Supporting information
for

Synthesis of Highly Enantio-enriched Stereoisomers of Hydroxy-GR24

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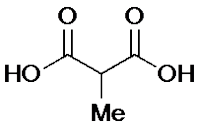
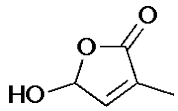
General experimental

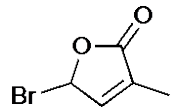
Reagent grade dichloromethane and triethylamine were freshly distilled from calcium hydride. Tetrahydrofuran and methanol were collected using an Innovative Technology Inc. PureSolv™ solvent purification system. All other solvents and reagents were used as received from commercial sources. Melting points were determined using a Stanford Research Systems Optimelt automated melting point system and are uncorrected. Infrared spectra were acquired neat on a Bruker Alpha-E ATR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AVANCE DPX300 (^{1}H frequency 300 MHz; ^{13}C frequency 75 MHz) or Bruker AVANCE DPX500 (^{1}H frequency 500 MHz; ^{13}C frequency 125 MHz). ^{1}H chemical shifts are expressed as parts per million (ppm) with residual chloroform (δ 7.26) or tetramethylsilane (δ 0.00) as reference and are reported as chemical shift (δ_H); relative integral; multiplicity (s = singlet, br = broad, d = doublet, t = triplet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet); and coupling constants (*J*) reported in Hz. ^{13}C NMR chemical shifts are expressed as parts per million (ppm) with deuterochloroform (δ 77.16) as internal reference and are reported as chemical shift (δ_C); multiplicity (assigned from DEPT experiments). High resolution mass spectra were recorded on a Bruker ApexII Fourier Transform Ion Cyclotron Resonance mass spectrometer with a 7.0 T magnet, fitted with an off-axis Analytical electrospray source. Enantioselective HPLC analyses were performed using an AD-H column (25% ^{i}PrOH in hexanes, 0.5 mLmin^{-1}) with a dual λ absorbance detector (254 and 270 nm). Column chromatography was performed using Grace Davidson 40-63 μm (230-400 mesh) silica gel using distilled solvents. Analytical thin layer chromatography was performed using preconditioned plates (Merck TLC silica gel 60 F254 on aluminium) and visualised using UV light (254 nm and 365 nm) and ethanolic anisaldehyde.



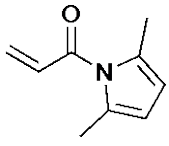
Methyl malonic acid. To a solution of aqueous KOH (5 M, 400 mL) at 0 °C was added diethyl methylmalonate (39.1 mL, 0.23 mol) and the reaction mixture was allowed to warm to room temperature. After 60 h, the reaction mixture was washed with Et_2O (2 × 100 mL) and the aqueous layer was acidified with HCl (6 M; 400 mL). After addition was complete the aqueous layer was extracted with ethyl acetate (7 × 200 mL) and the combined organic extracts were dried (Na_2SO_4) and concentrated *in vacuo* to provide methyl malonic acid (19.2 g, 71%) as a white solid, without the need for further purification. mp 134 °C, lit.[1] mp 134 °C; ^{1}H NMR (300 MHz, DMSO) δ 12.6 (2H, br s, $CO_2\underline{H}$), 3.30 (1H, q, *J* = 7.2 Hz, $C\underline{H}CO_2H$), 1.21 (3H, d, *J* = 7.2 Hz, $C\underline{H}_3CHCO_2H$); ^{13}C NMR (75 MHz, DMSO) δ 171.9, 45.9, 13.9.



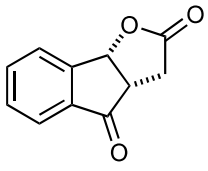
5-Hydroxy-3-methylfuran-2(5H)-one. To a solution of glyoxal (7.98 g, 40 wt % in H_2O, 54.1 mmol) in H_2O (45 mL) at room temperature was added methyl malonic acid (4.50 g, 38.8 mmol) followed by addition of H_2SO_4 (10 drops) and the reaction mixture was heated at reflux. After 16 h, the reaction was saturated with solid NaCl and the aqueous was extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (40% ethyl acetate/Pet. Ether) gave butenolide (2.27 g, 52%) as an orange/yellow solid. m.p 56.7–60.1 °C, lit.[2] mp 69–71 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.88 (1 H, m, $\underline{H}_{3'}$), 6.08 (1 H, m, $\underline{H}_{2'}$), 3.35 (1 H, br, O$\underline{H}$), 1.96 (3 H, m, $\underline{H}_{7'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 144.7, 133.6, 97.0, 10.4.



Bromobutenolide 17. To a solution of butenolide (0.394 g, 3.45 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added carbon tetrabromide (1.36 g, 4.14 mmol) followed by portionwise addition of triphenylphosphine (1.11 g, 4.14 mmol) with warming to room temperature. After 2.5 h, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (15–20% ethyl acetate/Pet. Ether) gave compound **17** (0.354 g, 58%) as a yellow oil. IR (neat) 3104, 1768, 1211, 1031, 945 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (1 H, s, $\underline{H}_{3'}$), 6.83 (1 H, s, $\underline{H}_{2'}$), 2.01 (3 H, s, $\underline{H}_{7'}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 147.4, 130.8, 74.8, 10.5.

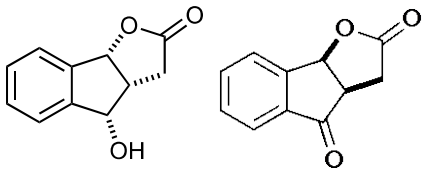


***N*-Acryloylpyrrole 15.** To a solution of acrylamide (1.05 g, 14.8 mmol) in toluene (120 mL) at room temperature was added 2,5-hexanedione (0.5 mL, 4.27 mmol) followed by *p*-toluenesulfonic acid (89.5 mg, 0.53 mmol) and the reaction mixture heated to reflux under Dean-Stark conditions. After 16 h, the reaction mixture was cooled to room temperature and the organics washed with H_2O (3×50 mL). The organic extract was dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% Et_2O/Pet. Ether) afforded **15** (0.427 g, 67%) as a yellow oil. IR (neat) 2926, 1693, 1539, 1403, 1363, 1300, 1258, 1073, 1044 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.69 (1H, dd, *J* = 17.0, 10.3 Hz, $\underline{H}_2$), 6.47 (1H, dd, *J* = 17.0, 1.4 Hz, $\underline{H}_{3a}$), 5.95 (1H, dd, *J* = 10.4, 1.4 Hz, $\underline{H}_{3b}$), 5.85 (2H, s, $\underline{H}_{3'-4'}$), 2.35 (6H, s, $\underline{H}_{6'-7'}$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.0, 132.1, 131.2, 130.1, 111.0, 15.6.



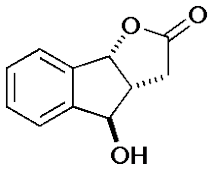
(±)

Lactone (±)-6. To a solution of thiazolium catalyst **16** (0.263 g, 0.975 mmol) in degassed THF (20 mL) at room temperature was added Cs_2CO_3 (0.315 g, 0.975 mmol) and the solution was degassed for a further 10 min until the solution turned pale yellow. To a separate flask containing phthalaldehyde (1.29 g, 9.75 mmol) in THF (20 mL) at room temperature was added a solution of **15** (0.728 g, 4.88 mmol) in THF (5 mL) and the solution degassed for 5 min. Following degassing, the solution was added *via* cannula to the carbene reaction flask. After 2.5 h, a further portion of Cs_2CO_3 (1.59 g, 4.88 mmol) was added and the reaction mixture was stirred at room temperature for 16 h. The reaction mixture was quenched by addition of saturated aqueous NH_4Cl (10 mL) and the organics extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed with brine (25 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (20–25% ethyl acetate/Pet. Ether then 2% ethyl acetate/CH_2Cl_2) afforded lactone **6** (0.352 g, 38%) as a pale orange solid. mp 109.9–112.2 °C, lit.[3] mp 113.5–114 °C; IR (neat) 1770, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.91–7.76 (3H, m, Ar<u>H</u>), 7.64–7.60 (1H, m Ar<u>H</u>), 6.01 (1H, d, *J* = 6.8 Hz, <u>H</u>$_{8b}$), 3.59 (1H, ddd, *J* = 12.5, 6.8, 4.5 Hz, <u>H</u>$_{3a}$), 3.09 (1H, dd, *J* = 19.0, 12.5 Hz, <u>H</u>$_3$), 2.80 (1H, dd, *J* =19.0, 4.5 Hz, <u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 174.7, 149.7, 136.2, 136.1, 131.2, 127.6, 124.5, 79.1, 45.8, 31.2.

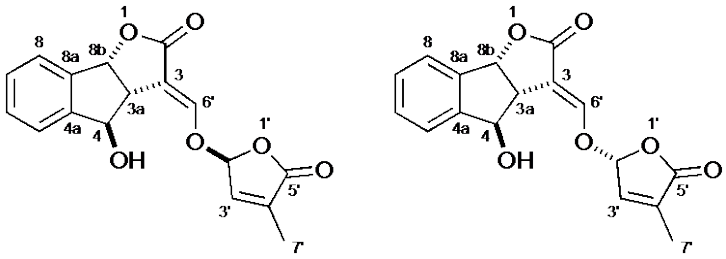


Alcohol (−)-7. To a solution of lactone **(±)-6** (201 mg, 1.07 mmol) in DMF (1.6 mL) at 0 °C was added (*S*,*S*)-RuTsDPEN (25 mg, 0.043 mmol) followed by the slow simultaneous addition of formic acid (0.2 mL, 5.34 mmol) and Hünig's base (0.37 mL, 2.14 mmol). After 6 h, the reaction mixture was quenched by addition of 1M HCl (5 mL) and the organics were extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (2, 5, 10% ethyl acetate/CH_2Cl_2) gave alcohol **(−)-7** (98.8 mg, 49%) as an off white solid. mp 139.5–142.7 ºC, lit.[3] mp 154.3–154.8 °C; $[\alpha]_D^{20}$ −44.7 (*c* 0.51, $CHCl_3$); IR (neat) 3430, 1759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.38 (4H, m, Ar<u>H</u>), 5.70 (1H, d, *J* = 7.1 Hz, <u>H</u>$_{8b}$), 5.25 (1H, d, *J* = 7.2 Hz, <u>H</u>$_4$), 3.51–3.43 (1H, m, <u>H</u>$_{3a}$), 2.84 (1H, dd, *J* = 18.4, 5.8 Hz, <u>H</u>$_3$), 2.63 (1H, dd, *J* = 18.4, 10.3 Hz, <u>H</u>$_3$), 2.55 (1H, br s, O<u>H</u>); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3, 144.2, 138.2, 130.5, 129.6, 126.3, 125.3, 84.3, 73.4, 43.4, 28.8; HRMS (ES^+) Calc for $C_{11}H_{10}O_3Na$ $[M+Na]^+$ 213.05222, found 213.05225.

and enantio-enriched ketone **(+)-6** (98.8 mg, 49%) as a yellow/brown solid: mp 90.5–95.3 °C, lit.[3] mp 113.5–114 °C; $[\alpha]_D^{20}$ +21.7 (*c* 1.07, $CHCl_3$); IR (neat) 1772, 1719 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84–7.74 (3H, m, Ar<u>H</u>), 7.64–7.59 (1H, m, Ar<u>H</u>), 6.00 (1H, d, *J* = 6.8 Hz, <u>H</u>$_{8b}$), 3.57 (1H, ddd, *J* = 12.5, 6.8, 4.5 Hz, <u>H</u>$_{3a}$), 3.06 (1H, dd, *J* = 19.0, 12.5 Hz, <u>H</u>$_3$), 2.78 (1H, dd, *J* =19.0, 4.5 Hz, <u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 174.7, 149.7, 136.2, 136.1, 131.1, 127.6, 124.4, 79.1, 45.8, 31.1.

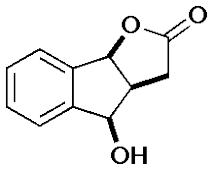


Alcohol (−)-8. To a solution of alcohol **(−)-7** (45.2 mg, 0.238 mmol) in THF (3 mL) at 0 °C was added PPh_3 (232 mg, 0.88 mmol) and benzoic acid (108.1 mg, 0.88 mmol) followed by slow addition of DIAD (0.17 mL, 0.856 mmol). After 16 h, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (15% ethyl acetate/Pet. Ether) provided semi-crude benzoic ester. To a solution of benzoic ester in MeOH (2 mL) at room temperature was added K_2CO_3 (48.1 mg, 0.333 mmol). After 3 h, the reaction mixture was quenched by addition of 1M HCl (5 mL) and the organics were extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (40–60% ethyl acetate/Pet. Ether) gave alcohol **(−)-8** (37.6 mg, 83% over two-steps) as a colourless oil. $[\alpha]_D^{20}$ −80.0 (*c* 0.96, $CHCl_3$); IR (neat) 3396, 1767 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.41 (4H, m, Ar$\underline{H}$), 6.02 (1H, d, *J* = 7.0 Hz, $\underline{H}_{8b}$), 5.13 (1H, d, *J* = 2.1 Hz, $\underline{H}_4$), 3.23 (1H, dddd, *J* = 10.4, 6.9, 6.0, 2.4 Hz, $\underline{H}_{3a}$), 2.93 (1H, dd, *J* = 18.4, 10.5 Hz, $\underline{H}_3$), 2.43 (1H, dd, *J* = 18.4, 5.9 Hz, $\underline{H}_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 143.9, 138.9, 130.7, 130.1, 126.6, 125.4, 85.8, 80.4, 47.9, 33.0; MS (ESI) m/z 212 ($[M + Na]^+$, 46), 403 ($[2M + Na]^+$, 100).

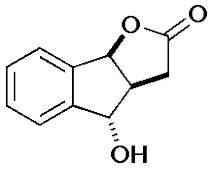


(−)-4-OH-*epi*-GR24 (−)-4 and (−)-4-OH-GR24. To a solution of alcohol **(−)-8** (33.4 mg, 0.176 mmol) in neat methyl formate (2 mL) was added at 0 °C potassium *tert*-butoxide (119.1 mg, 1.05 mmol) portion wise and the reaction allowed to warm to room temperature. After 3 h (starting material consumption indicated by TLC analysis), the reaction mixture was quenched by the addition of 1M HCl (5 mL) and the organics extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude enol product was taken up in DMF (1.5 mL) and K_2CO_3 (36.6 mg, 0.264 mmol) was added at room temperature. The reaction mixture was cooled to 0 °C and a solution of bromobutenolide **17** (50.8 mg, 0.287 mmol) in DMF (0.5 mL) was added *via* cannula. After 16 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the organics extracted with ethyl acetate (4×5 mL). The combined organic extracts were washed with a H_2O:brine mixture (1:1, 10 mL), washed with brine (10 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% ethyl acetate/Pet. Ether) provided a mixture of **(−)-4** (11.7 mg, 21%) as a white solid. mp 81.5–82.9 °C; $[\alpha]_D^{20}$ −254 (*c* 0.39, $CHCl_3$); IR (thin film) 3411, 1781, 1746, 1679 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.51 (2H, m, $\underline{H}_{6'}$ + Ar$\underline{H}$), 7.45–7.40 (3H, m, Ar$\underline{H}$), 6.98 (1H, t, *J* = 1.6 Hz, $\underline{H}_{3'}$), 6.23 (1H, t, *J* = 1.4 Hz, $\underline{H}_{2'}$), 6.06 (1H, d, *J* = 7.4 Hz, $\underline{H}_{8b}$), 5.32 (1H, br s, $\underline{H}_4$), 3.81 (1H, ddd, *J* = 7.5, 2.6, 2.0 Hz, $\underline{H}_{3a}$), 2.03 (3H, t, *J* = 1.5 Hz, $\underline{H}_{7'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 151.5, 143.9, 140.8, 139.3, 136.4, 130.7, 130.1, 126.6, 125.5, 110.4, 100.4, 84.1, 79.8, 50.6, 10.7; HRMS (ES^+) Calc for $C_{17}H_{14}O_6Na$ $[M+Na]^+$ 337.06826, found 337.06861.

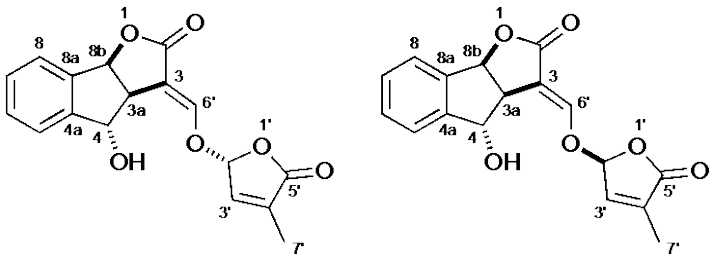
and **(−)-4-OH-*epi*-GR24** (10.6 mg, 19%) as a white solid. mp 164.7–170.2 °C; $[\alpha]_D^{20}$−185 (*c* 0.37, $CHCl_3$); IR (thin film) 3418, 1780, 1743, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55–7.51 (2H, m, $\underline{H}_{6'}$ + Ar$\underline{H}$), 7.45–7.40 (3H, m, Ar$\underline{H}$), 6.98 (1H, t, *J* = 1.6 Hz, $\underline{H}_{3'}$), 6.21 (1H, t, *J* = 1.4 Hz, $\underline{H}_{2'}$), 6.07 (1H, d, *J* = 7.5 Hz, $\underline{H}_{8b}$), 5.30 (1H, br s, $\underline{H}_4$), 3.82 (1H, ddd, *J* = 7.5, 2.6, 1.9 Hz, $\underline{H}_{3a}$), 2.04 (3H, t, *J* = 1.5 Hz, $\underline{H}_{7'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.0, 151.9, 143.9, 140.9, 139.2, 136.1, 130.7, 130.1, 126.6, 125.6, 110.3, 100.7, 84.1, 79.7, 50.5, 10.7; HRMS (ES^+) Calc for $C_{17}H_{14}O_6Na$ $[M+Na]^+$ 337.06826, found 337.06856.



Alcohol (+)-7. To a solution of lactone **(+)-6** (23.7 mg, 0.126 mmol) in EtOH (1 mL) at 0 °C was added $CeCl_3 \cdot 7H_2O$ (46.3 mg, 0.126 mmol) followed by slow addition of $NaBH_4$ (5.40 mg, 0.143 mmol). After 30 min, the reaction mixture was quenched by addition of 1M HCl (2 mL) and the organics were extracted with CH_2Cl_2 (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (5% ethyl acetate/CH_2Cl_2) provided alcohol **(+)-7** (16.3 mg, 68%) as a white solid. mp 136.7–141.9 °C, lit.[3] mp 154.3–154.8 °C; $[\alpha]_D^{20}$ +52.9 (*c* 1.21, $CHCl_3$); IR (neat) 3443, 1759 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.52–7.39 (4H, m, Ar<u>H</u>), 5.70 (1H, d, *J* = 7.1 Hz, <u>H</u>$_{8b}$), 5.27 (1H, d, *J* = 7.2 Hz, <u>H</u>$_4$), 3.48 (1H, dtd, *J* = 10.3, 7.1, 5.9 Hz, <u>H</u>$_{3a}$), 2.84 (1H, dd, *J* = 18.4, 5.9 Hz, <u>H</u>$_3$), 2.64 (1H, dd, *J* = 18.4, 10.3 Hz, <u>H</u>$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2, 144.1, 138.2, 130.5, 129.6, 126.3, 125.2, 84.3, 73.4, 43.4, 28.8; MS (ESI) m/z 212 ($[M + Na]^+$, 46), 403 ($[2M + Na]^+$, 100).



Alcohol (+)-8. To a solution of alcohol **(+)-7** (37.5 mg, 0.197 mmol) in THF (1.5 mL) at 0 °C was added PPh_3 (191.5 mg, 0.73 mmol) and benzoic acid (93.5 mg, 0.766 mmol) followed by slow addition of DIAD (0.14 mL, 0.71 mmol). After 16 h, the reaction mixture was concentrated *in vacuo*. Purification by flash column chromatography (15% ethyl acetate/Pet. Ether) provided semi-crude benzoic ester. To a solution of benzoic ester in MeOH (2 mL) at room temperature was added K_2CO_3 (42.2 mg, 0.305 mmol). After 3 h, the reaction mixture was quenched by addition of 1M HCl (2 mL) and the organics were extracted with ethyl acetate (3×5 mL). The combined organic extracts were washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (40–60% ethyl acetate/Pet. Ether) gave alcohol **(+)-8** (31.1 mg, 83% over two-steps) as a colourless oil. $[\alpha]_D^{20}$ +82.9 (*c* 0.99, $CHCl_3$); IR (neat) 3376, 1755 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.49–7.40 (4H, m, Ar<u>H</u>), 5.99 (1H, d, *J* = 6.9 Hz, <u>H</u>$_{8b}$), 5.09 (1H, d, *J* = 1.9 Hz, <u>H</u>$_4$), 3.22–3.17 (1H, m, <u>H</u>$_{3a}$), 2.90 (1H, dd, *J* = 18.4, 10.4 Hz, <u>H</u>$_3$), 2.41 (1H, dd, *J* = 18.4, 5.8 Hz, <u>H</u>$_3$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.4, 143.9, 138.8, 130.7, 130.0, 126.5, 125.4, 85.9, 80.3, 47.9, 33.0; HRMS (ES^+) Calc for $C_{11}H_{10}O_3Na$ $[M+Na]^+$ 213.05222, found 213.05244.



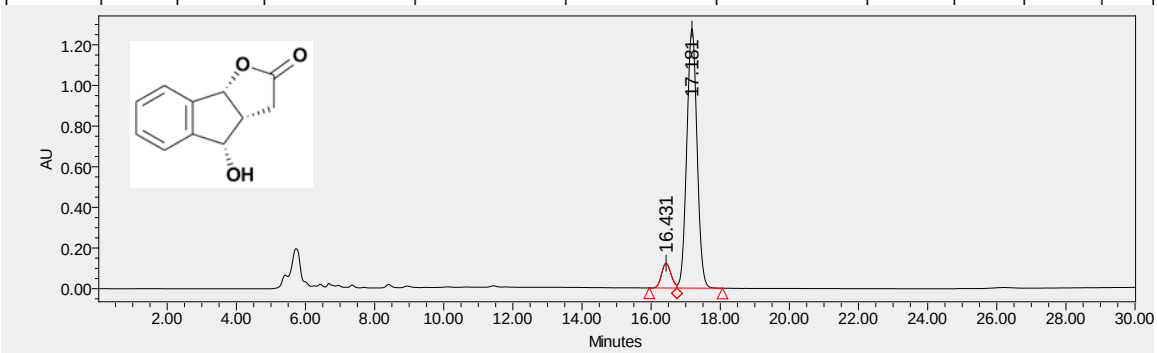
(+)-4-OH-GR24 (+)-4 and (+)-4-OH-*epi*-GR24. To a solution of alcohol **(+)-8** (28.4 mg, 0.149 mmol) in neat methyl formate (2 mL) was added at 0 °C potassium *tert*-butoxide (99.9 mg, 0.897 mmol) portion wise and the reaction allowed to warm to room temperature. After 3 h (starting material consumption indicative by TLC analysis), the reaction mixture was quenched by the addition of 1M HCl (5 mL) and the organics extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with

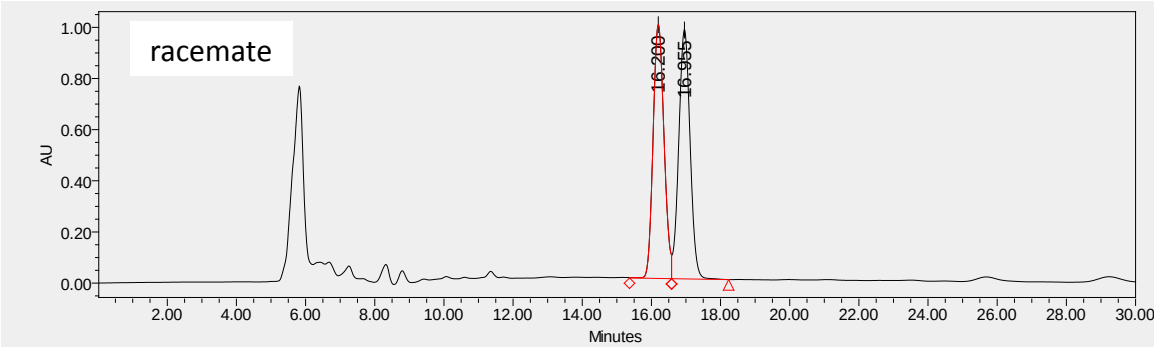
brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The crude enol product was taken up in DMF (1.5 mL) and K_2CO_3 (34.6 mg, 0.250 mmol) was added at room temperature. The reaction mixture was cooled to 0 °C and a solution of bromobutenolide **17** (39.9 mg, 0.224 mmol) in DMF (0.5 mL) was added *via* cannula. After 16 h, the reaction mixture was quenched by addition of saturated aqueous NH_4Cl (5 mL) and the organics extracted with ethyl acetate (4 × 5 mL). The combined organic extracts were washed with a H_2O:brine mixture (1:1, 5 mL), washed with brine (5 mL), dried (Na_2SO_4), filtered and concentrated *in vacuo*. Purification by flash column chromatography (60% ethyl acetate/Pet. Ether) provided a mixture of **(+)-4** (12.2 mg, 26%) as a white solid. mp 77.8–85.6 °C; $[\alpha]_D^{20}$ +299 (*c* 0.41, $CHCl_3$); IR (thin film) 3426, 1779, 1745, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54–7.52 (1H, m, ArH), 7.53 (1H, d, *J* = 2.6 Hz, $H_{6'}$), 7.46–7.41 (3H, m, ArH), 7.00–6.98 (1H, m, $H_{3'}$), 6.23 (1H, t, *J* = 1.4 Hz, $H_{2'}$), 6.07 (1H, d, *J* = 7.5 Hz, H_{8b}), 5.32 (1H, d, *J* = 3.5 Hz, H_4), 3.82 (1H, ddd, *J* = 7.5, 2.6, 1.9 Hz, H_{3a}), 2.30 (1H, br s, OH), 2.04 (3H, t, *J* = 1.5 Hz, $H_{7'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.0, 151.6, 143.8, 140.8, 139.2, 136.4, 130.7, 130.2, 126.6, 125.5, 110.2, 100.4, 84.1, 79.7, 50.5, 10.8; HRMS (ES^+) Calc for $C_{17}H_{14}O_6Na$ $[M+Na]^+$ 337.06826, found 337.06847.

and **(+)-4-OH-*epi*-GR24** (12.8 mg, 27%) as a white solid. mp 163.1–168.9 °C; $[\alpha]_D^{20}$ +186 (*c* 0.29, $CHCl_3$); IR (thin film) 3432, 1780, 1744, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (1H, d, *J* = 2.7 Hz, $H_{6'}$), 7.54–7.51 (1H, m, ArH), 7.46–7.40 (3H, m, ArH), 7.00–6.98 (1H, m, $H_{3'}$), 6.22 (1H, t, *J* = 1.4 Hz, $H_{2'}$), 6.08 (1H, d, *J* = 7.5 Hz, H_{8b}), 5.30 (1H, d, *J* = 2.2 Hz, H_4), 3.82 (1H, ddd, *J* = 7.5, 2.7, 1.8 Hz, H_{3a}), 2.30 (1H, br s, OH), 2.04 (3H, t, *J* = 1.5 Hz, $H_{7'}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.1, 152.0, 143.8, 140.9, 139.2, 136.1, 130.7, 130.1, 126.5, 125.6, 110.1, 100.7, 84.1, 79.6, 50.4, 10.8; HRMS (ES^+) Calc for $C_{17}H_{14}O_6Na$ $[M+Na]^+$ 337.06826, found 337.06857.

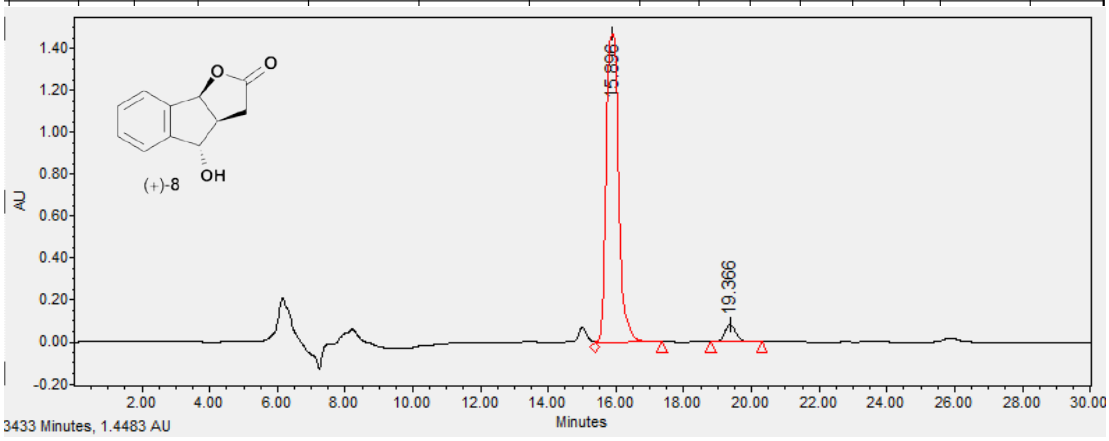
Enantioselective HPLC traces

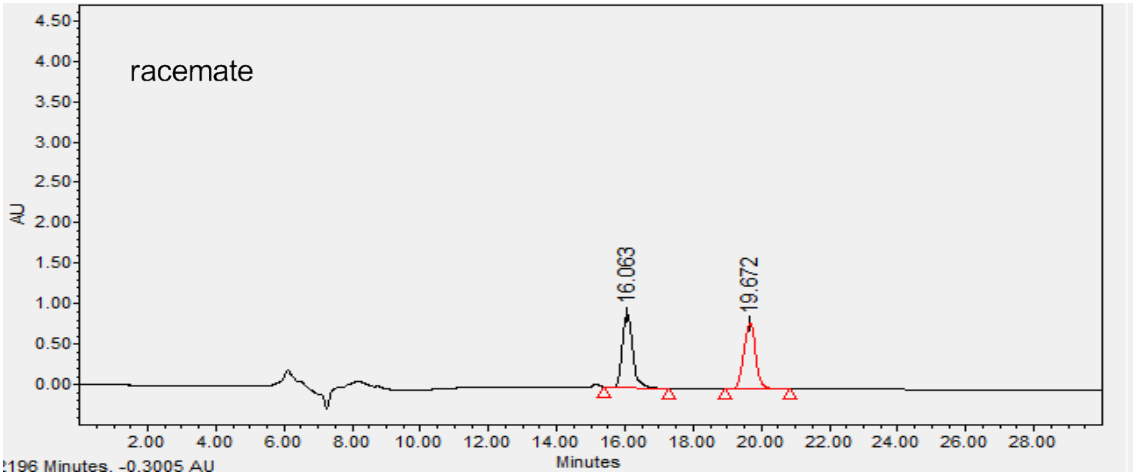
Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area	Height (μV)	Int Typ
16.431							1961247	6.93	112506	bb
17.181							26348665	93.07	1275015	VB

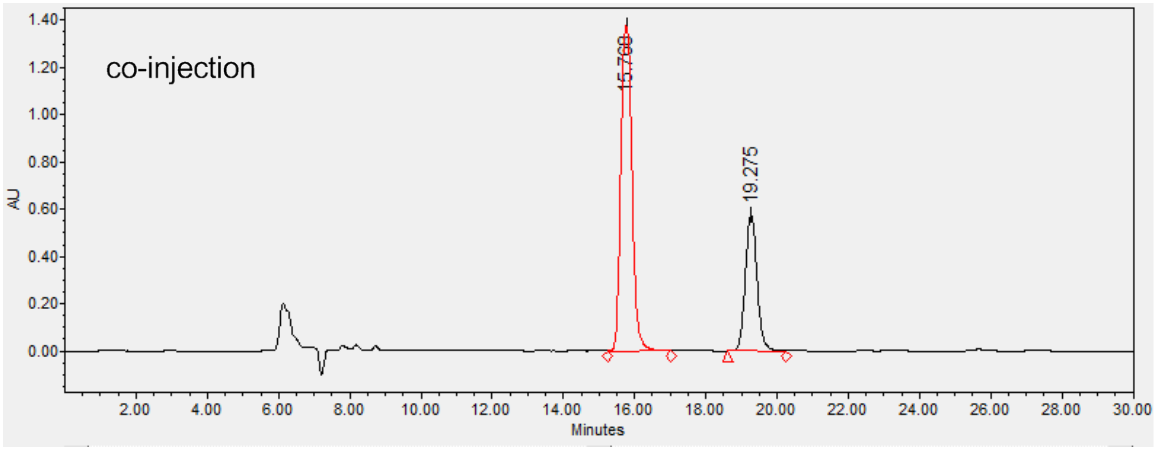




Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (µV*sec)	% Area	Height (µV)	Int Type	Amount	Units	Peak Type	Peak Codes
15.896							2642376	96.98	139858	BB			Unknown	
19.366							82368	3.02	3865	BB			Unknown	

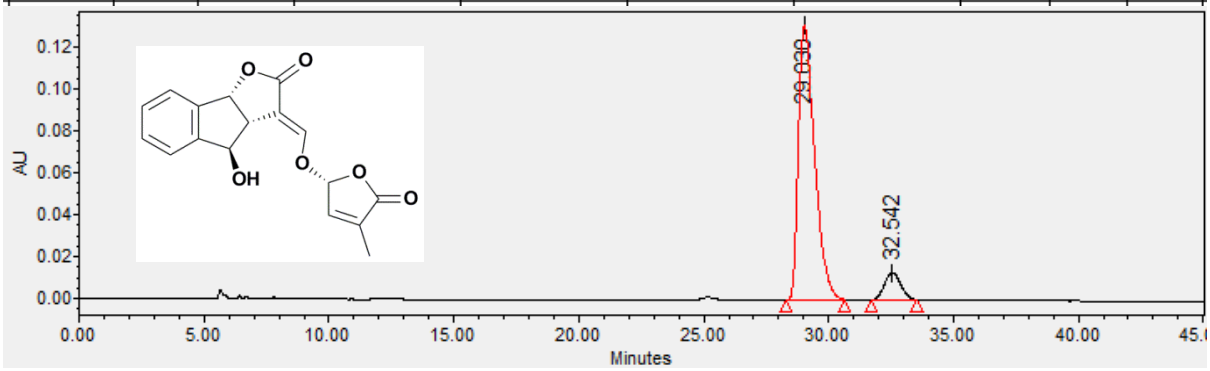


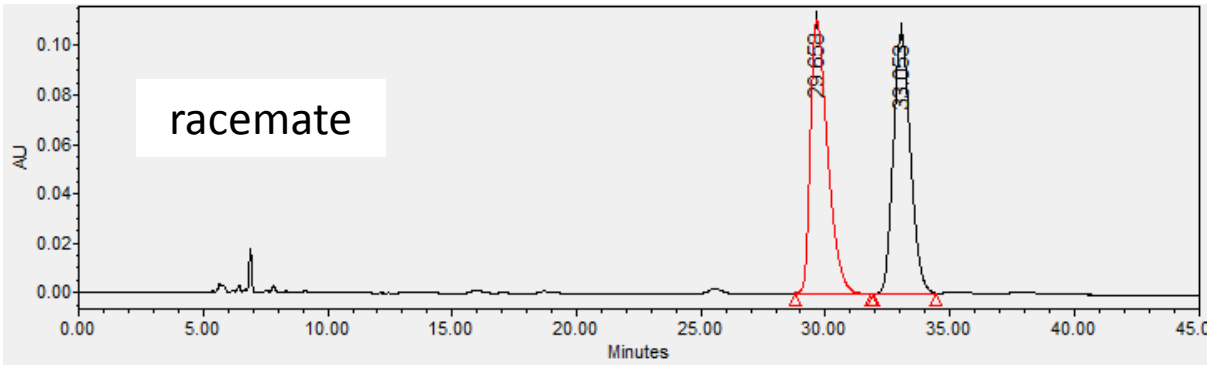


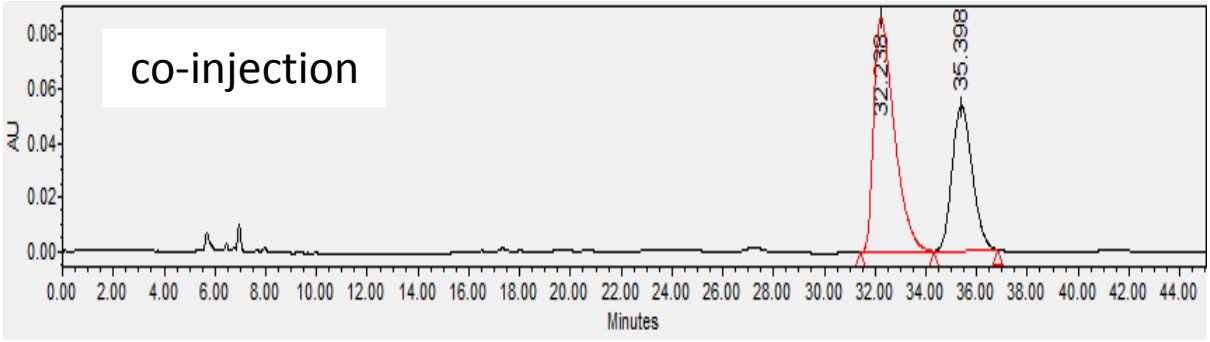


Enantioselective HPLC traces

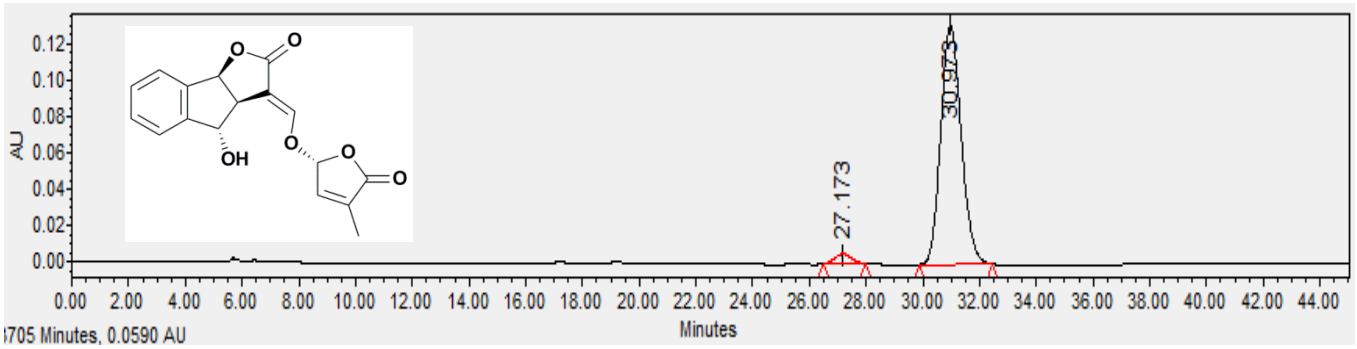
Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area	Height (μV)
29.030							5925098	90.89	130547
32.542							593653	9.11	13061

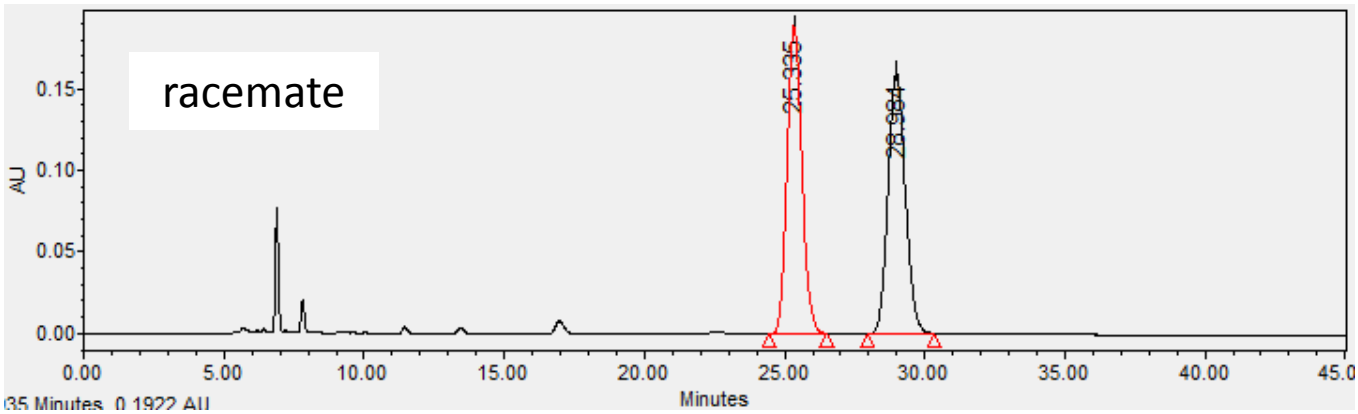


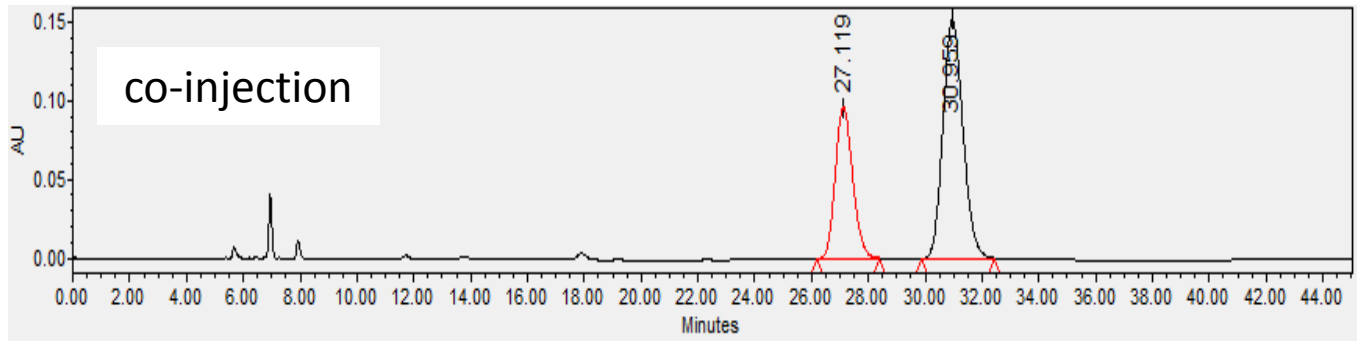




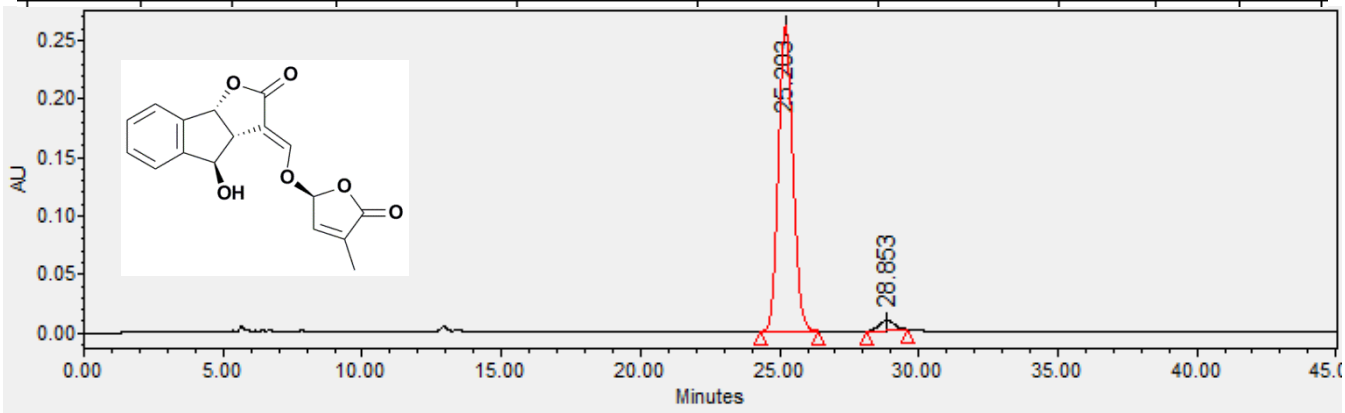
Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area	Height (μV)
27.173							222107	3.28	5410
30.973							6553544	96.72	131099

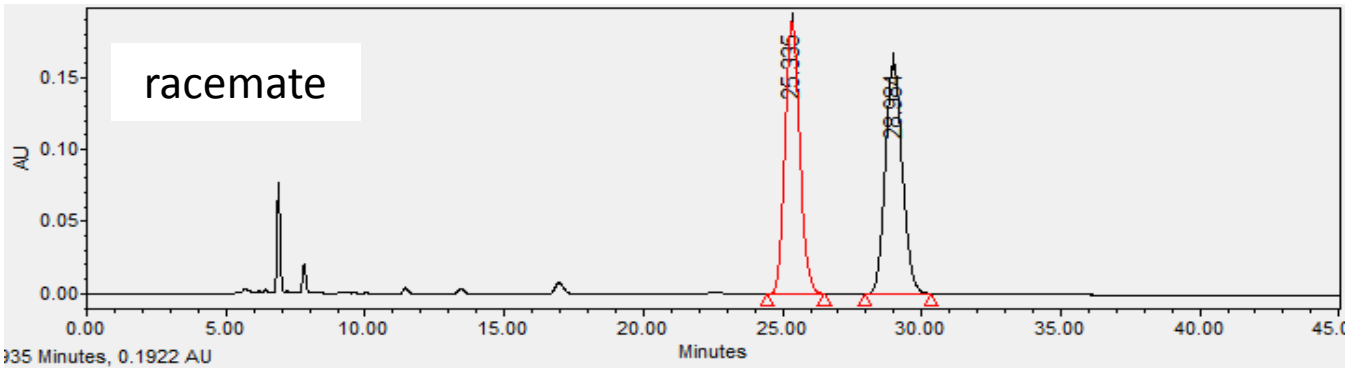


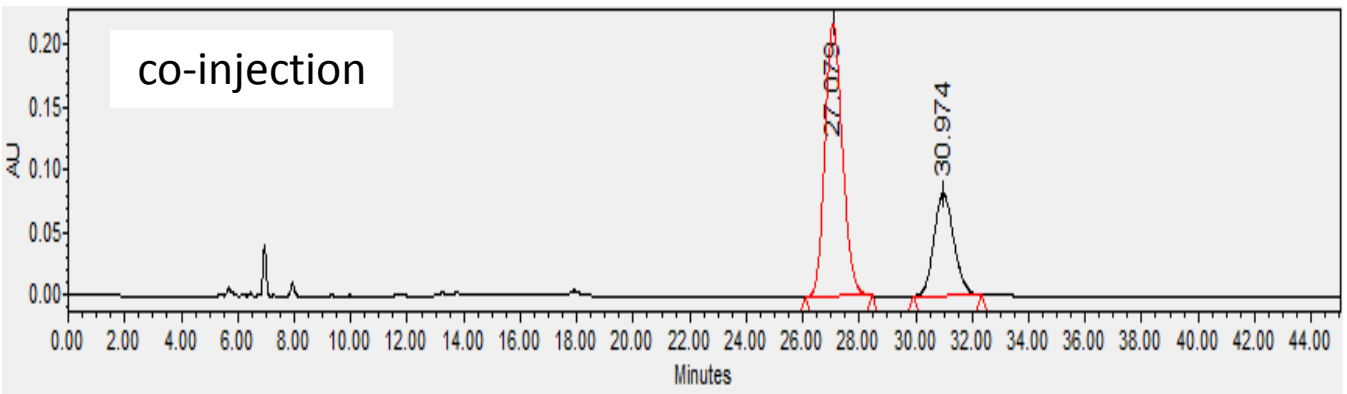




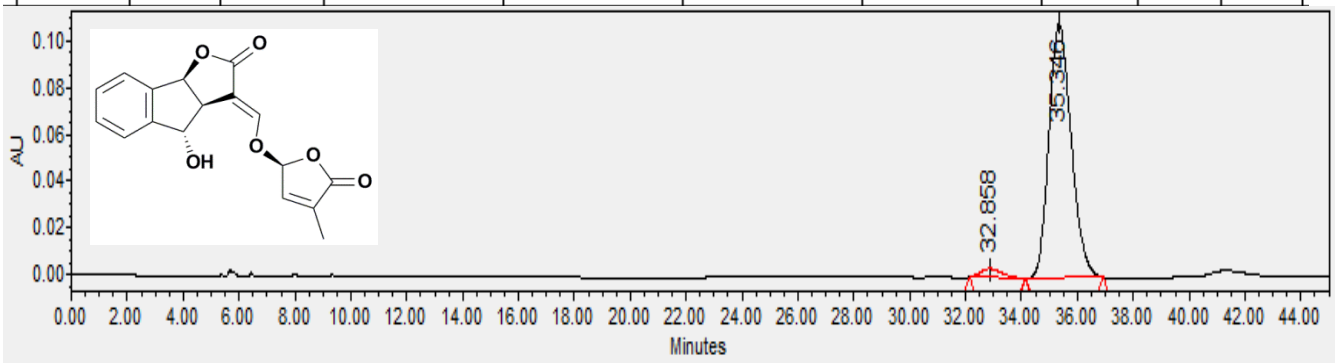
Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area	Height (μV)
25.203							9509975	96.82	260833
28.853							312739	3.18	8056

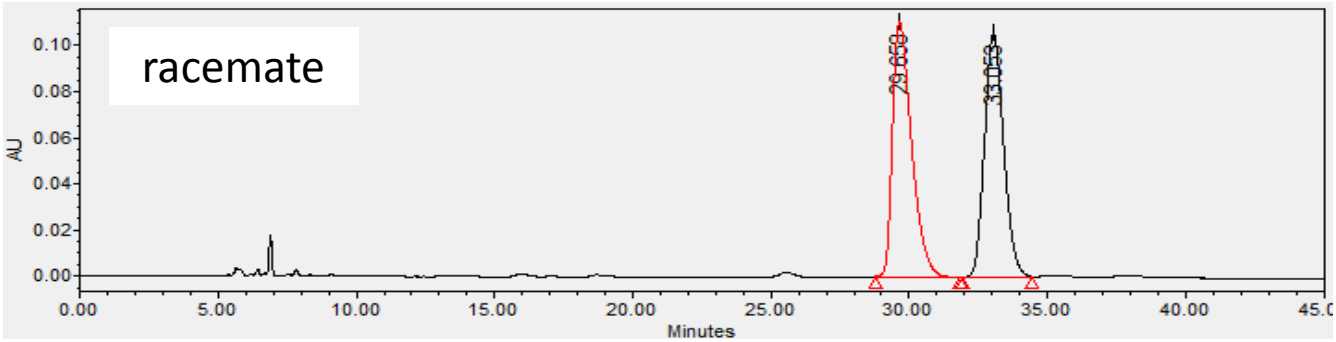


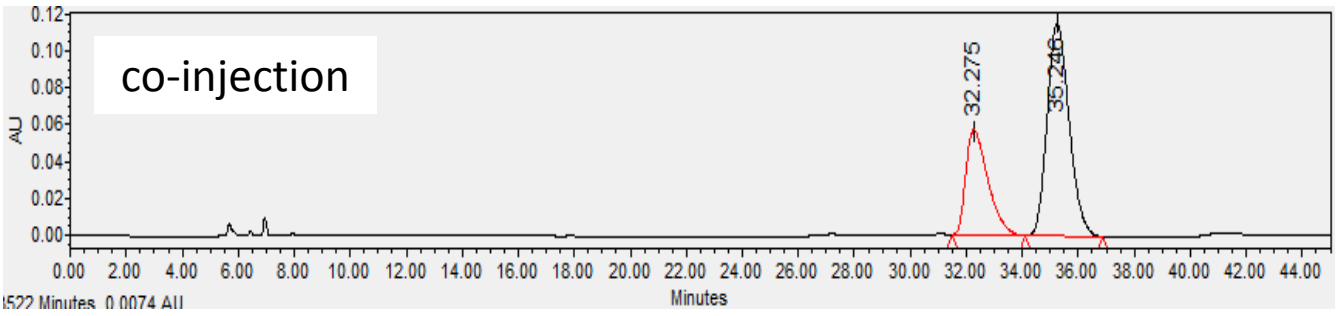




Retention Time (min)	Purity1 Angle	Purity1 Threshold	PDA/FLR Match1 Spect. Name	PDA/FLR Match1 Angle	PDA/FLR Match1 Threshold	PDA/FLR Match1 Lib. Name	Area (μV*sec)	% Area	Height (μV)
32.858							198789	3.20	3785
35.346							6014805	96.80	108667

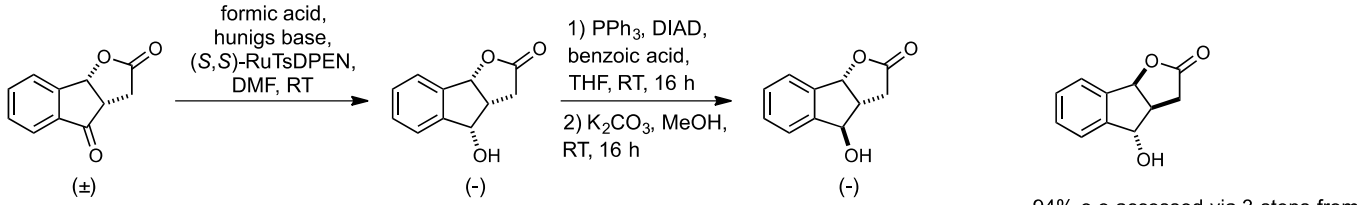






Racemisation studies

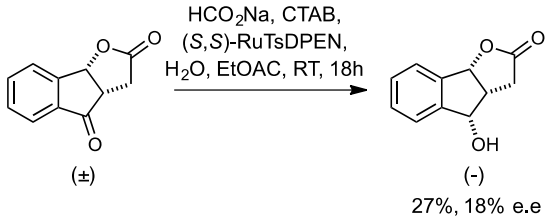
In order to ascertain the most appropriate conditions for maximizing both yield and level of enantioselectivity for the Noyori asymmetric kinetic resolution of alcohol (±)-**6**, the reaction time was varied and the *e.e*. of the corresponding *anti*-alcohol (−)-**8** was assessed by enantioselective HPLC.

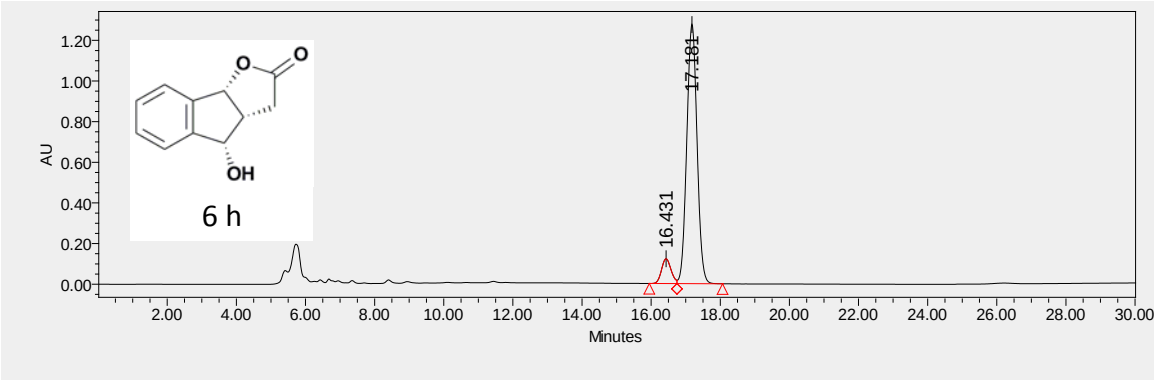


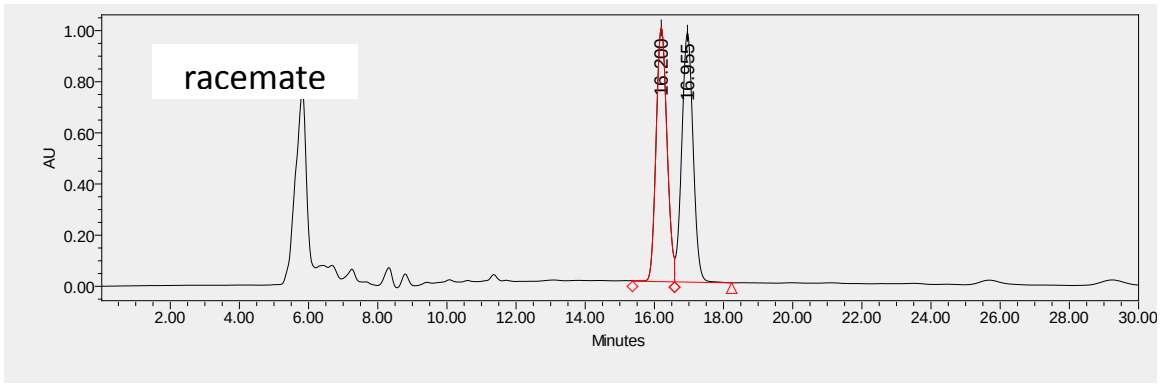
Time (h)	e.e (%)	yield (%)
18	64*	50
9	80	47
7	84	48
6	86	49
5	96	10

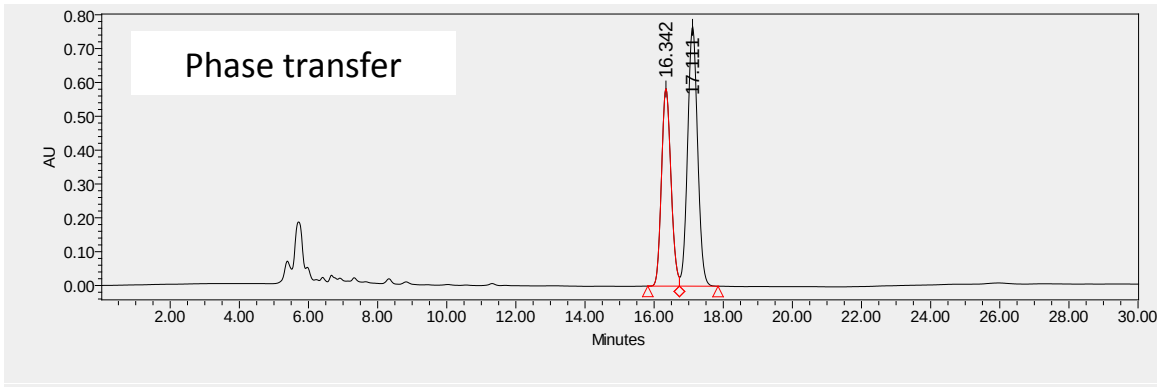
* e.e measured after Mitsunobu/K_2CO_3

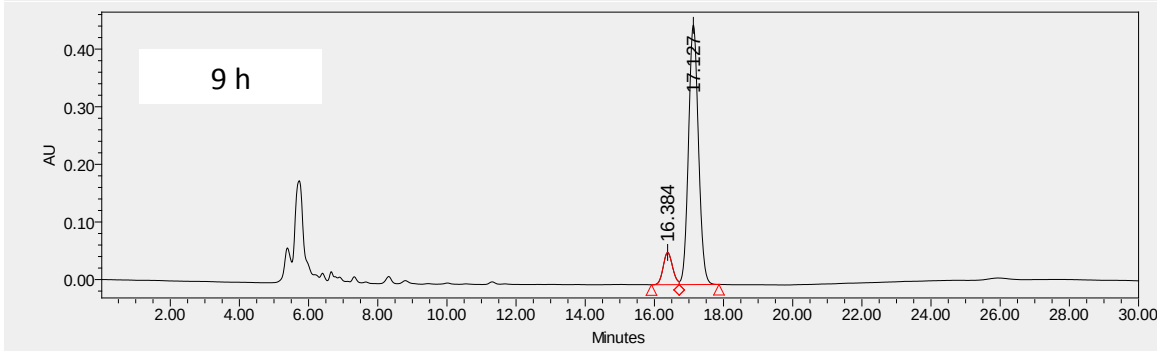
In order to ascertain whether the solvent or the catalyst were responsible for the observed racemization, the Noyori asymmetric kinetic resolution of alcohol (±)-**6** was carried out under phase transfer conditions that enable the catalyst to migrate into the organic phase. This suggests that the catalyst (or a decomposition product thereof) is responsible for the epimerisation.

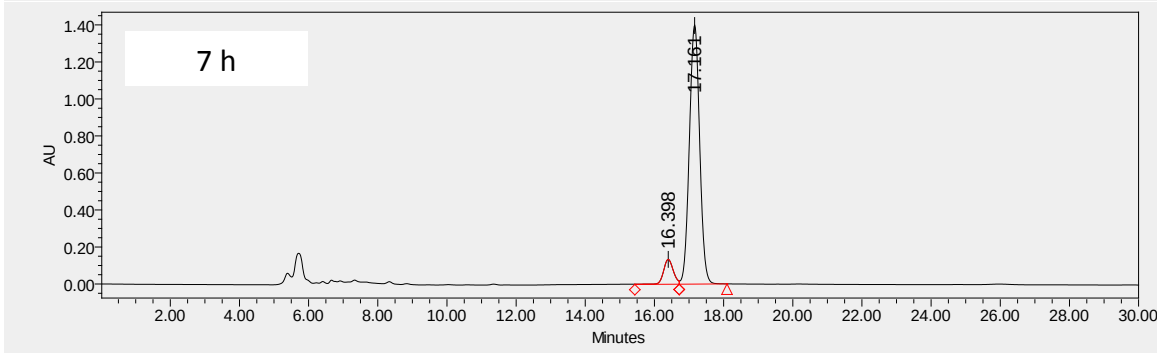


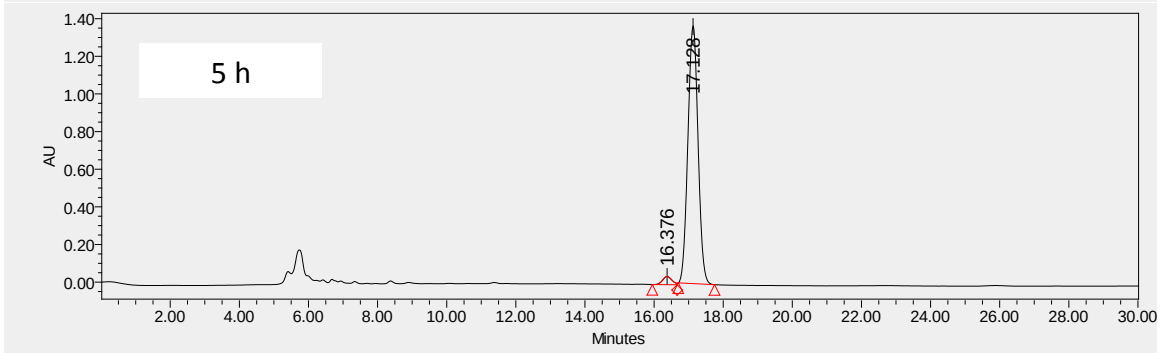



racemate
16.280
16.955
AU
Minutes

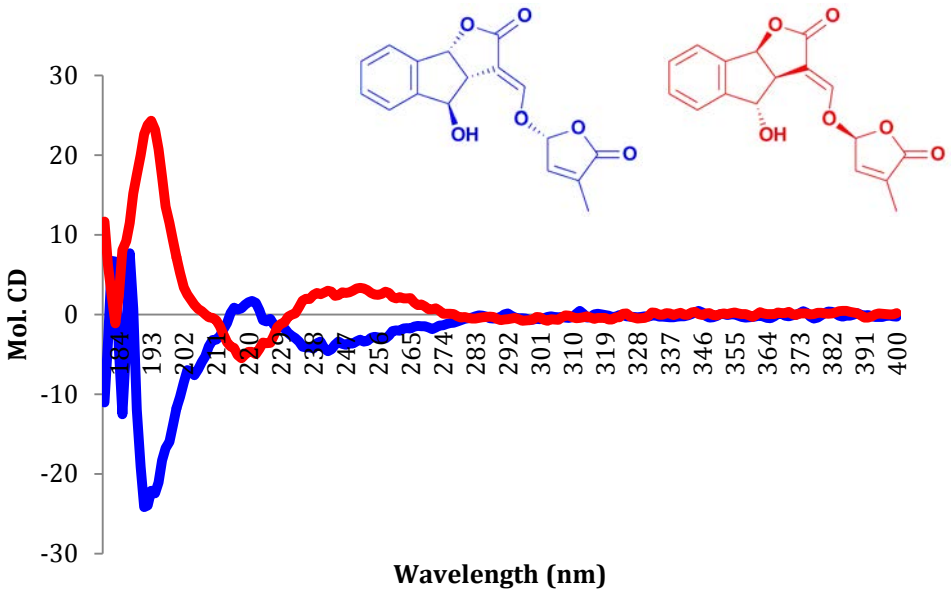

Phase transfer
16.342
17.111
AU
Minutes

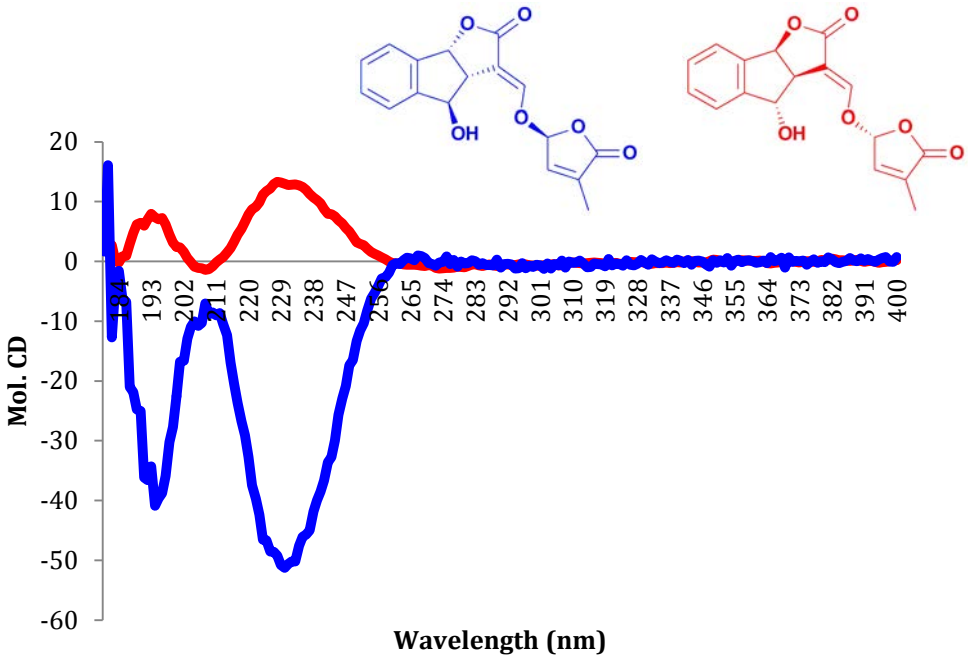

9 h
16.384
17.127
AU
Minutes


7 h
16.398
17.161
AU
Minutes


5 h
16.376
17.128
AU
Minutes

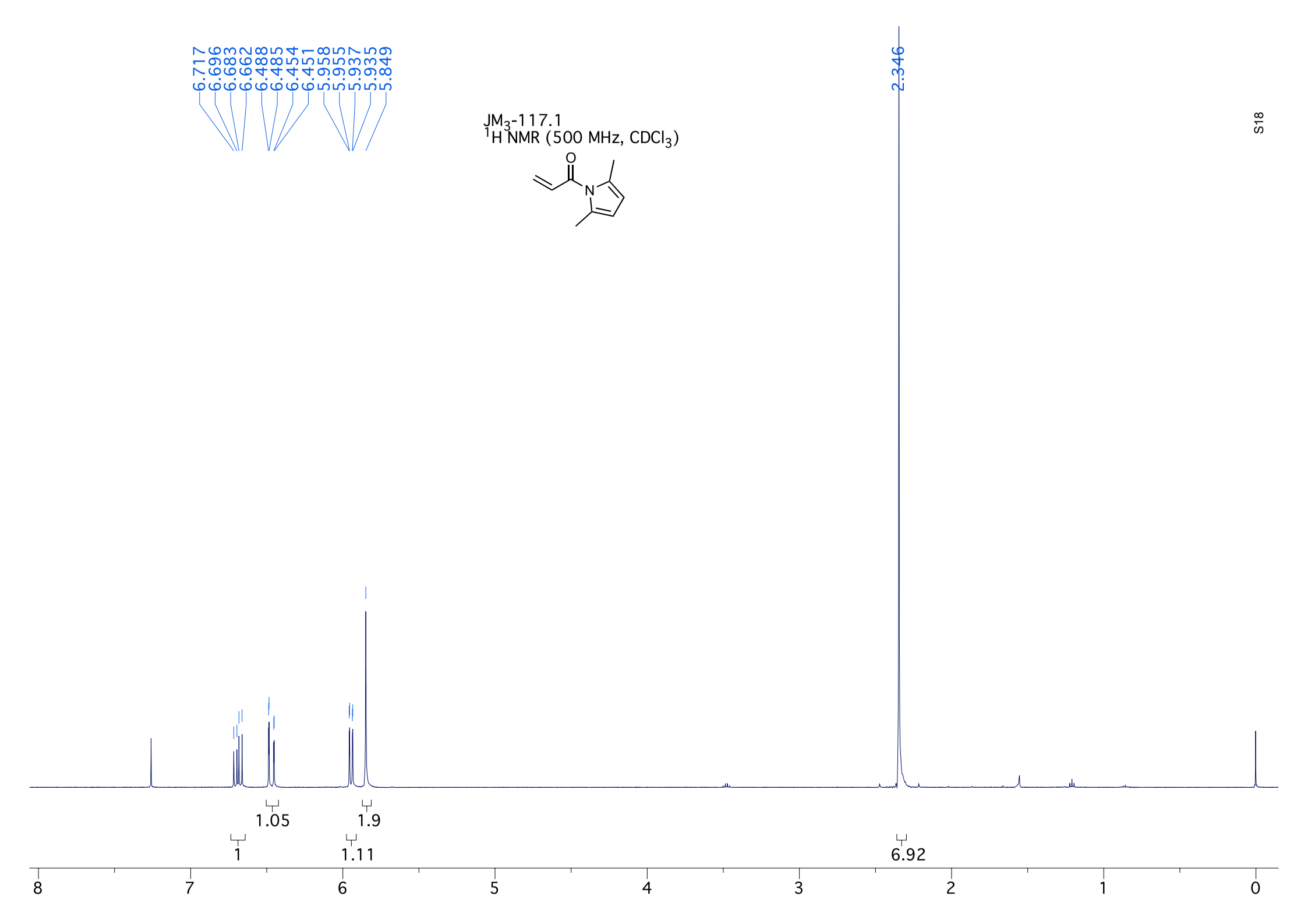
CD spectra

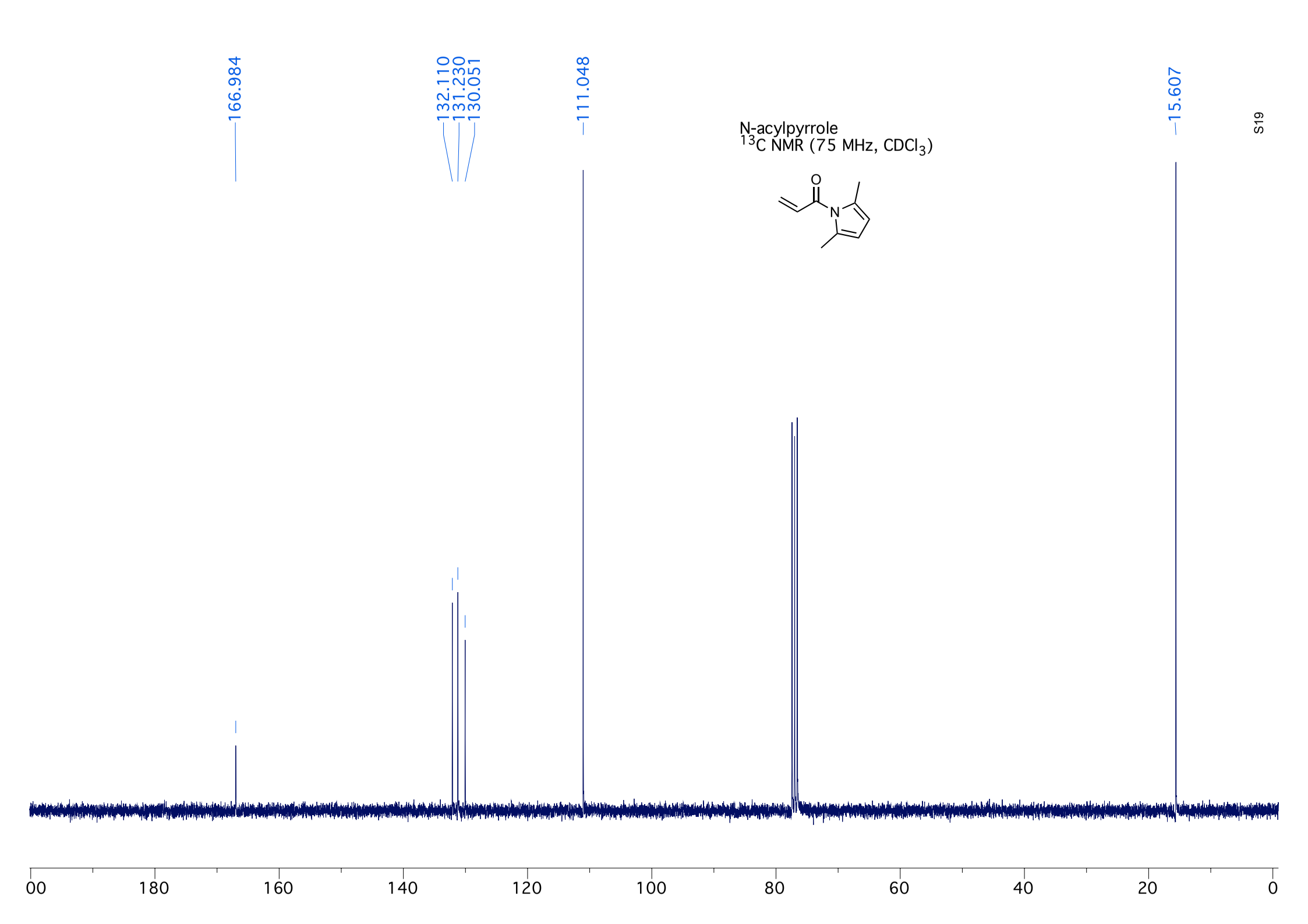

30
20
10
0
-10
-20
-30
Mol. CD
184
193
202
211
220
229
238
247
256
265
274
283
292
301
310
319
328
337
346
355
364
373
382
391
400
Wavelength (nm)
OH
OH

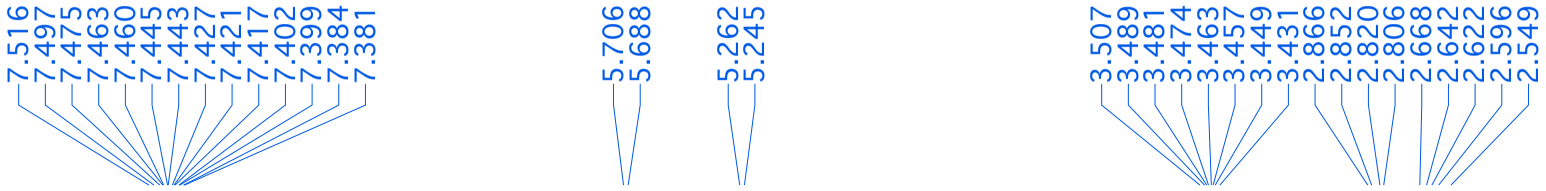

20
10
0
-10
-20
-30
-40
-50
-60
Mol. CD
184
193
202
211
220
229
238
247
256
265
274
283
292
301
310
319
328
337
346
355
364
373
382
391
400
Wavelength (nm)
OH
OH

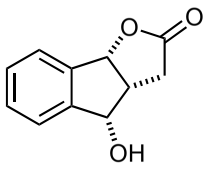
References

[1] L. J. Bromhead, J. Visser, C. S. P. McErlean, *J. Org. Chem.* **2014**, *79*, 1516-1520.
[2] G. K. Cooper, L. J. Dolby, *J. Org. Chem.* **1979**, *44*, 3414-3416.
[3] H. Malik, W. Kohlen, M. Jamil, F. P. J. T. Rutjes, B. Zwanenburg, *Org. Biomol. Chem.* **2011**, *9*, 2286-2293.

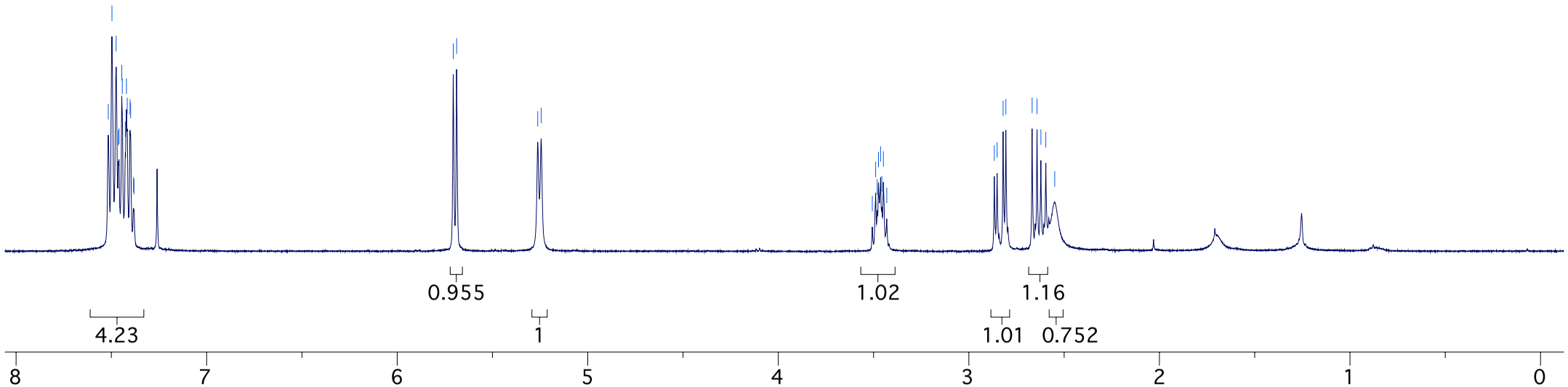

6.717
6.696
6.683
6.662
6.488
6.485
6.454
6.451
5.958
5.955
5.937
5.935
5.849
2.346
JM3-117.1
1H NMR (500 MHz, CDCl3)
O
N
S18
1.05
1.9
1
1.11
6.92
8
7
6
5
4
3
2
1
0

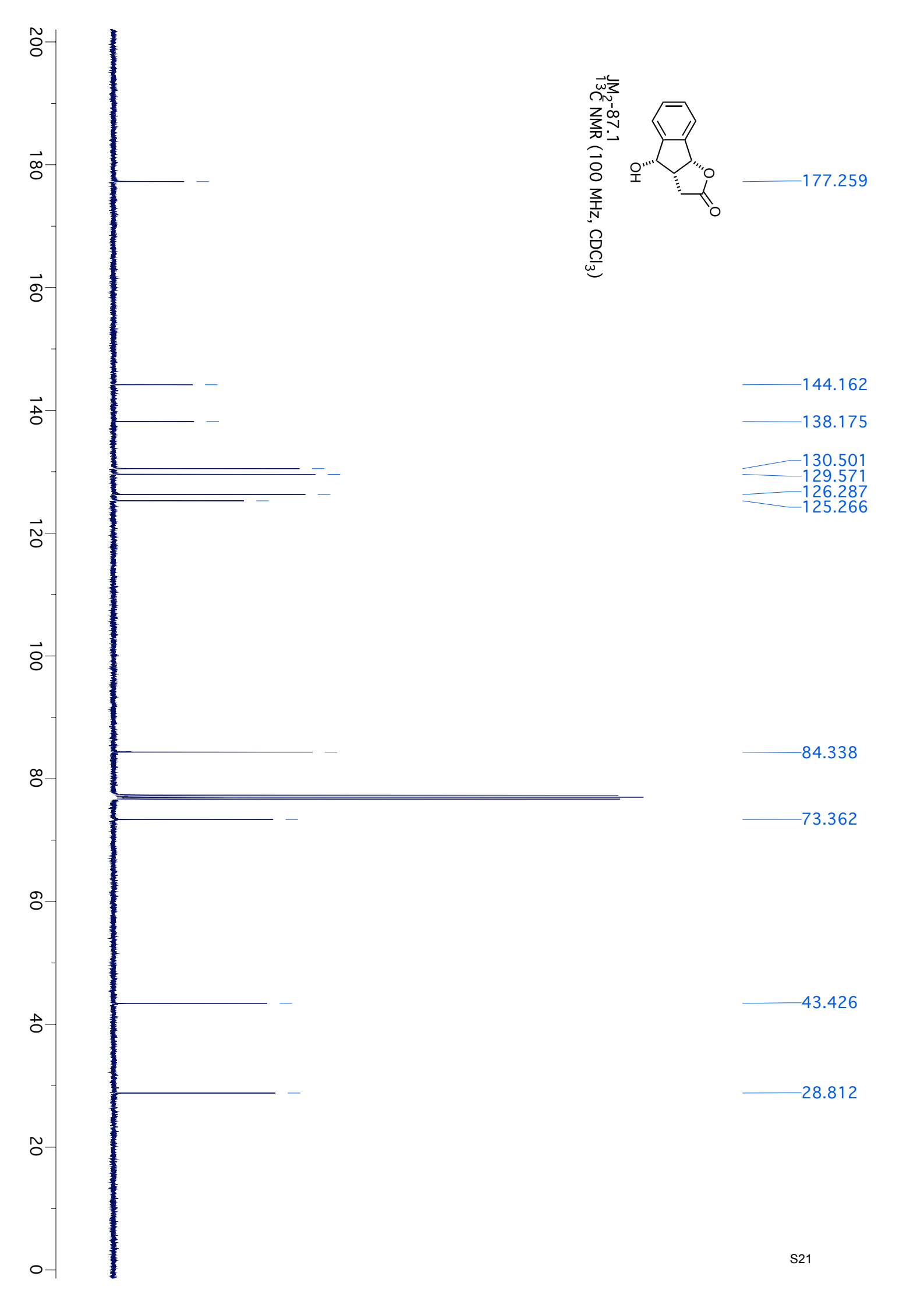

166.984
132.110
131.230
130.051
111.048
15.607
N-acylpyrrole
^{13}C NMR (75 MHz, $CDCl_3$)
O
N
S19
00
180
160
140
120
100
80
60
40
20
0



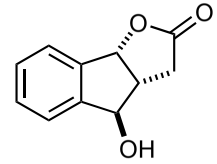


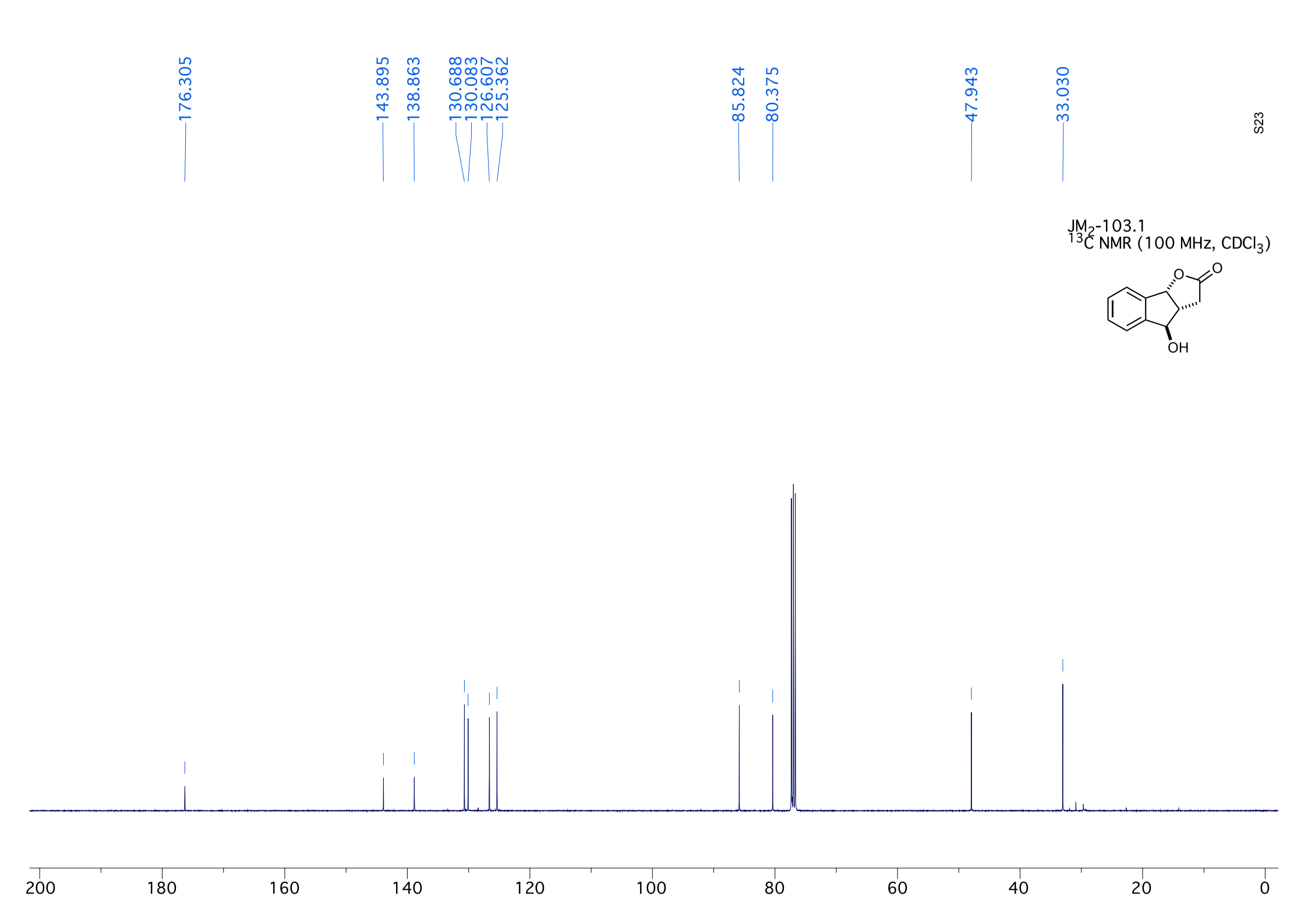
JM_2-87.1
^1H NMR (400 MHz, $CDCl_3$)

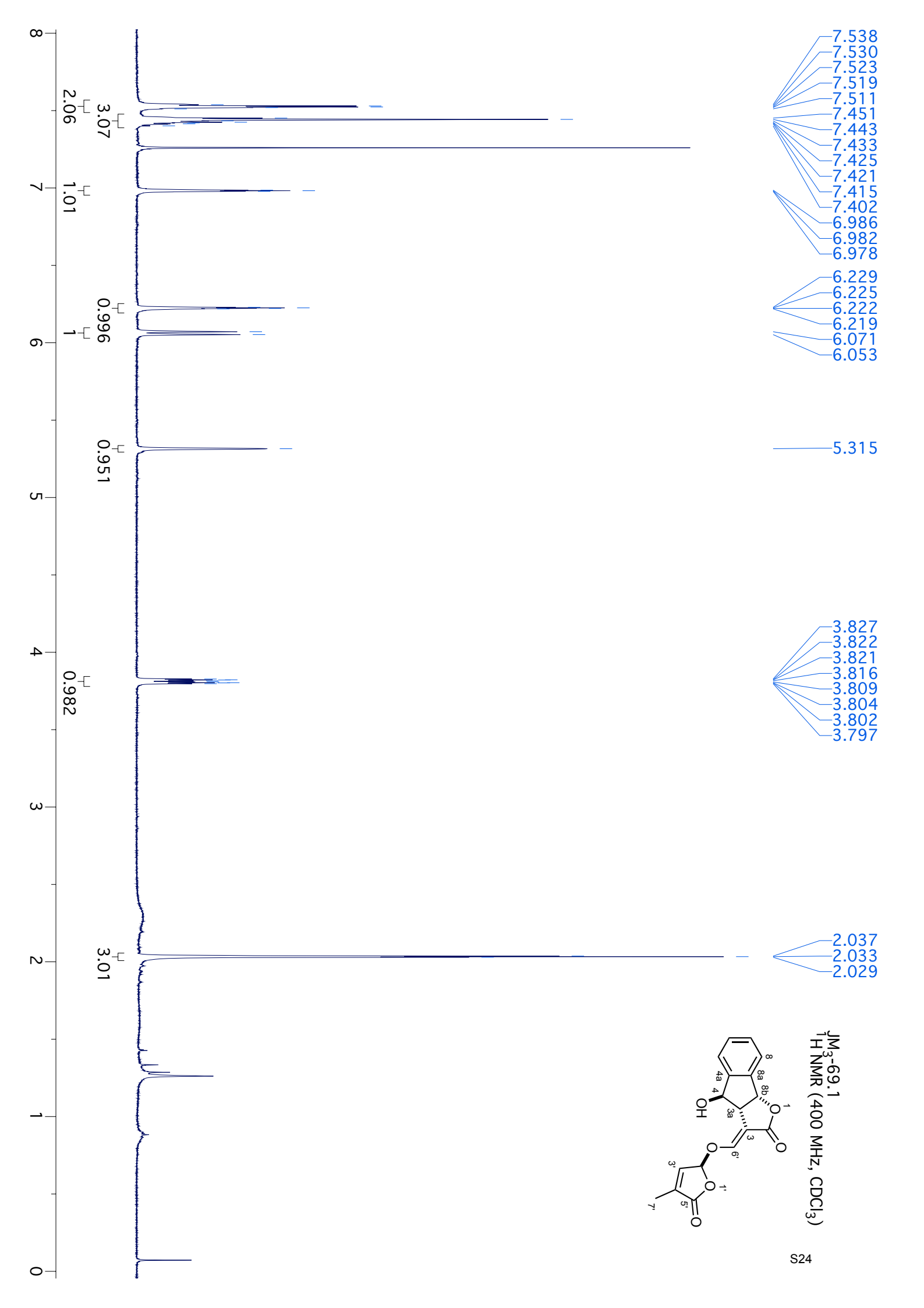


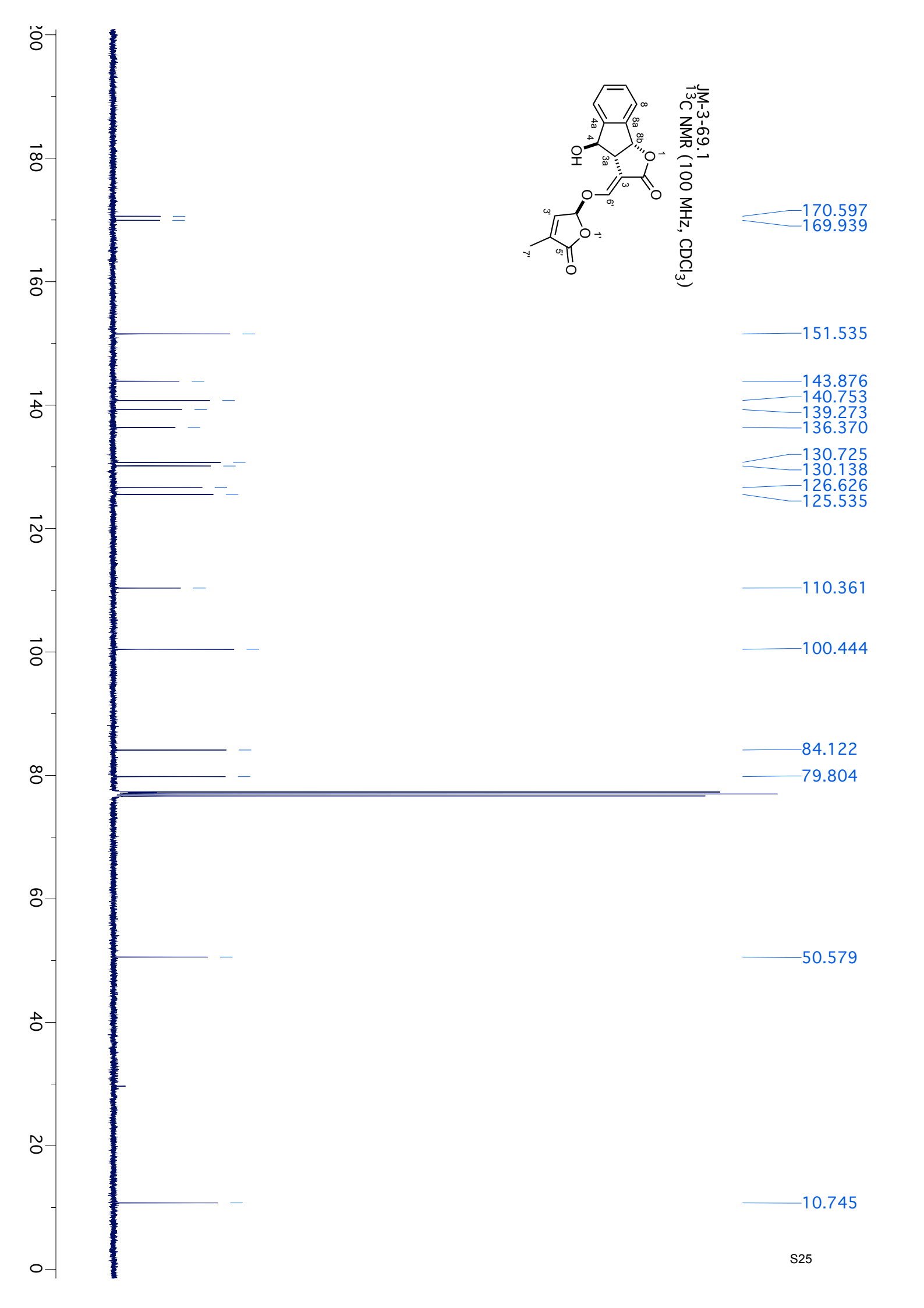

JM2-87.1
13C NMR (100 MHz, CDCl3)
OH
O
O
177.259
144.162
138.175
130.501
129.571
126.287
125.266
84.338
73.362
43.426
28.812
200
180
160
140
120
100
80
60
40
20
0

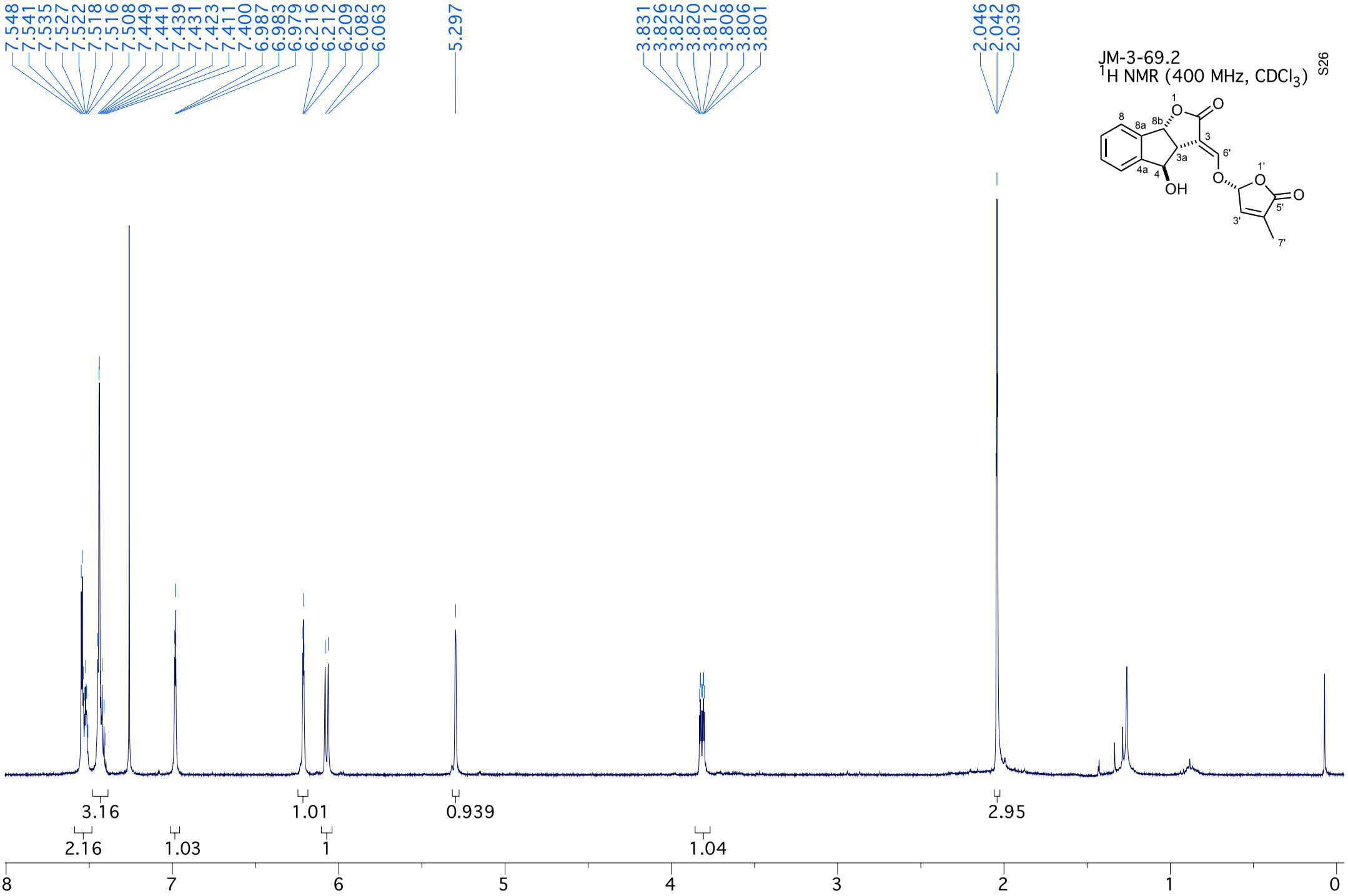
JM$_2$-103.1
^{1}H NMR (400 MHz, $CDCl_3$)

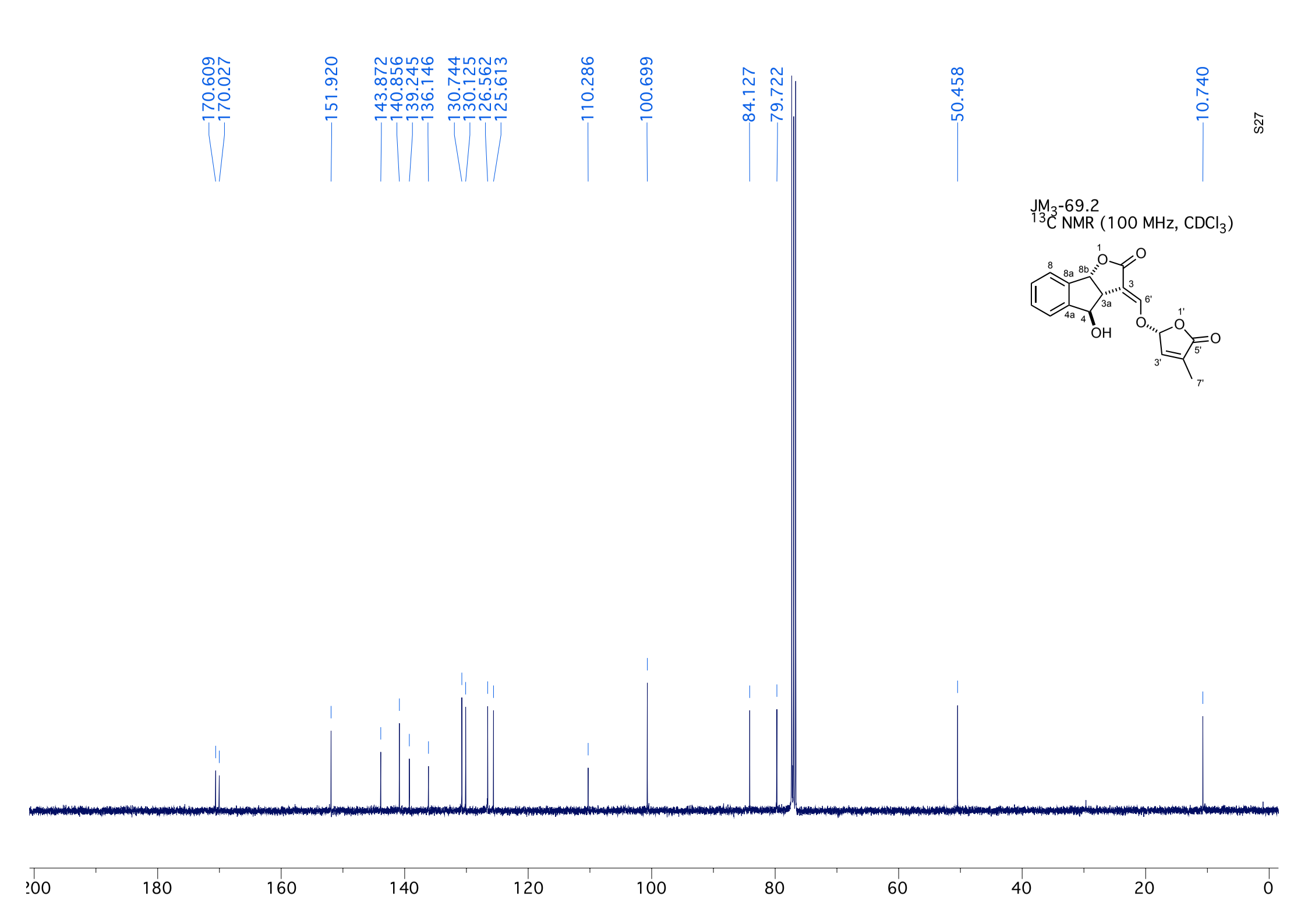



176.305
143.895
138.863
130.688
130.083
126.607
125.362
85.824
80.375
47.943
33.030
S23
JM2-103.1
13C NMR (100 MHz, CDCl3)
O
O
OH
200
180
160
140
120
100
80
60
40
20
0

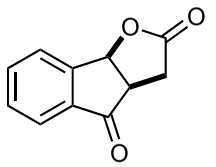

7.538
7.530
7.523
7.519
7.511
7.451
7.443
7.433
7.425
7.421
7.415
7.402
6.986
6.982
6.978
6.229
6.225
6.222
6.219
6.071
6.053
5.315
3.827
3.822
3.821
3.816
3.809
3.804
3.802
3.797
2.037
2.033
2.029
2.06
3.07
1.01
0.996
1
0.951
0.982
3.01
JM3-69.1
^{1}H NMR (400 MHz, $CDCl_3$)
OH


JM-3-69.1
^{13}C NMR (100 MHz, $CDCl_3$)
170.597
169.939
151.535
143.876
140.753
139.273
136.370
130.725
130.138
126.626
125.535
110.361
100.444
84.122
79.804
50.579
10.745
200
180
160
140
120
100
80
60
40
20
0

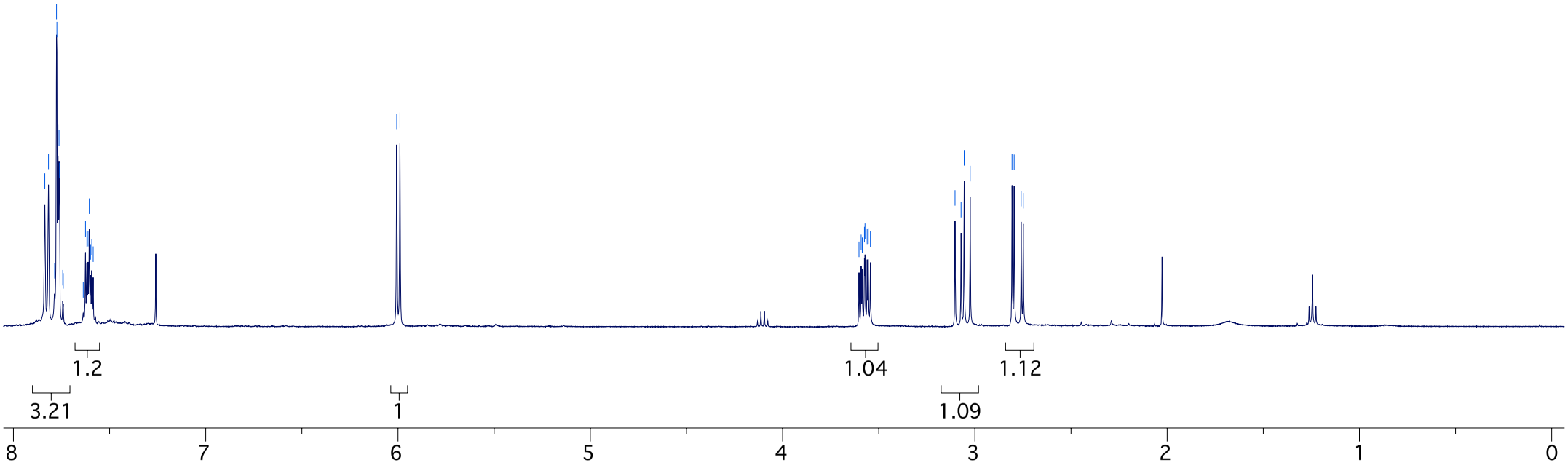

7.548
7.541
7.535
7.527
7.522
7.518
7.516
7.508
7.449
7.441
7.439
7.431
7.423
7.411
7.400
6.987
6.983
6.979
6.216
6.212
6.209
6.082
6.063
5.297
3.831
3.826
3.825
3.820
3.812
3.808
3.806
3.801
2.046
2.042
2.039
JM-3-69.2
1H NMR (400 MHz, CDCl3)
S26
3.16
1.01
0.939
2.95
2.16
1.03
1
1.04
8
7
6
5
4
3
2
1
0

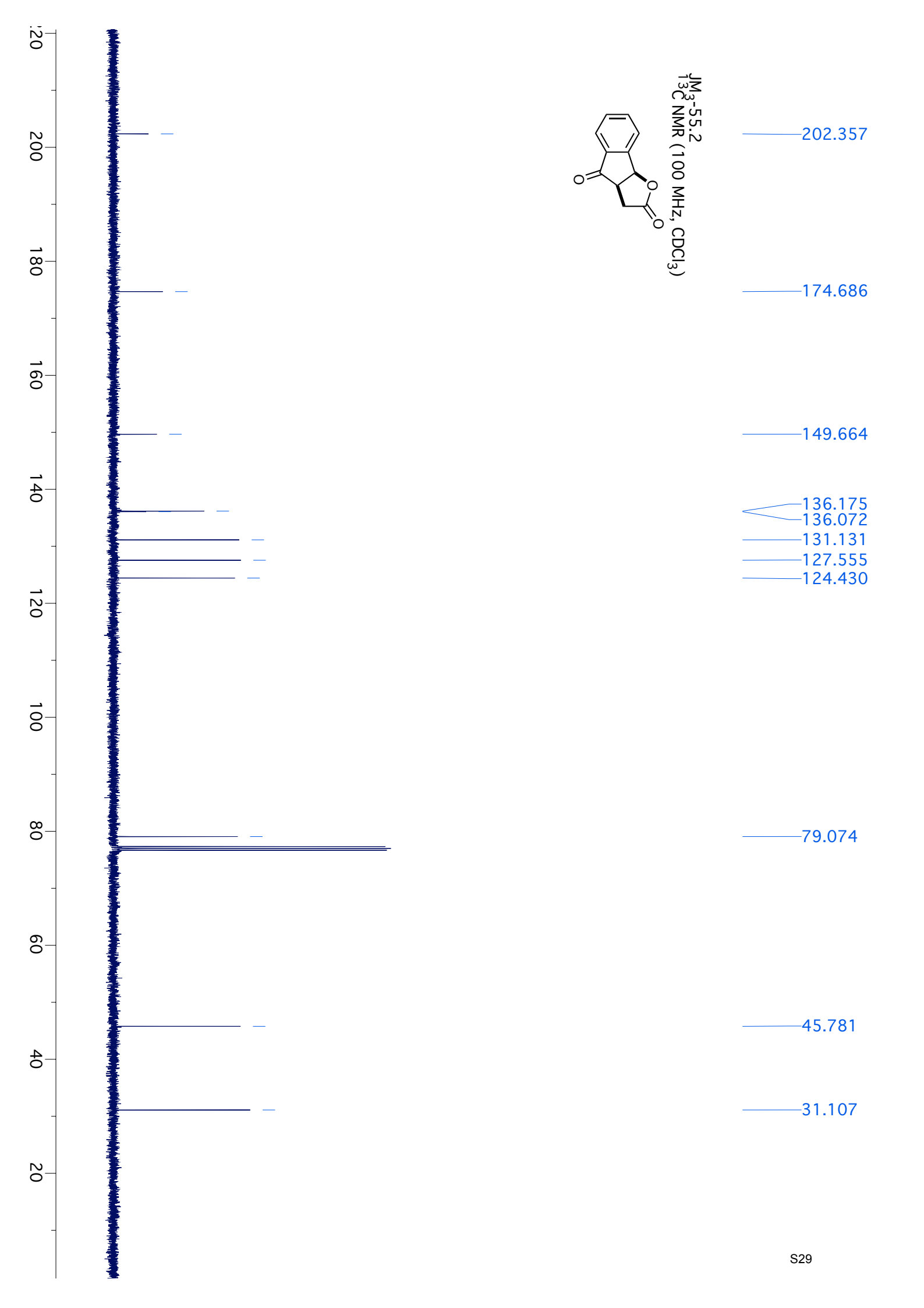

170.609
170.027
151.920
143.872
140.856
139.245
136.146
130.744
130.125
126.562
125.613
110.286
100.699
84.127
79.722
50.458
10.740
S27
JM3-69.2
13C NMR (100 MHz, CDCl3)
OH
200
180
160
140
120
100
80
60
40
20
0

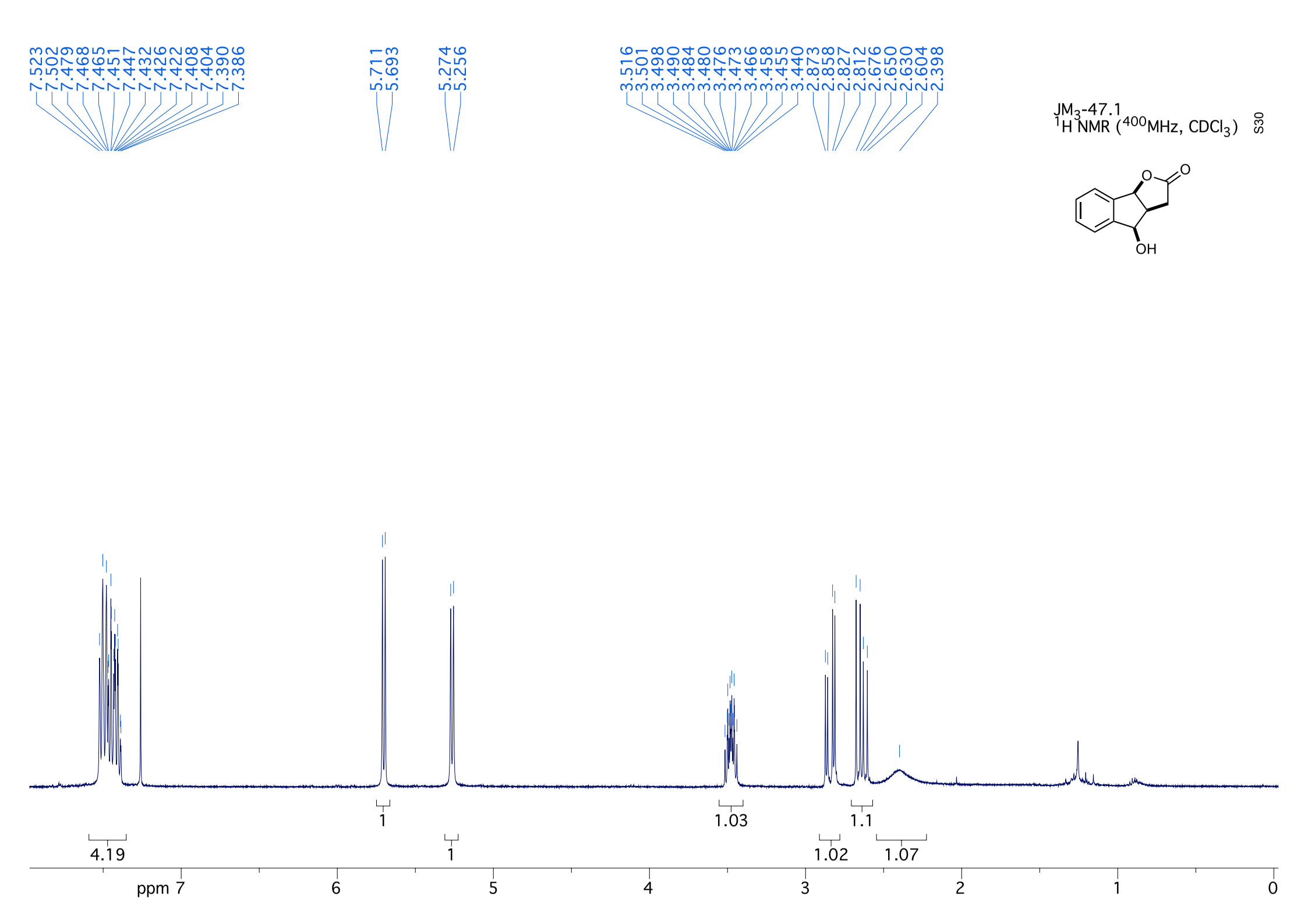
JM$_3$-55.2
^{1}H NMR (400 MHz, CDCl$_3$)

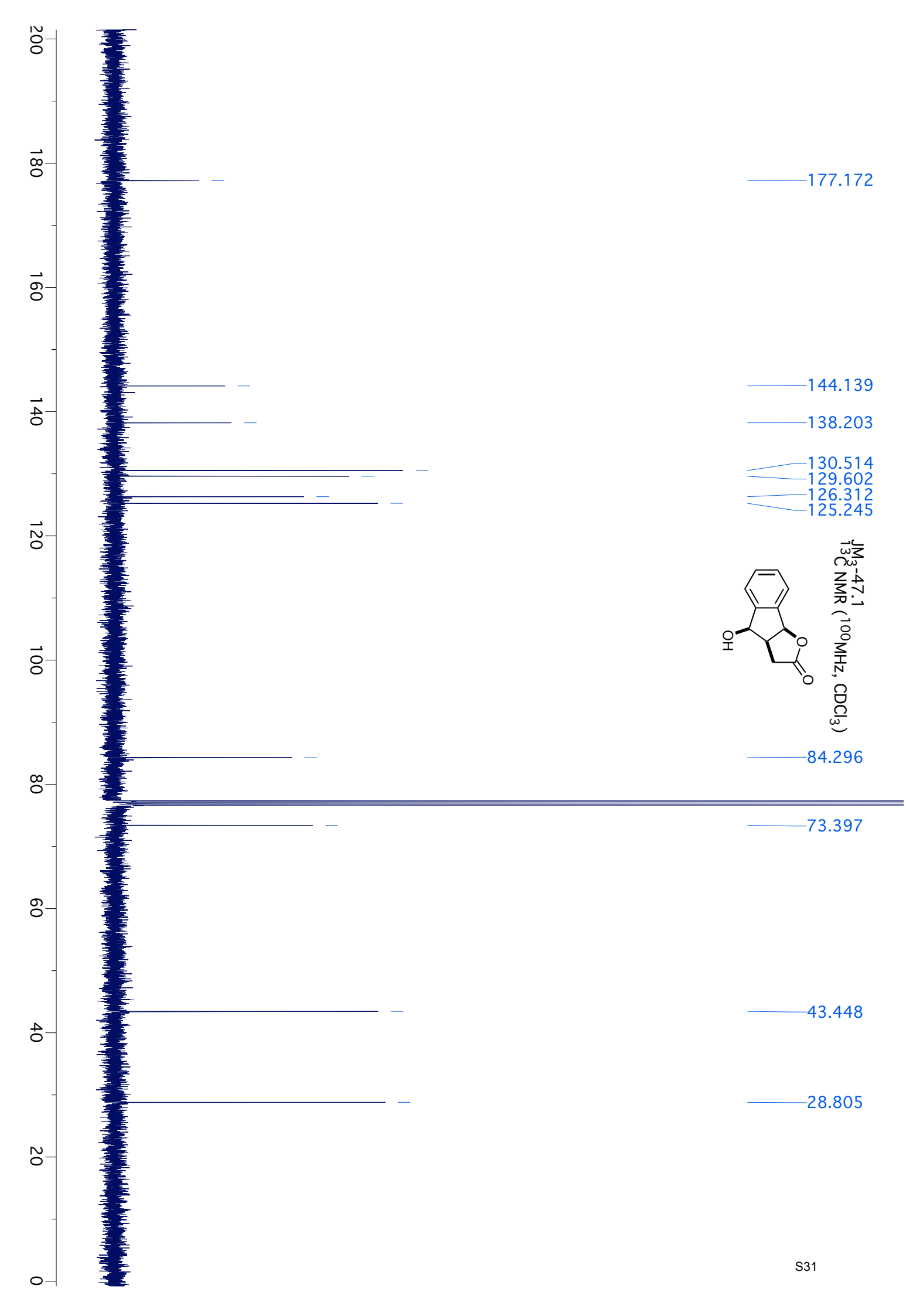


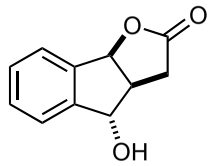
7.837
7.818
7.786
7.776
7.774
7.769
7.763
7.760
7.744
7.741
7.637
7.625
7.618
7.612
7.606
7.599
7.593
7.585
6.007
5.990
3.603
3.592
3.586
3.574
3.572
3.560
3.555
3.543
3.103
3.072
3.056
3.024
2.807
2.796
2.759
2.748



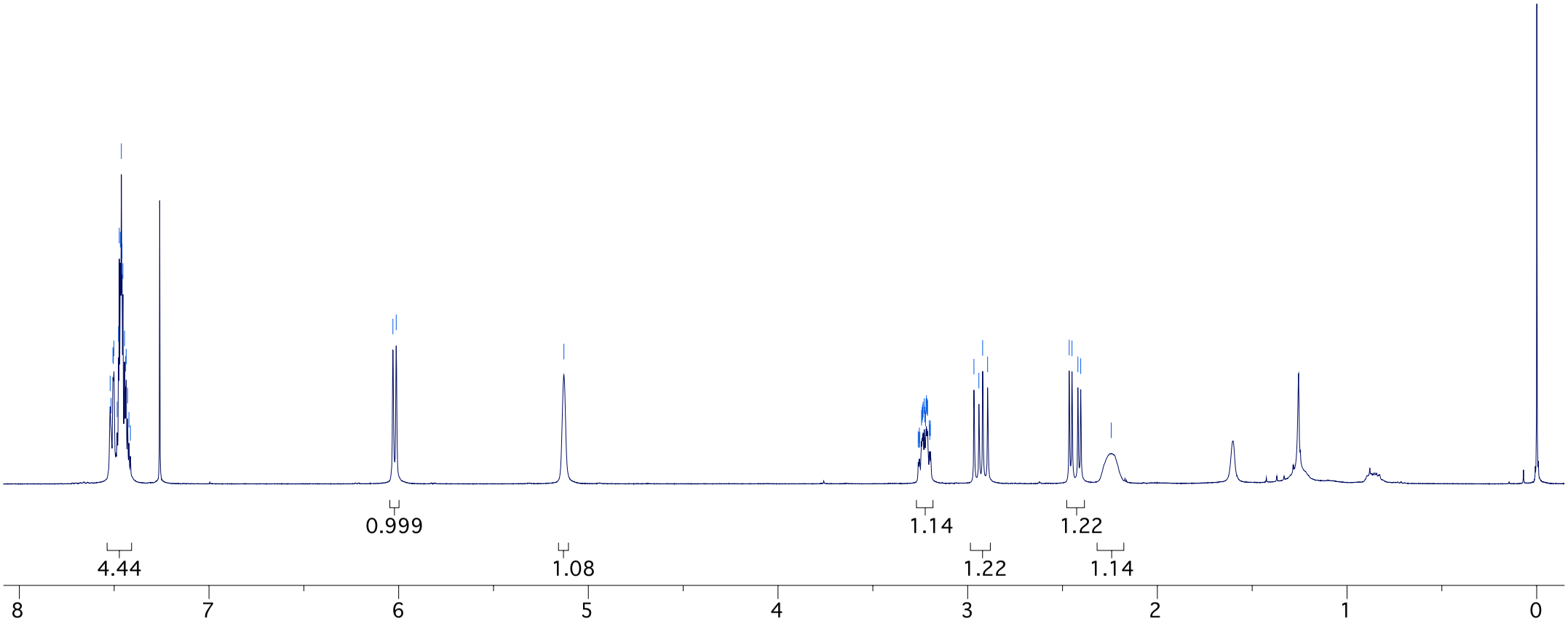

JM3-55.2
^{13}C NMR (100 MHz, $CDCl_3$)
202.357
174.686
149.664
136.175
136.072
131.131
127.555
124.430
79.074
45.781
31.107
220
200
180
160
140
120
100
80
60
40
20

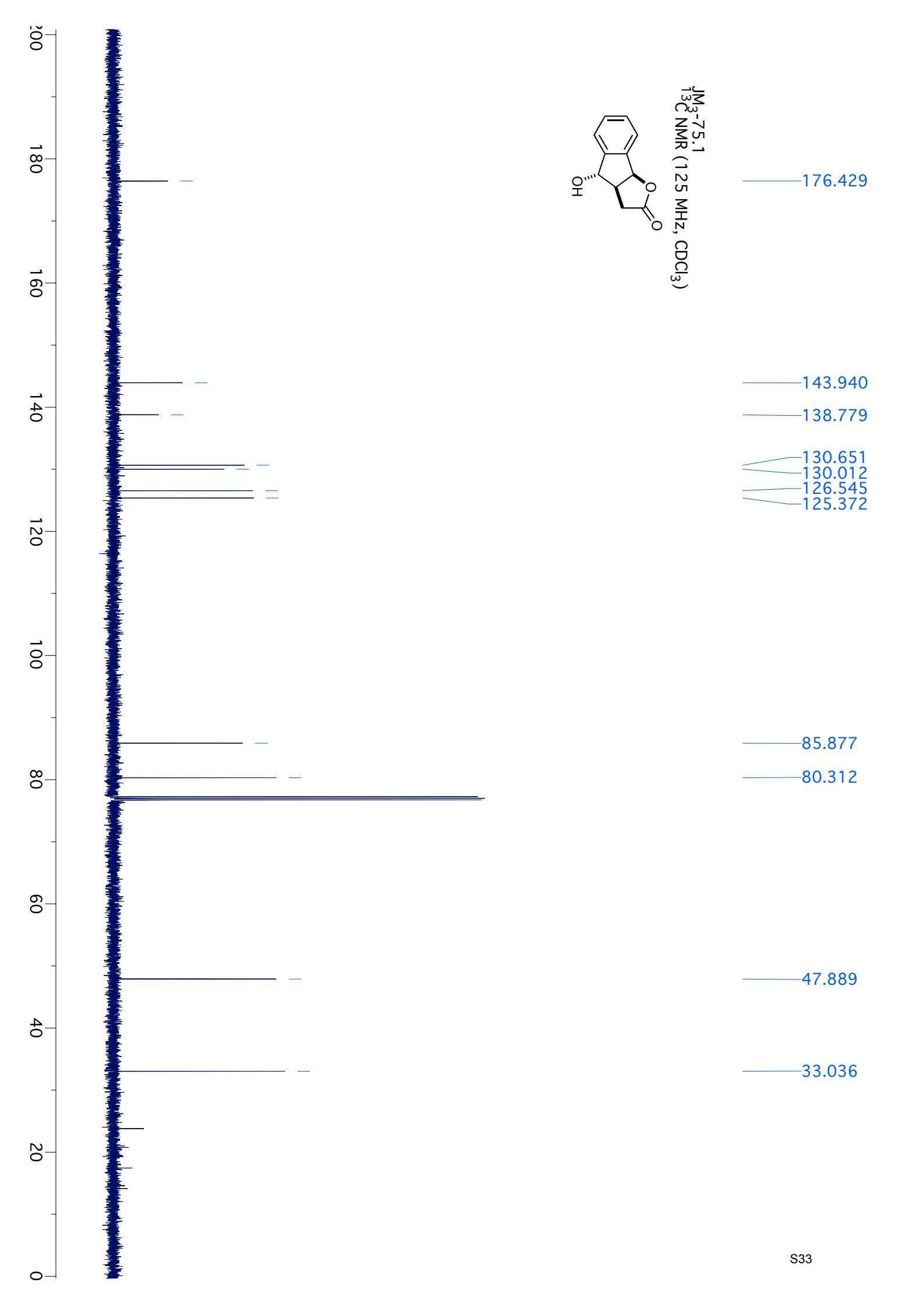

7.523
7.502
7.479
7.468
7.465
7.451
7.447
7.432
7.426
7.422
7.408
7.404
7.390
7.386
5.711
5.693
5.274
5.256
3.516
3.501
3.498
3.490
3.484
3.480
3.476
3.473
3.466
3.458
3.455
3.440
2.873
2.858
2.827
2.812
2.676
2.650
2.630
2.604
2.398
JM3-47.1
1H NMR (400MHz, CDCl3)
S30
O
O
OH
4.19
1
1
1.03
1.02
1.1
1.07
ppm 7
6
5
4
3
2
1
0

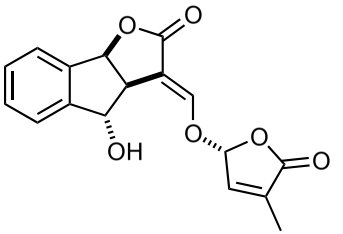

200
180
160
140
120
100
80
60
40
20
0
177.172
144.139
138.203
130.514
129.602
126.312
125.245
84.296
73.397
43.448
28.805
JM3-47.1
13C NMR (100MHz, CDCl3)
OH
O
O



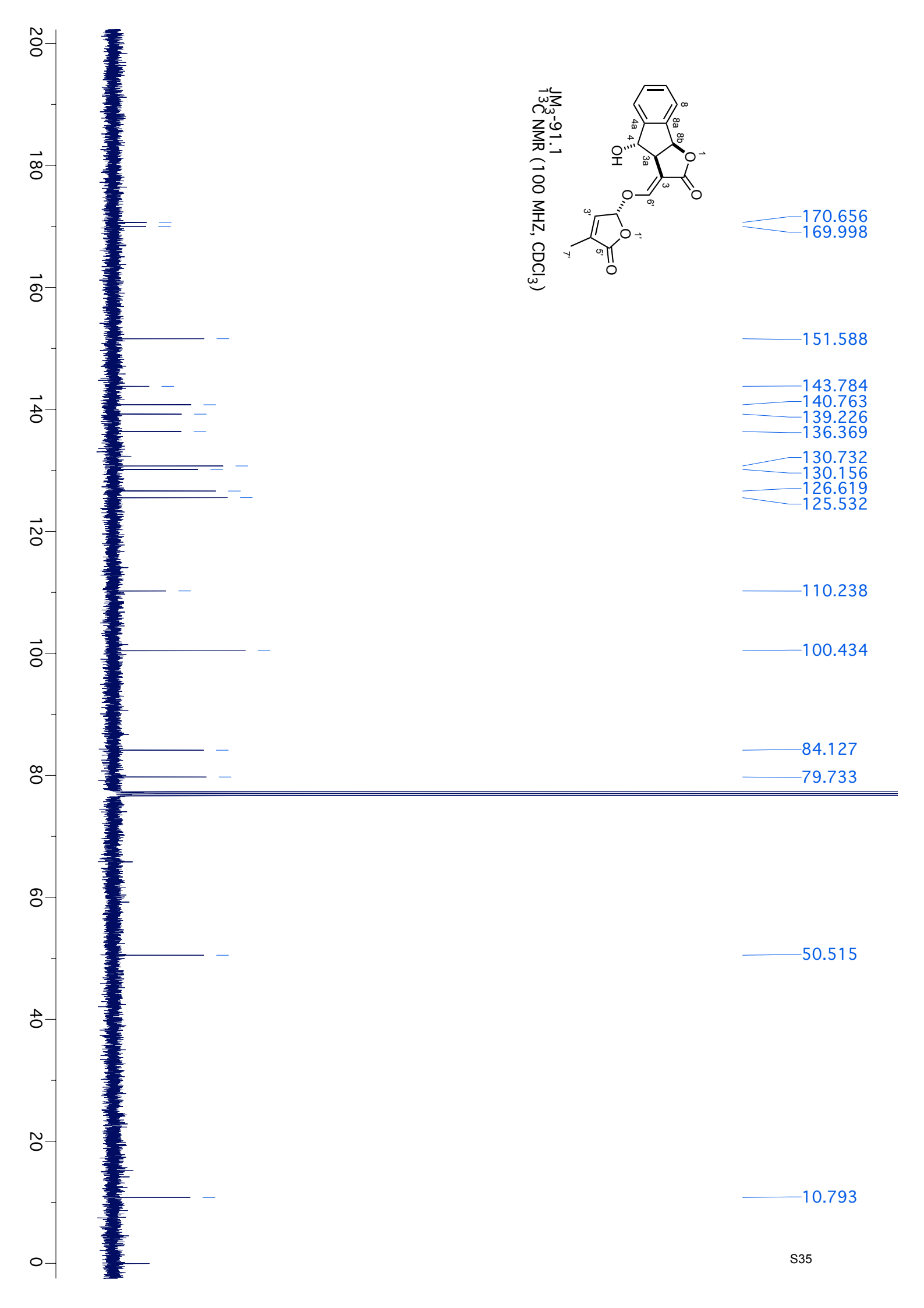
JM$_4$-37.1
^{1}H NMR (400 MHz, $CDCl_3$)

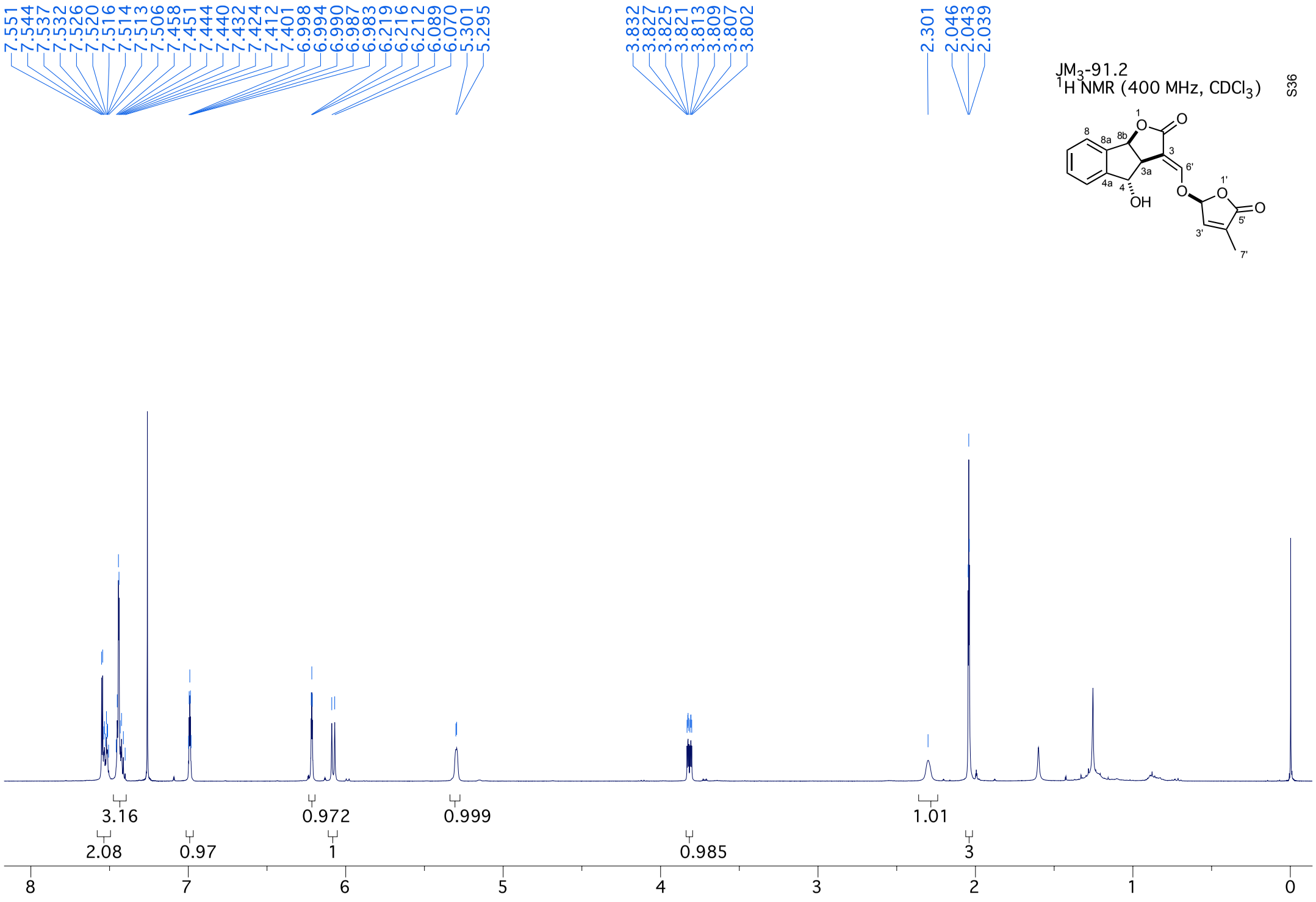


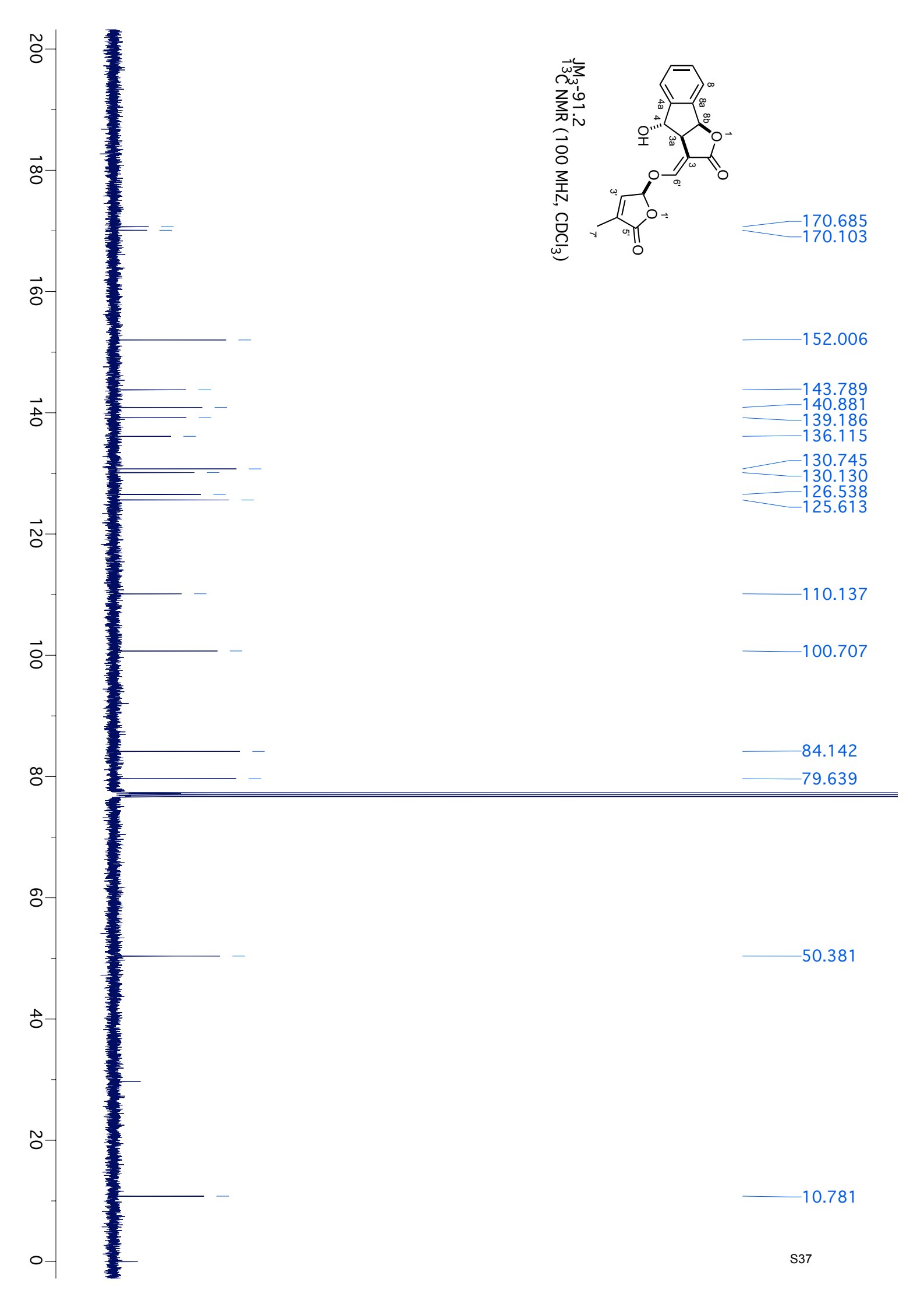

JM3-75.1
13C NMR (125 MHz, CDCl3)
OH
O
O
176.429
143.940
138.779
130.651
130.012
126.545
125.372
85.877
80.312
47.889
33.036
200
180
160
140
120
100
80
60
40
20
0



JM$_3$-91.1
^{1}H NMR (400 MHz, CDCl$_3$)


JM3-91.1
13C NMR (100 MHZ, CDCl3)
170.656
169.998
151.588
143.784
140.763
139.226
136.369
130.732
130.156
126.619
125.532
110.238
100.434
84.127
79.733
50.515
10.793
200
180
160
140
120
100
80
60
40
20
0


7.551
7.544
7.537
7.532
7.526
7.520
7.516
7.514
7.513
7.506
7.458
7.451
7.444
7.440
7.432
7.424
7.412
7.401
6.998
6.994
6.990
6.987
6.983
6.219
6.216
6.212
6.089
6.070
5.301
5.295
3.832
3.827
3.825
3.821
3.813
3.809
3.807
3.802
2.301
2.046
2.043
2.039
JM3-91.2
1H NMR (400 MHz, CDCl3)
S36
3.16
0.972
0.999
1.01
2.08
0.97
1
0.985
3
8
7
6
5
4
3
2
1
0


JM3-91.2
13C NMR (100 MHZ, CDCl3)
170.685
170.103
152.006
143.789
140.881
139.186
136.115
130.745
130.130
126.538
125.613
110.137
100.707
84.142
79.639
50.381
10.781
200
180
160
140
120
100
80
60
40
20
0