Supporting Information

Biomimetic asymmetric Synthesis of (*R*)-GTRI-02 and (3*S*,4*R*)-3,4-Dihydronaphthalen-1(2*H*)-ones

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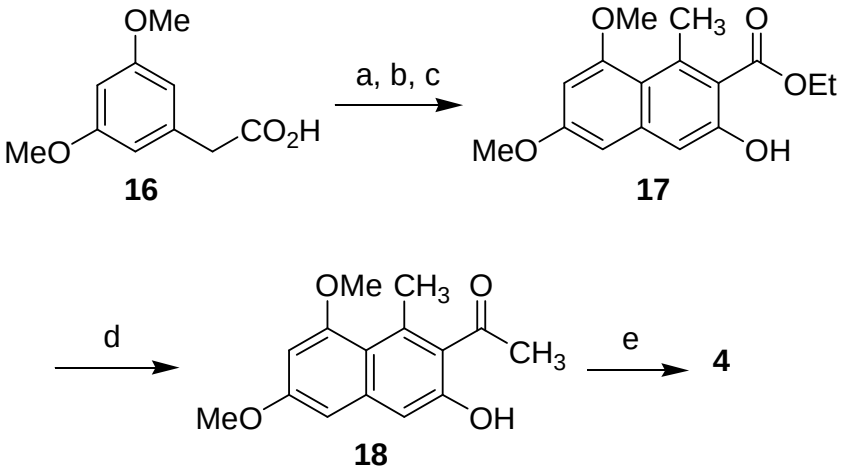
I. General Remarks

High-performance liquid chromatography (HPLC-DAD) was carried out on a HP 1100 chromatography system (Agilent). For preparative HPLC the column LiChrosorb RP-18 (250 x 10 mm) was used. GC-MS analysis was carried out on a HP 6890N Series GC-system (EI, 70 eV), equipped with a HP 5973 Network Mass Selective Detector (Agilent) using the column FS-Supreme-5 (CS-Chromatography-Service); L = 30 m, diameter = 0.25 mm, film = 0.25 µm. As temperature gradient $T_{0\ min}$ = 60 °C, $T_{3\ min}$ = 60 °C, $T_{14\ min}$ = 280 °C, $T_{19\ min}$ = 280 °C was used. Nuclear magnetic resonance (NMR) spectra were recorded at 24 °C on a DRX 400 (Bruker) operating at 400 and 100 MHz for ^{1}H and ^{13}C acquisitions, respectively. Chemical shifts (δ) of ^{1}H-NMR and ^{13}C-NMR spectra are reported in ppm with a solvent resonance as an internal standard (^{1}H-NMR: $CHCl_3$ 7.26, acetone-d_6 2.05, DMSO-d_6 2.50; ^{13}C-NMR: $CDCl_3$ 77.0, acetone-d_6 30.83, DMSO-d_6 39.43. The coupling constants (J) are given in Hz. CD spectra were recorded on a Jasco J-810 spectrophotometer (Jasco International Co). Optical rotation measurements were done on the polarimeter Modell 341 (PerkinElmer). FT-VCD and FT-IR spectra were recorded on a Bruker Tensor 27 FTIR spectrometer equipped with a Bruker PMA 50 VCD side-bench module with a resolution of 4 cm-1 in a 100 µm BaF2 cell. Molecular models of different geometries of (3a*S*,9b*R*)-7-Acetyl-2-(biphenyl-4-yl)-8-hydroxy-6-methyl-3a,4-dihydronaphtho[1,2-d][1,3,2]dioxaborol-5(9b*H*)-one **(20)** for quantum chemical calculations were obtained by applying the conformer search tool from SPARTAN 08 (Wavefunction, Inc., Irvine, CA, USA). Geometry optimization and calculation of IR/VCD spectra was performed using GAUSSIAN 09 (Gaussian, Inc., Wallingford, CT, USA).[6] X-ray single crystal diffractometer: Bruker AXS Apex II, CCD,

Microsource. All chemical reagents and solvents were obtained from Sigma-Aldrich, Fluka, Applichem, Roth or Acros. Glucose Dehydrogenase (GDH) was obtained from evocatal. Yields refer to chromatographically pure materials, conversions were calculated from the reactant-product ratios in crude NMR spectra. Bacterial expression and activity measurements were performed as described elsewhere.[1]

II. Experimental Section



Reagents and conditions: (a) $SOCl_2$, CH_2Cl_2, reflux, 1 h; (b) NaH, EAA, THF, rt, 1 h; (c) MSA, P_2O_5, rt, 3 h, 59; (d) MeLi, THF, rt, 1 h, 92%; (e) BBr_3, CH_2Cl_2, -80 °C to rt, 24 h, 45%.

Ethyl 3-hydroxy-6,8-dimethoxy-1-methyl-2-naphthoate (17)[2]

To a solution of phenylacetic acid **16** (3.69 g, 0.018 mol, 1 equiv) in dry CH_2Cl_2 (70 mL), thionyl chloride (2.73 mL, 2 equiv) was added. After 1 h at reflux, the solution was concentrated. To a suspension of NaH (2.26 g, 0.056 mol, 3 equiv) in THF (100 mL) ethyl acetoacetate (6.7 mL, 0.052 mol, 2.8 equiv) was added slowly. After stirring for 1 h,

a solution of the unpurified acid chloride in THF (50 mL) was added. After 1 h at room temperature 1 M HCl and EtOAc were added. The layers were separated and the aqueous layer was extracted three times with EtOAc. The organic layers were combined and washed with brine, dried over Mg_2SO_4, filtered, and concentrated. The residue was chromatographed (EtOAc/cyclohexane 15:85) to afford a tricarbonyl as clear oil. To a solution of this tricarbonyl in methansulfonic acid (70 mL), was added P_2O_5 (4.2 g). After 10 h at room temperature, ice was added and the resulting precipitate was filtered. The precipitate was then dissolved in EtOAc and washed with brine, dried over Mg_2SO_4 and concentrated. The residue obtained was chromatographed (EtOAc/cyclohexane 15:85) to afford ester **17** (3.23 g, 59% yield) as a pale yellow solid. R_f = 0.37 (EtOAc/cyclohexane 40:60).

^{1}H NMR ($CDCl_3$): δ (ppm) = 1.44 (t; J = 7.1 Hz, 3H, $CH_2\mathit{CH_3}$), 2.93 (s, 3H, Ph$\mathit{CH_3}$), 3.88 (s, 3H, O$\mathit{CH_3}$), 3.87 (s, 3H, O$\mathit{CH_3}$), 4.46 (q, J = 7.1 Hz, 2H, $\mathit{CH_2}CH_3$), 6.30 (d, J = 2.3 Hz, 1H, CH_{arom}), 6.49 (d, J = 2.3 Hz, 1H, CH_{arom}), 6.98 (s, 1H, CH_{arom}), 9.43 (s, 1H, OH).

^{13}C NMR ($CDCl_3$): δ (ppm) = 14.1 ($CH_2\mathit{CH_3}$), 22.8 (Ph$\mathit{CH_3}$), 55.2, 55.3 (O$\mathit{CH_3}$), 61.7 ($\mathit{CH_2}CH_3$), 97.0, 97.4, 108.9 (CH_{arom}), 115.9, 116.8, 139.8, 141.3 (C_{arom}), 155.0, 159.7, 160.2 (C-O_{arom}), 171.2 (1C, C=O).

GC-MS: t_R = 14.5 min, *m/z* (%) = 290 (100) [M^+], 261, 244, 216, 201.

1-(3-Hydroxy-6,8-dimethoxy-1-methylnaphthalen-2-yl)ethanone (18)

To a solution of ester **17** (3.23 g, 0.011 mol, 1 equiv) in dry THF (100 mL) at 0 °C, MeLi (33 mL, 1.6 M in Et_2O, 0.052 mmol, 4 equiv) was added dropwise. The solution was

stirred at this temperature for 10 min and then allowed to warm to rt. After 1 h, HCl (1 M), EtOAc were added. The aqueous layer was washed with EtOAc twice. The combined EtOAc layers were washed with brine, dried over Mg_2SO_4 and concentrated. The residue was chromatographed (EtOAc/cyclohexane 15:85) to obtain **18** (2.66 g, 92% yield) as a white solid. R_f = 0.23 (EtOAc/cyclohexane 40:60).

^{1}H NMR ($CDCl_3$): δ (ppm) = 2.64 (s, 3H, CO*CH$_3$*), 2.89 (s, 3H, Ph*CH$_3$*), 3.88 (s, 3H, O*CH$_3$*), 3.89 (s, 3H, O*CH$_3$*), 6.31 (d, J = 2.3 Hz, 1H, CH_{arom}), 6.49 (d, J = 2.3 Hz, 1H, CH_{arom}), 6.93 (s, 1H, CH_{arom}), 9.22 (s, 1H, OH).

^{13}C NMR ($CDCl_3$): δ (ppm) = 23.8 (Ph*CH$_3$*), 32.9 (CO*CH$_3$*), 55.3 (2C, O*CH$_3$*), 97.0, 97.5, 109.0 (CH_{arom}), 116.6, 126.0, 139.1, 139.7 (C_{arom}), 153.7, 159.8, 160.1 (C-O_{arom}), 207.9 (C=O).

GC-MS: t_R = 14.0 min, *m/z* (%) = 260 (62) [M^+], 245 (100).

1-(3,6,8-Trihydroxy-1-methylnaphthalen-2-yl)ethanone (4)

To a solution of compound **18** (1 g, 3.84 mmol, 1 equiv) in dry CH_2Cl_2 (100 mL) at -78 °C, BBr_3 (1 M in CH_2Cl_2, 19.2 mL, 19.2 mmol, 5 equiv) was added carefully over 2 min. After 5 min the solution was allowed to warm to rt. After 24 h, ice was added to the solution and it was further stirred for 30 min. The solution was diluted with sat. $NaHCO_3$ solution and the CH_2Cl_2 layer was dried over $MgSO_4$ and concentrated to recover 191 mg of compound **4**. The aqueous layer was further extracted with EtOAc (x 4). The combined EtOAc layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was chromatographed ($CHCl_3$/MeOH 95:5) to obtain **4** (153 mg, 45% yield) as a yellow solid. R_f = 0.18 ($CHCl_3$/MeOH 90:10).

^{1}H NMR (DMSO-d_6): δ (ppm) = 2.42 (s, 3H, COCH_3), 2.57 (s, 3H, PhCH_3), 6.28 (d, J = 2.3 Hz, 1H, CH_{arom}), 6.32 (d, J = 2.3 Hz, 1H, CH_{arom}), 6.66 (s, 1H, CH_{arom}), 9.34 (s, 1H, OH), 9.75 (s, 1H, OH), 9.79 (s, 1H, OH).

^{13}C NMR (DMSO-d_6): δ (ppm) = 19.5 (PhCH_3), 32.6 (COCH_3), 99.8, 99.9, 106.0 (CH_{arom}), 113.1, 129.6, 131.6, 138.2 (C_{arom}), 151.0, 156.0, 157.6 (C-OH_{arom}), 206.2 (C=O).

(*R*)-7-Acetyl-3,6-dihydroxy-8-methyl-3,4-dihydronaphthalen-1(2*H*)-one (GTRI-02, 3)[3]

In a flask, buffer (39 mL, Kpi = 50 mM, pH = 7.0, EDTA = 1 mM, DTT = 1 mM) was taken and bubbled with N_2. After 1 h, $NADP^+$ (19.2 mg, 25.8 µmol, 0.1 equiv), glucose (233 mg, 1290 µmol, 5 equiv) and glucose dehydrogenase (50 U) were added under N_2 atmosphere and the solution was stirred slowly to generate enough NADPH. After 1 h, compound **4** (60 mg, 258 µmol, 1 equiv) in 2-propanol (1.9 mL, 5% of the volume of buffer) was added to the solution, followed by addition of the enzyme T_4HN reductase (3.3 mL, 9 U, 2.7 U/mL). The solution was allowed to stir slowly under N2 atmosphere. After 24 h, H_2SO_4 (10% v/v) and EtOAc (20 mL) were added and the solution was stirred for 10 min. The denatured enzyme was filtered off and the solution obtained was extracted with EtOAc (x 3). The combined EtOAc layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue obtained was chromatographed ($CHCl_3$/MeOH 95:5) to afford impure compound **3** and **5** (0.5 mg, 0.7% yield).

GTRI-02 (**3**) was further purified by preparative HPLC to afford pure compound (6.1 mg, 10% yield).

Purification of GTRI-02 (3) by preparative HPLC:

Amount loaded: 30 mg dissolved in 500 µL of CH_3CN.

Eluting solvent: H_2O (0.1% HOAc)/CH_3CN 85/15.

Flow rate: 3.5 mL/min.

Injection volume: 100 µL.

Column: LiChrosorb RP-18 (250 x 10 mm).

t_R = 15.4 min.

R_f = 0.26 ($CHCl_3$/MeOH 90:10).

$[\alpha]^{20}_D$ = -16 (*c* 2.5, CH_3OH) (ref 3: $[\alpha]^{20}_D$ = -10 (*c* 0.2, CH_3OH).

^{1}H NMR (acetone-*d*$_6$): δ (ppm) = 2.42 (s, 3H, Ph*CH*$_3$), 2.45 (s, 3H, CO*CH*$_3$), 2.57 (ddd, *J* = 16.0, 8.1 Hz, 1H, H-4), 2.81 (dd, *J* = 16.0, 3.9 Hz, 1H, H-4), 2.91 (dd, *J* = 16.0, 7.5 Hz, 1H, H-2), 3.15 (dd, *J* = 16.0, 3.9 Hz, 1H, H-2), 4.28 (m, 1H, H-3), 6.72 (s, 1H, CH_{arom}), 9.67 (bs, 1H, OH).

^{13}C NMR (acetone-*d*$_6$): δ (ppm) = 19.1 (CH_3), 32.7 ($COCH_3$), 40.6 (C-4), 50.4 (C-2), 66.4 (C-3), 114.7 (C-5), 125.3 (C-8a), 131.9 (C-7), 139.6.5 (C-8), 146.5 (C-4a), 157.7 (C-6), 197.5 (C-1), 205.3 (*CO*CH_3).

CD: (c = 215 µmol.L^{-1}, l = 0.1 cm, acetonitrile), λ [nm] (Mol.CD) = 205 (-0.67), 215 (-8.53), 227 (-7.23), 239 (-3.11), 243 (-3.24), 273 (1.04), 297 (-0.96), 328 (0.55).

(3*S*,4*R*)-7-Acetyl-3,4,6-trihydroxy-8-methyl-3,4-dihydronaphthalen-1(2*H*)-one (5)

R_f = 0.12 ($CHCl_3$/MeOH 90/10).

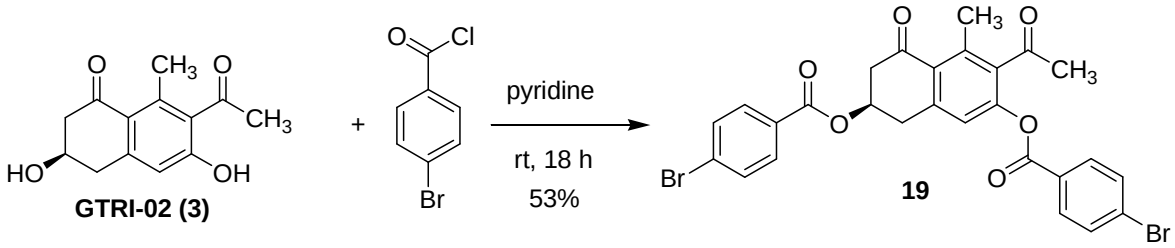
$[\alpha]^{20}_D$ = -0.08° (*c* 0.6, CH_3OH).

^{1}H NMR (acetone-*d*$_6$): δ (ppm) = 2.42 (s, 3H, Ph*CH*$_3$), 2.46 (s, 3H, CO*CH*$_3$), 2.77 (d, *J* = 4.2 Hz, 1H, H-2), 2.79 (d, *J* = 5.8 Hz, 1H, H-2), 4.31 (m, 1H, H-3), 4.83 (d, *J* = 2.3 Hz, 1H, H-4), 7.15 (s, 1H, CH_{arom}), 9.7 (bs, 1H, Ph*OH*).

^{13}C NMR (acetone-d_6): δ (ppm) = 18.9 (CH_3), 32.6 ($CO\mathit{CH_3}$), 46.1 (C-2), 70.3 (C-3), 71.6 (C-4), 113.8 (C-5), 124.2, 132.5, 139.2, 148.9 (C_{arom}), 157.9 (C-OH_{arom}), 196.7 (C-1, C=O), 205.3 ($\mathit{CO}CH_3$).

CD: (c = 1.79 mmol.L^{-1}, l = 1 cm, acetonitrile), λ [nm] (Mol.CD) = 232 (-0.14), 302 (-0.19), 344 (0.27).

(*R*)-6-Acetyl-5-methyl-4-oxo-1,2,3,4-tetrahydronaphthalene-2,7-diyl bis(4-bromobenzoate) (19)



Compound **3** (6.6 mg, 0.03 mmol, 1 equiv) and 4-bromo-benzoylchloride (16 mg, 0.07 mmol, 2.6 equiv) were dissolved in 300 µL of pyridine under nitrogen and stirred at room temperature. After 18 h, sat $NaHCO_3$ solution (1 mL) was added and extracted with EtOAc (3 x 5 mL), dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (EtOAc/cyclohexane 15:85) to obtain compound **19** (9 mg, 53% yield). R_f = 0.4 (EtOAc/cyclohexane 30/70).

^{1}H NMR ($CDCl_3$): δ (ppm) = 2.46 (s, 3H, Ph$\mathit{CH_3}$), 2.60 (s, 3H, $CO\mathit{CH_3}$), 3.01 (ddd, *J* = 16.7, 6.6, 1.2 Hz, 1H, H-4), 3.11 (dd, *J* = 16.7, 3.8 Hz, 1H, H-4), 3.33 (dd, *J* = 16.8, 5.9 Hz, 1H, H-2), 3.47 (dd, *J* = 16.8, 3.8 Hz, 1H, H-2), 5.65-5.69 (m, 1H, H-3), 7.17 (s, 1H,

CH_{arom}), 7.56 (d, *J* = 8.6 Hz, 2H, CH_{arom}), 7.66 (d, *J* = 8.6 Hz, 2H, CH_{arom}), 7.79 (d, *J* = 8.7 Hz, 2H, CH_{arom}), 7.96 (d, *J* = 8.7 Hz, 2H, CH_{arom}).

CD: (c = 50 µmol.L^{-1}, l = 1 cm, acetonitrile), λ [nm] (Mol.CD) = 203 (15.42), 239 (-10.92), 259 (18.49).

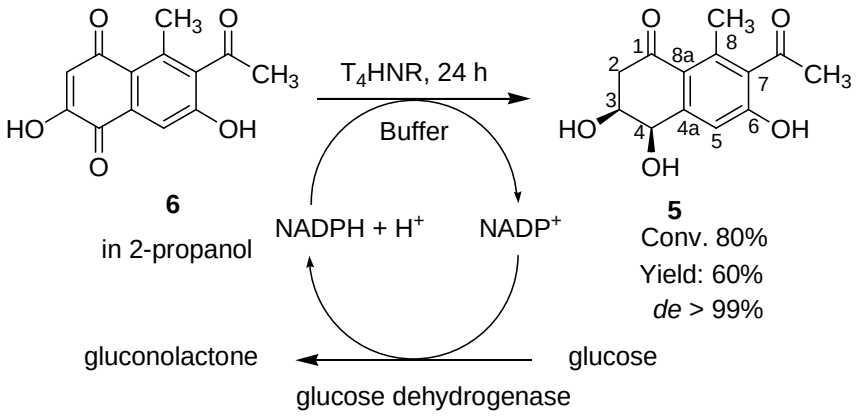
6-Acetyl-2,7-dihydroxy-5-methylnaphthalene-1,4-dione (6)

K_2CO_3 (143 mg, 1.03 mmol, 4 equiv) was added to a solution of compound **4** (60 mg, 0.26 mmol, 1 equiv) in DMF (1 mL). The resultant mixture was stirred at 25 °C for 15 h, open to air. Upon completion, the reaction contents were slowly acidified with concentrated HCl until a pH of 2 was reached. The resultant mixture was poured into water (5 mL) and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with water (2 × 5 mL), dried ($MgSO_4$) and concentrated. The resultant crude solid was purified by flash column chromatography (silica gel, Et_2O) to afford **6** (52 mg, 82% yield) as a yellow solid. R_f = 0.18 (MeOH/$CHCl_3$ 1:9).

^{1}H NMR (DMSO-*d*$_6$): δ (ppm) = 1.98 (s, 3H, PhCH_3), 2.00 (s, 3H, COCH_3), 5.57 (s, 1H, =CH), 6.96 (s, 1H, CH_{arom}), 10.76 (bs, 2H, OH).

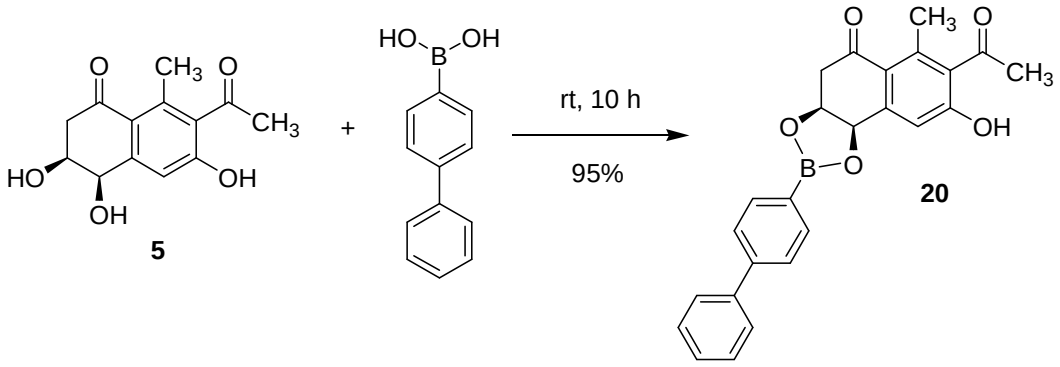
^{13}C NMR (DMSO-*d*$_6$): δ (ppm) = 17.7 (PhCH_3), 31.9 (COCH_3), 111.4 (=CH) 113.3 (CH_{arom}), 121.6, 133.6, 136.3, 137.6 (C_{arom}), 156.3, 157.0 (C-OH_{arom}), 181.2, 186.2 (C=O), 204.6 ($CO$$CH_3$).

Tetrahydroxynaphthalene reductase catalyzed reduction of hydroxynapthoquinone 6 to *cis*-ketodiol (5)



To a buffer solution (30 mL, Kpi = 50 mM, EDTA =1 mM, DTT = 1 mM), and nitrogen was bubbled for half an hour through it. Then, glucose (110 mg, 0.61 mmol, 5 equiv), $NADP^+$ (9.3 mg, 0.012 mmol, 0.1 equiv, 10 %) and glucose dehydrogenase (150 U) was added and the mixture was stirred slowly under nitrogen at room temperature. After 1 h, the substrate, **6** (30 mg, 0.12 mmol, 1 equiv) in 2-propanol (1.5 mL, 5 % v/v) was added slowly, while stirring. At last, 1,3,6,8-tetrahydroxynaphthalene reductase (1 mL, 11 U/mL, 11 U) was added and mixture was stirred slowly at rt. After 24 h, the solution was acidified with 10 % of H_2SO_4 (0.5 mL) and EtOAc (10 mL) was added and stirred vigorously, precipitating the enzyme. The solution was filtered with sintered glass with silica bed and washed with EtOAc (20 mL). The aqueous layer was extracted (x 2) with EtOAc and the combined organic layer was washed with brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford dark brown residue, conversion (80%, ^{1}H NMR) which was purified by using column chromatography ($CHCl_3$/MeOH 90/10) to yield 18 mg (60%) of (3*S*,4*R*)-7-Acetyl-3,4,6-trihydroxy-8-methyl-3,4-dihydronaphthalen-1(2*H*)-one (**5**).

(3a*S*,9b*R*)-7-Acetyl-2-(biphenyl-4-yl)-8-hydroxy-6-methyl-3a,4-dihydronaphtho[1,2-d][1,3,2]dioxaborol-5(9b*H*)-one (20)



Compound **5** (16 mg, 0.06 mmol, 1 equiv) and 4-biphenyl boronic acid (12.6 mg, 0.06 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (2mL). To this 4 Å mol sieves were added and the reaction mixture was stirred under nitrogen. After 10 h, the solution was filtered and the crude compound was used for ^{1}H NMR, CD, X-ray crystallography and VCD measurement.

^{1}H NMR ($CDCl_3$): δ (ppm) = 2.65 (s, 3H, CH_3), 2.72 (s, 3H, CH_3), 3.08 (dd, *J* = 14.8, 5.0 Hz, 1H, *CH_2*), 3.17 (dd, J = 14.8, 4.8 Hz, 1H, *CH_2*), 5.24-5.28 (m, 1H, CH_2*CH*(OB)), 5.65 (d, *J* = 7.6 Hz, 1H, Ph*CH*(OB)), 7.18 (s, 1H, CH_{arom}), 7.38 (t, *J* = 7.3 Hz, 1H, CH_{arom}), 7.46 (t, *J* = 7.5 Hz, 2H, CH_{arom}), 7.61-7-63 (m, 4H), 7.88 (d, *J* = 8.2 Hz, 2H, CH_{arom}), 10.65 (s, 1H, OH).

^{13}C NMR ($CDCl_3$): δ (ppm) = 21.4 (Ph*CH_3*), 32.7 (CO*CH_3*), 45.2 (CH_2), 74.4, 75.0 (CH), 117.1, 126.5, 127.2, 127.7, 128.8, 135.5 (CH_{arom}), 140.7, 141.7, 144.5, 145.3 (C_{arom}), 161.9 (C-OH_{arom}), 195.2, 207.1 (C=O).

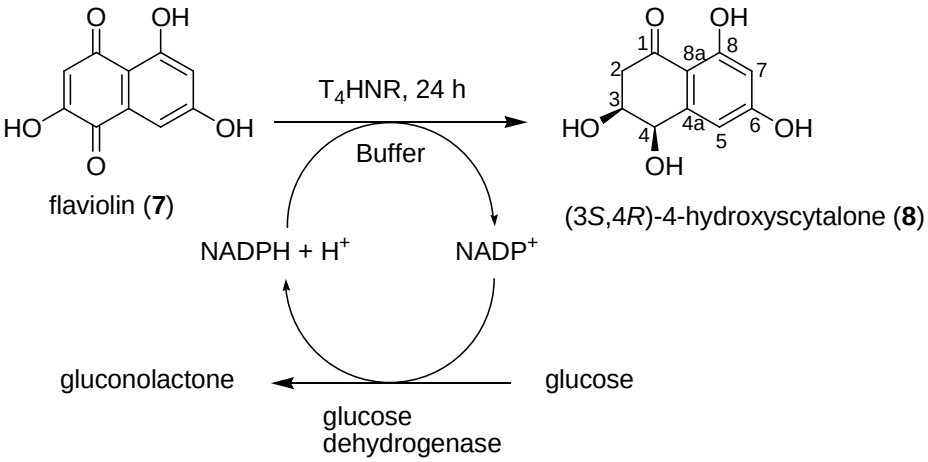
CD: (c = 54.6 µmol.L^{-1}, l = 1 cm, acetonitrile), λ [nm] (Mol.CD) = 211 (14.73), 246 (1.01), 277 (4.85).

Flaviolin (7)

Flaviolin was prepared in 96% yield by oxidation of tetrahydroxynaphthalene using method described elsewhere.[4] R_f = 0.15 (MeOH:$CHCH_3$, 1:9).

^{1}H NMR (acetone-d_6): δ (ppm) = 6.11 (s, 1H, enol-CH), 6.61 (d, J = 2.4 Hz, 1H, CH_{arom}), 7.08 (s, 1H, CH_{arom}), 9.92 (bs, 2H, PhOH), 12.53 (s, 1H, enol-OH).

Tetrahydroxynaphthalene reductase catalyzed reduction of flaviolin (7) to *cis*-4-hydroxyscytalone (8)



In a flask, buffer (10 mL, Kpi = 50 mM, pH = 7.0, EDTA = 1 mM, DTT = 1 mM) was taken, degassed thoroughly and followed by stirring under N_2. This was repeated several times. To this $NADP^+$ (3.8 mg, 4.8 µmol, 0.1 equiv), glucose (44 mg, 242 µmol, 5 equiv) and glucose dehydrogenase (50 U) were added under N_2 atmosphere and the solution was stirred slowly to generate enough NADPH. After 1 h, **7** (10 mg, 48.5 µmol, 1 equiv) in 2-propanol (0.5 mL, 5% of the volume of buffer) was added to the solution, followed by addition of the enzyme T_4HN reductase (1 mL, 11 U, 11 U/mL). The solution was allowed to stir slowly under N_2 atmosphere. After 24 h, few drops of H_2SO_4 (10% v/v)

and EtOAc (10 mL) were added and the solution was stirred for 10 min. The denatured enzyme was filtered off and the solution obtained was extracted with EtOAc (x 3). The combined EtOAc layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue obtained shows quantitative conversion (^{1}H NMR) and was chromatographed using $CHCl_3$/MeOH 90:10 to afford *cis*-**4**-hydroxyscytalone[5] (6.1 mg, 60% yield) as colourless solid. R_f = 0.15 ($CHCl_3$/MeOH 90/10).

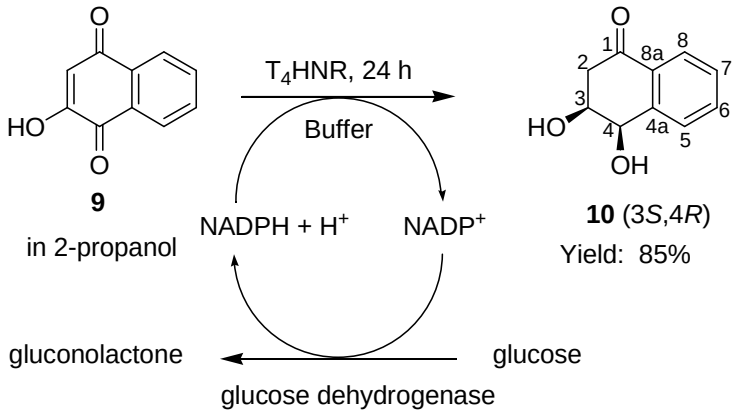
$[\alpha]^{20}_D$ = -51° (*c* 0.5, CH_3OH).

^{1}H NMR (acetone-*d_6*): δ (ppm) = 2.84 (dd, J = 4.7/1.8 Hz, 2H, CH_2, H-2), 4.14 (bs, 1H, OH), 4.33 (dt, J = 4.8/3.0 Hz, 1H, CH, H-3), 4.51 (bs, 1H, OH), 4.81 (d, J = 3.0 Hz, 1H, H-4), 6.22 (d, J = 2.3 Hz, 1H, CH_{arom}), 6.66 (dd, J = 2.3/1.0 Hz, 1H, CH_{arom}), 9.37 (bs, 1H, Ph*OH*) 12.76 (s, 1H, Ph*OH*).

^{13}C NMR (acetone-*d_6*): δ (ppm) = 44.8 (C-2), 71.4, 71.8 (C-3, C-4), 103.1 (CH_{arom}), 109.1 (CH_{arom}), 111.3, 149.5 (C_{arom}), 166.8, 166.9 (C-OH_{arom}), 202.6 (CO).

CD: (c = 142 µmol.L^{-1}, l = 1 cm, acetonitrile), λ [nm] (Mol.CD) = 236 (-2.60), 248 (-0.54), 268 (-2.44), 278 (-1.50), 300 (1.44), 324 (0.80).

Reduction of lawsone (9) with T_4HNR to (3*S*,4*R*)-3,4-dihydroxy-3,4-dihydronaphthalen-1(2*H*)-one (10)



To a buffer solution (78 mL, Kpi = 50 mM, EDTA =1 mM, DTT = 1 mM), nitrogen was bubbled for half an hour. Then, glucose (517 mg, 2.8 mmol, 5 equiv), $NADP^+$ (48 mg, 0.06 mmol, 0.1 equiv, 10 %) and glucose dehydrogenase (300 U) was added and the mixture was stirred slowly under nitrogen at room temperature. After 1 h, the substrate, lawsone (2-hydroxy-*p*-naphthaquinone) (100 mg, 0.57 mmol, 1 equiv) in 2-propanol (3.9 mL, 5 % v/v) was added slowly, while stirring. At last, 1,3,6,8-tetrahydroxynaphthalene reductase (5 mL, 3.3 U/mL, 16.5 U) was added and mixture was stirred slowly at rt. After 24 h, the solution was acidified with 10 % of H_2SO_4 (0.5 mL) and EtOAc (10 mL) was added and stirred vigorously, precipitating the enzyme. The solution was filtered with sintered glass with silica bed and washed with EtOAc (20 mL). The aqueous layer was extracted with EtOAc (x 2) and the combined organic layer was washed with brine (30 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed under reduced pressure to afford dark brown residue, which was purified by using column chromatography ($CHCl_3$/MeOH 90/10) to obtain **10** (92 mg, 90% yield) as colourless solid. R_f = 0.32 ($CHCl_3$/MeoH 90/10).

$[\alpha]^{20}_{D}$ = -0.25° (*c* 2.5, CH_3OH).

^{1}H NMR (acetone-*d_6* + D_2O): δ (ppm) = 2.80 (dd, J = 16.9/3.5 Hz, 1H, CH_2), 2.90 (dd, J = 16.9/6.5 Hz, 1H, CH_2), 4.37 (td, J = 6.5/3.2 Hz, 1H, 3-H), 4.96 (d, J = 2.8 Hz, 1H, 4-H), 7.40 (dt, J = 7.5/1.5 Hz, 1H, CH_{arom}), 7.60-7.68 (m, 2H, CH_{arom}), 7.86 (dd, J = 7.9/1.2 Hz, 1H, CH_{arom}).

^{13}C NMR (acetone-*d_6* + D_2O): δ (ppm) = *δ* 45.0 (C-2), 71.4, 71.5 (C-3, C-4), 127.3, 129.3, 130.2, 135.6, (CH_{arom}) 133.1, 145.5 (C_{arom}), 198.2 (CO).

CD: (c = 2.97 mmol.L^{-1}, l = 0.1 cm, acetonitrile), λ [nm] (Mol.CD) = 220 (-7.41), 240 (-0.15), 256 (-2.40), 266 (-1.53), 288 (-4.97), 318 (1.62).

(3a*S*,9b*R*)-2,2-dimethyl-3a,4-dihydronaphtho[1,2-d][1,3]dioxol-5(9b*H*)-one (11)

The diol **10** (10 mg, 0.05 mmol) was dissolved in dry CH_2Cl_2 (700 µL) and to it at 0 °C was added 2,2-dimethoxypropane (34 µL, 0.27 mmol, 5 equiv) followed by a catalytic amount of p-toluenesulfonic acid (2 mg). The reaction mixture was stirred for 30 min at rt. The resulting mixture was quenched with sat. aq. $NaHCO_3$, and extracted with CH_2Cl_2. Combined organic layer was washed with brine, dried ($MgSO_4$) and removed under reduced pressure. The residue was purified by column chromatography (EtOAc/cyclohexane 30/70) to obtain **9** (10.4 mg, 85% yield) and used for VCD-IR measurements.

^{1}H NMR ($CDCl_3$): *δ* (ppm) = 1.06 (d, J = 0.5 Hz, 3H, CH_3), 1.44 (d, J = 0.5 Hz, 3H, CH_3), 2.91 (dd, J = 17.0/3.9 Hz, 1H, H-2), 3.13 (dd, J = 17.0/3.7 Hz, 1H, H-2), 4.79 (td, J

= 5.0/3.9 Hz, 1H, H-3), 5.27 (d, J = 5.0 Hz, 1H, H-4), 7.40-7.45 (m,. 1H, CH_{arom}), 7.57-7.65 (m, 2H, CH_{arom}), 7.97 (dd, J = 7.9/1.4 Hz, 1H, CH_{arom}).

III. CD spectra

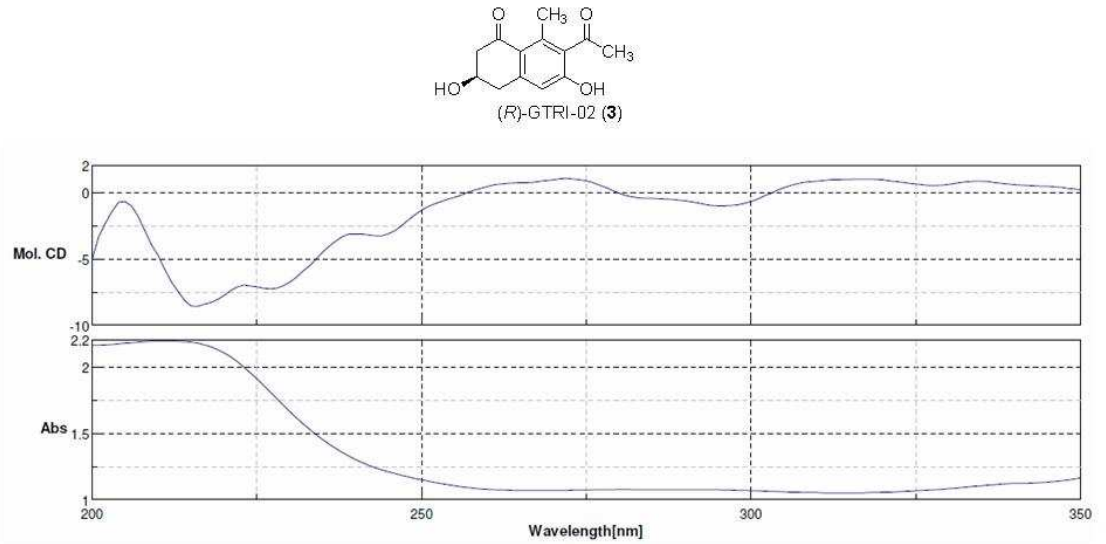


Figure 1. CD spectrum of (*R*)-**GTRI-02** in CH_3CN.

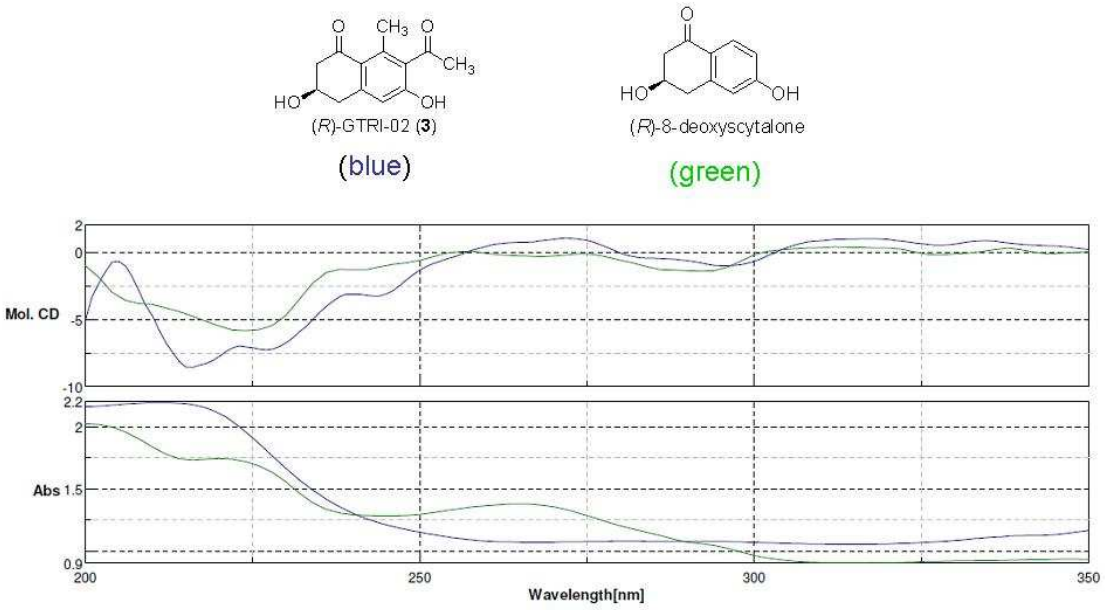


Figure 2. Comparison of CD spectrum of (*R*)-**GTRI-02** (**3**) and (*R*)-8-deoxyscytalone[1] in CH_3CN.

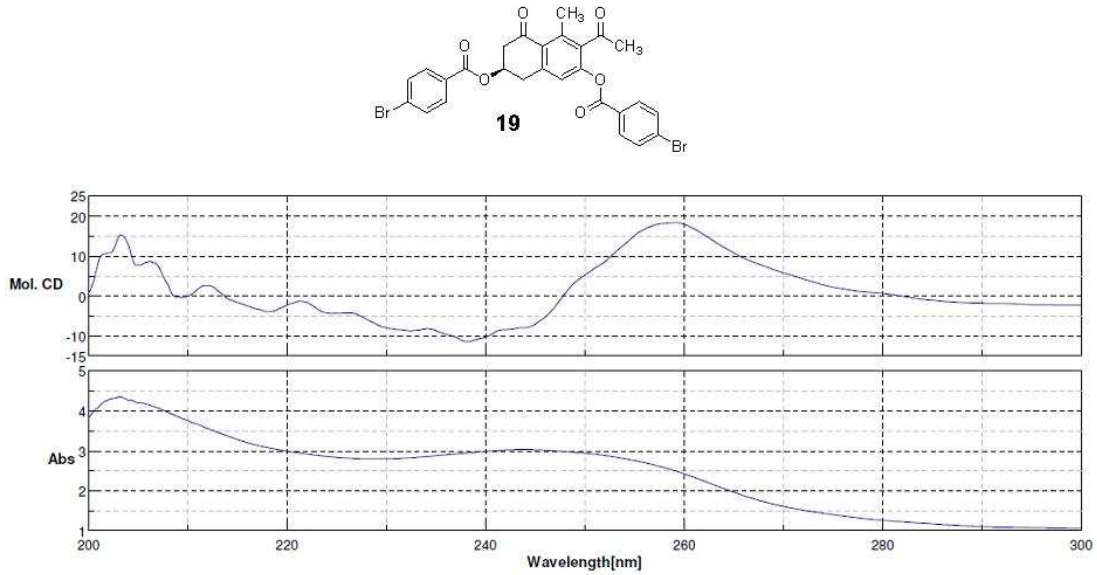


Figure 3. CD spectrum of *bis*-bromobenzoate derivative (**19**) of (*R*)-**GTRI-02** (**3**) in CH_3CN.

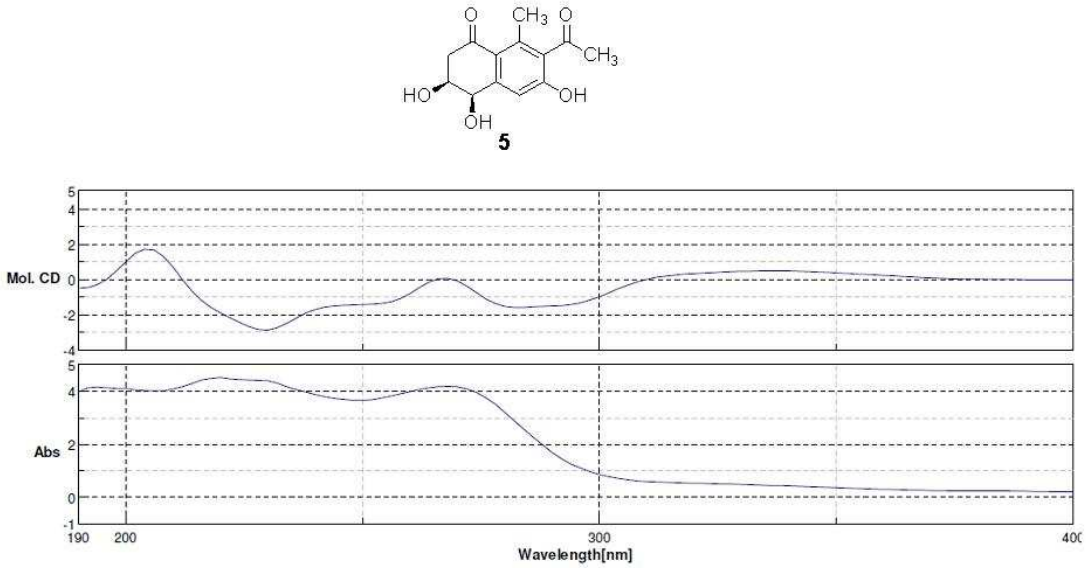


Figure 4. CD spectrum of *cis*-ketodiol (**5**) in CH_3CN.

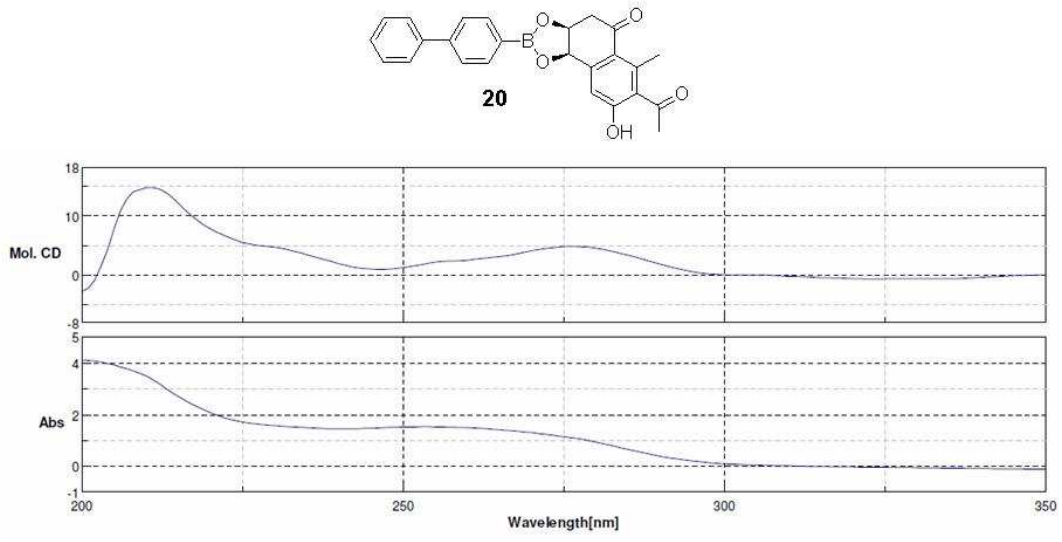


Figure 5. CD spectrum of biphenyl-borodioxa derivative **20** of *cis*-ketodiol **5** in CH_3CN.

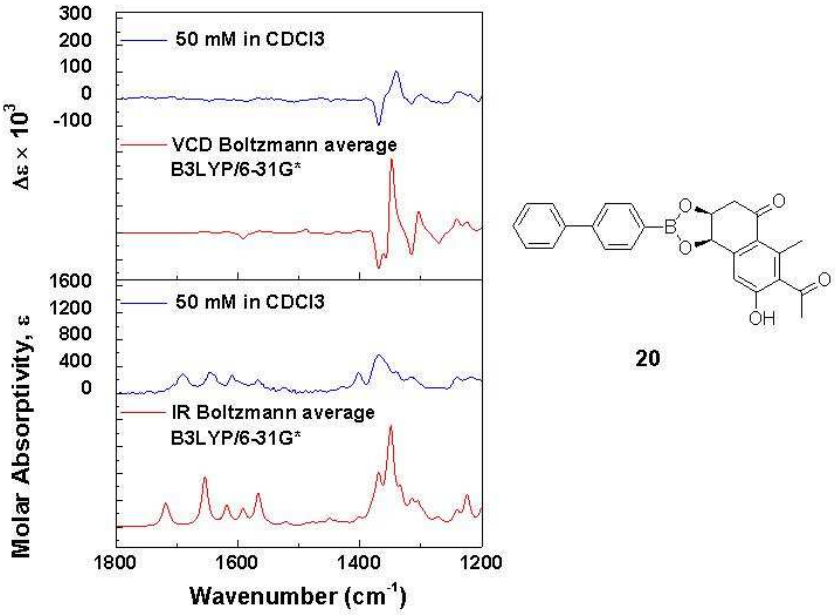


Figure 6. Experimental IR and VCD spectra of the biphenyl-borodioxa derivative **20** of *cis*-ketodiol **5** (50 mM in $CDCl_3$) and the theoretical IR and VCD spectra (B3LYP/6-31G*) calculated for the (3*S*,4*R*)-configured **20**. Good agreement in frequencies and sign between calculated and observed spectra allows for assignment of the absolute configuration.[6]

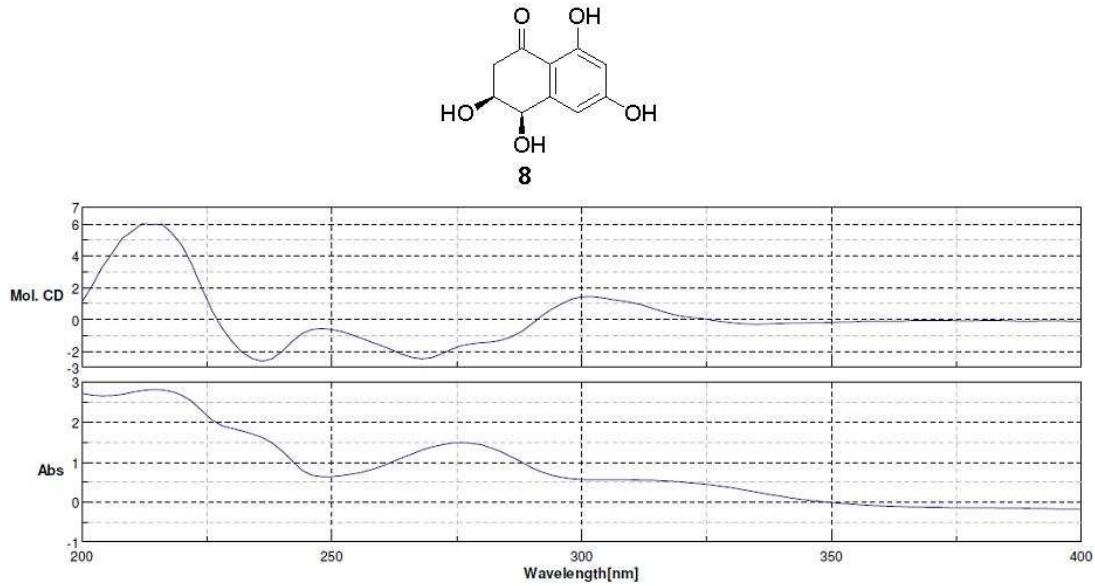


Figure 7. CD spectrum of (3*S*,4*R*)-cis-4-hydroxyscytalone (**8**) in CH_3CN.

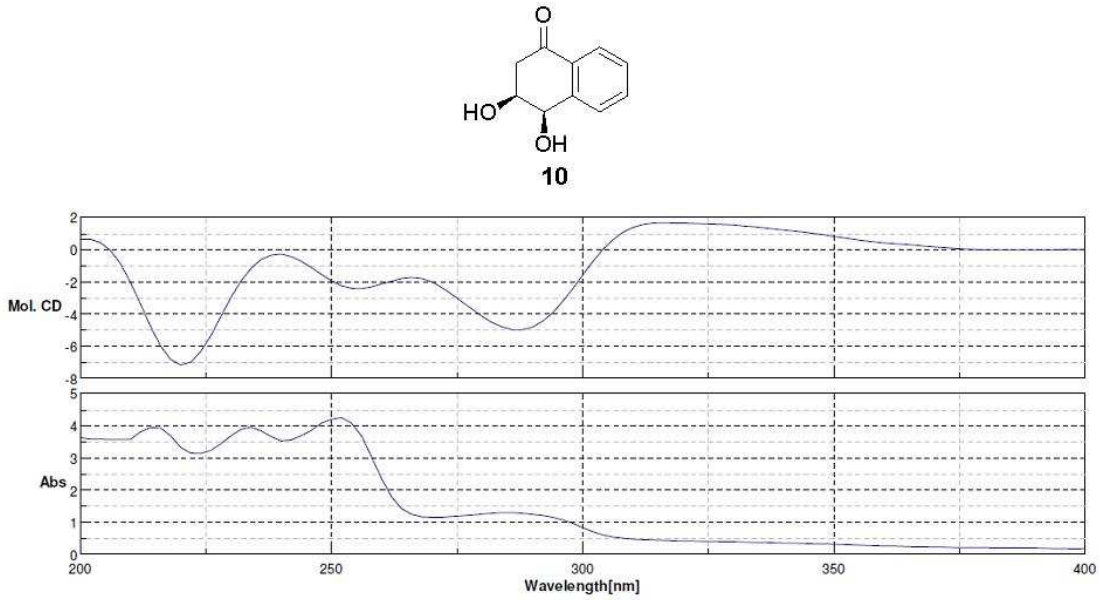
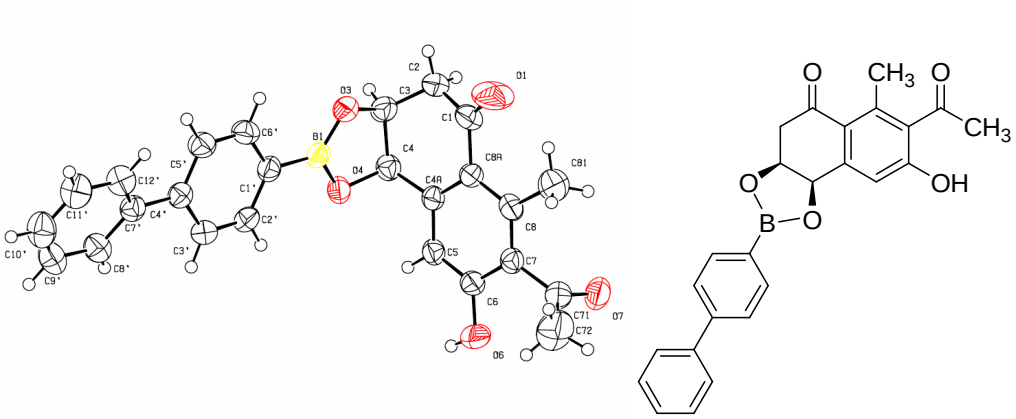


Figure 8. CD spectrum of (3*S*,4*R*)-cis-ketodiol (**10**) in CH_3CN.

IV. X-ray crystal structure analysis of 20

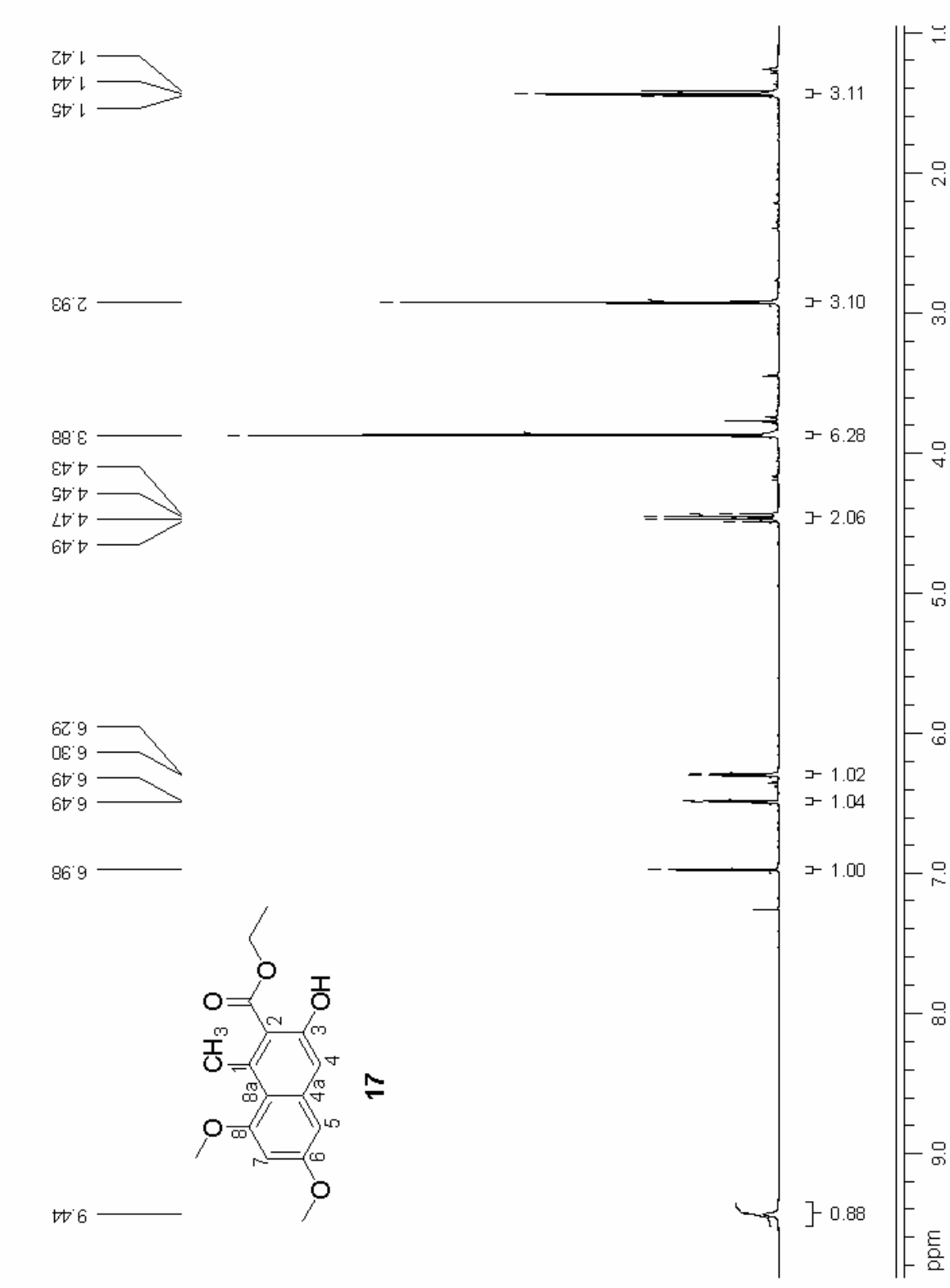


X-ray crystal structure analysis of **20**: formula $C_{25}H_{21}BO_5$, *M* = 412.24, colorless crystal 0.30 x 0.10 x 0.05 mm, *a* = 7.14747(10), *b* = 15.2642(2), *c* = 19.1468(3) Å, β = 90º, *V* = 2088.92(5)Å^3, ρcalc = 1.311 g cm^{-3}, μ = 0.090 mm^{-1}, *Z* = 4, orthorhombic, space group $P2_12_12_1$ (No. 19), λ = 0.71069 Å, *T* = 295(5) K, ω and φ scans, 29097 reflections collected (*±h: -9/+9, ±k: -19/18, ±l: -23/+24*), [(sinθ)/λ] = 0.60 Å^{-1}, 4794 independent (R_{int} = 0.033) and 3552 observed reflections [$I > 2\sigma(I)$], 281 refined parameters, *R* = 0.043, *wR*2 = 0.103, max. (min.) residual electron density 0.21 (-0.15) e Å^{-3}, Flack parameter 0.7(11), hydrogen atoms at O6 from difference fourier calculations, others calculated and refined as riding atoms. The structure was solved by direct methods with SHELXS-97.[7] In the subsequent full-matrix least-squares refinements using SHELXL-97[4] based on all data and 159 variable parameters all non-hydrogen atom positions were refined anisotropically, the calculated H-atom positions were treated using the riding model. CCDC 851647 contains the supplementary crystallographic data which can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam,ac,uk/data_request/cif, or from The Cambridge Crystallographic Data Centre 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)-1223–336–033; or deposit@ccdc.cam.ac.uk.

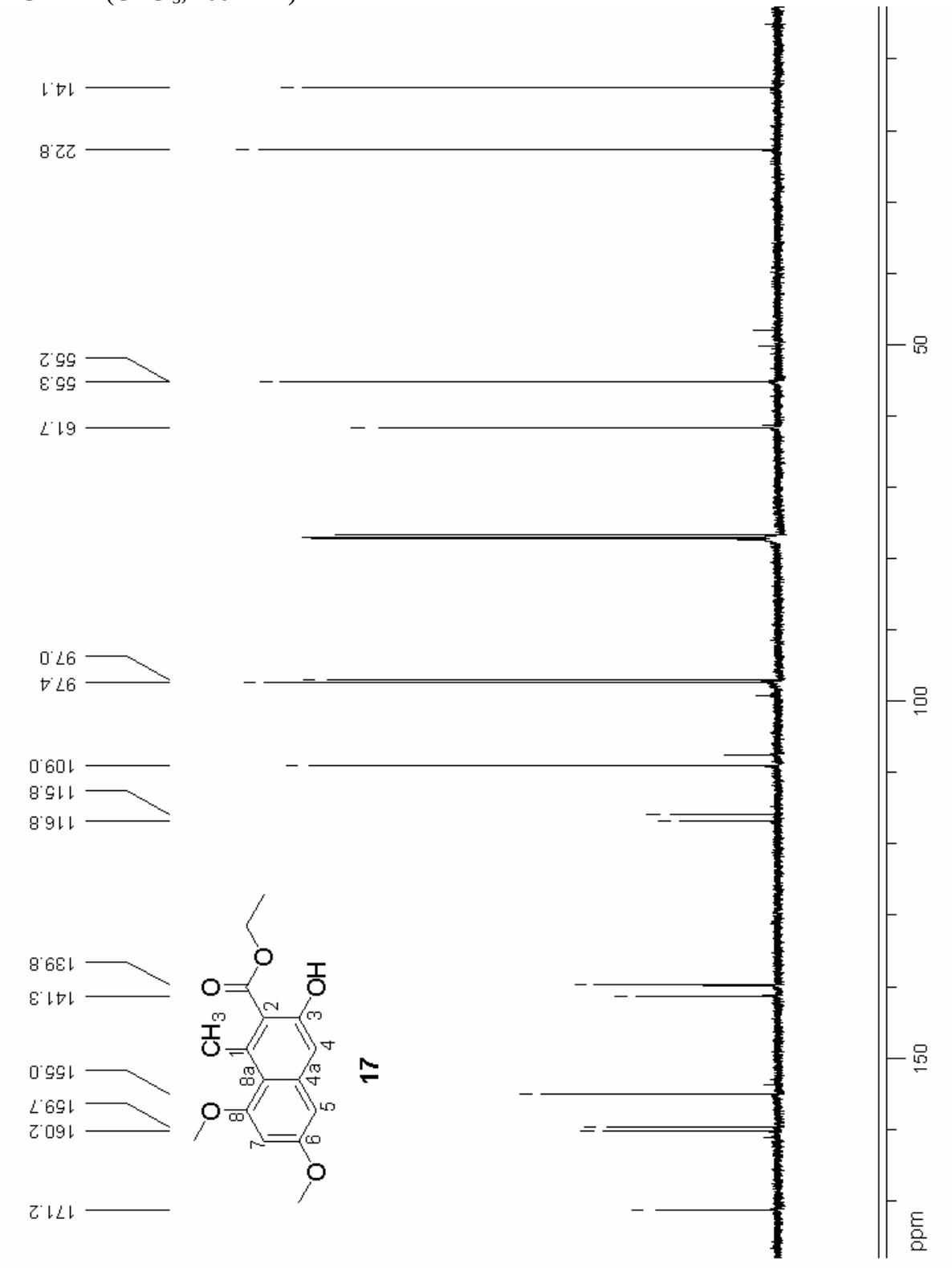
V.

^{1}H and ^{13}C NMR

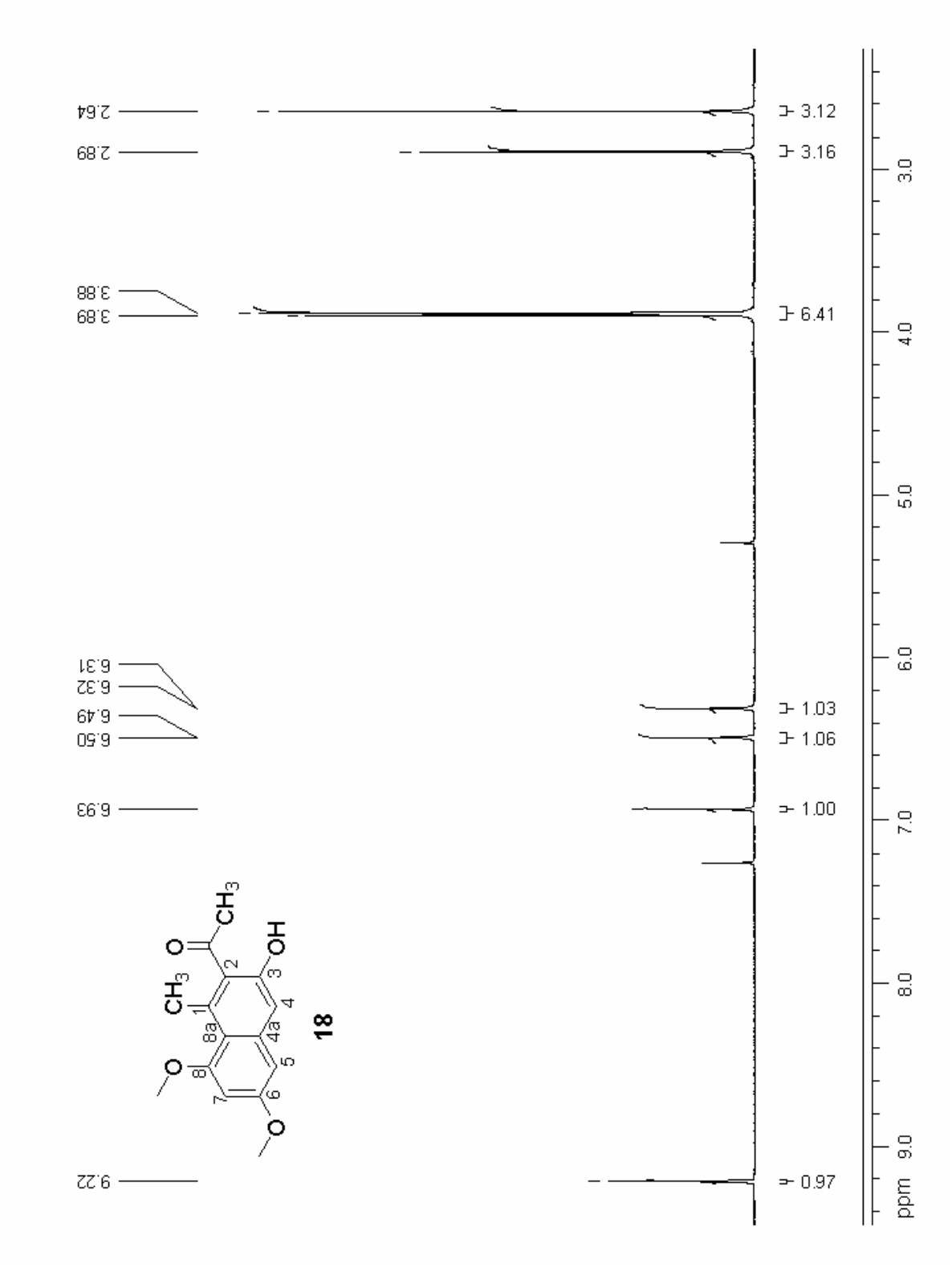
^{1}H NMR ($CDCl_3$, 400 MHz)



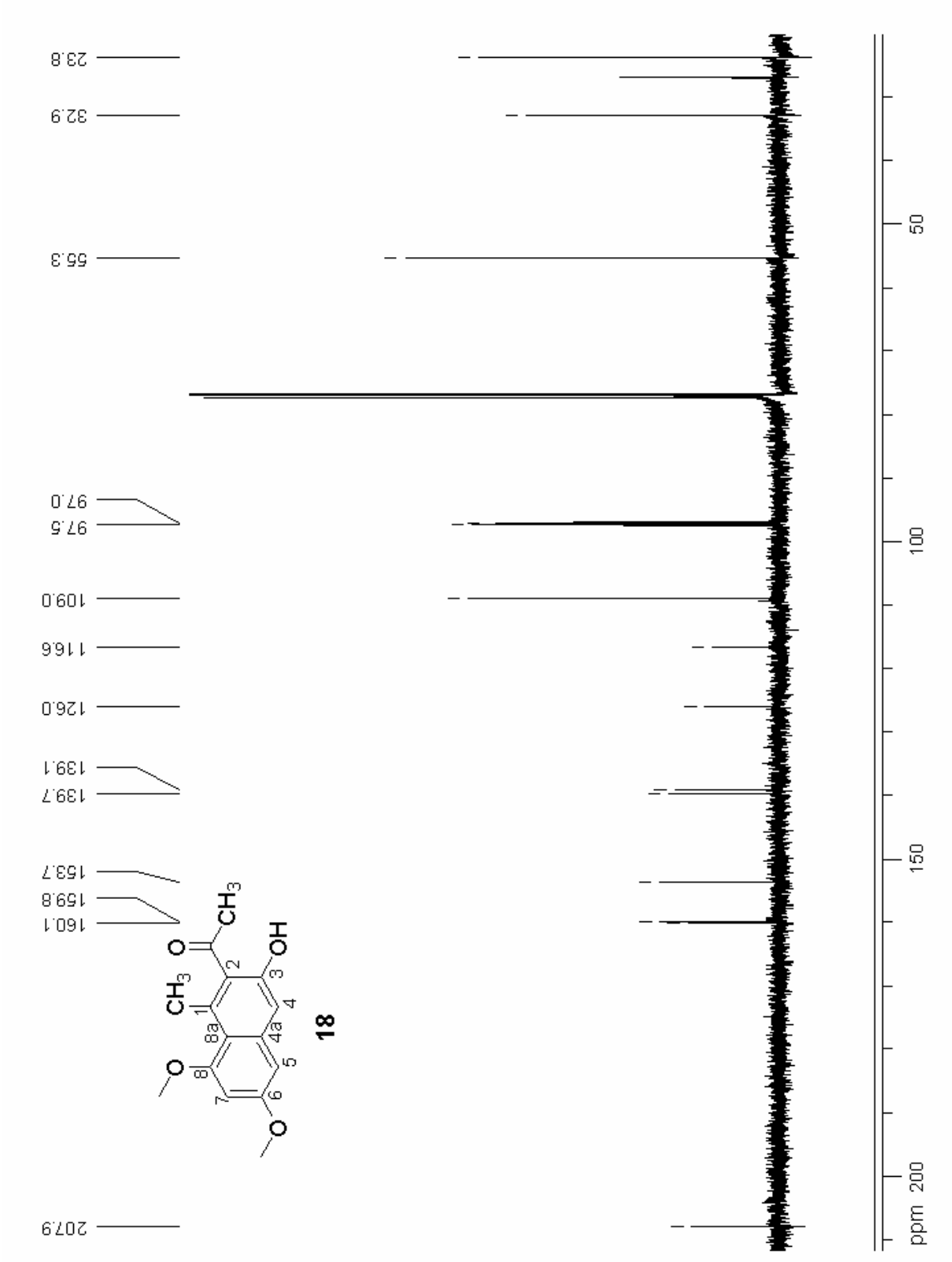
^{13}C NMR ($CDCl_3$, 100 MHz)



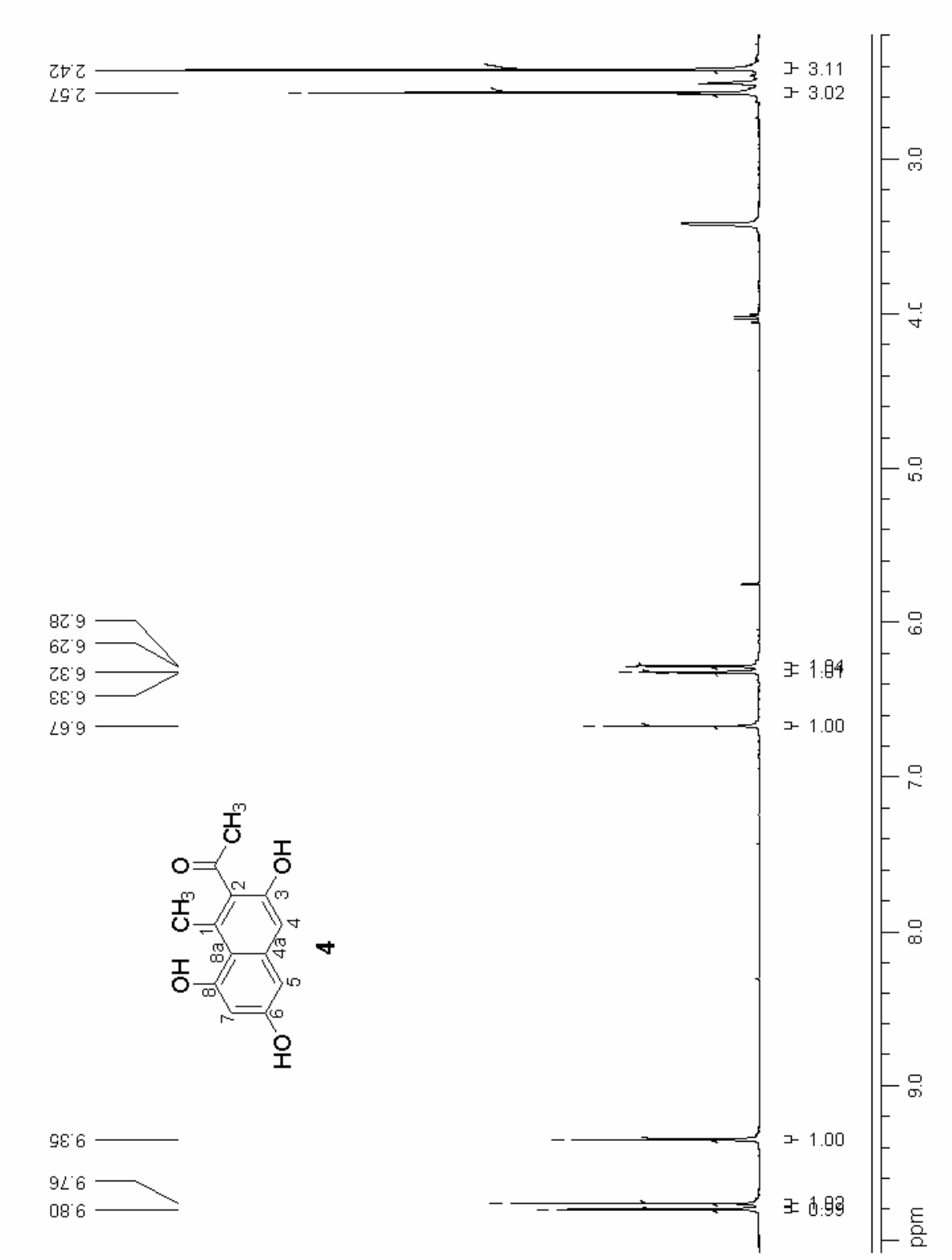
^{1}H NMR ($CDCl_3$, 400 MHz)



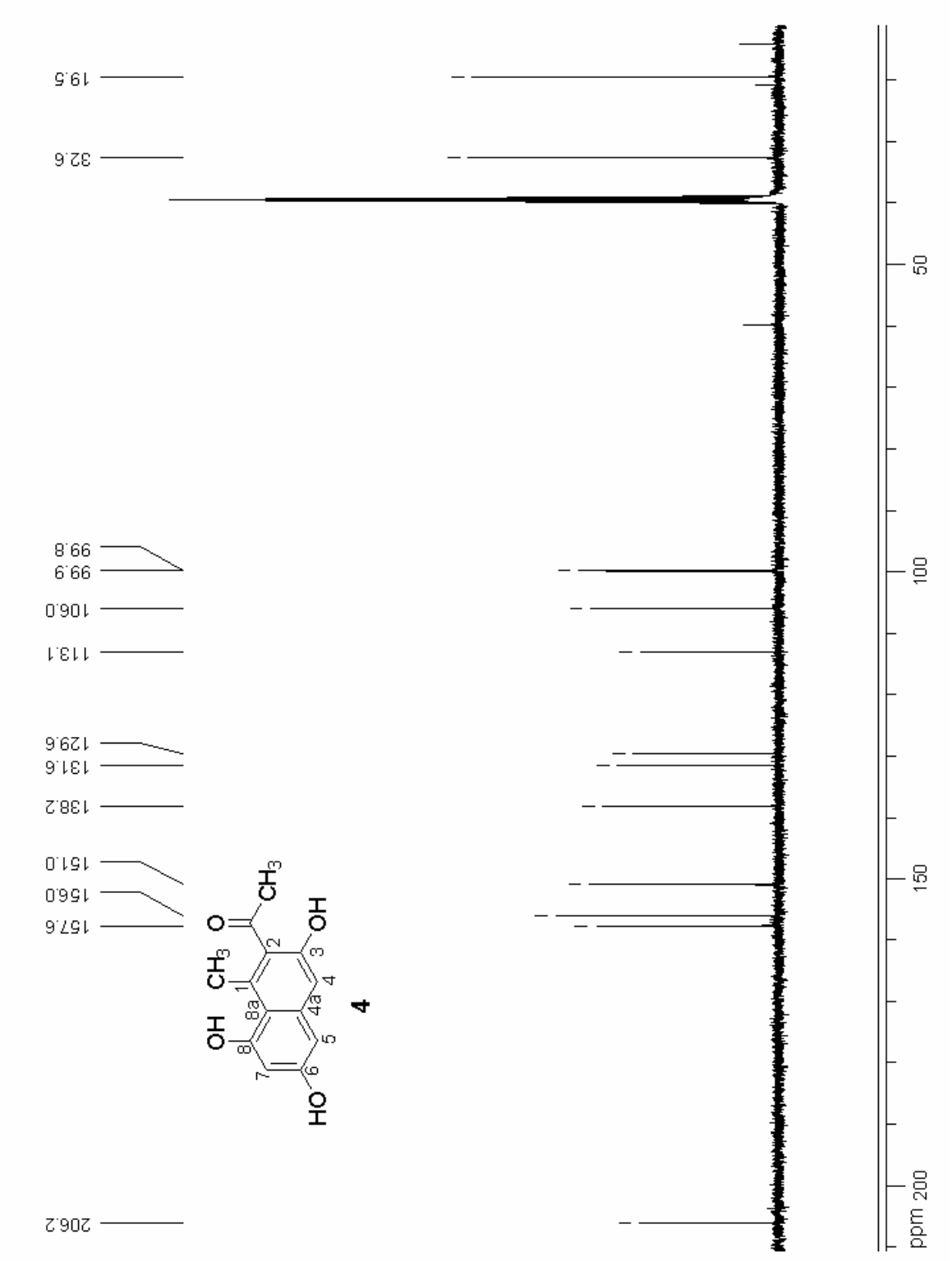
^{13}C NMR ($CDCl_3$, 100 MHz)



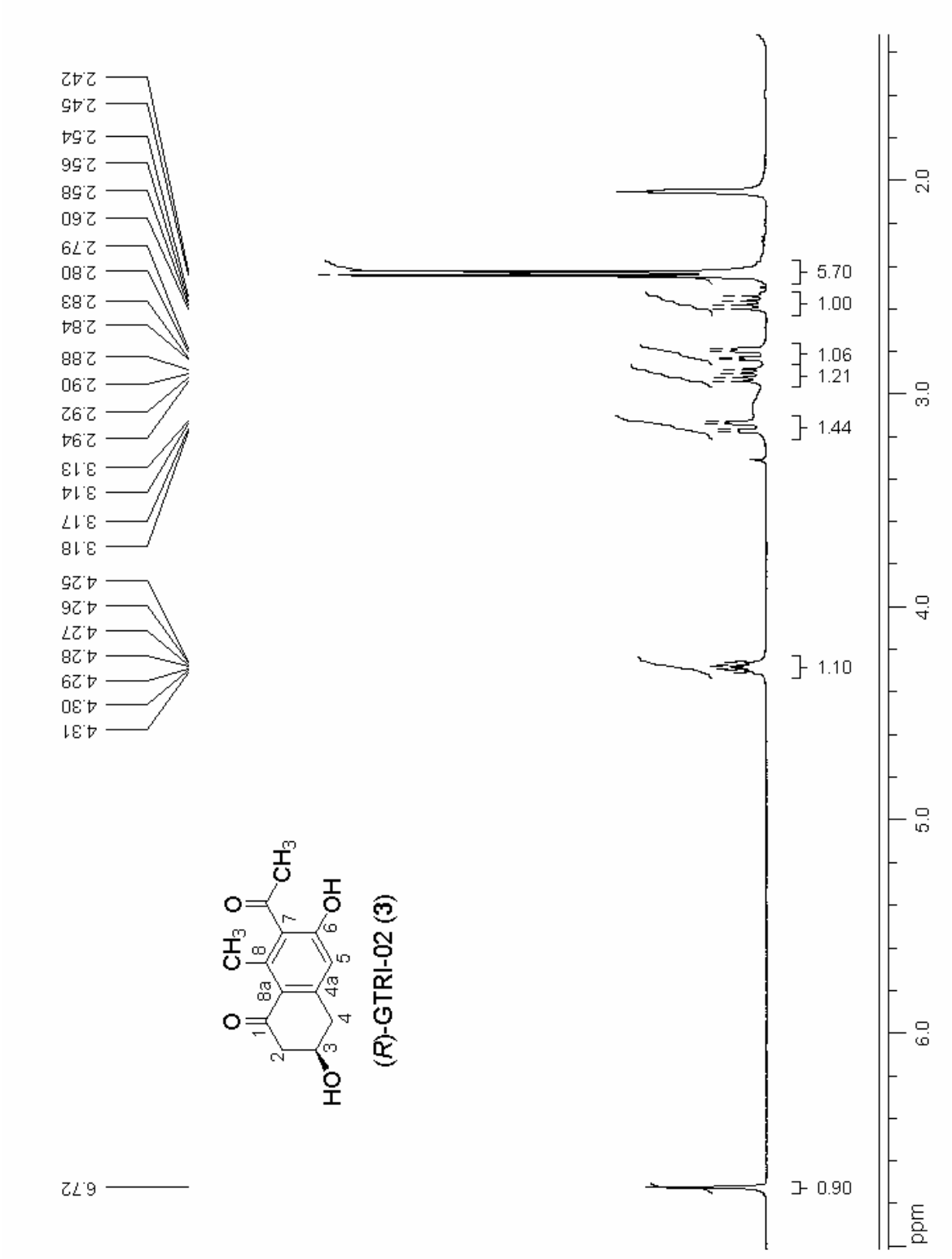
^{1}H NMR (DMSO-d_6, 400 MHz)



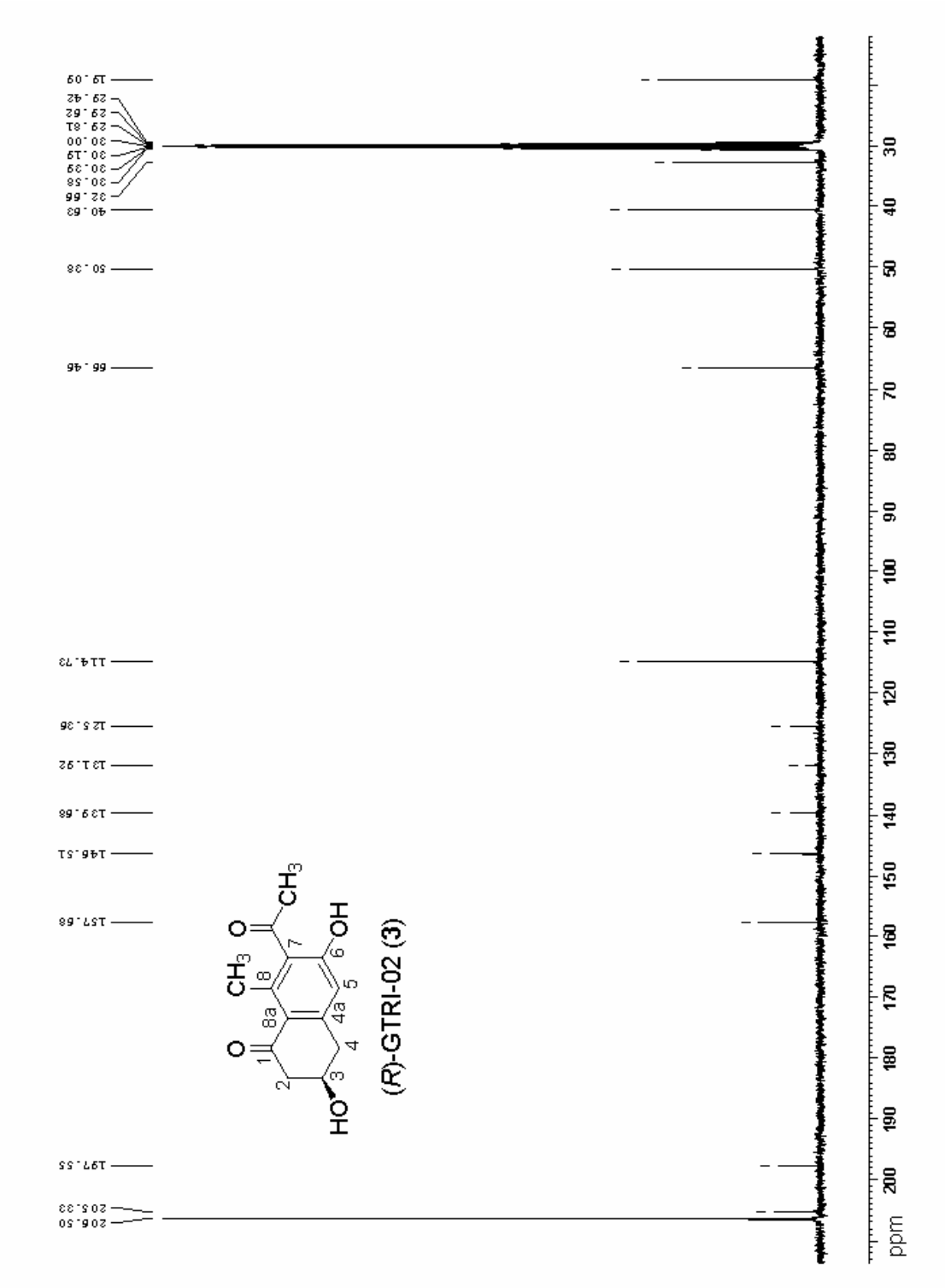
^{13}C NMR (DMSO-d_6, 100 MHz)



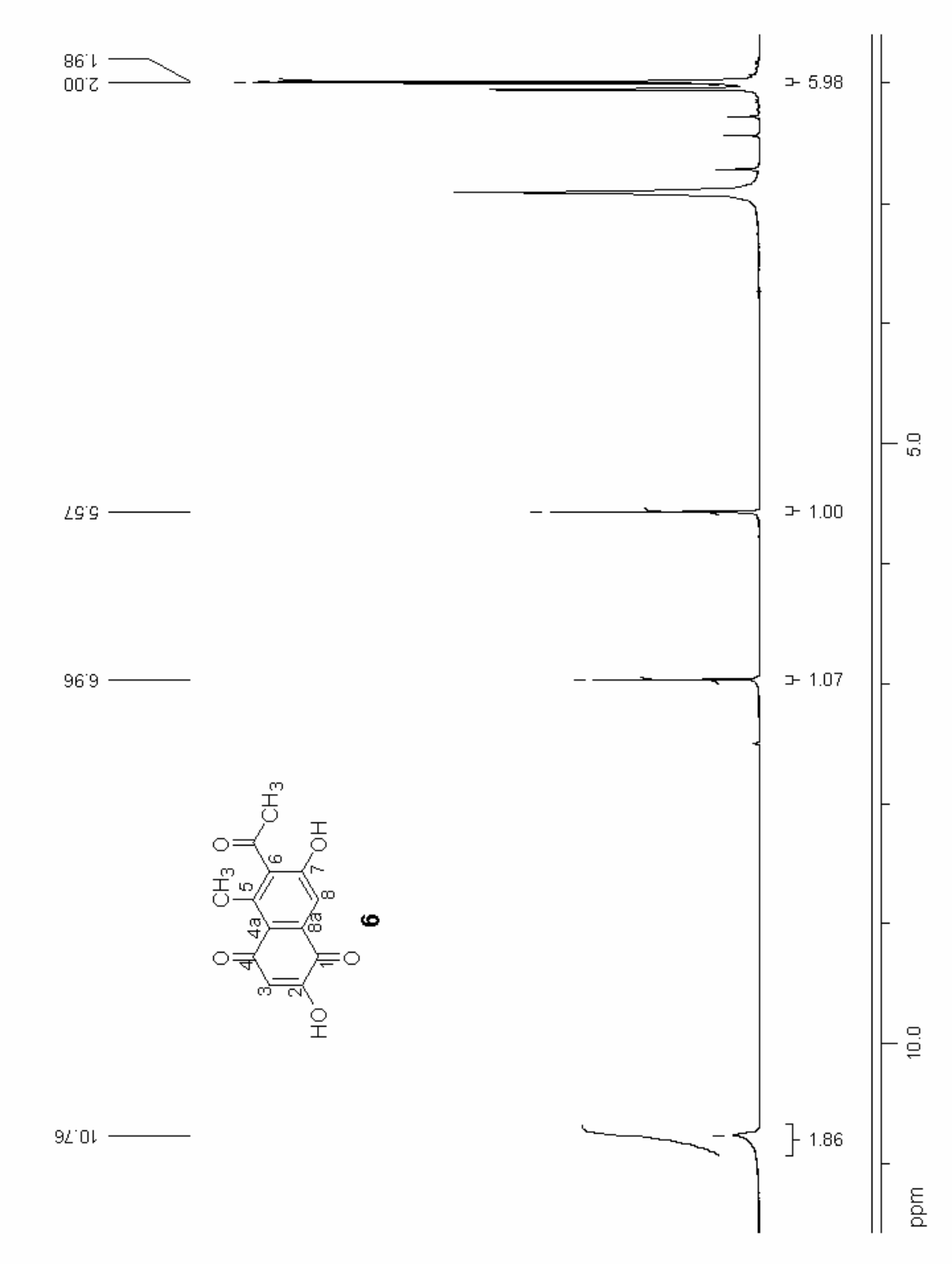
^{1}H NMR (acetone-d_6, 400 MHz)



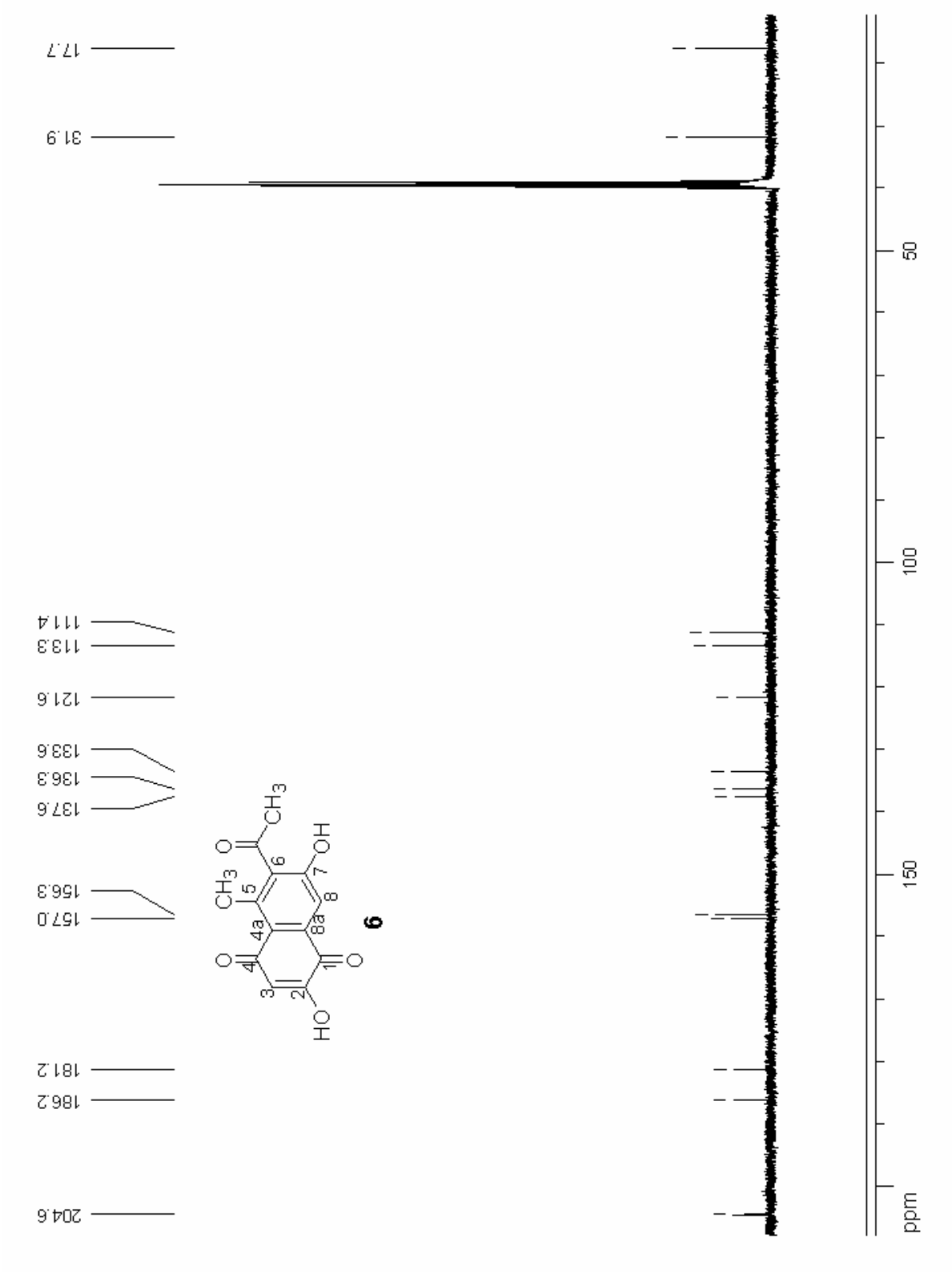
^{13}C NMR (acetone-d_6, 100 MHz)



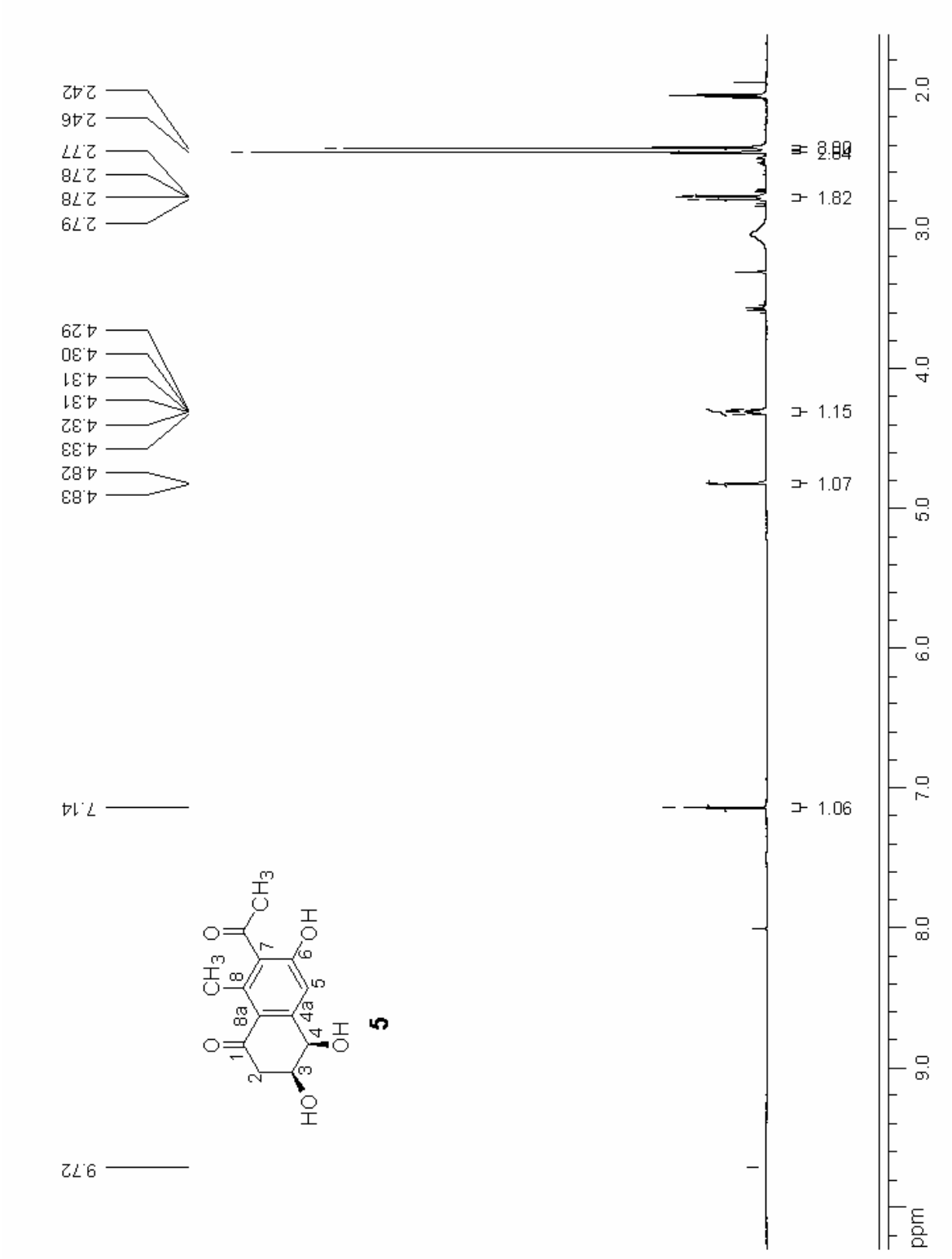
^{1}H NMR (DMSO-d_6, 400 MHz)



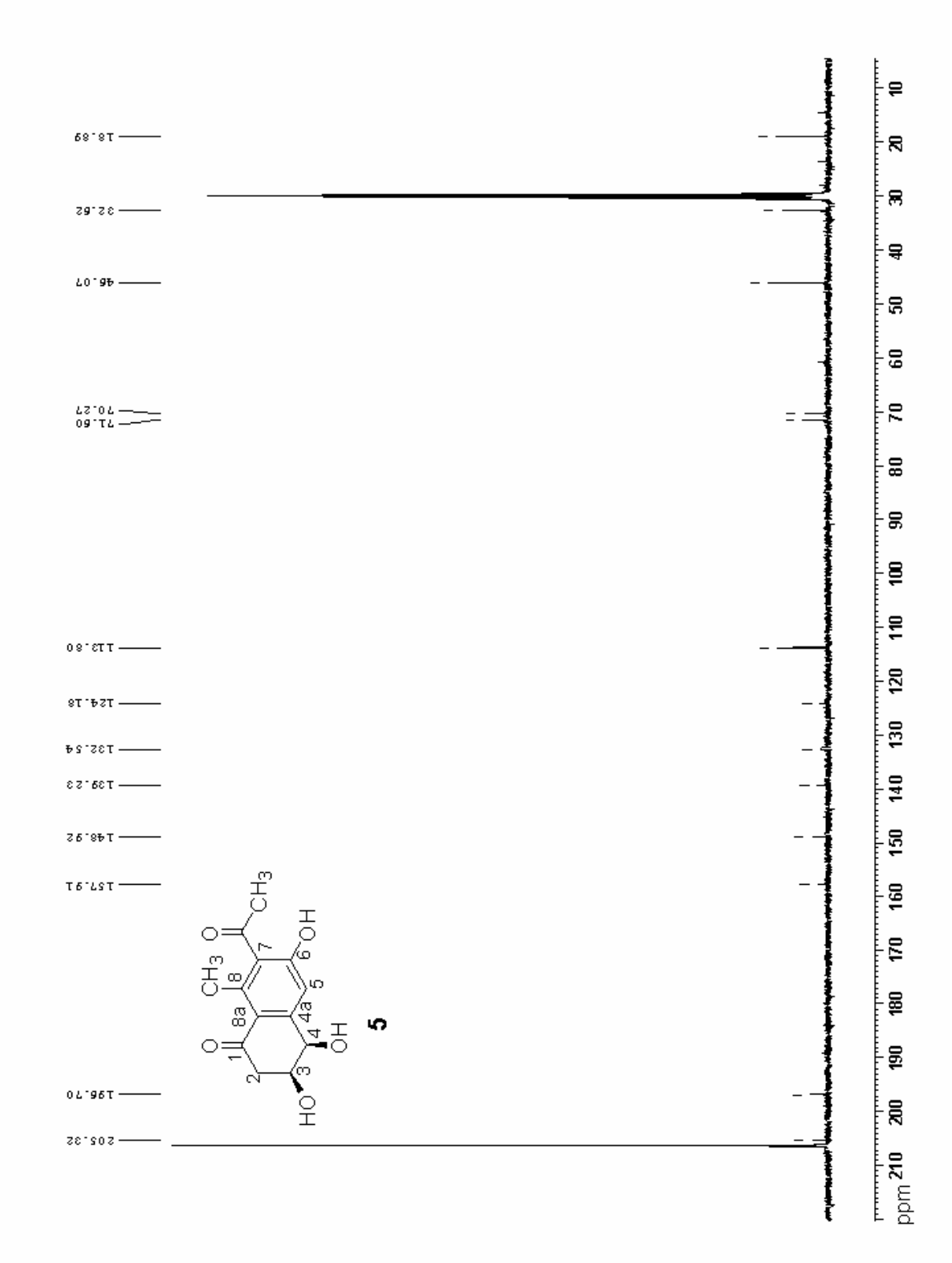
^{13}C NMR (DMSO-d_6, 100 MHz)



^{1}H NMR (acetone-d_6, 400 MHz)



^{13}C NMR (acetone-d_6, 100 MHz)



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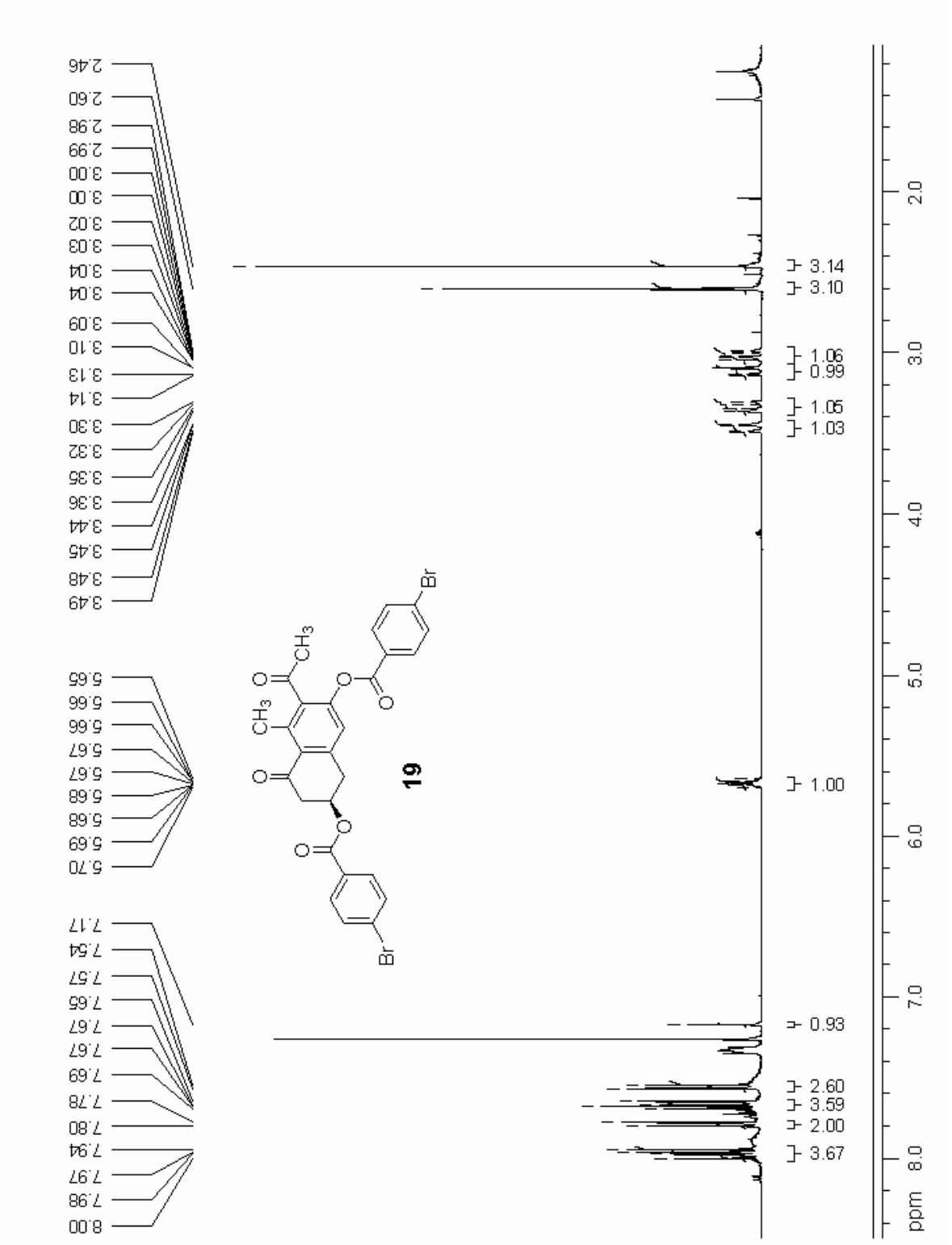
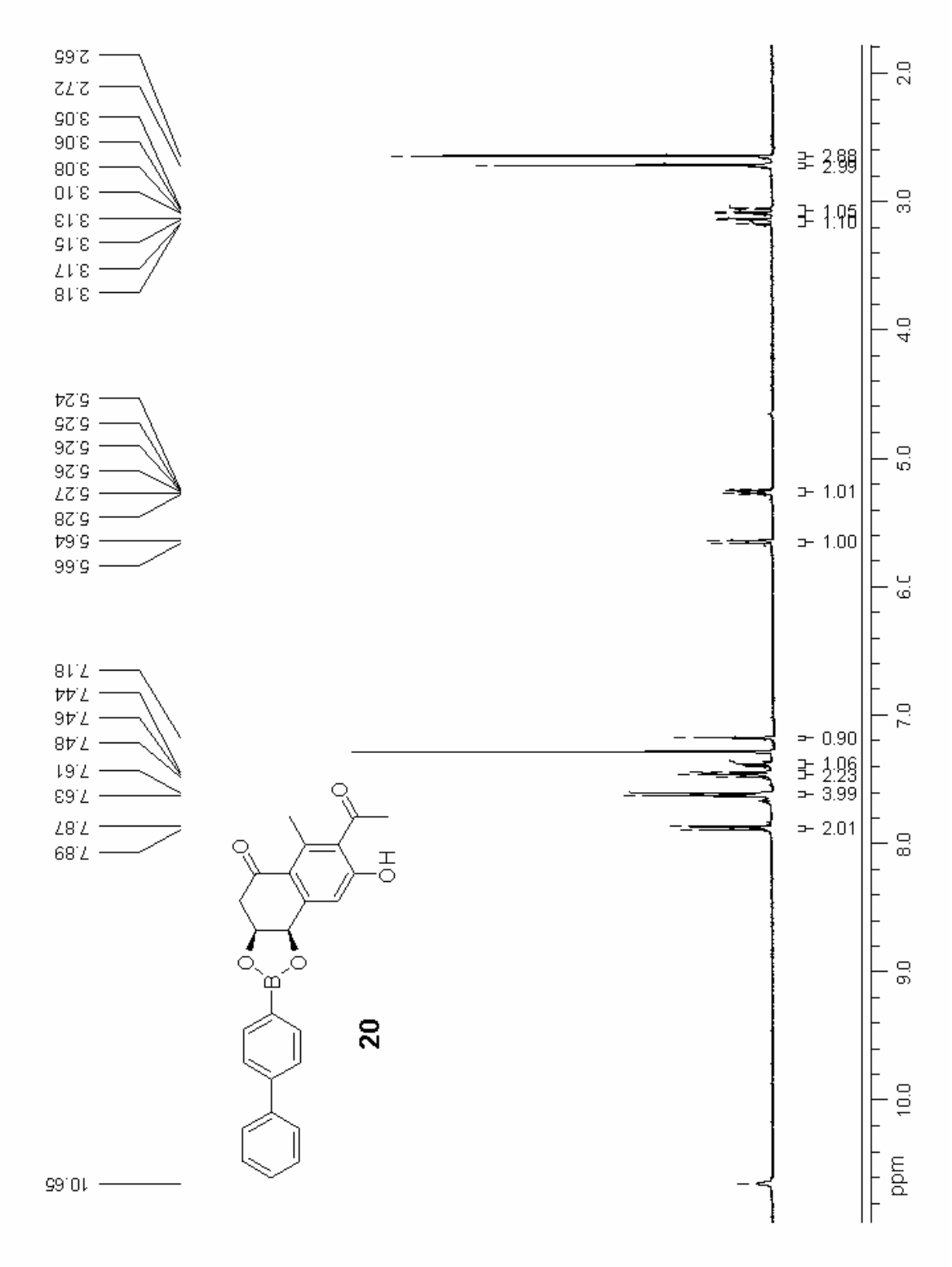


^{1}H NMR ($CDCl_3$, 400 MHz)



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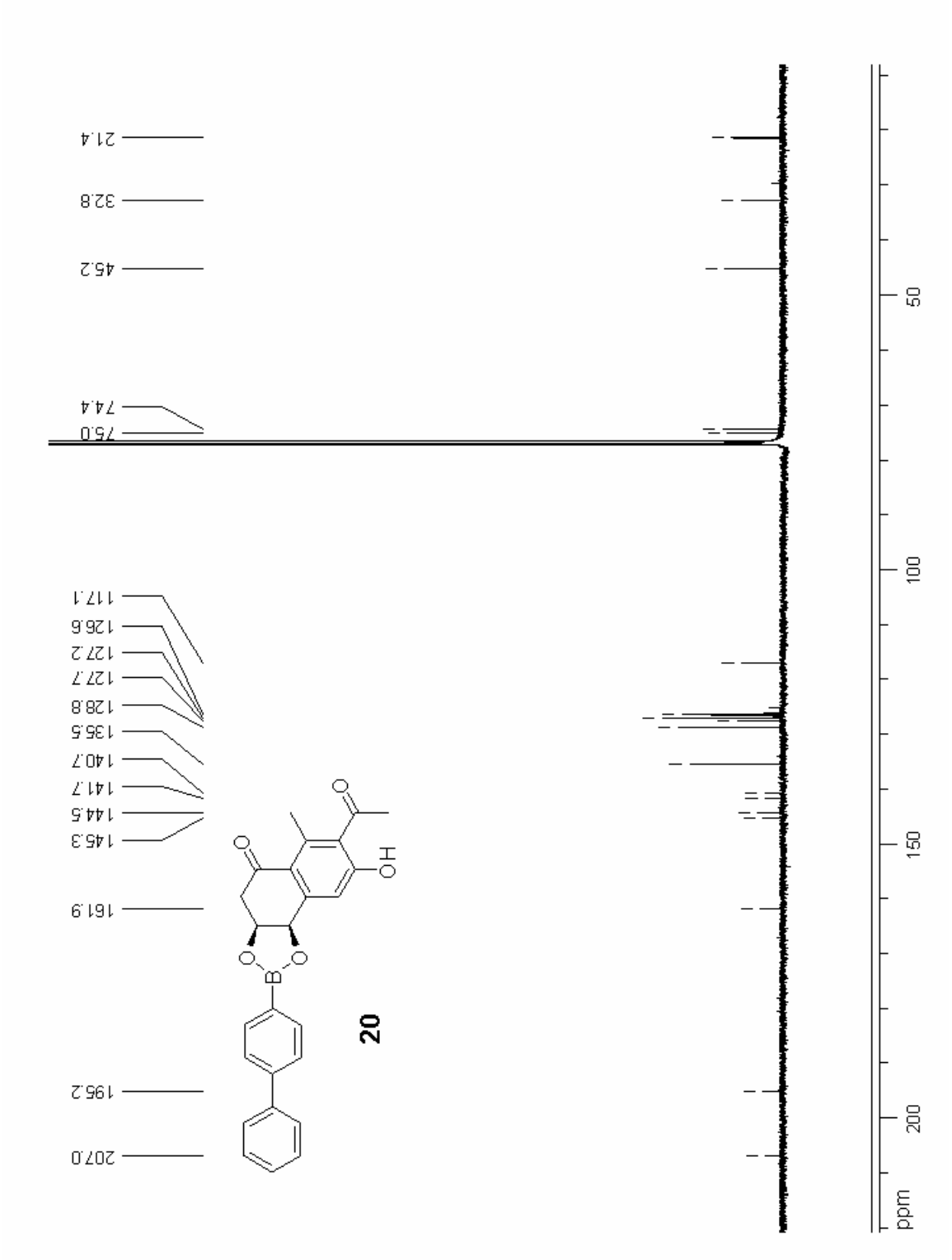
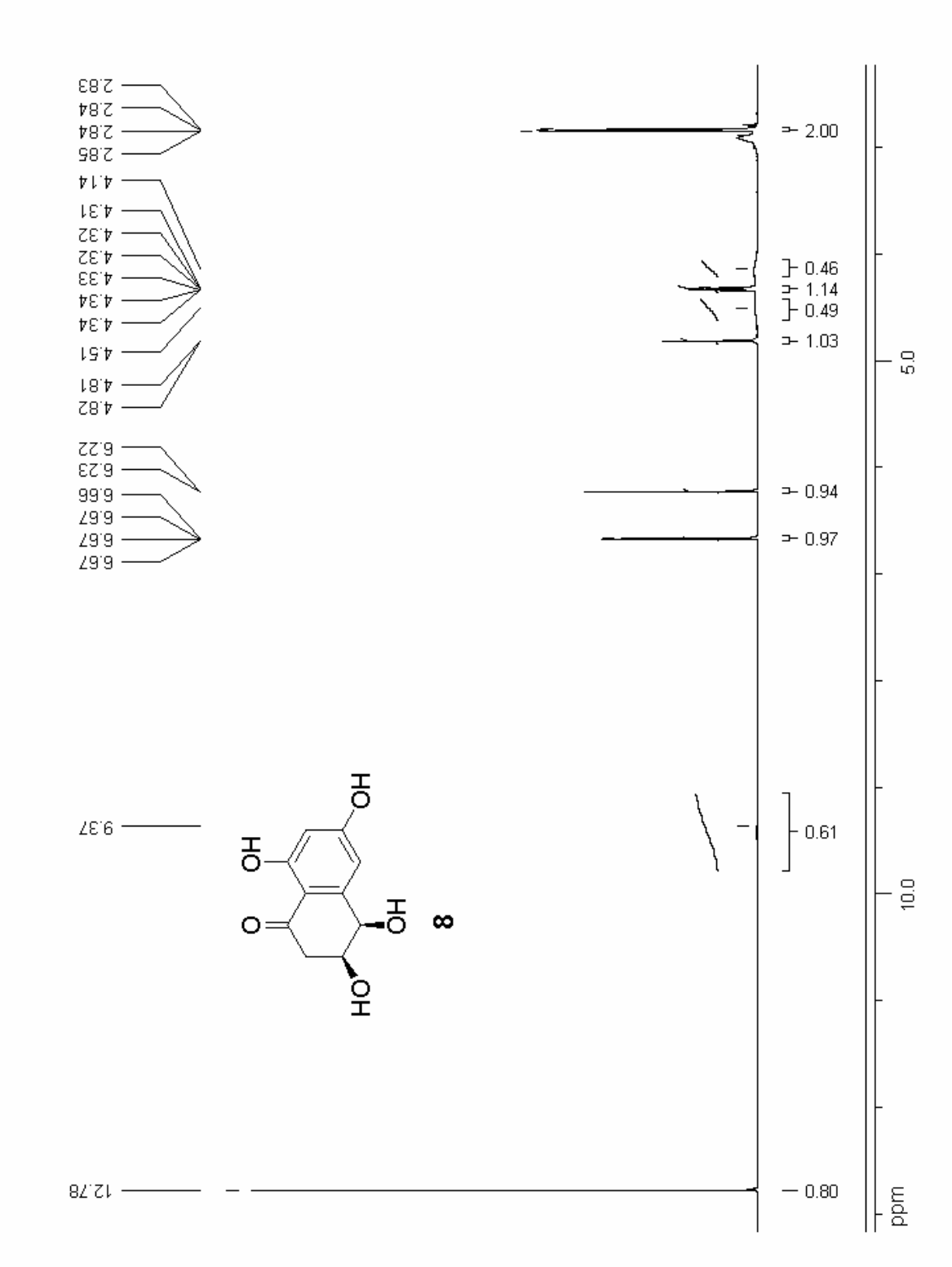
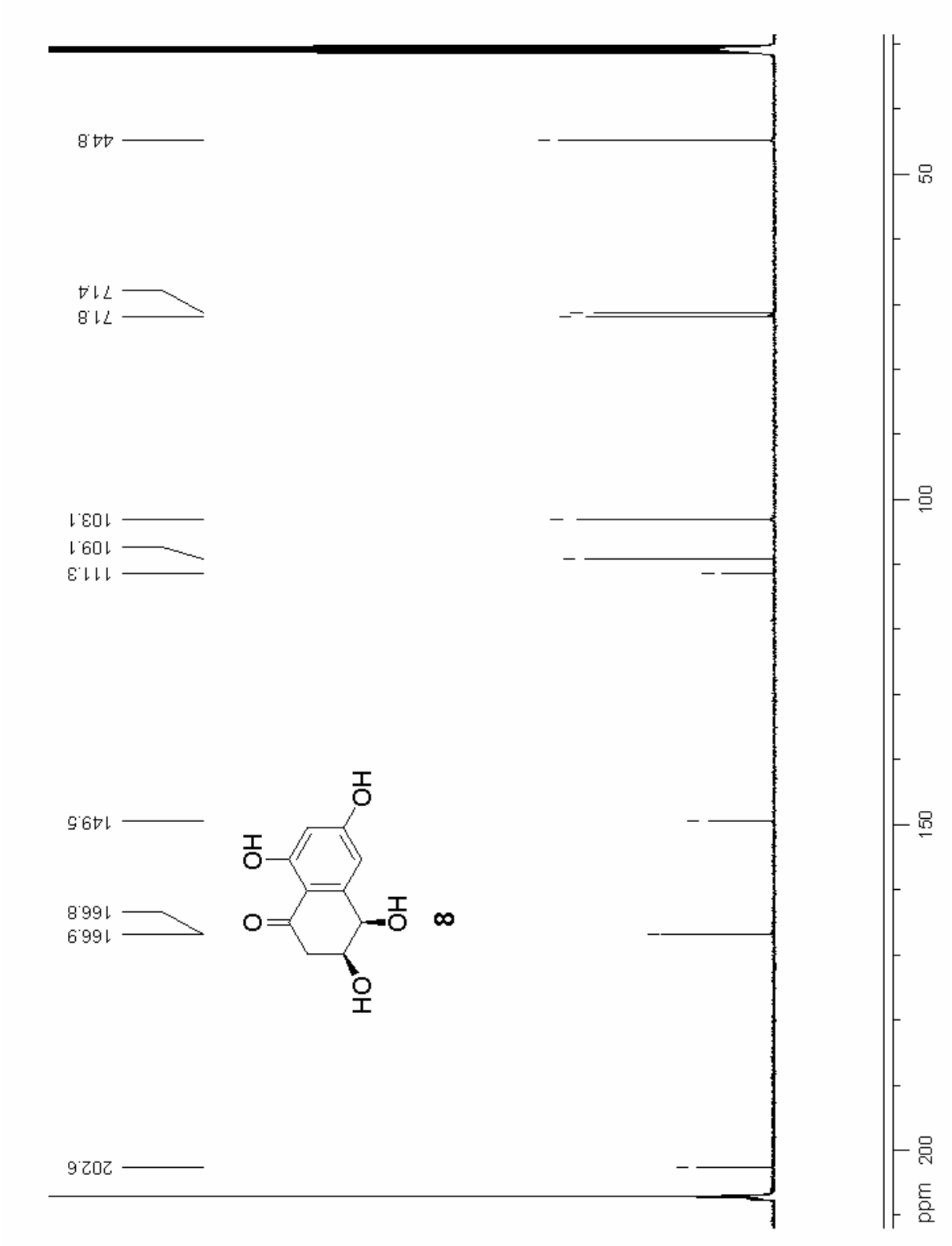


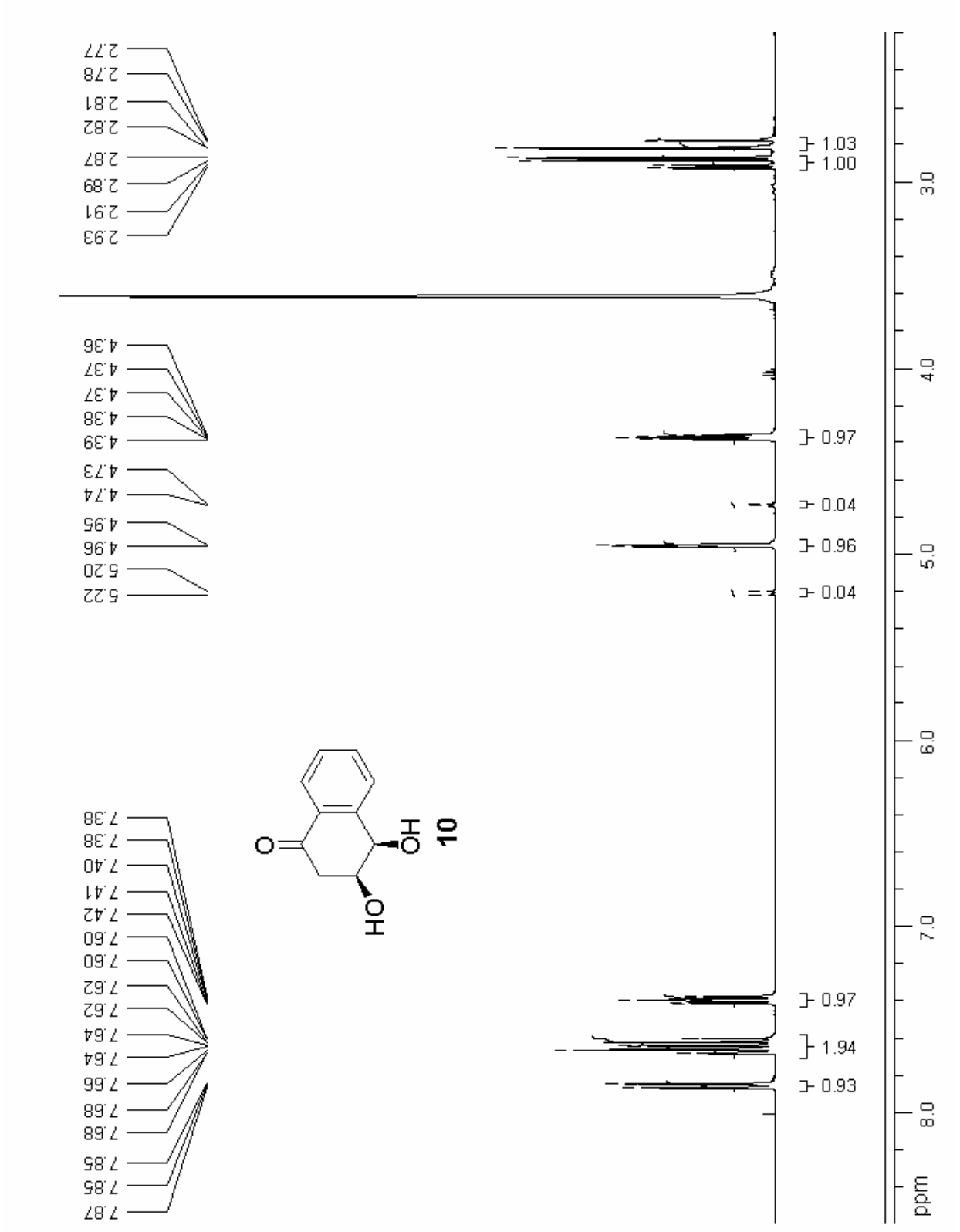
^{1}H NMR (acetone-d_6, 400 MHz)



^{13}C NMR (acetone-d_6, 100 MHz)



^{1}H NMR (acetone-d_6 +D_2O, 400 MHz)


2.77
2.78
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0.97
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0.96
0.04
0.97
1.94
0.93
3.0
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ppm
O
OH
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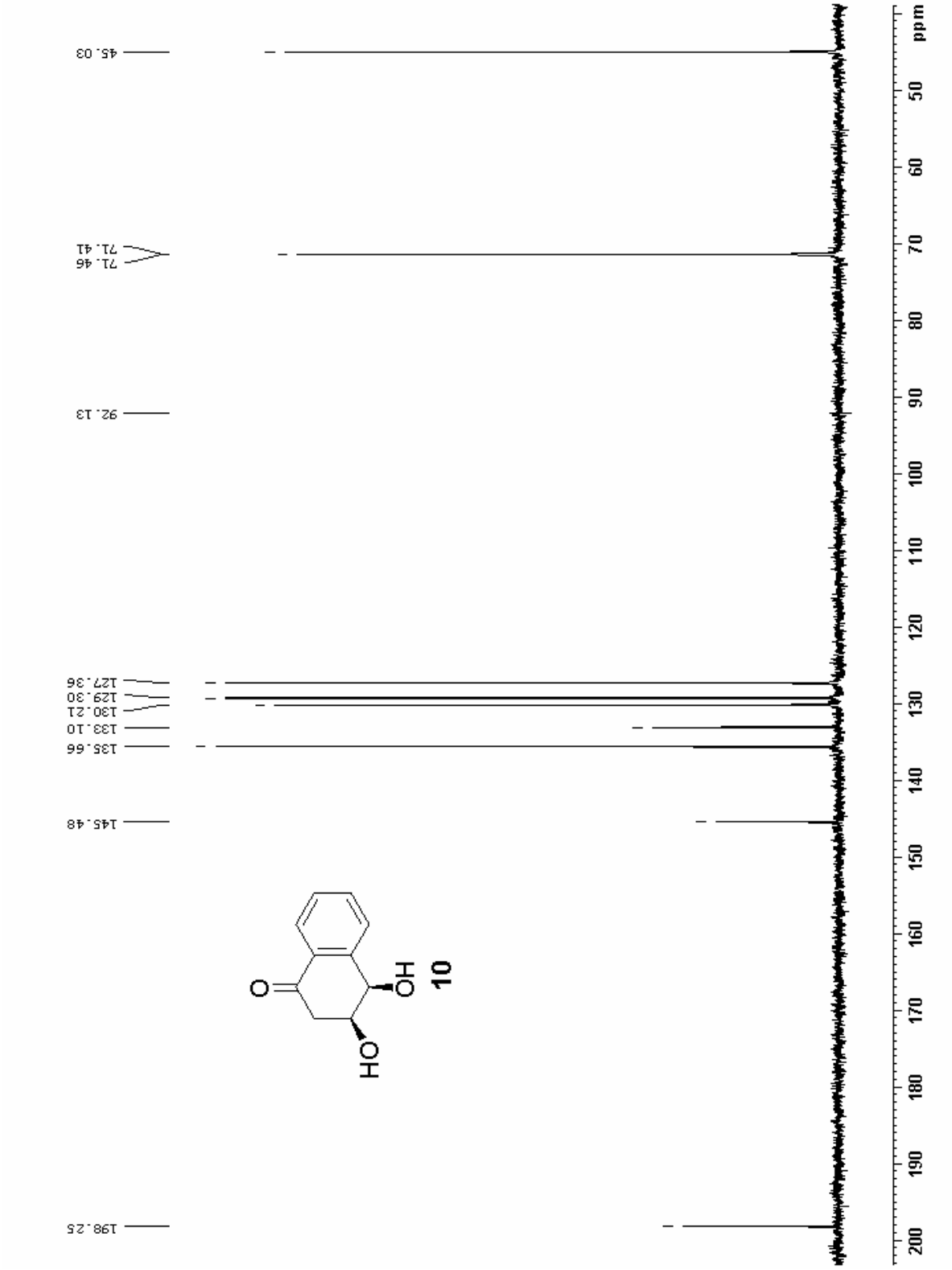
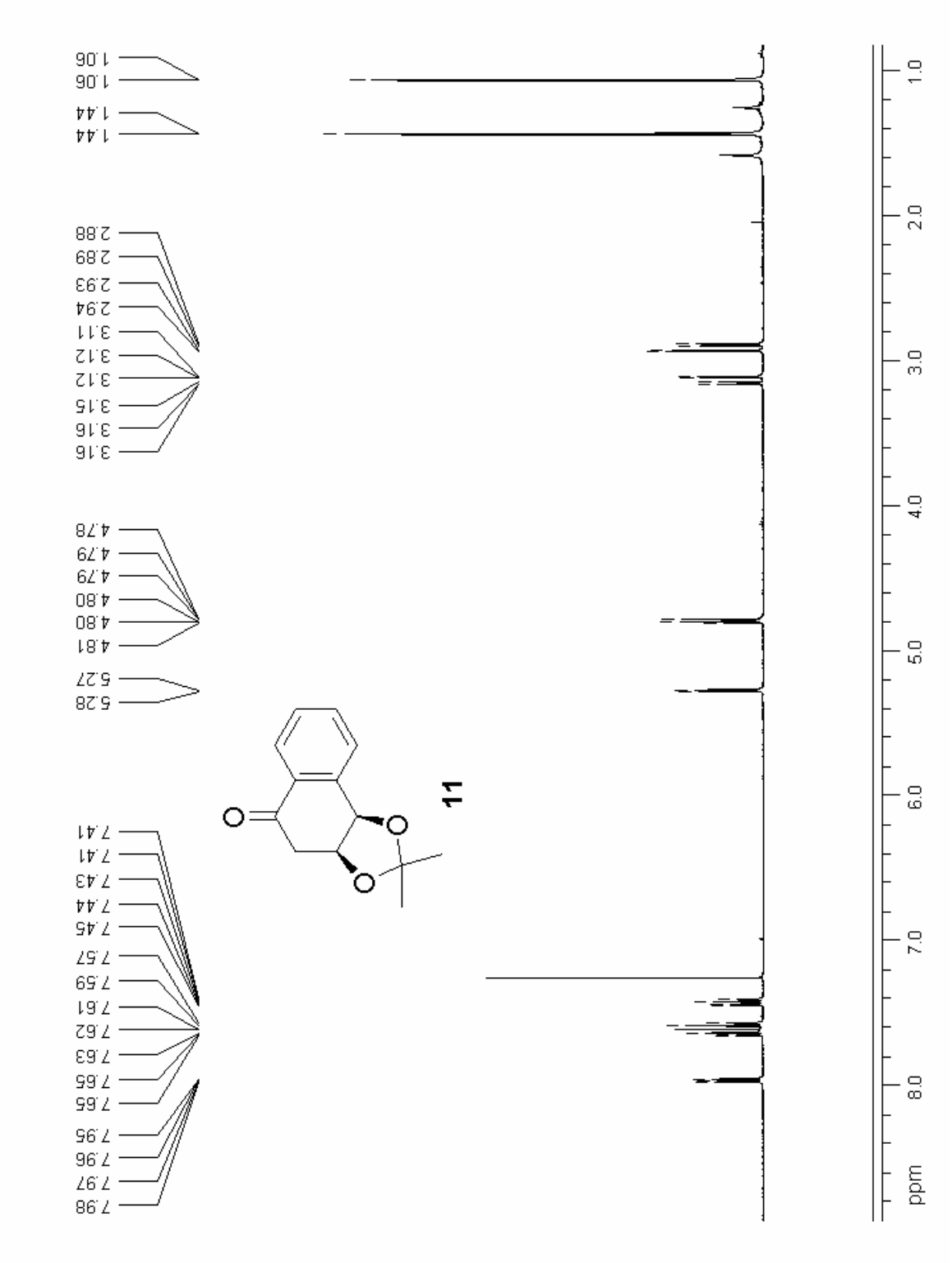
10

^{13}C NMR (acetone-d_6 + D_2O, 100 MHz)



^{1}H NMR ($CDCl_3$, 400 MHz)



VI. *Refrences*

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