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Haber-Independent, Diversity-Oriented Synthesis of Nitrogen Compounds from Biorenewable Chitin

Thuy Trang Pham, Xi Chen, Tilo Söhnel, Ning Yan and Jonathan Sperry*

j.sperry@auckland.ac.nz

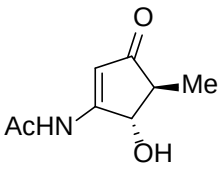
Electronic Supplementary Information

General Experimental Details

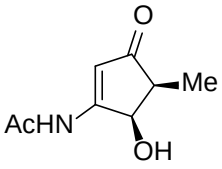
Commercially available reagents were used throughout without purification unless otherwise stated. Anhydrous solvents were used as supplied. Dichloromethane, methanol and tetrahydrofuran were dried using an LC Technology Solutions Inc. SP-1 solvent purification system under an atmosphere of dry nitrogen. All reactions were routinely carried out in oven-dried glassware under a nitrogen atmosphere unless otherwise stated. Analytical thin layer chromatography was performed using silica plates and compounds were visualized at 254 and/or 360 nm ultraviolet irradiation followed by staining ethanolic vanillin solution. Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer spectrum One Fourier Transform Infrared spectrometer as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). NMR spectra were recorded on either a Bruker AV300, AVIII400 or AVIIIHD500 spectrometer operating at 300, 400, 500 MHz for ^{1}H nuclei respectively and 75, 100, 125 MHz for ^{13}C nuclei respectively. Chemical shifts are reported in parts per million (ppm) relative to the tetramethylsilane peak recorded as δ 0.00 ppm in $CDCl_3$/TMS solvent, or the residual chloroform (δ 7.26 ppm), or DMSO (δ 2.50 ppm). The ^{13}C NMR values were referenced to the residual chloroform (δ 77.1 ppm), DMSO (δ 39.5 ppm). ^{13}C NMR values are reported as chemical shift δ and assignment. ^{1}H NMR shift values are reported as chemical shift δ, relative integral, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (*J* in Hz) and assignment. Assignments are made with the aid of COSY, NOESY, HMBC and edited HSQC experiments. All experiments were conducted at 298 K. Conventional NMR tubes (5 mm diameter, Norell) using a sample volume of 500 µL were used. High resolution mass spectra were obtained by electrospray ionization in positive ion mode at a nominal accelerating voltage of 70 eV on a Bruker micrOTOF-QII mass spectrometer.

X-ray diffraction analysis of single crystals of **3**, **9**, **10** and **14** were performed on a Rigaku Oxford Diffraction XtaLAB-Synergy-S single-crystal diffractometer with a PILATUS 200K hybrid pixel array detector using Cu Kα radiation (Table S1). The data were processed with the SHELX2016[1] and Olex2[2] software packages. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were inserted at calculated positions and refined with a riding model or without restrictions. Mercury 4.2.0[3] was used to visualize the molecular structures.

(±)-*Trans*-*N*-(5-hydroxy-4-methyl-3-oxocyclopent-1-en-1-yl)acetamide (*trans*-3) and **(±)-*cis*-*N*-(5-hydroxy-4-methyl-3-oxocyclopent-1-en-1-yl)acetamide (*cis*-3)**



***Trans*-3**



***Cis*-3**

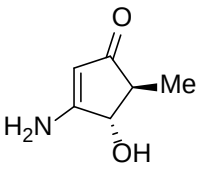
A mixture of the furfuryl alcohol **2** (1.50 g, 8.87 mmol) and magnesium chloride hexahydrate (7.21 g, 35.47 mmol) in water (340 mL) was stirred at 120 °C for 24 h. After completion, the mixture was concentrated *in vacuo* until small amount of water was left (~30 mL) and extracted with ethyl acetate (3 x 100 mL), washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel eluting with ethyl acetate to give the *title compound*s *trans*-**3** (479 mg, 2.83 mmol, 32%) and *cis*-**3** (120 mg, 0.709 mmol, 8%);

Trans-**3**: colourless solid; m.p. 136.9-138.1 °C; HRMS [ESI, $(M + Na)^+$] found 192.0633, $[C_8H_{11}NO_3 + Na]^+$ requires 192.0631; ν_{max} (neat)/cm^{-1} 3188, 3119, 3094, 3013, 2935, 2872, 1721, 1657, 1607, 1527, 1453, 1368, 1306, 1233, 1182, 1061, 1039, 1001; δ_H (400 MHz, $(CD_3)_2CO$) 9.48 (1 H, br s, NH), 6.24 (1 H, s, CH), 4.82 (1 H, d, *J* 5.2, CH), 4.42 (1 H, br s, OH), 2.20 -2.16 (4 H, m, CH and Me), 1.13 (3 H, d, *J* 7.2, Me); δ_C (100 MHz, $(CD_3)_2CO$) 204.9 (C), 170.6 (C), 165.6 (C), 112.0 (CH), 77.5 (CH), 49.3 (CH), 24.0 (Me), 13.5 (Me).

Cis-**3**: colourless solid; m.p. 158.6-161.8 °C; HRMS [ESI, $(M + Na)^+$] found 192.0638, $[C_8H_{11}NO_3 + Na]^+$ requires 192.0631; ν_{max} (neat)/cm^{-1} 3195, 3126, 3102, 3021, 2987, 2946, 2373, 2188, 1713, 1662, 1614, 1591, 1529, 1458, 1427, 1396, 1372, 1323, 1285, 1232, 1186, 1140, 1105, 1042, 1001; δ_H (400 MHz, $(CD_3)_2CO$) 9.54 (1 H, br s, NH), 6.26 (1 H, s, CH), 4.88 (1 H, t, *J* 6.6 Hz, CH), 4.49 (1 H, d, *J* 6.8, OH), 2.40 (1 H, pent, *J* 7.6, CH), 2.19 (3 H, s, Me),

1.04 (3 H, d, *J* 7.6, Me); δ_C (100 MHz, $(CD_3)_2CO$) 207.4 (C), 170.5 (C), 166.3 (C), 112.1 (CH), 71.6 (CH), 44.1 (CH), 24.0 (Me), 11.0 (Me).

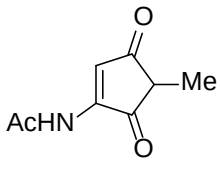
(±)-*Trans*-3-amino-4-hydroxy-5-methylcyclopent-2-en-1-one (4)



4

To a solution of compound **3** (400 mg, 2.36 mmol) in methanol (10 mL) wad added triethylamine (1.34 mL, 9.46 mmol) at room temperature. The mixture was stirred at 65 °C for 3 h, concentrated *in vacuo* and the residue purified by flash column chromatography on silica gel eluting with ethyl acetate-methanol (10:1) to give the *title compound* **4** (279 mg, 2.19 mmol, 93%) as a colourless solid; m.p. 154.4-156.3 °C; HRMS [ESI, $(M + H)^+$] found 128.0707, $[C_6H_9NO_2 + H]^+$ requires 128.0706; ν_{max} (neat)/cm^{-1} 3298, 3134, 2981, 2968, 2860, 1674, 1644, 1623, 1534, 1416, 1371, 1332, 1313, 1236, 1198, 1089, 1066; δ_H (400 MHz, $(CD_3)_2SO$) 7.34 (1 H, br s, NHH), 6.74 (1 H, br s, NHH), 5.42 (1 H, d, *J* 6.3, OH), 4.68 (1 H, s, CH), 4.05 (1 H, dd, *J* 5.4, 3.3, CH), 2.04 (1 H, dq, *J* 7.3, 3.3, CH), 1.02 (3 H, d, *J* 7.4, Me); δ_C (100 MHz, $(CD_3)_2SO$) 200.0 (C), 176.2 (C), 96.8 (CH), 75.9 (CH), 48.7 (CH), 14.0 (Me).

(±)-*N*-(4-methyl-3,5-dioxocyclopent-1-en-1-yl)acetamide (5)

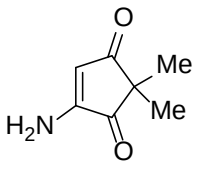


5

To a solution of compound **3** (400 mg, 2.36 mmol) in ethyl acetate (20 mL) was added 2-iodoxybenzoic acid (1.32 g, 4.73 mmol) at room temperature. The mixture was stirred at 60 °C

for 24 h, then filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (7:3) to give the *title compound* **5** (360 mg, 2.15 mmol, 91%) as a colourless solid; m.p. 158.0-159.8 °C; HRMS [ESI, $(M + Na)^+$] found 190.0473, $[C_8H_9NO_3 + Na]^+$ requires 190.0475; ν_{max} (neat)/cm^{-1} 3251, 3216, 3144, 2899, 1744, 1718, 1676, 1599, 1509, 1456, 1424, 1370, 1291, 1247, 1213, 1188, 1112, 1074, 1044, 1006; δ_H (400 MHz, $(CD_3)_2CO$) 9.48 (1 H, br s, NH), 7.22 (1 H, s, CH), 2.81 (1 H, q, *J* 7.5, CH), 2.29 (3 H, s, Me), 1.15 (3 H, d, *J* 7.8, Me); δ_C (100 MHz, $(CD_3)_2CO$) 202.4 (C), 201.4 (C), 171.0 (C), 151.8 (C), 124.1 (CH), 44.2 (CH), 24.0 (Me), 10.5 (Me).

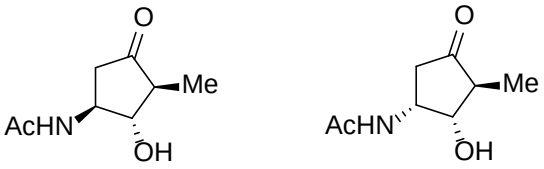
4-Amino-2,2-dimethylcyclopent-4-ene-1,3-dione (6)



6

To a solution of compound **5** (40 mg, 0.24 mmol) in ethyl acetate (1 mL) was added iodomethane (0.044 mL, 0.72 mmol) and sodium hydroxide (19 mg, 0.48 mmol). The resulting mixture was stirred at room temperature for 5 h, then methanol (0.2 mL) was added and the mixture was stirred at 40 °C for 3 h. Water (1 mL) was added and the mixture was extracted with ethyl acetate (3 x 15 mL), washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate to give the *title compound* **6** (22 mg, 0.16 mmol, 66%) as a colourless solid; m.p. 154.0-155.5 °C; HRMS [ESI, $(M + Na)^+$] found 162.0520, $[C_7H_9NO_2 + Na]^+$ requires 162.0525; ν_{max} (neat)/cm^{-1} 3042, 3316, 3281, 3242, 3204, 2979, 1747, 1685, 1617, 1563, 1465, 1406, 1378, 1309, 1257, 1232, 1207, 1133, 1086, 1032; δ_H (400 MHz, $(CD_3)_2CO$) 6.57 (2 H, br s, NH_2), 5.75 (1 H, s, CH), 1.05 (6 H, s, 2 × Me); δ_C (100 MHz, $(CD_3)_2CO$) 205.6 (C), 202.6 (C), 158.5 (C), 109.6 (CH), 46.4 (C), 20.7 (2 × Me).

***N*-((1*S**,2*S**,3*S**)-2-hydroxy-3-methyl-4-oxocyclopentyl)acetamide (7a)** and ***N*-((1*R**,2*S**,3*S**)-2-hydroxy-3-methyl-4-oxocyclopentyl)acetamide (7b)**

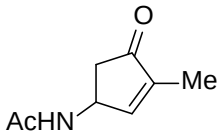


7a **7b**

10% Pd/C (4 mg) was added to a stirred solution of compound **3** (20 mg, 0.12 mmol) in ethyl acetate (2 mL) and the mixture was stirred under an atmosphere of hydrogen for 19 h at room temperature. The mixture was filtered through Celite, then concentrated *in vacuo*. The residue was purified by flash column chromatography eluting with ethyl acetate to give the *title compounds* **7a** and **7b** (10:1; inseparable) (8 mg, 0.05 mmol, 40%) as a colourless oil; HRMS [ESI, $(M + Na)^+$] found 194.0792, $[C_8H_{13}NO_3 + Na]^+$ requires 194.0788; ν_{max} (neat)/cm^{-1} 3269, 1739, 1635, 1554, 1455, 1408, 1375, 1304, 1173, 1078; δ_H (400 MHz, $(CD_3)_2CO$) (**7a**:**7b**, 10:1) 7.97 (1 H, br s, NH_{minor}), 7.53 (1H, br s, NH_{major}), 5.29 (1 H, d, *J* 3.0, OH_{major}), 4.58 (1 H, d, *J* 2.9, OH_{minor}), 4.29-4.22 (1 H, m, CH_{minor}), 4.18-4.10 (1 H, m, CH_{major}), 3.73 (1 H, ddd, *J* 10.5, 8.4, 2.6, CH_{major}), 2.77 (1 H, ddd, *J* 10.9, 9.0, 2.0, CH of CH_{2major}), 2.58 (1 H, dd, *J* 18.9, 7.8, CH_{minor}), 2.49-2.46 (1 H, m, CH of CH_{2minor}), 2.33 (1 H, ddd, *J* 8.8, 6.9, 1.8, CH_{major}), 2.28-2.20 (1 H, m, CH_{minor}), 2.14-2.08 (1 H, m, CH of CH_{2minor}), 2.11 (1 H, dd, *J* 18.8, 10.4, CH of CH_{2major}), 1.92 (3 H, s, Me_{major}), 1.87 (3 H, s, Me_{minor}), 1.06 (3 H, d, *J* 7.0, Me_{major}), 1.00 (3 H, d, *J* 7.3, Me_{minor}); δ_C (100 MHz, $(CD_3)_2CO$) 212.7 (C_{major}), 172.2 (C_{major}), 162.8 (C_{minor}), 81.5 (CH_{major}), 76.7 (CH_{minor}), 54.9 (CH_{major}), 53.2 (CH_{minor}), 52.7 (CH_{major}), 47.3 (CH_{minor}), 43.0 (CH_{2major}), 41.0 (CH_{2minor}), 22.9 (Me_{minor}), 22.8 (Me_{major}), 11.6 (Me_{major}), 8.0 (Me_{minor}), 1C_{minor} not observed.

[Major = **7a**; minor = **7b**]

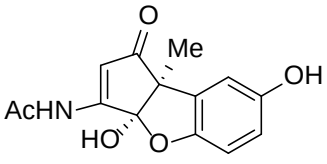
(±)-*N*-(3-methyl-4-oxocyclopent-2-en-1-yl)acetamide (8)



8

To a solution of compound **7** (9 mg, 0.05 mmol) in ethyl acetate (0.5 mL) was added *p*-toluenesulfonic acid (5 mg, 0.03 mmol) at room temperature. The mixture was stirred at 80 °C for 30 min, concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel eluting with ethyl acetate-methanol (10:1) to give the *title compound* **8** (7.5 mg, 0.05 mmol, 93%) as a colourless solid; m.p. 93.5-95.5 °C; HRMS [ESI, $(M + Na)^+$] found 176.0683, $[C_8H_{11}NO_2 + Na]^+$ requires 176.0682; ν_{max} (neat)/cm^{-1} 3277, 3072, 2926, 1708, 1635, 1539, 1432, 1401, 1373, 1320, 1283, 1197, 1100, 1076; δ_H (400 MHz, $CDCl_3$) 7.13-7.11 (1 H, m, CH), 6.26 (1 H, d, *J* 7.0, NH), 5.08-5.03 (1 H, m, CH), 2.83 (1 H, dd, *J* 18.8, 6.8, CH of CH_2), 2.13 (1 H, dd, *J* 18.8, 2.4, CH of CH_2), 1.95 (3 H, s, Me), 1.75 (3 H, t, *J* 1.8, Me); δ_C (100 MHz, $CDCl_3$) 206.7 (C), 170.0 (C), 155.5 (CH), 143.6 (C), 47.6 (CH), 42.1 (CH_2), 23.0 (Me), 9.9 (Me).

(±)-*cis*-*N*-(3a,7-dihydroxy-8b-methyl-1-oxo-3a,8b-dihydro-1*H*-cyclopenta[*b*]benzofuran-3-yl)acetamide (9)

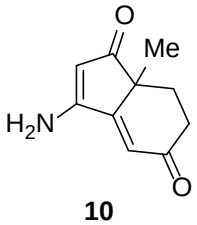


9

To a solution of compound **5** (20 mg, 0.12 mmol) in ethanol (0.6 mL) was added *p*-benzoquinone (26 mg, 0.24 mmol) at room temperature. The mixture was stirred at 60 ºC for 20 min, then concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (1:1) to give the *title compound* **9** (13 mg, 0.10

mmol, 79%) as an orange solid; m.p. >200 ºC (decomp.); HRMS [ESI, $(M + Na)^+$] found 298.0677, $[C_{14}H_{13}NO_5 + Na]^+$ requires 298.0686; ν_{max} (neat)/cm^{-1} 3189, 3102, 1680, 1616, 1521, 1492, 1465, 1443, 1373, 1250, 1231, 1208, 1133, 1110, 1101, 1033; δ_H (400 MHz, $(CD_3)_2SO$) 10.76 (1 H, s, NH), 8.99 (1 H, s, OH), 7.97 (1 H, s, OH), 6.65 (1 H, d, *J* 2.4, ArH), 6.62 (1 H, d, *J* 8.6, ArH), 6.57 (1 H, dd, *J* 8.6, 2.4, ArH), 6.38 (1 H, s, CH), 2.20 (3 H, s, Me), 1.28 (3 H, s, Me); δ_C (100 MHz, $(CD_3)_2SO$) 202.4 (C), 171.2 (C), 160.9 (C), 152.0 (C), 148.1 (C), 128.9 (C), 115.4 (CH), 113.4 (C), 110.5 (CH), 110.3 (CH), 109.7 (CH), 56.3 (C), 23.8 (Me), 16.0 (Me).

(±)-3-Amino-7a-methyl-7,7a-dihydro-1*H*-indene-1,5(6*H*)-dione (10)

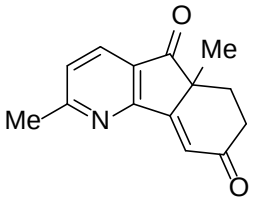


10

To a solution of compound **5** (20 mg, 0.12 mmol) and methyl vinyl ketone (0.01 mL, 0.12 mmol) in ethyl acetate (1 mL) was added sodium hydroxide (10 mg, 0.24 mmol). The mixture was stirred at room temperature for 15 min, then filtered and concentrated *in vacuo*. The residue was dissolved in methanol (0.5 mL), then sodium hydroxide (10 mg, 0.24 mmol) was added, and the mixture was stirred at room temperature for 6 h. Water was added and the mixture was extracted with ethyl acetate (3 x 20 mL), washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate to give the *title compound* **10** (19 mg, 0.11 mmol, 89%) as an orange solid; m.p. 180 °C (decomp.); HRMS [ESI, $(M + Na)^+$] found 200.0681, $[C_{10}H_{11}NO_2 + Na]^+$ requires 200.0682; ν_{max} (neat)/cm^{-1} 3391, 3211, 3037, 2930, 2871, 1719, 1642, 1616, 1548, 1467, 1448, 1412, 1377, 1347, 1308, 1261, 1220, 1198, 1102, 1078; δ_H (400 MHz, $(CD_3)_2CO$) 6.78 (2 H, br s, NH_2), 6.13 (1 H, s, CH), 5.15 (1 H, s, CH), 2.63 (1 H, ddd, *J* 18.9, 13.8, 5.6, CH of CH_2),

2.40 (1 H, ddt, *J* 18.4, 5.5, 1.2, CH of CH_2), 2.02 (1 H, ddd, *J* 13.0, 5.5, 1.6, CH of CH_2), 1.76 (1 H, dt, *J* 13.3, 5.4, CH of CH_2), 1.31 (3 H, s, Me); δ_C (100 MHz, $(CD_3)_2CO$) 202.3 (C), 198.6 (C), 165.4 (C), 162.4 (C), 117.5 (CH), 103.6 (CH), 46.0 (C), 34.7 (CH_2), 29.4 (CH_2), 22.9 (Me).

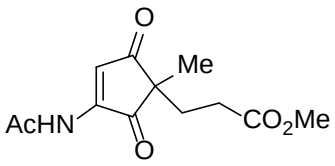
(±)-2,5a-Dimethyl-6,7-dihydro-5*H*-indeno[1,2-*b*]pyridine-5,8(5a*H*)-dione (11)



11

A mixture of compound **10** (15 mg, 0.09 mmol), methyl vinyl ketone (0.01 mL, 0.09 mmmol), potassium carbonate (47 mg, 0.34 mmol), copper bromide (5 mg, 0.04 mg) in acetonitrile (1.5 mL) was heated at 120 °C for 24 h. The mixture was filtered, concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (7:3) to give the *title compound* **11** (7 mg, 0.03 mmol, 36%) as a yellow solid; m.p. 103.1 – 106.3 °C; HRMS [ESI, $(M + Na)^+$] found 250.0841, $[C_{14}H_{13}NO_2 + Na]^+$ requires 250.0838; ν_{max} (neat)/cm^{-1} 2962, 2931, 1728, 1659, 1638, 1575, 1448, 1415, 1396, 1311, 1202, 1135, 1101; δ_H (400 MHz, $(CD_3)_2CO$) 8.06 (1 H, d, *J* 8.0, ArH), 7.59 (1 H, d, *J* 8.0, ArH), 6.46 (1 H, s, CH), 2.85-2.75 (1 H, m, CH of CH_2), 2.70 (3 H, s, Me), 2.54-2.48 (1 H, m, CH of CH_2), 2.26 (1 H, ddd, *J* 13.2, 5.6, 1.8, CH of CH_2), 2.11-2.03 (1 H, m, CH of CH_2), 1.45 (3 H, s, Me); δ_C (100 MHz, $(CD_3)_2CO$) 202.8 (C), 198.2 (C), 168.6 (C), 163.4 (C), 161.9 (C), 133.3 (CH), 128.8 (C), 127.7 (CH), 119.6 (CH), 49.0 (C), 34.5 (CH_2), 28.7 (CH_2), 25.5 (Me), 22.5 (Me).

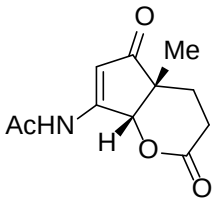
(±)-Methyl 3-(3-acetamido-1-methyl-2,5-dioxocyclopent-3-en-1-yl)propanoate (12)



12

A mixture of compound **5** (20 mg, 0.12 mmol) and methyl acrylate (0.06 mL, 0.60 mmol) in triethylamine (0.3 mL) was stirred at 80 °C for 1 hour. After completion, the mixture was purified by flash chromatography on silica gel eluting with ethyl acetate to give the *title compound* **12** (25 mg, 0.10 mmol, 82%) as a light yellow oil; HRMS [ESI, $(M + Na)^+$] found 276.0834, $[C_{12}H_{15}NO_5 + Na]^+$ requires 276.0842; ν_{max} (neat)/cm^{-1} 3400, 1726, 1684, 1607, 1516, 1454, 1439, 1372, 1295, 1213, 1147, 1101; δ_H (400 MHz, $CDCl_3$) 8.04 (1 H, br s, NH), 7.33 (1 H, s, CH), 3.62 (3 H, s, Me), 2.31-2.14 (5 H, m, CH_2 and Me), 1.99 (2 H, t, *J* 8.0, CH_2), 1.19 (3 H, s, Me); δ_C (100 MHz, $CDCl_3$) 204.2 (C), 203.2 (C), 172.7 (C), 168.9 (C), 148.6 (C), 123.4 (CH), 51.7 (Me), 47.8 (C), 29.09 (CH_2), 29.05 (CH_2), 24.1 (Me), 18.9 (Me).

(±)-*cis*-*N*-(4a-Methyl-2,5-dioxo-2,3,4,4a,5,7a-hexahydrocyclopenta[b]pyran-7-yl)acetamide (13)

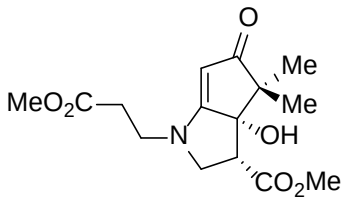


13

A mixture of compound **12** (20 mg, 0.08 mmol) and zinc (10 mg, 0.16 mmol) in acetic acid (0.4 mL) was stirred at 80 °C for 24 h. After completion, the mixture was poured into saturated aqueous sodium bicarbonate solution and extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate

to give the *title compound* **13** (9 mg, 0.04 mmol, 51%) as a colourless solid; m.p. 203.0-205.4 °C; HRMS [ESI, $(M + Na)^+$] found 246.0745, $[C_{11}H_{13}NO_4 + Na]^+$ requires 246.0737; ν_{max} (neat)/cm^{-1} 3290, 3224, 2928, 1745, 1689, 1616, 1521, 1465, 1432, 1366, 1328, 1312, 1272, 1240, 1221, 1158, 1120; δ_H (400 MHz, $CDCl_3$) 8.13 (1 H, br s, NH), 6.79 (1 H, s, CH), 5.00 (1 H, d, *J* 0.8, CH), 2.52-2.45 (1 H, m, CH of CH_2), 2.24 (3 H, s, Me), 2.23-2.12 (2 H, m, CH_2), 1.77 (1 H, m, CH of CH_2), 1.31 (3 H, s, Me); δ_C (100 MHz, $CDCl_3$) 205.7 (C), 170.7 (C), 169.2 (C), 159.2 (C), 115.2 (CH), 84.6 (CH), 43.4 (C), 28.4 (CH_2), 27.9 (CH_2), 24.3 (Me), 22.5 (Me).

(±)-Methyl-*cis*-3a-hydroxy-1-(3-methoxy-3-oxopropyl)-4,4-dimethyl-5-oxo-1,2,3,3a,4,5-hexahydrocyclopenta[*b*]pyrrole-3-carboxylate (14)

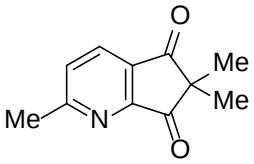


14

A mixture of compound **6** (20 mg, 0.14 mmol), cesium carbonate (187 mg, 0.58 mg), and methyl acrylate (0.4 mL) was stirred at 50 °C for 1 hour. After completion, the mixture was diluted with ethyl acetate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate-methanol (10:1) to give the *title compound* **14** (13 mg, 0.04 mmol, 29%) as a colourless solid; m.p. 127.1-129.4 °C; HRMS [ESI, $(M + Na)^+$] found 334.1264, $[C_{15}H_{21}NO_6 + Na]^+$ requires 334.1261; ν_{max} (neat)/cm^{-1} 3189, 2956, 1744, 1728, 1679, 1589, 1459, 1438, 1415, 1390, 1374, 1331, 1289, 1198, 1179, 1138; δ_H (400 MHz, $CDCl_3$) 4.65 (1 H, s, CH), 4.24 (1 H, t, *J* 9.8, CH of CH_2), 3.77 (3 H, s, Me), 3.70 (1 H, dd, *J* 10.3, 8.0, CH of CH_2), 3.68 (3 H, s, Me), 3.60 (2 H, dt, *J* 6.6, 3.5, CH_2), 3.29 (1 H, dd, *J* 9.4, 8.0, CH), 2.64 (2 H, t, *J* 6.5, CH_2), 1.20 (3 H, s, Me), 1.14 (3 H, s, Me), OH not observed; δ_C (100 MHz, $CDCl_3$) 209.2 (C), 177.0 (C), 171.4 (C), 169.7 (C), 88.9 (CH), 87.8

(C), 55.3 (CH_2), 52.19 (Me), 52.16 (Me), 51.0 (C), 46.3 (CH), 43.5 (CH_2), 31.9 (CH_2), 24.9 (Me), 16.7 (Me).

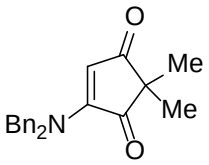
2,6,6-Trimethyl-5*H*-cyclopenta[*b*]pyridine-5,7(6*H*)-dione (15)



15

A mixture of compound **6** (20 mg, 0.14 mmol), methyl vinyl ketone (0.03 mL, 0.29 mmol), potassium carbonate (100 mg, 0.72 mmol), copper bromide (9 mg, 0.06 mg) in acetonitrile (2 mL) was heated at 80 °C for 24 h. The mixture was filtered, concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (1:1) to give the *title compound* **15** (9 mg, 0.05 mmol, 33%) as a yellow solid; m.p. 112.9-114.8 °C; HRMS [ESI, $(M + Na)^+$] found 212.0686, $[C_{11}H_{11}NO_2 + Na]^+$ requires 212.0682; ν_{max} (neat)/cm^{-1} 2969, 2932, 1753, 1710, 1586, 1568, 1465, 1457, 1381, 1293, 1258, 1155, 1098, 1052, 1003; δ_H (400 MHz, $CDCl_3$) 8.18 (1 H, d, *J* 8.1, CH), 7.59 (1 H, d, *J* 8.0, CH), 2.82 (3 H, s, Me), 1.34 (6 H, s, 2 × Me); δ_C (100 MHz, $CDCl_3$) 203.7 (C), 202.2 (C), 169.2 (C), 157.3 (C), 133.8 (C), 131.9 (CH), 129.3 (CH), 50.3 (C), 25.5 (Me), 20.2 (2 × Me).

4-(Dibenzylamino)-2,2-dimethylcyclopent-4-ene-1,3-dione (16)

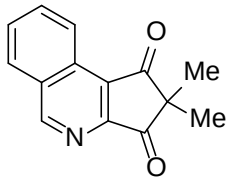


16

A mixture of compound **6** (20 mg, 0.14 mmol), benzyl bromide (0.04 mL, 0.30 mmol), cesium carbonate (94 mg, 0.29 mg) in acetonitrile (1 mL) was heated at 80 °C for 5 hours. The mixture

was diluted with ethyl acetate, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (3:7) to give the *title compound* **16** (32 mg, 0.10 mmol, 70%) as a yellow oil; HRMS [ESI, $(M + Na)^+$] found 342.1464, $[C_{21}H_{21}NO_2 + Na]^+$ requires 342.1465; ν_{max} (neat)/cm^{-1} 2966, 2928, 2866, 1730, 1676, 1591, 1578, 1495, 1451, 1419, 1369, 1301, 1264, 1240, 1147; δ_H (400 MHz, $CDCl_3$) 7.38-7.29 (6 H, m, 6 × ArH), 7.16 (4 H, d, *J* 6.9, 4 × ArH), 5.81 (1 H, s, CH), 4.73 (4 H, br s, 2 × CH_2), 1.21 (6 H, s, 2 x Me); δ_C (100 MHz, $CDCl_3$) 204.9 (C), 201.3 (C), 157.6 (C), 129.0 (6 × CH), 128.0 (4 × CH), 127.3 (2 × C), 111.9 (CH), 48.4 (C), 20.6 (2 × Me), 2 × CH_2 not observed.

2,2-Dimethyl-1*H*-cyclopenta[*c*]isoquinoline-1,3(2*H*)-dione (17)

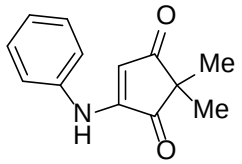


17

A mixture of compound **16** (20 mg, 0.06 mmol), palladium (II) acetate (14 mg, 0.06 mg) in acetic acid (0.5 mL) was heated to 120 °C for 5 h. The mixture was concentrated *in vacuo* and diluted with ethyl acetate, filtered and the filtrate was washed with saturated aqueous sodium bicarbonate solution, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (3:7) to give the *title compound* **17** (11 mg, 0.05 mmol, 78%) as a colourless solid; m.p. 157.7 – 161.1 °C; HRMS [ESI, $(M + Na)^+$] found 248.0682, $[C_{14}H_{11}NO_2 + Na]^+$ requires 248.0682; ν_{max} (neat)/cm^{-1} 2923, 2853, 1747, 1700, 1576, 1562, 1505, 1456, 1442, 1382, 1375, 1305, 1248, 1161, 1091, 1044; δ_H (400 MHz, $CDCl_3$) 9.65 (1 H, s, ArH), 9.10 (1 H, dd, *J* 8.6, 0.7, ArH), 8.22 (1 H, d, *J* 7.3, ArH), 8.06 (1 H, ddd, *J* 8.4, 7.0, 1.4, ArH), 7.94 (1 H, ddd, *J* 8.4, 7.0,

1.2, ArH), 1.41 (6 H, s, 2 × Me); δ_C (100 MHz, $CDCl_3$) 204.5 (C), 203.3 (C), 161.6 (CH), 153.5 (C), 134.4 (CH), 131.2 (CH), 130.9 (C), 130.4 (C), 128.9 (CH), 126.0 (CH), 50.0 (C), 20.3 (2 × Me), 1 C not observed.

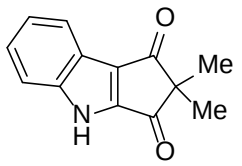
2,2-Dimethyl-4-(phenylamino)cyclopent-4-ene-1,3-dione (18)



18

A mixture of compound **6** (20 mg, 0.14 mmol), phenylboronic acid (35 mg, 0.29 mmmol), copper (II) acetate (26 mg, 0.14 mmol) in acetonitrile (1.5 mL) was heated at 80 °C for 3 h. After completion, the mixture was filtered, concentrated *in vacuo*, and the residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (3:7) to give the *title compound* **18** (15 mg, 0.07 mmol, 48%) as an orange oil; HRMS [ESI, $(M + Na)^+$] found 238.0838, $[C_{13}H_{13}NO_2 + Na]^+$ requires 238.0838; ν_{max} (neat)/cm^{-1} 3244, 2970, 2927, 2854, 1745, 1674, 1593, 1520, 1493, 1446, 1378, 1306, 1199, 1144; δ_H (400 MHz, $(CD_3)_2CO$) 8.45 (1 H, br s, NH), 7.48-7.41 (4 H, m, 4 × ArH), 7.20-7.16 (1 H, m, ArH), 6.32 (1 H, s, CH), 1.13 (6 H, s, 2 × Me); δ_C (100 MHz, $(CD_3)_2CO$) 205.29 (C), 203.24 (C), 153.0 (C), 140.2 (C), 130.3 (2 × CH), 125.3 (CH), 121.1. (2 × CH), 109.6 (CH), 46.0 (C), 20.6 (2 × Me).

2,2-Dimethylcyclopenta[*b*]indole-1,3(2*H*,4*H*)-dione (19)



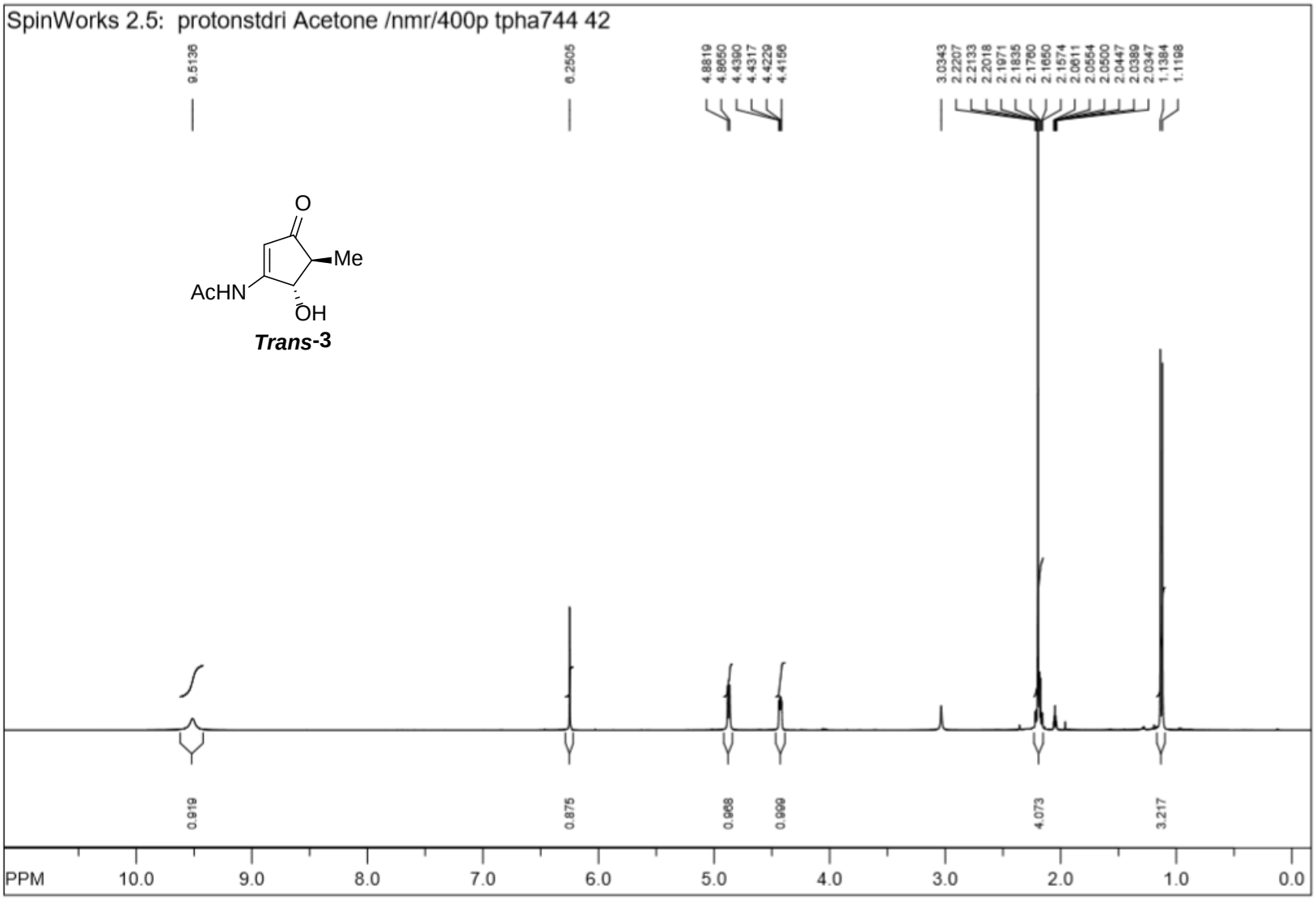
19

A mixture of compound **18** (10 mg, 0.05 mmol) and palladium (II) acetate (10 mg, 0.05 mg) in acetic acid (0.5 mL) was stirred at 110 °C for 7 h. The mixture was concentrated *in vacuo*, diluted with ethyl acetate, and filtered. The filtrate was washed with saturated aqueous sodium carbonate solution, brine, dried (Na_2SO_4), filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with ethyl acetate-light petroleum (1:5) to give the *title compound* **19** (8.7 mg, 0.04 mmol, 86%) as a colourless solid; m.p. 251.3-253.5 °C (decomp.); HRMS [ESI, $(M + H)^+$] found 214.0869, $[C_{13}H_{11}NO_2 + H]^+$ requires 214.0863; ν_{max} (neat)/cm^{-1} 3251, 2988, 2971, 2933, 1722, 1665, 1620, 1578, 1507, 1481, 1455, 1440, 1406, 1372, 1354, 1160, 1142, 1059; δ_H (400 MHz, $(CD_3)_2CO$) 11.75 (1 H, br s, NH), 7.97 (1 H, dt, *J* 8.1, 1.2, ArH), 7.72 (1 H, dt, *J* 8.5, 1.0, ArH), 7.56-7.51 (1 H, m, ArH), 7.43-7.39 (1 H, m, ArH), 1.28 (6 H, s, 2 × Me); δ_C (100 MHz, $(CD_3)_2CO$) 196.1 (C), 195.2 (C), 148.9 (C), 145.4 (C), 128.7 (CH), 126.1 (C), 124.4 (CH), 123.4 (CH), 121.3 (C), 115.2 (CH), 56.2 (C), 20.9 (2 × Me).

(1) G. Sheldrick, *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, 2015**, 71**, 3-8.

(2) O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. Puschmann, *J. Appl. Crystallogr.*, 2009**, 42**, 339-341.

(3) C. F. Macrae, P. R. Edgington, P. McCabe, E. Pidcock, G. P. Shields, R. Taylor, M. Towler and J. van de Streek, *J. Appl. Crystallogr.*, 2006**, 39**, 453-457.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4.4156
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2.2207
2.2133
2.2018
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2.1835
2.1760
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2.0611
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2.0447
2.0389
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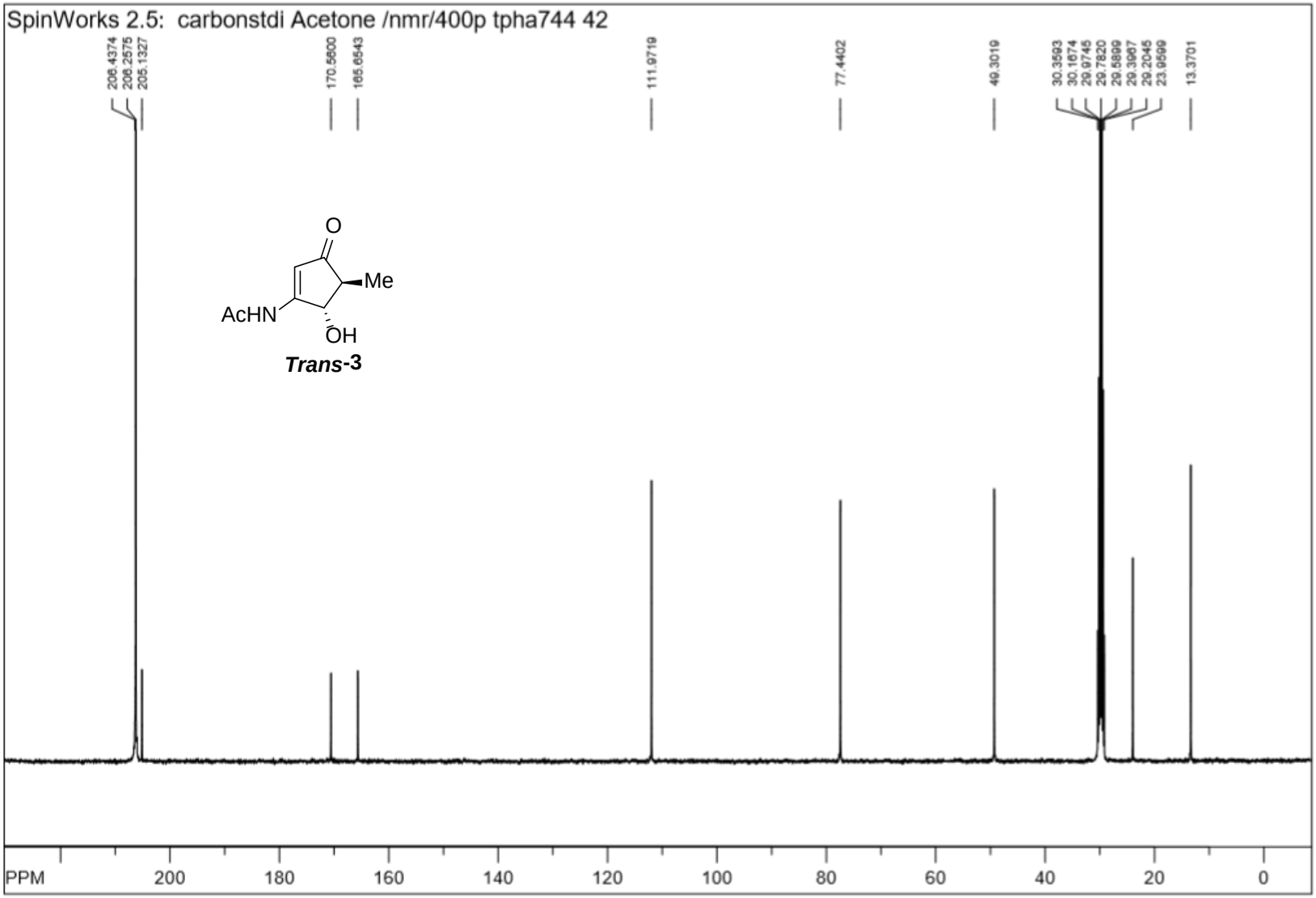
0.0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29.9745
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80
60
40
20
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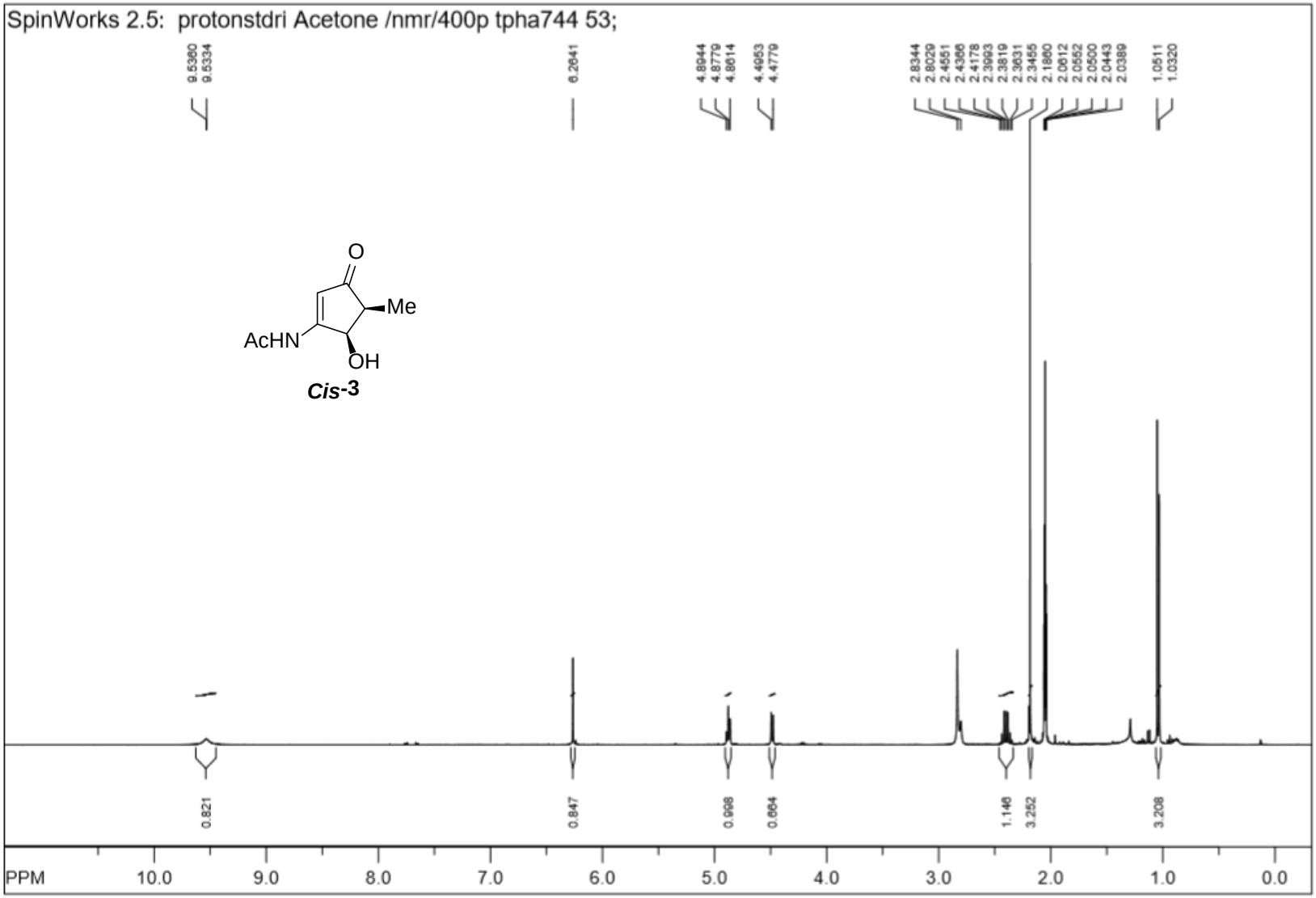
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1.0
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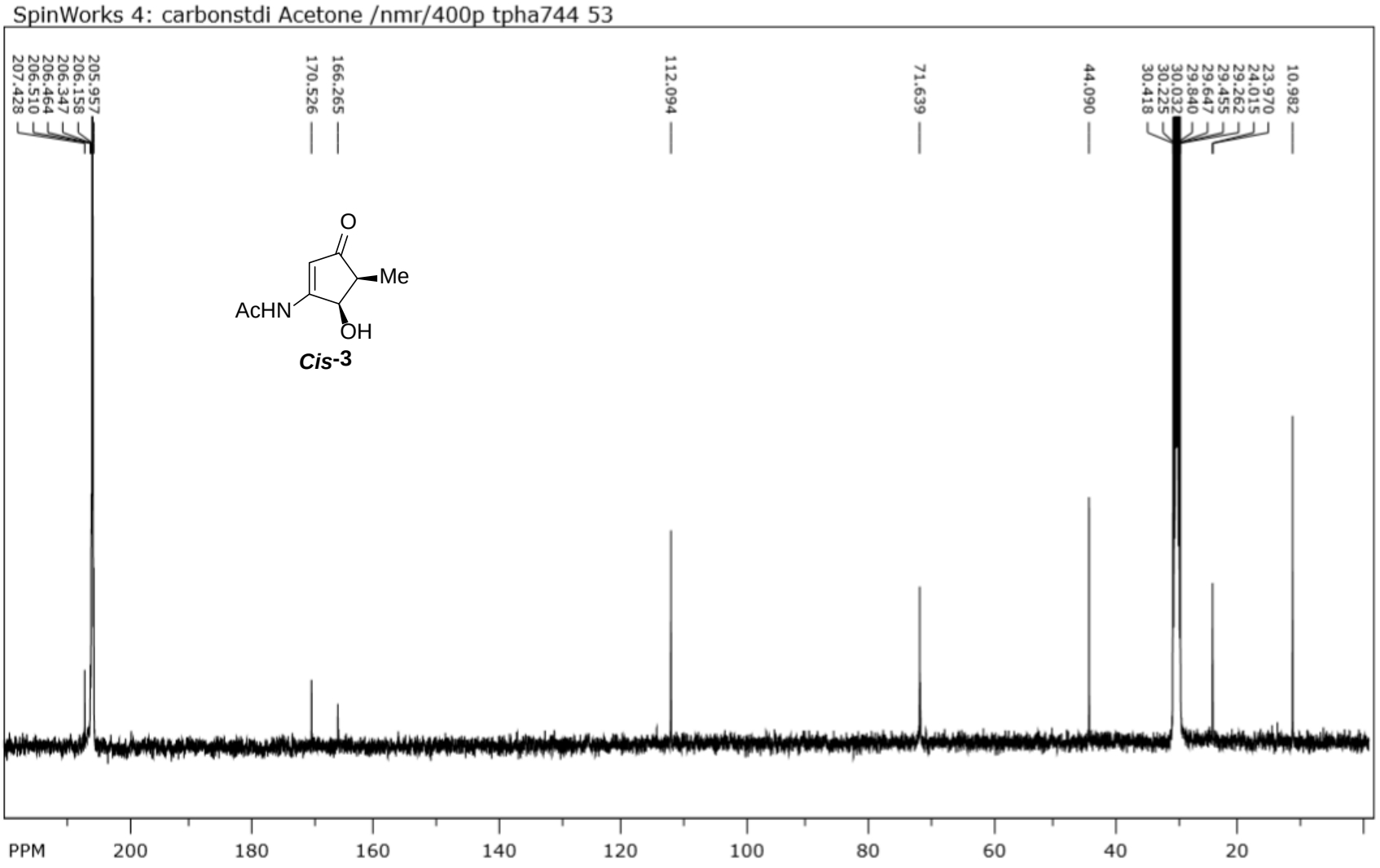
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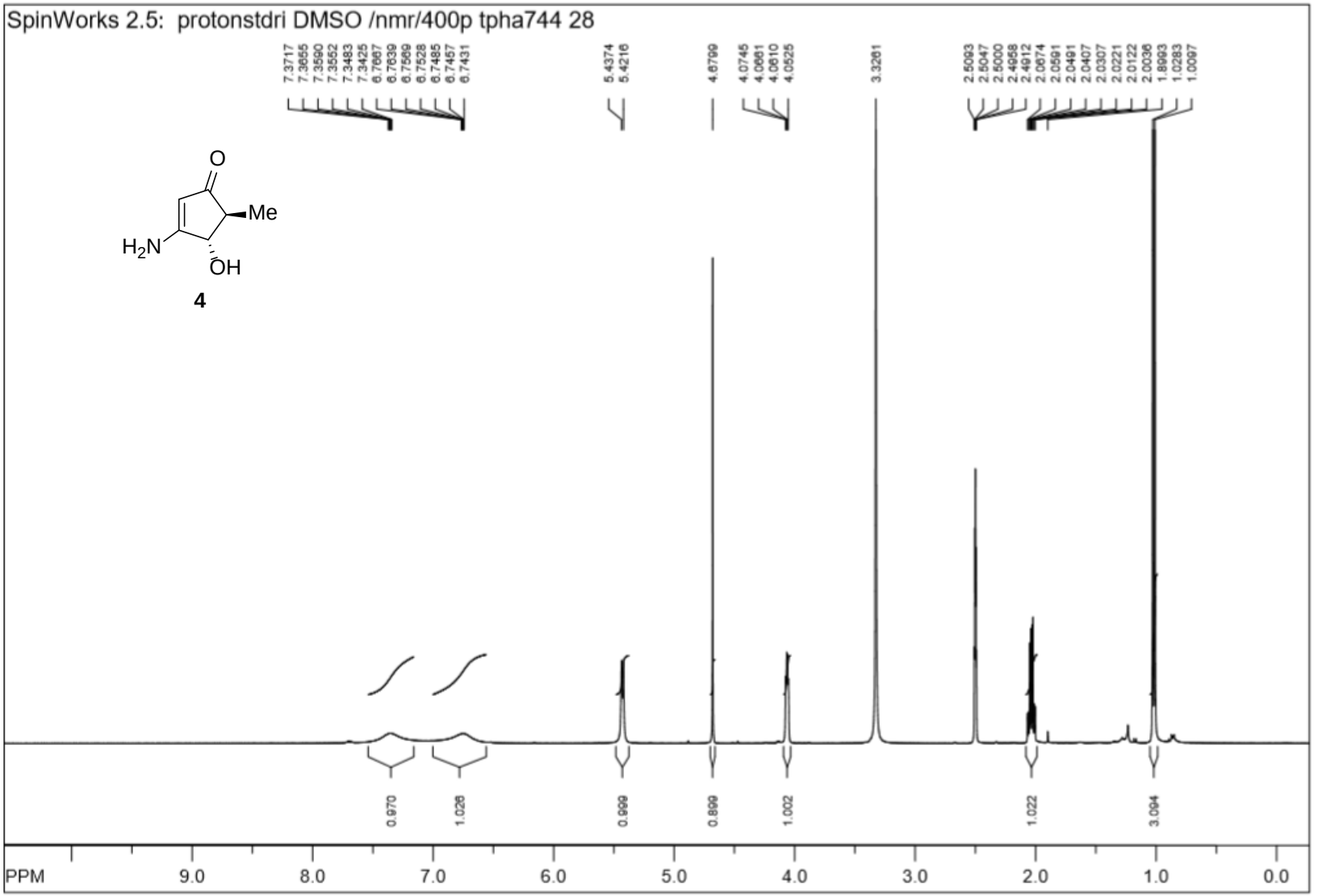
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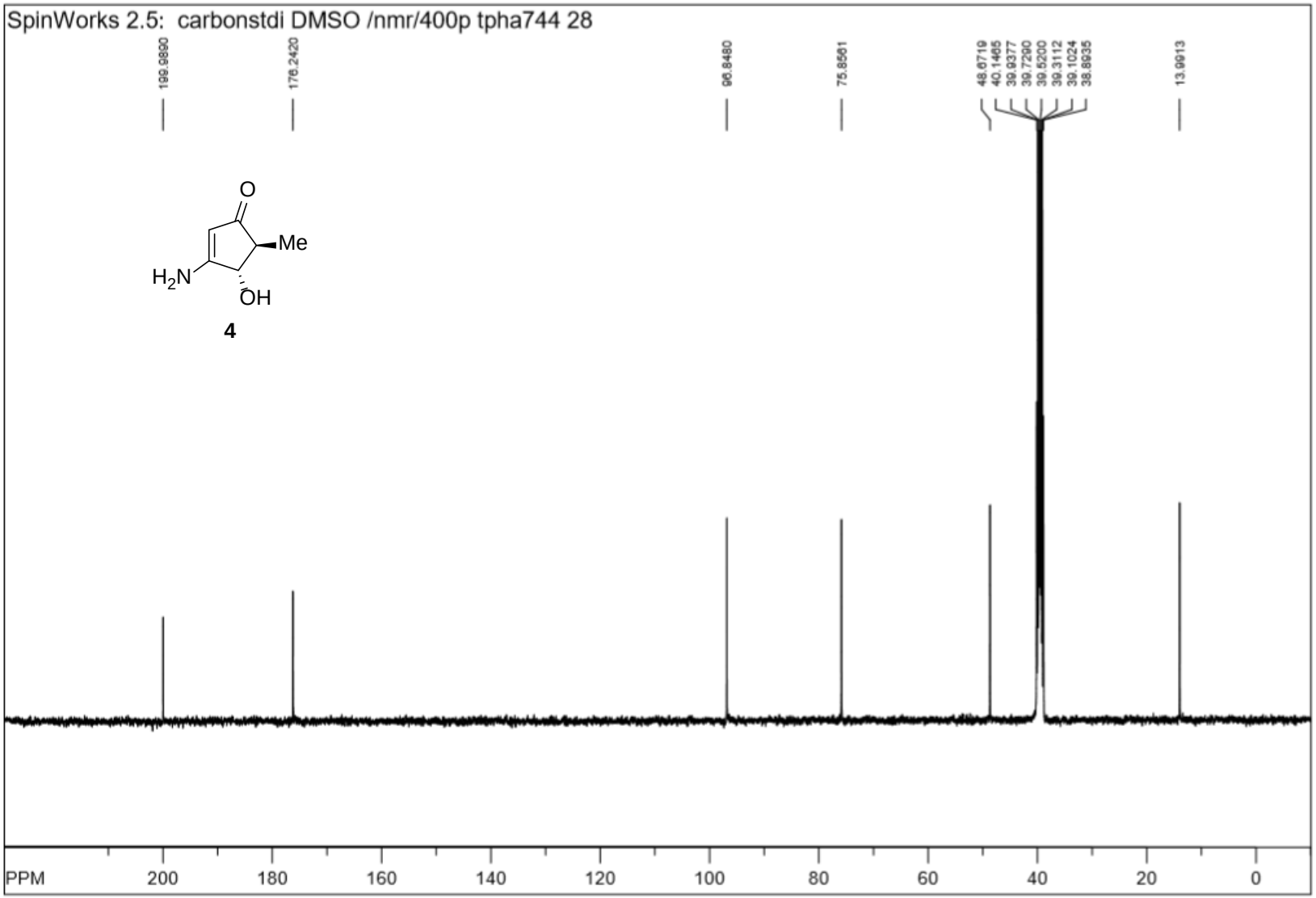
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38.8935
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140
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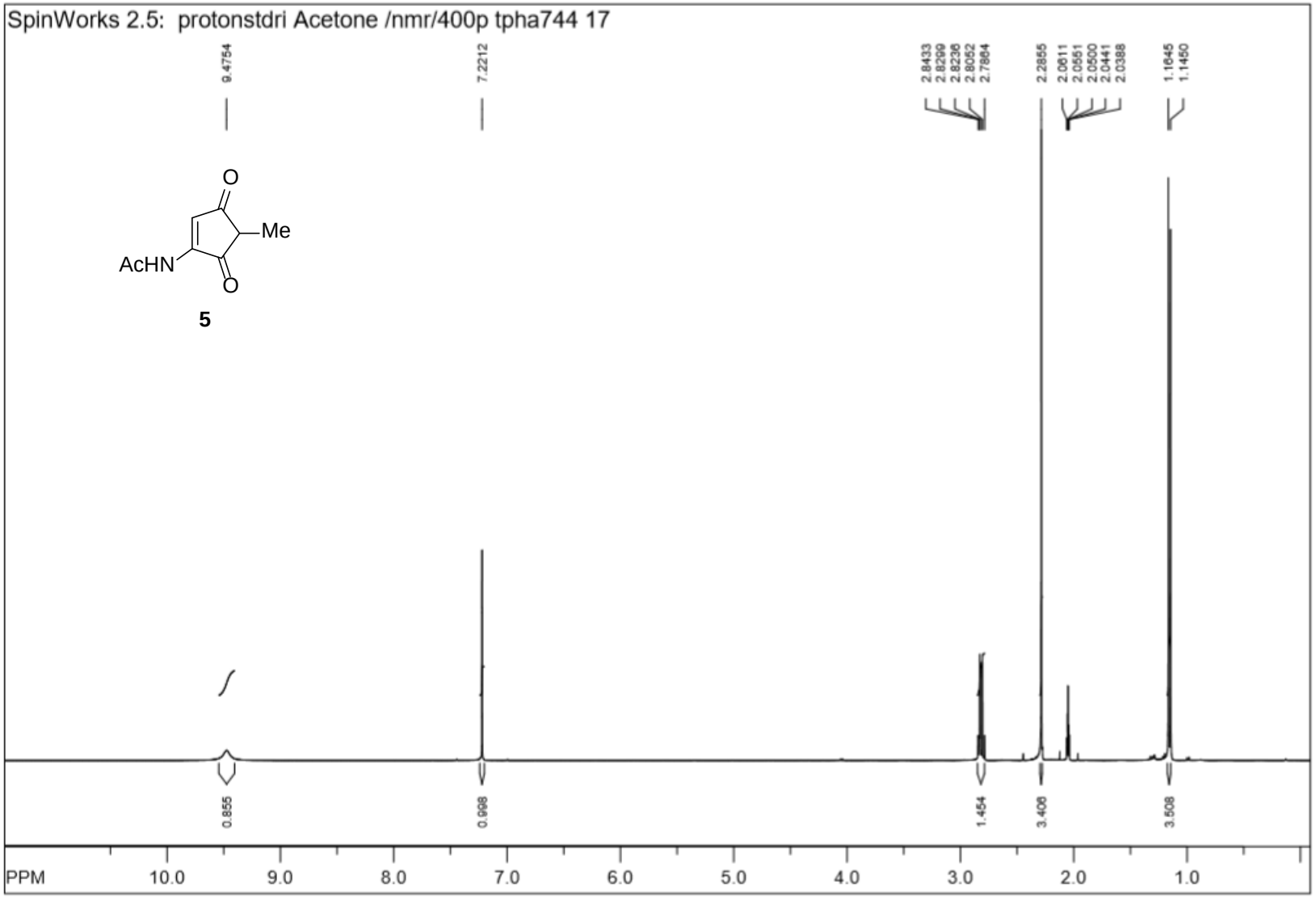
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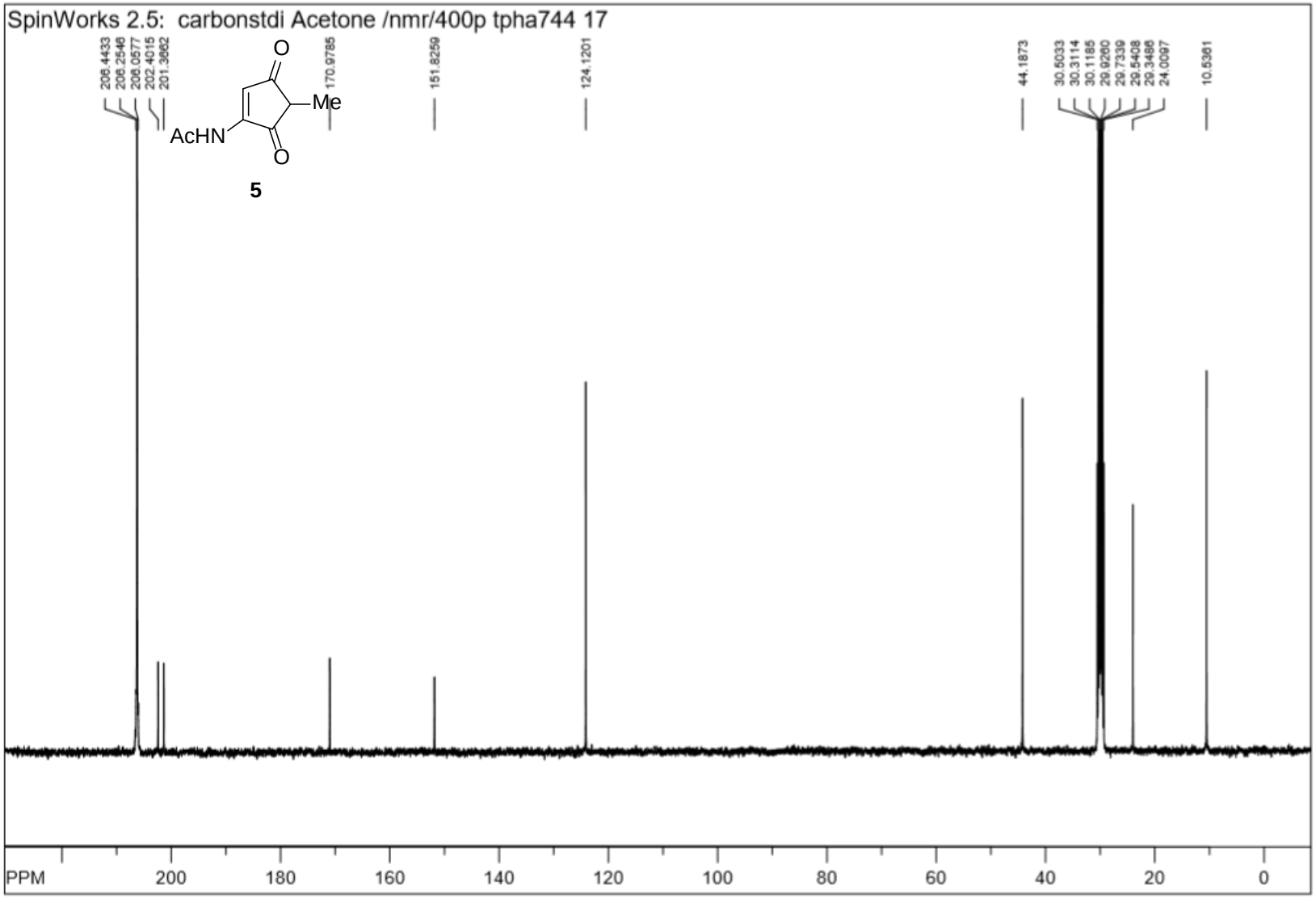
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20
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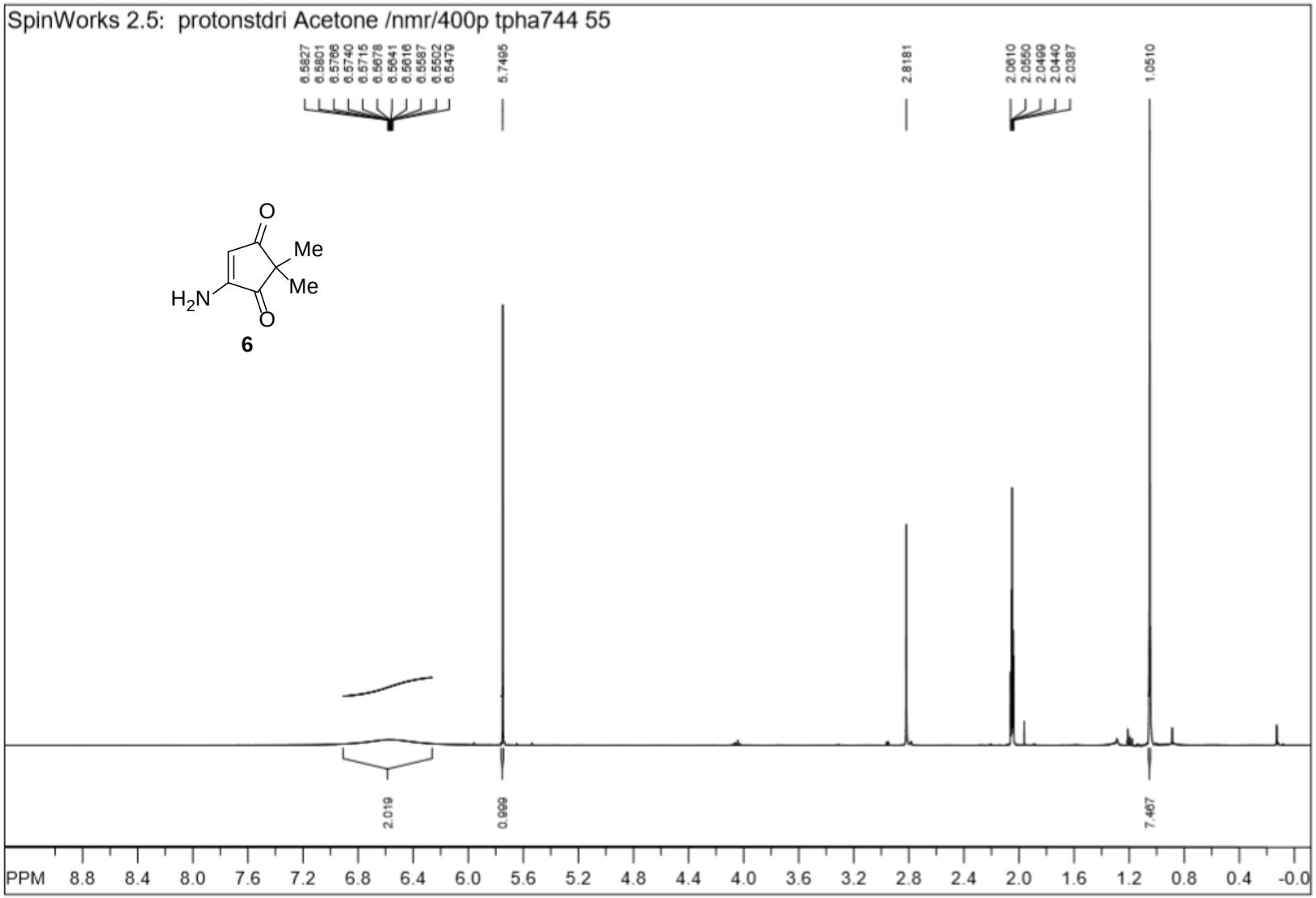
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2.0610
2.0550
2.0499
2.0440
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Me
Me
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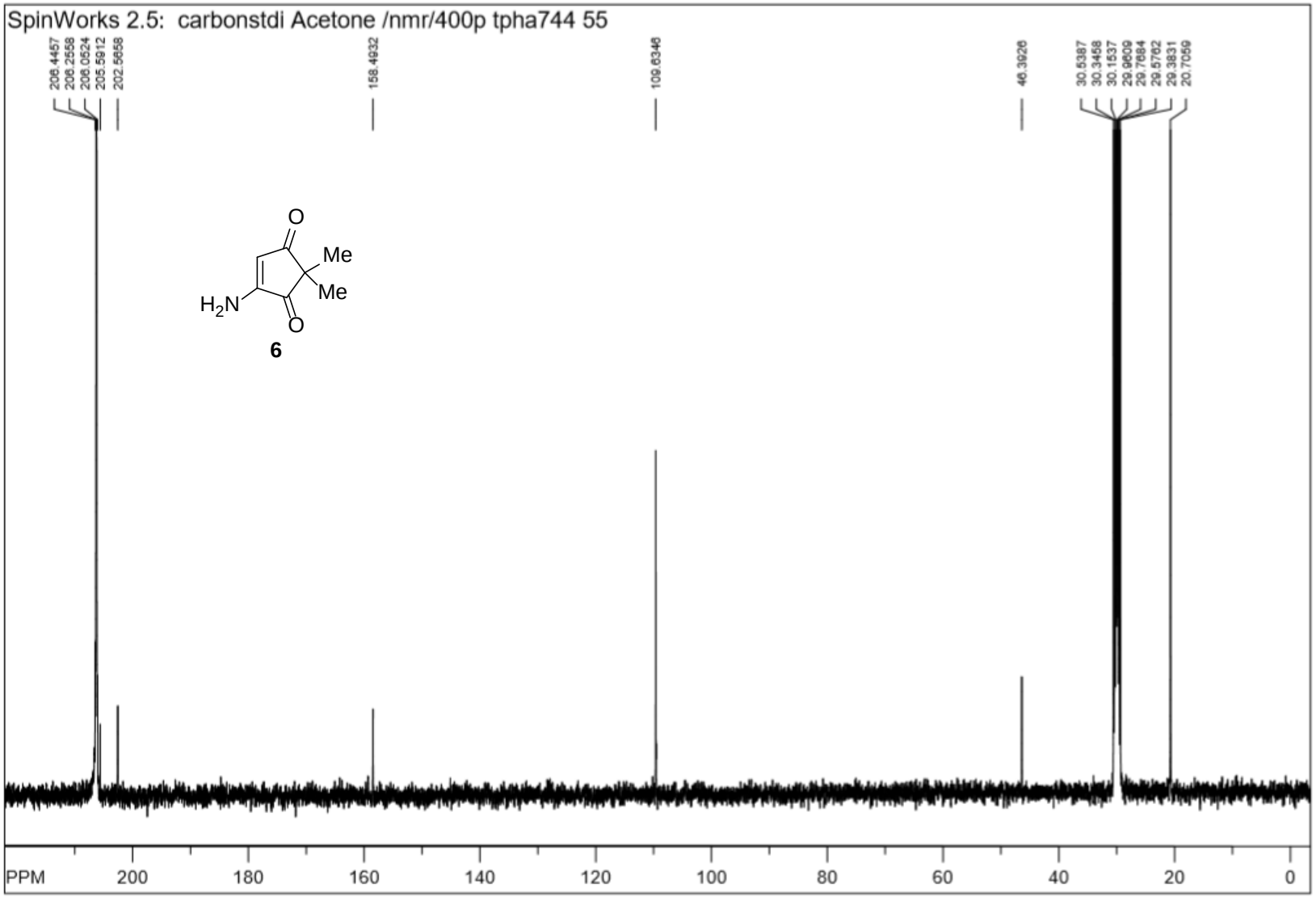
PPM 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 -0.0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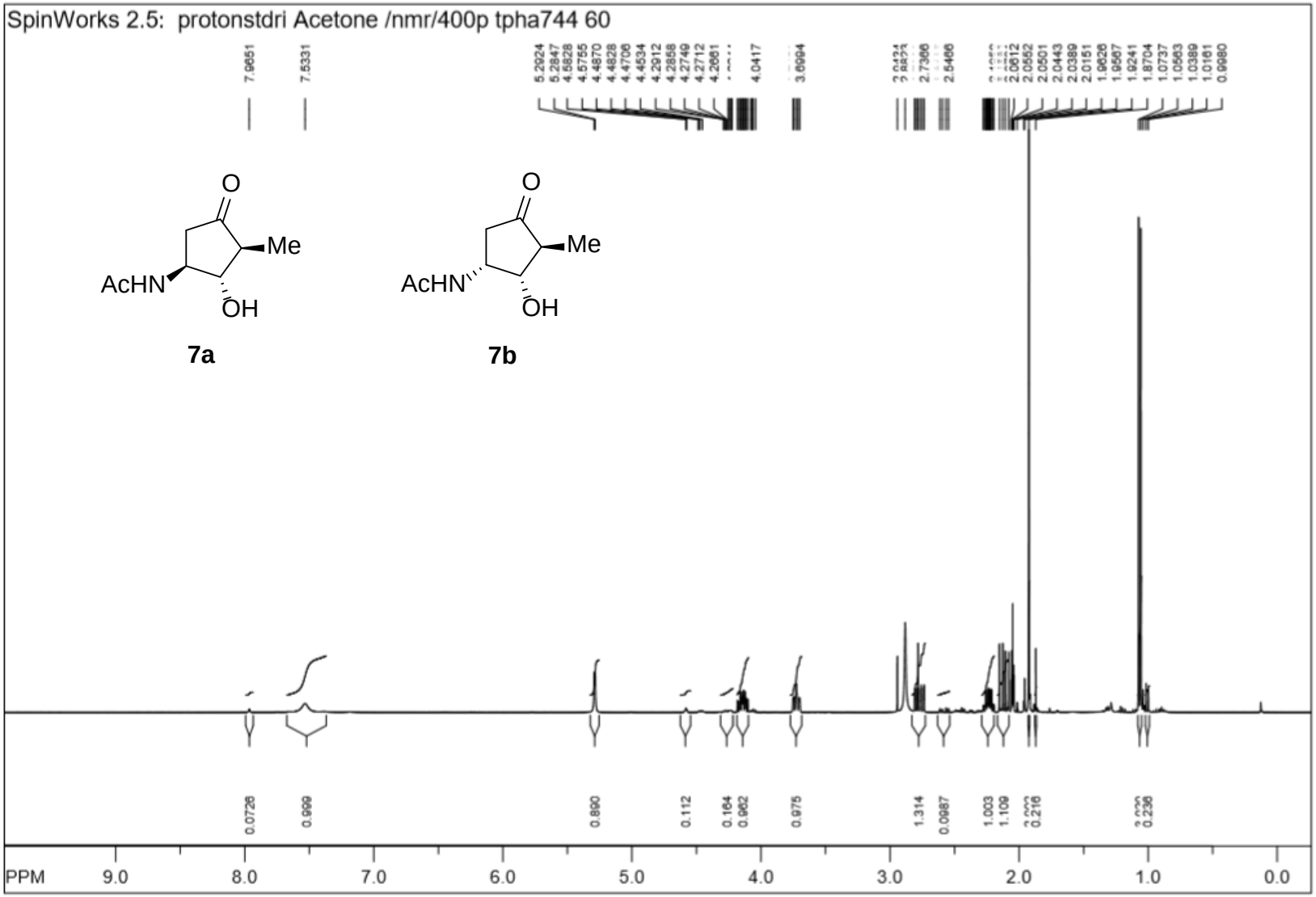
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4.4534
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4.2858
4.2749
4.2712
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4.0417
3.8994
2.7366
2.5466
2.0612
2.0552
2.0501
2.0443
2.0389
2.0151
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1.0737
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1.0389
1.0161
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Me
AcHN
OH
7a
O
Me
AcHN
OH
7b
0.0726
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0.164
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0.0987
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1.109
0.216
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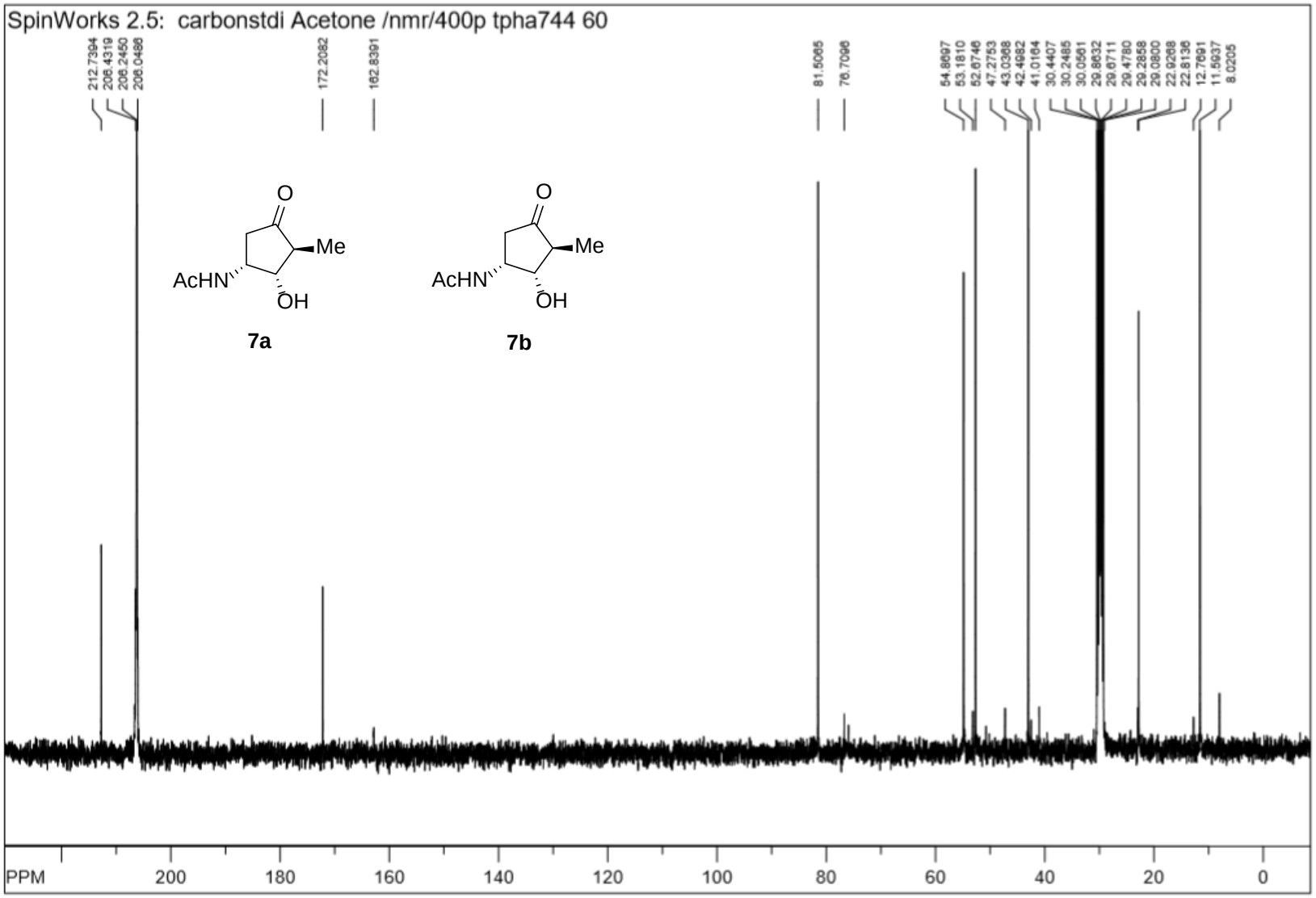
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52.6746
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29.0800
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22.8136
12.7691
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O
Me
AcHN
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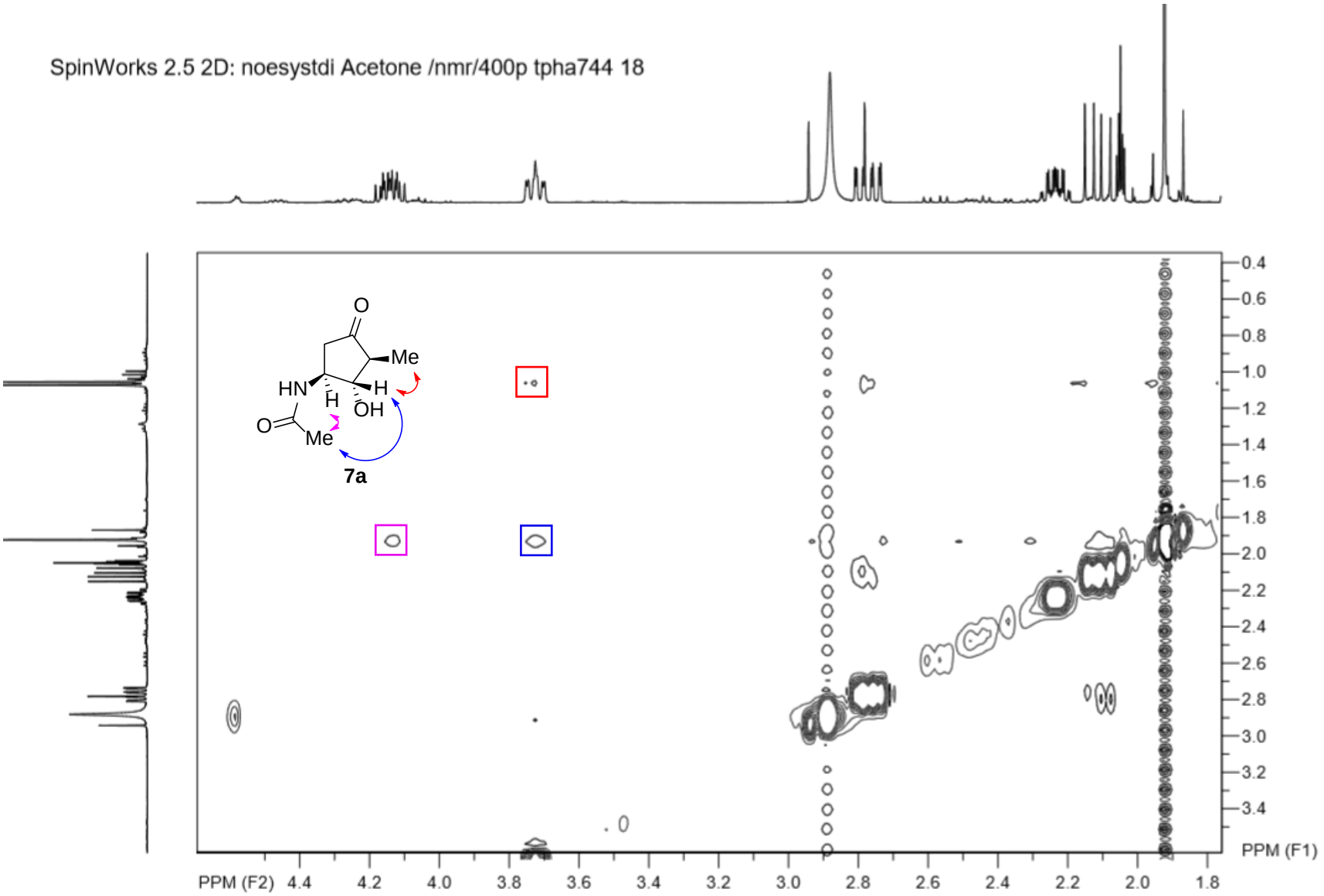
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HN
H
H
OH
O
Me
7a
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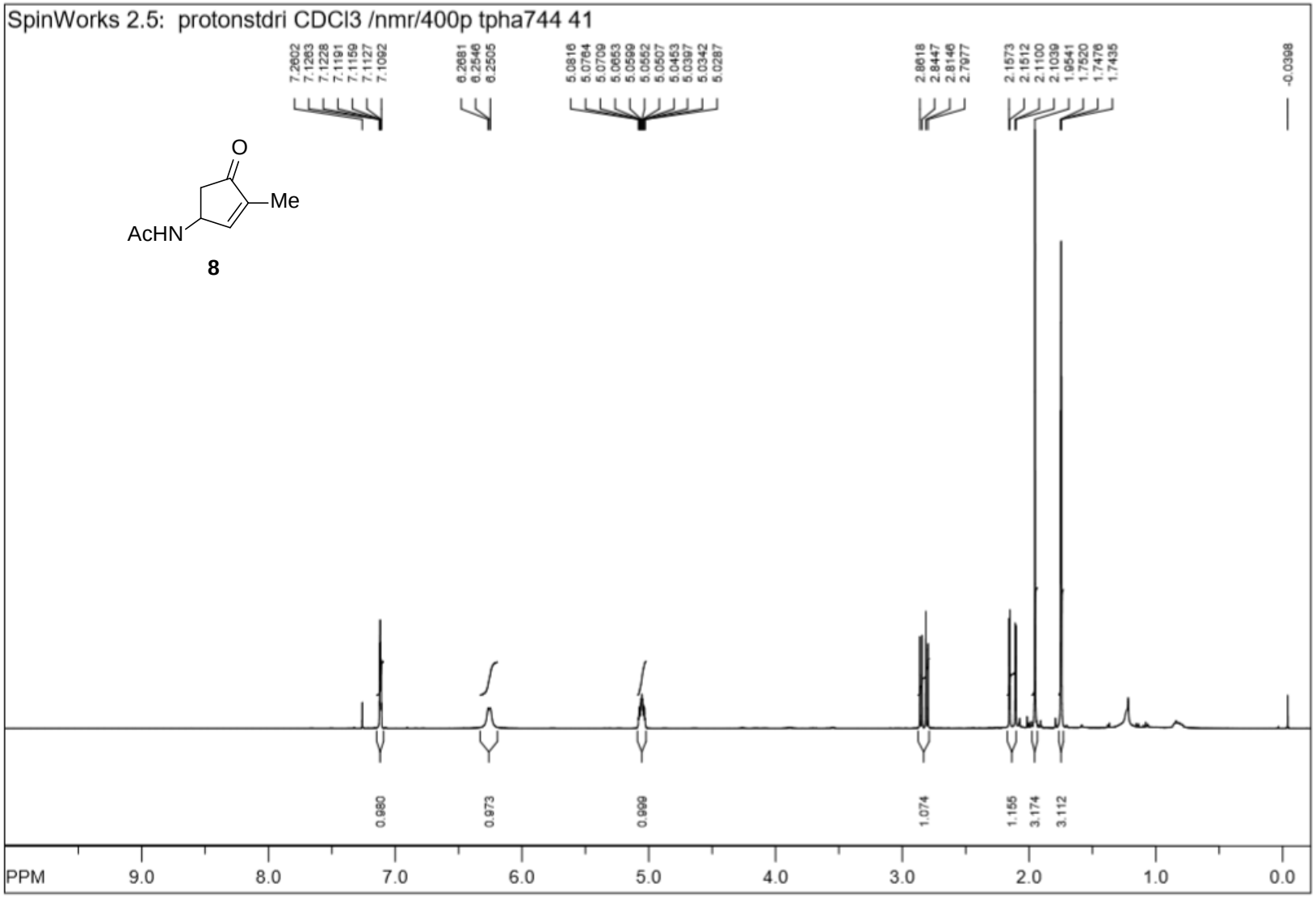
PPM (F1) 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8 2.0 2.2 2.4 2.6 2.8 3.0 3.2 3.4


SpinWorks 2.5: protonstdri CDCl3 /nmr/400p tpha744 41
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6.2546
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2.1512
2.1100
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1.7476
1.7435
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Me
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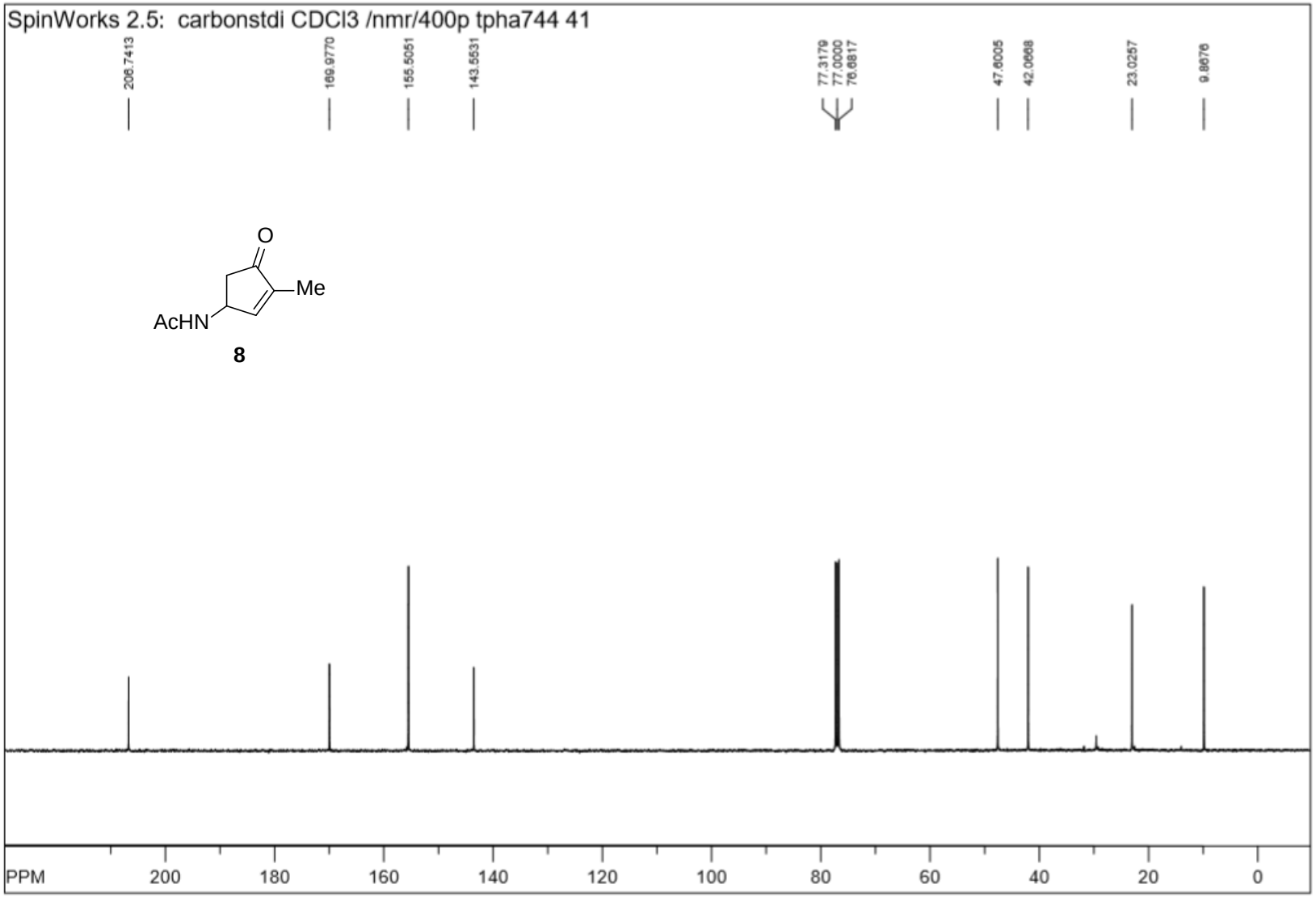
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Me
AcHN
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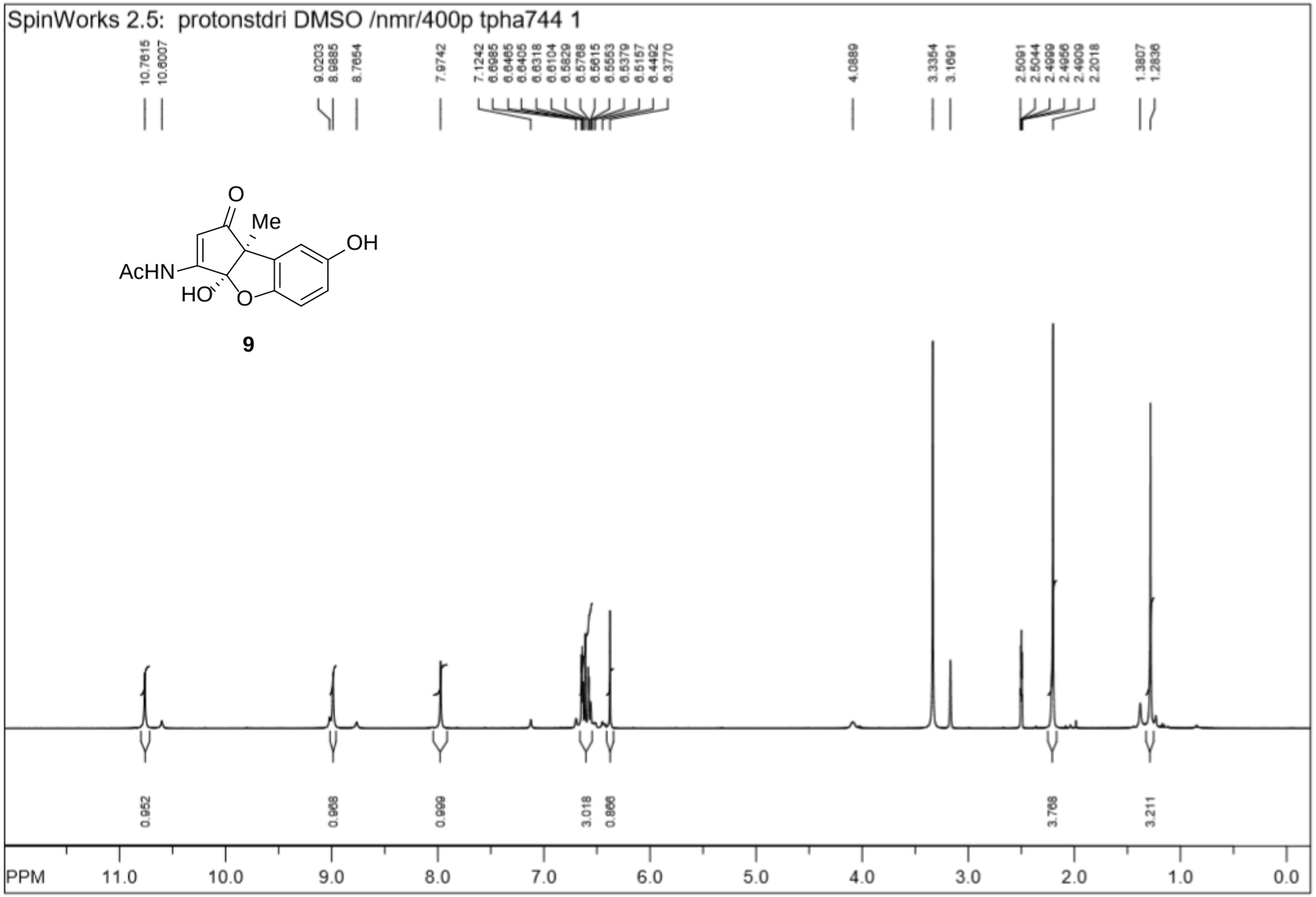
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7.1242
6.6985
6.6465
6.6405
6.6318
6.6104
6.5829
6.5768
6.5615
6.5553
6.5379
6.5157
6.4492
6.3770
4.0889
3.3354
3.1691
2.5091
2.5044
2.4999
2.4956
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2.2018
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O
Me
OH
AcHN
HO
O
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0.999
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PPM
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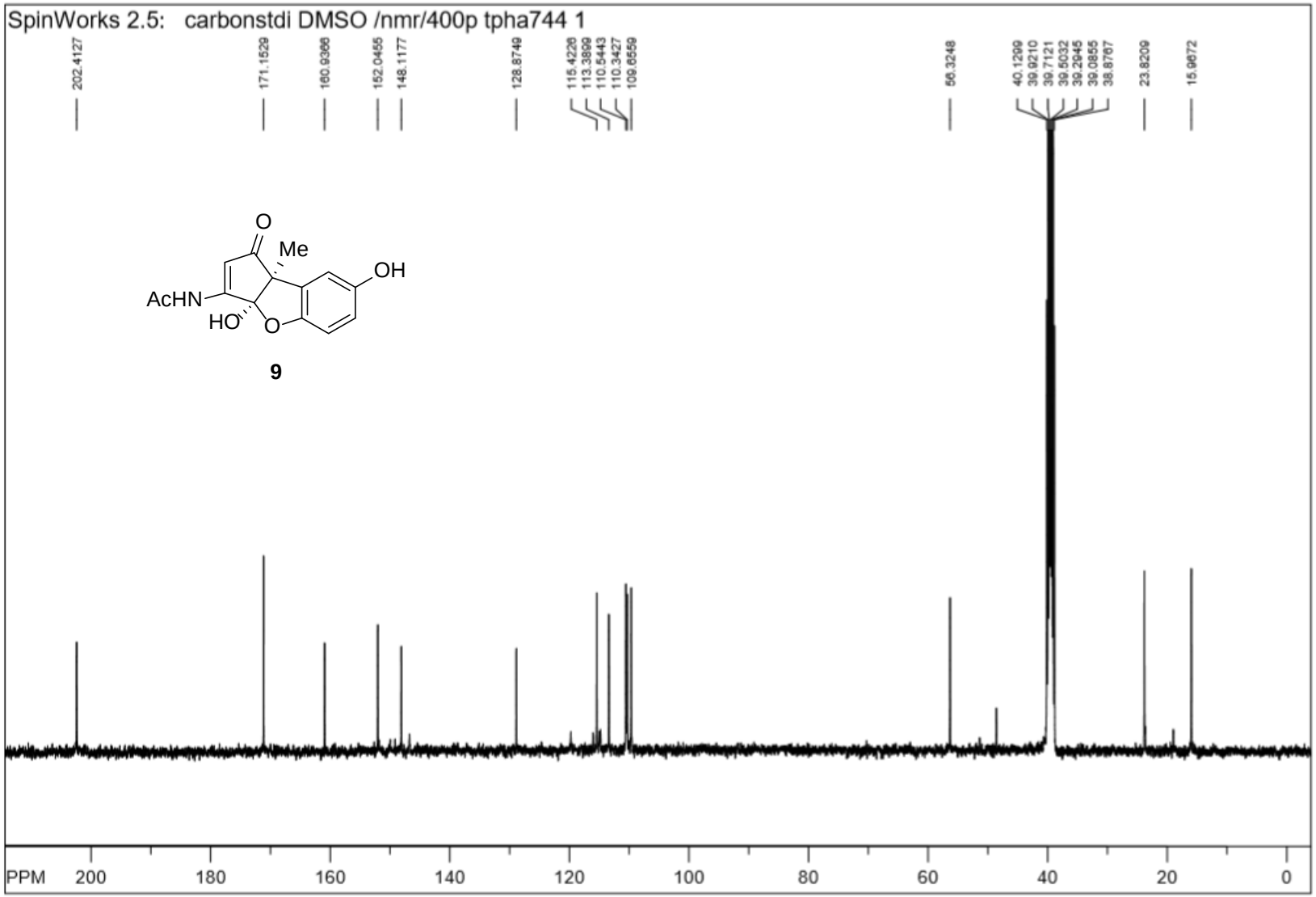
SpinWorks 2.5: carbonstdi DMSO /nmr/400p tpha744 1
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113.3899
110.5443
110.3427
109.6559
56.3248
40.1299
39.9210
39.7121
39.5032
39.2945
39.0855
38.8767
23.8209
15.9872
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OH
AcHN
HO
O
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PPM
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20
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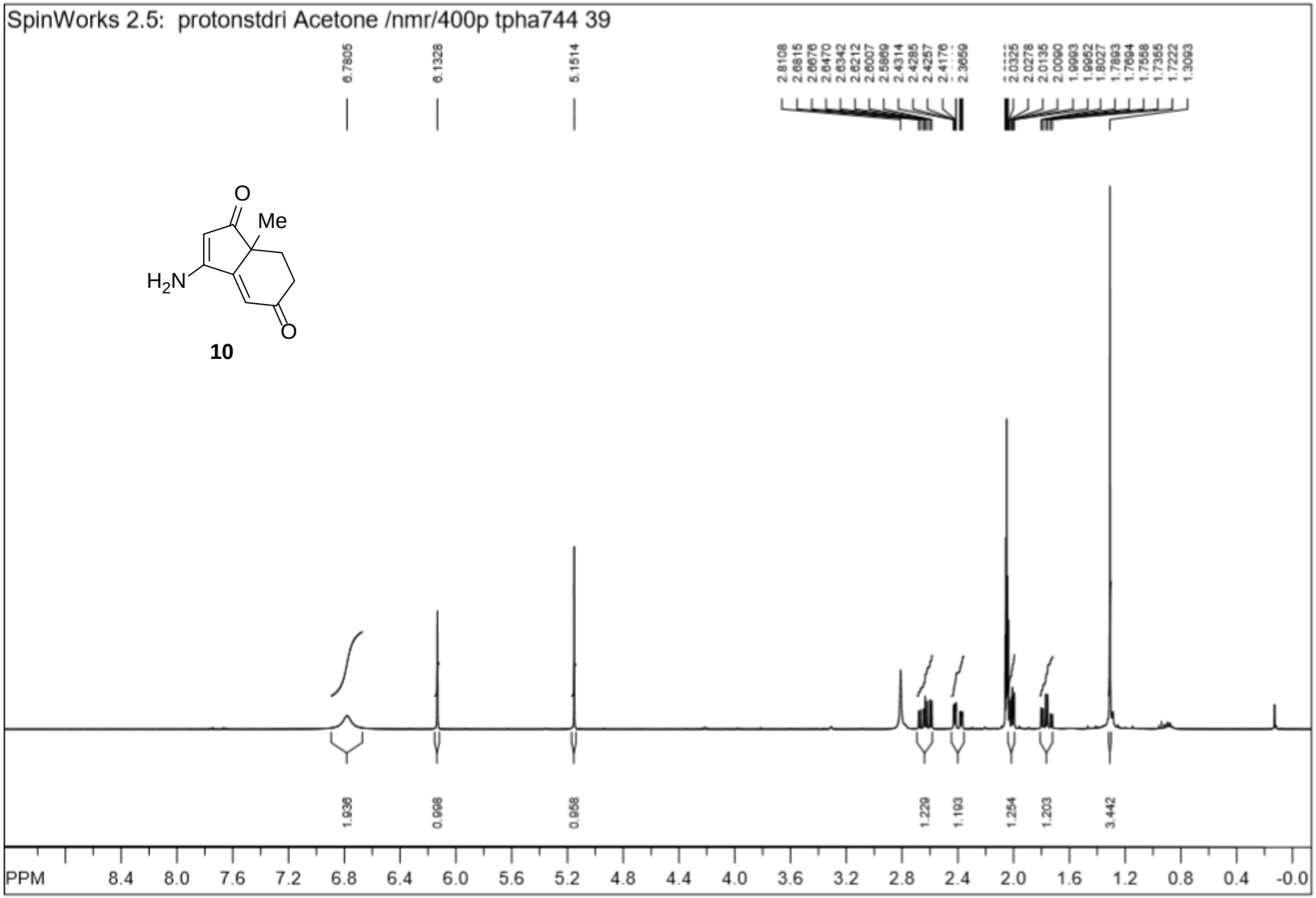
SpinWorks 2.5: protonstdri Acetone /nmr/400p tpha744 39
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5.1514
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2.6676
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2.6342
2.6212
2.6007
2.5869
2.4314
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2.4257
2.4176
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2.0135
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1.9952
1.8027
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1.7355
1.7222
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Me
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O
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1.254
1.203
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7.2
6.8
6.4
6.0
5.6
5.2
4.8
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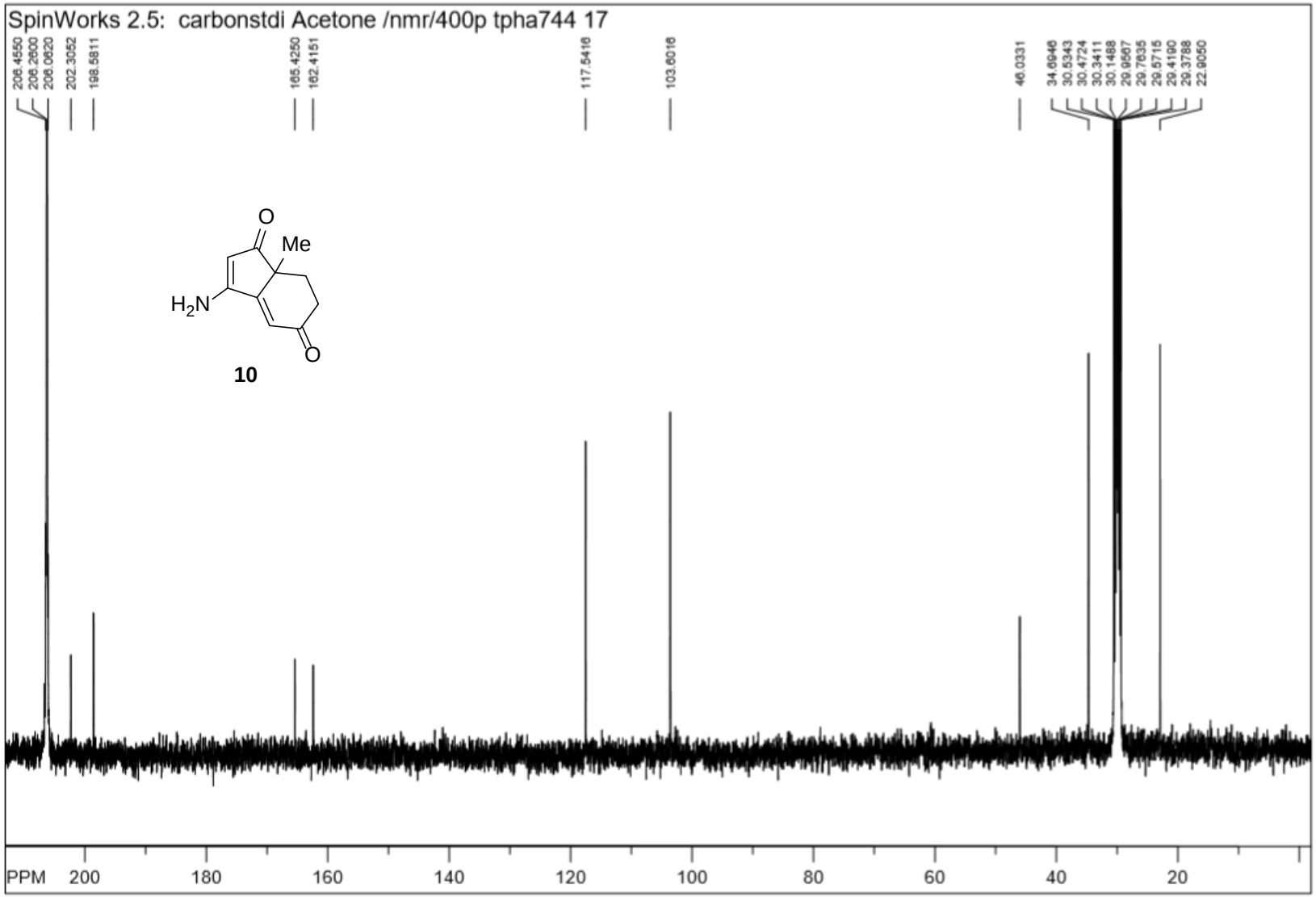
SpinWorks 2.5: carbonstdi Acetone /nmr/400p tpha744 17
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162.4151
117.5416
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46.0331
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30.4724
30.3411
30.1488
29.9567
29.7635
29.5715
29.4190
29.3788
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H_2N
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PPM
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60
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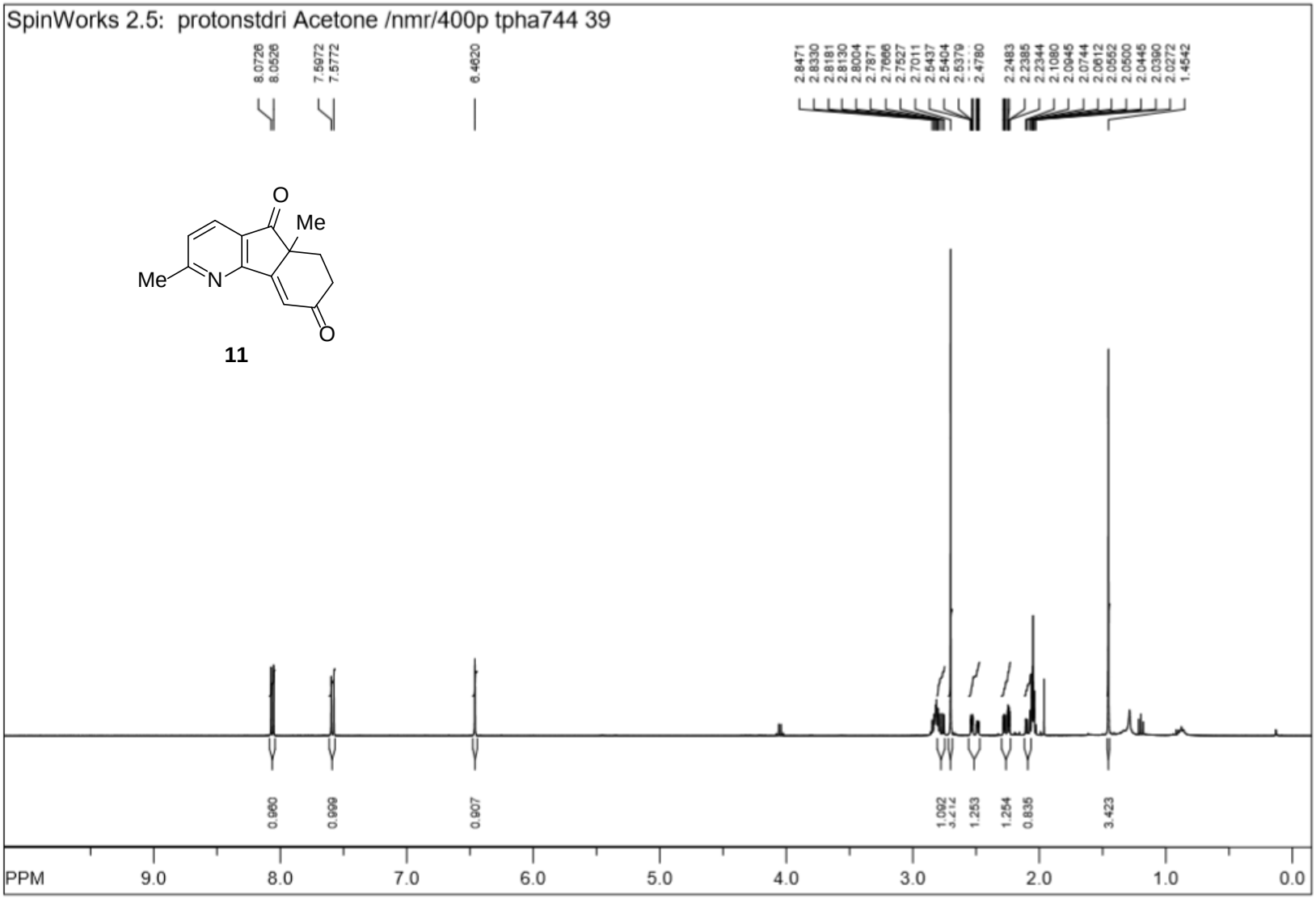
20

10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2.8181
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2.8004
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2.2483
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2.2344
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2.0744
2.0612
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2.0500
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Me
Me
N
O
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1.092
3.212
1.253
1.254
0.835
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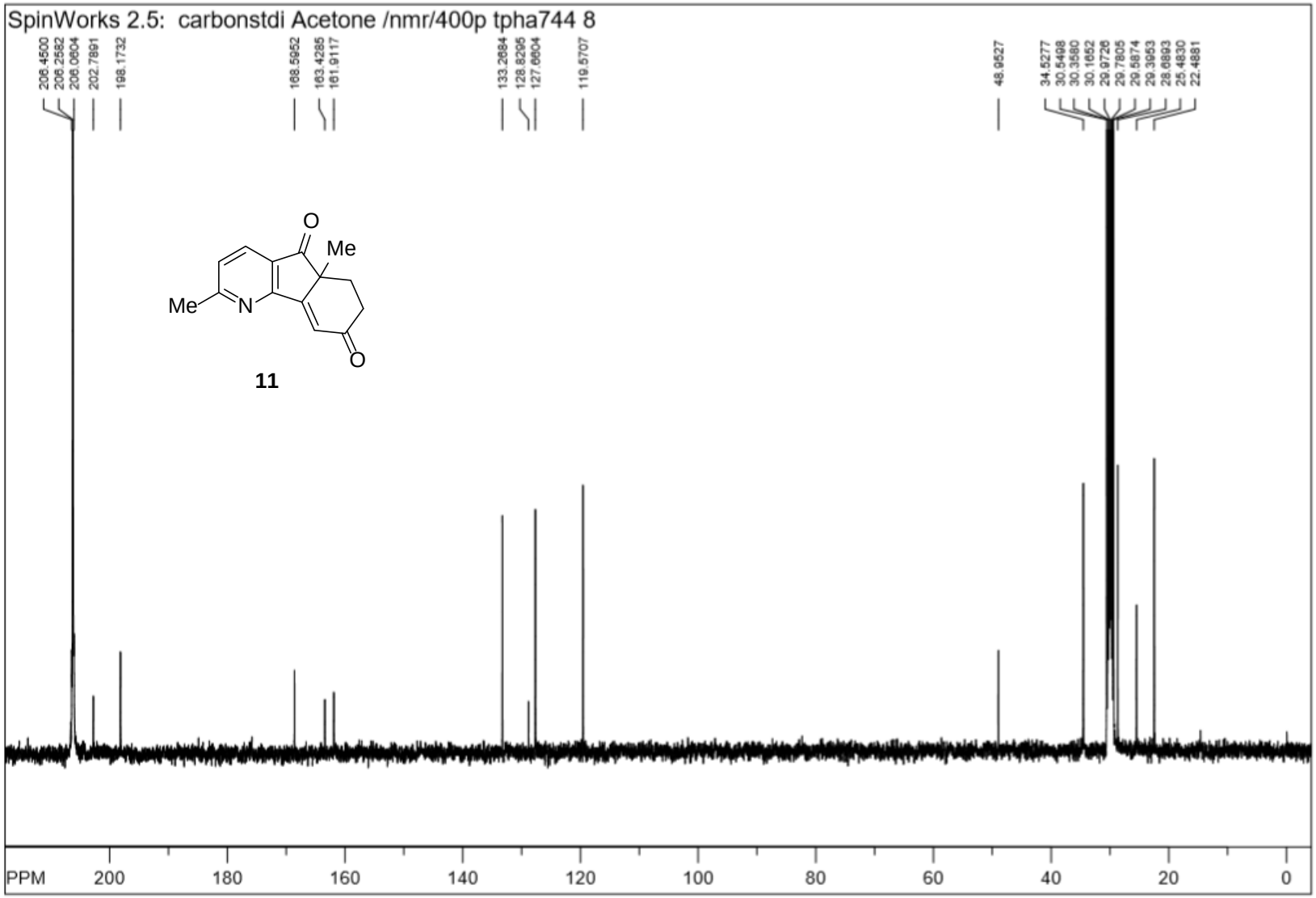
SpinWorks 2.5: carbonstdi Acetone /nmr/400p tpha744 8
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163.4285
161.9117
133.2684
128.8295
127.6804
119.5707
48.9527
34.5277
30.5498
30.3580
30.1652
29.9726
29.7805
29.5874
29.3953
28.6893
25.4830
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Me
N
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120
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40
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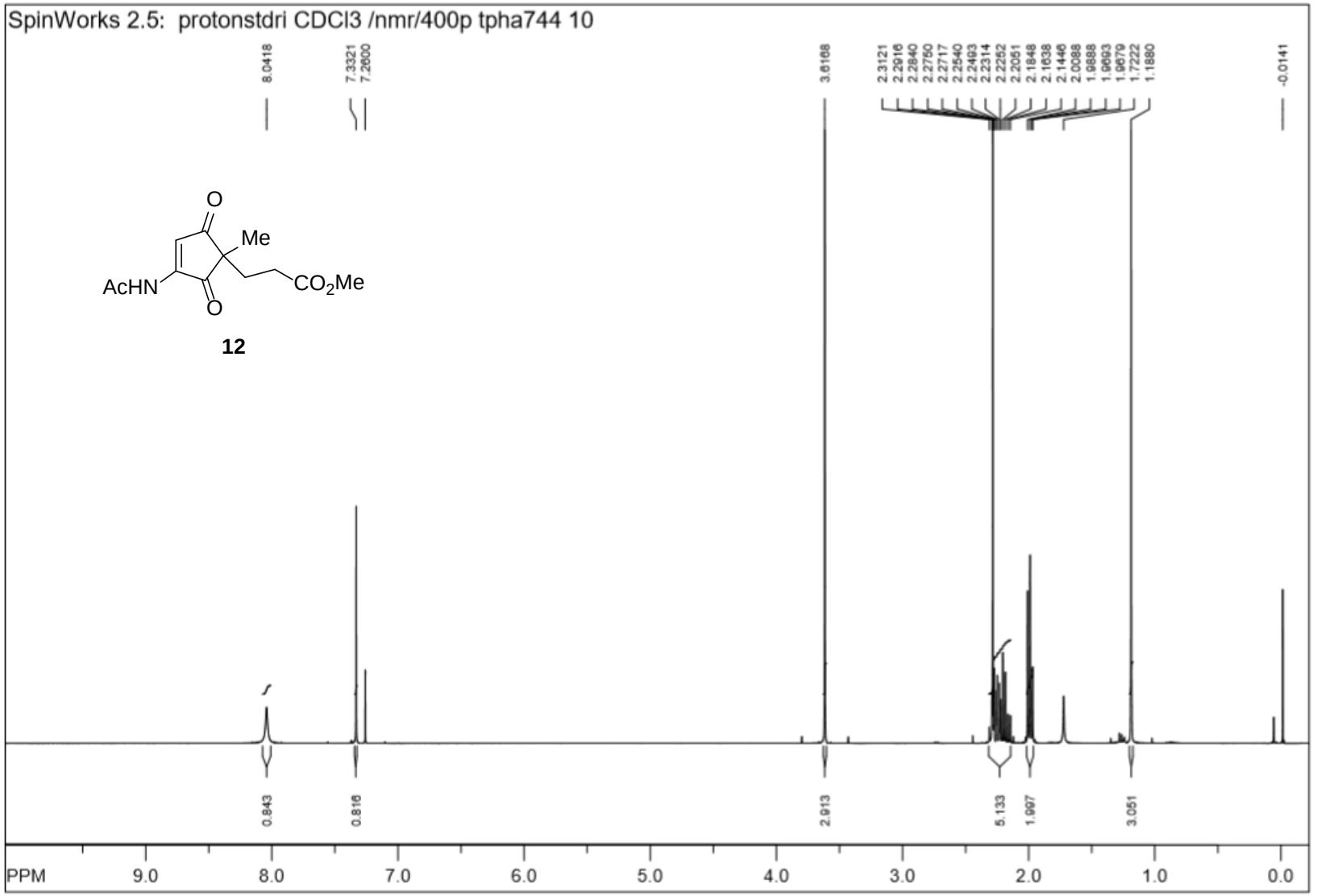
0

11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2.2750
2.2717
2.2540
2.2493
2.2314
2.2252
2.2051
2.1848
2.1638
2.1446
2.0088
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1.9693
1.9079
1.7222
1.1880
-0.0141
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Me
AcHN
CO2Me
O
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1.997
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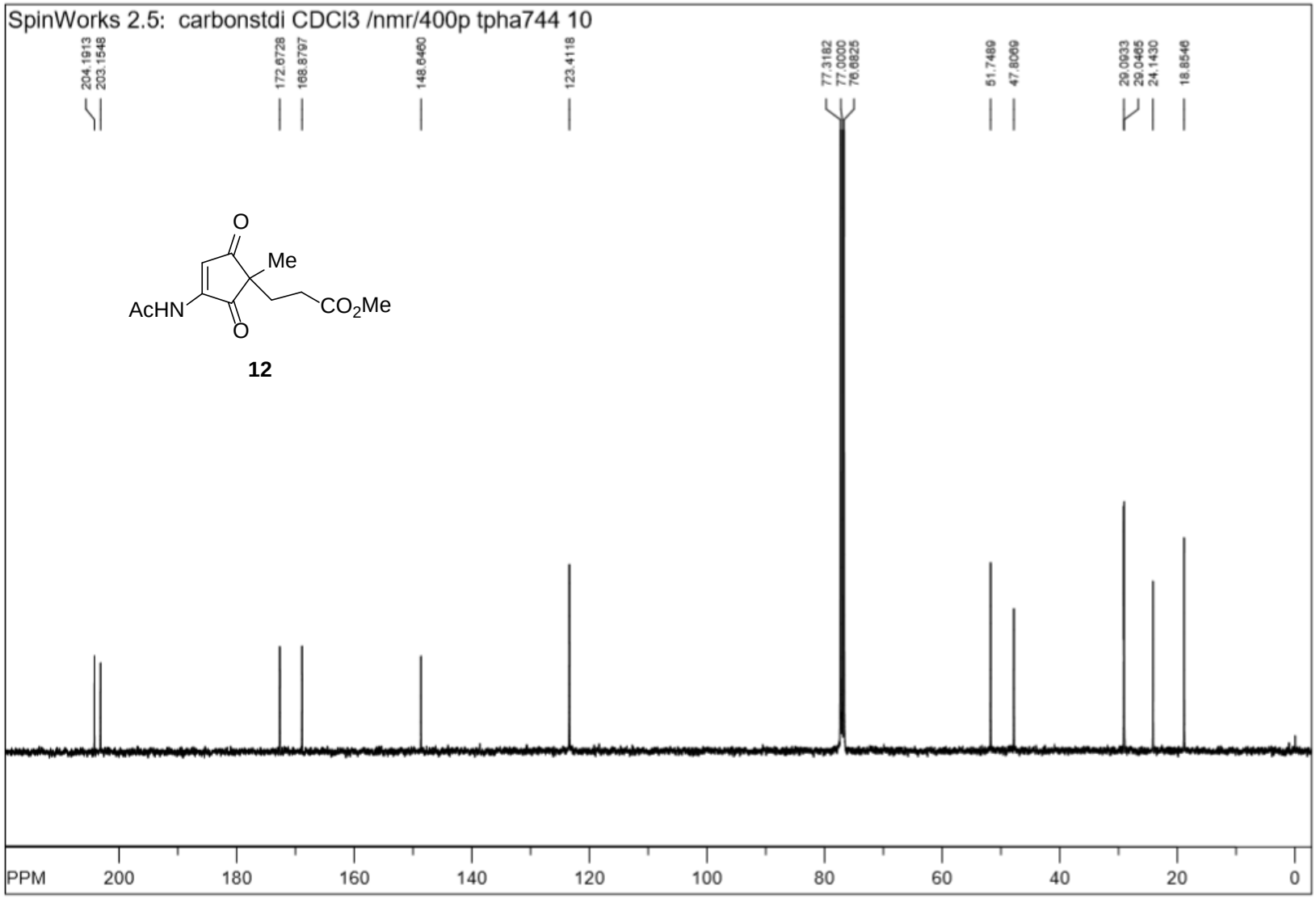
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77.0000
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47.8069
29.0933
29.0465
24.1430
18.8546
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CO2Me
O
12
PPM
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140
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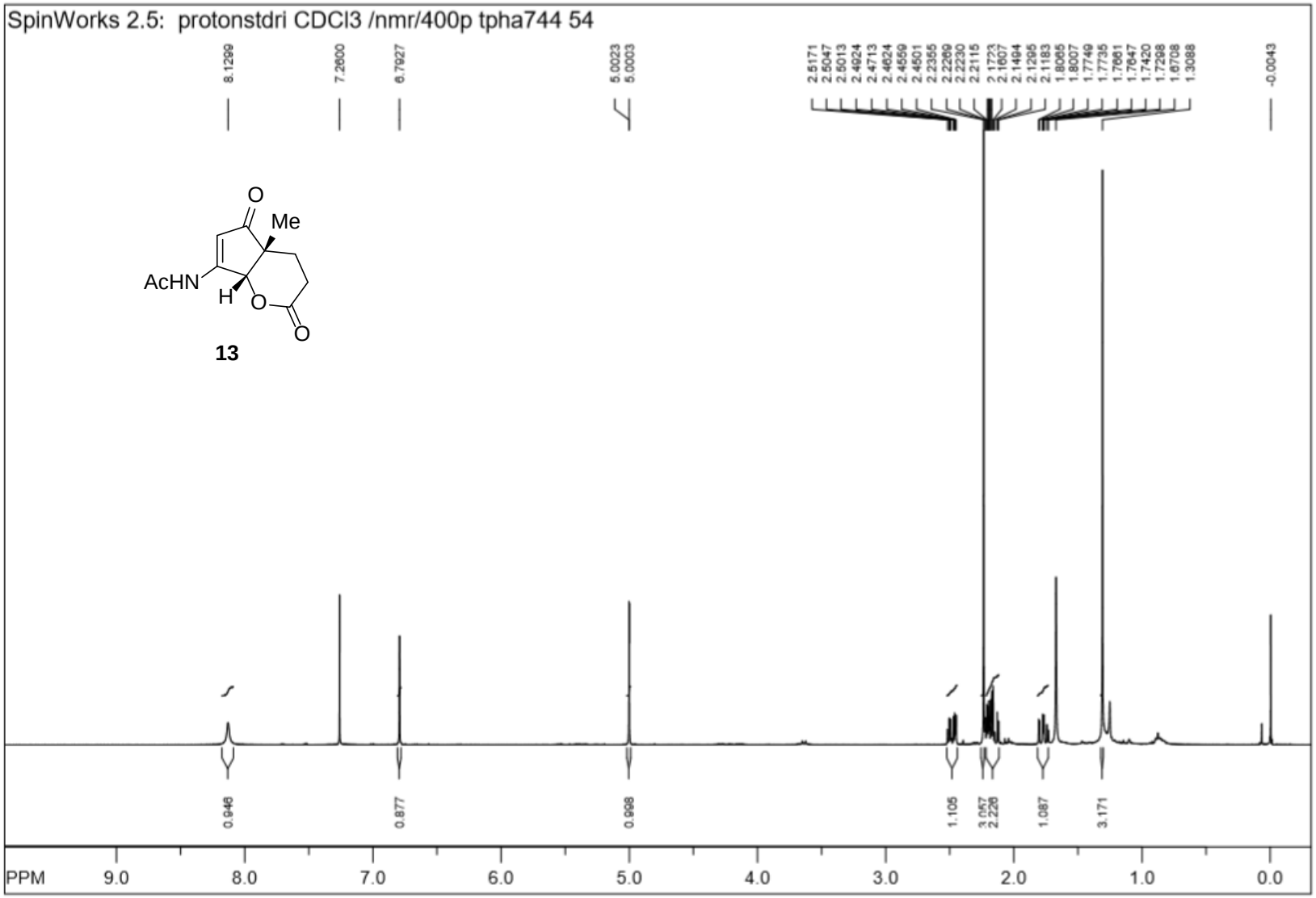
SpinWorks 2.5: protonstdri CDCl3 /nmr/400p tpha744 54
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2.4501
2.2355
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2.2230
2.2115
2.1723
2.1607
2.1494
2.1295
2.1183
1.8065
1.8007
1.7749
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1.7661
1.7647
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1.7298
1.6708
1.3088
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Me
AcHN
H
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3.057
2.226
1.087
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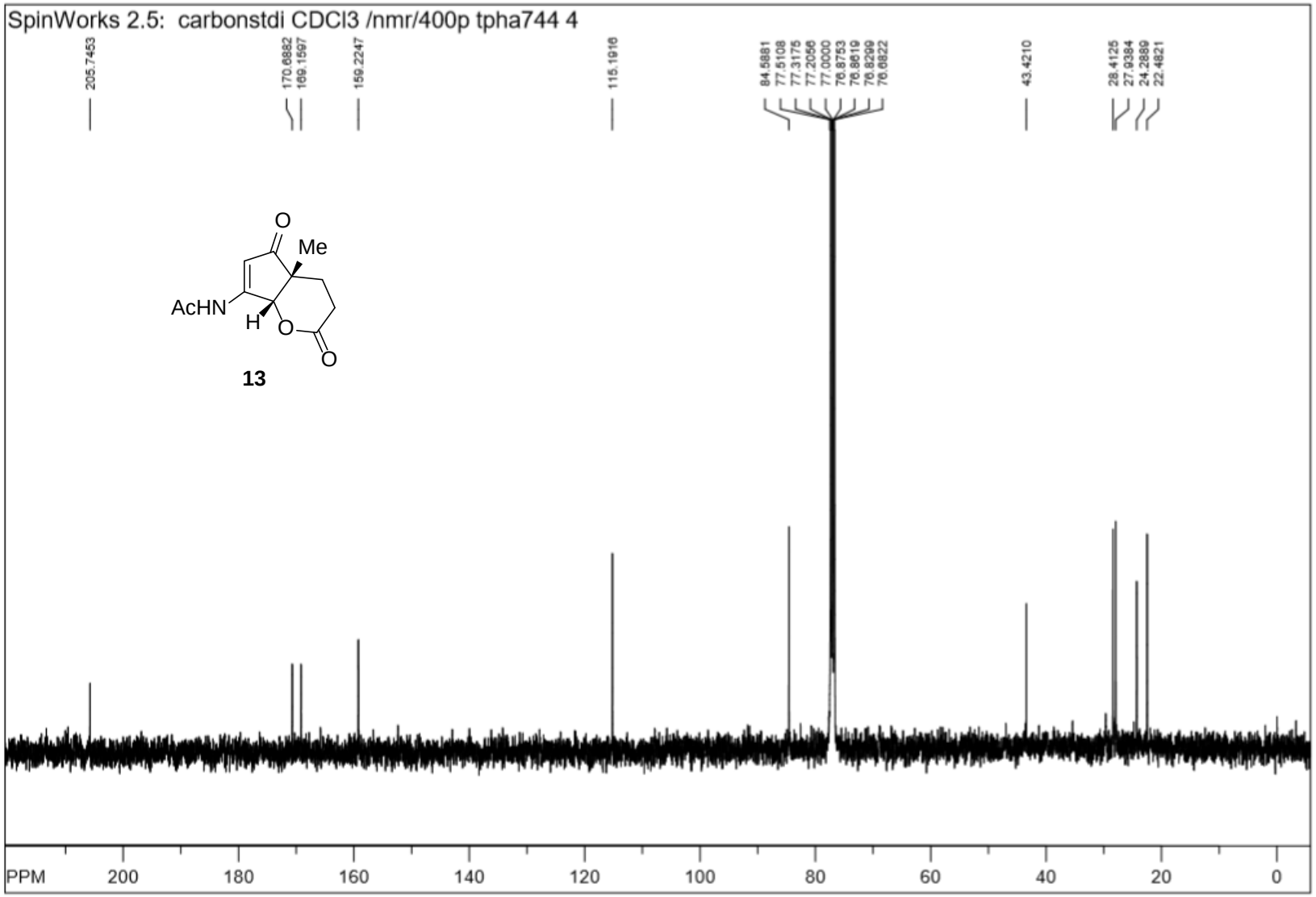
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76.8299
76.6822
43.4210
28.4125
27.9384
24.2889
22.4821
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Me
AcHN
H
O
O
13
PPM
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20
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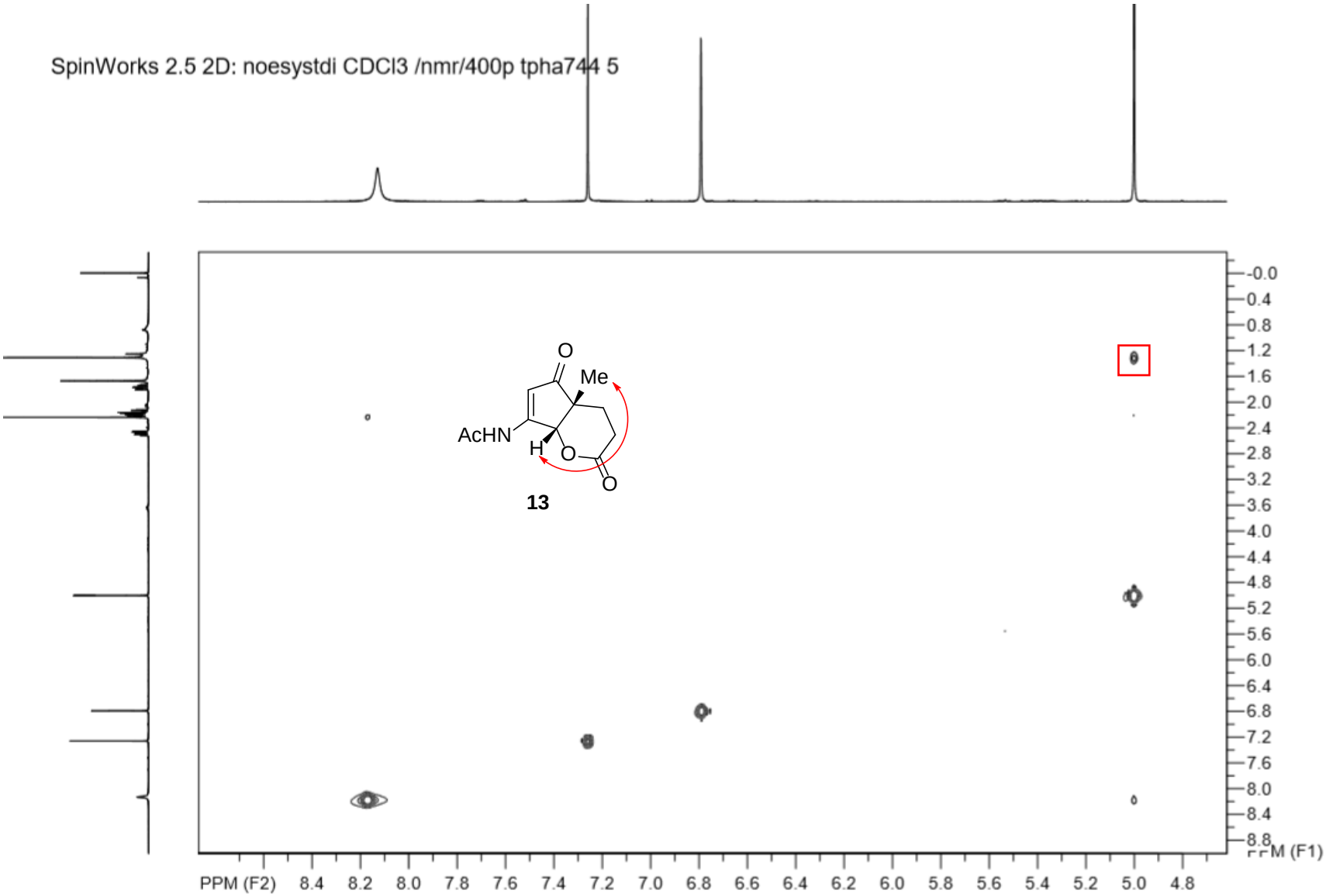
SpinWorks 2.5 2D: noesystdi CDCl3 /nmr/400p tpha744 5
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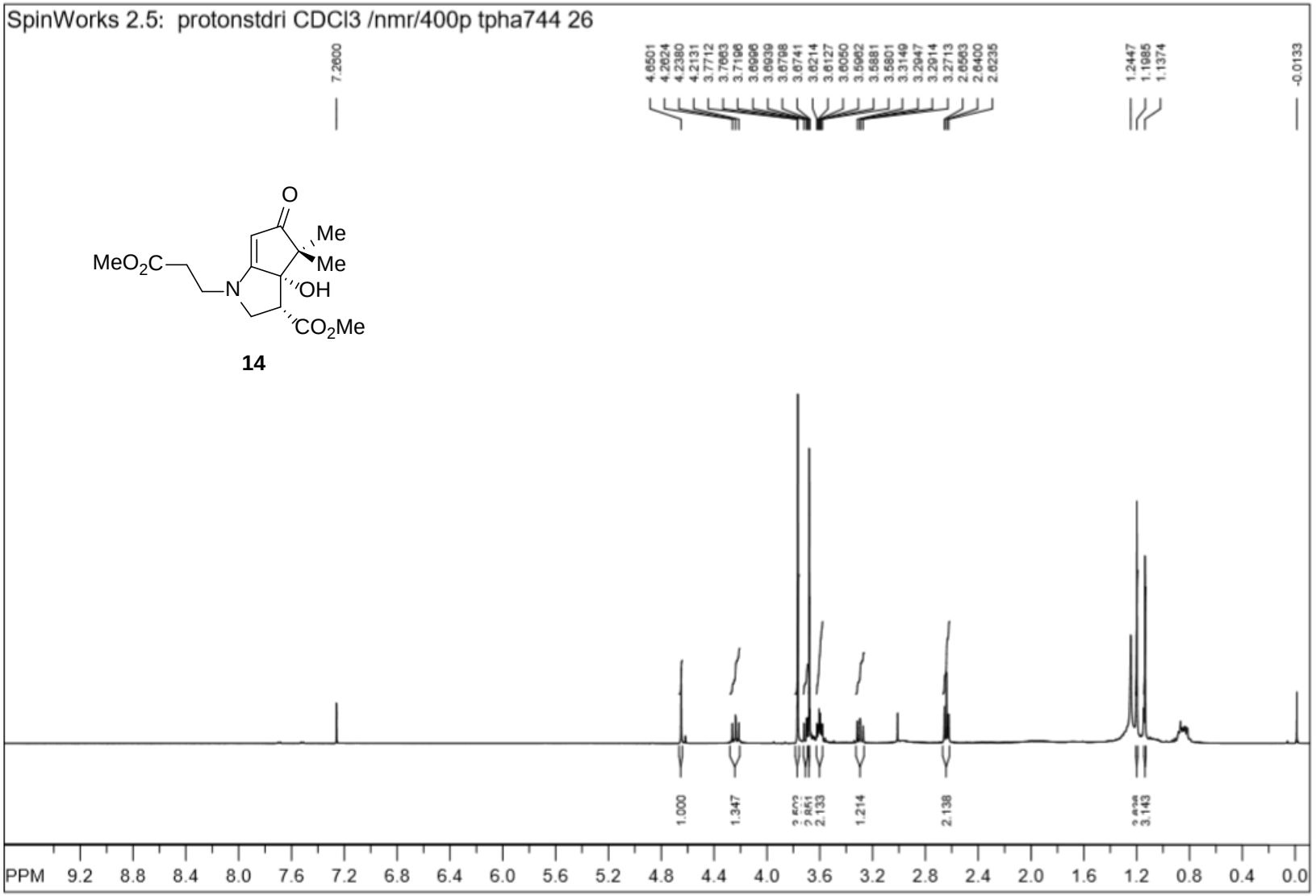
Me
AcHN
H
O
O
13
PPM (F2) 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8
-0.0 0.4 0.8 1.2 1.6 2.0 2.4 2.8 3.2 3.6 4.0 4.4 4.8 5.2 5.6 6.0 6.4 6.8 7.2 7.6 8.0 8.4 8.8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Me
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N
OH
CO2Me
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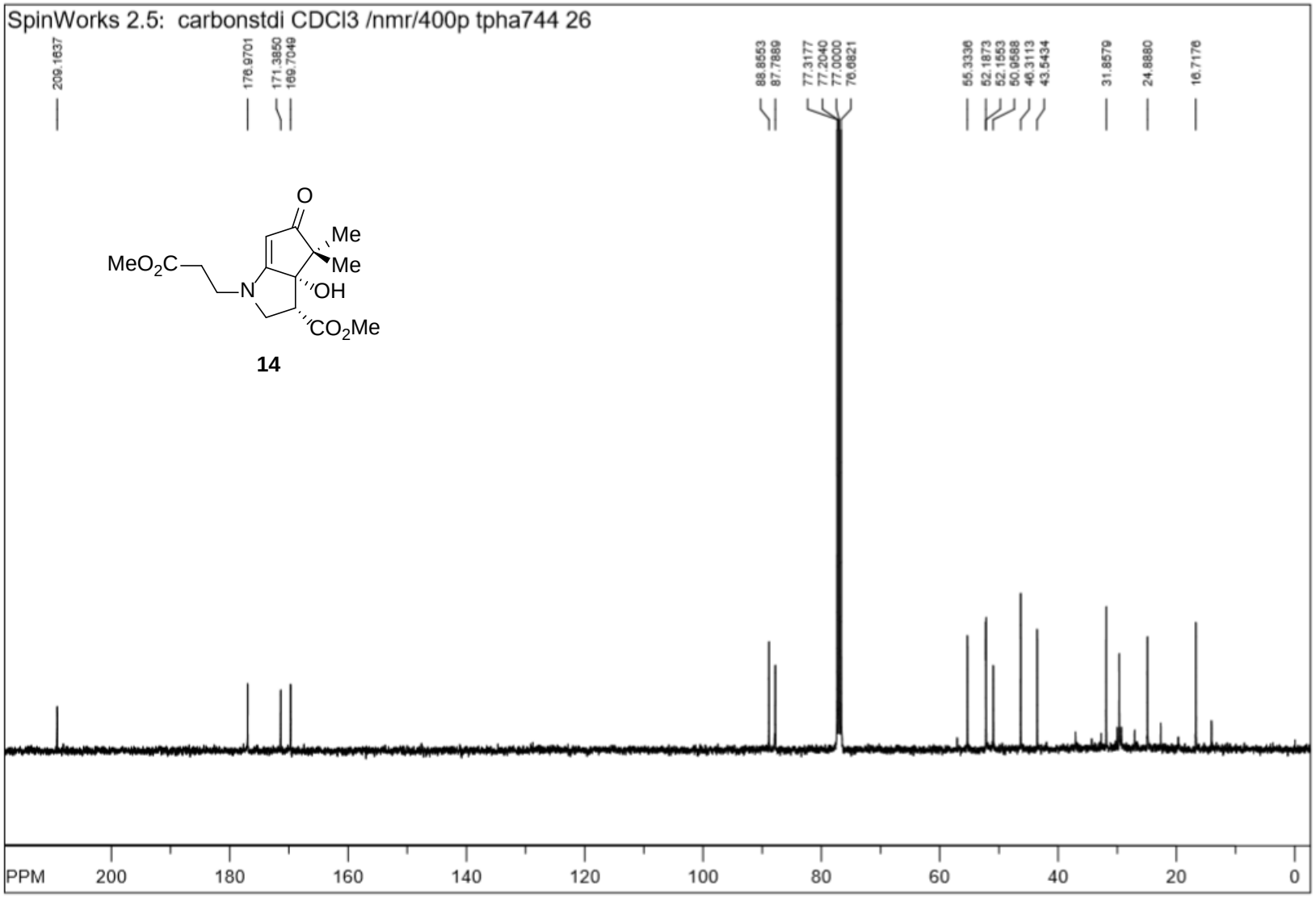
2.138
3.143
PPM 9.2 8.8 8.4 8.0 7.6 7.2 6.8 6.4 6.0 5.6 5.2 4.8 4.4 4.0 3.6 3.2 2.8 2.4 2.0 1.6 1.2 0.8 0.4 0.0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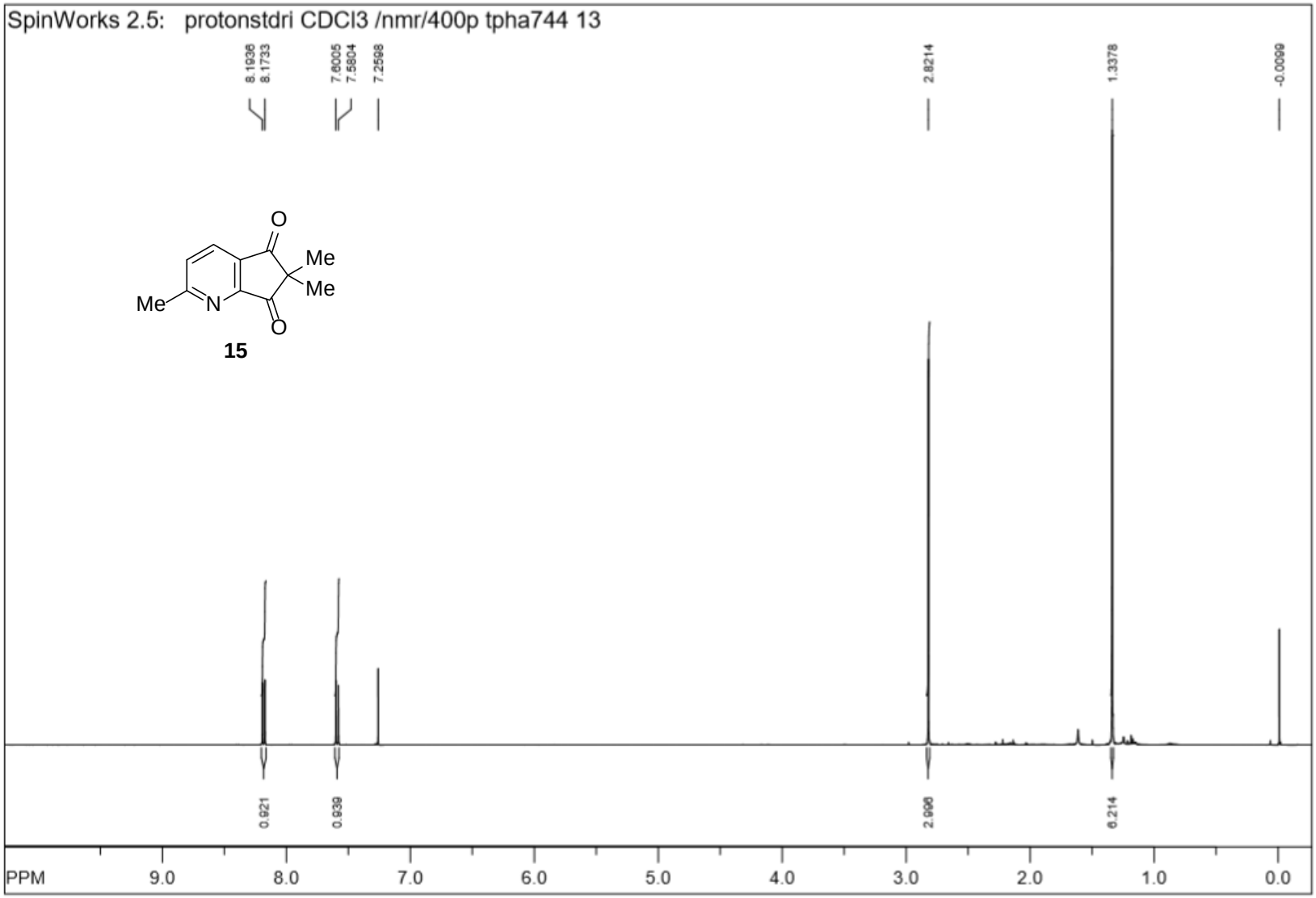
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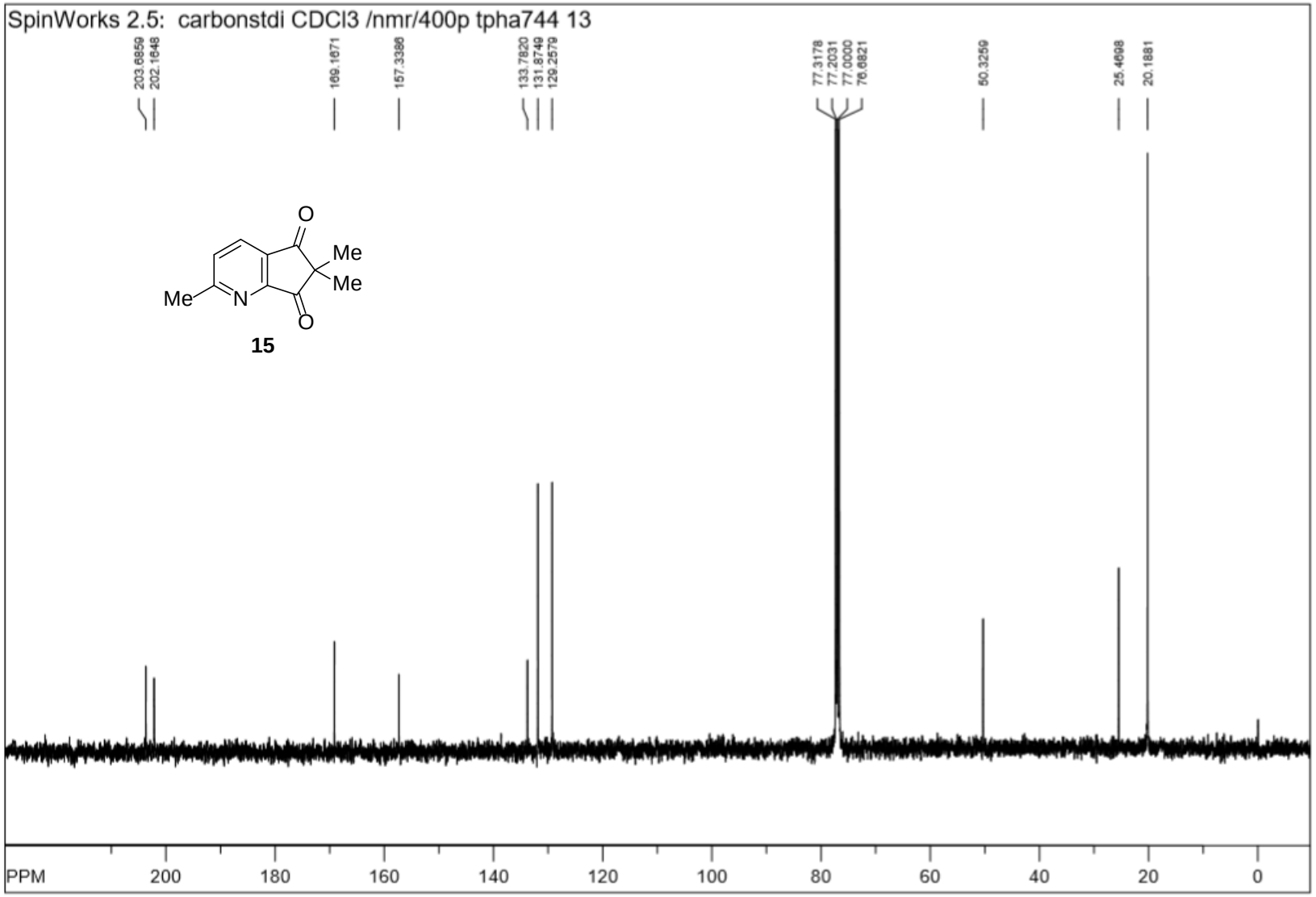
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20.1881
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PPM
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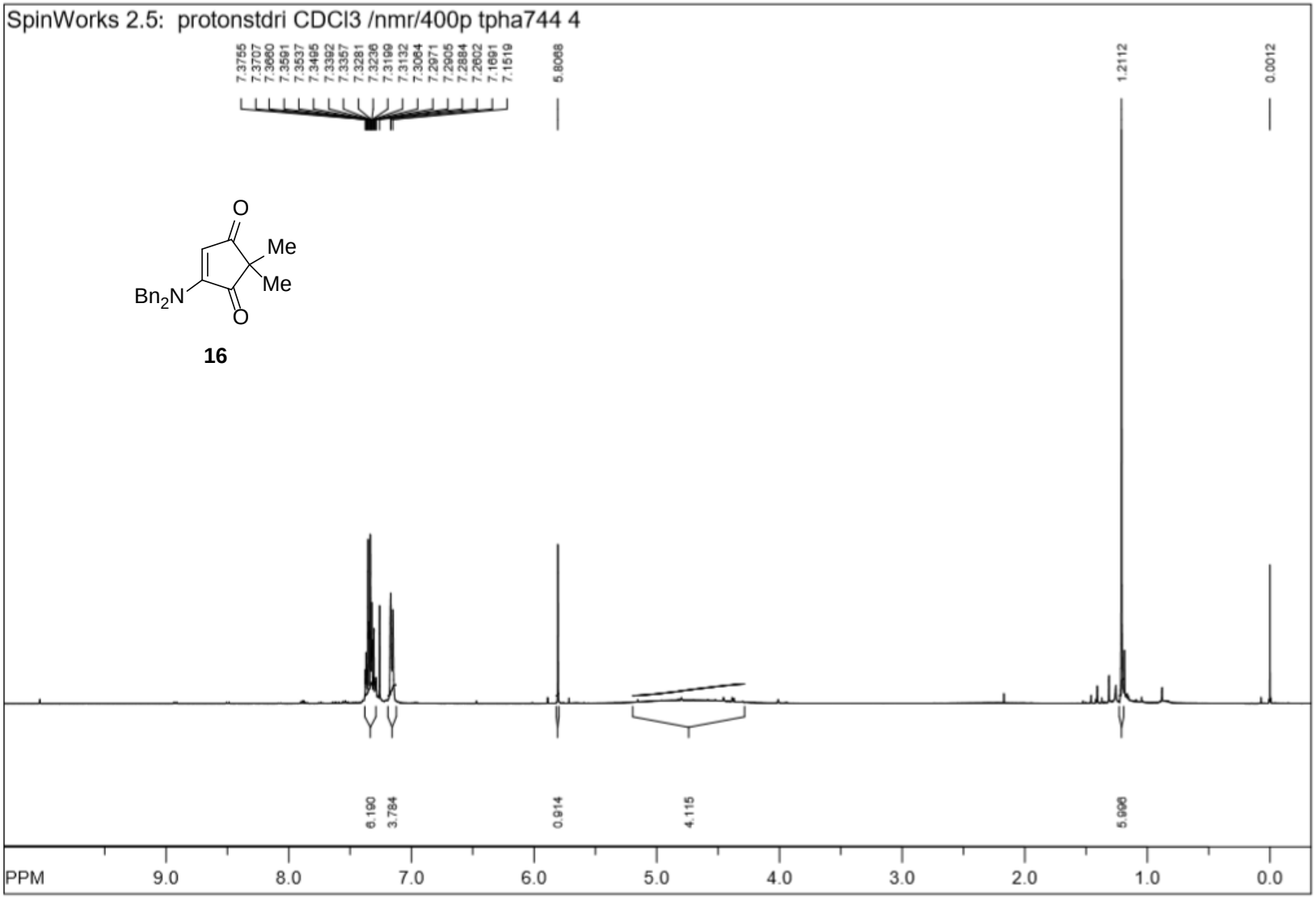
SpinWorks 2.5: protonstdri CDCl3 /nmr/400p tpha744 4
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7.3392
7.3357
7.3281
7.3236
7.3199
7.3132
7.3084
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Bn2N
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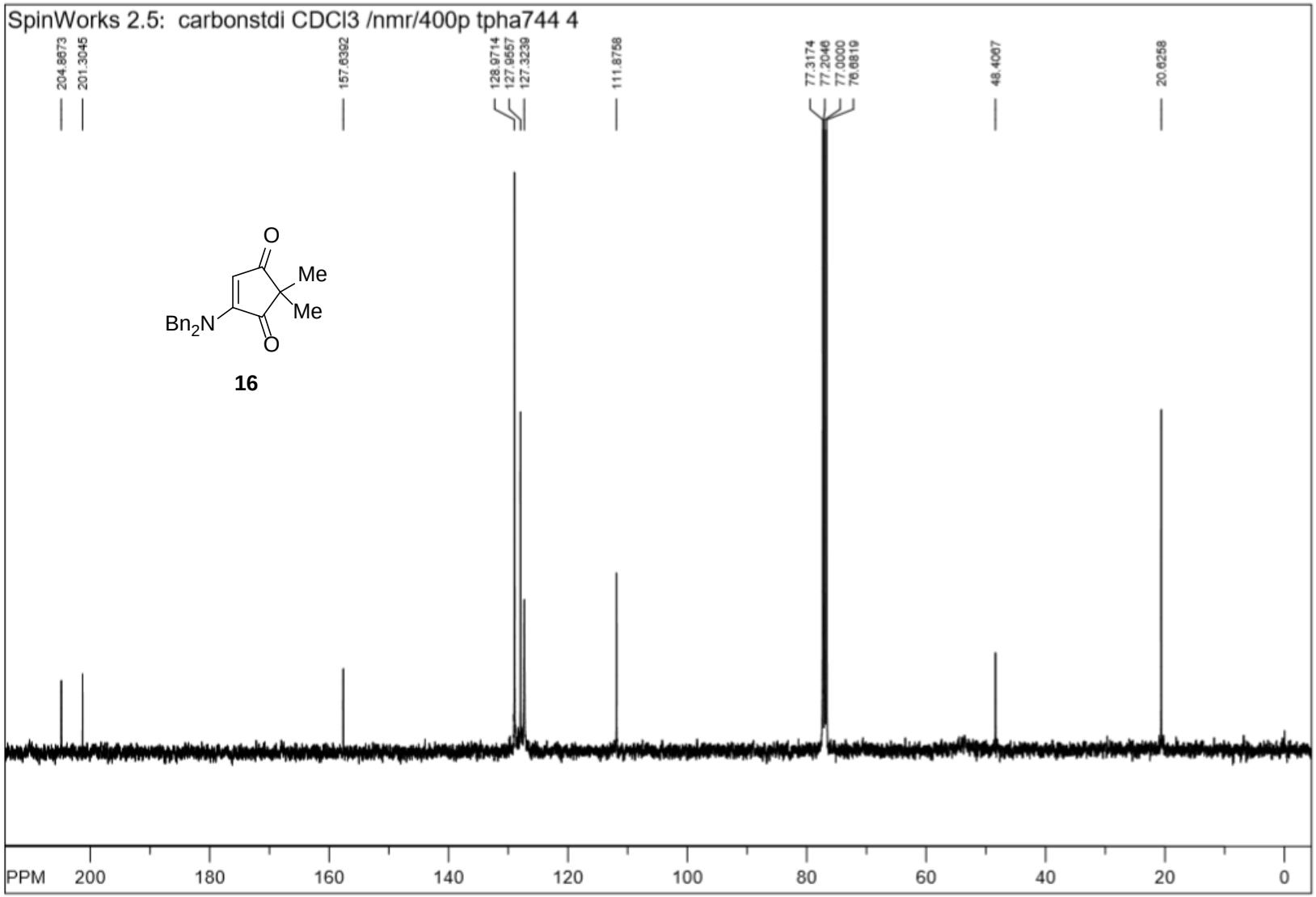
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Me
Me
Bn2N
O
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PPM
200
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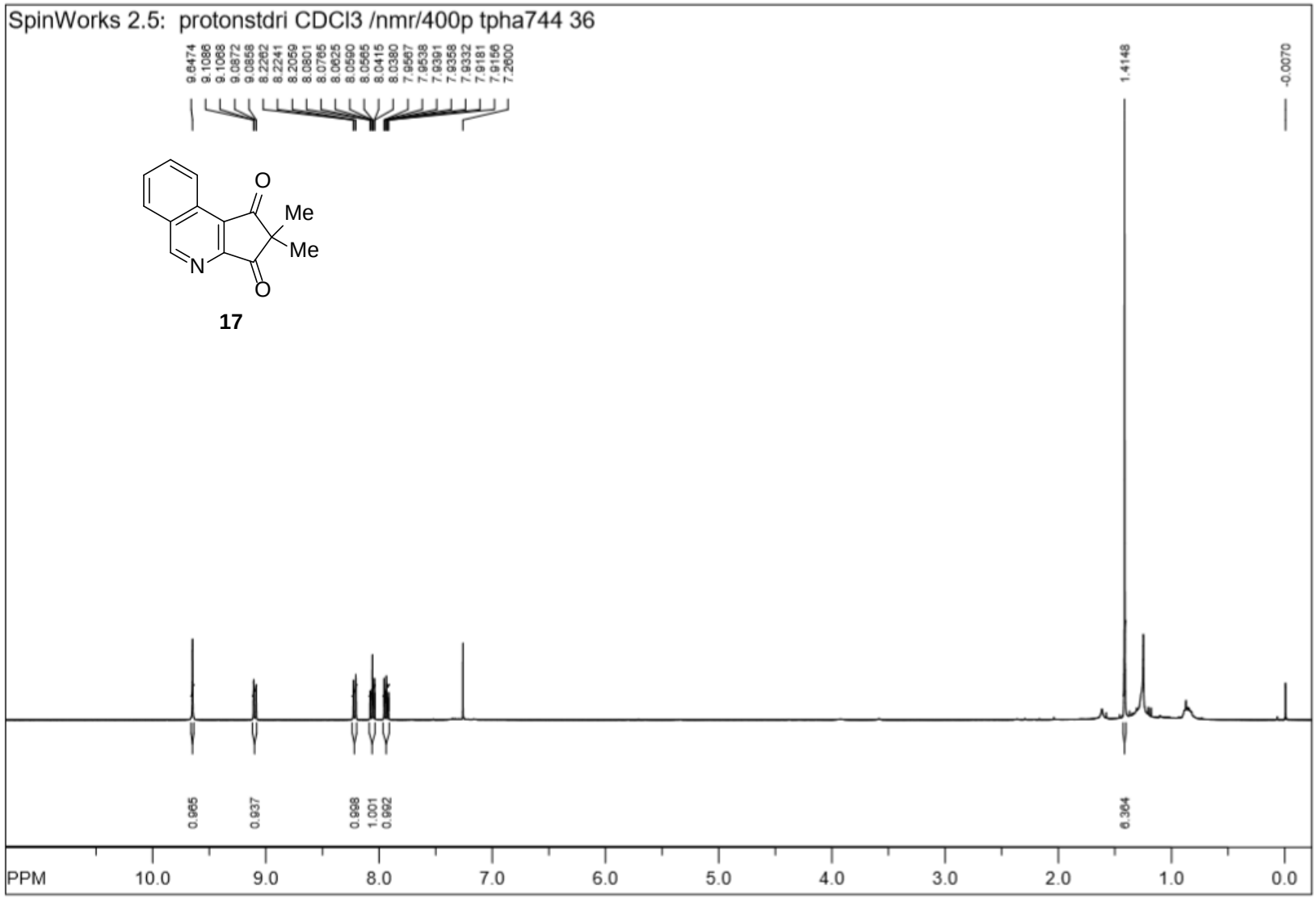
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8.0565
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Me
Me
N
O
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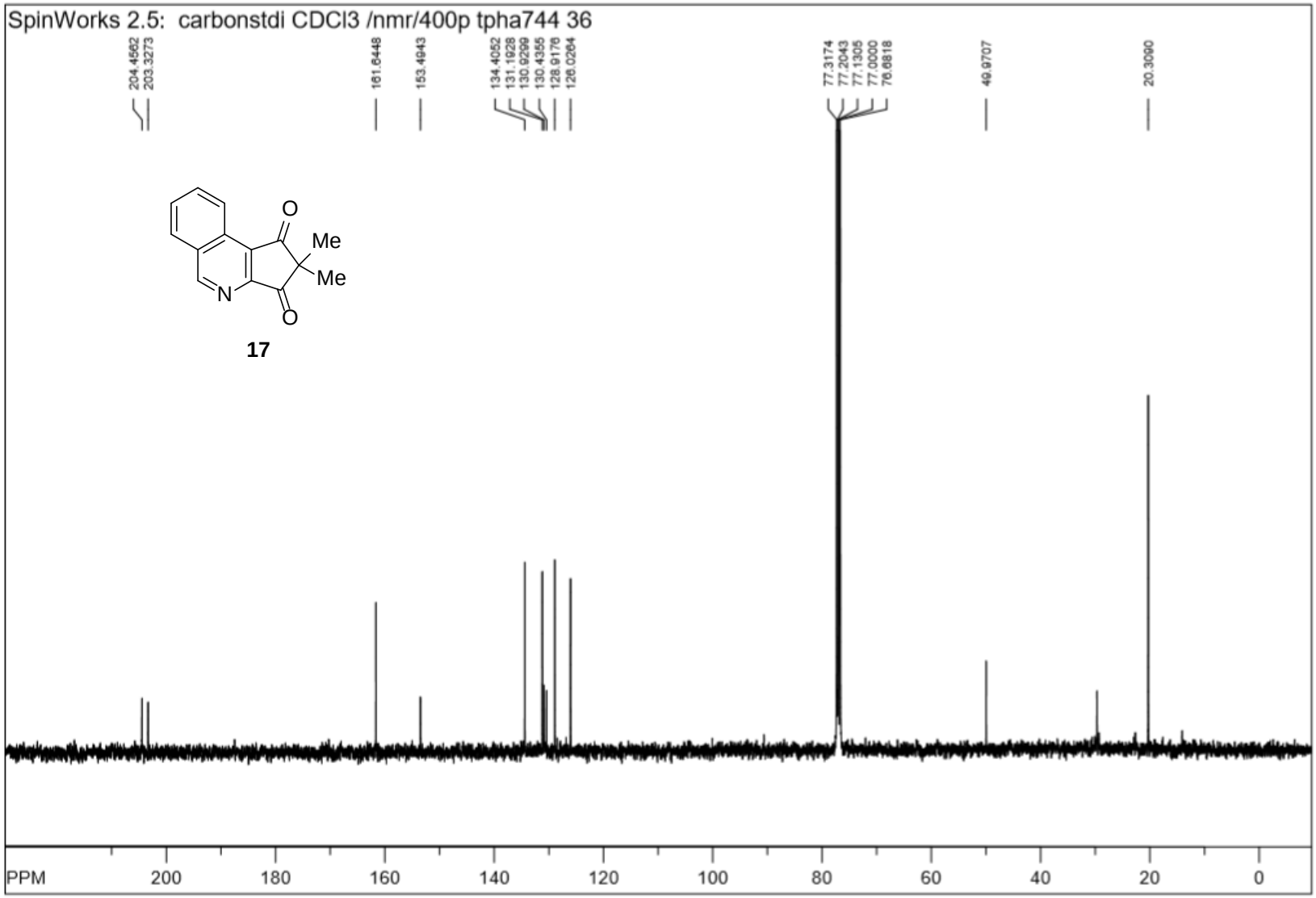
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128.9176
126.0264
77.3174
77.2043
77.1305
77.0000
76.6818
49.9707
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N
O
PPM
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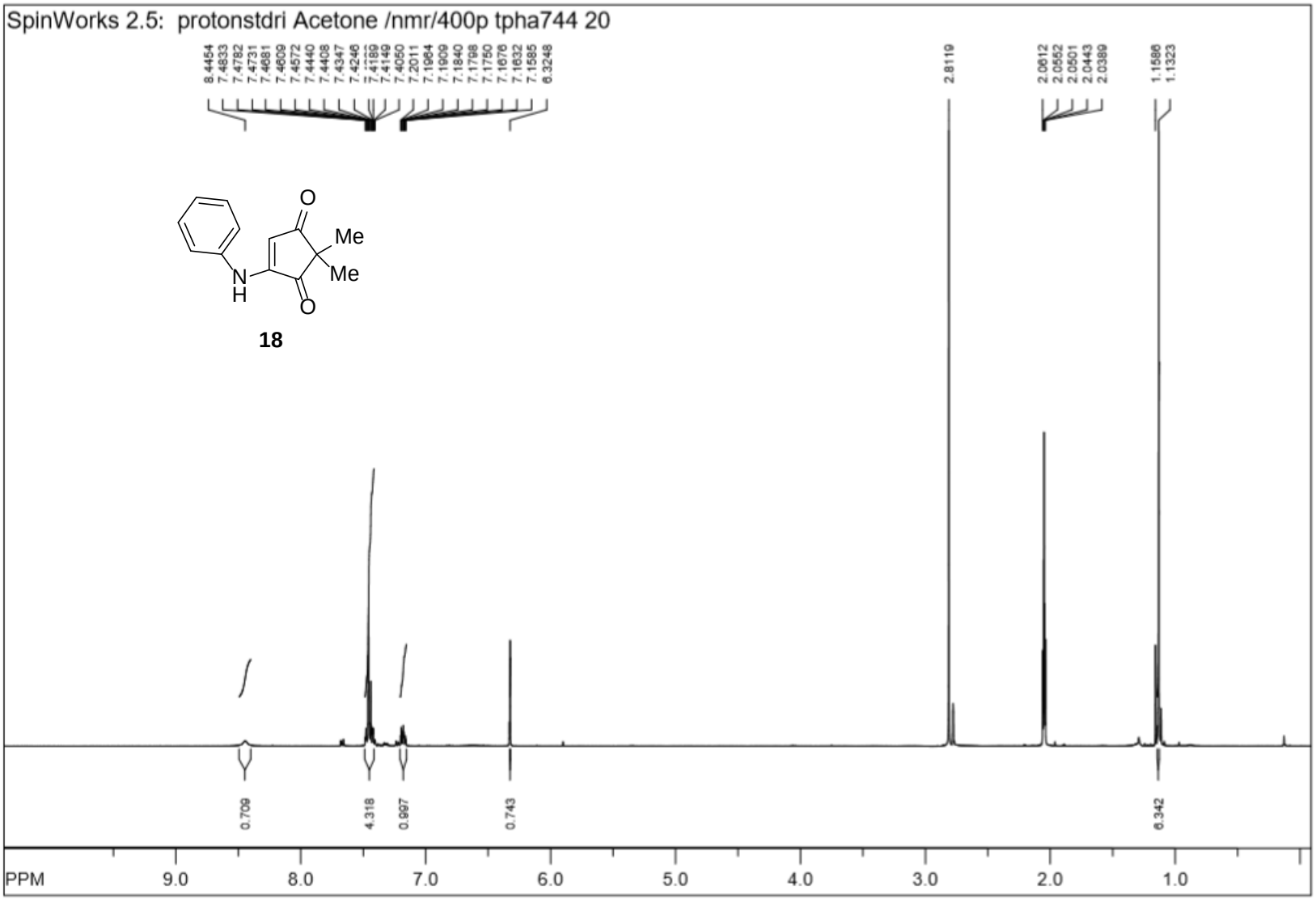
160
140
120
100
80
60
40
20
0

17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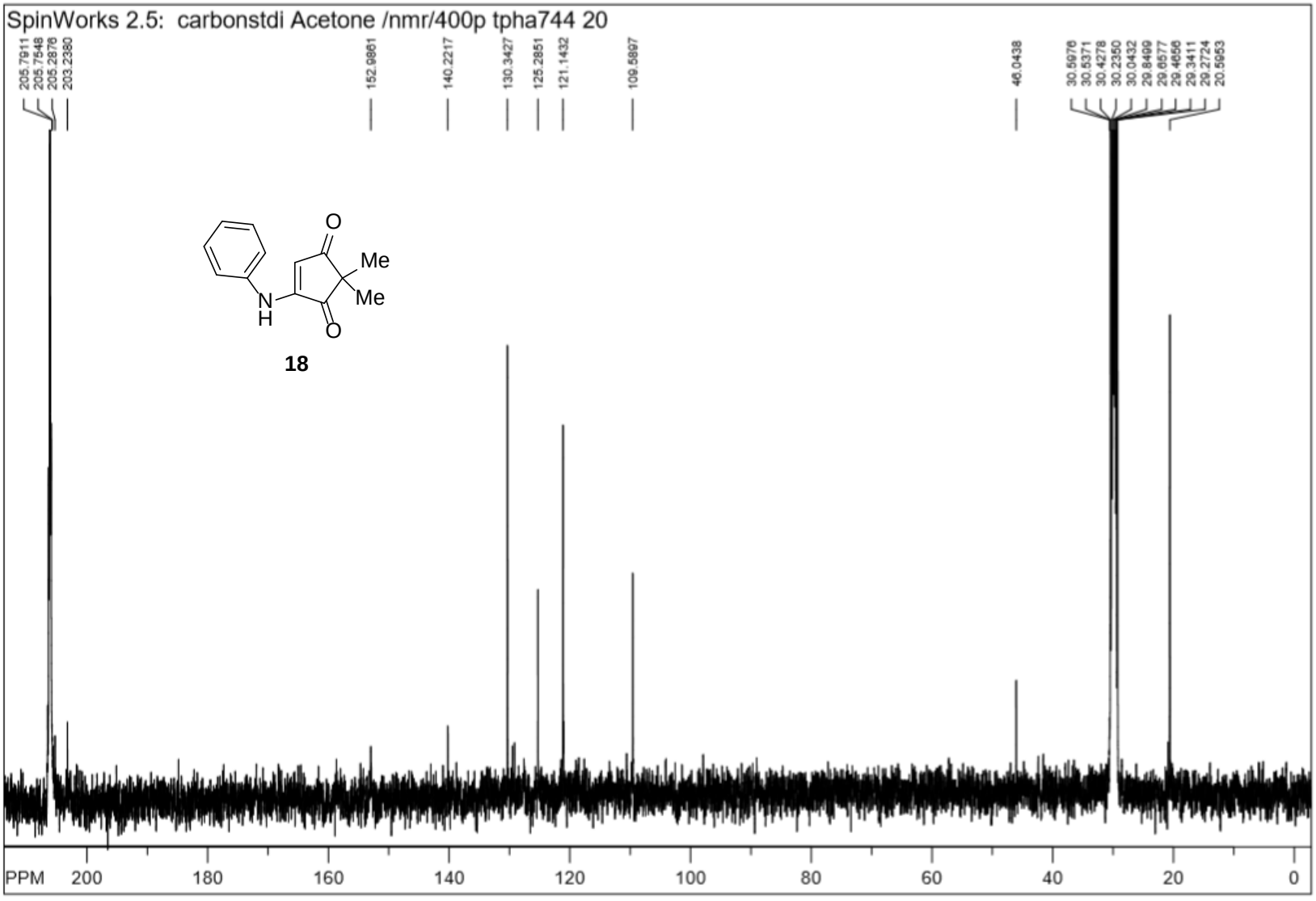
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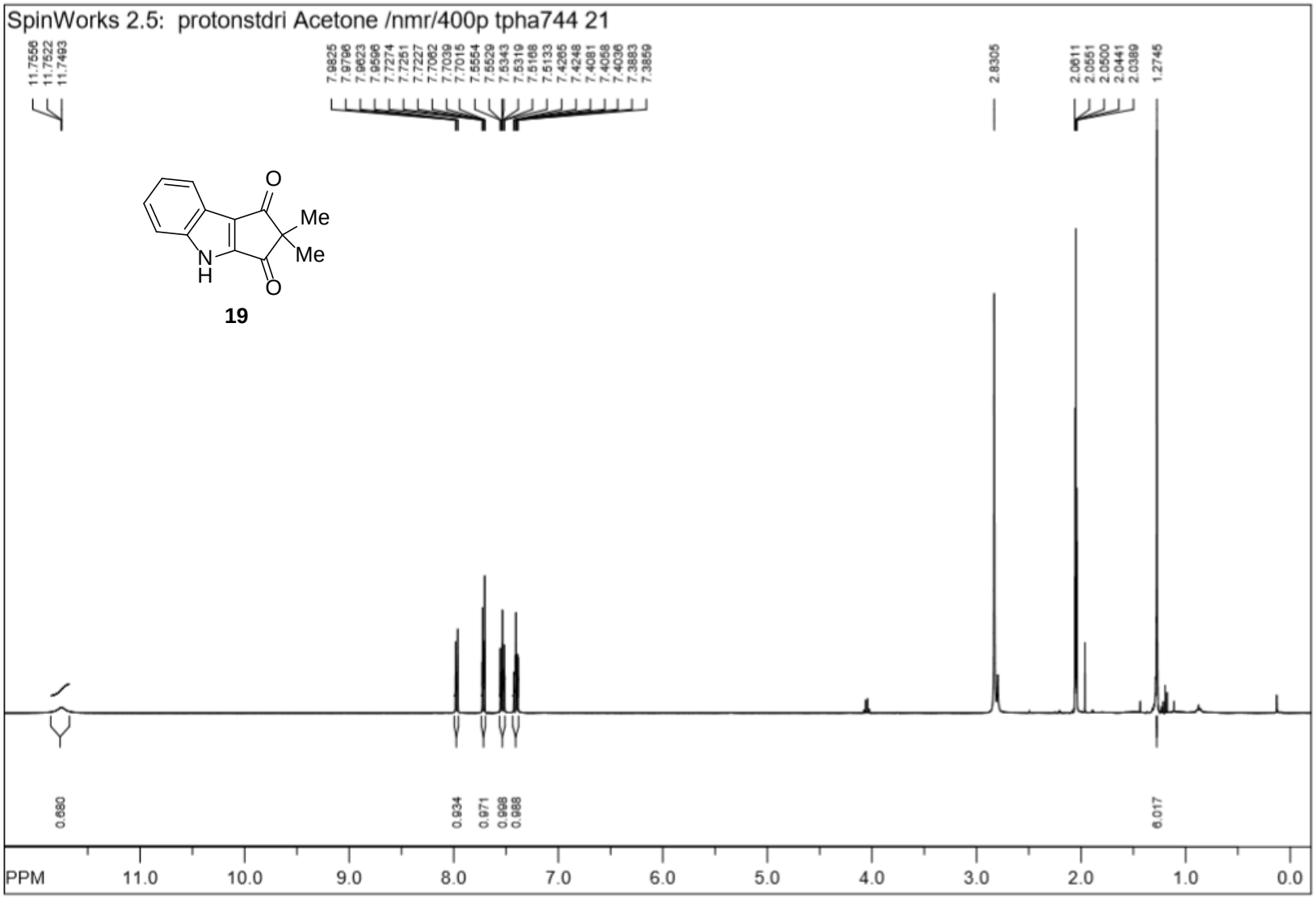
18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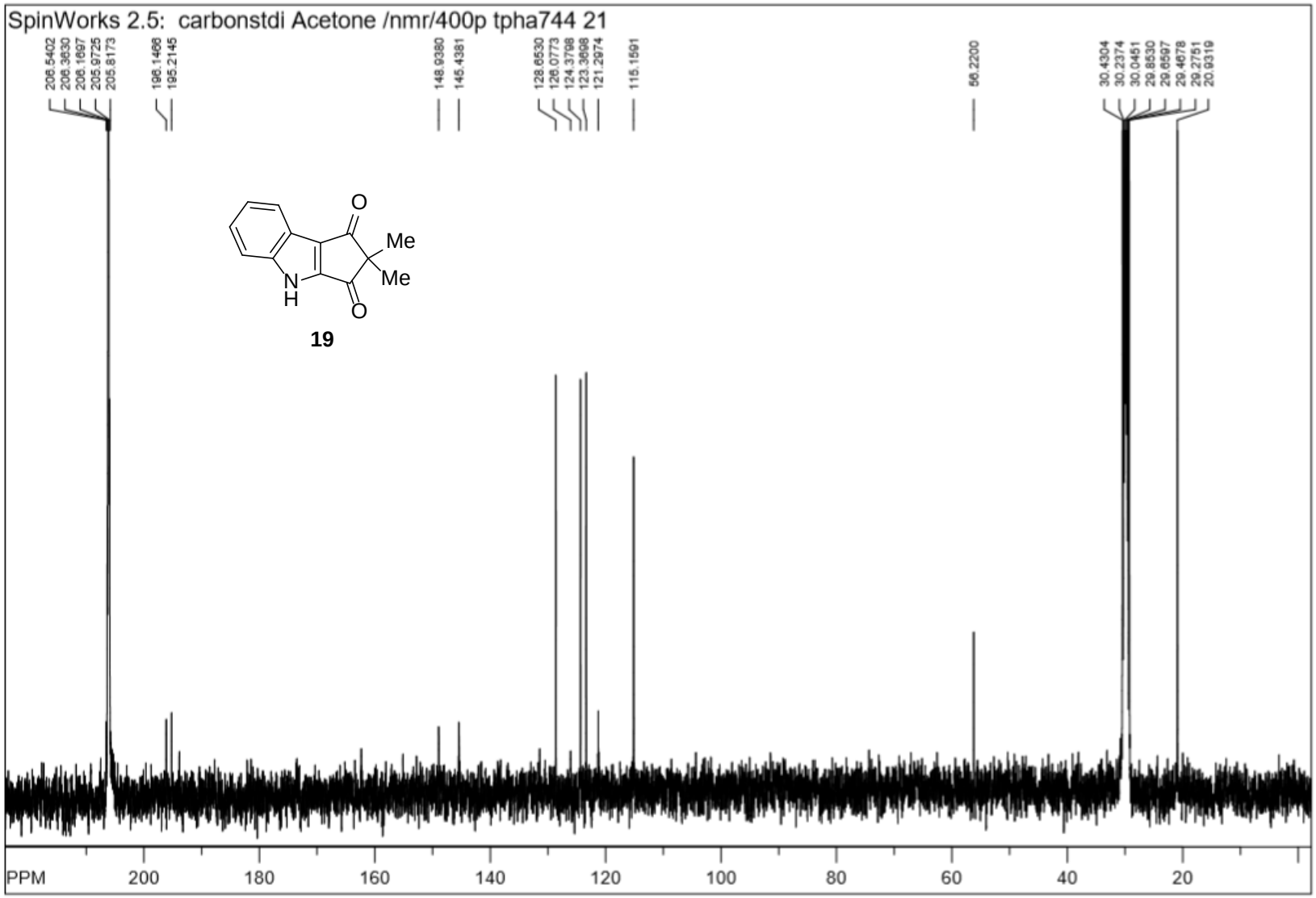
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20.9319
O
Me
Me
N
H
O
PPM
200
180
160
140
120
100
80
60
40
20

19

Crystal structure of **14**. Dashed lines show the intermolecular hydrogen bonding between the different molecules in the (bc) plane.

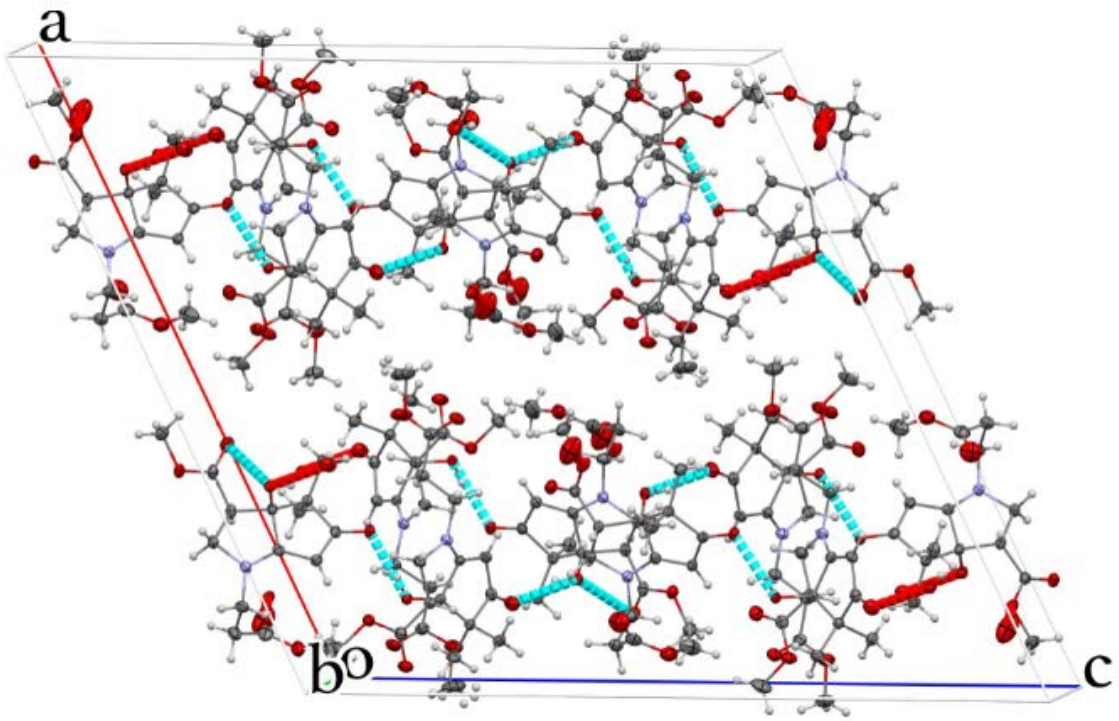

Table S1. X-ray diffraction data for compounds **3**, **9, 10** and **14**.

	3	**9**	**10**	**14**
CCDC	1975785	1975789	1975882	1975883
Formula	$C_8H_{11}NO_3$	$C_{14}H_{13}NO_5$	$C_{10}H_{11}NO_2$	$C_{15}H_{21}NO_6$
Formula weight (g mol^{-1})	169.18	275.25	177.20	311.33
Temperature (K)	106(7)	107(5)	107(4)	103(2)
Crystal size (mm)	0.14 × 0.14 × 0.05	0.12 × 0.12 × 0.10	0.18 × 0.13 × 0.11	0.12 × 0.10 × 0.05
Crystal system	orthorhombic	Orthorhombic	monoclinic	monoclinic
Space group	*Pbca*	$P2_12_12_1$	$P2_1/m$	$P2_1/n$
Unit cell dimensions	*a* = 11.7246(3) Å	*a* = 7.19640(10) Å	*a* = 7.1931(3) Å	*a* = 24.7484(3) Å
	b = 8.3285(2) Å	*b* = 11.9878(3) Å	*b* = 7.0581(4) Å	*b* = 10.7060(1) Å
	c = 16.9656(5) Å	*c* = 14.7510(3) Å	*c* = 8.4454(4) Å	*c* = 26.2577(3) Å
			β = 92.515(4)°	β = 115.723(1)°
Volume (Å^3)	1656.66(8)	1272.55(4)	428.35(3)	6267.71(13)
Z	8	4	2	16
Density$_{calcd}$ (mg m^{-3})	1.357	1.437	1.374	1.320
μ (mm^{-1})	0.875	0.930	0.788	0.858
***F*(000)**	720.0	576.0	188.0	2656.0
Radiation (wavelength, Å)	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)	CuKα (λ = 1.54184)
2Θ range (deg)	12.882 to 135.39	13.692 to 135.476	12.316 to 135.47	11.148 to 135.476
***h* range**	-14 to 11	-8 to 8	-8 to 8	-29 to 29
***k* range**	-7 to 9	-14 to 14	-8 to 8	-12 to 12
***l* range**	-20 to 19	-17 to 17	-10 to 10	-31 to 31
Reflections collected / unique	5662 / 1491	7454 / 2314	4192 / 847	80297 / 11351
R_{int}/R_{sigma}	0.0320/0.0295	0.0325/0.0315	0.0471/0.0354	0.0430/0.0258
Restraints / parameters	0 / 119	0 / 192	11 / 142	2 / 821
Goodness-of-fit	1.063	1.048	1.062	1.028
Final *R* indices [$I > 2\sigma(I)$]	R_1 = 0.0375, wR_2 = 0.0945	R_1 = 0.0277, wR_2 = 0.0719	R_1 = 0.0331, wR_2 = 0.0886	R_1 = 0.0428, wR_2 = 0.1120
***R* indices (all data)**	R_1 = 0.0425, wR_2 = 0.0977	R_1 = 0.0290, wR_2 = 0.0727	R_1 = 0.0365, wR_2 = 0.0915	R_1 = 0.0489, wR_2 = 0.1162
Largest diff. peak/hole eÅ^{-3}	0.21/-0.21	0.21/-0.16	0.23/-0.15	0.36/-0.22
Flack parameter	-	-0.02(9)	-	-