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Supporting Information for:

A one-pot, reductive amination/6-*endo-trig* cyclisation for the stereoselective synthesis of 6-substituted-4-oxopipecolic acids

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1. General Experimental

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a PureSolv 500 MD solvent purification system. All reactions were performed under an atmosphere of argon unless otherwise mentioned. Flash column chromatography was carried out using Fisher matrix silica 60. Macherey-Nagel aluminium-backed plates pre-coated with silica gel 60 (UV_{254}) were used for thin layer chromatography and were visualised by staining with $KMnO_4$. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX 400 spectrometer with chemical shift values in ppm relative to TMS (δ_H 0.00 and δ_C 0.0) or residual chloroform (δ_H 7.28 and δ_C 77.2) as standard. Proton and carbon assignments are based on two-dimensional COSY and DEPT experiments, respectively. Mass spectra were obtained using a JEOL JMS-700 spectrometer. Infrared spectra were obtained neat using a Shimadzu IRPrestige-21 spectrometer. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using an Autopol V polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. Melting points were determined on a Reichert platform melting point apparatus.

2. Experimental Procedures and Spectroscopic Data for All Compounds

Dimethyl (2*S*)-2-aminobutandioate hydrochloride[1]

To a suspension of L-aspartic acid (**4**) (5.0 g, 38 mmol) in methanol (100 mL) at 0 °C under argon was added dropwise thionyl chloride (3.8 mL, 53 mmol). The reaction mixture was allowed to warm to room temperature and then heated under reflux for 3 h. The solution was allowed to cool to room temperature and then concentrated *in vacuo*, azeotroping with toluene–dichloromethane to give dimethyl (2*S*)-2-aminobutandioate hydrochloride as a white solid (7.4 g, 100%). Mp 115–116 °C (lit.,[1] mp 114–115 °C); $[\alpha]_D^{24}$ +22.0 (*c* 1.0, MeOH); δ_H (400 MHz, DMSO-d_6) 2.99 (1H, dd, *J* 18.0, 5.5 Hz, 3-*H*H), 3.05 (1H, dd, *J* 18.0, 5.5 Hz, 3-H*H*), 3.66 (3H, s, OMe), 3.74 (3H, s, OMe), 4.35 (1H, t, *J* 5.5 Hz, 2-H), 8.72 (3H, s, CHNH_3^+); δ_C (100 MHz, DMSO-d_6) 34.0 (CH_2), 48.4 (CH), 52.2 (CH_3), 53.0 (CH_3), 168.7 (C), 169.6 (C); *m/z* (CI) 162 (MH^+, 100%), 148 (5), 102 (20).

Dimethyl (2*S*)-2-(tritylamino)butandioate (5)[2]

To a solution of dimethyl (2*S*)-2-aminobutandioate hydrochloride (7.4 g, 38 mmol) in dichloromethane (300 mL) at 0 °C under argon was added dropwise triethylamine (11 mL, 76 mmol) followed by triphenylmethyl chloride (13 g, 45 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 6 h. The mixture was diluted with dichloromethane (50 mL), washed with citric acid (2.0 M, 300 mL), water (300 mL), brine (300 mL), dried ($MgSO_4$),

and then concentrated *in vacuo* to give a colourless oil. The crude product was purified by column chromatography on silica eluting with 20% diethyl ether in petroleum ether to give dimethyl (2*S*)-2-(tritylamino)butandioate (**5**) as a white solid (15 g, 100%). Mp 71–72 °C (lit.,[2] mp 70–71 °C); $[\alpha]_D^{24}$ +36.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.51 (1H, dd, *J* 14.7, 7.0 Hz, 3-*H*H), 2.66 (1H, dd, *J* 14.7, 5.4 Hz, 3-H*H*), 2.93 (1H, d, *J* 10.1 Hz, NH), 3.25 (3H, s, OMe), 3.67 (3H, s, OMe), 3.68–3.73 (1H, m, 2-H), 7.15–7.20 (3H, m, ArH), 7.23–7.28 (6H, m, ArH), 7.46–7.51 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 39.0 (CH_2), 50.5 (CH), 50.7 (CH_3), 52.4 (CH_3), 69.9 (C), 125.2 (CH), 126.6 (CH), 127.5 (CH), 144.4 (C), 169.7 (C), 172.6 (C); *m/z* (EI) 403 (M^+, 1%), 326 (35), 243 (100), 165 (30), 83 (70).

Methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate (6)[2]

A solution of dimethyl methylphosphonate (3.5 mL, 33 mmol) in THF (40 mL) was cooled to −78 °C under argon. *n*-Butyl lithium (2.5 M in hexane, 14 mL, 34 mmol) was added dropwise and the reaction mixture was stirred for 0.75 h. In a separate reaction vessel, a solution of dimethyl (2*S*)-2-(tritylamino)butandioate (**5**) (6.0 g, 15 mmol) in THF (100 mL) was cooled to −78 °C under argon and the dimethyl methylphosphonate/*n*-butyl lithium solution was transferred *via* cannula into the flask and the reaction mixture stirred at −78 °C for 3 h to give a yellow solution. The reaction was quenched with a saturated solution of ammonium chloride (2.0 mL) and allowed to warm to room temperature. The mixture was concentrated *in vacuo*. The resulting residue was diluted with ethyl acetate (250 mL), washed with water (250 mL), brine (250 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 80% ethyl acetate in petroleum ether to give methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate (**6**) as a white solid (6.2 g, 84%). Mp 117–118 °C (lit.,[2] mp 117–119 °C); $[\alpha]_D^{24}$ +31.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 16.7, 6.9 Hz, 3-*H*H), 2.85–2.95 (2H, m, 3-H*H* and NH), 3.06 (2H, d, $J_{H–C–P}$ 22.7 Hz, 5-H_2), 3.29 (3H, s, OMe), 3.65–3.73 (1H, m, 2-H), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 7.15–7.21 (3H, m, ArH), 7.26 (6H, t, *J* 7.7 Hz, ArH), 7.47 (6H, d, *J* 7.7 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 41.8 (d, $J_{C–P}$ 128 Hz, CH_2), 48.7 (CH_2), 52.0 (CH_3), 52.9 (CH_3), 53.0 (CH_3), 53.1 (CH), 71.2 (C), 126.5 (CH), 127.9 (CH), 128.7 (CH), 145.6 (C), 174.0 (C), 199.2 (C); *m/z* (CI) 496 (MH^+, 1%), 301 (5), 254 (90), 243 (100), 237 (55), 167 (45).

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General Procedure: Synthesis of enone derived α-amino acid derivatives using a Horner-Wadsworth-Emmons reaction

Methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate (**6**) (0.40 mmol) was dissolved in acetonitrile (4.0 mL) at room temperature under argon. Anhydrous potassium carbonate (0.42 mmol) was added to the solution, and then an aldehyde (0.80 mmol) was added to the suspension and heated at 50 °C until the reaction was complete by TLC. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resultant residue was dissolved in ethyl acetate (30 mL) and washed with water (30 mL), brine (30 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 20–40% diethyl ether in petroleum ether.

Methyl (2*S*,5*E*)-4-oxo-8-phenyl-2-(tritylamino)oct-5-enoate (7)[3]

Using the general procedure above with 3-phenylpropionaldehyde (0.16 mL, 1.2 mmol) gave methyl (2*S*,5*E*)-4-oxo-8-phenyl-2-(tritylamino)oct-5-enoate (**7**) after 2 days as a colourless oil (0.29 g, 93%). Spectroscopic data consistent with literature.[3] ν_{max}/cm^{-1} (NaCl) 3027 (NH), 2948 (CH), 1738 (CO), 1667 (C=C), 1626, 1492, 1448, 1205; $[\alpha]_D^{27}$ +26.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.50 (2H, q, *J* 7.1 Hz, 7-H_2), 2.63 (1H, dd, *J* 15.3, 7.0 Hz, 3-*H*H), 2.70–2.80 (3H, m, 3-H*H* and 8-H_2), 2.85 (1H, br s, NH), 3.25 (3H, s, OMe), 3.67–3.74 (1H, m, 2-H), 6.06 (1H, d, *J* 15.9 Hz, 5-H), 6.76 (1H, dt, *J* 15.9, 7.1 Hz, 6-H), 7.12–7.30 (14H, m, ArH), 7.45–7.50 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 32.4 (CH_2), 32.6 (CH_2), 43.2 (CH_2), 50.1 (CH), 51.9 (CH_3), 69.5 (C), 124.5 (CH), 125.0 (CH), 126.1 (CH), 126.6 (CH), 126.7 (CH), 127.0 (CH), 129.2 (CH), 138.9 (C), 144.0 (C), 145.3 (CH), 172.7 (C), 195.8 (C); *m/z* (FAB) 504.2534 (MH^+. $C_{34}H_{34}NO_3$ requires 504.2539), 426 (69%), 252 (78), 243 (100), 166 (78), 160 (38).

Methyl (2*S*,5*E*)-8-methyl-4-oxo-2-(tritylamino)non-5-enoate (8)

Using the general procedure above with 3-methylbutyraldehyde (0.22 mL, 2.0 mmol) gave methyl (2*S*,5*E*)-8-methyl-4-oxo-2-(tritylamino)non-5-enoate (**8**) as a colourless oil (0.26 g, 57%). ν_{max}/cm^{-1} (NaCl) 3320 (NH), 3058, 3021, 2954 (CH), 1739 (CO), 1669 (CO), 1626 (C=C), 1491, 1448, 1435, 1207, 1172; $[\alpha]_D^{18}$ +18.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.91 (6H, d, *J* 6.7 Hz, 8-CH_3 and 9-H_3), 1.69–1.80 (1H, m, 8-H), 2.08 (2H, td, *J* 7.4, 1.3 Hz, 7-H_2), 2.63 (1H, dd, *J* 15.4, 7.1 Hz, 3-*H*H), 2.78 (1H, dd, *J* 15.4, 5.2 Hz, 3-H*H*), 2.84 (1H, d, *J* 10.0 Hz, NH), 3.27 (3H, s, OMe), 3.62–3.78 (1H, m, 2-H), 6.02 (1H, dt, *J* 15.9, 1.3 Hz, 5-H), 6.71 (1H, dt, *J* 15.9, 7.4 Hz, 6-H), 7.11–7.32 (9H, m, ArH), 7.40–7.55 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.5 (CH_3), 27.9 (CH), 41.8 (CH_2), 44.9

(CH_2), 52.0 (CH_3), 53.7 (CH), 71.3 (C), 126.6 (CH), 128.0 (CH), 128.9 (CH), 131.7 (CH), 145.9 (C), 147.5 (CH), 174.6 (C), 197.8 (C); *m/z* (FAB) 478.2359 (MNa^+. $C_{30}H_{33}NO_3Na$ requires 478.2358), 378 (12%), 243 (100), 213 (8), 166 (17), 134 (1), 113 (4), 75 (11).

Methyl (2*S*,5*E*)-4-oxo-2-(tritylamino)hept-5-enoate (9)

To a solution of methyl (2*S*)-5-(dimethoxyphosphoryl)-4-oxo-2-(tritylamino)pentanoate (**6**) (1.0 g, 2.0 mmol) in acetonitrile (20 mL) at room temperature under argon in a Schlenk tube was added anhydrous potassium carbonate (0.29 g, 2.1 mmol) and acetaldehyde (0.34 mL, 6.1 mmol). The sealed tube was heated to 40 °C and stirred for 4 days. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (60 mL), washed with water (60 mL), brine (60 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 15% diethyl ether in petroleum ether to give methyl (2*S*,5*E*)-4-oxo-2-(tritylamino)hept-5-enoate (**9**) as a colourless oil (0.65 g, 78%). ν_{max}/cm^{-1} (neat) 3320 (NH), 2963 (CH), 2360, 1735 (CO), 1668 (CO), 1629 (C=C), 1490, 1448, 1435, 1215, 1172; $[\alpha]_D^{25}$ +17.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.89 (3H, dd, *J* 6.8, 1.6 Hz, 7-H_3), 2.66 (1H, dd, *J* 15.4, 6.1 Hz, 3-*H*H), 2.79 (1H, dd, *J* 15.4, 6.1 Hz, 3-H*H*), 2.85 (1H, d, *J* 10.0 Hz, NH), 3.26 (3H, s, OMe), 3.63–3.79 (1H, m, 2-H), 6.07 (1H, dq, *J* 15.8, 1.6 Hz, 5-H), 6.77 (1H, dq, *J* 15.8, 6.8 Hz, 6-H), 7.10–7.34 (9H, m, ArH), 7.40–7.54 (6H, m, ArH); δ_C (100 MHz, $CDCl_3$) 18.4 (CH_3), 45.0 (CH_2), 52.0 (CH_3), 53.6 (CH), 71.2 (C), 126.5 (CH), 128.1 (CH), 128.8 (CH), 132.2 (CH), 143.7 (CH), 145.8 (C), 174.6 (C), 197.5 (C); *m/z* (FAB) 414.2068 (MH^+. $C_{27}H_{28}NO_3$ requires 414.2069), 336 (22%), 243 (100), 170 (32), 165 (14), 104 (1), 70 (10).

Methyl (2*S*,5*E*)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate (10)[3]

Using the general procedure above with benzaldehyde (0.50 g, 1.0 mmol) gave methyl (2*S*,5*E*)-4-oxo-6-phenyl-2-(tritylamino)hex-5-enoate (**10**) after 36 h as a yellow oil (0.46 g, 95%). Spectroscopic data consistent with literature.[3] ν_{max}/cm^{-1} (NaCl) 3023 (NH), 2950 (CH), 1737 (CO), 1657 (C=C), 1608, 1205; $[\alpha]_D^{25}$ +111.0 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.80 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.88–2.97 (2H, m, 3-H*H* and NH), 3.28 (3H, s, OMe), 3.79–3.89 (1H, m, 2-H), 6.69 (1H, d, *J* 16.2 Hz, 5-H), 7.14–7.29 (10H, m, ArH and 6-H), 7.37–7.41 (3H, m, ArH), 7.44–7.53 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 43.6 (CH_2), 50.0 (CH), 51.7 (CH_3), 69.2 (C), 124.5 (CH), 125.7 (CH), 126.1 (CH), 126.3 (CH), 127.4 (CH), 127.8 (CH), 128.6 (CH), 133.0 (C), 141.3 (C), 143.7 (CH), 172.4 (C), 195.5 (C); *m/z* (FAB) 476.2231 (MH^+. $C_{32}H_{30}NO_3$ requires 476.2226), 398 (15%), 259 (6), 243 (100), 232 (25), 166 (23), 132 (24).

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Methyl (2*S*,5*E*)-6-(4'-methoxyphenyl)-4-oxo-2-(tritylamino)hex-5-enoate (11)

Using the general procedure above with 4-methoxybenzaldehyde (0.25 g, 2.0 mmol) gave methyl (2*S*,5*E*)-6-(4'-methoxyphenyl)-4-oxo-2-(tritylamino)hex-5-enoate (**11**) as a colourless oil (0.32 g, 66%). ν_{max}/cm^{-1} (neat) 3320 (NH), 3057, 3021 (ArH), 2951 (CH), 1736 (CO), 1653 (CO), 1595 (C=C), 1510, 1447, 1252, 1171, 1028; $[\alpha]_D^{23}$ +54.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.78 (1H, dd, *J* 15.0, 7.0 Hz, 3-*H*H), 2.84–2.99 (2H, m, 3-H*H* and NH), 3.27 (3H, s, OMe), 3.71–3.93 (4H, m, 2-H and OMe), 6.59 (1H, d, *J* 16.1 Hz, 5-H), 6.92 (2H, d, *J* 8.7 Hz, ArH), 7.11–7.35 (9H, m, ArH), 7.39–7.59 (9H, m, 6-H and ArH); δ_C (100 MHz, $CDCl_3$) 45.7 (CH_2), 52.0 (CH_3), 54.0 (CH), 55.4 (CH_3), 71.3 (C), 114.5 (CH), 124.3 (CH), 126.6 (CH), 127.1 (C), 128.0 (CH), 128.9 (CH), 130.2 (CH), 143.2 (CH), 145.9 (C), 161.8 (C), 174.6 (C), 197.5 (C); *m/z* (FAB) 506.2329 (MH^+.$C_{33}H_{32}NO_4$ requires 506.2331), 428 (5%), 262 (11), 243 (100), 162 (18), 86 (5).

Methyl (2*S*,5*E*)-6-(4'-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate (12)[3]

Using the general procedure above with 4-bromobenzaldehyde (0.37 g, 2.0 mmol) gave methyl (2*S*,5*E*)-6-(4'-bromophenyl)-4-oxo-2-(tritylamino)hex-5-enoate (**12**) after 2 days as a white solid (0.54 g, 96%). Spectroscopic data consistent with literature.[3] Mp 134–135 °C; ν_{max}/cm^{-1} (NaCl) 3021 (NH), 2950 (CH), 1737 (CO), 1659 (C=C), 1608, 1488; $[\alpha]_D^{27}$ +64.6 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.77 (1H, dd, *J* 15.2, 7.0 Hz, 3-*H*H), 2.86–2.95 (2H, m, 3-H*H* and NH), 3.29 (3H, s, OMe), 3.75–3.83 (1H, m, 2-H), 6.66 (1H, d, *J* 16.2 Hz, 5-H), 7.14–7.21 (3H, m, ArH), 7.22–7.27 (7H, m, ArH and 6-H), 7.37–7.43 (2H, m, ArH), 7.46–7.57 (8H, m, ArH); δ_C (100 MHz, $CDCl_3$) 45.8 (CH_2), 51.9 (CH_3), 53.7 (CH), 71.2 (C), 124.9 (C), 126.2 (CH), 126.5 (CH), 127.9 (CH), 129.0 (CH), 129.7 (CH), 132.2 (CH), 133.3 (C), 141.7 (C), 145.7 (CH), 174.3 (C), 197.2 (C); *m/z* (FAB) 554.1332 (MH^+. $C_{32}H_{29}{}^{79}BrNO_3$ requires 554.1331), 478 (16%), 378 (3), 312 (13), 243 (100), 209 (16), 166 (43).

Methyl (2*S*,5*E*)-6-(3'-nitrobiphen-4-yl)-4-oxo-2-(tritylamino)hex-5-enoate (13)[3]

Using the general procedure above with 4-(3'-nitrophenyl)benzaldehyde (0.37 g, 1.7 mmol) gave methyl (2*S*,5*E*)-6-(3'-nitrobiphen-4-yl)-4-oxo-2-(tritylamino)hex-5-enoate (**13**) after 3 days as an off-white foam (0.19 g, 59%). Spectroscopic data consistent with literature.[3] ν_{max}/cm^{-1} (neat) 3030 (NH), 1736 (CO), 1657 (C=C), 1603, 1530, 1514, 1348; $[\alpha]_D^{23}$ +61.7 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.82 (1H, dd, *J* 15.2, 6.9 Hz, 3-*H*H), 2.90–3.02 (2H, m, 3-H*H* and NH), 3.30 (3H, s, OMe), 3.77–3.88 (1H, m, 2-H), 6.75 (1H, d, *J* 16.2 Hz, 5-H), 7.12–7.32 (9H, m, ArH), 7.45–7.73 (12H, m, ArH and 6-H), 7.93 (1H, d, *J* 7.9 Hz, ArH), 8.23 (1H, d, *J* 7.9 Hz, ArH), 8.48 (1H, s, ArH); δ_C (100

MHz, $CDCl_3$) 45.9 (CH_2), 52.1 (CH_3), 53.8 (CH), 71.3 (C), 121.9 (CH), 122.7 (CH), 126.6 (CH), 127.0 (CH), 127.7 (CH), 128.0 (CH), 128.9 (CH), 129.2 (CH), 130.0 (CH), 132.9 (CH), 134.7 (C), 140.6 (C), 141.7 (C), 142.2 (CH), 145.8 (C), 148.8 (C), 174.5 (C), 197.4 (C); *m/z* (FAB) 597.2384 (MH^+. $C_{38}H_{33}N_2O_5$ requires 597.2389), 519 (23%), 419 (5), 353 (32), 243 (100), 194 (9), 166 (54).

General Procedure: Synthesis of 6-substituted-4-oxo-L-pipecolic acids

To a solution of the trityl protected enone (2.5 mmol) in dichloromethane (25 mL) at room temperature under argon was added trifluoroacetic acid (25 mmol) and the reaction mixture was stirred for 2 h, and then concentrated *in vacuo*. The residue was dissolved in water (50 mL) and washed with diethyl ether (2 × 50 mL). The aqueous layer was concentrated *in vacuo*, azeotroping with ethyl acetate–chloroform to give the TFA salts. These were dissolved in tetrahydrofuran (25 mL) at room temperature under argon. To the solution was added 4Å molecular sieves, triethylamine (2.5 mmol) and benzaldehyde (2.5 mmol) and the mixture was stirred for 2 h. The reaction mixture was filtered and then concentrated *in vacuo*. The residue was dissolved in methanol (30 mL) at room temperature under argon and sodium cyanoborohydride (2.5 mmol) was added to the solution and allowed to stir for 1 h. The reaction mixture was quenched with a saturated sodium hydrogen carbonate solution (1.0 mL), and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (100 mL), then washed with a saturated sodium hydrogen carbonate solution (100 mL), brine (100 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 20%–25% diethyl ether in petroleum ether.

Methyl (2*S*,6*R*)-1-benzyl-4-oxo-6-phenethylpiperidine-2-carboxylate (16)

Using the general procedure above gave methyl (2*S*,6*R*)-1-benzyl-4-oxo-6-phenethylpiperidine-2-carboxylate (**16**) as a colourless oil (0.050 g, 53%). ν_{max}/cm^{-1} (neat) 3026 (ArH), 2963 (CH), 1731 (CO), 1715 (CO), 1496, 1453, 1437, 1216, 1171; $[\alpha]_D^{26}$ −31.5 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.68–1.86 (1H, m, 7-*H*H), 1.89–2.07 (1H, m, 7-H*H*), 2.37 (1H, dd, *J* 14.8, 7.4 Hz, 5-*H*H), 2.48–2.79 (5H, m, 3-H_2, 5-H*H* and 8-H_2), 3.25–3.39 (1H, m, 6-H), 3.70 (3H, s, OMe), 3.82 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.87 (1H, t, *J* 5.2 Hz, 2-H), 3.93 (1H, d, *J* 13.8 Hz, 1'-H*H*), 7.09–7.49 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 29.0 (CH_2), 32.4 (CH_2), 38.4 (CH_2), 41.5 (CH_2), 49.7 (CH), 49.9 (CH_2), 53.6 (CH_3), 56.8 (CH), 123.7 (CH), 125.1 (CH), 126.0 (CH), 126.2 (CH), 126.3 (CH), 136.2 (C), 139.3 (C), 169.8 (C), 205.0 (C); *m/z* (FAB) 352.1915 (MH^+. $C_{22}H_{26}NO_3$ requires 352.1913), 292 (77%), 260 (6), 246 (40), 218 (1), 178 (3), 158(2), 132 (4), 117 (6), 91 (93), 69 (5), 55 (5), 43 (4), 41 (4).

Methyl (2*S*,6*R*)-1-benzyl-6-*iso*-butyl-4-oxopiperidine-2-carboxylate (17)

Using the general procedure above gave methyl (2*S*,6*R*)-1-benzyl-6-*iso*-butyl-4-oxopiperidine-2-carboxylate (**17**) as a colourless oil (0.072 g, 50%). ν_{max}/cm^{-1} (neat) 2955 (CH), 2353, 1728 (CO), 1458, 1366, 1165, 1026; $[\alpha]_D^{23}$ −37.4 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.84 (3H, d, *J* 6.6 Hz, 8-CH_3), 0.85 (3H, d, *J* 6.6 Hz, 9-H_3), 1.08–1.34 (1H, m, 8-H), 1.49–1.82 (2H, m, 7-H_2), 2.23 (1H, ddd, *J* 14.8, 7.5, 1.3 Hz, 5-*H*H), 2.46–2.58 (2H, m, 3-*H*H and 5-H*H*), 2.64 (1H, ddd, *J* 15.2, 5.4, 1.3 Hz, 3-H*H*), 3.22–3.33 (1H, m, 6-H), 3.69 (3H, s, OMe), 3.78 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.82–3.90 (2H, m, 1'-H*H* and 2-H), 7.21–7.45 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.4 (CH_3), 22.7 (CH), 24.4 (CH_3), 39.9 (CH_2), 41.9 (CH_2), 43.8 (CH_2), 51.5 (CH_2), 52.1 (CH_3), 54.7 (CH), 59.4 (CH), 127.4 (CH), 128.5 (CH), 128.5 (CH), 138.7 (C), 172.3 (C), 207.6 (C); *m/z* (FAB) 304.1914 (MH^+. $C_{18}H_{26}NO_3$ requires 304.1913), 326 (30%), 244 (90), 241 (2), 202 (2), 170 (3), 132 (3), 117 (3), 91 (98), 70 (5).

Methyl (2*S*,6*R*)-1-benzyl-6-methyl-4-oxopiperidine-2-carboxylate (18)

Using the general procedure above gave methyl (2*S*,6*R*)-1-benzyl-6-methyl-4-oxopiperidine-2-carboxylate (**18**) as a colourless oil (0.22 g, 53%). ν_{max}/cm^{-1} (neat) 2966 (CH), 2954 , 2357, 1726 (CO), 1435, 1195, 1165; $[\alpha]_D^{25}$ −107.4 (*c* 0.7, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.21 (3H, d, *J* 6.3 Hz, 7-H_3), 2.23 (1H, dd, *J* 15.0, 8.7, Hz, 5-*H*H), 2.45–2.59 (3H, m, 3-H_2 and 5-H*H*), 3.25–3.43 (1H, m, 6-H), 3.62 (1H, d, *J* 13.7 Hz, 1'-*H*H), 3.71 (3H, s, OMe), 3.79 (1H, t, *J* 4.9 Hz, 2-H), 4.08 (1H, d, *J* 13.7 Hz, 1'-H*H*), 7.17–7.50 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 20.3 (CH_3), 42.7 (CH_2), 48.3 (CH_2), 51.7 (CH), 51.8 (CH_3), 53.5 (CH_2), 59.3 (CH), 127.3 (CH), 128.5 (CH), 128.7 (CH), 138.9 (C), 172.0 (C), 207.3 (C); *m/z* (FAB) 262.1447 (MH^+. $C_{15}H_{20}NO_3$ requires 262.1443), 260 (66%), 246 (8), 202 (100), 184 (9), 170 (4), 160 (3), 114 (5), 92 (83), 70 (4).

Methyl (2*S*,6*S*)-1-benzyl-4-oxo-6-phenylpiperidine-2-carboxylate (19)

Using the general procedure above gave methyl (2*S*,6*S*)-1-benzyl-4-oxo-6-phenylpiperidine-2-carboxylate (**19**) as a colourless oil (0.14 g, 37%). ν_{max}/cm^{-1} (NaCl) 3030 (ArH), 2952 (CH), 1731 (CO), 1494, 1454, 1197, 1162; $[\alpha]_D^{22}$ −119.0 (*c* 0.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.51 (1H, dt, *J* 14.8, 2.2 Hz, 3-*H*H), 2.61 (1H, dd, *J* 14.9, 9.8 Hz, 5-*H*H), 2.70 (1H, ddd, *J* 14.9, 4.8, 2.2 Hz, 5-H*H*), 2.76 (1H, dd, *J* 14.8, 6.5 Hz, 3-H*H*), 3.25 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.74–3.80 (4H, m, OMe and 1'-H*H*), 3.92 (1H, dd, *J* 6.5, 2.2 Hz, 2-H), 4.40 (1H, dd, *J* 9.8, 4.8 Hz, 6-H), 7.17–7.54 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 49.2 (CH_2), 51.6 (CH_3), 54.2 (CH_2), 58.6 (CH), 62.7 (CH), 127.4 (CH), 127.4 (CH), 128.0 (CH), 128.4 (CH), 128.6 (CH), 129.1 (CH), 138.3 (C), 142.9 (C),

172.0 (C), 206.0 (C); *m/z* (EI) 323.1519 (M^+. $C_{20}H_{21}NO_3$ requires 323.1521), 294 (3%), 264 (100), 232 (5), 161 (6), 131 (85), 103 (18), 91 (100), 83 (21), 65 (8).

Methyl (2*S*,6*S*)-1-benzyl-6-(4'-methoxyphenyl)-4-oxopiperidine-2-carboxylate (20)

Using the general procedure above gave methyl (2*S*,6*S*)-1-benzyl-6-(4'-methoxyphenyl)-4-oxopiperidine-2-carboxylate (**20**) as a yellow oil (0.060 g, 34%). ν_{max}/cm^{-1} (NaCl) 3030 (ArH), 2953 (CH), 1731 (CO), 1611, 1512, 1246, 1197, 1162; $[\alpha]_D^{22}$ −57.0 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.42 (1H, dt, *J* 14.9, 2.2 Hz, 3-*H*H), 2.52 (1H, dd, *J* 15.2, 9.6 Hz, 5-*H*H), 2.60 (1H, ddd, *J* 15.2, 4.7, 2.2 Hz, 5-H*H*), 2.67 (1H, dd, *J* 14.9, 6.7 Hz, 3-H*H*), 3.17 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.66–3.79 (7H, m, 1'-H*H* and 2 × OMe), 3.84 (1H, dd, *J* 6.7, 2.2 Hz, 2-H), 4.27 (1H, dd, *J* 9.6, 4.7 Hz, 6-H), 6.84 (2H, d, *J* 8.7 Hz, ArH), 7.12–7.28 (5H, m, ArH), 7.33 (2H, d, *J* 8.7 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 49.3 (CH_2), 51.6 (CH_3), 54.0 (CH_2), 55.3 (CH), 58.6 (CH), 62.0 (CH_3), 114.4 (CH), 127.3 (CH), 128.4 (CH), 128.5 (CH), 128.6 (CH), 134.9 (C), 138.5 (C), 159.3 (C), 172.0 (C), 206.3 (C); *m/z* (EI) 353.1629 (M^+. $C_{21}H_{23}NO_4$ requires 353.1627), 352 (4%), 294 (99), 262 (35), 224 (16), 203 (6), 161 (99), 134 (72), 91 (99), 65 (27), 44 (5).

Methyl (2*S*,6*S*)-1-benzyl-6-(4'-bromophenyl)-4-oxopiperidine-2-carboxylate (21)

Using the general procedure above gave methyl (2*S*,6*S*)-1-benzyl-6-(4'-bromophenyl)-4-oxopiperidine-2-carboxylate (**21**) as a colourless oil (0.14 g, 40%). ν_{max}/cm^{-1} (NaCl) 3029 (ArH), 2952 (CH), 1732 (CO), 1486, 1354, 1329, 1197, 1162; $[\alpha]_D^{23}$ −54.3 (*c* 1.1, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.39–2.52 (2H, m, 3-*H*H and 5-*H*H), 2.61 (1H, ddd, *J* 15.4, 4.7, 2.3 Hz, 5-H*H*), 2.69 (1H, ddd, *J* 14.9, 6.6, 0.6 Hz, 3-H*H*), 3.20 (1H, d, *J* 13.8 Hz, 1'-*H*H), 3.67 (1H, d, *J* 13.8 Hz, 1'-H*H*), 3.71 (3H, s, OMe), 3.85 (1H, dd, *J* 6.6, 2.2 Hz, 2-H), 4.34 (1H, dd, *J* 9.6, 4.7 Hz, 6-H), 7.14–7.37 (7H, m, ArH), 7.42–7.50 (2H, m, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 48.9 (CH_2), 51.7 (CH_3), 54.3 (CH_2), 58.5 (CH), 62.1 (CH), 121.7 (C), 127.5 (CH), 128.5 (CH), 128.6 (CH), 129.1 (CH), 132.3 (CH), 138.0 (C), 142.1 (C), 172.0 (C), 205.5 (C); *m/z* (CI) 402.0706 (MH^+. $C_{20}H_{21}{}^{79}BrNO_3$ requires 402.0705), 344 (16%), 342 (17), 324 (12), 246 (1), 178 (2), 133 (1), 91 (5).

Methyl (2*S*,6*S*)-1-benzyl-6-(3'-nitrobiphen-4-yl)-4-oxopiperidine-2-carboxylate (22)

Using the general procedure above gave methyl (2*S*,6*S*)-1-benzyl-6-(3'-nitrobiphen-4-yl)-4-oxopiperidine-2-carboxylate (**22**) as a colourless oil (0.033 g, 29%). ν_{max}/cm^{-1} (NaCl) 3029 (ArH), 2953 (CH), 1730 (CO), 1531, 1514, 1350, 1198, 1163; $[\alpha]_D^{22}$ −46.8 (*c* 1.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 2.48 (1H, dt, *J* 15.0, 2.2 Hz, 3-*H*H), 2.56 (1H, dd, *J* 15.2, 9.6 Hz, 5-*H*H), 2.68 (1H, ddd, *J* 15.2, 4.7, 2.2 Hz, 5-H*H*), 2.74 (1H, dd, *J* 15.0, 6.6 Hz, 3-H*H*), 3.27 (1H, d, *J* 13.8 Hz, 1'-*H*H),

3.66–3.79 (4H, m, 1'-H*H* and OMe), 3.89 (1H, dd, *J* 6.6, 2.2 Hz, 2-H), 4.45 (1H, dd, *J* 9.6, 4.7 Hz, 6-H), 7.11–7.34 (5H, m, ArH), 7.41–7.68 (5H, m, ArH), 7.93 (1H, d, *J* 7.6 Hz, ArH), 8.12 (1H, dd, *J* 7.6, 1.4 Hz, ArH), 8.38 (1H, s, ArH); δ_C (100 MHz, $CDCl_3$) 42.9 (CH_2), 49.0 (CH_2), 51.7 (CH_3), 54.4 (CH_2), 58.6 (CH), 62.3 (CH), 121.9 (CH), 122.2 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 128.5 (CH), 128.6 (CH), 129.8 (CH), 132.9 (CH), 138.1 (C), 138.4 (C), 142.3 (C), 143.5 (C), 148.7 (C), 172.0 (C), 205.7 (C); *m/z* (CI) 445.1756 (MH^+. $C_{26}H_{25}N_2O_5$ requires 445.1763), 415 (98%), 355 (15), 325 (7), 322 (5), 246 (4), 178 (4), 151 (4), 108 (12), 69 (11).

General Procedure: Synthesis of 6-substituted-4-hydroxypipecolic acids

To a solution of 6-substituted-4-oxopipecolic acid (0.44 mmol) in methanol (5.0 mL) under argon at 0 °C was added sodium borohydride (0.44 mmol). The reaction mixture was allowed to warm gradually to room temperature and stirred for 16 h. The reaction mixture was quenched with hydrochloric acid (1.0 M, 0.1 mL), and then concentrated *in vacuo*. The residue was dissolved in dichloromethane (20 mL), then washed with a saturated sodium hydrogen carbonate solution (20 mL), brine (20 mL), dried ($MgSO_4$), and then concentrated *in vacuo*. The crude products were purified by column chromatography on silica eluting with 40–50% diethyl ether in petroleum ether.

Methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-phenethylpiperidine-2-carboxylate (23)

Using the general procedure above gave methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-phenethylpiperidine-2-carboxylate (**23**) as a colourless oil (0.13 g, 67%). ν_{max}/cm^{-1} (neat) 3399 (OH), 2949 (CH), 2360, 2343, 1730 (CO), 1496, 1452, 1216, 1162; $[\alpha]_D^{23}$ −32.1 (*c* 1.0, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.36 (1H, q, *J* 11.5 Hz, 5-*H*H), 1.50 (1H, br s, OH), 1.58 (1H, ddd, *J* 12.6, 11.6, 5.6 Hz, 3-*H*H), 1.66–1.79 (1H, m, 7-*H*H), 1.81–1.92 (2H, m, 5-H*H* and 7-H*H*), 2.08 (1H, ddt, *J* 12.6, 4.4, 2.4 Hz, 3-H*H*), 2.54–2.72 (2H, m, 8-H_2), 3.11–3.32 (1H, m, 6-H), 3.52 (1H, dd, *J* 5.6, 2.4 Hz, 2-H), 3.57 (3H, s, OMe), 3.63 (1H, d, *J* 14.2 Hz, 1'-*H*H), 3.68–3.83 (1H, m, 4-H), 3.89 (1H, d, *J* 14.2 Hz, 1'-H*H*), 6.99–7.33 (10H, m, ArH); δ_C (100 MHz, $CDCl_3$) 31.2 (CH_2), 34.1 (CH_2), 35.8 (CH_2), 38.5 (CH_2), 51.5 (CH_3), 51.5 (CH_2), 54.2 (CH), 58.8 (CH), 66.5 (CH), 125.8 (CH), 127.1 (CH), 128.3 (CH), 128.4 (CH), 128.5 (CH), 139.7 (C), 142.5 (C), 173.7 (C); *m/z* (FAB) 354.2070 (MH^+. $C_{22}H_{28}NO_3$ requires 354.2069), 352 (20%), 336 (12), 294 (46), 248 (27), 207 (3), 193 (3), 172 (2), 147 (4), 117 (6), 91 (100), 74 (20).

Methyl (2*S*,4*S*,6*R*)-1-benzyl-6-*iso*-butyl-4-hydroxypiperidine-2-carboxylate (24)

Using the general procedure above gave methyl (2*S*,4*S*,6*R*)-1-benzyl-6-*iso*-butyl-4-hydroxypiperidine-2-carboxylate (**24**) as a colourless oil (0.022 g, 80%). ν_{max}/cm^{-1} (neat) 3373

(OH), 2953 (CH), 2360, 2342, 1730 (CO), 1368, 1215, 1151; $[\alpha]_D^{23}$ −27.9 (*c* 0.9, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 0.82 (3H, d, *J* 6.6 Hz, 8-CH_3), 0.89 (3H, d, *J* 6.6 Hz, 9-H_3), 1.03–1.12 (1H, m, 7-*H*H), 1.22 (1H, q, *J* 11.6 Hz, 5-*H*H), 1.43 (1H, br s, OH), 1.49–1.62 (3H, m, 3-*H*H and 7-H*H*), 1.67–1.79 (2H, m, 5-H*H* and 8-H), 2.08 (1H, ddt, *J* 12.8, 4.4, 2.2 Hz, 3-H*H*), 3.00–3.15 (1H, m, 6-H), 3.51 (1H, dd, *J* 5.6, 2.2 Hz, 2-H), 3.61 (3H, s, OMe), 3.67 (1H, d, *J* 14.4 Hz, 1'-*H*H), 3.70–3.82 (2H, m, 1'-H*H* and 4-H), 7.10–7.35 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 22.6 (CH), 23.0 (CH_3), 24.6 (CH_3), 32.3 (CH_2), 38.0 (CH_2), 43.4 (CH_2), 50.4 (CH_2), 51.5 (CH_3), 52.8 (CH), 59.0 (CH), 66.8 (CH), 126.9 (CH), 128.2 (CH), 128.4 (CH), 140.0 (C), 173.8 (C); *m/z* (CI) 306.2071 (MH^+. $C_{18}H_{28}NO_3$ requires 306.2069), 288 (82%), 275 (4), 246 (13), 198 (3), 138 (2), 113 (4), 81 (12).

Methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-methylpiperidine-2-carboxylate (25)

Using the general procedure above gave methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-methylpiperidine-2-carboxylate (**25**) as a colourless oil (0.096 g, 83%). ν_{max}/cm^{-1} (neat) 3380 (OH), 2934 (CH), 1731 (CO), 1370, 1190, 1174, 1152, 1146; $[\alpha]_D^{25}$ −89.0 (*c* 0.3, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.16 (3H, d, *J* 6.2 Hz, 7-H_3), 1.29 (1H, q, *J* 11.4 Hz, 5-*H*H), 1.53 (1H, br s, OH), 1.62 (1H, td, *J* 12.2, 6.0 Hz, 3-*H*H), 1.94 (1H, dtd, *J* 11.4, 5.1, 2.0 Hz, 5-H*H*), 2.18 (1H, ddt, *J* 12.2, 4.4, 2.0 Hz, 3-H*H*), 3.37–3.48 (1H, m, 6-H), 3.53–3.62 (2H, m, 2-H and 1'-*H*H), 3.67 (3H, s, OMe), 3.71–3.82 (1H, m, 4-H), 4.11 (1H, d, *J* 14.2 Hz, 1'-H*H*), 7.16–7.39 (5H, m, ArH); δ_C (100 MHz, $CDCl_3$) 21.8 (CH_3), 36.6 (CH_2), 43.9 (CH_2), 51.2 (CH), 51.5 (CH_3), 53.5 (CH_2), 59.1 (CH), 66.1 (CH), 126.9 (CH), 128.3 (CH), 128.3 (CH), 140.3 (C), 173.8 (C); *m/z* (CI) 264.1597 (MH^+. $C_{15}H_{22}NO_3$ requires 264.1600), 246 (62%), 232 (5), 204 (10), 172 (3), 156 (1), 124 (2), 113 (4), 81 (11), 71 (12).

Methyl (2*S*,4*S*,6*S*)-1-benzyl-4-hydroxy-6-phenylpiperidine-2-carboxylate (26)

Using the general procedure above gave methyl (2*S*,4*S*,6*S*)-1-benzyl-4-hydroxy-6-phenylpiperidine-2-carboxylate (**26**) as a colourless oil (0.052 g, 80%). ν_{max}/cm^{-1} (neat) 3383 (OH), 2951 (CH), 2359, 1729 (CO), 1493, 1454, 1216, 1200, 1166, 1119; $[\alpha]_D^{20}$ −5.8 (*c* 0.2, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.42 (1H, d, *J* 5.2 Hz, OH), 1.63 (1H, q, *J* 11.6 Hz, 5-*H*H), 1.79 (1H, td, *J* 12.2, 6.0 Hz, 3-*H*H), 2.07–2.30 (2H, m, 3-H*H* and 5-H*H*), 3.34 (1H, d, *J* 14.1 Hz, 1'-*H*H), 3.63–3.77 (5H, m, 2-H, 1'-H*H* and OMe), 3.84–4.01 (1H, m, 4-H), 4.51 (1H, dd, *J* 11.6, 3.2 Hz, 6-H), 7.14–7.39 (8H, m, ArH), 7.51 (2H, d, *J* 7.2 Hz, ArH); δ_C (100 MHz, $CDCl_3$) 36.7 (CH_2), 45.2 (CH_2), 51.2 (CH_3), 54.0 (CH_2), 57.7 (CH), 61.1 (CH), 65.8 (CH), 126.9 (CH), 127.4 (CH), 127.6 (CH), 128.3 (CH), 128.4 (CH), 128.7 (CH), 139.2 (C), 144.2 (C), 173.8 (C); *m/z* (CI) 326.1748 (MH^+. $C_{20}H_{24}NO_3$ requires 326.1756), 309 (59%), 266 (18), 248 (5), 218 (3), 186 (3), 161 (3), 137 (5), 97 (6), 69 (20).

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Methyl (2*S*,4*S*,6*R*)-4-hydroxy-6-methylpiperidine-2-carboxylate

To a solution of methyl (2*S*,4*S*,6*R*)-1-benzyl-4-hydroxy-6-methylpiperidine-2-carboxylate (**25**) (0.032 g, 0.18 mmol) in *tert*-butanol (3.0 mL) at room temperature under argon was added palladium (10% wt.) on activated carbon (0.077 g, 0.072 mmol) and ammonium formate (0.058 g, 0.92 mmol). The reaction mixture was heated under reflux and stirred for 24 h. The mixture was allowed to cool to room temperature, then diluted with methanol (10 mL), filtered through celite® and then concentrated *in vacuo*. The crude product was purified by column chromatography on silica eluting with 6% methanol in dichloromethane to give methyl (2*S*,4*S*,6*R*)-4-hydroxy-6-methylpiperidine-2-carboxylate as a colourless oil (0.015 g, 48%). ν_{max}/cm^{-1} (neat) 3438 (OH/NH), 3020, 2939 (CH), 1730 (CO), 1437, 1215, 1176; $[\alpha]_D^{28}$ +12.4 (*c* 0.5, $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.05–1.16 (4H, m, 5-*H*H and 7-H_3), 1.62 (1H, td, *J* 12.5, 5.8 Hz, 3-*H*H), 1.73 (2H, br s, OH and NH), 1.90 (1H, dtd, *J* 11.9, 4.5, 2.4 Hz, 5-H*H*), 2.44 (1H, ddt, *J* 12.5, 4.5, 2.4 Hz, 3-H*H*), 2.83–2.94 (1H, m, 6-H), 3.62–3.77 (4H, m, 4-H and OMe), 3.82 (1H, dd, *J* 5.8, 2.4 Hz, 2-H); δ_C (100 MHz, $CDCl_3$) 22.7 (CH_3), 35.1 (CH_2), 43.1 (CH_2), 46.6 (CH), 52.0 (CH_3), 55.7 (CH), 66.5 (CH), 174.4 (C); *m/z* (CI) 174.1131 (MH^+. $C_8H_{16}NO_3$ requires 174.1130), 156 (30%), 133 (10), 113 (13), 85 (65), 69 (98).

(2*S*,4*S*,6*R*)-4-Hydroxy-6-methylpiperidine-2-carboxylic acid (27)

A solution of methyl (2*S*,4*S*,6*R*)-4-hydroxy-6-methylpiperidine-2-carboxylate (0.012 g, 0.069 mmol) in hydrochloric acid (6.0 M, 5.0 mL) was heated under reflux and for 24 h. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo*. The residual oil was triturated with acetone to give an off-white solid. The product was purified by recrystallisation from methanol to give (2*S*,4*S*,6*R*)-4-hydroxy-6-methylpiperidine-2-carboxylic acid (**27**) as a white solid (0.017 g, 100%). Mp 139–141 °C (decomposition); ν_{max}/cm^{-1} (neat) 3333 (OH/NH), 2945 (CH), 2360, 1653, 1457, 1448, 1260, 1118, 1105; $[\alpha]_D^{24}$ +27.0 (*c* 0.7, MeOH); δ_H (400 MHz, CD_3OD) 1.23–1.63 (4H, m, 5-*H*H and 7-H_3), 1.98 (1H, ddd, *J* 15.9, 10.5, 5.4 Hz, 3-*H*H), 2.22–2.31 (1H, m, 5-H*H*), 2.59–2.71 (1H, m, 3-H*H*), 3.77–3.85 (1H, m, 6-H), 3.91–3.99 (1H, m, 4-H), 4.60 (1H, dd, *J* 5.4, 3.9 Hz, 2-H); δ_C (100 MHz, CD_3OD) 19.0 (CH_3), 34.1 (CH_2), 39.7 (CH_2), 49.3 (CH), 50.4 (CH), 64.0 (CH), 170.6 (C); *m/z* (CI) 160.0980 (MH^+. $C_7H_{14}NO_3$ requires 160.0974), 142 (29%), 123 (5), 114 (19), 85 (34), 69 (50).

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3. References

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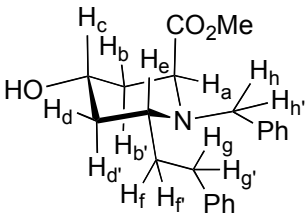
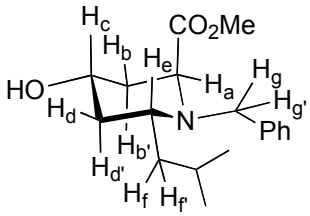
4. NOE Enhancements for 23, 24, 25 and 26



23

Saturation	% NOE
3.52 ppm (H_a)	1.4 (H_b)
	1.1 ($H_{b'}$)
	0.5 (H_h)
	0.5 ($H_{h'}$)
3.75 ppm (H_c)	1.6 (H_d)
	1.1 (H_b)
	1.2 (H_e)
3.21 ppm (H_e)	1.2 (H_f)
	2.6 (H_d/$H_{f'}$)
	1.0 (H_g)
	1.5 (H_c)



24

Saturation	% NOE
3.60 ppm (H_a)	1.2 ($H_{b'}$)
	0.9 (H_b)
	0.6 (H_g)
3.86 ppm (H_c)	0.7 (OH)
	1.1 (H_d)
	1.1 (H_b)
	0.9 (H_e)
3.17 ppm (H_e)	0.5 (CH_3)
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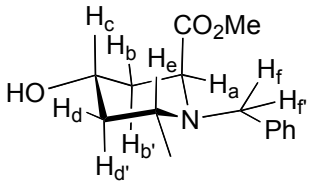
	1.0 (H_f)
	0.6 (H_d)
	0.3 (H_g)
	1.1 (H_c)



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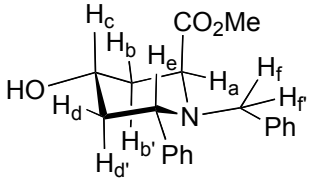
Saturation	% NOE
3.60 ppm (H_a)	0.7 ($H_{b'}$) 0.5 (H_b) 1.9 (H_f)
3.80 ppm (H_c)	0.4 (OH) 0.8 (H_d) 0.9 (H_b) 0.6 (H_e)
3.45 ppm (H_e)	1.1 (CH_3) 0.7 (H_d) 0.3 (H_f) 0.6 (H_c) 0.8 ($H_{f'}$)



26

Saturation	% NOE
3.71 ppm (H_a)	0.4 (H_b) 0.3 ($H_{b'}$) 1.7 (H_f)
3.96 ppm (H_c)	1.1 (OH) 1.2 (H_b) 1.2 (H_d) 1.1 (H_e)
4.53 ppm (H_e)	1.1 (H_d) 0.8 (H_f) 0.7 ($H_{f'}$) 0.8 (H_c)

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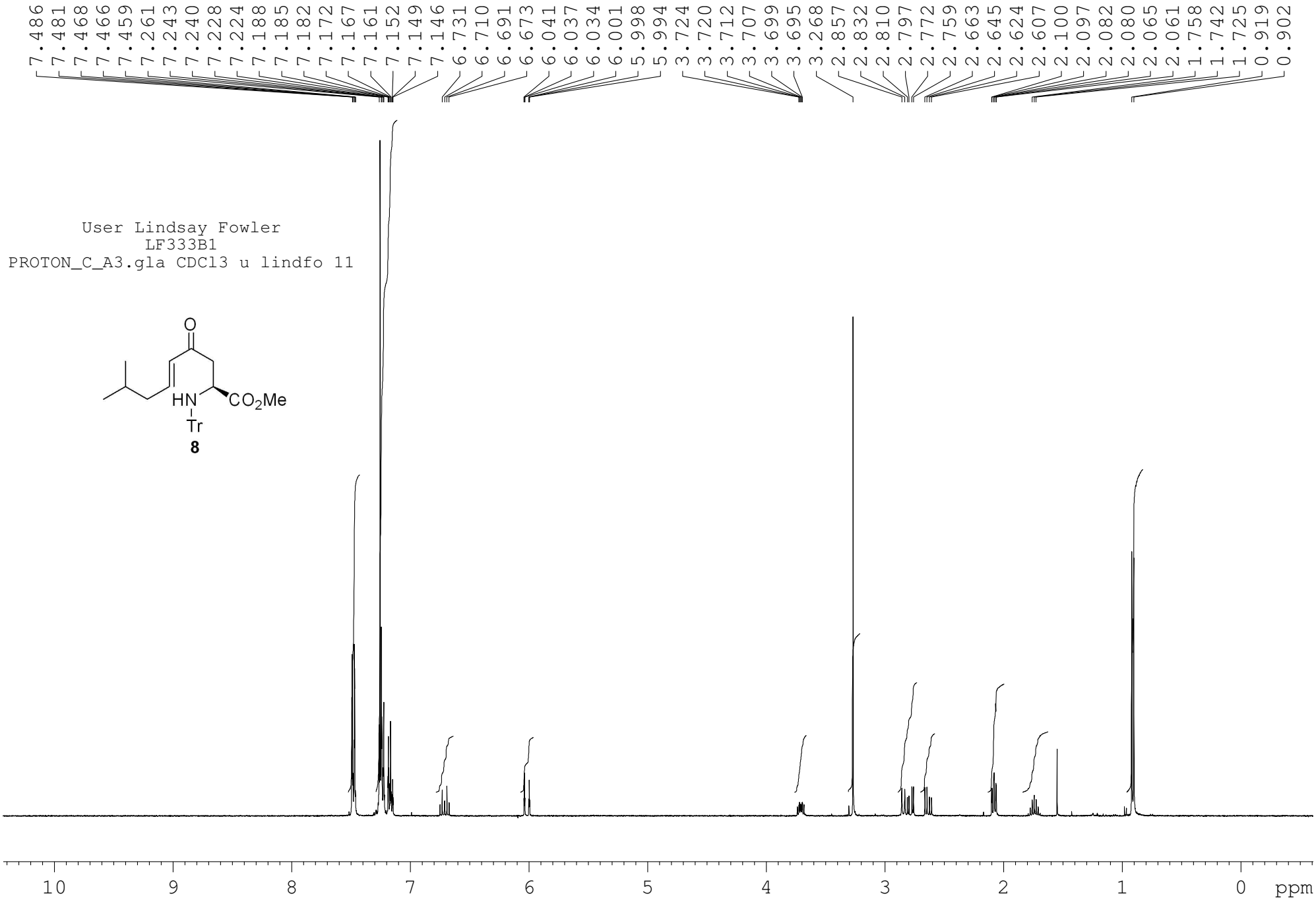

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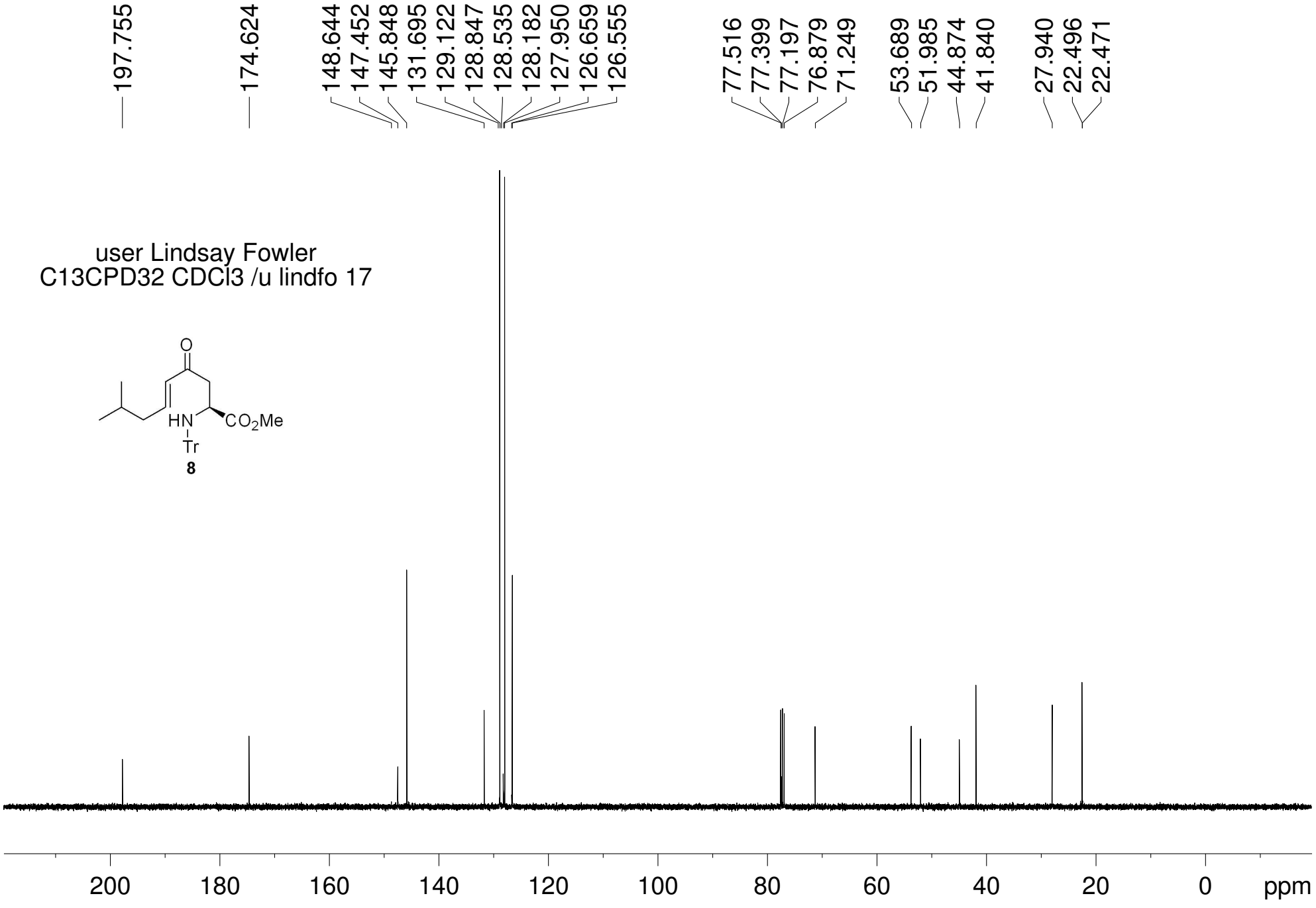

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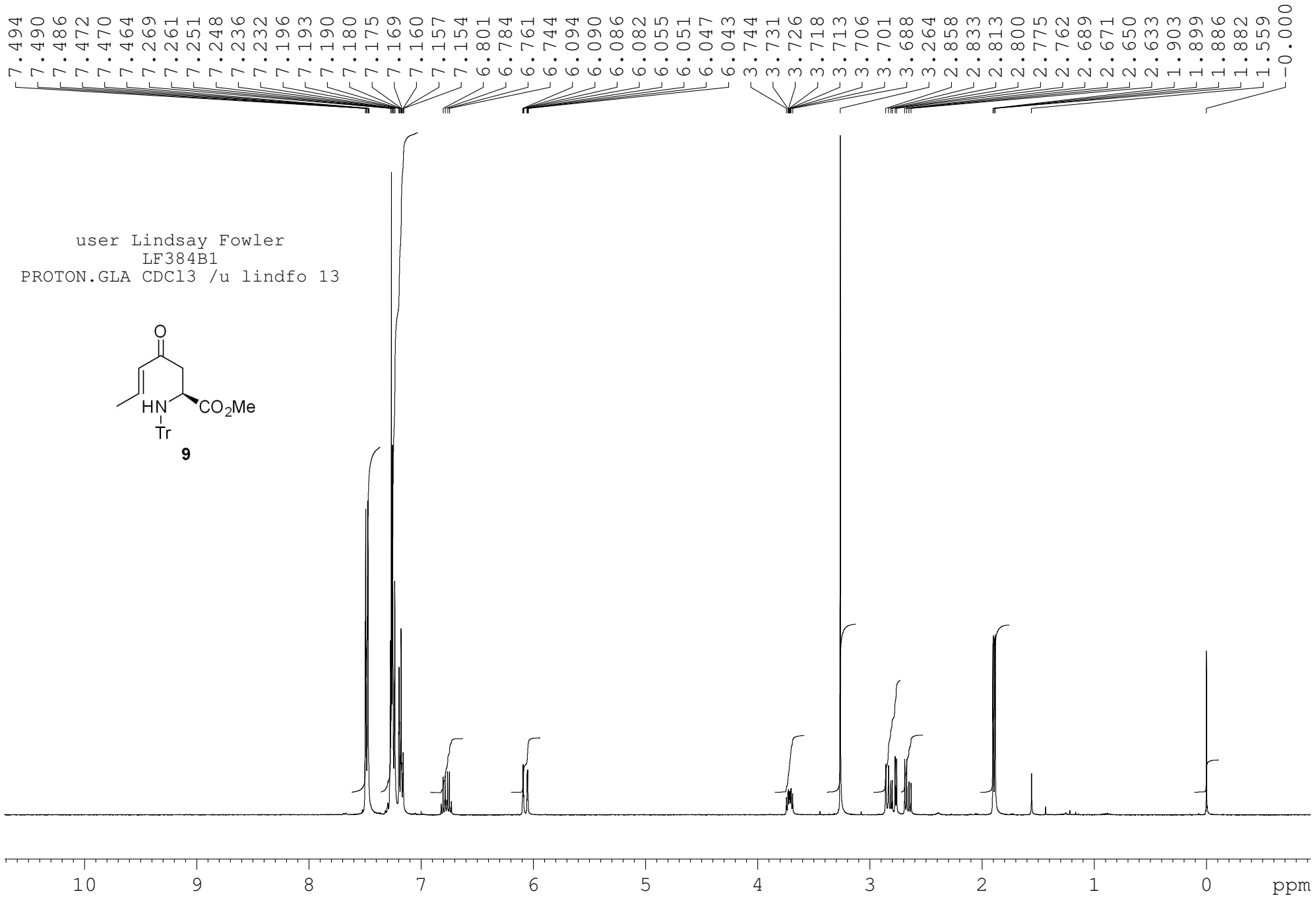

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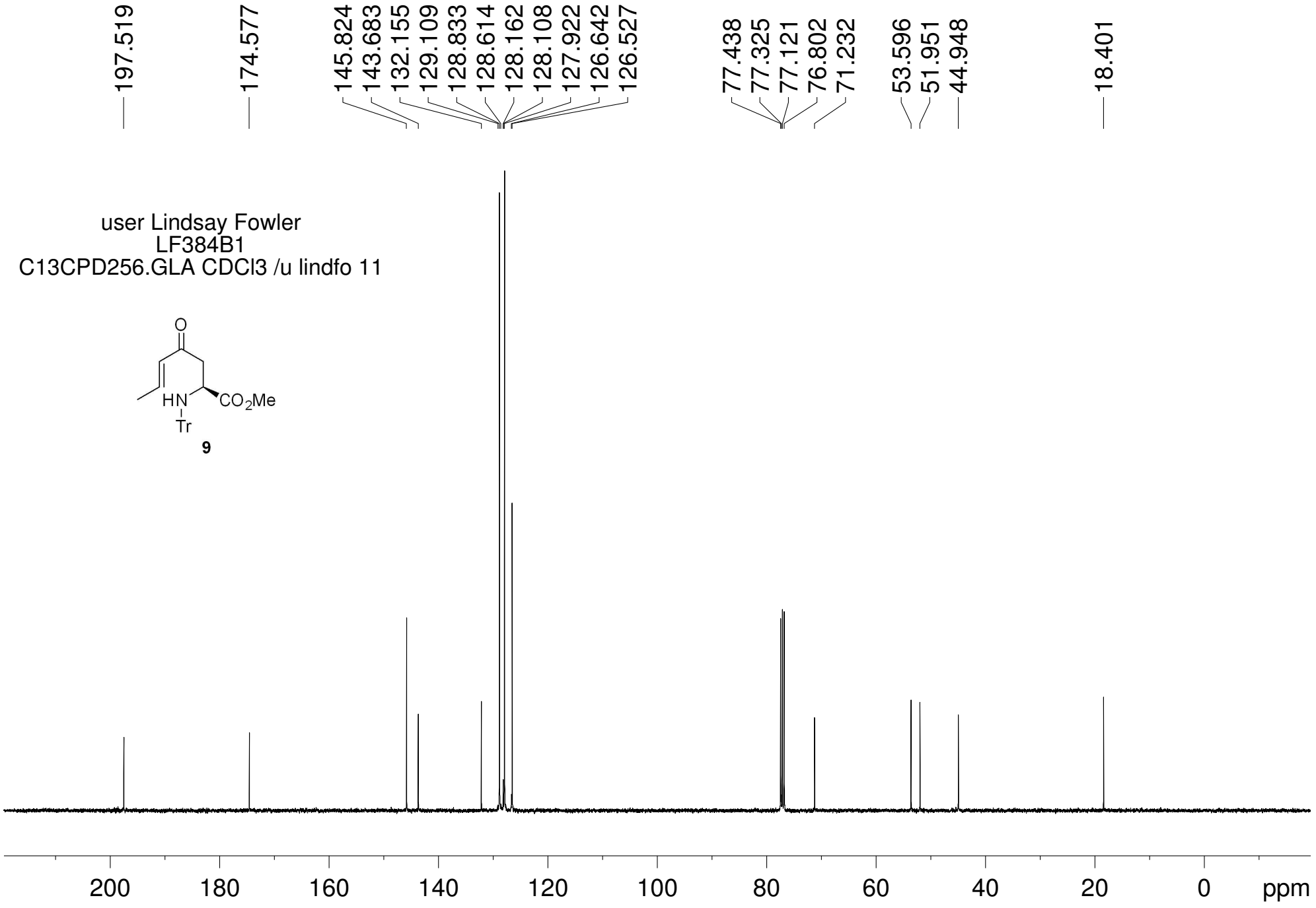

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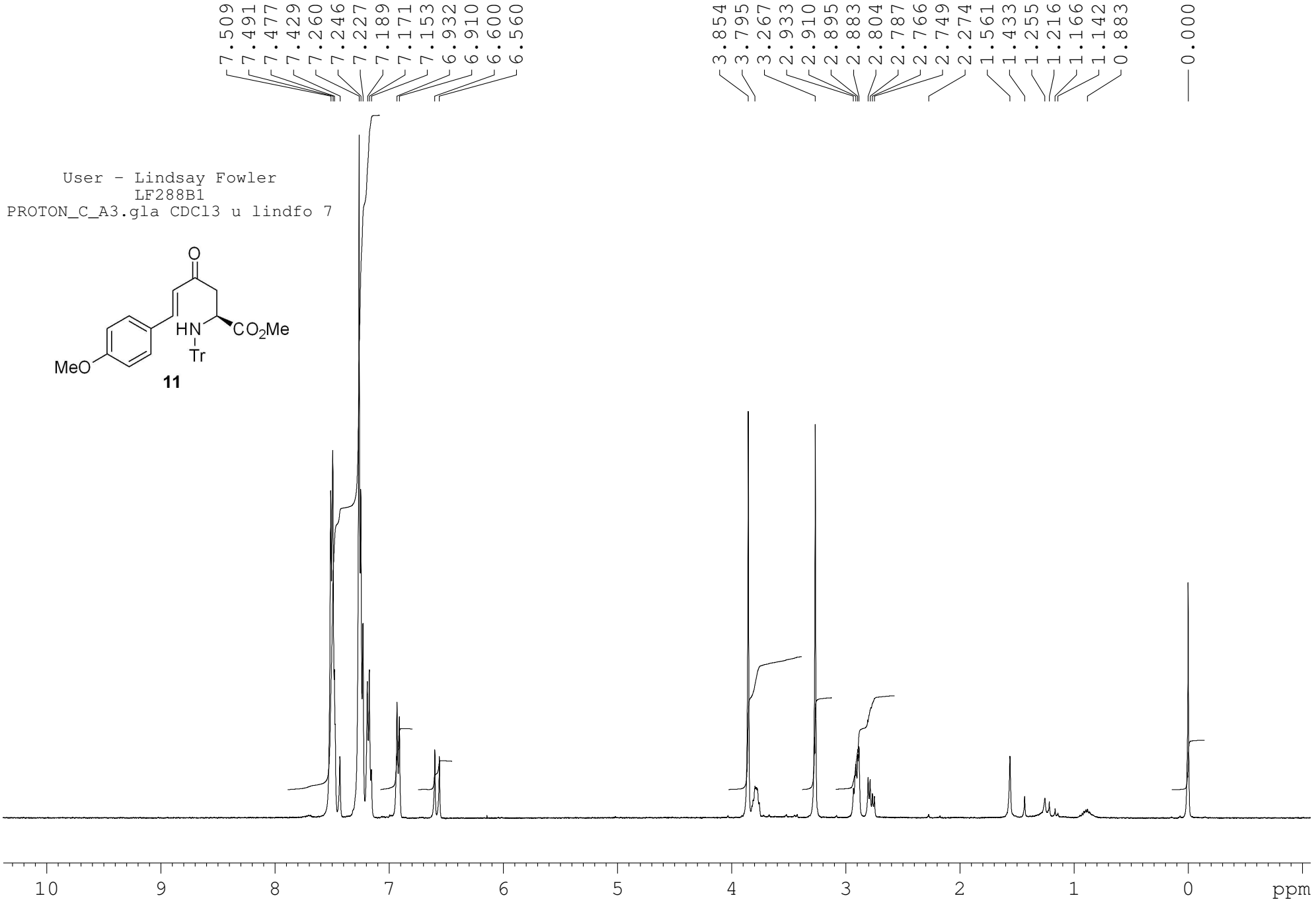

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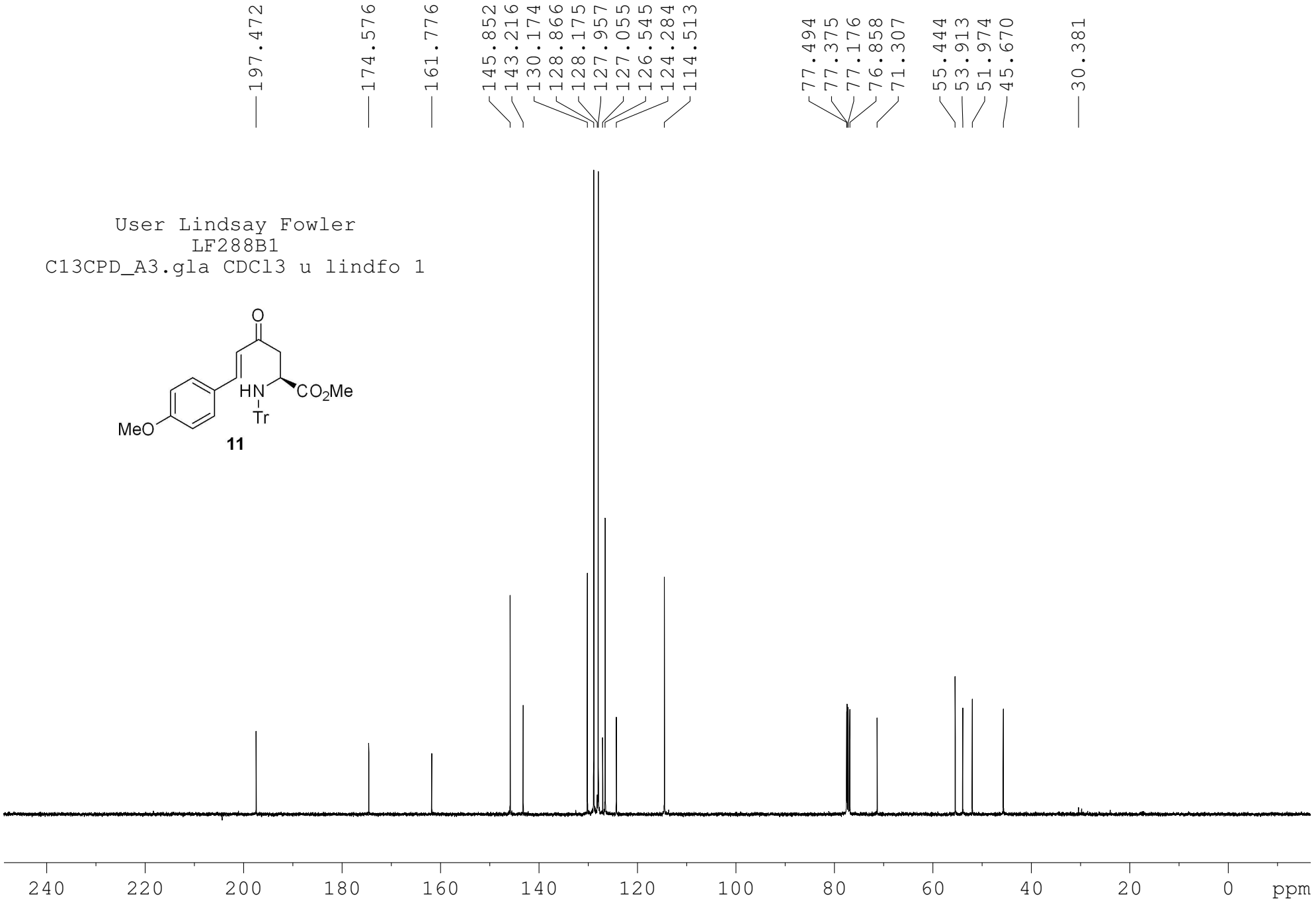

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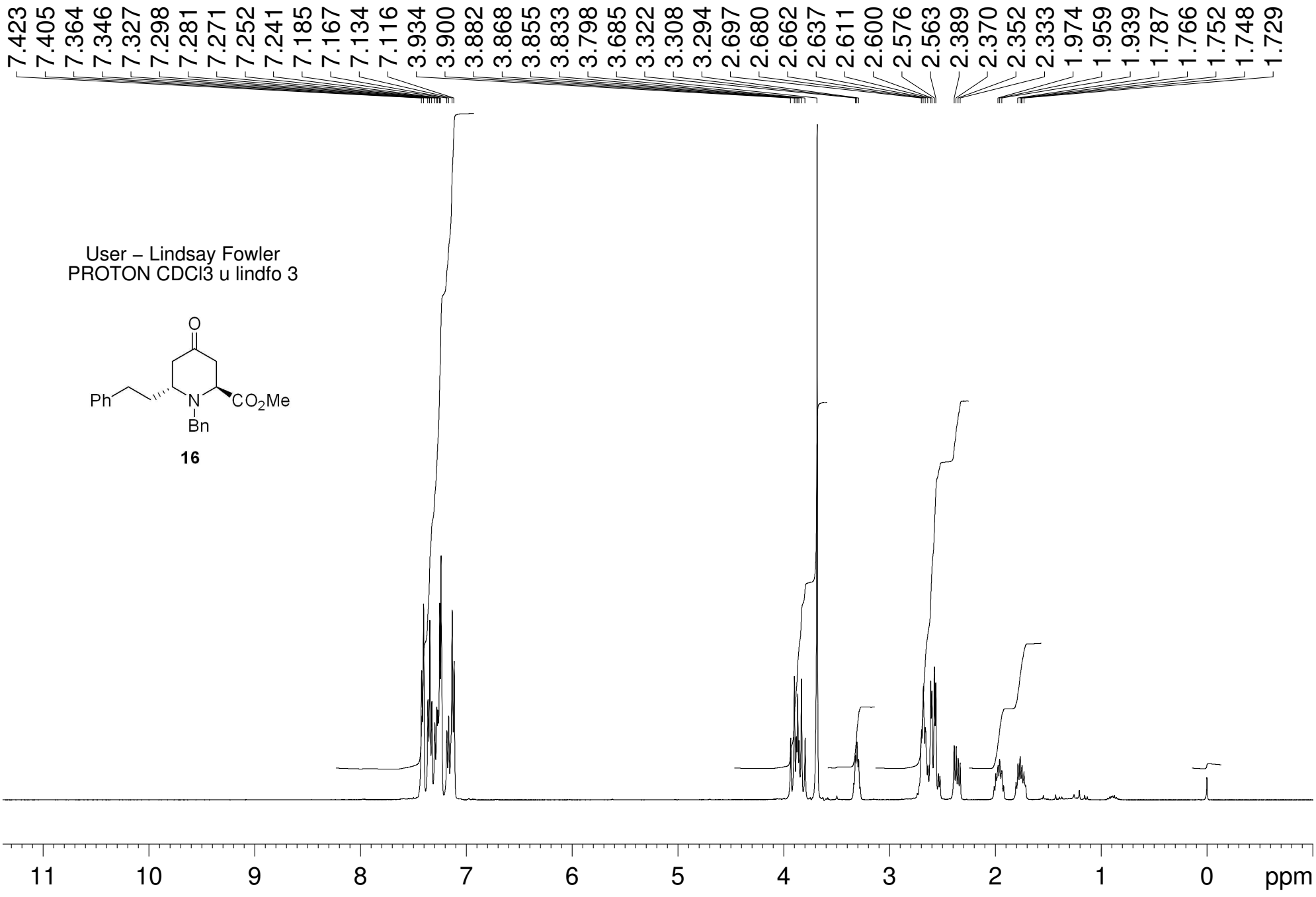

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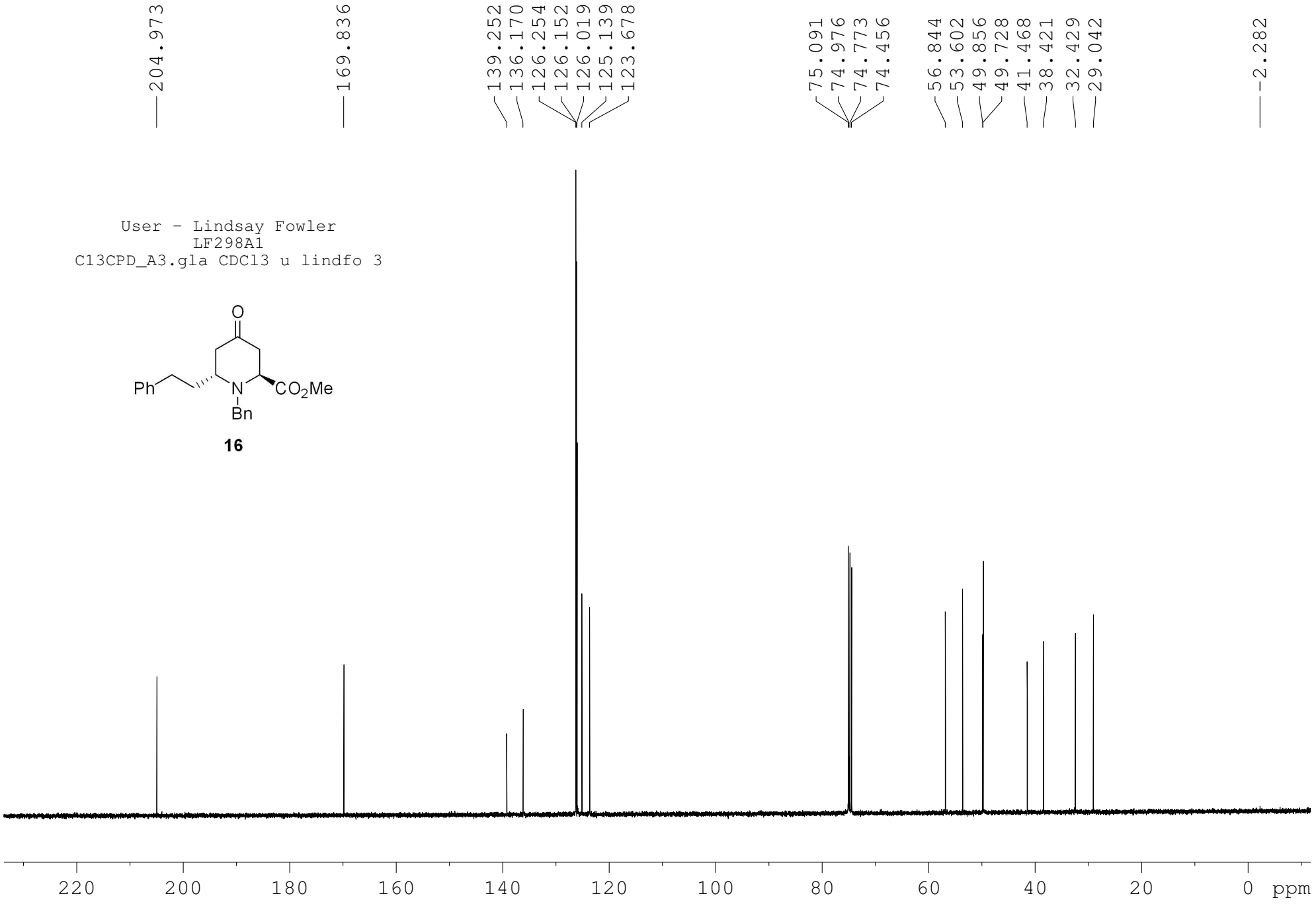

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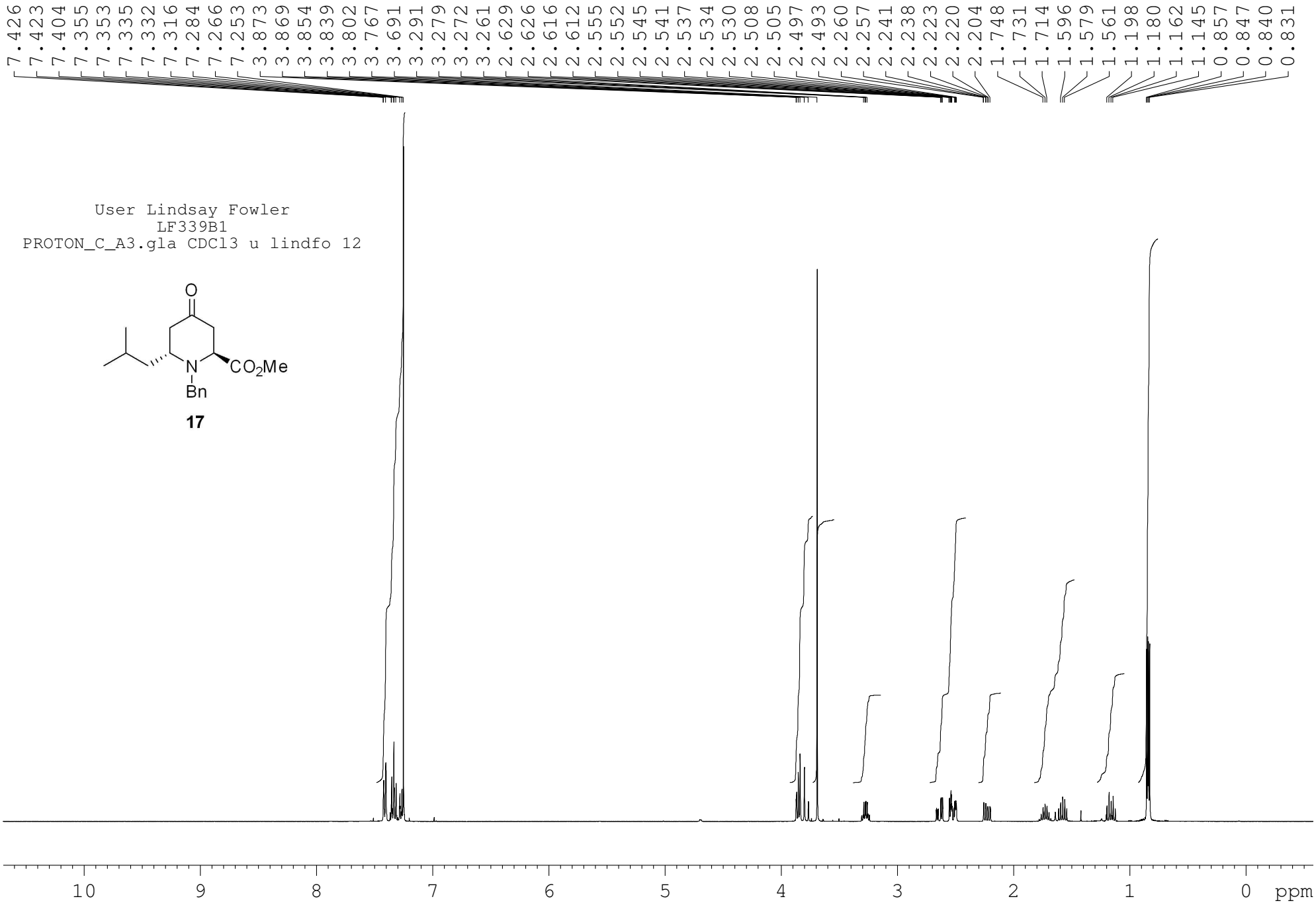

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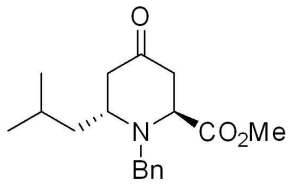

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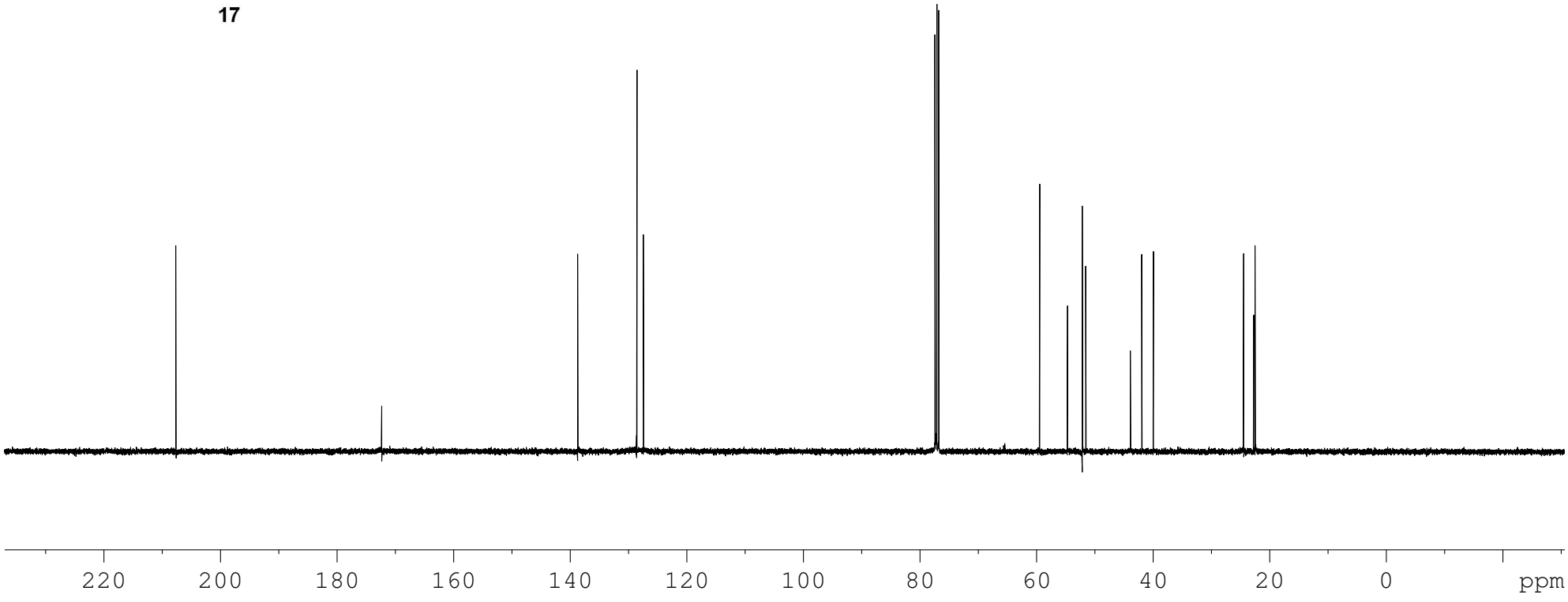

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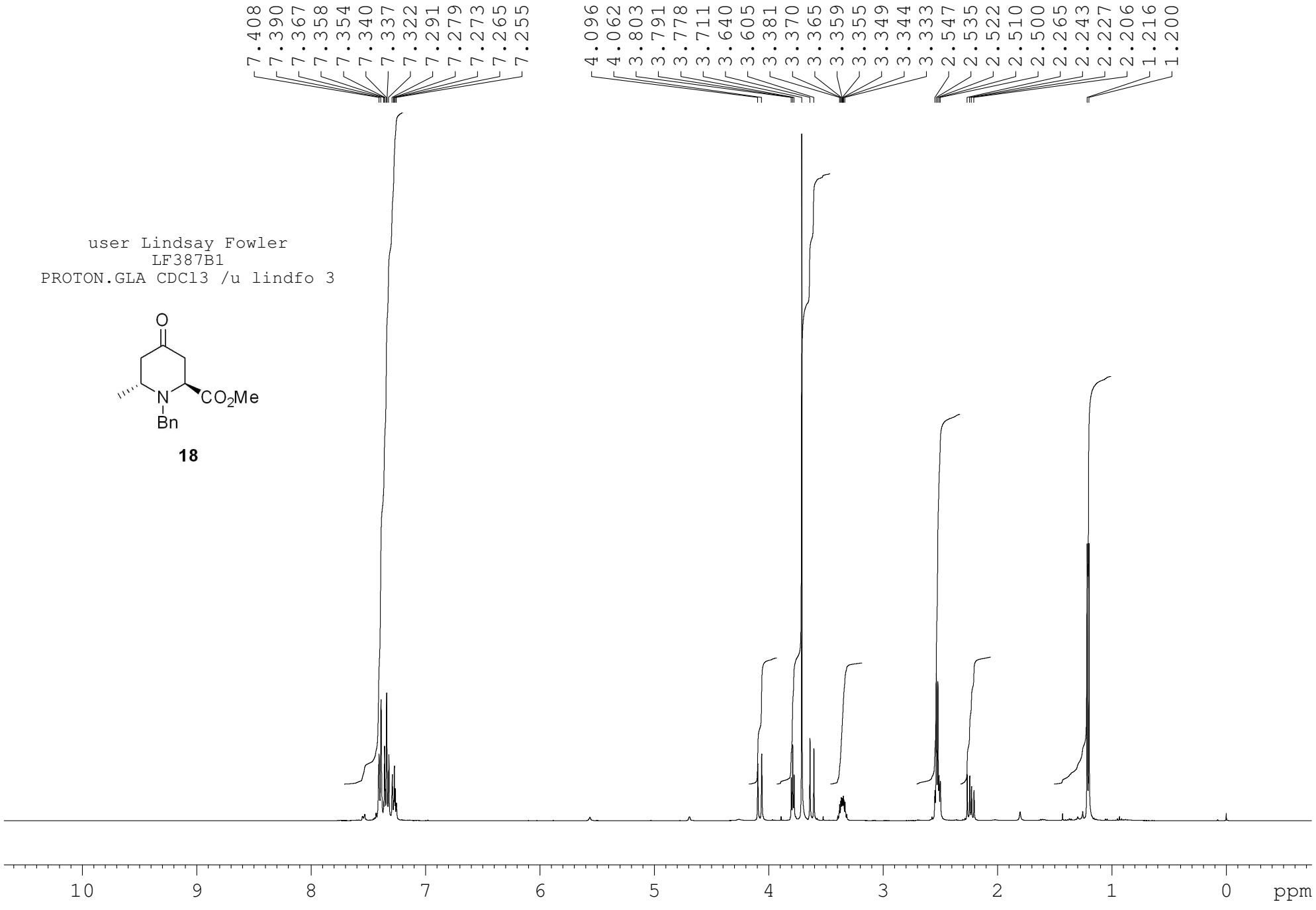

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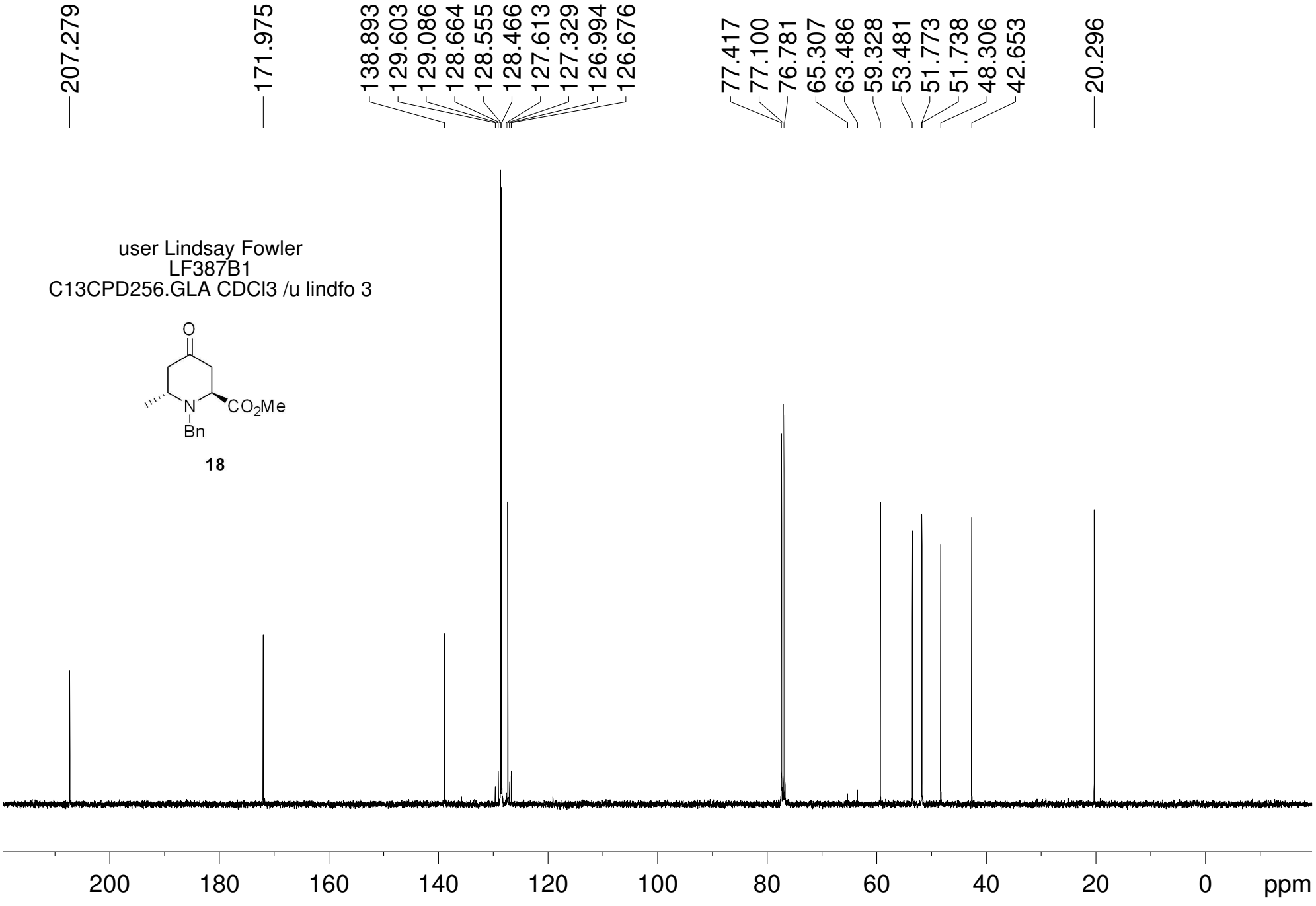

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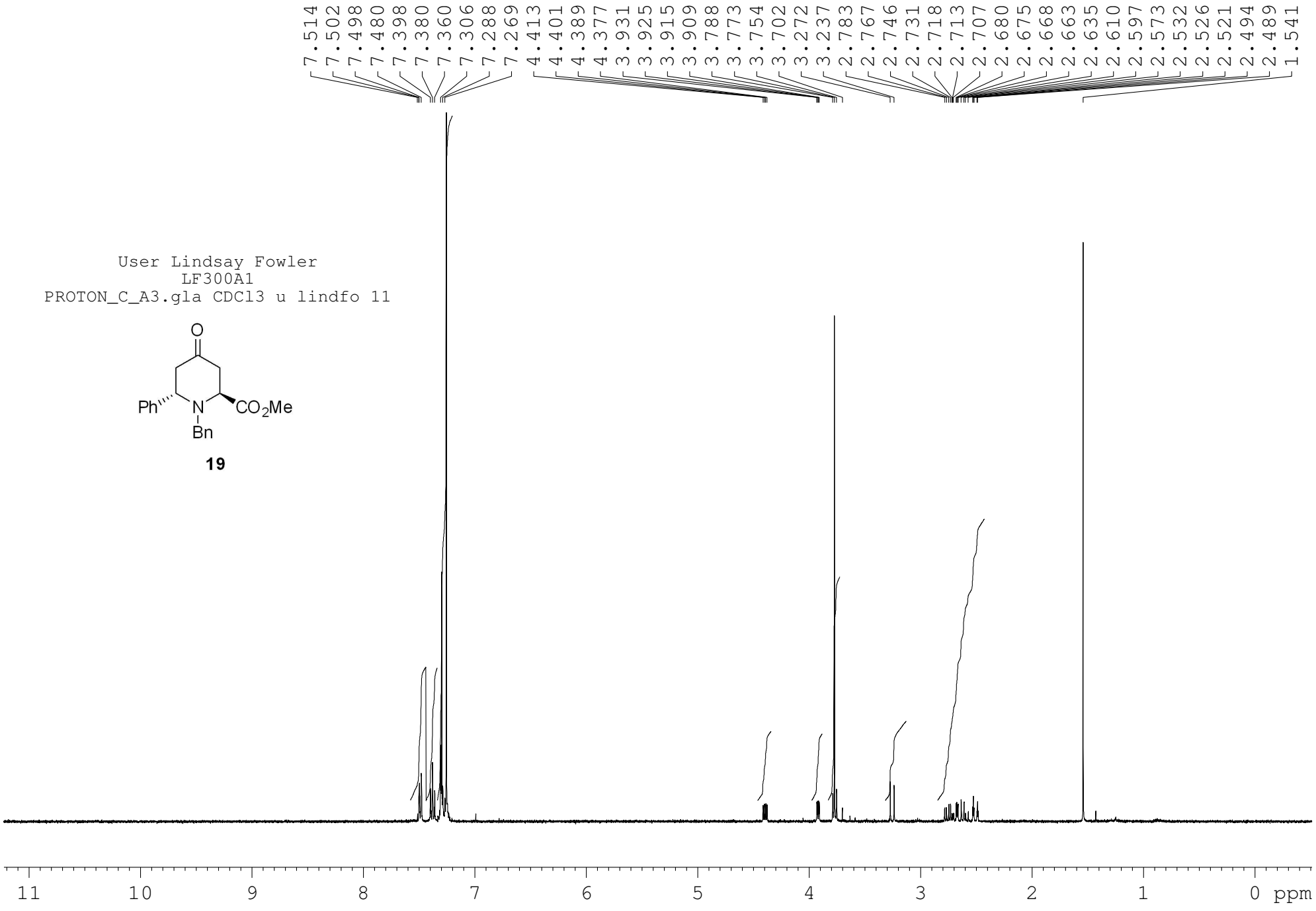

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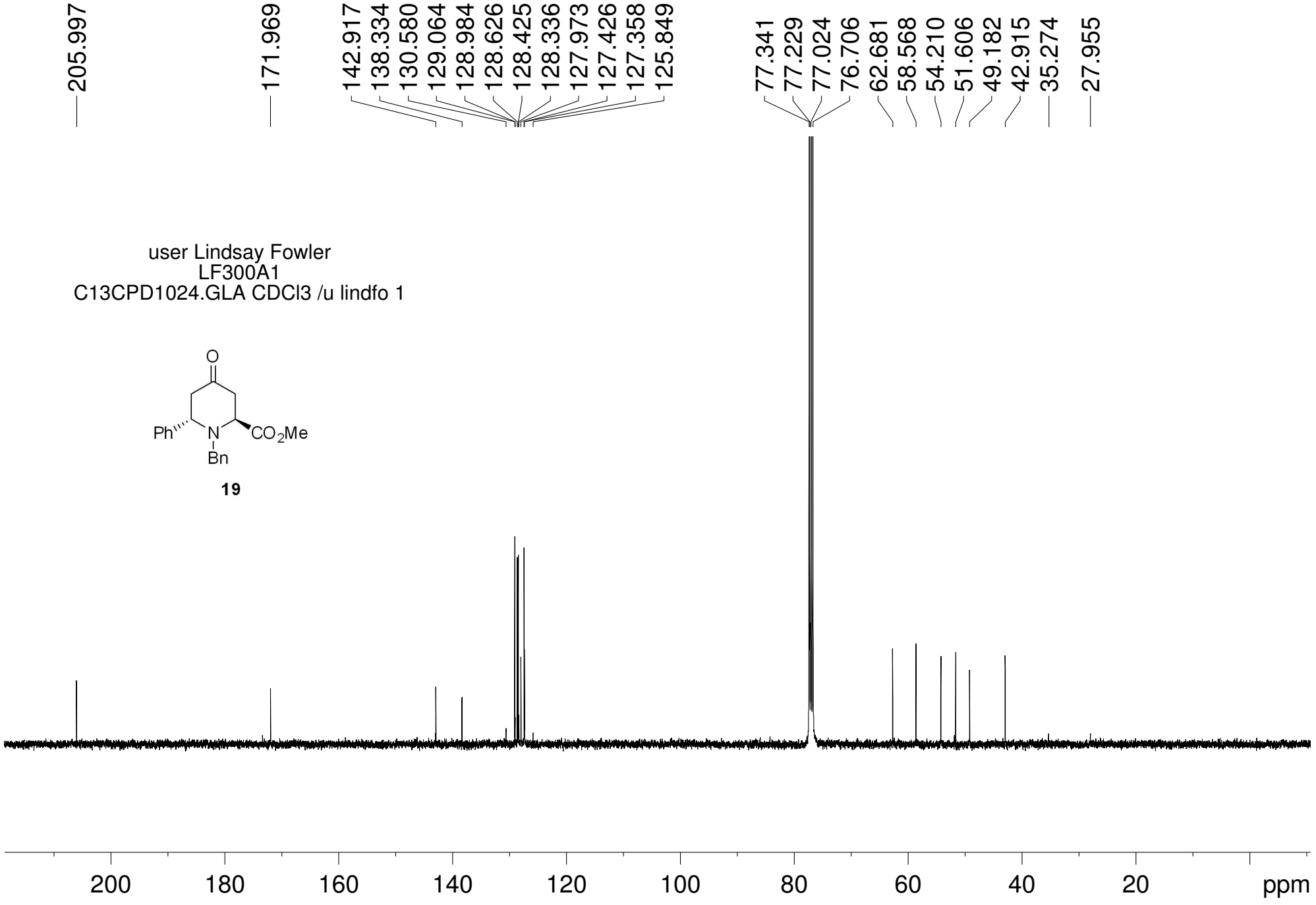

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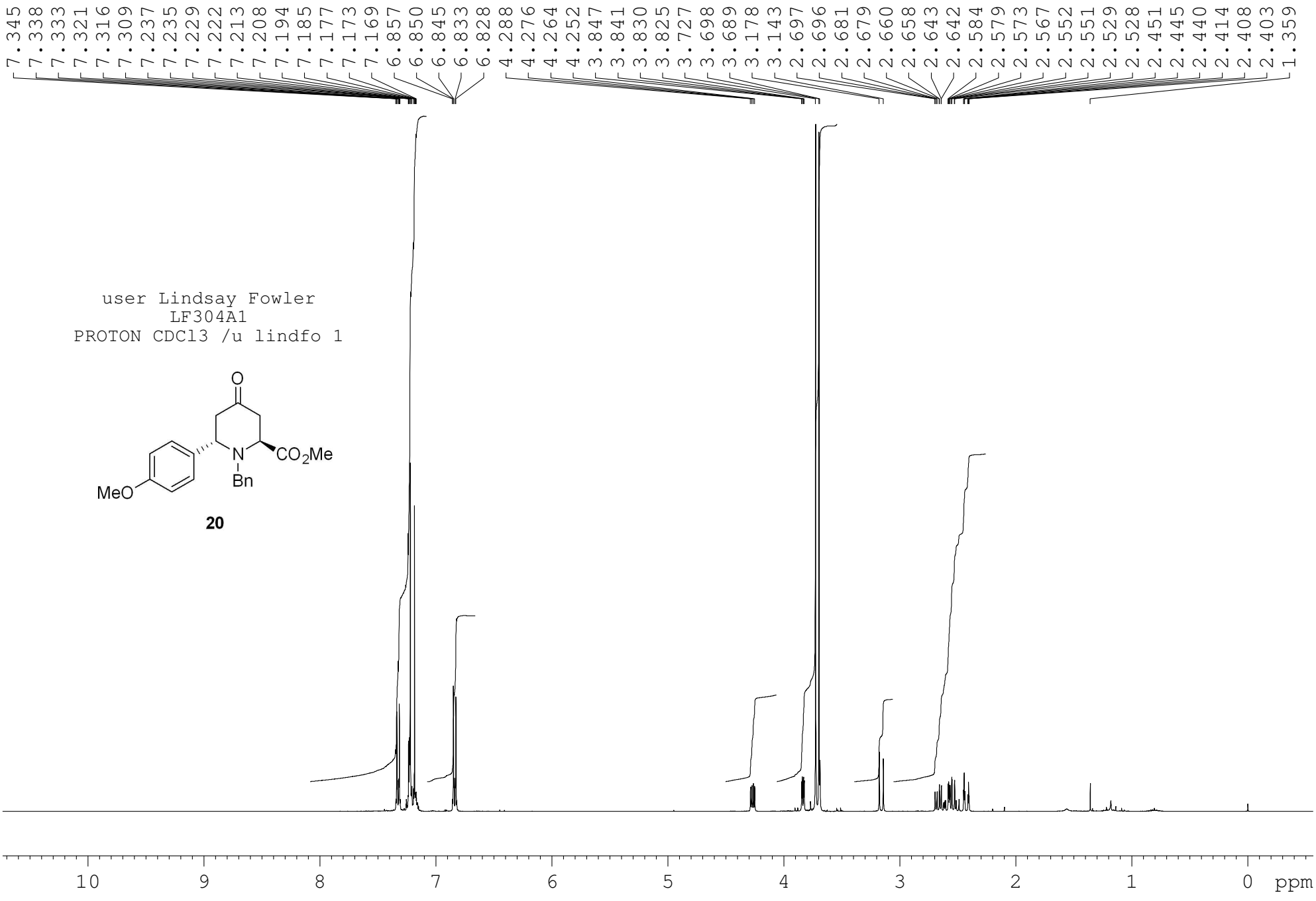

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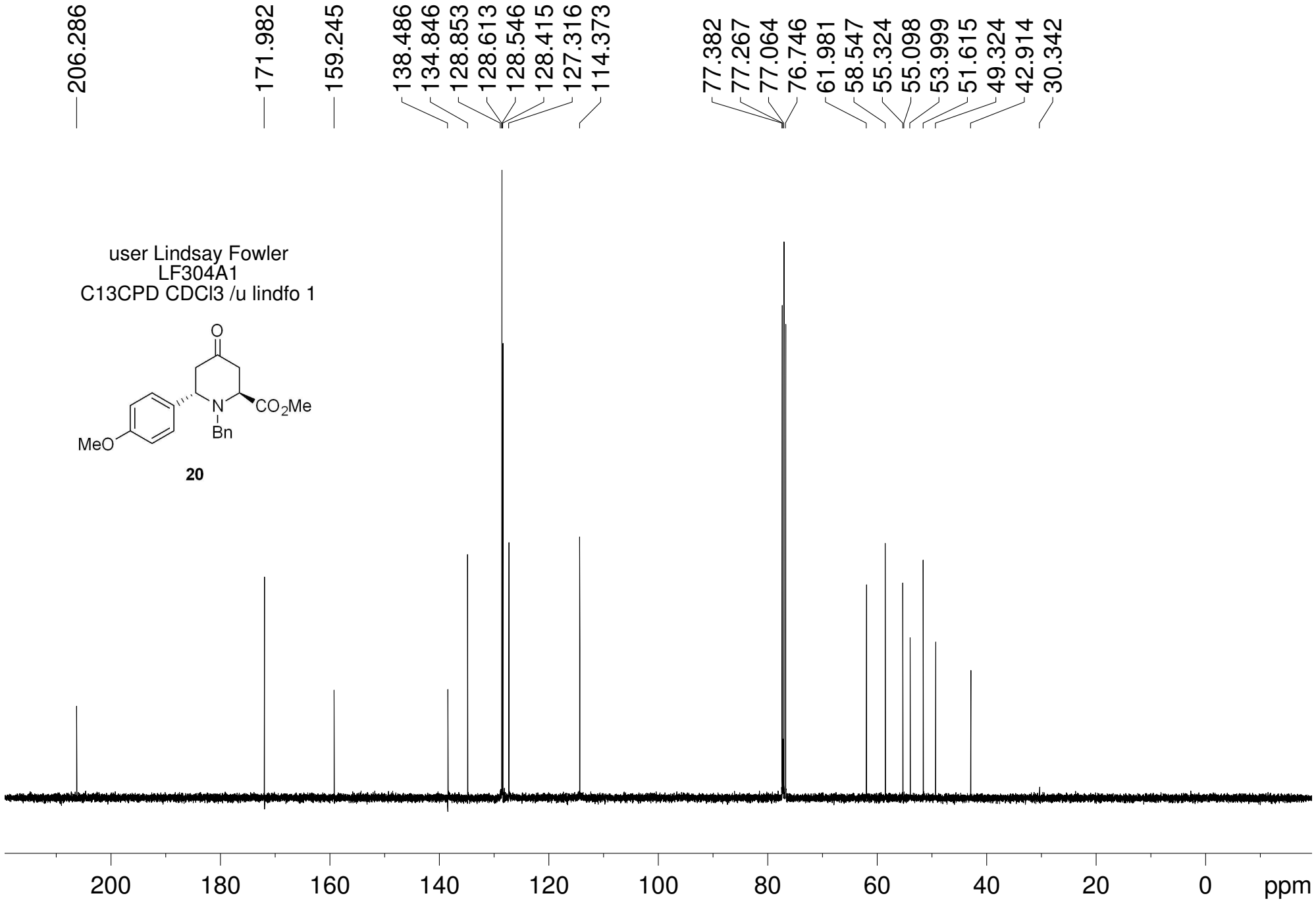

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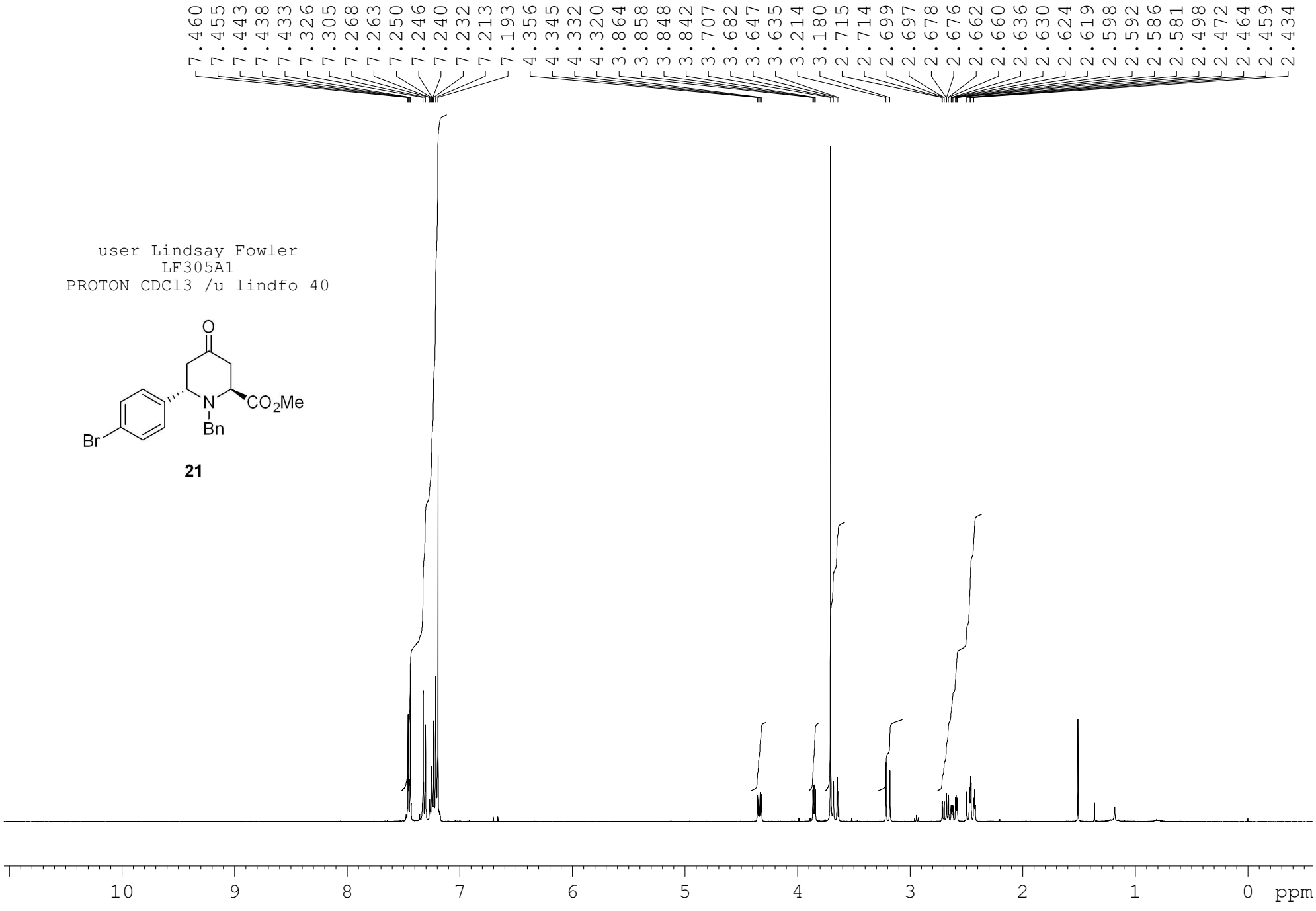

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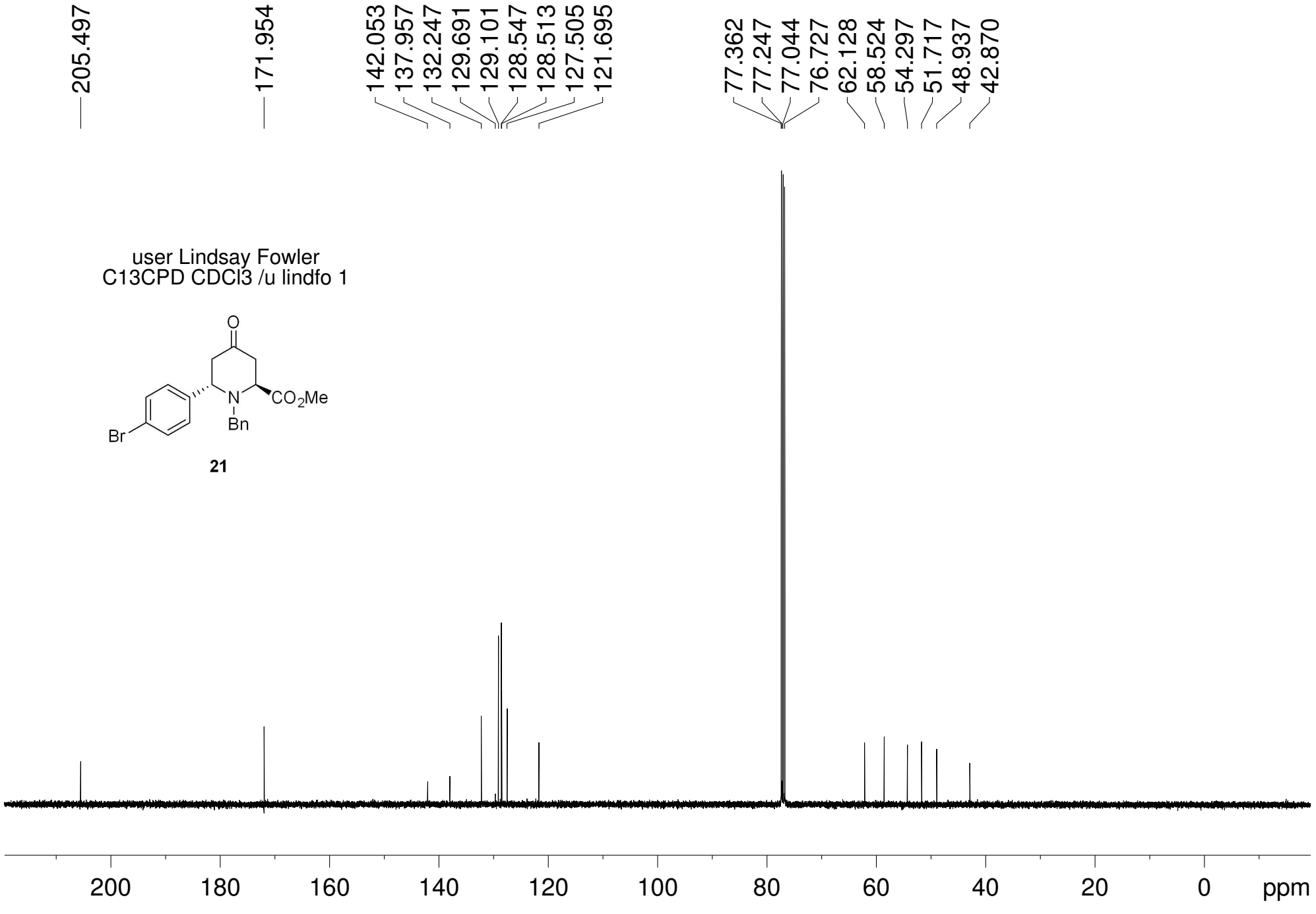

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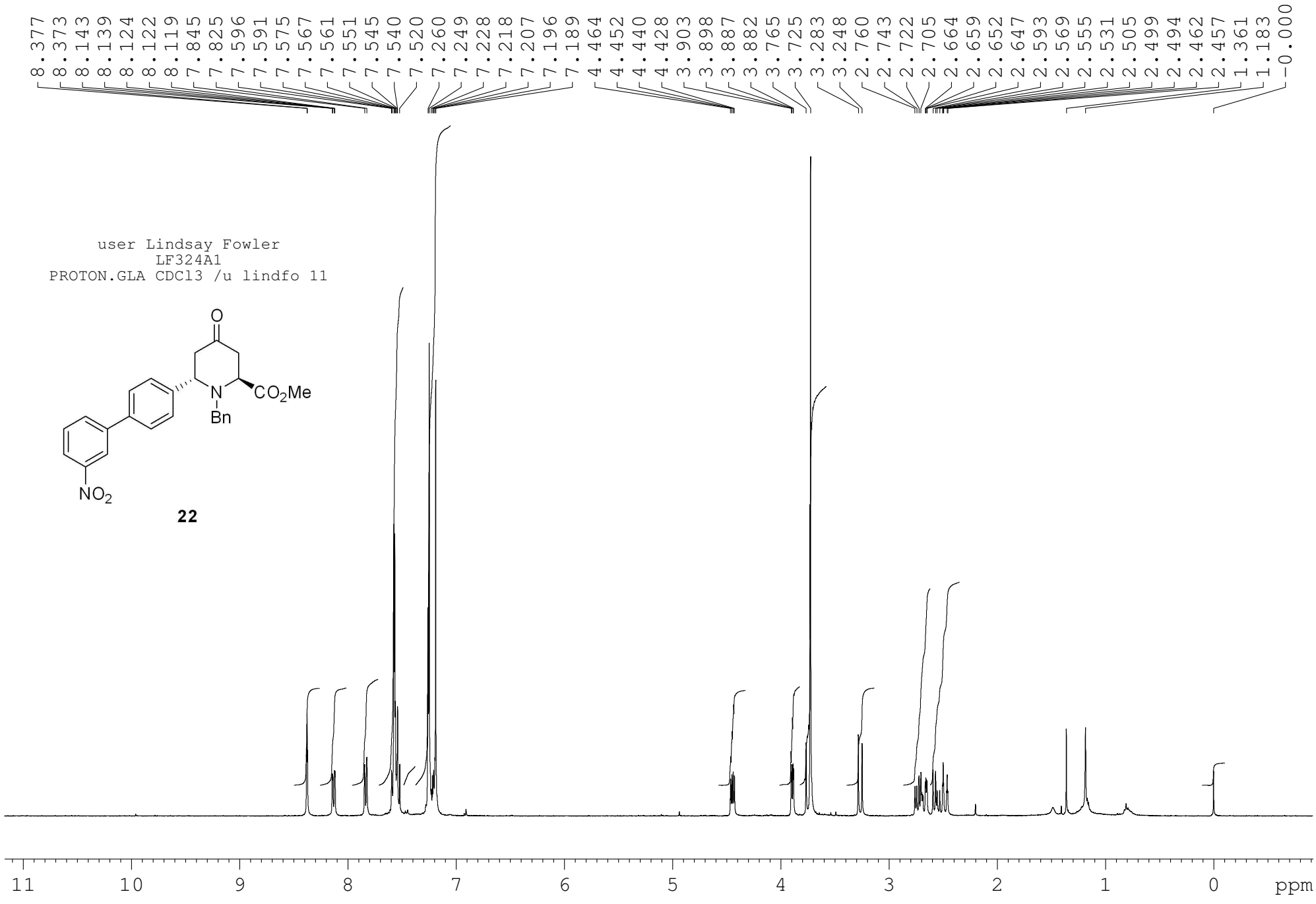

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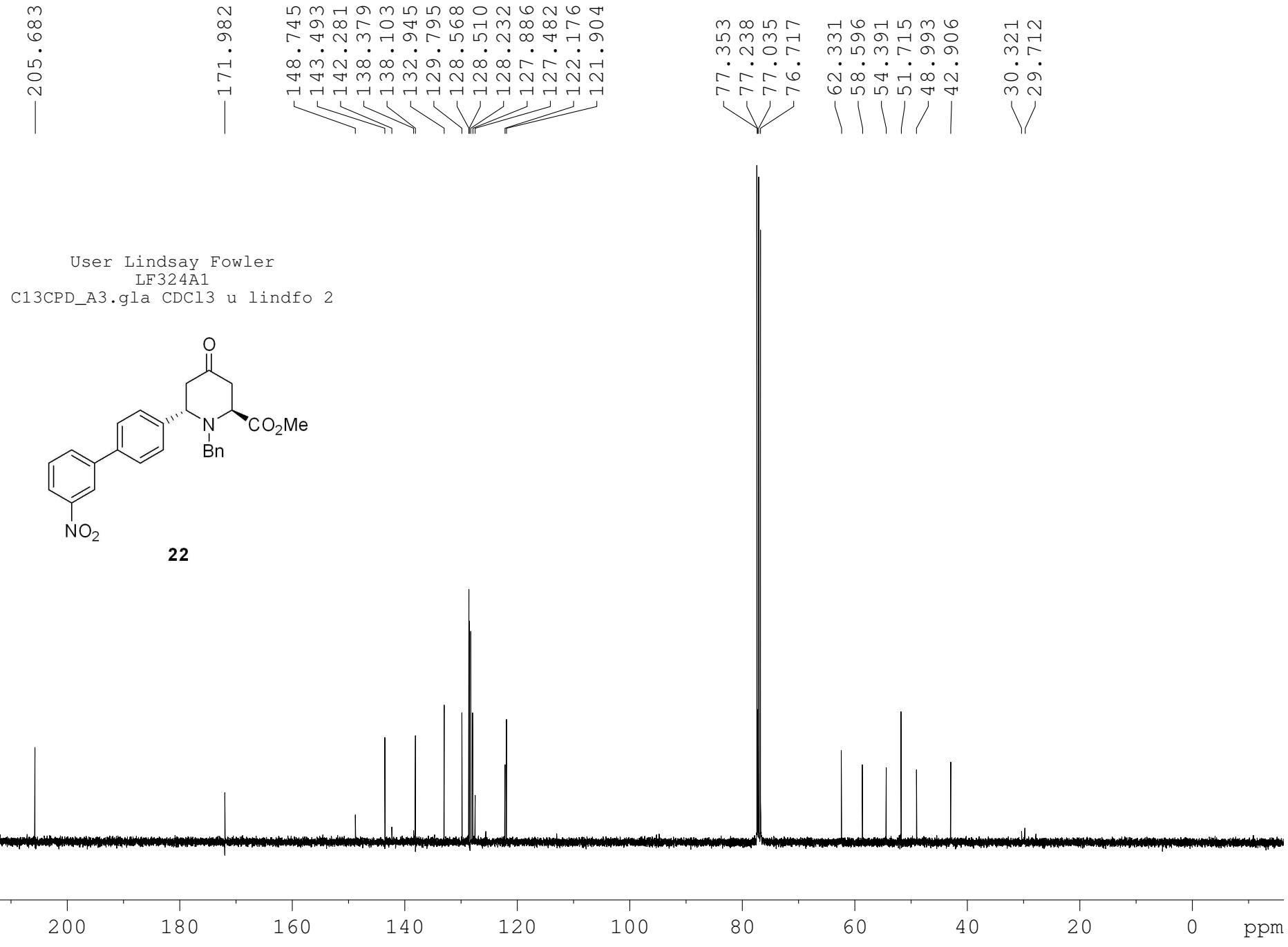

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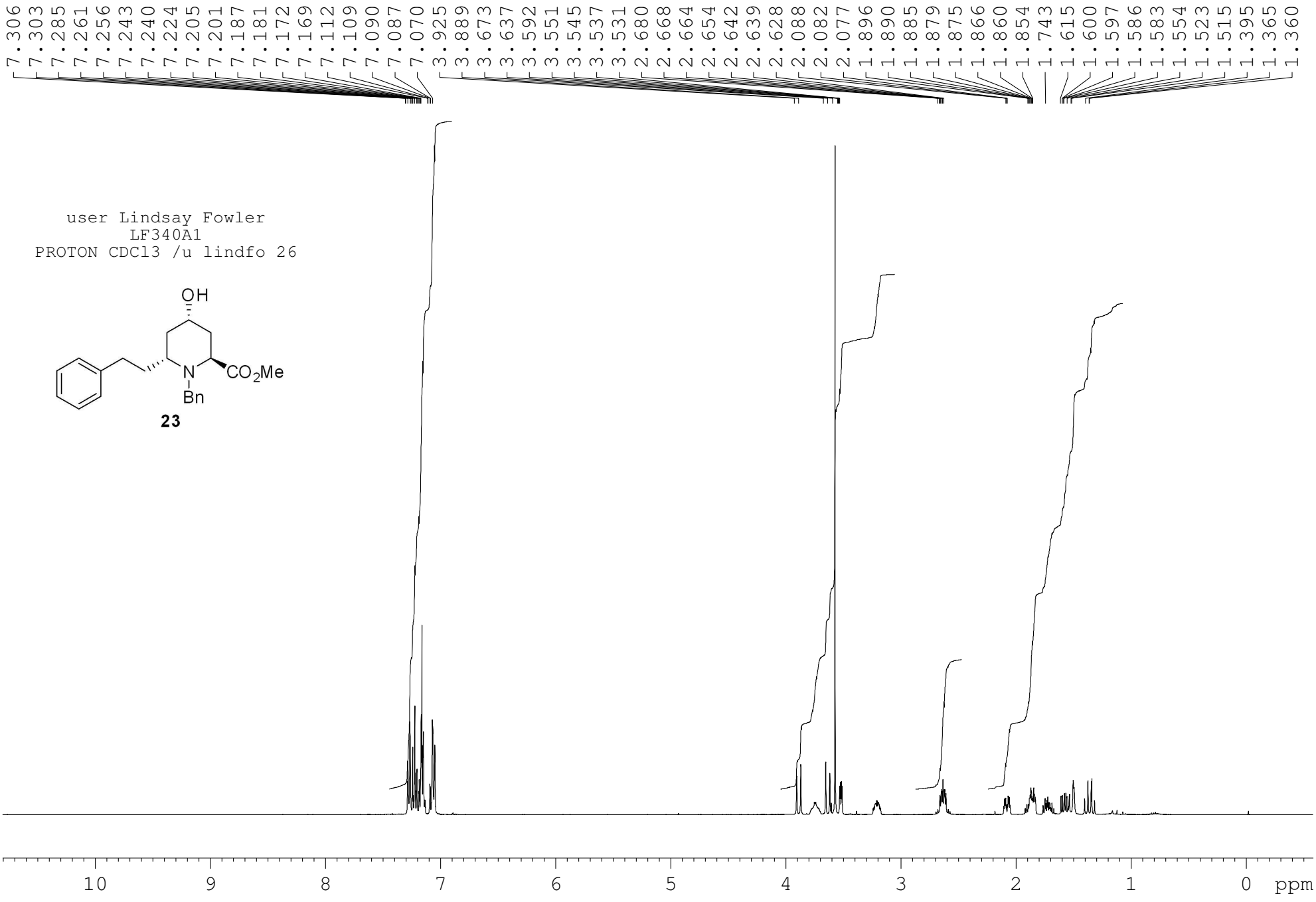

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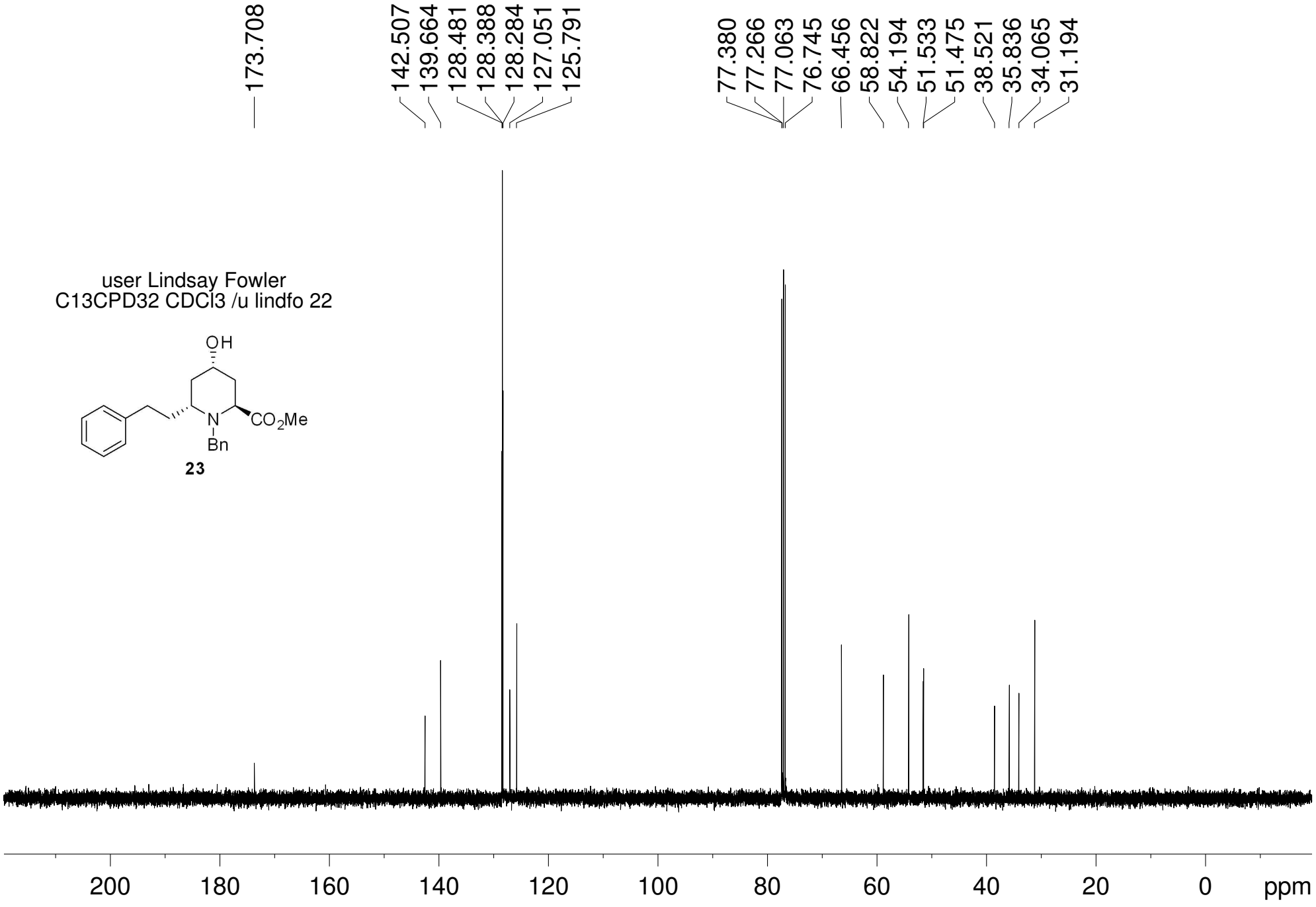

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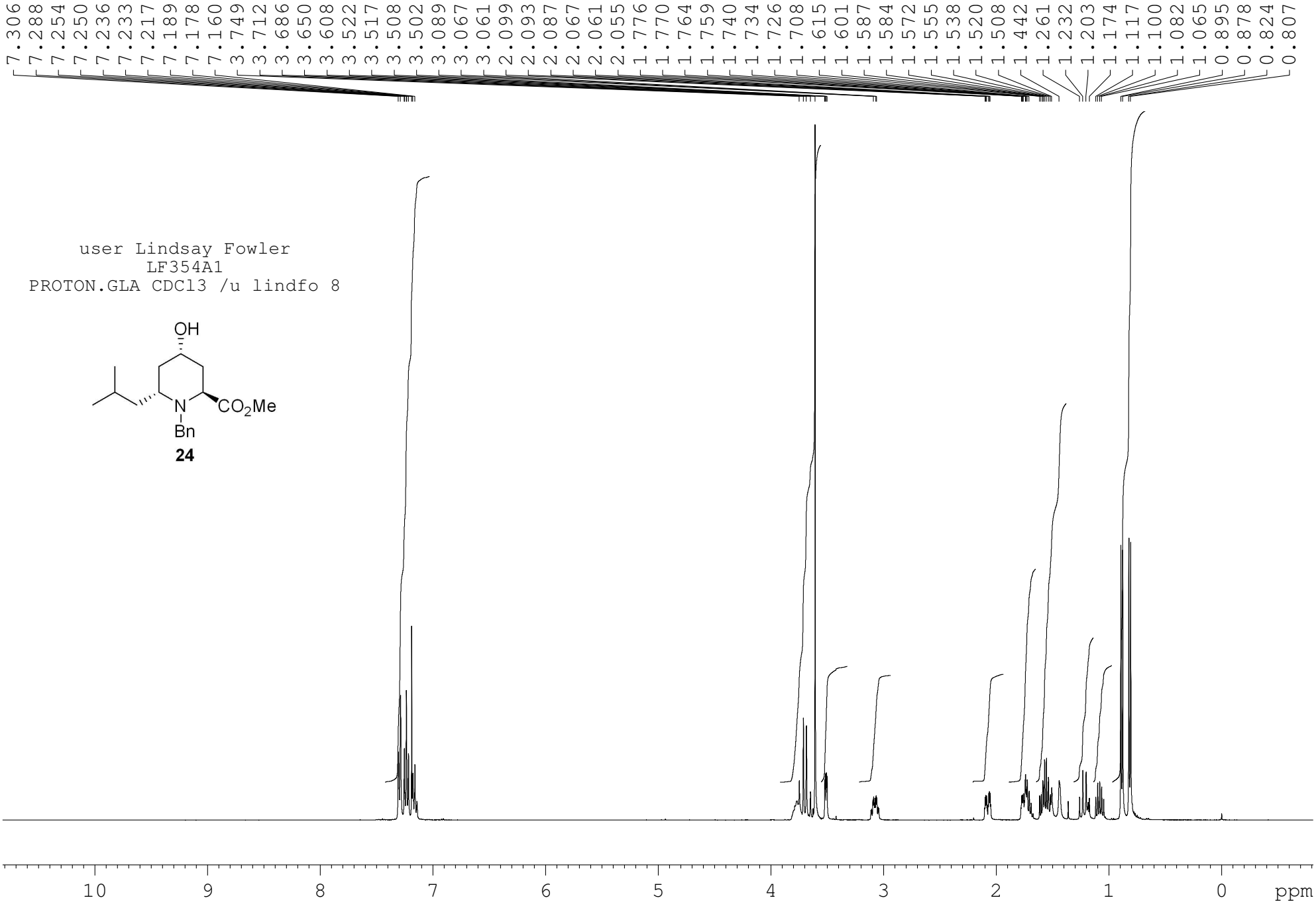

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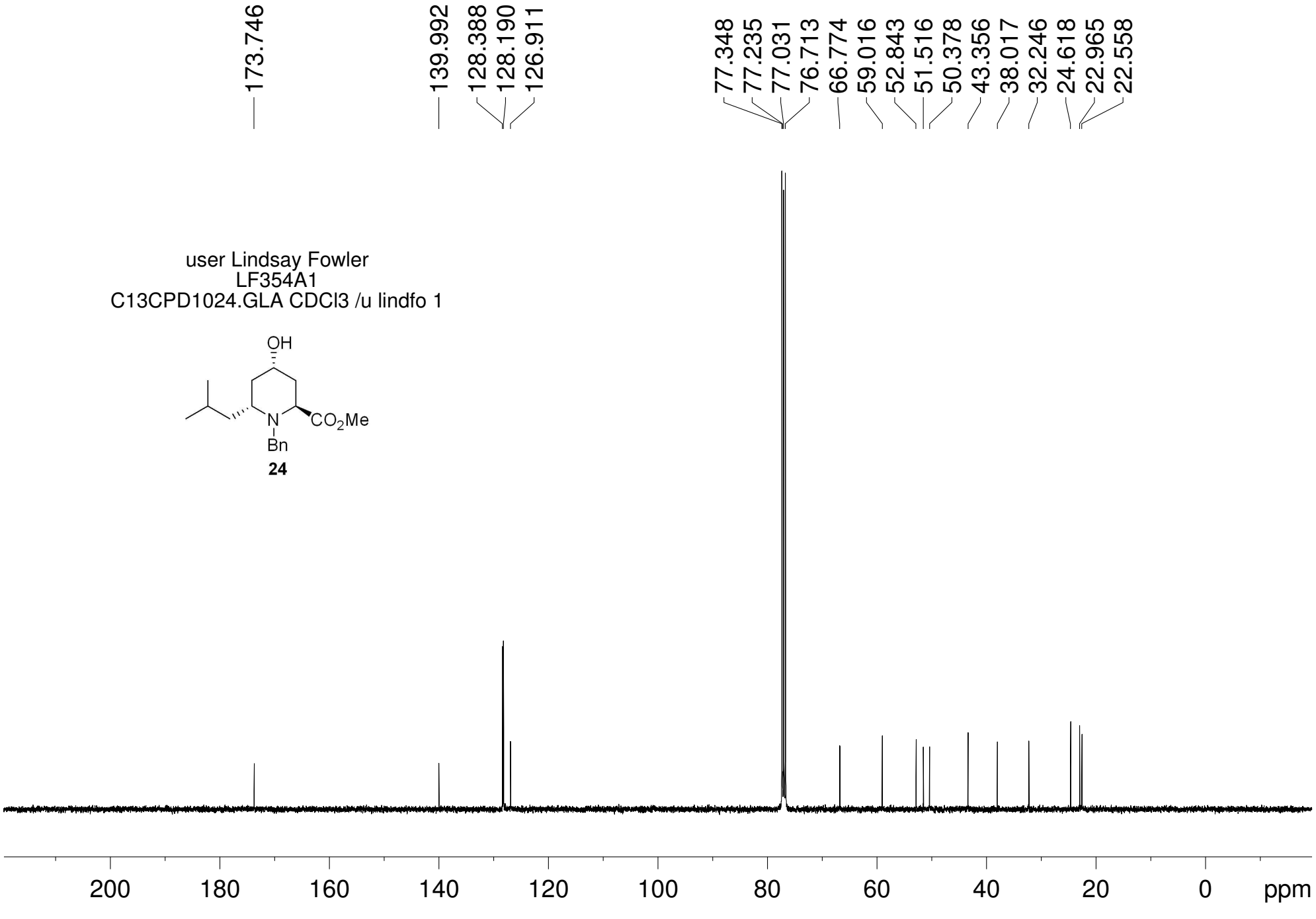

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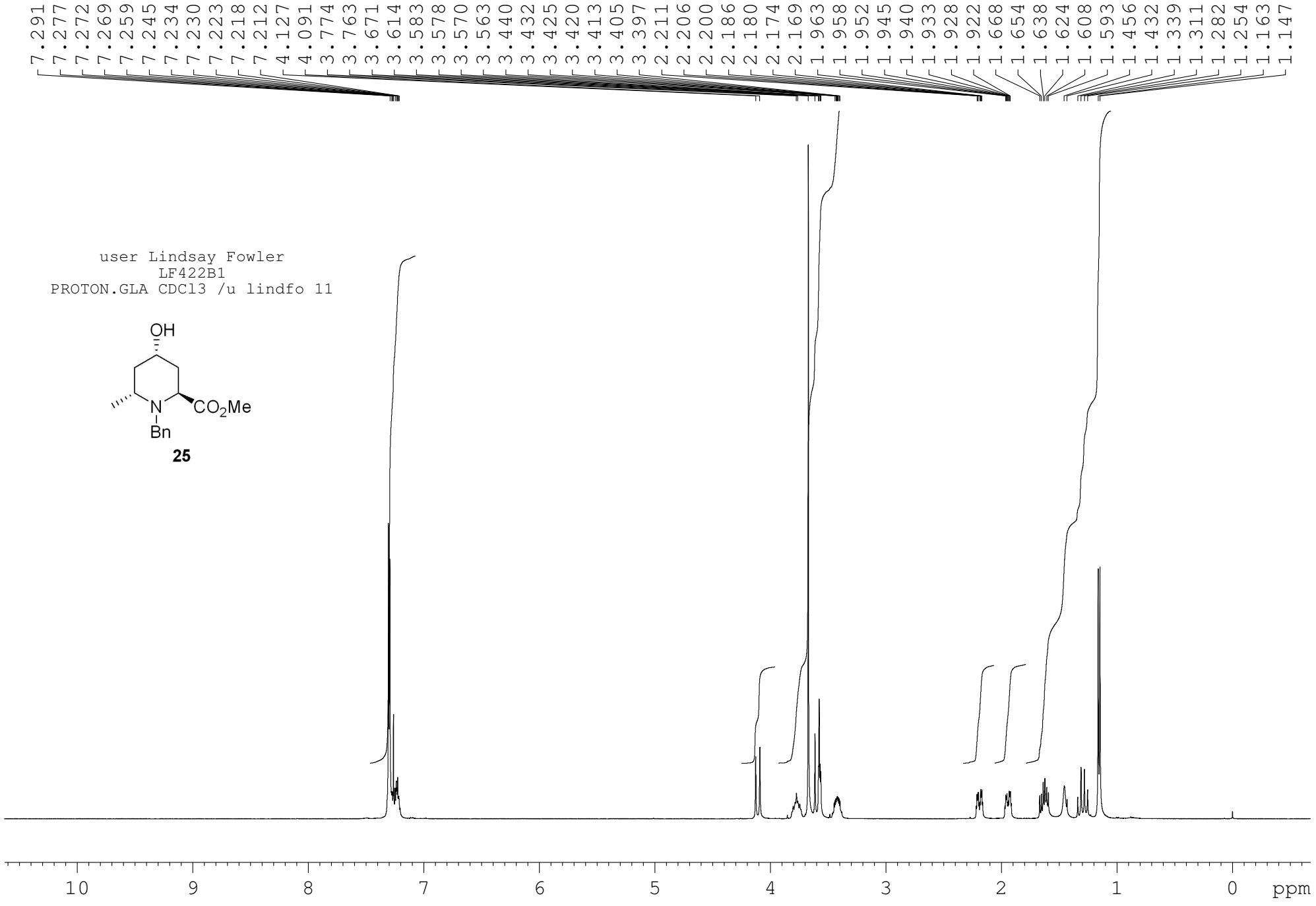

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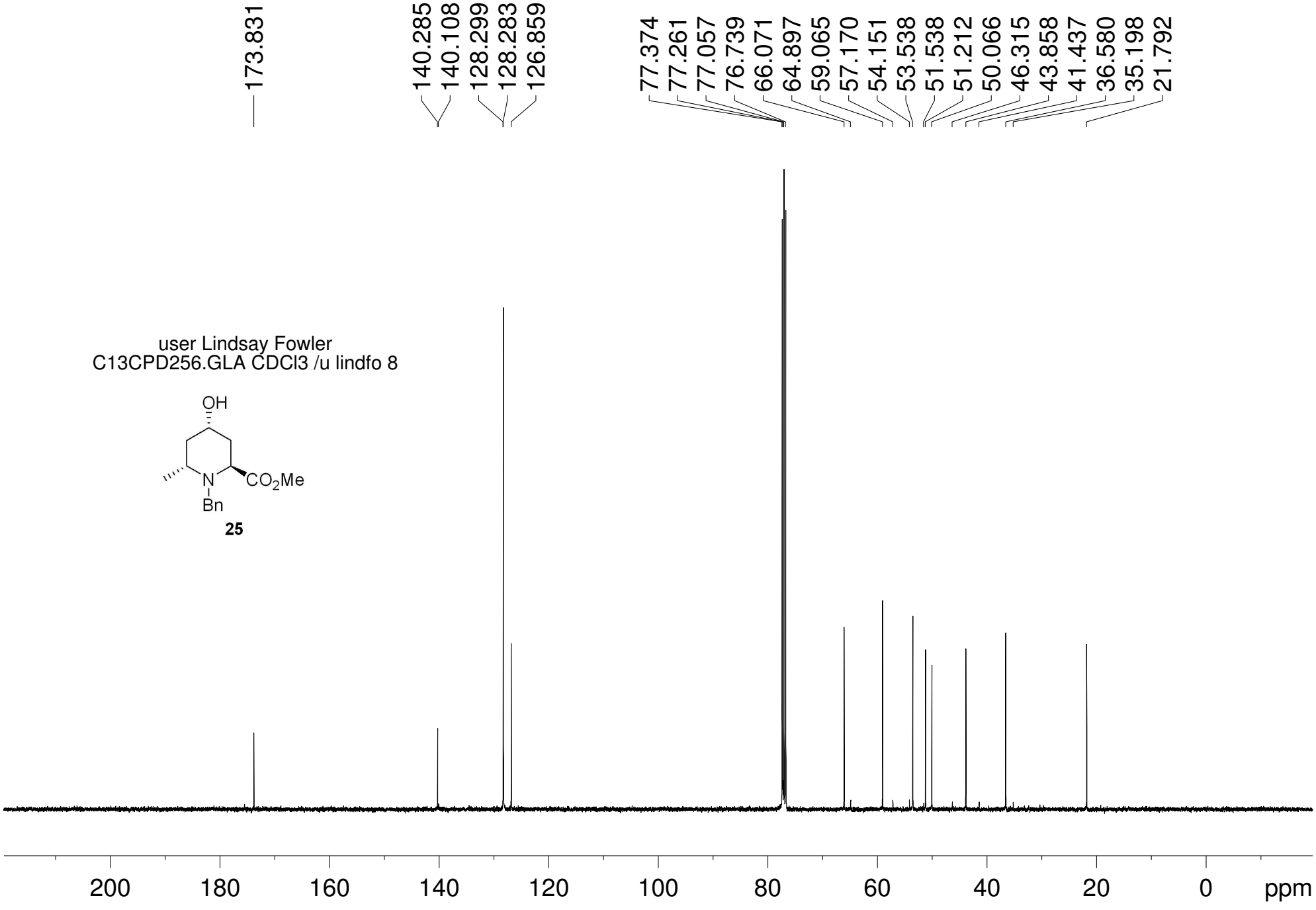

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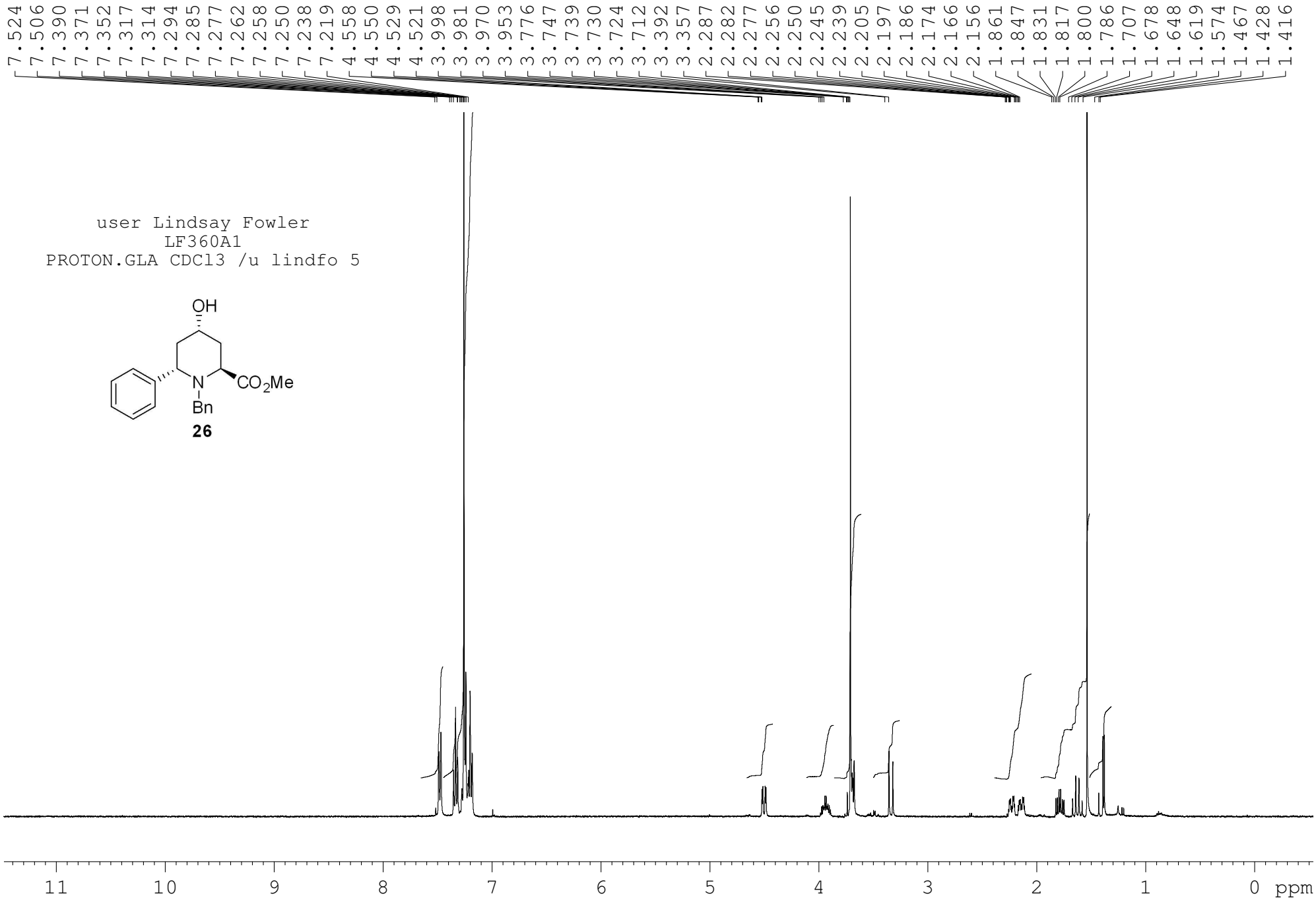

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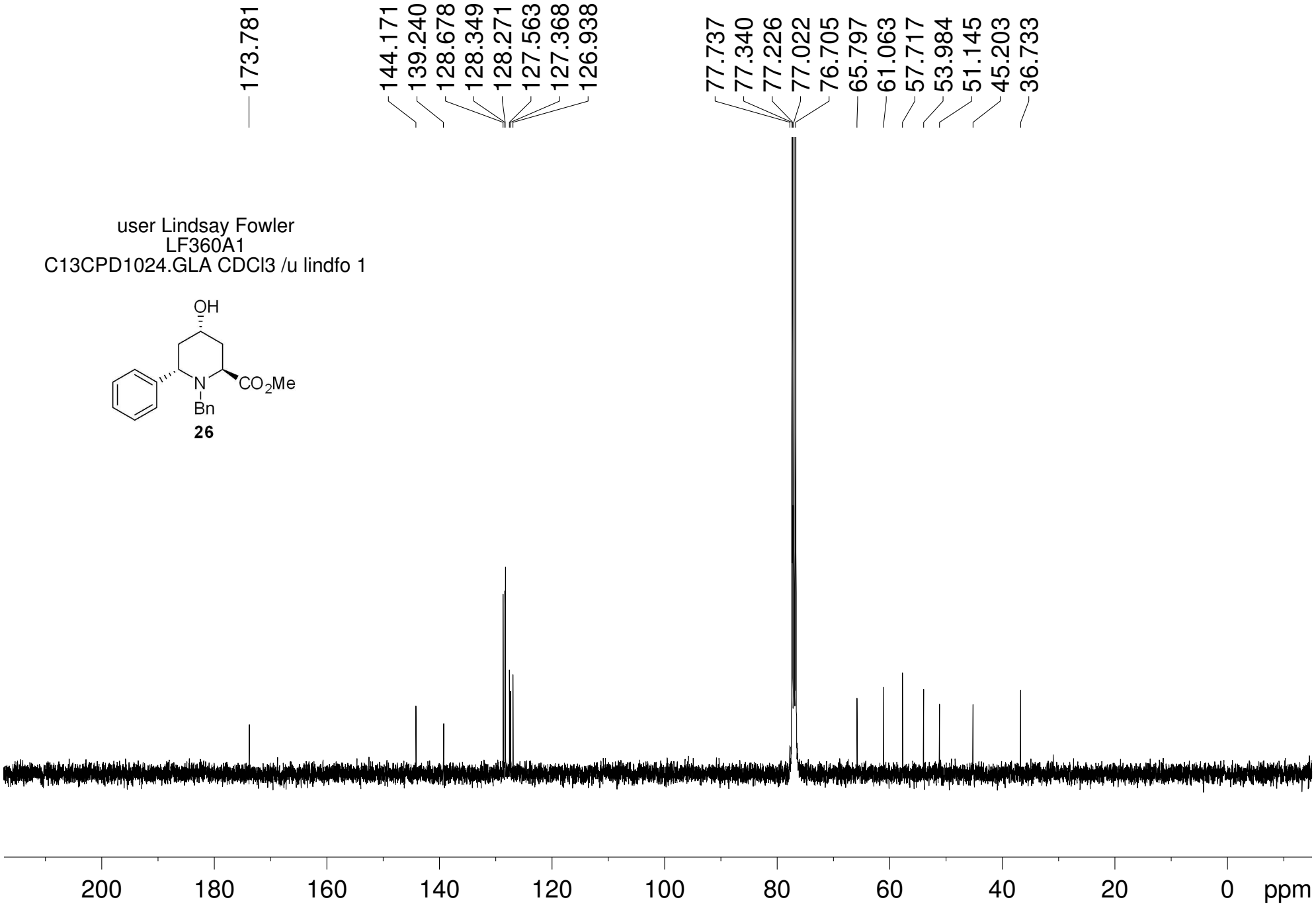

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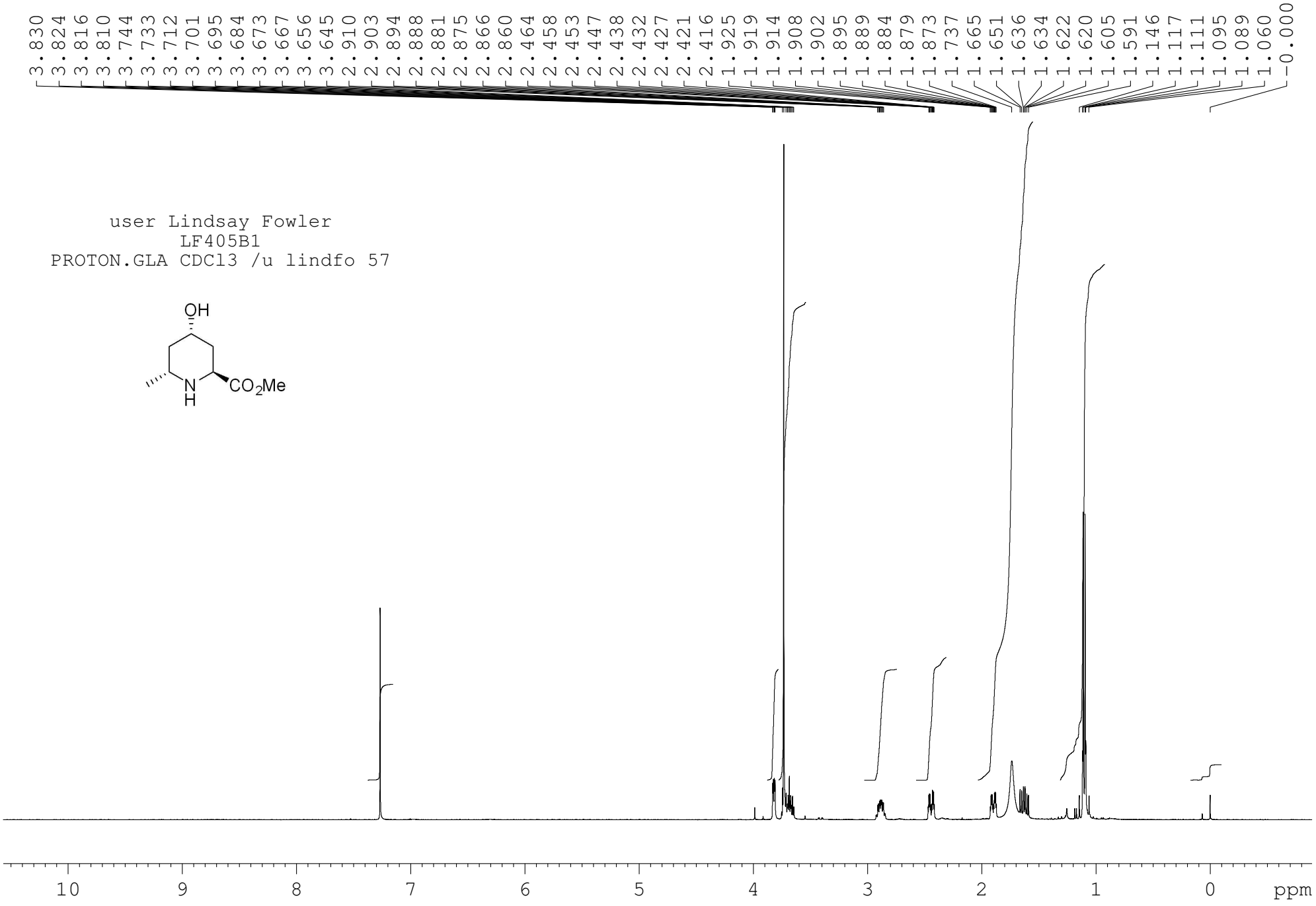

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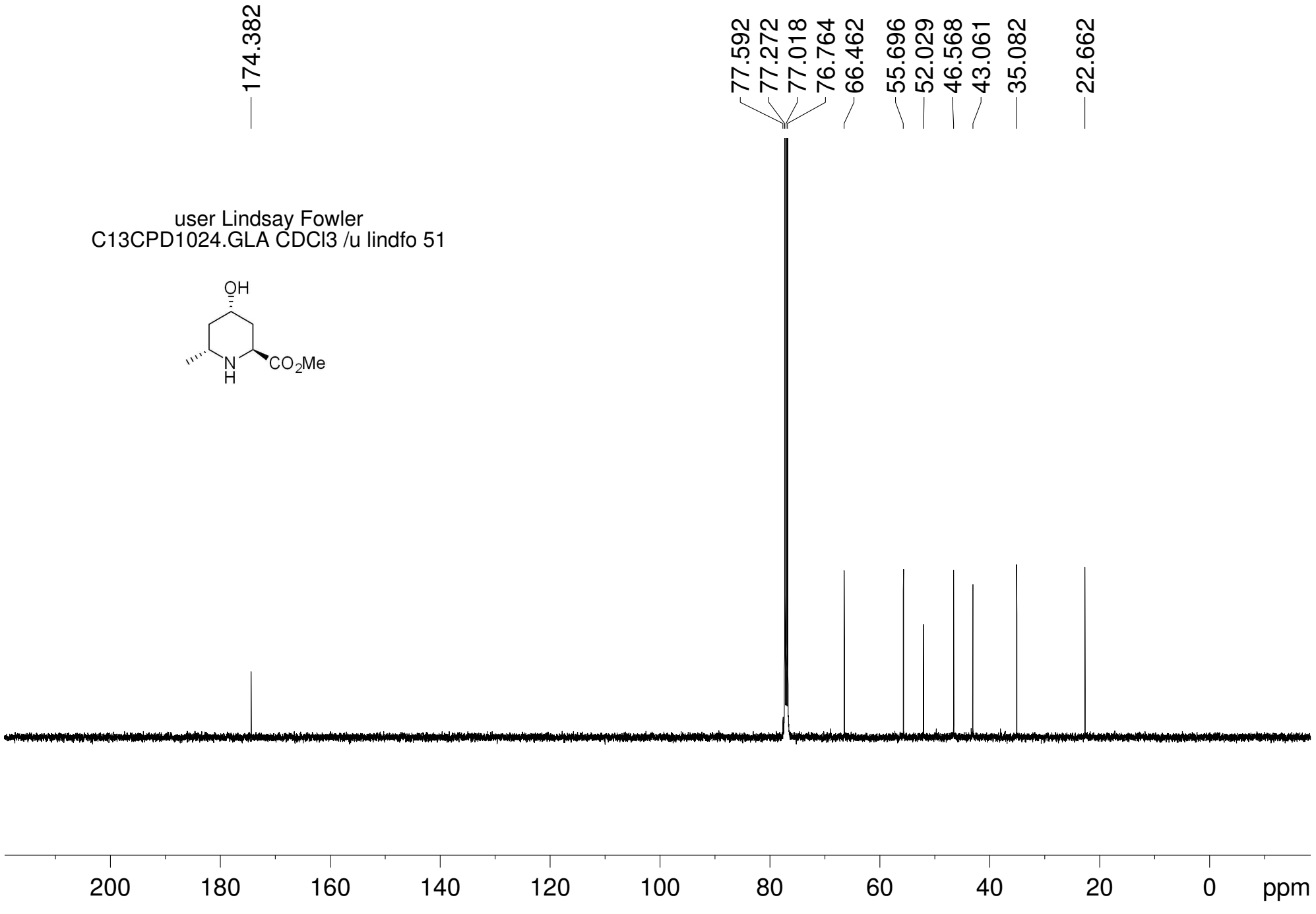

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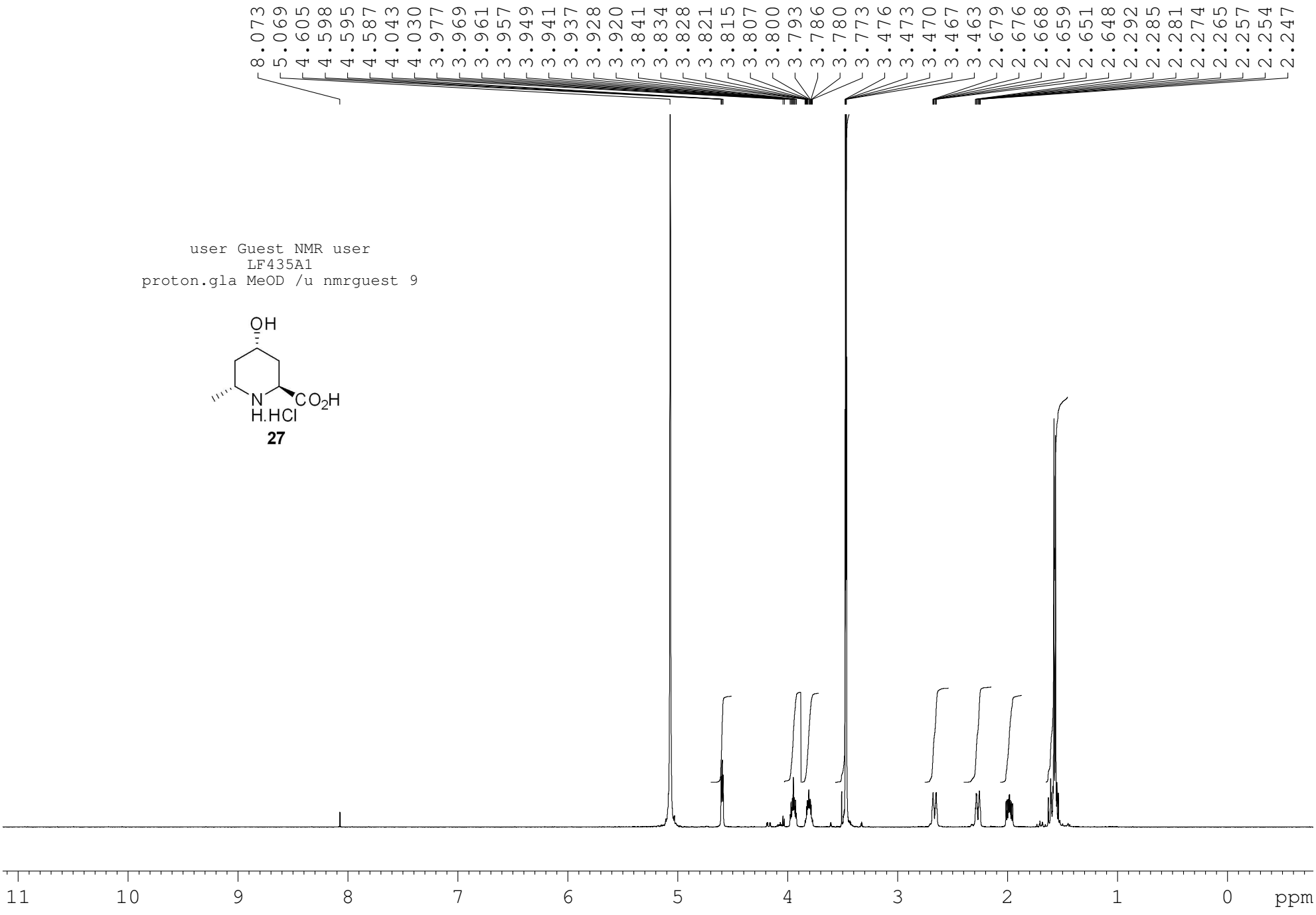

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