

Synthetic Studies on Borrelidin: Enantioselective Synthesis of the C1-C12 Fragment.

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Supporting Information

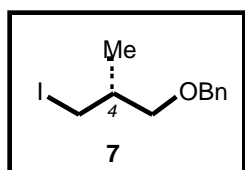
General Techniques. All reagents were commercially obtained (Aldrich, Acros) at highest commercial quality and used without further purification except where noted. Air- and moisture-sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Organic solutions were concentrated by rotary evaporation below 45 °C at approximately 20 mmHg. All non-aqueous reactions were carried out under anhydrous conditions using flame-dried glassware within an argon atmosphere in dry, freshly distilled solvents, unless otherwise noted. Tetrahydrofuran (THF), diethyl ether (Et₂O), dichloromethane (CH₂Cl₂), toluene (PhCH₃) and benzene (PhH) were purified by passage through a bed of activated alumina.¹ *N,N*-diisopropylethylamine (DIPEA), diisopropylamine, pyridine, triethylamine (TEA) and boron trifluoride etherate were distilled from calcium hydride prior to use.² Dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) were distilled from calcium hydride under reduced pressure (20 mmHg) and stored over 4Å molecular sieves until needed. Yields refer to

¹. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

². Perrin, D. D.; Armarego, W. L. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, **1988**.

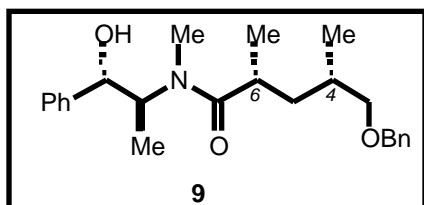
chromatographically and spectroscopically (^1H NMR, ^{13}C NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and 10% ethanolic phosphomolybdic acid (PMA) or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040-0.063 mm) was used for flash chromatography. Preparative thin-layer chromatography separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). NMR spectra were recorded on Varian Mercury 300, 400 and/or Unity 500 MHz instruments and calibrated using the residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad. IR spectra were recorded on a Nicolet 320 Avatar FT-IR spectrometer and values are reported in cm^{-1} units. Optical rotations were recorded on a Jasco P-1010 polarimeter and values are reported as follows: $[\alpha]_D^{25}$ (c: g/100ml, solvent). High resolution mass spectra (HRMS) were recorded on a VG 7070 HS mass spectrometer under chemical ionization (CI) conditions or on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions.

Key experimental procedures

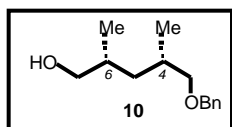


Iodide **7**: Imidazole (6.86 g, 101mmol) and iodine (23.0 g, 90.7 mmol) were added sequentially to a solution of triphenylphosphine (21.1 g, 80.6 mmol) in dichloromethane (250 ml) at 23°C. A solution of alcohol **4** (12.1 g, 67.2 mmol) in dichloromethane (30 ml) was added to the resulting fine suspension via cannula. After 2 h, dichloromethane was removed *in vacuo*. The solid residue was suspended in a minimal amount of dichloromethane (30 ml) and the suspension was loaded onto a column of silica gel eluting with 10% ether-petroleum ether to afford the iodide **7** (19.1 g, 65.8 mmol, 96%). **7**: colorless liquid; R_f = 0.48 (silica, 5% ether in hexanes); $[\alpha]_D^{25}$: -8.7 (c = 1.0,

CH₂Cl₂); IR (film) ν_{\max} 3030, 2962, 2858, 1454, 1362, 1200, 1101, 736, 697; ¹H NMR (400 MHz, C₆D₆) 7.28-7.10 (m, 5H), 4.26 (s, 2H), 3.11-3.00 (m, 4H), 1.53-1.41 (m, 1H), 0.77 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, C₆D₆) 138.8, 128.5, 127.6, 74.0, 73.1, 35.4, 17.90, 17.87, 14.3; HRMS, calcd for C₁₁H₁₅IO (M+ H⁺) 291.0247, found 291.0251.

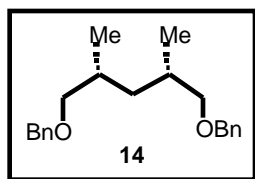


Amide **9**: A solution of *n*-butyllithium in hexanes (2.50 M, 27.96 ml, 69.9 mmol) was added via cannula to a suspension of lithium chloride (9.39 g, 222 mmol) and diisopropylamine (10.6 ml, 75.3 mmol) in THF (50 ml) at -78°C . The resulting suspension was warmed to 0°C briefly and then was cooled to -78°C . An ice-cooled solution of amide (+) **8** (8.12 g, 36.7 mmol) in THF (110 ml, followed by a 4-ml rinse) was added via cannula. The mixture was stirred at -78°C for 1 h, at 0°C for 15 min and at 23°C for 5 min. The mixture was cooled to 0°C and iodide **7** (5.08 g, 17.5 mmol) was added neat to the reaction via cannula. After being stirred for 18.5 h at 0°C , the reaction mixture was treated with half-saturated aqueous ammonium chloride solution (180 ml) and the resulting mixture was extracted with ethyl acetate (4 x 110 ml). The combined organic extracts were dried over sodium sulfate and concentrated. Purification of the residue by flash column chromatography (65% ether-hexanes) afforded amide **9** (6.52 g, 17.0 mmol, 97%). **9**: white solid; $R_f = 0.47$ (silica, ether); $[\alpha]_D^{25} +60.7$ (c = 1.0, CH₂Cl₂); IR (film) ν_{\max} 3383, 2967, 1619, 1453, 1099, 737, 700; HRMS, calcd for C₂₄H₃₃NO₃ (M+ H⁺) 384.2539, found 384.2534.

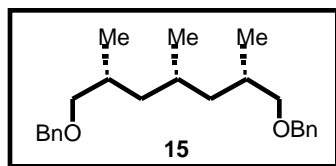


Alcohol **10**: A solution of *n*-butyllithium in hexanes (2.50 M, 18.6 ml, 46.5 mmol) was added to a solution of diisopropylamine (7.02 ml, 50.1 mmol) in tetrahydrofuran (50 ml) at -78°C . The resulting solution was stirred at -78°C for 10 min, then warmed to 0°C and held at that temperature for 10 min. Borane-ammonia

complex (90%, 1.64 g, 47.7 mmol) was added in one portion and the suspension was stirred at 0°C for 15 min and then was warmed to 23°C. After 15 min, the suspension was cooled to 0°C. A solution of amide **9** (4.56 g, 11.9 mmol) in tetrahydrofuran (30 ml, followed by a 5-ml rinse) was added via cannula over 3 min. The reaction mixture was warmed to 23°C, held at that temperature for 2 h and then cooled to 0°C where excess hydride was quenched by the careful addition of 3 N aqueous hydrochloric acid solution (120 ml). The mixture was stirred for 30 min at 0°C and then extracted with four 45-ml portions of ether. The combined organic extracts were washed sequentially with 3 N aqueous hydrochloric acid solution (20 ml) and brine (20 ml). The ether extracts were dried over magnesium sulfate and concentrated. Purification of the residue by flash column chromatography (35% ether-petroleum ether) afforded alcohol **10** (2.51 g, 11.3 mmol, 90% yield). **10**: colorless liquid; $R_f = 0.52$ (silica, 50% ether in hexanes); $[\alpha]_D^{25} +7.1$ ($c = 1.0$, CH_2Cl_2); IR (film) ν_{max} 3404, 2955, 2923, 2871, 1454, 1098, 1028, 736, 698; **$^1\text{H NMR}$** (400 MHz, CDCl_3) 7.40-7.23 (m, 5H), 4.50 (d, $J = 1.6$ Hz, 2H), 3.53-3.22 (m, 4H), 1.94-1.83 (m, 1H), 1.78-1.60 (m, 2H), 1.54-1.44 (m, 1H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H); **$^{13}\text{C NMR}$** (100 MHz, CDCl_3) 138.4, 128.2, 127.44, 127.38, 75.8, 73.0, 67.6, 37.5, 33.0, 30.9, 18.1, 17.6; HRMS, calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2$ ($\text{M} + \text{Na}^+$) 245.1516, found 245.1514.

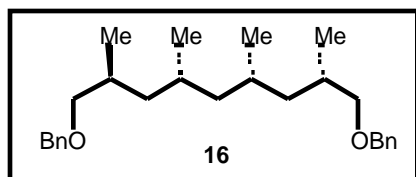


Benzyl ether **14**: yellow oil; $R_f = 0.50$ (silica, hexanes); $[\alpha]_D^{25} = 0$ ($c = 1.0$, CH_2Cl_2); IR (film) ν_{max} 2955, 2924, 2852, 1453, 1362, 1099, 735, 697; **$^1\text{H NMR}$** (400 MHz, CDCl_3) 7.37-7.24 (m, 5H), 4.49 (ABq, $J = 12.0$ Hz, 2H), 3.34 (ddd, $J = 9.2, 5.6, 1.2$ Hz, 1H), 3.21 (ddd, $J = 9.2, 7.4, 1.2$ Hz, 1H), 1.87 (sextet, $J = 6.8$ Hz, 1H), 1.51-1.43 (m, 1H), 0.96 (d, $J = 6.4$ Hz, 3H); **$^{13}\text{C NMR}$** (100 MHz, CDCl_3) 138.8, 128.2, 127.4, 127.3, 75.9, 72.9, 38.2, 31.0, 18.1; HRMS, calcd for $\text{C}_{21}\text{H}_{28}\text{O}_2$ ($\text{M} + \text{Na}^+$) 335.1987, found 335.1999.



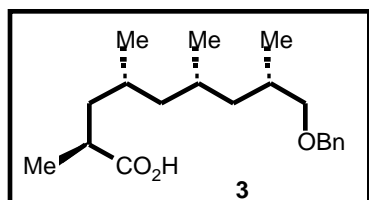
Benzyl ether **15**: colorless oil; $R_f = 0.63$ (silica, hexanes); $[\alpha]_D^{25} = 0$ ($c = 1.0$, CH_2Cl_2); IR (film) max 2953, 2922, 2851, 1453, 1360, 1097, 1026, 733, 695; $^1\text{H NMR}$ (400 MHz, CDCl_3) 7.37-

7.33 (m, 5H), 4.49 (ABq, $J = 12.4$ Hz, 2H), 3.35 (dd, $J = 8.8, 5.2$ Hz, 1H), 3.12 (dd, $J = 8.8, 7.2, 1.2$ Hz, 1H), 1.87 (m, 1H), 1.59 (sextet, $J = 6.8$ Hz, 1H), 1.38-1.26 (m, 2H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.89 (d, $J = 6.4$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 138.2, 128.2, 127.7, 127.4, 75.9, 72.9, 41.6, 30.9, 27.7, 21.0, 18.3; HRMS, calcd for $\text{C}_{24}\text{H}_{34}\text{O}_2$ ($\text{M}^+ \text{Na}^+$) 377.2457, found 377.2468.



Compound **16**: colorless oil; $R_f = 0.29$ (silica, hexanes); $[\alpha]_D^{25} = -10.61$ ($c = 1.0$, CH_2Cl_2); IR (film) max 2955, 2917, 2848, 1454, 1361, 1100, 734, 697; $^1\text{H NMR}$ (400

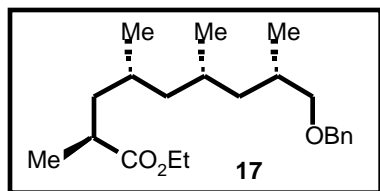
MHz, CDCl_3) 7.40-7.26 (m, 10H), 4.52 (ABq, $J = 12.4$ Hz, 4H), 3.37 (dd, $J = 9.2, 5.2$ Hz, 1H), 3.31 (dd, $J = 9.2, 6.0$ Hz, 1H), 3.25-3.20 (m, 2H) 1.93-1.85 (m, 2H), 1.66-1.56 (m, 3H), 1.37-1.17 (m, 3H), 1.10 (t, $J = 7.2$ Hz, 2H), 0.96 (d, $J = 6.4$ Hz, 3H), 0.92 (d, $J = 6.4$ Hz, 3H), 0.87 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 138.8, 128.3, 128.2, 127.7, 127.4, 127.4, 127.3, 127.3, 76.8, 76.0, 72.9, 72.1, 45.9, 41.8, 40.5, 30.9, 27.4, 27.1, 20.7, 20.2, 18.3, 16.7; HRMS, calcd for $\text{C}_{27}\text{H}_{40}\text{O}_2$ ($\text{M}^+ \text{Na}^+$) 419.2926, found 419.2941.



Acid **3**: A 100-ml round-bottomed flask was charged with amide (9.12 g, 19.5 mmol), aqueous *tetra-n*-butylammonium hydroxide solution (40% w/w, 63.26 g, 97.5 mmol), *tert*-butyl alcohol (25 ml) and water (75 ml), and the biphasic mixture was heated at

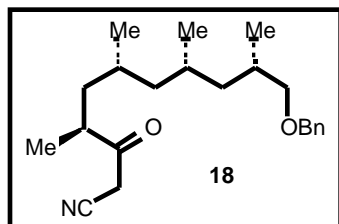
reflux for 24 h. The mixture was cooled to 23°C and then partitioned between 0.5 N aqueous sodium hydroxide solution (200 ml) and ether (150 ml). The aqueous layer was separated and

extracted with two 150-ml portions of ether and then brought to pH = 1 by the addition of 3 N aqueous hydrochloric acid solution. The acidified solution was saturated with sodium chloride and extracted with three 150-ml portions of ether. The combined ether extracts were washed with water (100 ml), then dried over sodium sulfate and concentrated to afford acid **3** (5.58 g, 17.4 mmol, 84%). **3**: colorless liquid; $R_f = 0.40$ (silica, 85% ether in hexanes); $[\alpha]_D^{25}$: +0.5 (c = 1.0, CH₂Cl₂); IR (film) ν_{\max} 2957, 2926, 1706, 1455, 1102, 735, 698; **¹H NMR** (400 MHz, CDCl₃) 7.40-7.24 (m, 5H), 4.51 (d, J = 4.8 Hz, 2H), 3.38-3.26 (m, 1H), 3.24-3.16 (m, 1H), 2.60-2.48 (m, 1H), 1.92-1.80 (m, 1H), 1.66-1.52 (m, 2H), 1.50-1.20 (m, 4H), 1.15 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.4 Hz, 3H), 0.864 (d, J = 6.0 Hz, 3H), 0.855 (d, J = 6.4 Hz, 3H), 1.00-0.80 (m, 2H); **¹³C NMR** (100 MHz, CDCl₃) 183.7, 138.6, 128.2, 127.4, 127.3, 75.7, 72.9, 45.2, 41.6, 40.2, 37.0, 30.8, 27.6, 27.4, 20.7, 20.0, 18.3, 16.4; HRMS, calcd for C₂₀H₃₂O₃ (M+ Na⁺) 343.2247, found 343.2241.



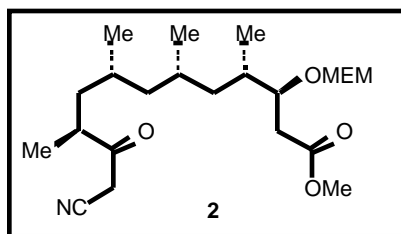
Ester **17**: A solution of the acid **3** (5.58 g, 17.4 mmol) and ethyl alcohol (1.22 ml, 20.9 mmol) in dichloromethane (100 ml) was treated with 1,3-dicyclohexylcarbodiimide (5.03 g, 24.4 mmol) and 4-dimethylaminopyridine (0.42 g, 3.48 mmol). The reaction mixture was stirred at room temperature for 2 h and diluted with ether (100 ml) and water (50 ml). The organic phase was separated and washed with water (50 ml) and brine (50 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give a crude oil. Purification by flash column chromatography (silica, 5% ether-hexanes) gave ester **17** (5.75 g, 16.5 mmol, 95%). **17**: colorless liquid; $R_f = 0.50$ (silica, 40% ether in hexanes); $[\alpha]_D^{25}$: +8.8 (c = 1.0, CH₂Cl₂); IR (film) ν_{\max} 2957, 2928, 1735, 1455, 1377, 1178, 1101, 736, 698; **¹H NMR** (400 MHz, CDCl₃) 7.32-7.18 (m, 5H), 4.42 (d, J = 4.4 Hz, 2H), 4.10-4.02 (m, 2H), 3.32-3.24 (m, 1H), 3.16-3.10 (m, 1H), 2.50-2.36 (m, 1H), 1.84-1.72 (m, 1H), 1.58-1.42 (m, 2H), 1.40-1.05 (m,

7H), 1.04 (d, $J = 7.2$ Hz, 3H), 0.88 (d, $J = 6.8$ Hz, 3H), 0.79 (d, $J = 6.4$ Hz, 3H), 0.76 (d, $J = 6.8$ Hz, 3H), 0.90-0.74 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 176.3, 138.4, 127.7, 126.9, 126.8, 75.1, 72.5, 59.4, 44.9, 41.1, 40.4, 36.7, 30.5, 27.4, 27.1, 20.4, 19.8, 18.1, 16.6, 13.8; HRMS, calcd for $\text{C}_{22}\text{H}_{36}\text{O}_3$ ($\text{M} + \text{H}^+$) 349.2743, found 349.2749.



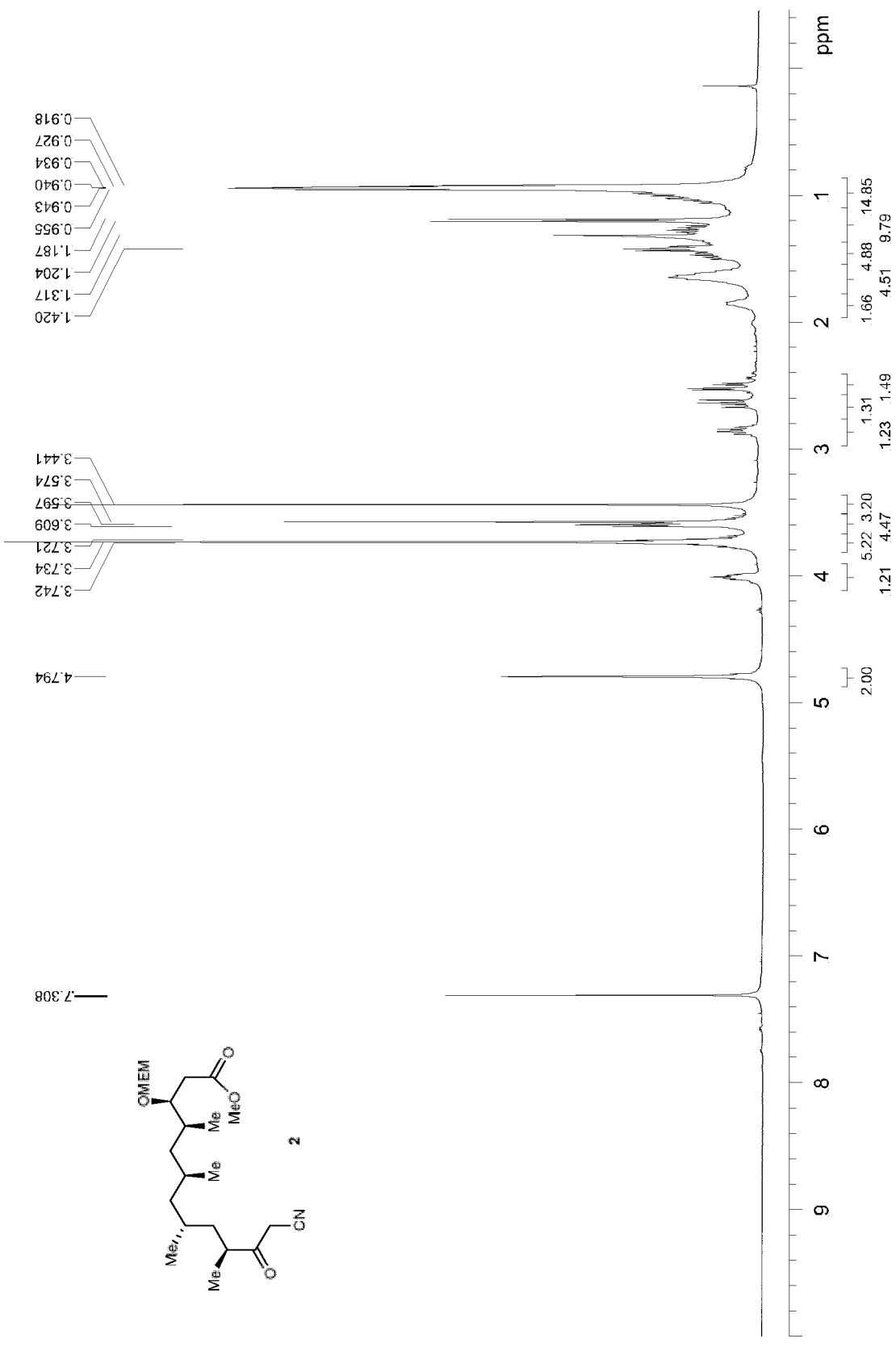
Ketonitrile **18**: colorless liquid; $R_f = 0.75$ (silica, 25% ether in hexanes); $[\alpha]_{\text{D}}^{25}$: +9.5 ($c = 1.0$, CH_2Cl_2); IR (film) max 2958, 2920, 2262, 1728, 1455, 1380, 1102, 738, 698; $^1\text{H NMR}$ (400 MHz, CDCl_3) 7.40-7.24 (m, 5H), 4.49 (d, $J = 3.6$ Hz, 2H), 3.48

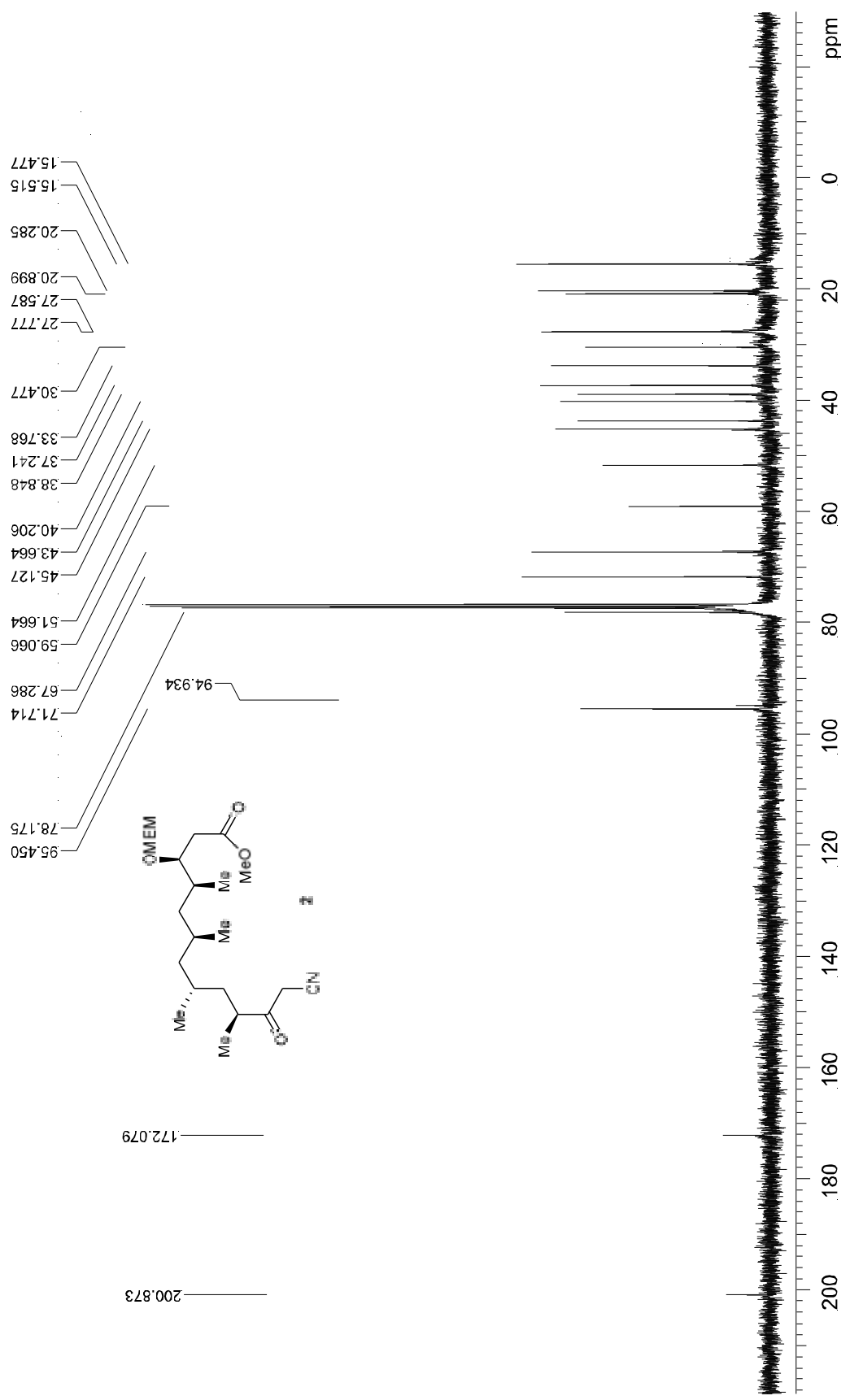
(s, 2H), 3.34-3.28 (m, 1H), 3.26-3.18 (m, 1H), 2.84-2.72 (m, 1H), 1.90-1.77 (m, 1H), 1.85-1.70 (m, 2H), 1.40-1.16 (m, 4H), 1.11 (d, $J = 6.8$ Hz, 3H), 0.94 (d, $J = 6.8$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H), 0.85 (d, $J = 6.4$ Hz, 3H), 1.02-0.85 (m, 2H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 201.2, 138.7, 128.2, 127.4, 127.3, 75.7, 72.9, 45.4, 43.5, 41.6, 38.9, 30.8, 30.3, 27.5, 27.3, 20.6, 19.8, 18.3, 15.3; HRMS, calcd for $\text{C}_{22}\text{H}_{33}\text{NO}_2$ ($\text{M} + \text{H}^+$) 344.2609, found 344.2617.

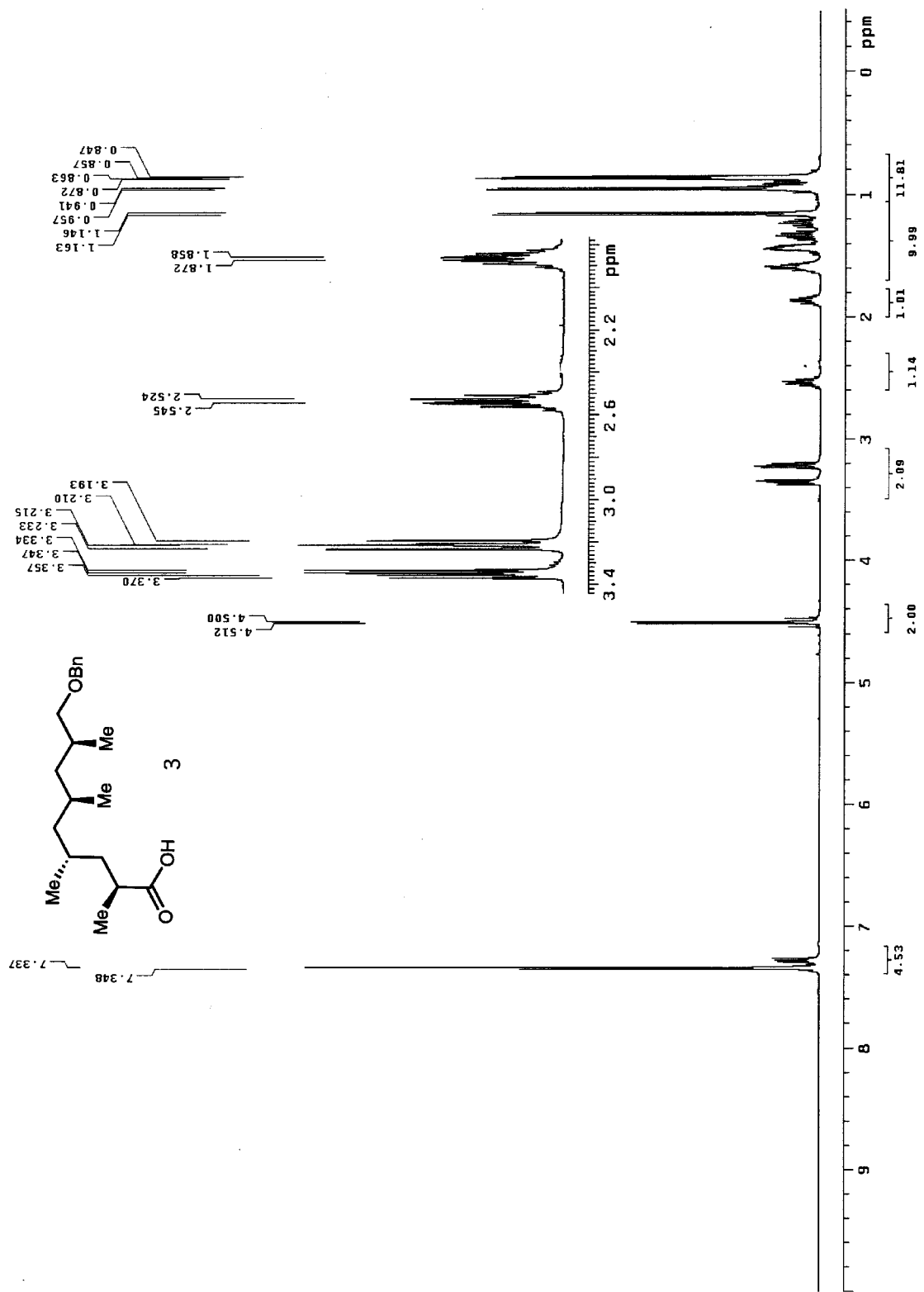


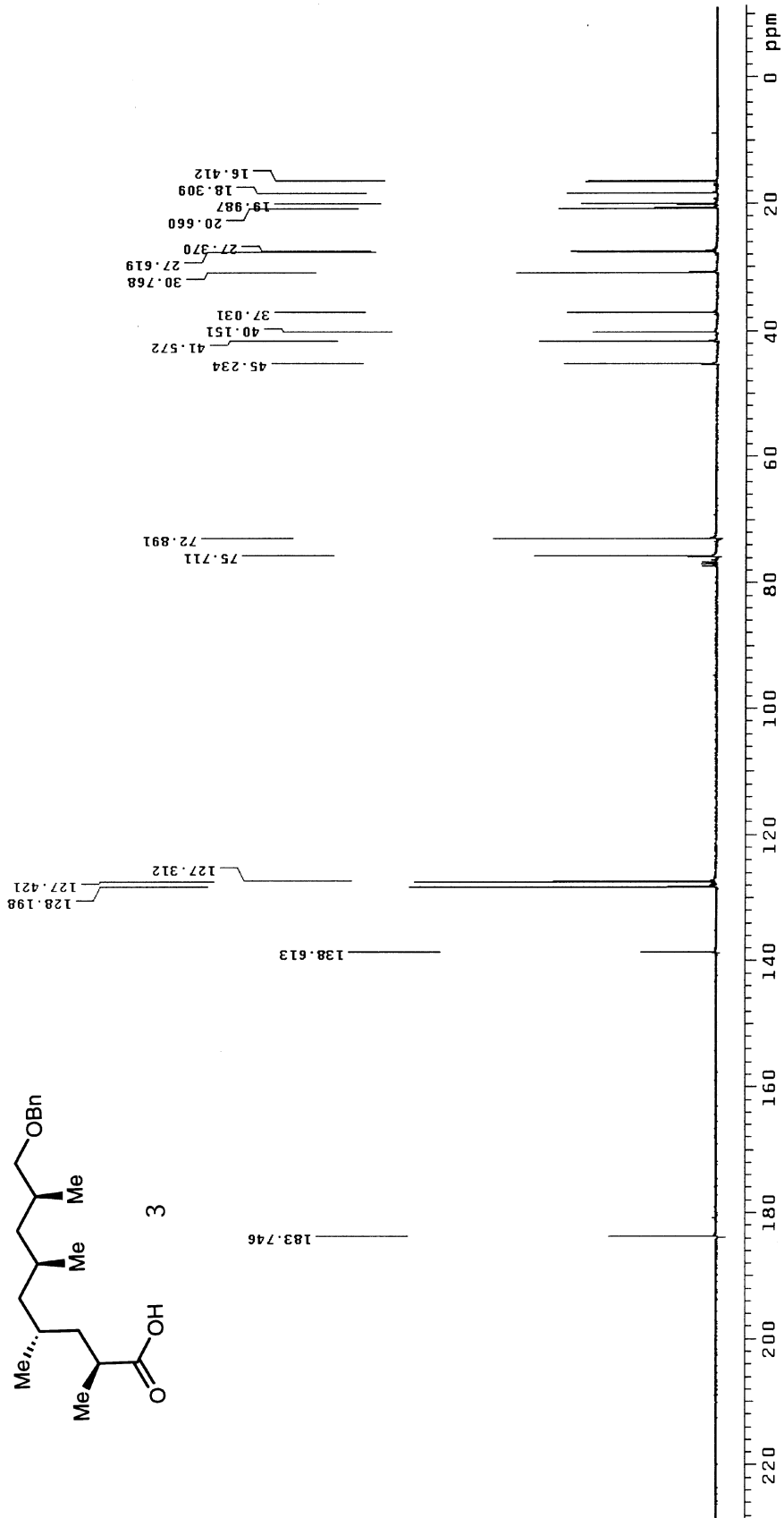
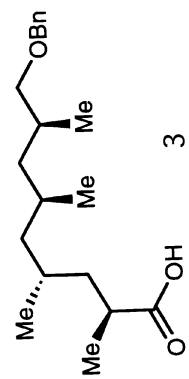
Ketonitrile **2**: colorless liquid; $R_f = 0.35$ (1:4 hexane/ether). $[\alpha]_{\text{D}}^{25}$: -21.40 ($c = 0.5$, CH_2Cl_2); IR (film) max 3437, 2922, 2259, 1732, 1459, 1107, 1040; $^1\text{H NMR}$ (400 MHz, CDCl_3) 4.72 (s, 2H), 3.97-3.92 (m, 1H), 3.72-3.61 (m, 5H), 3.54-3.49

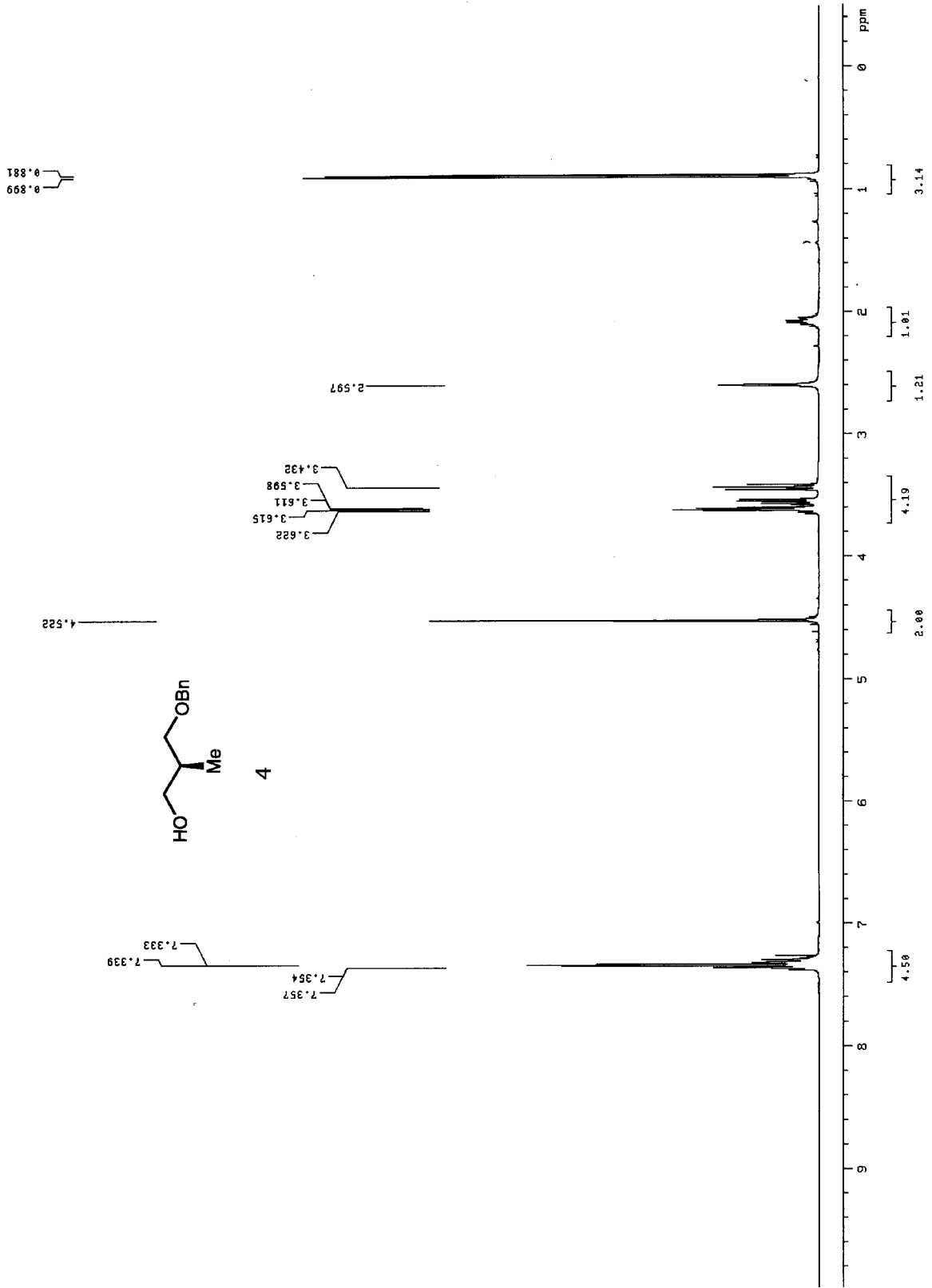
(m, 4H), 3.37 (s, 3H), 2.79 (m, 1H), 2.57 (dd, $J = 15.2, 7.6$, 1H), 2.39 (dd, $J = 15.2, 5.6$, 1H), 1.84-1.73 (m, 1H), 1.63-1.51 (m, 2H), 1.40-0.84 (m, 18H); $^{13}\text{C NMR}$ (100 MHz, CDCl_3) 200.9, 172.1, 95.4, 78.2, 77.3, 77.0, 76.7, 71.7, 67.3, 59.1, 51.7, 45.1, 43.7, 40.2, 38.8, 37.2, 33.8, 30.5, 20.9, 20.3, 15.5, 15.5. HRMS calcd. for $\text{C}_{22}\text{H}_{39}\text{NO}_6$ ($\text{M} + \text{Na}^+$) 436.2669, found 436.2668.

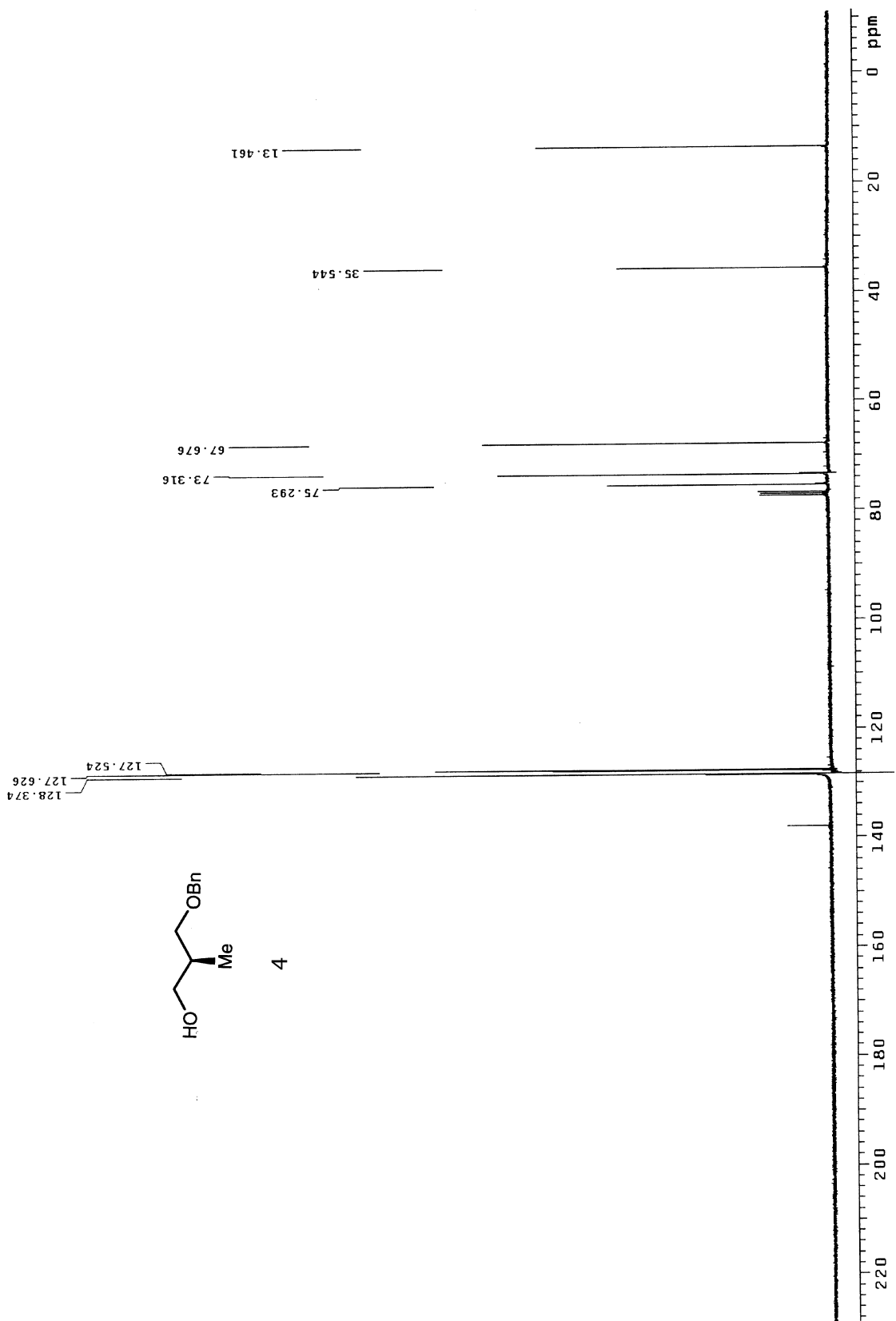


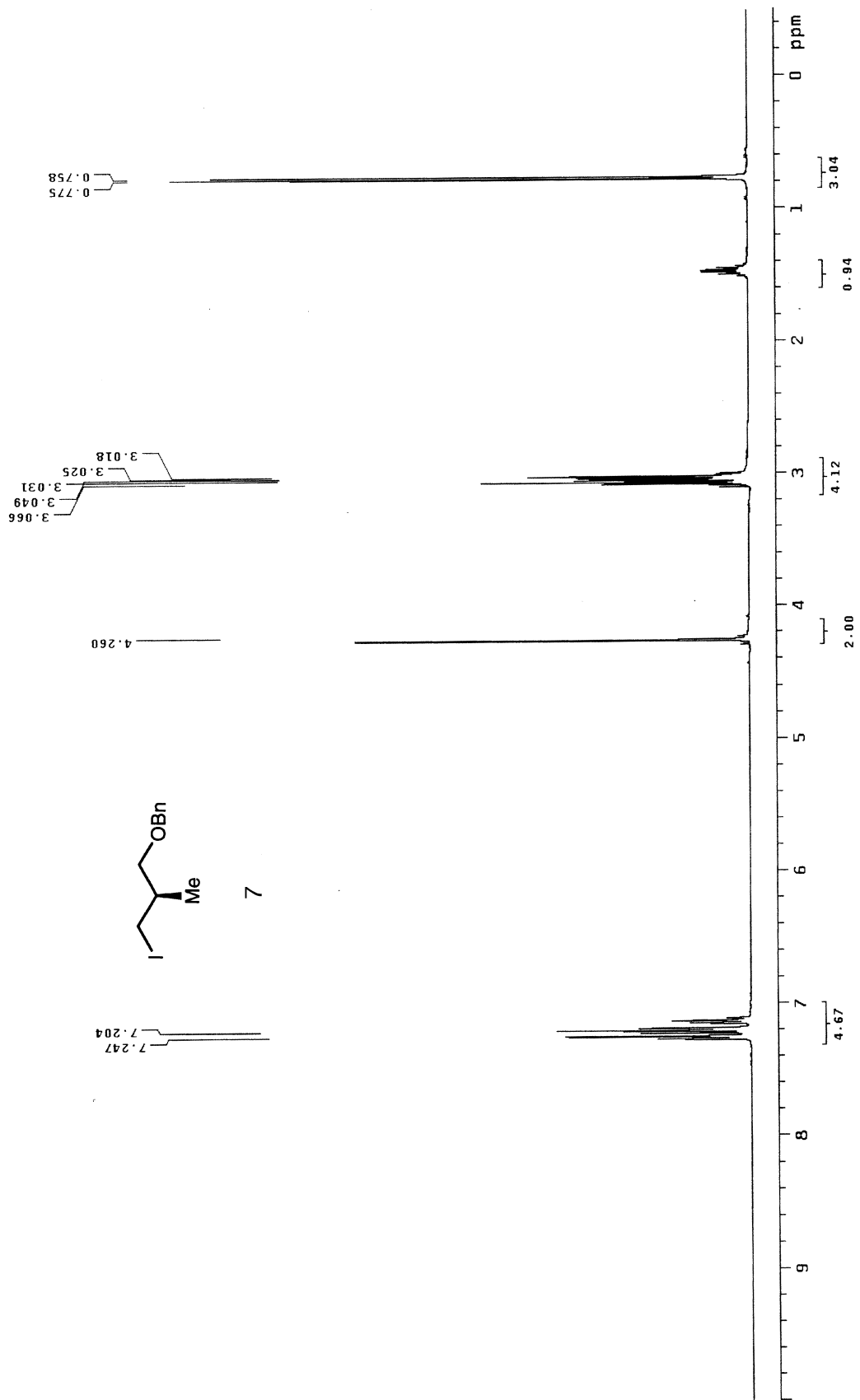


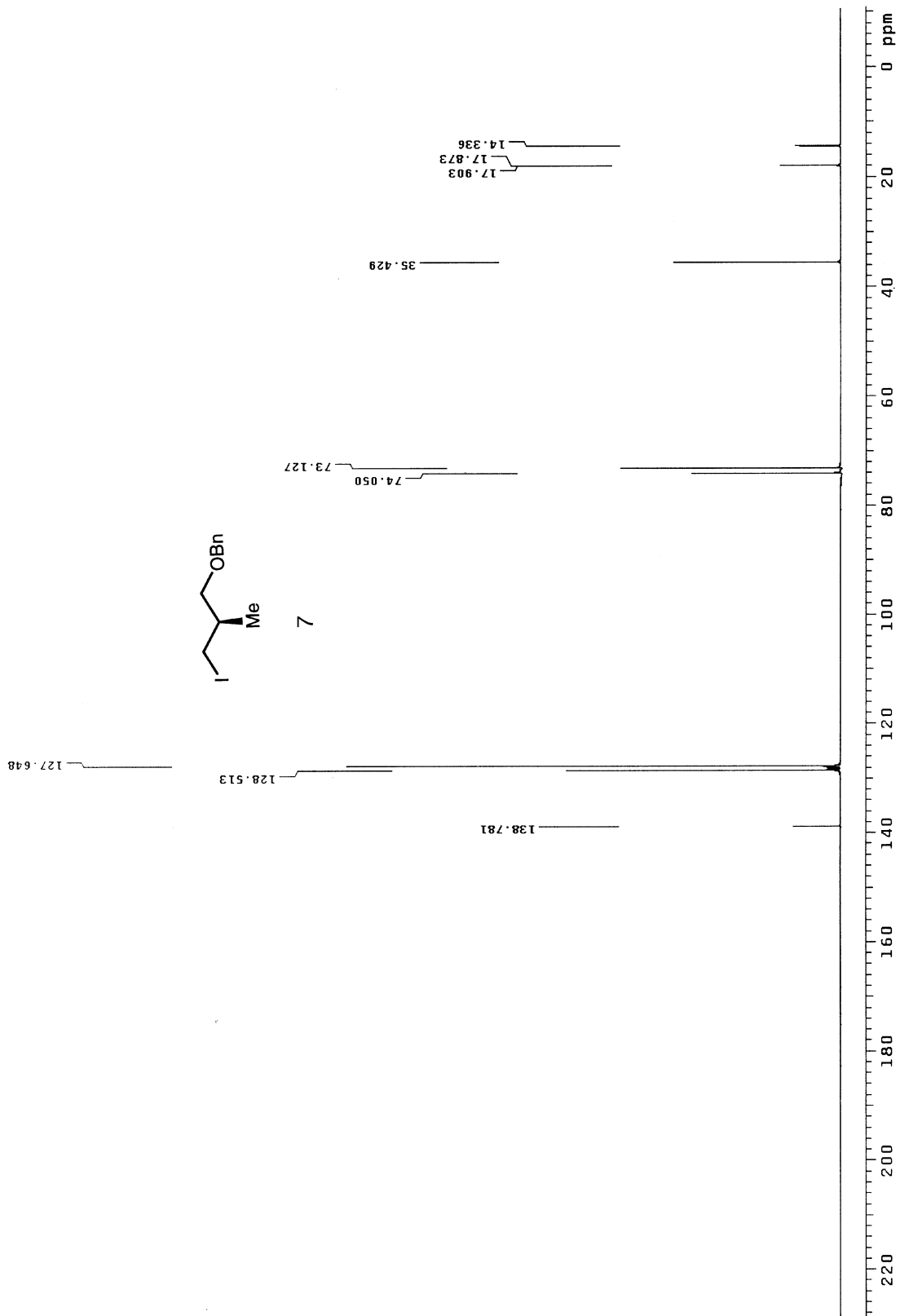


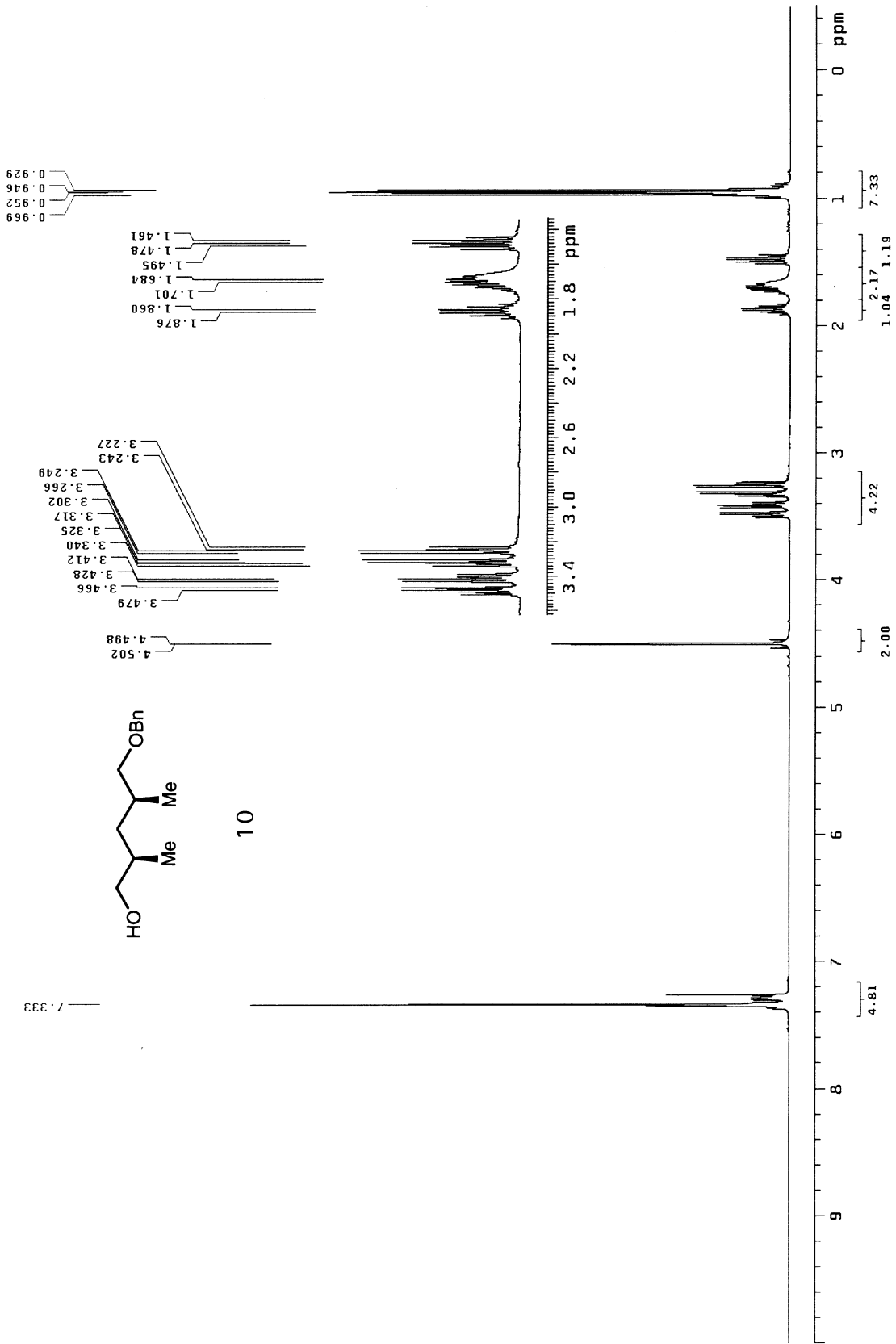


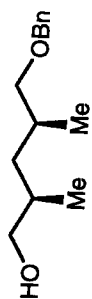




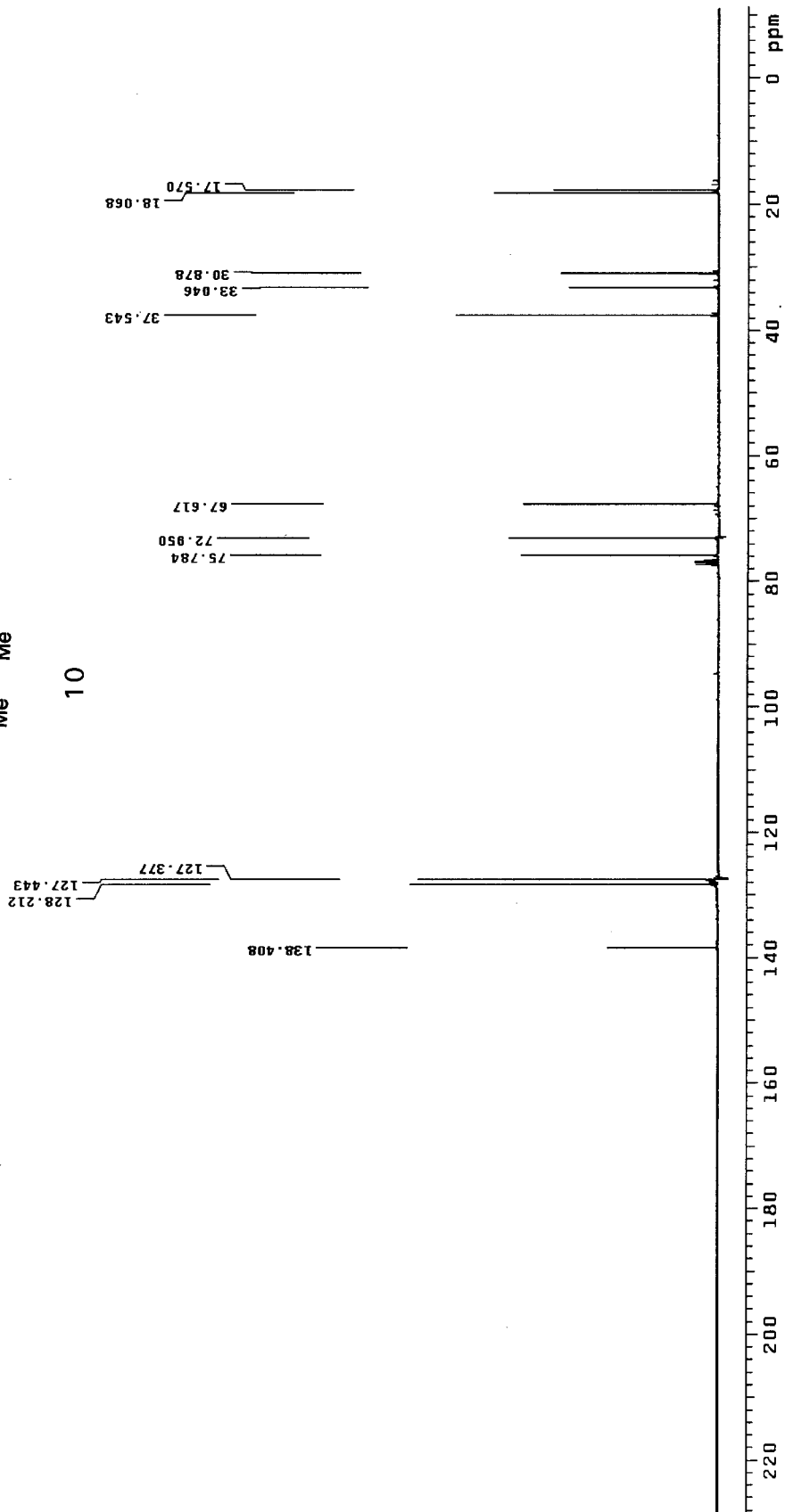


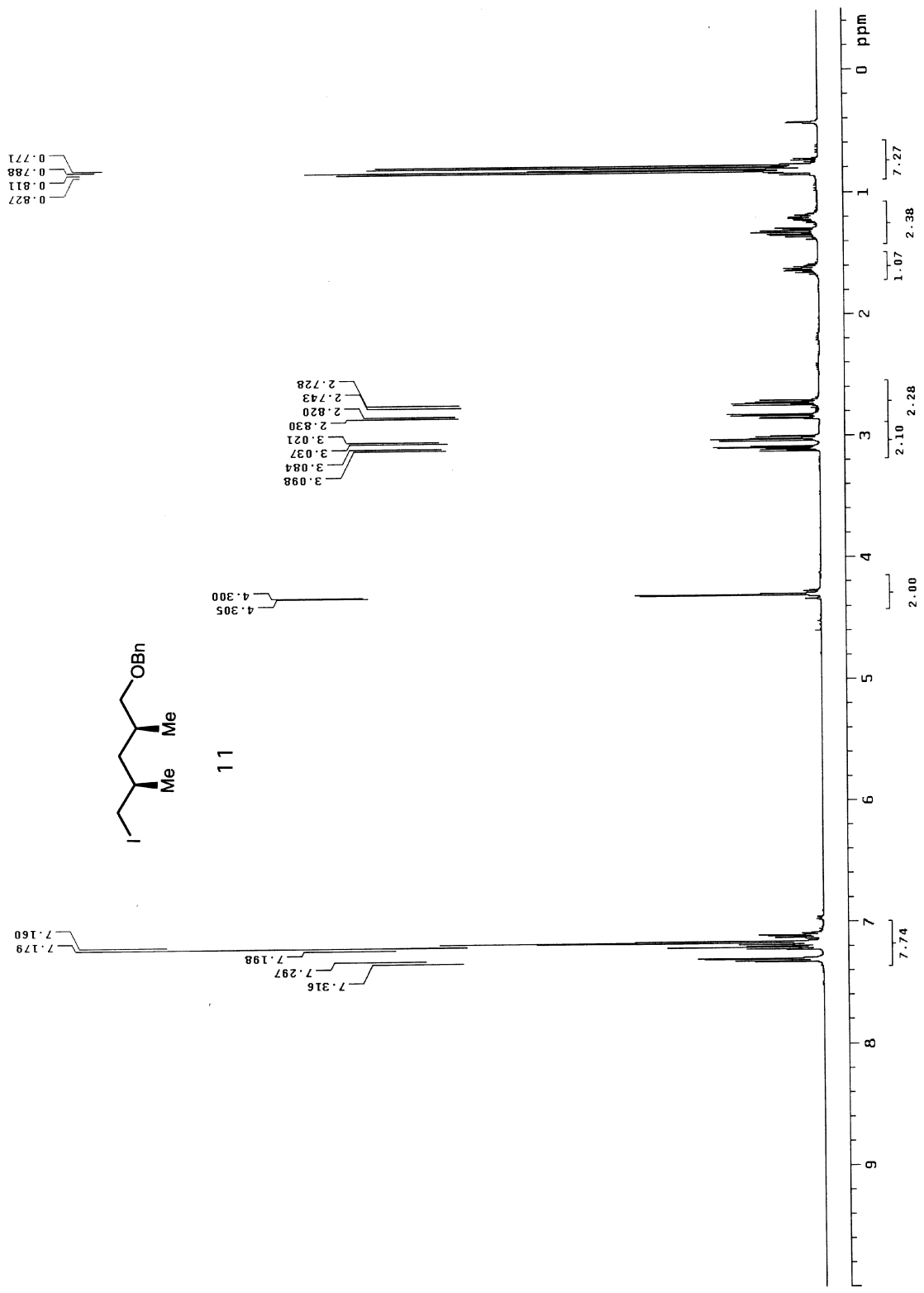


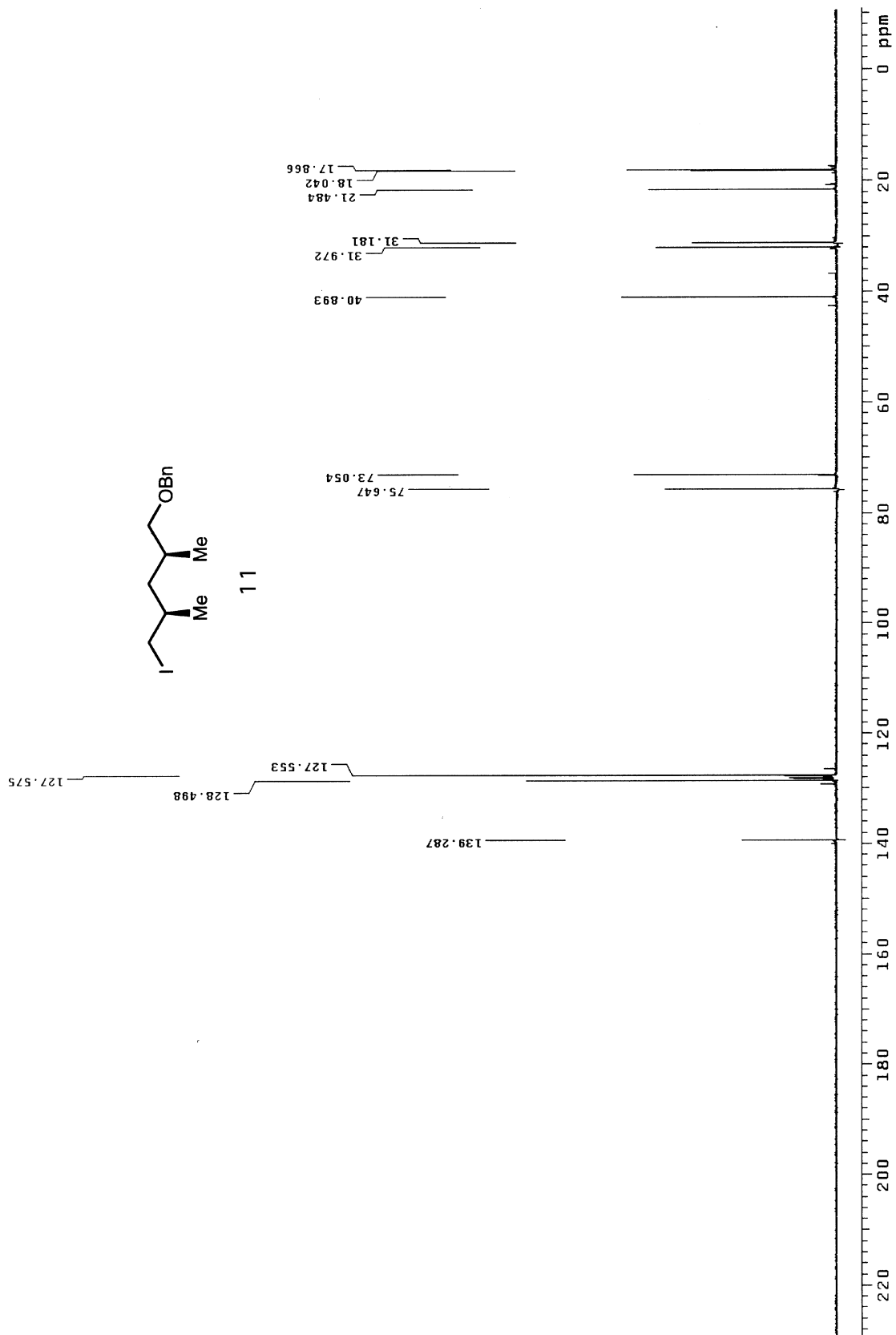


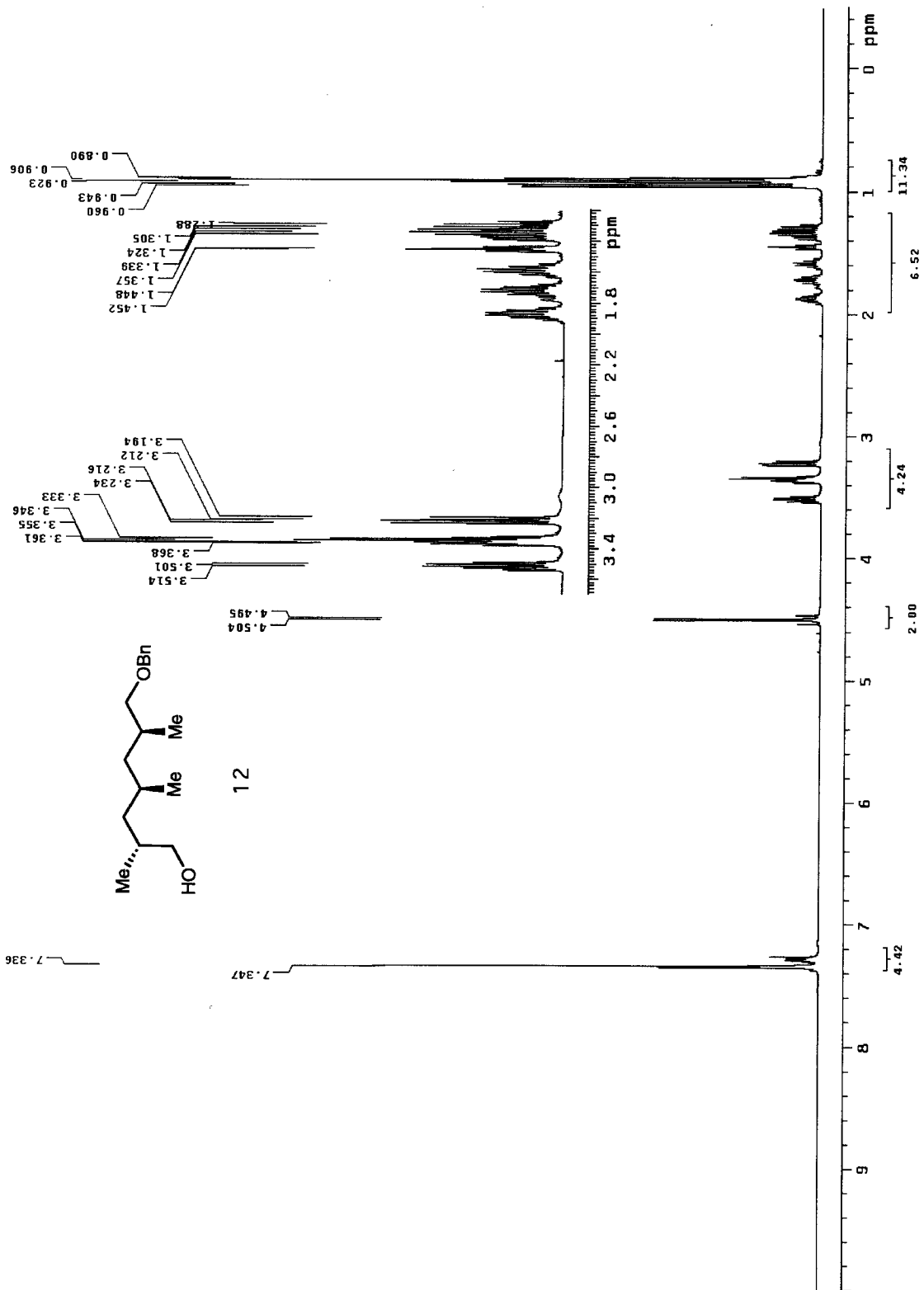


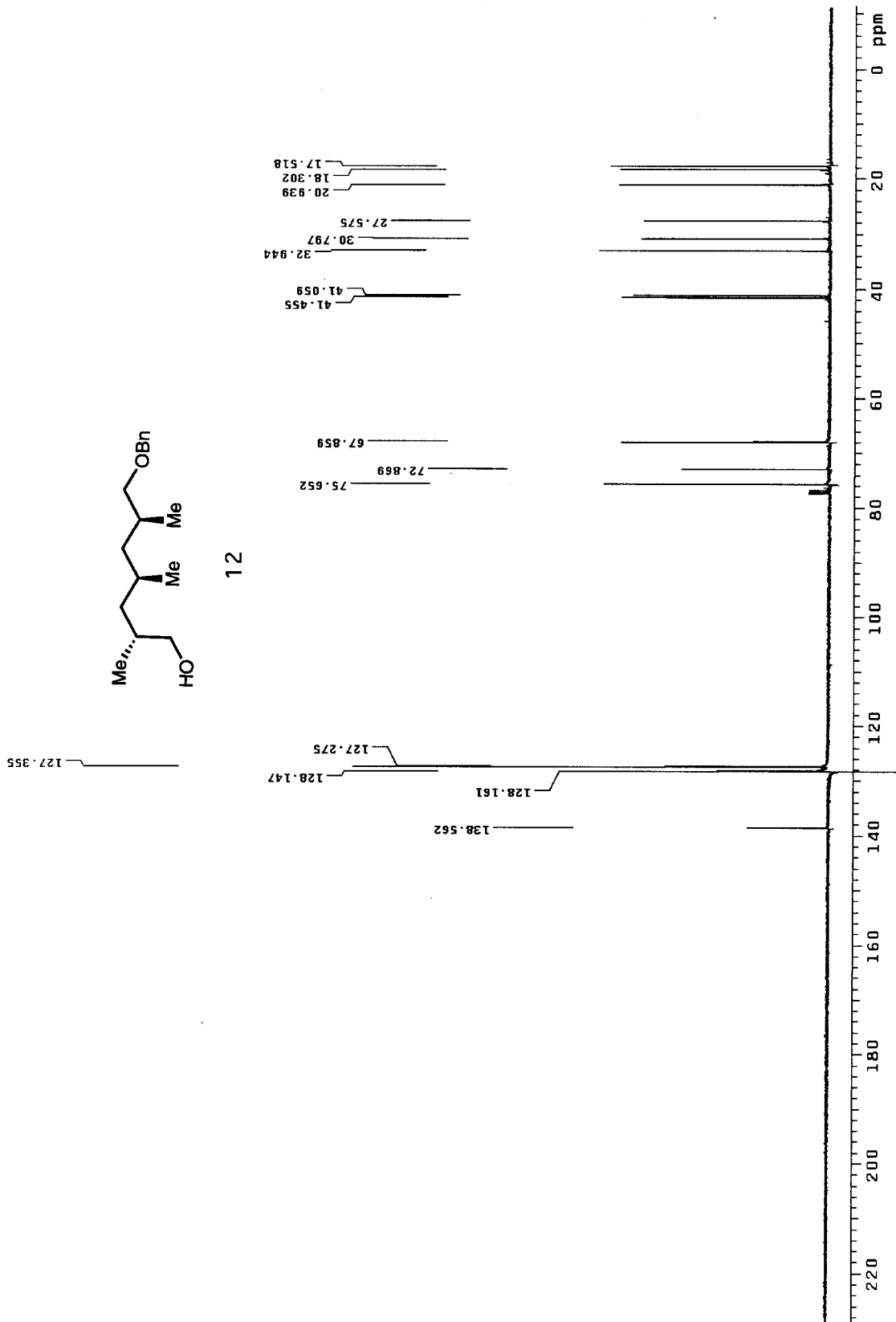
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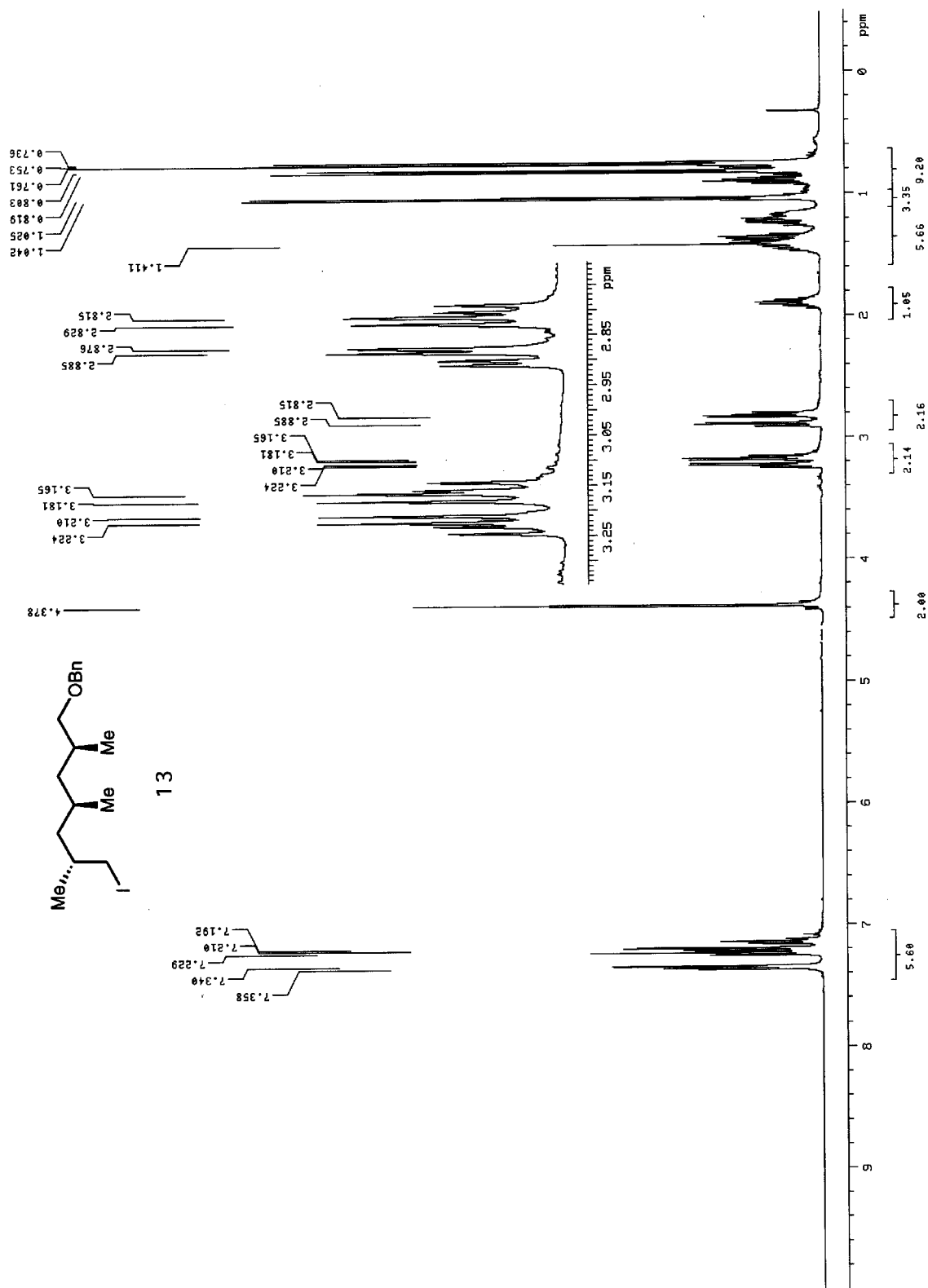


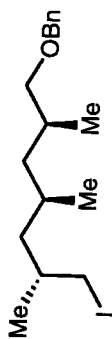












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