A Catalytic, Asymmetric Formal Synthesis of (+)-Hamigeran B

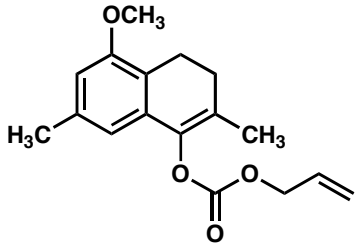
Herschel Mukherjee, Nolan T. McDougal, Scott C. Virgil, and Brian M. Stoltz

The Arnold and Mabel Beckman Laboratories of Chemical Synthesis, The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, and the Caltech Center for Catalysis and Chemical Synthesis, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125

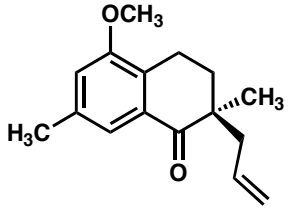
Table of Contents:

Materials and Methods. Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Solvents were dried by passage through an activated alumina column under argon. All the starting materials were purchased from commercial sources and used as received, unless otherwise stated. Liquids and solutions were transferred via syringe or positive-pressure cannula. Brine solutions refer to saturated aqueous sodium chloride solutions. Previously reported methods were used to prepare (*S*)-*t*-BuPHOX (**(*S*)-6**) and **(*S*)-7**.[1] Grubbs–Hoveyda 2nd generation catalyst **8** was a generous gift from Materia, Inc. Reaction temperatures were controlled by an IKAmag temperature modulator. Thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm) and visualized by UV fluorescence quenching, anisaldehyde, or $KMnO_4$ staining. SiliCycle® SiliaFlash® P60 Academic Silica Gel (particle size 40-63 μm; pore diameter 60 Å) was used for flash chromatography. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralpak OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries, Ltd. with 1 mL/min flow rate and visualization at 254 nm. Optical rotations were measured with a Jasco P-1010 polarimeter at 589 nm in spectrophotometric grade solvents. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 (at 300 MHz and 75 MHz respectively) and are reported relative to residual $CHCl_3$ (δ 7.26 and 77.0 ppm). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, comp = complex, br = broad, app = apparent. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). High-resolution mass spectra were obtained from the Caltech Mass Spectral Facility. Solvent screening for the asymmetric Tsuji allylation reaction was conducted using a Symyx Core Module within a nitrogen-filled glove box.

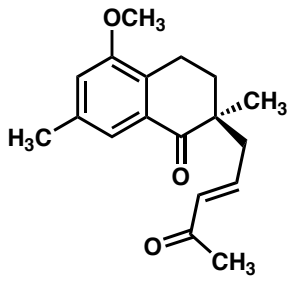
Experimental Procedures and Tabulated Spectroscopic Data.



Allyl 5-methoxy-2,7-dimethyl-3,4-dihydronaphthalen-1-yl carbonate (5): A 30% (w/w) dispersion of KH in mineral oil (300 mg, 2.2 mmol, 1.9 equiv) was charged to a round bottomed flask under N_2. Pentane (3 mL) was added, the mixture stirred for 1 min, then the solvent drawn off via syringe; this procedure was repeated three times. The oil-free KH was then suspended in THF (7 mL), and cooled to –78 °C (acetone/CO_2), then a solution of tetralone **4**[2] (250 mg, 1.20 mmol) in THF (5 mL) added dropwise. The mixture was allowed to warm to room temperature for 6 h. The resulting orange-red solution was cooled to –78 °C and neat allyl chloroformate (0.190 mL, 1.80 mmol, 1.5 equiv) was added over 5 min. The orange color immediately faded, resulting in a slightly yellow solution. The mixture was allowed to warm to room temperature over 18 h. The reaction was quenched with sat. $NH_4Cl_{(aq)}$ (5 mL), then partitioned between water (10 mL) and Et_2O (10 mL) the phases were separated, and the aqueous layer extracted with Et_2O (2 x 15 mL). The combined organic extracts were washed with brine, then dried over anhydrous $MgSO_4$. The solvents were evaporated in vacuo, yielding a pale yellow oil. Purification by silica gel chromatography (5% → 10% EtOAc in hexanes) afforded allyl enol carbonate **5** as a colorless oil (308 mg, 89% yield). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.59 (s, 2H), 5.99 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.42 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.31 (dd, *J* = 10.2, 1.5 Hz, 1H), 4.72 (d, *J* = 5.7 Hz, 2H), 3.80 (s, 3H), 2.80 (app t, *J* = 8.1 Hz. 2H), 2.36 (app t, *J* = 8.1 Hz, 2H), 2.30 (s, 3H), 1.81 (s, 3H); **^{13}C NMR** (75.4 MHz, $CDCl_3$): δ 155.7, 144.9, 140.3, 136.2, 131.3, 131.2, 124.0, 119.7, 118.5, 113.2, 110.4, 68.5, 55.0, 28.2, 21.4, 19.2, 16.2; **IR** (thin film, NaCl): 2923, 2838, 1760, 1607, 1583, 1260, 1230, 1032 cm^{-1}; **HRMS** (ESI-TOF) *m/z*: calc'd for $C_{17}H_{21}O_4$ $[M+H]^+$: 289.1440, found 289.1429.

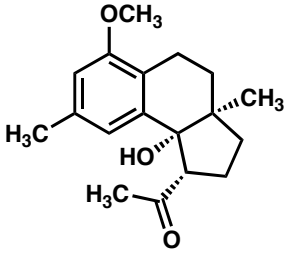


(*S*)-2-allyl-5-methoxy-2,7-dimethyl-3,4-dihydronaphthalen-1(2*H*)-one (3): A mixture of (*S*)-CF_3-^{t}Bu-Phox **7**[3] (15.5 mg, 0.026 mmol, 0.05 equiv) and $Pd_2(dba)_3$ (9.6 mg, 0.011 mmol, 0.02 equiv) in benzene (10 mL) was heated to 35 °C for 30 min, resulting in a yellow-orange solution. To this was added a solution of allyl enol carbonate **5** (151 mg, 0.524 mmol) in benzene (10 mL), and the mixture maintained at 35 °C for 1h. The reaction mixture was then evaporated in vacuo, and the red-brown residue purified by silica gel chromatography (4% EtOAc in hexanes). Tetralone **3** was obtained as a yellow oil (124 mg, 96% yield, 93% ee). Spectral data matched previously reported values.[2b] **$[\alpha]^{25}_D$** (*c* 0.85, CH_2Cl_2): –8.9°. Enantiometric excess was determined to be 94% ee via HPLC analysis using a Chiralcel OD-H column (0.1 % isopropanol in *n*-heptane, 0.7 mL min^{-1}, 254 nm); $t_{R\ major}$ = 33.2 min, $t_{R\ minor}$ = 36.9 min.

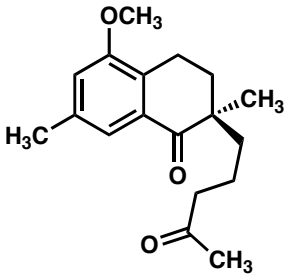


(*S*,*E*)-5-methoxy-2,7-dimethyl-2-(4-oxopent-2-enyl)-3,4-dihydronaphthalen-1(2*H*)-one (9): To a solution of Grubbs–Hoveyda 2nd generation catalyst **8** (62.6 mg, 0.102 mmol, 0.10 equiv) in benzene (25 mL) was added tetralone **3** (250.0 mg, 1.02 mmol) and methyl vinyl ketone (0.85 mL, 10.2 mmol, 10 equiv). The green solution was heated

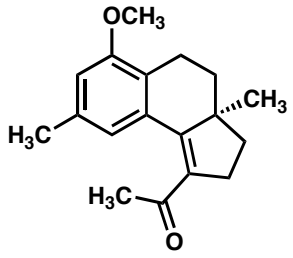
to 40 °C for 5 h. The red-black mixture was allowed to cool to room temperature, then evaporated in vacuo to a red-brown oil. The residue was purified by silica gel chromatography (10% → 18% EtOAc in hexanes), yielding enone **9** as a colorless oil (309 mg, 66% yield). **$[\alpha]^{25}_{D}$** (*c* 0.80, CH_2Cl_2): –42.7°; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.47 (s, 1H), 6.84 (s, 1H), 6.78 (dt, *J* = 15.9, 7.5 Hz, 1H), 6.09 (d, *J* = 15.9 Hz, 1H), 3.85 (s, 3H), 2.84 (m, 2H), 2.63 (ddd, *J* = 14.1, 7.5, 1.5 Hz, 1H), 2.42 (ddd, *J* = 14.1, 7.5, 1.5 Hz, 1H), 2.38 (s, 3H), 2.23 (s, 3H), 2.00 (m, 1H), 1.90 (m, 1H), 1.20 (s, 3H); **^{13}C NMR** (75.4 MHz, $CDCl_3$): δ 201.5, 198.3, 156.6, 144.1, 137.0, 134.1, 131.7, 129.1, 119.5, 115.3, 55.6, 44.6, 40.1, 33.2, 26.8, 21.9, 21.5, 18.9; **IR** (thin film, NaCl): 2930, 1675, 1610, 1282, 1255, 1137, 1028 cm^{-1}; **HRMS** (ESI-TOF) *m/z*: calc'd for $C_{18}H_{23}O_3$ $[M+H]^+$: 287.1647, found 287.1646.



1-((1*S*,3a*R*,9b*S*)-9b-hydroxy-6-methoxy-3a,8-dimethyl-2,3,3a,4,5,9b-hexahydro-1*H*-cyclopenta[*a*]naphthalen-1-yl)ethanone (11): This reaction was conducted in an N_2-filled dry-box. $[Ph_3PCuH]_6$ (345 mg, 0.18 mmol, 0.5 equiv) was dissolved dry, degassed toluene (8 mL), and cooled to –40 °C (acetonitrile/CO_2). A solution of enone **9** (100.2 mg, 0.350 mmol) in dry, degassed toluene (2 mL) was added, and the mixture maintained at –40 °C for 4 h. The reaction was removed from the dry-box, quenched by addition of sat. $NH_4Cl_{(aq)}$ (15 mL), and allowed to stir open to air for 10 h. The biphasic mixture was passed through a pad of silica gel (EtOAc), and the layers separated. The aqueous phase was extracted with EtOAc (2 x 5 mL), and the combined organic extracts washed with brine and dried over $MgSO_4$. The solvents were removed in vacuo, and the colorless residue purified by silica gel chromatography (5 → 10% EtOAc in hexanes), yielding alcohol **11** as a colorless oil (52.3 mg 52% yield) and diketone **10** as a slightly yellow oil (26.8 mg, 26% yield). Alcohol **11: $[\alpha]^{25}_{D}$** (*c* 0.72, $CHCl_3$): 73.5°; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.82 (s, 1H), 6.53 (s, 1H), 5.19 (s, 1H), 3.80 (s, 3H), 3.38 (t, *J* = 9.3 Hz, 1H), 2.73 (dd, *J* = 18.0, 6.0 Hz, 1H), 2.56 (ddd *J* = 18.0, 12.3, 6.0 Hz, 1H), 2.30 (s, 3H), 2.08 (s, 3H), 1.96-2.18 (m, 2H), 1.78-1.95 (m, 2H), 1.60 (m, 2H), 1.03 (s, 3H); **^{13}C NMR** (75.4 MHz, $CDCl_3$): δ 215.6, 156.5, 141.2, 136.2, 120.4, 119.1, 109.1, 83.0, 59.9, 55.2, 45.8, 37.7, 32.9, 32.7, 26.3, 21.7, 19.8, 17.8; **IR** (thin film, NaCl): 3445, 2930, 1694, 1612, 1593, 1463, 1349, 1280, 1191, 1084, 1043 cm^{-1}; **HRMS** (ESI-TOF) *m/z*: calc'd for $C_{18}H_{25}O_3$ $[M+H]^+$: 289.1804, found 289.1805.

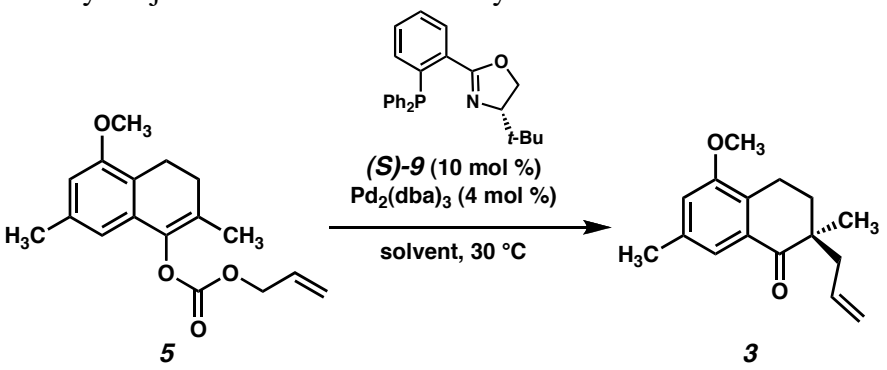


(*R*)-5-methoxy-2,7-dimethyl-2-(4-oxopentyl)-3,4-dihydronaphthalen-1(2*H*)-one (10): $[\alpha]^{25}_{D}$ (*c* 0.52, CH_2Cl_2): –4.3°; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44 (s, 1H), 6.82 (s, 1H), 3.85 (s, 3H), 2.81, (m, 2H), 2.40 (t, *J* = 6.9 Hz, 2H), 2.36 (s, 3H) 2.10 (s, 3H), 2.04 (dd, *J* = 6.9, 6.0 Hz, 1H), 1.89 (ddd, *J* = 6.9, 6.0, 1.2 Hz, 1H), 1.47-1.61 (m, 4H), 1.16 (s, 3H); **^{13}C NMR** (75.4 MHz, $CDCl_3$): δ 208.6, 202.7, 156.4, 136.6, 131.9, 129.2, 119.3, 114.9, 55.4, 44.1, 43.9, 35.6, 32.7, 29.7, 21.7, 21.3, 18.7, 18.3; **IR** (thin film, NaCl): 2931, 1715, 1680, 1459, 1354, 1281, 1139 cm^{-1}; **HRMS** (ESI-TOF) *m/z*: calc'd for $C_{18}H_{25}O_3$ $[M+H]^+$: 289.1804, found 289.1799.



(*R*)-1-(6-methoxy-3a,8-dimethyl-3,3a,4,5-tetrahydro-2*H*-cyclopenta[*a*]naphthalen-1-yl)ethanone (2): A solution of alcohol **11** (45.1 mg, 0.16 mmol) and 4-(dimethylamino)pyridine (5.7 mg, 0.05 mmol, 0.3 equiv) in pyridine (5 mL) was cooled to 0 °C (ice/water). To this solution was added neat $SOCl_2$ (170 μL, 2.35 mmol, 15 equiv), immediately turning the solution yellow. The mixture was maintained at 0 °C for 2.5 hr. The reaction mixture was quenched with 5 mL water, then extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with water and brine, then dried over $MgSO_4$, and evaporated in vacuo. The pale brown residue was purified by silica gel chromatography (6 → 10% EtOAc in hexanes), yielding enone **2** as a pale yellow oil (26.0 mg, 62% yield). Spectral data matched previously reported values.[4] $[\alpha]^{25}_{D}$ (*c* 0.74, $CHCl_3$): 130.7°

Solvent Screening Procedure: To 12 4 mL vials in a microtiter plate was added 100 μL of a Pd_2dba_3 solution (0.0042 M in THF) using a Symyx Core Module within a nitrogen-filled glove box. The Pd_2dba_3 solutions were evaporated to dryness under reduced pressure using a Genevac centrifugal evaporator within the glove box. To the dried vials charged with Pd_2dba_3 was added 180 μL of the desired solvent to be screened and 20 μL of (*S*)-*t*-BuPHOX ligand solution (0.052 M in 1:1 Hexane:$PhCH_3$). To the catalyst solutions, which had been stirred at 30°C for 30 min, was added 20 μL of an enol carbonate **5** solution (0.52 M in 1:1 Hexane:$PhCH_3$) and 80 μL of the same solvent to be screened. The reactions were stirred at 30 °C for 22 h. The crude reactions were purified via parallel silica gel chromatography, eluted with hexane: ethyl acetate = 19:1, using a Symyx Core Module within a fume hood. The fractions containing purified **3** were directly subjected to chiral HPLC analysis to determine % ee.



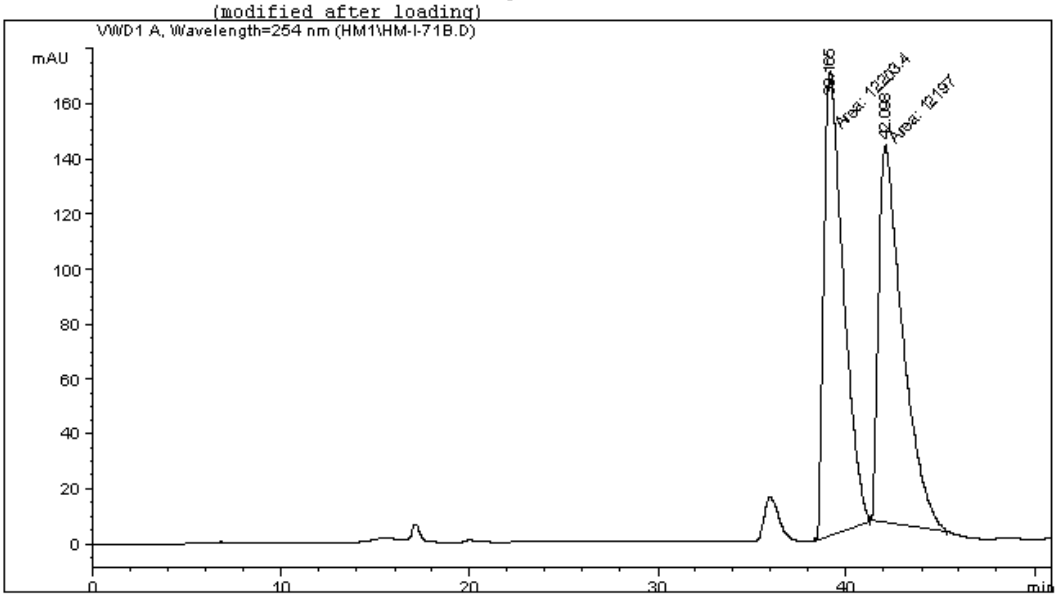
entry	solvent	ee (%)
1	PhH	93
2	$PhCH_3$	92
3	PhF	91
4	THF	90
5	$CH_2(OCH_3)$	88
6	*p*-dioxane	86
7	Et_2O	85
8	*t*-$BuOCH_3$	84
9	CCl_4	–
10	$PhCH_3$/Hexane (1:1)	91
11	THF/Hexane (1:1)	86
12	Et_2O/Hexane (1:1)	85

Chiral HPLC Data for Compounds (±)-3 and (+)-3.

Data File C:\HPCHEM\3\DATA\HM1\HM-I-71B.D Sample Name: HM-I-71b

HM-I-71b
0.1% IPA in heptane
Chiracel OD-H, 0.7 mL / min
50 minutes

```
======================================================================
Injection Date  : 1/21/2009 6:44:31 PM          Seq. Line :   3
Sample Name     : HM-I-71b                       Location : Vial 1
Acq. Operator   : HM                                Inj :   1
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\3\METHODS\HM-I-71.M
Last changed    : 1/21/2009 7:32:24 PM by HM
                  (modified after loading)
Analysis Method : C:\HPCHEM\3\METHODS\DEF LC.M
Last changed    : 2/26/2010 5:16:35 PM by ksp
                  (modified after loading)
```

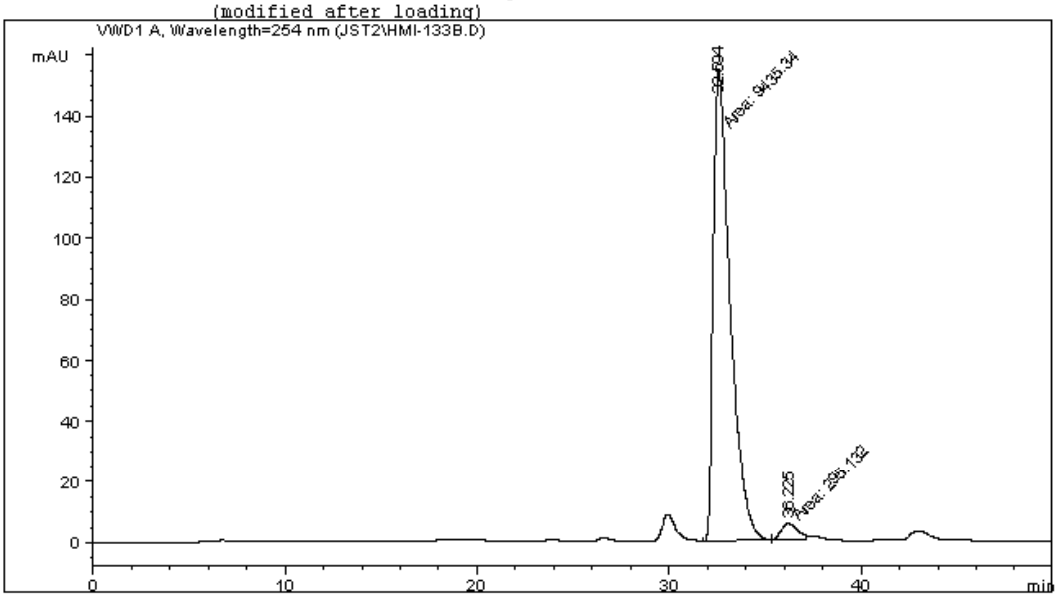



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]       [min]  mAU   *s   [mAU   ]      %
----|-------|----|-------|----------|----------|--------|
   1  39.165 MM    1.2046 1.22034e4   168.83820  50.0131
   2  42.098 MM    1.4805 1.21970e4   137.31056  49.9869

Totals :                  2.44003e4   306.14876

 Results obtained with enhanced integrator!
======================================================================
                        *** End of Report ***
```

Data File C:\HPCHEM\3\DATA\JST2\HMI-133B.D Sample Name: HM-I-133b

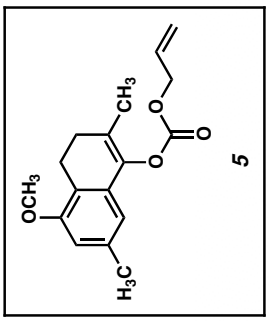
HM-I-133b
25 C, 4% Pd

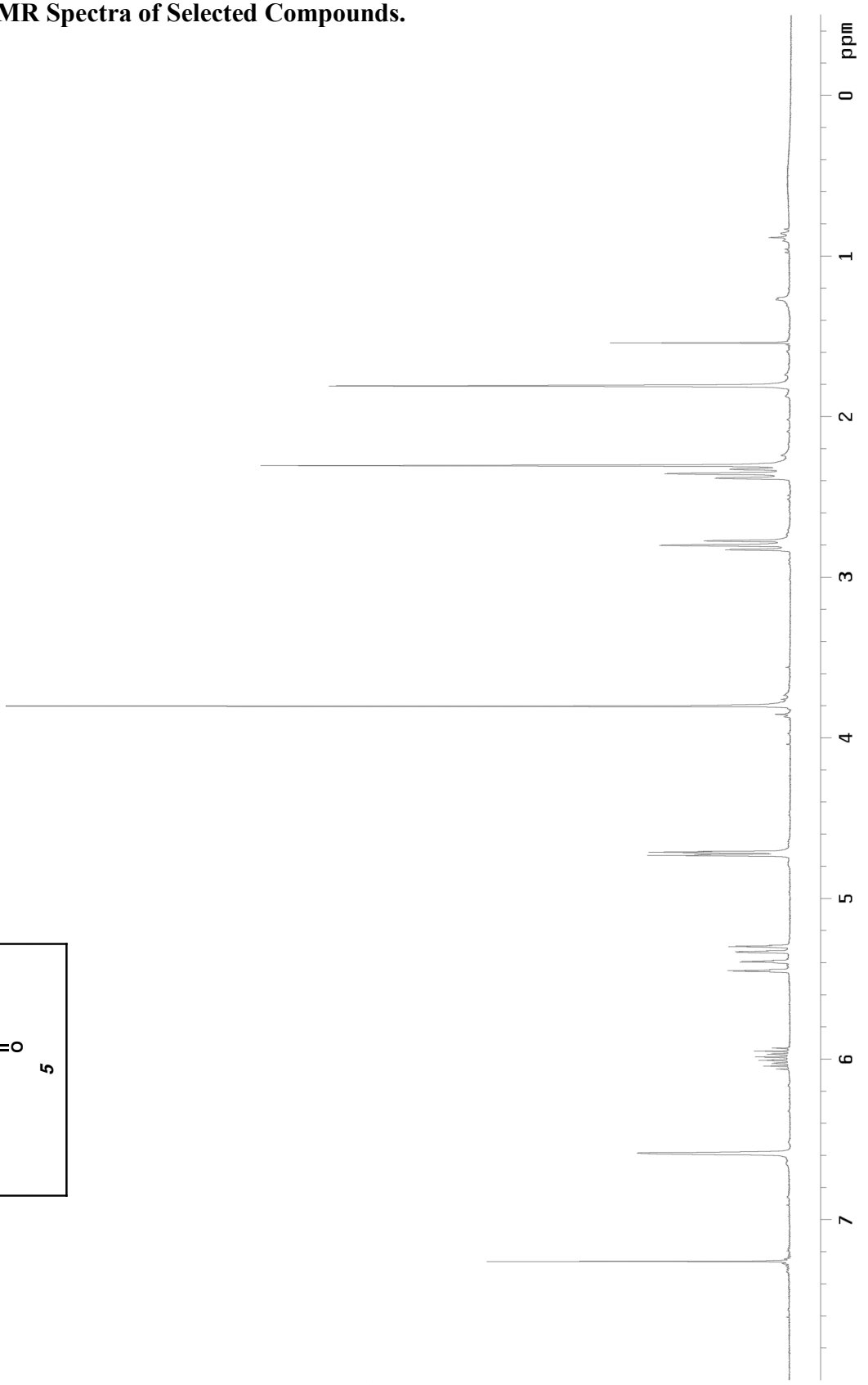
```
======================================================================
Injection Date  : 4/28/2009 1:49:29 PM          Seq. Line :   8
Sample Name     : HM-I-133b                      Location : Vial 2
Acq. Operator   : JST                               Inj :   1
                                                 Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\3\METHODS\HM-I-71.M
Last changed    : 1/21/2009 6:27:15 PM by jst
Analysis Method : C:\HPCHEM\3\METHODS\DEF LC.M
Last changed    : 2/26/2010 5:15:41 PM by ksp
                  (modified after loading)
```

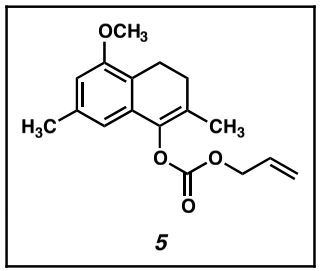



```
======================================================================
                        Area Percent Report
======================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]  mAU   *s   [mAU   ]       %
----|-------|----|-------|----------|----------|--------|
   1  32.594 MM    1.0174 9435.33789  154.56963  96.9669
   2  36.225 MM    0.9599  295.13242    5.12458   3.0331

Totals :                  9730.47031  159.69421

 Results obtained with enhanced integrator!
======================================================================
                          *** End of Report ***
```

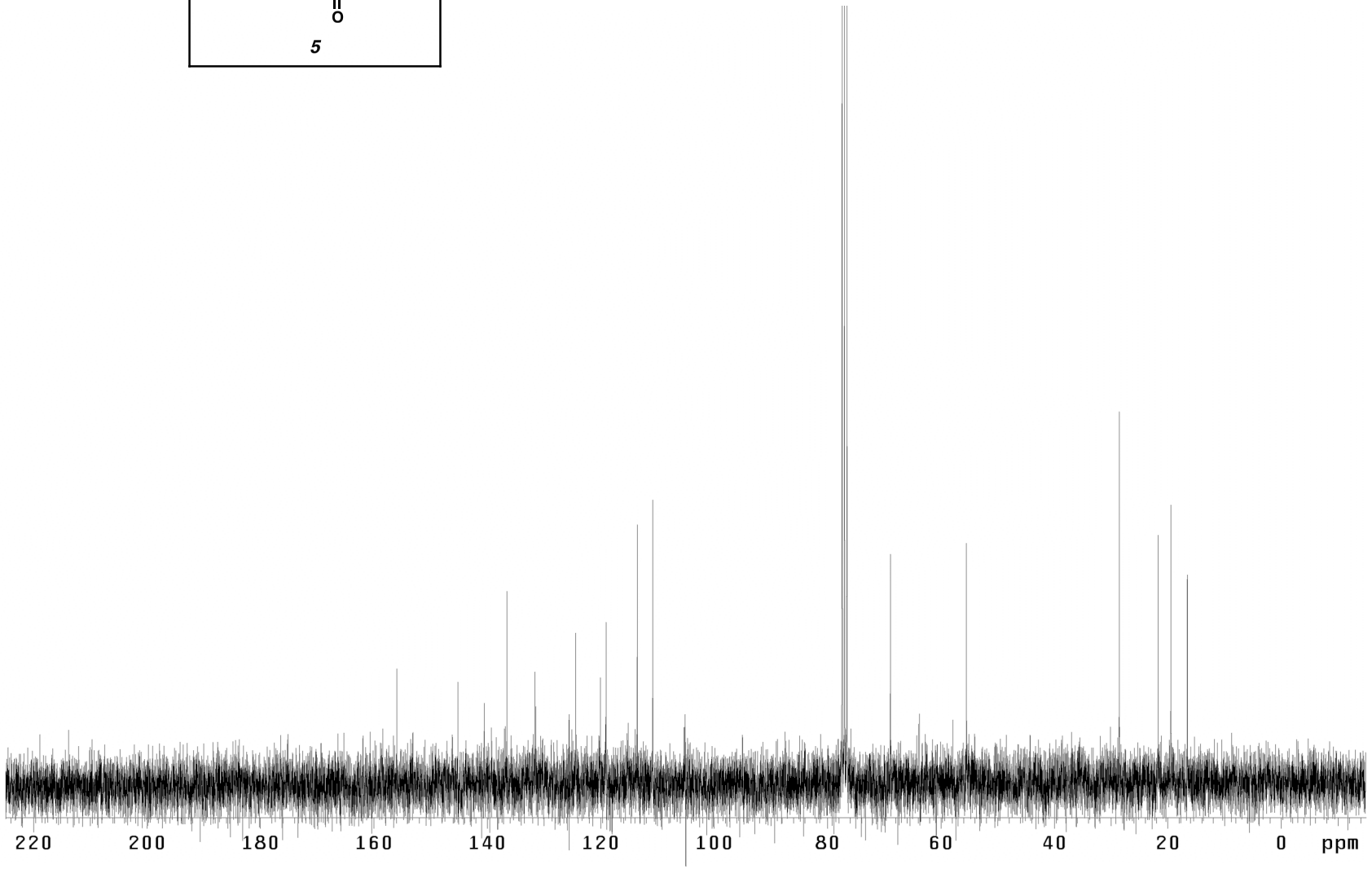
^{1}H and ^{13}C NMR Spectra of Selected Compounds.

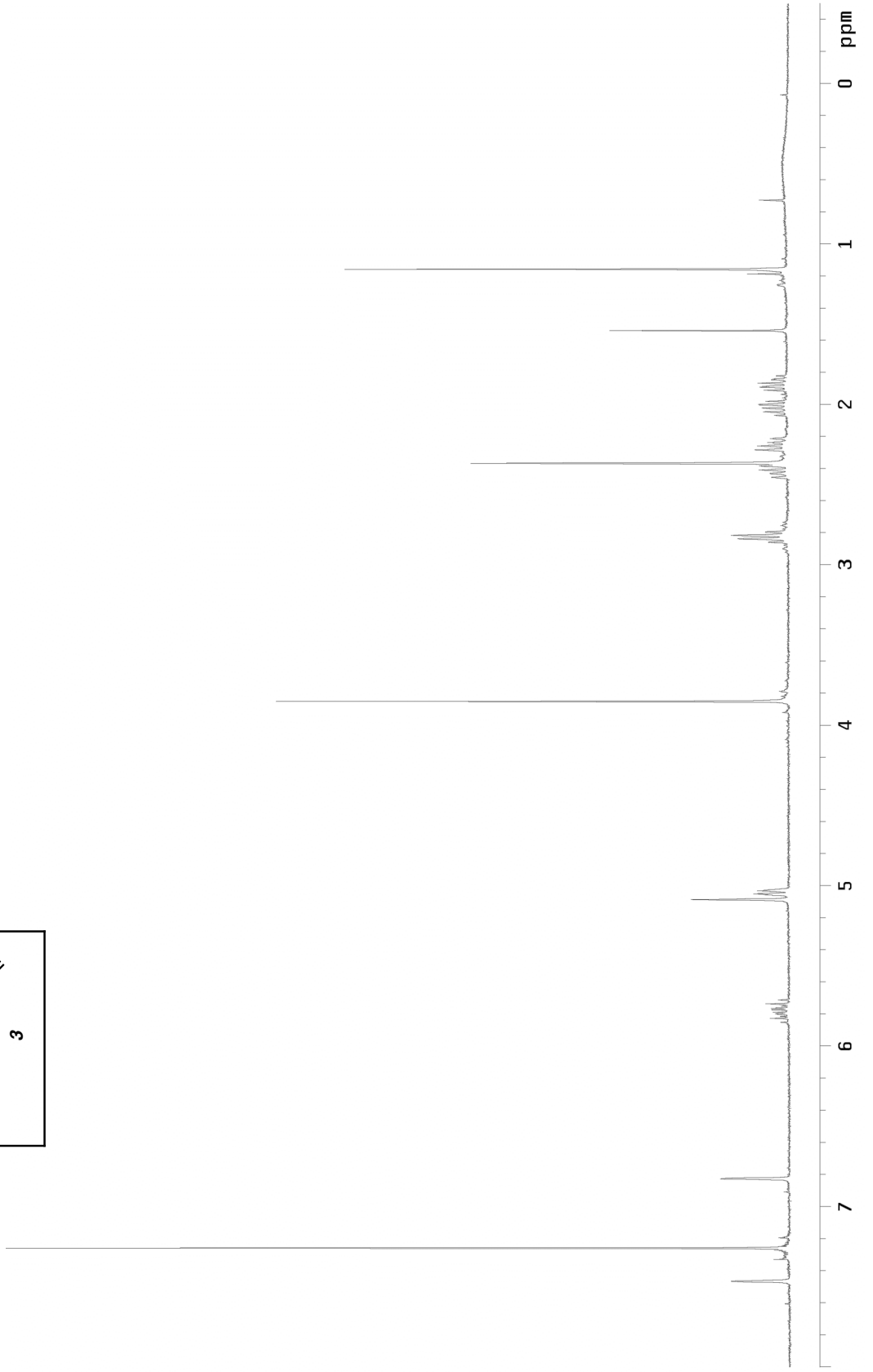


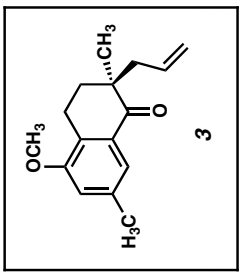




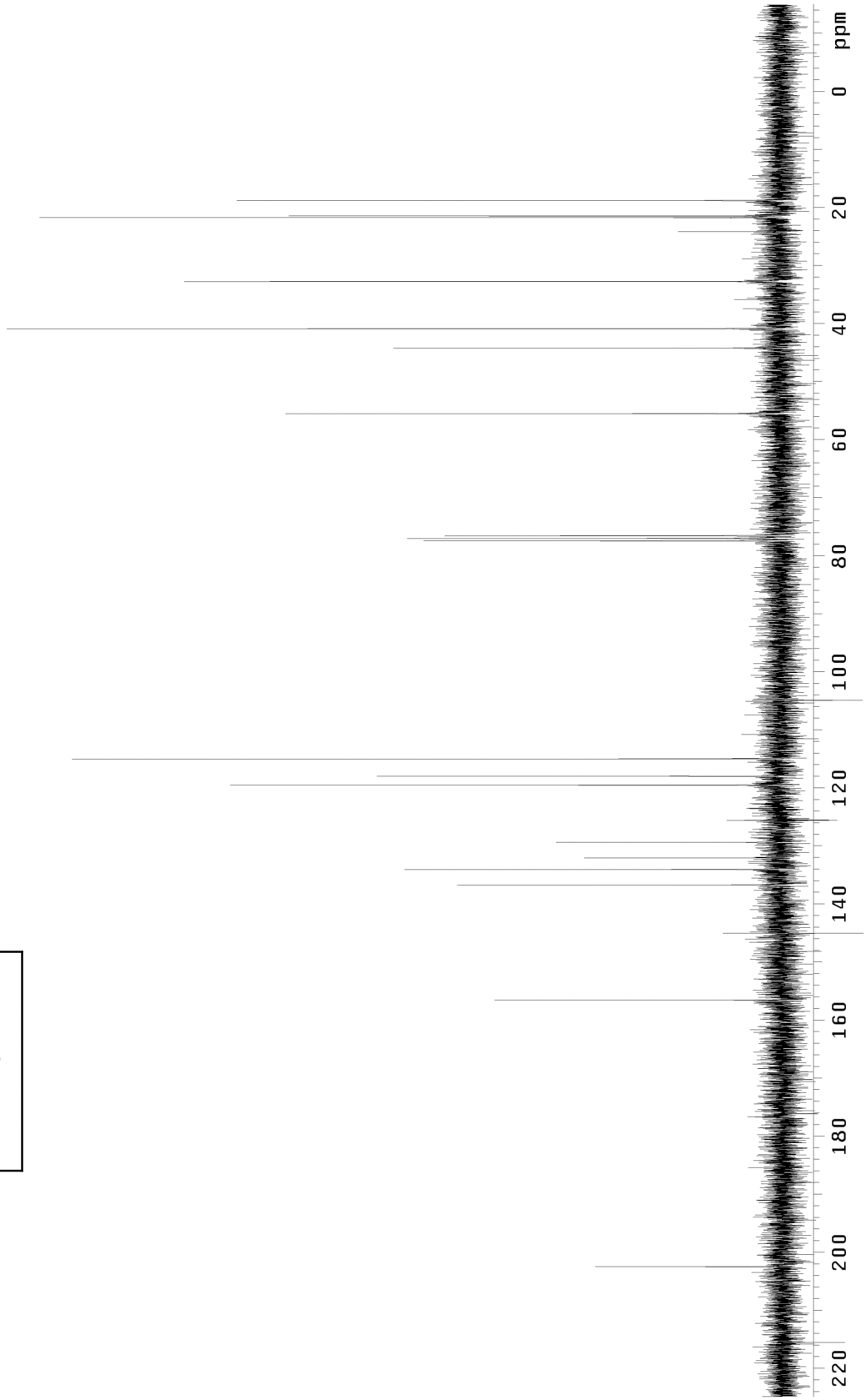
5

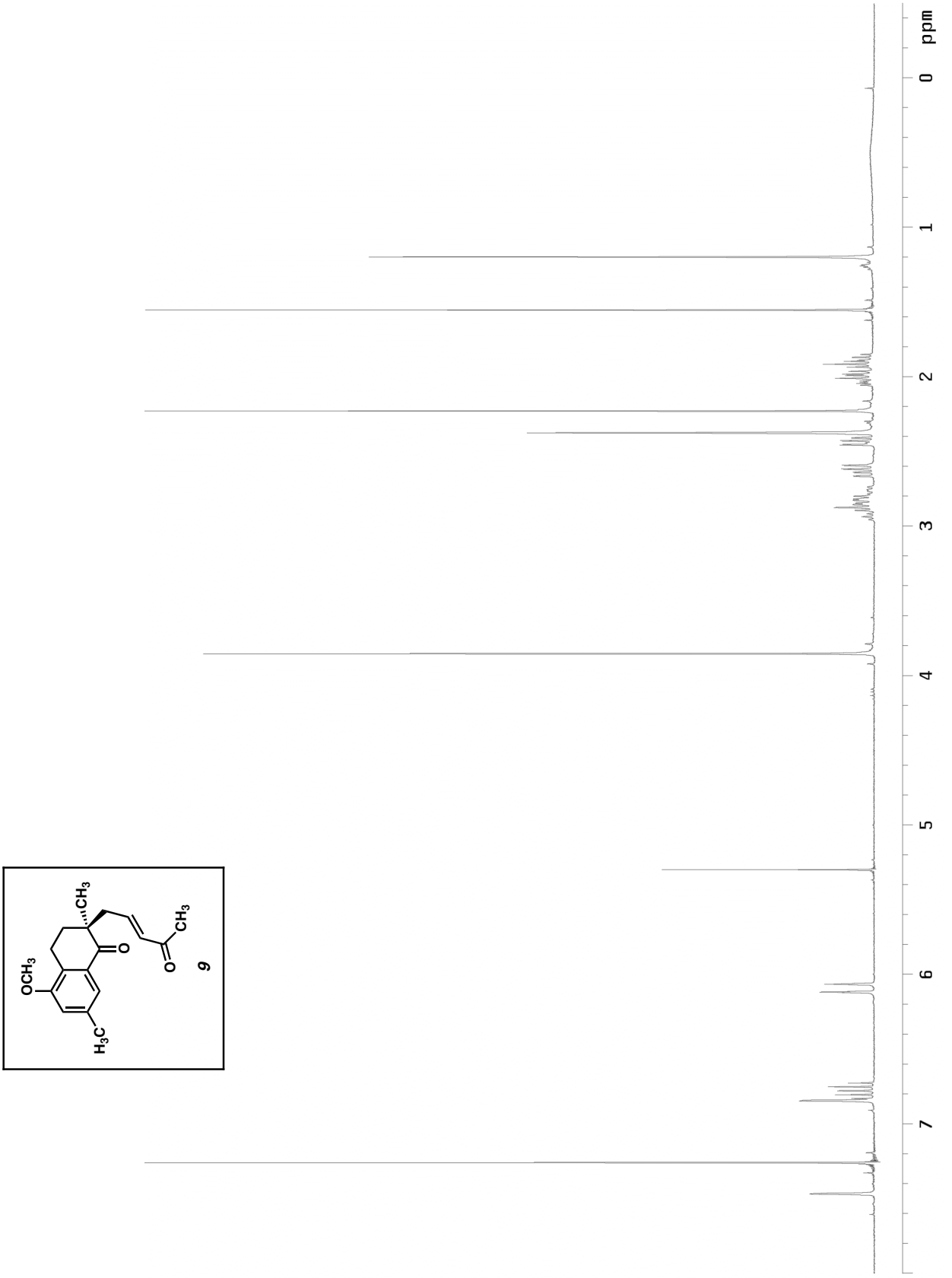


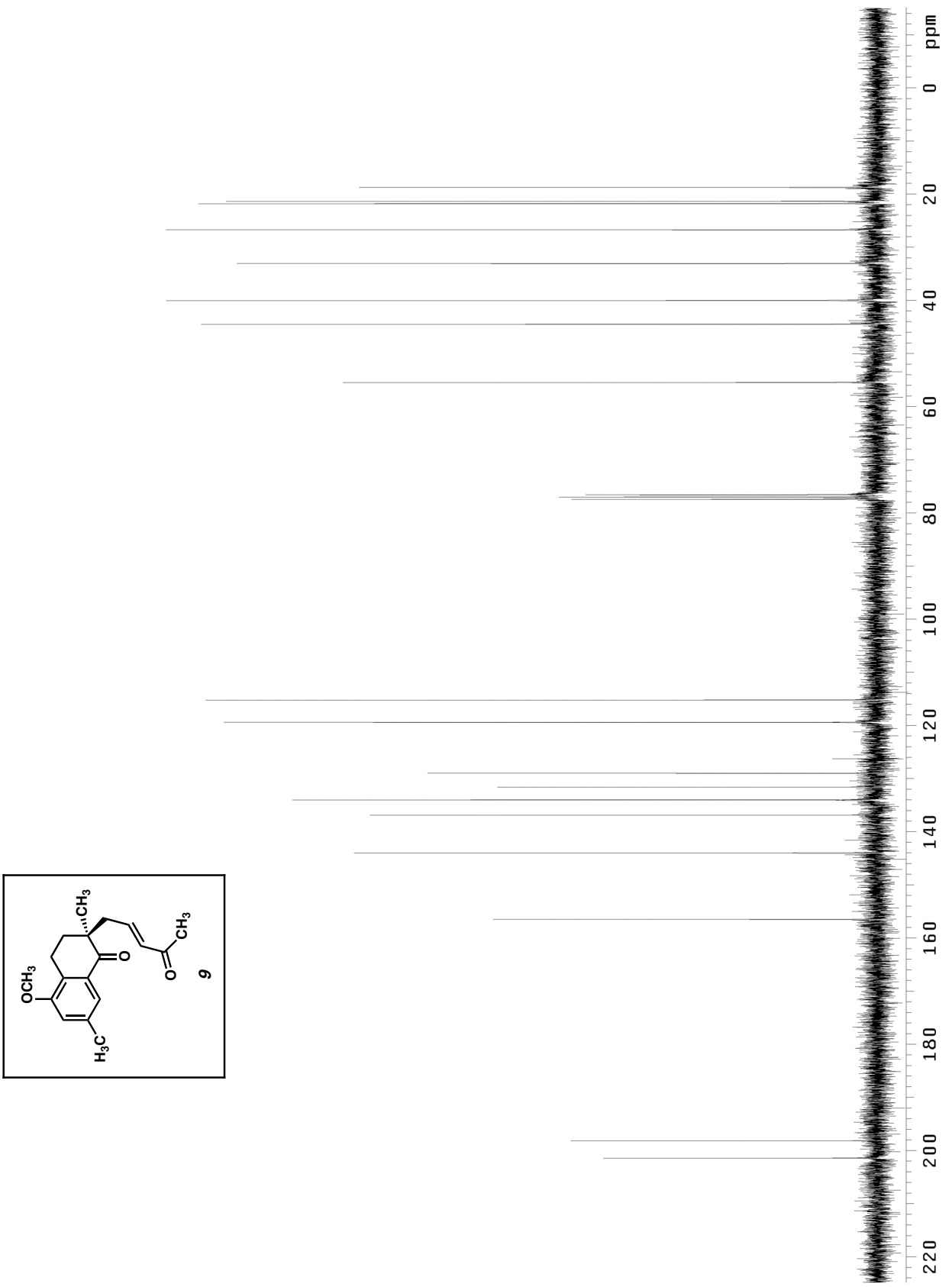

ppm
0
1
2
3
4
5
6
7
OCH3
CH3
O
H3C
3

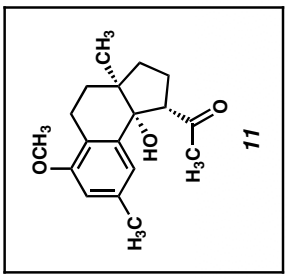


3

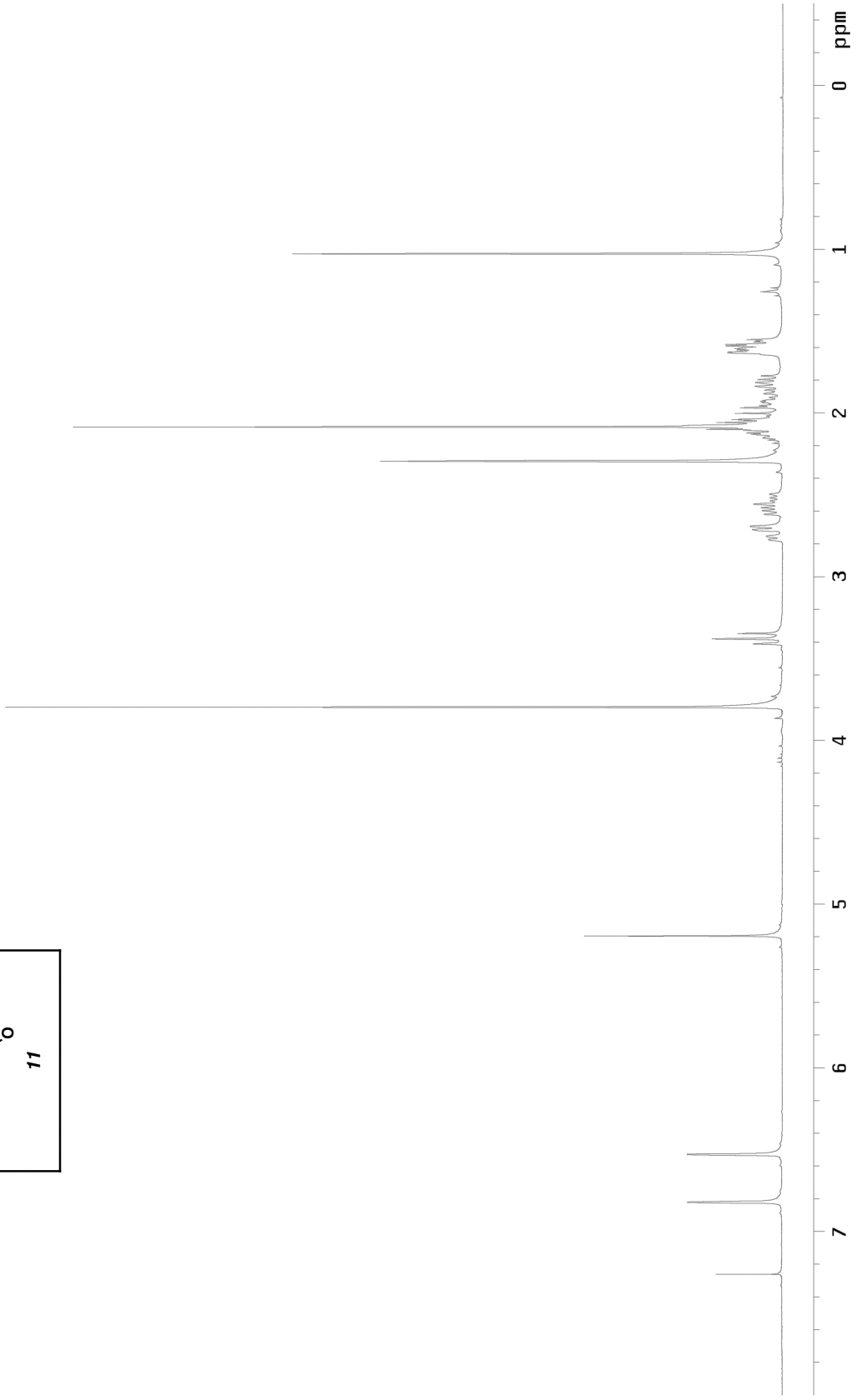


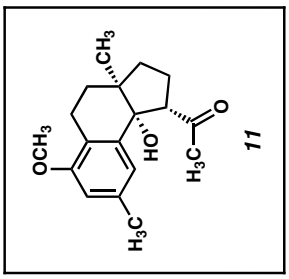

OCH3
H3C
CH3
O
O
CH3
9
ppm
0
1
2
3
4
5
6
7


ppm
0
20
40
60
80
100
120
140
160
180
200
220
OCH3
CH3
O
O
CH3
H3C
g

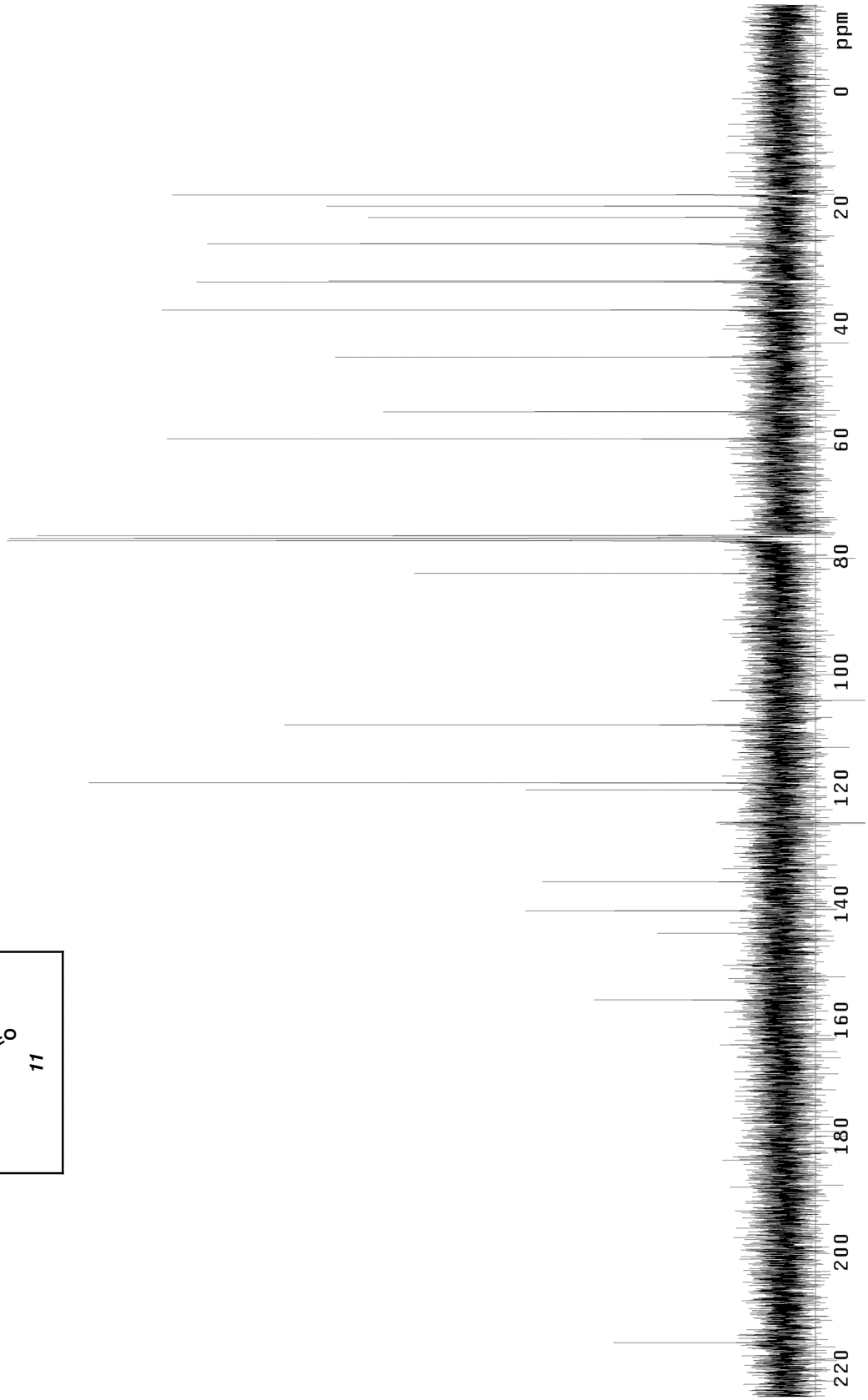


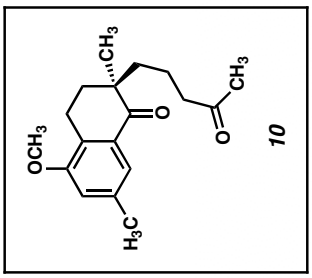
11



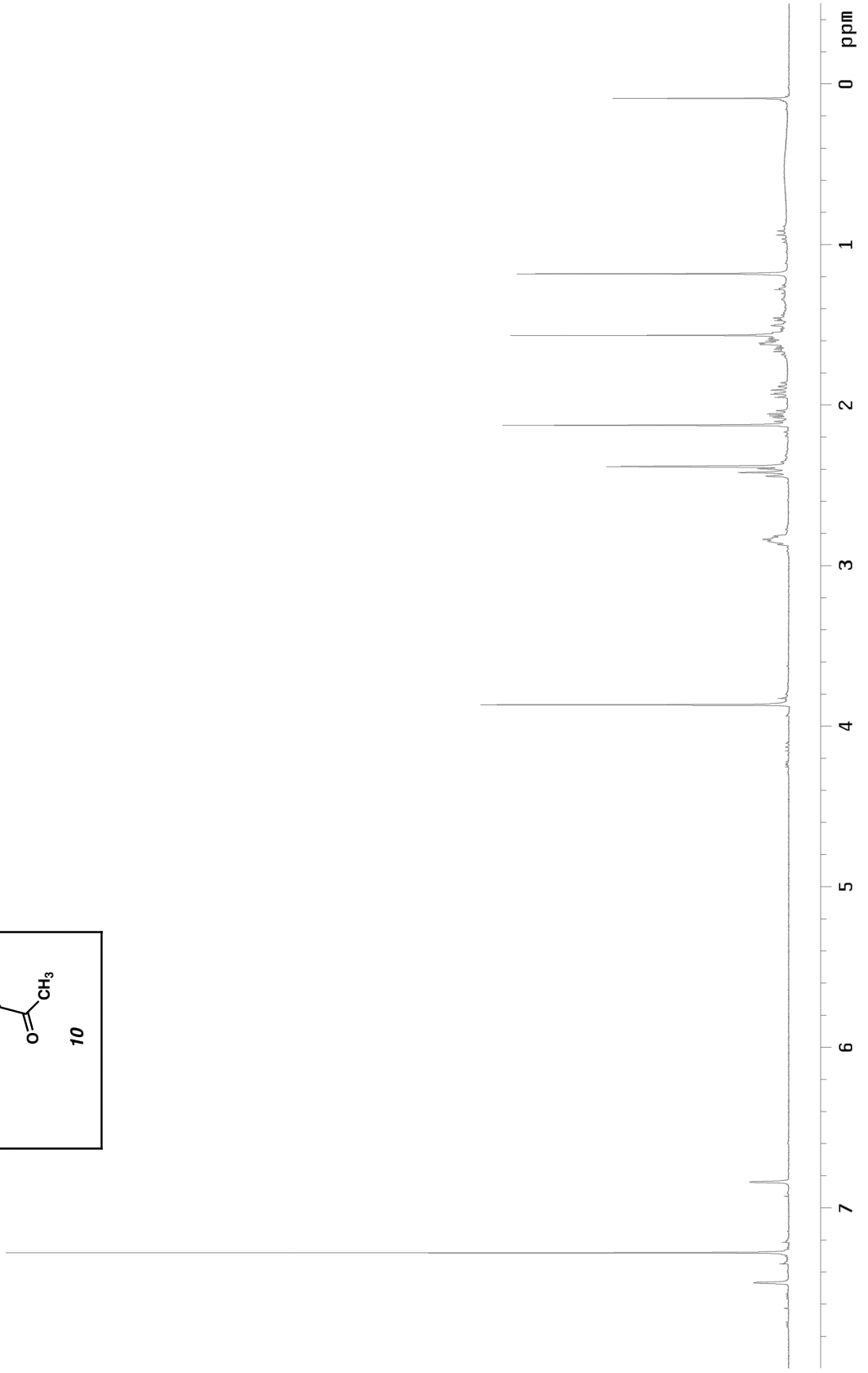


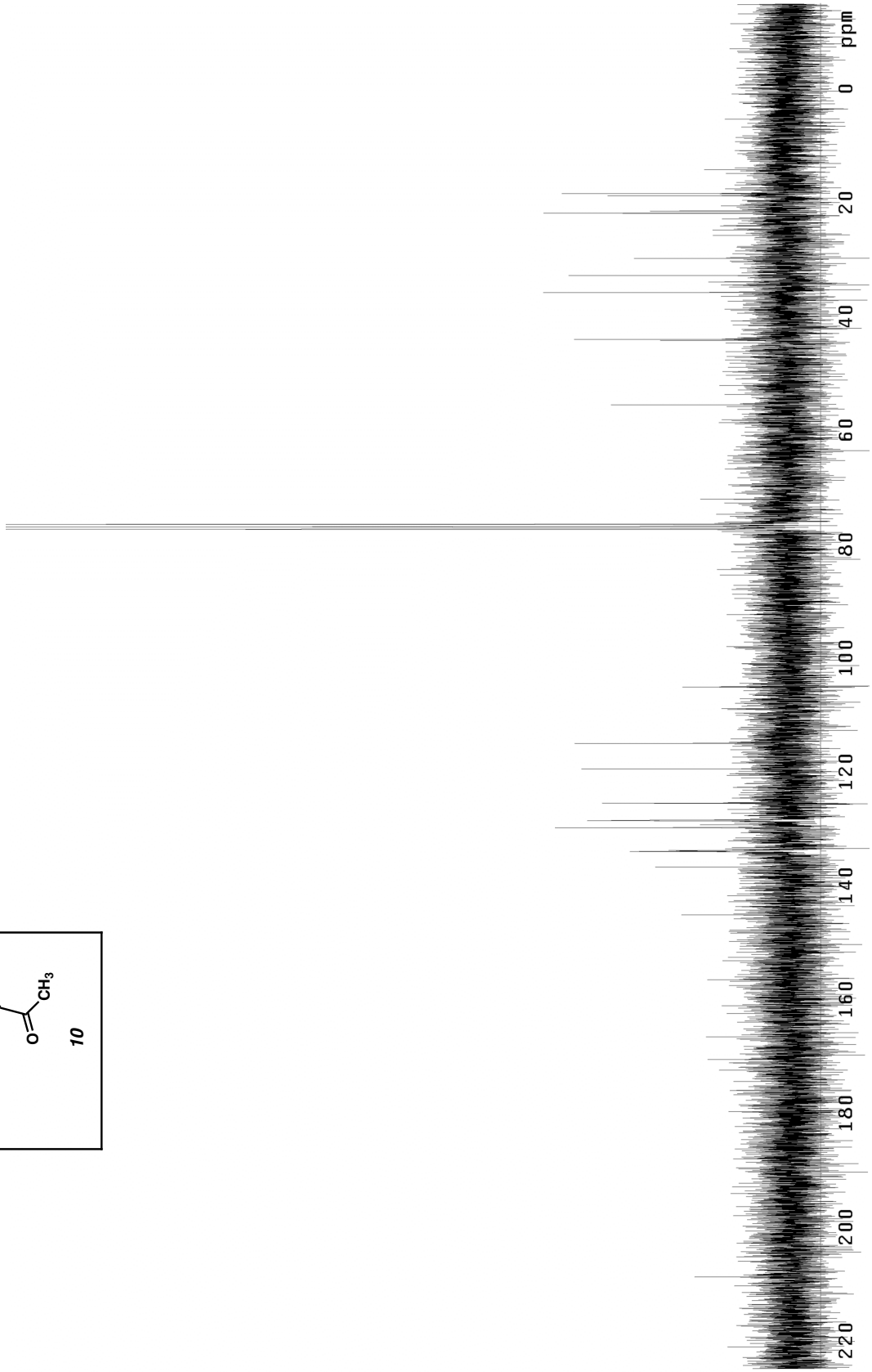
11

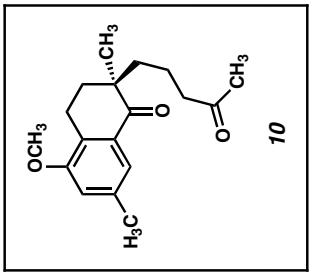




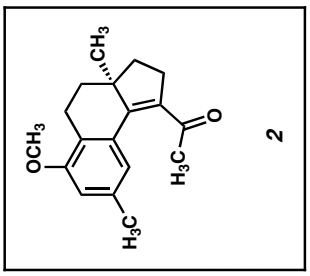
10

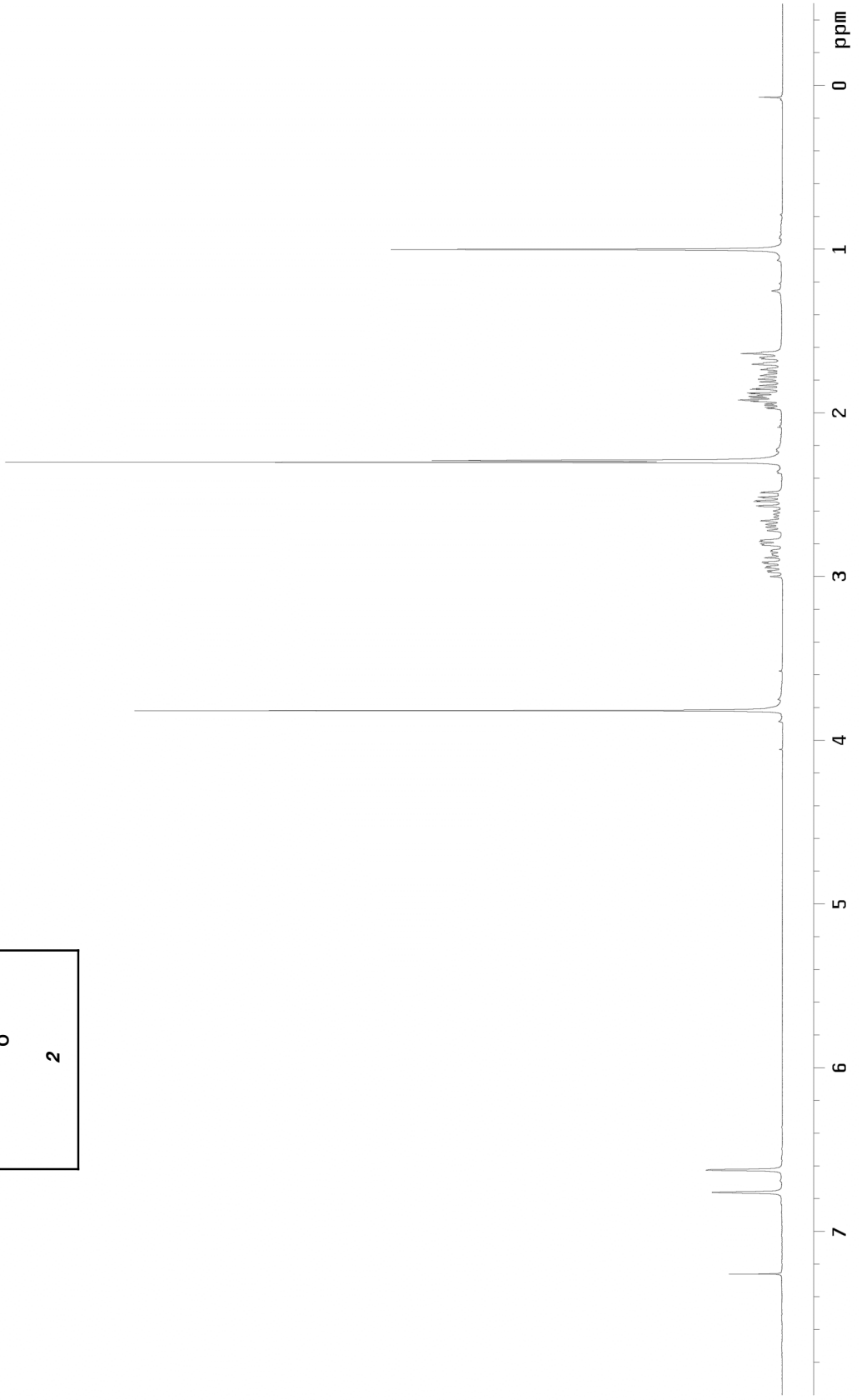


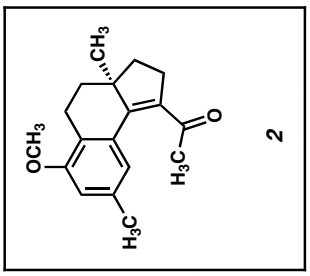




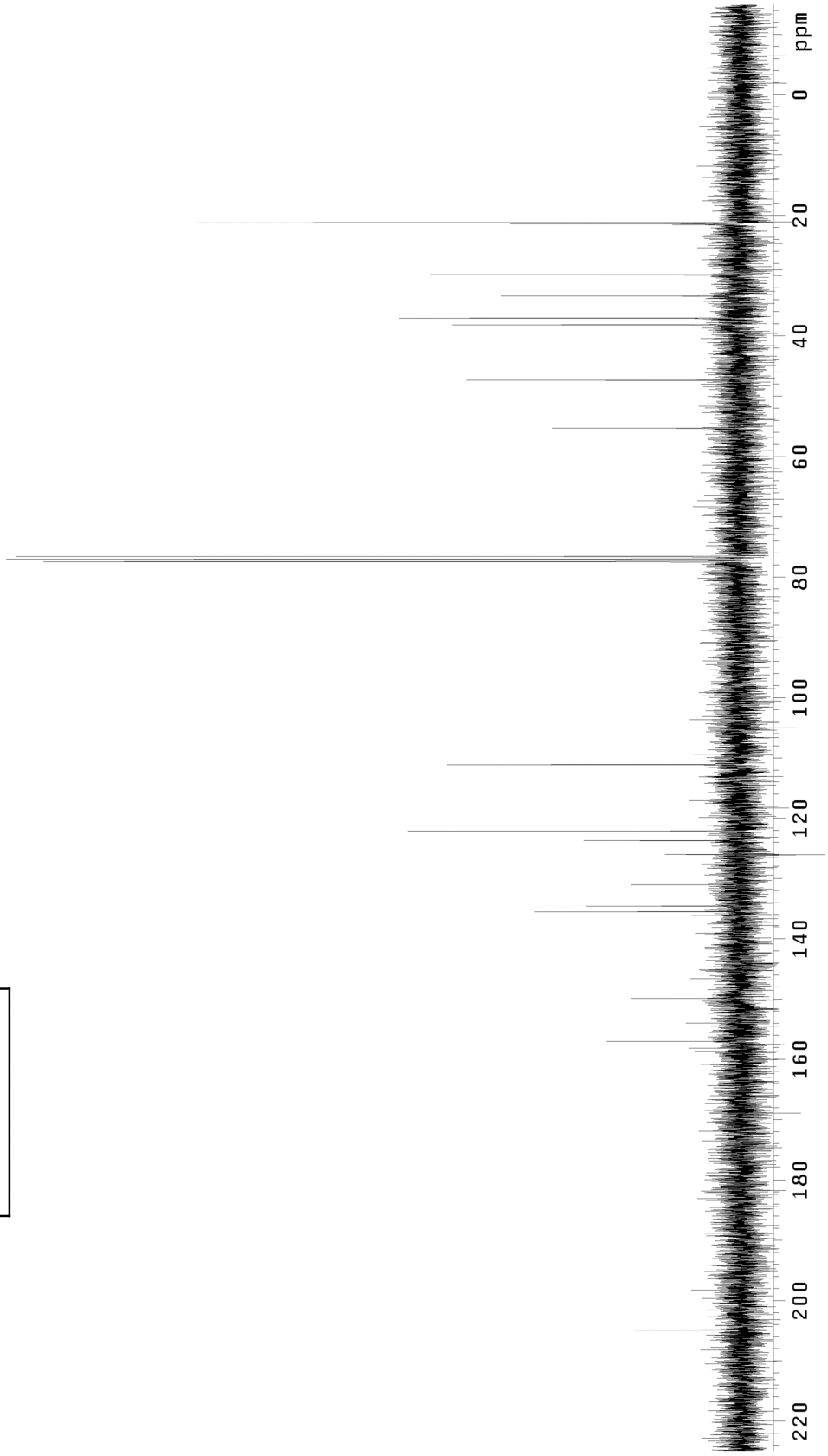
10


OCH3
CH3
H3C
H3C
O
2


ppm
0
1
2
3
4
5
6
7



2



(1) Tani, K.; Behenna, D. C.; McFadden R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531.
(2) (a) Ruzicka, von L.; Hösli, H.; Hofmann, K. *Helv. Chim. Acta* **1936**, *19*, 370–377. (b) Clive, D. L. J.; Wang, J. *J. Org. Chem.* **2004**, *69*, 2773–2784.
(3) (a) Tani, K.; Behenna, D. C.; McFadden, R. M.; Stoltz, B. M. *Org. Lett.* **2007**, *9*, 2529–2531. (b) McDougal, N. T.; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550–5554.
(4) Miesch, L.; Welsch, T.; Rietsch, V.; Miesch, M. *Chem. Eur. J.* **2009**, *15*, 4394–4401.