CuH-Catalyzed Reductive Aldol Reactions Generating Three Contiguous Asymmetric Stereocenters

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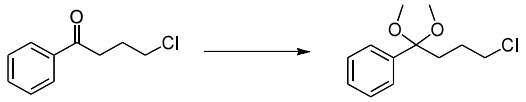
Supporting Information

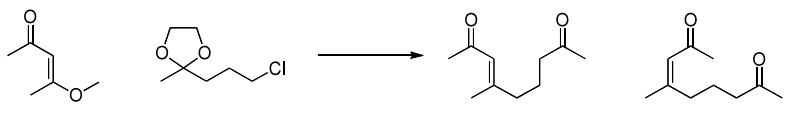
General considerations. All experiments were conducted under an argon atmosphere, in oven dried glassware with magnetic stirring, unless otherwise specified. All ligands were handled in a glove box under an inert atmosphere. Toluene and THF were freshly distilled from Na/benzophenone ketyl prior to use. Thin layer chromatography was performed using EM Science 60-F_{254} (250 nm) silica gel precoated plates; EM Science cat. No. 5714-3. Flash chromatography was performed using 200–425 mesh silica gel (Type 60A Grade 633) available from Fisher Scientific. Melting points were collected on a Fisher-Johns melting point apparatus. FT-IR spectra were recorded using a Jasco FT/IR-430 infrared spectrometer with either neat samples on NaCl plates, or KBr pellets. HRMS spectra were recorded at the UCSB mass spectrometry facility by Dr. James Pavlovich using a Micromass VG 70e magnetic sector by EI standard methods or a PE Sciex QStar quadrapole/time-of-flight tandem mass spectrometer by ESI standard methods. NMR spectra were recorded using Varian Inova spectrometers either at 400 or 500 MHz for ^{1}H, and 100 or 125 MHz for ^{13}C in $CDCl_3$ (5 mm tubes). Chemical shifts are referenced to chloroform solvent residual peaks (^{1}H = 7.27 ppm, ^{13}C = 77.23 ppm). Optical rotations were measured on a Perkin Elmer model 341 polarimeter. Chiral HPLC data was collected using a Shimadzu SPD-m20a Prominence diode array detector. Specified HPLC columns were manufactured by Daicel Chemical Industries Ltd. and equilibrated prior to use.

Preparation of keto enones



(4-Chloro-1,1-dimethoxybutyl)benzene. Trimethylorthoformate (10 mL) and 4-chlorobutyrophenone (2.1 mL, 13.1 mmol) were added to Montmorillonite K10 clay (~2 g) and stirred for 3 d. The reaction mixture was filtered though Celite, concentrated, and purified by Kugelrohr distillation to give the dimethyl ketal (2.84 g, 95%) as a colorless to light yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.43 (2 H, m), 7.38-7.25 (3 H, m), 3.37 (2 H, t, J = 6.4 Hz), 3.17 (6 H, s), 2.07-2.01 (2 H, m), 1.50-1.42 (2 H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.7, 128.3, 128.0, 127.0, 103.3, 48.8, 45.1, 34.7, 27.1; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{12}H_{17}O_2NaCl$: 251.0809, found: 251.0802.

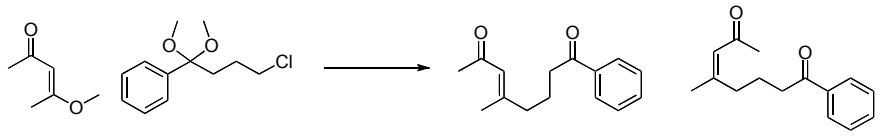
General procedure (Table 2, entries 1–5, 10). Lithium-high sodium (Li-Na 99%, ~0.5% Na, 451 mg, 65.0 mmol) and naphthalene (83.2 mg, 0.650 mmol) were stirred under an argon atmosphere for 2 h. THF (20 mL) was added and the heterogeneous solution was stirred an additional hour. The solution was cooled to –78 ˚C followed by the addition of alkyl chloride (13.0 mmol), and was strirred at that temperature for 2 h. Vinylogous ester (10.8 mmol) was then added and the mixture was allowed to warm to rt slowly and stir overnight. The reaction mixture was cooled to 0 ˚C, diluted with Et_2O (20 mL) and quenched with 3 M HCl (25 mL), then stirred for 1-3 h. The organic layer was separated, followed by extraction of the aqueous layer with Et_2O (2 x 25 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, concentrated, and then purified through a column of silica gel providing the corresponding keto enones. Enone geometries in the product(s) were determined by 1D nOe experiments.



E-**1** *Z*-**1**

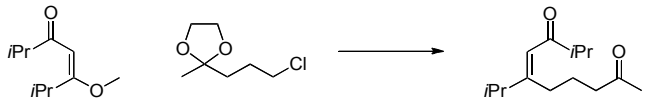
***E*-Keto enone (*E*-1, Table 2, entry 1).** Colorless oil: 52% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (1 H, d, *J* = 1.2 Hz), 2.42 (2 H, t, *J* = 7.6 Hz), 2.16 (3 H, s), 2.13 (3 H, s), 2.10 (2 H, t, *J* = 7.6 Hz), 2.09 (3 H, d, *J* = 0.8 Hz), 1.74 (2 H, m, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 199.0, 157.7, 124.1, 42.8, 40.3, 32.0, 30.2, 21.4, 19.3; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{10}H_{16}O_2$: 168.1150, found: 168.1144.

***Z*-Keto enone (*Z*-1, Table 2, entry 2).** Colorless oil; 28% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.08 (1 H, br s), 2.54 (2 H, t, *J* = 7.6 Hz), 2.47 (2 H, t, *J* = 7.6 Hz), 2.14 (3 H, s), 2.13 (3 H, s), 1.86 (3 H, d, *J* = 1.2 Hz), 1.72 (2 H, m, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.2, 198.5, 158.6, 124.7, 43.4, 32.8, 32.0, 30.2, 25.4, 22.2; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{10}H_{16}O_2$: 168.1150, found: 168.1145.

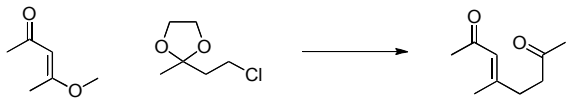


***E*-Keto enone (Table 2, entry 3).** Colorless oil; 38% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98-7.87 (2 H, m), 7.57 (1 H, br tt, *J* = 7.2, 1.2 Hz), 7.47 (2 H, br t, *J* = 7.6 Hz), 6.09 (1 H, br s), 2.98 (2 H, t, *J* = 7.2 Hz), 2.22 (2 H, br t, *J* = 7.2 Hz), 2.15 (3 H, s), 2.14 (3 H, d, *J* = 1.2 Hz), 1.95 (2 H, m, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.8, 199.0, 157.8, 137.1, 133.3, 128.8, 128.2, 124.2, 40.5, 37.7, 32.0, 21.9, 19.4; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{15}H_{18}O_2$: 230.1307, found: 230.1309.

***Z*-Keto enone (Table 2, entry 4).** Colorless oil; 19% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.94 (2 H, m), 7.55 (1 H, br tt, *J* = 7.2, 0.8 Hz), 7.45 (2 H, br t, *J* = 7.2 Hz), 6.10 (1 H, br s), 3.04 (2 H, t, *J* = 7.6 Hz), 2.67 (2 H, br t, *J* = 7.6 Hz), 2.14 (3 H, s), 1.91 (2 H, m, *J* = 7.6 Hz), 1.91 (3 H, d, *J* = 0.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.4, 198.5, 158.8, 137.2, 133.1, 128.7, 128.2, 124.8, 38.4, 33.0, 32.0, 25.4, 22.7; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{15}H_{18}O_2$: 230.1307, found: 230.1308.

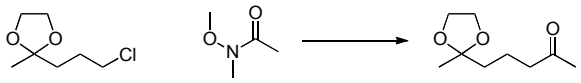


***E*-Keto enone (Table 2, entry 5).** Colorless oil; 41% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (1 H, br s), 2.60 (1 H, m, *J* = 7.0 Hz), 2.51 (2 H, t, *J* = 7.5 Hz), 2.46 (2 H, br t, *J* = 7.5 Hz), 2.37 (1 H, m, *J* = 7.0 Hz), 2.13 (3 H, s), 1.71-1.64 (2 H, m), 1.07 (6 H, d, *J* = 1.5 Hz), 1.06 (6 H, d, *J* = 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.3, 205.1, 168.9, 120.0, 44.0, 41.9, 36.6, 31.4, 30.1, 23.5, 21.8, 18.6; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{14}H_{24}O_2$: 224.1776, found: 224.1776.

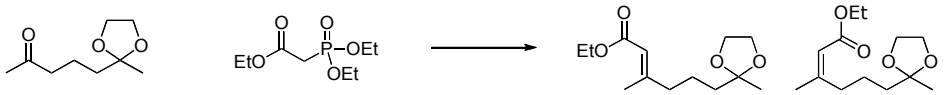


***E*-Keto enone (Table 2, entry 10).** Colorless oil; 37%% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.04 (1 H, d, *J* = 1.0 Hz), 2.60 (2 H, t, *J* = 9.5 Hz), 2.37 (2 H, t, *J* = 9.5 Hz), 2.155 (3 H, s), 2.150 (3 H, s), 2.09 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.3, 198.9, 156.6, 124.0, 41.3, 34.7, 32.0, 30.2, 19.4; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_9H_{14}O_2$: 154.0994, found: 154.0992.

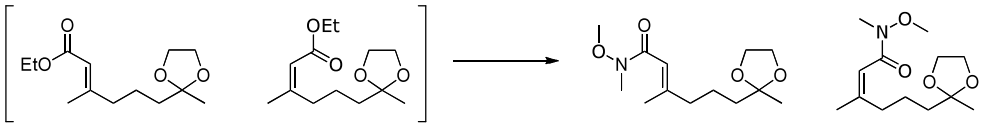
Preparation of additional keto enones (Table 2, entries 6–9)



5-(2-Methyl-1,3-dioxolan-2-yl)pentan-2-one. A dry, air free 100 mL round bottom flask was charged with lithium-high sodium (Li-Na 99%, ~0.5% Na, 450 mg, 64.8 mmol) and naphthalene (180 mg, 1.4 mmol). Dry THF (40 mL) was added and the contents of the flask were stirred at rt (notable color change to dark green) for 10 min before being cooled in a CO_2/acetone bath. Neat 2-(3-chloropropyl)-2-methyl-1,3-dioxolane (3.13 mL, 20.7 mmol) was added dropwise over 5 min (notable color change to light green) and the reaction was stirred in the CO_2/acetone bath for 2 h. Neat *N*-methoxy-*N*-methylacetamide (2.0 mL, 18.8 mmol) was added dropwise over 3 min. The reaction is allowed to slowly warm to rt over 3 h and stirred for an additional 8 h before being poured into 150 mL of saturated aqueous NH_4Cl. The quenched reaction is stirred for 3 h then extracted with Et_2O (3 x 150 mL) and the combined organic layers are washed with brine (1 x 100 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield a yellow oil. The crude product was purified through a column of silica gel (3:1 hexanes/Et_2O) to yield a colorless oil (2.10 g, 66%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.98-3.89 (4 H, m), 2.46 (2 H, t, J = 7.2 Hz), 2.14 (3 H, s), 1.74-1.59 (4 H, m), 1.32 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 110.0, 64.8, 43.8, 38.4, 30.1, 23.9, 18.5; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_9H_{13}O_3Na$: 195.0992, found: 195.0996.

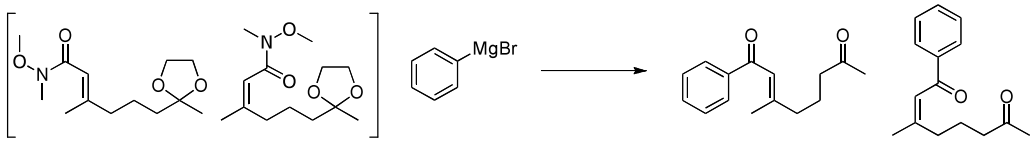


Ethyl-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)hex-2-enoate. A dry, air free 100 mL round bottom flask was charged with sodium-*tert*-butoxide (1.41 g, 14.7 mmol). THF (30 mL) was added and the suspension is cool in an ice bath. Neat diethylphosphonoacetic acid ethyl ester (2.9 mL, 14.9 mmol) was added dropwise over 3 min to form a clear solution which was stirred an additional 20 min submerged in an ice bath. A solution of 5-(2-methyl-1,3-dioxolan-2-yl)pentan-2-one (2.0 g, 11.6 mmol) in THF (6 mL) was added to the reaction via cannula. The reaction was heated in a 50 ˚C oil bath and stirred for 11 h before being concentrated under vacuum. Et_2O (50 mL) was added and the organic layer was washed with saturated aqueous NH_4Cl (50 mL), then H_2O (50 mL) and finally brine (50 mL) before being dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified through a column of silica gel (4:1 hexanes/Et_2O) to yield a colorless oil consisting of two inseparable isomers (2.69 g, 96%). NMR: mixture of isomers; see spectra; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{13}H_{22}O_4Na$: 265.1410, found: 265.1418.



***N*-Methoxy-*N*,3-dimethyl-6-(2-methyl-1,3-dioxolan-2-yl)hex-2-enamide.** *N,O*-dimethylhydroxylamine hydrochloride (2.16 g, 22.2 mmol) and THF (22 mL) were added to a dry, air free 100 mL round bottom flask charged with ethyl-3-methyl-6-(2-methyl-1,3-dioxolan-2-yl)hex-2-enoate (2.69 g, 11.1 mmol) and the solution was stirred at rt for 5 min before being cooled in a -15 ˚C bath. A solution of *i*-PrMgCl (2.0 M in Et_2O, 44.4 mmol) was added dropwise over 15 min causing a heavy precipitate to form. Stirring was continued by manually agitating the flask. Following total addition of the Grignard reagent, the flask was removed from the cooling bath and the reaction was stirred at rt for

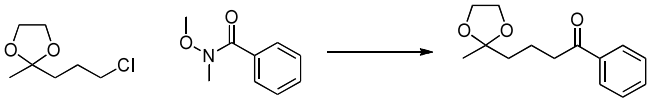
20 min. The reaction was poured into 100 mL of saturated aqueous NH_4Cl and stirred for 3 h. The quenched mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL) and dried over anhydrous Na_2SO_4 before being concentrated under vacuum. The crude product was purified through a column of silica gel (3:2 hexanes/EtOAc) to yield a colorless oil consisting of two isomers (1.78 g, 62%). NMR: mixture of isomers; see spectra; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{13}H_{23}NO_4Na$: 280.1519, found: 280.1528.



3-Methyl-1-phenyloct-2-ene-1,7-dione. A dry, air free 50 mL round bottom flask was charged with magnesium turnings (0.7 g, 28.8 mmol). The turnings were stirred vigorously for 10 min before adding THF (20 mL). Neat bromobenzene (1.5 mL, 14.2 mmol) was added to the stirring magnesium and the reaction is stirred for 3 h at rt. The phenylmagnesium bromide in THF was transferred to a dry flask containing a 0 ˚C solution of the Weinreb amide (1.78 g, 6.90 mmol) in THF (12 mL). The reaction was stirred for 30 min at 0 ˚C before adding 36 mL 1 M $HCl_{(aq)}$ and stirring overnight. The reaction was extracted with Et_2O (3 x 25 mL). The combined organic layers were washed with brine (1 x 30 mL) and dried over anhydrous Na_2SO_4 before being concentrated under vacuum. The crude product was purified through a column of silica gel (3:1 to 2:1 hexanes/Et_2O) to separate both *E* and *Z* isomers as colorless oils (1.25 g, 79%, 63:37 *E:Z*).

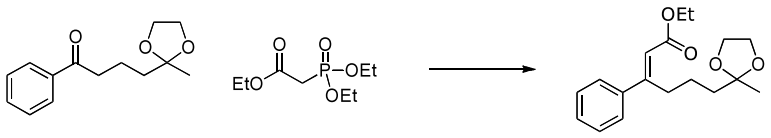
***E*-Keto enone (Table 2, entry 6).** 790 mg, 50%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-7.89 (2 H, m, *J* = 7.2 Hz), 7.53 (1 H, m, *J* = 7.2, 1.6 Hz), 7.48-7.42 (2 H, m, *J* = 7.2 Hz), 6.73 (1 H, d, *J* = 1.5 Hz), 2.49 (2 H, t, *J* = 7.2 Hz), 2.27 (2 H, t, *J* = 7.6 Hz), 2.19 (3 H, d, *J* = 1.5 Hz), 2.16 (3 H, s), 1.85 (2 H, qt, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 191.8, 159.2, 139.3, 132.6, 128.7, 128.4, 121.2, 42.8, 40.6, 30.3, 21.5, 19.8; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{15}H_{18}O_2$: 230.1317, found: 230.1307.

***Z*-Keto enone (Table 2, entry 7).** 460 mg, 29%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94-7.91 (2 H, m), 7.56-7.51 (1 H, m), 7.48-7.43 (2 H, m), 6.77 (1 H, s), 2.62 (2 H, t, *J* = 8 Hz), 2.55 (2 H, t, *J* = 7.5 Hz), 2.16 (3 H, s), 2.03 (3 H, d, *J* = 1.5 Hz), 1.83 (2 H, qn, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 191.3, 160.0, 139.3, 132.6, 128.7, 128.4, 122.0, 43.4, 33.5, 30.2, 25.7, 22.3; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{15}H_{18}O_2$: 230.1307, found: 230.1314.

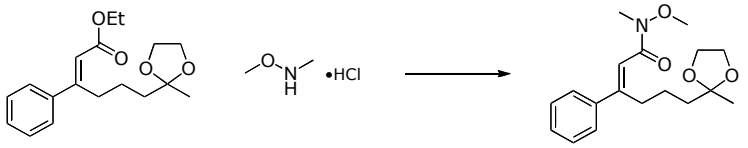


4-(2-Methyl-1,3-dioxolan-2-yl)-1-phenylbutan-1-one. A dry, air free 50 mL round bottom flask was charged with lithium-high sodium (Li-Na 99%, ~0.5% Na, 300 mg, 43.2 mmol) and naphthalene (100 mg, 0.8 mmol). Dry THF (30 mL) was added and the contents of the flask were stirred at rt (notable color change to dark green) for 15 min before being cooled in a CO_2/acetone bath. Neat 2-(3-chloropropyl)-2-methyl-1,3-dioxolane (2.4 mL, 15.9 mmol) was added dropwise over 5 min (notable color change to light green) and the reaction was stirred in the CO_2/acetone bath for 1.5 h. Neat *N*-methoxy-*N*-methylbenzamide (2.39 g, 14.4 mmol) was added dropwise over 5 min. The reaction was allowed to slowly warm to rt over 3 to 5 h and stirred for an additional 8 h before being poured into 150 mL of saturated $NH_4Cl_{(aq)}$. The quenched reaction was stirred for 3 h then extracted with Et_2O (3 x 100 mL) and the combined organic layers were washed with brine (1 x 100 mL), dried over anhydrous

Na_2SO_4 and concentrated under vacuum to yield an orange oil. The crude product was purified through a column of silica gel (3:1 hexanes/Et_2O) to yield a colorless oil (2.51 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98-7.95 (2 H, m, J = 8.5, 1.5 Hz), 7.56 (1 H, tt, 7.5, 1.5 Hz), 7.49-7.45 (2 H, m, J = 7.5, 1.5 Hz), 3.98-3.92 (4 H, m), 3.02 (2 H, t, J = 7.0 Hz), 1.90-1.84 (2 H, m), 1,78-1.73 (2 H, m), 1.35 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.3, 137.2, 133.1, 128.8, 128.2, 110.1, 64.9, 38.7, 38.6, 24.0, 19.0; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{14}H_{18}O_3Na$: 257.1148, found: 257.1160.

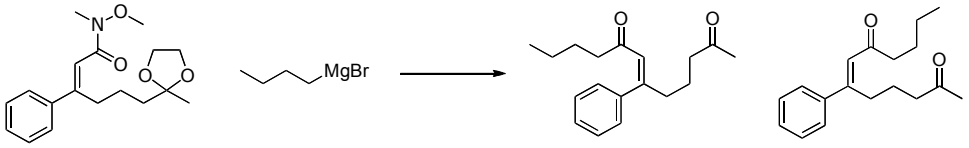


Ethyl 6-(2-methyl-1,3-dioxolan-2-yl)-3-phenylhex-2-enoate. A dry, air free 250 mL round bottom flask was charged with sodium-*tert*-butoxide (2.86 g, 29.8 mmol). THF (60 mL) was added and the suspension cooled in an ice bath. Neat diethylphosphonoacetic acid ethyl ester (6.2 mL, 31.8 mmol) was added dropwise over 5 min to form a clear solution which was stirred an additional 20 min submerged in an ice bath. A solution of 4-(2-methyl-1,3-dioxolan-2-yl)-1-phenylbutan-1-one (4.97 g, 21.2 mmol) in THF (10 mL) was added to the reaction through a cannula. The reaction was heated in a 50 ˚C oil bath and stirred overnight before being concentrated under vacuum. Et_2O (100 mL) was added and the organic layer was washed with saturated aqueous NH_4Cl (2 x 150 mL), then H_2O (150 mL) and finally brine (150 mL) before being dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified through a column of silica gel (4:1 hexanes/Et_2O) to yield a colorless oil consisting of two isomers (6.11 g, 95 %); the less polar isomer was isolated. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.41 (2 H, m), 7.39-7.34 (3 H, m), 6.03 (1 H, s), 4.21 (2 H, q, J = 7.0 Hz), 3.92-3.83 (4 H, m), 3.13 (2 H, t, J = 7.5 Hz), 1.71-1.67 (2 H, m), 1.57-1.49 (2 H, m), 1.32 (3 H, t, J = 7.5 Hz), 1.25 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.6, 160.6, 141.5, 129.1, 128.7, 126.9, 117.9, 110.1, 64.7, 60.1, 38.9, 31.0, 23.9, 23.7, 14.5; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{18}H_{24}O_4Na$: 327.1591, found: 327.1581.



***N*-Methoxy-*N*-methyl-6-(2-methyl-1,3-dioxolan-2-yl)-3-phenylhex-2-enamide.** *N,O*-dimethylhydroxylamine hydrochloride (2.10 g, 22.2 mmol) and THF (22 mL) were added to a dry, air free 100 mL round bottom flask charged with ethyl 6-(2-methyl-1,3-dioxolan-2-yl)-3-phenylhex-2-enoate (3.27 g, 10.7 mmol) and the solution was stirred at rt for 5 min before being cooled in a -15 ˚C bath. A solution of *i*-PrMgCl (2.0 M in Et_2O, 42.8 mmol) was added dropwise over 15 min causing a heavy precipitate to form. Stirring was continued by manually agitating the flask. Following total addition of the Grignard reagent, the flask was removed from the cooling bath and the reaction was stirred at rt for 1 h. The reaction was poured into 100 mL of saturated aqueous NH_4Cl and stirred for 3 h. The quenched mixture was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with brine (1 x 100 mL) and dried over anhydrous Na_2SO_4 before being concentrated under vacuum. The crude product was purified through a column of silica gel (3:2 hexanes/EtOAc) to yield a colorless oil (2.44 g, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45-7.41 (2 H, m, J = 6.5, 1.5 Hz), 7.40-7.33 (3 H, m), 6.46 (1 H, br s), 3.91-3.82 (4 H, m), 3.70 (3 H, s), 3.27 (3 H, s), 3.07 (2 H, t, J = 7.5 Hz), 1.71-1.65 (2 H, m), 1.56-1.47 (2 H, m), 1.24 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 128.7, 128.6, 127.0, 110.2, 64.7,

61.8, 38.9, 31.1, 23.8, 23.6; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{18}H_{25}NO_4Na$: 342.1676, found: 342.1679.

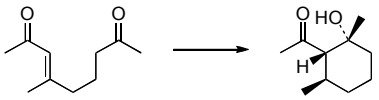


6-Phenyldodec-6-ene-2,8-dione. A dry, air free 25 mL round bottom flask was charged with magnesium turnings (100 mg, 4.1 mmol). The turnings were stirred vigorously for 2 h before adding THF (5 mL). After the flask was cooled in an ice/brine bath, neat 1-bromobutane (180 μL, 1.7 mmol) was added and the reaction was stirred for 3 h while warming to rt. The butylmagnesium bromide in THF was transferred to a dry flask containing a 0 ˚C solution of the Weinreb amide (0.26 g, 0.8 mmol) in THF (1 mL). The reaction was stirred for 2 h at 0 ˚C before adding 10 mL 1 M HCl and stirring overnight. The reaction was extracted with Et_2O (3 x 20 mL). The combined organic layers were washed with brine (1 x 20 mL) and dried over anhydrous Na_2SO_4 before being concentrated under vacuum. The crude product was purified through a column of silica gel (4:1 to 2:1 hexanes/Et_2O) to separate the *E* and *Z* isomers as colorless oils (200 mg, 93%, 67:33 *E:Z*).

***Z*-Keto enone (Table 2, entry 8).** 70 mg, 31%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50-7.46 (2 H, m), 7.41-7.36 (3 H, m), 6.45 (1 H, s), 3.03 (2 H, t, *J* = 7.5 Hz), 2.54 (2 H, t, *J* = 7.5 Hz), 2.51 (2 H, t, *J* = 7.5 Hz) 2.10 (3 H, s), 1.71 (2 H, qn, *J* = 7.5 Hz), 1.66-1.59 (2 H, m, *J* = 7.5 Hz), 1.36 (2 H, sex, *J* = 7.5 Hz), 0.93 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.1, 201.4, 158.0, 141.4, 129.3, 128.9, 127.0, 125.0, 44.9, 43.5, 30.4, 30.1, 26.6, 23.3, 22.6, 14.2; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{18}H_{24}O_2$: 272.1776, found: 272.1774.

***E*-Keto enone (Table 2, entry 9).** 130 mg, 62%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38-7.32 (3 H, m), 7.16-7.14 (2 H, m, *J* = 7.5, 1.5 Hz), 6.09 (1 H, s), 2.45 (2 H, t, *J* = 7.5 Hz), 2.44 (2 H, t, *J* = 7.5 Hz), 2.11 (2 H, t, *J* = 7.5 Hz), 2.11 (3 H, s), 1.67 (2 H, qn, *J* = 7.5 Hz), 1.40 (2 H, qn, *J* = 7.5 Hz), 1.12 (2 H, sex, 7.5 Hz), 0.77 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.4, 203.2, 154.8, 140.0, 128.6, 128.4, 127.7, 127.6, 42.9, 42.7, 39.5, 30.2, 26.5, 22.4, 21.7, 14.0; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{18}H_{24}O_2$: 272.1776, found: 272.1780.

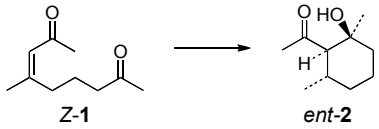
Reductive Aldol Cyclizations



E-**1** **2**

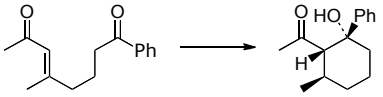
Representative procedure for enantioselective reductive aldol cyclizations. 1-((1*S*,2*R*,6*R*)-2-Hydroxy-2,6-dimethylcyclohexyl)ethanone (2, Table 2, entry 1). $Cu(OAc)_2$ (3.6 mg, 0.018 mmol) and (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 2.2 mg, 0.004 mmol) were added to a flame dried argon purged flask. Toluene (0.75 mL) was added and the suspension was stirred at 0 ˚C for 30 min. The flask was cooled to -20 ˚C and diethoxymethylsilane (DEMS; 81 μL, 0.508 mmol) was added and stirred an additional 30 min at that temperature. A solution of *E*-**1** (61 mg, 0.363 mmol in 0.75 mL toluene) was then added and the reaction mixture was allowed to warm to -10 ˚C and stirred an additional 12 h. A solution of NH_4F (~1 M in MeOH) was added dropwise and stirred at rt for 2 h to quench the reaction, followed by

dilution with saturated aqueous $NaHCO_3$. The resulting solution was extracted with Et_2O, dried over anhydrous $MgSO_4$, filtered, and then purified through a column of silica gel (17:1 hexanes/EtOAc) providing product **2** (56 mg, 91% yield) as a volatile white solid: R_f 0.35 (4:1 hexanes/EtOAc); mp 71–71.5 ˚C; IR (cm^{-1}) 3483, 2959, 2930, 2863, 2843, 1679, 1467, 1455, 1440, 1383; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (1 H, d, J = 2.0 Hz), 2.26 (3 H, d, J = 0.4 Hz), 2.24 (1 H, d, J = 11.6 Hz), 2.04-1.92 (1 H, m), 1.77 (1 H, qt, J = 13.6, 4.0 Hz), 1.71-1.64 (2 H, m), 1.50-1.43 (1 H, m), 1.17 (1 H, tdd, J = 13.2, 4.0, 2.4 Hz), 1.13 (3 H, s), 0.98-0.85 (1 H, m), 0.86 (3 H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.3, 70.3, 64.6, 38.6, 35.5, 34.6, 32.0, 29.9, 21.0, 20.7; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{10}H_{18}O_2$: 170.1307, found: 170.1314. HPLC conditions: Chiralpak AD-H column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, t = 10.8 min (major), 8.6 min (minor), indicating an ee of 96%.

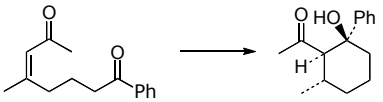


Z-**1** *ent*-**2**

1-((1*R*,2*S*,6*S*)-2-Hydroxy-2,6-dimethylcyclohexyl)ethanone (*ent*-2, Table 2, entry 2). According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (3.0 mg, 0.015 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.6 mg 0.003 mmol), toluene (0.60 mL), DEMS (72 μL, 0.45 mmol), *Z*-**1** (50 mg, 0.300 mmol in 0.60 mL toluene). The product was isolated (*ent*-**2**, 45 mg, 88%) with 96% ee. Spectroscopic data were identical to those reported for reductive aldol product **2**. HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{10}H_{18}O_2$: 170.1307, found: 170.1310. Chiralpak AD-H column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, t = 8.6 min (major), 10.8 min (minor).

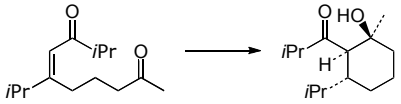


1-((1*S*,2*R*,6*R*)-2-Hydroxy-6-methyl-2-phenylcyclohexyl)ethanone (Table 2, entry 3). According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (1.6 mg, 0.008 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.1 mg 0.002 mmol), toluene (0.30 mL), DEMS (36 μL, 0.225 mmol), *E*-enone (35 mg, 0.150 mmol in 0.30 mL toluene). Chromatography on silica gel (19:1 hexanes/EtOAc) gave 27 mg (77%) of the product with 97% ee. R_f 0.42 (9:1 hexanes/EtOAc); mp 79.5–80.5 °C; IR (cm^{-1}) 3439, 2947, 2928, 2852, 1679, 1445, 1392, 1360, 1326; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (2 H, br d, J = 8.0 Hz), 7.32 (2 H, br t, J = 7.6 Hz), 7.21 (1 H, br tt, J = 7.2, 1.2 Hz), 4.39 (1 H, d, J = 2.4 Hz), 2.80 (1 H, d, J = 11.2 Hz), 2.24-2.07 (1 H, m), 2.03-1.88 (1 H, m), 1.82-1.55 (4 H, m), 1.73 (3 H, s), 1.12 (1 H, qd, J = 13.2, 4.0), 0.91 (3 H, d, J = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 217.8, 147.4, 128.5, 127.0, 124.9, 74.6, 64.6, 39.0, 35.2, 34.4, 32.3, 21.4, 20.9; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{15}H_{20}O_2Na$: 255.1356, found: 255.1355. HPLC conditions: Chiralpak OD-R column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, t = 5.0 min (major), 6.0 min (minor).

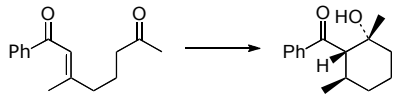


1-((1*R*,2*S*,6*S*)-2-Hydroxy-6-methyl-2-phenylcyclohexyl)ethanone (Table 2, entry 4). According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (1.6 mg, 0.008 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.1 mg 0.002 mmol), toluene (0.30 mL), DEMS (36 μL, 0.225 mmol), *Z*-enone (35 mg, 0.150 mmol in 0.30 mL toluene). The product was isolated (26 mg, 75%) with 97% ee.

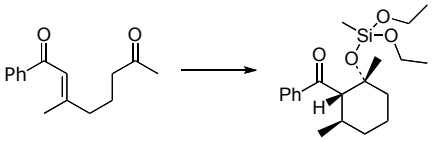
Spectroscopic data were identical to those reported for the reductive aldol product reported for entry 3. HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{15}H_{20}O_2Na$: 255.1356, found: 255.1361. HPLC conditions: Chiralpak OD-R column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, *t* = 6.0 min (major), 5.0 min (minor).



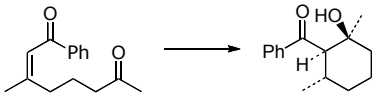
1-((1*R*,2*S*,6*R*)-2-hydroxy-6-isopropyl-2-methylcyclohexyl)-2-methylpropan-1-one (Table 2, entry 5). According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (1.6 mg, 0.008 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.1 mg 0.002 mmol), toluene (0.30 mL), DEMS (36 μL, 0.225 mmol), *E*-enone (34 mg, 0.150 mmol in 0.30 mL toluene). Chromatography on silica with (19:1 hexanes/EtOAc) gave 22 mg (66%) with 84% ee. R_f 0.60 (4:1 hexanes/EtOAc); mp 48.5–49.5 ˚C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.10 (1 H, d, *J* = 2.4 Hz), 2.65 (1 H, d, *J* = 11.6 Hz), 2.63 (1 H, m, *J* = 6.8 Hz), 1.98 (1 H, br tt, *J* = 11.6, 2.0 Hz), 1.80-1.62 (3 H, m), 1.56-1.49 (1 H, m), 1.49-1.29 (1 H, m), 1.22-1.12 (1 H, m), 1.15 (3 H, d, *J* = 6.8 Hz), 1.10 (3 H, s), 1.06 (3 H, d, *J* = 6.8 Hz), 0.99-0.85 (1 H, m), 0.90 (3 H, d, *J* = 6.8 Hz), 0.86 (3 H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.3, 71.2, 58.8, 44.0, 43.4, 39.3, 31.1, 29.1, 23.8, 22.1, 21.0, 18.5, 17.0, 16.4; HRMS (+ESI/TOF) *m/z*: $(M+Na)^+$ calcd for $C_{14}H_{26}O_2Na$: 249.1825, found: 249.1825. HPLC conditions: Chiralpak AD-H column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, *t* = 8.9 min (major), 6.3 min (minor).



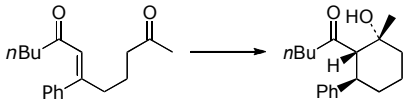
((1*S*,2*R*,6*R*)-2-Hydroxy-2,6-dimethylcyclohexyl)(phenyl)methanone (Table 2, entry 6). $Cu(OAc)_2$ (2.5 mg, 0.0125 mmol) and (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 4.1 mg, 0.0075 mmol) were added to a flame dried argon purged flask. Toluene (0.5 mL) was added and the suspension was stirred at rt for 30 min. The flask was cooled to 0 ˚C and diethoxymethylsilane (DEMS; 80 μL, 0.50 mmol) was added and stirred an additional 5 min at that temperature before being cooled to -20 ˚C. A solution of enone (58 mg, 0.250 mmol in 0.5 mL toluene) was then added and the reaction mixture was stirred an additional 14 h. The reaction was filtered through a short plug of silica gel before being concentrated under vacuum. Chromatography on silica (4:1 hexanes/Et_2O) gave 23 mg of the free alcohol reductive aldol product and 53 mg of the silyl-protected reductive aldol product (see entry below); both are colorless oils (98%); 85% ee (free alcohol product). R_f 0.40 (3:1 hexanes/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (1 H, m, *J* = 7.5 Hz), 7.51 (2 H, m, *J* = 7.5 Hz), 4.20 (1 H, d, *J* = 2.5 Hz), 3.17 (1 H, d, *J* = 11 Hz), 2.26-2.15 (1 H, m), 1.91 (1 H, qt, *J* = 13.5, 4.0 Hz), 1.81-1.75 (2 H, m), 1.58-1.52 (1 H, m), 1.30 (1 H, tdd, *J* = 13.5, 4.0, 2.5 Hz), 1.08 (3 H, s), 0.76 (3 H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.3, 139.1, 133.9, 129.0, 128.5, 71.0, 57.9, 38.9, 34.9, 32.9, 30.4, 21.2, 21.1; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{15}H_{20}O_2$: 232.1463, found: 232.1464; HPLC conditions: Chiralcel OD-H, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, *t* = 5.24 min (major), 4.95 min (minor).



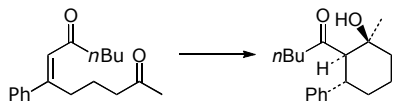
((1*S*,2*R*,6*R*)-2-(Diethoxy(methyl)silyloxy)-2,6-dimethylcyclohexyl)(phenyl)methanone. R_f 0.60 (3:1 hexanes/Et_2O); ^1H NMR (500 MHz, $CDCl_3$) δ 7.93 (2 H, d, *J* = 8.0 Hz), 7.54 (1 H, m, *J* = 7.5 Hz), 7.46 (2 H, t, *J* = 8.0 Hz), 3.88-3.77 (4 H, m), 3.02 (1 H, d, *J* = 10.5 Hz), 2.45-2.33 (1 H, m), 1.89-1.77 (3 H, m), 1.58-1.52 (1 H, m), 1.43-1.35 (1 H, m), 1.25-1.16 (9 H, m), 1.10-1.00 (1 H, m), 0.79 (3 H, d, *J* = 6.5 Hz), 0.11 (3 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ 202.2, 140.9, 132.5, 128.7, 128.2, 74.1, 58.4, 58.3, 41.3, 34.6, 30.7, 30.4, 21.3, 20.9, 18.51, 18.48, -4.3; HRMS (EI^+) *m/z*: $(M-C_2H_5O)^+$ calcd for $C_{18}H_{27}SiO_3$: 319.1729, found: 319.1721.



((1*R*,2*S*,6*S*)-2-Hydroxy-2,6-dimethylcyclohexyl)(phenyl)methanone (Table 2, entry 7). According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (2.5 mg, 0.0125 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.4 mg 0.0025 mmol), toluene (0.50 mL), DEMS (80 μL, 0.50 mmol), *Z*-enone (58 mg, 0.25 mmol in 0.50 mL toluene). The reaction was filtered through a short plug of silica gel before being concentrated under vacuum. Chromatography on silica (4:1 hexanes/Et_2O) gave 15 mg of the reductive aldol product and 66 mg of the silyl-protected reductive aldol product (see entry above); both are colorless oils (98% combined yield); 75% ee (free alcohol product). Spectroscopic data were identical to those reported for the reductive aldol product reported for entry 6; HPLC conditions: Chiralcel OD-H, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, *t* = 5.97 min (major), 6.62 min (minor).



1-((1*S*,2*R*,6*R*)-2-Hydroxy-2-methyl-6-phenylcyclohexyl)pentan-1-one (Table 2, entry 8). According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (2.5 mg, 0.0125 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.4 mg 0.0025 mmol), toluene (0.50 mL), DEMS (80 μL, 0.50 mmol), *Z*-enone (68 mg, 0.25 mmol in 0.50 mL toluene). Reaction was complete after 26 h at -10 ˚C. The reaction was filtered through a short plug of silica gel before being concentrated under vacuum and treated with 1.0 M TBAF in THF. Chromatography on silica (9:1 to 4:1 hexanes/ Et_2O) gave 57 mg of a white solid (83%) with 77% ee. R_f 0.60 (2:1 hexanes/Et_2O); mp 50–51 ˚C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30-7.26 (2 H, m), 7.20 (1 H, m, *J* = 7.5 Hz), 7.18-7.15 (2 H, m), 4.23 (1 H, d, *J* = 2.5 Hz), 3.11 (1 H, td, *J* = 12.5, 4.0 Hz), 2.68 (1 H, d, *J* = 11.5 Hz), 2.07 (1 H, ddd, *J* = 18.0, 8.5, 6.0 Hz), 1.95 (1 H, qt, 13.5, 3.5 Hz), 1.89-1.84 (1 H, m), 1.82-1.76 (1 H, m), 1.66-1.58 (2 H, m), 1.53 (1 H, ddd, *J* = 18.0, 8.5, 6.5 Hz), 1.34 (1 H, tdd, *J* = 13.5, 3.0, 1.5 Hz), 1.25-1.14 (1 H, m), 1.16 (3 H, s), 1.10-1.00 (1 H, m), 0.99-0.85 (2 H, m), 0.67 (3 H, t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 219.5, 143.7, 128.8, 127.9, 127.0, 70.7, 63.5, 47.2, 44.0, 38.5, 33.0, 30.0, 24.4, 21.9, 21.3, 13.9; HRMS (EI^+) *m/z*: $(M)^+$ calcd for $C_{18}H_{26}O_2$: 274.1933, found: 274.1934; HPLC conditions: Chiralpak AD-H column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, *t* = 14.2 min (major), 8.1 min (minor).



1-((1*R*,2*S*,6*S*)-2-Hydroxy-2-methyl-6-phenylcyclohexyl)pentan-1-one (Table 2, entry 9a). According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (2.5 mg,

0.0125 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.4 mg 0.0025 mmol), toluene (0.50 mL), DEMS (80 μL, 0.50 mmol), *Z*-enone (68 mg, 0.25 mmol in 0.50 mL toluene). Reaction was complete after 12 h at -10 ˚C. The reaction was filtered through a short plug of silica gel before being concentrated under vacuum and treated with 1.0 M TBAF in THF. Chromatography on silica (9:1 to 4:1 hexanes/Et_2O) gave 63 mg of a white solid (83%) with 64% ee. R_f 0.60 (2:1 hexanes/Et_2O). Spectroscopic data were identical to those reported for the reductive aldol product reported for entry 8; HPLC conditions: Chiralpak AD-H column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, *t* = 7.1 min (major), 10.5 min (minor).

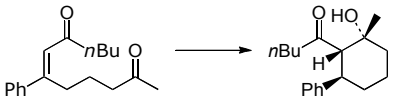
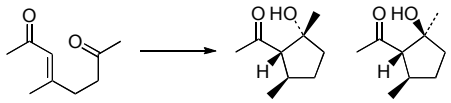


Table 2, entry 9b. According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (1.4 mg, 0.008 mmol), (*R*,*S*)-(4-CF_3Ph)$_2$PF-P(*t*-Bu)$_2$ (**II**,1.4 mg 0.002 mmol), toluene (0.30 mL), DEMS (36 μL, 0.272 mmol), enone (41 mg, 0.151 mmol in 0.30 mL toluene). The reductive aldol product was isolated (39 mg, 94%) with 97% ee. Spectroscopic data for this product were identical to those reported for that in Table 2, entry 8.



1-((1*S*,2*R*,5*R*)-2-Hydroxy-2,5-dimethylcyclopentyl)ethanone (Table 2, entry 10; 1st diastereomer).[i] According to the representative procedure, the following amounts were used: $Cu(OAc)_2$ (2.6 mg, 0.013 mmol), (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.4 mg 0.0026 mmol), toluene (0.60 mL), DEMS (83 μL, 0.52 mmol), *E*-enone (40 mg, 0.259 mmol in 0.60 mL toluene). Chromatography on silica with (4:1 hexanes/Et_2O) gave 18 mg (44%) of the product as a colorless oil with 97% ee. R_f 0.25 (1:1 hexanes/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (1 H, d, *J* = 1.0 Hz), 2.54-2.45 (1 H, m, *J* = 8.5 Hz), 2.37 (1 H, d, *J* = 10.0 Hz), 2.24 (3 H, s), 2.13-2.05 (1 H, m, *J* = 7.0 Hz), 1.80-1.66 (2 H, m), 1.34 (3 H, s), 1.29-1.21 (1 H, m), 1.10 (3 H, d, *J* = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.5, 81.7, 68.2, 41.0, 38.0, 33.4, 31.8, 27.9, 20.8; HRMS (EI$^+$) *m/z*: $(M)^+$ calcd for $C_9H_{16}O_2$: 156.1150, found: 156.1156; HPLC conditions: Chiralpak AD-H column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, t = 19.3 min (major), 16.6 min (minor).

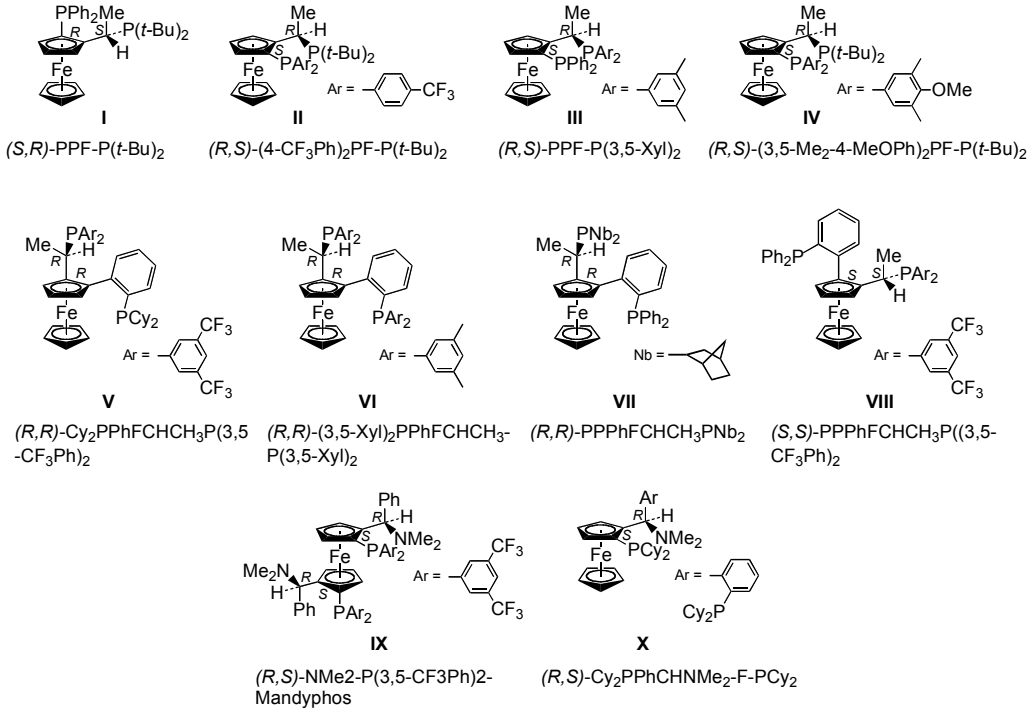
1-((1*S*,2*S*,5*R*)-2-Hydroxy-2,5-dimethylcyclopentyl)ethanone (Table 2, entry 10; 2nd diastereomer). Chromatography on silica with (4:1 hexanes/Et_2O) gave 12 mg (31%) of the reductive aldol product as a colorless oil with 92% ee. R_f 0.15 (1:1 hexanes/Et_2O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.59 (1 H, d, *J* = 10 Hz), 2.38-2.21 (1 H, m), 2.24 (3 H, m), 1.89-1.73 (4 H, m), 1.39-1.33 (1 H, m), 1.17 (3 H, s), 1.00 (3 H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.6, 81.6, 71.0, 42.6, 34.8, 32.3, 30.4, 25.5, 20.6; HRMS (EI$^+$) *m/z*: $(M)^+$ calcd for $C_9H_{16}O_2$: 156.1150, found: 156.1147; Chiralpak AD-H column, flow rate 1.0 mL/min, hexanes/*i*-PrOH = 98:2, t = 25.6 min (major), 31.1 min (minor).

Heterogeneous asymmetric reductive aldol using CuH. Conversion of *E*-1 to product 2 (Scheme 1, top). Toluene (0.3 mL) was added to was added to a flame-dried, argon-purged flask containing Cu/C (8% w/w, 28 mg, 0.033 mmol), NaOPh (3.8 mg, 0.033 mmol), and (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.6 mg 0.003 mmol), and stirred for 30 min at 0 ˚C. DEMS (80 μL, 0.501 mmol) was then added and allowed to stir an additional 30 min. The heterogeneous mixture was cooled to -10 ˚C and *E*-**1** (28 mg, 0.167 mmol in 0.30 mL toluene) was added and stirred at that temperature for 6 h. A quenching solution of NH_4F (~1 M in MeOH) was then added dropwise and allowed to stir at rt for 2 h, followed by

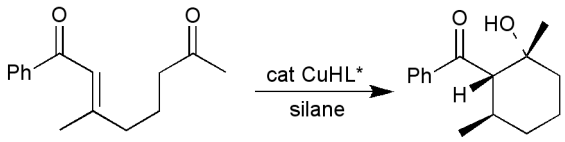
filtration through Celite. The solution was concentrated and then purified through a column of silica gel. The reductive aldol product (**2**) was isolated (24 mg, 84%) with 98% ee. Spectroscopic data were identical to those reported for **2** previously.

Aqueous reductive aldol with PTS in water. Conversion of *Z*-1 to product *ent*-2 (Scheme 1, bottom). Enone *Z*-**1** (30 mg, 0.179 mmol, in 0.3 mL toluene) was added to a flame-dried, argon-purged flask containing $Cu(OAc)_2$ (1.8 mg, 0.009 mmol) and (*S*,*R*)-PPF-P(*t*-Bu)$_2$ (**I**, 1.1 mg 0.002 mmol), and stirred for 30 min at 0 ˚C. Thereafter, the toluene was evacuated carefully leaving a residue of ligated copper and *Z*-**1**. The flask was cooled in an ice bath and diluted with PTS (2% by weight in water, 1.2 mL). $PhSiH_3$ (44 μL x 4, 0.358 mmol x 4) was then added in four portions (1 h intervals) and then allowed to stir at 5 ˚C for 5 h. The mixture was diluted with ethyl acetate (0.5 mL) and then purified through a column of silica gel. Product *ent*-**2** was isolated (25 mg, 81%) with 94% ee. Spectroscopic data were identical to those reported for *ent*-**2** previously.

Solvias Ligand Study

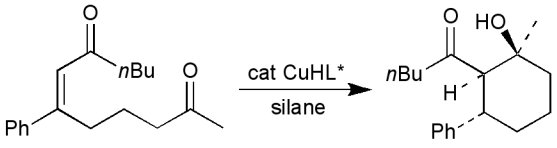


Screening Results



entry	L*	temp (°C)	*ee* (%)[b]
1	**II**	-10	75
2[d]	**III**	-10	-
3	**IV**	-10	60
4[d]	**VI**	-10	-
5	**VII**	-10 to rt	15
6	**VIII**	-10	7
7	**VIII**	-10	-73[e]
8[c]	**IX**	-10	-
9[c]	**X**	-10	-

[a] Conditions: 3-5% $Cu(OAc)_2$, 1% L*, 1.5 equiv DEMS, toluene. [b] Determined by chiral HPLC analysis (see Supporting Information). [c] No reaction. [d] Mixture of products. [e] Reaction run on *Z*-ketoenone.



entry	L*	temp (°C)	*ee* (%)[b]
1	**II**	0	87
2	**II**	-10	97
3	**III**	0	29
4	**IV**	-10	93
5[c]	**V**	0	-
6	**VI**	0	-58
7	**IX**	0	-59
8[c]	**X**	0	-

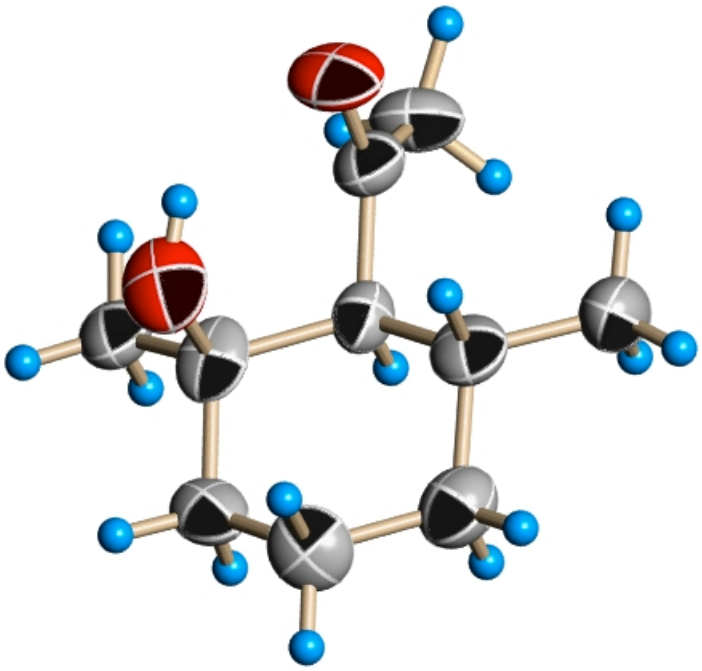
[a] Conditions: 3-5% $Cu(OAc)_2$, 1% L*, 1.5 equiv DEMS, toluene. [b] Determined by chiral HPLC analysis (see Supporting Information). [c] No reaction.

Structure determination of reductive aldol products

The relative and absolute stereochemistry of reductive aldol product **2** (entry 1), and reductive aldol product entry 4 (cf. Table 2 of manuscript), were determined by X-ray analysis using the direct method (see description provided below and data in .cif files). The determined stereochemistry of product **2** and product entry 4 (in the absolute) generated by X-ray analysis is in agreement with precedented asymmetric hydrosilylations of enone and enoate substrates[ii] with the nonracemic ligands used in this study. The β-hydroxy ketone long range ω-coupling of the non-exchangeable hydroxylic proton (δ 3.64, 1 H, J = 2.0 Hz) held in place by an H-bonding interaction to the adjacent ketone, evident in the ^{1}H NMR and COSY spectra of **2** (and ^{1}H NMR of each of the six-membered products, and one of the five membered product diastereomers; Table 2 of manuscript) suggests a *syn* relationship, as described by Chiu[iii] and Krische.[iv] A *trans* diaxial relationship is observed in all six-membered reductive aldol products for vicinal methine protons (e.g., **2**, J = 11.6 Hz). Noesy 1D experiments on the five-membered ring products (entry 10, Table 2 of manuscript) also support a *trans* relationship for the vicinal methine protons for each of the two diastereomers. Compared to the aforementioned X-ray structures, HPLC retention times of all reductive aldol product enantiomers were consistent relative to their respective starting keto-enone geometries and ligand stereochemistry. Relative retention times were used to subsequently determine reductive aldol product stereochemistry. The enantiomeric relationship between compounds **2** and *ent*-**2** was further corroborated by measuring specific rotation (**2** $[a]^{20}_D$ (91% *ee*) = +1.4˚ (c = 0.5, CH_2Cl_2); *ent*-**2** $[a]^{20}_D$ (90% *ee*) = -1.5˚ (c = 0.5, CH_2Cl_2)).

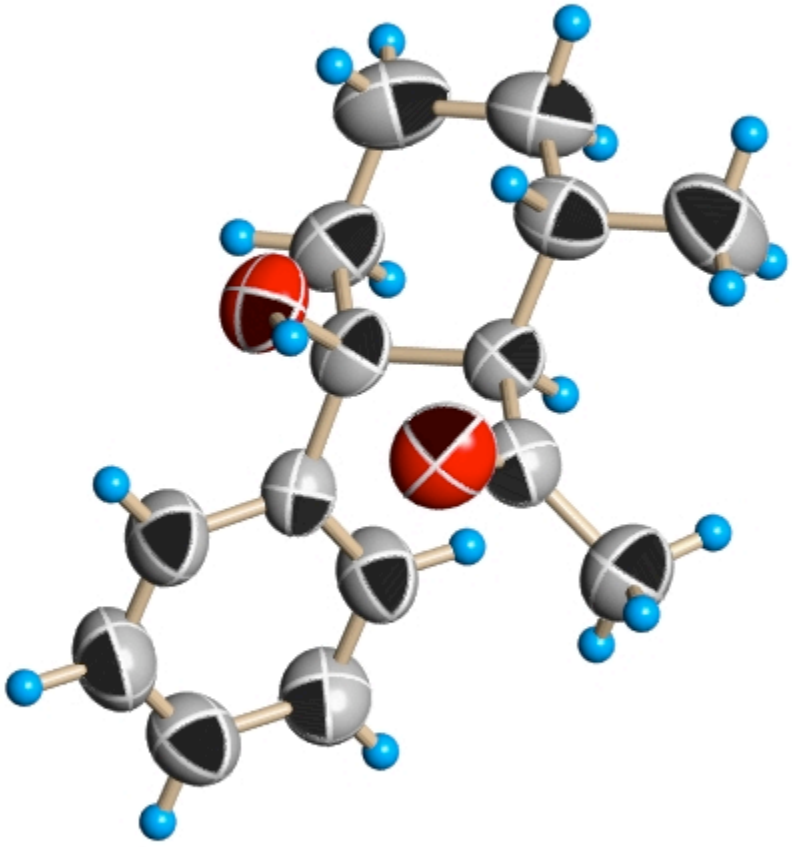
X-Ray crystallographic data for reductive aldol product 2 (entry 1)

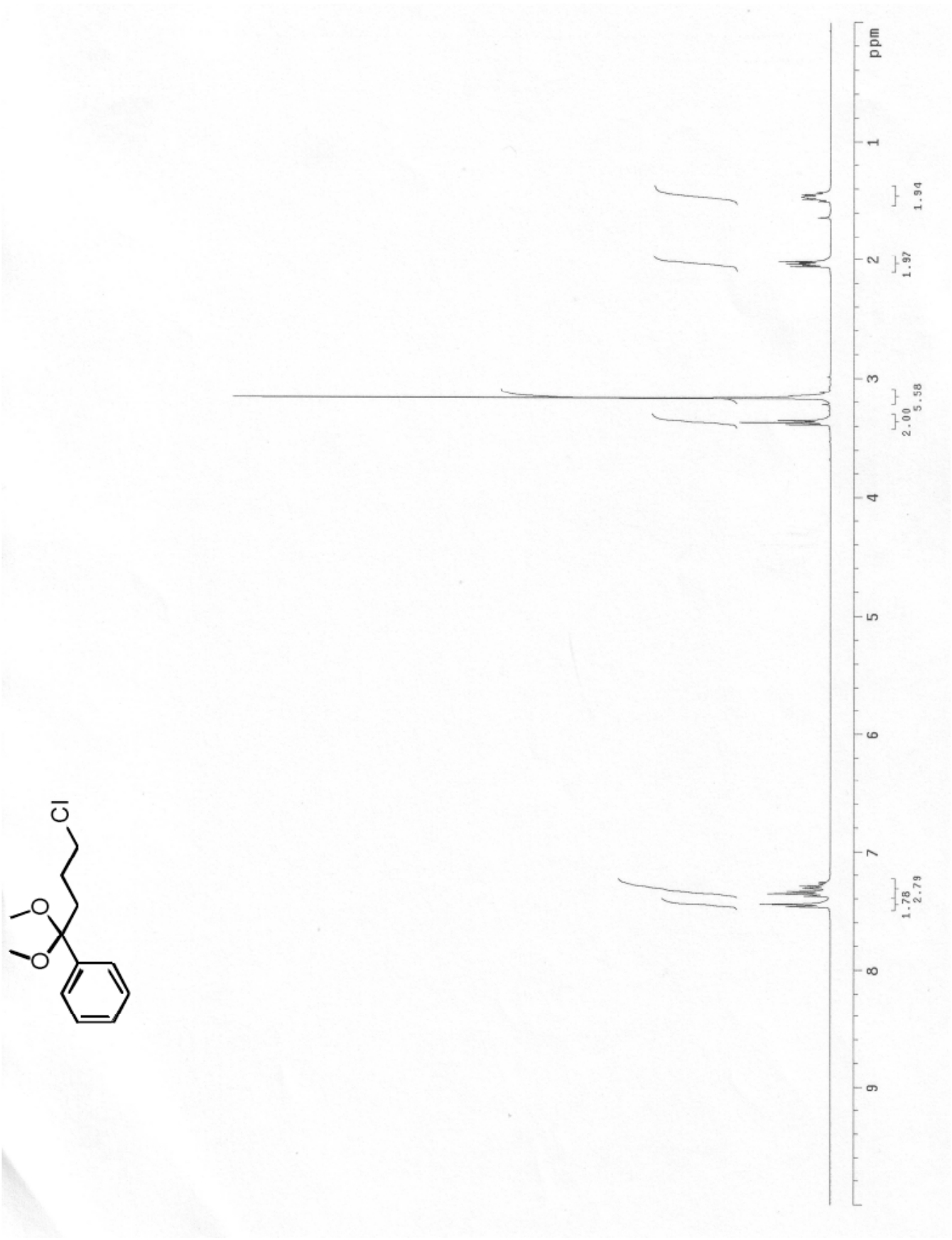
A crystal of 0.2x0.2x0.15 mm was used for single crystal X-ray diffraction analysis. The data collection was done at a Bruker diffractometer with Microstar Cu Rotating anode (Cu-Kα) and Proteum CCD detector. The structure was solved from direct method. The two possible enantiomers were tested in the structure refinements, and Flack Parameters[v] were 0.97(0.75) and -0.21(0.75), respectively. The structure of the enantiomer having smaller Flack parameter is illustrated:



X-Ray crystallographic data for reductive aldol product entry 4

A crystal of 0.2x0.15x0.05 mm was used for single crystal X-ray diffraction analysis. The data collection was done at a Bruker diffractometer with Microstar Cu Rotating anode (Cu-Kα) and Proteum CCD detector. The structure was solved from direct method. The two possible enantiomers were tested in the structure refinements, and Flack Parameters were 0.91(0.27) and 0.06(0.26), respectively. The structure of the enantiomer having smaller Flack parameter is illustrated:

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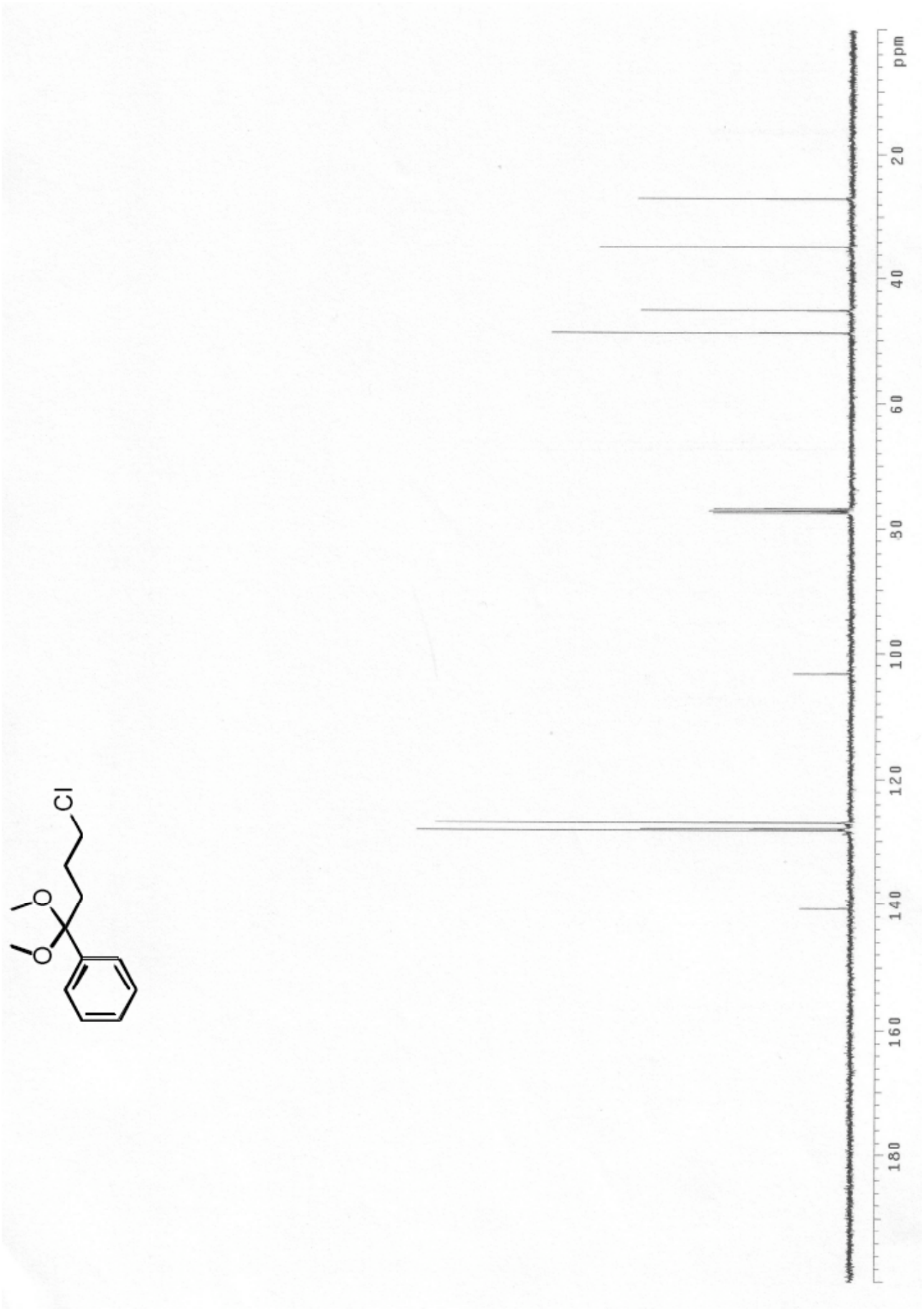
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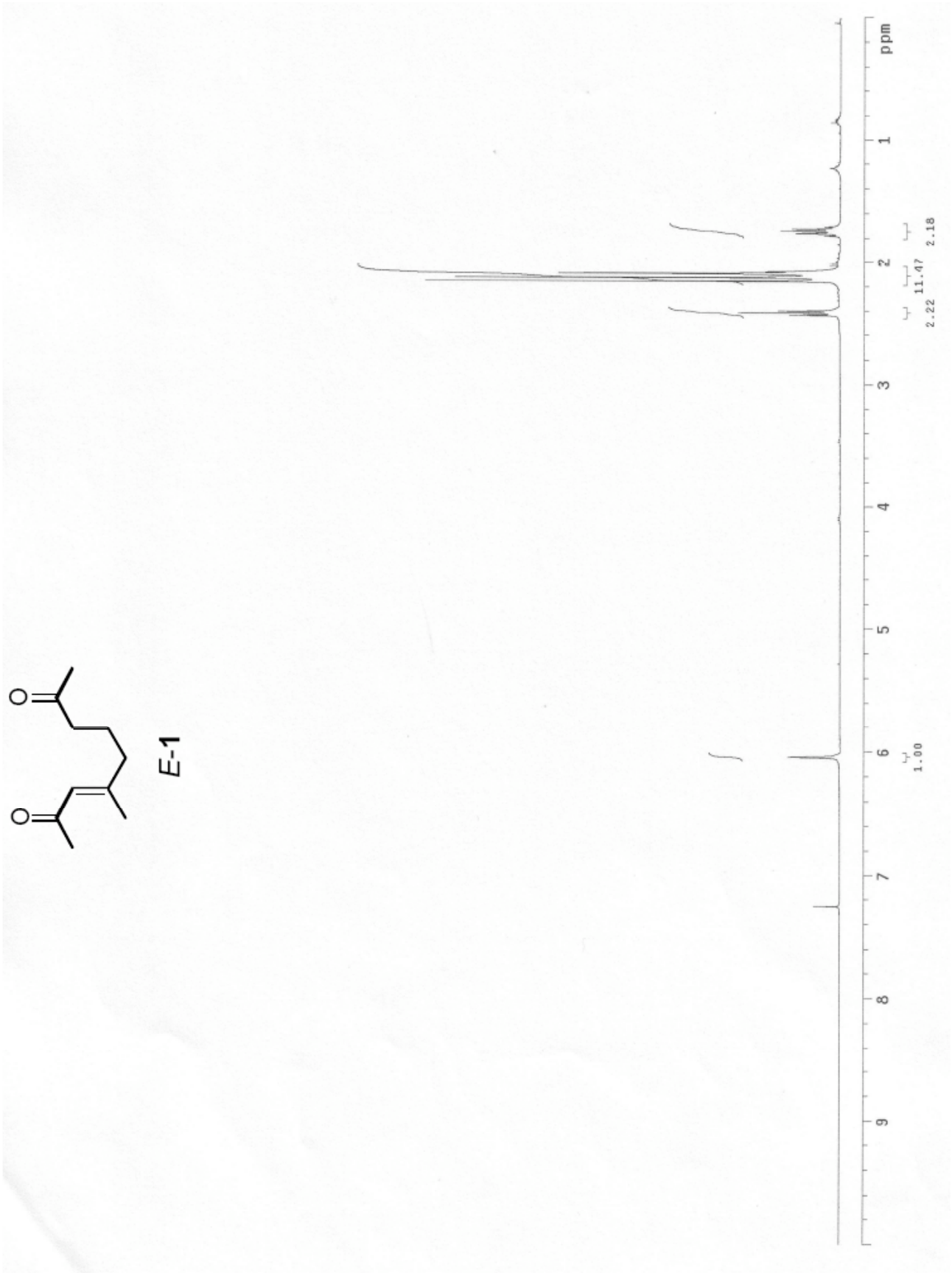

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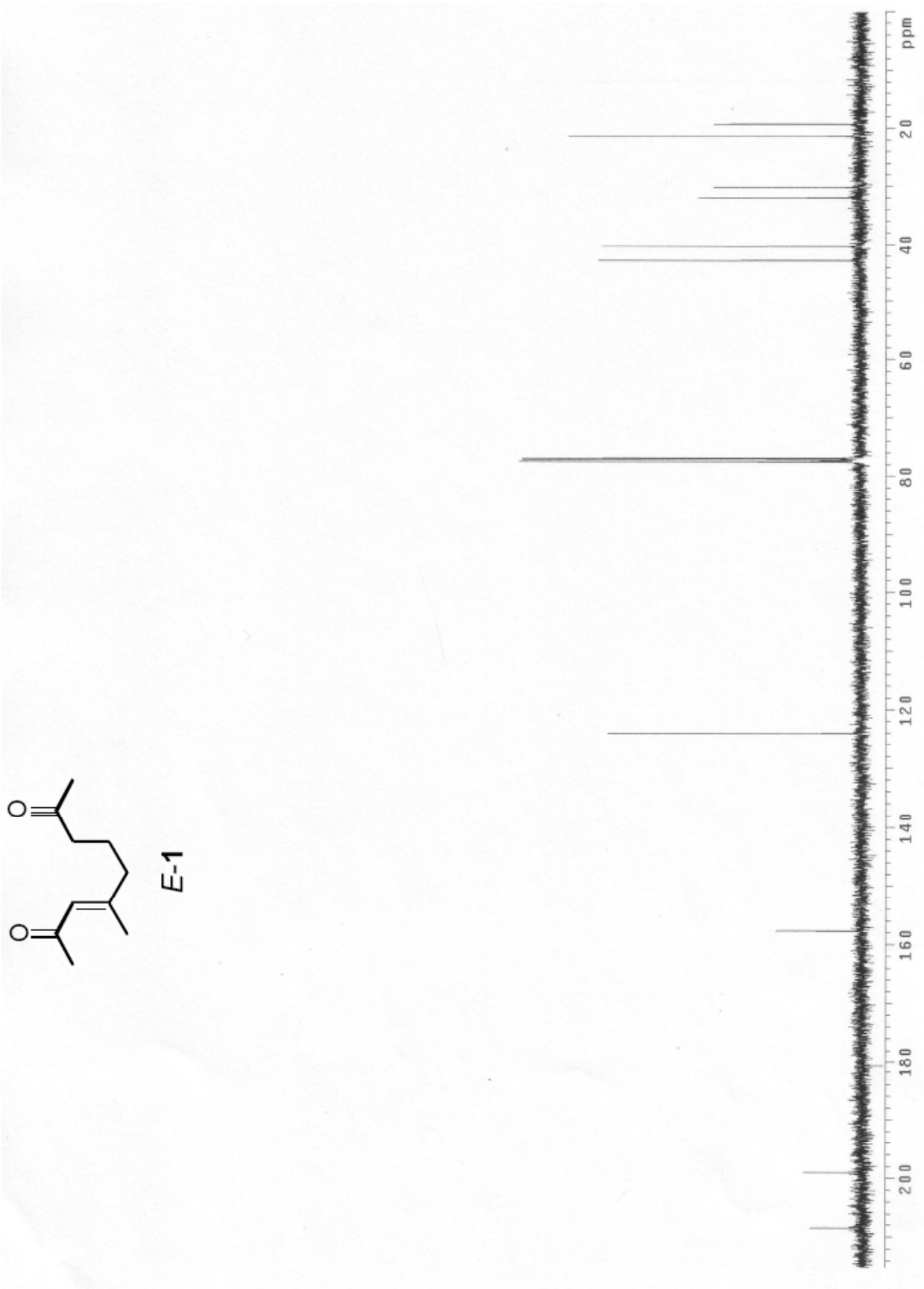

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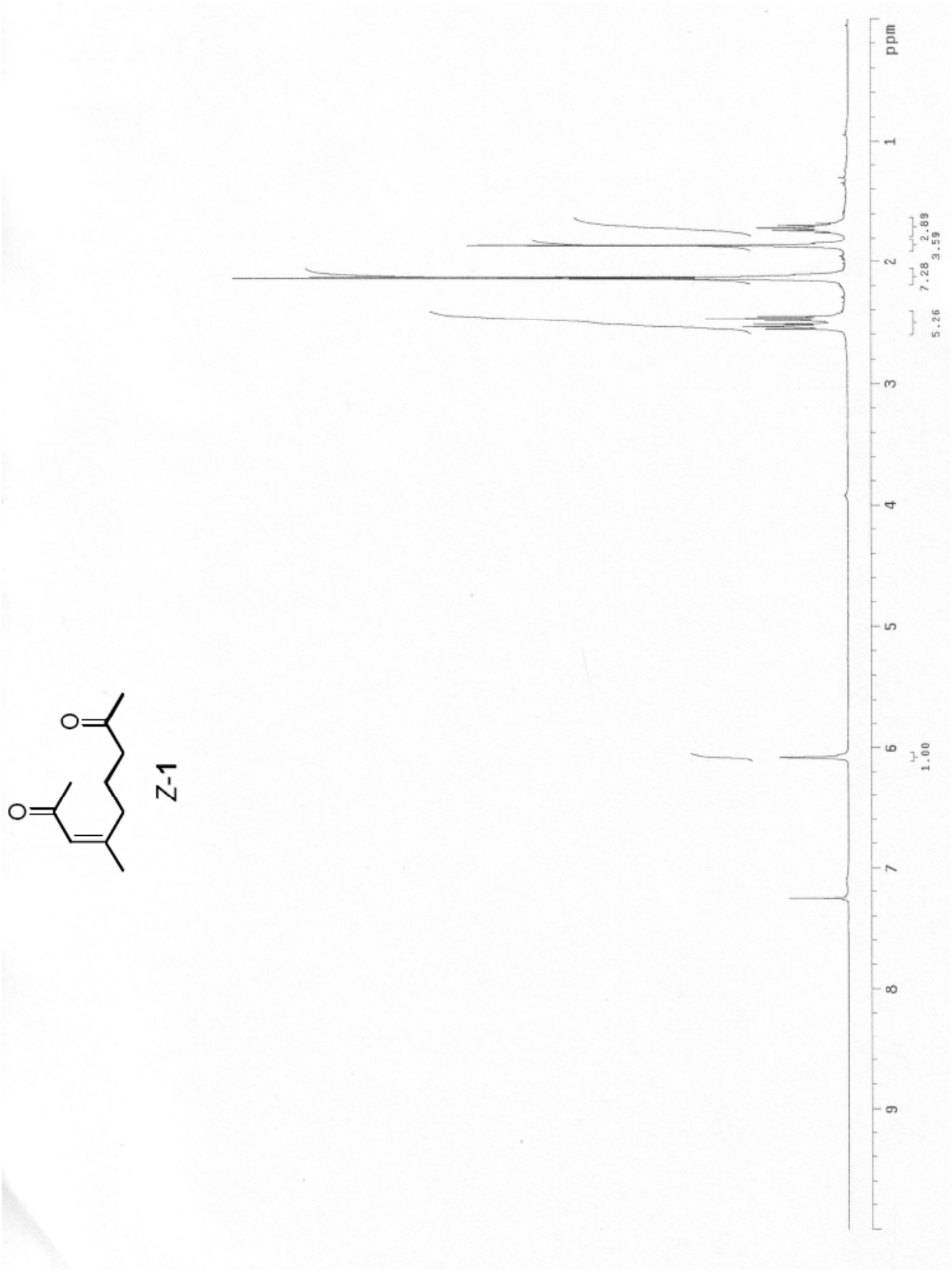

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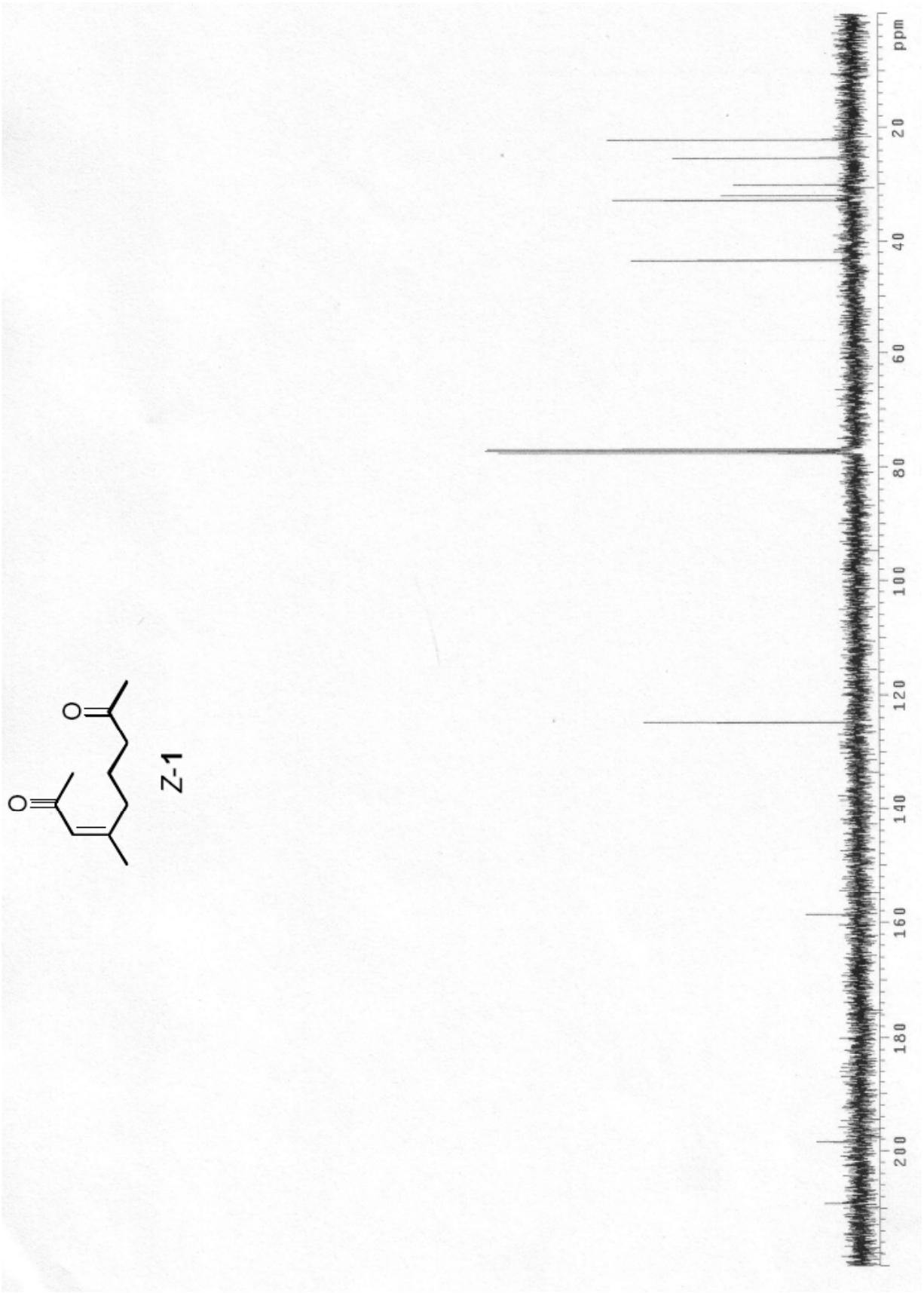

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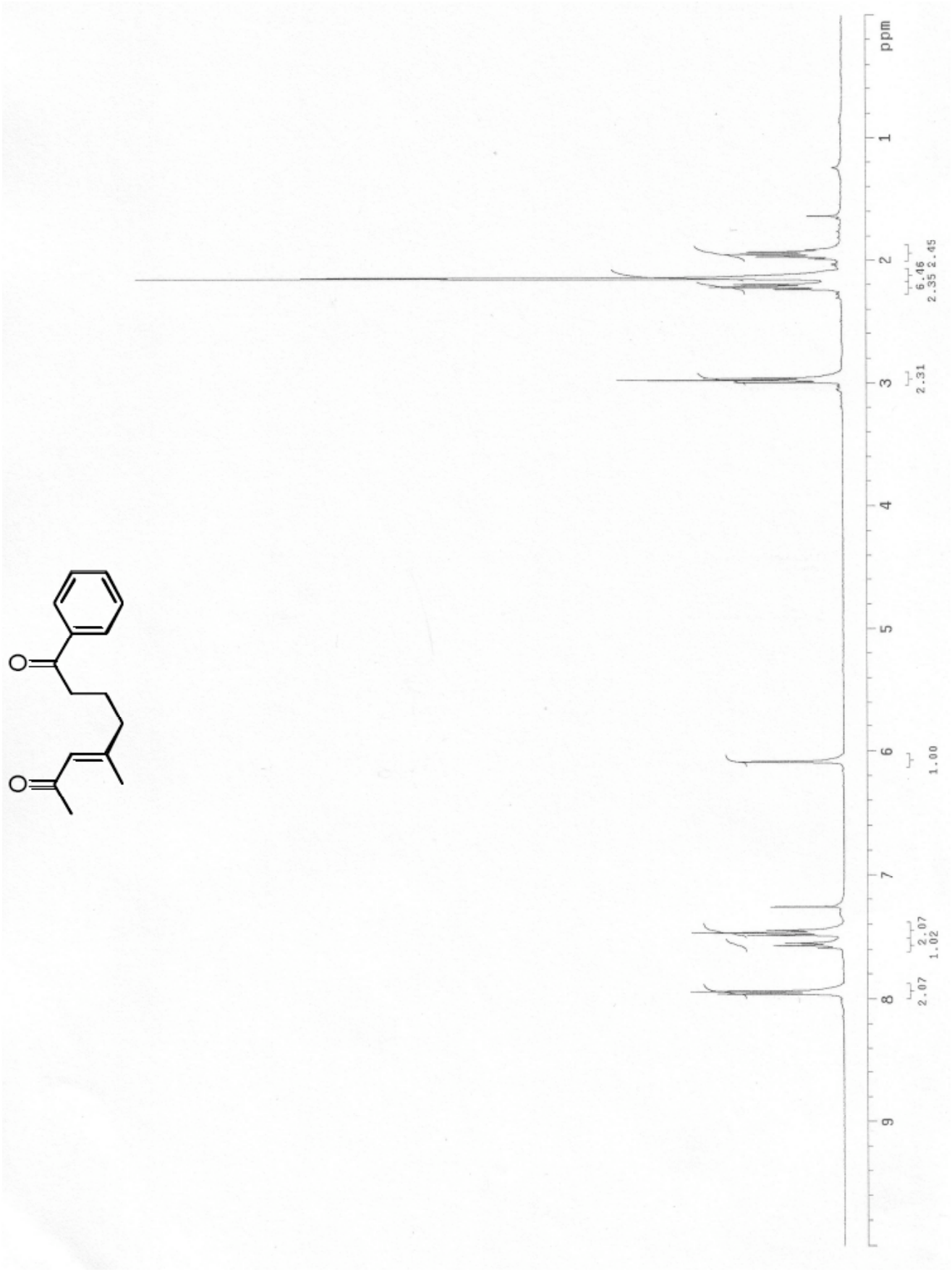

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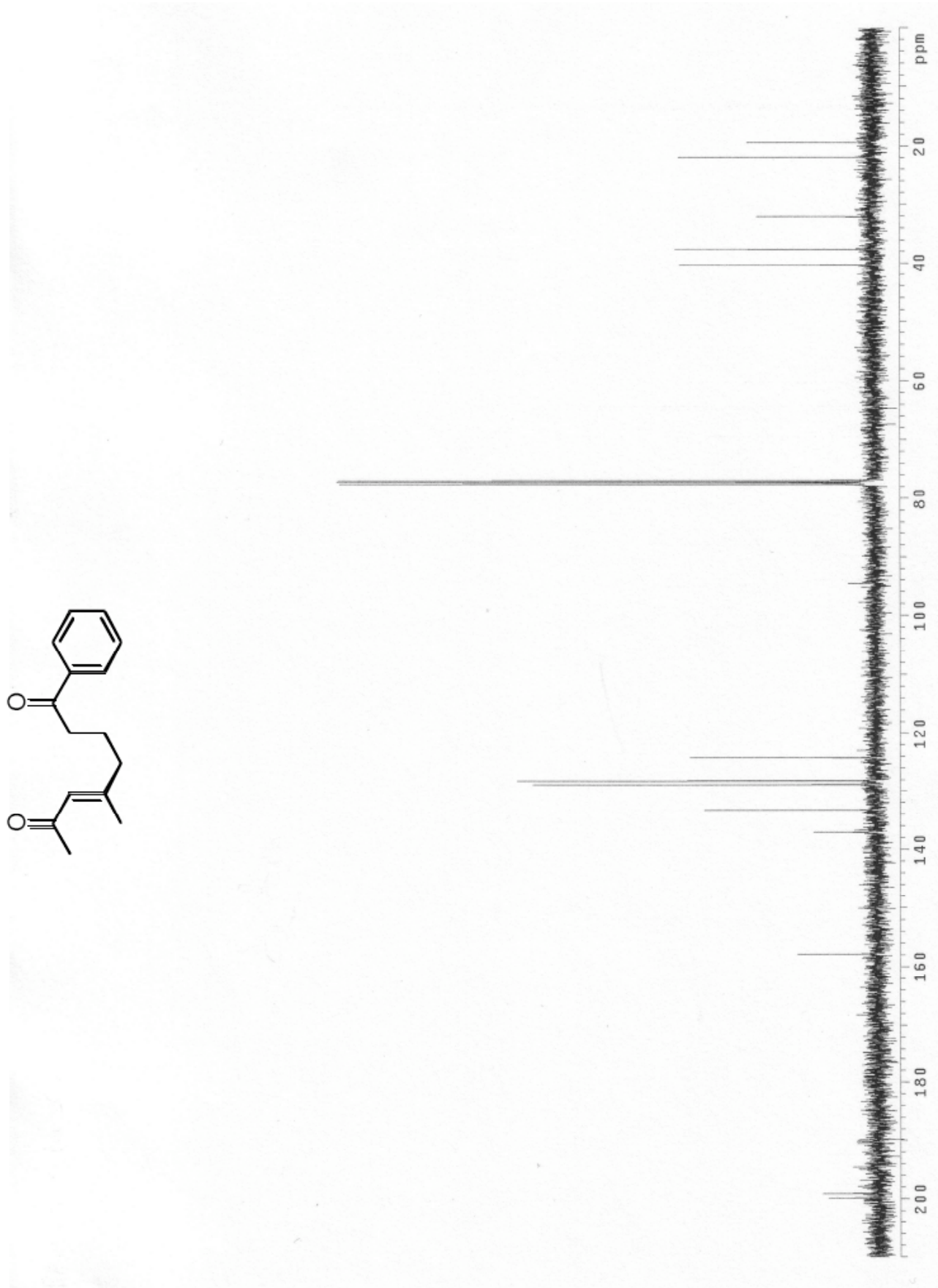

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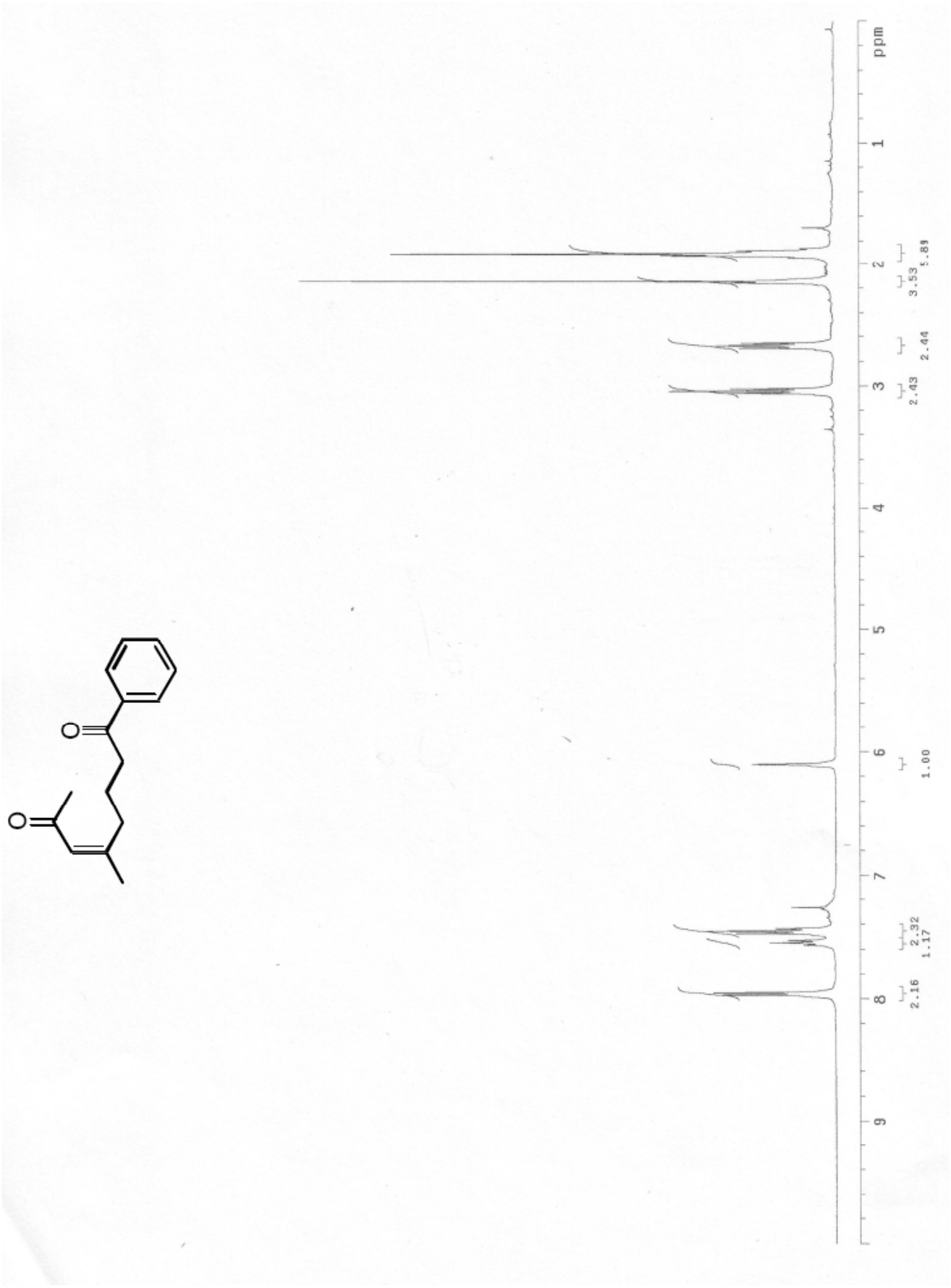

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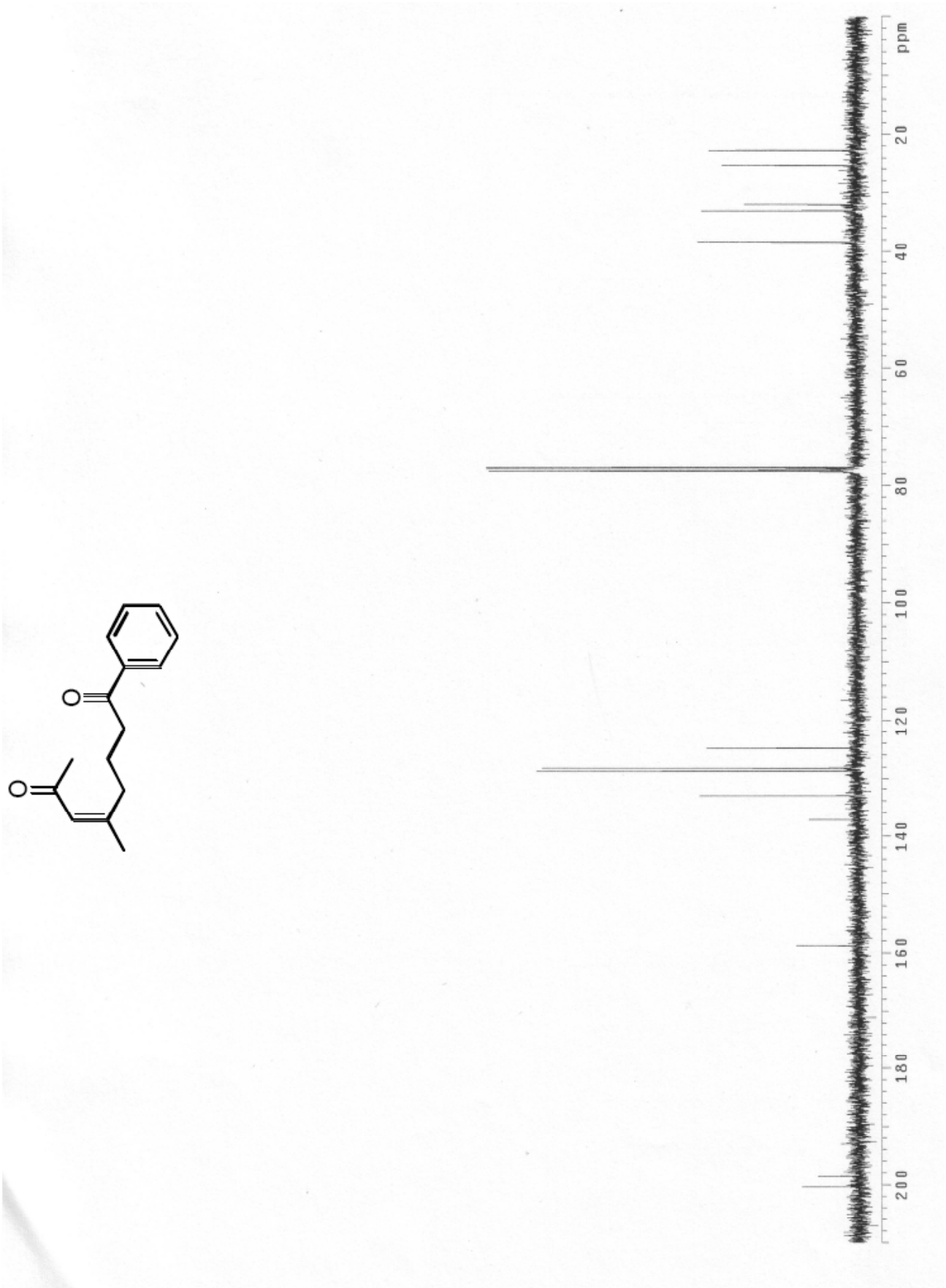

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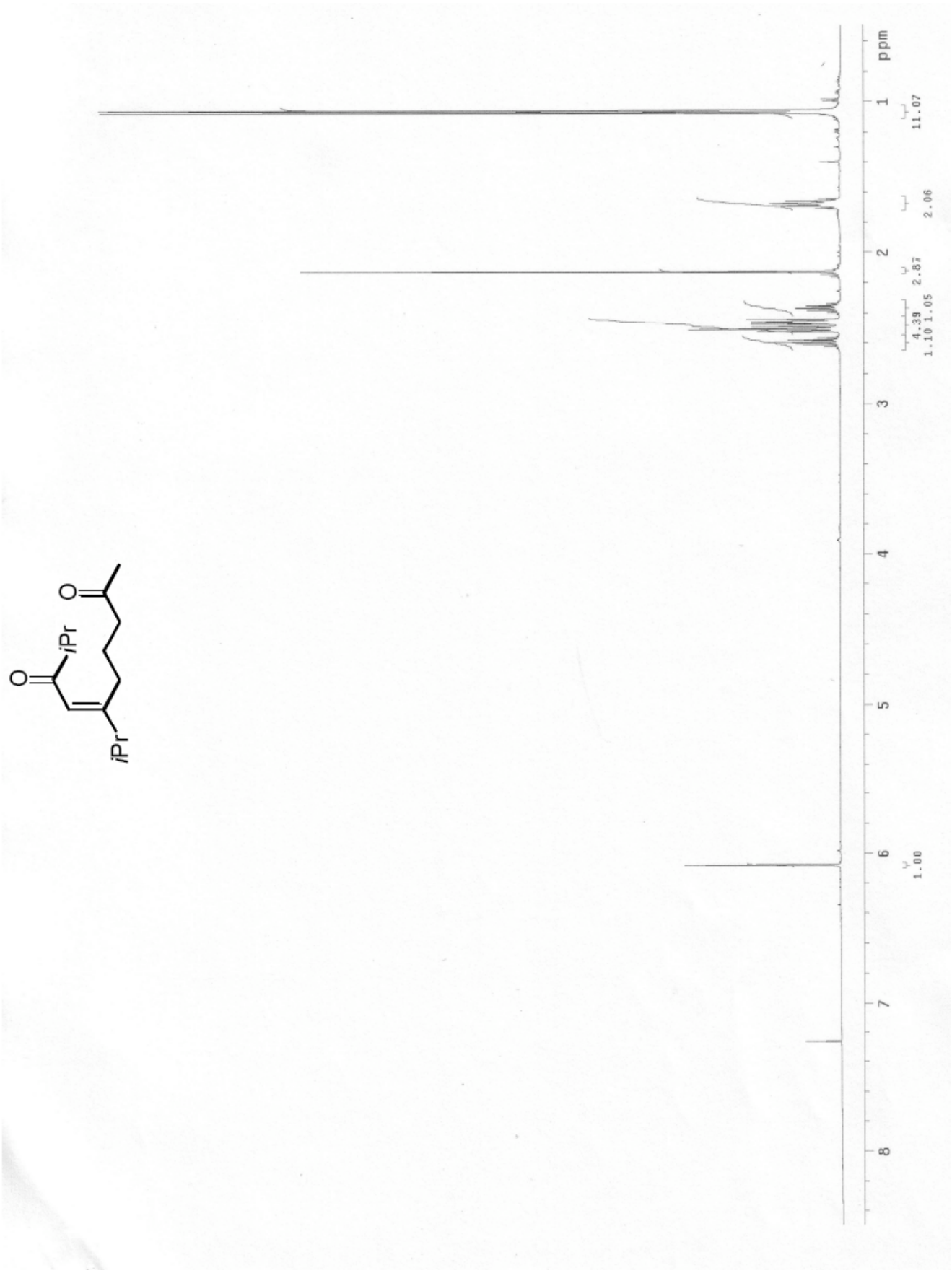

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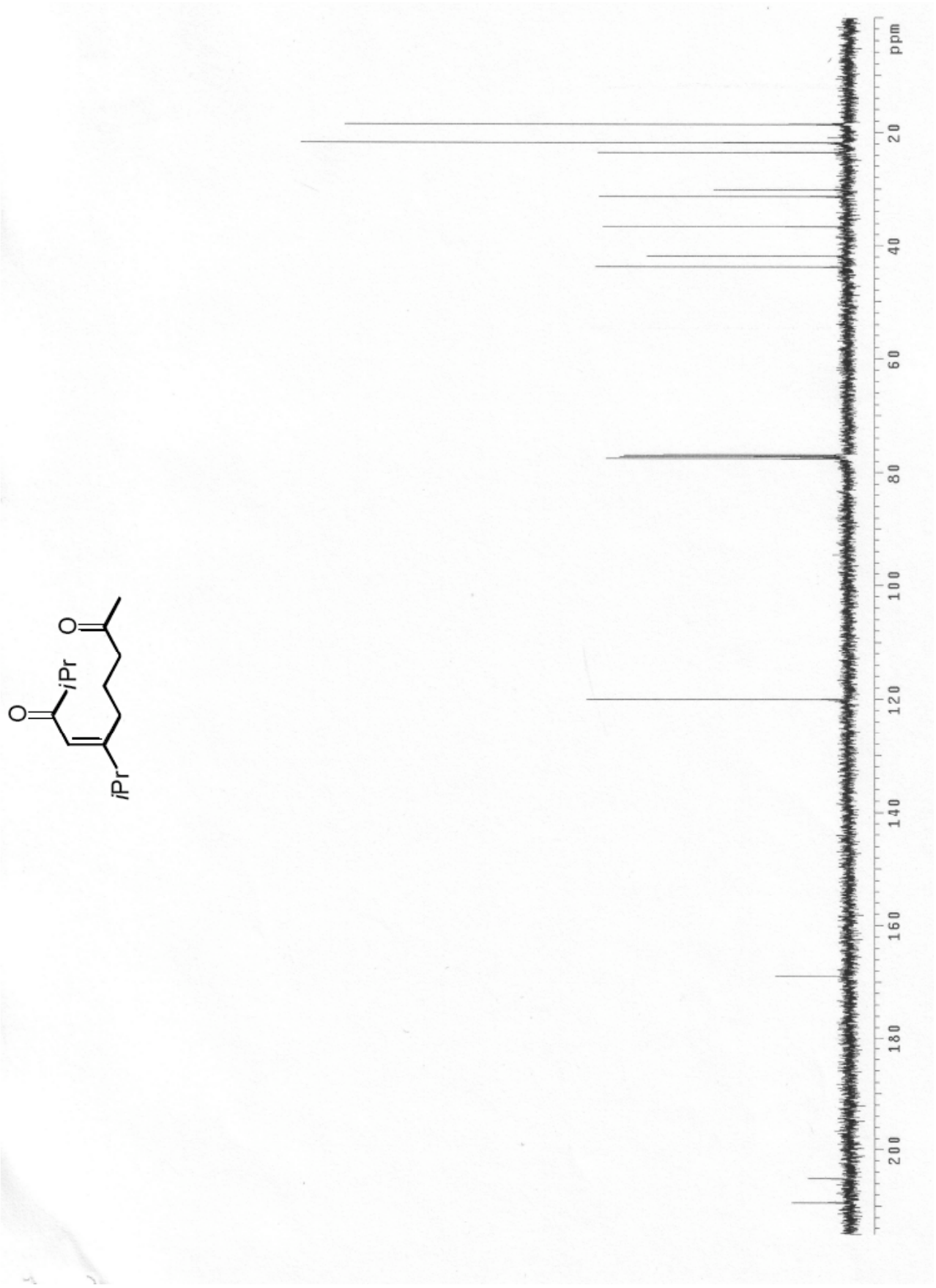

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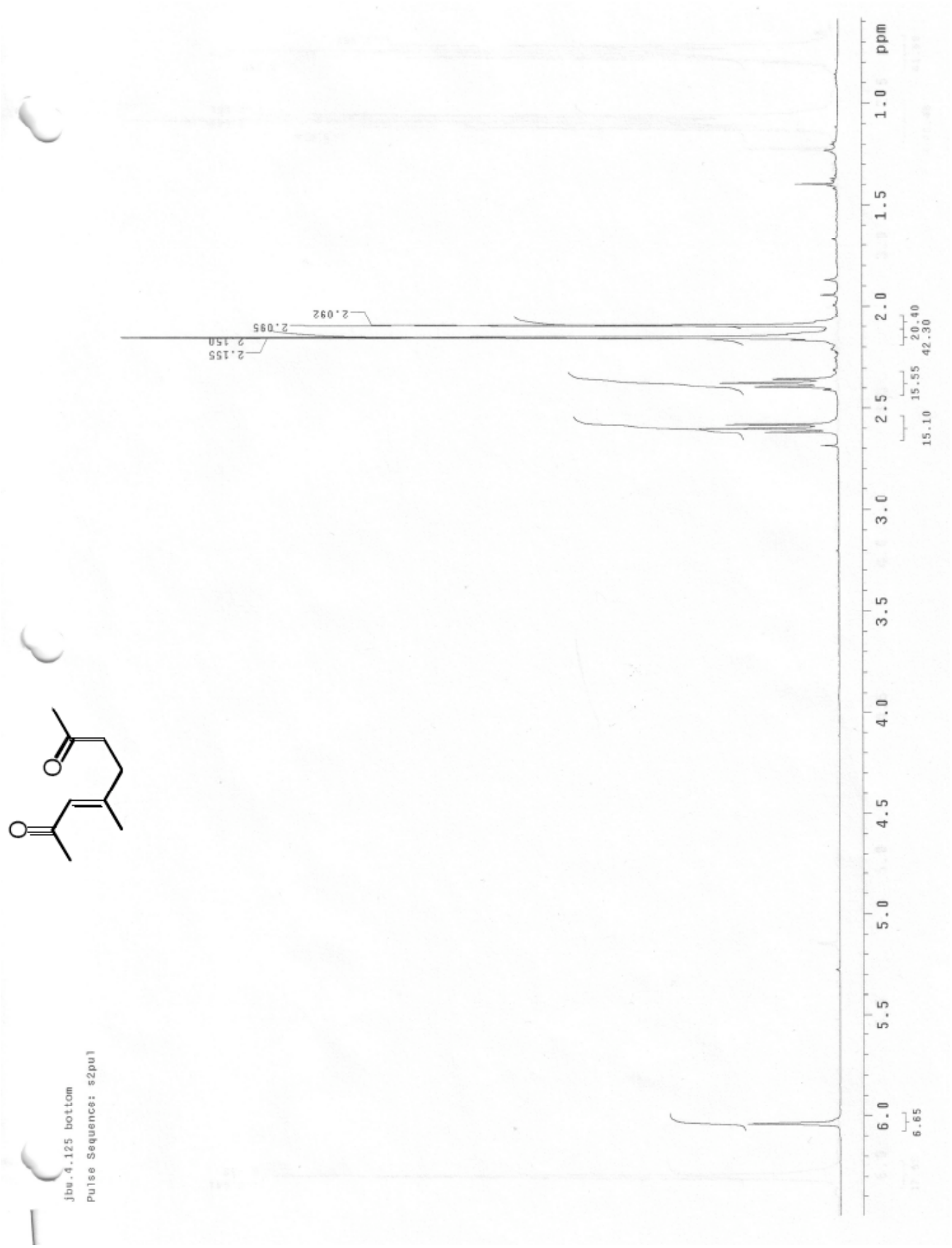
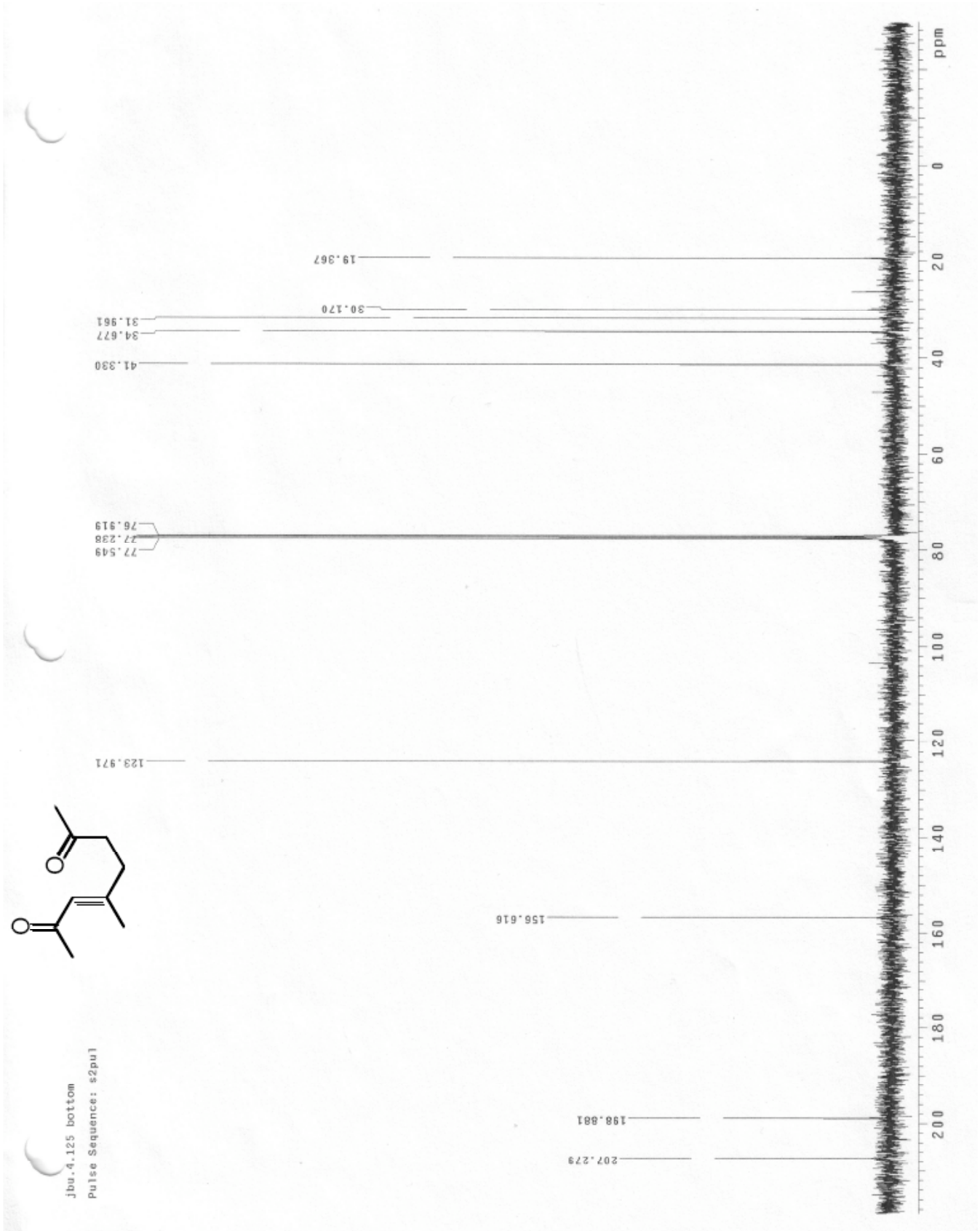


Starting Material: Table 2, Entry 10



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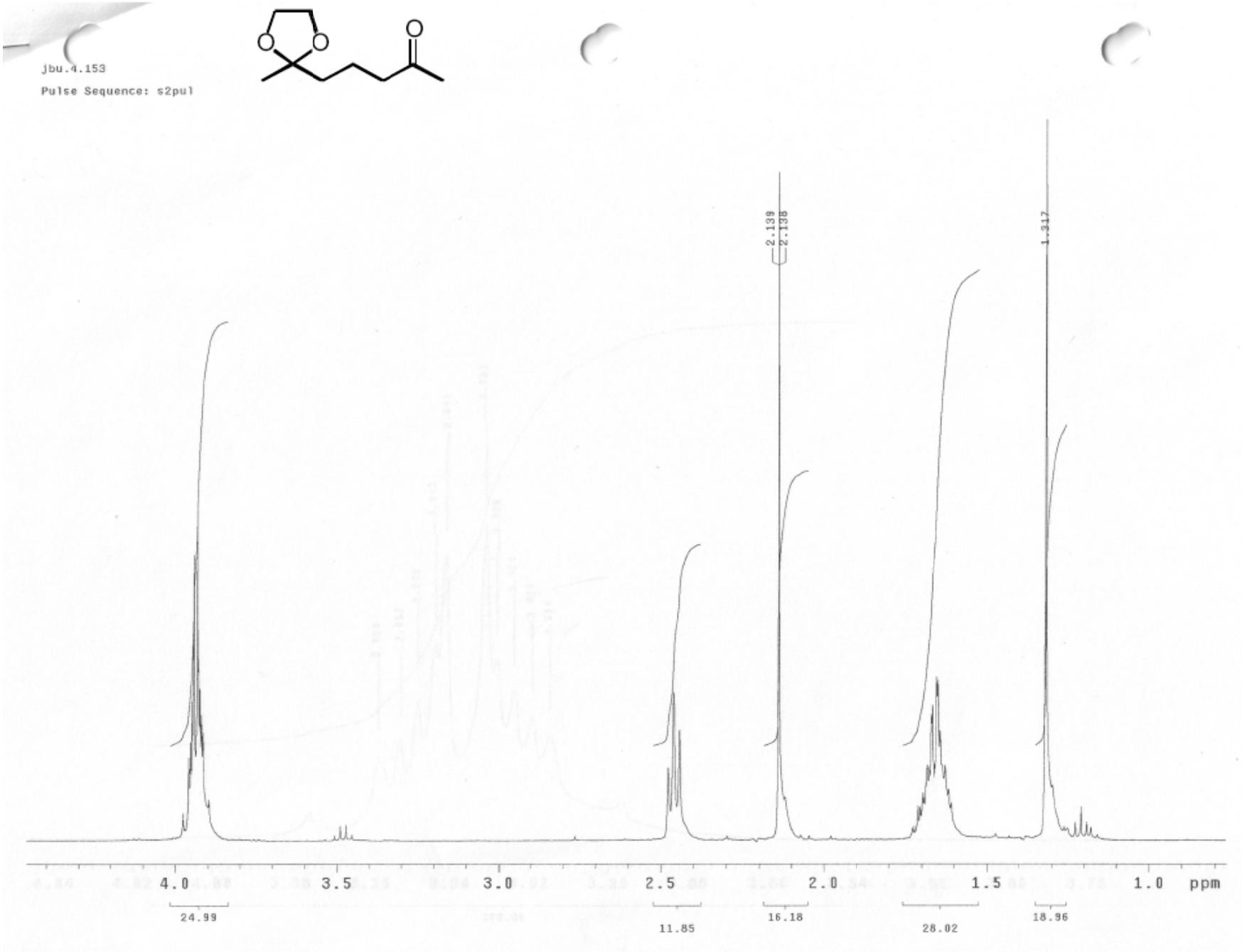
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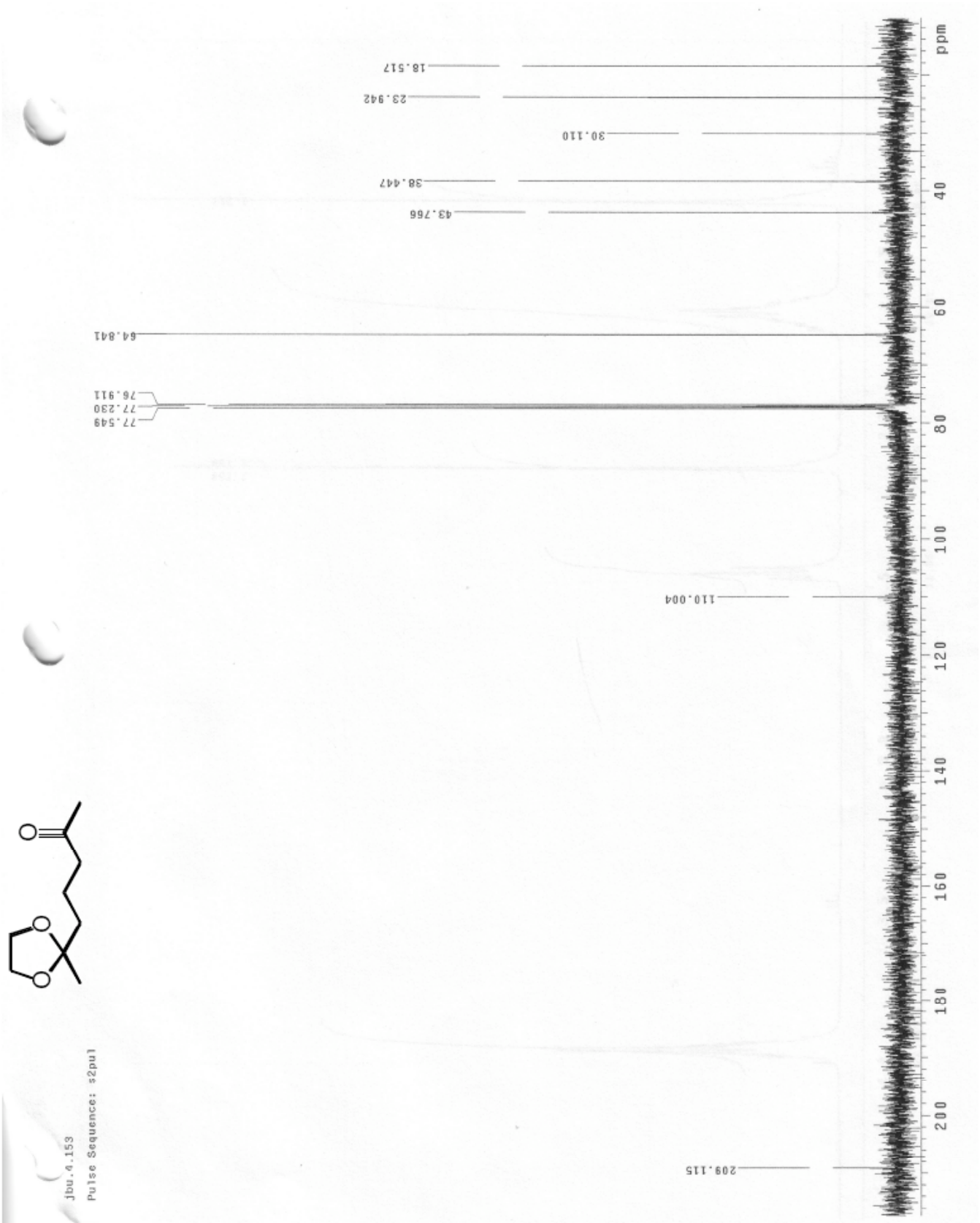
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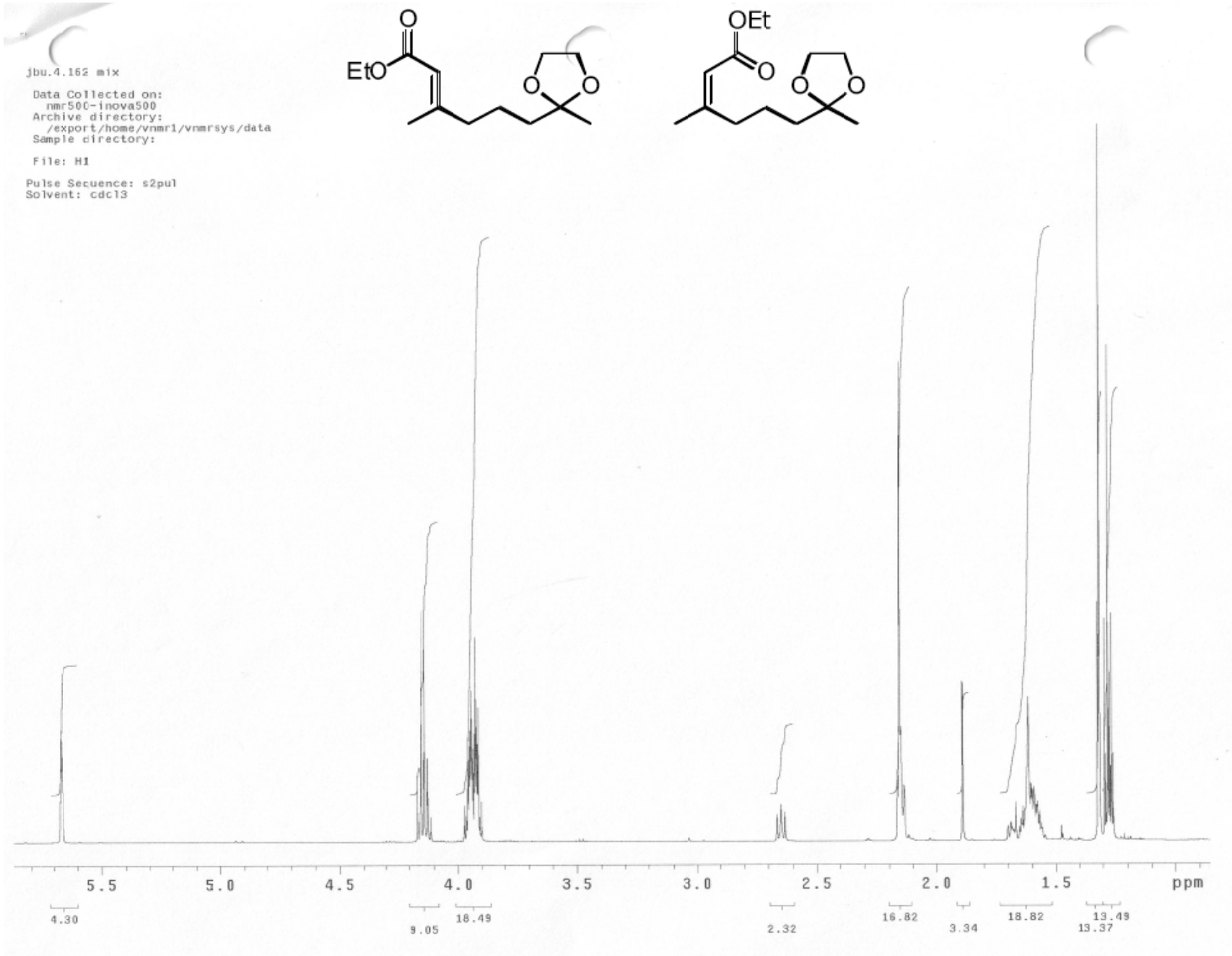
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OEt
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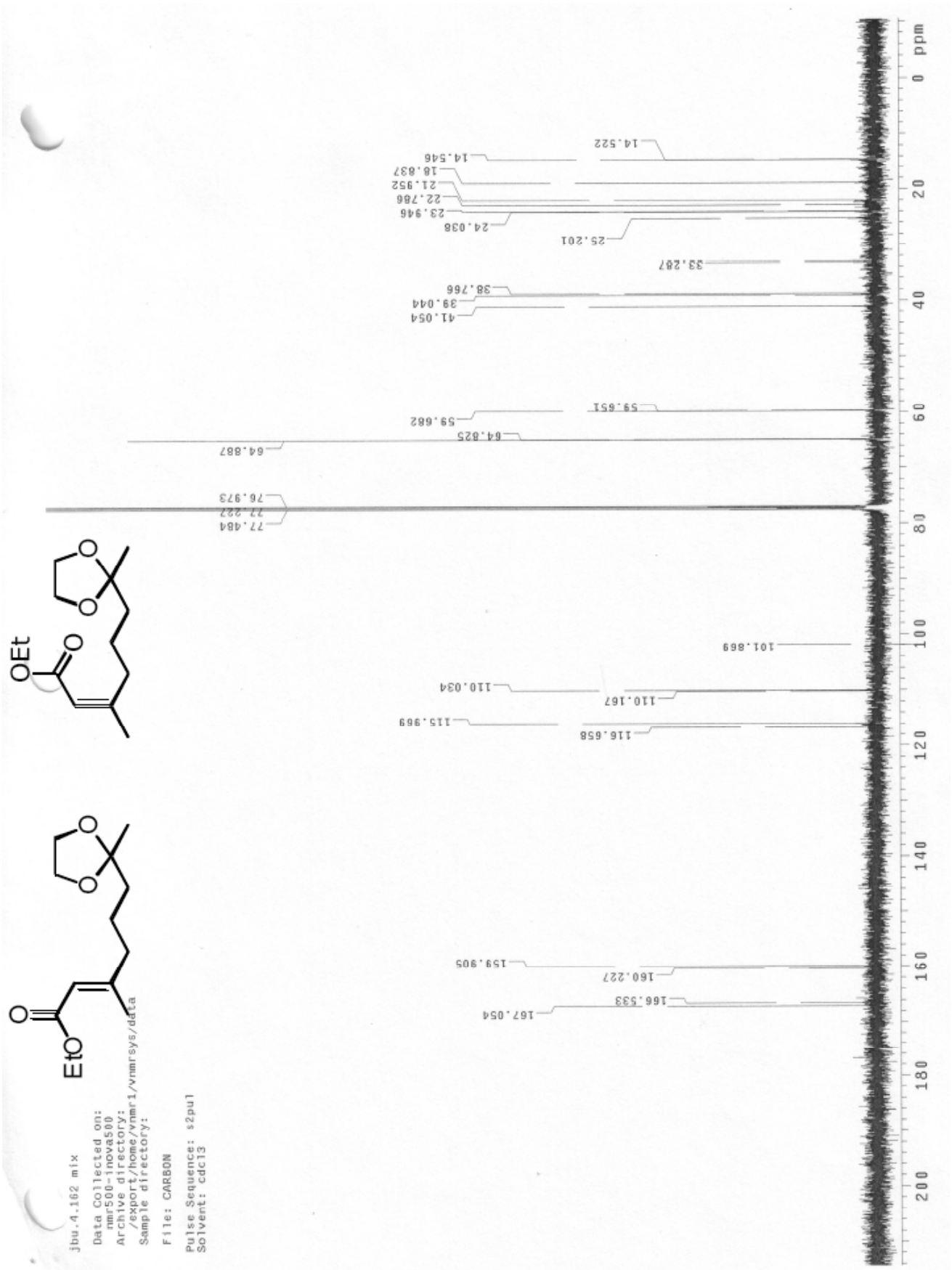
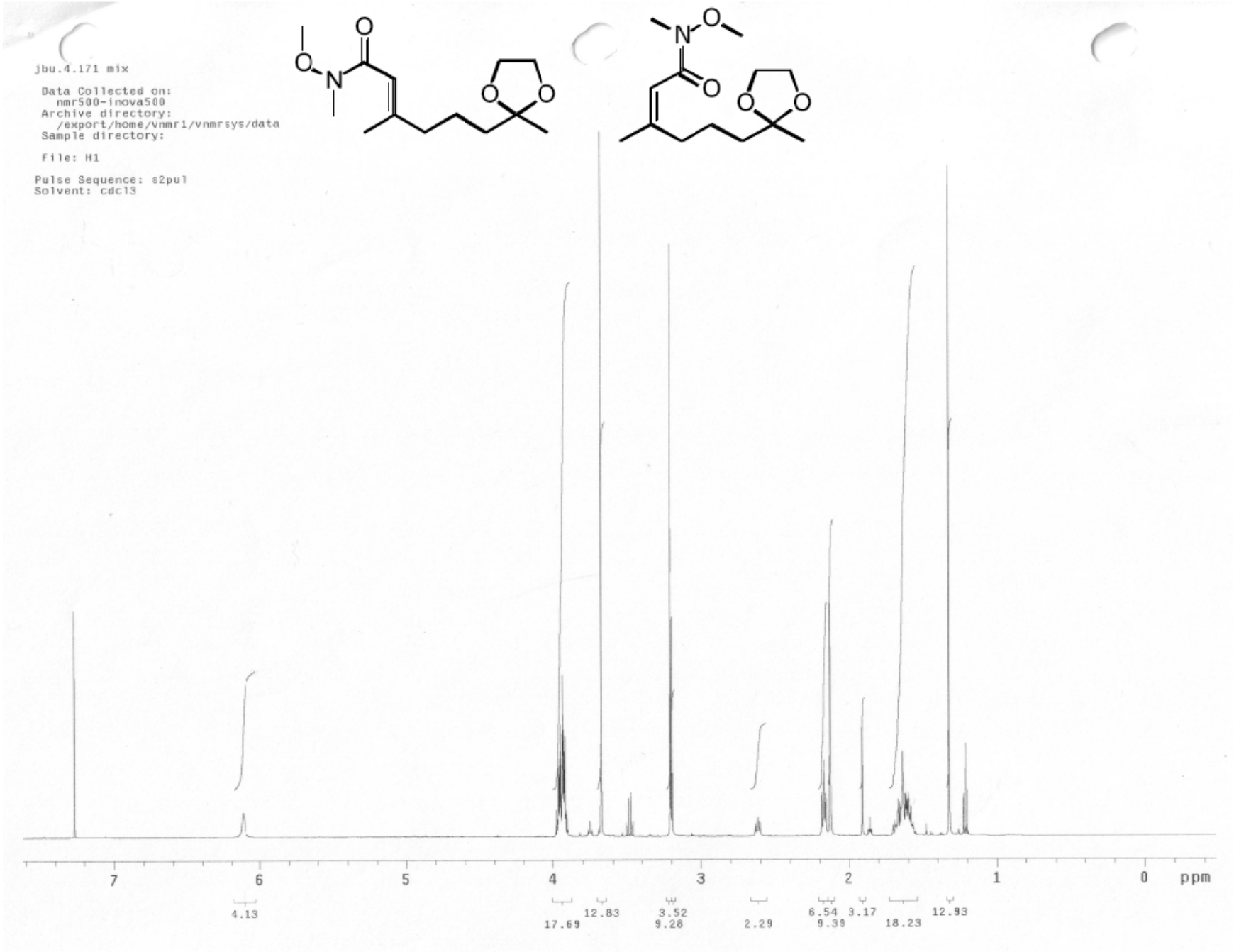
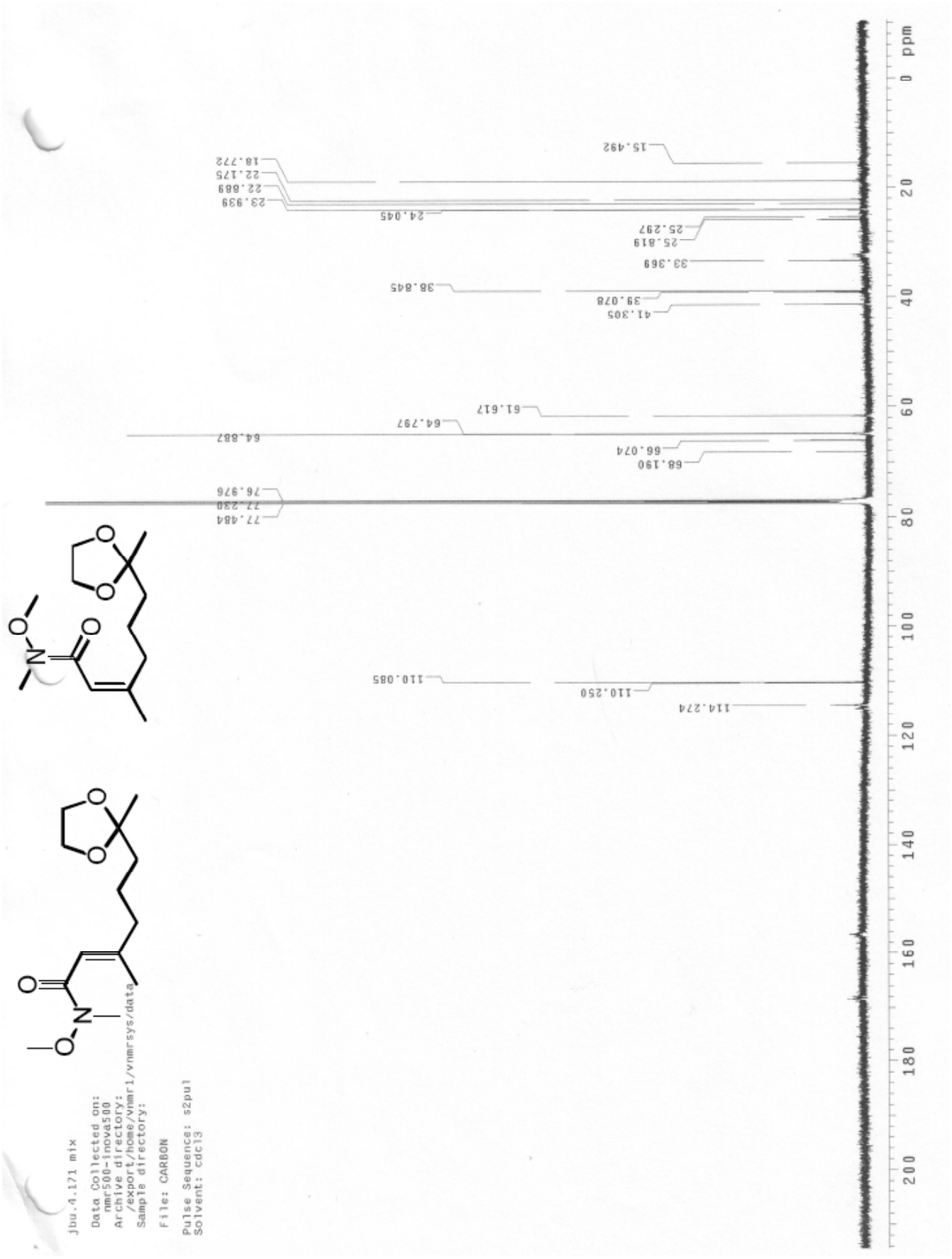
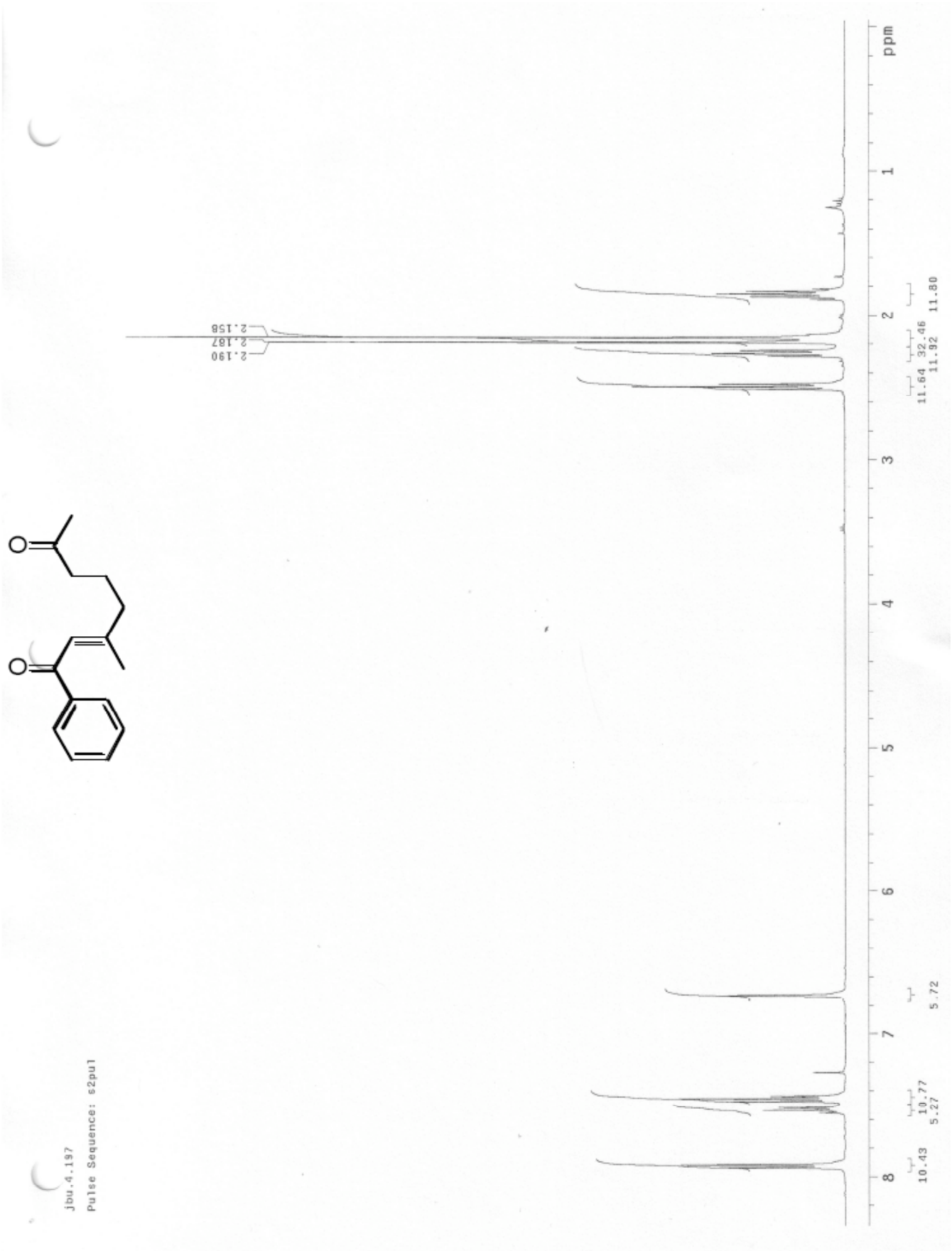
9.05
18.49
2.32
16.82
3.34
18.82
13.49
13.37

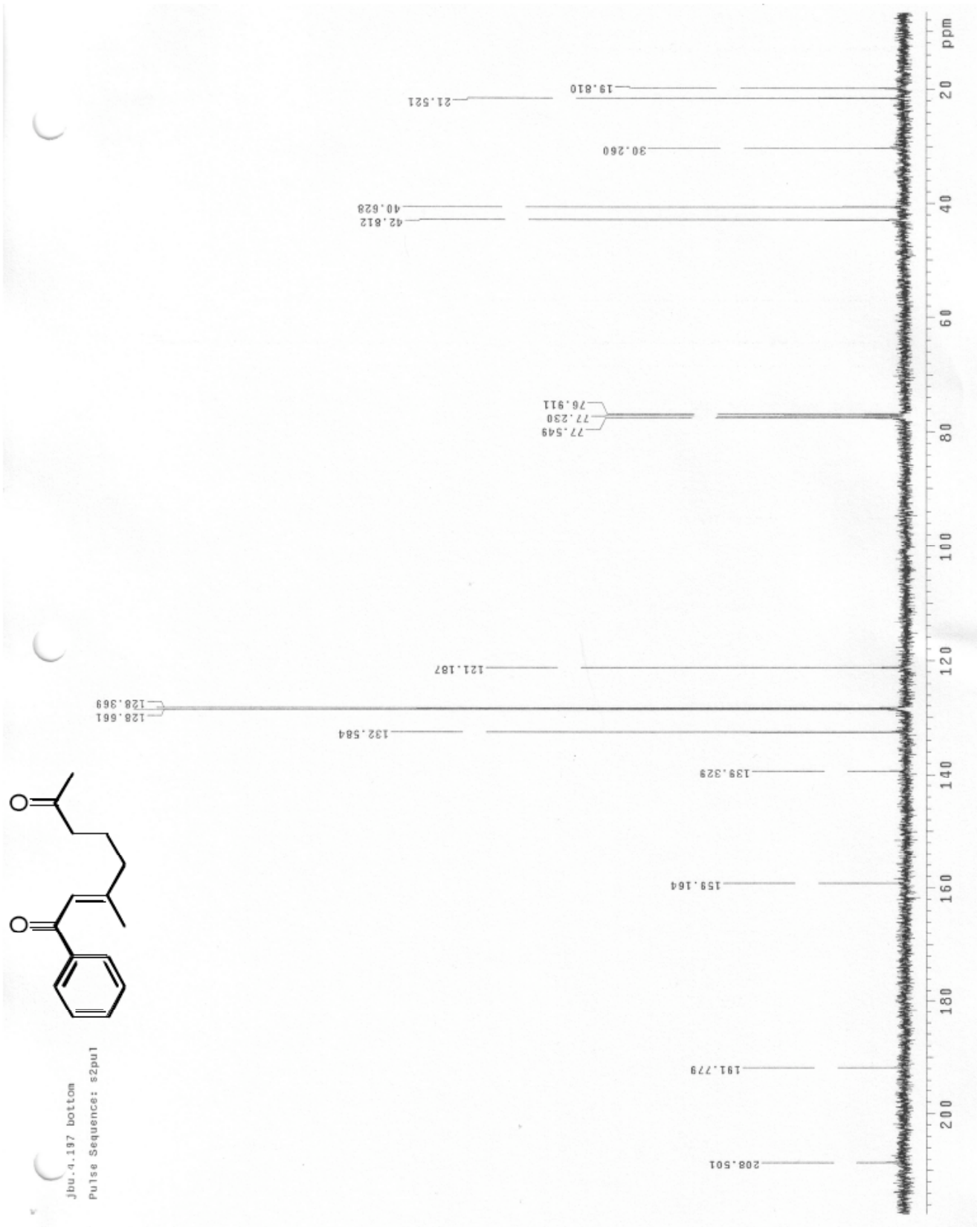

jbu.4.162 mix
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3
EtO
OEt
14.522
14.546
16.837
21.952
22.786
23.946
24.038
25.201
33.207
38.766
39.044
41.054
59.651
59.662
64.825
64.887
76.973
77.227
77.484
101.869
110.034
110.167
115.969
116.658
159.905
160.227
166.533
167.054
0 ppm
20
40
60
80
100
120
140
160
180
200


jbu.4.171 mix
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: H1
Pulse Sequence: s2pul
Solvent: cdcl3
7
6
5
4
3
2
1
0
ppm
4.13
17.69
12.83
3.52
9.28
2.29
6.54
9.39
3.17
18.23
12.93

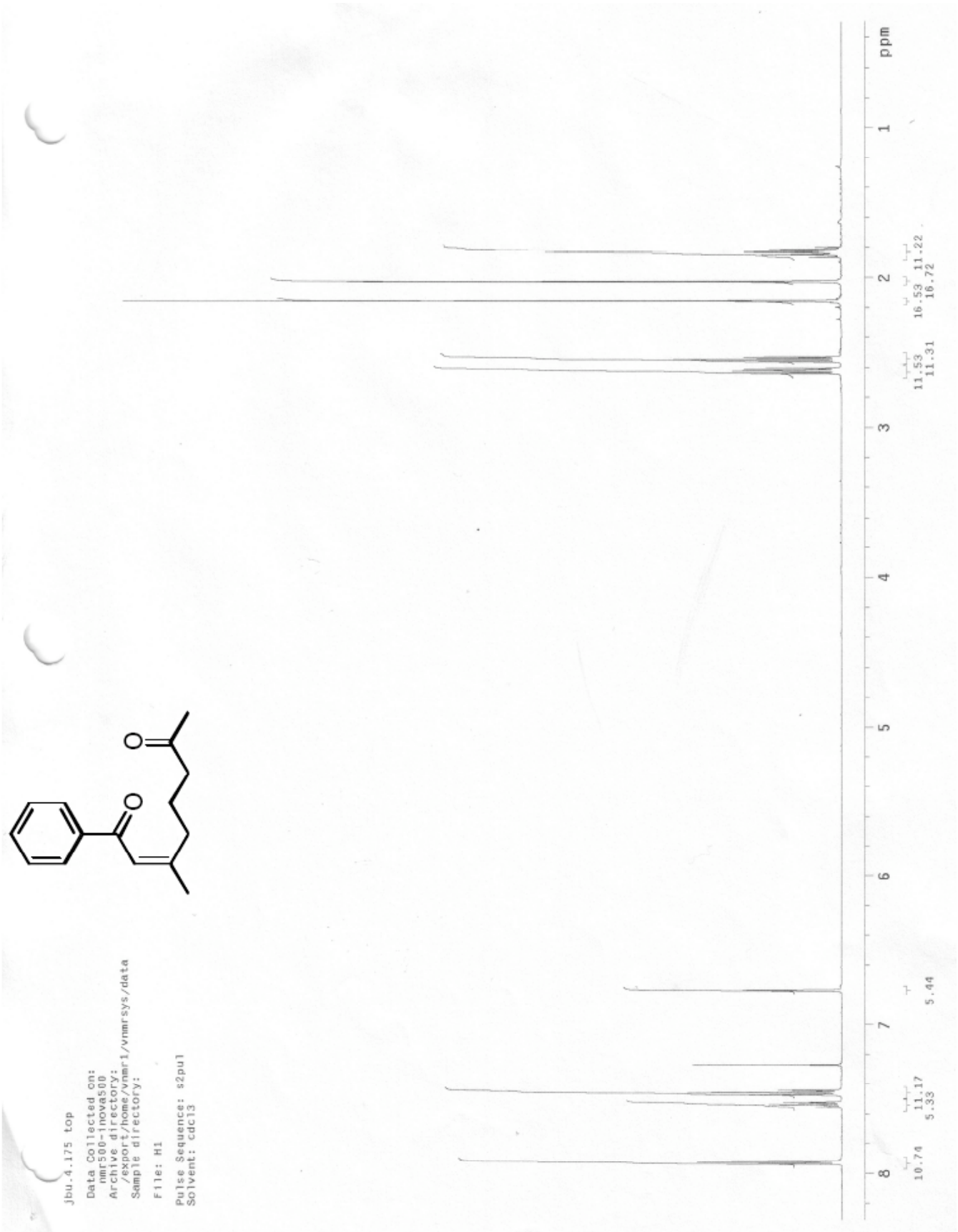

jbu.4.171 mix
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3
15.492
18.772
22.175
22.869
23.939
24.045
25.297
25.819
33.369
38.845
39.078
41.305
61.617
64.797
64.887
66.074
68.190
76.976
77.230
77.484
110.085
110.250
114.274
0
20
40
60
80
100
120
140
160
180
200
ppm



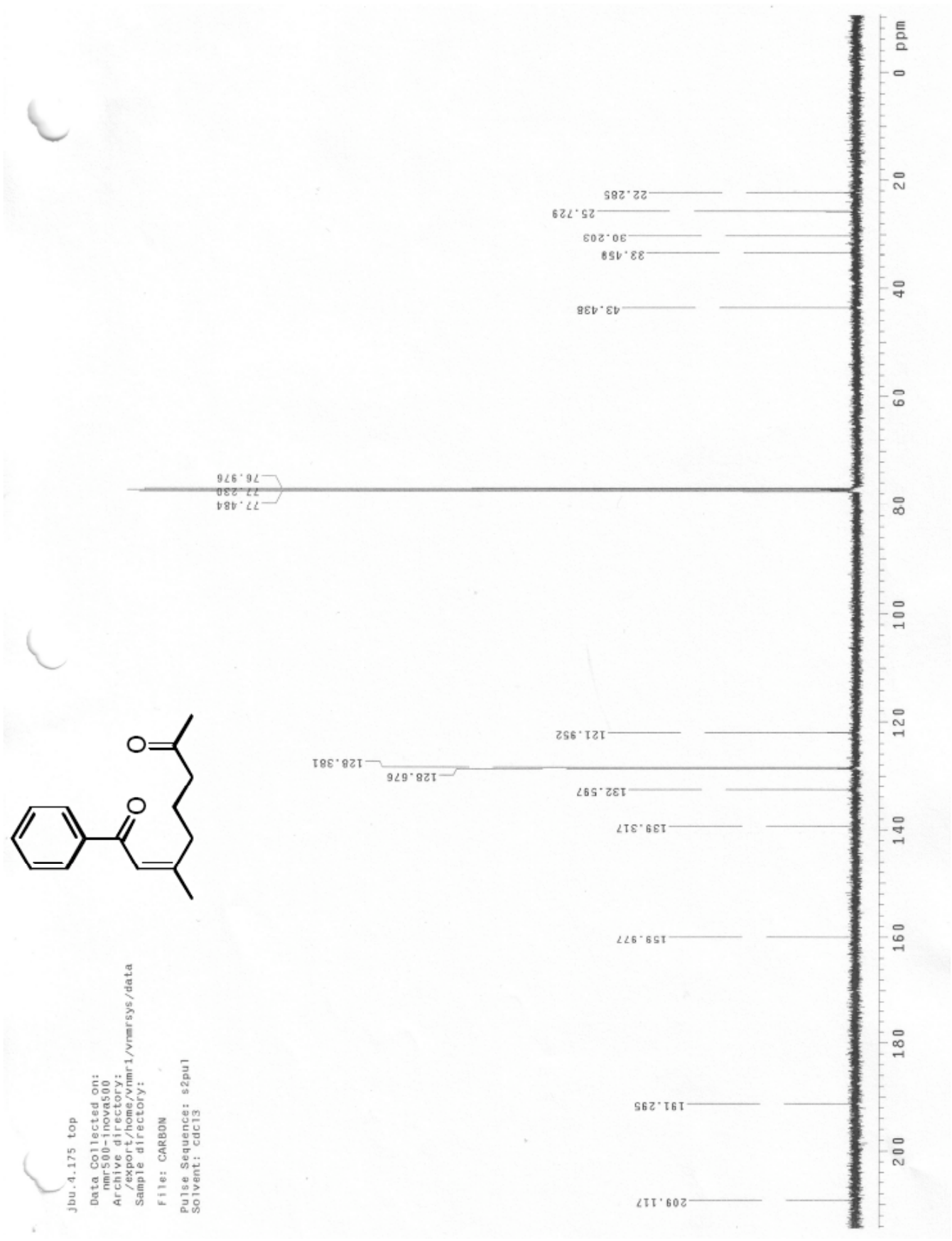
Starting Material: Table 2, Entry 6



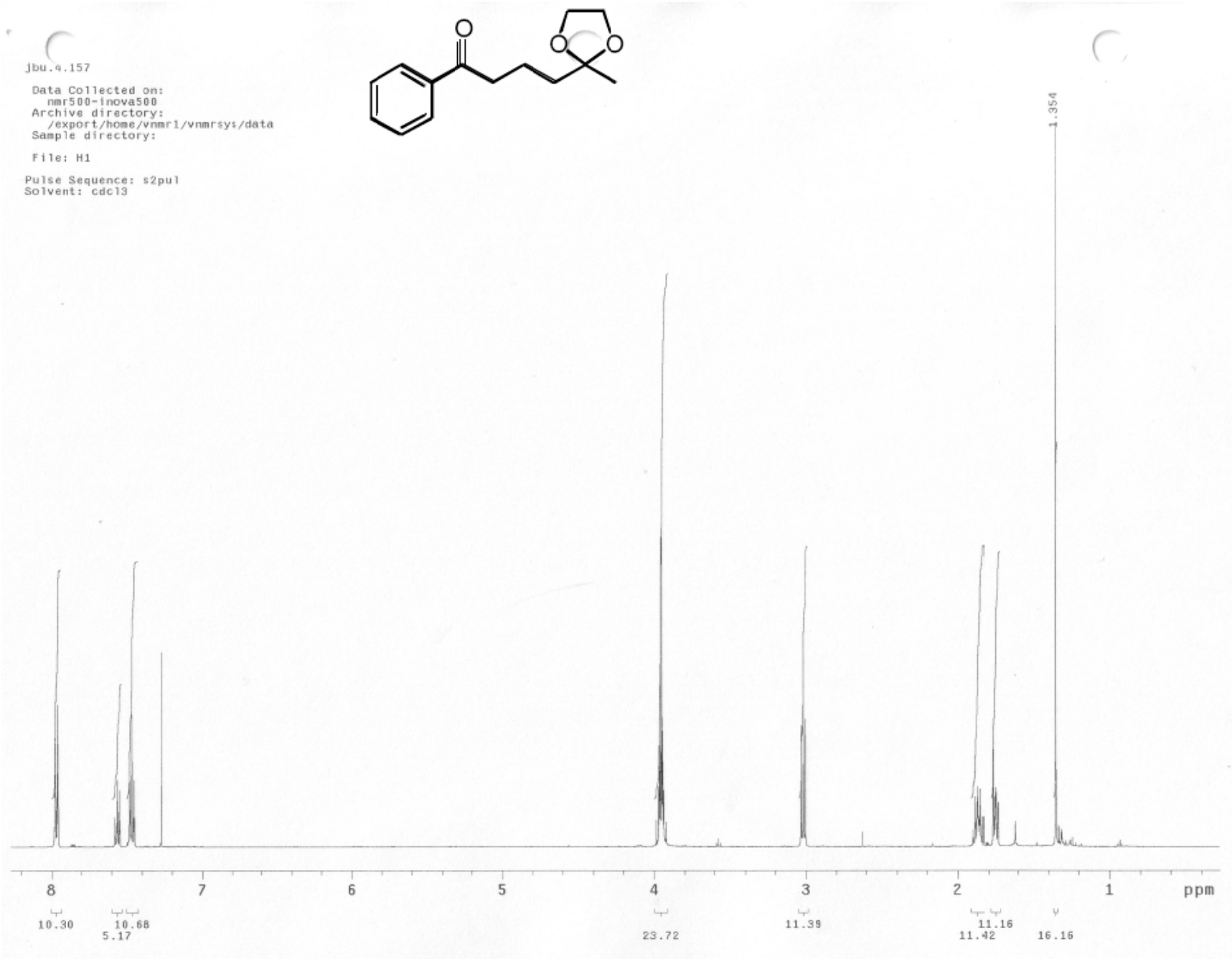
Starting Material: Table 2, Entry 6

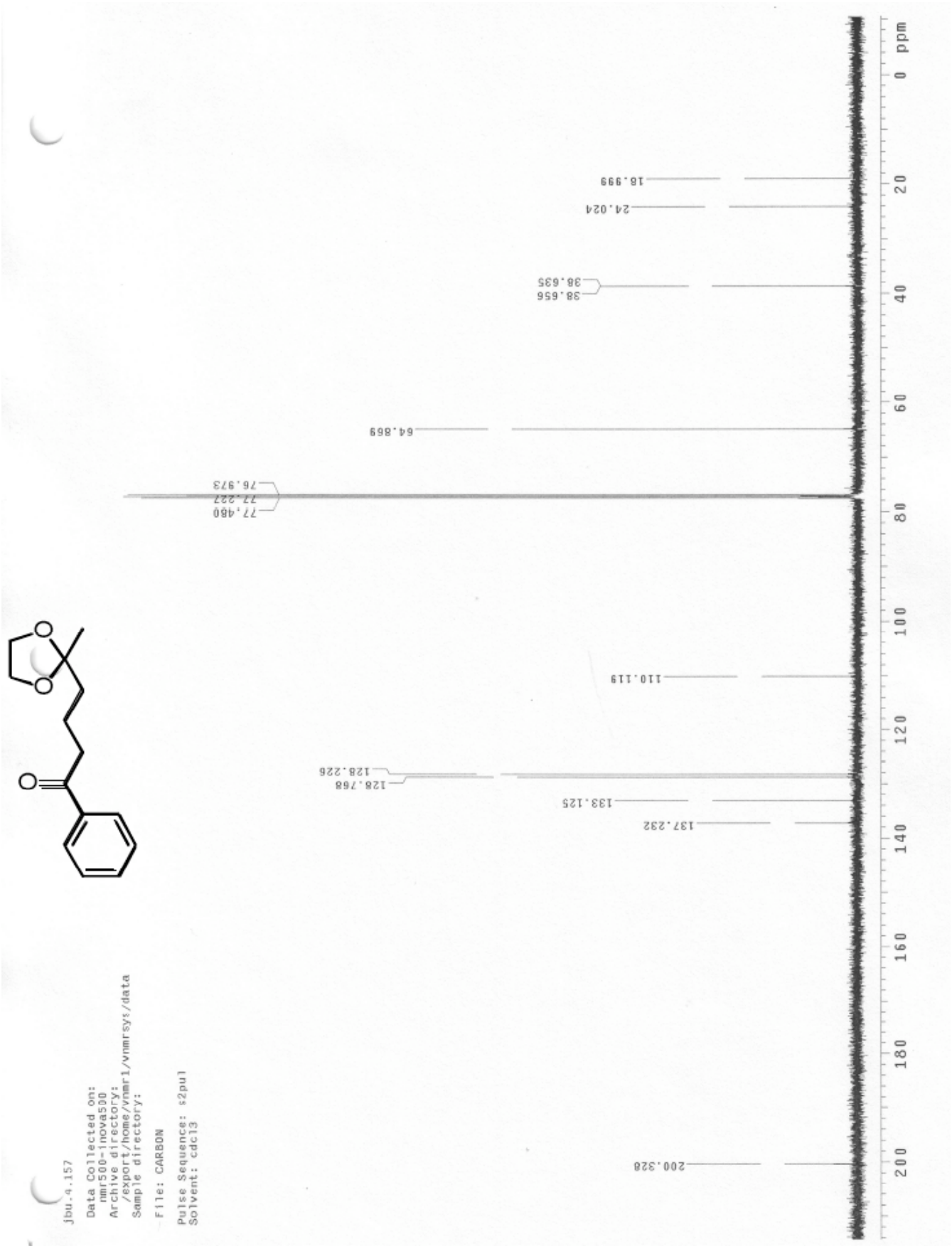


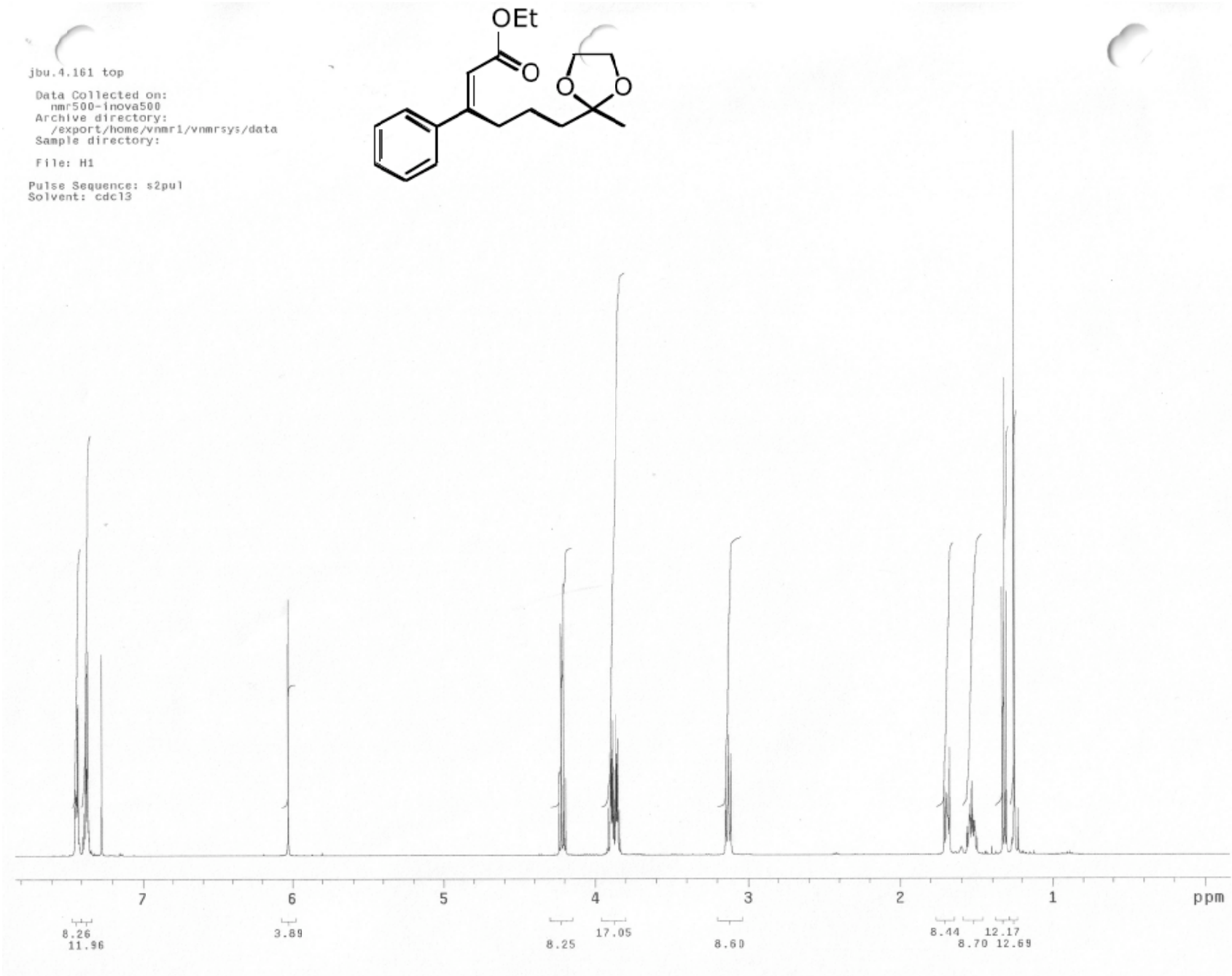
Starting Material: Table 2, Entry 7

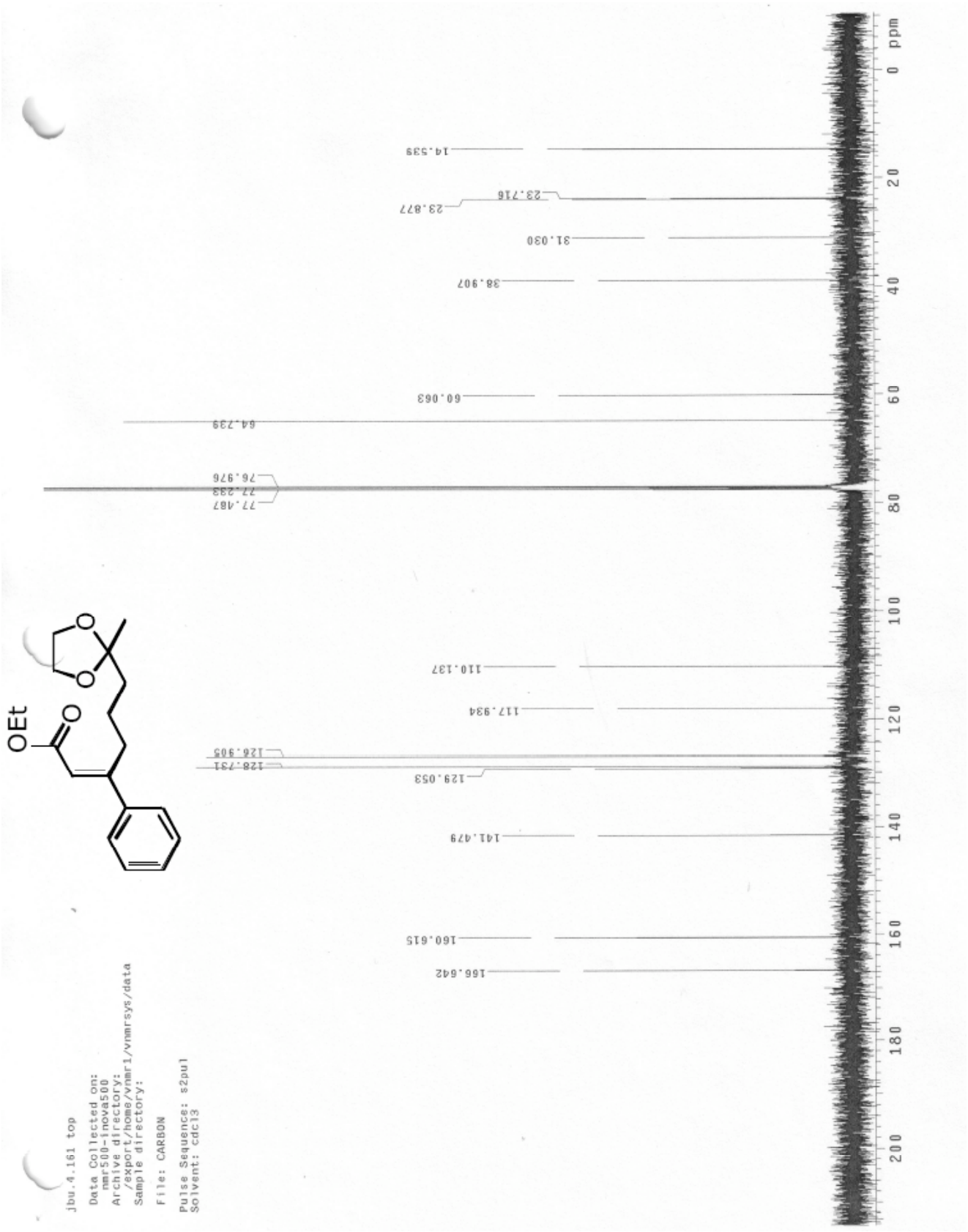


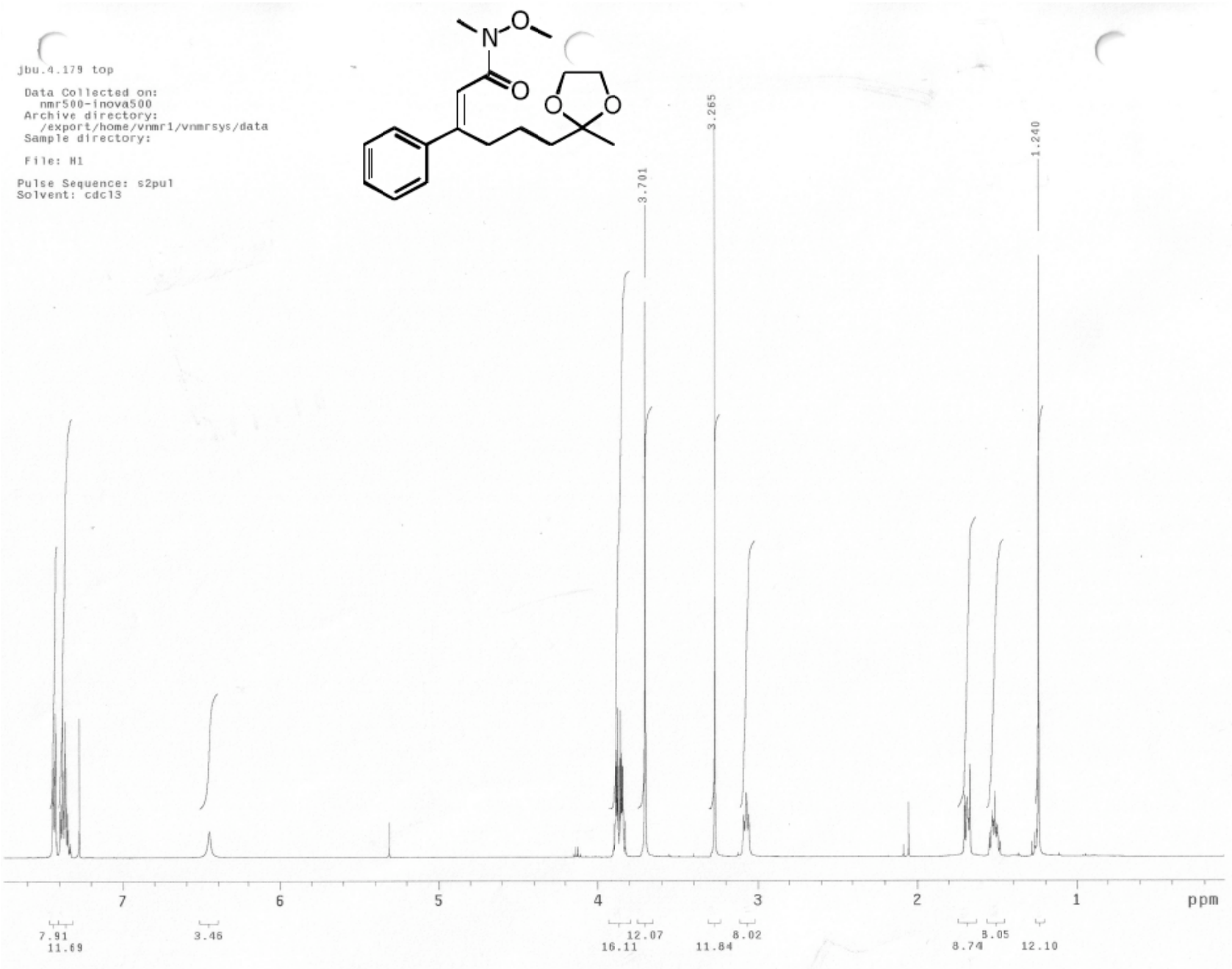
Starting Material: Table 2, Entry 7

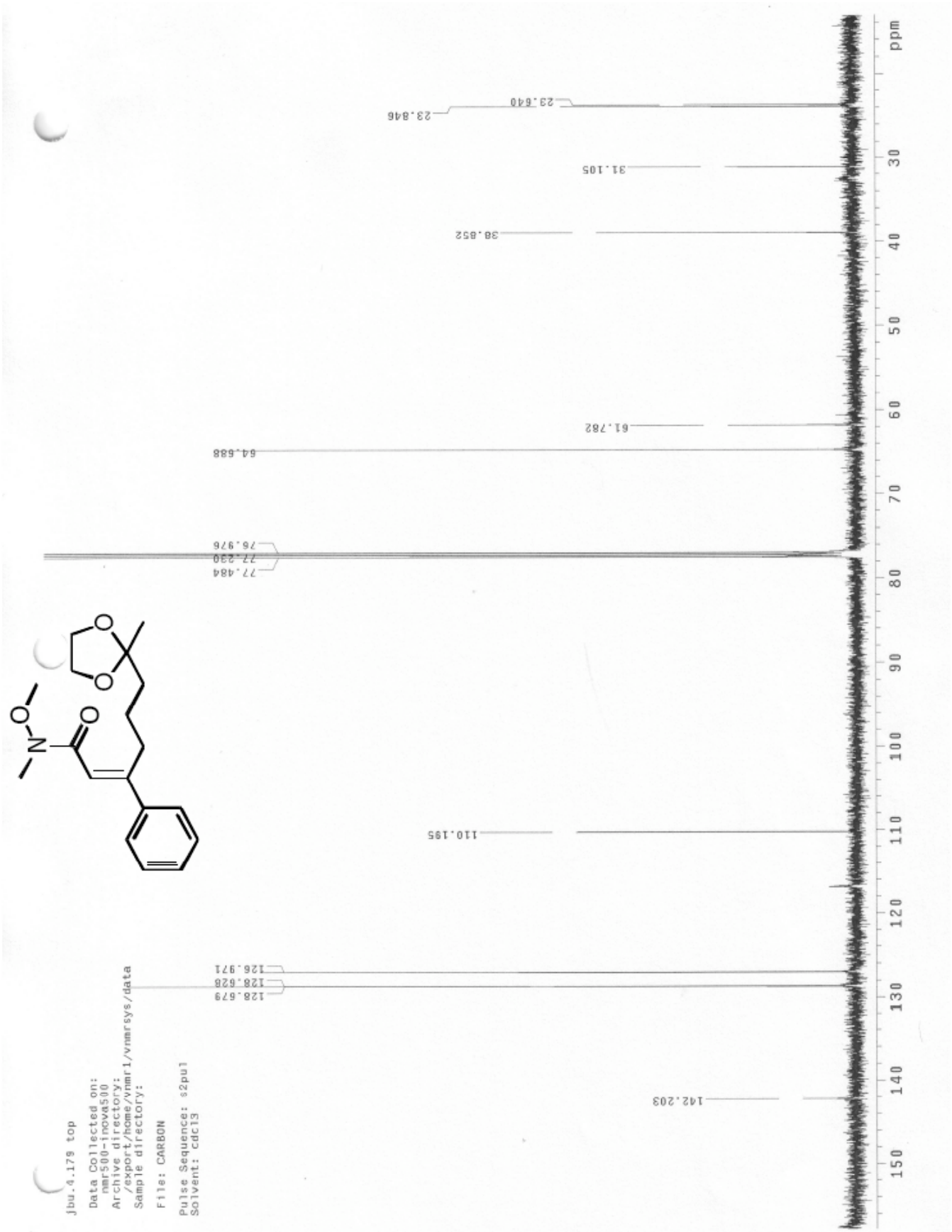

jbu.4.157
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: H1
Pulse Sequence: s2pul
Solvent: cdcl3
1.354
8
7
6
5
4
3
2
1
ppm
10.30
10.68
5.17
23.72
11.39
11.16
11.42
16.16

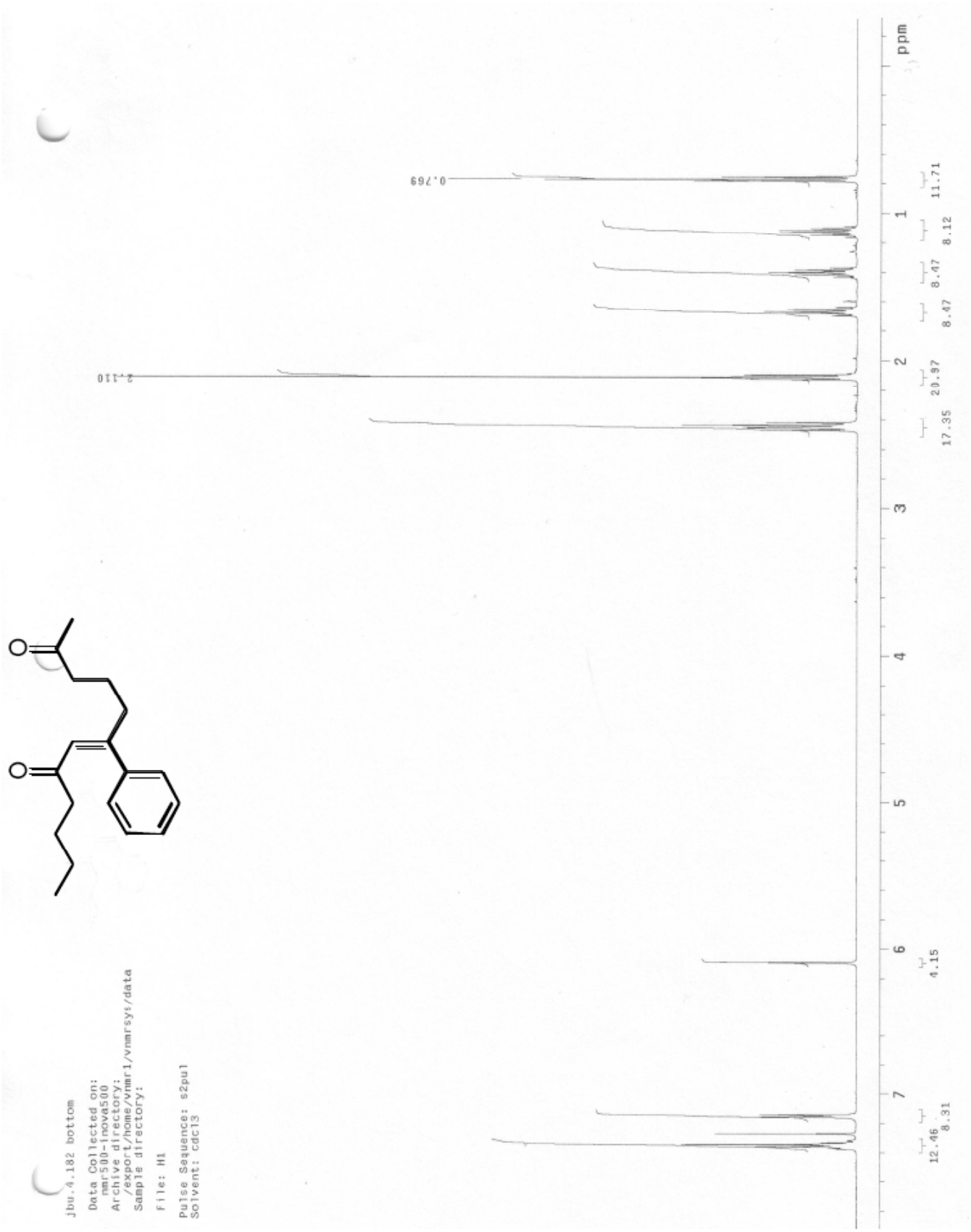

jbu.4.157
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3
200.328
137.232
133.125
128.768
128.226
110.119
77.480
77.227
76.973
64.869
38.656
38.635
24.024
16.999
0 ppm


jbu.4.161 top
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: H1
Pulse Sequence: s2pul
Solvent: cdcl3
OEt
O
O
O
7
6
5
4
3
2
1
ppm
8.26
11.96
3.89
8.25
17.05
8.60
8.44
8.70
12.17
12.69

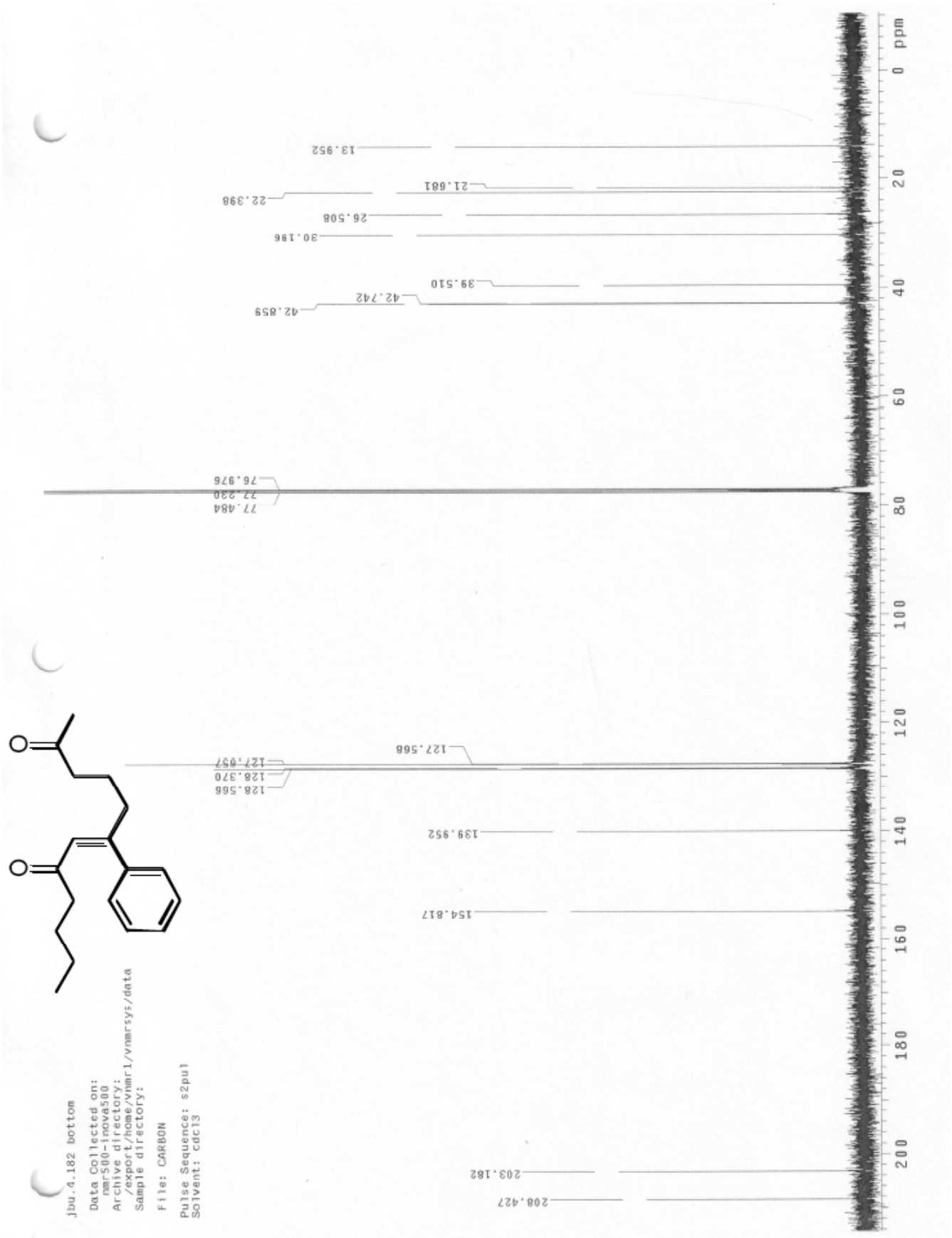

jbu.4.161 top
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3
OEt
14.539
23.716
23.877
31.030
38.907
60.063
64.239
76.976
77.233
77.487
110.137
117.934
126.905
128.731
129.053
141.479
160.615
166.642
0 ppm
20
40
60
80
100
120
140
160
180
200


jbu.4.179 top
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: H1
Pulse Sequence: s2pul
Solvent: cdcl3
3.701
3.265
1.240
7
6
5
4
3
2
1
ppm
7.91
11.69
3.46
16.11
12.07
11.84
8.02
8.74
8.05
12.10

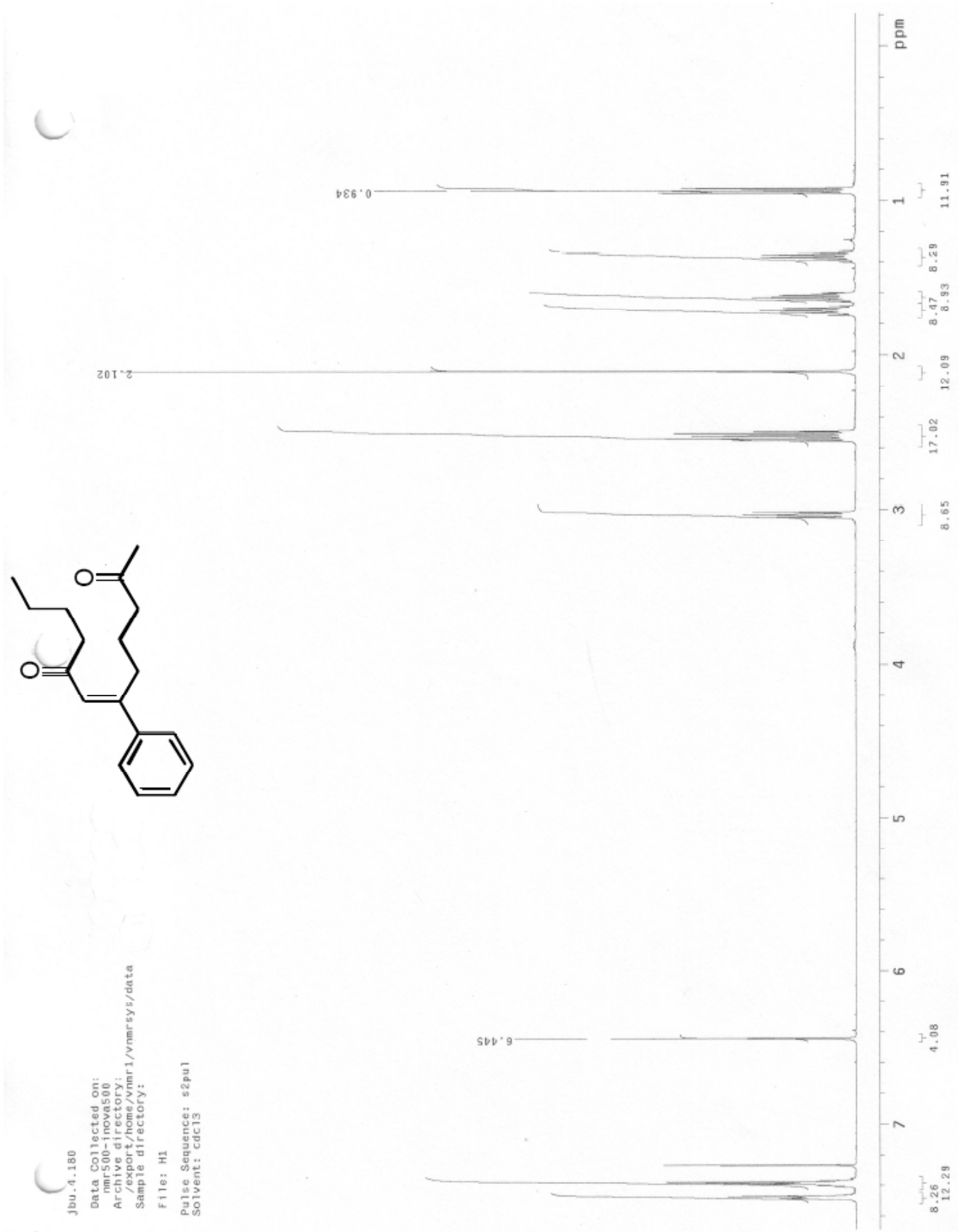

jbu.4.179 top
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3
142.203
128.679
128.628
126.971
110.195
77.484
77.230
76.976
64.688
61.782
38.852
31.105
23.846
23.640
ppm



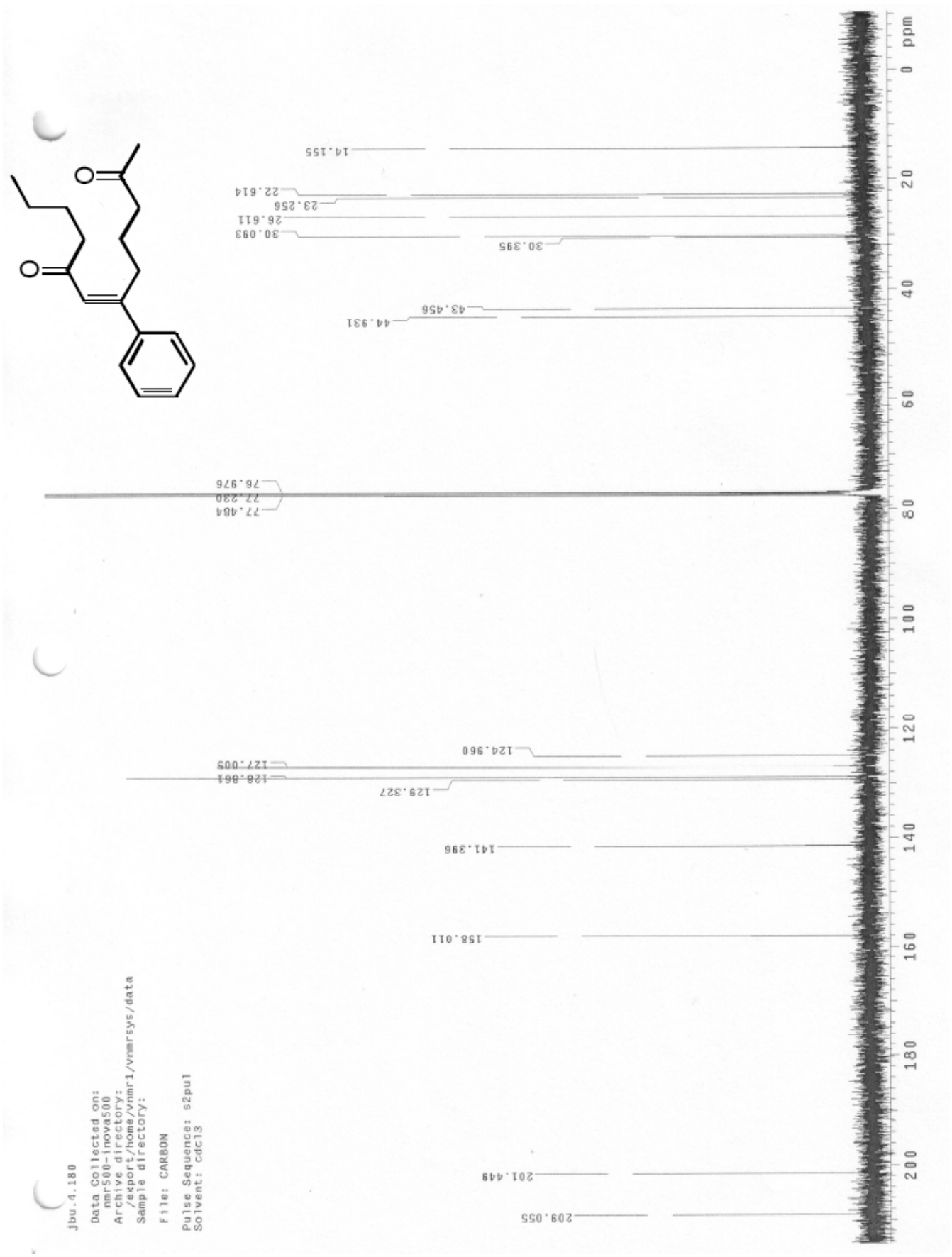
Starting Material: Table 2, Entry 8



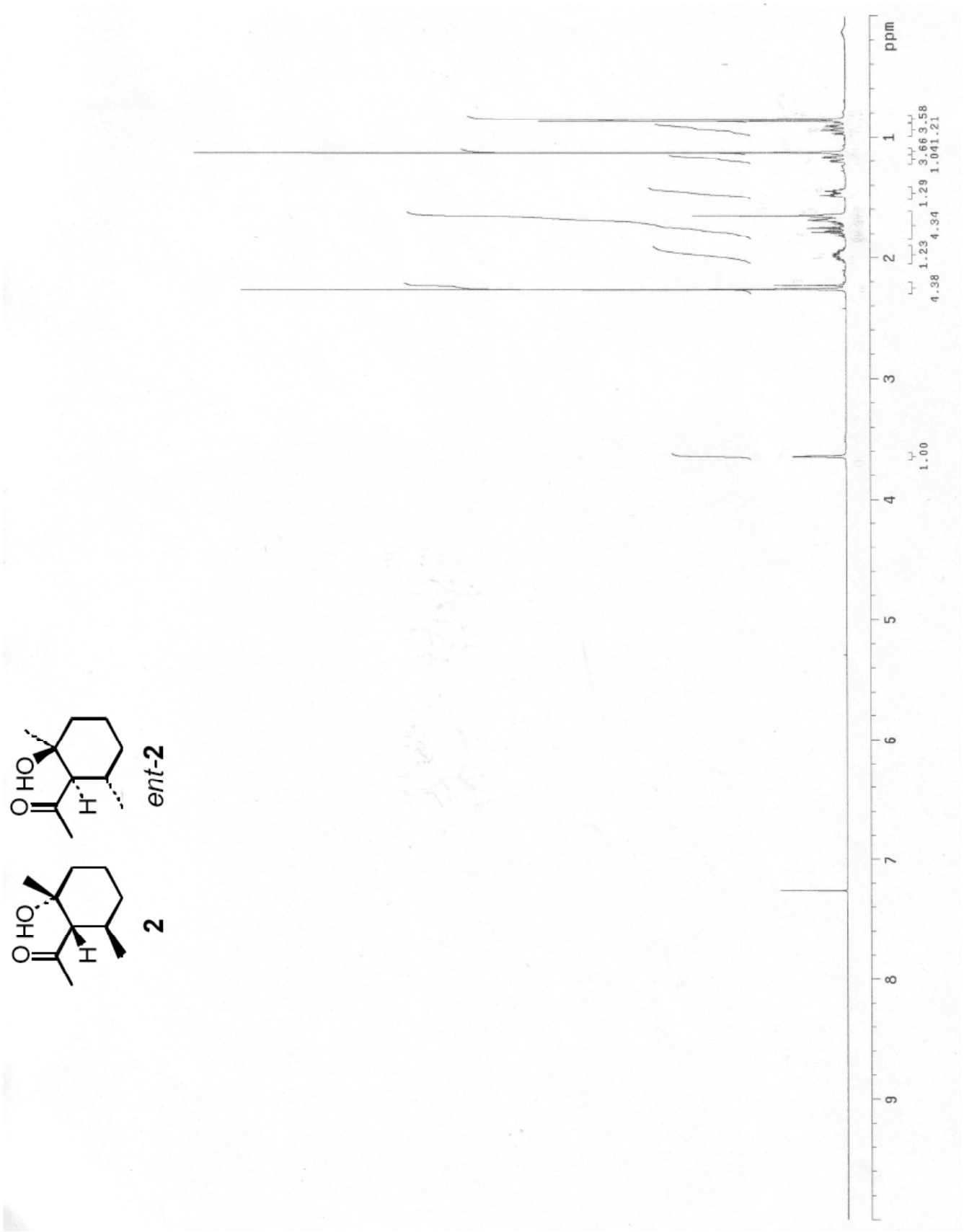
Starting Material: Table 2, Entry 8



Starting Material: Table 2, Entry 9



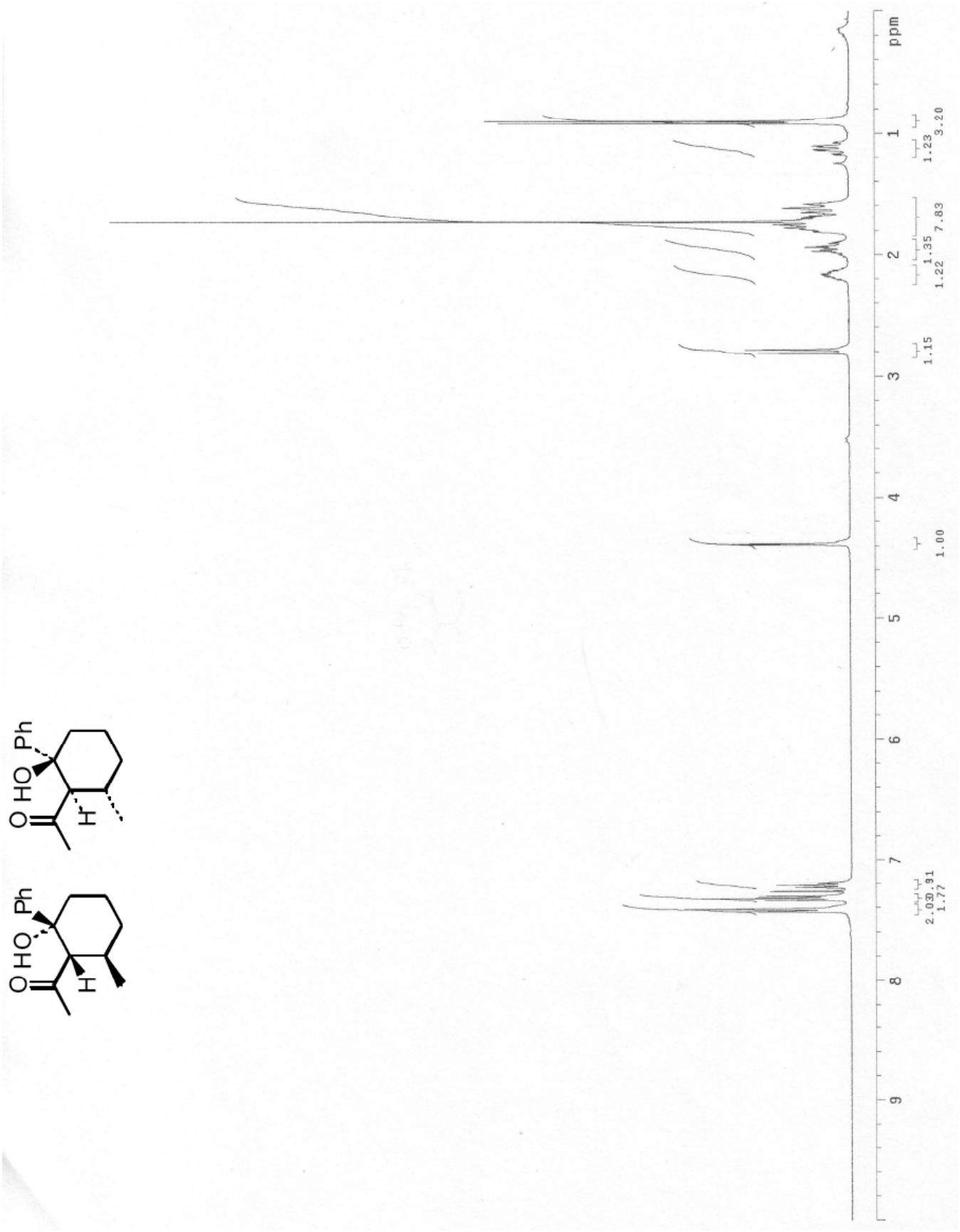
Starting Material: Table 2, Entry 9



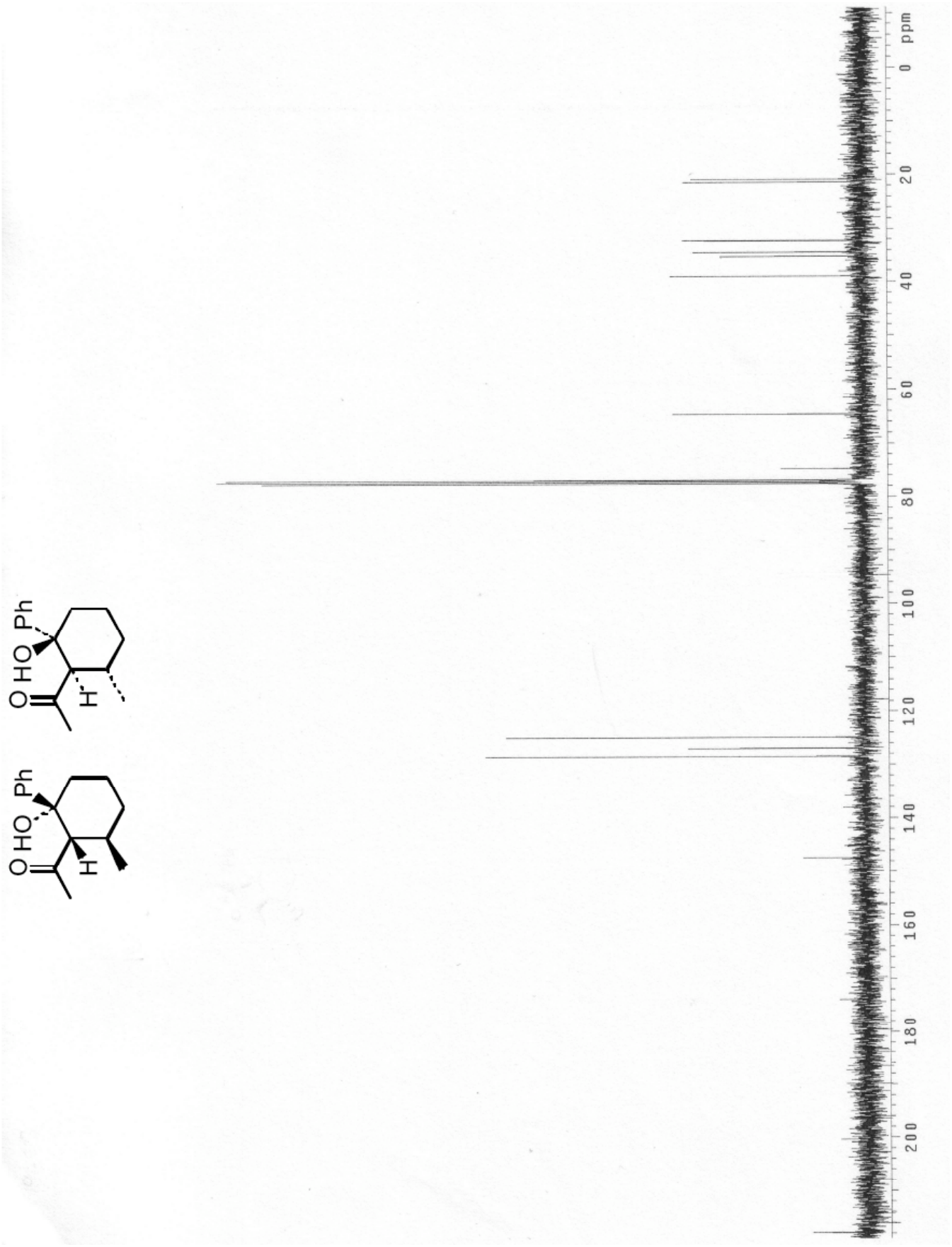
2 *ent*-**2**

Products: Table 2, Entries 1 and 2

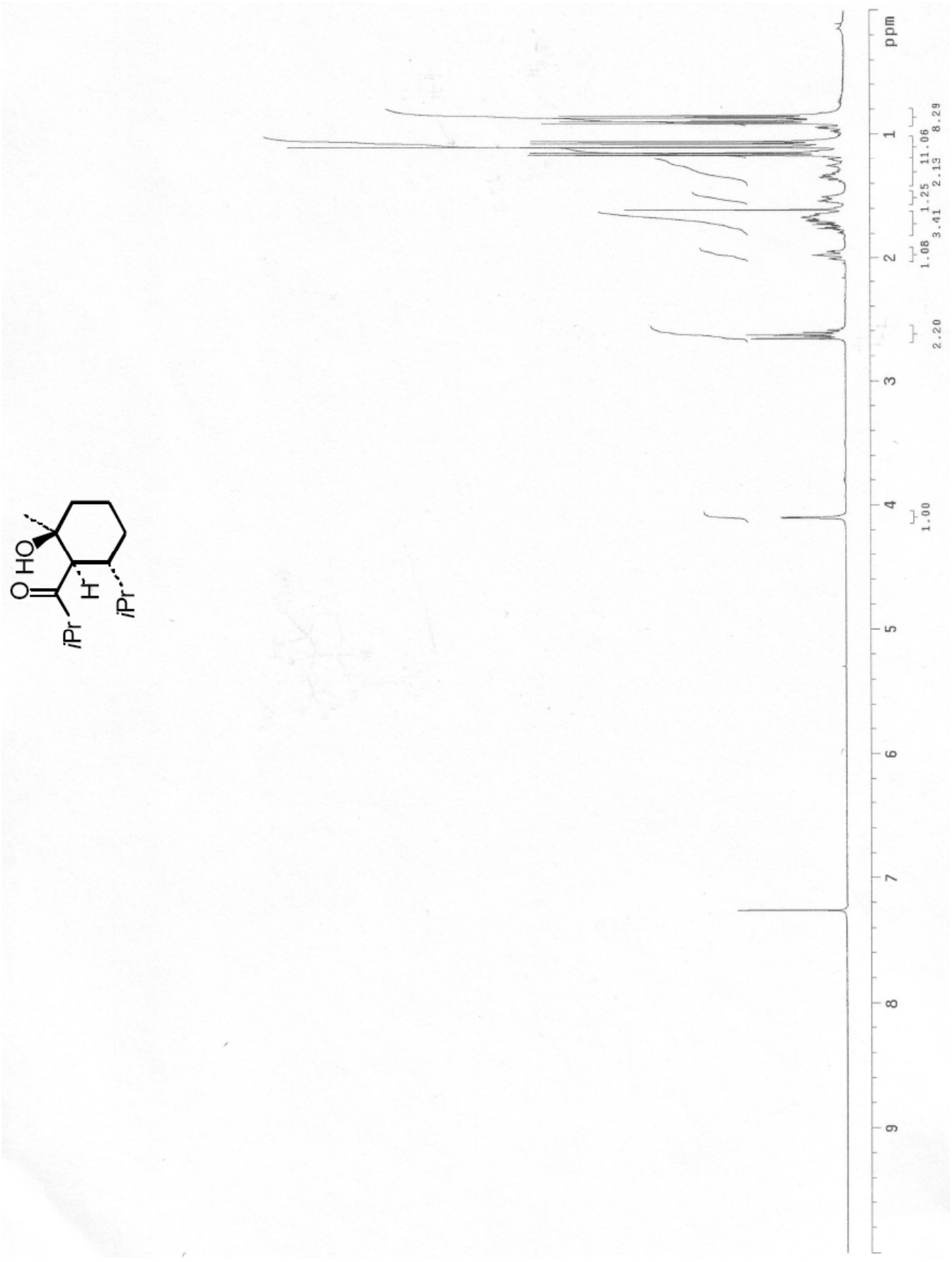
Products: Table 2, Entries 1 and 2



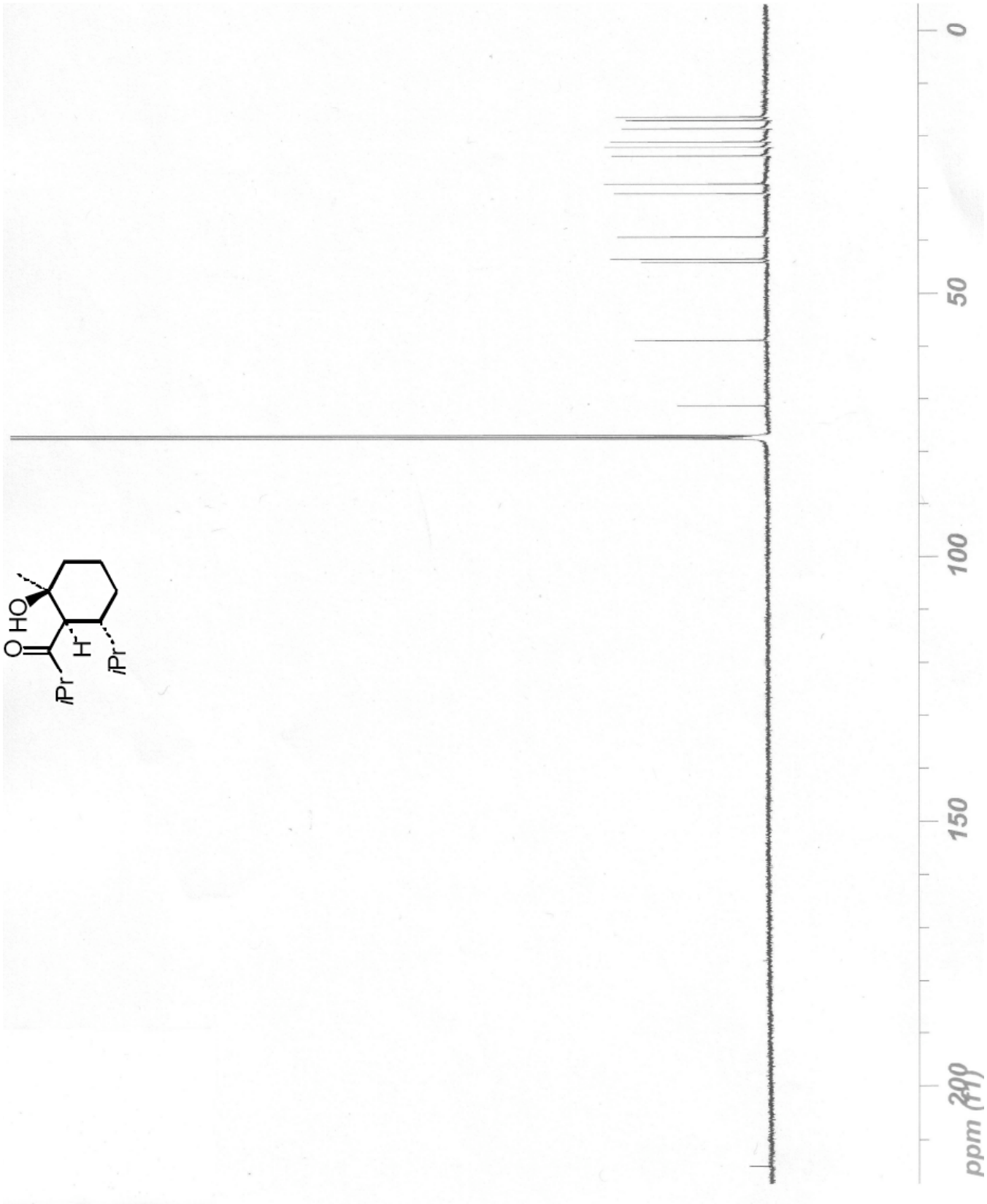
Products: Table 2, Entries 3 and 4



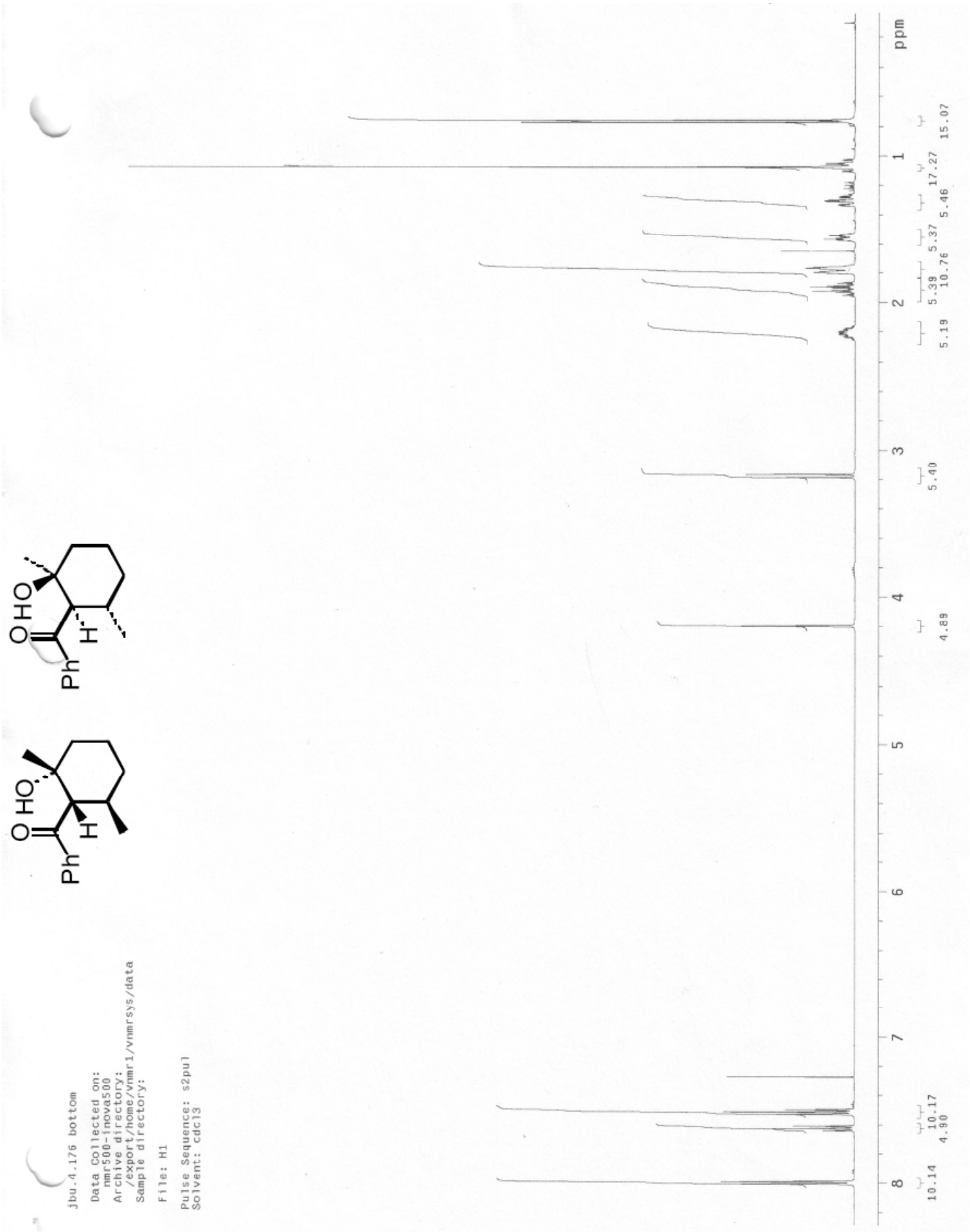
Products: Table 2, Entries 3 and 4



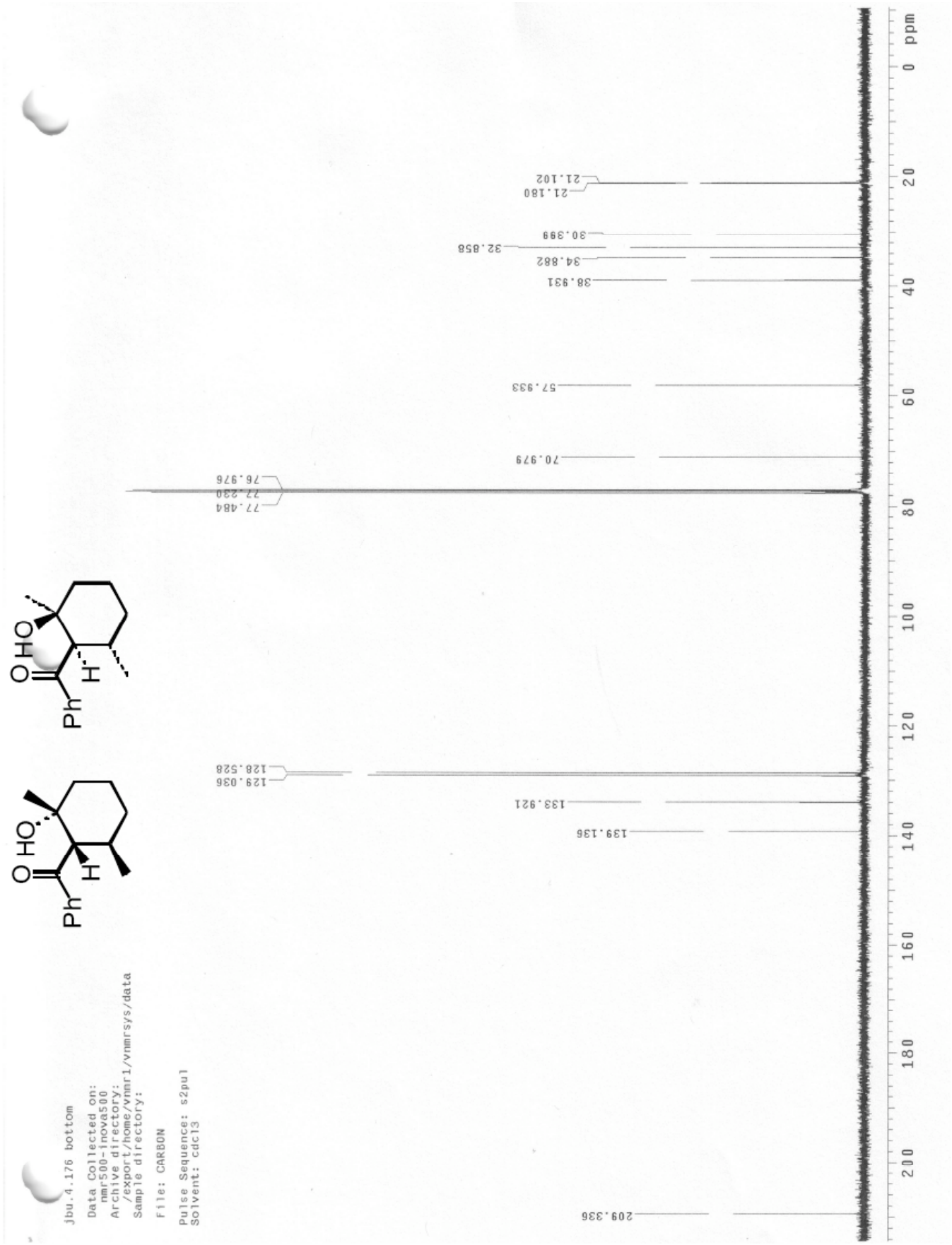
Product: Table 2, Entry 5



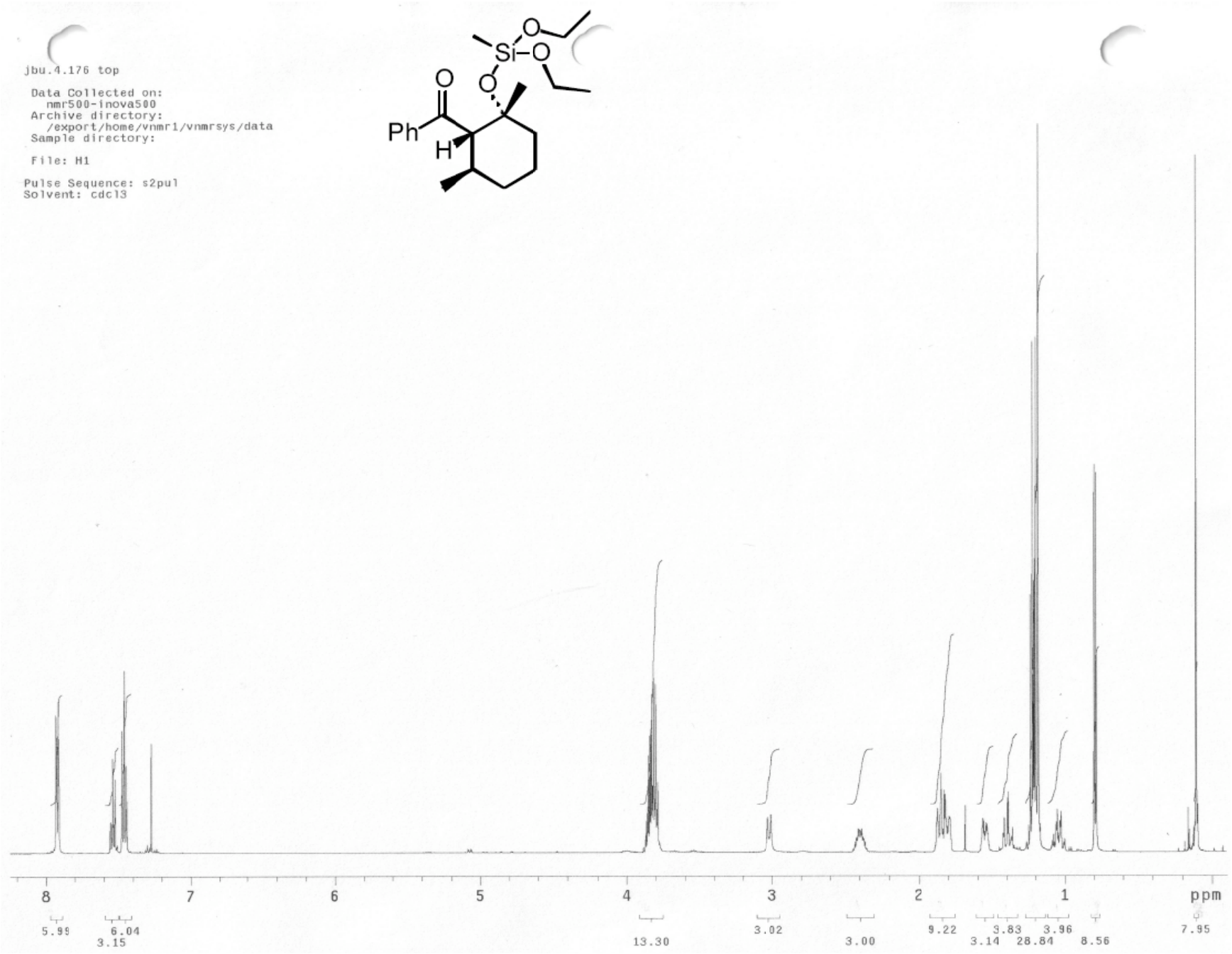
Product: Table 2, Entry 5

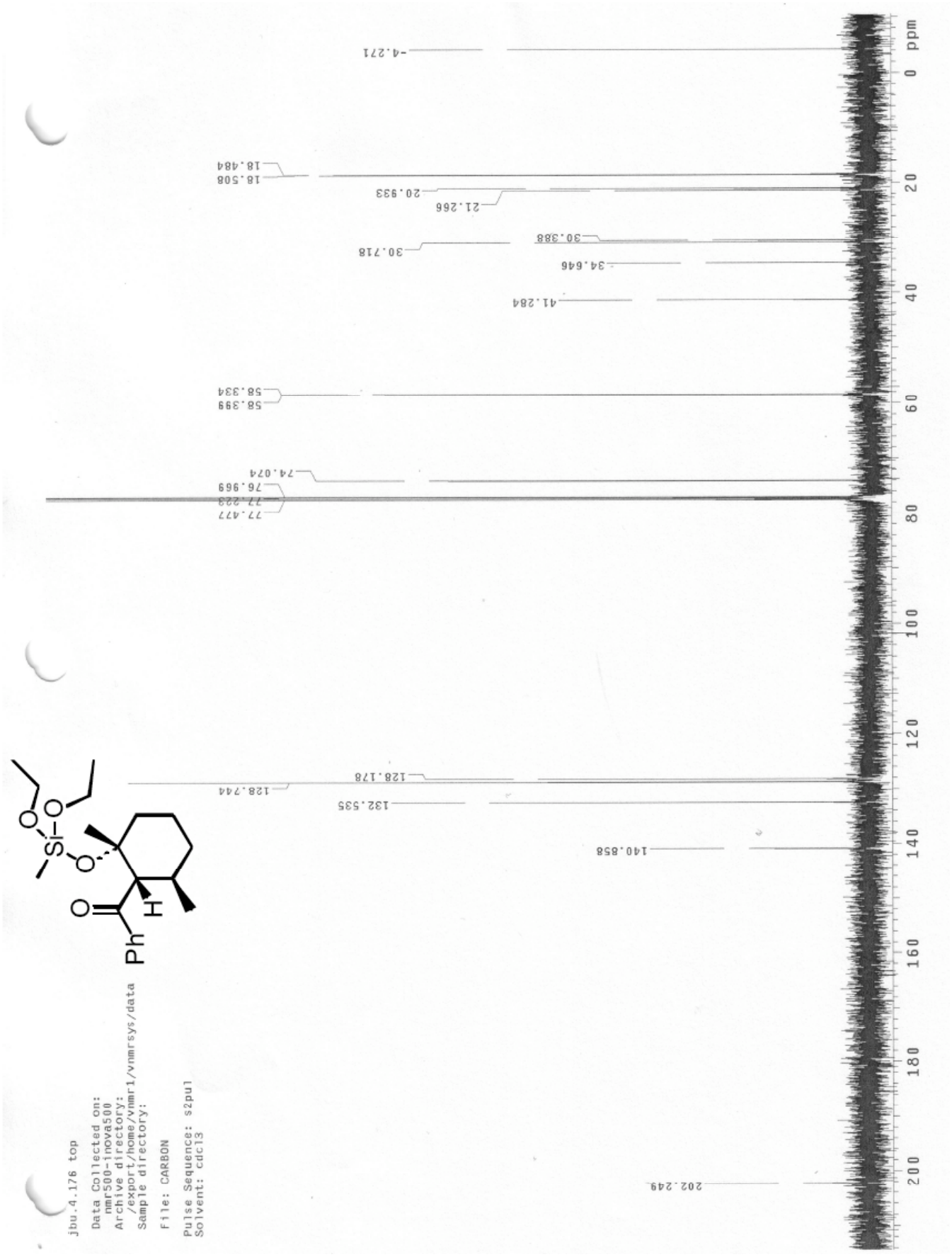


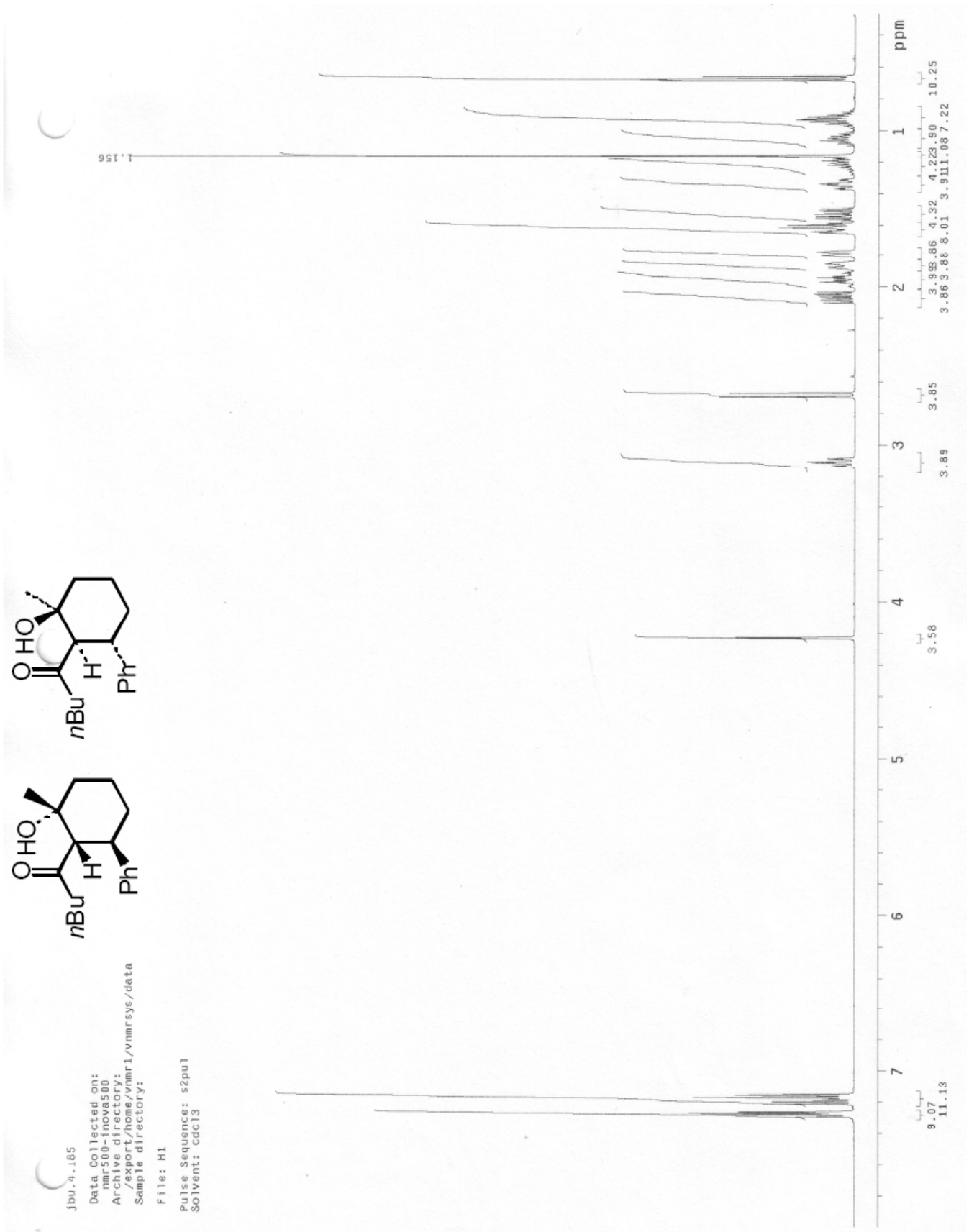
Products: Table 2, Entries 6 and 7



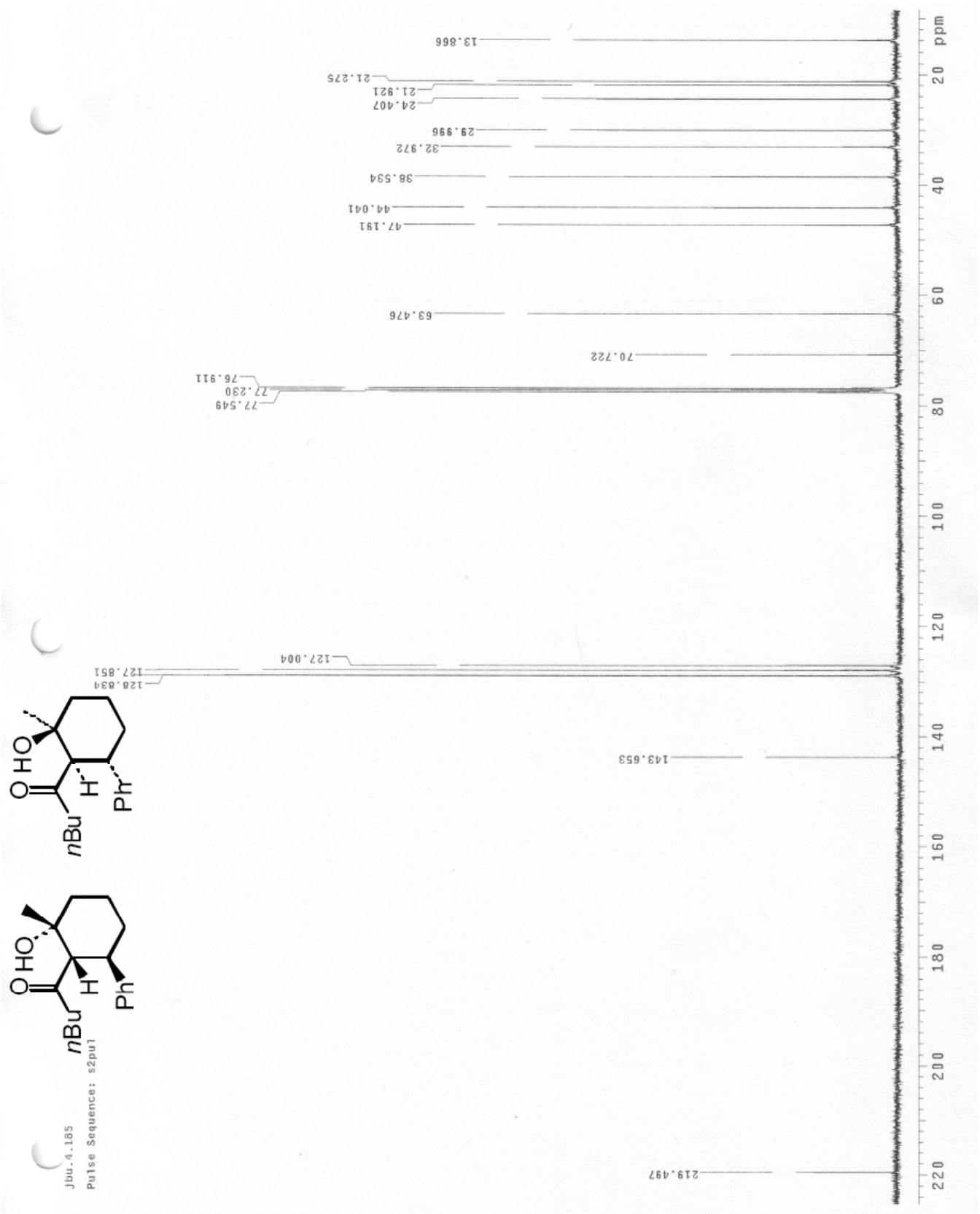
Products: Table 2, Entries 6 and 7


jbu.4.176 top
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: H1
Pulse Sequence: s2pul
Solvent: cdcl3
Ph
H
O
Si
O
O
8
7
6
5
4
3
2
1
ppm
5.99
6.04
3.15
13.30
3.02
3.00
9.22
3.14
3.83
28.84
3.96
8.56
7.95

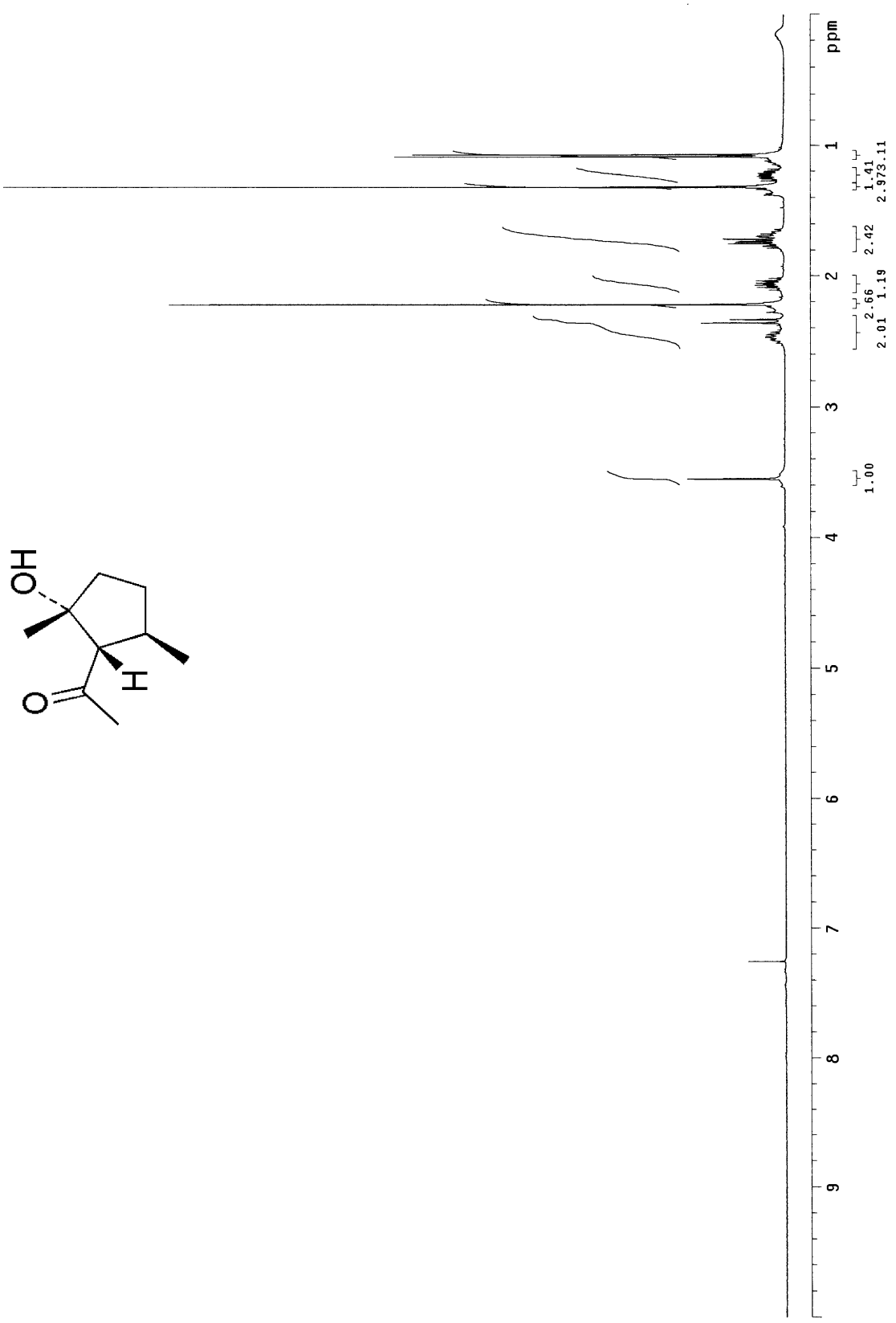

jbu.4.176 top
Data Collected on:
nmr500-inova500
Archive directory:
/export/home/vnmr1/vnmrsys/data
Sample directory:
File: CARBON
Pulse Sequence: s2pul
Solvent: cdcl3
-4.271
18.484
18.508
20.933
21.266
30.388
30.718
34.646
41.284
58.334
58.399
74.074
76.969
77.223
77.477
128.178
128.744
132.535
140.858
202.249
0 ppm
20
40
60
80
100
120
140
160
180
200
Si
O
O
O
O
H
Ph



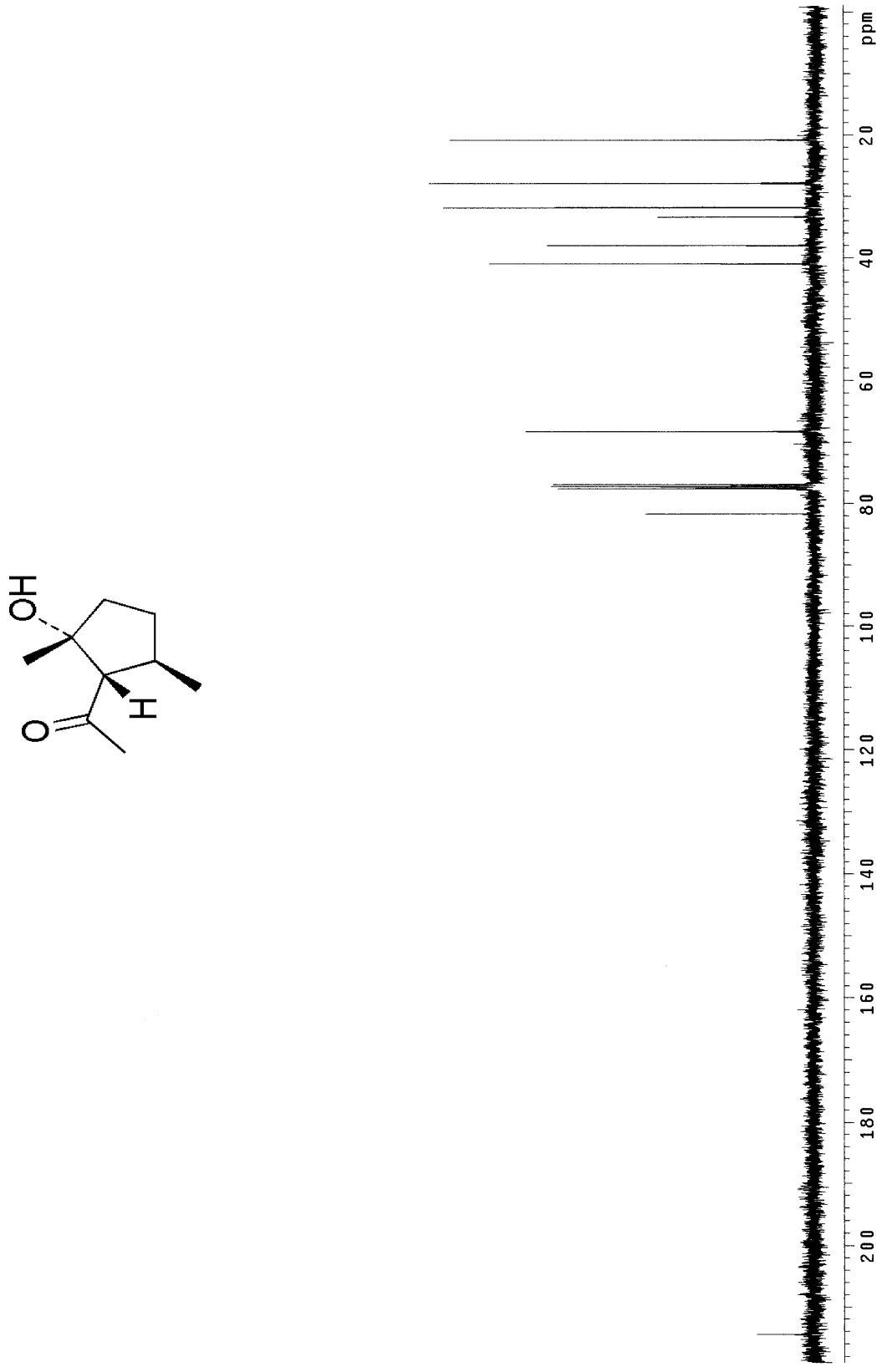
Products: Table 2, Entries 8 and 9



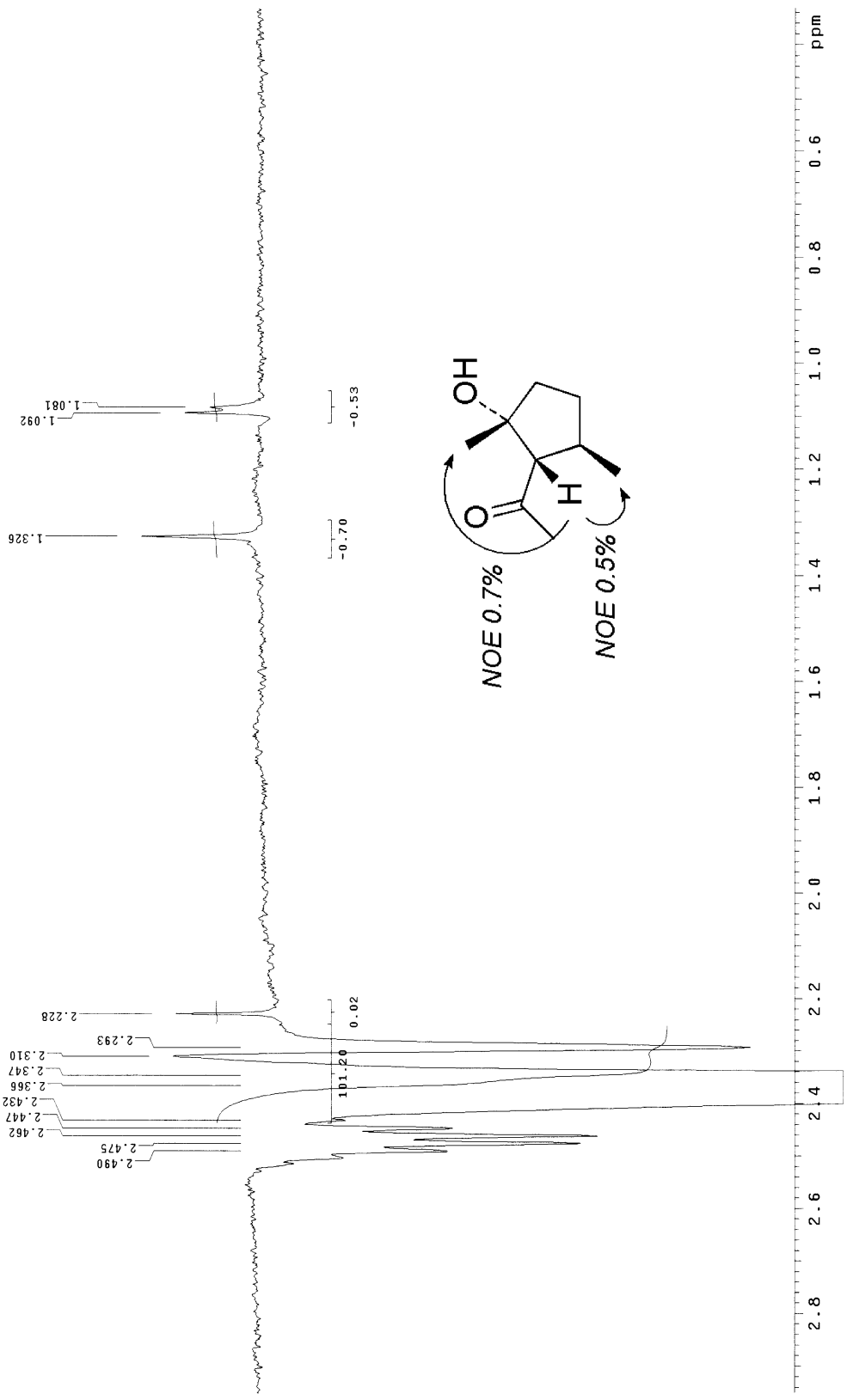
Products: Table 2, Entries 8 and 9



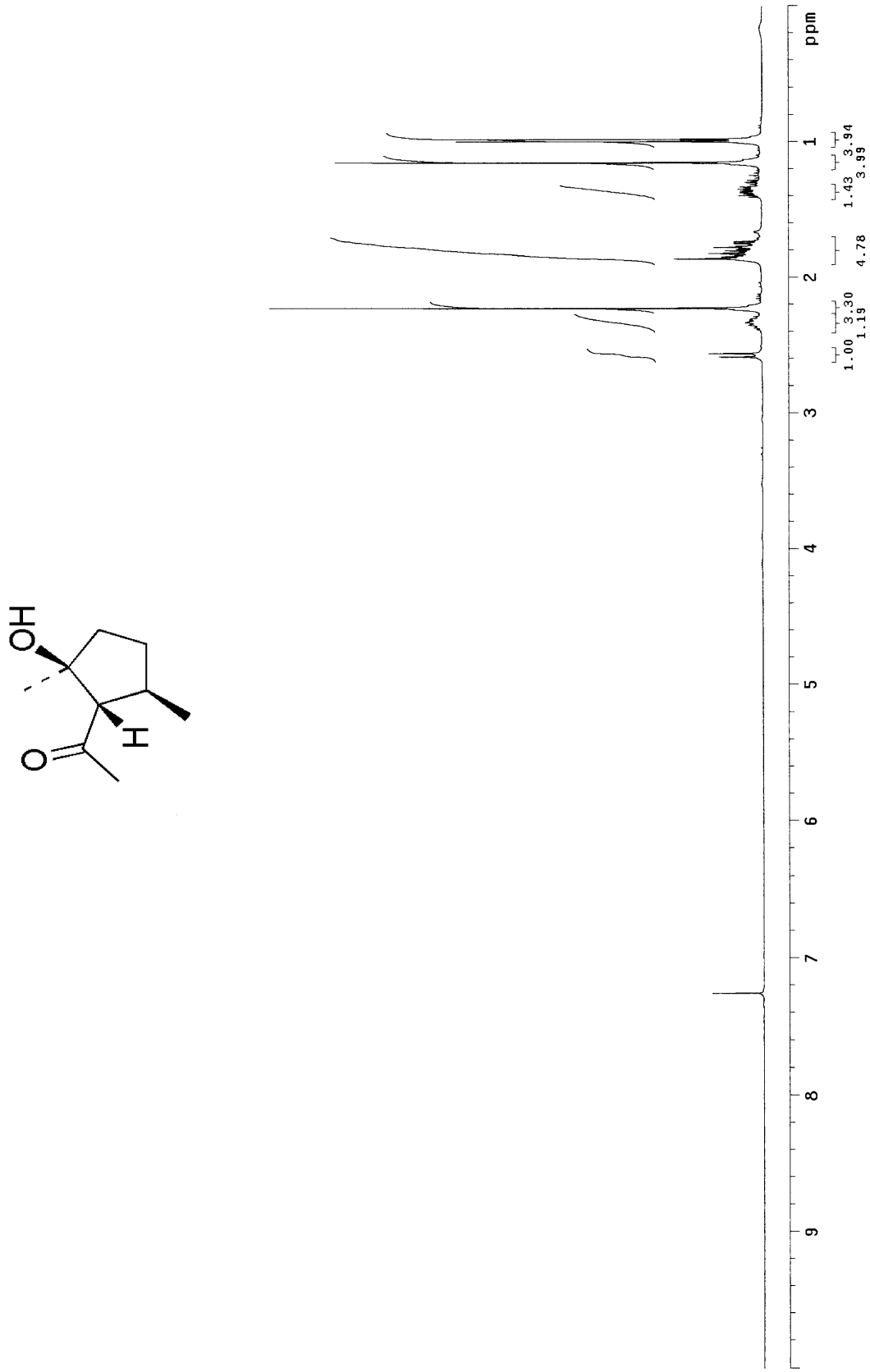
Product: Table 2, Entry 10 (1st diastereomer)



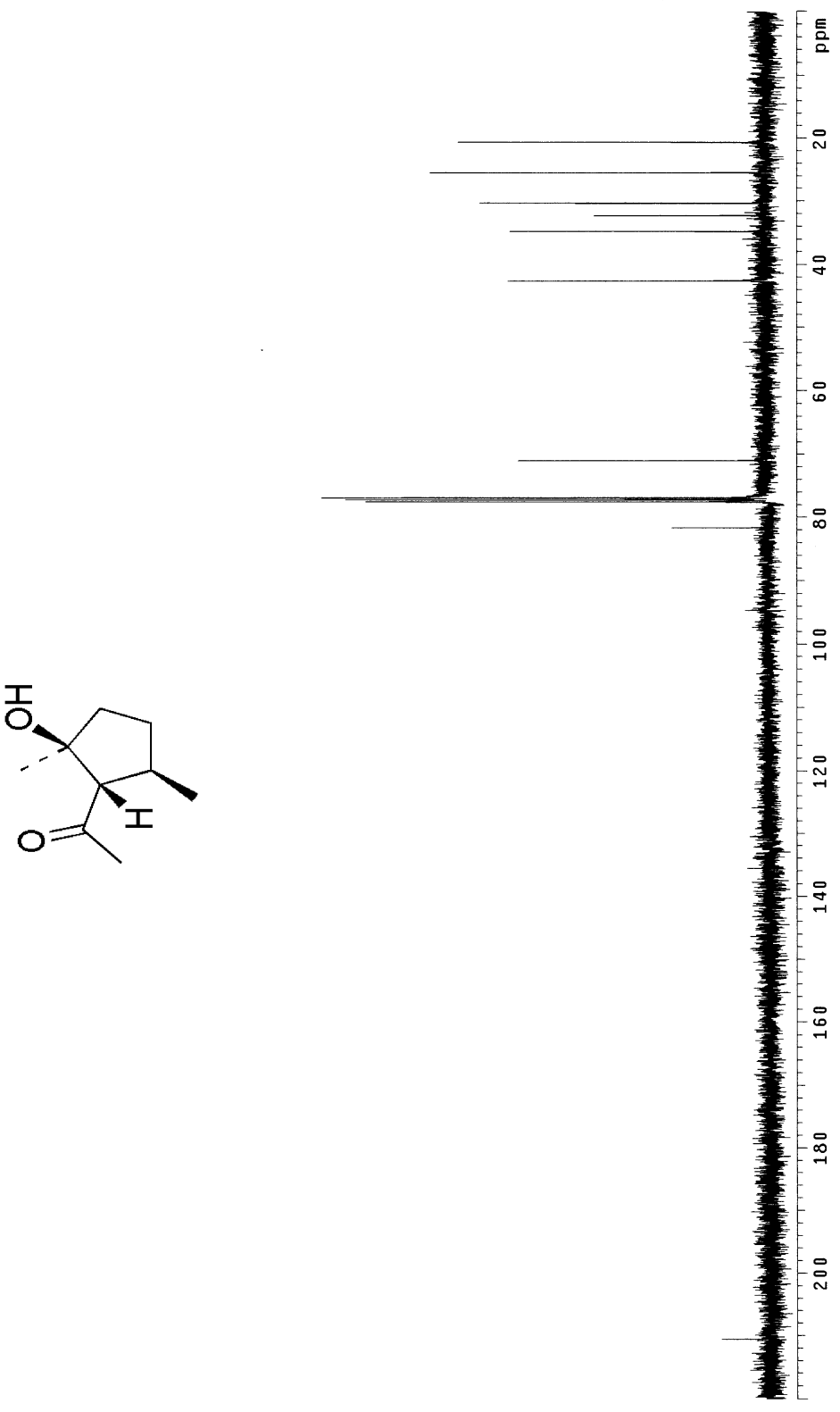
Product: Table 2, Entry 10 (1st diastereomer)



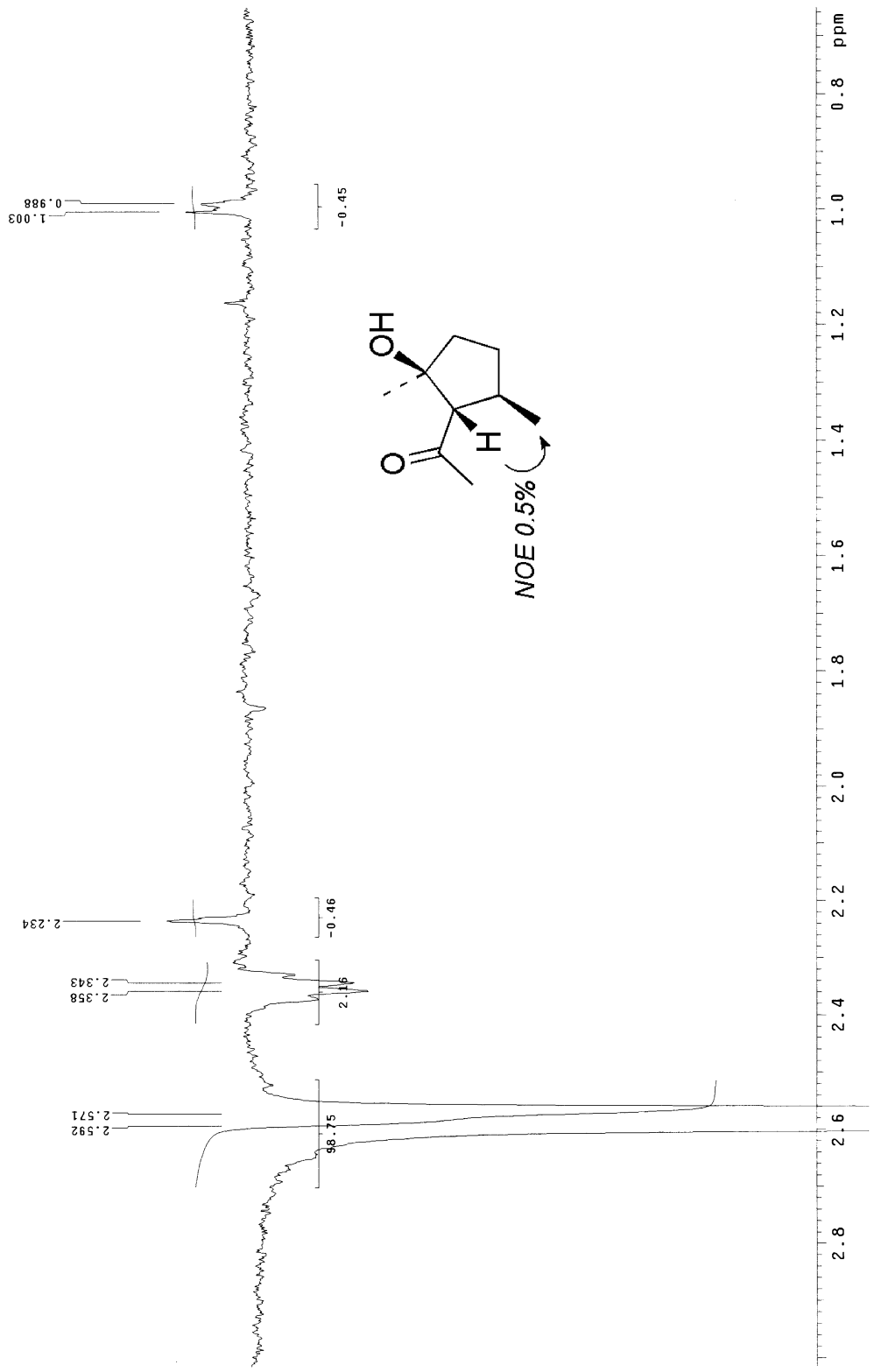
Product: Table 2, Entry 10 (1st diastereomer NOE)



Product: Table 2, Entry 10 (2nd diastereomer)



Product: Table 2, Entry 10 (2nd diastereomer)



Product: Table 2, Entry 10 (2nd diastereomer NOE)

[i] Clausen, C.; Wartchow, R.; Butenschön, H. *Eur. J. Org. Chem*. **2001**, 93-113.

[ii] (a) Lipshutz, B. H.; Servesko, J. M. *Angew. Chem. Int. Ed.* **2003**, *42*, 4789-4792. (b) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352-8353.

[iii] Chiu, P.; Szeto, C.-P.; Geng, Z.; Cheng, K.-F. *Org. Lett.* **2001**, *3*, 1901-1903.

[iv] Cauble, D. F.; Gipson, J. D.; Krische, M. J. *J. Am Chem. Soc.* **2003**, *125*, 1110-1111.

[v] Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876-881.