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Supporting Information

Novel Chiral Tetramic Acid–Derived Diols: Organocatalytic Facile Synthesis and Unique Structural Properties

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The following data are included in this material:

General methods:

All solvents and reagents were of reagent grade quality from Wako Pure Chemicals and Tokyo Chemical Industry (TCI), and used without further purification. All new compounds were characterized by NMR, IR, and elemental analysis. The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra operating at the frequencies of 300 and 75 MHz, respectively, were recorded on a JEOL JNM–AL300 spectrometer in chloroform–*d* ($CDCl_3$) unless otherwise noted. Chemical shifts are reported in parts per million (ppm) relative to TMS and the solvent used as internal standards, and the coupling constants are reported in hertz (Hz). Optical rotations were measured in 1 dm path length cell of 2 mL capacity using a JASCO Model DIP–1000 polarimeter at a wavelength of 589 nm. Reactions were monitored by thin layer chromatography (TLC) using 0.25 mm Merck silica gel 60–F254 precoated silica gel plates by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid in ethanol followed by heating. Column chromatography was performed on Kanto Chemical silica gel 60N eluting with the indicated solvent system. Melting points were measured with a Yanaco MP–S3 micro melting point apparatus. Fourier transform infrared (FTIR) spectra were recorded on a JASCO FT/IR–550 spectrometer. Elemental analyses were performed by JSL Model JM 10 instruments. The high–resolution mass spectroscopy (HRMS) measurement of **3a** was carried out on a JMS-700 spectrometer.

The reaction of 1a with 2a in the presence of piperidine and pyrrolidine:

Treatment of ethanolic solution of **1a** with **2a** in the presence of the catalytic amount (20 mol %) of piperidine at rt resulted in a relatively fast consumption of these starting materials and concomitant formation of **3a**, as shown by an appearance of a new single spot on TLC. The reaction reached completion after 3 h and consequently gave a 73% yield of **3a**. The observed ^{1}H NMR spectrum of **3a** obtained by this procedure (Figure S1a), which was roughly purified through silica–gel column chromatography, and that obtained by the proline–catalyzed reaction (Figure S1b) obviously differs from each other in terms of the spectral shapes typically in the region of 2.6–3.3 ppm. Comparison of these spectra with that of a 1:1 diastereomeric mixture of **3a** (Figure S1c) independently prepared from authentic racemic material of **1a** leads to a conclusion that the difference in the spectral profiles can be attributed to the formation of the diastereomeric counterpart during the piperidine–catalyzed reaction.

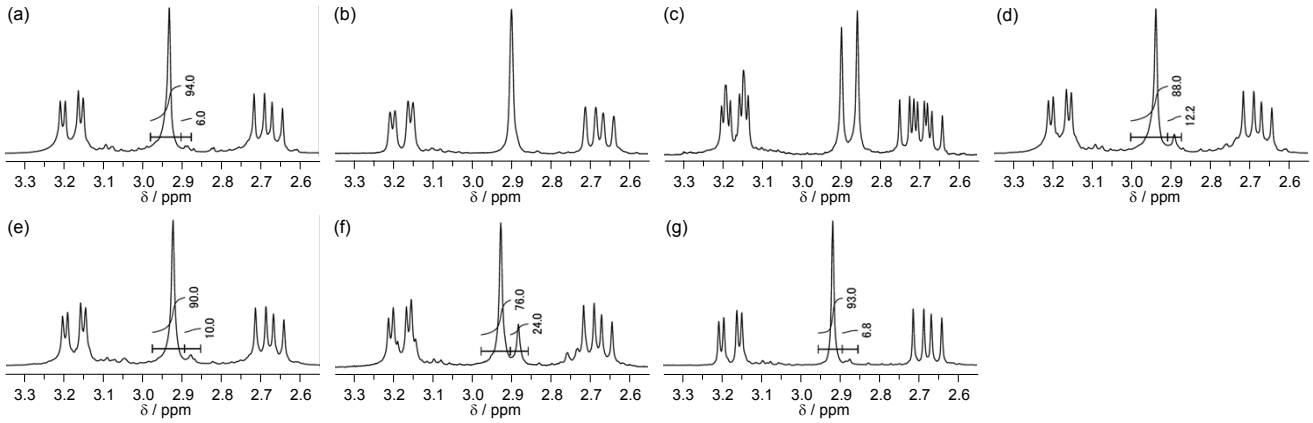


Figure S1. Comparison of ^{1}H NMR spectra of 3a (300 MHz, $CDCl_3$/acetone–d_6 = 1/1, δ in ppm): (a) **3a** produced in the presence of 20 mol % of piperidine at rt in EtOH for 3 h; (b) **3a** produced in the presence of 20 mol % of L-proline at rt in EtOH; (c) a 1:1 mixture of **3a** and *epi*–**3a** produced in the presence of 20 mol % of L-proline at rt in EtOH from *rac*–**1a**; (d) **3a** produced in the presence of 20 mol % of piperidine at rt in EtOH for 7 h; (e) **3a** produced in the presence of 20 mol % of pyrrolidine at rt in EtOH for 2 h; (f) **3a** produced in the presence of 20 mol % of pyrrolidine at rt in EtOH for 7 h; (g) **3a** exposed to an ethanolic solution of pyrrolidine (20 mol %) at rt for 7 h.

The degree of the epimerization could be estimated by ^{1}H NMR integration of the respective two

singlets for the methylene bridges to be **3a**:*epi*–**3a** = 94:6. When the reaction time was prolonged to 7 h, the yield of **3a** was slightly decreased to 68% with its diastereomeric ratio of 88:12 (Figure S1d). Similar behavior could be observed from the reaction with pyrrolidine (20 mol %); the reaction proceeded at rt to completion in 2 h to give a 78% yield of **3a** with the 90:10 ratio (Figure S1e), while the product yield was significantly decreased to 73% with its diastereomeric ratio of 76:24 after a prolonged reaction time of 7 h (Figure S1f). The validity of this assumption was corroborated by an observation that exposure of enantiopure **3a** to an ethanolic solution of pyrrolidine (20 mol % for **3a**) at rt for 7 h gave 95% recovery of this substrate as an approximately 93:7 diastereomeric mixture (Figure S1g).

^{1}H NMR spectra of 3b in acetone–d_6 and methanol–d_4:

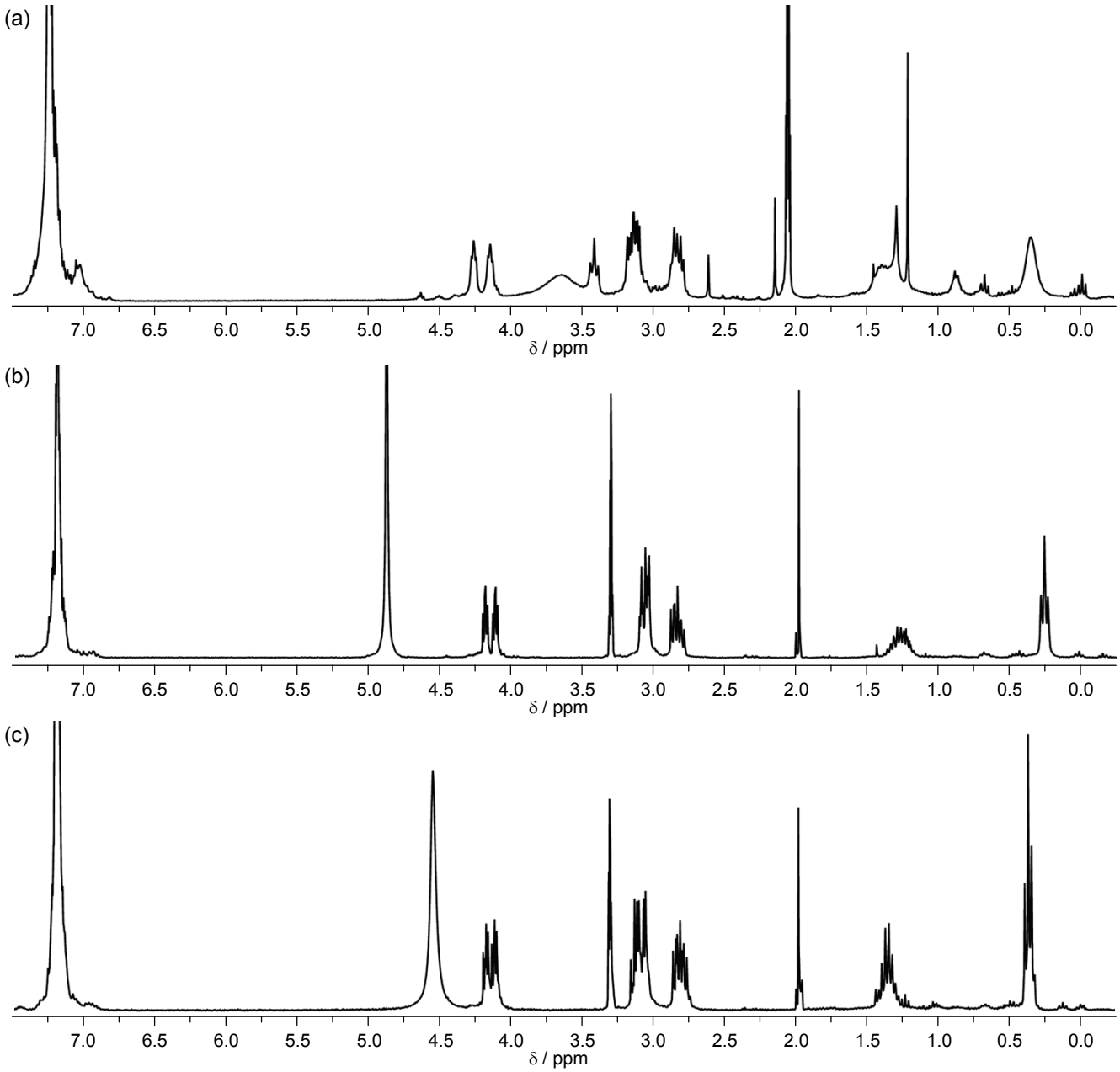


Figure S2. ^{1}H NMR spectra of 3b (300 MHz, δ in ppm) in (a) acetone–d_6, methanol–d_4 at (b) rt and (c) 55 ºC.

Experimental procedures and characterization data:

General procedure for the synthesis of 3

To a solution of tetramic acid **1** (0.24–0.60 mmol, 2.0 equiv) and aldehyde **2** (0.12–0.30 mmol, 1.0 equiv) in ethanol was added L–proline (20 mol %) to give a suspension of the reaction mixture, which was stirred until completion of the reaction (monitored by TLC). Then, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was subjected to isolate **3**.

Characterization for 3a

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 30/1) to give **3a** (43.1 mg, 96%) as a white powder: Decomposition point (D.p.) 73–74 ºC; $[\alpha]_D^{31}$ -99.6 (*c* 1.60 in $CHCl_3$); IR (KBr) 3409 (O–H), 3249 (N–H), 3030 (C–H), 2925 (C–H), 1656 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.0 (brs, 1H, O*H*), 7.32–7.19 (m, 10H, Ar*H*), 6.05 (brs, 2H, N*H*), 4.75 (brs, 1H, O*H*), 4.09 (dd, *J* = 3.2, 9.6 Hz, 2H, C*H*), 3.25 (dd, *J* = 3.2, 13.6 Hz, 2H, CH_2), 2.99 (s, 2H, CH_2), 2.57 (dd, *J* = 9.6, 13.6 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7 (*C*), 172.5 (*C*), 137.3 (*C*), 129.5 (*C*H), 128.9 (*C*H), 127.2 (*C*H), 103.3 (*C*), 58.7 (*C*H), 38.4 (*C*H_2), 12.9 (*C*H_2). Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.12; H, 5.84; N, 6.90.

Characterization for 3b

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 50/1) to give **3b** (56.0 mg, 100%) as a white powder: D.p. 121–122 ºC; $[\alpha]_D^{27}$ -107 (*c* 0.564 in $CHCl_3$); IR (KBr) 3404 (O–H), 3247 (N–H), 3030 (C–H), 2962 (C–H), 2928 (C–H), 1649 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ 12.5 (brs, 1H, O*H*), 11.5 (brs, 1H, O*H*), 8.07 (brs, 1H, N*H*), 7.44 (s, 1H, N*H*), 7.24–7.11 (m, 10H, Ar*H*), 4.19 (t, *J* = 4.2 Hz, 1H, C*H*), 3.99 (t, *J* = 5.1 Hz, 1H, C*H*), 3.21 (t, *J* = 8.1 Hz, 1H, C*H*), 2.98 (dd, *J* = 4.2, 13.6 Hz, 1H, CH_2), 2.93 (dd, *J* = 4.2, 13.6 Hz, 1H, CH_2), 2.85 (dd, *J* = 5.1, 13.8 Hz, 1H, CH_2), 2.73 (dd, *J* = 5.1, 13.8 Hz, 1H, CH_2), 1.17–0.95 (m, 2H, CH_2), 0.11 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (75 MHz, DMSO–d_6) δ 176.1 (*C*), 175.0 (*C*), 170.0 (*C*), 169.3 (*C*), 136.3 (*C*), 135.9 (*C*), 129.8 (2*C*H), 127.9 (*C*H), 127.8 (*C*H), 126.4 (*C*H), 126.3 (*C*H), 107.6 (*C*), 107.3 (*C*), 56.6 (*C*H), 56.0 (*C*H), 36.6 (*C*H_2), 36.4 (*C*H_2), 26.5 (*C*H), 24.1 (*C*H_2), 11.6 (*C*H_3). Anal. Calcd for $C_{26}H_{30}N_2O_5$: C, 69.31; H, 6.71; N, 6.22. Found: C, 69.70; H, 6.51; N, 6.47. HRMS (FAB) calcd for $C_{25}H_{27}N_2O_4$ $[M+H]^+$: 419.1971. Found: 419.1980.

Characterization for 3c

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 100/1–30/1) to give **3c** (69.9 mg, 82%) as a white powder: D.p. 193–194 ºC; $[\alpha]_D^{31}$ -40.5 (*c* 1.02 in MeOH); IR (KBr) 3410 (O–H), 3328 (N–H), 3031 (C–H), 2963 (C–H), 2926 (C–H), 1650 (C=O) cm^{-1}; ^1H NMR

(300 MHz, DMSO–d_6) δ 12.6 (brs, 1H, O*H*), 11.2 (brs, 1H, O*H*), 8.24 (s, 1H, N*H*), 7.20–7.14 (m, 11H, Ar*H*, N*H*), 4.22 (brs, 1H, C*H*), 4.00 (brs, 1H, C*H*), 3.04–2.72 (m, 5H, 2CH_2, C*H*), 1.53 (m, 1H, C*H*), 0.49–0.08 (m, 5H, 2CH_3, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6) δ 177.7 (*C*), 175.0 (*C*), 170.1 (*C*), 170.0 (*C*), 169.1 (*C*), 136.5 (2*C*), 136.4 (*C*), 129.9 (*C*H), 128.0 (*C*H), 127.9 (2*C*H), 126.5 (*C*H), 126.3 (*C*H), 107.7 (*C*), 107.5 (*C*), 107.4 (*C*), 107.2 (*C*), 56.9 (*C*H), 56.2 (*C*H), 36.6 (*C*H_2), 36.4 (*C*H_2), 34.0 (*C*H), 33.8 (*C*H) 31.1 (*C*H), 26.1 (*C*H_2), 26.0 (*C*H_2), 16.3 (*C*H_3), 16.1 (*C*H_3), 11.3 (*C*H_3), 10.9 (*C*H_3). Anal. Calcd for $C_{27}H_{30}N_2O_4$: C, 72.62; H, 6.77; N, 6.27. Found: C, 72.77; H, 6.91; N, 6.67.

Characterization for 3d

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 30/1) to give **3d** (59.1 mg, 100%) as a white powder: D.p. 139–140 ºC; $[\alpha]_D^{27}$ -60.4 (*c* 0.536 in $CHCl_3$); IR (KBr) 3410 (O–H), 3250 (N–H), 3060 (C–H), 3029 (C–H), 2925 (C–H), 1651 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO–d_6) δ 12.4 (brs, 1H, O*H*), 11.6 (brs, 1H, O*H*), 8.30 (s, 1H, N*H*), 7.64 (s, 1H, N*H*), 7.34–7.19 (m, 10H, Ar*H*), 6.92 (t, *J* = 7.1 Hz, 1H, Ar*H*), 6.80 (t, *J* = 7.4 Hz, 2H, Ar*H*), 5.85 (s, 2H, Ar*H*), 4.69 (s, 1H, C*H*), 4.38 (t, *J* = 3.5 Hz, 1H, C*H*), 4.14 (t, *J* = 4.5 Hz, 1H, C*H*), 3.09 (dd, *J* = 3.5, 13.7 Hz, 1H, CH_2), 3.00 (dd, *J* = 3.9, 13.7 Hz, 2H, CH_2), 2.85 (dd, *J* = 4.5, 13.7 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6) δ 176.7 (*C*), 174.4 (*C*), 170.7 (*C*), 170.2 (*C*), 140.3 (*C*), 136.2 (*C*), 135.5 (*C*), 130.1 (*C*H), 128.1 (*C*H), 128.0 (*C*H), 127.7 (*C*H), 126.7 (*C*H), 126.5 (*C*H), 125.0 (*C*H), 107.7 (*C*),

106.0 (*C*), 56.9 (*C*H), 56.2 (*C*H), 36.1 (*C*H_2), 35.7 (*C*H_2), 28.9 (*C*H). Anal. Calcd for $C_{30}H_{30}N_2O_5$: C, 72.27; H, 6.06; N, 5.62. Found: C, 72.17; H, 5.67; N, 6.02.

Characterization for 3e

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 60/1) to give **3e** (61.2 mg, 90%) as a white powder: D.p. 144–145 ºC; $[\alpha]_D^{29}$ -111 (*c* 0.920 in $CHCl_3$); IR (KBr) 3410 (O–H), 3273 (N–H), 3061 (C–H), 3029 (C–H), 2961 (C–H), 1652 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ 12.5 (brs, 1H, O*H*), 11.7 (brs, 1H, O*H*), 8.26 (brs, 1H, N*H*), 7.63 (brs, 1H, N*H*), 7.29–7.20 (m, 10H, Ar*H*), 6.83 (d, *J* = 7.8 Hz, 2H, Ar*H*), 5.87 (brs, 2H, Ar*H*), 4.67 (s, 1H, C*H*), 4.35 (t, *J* = 3.3 Hz, 1H, C*H*), 4.13 (t, *J* = 4.9 Hz, 1H, C*H*), 3.03–2.98 (m, 3H, 2CH_2), 2.83 (dd, *J* = 4.9, 14.0 Hz, 1H, CH_2), 1.21 (s, 9H, 3CH_3); ^{13}C NMR (75 MHz, DMSO–d_6) δ 176.7 (*C*), 174.7 (*C*), 170.7 (*C*), 170.2 (*C*), 147.1 (*C*), 137.6 (*C*), 136.3 (*C*), 135.7 (*C*), 130.1 (2*C*H), 128.1 (*C*H), 128.0 (*C*H), 126.6 (*C*H), 126.4 (*C*H), 126.2 (*C*H), 124.5 (*C*H), 107.7 (*C*), 106.1 (*C*), 56.9 (*C*H), 56.3 (*C*H), 36.3 (*C*H_2), 35.9 (*C*H_2), 33.7 (*C*), 31.2 (*C*H_3), 28.5 (*C*H). Anal. Calcd for $C_{34}H_{38}N_2O_5$: C, 73.62; H, 6.91; N, 5.05. Found: C, 73.97; H, 6.51; N, 5.43.

Characterization for 3f

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 30/1) to

give **3f** (73.3 mg, 99%) as a white powder: D.p. 134–135 ºC; $[\alpha]_D^{31}$ -86.5 (*c* 2.87 in $CHCl_3$); IR (KBr) 3413 (O–H), 3248 (N–H), 3062 (C–H), 3029 (C–H), 2924 (C–H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ 12.5 (brs, 1H, O*H*), 11.9 (brs, 1H, O*H*), 8.25 (brs, 1H, N*H*), 7.72 (s, 1H, N*H*), 7.27–7.15 (m, 10H, Ar*H*), 7.06 (d, *J* = 8.4 Hz, 1H, Ar*H*), 6.92 (t, *J* = 8.0 Hz, 1H, Ar*H*), 6.53 (s, 1H, Ar*H*), 6.05 (brs, 1H, Ar*H*), 4.79 (s, 1H, C*H*), 4.36 (t, *J* = 3.9 Hz 1H, C*H*), 4.16 (t, *J* = 5.1 Hz, 1H, C*H*), 3.04–2.99 (m, 3H, C*H*, CH_2), 2.80 (dd, *J* = 5.1, 13.8 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6) δ 176.4 (*C*), 174.4 (*C*), 171.1 (*C*), 170.6 (*C*), 143.8 (*C*), 136.3 (*C*), 135.6 (*C*), 132.6 (*C*H), 129.8 (*C*H), 128.1 (*C*H), 126.8 (*C*H), 126.5 (*C*H), 126.3 (*C*H), 125.6 (*C*H), 125.5 (*C*H), 106.9 (*C*), 105.8 (*C*), 56.9 (*C*H), 56.5 (*C*H), 36.4 (*C*H_2), 36.0 (*C*H_2), 29.2 (*C*H). Anal. Calcd for $C_{30}H_{29}ClN_2O_5$: C, 67.60; H, 5.48; N, 5.26. Found: C, 67.37; H, 5.25; N, 5.66.

Characterization for 3g

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 30/1) to give **3g** (75.1 mg, 99%) as a white powder. Single crystals were obtained by crystallization of this material from a chloroform-methanol solution.: D.p. 155–156 ºC; $[\alpha]_D^{29}$ +56.6 (*c* 2.76 in $CHCl_3$); IR (KBr) 3410 (O–H), 3284 (N–H), 3062 (C–H), 3030 (C–H), 2925 (C–H), 1650 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ 12.4 (brs, 1H, O*H*), 11.9 (brs, 1H, O*H*), 8.47 (brs, 1H, N*H*), 7.74 (s, 1H, N*H*), 7.57 (d, *J* = 8.7 Hz, 2H, Ar*H*), 7.34–7.20 (m, 10H, Ar*H*), 5.89 (brd, *J* = 7.2 Hz, 2H, Ar*H*), 4.73 (s, 1H,

C*H*), 4.43 (t, *J* = 3.9 Hz, 1H, C*H*), 4.18 (t, *J* = 4.2 Hz, 1H, C*H*), 3.14 (dd, *J* = 4.1, 14.3 Hz, 1H, CH_2), 3.00 (dd, *J* = 3.9, 14.1 Hz, 2H, CH_2), 2.88 (dd, *J* = 4.5, 13.8 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6) δ 176.4 (*C*), 173.7 (*C*), 171.4 (*C*), 170.5 (*C*), 149.2 (*C*), 145.3 (*C*), 136.0 (*C*), 135.3 (*C*), 130.2 (*C*H), 128.2 (*C*H), 128.0 (*C*H), 127.4 (*C*H), 126.7 (*C*H), 126.5 (*C*H), 122.7 (*C*H), 106.7 (*C*), 105.2 (*C*), 57.0 (*C*H), 56.2 (*C*H), 35.7 (*C*H_2), 35.4 (*C*H_2), 29.3 (*C*H). Anal. Calcd for $C_{30}H_{29}N_3O_7$: C, 66.29; H, 5.38; N, 7.73. Found: C, 65.90; H, 5.13; N, 8.12.

Characterization for 3h

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 100/1–30/1) to give **3h** (59.3 mg, 96%) as a pale yellow powder: D.p. 151–152 ºC; $[\alpha]_D^{27}$ -80.5 (*c* 0.522 in $CHCl_3$); IR (KBr) 3408 (O–H), 3261 (N–H), 3060 (C–H), 3029 (C–H), 2924 (C–H), 1650 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, DMSO–d_6) δ 12.5 (brs, 1H, O*H*), 12.1 (brs, 1H, O*H*), 8.16 (d, *J* = 8.1 Hz, 1H, Ar*H*), 8.01 (brs, 1H, N*H*), 7.84 (dd, *J* = 2.1, 7.5 Hz, 1H, Ar*H*), 7.76 (s, 1H, N*H*), 7.66 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.48–7.38 (m, 2H, Ar*H*), 7.31–7.09 (m, 11H, Ar*H*), 6.88 (s, 1H, Ar*H*), 5.51 (s, 1H, C*H*), 4.23 (t, *J* = 5.8 Hz, 1H, C*H*), 4.16 (t, *J* = 4.2 Hz, 1H, C*H*), 3.07 (dd, *J* = 4.2, 13.9 Hz, 1H, CH_2), 2.99 (dd, *J* = 4.2, 13.9 Hz, 1H, CH_2), 2.74 (dd, *J* = 5.8, 13.8 Hz, 1H, CH_2), 2.56 (dd, *J* = 5.8, 13.8 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6) δ 176.7 (*C*), 175.0 (*C*), 170.8 (*C*), 170.7 (*C*), 137.0 (*C*), 136.5 (*C*), 136.3 (*C*), 133.5 (*C*), 131.3 (*C*), 130.0 (*C*H), 129.7 (*C*H), 129.5 (*C*H), 128.5 (*C*H), 128.1 (2*C*H),

127.9 (*C*H), 126.5 (*C*H), 126.4 (*C*H), 125.6 (*C*H), 125.5 (*C*H), 125.3 (2*C*H), 124.2 (*C*H), 107.3 (*C*), 107.2 (*C*), 57.0 (*C*H), 56.6 (*C*H), 37.3 (*C*H_2), 36.6 (*C*H_2), 27.5 (*C*H). Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11. Found: C, 74.23; H, 5.50; N, 5.23.

Characterization for 3i

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 60/1) to give **3i** (56.7 mg, 96%) as a pale yellow powder: D.p. 141–142 ºC; $[\alpha]_D^{29}$ -165 (*c* 0.625 in $CHCl_3$); IR (KBr) 3411 (O–H), 3263 (N–H), 3060 (C–H), 3029 (C–H), 2925 (C–H), 1651 (C=O) cm^{-1}; ^1H NMR (300 MHz, DMSO–d_6) δ 12.4 (brs, 1H, O*H*), 11.9 (brs, 1H, O*H*), 8.25 (brs, 1H, N*H*), 7.77 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.72 (brs, 1H, N*H*), 7.54 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.46–7.37 (m, 3H, Ar*H*), 7.32–7.21 (m, 10 H, Ar*H*), 6.88 (s, 1H, Ar*H*), 6.33 (brs, 1H, Ar*H*), 4.96 (s, 1H, C*H*), 4.40 (t, *J* = 3.9 Hz, 1H, C*H*), 4.18 (t, *J* = 5.2 Hz, 1H, C*H*), 3.09–3.03 (m, 3H, 2CH_2), 2.84 (dd, *J* = 5.2, 13.8 Hz, 1H, CH_2); ^{13}C NMR (75 MHz, DMSO–d_6) δ 176.5 (*C*), 174.7 (*C*), 170.9 (*C*), 170.6 (*C*), 138.6 (*C*), 136.6 (*C*), 135.8 (*C*), 132.7 (*C*), 131.5 (*C*), 130.0 (*C*H), 129.9 (*C*H), 128.1 (2*C*H), 127.8 (*C*H), 127.4 (*C*H), 127.3 (*C*H), 126.8 (*C*H), 126.5 (*C*H), 126.1 (*C*H), 125.7 (*C*H), 125.2 (*C*H), 124.2 (*C*H), 107.3 (*C*), 106.4 (*C*), 57.0 (*C*H), 56.6 (*C*H), 36.6 (*C*H_2), 36.0 (*C*H_2), 29.4 (*C*H). Anal. Calcd for $C_{34}H_{32}N_2O_5$: C, 74.43; H, 5.88; N, 5.11. Found: C, 74.03; H, 5.51; N, 5.51.

Characterization for 3b'

The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 30/1) to give **3b'** (175 mg, 96%) as a white powder: D.p. 135–136 ºC; $[\alpha]_D^{30}$ +148 (*c* 3.31 in $CHCl_3$); IR (KBr) 3487 (O–H), 2977 (C–H), 2934 (C–H), 1761 (C=O), 1714 (C=O), 1643 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 12.1 (brs, 1H, O*H*), 11.2 (brs, 1H, O*H*), 7.19–7.02 (m, 10H, Ar*H*), 4.59 (dd, *J* = 2.9, 5.0 Hz, 1H, C*H*), 4.44 (m, 1H, C*H*), 3.50–3.40 (m, 2H, CH_2), 3.21 (m, 1H, C*H*), 3.18 (dd, *J* = 2.9, 14.0 Hz, 2H, CH_2), 1.61 (s, 9H, 3CH_3), 1.60 (s, 9H, 3CH_3), 1.04–0.88 (m, 2H, CH_2), -0.15 (m, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4 (*C*), 173.2 (*C*), 172.3 (*C*), 171.9 (*C*), 149.5 (*C*), 149.2 (*C*), 134.2 (*C*), 130.2 (*C*H), 130.1 (*C*H), 128.5 (*C*H), 128.4 (*C*H), 127.2 (*C*H), 108.4 (*C*), 108.0 (*C*), 83.3 (*C*), 83.0 (*C*), 60.3 (*C*H), 59.8 (*C*H), 34.7 (CH_2), 28.3 (*C*H_3), 27.5 (*C*H), 23.1 (*C*H_2), 11.7 (*C*H_3). Anal. Calcd for $C_{36}H_{46}N_2O_9$: C, 66.44; H, 7.12; N, 4.30. Found: C, 66.58; H, 6.73; N, 4.69.

Characterization for 4j

The crude product was purified by column chromatography (silica gel, hexane/EtOAc = 1/1–chloroform/MeOH = 10/1–toluene/MeOH = 10/1) to give **4j** (149 mg, 100%) as a red powder: D.p. 223–224 ºC; $[\alpha]_D^{24}$ -99.7 (*c* 1.08 in $CHCl_3$); IR (KBr) 3199 (N–H), 3051 (C–H), 1735 (C=O), 1693 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H, C*H*, major isomer), 8.68 (s, 1H, C*H*, minor isomer), 8.57 (s, 1H, Ar*H*, major isomer), 8.49 (s, 1H, Ar*H*, minor isomer), 8.08–7.96 (m, 2H, Ar*H*),

7.81 (dd, 1H, *J* = 3.0, 6.0 Hz, Ar*H*), 7.55–7.27 (m, 7H, Ar*H*), 7.23–7.11 (m, 2H, Ar*H*), 7.04 (s, 1H, N*H*, minor isomer), 6.94 (s, 1H, N*H*, major isomer), 4.29 (dd, *J* = 4.5, 6.3 Hz, 1H, C*H*, minor isomer), 4.12 (dd, *J* = 3.9, 8.1 Hz, 1H, C*H*, major isomer), 3.17–3.04 (m, 2H, CH_2), 2.80 (dd, *J* = 7.8, 13.8 Hz, 2H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.1 (*C*), 195.2 (*C*), 167.5 (*C*), 165.9 (*C*), 144.0 (*C*H), 143.7 (*C*H), 135.4 (*C*), 135.1 (*C*), 130.9 (*C*H), 130.3 (*C*H), 129.7 (*C*H), 129.4 (*C*), 129.2 (*C*H), 129.0 (*C*H), 128.8 (*C*H), 128.7 (*C*H), 128.1 (*C*), 127.2 (*C*H), 127.1 (*C*H), 127.0 (*C*H), 126.7 (*C*H), 126.2 (*C*), 126.1 (*C*), 125.6 (*C*H), 125.4 (*C*H), 125.3 (*C*H), 61.7 (*C*H), 61.4 (*C*H), 38.0 (*C*H_2), 37.8 (*C*H_2). Anal. Calcd for $C_{27}H_{23}NO_3$: C, 79.20; H, 5.66; N, 3.42. Found: C, 79.41; H, 5.26; N, 3.82.

Preparation of 4h

To a solution of tetramic acid **1a** (42.7 mg, 0.226 mmol, 2.0 equiv) and 1-naphthyl aldehyde **2h** (18.0 mg, 0.115 mmol, 1.0 equiv) in ethanol was added L–proline (2.6 mg, 20 mol %) to give a solution of the reaction mixture, which was stirred at rt for 5 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, chloroform/MeOH = 100/1) to give **4h** (22.8 mg, 62%) as a yellow powder: D.p. 184–185 ºC; $[\alpha]_D^{20}$ -265 (*c* 1.12 in $CHCl_3$); IR (KBr) 3184 (N–H), 3060 (C–H), 2925 (C–H), 1724 (C=O), 1683 (C=O) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.82 (d, *J* = 7.2 Hz, 1H, Ar*H*, minor

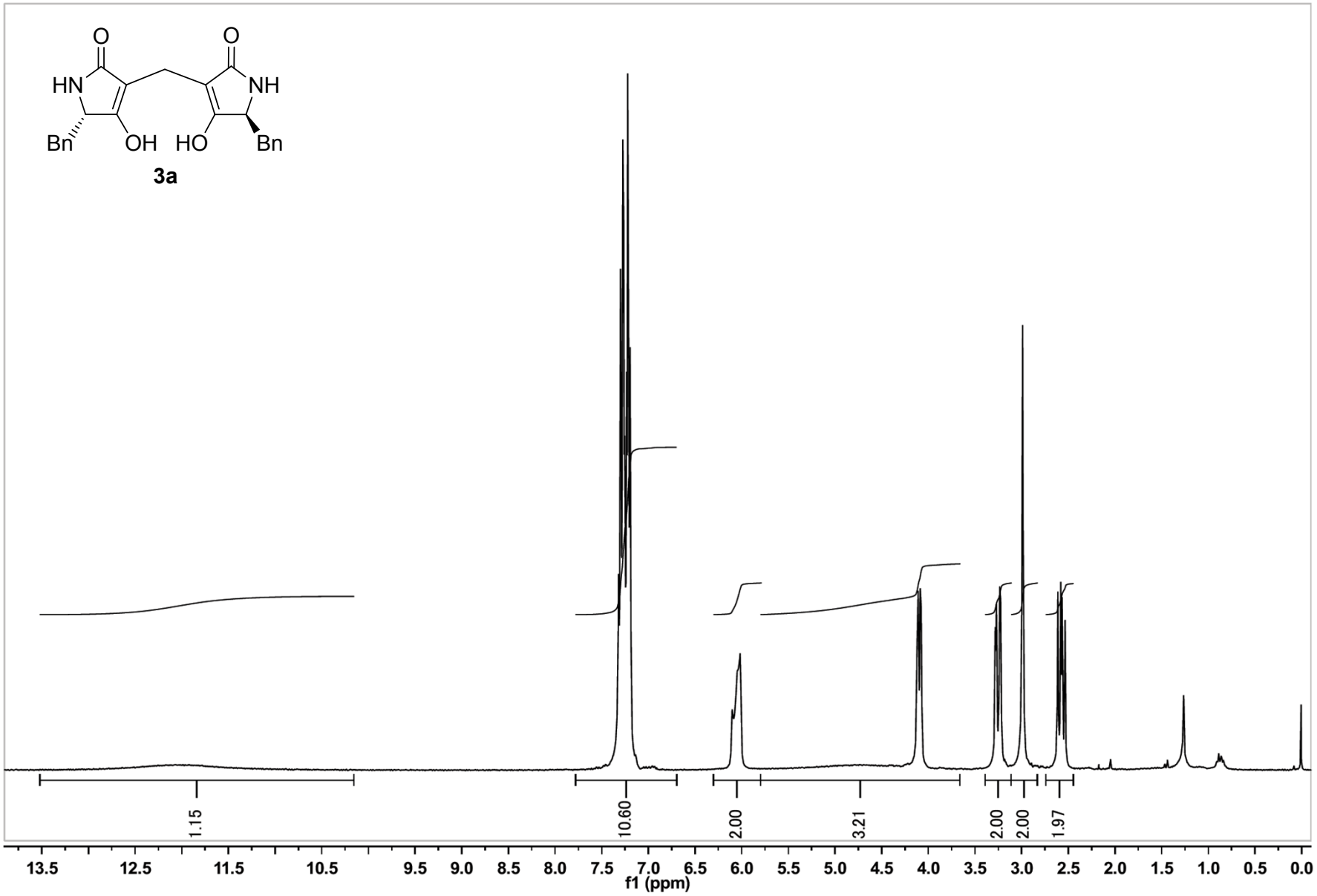
isomer), 8.78 (d, *J* = 7.5 Hz, 1H, Ar*H*, major isomer), 8.71 (s, 1H, C*H*, minor isomer), 8.56 (s, 1H, C*H*, major isomer), 8.23 (d, *J* = 8.1 Hz, 1H, Ar*H*, major isomer), 8.17 (d, *J* = 8.4 Hz, 1H, Ar*H*, minor isomer), 8.07 (d, *J* = 8.1 Hz, 1H, Ar*H*, major isomer), 8.02 (d, *J* = 8.4 Hz, 1H, Ar*H*, major isomer), 7.93–7.89 (m, 1H, Ar*H*), 7.67–7.53 (m, 3H, Ar*H*), 7.35–7.20 (m, 5H, Ar*H*), 6.85 (s, 1H, N*H*, major isomer), 6.75 (s, 1H, N*H*, minor isomer), 4.29 (dd, *J* = 3.6, 9.3 Hz, 1H, C*H*, minor isomer), 4.19 (dd, *J* = 3.9, 9.3 Hz, 1H, C*H*, major isomer), 3.38–3.28 (m, 1H, CH_2), 2.89–2.78 (m, 1H, CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7 (*C*), 196.5 (*C*), 168.8 (*C*), 167.1 (*C*), 146.1 (*C*H), 145.4 (*C*H), 136.2 (*C*), 134.5 (*C*H), 134.1 (*C*H), 133.7 (2*C*), 133.5 (*C*H), 133.2 (*C*), 131.8 (*C*H), 129.6 (*C*H), 129.4 (2*C*H), 129.2 (*C*H), 128.7 (*C*), 128.1 (*C*H), 127.9 (*C*H), 127.5 (*C*H), 126.7 (*C*H), 126.5 (*C*H), 125.5 (*C*H), 125.3 (*C*H), 124.7 (*C*), 124.2 (*C*), 123.7 (*C*H), 123.6 (*C*H), 62.2 (*C*H), 62.0 (*C*H), 38.9 (*C*H_2), 38.8 (*C*H_2). Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.31; H, 5.63; N, 4.68.

The reaction of 1a with acetone in the presence of a stoichiometric amount of L-proline

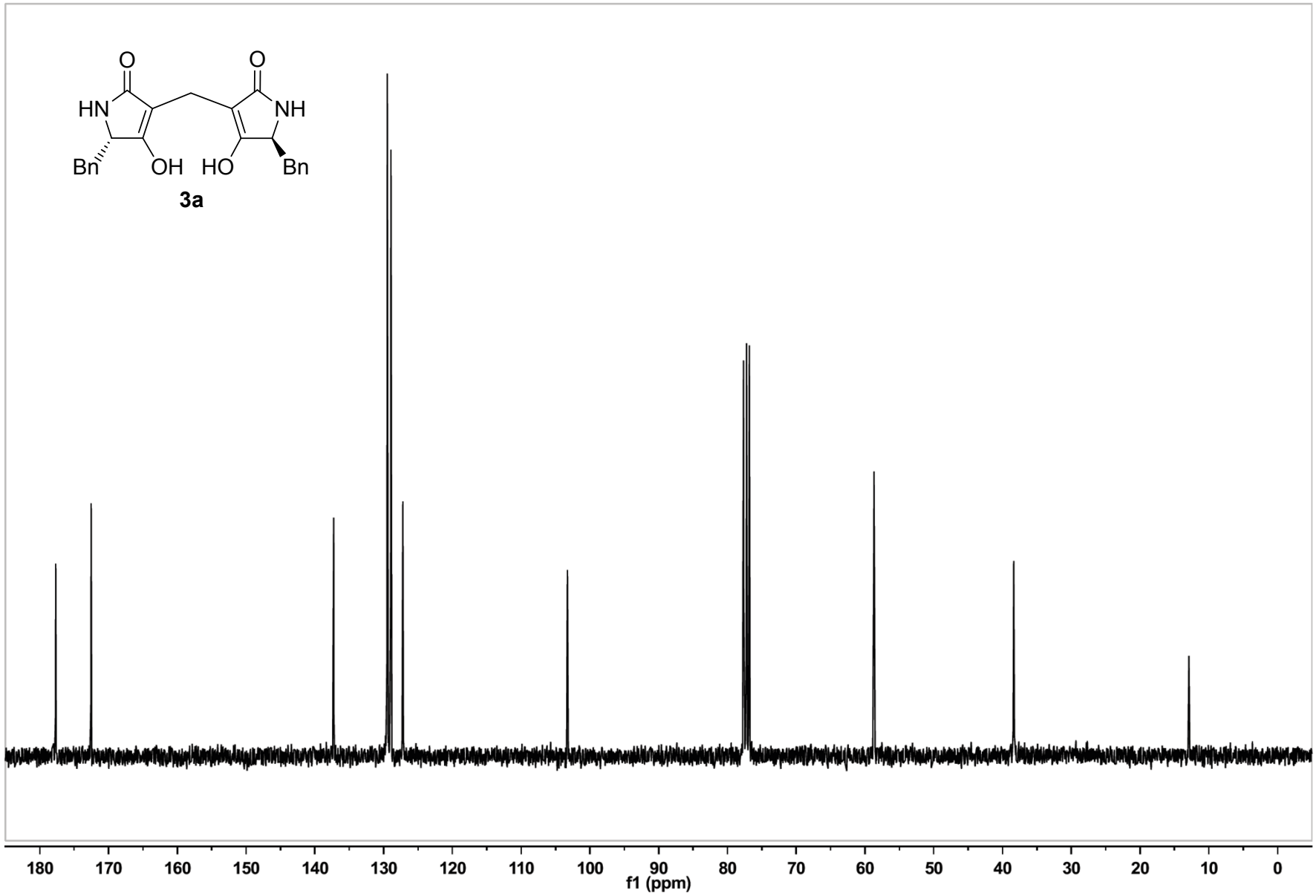
To a solution of tetramic acid **1a** (48.6 mg, 0.257 mmol, 2.1 equiv) and acetone (6.8 mg, 0.12 mmol, 1.0 equiv) in ethanol was added L–proline (13.5 mg, 0.117 mmol) to give a solution of the reaction mixture, which was stirred at rt for 8 h. Then, the solvent was removed under reduced pressure and the residue was dissolved in EtOAc, washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude product was purified by column chromatography

(silica gel, chloroform/MeOH = 100/1) to give **5** (27.4 mg, 100%) as a white powder: D.p. 147–148 ºC; $[\alpha]_D^{25}$ -232 (*c* 0.76 in $CHCl_3$); IR (KBr) 3194 (N–H), 3070 (C–H), 3031 (C–H), 1726 (C=O), 1683 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33–7.16 (m, 5H, Ar*H*), 6.62 (brs, 1H, N*H*), 4.00 (dd, *J* = 3.6, 9.6 Hz, 1H, C*H*), 3.24 (dd, *J* = 3.6, 13.8 Hz, 1H, C*H*), 2.35 (dd, *J* = 9.6, 13.8 Hz, 1H, C*H*), 2.51 (s, 3H, CH_3), 2.47 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.4 (*C*), 173.1 (*C*), 168.8 (*C*), 136.4 (*C*), 129.2 (*C*H), 128.8 (*C*H), 127.1 (*C*H), 121.7 (*C*), 61.6 (*C*H), 38.6 (CH_2), 23.8 (CH_3), 23.1 (CH_3). Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.32; H, 6.65; N, 6.02.

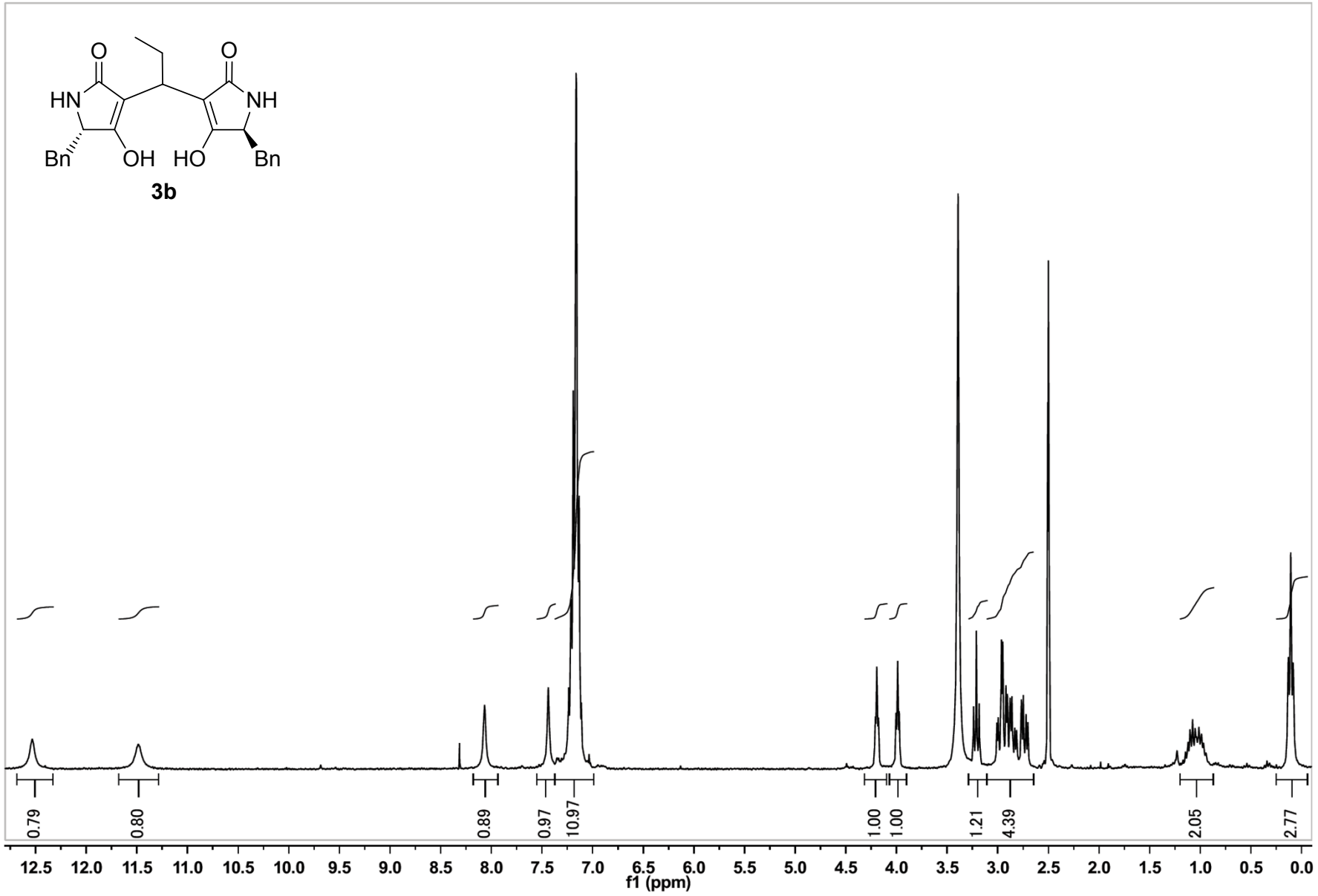
Compound **3a** (^{1}H NMR in $CDCl_3$)



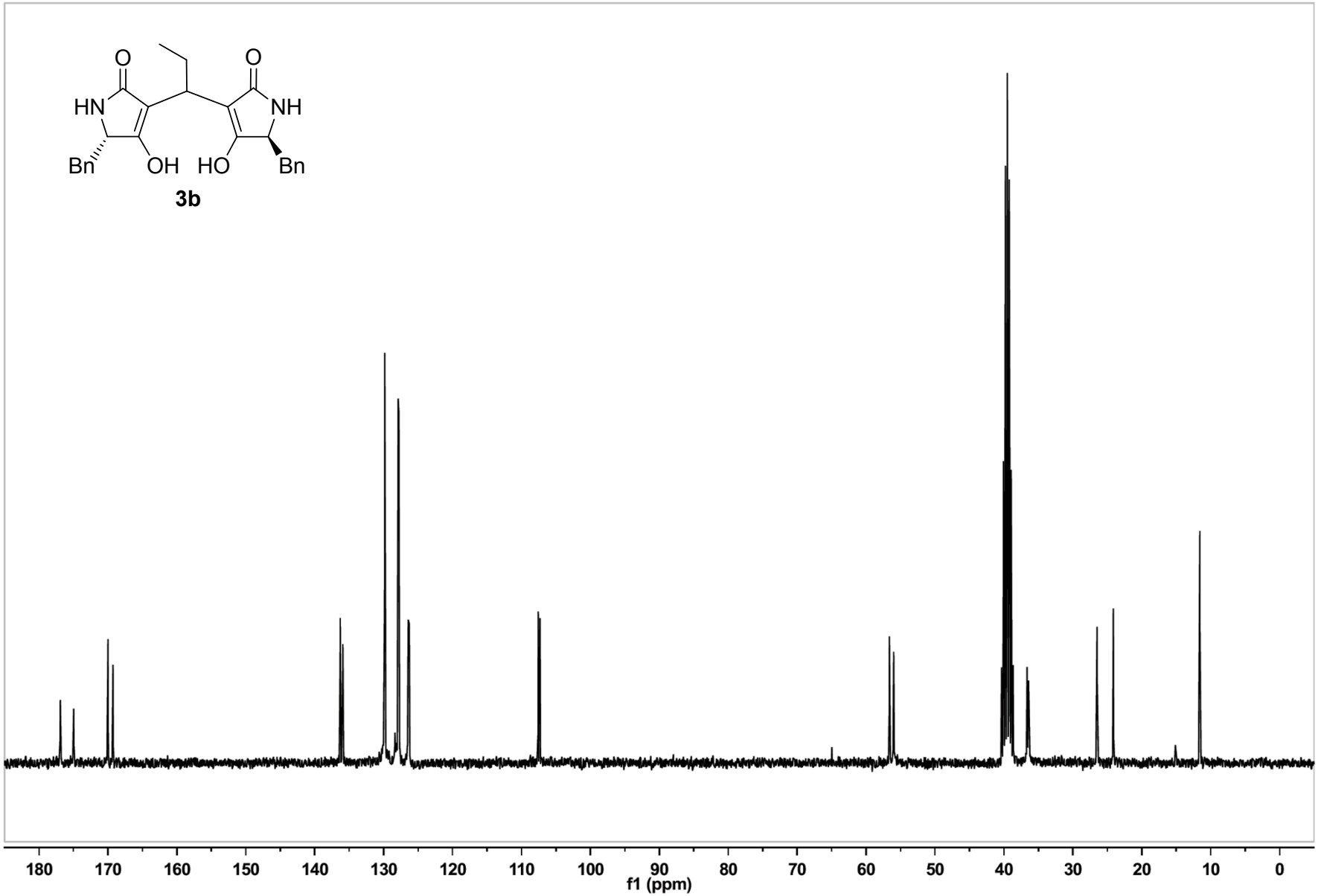
Compound **3a** (^{13}C NMR in $CDCl_3$)



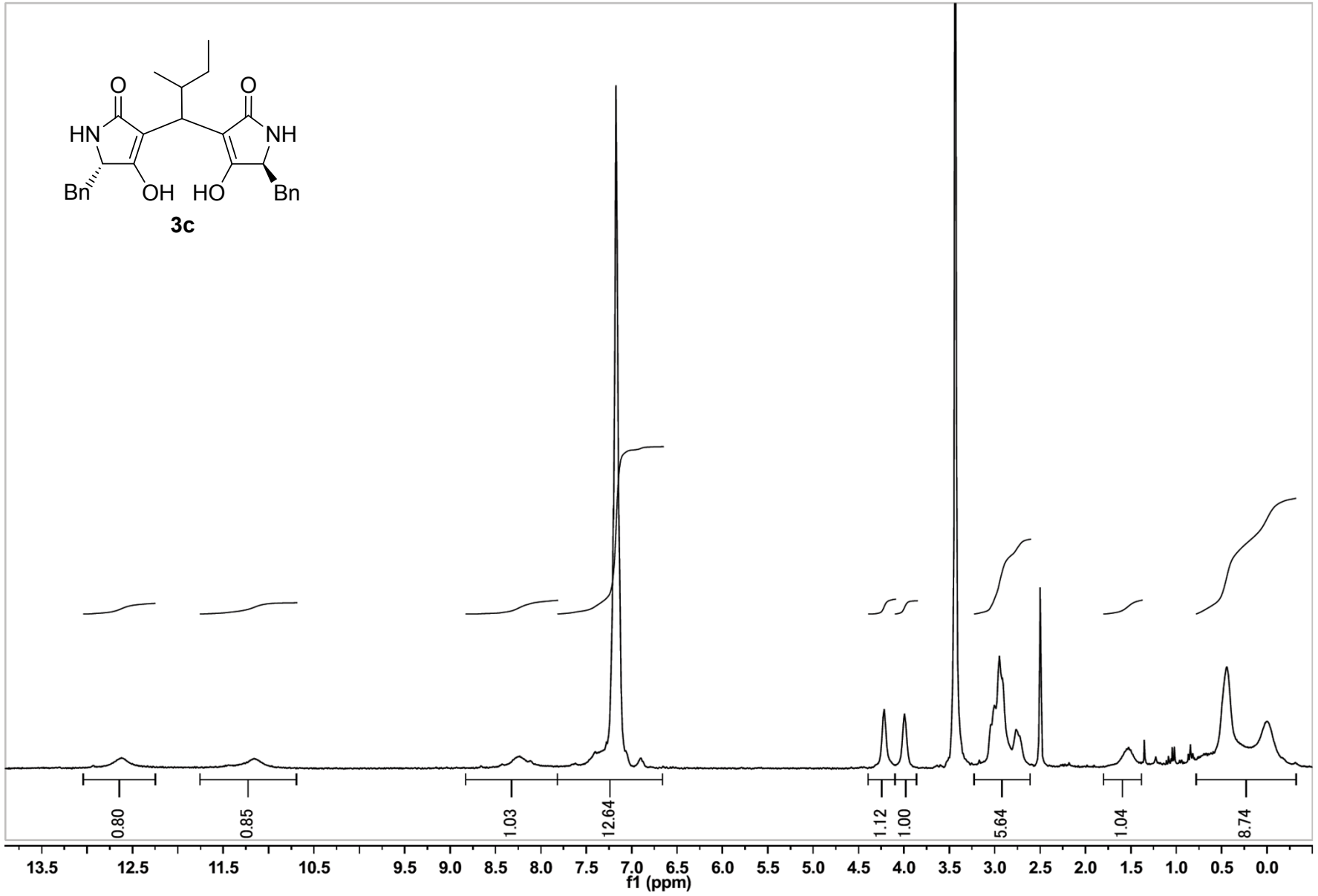
Compound **3b** (^{1}H NMR in DMSO–d_6)



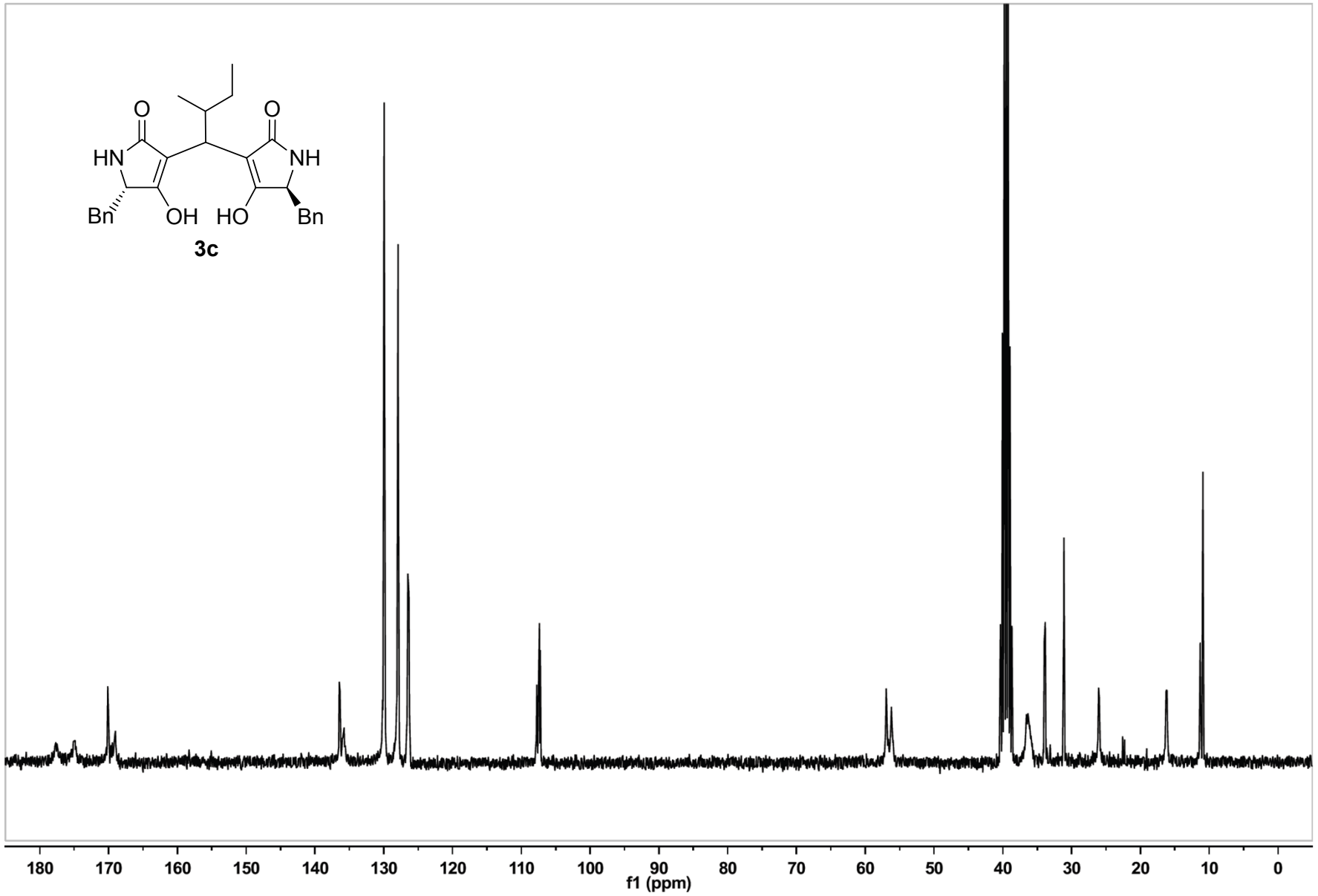
Compound **3b** (^{13}C NMR in DMSO–d_6)



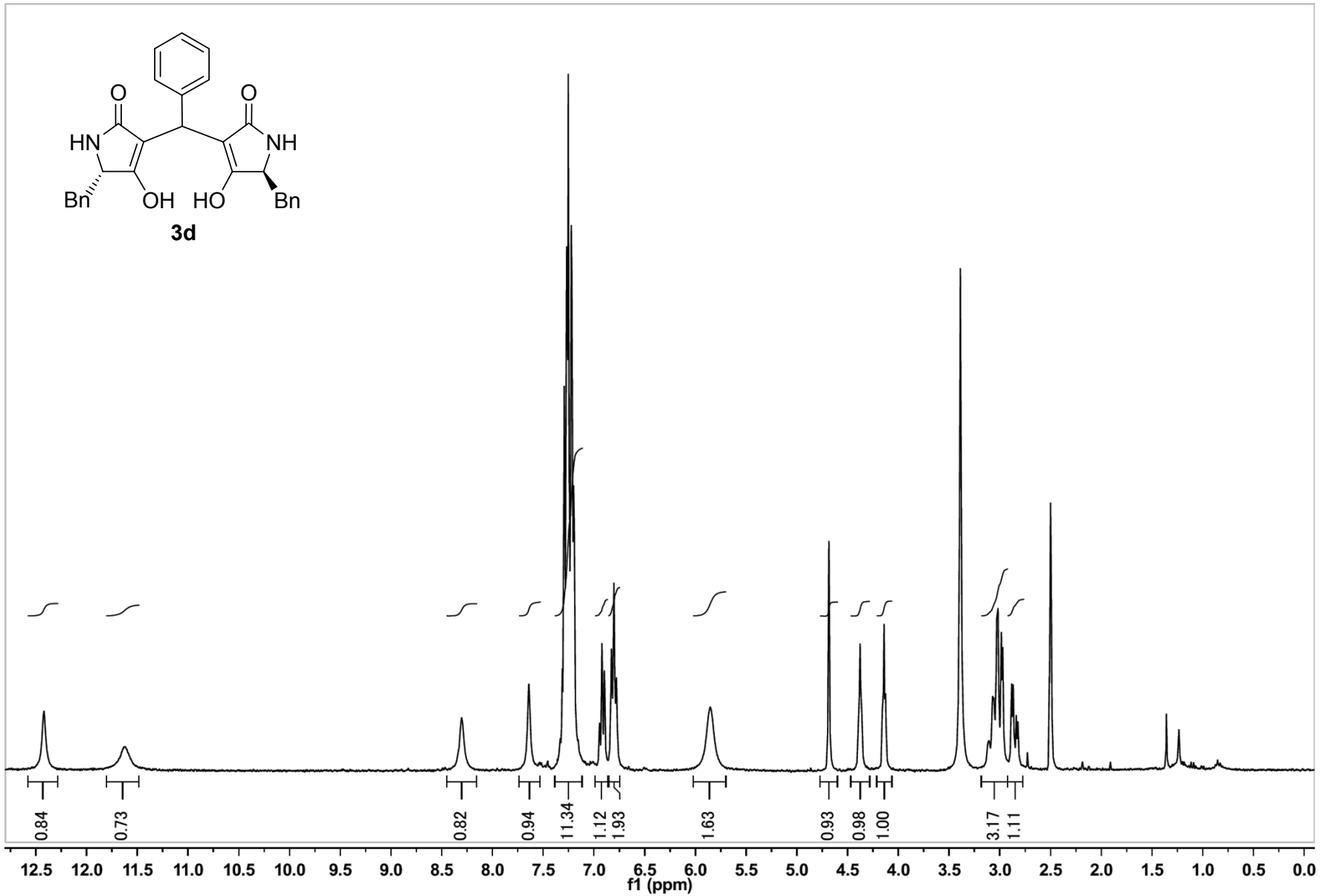
Compound **3c** (^{1}H NMR in DMSO–d_6)



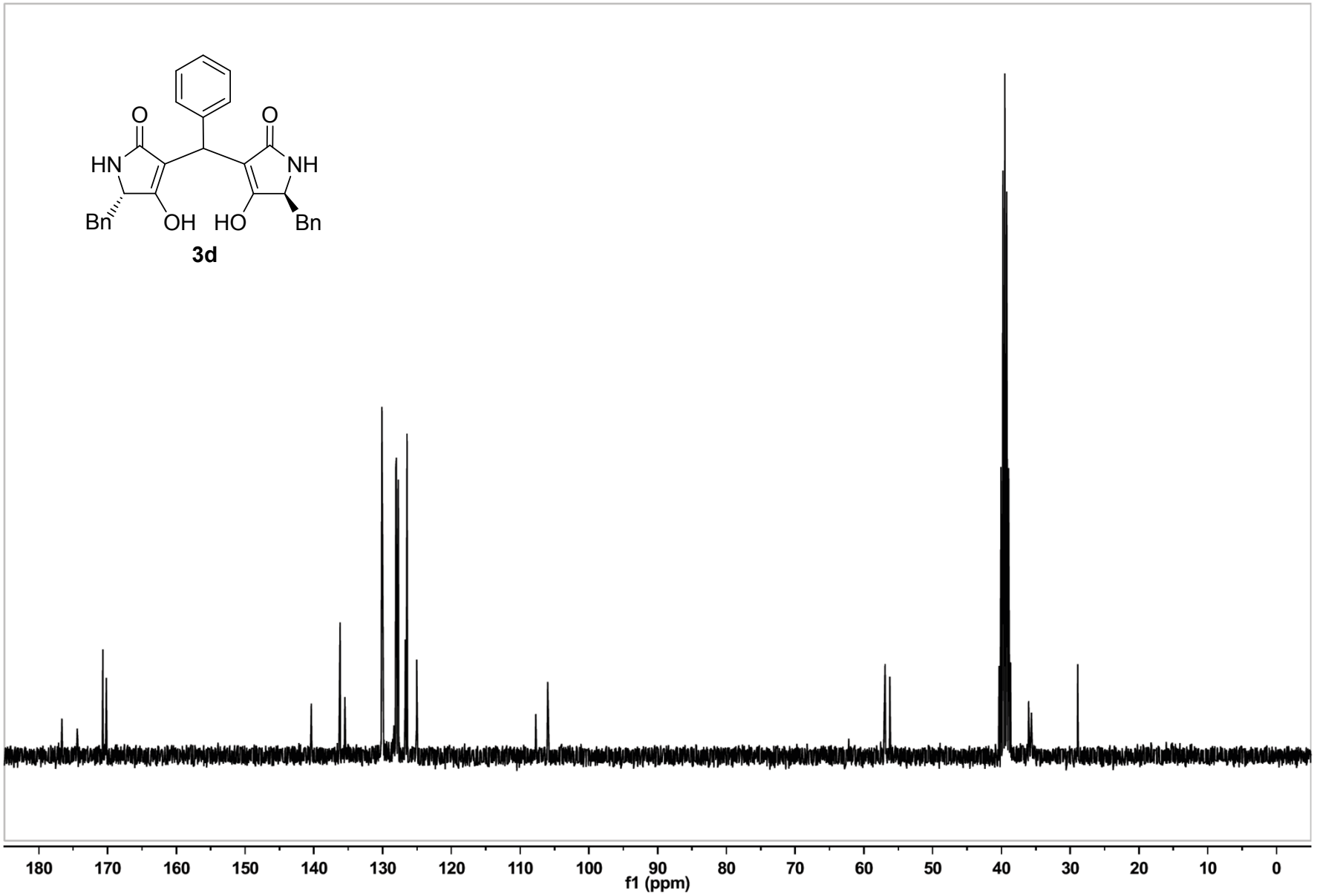
Compound **3c** (^{13}C NMR in DMSO–d_6)



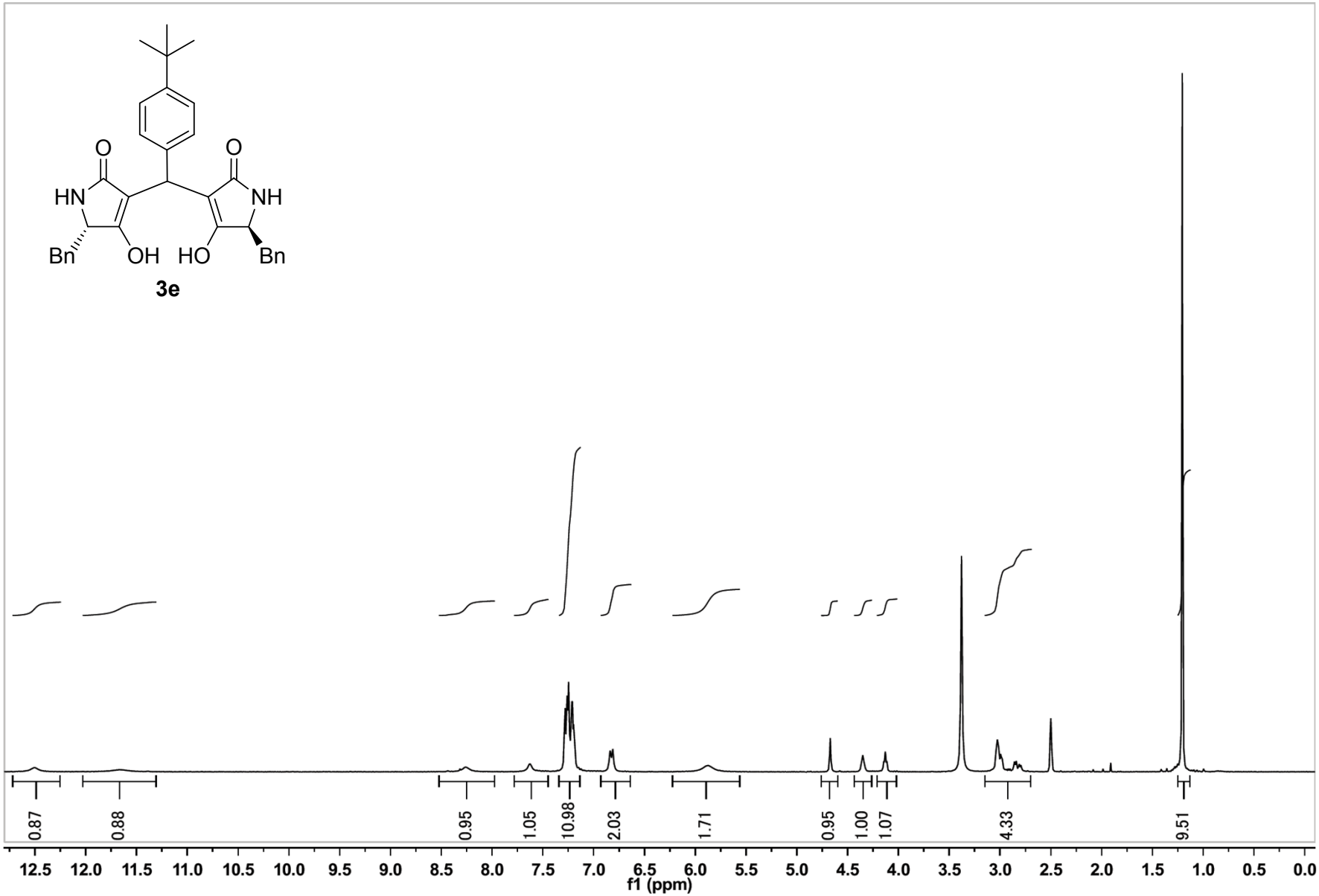
Compound **3d** (^{1}H NMR in DMSO–d_6)



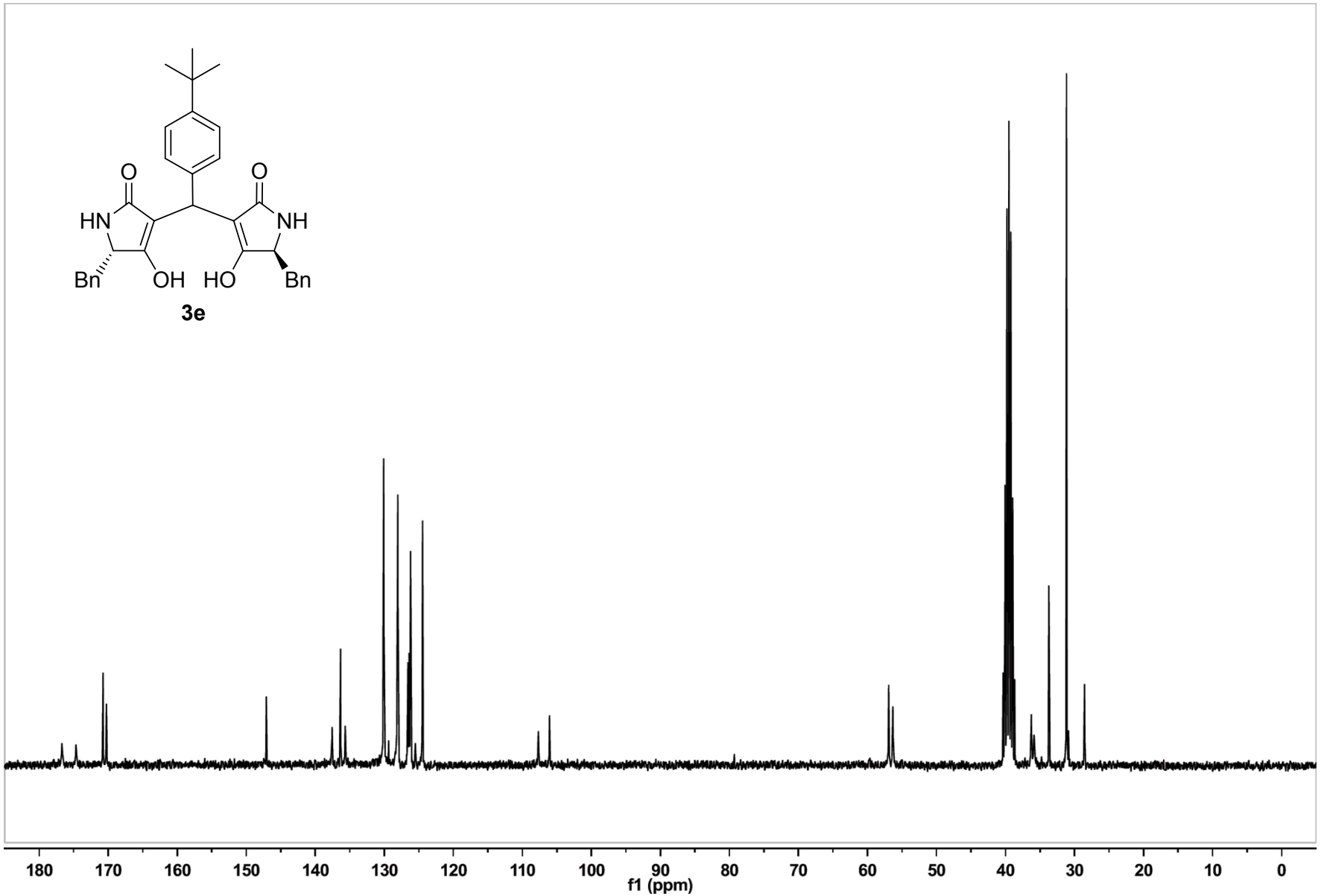
Compound **3d** (^{13}C NMR in DMSO–d_6)



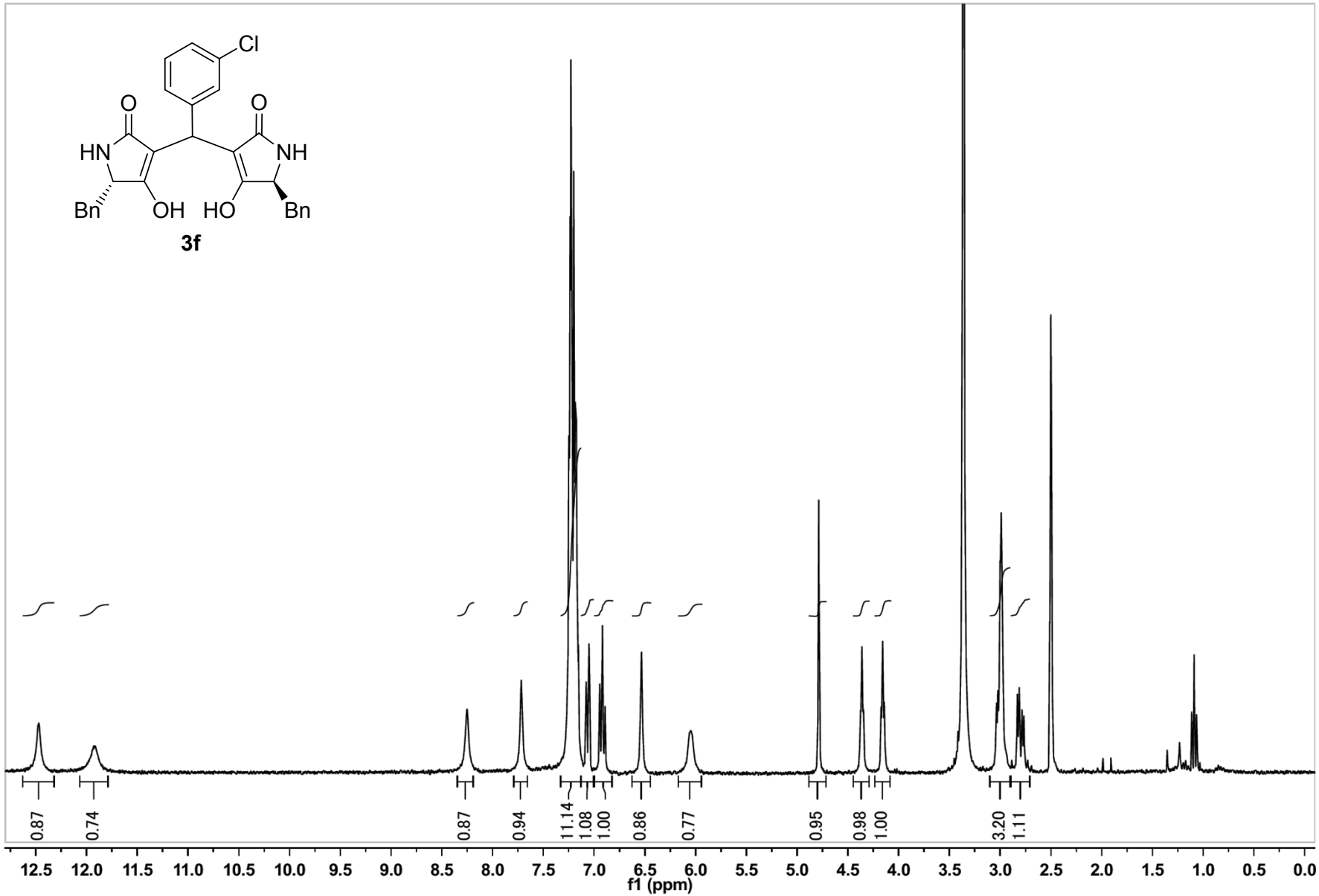
Compound **3e** (^{1}H NMR in DMSO–d_6)



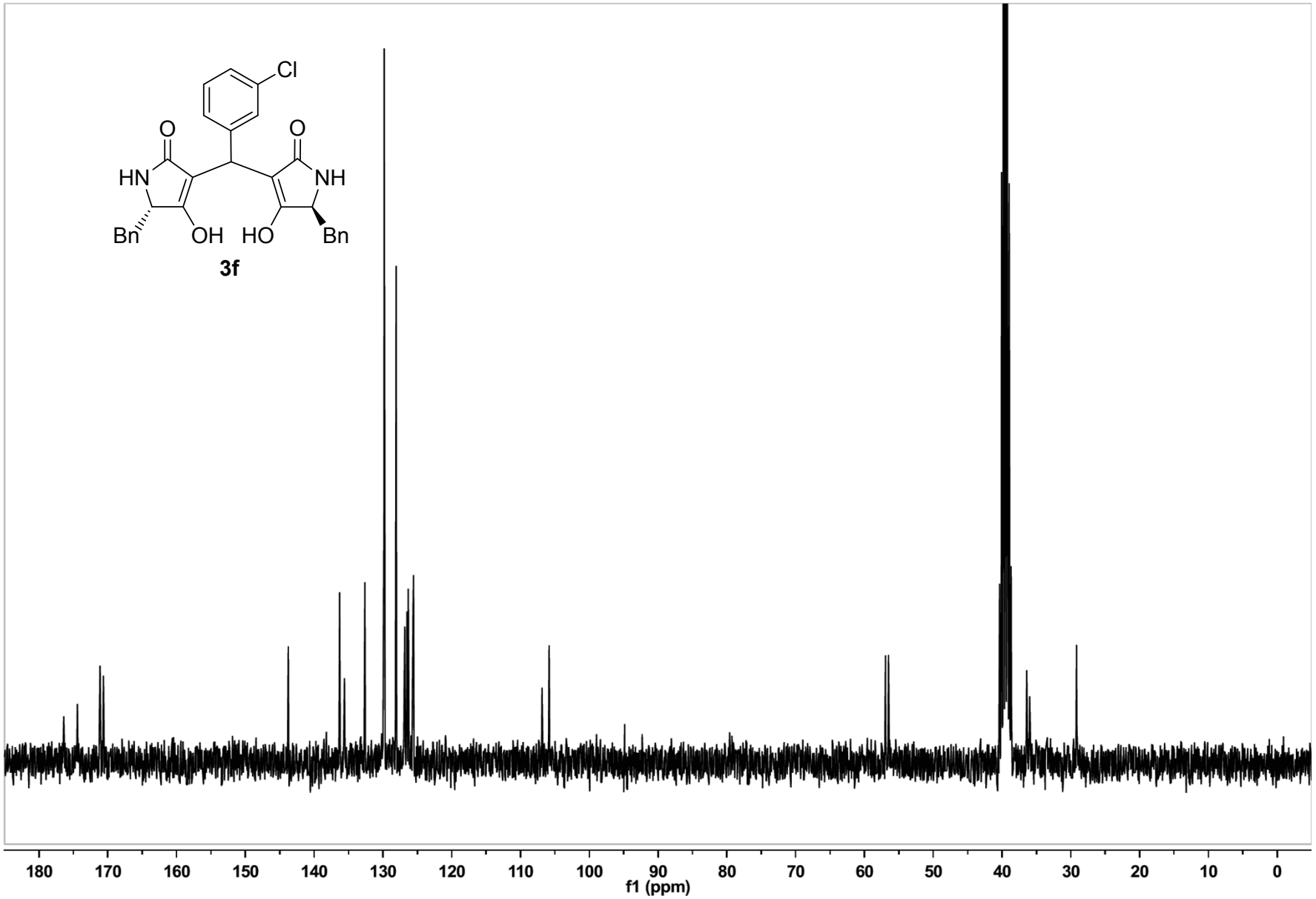
Compound **3e** (^{13}C NMR in DMSO–d_6)



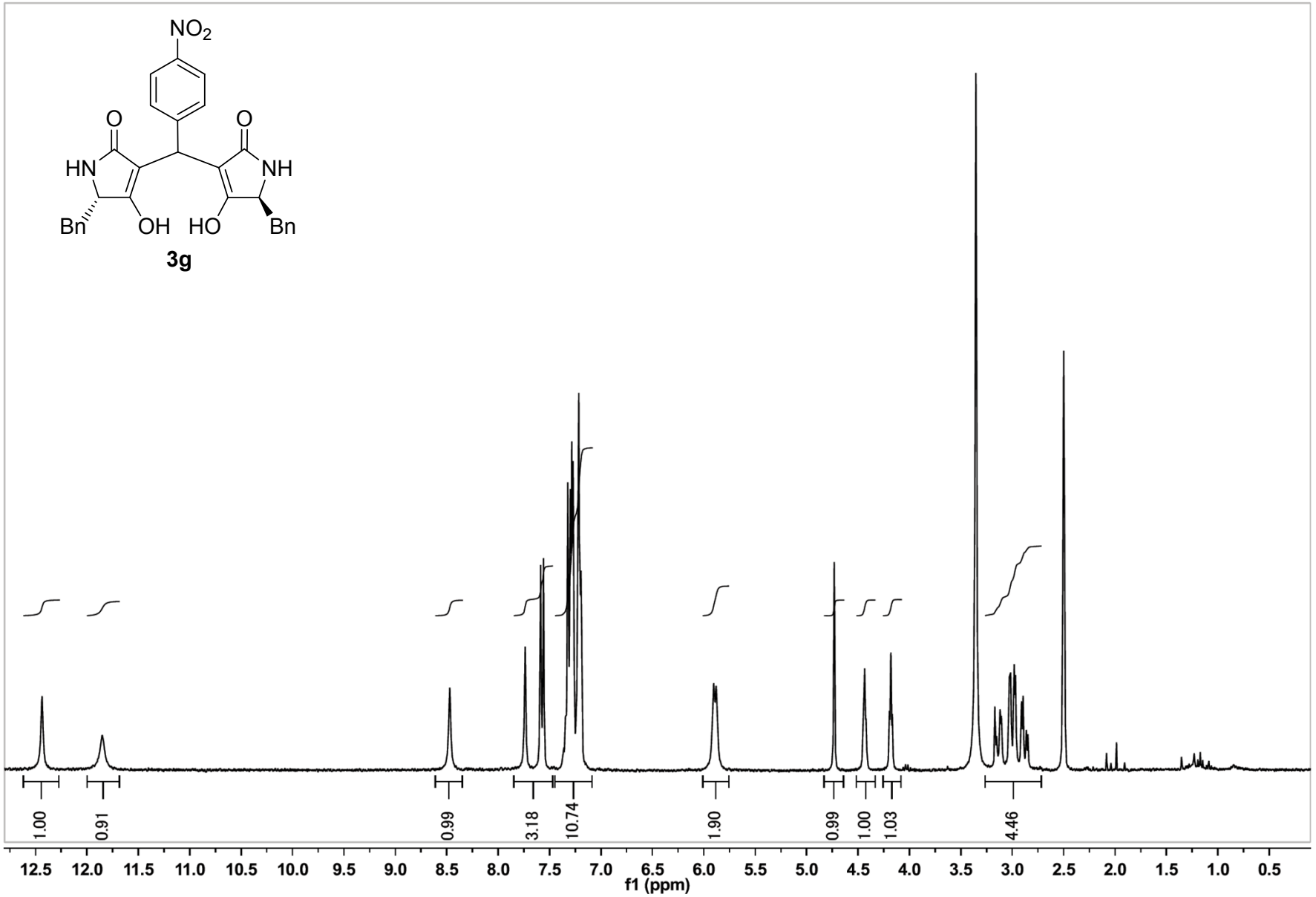
Compound **3f** (^{1}H NMR in DMSO–d_6)



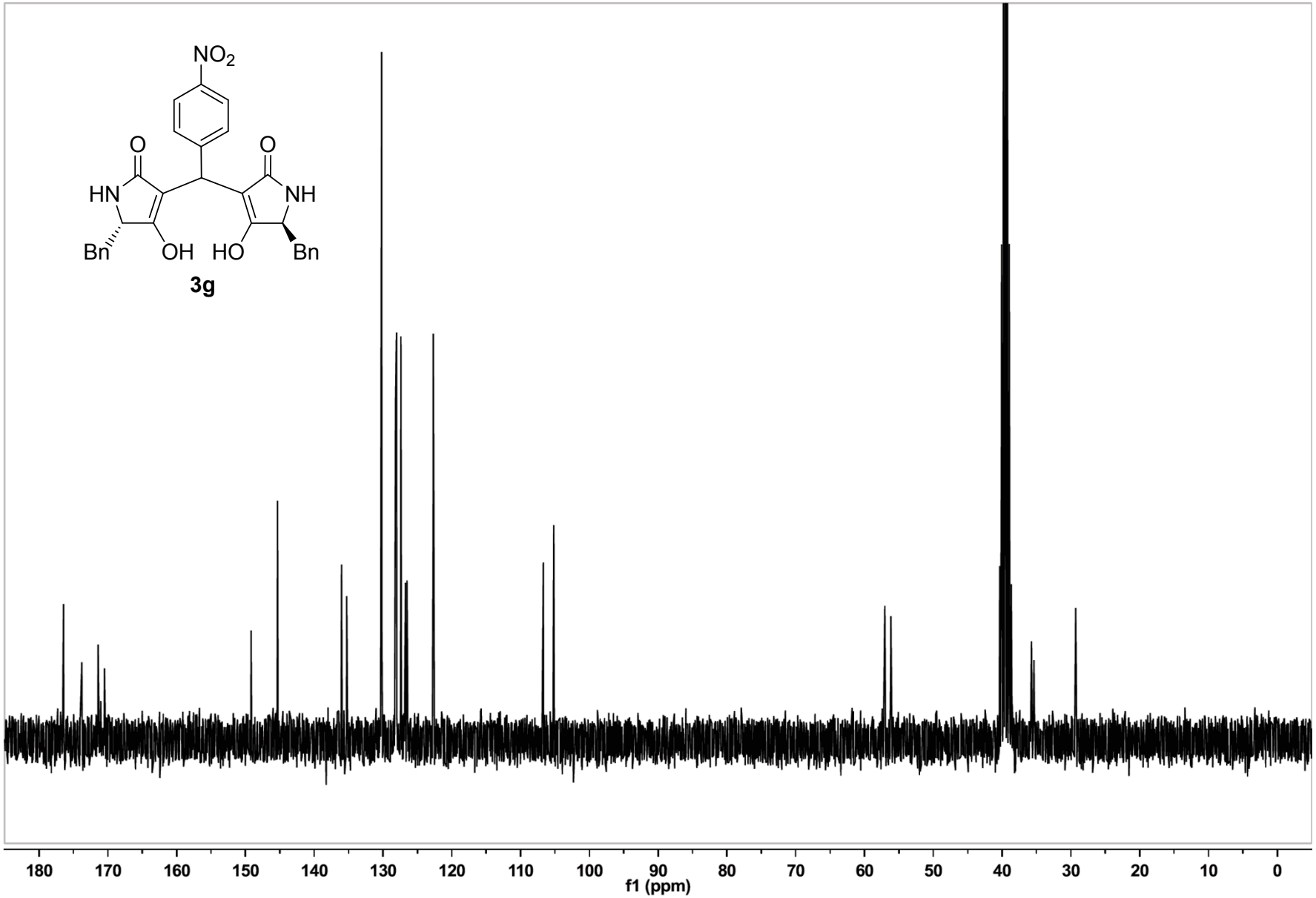
Compound **3f** (^{13}C NMR in DMSO–d_6)



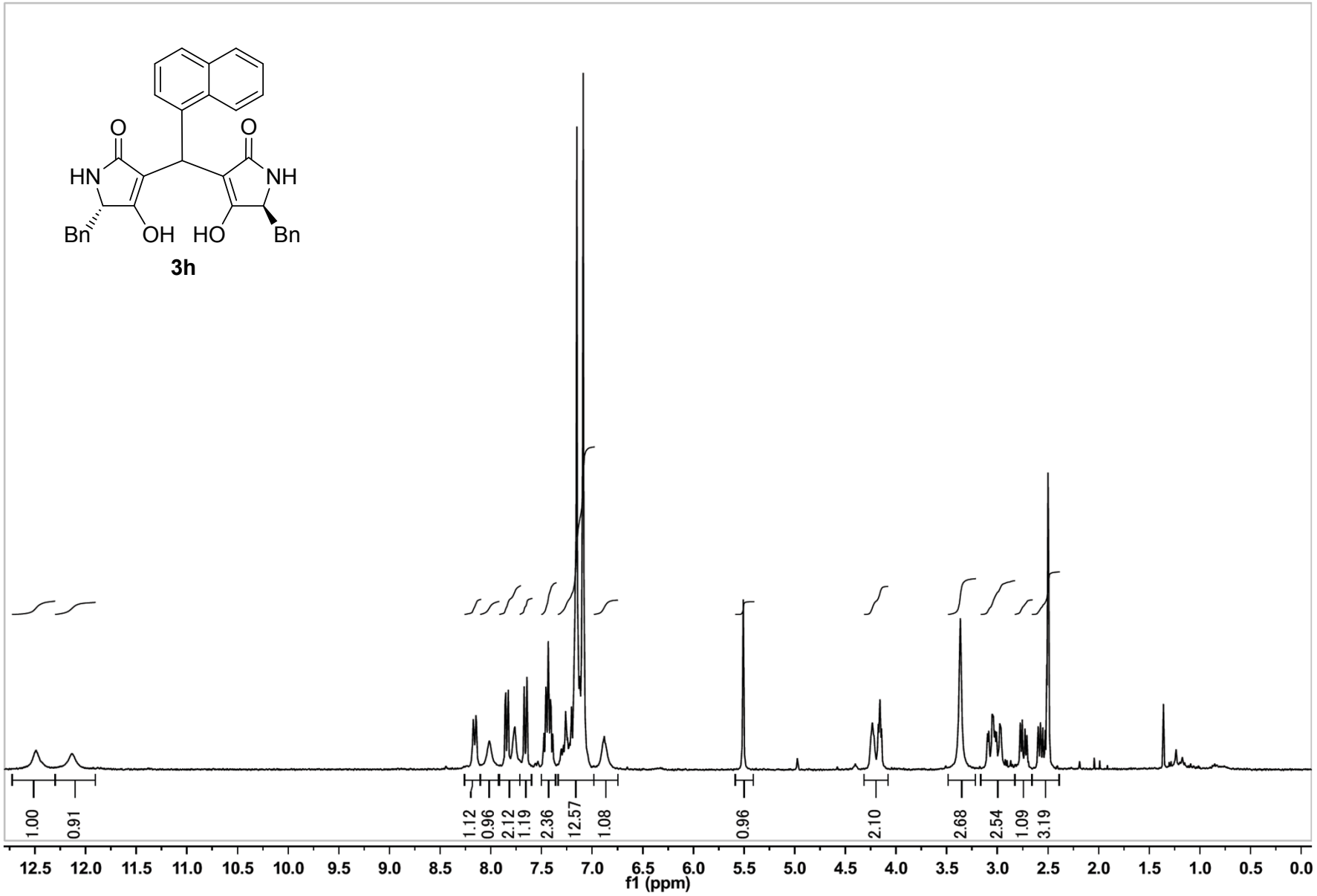
Compound **3g** (^{1}H NMR in DMSO–d_6)



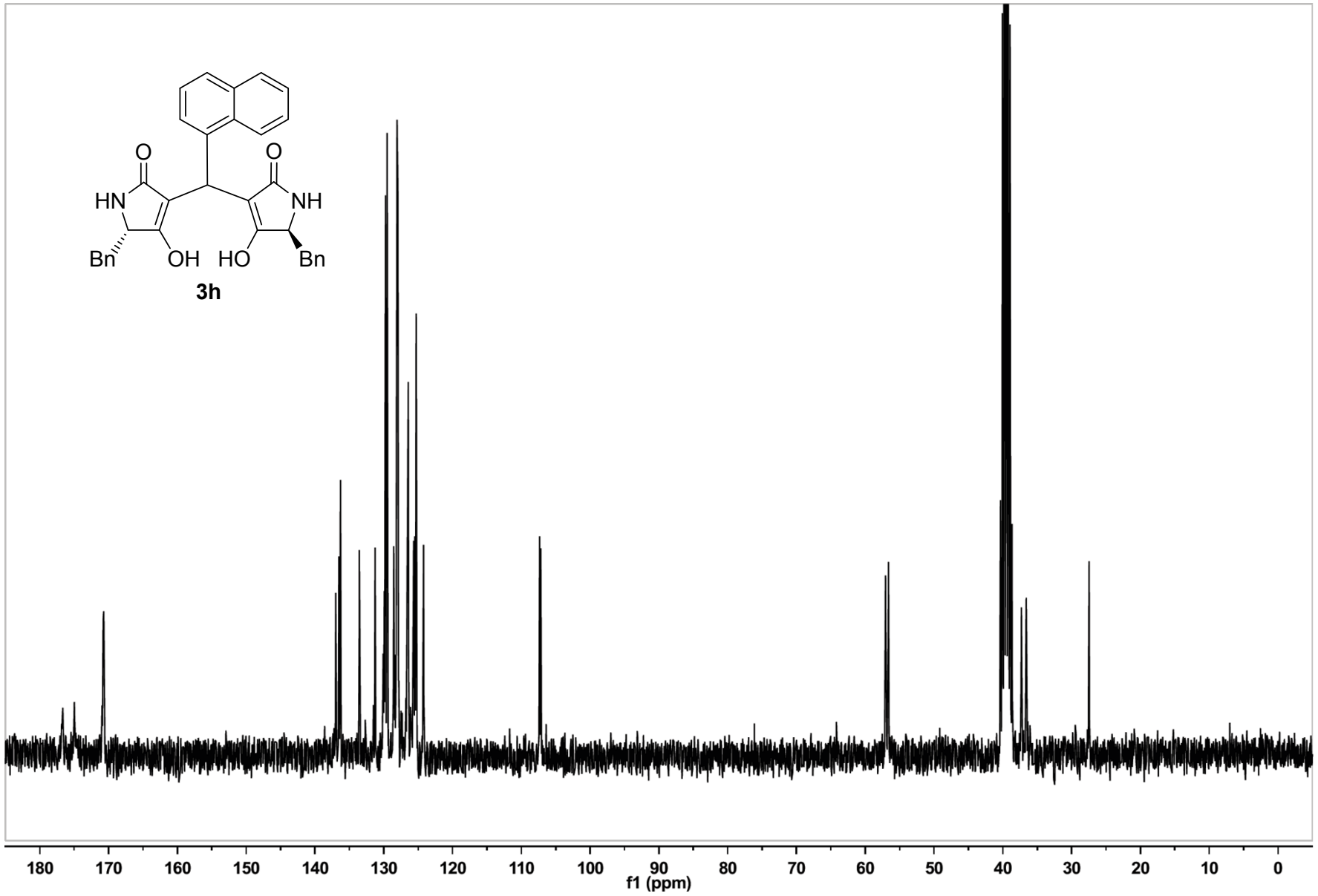
Compound **3g** (^{13}C NMR in DMSO–d_6)



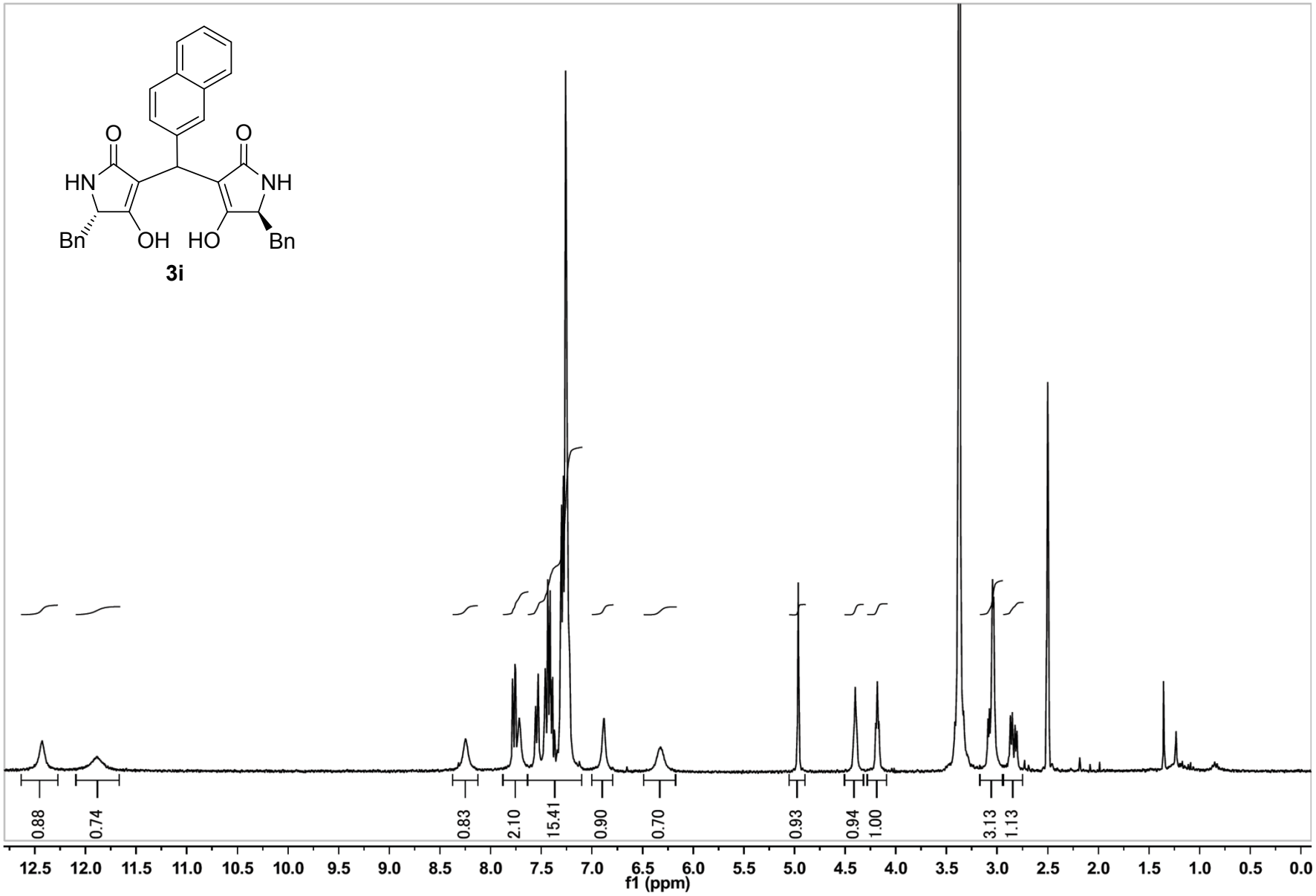
Compound **3h** (^{1}H NMR in DMSO–d_6)



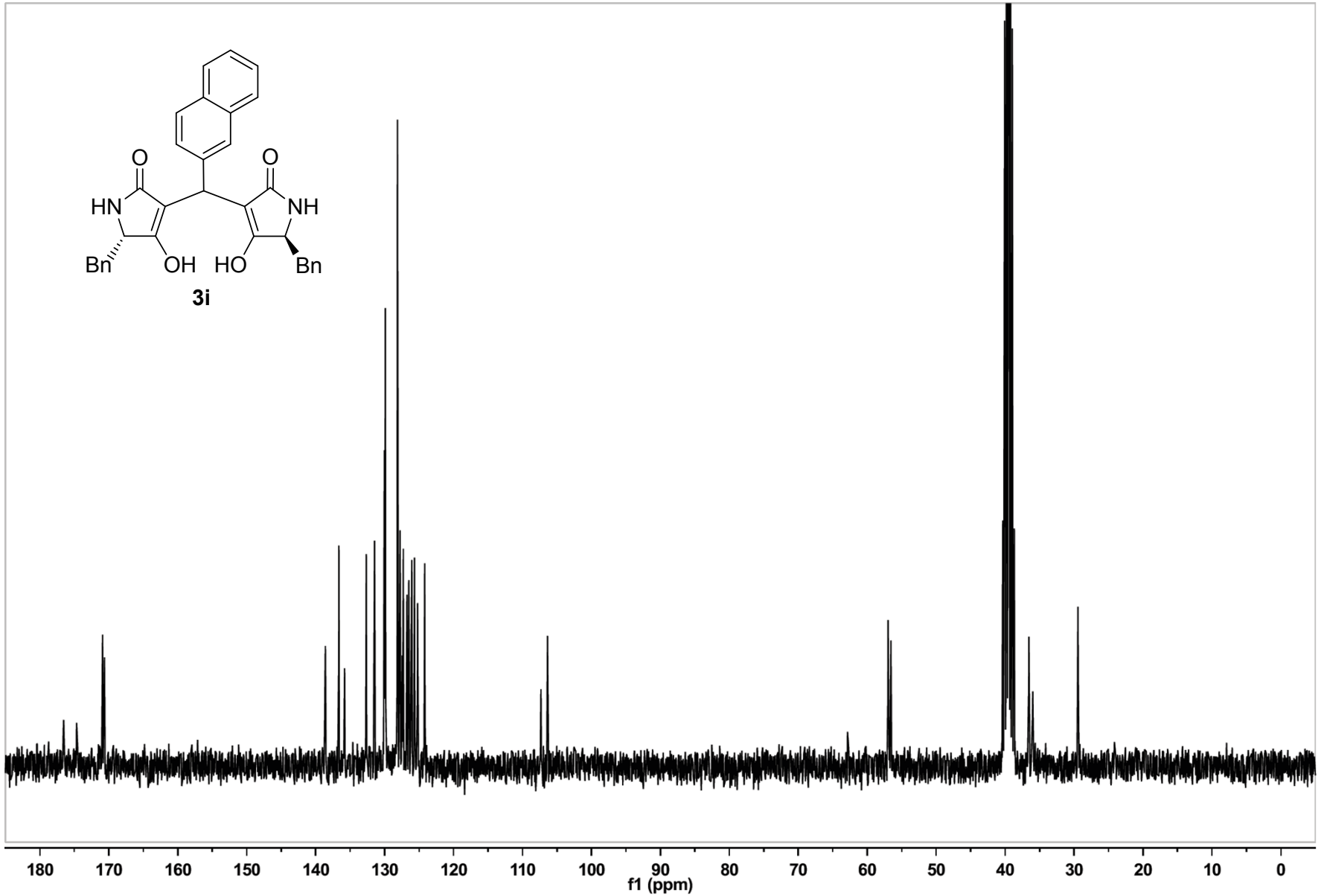
Compound **3h** (^{13}C NMR in DMSO–d_6)



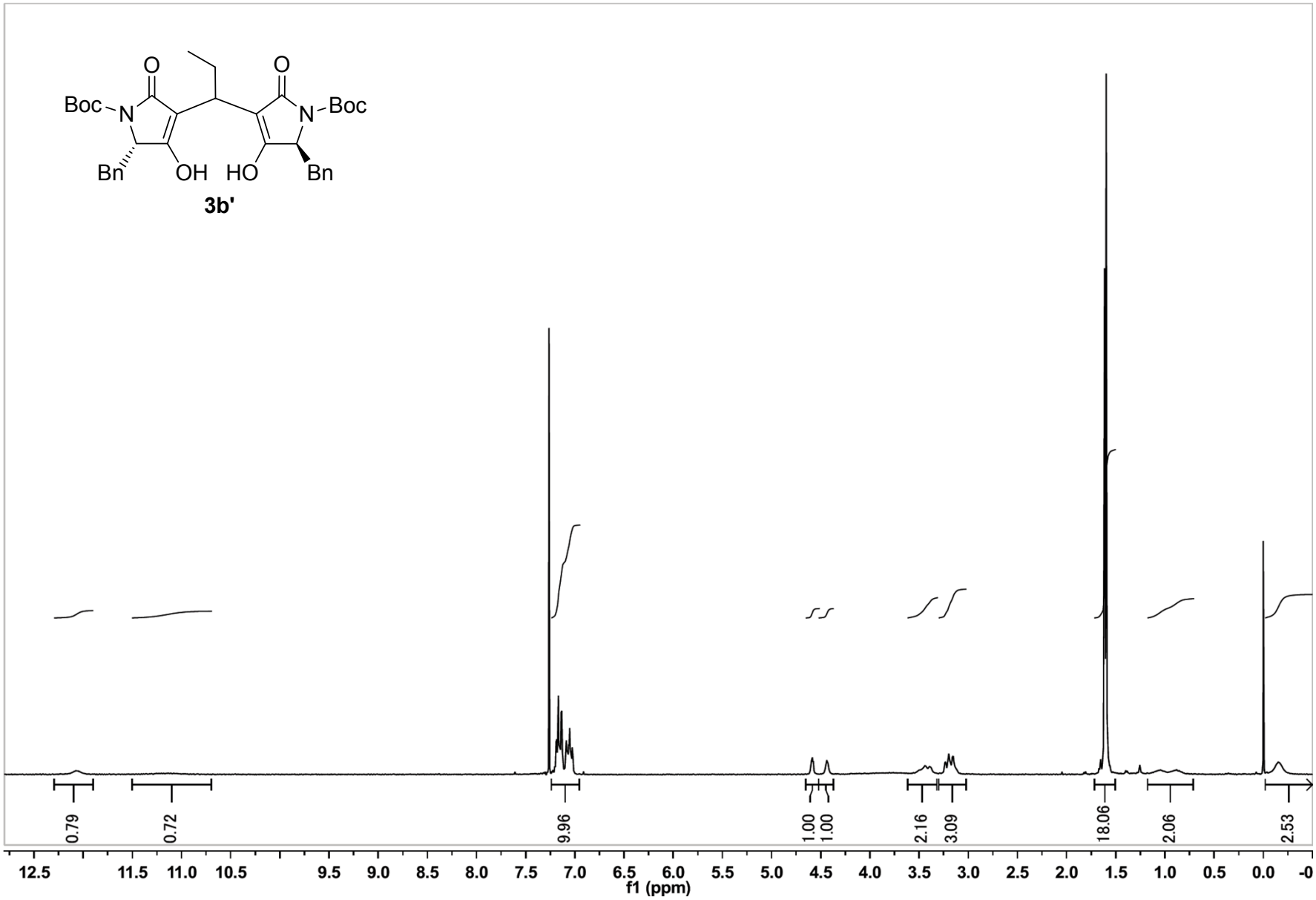
Compound **3i** (^{1}H NMR in DMSO–d_6)



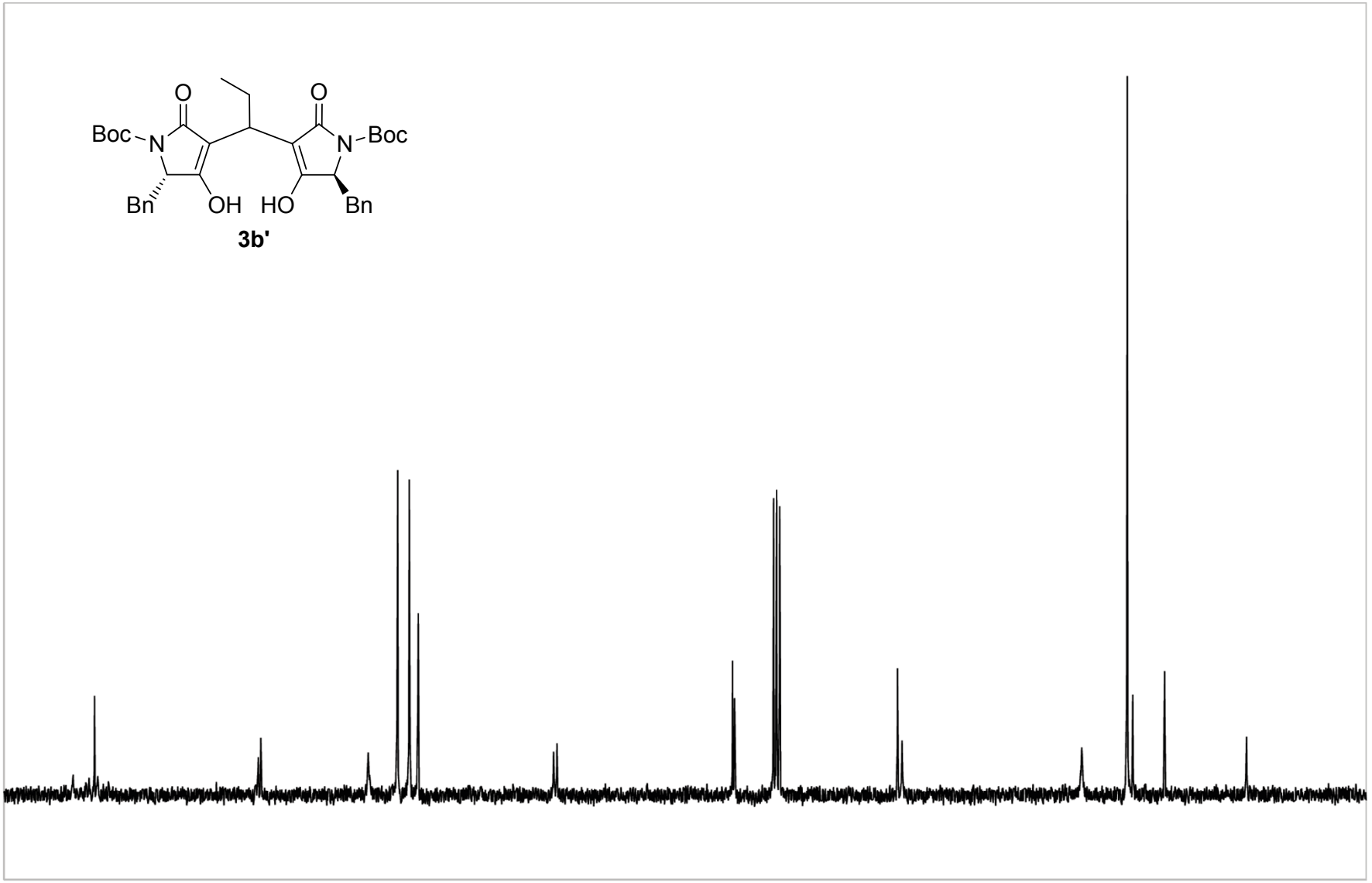
Compound **3i** (^{13}C NMR in DMSO–d_6)



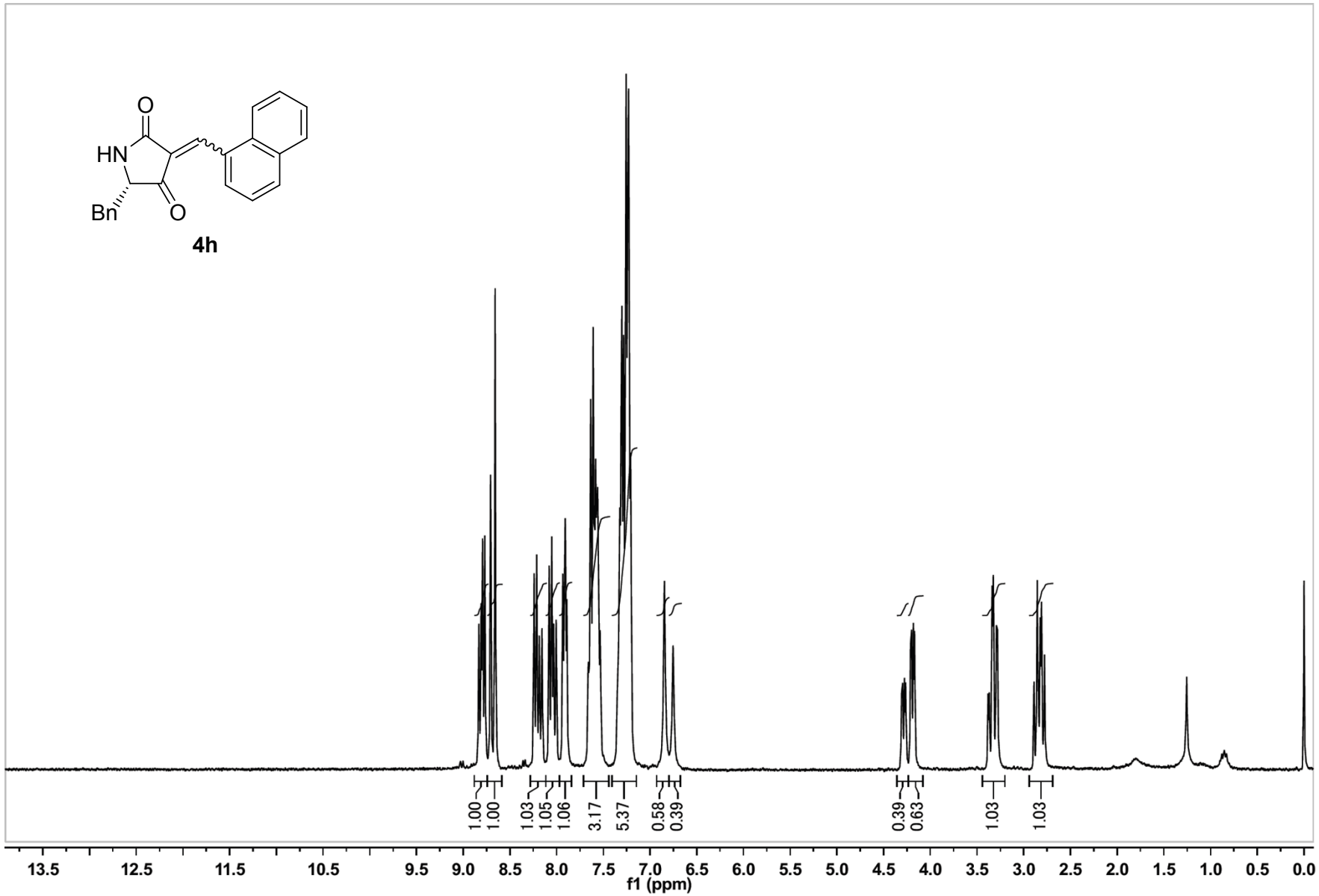
Compound **3b'** (^{1}H NMR in $CDCl_3$)



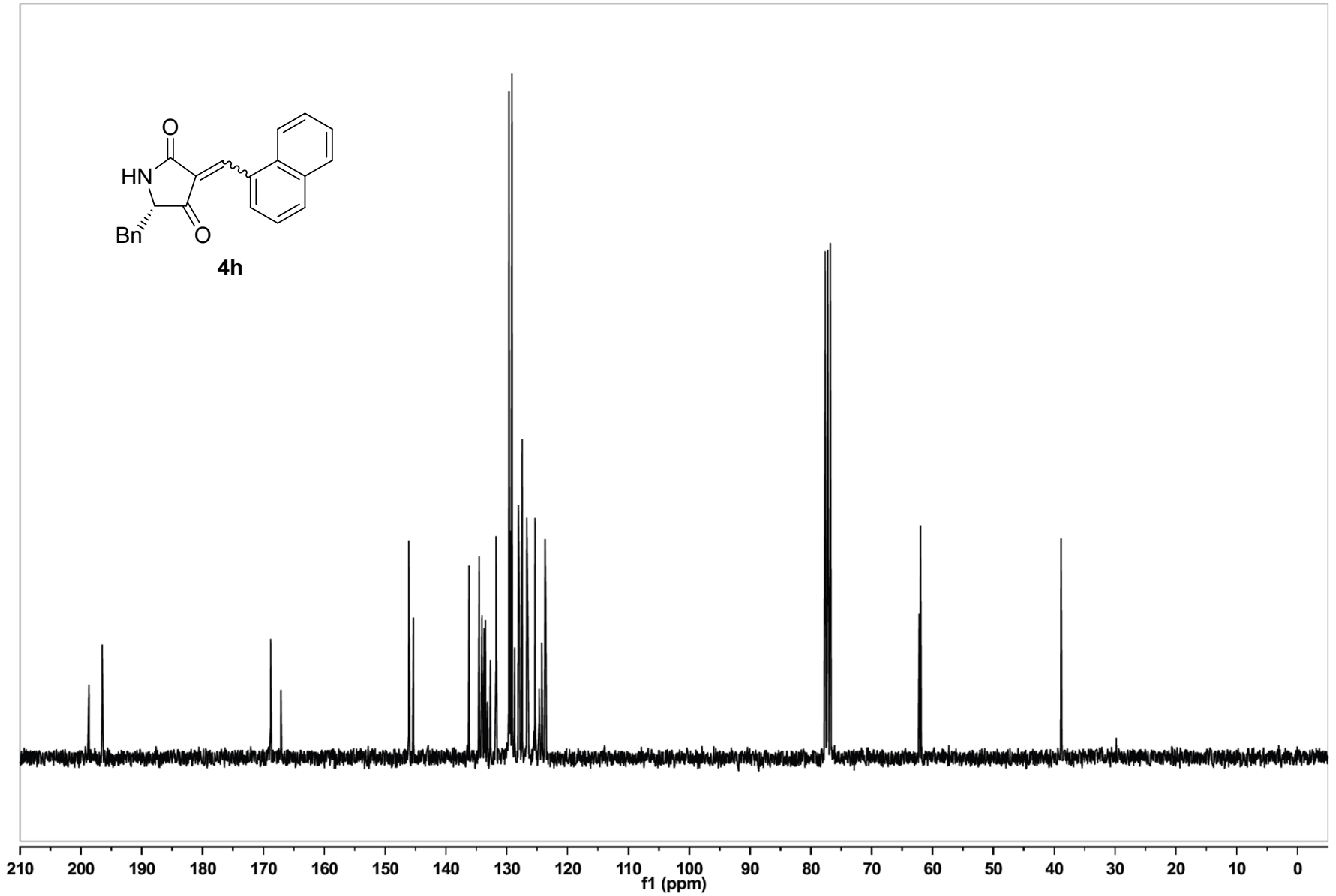
Compound **3b'** (^{13}C NMR in $CDCl_3$)



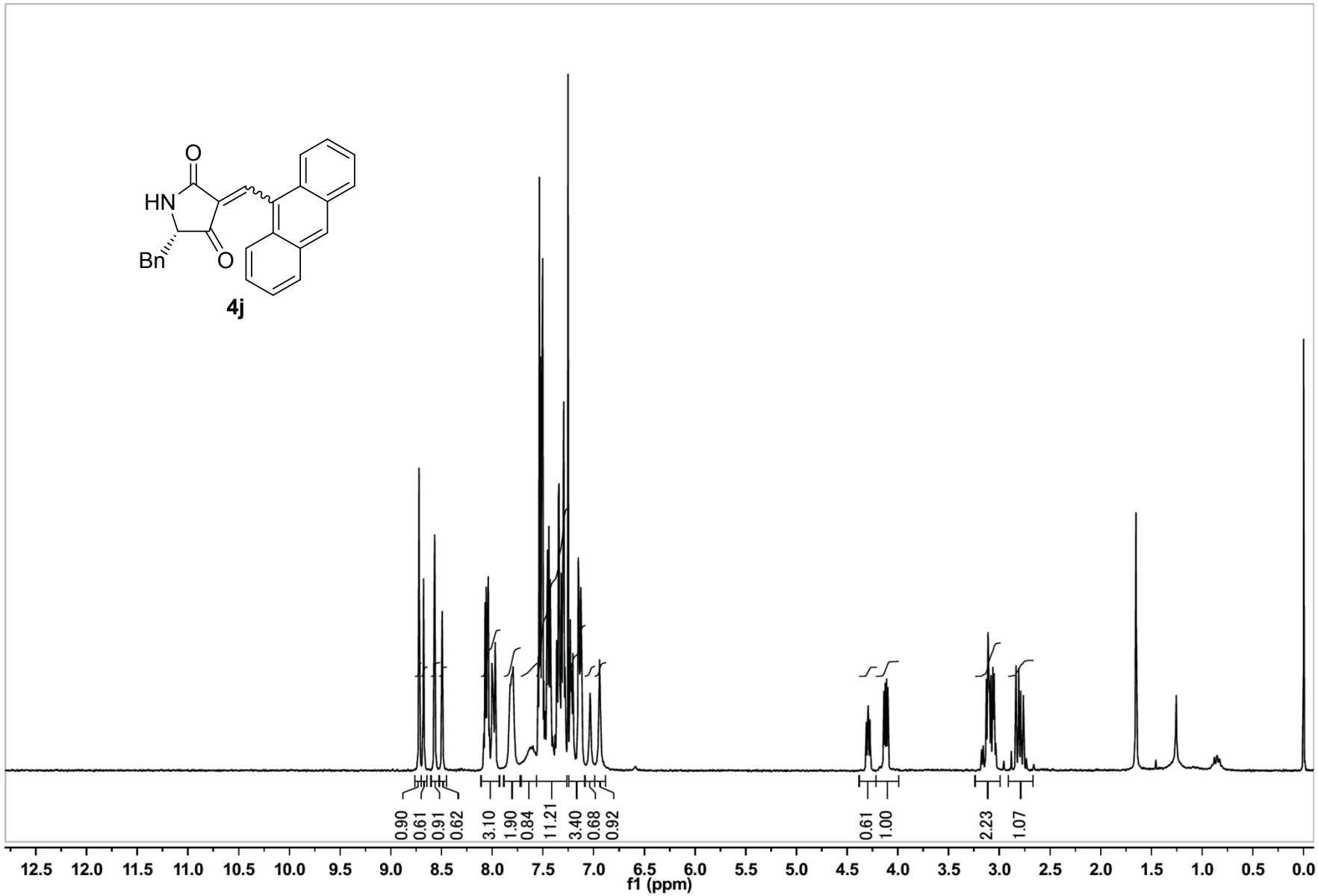
Compound **4h** (^{1}H NMR in $CDCl_3$)



Compound **4h** (^{13}C NMR in $CDCl_3$)



Compound **4j** (^{1}H NMR in $CDCl_3$)



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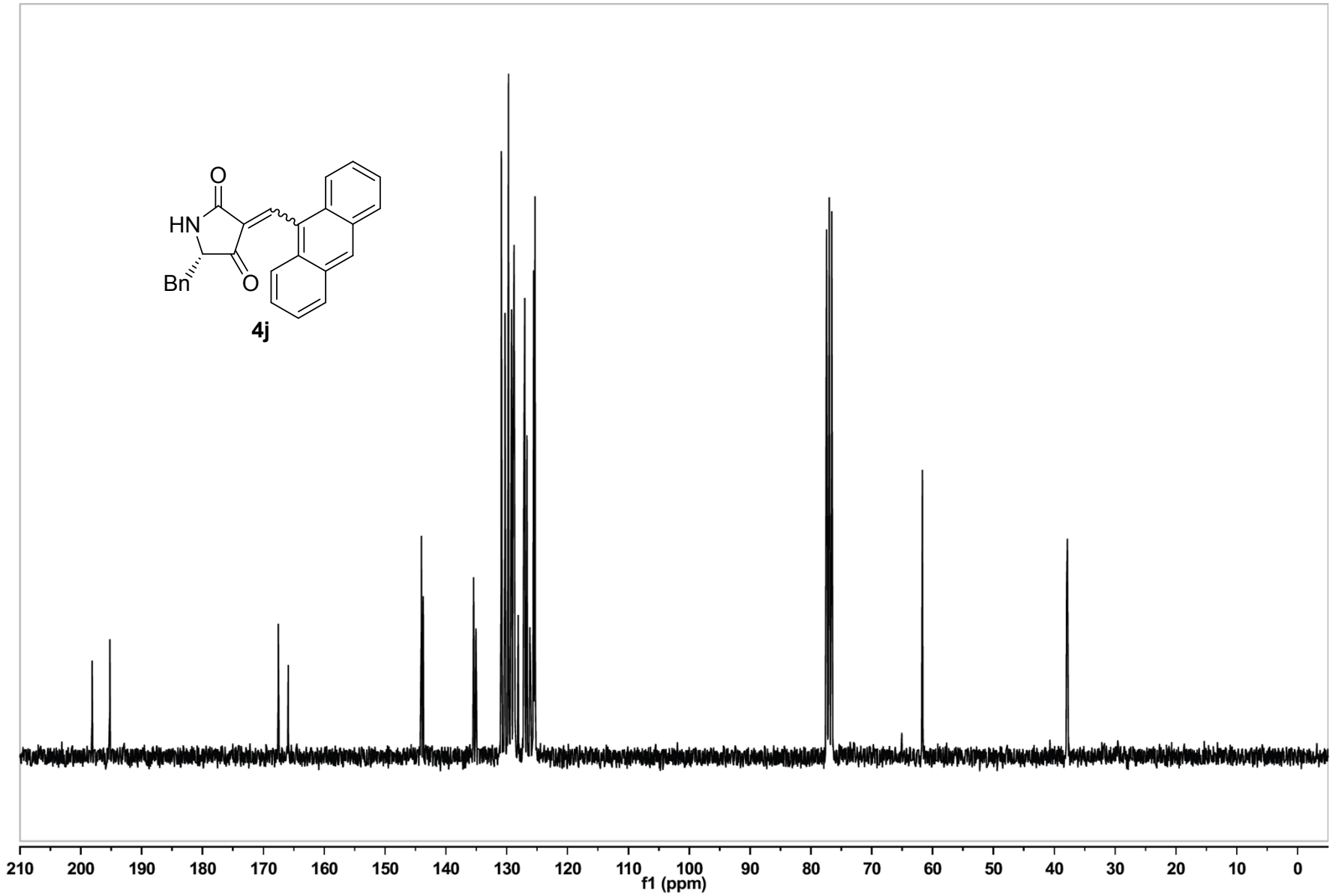
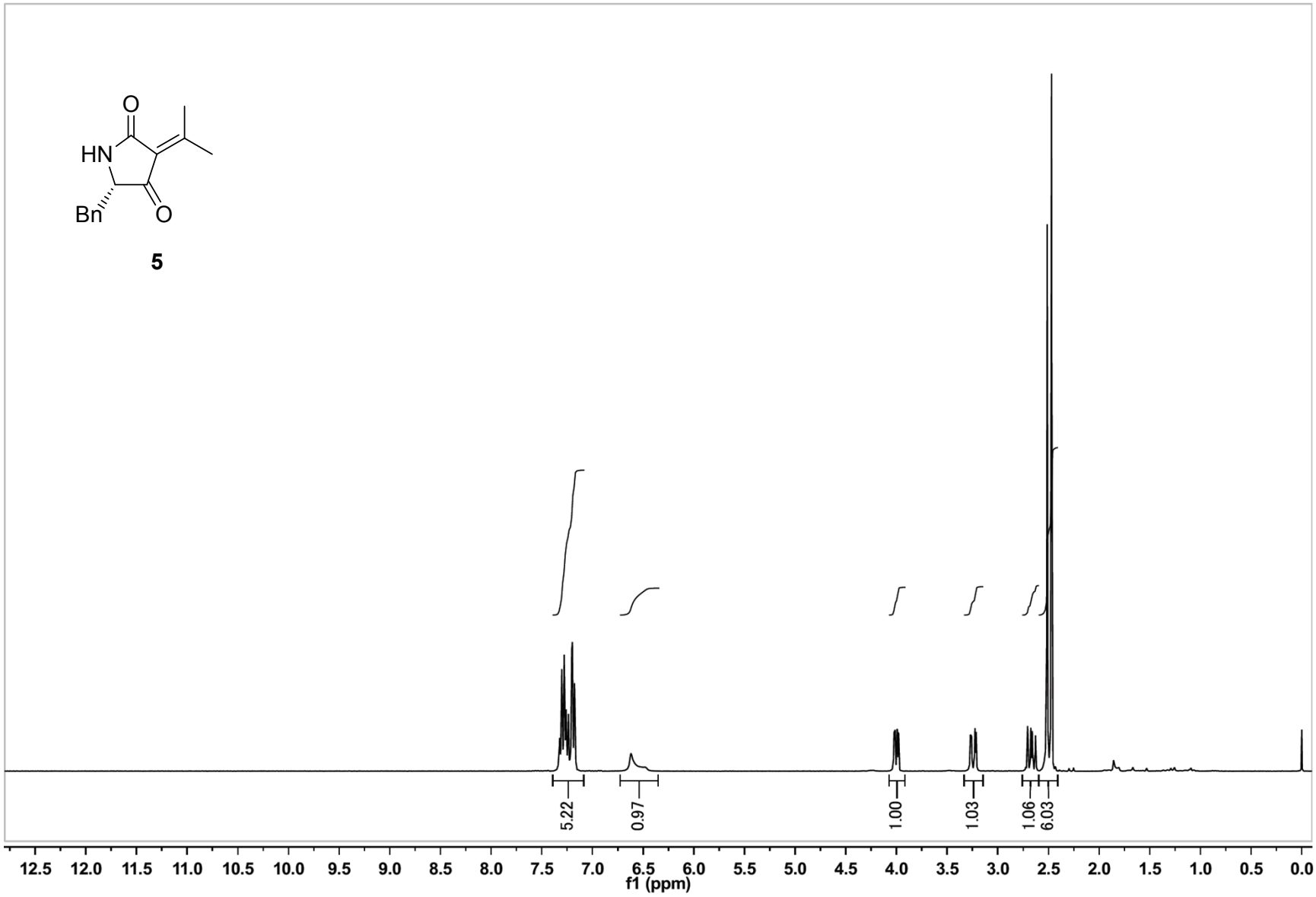


Compound **5** (^{1}H NMR in $CDCl_3$)



Compound **5** (^{13}C NMR in $CDCl_3$)