Supporting Information

A Photoreactive Analogue of the Immunosuppressant FTY720

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General Methods: All reactions were carried out under N_2. The solvents were dried by distillation over the drying agents indicated and were transferred under N_2: THF, from sodium/benzophenone; CH_2Cl_2, Et_3N, pyridine, and DMF from CaH_2; MeOH from Mg; acetone from $MgSO_4$. Flash chromatography was carried out with silica gel 60 (230-400 mesh). TLC was performed using 0.25-mm silica gel plates. The ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively. Chemical shifts are given in ppm relative to $CDCl_3$ (central resonance, δ 77.23). Melting points are uncorrected. All commercially available chemicals were used as received.

4-Hydroxyphenethyl Acetate (3).[1] A suspension of $NaHSO_4$ on silica (1 g) and 2-(4-hydroxyphenyl)ethanol (1.8 g, 20 mmol) in EtOAc (50 mL) and hexane (100 mL) was heated at reflux until TLC analysis (EtOAc/hexane 3:1) indicated that the starting material was completely consumed. The reaction mixture was allowed to cool to room temperature, and the resulting solid was removed by filtration. The solid was washed with EtOAc, and the filtrate was concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:3) to afford 3.6 g (98%) of acetate **3** as a colorless solid: R_f 0.30 (EtOAc/hexane 1:3); mp 57-59 °C (lit.[1] mp 57-58 °C); ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.86 (t, 2H, J = 7.2 Hz), 4.26 (t, 2H, J = 7.2 Hz), 6.81 (d, 2H, J = 8.4 Hz), 7.05 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 20.9, 34.0, 65.5, 115.4, 129.6, 129.9, 154.6, 172.1.

4-Hydroxy-3-nitrophenethyl Acetate.[2] A solution of **3** (3.4 g, 18.9 mmol) in glacial HOAc (5 mL) was added dropwise to 12 N HNO_3 (2.8 mL) at 10 °C with stirring. After the addition, glacial HOAc (5 mL) was added, and the reaction mixture was stirred at 15 °C for 1 h. The suspension was diluted with H_2O, and the precipitate was removed

by filtration, washed with H_2O, and dried under vacuum. The solid was purified by flash chromatography (elution with hexane) to give 3.5 g (83%) of the title compound as a yellow solid: R_f 0.43 (hexane); mp 51-52 °C; ^{1}H NMR ($CDCl_3$) δ 2.04 (s, 3H), 2.94 (t, 2H, *J* = 6.8 Hz), 4.28 (t, 2H, *J* = 6.8 Hz), 7.11 (d, 1H, *J* = 8.8 Hz), 7.46 (d, 1H, *J* = 8.8 Hz), 7.97 (s, 1H), 10.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.9, 33.9, 64.2, 120.1, 124.7, 130.4, 133.4, 138.4, 153.9, 170.9.

4-(2-Acetoxyethyl)-2-nitrophenyl Trifluoromethanesulfonate (4). To a solution of 4-hydroxy-3-nitrophenethyl acetate (3.0 g, 13.3 mmol) in CH_2Cl_2 (60 mL) and pyridine (5.2 mL, 63.8 mmol) at 0 °C was added a solution of triflic anhydride (2.7 mL, 16.0 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at room temperature for 1 h. After the starting material was completely consumed (TLC, EtOAc/hexane 1:3), the mixture was quenched with 20 mL of saturated aqueous $NaHCO_3$ solution, and the aqueous layer was extracted with EtOAc (2 x 100 mL). The organic layers were combined, dried ($MgSO_4$), and evaporated. The residue was further dried under high vacuum to give 4.6 g (97%) of triflate **4** as an off-white solid, which was used in the next step without further purification: R_f 0.20 (EtOAc/hexane 1:3); ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H), 3.07 (t, 2H, *J* = 6.6 Hz), 4.33 (t, 2H, *J* = 6.6 Hz), 7.40 (d, 1H, *J* = 8.4 Hz), 7.59 (d, 1H, *J* = 8.4 Hz), 8.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.8, 34.2, 63.4, 118.6 (q, *J* = 1201 Hz), 124.3, 127.0, 135.5, 140.2, 140.5, 141.5, 170.7; LR-MS (ESI, MNH_4^+) *m/z* calcd for $C_{11}H_{14}F_3N_2O_7O$ 375.3, found 375.0.

3-Nitro-4-((*E*)-oct-1-enyl)phenethyl Acetate (5). A suspension of triflate **4** (500 mg, 1.4 mmol), (*E*)-1-octen-1-ylboronic acid (328 mg, 2.3 mmol), $Pd(dppf)Cl_2$ (92.2 mg, 0.13 mmol), and K_2CO_3 (580 mg, 4.2 mmol) in 27.5 mL of THF/H_2O (10:1) was heated

at reflux overnight. The reaction mixture was cooled to room temperature and diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (2 x 80 mL), and the combined organic layer was washed with 1 % HCl, brine, and dried ($MgSO_4$). After removal of the solvents, the residue was purified by flash chromatography (EtOAc/hexane 3:1) to give 400 mg (89%) of **5** as a colorless oil: R_f 0.51 (EtOAc/hexane 3:1); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.33-1.36 (m, 6H), 1.48 (m, 2H), 2.04 (s, 3H), 2.26 (dt, 2H, *J* = 6.8, 6.8 Hz), 2.98 (t, 2H, *J* = 6.8 Hz), 4.29 (t, 2H, *J* = 6.8 Hz), 6.22 (dt, 1H, *J* = 15.6, 6.8 Hz), 6.80 (d, 1H, *J* = 15.6 Hz), 7.38 (d, 1H, *J* = 8.4 Hz), 7.52 (d, 1H, *J* = 8.4 Hz), 7.73 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.9, 22.6, 28.8, 30.0, 31.7, 33.2, 34.2, 64.0, 124.6, 128.5, 131.8, 133.3, 136.7, 137.8, 147.6, 170.8; LR-MS (ESI, MH^+) *m/z* calcd for $C_{18}H_{25}NO_4$ 320.2, found 320.1.

4-(2-Hydroxyethyl)-2-nitro-5-*n*-octylphenol (**5a**). A solution of *n*-octylmagnesium chloride (0.19 mL, 0.38 mmol, in 2.0 M in THF) was added to a solution of triflate **4** (112 mg, 0.31 mmol) and $Fe(acac)_3$ (11 mg, 0.031 mmol) in THF (10 mL) and *N*-methyl-2-pyrrolidinone (NMP) (0.18 mL, 1.85 mmol), causing an immediate color change from red to black. After the solution was stirred for 30 min at room temperature, additional octylmagnesium chloride (0.08 mL, 0.16 mmol), $Fe(acac)_3$ (5.5 mg, 0.016 mmol), and NMP (0.06 mL, 0.62 mmol) were added, and stirring was continued for another 30 min. The reaction was quenched with 1 M HCl, and the aqueous phase was extracted several times with EtOAc. The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was purified by flash chromatography (hexanes/EtOAc 3:1) to give product **5a** (46 mg, 50%) as a brown oil: ^{1}H NMR ($CDCl_3$): δ 0.87 (t, 3H, *J* = 6.8 Hz), 1.27-1.37 (m, 10H), 1.58 (m, 2H), 1.69 (br s, 1H), 2.63 (t, 2H, *J* = 7.8 Hz), 2.86

(t, 2H, *J* = 6.6 Hz), 3.85 (t, 2H, *J* = 6.6 Hz), 6.95 (s, 1H), 7.91 (s, 1H), 10.44 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 29.1, 29.4, 29.5, 30.3, 31.8, 33.1, 34.4, 62.6, 119.6, 125.3, 129.3, 131.5, 153.4, 153.5; LR-MS (ESI, MNa^+) *m/z* calcd for $C_{16}H_{25}NO_4Na$ 318.4, found 318.1.

2-(3-Nitro-4-((*E*-oct-1-enyl)phenyl)ethanol (6). A solution of **5** (330 mg, 1.03 mmol) and NaOMe (23 mg, 0.10 mmol) in MeOH (10 mL) was stirred for 4 h at room temperature. The solvent was evaporated, and the residue was purified by flash chromatography (EtOAc/hexane 1:3) to give 280 mg (98%) of **6** as a yellow oil: R_f 0.13 (EtOAc/hexane 1:3); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.29-1.35 (m, 6H), 1.45 (m, 2H), 2.06 (br s, 1H), 2.23 (dt, 2H, *J* = 6.8, 6.8 Hz), 2.87 (t, 2H, *J* = 6.4 Hz), 3.84 (t, 2H, *J* = 6.4 Hz), 6.19 (dt, 1H, *J* = 15.6, 6.8 Hz), 6.77 (d, 1H, *J* = 15.6 Hz), 7.38 (d, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 22.6, 28.9, 29.0, 38.2, 62.9, 124.56, 124.59, 128.4, 131.5, 133.64, 136.6, 138.9, 147.6; LR-MS (ESI, MH^+) *m/z* calcd for $C_{16}H_{23}NO_3$ 277.4, found 278.3.

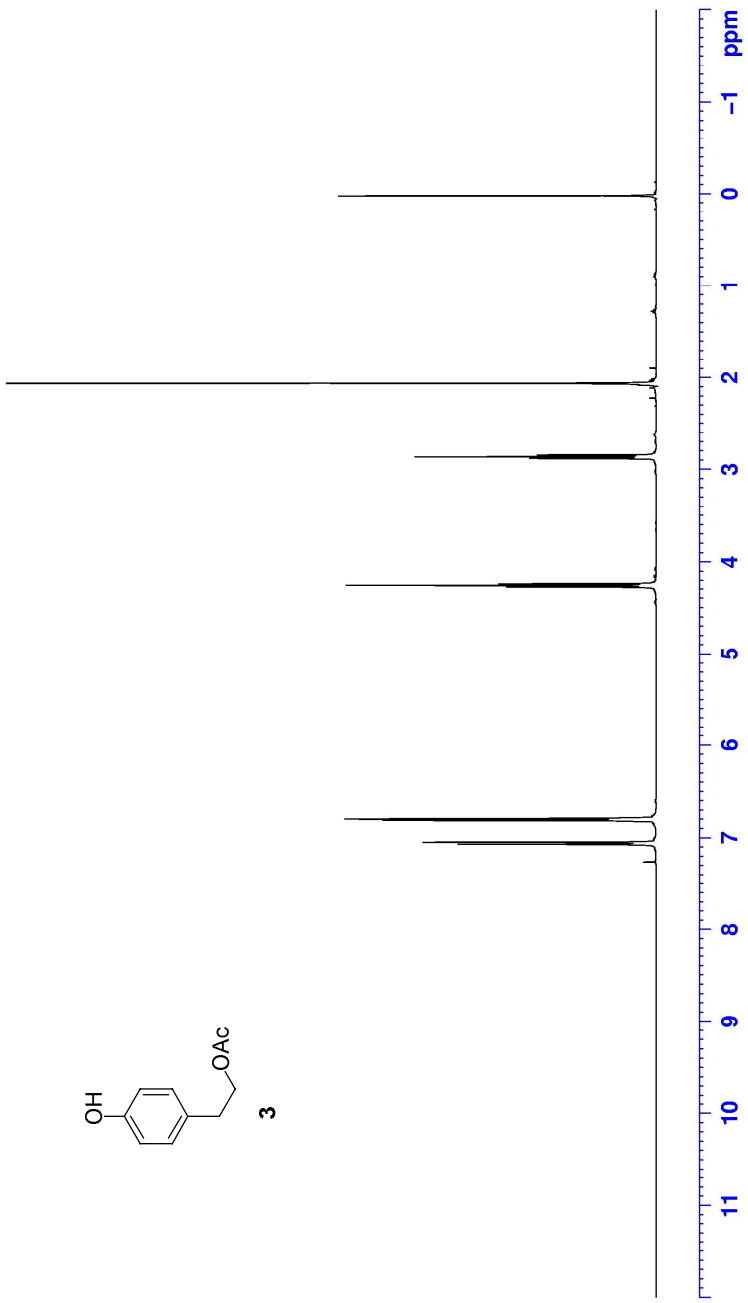
Diethyl 2-(3-Nitro-4-((*E*)-oct-1-enyl)phenethyl)malonate (9). To a suspension of diethyl malonate (19.6 mL, 0.13 mmol) and K_2CO_3 (45 mg, 0.33 mmol) in 5 mL of acetone was added **8** (50 mg, 0.13 mmol). After the reaction mixture was heated at reflux for 6 h, the reaction was quenched with H_2O (5 mL) and the aqueous layer was extracted with EtOAc (2 x 20 mL). The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (EtOAc/hexane 1:10) to give 42 mg (77%) of **9** as a light yellow oil: R_f 0.46 (EtOAc/hexane 1:10); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.27-1.36 (m, 12H), 1.48 (m, 2H), 2.23 (m, 4H), 2.71 (m, 2H), 3.32 (t, 1H, *J* = 7.4 Hz), 4.21 (m, 4H), 6.20 (dt, 1H, *J* = 15.6, 6.8 Hz), 6.78 (d, 1H, *J* = 15.6, 6.8 Hz), 7.35

(d, 1H, *J* = 8.0 Hz), 7.50 (d, 1H, *J* = 8.0 Hz), 7.68 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 28.8, 28.9, 29.8, 31.6, 32.5, 33.1, 51.0, 61.5, 124.1, 124.6, 128.5, 131.4, 133.0, 136.5, 140.5, 147.6; LR-MS (ESI, MH^+) *m/z* calcd for $C_{23}H_{33}NO_6$ 419.5, found 420.2.

Diethyl 2-(3-Nitro-4-((*E*)-oct-1-enyl)phenethyl)-2-aminomalonate (10). To a solution of **9** (42 mg, 0.10 mmol) in 5 mL of THF was added NaH (2.6 mg, 0.10 mmol). The reaction mixture was stirred for 20 min at room temperature, and *O*-(di-*p*-methoxyphenyl)phosphinylhydroxylamine (32 mg, 0.11 mmol) was added in one portion. A white precipitate was formed, which dissolved when the suspension was stirred overnight. The reaction was quenched with H_2O (10 mL), the product was extracted with EtOAc (2 x 50 mL), and the organic layer was dried ($MgSO_4$) and concentrated. Purification by flash chromatography (EtOAc/hexane 1:3) afforded 13 mg (31%) of amine **10** as a colorless wax: R_f 0.40 (EtOAc/hexane 1:3); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3H, *J* = 6.8 Hz), 1.26-1.36 (m, 12H), 1.46 (m, 2H), 1.97 (br s, 2H), 2.23 (m, 4H), 2.78 (m, 2H), 4.23 (q, 4H, *J* = 7.2 Hz), 6.20 (dt, 1H, *J* = 15.6, 6.8 Hz), 6.78 (d, 1H, *J* = 15.6 Hz), 7.35 (d, 1H, *J* = 8.0 Hz), 7.49 (d, 1H, *J* = 8.0 Hz), 7.69 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.0, 22.6, 28.8, 29.0, 29.4, 31.7, 33.2, 37.1, 62.4, 65.4, 124.0, 124.6, 128.4, 131.2, 133.0, 136.4, 141.2, 147.6, 171.2; LR-MS (ESI, MH^+) *m/z* calcd for $C_{23}H_{35}N_2O_6$ 435.5, found 435.2.

References:

1. Seidel, G.; Laurich, D.; Fürstner, A. *J. Org. Chem.* **2004**, *69*, 3950-3952.
2. Yamane, T.; Kondo, H.; Fuse, Y.; Hashizume, T.; Kano, F.; Yamashita, K.; Hosoe, K.; Watanabe, K. Japanese Patent 63045282 A2 (1988); *Chem. Abstr.* **1989**, *110*, 57408.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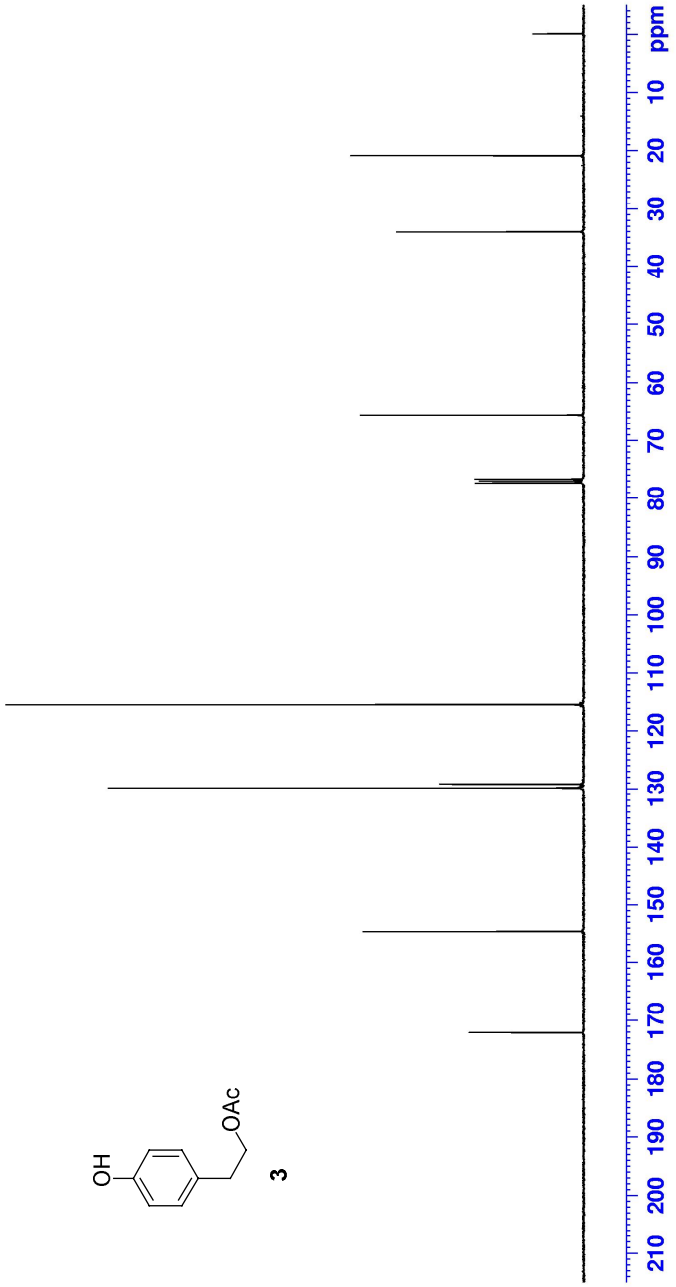
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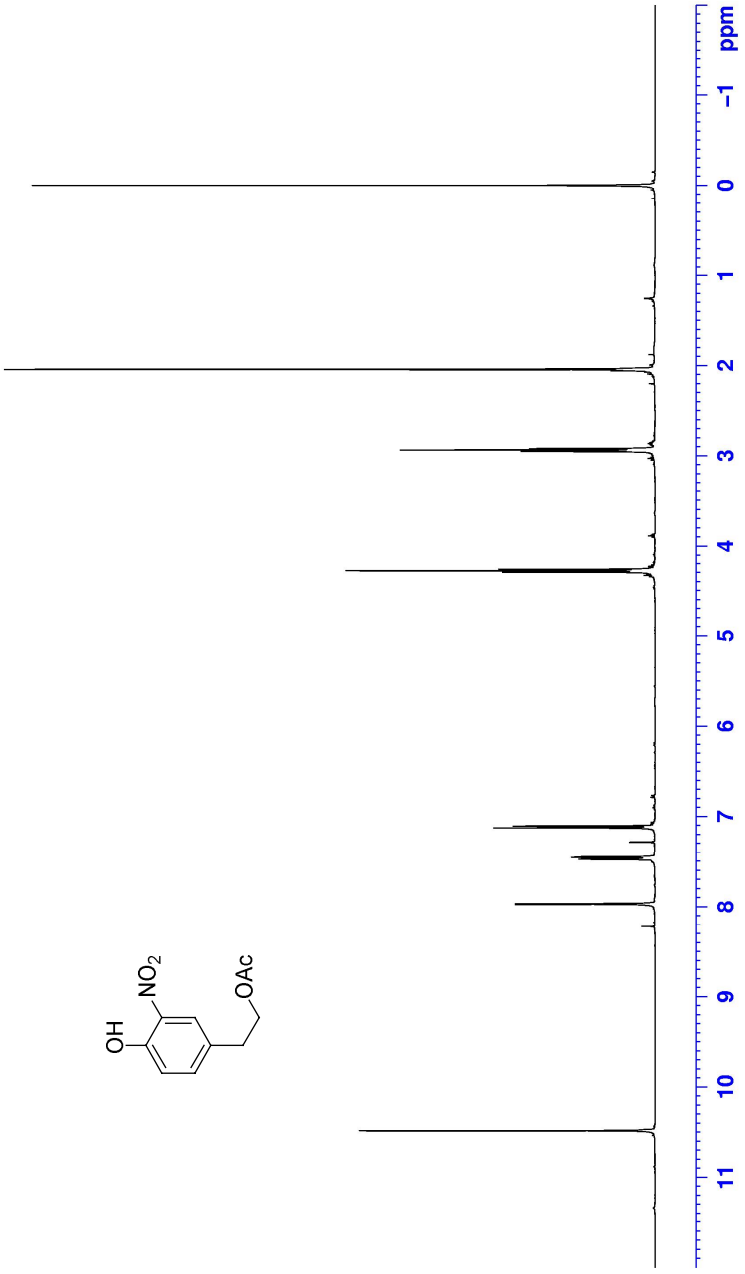
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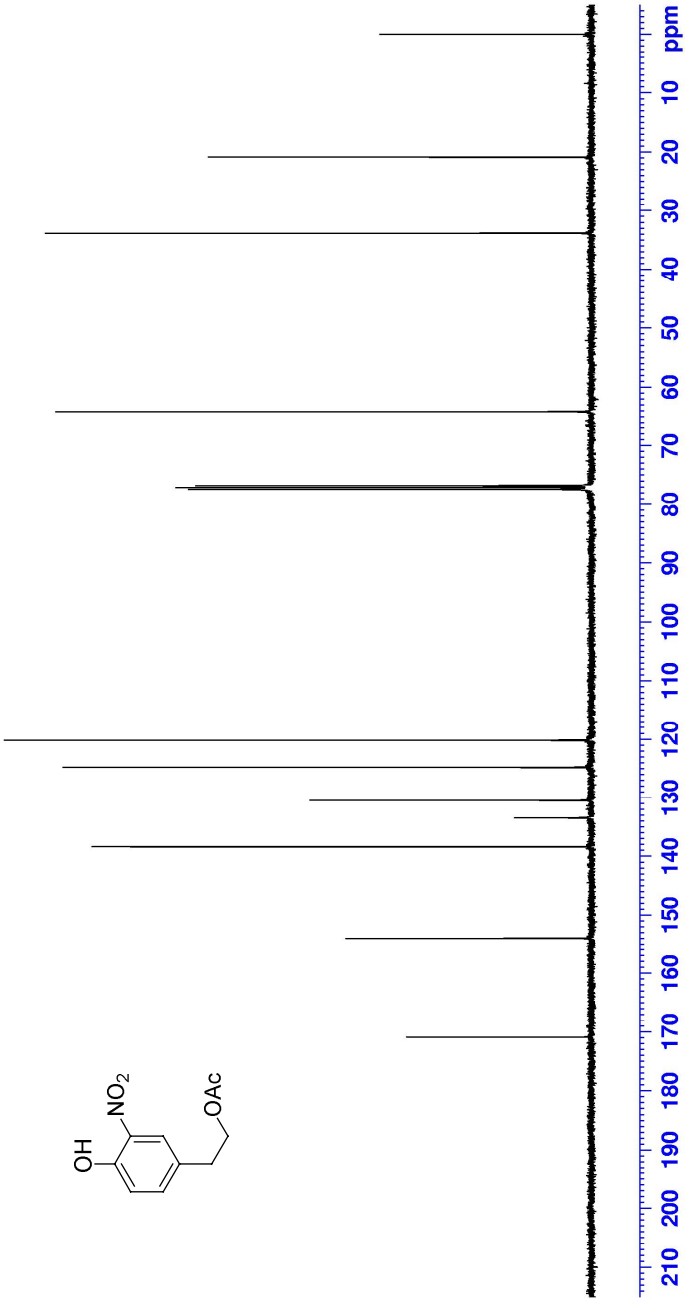
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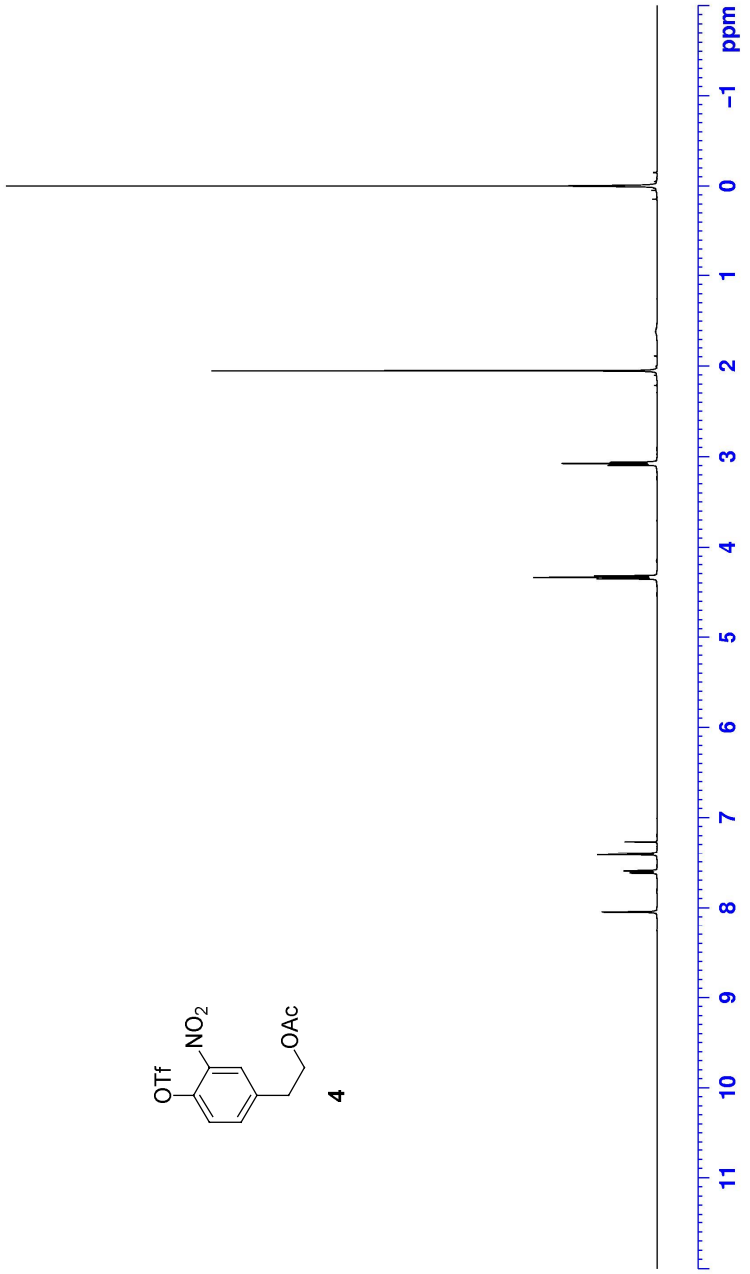
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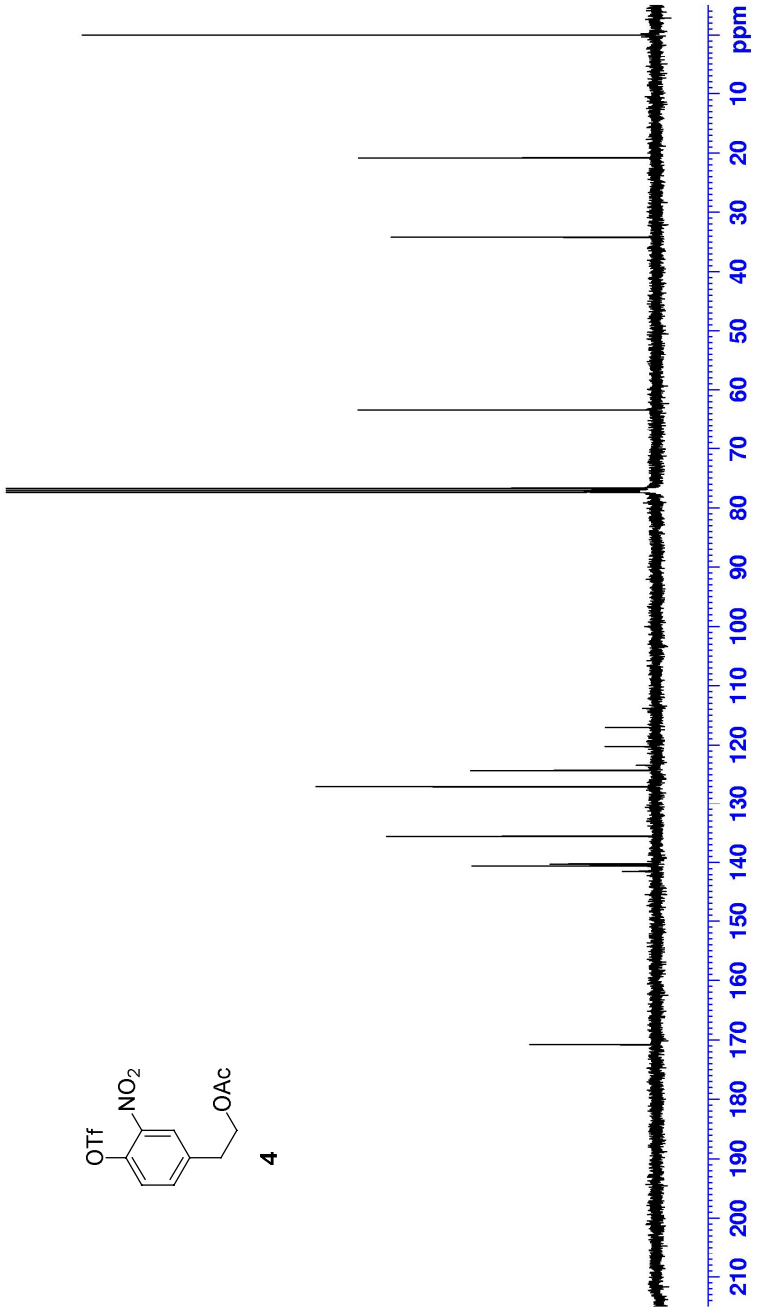
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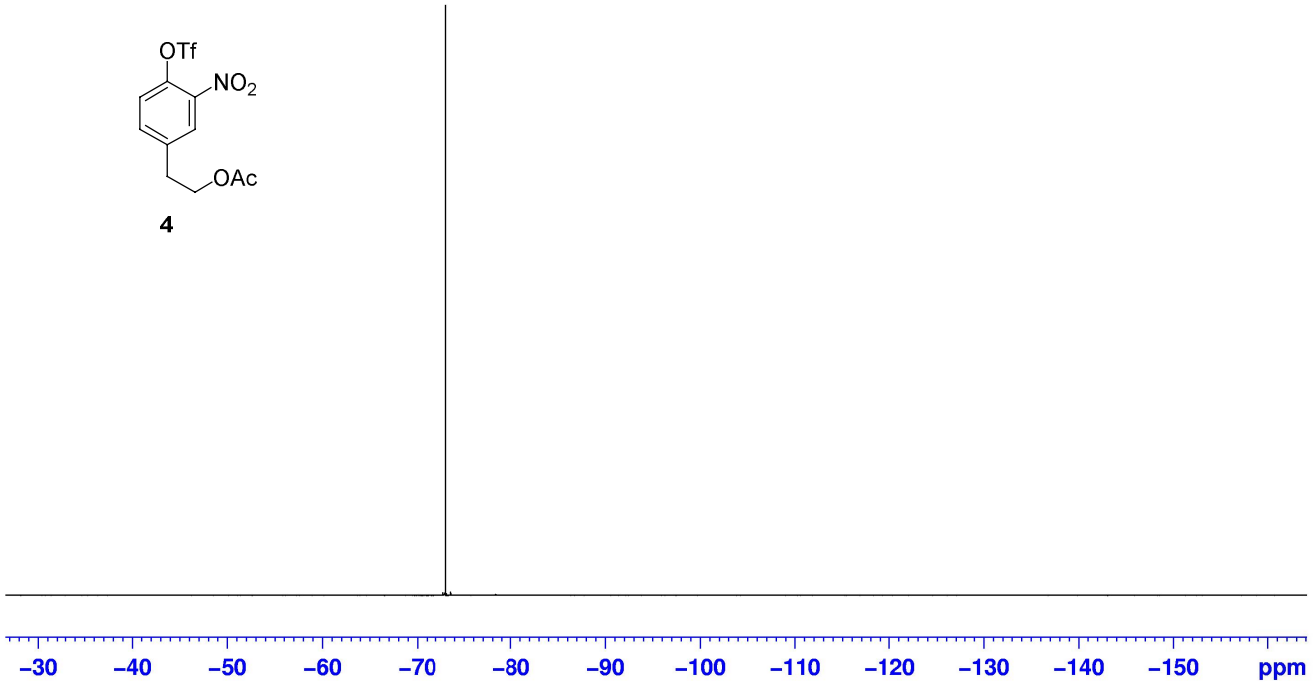
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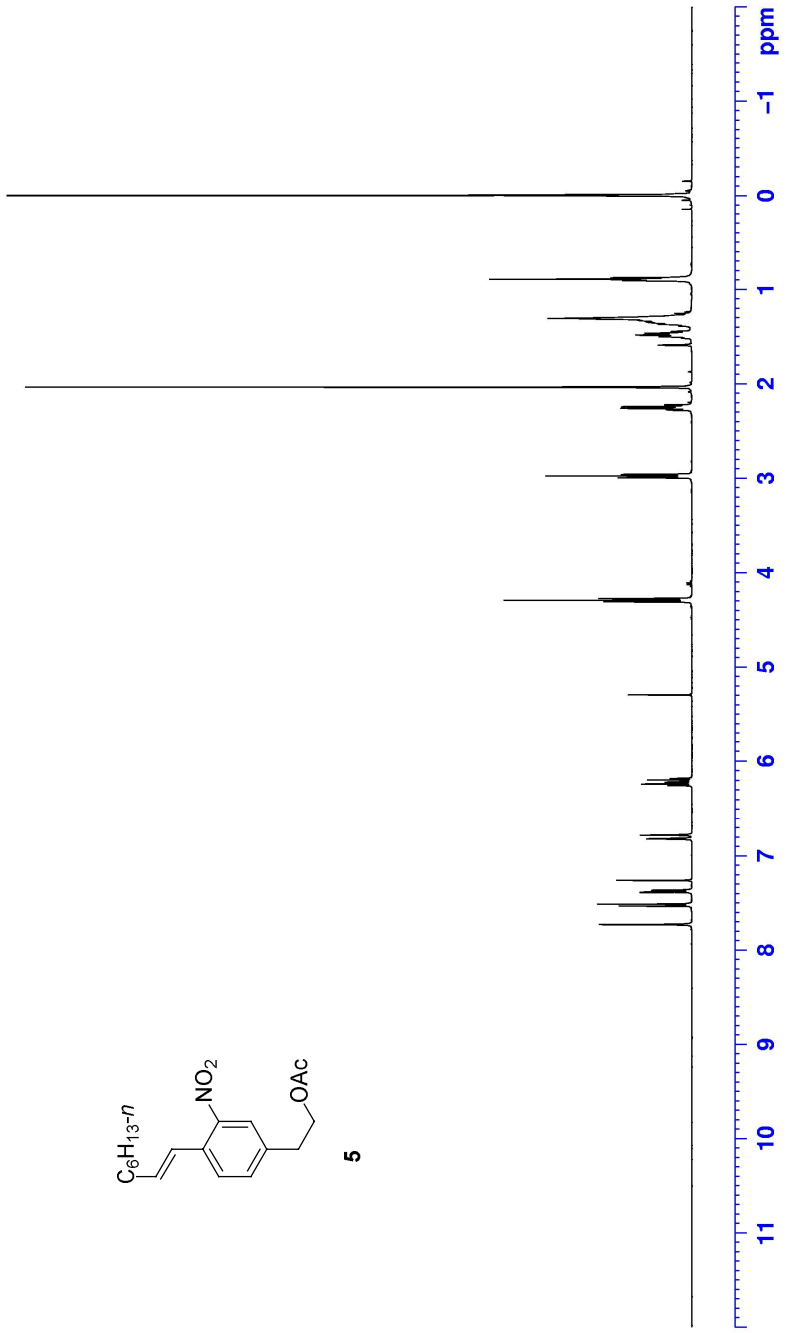
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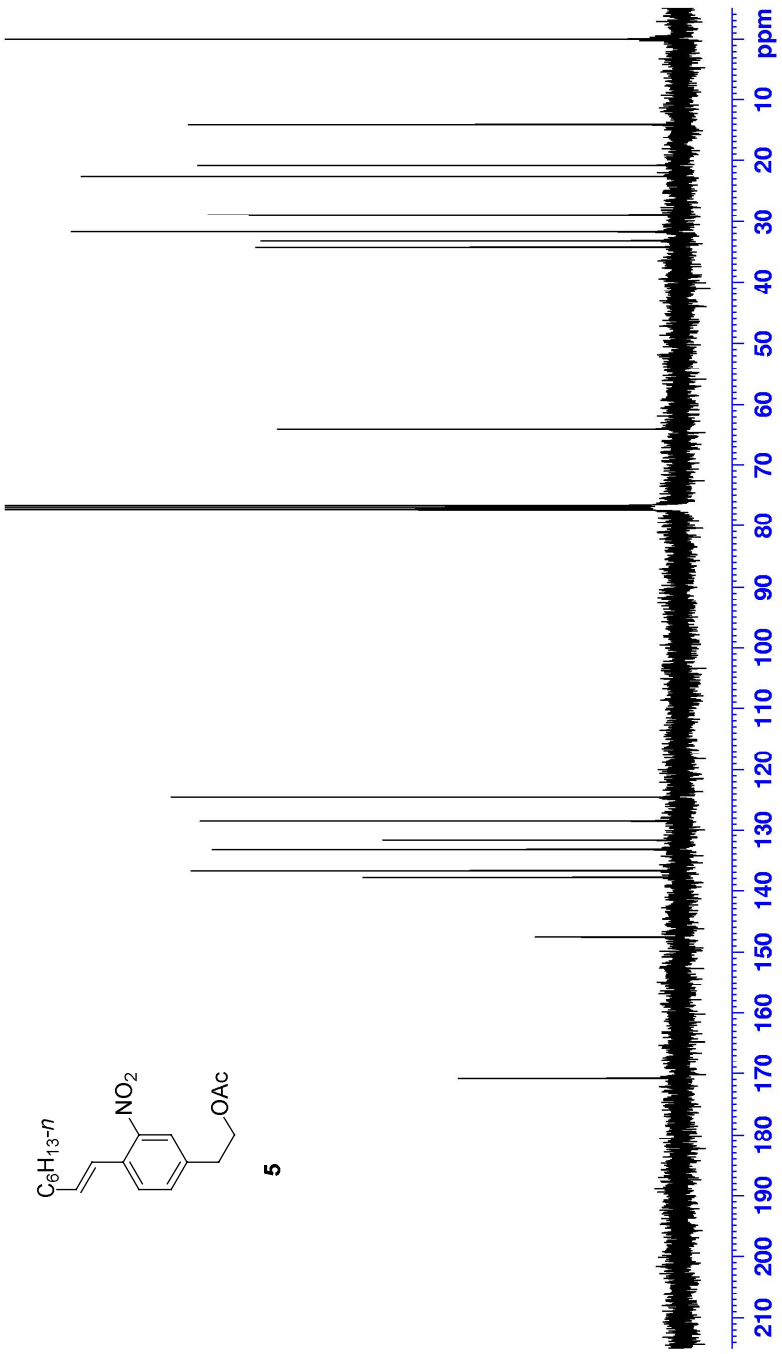
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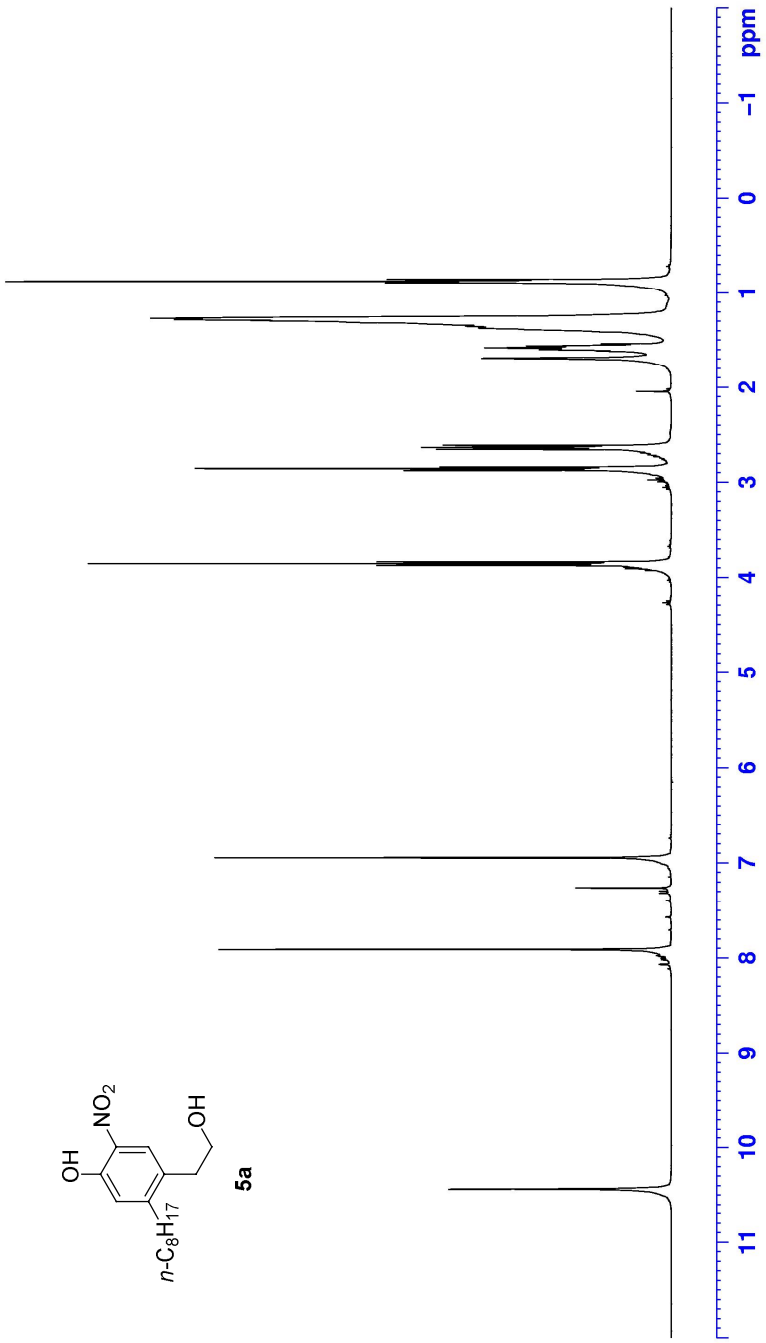
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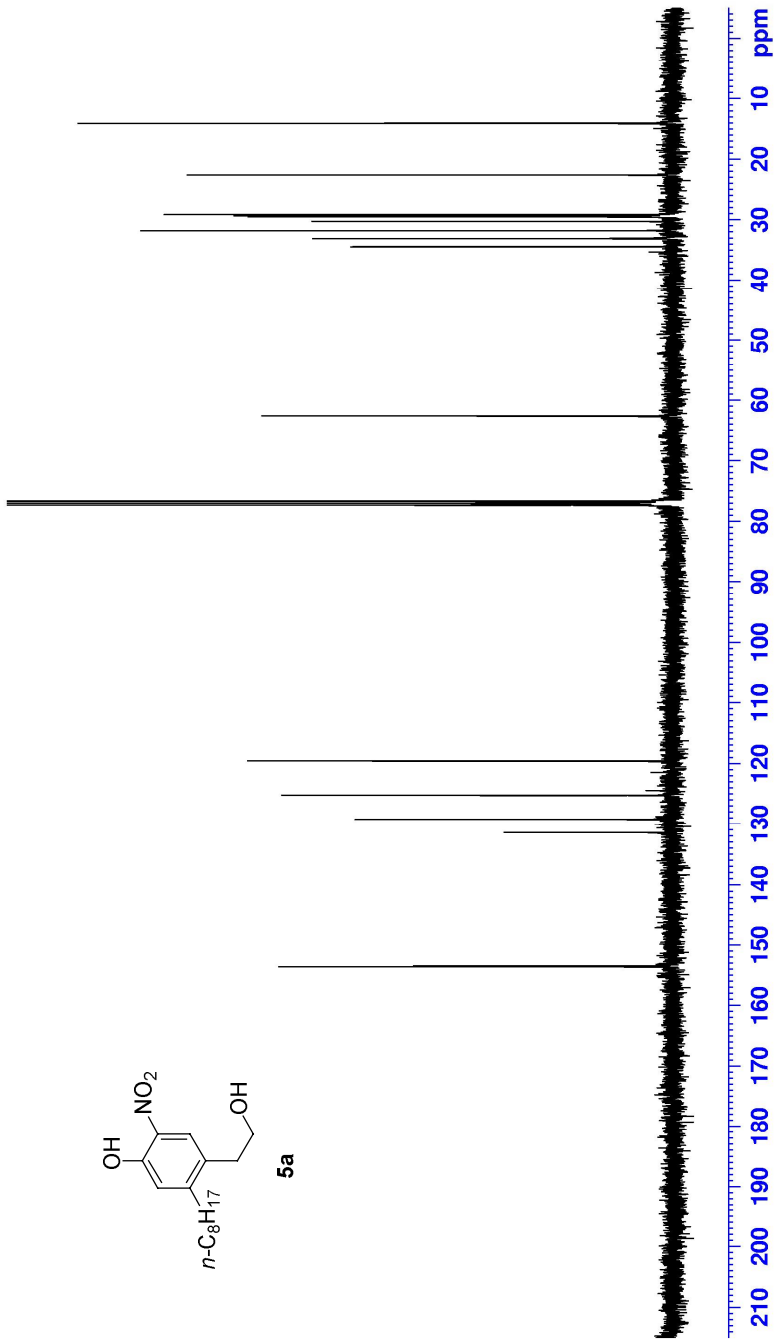
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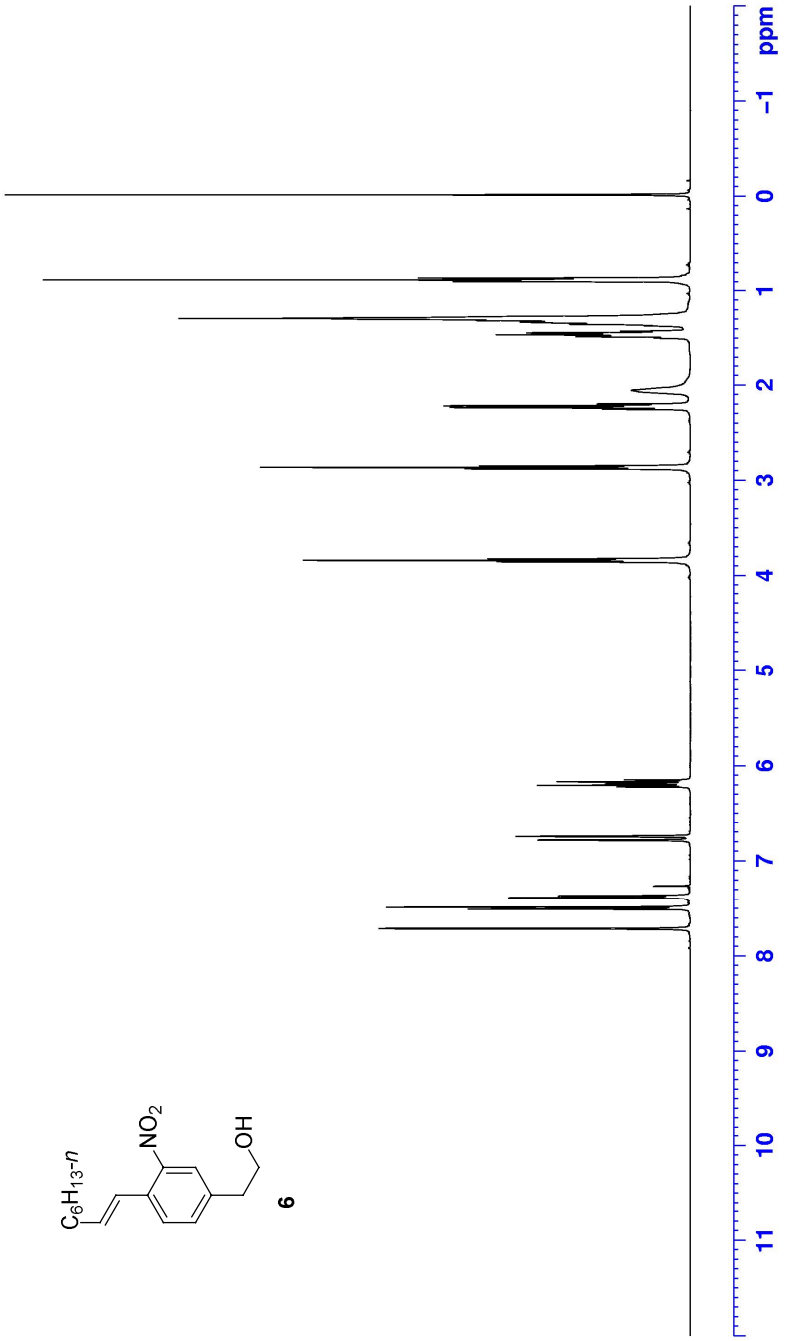
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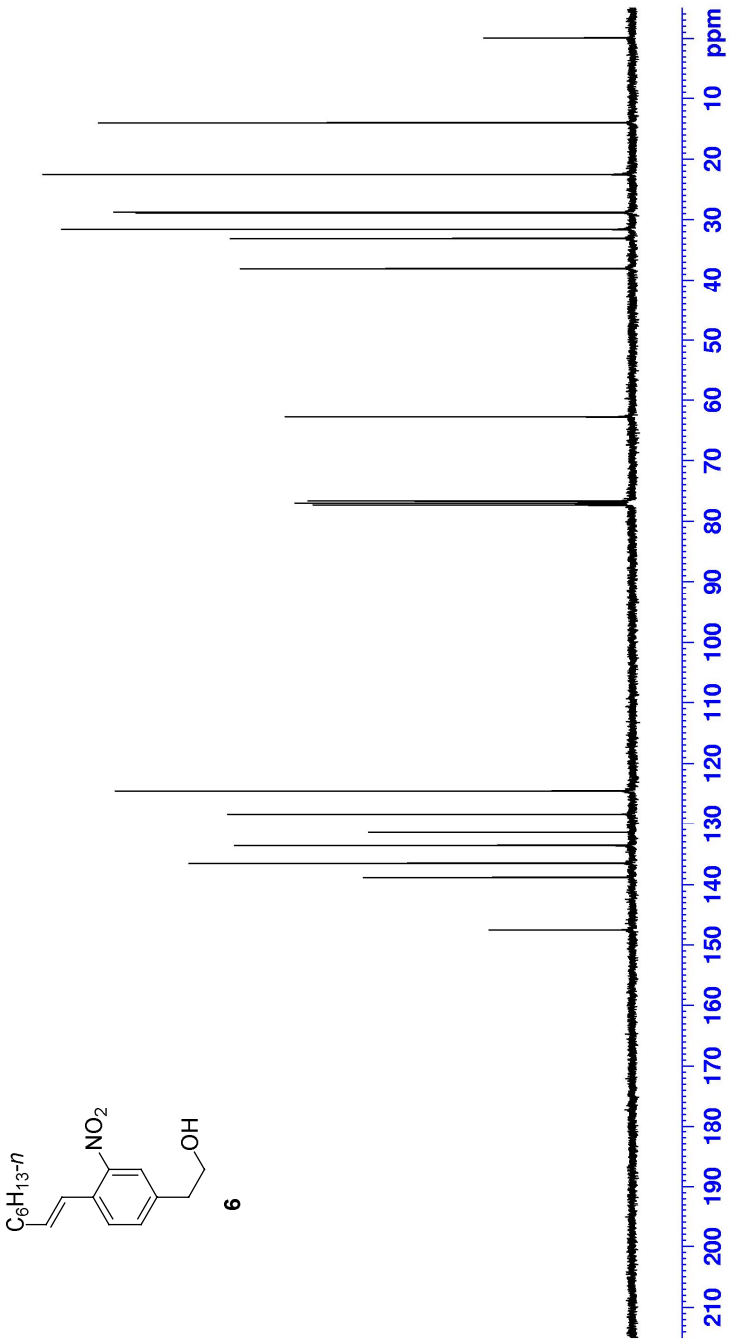
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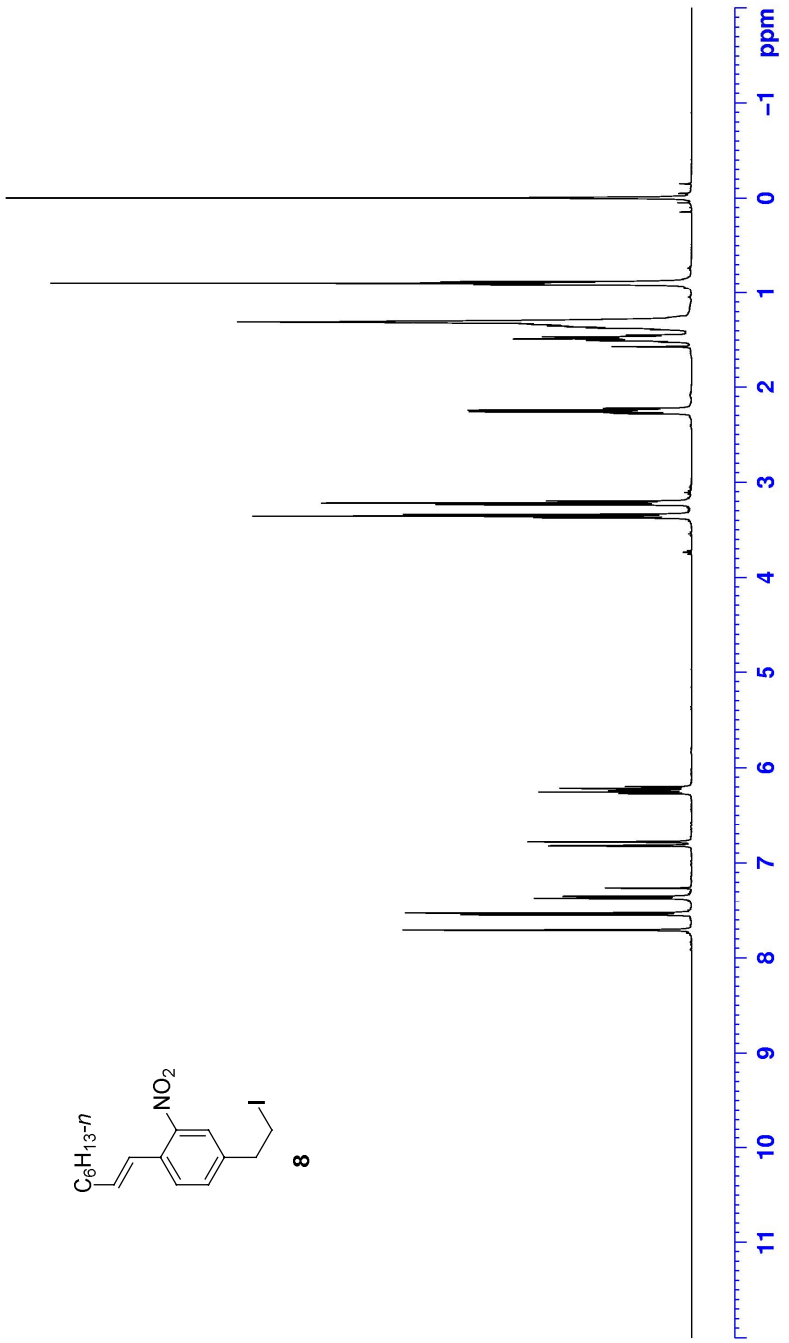

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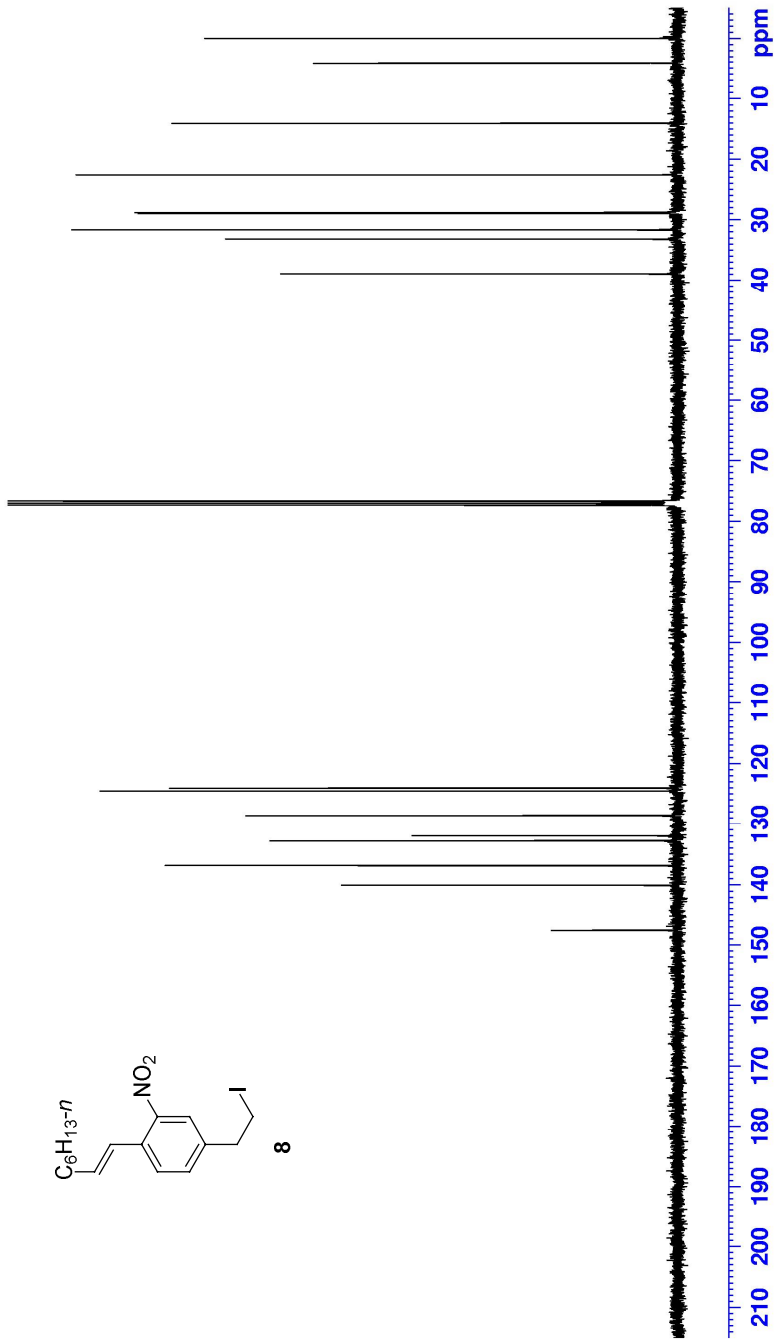
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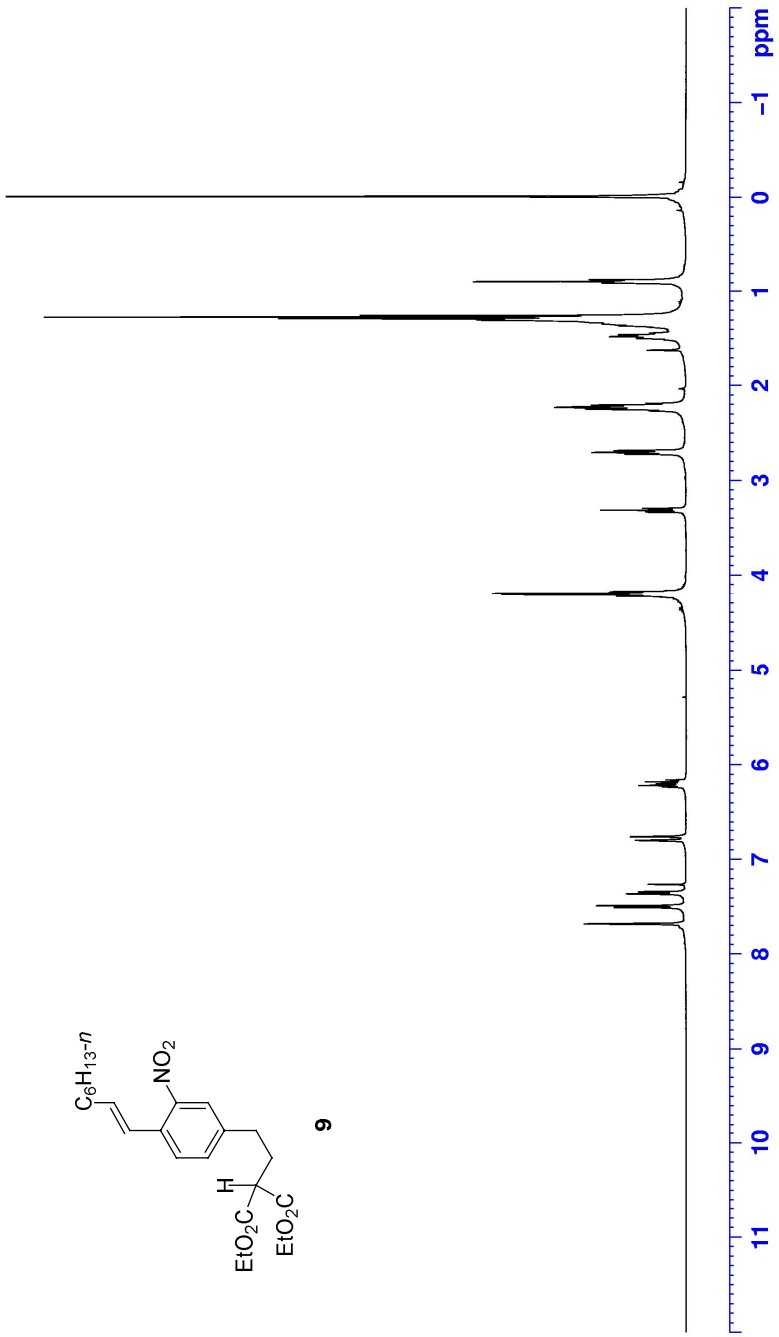
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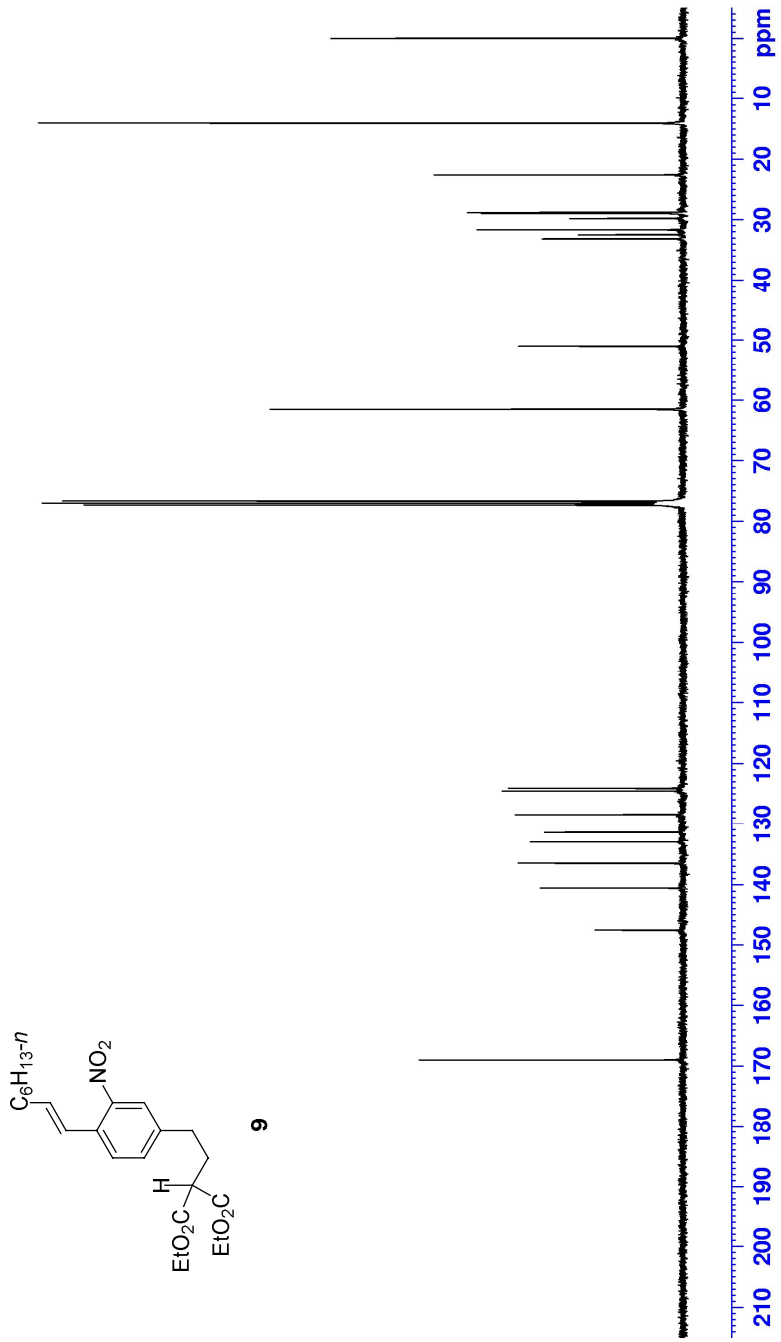
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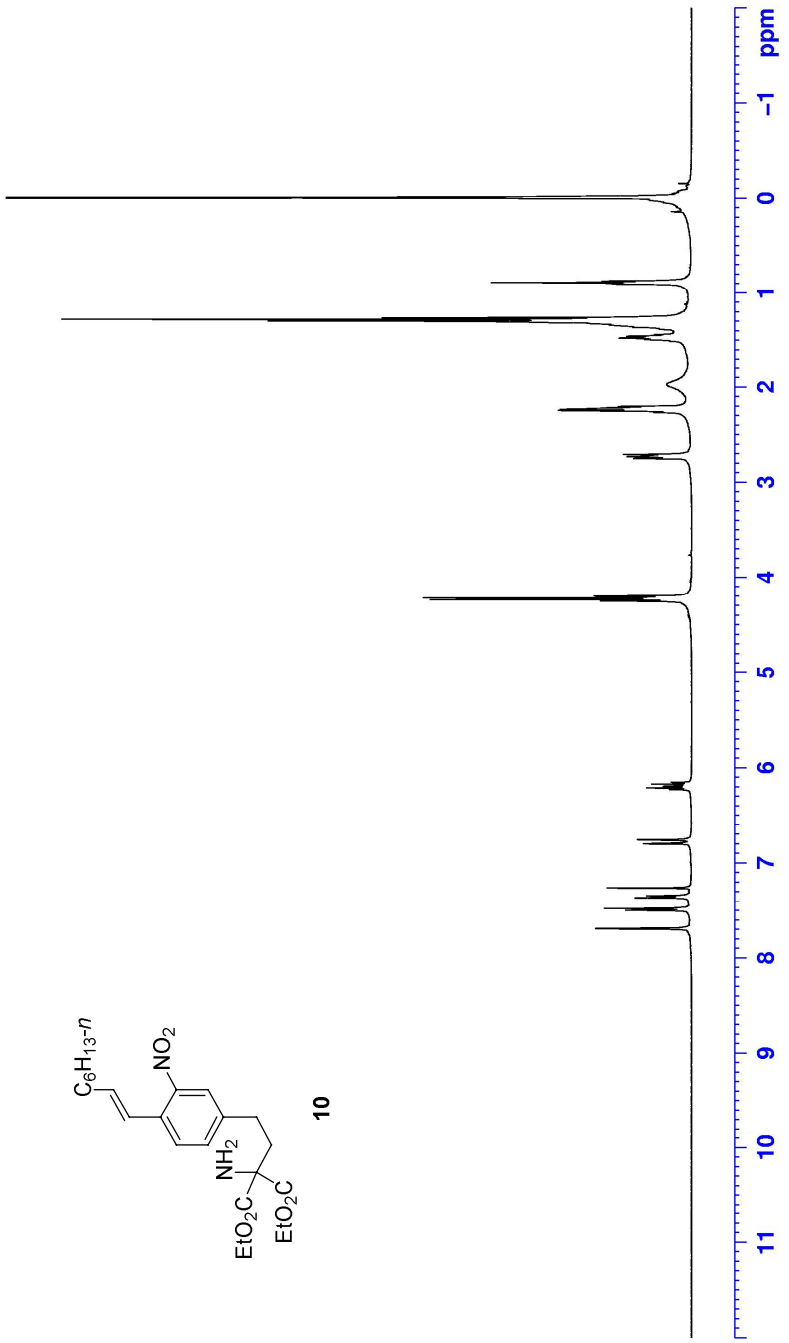
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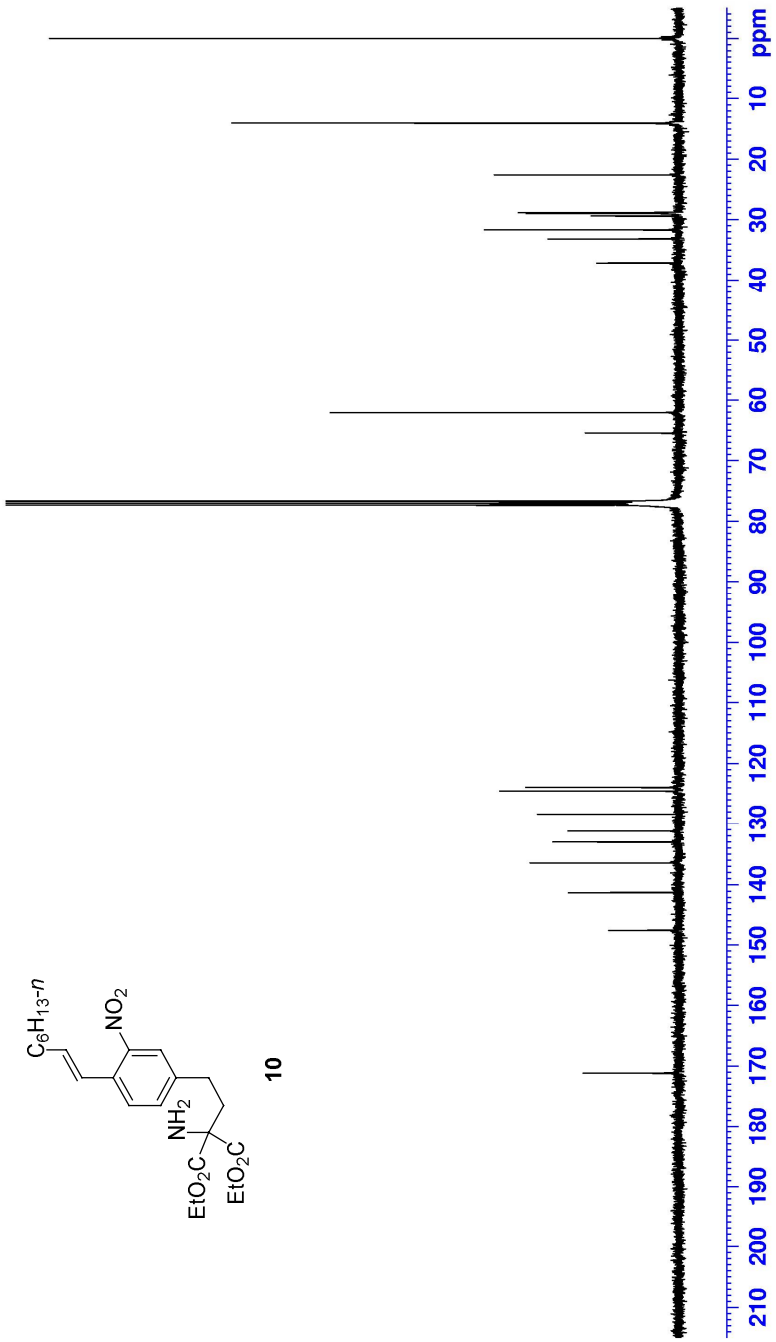
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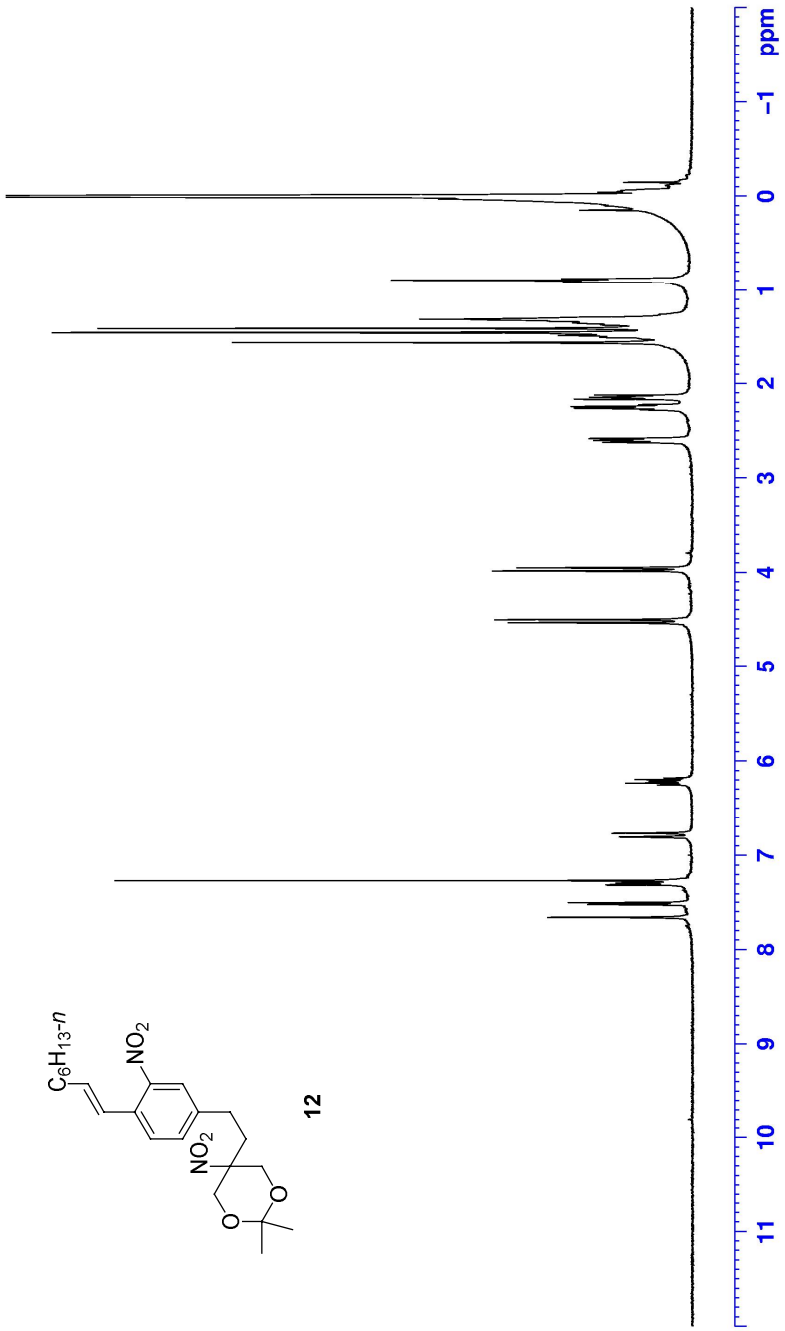
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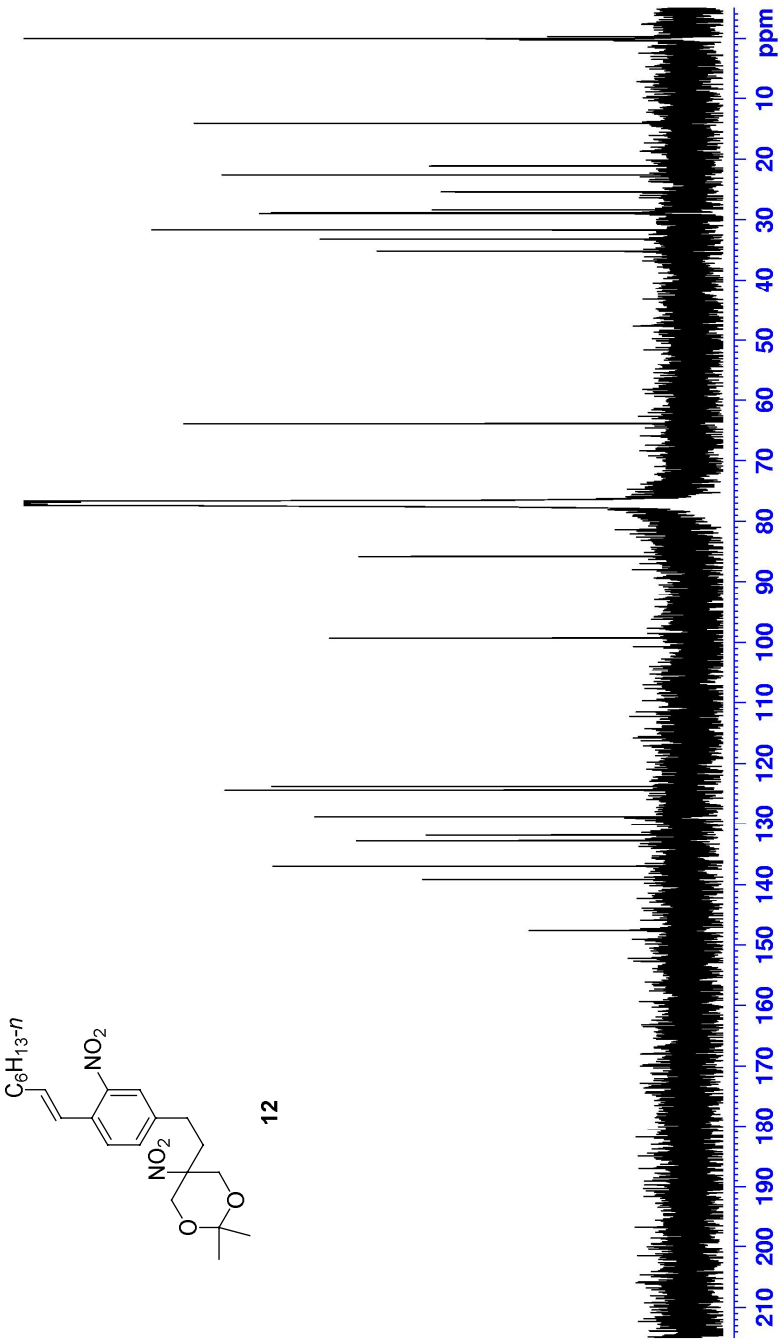
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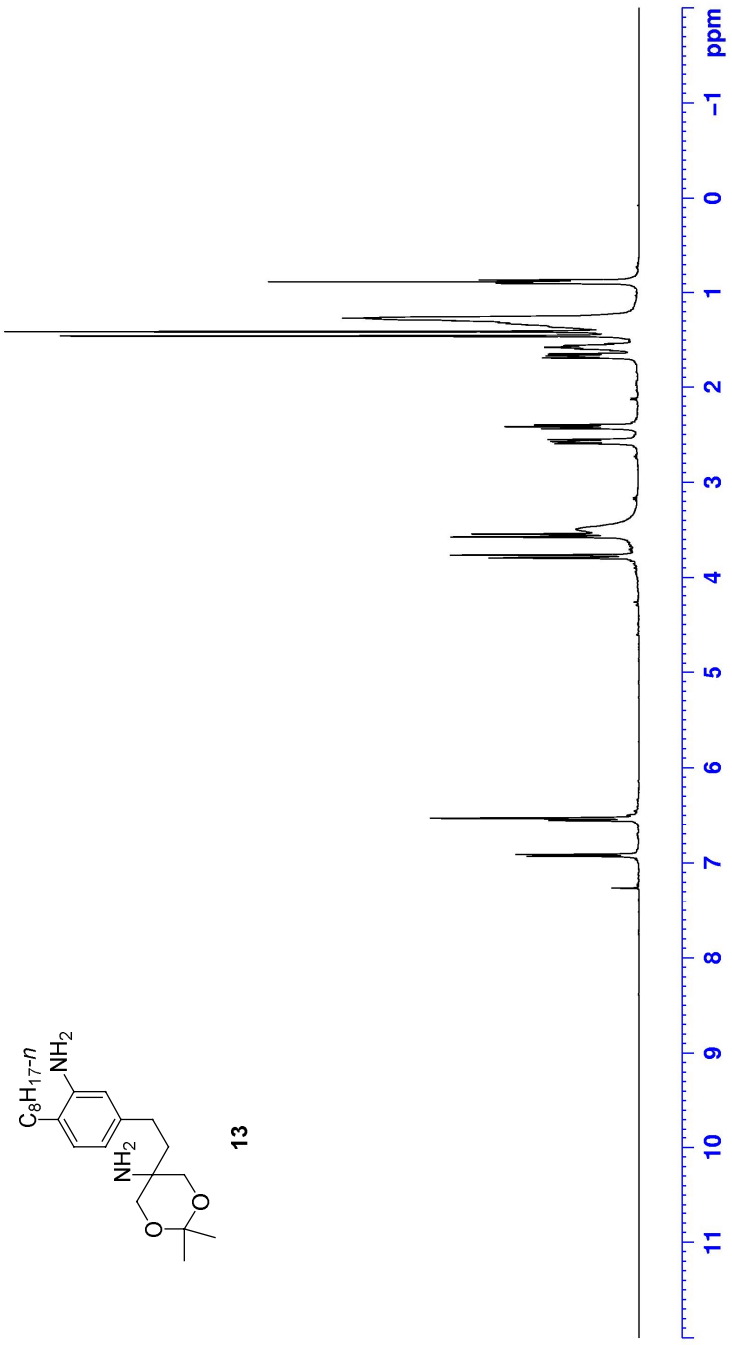
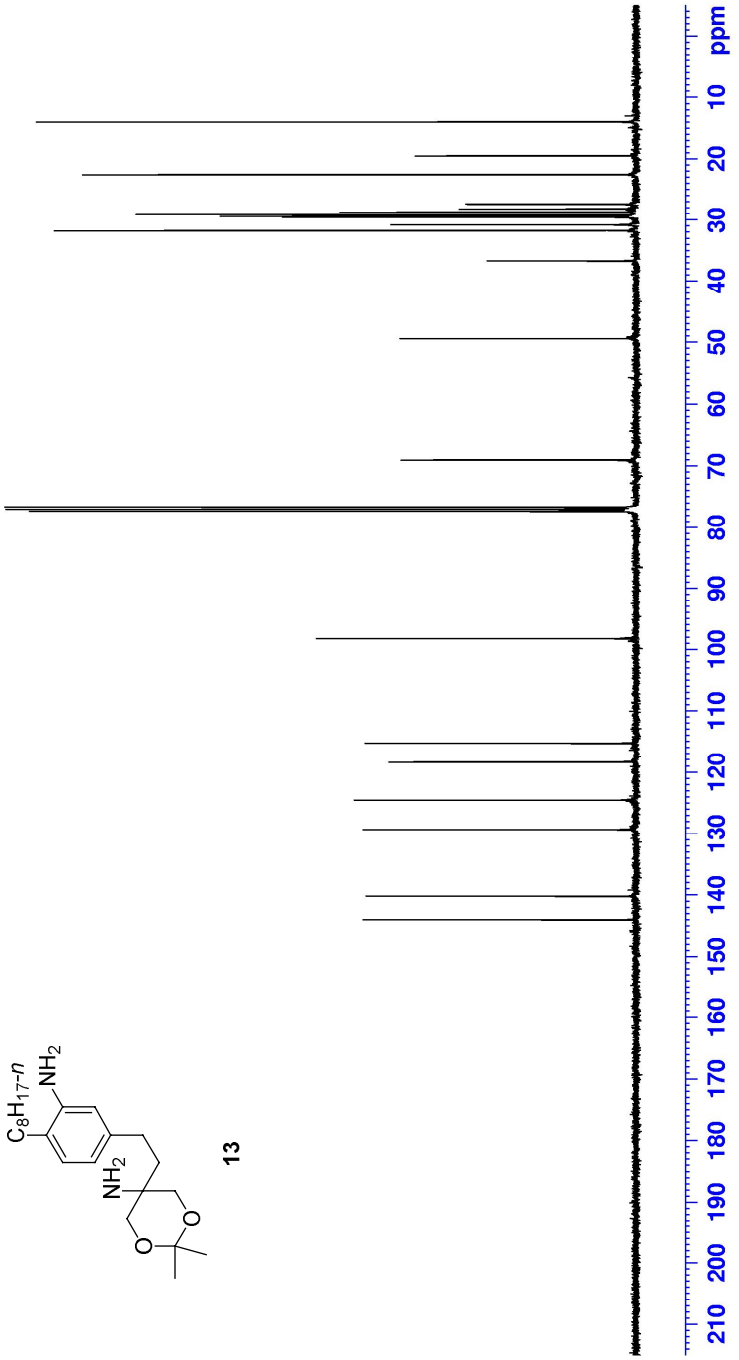
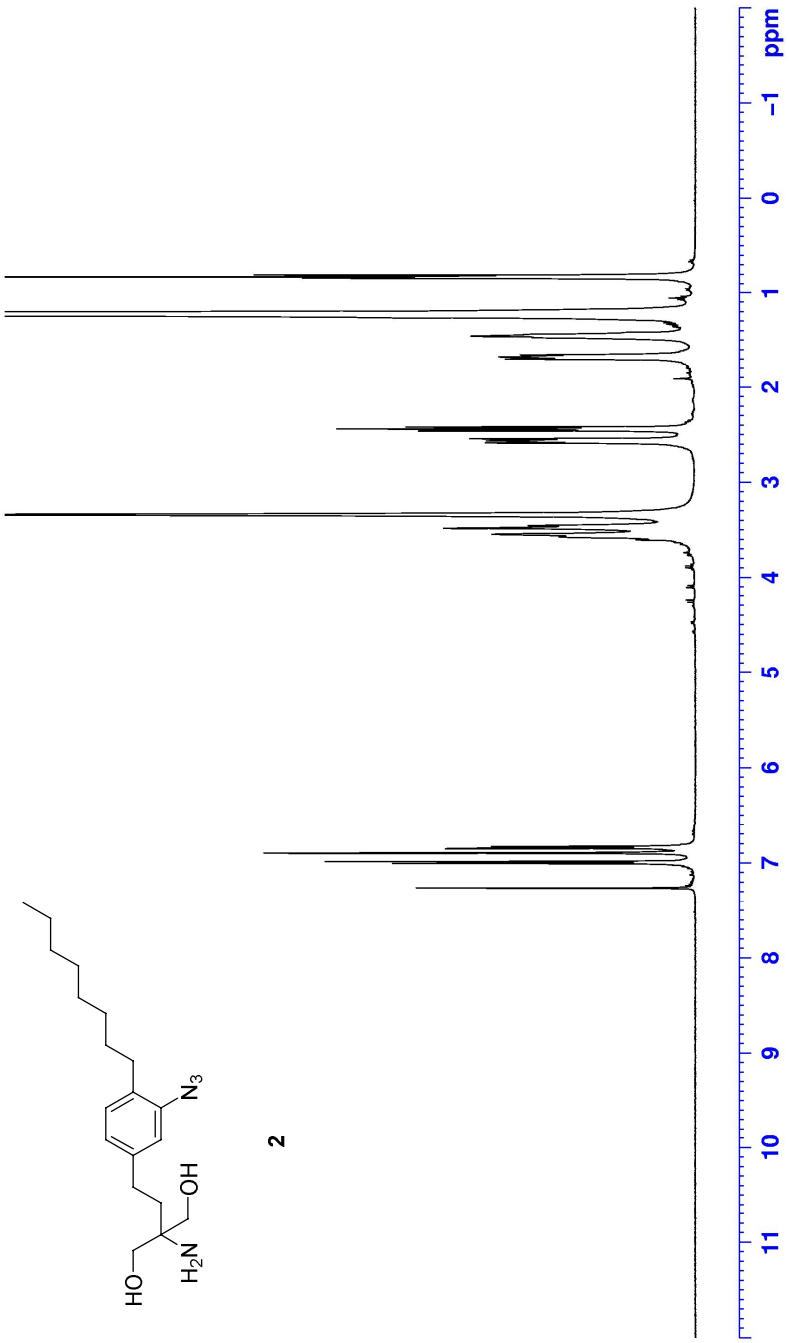
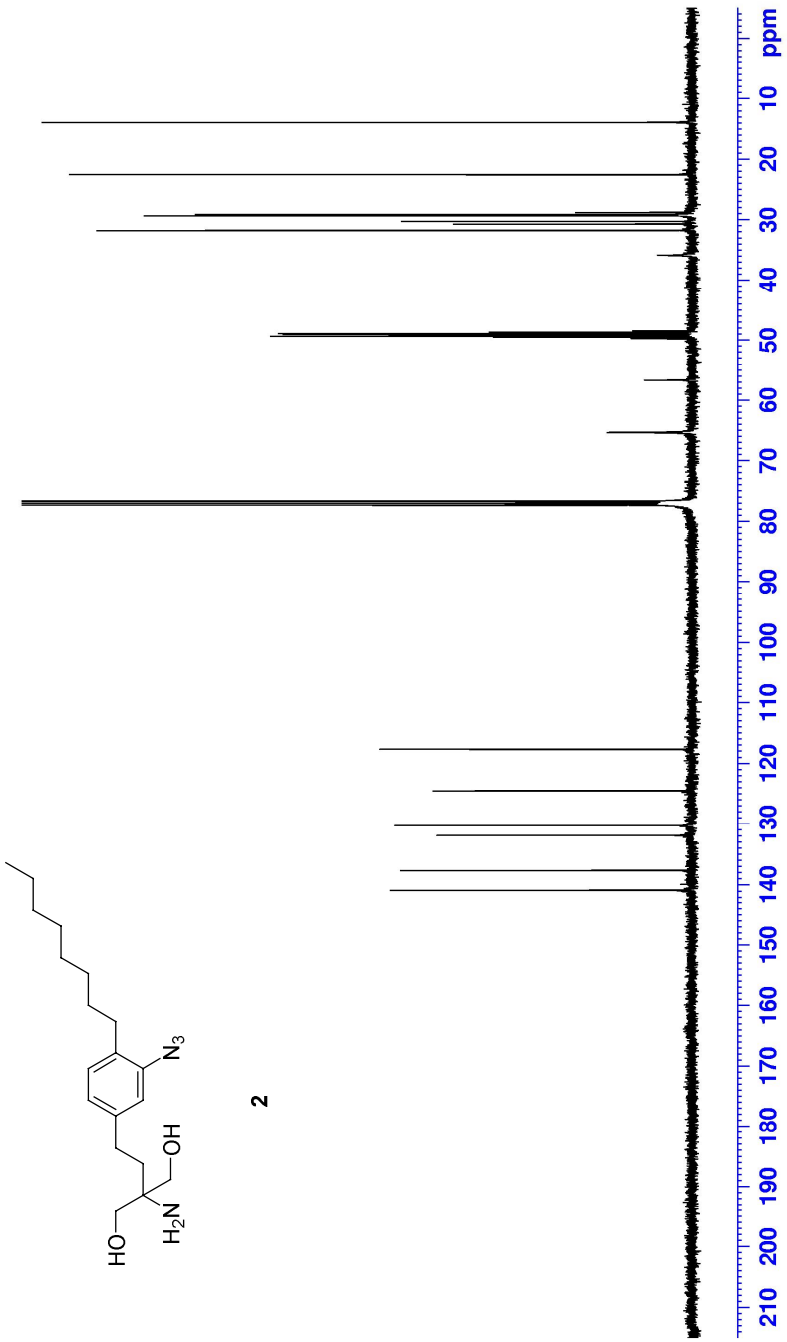
NO2
NO2
O
O
12
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210


C8H17-n
NH2
NH2
O
O
13
11
10
9
8
7
6
5
4
3
2
1
0
–1
ppm


ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210
C_8H_{17}-*n*
NH_2
NH_2
O
O

13


HO
H2N
OH
N3
2
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm


HO
H_2N
OH
N_3
2
ppm
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
210