SUPPORTING INFORMATION FOR

Amine Organocatalysis of Remote, Chemoselective C(sp^3)–H Hydroxylation

Philip L. Hahn, Jared M. Lowe, Yubo Xu, Kevin L. Burns, and Michael K. Hilinski

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22904-4319, United States

CONTENTS

1. General Information

Materials and Methods: All reagents were obtained commercially in the highest available purity and used without further purification unless otherwise noted. 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) was purchased from Oakwood Chemical Company and stored over 3 Å molecular sieves. Anhydrous solvents were obtained from a solvent purification system utilizing activated alumina columns under a positive pressure of argon. Reactions carried out at temperatures above room temperature (23 °C) were conducted in a pre-heated oil bath. Hydroxylation reactions were performed in phenolic screwcap 4 Dram vials under magnetic stirring. Flash column chromatography was performed using silica gel (230 - 400 mesh) purchased from Silicycle (Siliaflash P60). Elution of compounds was monitored by UV or PMA stain on TLC.

Instrumentation: ^{1}H and ^{13}C NMR spectra were measured on a Varian Inova 600 (600 MHz), Bruker Avance DRX 600 (600 MHz), or Bruker Avance III 800 (800 MHz) spectrometer and acquired at 300 K. Chemical shifts are reported in parts per million (ppm δ) referenced to the residual ^{1}H or ^{13}C resonance of the solvent. The following abbreviations are used singularly or in

combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m – multiplet, br – broad, and ap – apparent. High-resolution mass spectrometry was obtained using an Agilent Q-TOF ESI spectrometer.

2. Screening and Reaction Optimization

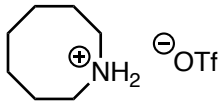
Reaction conditions were screened with 6-methyl-2-heptanol using the following general procedure: To a 2 dram screw cap vial equipped with a PTFE stir bar and charged with $NaHCO_3$ (84.0 mg, 1 mmol, 5 equiv), aldehyde (2 equiv), 1,2-bis(3,5-bis(trifluoromethyl)phenyl)diselane (1.2 mg, 0.002 mmol, 0.01 equiv), urea hydrogen peroxide (58.3 mg, 0.6 mmol, 3 equiv), and amine trifluoromethanesulfonate salt (1 equiv) in 1,1,1,3,3,3-hexafluoroisopropanol (2 mL) was added 6-methyl-2-heptanol (32.4 µL 0.2 mmol, 1 equiv). The vial was placed in a 50 °C oil bath and allowed to stir for 24 hours. Upon reaction completion the mixture was cooled to room temperature, then diluted with 5 mL CH_2Cl_2. *n*-Dodecane (0.0661 mmol, 15 µL) was added as an internal standard and reaction was sampled and analyzed on GC-FID. Yields are reported as corrected GC yields and chemoselectivity is reported as an uncorrected peak area ratio of **3a** to **5a**, except where isolated yields/selectivities are indicated.

3. Reagent and Substrate Synthesis

1,2-bis(3,5-bis(trifluoromethyl)phenyl)diselane was prepared according to literature procedure.[1]

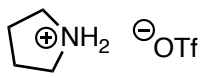
Compounds **2b**,[2] **2q**,[3] and **2t**[4] were prepared according to literature procedures.

Azocanium trifluoromethanesulfonate (catalyst A)



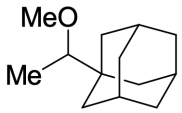
To a stirred solution of azocane (5.05 mL, 40 mmol, 1 equiv) in Et_2O (100 mL) cooled to -10 °C was added trifluoromethanesulfonic acid (3.51 mL, 40 mmol, 1 equiv) dropwise. After 1 h, the resulting white precipitate was filtered and washed with Hexanes/Et_2O (4:1, 2x 25 mL), then recrystallized from hot *i*PrOH/Et_2O followed by cooling to 0 °C to give product as colorless, oily crystals (8.37 g, 31.8 mmol, 79%). The salt is not measurably hygroscopic; however, it was stored in a desiccator as a precaution.

Pyrrolidinium trifluoromethanesulfonate (catalyst B)



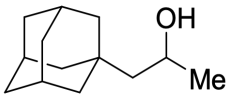
To a stirred solution of pyrrolidine (4.11 mL, 50 mmol, 1 equiv) in Et_2O (100 mL) cooled to 0 °C was added trifluoromethanesulfonic acid (4.39 mL, 50 mmol, 1 equiv) dropwise. After 1 h, the resulting white precipitate was filtered and washed with Et_2O (2x 25 mL), then recrystallized from hot *i*PrOH/Et_2O/Hexanes to give product as white, flaky crystals (10.29 g, 46.5 mmol, 93%). The salt is not measurably hygroscopic; however, it was stored in a desiccator as a precaution.

1-(1-methoxyethyl)adamantane (2c)



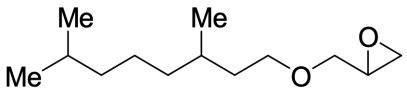
To a flame dried flask under N_2 with 1-(1-hydroxyethyl)adamantane (409 mg, 2.27 mmol, 1 equiv) in DMF (3 mL) at room temperature was added NaH (144 mg of a 60% dispersion, 3.41 mmol, 1 equiv) in one portion. After 30 min, MeI (1.09 mL, 4.54 mmol, 2 equiv) was added. The mixture was allowed to stir for 3 h, then quenched with 10 mL of H_2O and extracted with Et_2O (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and after evaporation of the solvent, the crude mixture was purified by flash chromatography on silica gel (0% to 10% Et_2O/Hexanes) to give a clear, non-viscous oil (419 mg, 2.15 mmol, 95% yield).
^{1}H NMR (800 MHz, $CDCl_3$) δ 3.31 (s, 3H), 2.70 (q, J = 6.3 Hz, 1H), 1.98–1.94 (m, 3H), 1.71–1.67 (m, 3H), 1.66–1.60 (m, 6H), 1.49-1.44 (m, 3H), 1.02 (d, J = 6.3 Hz, 3H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 85.7, 57.9, 38.3, 37.5, 37.0, 28.6, 12.0 ppm.
Elemental Analysis Calcd for $C_{13}H_{22}O$: C 80.35, H 11.41 Found: C 80.04, H 11.51.

1-(adamantan-1-yl)propan-2-ol (2d)



To a flame dried flask under N_2 with 1-(adamantan-1-yl)propan-2-one (prepared by literature procedure)[5] (1 eq, 5.63 mmol, 1.0819 g) in anhydrous MeOH cooled to 0 °C was added $NaBH_4$ in one lot. After 40 min, reaction was quenched with 10 mL H_2O, solvent was removed, and extracted with 2x 10 mL EtOAc. Combined organic layers were washed with H_2O (20 mL), brine (20 mL), then dried over Na_2SO_4, and cone. After evaporation of the solvent, the crude product was purified by flash chromatography on silica gel (20% Et_2O/hexanes) to give a colorless crystalline product (1.084 g, 5.58 mmol, 99% yield)
^{1}H NMR (800 MHz, $CDCl_3$) δ 4.05-4.01 (m, 1H), 1.95 (ap s, 3H), 1.72–1.68 (m, 3H), 1.66–1.62 (m, 3H), 1.58–1.54 (m, 6H), 1.29–1.25 (m, 1H), 1.22 (s, 1H), 1.24–1.19 (m, 1H), 1.17 (d, J = 6.2 Hz, 3H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 64.6, 54.4, 43.2, 37.2, 32.4, 28.8, 26.2 ppm
Elemental Analysis Calcd for $C_{13}H_{22}O$: C 80.35, H 11.41 Found: C 80.65, H 11.60.

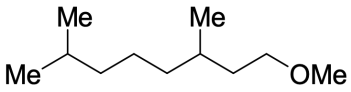
2-(((3,7-dimethyloctyl)oxy)methyl)oxirane (2i)



To a solution of mCPBA (999 mg, 5.9 mmo, 2 equiv) in CH_2Cl_2 (10 mL) cooled to 0 °C was added 1-(allyloxy)-3,7-dimethyloctane (564 mg, 2.84 mmol, 1 equiv). The resulting mixture was allowed to slowly warm to room temperature overnight. The mixture was then diluted with CH_2Cl_2 (15

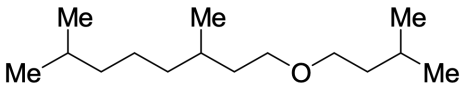
mL) and washed with saturated $NaHCO_3$ (2 x 25 mL) then brine (25 mL). The organic layer was then dried over MgSO4, filtered, and concentrated. The crude product mixture was then purified by flash chromatography on silica gel (5% EtOAc/Hex) to give **2i** as a colorless oil (429 mg, 2.00 mmol, 71% yield, 1:1 d.r.).
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.72–3.68 (m, 1H), 3.57–3.45 (m, 2H), 3.39–3.36 (m, 1H), 3.16–3.13 (m, 1H), 2.82–2.77 (m, 1H), 2.62–2.59 (m, 1H), 1.67–1.59 (m, 1H), 1.54–1.48 (m, 2H), 1.40-1.37 (m, 1H), 1.34–1.21 (m, 3H), 1.17–1.07 (m, 3H), 0.89–0.85 (m, 9H) ppm.
^{13}C NMR (150 MHz, $CDCl_3$) δ 71.6, 70.2, 51.1, 44.5, 39.4, 37.5, 36.9, 30.0, 28.1, 24.8, 22.9, 22.8, 19.8 ppm;
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{26}O_2$ 237.1831, found 237.1830.

1-methoxy-3,7-dimethyloctane (2j)



To a flame dried flask under N_2 was added 3,7-dimethyloctan-1-ol (1.91 mL, 10 mmol, 1 equiv) and THF (10 mL). The resulting mixture was cooled to 0 °C, and NaH (440 mg, 60% dispersion, 11 mmol, 1.1 equiv) was added carefully in one portion. After 20 min, MeI (1.1 eq, 11 mmol, 0.685 mL) was added. The resulting mixture was allowed to warm slowly to room temperature and stirred for 17 h. At this time, water (5 mL) was added, and the mixture was extracted with Et_2O (2 x 20 mL). The combined organic layers were dried over $MgSO_4$. After evaporation of the solvent, the crude mixture was purified by flash chromatography on silica gel (0% to 5% Et_2O/Hexanes) to give a colorless oil (1.31 g, 7.64 mmol, 76% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 3.44–3.36 (m, 2H), 3.32 (s, 3H), 1.64–1.57 (m, 1H), 1.57–1.47 (m, 2H), 1.39–1.21 (m, 4H), 1.17–1.06 (m, 3H), 0.89–0.84 (m, 9H) ppm.
^{13}C NMR (150 MHz, $CDCl_3$) δ 71.4, 58.7, 39.4, 37.6, 36.9, 30.0, 28.1, 24.8, 22.8, 22.7, 19.8 ppm. NMR spectra are consistent with literature reports.[6]

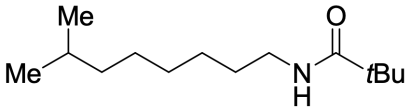
1-(isopentyloxy)-3,7-dimethyloctane (2k)



To a flame dried flask under N_2 was added isoamyl alcohol (2 eq, 10 mmol, 1.09 mL) and DMF (10 mL). The resulting mixture was cooled to 0 °C and NaH (0.6 g of a 60% dispersion, 15 mmol, 3 equiv) carefully in one portion. After 10 min, reaction was warmed to room temperature. After a further 20 min, 1-bromo-3,7-dimethyloctane (1.09 mL, 5 mmol, 1 equiv) was added. The resulting mixture was stirred for 4 h before being quenched with water (20 mL). The resulting mixture was extracted with Et_2O (2 x 20 mL). The combined organic layers were washed with water (3 x 50 mL) then dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (0% to 2% Et_2O/Hexanes) to give a pale yellow oil (599 mg, 2.62 mmol, 52% yield).

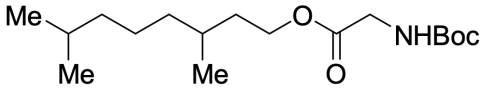
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.46–3.36 (m, 2H), 3.32 (s, 3H) 1.71-1.60 (m, 1H), 1.60–1.57 (m, 1H), 1.55–1.47 (m, 2H), 1.46–1.43 (m, 2H), 1.39–1.21 (m, 3H), 1.17–1.05 (m, 3H), 0.89 (d, J = 6.7 Hz, 6H), 0.87 – 0.84 (m, 9H) ppm.
^{13}C NMR (150 MHz, $CDCl_3$) δ 69.4, 69.4, 39.4, 38.8, 37.5, 37.0, 30.1, 28.1, 25.3, 24.8, 22.84, 22.79, 22.74, 19.8 ppm.
HRMS (EI/QTOF) m/z: $[M]^{\bullet+}$ Calcd for $C_{15}H_{32}O$ 228.2453, found 228.2458.

***N*-(7-methyloctyl)pivalamide (2p)**



To a flame-dried flask under N_2 charged with 7-methyloctane-1-amine (364 mg, 2.54 mmol, 1 equiv) and DMAP (31 mg, 0.25 mmol) in CH_2Cl_2 (20 mL) was added pivaloyl chloride (0.93 mL, 7.62 mmol, 3 equiv). The resulting mixture was allowed to stir at room temperature for 16 h, then quenched with saturated $NaHCO_3$ (20 mL). The organic layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL), then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography on silica gel (10% to 20% EtOAc/Hexanes) to give **2p** as a pale-yellow oil (504 mg, 2.22 mmol, 87% yield).
^{1}H NMR (800 MHz, $CDCl_3$) δ 5.70 (br s, 1H), 3.18 (td, J = 7.3, 5.6 Hz, 2H), 1.51 – 1.41 (m, 3H), 1.28 – 1.19 (m, 6H), 1.15 (s, 9H), 1.12 – 1.06 (m, 2H), 0.81 (d, J = 6.9 Hz, 6H) ppm.
^{13}C NMR (201 MHz, $CDCl_3$) δ 178.4, 39.6, 39.0, 38.7, 29.7, 29.6, 28.0, 27.7, 27.3, 27.3, 27.0, 22.7 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{29}NO$ 250.2147, found 250.2184.

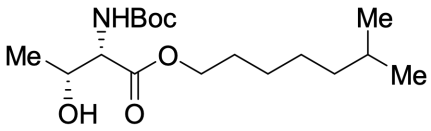
3,7-dimethyloctyl (tert-butoxycarbonyl)glycinate (2r)



To a flame dried flask was added Boc-*N*-glycine (876 mg, 5 mmol,1 equiv) followed by anhydrous CH_2Cl_2 (15 mL). The solution was cooled to 0 ˚C, whereupon *N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (1.15 g, 6 mmol, 3 equiv) was added. The solution was stirred for 15 min, then dimethylaminopyridine (61 mg, 0.5 mmol, 0.1 equiv) was added followed by 3,7-dimethyloctanol (965 µL, 5.05 mmol, 1 equiv). The resulting mixture was stirred overnight at room temperature. The resulting solution was then washed once with water (10 mL), then dried over sodium sulfate, filtered, and concentrated. The mixture was purified by flash chromatography (100 to 90:10 hexanes:ethyl acetate) to afford the product as a light yellow oil (677 mg, 43%).
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.03 (br, 1H), 4.23-4.10 (m, 2H), 3.93-3.84 (m, 2H), 1.65 (m, 1H), 1.55-1.47 (m, 2H), 1.43 (s, 9H), 1.46-1.38 (m, 1H), 1.32 – 1.19 (m, 3H), 1.16-1.07 (m, 3H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.85 (dd, *J* = 6.7, 1.0 Hz, 6H) ppm.

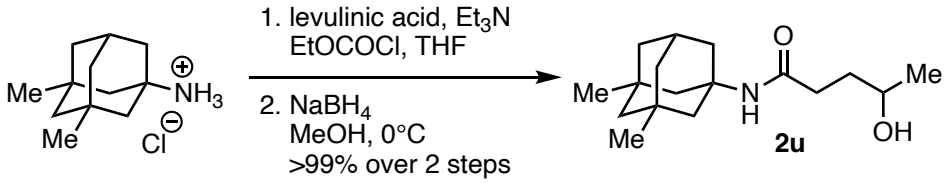
^{13}C NMR (200 MHz, $CDCl_3$) δ 170.6, 155.8, 80.0, 64.1, 42.6, 39.3, 37.2, 35.5, 29.9, 28.4, 28.1, 24.7, 22.8, 22.7, 19.6 ppm.
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{33}O_4N$ 338.2307 found 338.2313.

6-methylheptyl (tert-butoxycarbonyl)-*L*-threoninate (2s)

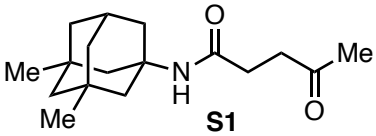


To a solution of Boc-*L*-Thr-OH (731 mg, 3.33 mmol, 1 equiv) and Et_3N (0.46 mL, 3.33 mmol, 1 equiv) in EtOAc (10 mL) under N_2 was added 1-bromo-6-methylheptane (643 mg, 3.33 mmol, 1 equiv). The resulting mixture was heated to 50 °C for 24 h. Upon completion, reaction was cooled and washed with sat. $NaHCO_3$ (10 mL), dried over Na_2SO_4, and concentrated. The crude mixture was then purified by flash chromatography on silica gel (25% EtOAc/Hexanes) to give a colorless, viscous oil (44.4 mg, 0.129 mmol, 4% yield).
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.35–5.31 (m, 1H), 4.28–4.20 (m, 2H), 4.16–4.12 (m, 2H), 2.22 (br s, 1H), 1.67–1.61 (m, 2H), 1.55–1.47 (m, 1H), 1.44 (s, 9H), 1.35–1.25 (m, 4H), 1.24 (d, J = 6.4 Hz, 3H), 1.19–1.11 (m, 2H), 0.85 (d, J = 6.7 Hz, 6H) ppm.
^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 156.3, 80.1, 68.4, 65.9, 58.9, 38.9, 28.7, 28.4, 28.2, 28.0, 27.1, 26.2, 22.7, 20.1 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{33}NO_5$ 354.2256, found 354.2260.

Preparation of N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)-4-hydroxypentanamide (**2u**)

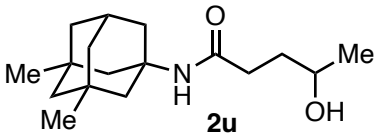


N-((1*r*,3*R*,5*S*,7*r*)-3,5-dimethyladamantan-1-yl)-4-oxopentanamide (**S1**)



Ketone **S1** was prepared from memantine•HCl by the following procedure: To a solution of levulinic acid (581 mg, 5 mmol, 1 equiv) in anhydrous THF (30 mL) was added triethylamine (0.70 mL, 5 mmol, 1 equiv). The resulting solution was cooled to 0 °C, then ethylchlorformate (0.39 mL, 5 mmol, 1 equiv) was added dropwise over 5 minutes. The resulting solution was allowed to stir for 20 minutes at 0 °C, then memantine•HCl (1.08 g, 5 mmol, 1 equiv) was added in one portion. The resulting solution was removed from the ice bath and allowed to stir at room temperature for 20 h before being quenched by the addition of water (5 mL). The resulting mixture was further diluted with EtOAc (30 mL) and 10% aqueous $KHSO_4$ (10 mL). The layers were separated, and the organic layer was washed with 10% aqueous $KHSO_4$ (5 mL) and brine (5mL),

then dried over sodium sulfate. After removal of the solvent, the resulting mixture was passed through a silica gel plug using 50% EtOAc/hexanes. After evaporation of the solvent, the resulting clear oil was carried on without further purification.



2u

Alcohol **2u** was prepared by first dissolving **S1** in MeOH and cooling to 0 ˚C. Sodium borohydride (2 equiv) was added and the reaction stirred for 30 minutes. The reaction was then quenched with water. Methanol was removed by vacuum and the mixture was extracted (2 x 25 mL) with ethyl acetate. The organic extracts were washed with brine and dried over sodium sulfate. The concentrated residue was purified on silica column using 75% EtOAc/hexanes to yield an amorphous colorless solid (140 mg, 5 mmol, >99%).
^{1}H NMR (800 MHz, $CDCl_3$) δ 3.77 (m, 1H), 3.61 (s, 1H), 2.23 (m, 2H), 2.09 (m, 1H), 1.77 (m, 3H), 1.60 (m, 5H), 1.32 (m, 2H), 1.25 (m, 2H), 1.12 (m, 5H), 0.80 (s, 6H) ppm.
^{13}C NMR (201 MHz, $CDCl_3$) δ 173.1, 67.3, 53.5, 50.6, 47.49, 47.48, 42.6 (2C), 40.1, 34.5, 34.2, 32.3 (2C), 30.08, 30.06, 23.7 (2C) ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for 302.2096, found 302.2097.

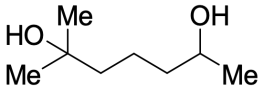
4. Hydroxylation Reactions

General Hydroxylation Procedure A: To a 4 dram vial equipped with a stir bar and containing $NaHCO_3$ (168 mg, 2 mmol, 2 equiv), paraformaldehyde (60 mg, 2 mmol, 2 equiv), 1,2-bis(3,5-bis(trifluoromethyl)phenyl)diselane (1 mol %, 0.01 mmol, 5.8 mg), urea hydrogen peroxide (194 mg, 2 mmol, 2 equiv), and azocanium trifluoromethanesulfonate (53 mg, 0.2 mmol, 0.2 equiv) was added 1,1,1,3,3,3-hexafluoroisopropanol (10 mL) followed by the substrate (1 mmol, 1 equiv). The vial was sealed with a screw cap and heated to 50 °C unless otherwise noted for 24 h or until complete by TLC. Upon completion, the vessel was cooled, and the mixture was diluted with CH_2Cl_2 (10 mL). The mixture was then filtered through Celite, eluting with CH_2Cl_2, then concentrated on rotary evaporator. The crude mixture was then purified by silica gel flash chromatography as noted.

General Hydroxylation Procedure B: To a 4 dram vial equipped with a stir bar and containing $NaHCO_3$ (168 mg, 2 mmol, 2 equiv), paraformaldehyde (60 mg, 2 mmol, 2 equiv), 1,2-bis(3,5-bis(trifluoromethyl)phenyl)diselane (5.8 mg, 0.01 mmol, 0.01 equiv), urea hydrogen peroxide (194 mg, 2 mmol, 2 equiv) and pyrrolidinium trifluoromethanesulfonate (22.1 mg, 0.1 mmol, 0.1 equiv) was added 1,1,1,3,3,3-hexafluoroisopropanol (10 mL) followed by the substrate (1 mmol, 1 equiv). The vial was sealed with a screw cap and heated to 50 °C unless otherwise noted for 24 h or until complete by TLC. Upon completion, the vessel was cooled, and the mixture was diluted with CH_2Cl_2 (10 mL). The mixture was then filtered through Celite, eluting with CH_2Cl_2, then

concentrated on rotary evaporator. The crude mixture was then purified by silica gel flash chromatography as noted.

2-methylheptane-2,6-diol (3a)



2-Methylheptane-2,6-diol was prepared according to general hydroxylation procedure A from 6-methyl-2-heptanol (130 mg, 162 µL, 1.00 mmol, 1 equiv). The crude product mixture was purified on a by silica gel flash chromatoraphy (50% to 75% EtOAc/hexanes) to give product **3a** as a clear oil (111 mg, 0.759 mmol, 75.9% yield), an inseparable mixture of 2° hydroxylation diastereomers tentatively assigned as **4a** (3.5 mg, 0.024 mmol, 2.4%, 32:1 site selectivity), unreacted **2a** (27 mg, 0.21 mmol, 21%) and ketone **5a** (0.9 mg, 0.007 mmol, 0.7%, ≥99:1 chemoselectivity).

Characterization data for 3a:

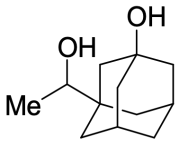
TLC (PMA, 50% EtOAc/Hexanes) $R_f = 0.18$.

^{1}H NMR (800 MHz, $CDCl_3$): δ 3.82 (dq, J = 12.3, 6.2 Hz, 1H), 1.83 (br m, 2H), 1.52–1.36 (m, 6H), 1.21 (s, 6H), 1.19 (d, J = 6.2 Hz, 3H) ppm.

^{13}C NMR (200 MHz, $CDCl_3$) δ 71.2, 68.1, 43.7, 39.8, 29.5, 29.3, 23.7, 20.6 ppm.

NMR spectra for **3a** and **5a** are consistent with literature reports.[6]

3-(1-hydroxyethyl)adamantan-1-ol (3b)



3-(1-Hydroxyethyl)adamantan-1-ol was prepared according to the general hydroxylation procedure B from 1-(adamantan-1-yl)ethan-1-ol (180 mg, 1 mmol, 1 equiv). After workup, the reaction mixture was purified by silica gel flash chromatography (75% to 90% EtOAc/hexanes) to give product **3b** as a colorless, viscous oil that slowly crystallized (167 mg, 0.85 mmol, 85% yield). Also recovered starting material (25 mg, 0.14 mmol, 14%). Chemoselectivity for aliphatic hydroxylation over alcohol oxidation was determined to be ≥85:1 based on 1% of the mass balance being unaccounted for.

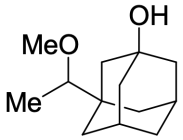
TLC (PMA, 90% EtOAc/Hexanes) $R_f = 0.38$

^{1}H NMR (800 MHz, $CDCl_3$): δ 3.32 (q, J = 6.4 Hz, 1H), 2.22 (br s, 2H), 2.20-2.17 (m, 2H), 1.67–1.58 (m, 4H), 1.55–1.47 (m, 3H), 1.47–1.42 (m, 2H), 1.40–1.37 (m, 1H), 1.37–1.33 (m, 2H), 1.07 (d, J = 6.4 Hz, 3H) ppm.

^{13}C NMR (200 MHz, $CDCl_3$) δ 75.0, 69.3, 45.6, 45.0, 40.8, 36.7, 36.5, 35.8, 30.6, 17.0 ppm.

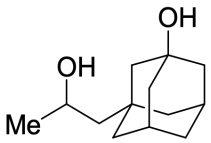
HRMS (EI/QTOF) m/z: $[M]^{\bullet+}$ Calcd for $C_{12}H_{20}O_2$ 196.1463, found 196.1471.

3-(1-methoxyethyl)adamantan-1-ol (3c)

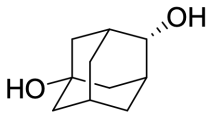


3-(1-Methoxyethyl)adamantan-1-ol was prepared according to the general hydroxylation procedure B starting from 1-(1-methoxyethyl)adamantane (106 mg, 0.547 mmol, 1 equiv). After workup, the reaction mixture was purified by silica gel flash chromatography (25% EtOAc/hexanes) to give product **3c** as an off-white solid (92.2 mg, 0.438 mmol, 80% yield). A total of 20% of the mass balance was unaccounted for, indicating ≥4:1 chemoselectivity.
TLC (PMA, 30% EtOAc/Hexanes) $R_f = 0.39$
^{1}H NMR (600 MHz, $CDCl_3$): δ 3.27 (s, 3H), 2.75 (q, J = 6.4 Hz, 1H), 2.22–2.16 (m, 2H), 1.75 (d, J = 4.3 Hz, 1H), 1.69–1.58 (m, 4H), 1.58–1.54 (m, 1H), 1.52–1.48 (m, 3H), 1.46–1.31 (m, 4H), 0.99 (d, J = 6.4 Hz, 3H) ppm.
^{13}C NMR (150 MHz, $CDCl_3$) δ 84.5, 68.9, 57.6, 46.0, 44.91, 44.89, 40.8, 36.7, 36.7, 35.7, 30.5, 30.4, 12.1 ppm.
EA Calcd for $C_{13}H_{22}O_2$: C 74.24; H 10.54. Found: C 74.11; H 10.57.

3-(2-hydroxypropyl)adamantan-1-ol (3d)



3-(2-Hydroxypropyl)adamantan-1-ol was prepared according to the general hydroxylation procedure B from 1-(adamantan-1-yl)propan-2-ol (38.9 mg, 0.2 mmol, 1 equiv). After workup, the reaction mixture was purified by silica gel flash chromatography (75% to 100% EtOAc/hexanes) to give product as a pale yellow, viscous oil (32.1 mg, 0.15 mmol, 76% yield). A total of 24% of the mass balance was unaccounted for, indicating ≥3:1 chemoselectivity.
TLC (PMA, EtOAc) $R_f = 0.47$
^{1}H NMR (600 MHz, $CDCl_3$): δ 4.05–4.00 (m, 1H), 2.21–2.16 (m, 2H), 1.71–1.61 (m, 4H), 1.57–1.42 (m, 8H), 1.41–1.24 (m, 4H), 1.19 (d, J = 6.2 Hz, 3H) ppm.
^{13}C NMR (150 MHz, $CDCl_3$) δ 69.2, 64.6, 52.9, 50.6, 44.79, 44.76, 41.8, 41.6, 36.1, 35.6, 30.9, 30.8, 26.3 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{22}O_2$ 233.1518, found 233.1518.
***Z*-adamantane-1,4-diol (3e)**

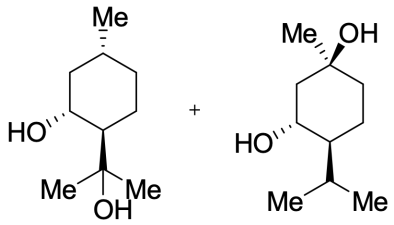


Z-adamantane-1,4-diol was prepared according to general hydroxylation procedure B from 2-adamantanol (**2e** 153 mg, 1 mmol, 1 equiv). After workup, the reaction mixture was purified by silica gel flash chromatography (10% to 100% EtOAc/hexanes) to give product as a white

crystalline solid (67.1 mg, 0.399 mmol, 40% yield, 34:1 d.r. by ^{1}H NMR). A mixture of starting material and ketone side product was recovered (42.4 mg) that by ^{1}H NMR integration was determined to contain 40.4 mg of **2e** (0.265 mmol, 27%) and 2.0 mg of 2-adamantanone (0.013 mmol, 1.3%), indicating chemoselectivity for aliphatic over alcohol oxidation of 31:1.
TLC (PMA, 80% EtOAc/Hexanes) R_f = 0.18
^{1}H NMR (800 MHz, CD_3OD): δ 3.68 (ap s, 1H), 2.11–2.07 (m, 4H), 2.03–2.00 (m, 1H), 1.72–1.66 (m, 4H), 1.63–1.60 (m, 2H), 1.46–1.42 (m, 2H) ppm.
^{13}C NMR (150 MHz, CD_3OD) δ 73.4, 68.2, 46.0, 39.5 (2C), 38.3 (2C), 36.1 (2C), 30.9 ppm.
NMR spectra are consistent with literature reports.[7–9]

(1*R*,2*R*,5*R*)-2-(2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol (3f) and

(1*S*,3*R*,4*S*)-4-isopropyl-1-methylcyclohexane-1,3-diol (3f')

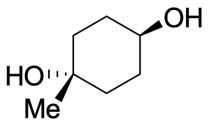


The title compounds were prepared according to the general hydroxylation procedure A from (–)-menthol (157 mg, 1 mmol, 1 equiv). After workup, the reaction mixture was purified by silica gel flash chromatography (25% to 50% EtOAc/hexanes) to give product **3f** as a colorless oil that slowly crystalized (46.2 mg, 0.268 mmol, 27% yield) and product **3f'** as a colorless oil (26.6 mg, 0.154 mmol, 15% yield). Also recovered unreacted menthol (60.3 mg, 39%). A total of 19% of the mass balance was unaccounted for, indicating ≥2:1 chemoselectivity.

(1*R*,2*R*,5*R*)-2-(2-hydroxypropan-2-yl)-5-methylcyclohexan-1-ol **(3f)**
TLC (PMA, 40% EtOAc/Hexanes) R_f = 0.44;
^{1}H NMR (800 MHz, $CDCl_3$): δ 3.99 (br s, 2H), 3.69 (td, J = 10.5, 4.3 Hz, 1H), 1.96–1.93 (m, 1H), 1.72–1.65 (m, 2H), 1.46–1.38 (m, 1H), 1.39–1.35 (m, 1H), 1.20 (s, 6H), 1.05–1.01 (m, 1H), 0.95–0.84 (m, 5H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 75.3, 73.1, 53.6, 44.8, 34.7, 31.5, 30.3, 27.3, 23.9, 22.1 ppm.
NMR spectra are consistent with literature reports.[10,11]

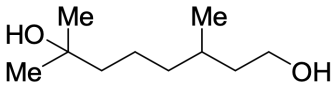
(1*S*,3*R*,4*S*)-4-isopropyl-1-methylcyclohexane-1,3-diol **(3f')**
TLC (PMA, 40% EtOAc/Hexanes) R_f = .22;
^{1}H NMR (800 MHz, $CDCl_3$): δ 3.76 (td, J = 10.7, 4.5 Hz, 1H), 2.20–2.16 (m, J = 7.9, 1H), 2.00 (ddd, J = 12.9, 4.5, 2.8 Hz, 1H), 1.63–1.61 (m, 1H), 1.50–1.47 (m, 1H), 1.40–1.31 (m, 3H), 1.25 (s, 3H), 1.15–1.10 (m, 1H), 0.95 (d, J = 7.0 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H) ppm.
^{13}C NMR (201 MHz, $CDCl_3$) δ 71.7, 68.7, 50.2, 48.3, 38.6, 31.7, 26.0, 21.2, 19.1, 16.3 ppm.
NMR spectra are consistent with literature reports.[11]

***trans*-1-methylcyclohexane-1,4-diol (3g)**



trans-1-methylcyclohexane-1,4-diol was prepared according to general hydroxylation procedure A from *cis*-4-methylcyclohexanol (114 mg, 125 µL, 1 mmol, 1 equiv). After workup, the reaction mixture was purified on by silica gel flash chromatography (25% to 50% EtOAc/hexanes) to give product as a white solid (45.8 mg, 0.352 mmol, 35% yield). Also isolated 4-methylcyclohexanone (4.9 mg, 4.4%, 8:1 chemoselectivity) and unreacted starting material (11 mg, 10%).
TLC (PMA, 50% EtOAc/Hexanes) $R_f = 0.15$.
^{1}H NMR (800 MHz, MeOD): δ 3.76–3.72 (m, 1H), 1.88–1.82 (m, 2H), 1.71–1.67 (m, 2H), 1.49–1.43 (m, 4H), 1.21 (s, 3H) ppm.
^{13}C NMR (200 MHz, MeOD) δ 70.3, 68.8, 36.2. (2C), 31.3 (2C)), 28.4 ppm.
NMR spectra are consistent with literature reports.[12]

3,7-dimethyloctane-1,7-diol (3h)

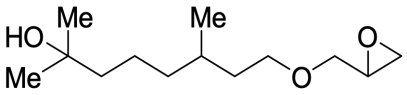


3,7-Dimethyloctane-1,7-diol was prepared according to the general hydroxylation procedure A from 3,7-dimethyloctan-1-ol (38.2 µL, 0.2 mmol, 1 equiv.) After workup, the reaction mixture was purified on a silica flash column (25% to 50% EtOAc/hexanes) to give product **4a** as a colorless oil (27.5 mg, 0.158 mmol, 79% yield). Also recovered starting material (6.2 mg, 0.039 mmol, 20% recovered). A total of 1% of the mass balance was unaccounted for, indicating ≥79:1 chemoselectivity and ≥79:1 site selectivity.

TLC (PMA, 50% EtOAc/Hexanes) $R_f = 0.28$.
^{1}H NMR (800 MHz, $CDCl_3$): δ 3.71–3.62 (m, 2H), 1.74 (br s, 2H), 1.62–1.54 (m, 2H), 1.47–1.27 (m, 6H), 1.20 (s, 6H), 1.151.16–1.12 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 71.2, 61.2, 44.2, 40.0, 37.7, 29.6, 29.4, 29.3, 21.8, 19.8 ppm.
NMR spectra are consistent with literature reports.[6]

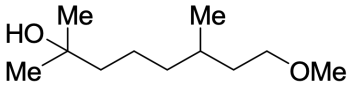
In a separate reaction, 3,7-dimethyloctan-1-ol (1.0 g, 6.3 mmol) was hydroxylated using the general hydroxylation procedure A above, with amounts of reagents adjusted to meet the larger scale. The product was isolated as a colorless oil (921 mg, 5.3 mmol, 84%). 3,7-dihydrocitronellal was also observed in mixed fractions after chromatography; chemoselectivity was determined to be ≥99:1 for **3h**:C1 aldehyde based on ^{1}H NMR integration.

2,6-dimethyl-8-(oxiran-2-ylmethoxy)octan-2-ol (3i)

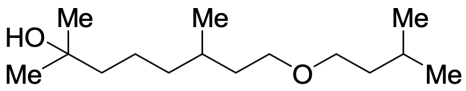


2,6-dimethyl-8-(oxiran-2-ylmethoxy)octan-2-ol was prepared according to the general hydroxylation procedure A from 2-(((3,7-dimethyloctyl)oxy)methyl)oxirane (42.9 mg, 0.2 mmol, 1 equiv). After workup, the reaction mixture was purified on by silica gel flash chromatography (25% to 50% EtOAc/hexanes) to give product (as an inseparable mixture of with 2° hydroxylation products) as a pale yellow oil (29.8 mg, 0.13 mmol, 65% yield, 2:1 site selectivity C7-3˚:2˚) along with recovered starting material **2i** (15 mg, 35%). Based on the complete balance of the starting material being accounted for, chemoselectivity for this reaction was determined to be ≥99:1.
TLC (PMA, 25% EtOAc/Hexanes) $R_f = 0.19$.
^{1}H NMR (800 MHz, $CDCl_3$): δ 3.72–3.69 (m, 1H), 3.57–3.46 (m, 2H), 3.38–3.35 (m, 1H), 3.15–3.13 (m, 1H), 2.80–2.78 (m, 1H), 2.61–2.59 (m, 1H), 1.67–1.61 (m, 2H), 1.59–1.55 (m, 1H), 1.47–1.26 (m, 6H), 1.20 (s, 6H), 1.18–1.11 (m, 1H), 0.89 (d, J = 6.7 Hz, 3H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 71.6, 71.2, 70.0, 51.1, 44.5, 44.3, 37.7, 36.8, 30.0, 29.5, 29.3, 21.8, 19.8 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{13}H_{26}O_3$ 253.1780, found 253.1777.

8-methoxy-2,6-dimethyloctan-2-ol (3j)



8-Methoxy-2,6-dimethyloctan-2-ol was prepared according to the general hydroxylation procedure A from 1-methoxy-3,7-dimethyloctane (174 mg, 1 mmol, 1 equiv). After workup, the reaction mixture was purified on by silica gel flash chromatography (10% to 25% EtOAc/hexanes) to give product **3j** (as an inseparable mixture with 2° hydroxylation products) as a clear oil (112.2 mg, 0.60 mmol, 60% yield, 5:1 site selectivity C7-3˚:2˚), along with recovered starting material **2j** (58 mg, 34%). With 6% of the material unaccounted for, overall chemoselectivity for the reaction was determined to be ≥10:1.
TLC (PMA, 20% EtOAc/Hexanes) $R_f = 0.25$.
^{1}H NMR (800 MHz, $CDCl_3$): δ 3.4–3.36 (m, 2H), 3.33 (s, 3H), 1.63–1.60 (m, 1H), 1.59–1.54, (m, 1H), 1.48–1.27 (m, 7H), 1.21 (s, 6H), 1.18–1.11 (m, 1H), 0.89 (d, J = 6.6 Hz, 3H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 71.3, 71.2, 58.7, 44.3, 37.8, 36.8, 30.0, 29.5, 29.4, 21.8, 19.8 ppm.
NMR spectra are consistent with literature reports.[6,13]
8-(isopentyloxy)-2,6-dimethyloctan-2-ol (3k)

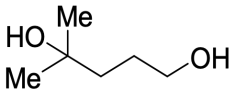


8-(Isopentyloxy)-2,6-dimethyloctan-2-ol was prepared according to the general hydroxylation procedure A using 1-(isopentyloxy)-3,7-dimethyloctane (46.7 mg, 0.2 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (10% to 20% EtOAc/hexanes) to give product as a clear oil (18.6 mg, 0.076 mmol, 38% yield). Also collected a mix of 2° (C5/C6)

hydroxylation diastereomers (3.3 mg, 6.7%, 6:1 site-selectivity for 3°/2° hydroxylation) and unreacted starting material (10 mg, 0.044 mmol, 22%). A minor peak was observed in the GC trace corresponding to 3,7-dimethyloctanal; comparison of peak area with that for **3k** indicated chemoselectivity of 41:1 for remote hydroxylation vs C1 oxidation.

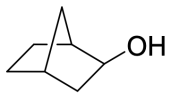
TLC (PMA, 10% EtOAc/Hexanes) $R_f = 0.27$.
^{1}H NMR (800 MHz, $CDCl_3$): δ 3.46–3.38 (m, 4H), 1.72–1.65 (m, 1H), 1.63–1.58 (m, 1H), 1.58–1.51 (m, 1H), 1.48–1.23 (m, 9H), 1.20 (s, 6H), 0.90–0.87 (m, 9H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 71.2, 69.5, 69.3, 44.3, 38.7, 37.8, 36.9, 30.1, 29.4, 29.3, 25.3, 22.80, 22.79, 21.8, 19.8 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{15}H_{32}O_2$ 267.2300, found 267.2316.

4-methylpentane-1,4-diol (3l)



4-Methylpentane-1,4-diol was prepared according to a modified version of hydroxylation procedure B from 4-methyl-1-pentanol (128 µL, 1 mmol, 1 equiv), using $NaHCO_3$ (420 mg, 5 mmol, 5 equiv), paraformaldehyde (60 mg, 2 mmol, 2 equiv), 1,2-bis(3,5-bis(trifluoromethyl)phenyl)diselane (5.8 mg, 0.01 mmol, 0.01 equiv), urea hydrogen peroxide (292 mg, 3 mmol, 3 equiv) and pyrrolidinium trifluoromethanesulfonate (221 mg, 1 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (2% to 5% MeOH/DCM) to give product **3l** as a white solid (50.8 mg, 0.430 mmol, 43% yield) and recovered starting material (33 mg, 0.28 mol, 28%).
TLC (PMA, 5% MeOH/DCM) $R_f = 0.33$.
^{1}H NMR (800 MHz, $CDCl_3$): δ 3.66–3.64 (m, 2H), 2.65–2.53 (m, 2H), 1.70–1.63 (m, 2H), 1.58–1.56 (m, 2H), 1.23 (s, 6H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 70.9, 63.6, 40.6, 29.6, 27.7 ppm.
NMR spectra are consistent with literature reports.[76]

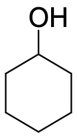
***exo*-norborneol (3m)**



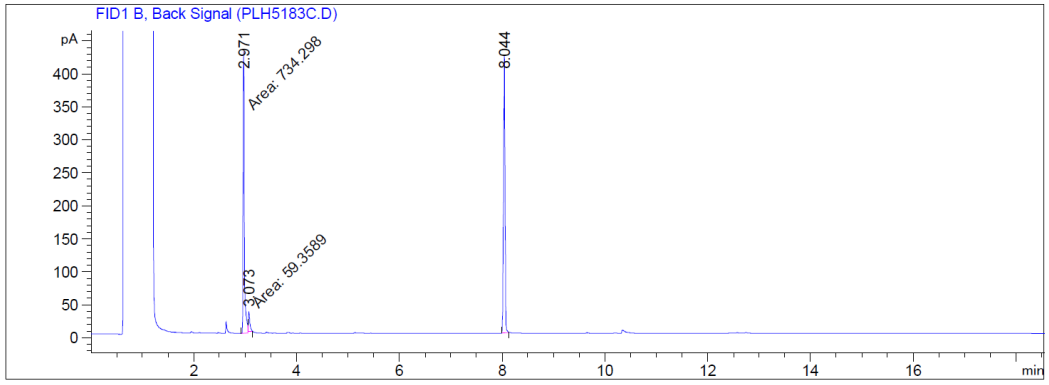
exo-Norborneol was prepared according to the general hydroxylation procedure A from norbornane (98 mg, 1 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (25% EtOAc/hexanes) to give product as a colorless, crystalline solid that sublimes easily at rt under reduced pressure (71.1 mg, 0.634 mmol, 63% yield, 13:1 exo/endo). Also isolated 2-oxabicyclo[3.2.1]octan-3-one (7.0 mg, 5.5%), indicating a alcohol:ketone selectivity of 12:1.
TLC (PMA, 25% EtOAc/Hexanes) $R_f = 0.49$.

^{1}H NMR (600 MHz, $CDCl_3$): δ 3.75 (d, J = 6.9 Hz, 1H), 2.40–2.20 (m, 1H), 2.20–2.10 (m, 1H), 1.90–1.78 (m, 1H), 1.67–1.64 (m, 1H), 1.58–1.25 (m, 4H), 1.14–1.10 (m, 1H), 1.04–0.97 (m, 2H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 75.2, 44.3, 42.3, 35.5, 34.5, 28.2, 24.5 ppm.
NMR spectra are consistent with literature reports.[13]

cyclohexanol (3n)



Cyclohexanol was prepared according to the general hydroxylation procedure A, with the exception that gas chromatography of the crude reaction mixture was used to determine yield, from cyclohexane (21.6 µL, 0.2 mmol, 1 equiv). Mixtures of authentic samples of cyclohexanol and cyclohexanone each with *n*-dodecane were analyzed by GC to determine burn ratio of 2.35 for cyclohexanol and 2.42 for cyclohexanone. Upon completion, reaction was cooled and diluted with CH_2Cl_2 (10 mL). *n*-Dodecane (0.3 eq, 0.066 mmol, 15 µL) was added as an internal standard and reaction was sampled and analyzed on GC-FID to give a corrected yield of 68% of **3n** and 5% of cyclohexanone.

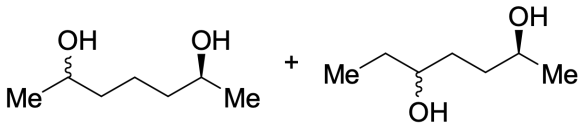



```
=====================================================================
                      Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   2.971 MM    0.0284  734.29797  431.11108 44.39845
   2   3.073 MM    0.0324   59.35893   30.57620  3.58907
   3   8.044 BB    0.0318  860.22510  421.08594 52.01248
```

Compound

cyclohexanol
cyclohexanone
n-dodecane

2,6-heptanediol (3o) and 2,5-heptanediol (3o')

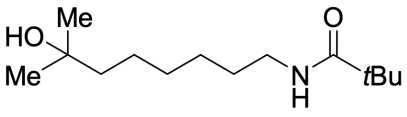


The title compounds were prepared according to the general hydroxylation procedure A from 2-heptanol (116 mg, 142 μL, 1 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (50% to 75% EtOAc/hexanes) to give product **3o** as a pale-yellow oil (30.5 mg, 0.231 mmol, 23% yield, 1:1 d.r.) and product **3o'** as a pale-yellow oil (16.3 mg, 0.123 mmol, 12% yield, 1:1 d.r.). Also recovered unreacted starting material (73 mg, 63%) and 2-heptanone (2.2 mg, 2%), indicating 18:1 chemoselectivity and 2:1 site selectivity. Based on mass balance, ≤1% of the material was accounted for, indicating ≥35:1 selectivity for C5/C6 alcohol vs C5/C6 ketone products.

2,6-heptanediol, 1:1 mixture of diastereomers **(3o)**
TLC (PMA, 75% EtOAc/Hexanes) R_f = 0.21
^{1}H NMR (800 MHz, CD_3OD): δ 3.74–3.70 (m, 2H), 1.55–1.30 (m, 6H), 1.15 (d, J = 6.2 Hz, 6H) ppm.
^{13}C NMR (200 MHz, CD_3OD) δ 68.5, 40.2, 40.2, 23.48, 23.47, 23.15, 23.10 ppm.
NMR spectra are consistent with literature reports.[14]

2,5-heptanediol, 1:1 mixture of diastereomers **(3o')**
TLC (PMA, 75% EtOAc/Hexanes) R_f = 0.29
^{1}H NMR (800 MHz, CD_3OD): δ 3.75–3.70 (m, 1H), 3.46–3.42 (m, 1H), 1.64–1.28 (m, 6H), 1.16 (d, J = 6.1 Hz, 3H), 0.94 (t, J = 7 Hz, 3H) ppm.
^{13}C NMR (200 MHz, CD_3OD) δ 74.1, 73.9, 68.9, 68.6, 36.4, 36.3, 34.2, 34.0, 31.08, 31.07, 23.6, 23.5, 10.38, 10.36 ppm;
NMR spectra are consistent with literature reports.[15]

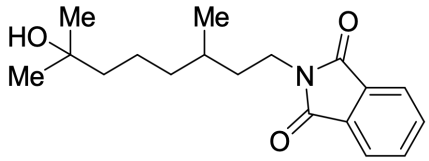
***N*-(7-hydroxy-7-methyloctyl)pivalamide (3p)**



N-(7-hydroxy-7-methyloctyl)pivalamide was prepared according to the general hydroxylation procedure A from N-(7-methyloctyl)pivalamide (45.7 mg, 0.201 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (25% to 50% EtOAc/hexanes) to give product as a colorless oil (34.2 mg, 0.140 mmol, 70% yield). Also collected distal (C6) 2° hydroxylation product (2.3 mg, 0.0094 mmol, 4.7%, 15:1 site selectivity).

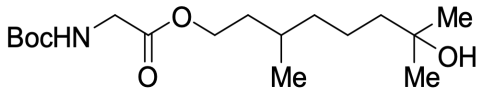
TLC (PMA, 50% EtOAc/Hexanes) $R_f = 0.22$
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.60 (br s, 1H), 3.22 (dt, J = 7.2, 5.8 Hz, 2H), 1.52–1.41 (m, 4H), 1.37–1.27 (m, 6H), 1.20 (s, 6H), 1.18 (s, 9H) ppm.
^{13}C NMR (151 MHz, $CDCl_3$) δ 178.8, 71.2, 43.9, 39.7, 38.8, 29.9, 29.7, 29.4 (2C) , 27.7 (3C), 27.0, 24.3 ppm.
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{29}NO_2$ 244.2277, found 244.2274.

2-(7-hydroxy-3,7-dimethyloctyl)isoindoline-1,3-dione (3q)



2-(7-Hydroxy-3,7-dimethyloctyl)isoindoline-1,3-dione was prepared according to the general hydroxylation A procedure from 2-(3,7-dimethyloctyl)isoindoline-1,3-dione (73.2 mg, 0.255 mmol, 1 equiv). After workup, the reaction mixture was purified by silica gel flash chromatography (10% to 25% EtOAc/hexanes) to give product **3q** as a pale yellow oil (38.5 mg, 0.127 mmol, 50% yield). Starting material (32.7 mg, 0.114 mmol, 45%) and a mixture of secondary hydroxylation products (3.4 mg, 0.011 mmol, 4.3%) were also collected, indicating 12:1 site selectivity. A total of 0.7% of the mass balance was unaccounted for, indicating ≥78:1 chemoselectivity for aliphatic C–H hydroxylation over other oxidation reactions.
TLC (PMA, 25% EtOAc/Hexanes) $R_f = 0.32$.
^{1}H NMR (800 MHz, $CDCl_3$): δ 7.81 (dd, J = 5.5, 3.0 Hz, 2H), 7.68 (dd, J = 5.5, 3.0 Hz, 2H), 3.72–3.64 (m, 2H), 1.71–1.65 (m, 1H), 1.51–1.26 (m, 8H), 1.18 (s, 6H), 0.96 (d, J = 6.4 Hz, 3H) ppm.
^{13}C NMR (200 MHz, $CDCl_3$) δ 168.5 (2C), 133.9 (2C), 132.3 (2C), 123.2 (2C), 71.0, 44.2, 37.3, 36.4, 35.5, 30.7, 29.4, 29.3, 21.6, 19.5 ppm.
NMR spectra are consistent with literature reports.[13]

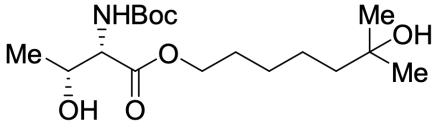
7-hydroxy-3,7-dimethyloctyl (tert-butoxycarbonyl)glycinate (3r)



7-hydroxy-3,7-dimethyloctyl (tert-butoxycarbonyl)glycinate was prepared according to the general hydroxylation procedure A from 3,7-dimethyloctyl (tert-butoxycarbonyl)glycinate (63 mg, 0.2 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (99% to 95% DCM/MeOH) to give product **3r** as a colorless oil (30 mg, 0.09 mmol, 45% yield). Also recovered unreacted starting material (32 mg, 50%). A total of 5% of the mass balance was unaccounted for, indicating ≥9:1 chemoselectivity and site selectivity.
^{1}H NMR (800 MHz, $CDCl_3$) δ 5.01 (br s, 1H), 4.20 (m, 2H), 3.89 (m, 2H), 1.71-1.64 (m, 1H), 1.60-1.52 (m, 2H), 1.45 (s, 11H), 1.35-1.27 (m, 3H), 1.21 (s, 6H), 1.18-1.13 (m, 1H), 0.91 (d, J=6.4 Hz, 3H).

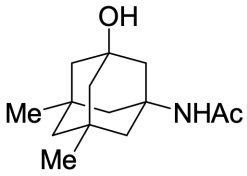
^{13}C NMR (200 MHz, $CDCl_3$) δ 170.6, 155.8, 80.1, 71.1, 64.0, 44.2, 42.6, 37.4, 35.5, 29.9, 29.5, 29.4, 28.5 (3C), 21.7, 19.6 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}H_{33}NO_5$ 354.2257, found 354.2257.

6-hydroxy-6-methylheptyl (tert-butoxycarbonyl)-*L*-threoninate (3s)



6-hydroxy-6-methylheptyl (tert-butoxycarbonyl)-L-threoninate was prepared according to a modified version of general hydroxylation procedure B from 6-methylheptyl (tert-butoxycarbonyl)-*L*-threoninate (44 mg, 0.128 mmol, 1 equiv), using $NaHCO_3$ (54.1 mg, 0.64 mmol, 5 equiv), paraformaldehyde (8.0 mg, 0.256 mmol. 2 equiv), 1,2-bis(3,5-bis(trifluoromethyl)phenyl)diselane (0.8 mg, 0.0013 mmol. 0.01 equiv), urea hydrogen peroxide (37.5 mg, 0.384 mmol, 3 equiv), and pyrrolidinium trifluoromethanesulfonate (28.8 mg, 0.128 mmol, 1 equiv) in 1,1,1,3,3,3-hexafluoroisopropanol (1.3 mL). After workup, the reaction mixture was purified on a silica flash column (25% to 50% EtOAc/hexanes) to give product **3s** as colorless oil (16.8 mg, 0.0484 mmol, 38% yield). Also recovered unreacted starting material (28.0 mg, 62%). Chemoselectivity and site selectivity determined as ≥99:1 based on 100% combined yield of **3s** and starting material.
TLC (PMA, 50% EtOAc/Hexanes) R_f = 0.28.
^{1}H NMR (600 MHz, $CDCl_3$): δ 5.31 (br d, J = 9.1 Hz, 1H), 4.34–4.12 (m, 4H), 1.71–1.67 (m, 2H), 1.49–1.45 (m, 11H), 1.43–1.35 (m, 4H), 1.25 (d, J = 6.4 Hz, 3H), 1.21 (s, 6H) ppm.
^{13}C NMR (201 MHz, $CDCl_3$) δ 171.7, 156.3, 80.2, 71.1, 68.3, 65.8, 58.9, 43.8, 29.45, 29.44, 28.5 (3C), 26.6, 23.9 (2C), 20.2 ppm.
HRMS (ESI/QTOF) m/z: $[M + H]^+$ Calcd for $C_{17}H_{33}NO_6$ 370.2206, found 370.2210.

***N*-(3-hydroxy-5,7-dimethyladamantan-1-yl)acetamide (3t)**

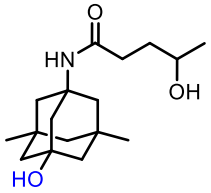


N-(3-Hydroxy-5,7-dimethyladamantan-1-yl)acetamide was prepared according to the general hydroxylation procedure A from *N*-(3,5-dimethyladamantan-1-yl)acetamide (221.3 mg, 1.0 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (0% to 10% MeOH/EtOAc) to give product as colorless solid (202 mg, 0.85 mmol, 85% yield).
TLC (PMA, 90% EtOAc/Hexanes) R_f = 0.15.
^{1}H NMR (800 MHz, $CDCl_3$): δ 5.21 (br s, 1H), 1.91 (s, 3H), 1.87 (s, 2H), 1.60 (br s, 1H), 1.65–1.57 (m, 4H), 1.42–1.40 (m, 2H), 1.34–1.32 (m, 2H), 1.14–1.07 (m. 2H), 0.92 (s, 6H) ppm.

^{13}C NMR (200 MHz, $CDCl_3$) δ 169.8, 70.4, 55.3 (2C), 50.4, 49.6, 47.6, 46.6 (2C), 34.2, 29.3 (2C), 24.6 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{14}H_{23}NO_2$ 260.1627, found 260.1630.

In a separate reaction, *N*-(3,5-dimethyladamantan-1-yl)acetamide (221.3 mg, 1.0 mmol) was hydroxylated using the general hydroxylation procedure B. The product was isolated as a colorless solid (209 mg, 0.88 mmol, 88%).

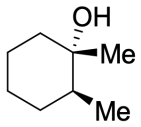
4-hydroxy-N-((1r,3s,5R,7S)-3-hydroxy-5,7-dimethyladamantan-1-yl)pentanamide (3u)



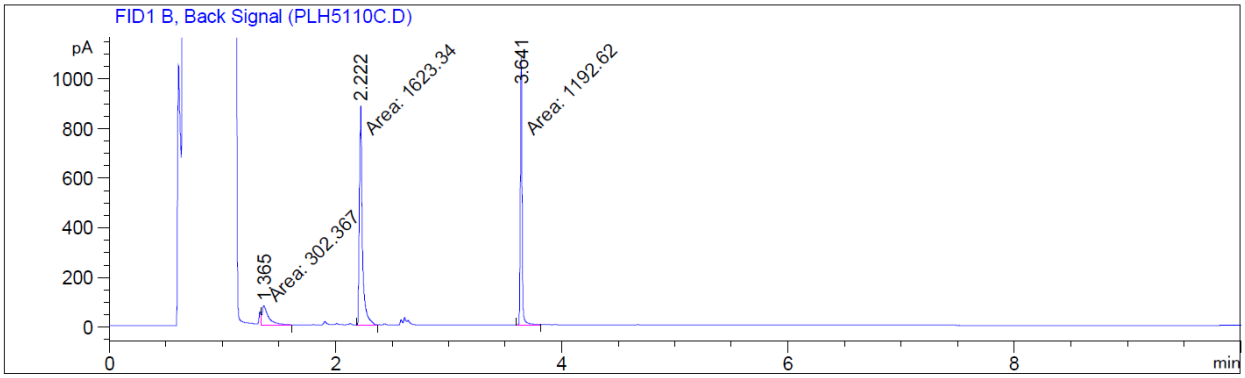
The title compound was prepared according to the general hydroxylation procedure from N-((1r,3R,5S,7r)-3,5-dimethyladamantan-1-yl)-4-hydroxypentanamide (56 mg, 0.2 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (0% to 10% MeOH/CH_2Cl_2) to give product as colorless solid (32 mg, 0.11 mmol, 55% yield) along with recovered starting material (25 mg, 0.089 mmol, 45% yield). Since the combined yield of starting material and product was 100%, both site selectivity and chemoselectivity of the reaction were calculated to be ≥99:1.

TLC (PMA, 10 % MeOH/CH_2Cl_2) R_f = 0.4.
^{1}H NMR (800 MHz, CD_3OD) δ 3.71 (m, 1H), 3.35 (s, 2H), 2.21 (m, 2H), 1.85 (s, 2H), 1.72–1.60 (m, 4H), 1.56 (d, J = 12.0 Hz, 2H), 1.38 (d, J = 11.5 Hz, 2H), 1.31 (d, J = 11.6 Hz, 2H), 1.16 (d, 3H), 1.14–1.07 (m, 2H), 0.92 (s, 6H) ppm.
^{13}C NMR (201 MHz, CD_3OD) δ 175.5, 70.8, 68.0, 56.0, 51.2 (2C), 50.7, 49.9, 47.9, 47.3, 36.1, 34.9 (2C), 34.4, 29.9 (2C), 23.4 ppm.
HRMS (ESI/QTOF) m/z: $[M + Na]^+$ Calcd for $C_{17}N_{29}NO_3$ 318.2045, found 318.2048.

***cis*-1,2-dimethylcyclohexan-1-ol (3v)**

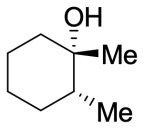


cis-1,2-Dimethylcyclohexan-1-ol was prepared according to general hydroxylation procedure B from *cis*-1,2-dimethylcyclohexane (28.1 µL, 0.2 mmol, 1 equiv). The reaction was performed at 23 °C for 24 hr. Mixtures of authentic samples of **3v** and *n*-dodecane were analyzed by GC to determine a burn ratio of 2.02. Upon completion, reaction was cooled and diluted with DCM (10 mL). *n*-Dodecane (0.0661 mmol, 15 µL) was added as an internal standard and reaction was sampled and analyzed on GC-FID to give a corrected yield of 90% of **3v**.




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 B, Back Signal

Peak RetTime Type  Width     Area      Height     Area      Compound
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
   1   1.365 MM    0.0656  302.36667   76.81073  9.69642     cis-1,2-dimethylcyclohexane
   2   2.222 MM    0.0307 1623.34253  882.28430 52.05804     cis-1,2-dimethylcyclohexane-1-ol
   3   3.641 MM    0.0183 1192.62292 1084.78296 38.24554     n-dodecane
```

***trans*-1,2-dimethylcyclohexan-1-ol (3w)**



trans-1,2-dimethylcyclohexan-1-ol was prepared according to the general hydroxylation procedure A using *trans*-1,2-dimethylcyclohexane (28.8 µL, 0.2 mmol, 1 equiv). After workup, the reaction mixture was purified on a silica flash column (15% EtOAc/hexanes) to give product **3w** as yellow oil (17.8 mg, 0.14 mmol, 70% yield).
TLC (PMA, 20% EtOAc/Hexanes) R_f = 0.88.
^{1}H NMR (600 MHz, $CDCl_3$) δ 1.70–1.17 (m, 10H), 1.15 (s, 3H), 0.88 (d, J = 6.7 Hz, 3H) ppm.
^{13}C NMR (150 MHz, $CDCl_3$) δ 71.3, 40.4, 40.0, 30.7, 28.7, 26.0, 22.2, 15.3 ppm.
NMR spectra are consistent with literature reports.[16]

5. References

(1) Handoko; Benslimane, Z.; Arora, P. S. Diselenide-Mediated Catalytic Functionalization of Hydrophosphoryl Compounds. *Org. Lett.* **2020**, *22*, 5811.

(2) Hatzakis, N. S.; Smonou, I. Asymmetric Transesterification of Secondary Alcohols Catalyzed by Feruloyl Esterase from Humicola Insolens. *Bioorganic Chem.* **2005**, *33*, 325.

(3) Nishida, A.; Honma, N.; Nakajima, T.; Mizoshita, M.; Itami, K. Latent Heat Storage Material. JP2016190894 (A), November 10, 2016.

(4) Lin, J.; Chen, F.; Wang, S.; Xu, X.; Kuang, Z.; Shen, X.; Zhu, W.; Chen, W.; Li, M. Method for Synthesizing N-Alkanoyl Memantine. CN109824534 (A), May 31, 2019.

(5) Huang, H.; Liu, G.; Ren, J.; Chen, D.; Li, Y.; Su, Z. IDO Inhibitor Compound, Pharmaceutical Compound and Application. CN107176956 (A), September 19, 2017.

(6) Wang, D.; Shuler, W. G.; Pierce, C. J.; Hilinski, M. K. An Iminium Salt Organocatalyst for Selective Aliphatic C–H Hydroxylation. *Org. Lett.* **2016**, *18*, 3826.

(7) Geluk, H. W.; Schlatmann, J. L. M. A. Hydride Transfer Reactions of the Adamantyl Cation—II: Synthesis of 1,3- and 1,4-Disubstituted Adamantanes. *Tetrahedron* **1968**, *24*, 5369.

(8) Mitsukura, K.; Sakamoto, H.; Kubo, H.; Yoshida, T.; Nagasawa, T. Bioconversion of 1-Adamantanol to 1,3-Adamantanediol Using Streptomyces Sp. SA8 Oxidation System. *J. Biosci. Bioeng.* **2010**, *109*, 550.

(9) Cheung, C. K.; Tseng, L. T.; Lin, M. H.; Srivastava, S.; Le Noble, W. J. Geometric Equivalents of Enantiomers in Studies of the Stereochemical Course of Substitution at Carbon. Electronic Effects in Nucleophilic Addition to Carbonyl Groups and to Carbocations. Virtual Proof of the Existence of .Sigma. Participation by Unstrained Carbon-Carbon Bonds. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

(10) Hong, B.-C.; Wu, M.-F.; Tseng, H.-C.; Liao, J.-H. Enantioselective Organocatalytic Formal [3 + 3]-Cycloaddition of α,β-Unsaturated Aldehydes and Application to the Asymmetric Synthesis of (−)-Isopulegol Hydrate and (−)-Cubebaol. *Org. Lett.* **2006**, *8*, 2217.

(11) Asakawa, Y.; Matsuda, R.; Tori, M.; Hashimoto, T. Preparation of Biologically Active Substances and Animal and Microbial Metabolites from Menthols, Cineoles and Kauranes. *Phytochemistry* **1988**, *27*, 3861.

(12) Bushweller, J. H.; Anzalone, L.; Spencer, T. A. Synthesis of Cis- and Trans-1-Methylcyclohexane-1,4-Diols and Their 4-Hemisuccinate Esters. *Synth. Commun.* **1989**, *19*, 745.

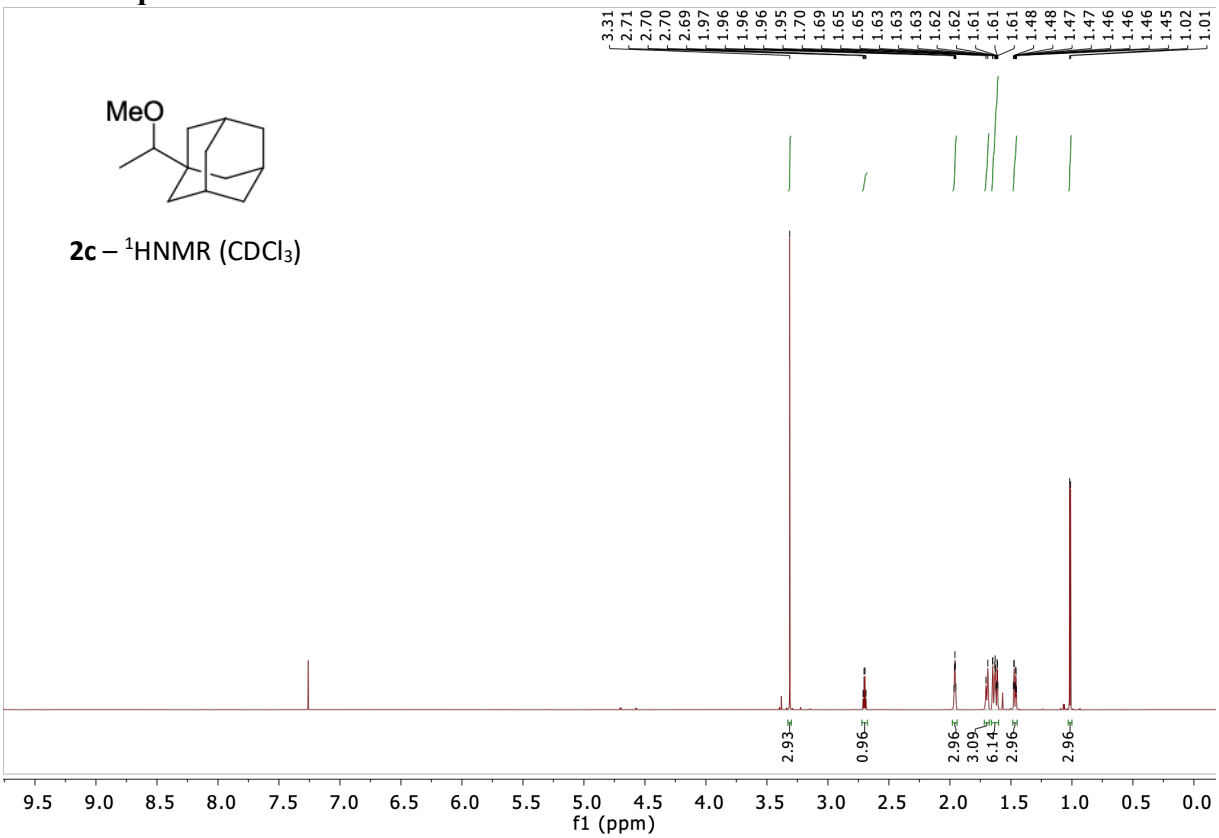
(13) Shuler, W. G.; Johnson, S. L.; Hilinski, M. K. Organocatalytic, Dioxirane-Mediated C–H Hydroxylation under Mild Conditions Using Oxone. *Org. Lett.* **2017**, *19*, 4790.

(14) Overberger, C. G.; Merkel, T. F. Syntheses of Seven-Membered Cyclic Azo Compounds. *J. Org. Chem.* **1981**, *46*, 442.

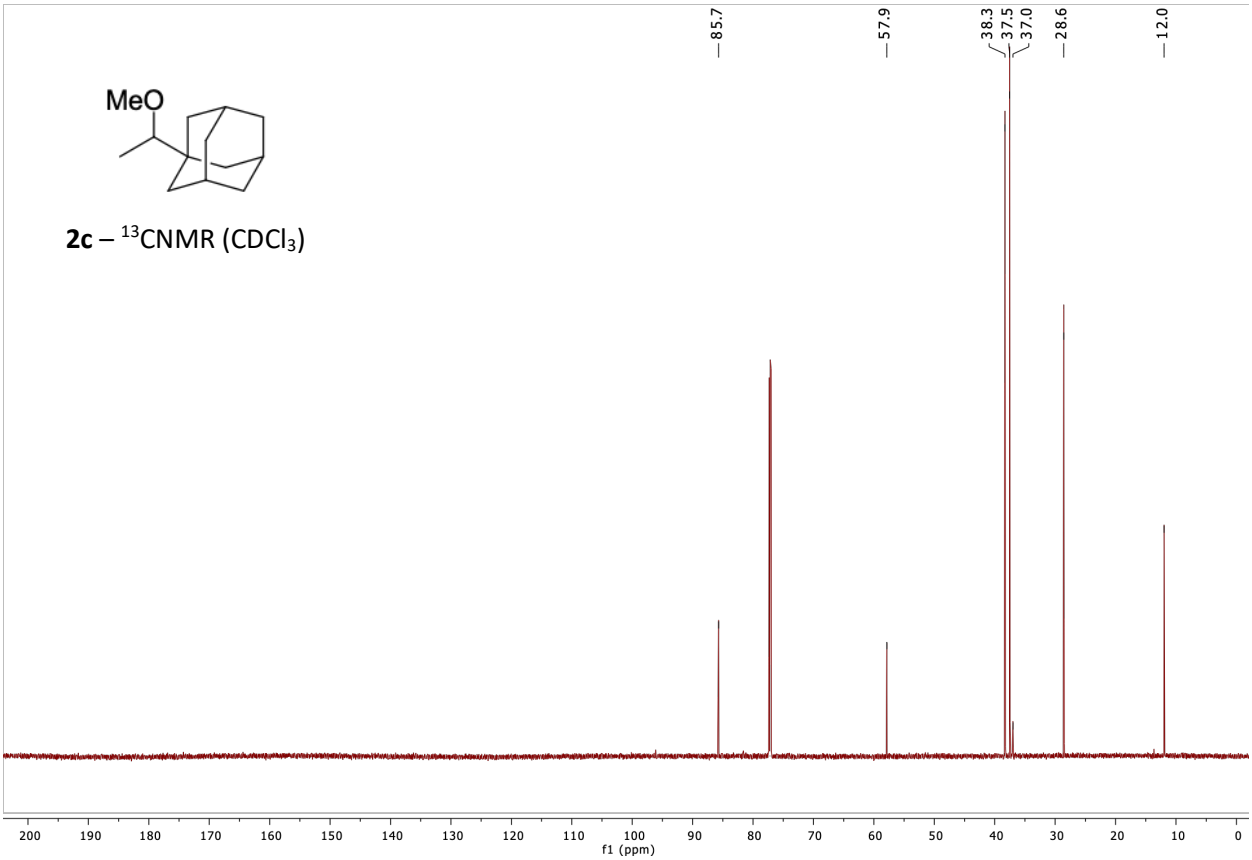
(15) Borén, L.; Leijondahl, K.; Bäckvall, J.-E. Dynamic Kinetic Asymmetric Transformation of 1,4-Diols and the Preparation of Trans-2,5-Disubstituted Pyrrolidines. *50th Anniv. Spec. Issue* **2009**, *50*, 3237.

(16) Larson, G. L.; Prieto, J. A.; Ortiz, E. The Preparation and Chemistry of (r)-(1-Naphthyl)Phenylmethylsilylmethyllithium: Stereochemistry at Silicon in the Elimination of β-Hydroxysilanes. *Tetrahedron* **1988**, *44*, 3781.

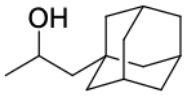
6. NMR Spectra



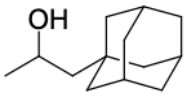
2c – ^{1}HNMR ($CDCl_3$)



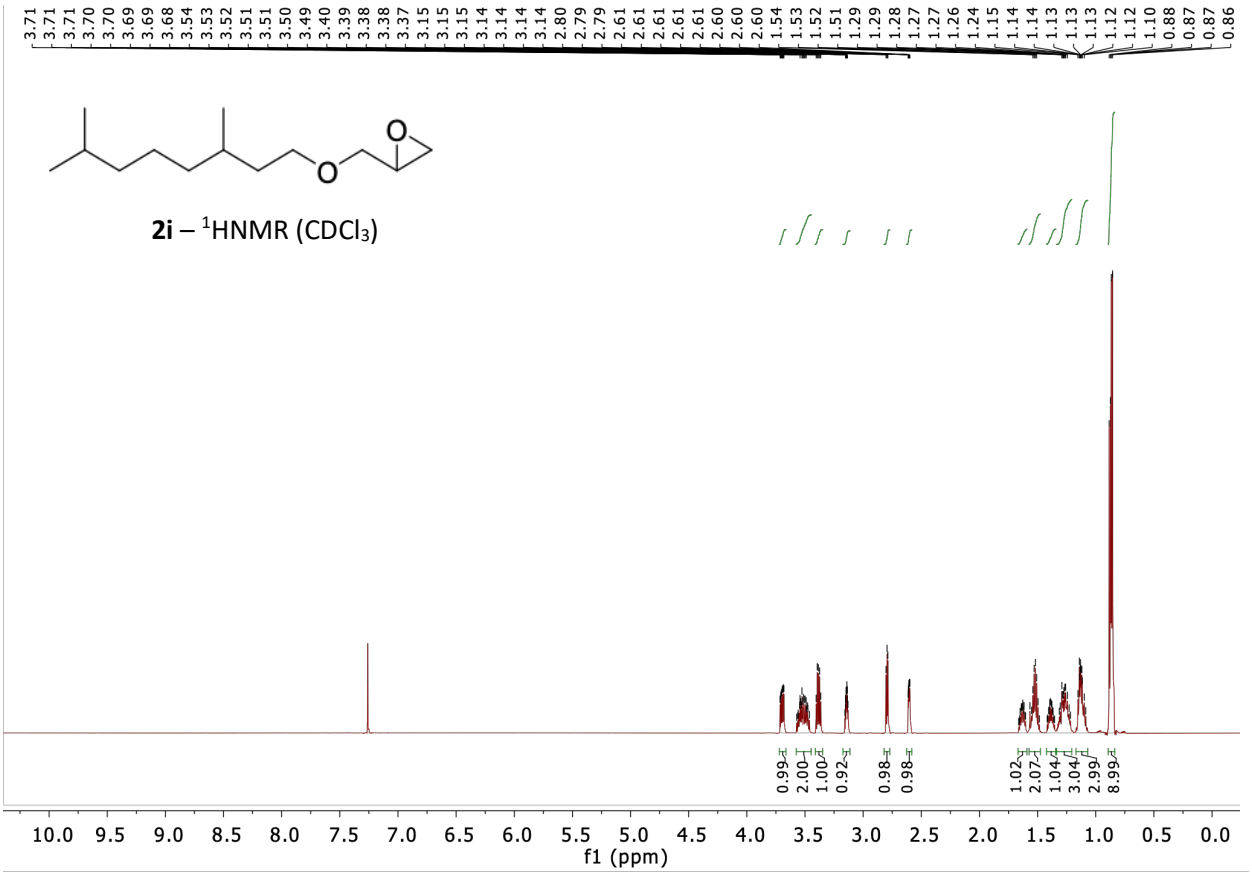
2c – ^{13}CNMR ($CDCl_3$)



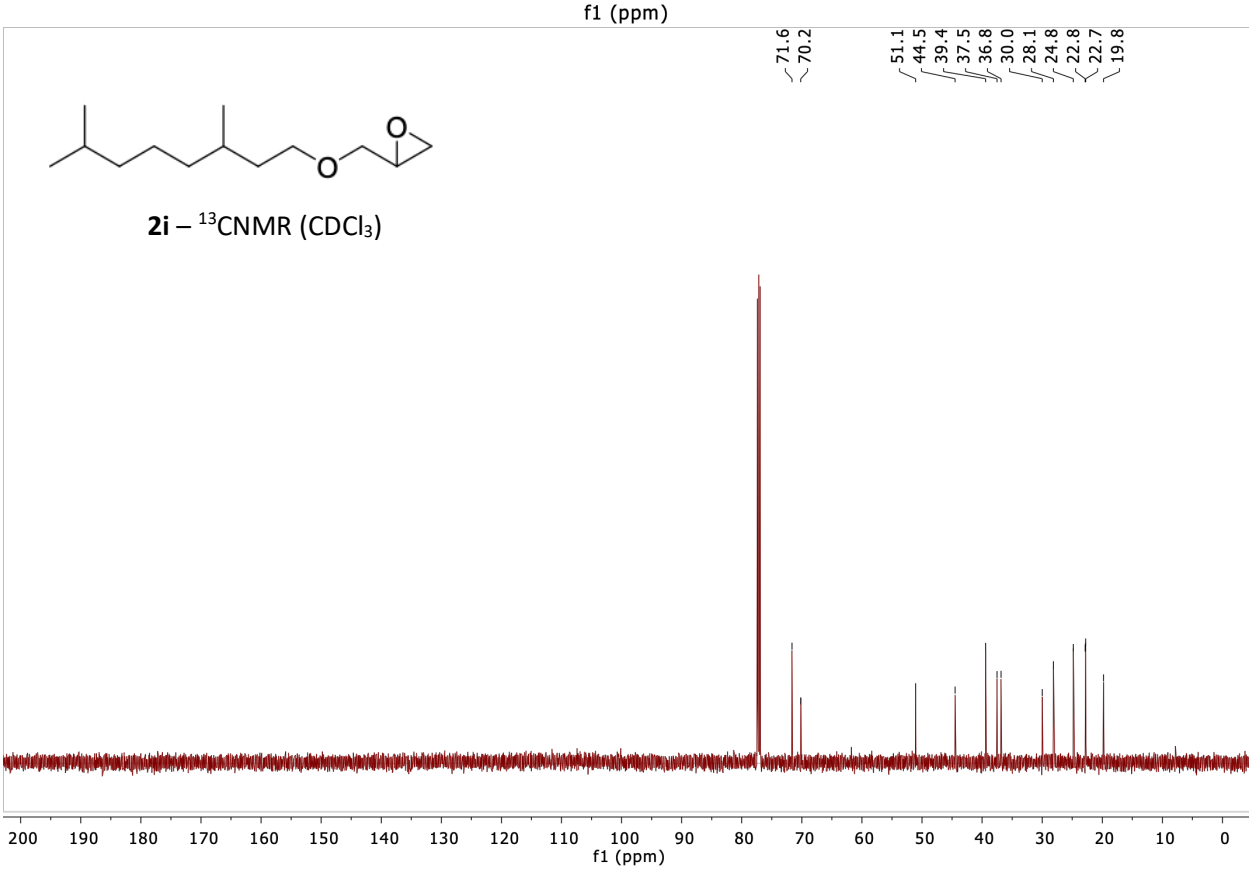
2d – ^{1}HNMR ($CDCl_3$)



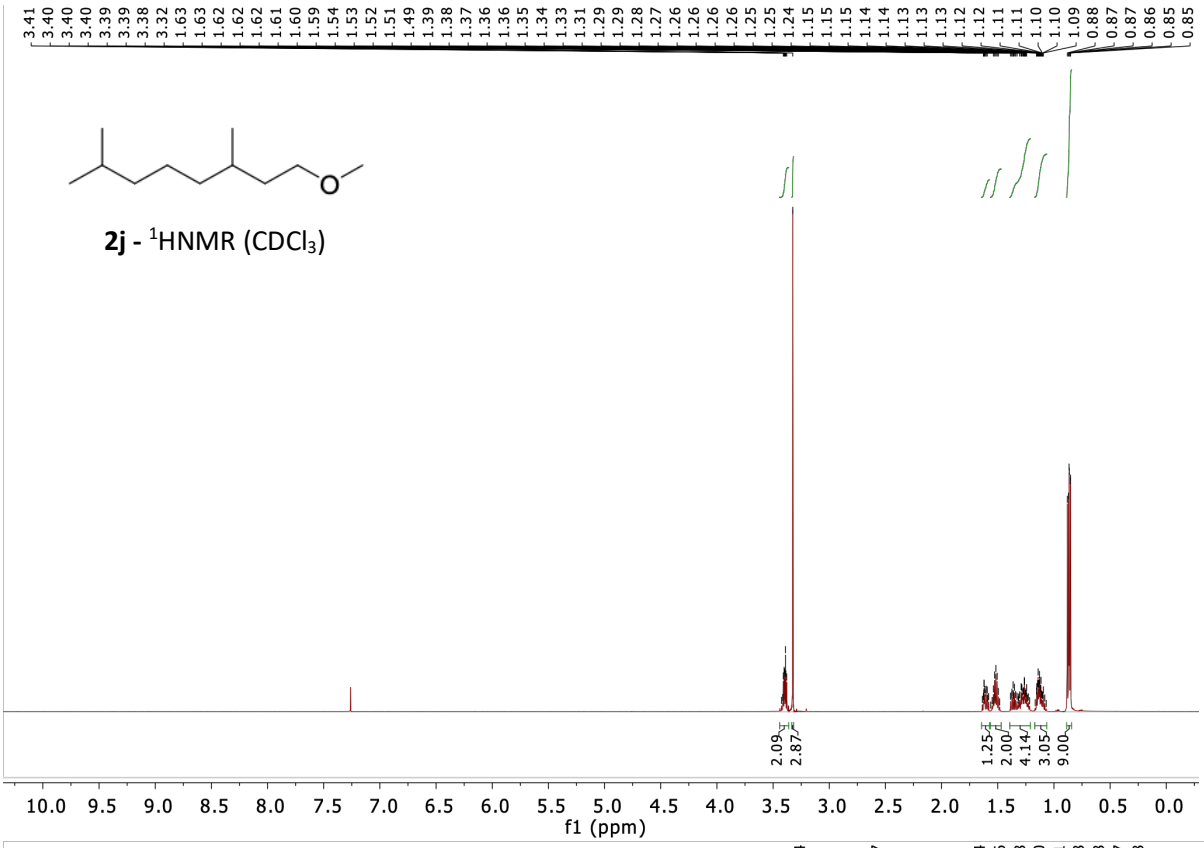
2d – ^{13}CNMR ($CDCl_3$)



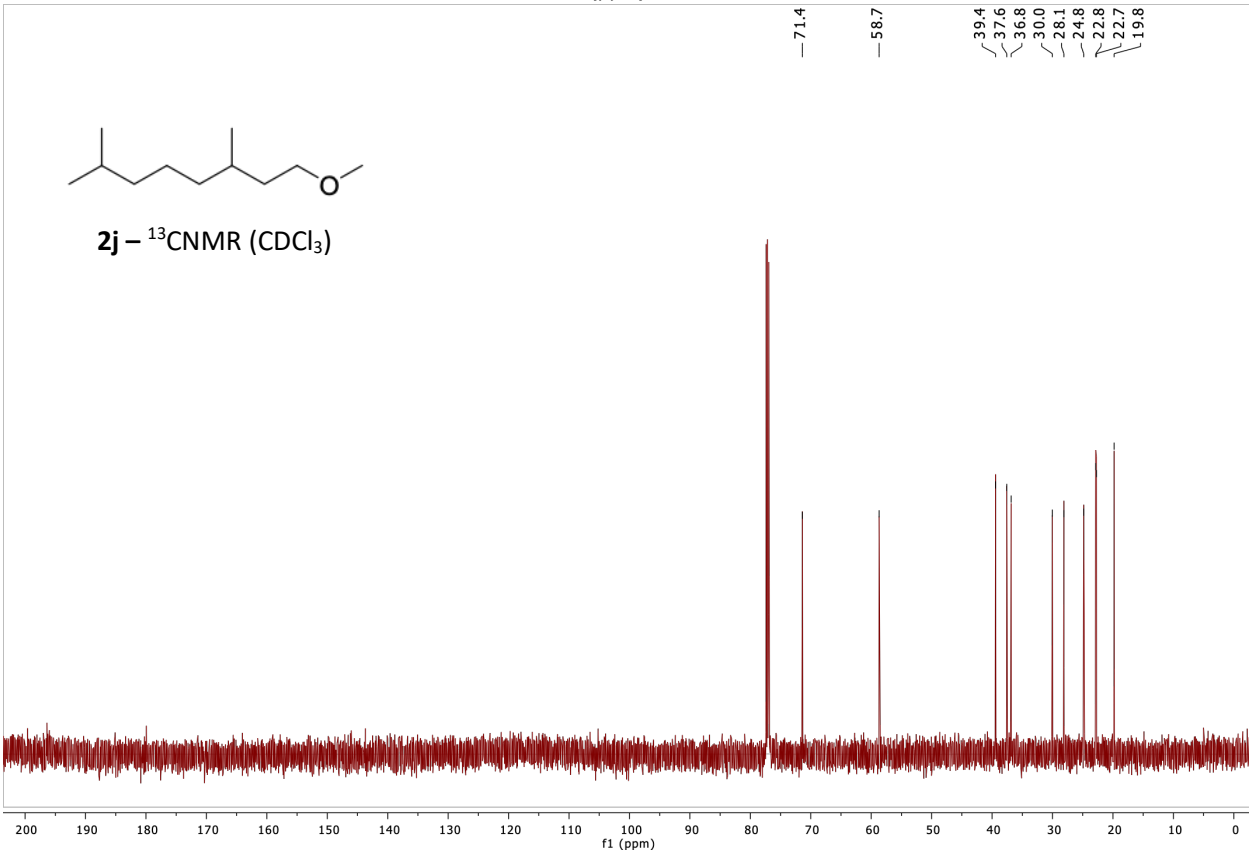
2i – ^{1}HNMR ($CDCl_3$)



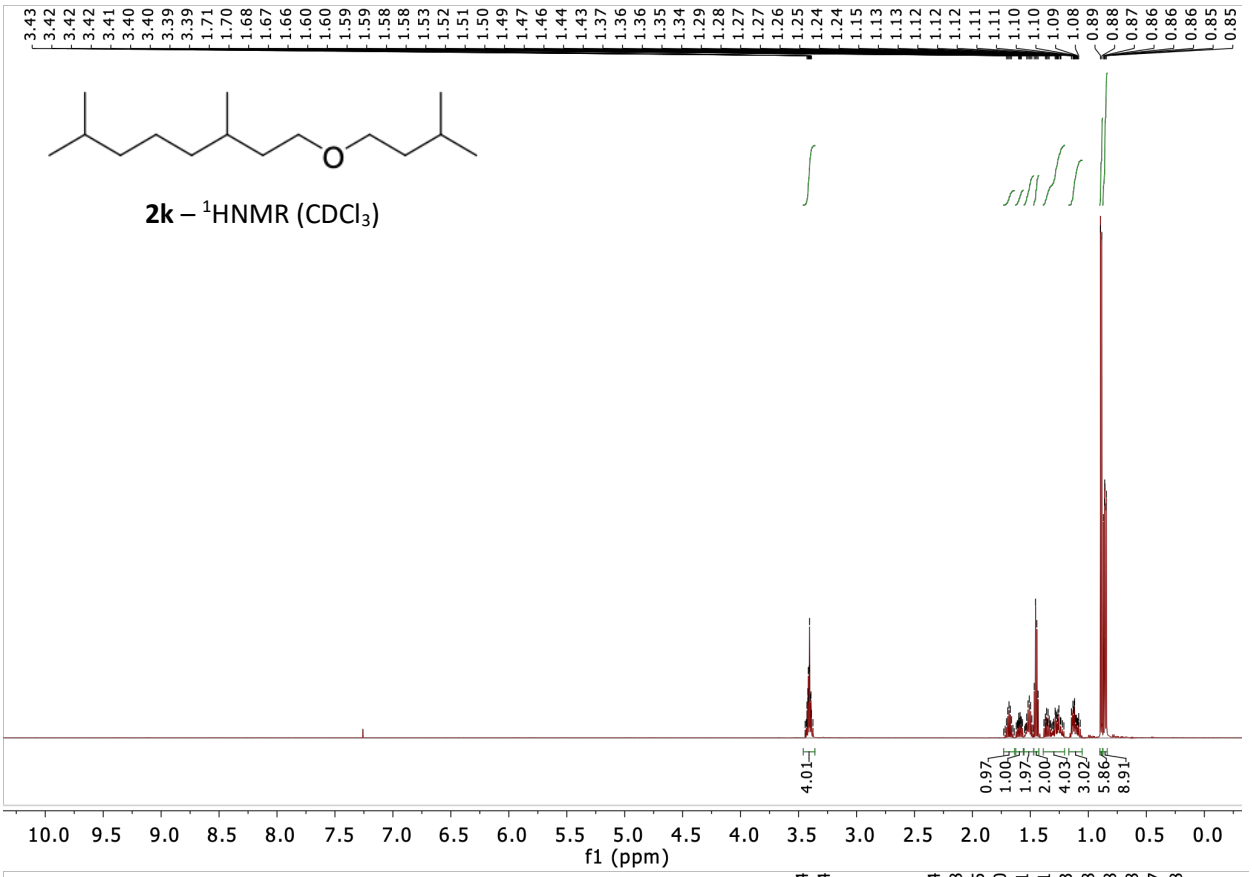
2i – ^{13}CNMR ($CDCl_3$)



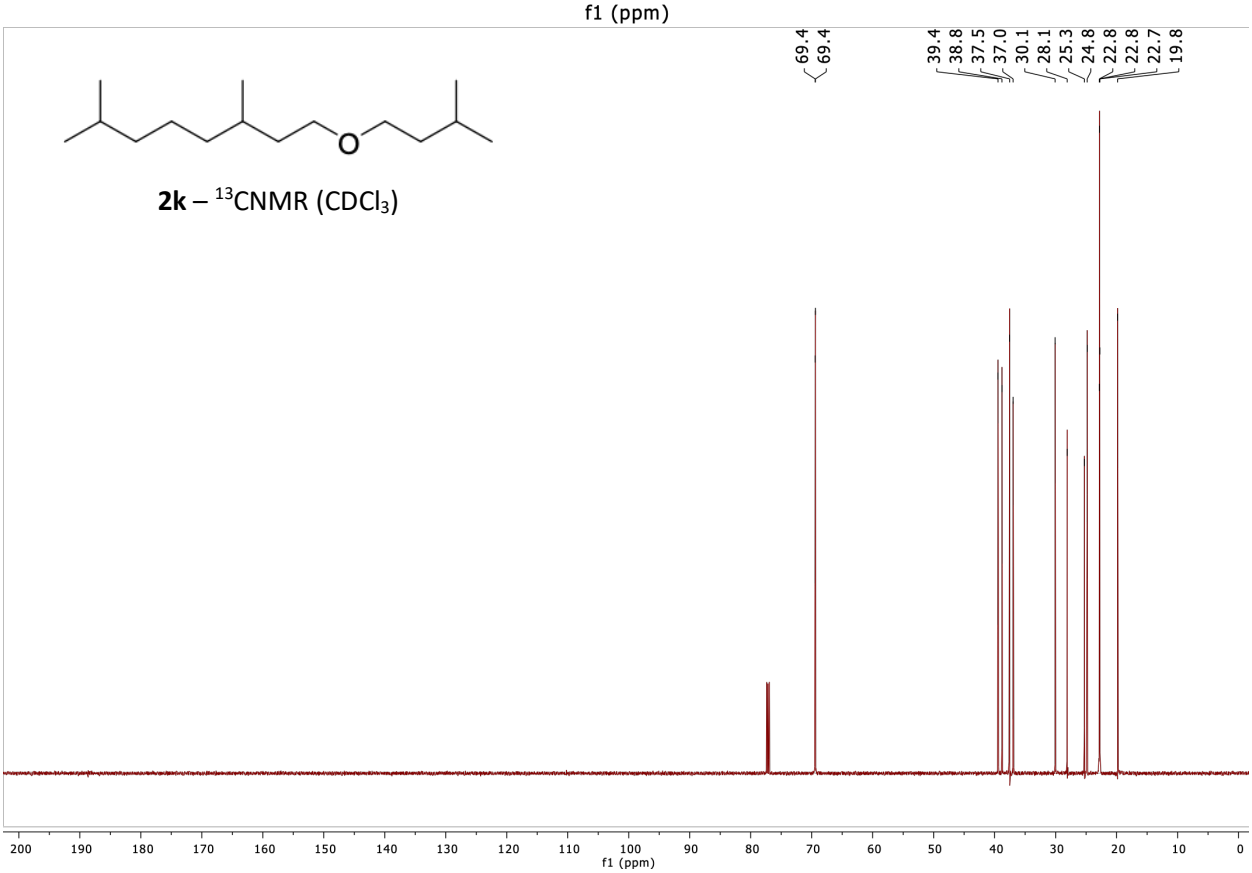
2j - ^{1}HNMR ($CDCl_3$)



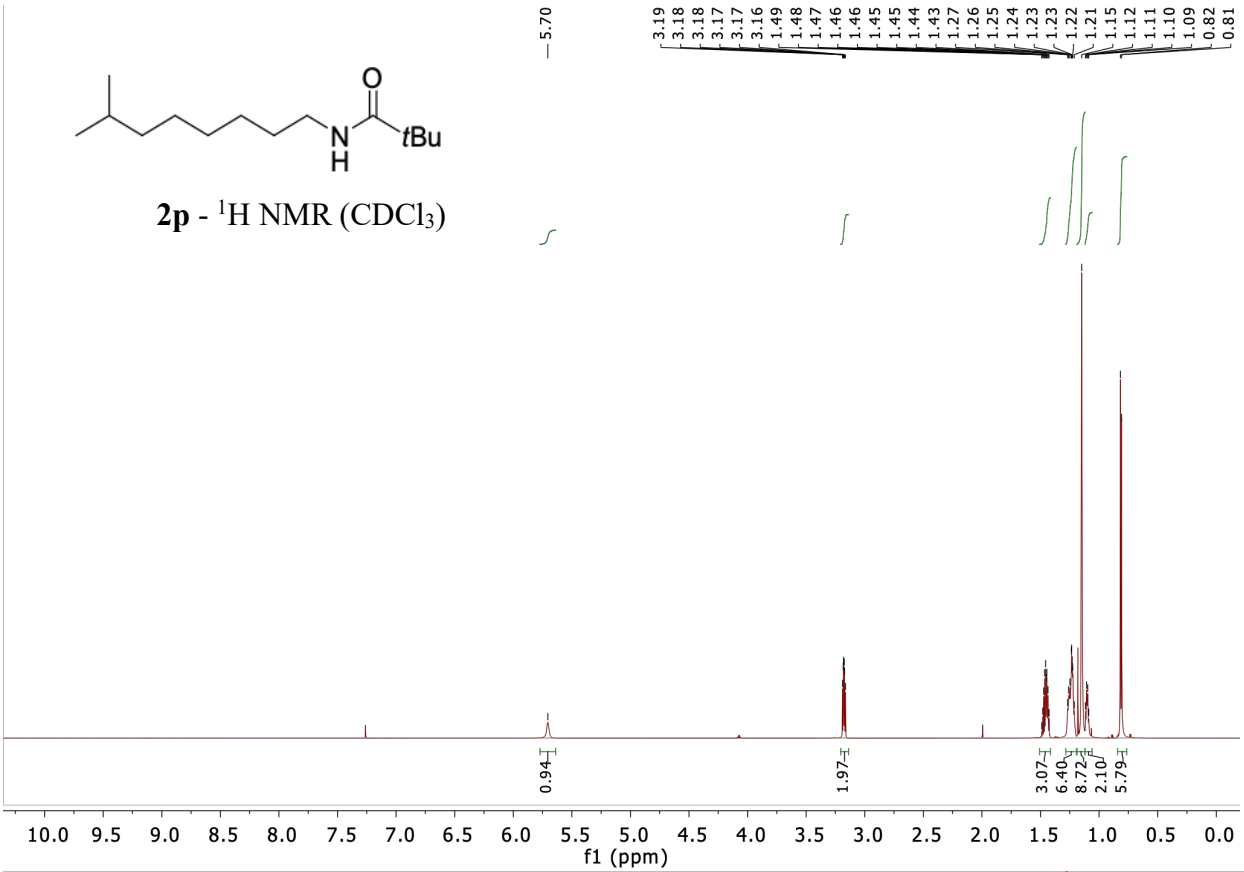
2j – ^{13}CNMR ($CDCl_3$)



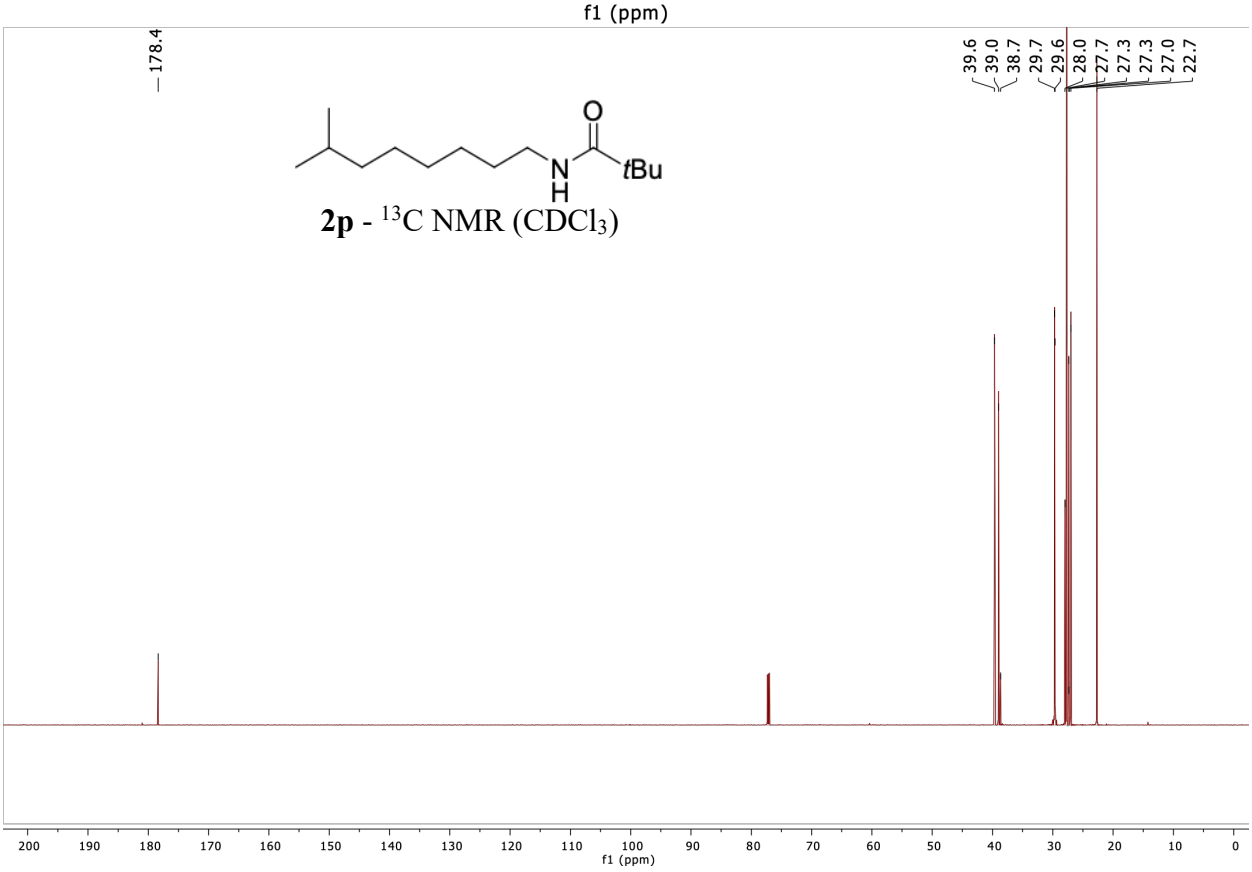
2k – ^{1}HNMR ($CDCl_3$)



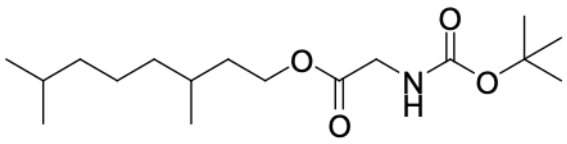
2k – ^{13}CNMR ($CDCl_3$)



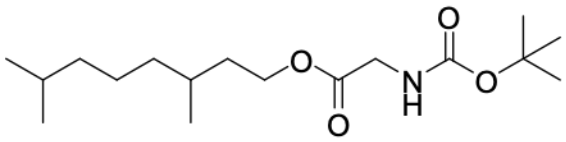
2p - ^{1}H NMR ($CDCl_3$)



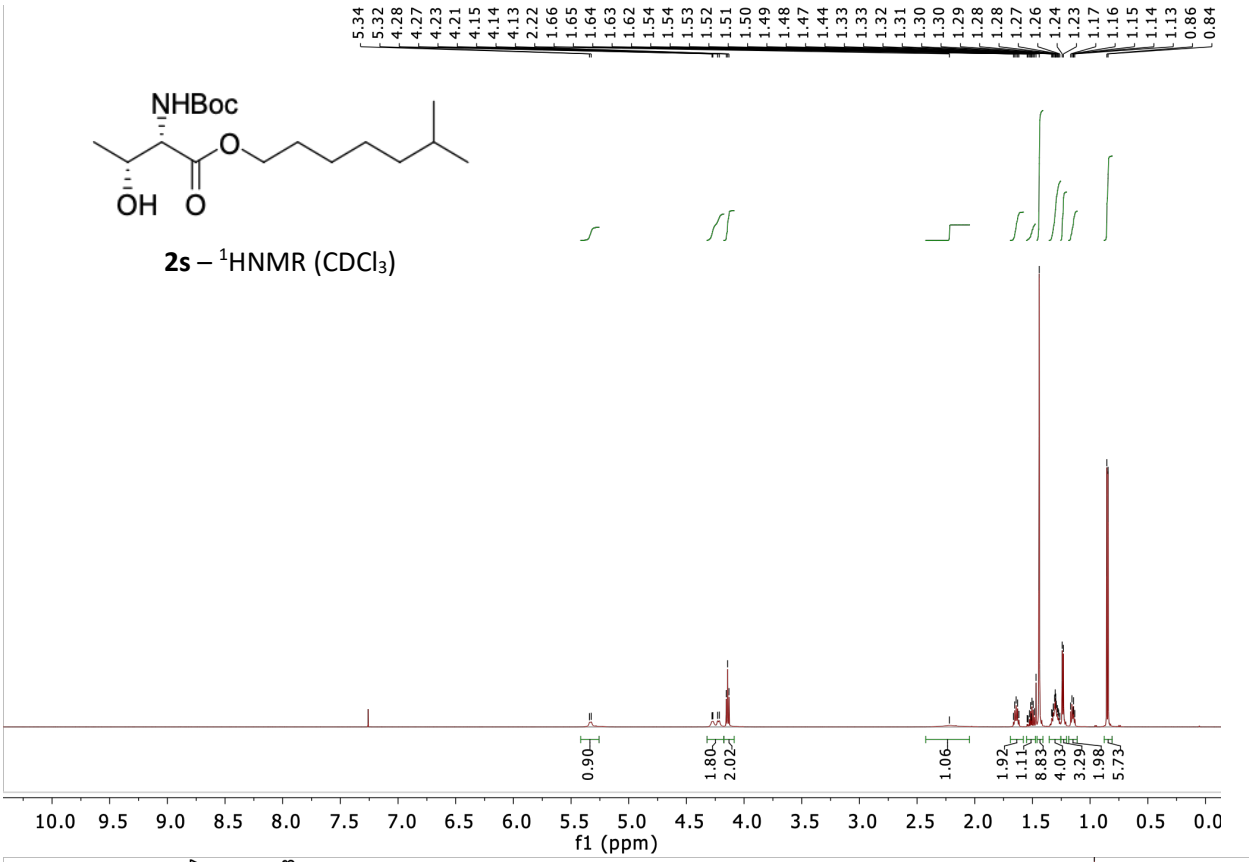
2p - ^{13}C NMR ($CDCl_3$)



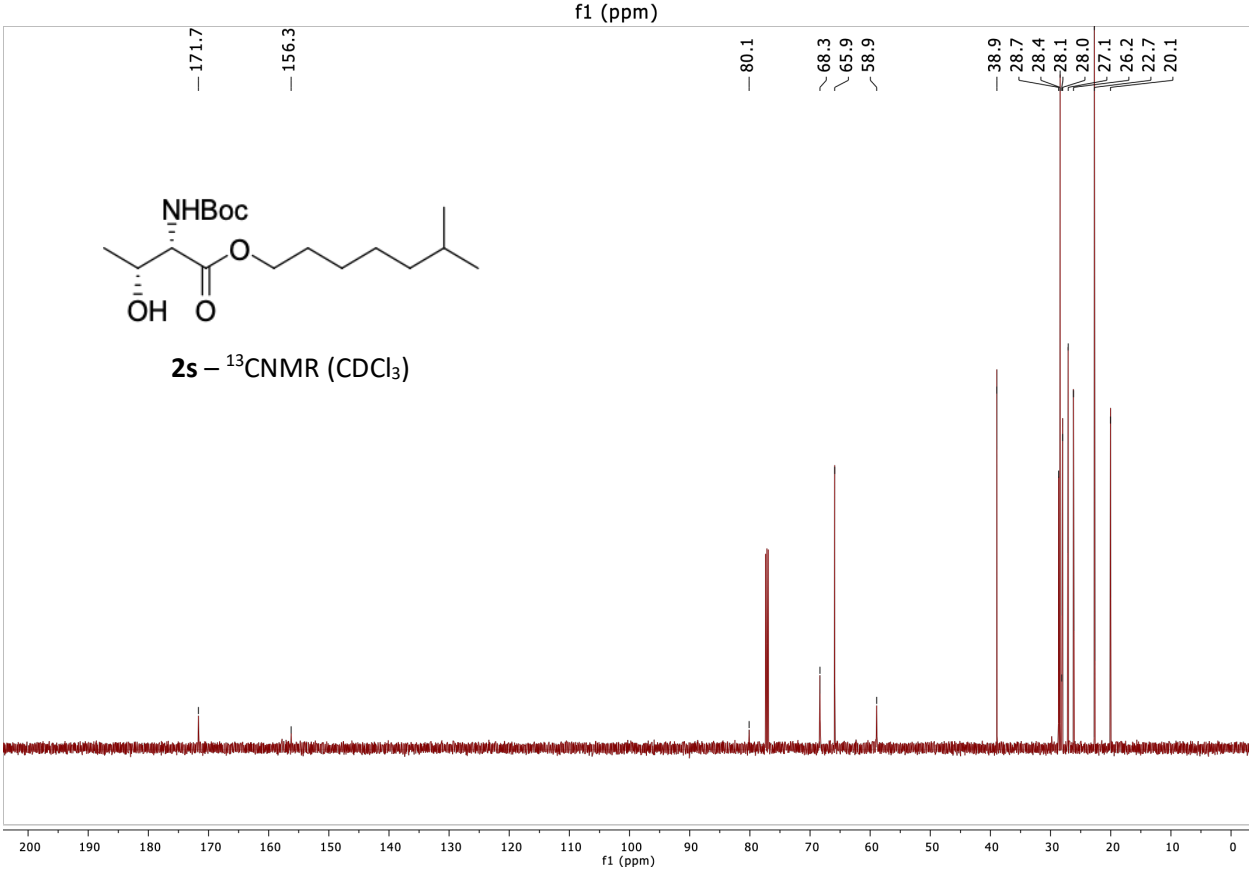
2r – ^{1}HNMR ($CDCl_3$)



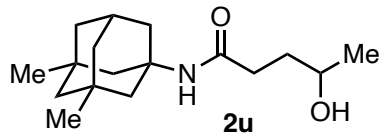
2r – ^{13}CNMR ($CDCl_3$)



2s – ^{1}HNMR ($CDCl_3$)

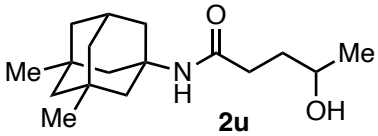


2s – ^{13}CNMR ($CDCl_3$)



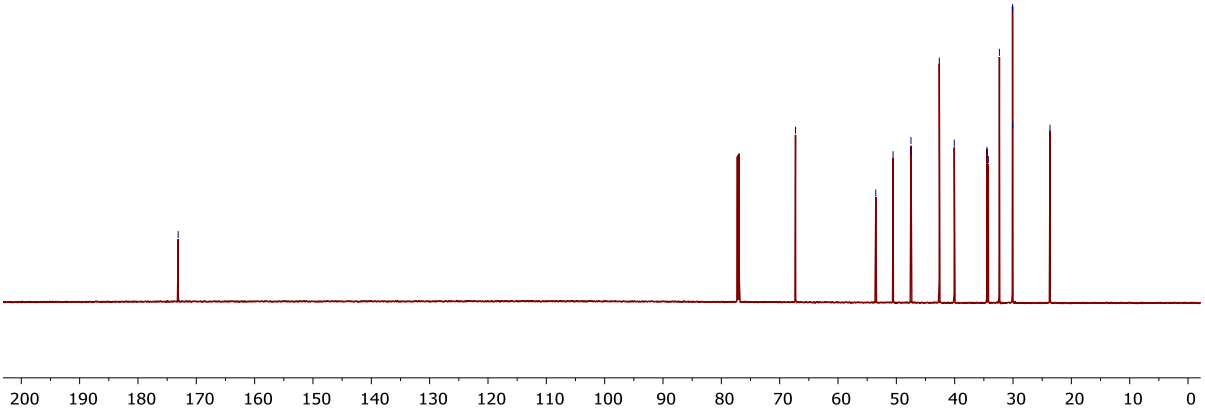
2u

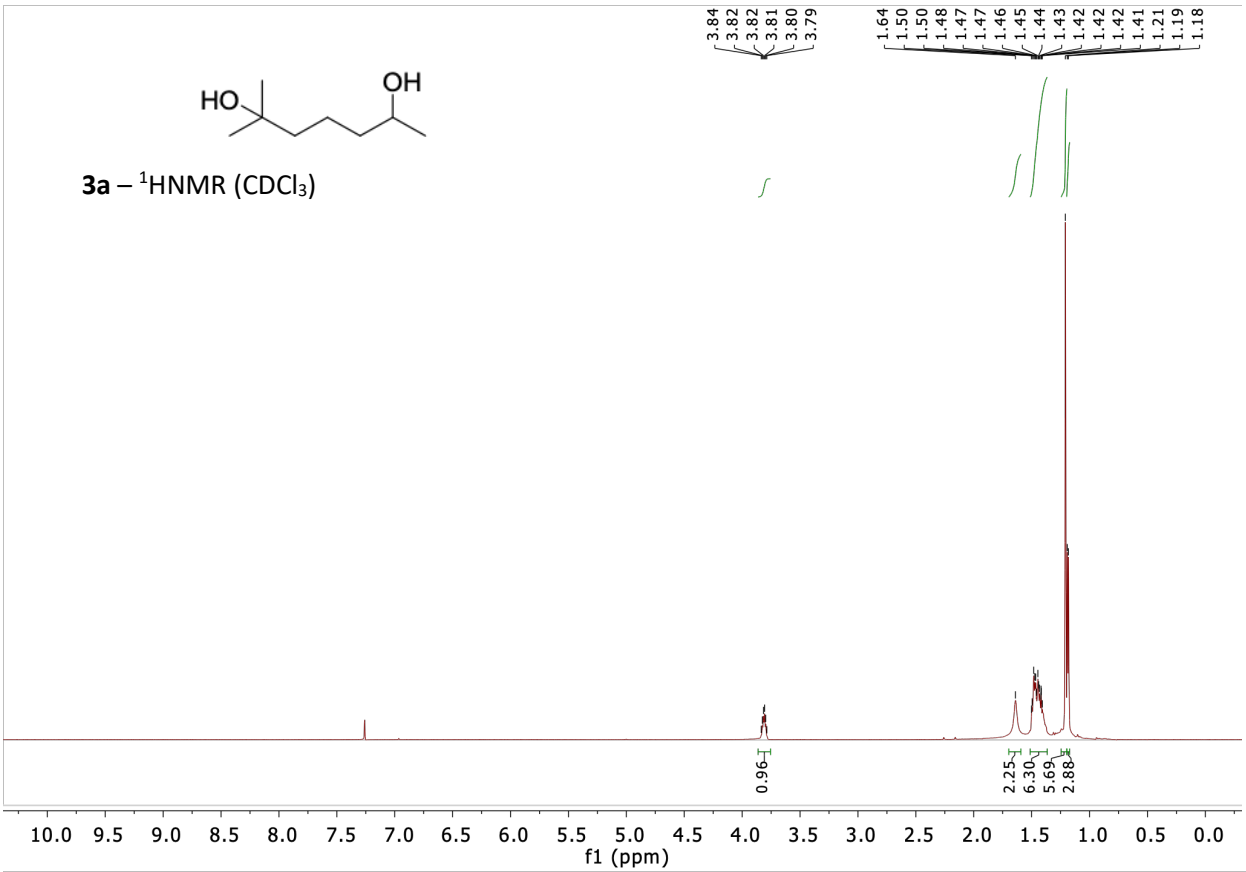
^{1}H NMR, $CDCl_3$



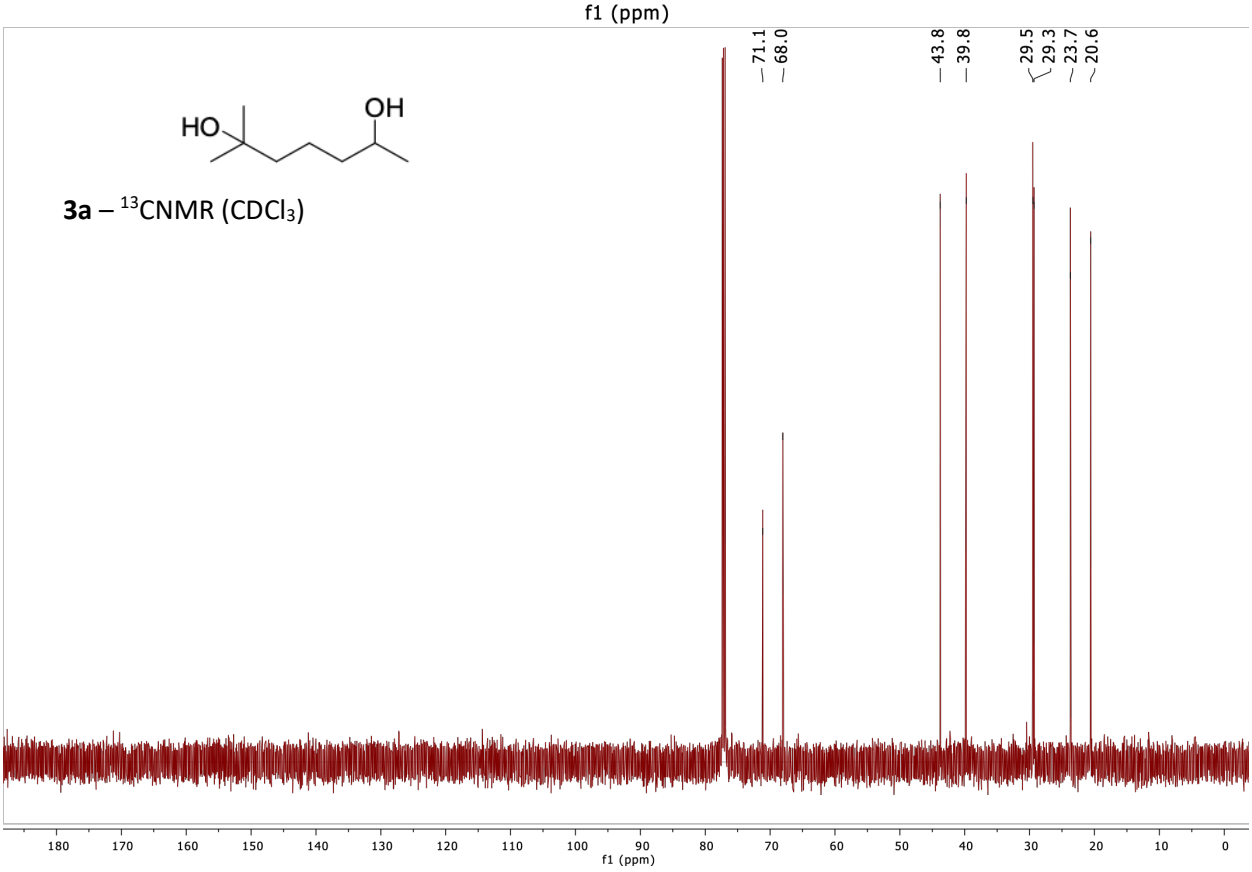
2u

^{13}C NMR, $CDCl_3$

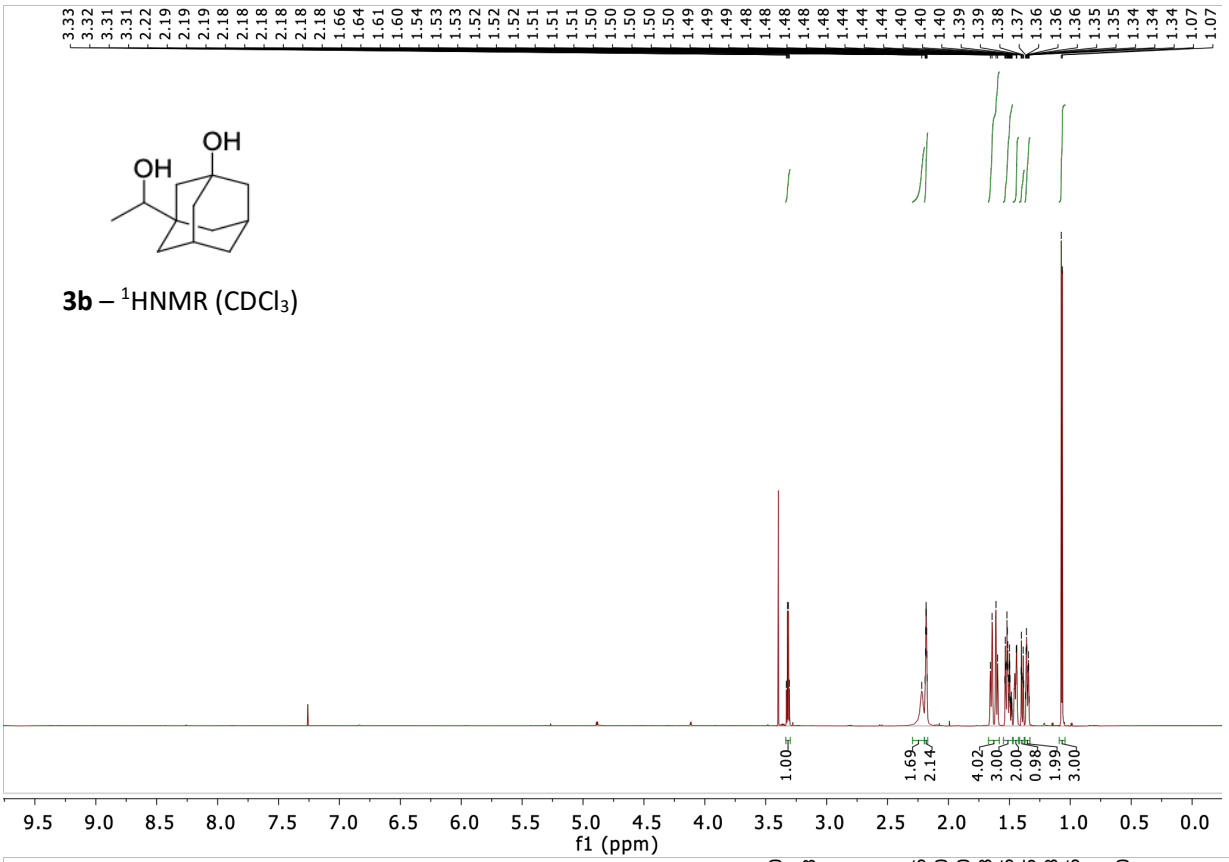




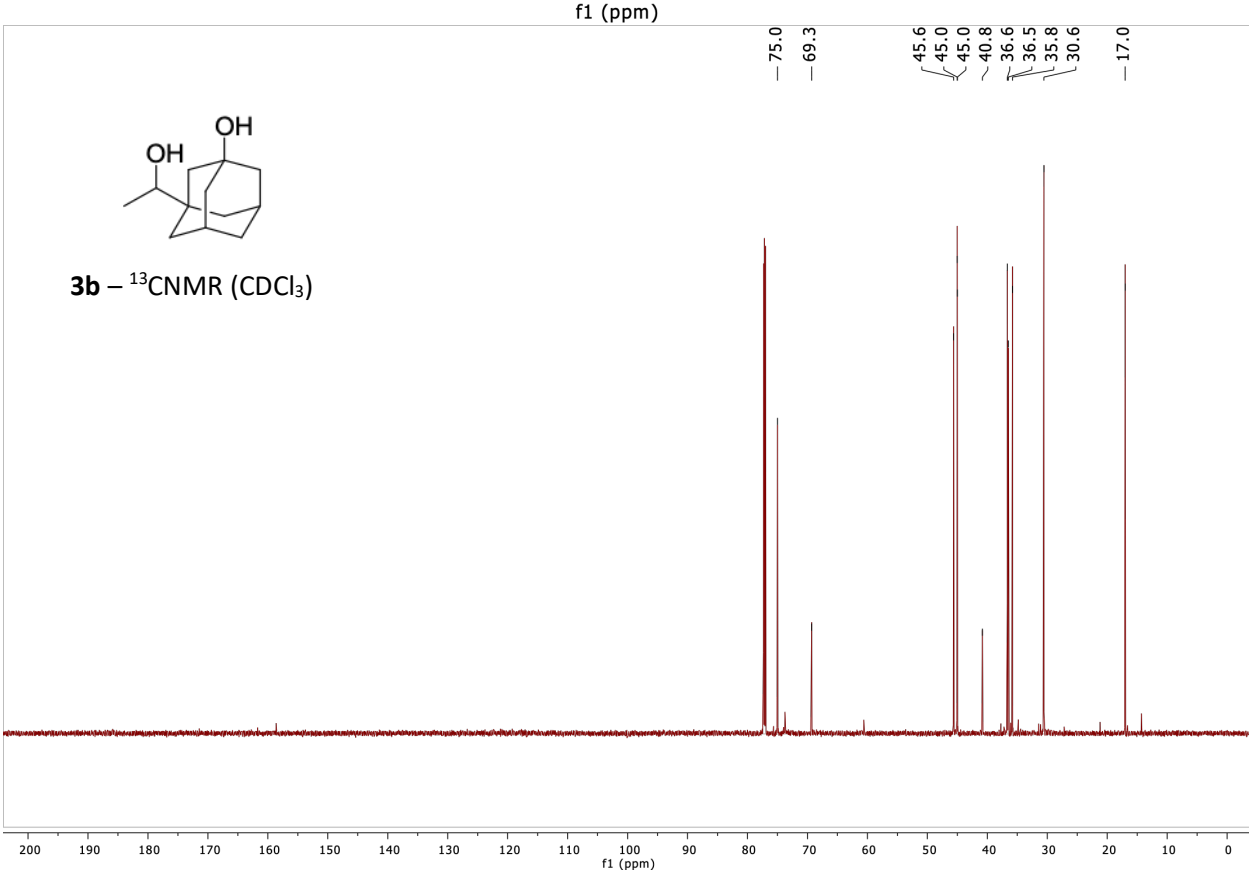
3a – ^{1}HNMR ($CDCl_3$)



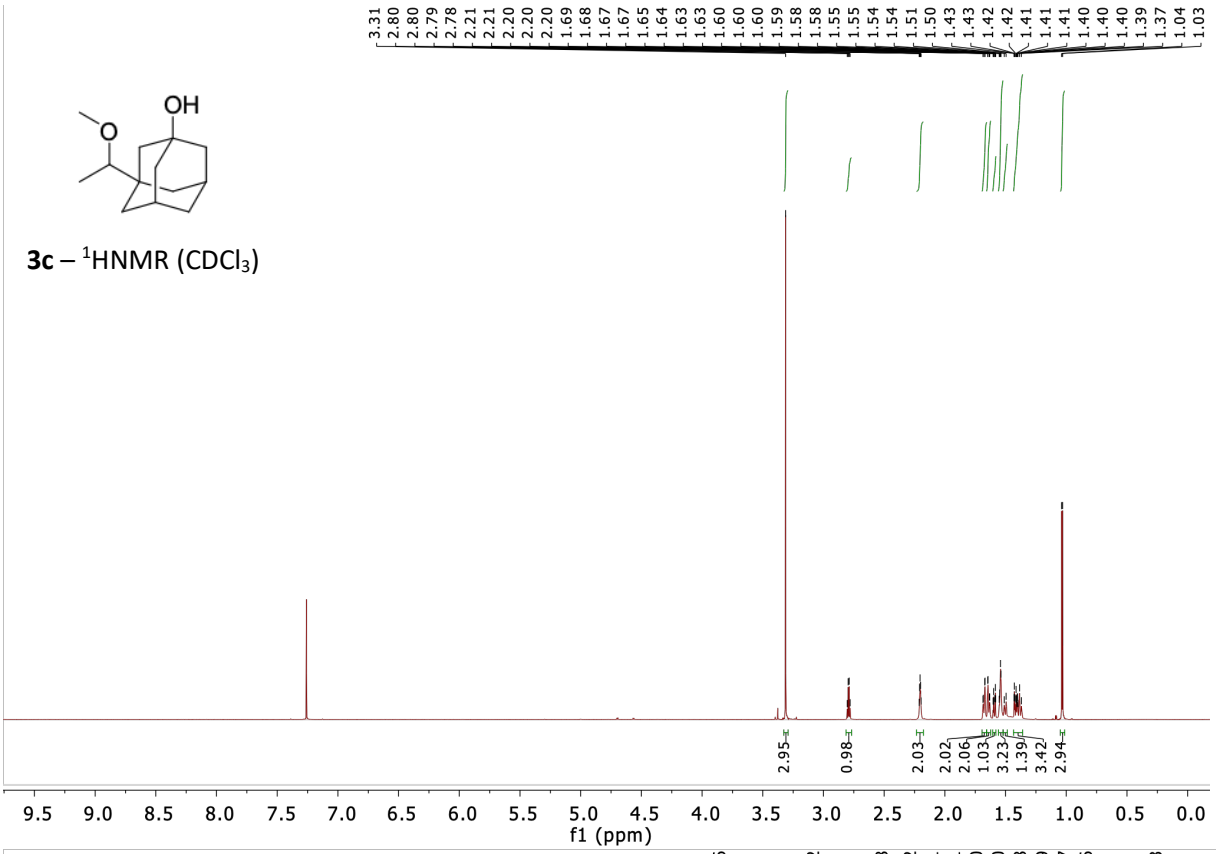
3a – ^{13}CNMR ($CDCl_3$)



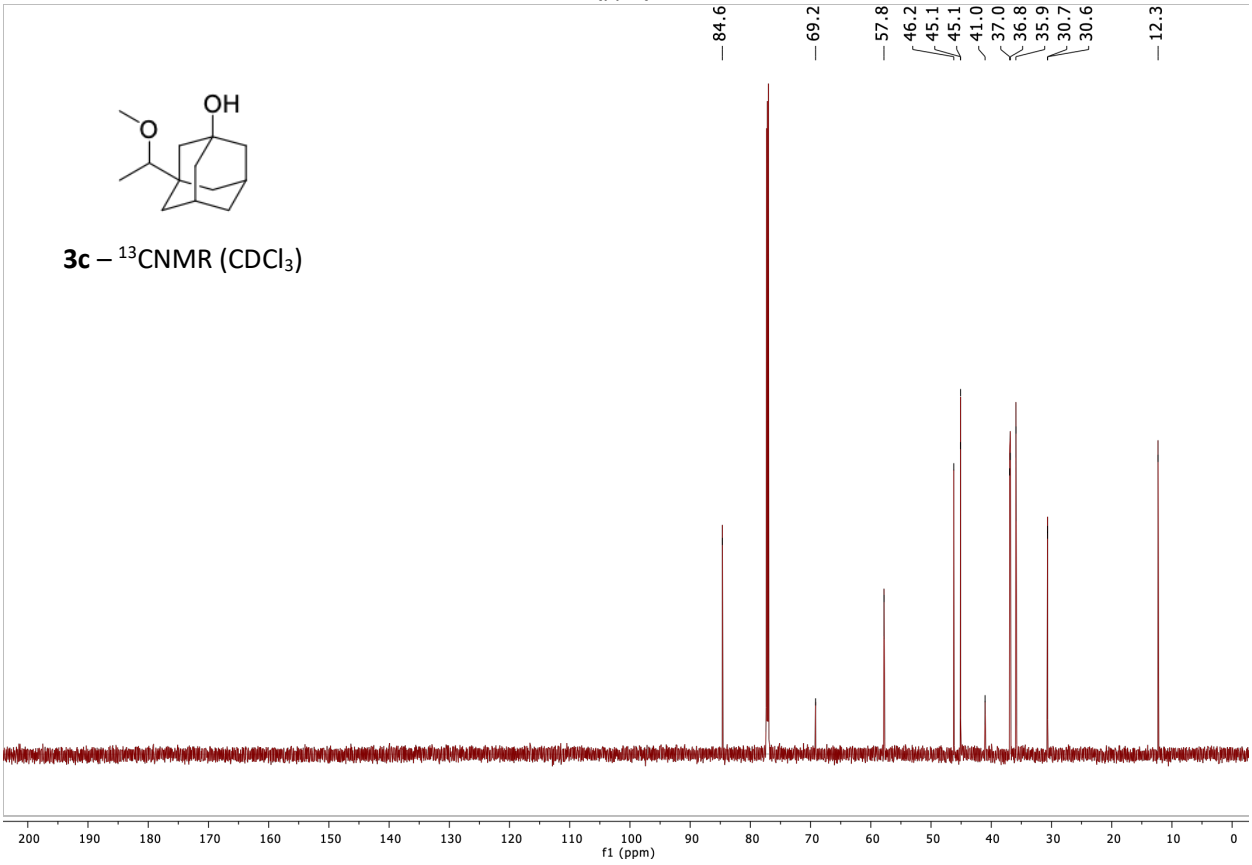
3b – ^{1}HNMR ($CDCl_3$)



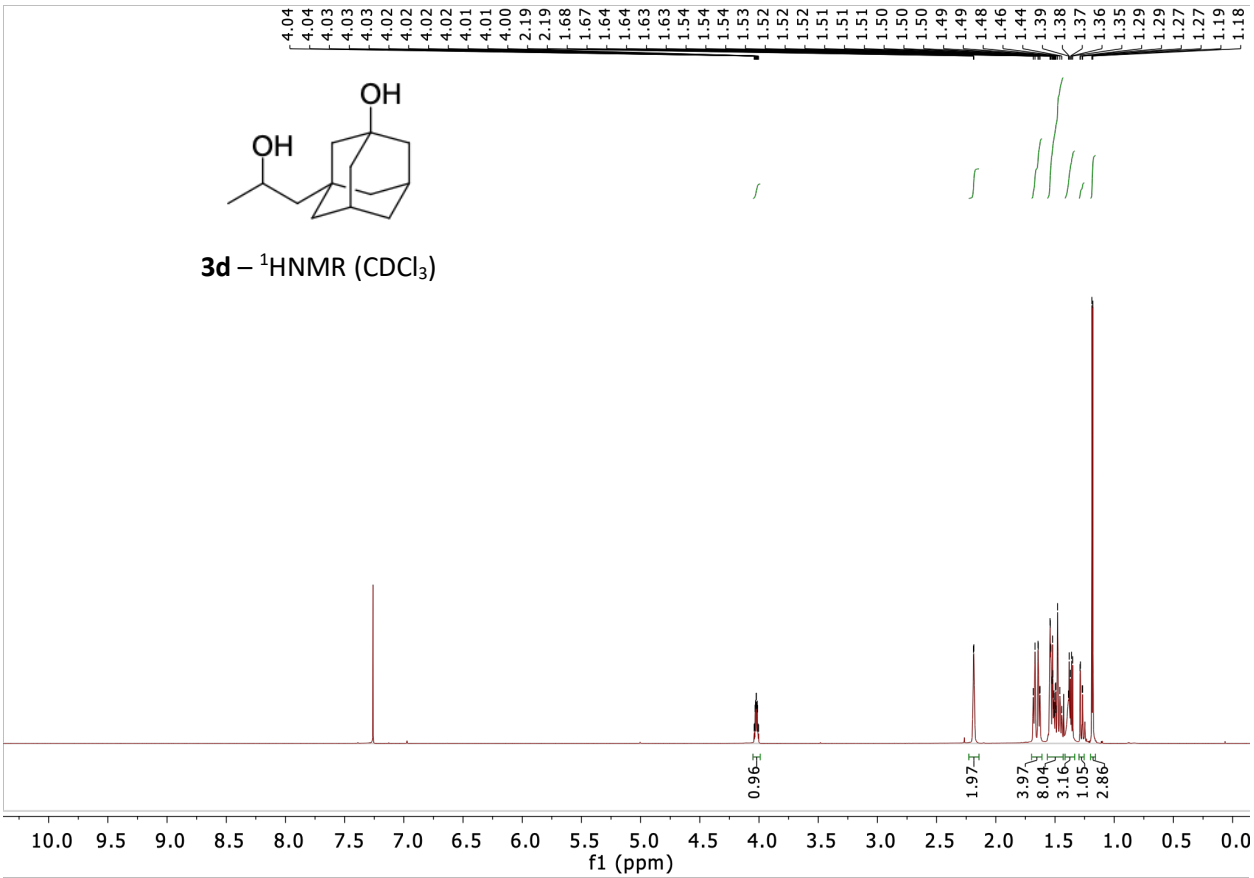
3b – ^{13}CNMR ($CDCl_3$)



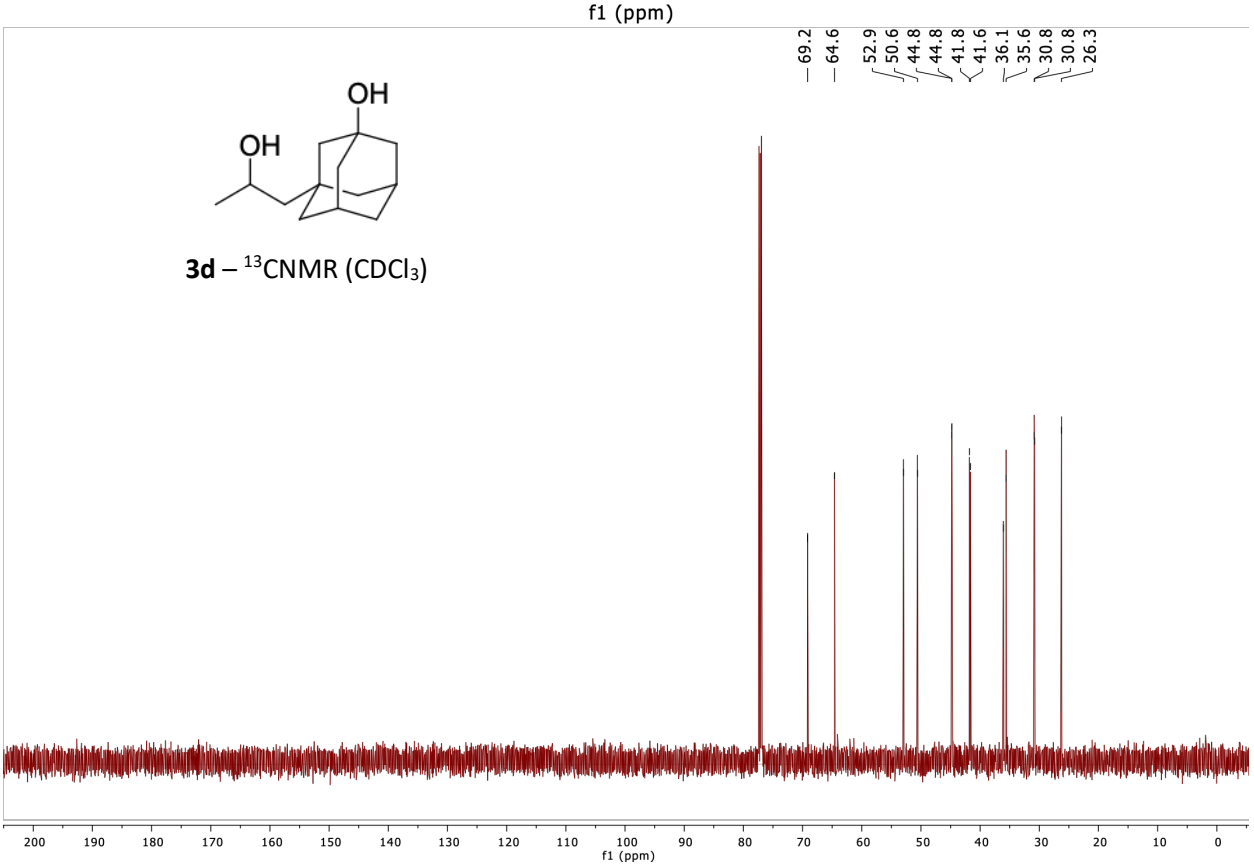
3c – ^{1}HNMR ($CDCl_3$)



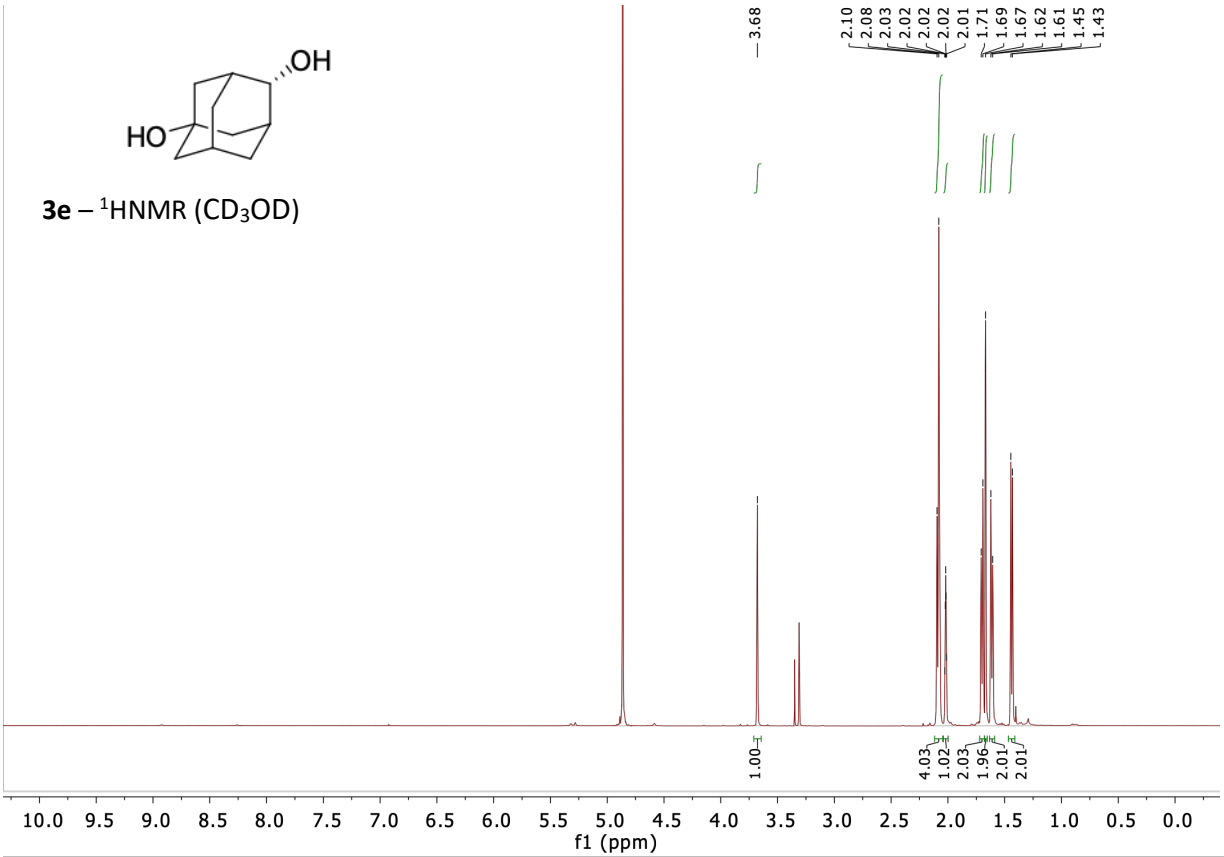
3c – ^{13}CNMR ($CDCl_3$)



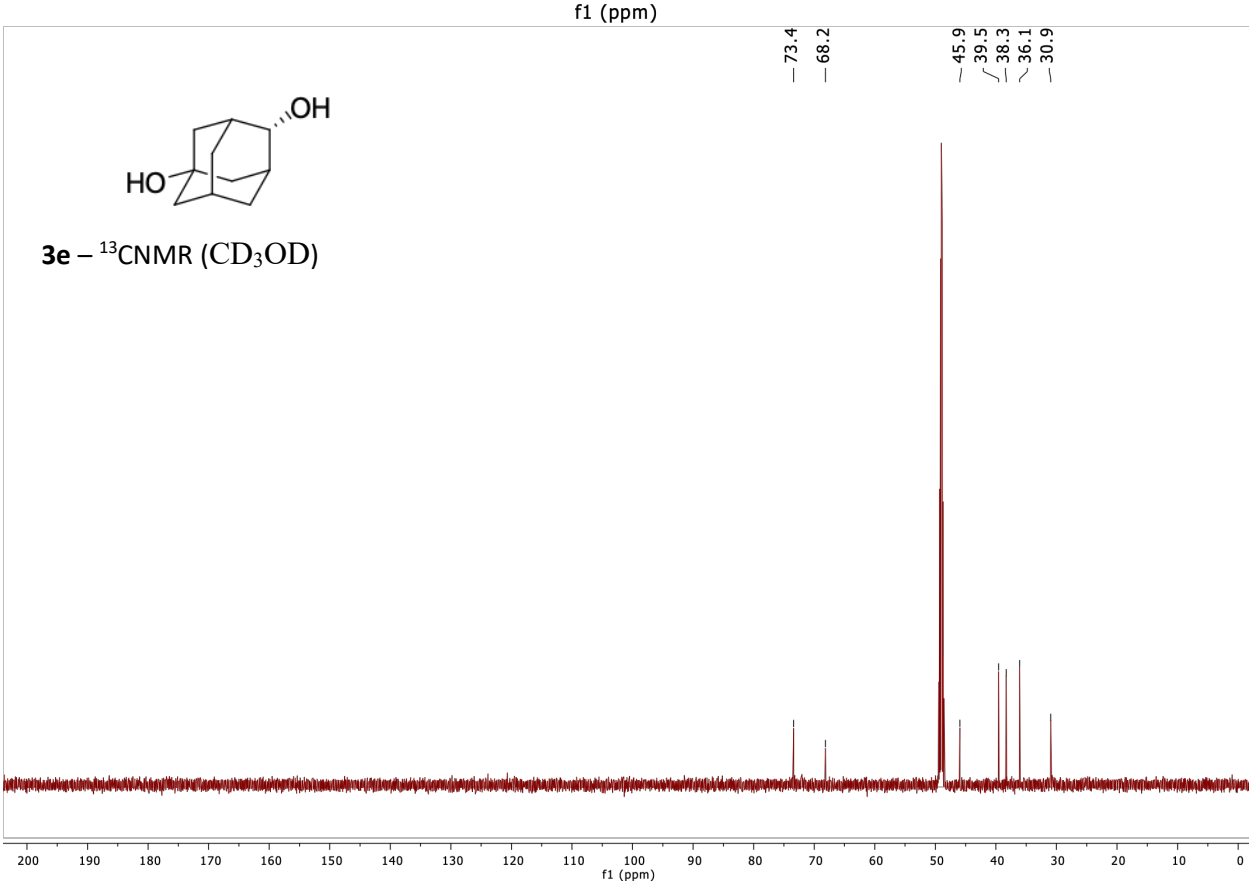
3d – ^{1}HNMR ($CDCl_3$)



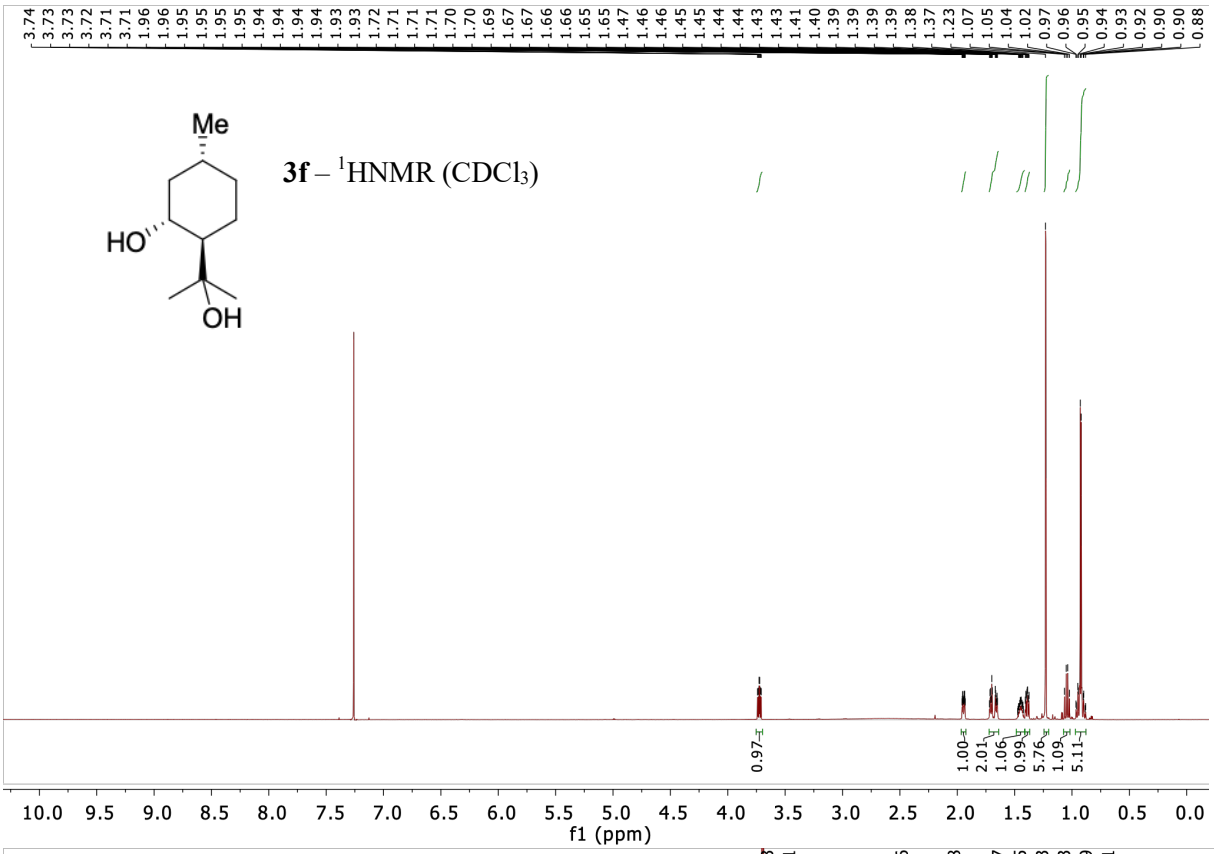
3d – ^{13}CNMR ($CDCl_3$)

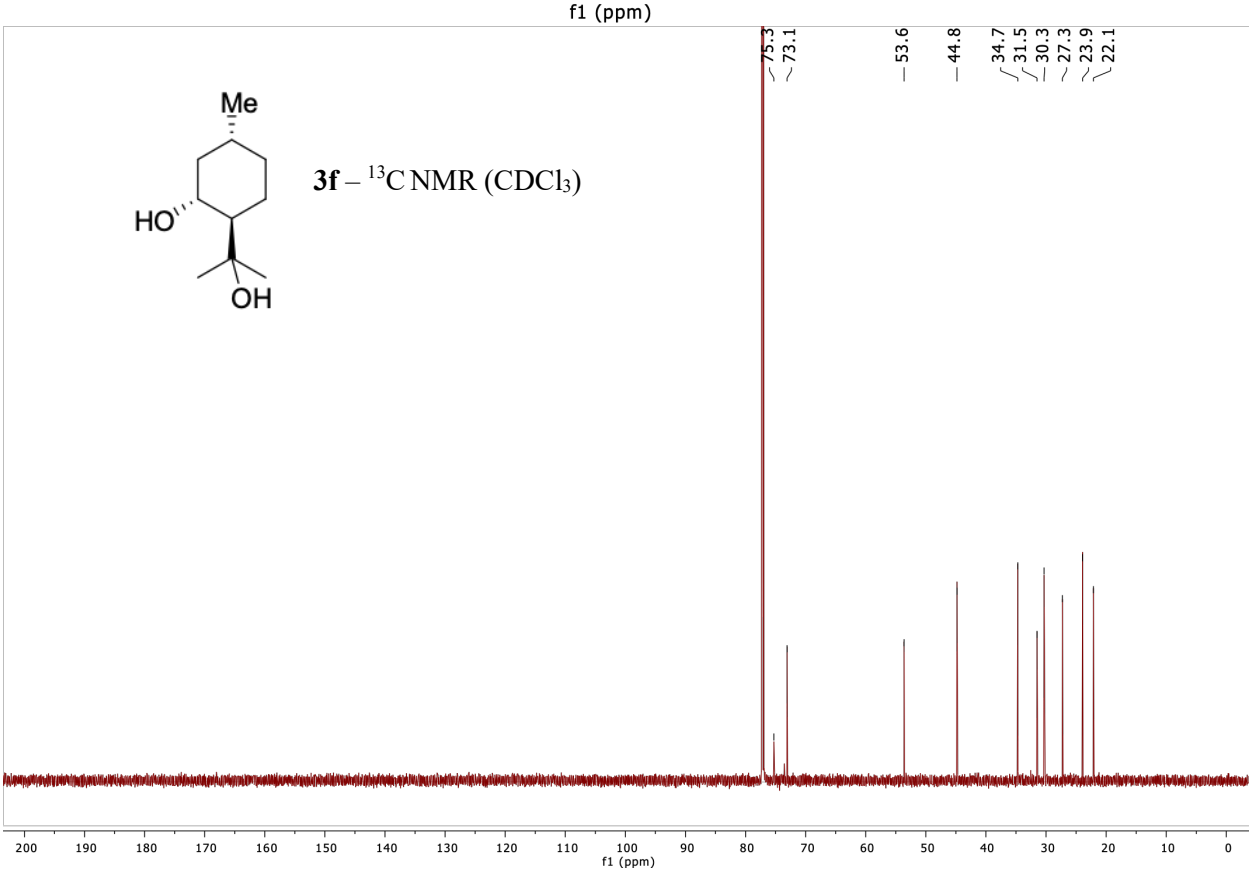


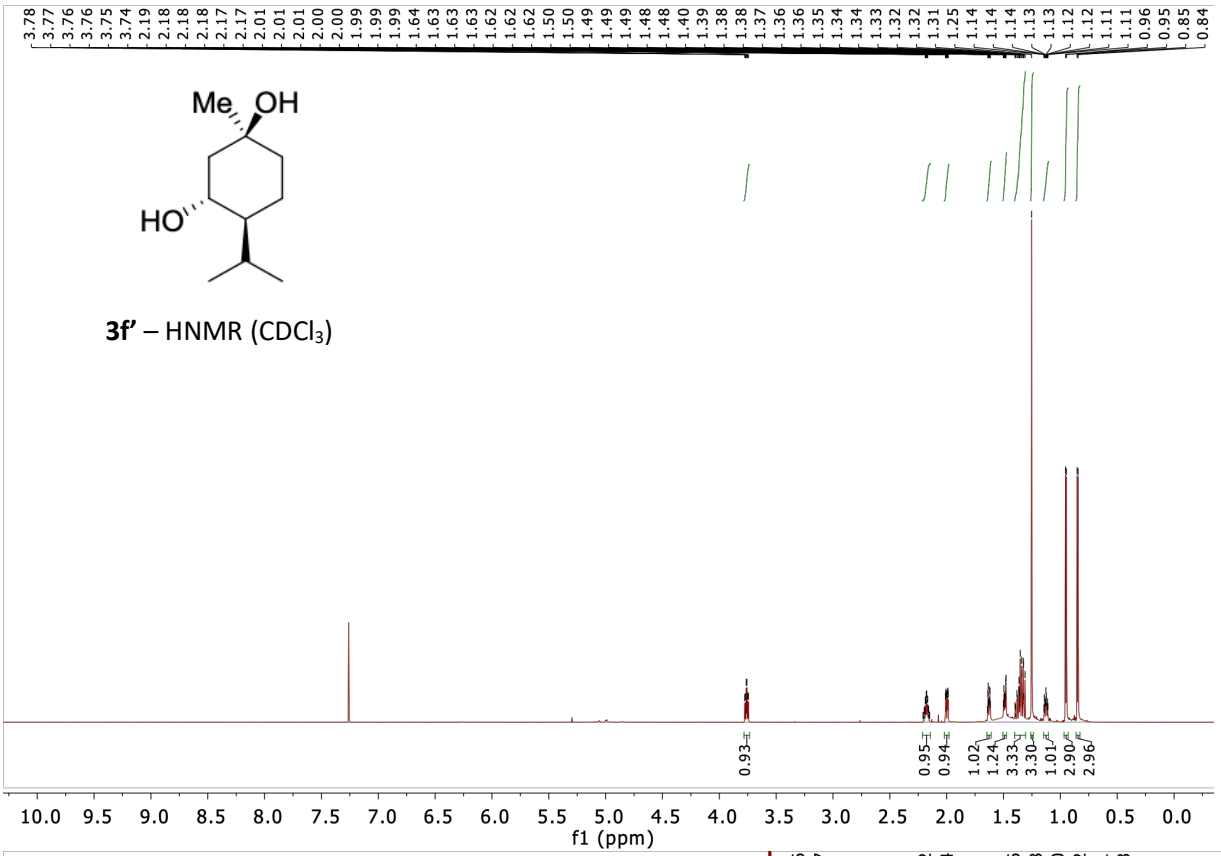
3e – ^{1}HNMR (CD_3OD)



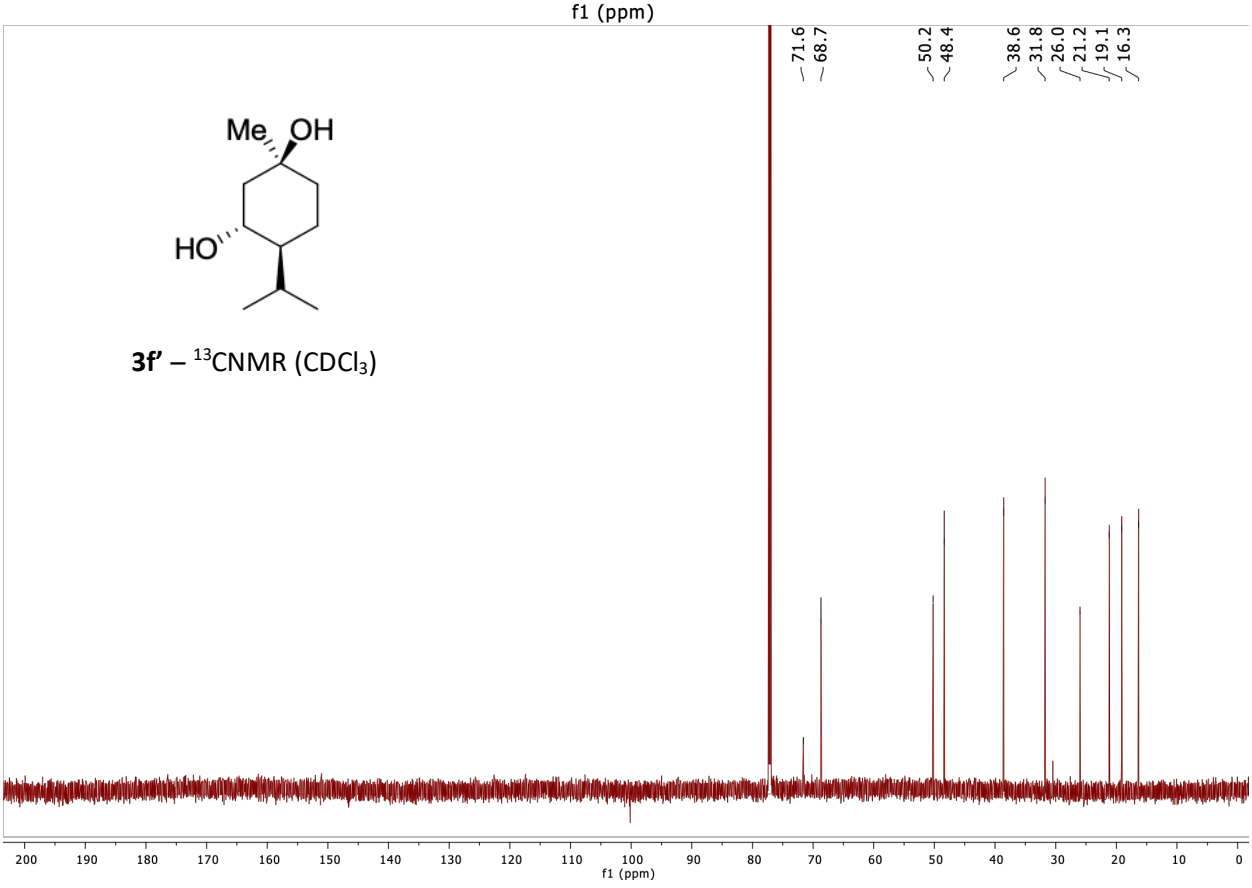
3e – ^{13}CNMR (CD_3OD)


Me
HO
OH
3f – 1HNMR (CDCl3)
f1 (ppm)

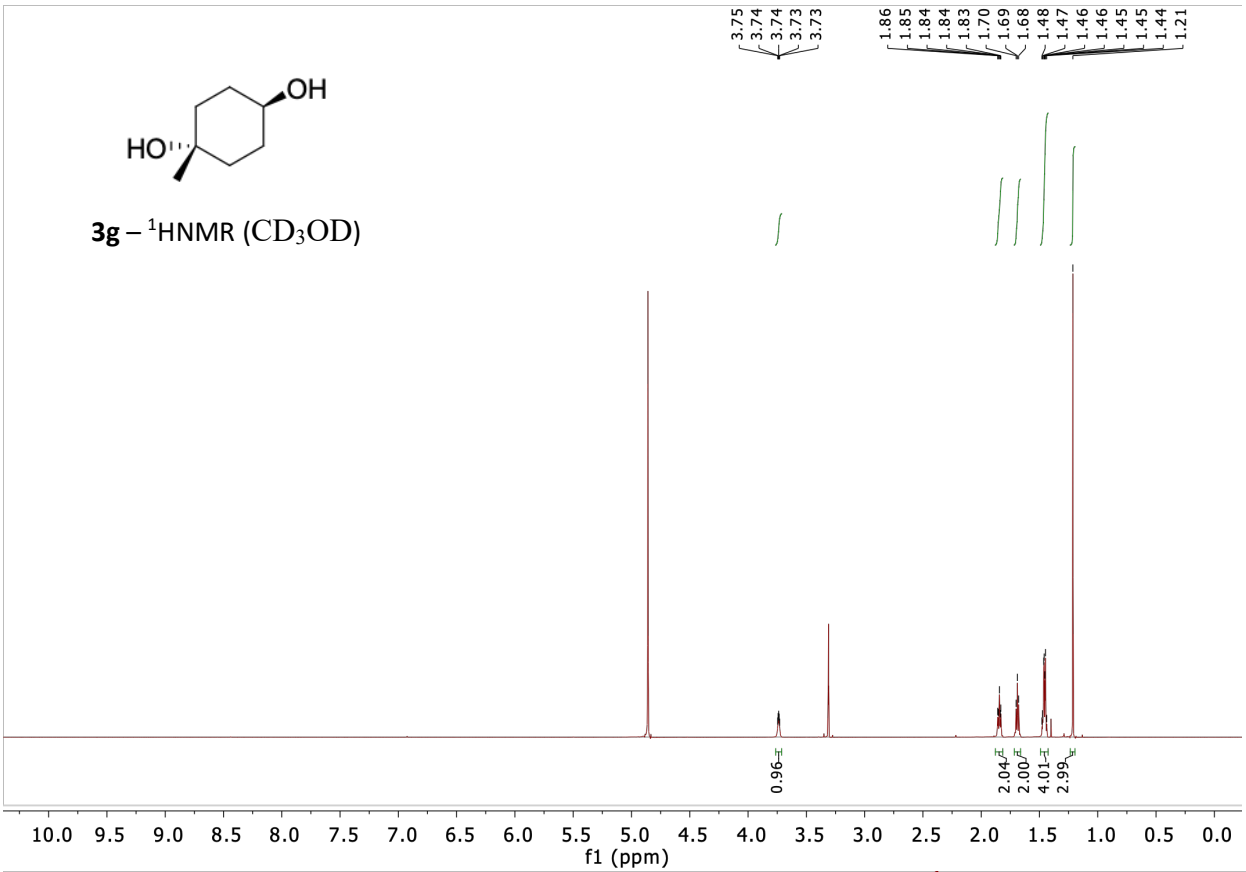

Me
HO
OH
3f – 13C NMR (CDCl3)
f1 (ppm)



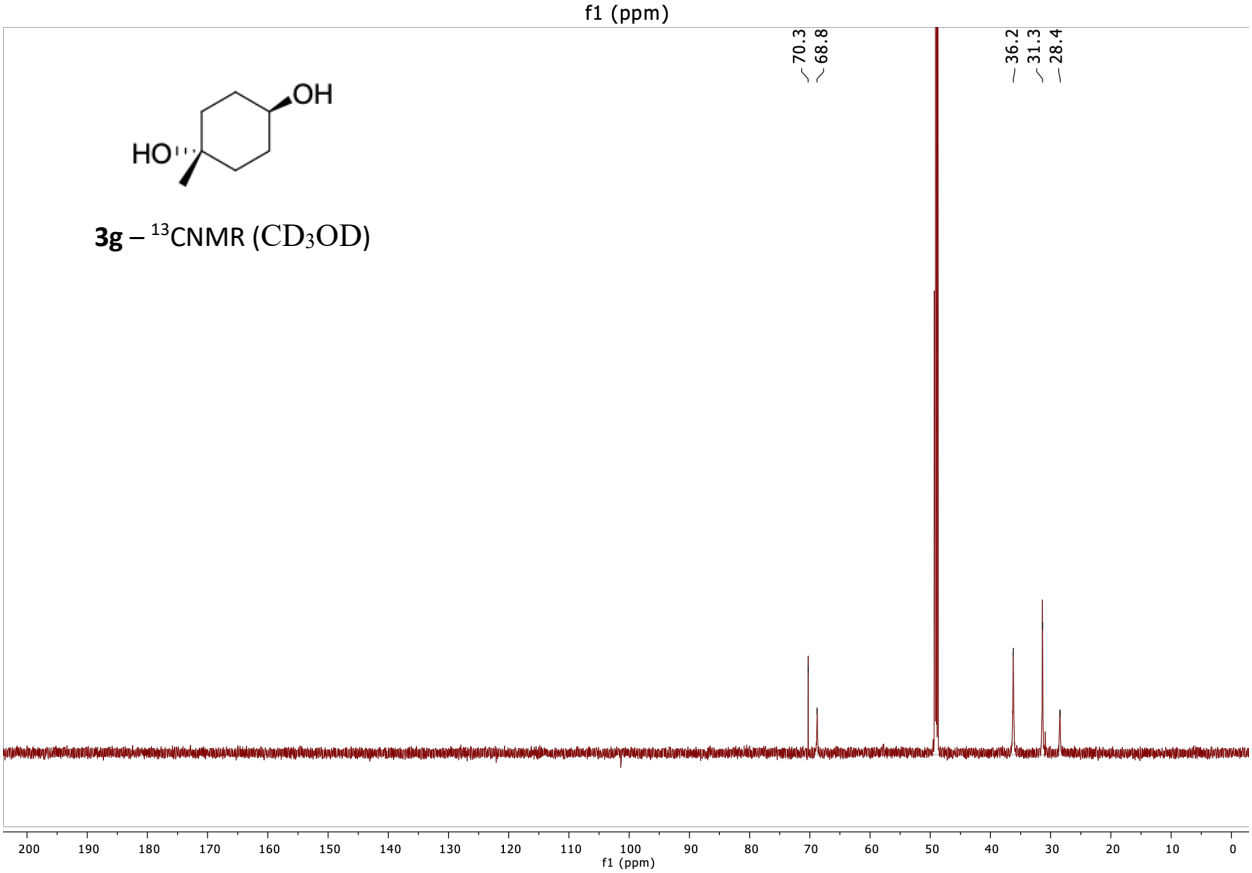
3f' – HNMR ($CDCl_3$)



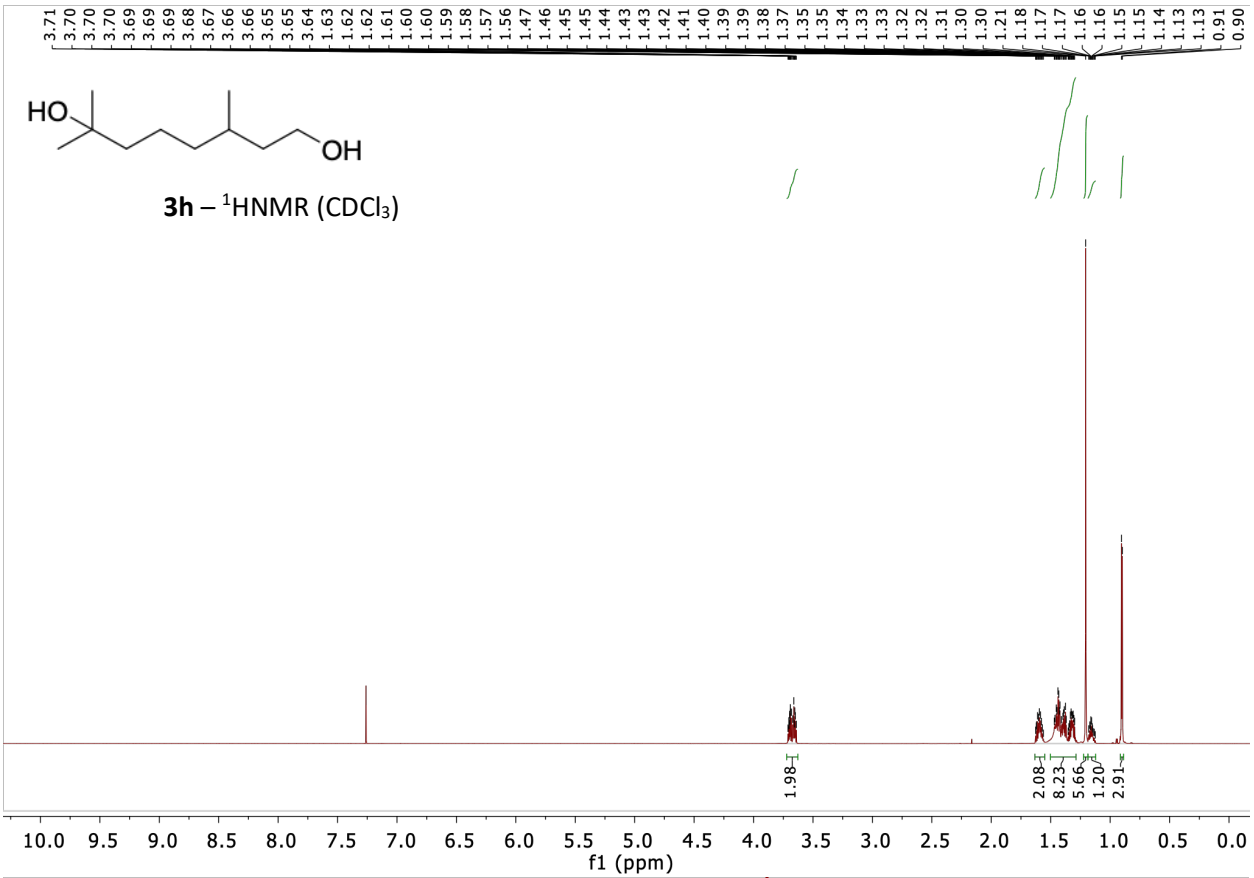
3f' – ^{13}CNMR ($CDCl_3$)



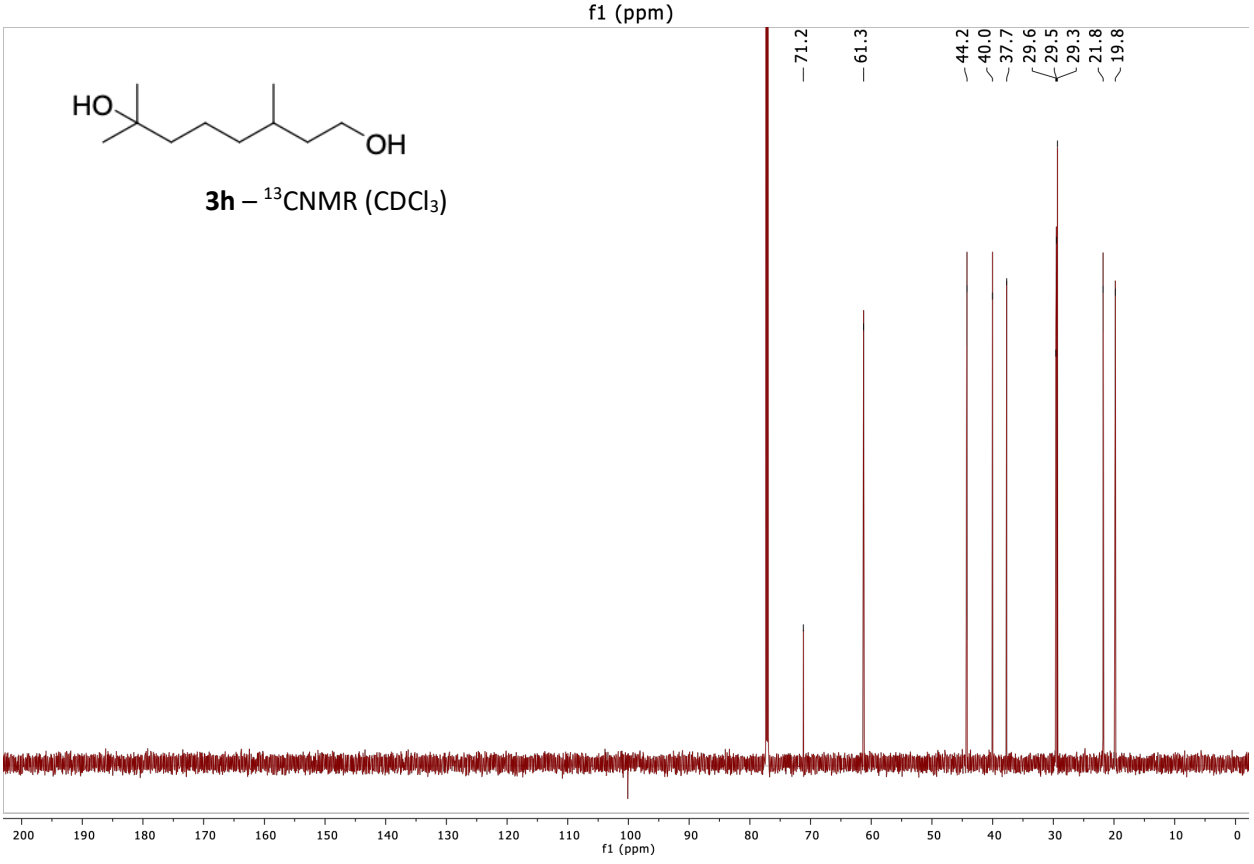
3g – ^{1}HNMR (CD_3OD)



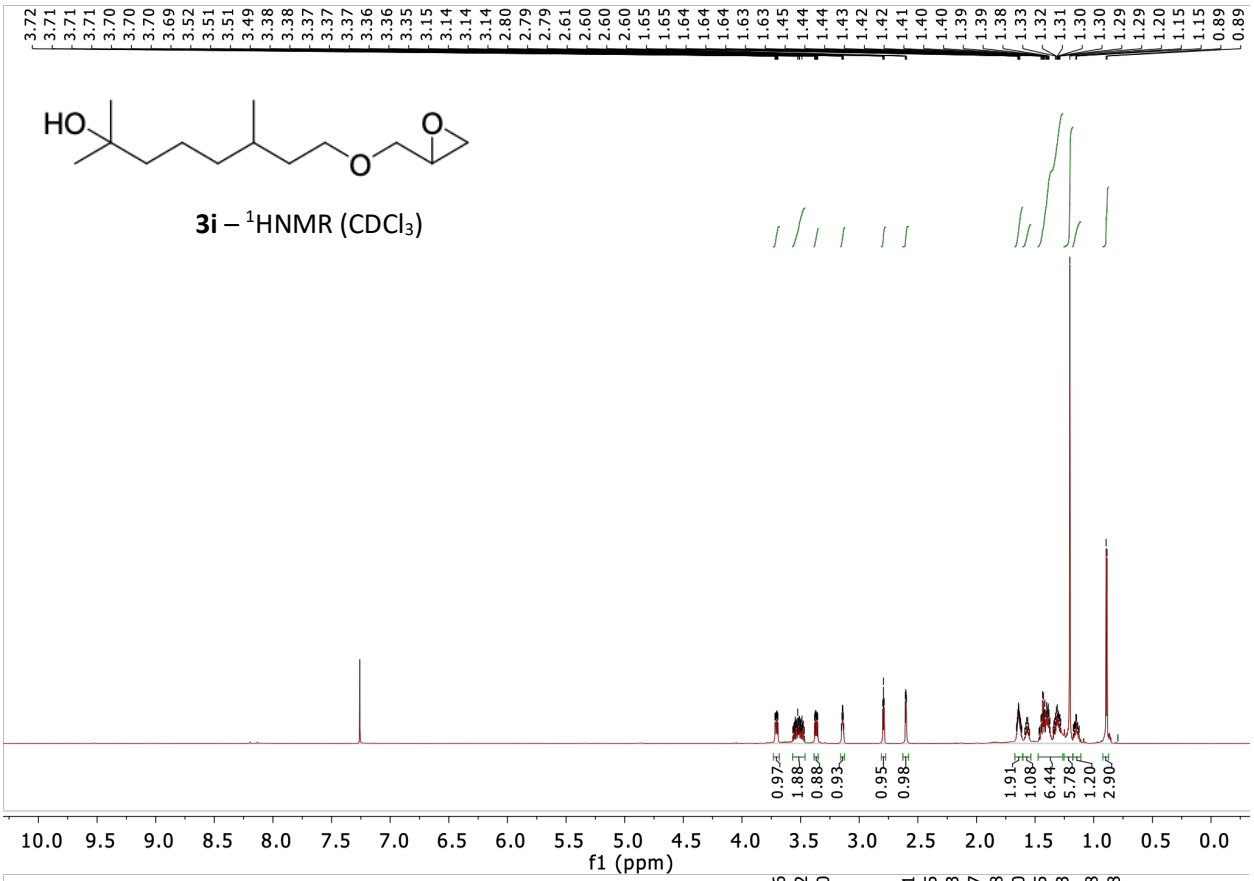
3g – ^{13}CNMR (CD_3OD)



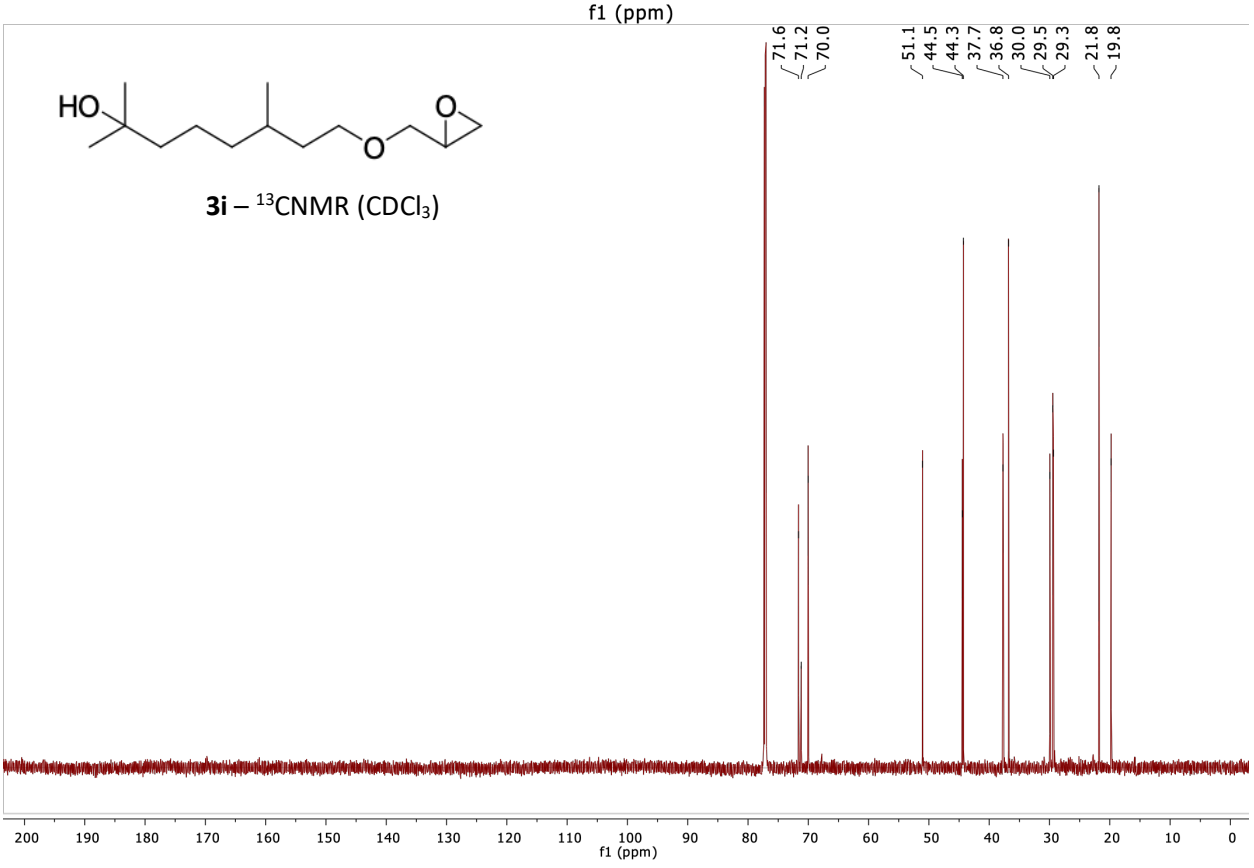
3h – ^{1}HNMR ($CDCl_3$)



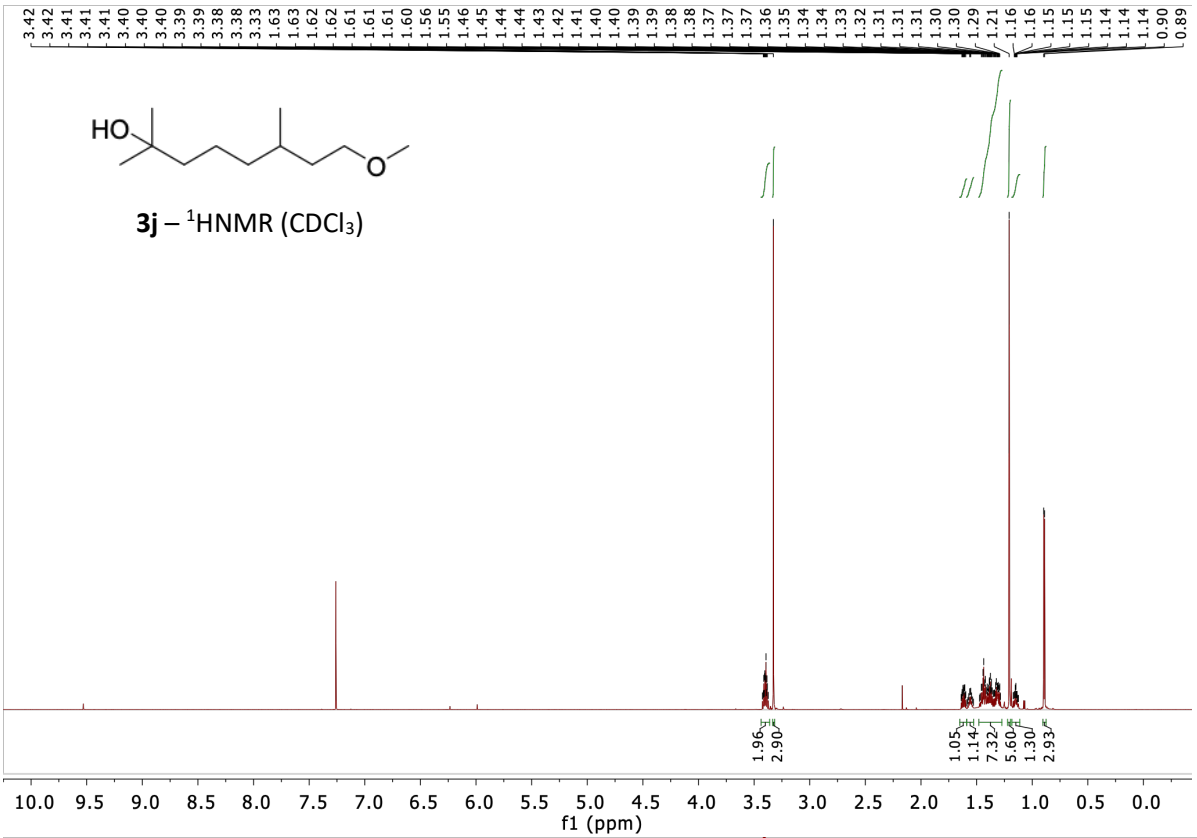
3h – ^{13}CNMR ($CDCl_3$)



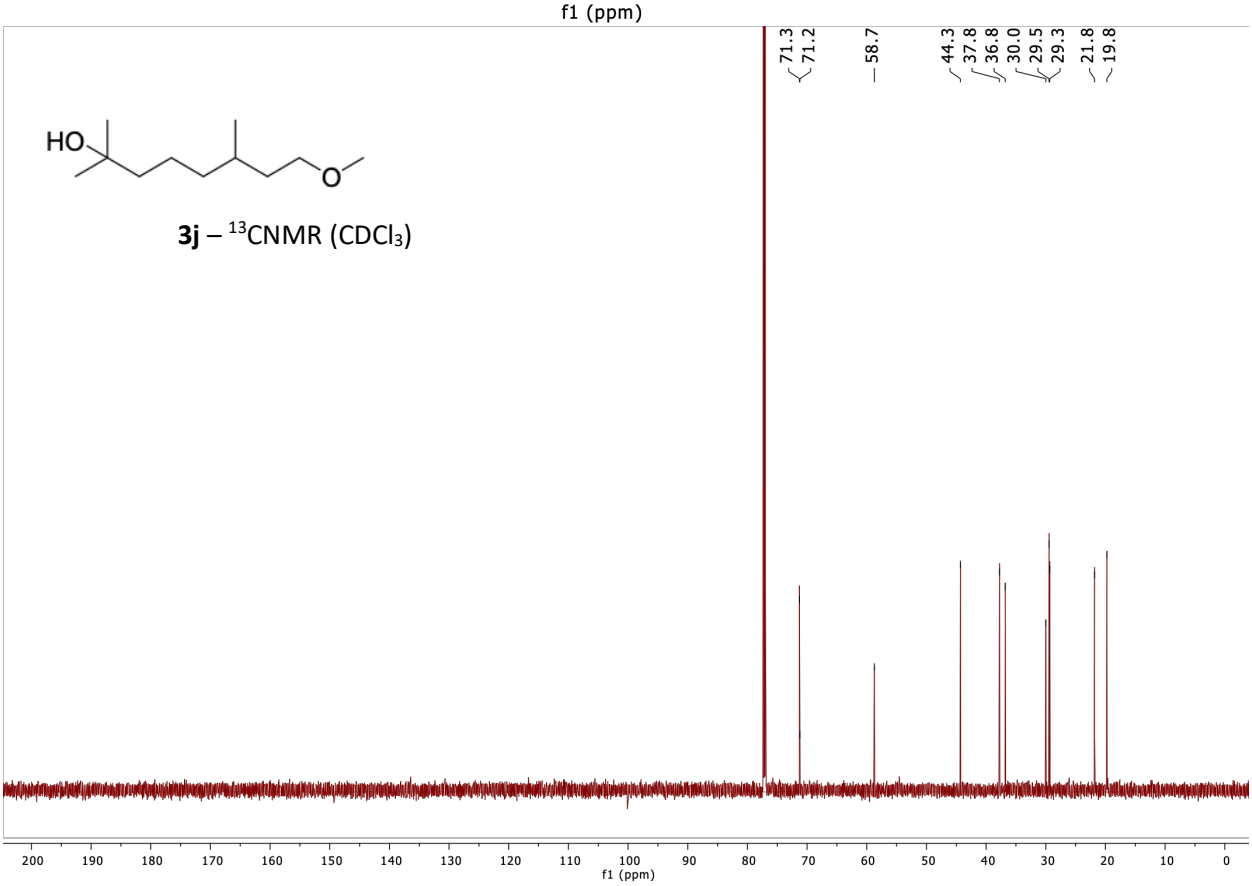
3i – ^{1}HNMR ($CDCl_3$)



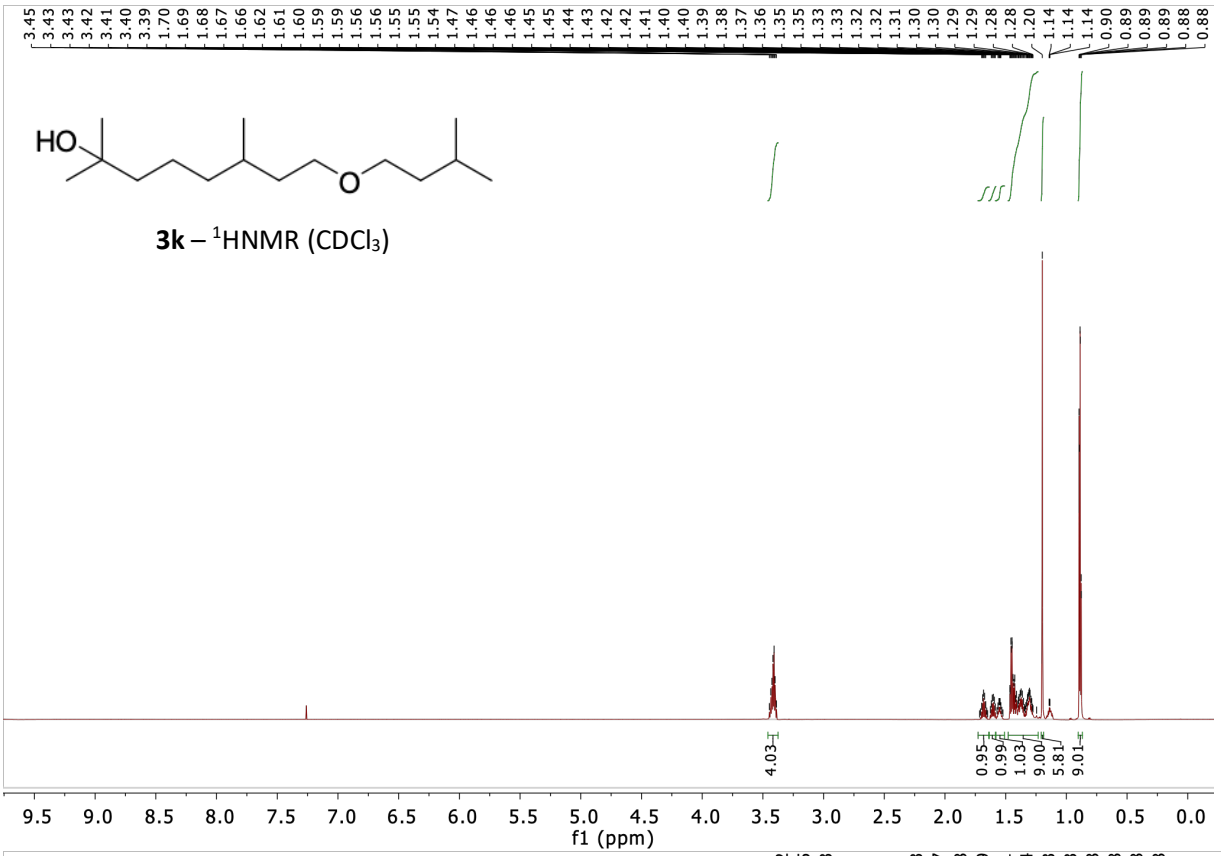
3i – ^{13}CNMR ($CDCl_3$)



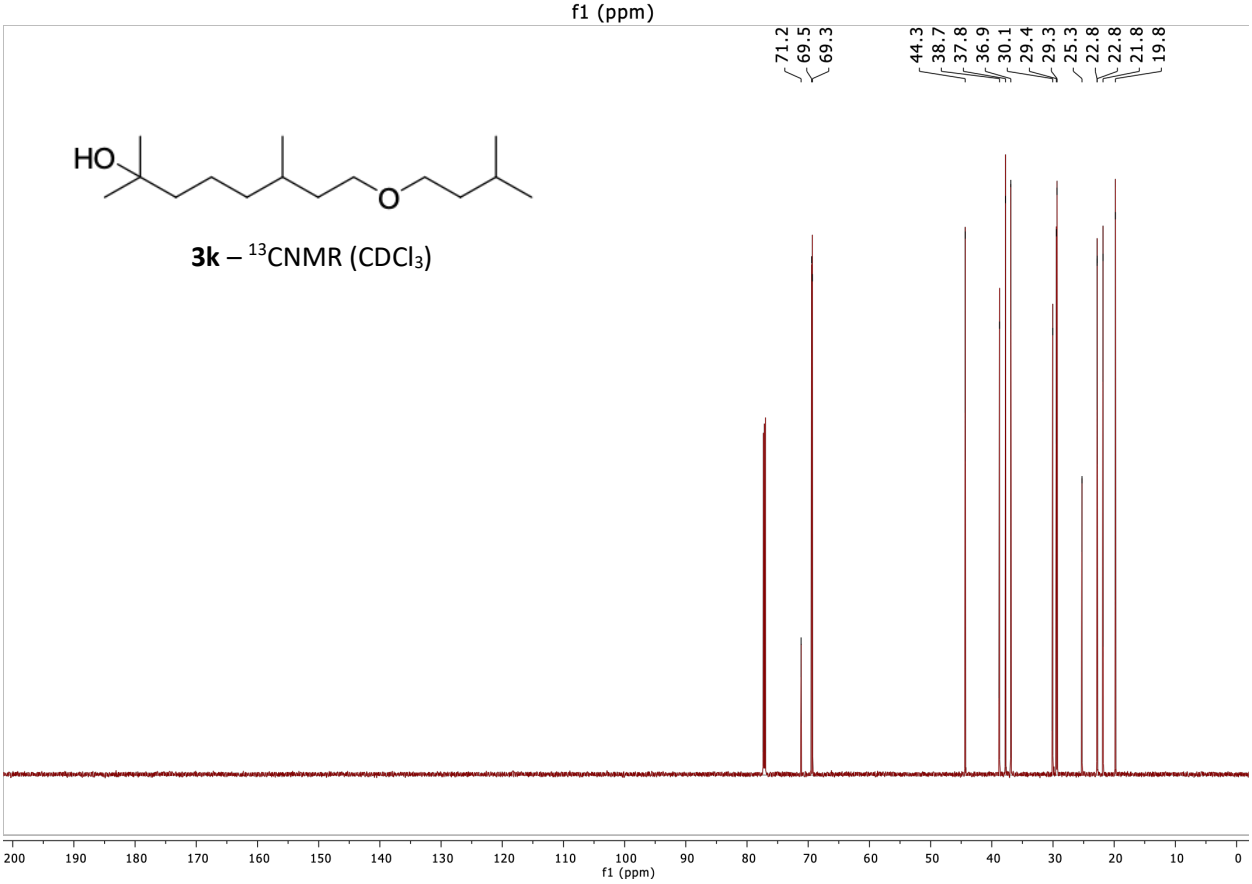
3j – ^{1}HNMR ($CDCl_3$)



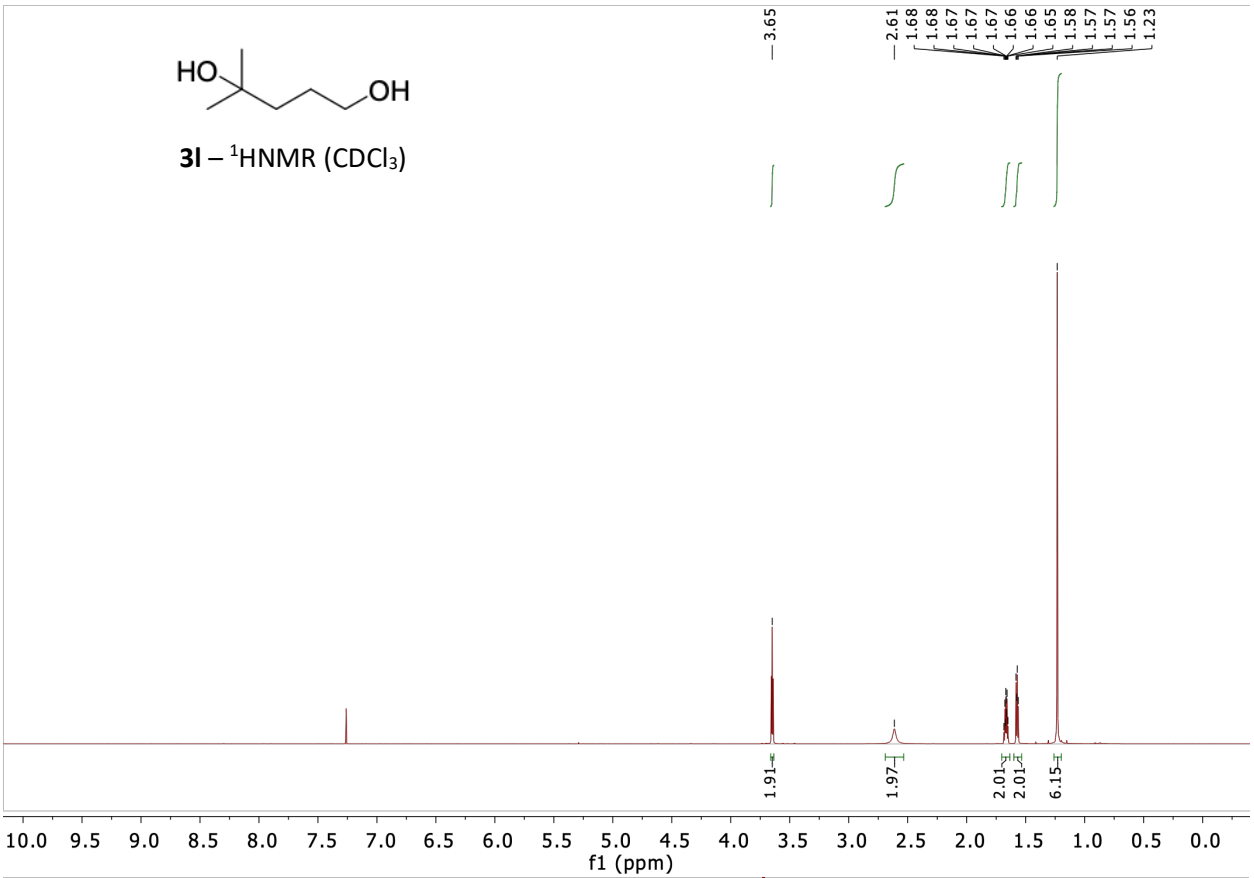
3j – ^{13}CNMR ($CDCl_3$)



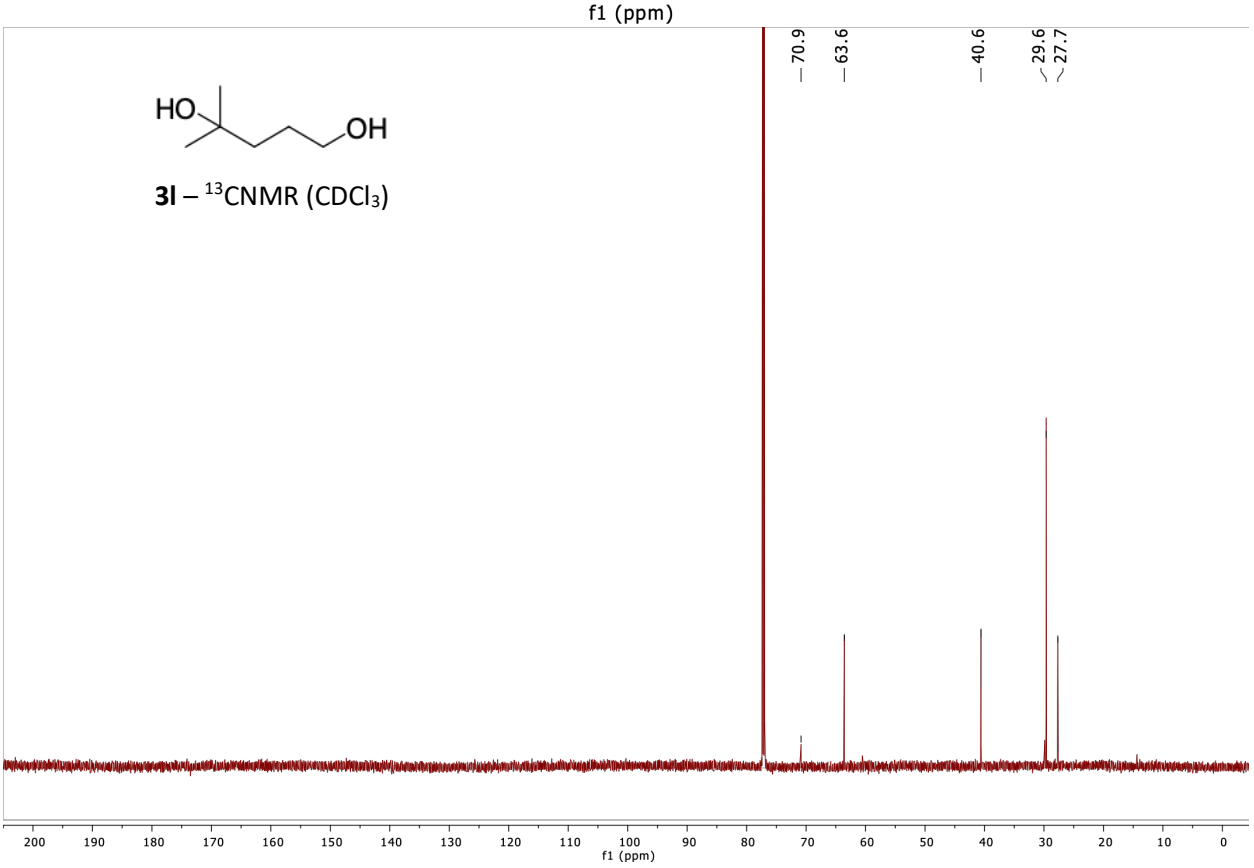
3k – ^{1}HNMR ($CDCl_3$)



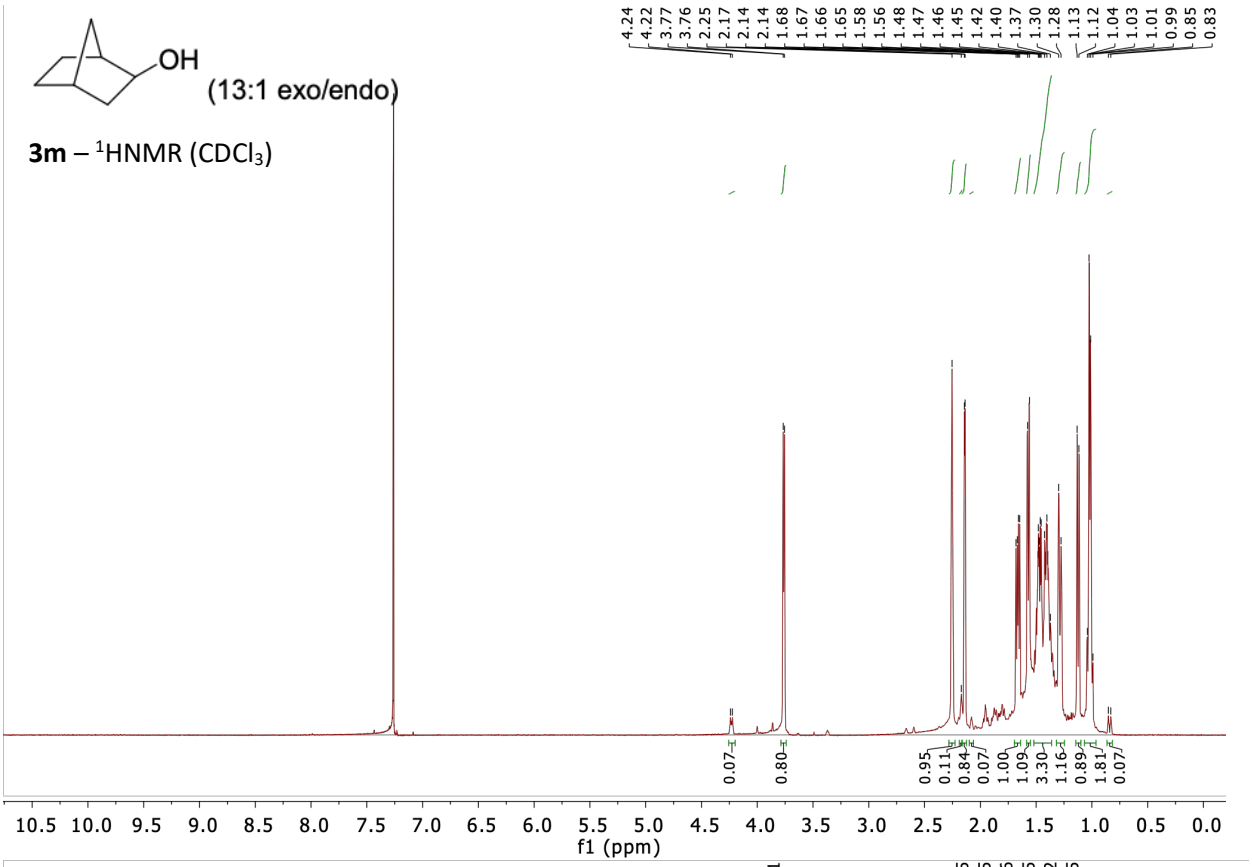
3k – ^{13}CNMR ($CDCl_3$)

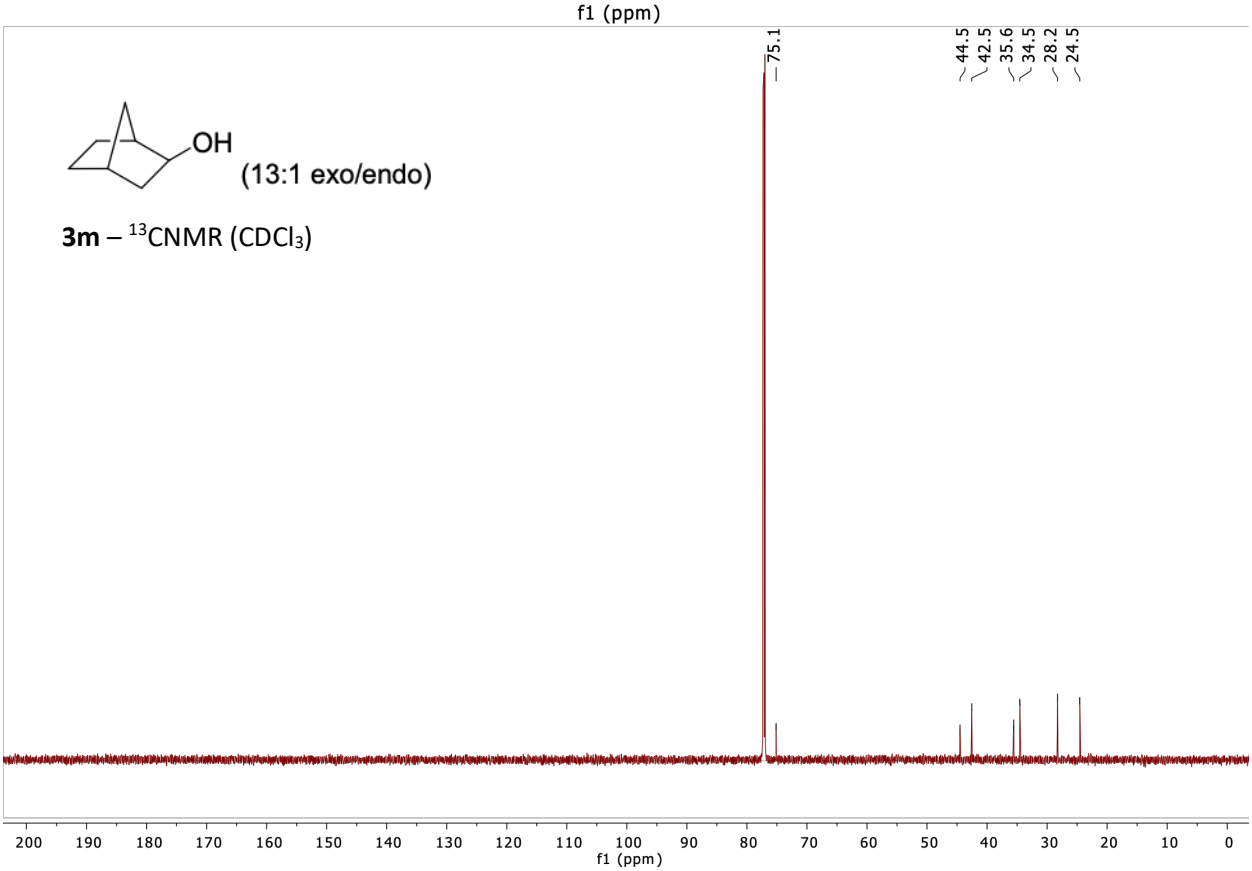


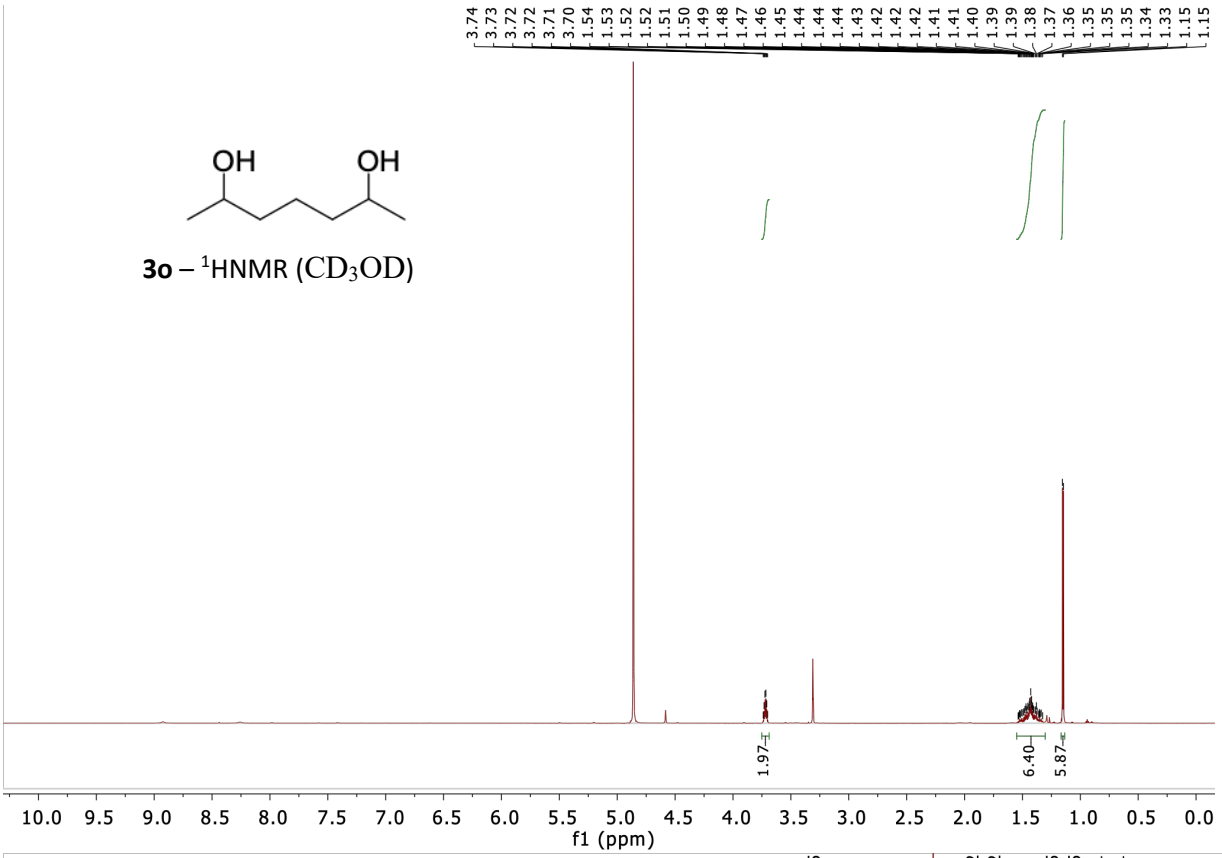
3l – ^{1}HNMR ($CDCl_3$)



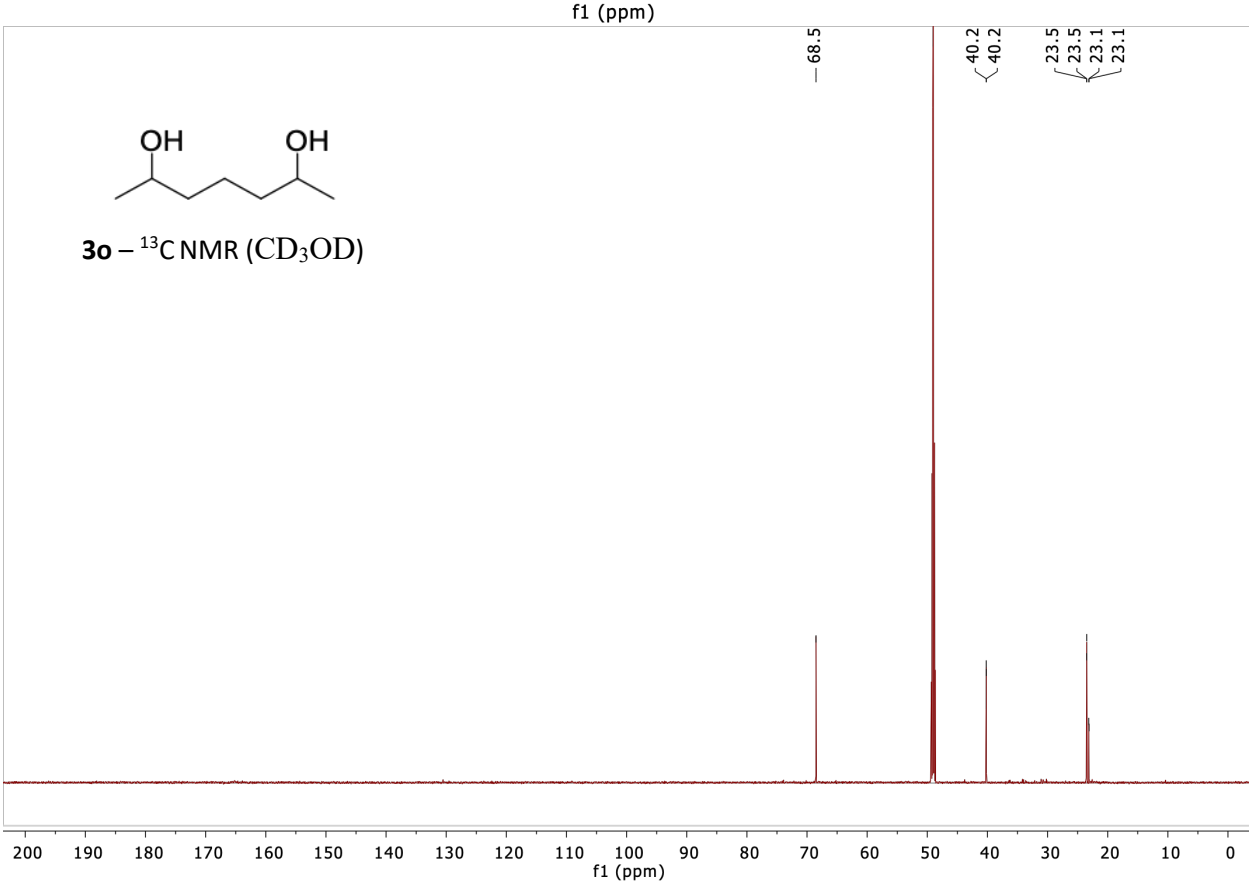
3l – ^{13}CNMR ($CDCl_3$)


OH
(13:1 exo/endo)
3m – 1HNMR (CDCl3)
4.24
4.22
3.77
3.76
2.25
2.17
2.14
2.14
1.68
1.67
1.66
1.65
1.58
1.56
1.48
1.47
1.46
1.45
1.42
1.40
1.37
1.30
1.28
1.13
1.12
1.04
1.03
1.01
0.99
0.85
0.83
0.07
0.80
0.95
0.11
0.84
0.07
1.00
1.09
3.30
1.16
0.89
1.81
0.07
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

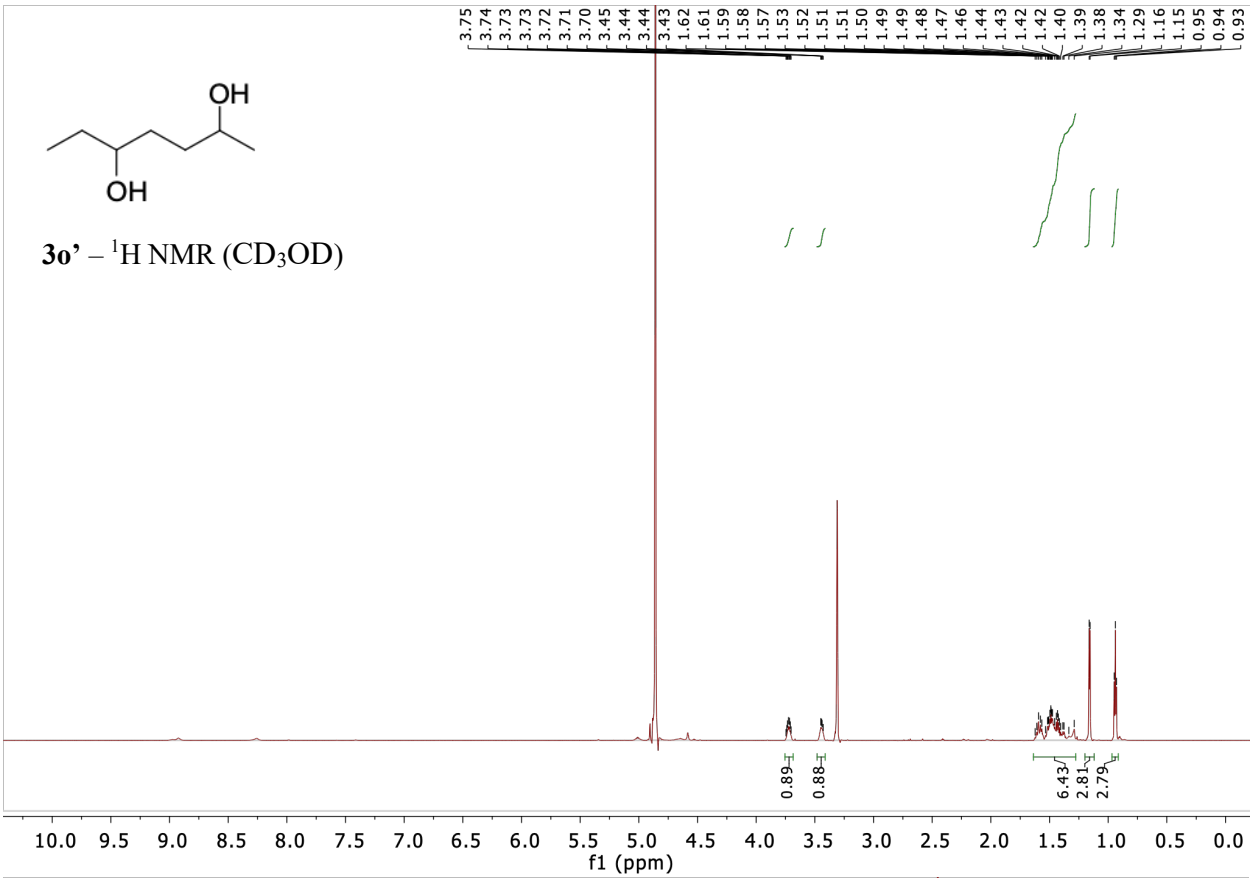

OH
(13:1 exo/endo)
3m – 13CNMR (CDCl3)
75.1
44.5
42.5
35.6
34.5
28.2
24.5
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



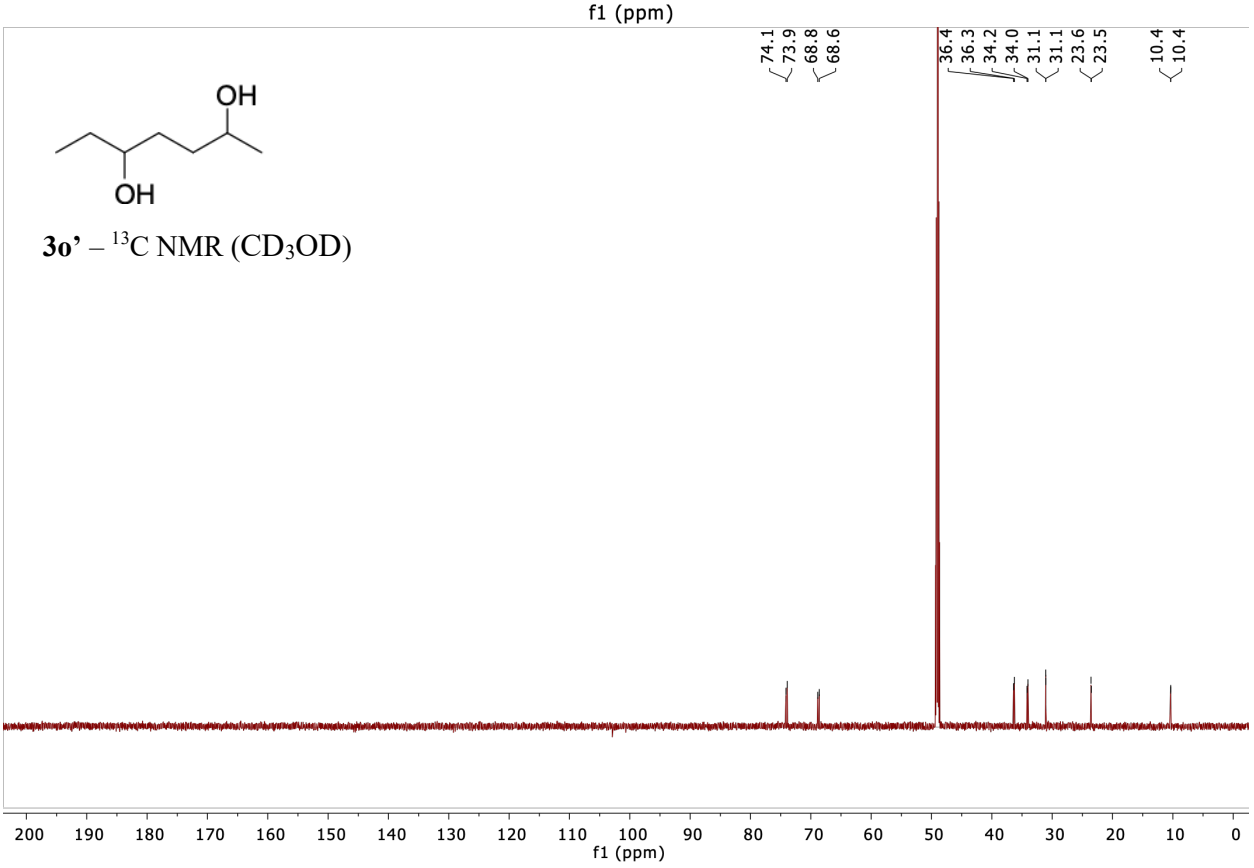
3o – ^{1}HNMR (CD_3OD)



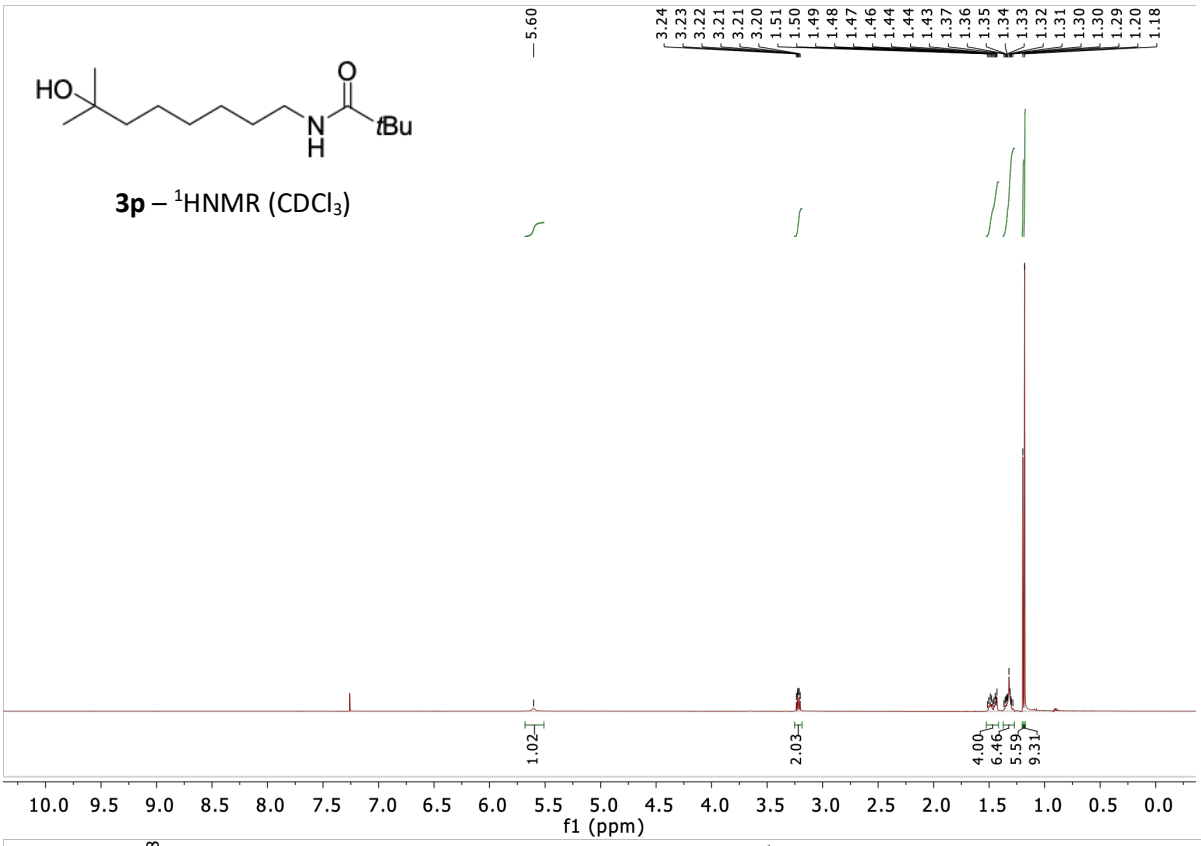
3o – ^{13}C NMR (CD_3OD)



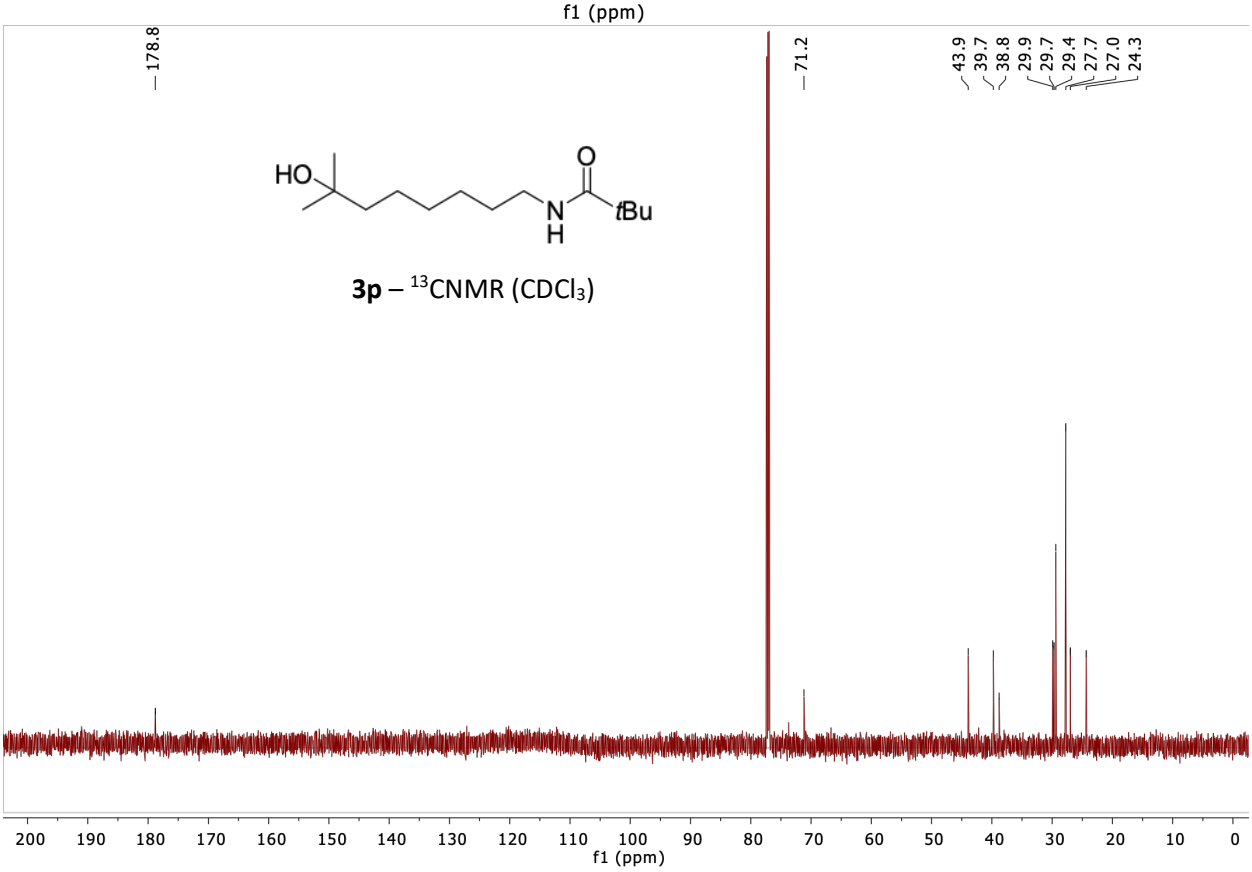
3o' – ^{1}H NMR (CD_3OD)



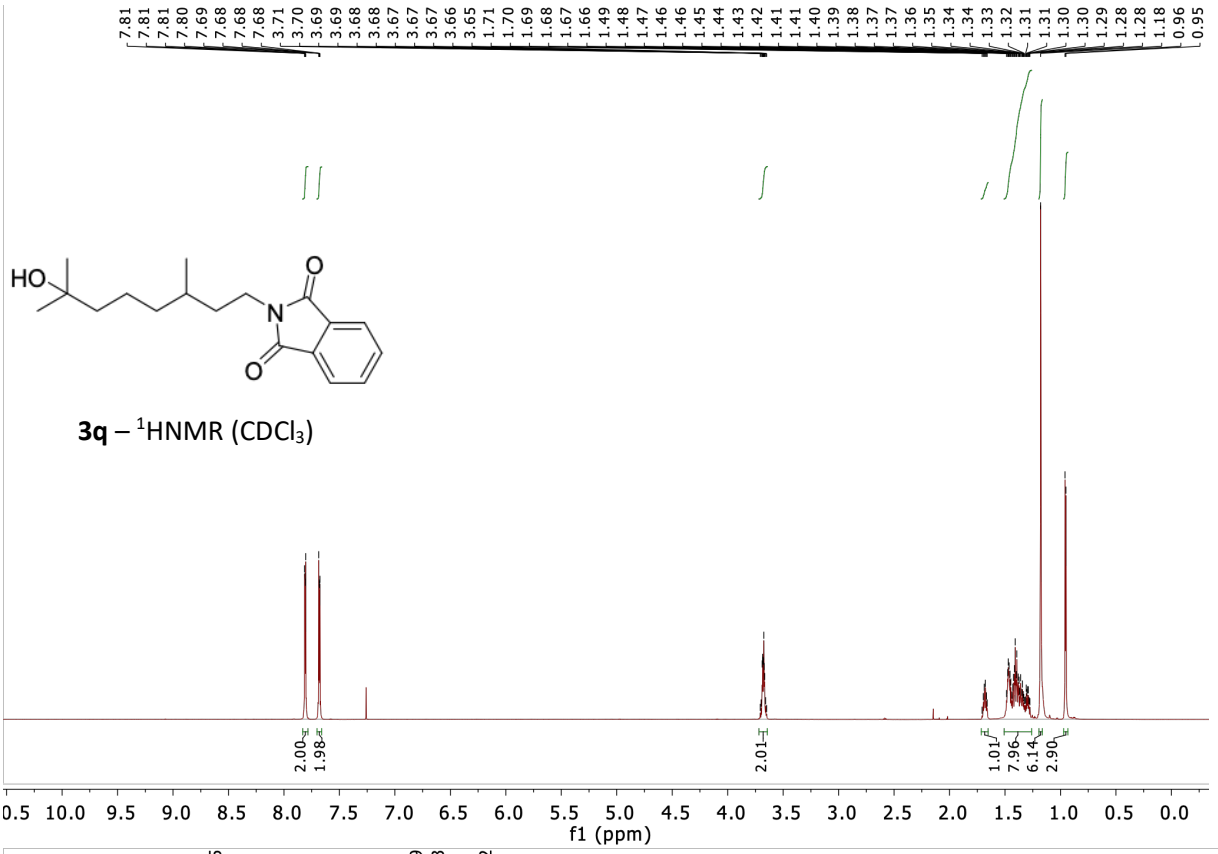
3o' – ^{13}C NMR (CD_3OD)



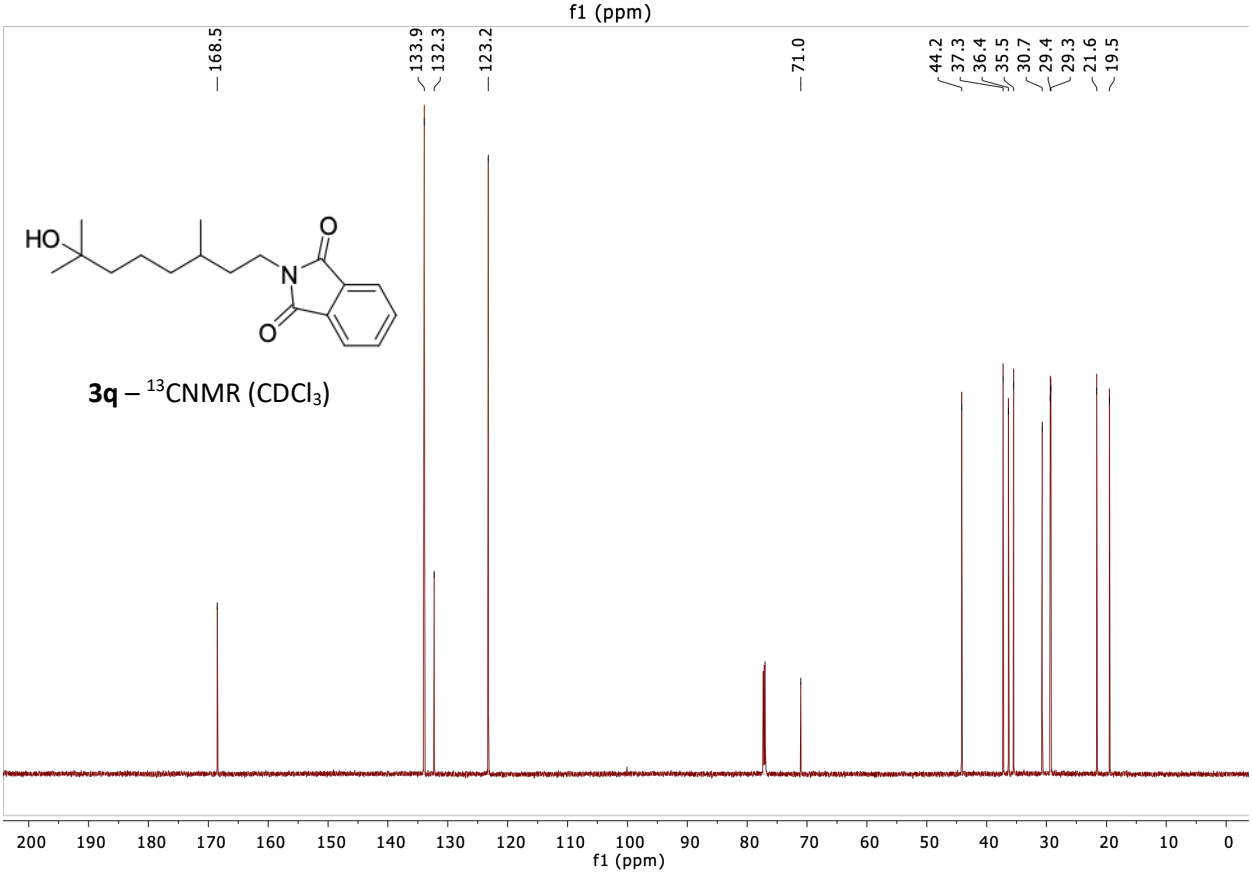
3p – ^{1}HNMR ($CDCl_3$)



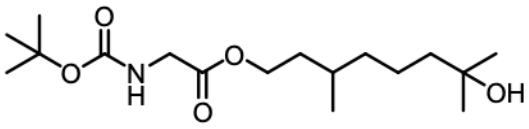
3p – ^{13}CNMR ($CDCl_3$)



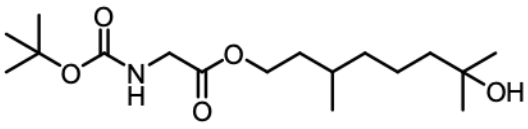
3q – ^{1}HNMR ($CDCl_3$)



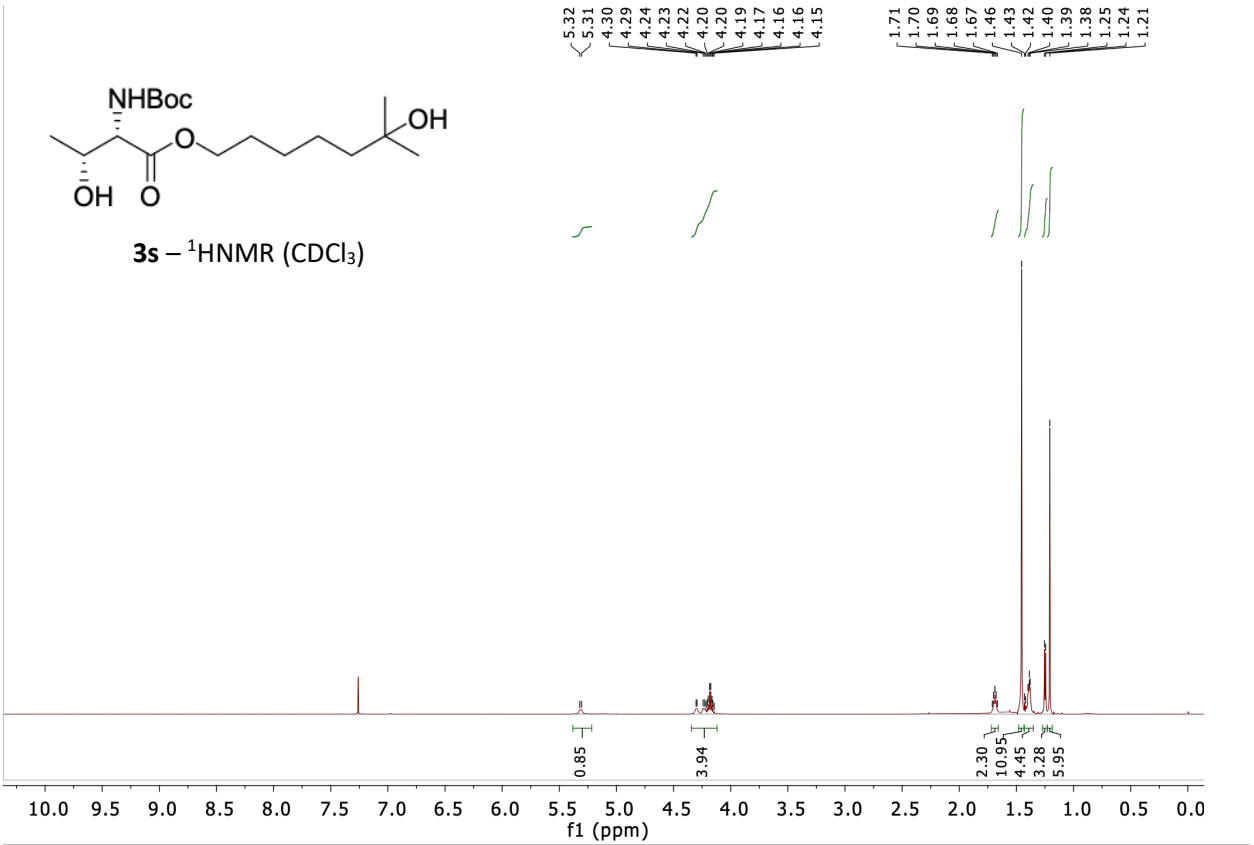
3q – ^{13}CNMR ($CDCl_3$)



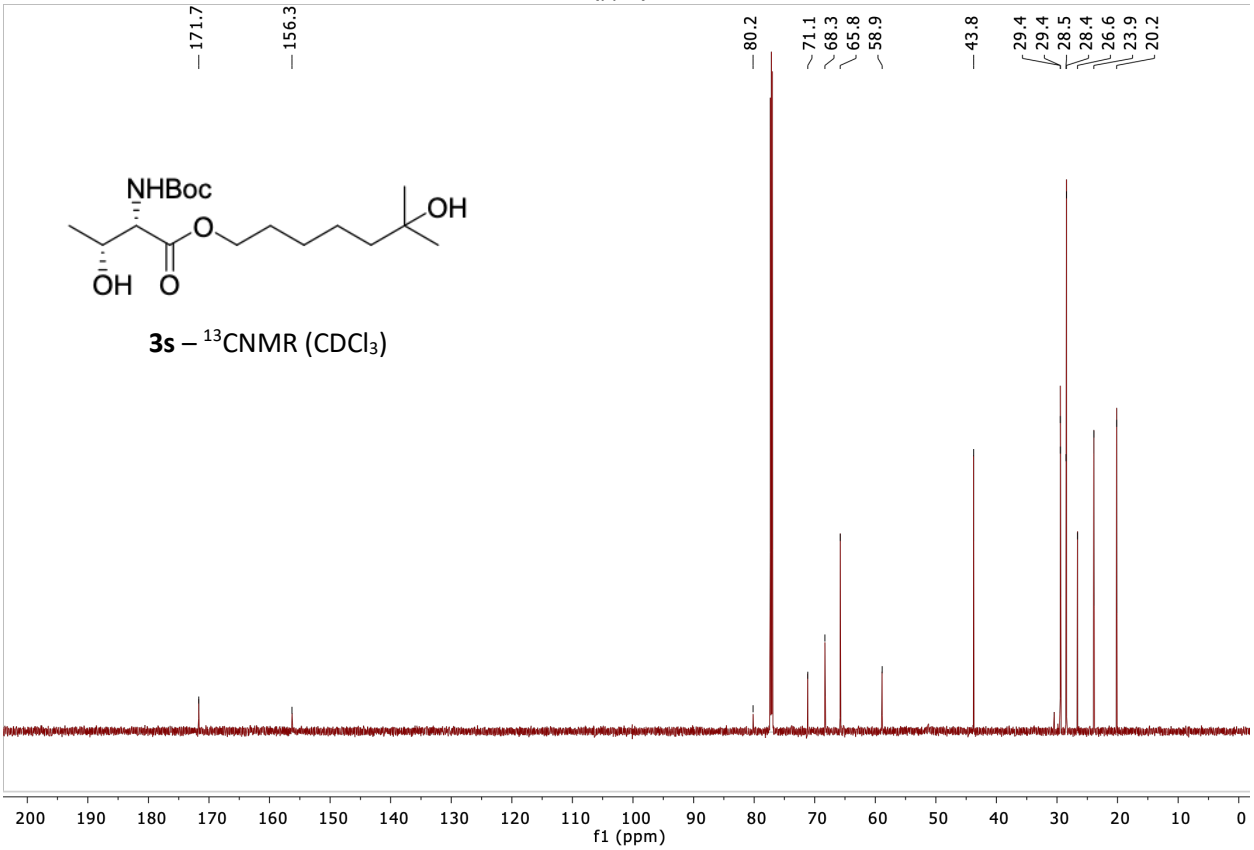
3r – ^{1}HNMR ($CDCl_3$)



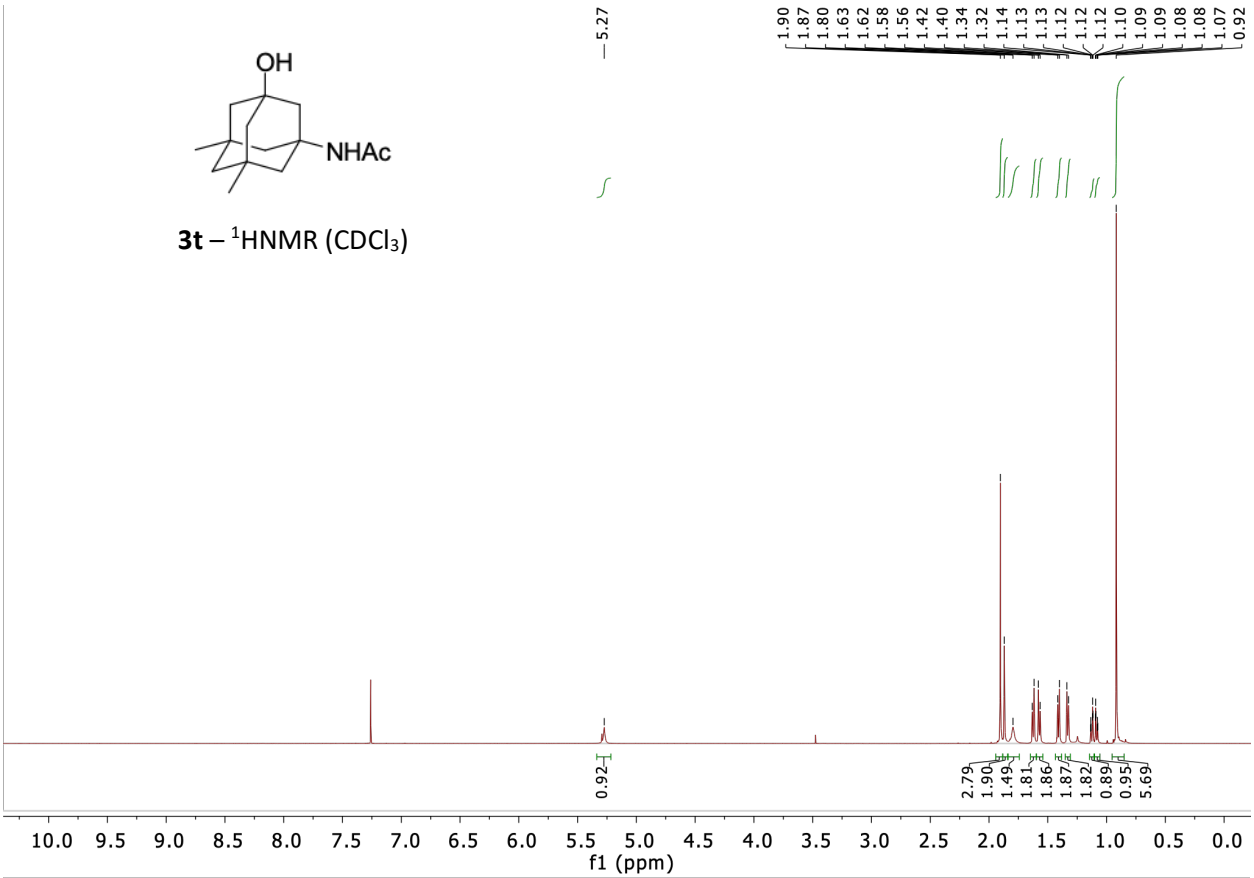
3r – ^{13}CNMR ($CDCl_3$)



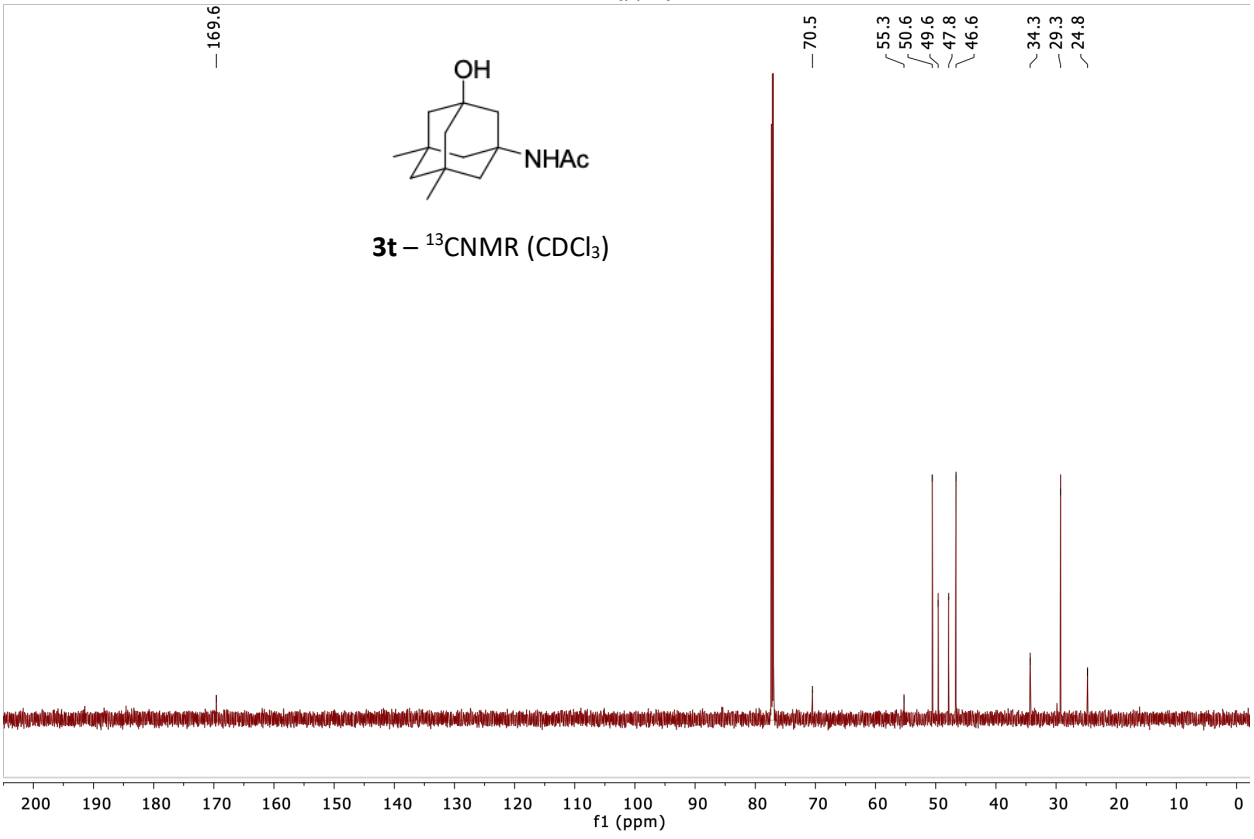
3s – ^{1}HNMR ($CDCl_3$)



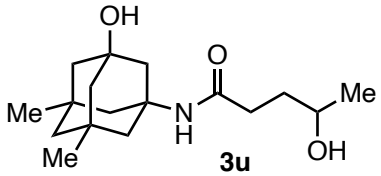
3s – ^{13}CNMR ($CDCl_3$)



3t – ^{1}HNMR ($CDCl_3$)

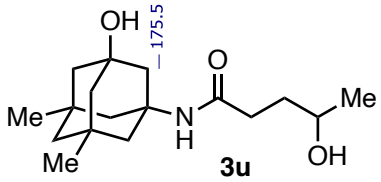


3t – ^{13}CNMR ($CDCl_3$)



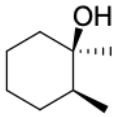
3u

^{1}H NMR, CD_3OD

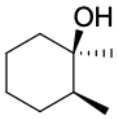


3u

^{13}C NMR, CD_3OD



3w – ^{1}HNMR ($CDCl_3$)



3w – ^{13}CNMR ($CDCl_3$)