REVISED

Approach toward the total synthesis of orevactaene. Part 2. Convergent and stereoselective synthesis of the C18–C31 domain of orevactaene. Evidence for the relative configuration of the side chain

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SUPPORTING INFORMATION

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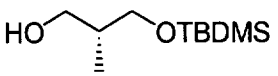
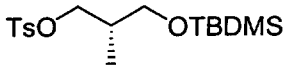
Experimental Section

(2*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methyl-1-propanol (11). To a cold (0 °C) solution of methyl (*S*)-(+)-3-hydroxy-2-methylpropionate (**9**) (5.38 g, 45.55 mmol) and imidazole (4.65 g, 68.30 mmol) in 80 mL of dry DMF was added *tert*-butyldimethylsilyl chloride (8.92 g, 59.20 mmol). The mixture was stirred at 0 °C for 6 h and then at rt for 16 h. The reaction mixture was diluted with 200 mL of Et_2O and washed with water (3 × 100 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 10.57 g (quant.) of **10** as a colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.03 (s, 6H), 0.89 (s, 9H), 1.15 (d, J = 7.0 Hz, 3H), 2.66 (m, 1H), 3.66 (dd, J = 6.3, 9.5 Hz, 1H), 3.69 (s, 3H), 3.79 (dd, J = 7.4, 9.5 Hz, 1H). The crude product was used in the next step without purification.

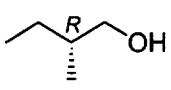


To a cold (–78 °C) solution of crude **10** (10.56 g, 45.55 mmol) in 140 mL of dry THF was added dropwise DIBAL-H (125 mL, 125 mmol, 1 M solution in toluene). Stirring was continued for 1 h at –78 °C and then for 2.5 h at rt. Upon cooling the reaction mixture back to –78 °C, 10 mL of anhydrous methanol was added and the mixture was kept 15 min at –78 °C and 45 min at rt followed by addition of aqueous saturated sodium potassium tartrate (250 mL) and Et_2O (250 mL). The mixture was stirred at rt until the two layers separated. The aqueous phase was extracted with Et_2O (4 × 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to give 9.13 g (98%, 2 steps) of alcohol **11** as a colorless oil: R_f 0.12 (15% EtOAc/hexanes); $[\alpha]_D$ +5.7 (*c* 1.09, $CHCl_3$) [lit.[1] $[\alpha]_D$ +5.9 (*c* 1.13, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.09 (s, 6H), 0.86 (d, J = 6.9 Hz, 3H), 0.92 (s, 9H), 1.96 (m, 1H), 3.10 (br s, 1H), 3.55–3.69 (m, 3H), 3.76 (dd, J = 4.3, 9.8 Hz, 1H).

The ^{1}H NMR spectrum was in agreement with that reported in the literature.[1] The product was used in the following step without further purification.

(2*S*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpropyl 4-methylbenzenesulfonate (12).  To a cold (0 °C) solution of **11** (9.13 g, 44.67 mmol) in 150 mL of dry pyridine was added tosyl chloride (12.78 g, 67.00 mmol, 1.5 equiv). The mixture was stirred for 6 h at 0 °C, warmed to rt, and then further stirred for 16 h. Then the reaction was quenched with saturated aqueous ammonium chloride (500 mL) and the mixture was extracted with Et_2O (4 × 150 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 after which the ether was evaporated and the bulk of pyridine was removed by azeotropic distillation with benzene. The residue was dissolved in ether (500 mL), washed successively with water, $CuSO_4$ solution and brine. Following drying over anhydrous Na_2SO_4, the solution was concentrated *in vacuo* to give 14.74 g (92%) of **12** as a colorless oil: R_f 0.45 (15% EtOAc/hexanes); $[\alpha]_D$ +2.8 (*c* 1.03, $CHCl_3$) [lit.[1] $[\alpha]_D$ +2.6 (*c* 0.99, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.00 (s, 6H), 0.84 (s, 9H), 0.92 (d, J = 6.9 Hz, 3H), 1.98 (m, 1H), 2.47 (s, 3H), 3.43 (dd, J = 6.7, 9.9 Hz, 1H), 3.52 (dd, J = 5.0, 9.9 Hz, 1H), 3.95 (dd, J = 5.9, 9.0 Hz, 1H), 4.04 (dd, J = 6.1, 9.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 2H), 7.80 (d, J = 8.0 Hz, 2H).

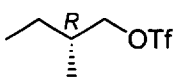
The ^{1}H NMR spectrum was in agreement with that reported in the literature.[1] The product was used in the following step without further purification.

(2*R*)-2-Methyl-1-butanol (14).  Methyllithium (291.4 mL, 0.408 mol, 1.4 M solution in Et_2O) was added to a cooled (0 °C) suspension of dried copper(I) iodide (38.85 g, 0.204 mol) in dry diethyl ether (500 mL). This mixture was stirred for 45 min and then cooled to –78 °C. A solution of **12** (14.68 g, 40.77 mmol) in dry diethyl ether (200 mL) was then added. The reaction mixture was stirred at rt for 2 h and then poured at 0 °C into a mixture of saturated ammonium chloride and 29% aqueous ammonia solution (1500 mL, 4:1). The aqueous layer was extracted with diethyl ether (4 × 350 mL). The combined organic layers were washed with brine, dried (anhydrous

$MgSO_4$) and concentrated *in vacuo*. The crude **13** was used directly in the following step without further purification: R_f 0.73 (pentane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.06 (s, 6H), 0.87–0.92 (m, 6H), 0.92 (s, 9H), 1.09 (m, 1H), 1.41–1.55 (m, 2H), 3.39 (dd, J = 6.2, 9.8 Hz, 1H), 3.47 (dd, J = 5.9, 9.8 Hz, 1H). To a solution of crude **13** in dry THF (50 mL) was added TBAF (50 mL, 50 mmol, 1 M solution in THF). The mixture was stirred for 16 h at rt, poured into saturated ammonium chloride solution and extracted with pentane (4 × 200 mL). The pentane solution was washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was chromatographed (silica gel, 10:1 pentane/ether) to afford 2.92 g (81%, 2 steps) of **14** as a colorless liquid: R_f 0.39 (1:3 EtOAc/hexanes); $[\alpha]_D$ +5.8 (*c* 1.09, $CHCl_3$) [lit.[2] $[\alpha]_D$ +5.89 (*c* 1.08, $CHCl_3$); commercially available (2*S*)-2-methyl-1-butanol (**16**): $[\alpha]_D$ –5.8 (neat)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (m, 6H), 1.17 (m, 1H), 1.48 (m, 1H), 1.56 (m, 1H), 3.45 (dd, J = 6.3, 10.1 Hz, 1H), 3.54 (dd, J = 5.8, 10.1 Hz, 1H).

^{1}H NMR spectrum of the synthetic sample was identical with the commercial sample of (2*S*)-2-methyl-1-butanol (**16**).

(2*R*)-2-Methylbutyl trifluoromethanesulfonate (15). To a cooled (–78 °C) solution of

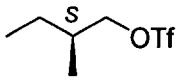


14 (3 mL, 2.43 g, 27.6 mmol) in CH_2Cl_2 (100 mL) was added freshly distilled dry pyridine (2.7 mL, 2.61 g, 33.0 mmol). After the solution was stirred an additional 30 min, triflic anhydride (4.74 mL, 7.95 g, 28.2 mmol) was added dropwise over a 30 min period, after which the reaction mixture was kept at –78 °C for an additional 2 h. The reaction was then quenched with brine (350 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were dried (anhydrous Na_2SO_4), concentrated *in vacuo*, and chromatographed (florisil, 10% EtOAc/hexanes) followed by vacuum distillation (60–65 °C, 0.5 Torr)[3] to give 4.31 g (71%) of **15** as a colorless liquid: $[\alpha]_D$ +0.8 (*c* 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400

MHz) δ 0.97 (t, J = 7.5 Hz, 3H), 1.04 (d, J = 6.8 Hz, 3H), 1.31 (m, 1H), 1.51 (m, 1H), 1.91 (m, 1H), 4.37 (dd, J = 6.5, 9.5 Hz, 1H), 4.42 (dd, J = 5.6, 9.5 Hz, 1H).

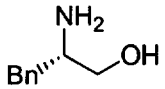
Spectral data were in agreement with that reported in the literature.[4]

(2*S*)-2-Methylbutyl trifluoromethanesulfonate (17). Using the same reaction



conditions described above for the preparation of **15**, 1.45 g (16.46 mmol) of **16**, pyridine (1.55 mL, 1.52 g, 19.16 mmol), and triflic anhydride (2.82 mL, 4.74 g, 16.78 mmol) provided 2.57 g (colorless liquid, 71%) of **17** following chromatography (florisil, 10% EtOAc/hexanes) and vacuum distillation: $[\alpha]_D$ – 0.7 (*c* 0.84, $CHCl_3$); ^1H NMR spectrum of the (2*S*)-2-methylbutyl trifluoromethanesulfonate (**17**) was identical with the sample of (2*R*)-2-methylbutyl trifluoromethanesulfonate (**15**).

(*S*)-Phenylalaninol (19). To a cold (0 °C) solution of lithium borohydride (1.32 g, 60.54



mmol) in 30 mL of THF was added trimethylsilyl chloride (15.40 mL, 121.1 mmol). The ice/water bath was removed and the mixture was stirred at rt for 15 min. The mixture was cooled to 0 °C and (*S*)-phenylalanine (**18**) (5.00 g, 30.27 mmol) was added. The ice/water bath was removed and the reaction mixture was stirred for 16 h. The mixture was cooled again to 0 °C and methanol (45 mL) was added dropwise followed by 25 mL of a 2.5 M sodium hydroxide solution. The organic solvents were evaporated *in vacuo*, and the residue was extracted with chloroform (5 × 50 mL). The combined extracts were dried (anhydrous Na_2SO_4), filtered, and evaporated *in vacuo* to leave 4.55 g (99%) of **19** as a white crystalline solid: mp 87–89 °C [lit. [5] mp 88.5–91 °C]; $[\alpha]_D$ –22.8 (*c* 1.02, EtOH) [lit.[5] $[\alpha]_D$ –24.7 (*c* 1.03, EtOH)]. The product was used in the following step without further purification.

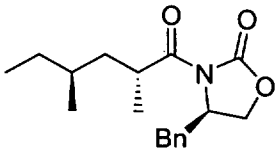
(4*S*)-4-Benzyl-2-oxazolidinone (20). A mixture of **19** (4.55 g, 30.09 mmol), dry potassium carbonate (0.42 g, 3.84 mmol) and diethyl carbonate (10 mL, 9.75 g, 82.54 mmol) was carefully heated to 130–135 °C, and ethanol was allowed to distil as it was formed. After ca. 5–6 h, the light brown slurry was cooled to rt, diluted with dichloromethane (400 mL), and filtered through a Celite pad to remove potassium carbonate. The organic layer was washed with aqueous sodium hydrogen carbonate (2 × 100 mL; 10% w/v), dried over anhydrous Na_2SO_4 and the solvent was removed *in vacuo* to afford a pale yellow crystalline solid which was chromatographed (silica gel, 4:1 EtOAc/hexanes) to provide 4.00 g (75%) of **20** as colorless needles: mp 85–88 °C [lit.[5] mp 84.5–86.5 °C]; $[\alpha]_D$ +4.9 (*c* 1.1, EtOH) [lit.[5] $[\alpha]_D$ +4.9 (*c* 1.10, EtOH)]. The ^{1}H NMR spectrum was in agreement with that reported in the literature.[5]

(4*S*)-4-Benzyl-3-propionyl-2-oxazolidinone (21). To a cold (–78 °C) solution of **20** (2.19 g, 12.4 mmol) in 40 mL of THF was added *n*-BuLi (10 mL, 13.0 mmol, 1.3 M solution in hexanes) dropwise over a 10 min period. The mixture was stirred at –78 °C for 10 min and propionyl chloride (1.18 mL, 1.26 g, 13.6 mmol) was added. The reaction mixture was kept at –78 °C for 1 h and then it was slowly warmed to rt over 30 min. The reaction mixture was quenched with a solution of saturated ammonium chloride (8 mL). The bulk of the THF was removed on a rotary evaporator and the resulting slurry was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were washed with 1 M NaOH (20 mL), brine (20 mL), dried over anhydrous Na_2SO_4, and evaporated. The residue was chromatographed (silica gel, 1:2 EtOAc/hexanes) to afford 2.095 g (73%) of **21** as a colorless crystalline solid: mp 42–46 °C [lit.[6] mp 44–46 °C]; $[\alpha]_D$ +93.7 (*c* 1.04, EtOH) [lit.[6] $[\alpha]_D$ +92.9 (*c* 1.01, EtOH); commercially available (4*S*)-4-benzyl-3-propionyl-2-oxazolidinone: $[\alpha]_D$ +97 (*c* 1.00, EtOH)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.23 (t, J = 7.1 Hz, 3H), 2.80 (dd, J = 9.7, 13.1

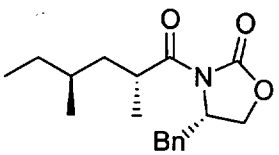
Hz, 1H), 2.98 (m, 2H), 3.32 (dd, J = 2.9, 13.1 Hz, 1H), 4.20 (m, 2H), 4.69 (m, 1H), 7.15–7.37 (m, 5H).

^{1}H NMR spectrum of the synthetic sample was in agreement with that of the commercial sample and with that reported in the literature.[6]

(4*R*)-4-Benzyl-3-[(2*R*,4*S*)-2,4-dimethylhexanoyl]-1,3-oxazolidin-2-one was isolated, while purifying oxazolidinone **27**, as a yellow oil: 90 mg (3.5%); less polar compound on TLC: R_f 0.61 (1:1 EtOAc/hexanes); $[\alpha]_D$ –48.9 (*c* 2.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.90 (t, J = 7.6 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H), 1.14–1.23 (m, 1H), 1.22 (d, J = 6.7 Hz, 3H), 1.28–1.48 (m, 3H), 1.53–1.62 (m, 1H), 2.79 (dd, J = 9.8, 13.2 Hz, 1H), 3.30 (dd, J = 2.1, 13.2 Hz, 1H), 3.85 (qdd, J = 6.7, 6.7, 6.7 Hz, 1H), 4.17–4.24 (m, 2H), 4.69 (m, 1H), 7.23–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.3 (–), 17.2 (–), 18.8 (–), 29.8 (+), 32.1 (–), 35.4 (–), 37.9 (+), 40.1 (+), 55.4 (–), 66.0 (+), 127.3 (–), 128.9 (–), 129.4 (–), 135.4 (+), 153.1 (+), 177.7 (+).

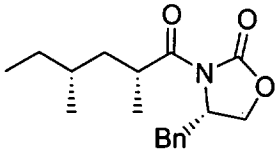


(4*S*)-4-Benzyl-3-[(2*R*,4*S*)-2,4-dimethylhexanoyl]-1,3-oxazolidin-2-one (22). Following the general procedure described above for the preparation of **27**, 726 mg (3.16 mmol) of **21**, trifluoromethanesulfonate **17** (579 mg, 2.63 mmol) and lithium diisopropylamide (1.8 mL, 3.6 mmol, 2 M solution in heptane/THF/ethyl benzene) provided 567 mg of **22** (71%) following flash chromatography (silica gel, 1:5 EtOAc/hexanes) as a yellow oil: R_f 0.35 (1:5 EtOAc/hexanes); $[\alpha]_D$ +42.3 (*c* 2.21, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.92 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 5.8 Hz, 3H), 1.18 (d, J = 6.7 Hz, 3H), 1.22 (m, 1H), 1.35–1.53 (m, 3H), 1.63 (m, 1H), 2.76 (dd, J = 9.8, 13.3 Hz, 1H), 3.31 (dd, J = 2.7, 13.3 Hz, 1H), 3.88 (qdd, J = 6.8, 6.8, 6.8 Hz, 1H), 4.15–4.23 (m, 2H), 4.71 (m, 1H), 7.23–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz,



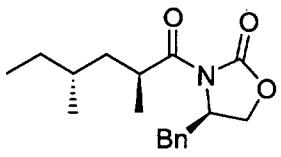
APT pulse sequence: evens up (+), odds down (–)) δ11.4 (–), 16.8 (–), 18.7 (–), 29.9 (+), 32.2 (–), 35.4 (–), 38.1 (+), 40.5 (+), 55.4 (–), 66.0 (+), 127.3 (–), 128.9 (–), 129.4 (–), 135.4 (+), 153.0 (+), 177.9 (+).

(4*S*)-4-Benzyl-3-[(2*R*,4*R*)-2,4-dimethylhexanoyl]-1,3-oxazolidin-2-one (23).



Following the general procedure described above for the preparation of **27**, 1.42 g (6.10 mmol) of **21**, trifluoromethanesulfonate **15** (1.12 g, 5.09 mmol) and lithium diisopropylamide (3.4 mL, 6.8 mmol, 2 M solution in heptane/THF/ethyl benzene) provided 1.05 g of **23** (68%) following flash chromatography (silica gel, 1:5 EtOAc/hexanes) as a yellow oil: R_f 0.58 (1:1 EtOAc/hexanes); $[\alpha]_D$ +28.1 (*c* 2.19, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.91 (t, J = 7.6 Hz, 3H), 0.93 (d, J = 6.1 Hz, 3H), 1.19 (d, J = 6.8 Hz, 3H), 1.13–1.25 (m, 2H), 1.34–1.48 (m, 2H), 1.89 (m, 1H), 2.76 (dd, J = 9.8, 13.3 Hz, 1H), 3.31 (dd, J = 2.7, 13.3 Hz, 1H), 3.96 (qdd, J = 6.7, 6.7, 6.7 Hz, 1H), 4.15–4.23 (m, 2H), 4.71 (m, 1H), 7.23–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.3 (–), 18.0 (–), 19.5 (–), 29.3 (+), 32.4 (–), 35.3 (–), 38.1 (+), 41.1 (+), 55.4 (–), 66.0 (+), 127.4 (–), 129.0 (–), 129.5 (–), 135.4 (+), 153.1 (+), 177.7 (+).

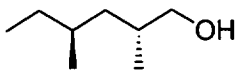
(4*R*)-4-Benzyl-3-[(2*S*,4*R*)-2,4-dimethylhexanoyl]-1,3-oxazolidin-2-one (28).



Following the general procedure described above for the preparation of **27**, 754 mg (3.23 mmol) of **26**, trifluoromethanesulfonate **15** (592 mg, 2.69 mmol) and lithium diisopropylamide (1.85 mL, 3.7 mmol, 2 M solution in heptane/THF/ethyl benzene) provided 579 mg of **28** (71%) following flash chromatography (silica gel, 1:5 EtOAc/hexanes) as a yellow oil: R_f 0.35 (1:5 EtOAc/hexanes); $[\alpha]_D$ –41.7 (*c* 2.23, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.92 (t, J = 7.1 Hz, 3H), 0.94 (d, J = 5.8 Hz, 3H),

1.18 (d, J = 6.7 Hz, 3H), 1.22 (m, 1H), 1.35–1.52 (m, 3H), 1.63 (m, 1H), 2.76 (dd, J = 9.8, 13.3 Hz, 1H), 3.31 (dd, J = 2.7, 13.3 Hz, 1H), 3.88 (qdd, J = 6.8, 6.8, 6.8 Hz, 1H), 4.15–4.23 (m, 2H), 4.71 (m, 1H), 7.23–7.37 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.3 (–), 16.7 (–), 18.6 (–), 29.9 (+), 32.1 (–), 35.3 (–), 38.0 (+), 40.5 (+), 55.3 (–), 65.9 (+), 127.3 (–), 128.9 (–), 129.4 (–), 135.4 (+), 153.0 (+), 177.8 (+).

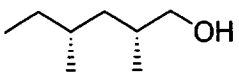
(2*R*,4*S*)-2,4-Dimethyl-1-hexanol (24). Following the general procedure described above



for the preparation of **29**, imide **22** (566 mg, 1.87 mmol), lithium borohydride (47 mg, 2.15 mmol) and methanol (87 μL, 2.15 mmol) provided 218 mg (90%) of **24** following flash chromatography (silica gel, 2:3 Et_2O/pentane) as a colorless liquid: R_f 0.38 (30% EtOAc/hexanes); $[\alpha]_D$ +20.3 (c 0.79, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.86 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.07–1.26 (m, 3H), 1.32 (m, 1H), 1.44 (m, 1H), 1.73 (m, 1H), 3.43 (dd, J = 6.7, 10.4 Hz, 1H), 3.51 (dd, J = 5.7, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ 11.4 (–), 16.4 (–), 18.9 (–), 30.4 (+), 31.6 (–), 33.3 (–), 40.3 (+), 69.1 (+).

These data agree with those reported in the literature.[7]

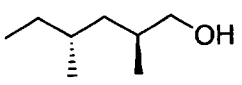
(2*R*,4*R*)-2,4-Dimethyl-1-hexanol (25). Following the general procedure described



above for the preparation of **29**, imide **23** (906 mg, 2.99 mmol), lithium borohydride (75 mg, 3.44 mmol) and methanol (140 μL, 3.44 mmol) provided 354 mg (91%) of **25** following flash chromatography (silica gel, 2:3 Et_2O/pentane) as a colorless liquid: R_f 0.38 (30% EtOAc/hexanes); $[\alpha]_D$ +3.7 (c 1.67, $CHCl_3$) [lit.[8] $[\alpha]_D$ +3.7 (c 1.67, $CHCl_3$)]; ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.87 (t, J = 7.3 Hz, 3H), 0.88 (d, J = 6.2 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H), 0.86–0.97 (m, 1H), 1.10 (m, 1H), 1.21–1.49 (m, 3H), 1.71 (m, 1H), 3.39 (dd, J = 6.8, 10.3 Hz, 1H), 3.53 (dd, J = 5.0,

10.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.1 (–), 17.3 (–), 19.8 (–), 29.0 (+), 31.6 (–), 33.2 (–), 40.6 (+), 68.4 (+). These data agree with those reported in the literature.[8]

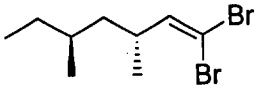
(2*S*,4*R*)-2,4-Dimethyl-1-hexanol (30). Following the general procedure described above



for the preparation of **29**, imide **28** (567 mg, 1.87 mmol), lithium borohydride (47 mg, 2.15 mmol) and methanol (87 μL, 2.15 mmol) provided 215 mg (89%) of **30** following flash chromatography (silica gel, 2:3 Et_2O/pentane) as a colorless liquid: R_f 0.38 (30% EtOAc/hexanes); $[\alpha]_D$ –20.1 (*c* 0.80, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.86 (d, J = 6.9 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.07–1.26 (m, 3H), 1.32 (m, 1H), 1.44 (m, 1H), 1.73 (m, 1H), 3.43 (dd, J = 6.7, 10.4 Hz, 1H), 3.51 (dd, J = 5.7, 10.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.4 (–), 16.4 (–), 18.9 (–), 30.4 (+), 31.6 (–), 33.3 (–), 40.3 (+), 69.1 (+).

These data agree with those reported in the literature for the antipode of **30**.[7]

(3*R*,5*S*)-1,1-Dibromo-3,5-dimethyl-1-heptene (32). The synthesis of dibromoalkene **32**

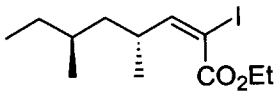


was carried out following the procedure outlined for the preparation of **31**. Thus, oxalyl chloride (0.18 mL, 262 mg, 2.06 mmol), dimethyl sulfoxide (0.26 mL, 286 mg, 3.66 mmol), alcohol **24** (186 mg, 1.43 mmol), triethylamine (0.97 mL, 704 mg, 6.96 mmol), Ph_3P (1.353 g, 5.16 mmol) and CBr_4 (866 mg, 2.61 mmol) provided 319 mg of **32** (79%, 2 steps) following flash chromatography (florisil, hexanes) as a colorless oil: R_f 0.66 (hexanes); $[\alpha]_D$ –3.0 (*c* 1.48, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.89 (t, J = 5.5 Hz, 3H), 0.89 (d, J = 5.6 Hz, 3H), 1.00 (d, J = 6.6 Hz, 3H), 1.10–1.45 (m, 5H), 2.56 (m, 1H), 6.19 (d, J = 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.1 (–), 19.1 (–), 19.3 (–), 29.2 (+), 31.9 (–), 36.1 (–), 43.2 (+), 86.8 (+), 144.8 (–).

Ethyl (4*R*,6*S*)-4,6-dimethyl-2-octynoate (34). The synthesis of alkyne **34** was carried out following the procedure outlined for the preparation of **33**. Thus, **32** (154 mg, 0.542 mmol), *n*-BuLi (1.02 mL, 1.623 mmol, 1.6 M solution in hexanes), and ethyl chloroformate (0.13 mL, 147 mg, 1.355 mmol) provided 95 mg of **34** (90%) following flash chromatography (silica gel, 1:9 Et_2O/hexanes) as a yellow oil: R_f 0.46 (1:9 Et_2O/hexanes); $[\alpha]_D$ +27.9 (*c* 1.78, CH_2Cl_2); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.0 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 1.14 (m, 1H), 1.21 (d, J = 6.8 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.36–1.48 (m, 3H), 1.55 (m, 1H), 2.63 (dq, J = 7.1, 7.1 Hz, 1H), 4.22 (q, J = 7.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ 10.9 (–), 14.0 (–), 19.1 (–), 19.9 (–), 23.5 (–), 29.7 (+), 32.0 (–), 42.9 (+), 61.6 (+), 73.0 (+), 93.6 (+), 154.0 (+).

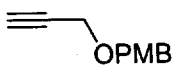
Ethyl (*E*,4*R*,6*S*)-4,6-dimethyl-2-(tributylstannyl)-2-octenoate (36). The synthesis of **36** was completed following the procedure outlined for the preparation of **35**. Thus, **34** (62 mg, 0.316 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol) and *n*-Bu_3SnH (0.09 mL, 97 mg, 0.334 mmol) provided 145 mg of **36** (94%) following flash chromatography (silica gel, 1:4 benzene/hexanes) as a colorless oil: R_f 0.34 (3:7 benzene/hexanes); $[\alpha]_D$ –25.2 (*c* 2.32, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 0.84–1.17 (m, 26H), 1.22–1.41 (m, 12H), 1.44–1.58 (m, 6H), 3.06 (m, 1H), 4.16 (q, J = 7.0 Hz, 2H), 5.75 (d, J = 9.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ 10.3 (+), 11.2 (–), 13.7 (–), 14.4 (–), 19.6 (–), 20.6 (–), 27.2 (+), 28.9 (+), 29.0 (+), 32.2 (–), 33.9 (–), 44.3 (+), 59.9 (+), 133.3 (+), 159.0 (–), 171.4 (+).

Ethyl (*E*,4*R*,6*S*)-2-iodo-4,6-dimethyl-2-octenoate (38). The synthesis of **38** was



completed following the procedure outlined for the preparation of **37**. Thus, **36** (112 mg, 0.230 mmol) and iodine (63 mg, 0.248 mmol) provided 68 mg of **38** (91%) following flash chromatography (silica gel, 3:7 benzene/hexanes) as a yellow oil: R_f 0.34 (3:7 benzene/hexanes); $[\alpha]_D$ –33.7 (*c* 1.00, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ0.86 (t, J = 6.3 Hz, 3H), 0.87 (d, J = 5.9 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H), 1.06–1.38 (m, 5H), 1.34 (t, J = 7.0 Hz, 3H), 3.15 (m, 1H), 4.27 (q, J = 7.0 Hz, 2H), 6.65 (d, J = 10.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.1 (–), 14.1 (–), 19.3 (–), 19.7 (–), 29.2 (+), 32.0 (–), 35.7 (–), 43.7 (+), 62.1 (+), 82.8 (+), 161.1 (–), 164.1 (+).

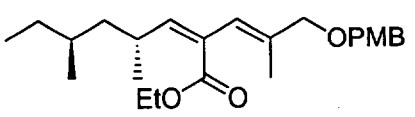
1-Methoxy-4-[(2-propynyloxy)methyl]benzene (40). To a solution of propargyl



alcohol (**39**) (1.8 mL, 1.73 g, 30.92 mmol) in dry THF (50 mL) at rt was added NaH (1.71 g, 42.75 mmol, 60% dispersion in mineral oil). After stirring for 30 min, NaI (6.41 g, 42.75 mmol, dried 24 h at 70 °C at 0.5 Torr) and 4-methoxybenzyl chloride (5.85 mL, 6.75 g, 43.14 mmol) were added. The reaction mixture was heated at reflux for 18 h, cooled to 0 °C and quenched with 80 mL of water. The layers were separated and the aqueous layer was extracted with Et_2O (4 × 75 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and evaporated *in vacuo*. The residue was purified by flash chromatography (silica gel, 1:9 Et_2O/hexanes) to give **40** (4.61 g, 85%) as a yellow oil: R_f 0.29 (1:9 Et_2O/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz) δ2.51 (s, 1H), 3.82 (s, 3H), 4.17 (s, 2H), 4.57 (s, 2H), 6.92 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.3 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ55.3 (–), 56.7 (+), 71.2 (+), 74.6 (+), 79.9 (+), 113.9 (–), 129.4 (+), 129.8 (–), 159.5 (+).

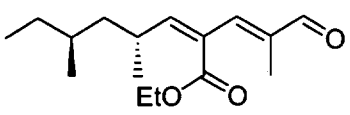
The data were in agreement with those reported in the literature.[9]

Ethyl (*Z*,4*R*,6*S*)-2-{(*E*)-3-[(4-methoxybenzyl)oxy]-2-methyl-1-propenyl}-4,6-dimethyl-2-octenoate (48). The synthesis of **48** was carried out following the procedure



outlined for the preparation of **47**. Thus, **43** (64.8 mg, 0.20 mmol), *n*-BuLi (0.19 mL, 0.30 mmol, 1.6 M solution in hexanes), $(i\text{-PrO})_3B$ (73 μL, 59.5 mg, 0.32 mmol), NaOH (58 mg, 1.45 mmol, solution in 0.25 mL of degassed water), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol) and **38** (47 mg, 0.15 mmol) provided 41 mg of **48** (73%) following flash chromatography (silica gel, 1:5 Et_2O/hexanes) as a colorless oil: R_f 0.28 (1:5 Et_2O/hexanes); $[\alpha]_D$ –17.3 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ0.87 (t, J = 6.5 Hz, 3H), 0.88 (d, J = 6.3 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H), 1.14 (m, 2H), 1.26–1.42 (m, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.74 (s, 3H), 3.05 (m, 1H), 3.83 (s, 3H), 3.96 (s, 2H), 4.25 (q, J = 7.1 Hz, 2H), 4.44 (s, 2H), 5.67 (d, J = 10.2 Hz, 1H), 6.10 (s, 1H), 6.90 (d, J = 8.5 Hz, 2H), 7.29 (d, J = 8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ11.1 (–), 14.3 (–), 15.1 (–), 19.4 (–), 20.5 (–), 29.2 (+), 31.5 (–), 32.1 (–), 44.4 (+), 55.3 (–), 60.4 (+), 71.4 (+), 75.8 (+), 113.8 (–), 124.9 (–), 128.3 (+), 129.4 (–), 130.6 (+), 134.8 (+), 149.1 (–), 159.21 (+), 168.1 (+).

Ethyl (*Z*,4*R*,6*S*)-4,6-dimethyl-2-[(*E*)-2-methyl-3-oxo-1-propenyl]-2-octenoate (50).



The synthesis of **50** was carried out following the procedure outlined for the preparation of **49**. Thus, **48** (18 mg, 46.3 μmol) and DDQ (32 mg, 141 μmol) provided 11 mg of **50** (89%) following flash chromatography (silica gel, 1:5 Et_2O/hexanes) as a yellow oil: R_f 0.30 (1:5 Et_2O/hexanes); $[\alpha]_D$ –44.4 (*c* 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ0.88 (t, J = 7.1 Hz, 3H), 0.89 (d, J = 6.3 Hz, 3H), 1.07 (d, J = 6.5 Hz, 3H), 1.11–1.41 (m, 5H), 1.37 (t, J = 7.0 Hz, 3H), 1.82 (s, 3H), 3.07 (m, 1H), 4.31 (q, J = 7.0 Hz, 2H), 6.06 (d, J = 10.3 Hz, 1H), 6.90 (s, 1H), 9.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, APT pulse sequence: evens up (+), odds down (–)) δ10.2 (–), 11.1 (–), 14.2 (–), 19.4 (–), 20.2 (–),

29.2 (+), 32.16 (–), 32.23 (–), 44.1 (+), 61.1 (+), 128.6 (+), 137.7 (+), 147.0 (–), 154.5 (–), 166.9 (+), 195.1 (–).

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[3] Note: heating the oil bath over 65 °C results in spontaneous elimination of TfOH.
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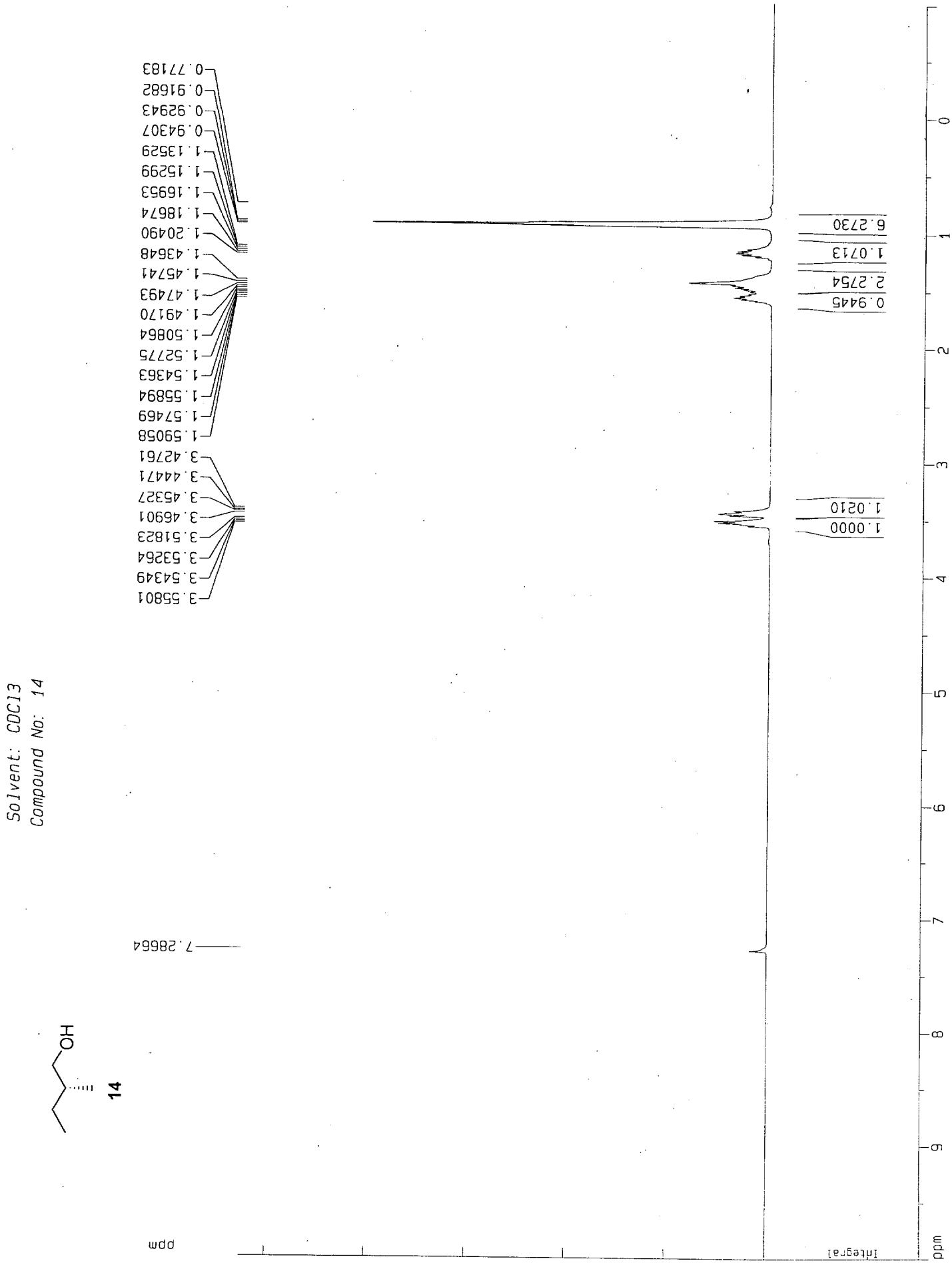

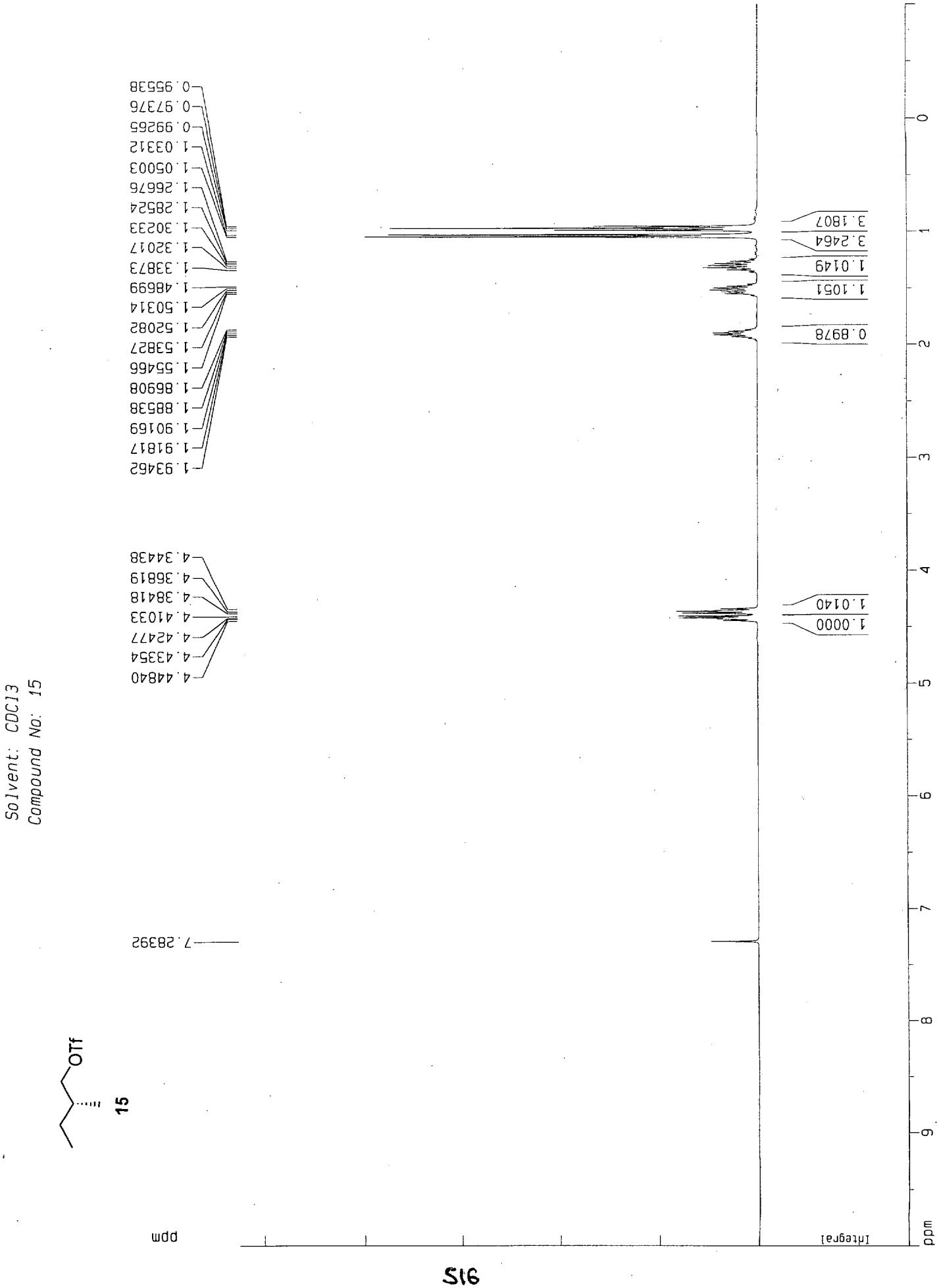

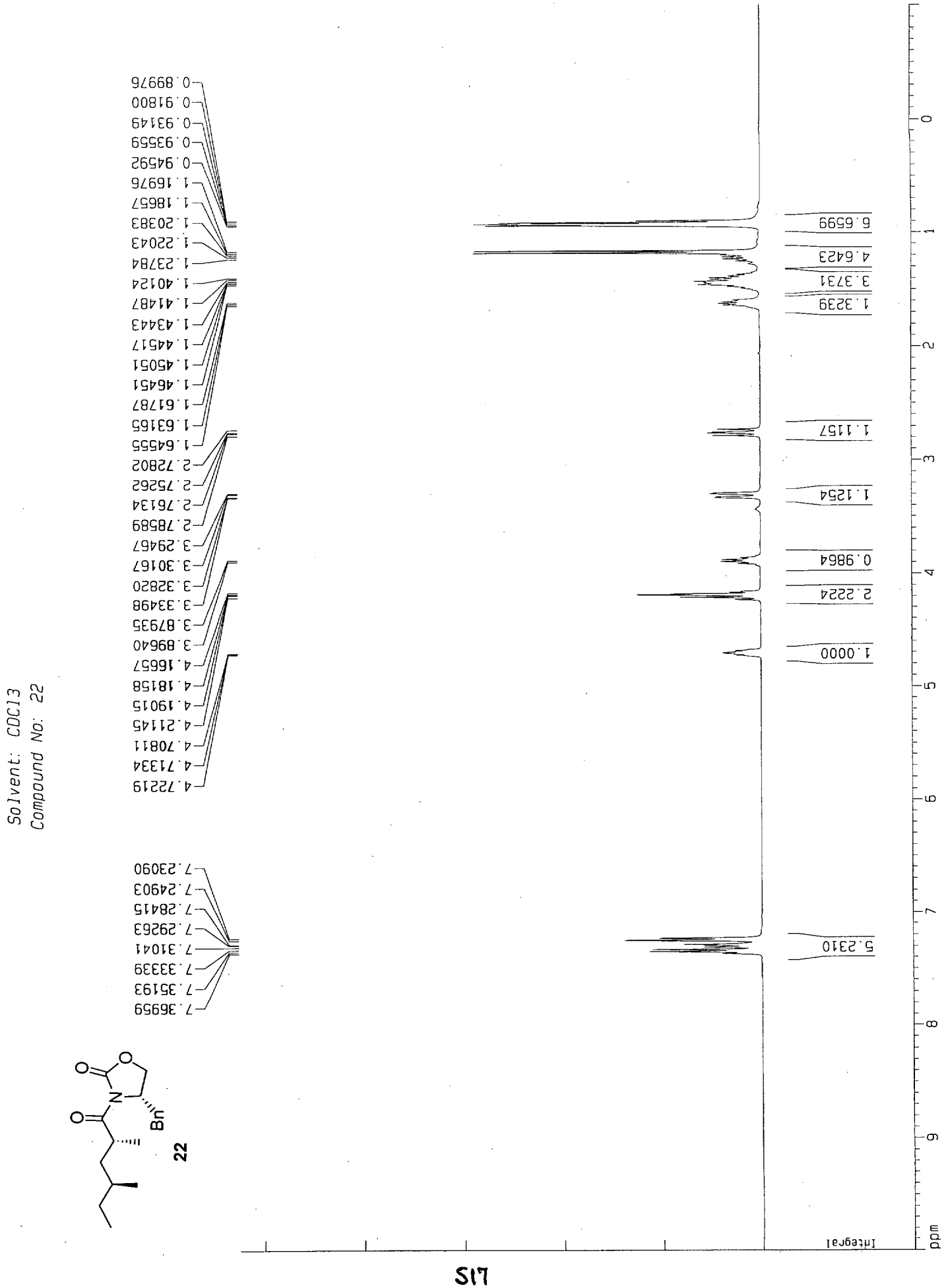

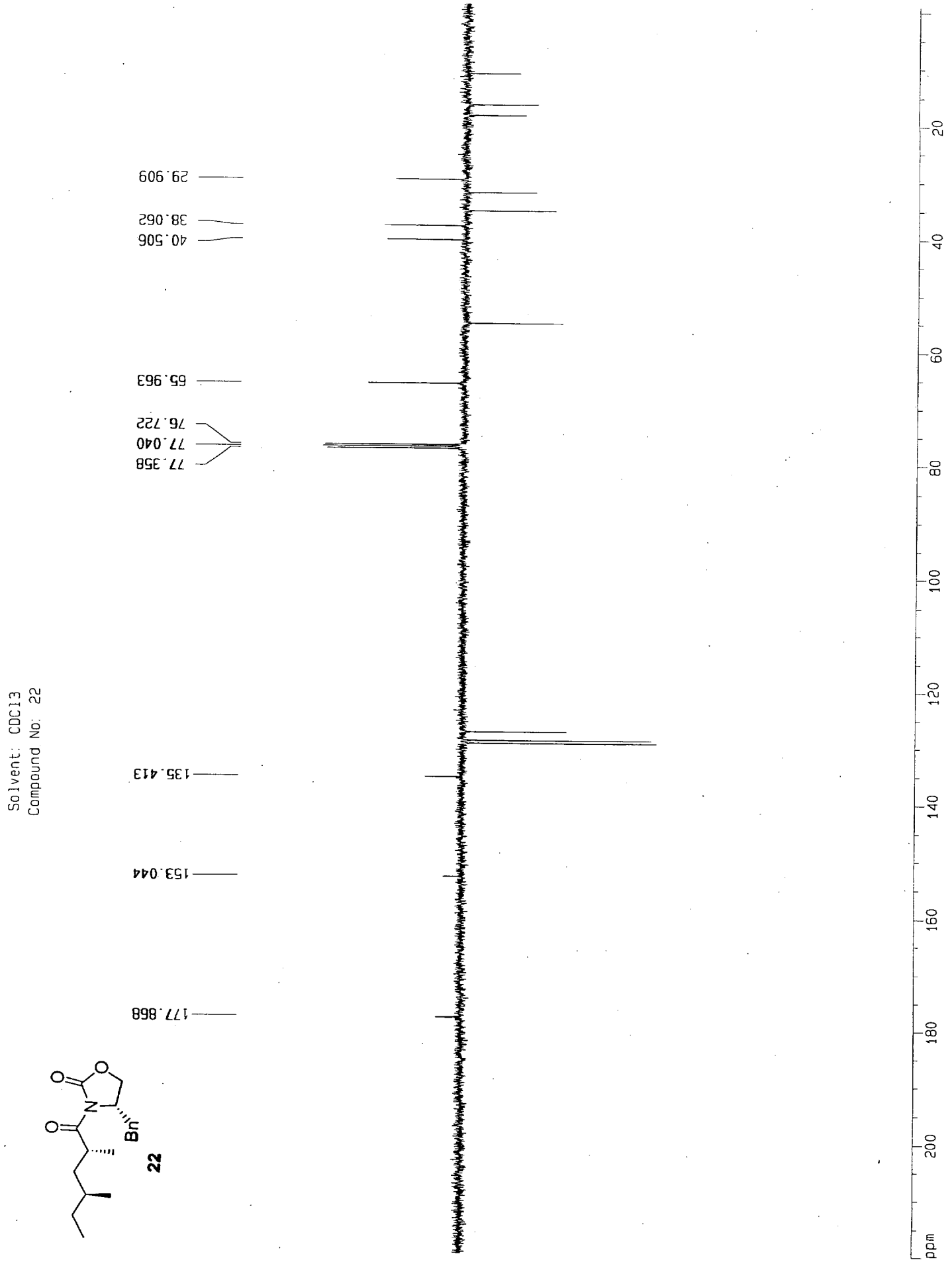

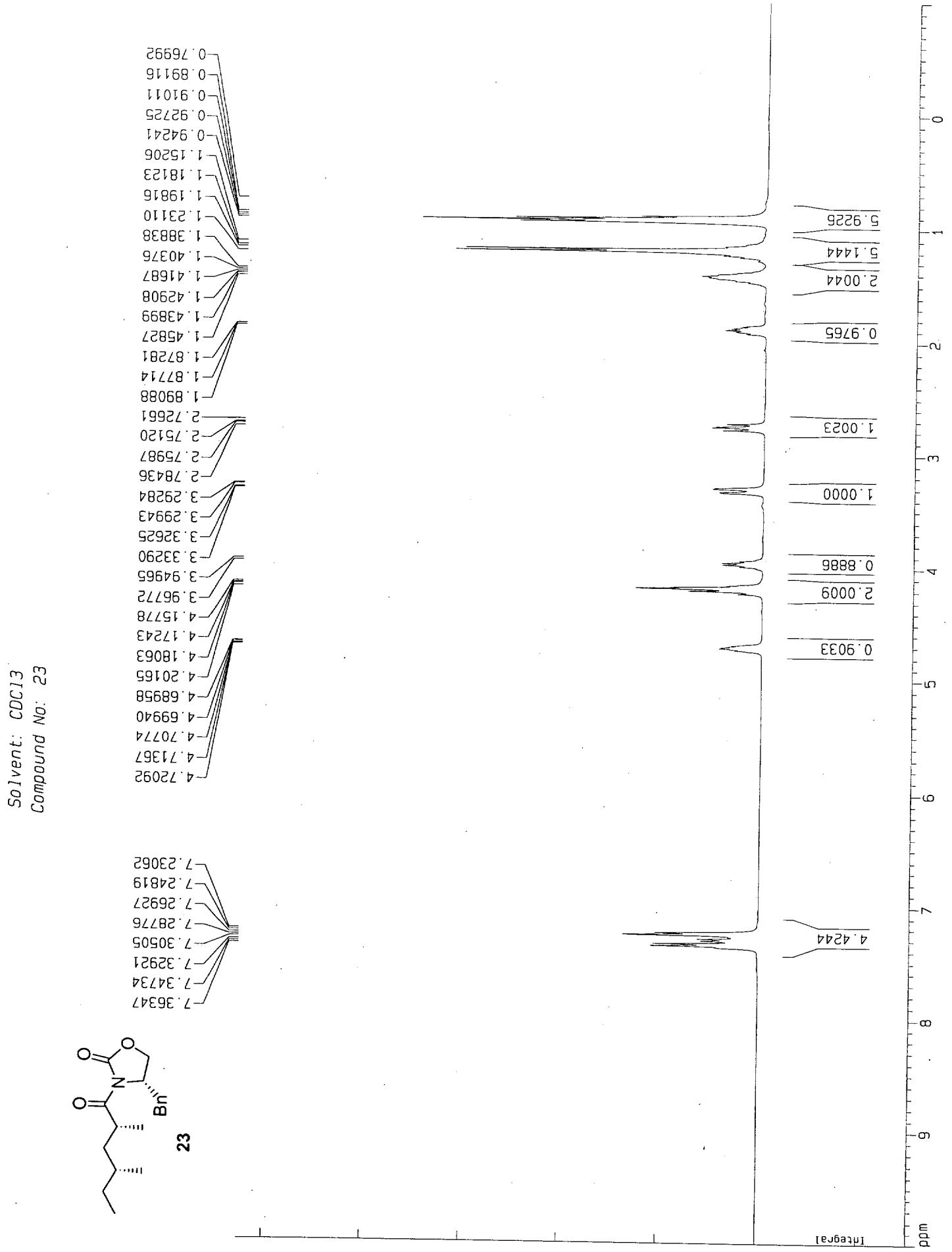

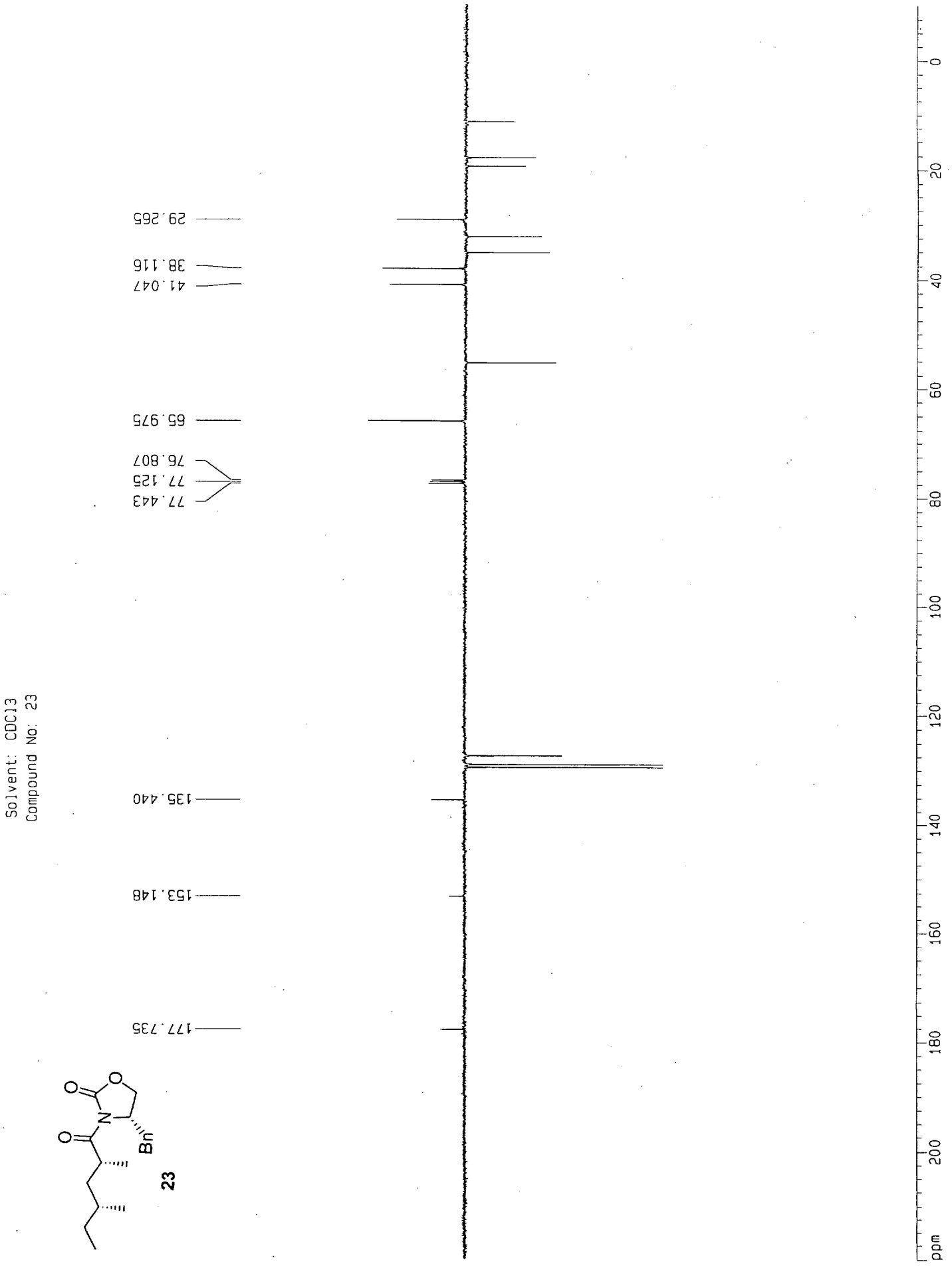

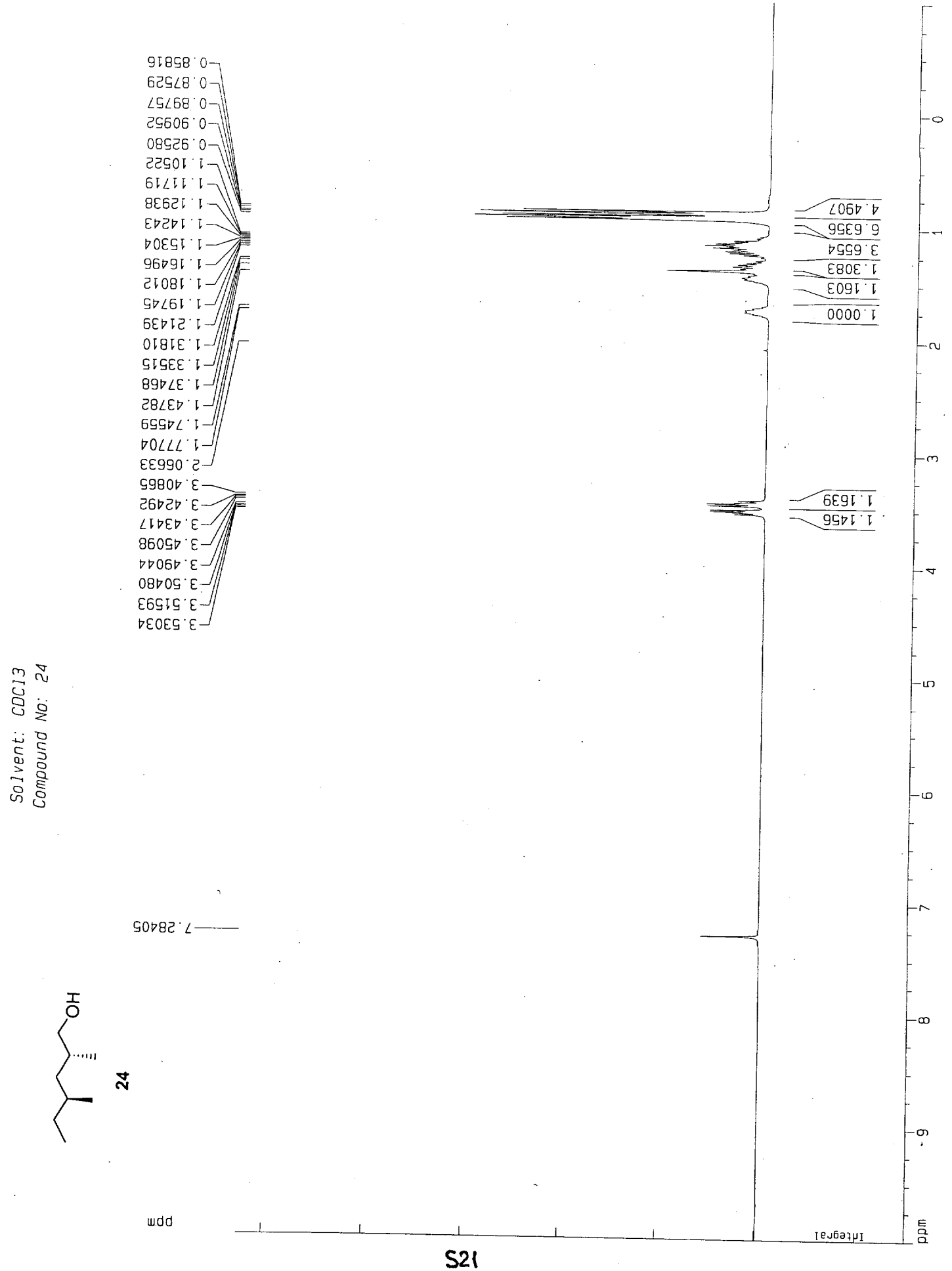

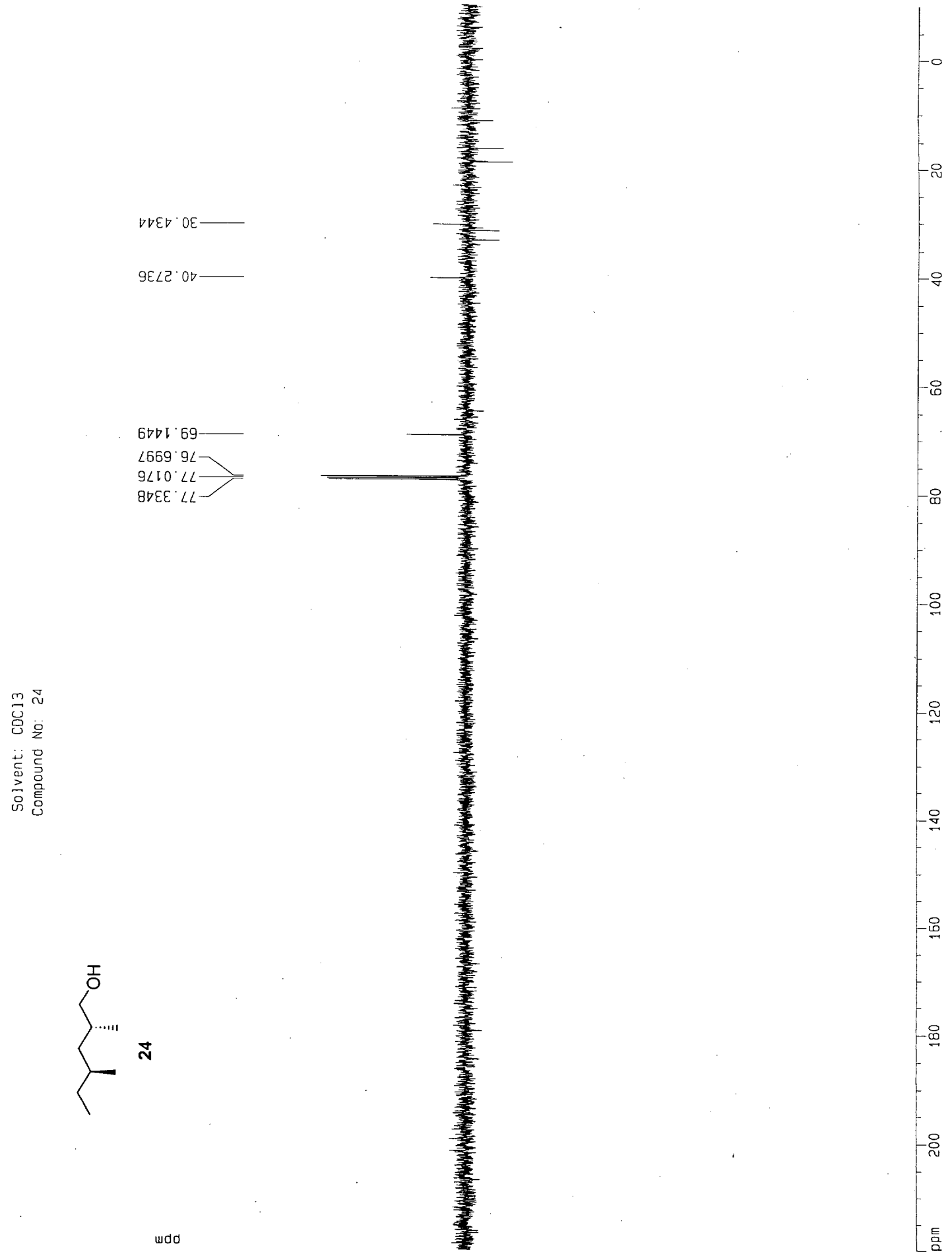

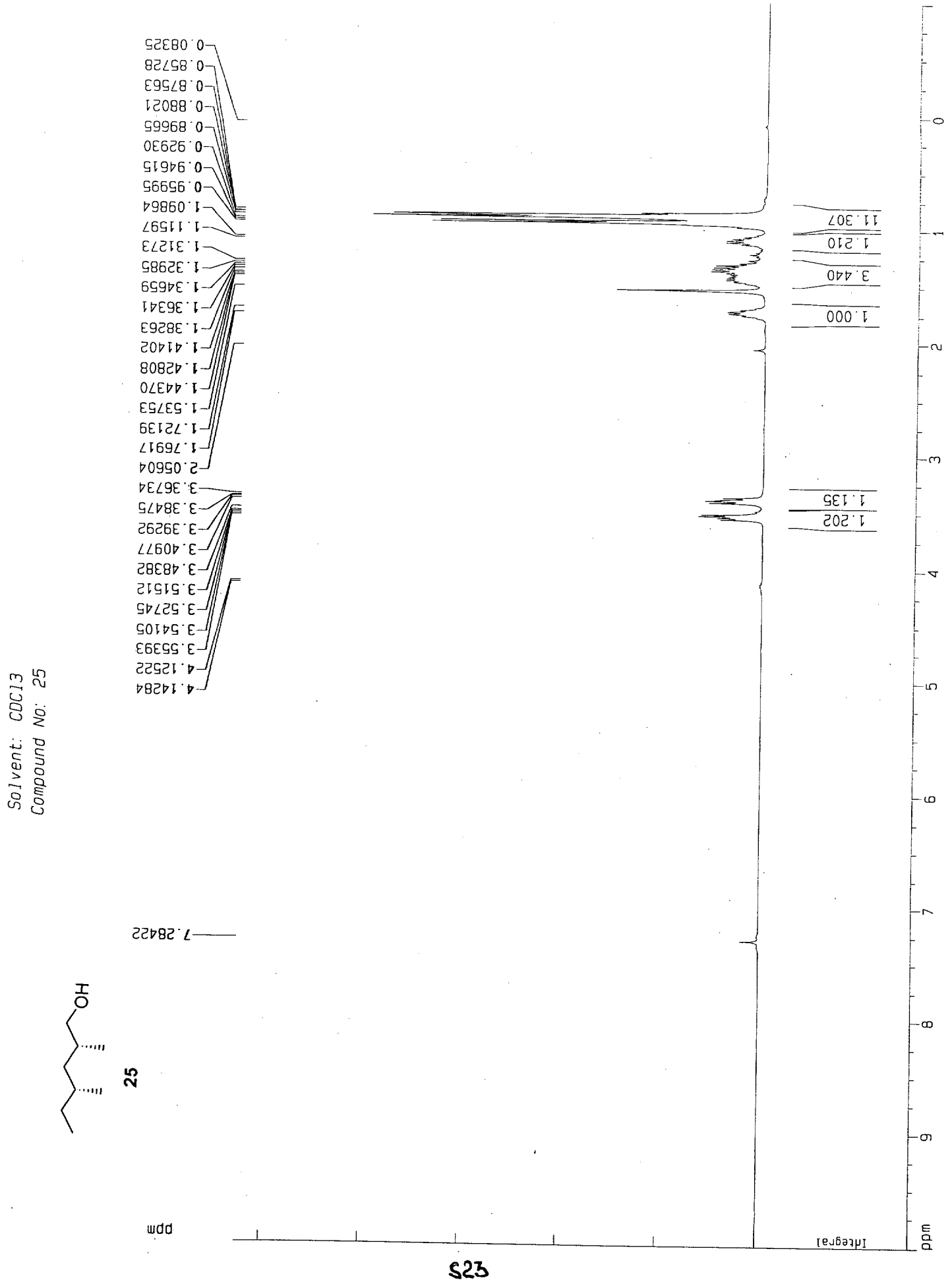

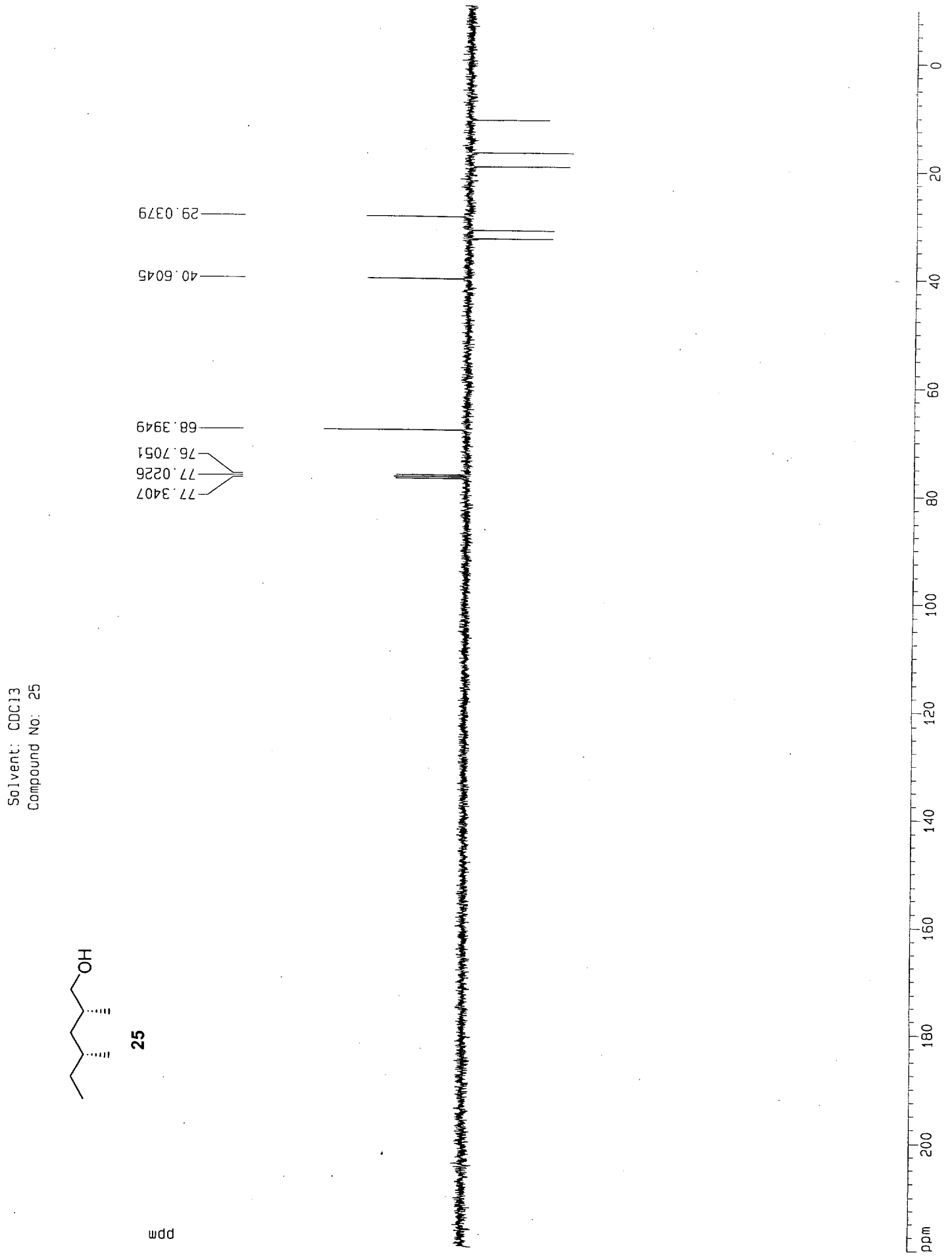

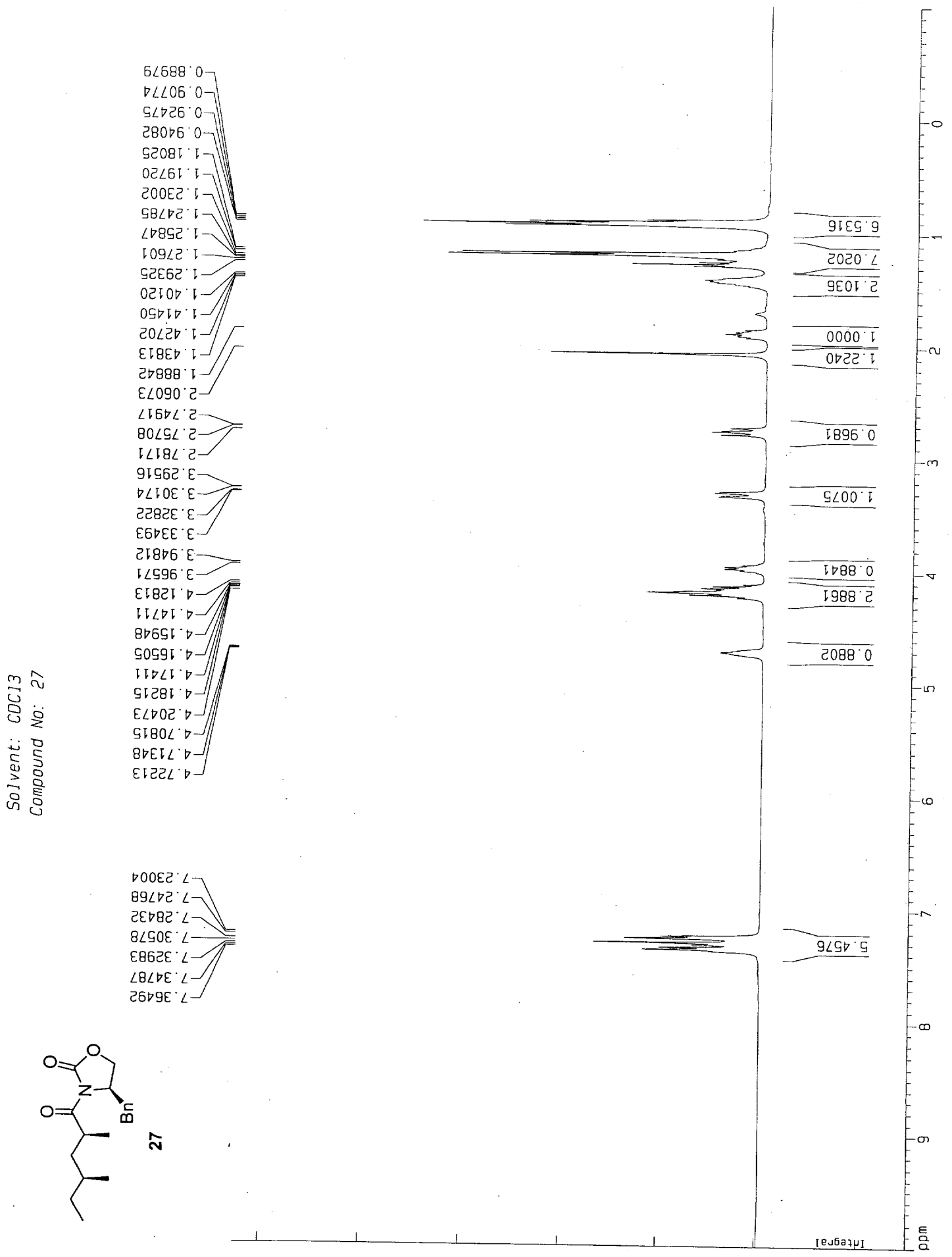

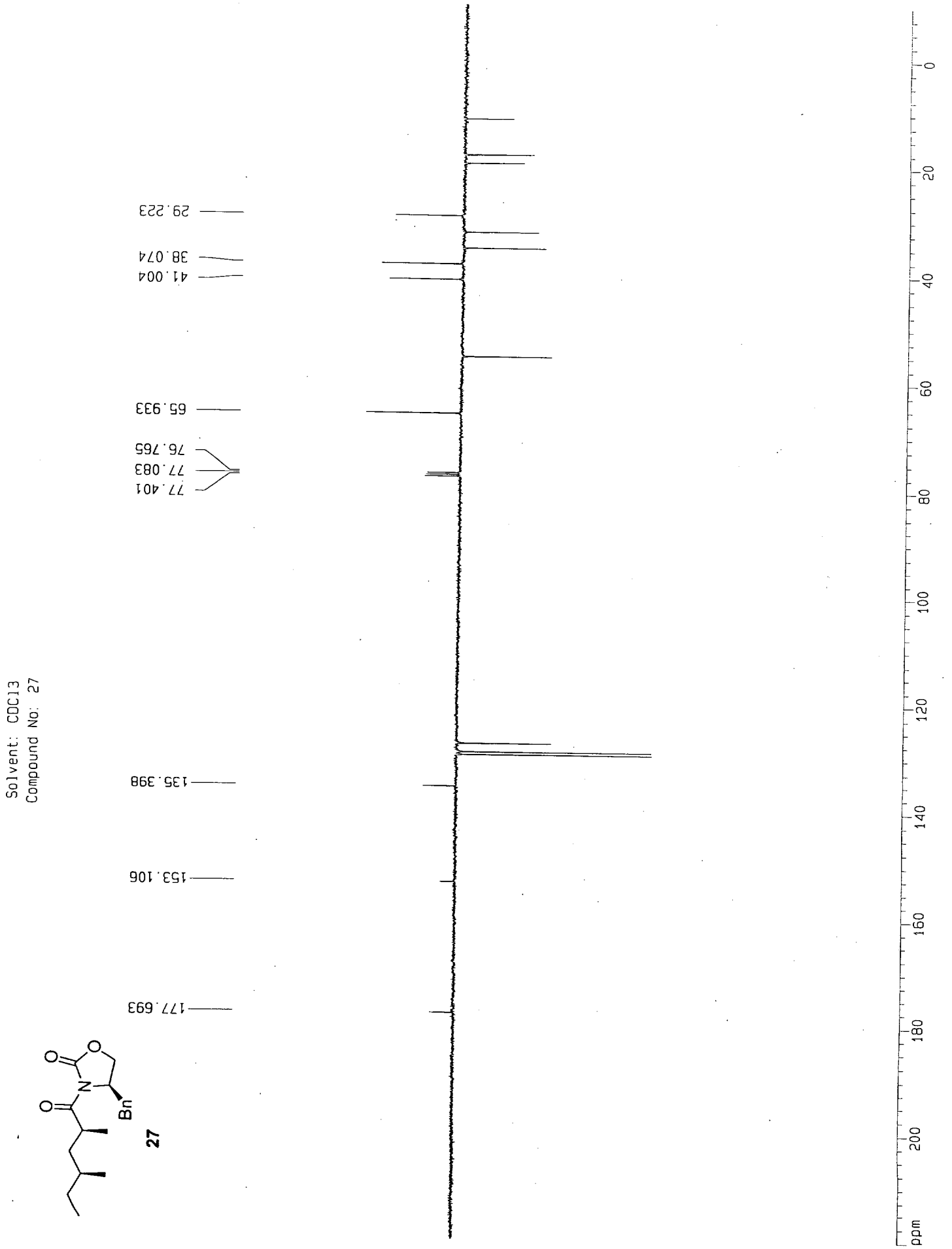

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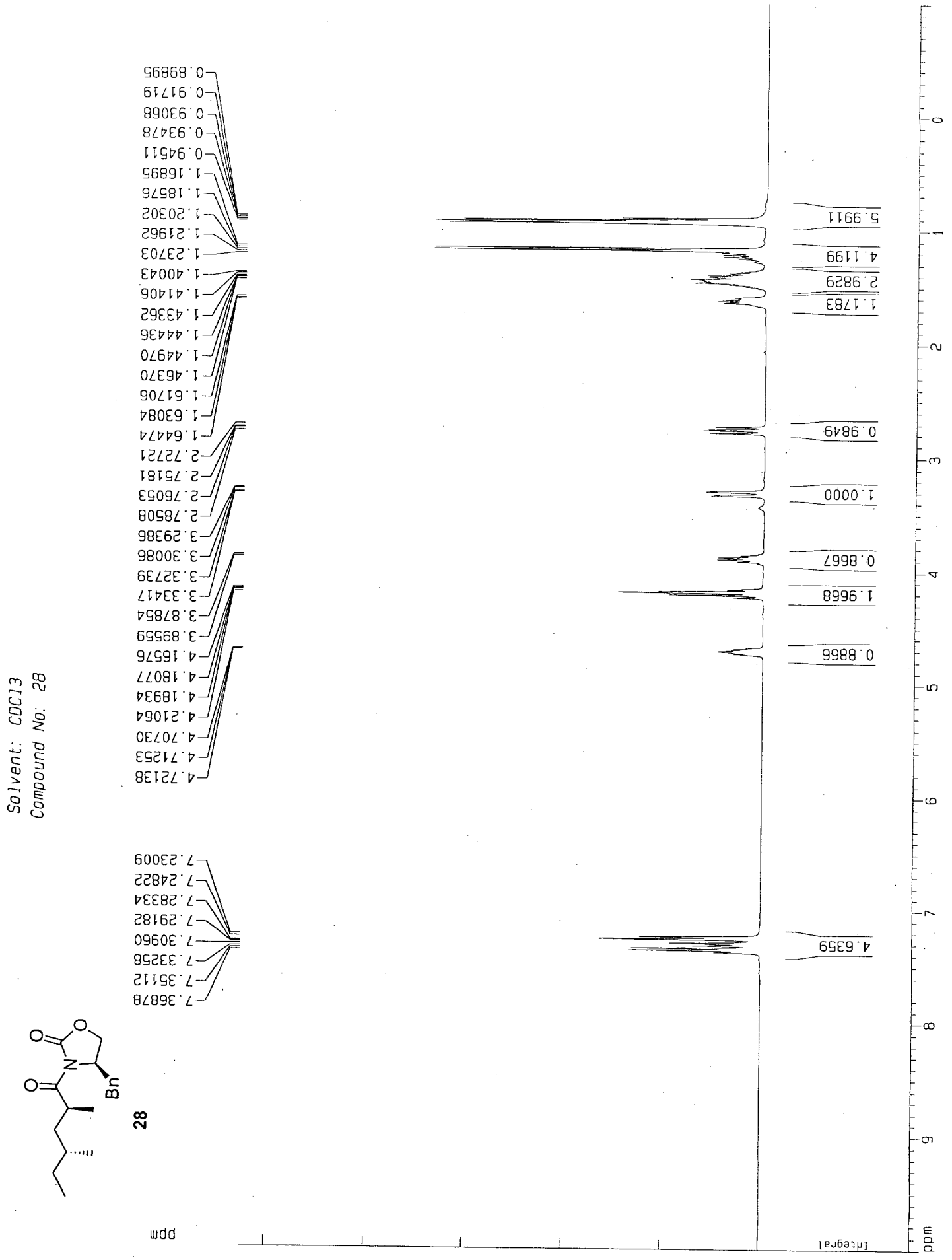

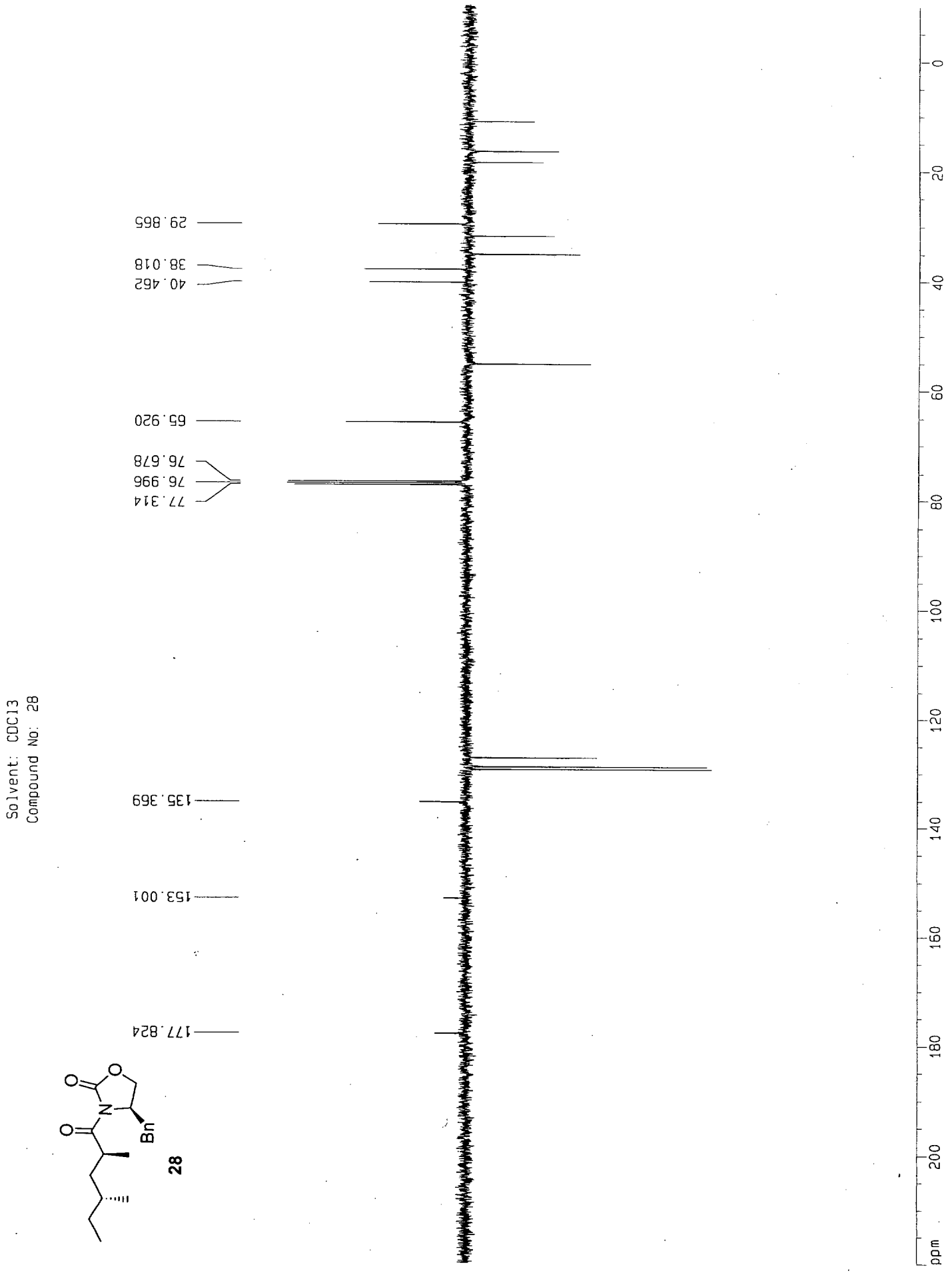

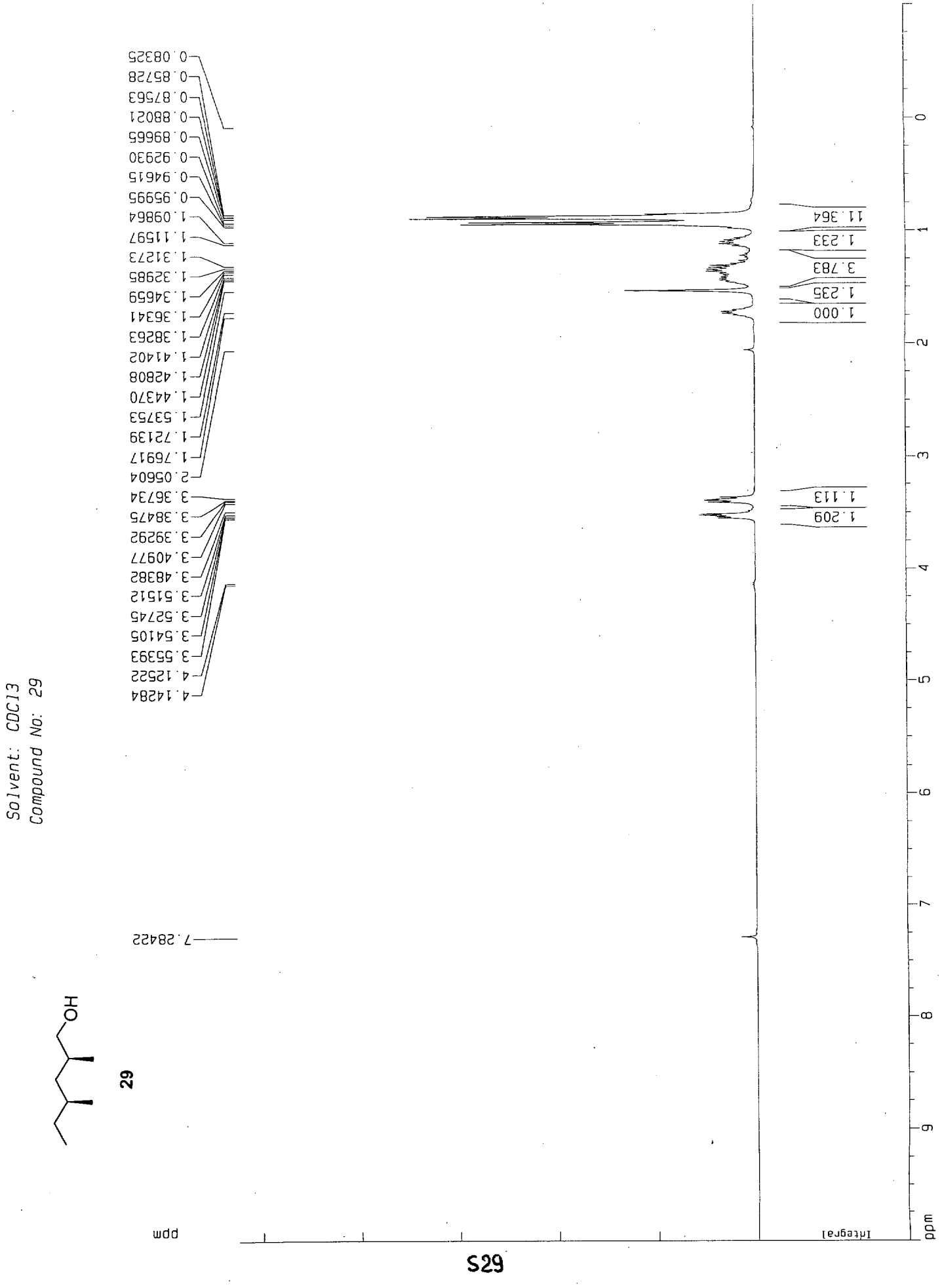

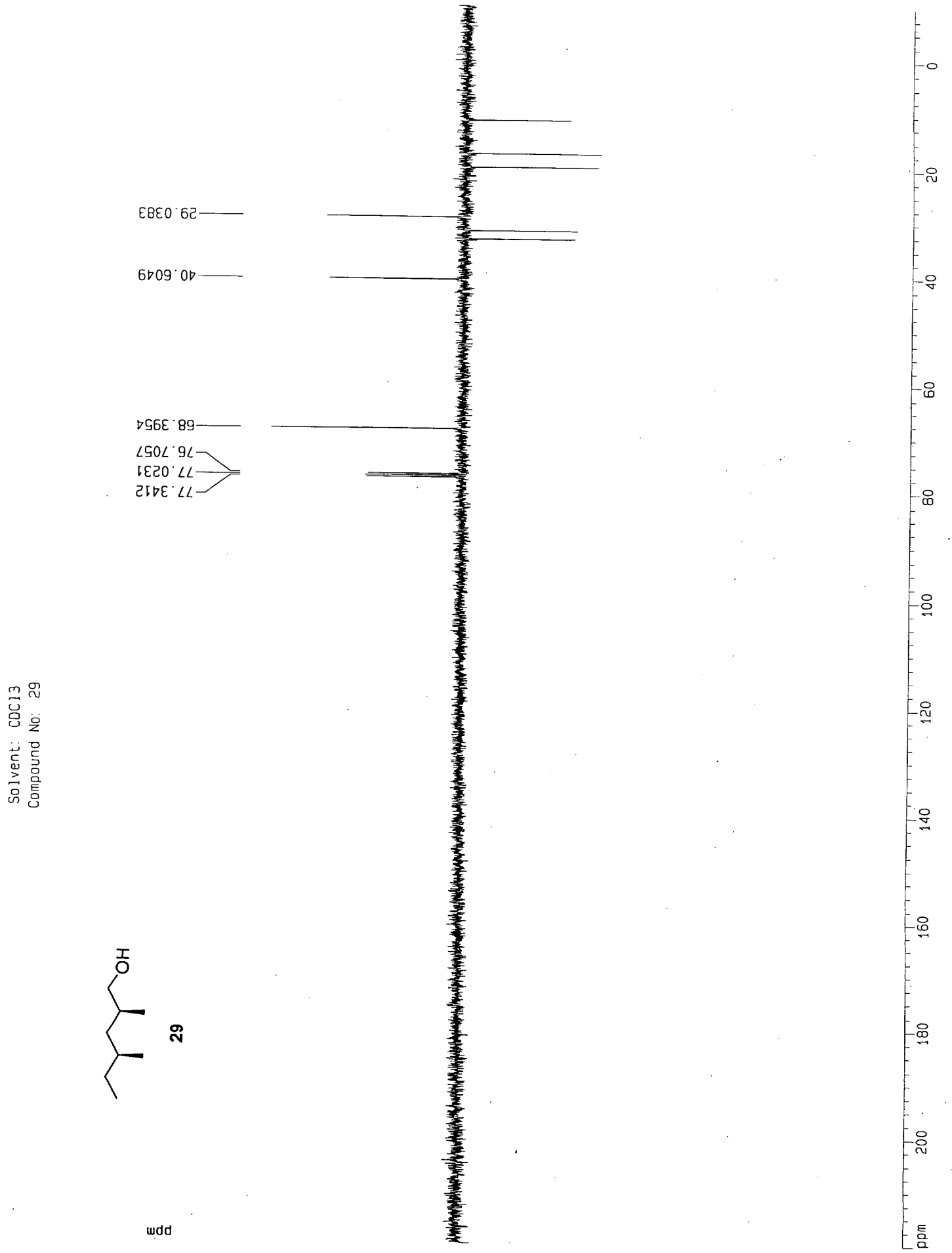

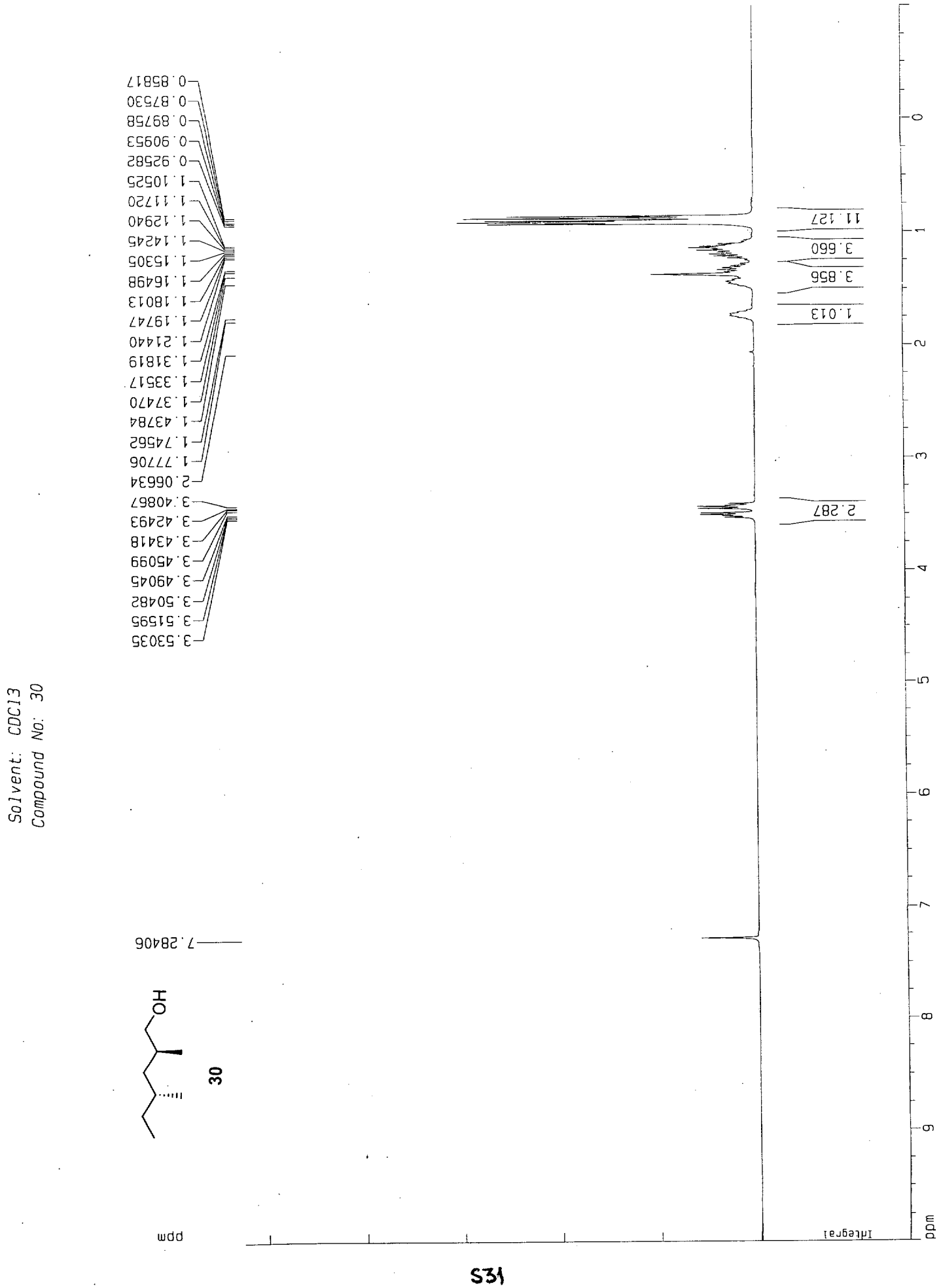

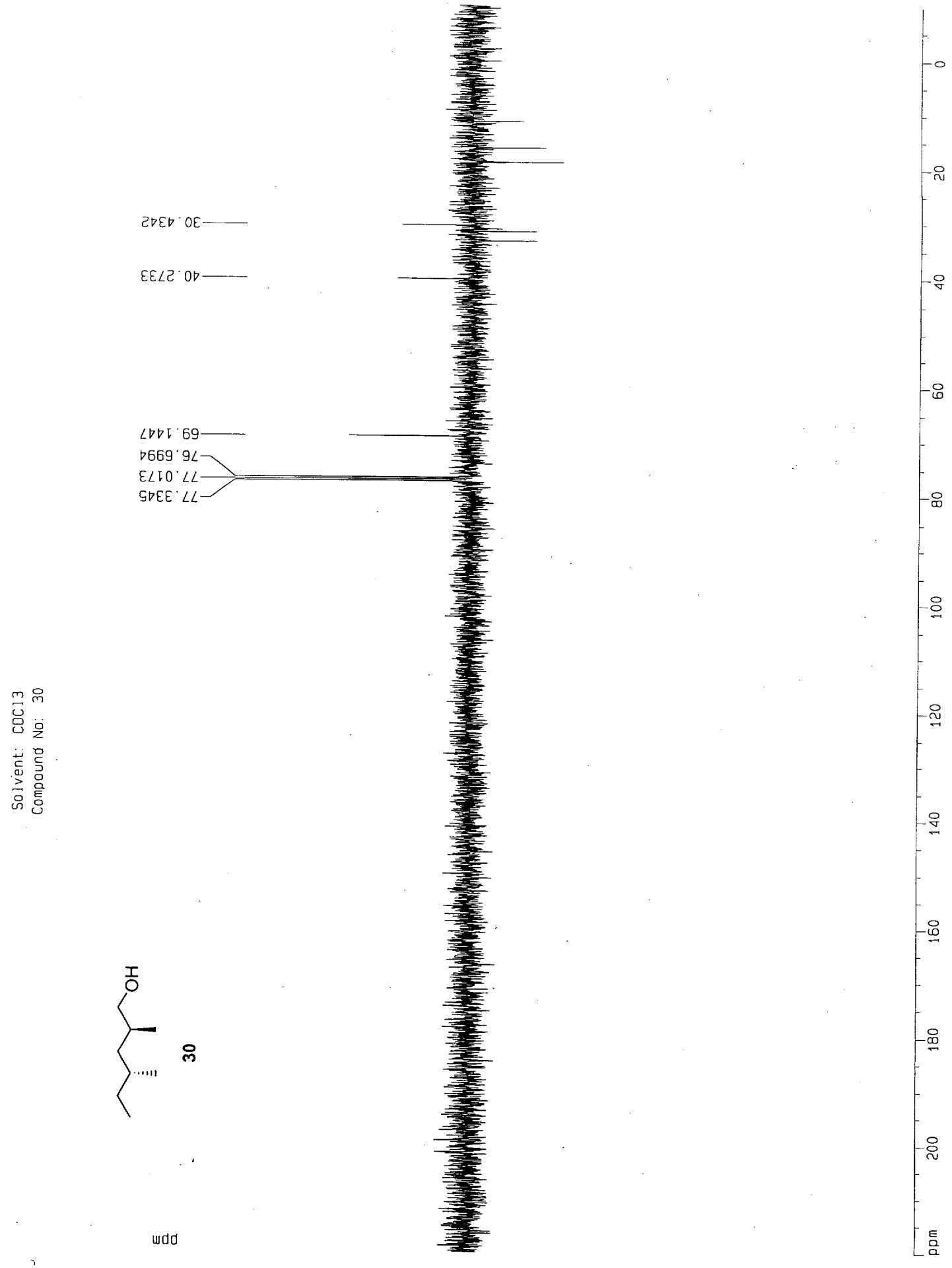

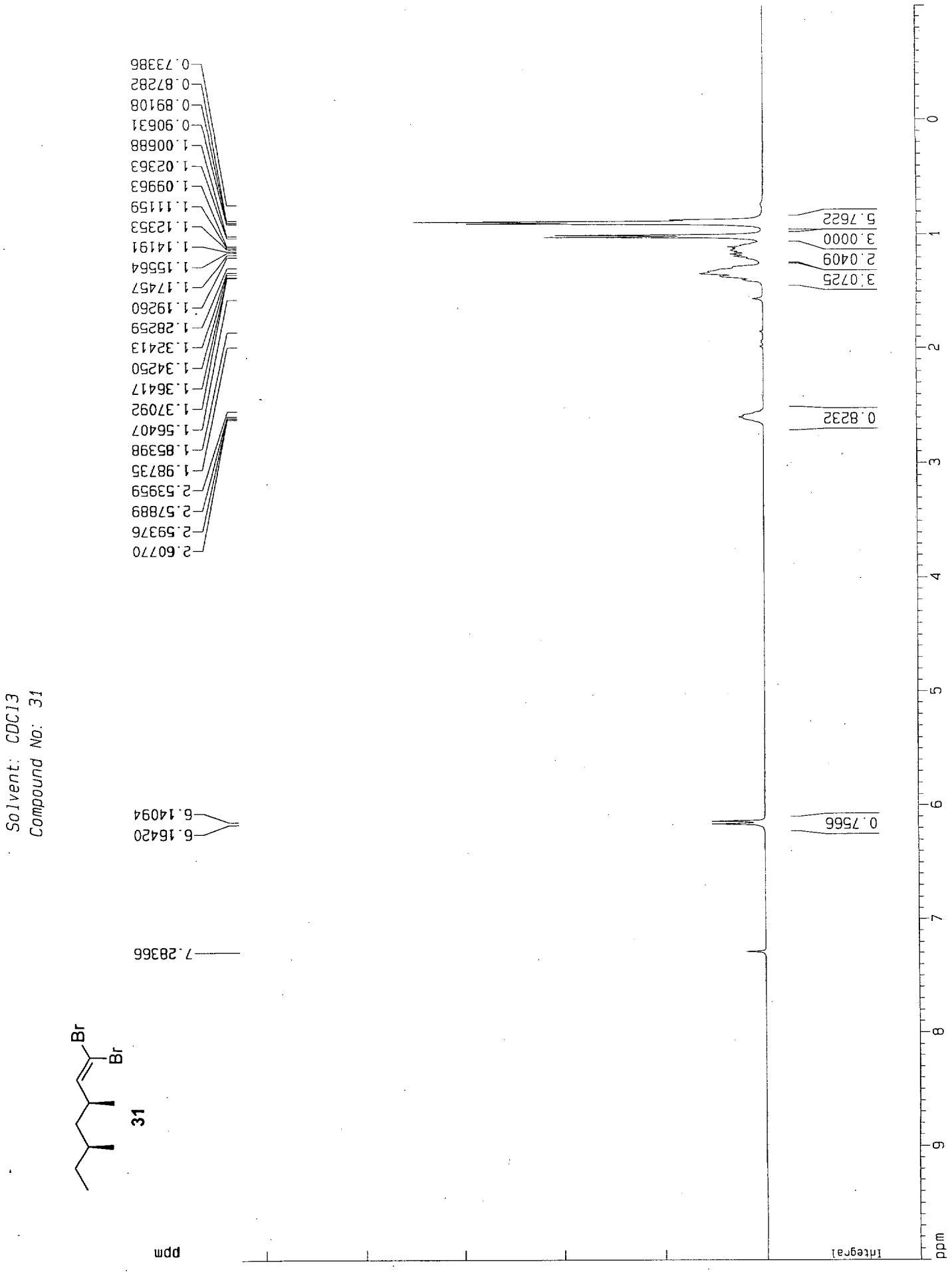
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