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SUPPORTING INFORMATION

Title: Organocatalytic Asymmetric β-Hydroxylation of α,β-Unsaturated Ketones
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Ref. No.: O200700873

General Methods. The ^{1}H and ^{13}C NMR spectra were recorded at 600 MHz and 150 MHz or 400 MHz and 100 MHz, respectively. The chemical shifts (δ) are referenced to residual signals of the solvents ($CHCl_3$ – 7.26 ppm for ^{1}H NMR and 77.0 ppm for ^{13}C NMR). Coupling constants are given in Hz. Carbon types were determined by DEPT ^{13}C NMR experiments. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. Purification of reaction products was carried out by flash chromatography (FC) on silica gel (230-400 mesh) according to the method of Still.[1] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Mass spectra were obtained from the Department of Organic Chemistry *"A. Mangini"* Mass Spectroscopy facility. Optical rotations are reported as follows: $[\alpha]^{rt}_{D}$ (*c* in g per 100 mL, solvent). All reactions were carried out in air and using undistilled solvent, without any precautions to exclude moisture unless otherwise noted.

Materials. Commercial grade reagents and solvents were used without further purification; otherwise, where necessary, they were purified as recommended.[2] Oximes **1** were purchased from AlfaAesar and used as received. α,β-Unsaturated ketones were purchased and used as received, prepared by Wittig reaction with commercially available acetylmethylene-triphenylphosphorane (R_2= Me), or with Grignard reaction on the corresponding unsatured aldehyde followed by oxidation with MnO_2 (R_2= Et). *N*-protected amino acids were purchased from Aldrich or Fluka and used as received.
9-Amino(9-deoxy)*epi*-hydroquinine was prepared from commercially available hydroquinine following the literature procedure.[3]

Determination of Enantiomeric Purity. Chiral HPLC analysis was performed on an Agilent 1100-series instrumentation. Daicel Chiralpak AD-H or AS-H columns and Daicel Chiralcel OD-H with i-PrOH/hexane as the eluent were used. HPLC traces were compared to racemic samples prepared by benzylamine·TFA-catalyzed reaction.

Determination of Absolute Configuration. The absolute configuration of the optically active compound **3e** was determined by reductive cleavage to afford **4** and subsequent comparison of the measured optical rotation of **4** with literature value. [4] All other absolute configurations were assigned by analogy based on an uniform reaction mechanism and the uniform elution order observed in the HPLC chromatograms.

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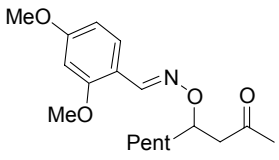
[1] W. C. Still, M. Kahn, A. J. Mitra, *J. Org. Chem.* 1978, ***43***, 2923.
[2] W. L. F. Armarengo, D. D. Perrin, In *Purification of Laboratory Chemicals*, 4th ed.; Butterworth Heinemann: Oxford, 1996.
[3] B. Vakulya, Sz. Varga, A. Csámpai, T. Soos, *Org. Lett.* 2005, ***7***, 1967.
[4] E. M. Carreira, W.Lee and R. A. Singer, *J. Am. Chem. Soc.*, 1995, **117**, 3649.

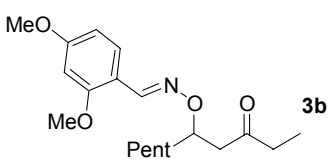
Experimental Procedures

General Procedure for the Organocatalytic β-hydroxylation of α,β-unsaturated ketones. All the reactions were carried out in undistilled Et_2O without any precautions to exclude water. In an ordinary test tube equipped with a magnetic stirring bar, 9-amino(9-deoxy)epi-hydroquinine (10 or 20 mol%) and D-*N*-Boc phenylglycine (15 or 30 mol%) as the chiral counter-anion were dissolved in 1 mL of Et_2O. The solution was stirred for 20 minutes at room temperature to allow the formation of the catalytic salt **A**. After addition of α,β-unsaturated ketones (0.2 mmol), the mixture was stirred at room temperature for 10 minutes. Then oxime (0.6 mmol, 3 equiv.) was added in one portion, the tube was closed with a rubber stopper and stirring was continued for the indicated time. Then the crude reaction mixture was diluted with hexane (2 mL) and flushed through a plug of silica, using hexane/Et_2O 1/1 as the eluent. Solvent was removed *in vacuo*, and the residue was purified by flash chromatography to yield the desired product.



3a

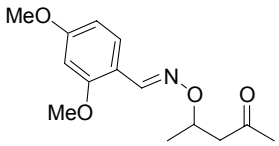
2,4-Dimethoxy-benzaldehyde *O*-[1-(2-oxo-propyl)-hexyl]-oxime-3a (Table 2, entry 1). The reaction was carried out at RT for 40 h following the general procedure. The title compound was isolated by column chromatography (hexane/Acetone = 95/5) in 52% yield and 90% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (80/20 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 6.2 min; τ_{major} = 6.5 min). $[\alpha]^{rt}_D$= + 2.8 (*c* = 1.2, $CHCl_3$, 90% ee). HRMS: *m/z* calcd for $C_{18}H_{27}NO_4$: 321,1940; found: 321.1943. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.21-1.50 (m, 6H), 1.52-1.75 (m, 2H), 2.20 (s, 3H), 2.86 (dd, *J* = 4.8, 15.6 Hz, 1H), 2.56 (dd, *J* = 7.4, 15.6 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.55-4.61 (m, 1H), 6.41 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, , *J* = 2.4, 8.8 Hz, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.4, 22.5, 25.0, 30.9, 31.7, 34.0, 48.6, 55.4, 55.5, 79.4, 98.1, 105.4, 113.9, 127.2, 144.2, 158.7, 162.3, 207.7.



3b

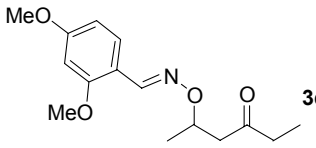
2,4-Dimethoxy-benzaldehyde *O*-[1-(2-oxo-butyl)-hexyl]-oxime – 3b (Table 2, entry 2). The reaction was carried out at RT for 48 h following the general procedure. The title compound was isolated by column chromatography (hexane/Acetone = 95/5) in 56% yield and 94% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 6.6 min; τ_{major} = 7.1 min). $[\alpha]^{rt}_D$= - 8.1 (*c* = 1.5, $CHCl_3$, 94% ee). HRMS: *m/z* calcd for $C_{19}H_{29}NO_4$: 335.2097; found: 335.2095. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.04 (t, *J* = 7.2 Hz, 3H), 1.25-1.47 (m, 6H), 1.52-1.75 (m, 2H), 3.74 (q, *J* = 7.2 Hz, 2H), 2.54 (dd, *J* = 5.2, 15.2 Hz, 1H), 2.56 (dd, *J* = 7.2, 15.2 Hz, 1H), 3.80 (s,

3H), 3.82 (s, 3H), 4.55-4.61 (m, 1H), 6.41 (d, J = 2.4 Hz, 1H), 6.48 (dd, , J = 2.4, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 14.0, 22.5, 25.1, 31.7, 34.0, 36.8, 47.3, 55.4, 55.5, 79.4, 98.1, 105.4, 114.0, 127.2, 144.1, 158.7, 162.3, 210.2.



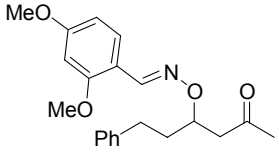
3c

2,4-Dimethoxy-benzaldehyde *O*-(1-methyl-3-oxo-butyl)-oxime – 3c (Table 2, entry 3). The reaction was carried out at RT for 40 h following the general procedure. The title compound was isolated by column chromatography (hexane/Acetone = 95/5) in 53% yield and 80% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 9.9 min; τ_{major} = 10.4 min). $[\alpha]^{rt}_D$= + 4.9 (c = 0.8, $CHCl_3$, 80% ee). HRMS: *m/z* calcd for $C_{14}H_{19}NO_4$: 265.131409; found: 265.13140. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, J = 6.4 Hz, 3H), 2.20 (s, 3H), 2.56 (dd, J = 5.6, 15.6 Hz, 1H), 2.90 (dd, J = 7.2, 15.6 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.68-4.75 (m, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.48 (dd, , J = 2.4, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.9, 30.8, 50.0, 55.4, 55.5, 75.4, 98.2, 105.4, 113.9, 127.3, 144.5, 158.8, 162.3, 207.3.



3d

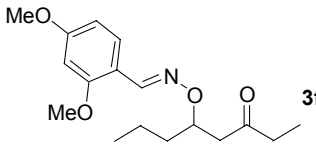
2,4-Dimethoxy-benzaldehyde *O*-(1-methyl-3-oxo-pentyl)-oxime – 3d (Table 2, entry 4). The reaction was carried out at RT for 60 h following the general procedure. The title compound was isolated by column chromatography (hexane/Acetone = 95/5) in 46% yield and 88% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (95/5 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 11.7 min; τ_{major} = 12.4 min). $[\alpha]^{rt}_D$= -4.8 (c = 1.2, $CHCl_3$, 88% ee). HRMS: *m/z* calcd for $C_{15}H_{21}NO_4$: 279.147059; found: 279.14720. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.05 (t, J = 7.2 Hz, 3H), 1.32 (d, J = 6.4 Hz, 3H), 2.49 (q, J = 7.2 Hz, 2H), 2.52 (dd, J = 5.6, 15.6 Hz, 1H), 2.90 (dd, J = 6.8, 15.6 Hz, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.68-4.75 (m, 1H), 6.42 (d, J = 2.4 Hz, 1H), 6.48 (dd, , J = 2.4, 8.8 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 19.9, 36.8, 48.8, 55.4, 55.5, 75.5, 98.2, 105.4, 113.9, 127.3, 144.4, 158.8, 162.3, 209.8.



3e

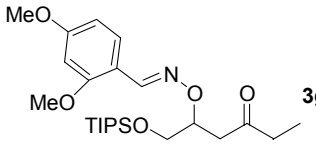
2,4-Dimethoxy-benzaldehyde *O*-(3-oxo-1-phenethyl-butyl)-oxime – 3e (Table 2, entry 5). The reaction was carried out at RT for 40 h following the general procedure. The title compound was isolated by column chromatography (hexane/Acetone = 95/5) in 55% yield and 90% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 18.6 min; τ_{major} = 20.4 min). $[\alpha]^{rt}_D$= +10.4 (c =

1.0, $CHCl_3$, 90% ee). HRMS: *m/z* calcd for $C_{21}H_{25}NO_4$: 355,1784; found: 355,1780. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.87-1.93 (m, 1H), 1.99-2.06 (m, 1H), 2.17 (s, 3H), 2.58 (dd, *J* = 5.4, 15.6 Hz, 1H), 2.68-2.73 (m, 1H), 2.78-2.83 (m, 1H), 2.91 (dd, *J* = 7.2, 15.6 Hz, 1H), 3.80 (s, 3H), 3.81 (s, 3H), 4.60-4.64 (m, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, , *J* = 2.4, 9.0 Hz, 1H), 7.15-7.27 (m, 5H), 2.78-2.83 (m, 1H), 7.68 (d, *J* = 9.0 Hz, 1H), 8.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.8, 31.7, 35.8, 48.5, 55.4, 55.5, 78.5, 98.1, 105.4, 113.8, 125.8, 127.3, 128.3, 128.4, 141.9, 144.5, 158.8, 162.4, 207.4.



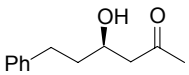
3f

2,4-Dimethoxy-benzaldehyde *O*-(3-oxo-1-propyl-pentyl)-oxime – 3f (Table 2, entry 6). The reaction was carried out at RT for 55 h following the general procedure. The title compound was isolated by column chromatography (hexane/Acetone = 95/5) in 55% yield and 92% ee. The ee was determined by HPLC analysis using a Chiralcel OD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 6.9 min; τ_{major} = 7.4 min). $[\alpha]^{rt}_D$= -12.6 (*c* = 1.1, $CHCl_3$, 92% ee). HRMS: *m/z* calcd for $C_{17}H_{25}NO_4$: 307.178359; found: 307.1783. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91-0.96 (m, 3H), 1.00-1.06 (m, 3H), 1.38-1.80 (m, 4H), 2.43-2.62 (m, 3H), 2.84-2.93 (m, 1H), 3.80 (s, 3H), 3.82 (s, 3H), 4.57-4.62 (m, 1H), 6.42 (d, *J* = 2.4 Hz, 1H), 6.48 (dd, , *J* = 2.4, 8.4 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.6, 14.0, 18.7, 36.1, 36.9, 47.4, 55.4, 55.6, 79.2, 98.1, 105.4, 113.9, 127.2, 144.1, 158.7, 162.3, 210.2.



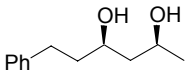
3g

2,4-Dimethoxy-benzaldehyde *O*-(3-oxo-1-triisopropylsilanyloxymethyl-pentyl)-oxime – 3g (Table 2, entry 7). The reaction was carried out at RT for 60 h following the general procedure. The title compound was isolated by column chromatography (hexane/Acetone = 95/5) in 35% yield and 80% ee. The ee was determined by HPLC analysis using a Chiralpak AS-H column (95/5 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 5.4 min; τ_{minor} = 6.7 min). $[\alpha]^{rt}_D$= -19.2 (*c* = 0.5, $CHCl_3$, 80% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.89-1.07 (m, 24H), 2.43-2.47 (m, 2H), 2.74-2.76 (m, 2H), 3.69-3.89 (m, 2H), 3.73 (s, 3H), 3.75 (s, 3H), 4.57-4.62 (m, 1H), 6.34 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, , *J* = 2.4, 9.0 Hz, 1H), 7.60 (d, *J* = 9.0 Hz, 1H), 8.26 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 7.6, 11.9, 18.0, 36.7, 43.6, 55.4, 55.5, 64.2, 79.8, 98.2, 105.4, 113.9, 127.3, 144.6, 158.8, 162.3, 209.9.



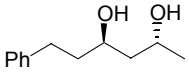
4

(*R*)-4-Hydroxy-6-phenyl-hexan-2-one[4] **– 4** (Scheme 4). To a suspension of oxime ether **3e** (0.15 M) in AcOH/H_2O (1:1 v/v) was added Zn powder (40 equiv) under argon atmosphere. After being stirred for 24h the reaction mixture was diluted with Et_2O, filtered and extracted with Et_2O. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure.[5] The title compound was isolated by column chromatography (hexane/AcOEt = 80/20) in 96% yield and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.3 min; τ_{major} = 11.4 min). $[\alpha]^{rt}_D$= -12.0 (*c* = 1.1, $CHCl_3$, 88% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63-1.73 (m, 1H), 1.78-1.87 (m, 1H), 2.16 (s, 3H), 2.58-2.61 (m, 2H), 2.65-2.86 (m, 2H), 3.10 (bs, 1H), 4.02-4.08 (m, 1H), 7.15-7.27 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7, 31.7, 37.9, 49.9, 66.7, 125.8, 128.3, 128.4, 147.8, 209.8.



syn-**5**

(2*S*,4*R*)-6-Phenyl-hexane-2,4-diol – ***syn*-5** (Scheme 1). The syn reduction was carried out following the literature procedure[6] yielding crude *syn* compound **5** in a 9/1 diastereomeric ratio. The title compound was isolated by column chromatography (CH_2Cl_2/Acetone = 90/10) in 99% yield, 9/1 dr and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{major} = 9.4 min; τ_{minor} = 9.8 min). $[\alpha]^{rt}_D$= +11.7 (*c* = 0.6, $CHCl_3$, 88% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 6.6 Hz, 3H), 1.50-1.59 (m, 2H), 1.71-1.80 (m, 2H), 2.63-2.77 (m, 2H), 3.29 (bs, 1H), 3.43 (bs, 1H), 3.86-3.90 (m, 1H), 4.00-4.05 (m, 1H), 7.17-7.29 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 24.2, 31.6, 39.7, 44.6, 69.1, 72.2, 125.8, 128.3, 128.4, 141.9.



anti-**5**

(2*R*,4*R*)-6-Phenyl-hexane-2,4-diol – ***anti*-5** (Scheme 1). To a solution of **4** (0.1 M) in AcOH was added Me_4NBH_4 (2 equiv) under argon atmosphere. After being stirred for 4h the reaction mixture was diluted with Et_2O, quenched with H_2O, and extracted with Et_2O.[7] The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure yielding crude *anti* compound **5** in a 2.5/1 diastereomeric ratio. The title compound was isolated by column chromatography (gradient CH_2Cl_2/Acetone from 99/1 to 9/1) in 38% yield, 95/5 dr and 88% ee. The ee was determined by HPLC analysis using a Chiralpak AD-H column (90/10 hexane/*i*-PrOH; flow rate 0.75 mL/min; λ = 214, 254 nm; τ_{minor} = 10.0 min; τ_{major} = 10.6 min). $[\alpha]^{rt}_D$= +2.7 (*c* = 0.6, $CHCl_3$, 88% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23 (d, *J* = 9.6 Hz, 3H), 1.62-1.89 (m, 4H), 2.65-2.84 (m, 2H), 3.95-4.00 (m, 1H), 4.14-4.20 (m, 1H), 7.17-7.29 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6, 32.2, 39.0, 44.0, 65.5, 68.8, 125.8, 128.3, 128.4, 141.9.

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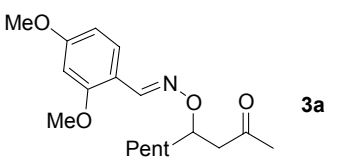
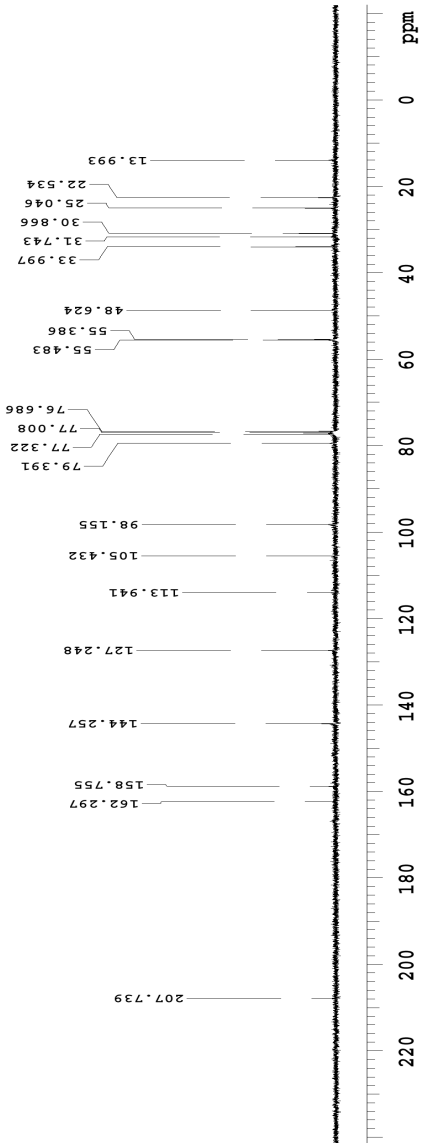
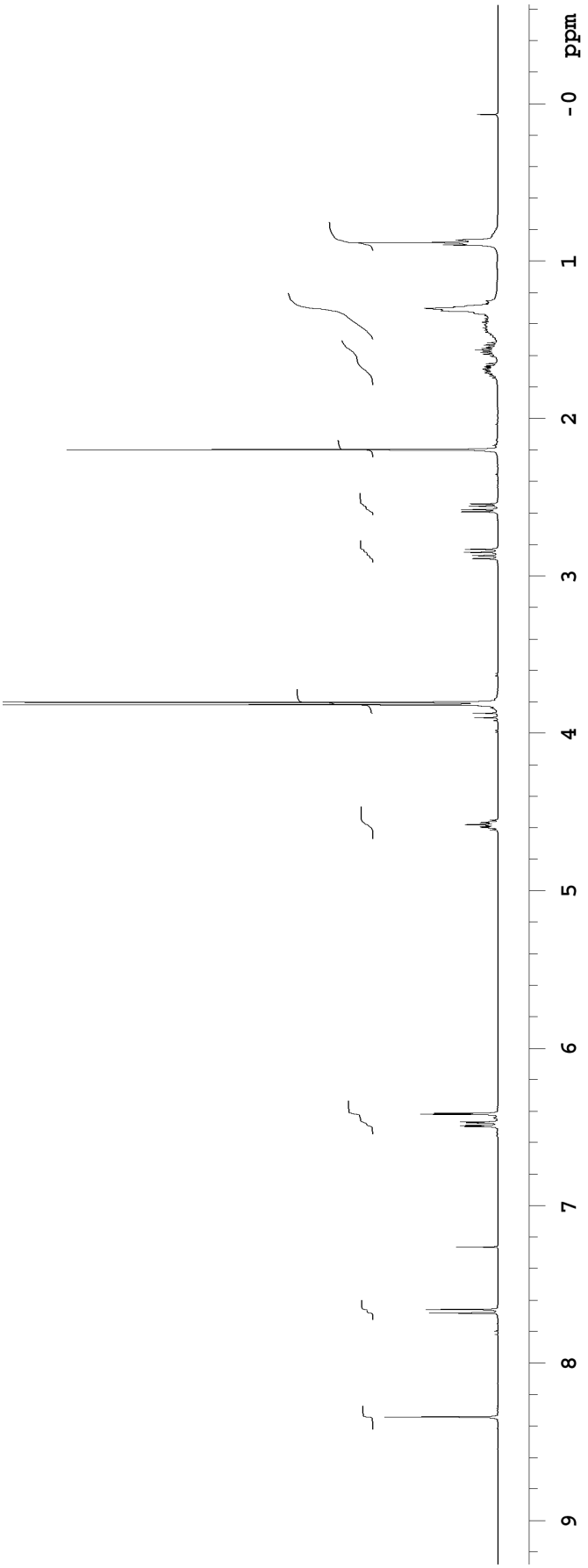
[5] H. Miyabe, A. Matsumura, K. Moriyama, and Y. Takemoto, *Org. Lett.*, 2004, **6**, 4631.
[6] G. Bartoli, M. Bosco, M. C. Bellucci, R. Dalpozzo, E. Marcantoni and L. Sambri, *Org. Lett.*, 2000, **2**, 45.
[7] We have used a modified version of the literature procedure: D. A. Evans, K. T. Chapman and E. M. Carreira, *J. Am. Chem. Soc*., 1988, **110**, 3560.

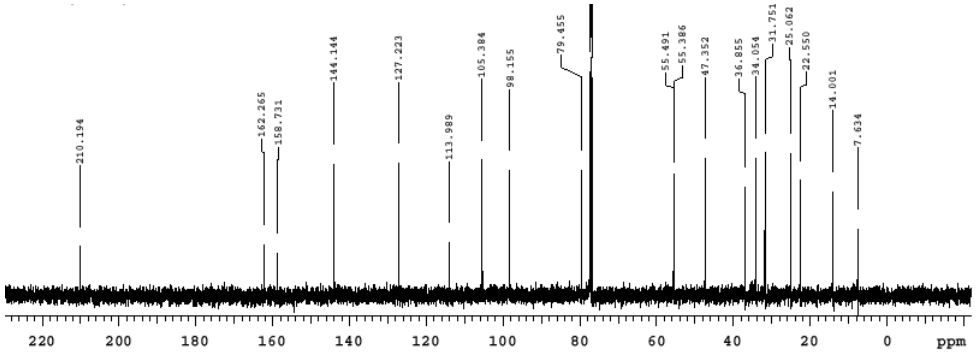
Representative NMR spectra



3a



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40
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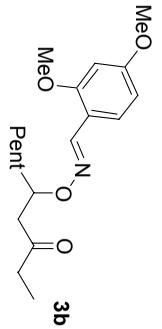
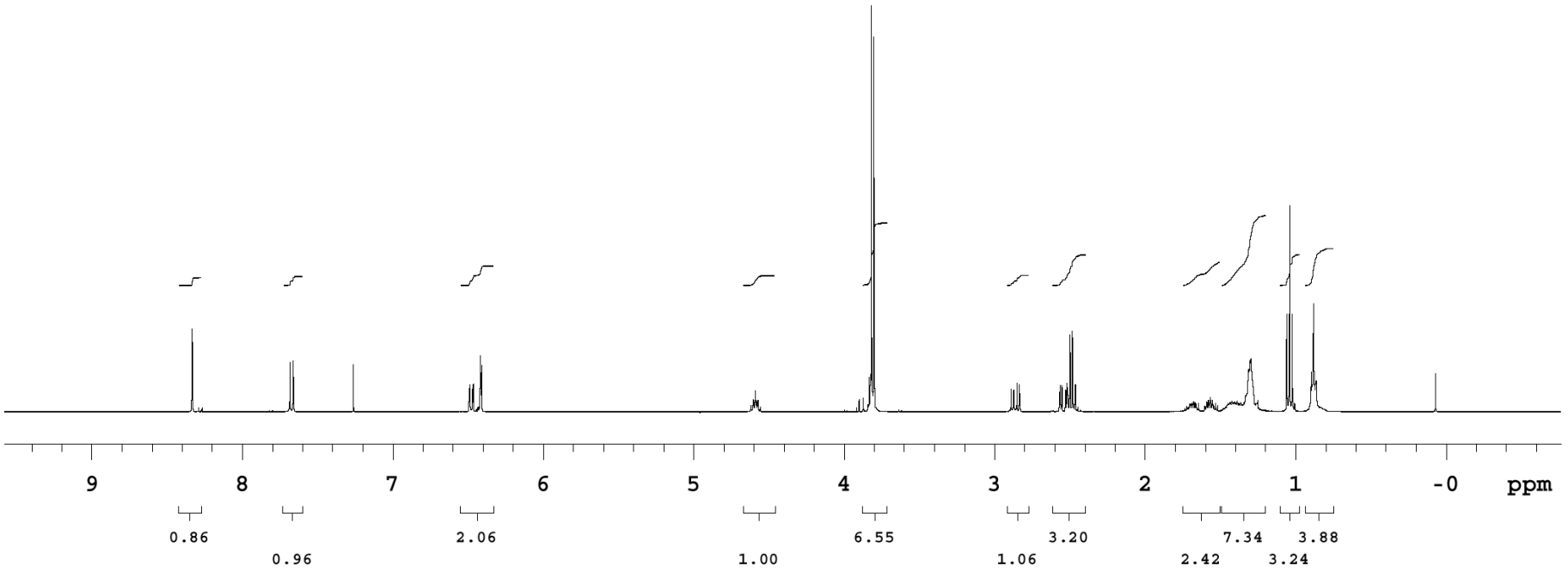
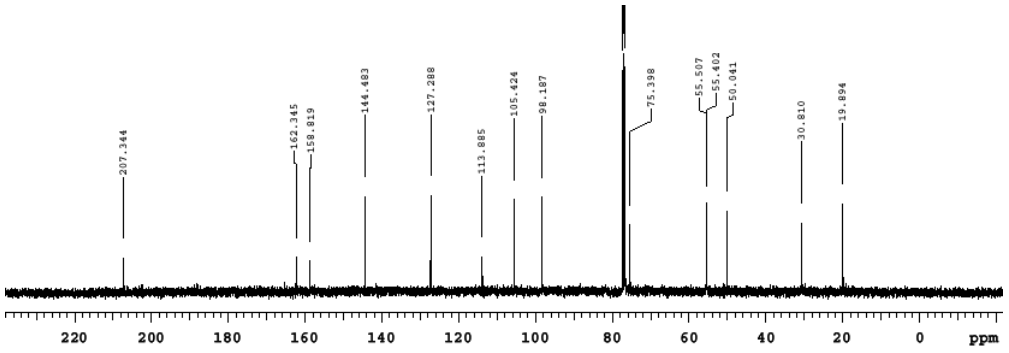
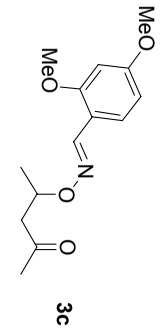
0
ppm

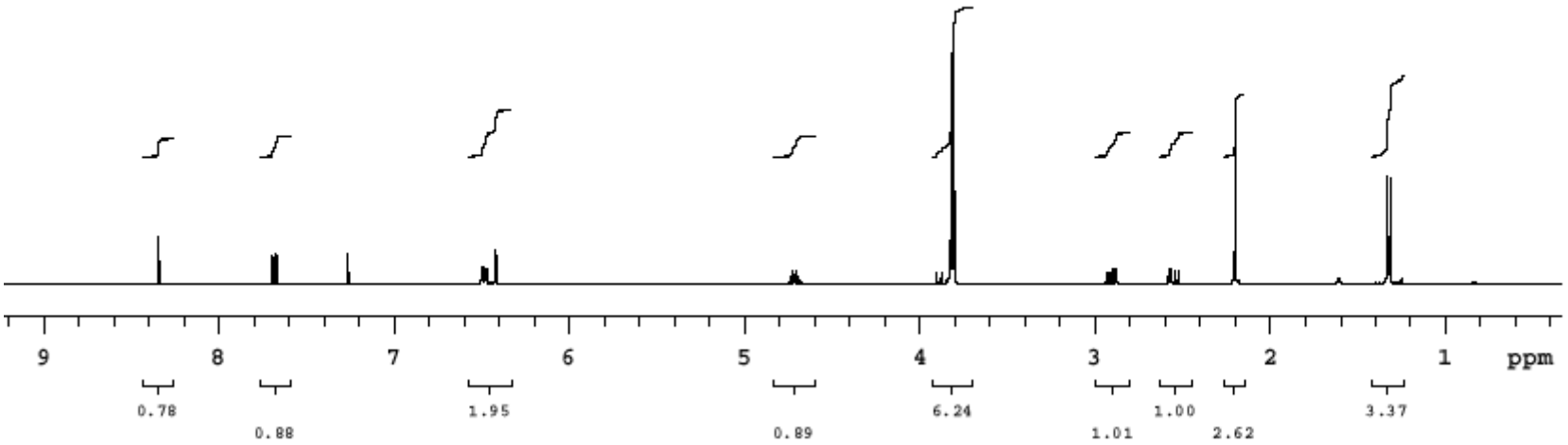

MeO
MeO
Pent
N
O
O
3b

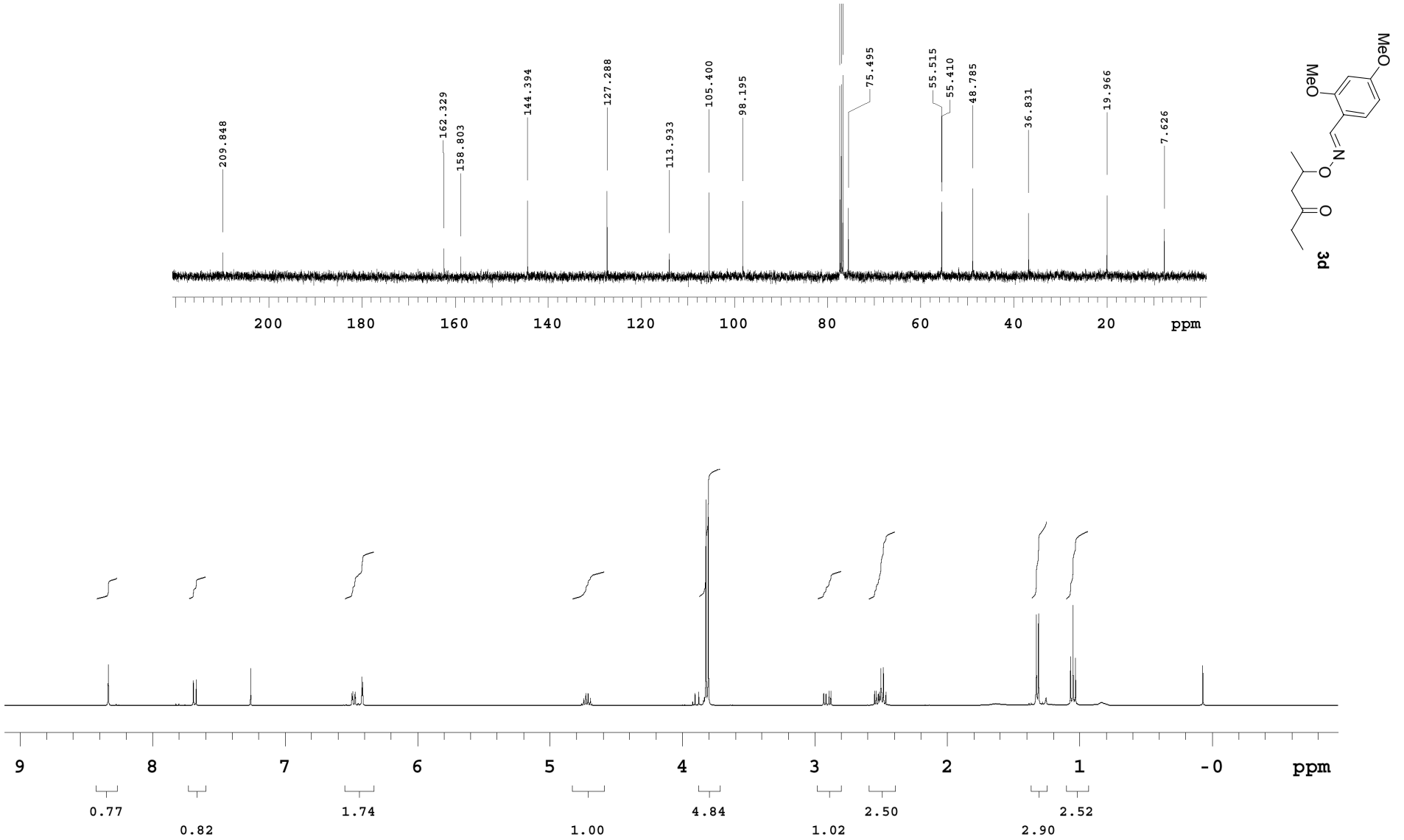

9
8
7
6
5
4
3
2
1
-0
ppm
0.86
0.96
2.06
1.00
6.55
1.06
3.20
2.42
7.34
3.24
3.88

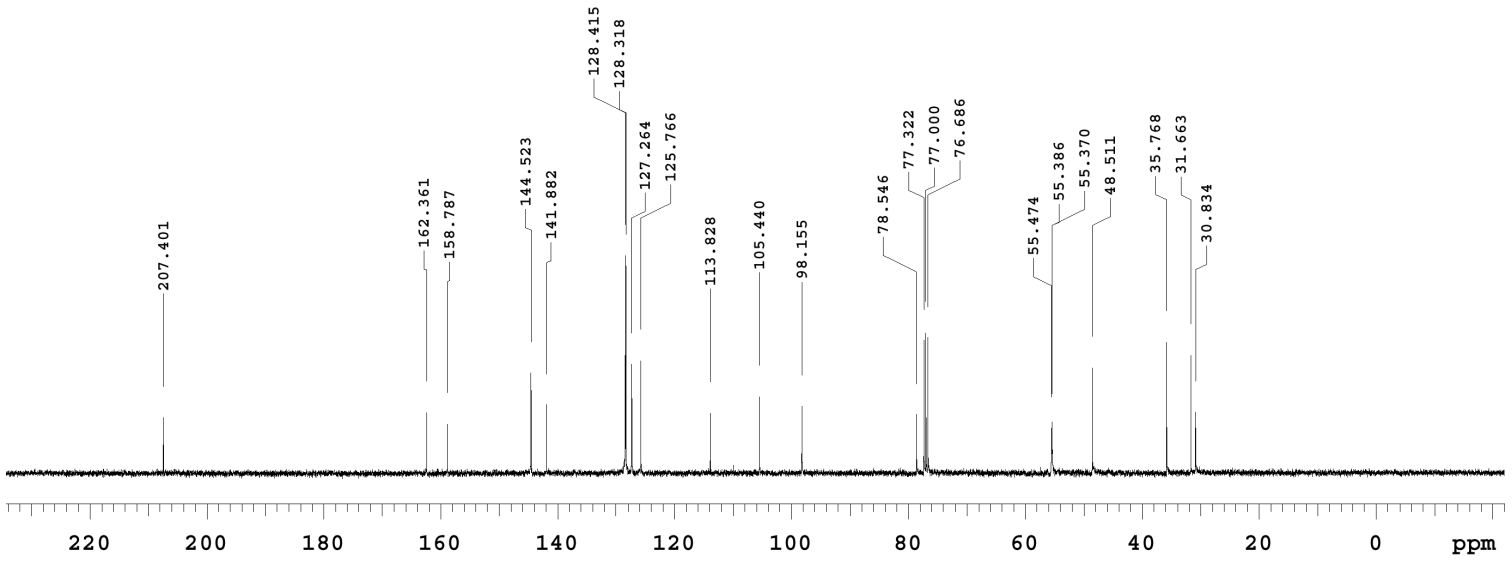

207.344
162.345
159.819
144.483
127.288
113.885
105.424
98.187
75.398
55.507
55.402
50.041
30.810
19.894
220
200
180
160
140
120
100
80
60
40
20
0
ppm

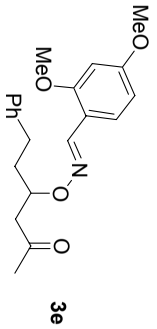

MeO
MeO
N
O
O

3c

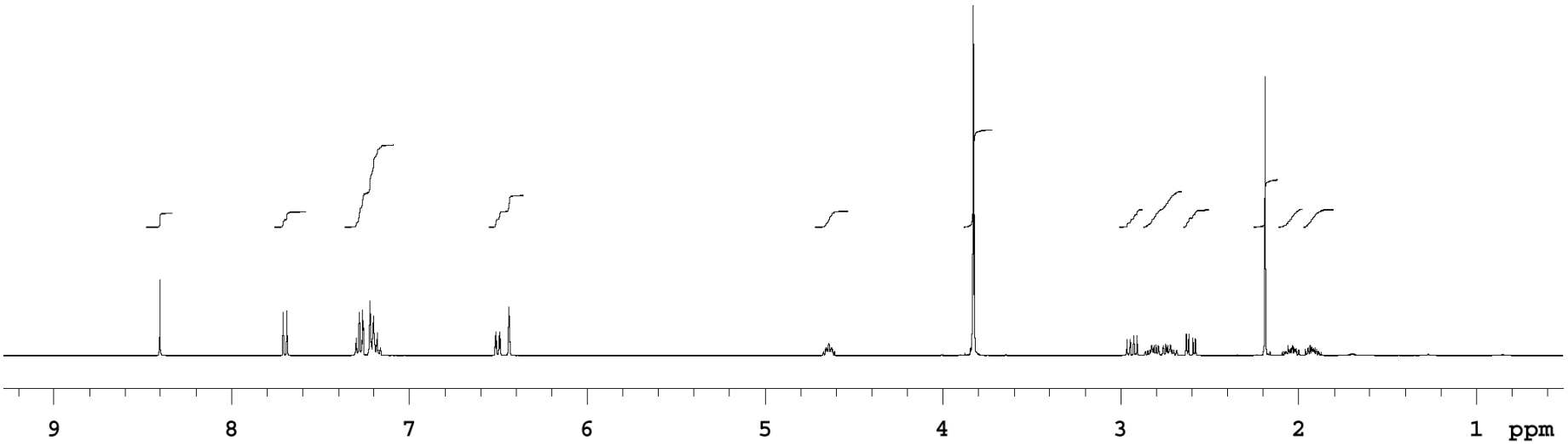

9
8
7
6
5
4
3
2
1
ppm
0.78
0.88
1.95
0.89
6.24
1.01
1.00
2.62
3.37

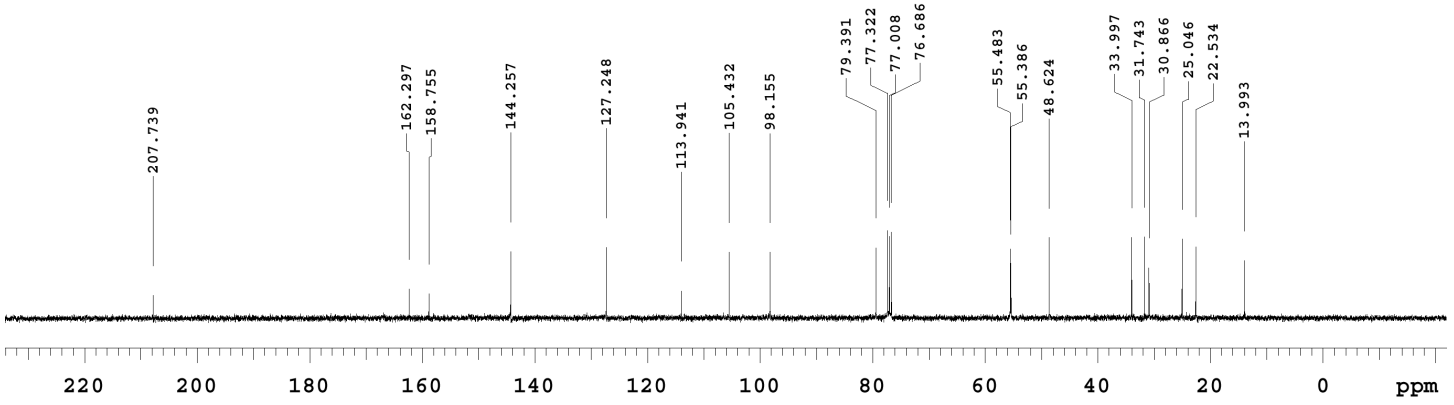

209.848
162.329
158.803
144.394
127.288
113.933
105.400
98.195
75.495
55.515
55.410
48.785
36.831
19.966
7.626
200
180
160
140
120
100
80
60
40
20
ppm
MeO
MeO
N
O
O
3d
9
8
7
6
5
4
3
2
1
-0
ppm
0.77
0.82
1.74
1.00
4.84
1.02
2.50
2.90
2.52

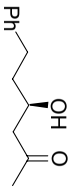

207.401
162.361
158.787
144.523
141.882
128.415
128.318
127.264
125.766
113.828
105.440
98.155
78.546
77.322
77.000
76.686
55.474
55.386
55.370
48.511
35.768
31.663
30.834
220
200
180
160
140
120
100
80
60
40
20
0
ppm


MeO
MeO
Ph
N
O
O

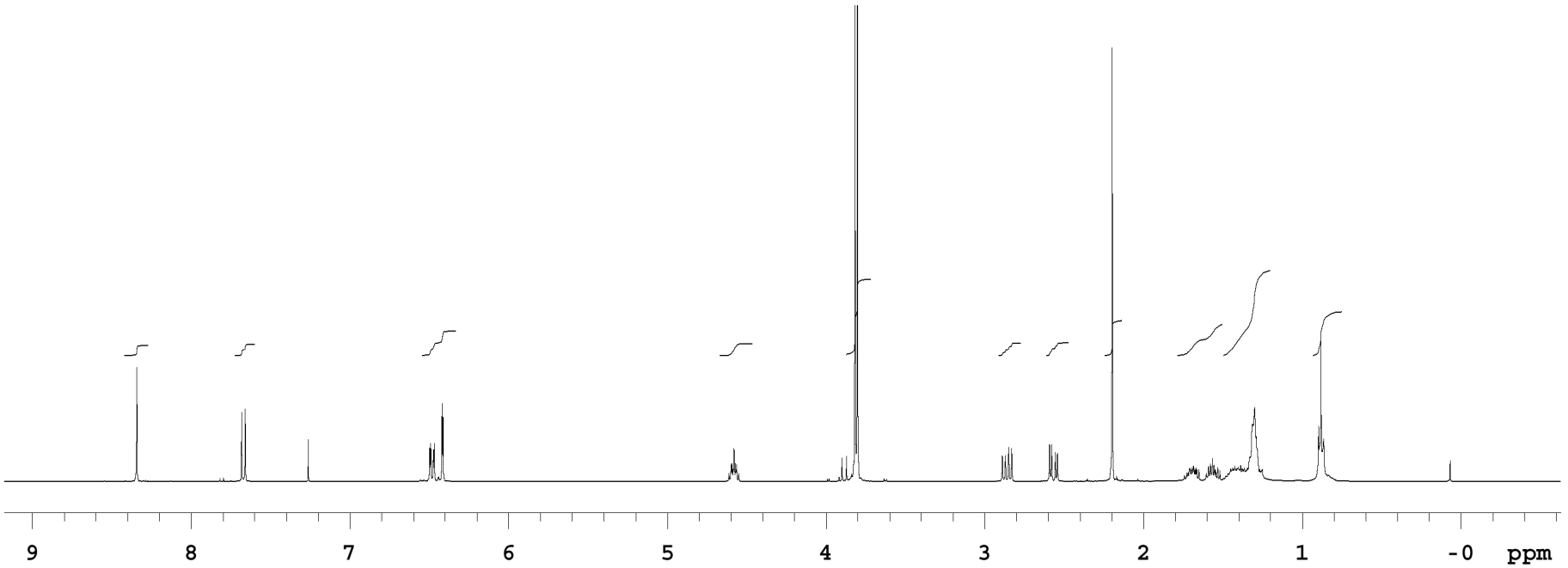
3e


9
8
7
6
5
4
3
2
1
ppm


207.739
162.297
158.755
144.257
127.248
113.941
105.432
98.155
79.391
77.322
77.008
76.686
55.483
55.386
48.624
33.997
31.743
30.866
25.046
22.534
13.993
220
200
180
160
140
120
100
80
60
40
20
0
ppm


Ph
OH
O

4


9
8
7
6
5
4
3
2
1
-0
ppm