Combining Two-Directional Synthesis and Tandem Reactions: Synthesis of Trioxadispiroketals

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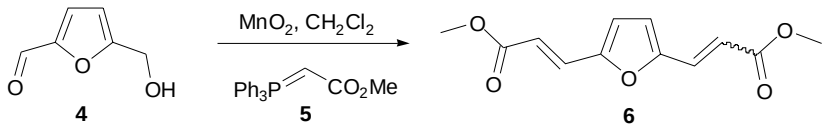
Contents:

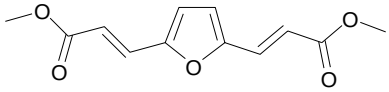
3-[5(2-Methoxycarbonyl-vinyl-)-furan-2-yl]-acrylic acid methyl ester



4 **5** **6**

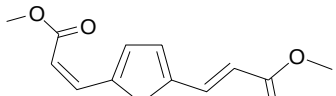
A mixture of 5-hydroxymethyl-2-furaldehyde (1g, 7.9 mmol), (methoxycarbonylmethylen)-triphenylphosphorane **5** (6.36g, 19 mmol, 2.4 eq) and manganese (iv) oxide (6.89g, 79 mmol, 10 eq) in CH_2Cl_2 (20mL) was stirred under argon for 4 days. The reaction mixture was filtered through celite and reduced *in vacuo.* Purification by column chromatography over silica gel (eluting with 1:1 petrol ether/ethyl acetate) gave 3-[5-(2-Methoxycarbonyl-vinyl-)-furan-2-yl]-acrylic acid methyl ester **6** (1.63g, 87%) as a yellow crystalline solid.

Spectral Data for the 2 isomers:



6 (*E,E*)

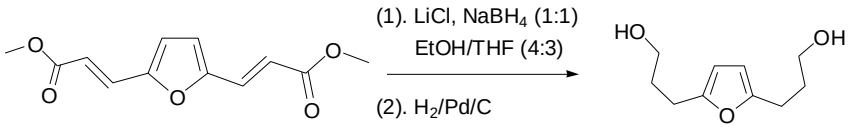
IR: 2923, 2853, 1727, 1640, 1461. MS: *m/z* = [M+H] 236.1 (100), 205.1 (95), 63.2 (98). HRMS: Calcd for $C_{12}H_{12}O_5$ [M+H]: 237.0757. Found: 237.0757. δ_H (400 MHz, $CDCl_3$); 7.33 (2H, d, *J* 15.7), 6.56 (2H, s), 6.36 (2H, d, *J* 15.7), 3.74 (3H, s). δ_C (400 MHz, $CDCl_3$); 167.3, 152.6, 130.5, 117.8, 117.0, 52.1.



6 (*E,Z*)

IR: 2923, 2853, 1727, 1635. MS: *m/z* = [M+NH_4^+] 254.2 (100), 84.2 (88), 72.2 (98). HRMS: Calcd for $C_{12}H_{12}O_5$ [M+NH_4^+]: 254.1023. Found: 254.1024. δ_H (400 MHz, $CDCl_3$); 7.65 (1H, d, *J* 3.7), 7.34 (1H, d, *J* 15.7), 6.72 (1H, d, *J* 12.9), 6.64 (1H, d, *J* 3.7), 6.32 (1H, d, *J* 15.7), 5.80 (1H, d, *J* 12.9), 3.73 (3H, s), 3.71 (3H, s). δ_C (400 MHz, $CDCl_3$); 166.4, 152.42, 151.68, 130.8, 129.9, 119.3, 117.5, 117.4, 116.7, 52.0, 51.8.

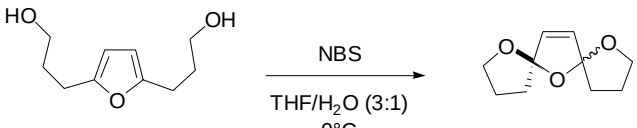
3-[5-(3-Hydroxy-propyl)-furan-2-yl]-propan-1-ol



6 **7**

To a solution of **6** (0.02g, 0.085 mmol), in a (4:3) EtOH/THF solvent system (3mL) was added LiCl (0.072g, 1.7 mmol, 20 eq), and $NaBH_4$ (0.064g, 1.7 mmol, 20 eq), and the reaction mixture was allowed to stir under argon at room temperature for 12hrs. A saturated aqueous solution of sodium hydrogen carbonate (2mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3x10ml). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and reduced *in vacuo*. Purification by column chromatography (eluting with 1:5 petrol ether/ethyl acetate) gave 3-[5-(3-Hydroxy-propyl)-furan-2-yl]-propan-1-ol **7** (0.011g, 71%) as a colourless oil. IR: 3386.0, 2925.2, 1567.3, 1446.2, 1434.7, 1010.3, 785.3, 670.2.). *m/z* = [M+H] 202.2 (27), 185.1 (100). HRMS: Calcd for $C_{10}H_{16}O_3$ [M+H]: 185.1172. Found: 185.1172. δ_H (400 MHz, $CDCl_3$); 5.88 (2H, s), 3.66 (4H, t, *J* 6.4), 2.67 (4H, t, *J* 7.4), 2.24 (2H, s), 1.87 (4H, tt, *J* 6.4 +7.4). δ_C (400 MHz, $CDCl_3$); 153.9, 105.4, 61.9, 30.9, 24.3.

1,6,8-Trioxa-dispiro[4.1.4.2]tridec-12-ene

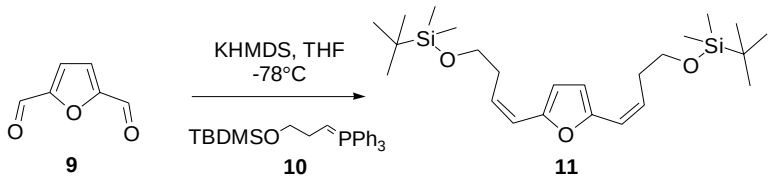


7 **8**

To a stirred solution of diol **7** (0.035g, $1.90x10^{-4}$M) in a (3:1) THF/H_2O solvent system (2mL) at 0°C was added portion wise over 20 minutes *N*-bromosuccinimide (0.041g, $2.3x10^{-4}$M, 1.2eq). After the addition the reaction was allowed to stir for a further 20 minutes at 0°C. A saturated aqueous solution of sodium thiosulphate (1mL) was added and the mixture was allowed to stir for 5 minutes before the addition of a saturated aqueous solution of sodium hydrogen carbonate (2mL) and diethyl ether (5mL). The organic layer was separated, washed with a saturated aqueous solution of sodium hydrogen carbonate (1x5mL), dried over anhydrous sodium sulphate and reduced *in vacuo*. Purification by column chromatography over silica gel (eluting with 1:1 hexane/ethyl acetate) gave 1,6,8-trioxa-dispiro[4.1.4.2]tridec-12-ene **8** (0.016g, 46%) as a colourless solid. IR: 2956, 2853, 1720, 1456, 1074. 1021. MS: *m/z* = [M+H]: 183.1 (100), 152.1 (32), 98.1 (32). HRMS: Calcd for $C_{10}H_{14}O_3$ [M+H]:

183.1016. Found: 183.1016. δ_H (400 MHz, C_6D_6); 5.81 (1H, s), 5.79 (1H, s), 4.02-4.09 (2H, m), 3.68-3.74 (2H, m), 2.20-2.26 (1H, m), 1.95-2.07 (2H, m), 1.81-1.89 (1H, m), 1.68-1.79 (2H, m), 1.51-1.62 (2H, m); δ_C (300 MHz, C_6D_6); 132.11, 131.82, 116.28, 115.28, 66.98, 66.92, 35.93, 35.62, 23.69, 23.64.

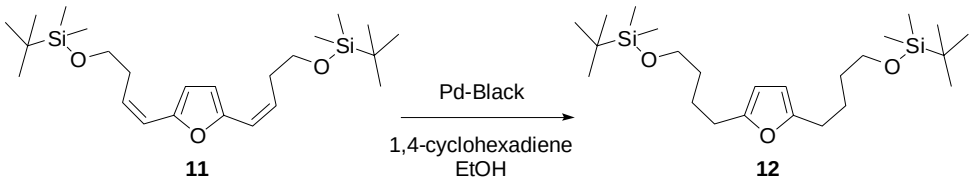
2,5-Bis-[4-(*tert*-butyl-dimethyl-silanyl-oxy)-but-1-enyl]-furan



9 **10** **11**

To a stirred suspension of phosphonium salt **10** (2.1g, 4 mmol, 2.2eq) in THF (30mL) at -78°C under argon, was added a solution of KHMDS (0.5M solution in toluene, 8.1 mL, 4 mmol, 2.2eq) and the resulting orange mixture was stirred for 30 minutes. To this mixture was then added a solution of difuraldehyde **9** (0.23g, 1.8 mmol) in THF (10 mL) and the reaction was allowed to warm to room temperature over 2 hours. A saturated aqueous solution of ammonium chloride (20 mL) was added, followed by ethyl acetate (20 mL). The aqueous layer was separated and extracted with ethyl acetate (3x20 mL) and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$ and reduced *in vacuo*. Purification by column chromatography (2 columns firstly eluting with 1:1 petrol ether/ethyl acetate, then 10:1 petrol ether/ethyl acetate) gave 2,5-Bis-[4-(*tert*-butyl-dimethyl-silanyl-oxy)-but-1-enyl]-furan **11** (0.42g, 54%) as a yellow oil. IR: 2954.8, 2927.8, 2856.2, 1700.1, 1652.6. MS: *m/z* = [M+H]: 458.4 (40), 454.4 (70), 69.3 (100). HRMS: Calcd for $C_{24}H_{44}O_3Si_2$ [M+NH_4^+]: 454.3167. Found: 454.3168. δ_H (400 MHz, $CDCl_3$); 6.24 (2H, s), 6.19 (2H, dt, *J* 9.80, 1.46), 5.57 (2H, dt, *J* 9.8, 6.0), 3.72 (4H, t, *J* 5.5), 2.69 (4H, dt, 5.5, 1.4), 0.87 (18H, s), 0.04 (12H, s). δ_C (400 MHz, $CDCl_3$); 152.18, 127.10, 118.41, 110.97, 62.65, 32.98, 25.93, 18.33, -5.28.

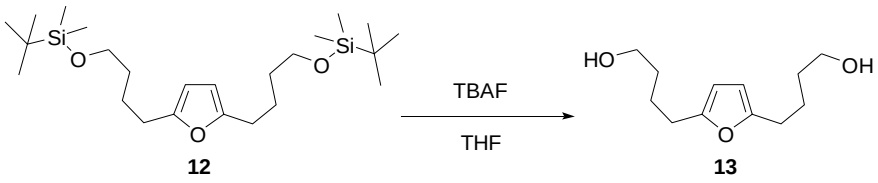
2,5-Bis-[4-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-furan



11 **12**

A solution of di-olefin (0.15g, 0.34 mmol) in EtOH (20 mL), under argon at room temperature was treated with Pd-Black (0.6g, 4 eq by weight) and 1,4-cyclohexadiene (1.1g, 13.7 mmol, 40 eq) and the reaction was stirred at room temperature for 2 hours. The reaction mixture was filtered through celite and reduced *in vacuo* to give 2,5-Bis-[4-(*tert*-butyl-dimethyl-silanyloxy)-butyl]-furan **12** (0.148g, 98%) as a colourless oil. IR: 2927.8, 2856.8, 1471.5, 1462.7, 1388.5, 1360.8, 1256.2, 1103.9. MS: *m/z* = [M+NH_4]: 458.4 (100), 69.3 (41), 63.3 (46). HRMS: Calcd for $C_{24}H_{48}O_3Si_2$ [M+NH_4^+]: 458.3480. Found: 458.3486. δ_H (400 MHz, $CDCl_3$); 5.84 (2H, s), 3.63 (4H, t, *J* 6.3), 2.58 (4H, t, *J* 7.4), 1.62-1.70 (4H, m), 1.53-1.60 (4H, m), 0.9 (18H, s), 0.04 (12H, s). δ_C (400 MHz, $CDCl_3$); 154.37, 104.97, 62.91, 32.31, 27.80, 25.96, 24.42, 18.35, -5.30.

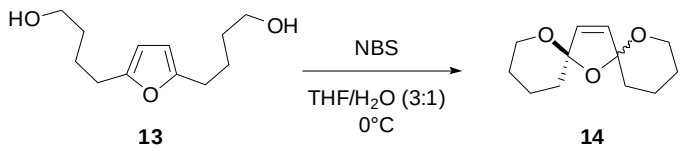
4-[5-(4-Hydroxy-butyl)-furan-2-yl]-butan-1-ol



12 **13**

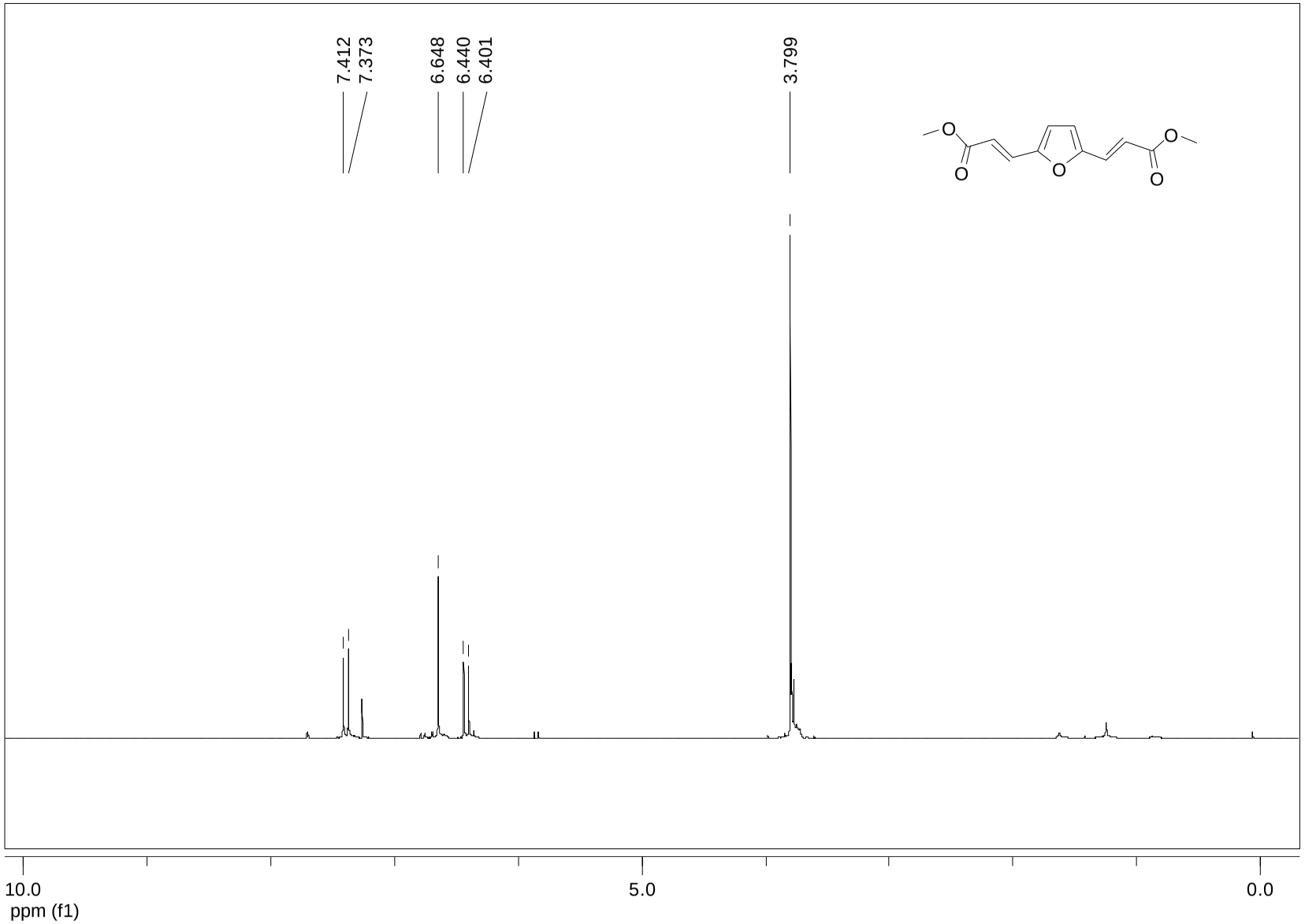
A solution of silyl ether **12** (0.135g, 0.31 mmol) in THF (5 mL) under an atmosphere of argon at room temperature was treated with a solution of tetra-^{n}butyl ammonium fluoride (1M in THF, 0.67 mL, 2.2 eq) and the reaction mixture was allowed to stir at room temperature for 2 hours before the addition of brine (2 mL). The aqueous layer was separated and extracted with diethyl ether (3 x 10 mL). The combined extracts were washed with saturated $NaHCO_3$, dried over anhydrous $MgSO_4$ and reduced *in vacuo*. Purification by column chromatography (eluting with 1:5 petrol ether/ethyl acetate) gave 4-[5-(4-Hydroxy-butyl)-furan-2-yl]-butan-1-ol **13** (0.035g, 54%) as a colourless oil. IR: 3337.3, 2925.6, 1652.6, 1559.7, 1456.5, 1063.1. MS: *m/z* = [M+H]: 213.1 (100), 195.1 (20). HRMS: Calcd for $C_{12}H_{20}O_3$ [M+H^+]: 213.1485. Found: 213.1483. δ_H (400 MHz, $CDCl_3$); 5.84 (2H, s), 3.63 (4H, t, *J* 6.3), 2.59 (4H, t, *J* 7.2), 1.64-1.71 (4H, m), 1.55-1.62 (4H, m). δ_C (400 MHz, $CDCl_3$); 154.14, 105.26, 62.64, 32.12, 27.70, 24.35.

1,7,9-Trioxa-dispiro[5.1.5.2]pentadec-14-ene



13 **14**

To a stirred solution of diol **13** (0.045g, 2.12×10^{-4}M) in a (3:1) THF/H_2O solvent system (2mL) at 0°C was added portion wise over 20 minutes *N*-bromosuccinimide (0.045g, 2.5×10^{-4}M, 1.2eq). After addition the reaction was allowed to stir for a further 20 minutes at 0°C. A saturated aqueous solution of sodium thiosulphate (1mL) was added and the mixture was allowed to stir for 5 minutes before the addition of a saturated aqueous solution of sodium hydrogen carbonate (2mL) and diethyl ether (5mL). The organic layer was separated, washed with a saturated aqueous solution of sodium hydrogen carbonate (1x5mL), dried over anhydrous sodium sulphate and reduced *in vacuo*. Purification by column chromatography over silica gel (eluting with 1:1 hexane/ethyl acetate) gave 1,7,9-Trioxa-dispiro[5.1.5.2]pentadec-14-ene **14** (0.029g, 65%) as a colourless solid. IR: 2940, 2870, 1653. MS: *m/z* = [M+H] 161.0 (100), 211.1 (80). HRMS: Calcd for $C_{12}H_{18}O_3$ [M+H]: 211.1329. Found: 211.1329. δ_H (400 MHz, C_6D_6); 5.93 (1H, s), 5.90 (1H, s), 3.98-4.06 (2H, m), 3.70-3.82 (2H, m), 1.86-1.98 (2H, m), 1.51-1.79 (10H, m); δ_C (400 MHz, C_6D_6); 134.05, 133.99, 109.71, 106.85, 63.66, 63.50, 35.30, 34.76, 25.21, 25.15, 19.84, 19.77.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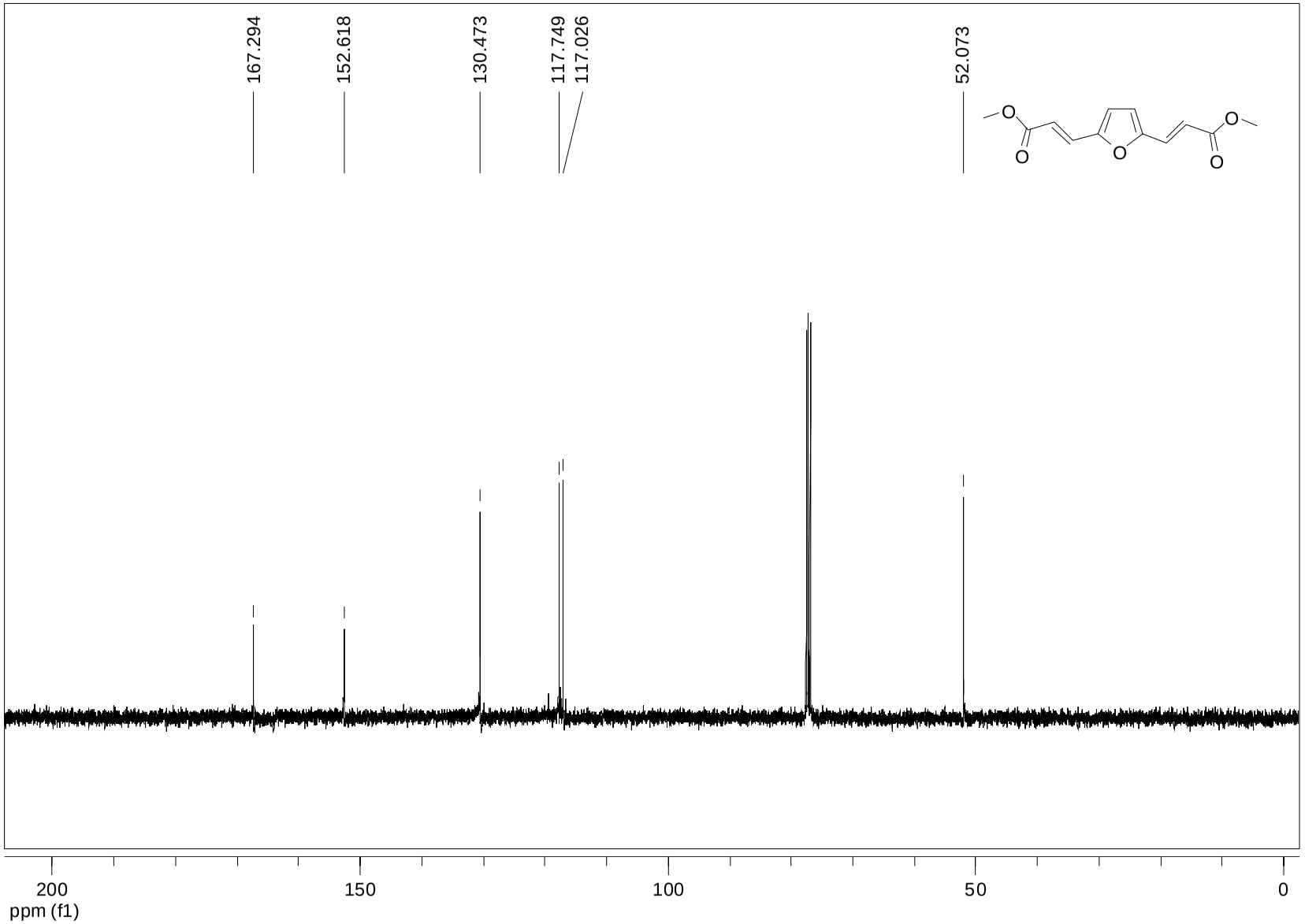
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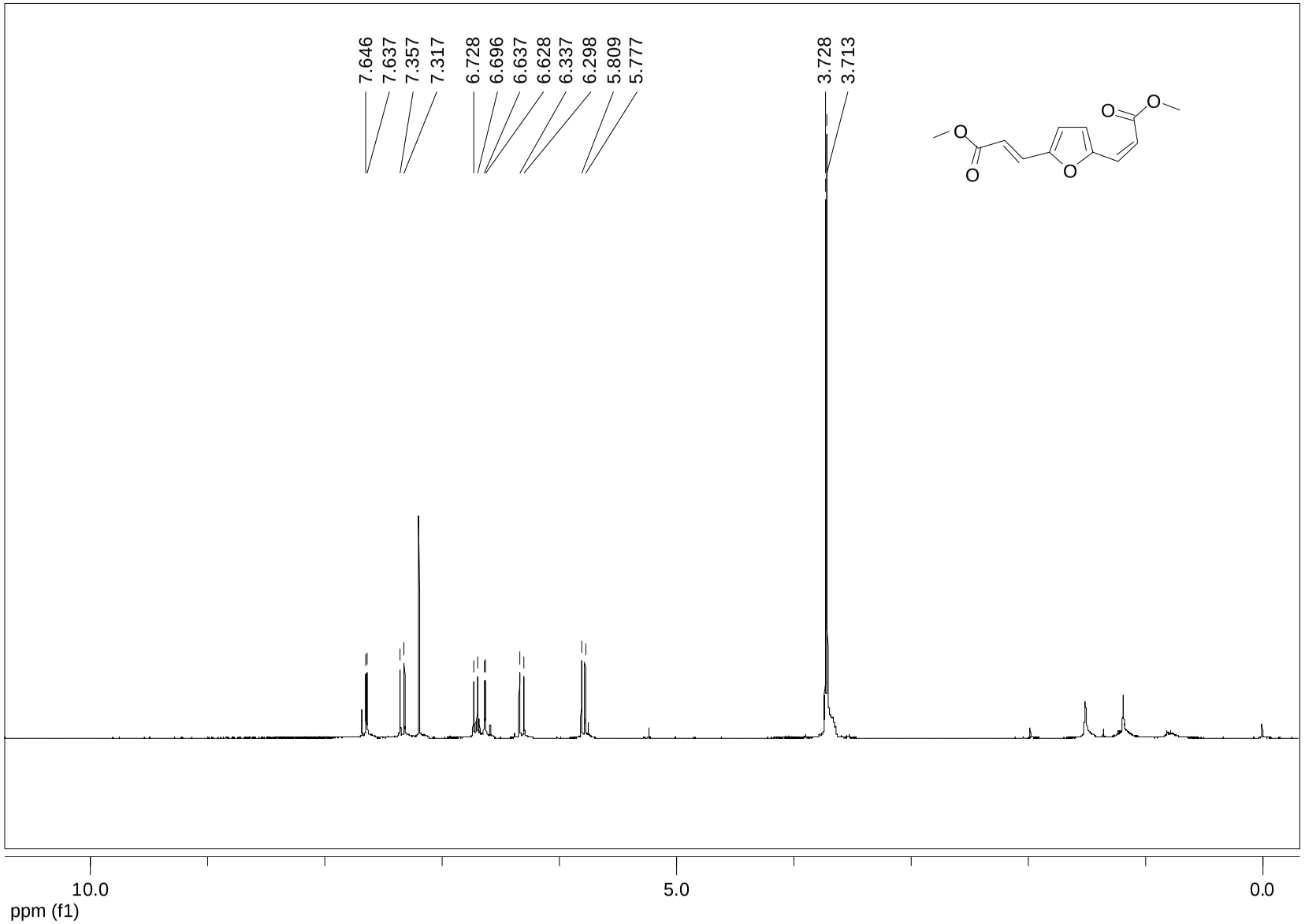
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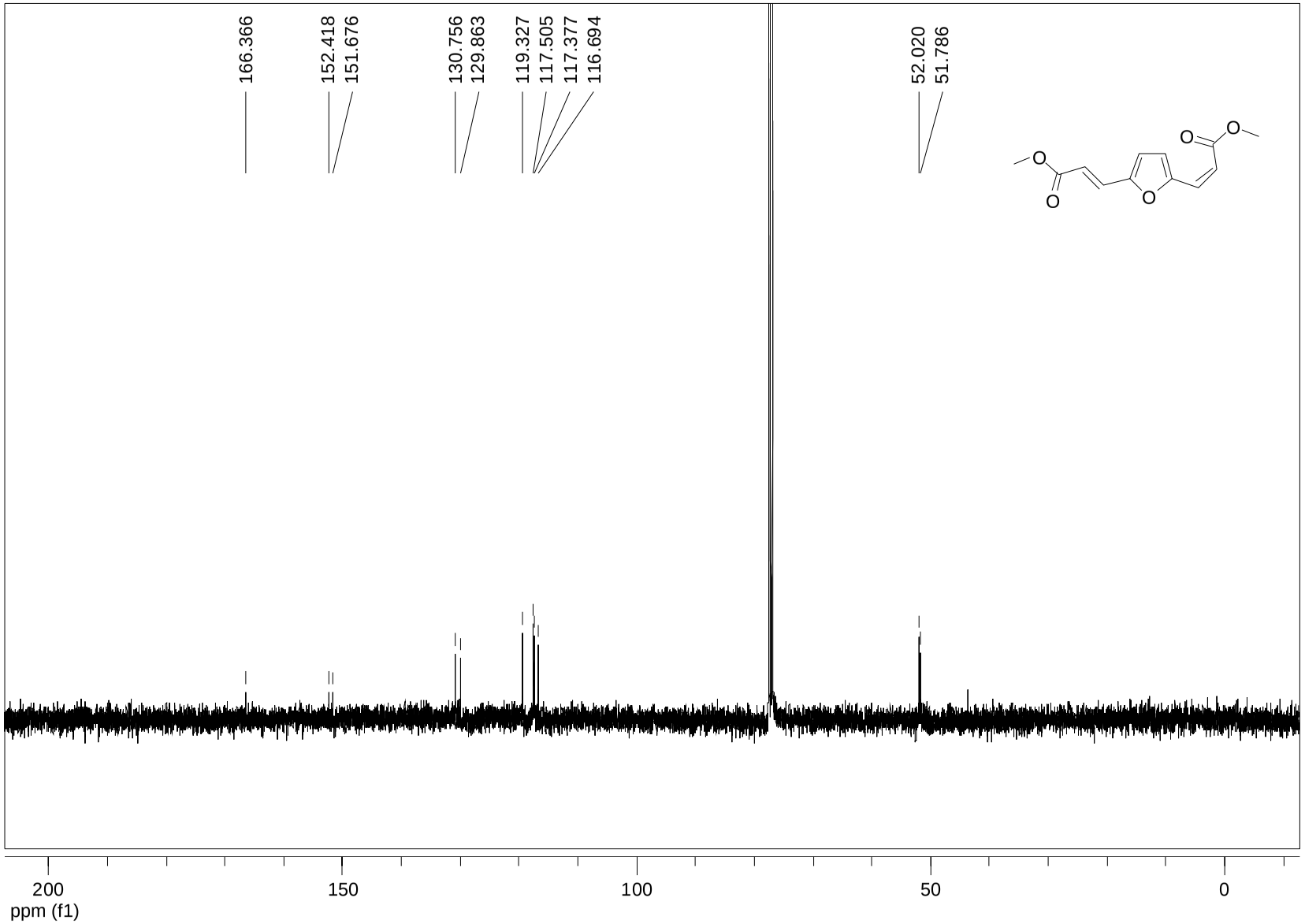
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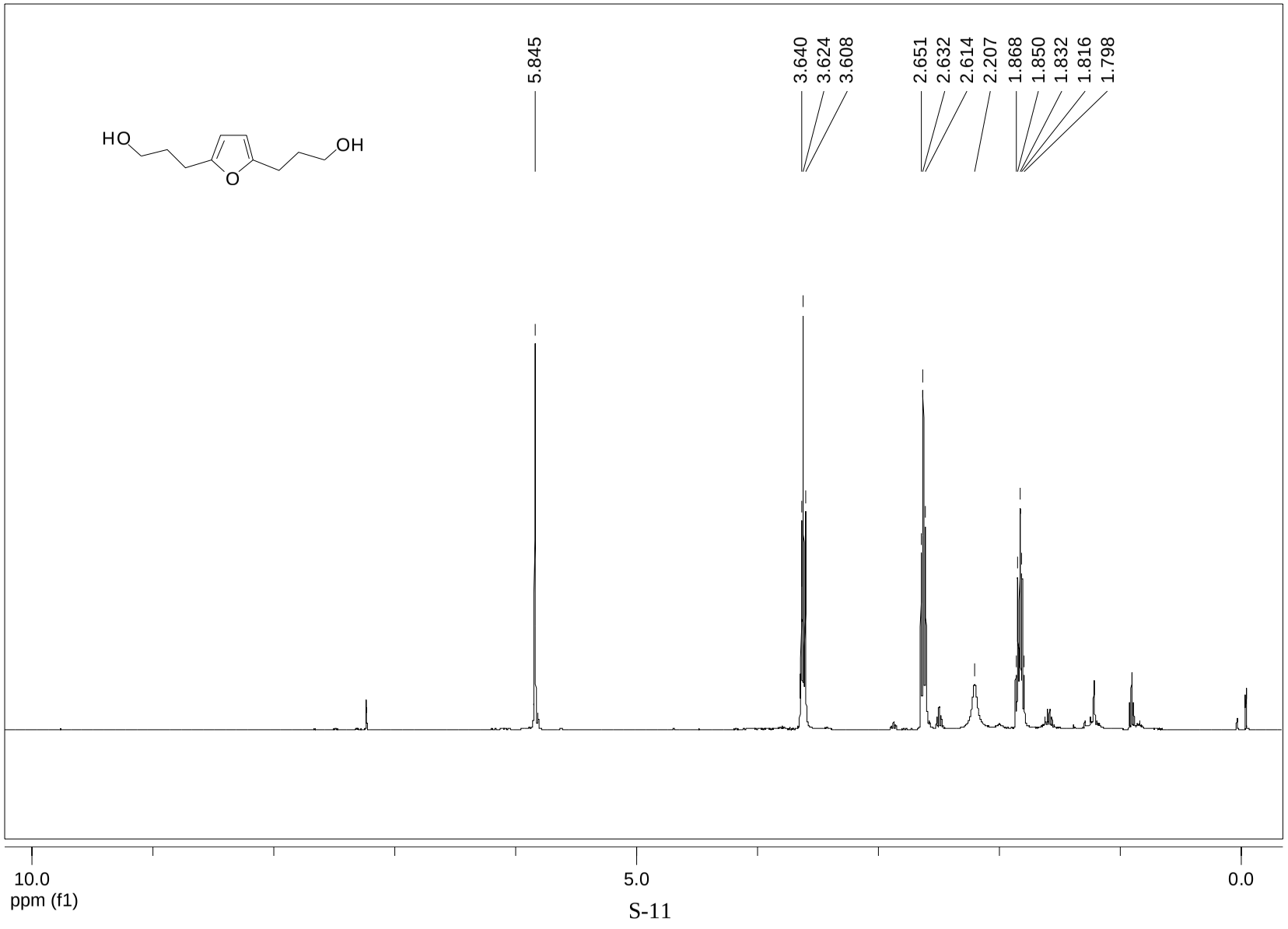
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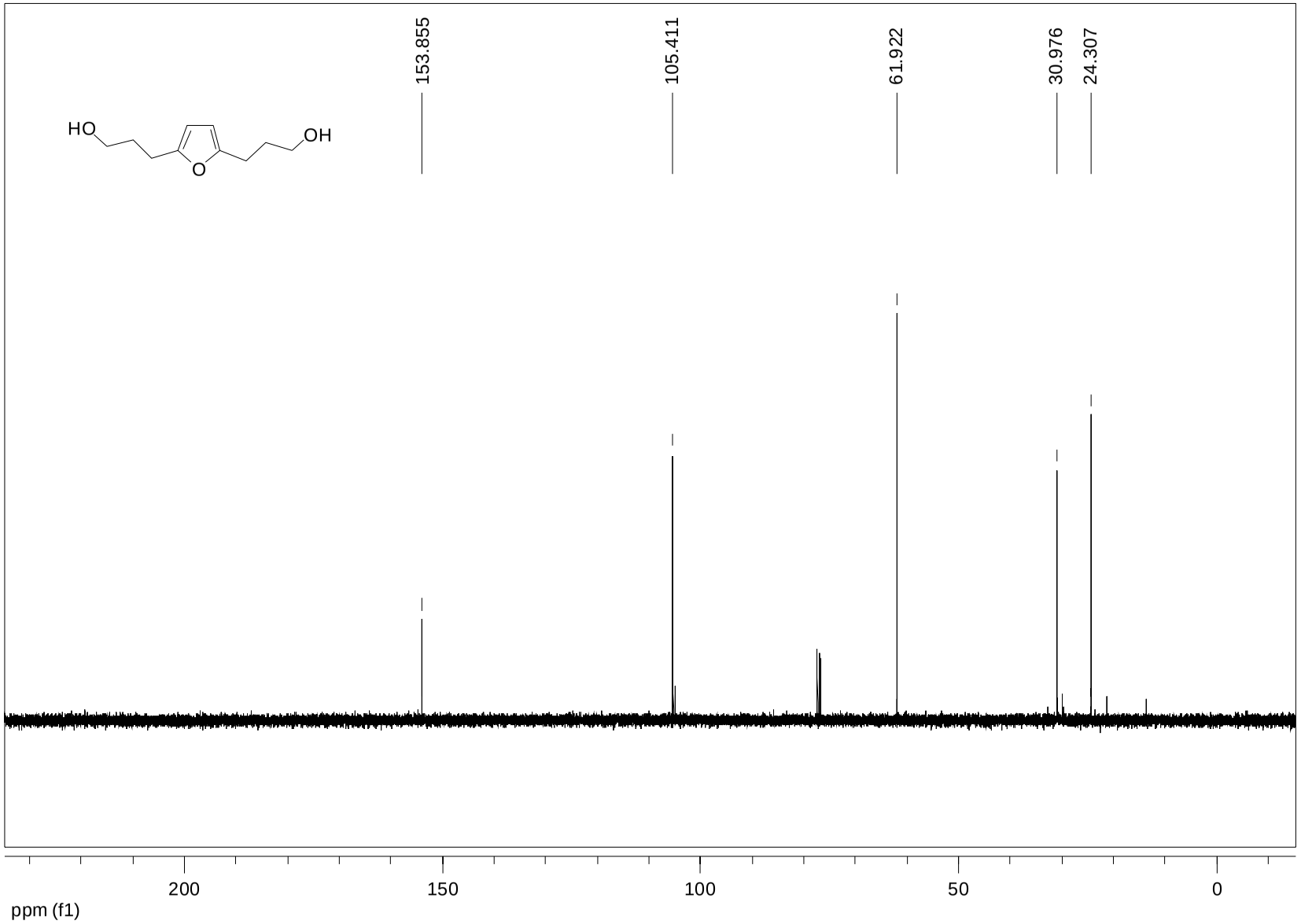
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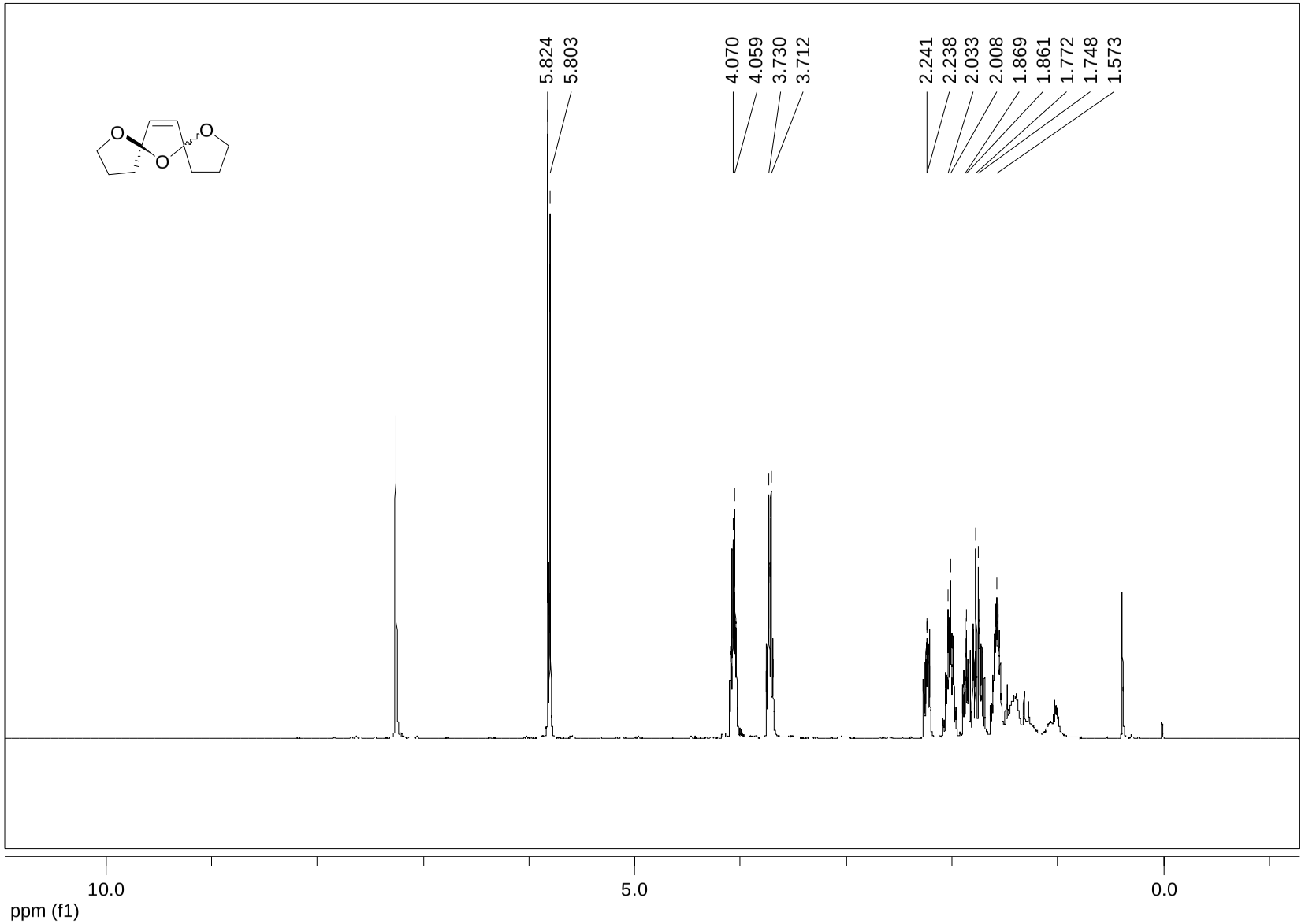
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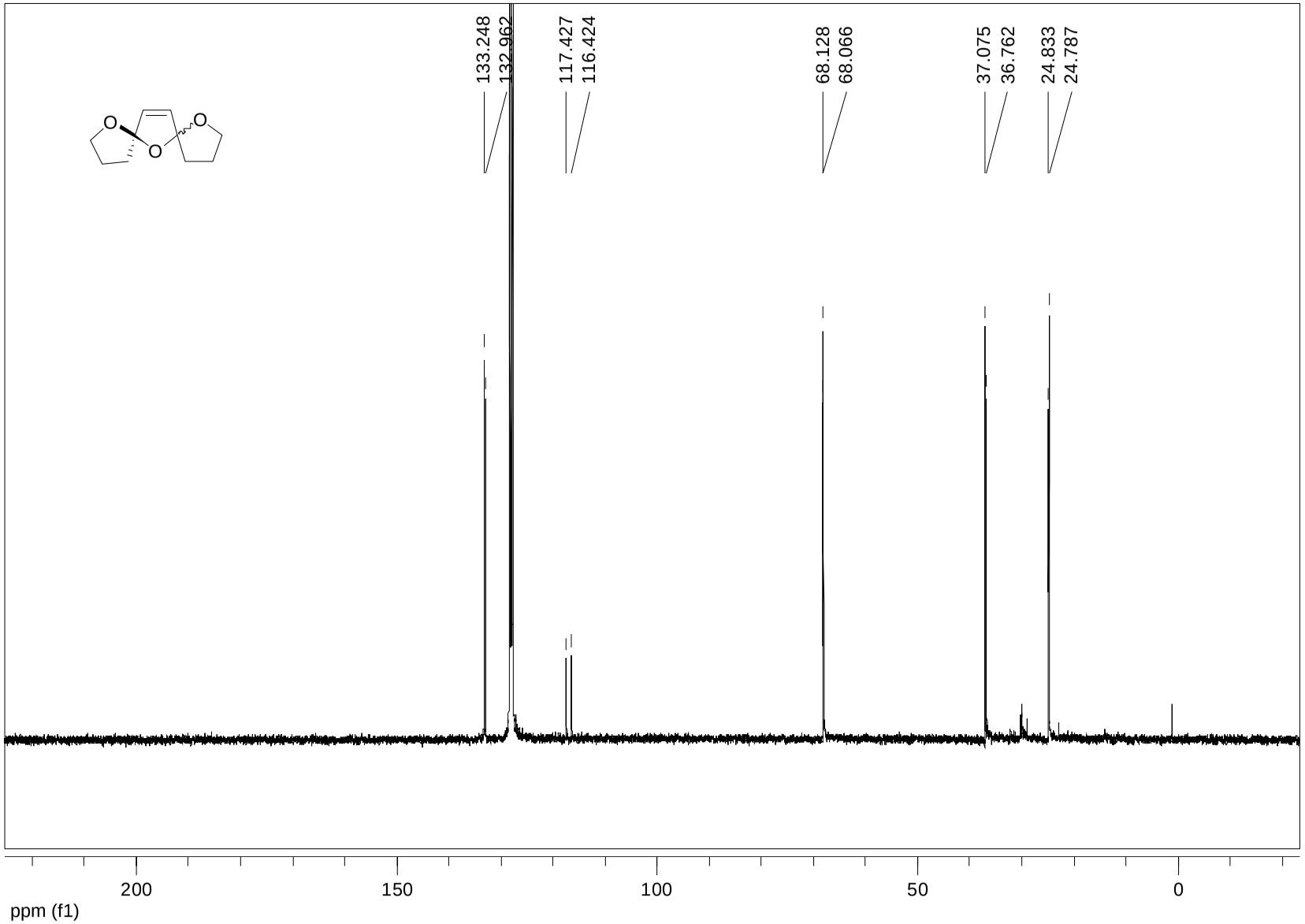
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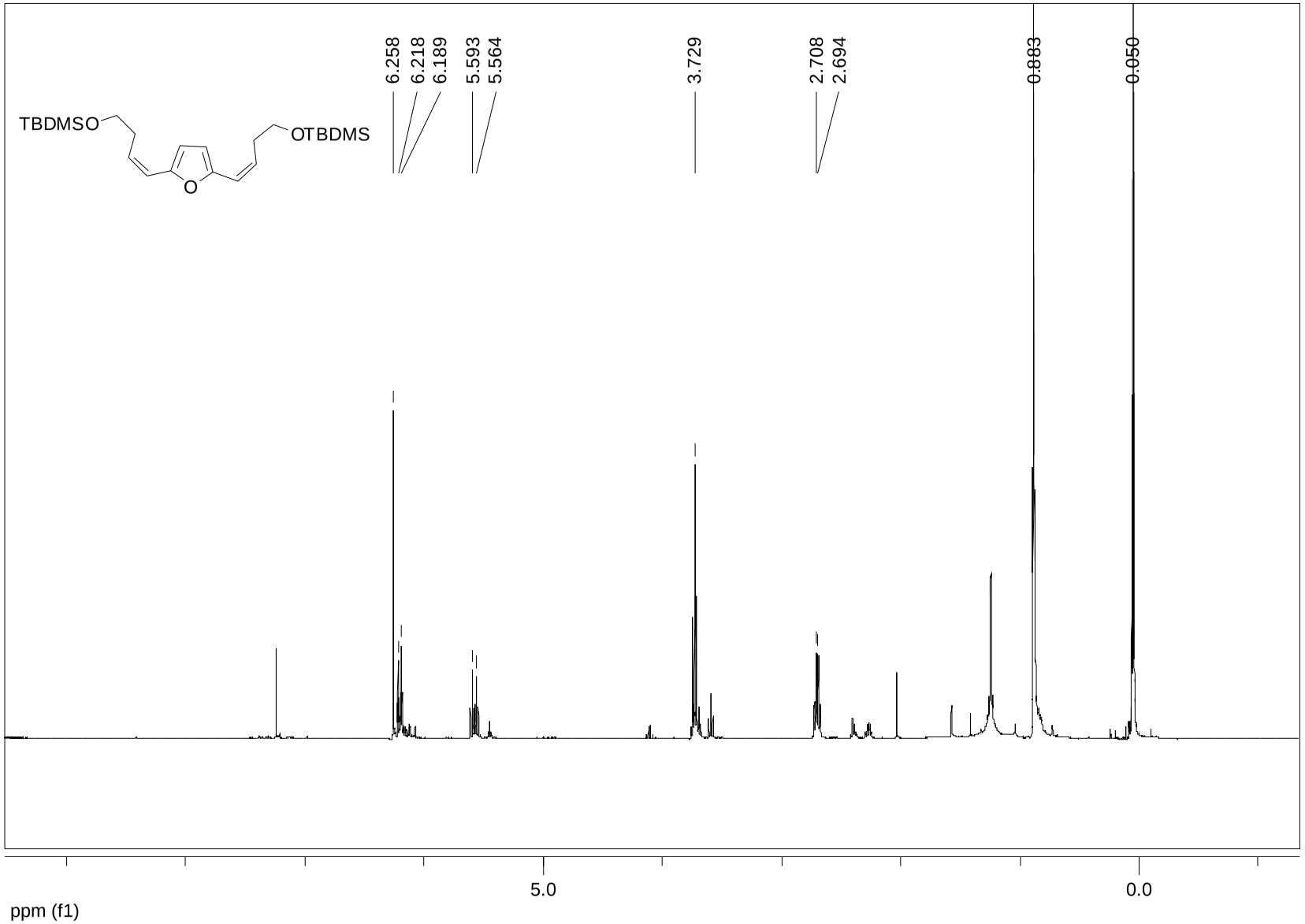
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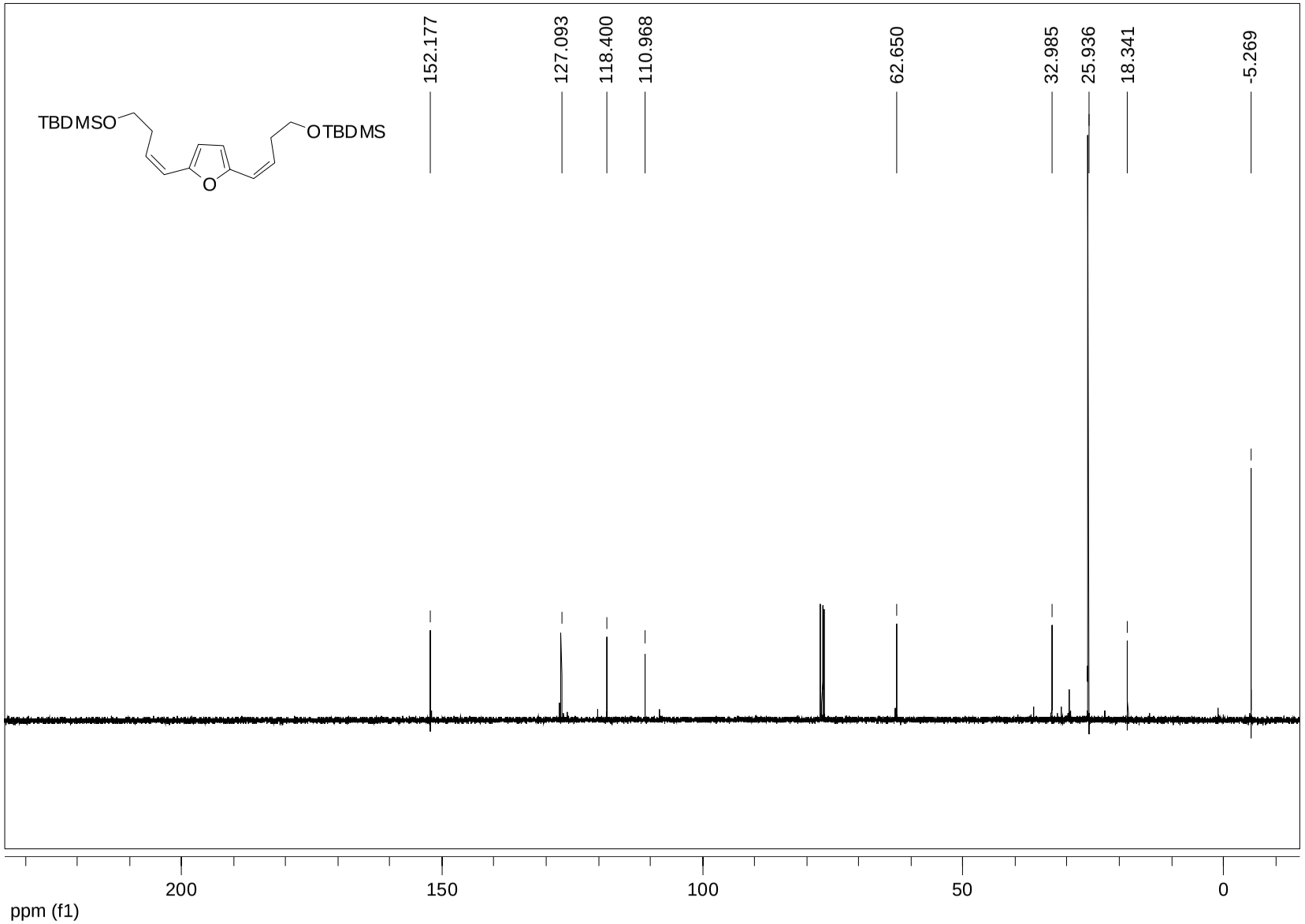
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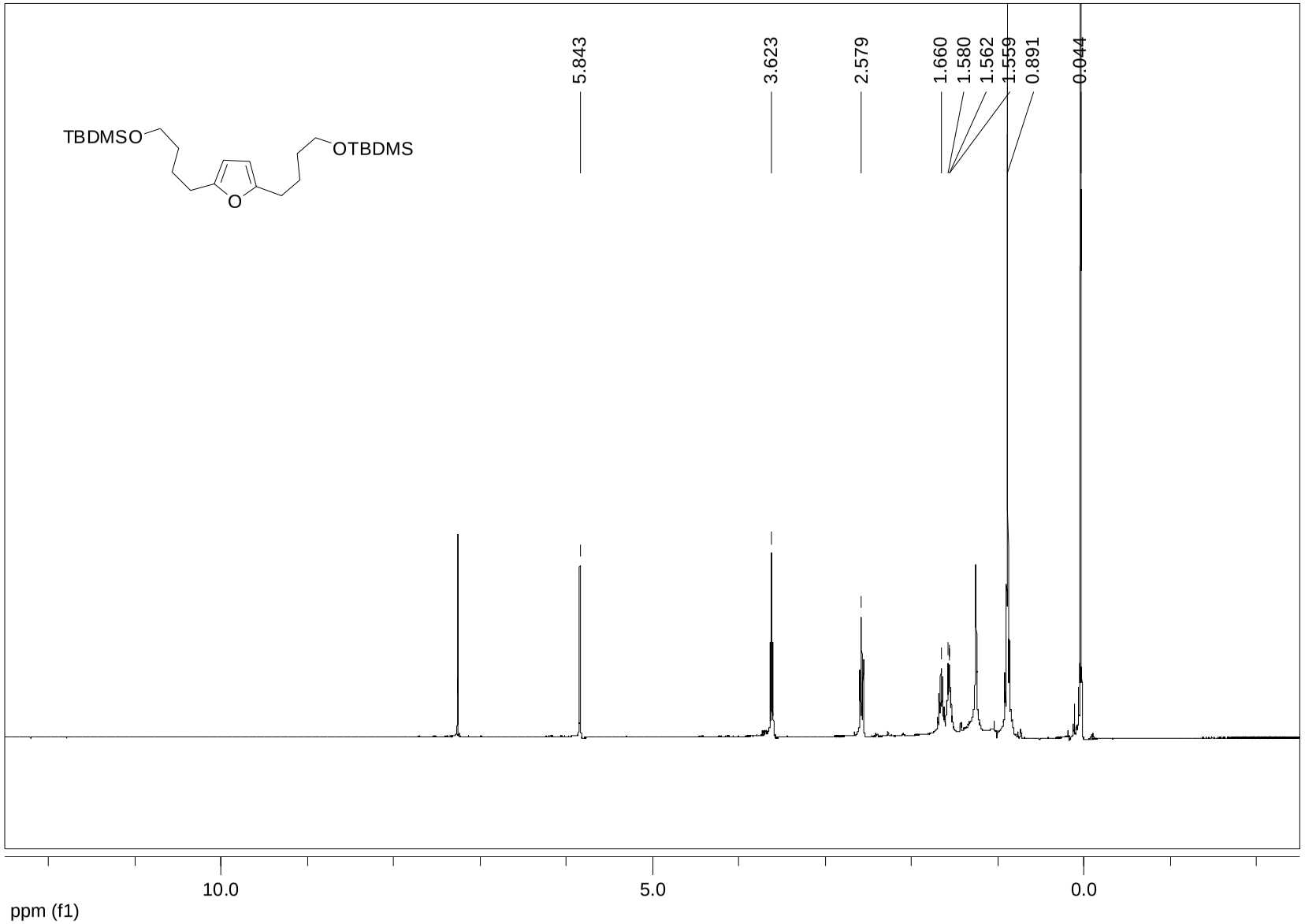
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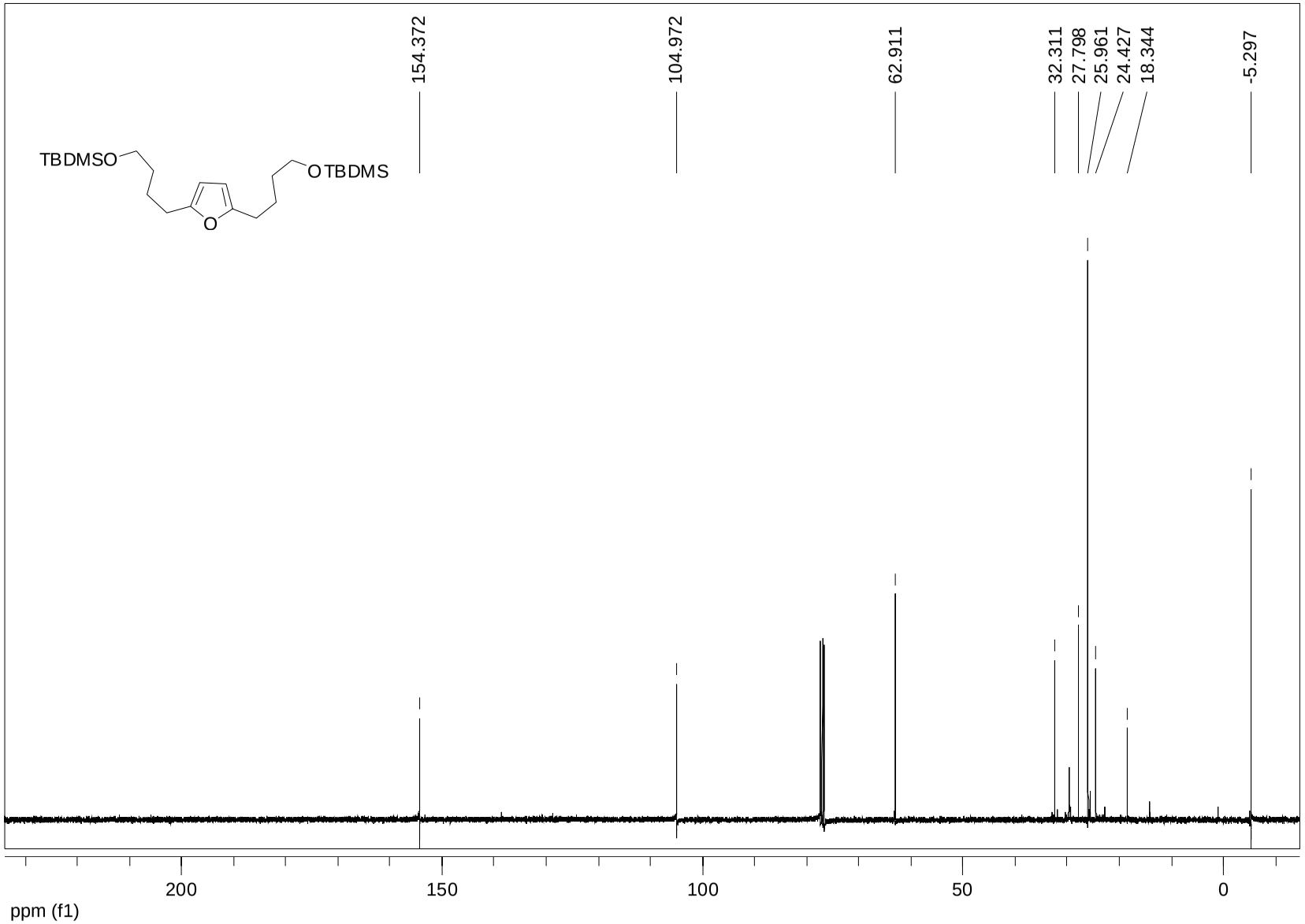
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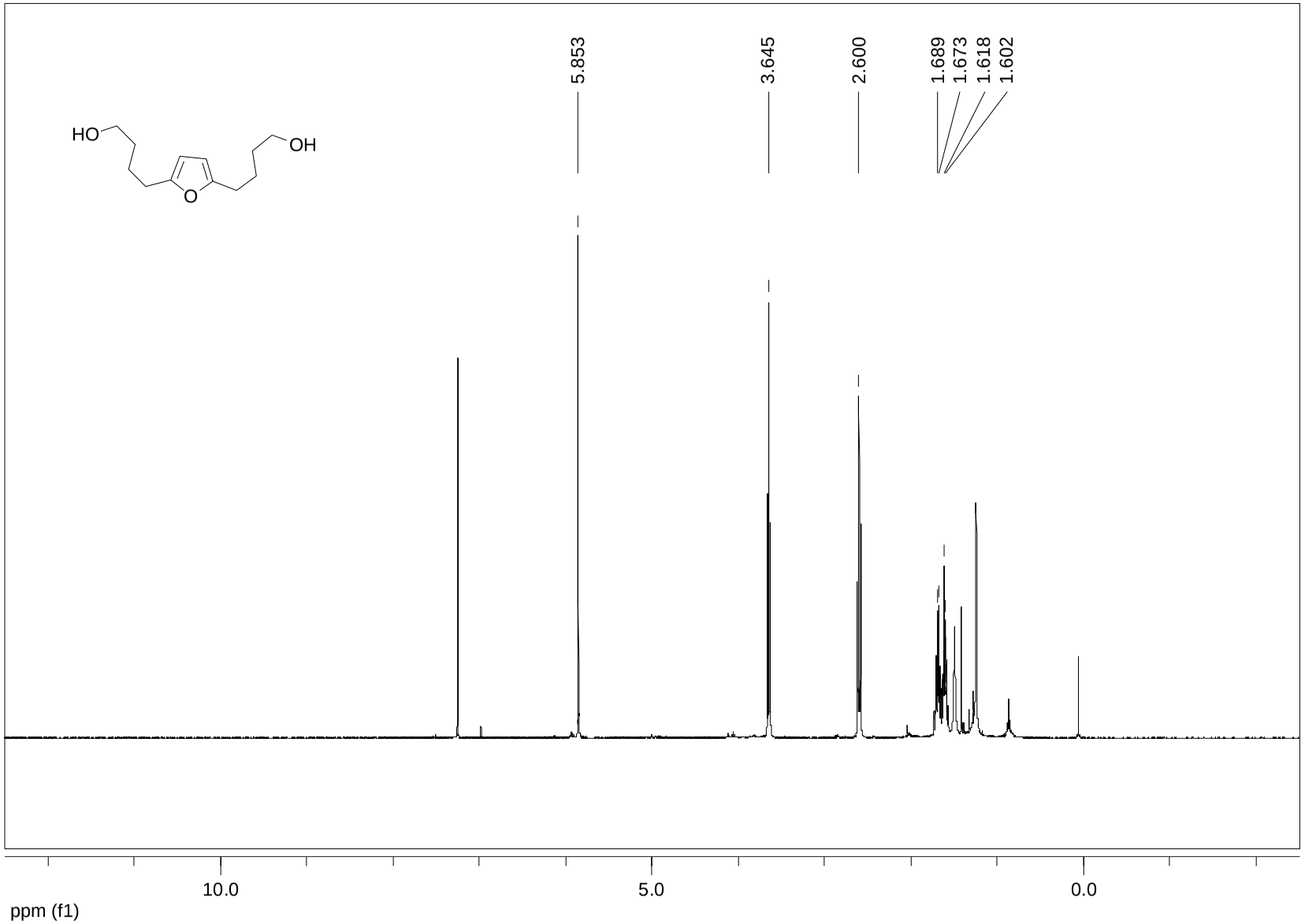
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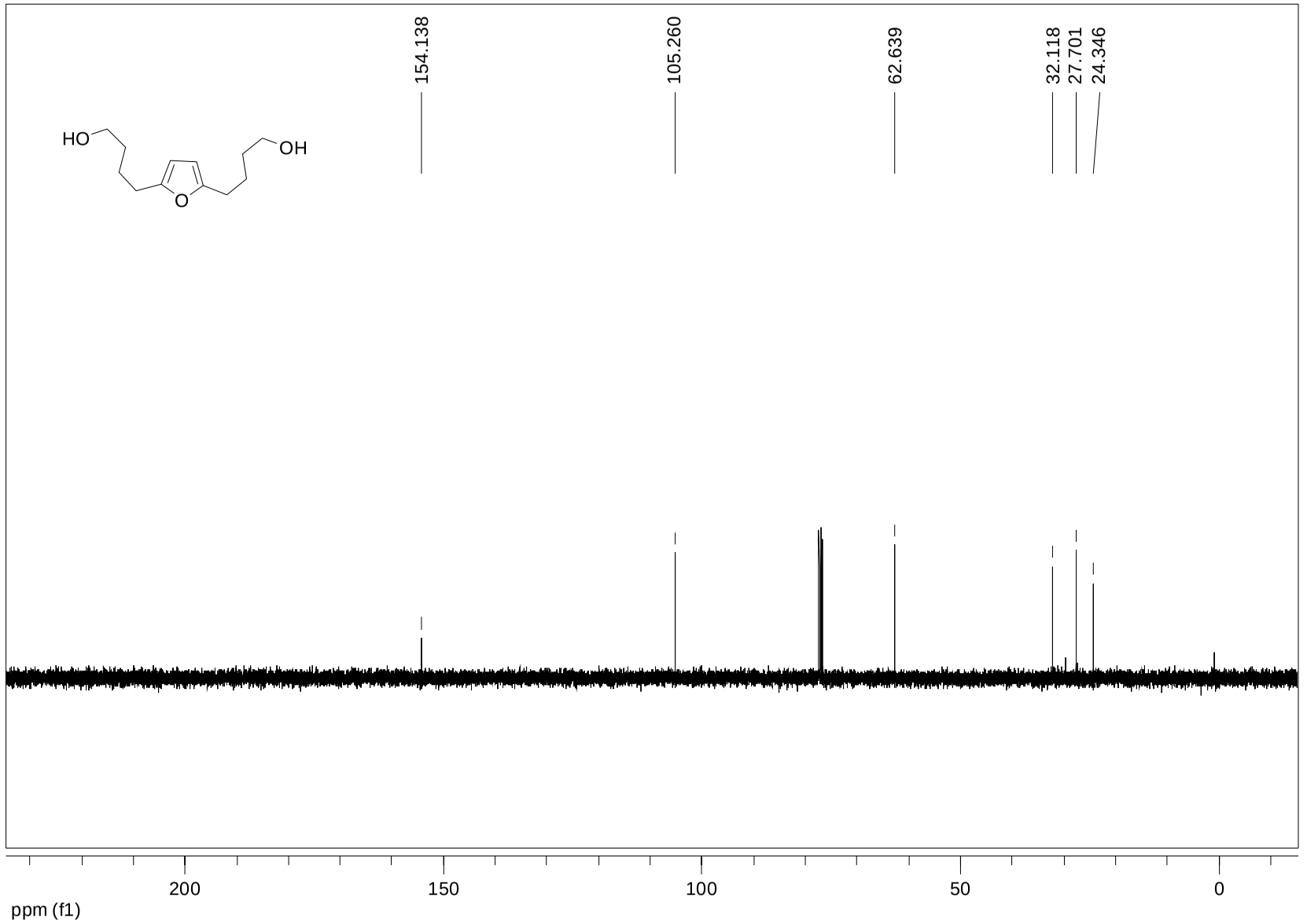
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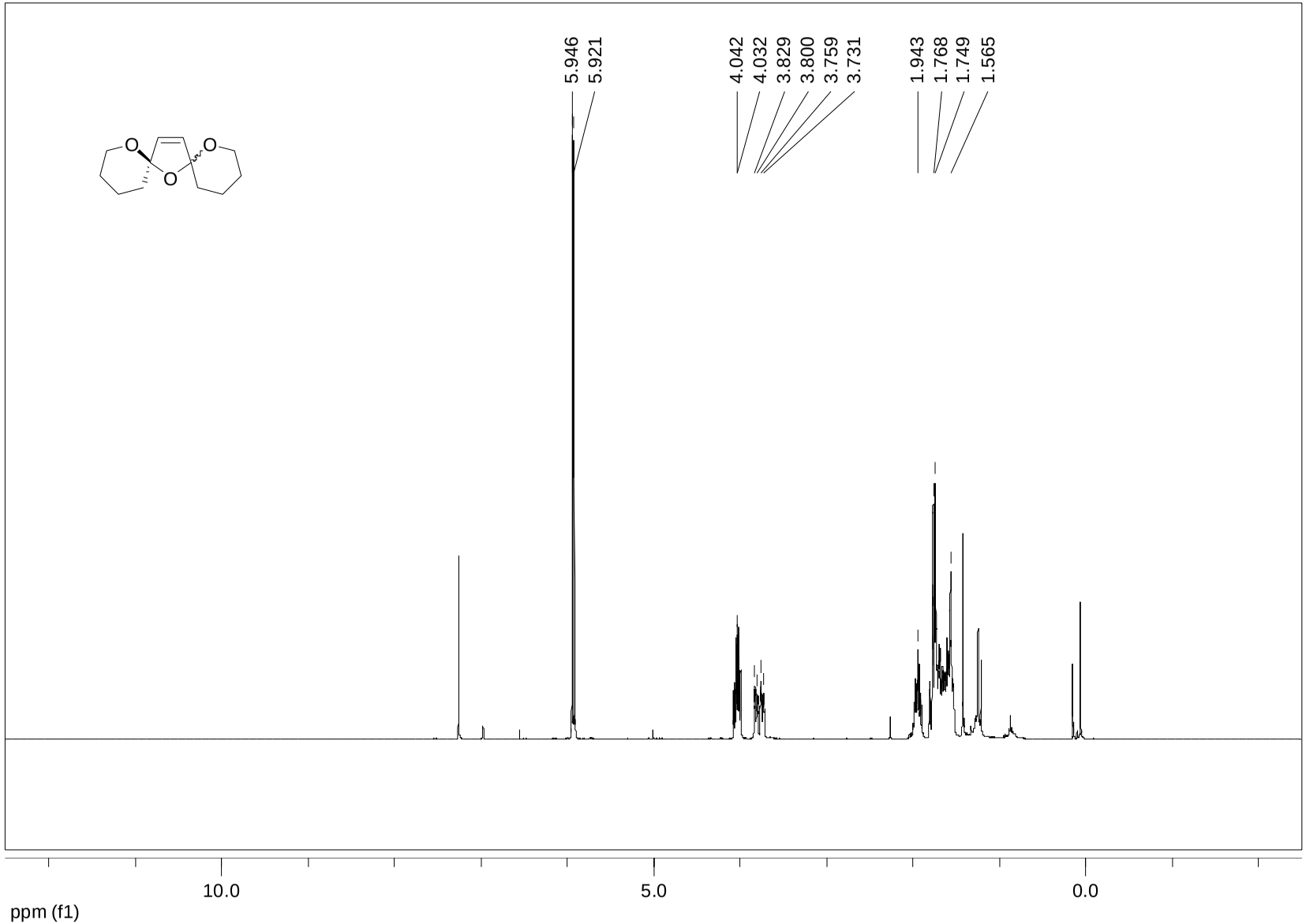
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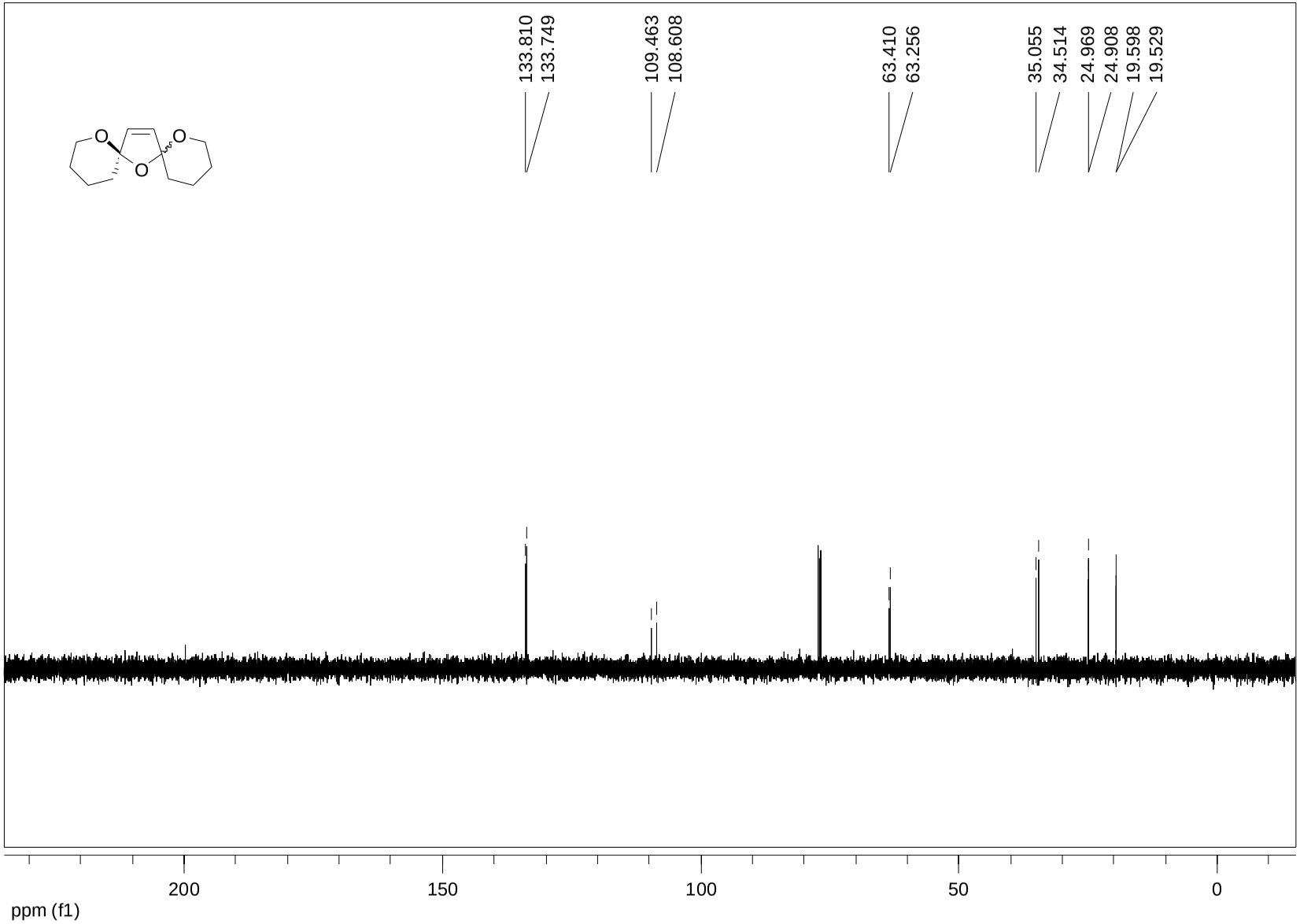
1.943
1.768
1.749
1.565
O
O
O
10.0
5.0
0.0
ppm (f1)


133.810
133.749
109.463
108.608
63.410
63.256
35.055
34.514
24.969
24.908
19.598
19.529
O
O
O
200
150
100
50
0
ppm (f1)