SUPPORTING INFORMATION

Cyclopentane Construction by Rh-Catalyzed Intramolecular C-H Insertion: Relative Reactivity of a Range of Catalysts

Supporting Information

Contents:

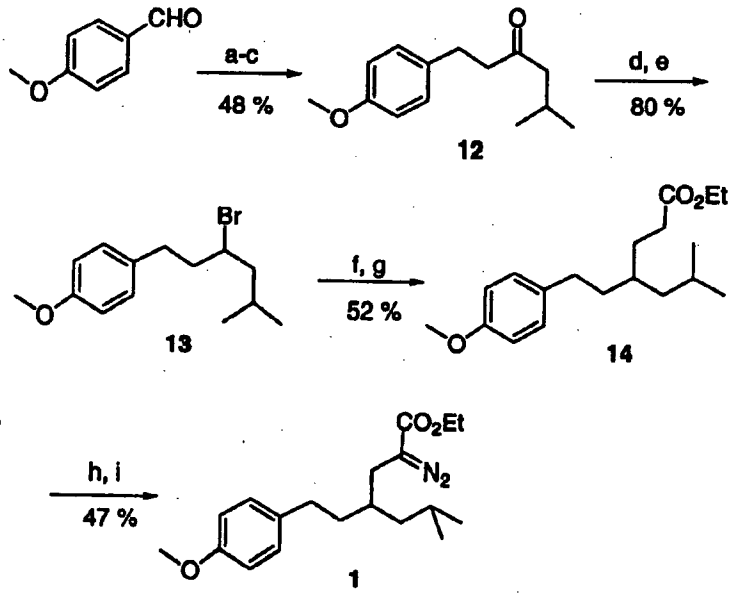
Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ at 400 and 100 MHz, respectively. ^{13}C multiplicities were determined with the aid of a JVERT sequence, differentiating the signals for methylene and quaternary carbons as up (u), from methyl and methine carbons as down (d). The infrared (IR) spectra were determined as neat oils. Mass spectra (MS) were obtained by chemical ionization. R_f values indicated refer to thin-layer chromatography on 2.5 x 10 cm, 250-μm analytical plates coated with silica gel GF and developed in the solvent indicated. The HPLC analysis on the alcohol mixture was performed using a normal phase 10μ silica gel column with 5 % EtOAc in hexanes as the eluant and monitoring at 254 nm. The flow rates for the analytical columns were 1 mL/ min and preparative HPLC was 2.5 mL/min. Column chromatography was performed with Merck 35-60μ silica gel, following the procedure of Still.[1a] Where specified, TLC mesh silica was employed, following the procedure described by Taber.[1b] Solvent mixtures are volume/volume. PE is petroleum ether. EtOAc is ethyl acetate. THF and diethyl ether were distilled from sodium/benzophenone under N_2 and used immediately. CH_2Cl_2 was distilled from CaH_2 under N_2 immediately before use and passed through a pad of activated (110 °C, 12h) K_2CO_3 immediately before use. All reactions were carried out in flame-dried glassware under a positive pressure of N_2 unless otherwise indicated.

Preparation of α-Diazo Ester 1

The preparation of **1** was accomplished in nine steps from *p*-methoxy benzaldehyde and methyl isobutyl ketone (MIBK) (**Scheme 2**). Deprotonation of MIBK with LDA followed by addition of the enolate to *p*-methoxy benzaldehyde gave the β-hydroxy ketone, which dehydrated smoothly to give the corresponding enone.

SCHEME 2[a]



[a] Conditions : a) LDA, THF, -78 C, methyl isobutyl ketone; b) p-TsOH, THF; c) H_2, Pd/C, MeOH; d) $NaBH_4$, MeOH; e) CBr_4, Ph_3P, CH_2Cl_2; f) NaI, acetone; g) $FeCl_3$, pyrdine, Zn dust, NaI, ethyl acrylate; h) LHMDS, $CF_3CO_2CH_2CF_3$; i) DBU, pNBSA, CH_2Cl_2.

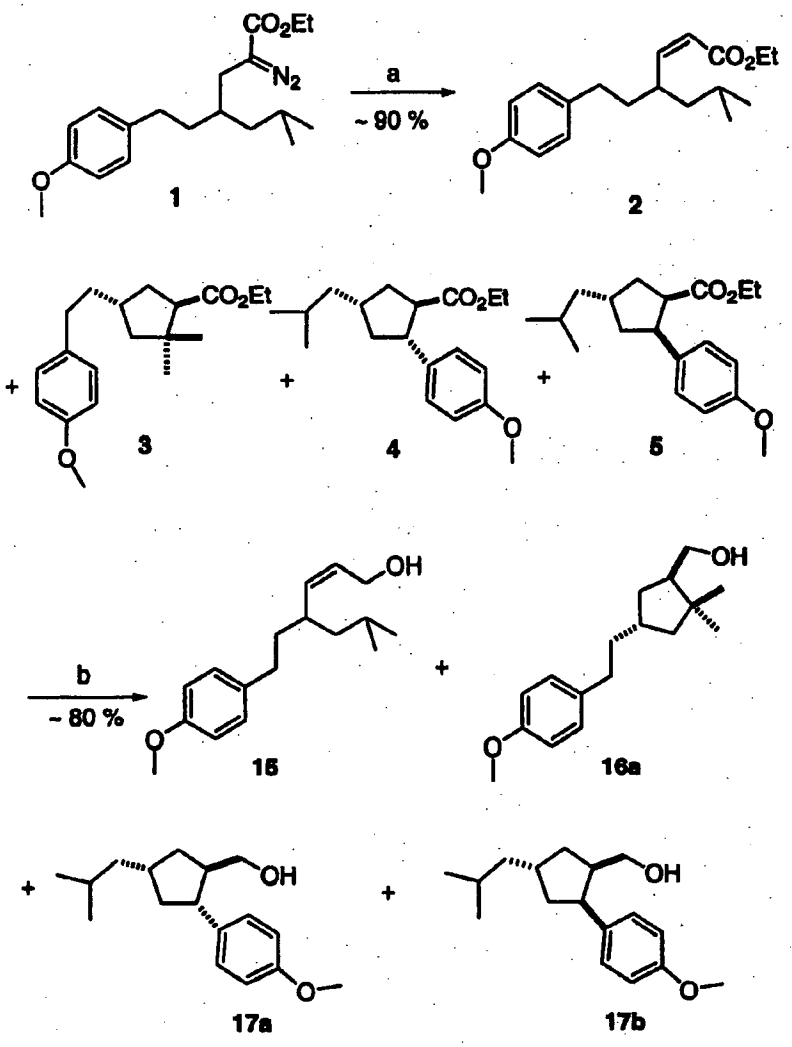
Hydrogenation then gave the desired ketone **12** in 48% overall yield (3 steps) from p-anisaldehyde. The ketone was reduced with $NaBH_4$ and the resulting alcohol was converted to the bromide **13**. Conversion of the bromide to the iodide followed by an iron-mediated radical addition to ethyl acrylate[2] gave the three-carbon homologated ester

14. Finally, diazo transfer[3] was accomplished using a procedure developed in our laboratories, to give the desired ester **1**.

Product Analysis

The diazo ester **1** upon exposure to a Rh(II) catalyst (**Scheme 3**) underwent intramolecular C-H insertion to give the CH and CH_2 insertion products **3**, **4** and **5** along with the elimination product **2**.

SCHEME 3[a]

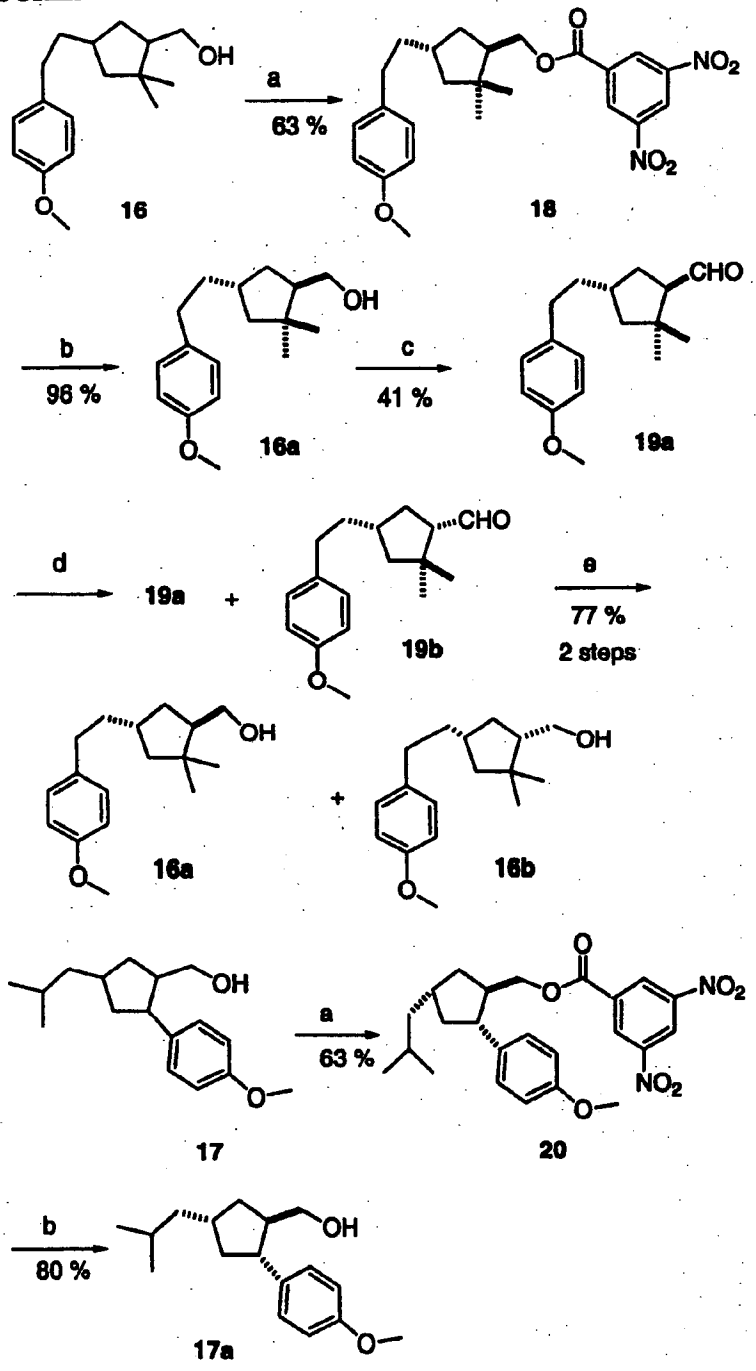


[a] Conditions: a) Rh_2L_4, CH_2Cl_2, r.t.; b) $LiAlH_4$, THF.

The esters were not resolved by conventional chromatography techniques. The mixture was therefore reduced with $LiAlH_4$ to give the corresponding mixture of alcohols. Oxidation with MnO_2 was used to remove**15** from the mixture.

The mixture of alcohols **16** and **17** was converted (**Scheme 4**) to the corresponding 3, 5-dinitrobenzoate esters **18** and **20**. These esters could be separated by silica gel chromatography. The purified major diastereomers **18** and **20** were converted back to the alcohols **16a** and **17a** by exposure to potassium carbonate in methanol. Thus, it was possible to obtain pure samples of the major CH and CH_2 insertion products for characterization and for HPLC analysis. The relative configurations of **16** and **17** were assigned by analogy to our previous work.[3a]

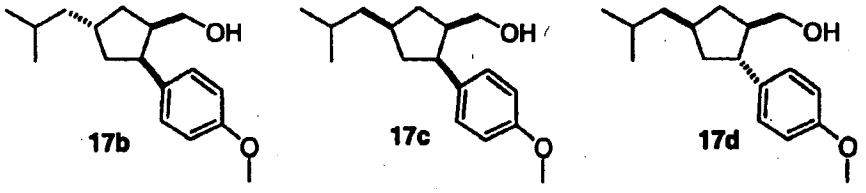
SCHEME 4[a]



[a]Conditions: a) 3, 5-Dinitrobenzoyl chloride, pyridine, DMAP (cat) 12h; b) K_2CO_3, MeOH; c) DMP, CH_2Cl_2, r.t ; d) KO^{t}Bu, THF; e) $LiAlH_4$, THF.

The pure alcohol **16a** (**Scheme 4**) was oxidized by Dess-Martin periodinane[4] to give the corresponding aldehyde **19a**. The aldehyde **19a** was epimerized by treating with potassium *tert*-butoxide in THF to give a mixture of aldehydes **19a** and **19b**. The mixture was reduced with $LiAlH_4$ to provide an authentic mixture of alcohols **16a** and **16b**. This allowed the identification of these two peaks in the HPLC chromatogram.

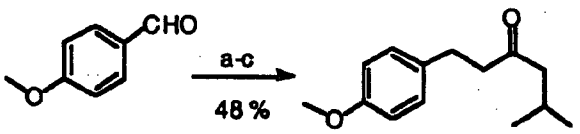
The HPLC analysis on the alcohol mixture was performed using a normal phase 10μ silica gel column with 5 % EtOAc in hexanes as the eluant, monitoring at 254 nm. The methylene insertion products **17c** (r_t = 30.5 min(minor-cis)), **17b** (r_t = 36.8 min (major-cis)) and **17a** (r_t = 38.7 min(major-trans)) eluted before the methine insertion products **16a** (r_t = 43.3 min (major)) and **16b** (r_t = 41.9 min (minor)). Alcohols **16a** and **17a** were always the dominant products from the cyclization. Alcohol **17d** was not observed.



This peak assignment was supported by ^1H NMR analysis of the pure alcohols separated by preparative HPLC. The major methine insertion diastereomer **16a** had a unique proton (in the mixture from cyclization) at δ 3.71, while the minor methine insertion diastereomer **16b** had a unique proton at δ 1.90. In the methylene insertion series, the major methylene insertion diastereomer **17a** had a unique proton at δ 2.67 while the cis methylene insertion diastereomer **17b** had a unique proton at δ 2.47 and the cis methylene insertion diastereomer **17c** had a unique proton at δ 3.33. Thus, the sum of the methine integrations divided by the sum of the methylene integrations gave us the

ratio of CH/ CH_2. While the HPLC ratios were more precise, the ^1H NMR ratios (see below) tracked reasonably well, and could be sufficient if a new Rh (II) catalyst was to be characterized.

Experimental Section



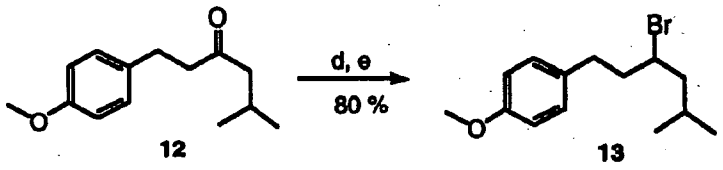
12

Synthesis of Ketone (12). n-BuLi (54.8 mL, 120 mmol, 2.19 M in hexanes) was added slowly to diisopropylamine (16.8 mL, 120 mmol) in 55 mL of THF at –78 °C. The mixture was stirred under N_2 for 30 min, then methyl isobutyl ketone (130 mL, 105 mmol) was added over 20 min. The reaction mixture was stirred for 30 min, then *p*-anisaldehyde (11.6 mL, 95 mmol) was added dropwise over 5 min. The reaction mixture was allowed to stir and come to room temperature over 1h. It was then quenched carefully by addition of 40 mL of saturated aqueous NH_4Cl. The mixture was partitioned between MTBE and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated to give 23.7 g of crude hydroxy ketone as an orange oil, TLC R_f = 0.44 (30% MTBE/ PE).

To 23.0 g (100.4 mmol) of the crude hydroxy ketone in 250 mL of dry THF was added in four portions *p*-TsOH (9.45 g, 36.8 mmol) over 10 min. The reaction mixture was heated to reflux for two hours, then cooled to 0 °C and quenched carefully with saturated aqueous $NaHCO_3$. The resulting mixture was partitioned between MTBE and, sequentially, saturated aqueous $NaHCO_3$ and brine. The combined organic extract was

dried (Na_2SO_4) and concentrated to give 18.9 g of the crude enone as an orange oil, TLC R_f = 0.46 (30% MTBE/ PE).

To 18.3 g (83.9 mmol) of the crude enone in 300 mL of methanol was added 1.77 g of 5 % Pd/C. The suspension was stirred under an H_2 balloon at room temperature for 1.5 h (TLC control). The reaction mixture was filtered through a pad of Celite, then concentrated *in vacuo*. The residue was chromatographed to give 9.89 g (47% over 3 steps from *p*-anisaldehyde) of the desired ketone **12** as a clear oil, TLC R_f = 0.65 (30% MTBE/ PE). ^{1}H NMR: δ 7.11 (2 H, d, J = 8.3 Hz); 6.83 (2 H, d, J = 8.3 Hz); 3.79 (3 H, s); 2.84 (2 H, t, J = 7.5 Hz); 2.68 (2 H, t, J = 7.5 Hz); 2.26 (2 H, t, J = 6.9 Hz); 2.11 (1 H, m); 0.91 (3 H, s); 0.89 (3 H, s). ^{13}C NMR : δ d 22.6, 24.6, 55.3, 113.9, 129.3, u 28.9, 45.1, 52.1, 133.3, 157.9, 210.2. IR : 2952, 2869,1711, 1610, 1515 cm^{-1}. MS (*m/z*,): 221 (M + H$^+$), 162, 135, 121 (100%), 84. HRMS calculated for $C_{14}H_{20}O_2$ 220.1465, found 220.1463.

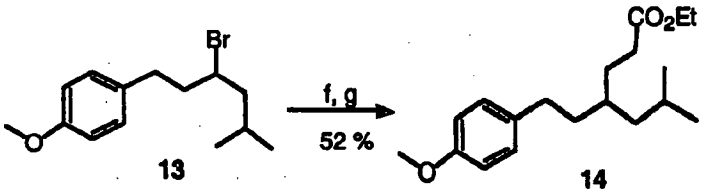


12 13

Synthesis of Bromide (13). To ketone **12** (910 mg, 4.14 mmol) in 16 mL of methanol at 0 °C was added $NaBH_4$ (311 mg, 8.26 mmol) in one portion. The reaction mixture was stirred from 0 °C to 10 °C for 50 min (TLC control). The mixture was then partitioned between MTBE and, sequentially, saturated aqueous NH_4Cl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated to give an oil. The residue was

chromatographed to give 869 mg (94% yield) of the alcohol as a clear oil, TLC $R_f = 0.21$ (15% MTBE/ PE).

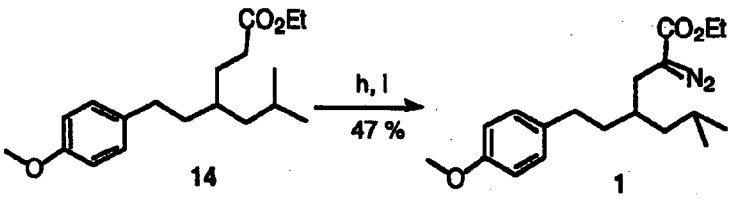
To the alcohol (5.88 g, 26.5 mmol) in 88 mL of CH_2Cl_2 at 0 °C was added 9.0 g (34.4 mmol) of Ph_3P in one portion followed by CBr_4 (10.5 g, 34.3 mmol) in three portions over 5 min. The reaction mixture was stirred at 0 °C for 3 h. The solvent was then removed and the residue was chromatographed to give 6.35 g (85% yield) of the bromide **13** as a colorless oil, TLC $R_f = 0.79$ (15% MTBE/ PE). ^{1}H NMR : δ 7.12 (2 H, d, J = 8.5 Hz); 6.83 (2 H, d, J = 8.5 Hz); 4.02 (1 H, m); 3.78 (3 H, s); 2.84 (1 H, m); 2. 7 (1 H, m); 2.06 (2 H, m); 1.87 (2 H, m); 1.54 (1 H, ddd, J = 4.7, 8.5, 14.0 Hz); 0.89 (3 H, d, J = 6.5 Hz); 0.85 (3 H, d, J = 6.5 Hz). ^{13}C NMR : δ d 21.5, 23.2, 26.6, 55.4, 56.3, 114.0, 129.6, u 32.9, 41.6, 48.4, 133.3, 158.1. IR: 2956,1614, 1505, 1369, 1240 cm^{-1}. HRMS calculated for $C_{14}H_{21}OBr$ 284.0776, found 284.0774.



Synthesis of ester (14). To bromide **13** (2.59 g, 9.1 2 mmol) in 30 mL of acetone at room temperature was added 100 mg of Cu powder, followed by NaI (2.04 g, 13.7 mmol). The reaction mixture was heated to reflux for 12 h, then the solids were filtered off and the filtrate was concentrated. The residue was chromatographed to give 2.61 g (74% yield) of the iodide as a yellow oil, TLC $R_f = 0.48$ (2% MTBE/ PE).

To $FeCl_3$ (3.24 g, 12 mmol) in 23 mL of pyridine was added NaI (3.6 g, 24 mmol) at room temperature. To this reaction mixture was added Zn dust (9.18 g, 145 mmol) in

four portions, which resulted in an exotherm. This was followed by the addition of a mixture of the above iodide (8.0 g, 24 mmol) and ethyl acrylate (28.0 mL, 265 mmol) over 5 min. The dark brown reaction mixture was stirred for 1 h at room temperature. The mixture was then partitioned between MTBE and, sequentially, aqueous 3N HCl and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give 3.83 g (52% yield from bromide **13**) of the desired ester **14** as a clear oil, TLC R_f = 0.51 (6% MTBE/ PE). ^{1}H NMR : δ 7.1 (2 H, d, J = 8.6 Hz); 6.83 (2 H, d, J = 8.6 Hz); 4.14 (2 H, q, J = 7.1 Hz); 3.79 (3 H, s); 2.54 (2 H, dt, J = 1.6, 8.0 Hz); 2.3 (2 H, t, J = 8.0 Hz); 1.65 (3 H, m); 1.57 (2 H, m); 1.54 (2 H, m); 1.27 (3 H, t, J = 7.1 Hz); 1.2 (1 H, m); 0.87 (6 H, t, J = 6.3 Hz). ^{13}C NMR : δ d 14.5, 23.1, 25.4, 34.4 55.4, 113.9, 129.4, u 28.9, 32.0, 35.9, 43.4, 60.4, 135.1, 157.8, 174.3. IR: 2954,1724, 1609, 1515, 1467 cm^{-1}. HRMS calculated for $C_{19}H_{30}O_3$ 329.2093, found 329.2095. Anal. Calcd for $C_{19}H_{30}O_3$: C, 74.47; H, 9.87, Found : C, 74.14; H, 10.21.



Synthesis of Diazo Ester (1). To lithium bis(trimethylsilyl) amide (19.9 mmol) in 60 mL of THF at -78 °C was added ester **14** (1.46 g, 4.76 mmol) in 10 mL of THF over 5 min. After 40 min, the reaction mixture was warmed to -40 °C, and 2,2,2-trifluroethyltrifluoroacetate (0.89 mL, 6.6 mmol) was added. After 12 h at RT, the mixture was partitioned between saturated NH_4Cl and MTBE. The combined organic extract was dried ($NaSO_4$) and concentrated. The residue was dissolved in 15 mL of

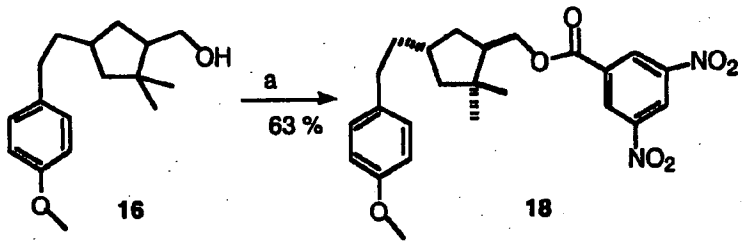
CH_2Cl_2 at 0 °C and DBU (1.4 mL, 9.2 mmol) was added in the dark. After 10 min, *p*-nitrobenzenesulfonyl azide (3.13 g, 13.7 mmol) was added. After 12 h at RT, the mixture was partitioned between MTBE and 1N aqueous NaOH. The combined organic extract was dried ($NaSO_4$) and concentrated. The residue was chromatographed to give 744 mg (47 % yield) of diazoester **1** as a bright yellow oil, TLC R_f = 0.14 (4% MTBE/ PE). ^{1}H NMR δ 7.09 (2 H, d, J = 8.5 Hz); 6.83 (2 H, d, J = 8.5 Hz); 4.23 (2 H, q, J = 7.1 Hz); 3.79 (3 H, s); 2.55 (2 H, m); 2.31 (2 H m); 1.59 (4 H, m); 1.28 (3 H, t, J = 7.1 Hz); 1.22 (2 H, m); 0.89 (3 H, d, J = 6.6 Hz); 0.86 (3 H, d, J = 6.6 Hz). ^{13}C NMR δ d 14.6, 22.9, 25.4, 34.7, 55.3, 113.8, 129.3, u 27.8, 31.8, 35.7, 43.1, 60.4, 60.9,134.6, 157.8, 174.3. IR : 2947, 2076, 1685, 1604, 1500 cm^{-1}. HRMS calculated for $C_{19}H_{28}O_3N_2$ 355.1989, found 355.1998

Representative Procedure for the Rh(II)-mediated insertion reactions. To Rh_2Oct_4 (1.3 mg, μmol) in 1 mL of CH_2Cl_2 was added dropwise the diazo ester **1** (86 mg, 0.26 mmol) in 2.1 mL of CH_2Cl_2 over 20 min at room temperature. The reaction mixture was stirred for 12 h (TLC and IR control) and then the solvent was removed. The residue was chromatographed to give 68 mg (87% yield) of the mixture of alkene (**2**) and the insertion product (CH+CH_2). HPLC analysis and ^{1}H NMR analysis of this mixture gave the desired I/A ratios. For **2** : TLC, R_f = 0.4 (5% MTBE/PE). ^{1}H NMR δ 7.08 (2 H, d, J = 8.5 Hz); 6.81 (2 H, d, J = 8.5 Hz); 5.93 (1 H, t, J = 11.6 Hz); 5.82 (1 H, d, J = 11.6 Hz); 4.16 (2 H, q, J = 7.2 Hz); 3.79 (3 H, s); 3.63 (1 H, m); 1.49 (2 H, m); 1.28 (3 H, t, J = 7.2 Hz); 0.88 (6 H, dd, J = 2.6, 6.5 Hz); 1.23 (2 H, m). ^{13}C NMR δ d 14.5, 22.3, 23.6, 26.1, 36.3, 55.4, 113.8, 120.1, 129.3, 154.8, u 32.9, 37.9, 44.9, 60.0, 134.9, 157.8, 166.7. IR : 2952,1718, 1642, 1507, 1460 cm^{-1}. HRMS calculated for $C_{19}H_{28}O_3$ 260.1776, found

260.1766.

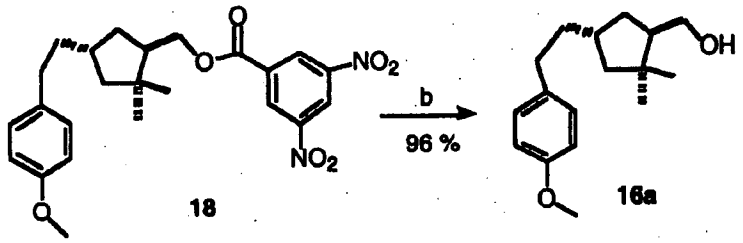
Representative Procedure for the $LiAlH_4$ reduction of the esters. To the mixture of esters **2-4** (28 mg, 0.091 mmol) in 290 μL THF at 0 °C was added in one portion 7.8 mg (0.21 mmol) of $LiAlH_4$. The reaction mixture was stirred from 0 °C to room temperature over 40 min (TLC control) and then diluted with 400 μL of 1 N aqueous HCl. The reaction mixture was extracted with MTBE and the organic layer was washed with brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give 24 mg (99% yield) of the alcohol mixture **15-17** as clear oil. For **15** : TLC R_f = 0.18 (20% MTBE/PE). ^{1}H NMR: δ 7.07 (2 H, d, J = 8.5 Hz); 6.83 (2 H, d, J = 8.5 Hz); 5.66 (1 H, dt, J = 6.8, 10.7 Hz); 5.25 (1 H, t, J = 10.7 Hz); 4.14 (1 H, t, J = 6.8 Hz); 2.58 (1 H, m); 2.42 (2 H, m); 1.85 (3 H, m); 1.69 (1 H, m); 1.53 (1 H, m); 1.43 (1 H, m); 0.86 (3 H, d, J = 6.5 Hz); 0.83 (3 H, d, J = 6.5 Hz). ^{13}C NMR δ d 22.2, 23.7, 25.7, 35.3, 55.4, 113.9, 128.7, 129.4, 137.8, u 32.8, 37.9, 45.3, 59.3, 134.7, 157.8. IR 2947, 2846, 1603, 1509, 1462 cm^{-1}. LRMS 262 (M^+), 134, 121 (100 %). HRMS calculated for $C_{17}H_{26}O_2Na$ (M + Na) 285.1841, found 285.1831.

Representative Procedure for MnO_2 oxidation of the alcohol mixture. To the alcohol mixture **15-17**(23.7 mg, 0.087 mmol) in 290 μL of CH_2Cl_2 at room temperature was added activated MnO_2 (26 mg, 0.26 mmol) in one portion. The reaction mixture was stirred at room temperature for 2 h (TLC control) and then the solvent was removed. The residue was chromatographed to give 19.0 mg (83% yield) of the alcohol mixture **16-17**, TLC R_f = 0.18 (20% MTBE/ PE). This alcohol mixture was subjected to ^{1}H NMR and HPLC analysis to give the CH/CH_2 ratios.

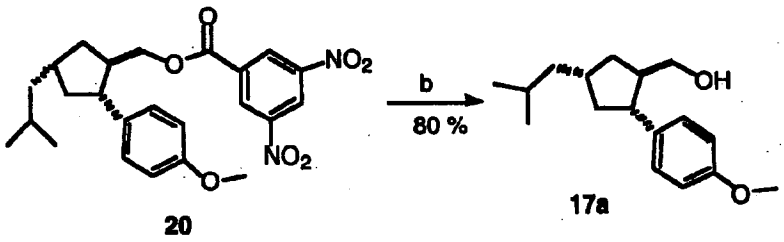


Synthesis of 18 and 20. To the mixture of alcohols **16-17** (700 mg, 2.67 mmol) in 10 mL of pyridine was added 3, 5-dinitrobenzoylchloride (1.23 g, 5.34 mmol). The reaction mixture was stirred at room temperature for 12 h and then partitioned between MTBE and, sequentially, 3 N aqueous HCl, and brine. The combined organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give 764 mg (63% yield) of the 3,5-dinitrobenzoate esters, including 156 mg of **18**, 184 mg of **20** and 424 mg of a mixtures of **18** and **20** with other 3,5-dinitrobenzoate esters. For **18** : TLC R_f = 0.78 (7% EtOAc/ PE). ^{1}H NMR δ : 9.23 (1H, t, J = 2.0 Hz); 9.16 (2H, t, J = 2.0 Hz); 7.09 (2H, d, J = 8.4 Hz); 6.82 (2H, d, J = 8.4 Hz); 3.79 (3H, s); 2.55 (2H, t, J = 7.8 Hz); 2.09 (2H, m); 1.75 (2H, m); 1.65 (3H, m); 1.24 (1H, t, J = 11.4 Hz); 1.16 (3H, s); 0.93 (3 H, s). ^{13}C NMR δ d 129.6, 129.4, 122.5, 113.9, 55.4, 47.1, 35.1, 28.9, 22.2, u 162.8, 157.8, 148.9, 134.8, 68.9, 50.2, 41.4, 39.8, 35.1, 34.0. IR 3099, 2929, 1726, 1544, 1346 cm^{-1}. HRMS calcd for $C_{24}H_{28}N_2O_7$ 456.1897 found 456.1893. For **20**: TLC R_f = 0.65 (7% EtOAc/ PE). ^{1}H NMR δ : 9.16 (1H, d, J = 2.6 Hz); 8.79 (2H, d, J = 2.6 Hz); 7.11 (2H, d, J = 8.6 Hz); 6.67 (2H, d, J = 8.6 Hz); 4.47 (1H, m); 4.38 (1H, dd, J = 8.4, 10.8 Hz); 3.66 (3H, s); 2.73 (1H, m); 2.64 (1H, m); 2.19 (2H, m); 1.69 (2H, m); 1.33 (4H, m); 0.91 (3H, s); 0.89 (3H, s). ^{13}C NMR δ d 128.9, 128.1, 122.1, 113.8, 55.1, 50.8, 44.7, 36.2, 26.9,

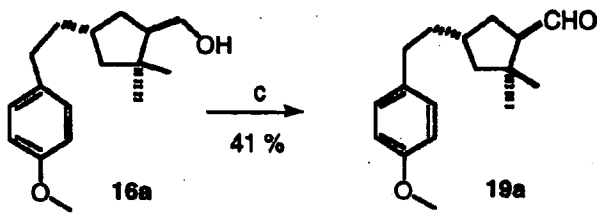
23.0, 22.9, u 162.5, 157.9, 148.4, 136.3, 133.8, 70.6, 46.1, 44.5, 35.4. IR 3099, 1726, 1679, 1509, 1462 cm^{-1}. HRMS calculated for $C_{24}H_{28}N_2O_7$ 456.1897, found 456.1896.



Synthesis of Alcohol (16a). To 87 mg of **18** (0.19 mmol) in 700 μL of methanol was added K_2CO_3 (140 mg, 1.01 mmol) at room temperature. The reaction mixture was stirred for 1 h (TLC control) after which the solids were filtered off. The residue was chromatographed to give 48 mg (96% yield) of the alcohol **16a** as a clear oil, TLC R_f = 0.55 (30% MTBE/ PE). ^{1}H NMR δ : 7.09 (2H, d, J = 6.6 Hz); 6.83(2H, d, J = 6.6 Hz); 3.79 (3H, s); 3.72 (1H, dt, J = 5.5, 10.4 Hz); 3.48 (1H, ddd, J = 4.8, 8.3, 10.4 Hz); 2.53 (2H, t, J = 7.9 Hz); 2.01 (1H, m); 1.79 (1H, m); 1.64 (4H, m); 1.16 (2H, m); 1.12 (3H, s); 0.81 (3H, s). ^{13}C NMR δ d 22.1, 29.1, 35.1, 50.8, 55.4, 113.8, 129.4, u 34.1, 35.2, 40.1, 41.1, 50.5, 64.8, 135.1, 157.7. IR: 3384, 2926, 1609, 1457 cm^{-1}. LRMS 262 (M^+), 244, 187, 134, 121 (100 %), 101, 91. HRMS calculated for $C_{17}H_{26}O_2$ 262.1933, found 262.1924.



Synthesis of Alcohol (17a). To 140 mg of **20** (0.31 mmol) in 1 mL of methanol was added K_2CO_3 (213 mg, 1.54 mmol) at room temperature. The reaction mixture was stirred for 40 min (TLC control) after which the solids were filtered off. The residue was chromtographed to give 65 mg (80% yield) of the alcohol **17a** as a clear oil, TLC R_f = 0.58 (30% MTBE/ PE). ^{1}H NMR δ : 7.17(2H, d, J = 8.7 Hz); 6.85 (2H, d, J = 8.7 Hz); 3.79 (3H, s); 3.61 (1H, m); 3.49 (1H, ddd, J = 6.5, 10.7, 13.4 Hz); 2.66 (1H, dq, J = 6.5, 9.5 Hz); 2.16 (3H, m); 1.75 (1H, m); 1.57 (2H, m); 1.29 (3H, t, J = 7.2 Hz); 0.9 (3H, s); 0.89 (3H, s). ^{13}C NMR δ d 128.5, 114.1, 55.5, 49.1, 48.9, 36.5, 27.0, 23.2, 23.0, u 158.1, 137.1, 66.6, 46.2, 44.0, 35.8. IR: 3357, 2866, 1604, 1461 cm^{-1}. LRMS 262 (M^+), 244, 203, 187 (100%), 173, 159, 148, 134, 121, 108. HRMS calculated for $C_{17}H_{26}O_2$ 262.1933, found 262.1933.



Synthesis of Aldehyde (19a). To alcohol **16a** (2.1 mg, 0.008 mmol) in 200 μL of CH_2Cl_2 was added Dess-Martin periodinane[8] (5.1 mg, 0.012 mmol) at room temperature. The reaction mixture was stirred for 1 h and then diluted with CH_2Cl_2. The mixture was partitioned between CH_2Cl_2 and, sequentially, aqueous saturated $NaHCO_3$, water and brine. The combined organic extract was dried (Na_2SO_4) and concentrated to give an oil. The residue was chromatographed to give 2.0 mg (96% yield) of **19a**. TLC R_f = 0.78 (20% MTBE/ PE). ^{1}H NMR δ : 9.72 (1H, s); 7.1 (2H, d, J = 8.5 Hz); 6.84 (2H, d, J = 8.4

Hz); 3.79 (3H, s); 2.54 (2H, t, J = 8.4 Hz); 2.46 (1H, ddd, J = 2.7, 8.4, 11.8 Hz); 2.35 (1H, dd, J = 8.4, 13.6 Hz); 2.14 (1H, m); 1.73 (1H, dd, J = 7.1, 11.8 Hz); 1.62 (3H, m); 1.47 (1H, ddd, J = 6.3, 9.2, 13.6 Hz); 12.5 (3H, s); 0.95 (3H, s). ^{13}C NMR δ d 205.4, 129.4, 113.9, 60.7, 55.5, 36.1, 29.3, 23.3, u 157.8, 134.7, 50.5, 44.0, 39.6, 34.1, 30.8. IR: 2924, 1715, 1576, 1446, 1363 cm^{-1}. HRMS calculated for $C_{17}H_{24}O_2$ 260.1776, found 260.1773.

Epimerization of Aldehyde 19a. To aldehyde **19a** (2.2 mg, 0.008 mmol) in 50 μL of THF at 0 °C was added KO^{t}Bu (1.9mg, 0.017 mmol) in one portion. The reaction mixture was stirred at 0 °C for 1h and room temperature for 1 h. The reaction mixture was then partitioned between MTBE and 0.5 N aqueous HCl. The organic layer was washed sequentially, with brine, dried (Na_2SO_4) and concentrated. The residue was chromatographed to give 2.0 mg of a mixture of **19a and 19b.** TLC R_f = 0.39 for **19a** and 0.29 for **19b** (10% MTBE/ PE).

To 2.0 mg of the mixture of **19a** and **19b** in 30 μL of THF at 0 °C was added $LiAlH_4$ (1.2 mg, 0.017 mmol). The mixture was stirred from 0 °C to 5 °C over 40 minutes. Then, the reaction mixture was partitioned between MTBE and, sequentially, 0.5 N aqueous HCl and brine. The organic extract was dried (Na_2SO_4) and concentrated. The residue was chromatographed to give 1.7 mg (77% yield for 2 steps) of a mixture of **16a** and **16b**, TLC R_f = 0.31 (30% MTBE/ PE).

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1. a) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923. b) Taber, D. F. *J. Org. Chem.* **1982**, *47*, 1351.

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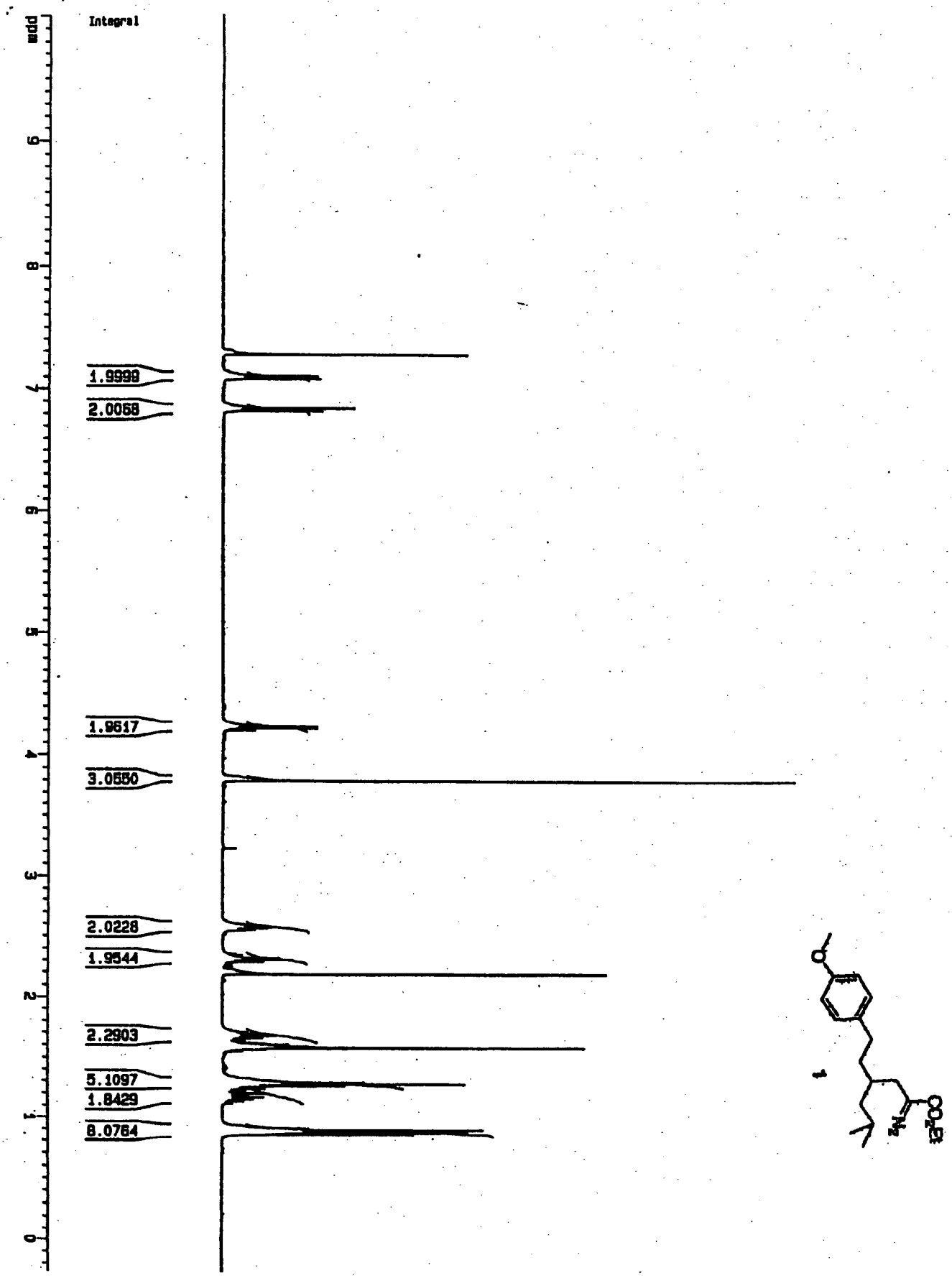

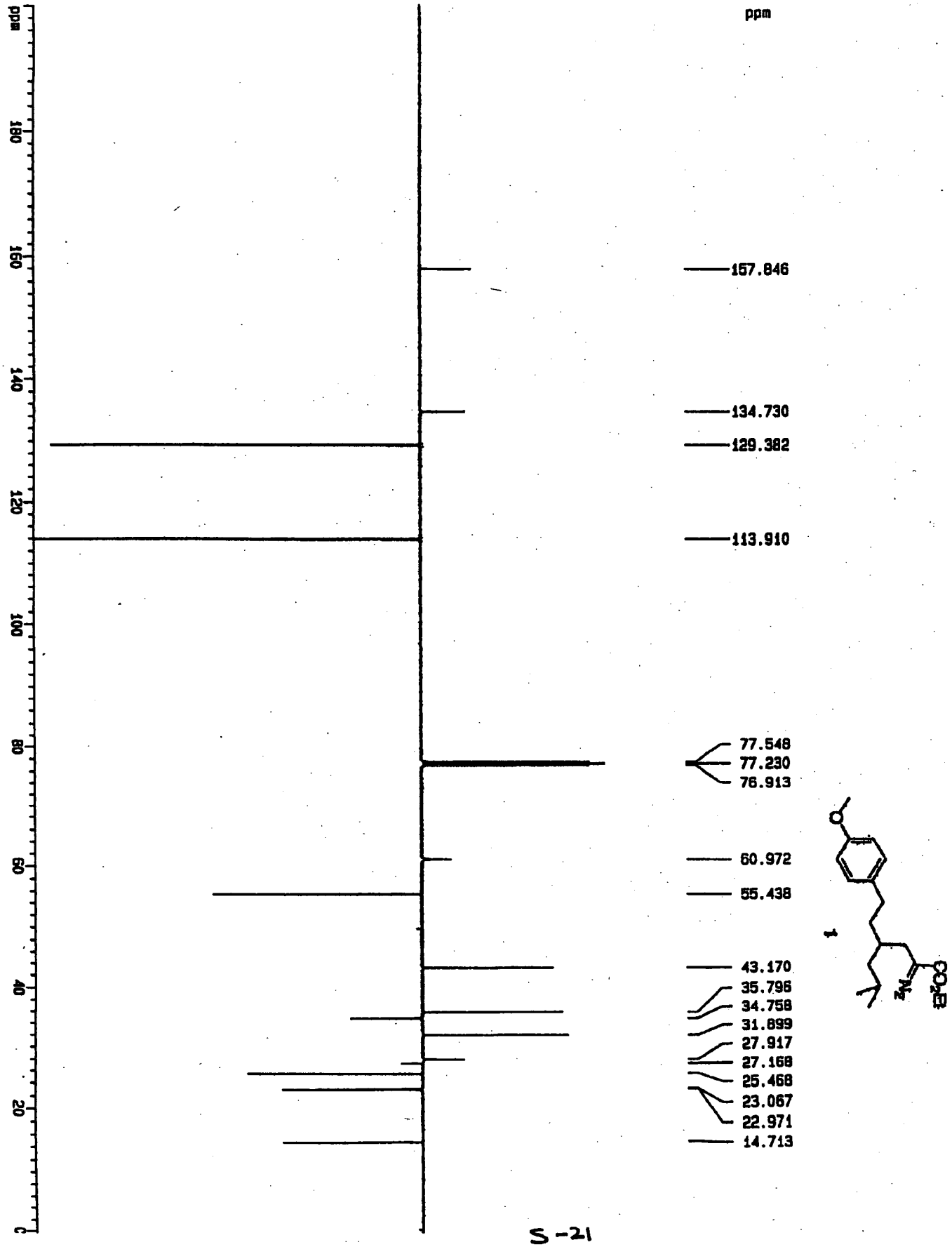

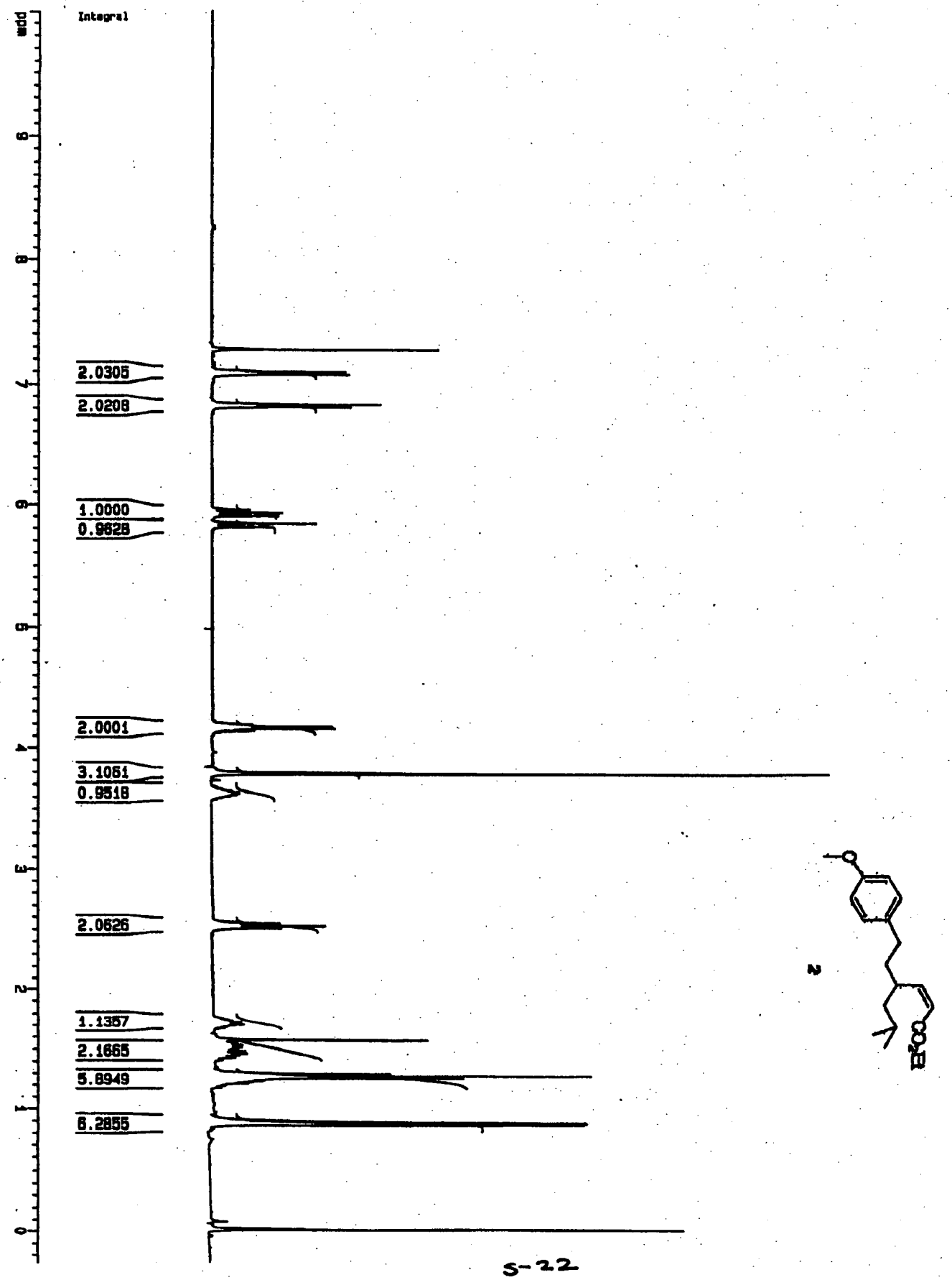

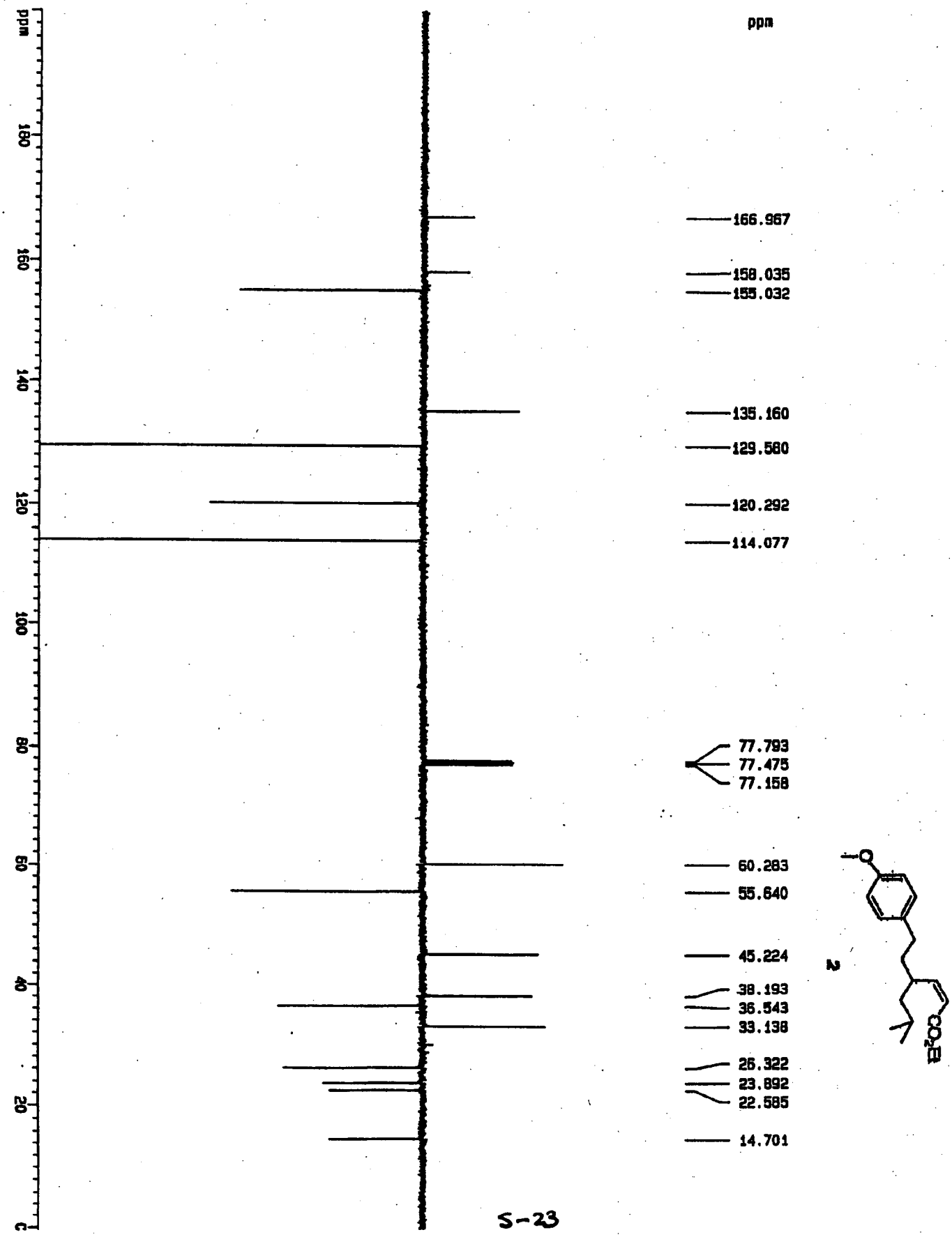

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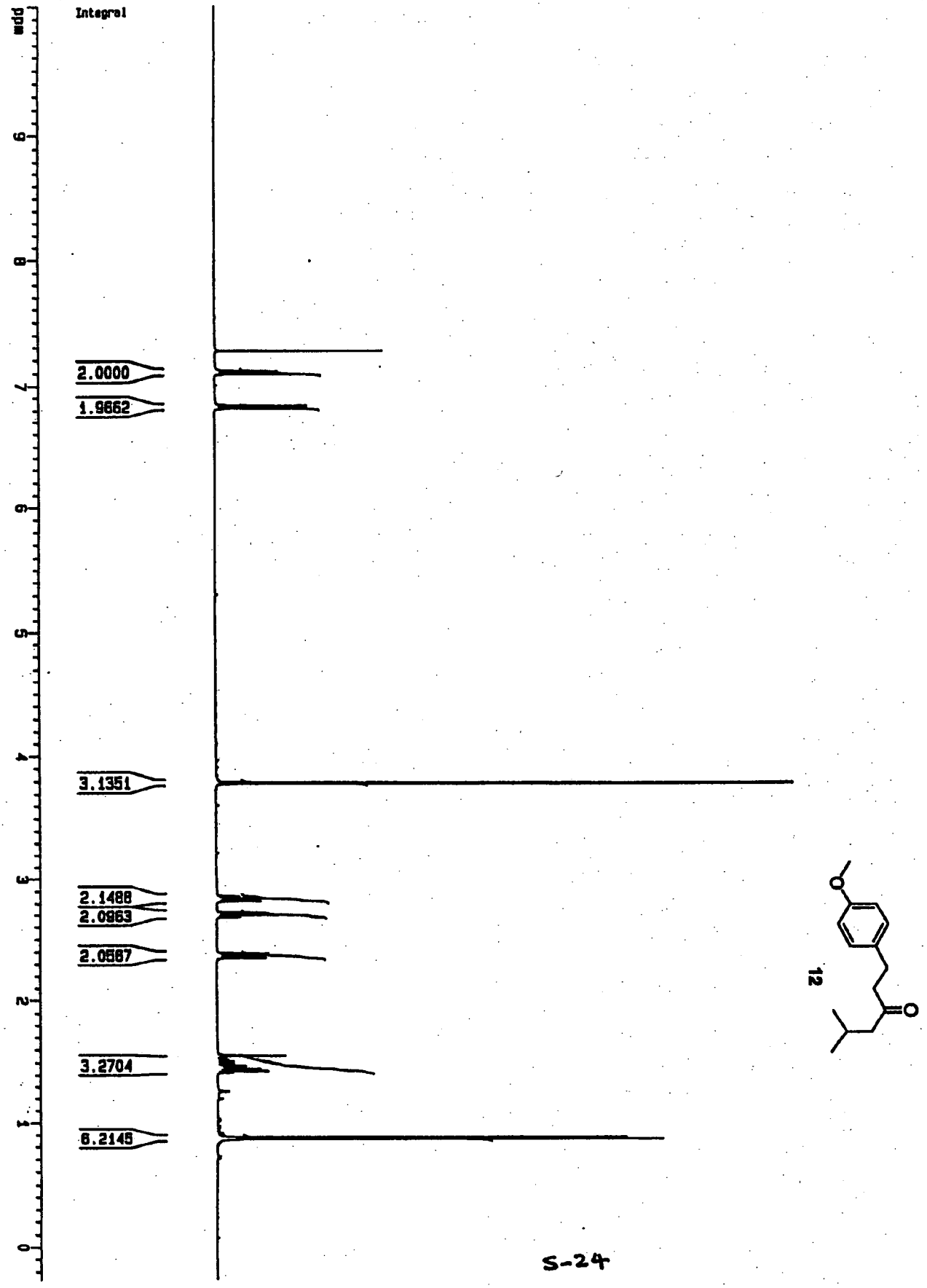
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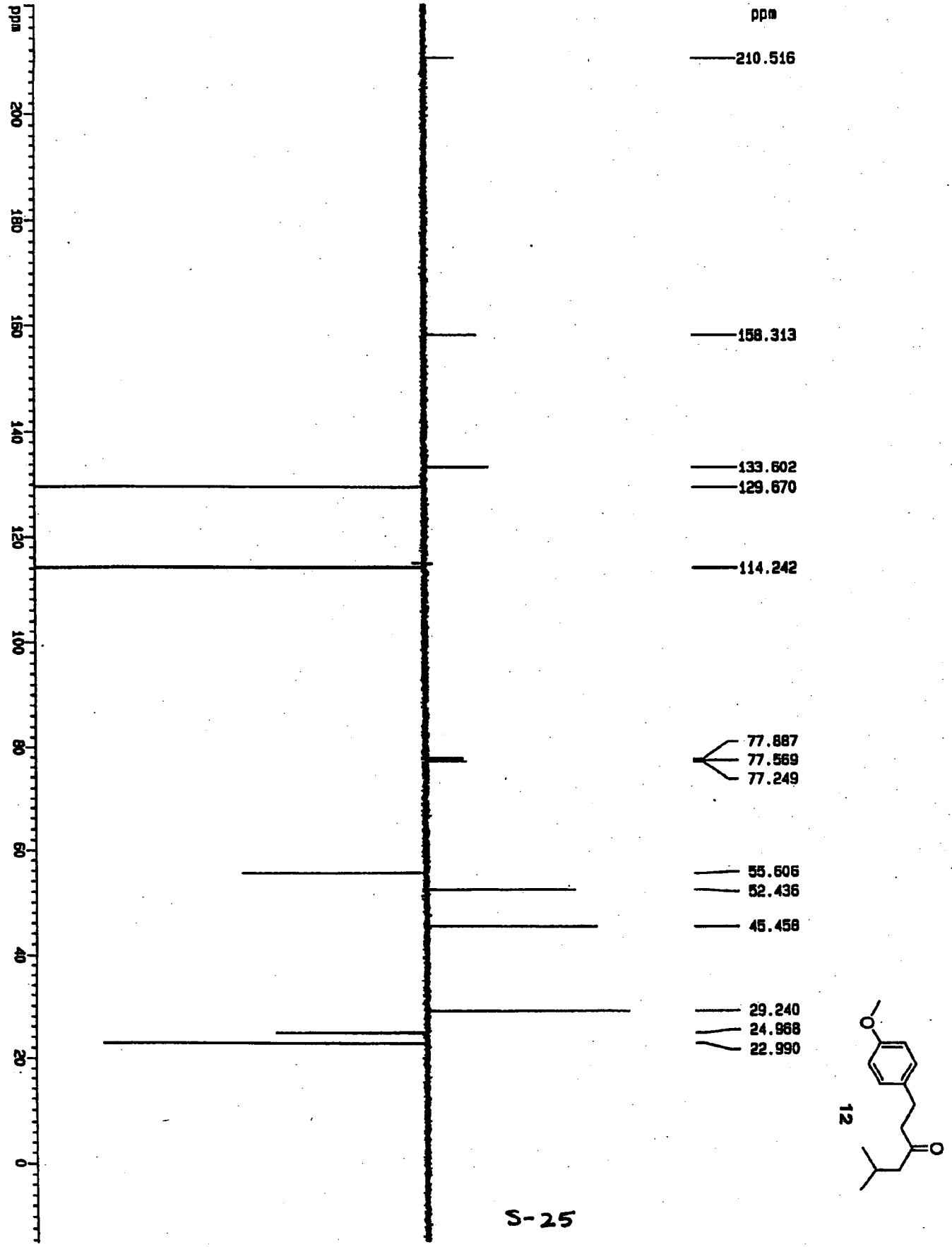

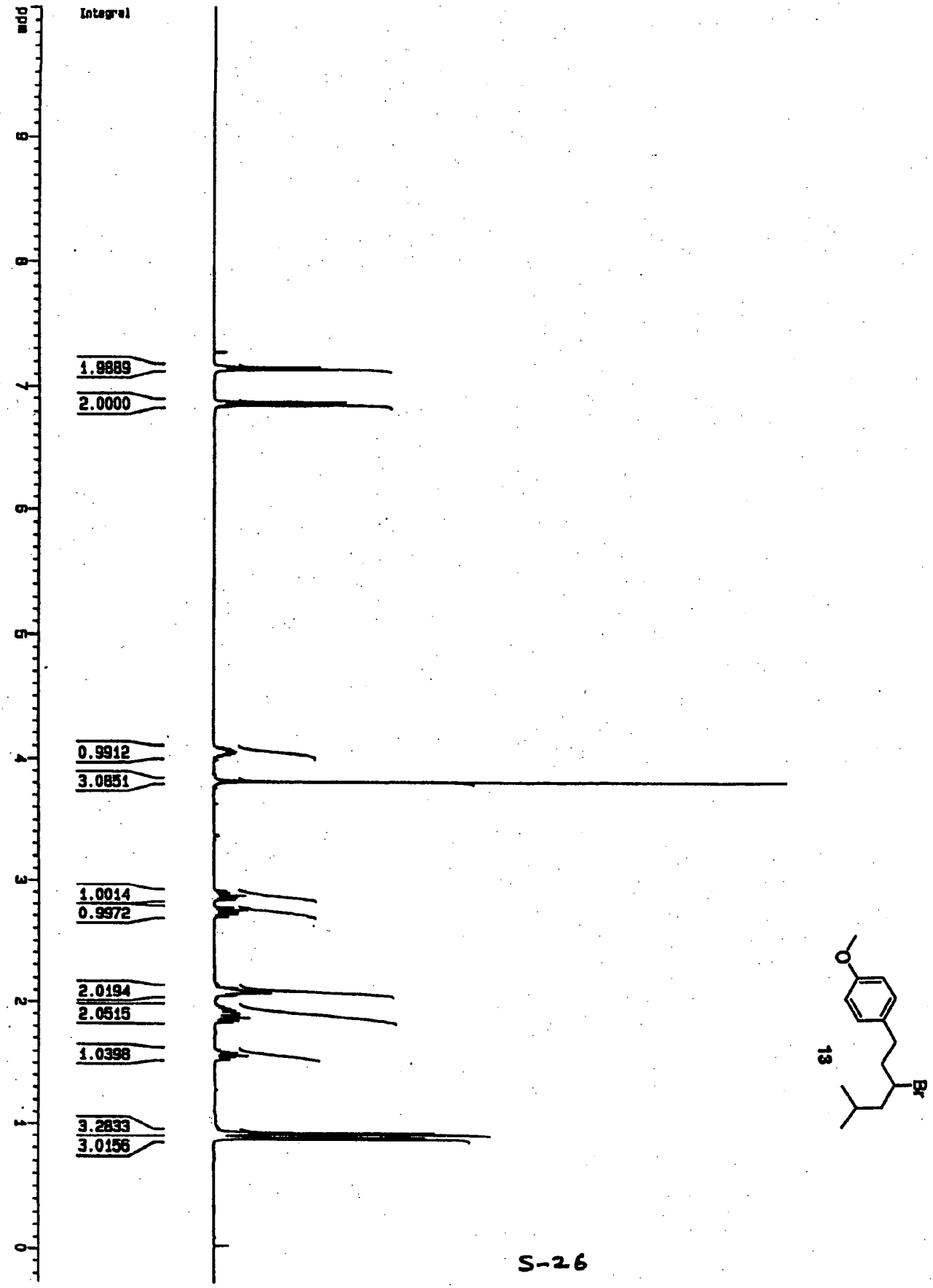
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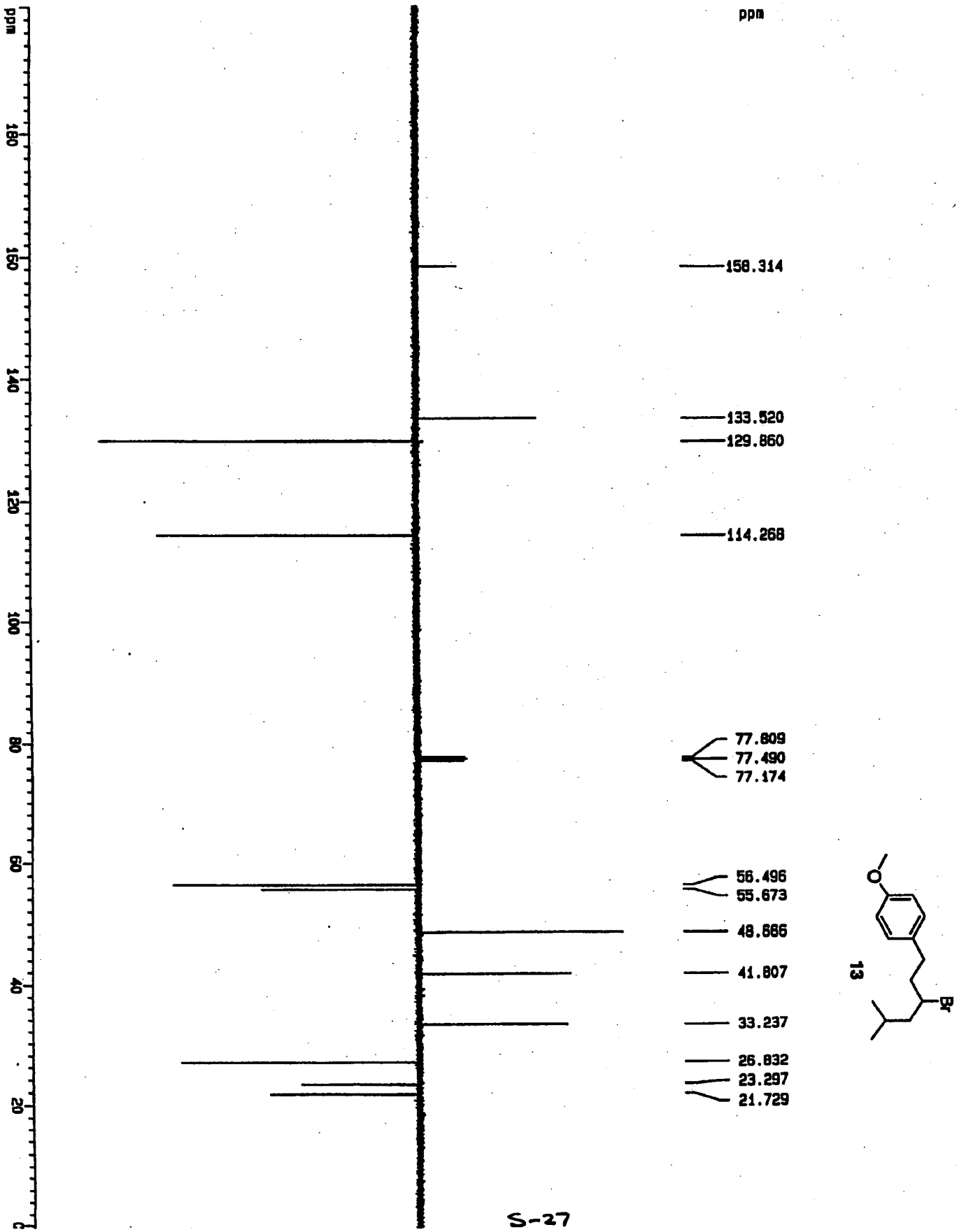
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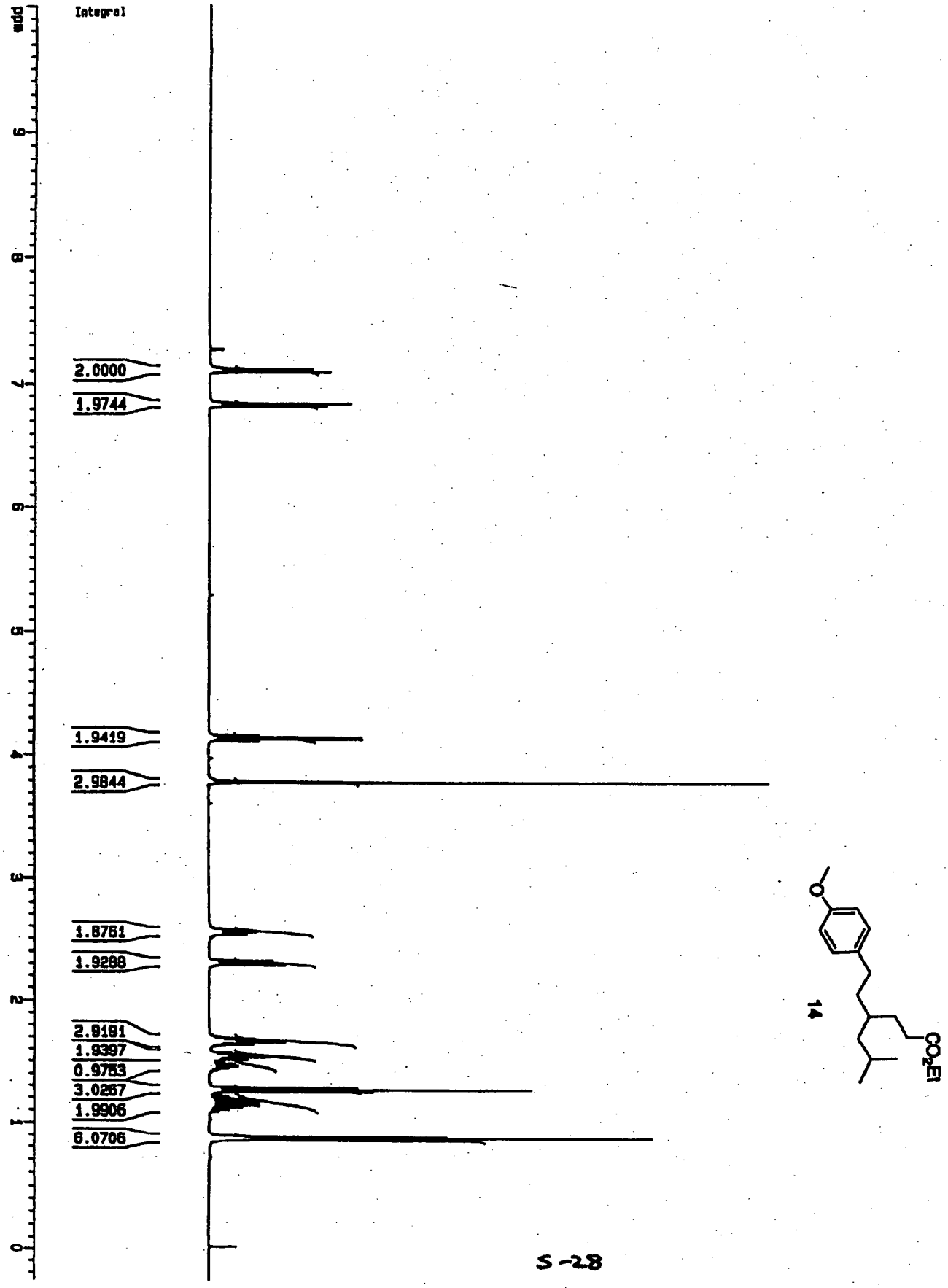
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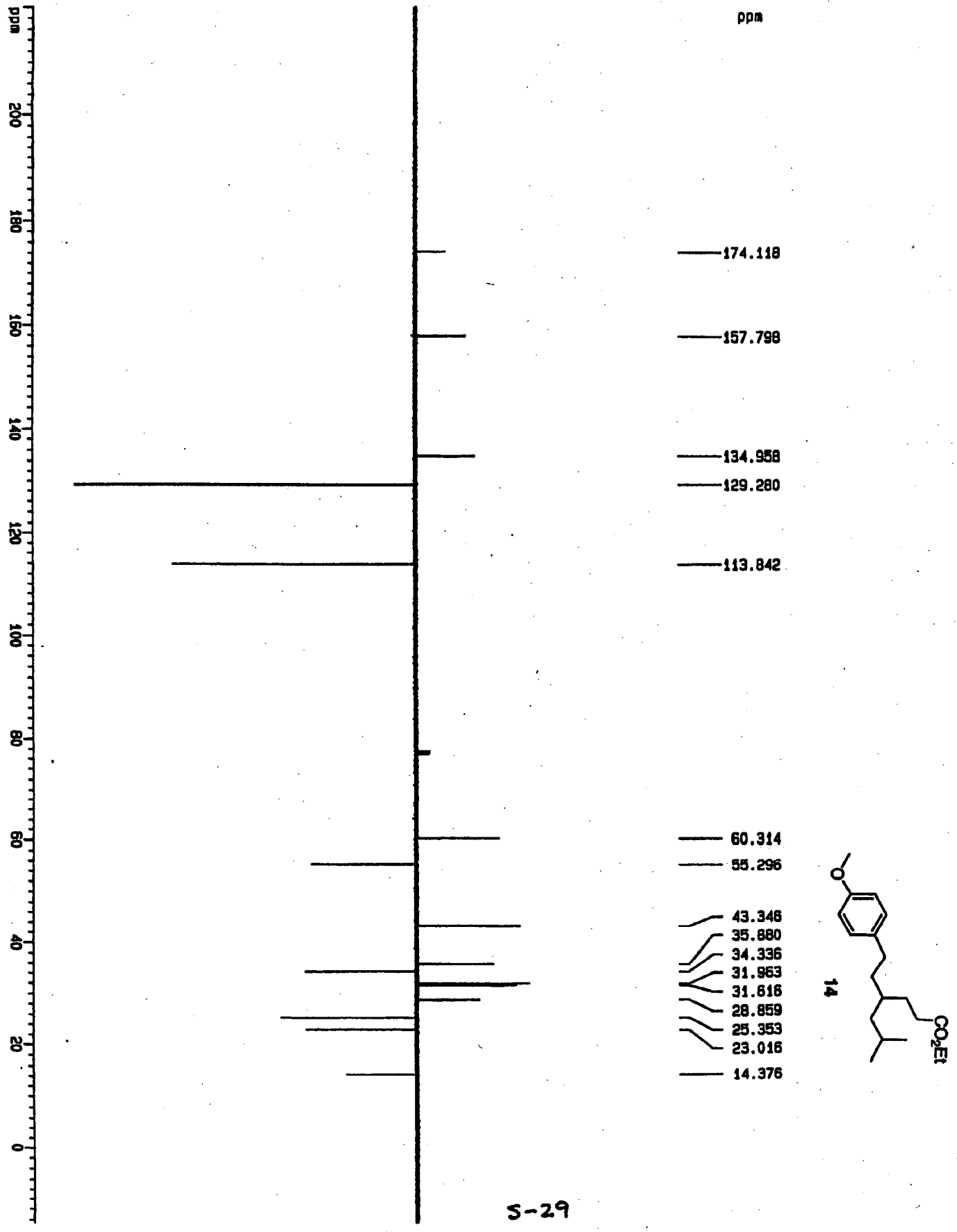

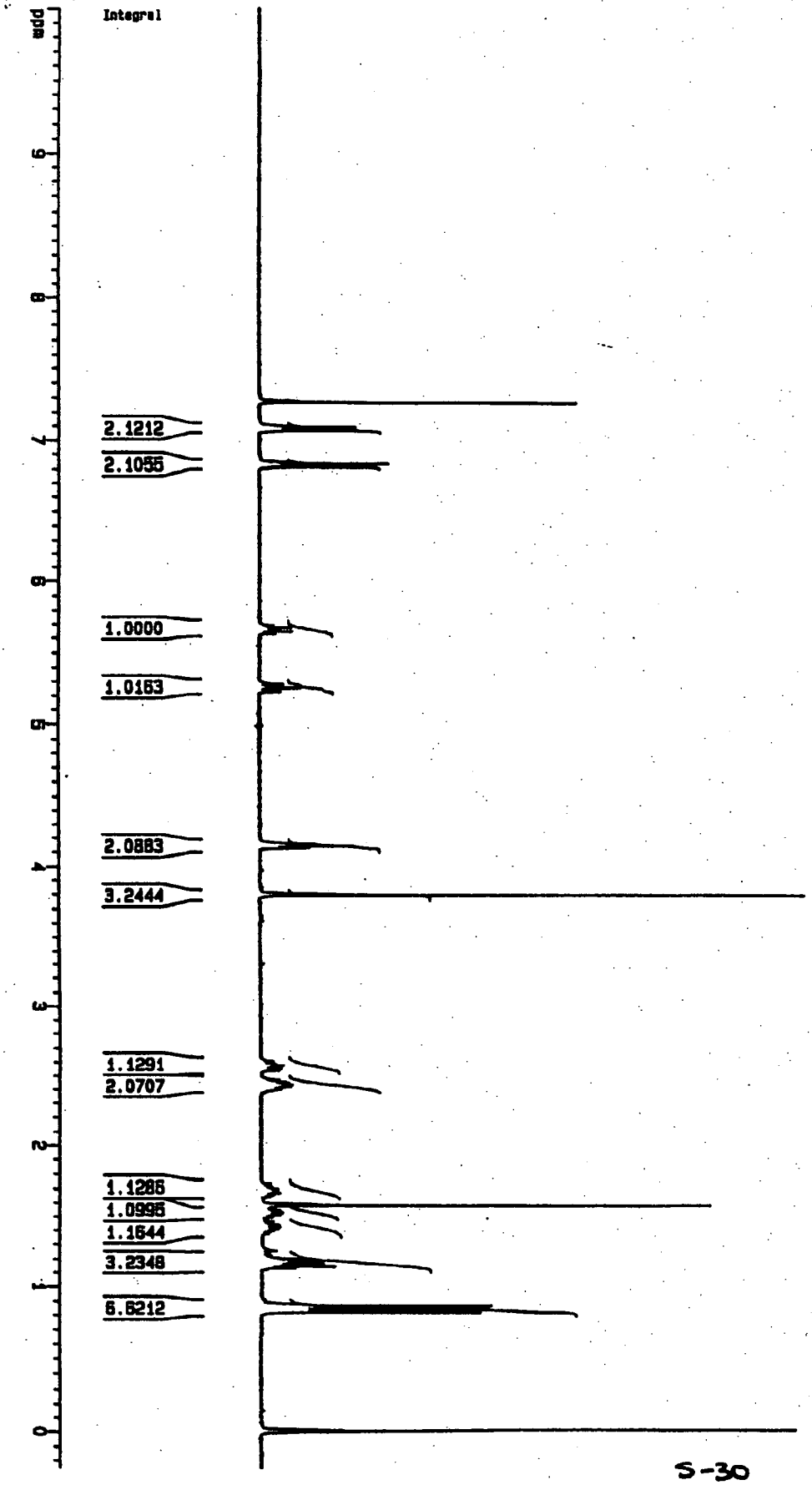
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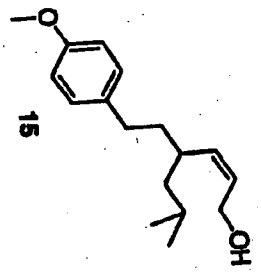
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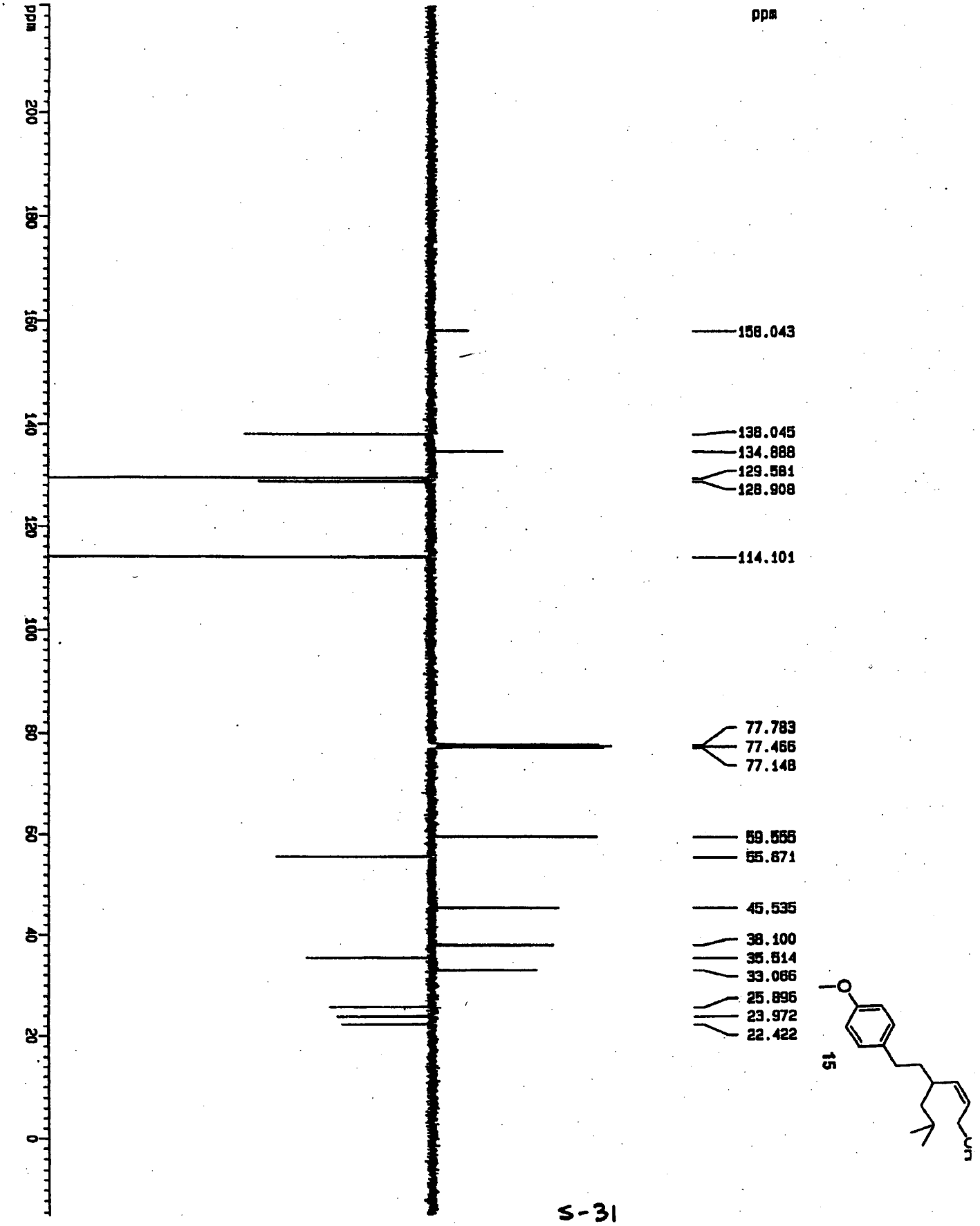
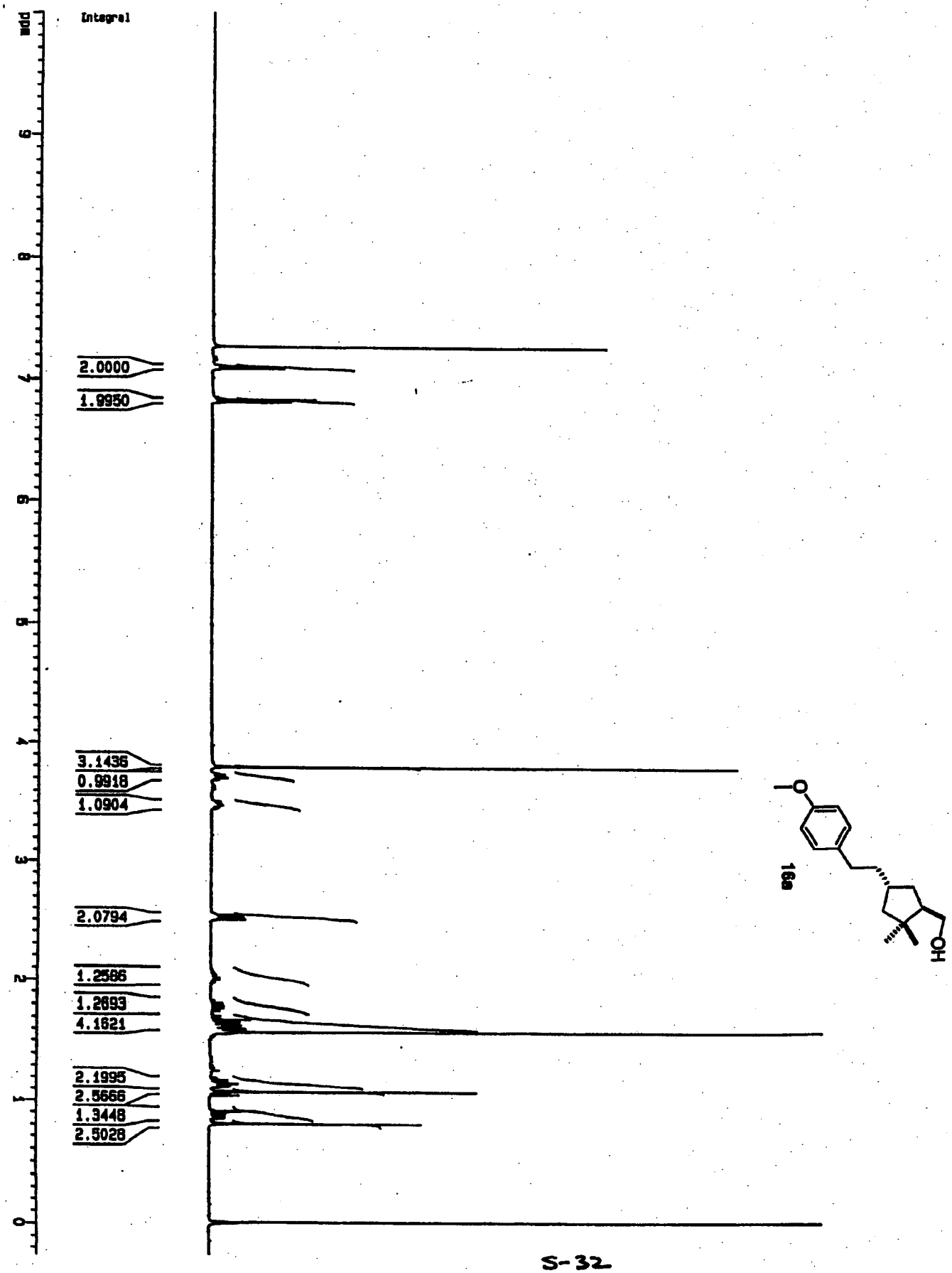
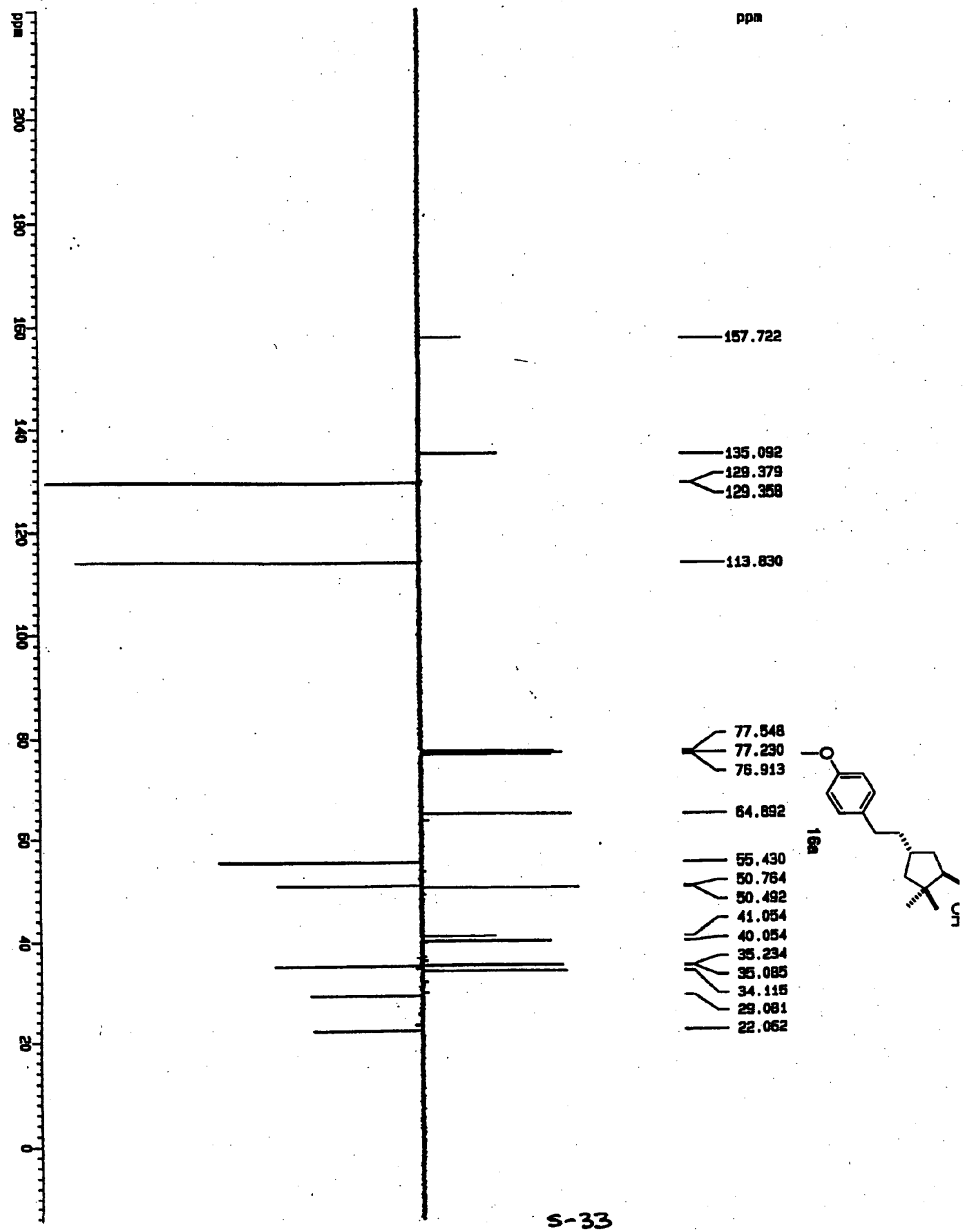
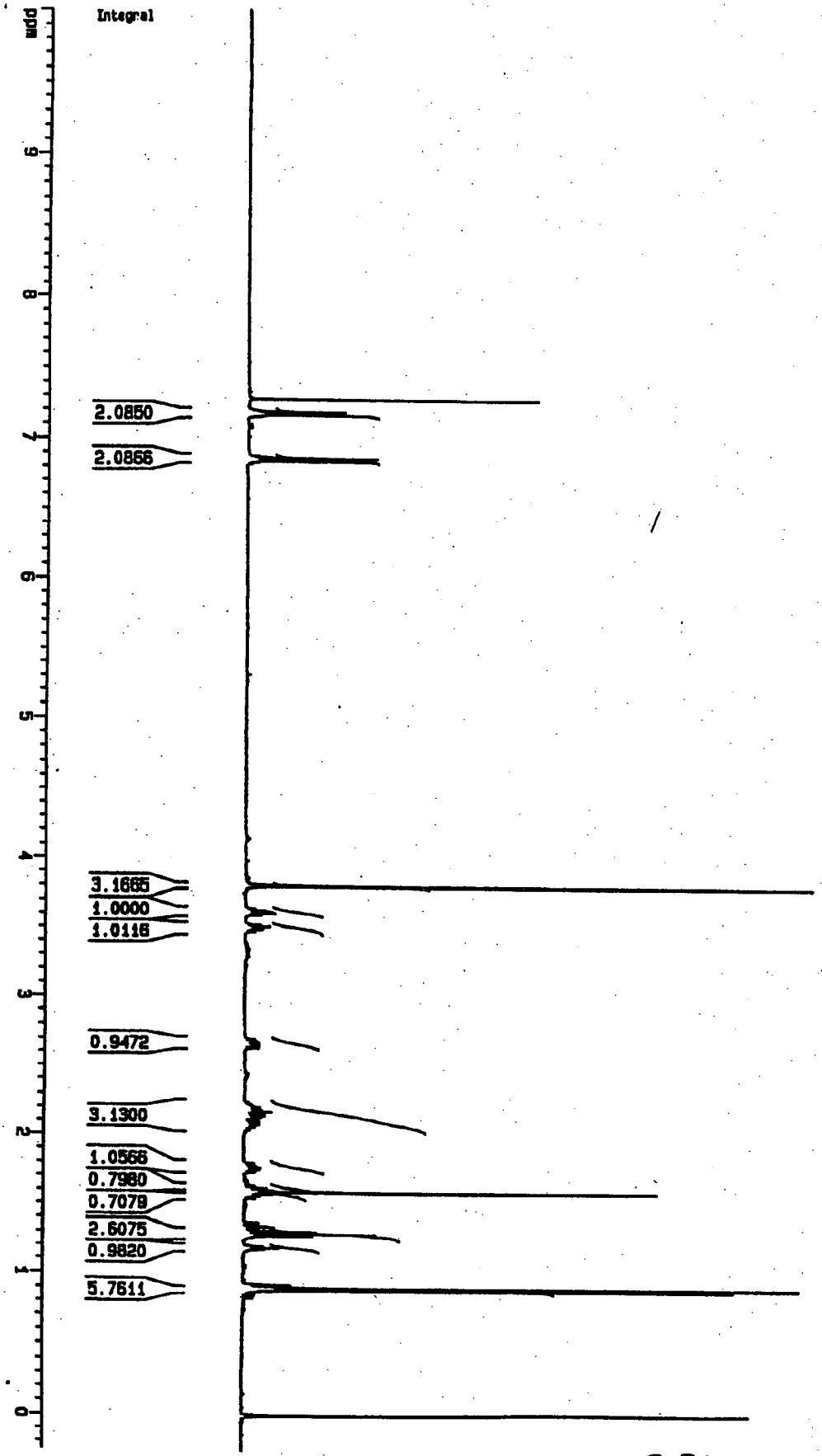
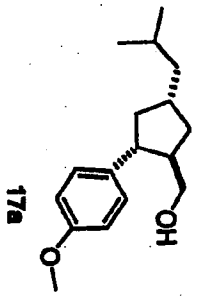
S-30

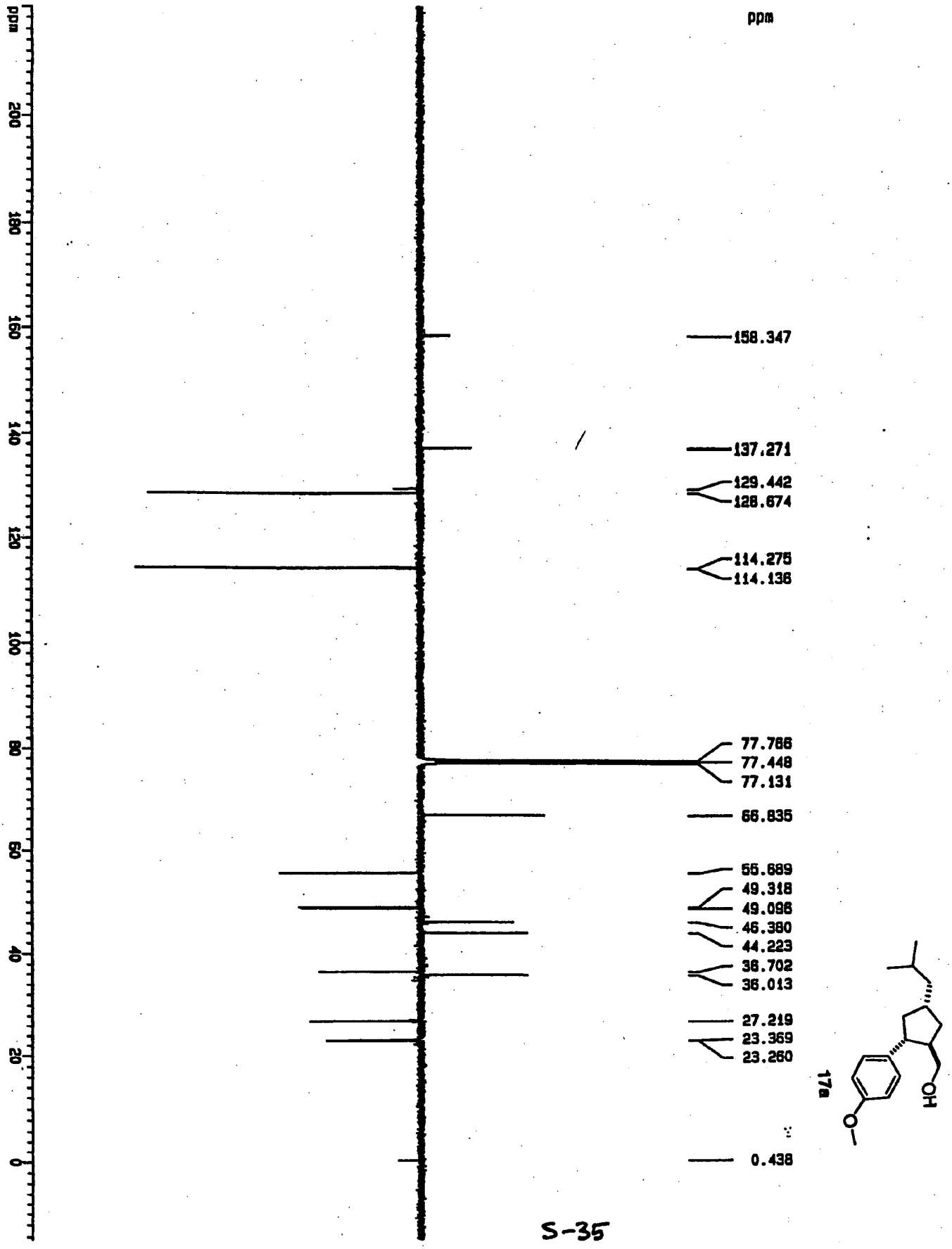


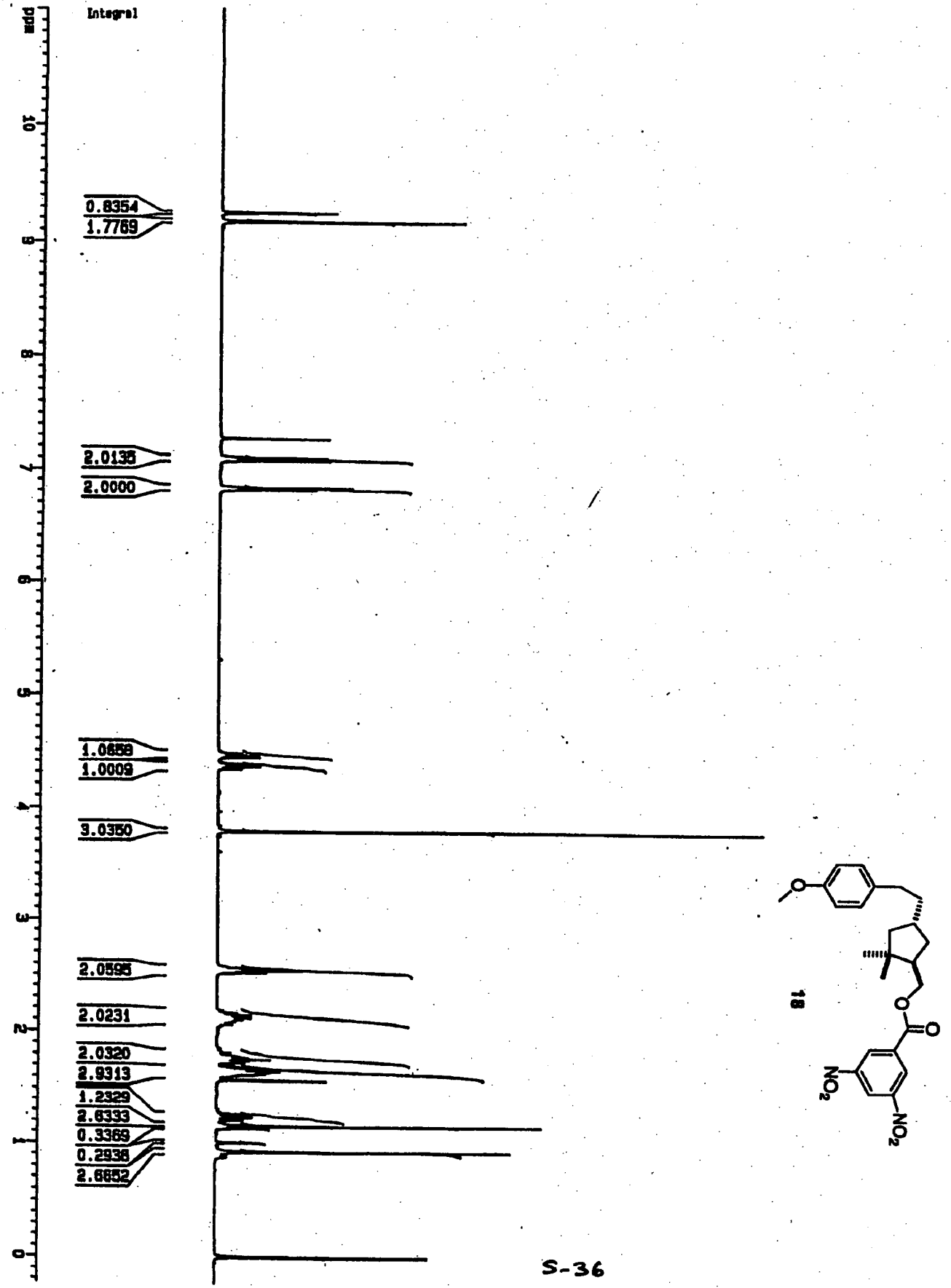








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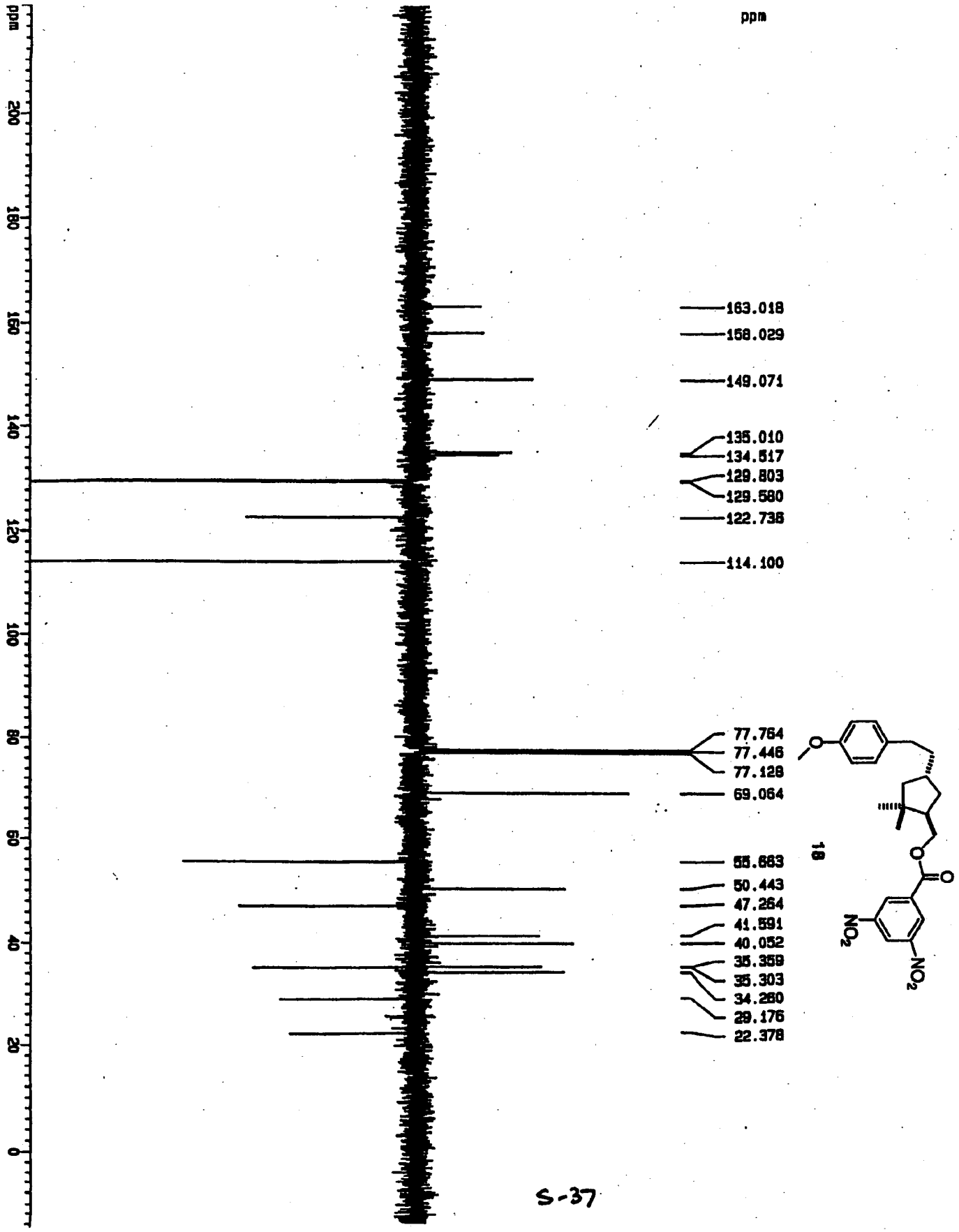

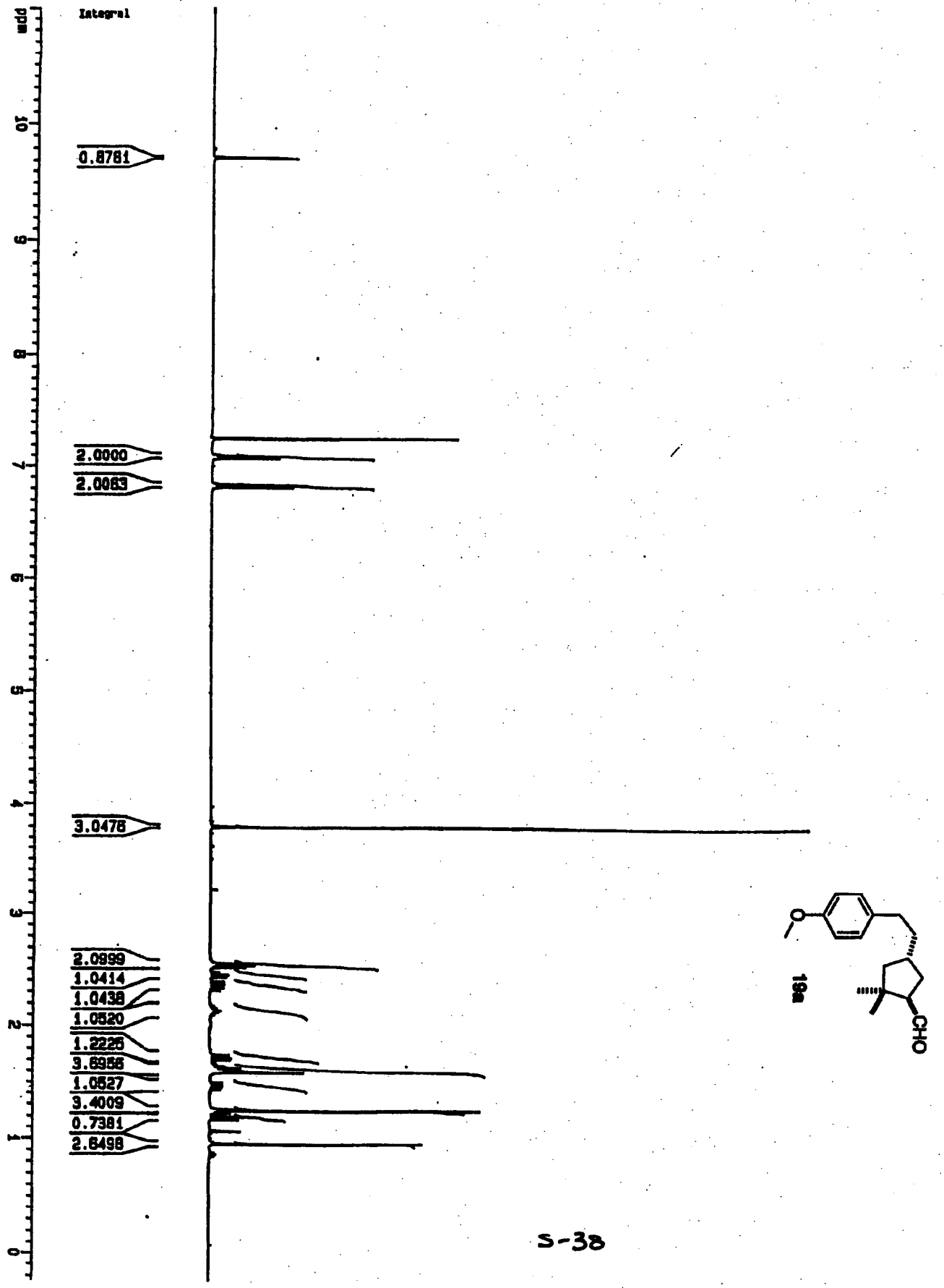
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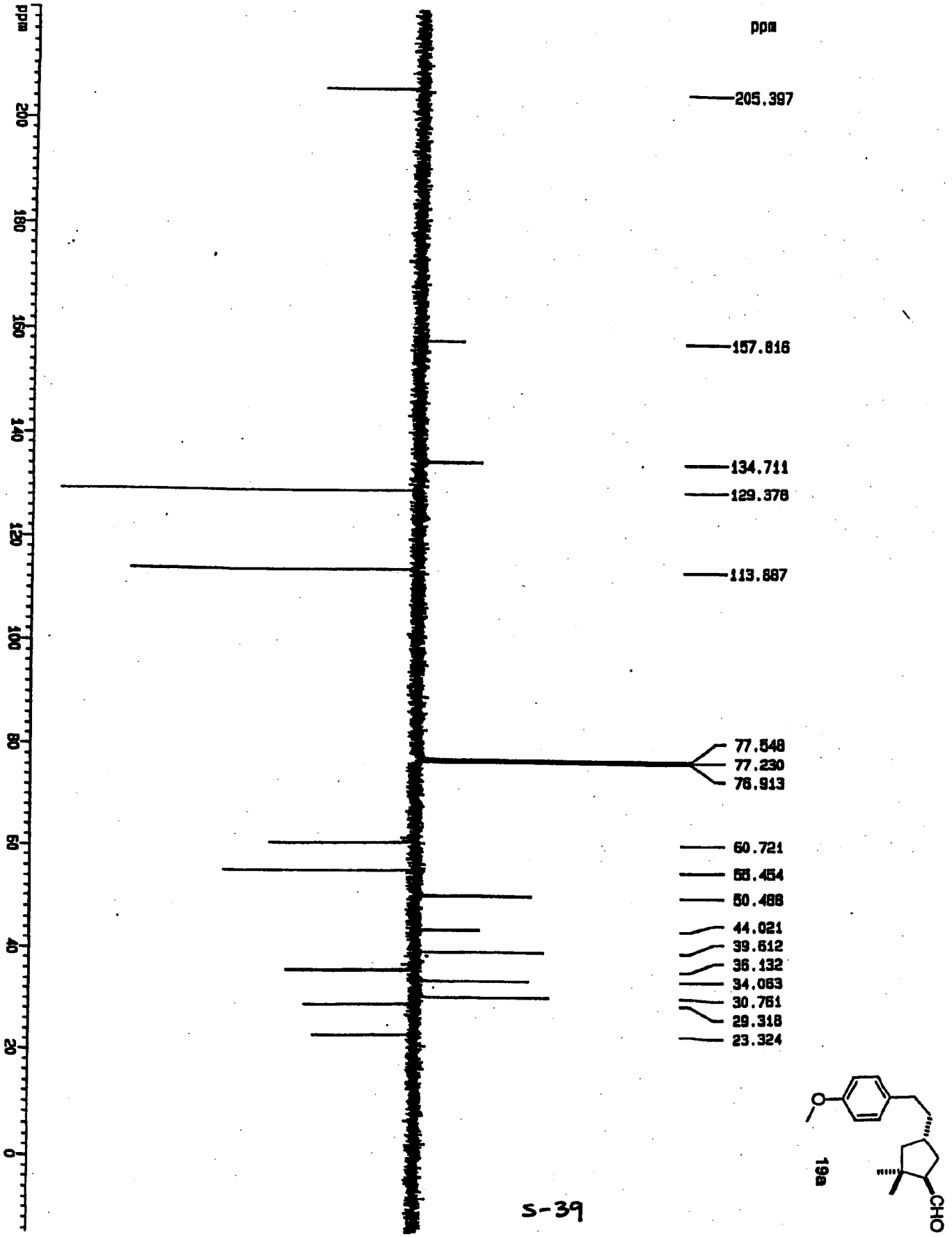
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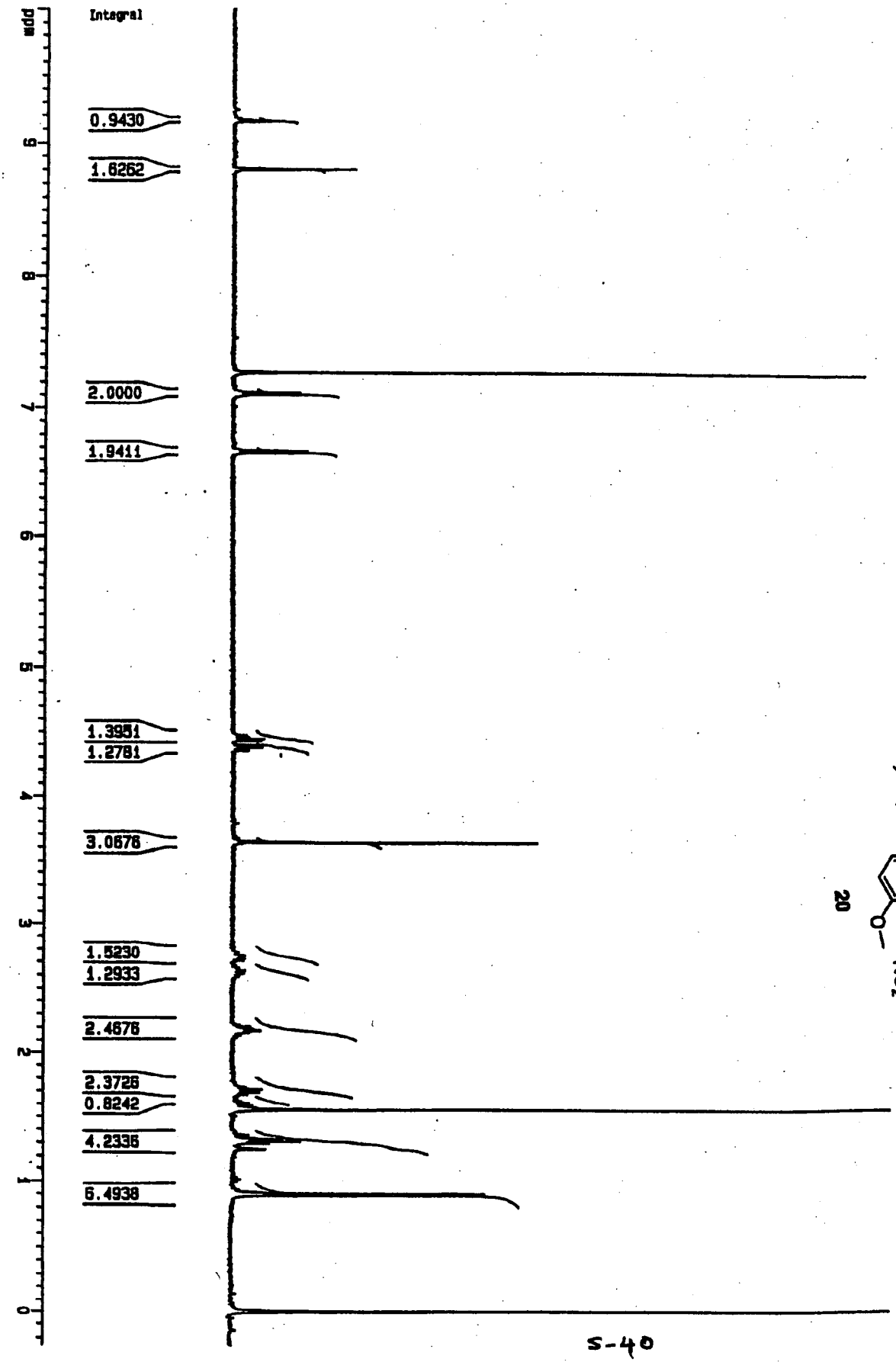

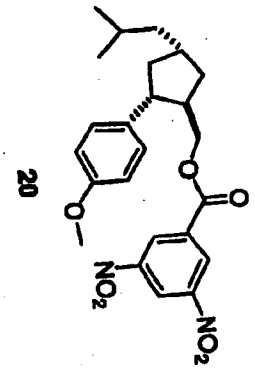

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