

Synthesis of bio-based surfactants from cashew nutshell liquid in water

V. Bragoni, R. K. Rit, R. Kirchmann, A. S. Trita and L. J. Goossen*

*Ruhr-Universität Bochum, Lehrstuhl für Organische Chemie I, Geb. ZEMOS, Universitätsstraße 150,
44801 Bochum*

Fax.: +49 234 32 14675, E-mail: lukas.goossen@ruhr-uni-bochum.de

Supporting Information

Contents

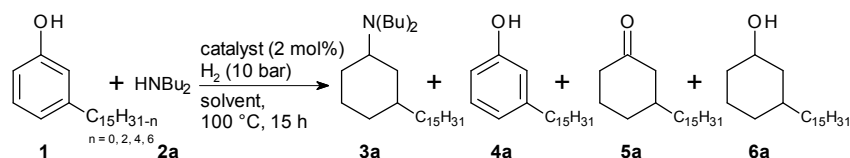
General methods.....	3
Additional Screening Experiments	3
General procedure 1 for the synthesis of cyclohexyl amines.....	4
General procedure 2 for the large scale synthesis of cyclohexyl amines.....	4
General procedure for the synthesis of <i>N</i> -oxides.....	4
Mechanistic investigations	5
Determination of surface tension and CMC.....	5
Synthesis and characterization of products	7
References.....	13
NMR spectra.....	14

General methods

All reactions were performed in oven-dried glassware containing a Teflon-coated stirring bar and dry septum. All reactions were monitored by GC using *n*-hexadecane as an internal standard. Response factors of the products with regard to *n*-hexadecane were obtained experimentally by analysing known quantities of the substances. GC analyses were carried out using a HP6890 with HP-5 capillary column (Phenyl Methyl Siloxane 30 m x 320 x 0.25, 100/2.3-30-300/3) and a time program beginning with 2 min at 60 °C followed by 30 °C/min ramp to 300 °C, then 8 min at this temperature. NMR spectra were recorded at ambient temperature using CDCl₃ as solvent, with proton, and carbon resonances at 400/300 and 100/75 MHz, respectively. All NMR data are reported in ppm relative to the solvent signal. Column chromatography was performed on a CombiFlash Companion (Isco) or on a Reveleris X2 (BUCHI) Flash Chromatography-System using Reveleris packed columns (12 g). HRMS analyses and mass spectrometric data were acquired on a Waters GCT Premier CAB163 with a TOF mass analyzer or on a Bruker Q-TOF Compact. Mass spectrometric data were also acquired on a GC-MS Agilent 5977B MSD. The MS ionization was achieved by EI+. CHN-elemental analyses were performed with a Hanau Elemental Analyzer vario Micro cube. Melting points were measured on a Mettler FP 61. Infrared spectra were recorded on Bruker Vertex 70 Spectrometer with Universal ATR Sampling Accessory. Surface tension was determined by the drop Shape analyser DSA 100 (KRUESS) connected to a syringe pump 100DX (Isco). Each measurement was taken at room temperature (ca. 25 °C). Commercial substrates and solvents were used as received unless otherwise stated. The cardanol mixture NC700 [CAS No.: 8007-24-7] was received from Cardolite and used after brief purification via acidic and basic aqueous work-up with a final purity of 90%.

Additional Screening Experiments

Table S1. Optimization of the reaction conditions



Entry	Equiv. 2a	Solvent	Catalyst	3a (%)	4a (%)	5a (%)	6a (%)
1	1.1	EtOH	Pd/C	15	75	trace	-
2	"	<i>i</i> PrOH	"	11	80	trace	-
3	"	toluene	"	17	67	6	-
4 ^b	"	"	"	12	88	-	-
5	"	cyclohexane	"	15	69	8	-
6	"	mesitylene	"	11	73	4	-
7 ^b	"	<i>p</i> -xylene	"	8	89	-	-
8 ^c	"	"	"	7	91	-	-
9	"	diglyme	"	8	81	trace	-
10	"	H ₂ O/ <i>i</i> PrOH	"	52	25	6	trace
11	"	H ₂ O	"	90	10	-	-
12	"	"	Pd/BaCO ₃	-	94	-	-
13	"	"	Pd/Al ₂ O ₃	-	90	trace	-

14	"	"	Pd/BaSO ₄	-	94	-	-
15	"	"	Pd/(OH) ₂	66	33	-	-
16	"	"	Rh/C	49	-	49	-
17	"	"	Rh/Al ₂ O ₃	37	-	45	12
18	"	"	Ru/C	-	-	97	-
19	"	"	Ru/Al ₂ O ₃	-	-	97	-
20	"	"	Al/Ni	-	92	-	-
21	"	"	Pt/C	-	97	trace	-
22 ^d	"	"	Pd/C	18	80	-	-
23	0.9	"	"	81	-	6	-
24	1.2	"	"	81	14	-	-
25	1.5	"	"	42	56	-	-
26	-	"	"	-	33	6	58
27 ^e	1.1	"	"	40	41	trace	trace
28 ^f	"	"	"	90	-	trace	-
29 ^g	"	"	"	61	7	12	-

[a] Reaction conditions: 0.5 mmol **1a**, 2 mol% catalyst **2a**, 10 bar H₂, 2 mL solvent, 100 °C, 15 h. Yields determined by GC using *n*-hexadecane as internal standard. [b] 5 mol% In(OTf)₃. [c] 5 mol% Hf(OTf)₄. [d] 1 mol% Pd/C. [e] 80 °C. [f] 5 bar H₂. [g] 1 bar H₂.

General procedure 1 for the synthesis of cyclohexyl amines

An oven-dried 10 mL headspace vial with Teflon-coated stirring bar was charged with palladium on charcoal (0.02 mmol, 10 wt%, 21.3 mg), cardanol (**1**, 1.00 mmol, 332 mg), an amine (1.10 mmol) and water (3 mL). The vial was closed with a septum cap, penetrated with a cannula for pressure equilibration and placed into an autoclave. The system was purged twice with H₂ (10 bar) and finally pressurized to 5 bar. The resulting mixture was stirred (300 rpm) at 100 °C for 15 h. After cooling down to r.t., the pressure was slowly released under constant stirring at 300 rpm. The mixture was diluted with 20 mL of diethyl ether, washed with KOH solution 2M (20 ml) and water (2 x 10 ml). The aqueous phases were extracted with diethyl ether (2 x 15 ml), the combined organic layers were washed with brine (10 ml), filtered over celite and MgSO₄ and the solvent was removed under reduced pressure. The residue was separated by column chromatography (SiO₂, Chloroform containing 1.5 vol% NEt₃/ethyl acetate gradient) yielding the corresponding cyclohexyl amine derivative.

General procedure 2 for the large scale synthesis of cyclohexyl amines

A 1 L Parr autoclave was charged with Pd/C, cardanol and an amine. A solution of water (165 ml) and isopropanol (85 ml) was added. The system was purged twice with H₂ (30 bar) and finally pressurized at 40 bar. The mixture was stirred at 1000 rpm at 100 °C for 15 h. After cooling down to r.t., the pressure was slowly released. The mixture was filtered through celite and diluted with 150 mL of pentane. Sulfuric acid was added to reach pH 2 and the organic layer was removed. The water phase was washed with pentane (2 x 50 mL) and ethyl acetate (50 mL). The water phase was neutralized with NaOH and extracted with diethyl ether (4 x 40 mL). The solvent was removed under reduced pressure yielding the corresponding product.

General procedure for the synthesis of *N*-oxides

Hydrogen peroxide (3.00 mmol, 35 wt%, 292 mg, 0.26 mL) was added to a headspace vial and cooled to 0 °C. Corresponding cyclohexyl amine (1 mmol) was added drop-wise over 5 minutes. The solution was allowed to warm to room temperature and stirred for 30 minutes before heating to 30 °C for additional 10 minutes. After that, the solvent was removed under reduced pressure (60 °C). The residue was dried under vacuum yielding the corresponding product

Procedure for the one-pot amination/oxidation sequence

The reductive amination of cardanol **1** (1.00 mmol, 332 mg) and dimethyl amine (1.10 mmol, 40 wt%, 124 mg, 146 μ L) with Pd/C (0.02 mmol, 10 wt%, 21.3 mg) was performed following the general procedure 1. After the reaction time, the mixture was cooled down to 0 °C. Hydrogen peroxide (10.0 mmol, 35 wt%, 972 mg, 875 μ L) was added dropwise over 5 minutes *via* syringe. The mixture was allowed to warm to room temperature and stirred for 30 minutes. The solution was heated to 30 °C and stirred for additional 10 minutes. The mixture was diluted with 3 ml of water and washed with pentane (2 x 5 mL). The combined organic phases were extracted with water (2 x 5 mL) and the combined aqueous phases were concentrated under reduced pressure at 60 °C. The residue was dried under reduced pressure yielding **3b** as yellowish solid (252 mg, 71%).

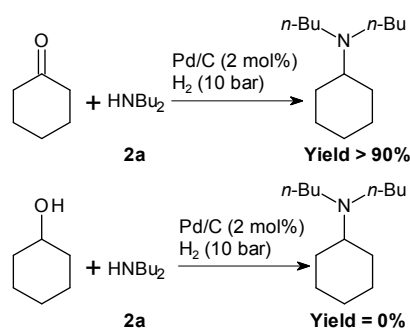
E-factor calculation^{1,2}:

$$E \text{ (withouth water)} = \frac{(332 + 49.6 + 21.3 + 340.2 - 248) \text{ mg}}{248 \text{ mg}} = 1.99$$

$$E \text{ (including water)} = \frac{(332 + 124 + 21.3 + 972 - 248) \text{ mg}}{248 \text{ mg}} = 4.84$$

Mechanistic investigations

Reductive amination of cyclohexanone and cyclohexanol



Scheme S1. Control experiments. 0.5 mmol of cyclohexanone or cyclohexanol, 0.55 mmol **2a**, 2 mol% Pd/C, 10 bar H₂, 2 mL H₂O, 100 °C, 15 h.

Determination of surface tension and CMC

The surface tension of aqueous solutions of the surfactants **4b**, **5b** and **6b** and their critical micellar concentration were determined via the pendant drop method. The surface tension of deionised water, was determined at the beginning of the measurements. The surface tension of aqueous solutions **4b**, **5b** and **6b** were measured over a wide concentration range to determine the critical micellar concentration (CMC). The concentration range of the solutions for each surfactant, spaced from 0.1 M to 30 mM aqueous solution. The surface tension of water (68-69 mN/m) was measured before each set of measurements. The surface tension of the surfactant solutions was measured three times for

each concentration and the average values of the three measurements were plotted as a function of $\log C$ (figure S1).

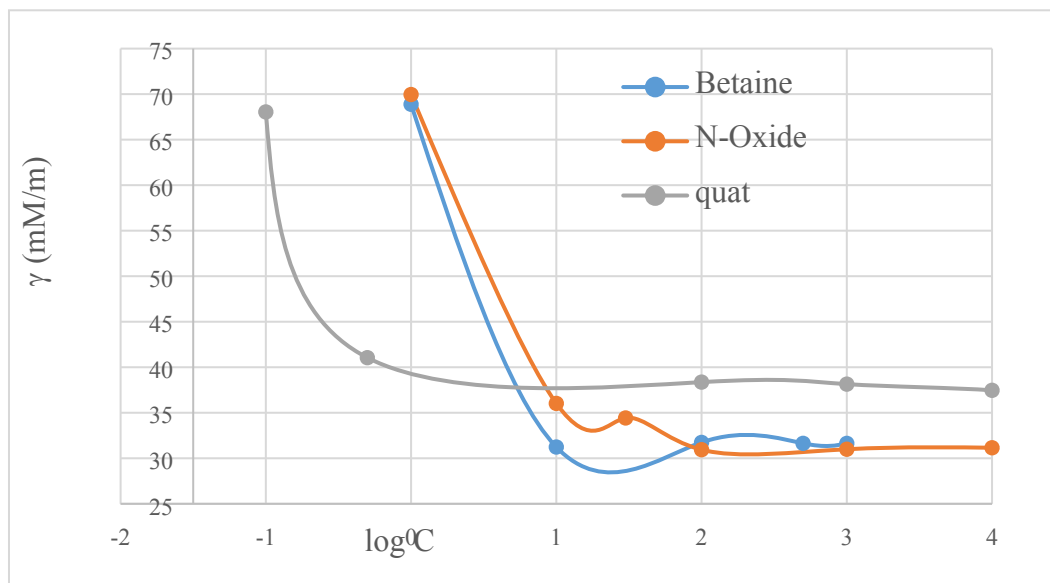
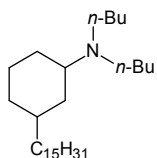


Fig. S1. The plots of the surface tension (γ in mN/m) versus $\log C$ (concentration of surfactant in μM) at r.t..

Synthesis and characterization of products

N,N-dibutyl-3-pentadecylcyclohexylamine (**3a**)



Compound **3a** was prepared following the general procedure 1 from **1** (0.50 mmol, 166 mg) and di-*n*-butyl amine (0.55 mmol, 71.4 mg) but with a hydrogen pressure of 10 bar. **3a** was isolated as yellow oil (181 mg, 86%, mixture of diastereomers).

Additionally, compound **3a** was prepared in preparative scale following general procedure 2, starting from **1** (50.0 mmol, 14.92 g) and di-*n*-butyl amine (50.0 mmol, 6.53 g), yielding **3a** (14.0 g, 33.0 mmol, 66%).

IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ = 2955 (m), 2921 (s), 2852 (s), 1464 (m), 1377 (w), 721 (w).

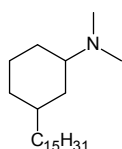
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.56 - 2.70 (m, 1 H), 2.35 - 2.48 (m, 4 H), 1.77 (d, $J=3.1$ Hz, 1 H), 1.14 - 1.70 (m, 44 H), 0.84 - 0.95 (m, 9 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 60, 54.3, 50.5, 50.1, 37.7, 37.6, 35.9, 33.4, 33.2, 32.9, 31.9, 31.6, 30.8, 30.7, 30.0, 29.9, 29.71, 29.67, 29.44, 29.37, 28.5, 27.8, 27.0, 25.6, 22.7, 21.0, 20.75, 20.74, 14.14, 14.10 ppm.

MS (EI-TOF) m/z (%): 421 (4) [M^+], 379 (25), 378 (100), 322 (7), 210 (16), 168 (15), 97 (12).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{29}\text{H}_{59}\text{N}$: 421.4648; found: 421.4641.

N,N-dimethyl-3-pentadecylcyclohexylamine (**3b**)



Compound **3b** was prepared following the general procedure 1 from **1** and dimethyl amine (1.1 mmol, 124 mg) but with a hydrogen pressure of 10 bar. **3b** was isolated as yellow oil (287 mg, 85%, mixture of diastereomers).

Additionally, compound **3b** was prepared in preparative scale following general procedure 2, starting from **1** (68 mmol, 20 g) and dimethyl amine (81.6 mmol, 40 wt%, 9.2 g), yielding **3b** (14.8 g, 43.0 mmol, 64%).

IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ = 2920 (s), 2852 (s), 2810 (w), 2766 (m), 1463 (m), 1042 (w), 998 (w), 721 (w).

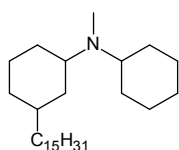
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.24 (s, 6 H), 2.14 - 2.21 (m, 1 H), 1.13 - 1.78 (m, 37 H), 0.88 (s, 3 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 60.0, 42.7, 34.8, 34.6, 32.2, 31.9, 31.7, 29.9, 29.7, 29.6, 29.3, 29.1, 27.4, 22.7, 20.5, 14.1 ppm.

MS (EI-TOF) m/z (%): 337 (29) [M^+], 295 (22), 294 (100), 266 (9), 127 (10), 126 (99), 84 (63).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{23}\text{H}_{47}\text{N}$: 337.3709; found: 337.3705.

***N*-cyclohexyl-*N*-methyl-3-pentadecylcyclohexylamine (3c)**



Compound **3c** was prepared following the general procedure 1 from **1** and *N*-methylaniline (1.1 mmol, 119 mg) and isolated as colorless oil (283 mg, 70%, mixture of diastereomers).

IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ = 2920 (s), 2851 (s), 2783 (w), 1451 (m), 1262 (w), 1013 (w), 891 (w), 721 (w).

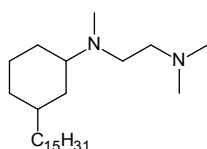
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.61 - 2.75 (m, 1 H), 2.53 (d, $J=7.6$ Hz, 1 H), 2.17 - 2.28 (m, 3 H), 1.77 (br. s., 6 H), 1.53 - 1.67 (m, 3 H), 1.45 (d, $J=7.1$ Hz, 3 H), 1.14 - 1.36 (m, 35 H), 0.89 (t, $J=6.2$ Hz, 3 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 59.3, 58.4, 54.1, 37.7, 37.6, 34.8, 33.6, 32.8, 32.87, 32.8, 31.9, 31.1, 30.5, 30.4, 30.0, 29.9, 29.8, 29.78, 29.71, 29.69, 29.65, 29.3, 27.7, 26.9, 26.4, 26.3, 26.2, 22.7, 20.9, 14.1 ppm.

MS (EI-TOF) m/z (%): 405 (24) [M^+], 404 (30), 363 (26), 362 (100), 334 (21), 195 (12), 194 (77), 152 (54).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{28}\text{H}_{55}\text{N}$: 405.4335; found: 405.4342.

***N*¹,*N*¹,*N*²-trimethyl-*N*²-(3-pentadecylcyclohexyl)ethane-1,2-diamine (3d)**



Compound **3d** was prepared following the general procedure 1 from **1** (0.5 mmol, 166 mg) and *N,N,N'*-trimethylethylenediamine (0.55 mmol, 56.8 mg) and isolated as pale yellow oil (145 mg, 74%, mixture of diastereomers).

IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ = 2921 (s), 2852 (s), 2815 (w), 2765 (w), 1746 (w), 1463 (m), 1365 (w), 1263 (w), 1037 (m), 721 (w).

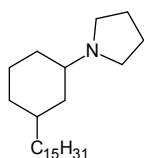
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.57 (br. s., 3 H), 2.42 (s, 2 H), 2.21 - 2.33 (m, 9 H), 1.73 - 1.87 (m, 1 H), 1.53 (br. s., 4 H), 1.14 - 1.48 (m, 32 H), 0.83 - 0.94 (m, 3 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 58.0, 57.4, 51.5, 45.8, 38.6, 33.2, 32.9, 31.9, 30.8, 30.3, 29.9, 29.7, 29.65, 29.3, 28.8, 27.7, 22.7, 20.7, 14.1 ppm.

MS (EI-TOF) m/z (%): 394 (1) [M^+], 337 (30), 336 (100), 297 (7), 280 (2), 236 (1), 126 (9), 84 (16).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{26}\text{H}_{54}\text{N}_2$: 394.4287; found: 394.4279.

***N,N*-tetramethylen-3-pentadecylcyclohexylamine (3e)**



Compound **3e** was prepared following the general procedure 1 from **1** and pyrrolidin (1.1 mmol, 79 mg) with a hydrogen pressure of 10 bar. **3g** was isolated as yellowish solid (270 mg, 74%, mixture of diastereomers).

m.p.: 35-37 °C.

Elemental analysis found: C, 82.2; H, 13.4; N, 3.8. Calc. for $\text{C}_{25}\text{H}_{49}\text{N}$: C, 82.6; H, 13.6; N, 3.8%.

IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ = 2949 (w), 2916 (s), 2849 (s), 2781 (m), 1463 (m), 907 (w), 720 (m).

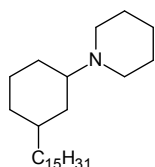
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.51 (br. s., 4 H), 1.93 - 2.21 (m, 2 H), 1.77 (s, 9 H), 1.27 (s, 31 H), 0.89 (s, 3 H) ppm.

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ = 63.7, 60.1, 51.9, 51.5, 39.1, 37.5, 37.1, 36.7, 35.3, 32.7, 32.03, 32.0, 31.9, 31.5, 30.0, 29.7, 29.66, 29.4, 27.3, 26.9, 25.0, 23.4, 23.2, 22.7, 20.4, 14.1 ppm.

MS (EI-TOF) m/z (%): 363 (22) [M^+], 321 (20), 320 (85), 153 (12), 152 (100), 110 (66), 97 (17).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{25}\text{H}_{49}\text{N}$: 363.3865; found: 363.3871.

***N*-(3-pentadecylcyclohexyl)piperidine (3f)**



Compound **3f** was prepared following the general procedure 1 from **1** and piperidine (1.1 mmol, 94.6 mg). **3j** was isolated as orange-yellow solid in 80% yield (300mg) when a pressure of 5 bar was used and in 84% yield (317 mg) when a pressure of 10 bar was employed (mixture of diastereomers).

m.p.: 32-33 °C.

Elemental analysis found: C, 82.2; H, 13.5; N, 3.5. Calc. for $\text{C}_{26}\text{H}_{51}\text{N}$: C, 82.7; H, 13.6; N, 3.7%.

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2916 (s), 2850 (s), 1469 (m), 1150 (w), 1112 (m), 717 (m).

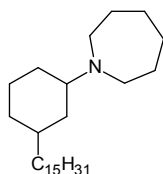
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.41 - 2.58 (m, 4 H), 2.25 - 2.39 (m, 1 H), 1.18 - 1.92 (m, 43 H), 0.88 (s, 3 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 64.21, 58.9, 50.37, 50.1, 37.61, 37.60, 35.7, 33.42, 33.38, 33.3, 32.96, 31.9, 31.02, 29.95, 29.93, 29.69, 29.65, 29.4, 28.9, 28.03, 27.7, 26.9, 26.6, 26.5, 25.6, 24.97, 24.9, 22.7, 20.9, 14.1 ppm.

MS (EI-TOF) m/z (%): 377 (30) [M^+], 335 (22), 334 (89), 167 (14), 166 (100), 124 (67), 84 (11).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{26}\text{H}_{51}\text{N}$: 377.4022; found: 377.4026.

***N,N*-Hexamethylen-3-pentadecylcyclohexylamine (3g)**



Compound **3j** was prepared following the general procedure 1 from **1** and hexamethyleneimine (1.1 mmol, 110 mg) with a hydrogen pressure of 10 bar. **3f** was isolated as light yellow oil (302 mg, 77%, mixture of diastereomers).

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2919 (s), 2851 (s), 1456 (m), 1356 (w), 1127 (w), 967 (w), 921 (w).

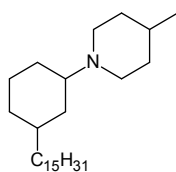
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.77 - 2.95 (m, 4 H), 1.34 - 2.05 (m, 17 H), 1.13 - 1.33 (m, 29 H), 0.81 - 0.89 (m, 3 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 51.2, 51.1, 48.2, 39.1, 37.31, 37.27, 36.6, 32.9, 31.9, 31.3, 29.9, 29.8, 29.7, 29.64, 29.62, 29.3, 28.7, 27.7, 27.1, 27.0, 26.8, 25.3, 25.1, 22.6, 20.5, 14.1 ppm.

MS (EI-TOF) m/z (%): 391 (26) [M^+], 390 (10), 376 (13), 349 (21), 348 (100), 181 (12), 180 (94), 138 (63).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{27}\text{H}_{53}\text{N}$: 391.4178; found: 391.4173.

4-methyl-1-(3-pentadecylcyclohexyl)piperidine (3h)



Compound **3g** was prepared following the general procedure 1 from **1** and 4-methylpiperidine (1.1 mmol, 111 mg) and isolated as pale-yellow oil (239 mg, 61%, mixture of diastereomers).

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2919 (s), 2851 (s), 1456 (m), 1259 (w), 1075 (w), 971 (w), 720 (w).

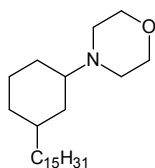
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.81 - 2.95 (m, 2 H), 1.96 - 2.42 (m, 3 H), 1.62 (d, $J=13.6$ Hz, 7 H), 1.26 (s, 35 H), 0.84 - 0.93 (m, 6 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 63.8, 58.6, 49.9, 49.8, 49.6, 49.1, 37.59, 37.56, 35.8, 34.9, 34.8, 33.6, 33.4, 33.2, 32.9, 31.9, 31.2, 31.1, 31.0, 30.0, 29.9, 29.68, 29.65, 29.4, 29.0, 28.1, 27.7, 26.9, 25.5, 22.7, 22.0, 21.9, 20.8, 14.1 ppm.

MS (EI-TOF) m/z (%): 391 (43) [M^+], 349 (20), 348 (83), 181 (13), 180 (100), 138 (57).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{27}\text{H}_{53}\text{N}$: 391.4178; found: 391.4174.

N-(3-pentadecylcyclohexyl)morpholine (3i)



Compound **3h** was prepared following the general procedure 1 from **1** and morpholin (1.1 mmol, 95.8 mg) and isolated as colorless solid (322 mg, 85%, mixture of diastereomers).

m.p.: 49-51 °C.

Elemental analysis found: C, 78.8; H, 12.8; N, 3.4. Calc. for $\text{C}_{25}\text{H}_{49}\text{NO}$: C, 79.1; H, 13.0; N, 3.7%.

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2951 (w), 2915 (s), 2848 (s), 1463 (m), 1267 (m), 1122 (s), 988 (m), 884 (m), 719 (w).

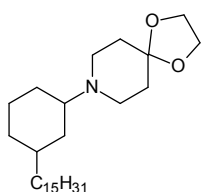
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 3.71 (t, $J=4.6$ Hz, 4 H), 2.42 - 2.61 (m, 4 H), 2.16 - 2.32 (m, 1 H), 1.14 - 1.96 (m, 37 H), 0.84 - 0.92 (m, 3 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 67.5, 67.4, 63.7, 58.9, 50.2, 49.6, 37.5, 37.3, 35.8, 34.6, 33.9, 32.9, 32.2, 31.9, 31.6, 29.9, 29.7, 29.6, 29.4, 28.6, 28.3, 27.4, 26.9, 25.3, 22.7, 20.5, 14.1 ppm.

MS (EI-TOF) m/z (%): 379 (27) [M^+], 337 (20), 336 (79), 169 (12), 168 (100), 126 (63), 97 (29).

HRMS-EI (TOF): [M^+] calcd. for $\text{C}_{25}\text{H}_{49}\text{NO}$: 379.3814; found: 379.3820.

8-(3-pentadecylcyclohexyl)-1,4-dioxo-8-azaspiro[4.5]decane (3j)



Compound **3i** was prepared following the general procedure 1 from **1** and 1,4-Dioxo-8-azaspiro[4.5]decane (1.1 mmol, 161 mg) and isolated as colorless solid (291 mg, 67%, mixture of diastereomers).

m.p.: 36-37 °C.

Elemental analysis found: C, 77.0; H, 12.2; N, 3.1. Calc. for C₂₈H₅₁NO₂: C, 77.2; H, 12.3; N, 3.2%.

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2952 (w), 2917 (s), 2849 (s), 1466 (m), 1133 (w), 1070 (m), 1038 (m), 914 (m), 943 (w), 721 (w).

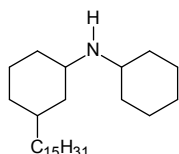
¹H-NMR (300 MHz, CDCl₃) δ = 3.95 (s, 4 H), 2.62 (br. s., 4 H), 2.33 - 2.52 (m, 1 H), 1.33 - 1.98 (m, 13 H), 1.07 - 1.32 (m, 28 H), 0.88 (s, 3 H) ppm.

¹³C-NMR (75 MHz, CDCl₃) δ = 107.5, 65.5, 64.2, 58.1, 47.1, 46.8, 37.5, 35.1, 33.6, 33.4, 32.9, 31.9, 30.9, 29.94, 29.90, 29.68, 29.65, 29.4, 29.1, 27.7, 26.9, 25.5, 22.7, 20.8, 14.1 ppm.

MS (EI-TOF) m/z (%): 435 (36) [M⁺], 393 (18), 392 (70), 349 (6), 225 (15), 224 (100), 182 (51), 156 (10).

HRMS-EI (TOF): [M⁺] calcd. for C₂₈H₅₃NO₂: 435.4076; found: 435.4060.

N-cyclohexyl-3-pentadecylcyclohexylamine (3k)



Compound **3k** was prepared following the general procedure 1 from **1** and cyclohexylamine (1.1 mmol, 110 mg) and isolated as yellowish oil (332 mg, 85%, mixture of diastereomers).

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2920 (s), 2851 (s), 2667 (w), 1464 (m), 1448 (m), 1368 (w), 1144 (w), 1113 (w), 887 (w), 719 (m).

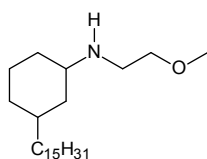
¹H-NMR (300 MHz, CDCl₃) δ = 2.84 - 2.95 (m, 1 H), 2.38 - 2.63 (m, 1 H), 1.37 - 1.94 (m, 11 H), 0.92 - 1.36 (m, 35 H), 0.84 - 0.91 (m, 3 H), 0.55 - 0.83 (m, 1 H) ppm.

¹³C-NMR (75 MHz, CDCl₃) δ = 53.3, 53.2, 53.1, 42.2, 41.5, 38.1, 37.4, 36.9, 35.4, 34.5, 34.4, 34.3, 34.1, 32.9, 32.1, 32.0, 31.9, 31.8, 29.94, 29.92, 29.7, 29.65, 29.64, 29.3, 27.2, 26.9, 26.21, 26.18, 25.3, 25.2, 25.1, 22.7, 20.4, 14.1 ppm.

MS (EI-TOF) m/z (%): 391 (1) [M⁺], 337 (31), 336 (7), 295 (17), 294 (100), 126 (62), 84 (31).

HRMS-EI (TOF): [M⁺] calcd. for C₂₇H₅₃N: 391.4178; found: 391.4166.

N-(2-methoxyethyl)-3-pentadecylcyclohexylamine (3l)



Compound **3l** was prepared following the general procedure 1 from **1** and 2-methoxyethylamine (1.1 mmol, 83.5 mg) and isolated as yellow oil (283 mg, 70%, mixture of diastereoisomers).

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2920 (s), 2851 (s), 1458 (m), 1116 (m), 721 (m).

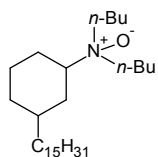
¹H-NMR (300 MHz, CDCl₃) δ = 3.46 - 3.55 (m, 2 H), 3.32 - 3.39 (m, 3 H), 2.77 (dd, *J*=5.4, 1.4 Hz, 2 H), 1.85 - 1.98 (m, 1 H), 1.41 - 1.81 (m, 7 H), 0.94 - 1.39 (m, 31 H), 0.83 - 0.93 (m, 3 H) ppm.

¹³C-NMR (75 MHz, CDCl₃) δ = 72.4, 72.3, 58.74, 52.72, 57.0, 52.4, 49.7, 46.4, 40.5, 37.5, 37.3, 36.7, 35.5, 33.5, 32.9, 32.0, 31.9, 31.8, 31.5, 30.0, 29.9, 29.7, 29.6, 29.3, 27.2, 26.9, 24.9, 22.7, 20.3, 14.1 ppm.

MS (EI-TOF) m/z (%): 367 (2) [M⁺], 323 (22), 322 (100), 294 (3), 156 (5), 114 (4), 97 (18).

HRMS-EI (TOF): [M⁺] calcd. for C₂₄H₄₉NO: 367.3814; found: 367.3831.

***N,N*-dibutyl-3-pentadecylcyclohexan-1-amine oxide (4a)**



Compound **4a** was prepared following the general procedure for synthesis of *N*-oxides from **3a** (1 mmol, 422 mg) and isolated yellowish oil (406 mg, 93 %).

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2956 (m), 2921 (s), 2852 (s), 1458 (m), 1377 (m), 976 (w), 897 (m), 720 (m).

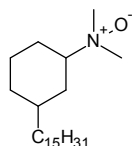
$^1\text{H-NMR}$ (300 MHz, CDCl_3) δ = 2.99 - 3.38 (m, 5 H), 2.11 - 2.46 (m, 1 H), 1.49 - 2.01 (m, 9 H), 1.13 - 1.42 (m, 34 H), 0.96 (t, $J=7.3$ Hz, 6 H), 0.69 - 0.91 (m, 4 H) ppm.

$^{13}\text{C-NMR}$ (75 MHz, CDCl_3) δ = 73.6, 69.4, 62.2, 61.8, 37.4, 37.1, 36.6, 33.7, 31.9, 31.4, 30.2, 29.8, 29.7, 29.65, 29.62, 29.3, 28.6, 28.1, 26.8, 26.1, 24.8, 24.5, 22.6, 20.5, 20.3, 20.2, 14.1, 13.9, ppm.

MS (EI-TOF) m/z (%): 421 (1) [(M - O)+], 337 (23), 323 (14), 295 (20), 294 (100), 290 (54), 126 (69), 112 (29).

HRMS-ESI (TOF): [(M + H)⁺] calcd. for $\text{C}_{29}\text{H}_{59}\text{NOH}$: 438.4669; found: 438.4667.

***N,N*-dimethyl-3-pentadecylcyclohexan-1-amine oxide (4b)**



Compound **4b** was prepared following the general procedure for synthesis of *N*-oxides from **3b** (1.0 mmol, 338 mg) and isolated as pale-yellow solid (331 mg, 94%).

Compound **4b** was also prepared following the procedure for the one-pot amination/oxidation sequence from **1** and dimethyl amine and isolated as yellowish solid (252 mg, 71%)

m.p.: 92-93 °C.

IR (ATR) $\tilde{\nu}_{\text{max}}/\text{cm}^{-1}$ = 2953 (w), 2916 (s), 2849 (s), 1585 (w), 1469 (m), 963, 1427 (m), 1377 (w), 1190 (w), 936 (w), 718 (m).

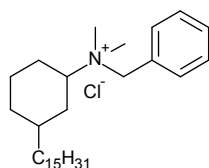
$^1\text{H-NMR}$ (400 MHz, CDCl_3) δ = 3.23 - 3.38 (m, 1 H), 3.09 - 3.22 (m, 6 H), 2.34 - 2.46 (m, 1 H), 2.13 - 2.25 (m, 1 H), 1.87 - 2.09 (m, 1 H), 1.66 - 1.81 (m, 1 H), 1.16 - 1.65 (m, 33 H), 0.83 - 0.91 (m, 3 H) ppm.

$^{13}\text{C-NMR}$ (100 MHz, CDCl_3) δ = 78.1, 74.0, 55.1, 54.8, 54.7, 54.3, 37.11, 33.9, 33.5, 31.9, 31.2, 31.1, 29.8, 29.62, 29.59, 29.56, 29.3, 28.4, 27.8, 27.3, 27.2, 26.7, 24.7, 22.6, 20.2, 14.1 ppm.

MS (EI-TOF) m/z (%): 337 (23) [(M - O)+], 323 (28), 322 (12), 295 (18), 294 (91), 281 (20), 280 (100), 278 (10), 126 (66), 124 (10), 112 (54).

HRMS-ESI (TOF): [(M + H)⁺] calcd. for $\text{C}_{23}\text{H}_{47}\text{NOH}$: 354.3730; found: 354.3717.

***N*-benzyl-*N,N*-dimethyl-3-tetradecylcyclohexan-1-aminium (5b)**



An oven-dried 20 mL headspace vial with Teflon-coated stirring bar was charged with cyclohexyl amine **3b** (0.50 mmol, 169 mg), EtOH (2mL) and benzyl chloride (0.5 mmol, 63.9 mg). The vial was closed with a septum cap, and the resulting mixture was stirred at 85 °C for 15 h. After the

reaction was complete, the solvent was removed under reduced pressure. The residue was washed with Et₂O (2 x 5 mL) and dried under reduced pressure yielding the desired product **5b** as colorless solid (87 mg, 62%).

m.p.: 179-181 °C.

IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ = 2921 (s), 2852 (s), 1633 (w), 1456 (m), 1418 (m), 1378 (w), 1216 (w), 907, (w), 737 (m), 703 (m).

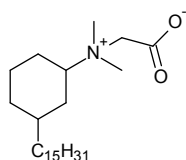
¹H-NMR (300 MHz, CDCl₃) δ = 7.62 - 7.73 (m, 2 H), 7.46 (dd, *J*=1.5, 0.4 Hz, 3 H), 5.06 (s, 2 H), 3.47 - 3.65 (m, 1 H), 3.25 (d, *J*=8.4 Hz, 5 H), 1.70 - 2.43 (m, 5 H), 1.10 - 1.68 (m, 33 H), 0.81 - 0.91 (m, 3 H) ppm.

¹³C-NMR (75 MHz, CDCl₃) δ = 133.2, 133.1, 130.5, 129.14, 129.05, 127.6, 66.8, 64.7, 47.4, 47.1, 37.1, 36.9, 33.7, 33.0, 31.8, 31.0, 30.4, 29.7, 29.62, 29.59, 29.57, 29.55, 29.5, 29.48, 29.3, 27.8, 27.6, 26.8, 26.7, 22.6, 20.1, 14.0 ppm.

MS (EI-solid) *m/z* (%): 445 (2) [(M - Cl, Me)+], 370 (5), 337 (24), 295 (23), 294 (100), 266 (6), 202 (6), 126 (95).

HRMS-ESI (TOF): [(M - Cl)⁺] calcd. for C₃₀H₅₄N: 428.4251; found: 428.4250.

2-(dimethyl(3-tetradecylcyclohexyl)ammonio)acetate (6b)



An oven-dried 20 mL headspace vial with Teflon-coated stirring bar was charged with bromoacetic acid (2.00 mmol, 278 mg), cyclohexyl amine **3b** (2.00 mmol), MeOH (2 mL) and H₂O (2 mL). Sodium bicarbonate (2.00 mmol, 338 mg) was added dropwise to the mixture to keep the solution at pH 7-8. The resulting mixture was stirred at 80°C for 10h. Upon completion, the solvent was evaporated under reduced pressure and the residue was washed with Et₂O (3 X 5 mL). Residual Et₂O was removed under vacuum. The residue was dissolved in dichloromethane (10 mL) and washed with water (2 x 5 mL). The combined organic layers were filtered over MgSO₄ and the solvent was removed under reduced pressure yielded the corresponding betaine **6b** as light brown solid (529 mg, 67%).

m.p.: 154 - 156 °C.

IR (ATR) $\tilde{\nu}_{\max}/\text{cm}^{-1}$ = 2917 (s), 2850 (s), 1628 (s), 1467 (m), 1392 (m), 1324 (m), 880 (w), 721 (m).

¹H-NMR (300 MHz, CDCl₃) δ = 4.05 - 4.21 (m, 1 H), 3.83 (s, 2 H), 3.12 - 3.25 (m, 6 H), 1.88 - 2.24 (m, 3 H), 1.69 - 1.81 (m, 1 H), 1.51 - 1.63 (m, 2 H), 1.24 (s, 31 H), 0.86 (s, 3 H) ppm.

¹³C-NMR (75 MHz, CDCl₃) δ = 165.4, 165.2, 71.2, 68.3, 63.9, 63.6, 48.1, 47.9, 47.8, 36.9, 36.8, 33.5, 32.7, 31.7, 31.2, 30.7, 30.3, 29.6, 29.5, 29.48, 29.4, 29.2, 27.8, 27.7, 26.6, 26.4, 26.1, 24.4, 22.5, 20.2, 13.9 ppm.

MS (Ion trap, EI) *m/z* (%): 337 (10) [(M - CH₂CO₂)⁺], 308 (1), 294 (70), 156 (100), 84 (75), 71 (15).

HRMS-ESI (TOF): [(M + H)⁺] calcd. for C₂₅H₄₉NO₂H: 396.3836; found: 396.3828.

References

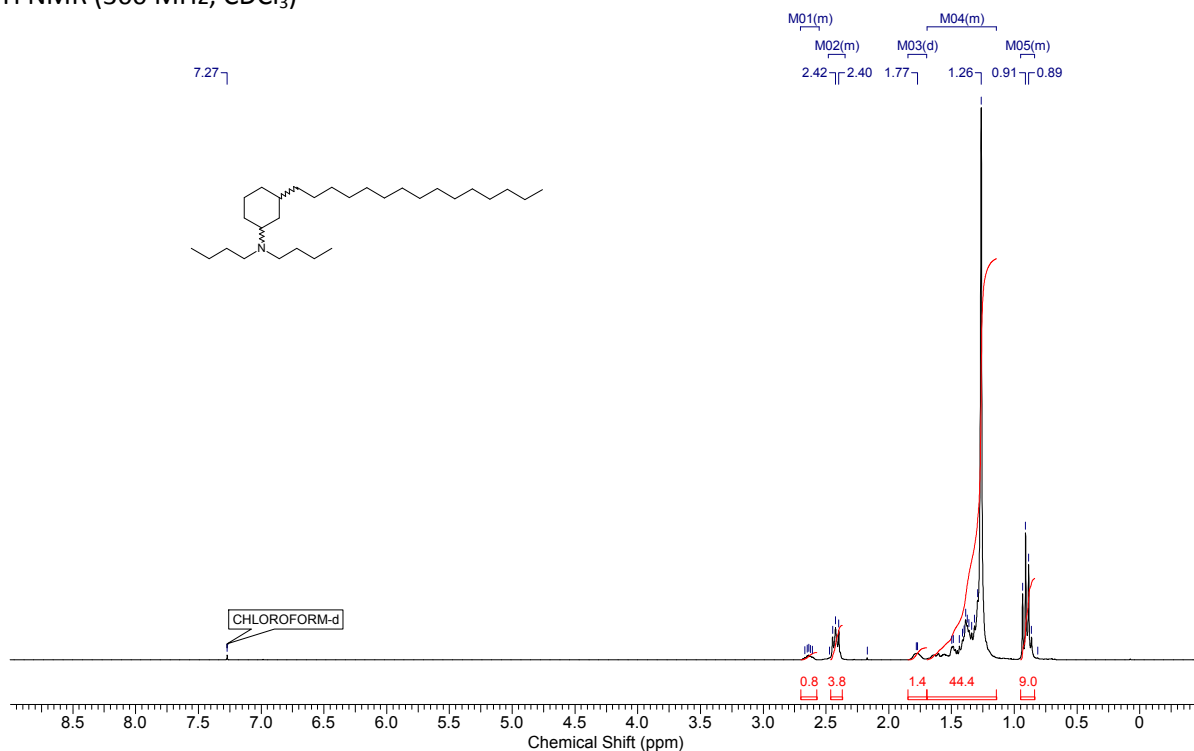
1 R. A. Sheldon, *Chem. Soc. Rev.*, 2012, **41**, 1437–1451.

2 Welcome to www.sheldon.nl, <http://www.sheldon.nl/bi/EFactor.aspx>, (accessed March 22, 2018).

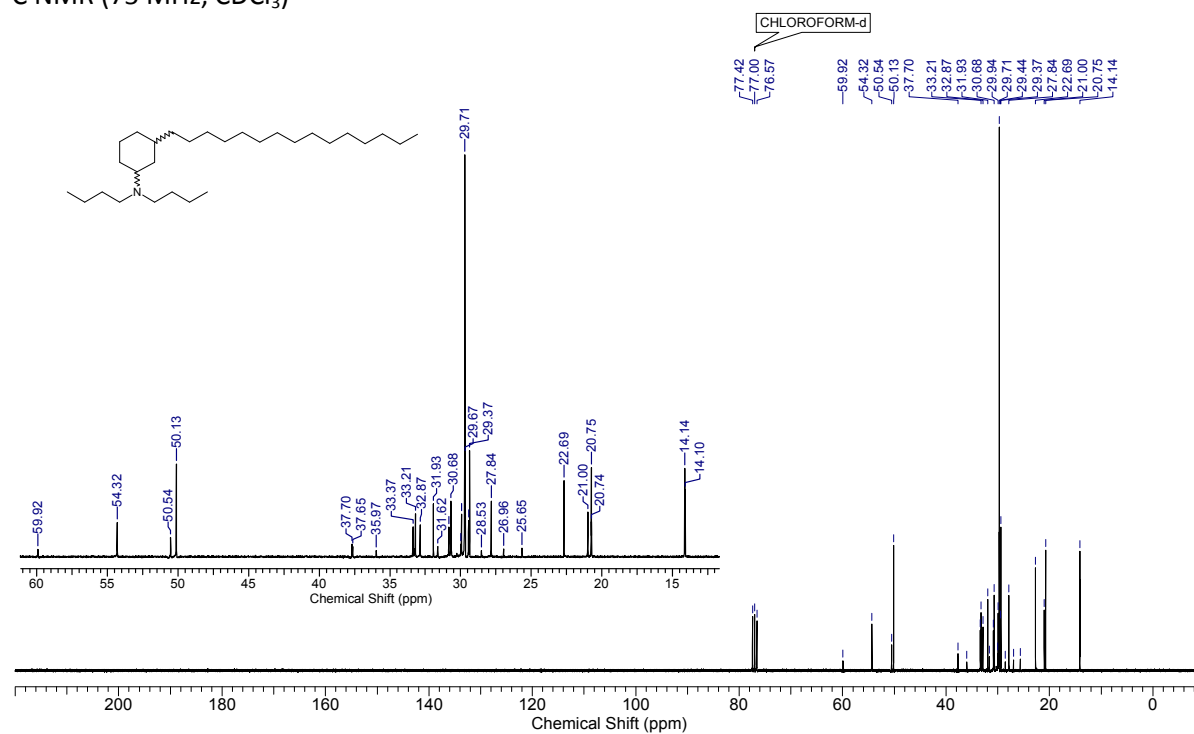
NMR spectra

N,N-dibutyl-3-pentadecylcyclohexylamine (3a)

^1H NMR (300 MHz, CDCl_3)

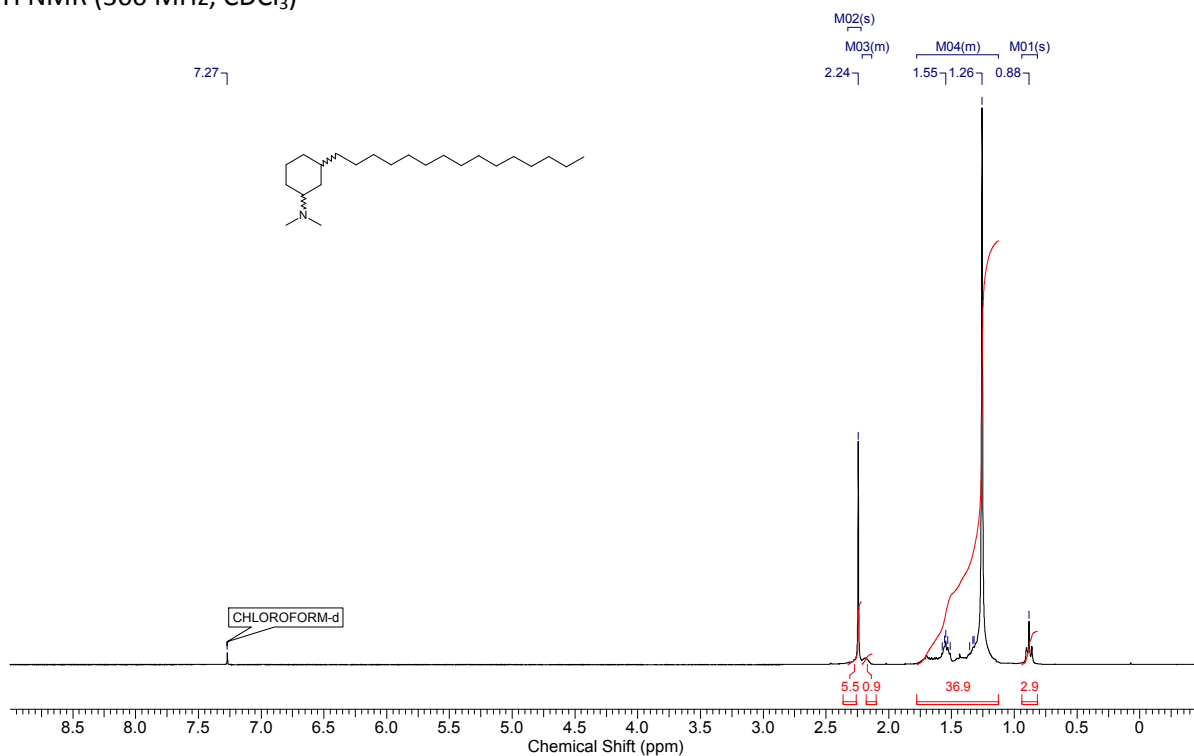


^{13}C NMR (75 MHz, CDCl_3)

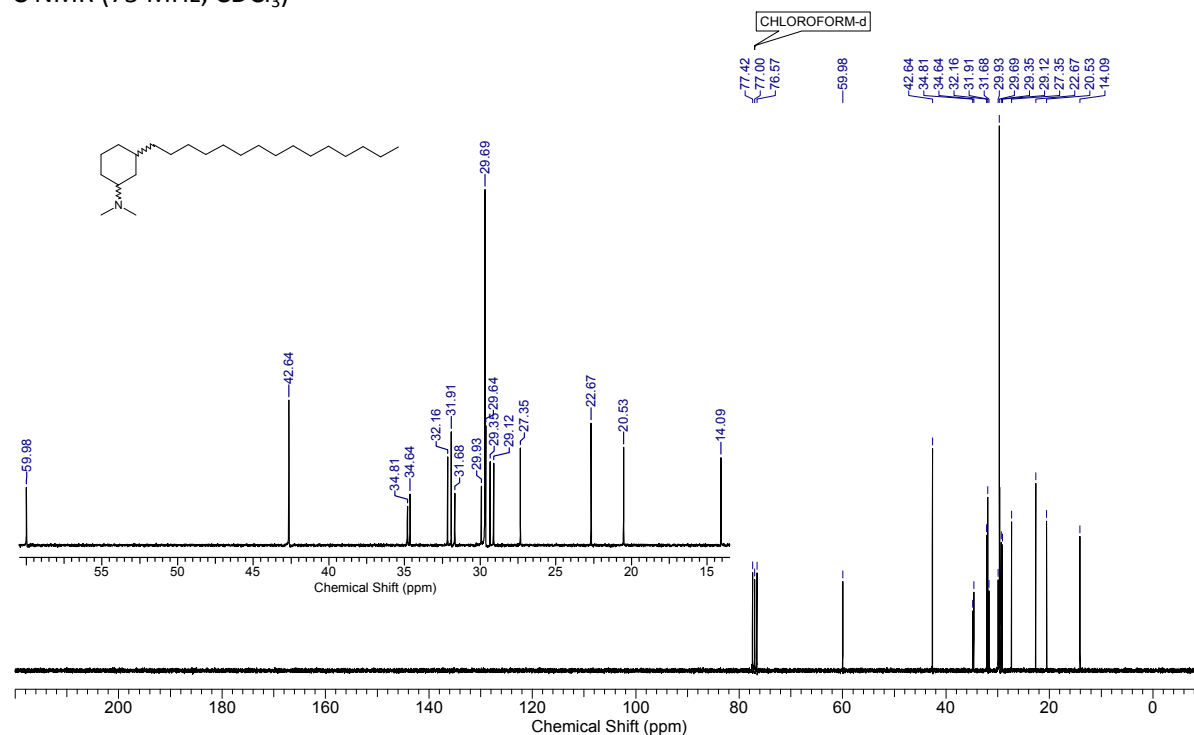


N,N-dimethyl-3-pentadecylcyclohexylamine (**3b**)

^1H NMR (300 MHz, CDCl_3)

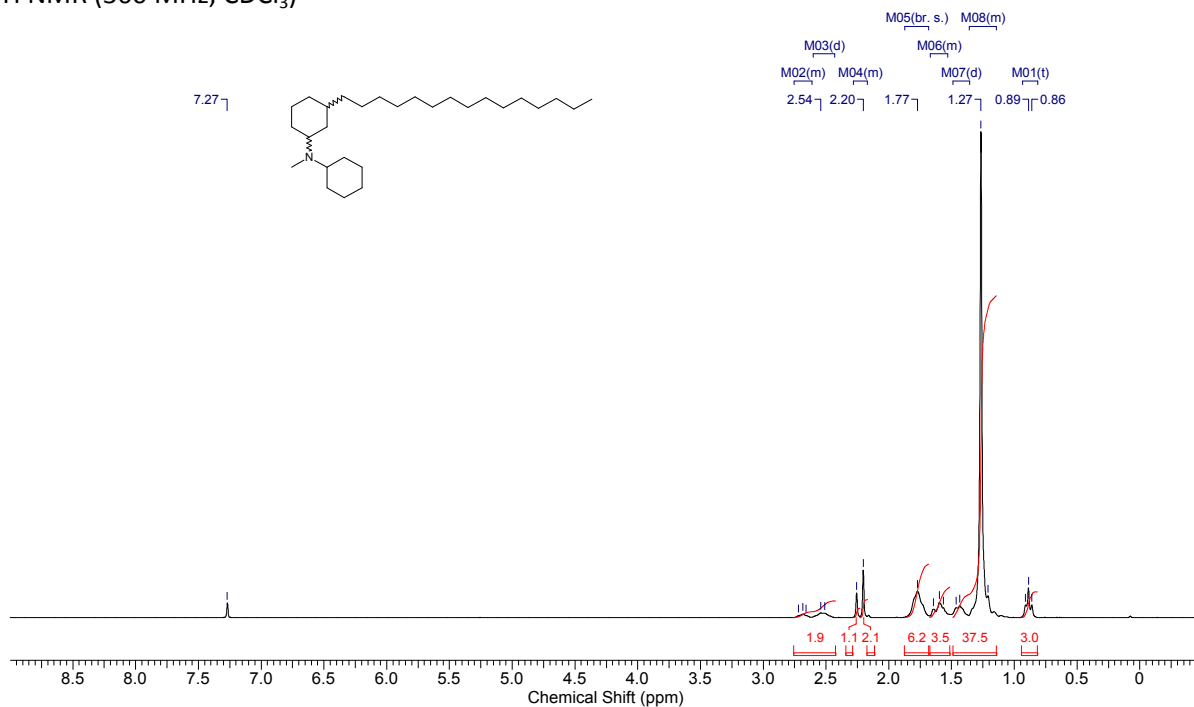


^{13}C NMR (75 MHz, CDCl_3)

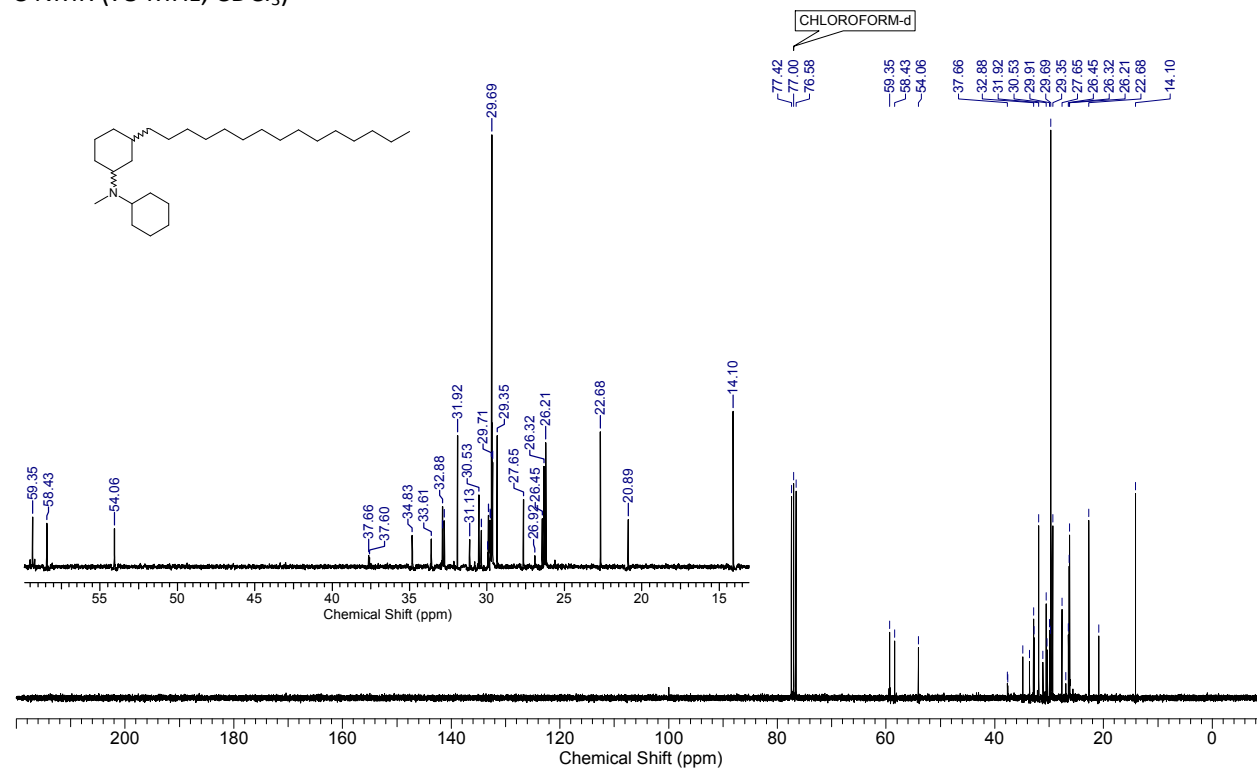


***N*-cyclohexyl-*N*-methyl-3-pentadecylcyclohexylamine (3c)**

¹H NMR (300 MHz, CDCl₃)

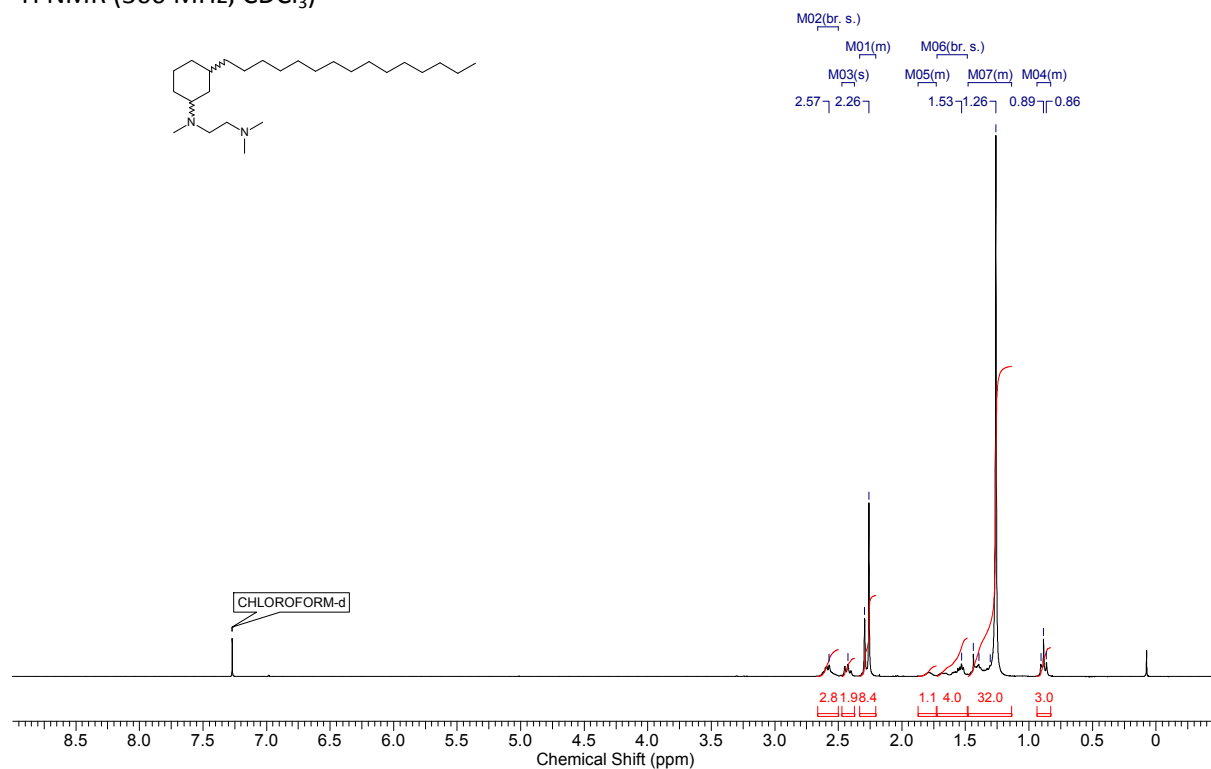


¹³C NMR (75 MHz, CDCl₃)

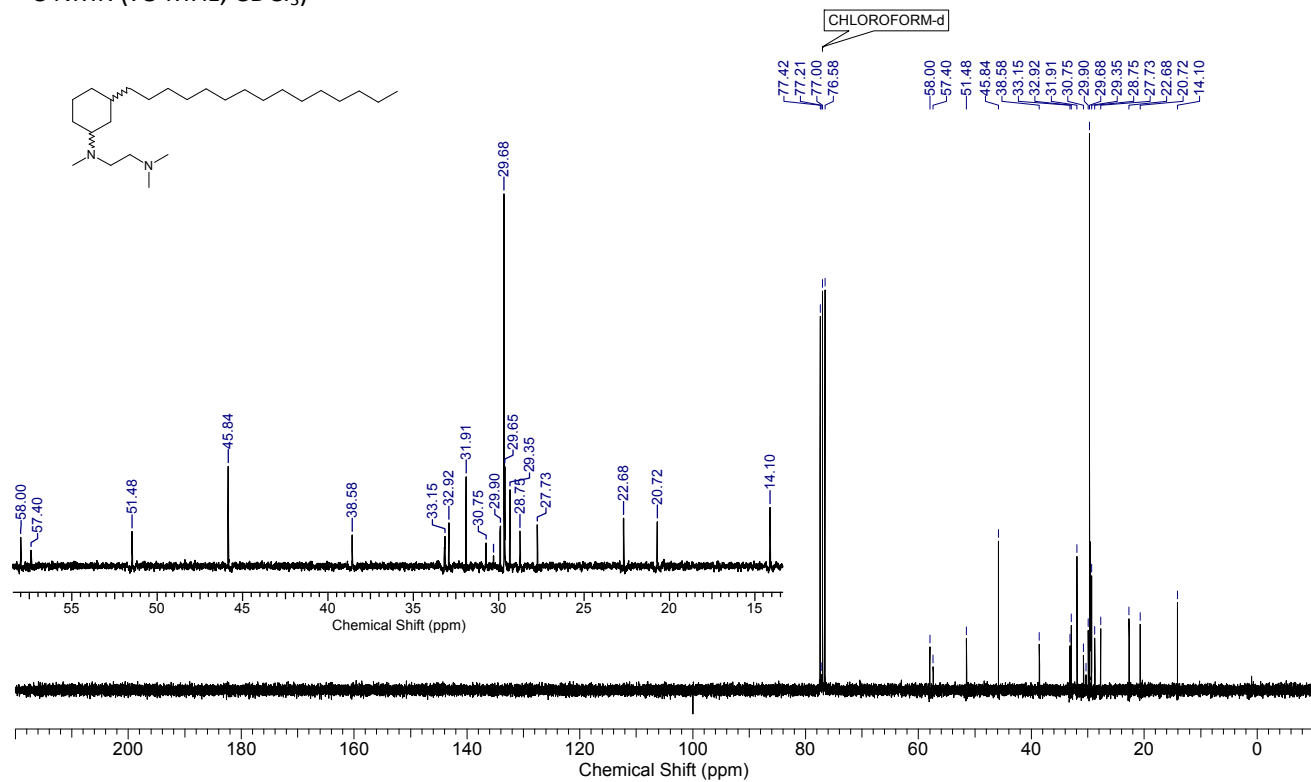


N^1,N^1,N^2 -trimethyl- N^2 -(3-pentadecylcyclohexyl)ethane-1,2-diamine (3d)

^1H NMR (300 MHz, CDCl_3)

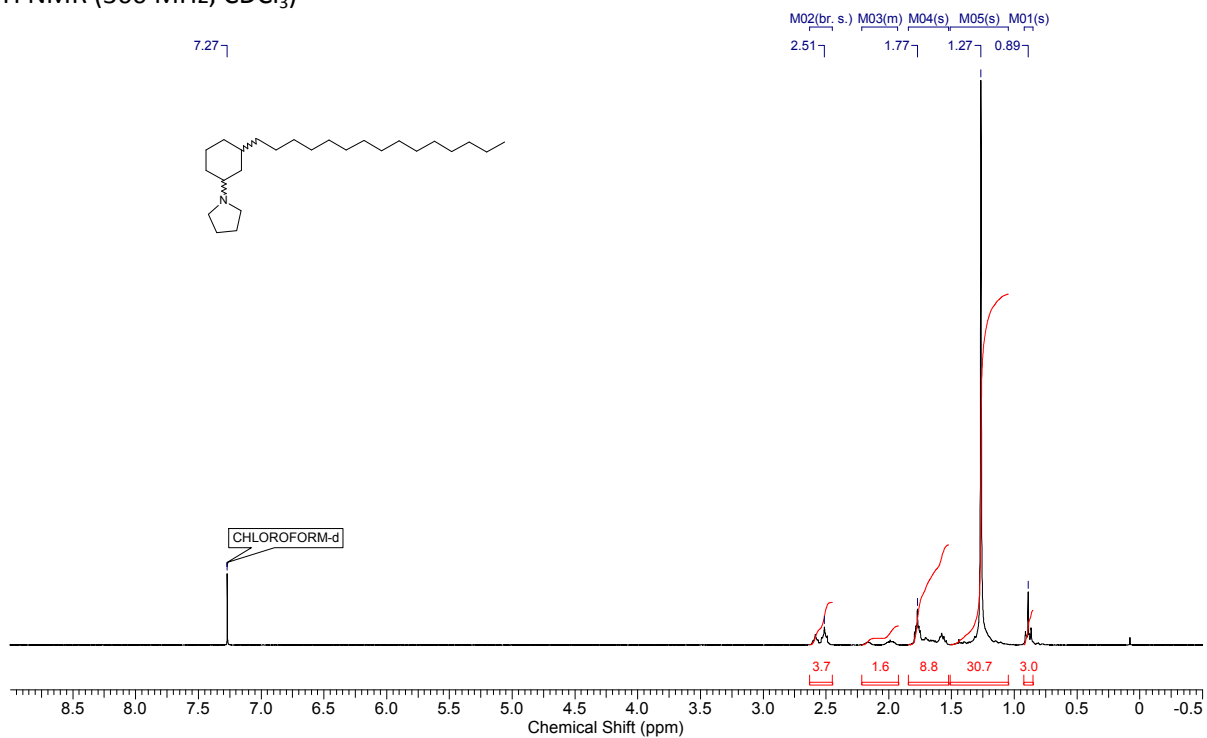


^{13}C NMR (75 MHz, CDCl_3)

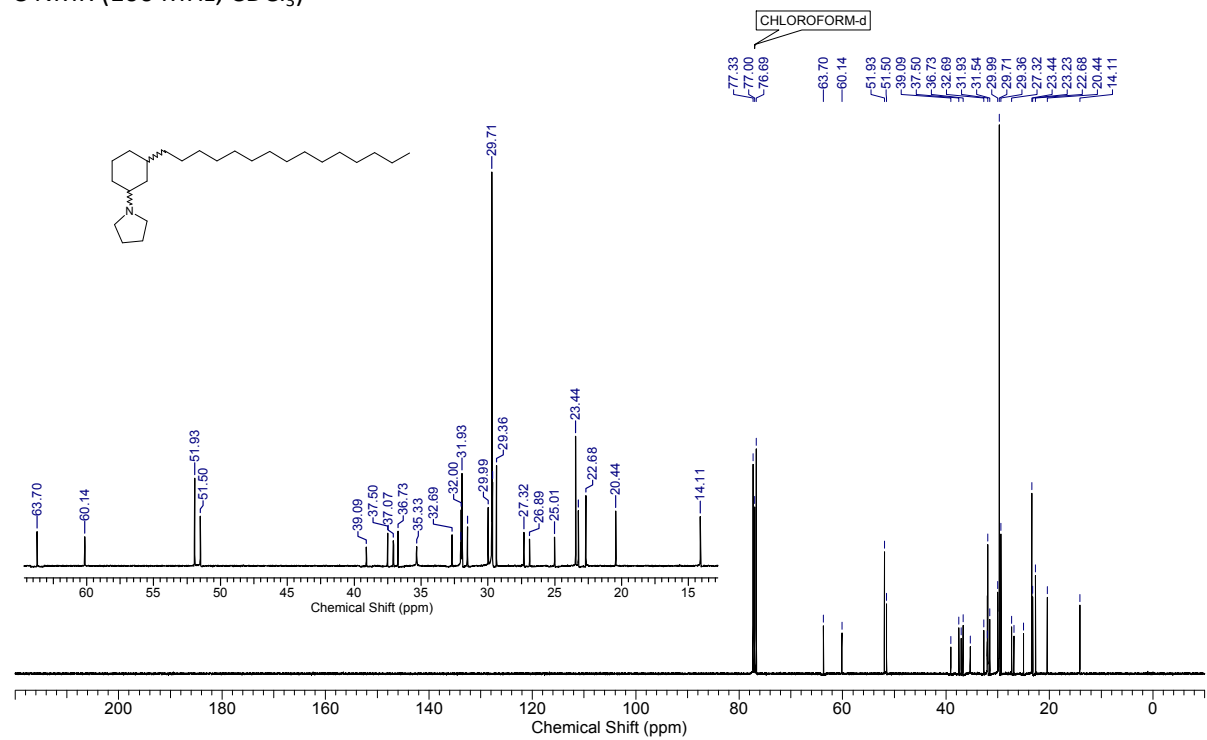


N,N-tetramethylen-3-pentadecylcyclohexylamine (3e)

¹H NMR (300 MHz, CDCl₃)

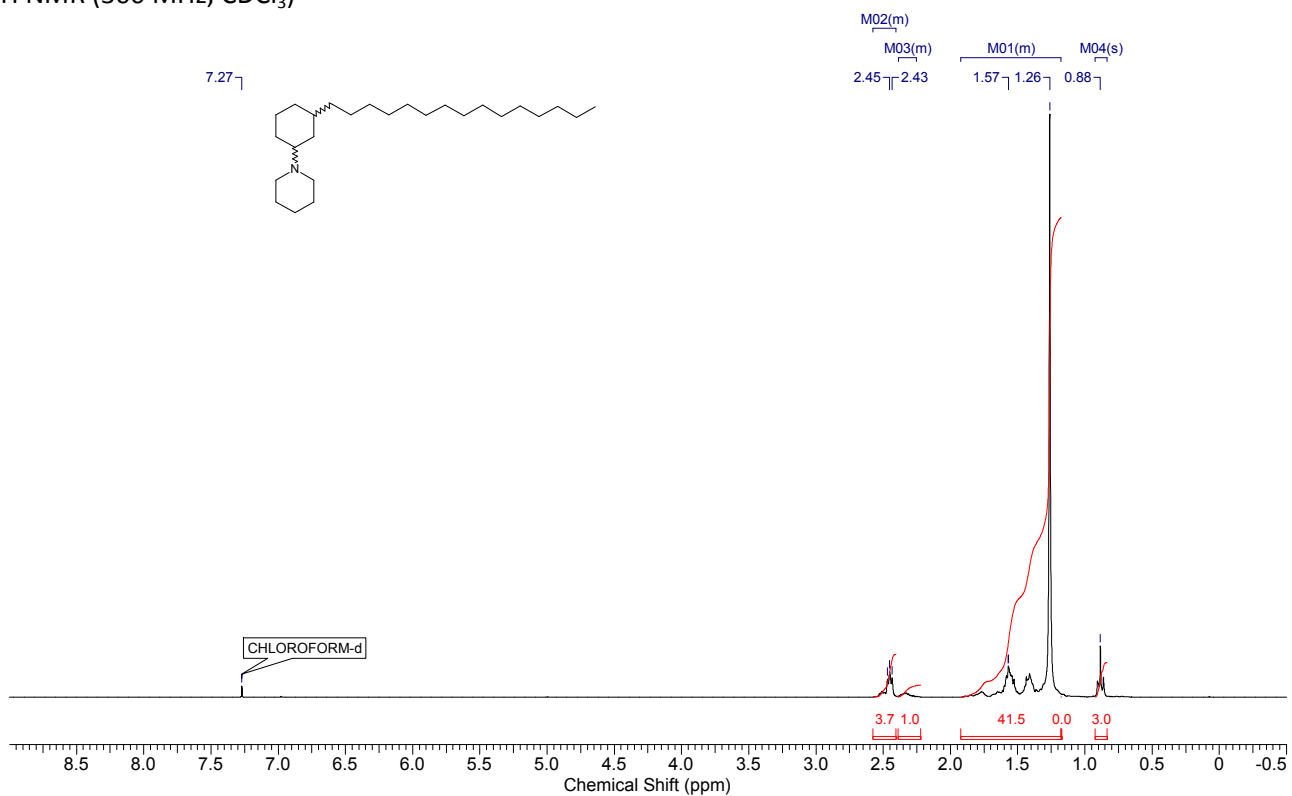


¹³C NMR (100 MHz, CDCl₃)

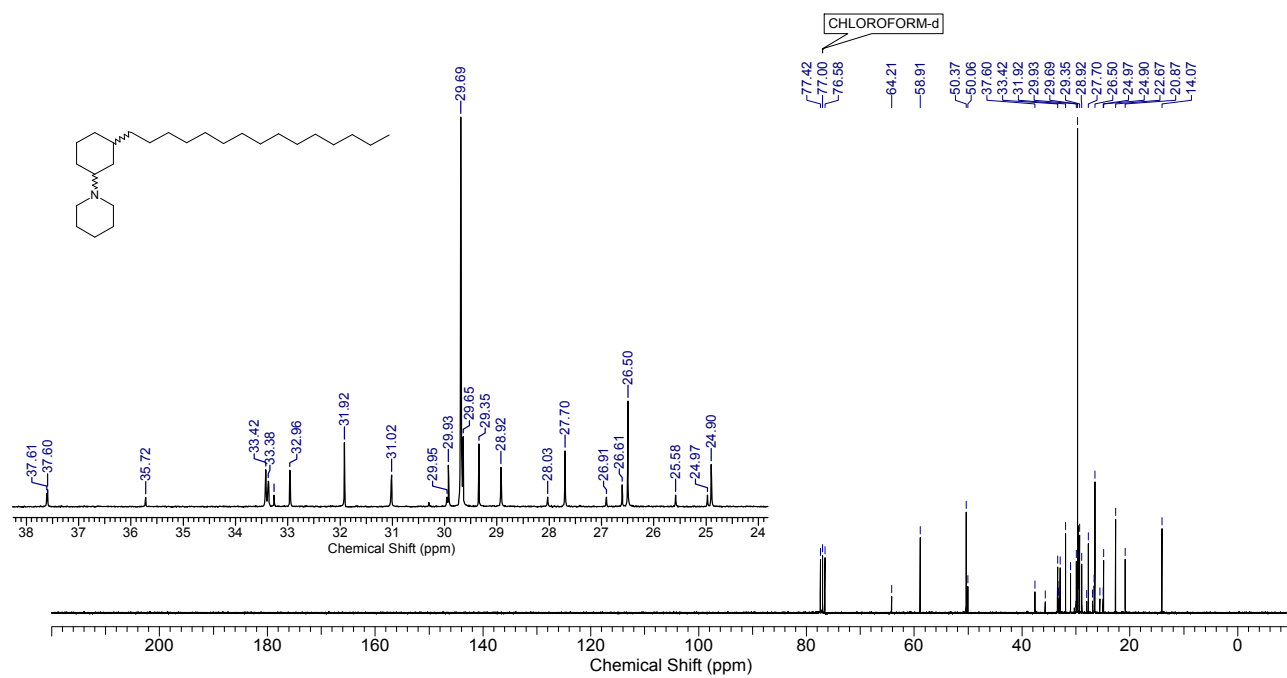


***N*-(3-pentadecylcyclohexyl)piperidine (3f)**

¹H NMR (300 MHz, CDCl₃)

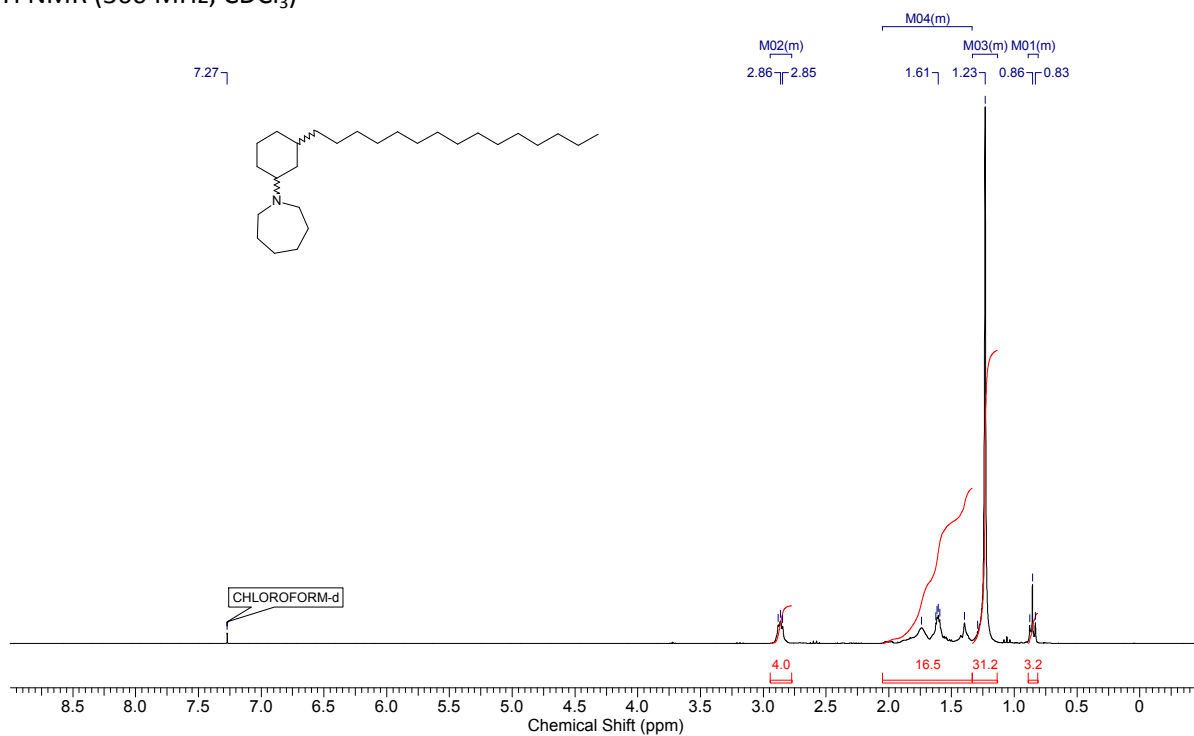


¹³C NMR (75 MHz, CDCl₃)

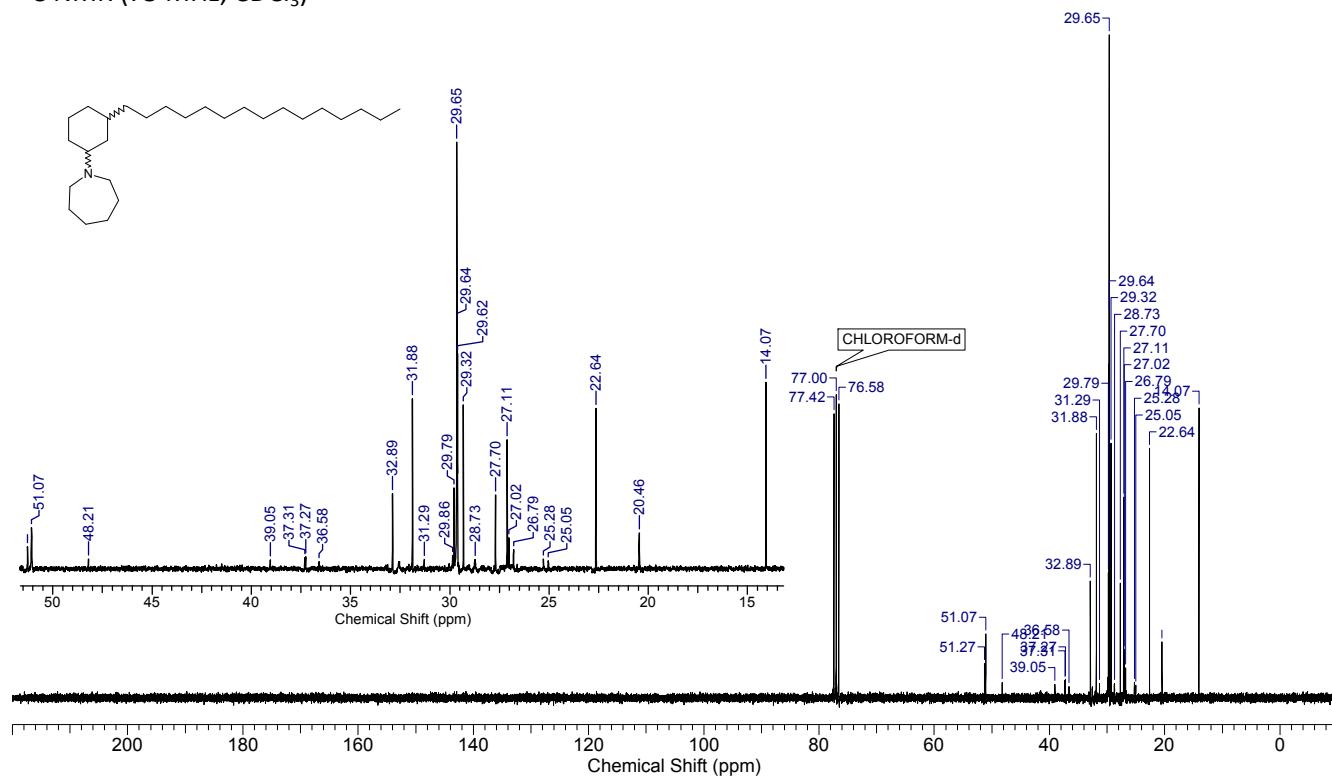


N,N-Hexamethylen-3-pentadecylcyclohexylamine (3g)

¹H NMR (300 MHz, CDCl₃)

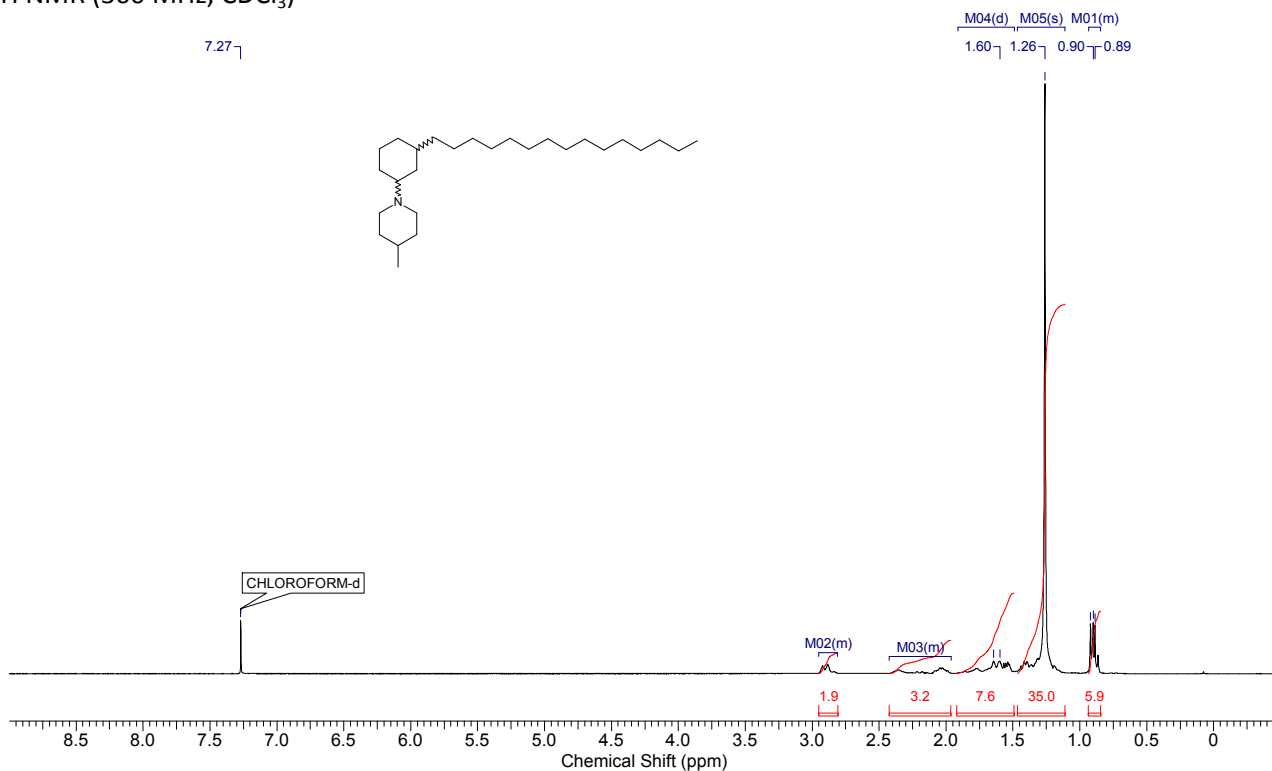


¹³C NMR (75 MHz, CDCl₃)

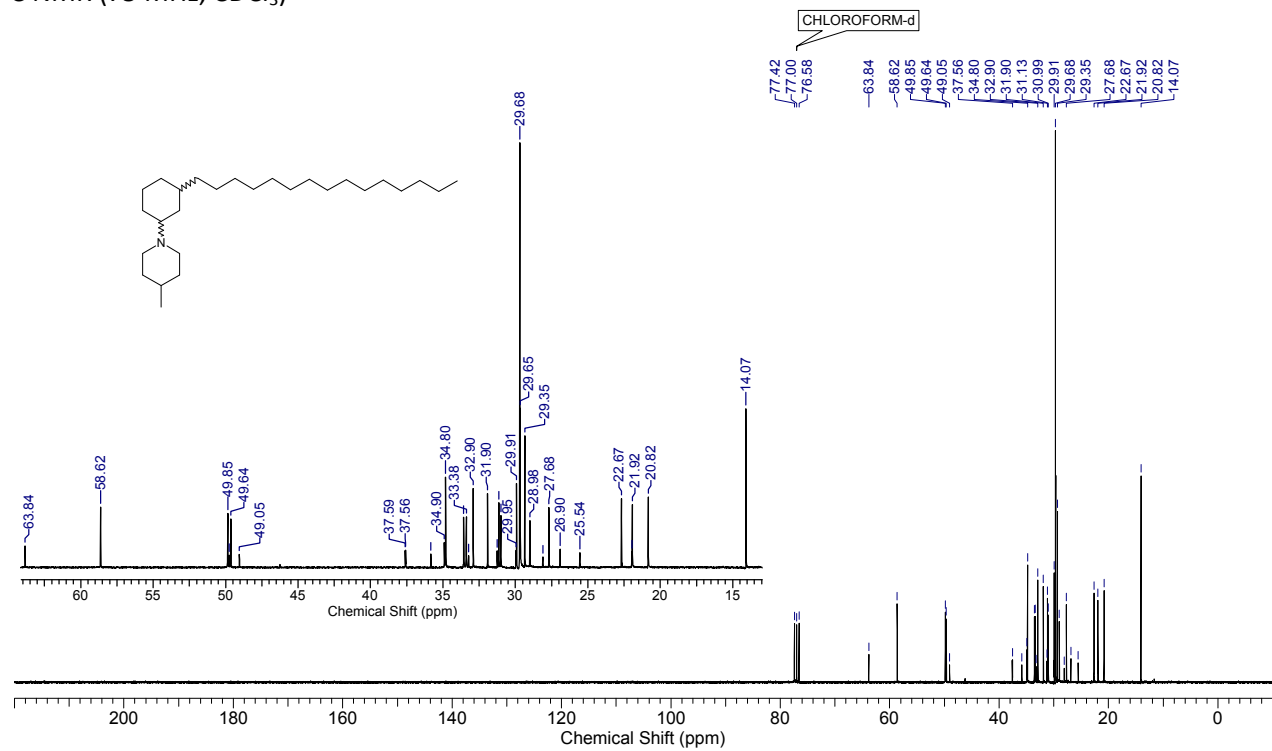


4-methyl-1-(3-pentadecylcyclohexyl)piperidine (3h)

^1H NMR (300 MHz, CDCl_3)

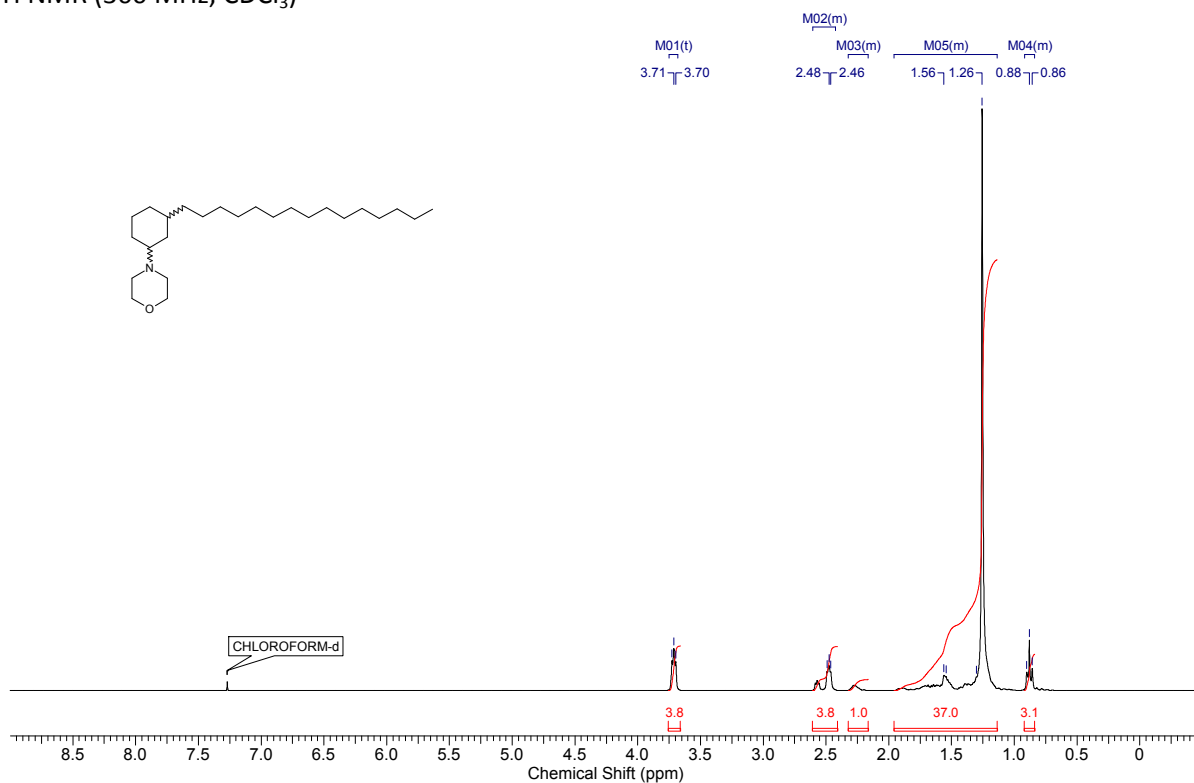


^{13}C NMR (75 MHz, CDCl_3)

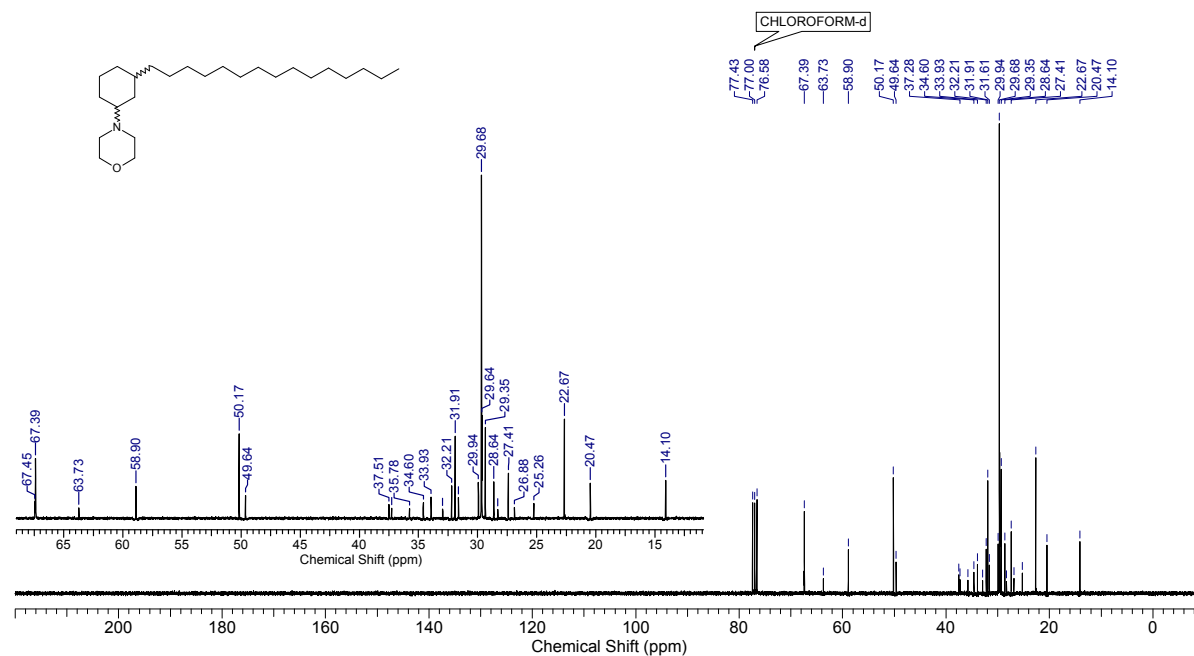


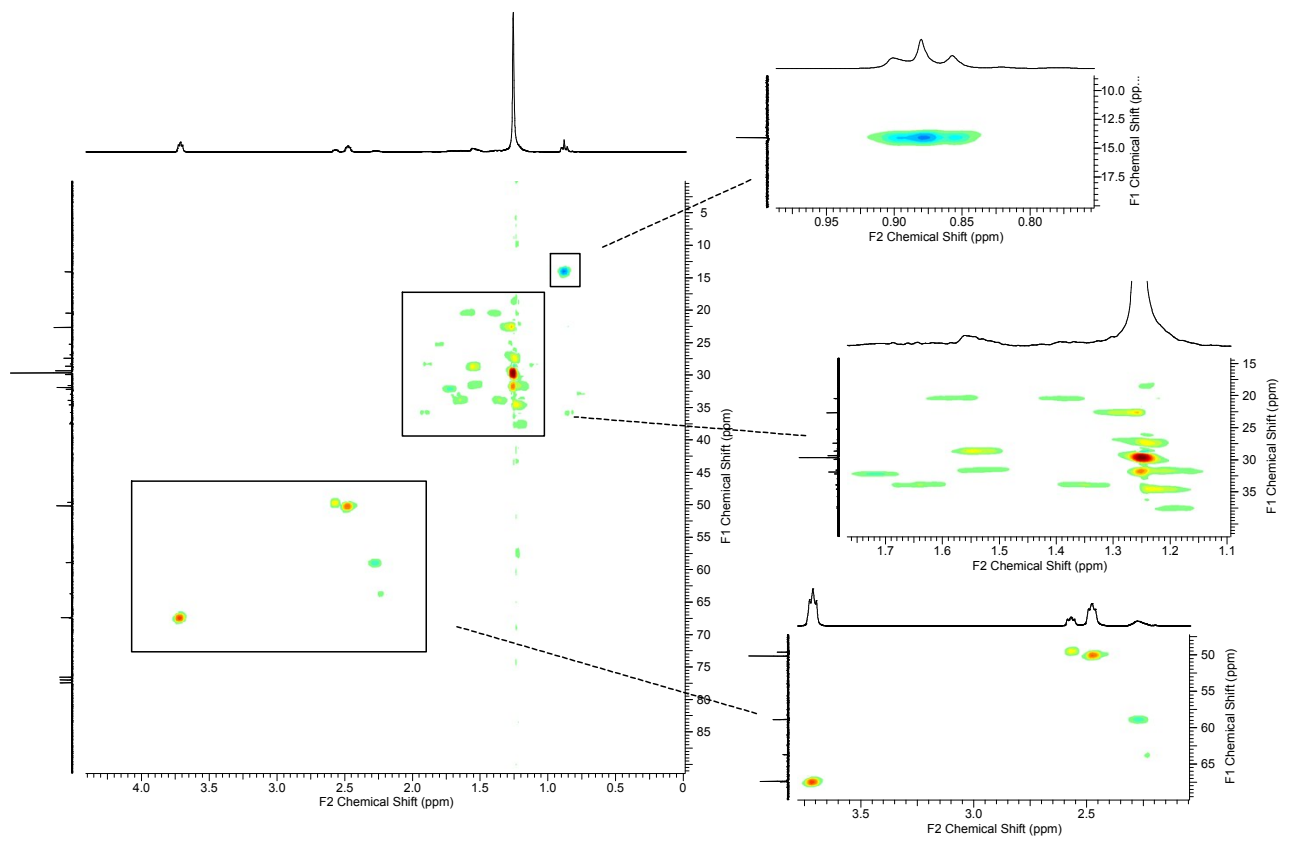
***N*-(3-pentadecylcyclohexyl)morpholine (3i)**

¹H NMR (300 MHz, CDCl₃)



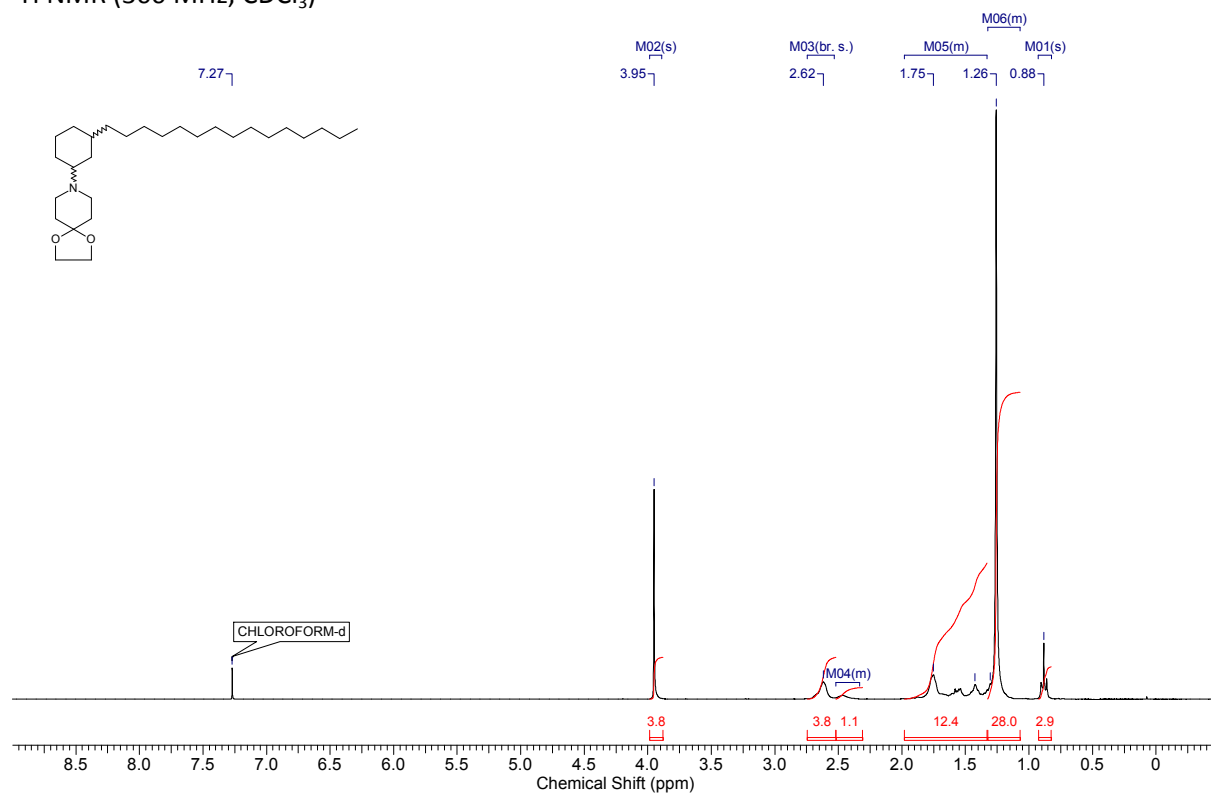
¹³C NMR (75 MHz, CDCl₃)



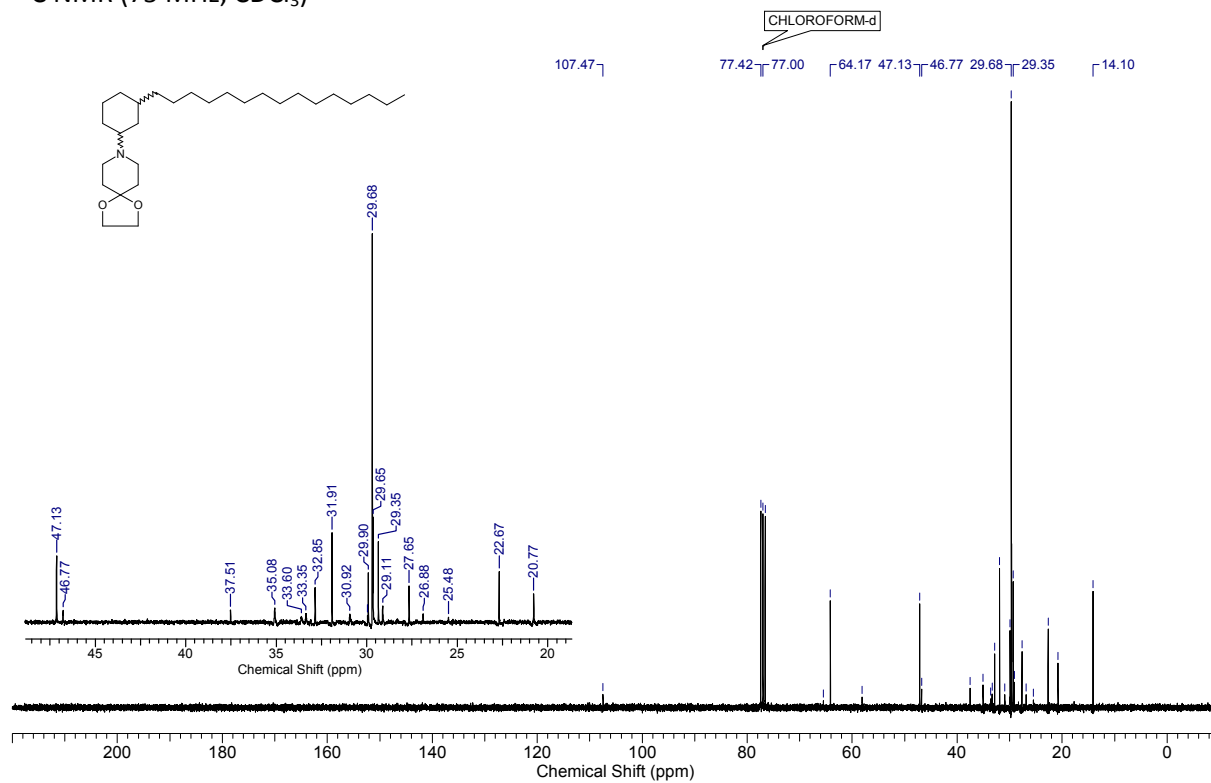


***N*-(3-pentadecylcyclohexyl)morpholine (3i)**

¹H NMR (300 MHz, CDCl₃)

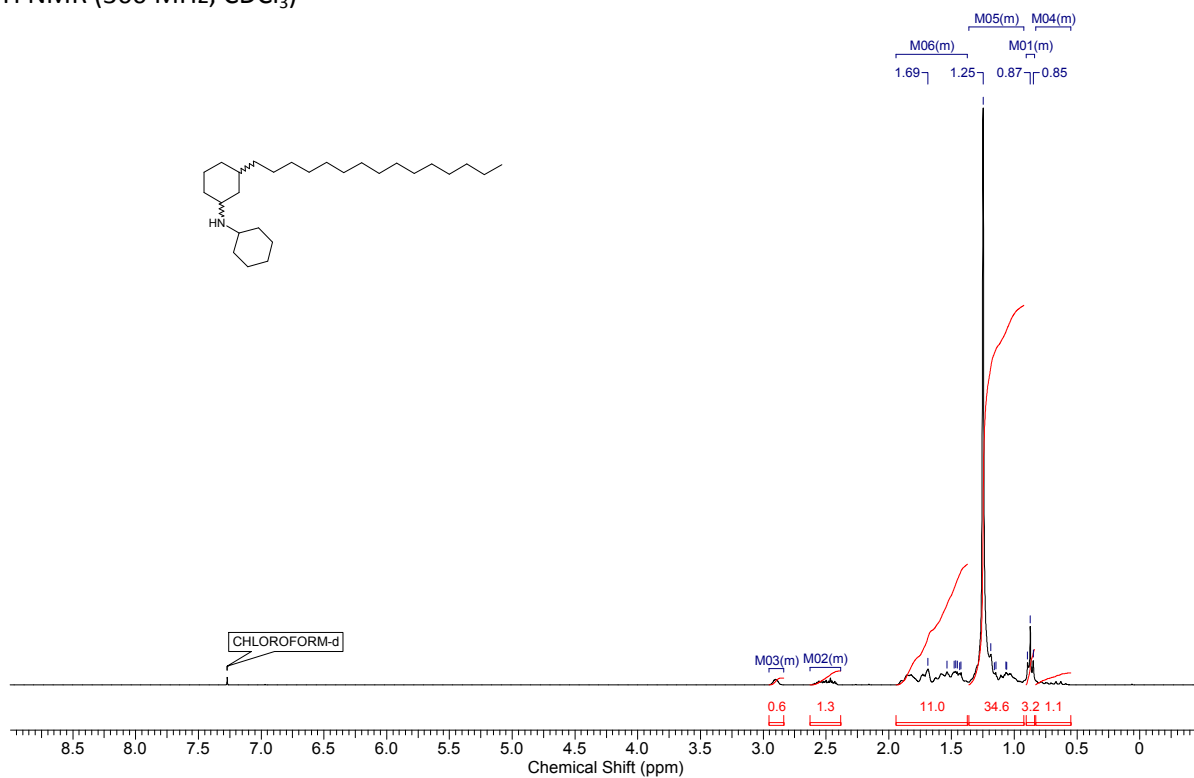


¹³C NMR (75 MHz, CDCl₃)

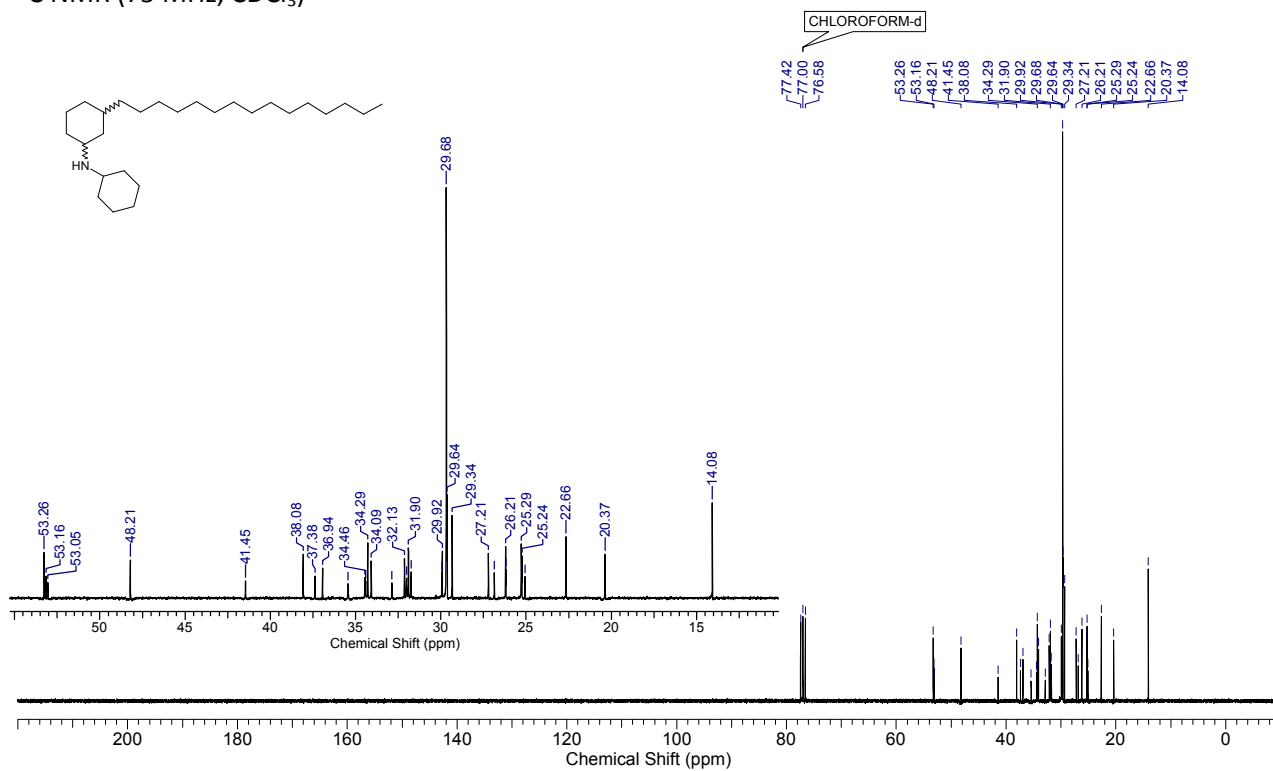


N-cyclohexyl-3-pentadecylcyclohexylamine (3k)

^1H NMR (300 MHz, CDCl_3)

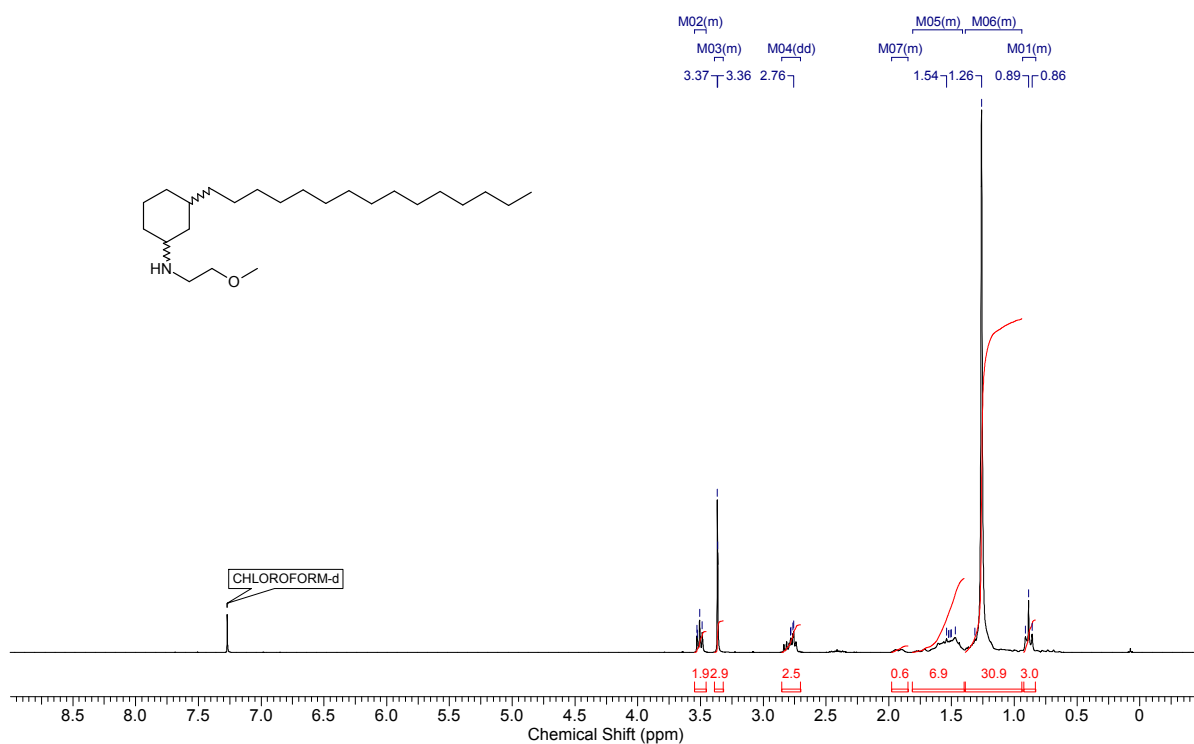


^{13}C NMR (75 MHz, CDCl_3)

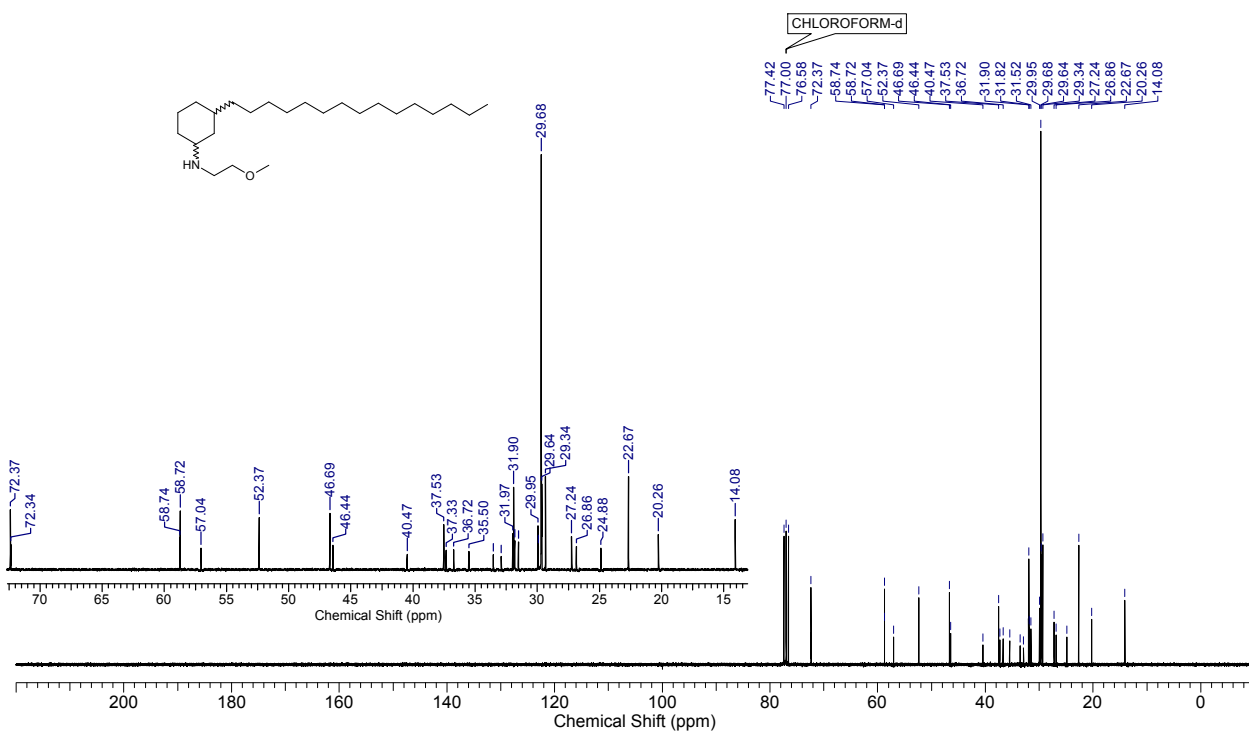


***N*-(2-methoxyethyl)-3-pentadecylcyclohexylamine (31)**

¹H NMR (300 MHz, CDCl₃)

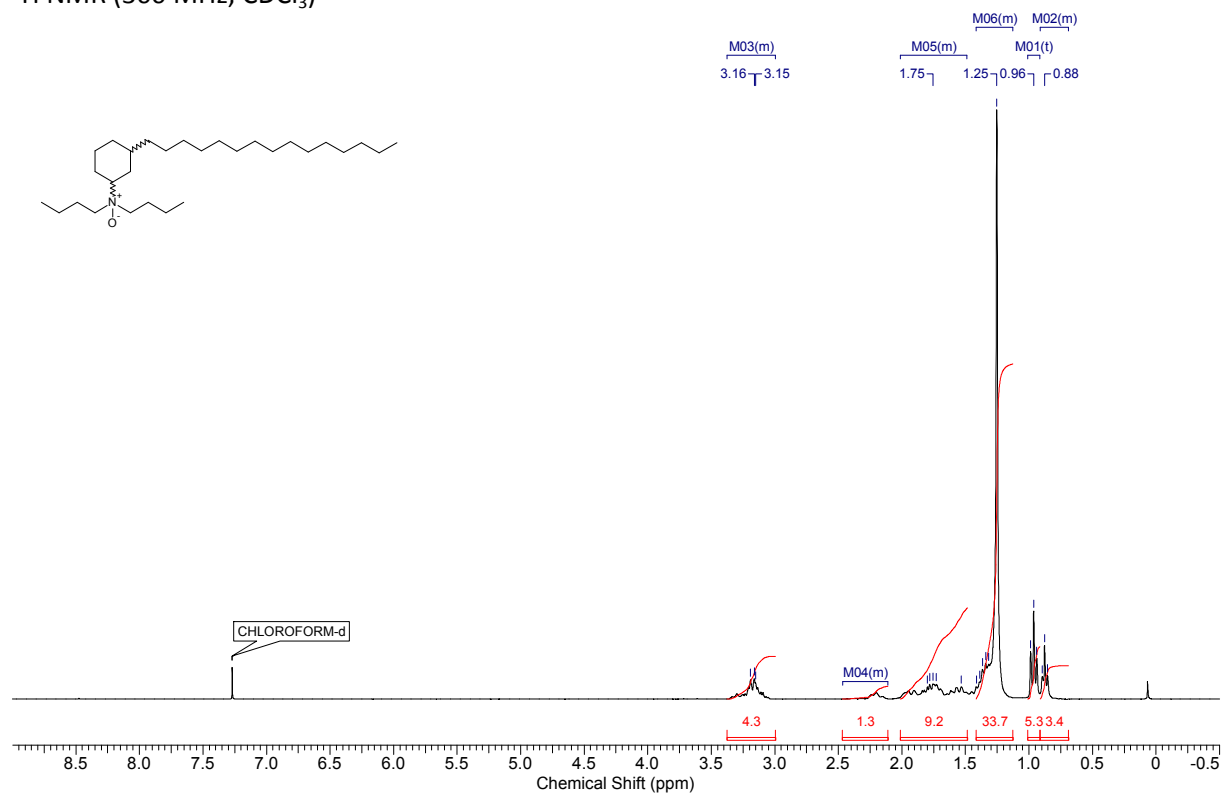


¹³C NMR (75 MHz, CDCl₃)

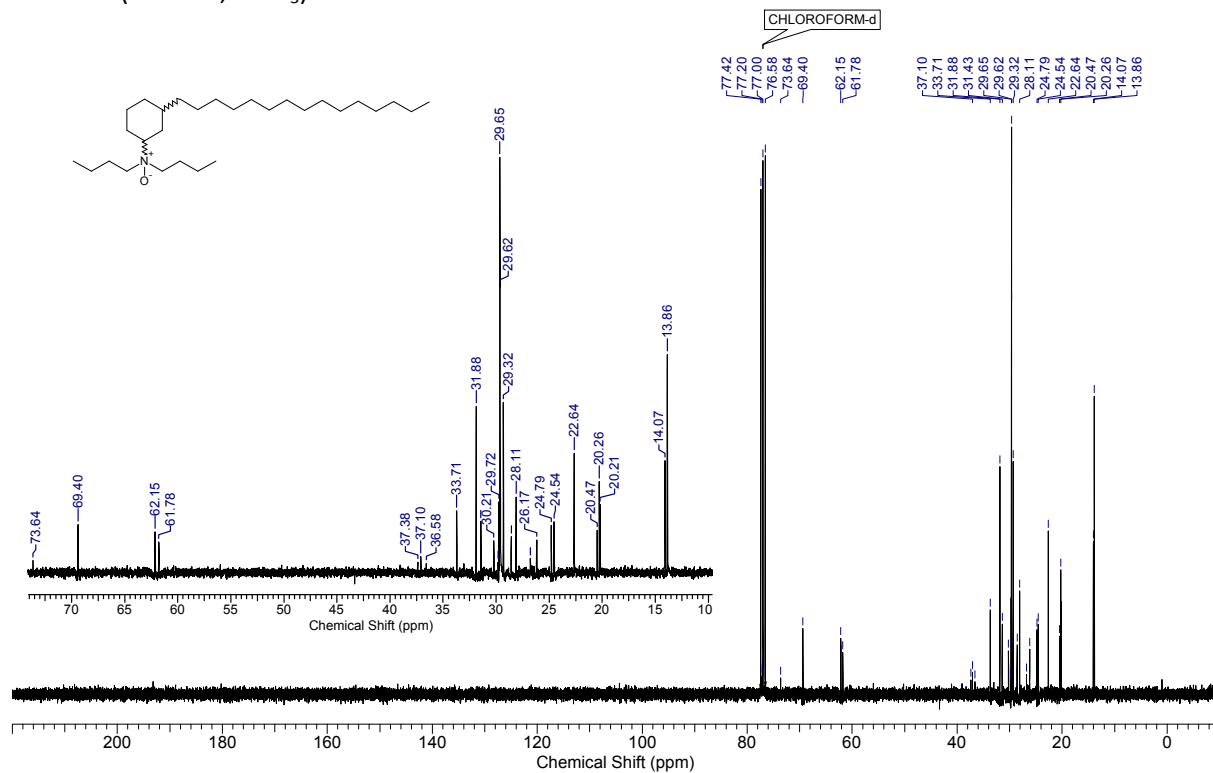


N,N-dibutyl-3-pentadecylcyclohexan-1-amine oxide (4a)

^1H NMR (300 MHz, CDCl_3)

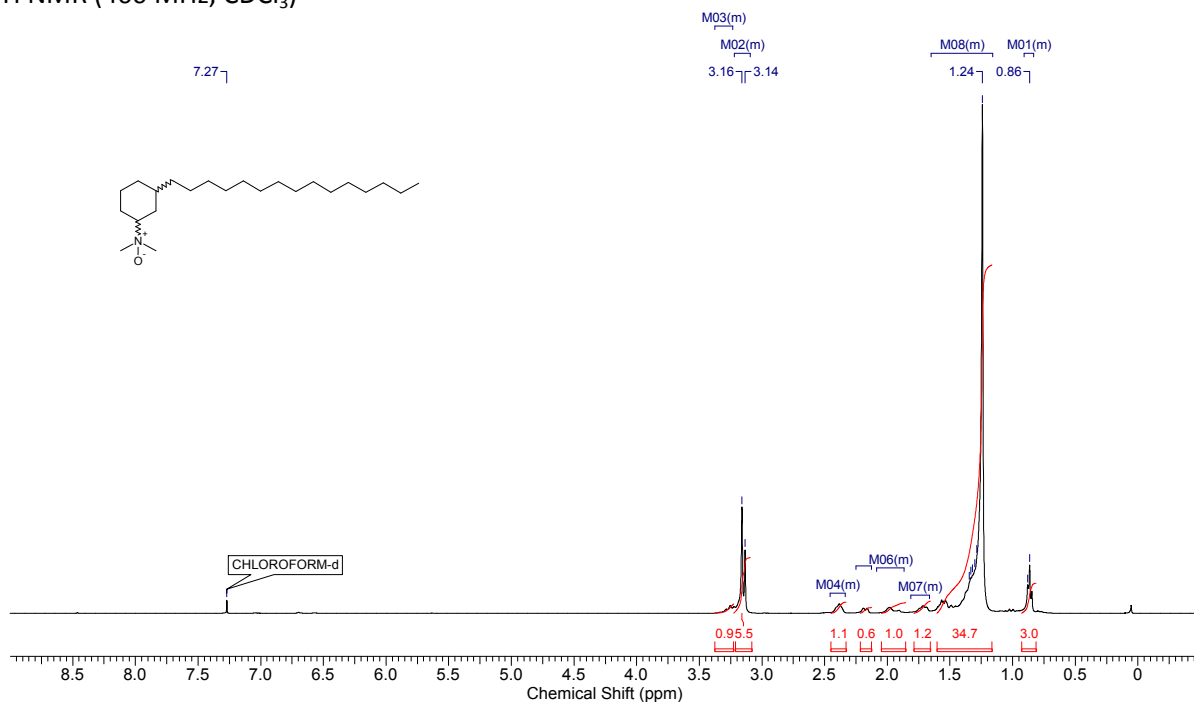


^{13}C NMR (75 MHz, CDCl_3)

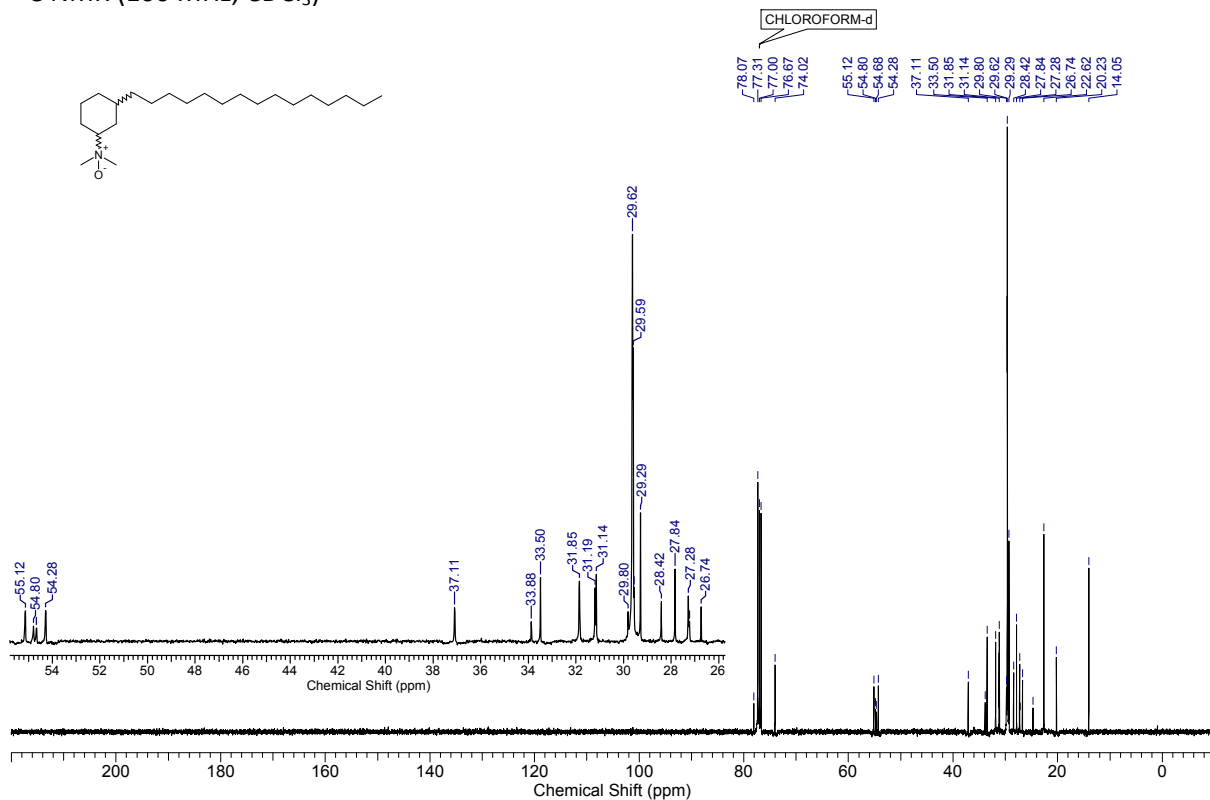


N,N-dimethyl-3-pentadecylcyclohexan-1-amine oxide (4b)

¹H NMR (400 MHz, CDCl₃)

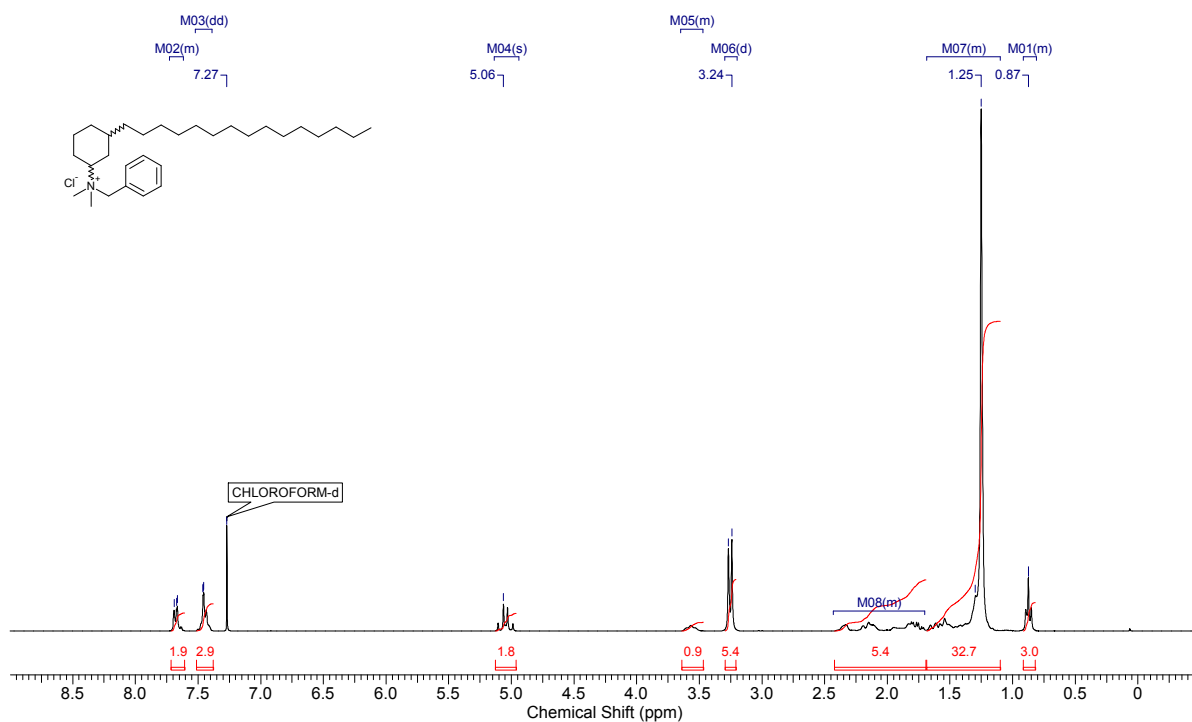


¹³C NMR (100 MHz, CDCl₃)

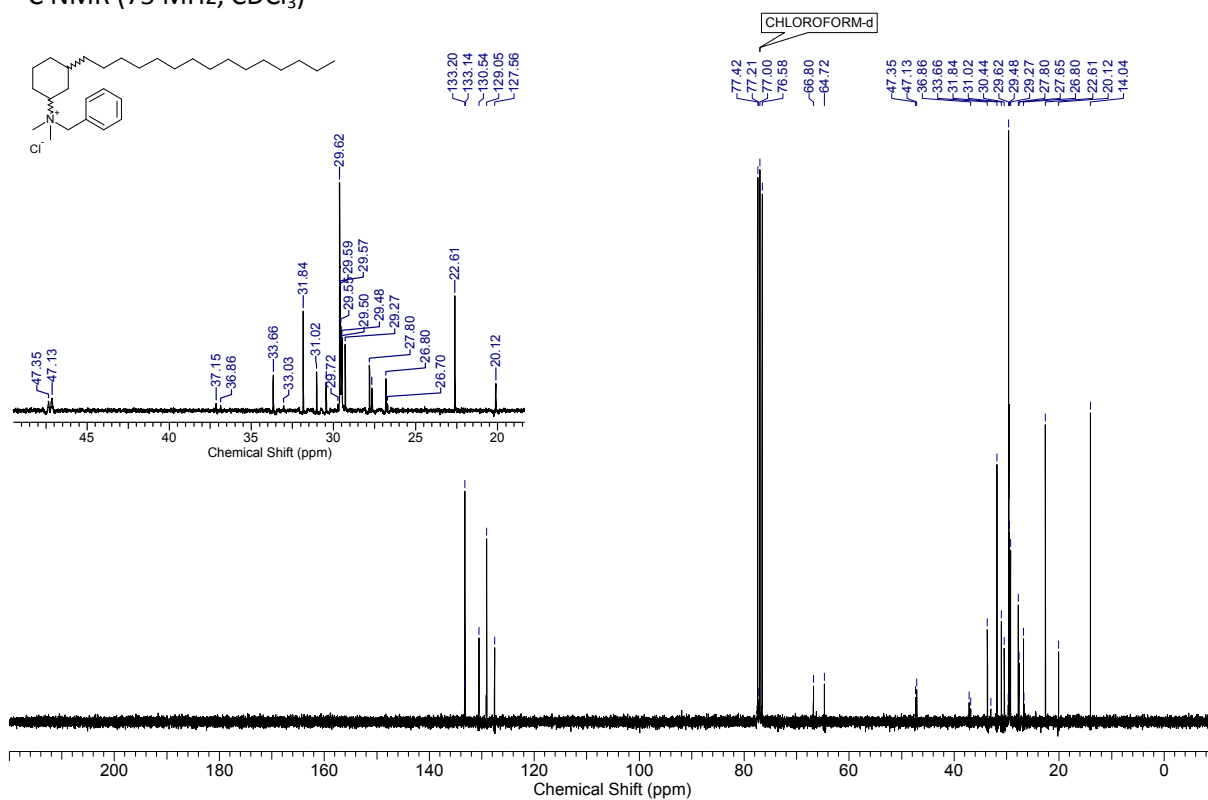


N-benzyl-N,N-dimethyl-3-tetradecylcyclohexan-1-aminium (5b)

^1H NMR (300 MHz, CDCl_3)

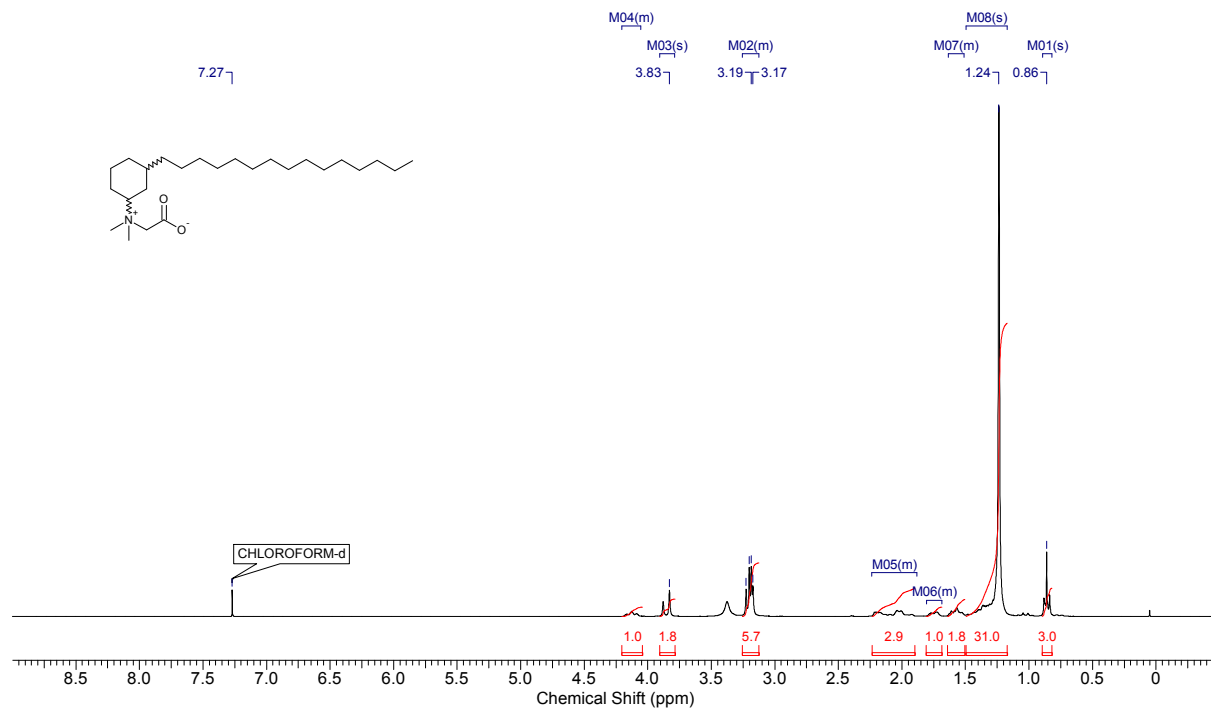


^{13}C NMR (75 MHz, CDCl_3)



2-(dimethyl(3-tetradecylcyclohexyl)ammonio)acetate (6b)

^1H NMR (300 MHz, CDCl_3)



^{13}C NMR (75 MHz, CDCl_3)

