Supporting Information

Metal free decarboxylative aminoxylation of carboxylic acids using a biphasic solvent system

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1 Materials and methods

1.1 General information

^{1}H NMR spectra were recorded at 400 MHz with a BRUKER Avance-400 and BRUKER Ascend-400 or at 600 MHz with a BRUKER Ascend-600 spectrometer at 323 K. ^{19}F NMR spectra were recorded at 376 MHz with a BRUKER Ascend-400 at 323 K. ^{13}C NMR spectra were recorded at 100 MHz with a BRUKER Avance-400 and BRUKER Ascend-400 or at 150 MHz with a BRUKER Ascend-600 instrument. Multiplicities are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, qu = quintet, sex = sextet, h = heptet, m = multiplet, br = broad. Substitutions of carbons are described using the following abbreviations: p = primary, s = secondary, t = tertiary, q = quaternary. Chemical shift values of ^{1}H and ^{13}C NMR spectra are commonly reported in ppm relative to residual solvent signal as internal standard. The multiplicities refer to the resonances in the off-resonance decoupled spectra and were elucidated using phase-sensitive HSQC experiments.

Mass spectra were obtained with a lockspray dual ion source in combination with a WATERS Alliance 2695 LC system, or with a type Q-TOF premier (Micromass) spectrometer (ESI mode) in combination with a WATERS Acquity UPLC system equipped with a WATERS Acquity UPLC BEH C18 1.7 μm (SN 01473711315545) column (solvent A: water + 0.1% {v/v} formic acid, solvent B: MeCN or MeOH {given in experimental part} + 0.1% {v/v} formic acid; flow rate = 0.4 mL/min; gradient {t [min]/solvent B [%]}: {0/5} {2.5/95} {6.5/95} {6.6/5} {8/5}; retention times {r_t} given in the experimental part). Ion mass signals (*m/z*) are reported as values in atomic mass units.

High-resolution mass spectrometry (HRMS) was measured with a Micromass LCT with lockspray source. The injection proceeded in loop-mode with a HPLC system by WATERS (Alliance 2695). Alternatively, mass spectra were recorded with an Acquity-UPLC system by WATERS in combination with a Q-Tof Premier mass spectrometer by WATERS in lockspray mode. The ionization happened by electrospray ionization (ESI) or by chemical ionization at atmospheric pressure (APCI). The calculated and found mass are reported. GC/MS analyses were carried out with an HP 6890 chromatograph with KAS 4, coupled to an HP 5973 quadrupole mass selective detector. Samples were analyzed on an Optima 5 column (poly(5%-phenyl-95%-methylsiloxane), 30 m x 0.32 mm i.d. x film thickness 0.25 μm). Carrier gas, He; injector temp., 60 °C to 300 °C at 12 °C/min, splitless; temp. program: 50 °C (isothermal 1 min) to 300 °C, at 20 °C/min and held isothermal for 6 min at 300 °C; ion source: EI, ionization energy, 70 eV; electron mass spectra were acquired over the mass range of 40 – 500 amu.

Analytical thin-layer chromatography was performed using precoated silica gel plates (MACHERY NAGEL) and the spots were visualized with UV light at 254 nm or alternatively by staining with permanganate, 4-methoxybenzaldehyde or cerium sulfate solutions. Commercially available reagents, chromatography type or dry solvents were used as received or purified by standard techniques according to the literature.[S1] (15-Oxo-7-azadispiro[5.1.5.3]hexadec-7-yl)oxidanyl (**14c**),[S2] 2,5,5-trimethyl-2-phenylpyrrolidin-1-yloxyl (**14d**)[S3] and 4-*tert*-butyl-2,2,6,6-tetraethyl-3-oxo-piperazin-1-oxyl (**14f**)[S4] were synthesized according to literature-known procedures.

Flash column chromatography was performed using mesh silica by MACHERY NAGEL (grain size 40 - 63 μm), with the indicated solvent system according to the standard techniques.

Melting points were determined on an SRS OptiMelt apparatus and are not corrected.

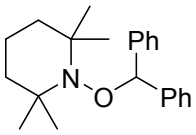
2 Chemical syntheses

2.1 Decarboxylative aminoxylation of carboxylic acids

General procedure for synthesis of alkoxyamines

A vial charged with the carboxylic acid (200 µmol, 1.00 equiv.), the aminoxyl radical (400 *µ*mol, 2.00 equiv.), potassium carbonate (41 mg, 300 µmol, 1.50 equiv.) and potassium peroxodisulfate (54 mg, 200 *µ*mol, 1.00 equiv.) was evacuated and purged with argon. Then 1,2-dichloroethane (1.50 mL) and water (0.50 mL) were added. The biphasic mixture was allowed to stir 20 h at 80 °C under an argon atmosphere. Then, the reaction mixture was diluted water (5.00 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic phases were washed with a solution of NaCl (sat. in H_2O, 10.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure.

1-(Benzhydryloxy)-2,2,6,6-tetramethylpiperidine (12a)



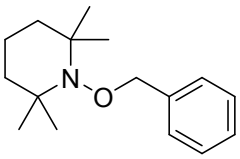
12a

This compound was prepared according to the general procedure using diphenylacetic acid (**1a**) and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12a** was collected as a colorless solid (38 mg, 117 *µ*mol, 59%).

R_f = 0.34 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.41 (d, *J* = 7.4 Hz, 4H, Ar*H*), 7.30 (t, *J* = 7.6 Hz, 4H, Ar*H*), 7.19 (t, *J* = 7.2 Hz, 2H, Ar*H*), 5.64 (s, 1H, C*H*ON), 1.43-1.26 (m, 6H, 3x CH_2), 1.16 (s, 6H, 2x CH_3), 0.74 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 144.6 (q, 2x Ar*C*), 127.9 (t, 4x Ar*C*), 126.5 (t, 4x Ar*C*), 126.3 (t, 2x Ar*C*), 90.5 (t, *C*ON), 59.6 (q, 2×*C*$(CH_3)_2$), 40.2 (s, 2×*C*H_2), 33.7 (p, 2×*C*H_3), 20.2 (p, 2×*C*H_3), 16.9 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S5]

1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (12b)



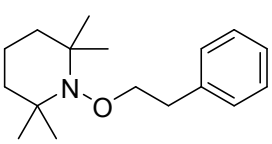
12b

This compound was prepared according to the general procedure using phenylacetic acid and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12b** was collected as a pale-yellow oil (41 mg, 166 *µ*mol, 83%).

R_f = 0.50 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 600 MHz): *δ* [ppm] 7.38 - 7.28 (m, 5H, Ar*H*), 4.83 (s, 2H, CH_2ON), 1.64 - 1.34 (m, 6H, 3×CH_2), 1.26 (s, 6H, 2×CH_3), 1.16 (s, 6H, 2×CH_3); **^{13}C-NMR** ($CDCl_3$, 150 MHz): *δ* [ppm] 138.5 (q, Ar*C*), 128.4 (t, 2×Ar*C*), 127.6 (t, 2×Ar*C*), 127.4 (t, Ar*C*), 78.9 (s, *C*H_2ON), 60.2 (q, 2×*C*$(CH_3)_2$), 39.9 (s, 2×*C*H_2), 33.2 (p, 2×*C*H_3), 20.4 (p, 2×*C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S6]

2,2,6,6-Tetramethyl-1-phenethoxypiperidine (12c)



12c

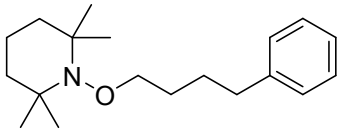
This compound was prepared according to the general procedure using 3-phenylpropanoic acid and TEMPO. The product was then purified using

flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12c** was collected as a pale-yellow oil (33 mg, 126 *µ*mol, 63%).

R_f = 0.41 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.30 – 7.17 (m, 5H, Ar*H*), 3.95 (t, *J* = 7.0 Hz, 2H, CH_2ON), 2.83 (t, *J* = 7.0 Hz, 2H, CH_2CH_2ON), 1.56 – 1.23 (m, 6H, 3x CH_2), 1.07 (s, 12H, 4x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 139.8 (q, Ar*C*), 129.2 (t, 2x Ar*C*), 128.2 (t, 2x Ar*C*), 126.0 (t, Ar*C*), 77.6 (s, *C*H_2ON), 59.8 (q, 2×*C*$(CH_3)_2$), 39.7 (s, 2×*C*H_2), 35.5 (s, Ph*C*H_2), 33.1 (p, 2×*C*H_3), 20.3 (p, 2×*C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S7]

2,2,6,6-Tetramethyl-1-(4-phenylbutoxy)piperidine (12d)

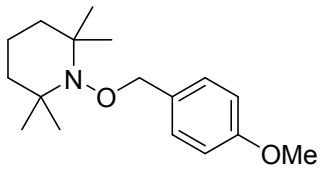


12d

This compound was prepared according to the general procedure using 5-phenylvaleric acid and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12d** was collected as a colorless oil (11 mg, 38 *µ*mol, 19%).

R_f = 0.27 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.28 (t, *J* = 6.5 Hz, 2H, Ar*H*), 7.18 (t, *J* = 8.1 Hz, 3H, Ar*H*), 3.76 (t, *J* = 6.5 Hz, 2H, CH_2ON), 2.64 (t, *J* = 7.7 Hz, 2H, PhCH_2), 1.71 (qi, *J* = 7.6 Hz, 2H, PhCH_2CH_2), 1.60 – 1.53 (m, 2H, CH_2CH_2ON), 1.46 – 1.23 (m, 6H, 3x CH_2), 1.15 (s, 6H, 2x CH_3), 1.09 (s, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 150 MHz): *δ* [ppm] 142.8 (q, Ar*C*), 128.6 (t, 2x Ar*C*), 128.4 (t, 2x Ar*C*), 125.8 (t, Ar*C*), 76.7 (s, *C*H2ON), 59.8 (q, 2×*C*$(CH_3)_2$), 39.7 (s, 2×*C*H_2), 36.1 (s, Ph*C*H_2), 33.2 (p, 2×*C*H_3), 28.6 (s, PhCH_2*C*H_2), 28.5 (s, *C*H_2CH_2ON), 20.3 (p, 2x *C*H_3), 17.3 (s, *C*$H_2(CH_2)$); **HRMS (ESI)** (*m/z*): calcd. for $C_{19}H_{31}NO$ $[M+H^+]^+$ 290.2484, found 290.2484.

1-((4-Methoxybenzyl)oxy)-2,2,6,6-tetramethylpiperidine (12e)



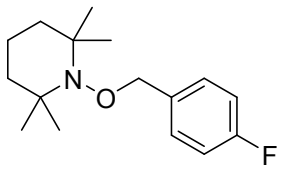
12e

This compound was prepared according to the general procedure using 4-methoxyphenylacetic acid and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12e** was collected as a pale-yellow oil (30 mg, 108 *µ*mol, 54%).

R_f = 0.31 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.30 (d, *J* = 8.6 Hz, 2H, Ar*H*), 6.88 (d, *J* = 8.6 Hz, 2H, Ar*H*), 4.74 (s, 2H, CH_2ON), 6.88 (s, 3H, OCH_3), 1.62 – 1.33 (m, 6H, 3x CH_2), 1.27 (s, 6H, 2x CH_3), 1.14 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 159.1 (q, Ar*C*), 130.5 (q, Ar*C*), 129.3 (t, 2x Ar*C*), 113.8 (t, 2x Ar*C*), 78.6 (s, *C*H_2ON), 60.1 (q, 2×*C*$(CH_3)_2$), 55.4 (p, O*C*H_3), 39.9 (s, 2×*C*H_2), 33.3 (p, 2×*C*H_3), 20.4 (p, 2×*C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S8]

1-((4-Fluorobenzyl)oxy)-2,2,6,6-tetramethylpiperidine (12f)



12f

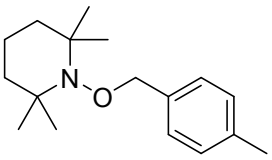
This compound was prepared according to the general procedure using 4-fluorophenylacetic acid and TEMPO. The product was then purified using

flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12f** was collected as a pale-yellow oil (41 mg, 155 *µ*mol, 77%).

R_f = 0.37 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.32 (dd, *J* = 8.4, 5.6 Hz, 2H, Ar*H*), 7.02 (t, *J* = 8.7 Hz, 2H, Ar*H*), 4.78 (s, 2H, CH_2ON), 1.62 – 1.34 (m, 6H, 3x CH_2), 1.25 (s, 6H, 2x CH_3), 1.14 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 162.3 (d, *J* = 245.0 Hz, q, Ar*C*F), 134.1 (d, *J* = 3.2 Hz, q, Ar*C*), 129.3 (d, *J* = 8.0 Hz, t, 2x Ar*C*), 115.2 (d, *J* = 21.2 Hz, t, 2x Ar*C*), 78.2 (d, *J* = 0.4 Hz, s, *C*H_2ON), 60.1 (q, 2×*C*$(CH_3)_2$), 39.8 (s, 2×*C*H_2), 33.2 (p, 2×*C*H_3), 20.4 (p, 2×*C*H_3), 17.2 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S9]

2,2,6,6-Tetramethyl-1-((4-methylbenzyl)oxy)piperidine (12g)



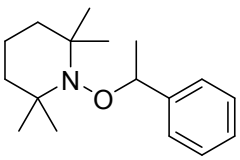
12g

This compound was prepared according to the general procedure using 4-methylphenylacetic acid and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12g** was collected as a colorless oil (37 mg, 142 *µ*mol, 71%).

R_f = 0.38 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 600 MHz): *δ* [ppm] 7.27 (d, *J* = 7.9 Hz, 2H, Ar*H*), 7.16 (d, *J* = 7.9 Hz, 2H, Ar*H*), 4.79 (s, 2H, CH_2ON), 2.36 (s, 3H, PhCH_3), 1.64 – 1.35 (m, 6H, 3x CH_2), 1.28 (s, 6H, 2x CH_3), 1.16 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 150 MHz): *δ* [ppm] 137.1 (q, Ar*C*), 135.4 (q, Ar*C*), 129.1 (t, 2x Ar*C*), 127.8 (t, 2x Ar*C*), 78.8 (s *C*H_2ON), 60.1 (q, 2×*C*$(CH_3)_2$), 39.9 (s, 2×*C*H_2), 33.3 (p, 2×*C*H_3), 21.3 (p, Ph*C*H_3), 20.4 (p, 2×*C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S9]

2,2,6,6-Tetramethyl-1-(1-phenylethoxy)piperidine (12h)



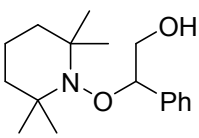
12h

This compound was prepared according to the general procedure using 2-phenylpropanoic acid and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12h** was collected as a colorless oil (32 mg, 122 *µ*mol, 61%).

R_f = 0.39 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.43 – 7.29 (m, 4H, Ar*H*), 7.25 – 7.21 (m, 1H, Ar*H*), 4.79 (q, *J* = 6.7 Hz, C*H*ON), 1.62 – 1.34 (m, 6H, 3x CH_2), 1,49 (d, *J* = 6.7 Hz, CH_3CHON), 1.30 (s, 3H, CH_3), 1.18 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 0.67 (s, 3H, CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 146.0 (q, Ar*C*), 128.1 (t, 2x Ar*C*), 126.9 (t, Ar*C*), 126.7 (t, 2x Ar*C*), 83.3 (t, *C*HON), 59.8 (q, 2x *C*$(CH_3)_2$), 40.5 (s, 2x *C*H_2), 34.6 (p, *C*H_3), 34.3 (p, *C*H_3), 23.7 (p, *C*H_3), 20.5 (p, 2x *C*H_3), 17.4 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S10]

2-Phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethan-1-ol (12i)



12i

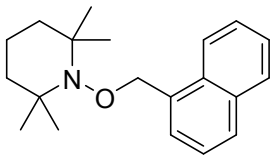
This compound was prepared according to the general procedure using tropic acid and TEMPO. The product was then purified using flash column chromatography

(petroleum ether:EtOAc 15:1 -> 5:1). The alkoxyamine **12i** was collected as a pale yellow oil (32 mg, 115 *µ*mol, 58%).

R_f = 0.32 (petroleum ether:EtOAc 10:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.38 – 7.28 (m, 5H, Ar*H*), 5.86 (bs, 1H, O*H*), 5.31 (dd, *J* = 9.5, 2.4 Hz, 1H, C*H*ON), 4.23 (dd, *J* = 12.2, 9.5 Hz, 1H, C*H*HOH), 3.73 (dd, *J* = 12.2, 2.6 Hz, 1H, CH*H*OH), 1.66 – 1.38 (m, 6H, 3x CH_2), 1.52 (s, 3H, CH_3), 1.35 (s, 3H, CH_3), 1.23 (s, 3H, CH_3), 1.16 (s, 3H, CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 138.9 (q, Ar*C*), 128.3 (t, 2x Ar*C*), 127.9 (t, Ar*C*), 126.8 (t, 2x Ar*C*), 83.6 (t, *C*HON), 69.7 (s, *C*H_2OH), 61.7 (q, *C*$(CH_3)_2$), 60.4 (q, *C*$(CH_3)_2$), 40.4 (s, *C*H_2), 40.2 (s, *C*H_2), 34.6 (p, *C*H_3), 32.8 (p, *C*H_3), 20.7 (p, *C*H_3), 20.4 (p, *C*H_3), 17.2 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S11]

2,2,6,6-Tetramethyl-1-(naphthalen-1-ylmethoxy)piperidine (12j)



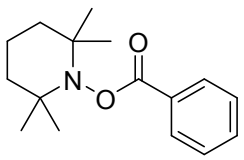
12j

This compound was prepared according to the general procedure using naphthaleneacetic acid and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12j** was collected as a colorless oil (45 mg, 151 *µ*mol, 76%).

R_f = 0.36 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 8.05 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.88 (d, *J* = 8.1 Hz, 1H, Ar*H*), 7.80 (d, *J* = 8.3 Hz, 1H, Ar*H*), 7.65 (d, *J* = 7.0 Hz, 1H, Ar*H*), 7.56 – 7.47 (m, 3H, Ar*H*), 5.33 (s, 2H, CH_2ON), 1.66 – 1.38 (m, 6H, 3x CH_2), 1.34 (s, 6H, 2x CH_3); 1.21 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 134.6 (q, Ar*C*), 133.6 (q, Ar*C*), 131.4 (q, Ar*C*), 128.6 (t, Ar*C*), 127.7 (t, Ar*C*), 126.0 (t, Ar*C*), 125.6 (t, Ar*C*), 125.6 (t, Ar*C*), 125.0 (t, Ar*C*), 124.0 (t, Ar*C*), 77.0 (s, *C*H_2ON), 60.2 (q, 2× *C*$(CH_3)_2$), 39.9 (s, 2× *C*H_2), 33.3 (p, 2× *C*H_3), 20.5 (p, 2× *C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S12]

2,2,6,6-Tetramethylpiperidin-1-yl benzoate (12k)



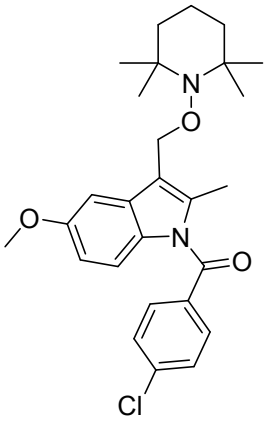
12k

This compound was prepared according to the general procedure using phenylglyoxylic acid and TEMPO. The product was then purified using flash column chromatography (petroleum ether:Et_2O 6:1). The ester **12k** was collected as a colorless solid (20 mg, 77 *µ*mol, 38%).

R_f = 0.62 (petroleum ether:Et_2O 6:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 8.07 (dd, *J* = 8.4, 1.2 Hz, 2H, Ar*H*), 7.56 (tt, *J* = 7.4, 1.3 Hz, 1H, Ar*H*), 7.46 (t, *J* = 7.6 Hz, 2H, Ar*H*), 1.81 – 1.43 (m, 6H, 3x CH_2), 1.27 (s, 6H, 2x CH_3), 1.12 s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 166.5 (q, C=O), 133.0 (t, Ar*C*), 129.9 (q, Ar*C*), 129.7 (t, 2x Ar*C*), 128.6 (t, 2x Ar*C*), 60.5 (q, 2×*C*$(CH_3)_2$), 39.2 (s, 2×*C*H_2), 32.1 (p, 2×*C*H_3), 21.0 (p, 2×*C*H_3), 17.1 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S13]

(4-Chlorophenyl)(5-methoxy-2-methyl-3-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-1*H*-indol-1-yl)methanone (12l)

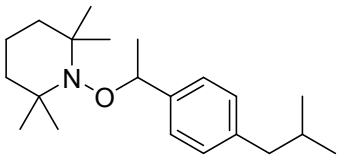


12l

This compound was prepared according to the general procedure using indomethacin and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 10:1). The alkoxyamine **12l** was afforded as a yellow oil (28 mg, 60 *µ*mol, 31%).

R_f = 0.43 (petroleum ether:EtOAc 10:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] ; 7.76 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.55 (d, *J* = 8.0 Hz, 2H, Ar*H*), 7.22 (d, *J* = 1.6 Hz, 1H, Ar*H*), 6.92 (d, *J* = 8.9 Hz, 1H, Ar*H*), 6.74 (dd, *J* = 8.9, 1.6 Hz, 1H, Ar*H*), 4.99 (s, 2H, CH_2ON), 3.91 (s, 3H, OCH_3), 2.51 (s, 3H, ArCH_3), 1.70 – 1.46 (m, 6H, 3x CH_2), 1.44 (s, 6H, 2x CH_3), 1.20 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 168.6 (q, *C*=ON), 156.0 (q, Ar*C*OCH_3), 139.4 (q, Ar*C*Cl), 136.5 (q, Ar*C*CH_3), 134.1 (q, Ar*C*C=O), 131.4 (t, 2x Ar*C*), 131.04 (q, Ar*C*), 131.03 (q, Ar*C*), 129.3 (t, 2x Ar*C*), 116.8 (q, Ar*C*CH_2ON), 114.9 (t, Ar*C*), 111.6 (t, Ar*C*), 102.2 (t, Ar*C*), 69.9 (s, *C*H_2ON), 60.0 (q, 2×*C*$(CH_3)_2$), 55.8 (p, O*C*H_3), 39.9 (s, 2× *C*H_2), 33.6 (p, 2× *C*H_3), 20.3 (p, 2× *C*H_3), 17.3 (s, *C*$H_2(CH_2)_2$), 13.7 (p, *C*H_3CNC=O); **HRMS (ESI)** (*m/z*): calcd. for $C_{27}H_{33}N_2O_3NaCl$ $[M+Na^+]^+$ 491.2077, found 491.2073.

1-(1-(4-Isobutylphenyl)ethoxy)-2,2,6,6-tetramethylpiperidine (12m)



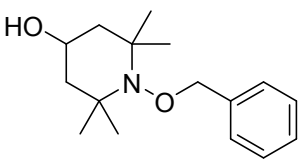
12m

This compound was prepared according to the general procedure using ibuprofen and TEMPO. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1). The alkoxyamine **12m** was afforded as a pale-yellow oil (38 mg, 120 *µ*mol, 60%).

R_f = 0.36 (petroleum ether:EtOAc 50:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.22 (d, *J* = 7.9 Hz, 2H, Ar*H*), 7.08 (d, *J* = 7.9 Hz, 2H, Ar*H*), 4.75 (q, *J* = 6.6 Hz, 1H, C*H*ON), 2.46 (d, *J* = 7.2 Hz, 2H, PhCH_2), 1.86 (h, *J* = 6.8 Hz, 1H, C*H*$(CH_3)_2$), 1.54 – 1.27 (m, 6H, 3x CH_2), 1.48 (d, *J* = 6.7 Hz, 3H, CH_3CHON), 1.29 (s, 3H, CH_3), 1.17 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 0.89 (d, *J* = 6.6 Hz, 6H, 2x $(CH_3)_2$CH), 0.63 (s, 3H, CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 143.1 (q, Ar*C*CH_2), 140.3 (q, Ar*C*CH), 128.8 (t, 2x Ar*C*), 126.6 (t, 2x Ar*C*), 82.9 (t, *C*HON), 59.8 (q, 2×*C*$(CH_3)_2$), 45.3 (s, Ar*C*H_2), 40.5 (s, 2× *C*H_2), 34.5 (p, *C*H_3), 34.2 (p, *C*H_3), 30.4 (p, *C*H_3CHON), 29.8 (t, *C*H$(CH_3)_2$), 23.4 (p, C*C*H_3), 22.50 (p, *C*H_3CH), 22.49 (p, *C*H_3CHCH_2), 20.5 (p, C*C*H_3), 17.4 (s, *C*$H_2(CH_2)_2$).

The analytical data are consistent with those reported in the literature.[S14]

1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-ol (15a)



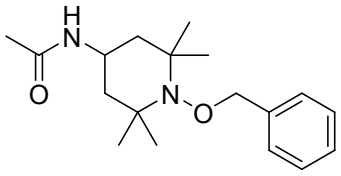
15a

This compound was prepared according to the general procedure using phenylacetic acid and 4-OH-TEMPO (**14a**). The product was then purified using flash column chromatography (petroleum ether:EtOAc 2:1 -> 1:1). The alkoxyamine **15a** was collected as a pale-yellow oil (39 mg, 148 *µ*mol, 74%).

R_f = 0.44 (petroleum ether:EtOAc 3:2); **^{1}H-NMR** ($CDCl_3$, 600 MHz): *δ* [ppm] 7.41 – 7.38 (m, 4H, Ar*H*), 7.35 – 7.32 (m, 1H, Ar*H*), 4.88 (s, 2H, CH_2ON), 4.07 (t, *J* = 11.0 Hz, 1H, C*H*OH), 1.90 (d, *J* = 10.6 Hz, CH_2, 2H), 1.58 (t, *J* = 11.4 Hz, 2H, CH_2), 1.35 (s, 6H, 2x CH_3), 1.26 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 150 MHz): *δ* [ppm] 137.3 (q, Ar*C*), 127.6 (t, 2x Ar*C*), 126.8 (t, 2x Ar*C*), 126.7 (t, Ar*C*), 78.2 (s, *C*H_2ON), 62.5 (t, *C*HOH). 59.6 (q, 2× *C*$(CH_3)_2$), 47.7 (s, 2× CH_2), 32.5 (p, 2× *C*H_3), 20.5 (p, 2× *C*H_3).

The analytical data are consistent with those reported in the literature.[S14]

***N*-(1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-yl)acetamide (15b)**

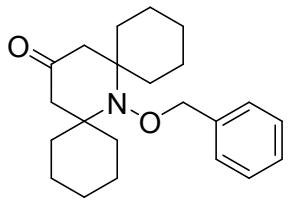


15b

This compound was prepared according to the general procedure using phenylacetic acid and 4-acetamido-TEMPO (**14b**). The product was then purified using flash column chromatography (dichloromethane:MeOH 95:5). The alkoxyamine **15b** was collected as a colorless solid (50 mg, 164 *μ*mol, 82%).

R_f = 0.41 (dichloromethane:MeOH 95:5); **mp.** = 126 °C; **^{1}H-NMR** ($CDCl_3$, 600 MHz): *δ* [ppm] 7.35 – 7.33 (m, 4H, Ar*H*), 7.30 – 7.27 (m, 1H, Ar*H*), 5.44 (bs, 1H, N*H*), 4.82 (s, 2H, CH_2ON), 4.17 (t, *J* = 13.3 Hz, 1H, C*H*NH), 1.96 (s, 3H, CH_3C=O), 1.82 (dd, *J* = 12.3, 3.1 Hz, 2H, CH_2), 1.38 (t, *J* = 12.0 Hz, 2H, CH_2), 1.28 (s, 6H, 2x CH_3), 1.26 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 150 MHz): *δ* [ppm] 169.2 (q, *C*=O), 137.3 (q, Ar*C*), 128.2 (t, 2x Ar*C*), 127.3 (t, 3x Ar*C*), 78.7 (s, *C*H_2ON), 60.1 (q, 2× *C*$(CH_3)_2$). 45.7 (s, 2× CH_2), 40.9 (t, *C*HNH), 32.9 (p, 2× *C*H_3), 23.5 (s, CH_3), 20.7 (p, 2× *C*H_3); **HRMS (ESI)** (*m/z*): calcd. for $C_{18}H_{29}N_2O_2$ $[M+H^+]^+$ 305.2229, found 305.2228.

7-(Benzyloxy)-7-azadispiro[5.1.5^8.3^6]hexadecan-15-one (15c)

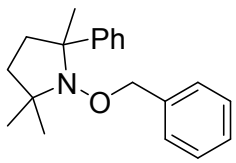


15c

This compound was prepared according to the general procedure using phenylacetic acid and (15-oxo-7-azadispiro[5.1.5.3]hexadec-7-yl)oxidanyl (**14c**). The product was then purified using flash column chromatography (petroleum ether:EtOAc 9:1). The alkoxyamine **15c** was collected as a colorless oil (40 mg, 117 *μ*mol, 58%).

R_f = 0.35 (petroleum ether:EtOAc 9:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.38 – 7.28 (m, 5H, Ar*H*), 4.92 (s, 2H, CH_2ON), 2.78 (d, *J* = 13.3 Hz, 2H, 2x C*H*HC=O), 2.38 (d, *J* = 13.4 Hz, 2H, 2x CH*H*C=O), 2.03 (td, *J* = 19.5, 4.3 Hz, 2H, CH_2), 1.97 (td, *J* = 12.6, 3.7 Hz, 2H, CH_2), 1.80 – 1.56 (m, 10H, 5x CH_2), 1.43 – 1.26 (m, 4H, 2x CH_2), 1.18 – 1.07 (m, 2H, CH_2); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 209.4 (q, C=O), 137.6 (q, Ar*C*), 128.5 (t, 2x Ar*C*), 127.7 (q, Ar*C*), 127.4 (t, 2x Ar*C*), 79.5 (s, *C*H_2ON), 67.6 (q, 2x *C*Cy), 47.2 (s, 2x *C*H_2C=O), 39.2 (s, 2x *C*H_2), 32.5 (s, 2x *C*H_2), 25.6 (s, 2x *C*H_2), 23.1 (s, 2x *C*H_2), 22.8 (s, 2x *C*H_2); **HRMS (ESI)** (*m/z*): calcd. for $C_{22}H_{31}NO_2$ $[M+H^+]^+$ 342.2433, found 342.2436.

1-(Benzyloxy)-2,2,5-trimethyl-5-phenylpyrrolidine (15d)



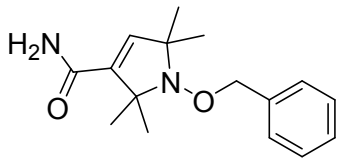
15d

This compound was prepared according to the general procedure using phenylacetic acid and 2,5,5-trimethyl-2-phenylpyrrolidin-1-yloxyl (**14d**). The product was then purified using flash column chromatography (petroleum

ether:EtOAc 50:1). The alkoxyamine **15d** was afforded as a colorless oil (35 mg, 122 *µ*mol, 61%).

R_f = 0.45 (petroleum ether:EtOAc 20:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.37 (d, *J* = 7.4 Hz, 2H, Ar*H*), 7.37 – 7.22 (m, 8H, Ar*H*), 4.65 (d, *J* = 10.8 Hz, 1H, C*H*HON), 4.51 (d, *J* = 10.8 Hz, 1H, CH*H*ON), 2.06 – 1.92 (m, 2H, CH_2), 1.77 – 1.67 (m, 2H, CH_2), 1.65 (s, 3H, CH_3), 1.30 (s, 3H, CH_3), 1.29 (s, 3H, CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 151.2 (q, Ar*C*), 138.3 (q, Ar*C*), 128.4 (t, 2x Ar*C*), 128.2 (t, 2x Ar*C*), 127.9 (t, 2x Ar*C*), 127.6 (q, Ar*C*), 126.3 (t, 2x Ar*C*), 126.0 (t, Ar*C*), 77.6 (s, *C*H_2ON), 68.5 (q, *C*(CH_3)Ph), 64.6 (q, *C*(CH_3)$_2$), 39.3 (s, *C*H_2), 36.0 (s, *C*H_2), 30.4 (p, *C*H_3), 23.5 (p, 2x *C*H_3); **HRMS (ESI)** (*m/z*): calcd. for $C_{20}H_{26}NO$ $[M+H^+]^+$ 296.2014, found 296.2013.

1-(Benzyloxy)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide (15e)

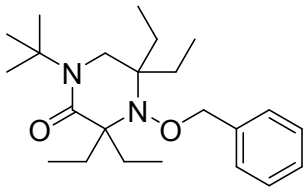


15e

This compound was prepared according to the general procedure using phenylacetic acid and 3-carbamoyl-2,2,5,5-tetramethyl-2,5-dihydropyrrol-1-oxyl (**14e**). The product was then purified using flash column chromatography (petroleum ether:EtOAc 3:2). The alkoxyamine **15e** was collected as a colorless solid (17 mg, 62 *µ*mol, 31%).

R_f = 0.29 (petroleum ether:EtOAc 3:2); **mp.** = 123 °C; **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.40 – 7.28 (m, 5H, Ar*H*), 6.05 (s, 1H, C*H*=$CONH_2$), 5.59 (bs, 2H, NH_2), 4.85 (s, 2H, CH_2ON), 1.45 (s, 6H, 2x CH_3), 1.27 (s, 6H, 2x CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 166.8 (q, *C*ONH_2), 139.7 (q, *C*$CONH_2$), 139.5 (t, *C*H=C$CONH_2$), 138.2 (q, Ar*C*), 128.6 (t, 2x Ar*C*), 128.4 (t, 2x Ar*C*), 127.9 (t, Ar*C*), 79.5 (*C*H_2ON), 70.9 (q, *C*(CH_3)$_2$), 68.0 (q, *C*(CH_3)$_2$), 29.8 (p, 2x *C*H_3), 23.1 (p, 2x *C*H_3); **HRMS (ESI)** (*m/z*): calcd. for $C_{16}H_{23}N_2O_2$ $[M+H^+]^+$ 275.1760, found 275.1775.

4-(Benzyloxy)-1-(*tert*-butyl)-3,3,5,5-tetraethylpiperazin-2-one (15f)



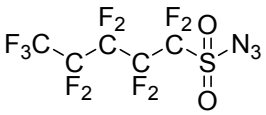
15f

This compound was prepared according to the general procedure using phenylacetic acid and 4-*tert*-butyl-2,2,6,6-tetraethyl-3-oxo-piperazin-1-oxyl (**14f**). The product was then purified using flash column chromatography (petroleum ether:MTBE 10:1). The alkoxyamine **15f** was collected as a colorless viscous oil (22 mg, 59 *µ*mol, 29%).

R_f = 0.33 (petroleum ether:MTBE 10:1); **^{1}H-NMR** ($CDCl_3$, 400 MHz): *δ* [ppm] 7.36 – 7.26 (m, 5H, Ar*C*), 4.76 (q, *J* = 12.4 Hz, 2H, CH_2ON), 3.23 (d, *J* = 12.6 Hz, 1H, C*H*HN), 3.07 (d, *J* = 12.6 Hz, 1H, CH*H*N), 2.07 – 1.93 (m, 2H, CH_2CH_3), 1.89 – 1.70 (m, 4H, 2x CH_2CH_3), 1.63 – 1.56 (m, 2H, CH_2CH_3), 1.41 (s, 3xCCH_3), 1.00 (t, *J* = 7.4 Hz, 9H, 3x CH_2CH_3), 0.92 (t, *J* = 7.4 Hz, 3H, CH_2CH_3); **^{13}C-NMR** ($CDCl_3$, 100 MHz): *δ* [ppm] 173.2 (q, *C*=ON), 137.6 (q, Ar*C*), 128.4 (t, Ar*C*), 127.9 (t, Ar*C*), 127.7 (q, Ar*C*), 77.9 (s, *C*H_2ON), 73.0 (q, CO*C*(C_2H_5)$_2$), 62.8 (q, CH_2*C*(C_2H_5)$_2$), 57.4 (q, *C*(CH_3)$_3$), 47.1 (s, *C*H_2N), 33.1 (s, *C*H_2CH_3), 29.0 (), 28.3 (p, 3x C(*C*H3)$_3$), 26.5 (s, *C*H_2CH_3), 24.2 (s, *C*H_2CH_3), 11.4 (p, CH_2*C*H_3), 9.4 (p, CH_2*C*H_3), 9.1 (p, CH_2*C*H_3), 8.2 (p, CH_2*C*H_3); **HRMS (ESI)** (*m/z*): calcd. for $C_{23}H_{38}N_2O_2Na$ $[M+Na^+]^+$ 397.2831, found 397.2831.

2.2 Total Synthesis of (±)-Indatraline

1,1,2,2,3,3,4,4,5,5,5-Undecafluoropentane-1-sulfonyl azide (S1)



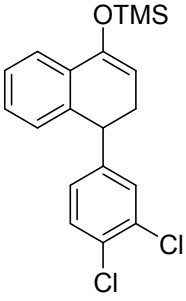
XX

Perfluorobutanesulfonyl fluoride (2.00 g, 6.36 mmol, 1.00 equiv.) was added to a solution of sodium azide (413 mg, 6.63 mmol, 1.00 equiv.) in dry methanol (7.30 mL). The mixture was stirred for 18 h at ambient temperature. Then, it was passed over a fritted glass funnel to remove the solid precipitates. The filtrate was diluted with H_2O (10.0 mL). The fluorous phase was collected and dried over sodium sulfate to afford the neat nonaflyl azide (**S1**) as a colorless oil (1.06 g, 3.25 mmol, 51%).

^{19}F NMR (376 MHz, $CDCl_3$): δ [ppm] -80.9 (tt, J = 14.5, 2.5 Hz, 3F, CF_3), -189.6 (tq, J = 20.5, 2.5 Hz, 2F, CF_2CF$_3$), -121.1 – -121.2 (m, 2F, $SO_2CF_2CF_2$), -126.0 – -126.2 (m, 2F, SO_2CF_2); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 118.9 – 118.0 (m, 1C, CF_3), 166.0 – 115.0 (m, 1C, CF_2SO_2), 113.7 – 105.3 (m, 2C, 2xCF_2).

The analytical data are consistent with those reported in the literature.[S15]

((4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1-yl)oxy)trimethylsilane (19)

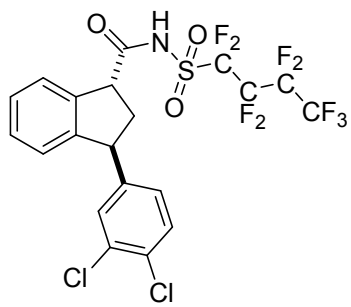


19

To a solution of the tetralone **18** (1.00 g, 3.26 mmol, 1.00 equiv.) in dry CH_2Cl_2 (5.00 mL) trimethylamine (498 μL, 3.59 mmol, 1.10 equiv.) and TMSOTf (591 μL, 13.26 mmol, 1.00 equiv.) were added at 0 °C. The reaction was stirred at the same temperature for 30 min, and immediately subjected to flash column chromatography on silica that had been pre-treated with ethyl acetate and petroleum ether (1:10). The compound was eluted with petroleum ether. The silyl enol ether **19** was obtained as a colorless oil (1.13 g, 3.11 mmol, 95%) and stored in a dry flask under argon at 0 °C until future use.

R_f = 0.20 (petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$): δ [ppm] 7.51 (d, J = 7.7 Hz, 1H, ArH), 7.31 (d, J = 8.3 Hz, 1H, ArH), 7.24 (t, J = 8.4 Hz, 2H, ArH), 7.12 (td, J = 11.1, 1.1 Hz, 1H, ArH), 7.00 (dd, J = 8.3, 1.9 Hz, 1H, ArH), 6.81 (d, J = 7.5 Hz, 1H, ArH), 5.07 (t, J = 4.6 Hz, 1H, CH=COTMS), 4.02 (t, J = 7.6 Hz, 1H, CHAr), 2.70 (ddd, J = 16.5, 7.0, 4.5 Hz, 1H, CHH), 2.52 (ddd, J = 16.5, 8.2, 4.8 Hz, 1H, CHH), 0.24 (s, 9H, Si(CH_3)$_3$); **^{13}C NMR** (100 MHz, $CDCl_3$): δ [ppm] 148.2 (q. COTMS), 144.9 (q, ArC), 138.0 (q, ArC), 133.5 (q, ArC), 132.4 (q, ArC), 130.44 (q, ArC), 130.38 (t, ArC), 130.35 (t, ArC), 128.1 (t, ArC), 128.0 (t, ArC), 127.6 (t, ArC), 127.2 (t, ArC), 122.6 (t, ArC), 103.0 (t, CH=COTMS), 43.3 (t, CHAr), 30.7 (s, CH$_2$), 0.4 (p, 3x CH$_3$); **HRMS** (**EI**) (*m/z*) calcd. for $C_{19}H_{20}Cl_2OSi$ 362.0660, found 362.0669.

3-(3,4-Dichlorophenyl)-*N*-((perfluorobutyl)sulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide (20)



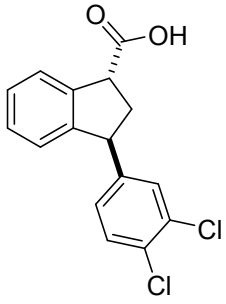
20

TMS-enol ether **19** (500 mg, 1.38 mmol, 1.00 equiv.) was added to a solution of perfluorobutanesulfonyl azide (**S1**) (492 mg, 1.51 mmol, 1.10 equiv.) in acetonitrile (4.60 mL) at ambient temperature. The reaction mixture was then stirred for 20 h at 40 °C. Subsequently, the solvent was removed by evaporation. The residue obtained was

purified by flash-column chromatography (CH_2Cl_2/EtOAc = 1:0 -> 1:1). The *N*-acyl sulfonamide **20** was obtained as an inseparable mixture of diastereomers (*anti:syn* 9:1) as a colorless solid (571 mg, 971 *µ*mol, 71% yield).

R_f = 0.41 (CH_2Cl_2/EtOAc = 1:1); **mp.** = 96-99 °C; **^{1}H NMR** (400 MHz, DMSO): *δ* [ppm] 7.58 – 7.53 (m, 1H, Ar*H*), 7.47 – 7.38 (m, 2H, Ar*H*), 7.24 – 7.11 (m, 3H, Ar*H*), 6.87 (d, *J* = 7.1 Hz, 1H, Ar*H*, major), 6.77 (d, *J* = 7.1 Hz, 1H, Ar*H*, minor), 4.55 (t, *J* = 7.6 Hz, 1H, C*H*C=O, major), 4.33 (t, *J* = 8.9 Hz, 1H, C*H*C=O, minor), 3.96 (dd, *J* = 8.1, 3.9 Hz, 1H, C*H*($C_6H_3Cl_2$), major), 3.87 (t, *J* = 8.7 Hz, 1H, C*H*($C_6H_3Cl_2$), minor), 2.79 (ddd, *J* = 12.7, 8.5, 4.2 Hz, 1H, C*H*H, major), 2.66 – 2.58 (m, 1H, C*H*H, minor), 2.32 – 2.23 (m, 1H, CH*H*, minor), 2.09 (dt, *J* = 12.9, 7.7 Hz, 1H, CH*H*, major); **^{19}F NMR** (376 MHz, MeOD): *δ* [ppm] -82.7 (tt, *J* = 10.0, 2.6 Hz, 3F, C*F*$_3$), -114.0 (t, *J* = 14.3 Hz, 2F, C*F*$_2$SO2), -122.4 – -122.6 (m, 2F, C*F*$_2$CF$_3$), -127.3 – -127.4 (m, 2F, C*F*$_2$CF$_2$SO$_2$); **^{13}C NMR** (100 MHz, DMSO-*d*6): *δ* [ppm] 177.3 (q, CON), 146.9 (q, Ar*C*), 145.9 (q, Ar*C*), 143.7 (q, Ar*C*), 131.0 (q, Ar*C*), 130.7 (t, Ar*C*), 129.7 (t, Ar*C*), 128.8 (q, Ar*C*), 128.1 (t, Ar*C*), 127.1 (t, Ar*C*), 126.7 (t, Ar*C*), 125.0 (t, Ar*C*), 124.4 (t, Ar*C*), 118.5 – 110.5 (m, 4C, *C*F2*C*F2*C*F2*C*F3), 53.2 (t, *C*HC=O), 48.9 (t, *C*H($C_6H_3Cl_2$)), 38.8 (s, *C*H_2); **HRMS (ESI)** (*m/z*): calcd. for $C_{20}H_{11}NO_3SCl_2F_9$ [M – H$^+$]$^-$ 585.9693, found 585.9695.

3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid (21)



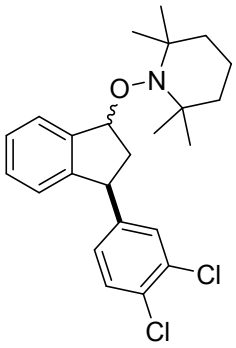
21

N-acyl sulfonamide **20** (552 mg, 938 *µ*mol, 1.00 equiv.) was dissolved in a mixture of 1,4-dioxane (9.40 mL) and sulfuric acid (25% in H_2O, 9.40 mL). The reaction mixture was refluxed for 20 h. Subsequently, water (5.00 mL) and CH_2Cl_2 (5.00 mL) were added. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (3x 5.00 mL). The combined organic phases were basified with NaOH (1M in H_2O, 20.0 mL). The phases were separated and the organic phase was extracted with NaOH (1M in H_2O, 2x 20.0 mL). The combined aqueous phases were washed with CH_2Cl_2 (20.0 mL) and then acidified to pH=1 using HCl (37% in H_2O). The white suspension was extracted with EtOAc (3x 50.0 mL). The combined organic phases were dried over $MgSO_4$, filtrated and concentrated under reduced pressure. Residues of nonaflyl amine were removed by sublimation at 80 °C under high vacuum. The carboxylic acid **21** was obtained a pale-yellow solid (251 mg, 817 *µ*mol, 87% yield).

^{1}H NMR (400 MHz, DMSO-d_6): *δ* [ppm] 12.52 (bs, 1H, CO_2H), 7,59 (d, *J* = 8.3 Hz, 1H Ar*H*, minor), 7.56 (d, *J* = 8.3 Hz, 1H, Ar*H*, major), 7.47 – 7.42 (m, 2H, Ar*H*), 7.27 – 7.15 (m, 3H, Ar*H*), 6.91 (d, *J* = 7.3 Hz, 1H, Ar*H*, major), 6.86 (d, *J* = 7.2 Hz, 1H, Ar*H*, minor), 4.59 (t, *J* = 8.0 Hz, 1H, C*H*CO_2H, major), 4.41 (t, *J* = 8.7 Hz, 1H, C*H*CO_2H, minor), 4.17 (dd, *J* = 8.3, 3.3 Hz, 1H, *C*H($C_6H_3Cl_2$), major), 4.09 (t, *J* = 8.7 Hz, 1H, *C*H($C_6H_3Cl_2$), minor), 2.79 (ddd, *J* = 13.1, 8.4, 4.1 Hz, 1H, C*H*H), 2.24 (dt, *J* = 13.2, 8.1 Hz, 1H, CH*H*); **^{13}C NMR** (100 MHz, DMSO-d_6): *δ* [ppm] 174.6 (q, *C*O_2H), 146.2 (q, Ar*C*), 145.9 (q, Ar*C*), 141.4 (q, Ar*C*), 131.1 (q, Ar*C*), 130.7 (t, Ar*C*), 129.9 (t, Ar*C*), 129.0 (q, Ar*C*), 128.2 (t, Ar*C*), 127.8 (t, Ar*C*), 127.2 (t, Ar*C*), 125.0 (t, Ar*C*), 124.7 (t, Ar*C*), 48.9 (t, *C*HC=O), 48.6 (t, *C*H($C_6H_3Cl_2$)), 38.2 (s, *C*H_2).

The analytical data are consistent with those reported in the literature.[S16]

1-((3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (22)

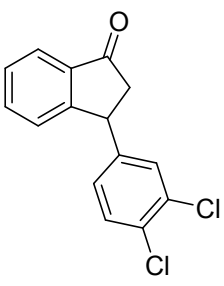


22

A vial charged with the carboxylic acid **21** (62 mg, 200 *µ*mol, 1.00 equiv.), TEMPO (64 mg, 400 *µ*mol, 2.00 equiv.), potassium carbonate (41 mg, 300 *µ*mol, 1.50 equiv.) and potassium peroxodisulfate (54 mg, 200 µmol, 1.00 equiv.) was evacuated and purged with argon. Then 1,2-dichloroethane (1.50 mL) and water (0.50 mL) were added. The biphasic mixture was allowed to stir 20 h at 80 °C under an argon atmosphere. Then, the reaction mixture was diluted water (5.00 mL) and extracted with EtOAc (3x 10.0 mL). The combined organic phases were washed with a solution of NaCl (sat. in H_2O, 10.0 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was then purified using flash column chromatography (petroleum ether:EtOAc 50:1 -> 10:1). The alkoxyamine **22** was collected as an inseparable mixture of diastereomers (*anti:syn* 1:1.3) as a viscous red oil (43 mg, 103 *µ*mol, 51%).

R_f = 0.41 (EtOAc/petroleum ether = 20:1); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* [ppm] 7.68 (d, *J* = 7.4 Hz, 1H, Ar*H*, minor), 7.64 (t, *J* = 4.3 Hz, 1H, Ar*H*, major), 7.41 – 7.22 (m, 4H, Ar*H*), 7.09 (d, *J* = 8.1 Hz, 1H, Ar*H*, minor), 6.99 (t, *J* = 3.9 Hz, 1H, Ar*H*, major), 6.94 (d, *J* = 8.1 Hz, 1H, Ar*H*, major), 6.89 (d, *J* = 7.3 Hz, 1H, Ar*H*, minor), 5.46 (t, *J* = 4.9 Hz, 1H, C*H*ON, major), 5.41 (t, *J* = 7.6 Hz, 1H, C*H*ON, minor), 4.48 (t, *J* = 6.9 Hz, 1H, C*H*($C_6H_3Cl_2$), major), 3.99 (dd, *J* = 10.1, 6.8 Hz, 1H, C*H*($C_6H_3Cl_2$), minor), 3.00 (dt, *J* = 12.3, 6.4 Hz, 1H, C*H*H, minor), 2.72 (ddd, *J* = 12.5, 7.7, 4.2 Hz, 1H, C*H*H, major), 2.28 (dt, *J* = 12.9, 6.3 Hz, 1H, CH*H*, major), 2.02 (q, *J* = 10.6 Hz, 1H, CH*H*, minor), 1.59 – 1.13 (m, 15H, 3x CH_2 + 3x CH_3), 0.87 (s, 3H, CH_3); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* [ppm]; 146.1 (q, Ar*C*, major), 145.5 (q, Ar*C*, major), 144.5 (q, Ar*C*, minor), 144.3 (q, Ar*C*, minor), 144.1 (q, Ar*C*, minor), 144.0 (q, Ar*C*, major), 132.6 (q, Ar*C*, minor), 132.5 (q, Ar*C*, major), 130.59 (q, Ar*C*, major), 130.58 (t, Ar*C*, minor), 130.53 (t, Ar*C*, minor), 130.49 (t, Ar*C*, major), 130.3 (q, Ar*C*, minor), 130.0 (t, Ar*C*, major), 128.8 (t, Ar*C*, major), 128.2 (t, Ar*C*, minor), 128.0 (t, Ar*C*, minor), 127.5 (t, Ar*C*, major), 127.1 (t, Ar*C*, minor), 126.8 (t, Ar*C*, major), 126.7 (t, Ar*C*, major),125.0 (t, Ar*C*, major), 124.7 (t, Ar*C*, minor), 124.5 (t, Ar*C*, minor), 87.3 (t, *C*HON, minor), 86.0 (*t*, *C*HON, major), 61.2 (q, *C*(CH_3)$_2$, major), 60.3 (q, *C*(CH_3)$_2$, minor), 59.9 (q, *C*(CH_3)$_2$, minor), 59.1 (q, *C*(CH_3)$_2$, major), 48.4 (t, *C*H($C_6H_3Cl_2$, major), 47.6 (s, *C*H_2, minor), 47.4 (t, *C*H($C_6H_3Cl_2$, minor), 44.7 (s, *C*H_2, major), 40.6 (s, 2x *C*H_2C(CH_3)$_2$, minor), 40.5 (s, 2x *C*H_2C(CH_3)$_2$, major), 34.91 (p, *C*H_3, minor), 34.86 (p, *C*H_3, major), 33.4 (p, *C*H_3, major), 33.2 (p, *C*H_3, minor), 20.6 (p, 2x *C*H_3, major), 20.5 (p, 2x *C*H_3, minor), 17.4 (s, *C*H_2(CH_2)$_2$, major), 17.3 (s, *C*H_2(CH_2)$_2$, minor); **HRMS (ESI)** (*m/z*): calcd. for $C_{24}H_{29}Cl_2NO$ [M + H^+]$^+$ 418.1704, found 418.1708.

3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one (23)



23

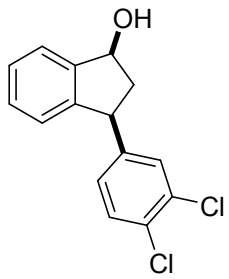
To a solution of the alkoxyamine **22** (80 mg, 191 *µ*mol, 1.00 equiv.) in CH_2Cl_2 (3.00 mL), *m*CPBA was added portionwise at 0 °C. The mixture was stirred at the same temperature for 90 min, then, the aqueous $Na_2S_2O_3$ (5.00 mL) was added to quench the reaction and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3x 5.00 mL). The combined organic phases were washed with aqueous $NaHCO_3$ (10.0 mL) and with brine (10.0 mL), dried over $MgSO_4$,

filtered and concentrated. The crude product was purified by column chromatography (petroleum ether:EtOAc 15:1 -> 5:1) and washed with ice-cold petroleum ether. The indenone **23** was collected as colorless solid (49 mg, 177 *µ*mol, 92%).

R_f = 0.26 (EtOAc/petroleum ether = 10:1); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* [ppm] 7.83 (d. *J* = 7.6 Hz, 1H, Ar*H*), 7.61 (td. *J* = 7.5, 1.2 Hz, 1H, Ar*H*), 7.46 (t. *J* = 7.5 Hz, 1H, Ar*H*), 7.38 (d. *J* = 8.2 Hz, 1H, Ar*H*), 7.26 (d. *J* = 7.7 Hz, 1H, Ar*H*), 7.23 (d. *J* = 2.1 Hz, 1H, Ar*H*), 7.23 (dd. *J* = 8.2, 2.1 Hz, 1H, Ar*H*), 4.55 (dd. *J* = 8.1, 3.8 Hz, 1H, C*H*($C_6H_4Cl_2$)), 3.23 (dd. *J* = 19.2, 8.1 Hz, 1H, C*H*H), 2.62 (dd. *J* = 19.2, 3.9 Hz, 1H, CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* [ppm] 205.1 (q, C=O), 156.7 (q, Ar*C*), 144.1 (q, Ar*C*), 136.9 (q, Ar*C*), 135.5 (t, Ar*C*), 133.1 (q, Ar*C*), 131.2 (q, Ar*C*), 131.0 (t, Ar*C*), 129.8 (t, Ar*C*), 128.5 (t, Ar*C*), 127.1 (t, Ar*C*), 126.8 (t, Ar*C*), 123.8 (t, Ar*C*), 46.6 (s, *C*H_2), 43.7 (t, *C*H($C_6H_3Cl_2$)).

The analytical data are consistent with those reported in the literature.[S17]

3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (24)



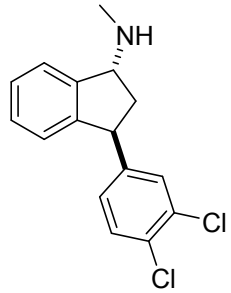
24

Based on a procedure by DAVIES[S18], Indenone **23** (21 mg, 76 *µ*mol, 1.00 equiv.) was dissolved in anhydrous THF (230 *µ*L) and cooled to –10 °C. K-Selectride® (1M in THF, 152 *µ*L, 152 *µ*mol, 2.00 equiv.) was added dropwise and the reaction mixture was stirred for 4 h at –10 °C. Then, water (500 *µ*L) was added slowly and the solution was stirred for 30 min at ambient temperature. THF was removed under reduced pressure and the mixture was portioned between water (5.0 mL) and EtOAc (5.0 mL). The phases were separated and the aqueous was re-extracted with EtOAc (2 × 5.0 mL). The combined organic layers were washed with water (10.0 mL) and with brine (10.0 mL), and the solvent was removed under reduced pressure. The residue was subjected to column chromatography (petroleum ether:EtOAc 10:1 -> 3:1) to give *syn*-alcohol **24** (*dr* > 20:1) as a colorless solid (15 mg, 54 *µ*mol, 71%).

R_f = 0.42 (EtOAc/petroleum ether = 4:1); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* [ppm] 7.48 (d, *J* = 7.4 Hz, 1H, Ar*H*), 7.39 – 7.23 (m, 4H, Ar*H*), 7.07 (dd, *J* = 8.3, 2.0 Hz, 1H, Ar*H*), 6.93 (d, *J* = 7.3 Hz, 1H, Ar*H*), 5.30 (t, *J* = 7.1 Hz, 1H, C*H*OH), 4.16 (t, *J* = 8.2 Hz, 1H, C*H*($C_6H_3Cl_2$)), 3.02 (dt, *J* = 14.5, 6.6 Hz, 1H, C*H*H), 2.07 (bs, 1H, O*H*), 1.90 (ddd, *J* = 12.9, 8.8, 7.4 Hz, 1H, CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* [ppm] 145.3 (q, Ar*C*), 144.8 (q, Ar*C*), 144.6 (q, Ar*C*),132.7 (q, Ar*C*), 130.7 (t, Ar*C*), 130.4 (t, Ar*C*), 129.8 (q, Ar*C*), 128.8 (t, Ar*C*), 127.83 (t, Ar*C*), 127.80 (t, Ar*C*), 125.1 (t, Ar*C*), 124.1 (t, Ar*C*), 75.0 (t, *C*HOH), 47.7 (t, *C*H($C_6H_3Cl_2$)), 46.9 (s, *C*H_2).

The analytical data are consistent with those reported in the literature.[S18]

(±)-Indatraline (16)



16

Following a protocol of FROIMOWITZ[S19], Et_3N (56 *µ*L, 400 *µ*mol, 4.00 equiv.) was added to a solution of *syn*-alcohol **24** (28 mg, 100 *µ*mol, 1.00 equiv.) in anhydrous THF (850 *µ*L). The mixture was cooled to –20 °C, methananesulfonyl chloride (16 *µ*L, 200 *µ*mol, 2.00 equiv.) was added dropwise, and the reaction mixture was stirred for 1 h at –20°C. Then, a solution of methylamine (1.00 mL, 2.0M in THF, 2.00 mmol, 20.0 equiv.) was added slowly. Over 90 min, the mixture

was allowed to warm to ambient temperature and then stirred for 20 h. The solvent was removed in vacuo. Subsequently, water (10.0 mL) and EtOAc (10.0 mL) were added. The phases were separated and the aqueous layer was re-extracted with EtOAc (3 × 10.0 mL). The combined organic layers were washed with brine (2 × 20.0 mL), dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and the residue was subjected to column chromatography (SiO2 treated with Et_3N, petroleum ether/EtOAc 2:3, then EtOAc) to give (±)-indatraline (**16**) as a yellow oil (23 mg, 82 *µ*mol, 82%).

R_f = 0.24 (CH_2Cl_2/MeOH = 15:1); **^{1}H NMR** (400 MHz, $CDCl_3$): *δ* [ppm] 7.40 (d, *J* = 6.8 Hz, 1H, Ar*H*), 7.35 (d, *J* = 8.2 Hz, 1H, Ar*H*), 7.29 – 7.22 (m, 3H, Ar*H*), 6.97 (d, *J* = 8.0 Hz, 2H, Ar*H*), 4.51 (t, *J* = 7.6 Hz, 1H, C*H*($C_6H_3Cl_2$)), 4.27 (dd, *J* = 6.6, 3.1 Hz, 1H, C*H*NHMe), 2.51 (s, 3H, C*H*$_3$N), 2.45 (ddd, *J* = 13.1, 7.9, 3.2 Hz, 1H, C*H*H), 2.24 (qi, *J* = 6.9 Hz, 1H, CH*H*); **^{13}C NMR** (100 MHz, $CDCl_3$): *δ* [ppm] 145.7 (q, Ar*C*), 145.6 (q, Ar*C*), 145.0 (q, Ar*C*), 132.6 (q, Ar*C*), 130.6 (t, Ar*C*), 130.4 (q, Ar*C*), 130.0 (t, Ar*C*), 128.5 (t, Ar*C*), 127.6 (t, Ar*C*), 127.4 (t, Ar*C*), 125.4 (t, Ar*C*), 124.8 (t, Ar*C*), 63.8 (t, *C*HNHMe), 48.7 (t, *C*H($C_6H_3Cl_2$)), 43.4 (s, CH_2), 34.3 (p, *C*H_3NH); **HRMS (ESI)** (*m/z*): calcd. for $C_{16}H_{16}NCl_2$ $[M + H^+]^+$ 292.0660, found 292.0669.

The analytical data are consistent with those reported in the literature.[S19]

3 References

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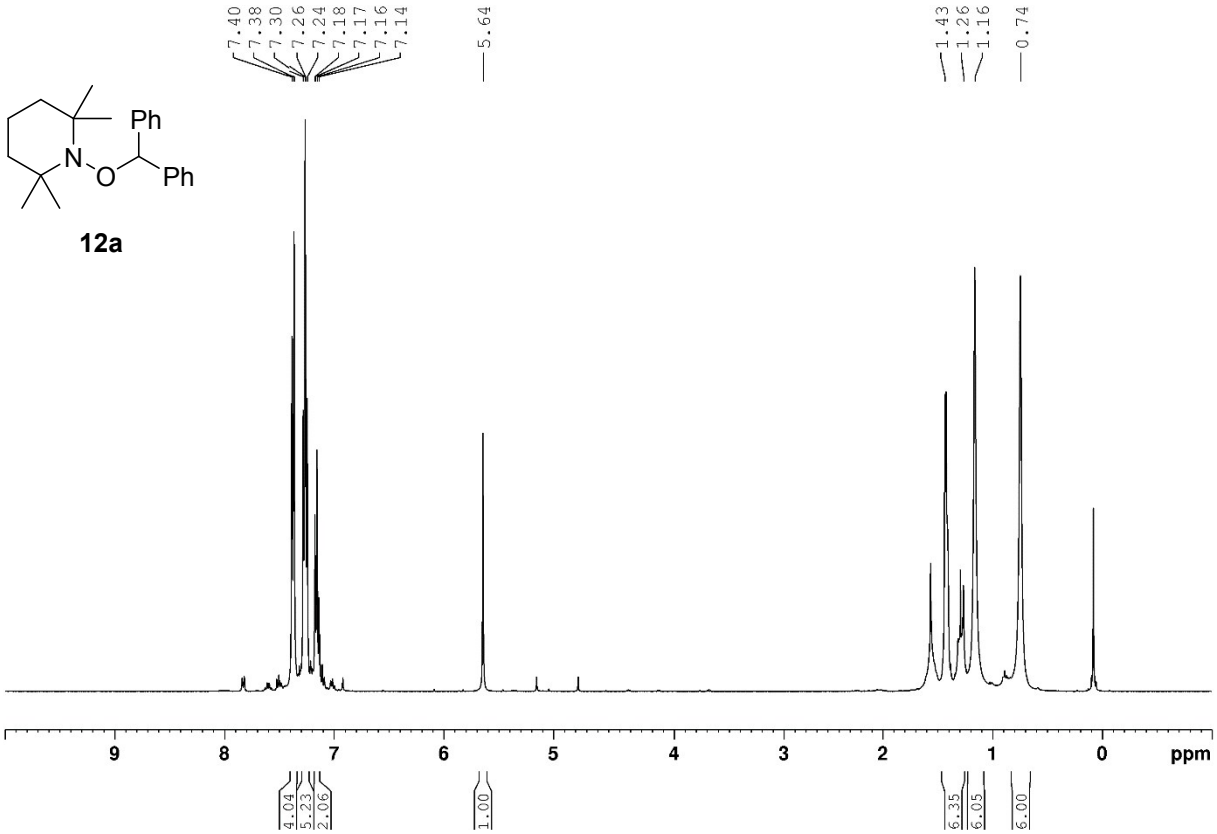
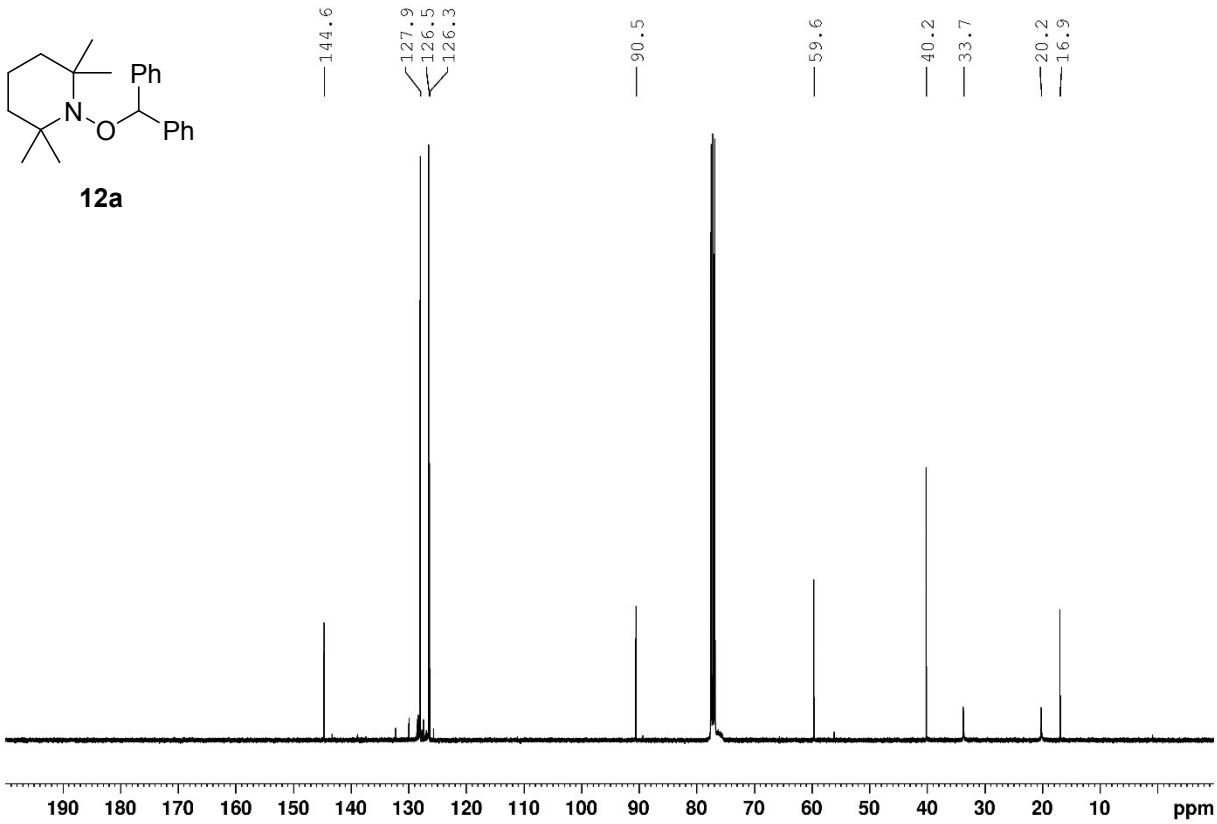
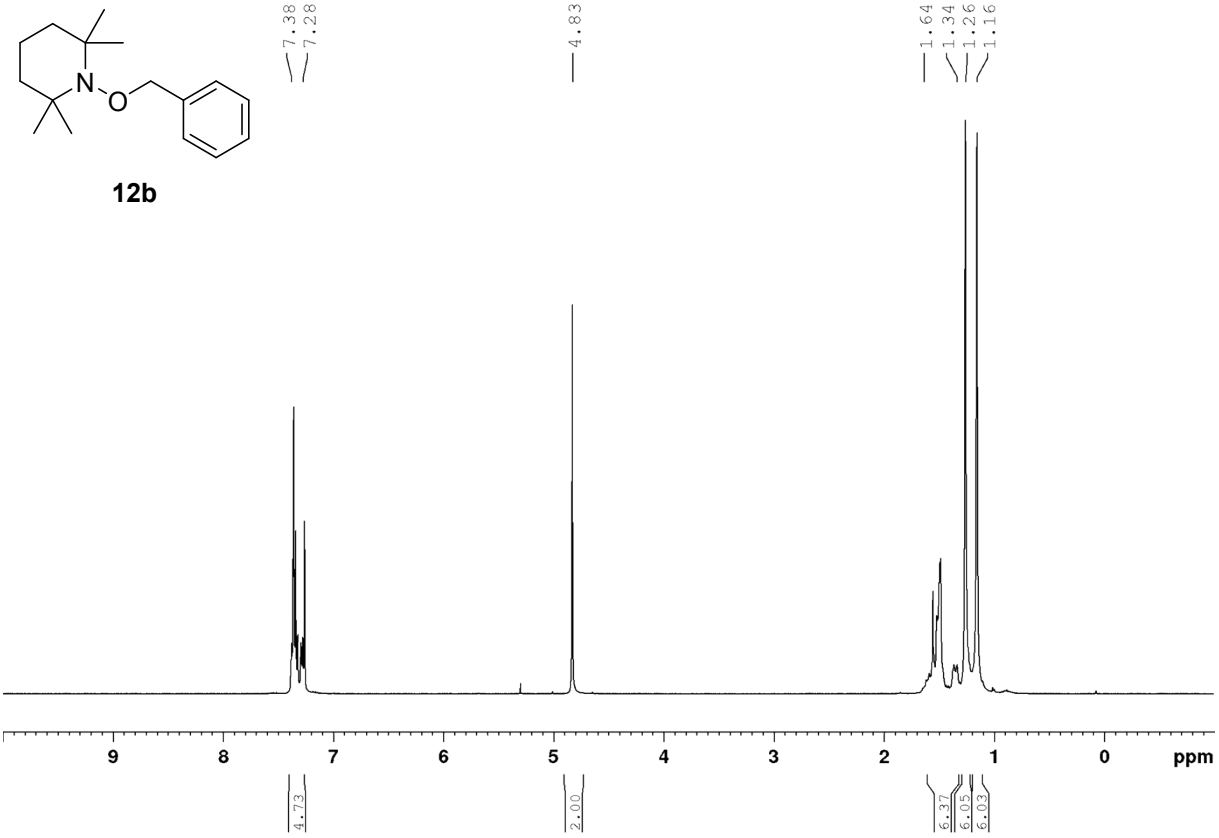
4 Attachments: NMR spectra

1-(Benzhydryloxy)-2,2,6,6-tetramethylpiperidine (12a)

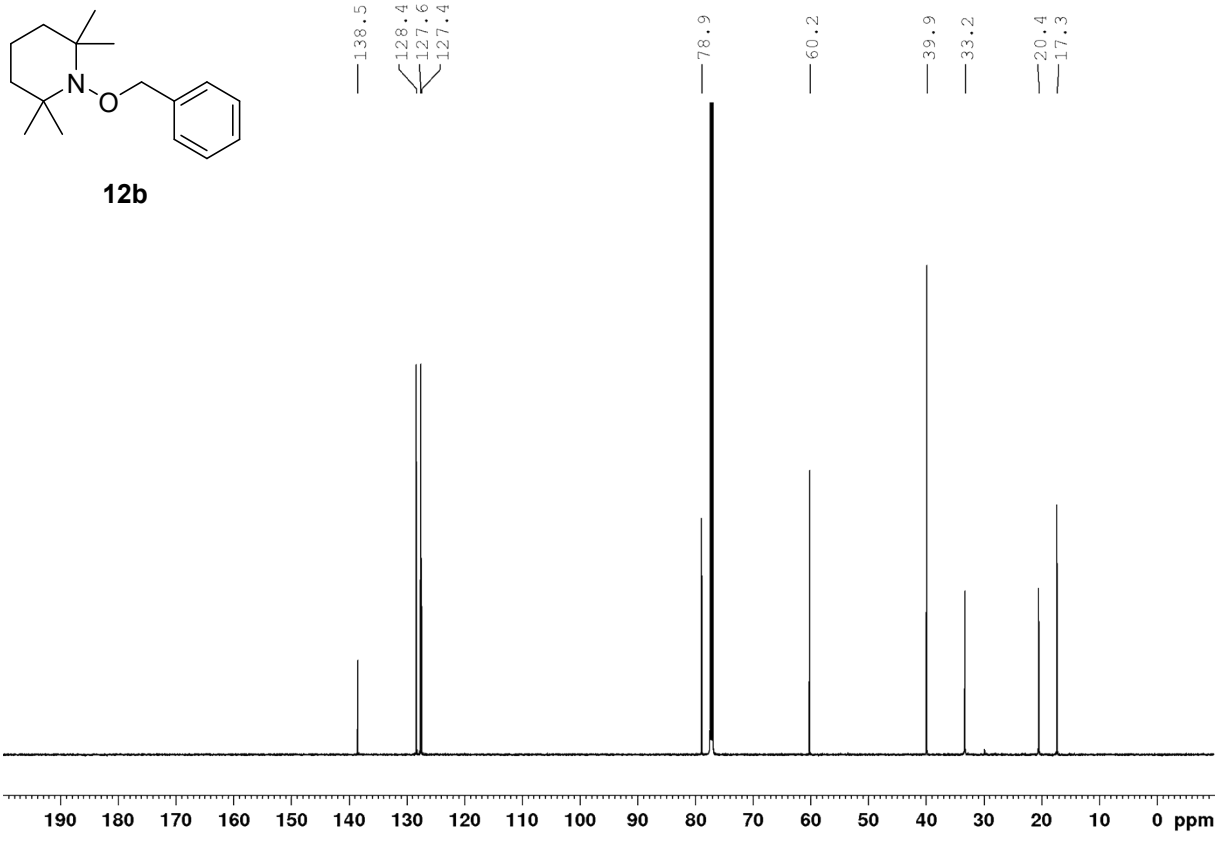




1-(Benzyloxy)-2,2,6,6-tetramethylpiperidine (12b)

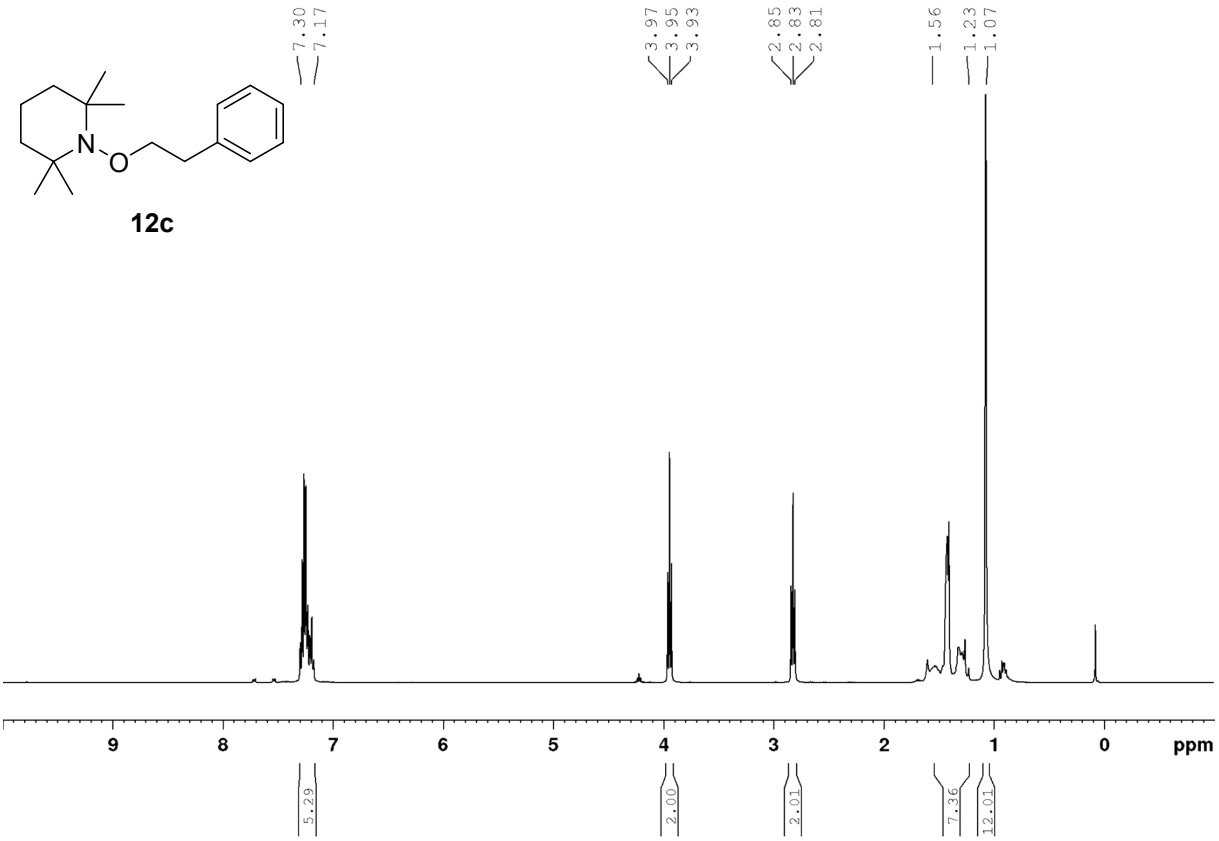


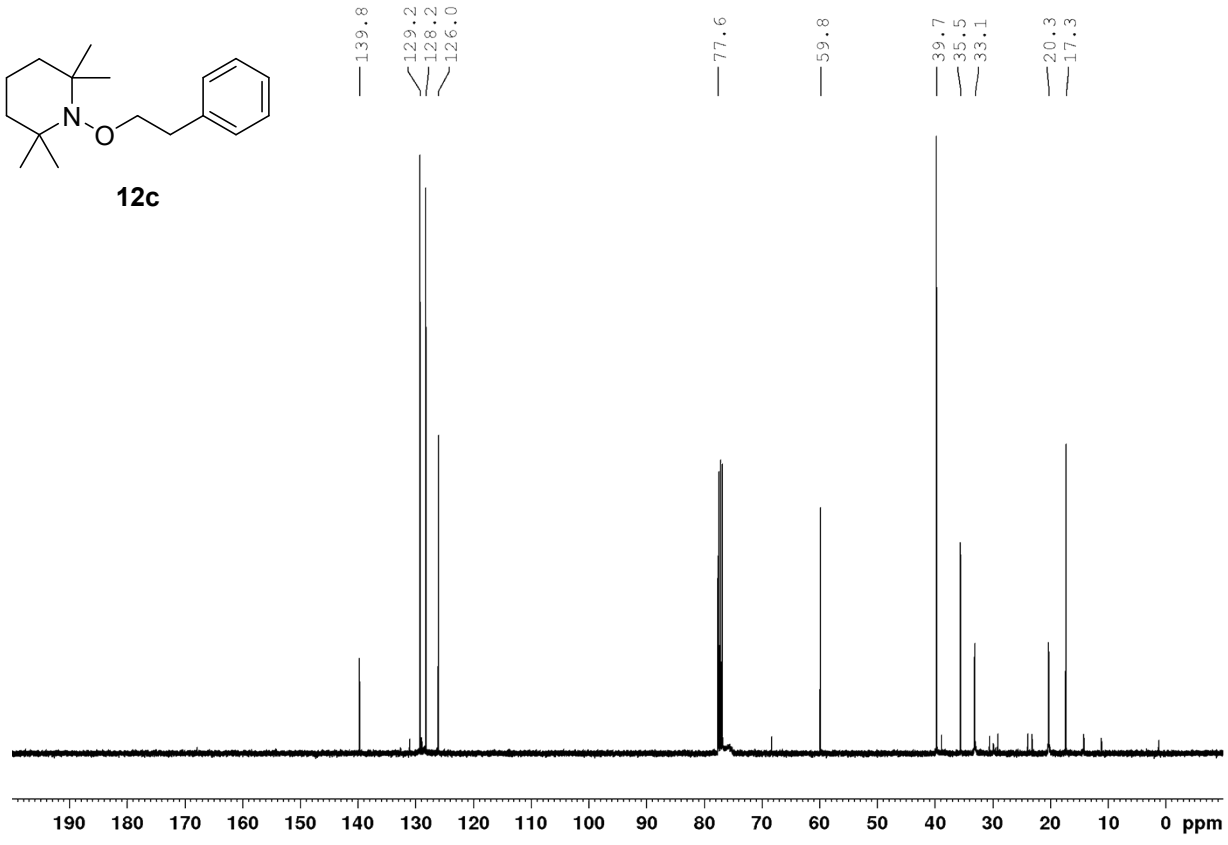
12b



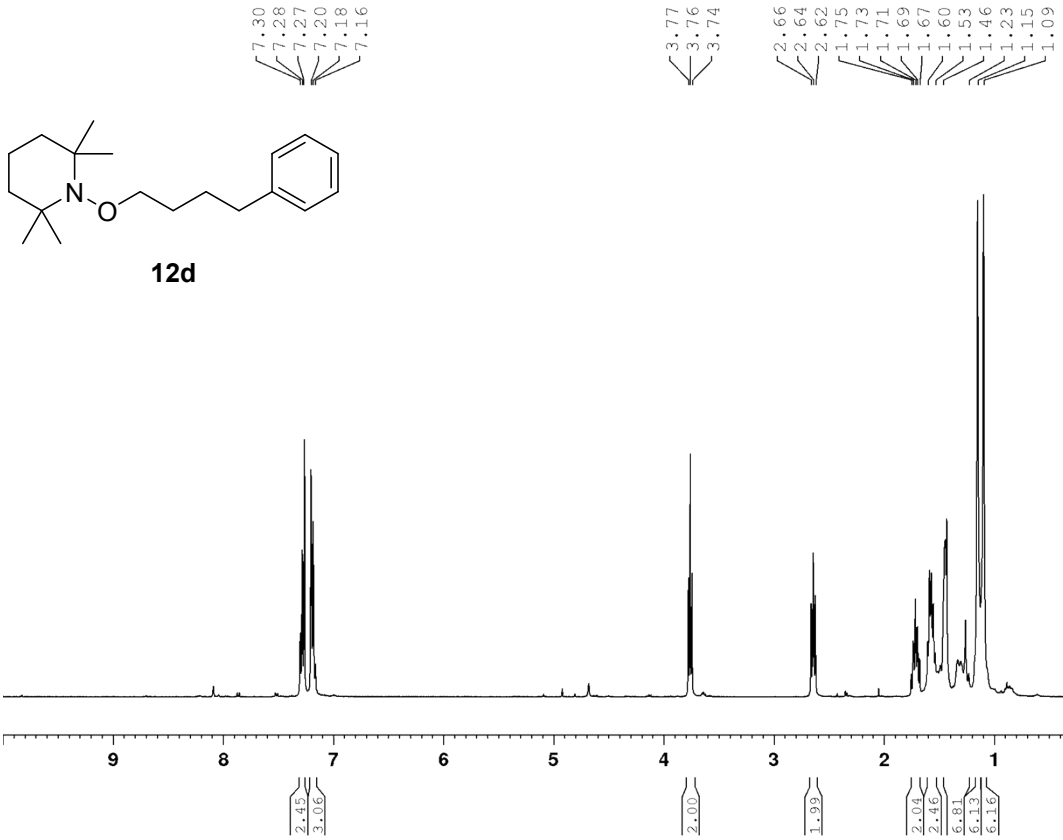
12b

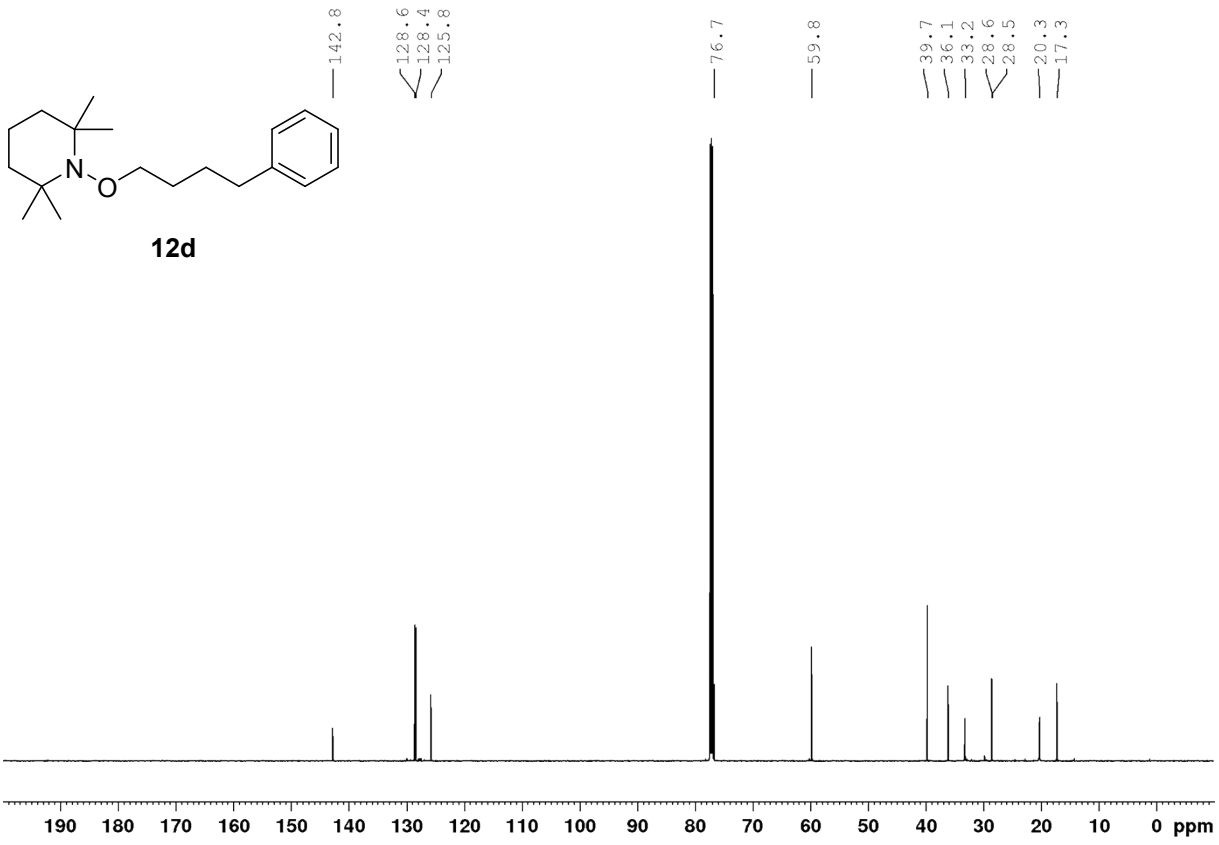
2,2,6,6-Tetramethyl-1-phenethoxypiperidine (12c)



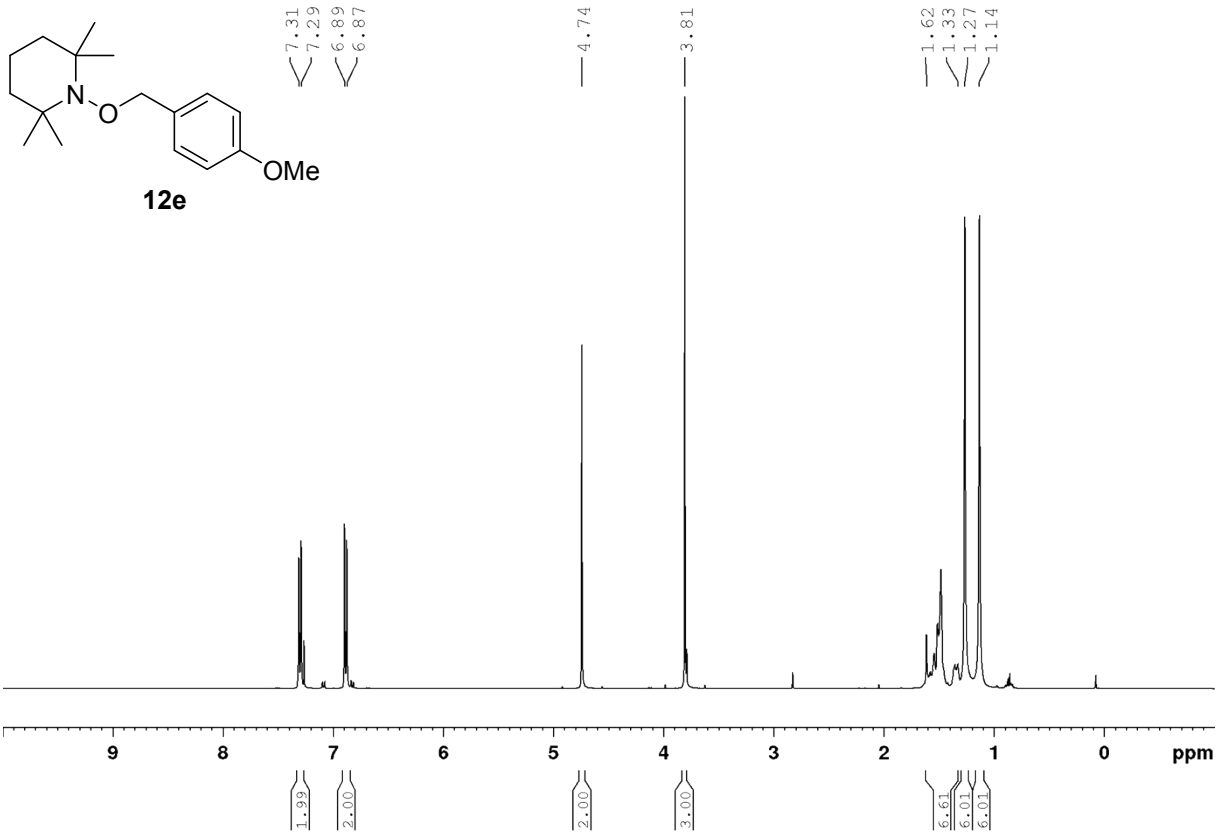


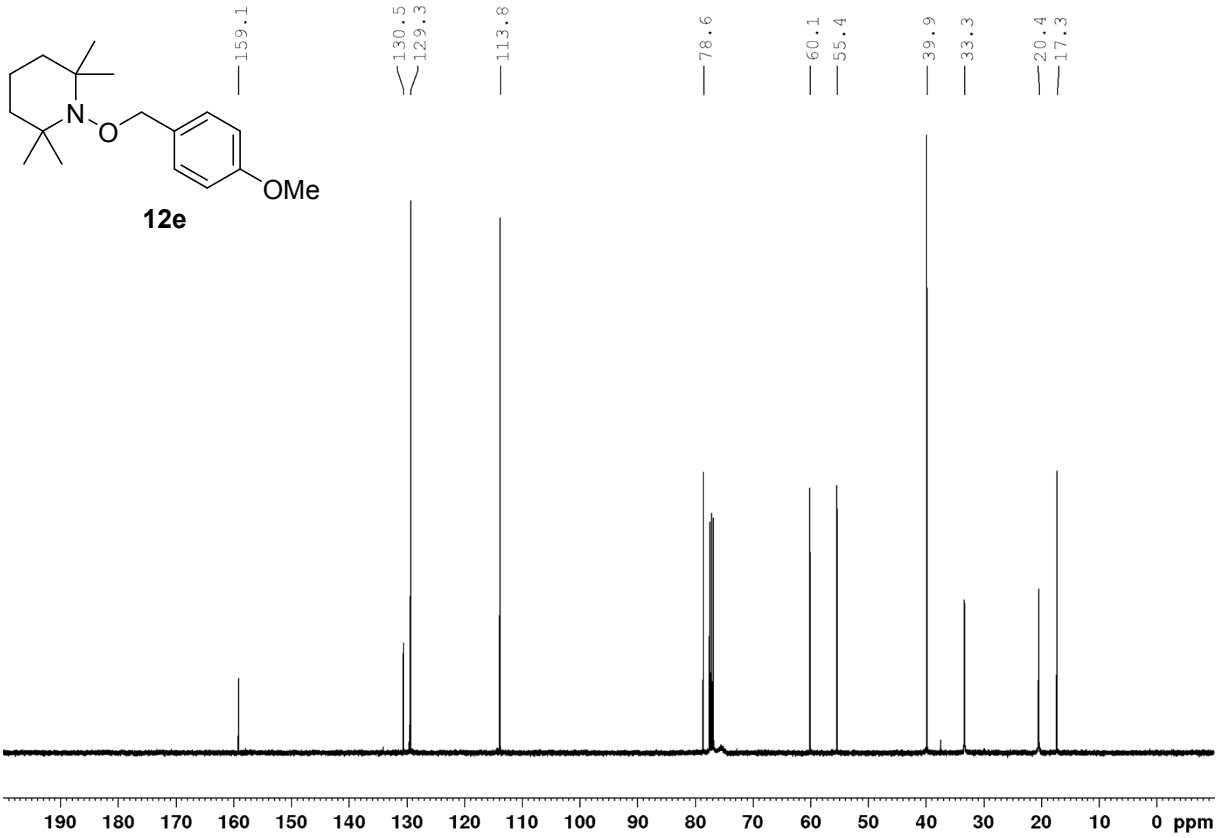
2,2,6,6-Tetramethyl-1-(4-phenylbutoxy)piperidine (12d)



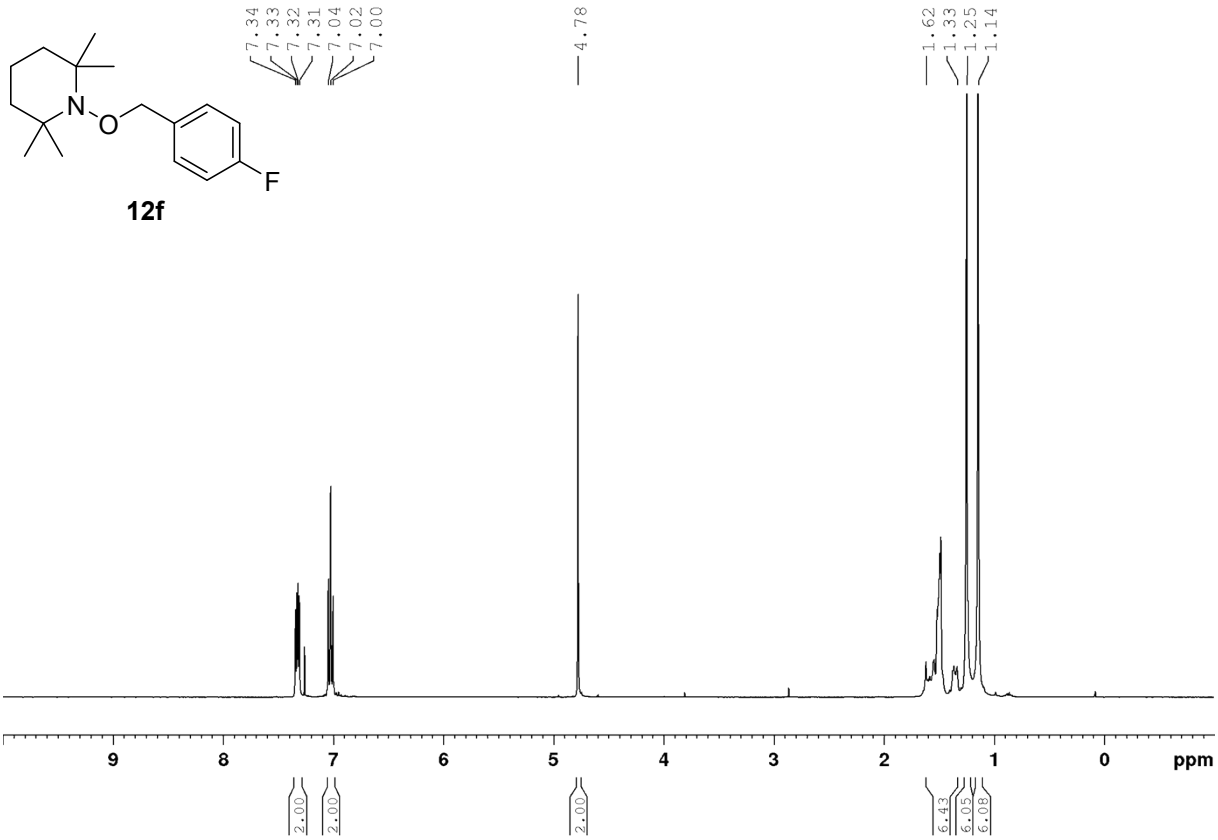


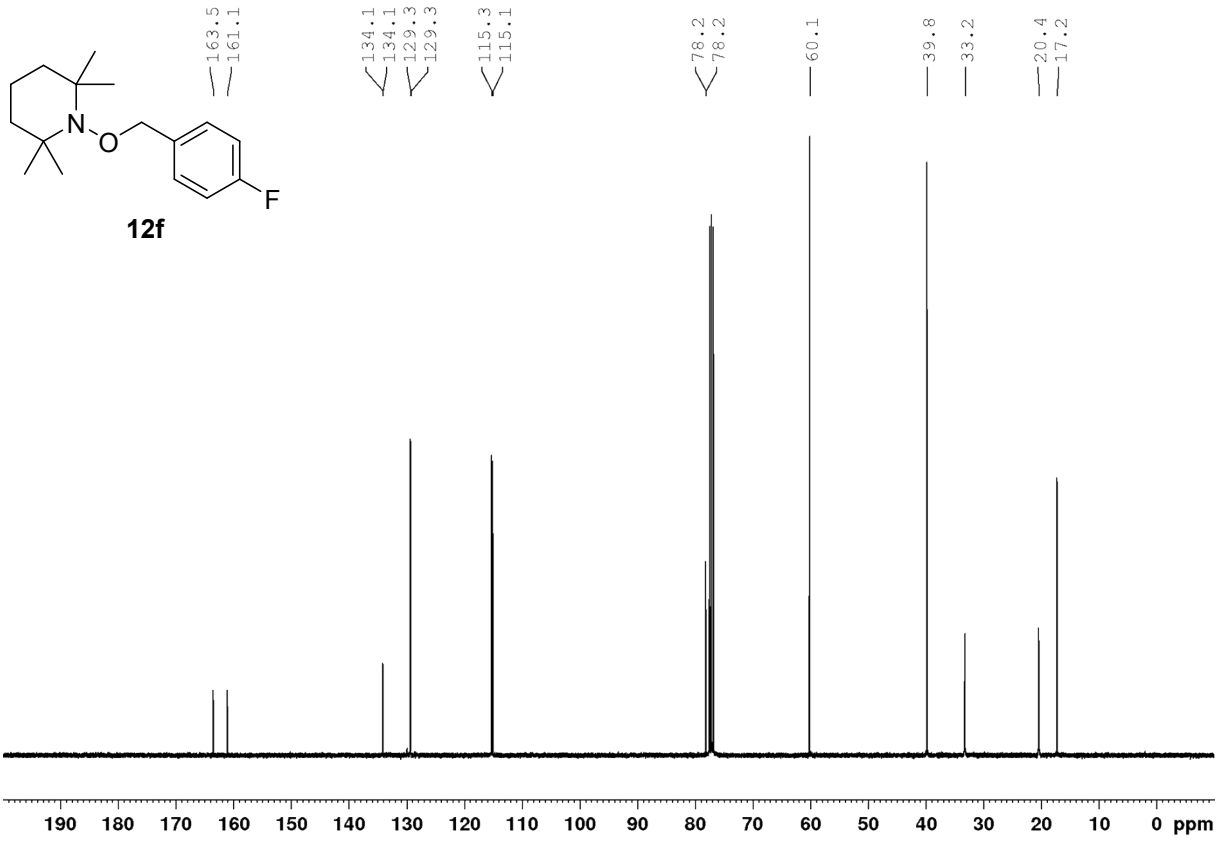
1-((4-Methoxybenzyl)oxy)-2,2,6,6-tetramethylpiperidine (12e)



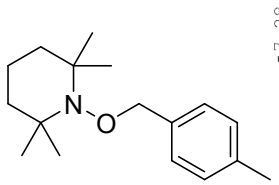


1-((4-Fluorobenzyl)oxy)-2,2,6,6-tetramethylpiperidine (12f)

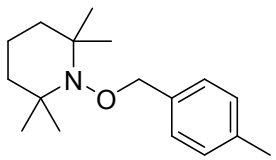




2,2,6,6-Tetramethyl-1-((4-methylbenzyl)oxy)piperidine (12g)

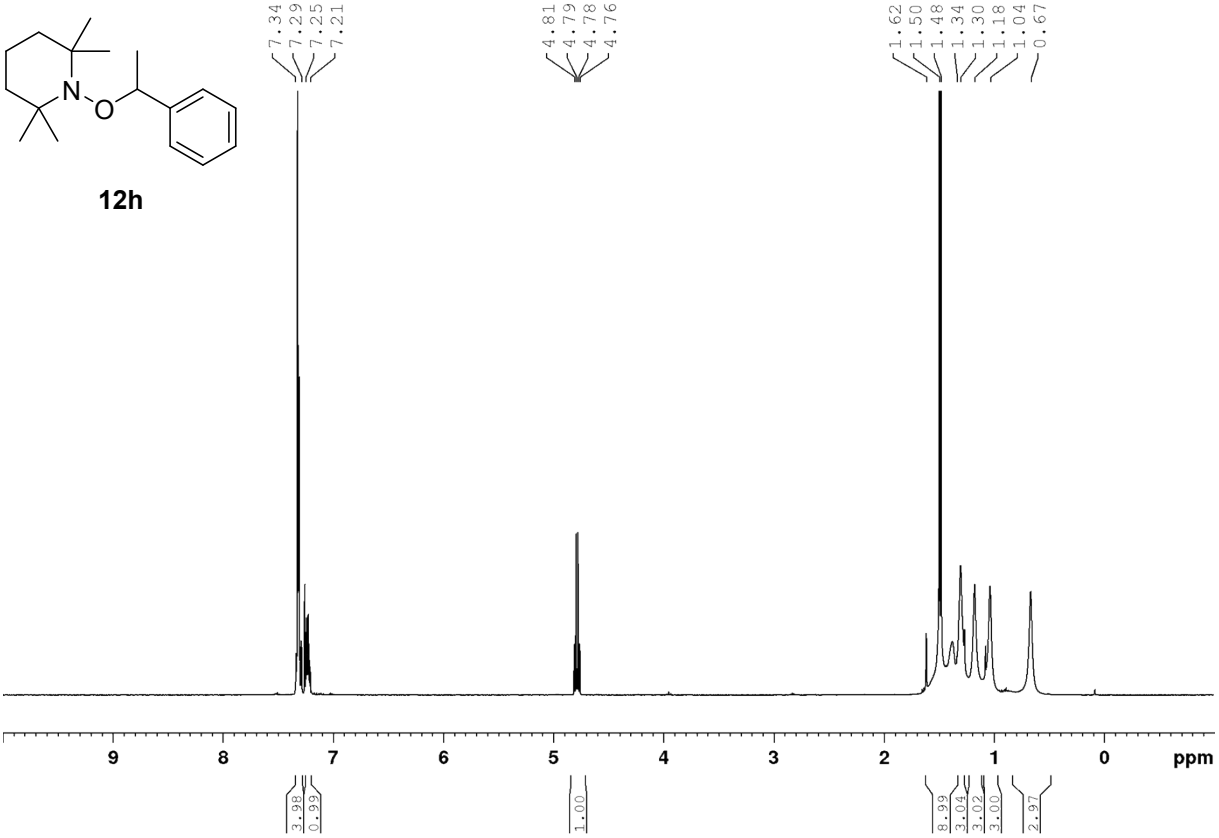


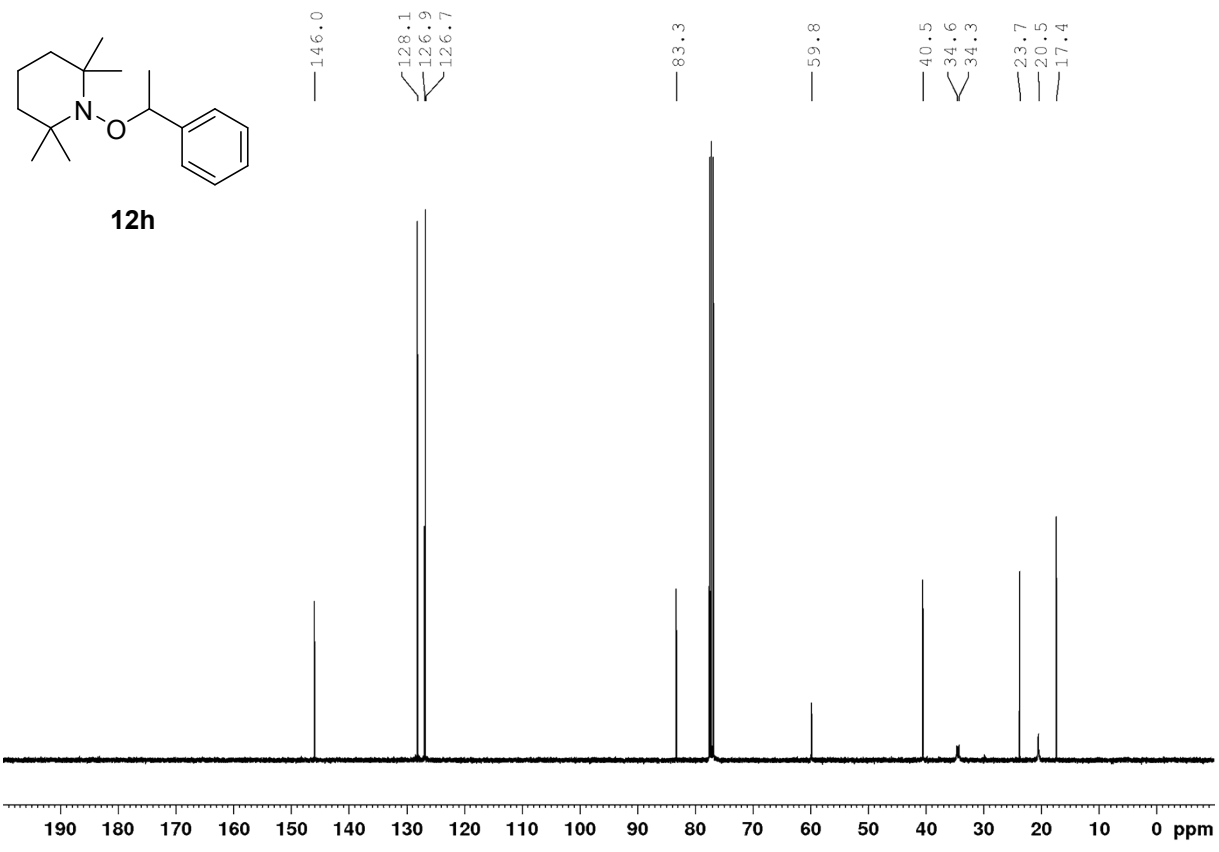
12g



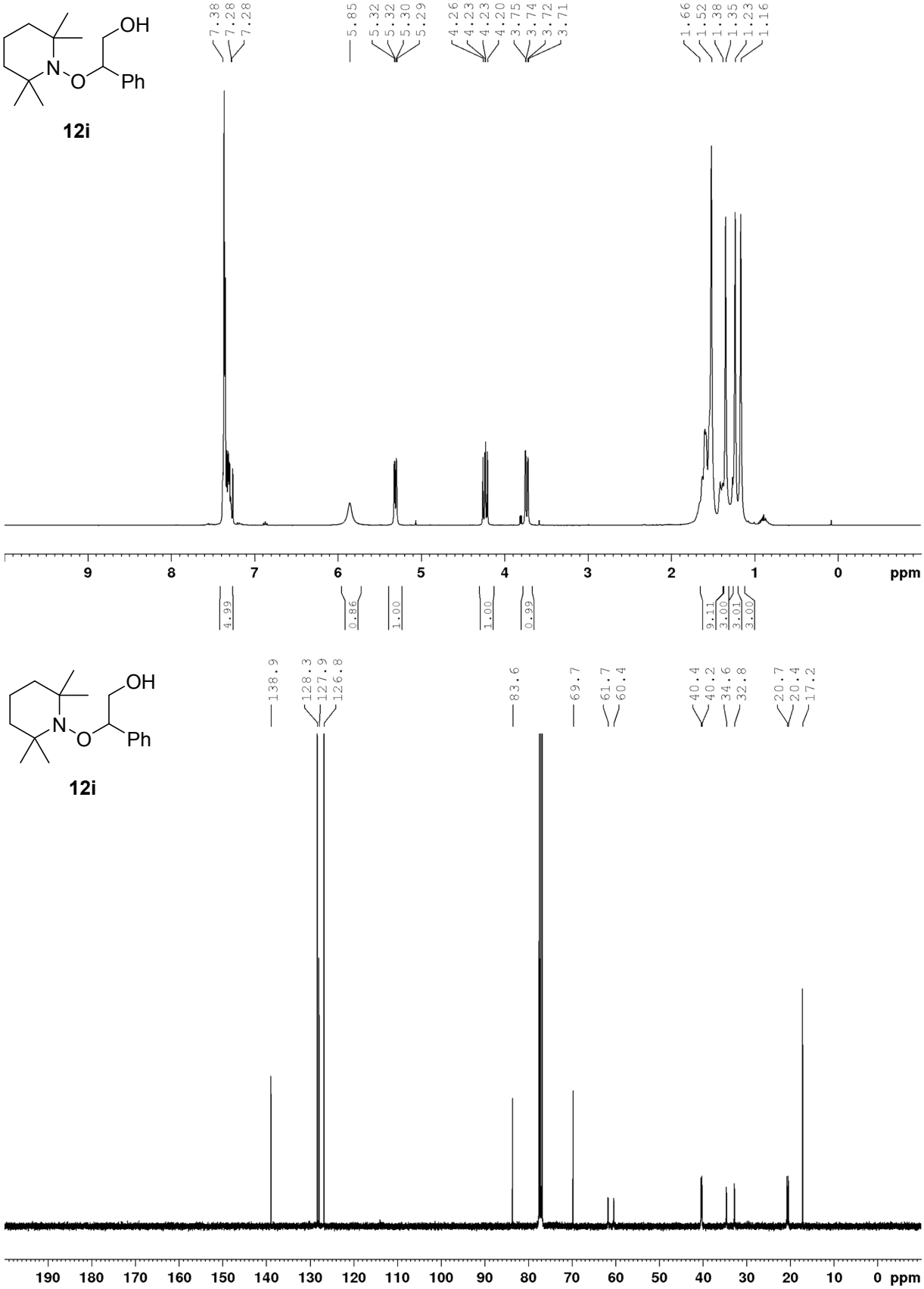
12g

2,2,6,6-Tetramethyl-1-(1-phenylethoxy)piperidine (12h)

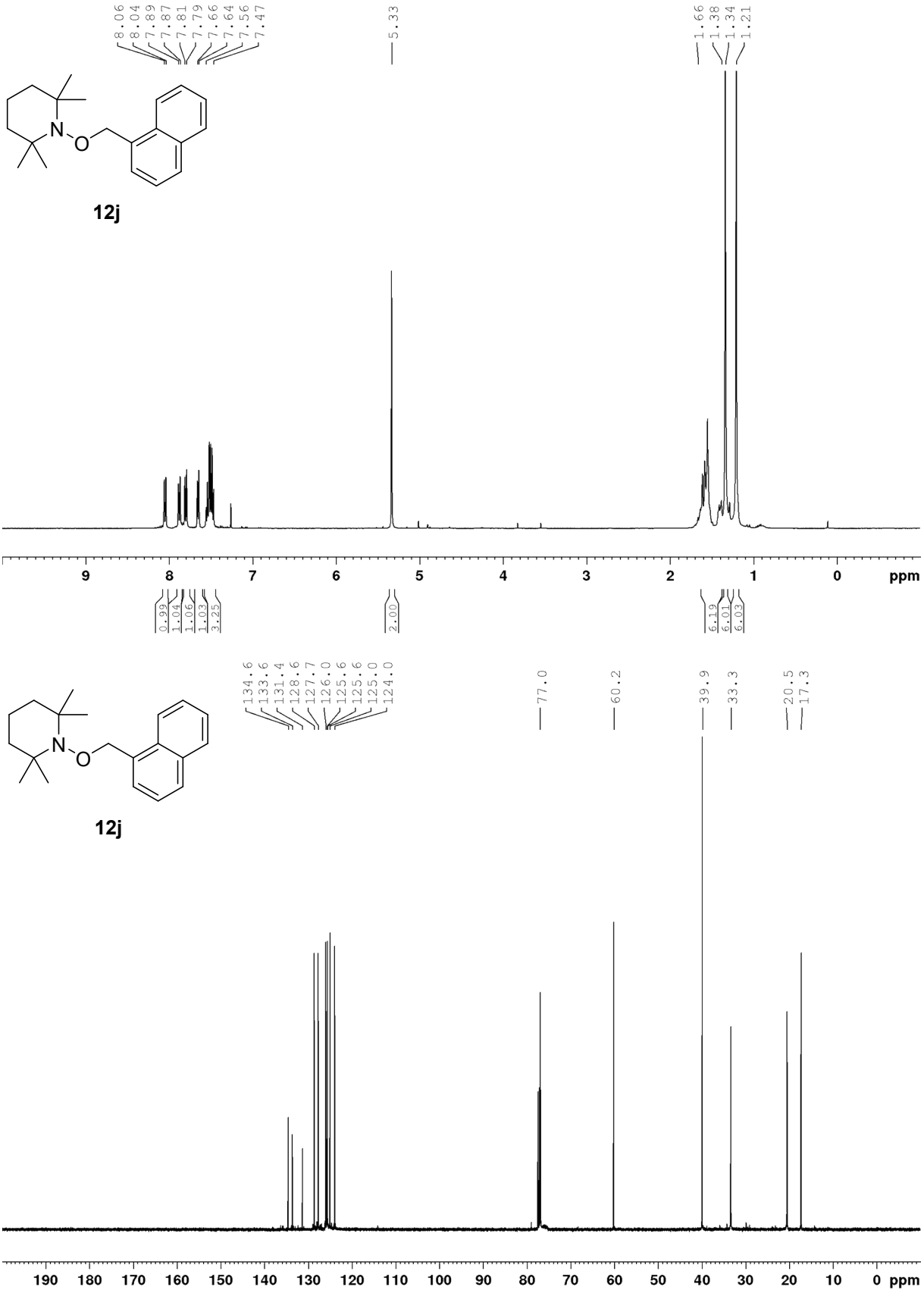




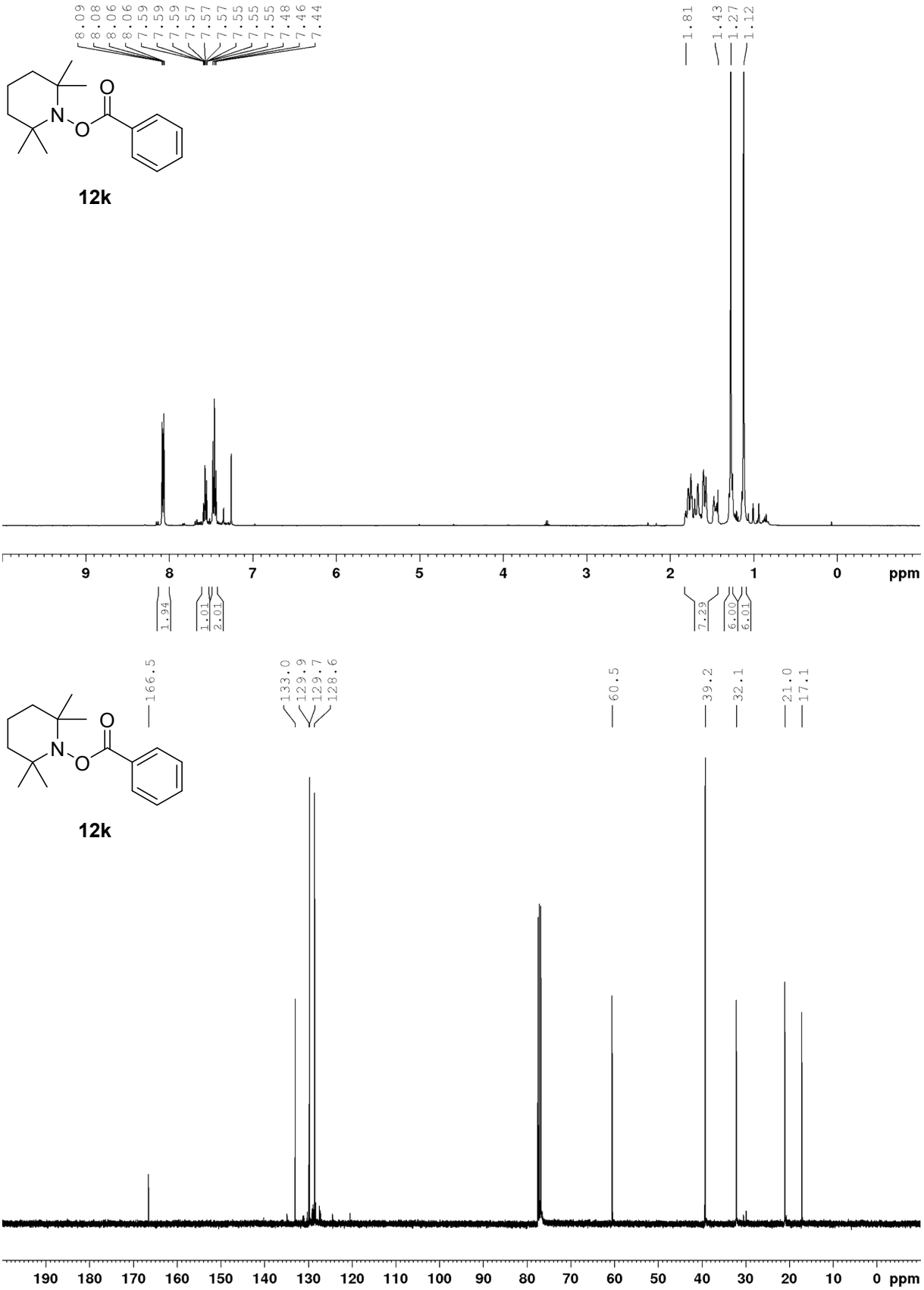
2-Phenyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)ethan-1-ol (12i)



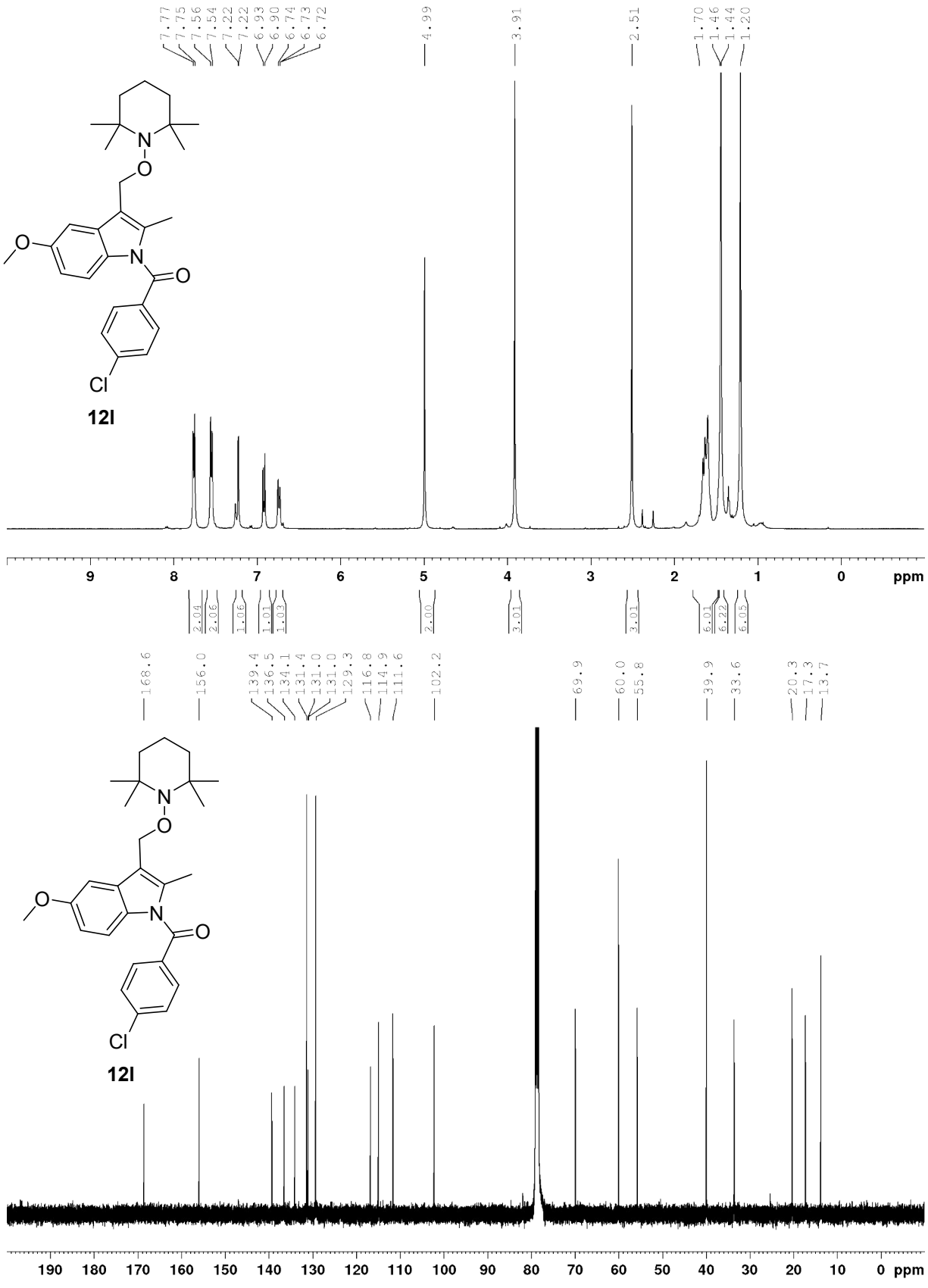
2,2,6,6-Tetramethyl-1-(naphthalen-1-ylmethoxy)piperidine (12j)



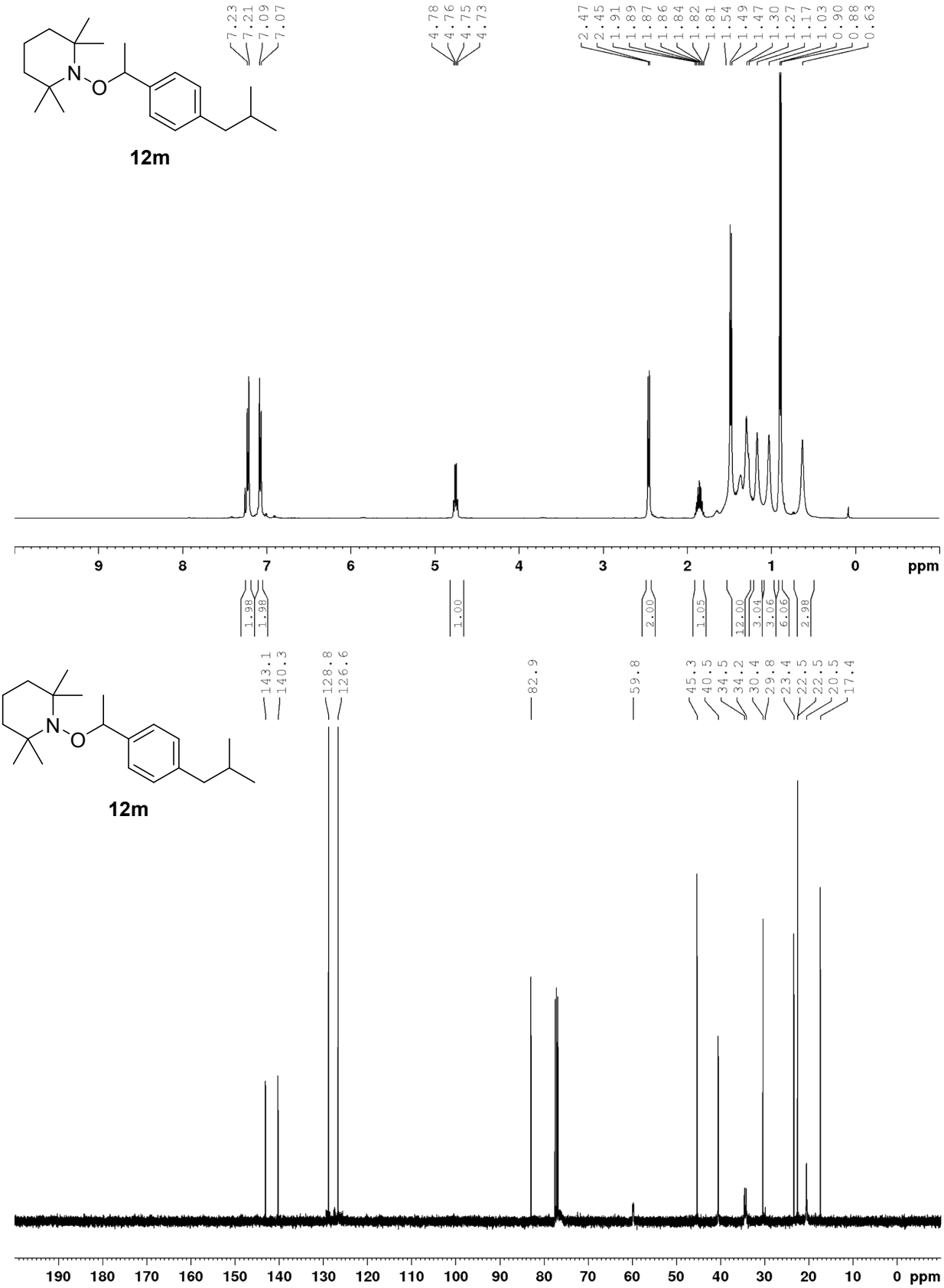
2,2,6,6-Tetramethylpiperidin-1-yl benzoate (12k)



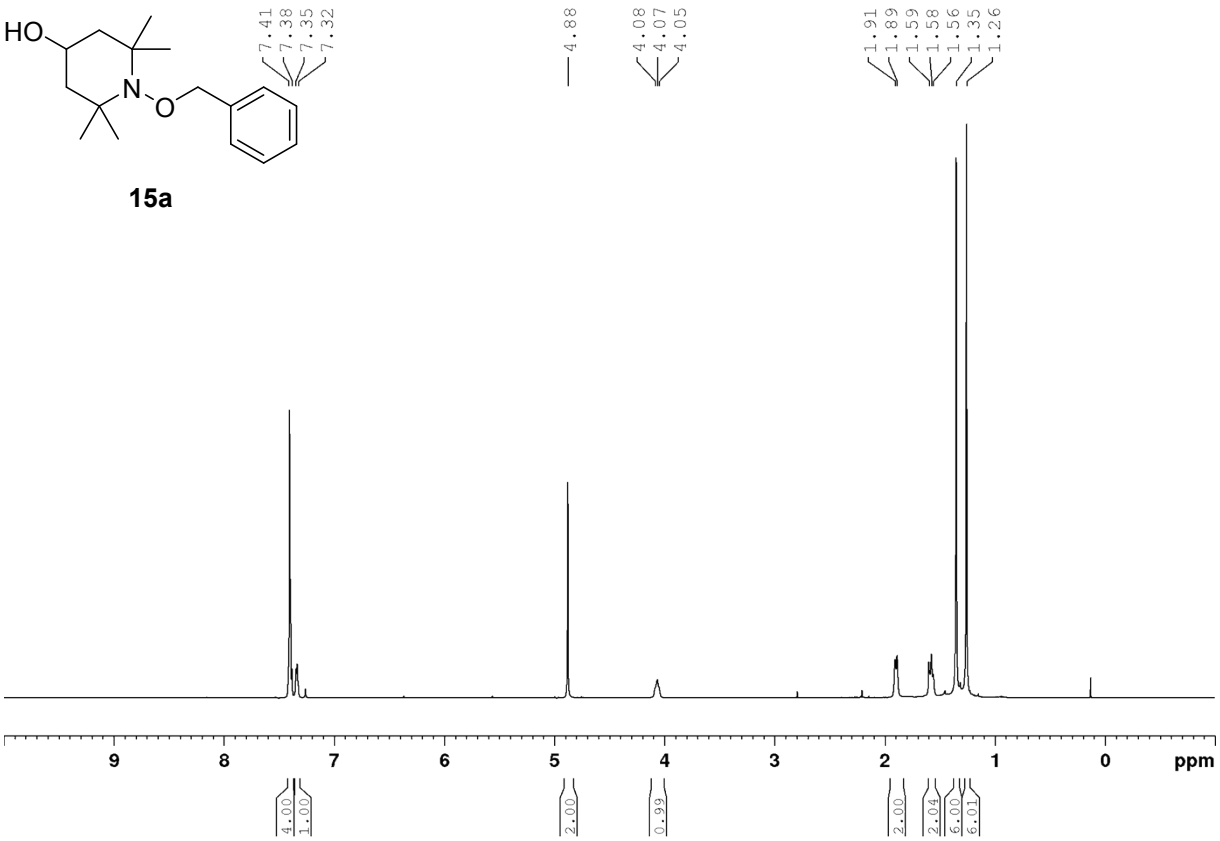
(4-Chlorophenyl)(5-methoxy-2-methyl-3-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-1*H*-indol-1-yl)methanone (12l)

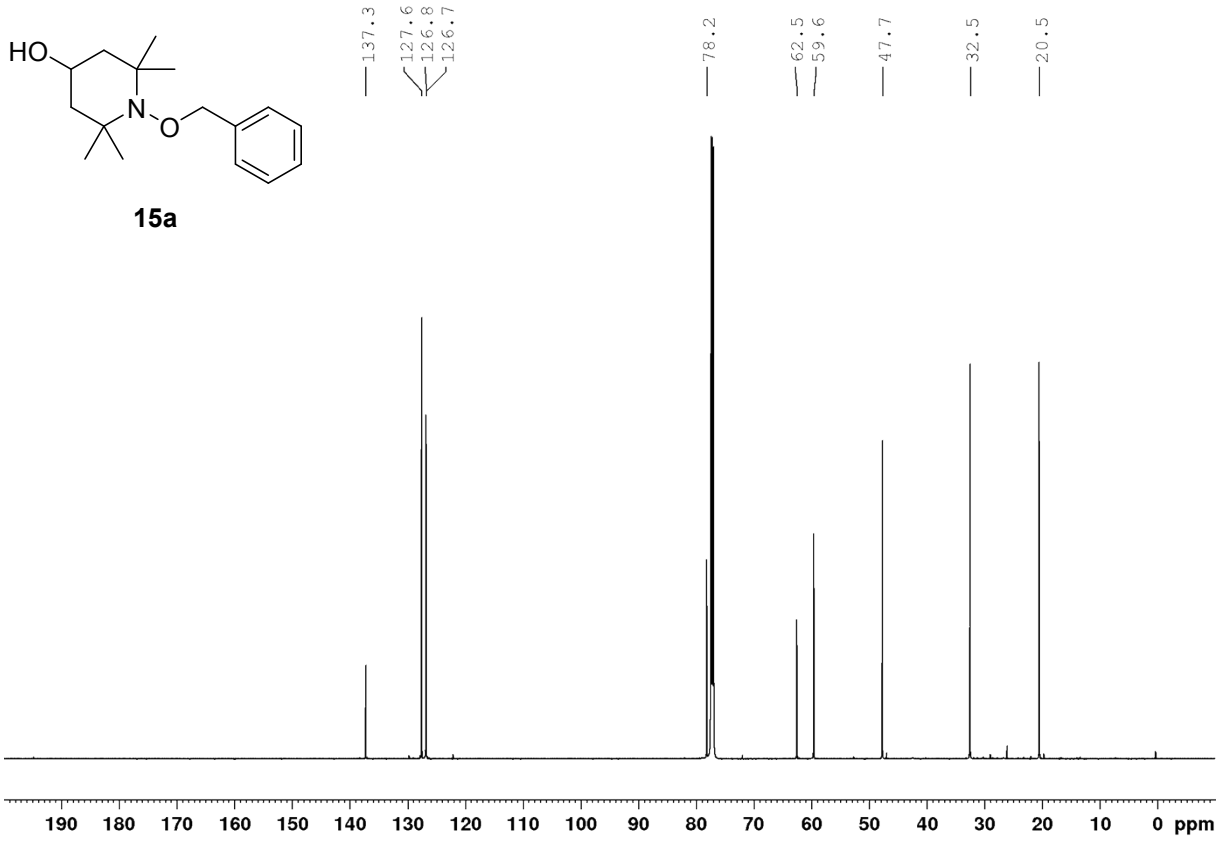


1-(1-(4-Isobutylphenyl)ethoxy)-2,2,6,6-tetramethylpiperidine (12m)

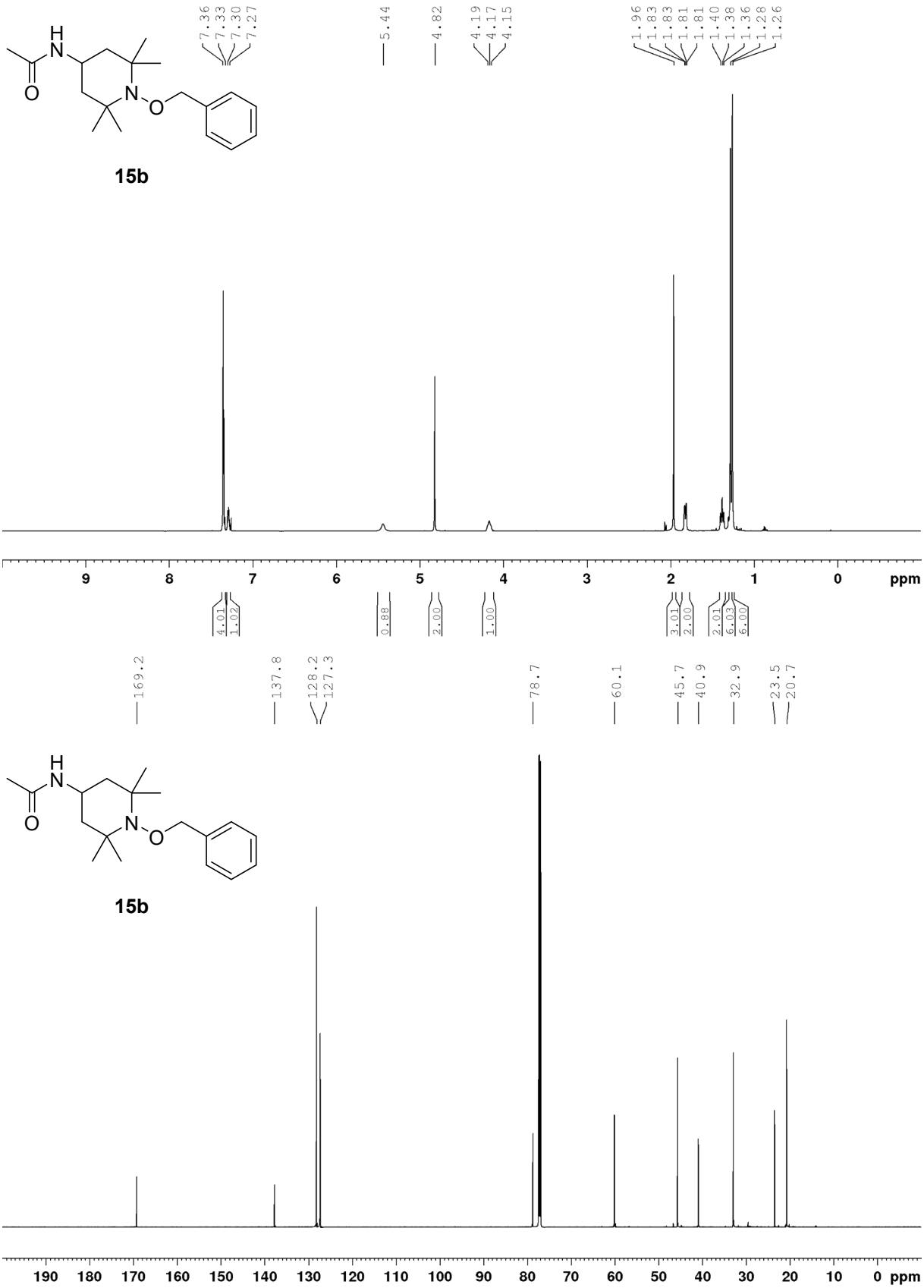


1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-ol (15a)

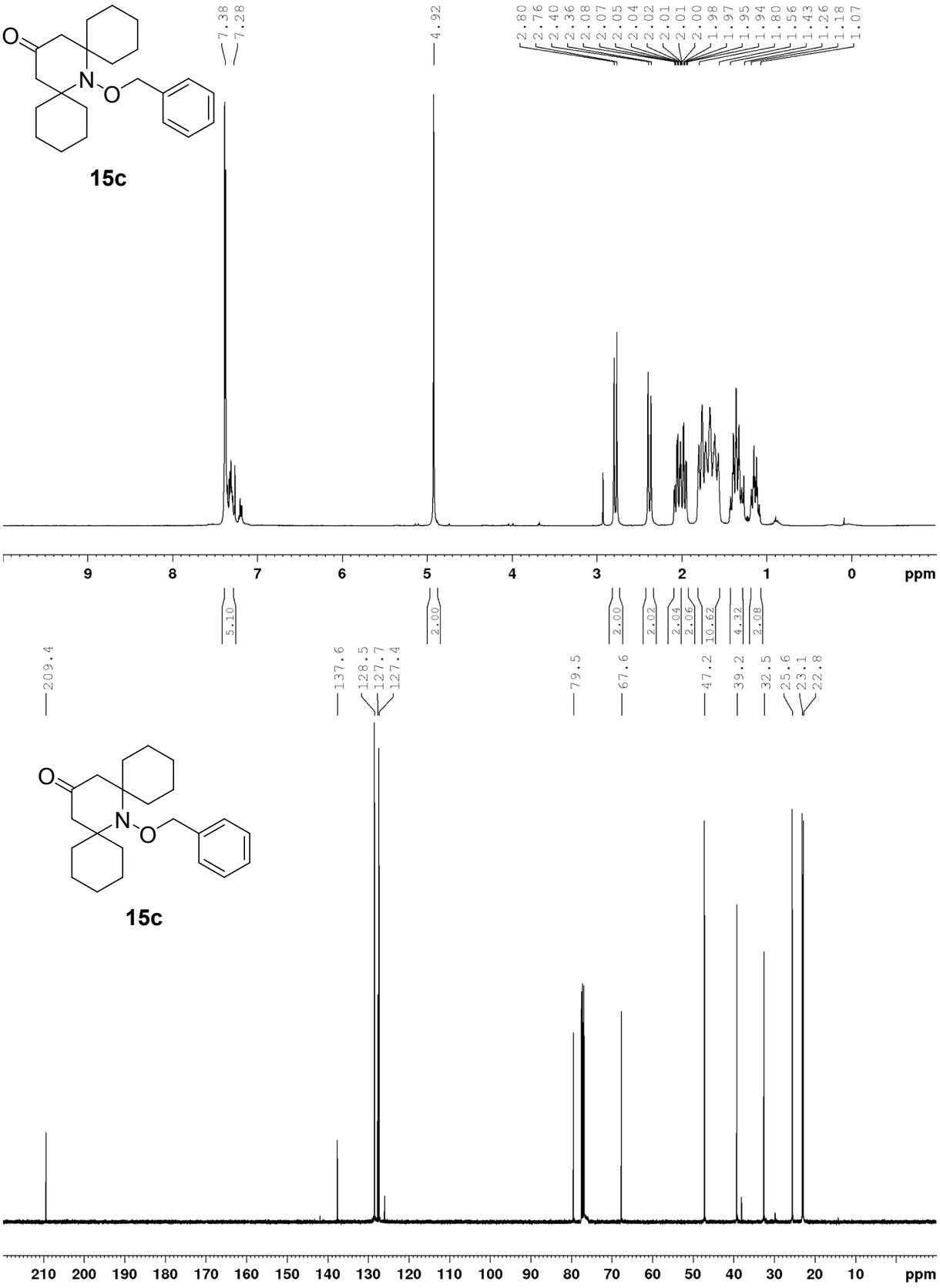




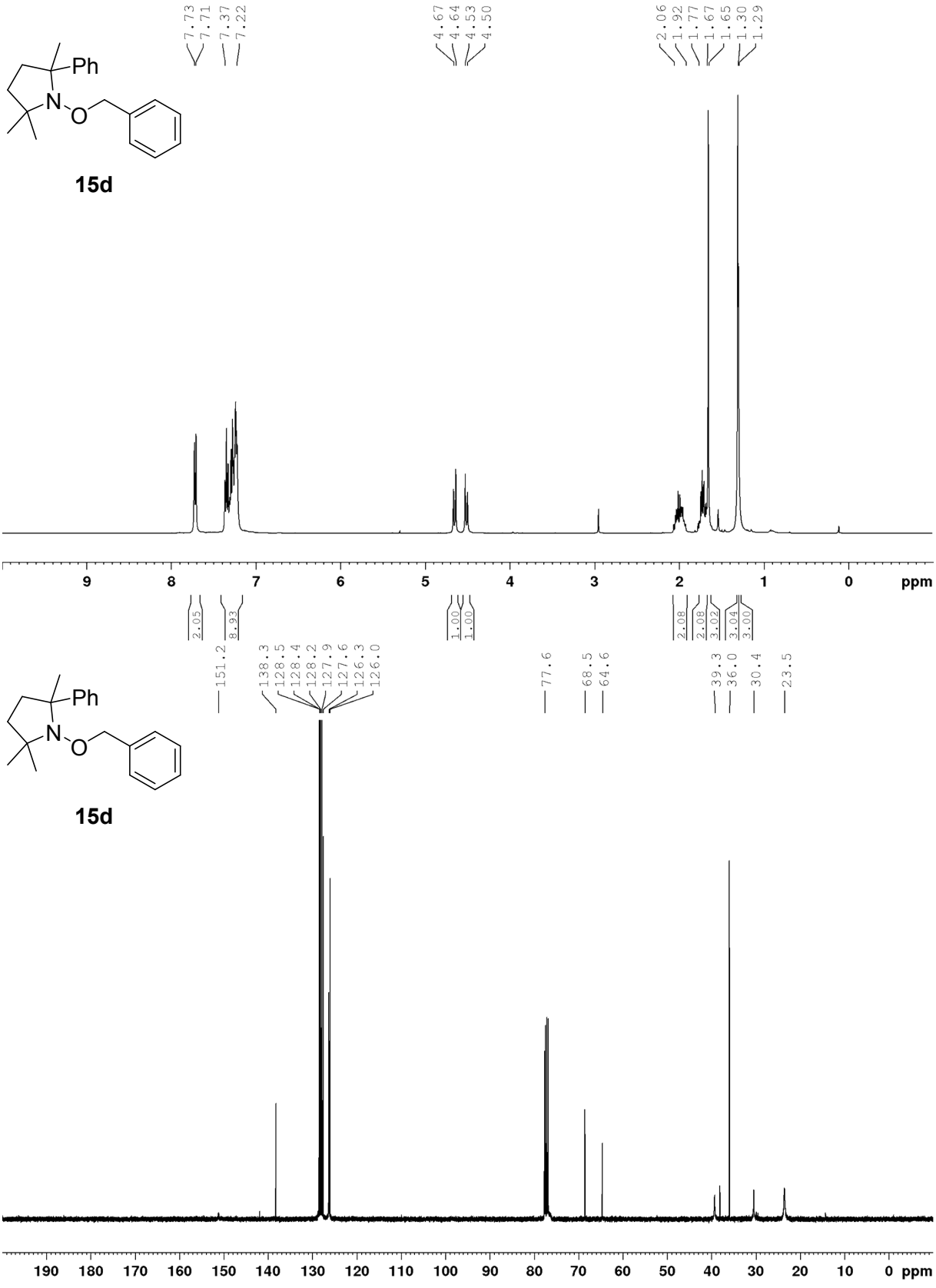
***N*-(1-(Benzyloxy)-2,2,6,6-tetramethylpiperidin-4-yl)acetamide (15b)**



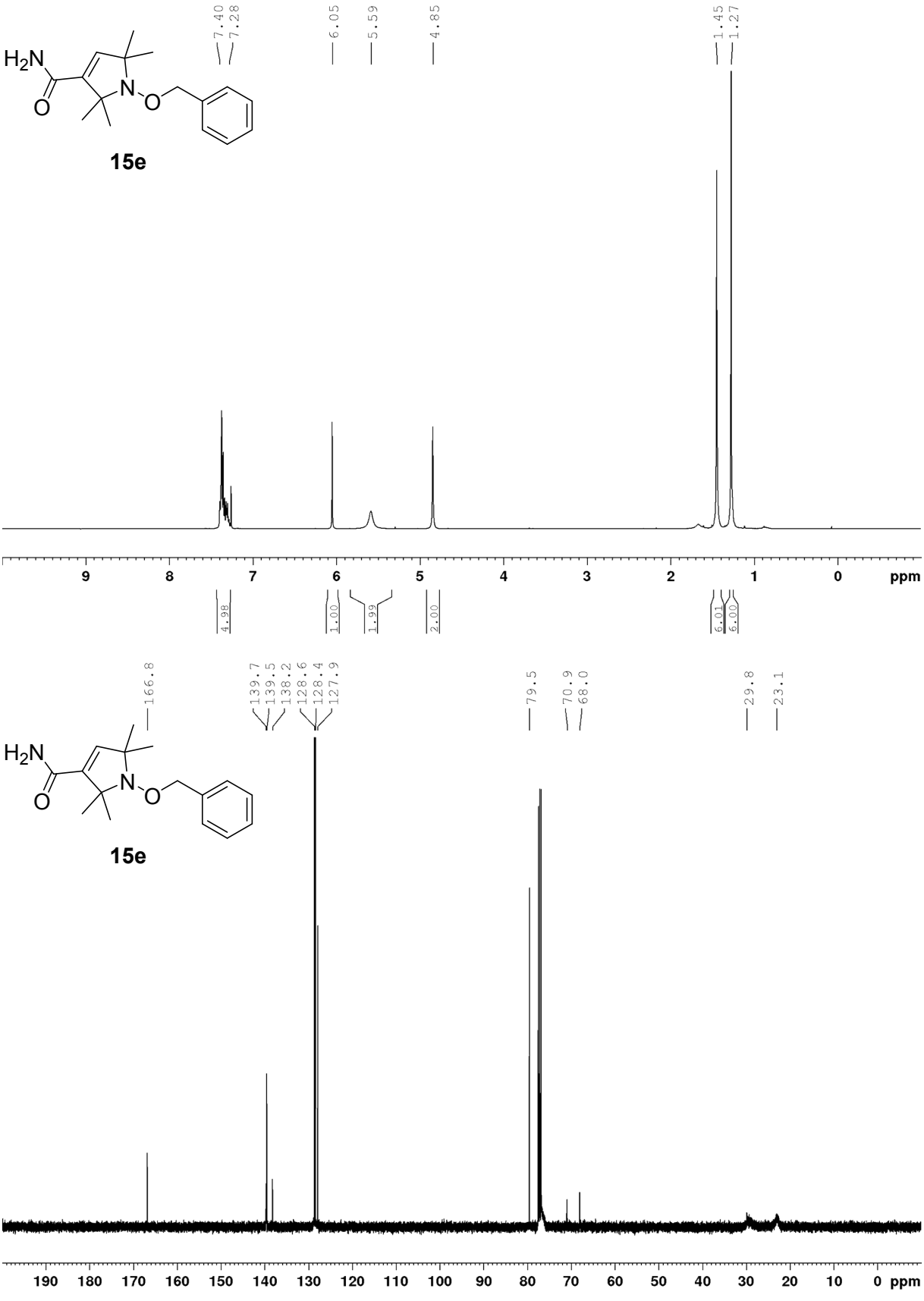
7-(Benzyloxy)-7-azadispiro[5.1.5^{8}.3^{6}]hexadecan-15-one (15c)



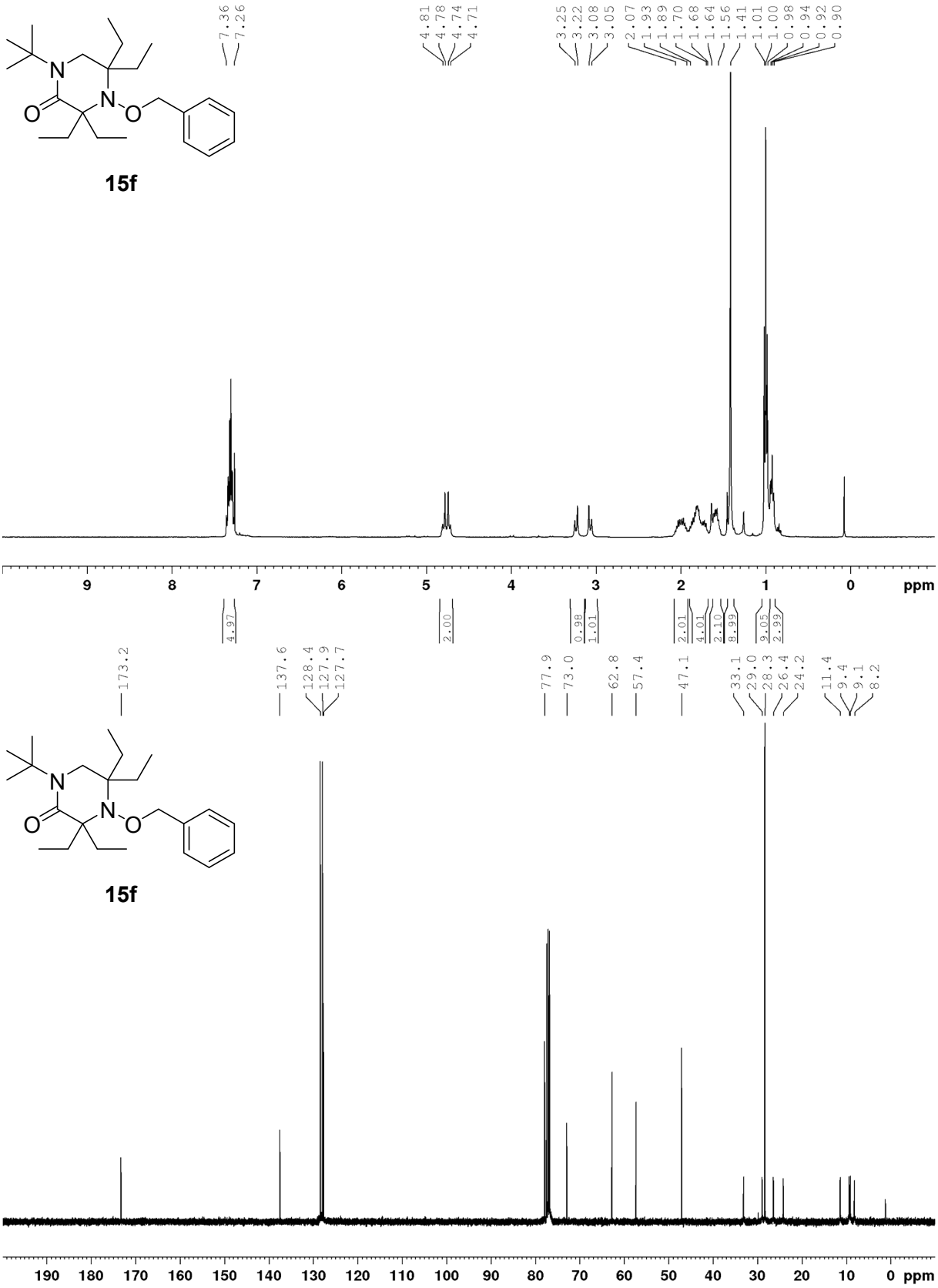
1-(Benzyloxy)-2,2,5-trimethyl-5-phenylpyrrolidine (15d)



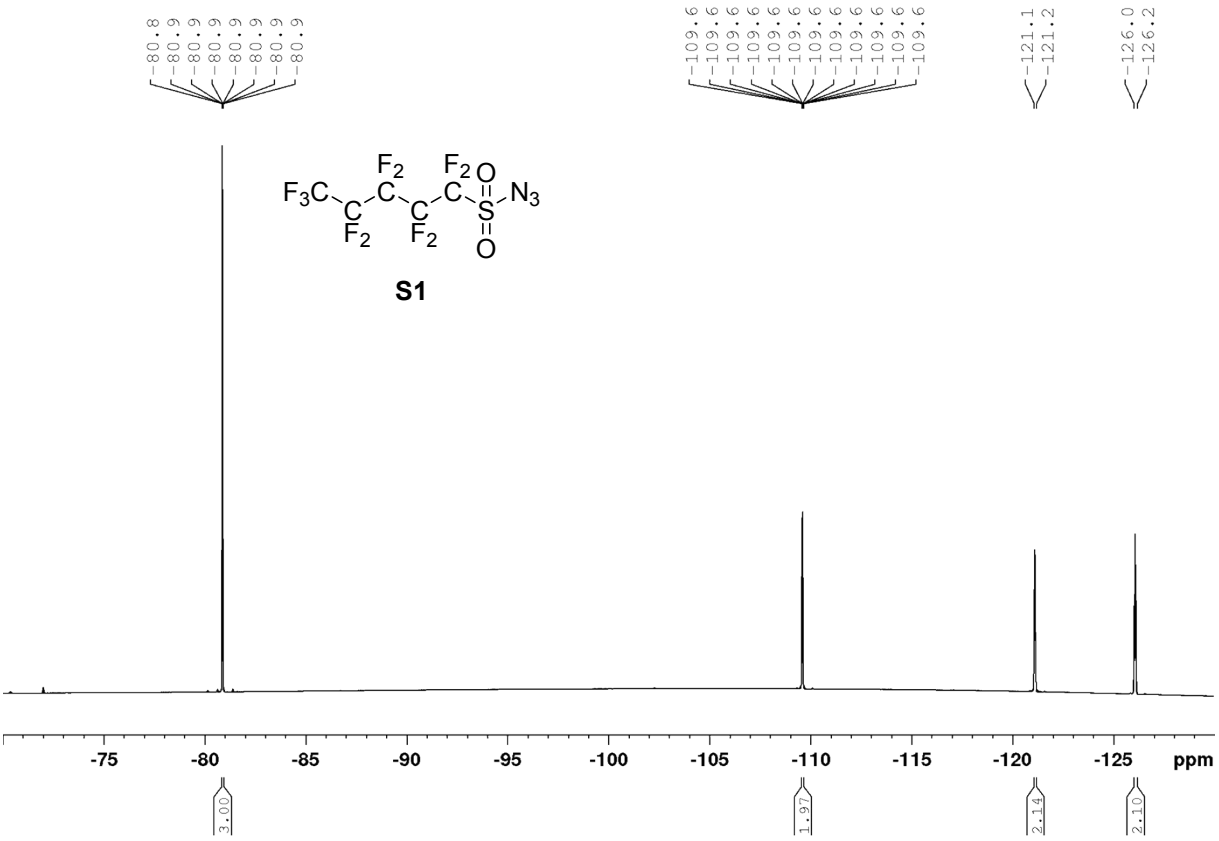
1-(Benzyloxy)-2,2,5,5-tetramethyl-2,5-dihydro-1*H*-pyrrole-3-carboxamide (15e)

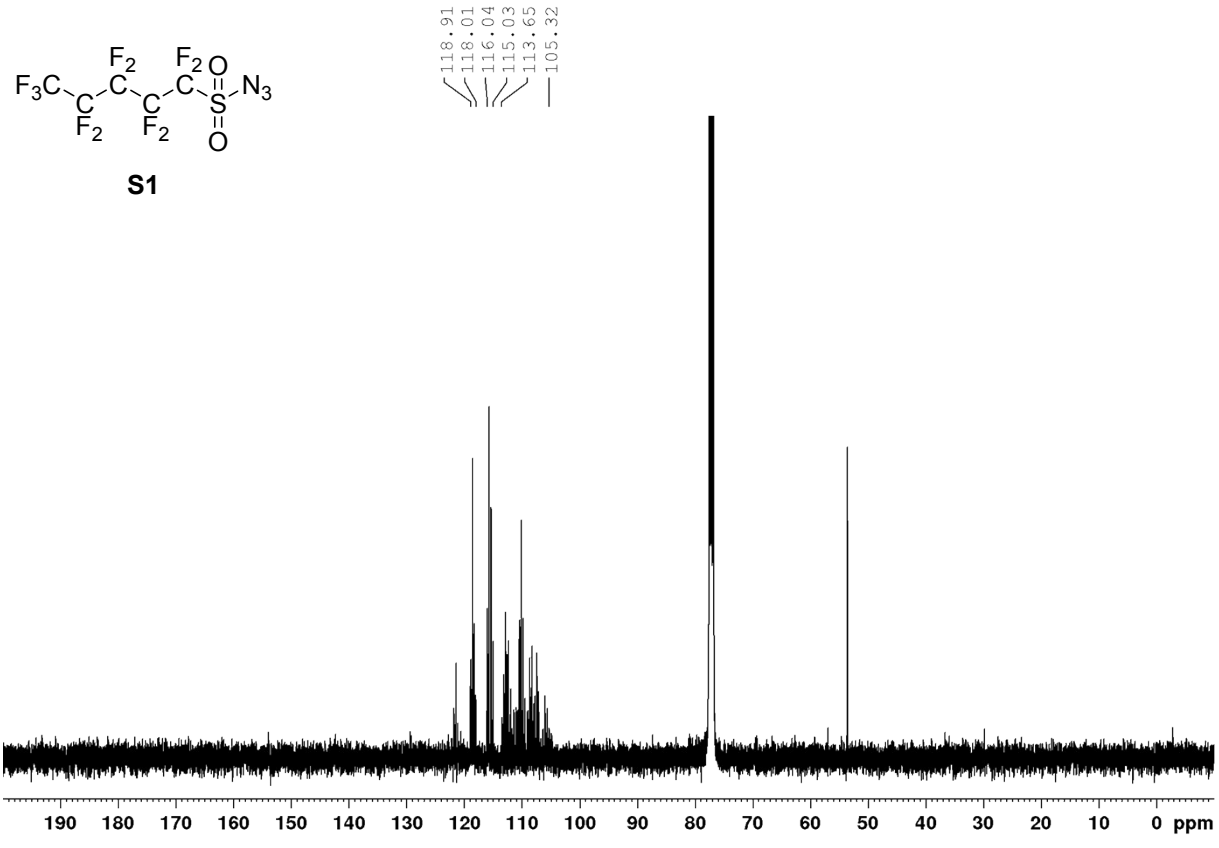


4-(Benzyloxy)-1-(*tert*-butyl)-3,3,5,5-tetraethylpiperazin-2-one (15f)

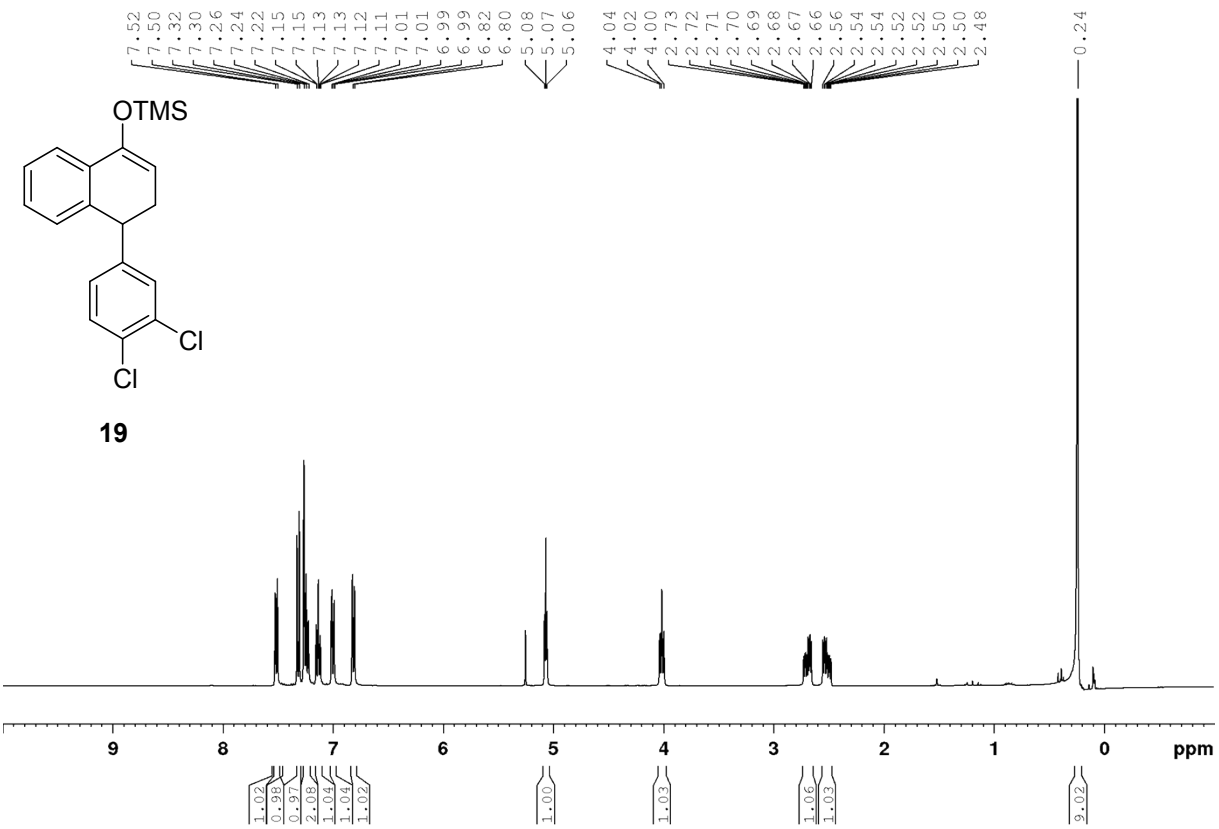


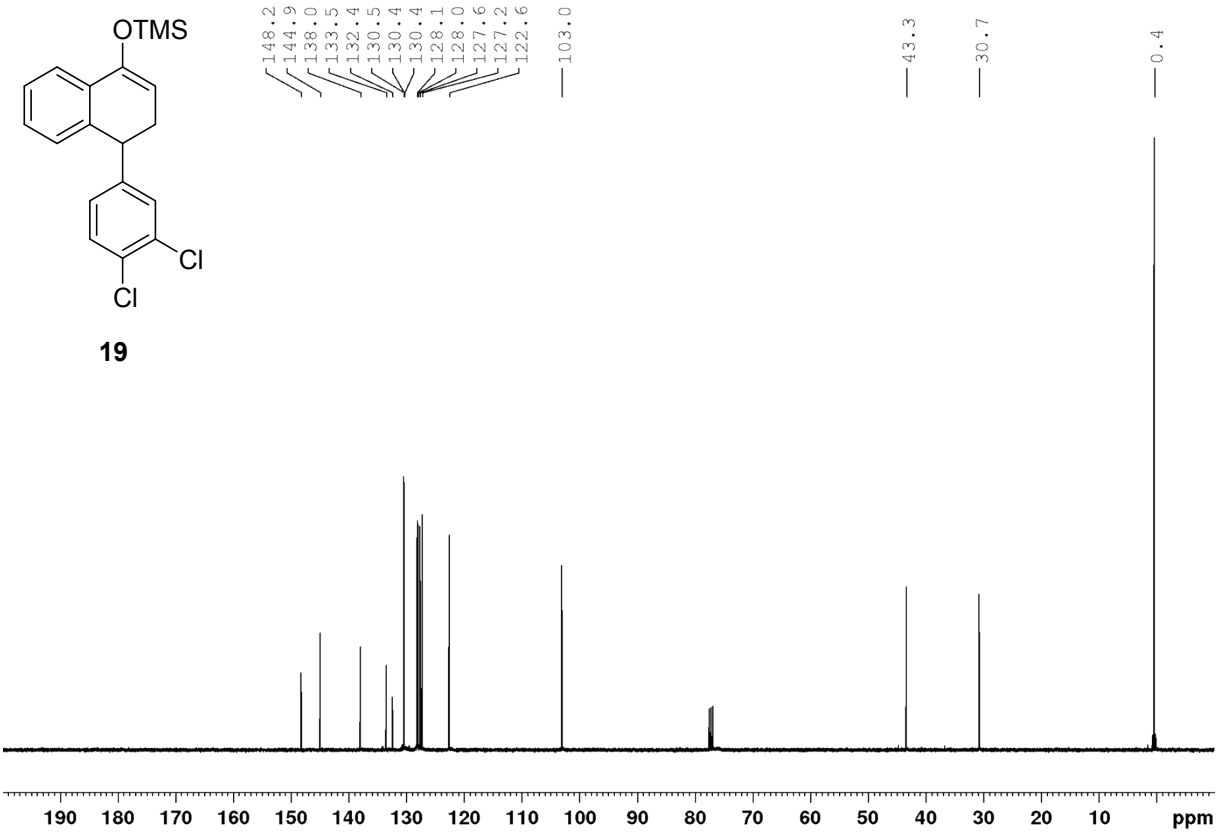
1,1,2,2,3,3,4,4,5,5,5-Undecafluoropentane-1-sulfonyl azide (S1)



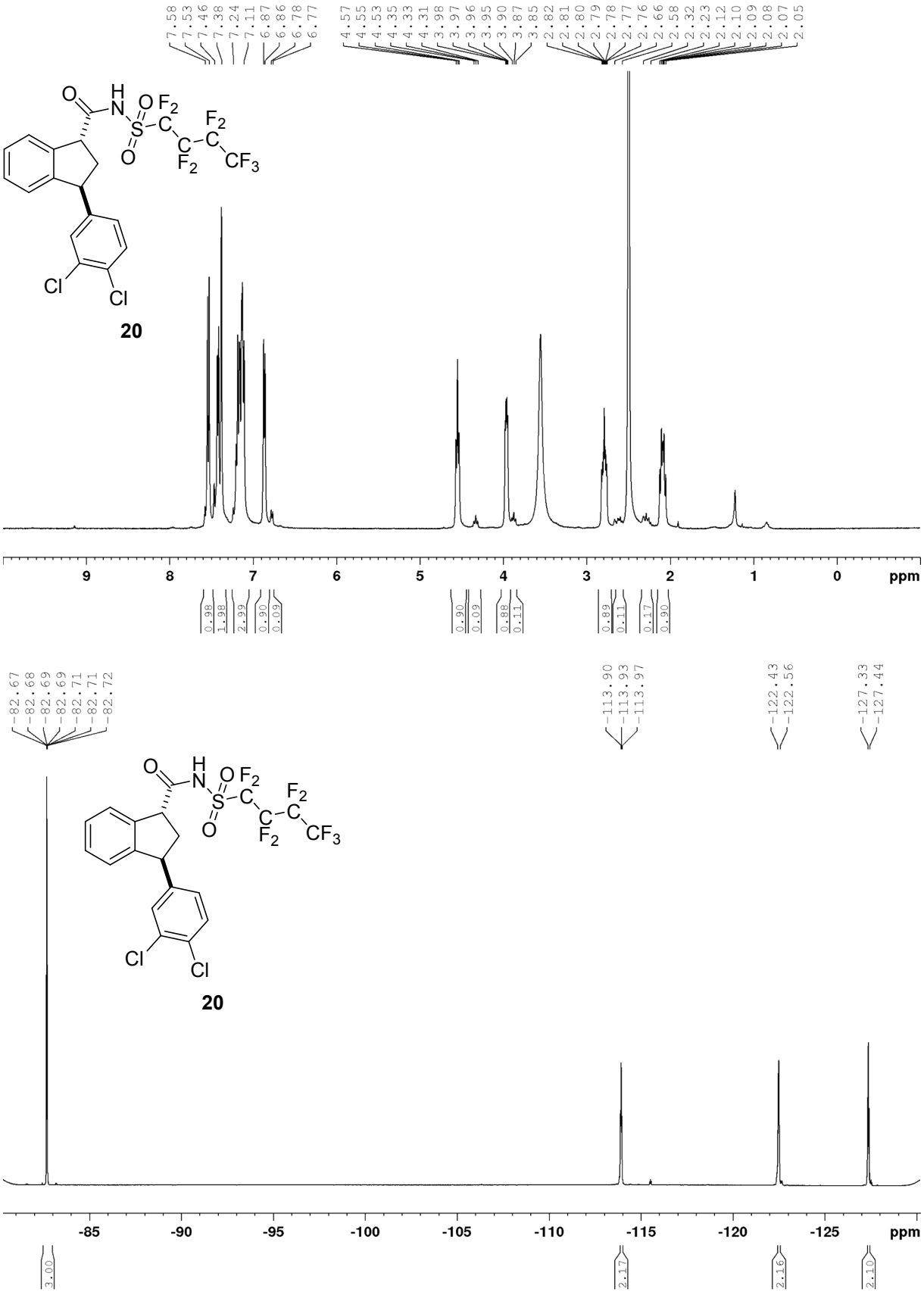


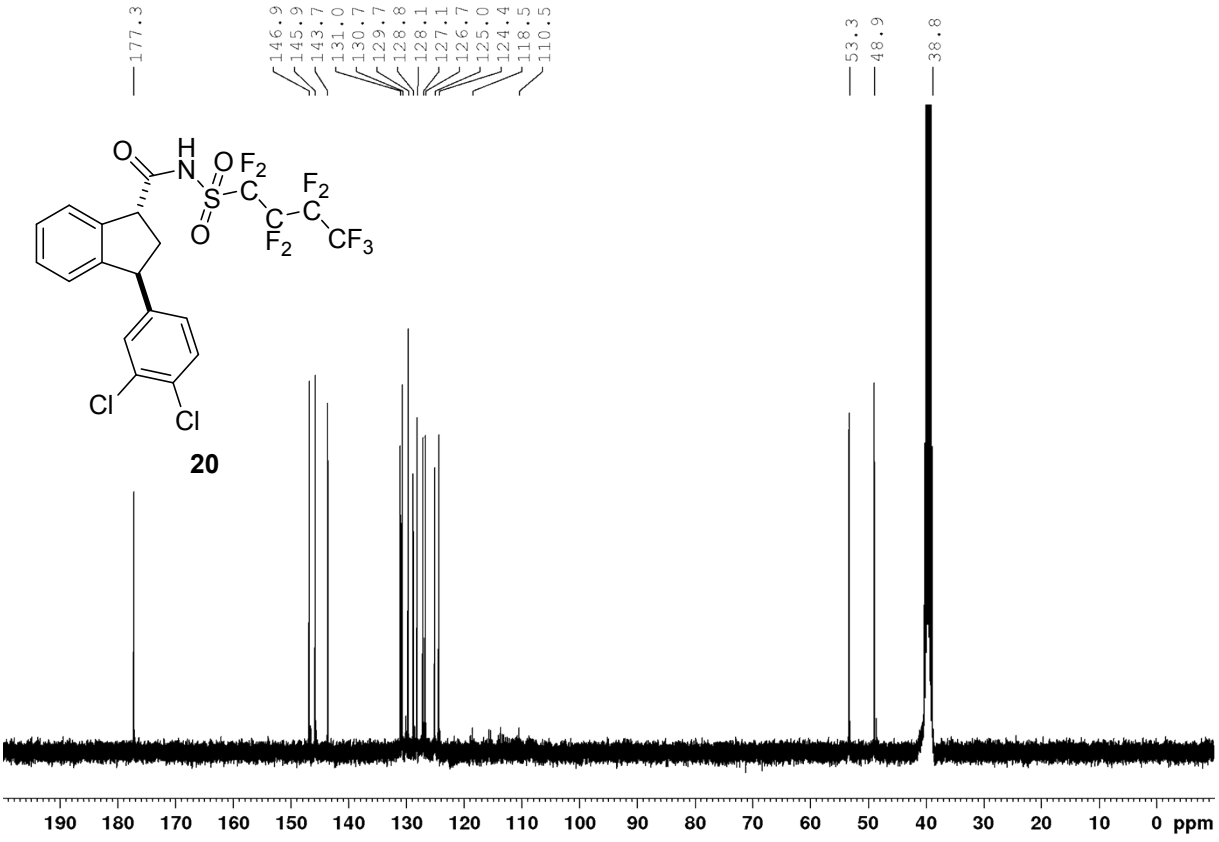
((4-(3,4-Dichlorophenyl)-3,4-dihydronaphthalen-1-yl)oxy)trimethylsilane (19)



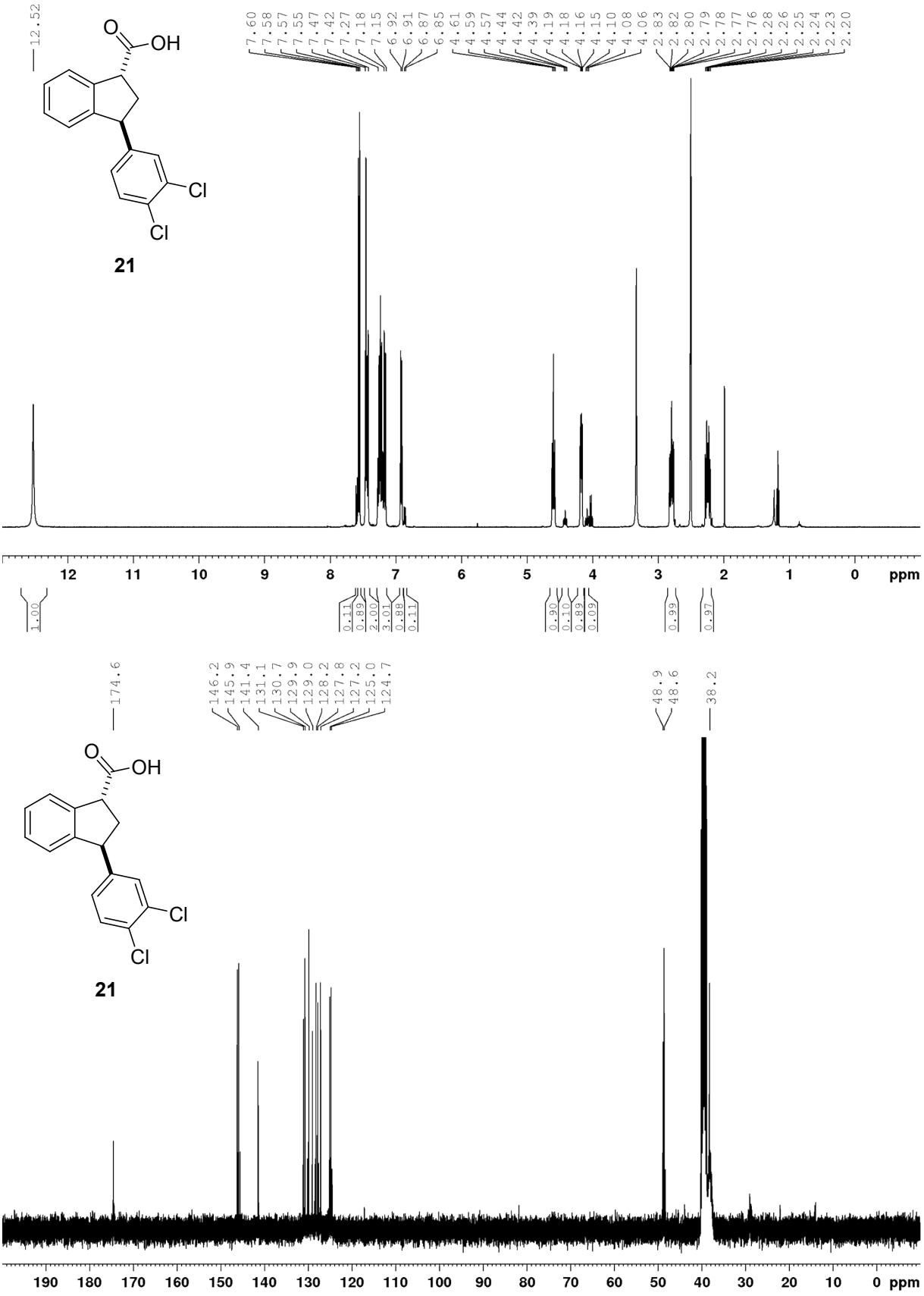


3-(3,4-Dichlorophenyl)-*N*-((perfluorobutyl)sulfonyl)-2,3-dihydro-1*H*-indene-1-carboxamide (20)

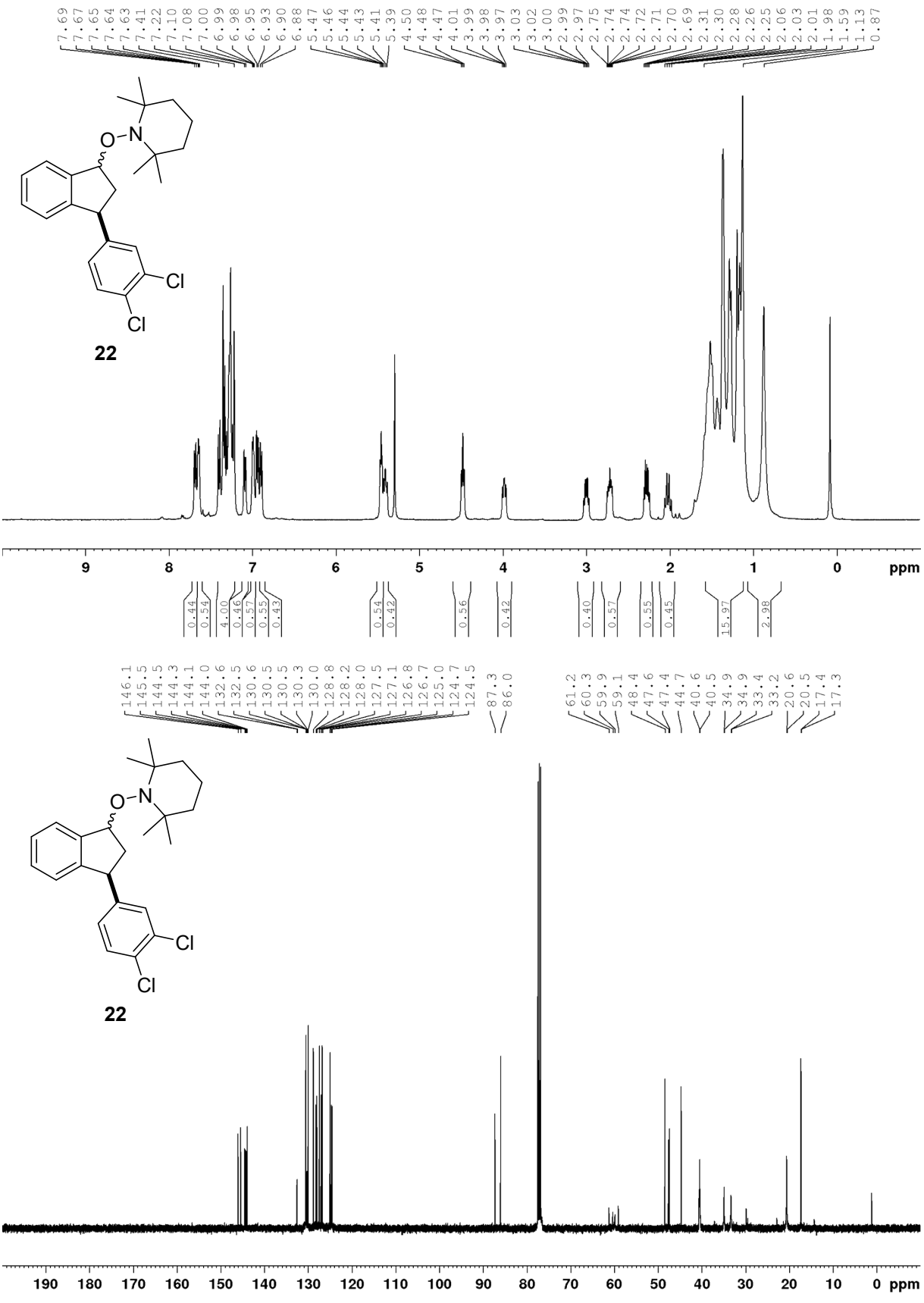



177.3
146.9
145.9
143.7
131.0
130.7
129.7
128.8
128.1
127.1
126.7
125.0
124.4
118.5
110.5
53.3
48.9
38.8
O
H
N
O
S
O
O
F2
C
C
F2
F2
C
CF3
Cl
Cl
20
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0 ppm

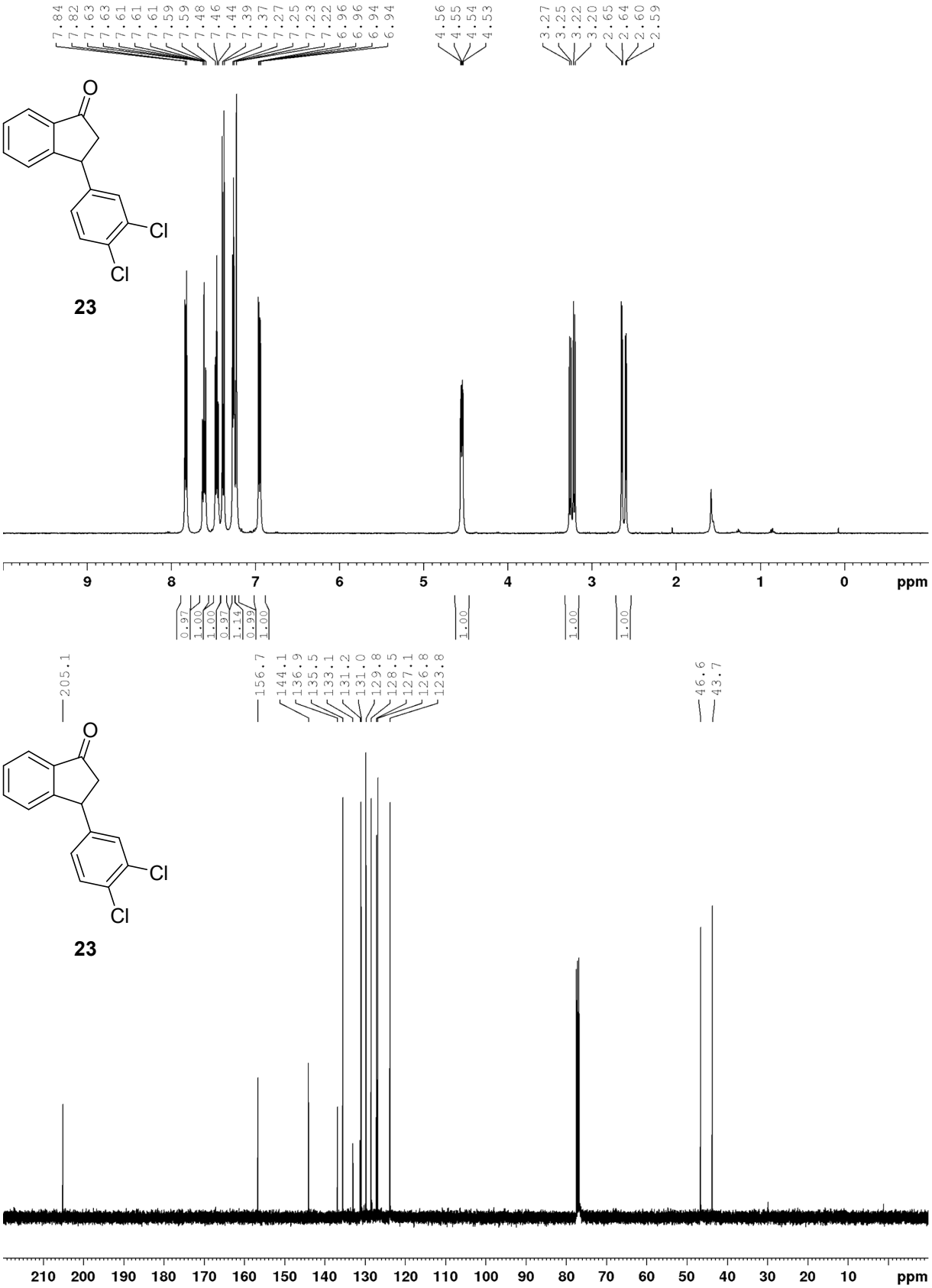
3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-indene-1-carboxylic acid (21)



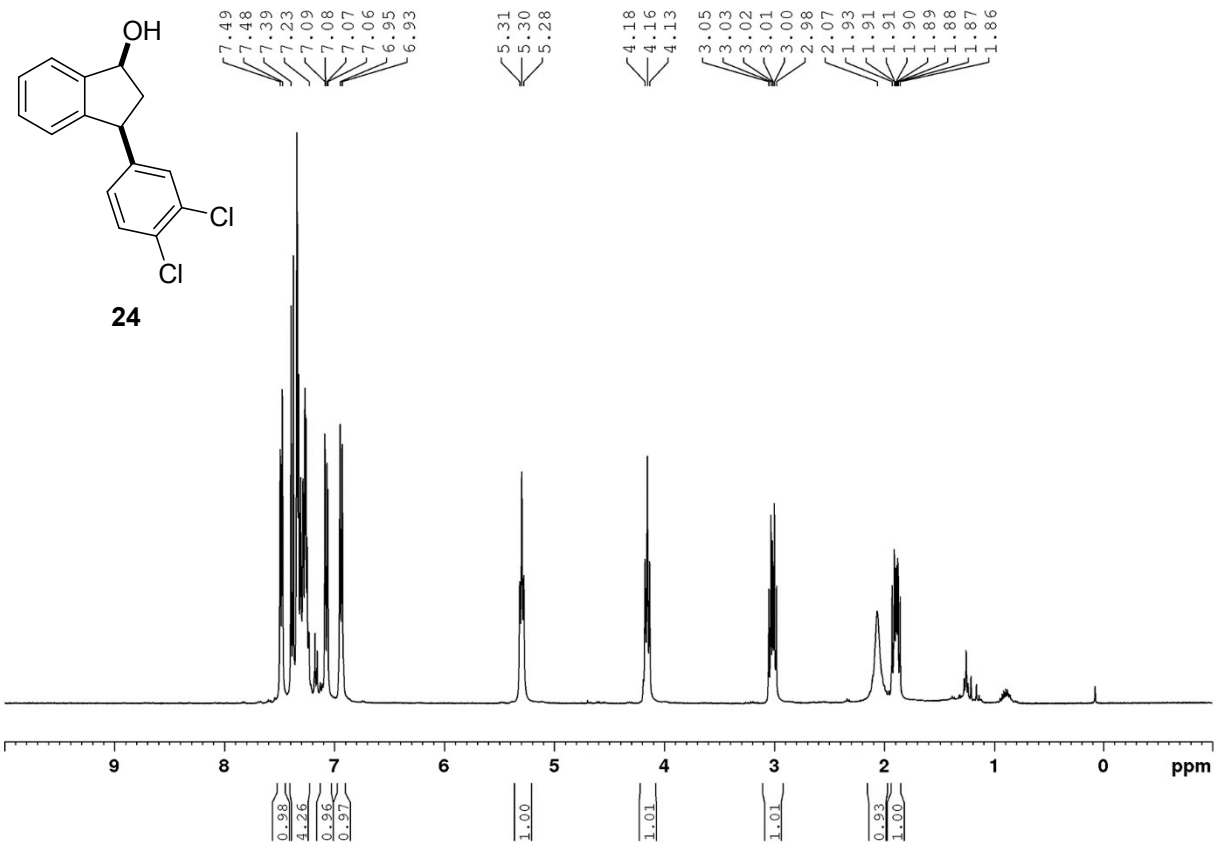
1-((3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-yl)oxy)-2,2,6,6-tetramethylpiperidine (22)

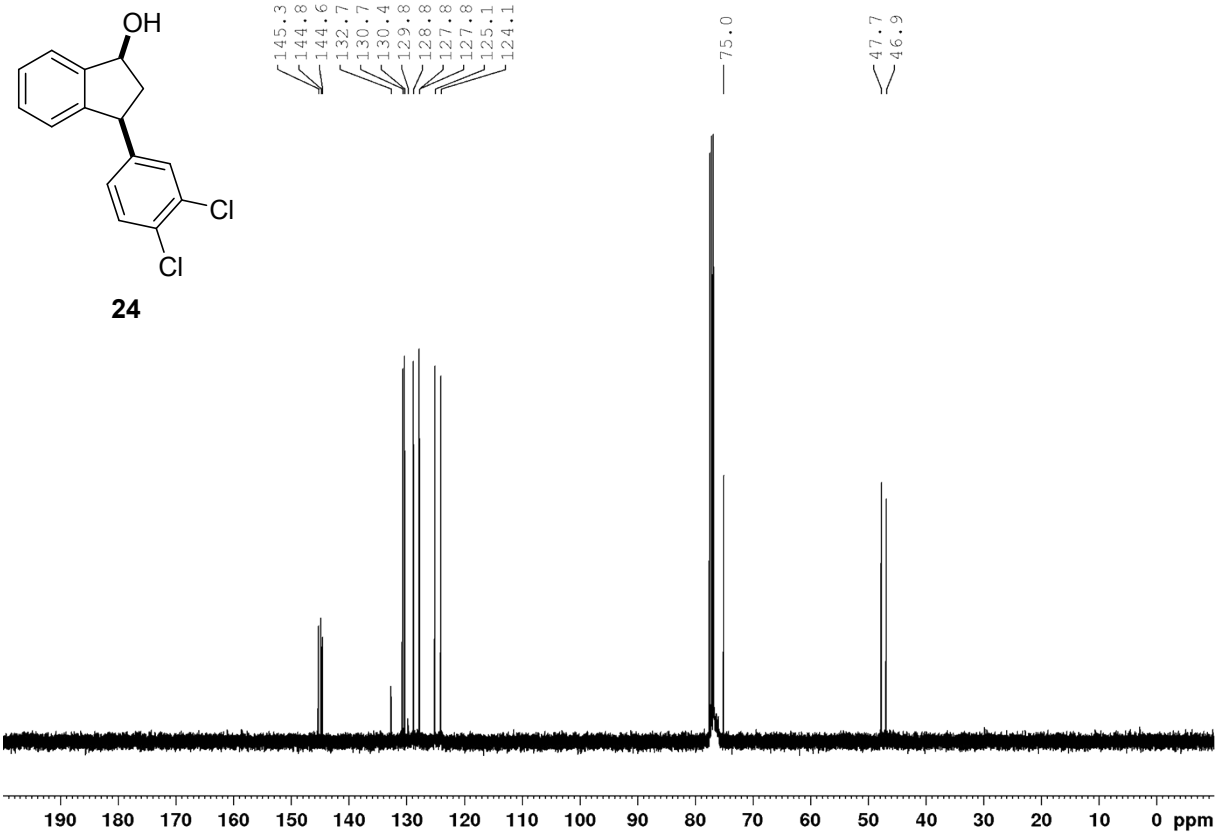


3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-one (23)



3-(3,4-Dichlorophenyl)-2,3-dihydro-1*H*-inden-1-ol (24)





(±)-Indatraline (16)