Computationally-Guided Organometallic Chemistry: Preparation of the Heptacyclic Pyrazine Core of Ritterazine N

Douglass F. Taber and Karen V. Taluskie

Department of Chemistry and Biochemistry, University of Delaware, Newark DE 19716

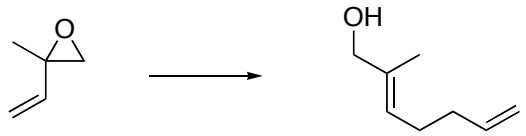
taberdf@udel.edu

Supporting Information

Contents:

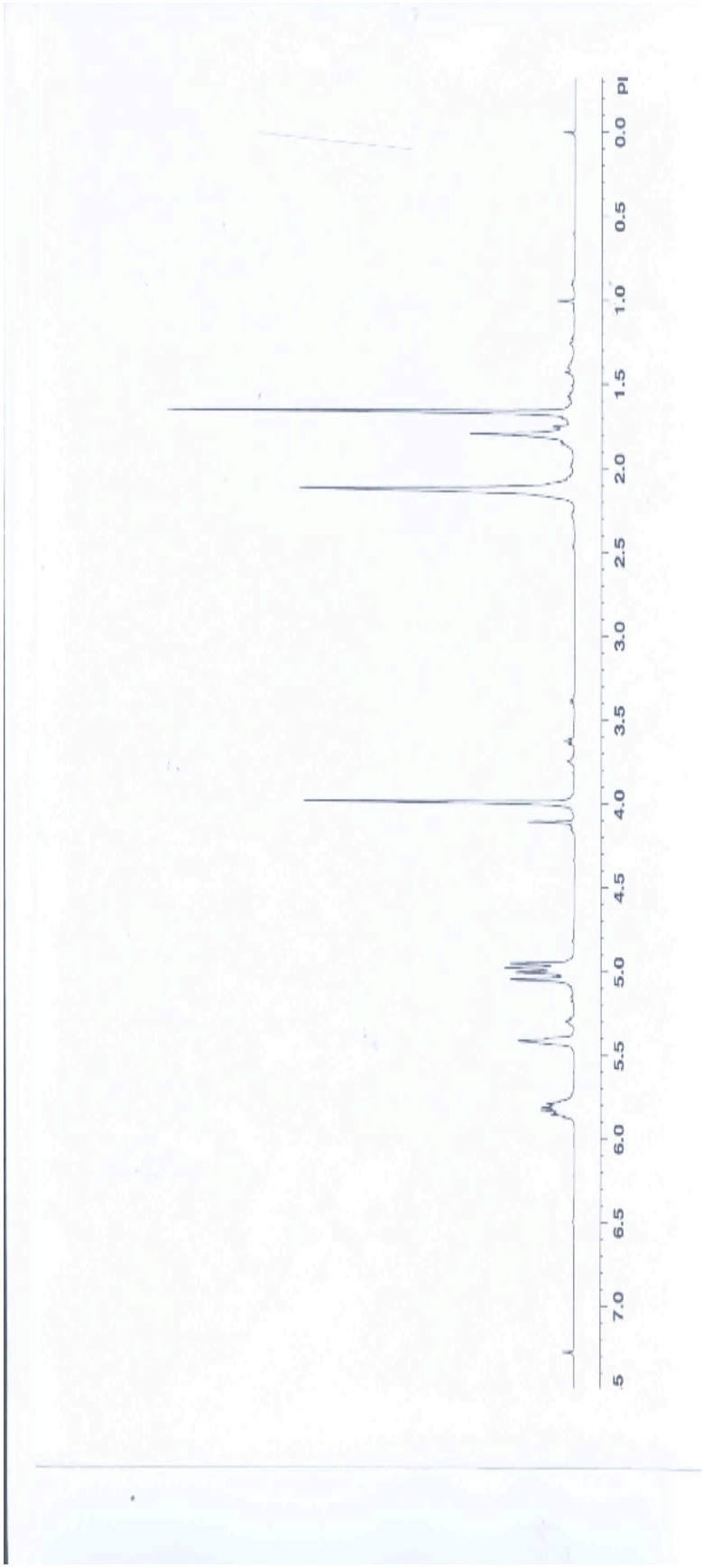
General Experimental Procedures

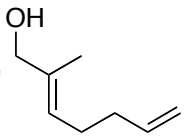
^{1}H NMR and ^{13}C NMR were measured in $CDCl_3$ at 400 MHz for ^{1}H and 100 MHz for ^{13}C. ^{13}C multiplicities were determined with the aid of a JVERT pulse sequence, differentiating the signals for methyl and methine carbons as "d" from methylene and quaternary carbons as "u". The infrared (IR) spectra were determined as neat oils. All substances gave spectroscopic data consistent with being >95% the assigned structure. R_f values indicated refer to thin-layer chromatography (TLC) on 2.5 cm x 10 cm x 250 μm analytical plates coated with silica gel GF, developed in the solvent system indicated. Flash chromatography was performed as described by Still using silica gel 60 (230-400 mesh). Dichloromethane (CH_2Cl_2) and toluene were distilled from calcium hydride prior to use. Tetrahydrofuran (THF) was distilled from sodium and benzophenone prior to use. MTBE is methyl t-butyl ether. PE is petroleum ether. 2-Methyl-2-vinyl oxirane (95%) was purchased from Aldrich and used without further purification. All reactions were performed with stirring under a nitrogen atmosphere unless otherwise specified.



7 **8**

Allylic Alcohol 8. To a stirred solution of the epoxide **7** (25.0 g, 297 mmol) in THF (198 mL) at –30 °C was added copper bromide dimethyl sulfide complex (1.59 g, 7.7 mmol). Allyl magnesium chloride (2.0 M, 446 mmol) was then added dropwise over one hour to the reaction mixture at –30 °C. After an additional two hours, the reaction mixture was warmed to –20 °C, then partitioned between saturated aqueous NH_4Cl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was distilled bulb to bulb (bp 40-55 °C at 2 mm) to afford the allylic alcohol **8** (36.4 g, 87% yield) as a colorless oil: TLC R_f (hexanes/MTBE = 6/4) = 0.36; ^{1}H NMR (400 MHz, $CDCl_3$; signals of the (E)-isomer): δ 5.78-5.86 (1H, m), 5.41 (1H, s), 5.05 (1H, s), 4.95-5.00 (1H, t, J = 10 Hz), 3.99 (2H, s), 2.13 (4H, s), 1.67 (3H, s); selected signals of the (Z)-isomer: δ 4.11 (s), 1.80 (s); ratio of E to Z is 7.3 to 1; ^{13}C NMR δ u 135.3, 114.8, 68.9, 33.7, 27.2; d 138.5, 125.5, 13.9; IR (film) 3326, 3077, 2977, 2920, 2859, 1826, 1674, 1640, 1440, 1415, 1385, 1223, 1004, 911, 848; LRMS *m/z* (rel intensity) 108 (M^+ - H_2O, 20), 97 (6), 95 (14), 93 (29), 43 (100). These data are congruent with those previously reported.





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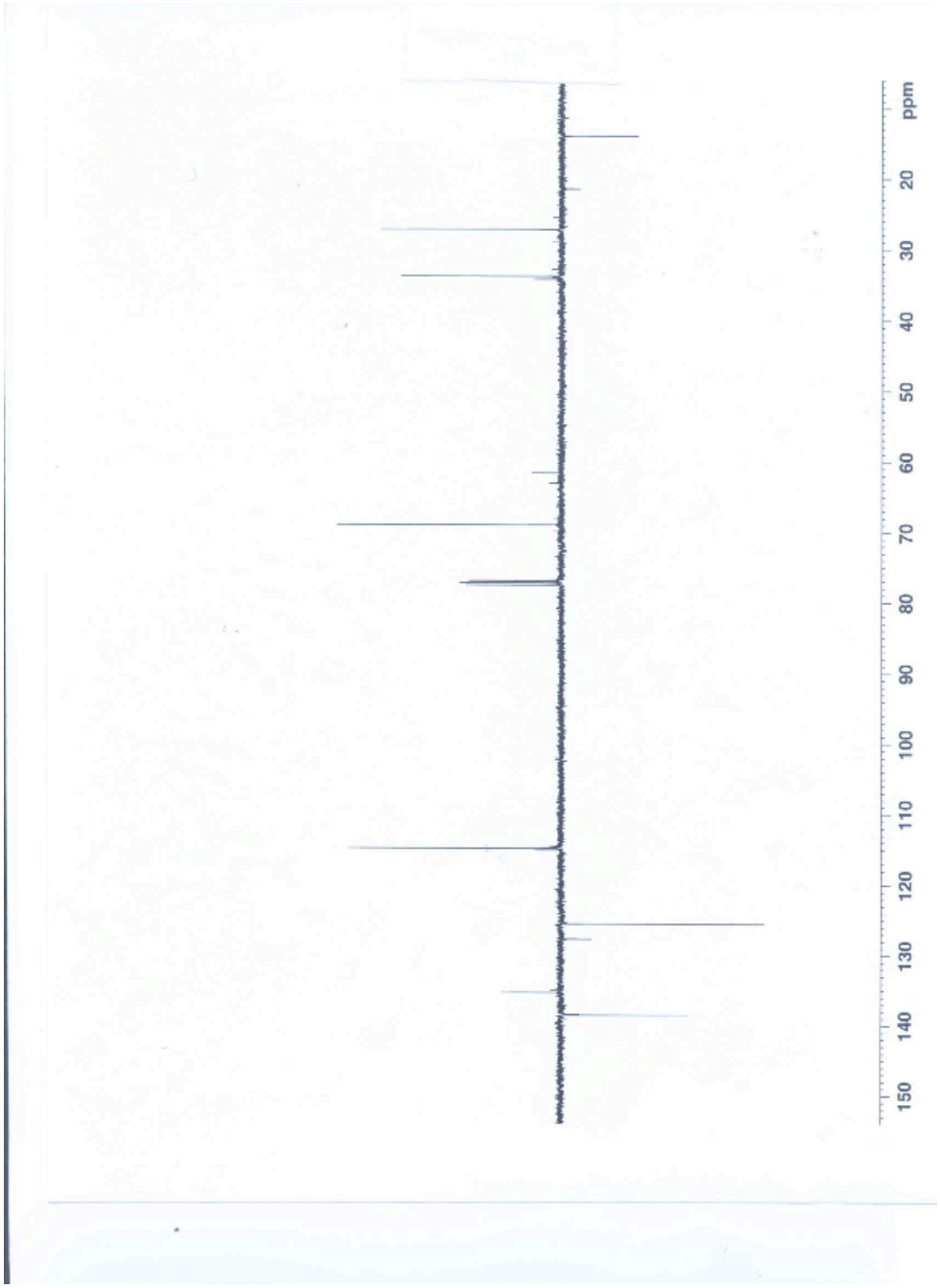

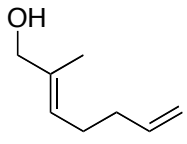

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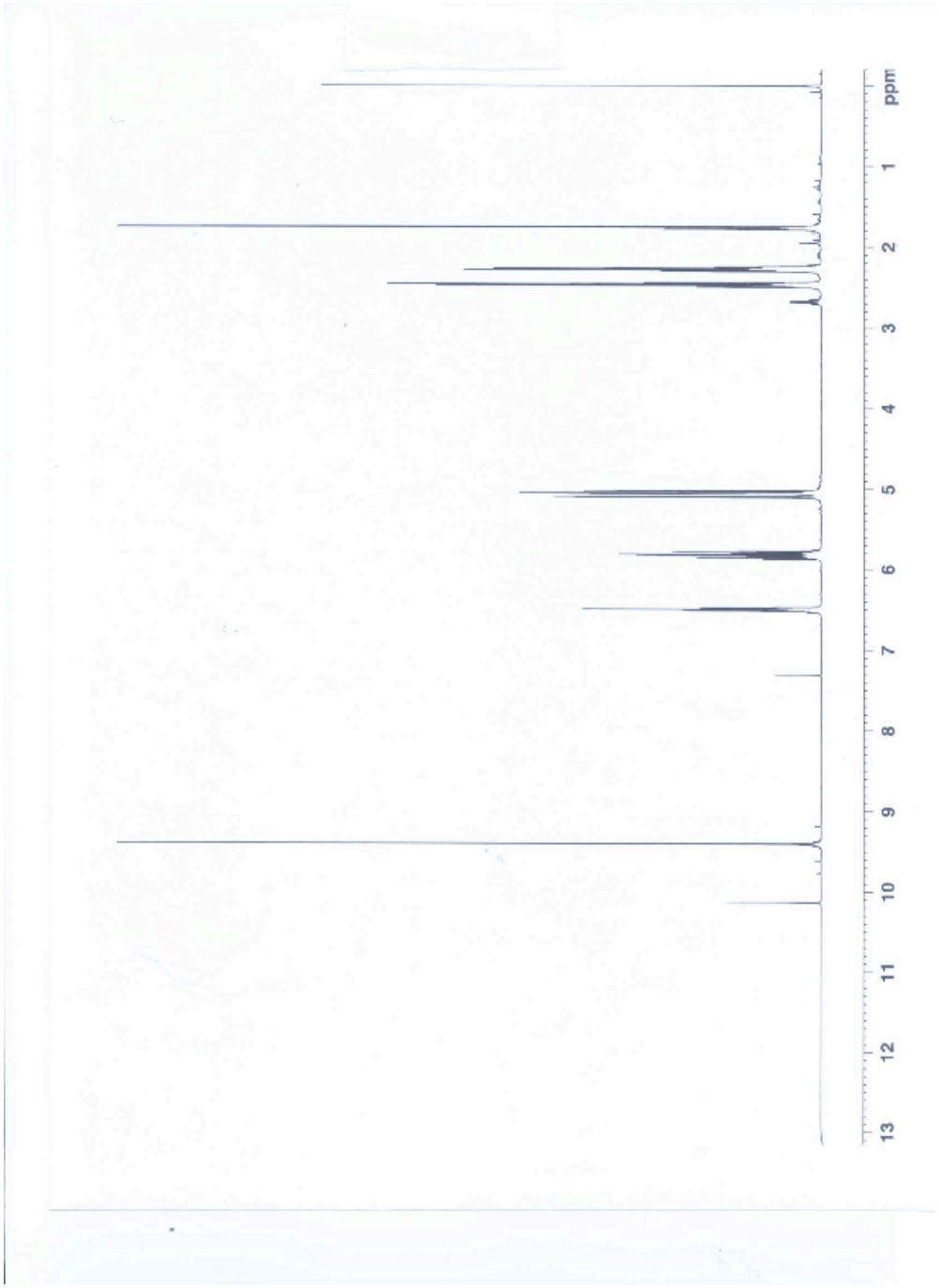

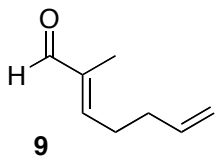

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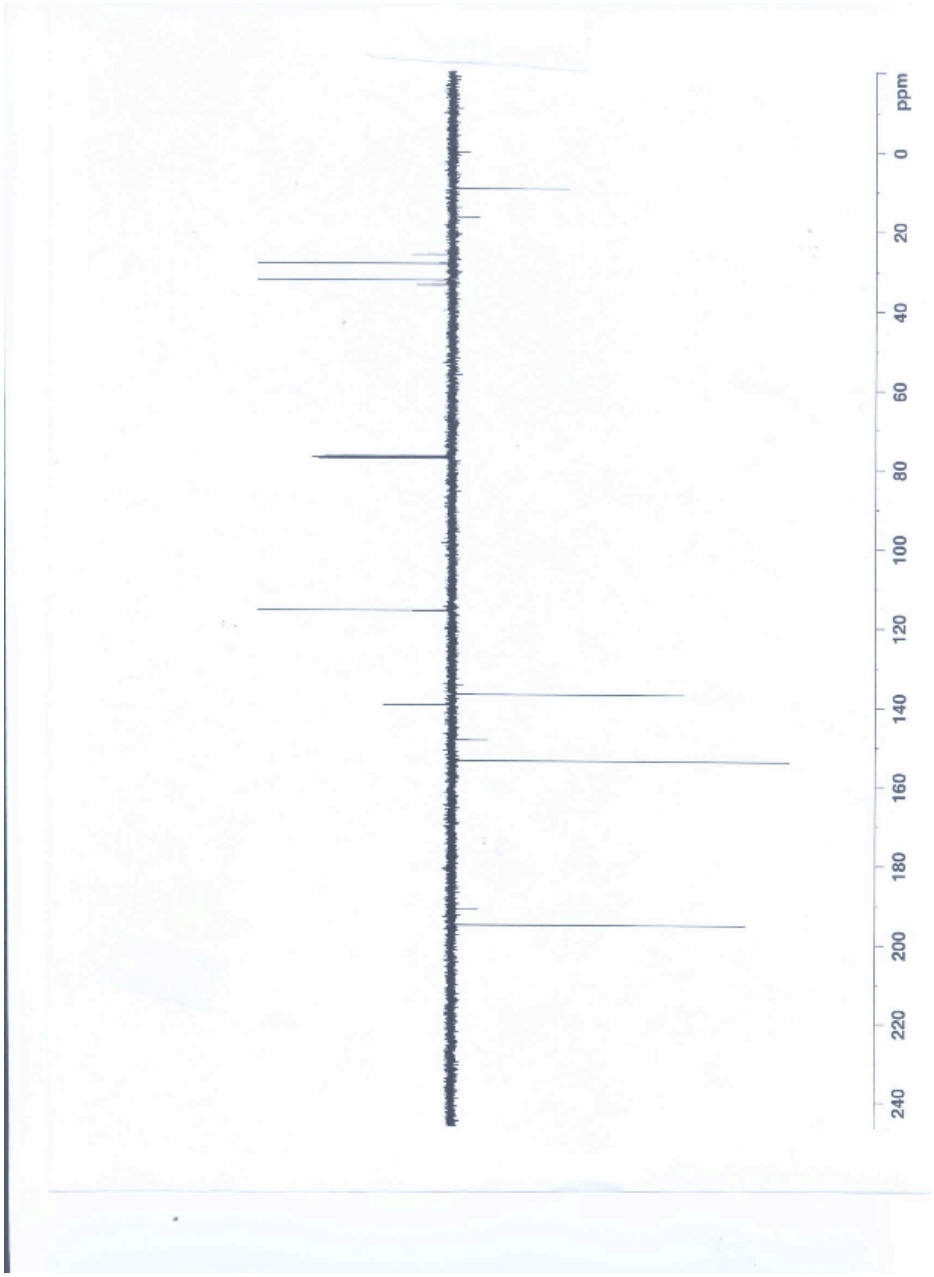

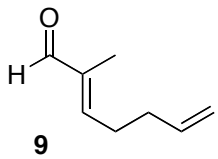

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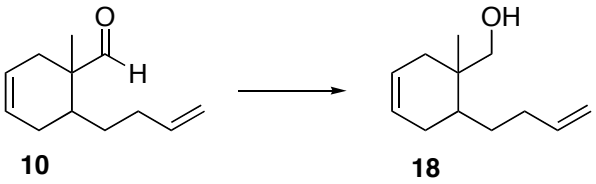
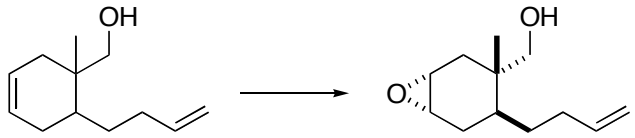


10 **18**

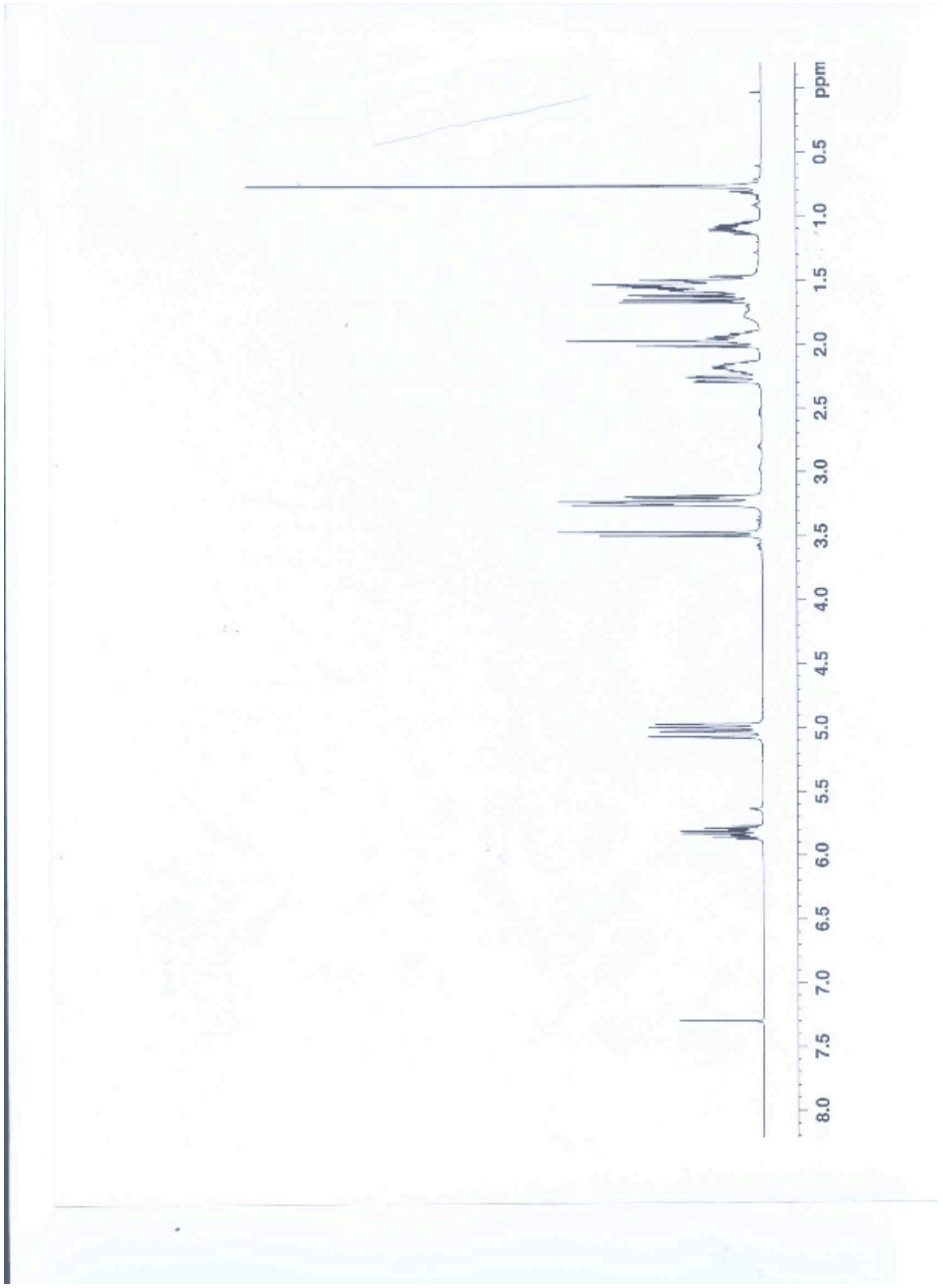
The yields indicated in Scheme 2 are accurate. As can be seen from the spectra above, the aldehyde **10** contained minor contaminants, which were carried through to ketone **5**. To prepare analytically-pure samples of **10**, **6**, and **5**, we carefully purified **10**, as outlined below. The diols **12a**-**12c**, prepared from diene **10** still containing minor contaminants, were analytically pure. The yield for the epoxide **14** is for analytically pure material, from ketone **5** prepared from diene **10** still containing minor contaminants.

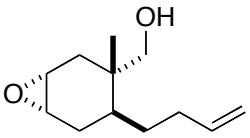
Purification of the Aldehyde 10. To a stirred solution of cyclic aldehyde **10** (3.97 g, 22.3 mmol) in methanol (112 mL) was added $NaBH_4$ (1.69 g, 44.6 mmol). After 15 minutes, the reaction mixture was partitioned between EtOAc and saturated aqueous NH_4Cl. The organic extract was dried (Na_2SO_4) and concentrated. The residue was adsorbed onto silica gel and chromatographed to afford the alcohol **18** (2.36 g, 59% yield) as a mixture of diastereomers.



18 19

Epoxy Alcohol 19. To a stirred solution of alcohol **18** (3.28 g, 18.2 mmol) and CH_2Cl_2 (121 mL) was added mCPBA (4.41 g, 25.5 mmol). After 30 min, the reaction mixture was partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed using TLC mesh silica gel to afford the epoxide **19** (1.81 g, 51% yield) as a colorless oil: TLC R_f (CH_2Cl_2/EtOAC = 7/3) = 0.48; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78-5.88 (1H, m), 4.97-5.08 (2H, m), 3.47-3.50 (1H, d, J = 8 Hz), 3.19-3.26 (3H, m), 2.26-2.29 (1H, d, J = 12 Hz), 2.15-2.19 (1H, m), 1.93-2.01 (2H, m), 1.47-1.67 (5H, m), 1.05-1.12 (1H, m), 0.76 (3H, s); ^{13}C NMR δ u 26.7, 28.2, 31.5, 34.5, 35.7, 69.5, 114.8; d 16.8, 32.0, 51.0, 52.7, 138.9; IR (film) 3439, 3074, 2924, 1640, 1433, 1380, 1263, 1165, 1044, 909, 810, 755; LRMS *m/z* (rel intensity) 196 (<1), 178 (<1), 165 (13), 147 (20), 133 (19), 119 (34), 105 (100), 93 (94), 79 (84), 67 (71), 55 (81); HRMS calcd for $C_{12}H_{19}O$ (M^+ - OH) 179.143590, obsd 179.143979.





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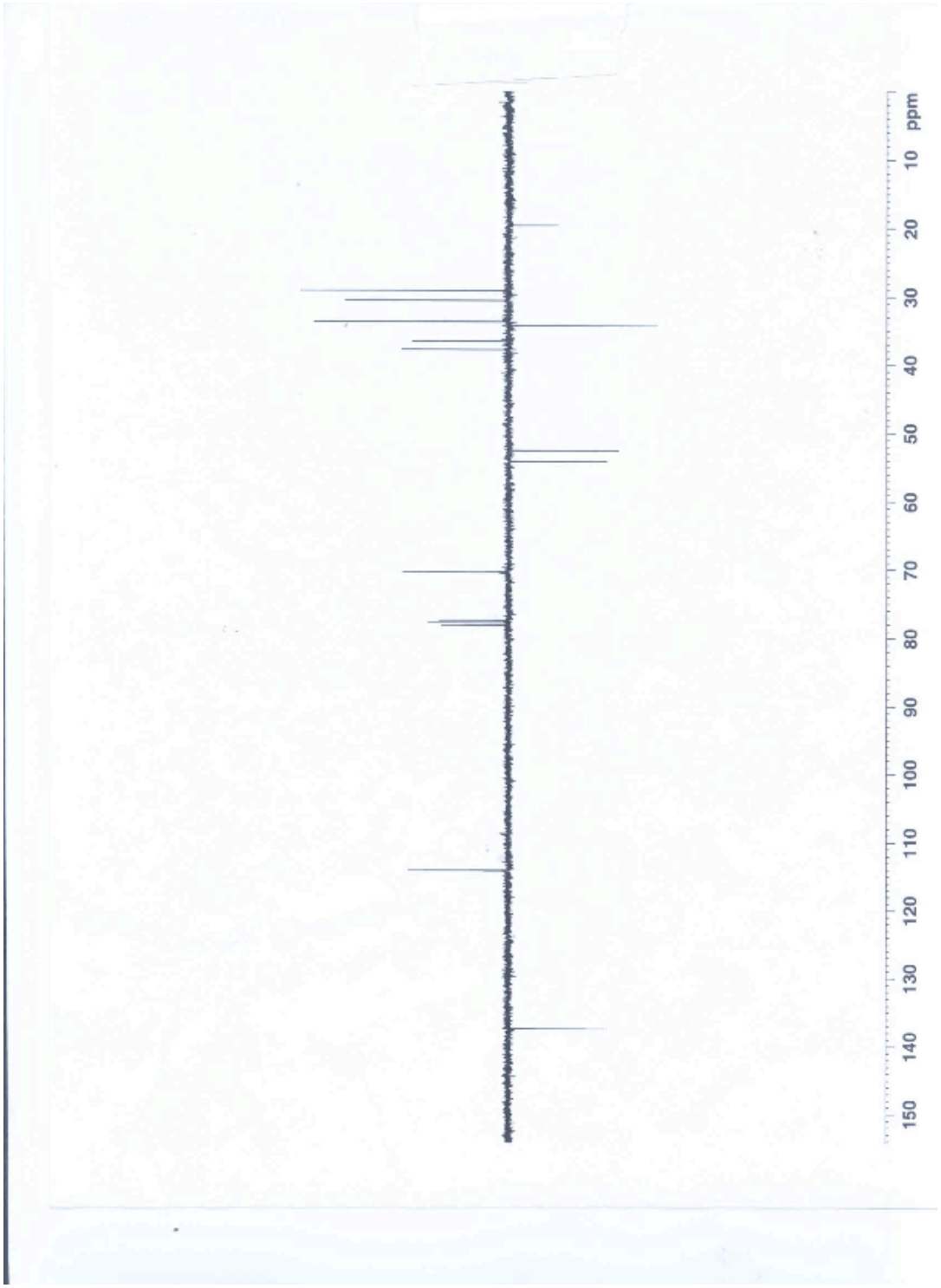

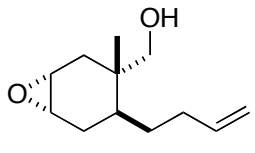

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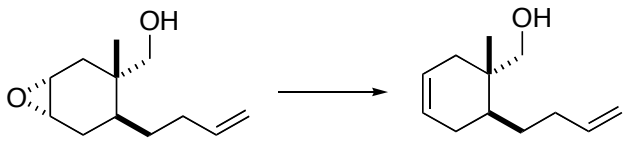
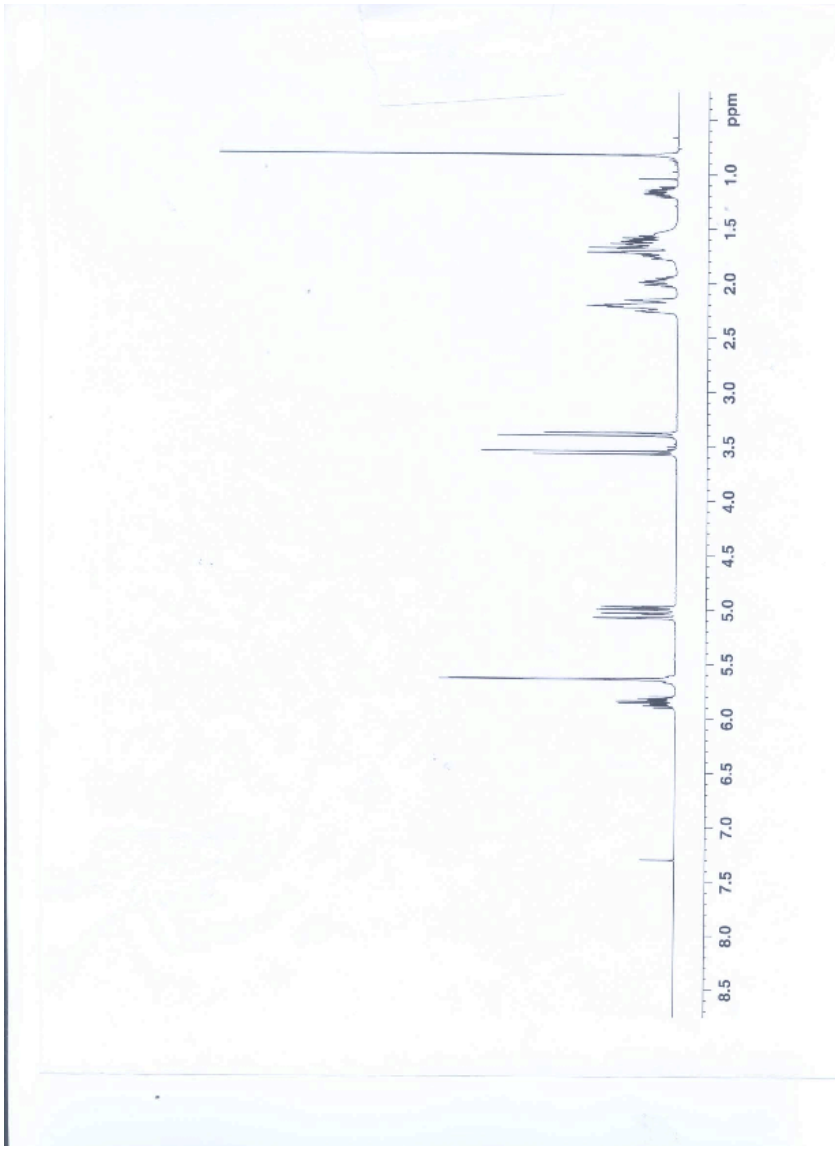
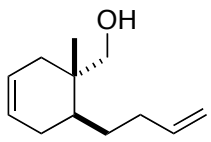


19 **18**

Deoxygenation. To a stirred solution of NaI (6.00 g, 39.9 mmol) and CH_3CN (53 mL) was added TMSCl (2.17 g, 20.0 mmol) dropwise. Epoxide **19** (2.61 g, 13.3 mmol) was then added over 5 min to the reaction mixture in an additional 10 mL of CH_3CN. After 30 min, the reaction mixture was partitioned between Et_2O and saturated aqueous $Na_2S_2O_3$. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the alcohol **18** (1.13 g, 47% yield) as a pale yellow oil: TLC R_f (PE/MTBE = 7/3) = 0.55; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.81-5.88 (1H, m), 5.64 (2H, s), 4.97-5.08 (2H, m), 3.54-3.57 (1H, d, *J* = 11 Hz), 3.37-3.40 (1H, d, *J* = 11 Hz), 2.15-2.25 (3H, m), 1.90-2.01 (1H, m), 1.58-1.74 (5H, m), 1.14-1.18 (1H, m), 0.81 (3H, s); ^{13}C NMR δ u 28.0, 28.6, 32.0, 35.0, 36.7, 70.1, 114.7; d 17.0, 36.2, 125.6, 125.6, 139.3; IR (film) 3355, 3075, 3021, 2918, 2885, 2835, 1640, 1454, 1433, 1376, 1278, 1035, 993, 908; LRMS *m/z* (rel intensity) 162 (M^+ - H_2O, 3), 149 (81), 133 (17), 121 (17), 107 (56), 91 (81), 79 (100), 67 (34), 55 (18); HRMS calcd for $C_{12}H_{18}$ (M^+ - H_2O) 162.140851, obsd 162.140307.





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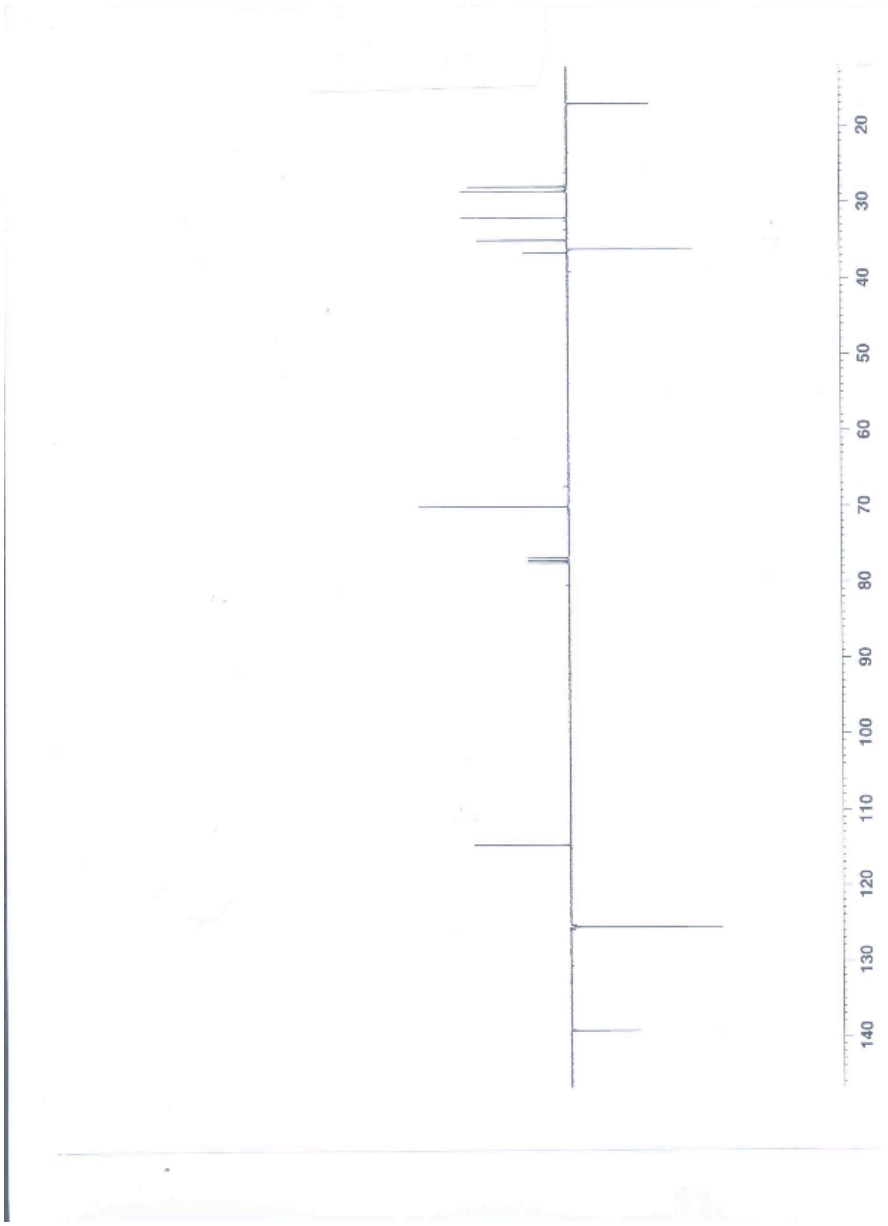

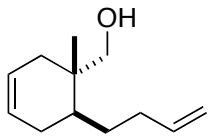

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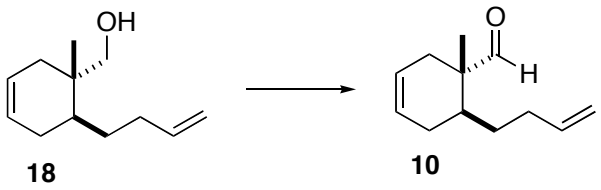
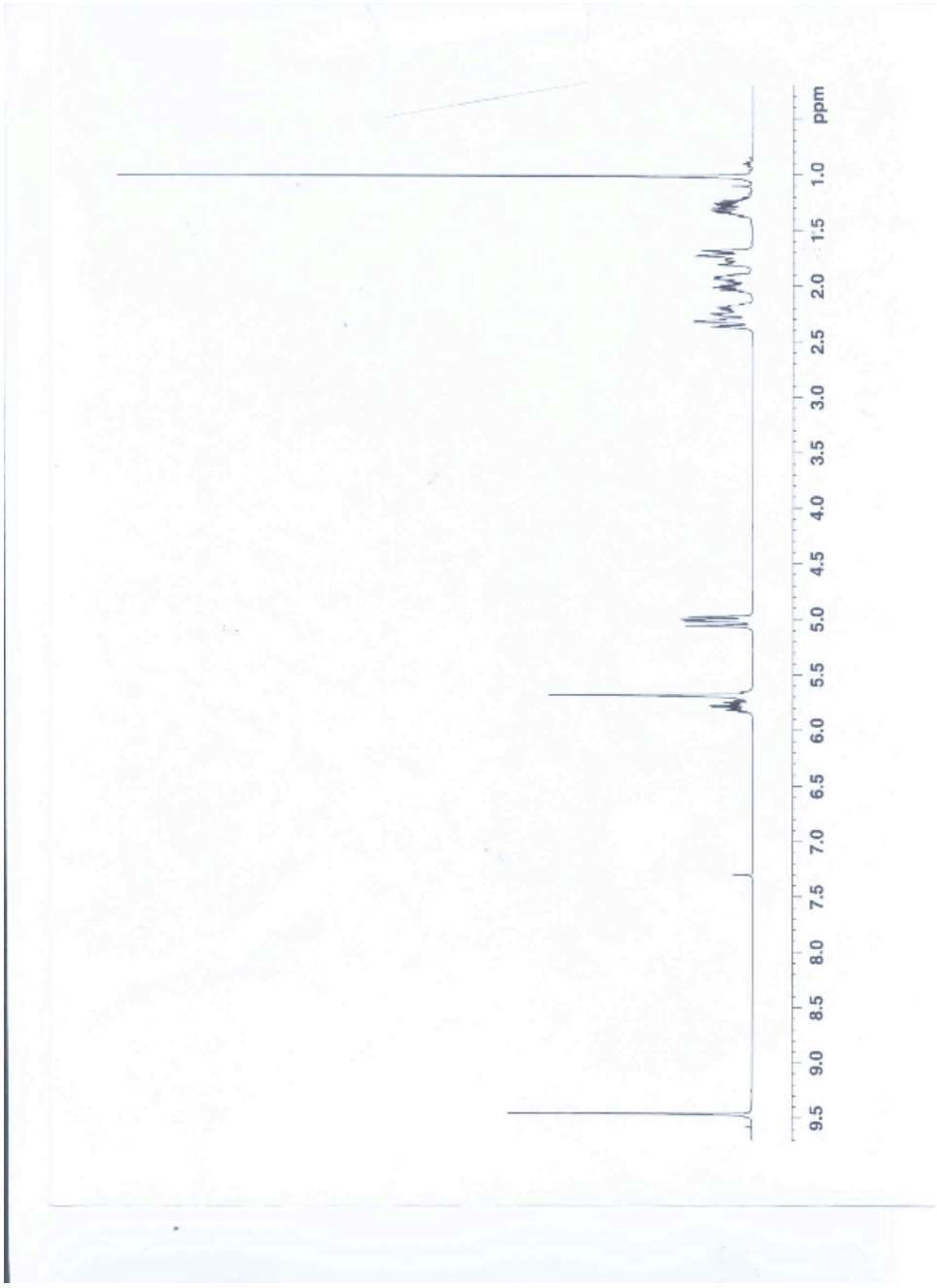
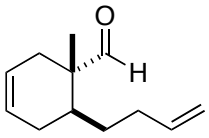


18 **10**

Oxidation. To a stirred solution of the alcohol **18** (459 mg, 2.55 mmol) in CH_2Cl_2 (17 mL) at room temperature was added Dess-Martin periodinane (2.17 g, 5.11 mmol). After an additional 20 minutes, the reaction mixture was partitioned between CH_2Cl_2 and a one to one mixture of saturated aqueous $Na_2S_2O_3$ and saturated aqueous $NaHCO_3$. The organic extract was dried (Na_2SO_4) and concentrated. The residue was adsorbed onto silica gel and chromatographed to afford the aldehyde **10** (361 mg, 80% yield) as a colorless oil, full characterization of which is noted in the experimental section.





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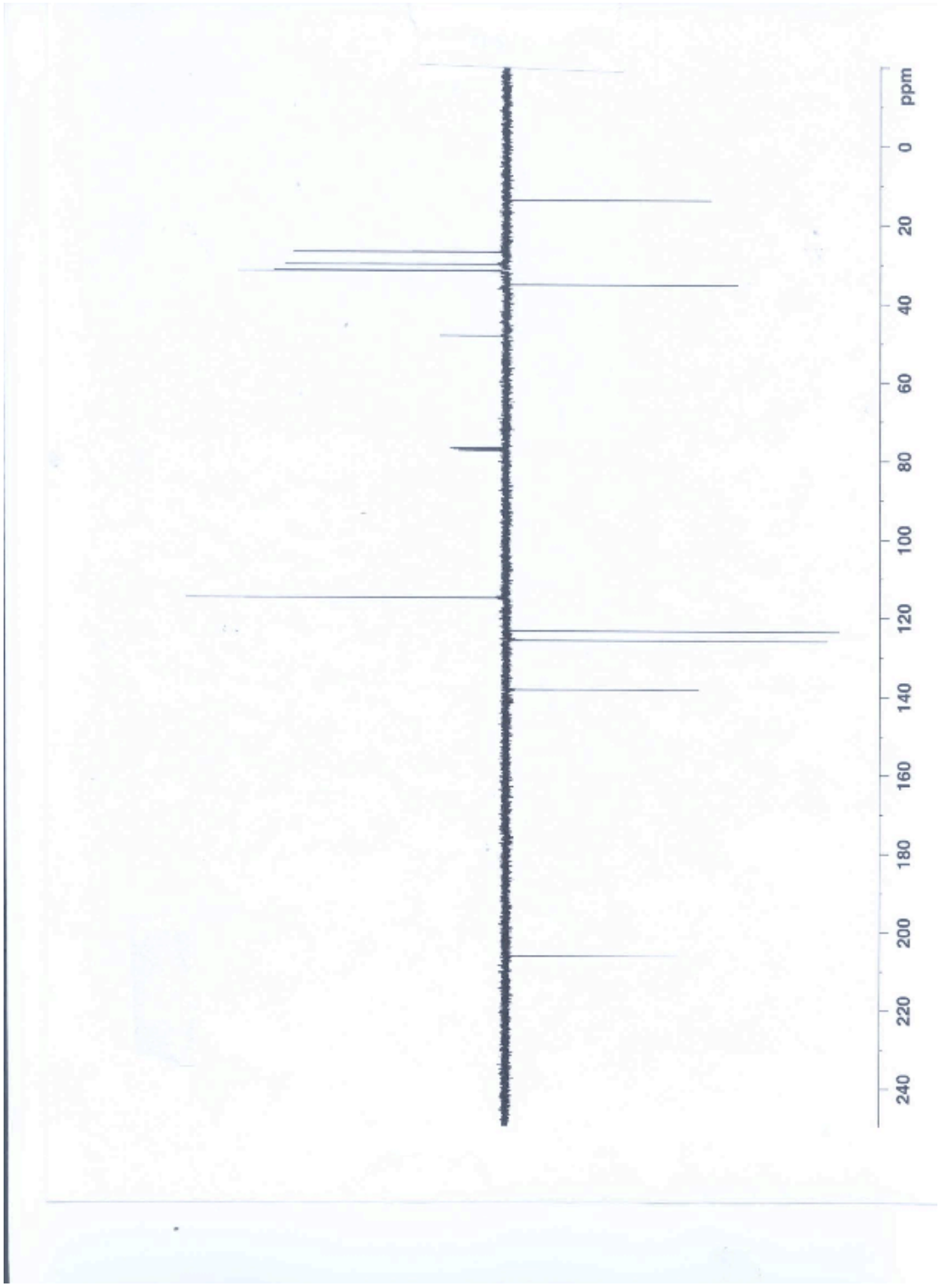

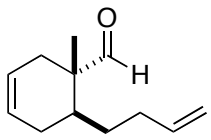

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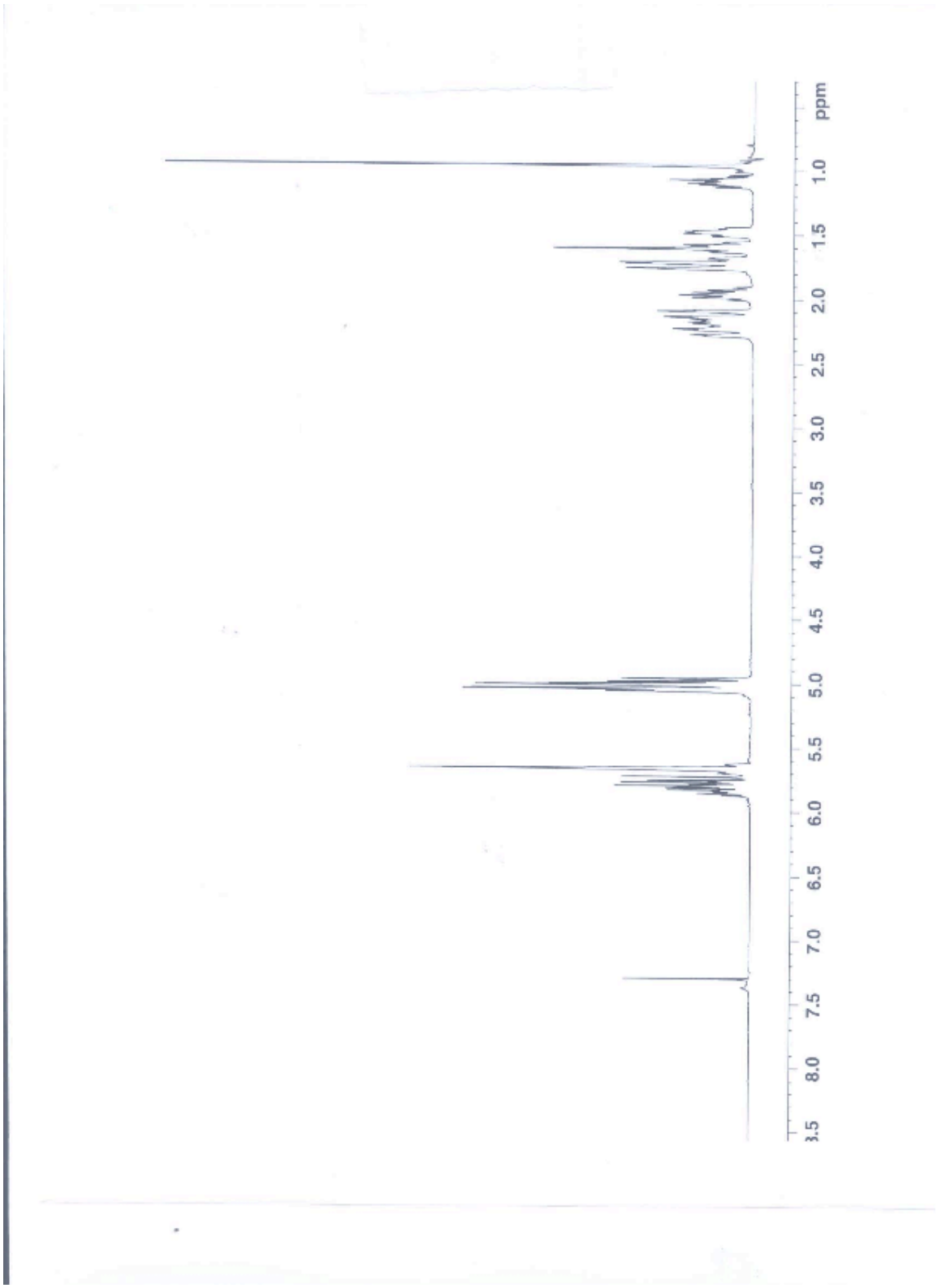

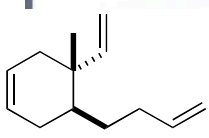

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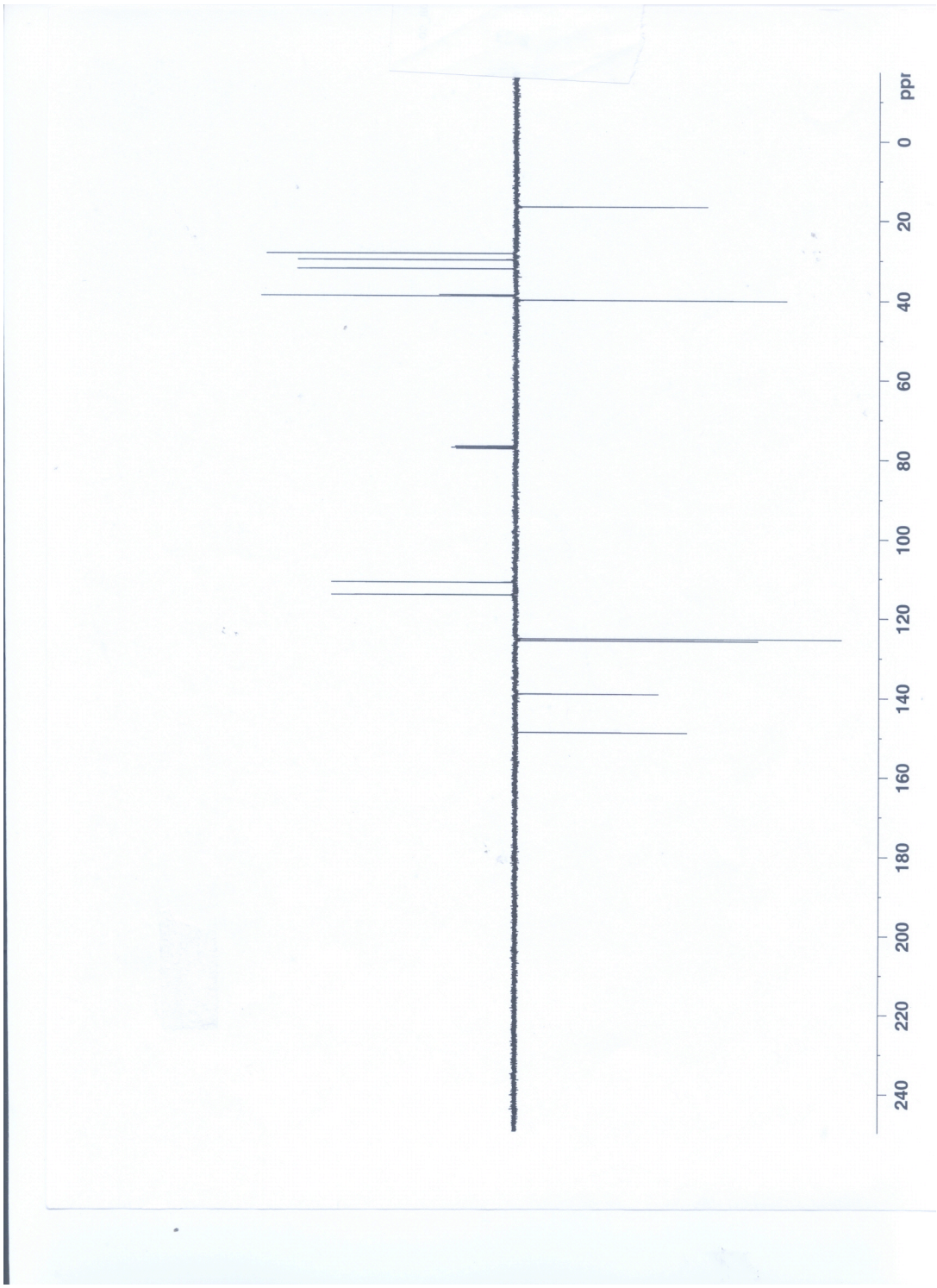

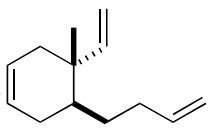

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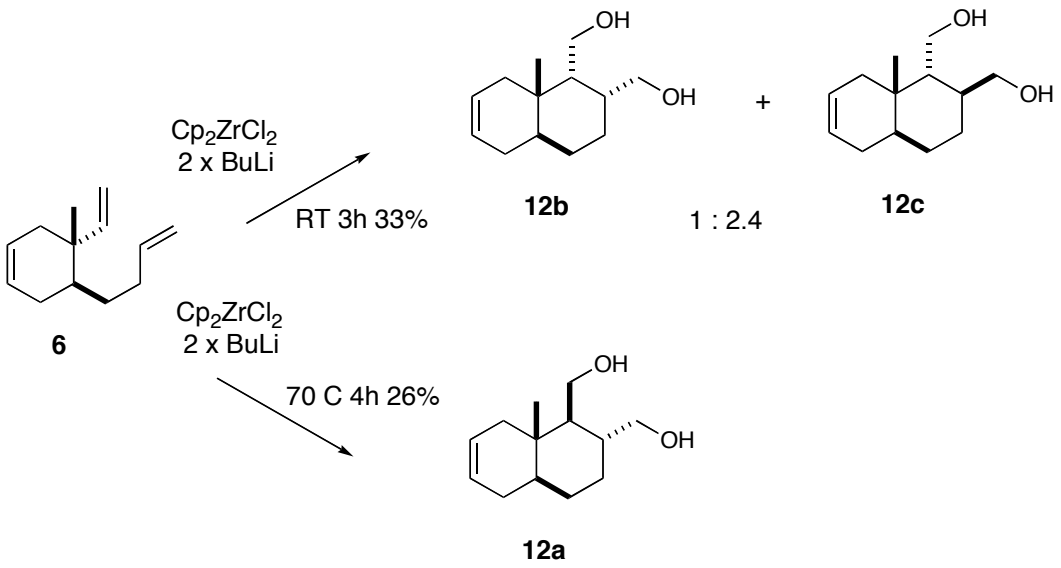
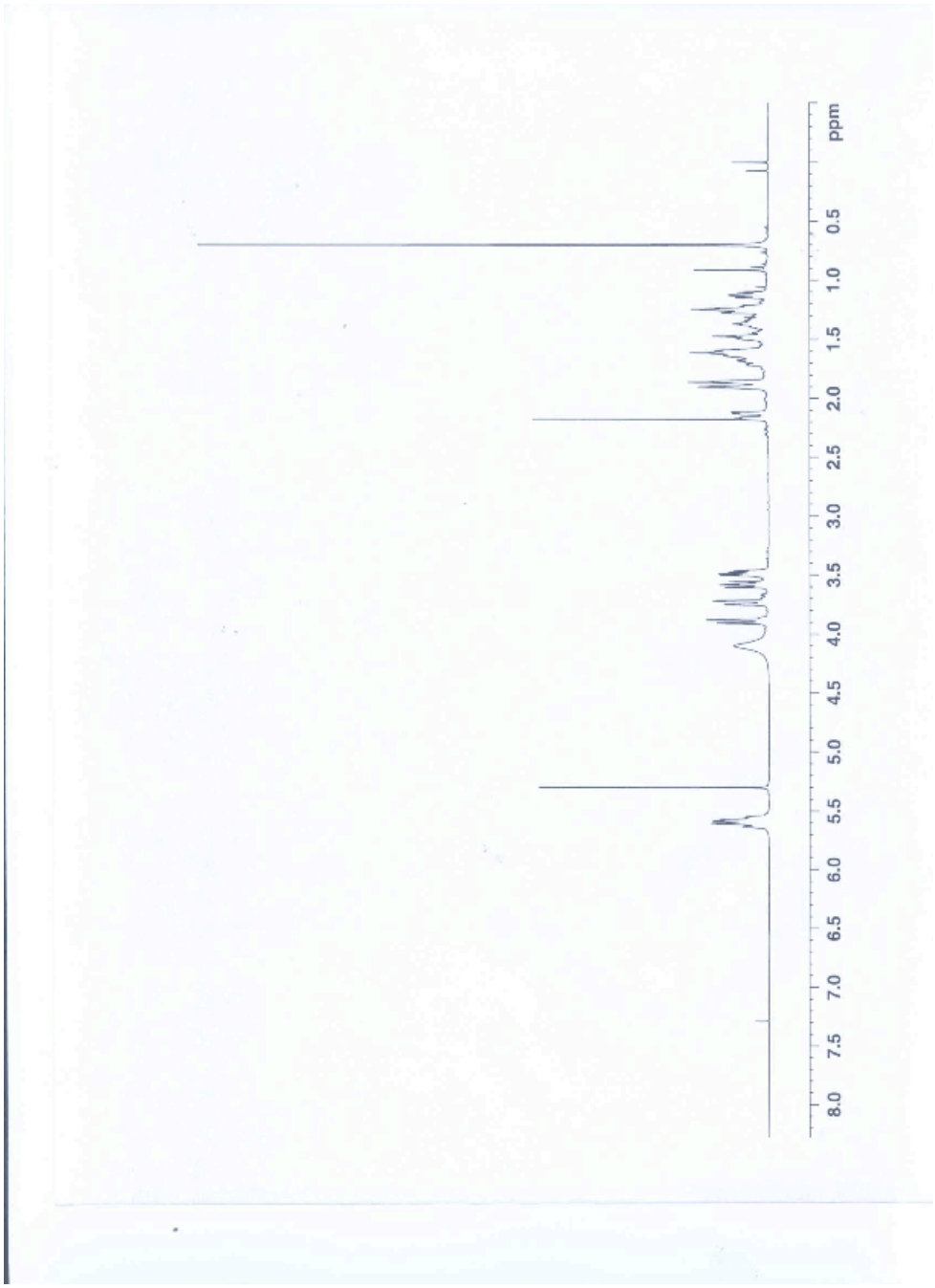
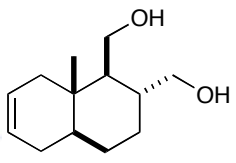


Diols 12a-c. Zirconocene dichloride (2.32 g, 7.95 mmol) was added to a 100 mL round-bottom flask. Triene **6** (1.0 g, 5.6 mmol) in toluene (19 mL) was added to the flask. The reaction mixture was cooled to –78 °C and *n*-BuLi was added (2.01 M in toluene, 7.9 mL) via syringe. The reaction was warmed to room temperature and stirred for three hours (**12c, 12b**); or, the reaction was warmed to room temperature over 15 minutes and then was heated to 70° C for 4 h (**12a**). Molecular oxygen was bubbled through the reaction mixture for 1 h at –78 °C to room temperature. Sodium borohydride was added (665 mg, 17.58 mmol) and the reaction was stirred at room temperature for 18 h. The reaction mixture was partitioned between diethyl ether and a one to one mixture of 5% aqueous H_2SO_4 and saturated aqueous Na_2SO_4. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to afford the diols **12a-c** (see above for yields) as a colorless oil: **12a** TLC R_f (CH_2Cl_2/acetone = 6/4) = 0.54; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.57-5.61 (2H, m), 4.10 (2H, s), 3.88-3.91 (1H, d, J = 12 Hz), 3.71-3.75 (1H, dd, J = 3 Hz, J = 11 Hz), 3.56-3.61 (1H, m), 3.46-3.50 (1H, m), 2.11-2.18 (2H, m), 1.85-1.90 (2H, m), 1.58-1.74 (2H, m), 1.46-1.49 (1H, m), 1.35-1.38 (1H, m), 1.22-1.27 (2H, m), 1.10-1.14 (1H, m), 0.70 (3H, s); ^{13}C NMR δ u 28.8, 30.1, 30.2, 35.1, 39.9, 62.1, 67.5; d

12.5, 40.3, 41.0, 54.4, 125.5, 125.9. **12b** TLC R_f (CH_2Cl_2/acetone = 6/4) = 0.41; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60-5.63 (2H, m), 3.77-3.784 (2H, m), 3.60-3.62 (2H, d, J = 7.2 Hz), 2.37-2.39 (1H, m), 2.18 (2H, s), 1.90-1.92 (2H, m), 1.48-1.90 (4H, m), 1.23-1.38 (4H, m), 0.97 (3H, s); ^{13}C NMR δ u 24.3, 26.4, 28.9, 30.7, 36.6, 59.1, 66.3; d 19.3, 35.1, 37.3, 49.3, 125.6, 126.1. **12c** TLC R_f (CH_2Cl_2/acetone = 6/4) = 0.31; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56-5.62 (2H, m), 3.86-3.90 (1H, m), 3.75-3.80 (1H, m), 3.61-3.68 (1H, m), 3.51-3.56 (1H, m), 2.78-2.81 (1H, m), 2.63-2.69 (1H, m), 2.17 (1H, s), 1.89-1.93 (1H, m), 1.81-1.85 (1H, m), 1.64-1.70 (1H, m), 1.58-1.62 (3H, m), 1.46-1.49 (1H, m), 1.38-1.39 (1H, m), 1.20-1.32 (2H, m), 0.90 (3H, s); ^{13}C NMR δ u 23.7, 24.7, 30.2, 34.4, 35.3, 62.3, 66.0; d 19.2, 36.7, 36.8, 48.9, 126.4, 126.8.





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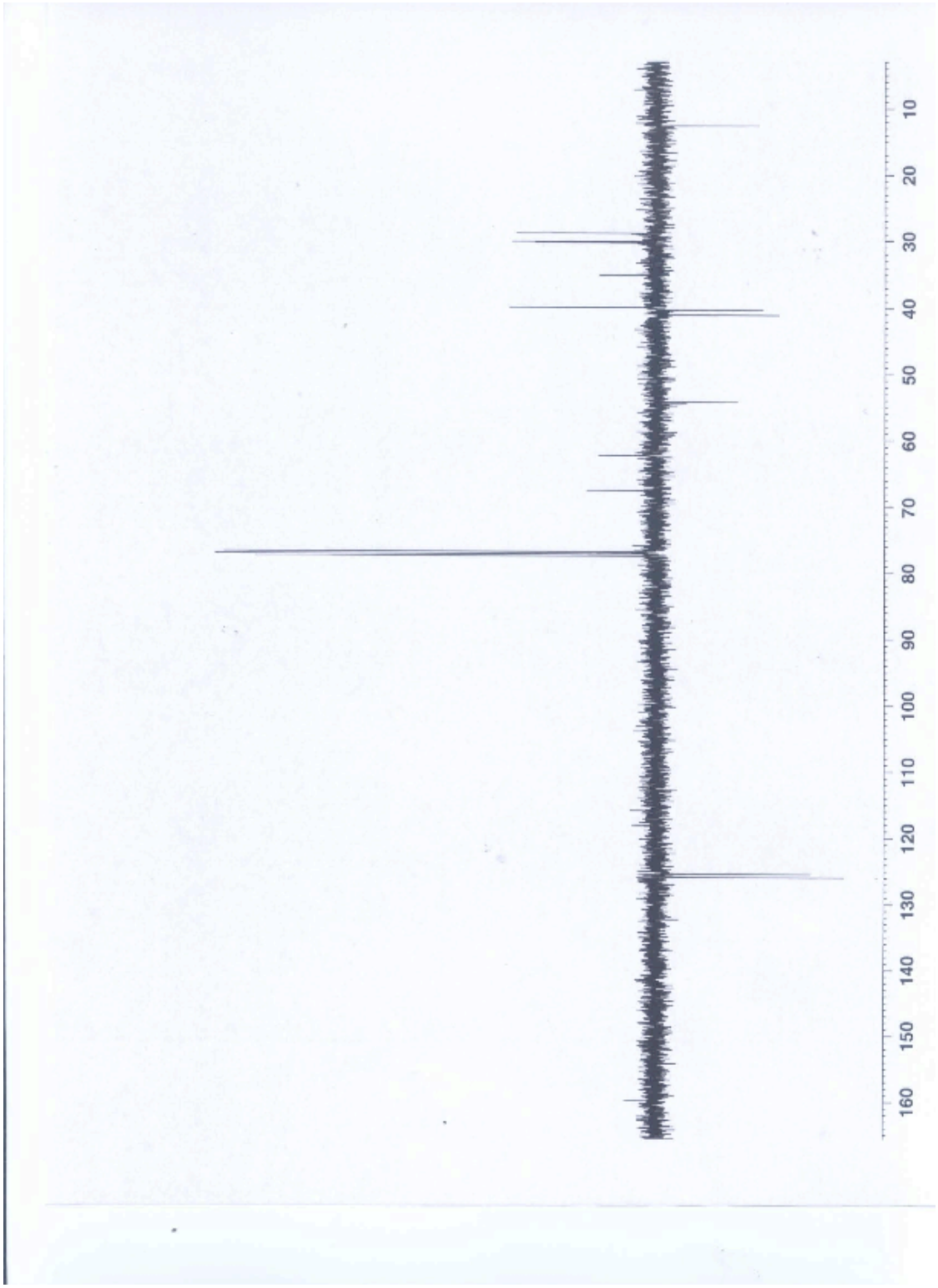

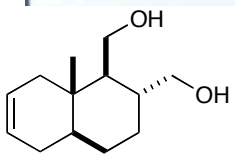

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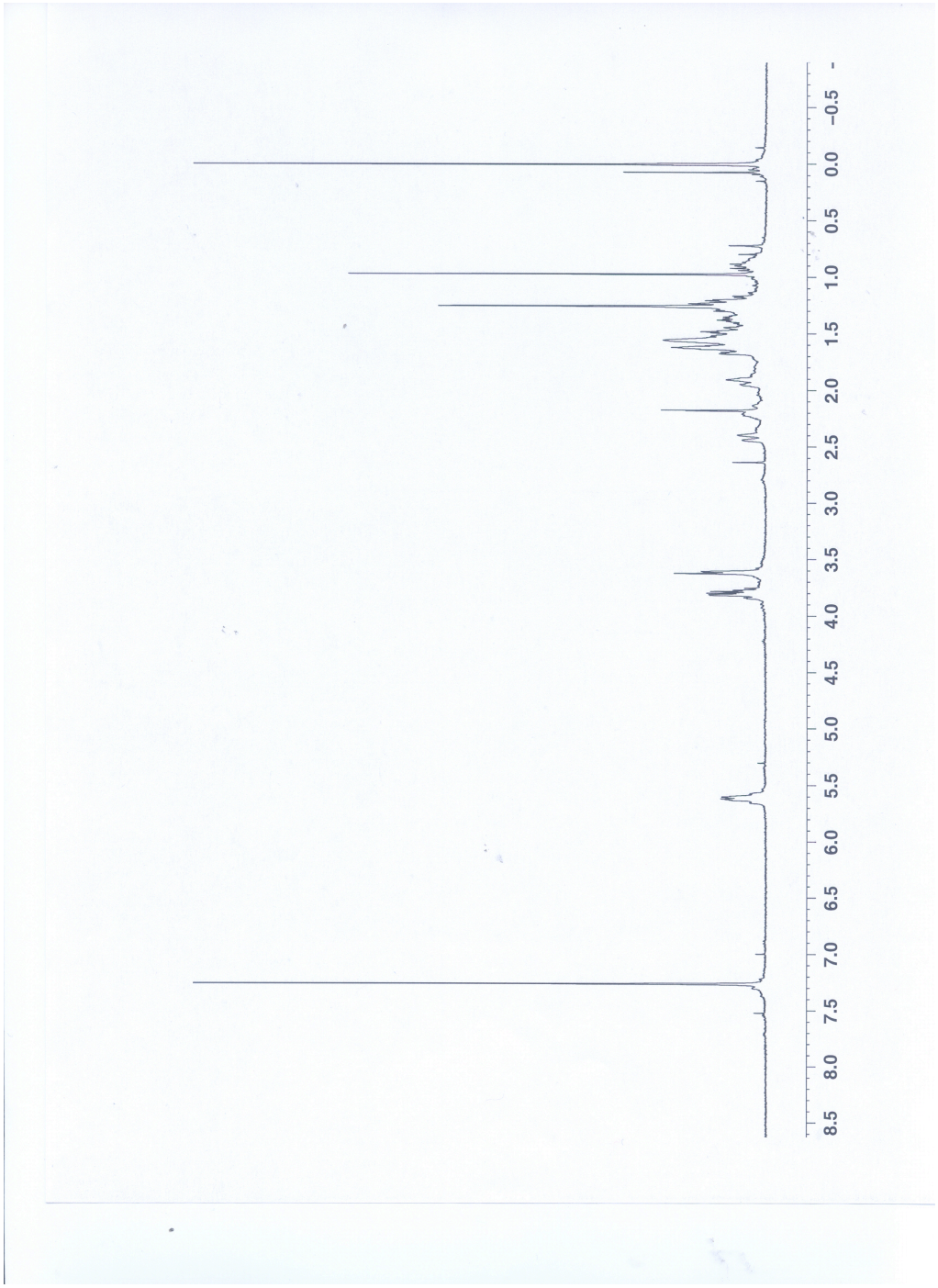

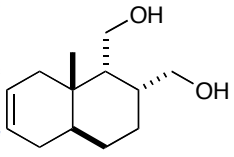

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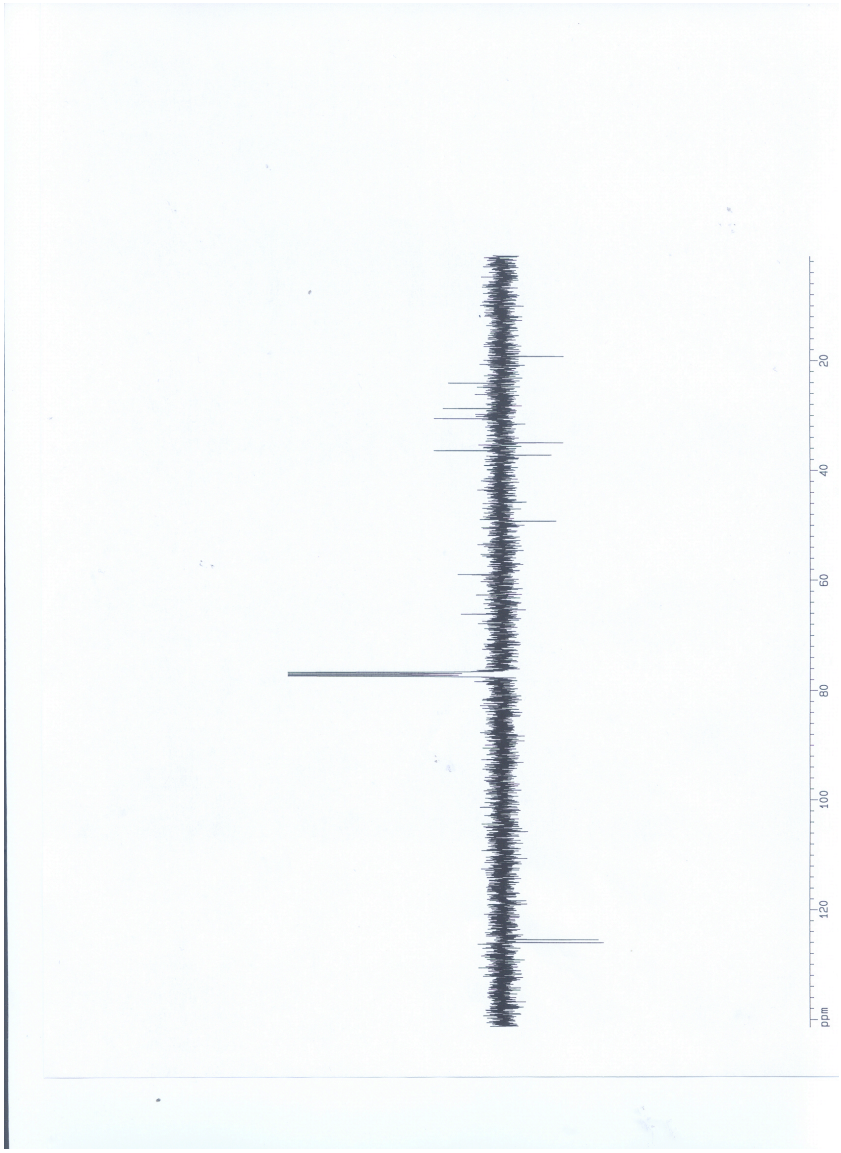

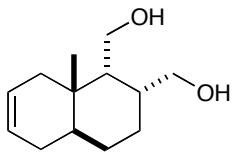

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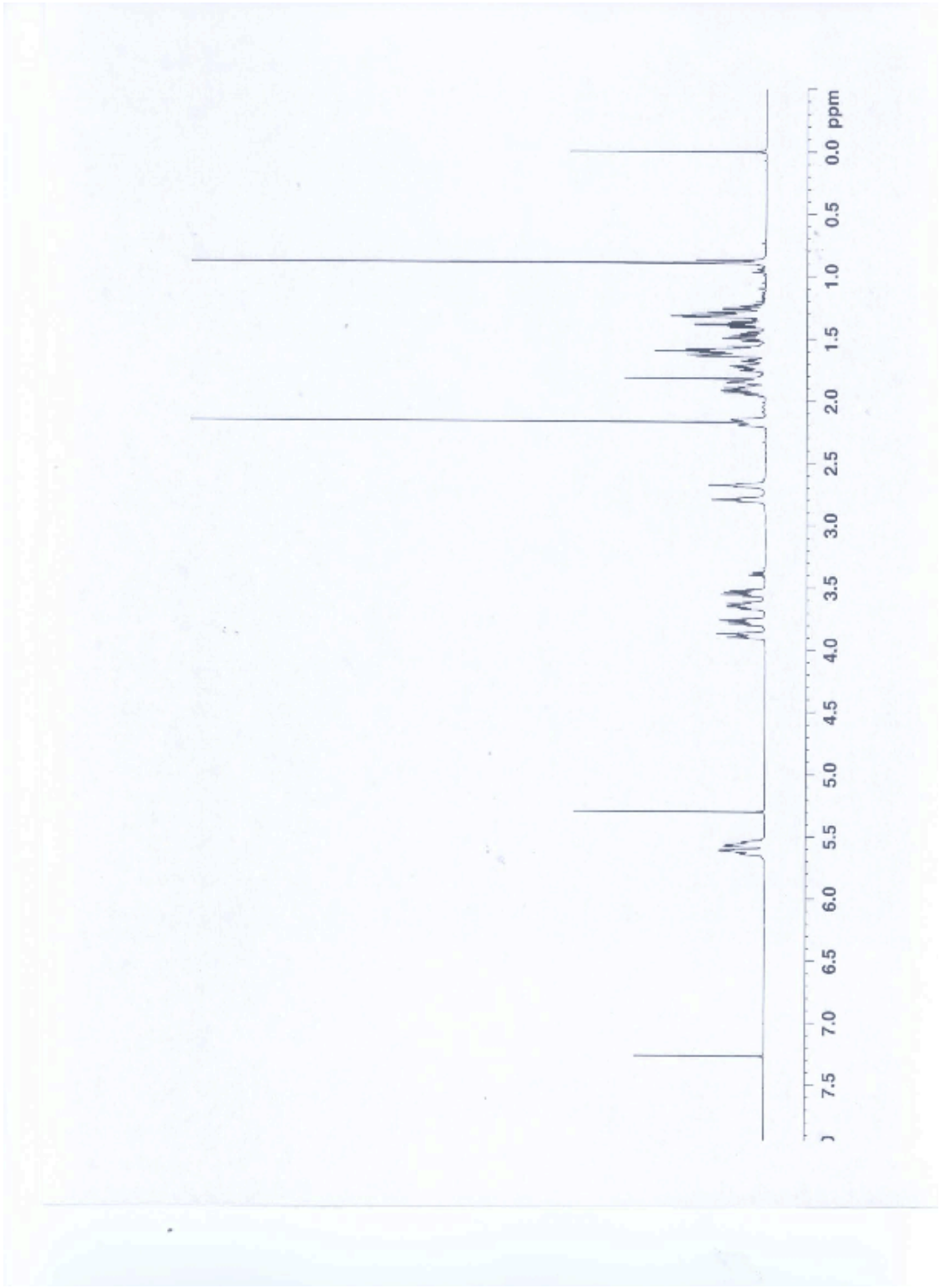
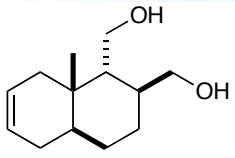
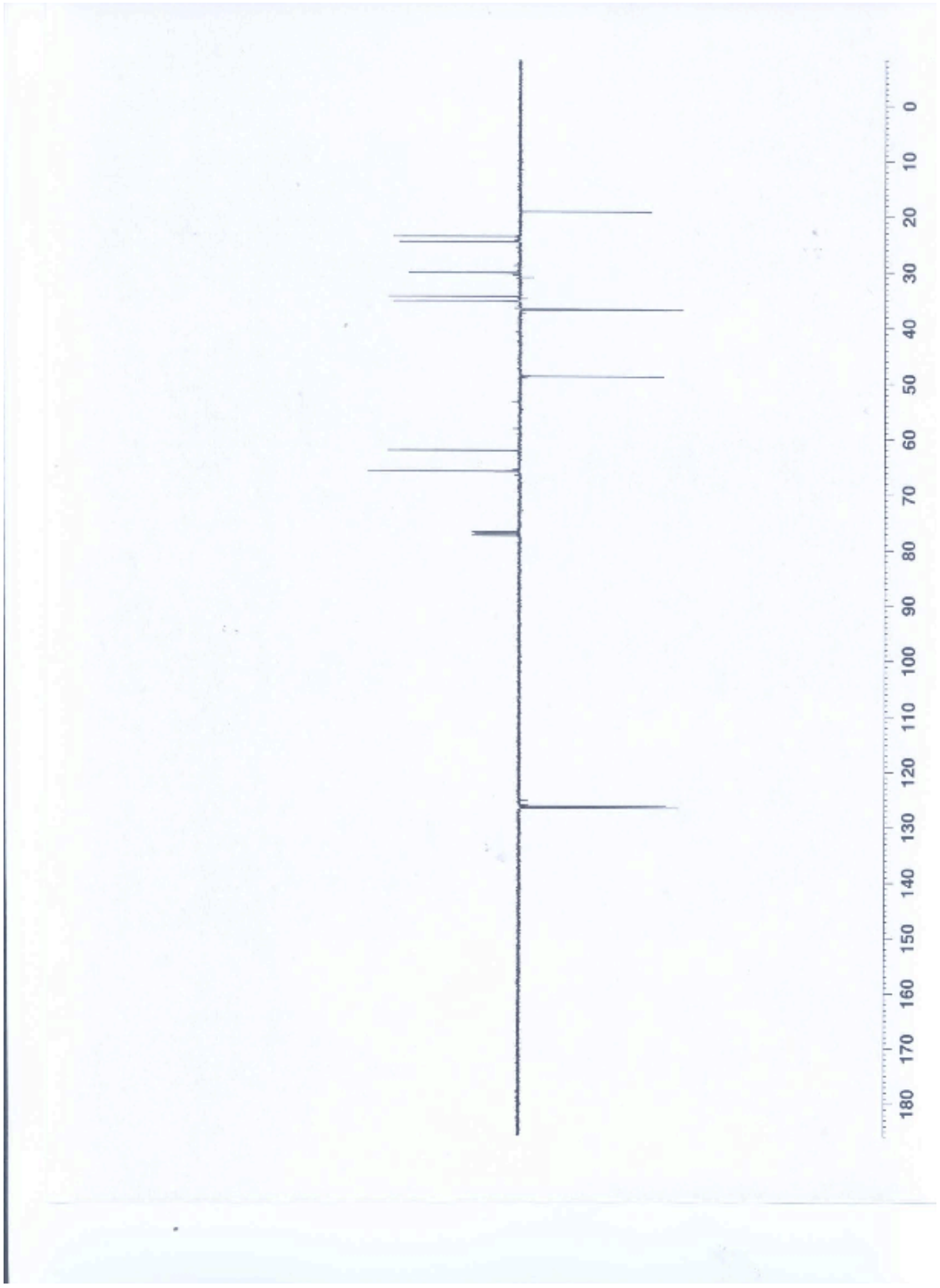




12c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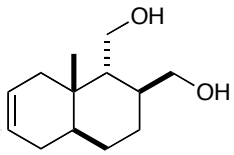
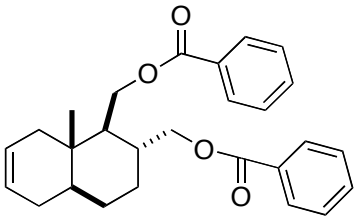
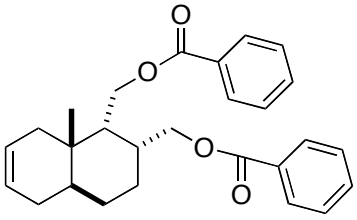

OH
OH

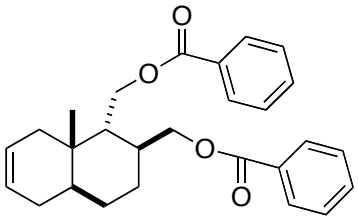
12c



Thermodynamic
13a

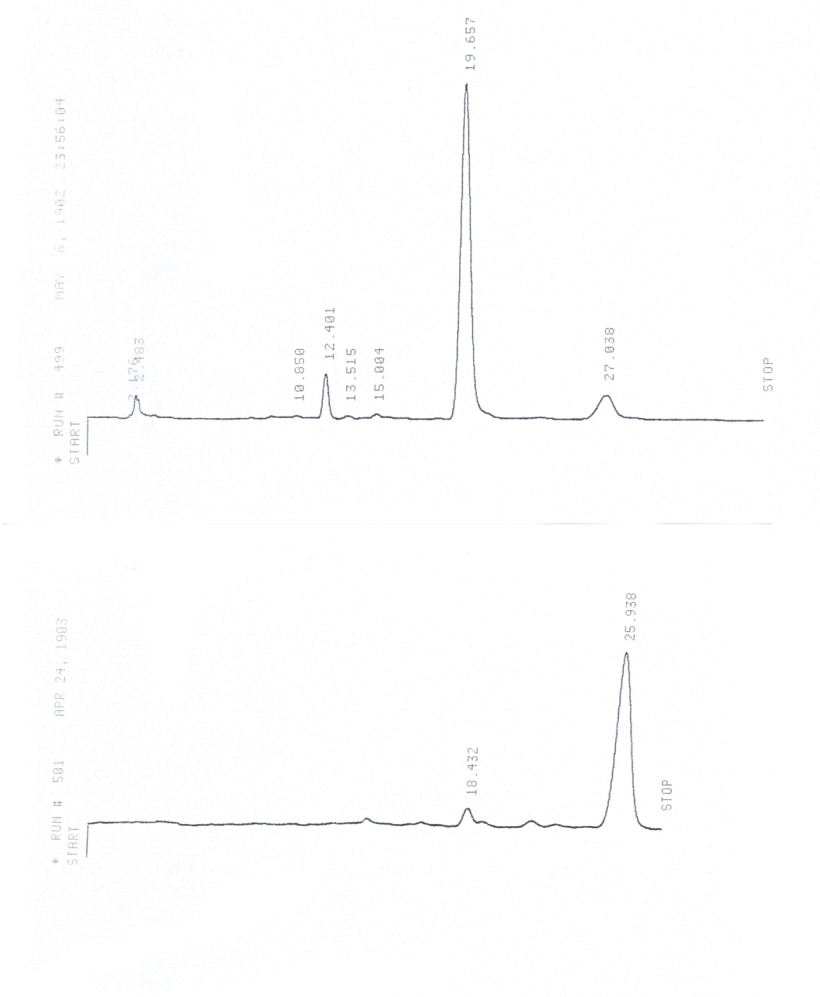


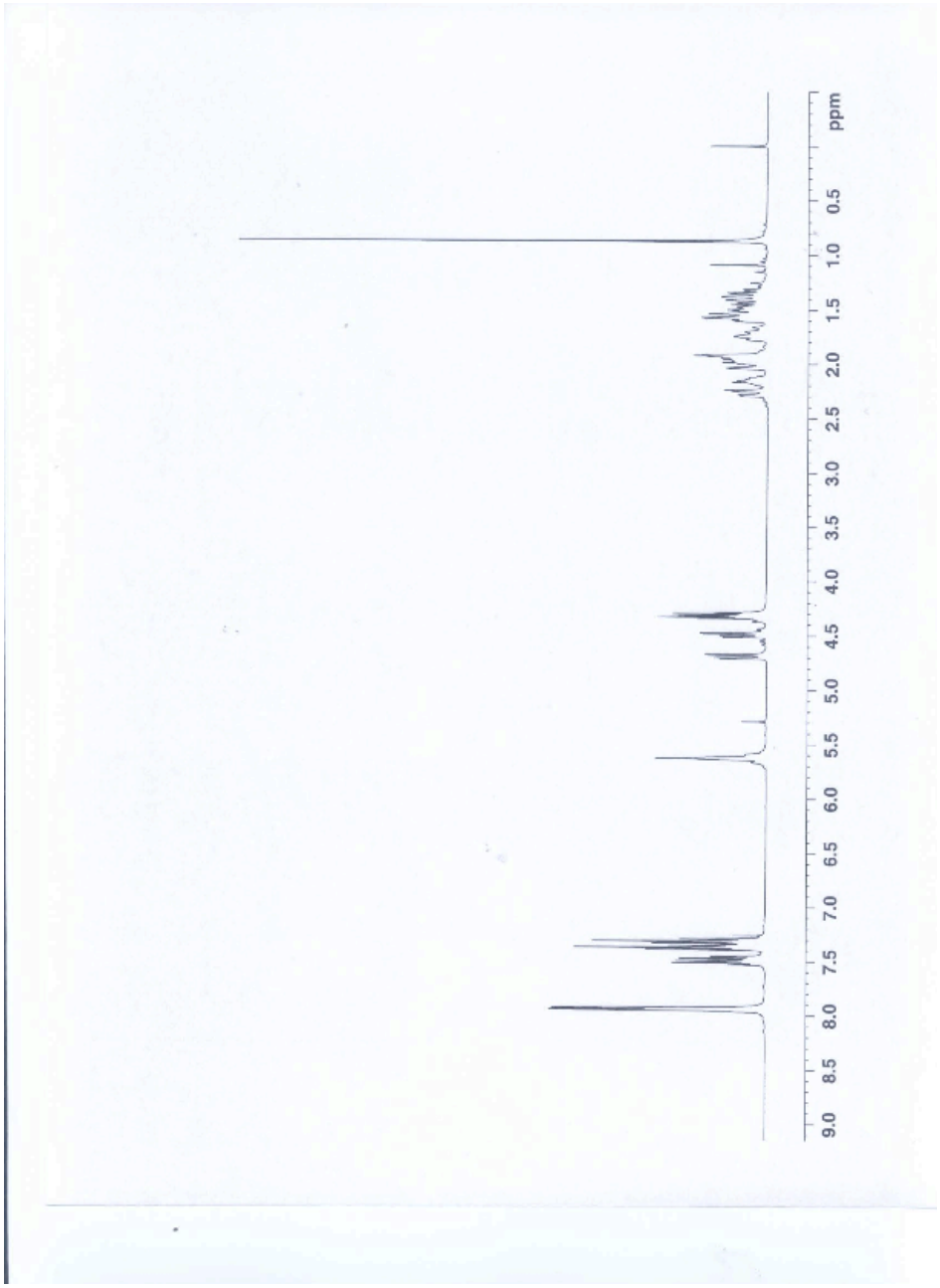
Minor Kinetic
13b

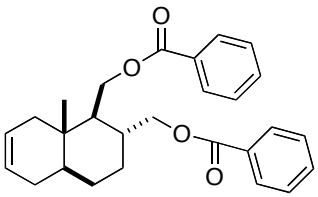


Major Kinetic
13c

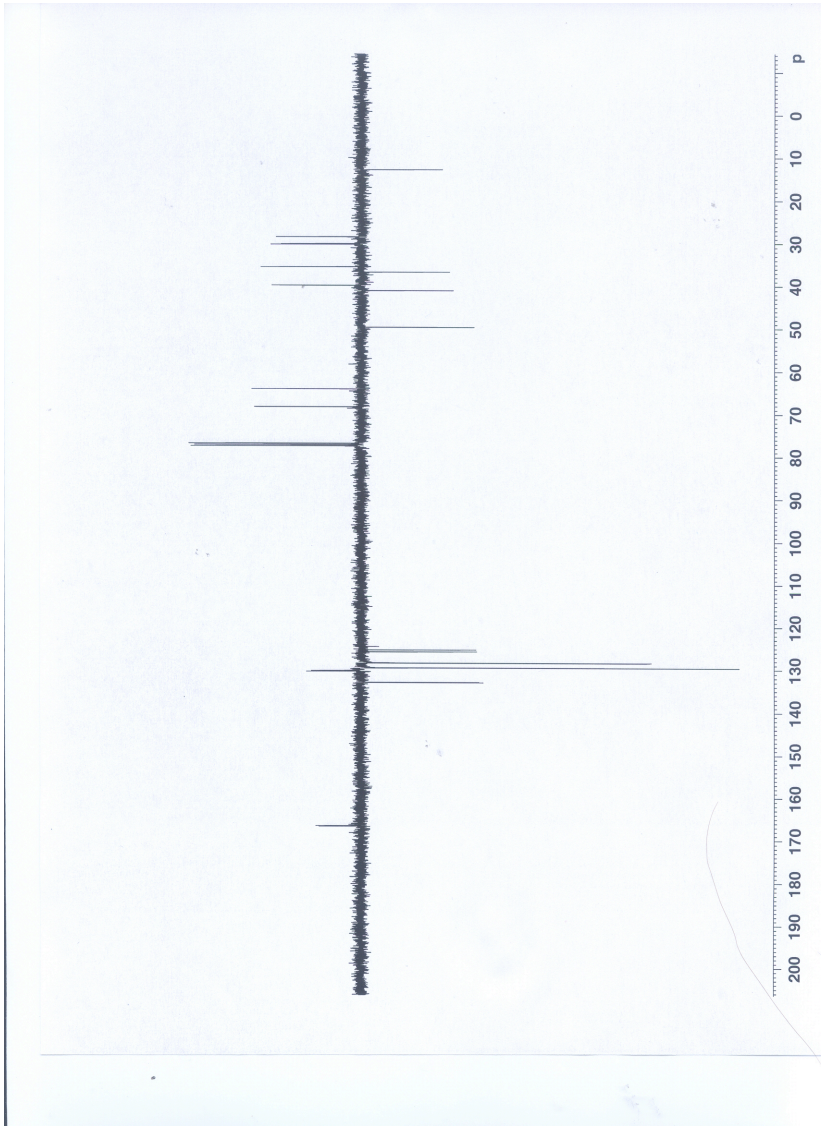
HPLC Details for 13a-c. A Whatman analytical column, normal phase, 25 cm partisil 10 was used in the HPLC study. The solvent system was 2% ethyl acetate/hexanes. The study required thirty minutes in order for all the benzoates to elute. First to elute was excess benzoyl chloride at 3.4 minutes, **13b** eluted at 12 minutes, followed by **13c** at 19.6 minutes and **13a** eluted after 27 minutes.

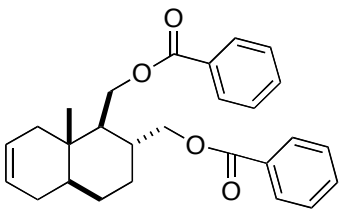




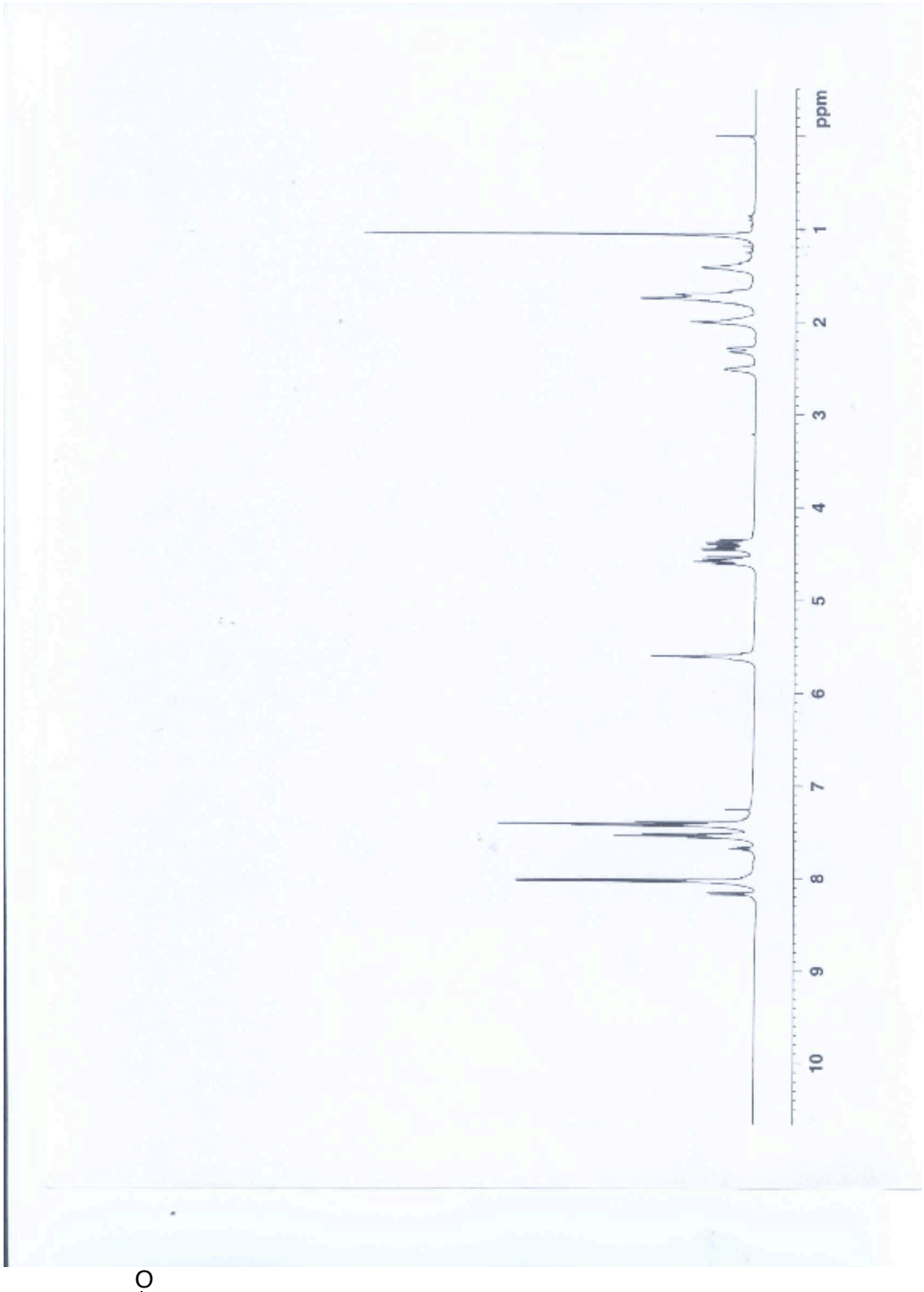


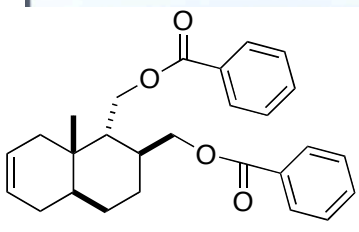
Thermodynamic
13a



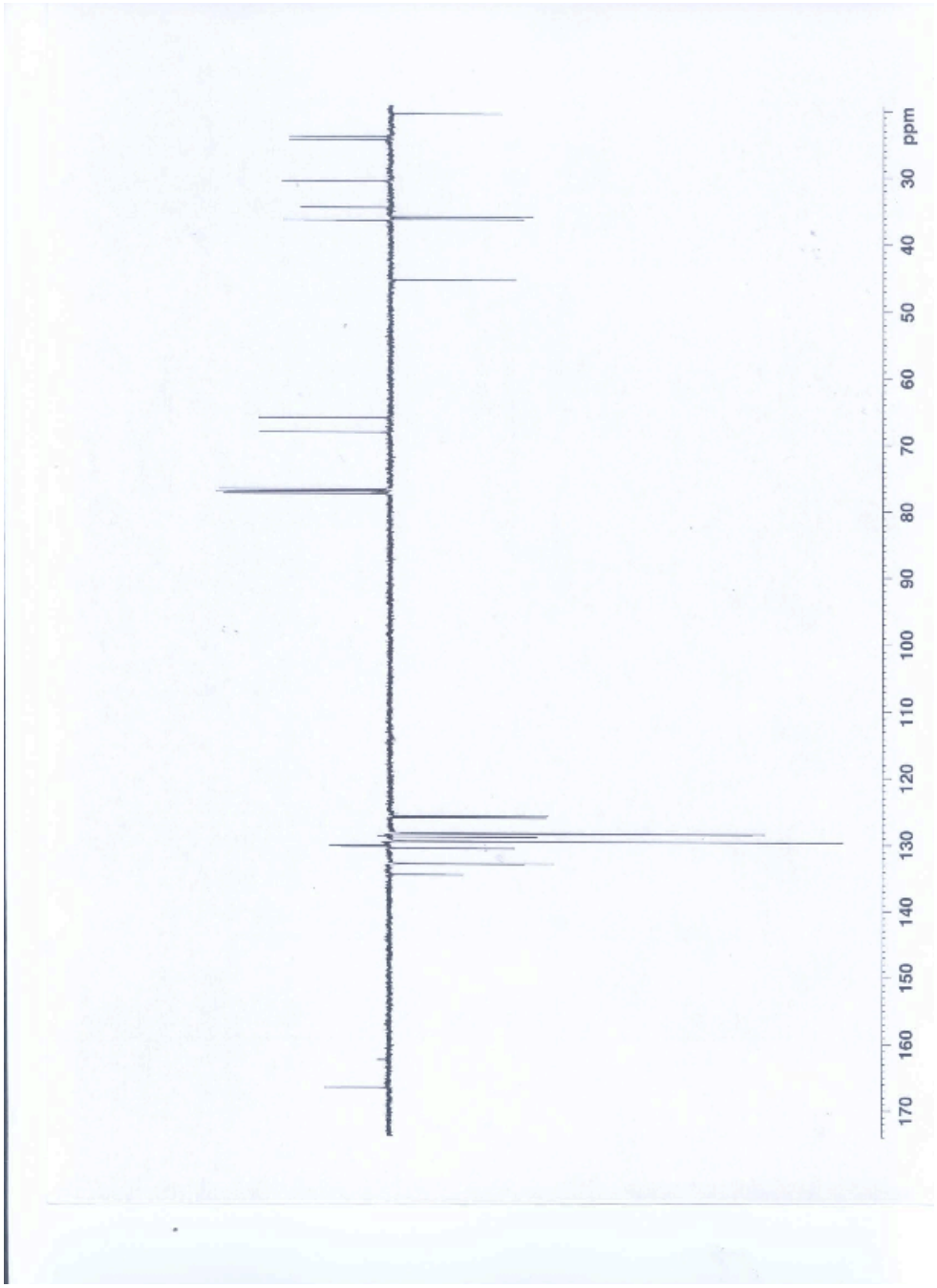


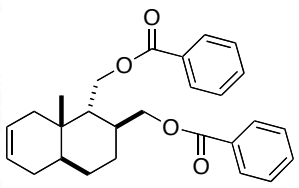
Thermodynamic
13a



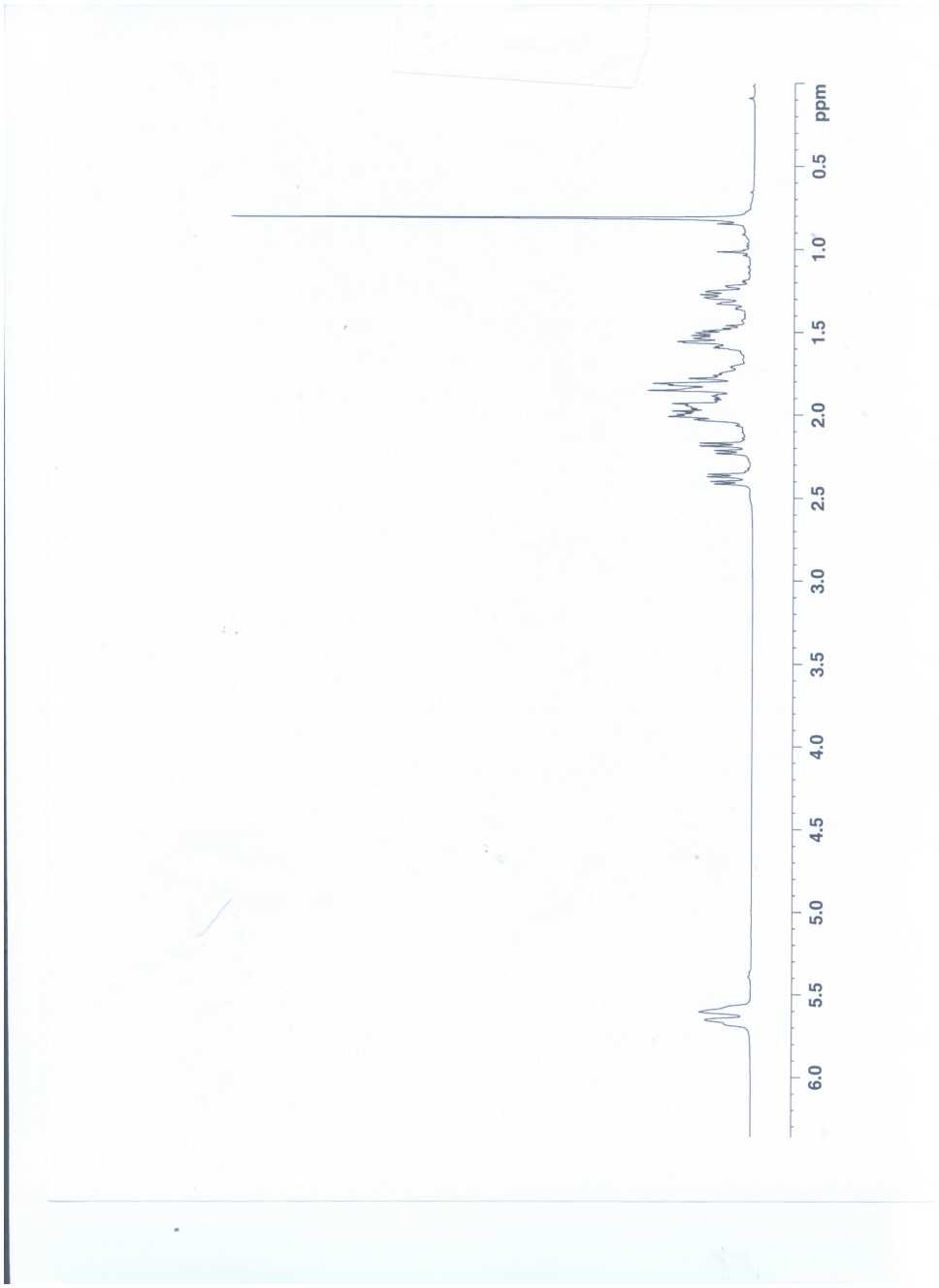


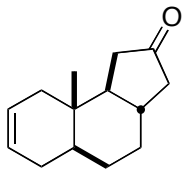
Major Kinetic
13c





Major Kinetic
13c





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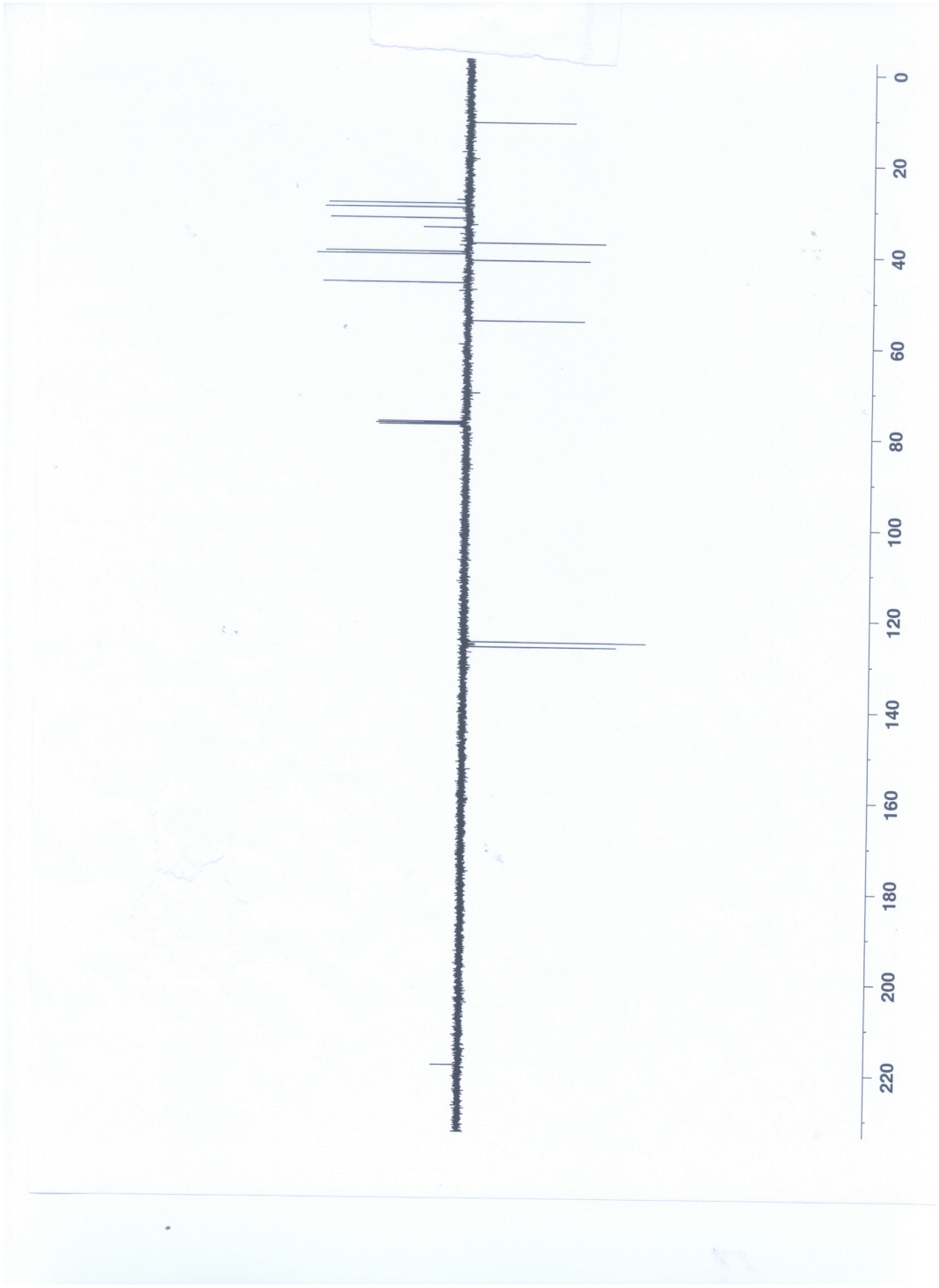

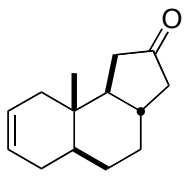

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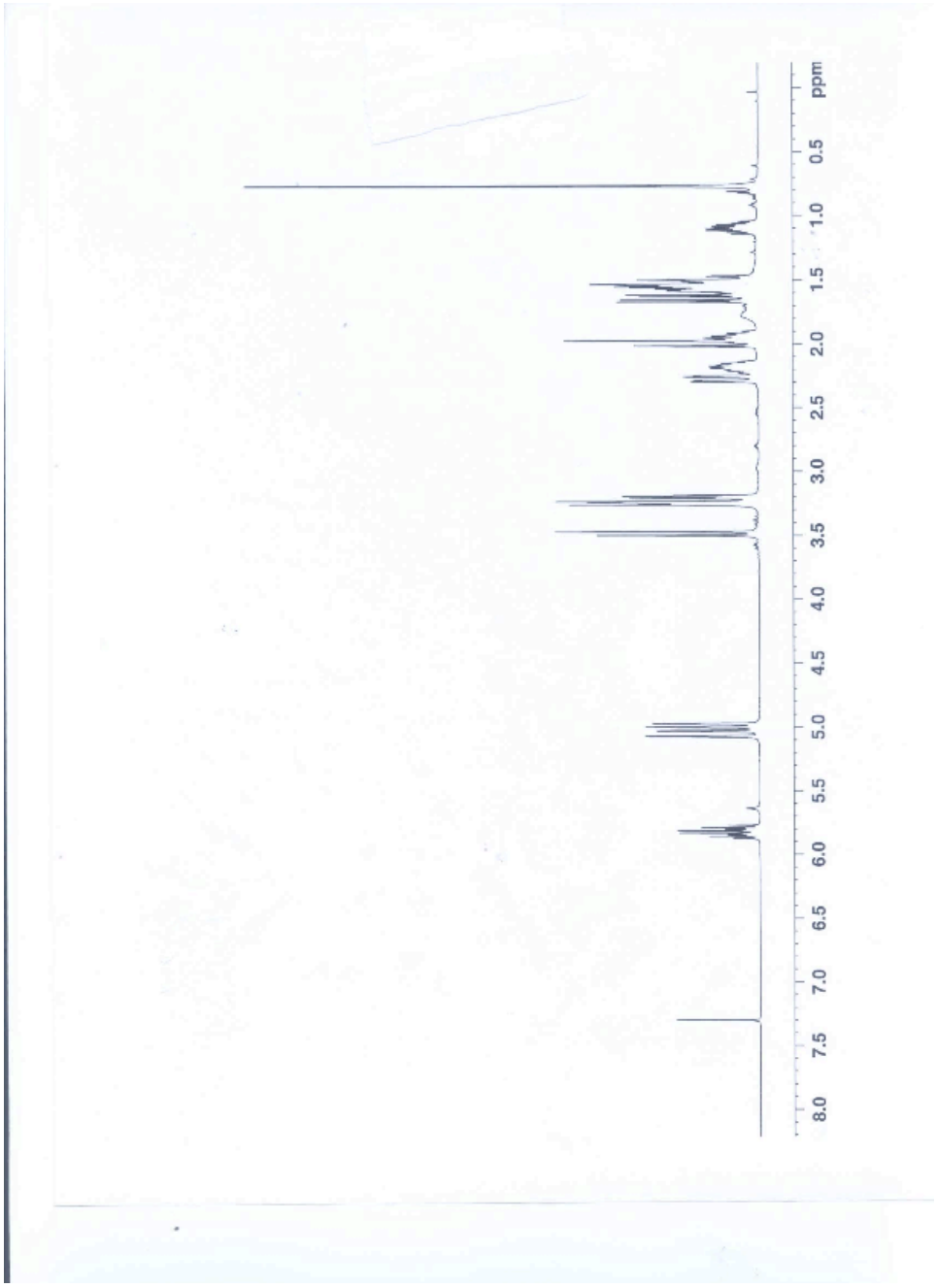

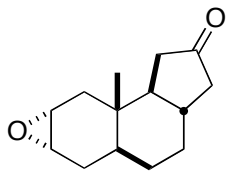

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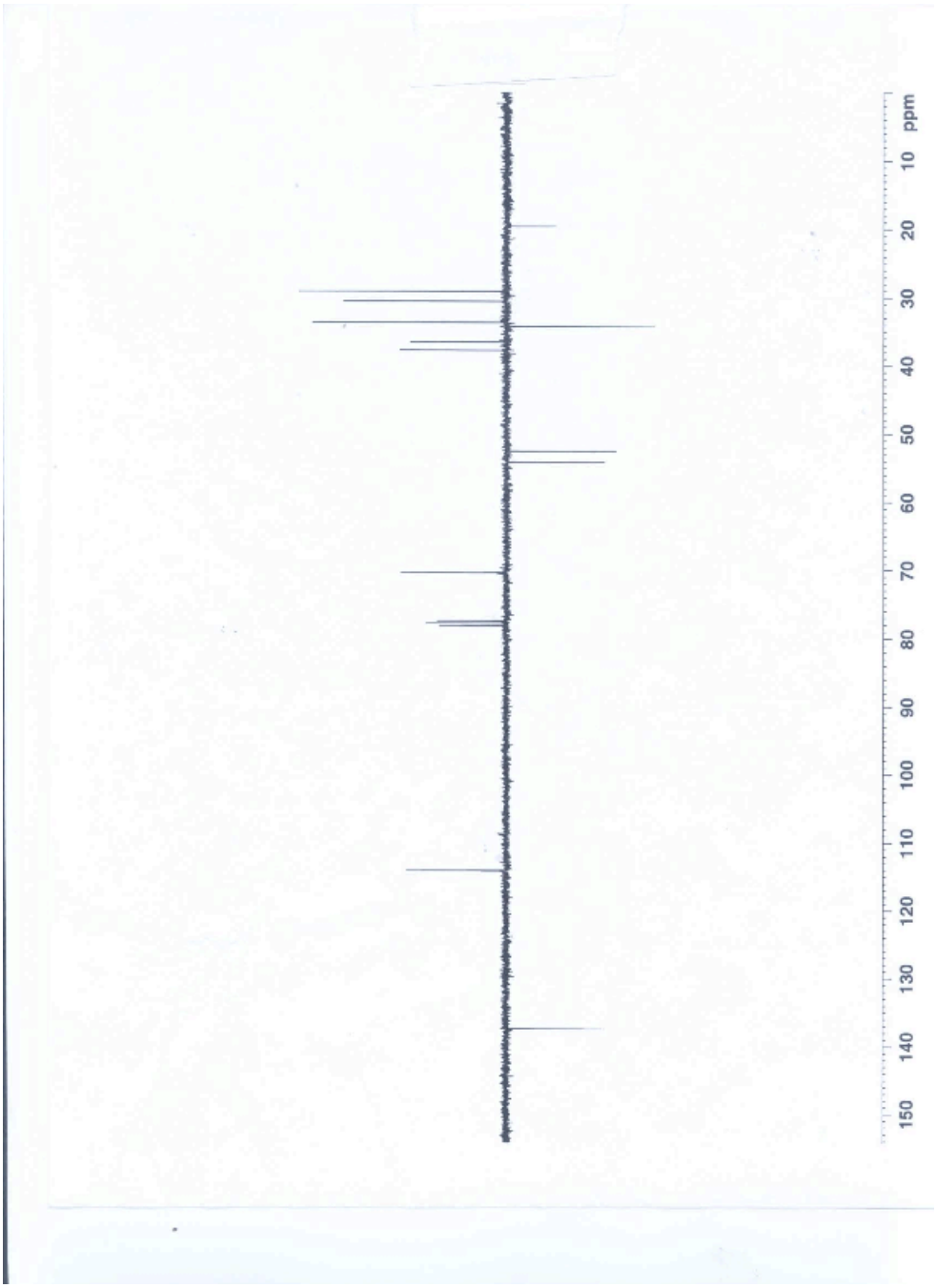

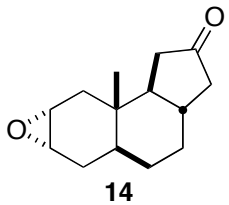

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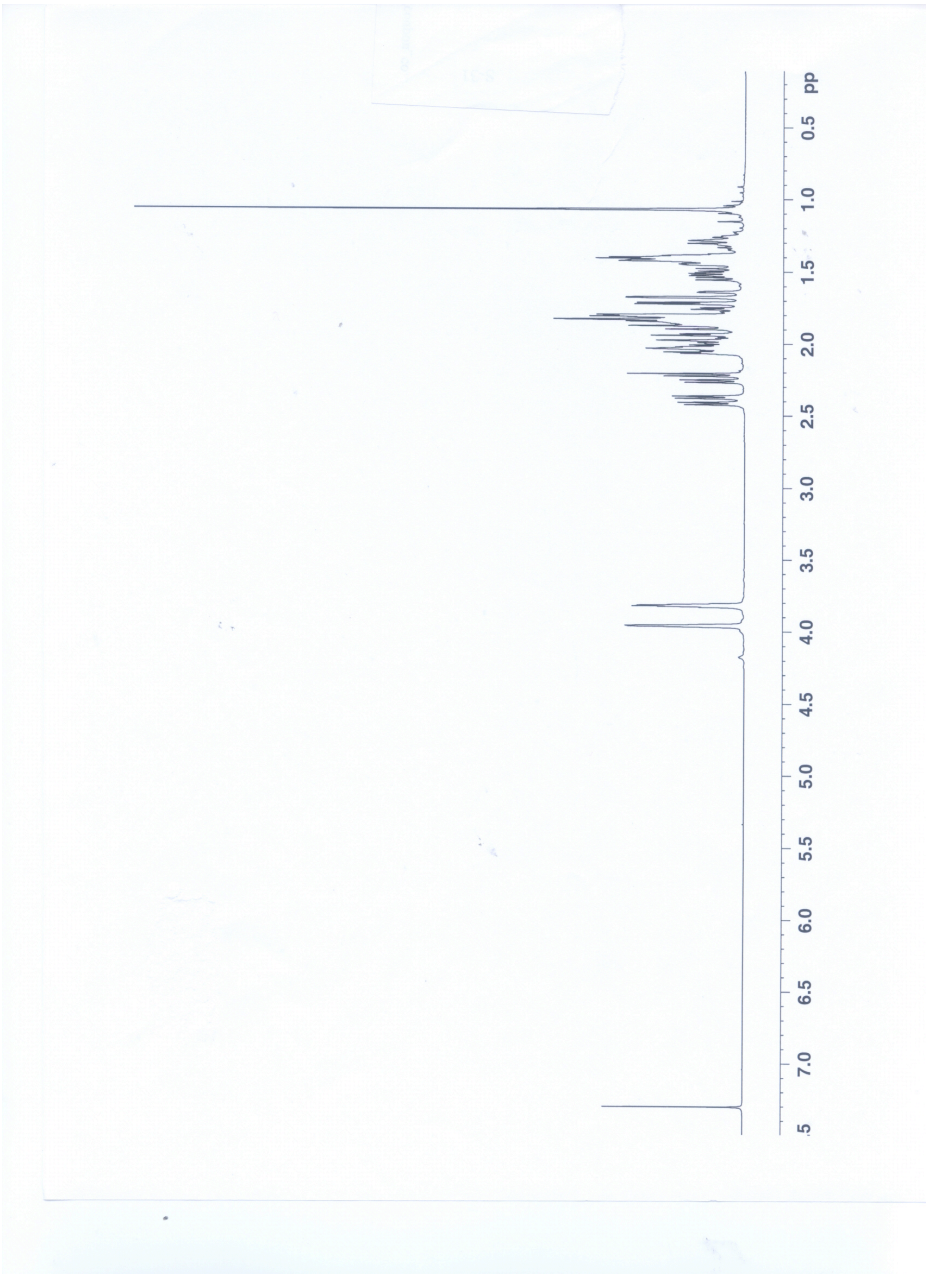

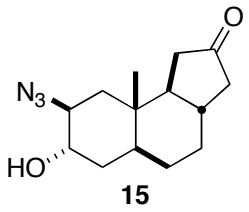

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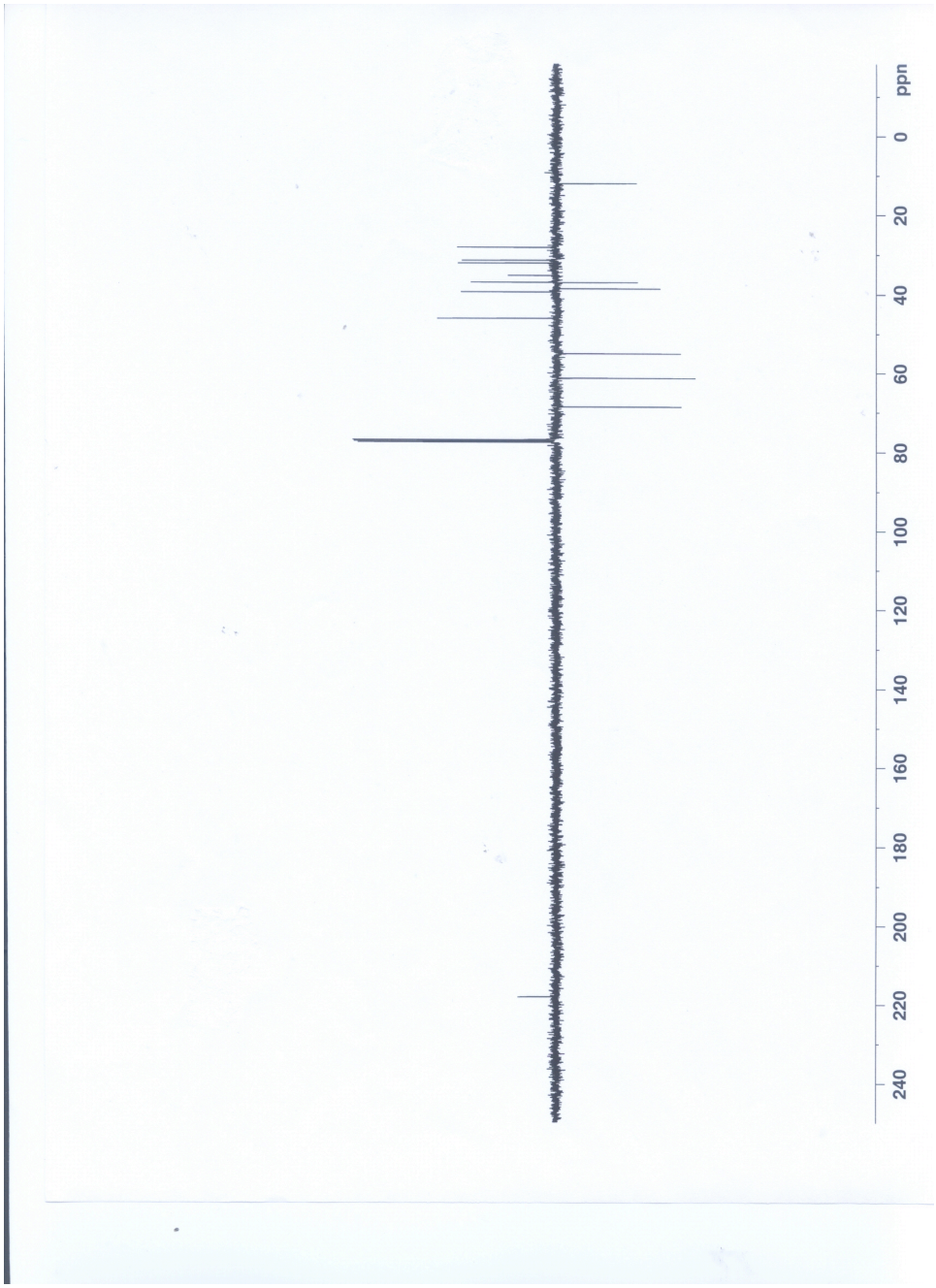

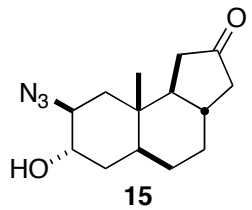

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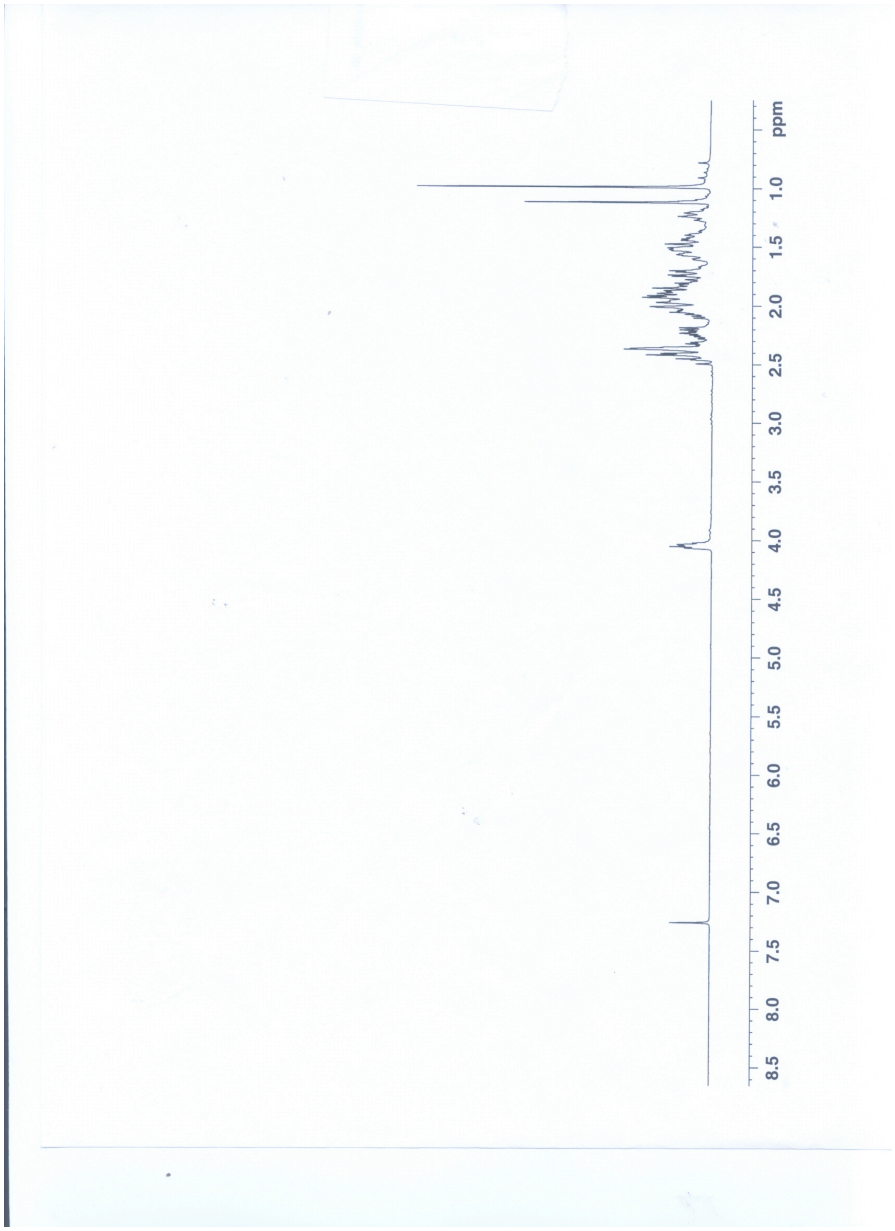

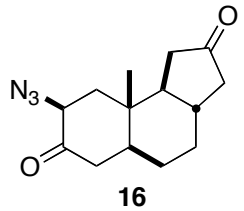

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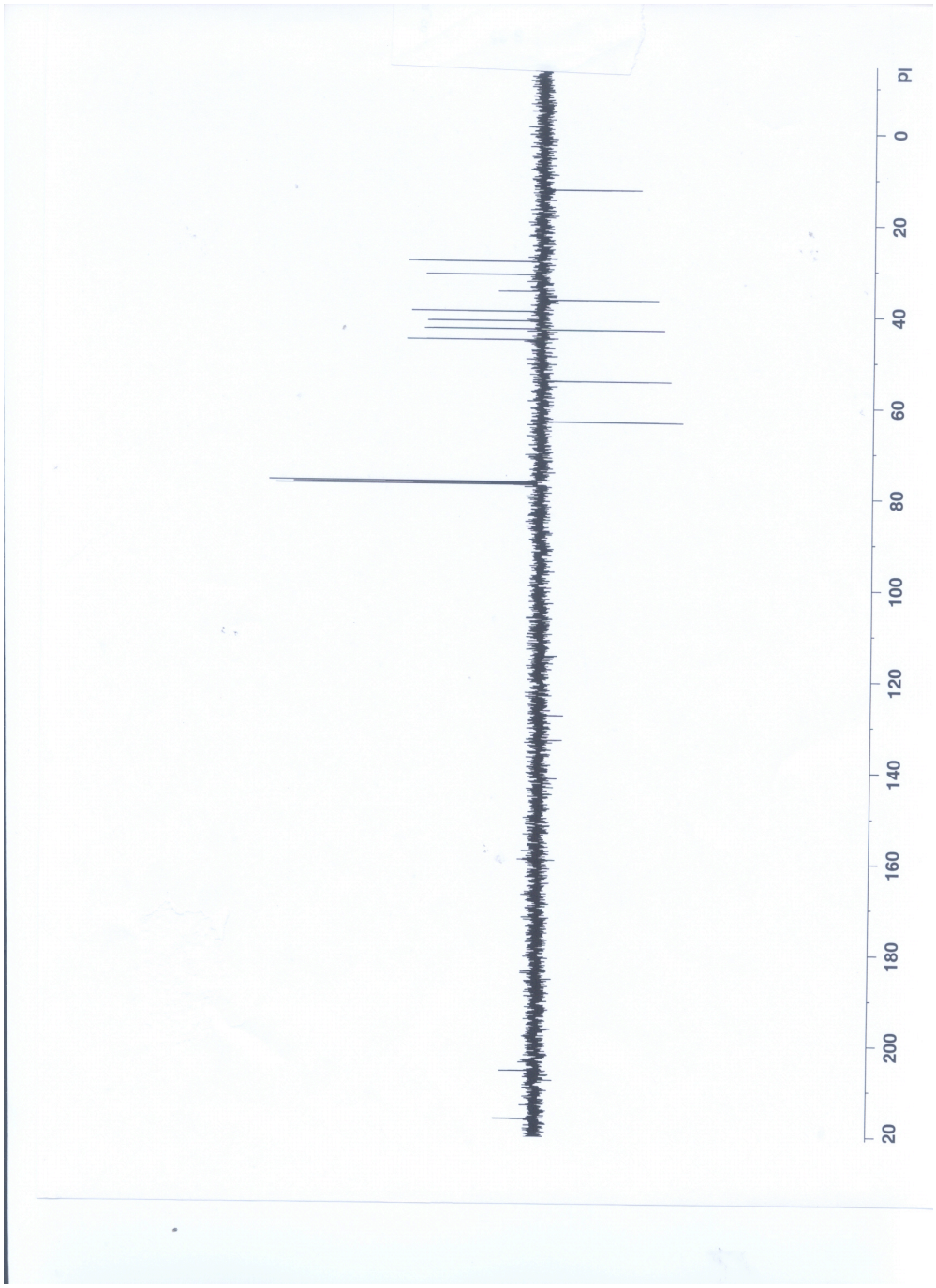

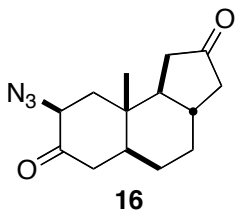

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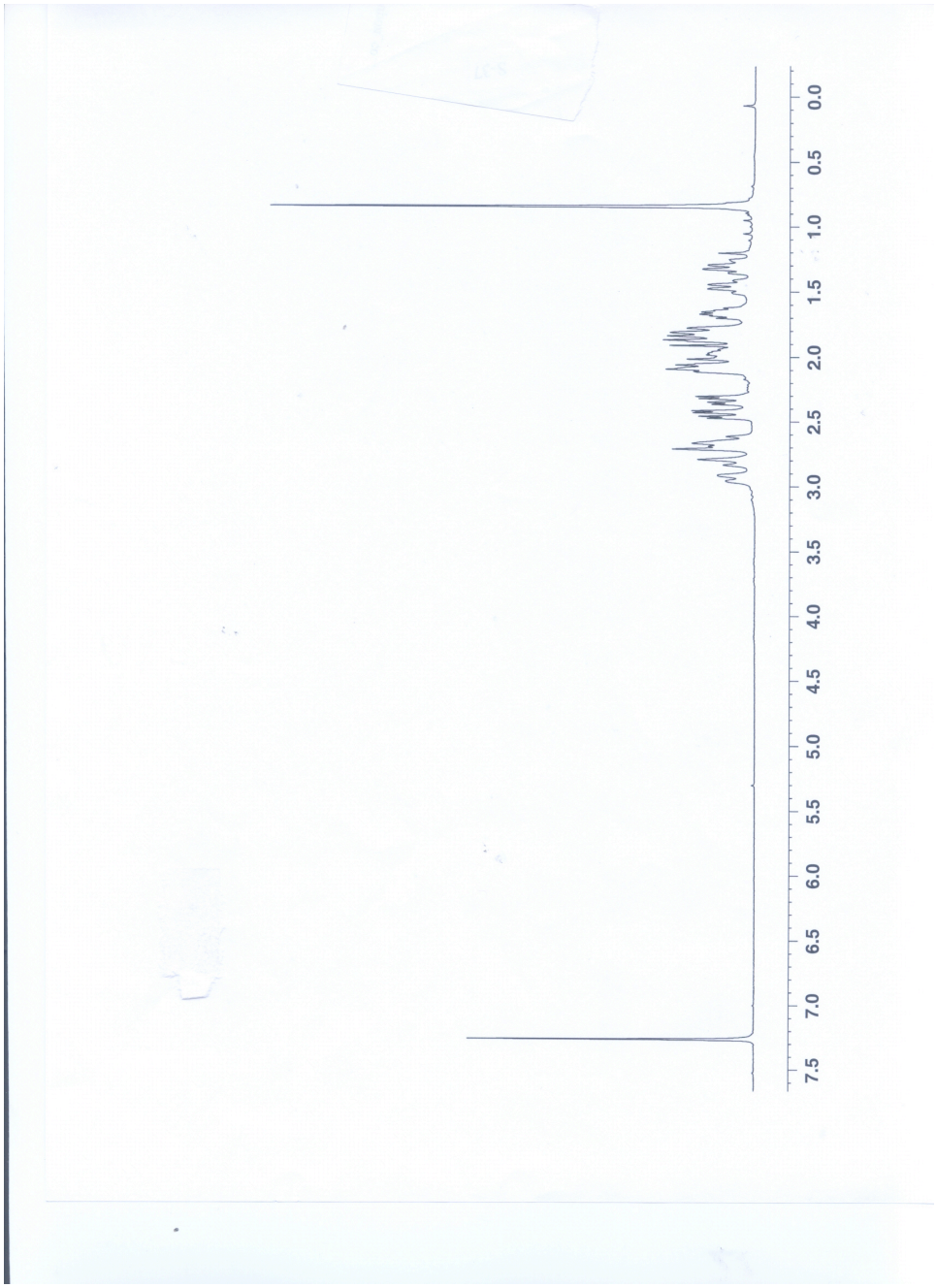

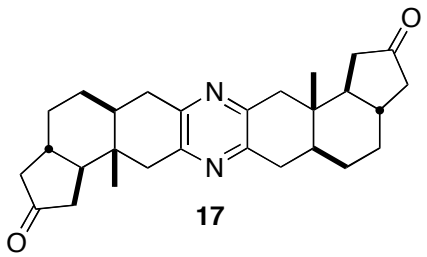

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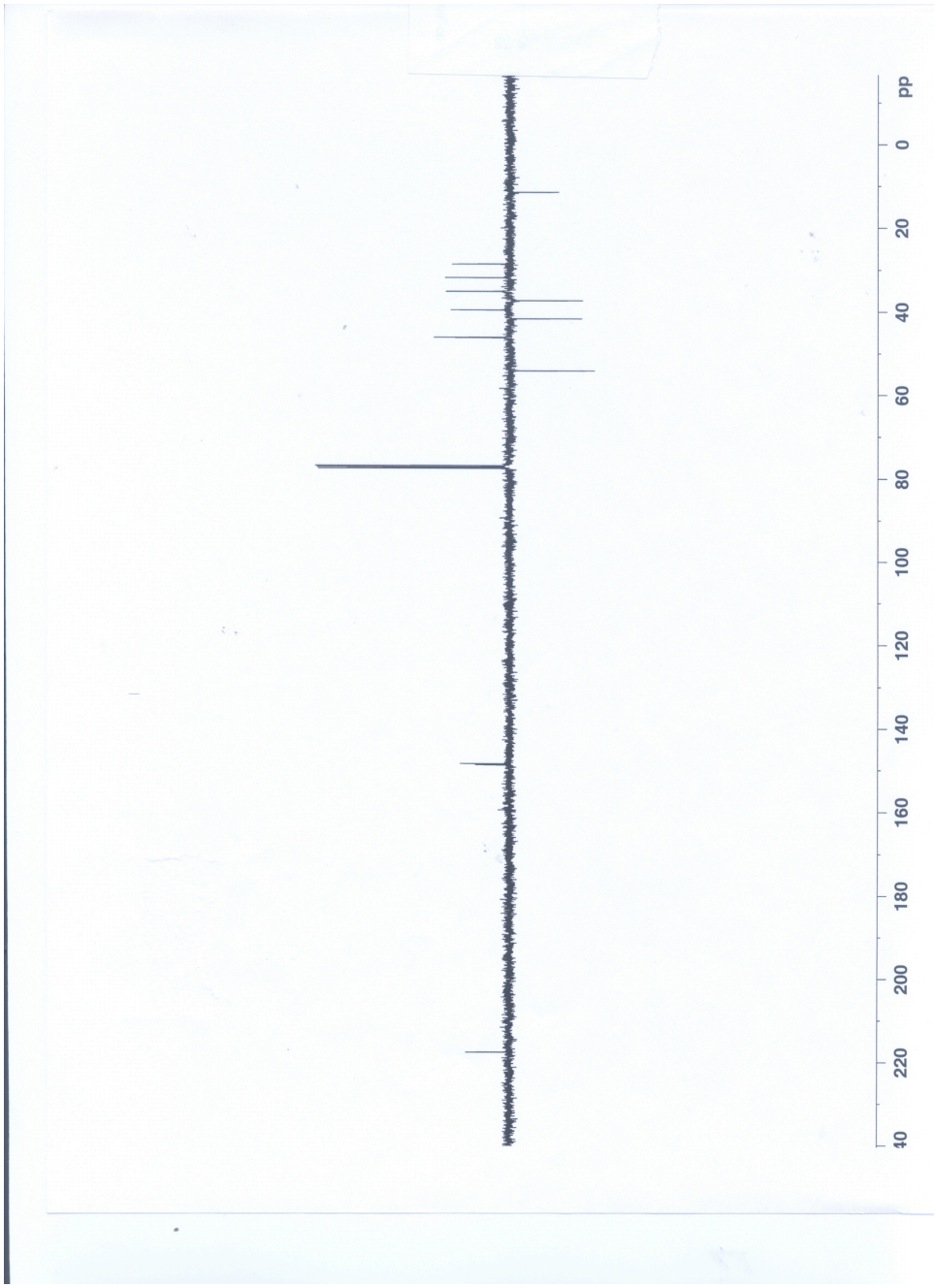

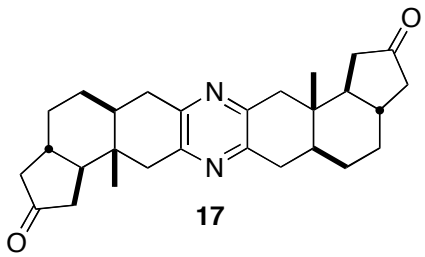

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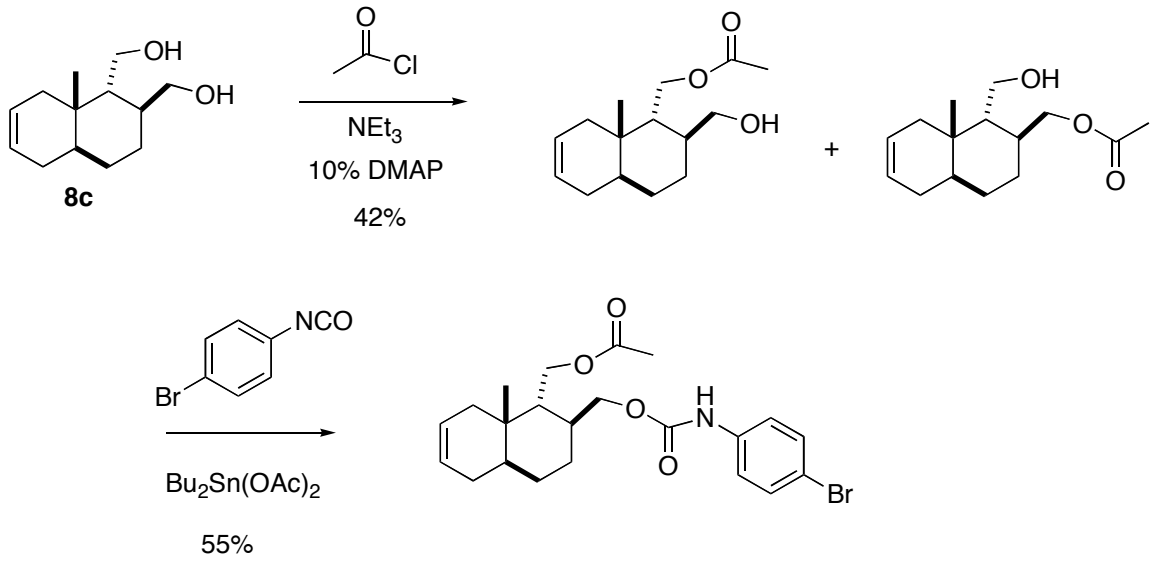

Confirmation of Diol 12c. Acetyl chloride in a solution of CH_2Cl_2 (0.12 M, 1 mL) was added to diol **12c** (0.12 mmol, 25.1 mg). Triethylamine in a solution of CH_2Cl_2 (0.12 M, 1 mL) was added to the reaction mixture. DMAP (0.03 mmol, 3.5 mg) was then added. After one hour, the solvent was evaporated and the residue was chromatographed to yield the monoacetates (1:1, total 12.8 mg, 42% yield). TLC R_f (CH_2Cl_2/MTBE/PE = 0.25/1.25/8.5) = 0.39, 0.49. For the more polar monoacetate: ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (3H, s), 1.22-1.31 (2H, m), 1.59-1.70 (7H, m), 1.94-1.95 (1H, m), 2.04 (3H, s), 2.05-2.11 (1H, m), 3.63-3.64 (1H, m), 3.76-3.79 (1H, m), 4.03-4.08 (1H, m), 4.25-4.29 (1H, m), 5.52-5.60 (2H, m); ^{13}C NMR δ u 23.6, 24.4, 30.6, 34.5, 36.3, 66.1, 66.3, 171.4; d 20.1, 21.4, 36.4, 39.5, 45.0, 126.0, 126.3.

To the more polar monoacetate (0.08 mmol, 20.2 mg) in toluene (0.4 mL) was added 4-bromophenyl isocyanate (0.16 mmol, 31.7 mg) and dibutyl tin diacetate (5.6 mg, 0.16 mmol). The reaction was stirred for 18 hours at 100 °C. The reaction was partitioned between MTBE and brine. The combined organic extract was dried (Na_2SO_4)

and concentrated. The residue was chromatographed to yield the carbamate (19.6 mg, 55%) as a beige solid: mp 141-143 °C; TLC R_f (CH_2Cl_2/MTBE/PE = 0.5/0.25/7) = 0.56. The carbamate was placed into a glass vial and dissolved in a minimal amount (~0.2 mL) of CH_2Cl_2. This vial was placed inside a larger vial. Heptane (5 mL) was poured into the larger vial and the larger vial was sealed. The saturated atmosphere led to the crystalline carbamate after approximately one week. The carbamate structure was established by x-ray crystallography.