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Supporting Information

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Supporting Information-1

Total Synthesis of (+)-Neopeltolide via Prins Macrocyclization

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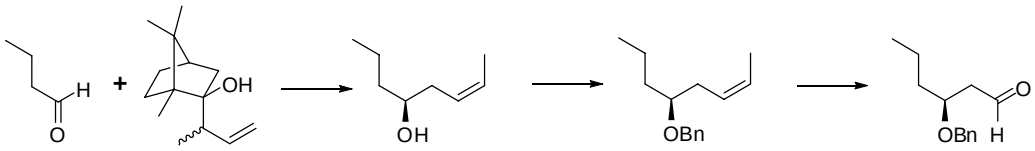
General Information

^{1}H- and ^{13}C-NMR spectra were obtained on a Bruker DPX-300 (300 MHz), a Bruker Avance-600 (600 MHz), and a Varian/Oxford As-500 (500 MHz) spectrophotometer. Chemical shift values were recorded as parts per million relative to tetramethylsilane as an internal standard unless otherwise indicated, and coupling constants in Hertz. Mass spectra were recorded on a JEOL JMS 600W spectrometer using electron impact (EI) or chemical ionization (CI) method, and a JEOL JMS AX505WA spectrometer using fast atom bombardment (FAB) method. Significant fragments are reported in the following fashion: *m*/*z* (relative intensity). Optical rotation data were obtained on a JASCO P-1030 automatic polarimeter.

The progress of reaction was checked on TLC plates (Merck 5554 Kiesel gel 60 F254), and the spots were visualized under 254 nm UV light and/or charring after dipping the TLC plates into a vanillin solution (9.0 g of vanillin and 1.5 mL of concentrated sulfuric acid in 300 mL of MeOH), a $KMnO_4$ solution (3 g of $KMnO_4$, 20 g of K_2CO_3, and 5 mL of 5% NaOH solution in 300 mL of water), or a phosphomolybdic acid solution (250 mg phosphomolybdic acid in 50 mL EtOH). Column chromatography was performed on silica gel (Merck 9385 Kiesel gel 60) using hexanes-EtOAc (v/v). The solvents were simple distilled unless otherwise noted.

Unless otherwise specified, all reactions were conducted under a slight positive pressure of dry nitrogen. The usual work-up refers to washing the quenched reaction mixture with brine, drying the organic extracts over anhydrous $MgSO_4$ and evaporating under reduced pressure using a rotary evaporator.

All solvents used in reactions were dried under nitrogen atmosphere. THF was distilled from Na-benzophenone and CH_2Cl_2 was distilled from P_2O_5. Benzene was washed with conc. H_2SO_4, distilled from Na-benzophenone, and stored over 4 Å molecular sieves. Et_2O was distilled from LAH. Pyridine and TEA was distilled over KOH and stored over 4 Å molecular sieves.



3 **4** **3A** **3B** **5**

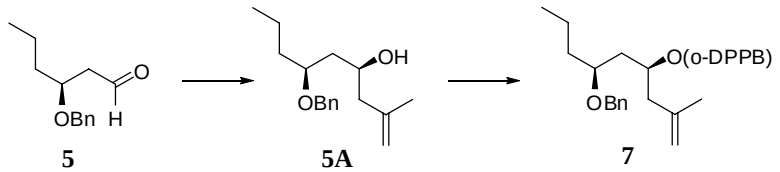
Aldehyde **5**

Camphorsulfonic acid (60 mg, 0.26 mmol), alcohol **4** (1.6 g, 7.86 mmol) were added to a solution of aldehyde **3** (0.24 mL, 2.62 mmol) in CH_2Cl_2 (0.4 mL) at room temperature. This mixture was stirred at room temperature for 3 days, and the reaction mixture was concentrated under reduced pressure. Purification of residue by flash column chromatography (hexanes-EtOAc, 10:1) provided alcohol **3A** (245mg, 73%). R_f 0.40 (hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.69–5.62 (m, 1 H), 5.47–5.42 (m, 1 H), 3.66–3.60 (m, 1 H), 2.23 (t, J = 6.8 Hz, 2 H), 1.65 (d, J = 6.5 Hz, 3 H), 1.51–1.44 (m, 3 H), 1.40–1.35 (m, 1 H), 0.93 ppm (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 127.5, 126.4, 71.5, 39.3, 35.2, 19.2, 14.3, 13.3 ppm; IR (neat): ν_{max} = 3478, 2958, 2872, 1748, 1455, 1360, 1173, 1055, 941, 610 cm^{-1}; MS *m*/*z* (CI, relative intensity): 127 (M^+−1, 54), 111 (36), 101 (10), 73 (100), 55 (32); HRMS (CI) calcd. for $C_8H_{15}O$ (M^+−1) 127.1123, found 127.1123; $[\alpha]^{28}_D$ +3.12 (*c* 1.00, $CHCl_3$).

NaH (60% dispersion in mineral oil, 305 mg, 7.65 mol), BnBr (1.13 mL, 9.56 mmol), TBAI(212 mg, 0.57 mmol) were added to a solution of alcohol **3A** (245 mg, 1.91 mmol) in THF-DMF (5:1, 5.0 mL) at 0 °C and the reaction mixture was allowed to warm to room temperature. After 12 h, the reaction was quenched by addition of sat. NH_4Cl solution (2 mL). The reaction mixture was extracted with Et_2O (10 mL x 3). The organic extracts were washed with brine (10 mL x 3), dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 30:1) gave benzyl ether **3B** (195 mg, 75%). R_f 0.72 (hexanes-EtOAc, 20:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.24 (m, 5 H), 5.57–5.52 (m, 1 H), 5.49–5.43 (m, 1 H), 4.85 and 4.49 (ABq, J_{AB} = 11.5 Hz, 2 H), 3.46–3.41 (m, 1 H), 2.36–2.28 (m, 2 H), 1.63 (d, J = 8.5 Hz, 3 H), 1.55–1.43 (m, 3 H), 1.38–1.33 (m, 1 H), 0.90 ppm (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.3, 128.5, 128.0, 127.6, 126.8, 125.8, 79.0, 71.2, 36.5, 31.5, 19.0, 14.5, 13.2 ppm; IR (neat): ν_{max} = 3064, 3024, 2958, 2932, 2870, 1741, 1657, 1605, 1496, 1455, 1206, 1070, 1028, 909, 816, 696 cm^{-1}; MS *m*/*z* (CI, relative intensity): 219 (M^++1, 5), 201 (12), 201 (12), 191 (11), 175 (3), 163 (14), 145

(3), 131 (5), 111 (54), 91 (67), 75 (100); HRMS (CI) calcd. for $C_{15}H_{23}O$ (M^++1) 219.1749, found 219.1749; $[\alpha]^{28}_D$ −25.6 (*c* 1.00, $CHCl_3$).

O_3 was introduced to a stirred solution of benzyl ether **3B** (195 mg, 0.89 mmol) in CH_2Cl_2 (9 mL) over a period of 30 min at –78 °C. Following addition of PPh_3 (700 mg, 2.67 mmol), the reaction mixture was allowed to warm to room temperature. After stirring for 3 h, solvent was evaporated and the residue was purified by flash column chromatography (hexanes-EtOAc, 20:1) to give aldehyde **5** (156 mg, 85%). R_f 0.41 (hexanes-EtOAc, 8:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.80 (dd, J = 2.0 Hz, J = 3.0 Hz, 1 H), 7.36–7.26 (m, 5 H), 4.56 and 4.52 (ABq, J_{AB} = 11.5 Hz, 2 H), 3.98–3.93 (m, 1 H), 2.70–2.65 (m, 1 H), 2.58–2.54 (m, 1 H), 1.71–1.64 (m, 1 H), 1.59–1.51 (m, 1 H), 1.45–1.36 (m, 2 H), 0.93 ppm (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.0, 138.5, 128.7, 128.0, 127.9, 74.4, 71.5, 48.5, 36.7, 18.6, 14.3 ppm; IR (neat): ν_{max} = 3427, 3088, 3064, 3031, 2959, 2726, 1725, 1604, 1455, 1383, 1354, 1206, 1096, 1027, 915, 850, 736, 606 cm^{-1}; MS *m*/*z* (CI, relative intensity): 207 (M^++1, 4), 189 (2), 163 (16), 119 (5), 115 (5), 107 (10), 99 (19), 91 (100), 84 (5), 75 (18), 57 (6); HRMS (CI) calcd. for $C_{13}H_{19}O_2$ (M^++1) 207.1385, found 207.1385; $[\alpha]^{28}_D$ +14.5 (*c* 1.00, $CHCl_3$).



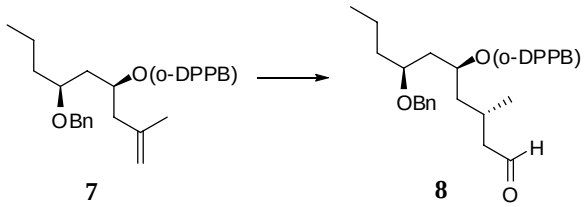
5 **5A** **7**

Ester **7**

$TiCl_4$ (1.0 M in CH_2Cl_2, 0.4 mL) was added to a solution of aldehyde **5** (70 mg, 0.34 mmol) in CH_2Cl_2 (3.4 mL) at –78 °C under N_2. After 5 min, $CH_2C(CH_3)CH_2TMS$ (0.60 ml, 3.4 mmol) was added to the solution, and the resulting solution was stirred for 1 h at –78 °C. The reaction was quenched by addition of saturated $NaHCO_3$ solution (5 mL). The reaction mixture was extracted with CH_2Cl_2 (10 mL x 3), and the organic extracts were dried over $MgSO_4$, filtered and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc 10:1) gave alcohol **5A** (87 mg, 98%). R_f 0.41 (hexanes-EtOAc, 8:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.35–7.26 (m, 5 H), 4.84 (s, 1 H), 4.76 (s, 1 H), 4.59 and 4.54 (ABq, J_{AB} = 11.5 Hz, 2 H), 4.06–4.04 (m, 1 H), 3.76–3.71 (m, 1 H), 2.60 (d, J = 3.0 Hz, 3 H), 2.19 and 2.13 (ABX, J_{AB} = 16.2 Hz, J_{AX} = 8.0 Hz, J_{BX} = 5.0 Hz, 2 H), 1.75 (s, 3 H), 1.72–1.61 (m, 3 H), 1.55–1.48 (m, 1 H), 1.43–1.35 (m, 1 H), 0.93 ppm (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ =

143.1, 138.8, 128.6, 128.1, 127.9, 113.3, 77.1, 71.6, 66.2, 46.6, 40.4, 36.3, 22.7, 18.9, 14.5 ppm; IR (neat): ν_{max} = 3465, 3069, 3030, 2933, 2871, 1646, 1496, 1454, 1382, 1207, 1068, 889 cm^{-1}; MS *m/z* (CI, relative intensity): 263 (M^++1, 100), 297 (8), 277 (4), 245 (30), 227 (10), 207 (85), 189 (8), 163 (37), 153 (8), 137 (49), 119 (11), 91 (84); HRMS (CI) calcd. for $C_{17}H_{27}O_2$ (M^++1) 263.2011, found 263.2012; $[\alpha]^{28}_D$ +36.1 (*c* 1.00, $CHCl_3$).

2-(Diphenylphosphino)benzoic acid (350 mg, 1.14 mmol), DCC (470 mg, 2.28 mmol), DMAP (50 mg, 0.38 mmol) were added to a solution of alcohol **5A** (200 mg, 0.76 mmol) in CH_2Cl_2 (7.6 mL) at room temperature. This mixture was stirred at room temperature for 15 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexanes-EtOAc, 20:1) provided ester **7** (337mg, 80%). R_f 0.62 (hexanes-EtOAc, 8:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.05–8.03 (m, 1 H), 7.39–7.20 (m, 17 H), 6.91–6.88 (m, 1 H), 5.52–5.47 (m, 1 H), 4.69 (s, 1 H), 4.65 (s, 1 H), 4.33 and 4.24 (ABq, J_{AB} = 10.5 Hz, 2 H), 3.37–3.33 (m, 1 H), 2.26 and 2.11 (ABX, J_{AB} = 16.5 Hz, J_{AX} = 7.2 Hz, J_{BX} = 6.2 Hz, 2 H), 1.71–1.54 (m, 2 H), 1.67 (s, 3 H), 1.51–1.46 (m, 1 H), 1.43–1.39 (m, 1 H), 1.37–1.27 (m, 2 H), 0.90 ppm (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 142.0, 140.5, 140.3, 139.1, 138.7, 138.6, 138.5, 135.2, 135.0, 134.6, 134.5, 134.4, 134.0, 133.9, 131.9, 130.9, 130.9, 128.8, 128.7, 128.7, 128.7, 128.7, 128.6, 128.5, 128.4, 128.4, 127.6, 113.7, 75.9, 72.0, 71.1, 43.8, 39.7, 36.8, 22.7, 18.5, 14.6 ppm; IR (neat): ν_{max} = 3848, 3733, 3646, 3068, 2959, 2870, 2350, 2317, 1714, 1714, 1647, 1585, 1455, 1383, 1270, 1055, 892, 846 cm^{-1}; MS *m/z* (CI, relative intensity): 551 (M^++1, 100), 579 (9), 567 (9), 507 (1), 473 (3), 461 (5), 335 (3), 323 (11), 305 (18), 245 (10), 137 (5), 107 (23); HRMS (CI) calcd. for $C_{36}H_{40}O_3P$ (M^++1) 551.2715, found 551.2716; $[\alpha]^{27}_D$ +74.8 (*c* 1.00, $CHCl_3$).

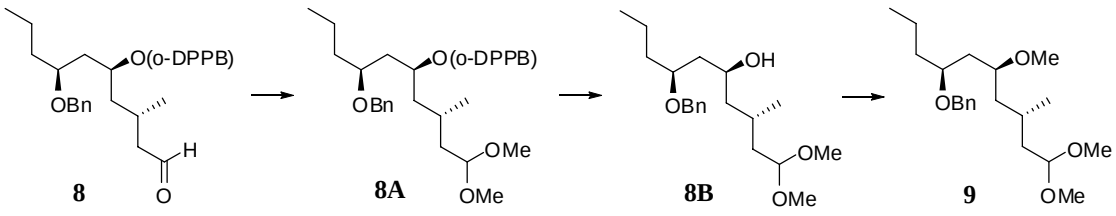


7 **8**

Aldehyde **8**

To a solution of $Rh(CO)_2(acac)$ (46 mg, 0.18 mmol) in toluene (1 mL) was added $P(OPh)_3$ (0.23 mL, 0.90 mmol) and the reaction mixture was stirred at room

temperature. The intense yellow color faded after 10 min. At this time the ester **7** (330 mg, 0.60 mmol) in toluene (5 mL) was added and the reaction mixture was then transferred into a well-dried, argon-purged autoclave. The argon atmosphere was removed by pressurizing/depressurizing cycle (three times 5 bar H_2/CO), and finally the autoclave was pressurized with 40 bar H_2/CO and heated in an oil bath to 30 ^oC for 14 days. Subsequently the autoclave was cooled to room temperature, depressurized and the solution was filtered through a silica-pad and rinsed with ether. The solvent was removed in vacuo and separation of the product mixture (d.r. = ~5:1) by flash column chromatography (hexanes-EtOAc, 10:1) provided aldehyde **8** (227 mg, 65%). R_f 0.32 (hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.63 (t, J = 2.3 Hz, 1 H), 8.10–8.07 (m, 1 H), 7.42–7.22 (m, 17 H), 6.91–6.89 (m, 1 H), 5.44–5.41 (m, 1 H), 4.35 and 4.24 (ABq, J_{AB} = 10.5 Hz, 2 H), 3.33–3.30 (m, 1 H), 2.27–2.22 (m, 1 H), 2.17–2.12 (m, 1 H), 2.01–1.97 (m, 1 H), 1.59 (t, J = 6.0 Hz, 2 H), 1.55–1.25 (m, 6 H), 0.90 (d, J = 6.5 Hz, 3 H), 0.89 ppm (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.9, 202.9, 166.9, 166.9, 140.5, 140.3, 139.0, 138.5, 138.4, 134.9, 134.7, 134.7, 134.4, 134.2, 134.1, 134.0, 132.2, 131.1, 131.1, 128.9, 128.8, 128.8, 128.7, 128.5, 128.5, 127.7, 76.0, 71.9, 71.1, 51.4, 42.6, 40.7, 36.6, 30.6, 25.1, 19.9, 19.4, 14.6 ppm; IR (neat): ν_{max} = 2926, 2855, 1714, 1585, 1462, 1434, 1382, 1252, 1105, 1056, 746, 697, 543 cm^{-1}; MS *m*/*z* (CI, relative intensity): 581 (M^++1, 100), 609 (10), 597 (80), 553 (1), 503 (1), 323 (1), 305 (11), 107 (2); HRMS (CI) calcd. for $C_{37}H_{42}O_4P$ (M^++1) 581.2821, found 581.2821; $[\alpha]^{26}_D$ +22.9 (*c* 1.50, $CHCl_3$).



Dimethyl acetal **9**

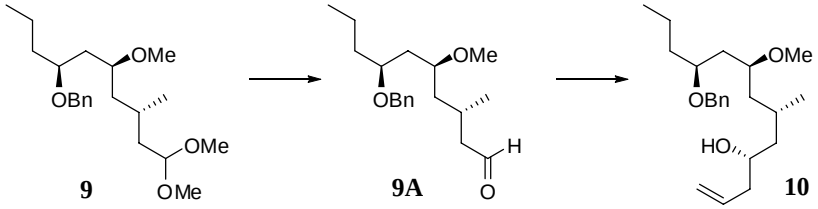
Conc. H_2SO_4 (2 drops) was added to a solution of aldehyde **8** (250 mg, 0.43 mmol) in trimethyl orthoformate (8.6 mL) and MeOH (8.6 mL) at room temperature. After 30 min, the reaction mixture was quenched by TEA (1.0 mL) and concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexanes-EtOAc, 15:1) provided acetal **8A** (194 mg, 72%). R_f 0.32 (hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.08–8.06 (m, 1 H), 7.40–7.22 (m, 17 H), 6.91–6.88 (m, 1 H), 5.46–5.41 (m, 1 H), 4.42 (t, J = 5.7 Hz, 1 H), 4.31 and 4.23 (ABq, J_{AB} =

11.0 Hz, 2 H), 3.30–3.25 (m, 1 H), 3.26 (s, 3 H), 3.24 (s, 3 H), 1.64–1.52 (m, 5 H), 1.48–1.20 (m, 6 H), 0.89 (d, J = 13.5 Hz, 3 H), 0.87 ppm (t, J = 6.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 140.5, 140.4, 139.1, 138.7, 138.6, 138.6, 138.5, 135.1, 135.0, 134.6, 134.5, 143.3, 134.1, 133.9, 132.0, 130.9, 130.9, 128.8, 128.7, 128.7, 128.7, 128.6, 128.5, 128.4, 127.6, 103.2, 76.1, 71.9, 71.3, 52.9, 52.4, 43.0, 40.7, 40.1, 36.7, 30.6, 26.0, 19.9, 18.4, 14.6 ppm; IR (neat): ν_{max} = 2931, 1709, 1461, 1434, 1252, 1126, 1056, 745, 697, 502 cm^{-1}; MS *m*/*z* (CI, relative intensity): 627 (M^++1, 37), 655 (16), 639 (3), 611 (18), 595 (100), 549 (2), 517 (3), 351 (3), 323 (8), 305 (31), 289 (4), 107 (8); HRMS (CI) calcd. for $C_{39}H_{48}O_5P$ (M^++1) 627.3239, found 627.3238; $[\alpha]^{26}_D$ +108.8 (*c* 0.33, $CHCl_3$).

KOH (170 mg, 3.03 mmol) was added to a solution of acetal **8A** (190 mg, 0.30 mmol) in EtOH(3 mL). This reaction mixture was heated under reflux. After 3 h, the reaction mixture was diluted with Et_2O (6 mL), and poured into sat. NH_4Cl solution (4 mL). The reaction mixture was extracted with Et_2O (10 mL x 3), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 8:1) provided alcohol **8B** (101 mg, 99%). R_f 0.31 (hexanes-EtOAc, 2:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.34–7.26 (m, 5 H), 4.58 and 4.52 (ABq, J_{AB} = 11.5 Hz, 2 H), 4.47 (t, J = 5.7 Hz, 1 H), 4.00–3.96 (m, 1 H), 3.73–3.68 (m, 1 H), 3.31 (s, 3 H), 3.30 (s, 3 H), 2.65 (bs, 1 H), 1.83–1.79 (m, 1 H), 1.74–1.63 (m, 2 H), 1.65–1.56 (m, 2 H), 1.46–1.40 (m, 1 H), 1.41–1.33 (m, 2 H), 1.17–1.11 (m, 1 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.93 ppm (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.7, 128.7, 128.1, 127.9, 103.3, 77.1, 71.4, 66.4, 52.9, 52.6, 45.5, 40.9, 40.4, 36.0, 26.1, 20.0, 19.0, 14.5 ppm; IR (neat): ν_{max} = 3788, 3470, 3419, 2940, 2345, 2292, 2094, 1646, 1383, 1128, 1035, 756 cm^{-1}; MS *m*/*z* (FAB, relative intensity): 339 (M^++1, 3), 307 (5), 305 (3), 275 (38), 271 (2), 219 (2), 199 (4), 169 (30), 154 (22), 137 (20), 107 (15), 91 (100), 85 (35), 55 (25), 41 (15); HRMS (FAB) calcd. for $C_{20}H_{35}O_4$ (M^++1) 339.2535, found 339.2532; $[\alpha]^{28}_D$ +18.1 (*c* 1.00, $CHCl_3$).

NaH (60% dispersion in mineral oil, 60 mg, 1.50 mol), MeI (0.15 mL, 2.40 mmol) were added to a solution of alcohol **8B** (100 mg, 0.30 mmol) in THF (1.5 mL) at 0 ^{o}C and the reaction mixture was allowed to warm to room temperature. After 12 h, the reaction was quenched by addition of sat. NH_4Cl solution (2 mL). The reaction mixture was extracted with Et_2O (10 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 20:1) gave dimethyl acetal **9** (92 mg, 87%). R_f 0.62

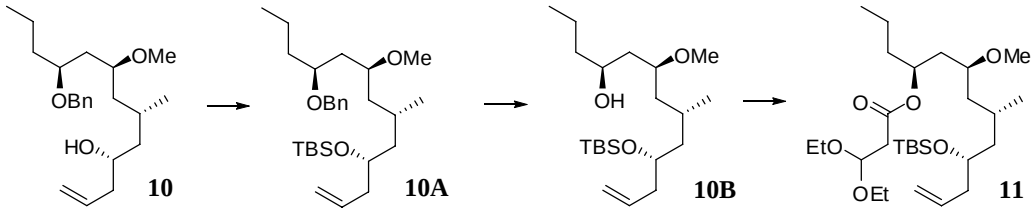
(hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.36–7.28 (m, 5 H), 4.57 and 4.46 (ABq, J_{AB} = 11.5 Hz, 2 H), 4.46 (t, J = 5.8 Hz, 1 H), 3.61–3.57 (m, 1 H), 3.50–3.45 (m, 1 H), 3.31 (s, 3 H), 3.27 (s, 3 H), 3.26 (s, 3 H), 1.76–1.71 (m, 1 H), 1.67–1.55 (m, 4 H), 1.42–1.36 (m, 4 H), 1.21–1.16 (m, 1 H), 0.95 (d, J = 7.0 Hz, 3 H), 0.93 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.3, 128.5, 128.0, 127.6, 103.2, 76.1, 76.0, 71.3, 56.5, 53.1, 52.1, 42.4, 40.5, 40.2, 36.8, 26.2, 20.5, 18.5, 14.6 ppm; IR (neat): ν_{max} = 3860, 3646, 2954, 2828, 2318, 1797, 1689, 1647, 1564, 1469, 1455, 1192, 1131, 836, 800 cm^{-1}; MS *m*/*z* (CI, relative intensity): 351 (M^+−1, 2), 321 (59), 288 (10), 277 (2), 249 (7), 229 (4), 213 (100), 199 (8), 183 (16), 163 (200), 149 (6), 91 (19); HRMS (CI) calcd. for $C_{21}H_{35}O_4$ (M^+−1) 351.2535, found 351.2533; $[\alpha]^{28}_D$ +3.12 (*c* 1.00, $CHCl_3$).



Homoallylic alcohol **10**

2 N HCl (0.33 mL) was added to a solution of dimethyl acetal **9** (231 mg, 0.66 mmol) in acetone (0.16 mL) at room temperature. After 2 h, the reaction mixture was diluted with Et_2O (3 mL), poured into sat. NH_4Cl (2 mL). The reaction mixture was extracted with Et_2O (5 mL x 3), and the combined extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 20:1) provided aldehyde **9A** (200 mg, 99%). R_f 0.62 (hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.72 (t, J = 2.0 Hz, 1 H), 7.34–7.26 (m, 5 H), 4.58 and 4.44 (ABq, J_{AB} = 11.2 Hz, 2 H), 3.60–3.55 (m, 1 H), 3.47–3.42 (m, 1 H), 3.26 (s, 3 H), 2.43–2.37 (m, 1 H), 2.27–2.20 (m, 2 H), 1.67–1.46 (m, 5 H), 1.43–1.37 (m, 2 H), 1.32–1.26 (m, 1 H), 0.99 (d, J = 6.0 Hz, 3 H), 0.93 ppm (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.8, 139.1, 128.6, 128.1, 127.7, 76.1, 76.1, 71.3, 56.6, 51.6, 42.0, 40.3, 36.7, 25.3, 20.5, 18.5, 14.6 ppm; IR (neat): ν_{max} = 3850, 3645, 2985, 2824, 2715, 2351, 1725, 1496, 1455, 1273, 1067, 837, 699 cm^{-1}; MS *m*/*z* (CI, relative intensity): 307 (M^++1, 100), 321 (2), 289 (13), 275 (10), 199 (12), 183 (3), 167 (27), 149 (6), 129 (7), 113 (2), 99 (4), 85 (3); HRMS (CI) calcd. for $C_{19}H_{31}O_3$ (M^++1) 307.2273, found 307.2276; $[\alpha]^{27}_D$ +22.4 (*c* 1.00, $CHCl_3$).

A stirred solution of (−)-DIP-chloride (300 mg, 1.04 mmol) in ether (3 mL) was cooled to −78 °C, and treated with allylmagnesium bromide (1.0 M in Et_2O, 0.78 mL, 0.78 mmol) under argon. The solution was stirred for 1 h and allowed to warm to room temperature over further 1 h. The solution was cooled to −78 °C and treated with a solution of aldehyde **9A** (159 mg, 0.52 mmol) in ether (2 mL). The reaction mixture was stirred for 1 h and allowed to warm to room temperature over 1 h. The solution was treated with a pre-formed mixture of 3 N NaOH (5 mL) and 30% H_2O_2 (2 mL). After stirring for 3 h, the organic layer was separated, washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated. Separation of the crude product mixture (d.r. = 5.5:1) in the residue by flash column chromatography (hexanes-EtOAc, 10:1) provided homoallylic alcohol **10** (127 mg, 70%). R_f 0.31 (hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.37–7.28 (m, 5 H), 5.86–5.77 (m, 1 H), 5.13–5.10 (m, 2 H), 4.58 and 4.45 (ABq, J_{AB} = 11.3 Hz, 2 H), 3.75–3.70 (m, 1 H), 3.62–3.57 (m, 1 H), 3.49–3.44 (m, 1 H), 3.27 (s, 3 H), 2.27–2.21 (m, 1 H), 2.15–2.09 (m, 1 H), 1.88–1.81 (m, 1 H), 1.63–1.37 (m, 8 H), 1.24–1.18 (m, 2 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.93 ppm (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.2, 135.2, 128.6, 128.1, 127.7, 118.1, 76.3, 76.2, 71.2, 68.7, 56.7, 44.8, 43.0, 42.8, 40.4, 36.7, 26.5, 20.2, 18.5, 14.6 ppm; IR (neat): ν_{max} = 3850, 3645, 3435, 3067, 3030, 2958, 2872, 2351, 1808, 1641, 1496, 1383, 1206, 1149, 1059, 916, 748 cm^{-1}; MS *m*/*z* (CI, relative intensity): 349 (M^++1, 100), 331 (6), 317 (17), 307 (7), 275 (3), 241 (5), 221 (3), 209 (54), 191 (15), 167 (8), 139 (15), 91 (10); HRMS (CI) calcd. for $C_{22}H_{37}O_3$ (M^++1) 349.2743, found 349.2742; $[\alpha]^{27}_D$ +34.4 (*c* 3.00, $CHCl_3$).



Ester **11**

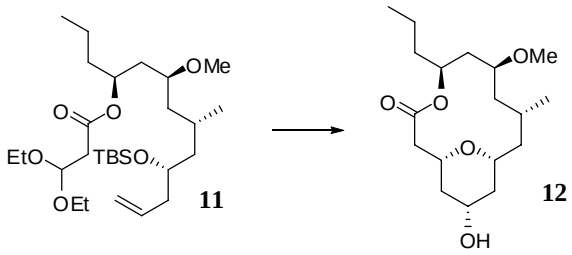
2,6-Lutidine (0.17 mL, 1.44 mmol) was added to a solution of homoallyllic alcohol **10** (100 mg, 0.287 mmol) in CH_2Cl_2 (3 mL). After cooling to 0 °C, TBSOTf (0.20 mL, 0.86 mmol) was added dropwise and the resulting mixture was warmed up to room temperature. The reaction was complete within 1 h and quenched by sat. NH_4Cl solution (2 mL). The reaction mixture was extracted with ether (5 mL x 3), and the extracts were dried over $MgSO_4$, filtered, and concentrated. Flash column

chromatography (hexanes-EtOAc, 20:1) provided TBS ether **10A** (130 mg, 98%). R_f 0.75 (hexanes-EtOAc, 8:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38–7.29 (m, 5 H), 5.85–5.77 (m, 1 H), 5.05–5.02 (m, 2 H), 4.59 and 4.47 (ABq, J_{AB} = 11.5 Hz, 2 H), 3.82–3.77 (m, 1 H), 3.64–3.59 (m, 1 H), 3.51–3.47 (m, 1 H), 3.27 (s, 3 H), 2.23 (t, *J* = 6.5 Hz, 2 H), 1.84–1.77 (m, 1 H), 1.62–1.56 (m, 3 H), 1.54–1.48 (m, 2 H), 1.48–1.38 (m, 3 H), 1.21–1.15 (m, 2 H), 0.93 (t, *J* = 7.2 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.89 (s, 9 H), 0.07 ppm (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 139.4, 135.4, 128.5, 128.0, 127.6, 117.0, 76.1, 76.0, 71.0, 69.8, 56.7, 45.0, 43.1, 43.0, 40.6, 36.8, 26.2, 25.9, 20.1, 18.5, 20.1, 18.5, 14.6, −3.8, −4.3 ppm; IR (neat): ν_{max} = 3848, 3733, 3646, 2956, 2931, 2318, 1797, 1680, 1564, 1462, 1255, 1067, 913, 835 cm^{-1}; MS *m*/*z* (CI, relative intensity): 463 (M^++1, 100), 479 (2), 421 (3), 491 (2), 355 (5), 331 (7), 313 (14), 299 (8), 285 (8), 223 (9), 209 (4), 191 (17); HRMS (CI) calcd. for $C_{28}H_{51}O_3Si$ (M^++1) 463.3607, found 463.3611; $[\alpha]^{29}_D$ +39.7 (*c* 4.00, $CHCl_3$).

DDQ (636 mg, 2.80 mmol) was added to a solution of TBS ether **10A** (130 mg, 0.28 mmol) in 1,2-dichloroethane (28 mL) and pH 7 buffer solution (5.6 mL) at room temperature. After 12 h, the reaction was quenched by addition of sat. $NaHCO_3$ solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (30 mL x 3), and the extracts were dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 8:1) provided alcohol **10B** (89 mg, 85%). R_f 0.45 (hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.83–5.75 (m, 1 H), 5.05–5.02 (m, 2 H), 3.94–3.88 (m, 1 H), 3.82–3.76 (m, 1 H), 3.60–3.55 (m, 1 H), 3.36 (s, 3 H), 3.04 (d, *J* = 3.0 Hz, 1 H), 2.22 (t, *J* = 6.5 Hz, 2 H), 1.79–1.69 (m, 2 H), 1.68–1.61 (m, 1 H), 1.54–1.42 (m, 3 H), 1.39–1.33 (m, 1 H), 1.29–1.22 (m, 1 H), 1.18–1.13 (m, 1 H), 0.93 (t, *J* = 7.0 Hz, 3 H), 0.90 (d, *J* = 7.0 Hz, 3 H), 0.88 (s, 9 H), 0.07-0.05 ppm (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 135.2, 117.1, 78.0, 69.7, 68.7, 56.9, 44.4, 43.1, 41.8, 40.2, 39.4, 26.1, 26.0, 20.2, 19.1, 14.4, −3.9, −4.4 ppm; IR (neat): ν_{max} = 3451, 3076, 2930, 2857, 2370, 2340, 1830, 1738, 1640, 1463, 1088, 912, 806 cm^{-1}; MS *m*/*z* (CI, relative intensity): 373 (M^++1, 100), 355 (7), 331 (3), 313 (4), 285 (11), 241 (39), 209 (31), 199 (35), 167 (4); HRMS (CI) calcd. for $C_{21}H_{45}O_3Si$ (M^++1) 373.3138, found 373.3135; $[\alpha]^{28}_D$ +39.4 (*c* 2.00, $CHCl_3$).

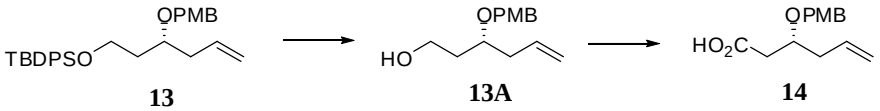
$(EtO)_2CHCH_2CO_2H$ (75 mg, 0.46 mmol), DCC (198 mg, 0.96 mmol), DMAP (8 mg, 0.07 mmol) were added to a solution of the alcohol **10B** (85 mg, 0.23 mmol) in CH_2Cl_2 (2.3 mL) at room temperature. This mixture was stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. Purification of

residue by flash column chromatography (hexanes-EtOAc, 20:1) provided ester **11** (115 mg, 97%). R_f 0.43 (hexanes-EtOAc, 8:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.83–5.75 (m, 1 H), 5.17–5.12 (m, 1 H), 5.05–5.02 (m, 2 H), 4.98–4.96 (m, 1 H), 3.81–3.76 (m, 1 H), 3.70–3.64 (m, 2 H), 3.58–3.52 (m, 2 H), 3.30 (s, 3 H), 3.24–3.21 (m, 1 H), 2.65 (d, *J* = 5.5 Hz, 2 H), 2.22 (t, *J* = 6.5 Hz, 2 H), 1.80–1.74 (m, 1 H), 1.67–1.58 (m, 2 H), 1.57–1.46 (m, 3 H), 1.45–1.38 (m, 1 H), 1.36–1.30 (m, 2 H), 1.19 (t, *J* = 6.8 Hz, 6 H), 1.17–1.12 (m, 2 H), 0.93–0.88 (m, 15 H), 0.66 ppm (d, *J* = 5.0 Hz, 6 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.9, 135.3, 117.0, 99.9, 75.8, 71.7, 69.7, 62.0, 61.8, 57.3, 44.7, 43.0, 40.4, 40.1, 37.4, 26.1, 25.8, 20.1, 18.6, 18.3, 15.5, 14.2, −3.9, −4.4 ppm; IR (neat): ν_{max} = 2958, 2930, 2350, 2330, 2317, 1737, 1640, 1193, 1130, 1065, 913, 835, 805 cm^{-1}; MS *m*/*z* (CI, relative intensity): 517 (M^++1, 5), 501 (6), 471 (100), 439 (9), 429 (9), 413 (5), 355 (7), 339 (24), 313 (6), 223 (11), 191 (6), 103 (10); HRMS (CI) calcd. for $C_{28}H_{57}O_6Si$ (M^++1) 517.3924, found 517.3933; $[\alpha]^{28}_D$ +38.3 (*c* 1.00, $CHCl_3$).



Macrolide **12**

TMSOAc (0.26 mL, 1.74 mmol) was added to a solution of ester **11** (30 mg, 0.058 mmol) in AcOH (5.8 mL) at room temperature. TESOTf (0.26 mL, 1.16 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into ether (20 mL), and sat. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with ether (20 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield a colorless oil. This crude product was dissolved in MeOH (1.2 mL), and then K_2CO_3 (80 mg, 0.58 mmol) was added. This reaction mixture was stirred for 3 h at room temperature and then concentrated. The residue was dissolved in water (5 mL), and ether (5 mL). The layers were separated, and the aqueous layer was extracted with ether (5 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue was separated by flash column chromatography (hexanes-EtOAc, 3:1) to afford macrolide **12** (9.0 mg, 47%, d.r. = 9:1). (Spectroscopic data of the pure sample of **12** are presented on page 14.)



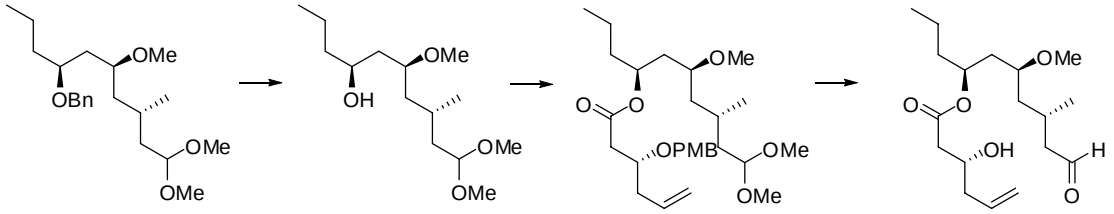
13 **13A** **14**

Carboxylic acid **14**

TBAF (1 M in THF, 1.32 mL, 13.2 mmol) was added dropwise to a solution of olefin **13** (2.1 g, 4.40 mmol) in THF (40 mL). After 12 h, the reaction mixture was concentrated, and the residue was separated by flash column chromatography (hexanes-EtOAc, 4:1) to provide alcohol **13A** (810 mg, 78%). R_f 0.75 (hexanes-EtOAc, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.27–7.26 (m, 2 H), 6.88 (d, J = 8.5 Hz, 2 H), 5.86–5.77 (m, 1 H), 5.13–5.08 (m, 2 H), 4.59 and 4.42 (ABq, J_{AB} = 12.5 Hz, 2 H), 3.80 (s, 3 H), 3.79–3.66 (m, 3 H), 2.46–2.40 (m, 1 H), 2.37–2.32 (m, 1 H), 1.81–1.71 ppm (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5, 134.5, 130.5, 129.7, 117.8, 114.1, 77.8, 70.9, 61.1, 55.5, 38.3, 36.2 ppm; IR (neat): ν_{max} = 3418, 2933, 1613, 1513, 1383, 1248, 1174, 1035, 916, 822 cm^{-1}; MS m/z (CI, relative intensity): 235 (M^+−1, 19), 241 (4), 161 (1), 149 (3), 129 (5), 121 (100); HRMS (CI) calcd. for $C_{14}H_{19}O_3$ (M^+−1) 235.1334, found 235.1340; $[\alpha]^{28}_D$ −66.2 (c 0.60, $CHCl_3$).

Dess-Martin periodinane (2.9 g, 6.86 mmol) was added to a solution of alcohol **13A** (810 mg, 3.43 mmol) in CH_2Cl_2 (68 mL). The reaction mixture was stirred at room temperature for 1 h and the reaction was quenched by addition of sat. $Na_2S_2O_3$ solution (30 mL). The reaction mixture was extracted with CH_2Cl_2 (60 mL x 3). The organic extracts were dried over $MgSO_4$, filtered, and concentrated. This crude aldehyde was dissolved in t-BuOH (160 mL) and 2-methyl-2-butene (40 mL). After cooling to 0 °C, $NaClO_2$ (806 mg, 8.92 mmol) and NaH_2PO_4 (1.49 g, 8.92 mmol) in water (27 mL) was added to the solution. The reaction mixture was stirred vigorously for 30 min at room temperature, diluted with EtOAc (200 mL), and quenched by water (100 mL). The aqueous phase was extracted with EtOAc (200 mL x 2) and the combined organic phase was washed with brine (100 mL), dried over $MgSO_4$, filtered, and concentrated. Flash column chromatography ($CHCl_3$-MeOH, 30:1) provided acid **14** (833 mg, 97%). R_f 0.43 ($CHCl_3$-MeOH, 10:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.25 (d, J = 8.0 Hz, 2 H), 6.86 (d, J = 8.0 Hz, 2 H), 5.85–5.77 (m, 1 H), 5.14–5.11 (m, 2 H), 4.55 and 4.50 (ABq, J_{AB} = 11.0 Hz, 2 H), 3.96–3.92 (m, 1 H), 3.79 (s, 3 H), 2.62–2.54 (m, 2 H), 2.44–2.33 ppm (m, 2 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.1, 159.5, 133.8, 130.3, 129.7, 118.5, 114.1, 74.9, 71.5, 55.5, 39.4, 38.5 ppm; IR (neat): ν_{max} = 2933, 1711, 1613, 1513, 1383, 1302, 1248, 1174, 1075, 1034, 919, 822 cm^{-1}; MS m/z (CI, relative intensity): 249 (M^+−1, 49),

279 (4), 219 (1), 164 (2), 149 (9), 137 (3), 121 (100), 83 (4); HRMS (CI) calcd. for $C_{14}H_{17}O_4$ (M^+-1) 249.1127, found 249.1126; $[\alpha]^{28}_D$ −21.1 (*c* 2.00, $CHCl_3$).



9 **9B** **9C** **15**

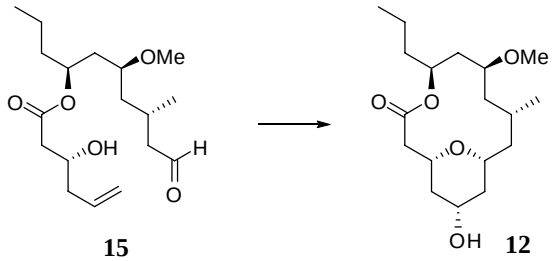
Aldehyde **15**

Palladium on activated carbon (10% w/w, 36 mg, 0.034 mmol) was added to a solution of acetal **9** (60 mg, 0.17 mmol) in MeOH (1.7 mL). The reaction mixture was stirred under hydrogen atmosphere at room temperature. After 1 h, the solution was filtered and the filtrate was concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 4:1) provided alcohol **9B** (45 mg, 100%). R_f 0.43 (hexanes-EtOAc, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.47 (dd, *J* = 4.8 Hz, *J* = 8.1 Hz, 1 H), 3.92–3.88 (m, 1 H), 3.60–3.55 (m, 1 H), 3.37 (s, 3 H), 3.32 (s, 3 H), 3.31 (s, 3 H), 2.97 (s, 1 H), 1.75–1.69 (m, 3 H), 1.68–1.63 (m, 1 H), 1.55–1.50 (m, 1 H), 1.50–1.34 (m, 5 H), 1.25–1.20 (m, 1 H), 0.96 (d, *J* = 6.5 Hz, 3 H), 0.93 ppm (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 103.3, 77.8, 68.8, 56.9, 53.1, 52.6, 41.4, 40.3, 40.0, 39.6, 26.3, 20.5, 19.1, 14.4 ppm; IR (neat): ν_{max} = 3465, 2930, 1742, 1462, 1377, 1192, 1126, 1055, 969, 808 cm^{-1}; MS *m*/*z* (CI, relative intensity): 285 (3), 245 (3), 229 (9), 213 (84), 199 (100), 181 (6), 159 (45), 149 (2), 129 (8), 85 (4); $[\alpha]^{29}_D$ +13.1 (*c* 1.00, $CHCl_3$).

Acid **14** (65 mg, 0.26 mmol), DCC (105 mg, 0.51 mmol), DMAP (6 mg, 0.051 mmol) were added to a solution of alcohol **9B** (45 mg, 0.17 mmol) in CH_2Cl_2 (1.7 mL) at room temperature. This mixture was stirred at room temperature for 3 h, the reaction mixture was concentrated under reduced pressure. Purification of the residue by flash column chromatography (hexanes-EtOAc, 15:1) provided ester **9C** (77mg, 92%). R_f 0.40 (hexanes-EtOAc, 4:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.5 Hz, 2 H), 6.85 (d, *J* = 8.5 Hz, 2 H), 5.86–5.79 (m, 1 H), 5.14–5.08 (m, 1 H), 5.12–5.08 (m, 2 H), 4.51 and 4.49 (ABq, J_{AB} = 11.0 Hz, 2 H), 4.45 (dd, *J* = 5.2 Hz, *J* = 8.1 Hz, 1 H), 3.99–3.96 (m, 1 H), 3.79 (s, 3 H), 3.31 (s, 3 H), 3.29 (s, 3 H), 3.28 (s, 3 H), 3.25–3.21 (m, 1 H), 2.55 and 2.47 (ABX, J_{AB} = 18.6 Hz, J_{AX} = 8.0 Hz, J_{BX} = 5.0 Hz, 2 H), 2.38–2.34 (m, 2 H), 1.75–1.67 (m, 1 H), 1.65–1.44 (m, 5 H), 1.40–1.35 (m, 2 H), 1.36–1.25 (m, 2 H),

1.19–1.14 (m, 1 H), 0.94 (d, J = 6.5 Hz, 3 H), 0.87 ppm (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.6, 159.4, 134.3, 130.8, 129.5, 118.0, 113.9, 103.2, 75.9, 75.5, 71.8, 71.6, 57.0, 55.5, 53.2, 52.3, 42.4, 40.1, 40.0, 39.9, 38.7, 37.4, 26.1, 20.5, 18.7, 14.2 ppm; IR (neat): ν_{max} = 2934, 2832, 1730, 1614, 1514, 1663, 1383, 1320, 1174, 1125, 1091, 915, 822 cm^{-1}; MS m/z (CI, relative intensity): 493 (M^+−1, 4), 463 (100), 431 (18), 387 (2), 363 (2), 333 (62), 301 (13), 269 (3), 243 (2), 213 (58), 181 (4), 121 (81); HRMS (CI) calcd. for $C_{28}H_{45}O_7$ (M^+−1) 493.3165, found 493.3164; $[\alpha]^{29}_D$ −5.63 (c 1.00, $CHCl_3$).

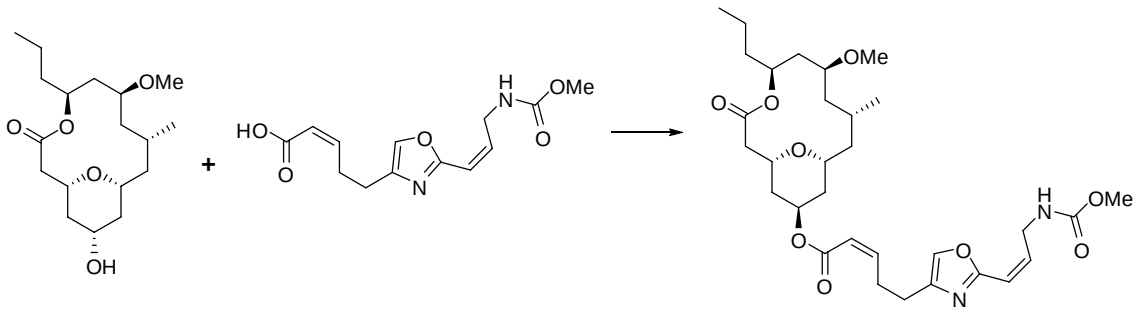
DDQ (354 mg, 1.56 mmol) was added to a solution of ester **9C** (77 mg, 0.16 mmol) in CH_2Cl_2 (16 mL) and pH 7 buffer solution (3.2 mL) at room temperature. After 36 h, the reaction was quenched by addition of sat. $NaHCO_3$ (10 mL). The reaction mixture was extracted with CH_2Cl_2 (20 mL x 3), dried over $MgSO_4$, filtered, and concentrated. Purification of the residue by flash column chromatography (hexanes-EtOAc, 10:1) provided aldehyde **15** (48 mg, 92%). R_f 0.55 (hexanes-EtOAc, 4:1). δ = 9.75 (t, J = 2.0 Hz, 1 H), 5.88–5.80 (m, 1 H), 5.17–5.13 (m, 1 H), 5.17–5.12 (m, 2 H), 4.11–4.06 (m, 1 H), 3.30–3.26 (m, 1 H), 3.30 (s, 3 H), 3.17 (d, J = 4.0 Hz, 1 H), 2.52 and 2.42 (ABX, J_{AB} = 19.2 Hz, J_{AX} = 3.0 Hz, J_{BX} = 9.0 Hz, 2 H), 2.43–2.40 (m, 1 H), 2.32–2.20 (m, 4 H), 1.75–1.64 (m, 2 H), 1.62–1.53 (m, 2 H), 1.52–1.46 (m, 1 H), 1.37–1.25 (m, 3 H), 1.00 (d, J = 6.5 Hz, 3 H), 0.91 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 202.6, 172.3, 134.3, 118.3, 76.1, 71.8, 67.8, 56.9, 51.5, 41.6, 41.5, 41.2, 39.0, 37.3, 25.2, 20.6, 18.7, 14.2 ppm; IR (neat): ν_{max} = 3848, 3733, 3646, 3564, 3479, 3077, 2960, 2717, 2350, 2310, 1729, 1642, 1564, 1383, 1173, 837, 702 cm^{-1}; MS m/z (CI, relative intensity): 329 (M^++1, 35), 297 (23), 255 (5), 239 (3), 227 (7), 199 (52), 181 (2), 167 (100), 149 (14), 129 (25), 113 (6), 99 (9); HRMS (CI) calcd. for $C_{18}H_{33}O_5$ (M^++1) 329.2328, found 329.2326; $[\alpha]^{28}_D$ −12.8 (c 0.30, $CHCl_3$).



15 **12**

Macrolide **12**

TMSOAc (0.40 mL, 2.73 mmol) was added to a solution of aldehyde **15** (30 mg, 0.091 mmol) in AcOH (9.0 mL) at room temperature. TESOTf (0.40 mL, 1.82 mmol) was added dropwise to the resulting solution at the same temperature. After 30 min, the reaction mixture was poured into ether (20 mL), and sat. $NaHCO_3$ (20 mL). The layers were separated, and the aqueous layer was extracted with ether (20 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to yield a colorless oil. This crude product was dissolved in MeOH (2 mL), and then K_2CO_3 (125 mg, 0.91 mmol) was added. This reaction mixture was stirred for 3 h at room temperature and then concentrated. The residue was dissolved in water (5 mL), and ether (5 mL). The layers were separated, and the aqueous layer was extracted with ether (5 mL x 3). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The residue as purified by flash column chromatography (hexanes-EtOAc, 3:1) to afford macrolide **12** (20.0 mg, 68%). R_f 0.28 (hexanes-EtOAc, 1:1). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.17–5.13 (m, 1 H), 3.83–3.76 (m, 1 H), 3.76–3.71 (m, 1 H), 3.60–3.56 (m, 1 H), 3.31 (s, 3 H), 3.20–3.15 (m, 1 H), 2.62 and 2.43 (ABX, J_{AB} = 14.5 Hz, J_{AX} = 4.0 Hz, J_{BX} = 11.0 Hz, 2 H), 1.99–1.95 (m, 1 H), 1.88–1.83 (m, 2 H), 1.74–1.67 (m, 2 H), 1.61–1.56 (m, 1 H), 1.54–1.45 (m, 2 H), 1.42–1.41 (m, 1 H), 1.39–1.29 (m, 3 H), 1.26–1.11 (m, 3 H), 0.99 (d, J = 6.9 Hz, 3 H), 0.94 ppm (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 171.1, 78.9, 75.8, 73.5, 72.5, 68.3, 56.5, 44.3, 42.5, 42.5, 42.2, 41.0, 40.2, 37.1, 31.5, 25.8, 19.2, 14.1 ppm; IR (neat): ν_{max} = 3420, 2953, 2871, 2351, 2318, 1730, 1647, 1383, 1156, 937, 798, 705 cm^{-1}; MS *m*/*z* (CI, relative intensity): 329 (M^++1, 100), 311 (84), 297 (81), 279 (66), 267 (6), 241 (26), 209 (1), 199 (3), 181 (5), 155 (4), 141 (7), 113 (11), 85 (2); HRMS (CI) calcd. for $C_{18}H_{33}O_5$ (M^++1) 329.2328, found 329.2327. $[\alpha]^{29}_D$ +22.2 (*c* 1.00, $CHCl_3$).



12 **2** **(+)-Neopeltolide (1)**

(+)-Neopeltolide **1**

Ph_3P (28 mg, 0.11 mmol), acid **2** (25 mg, 0.09 mmol) and DIAD (0.021 mL, 0.11 mmol) were added to a solution of macrolide **12** (10 mg, 0.03 mmol) in benzene (1.5 mL) at room temperture. After 30 min, the solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexanes-EtOAc, 3:1) to afford (+)-Neopeltolide (14 mg, 79%). R_f 0.33 (hexanes-EtOAc, 1:1). ^{1}H NMR (600 MHz, CD_3OD): δ = 7.66 (s, 1 H), 6.37 (dt, *J* = 11.5 Hz, *J* = 7.4 Hz, 1 H), 6.29 (dt, *J* = 11.8 Hz, *J* = 2.0 Hz, 1 H), 6.03 (dt, *J* = 12.0 Hz, *J* = 6.1 Hz, 1 H), 5.88 (dt, *J* = 11.5 Hz, *J* = 1.6 Hz, 1 H), 5.20 (m, 1 H), 5.16 (dt, *J* = 14.7 Hz, *J* = 5.1 Hz, 1 H), 4.30 (bd, *J* = 4.5 Hz, 2 H), 4.06 (dddd, *J* = 11.5 Hz, *J* = 11.5 Hz, *J* = 4.1 Hz, *J* = 2.1 Hz, 1 H), 3.66 (m, 1 H), 3.64 (s, 3 H), 3.56 (bt, *J* = 9.8 Hz, 1 H), 3.27 (s, 3 H), 3.01 (m, 2 H), 2.71 (dd, *J* = 7.1 Hz, *J* = 7.1 Hz, 2 H), 2.69 (dd, *J* = 12.0 Hz, *J* = 7.8 Hz, 1 H), 2.29 (dd, *J* = 14.8 Hz, *J* = 11.0 Hz, 2 H), 1.87 (m, 1 H), 1.83 (m, 1 H), 1.72 (m, 1 H), 1.67 (m, 1 H), 1.57 (m, 1 H), 1.54 (m, 1 H), 1.51 (m, 1 H), 1.48 (m, 1 H), 1.40 (m, 1 H), 1.36 (m, 1 H), 1.32 (m, 2 H), 1.28 (m, 1 H), 1.26 (m, 1 H), 1.11 (m, 1 H), 0.97 (d, *J* = 6.7 Hz, 3 H), 0.93 ppm (t, *J* = 7.4 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3OD): δ = 173.1, 166.9, 161.9, 159.6, 150.0, 142.3, 139.3, 136.0, 121.7, 116.0, 77.2, 77.1, 73.9, 71.3, 69.2, 56.4, 52.6, 45.3, 43.5, 43.2, 41.1, 41.1, 38.0, 37.4, 36.2, 32.6, 29.0, 26.4, 26.0, 20.0, 14.2 ppm; IR (neat): ν_{max} = 3353, 3131, 2955, 2921, 2370, 2340, 1714, 1248, 1516, 1416, 1383, 1248, 1180, 1063, 993, 820 cm^{-1}; MS *m/z* (CI, relative intensity): 591 (M^++1, 100), 631 (3), 619 (7), 559 (14), 309 (4), 297 (2), 279 (4), 76 (9); HRMS (CI) calcd. for $C_{31}H_{47}O_9N_2$ (M^++1) 591.3281, found 591.3280; $[\alpha]^{27}_D$ +25.8 (*c* 0.65, CH_3OH).

Comparison of ^{1}H NMR data for synthetic and natural samples of Neopeltolide(1)

Natural sample (600 MHz, CD_3OD)	**Synthetic sample** (600 MHz, CD_3OD)
7.64, s	7.66, s
6.33, dt (11.7, 7.6)	6.37, dt (11.5, 7.4)
6.24, dt (11.7, 2.1)	6.29, dt (11.8, 2.0)
6.02, dt (11.7, 6.2)	6.03, dt (12.0, 6.1)
5.86, dt (11.7, 1.4)	5.88, dt (11.5, 1.6)
5.17, m	5.20, m
5.14, dt (4.8, 9.6)	5.16, dt (14.7, 5.1)
4.28, bd (4.8)	4.30, bd (4.5)
4.04, ddt (4.1, 2.1, 11.7)	4.06, dddd (11.5, 11.5, 4.1, 2.1)
3.64, m	3.66, m
3.62, s	3.64, s
3.55, bt (10.3)	3.56, bt (9.8)
3.23, s	3.27, s
2.98, m	3.01, m
2.68, dd (7.6, 7.6)	2.71, dd (7.1, 7.1)
2.66, dd (15.1, 4.1)	2.69, dd (12.0, 7.8)
2.26, dd (15.1, 11.0)	2.29, dd (14.8, 11.0)
1.83, m	1.87, m
1.78, m	1.83, m
1.68, m	1.72, m
1.64, m	1.67, m
1.54, m	1.57, m
1.49, m	1.54, m
1.48, m	1.51, m
1.46, m	1.48, m
1.38, m	1.40, m
1.36, m	1.36, m
1.33, m	1.32, m
1.28, m	1.28, m
1.25, m	1.26, m
1.08, m	1.11, m
0.94, d (6.9)	0.97, d (6.7)
0.92, t (7.6)	0.93, t (7.4)

Comparison of ^{13}C NMR data for synthetic and natural samples of Neopeltolide(1)

Natural sample (125 MHz, CD_3OD)	**Synthetic sample** (150 MHz, CD_3OD)
173.0	173.1
166.9	166.9
161.9	161.9
159.6	159.6
150.0	150.0
142.3	142.3
139.2	139.3
135.9	136.0
121.7	121.7
115.7	116.0
77.1	77.2
77.0	77.1
73.9	73.9
71.3	71.3
69.2	69.2
56.4	56.4
52.6	52.6
45.2	45.3
43.5	43.5
43.2	43.2
41.0	41.1
41.0	41.1
37.9	38.0
37.4	37.4
36.2	36.2
32.6	32.6
29.0	29.0
26.4	26.4
26.0	26.0
20.0	20.0
14.1	14.2

Supporting Information-2

Total Synthesis of (+)-Neopeltolide via Prins Macrocyclization

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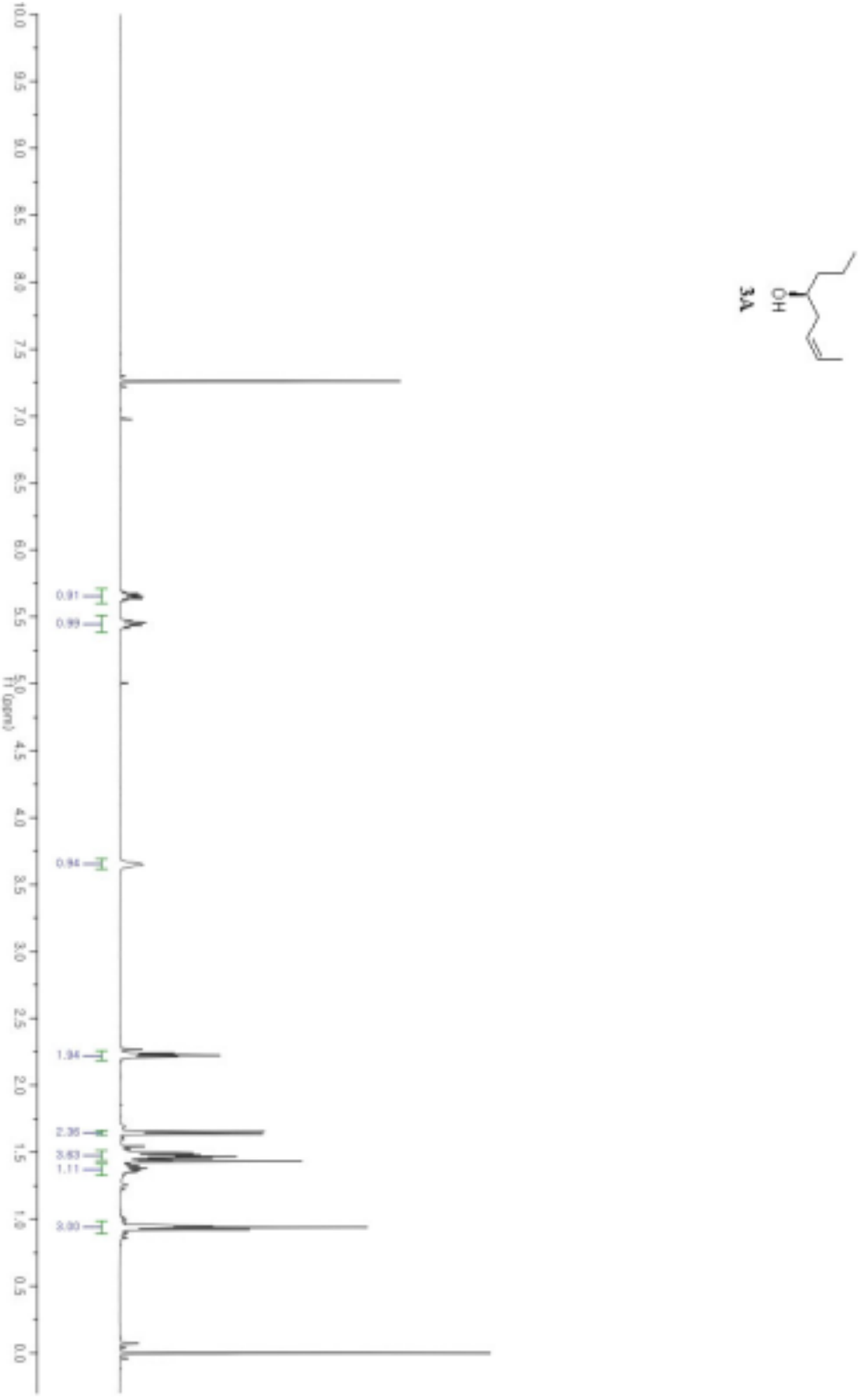
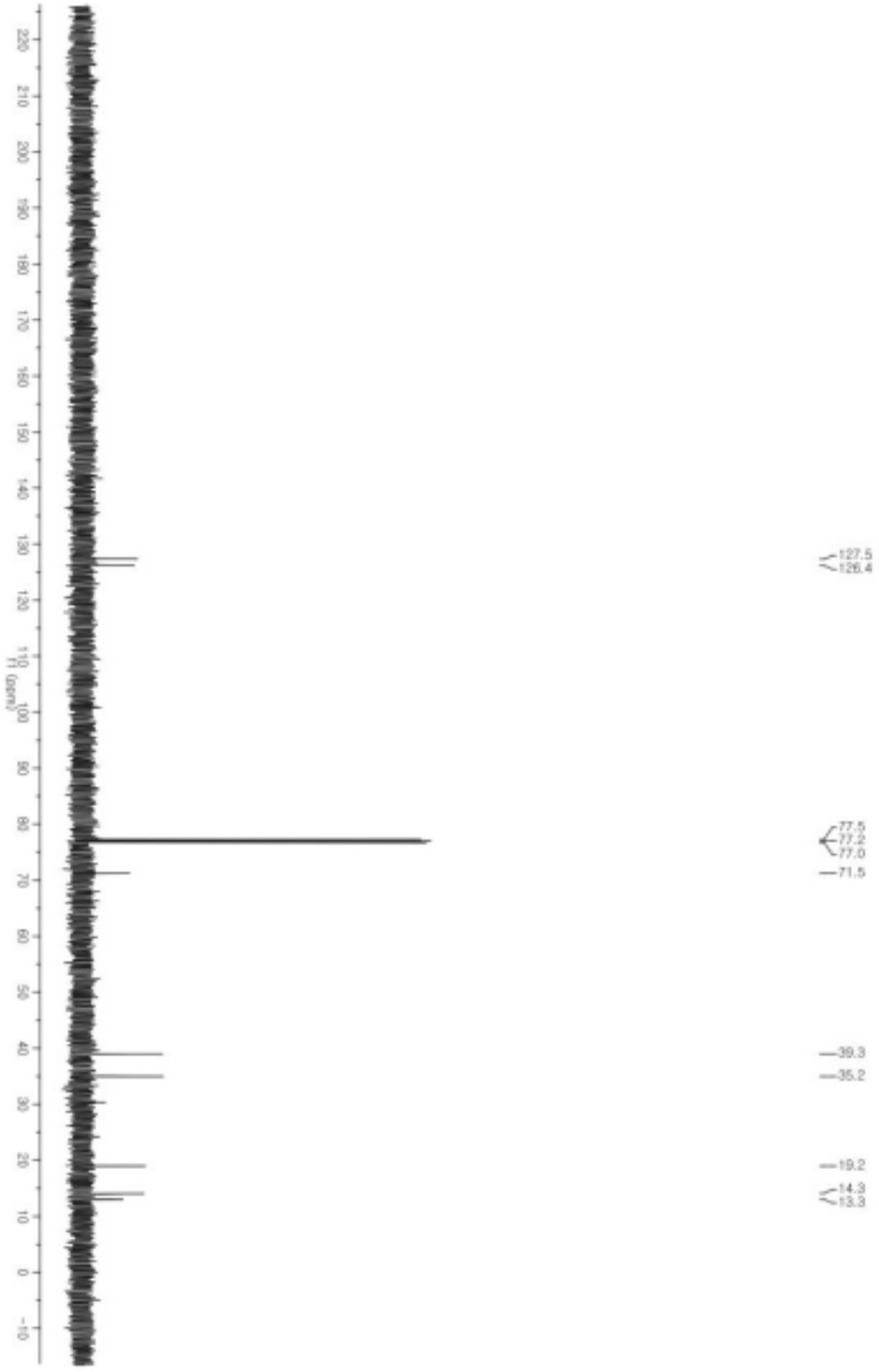
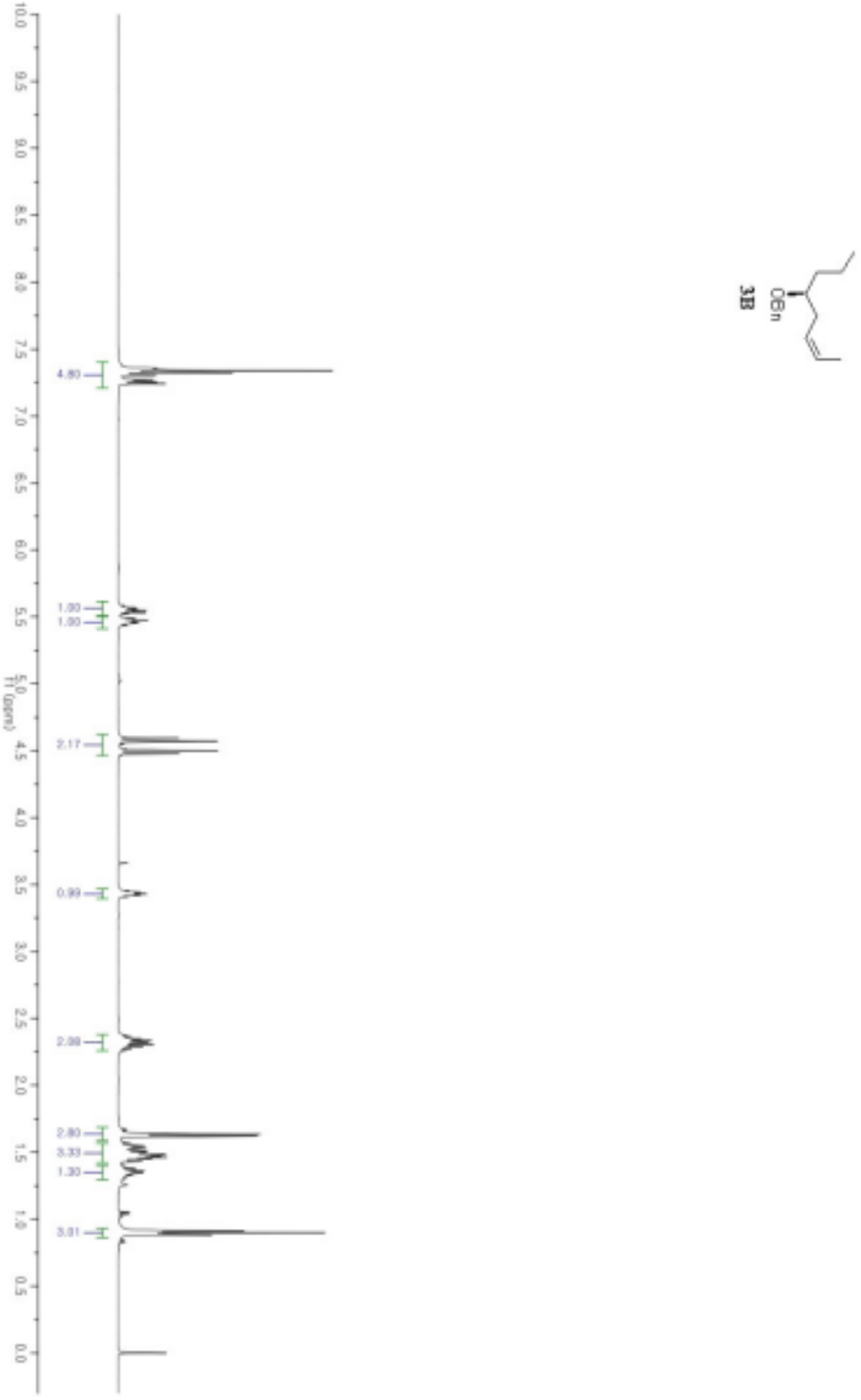


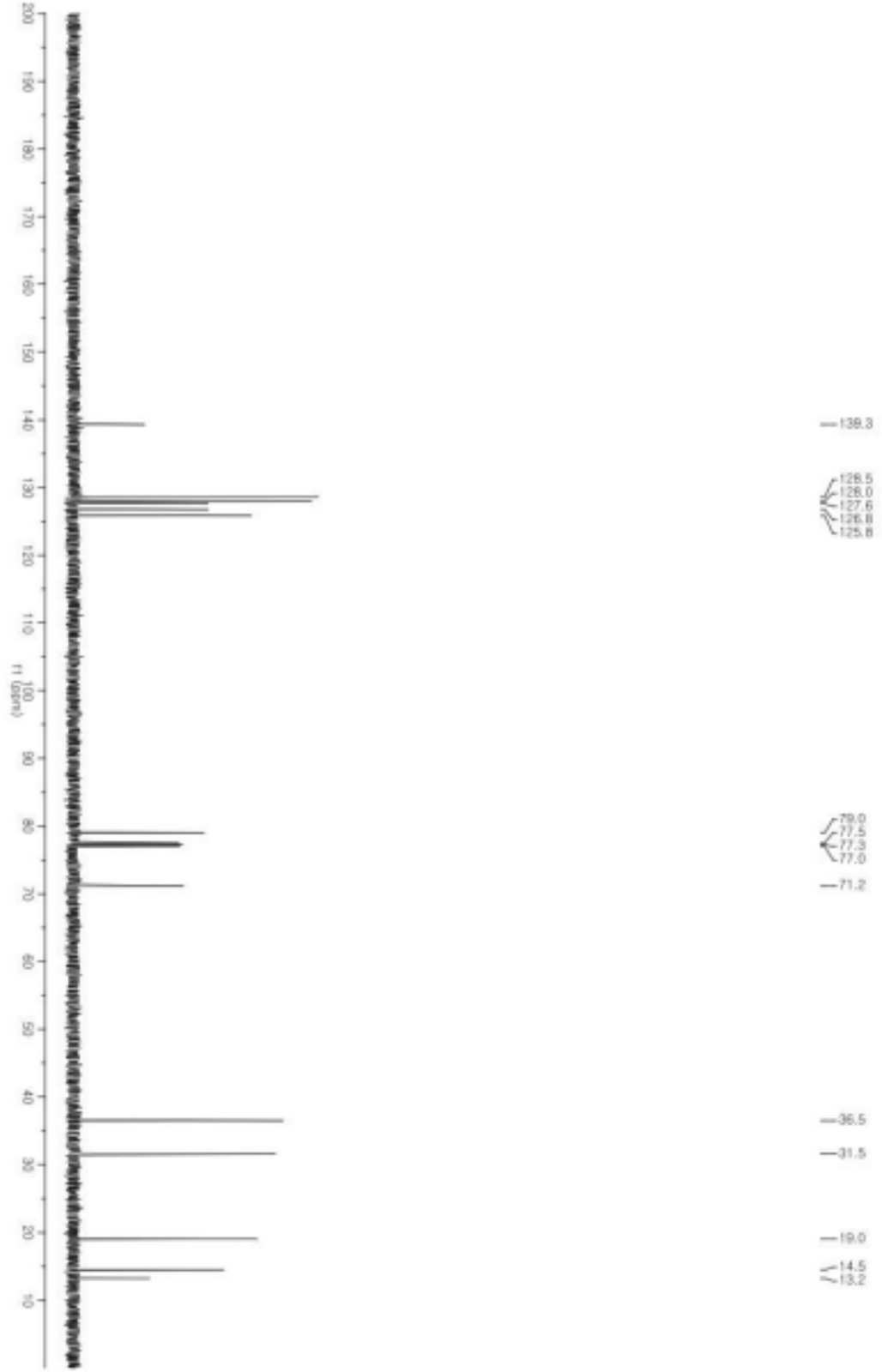
^{1}H-NMR (500 MHz, $CDCl_3$) of **3A**



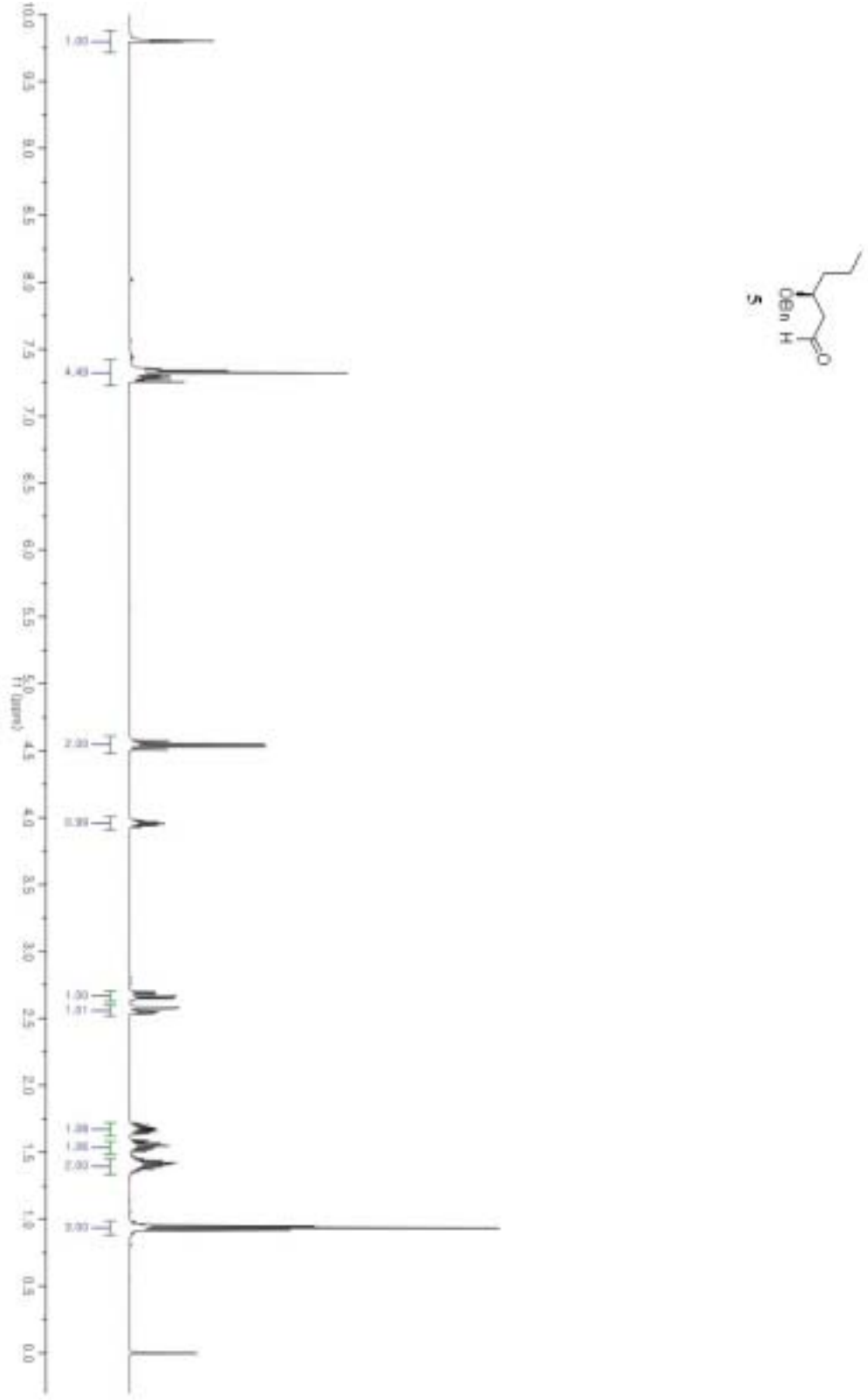
^{13}C-NMR (125 MHz, $CDCl_3$) of **3A**



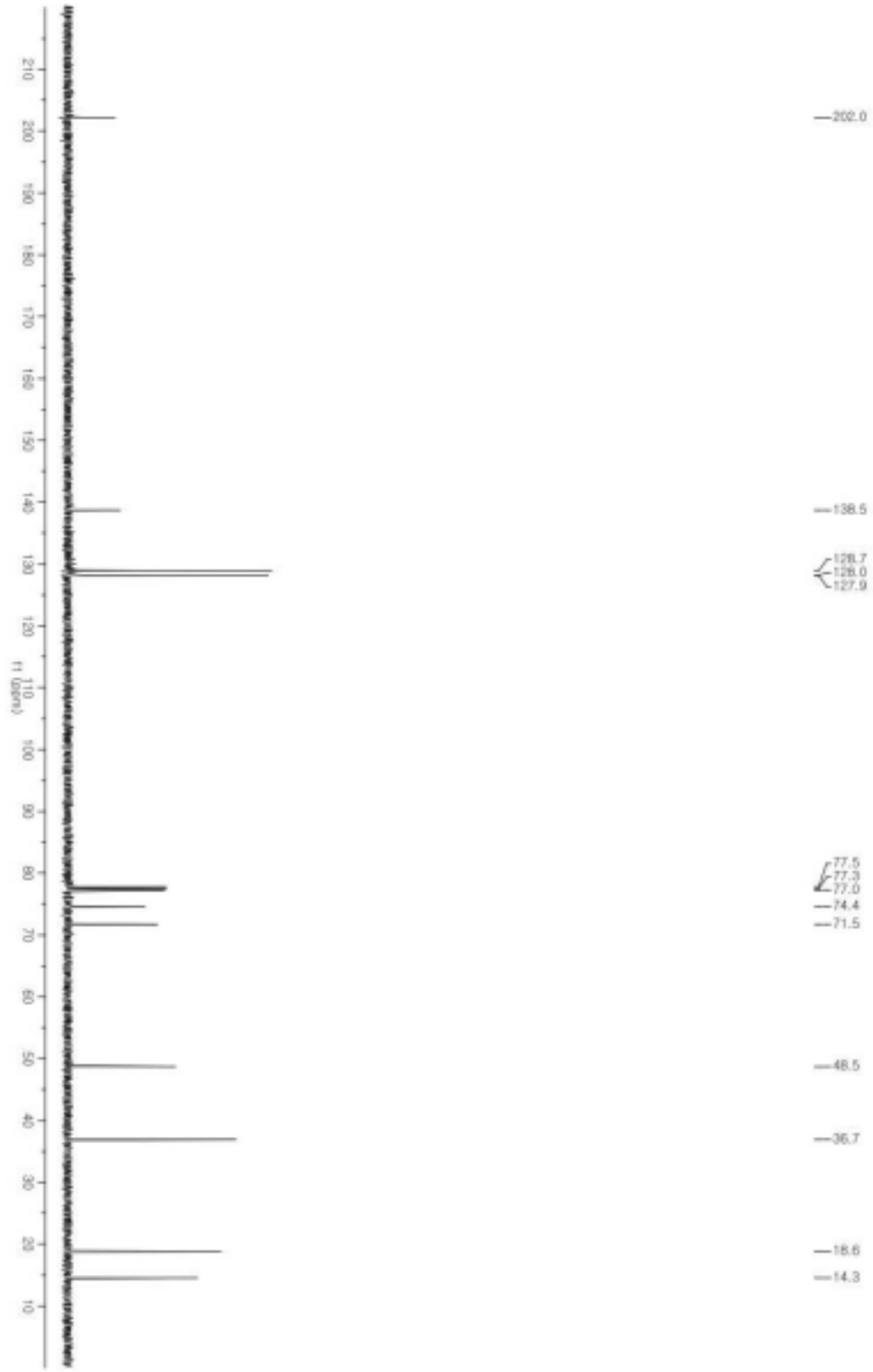
^{1}H-NMR (500 MHz, $CDCl_3$) of **3B**



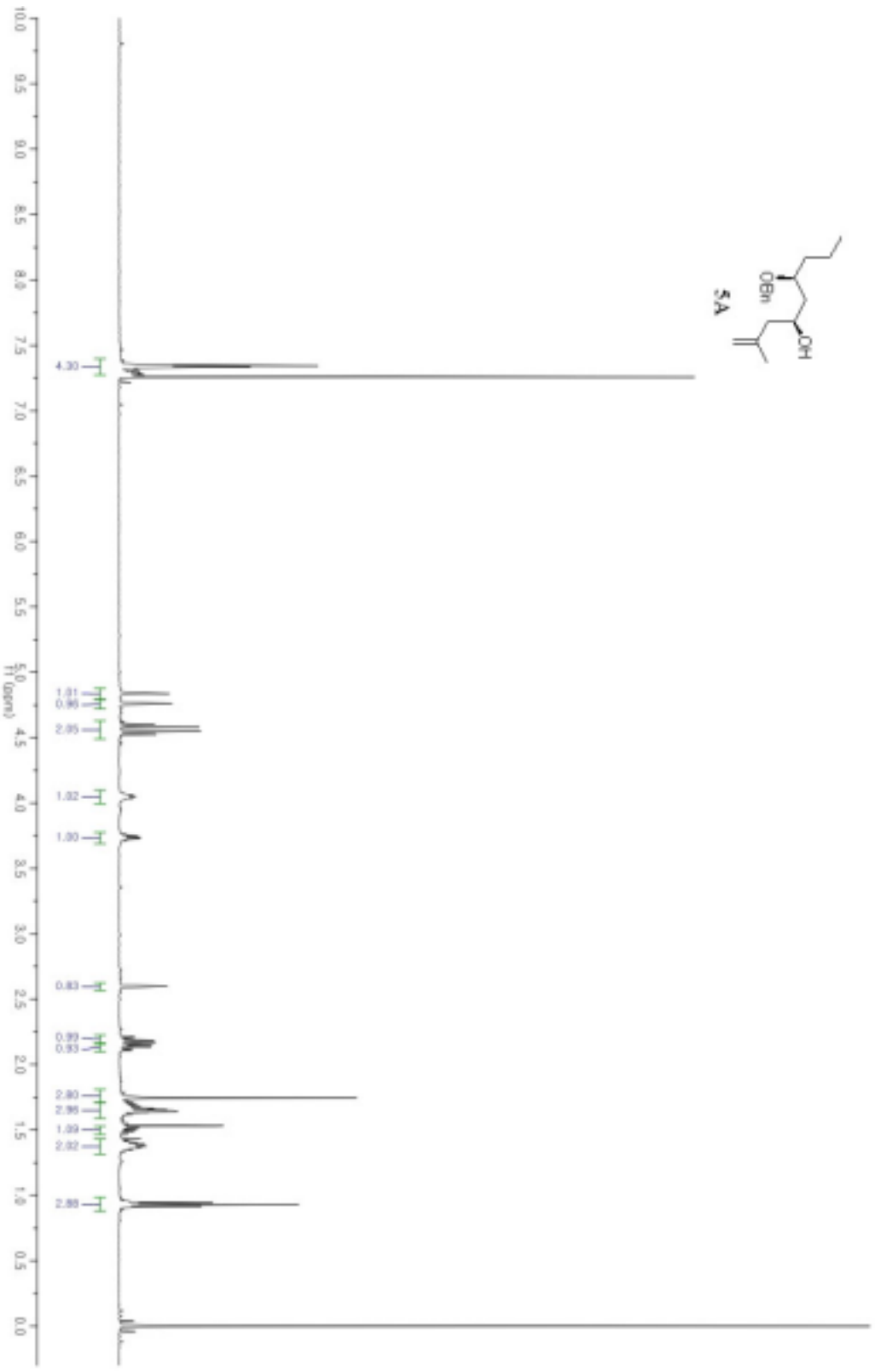
^{13}C-NMR (500 MHz, $CDCl_3$) of **3B**



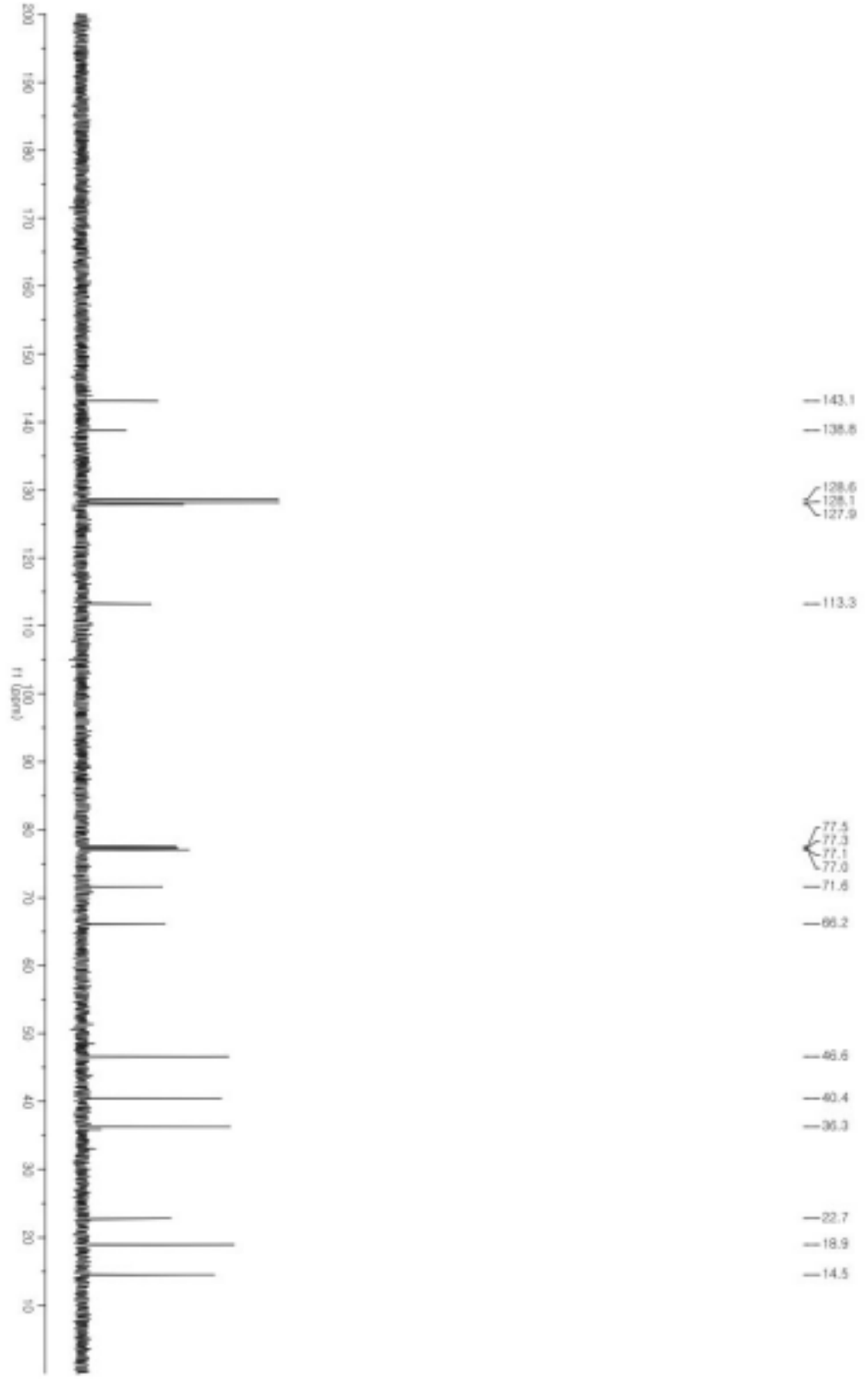
^{1}H-NMR (500 MHz, $CDCl_3$) of **5**



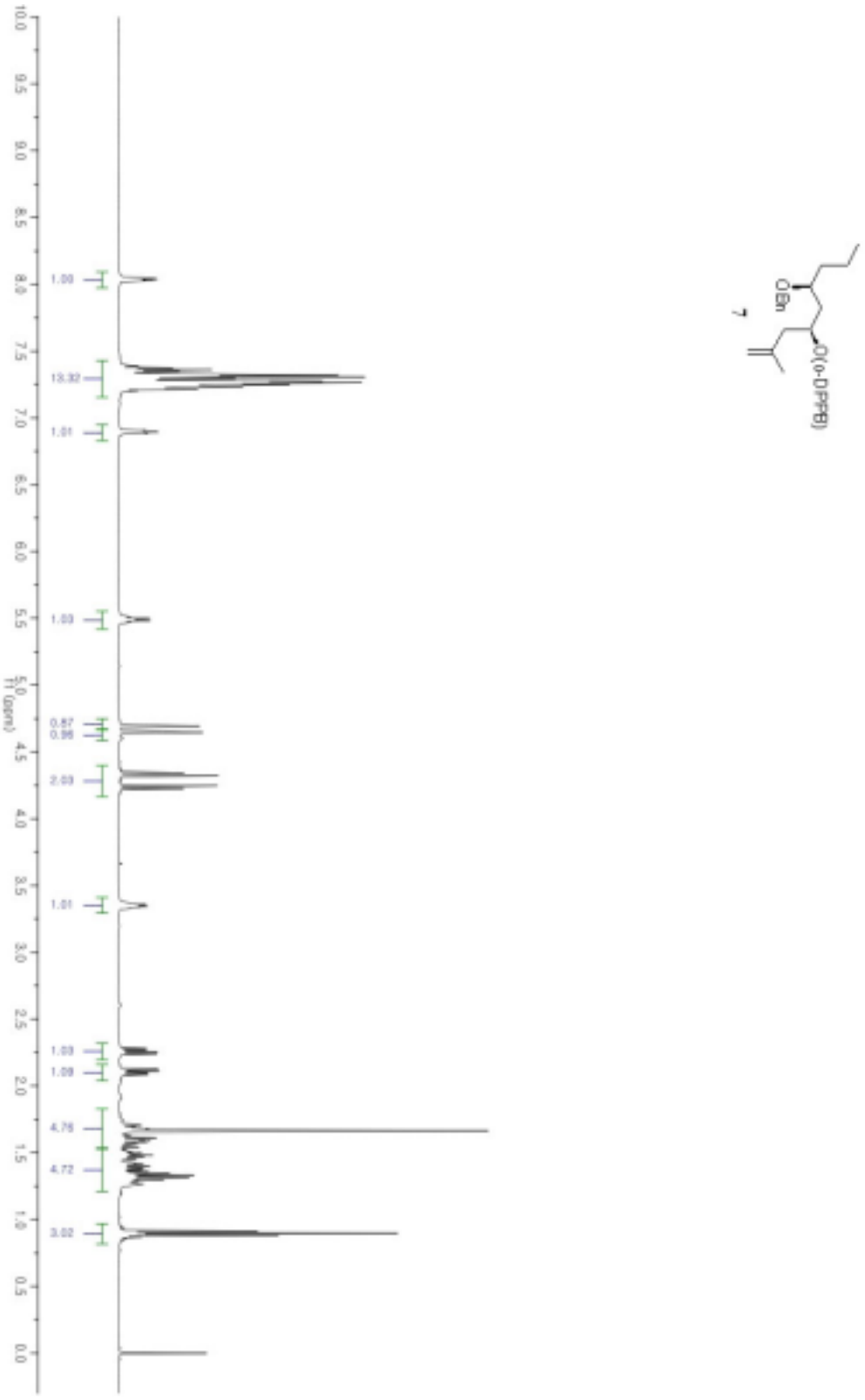
^{13}C-NMR (125 MHz, $CDCl_3$) of **5**



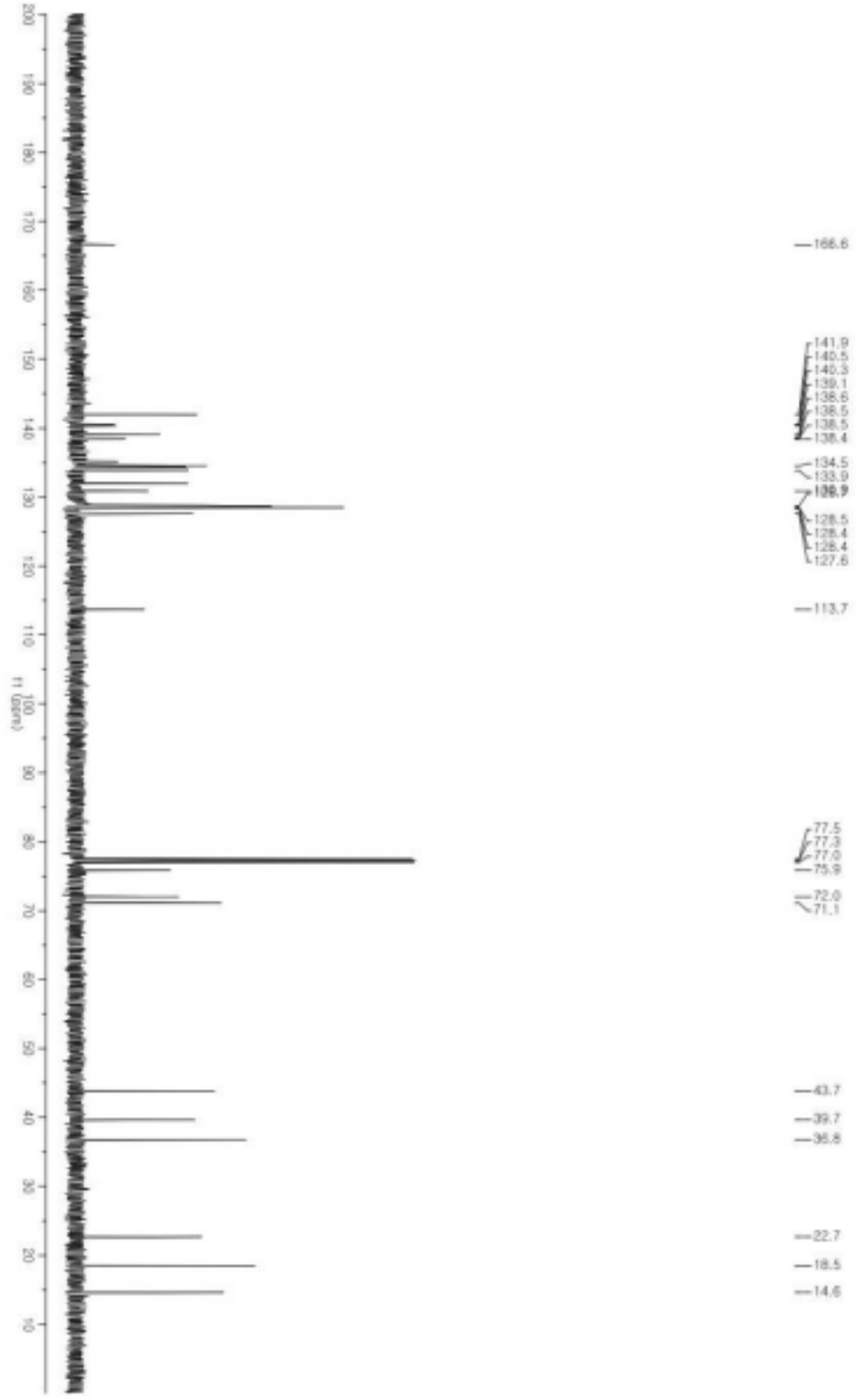
^{1}H-NMR (500 MHz, $CDCl_3$) of 5A



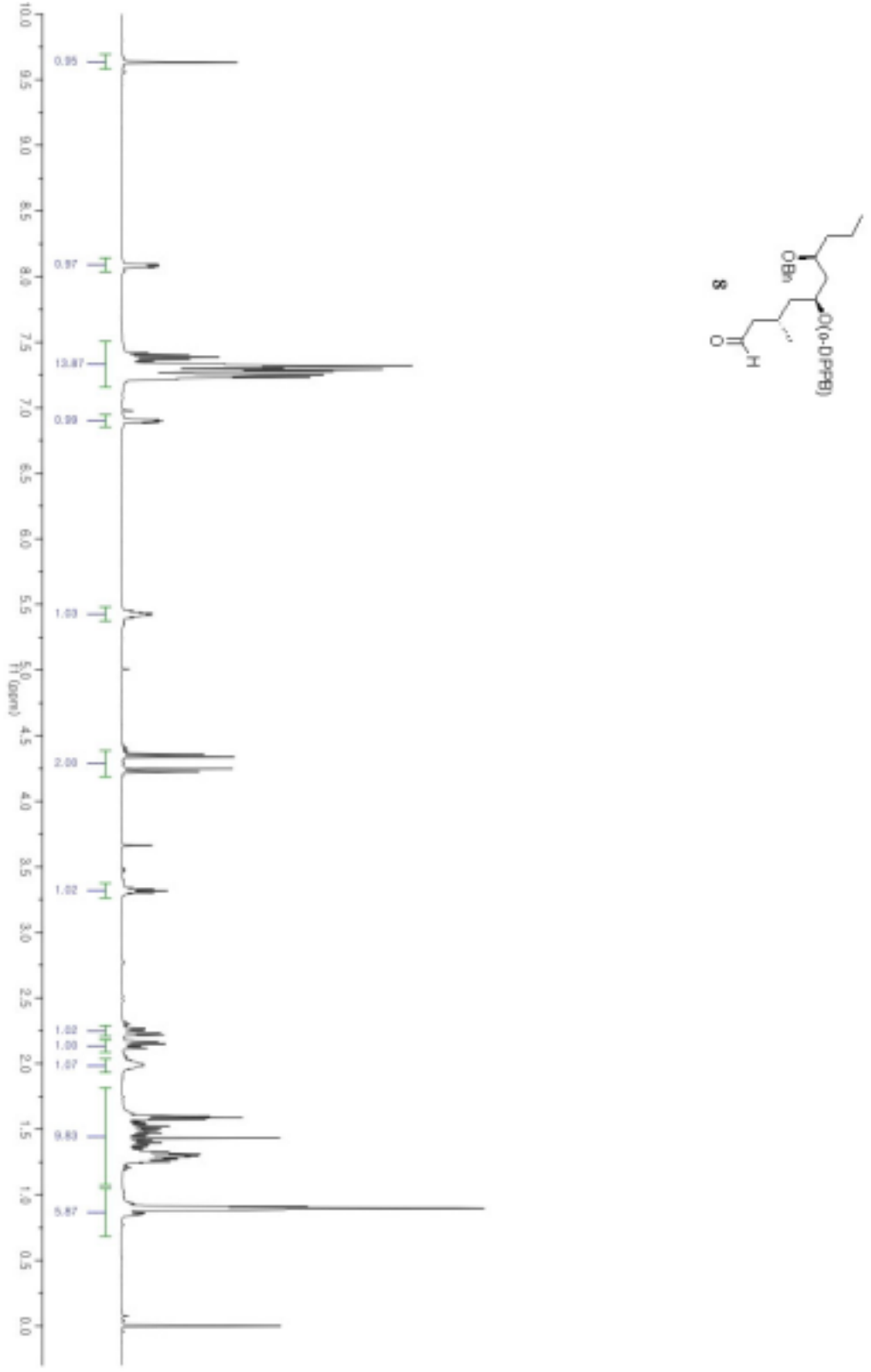
^{13}C-NMR (125 MHz, $CDCl_3$) of **5A**



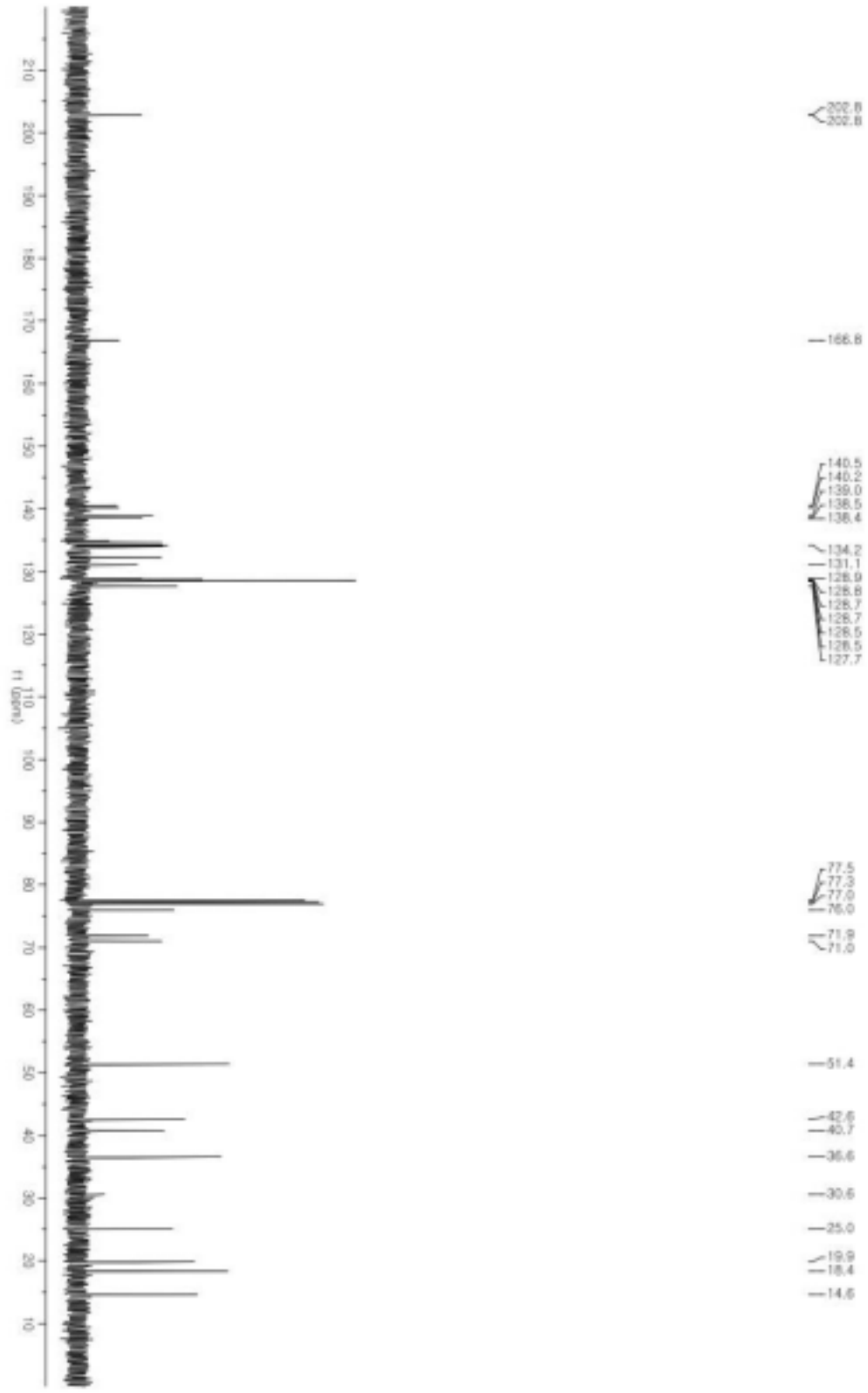
^{1}H-NMR (500 MHz, $CDCl_3$) of **7**



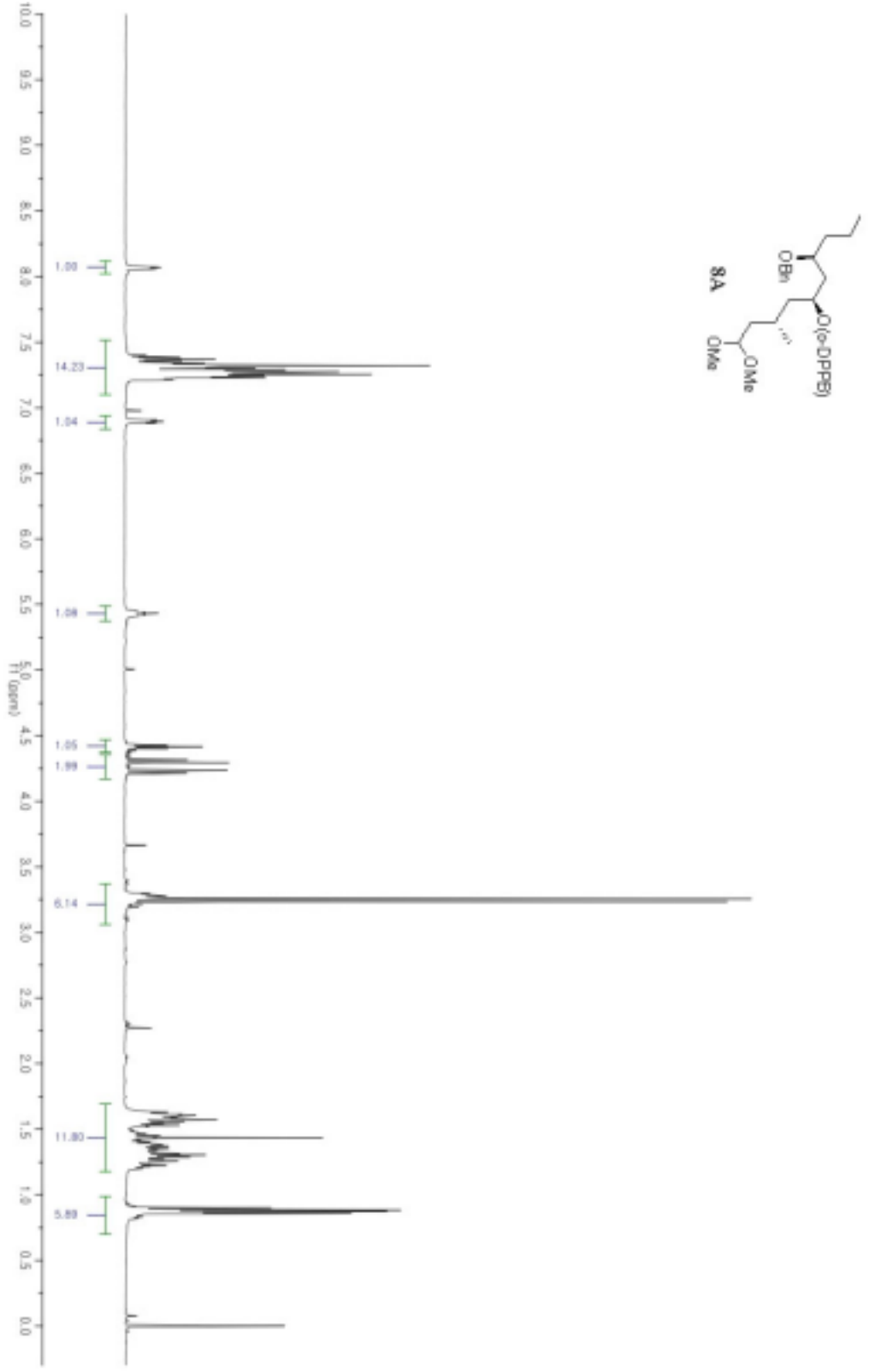
^{13}C-NMR (125 MHz, $CDCl_3$) of **7**



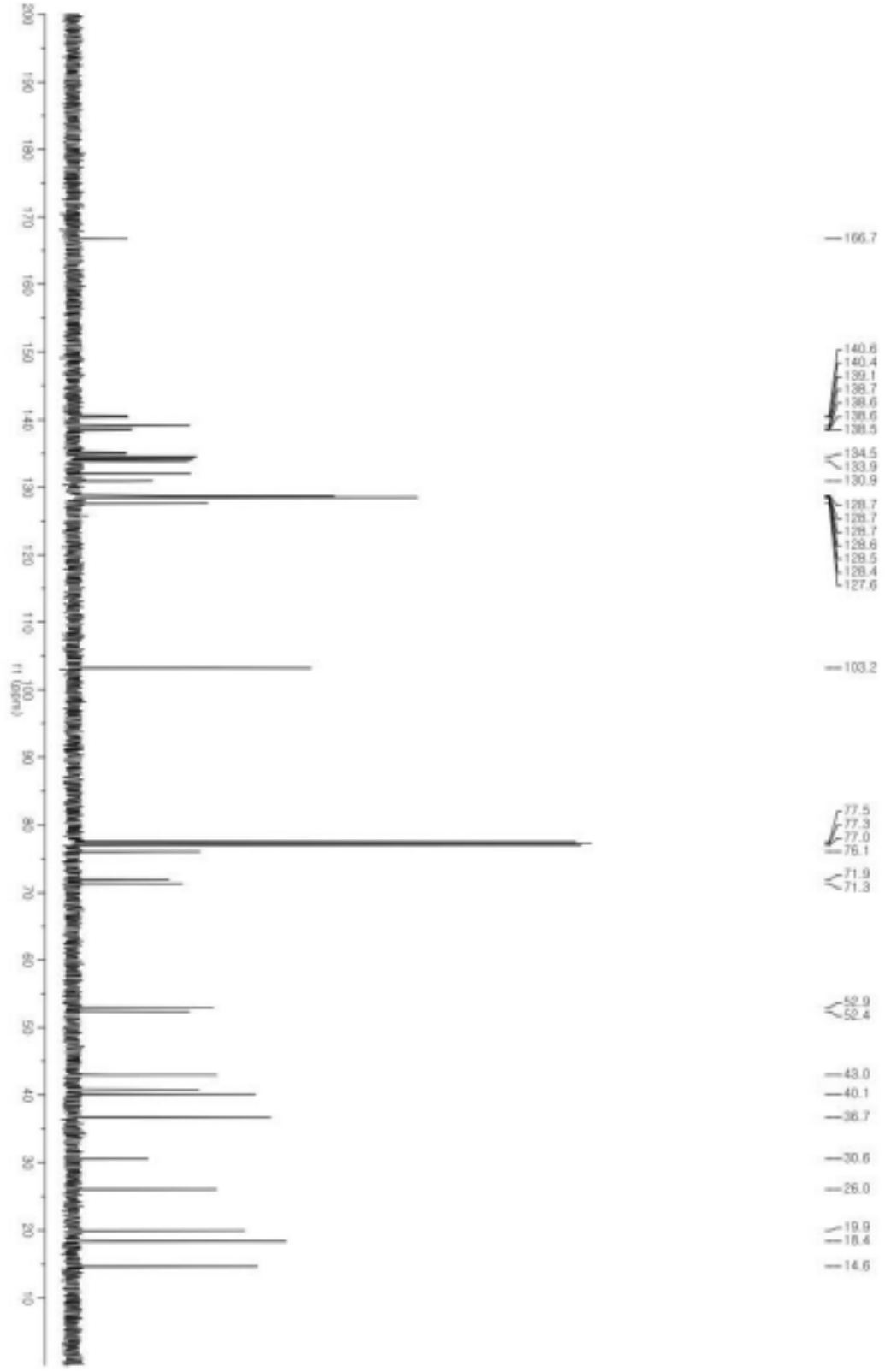
^{1}H-NMR (500 MHz, $CDCl_3$) of **8**



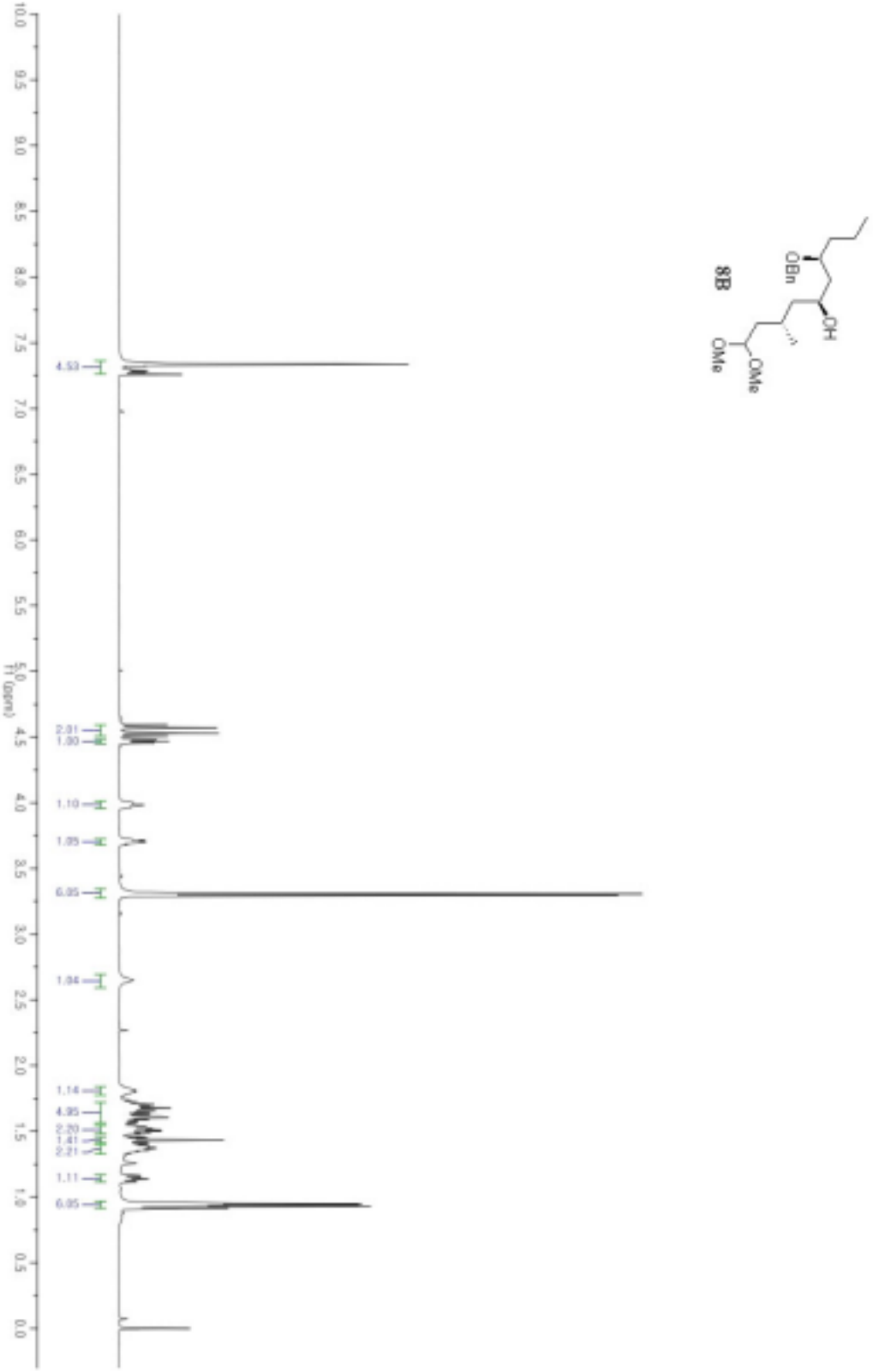
^{13}C-NMR (125 MHz, $CDCl_3$) of **8**



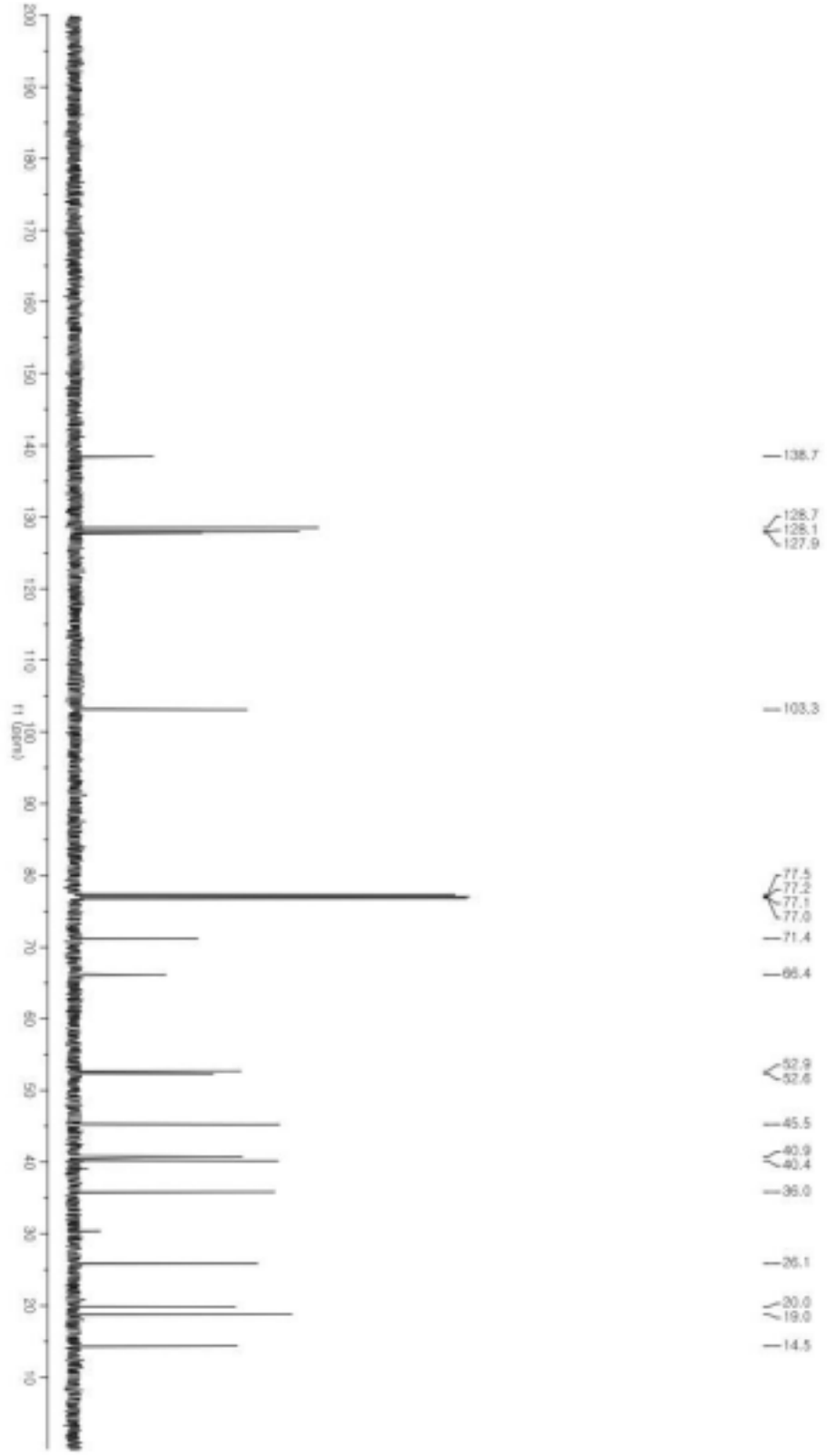
^{1}H-NMR (500 MHz, $CDCl_3$) of **8A**



^{13}C-NMR (125 MHz, $CDCl_3$) of **8A**



^{1}H-NMR (500 MHz, $CDCl_3$) of **8B**



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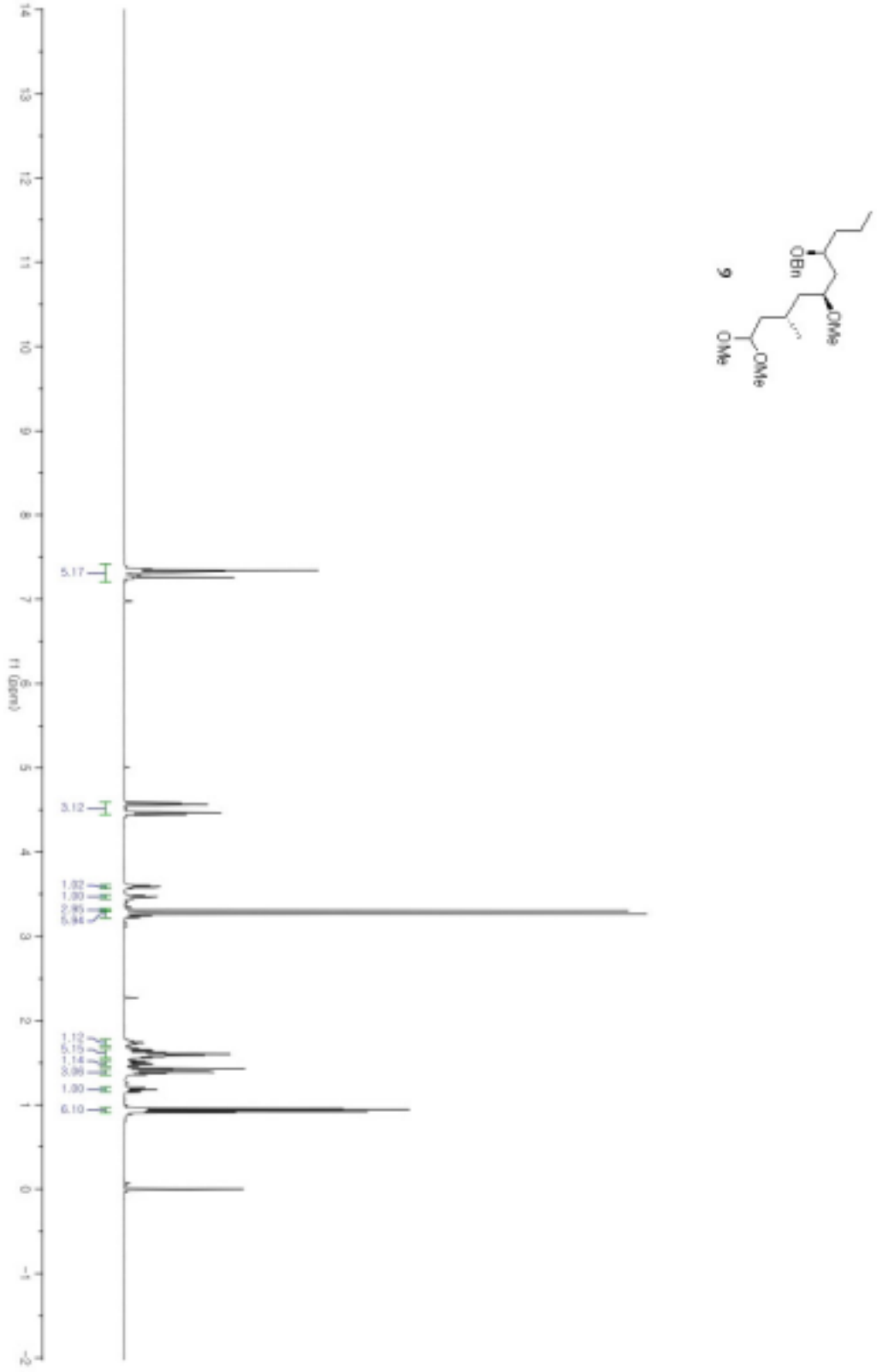
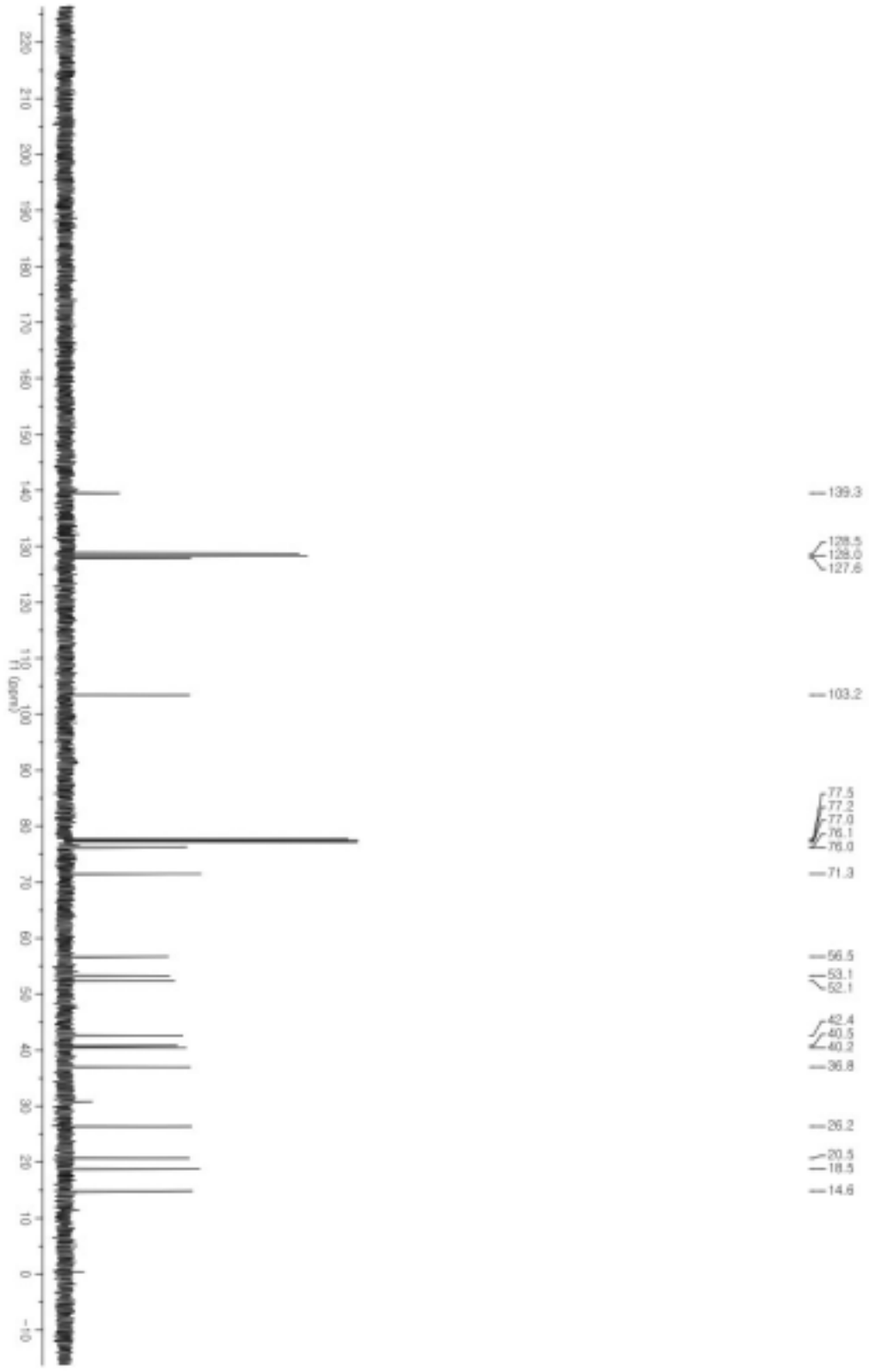
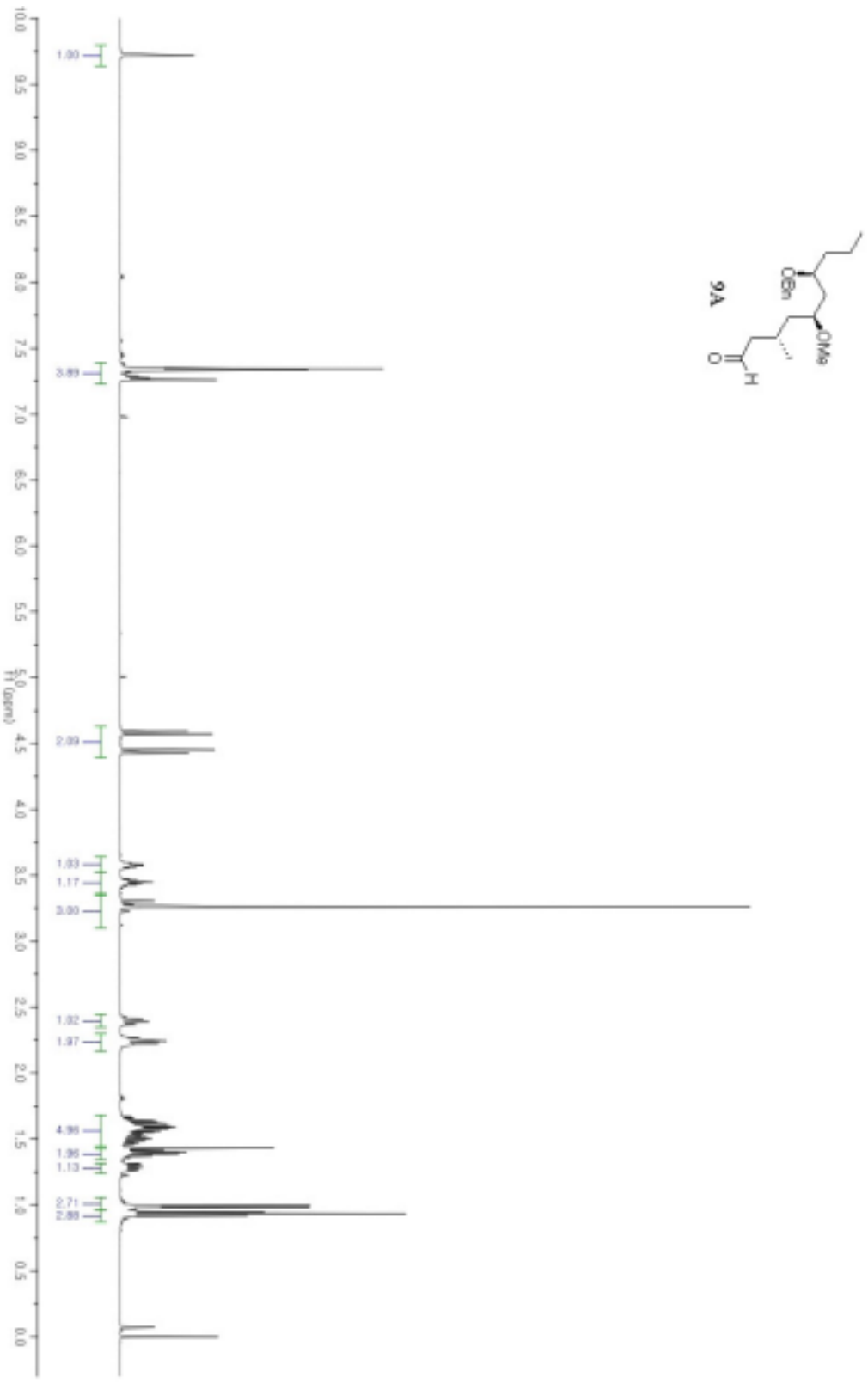


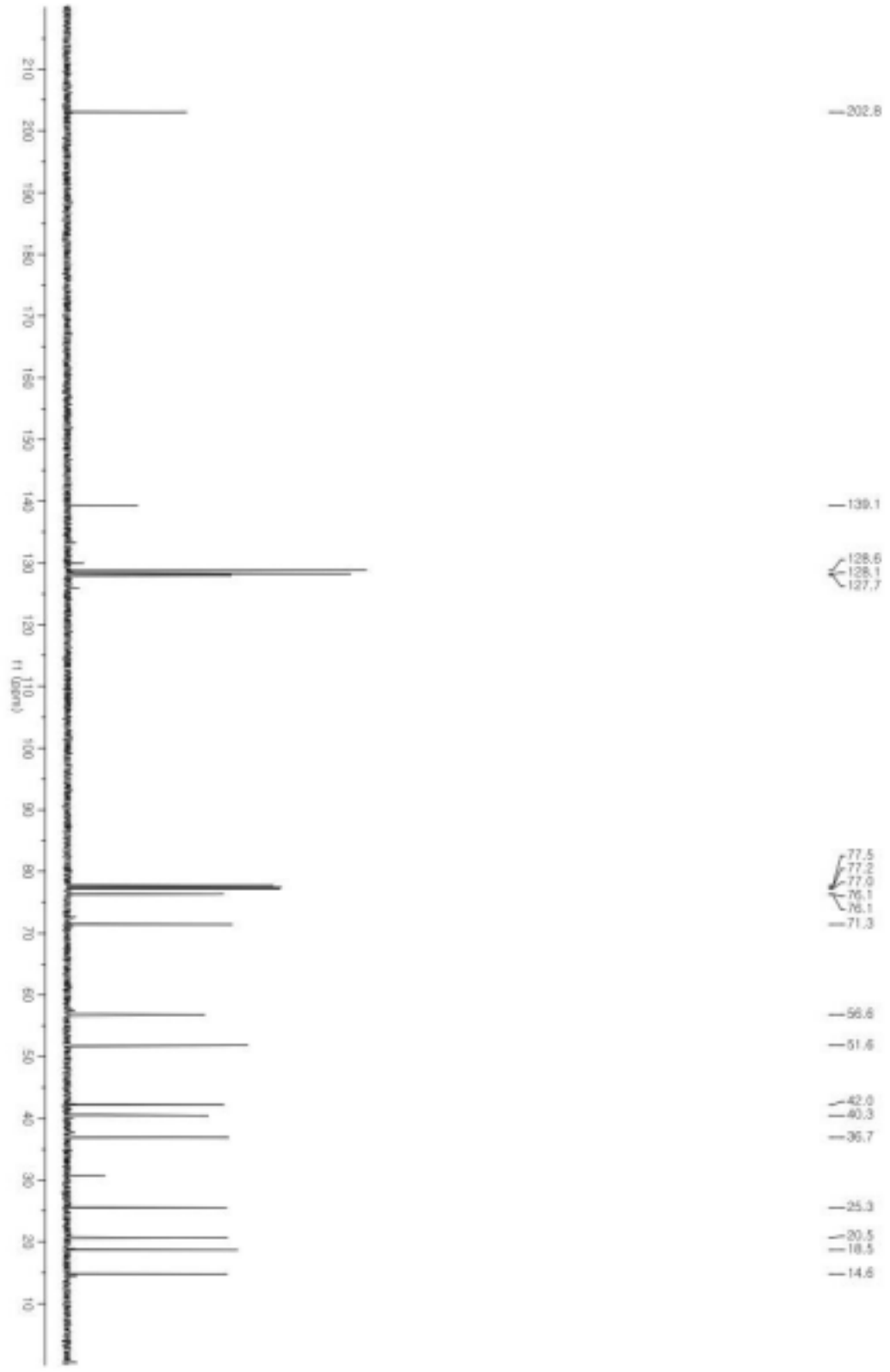
^{1}H-NMR (500 MHz, $CDCl_3$) of **9**



^{13}C-NMR (125 MHz, $CDCl_3$) of **9**



^{1}H-NMR (500 MHz, $CDCl_3$) of **9A**



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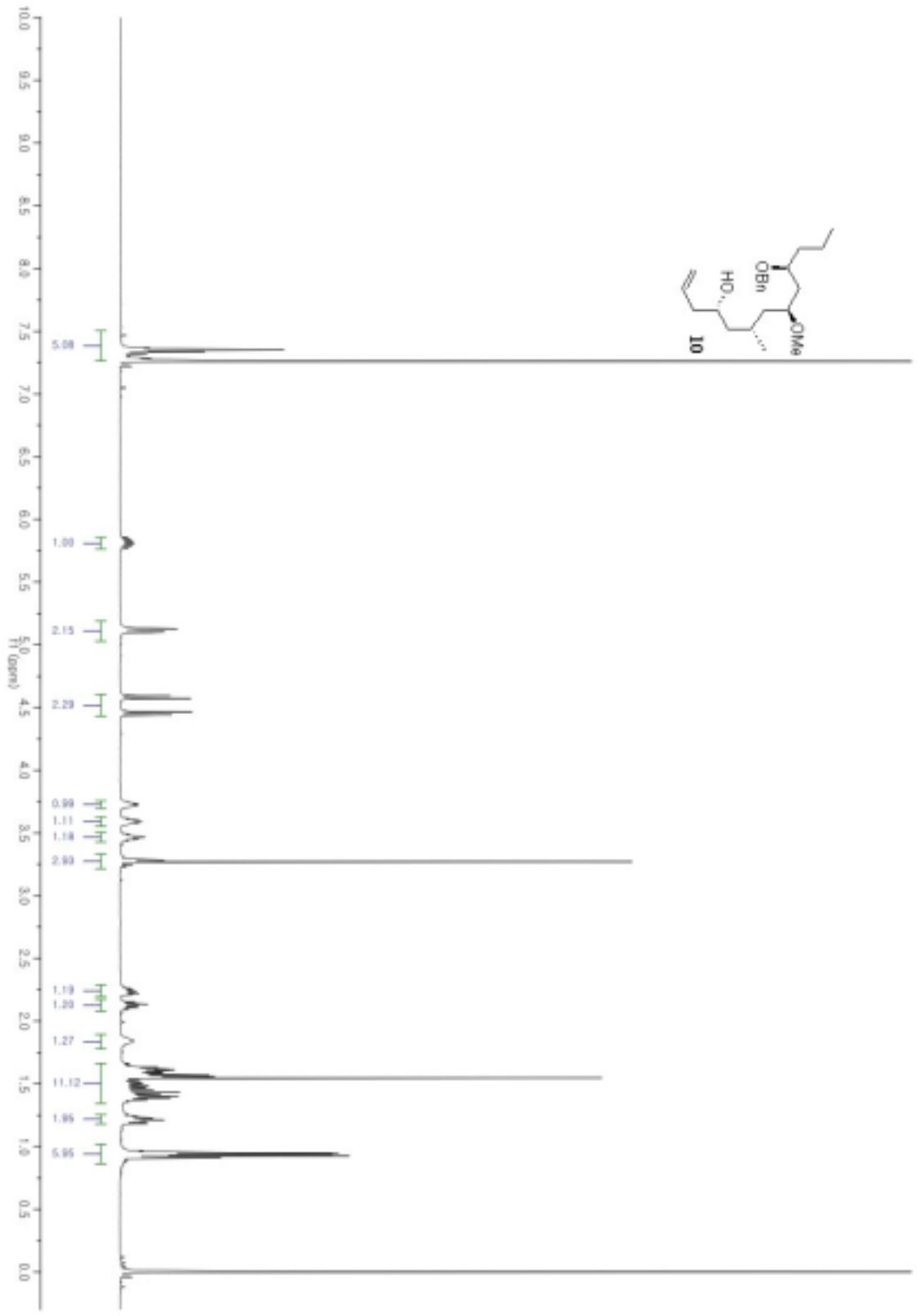
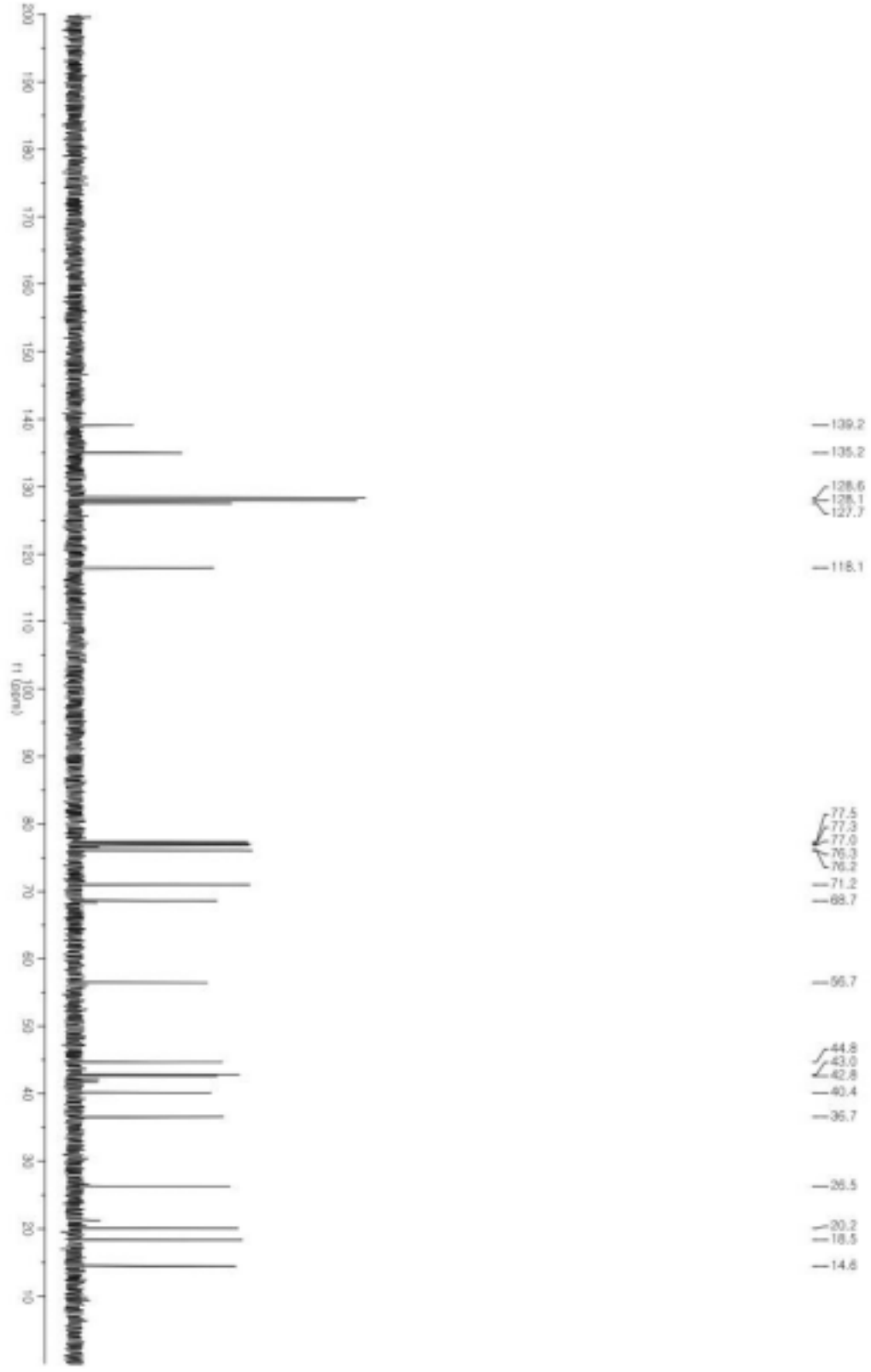


^{1}H-NMR (500 MHz, $CDCl_3$) of **10**



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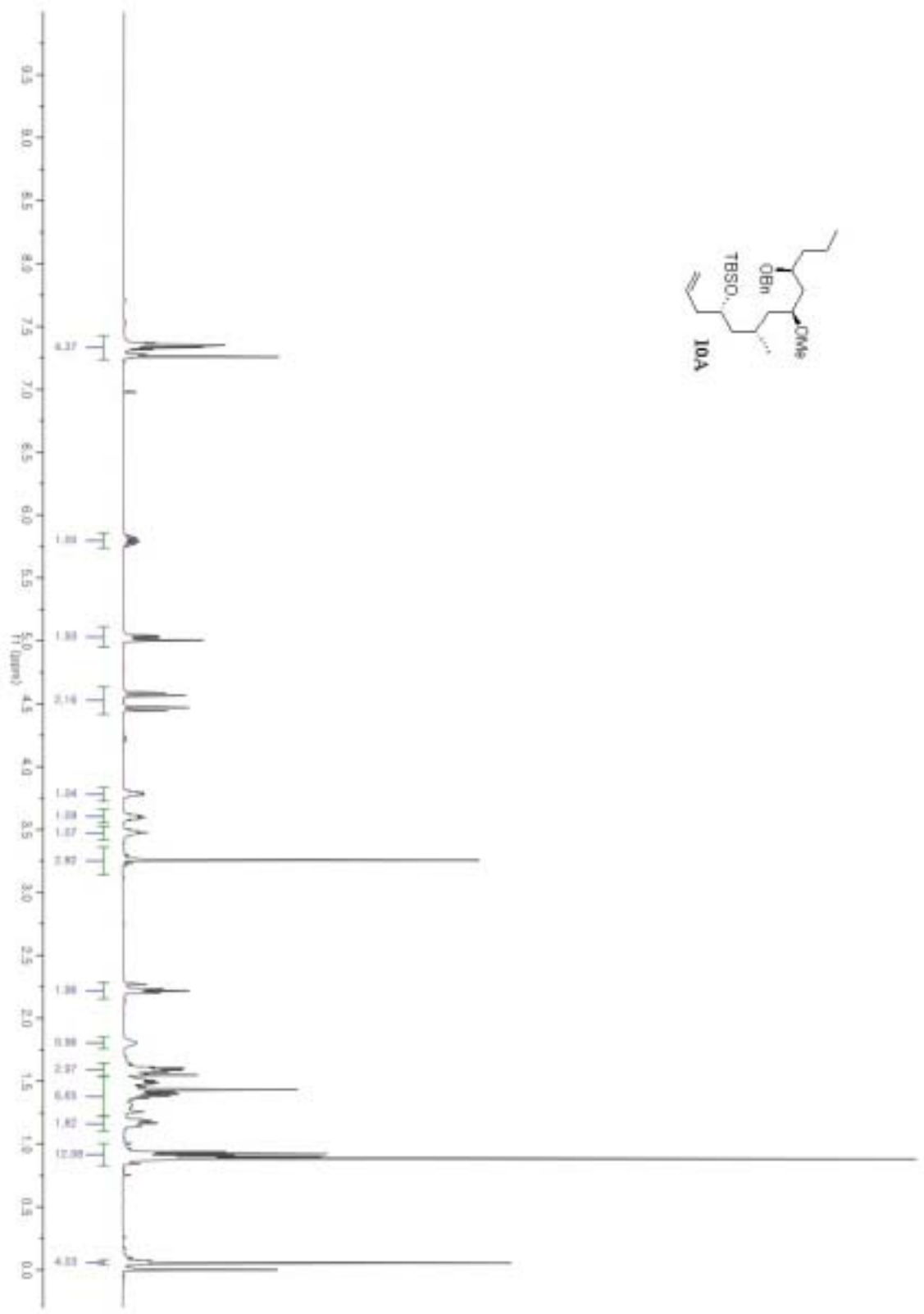
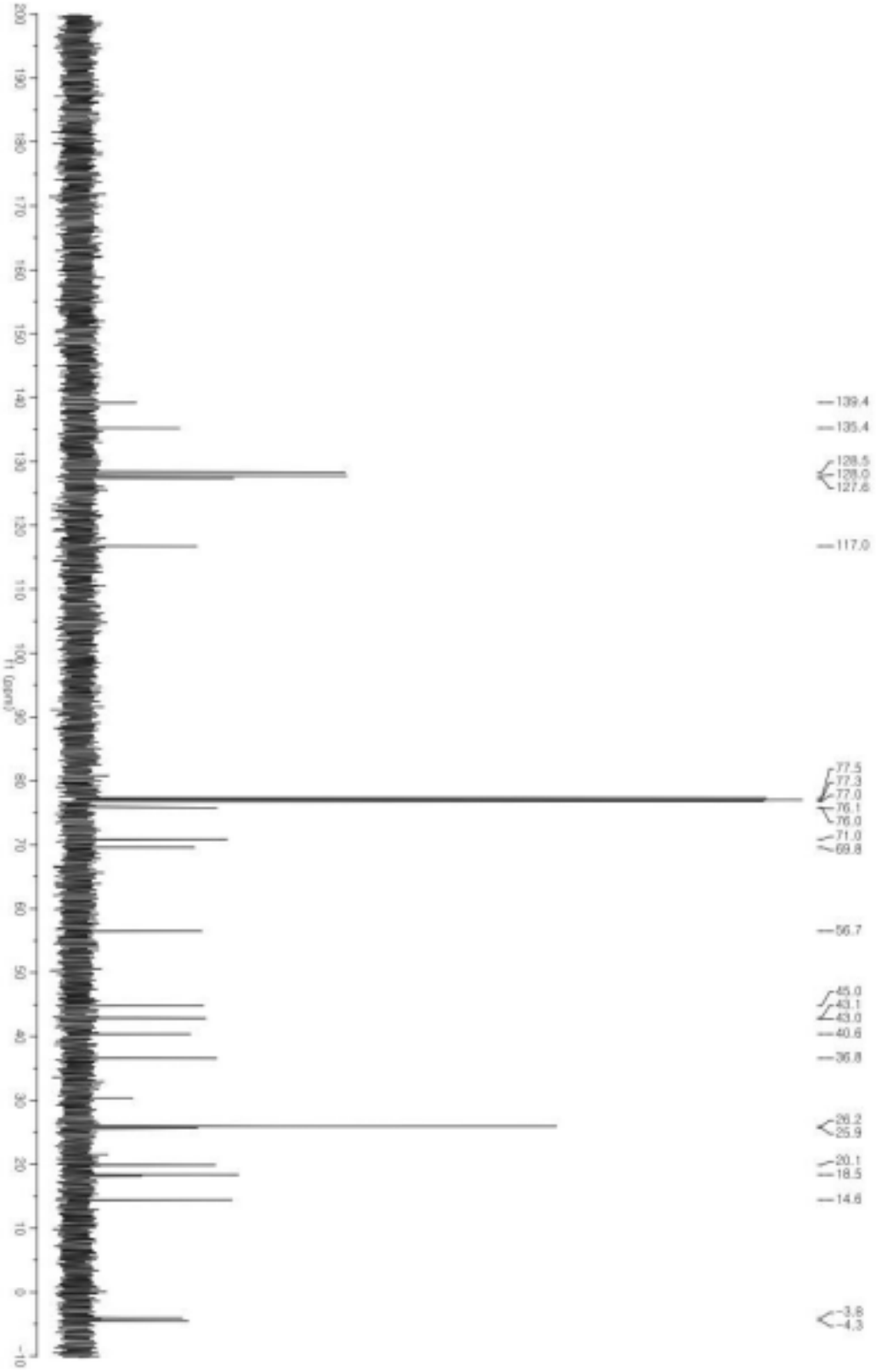
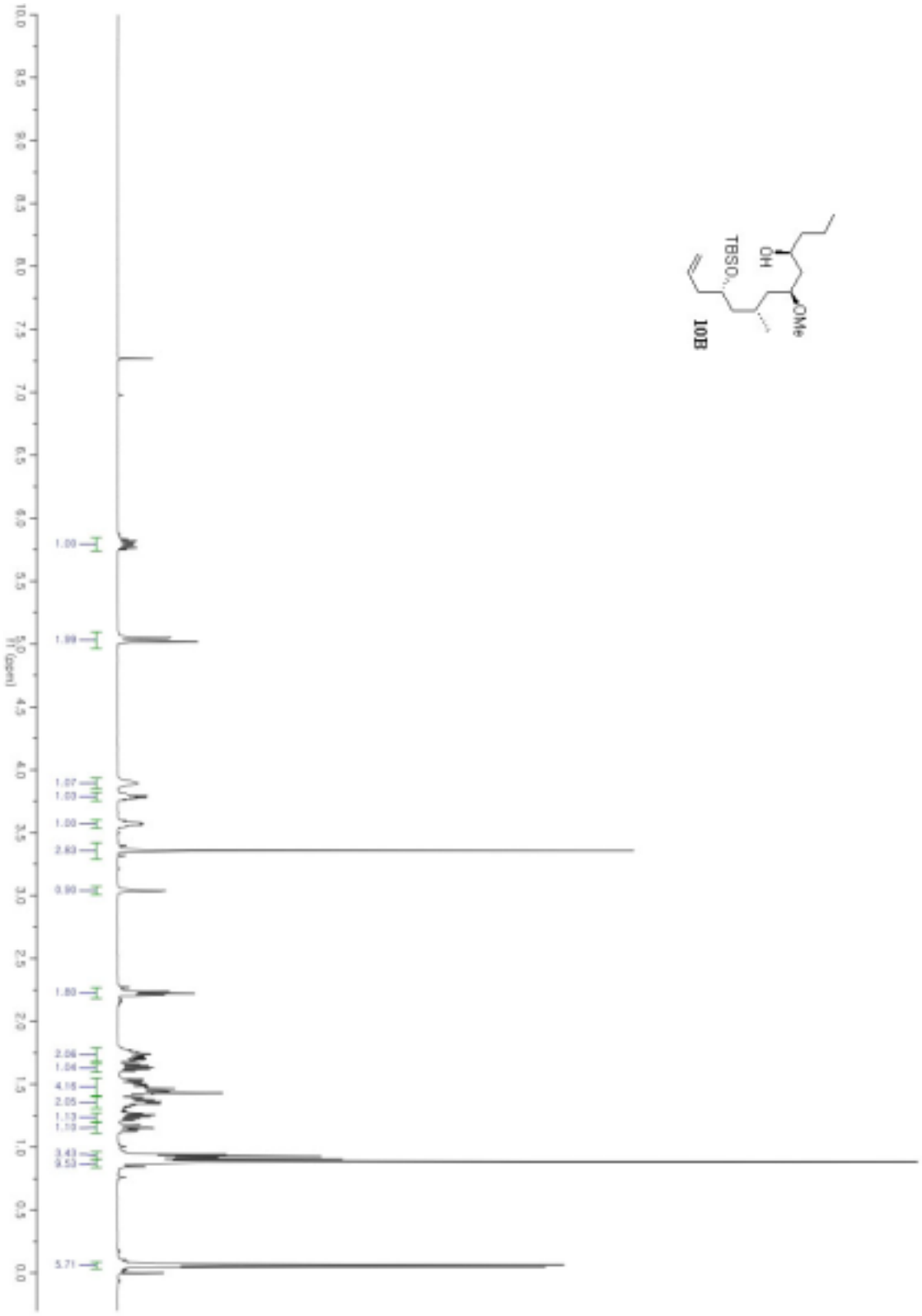


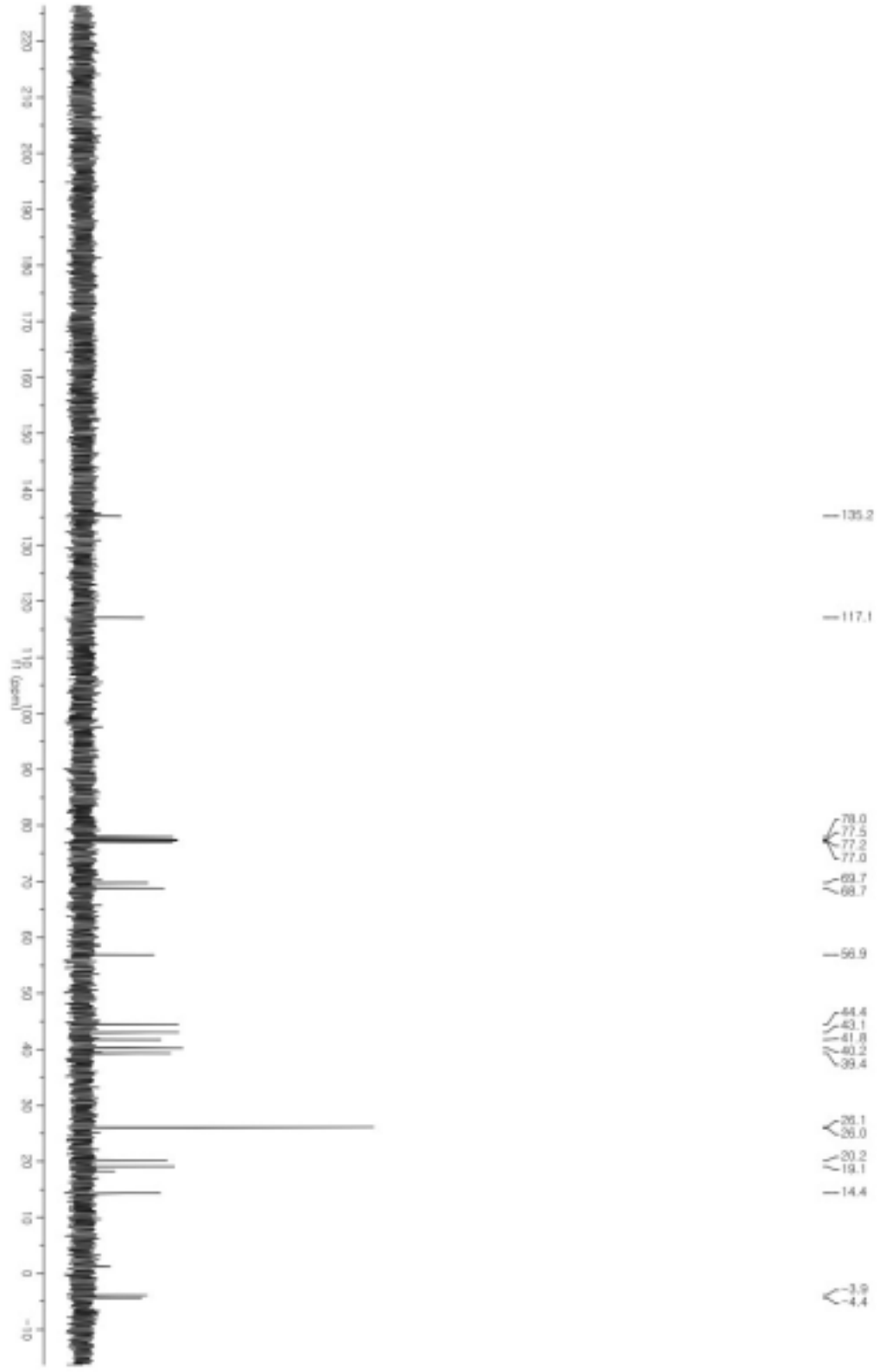
^{1}H-NMR (500 MHz, $CDCl_3$) of **10A**



^{13}C-NMR (125 MHz, $CDCl_3$) of **10A**

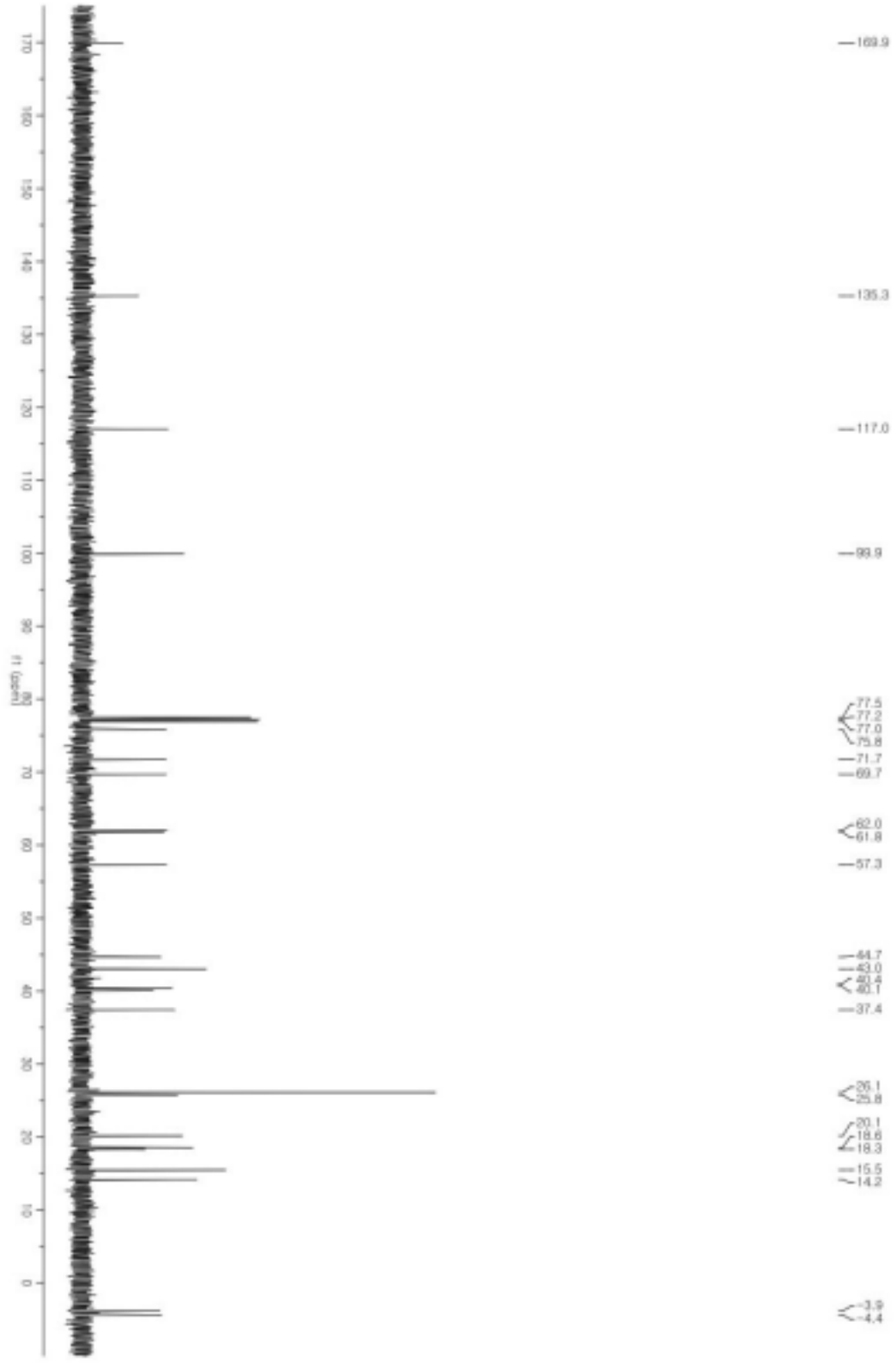


^{1}H-NMR (500 MHz, $CDCl_3$) of **10B**

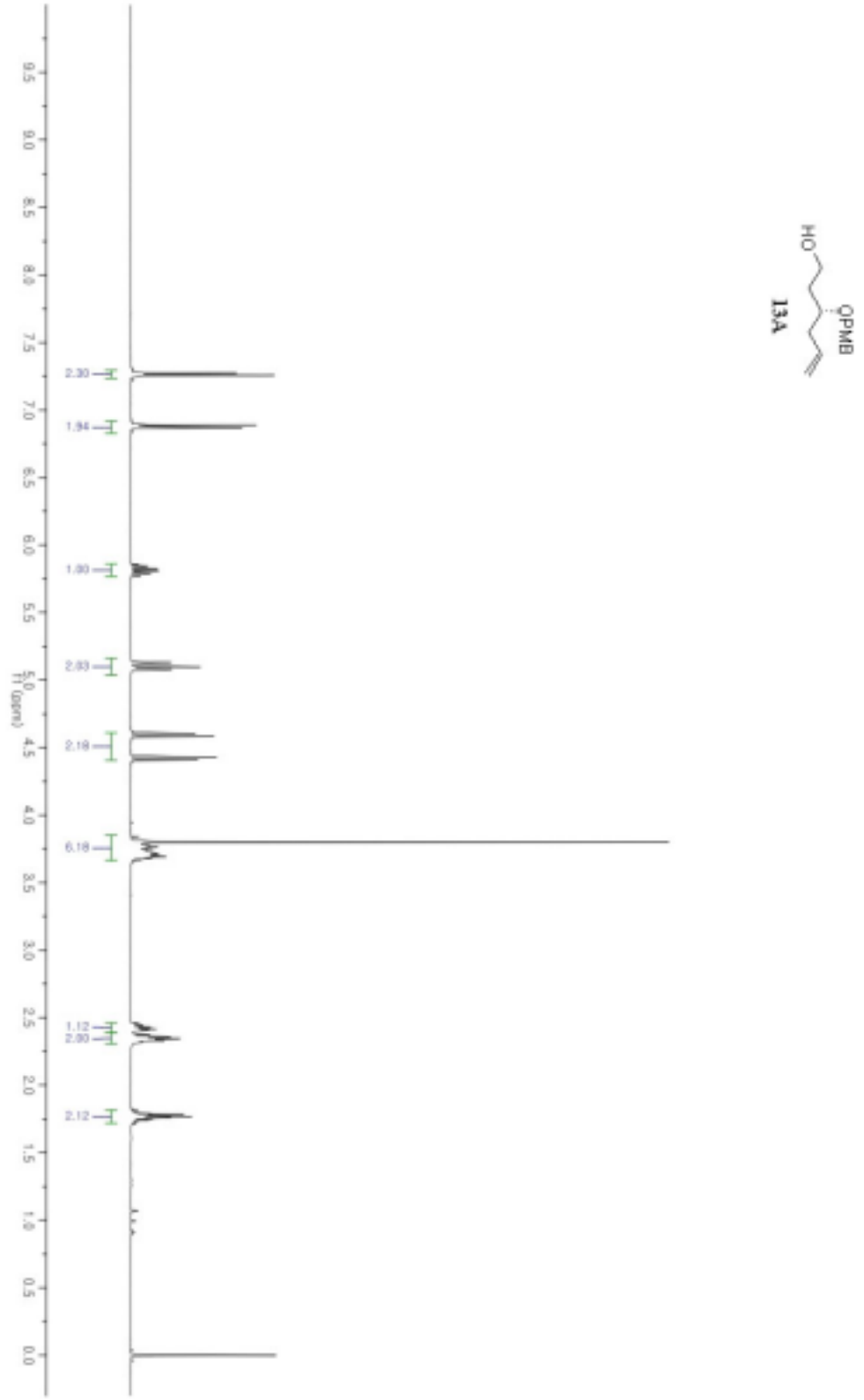


^{13}C-NMR (125 MHz, $CDCl_3$) of **10B**

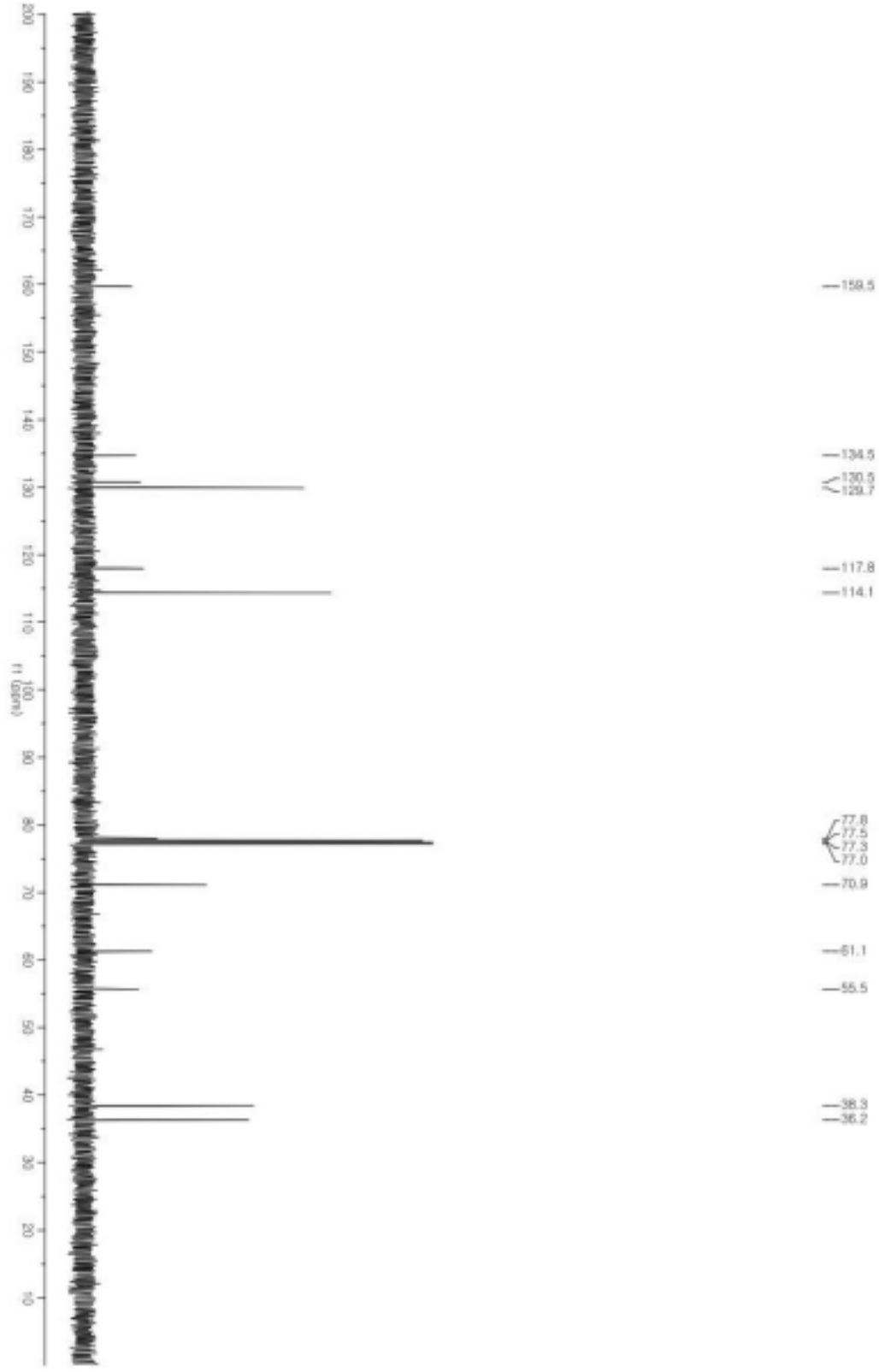
^{1}H-NMR (500 MHz, $CDCl_3$) of **11**



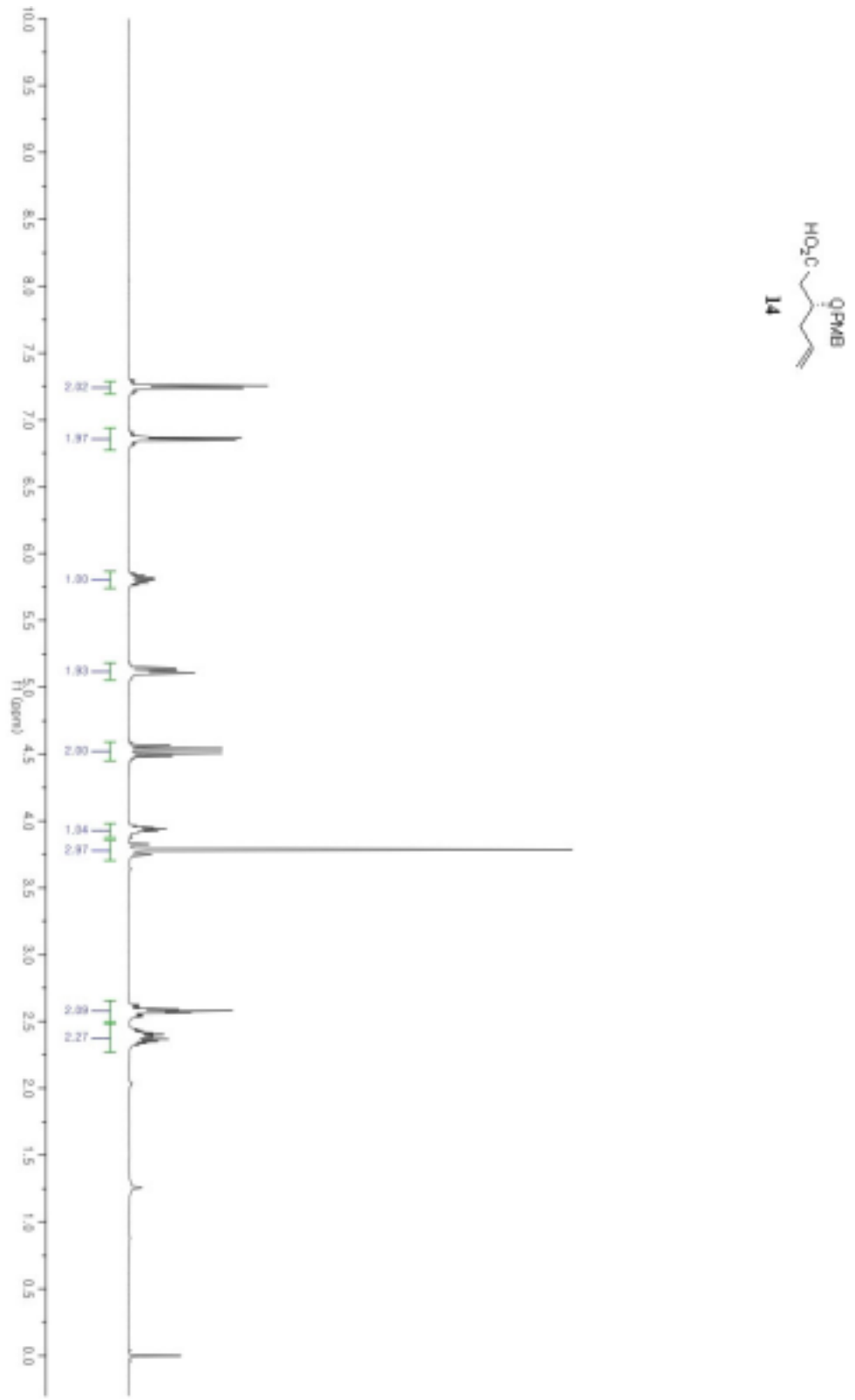
^{13}C-NMR (125 MHz, $CDCl_3$) of **11**



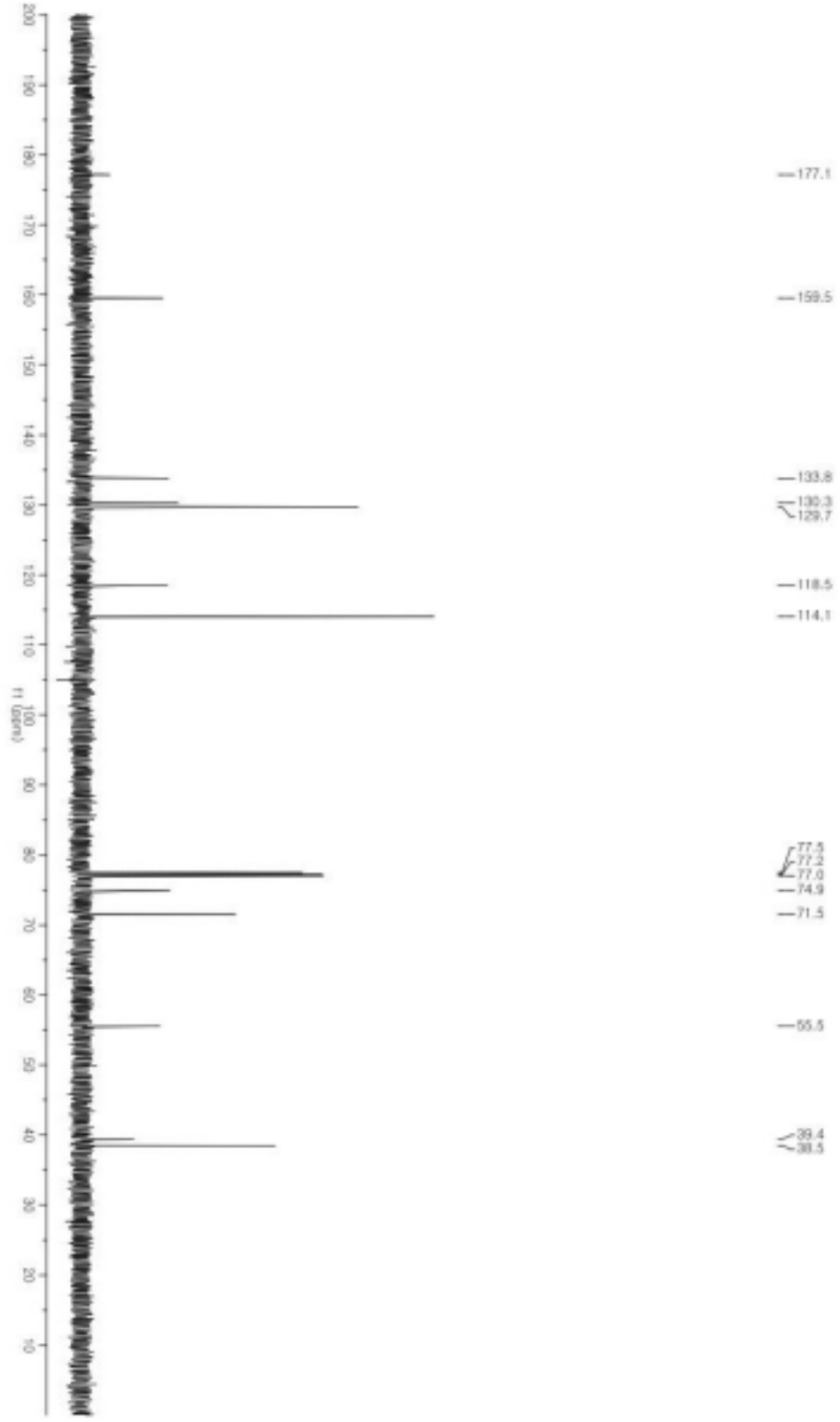
^{1}H-NMR (500 MHz, $CDCl_3$) of **13A**



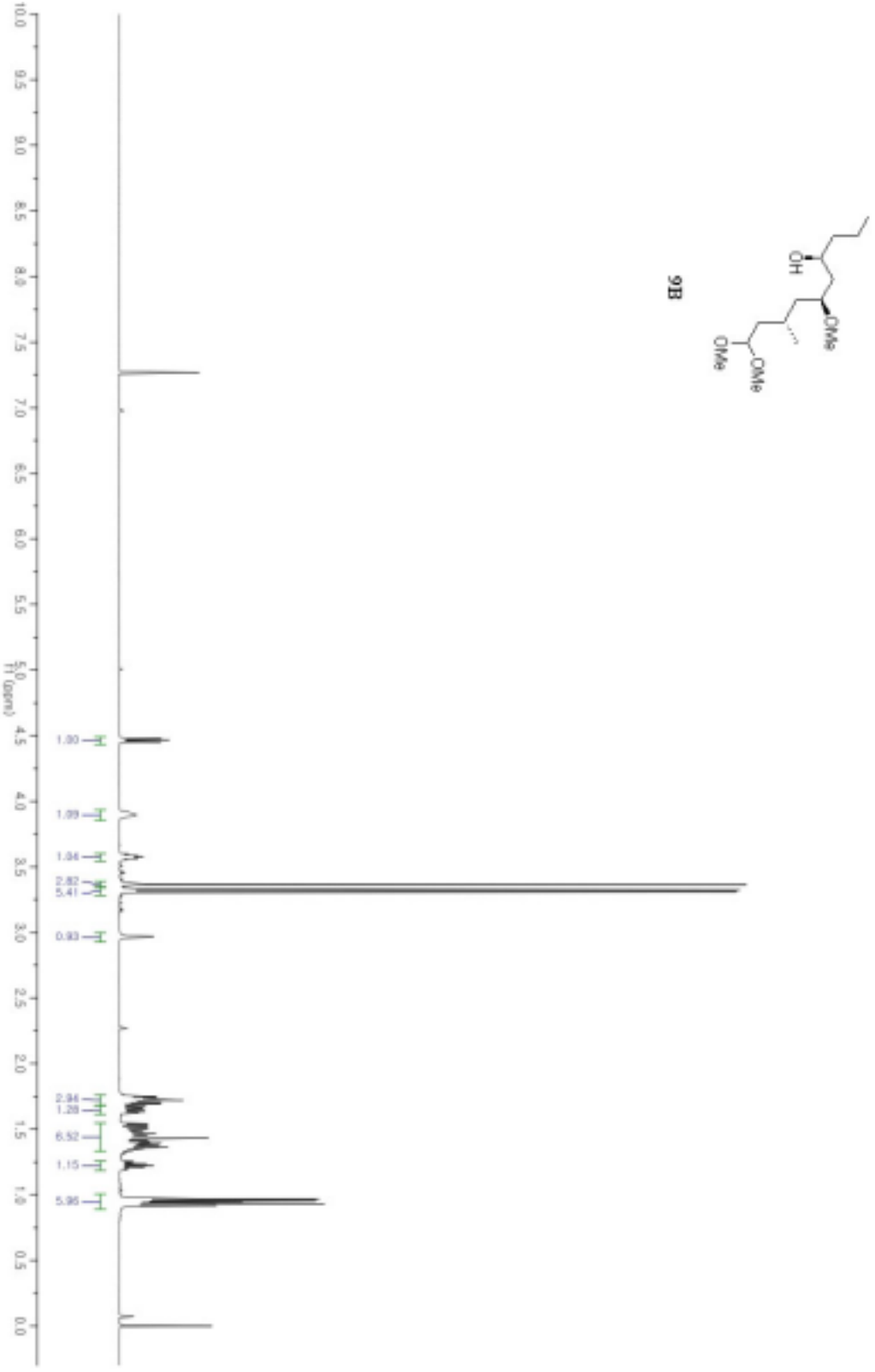
^{13}C-NMR (125 MHz, $CDCl_3$) of **13A**



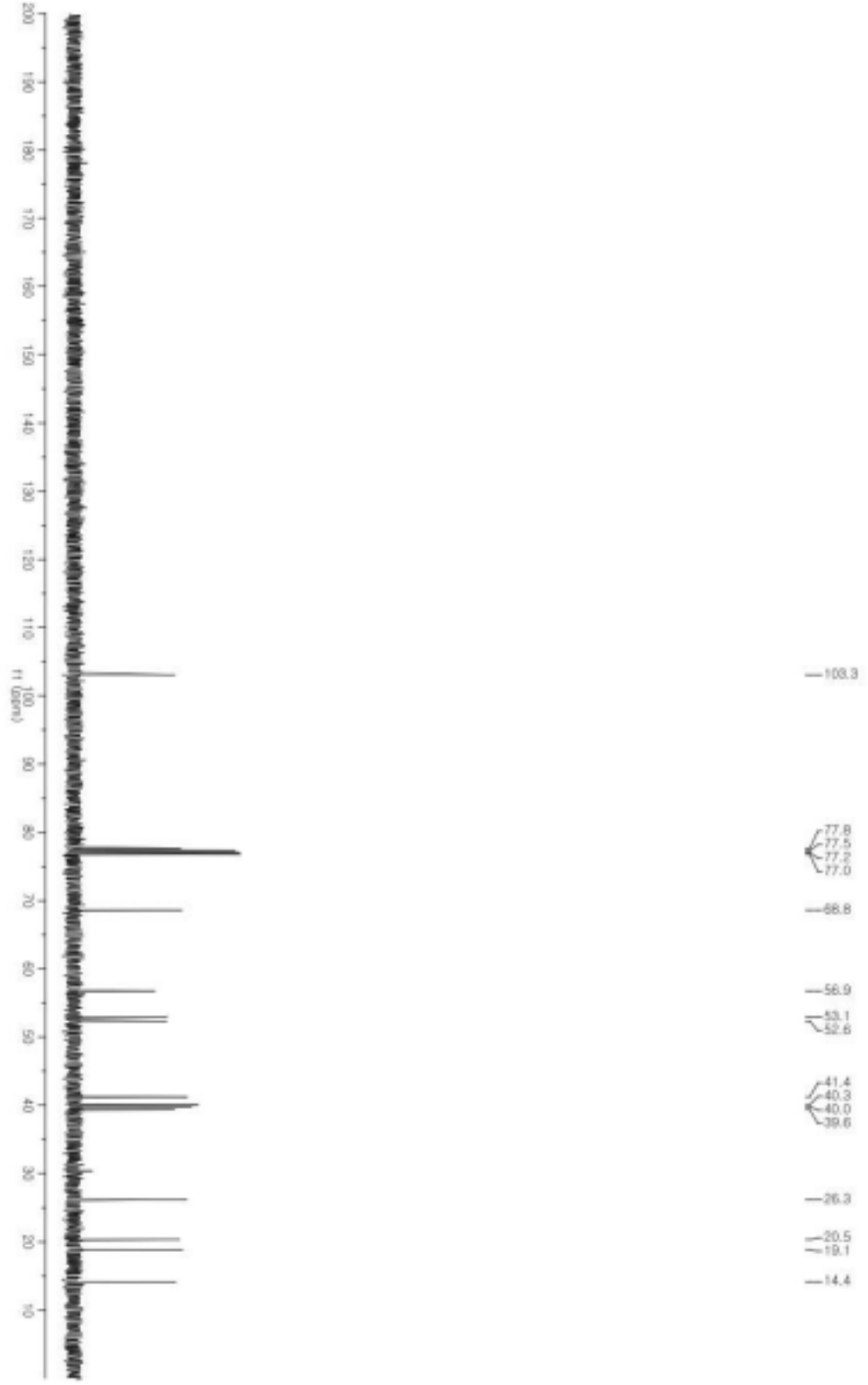
^{1}H-NMR (500 MHz, $CDCl_3$) of **14**



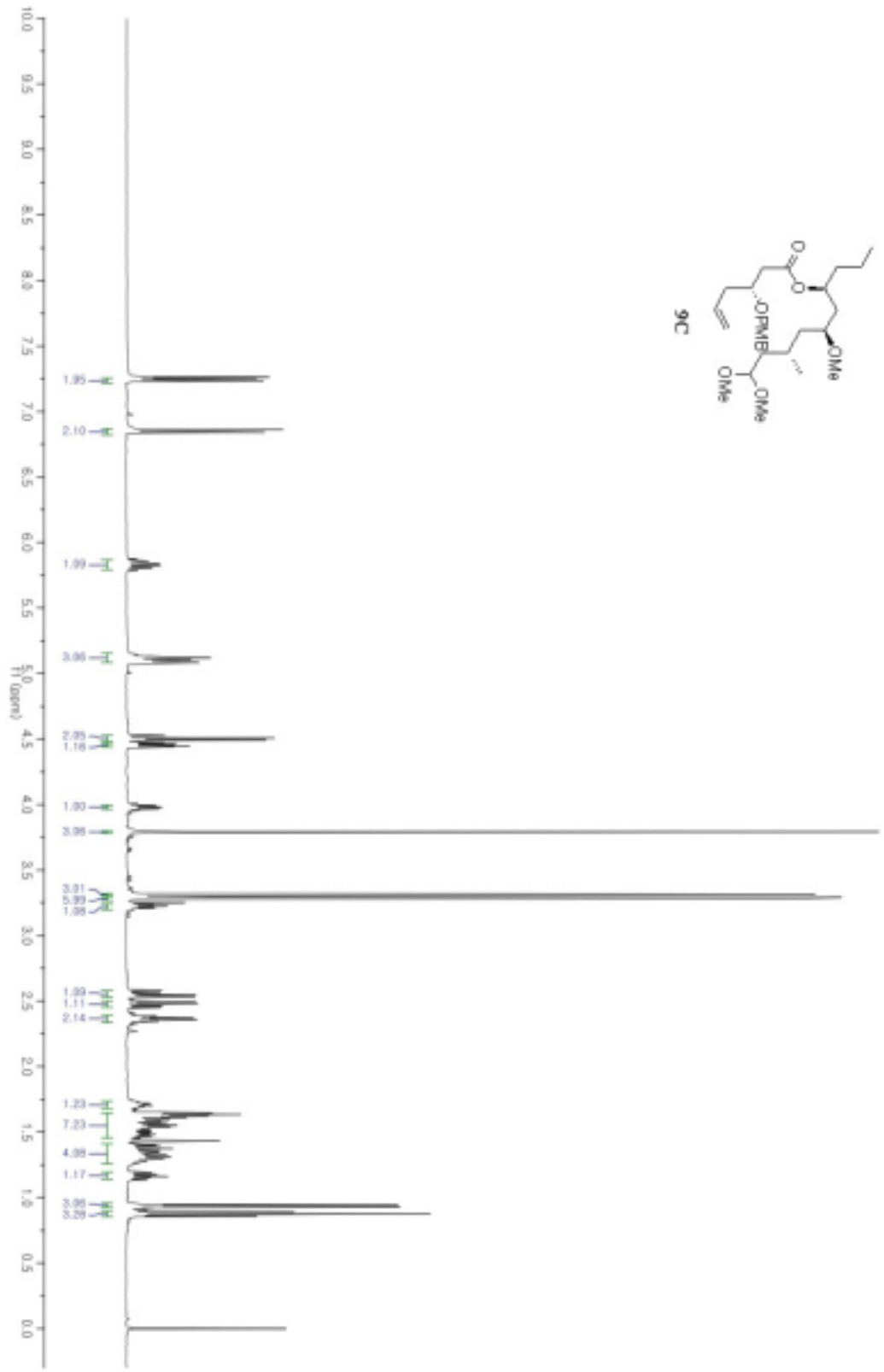
^{13}C-NMR (125 MHz, $CDCl_3$) of **14**



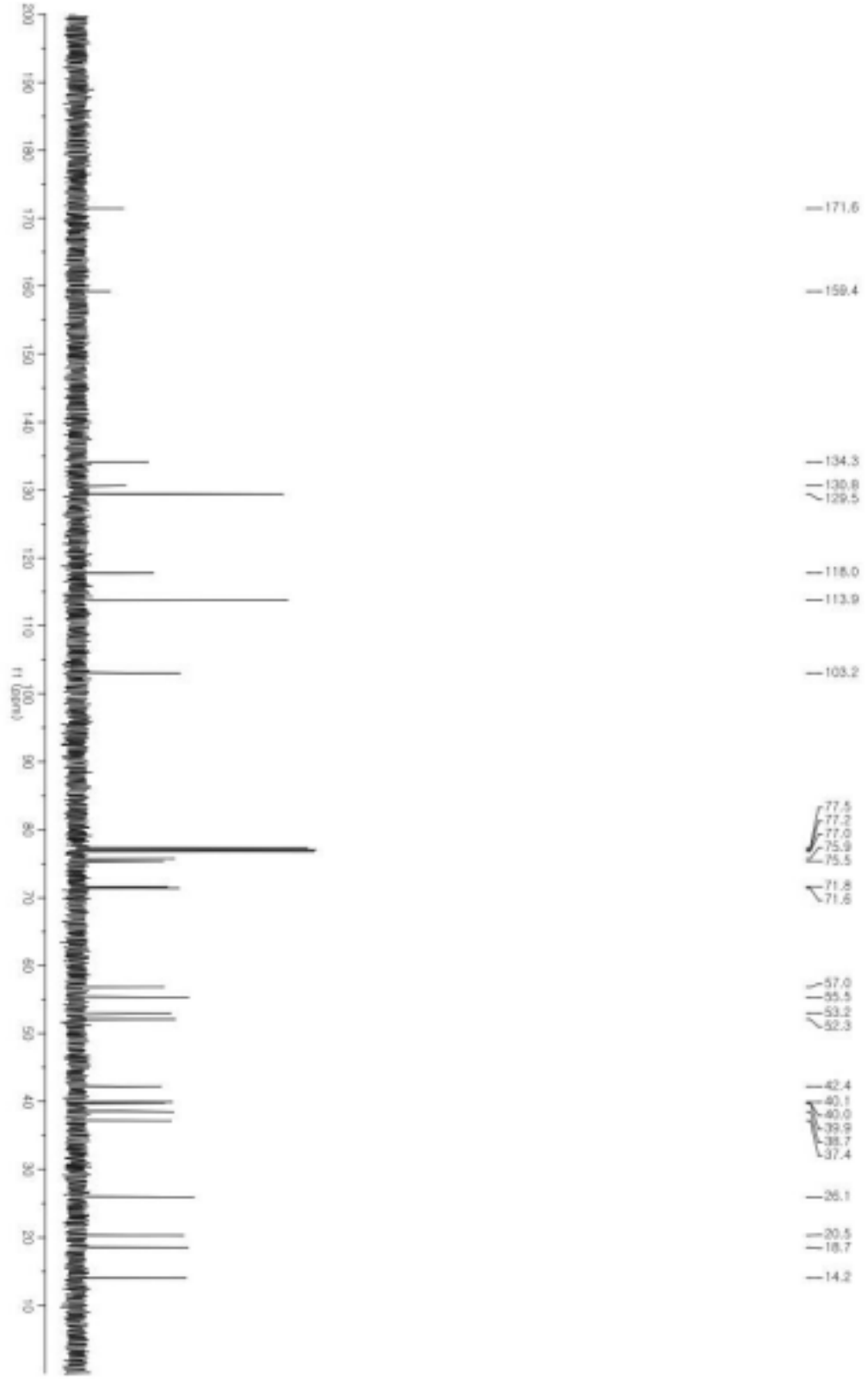
^{1}H-NMR (500 MHz, $CDCl_3$) of **9B**



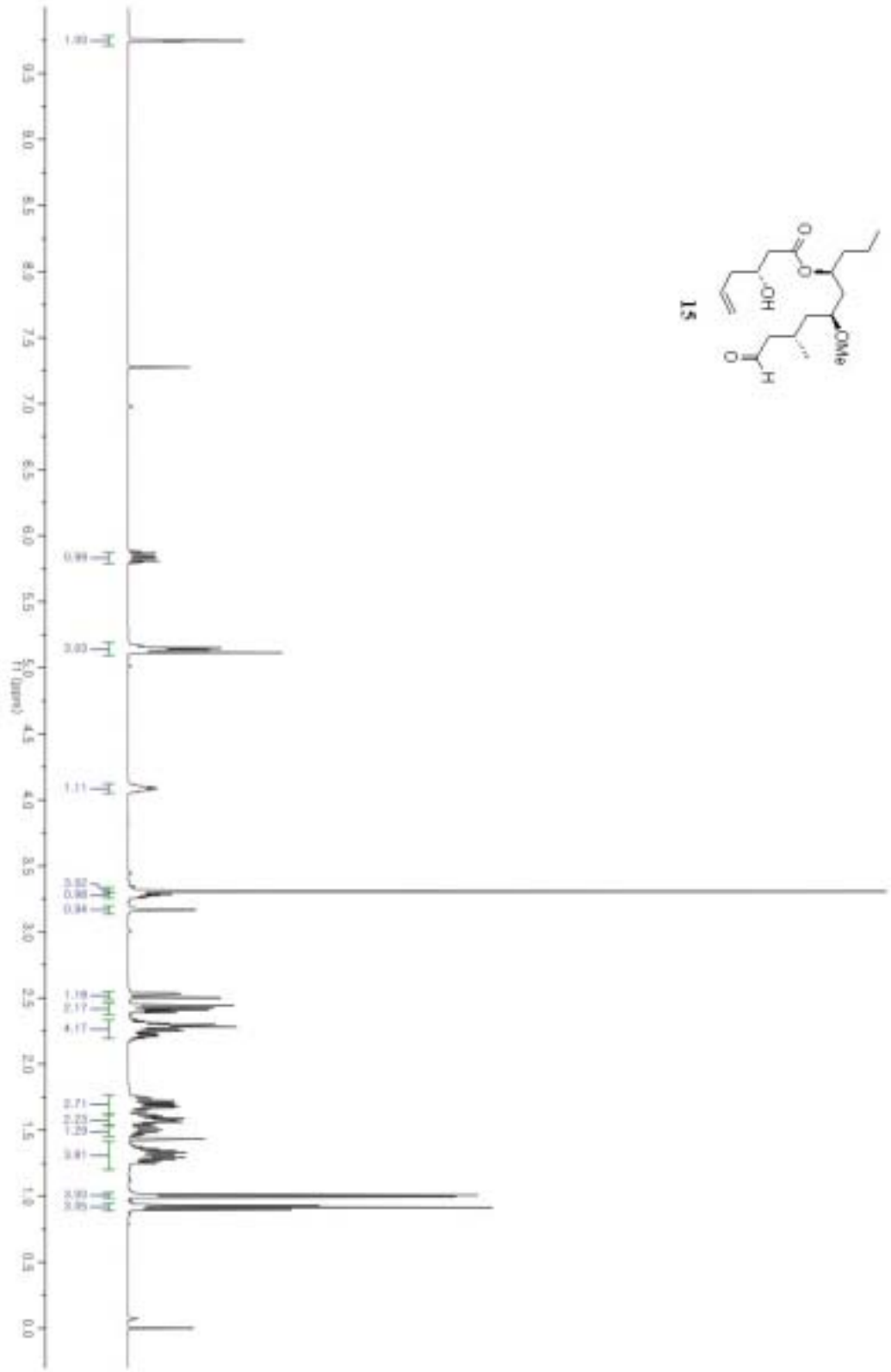
^{13}C-NMR (125 MHz, $CDCl_3$) of **9B**



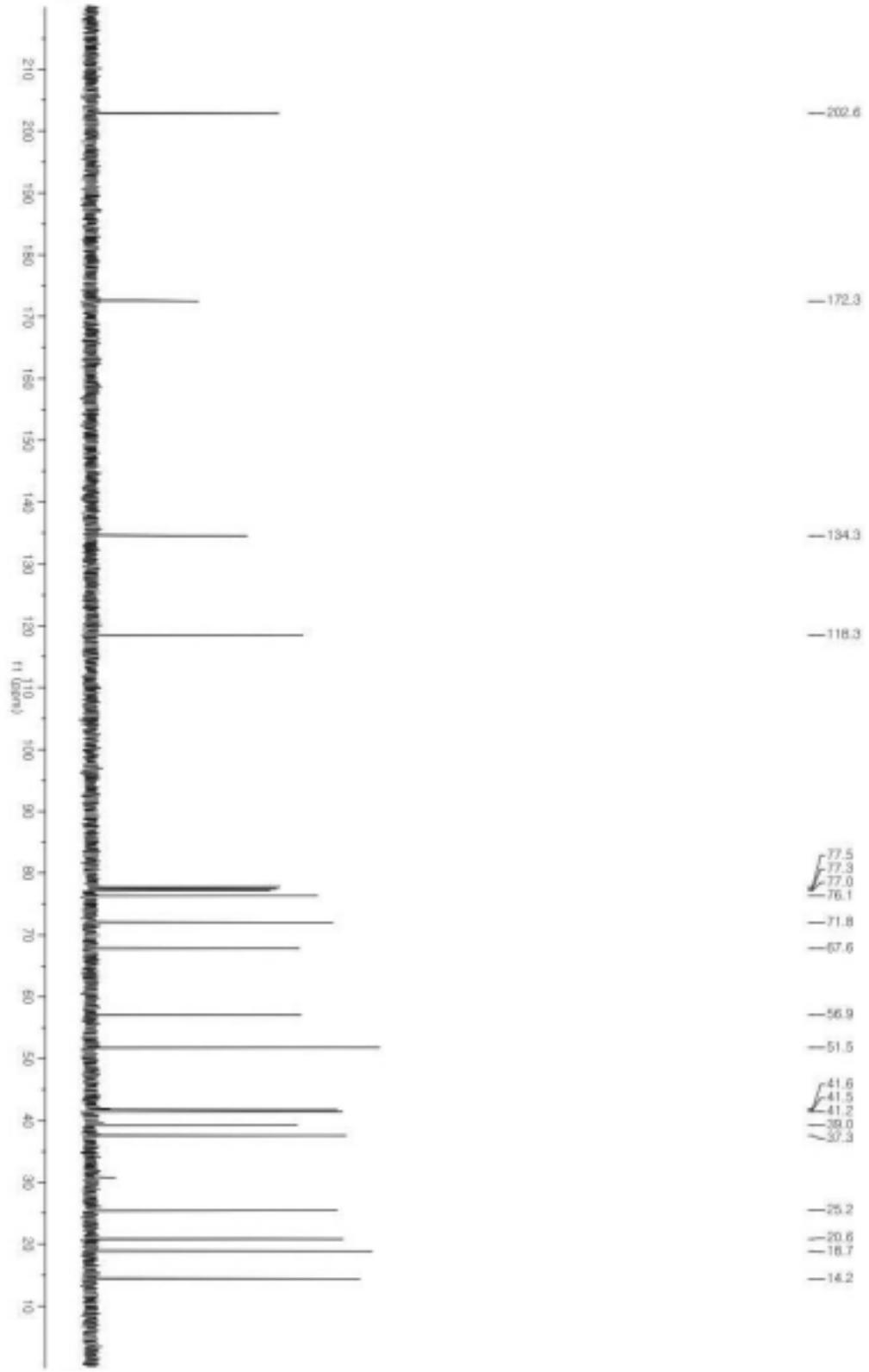
^{1}H-NMR (500 MHz, $CDCl_3$) of **9C**



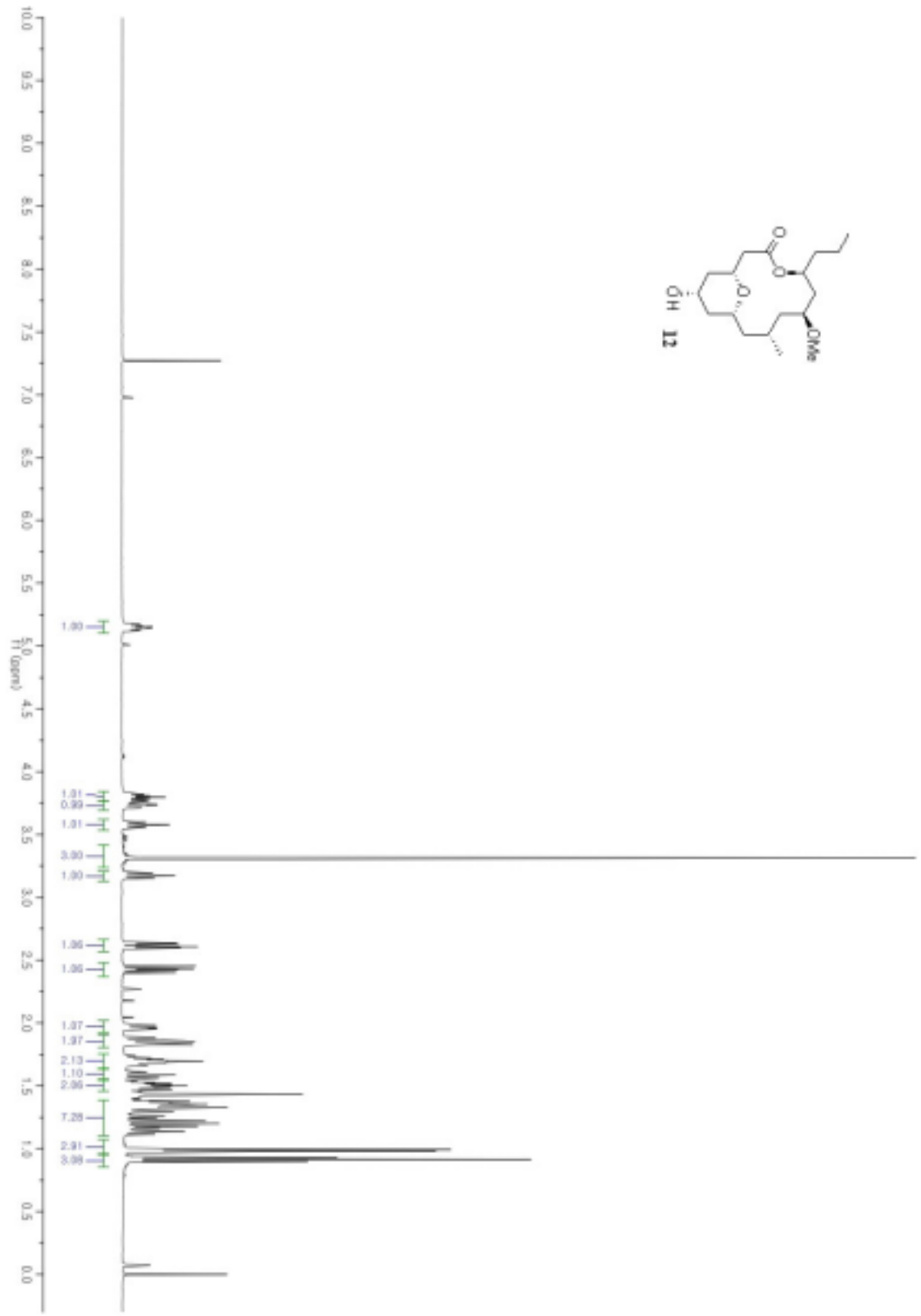
^{13}C-NMR (125 MHz, $CDCl_3$) of **9C**



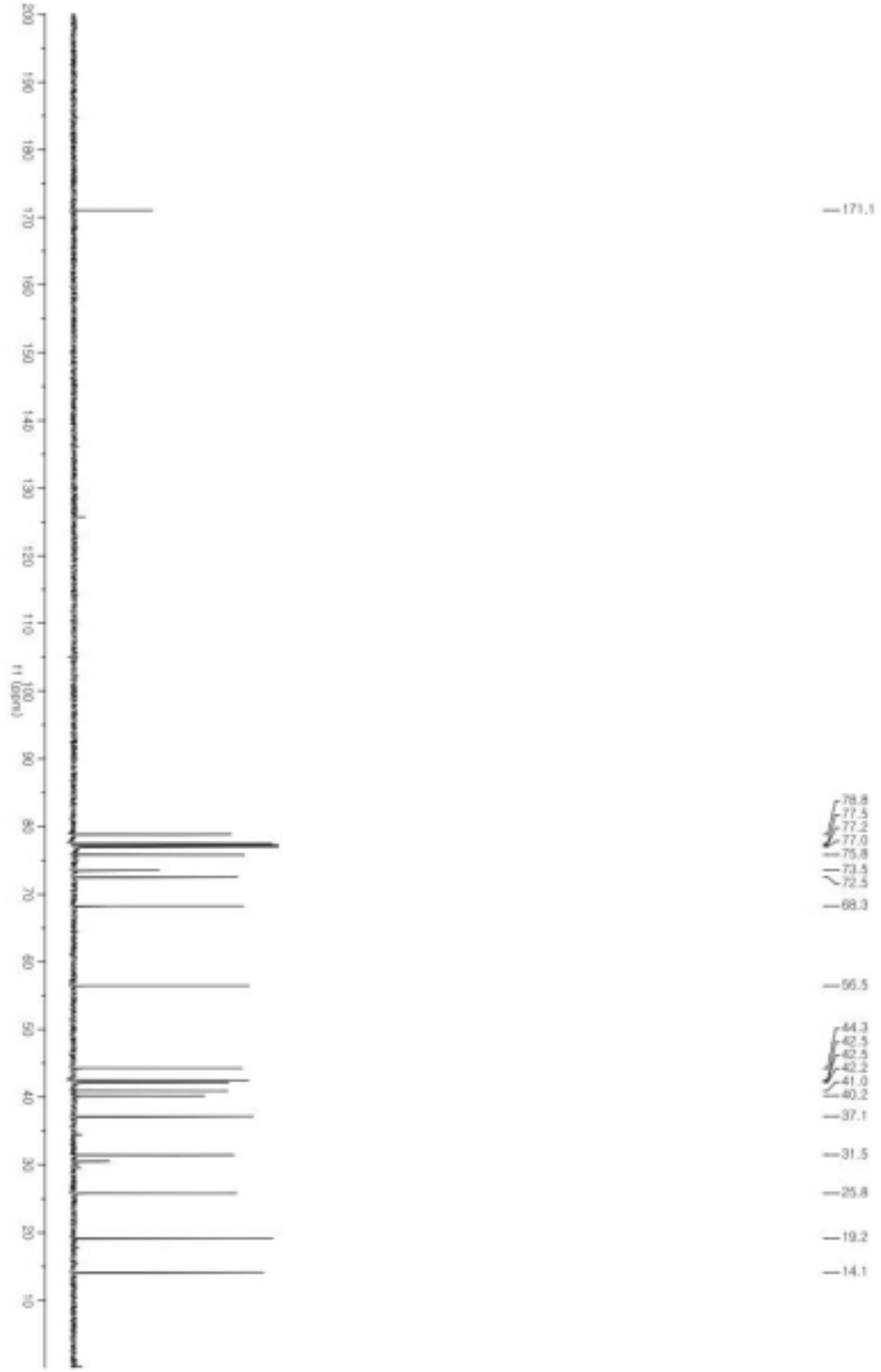
^{1}H-NMR (500 MHz, $CDCl_3$) of **15**



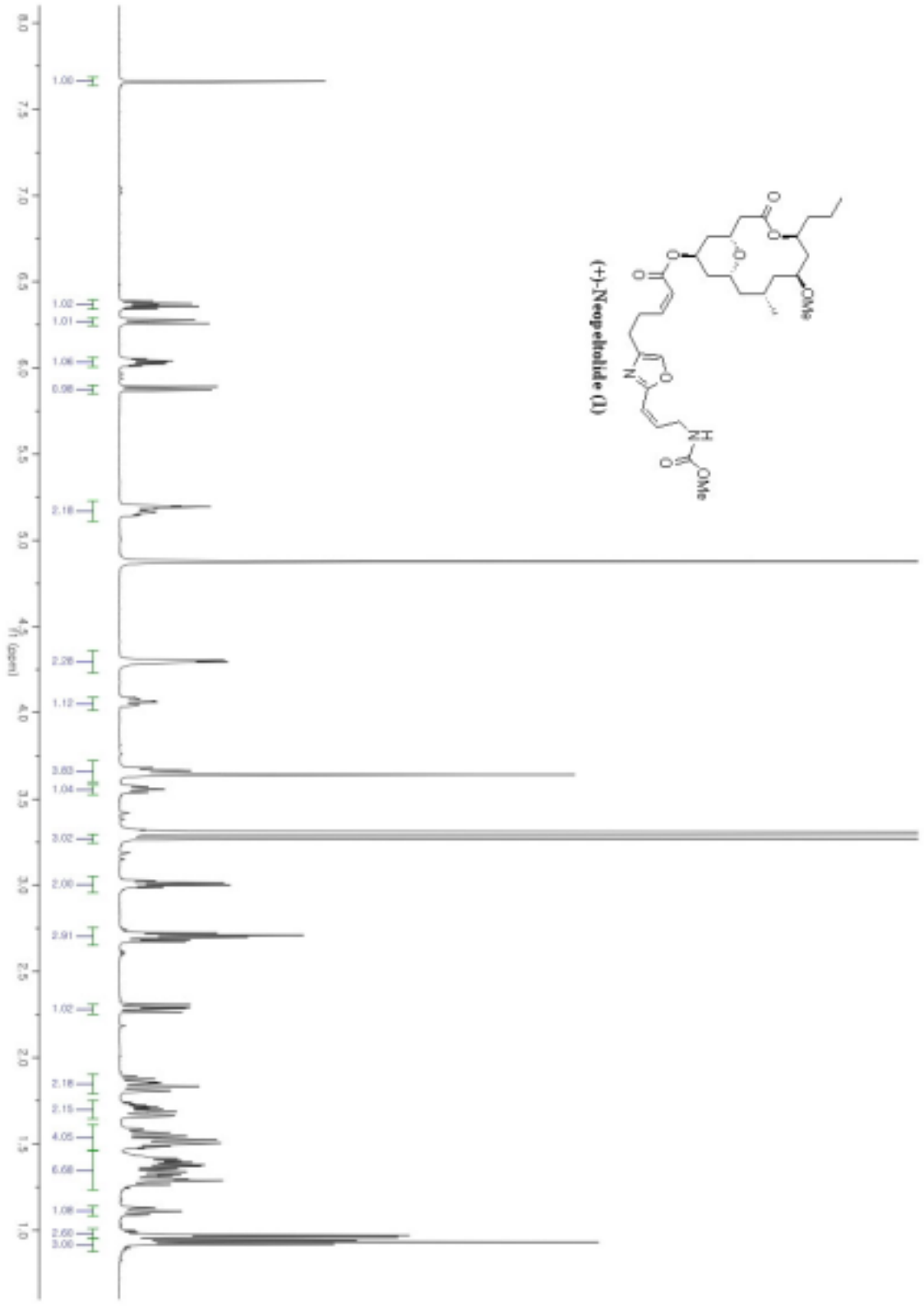
^{13}C-NMR (125 MHz, $CDCl_3$) of **15**



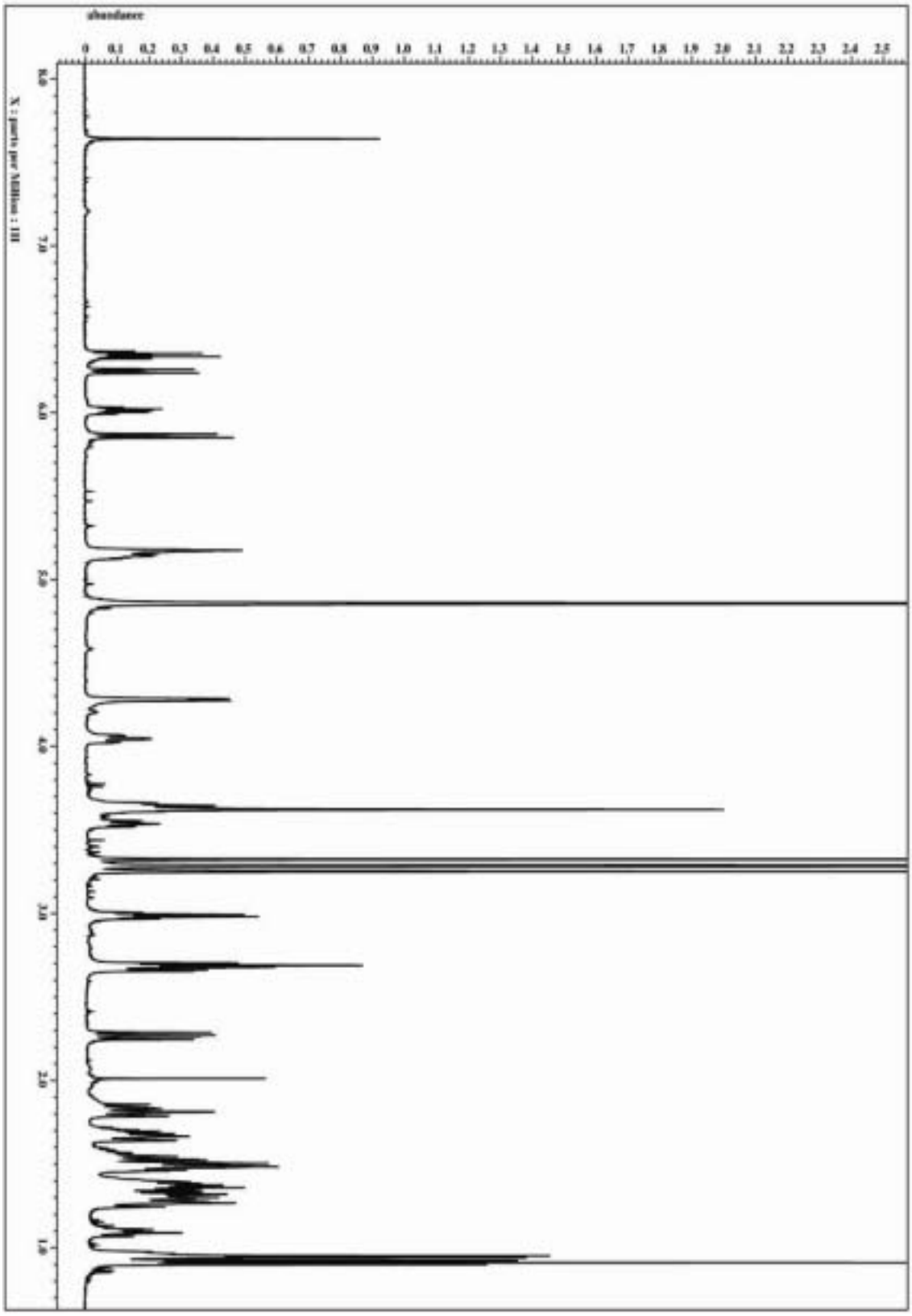
^{1}H-NMR (500 MHz, $CDCl_3$) of **12**



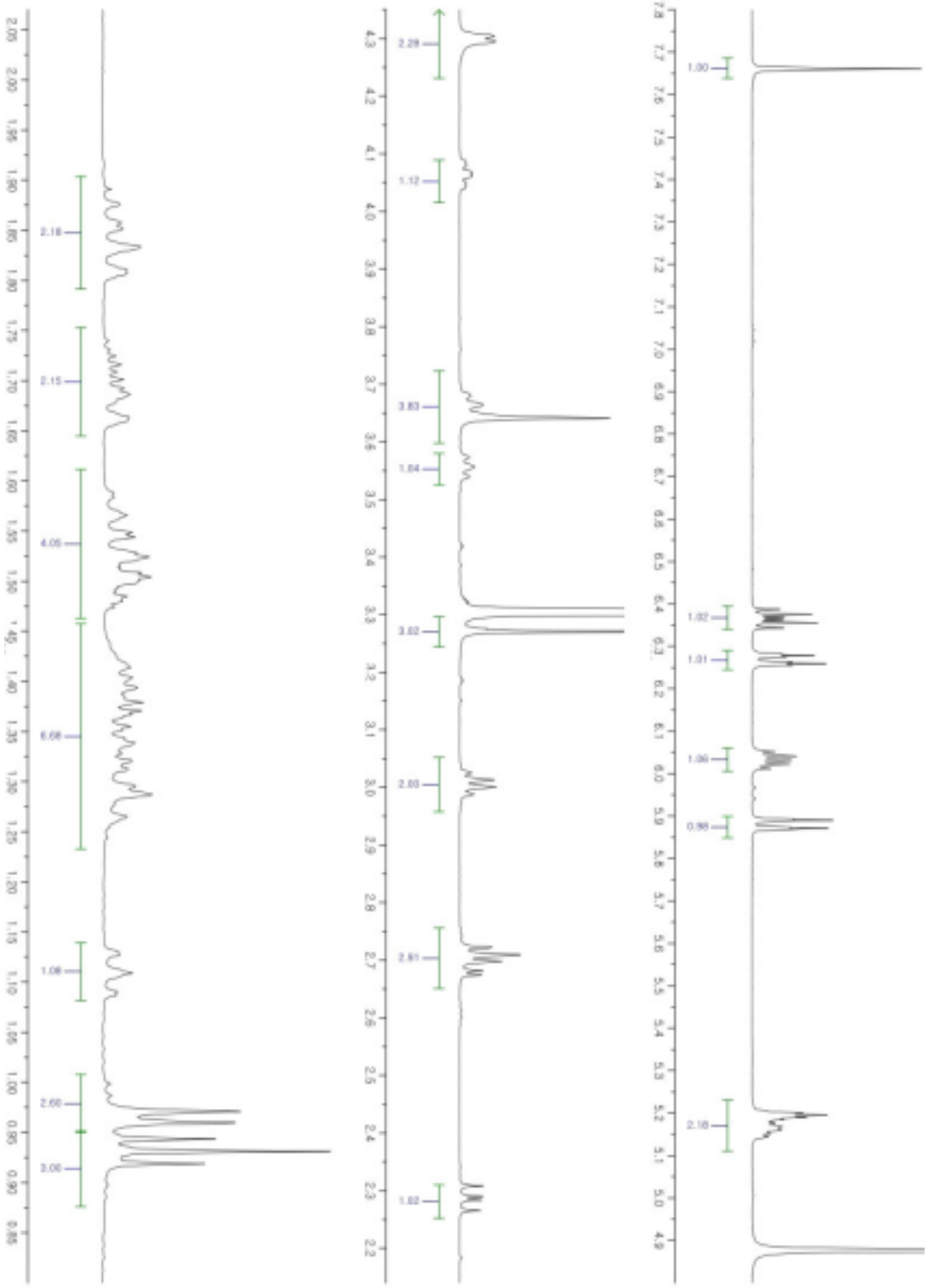
^{13}C-NMR (125 MHz, $CDCl_3$) of **12**



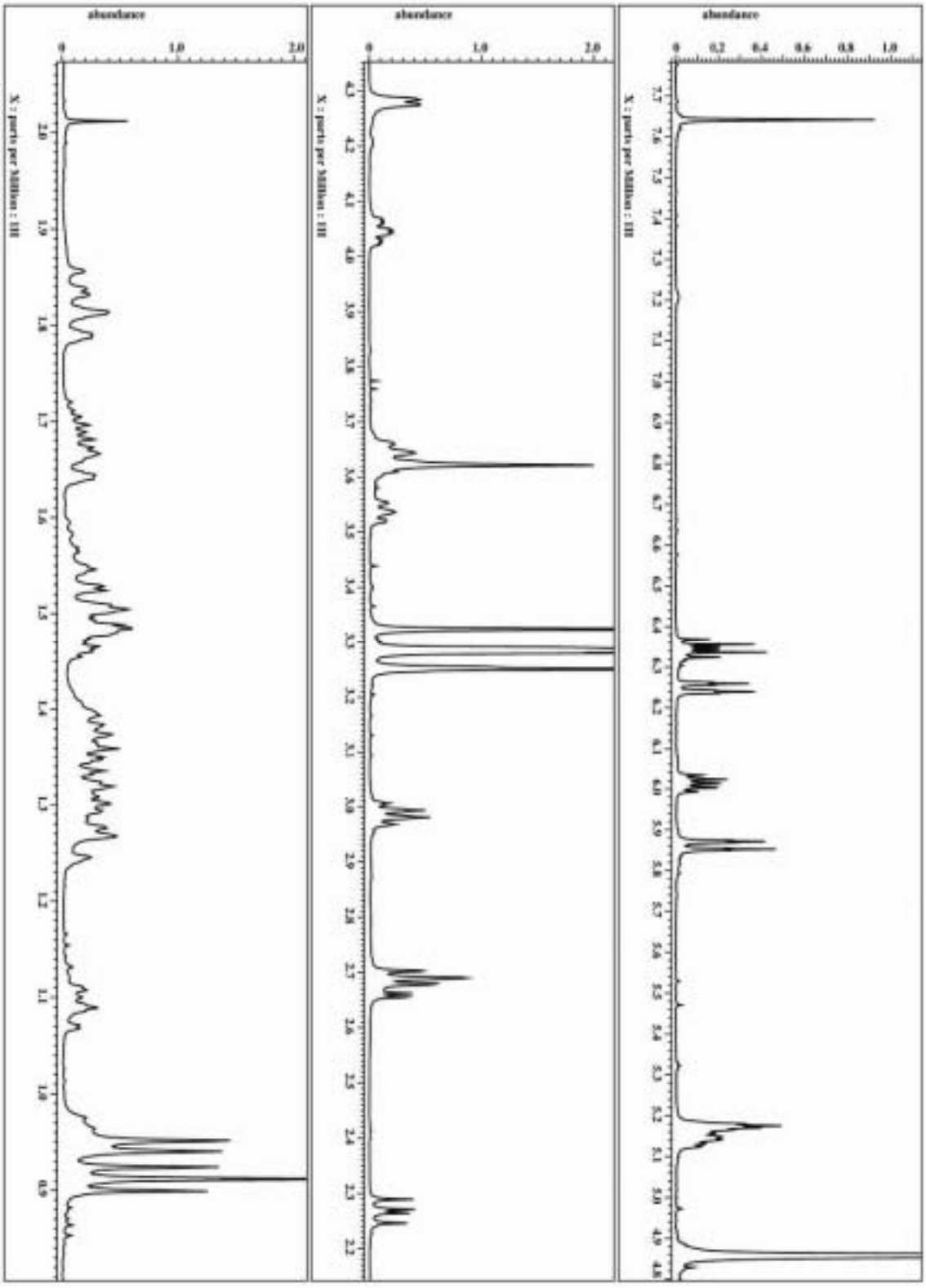
^{1}H-NMR (600 MHz, CD_3OD) of the synthetic sample of (+)-Neopeltolide (**1**)



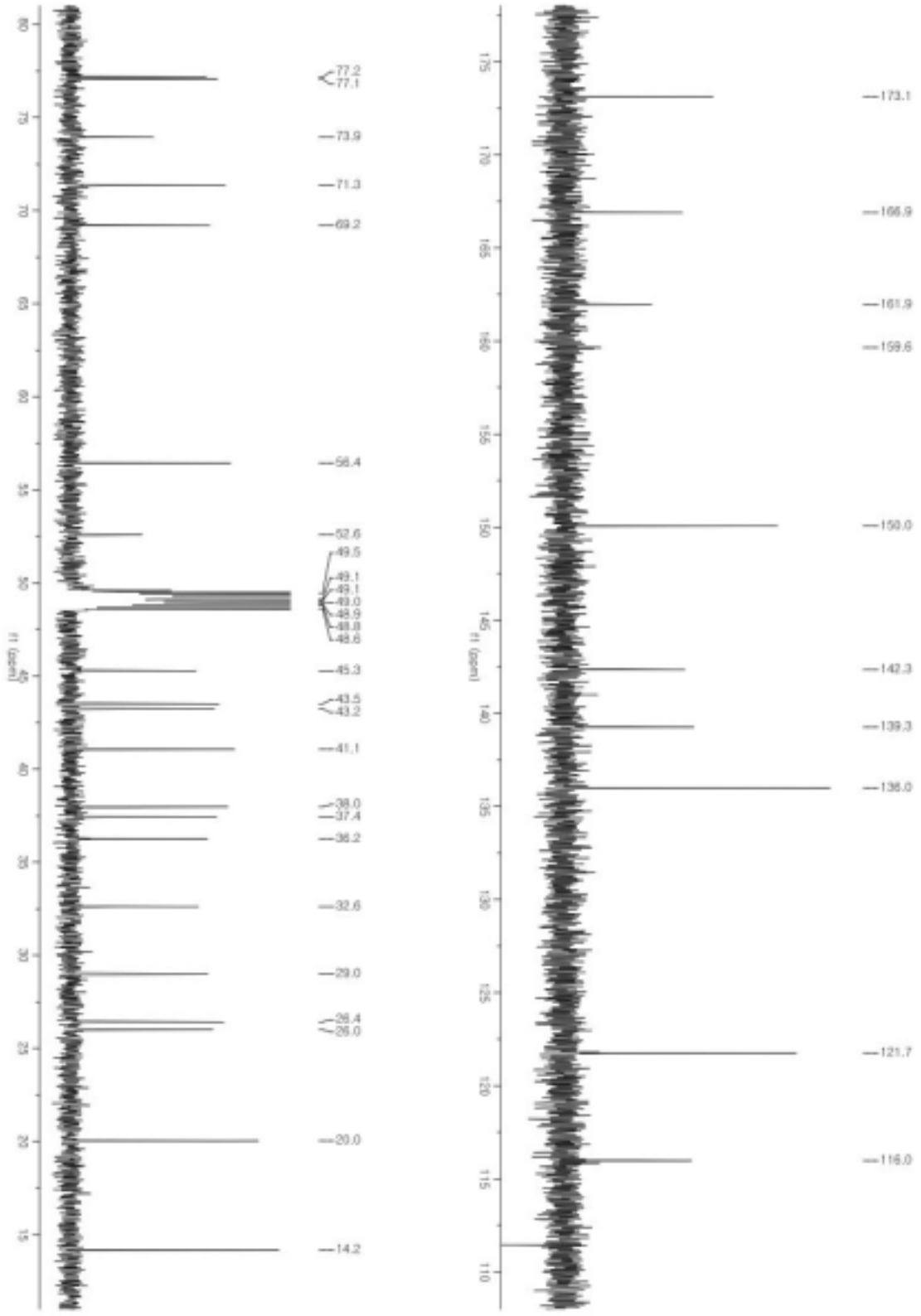
^{1}H-NMR (600 MHz, CD_3OD) of the natural sample of (+)-Neopeltolide (**1**)



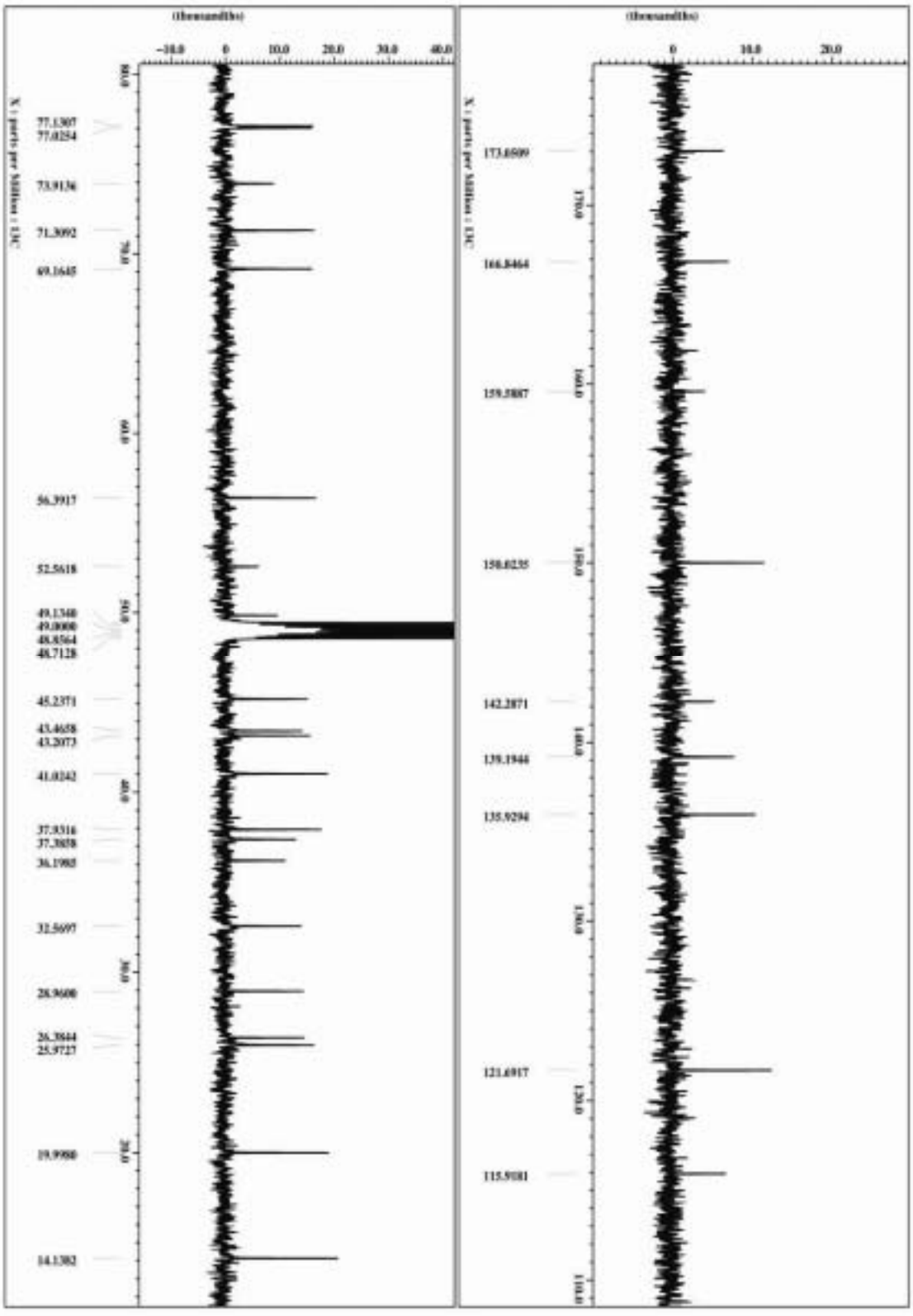
^{1}H-NMR (600 MHz, CD_3OD) of the synthetic sample of (+)-Neopeltolide (**1**)



^{1}H-NMR (600 MHz, CD_3OD) of the natural sample of (+)-Neopeltolide (**1**)



^{13}C-NMR (150 MHz, CD_3OD) of the synthetic sample of (+)-Neopeltolide (**1**)



^{13}C-NMR (125 MHz, CD_3OD) of the natural sample of (+)-Neopeltolide (**1**)