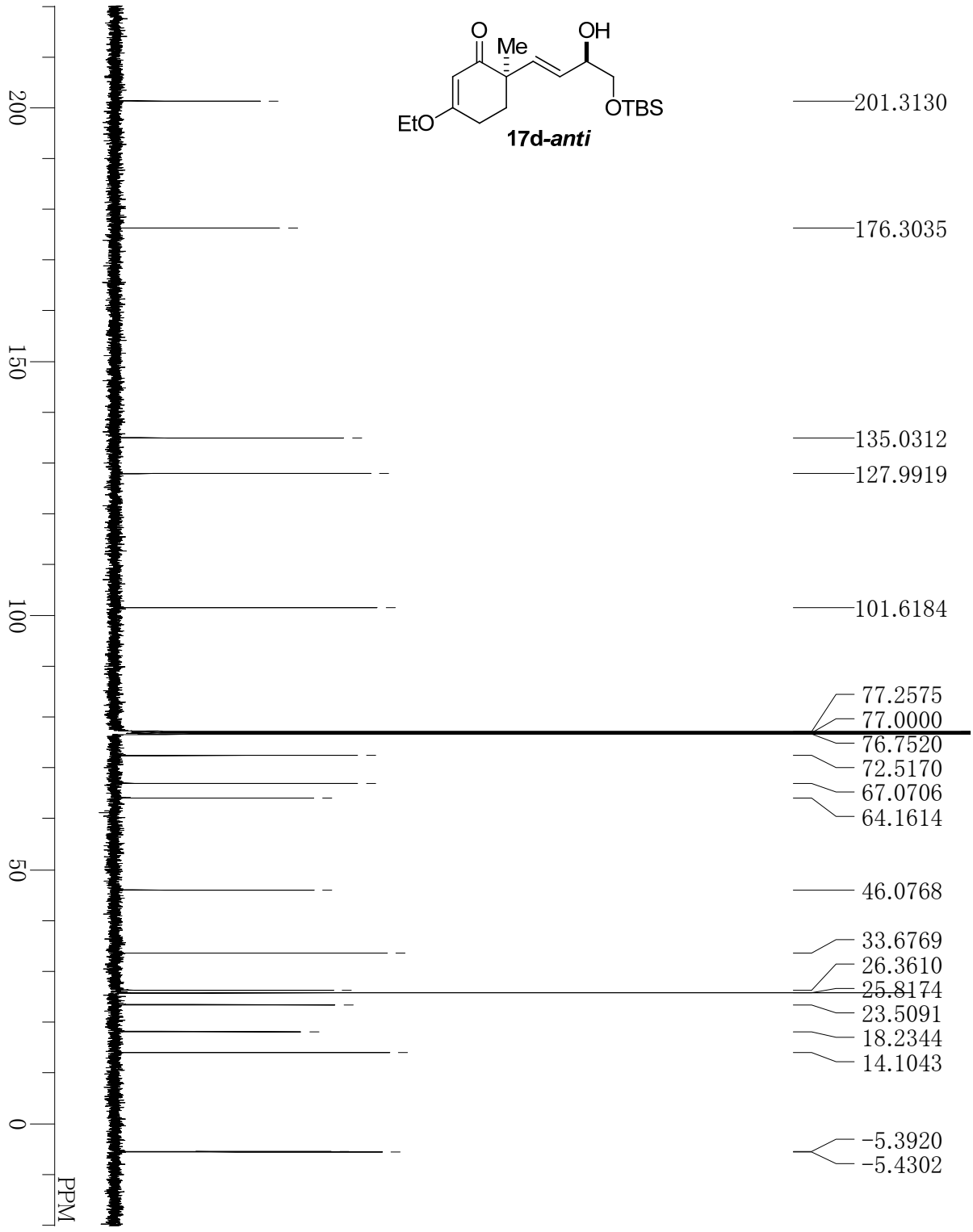


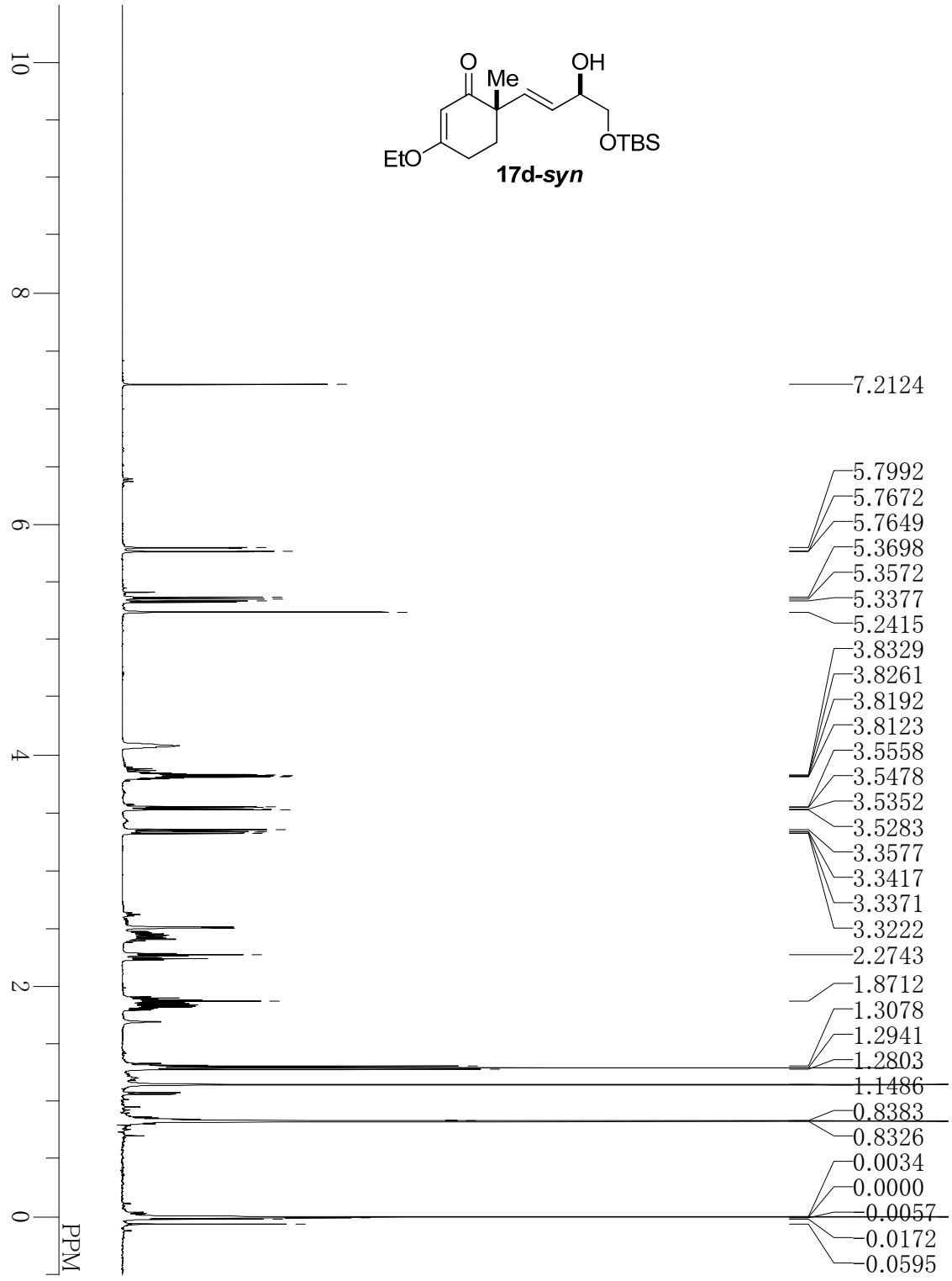


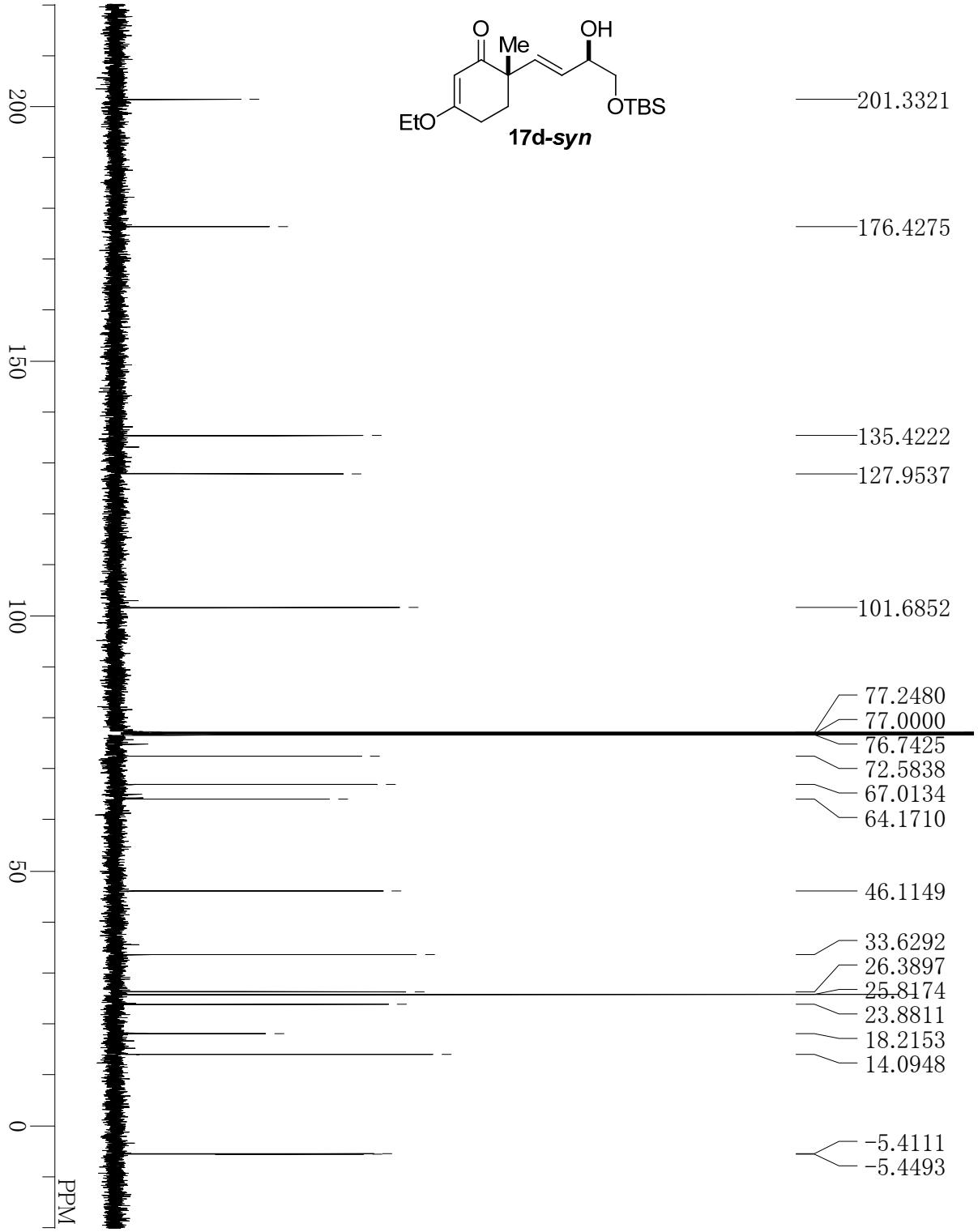


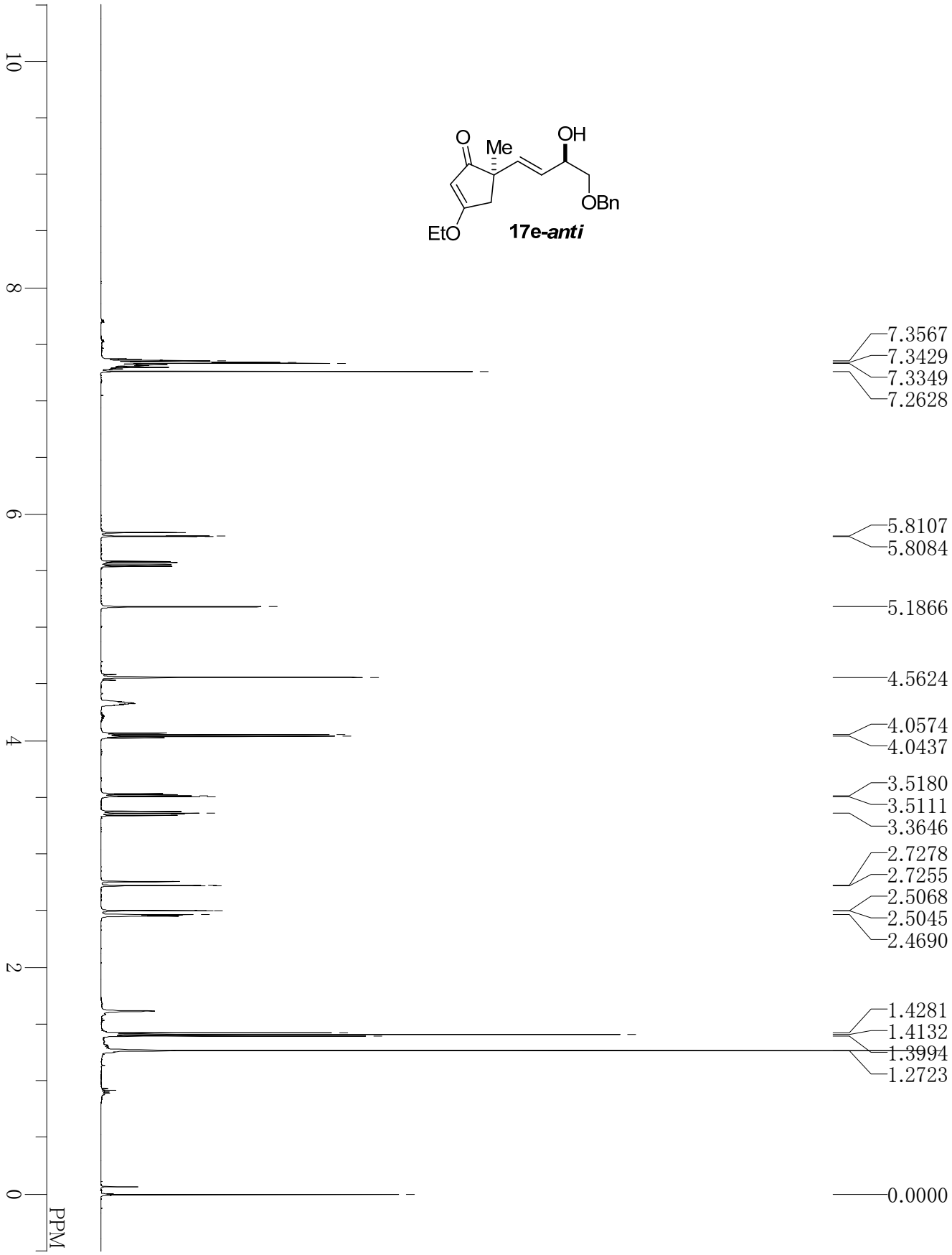


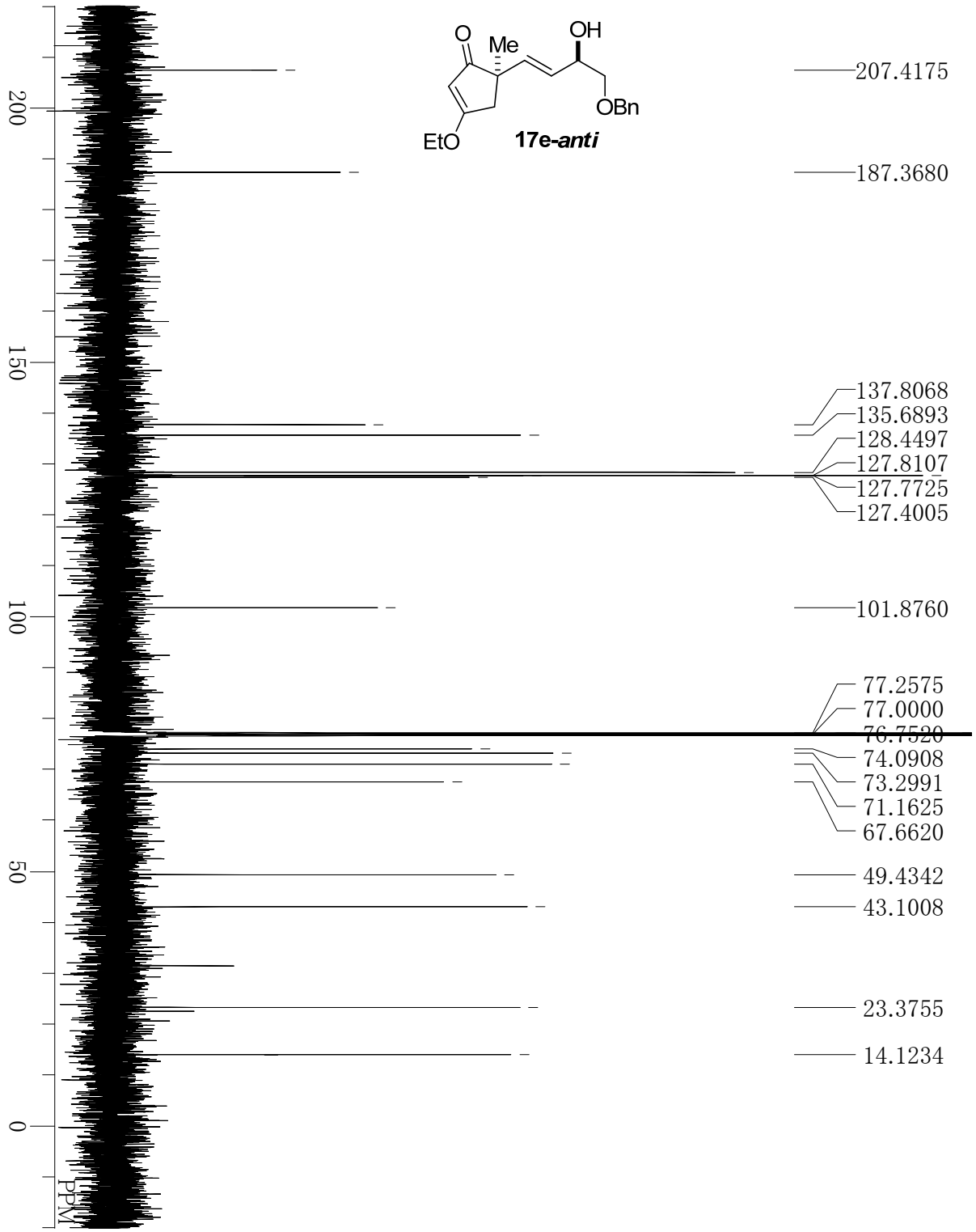


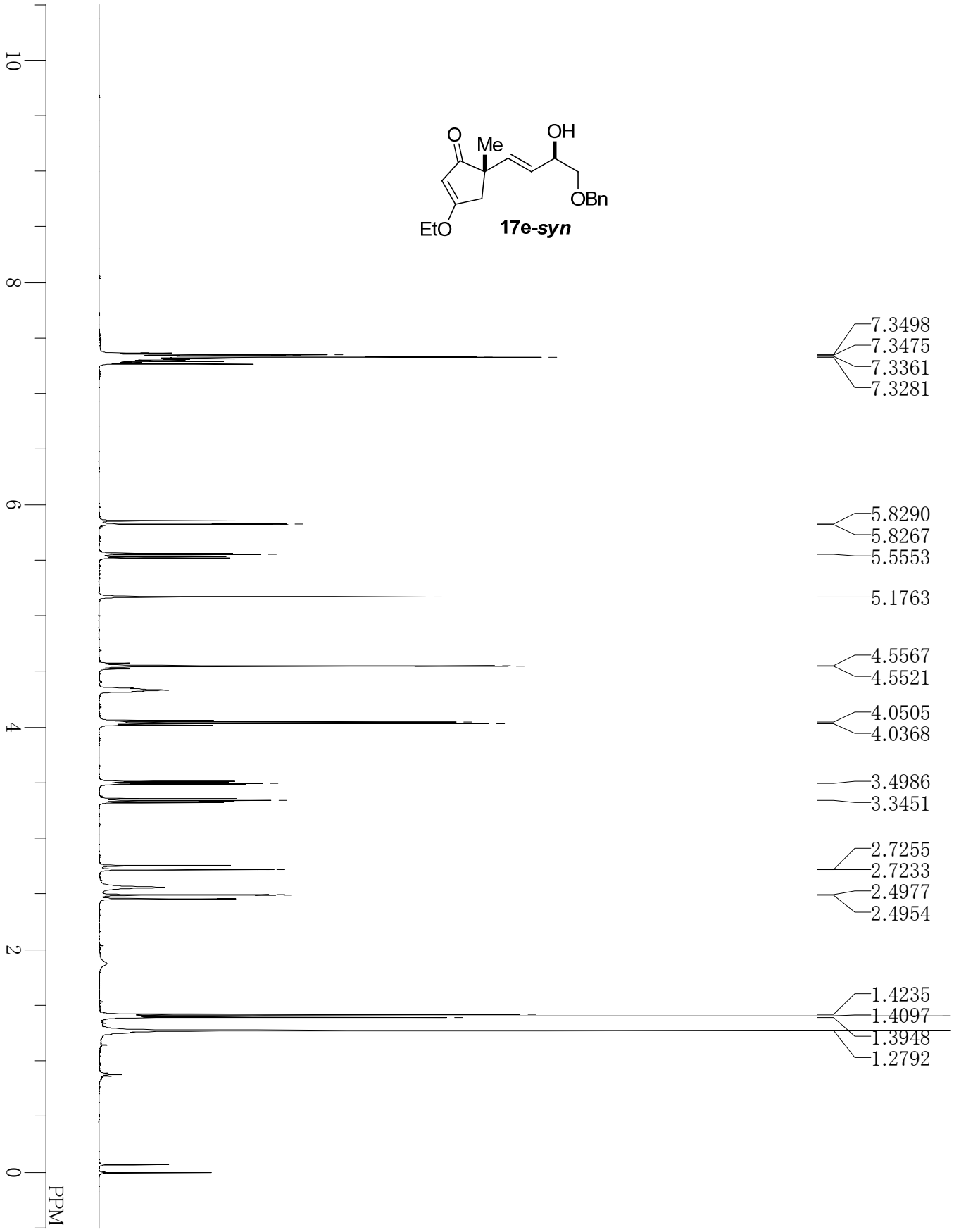


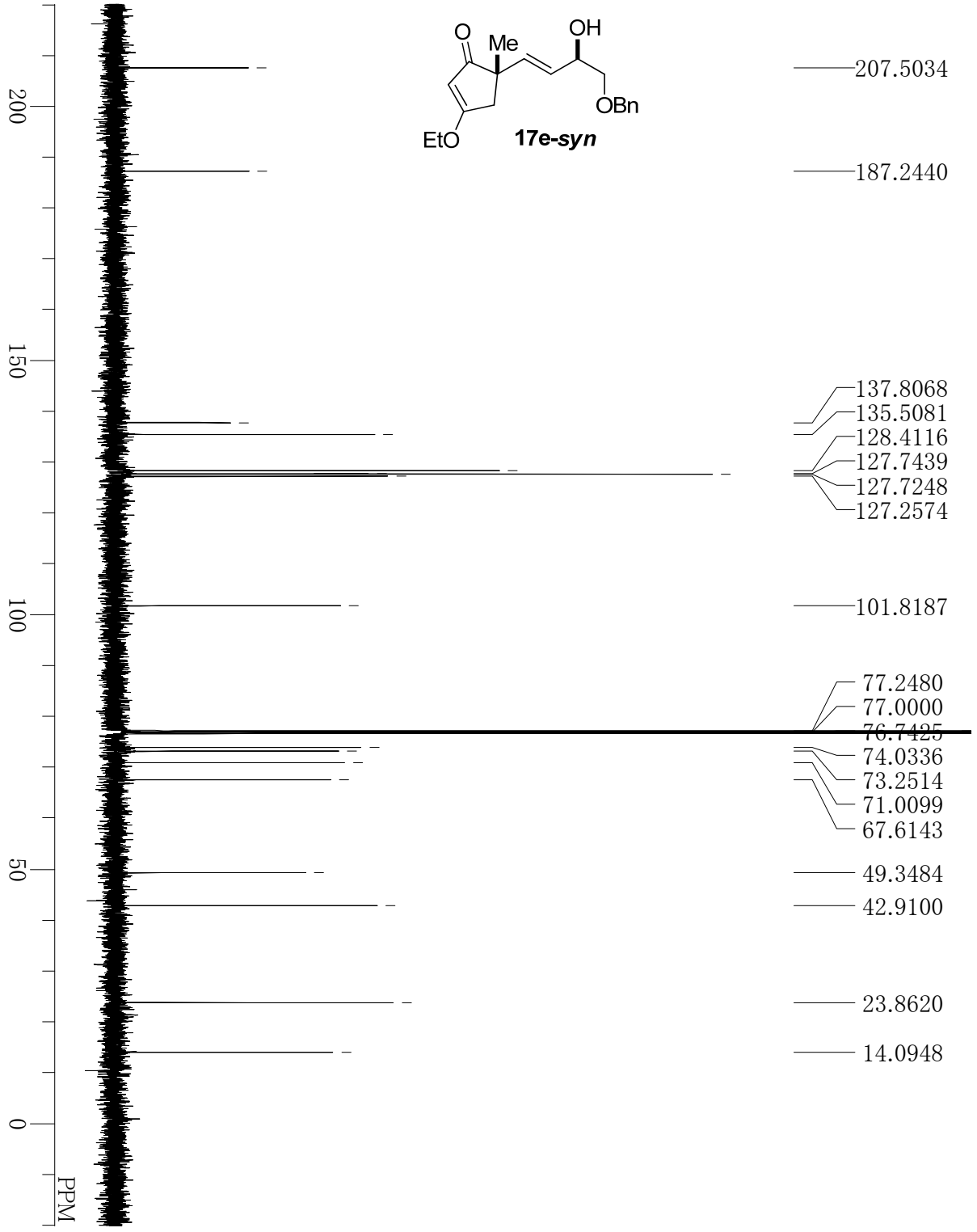


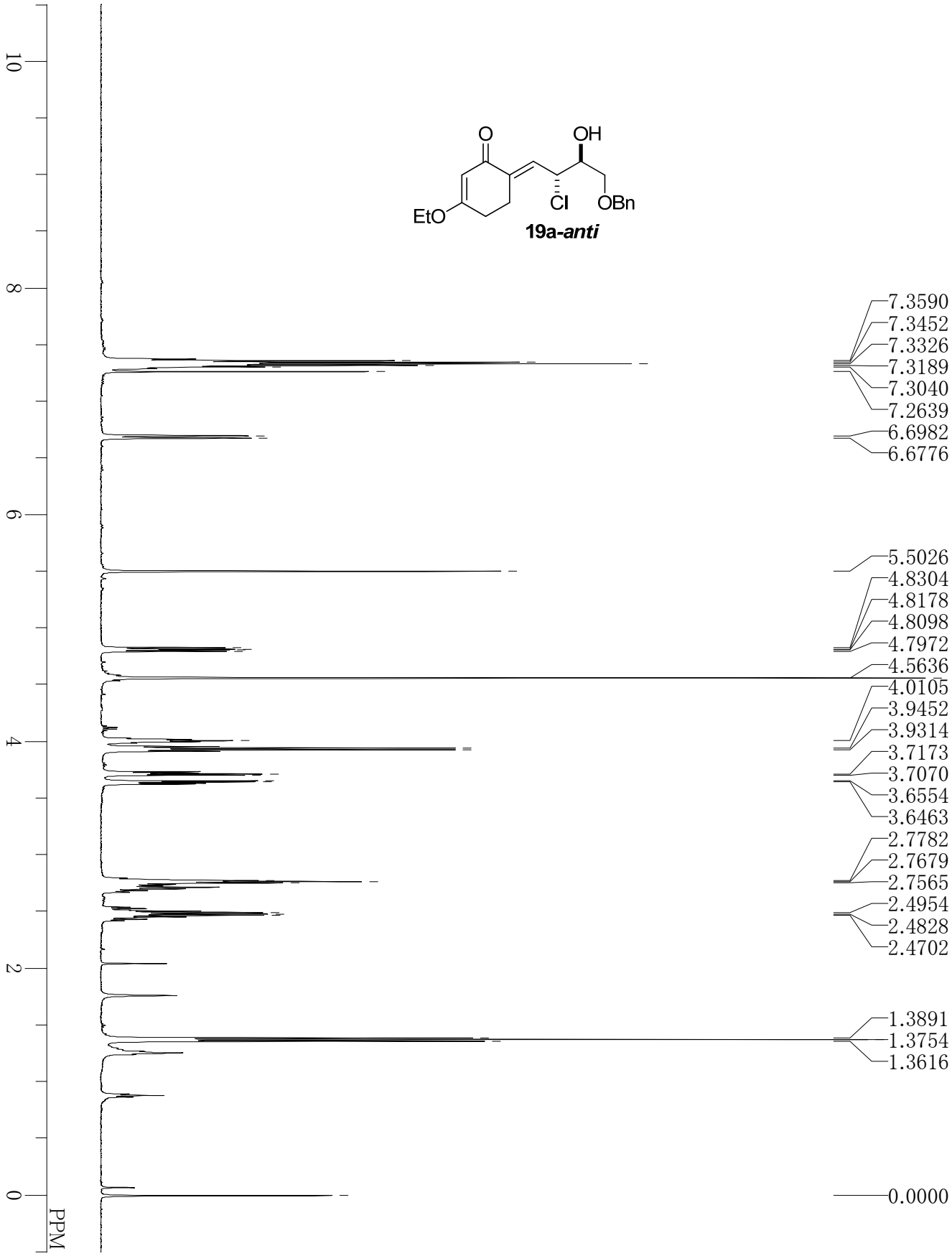


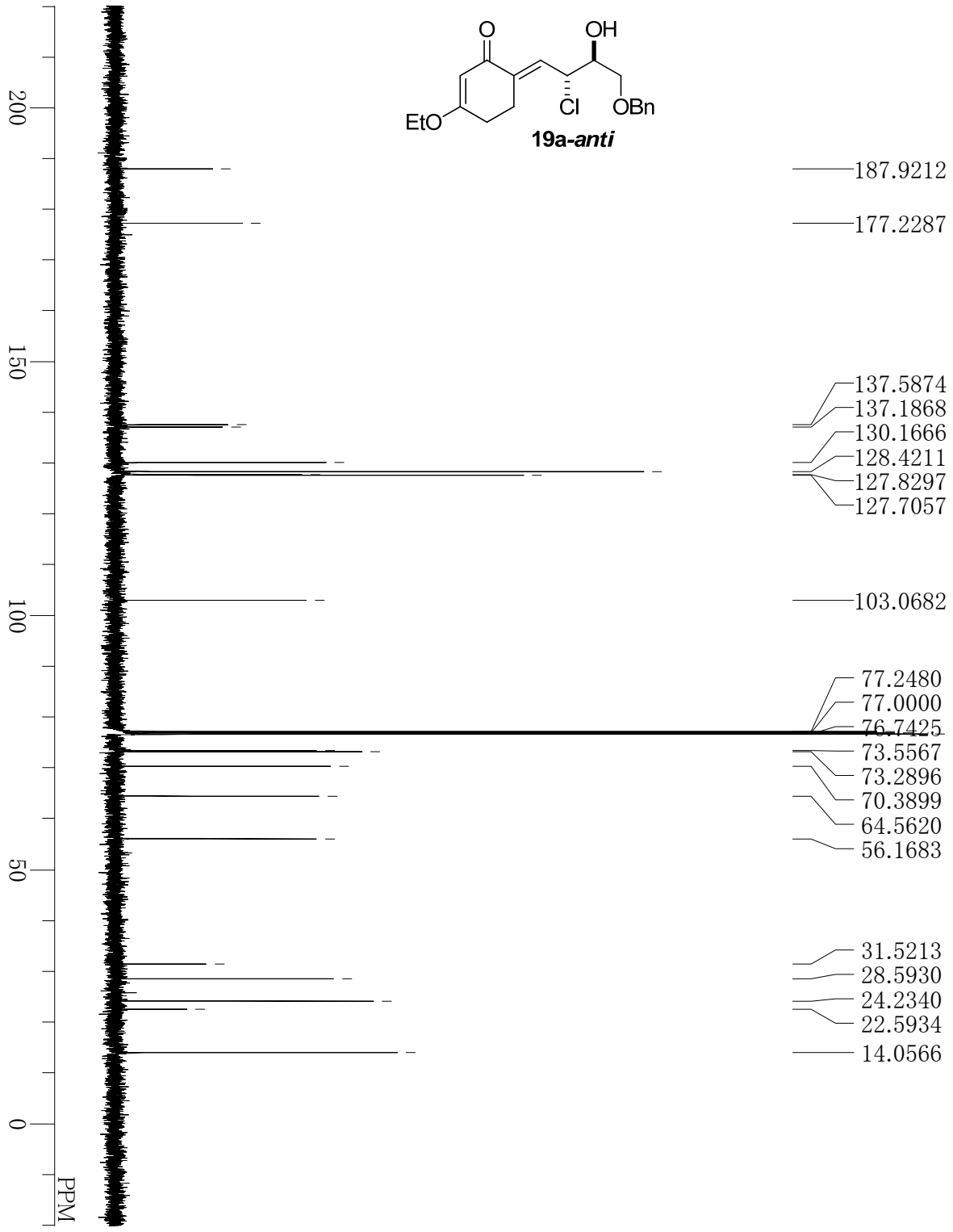


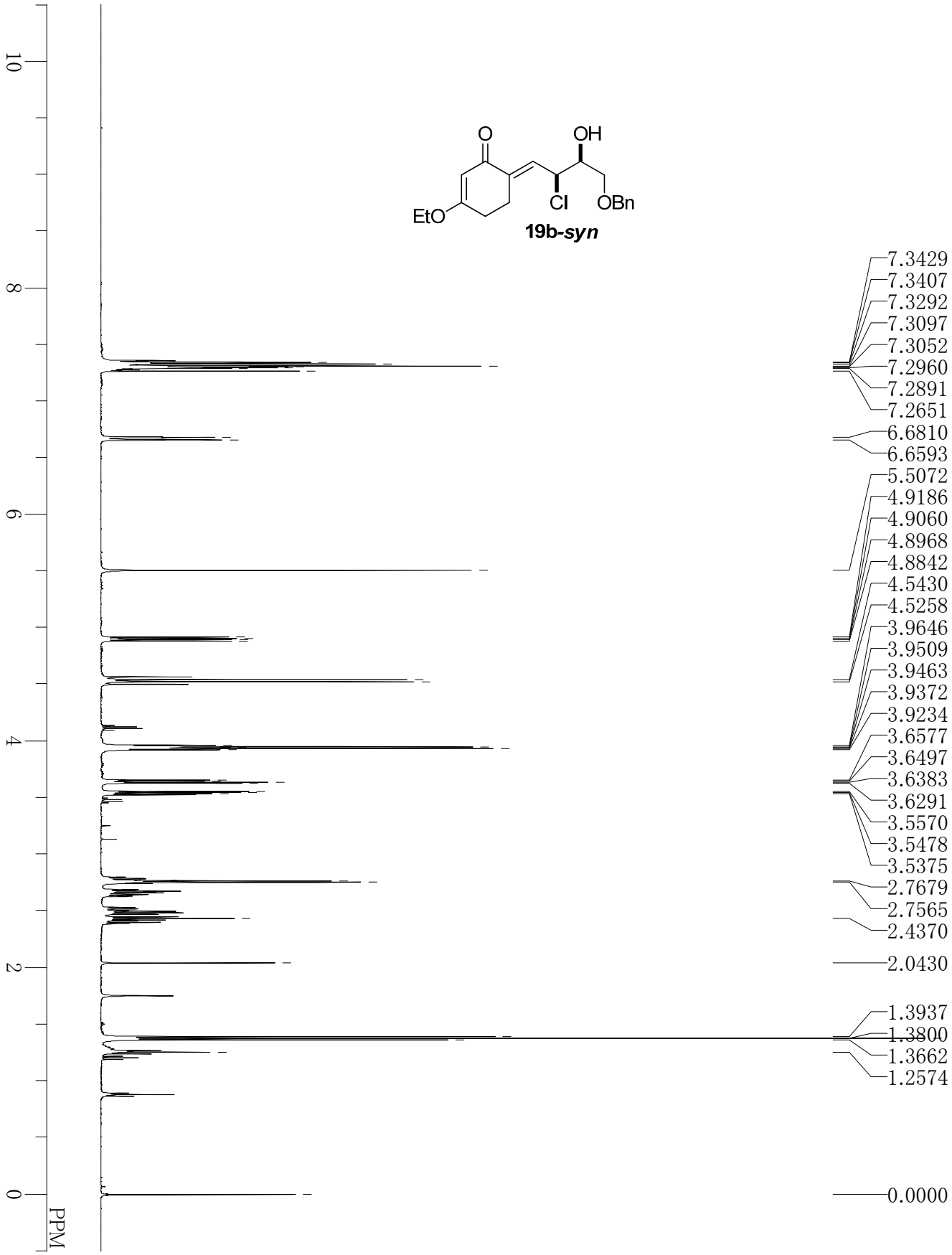


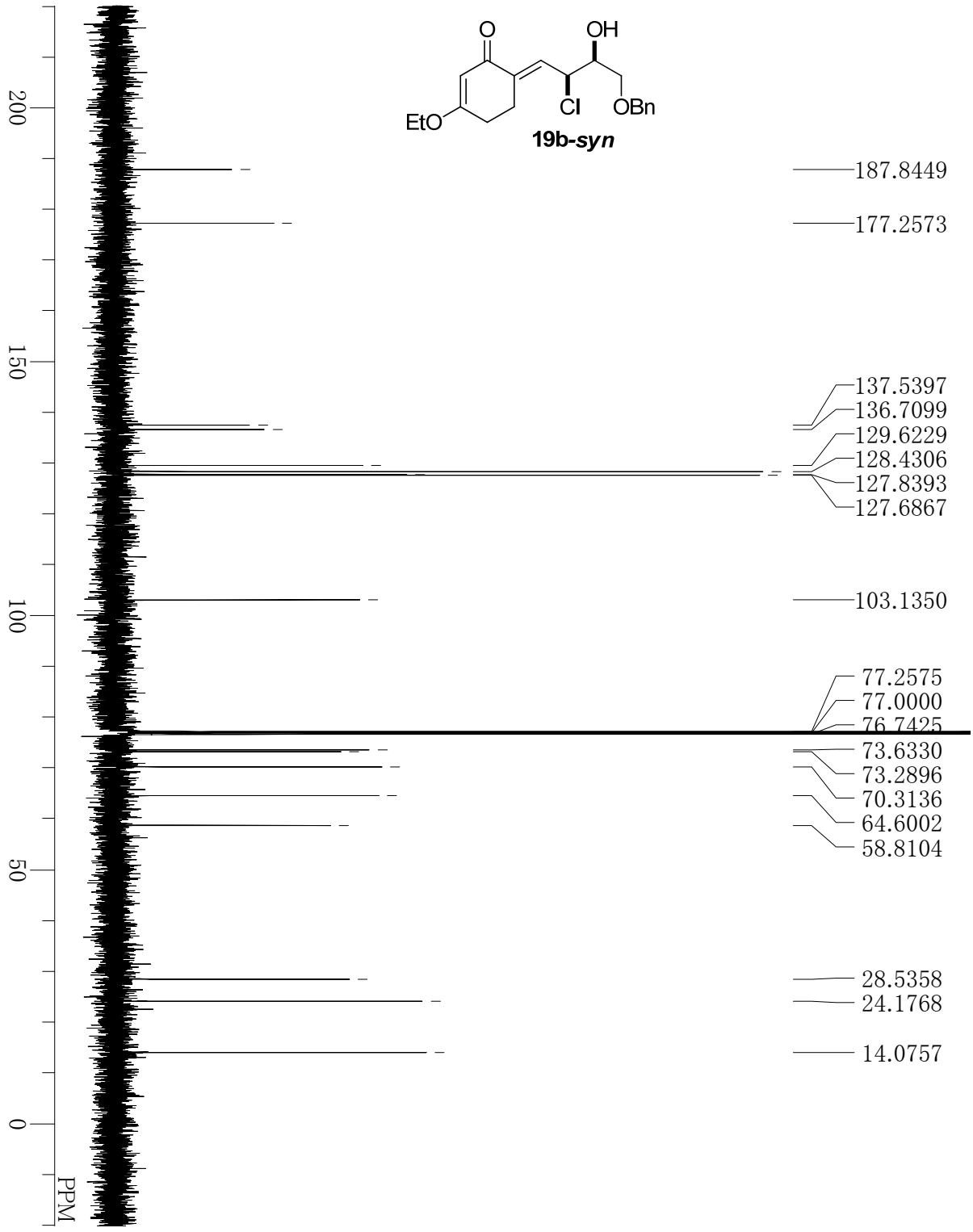


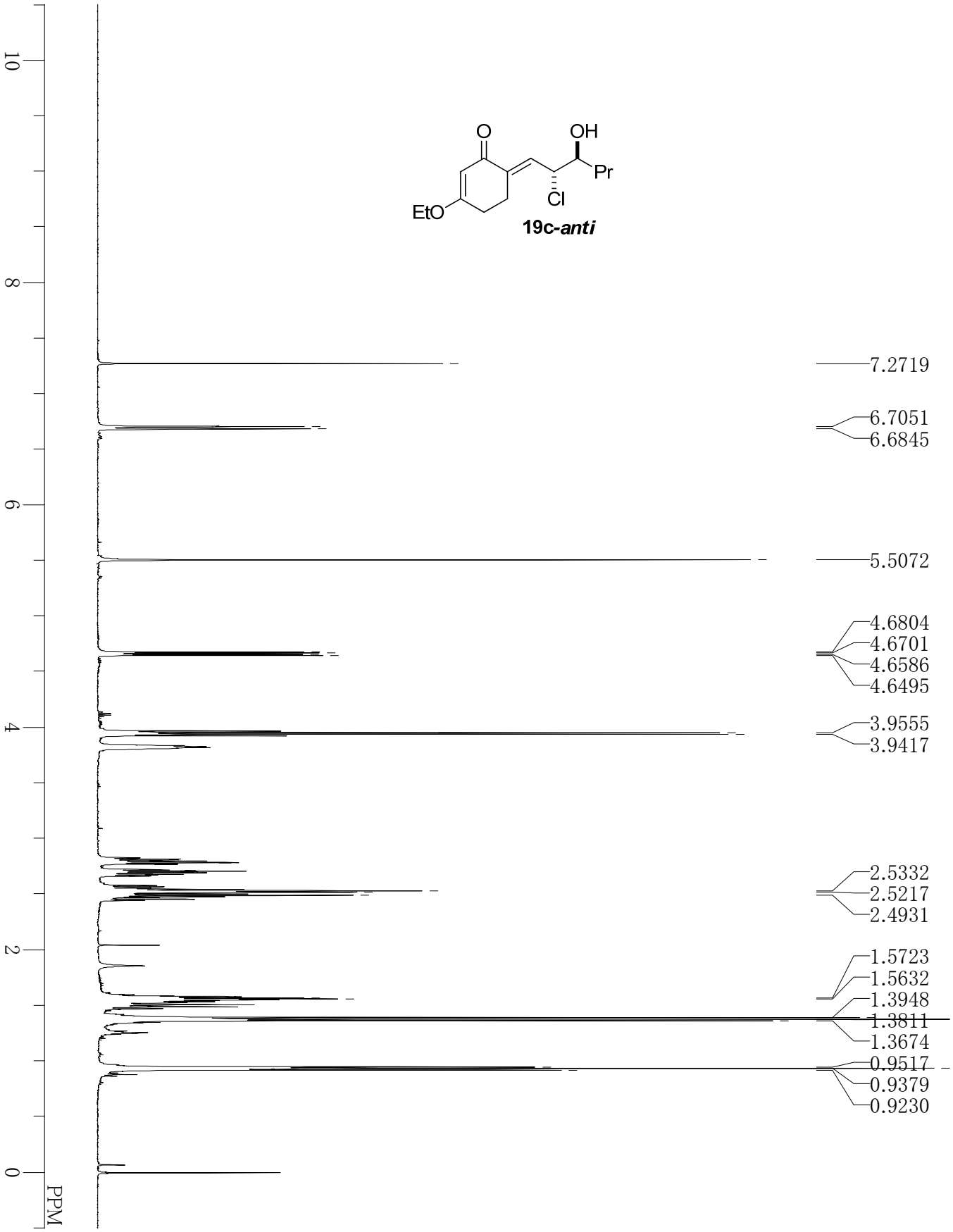


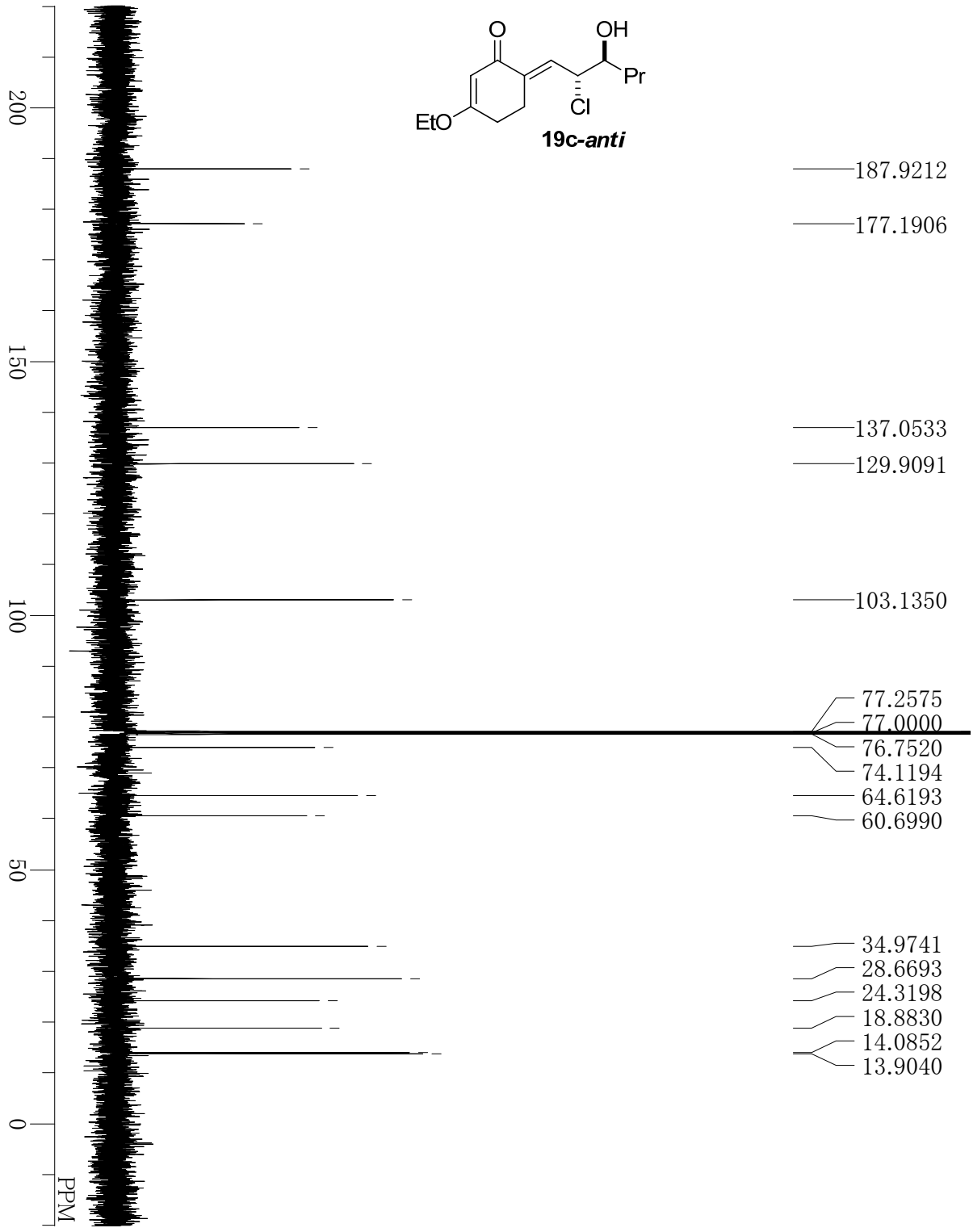


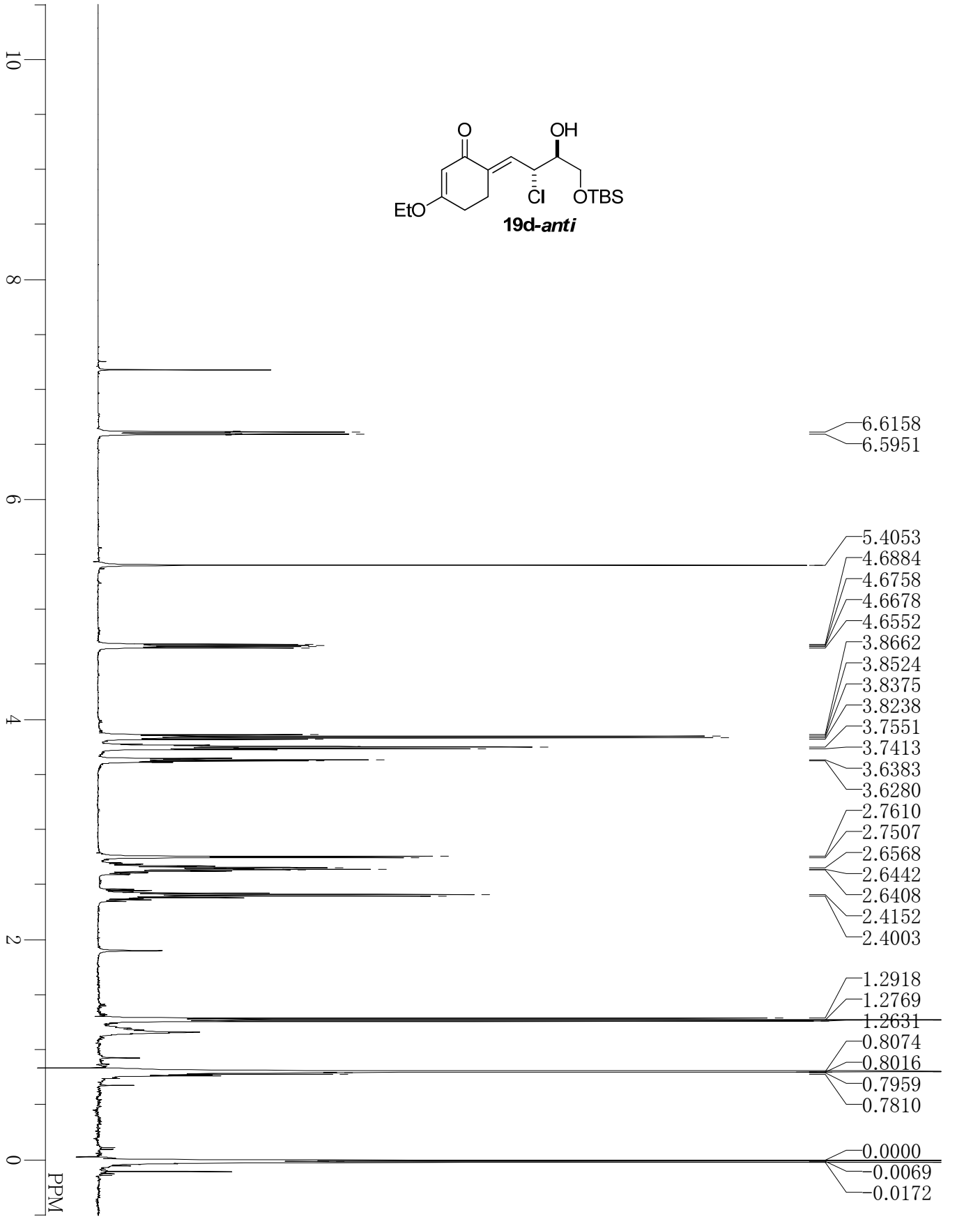


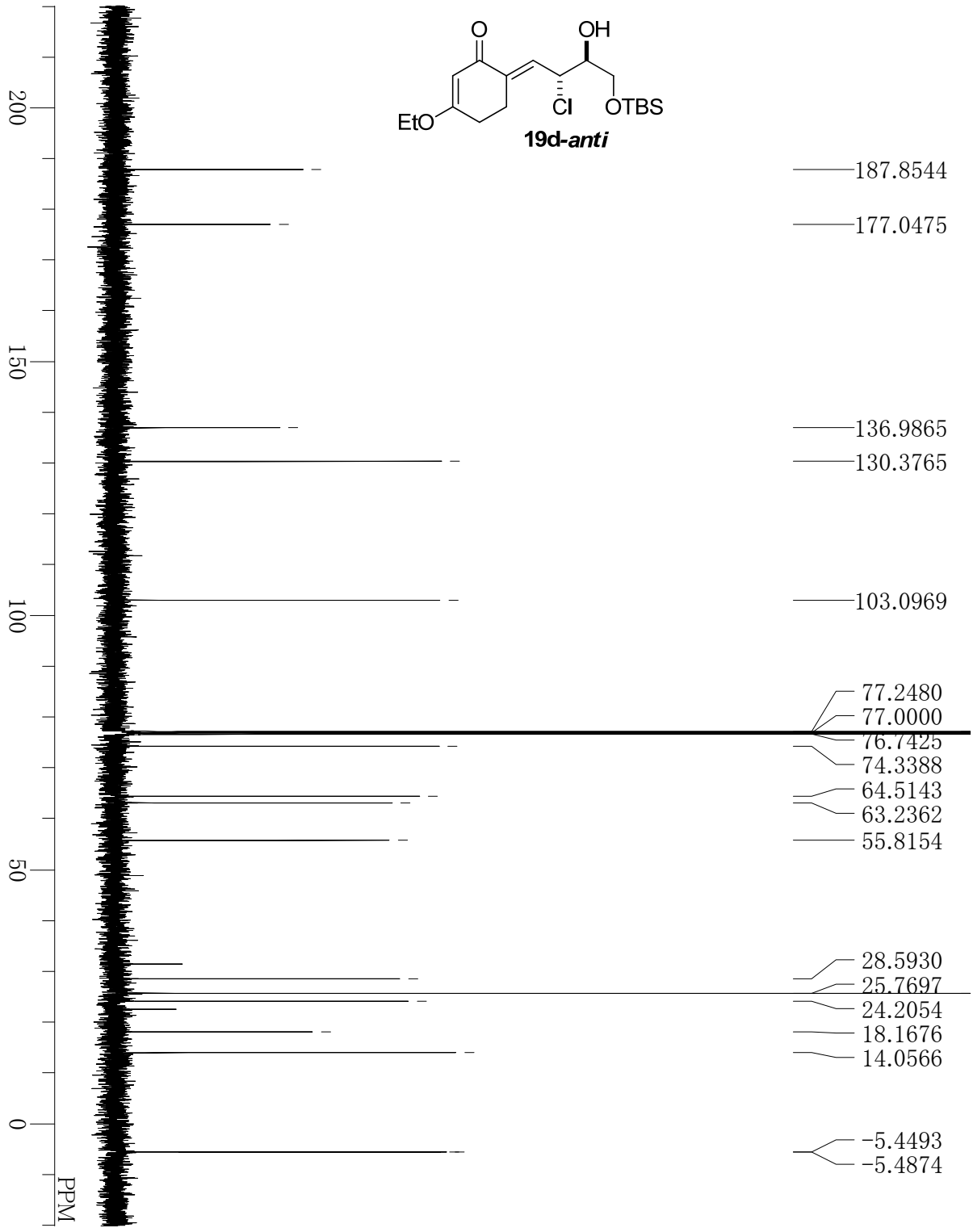


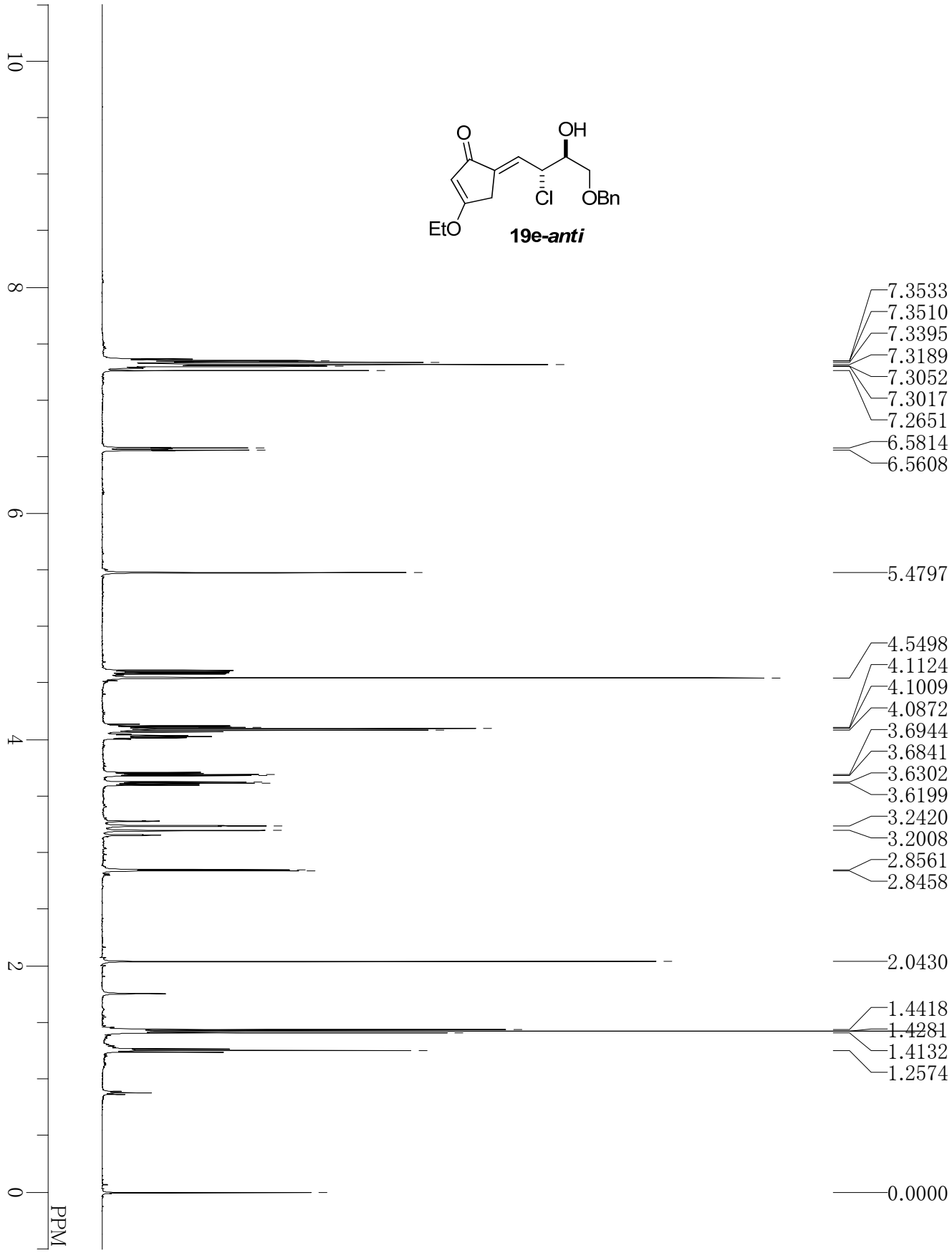


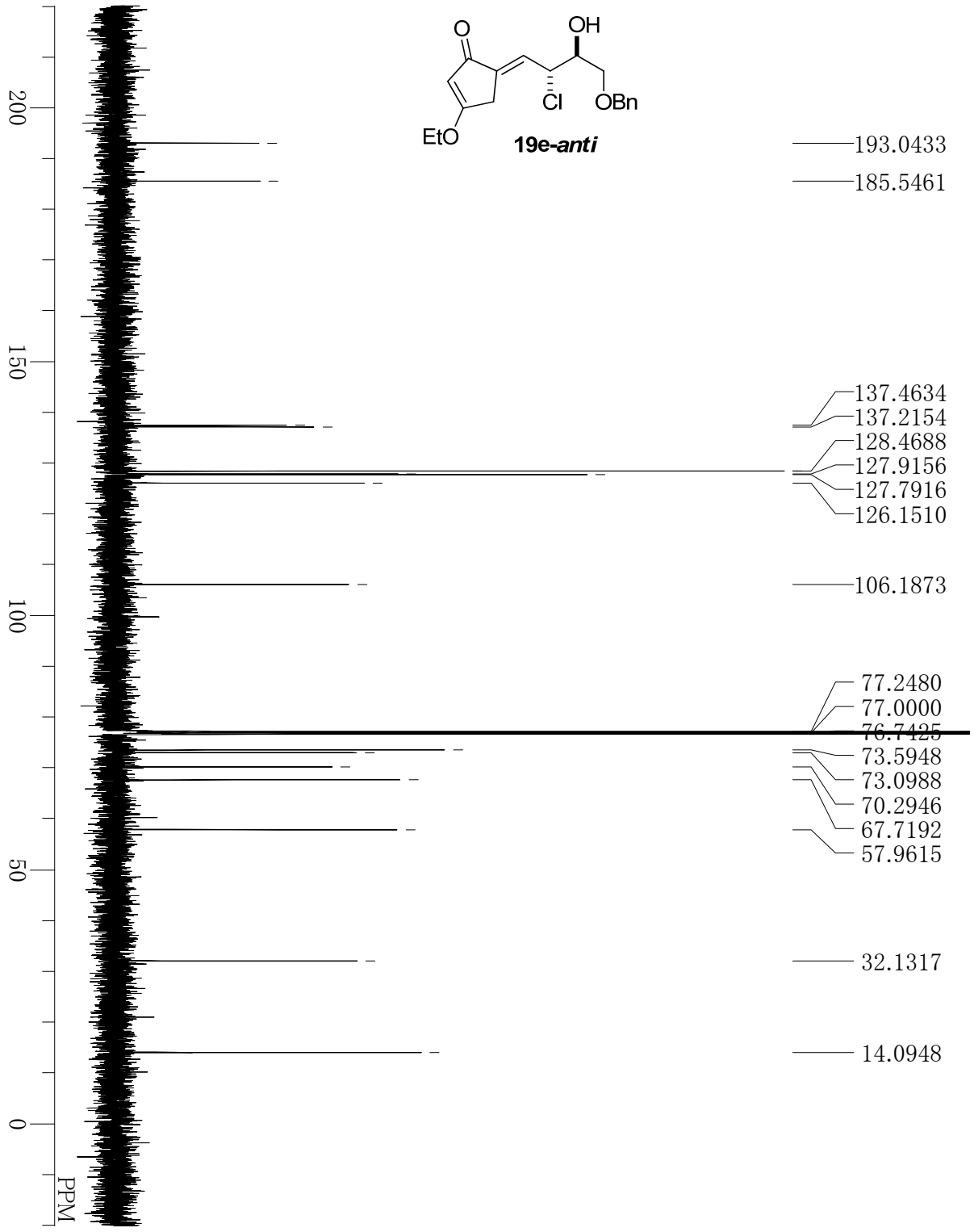


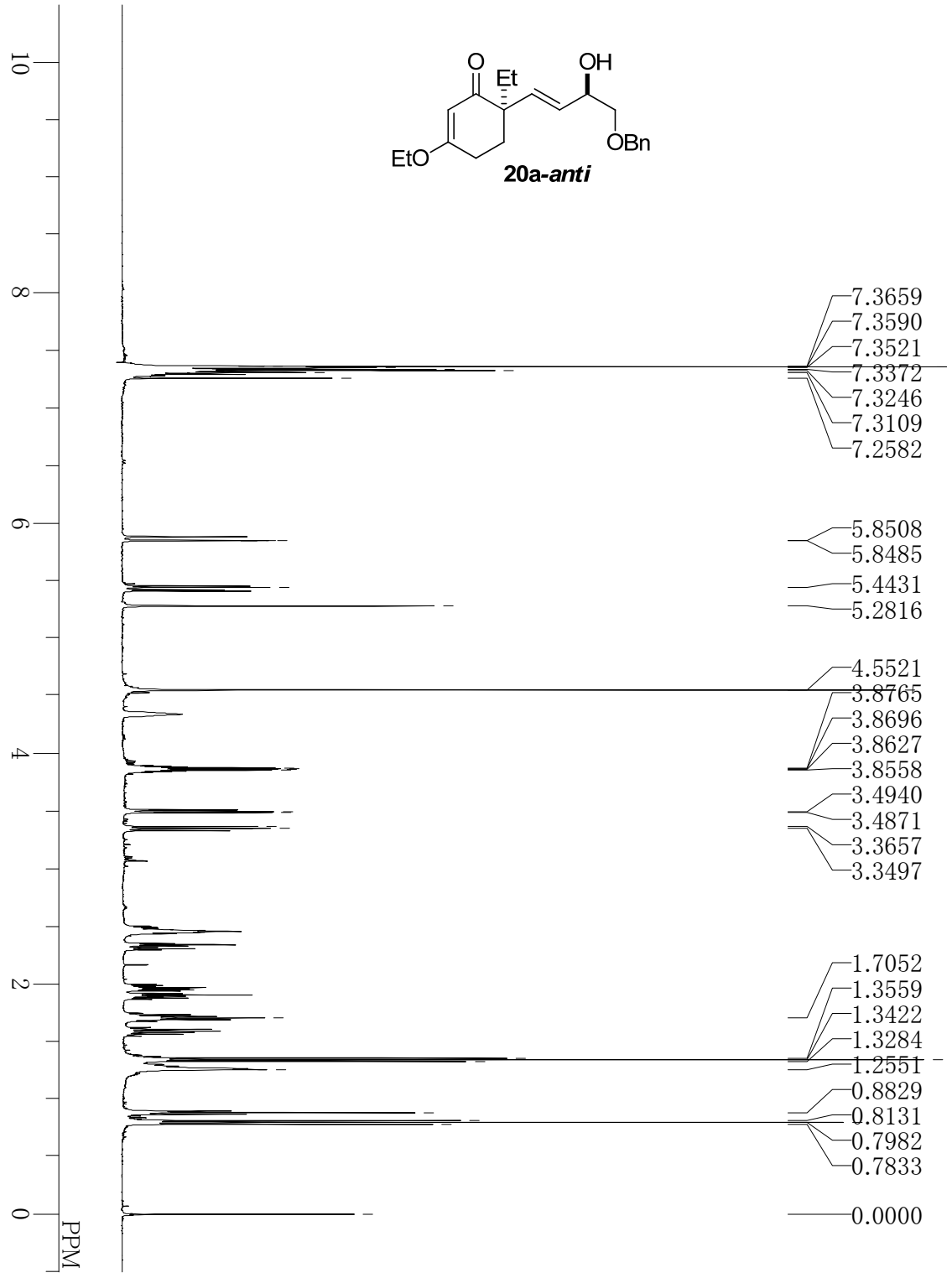


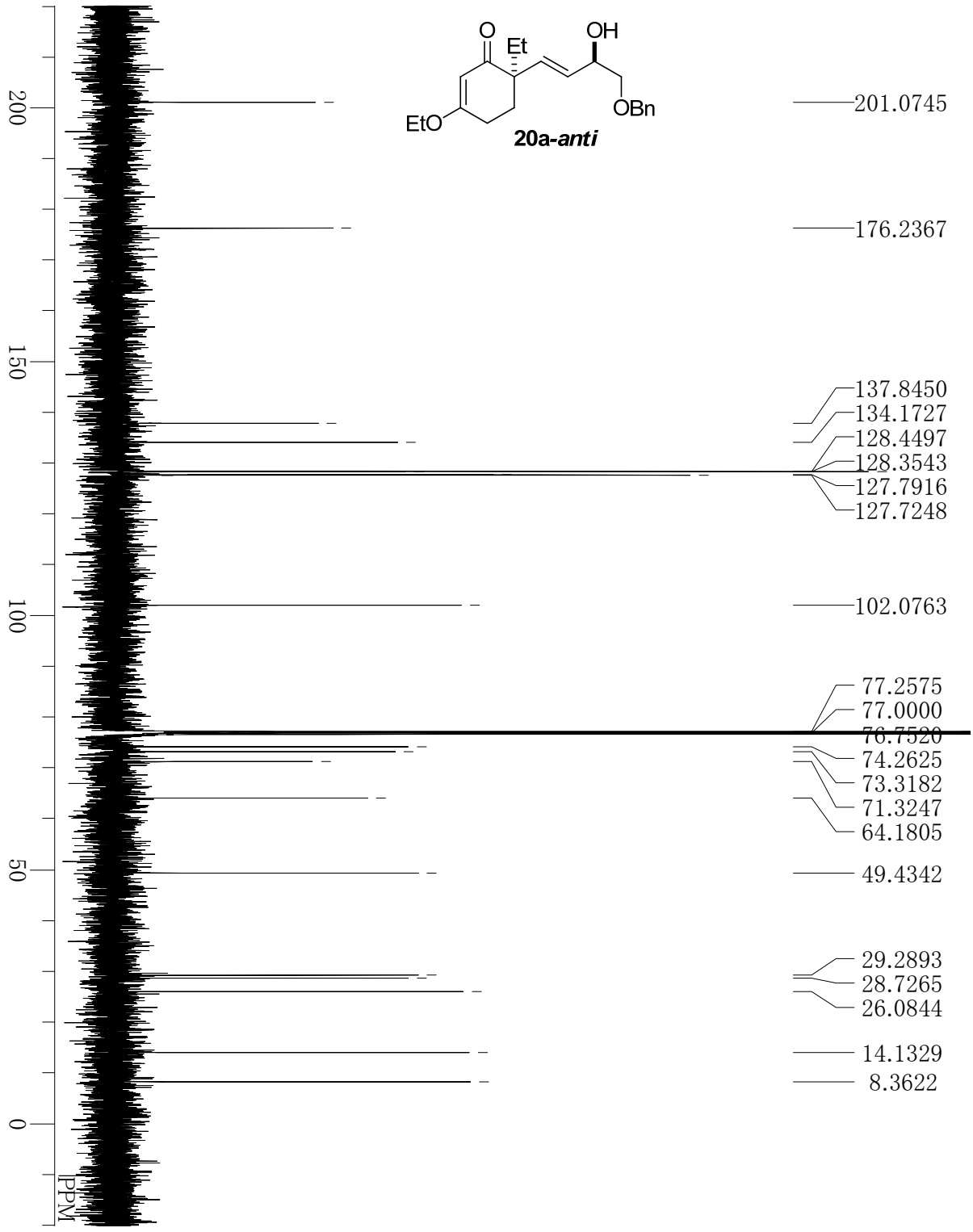


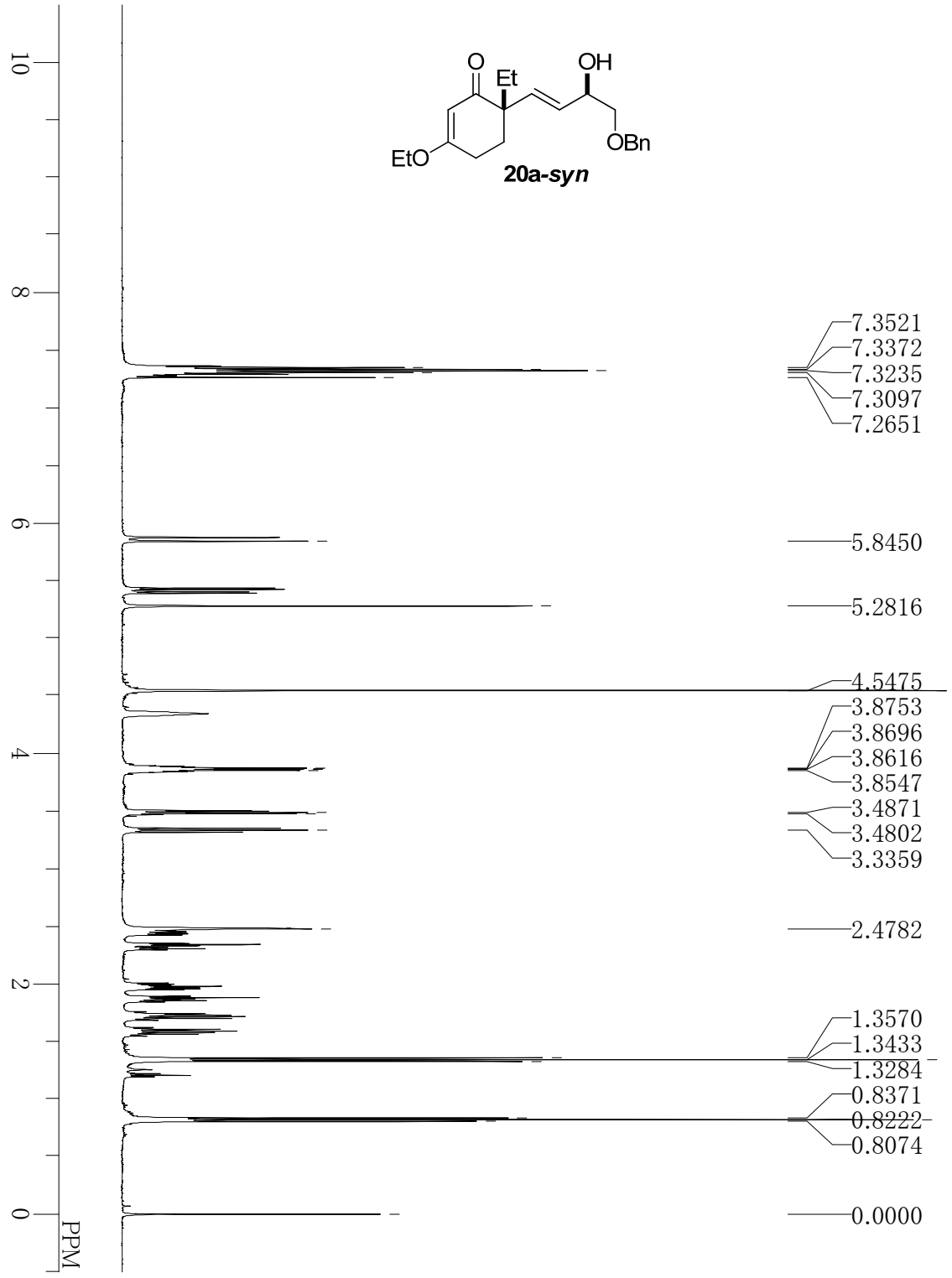


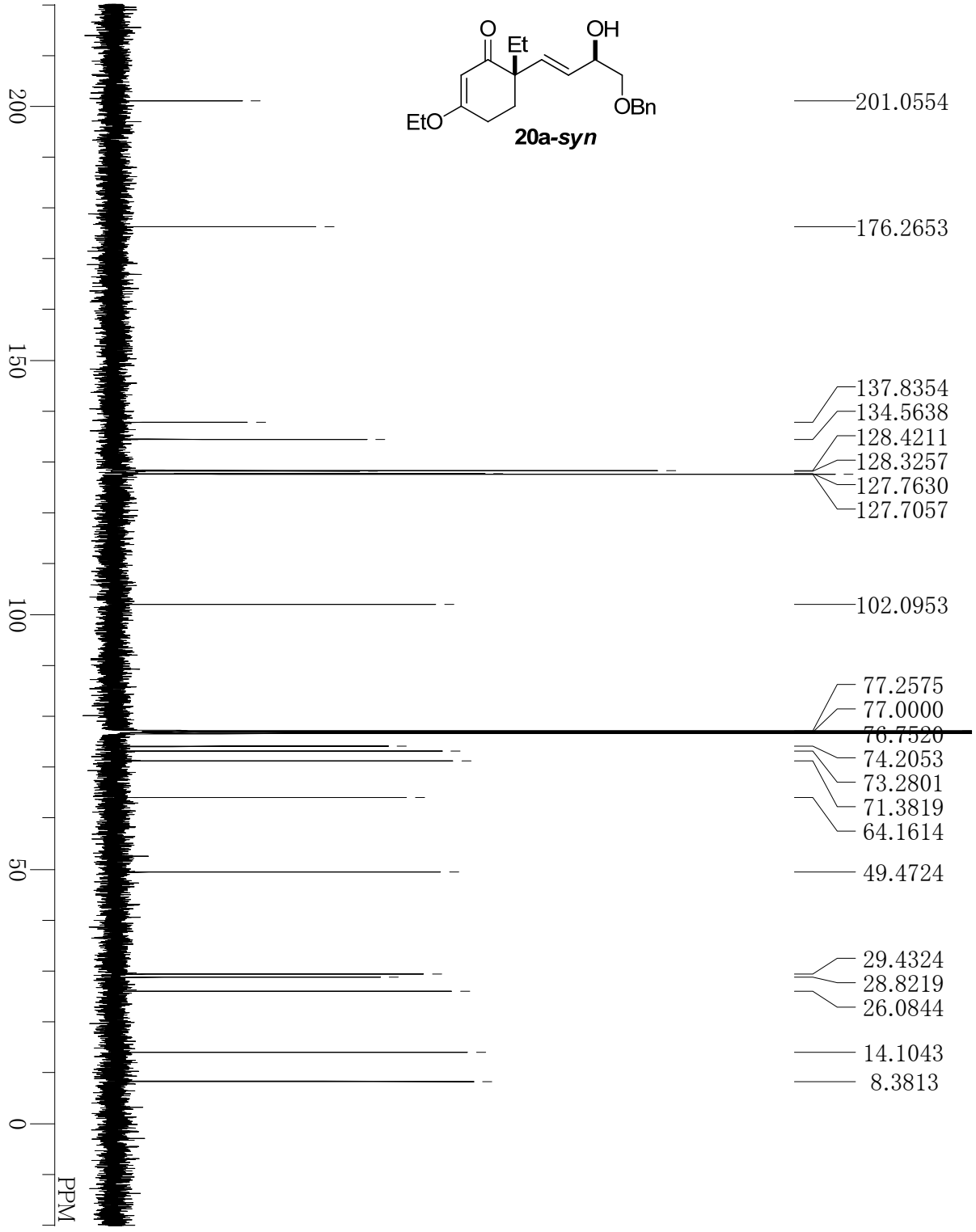


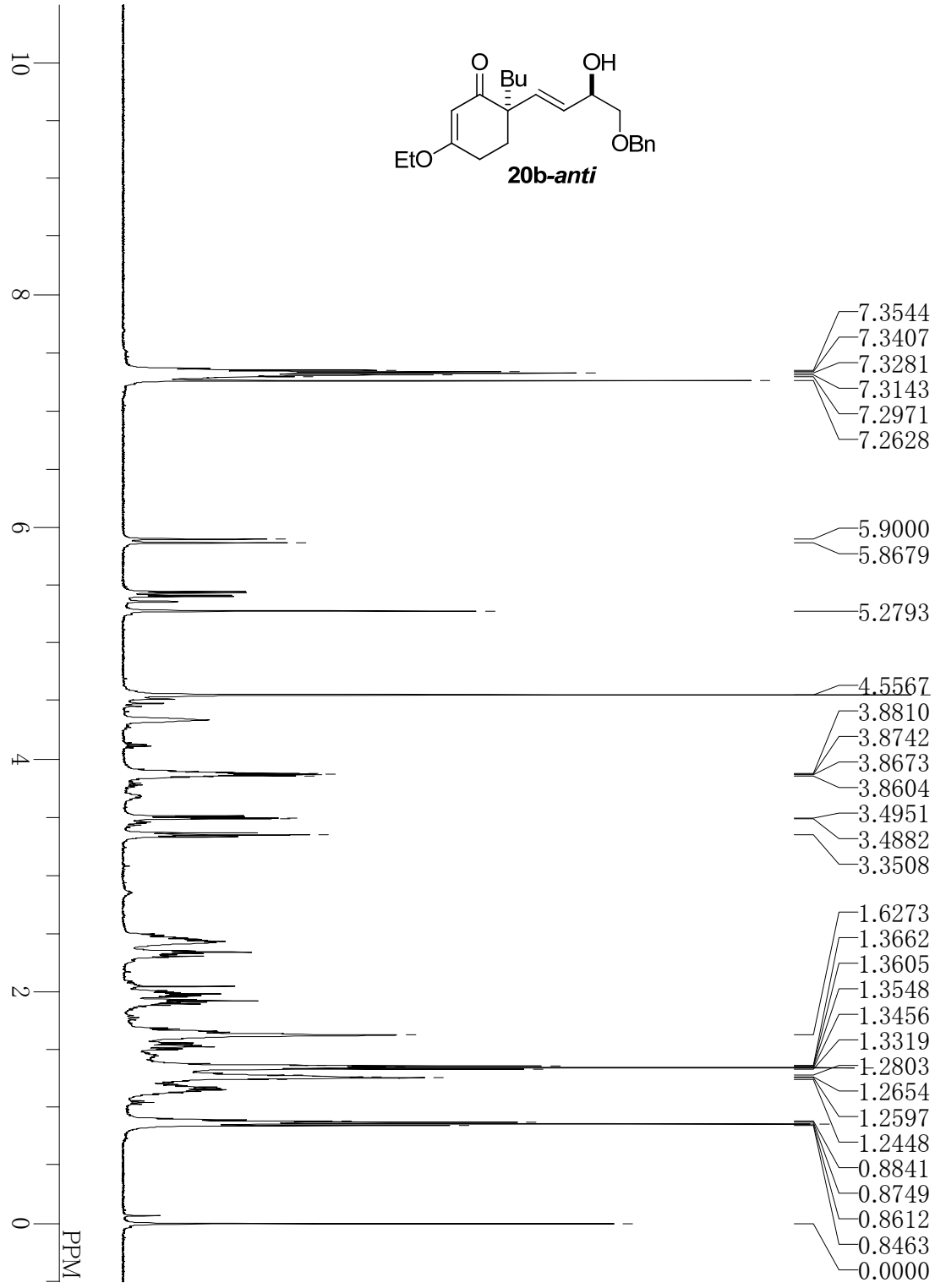


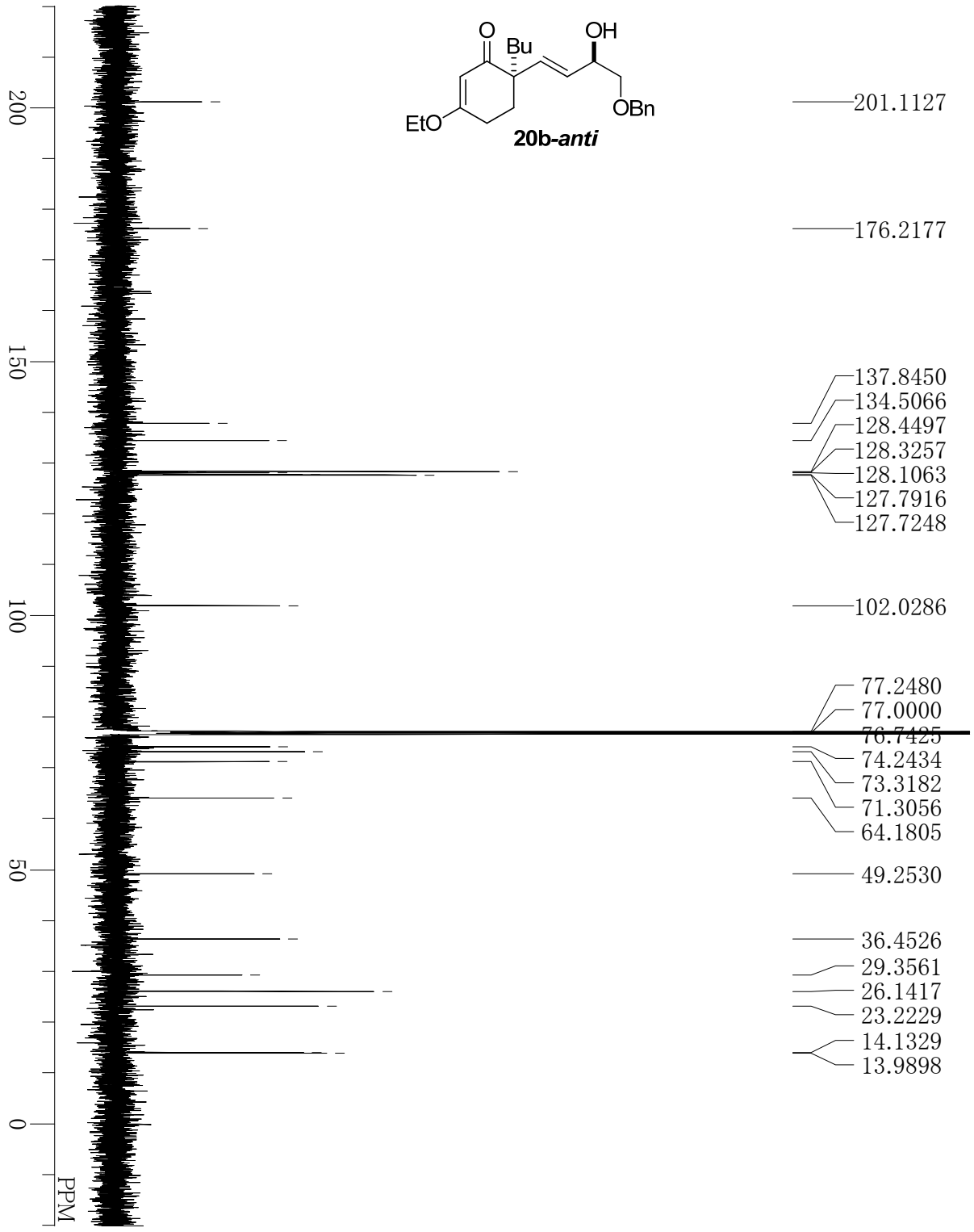


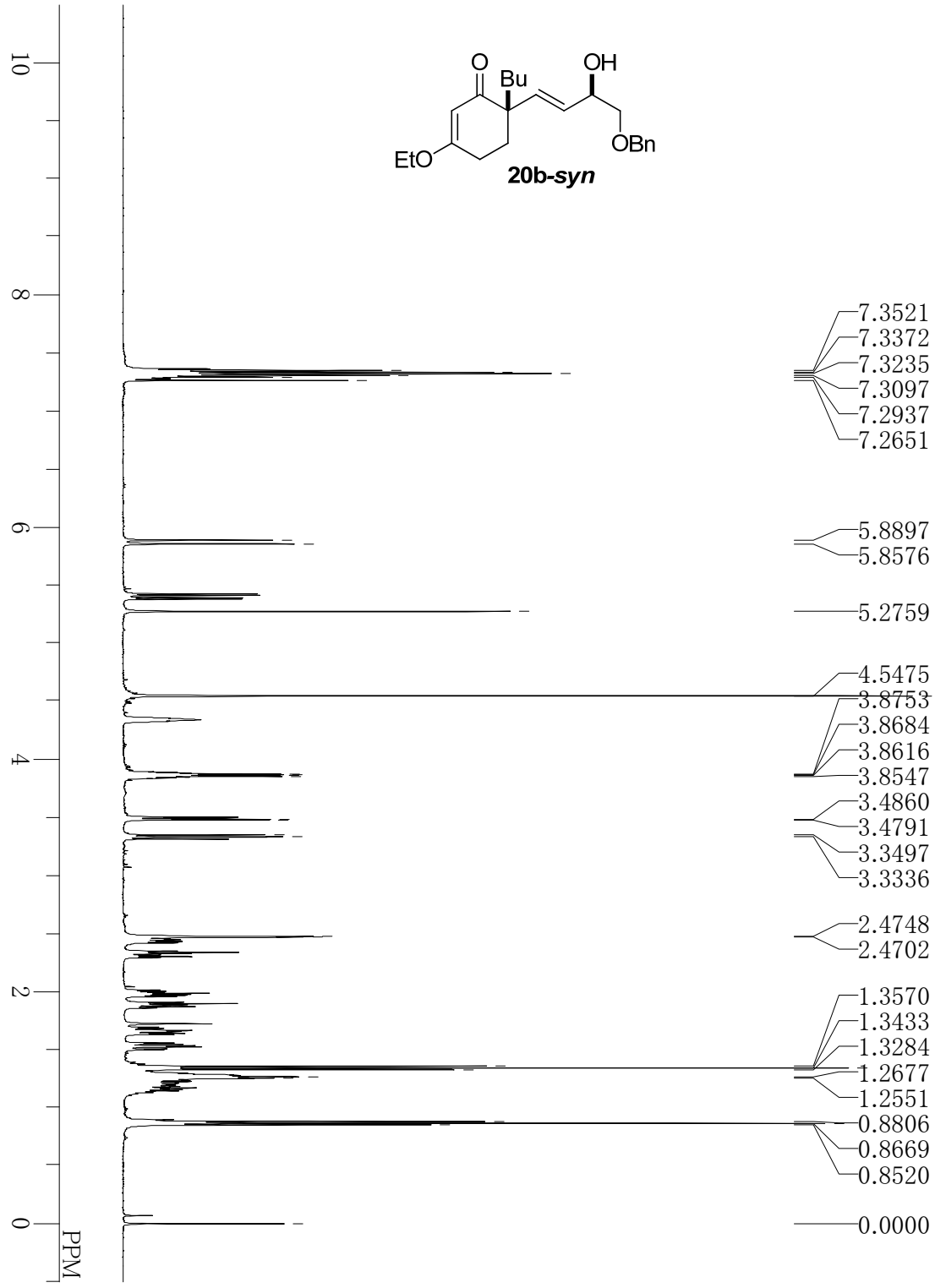


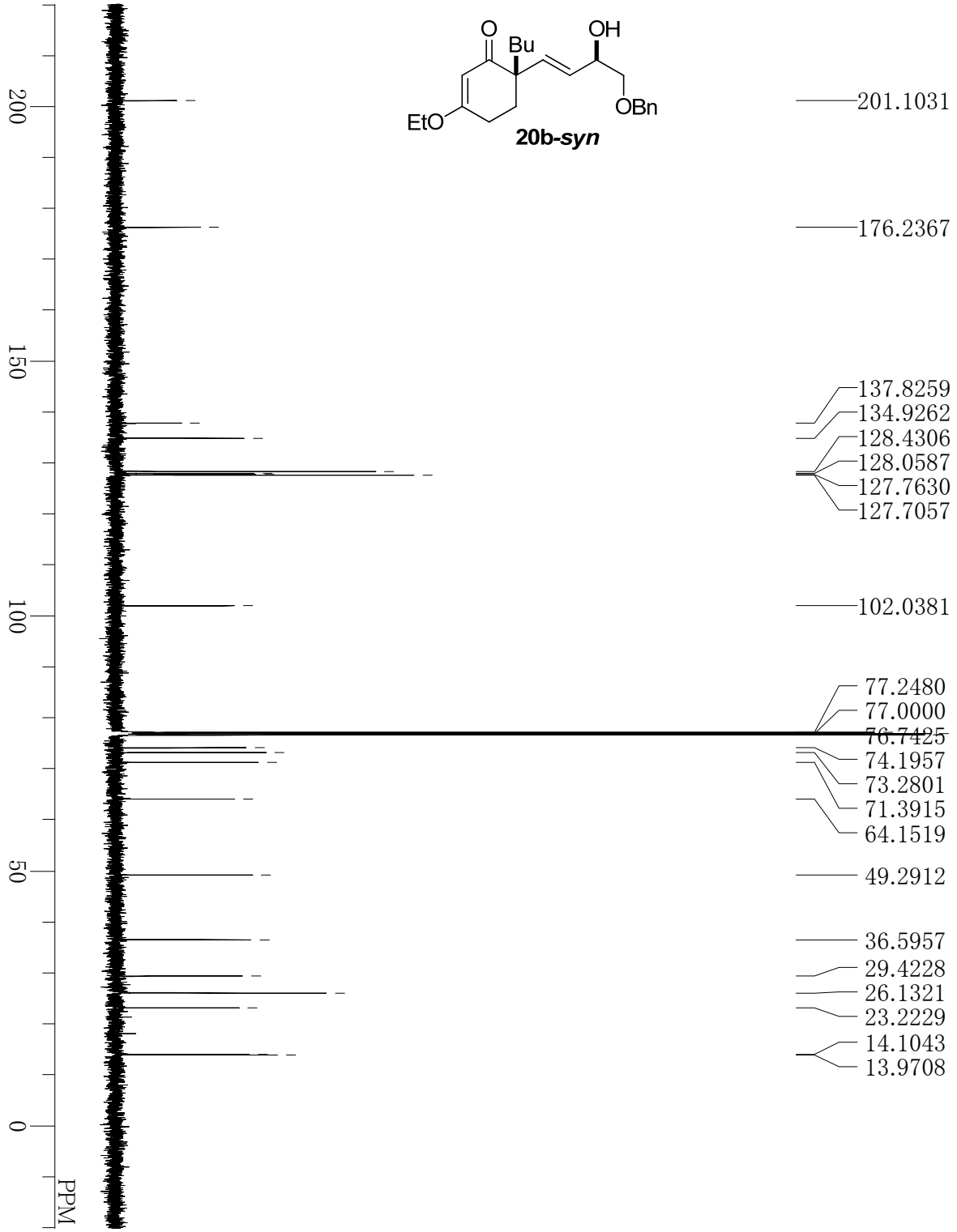


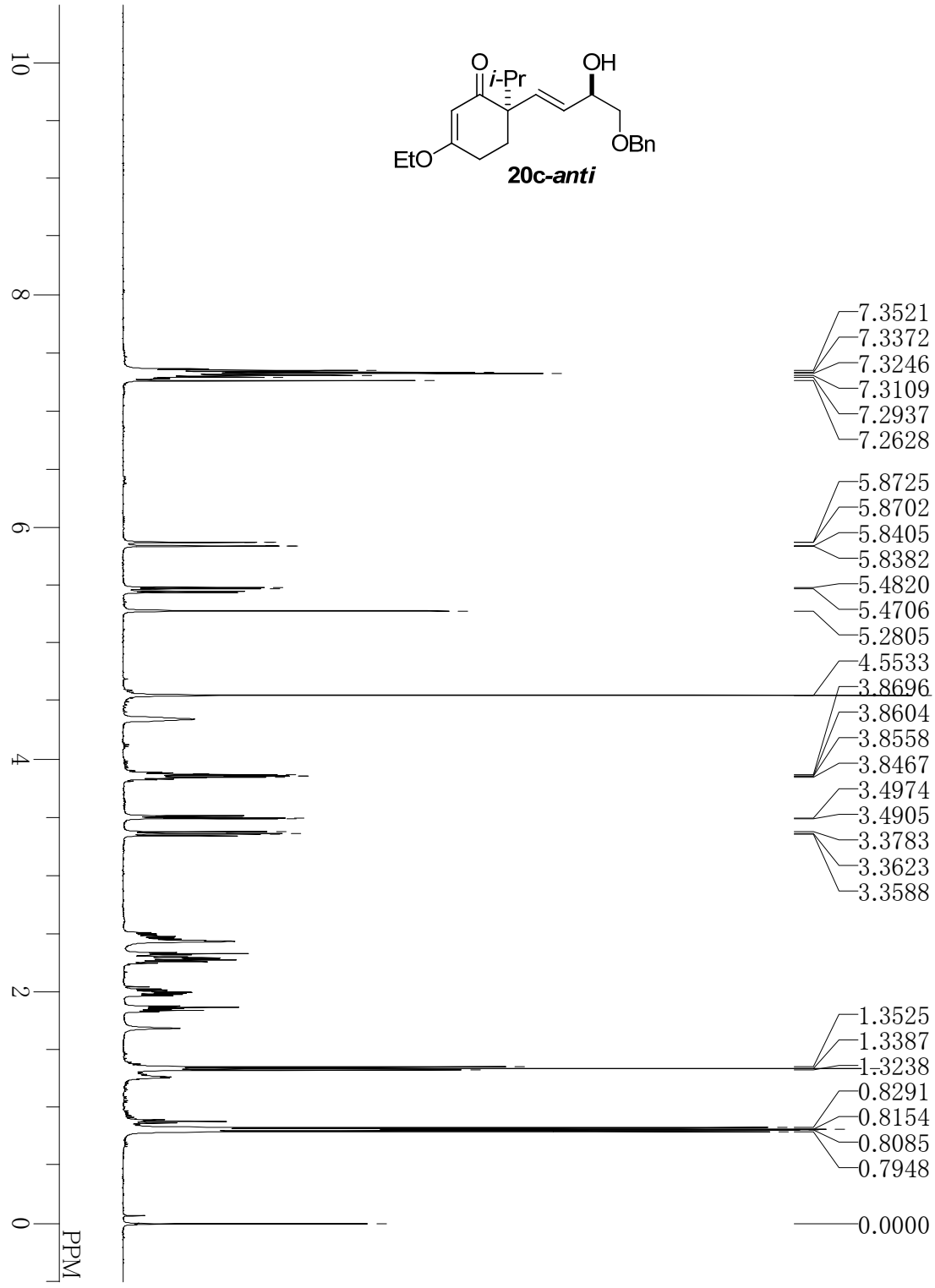


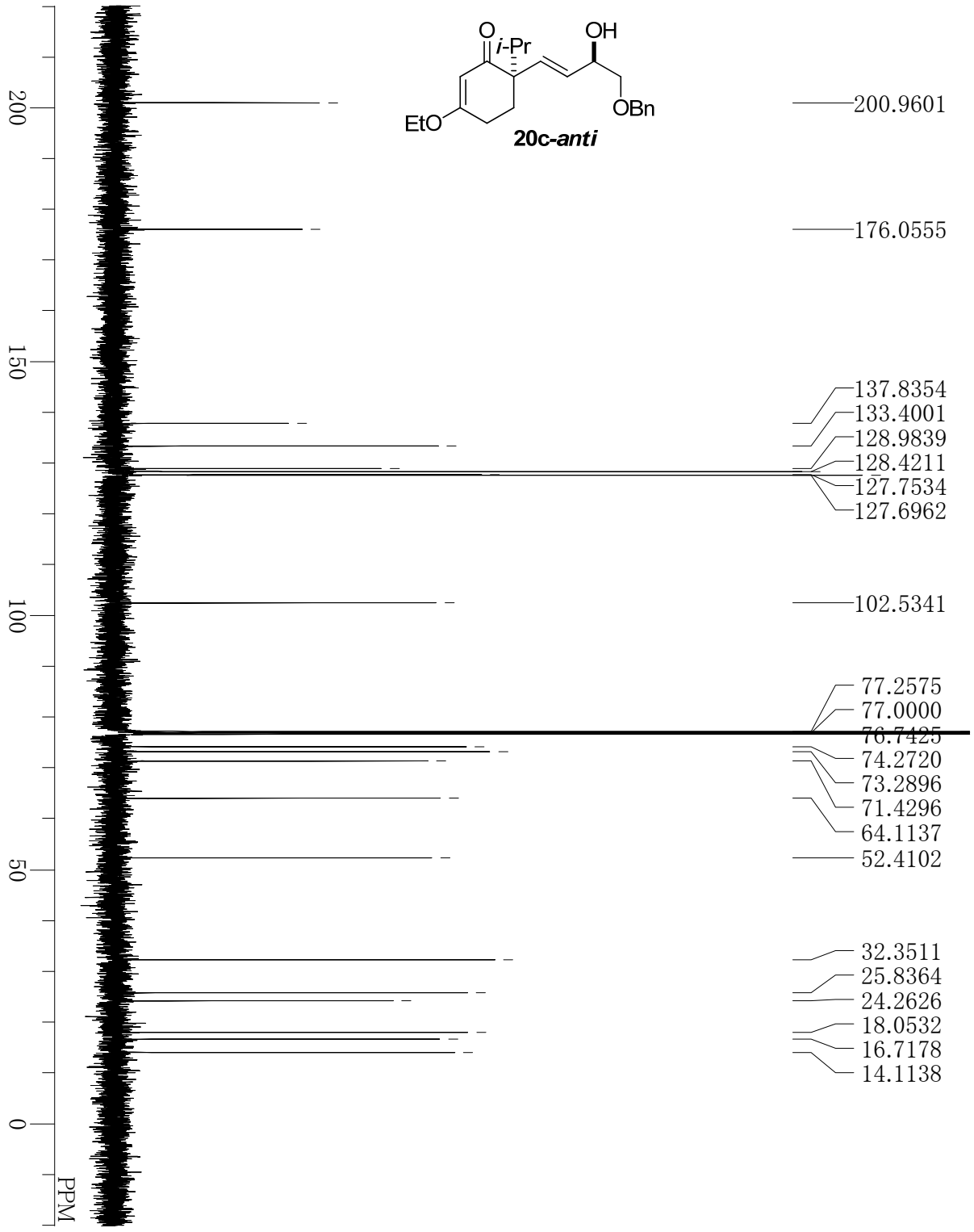


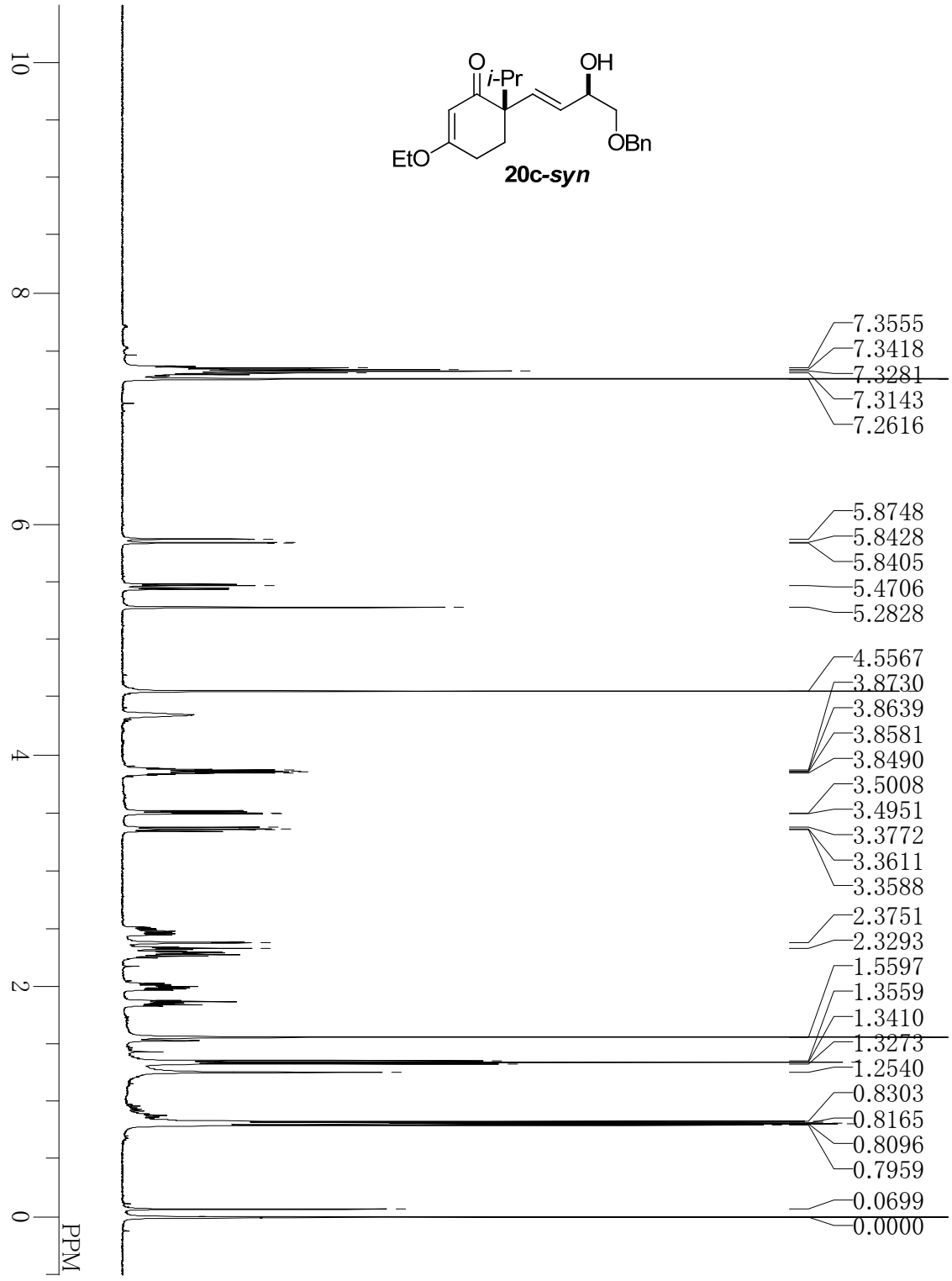


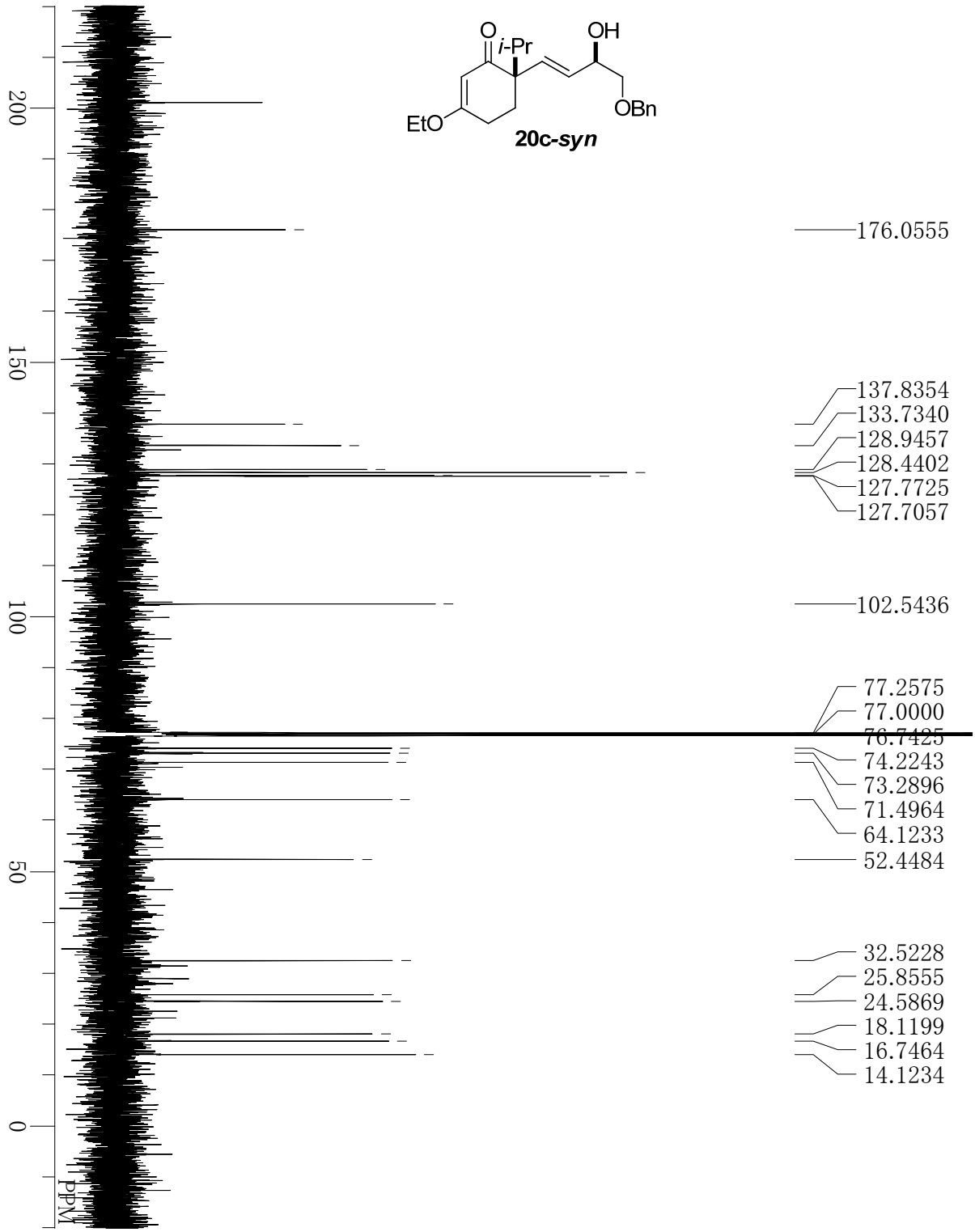


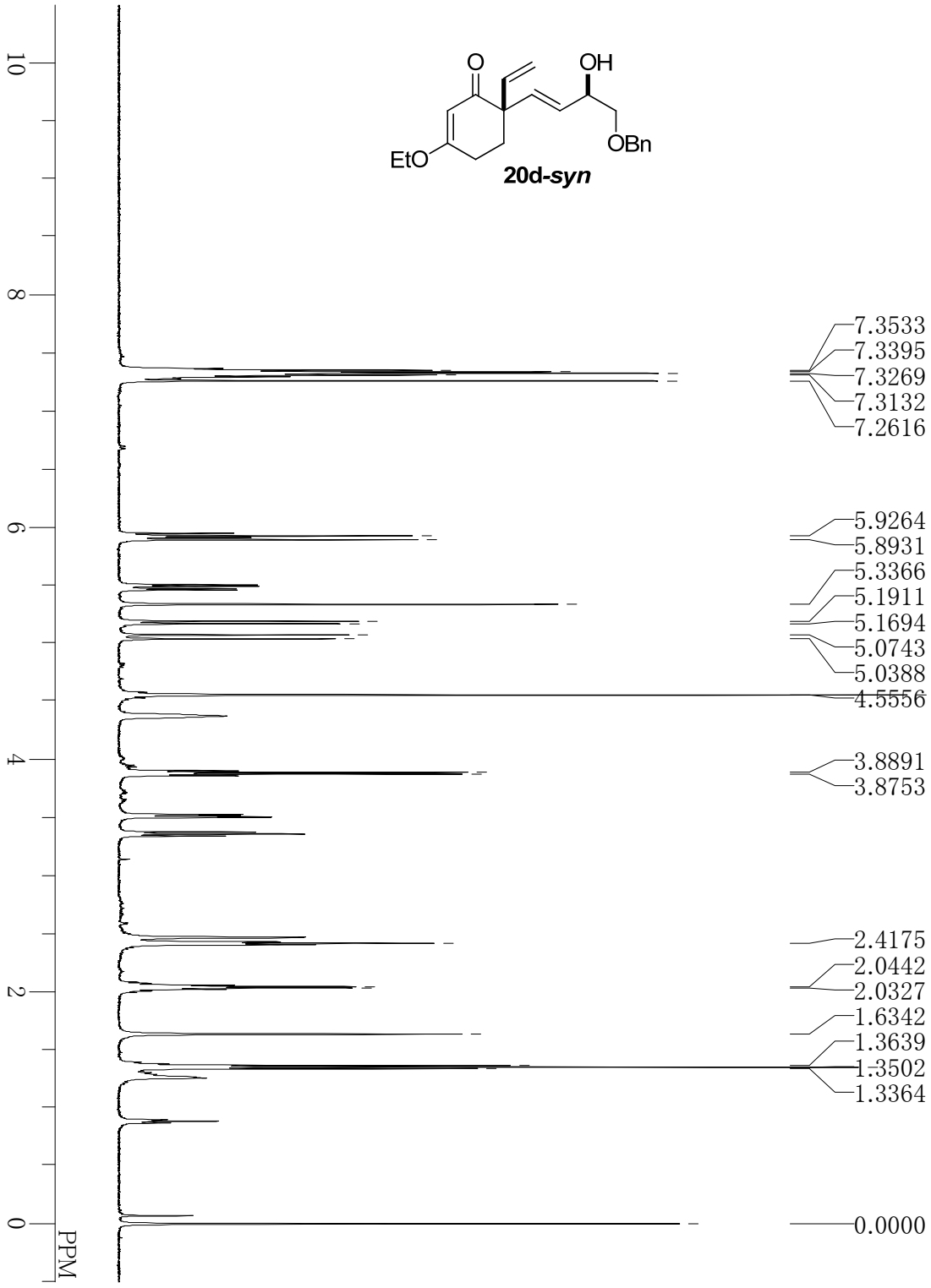


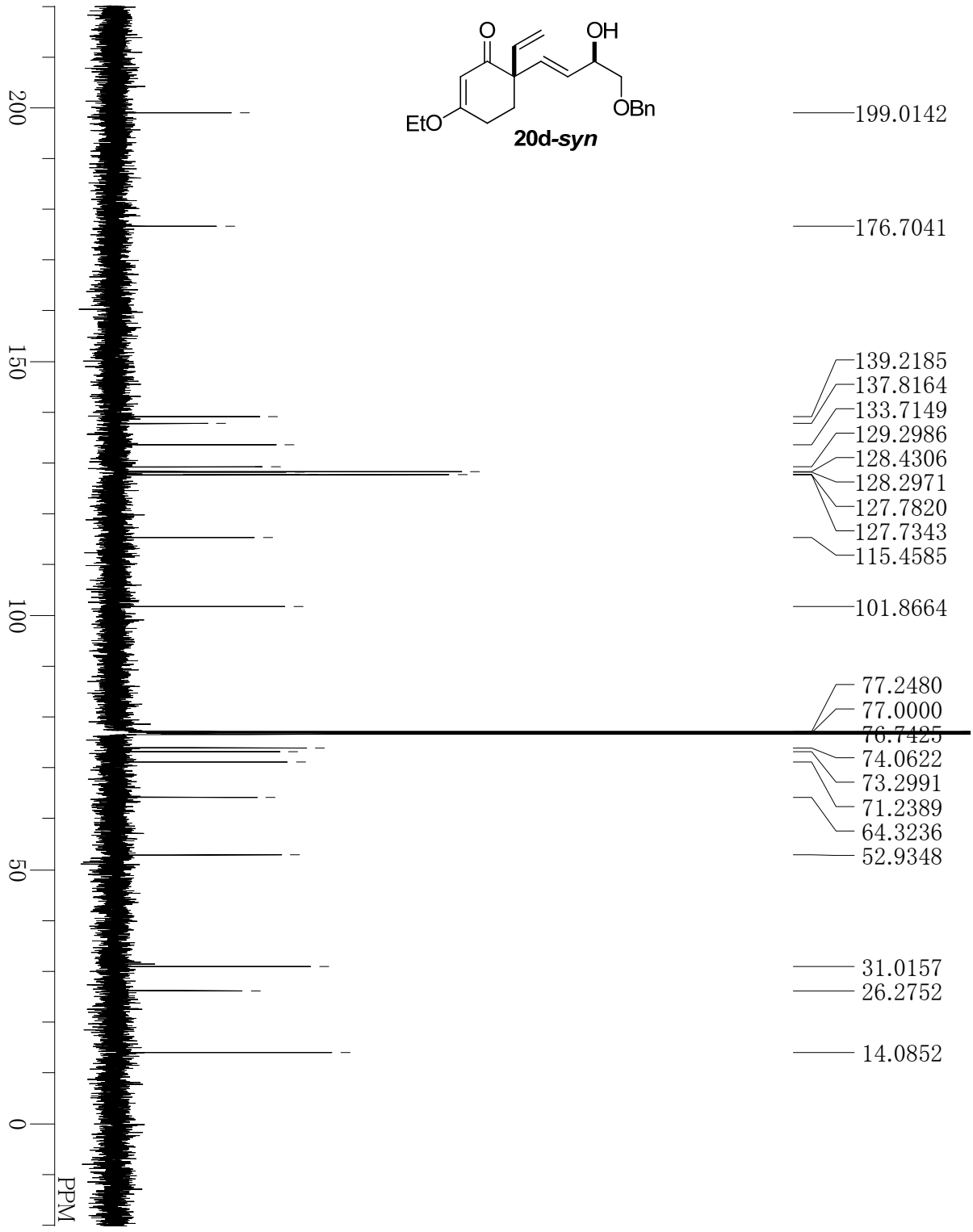


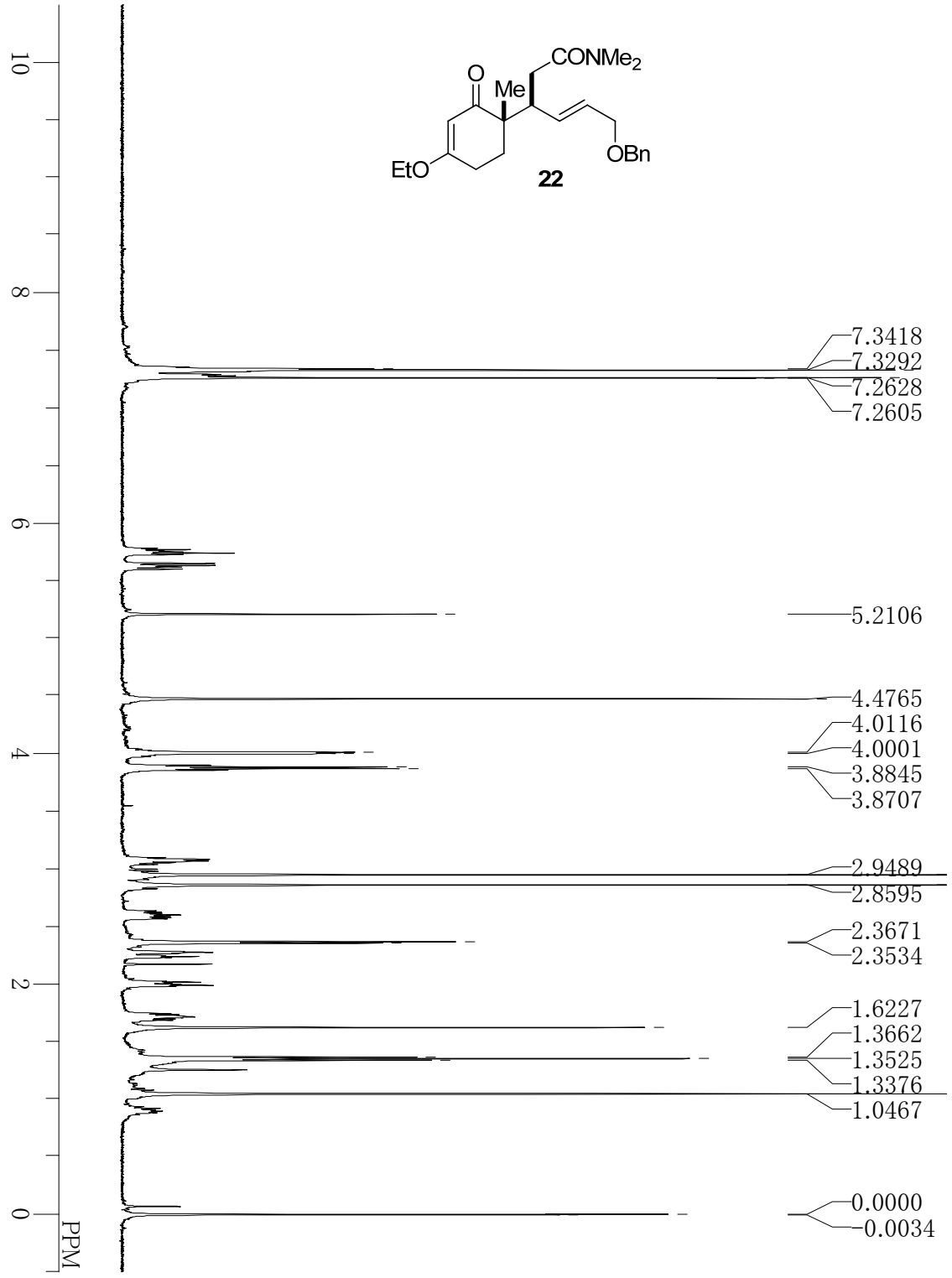


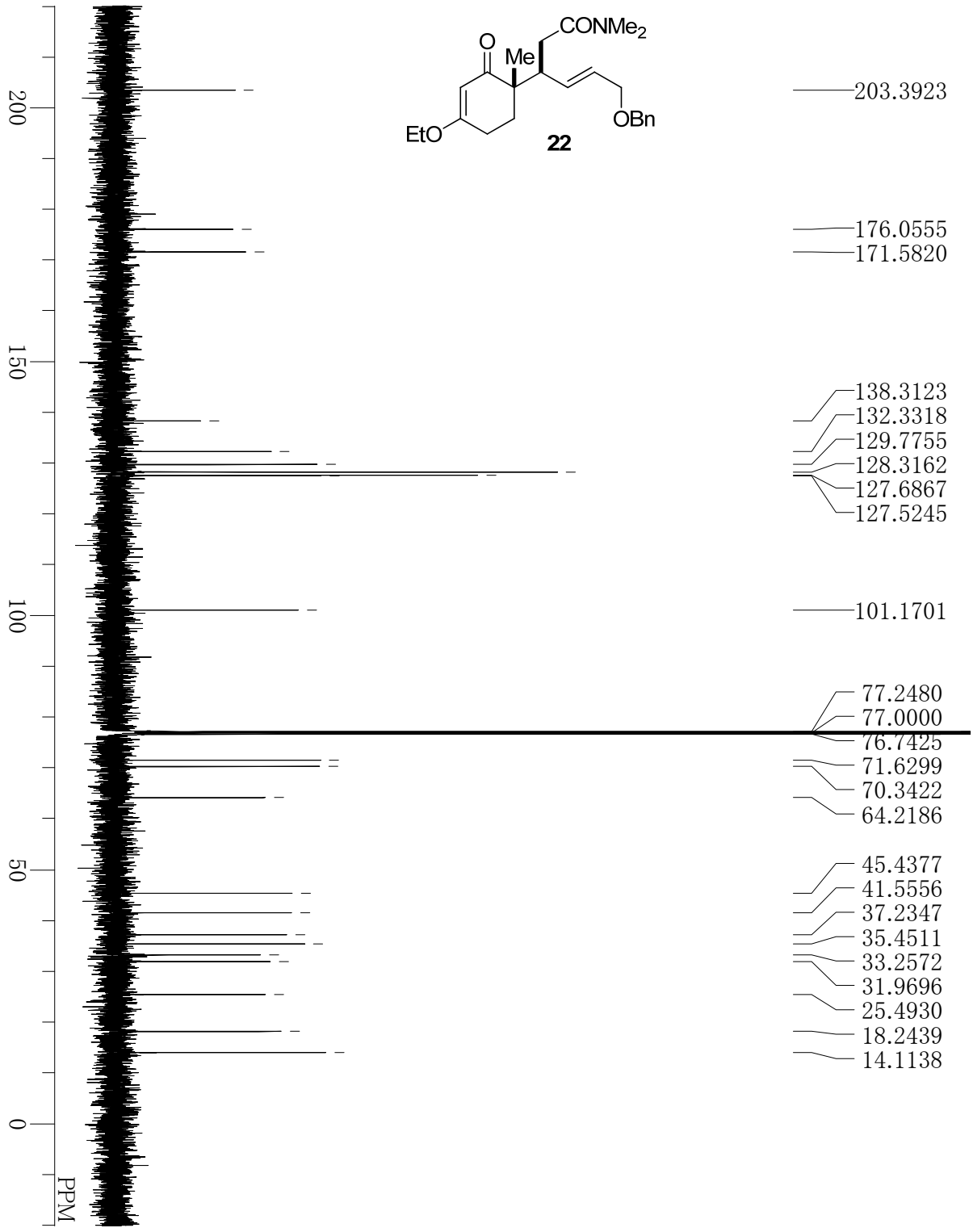


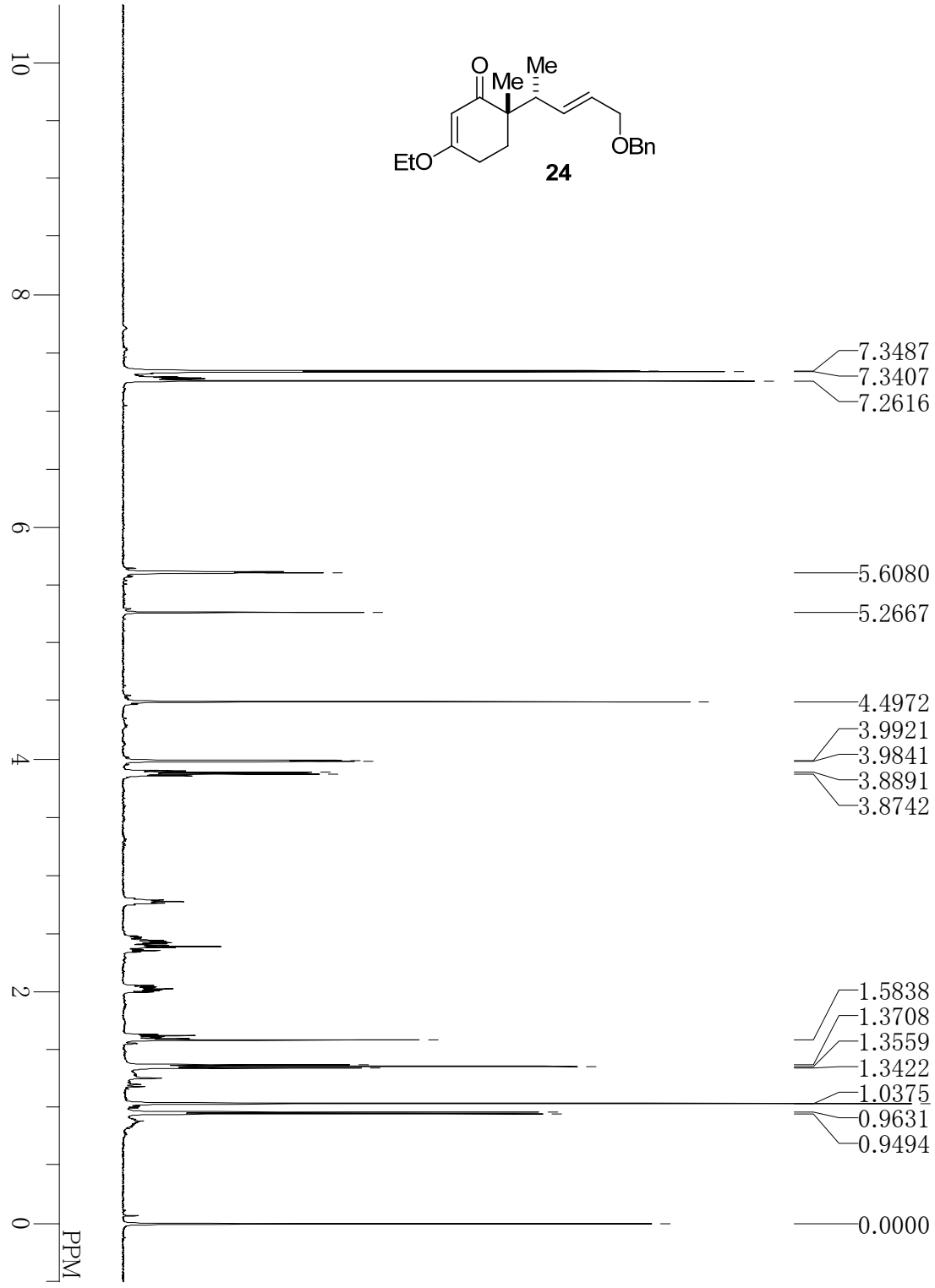


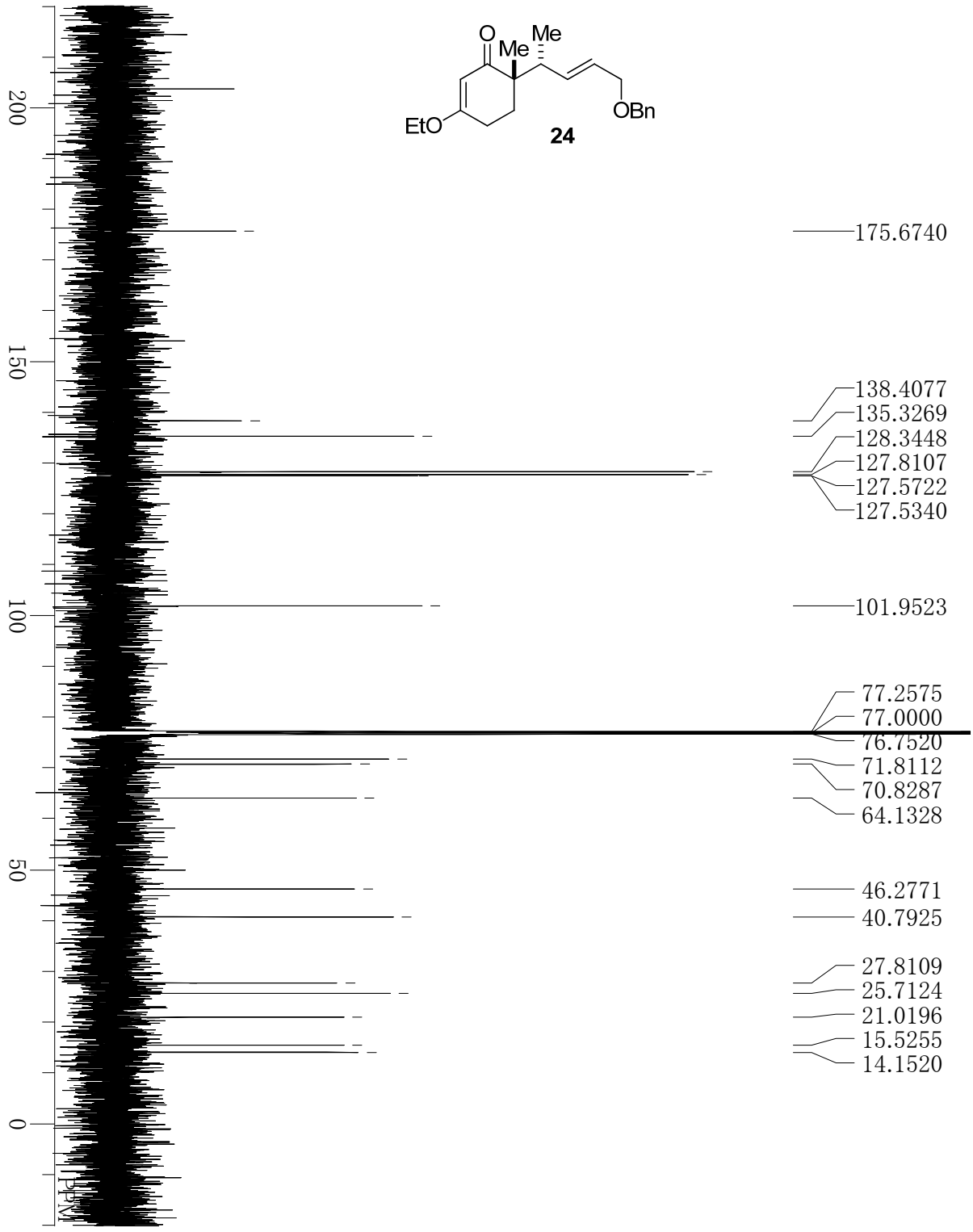


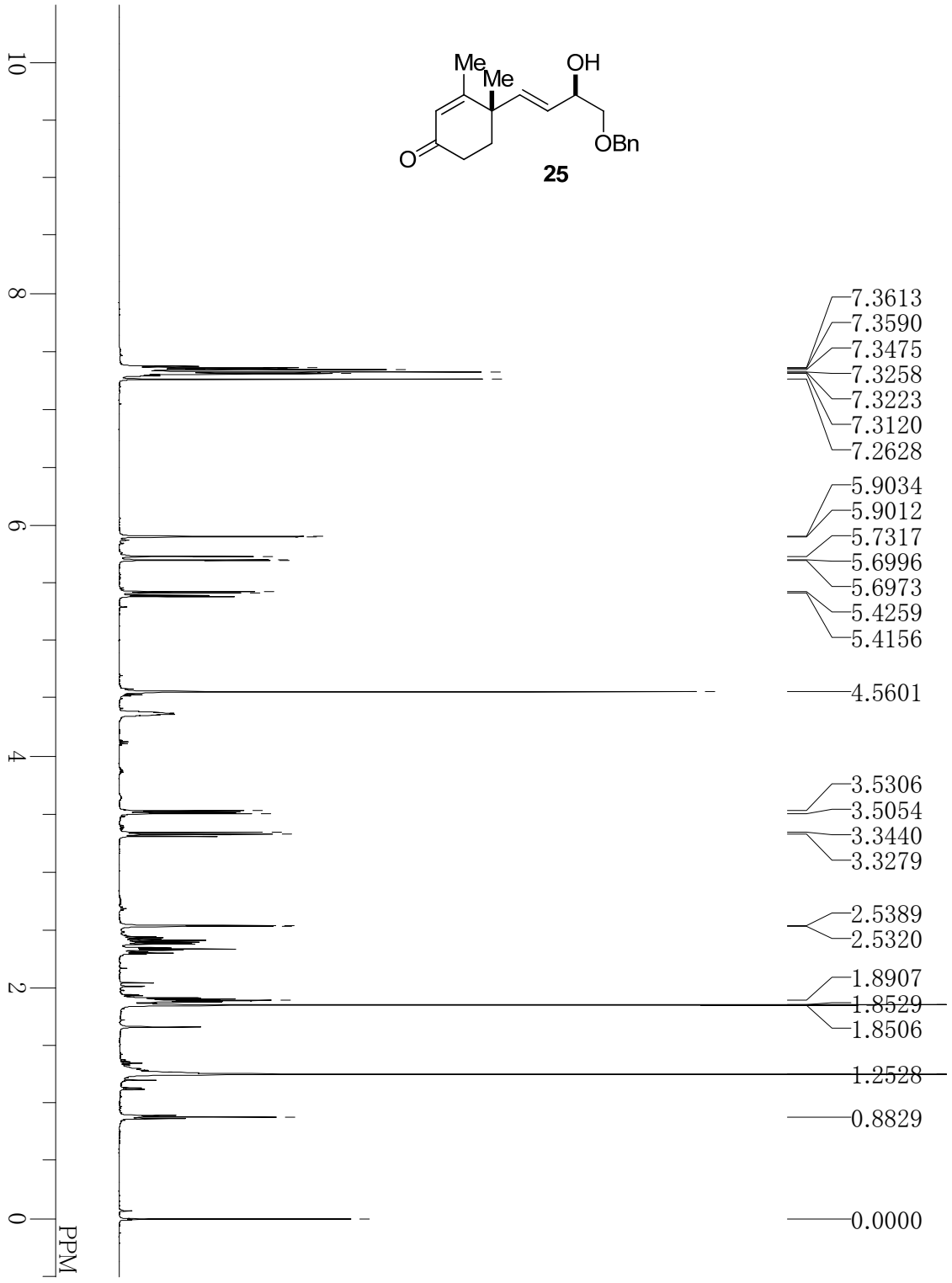


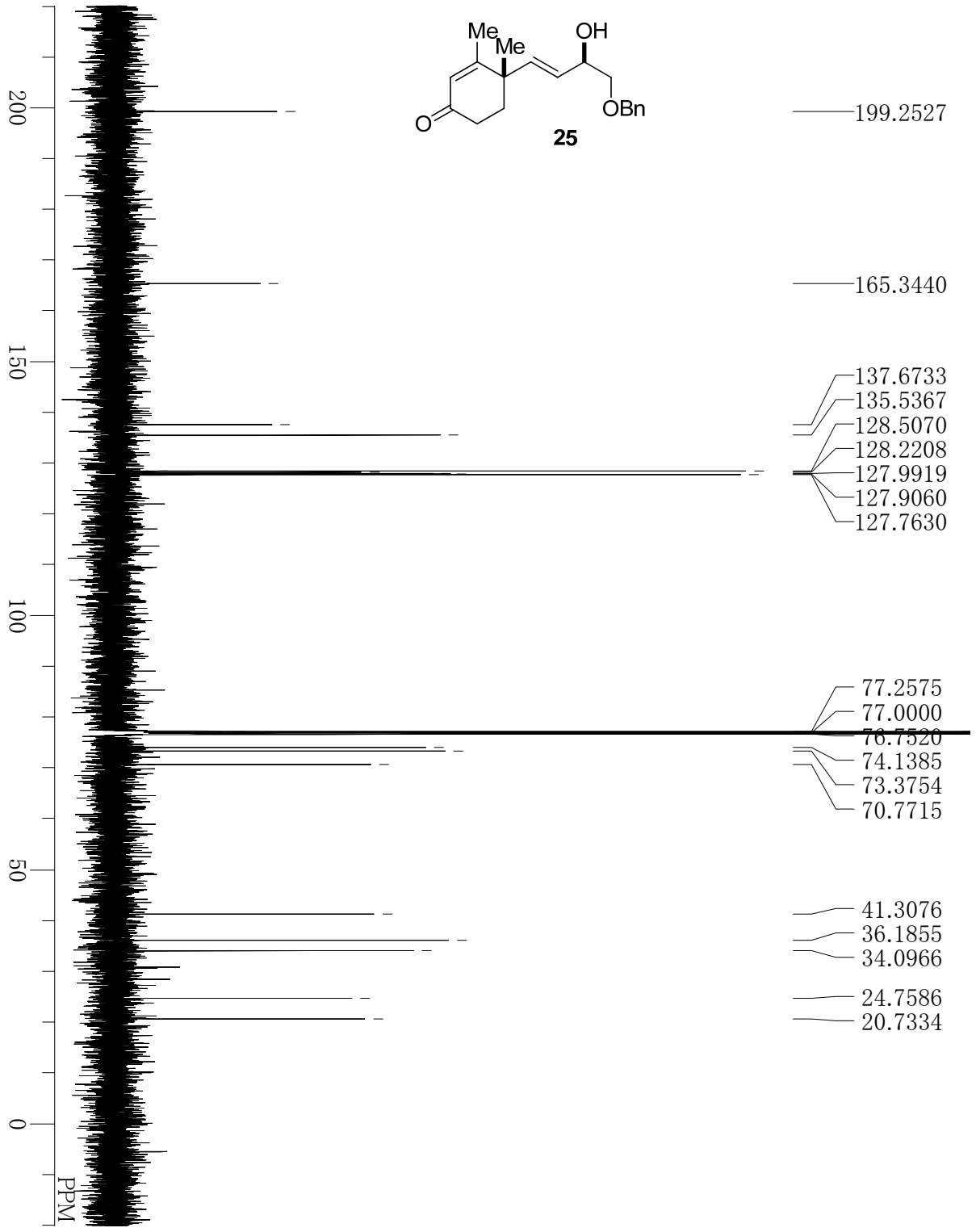


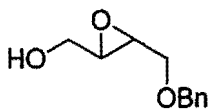












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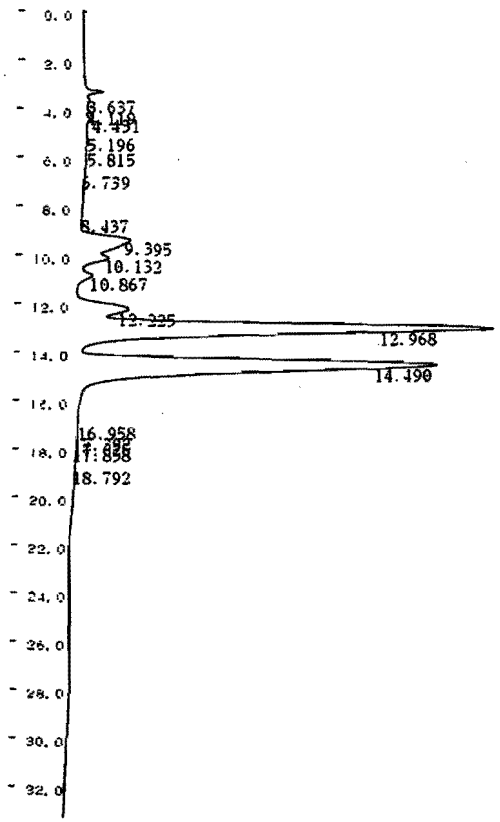
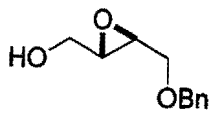


** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	1	3.637	95	12			0.0511	
	2	4.119	105	21			0.056	
	3	4.431	237	27			0.1268	
	4	5.196	24	5			0.0127	
	5	5.815	22	5			0.0115	
	8	9.395	11189	301			5.9909	
	9	10.132	4024	177	V		2.1543	
	10	10.867	2042	90	V		1.0933	
	11	12.225	10391	313			5.5636	
	12	12.968	77203	2473	V		41.3359	
	13	14.49	81192	2137	SV		43.4717	
	14	16.958	12	2	T		0.0062	
	15	17.392	65	4	TV		0.0349	
	16	17.625	47	5	TV		0.0253	
	17	17.858	57	4	TV		0.0305	
	18	18.792	66	3	TV		0.0354	
		TOTAL	186770	5577			100	

C-R&A CHROMATOPAC CH=1 Report No.=7 DATA=1:@CHROM1.C06 10/02/27 12:45:12



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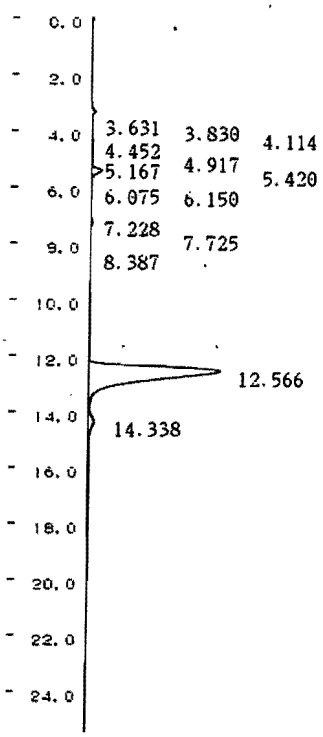
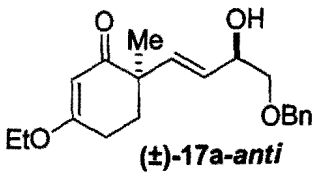


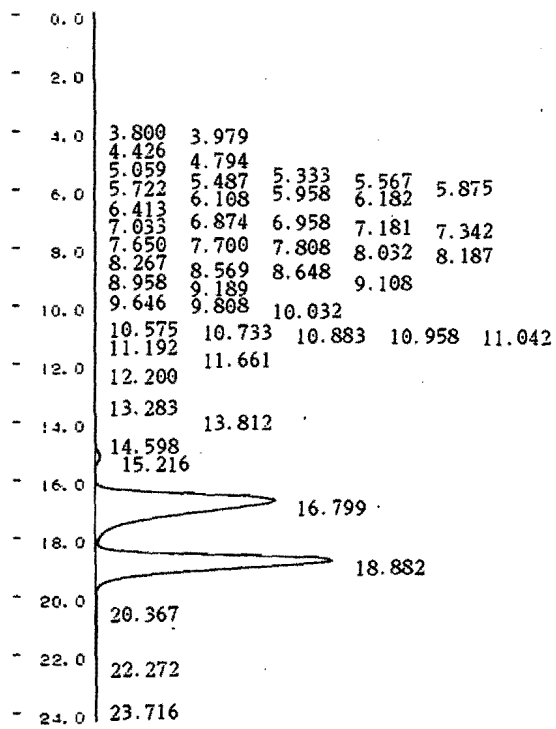
** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	1	3.631	133	20			0.0719	
	2	3.83	234	35	V		0.1264	
	3	4.114	63	11			0.0343	
	4	4.452	94	13			0.0508	
	8	4.917	27	4			0.0145	
	9	5.167	32	9	V		0.0171	
	10	5.42	5909	434	SV		3.1933	
	13	6.075	26	6	TV		0.0142	
	14	6.15	13	5	TV		0.0068	
	16	7.228	1362	74	S		0.7363	
	17	7.725	12	2	T		0.0062	
	19	8.387	86	7	V		0.0466	
	20	12.566	169587	5372			91.6553	
	21	14.338	7450	207	SV		4.0264	
		TOTAL	185027	6198			100	

C-R8A CHROMATOPAC CH=1 Report No.=10 DATA=1:@CHRM1.C08 10/02/27 14:09:



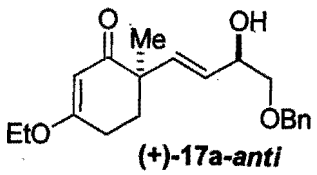
(±)-17a-*anti*



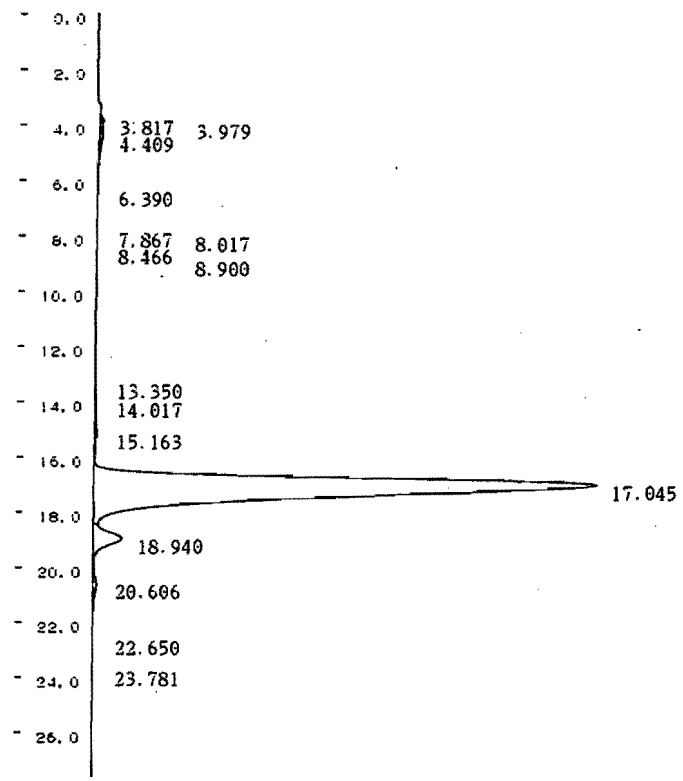
** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	51	15.216	41231	1575	V		0.7951	
	52	16.799	2613596	56305			50.4018	
	53	18.882	2494240	74121	SV		48.1001	
	54	20.367	4813	128	T		0.0928	
	55	22.272	5498	148	T		0.106	
	56	23.716	13114	431	T		0.2529	
		TOTAL	5185520	133518			100	

C-R8A CHROMATOPAC CH=1 Report No.=26 DATA=1:@CHRM1.C21 10/03/08 21:02



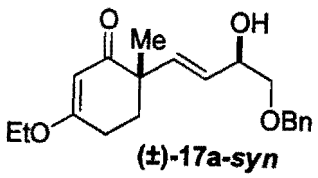
(+)-17a-*anti*



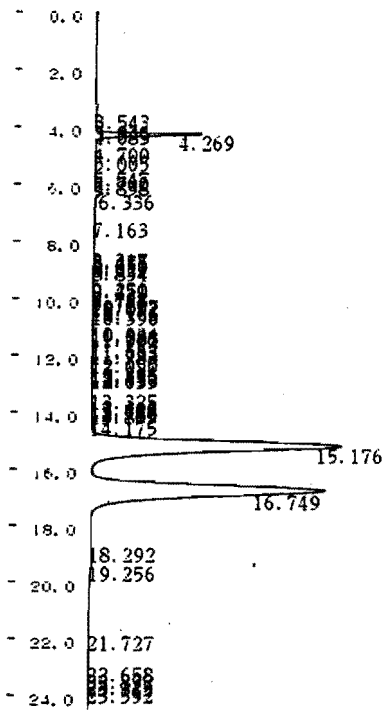
** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	1	3.817	1597	161			0.1589	
	2	3.979	2893	150	V		0.2879	
	3	4.409	4436	153	V		0.4415	
	4	6.39	50	7			0.0049	
	5	7.867	104	11			0.0103	
	6	8.017	109	17	V		0.0108	
	7	8.466	1133	30	V		0.1128	
	8	8.9	595	22	V		0.0592	
	9	13.35	31	3			0.0031	
	10	14.017	679	32	V		0.0675	
	11	15.163	5427	95	V		0.5402	
	12	17.045	940470	20773	V		93.6098	
	13	18.94	39296	1167	V		3.9113	
	14	20.606	6857	157	V		0.6825	
	15	22.65	322	7	V		0.0321	
	16	23.781	674	9	V		0.067	
		TOTAL	1004671	22793			100	

C-R8A CHROMATOPAC CH=1 Report No.=30 DATA=1:@CHRM1.C22 10/03/08 21:53:



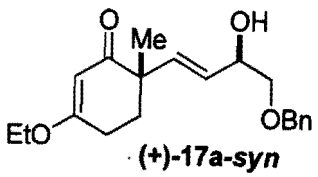
(±)-17a-*syn*



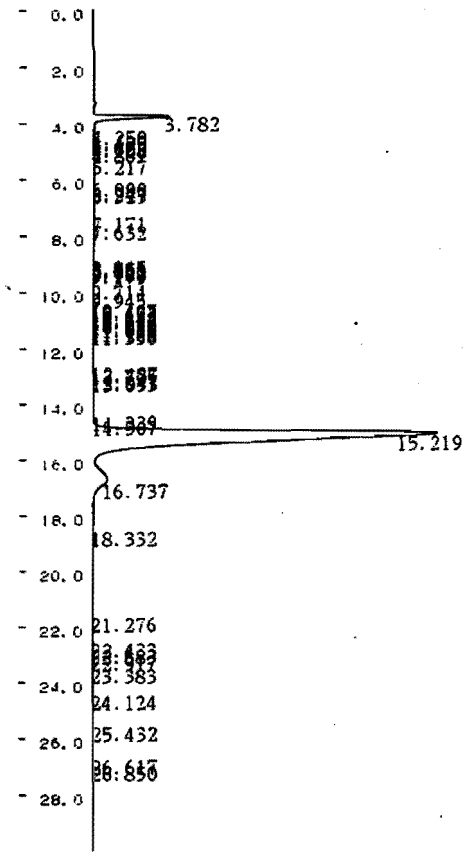
** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	1	3.543	54	14			0.0094	
	2	3.93	66	11			0.0115	
	4	4.269	30888	4307	S		5.3529	
	6	5.005	77	13	T		0.0134	
	7	5.547	10	4			0.0018	
	39	13.708	10	6	V		0.0018	
	42	14.175	28	4			0.0048	
	43	15.176	266029	10143	V		46.1033	
	44	16.749	270803	9478	V		46.9305	
	45	18.292	1084	30	V		0.1878	
	46	19.256	3799	81	V		0.6584	
	47	21.727	240	9			0.0415	
	48	22.658	38	3			0.0066	
	49	22.892	82	6	V		0.0142	
	50	23.125	85	8	V		0.0147	
	51	23.343	50	10	V		0.0086	
	52	23.592	182	9	V		0.0316	
		TOTAL	577030	24563			100	

C-R8A CHROMATOPAC CH=1 Report No.=3 DATA=1:@CHRM1.C03 10/03/10 11:34



(+)-17a-*syn*



** CALCULATION REPORT **

CH	PKNO	TIME	AREA	HEIGHT	MK	IDNO	CONC	NAME
1	1	3.782	25288	3102	S		6.0269	
	9	6.09	13	4			0.0031	
	35	14.567	31	7	V		0.0075	
	36	15.219	367991	14219	V		87.7037	
	37	16.737	24091	598	V		5.7416	
	38	18.332	518	13	V		0.1235	
	39	21.276	54	4			0.0129	
	40	22.433	58	4			0.0138	
	41	22.683	24	3	V		0.0056	
	43	23.383	35	2	V		0.0083	
	44	24.124	187	6	V		0.0446	
	45	25.432	1013	19	V		0.2414	
	46	26.617	48	3	V		0.0114	
		TOTAL	419584	18042			100	

C-R8A CHROMATOPAC CH=1 Report No.=4 DATA=1:@CHRM1.C04 10/03/10 12:44: