Total Synthesis of 10-Isocyano-4-cadinene and Determination of Its Absolute Configuration

Keisuke Nishikawa,[a] Hiroshi Nakahara,[a] Yousuke Shirokura,[a] Yasuyuki Nogata,[b] Erina Yoshimura,[c] Taiki Umezawa,[a] Tatsufumi Okino,[a] and Fuyuhiko Matsuda*[a]

[a] *Division of Environmental Materials Science, Graduate School of Environmental Science, Hokkaido University, Sapporo 060-0810, Japan*

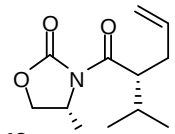
[b] *Environmental Science Research Laboratory, Central Research Institute of Electric Power Industry, 1646 Abiko, Abiko, Chiba 270-1194, Japan*

[c] *CERES, Inc., 1-6-1 Ogawa-cho, Kanda, Chiyoda-ku, Tokyo 101-0052, Japan*

fmatsuda@ees.hokudai.ac.jp

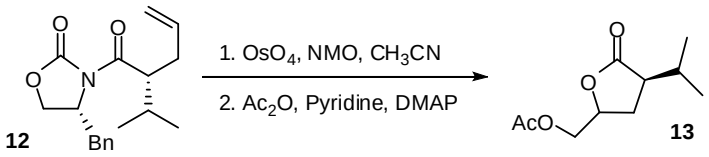
SUPPORTING INFORMATION

General Methods: Optical rotations were obtained on a Horiba SEPA-300. Melting points were measured on a Yazawa micromelting point BY-1. IR spectra were recorded on a JASCO IR Report 100 spectrometer using a NaCl cell or KBr disk. ^{1}H- and ^{13}C-NMR spectra were recorded using a JNM-EX 400 (400 MHz and 100 MHz) spectrometer. Chemical shifts were reported in ppm downfield from the peak of Me_3Si (TMS) used as the internal standard. Splitting patterns were designated as "s, d, t, q, and m" to indicate "singlet, doublet, triplet, quartet, and multiplet," respectively. Tetrahydrofuran (THF) and ether were distilled from Na metal / benzophenone ketyl. Dichloromethane (CH_2Cl_2), triethylamine (Et_3N), iodomethane (MeI) and hexamethylphosphoramide (HMPA) were distilled from CaH_2. All commercially obtained reagents were used as received. Analytical and preparative TLC were carried out using pre-coated silica gel plates (Macherey-Nagel DC-Fertigplatten SIL G-25 UV_{254}). The silica gel used for the column chromatographies was Merck Kieselgel 60 Art 7734.



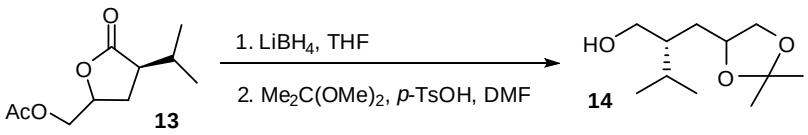
12

(*R*)-3-[(*R*)-2-Isopropylpent-4-enoyl]-4-benzyloxazolidin-2-one (12):[1] Evans alkylation of (*R*)-3-(3-methylbutanoyl)-4-benzyloxazolidin-2-one was performed using the previously described procedure[1] to afford **12** as a colorless oil: $[\alpha]_D^{23}$ = –65.4 (*c* = 0.67, $CHCl_3$); IR (neat) 3064, 3022, 2958, 2914, 2866, 1776, 1694, 1639, 1603, 1495, 1452, 1383, 1347, 1289, 1232, 1207, 1124, 1099, 1074, 1050, 1000, 916, 839, 762, 746, 702 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.97 (6H, d, *J* = 6.8 Hz), 2.01 (1H, octet, *J* = 6.8 Hz), 2.34–2.54 (2H, m), 2.64 (1H, dd, *J* = 10.2, 13.4 Hz), 3.31 (1H, dd, *J* = 3.2, 13.4 Hz), 3.86 (1H, m), 4.10–4.17 (2H, m), 4.69 (1H, m), 5.02 (1H, d, *J* = 10.2 Hz), 5.10 (1H, dd, *J* = 1.4, 17.1 Hz), 5.82 (1H, m), 7.20–7.37 (5H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.3, 20.9, 30.3, 33.7, 38.1, 48.2, 55.7, 65.7, 116.8, 127.2, 128.8, 129.3, 135.44, 135.50, 153.1, 175.6; EI-MS m/z 301 (M^+); High-Resolution EI-MS m/z 301.1677 (M^+, calcd for $C_{18}H_{23}NO_3$ 301.1678).



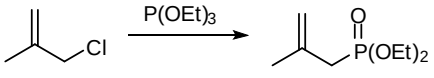
[(2*S*,4*R*)-Tetrahydro-4-isopropyl-5-oxofuran-2-yl]methyl Acetate and [(2*R*,4*R*)-Tetrahydro-4-isopropyl-5-oxofuran-2-yl]methyl Acetate (13): To a solution of **12** (19.8 g, 65.8 mmol) in CH_3CN (165 mL) were added NMO (50.0% in H_2O, 30.8 mL, 132 mmol) and OsO_4 (0.020 M in H_2O, 32.9 mL, 0.658 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 15 h, quenched with saturated aqueous Na_2SO_3 and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude lactone was used immediately for the next step.

The lactone was dissolved in pyridine (18 mL) and cooled to 0 °C. Ac_2O (31.0 mL, 329 mmol) and DMAP (80.3 mg, 0.658 mmol) were added to the solution under Ar atmosphere. The mixture was stirred for 2 h at 0 °C, quenched with MeOH (26 mL) at 0 °C, diluted with EtOAc and washed with saturated aqueous $CuSO_4$, H_2O and saturated aqueous $NaHCO_3$. The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (EtOAc/hexane, 10:90) to give **13** (12.9 g, 64.5 mmol, 98% in 2 steps) as a colorless oil in a 1:1 ratio of two diastereomers: IR (neat) 2956, 2870, 1770, 1740, 1643, 1466, 1369, 1339, 1234, 1166, 1120, 1075, 1043, 972, 843, 796, 746, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.94, 1.05 (each 1.5H, d, J = 7.1 Hz), 0.95, 1.04 (each 1.5H, d, J = 6.8 Hz), 1.79 (0.5H, dt, J = 10.2, 12.2 Hz), 2.01–2.32 (2.5H, m), 2.10 (3H, s), 2.64 (1H, m), 4.11 (0.5H, d, J = 12.2 Hz), 4.13 (0.5H, dd, J = 1.7, 12.2Hz), 4.26 (0.5H, dd, J = 3.6, 12.2 Hz), 4.34 (0.5H, dd, J = 2.9, 12.2 Hz), 4.57 (0.5H, m), 4.67 (0.5H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.1, 18.3, 20.3, 20.5, 20.66, 20.73, 25.86, 25.93, 27.6, 28.8, 45.1, 46.2, 64.9, 65.6, 74.9, 75.2, 170.3, 170.4, 177.0, 177.8; FAB-MS m/z 201 (M^++H); High-Resolution FAB-MS m/z 201.1140 (M^++H, calcd for $C_{10}H_{17}O_4$ 201.1127).



(*R*)-3-Methyl-2-{[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}butan-1-ol and (*R*)-3-Methyl-2-{[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]methyl}butan-1-ol (14): 13 (5.32 g, 26.6 mmol) was dissolved in THF (53 mL) under Ar atmosphere and cooled to 0 °C. $LiBH_4$ (2.90 g, 133 mmol) was added to the solution. The mixture was stirred for 15 min, warmed to room temperature and stirred for 12 h. The reaction was slowly quenched with 1 N HCl (140 mL) at 0 °C, filtered through a celite pad, washed with THF and concentrated under reduced pressure to obtain the crude triol which was directly reacted in the following reaction.

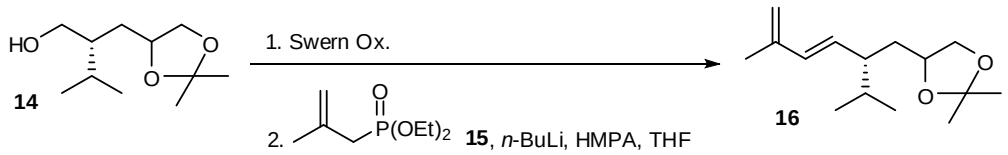
To a solution of the triol in DMF (24 mL) were added 2,2-dimethoxypropane (11.1 mL, 90.4 mmol) and *p*-TsOH•H_2O (2.53 g, 13.3 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 15 h, quenched with saturated aqueous $NaHCO_3$ and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 10:90) provided **14** (4.54 g, 22.4 mmol, 84% in 2 steps) as a colorless oil in a 3:2 mixture of two diastereomers: IR (neat) 3426, 2950, 2866, 1464, 1368, 1247, 1216, 1159, 1058, 923, 863, 791 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.88, 0.90, 0.94 (total 6H, *d*, J = 6.8 Hz), 1.36, 1.37, 1.43 (total 6H, each s), 1.44–1.61 (1.6H, m), 1.61–1.88 (2.4H, m), 2.28 (0.6H, t, J = 5.8 Hz), 3.03 (0.4H, dd, J = 5.0, 7.9 Hz), 3.47–3.72 (3H, m), 4.02–4.20 (1.4H, m), 4.25 (0.6H, quintet, J = 6.4 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.1, 19.6, 19.9, 20.1, 25.7, 25.9, 26.89, 26.91, 28.2, 30.3, 32.5, 33.8, 43.4, 45.7, 63.9, 64.8, 69.7, 70.0, 74.0, 76.2, 108.8, 109.2; EI-MS m/z 203 (M^+); High-Resolution EI-MS m/z 203.1654 (M^+, calcd for $C_{11}H_{22}O_3$ 203.1647).



3-Chloro-2-methylpropene **15**

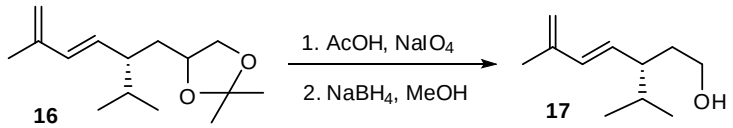
Diethyl (2-Methylallyl)phosphonate (15):[2] A mixture of triethyl phosphite (19.3 g, 31.6 mmol) and 3-chloro-2-methylpropene (31.6 g, 348 mmol) was heated at reflux for 9 days at 130 °C. Evaporation of the remaining 3-chloro-2-methylpropene afforded **15** (6.07 g, 31.6 mmol) as a colorless oil, which was directly employed in the next reaction: IR (neat)

3470, 3072, 2978, 2904, 1645, 1475, 1443, 1389, 1283, 1250, 1161, 1096, 1055, 1027, 963, 893, 859, 837, 795, 769, 736, 679 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 1.32 (6H, t, *J* = 7.2 Hz), 1.88 (3H, s), 2.56 (1H, s), 2.61 (1H, s), 4.05–4.18 (4H, m), 4.88 (1H, d, *J* = 5.1 Hz), 4.94 (1H, d, *J* = 3.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 16.39, 16.45, 23.62, 23.64, 34.7, 36.1, 61.78, 61.85, 115.2, 115.3, 136.0, 136.1; EI-MS m/z 192 (M^+); High-Resolution EI-MS m/z 192.0910 (M^+, calcd for $C_8H_{17}O_3P$ 192.0915).



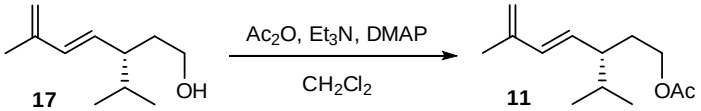
(*S*)-4-[(*R*,*E*)-2-Isopropyl-5-methylhexa-3,5-dienyl]-2,2-dimethyl-1,3-dioxolane and (*R*)-4-[(*R*,*E*)-2-Isopropyl-5-methylhexa-3,5-dienyl]-2,2-dimethyl-1,3-dioxolane (16): DMSO (5.68 mL, 80.0 mmol) was added at –78 °C under Ar atmosphere to a solution of oxalyl chloride (3.49 mL, 40.0 mmol) in CH_2Cl_2 (95 mL). After stirring for 15 min, a solution of **14** (2.89 g, 14.3 mmol) in CH_2Cl_2 (29 mL) was added dropwise. After stirring for 50 min, the white suspension was treated with Et_3N (14.9 mL, 107 mmol). The reaction was allowed to warm to room temperature and stirred for 1 h. Saturated aqueous NH_4Cl was added to the solution and the mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed *in vacuo*, the resulting crude aldehyde was used directly in the next reaction.

To a solution of **15** (8.24 g, 42.9 mmol) in THF (65 mL), *n*-BuLi (2.64 M in hexane, 16.2 mL, 42.9 mmol) was added dropwise at –78 °C under Ar atmosphere. After stirring for 30 min, HMPA (14.9 mL, 85.7 mmol) was added dropwise. A solution of the aldehyde in THF (20 mL) was next added dropwise. The mixture was gradually warmed to room temperature over 3 h, stirred for 12 h, quenched with saturated aqueous NH_4Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 3:97) provided **16** (2.86 g, 12.0 mmol, 84% in 2 steps) as a colorless oil in a 3:2 ratio of two diastereomers: IR (neat) 3076, 2952, 2866, 1606, 1452, 1367, 1242, 1217, 1159, 1109, 1062, 969, 882, 826, 790 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.84, 0.88 (each 1.2H, d, *J* = 6.8 Hz), 0.85, 0.89 (each 1.8H, d, *J* = 6.8 Hz), 1.33, 1.40 (each 1.8H, brs), 1.33, 1.40 (each 1.2H, brs), 1.40–1.70 (2H, m), 1.70–1.89 (1.4H, m), 1.83 (3H, brs), 2.08 (0.6H, m), 3.40–3.53 (1H, m), 3.93–4.09 (2H, m), 4.88 (2H, brs), 5.36 (0.6H, dd, *J* = 10.0, 15.6 Hz), 5.43 (0.4H, dd, *J* = 9.2, 15.6 Hz), 6.05 (0.4H, d, *J* = 15.6 Hz), 6.13 (0.6H, d, *J* = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.8, 18.9, 19.0, 20.5, 20.6, 25.8, 27.0, 27.1, 32.4, 32.6, 36.4, 37.0, 46.35, 46.44, 69.4, 70.0, 74.6, 75.0, 108.1, 108.3, 114.7, 114.8, 131.47, 131.52, 134.0, 134.4, 141.6; EI-MS m/z 238 (M^+), 223 (M^+–CH_3); High-Resolution EI-MS m/z 238.1937 (M^+, calcd for $C_{15}H_{26}O_2$ 238.1933).

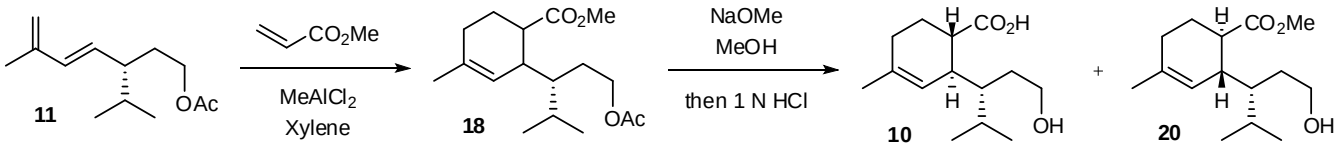


(*R*,*E*)-3-Isopropyl-6-methylhepta-4,6-dien-1-ol (17): To a solution of **16** (32.6 g, 137 mmol) in 80% aqueous AcOH (685 mL) was added $NaIO_4$ (73.3 g, 343 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 4 h at room temperature, diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with 15% NaOH aqueous solution and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude aldehyde was directly reacted in the next reaction.

A solution of the aldehyde in MeOH (274 mL) was cooled to 0 °C under Ar atmosphere. After $NaBH_4$ (2.59 g, 68.5 mmol) was added to this solution, the mixture was stirred for 30 min, quenched with saturated aqueous NH_4Cl and concentrated *in vacuo*. The aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to give **17** (19.8 g, 118 mmol, 86% in 2 steps) as a colorless oil: $[\alpha]_D^{23}$ = +15.5 (*c* = 2.03, MeOH); IR (neat) 3350, 3074, 2950, 2866, 1606, 1464, 1452, 1383, 1366, 1257, 1165, 1047, 969, 883 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85, 0.90 (each 3H, d, *J* = 6.8 Hz), 1.40–1.70 (3H, m), 1.76 (1H, m), 1.84 (3H, s), 1.99 (1H, m), 3.52–3.71 (2H, m), 4.88 (2H, s), 5.44 (1H, dd, *J* = 9.5, 15.6 Hz), 6.13 (1H, d, *J* = 15.6 Hz); ^{1}H-NMR (C_6D_6, 400 MHz) δ 0.83, 0.89 (each 3H, d, *J* = 6.6 Hz), 1.36–1.62 (2H, m), 1.70 (1H, m), 1.76 (3H, s), 2.01 (1H, m), 3.40–3.67 (2H, m), 4.88, 4.92 (each 1H, s), 5.39 (1H, dd, *J* = 9.5, 15.6 Hz), 6.16 (1H, d, *J* = 15.6 Hz); ^{13}C-NMR (C_6D_6, 100 MHz) δ 19.7, 20.0, 21.7, 33.4, 36.6, 47.1, 61.9, 115.6, 133.1, 135.3, 142.7; EI-MS m/z 168 (M^+), 153 (M^+–CH_3); High-Resolution EI-MS m/z 168.1520 (M^+, calcd for $C_{11}H_{20}O$ 168.1514).



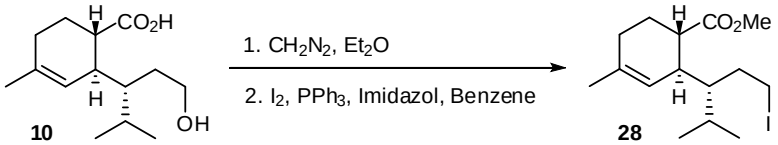
(*R*,*E*)-3-Isopropyl-6-methylhepta-4,6-dienyl Acetate (11): To a solution of **17** (6.06 g, 36.0 mmol) in CH_2Cl_2 (120 mL) were added Et_3N (20.0 mL, 144 mmol), Ac_2O (6.80 mL, 72.0 mmol) and DMAP (220 mg, 1.80 mmol) at 0 °C under Ar atmosphere. The mixture was stirred for 30 min at 0 °C, diluted with CH_2Cl_2, washed with brine and saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc/hexane, 5:95) afforded **11** (7.50 g, 35.6 mmol, 99%) as a colorless oil: $[\alpha]_D^{23}$ = +7.7 (*c* = 4.74, $CHCl_3$); IR (neat) 3076, 2952, 2866, 1739, 1606, 1464, 1384, 1365, 1235, 1037, 969, 884, 807 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.85, 0.89 (each 3H, d, *J* = 6.8 Hz), 1.49–1.69 (2H, m), 1.81 (1H, m), 1.83 (3H, s), 1.96 (1H, m), 2.03 (3H, s), 3.97 (1H, m), 4.08 (1H, m), 4.88 (2H, s), 5.39 (1H, dd, *J* = 9.2, 15.6 Hz), 6.08 (1H, d, *J* = 15.6 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.7, 19.0, 20.5, 20.9, 31.2, 32.2, 46.2, 63.3, 114.7, 131.1, 134.3, 141.6, 170.8; EI-MS m/z 210 (M^+); High-Resolution EI-MS m/z 210.1617 (M^+, calcd for $C_{13}H_{22}O_2$ 210.1620).



(1*S*,2*S*)-2-[(*R*)-1-Hydroxy-4-methylpentan-3-yl]-4-methylcyclohex-3-enecarboxylic Acid (10) and (1*R*,2*R*)-Methyl 2-[(*R*)-1-Hydroxy-4-methylpentan-3-yl]-4-methylcyclohex-3-enecarboxylate (20): To a solution of methyl acrylate (5.85 mL, 64.8 mmol) in xylene (54.2 mL) was added $MeAlCl_2$ (1.0 M in hexane, 23.8 mL, 23.8 mmol) dropwise at 0 °C under Ar atmosphere. A solution of **11** (2.28 g, 10.8 mmol) in xylene (54 mL) was next added dropwise. The mixture was stirred for 3 h at 0 °C and gradually warmed to room temperature over 5 h. The mixture was quenched with saturated aqueous NH_4Cl. After the two layers were separated, the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to give the Diels-Alder adduct **18** (2.24 g, 7.56 mmol, 70%) as a colorless oil which was a mixture of four diastereomers: ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.77, 0.78, 0.83, 0.85, 0.87, 0.88, 0.93, 0.94 (total 6H, d, *J* = 6.8 Hz), 1.18–2.12 (10H, m), 1.66, 1.68 (total 3H, each s), 2.03, 2.038, 2.042, 2.05 (total 3H, each s), 2.15–2.42, 2.42–2.89 (total 2H, each m), 3.65, 3.66, 3.67, 3.68 (total 3H, each s), 3.91–4.14 (2H, m), 5.21, 5.31, 5.34, 5.40 (total 1H, each s).

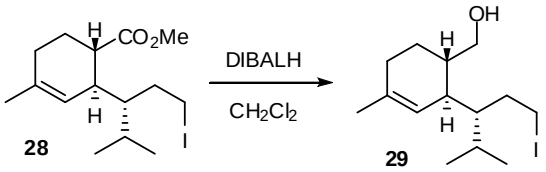
NaOMe solution was prepared by adding Na metal (9.32 g, 405 mmol) in small pieces to MeOH (160 mL) at room temperature. The mixture was stirred until the metal was completely consumed. To the mixture was added a solution of **18** (4.80 g, 16.2 mmol) in MeOH (41 mL). The mixture was stirred for 24 h, slowly quenched with 1 N HCl to pH 1 at 0 °C and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 20:80) to give **10** (2.60 g, 10.8 mmol, 67%) and **20** (1.37 g, 5.40 mmol, 33%) as colorless oils: $[\alpha]_D^{23}$ = +20.2 (*c* = 0.53, $CHCl_3$); IR (neat) 3010, 2950, 2868, 1700, 1449, 1432, 1409, 1384, 1365, 1293, 1259, 1239, 1191, 1045, 1009, 893, 875, 811, 771, 701 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.83, 0.89 (each 3H, d, *J* = 6.8 Hz), 1.35 (1H, m), 1.48 (1H, m), 1.63–1.82 (4H, m), 1.67 (3H, s), 1.88–2.11 (3H, m), 2.55 (1H, dt, *J* = 2.2, 10.1 Hz), 2.62 (1H, m), 3.63–3.80 (2H, m), 5.33 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 19.0, 23.4, 23.7, 26.4, 27.7, 29.1, 30.2, 39.2, 42.2, 43.3, 61.4, 121.3, 133.3, 181.0; FAB-MS m/z 239 (M^+–H); High-Resolution FAB-MS m/z 239.1642 (M^+–H, calcd for $C_{14}H_{23}O_3$ 239.1647). **20**: A colorless oil; $[\alpha]_D^{23}$ = –34.2 (*c* = 5.56, $CHCl_3$); IR (neat) 3428, 2948, 2866, 1733, 1432, 1370, 1261, 1239, 1191, 1160, 1045, 1011, 936, 872, 811 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.91, 0.92 (each 3H, d, *J* = 6.8 Hz), 1.37–1.58 (2H, m), 1.62–1.85 (3H, m), 1.66 (3H, s), 1.85–2.10 (3H, m), 2.37 (1H, dt, *J* = 2.7, 10.2 Hz), 2.68 (1H, d, *J* = 10.2 Hz), 2.78 (1H, brs), 3.48–3.69 (2H, m), 3.68 (3H, s), 5.22 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 20.4, 21.2, 23.7, 26.5, 29.3, 30.9, 32.2, 38.9, 43.3, 44.8, 51.5, 63.0, 121.2, 134.6, 176.7; EI-MS m/z 254 (M^+), 236 (M^+–H_2O); High-Resolution EI-MS m/z 254.1881 (M^+, calcd for $C_{15}H_{26}O_3$ 254.1882).

Preparation of Diazomethane: To a solution of KOH (6.08 g) in Et_2O (76 mL) and H_2O (15 mL) was slowly added 1-methyl-3-nitro-1-nitrosoguanidine (MNNG) (1.24 g, 5.16 mmol) at 0 °C. After stirring for 30 min, the organic layers were directly employed as a solution of CH_2N_2 in Et_2O in the following reaction.



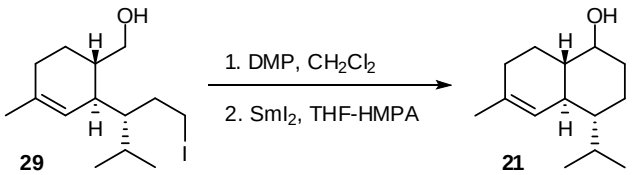
(1*S*,2*S*)-Methyl 2-[(*R*)-1-Iodo-4-methylpentan-3-yl]-4-methylcyclohex-3-enecarboxylate (28): To a solution of **10** (764 mg, 3.18 mmol) in MeOH (0.10 mL) was added CH_2N_2 in Et_2O (47 mL) at room temperature under Ar atmosphere. The mixture was stirred for 2 h at room temperature, then concentrated under reduced pressure. The crude ester **19** was directly employed in the next reaction.

A solution of **19** in benzene (18 mL) was cooled to 0 °C under Ar atmosphere. Next, imidazole (325 mg, 4.78 mmol), triphenylphosphine (1.25 g, 4.78 mmol) and I_2 (2.26 g, 8.90 mmol) were added to the solution. The mixture was stirred for 1 h at room temperature and quenched with saturated aqueous Na_2SO_3. After the two layers were separated, the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to give **28** (1.10 g, 3.02 mmol, 95% in 2 steps) as a colorless oil: $[\alpha]_D^{23}$ = +43.8 (*c* = 1.81, $CHCl_3$); IR (neat) 2948, 2918, 2864, 1731, 1684, 1432, 1381, 1364, 1308, 1258, 1189, 1160, 1103, 1055, 1030, 843, 802, 725 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82, 0.90 (each 3H, d, *J* = 6.8 Hz), 1.24 (1H, m), 1.67 (3H, s), 1.68–2.05 (7H, m), 2.50 (1H, t, *J* = 11.5 Hz), 2.59 (1H, brs), 3.12 (1H, q, *J* = 8.6 Hz), 3.29 (1H, dt, *J* = 5.1, 9.3 Hz), 3.70 (3H, s), 5.29 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 6.5, 19.2, 23.2, 23.8, 26.4, 27.7, 29.1, 32.6, 39.6, 43.4, 47.6, 51.7, 121.4, 133.9, 176.3; EI-MS m/z 364 (M^+), 237 (M^+–I); High-Resolution EI-MS m/z 364.0901 (M^+, calcd for $C_{15}H_{25}IO_2$ 364.0900).



[(1*S*,2*S*)-2-[(*R*)-1-Iodo-4-methylpentan-3-yl]-4-methylcyclohex-3-enyl]methanol (29): A solution of **28** (880 mg, 2.42 mmol) in CH_2Cl_2 (8.1 mL) was cooled to 0 °C under Ar atmosphere. DIBAL-H (1.01 M in toluene, 4.78 mL, 4.83 mmol) was added dropwise to the solution. The mixture was stirred for 1 h, quenched with MeOH (0.97 mL) and a trace of H_2O at 0 °C, filtered through a celite pad, washed with CH_2Cl_2 and concentrated *in vacuo*. Purification by silica gel column chromatography (EtOAc/hexane, 10:90) yielded **29** (807 mg, 2.40 mmol, 99%) as a colorless oil: $[\alpha]_D^{23}$ = +37.7 (*c* = 3.84, $CHCl_3$); IR (neat) 3334, 3035, 2950, 2918, 2866, 2724, 1722, 1669, 1463, 1446, 1432, 1384, 1365, 1264, 1238, 1167, 1048, 1021, 974, 937, 877, 848, 806 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.82, 0.90 (each 3H, d, *J* = 6.8 Hz), 1.38 (1H, m), 1.49–2.04 (10H, m), 1.65 (3H, s), 3.15 (1H, q, *J* = 9.3 Hz), 3.27 (1H, dt, *J* = 5.4, 9.3 Hz), 3.54 (1H, dd, *J* = 7.0, 10.6 Hz), 3.63 (1H, dd, *J* = 5.0, 10.6 Hz), 5.27 (1H, brs); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 7.5, 18.3, 22.9, 23.91, 23.94, 27.8, 28.0, 32.3, 37.3, 38.1, 47.3, 65.4, 121.9, 134.1; EI-MS m/z 336 (M^+); High-Resolution EI-MS m/z 336.0950 (M^+, calcd for $C_{14}H_{25}IO$ 336.0951).

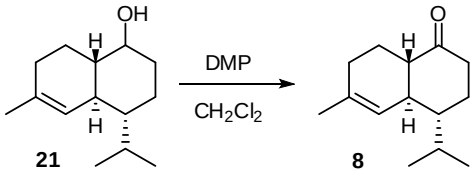
Preparation of THF solution of SmI_2-HMPA: To a slurry of Sm metal powder (1.50 g, 9.98 mmol) in THF (50 mL) was added CH_2I_2 (0.450 mL, 5.60 mmol) at room temperature under Ar atmosphere and the mixture was stirred overnight. HMPA (3.89 mL, 22.4 mmol) was added, and the initially blue solution turned deep purple. The resulting solution was directly used to affect the following reductive cyclization.



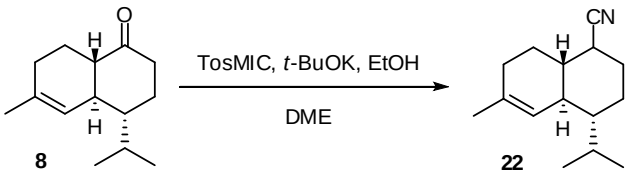
(1*R*,4*R*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-4-isopropyl-6-methylnaphthalen-1-ol (*Axial*-21) and (1*S*,4*R*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-4-isopropyl-6-methylnaphthalen-1-ol (*Equatorial*-21): To a solution of **29** (623 mg, 1.85 mmol) in CH_2Cl_2 (19 mL) was added Dess-Martin periodinane (DMP) (1.95 g, 4.63 mmol) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and

extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde **9** was directly used in the next step.

After a solution of **9** in THF (19 mL) was degassed by the freeze treatment, 0.100 M THF-HMPA solution of SmI_2 (55.5 mL, 5.55 mmol) was added at room temperature under Ar atmosphere. The mixture was stirred for 30 min, then quenched with saturated aqueous $NaHCO_3$. After the two layers were separated, the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The product was purified by silica gel column chromatography (EtOAc/hexane, 5:95) to give *equatorial*-**21** (254 mg, 1.22 mmol, 66% in 2 steps) as white crystals and *axial*-**21** (109 mg, 0.522 mmol, 28% in 2 steps) as a colorless oil: *Equatorial*-**21**: mp 99–102 °C; $[\alpha]_D^{23}$ = +37.3 (*c* = 2.80, $CHCl_3$); IR (KBr) 3414, 3048, 3006, 2948, 2912, 2852, 1701, 1664, 1453, 1384, 1366, 1353, 1335, 1314, 1283, 1238, 1226, 1187, 1157, 1138, 1112, 1091, 1054, 1028, 1012, 989, 978, 955, 906, 884, 855, 835, 805, 793 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.74, 0.91 (each 3H, d, *J* = 6.8 Hz), 0.98–1.34 (5H, m), 1.56–1.72 (3H, m), 1.66 (3H, s), 1.92–2.08 (3H, m), 2.10–2.24 (2H, m), 3.24 (1H, dt, *J* = 4.4, 10.3 Hz), 5.50 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.1, 21.6, 22.7, 24.0, 25.4, 26.1, 30.2, 35.6, 41.2, 45.8, 47.5, 74.2, 121.5, 134.9; EI-MS m/z 208 (M^+), 190 (M^+–H_2O); High-Resolution EI-MS m/z 208.1824 (M^+, calcd for $C_{14}H_{24}O$ 208.1827). *Axial*-**21**: $[\alpha]_D^{23}$ = –9.3 (*c* = 4.73, $CHCl_3$); IR (neat) 3364, 3044, 3000, 2950, 2952, 2862, 1684, 1462, 1447, 1388, 1368, 1333, 1297, 1212, 1188, 1138, 1118, 1094, 1074, 1054, 979, 951, 927, 886, 860, 792, 758, 727 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79, 0.91 (each 3H, d, *J* = 6.8 Hz), 1.02 (1H, m), 1.18–1.67 (7H, m), 1.66 (3H, s), 1.83–2.25 (5H, m), 3.85 (1H, d, *J* = 2.0 Hz), 5.56 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.3, 18.5, 21.5, 23.9, 26.2, 27.0, 30.8, 33.4, 35.8, 44.2, 46.8, 70.6, 122.5, 134.3; EI-MS m/z 208 (M^+) 190 (M^+–H_2O); High-Resolution EI-MS m/z 208.1823 (M^+, calcd for $C_{14}H_{24}O$ 208.1827).

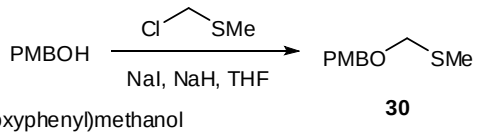


(4*R*,4a*S*,8a*S*)-2,3,4,4a,8,8a-Hexahydro-4-isopropyl-6-methylnaphthalen-1(7*H*)-one (8): DMP (1.08 g, 2.55 mmol) was added to a solution of **21** (213 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to give **8** (198 mg, 0.959 mmol, 94%) as white crystals: mp 28–31 °C; $[\alpha]_D^{23}$ = –84.1 (*c* = 4.48, $CHCl_3$); IR (KBr) 3040, 3004, 2952, 2922, 2864, 2826, 2720, 1712, 1451, 1429, 1367, 1313, 1291, 1259, 1234, 1204, 1185, 1143, 1065, 1030, 1015, 971, 954, 941, 902, 874, 847, 830, 803, 784 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.78, 0.99 (each 3H, d, *J* = 6.8 Hz), 1.36–1.60 (4H, m), 1.69 (3H, s), 1.90–2.47 (8H, m), 5.55 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.0, 21.6, 21.9, 23.8, 25.4, 26.4, 29.7, 41.1, 44.3, 46.0, 51.1, 121.3, 135.7, 212.7; EI-MS m/z 206 (M^+); High-Resolution EI-MS m/z 206.1679 (M^+, calcd for $C_{14}H_{22}O$ 206.1671).

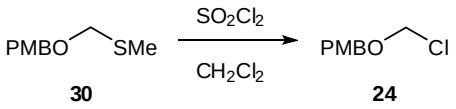


(1*R*,4*R*,4a*R*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-4-isopropyl-6-methylnaphthalene-1-carbonitrile and (1*S*,4*R*,4a*R*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-4-isopropyl-6-methylnaphthalene-1-carbonitrile (22): To a solution of **8** (195 mg, 0.943 mmol) in DME (4.7 mL) were added EtOH (0.155 mL, 2.64 mmol) and *p*-toluenesulfonylmethyl isocyanide (TosMIC) (331 mg, 1.70 mmol). After *t*-BuOK (359 mg, 3.21 mmol) was slowly added at 5-10 °C to the solution, the mixture was warmed to room temperature and stirred for 1 h. The mixture was quenched with H_2O, neutralized with 1 N HCl to pH 7 and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to afford **22** (170 mg, 0.784 mmol, 83%) as a colorless oil in a 1:1 mixture of two diastereomers: IR (neat) 3046, 3004, 2952, 2924, 2862, 2722, 2230, 1723, 1664, 1444, 1384, 1367, 1321, 1287, 1258, 1209, 1187, 1168, 1158, 1138, 1119, 1102, 1046, 1018, 986, 961, 921, 902, 877, 851, 835, 791 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.74, 0.82, 0.91, 0.92 (each 1.5H, d, *J* = 7.2 Hz), 1.29–1.48 (3H, m), 1.57–1.82 (4H, m), 1.67 (3H, s), 1.91–2.28 (5.5H, m), 2.83 (0.5H, brs), 5.49, 5.53 (each 0.5H, brs); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.0, 15.2, 21.0, 21.3, 21.4, 23.7, 23.8, 23.9, 26.0, 26.1, 28.4, 28.5, 29.0, 29.8, 30.1, 30.3, 33.9, 35.0,

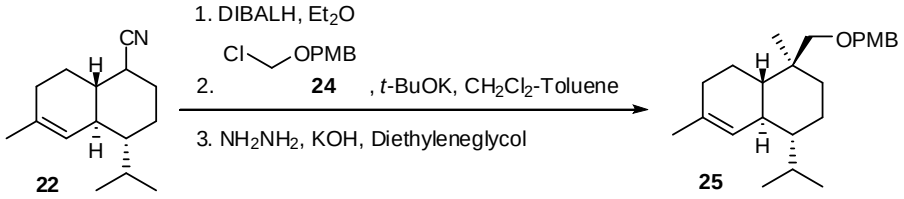
39.1, 41.0, 42.5, 42.8, 45.6, 46.3, 120.66, 120.69, 121.2, 122.1, 134.7, 135.3; EI-MS m/z 217 (M^+); High-Resolution EI-MS m/z 217.1831 (M^+, calcd for $C_{15}H_{23}N$ 217.1831).



(4-Methoxyphenyl)methoxymethyl Methyl Sulfide (30):[3] After a solution of NaI (3.61 g, 24.1 mmol) and NaH (55%, 2.10 g, 48.2 mmol) in THF (27 mL) was cooled to 0 °C under Ar atmosphere, (4-methoxyphenyl)methanol (3.00 mL, 24.1 mmol) was added dropwise to the solution. The mixture was warmed to room temperature and stirred for 1 h. Chloromethyl methyl sulfide (1.99 mL, 24.1 mmol) was added at 0 °C. The mixture was stirred for 12 h at room temperature, quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 5:95) provided **30** (4.54 g, 22.9 mmol, 95%) as a colorless oil: IR (neat) 2990, 2950, 2914, 2830, 1610, 1582, 1510, 1461, 1439, 1379, 1299, 1246, 1172, 1108, 1059, 1035, 957, 909, 818, 760, 729, 680 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 2.18 (3H, s), 3.80 (3H, s), 4.55 (2H, s), 4.66 (2H, s), 6.88, 7.28 (each 2H, d, J = 8.5 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 13.9, 55.3, 69.0, 74.0, 113.8, 129.4, 129.7, 159.2; EI-MS m/z 198 (M^+); High-Resolution EI-MS m/z 198.0713 (M^+, calcd for $C_{10}H_{14}O_2S$ 198.0715).



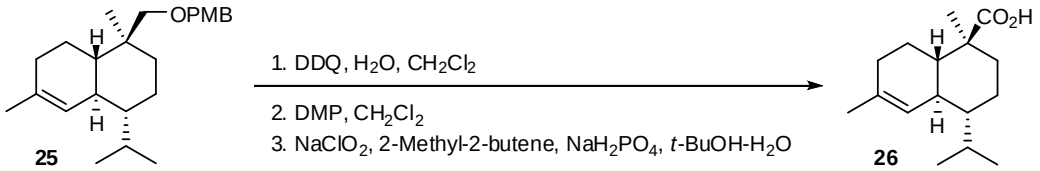
1-[(Chloromethoxy)methyl]-4-methoxybenzene (24):[3] To a solution of **30** (4.64 g, 23.4 mmol) in CH_2Cl_2 (59 mL) was added dropwise SO_2Cl_2 (2.41 mL, 25.7 mmol) at –78 °C under Ar atmosphere. The resulting solution of crude **24** was used directly in the following step.



(1*S*,4*R*,4a*S*,8a*S*)-1-[(4-Methoxybenzoyloxy)methyl]-1,2,3,4,4a,7,8,8a-octahydro-4-isopropyl-1,6-dimethylnaphthalene (25): DIBAL-H (0.99 M in toluene, 0.901 mL, 0.892 mmol) was added to a solution of **22** (96.9 mg, 0.446 mol) in Et_2O (1.5 mL) at 0 °C under Ar atmosphere. The mixture was stirred for 15 min, quenched with 1 N HCl, stirred for another 30 min and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude aldehyde **23** was immediately employed in the next reaction.

A solution of **23** in toluene (6.4 mL) and CH_2Cl_2 (6.4 mL) was cooled to 0 °C under Ar atmosphere. After *t*-BuOK (350 mg, 3.12 mmol) was added to the solution, the mixture was stirred for 10 min at room temperature. A solution of **24** (1.00 g, 5.35 mmol) in toluene (6.4 mL) and CH_2Cl_2 (6.4 mL) was added dropwise at 0 °C. The mixture was gradually warmed to room temperature over 2 h, quenched with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed *in vacuo*, the resulting residue was purified by silica gel column chromatography (EtOAc/hexane, 3:97) to give the PMB ether.

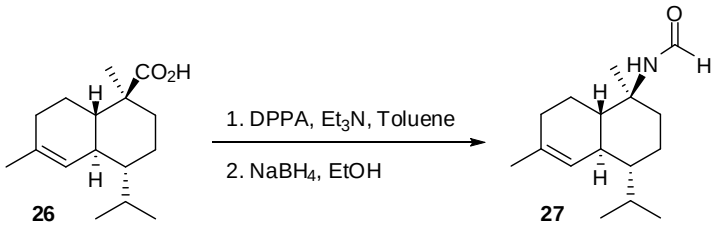
To a solution of the PMB ether in diethylene glycol (18 mL) were added KOH (450 mg, 8.03 mmol) and $NH_2NH_2 \cdot H_2O$ (0.546 mL, 11.2 mmol) at room temperature under Ar atmosphere. The mixture was heated at 180 °C for 2 h, diluted with EtOAc, washed with saturated aqueous NH_4Cl, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Silica gel column chromatography (EtOAc/hexane, 1:99) provided **25** (67.0 mg, 0.187 mmol, 42% in 3 steps) as a colorless oil: $[\alpha]_D^{23}$ = +7.9 (*c* = 1.24, $CHCl_3$); IR (neat) 3060, 2950, 2924, 2850, 2720, 1728, 1611, 1582, 1510, 1461, 1453, 1364, 1299, 1245, 1206, 1170, 1091, 1038, 884, 875, 821, 752 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.75 (3H, s), 0.78, 0.90 (each 3H, d, J = 6.8 Hz), 0.97 (1H, m), 1.07–1.70 (6H, m), 1.65 (3H, s), 1.78–2.00 (4H, m), 2.14 (1H, m), 3.07, 3.26 (each 1H, d, J = 8.8 Hz), 3.81 (3H, s), 4.38, 4.46 (each 1H, d, J = 12.0 Hz), 5.53 (1H, s), 6.87, 7.24 (each 2H, d, J = 8.7 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.4, 16.2, 19.8, 21.6, 23.7, 24.0, 26.3, 31.3, 36.1, 37.0, 37.5, 43.2, 46.9, 55.3, 72.8, 78.5, 113.5, 123.1, 128.7, 131.1, 134.2, 158.7; EI-MS m/z 356 (M^+); High-Resolution EI-MS m/z 356.2717 (M^+, calcd for $C_{24}H_{36}O_2$ 356.2715).



(1*S*,4*R*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-4-isopropyl-1,6-dimethylnaphthalene-1-carboxylic Acid (26): To a solution of **25** (7.10 mg, 19.9 μmol) in CH_2Cl_2 (2.0 mL) were added H_2O (0.10 mL) and DDQ (6.8 mg, 29.9 μmol) at room temperature under Ar atmosphere. The mixture was stirred for 1 h, quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude alcohol was immediately employed in the next step.

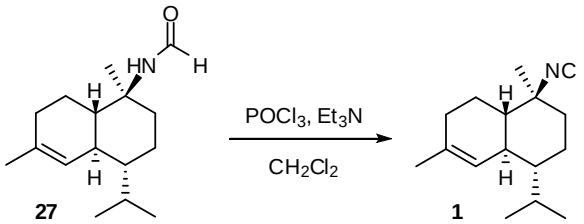
DMP (21.0 mg, 49.8 μmol) was added to a solution of the alcohol in CH_2Cl_2 (2.0 mL) at room temperature under Ar atmosphere. The mixture was stirred for 1 h and quenched with saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. After the two layers were separated, the aqueous solution was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude aldehyde was directly used in the following reaction.

To a solution of the aldehyde in *t*-BuOH (0.27 mL) and H_2O (0.13 mL) were added NaH_2PO_4 (11.9 mg, 99.5 μmol) and 2-methyl-2-butene (28.5 μL, 0.269 mmol) at room temperature. After stirring for 30 min, $NaClO_2$ (11.2 mg, 99.5 μmol) was slowly added for 30 min. The mixture was diluted with saturated aqueous NaCl and extracted with EtOAc, washed with brine, dried over Na_2SO_4 and filtered. After the solvent was removed *in vacuo*, the residue was purified by silica gel column chromatography (EtOAc/hexane, 10:90) to afford **26** (4.00 mg, 16.0 μmol, 81% in 3 steps) as a colorless oil: $[\alpha]_D^{23}$ = +36.2 (*c* = 0.92, $CHCl_3$); IR (neat) 2950, 2924, 2910, 2864, 1695, 1463, 1451, 1404, 1383, 1286, 1257, 1239, 1202, 1190, 1120, 1070, 1045, 949, 906, 871, 816 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.79, 0.92 (each 3H, d, *J* = 6.8 Hz), 1.04–1.44 (4H, m), 1.12 (3H, s), 1.47–2.11 (7H, m), 1.66 (3H, s), 2.18 (1H, m), 5.52 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 14.6, 15.3, 19.6, 21.5, 24.0, 26.0, 26.2, 31.1, 36.8, 37.1, 44.1, 46.4, 46.6, 122.1, 134.6, 184.0; EI-MS m/z 250 (M^+); High-Resolution EI-MS m/z 250.1935 (M^+, calcd for $C_{16}H_{26}O_2$ 250.1933).



***N*-[(1*R*,4*S*,4a*S*,8a*S*)-1,2,3,4,4a,5,6,8a-Octahydro-1-isopropyl-4,7-dimethylnaphthalen-4-yl]formamide (10-Formamido-4-cadinene) (27):** To a solution of **26** (8.70 mg, 34.8 μmol) in toluene (0.99 mL) were added diphenylphosphoryl azide (DPPA) (9.0 μL, 41.7 μmol) and Et_3N (5.8 μL, 41.7 μmol) at room temperature under Ar atmosphere. The mixture was stirred for 30 min, heated to 100 °C and stirred for 1 h, filtered and concentrated *in vacuo*. The crude isocyanate was used immediately in the next reaction.

After a solution of the isocyanate in EtOH (0.70 mL) under Ar atmosphere was cooled to 0 °C, $NaBH_4$ (3.9 mg, 0.104 mmol) was added to the solution. The reaction was stirred for 3 h at room temperature, diluted with H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (EtOAc/hexane, 30:70) to afford **27** (7.60 mg, 30.4 μmol, 88% in 2 steps) as a colorless oil: $[\alpha]_D^{23}$ = +28.4 (*c* = 0.66, $CHCl_3$); IR (neat) 3278, 3050, 2950, 2918, 2848, 1675, 1664, 1535, 1463, 1451, 1384, 1313, 1259, 1192, 1152, 1127, 1071, 1046, 876 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.77, 0.78, 0.91, 0.92 (total 6H, each d, *J* = 6.8 Hz), 0.99–1.38 (3H, m), 1.22, 1.26 (total 3H, each s), 1.49–1.67 (2H, m), 1.67 (3H, s), 1.76–2.26 (7H, m), 5.16, 5.74 (total 1H, each brs), 5.49 (1H, s), 8.07, 8.28 (total 1H, each d, *J* = 12.5 and 2.2 Hz); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.2, 18.9, 19.1, 20.8, 21.6, 23.1, 23.5, 23.8, 26.07, 26.11, 30.96, 31.05, 37.5, 38.6, 38.8, 41.9, 45.8, 46.3, 46.4, 49.1, 55.8, 57.4, 121.8, 122.2, 134.5, 134.8, 160.2, 162.6; FAB-MS m/z 250 (M^++H); High-Resolution FAB-MS m/z 250.2166 (M^++H, calcd for $C_{16}H_{28}NO$ 250.2171).



(1*S*,4*R*,4a*S*,8a*S*)-1,2,3,4,4a,7,8,8a-Octahydro-1-isocyano-4-isopropyl-1,6-dimethylnaphthalene (**10-Isocyano-4-cadinene**) (**1**): After **27** (6.30 mg, 25.3 μmol) was dissolved in CH_2Cl_2 (2.5 mL) and cooled to 0 °C under Ar atmosphere, $POCl_3$ (6.90 μL, 75.8 μmol) and Et_3N (31.7 μL, 0.228 mmol) were added to the solution and the mixture was stirred for 30 min. The reaction was stirred for 1 h at room temperature, quenched with cooled H_2O and extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification over silica gel column chromatography (EtOAc/hexane, 1:99) gave **1** (5.50 mg, 23.8 μmol, 94%) as a colorless oil: $[\alpha]_D^{23}$ = +59.8 (*c* = 0.65, $CHCl_3$); IR (neat) 3052, 2922, 2864, 2729, 2122, 1733, 1464, 1452, 1381, 1259, 1210, 1170, 1152, 1127, 1080, 1043, 1012, 955, 908, 884, 871, 809 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 0.76, 0.91 (each 3H, d, *J* = 6.8 Hz), 1.01–1.19 (2H, m), 1.19–1.41 (2H, m), 1.30 (3H, s), 1.54–1.78 (2H, m), 1.68 (3H, s), 1.83 (1H, m), 1.95–2.22 (5H, m), 5.46 (1H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 15.2, 20.2, 20.4, 21.5, 23.8, 23.9, 26.0, 30.8, 38.0, 40.7, 46.3, 48.1, 60.8 (as a triplet), 121.1, 135.2, 151.8 (as a triplet); EI-MS m/z 231 (M^+), 216 (M^+–CH_3); High-Resolution EI-MS m/z 231.1975 (M^+, calcd for $C_{16}H_{25}N$ 231.1987).

Antifouling assay.[4] Adult barnacles, *Balanus amphitrite*, attached to bamboo poles were procured from oyster farms in Lake Hamana, Shizuoka, and maintained in an aquarium at 20 °C by feeding on *Artemia salina* nauplii. Broods released I-II stage nauplii upon immersion in seawater after being dried overnight. Nauplii thus obtained were cultured in 80% filtered seawater (filtered seawater diluted to 80% by deionized water) including penicillin G (20 μg/mL, ICN Biochemical) and streptomycin sulfate (30 μg/mL, Wako Pure Chemical Industries, Ltd.) at 25 °C by feeding with the diatom *Chaetoceros gracillis* (about 40 x 10^4 cells/mL). Larvae reached the cyprid stage in 5 days. The cyprids were collected, then stored at 4 °C until use.

Test samples were dissolved in ethanol. Aliquots of the solution were supplied to wells of 24-well polystyrene tissue culture plates and air-dried. To each well were added 2 mL of 80% filtered seawater and six one-day-old cyprids. Four wells were used for each concentration. The plates were kept in the dark for 48 h at 25 °C, and the number of larvae that attached, metamorphosed, died, or did not settle were counted under a microscope. Each concentration was repeated 3 times. The antifouling activity of compounds was expressed as an EC_{50} value, which indicated the concentration that reduces the larval settlement to 50% of the control. The EC_{50} values were calculated by a probit analysis.

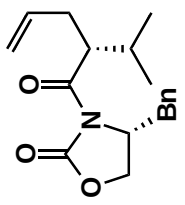
References

(1) (a) Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Synlett* **1999**, 744-746. (b) Rüeger, H.; Stutz, S.; Spindler, F.; Maibaum, J. *Tetrahedron* **2000**, *41*, 10085-10089.

(2) (a) Probst, M. F.; Modro, A. M.; Modro, T. A. *Can. J. Chem*. **1997**, *75*, 1131-1135. (b) Wang, Y.; West, F. G. *Synthesis* **2002**, 99-103.

(3) (a) Benneche, T.; Strande, P.; Undheim, K. *Synthesis* **1983**, 762-763. (b) Gomez, C.; Macia, B.; Lillo, V. J.; Yus, M. *Tetrahedron* **2006**, *62*, 9832-9839.

(4) Kitano, Y.; Nogata, Y.; Shinshima, K.; Yoshimura, E.; Chiba, K.; Tada, M.; Sakaguchi, I. *Biofouling* **2004**, *20*, 93-100.



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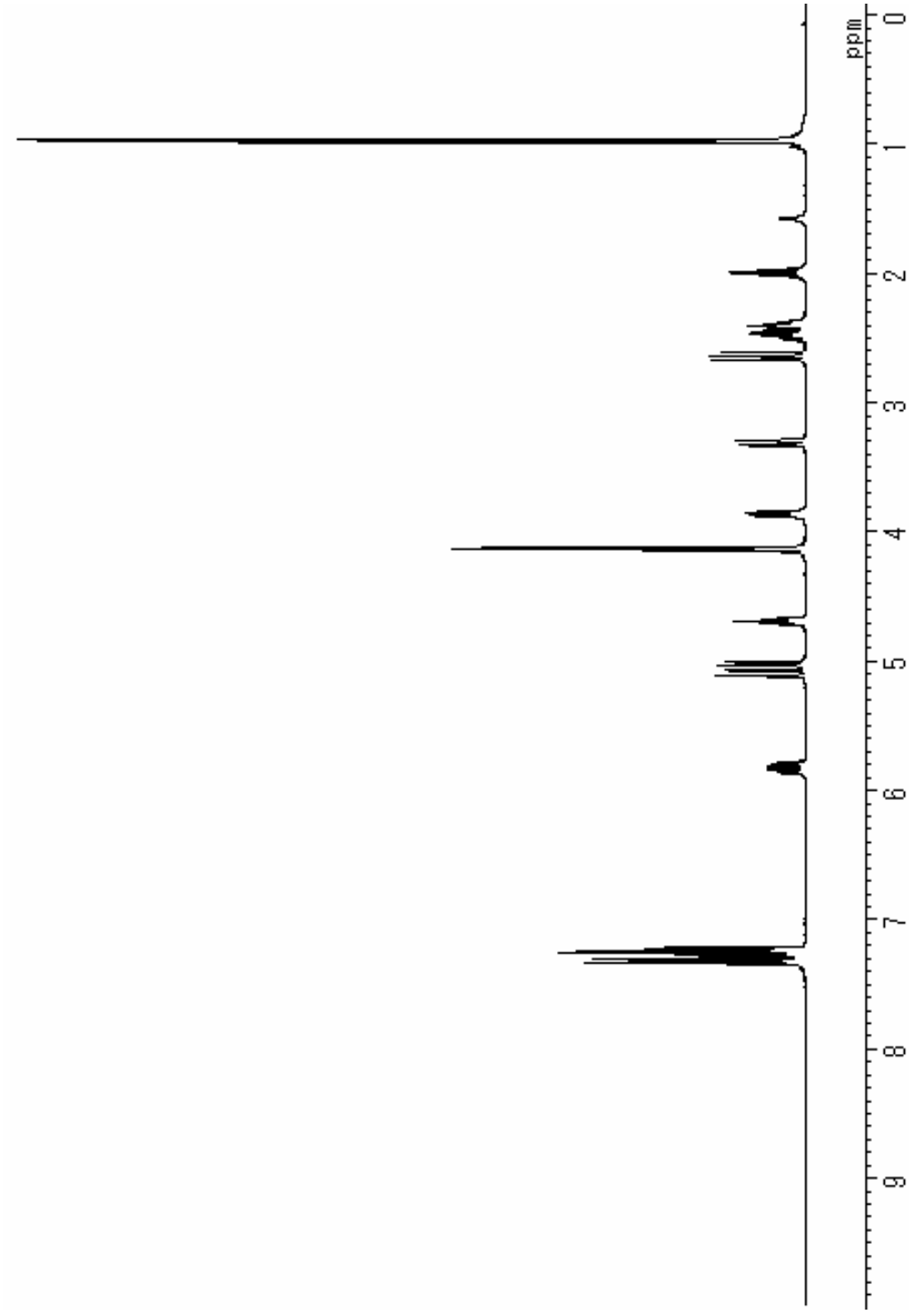

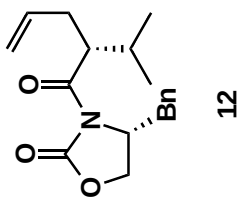
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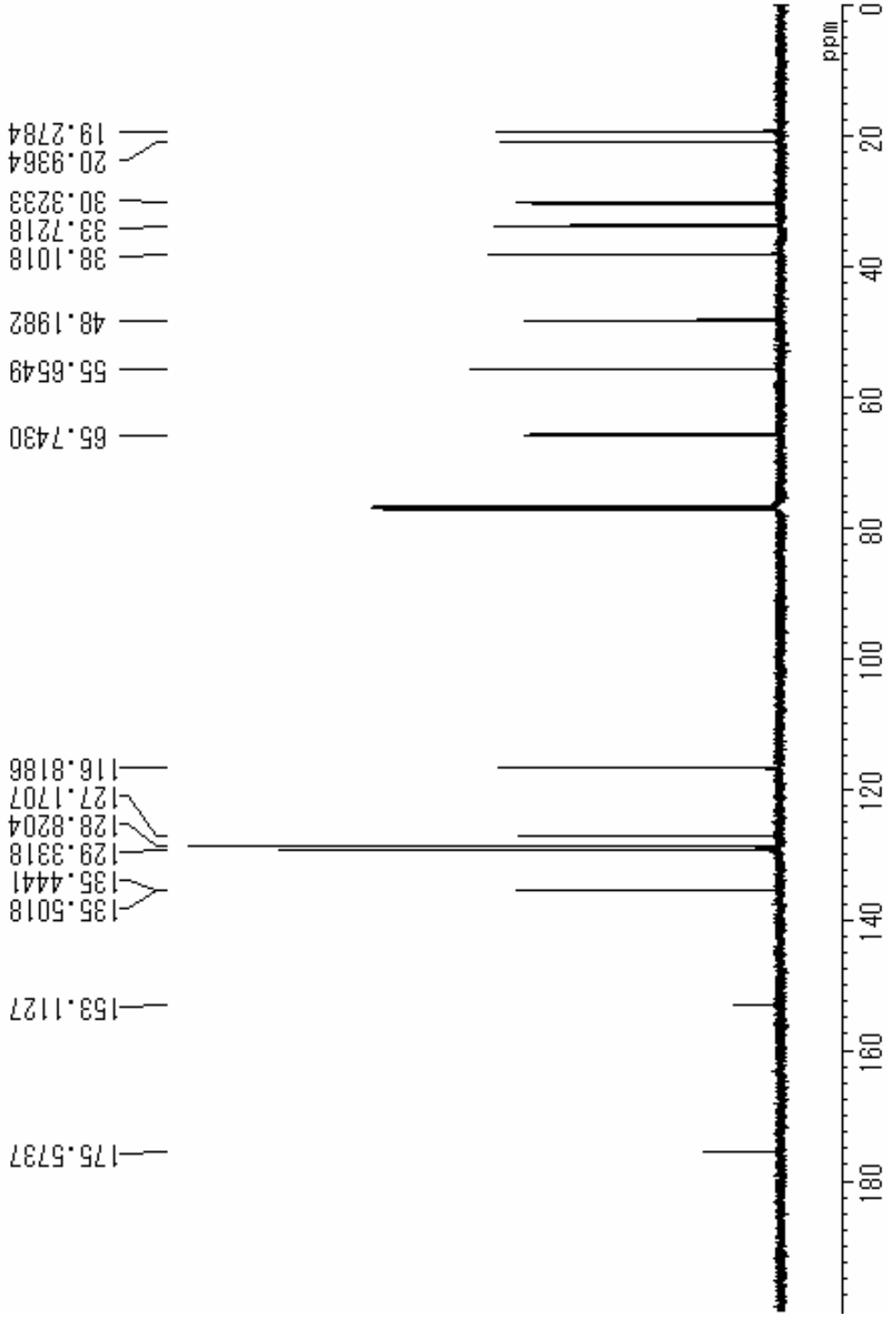
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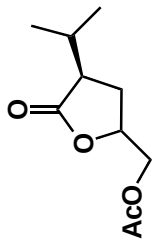

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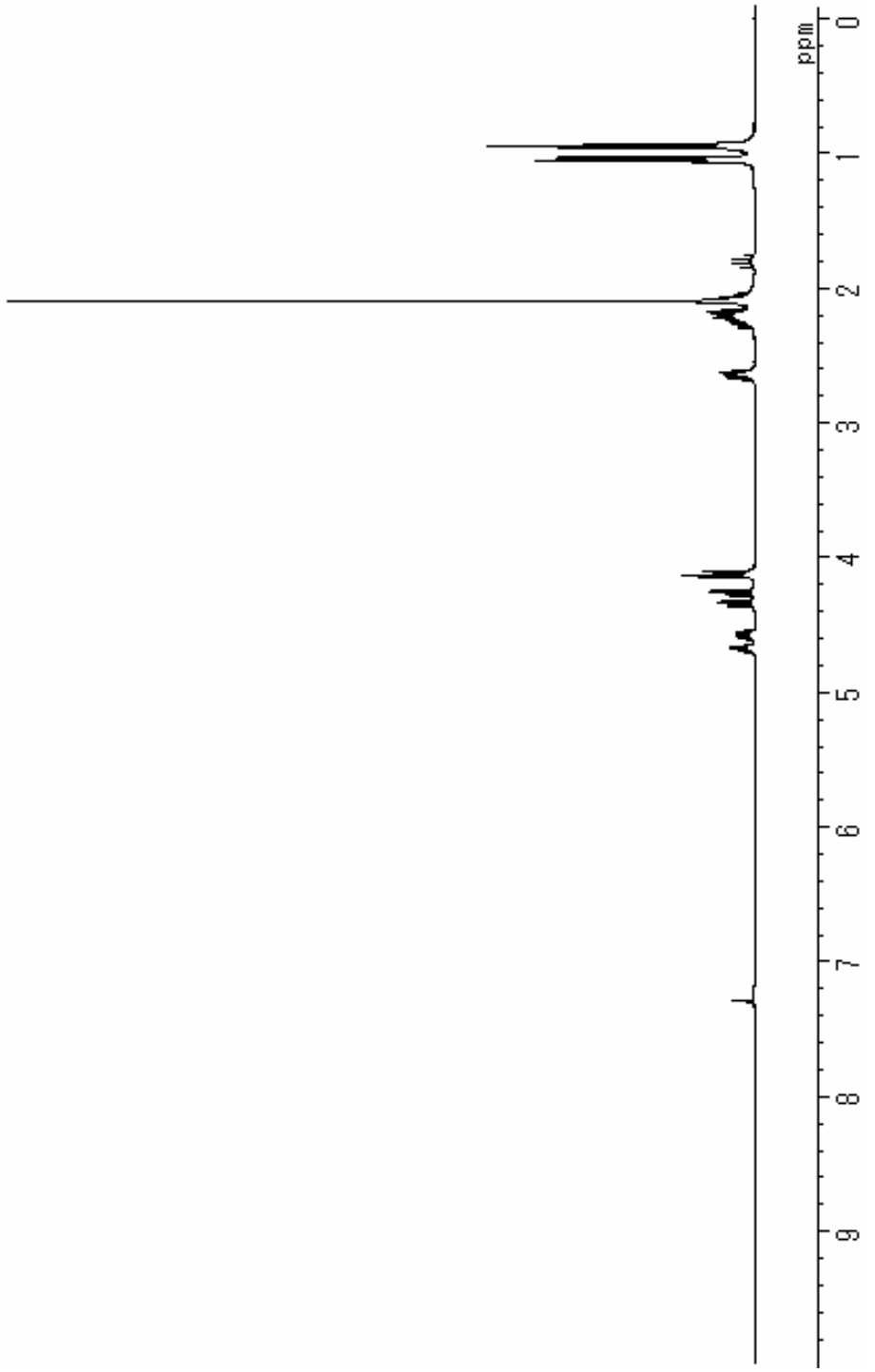

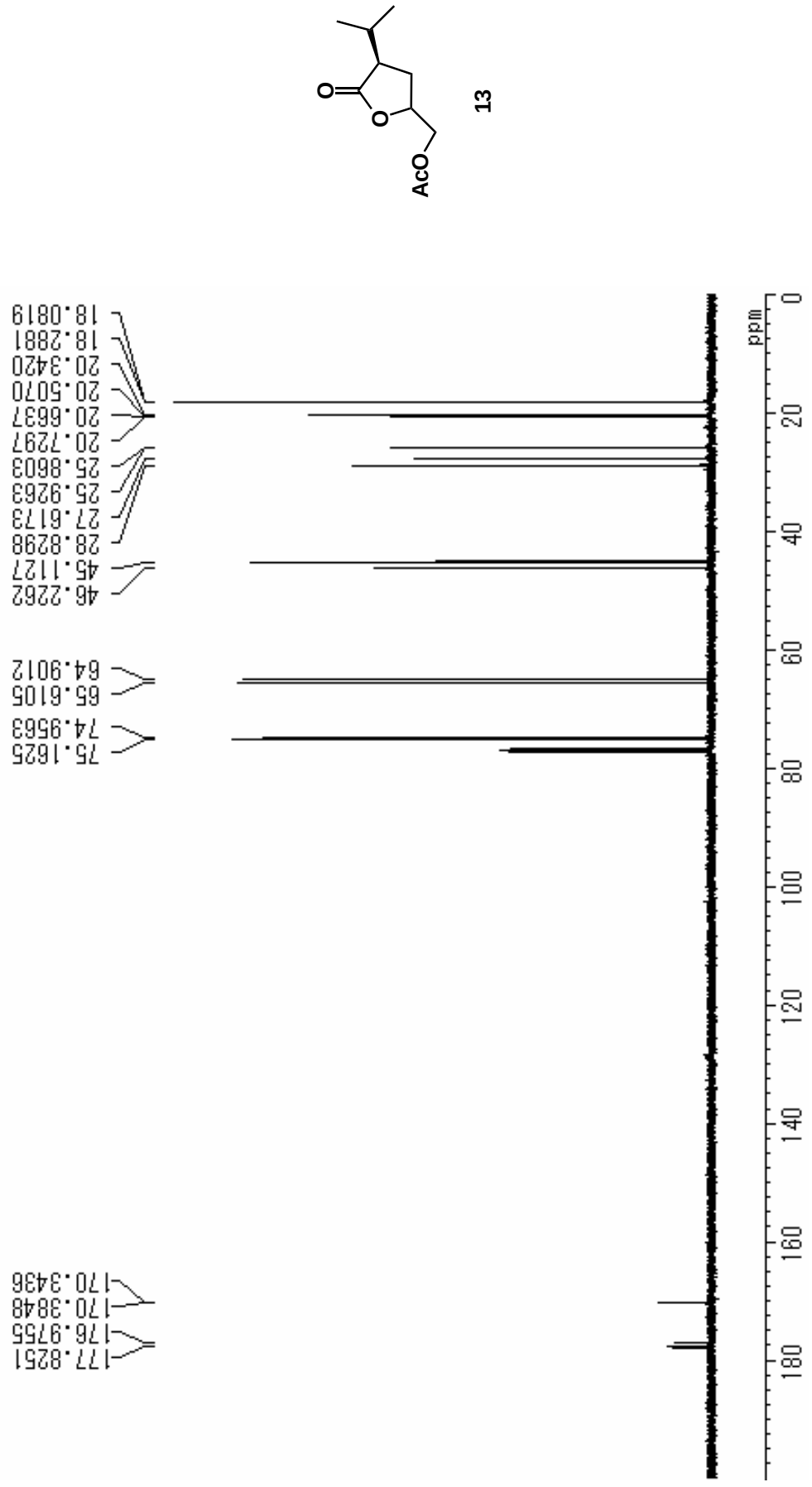
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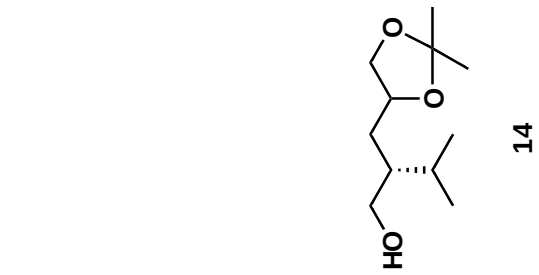

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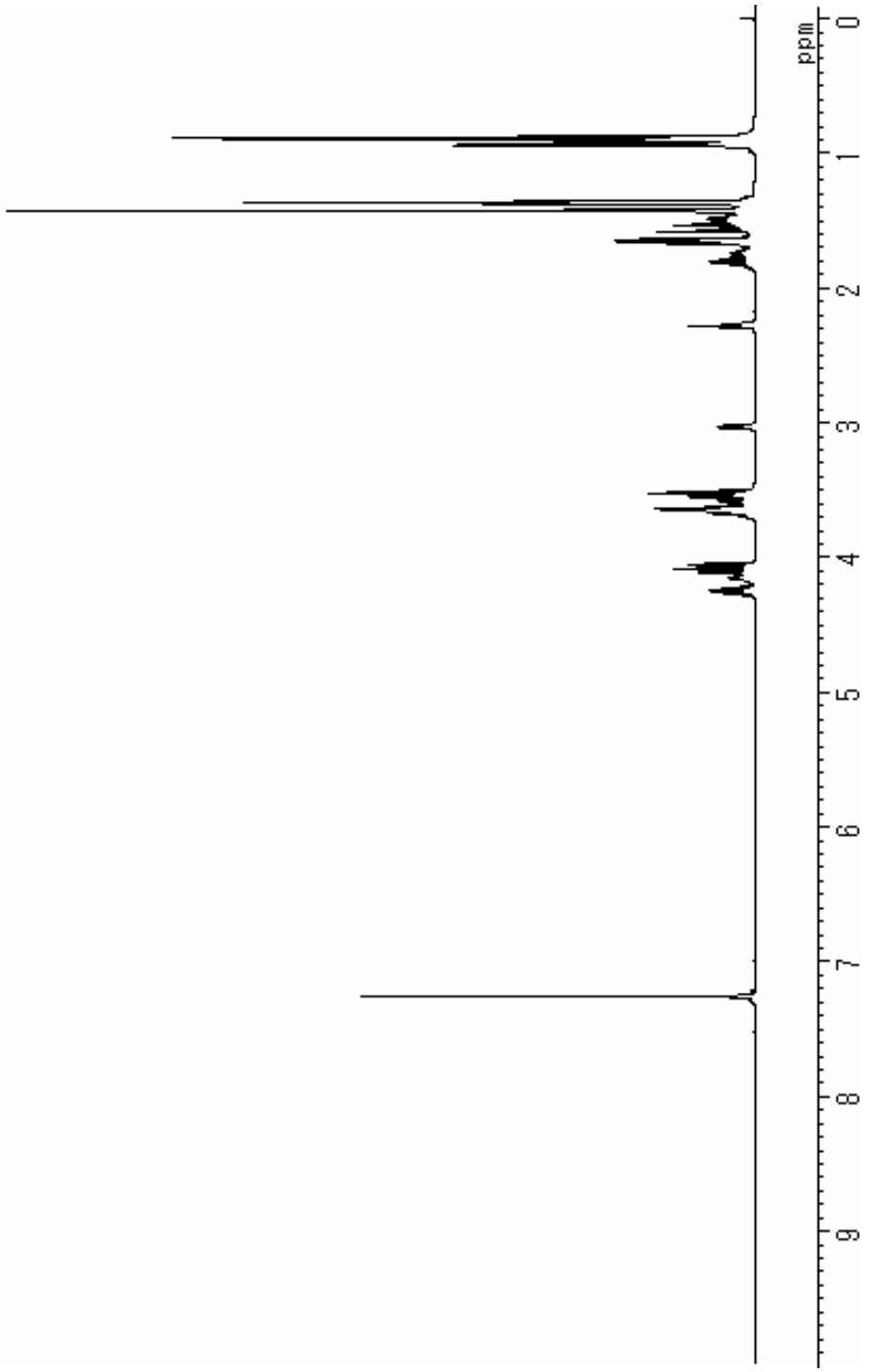

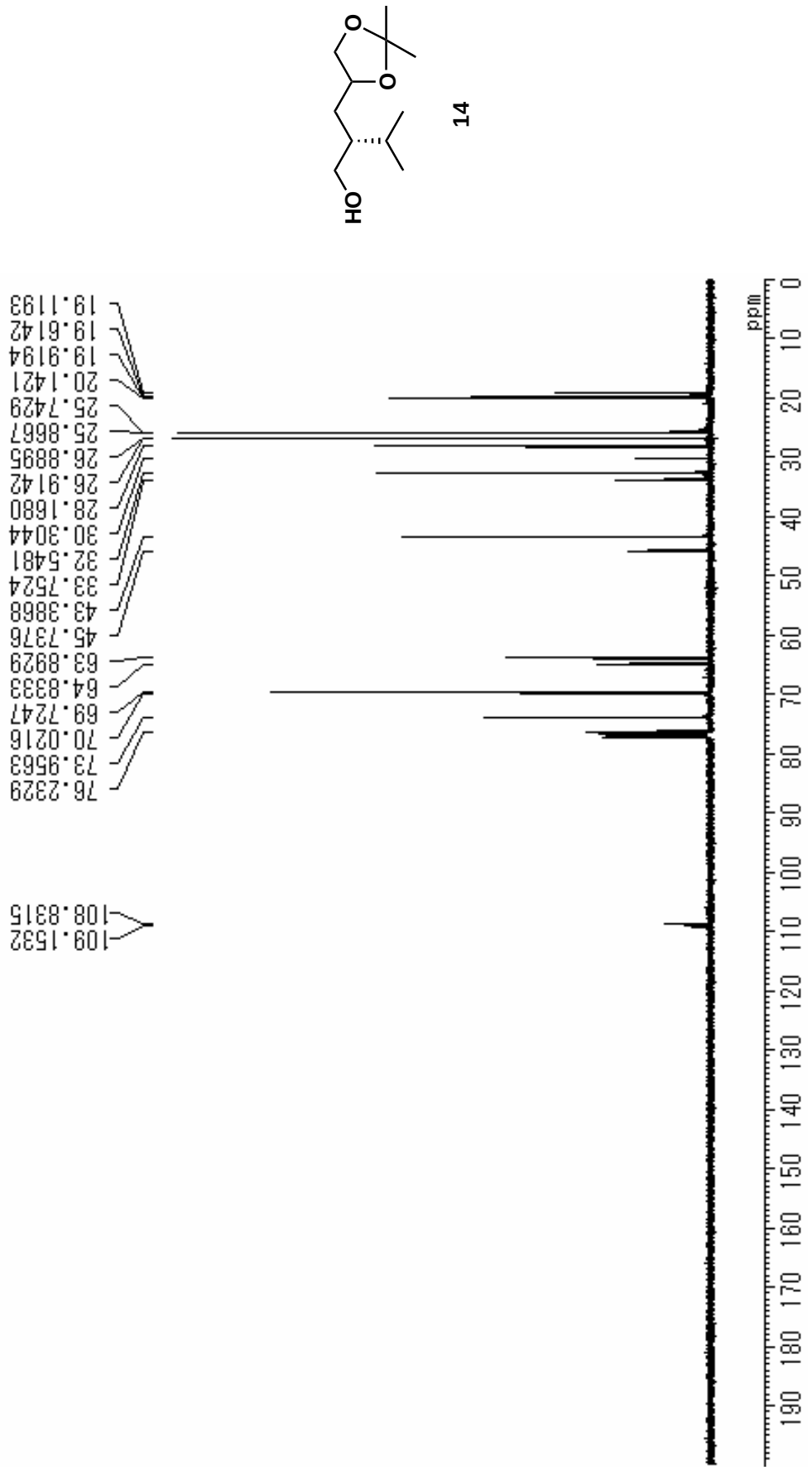
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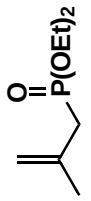

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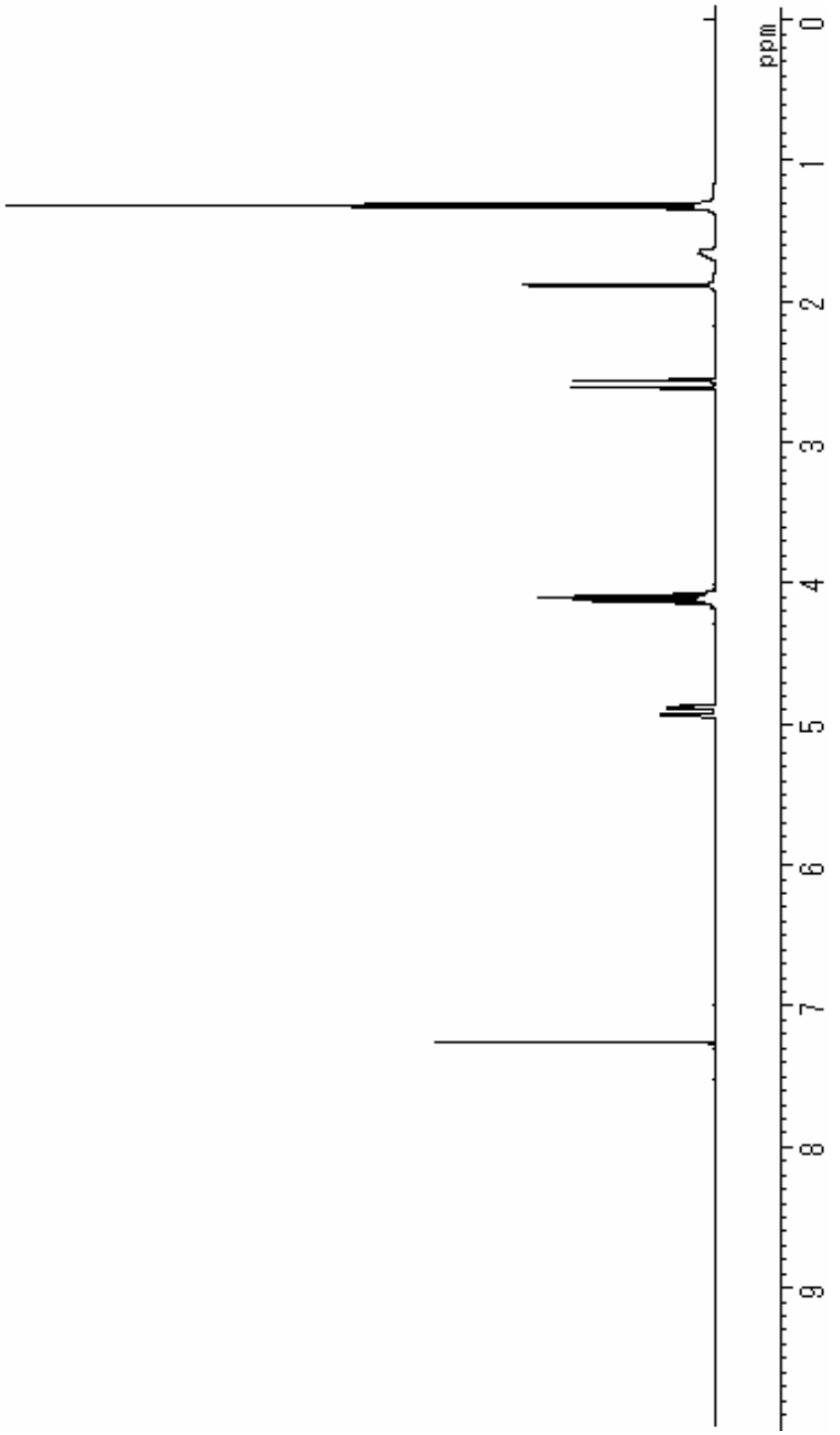

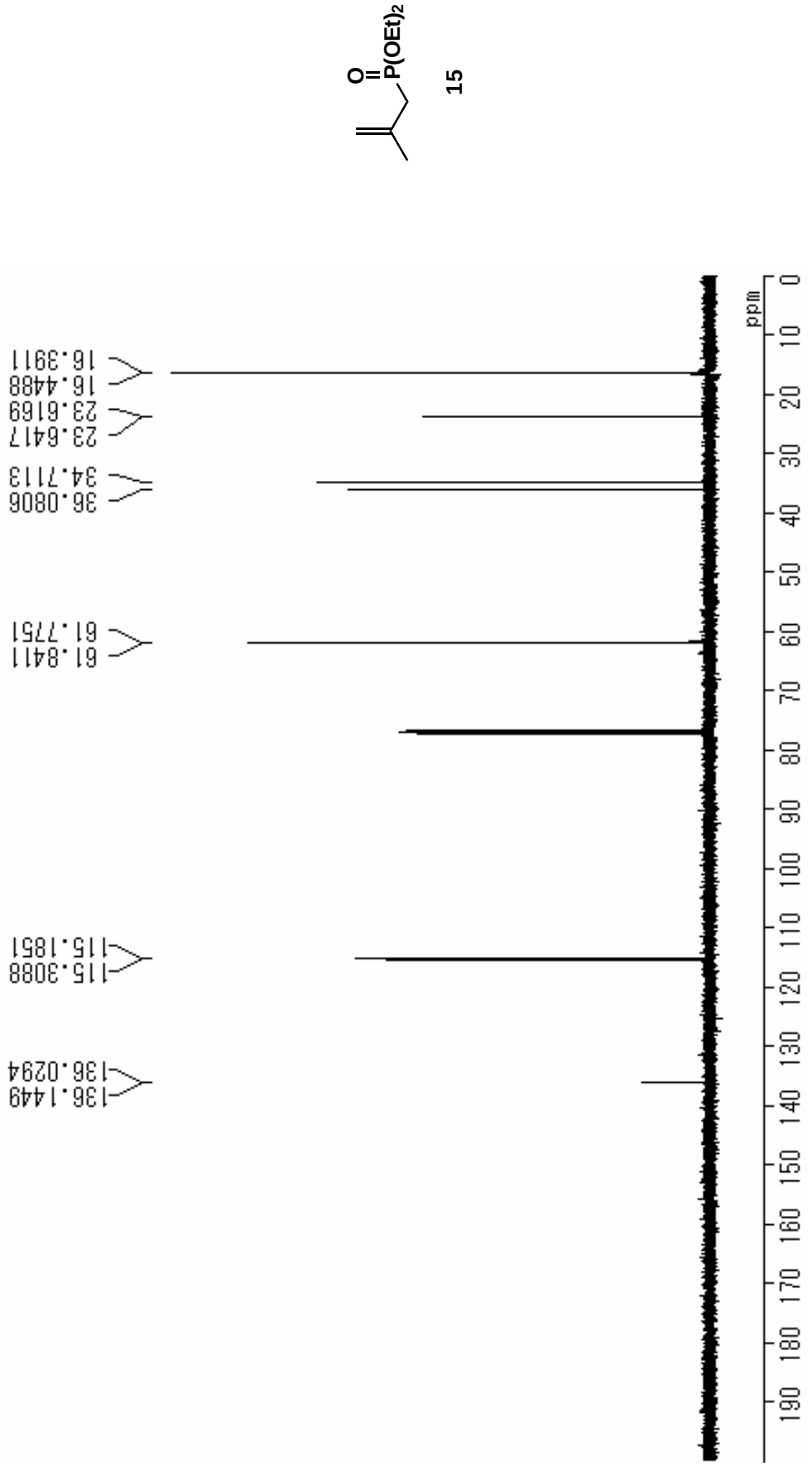
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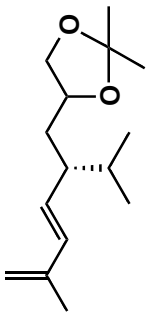

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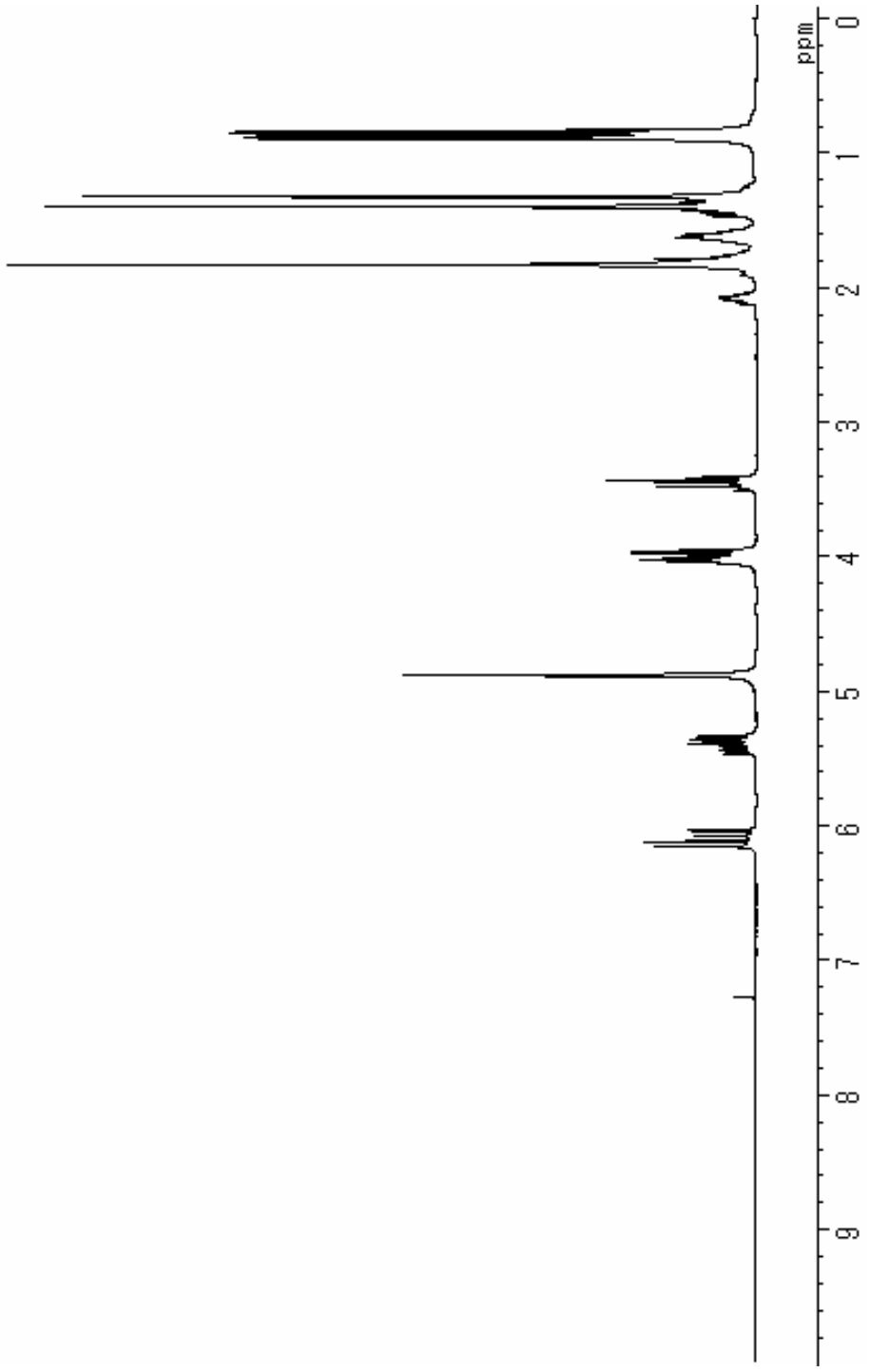

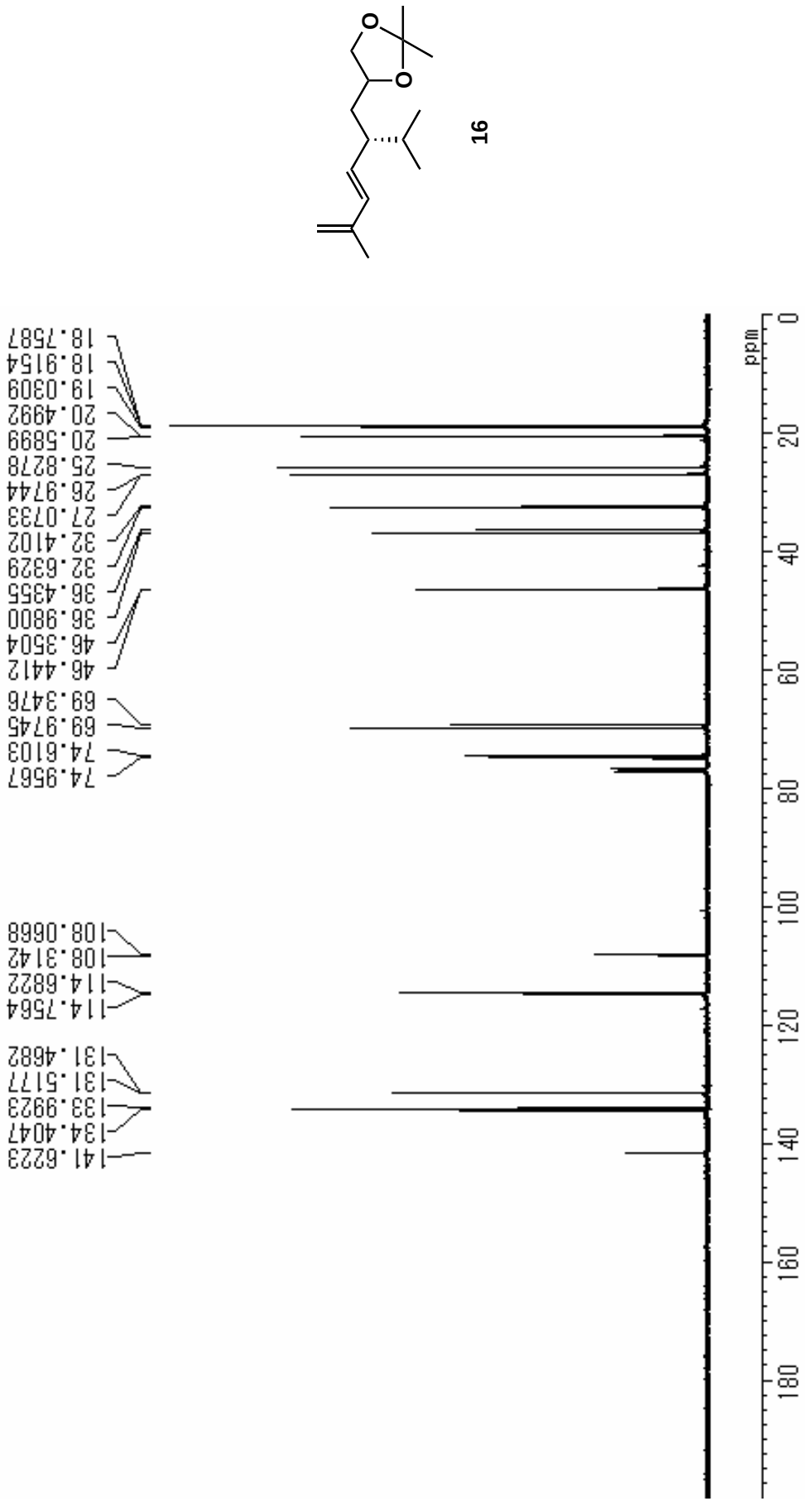
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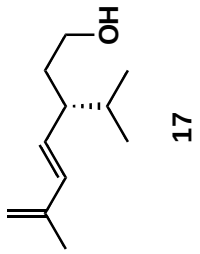

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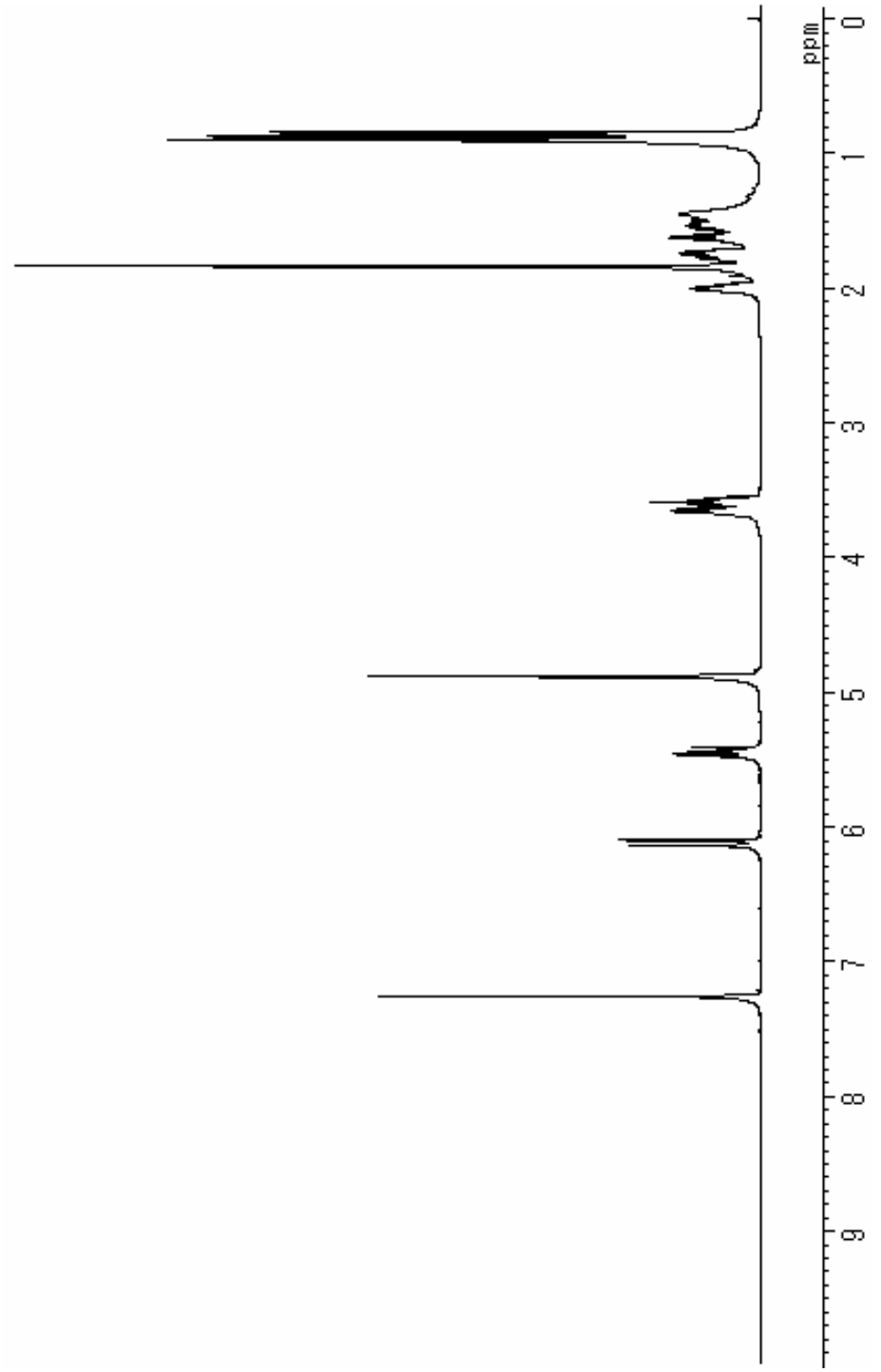

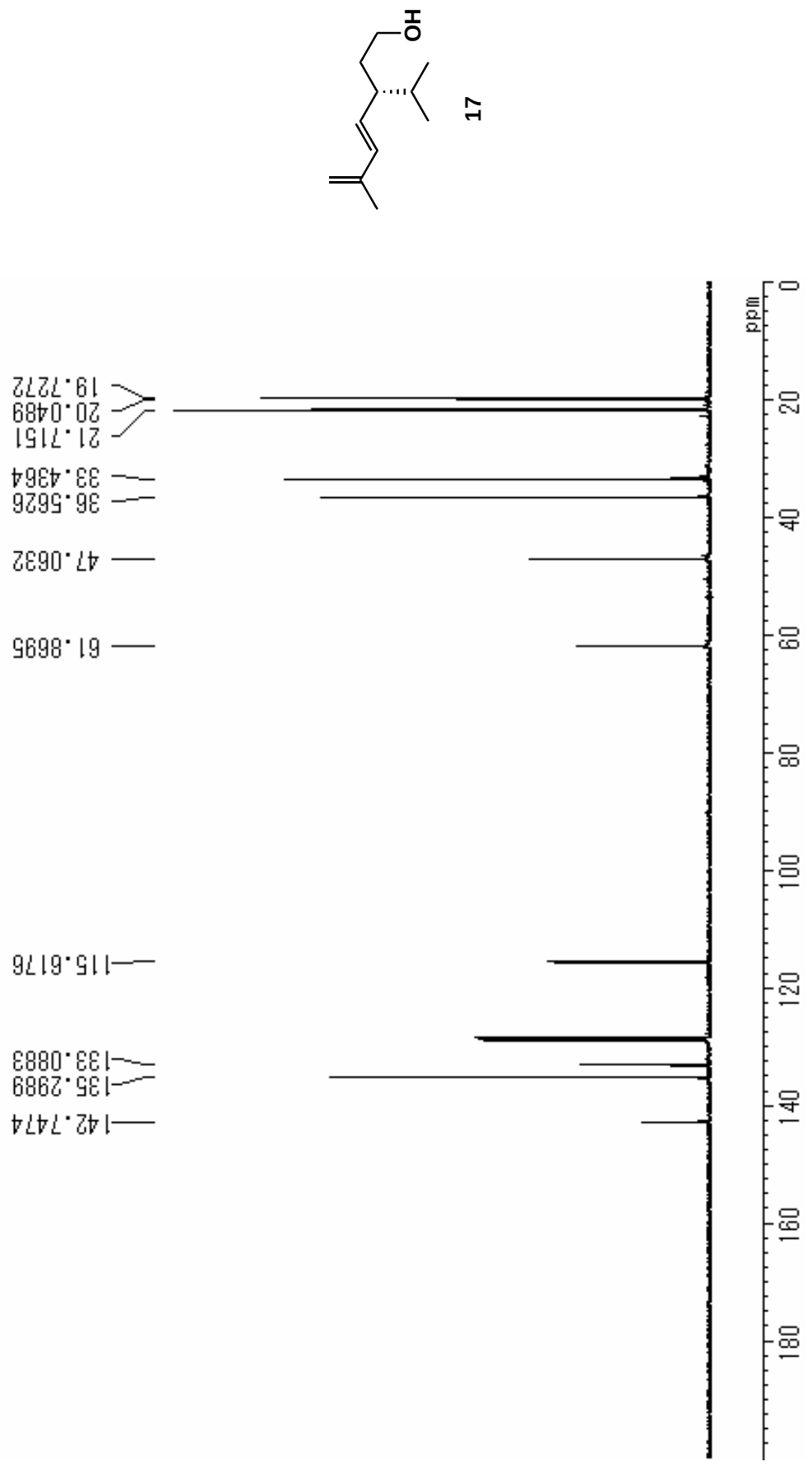
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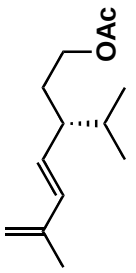

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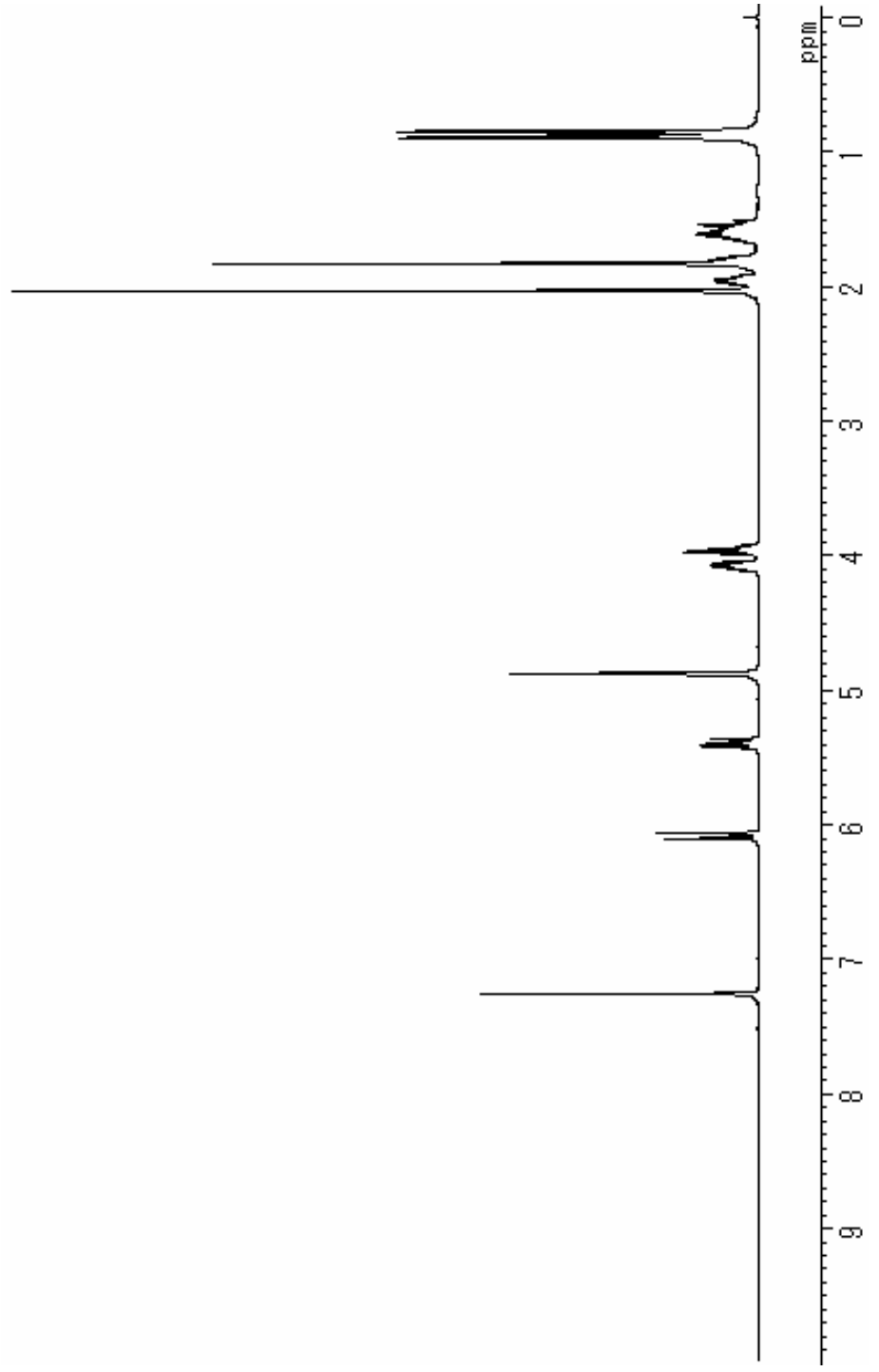

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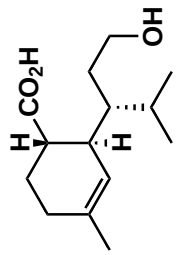

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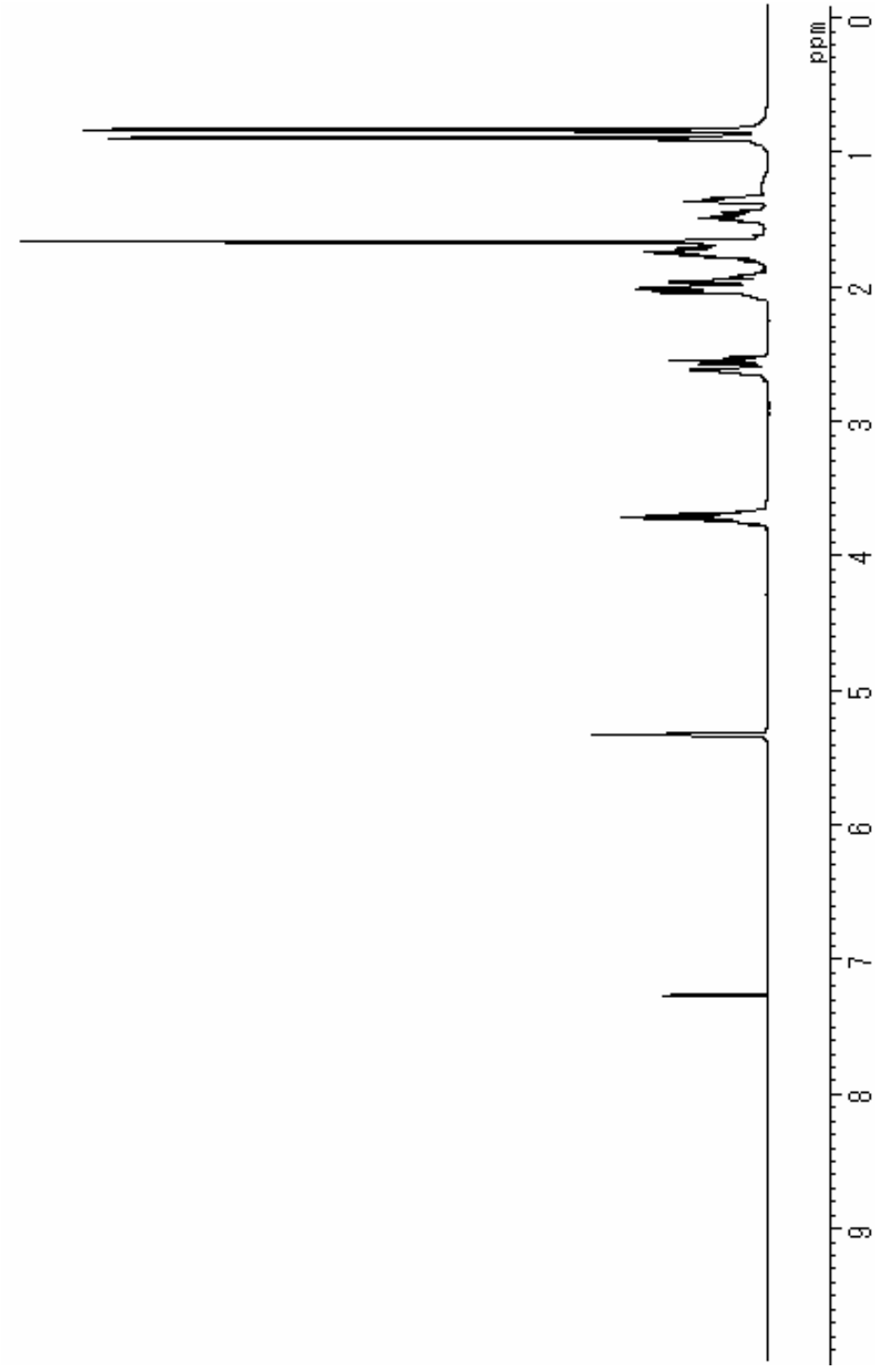

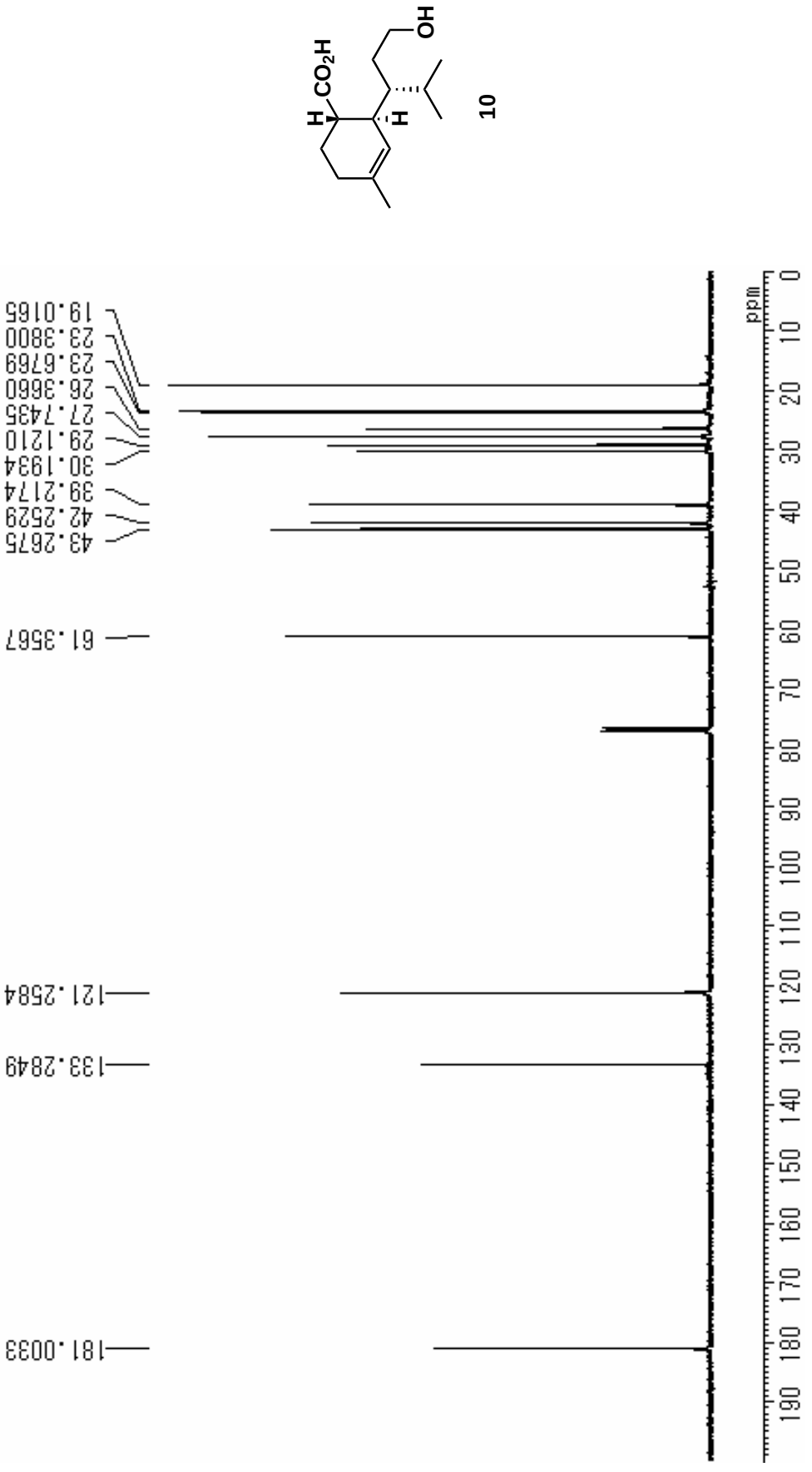
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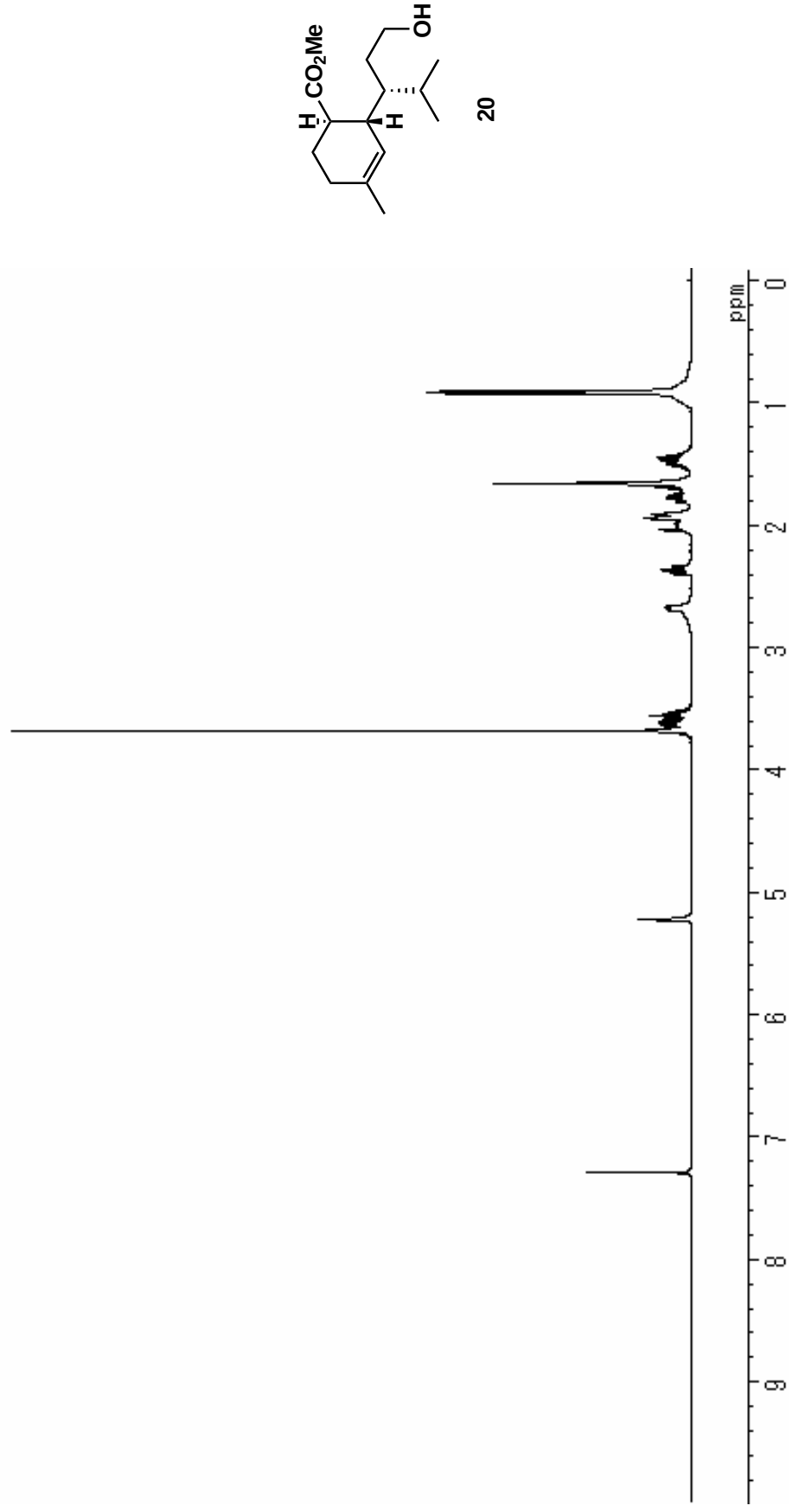
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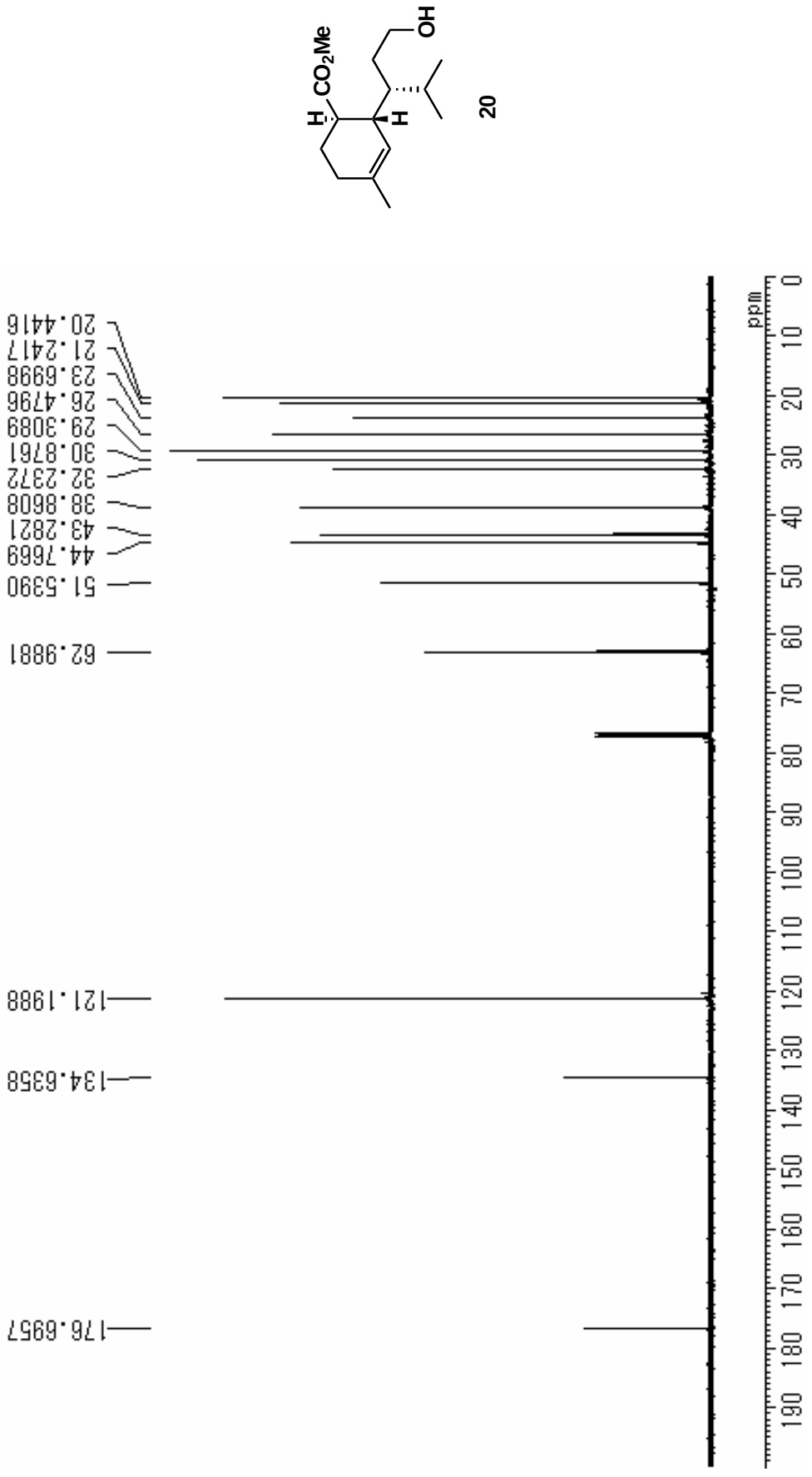
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190
20.4416
21.2417
23.6998
26.4796
29.3089
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62.9881
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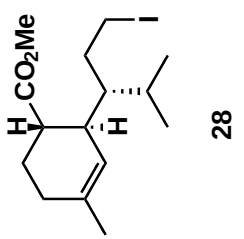
176.6957



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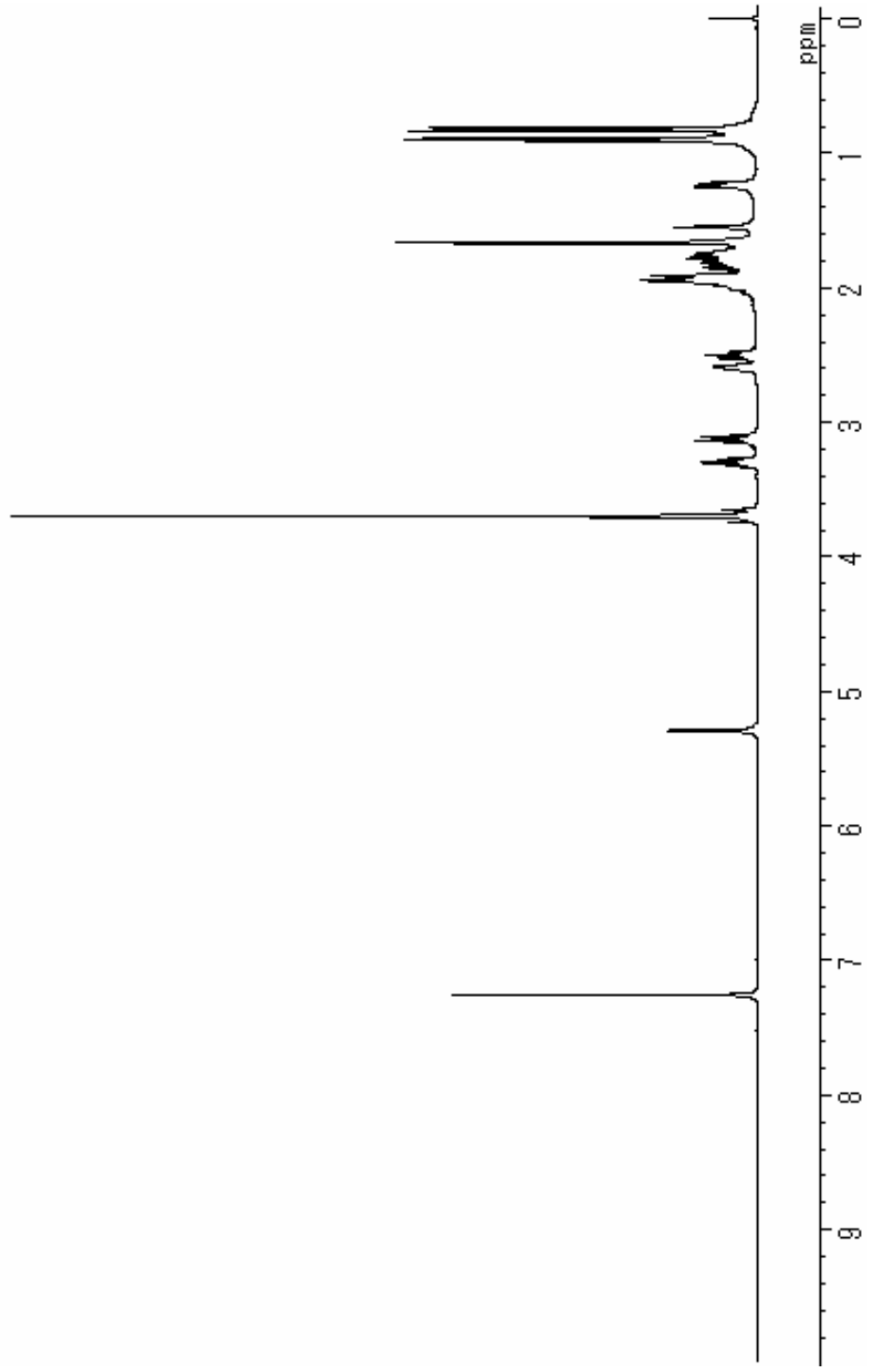

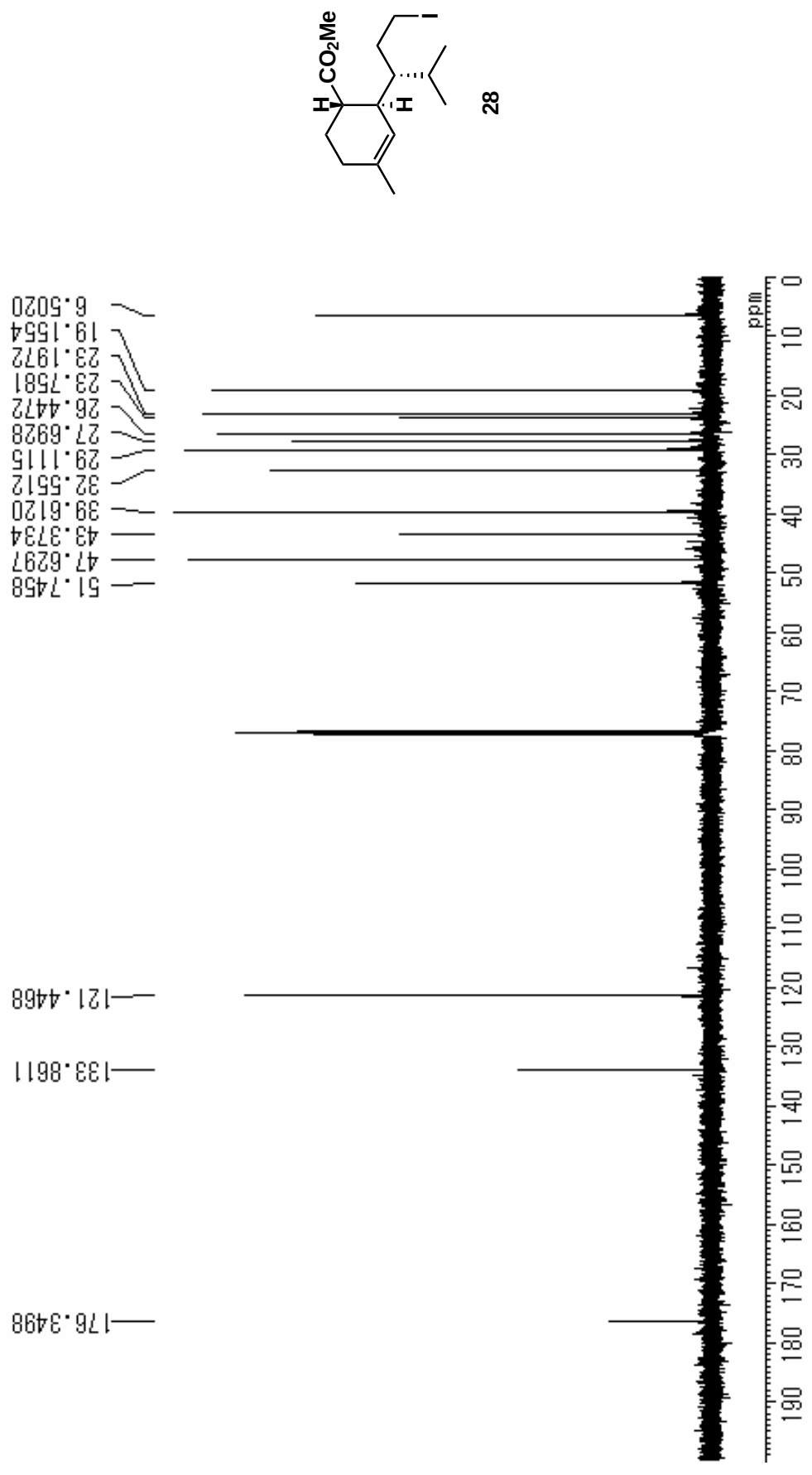
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H
H
I
28
ppm
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130
140
150
160
170
180
190
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133.8611
121.4468
51.7458
47.6297
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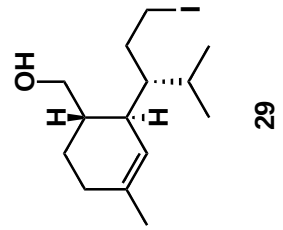
23.7581
23.1972
19.1554
6.5020



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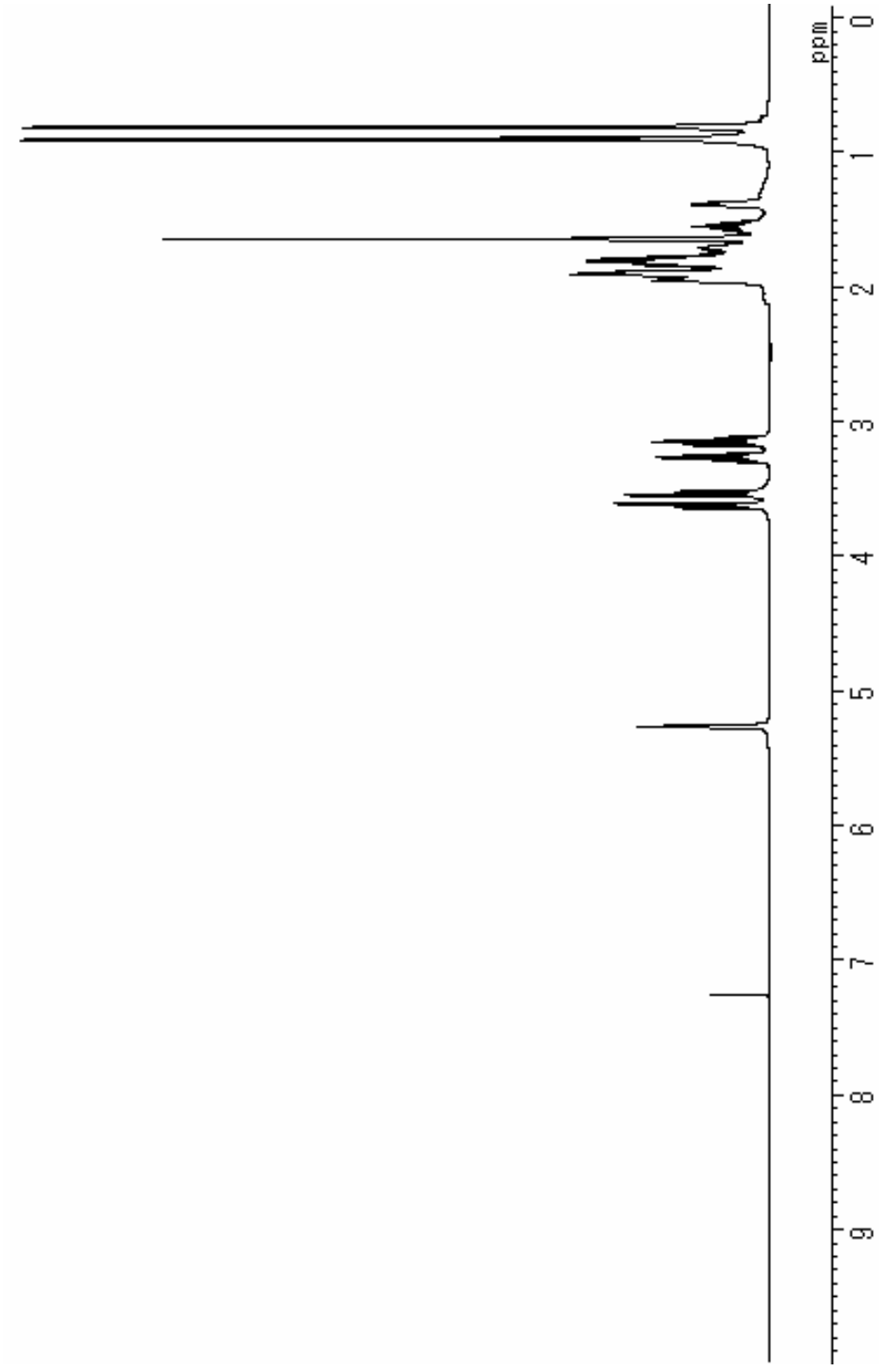

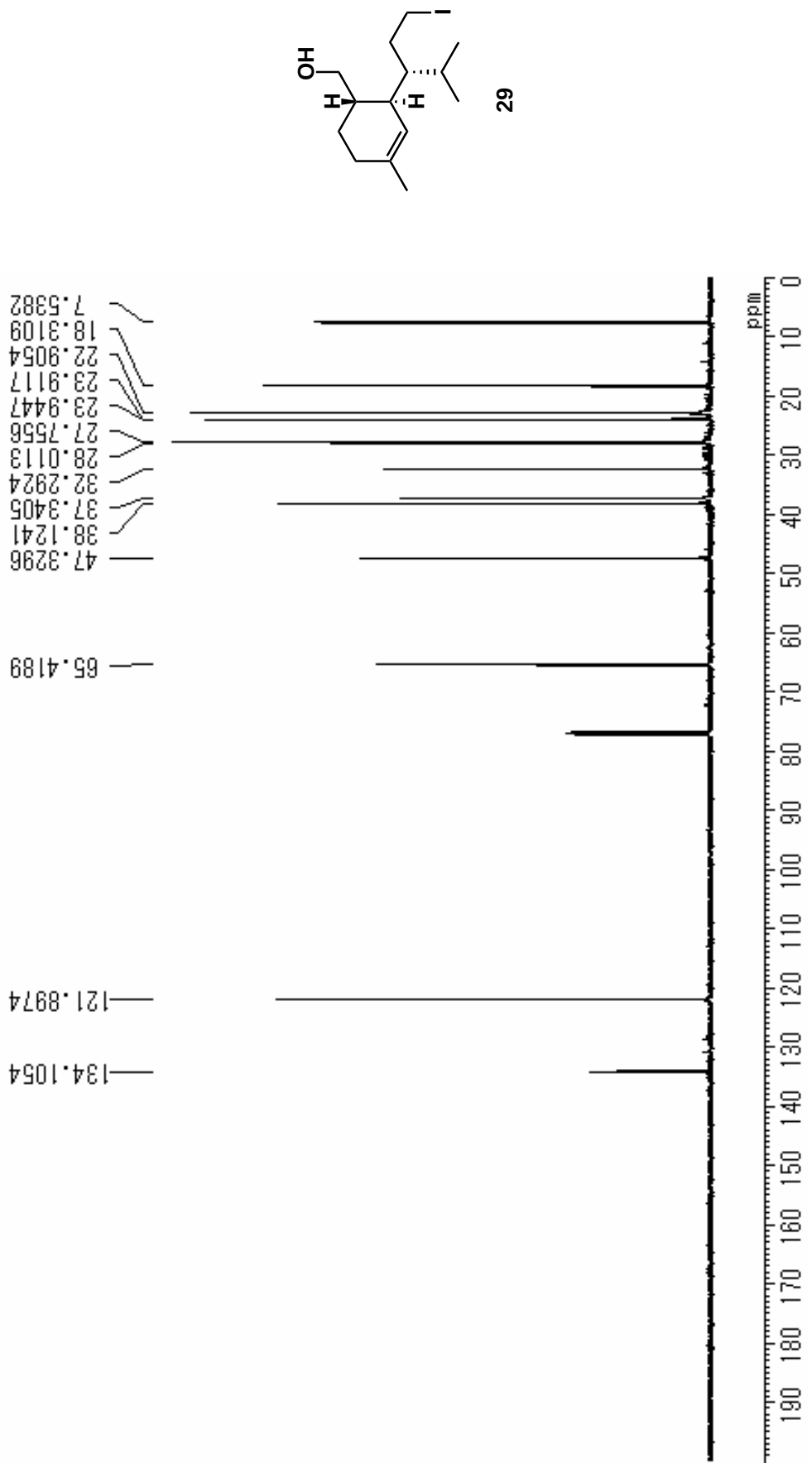
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H
H
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22.9054
23.9117
23.9447
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28.0113
32.2924
37.3405
38.1241
47.3296
65.4189
121.8974
134.1054
ppm
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80
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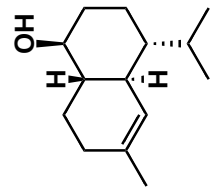
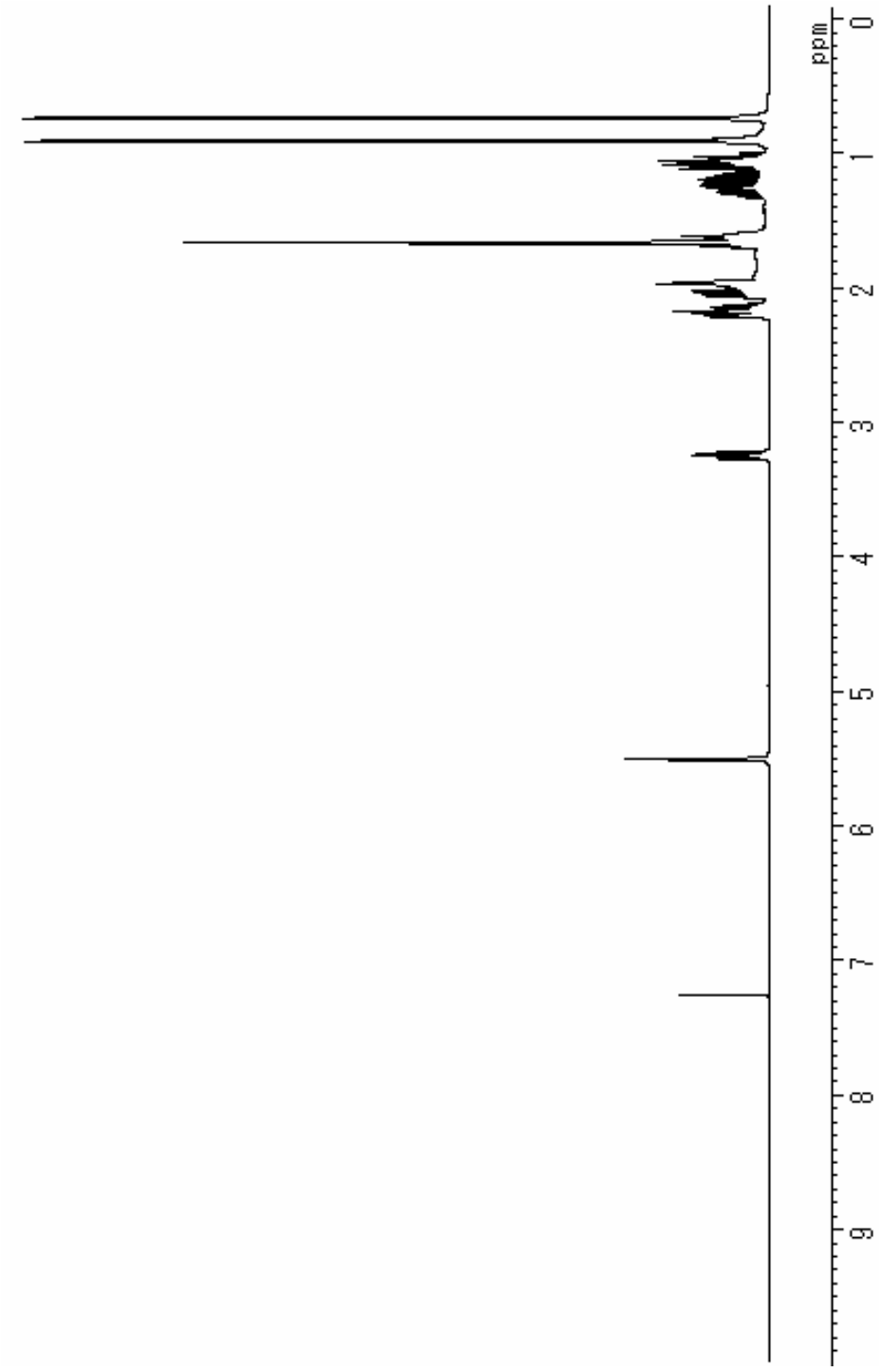
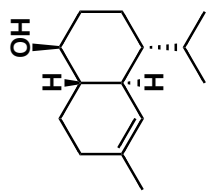
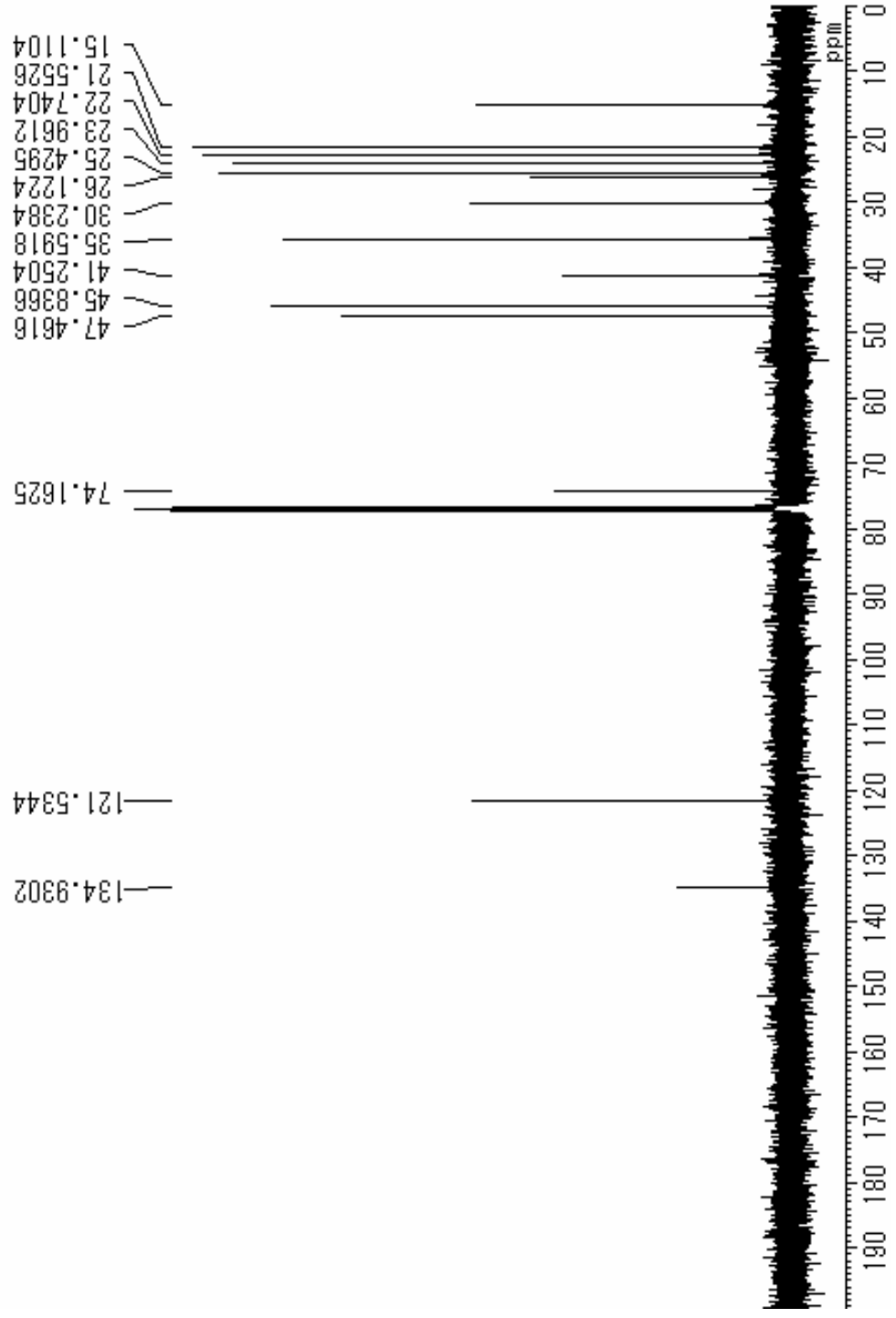


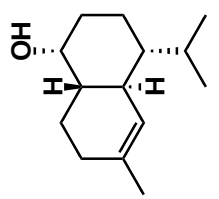
equatorial-**21**



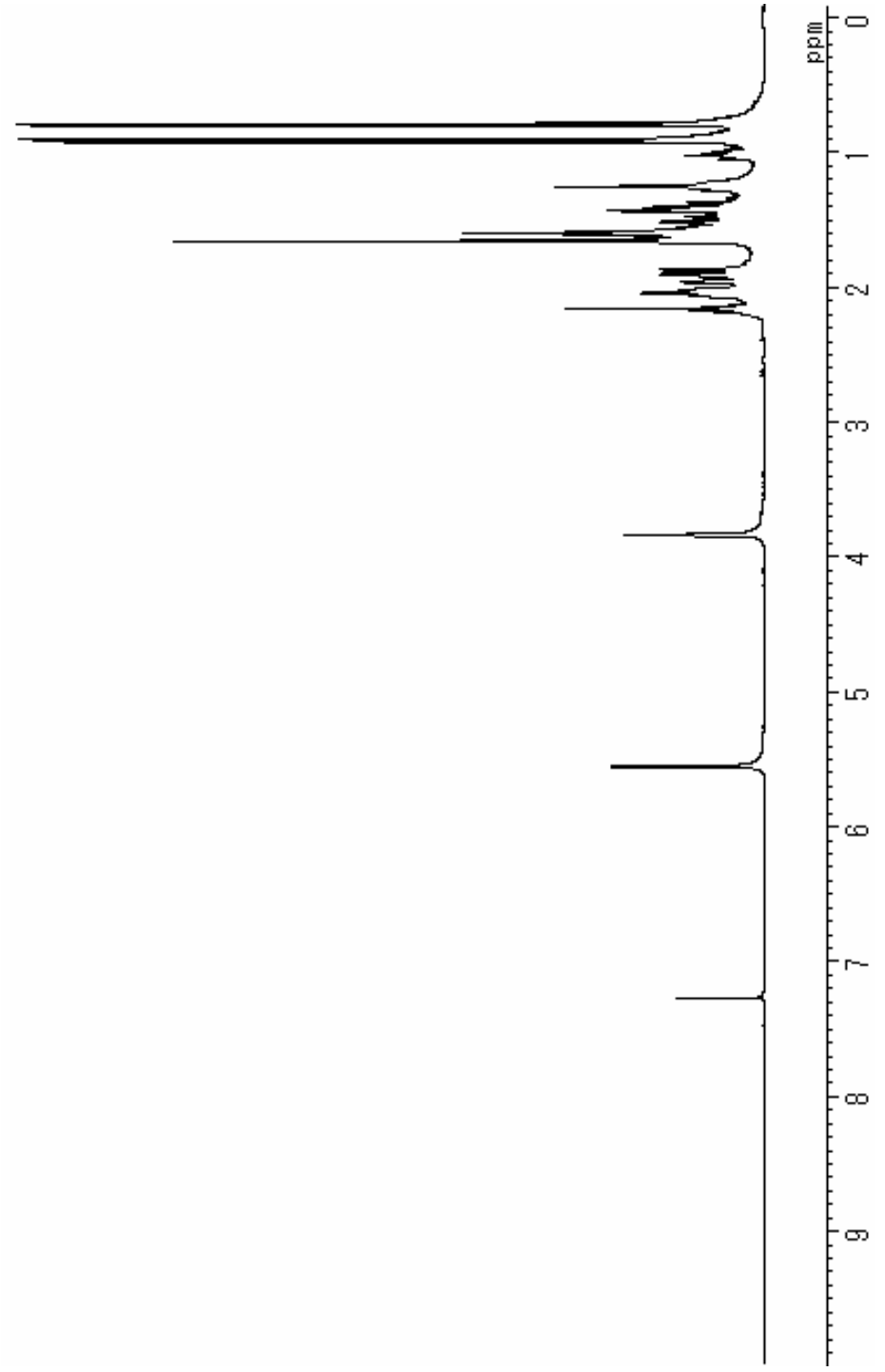


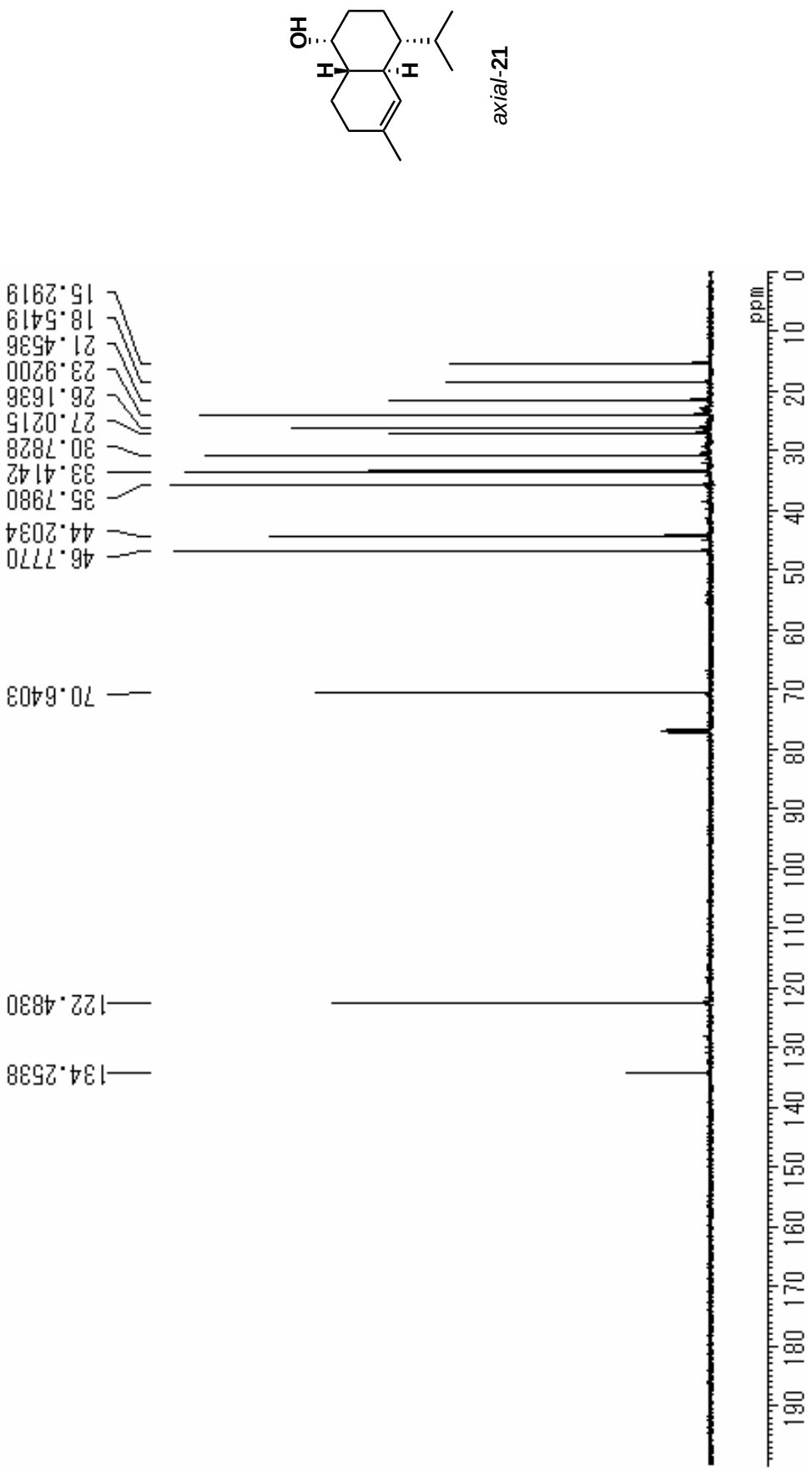
equatorial-**21**





axial-**21**

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H
axial-21
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100
110
120
130
140
150
160
170
180
190
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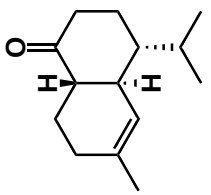
18.5419
21.4536
23.9200
26.1636
27.0215
30.7828
33.4142
35.7980
44.2034
46.7770
70.6403
122.4830
134.2538



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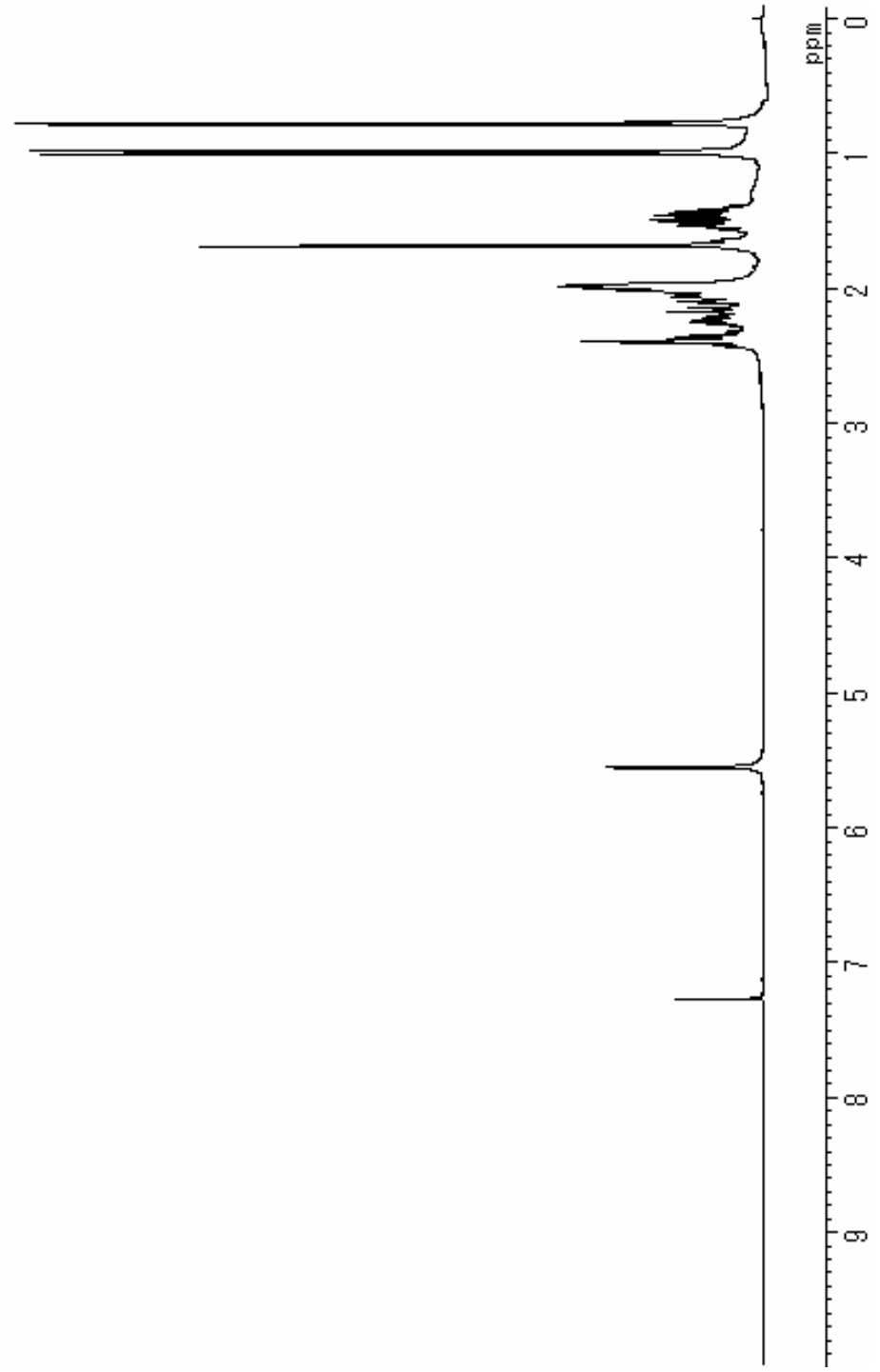
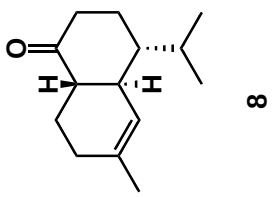
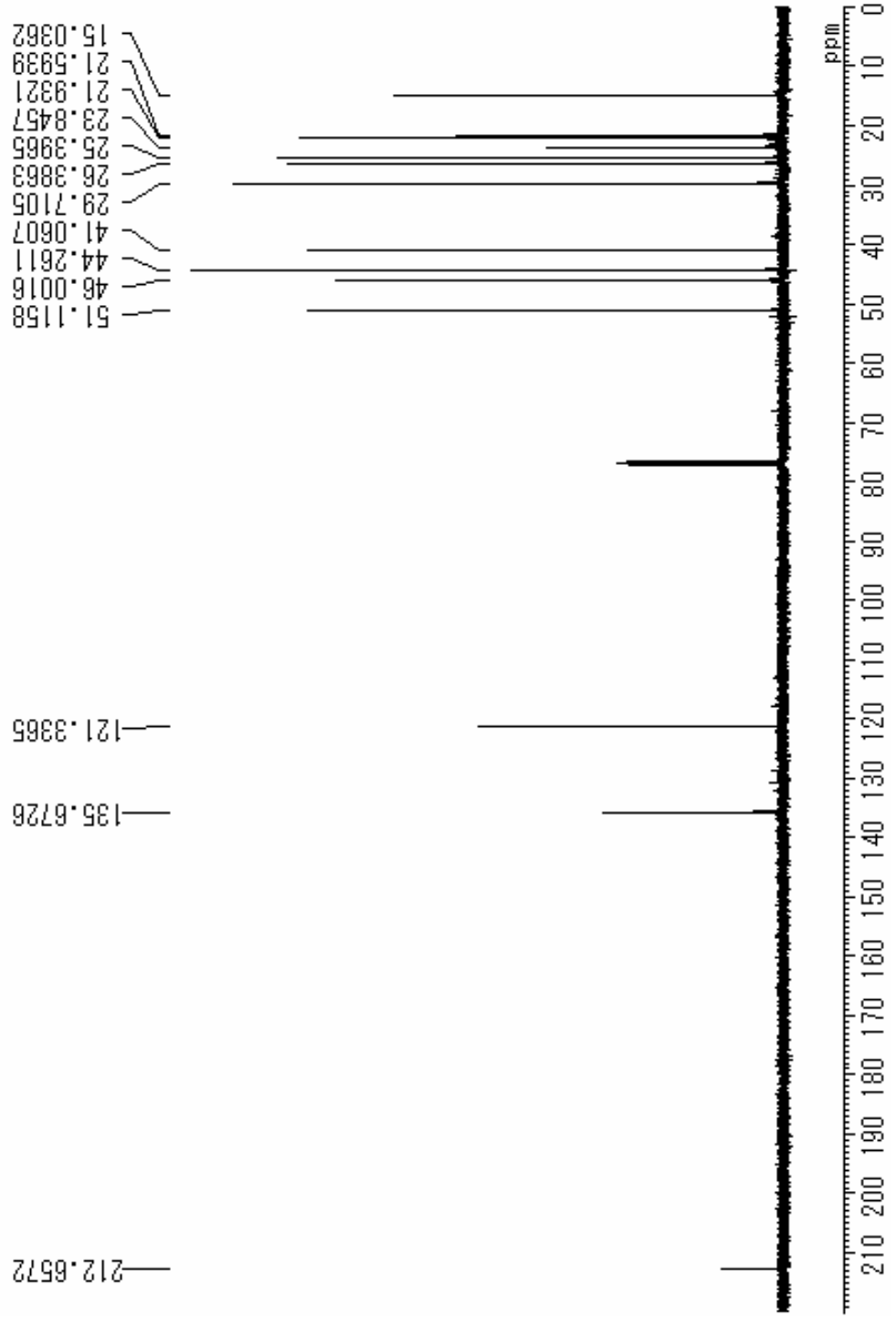



O
H
H

8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121.3365
51.1158
46.0016
44.2611
41.0607
29.7105
26.3863
25.3965
23.8457
21.9321
21.5939
15.0362
ppm
0
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60
70
80
90
100
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120
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140
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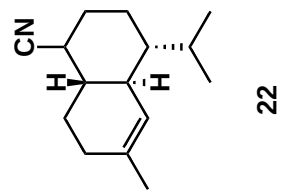
170
180
190
200
210



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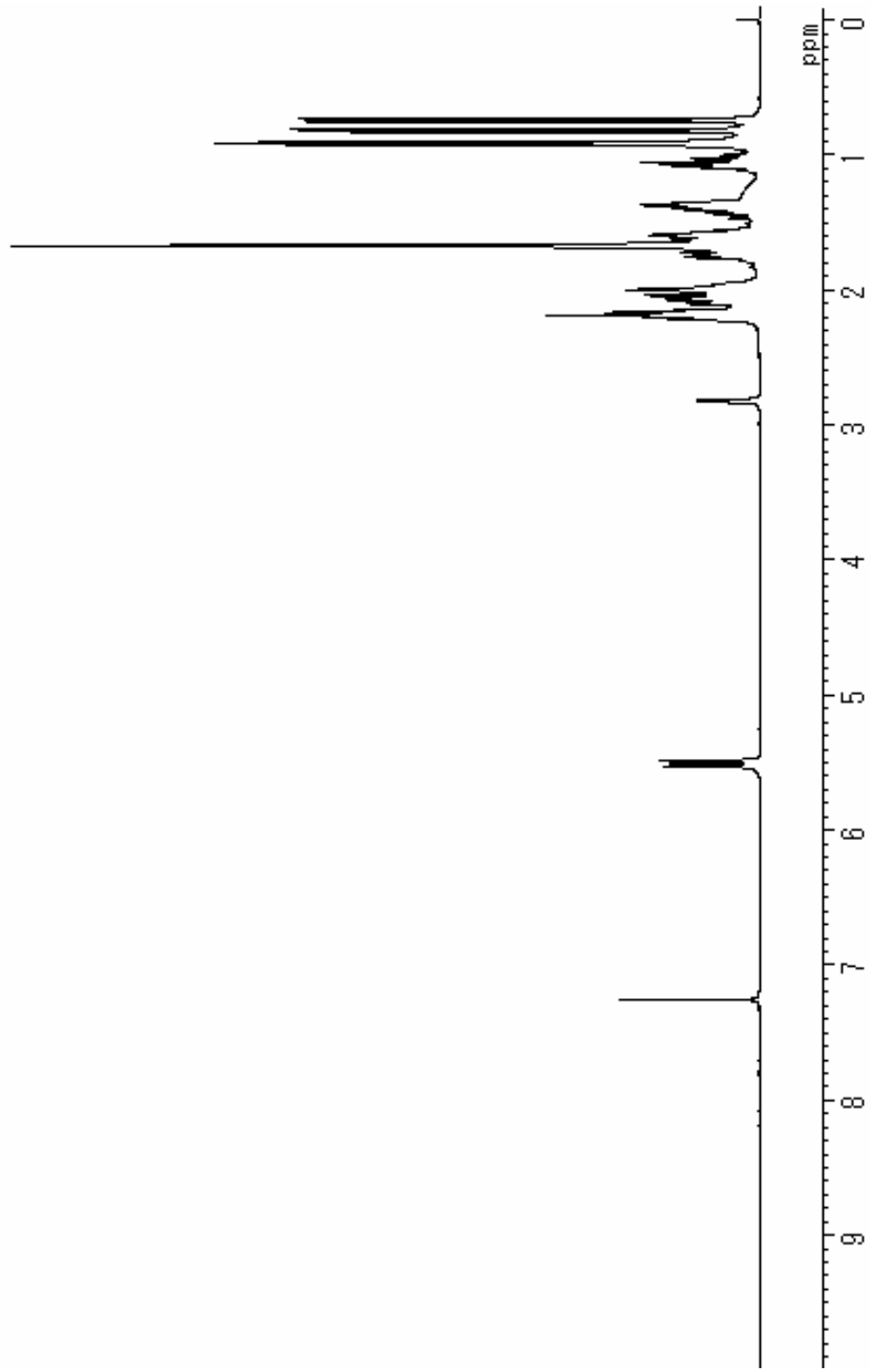
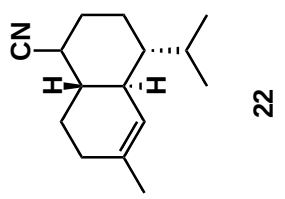
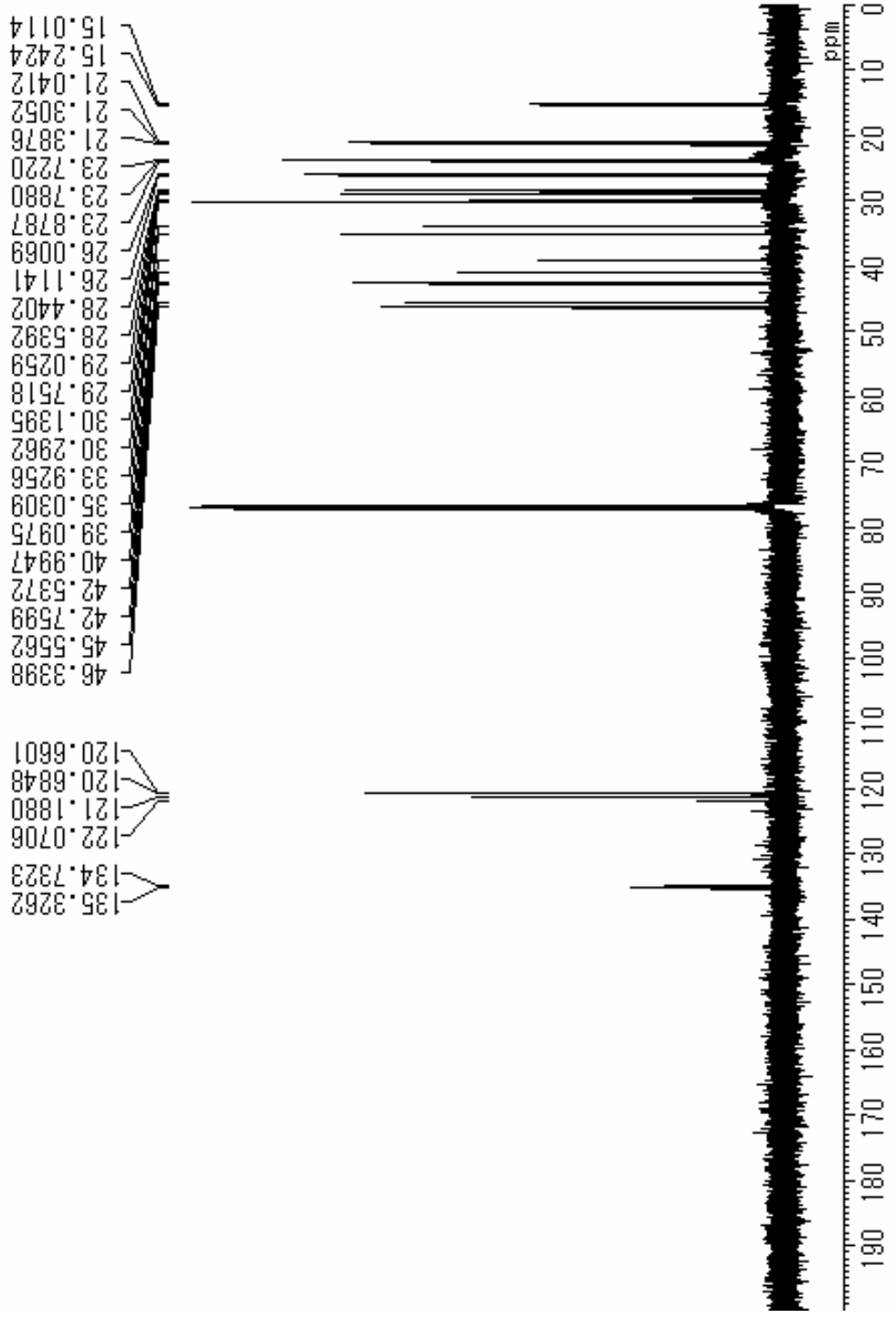



CN
H
H

22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100
110
120
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140
150
160
170
180
190
15.0114
15.2424
21.0412
21.3052
21.3876
23.7220
23.7880
23.8787
26.0069
26.1141
28.4402
28.5392
29.0259
29.7518
30.1395
30.2962
33.9256
35.0309
39.0975
40.9947
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134.7323
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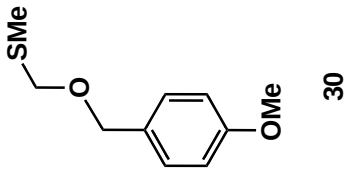

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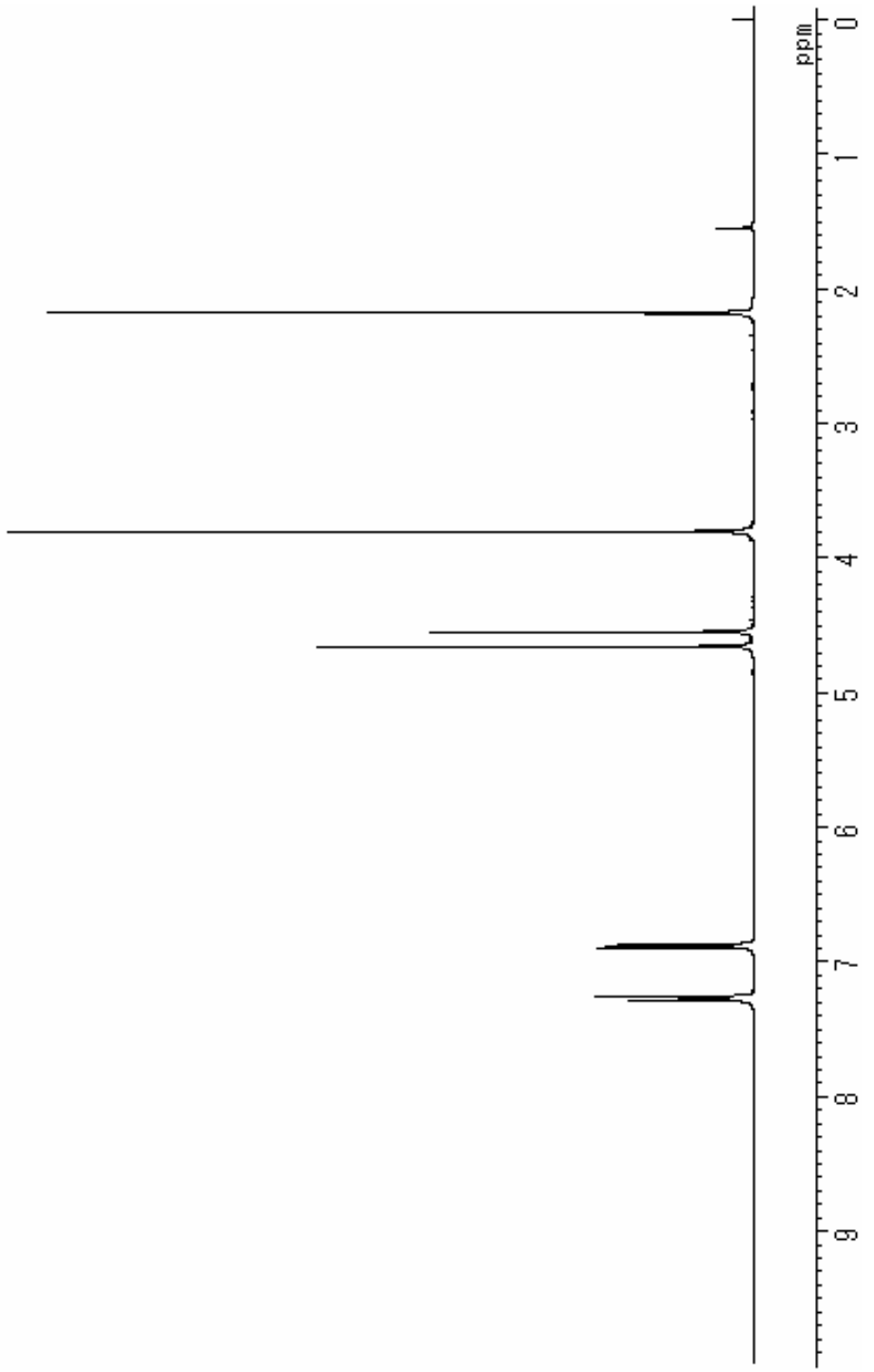
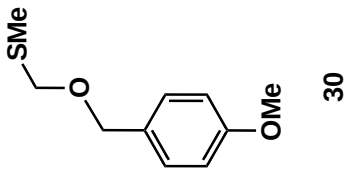
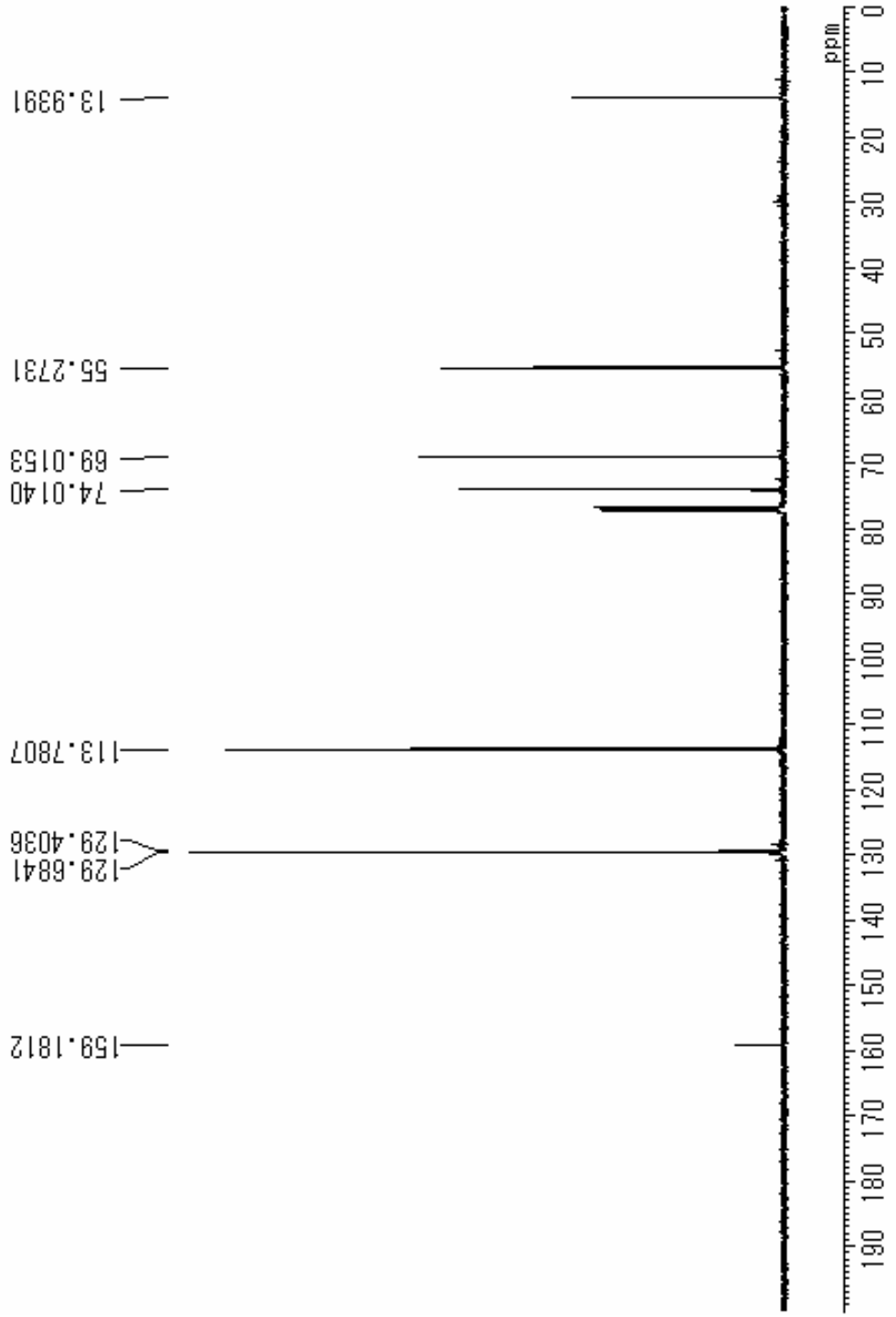



SMe
O
OMe

30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113.7807
129.4036
129.6841
159.1812
ppm
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50
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70
80
90
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120
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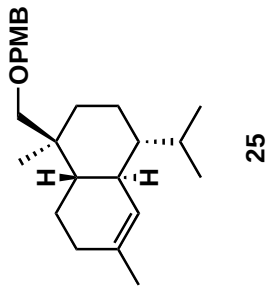
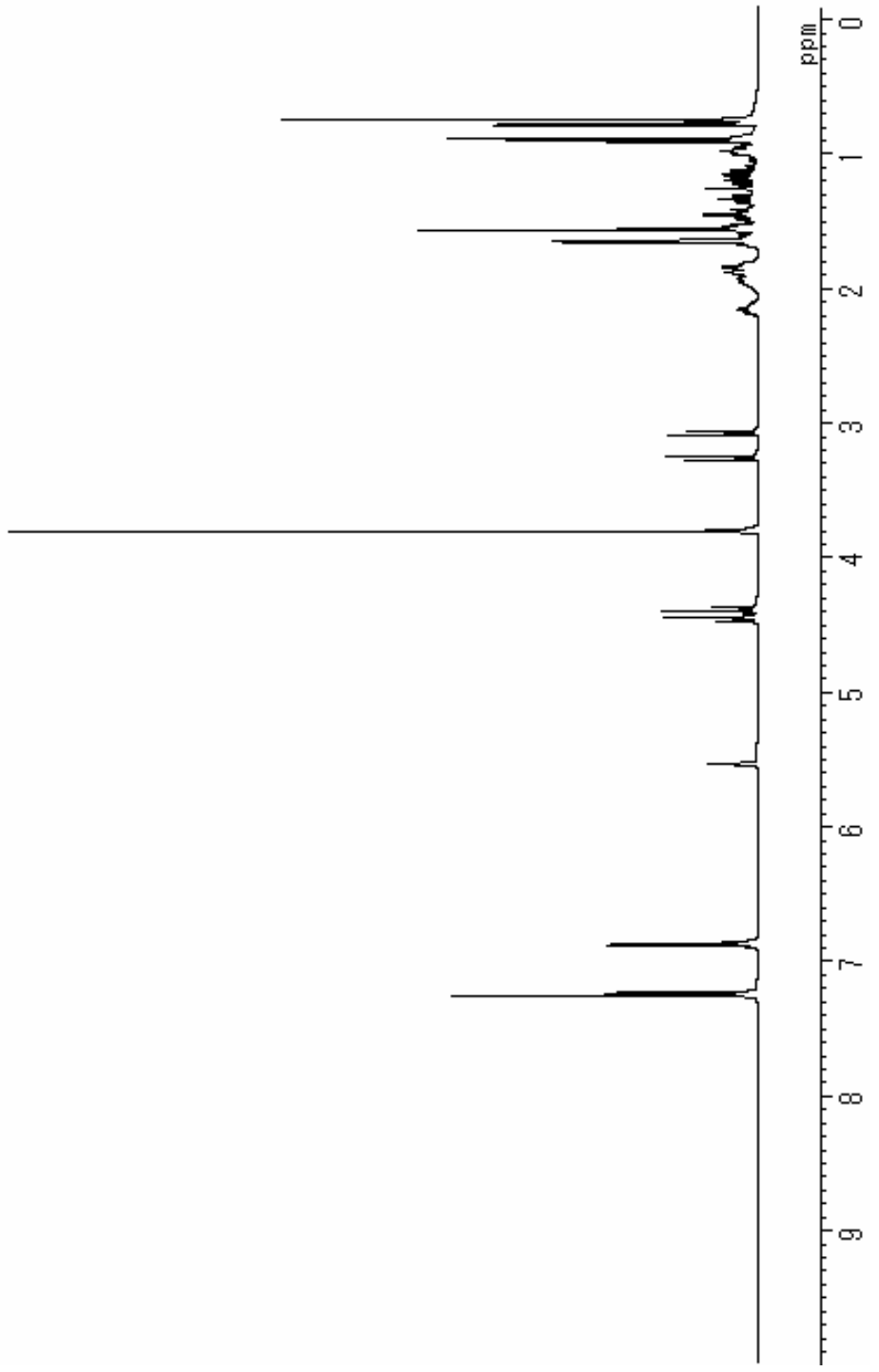
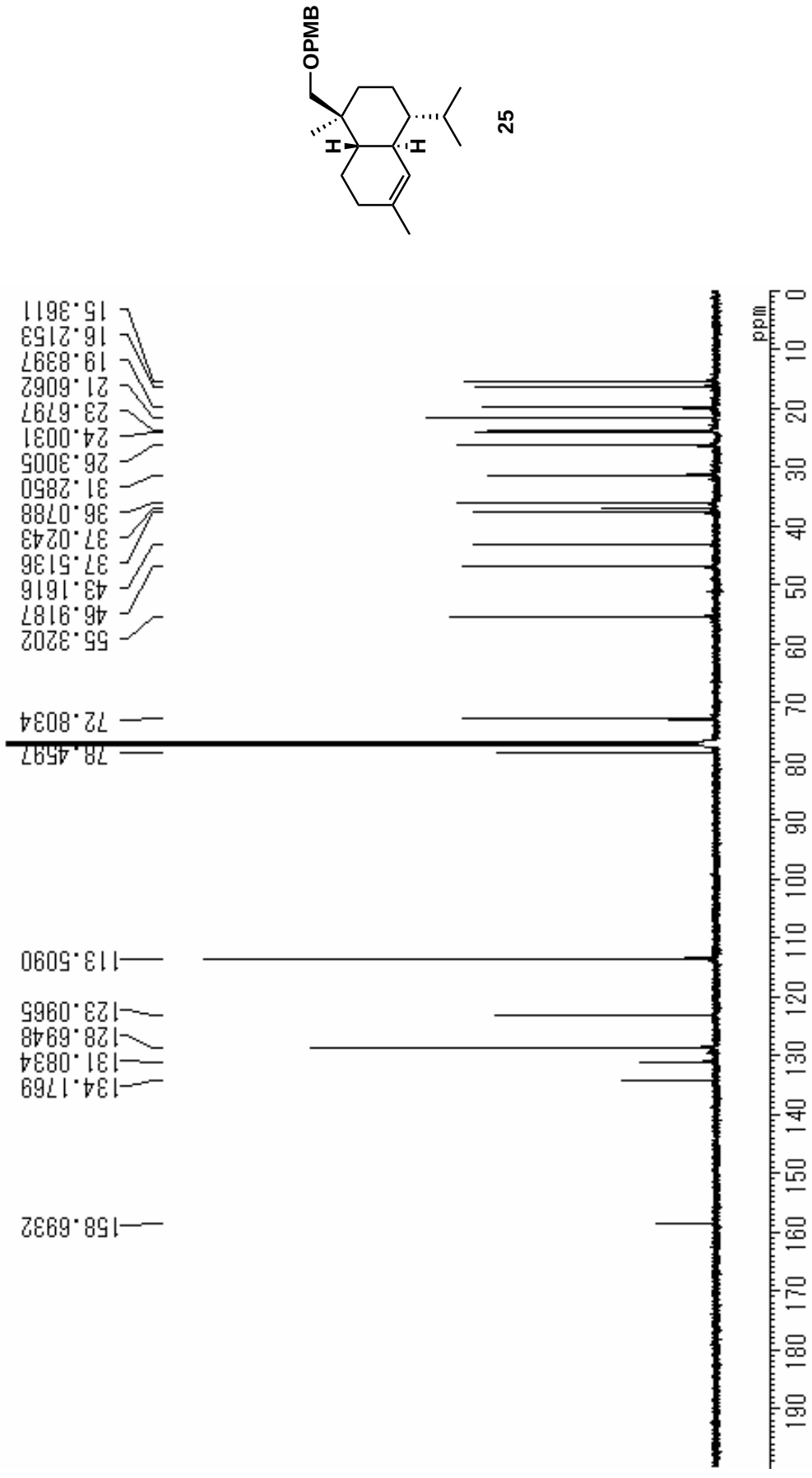
170
180
190



25

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23.6797
24.0031
26.3005
31.2850
36.0788
37.0243
37.5136
43.1616
46.9187
55.3202
72.8034
78.4597
113.5090
123.0965
128.6948
131.0834
134.1769
158.6932
ppm
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80
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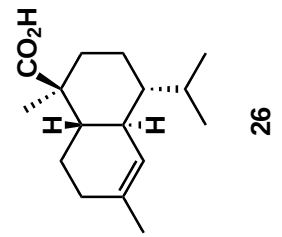
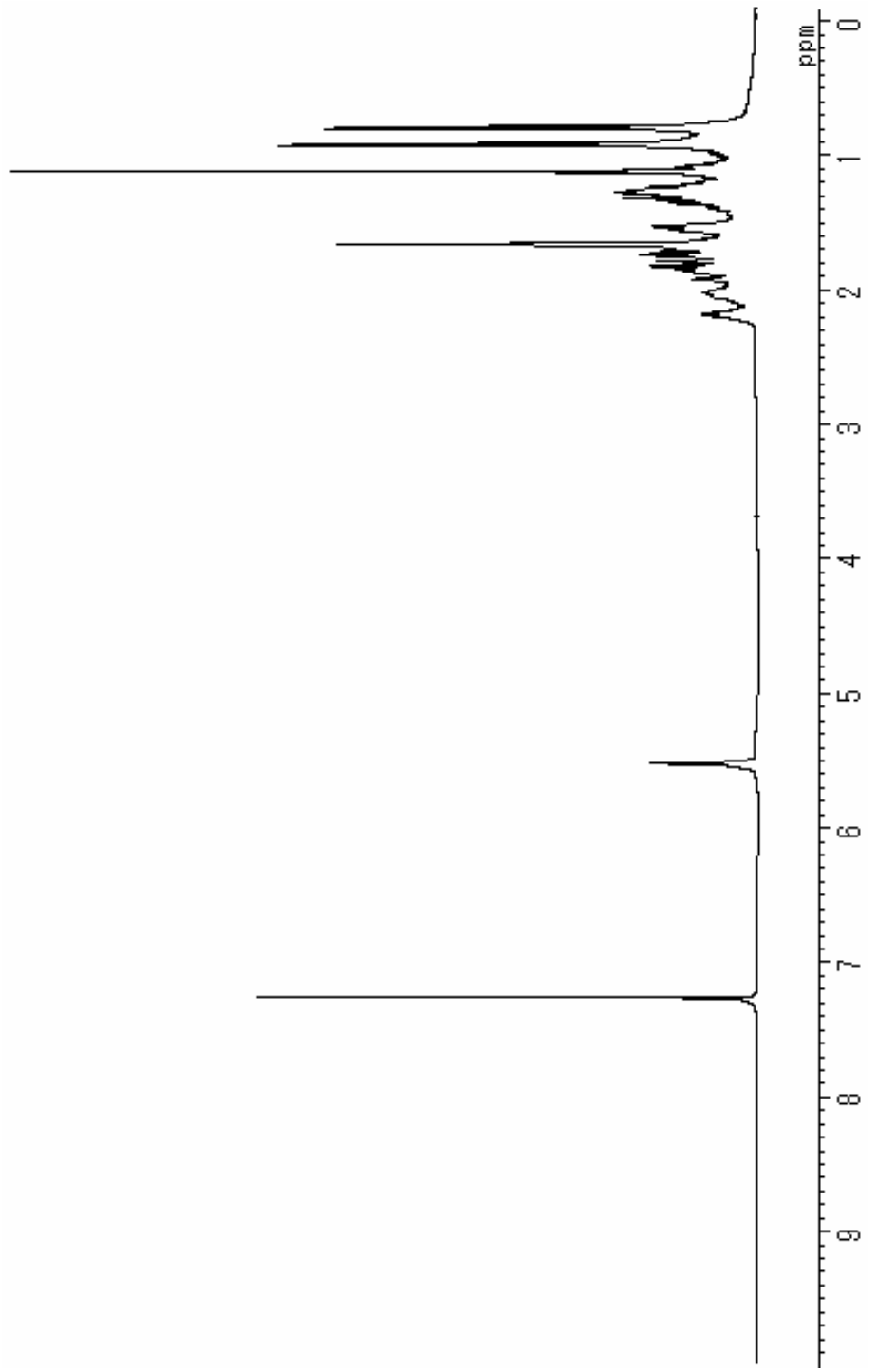
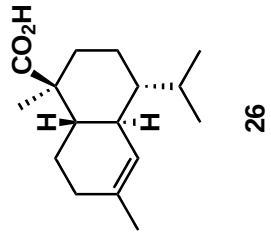
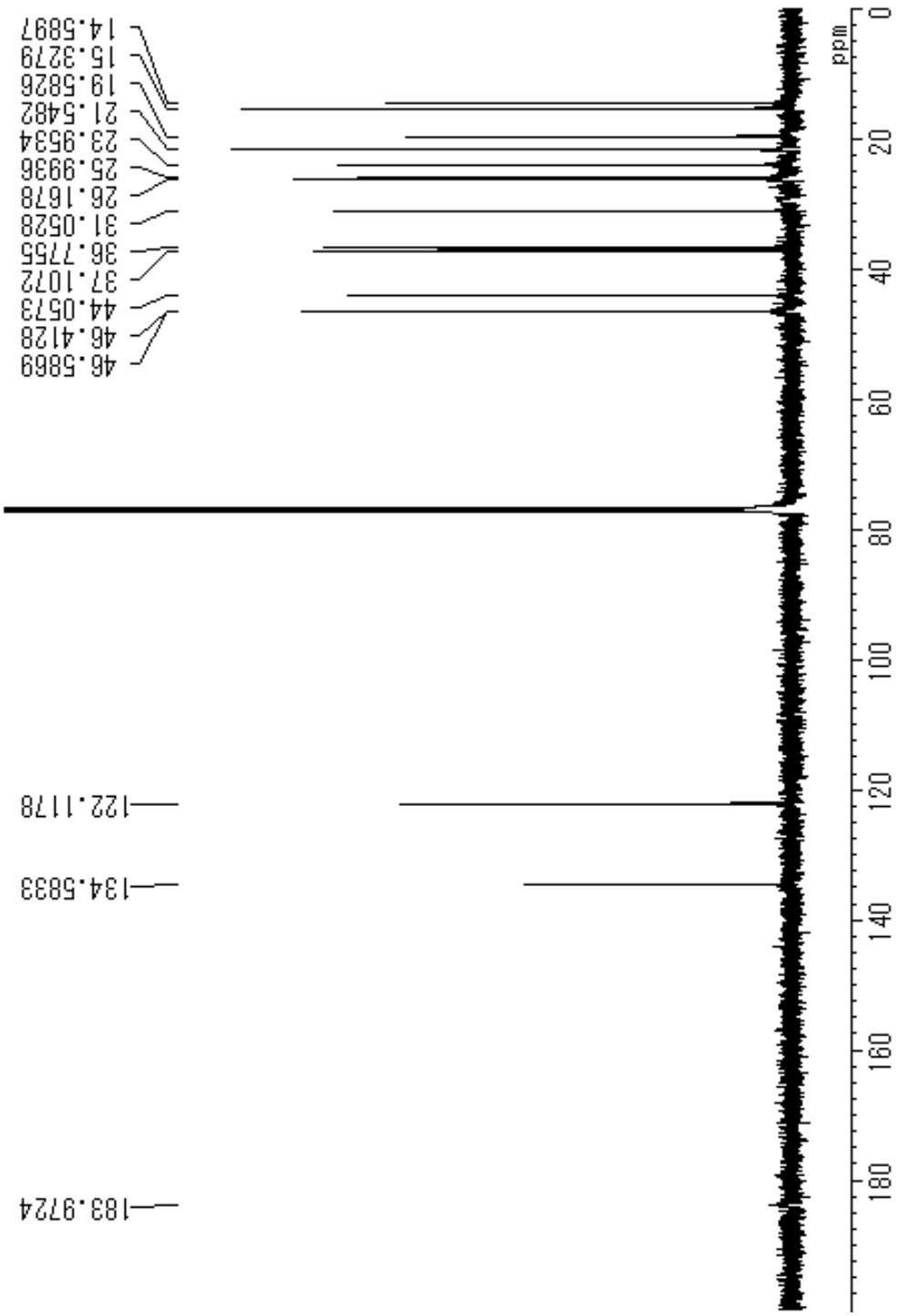


26




CO2H
H
H

26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26.1678
31.0528
36.7755
37.1072
44.0573
46.4128
46.5869
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134.5833
183.9724
ppm
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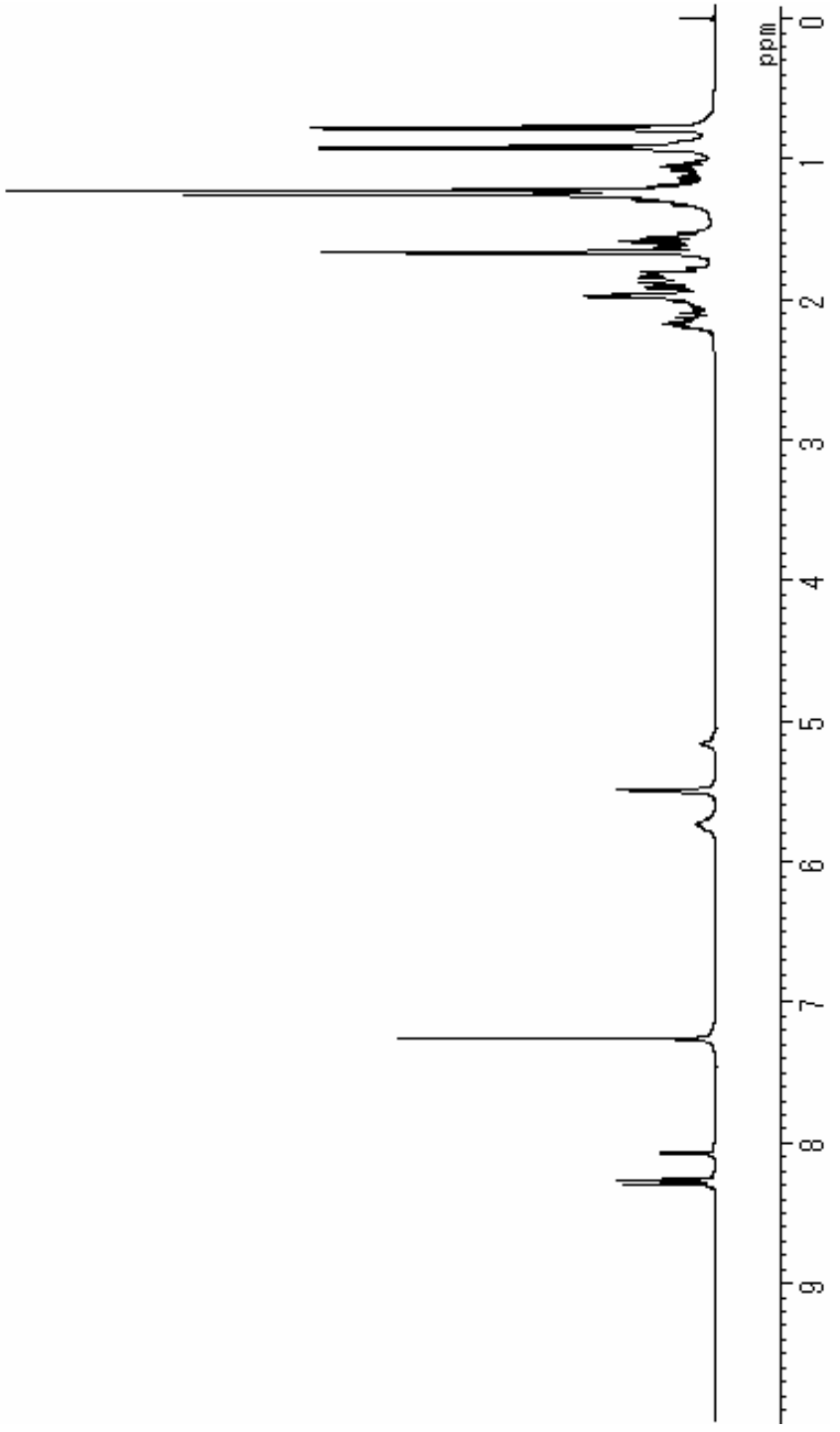
60
80
100
120
140
160
180


O
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HN
H
H
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ppm
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6
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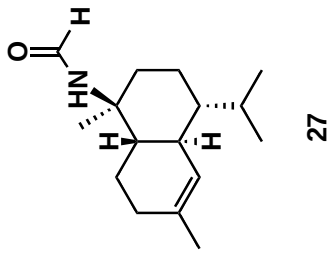
8
9


O
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HN
H
H

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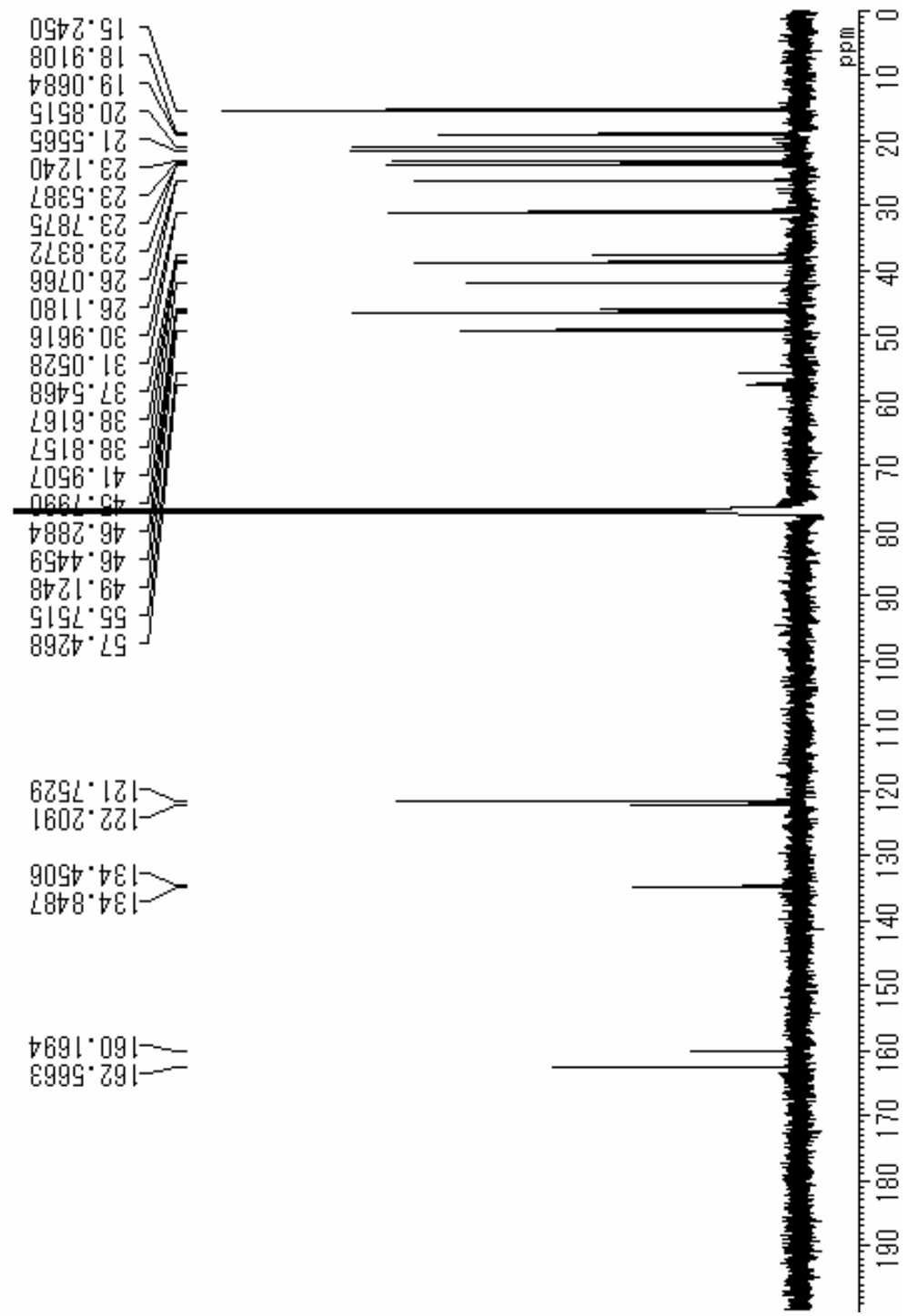
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23.8372
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49.1248
55.7515
57.4268
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122.2091
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134.8487
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162.5663
ppm
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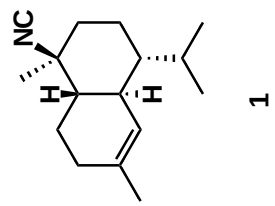

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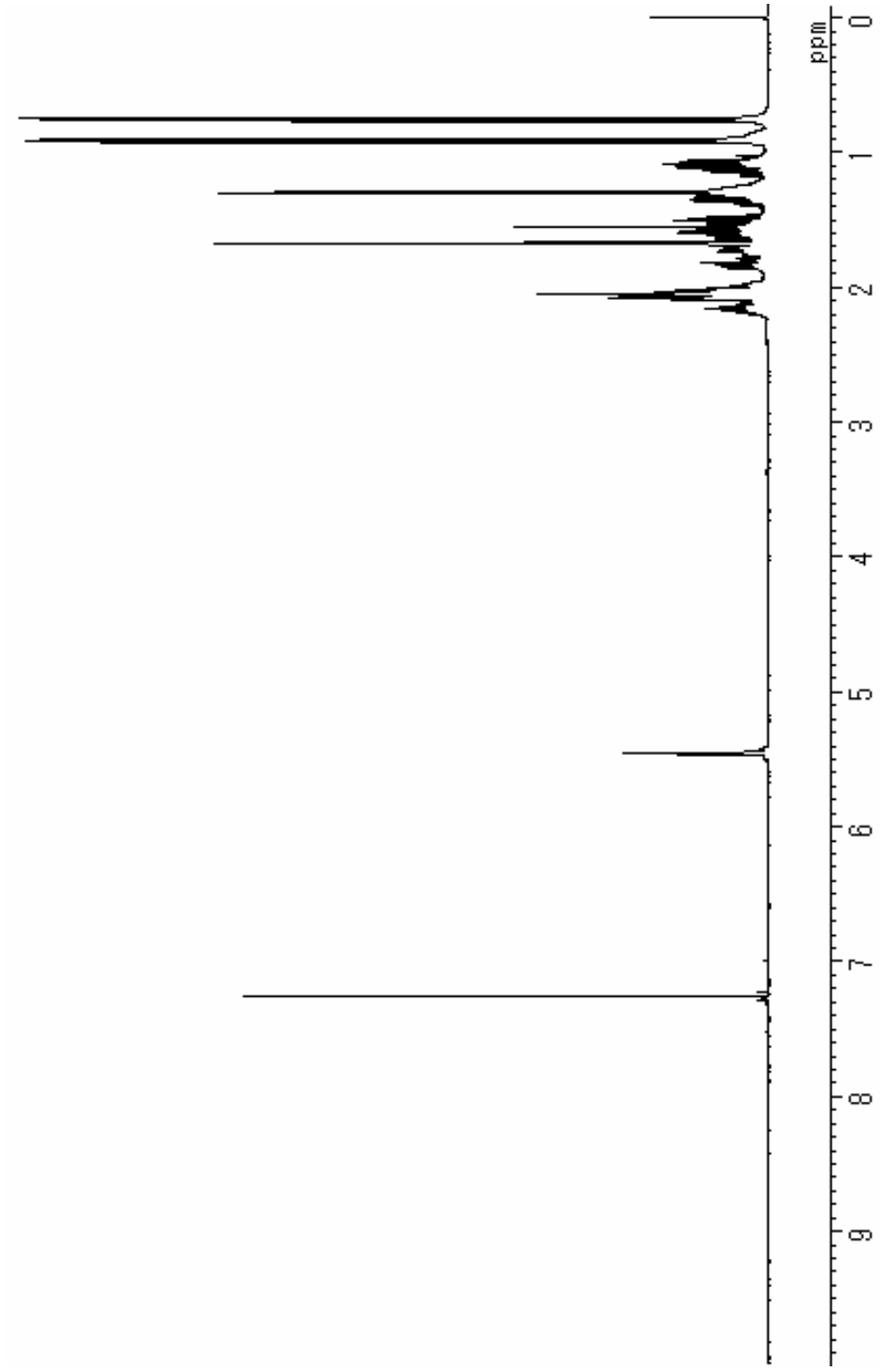
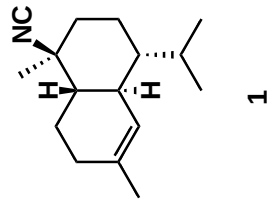
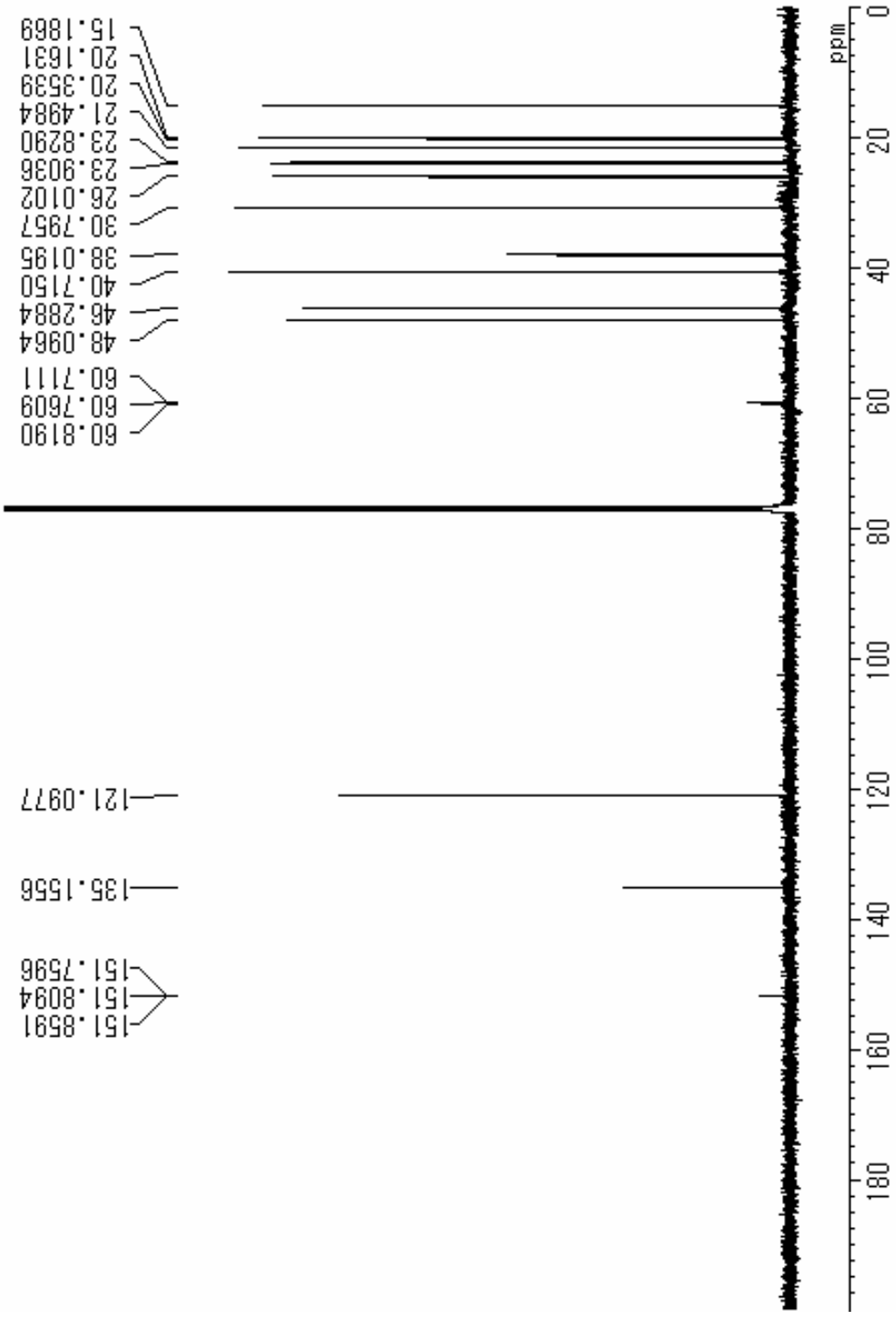



NC
H
H

1


ppm
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180
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23.9036
26.0102
30.7957
38.0195
40.7150
46.2884
48.0964
60.7111
60.7609
60.8190
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151.7596
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