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Supporting Information

Hydroaminomethylation of methyl 10-undecenoate with integrated catalyst recycling via thermomorphic multiphase system for the continuous production of renewable amines

Anna Kampwerth[1], Tim B. Riemer[1], Jonathan Pöttker-Menke[1], Nadine Oppenberg[1], Arno Windisch[1], Dieter Vogt[1], and Thomas Seidensticker[1*]

TU Dortmund University, Department for Biochemical and Chemical Engineering, Laboratory of Industrial Chemistry, Emil-Figge-Straße 66, 44227 Dortmund, Germany

* E-mail: thomas.seidensticker@tu-dortmund.de

Content

1. **Experimental section and setups**

Setup for recycling experiments

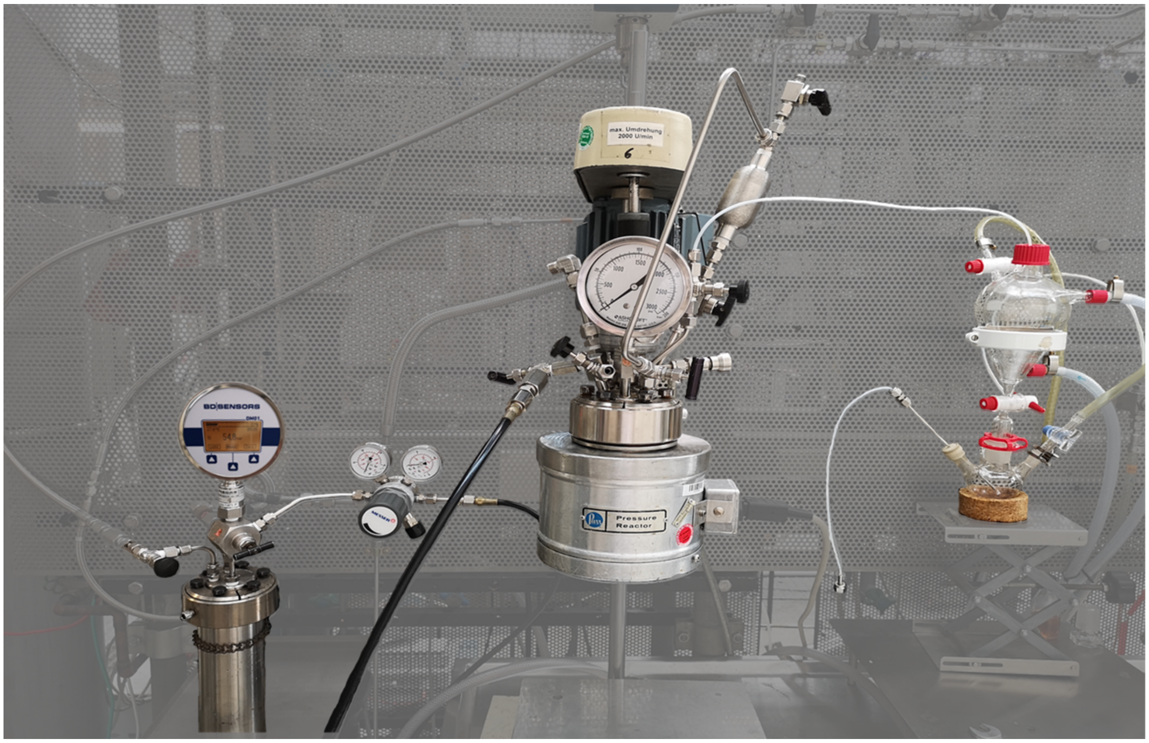


Figure S1: Setup for the recycling experiments in the 300 mL autoclave.

Batch experiments:

The batch experiments were performed in a 300 mL stirred tank reactor. A gas reservoir (V = 1L) is used to provide a continuous hydrogen:carbon monoxide (2:1 ratio) pressure of 36 bar in the reactor. The gas reservoir is pressurized to 75 bar with the mixture of hydrogen and carbon monoxide and a pressure controller reduces the pressure to the reactor. The pressure drop in the gas storage tank caused by the reaction is measured with a digital pressure sensor. For filling the methyl 10-undeneoate to the reaction mixture, the reactor is equipped with a dropping funnel with pressure equilibration.

General procedure of a hydroaminomethylation in batch setup:

The total mass used for all experiments was 100 g. The catalyst Rh(acac)(COD) (0.1 mol%) and SulfoXantphos (0.7 mol%), the solvents methanol and dodecane (w/w 1:1) and the used amine (1 eq.) were filled in the reactor. The autoclave was then closed and rinsed multiple times with argon. Afterwards it is pressurized with 10 bar hydrogen/carbon monoxide and heated up to the reaction temperature of 125 °C. Then the pressure was increased to 36 bar and about 15 minutes were needed for saturation of the reaction mixture with the gas. To start the reaction, the methyl 10-undeneoate (10 w%) is fed into the reactor via the dropping funnel. The pressure-time curves were recorded with the pressure sensor the gas reservoir is equipped with. After the reaction, the reactor was cooled with an ice bath and carefully depressurised. The reaction mixture was filled in a separating funnel and was cooled to 10 °C for 15 minutes. Afterwards, the two phases were separated, and a sample was taken from both phases for GC-FID analysis.

The reactor was cooled with an ice bath after the reaction for the recycling experiments and carefully depressurised to less than 3 bar. A separatory funnel with a glass flask for the catalyst phase was inerted with argon. The reaction solution from the reactor was transferred to the separating funnel using the slight overpressure and argon counter-flow and then separated at 10 °C for 15 minutes. Afterwards, the catalyst phase was released into the inertized glass flask and, from there transferred to the reactor with a slight argon overpressure. After adding the amount of amine substrate into the reactor and methyl 10-undecenoate into the dropping funnel, the next recycling run was started. A sample was taken from the product phase for GC-FID analysis.

Continuous operation:

The continuous experiment was performed in a 1000 mL continuous stirred tank reactor (CSTR) with a blade stirrer and a baffle. UME is purified from peroxides with an aluminum oxide column before the experiment. All solvents and substrates are degassed for 30 minutes in an ultrasonic bath with argon. In an ultrasonic bath, the precursor Rh(acac)(COD) and the ligand SulfoXantphos were dissolved in degassed methanol. The miniplant was inertized by alternating between vacuum and nitrogen several times. The membrane module was connected to the system in nitrogen counterflow and then flooded several times with nitrogen. A vacuum is then added to the CSTR, and the degassed catalyst solution is drawn into the reactor, and preforming is carried out for 1 hour at 125 °C and 36 bar synthesis gas (H_2:CO=2:1). The degassed nonpolar phase (UME and dodecane) and diethylamine are transferred into the dropping funnel of the reactor *via* a vacuum. After completion of the preforming, the catalyst solution is partly discharged from the reactor into the rest of the miniplant (decanter, buffer tank of membrane loop). Then, the reactor is decoupled from the rest of the system again. Afterwards, the nonpolar phase and diethylamine are added to the reactor *via* dropping funnel, and the batch reaction is carried out for 1 hour. After the batch reaction, the reactor is connected to the rest of the system by opening the respective valves. The recycle, membrane, and all substrate pumps are started to switch to continuous operation. The controlled gas dosing of carbon monoxide and hydrogen into the miniplant takes place *via* two mass flow controllers (MFCs). To achieve a constant methanol mass in the system, the methanol losses over the product and permeate streams are compensated with an additional pump for the methanol makeup. During plant operation, a sample of the product phase is taken every 2 hours in the decanter for GC-FID and ICP-OES analysis. In addition, the compositions of the recycle phase and the permeate phase are determined during plant operation. The water concentration of the recycle and permeate stream is obtained *via* GC-TCD analysis.

2. **Chemicals used**

All chemicals used are listed in the table below.

Table S1: list of chemicals.

name	**purity**	**company**
methyl 10-undecenoate	96 %	TCI
***n*-diethylamine**	99 %	FISCHER SCIENTIFIC
ethylamine	30% in methanol	TCI
***n*-dipropylamine**	99 %	ACROS ORGANICS
***n*-butylamine**	>99 %	ACROS ORGANICS
di-*n*-butylamine	98 %	ABCR
pyrrolidine	>99 %	ACROS ORGANICS
piperazine	66 %	ACROS ORGANICS
imidazole	99,5	SIGMA ALDRICH
piperidine	99 %	MERCK
morpholine	>99 %	MERCK
di-*iso*-propylamine	>99 %	ACROS ORGANICS
sarcosine	98 %	ABCR
valine	99 %	TCI
proline	>99%	ACROS ORGANICS
***n*-dodecane**	>99 %	ABCR GMBH
methanol	>99.5	CARL ROTH
isopropanol	>99.7 %	VWR
Rh(acac)(COD)	99.9 %	UMICORE
SulfoXantphos	-	MOLISA
argon	99.996 %	MESSER INDUSTRIEGASE GMBH
hydrogen	99.999 %	MESSER INDUSTRIEGASE GMBH
carbon monoxide	98 %	MESSER INDUSTRIEGASE GMBH
nitrogen	99.5 %	MESSER INDUSTRIEGASE GMBH

3. **Analytics**

NMR-Spectroscopy: ^{1}H- and ^{13}C-NMR-spectra were recorded with the spectrometer from BRUKER (Bruker Avance III HD NanoBay - 400 MHz) with the frequency and solvent noted. Chemical shifts δ are given in ppm relative to tetramethylsilane.

Gaschromatography: Conversion and yield of the batch and recycle reactions were determined via GC on an AGILENT TECHNOLOGIES INC. gas chromatograph of the model Intuvo 9000 with a flame ionization detector (FID). A HP-5 column was used (30 m long, 0.32 mm diameter, 0.25 µm thickness of the layer, 1 minutes at 40 °C, heating rate 25°C/min to 140 °C, heating rate 5 °C/min to 180, heating rate 40 °C/min to 320 °C, holding for 6 minutes, heating rate 40 °C/min to 350 °C, holding for 5 minutes). The split was set to 1:100 and the inlet temperature was 350 °C. Di-*n*-butyl ether was chosen as internal standard and response factors of the substrates and products were obtained experimentally by analyzing known quantities of the substances. For a sample, a certain amount of substrate or product, 25 mg di-*n*-butyl ether was used and diluted to 1 g total mass with isopropanol.

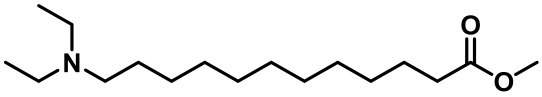
The product, recycle and permeate samples of the continuous miniplant operation were measured with an Agilent Technologies (7890A) GC with a FID, that is equipped with an HP-5 column (30 m long, 0.32 mm diameter, 0.25 µm thickness of the layer, 1 minute at 40 °C, heating rate 25 °C/min to 140 °C, heating rate 5 °C/min to 180 °C, heating rate 40 °C/min to 320 °C, holding for 6 minutes). Nitrogen was used as a carrier gas, and the injection volume was 1 µL with a split of 1:100 and an inlet temperature of 250 °C. The water concentration was measured with the same GC and column with a thermal conductivity detector (TCD) with helium as carrier gas (2.9 minutes at 30 °C, heating rate 30 °C/min to 110°C, heating rate 10 °C/min to 130 °C, heating rate 20 °C/min to 152 °C, heating rate 12 °C/min to 198 °C, heating rate 50 °C/min to 320 °C, holding for 4 minutes). An injection volume of 1 µL injection volume and a split ratio of 1:60 were used with an inlet temperature of 230 °C. The samples were prepared with 450 mg of the to-be-analyzed solution, 50 mg of di-*n*-butyl ether as internal standard, and 500 mg of isopropanol.

High-Resolution Mass Spectrometry (HR-MS): Samples for HRMS were diluted in methanol to a concentration of 100 µg·mL^{-1} and measured with an LTQ-Orbitrap (THERMO SCIENTIFIC).

ICP-OES-Analytics: The ICP-OES analysis (Optical Emission Spectrometry with Inductively Coupled Plasma) of the palladium and phosphorus leaching into the organic product phase was performed on a Plasma Quant PQ 9000 spectrometer. Samples with a concentration of rhodium or phosphorus below the detection limit of 1 ppm were evaporated and measured again to obtain the accurate concentration.

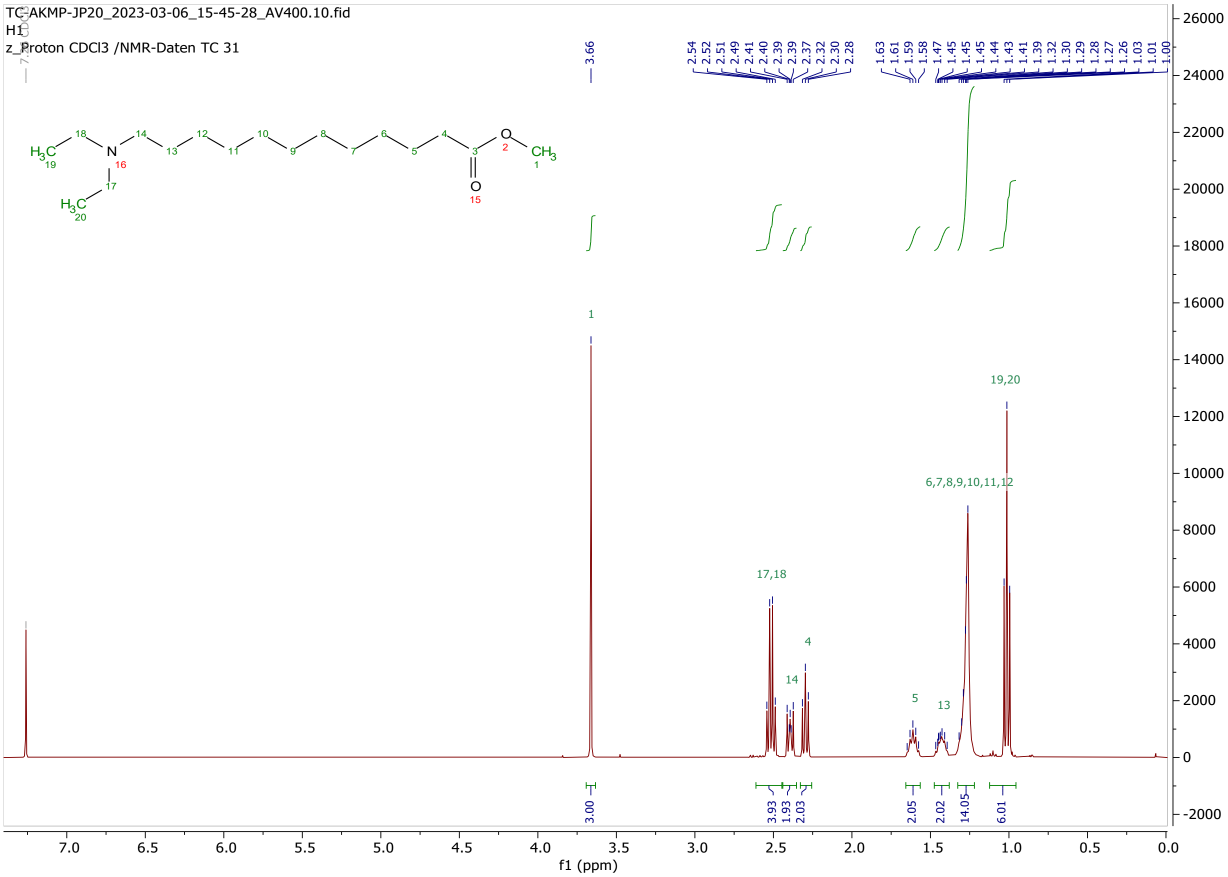
4. Product identification: Isolation, identification, and calibration

Methyl 12-(diethylamino)dodecanoate (*l*-4a)

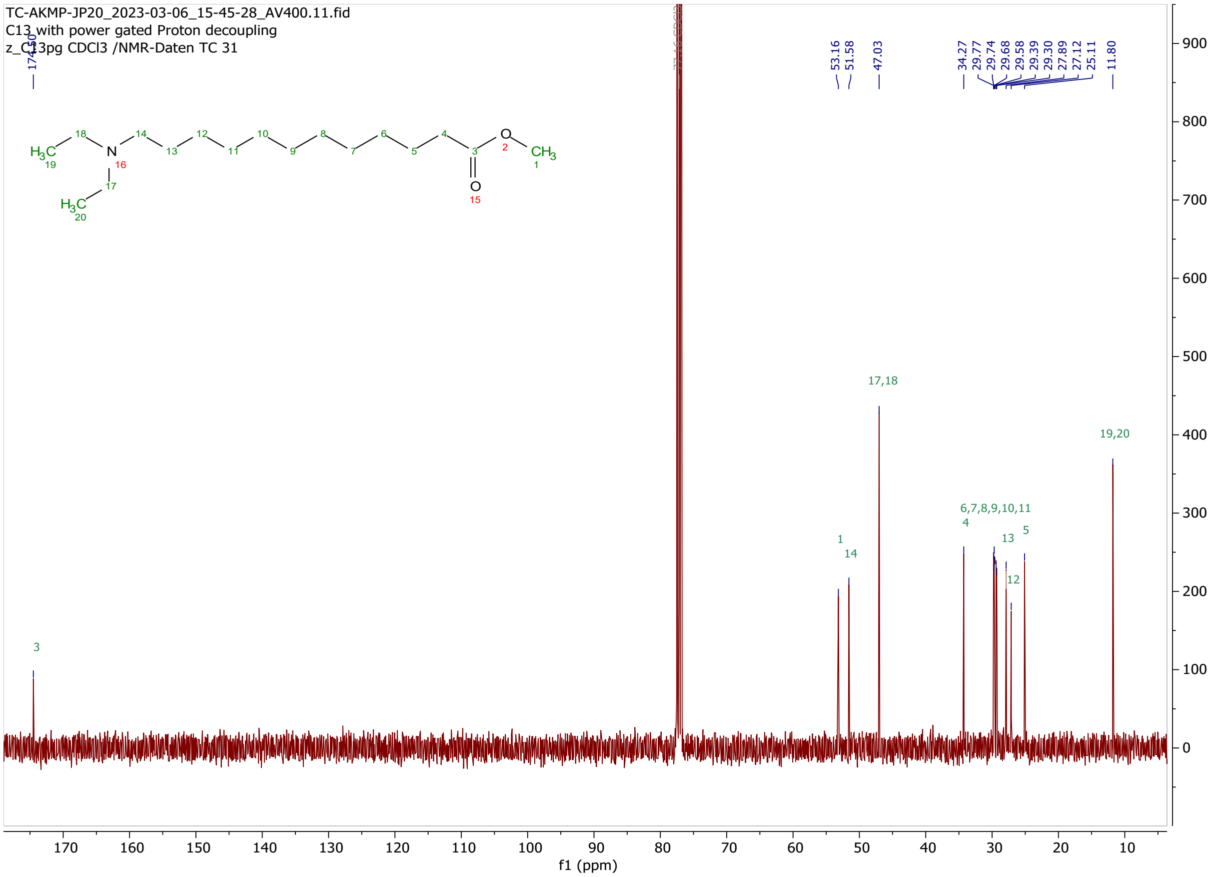


NMR Spectroscopy: The spectroscopic data correspond to those previously reported in the literature. [1]

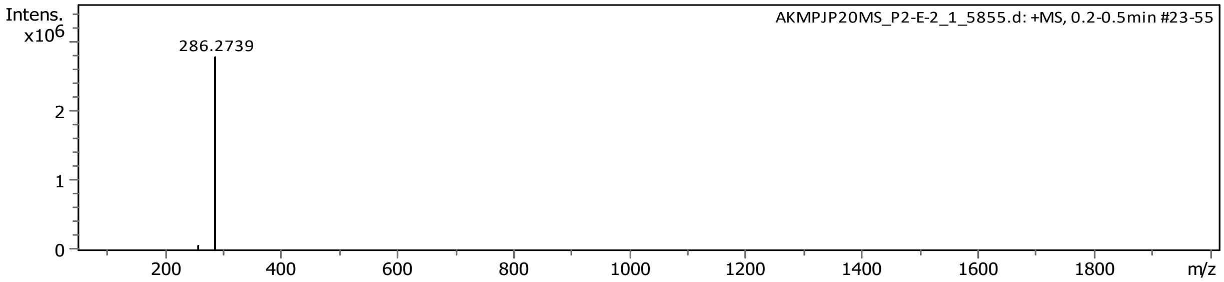
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) = 3.66 (s, 3H, **1**), 2.53 (q, *J* = 7.2 Hz, 4H, **17-18***), 2.44 – 2.35* (m, 2H, **14**), 2.30 (t, J = 7.5 Hz, 2H, **4**), 1.61 (p, J = 7.2 Hz, 2H, **5**), 1.48 – 1.38 (m, 2H, **13**), 1.33 – 1.22 (m, 14H, **6-12**), 1.01 (t, J = 7.1 Hz, 6H, **19-20**).



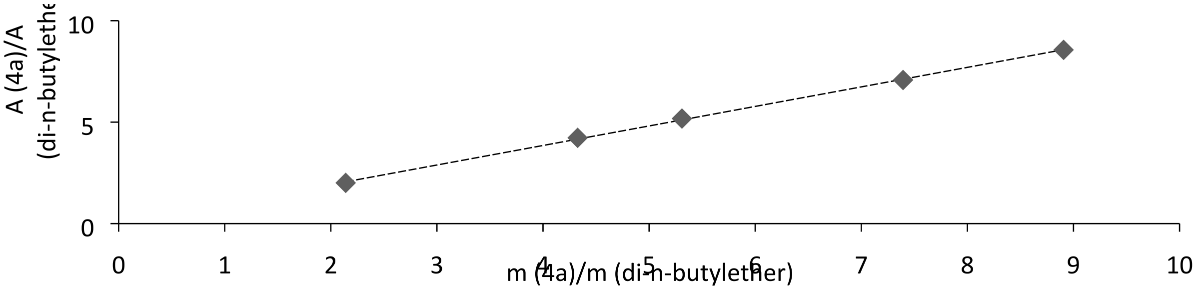
^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm) = 174.50 (C3), 53.16 (C14), 51.58 (C1), 47.03 (C17-18), 34.27 (C4), 29.77-29.30 (C6-11), 27.89 (C13), 27.12 (C12), 25.11 (C5), 11.80 (C19-20).



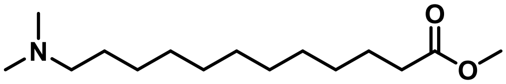
HR-MS (ESI): calcd. $[M+H]^+$ = 286.2741, found $[M+H]^+$ = 286.2739.



GC-Calibration:

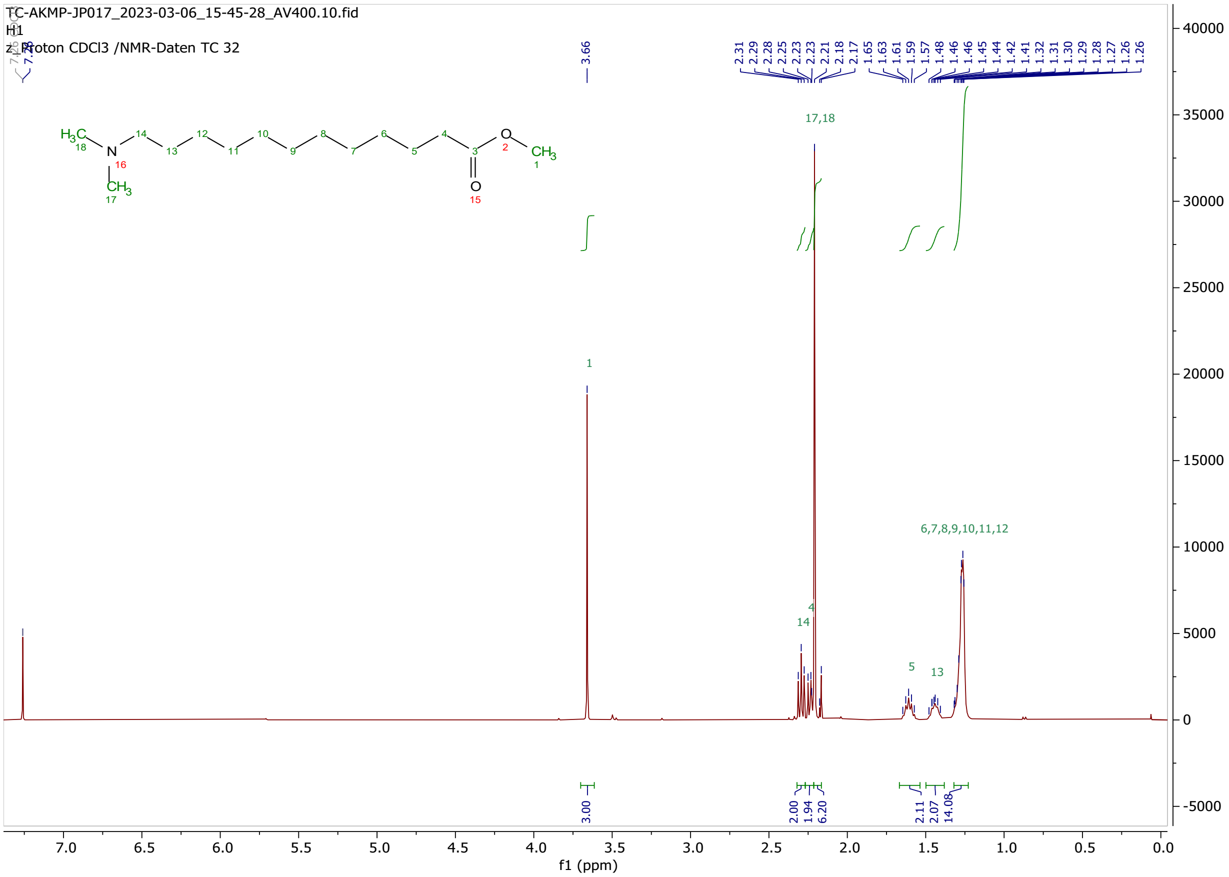


Methyl 12-(dimethylamino)dodecanoate (*l*-4b)

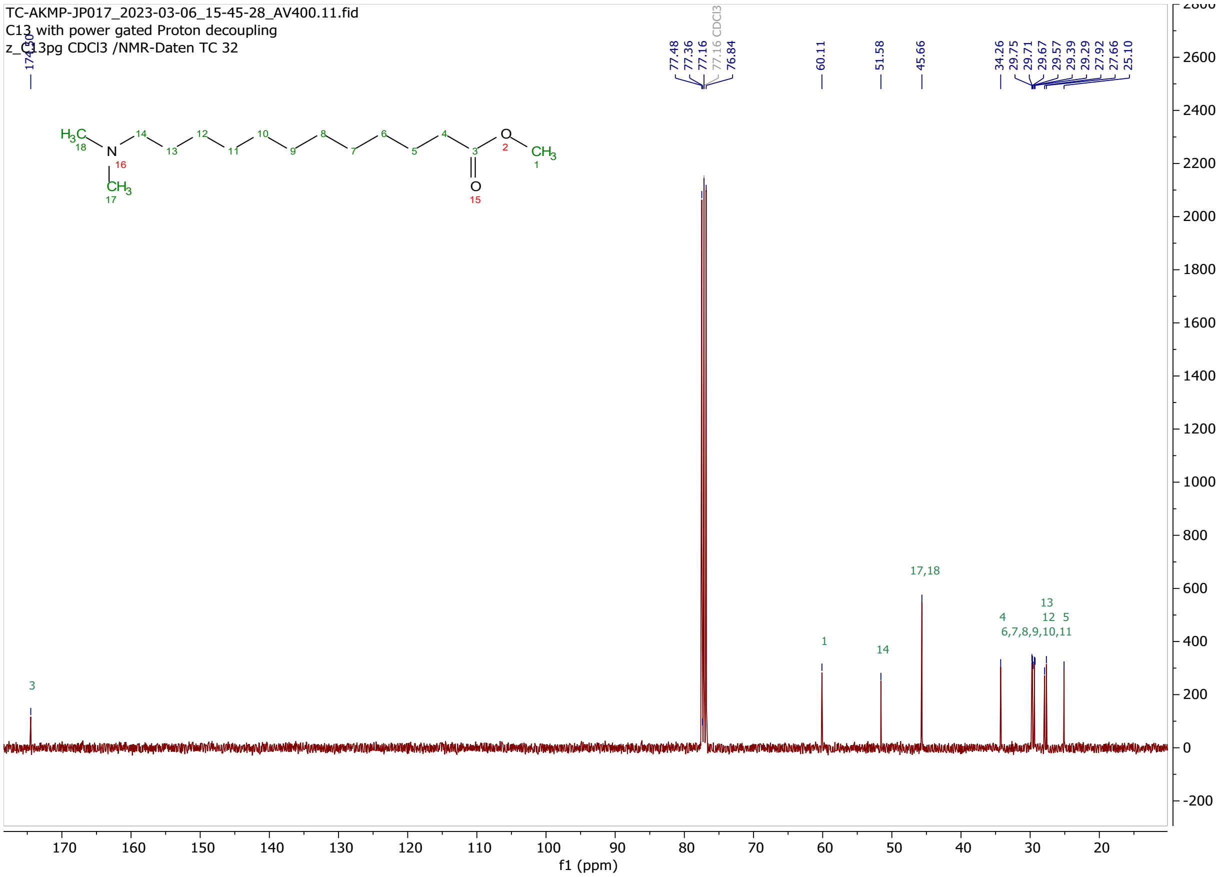


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

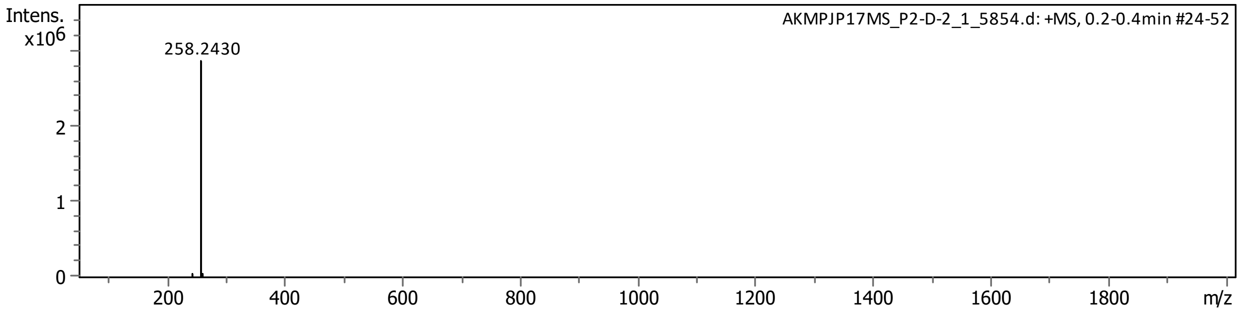
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.66 (s, 3H, **1**), 2.29 (t, J = 7.6 Hz, 2H, **14**), 2.26-2.22 (m, 2H, **4**), 2.21 (s, 6H, **17-18**), 1.61 (p, J = 7.4 Hz, 2H, **5**), 1.50 – 1.38 (m, 2H, **13**), 1.32-1.24 (m, 14H, **6-12**).



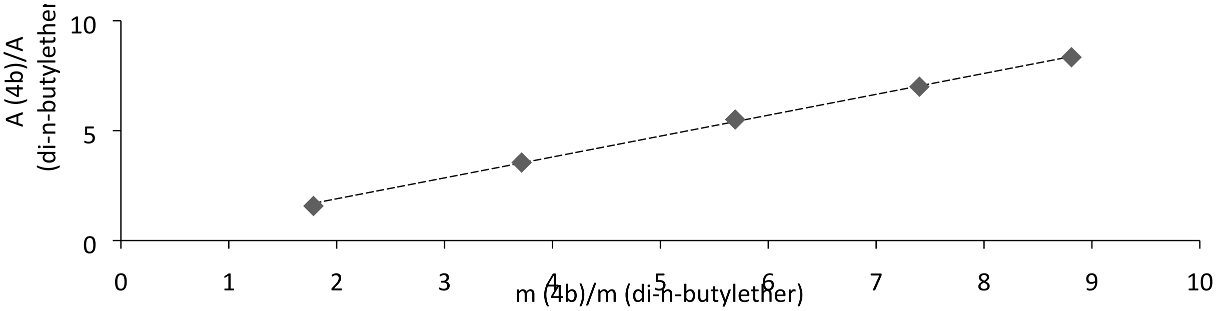
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 174.50 (C3), 60.11 (C1), 51.58 (C14), 45.66 (C17-18), 34.26 (C4), 29.75-25.10 (C6-C11), 27.92 (C13), 27.66 (C12), 25.10 (C5).



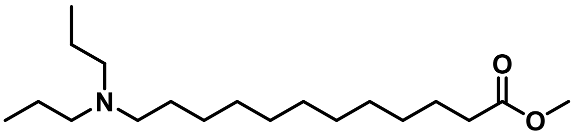
HR-MS (ESI): calcd. $[M+H]^+$ = 258.2428, found $[M+H]^+$ = 258.2430.



GC-Calibration:

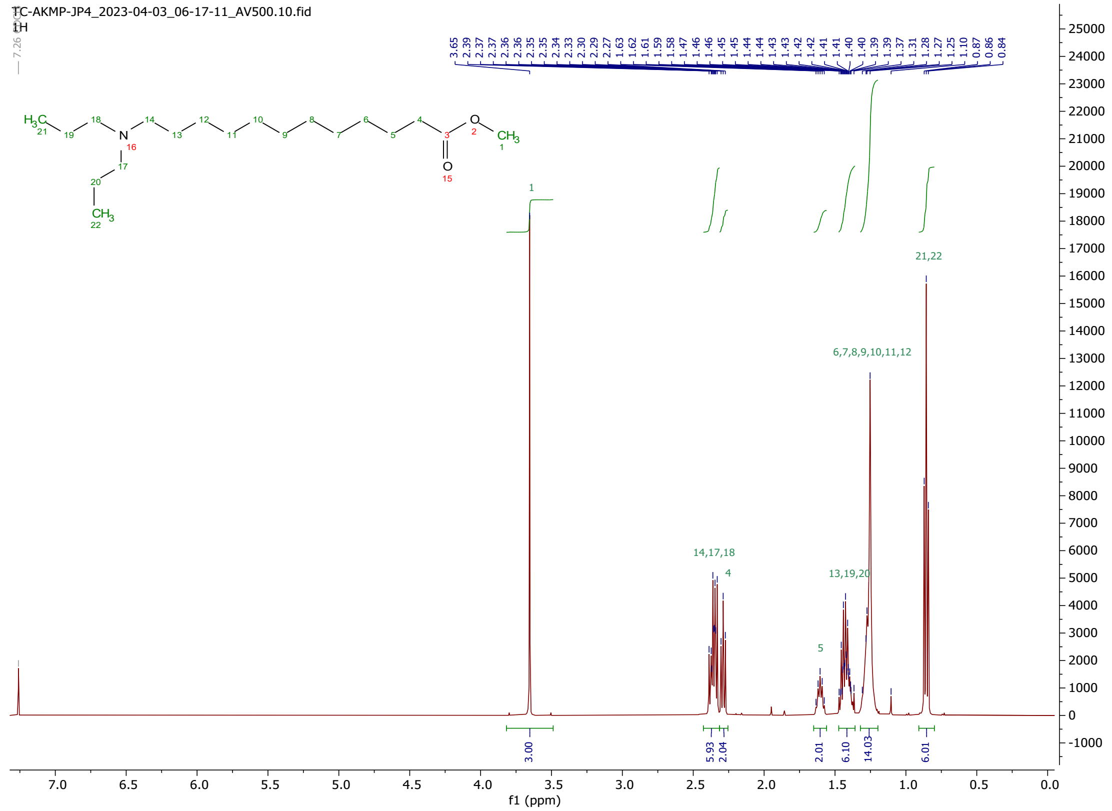


Methyl 12-(di-*n*-propylamino)dodecanoate (*l*-4c)

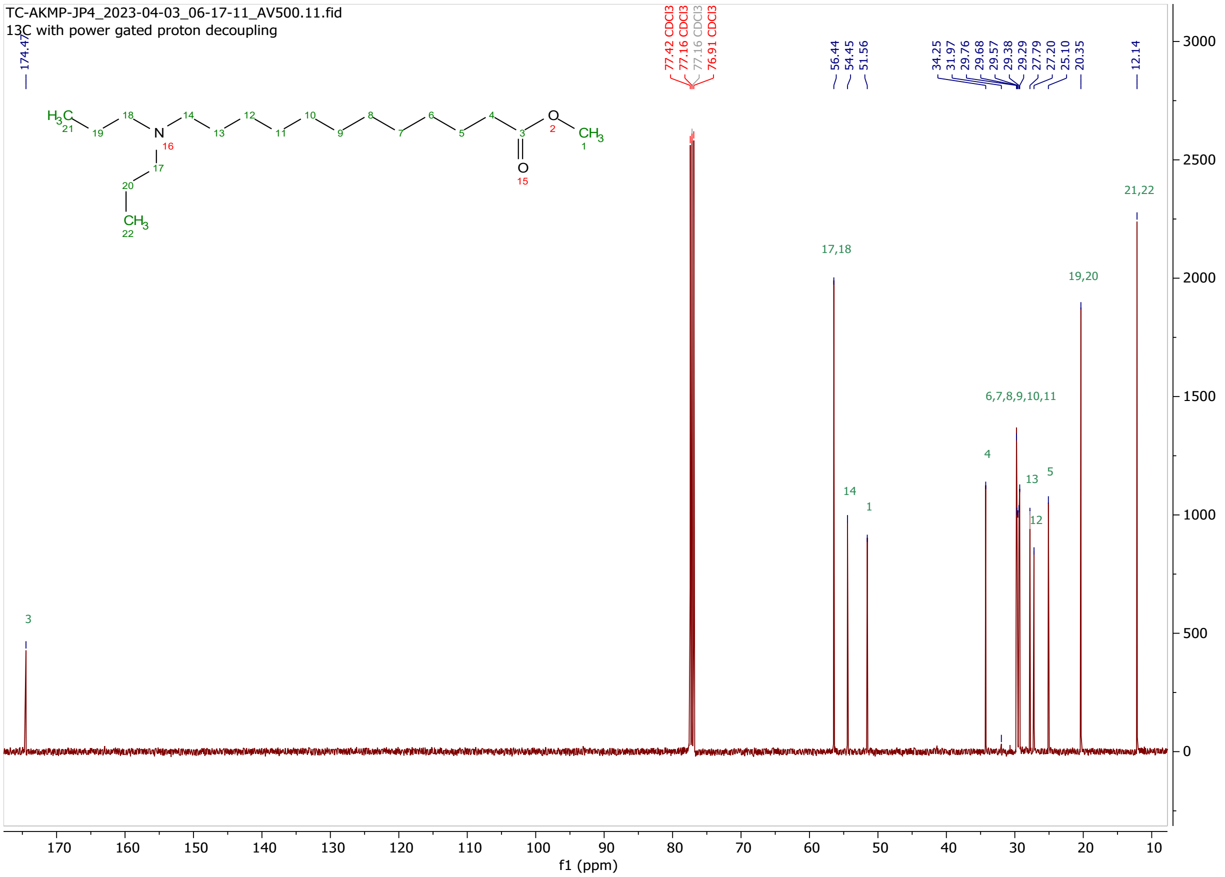


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

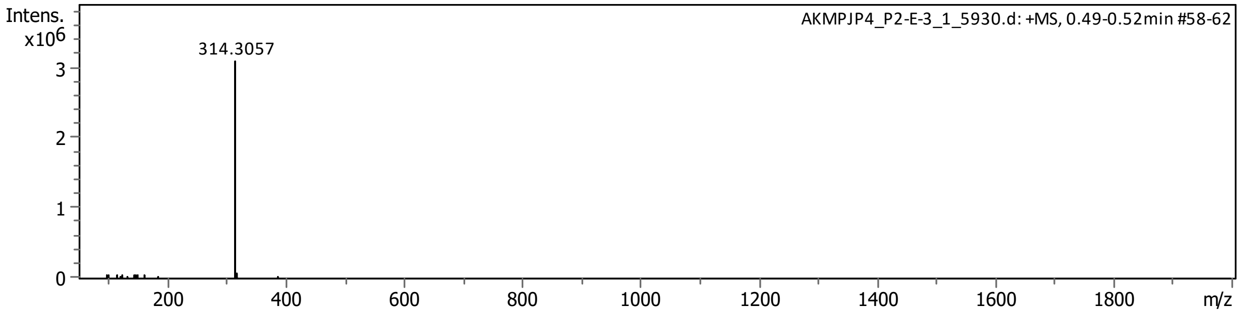
^{1}H-NMR (500 MHz, CDCl$_3$) δ (ppm) = 3.65 (s, 3H, **1**), 2.42–2.31 (m, 6H, **14, 17-18**), 2.29 (t, J = 7.3 Hz, 2H, **4**), 1.60 (p, J = 7.3 Hz, 2H, **5**), 1.47–1.36 (m, 6H, **13, 19-20**), 1.31–1.25 (m, 14H, **6-12**), 0.86 (t, J = 7.4 Hz, 6H, **21-22**).



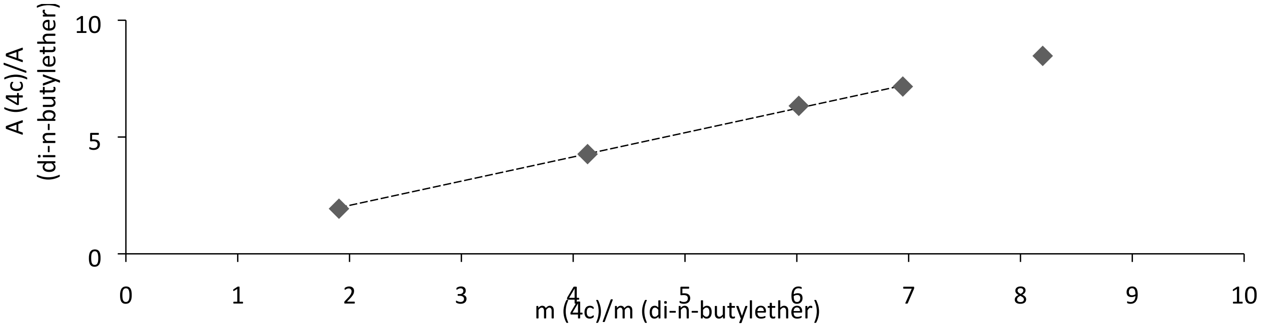
^{13}C-NMR (126 MHz, CDCl$_3$) δ (ppm) = 174.47 (C3), 56.44 (C17-18), 54.45 (C14), 51.56 (C1), 34.25 (C4), 31.97-29.29 (C6-C11), 27.79 (C13), 27.20 (C12), 25.10 (C5), 20.35 (C19-20), 12.14 (C21-22).



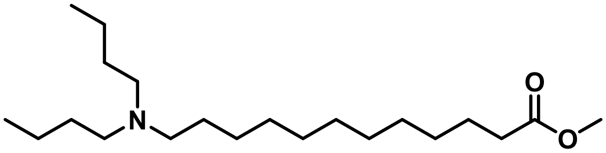
HR-MS (ESI): calcd. [M+H]$^+$ = 314.3054, found [M+H]$^+$ = 314.3057.



GC-Calibration:

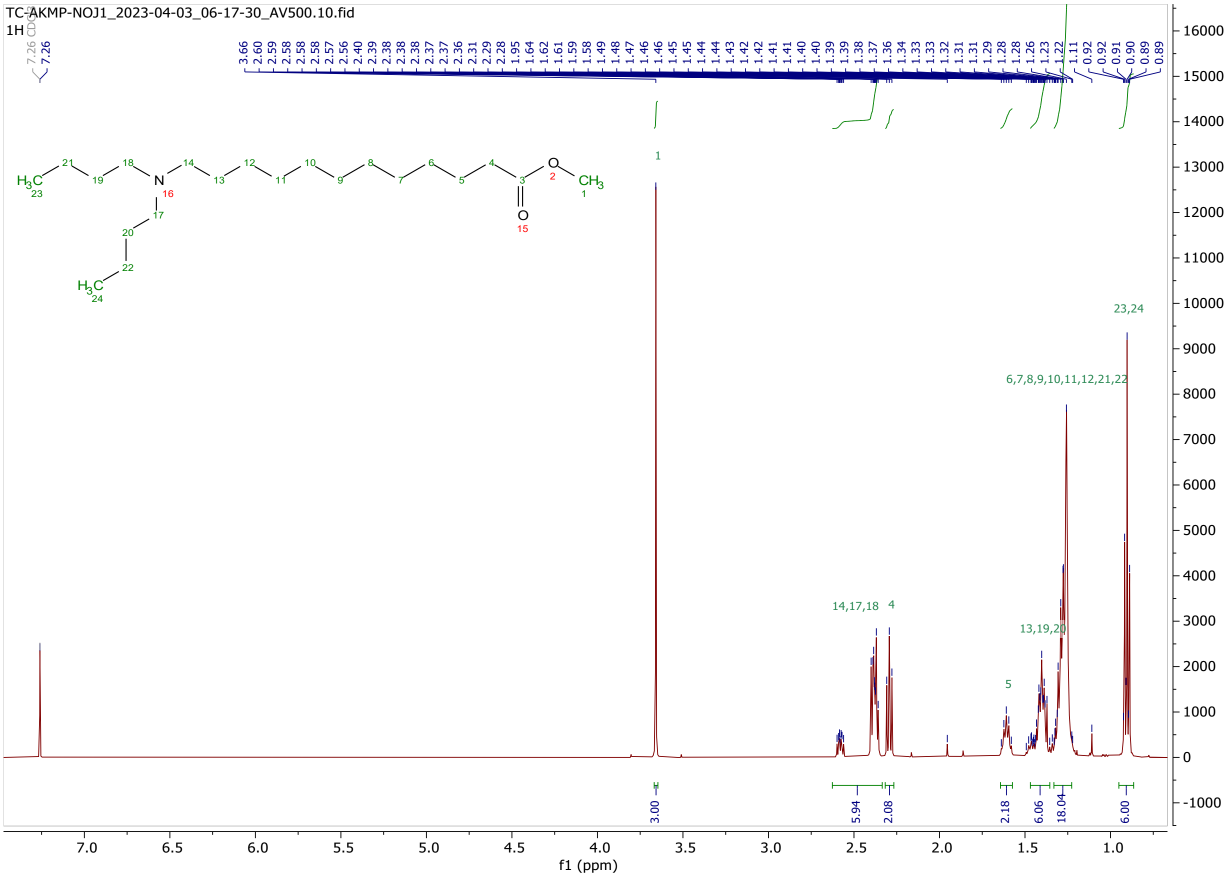


Methyl 12-(di-*n*-butylamino)dodecanoate (*l*-4d)

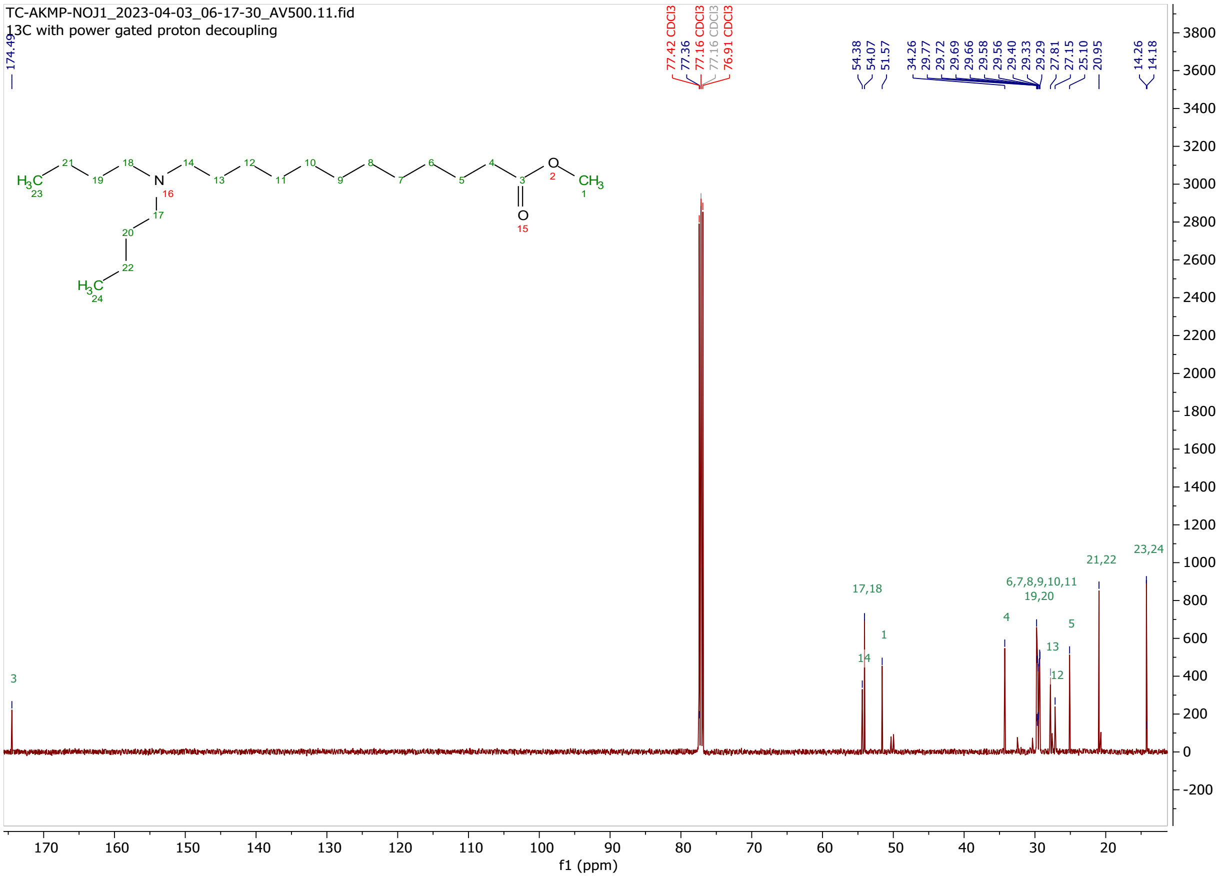


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

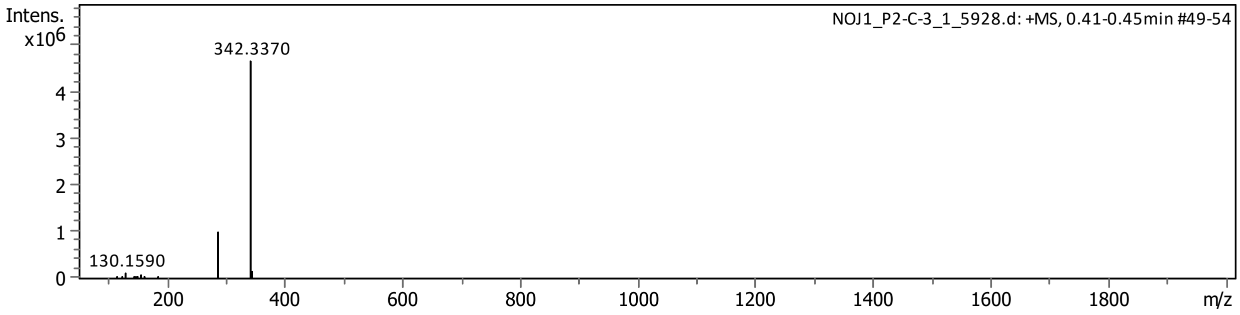
^{1}H-NMR (500 MHz, $CDCl_3$) δ (ppm) = 3.66 (s, 3H, **1**), 2.60–2.36 (m, 6H, **14, 17-18**), 2.29 (t, J = 7.6 Hz, 2H, **4**), 1.61 (p, J = 7.3 Hz, 2H, **5**), 1.47–1.35 (m, 6H, **13, 19-20**), 1.33–1.23 (m, 14H, **6-12, 21-22**), 0.90 (t, J = 7.3 Hz, 6H, **23-24**).



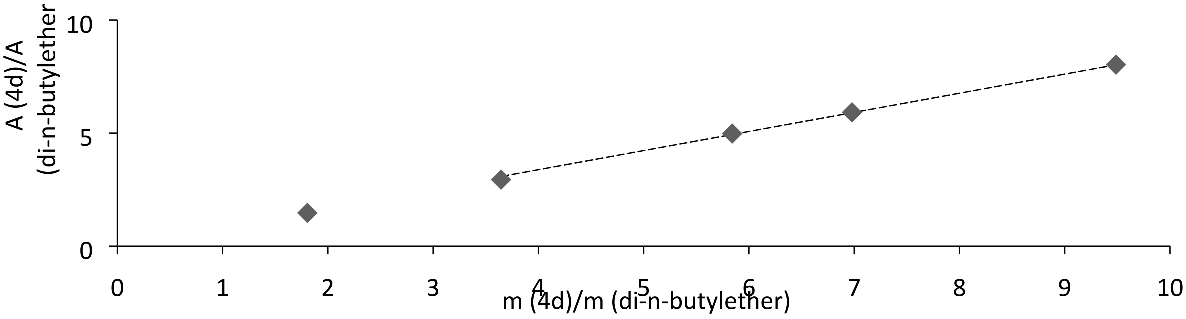
^{13}C-NMR (126 MHz, $CDCl_3$) δ (ppm) = 174.49 (C3), 54.38 (C14), 54.07 (C17-18), 51.57 (C1), 34.26 (C4), 29.77-29.29 (C6-C11, C19-20), 27.81 (C13), 27.15 (C12), 25.10 (C5), 20.95 (C21-22), 12.26 (C23-24).



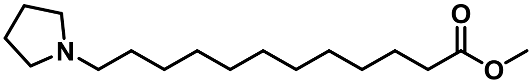
HR-MS (ESI): calcd. $[M+H]^+$ = 342.3367, found $[M+H]^+$ = 342.3370.



GC-Calibration:

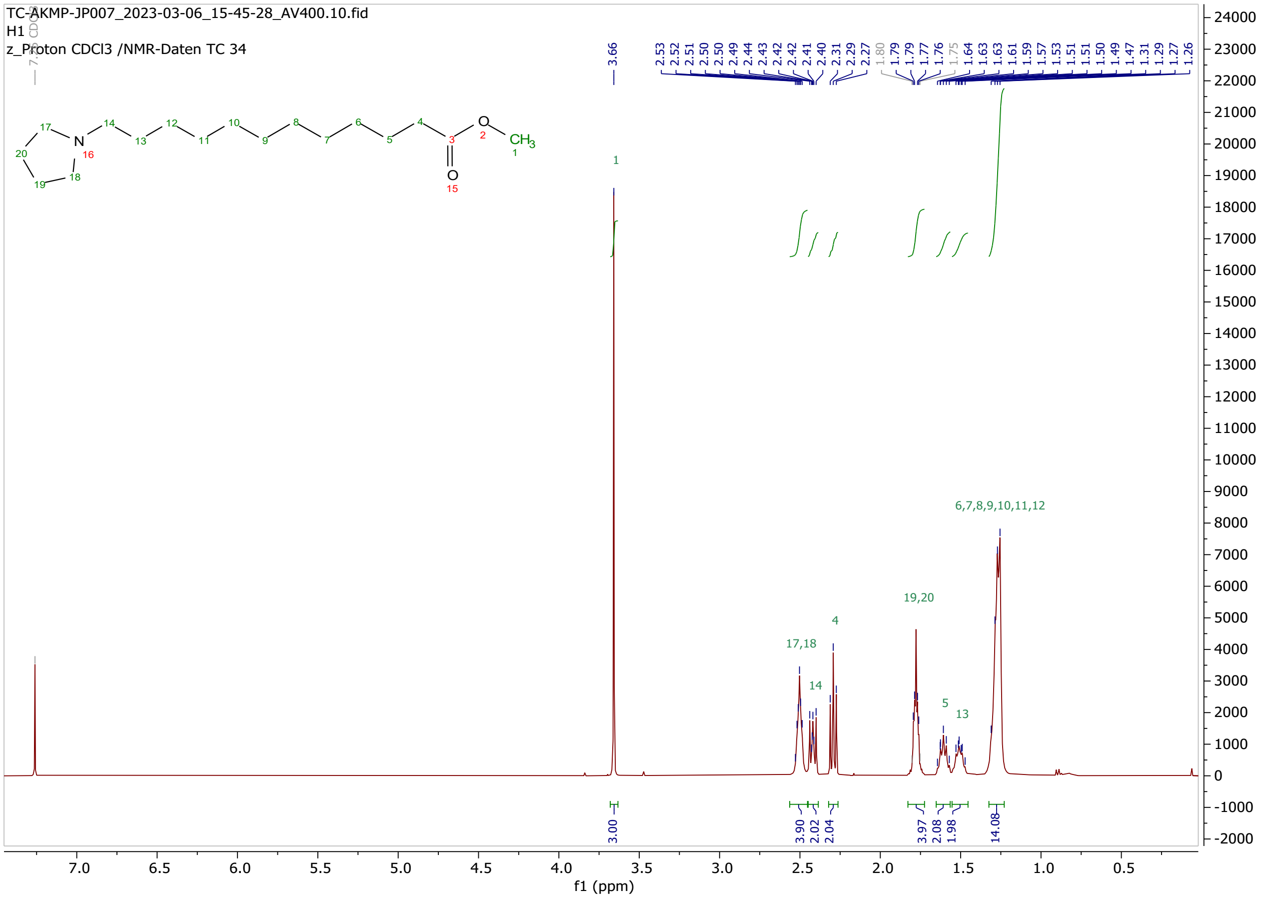


Methyl 12-(pyrrolidin-1-yl)dodecanoate (*l*-4f)

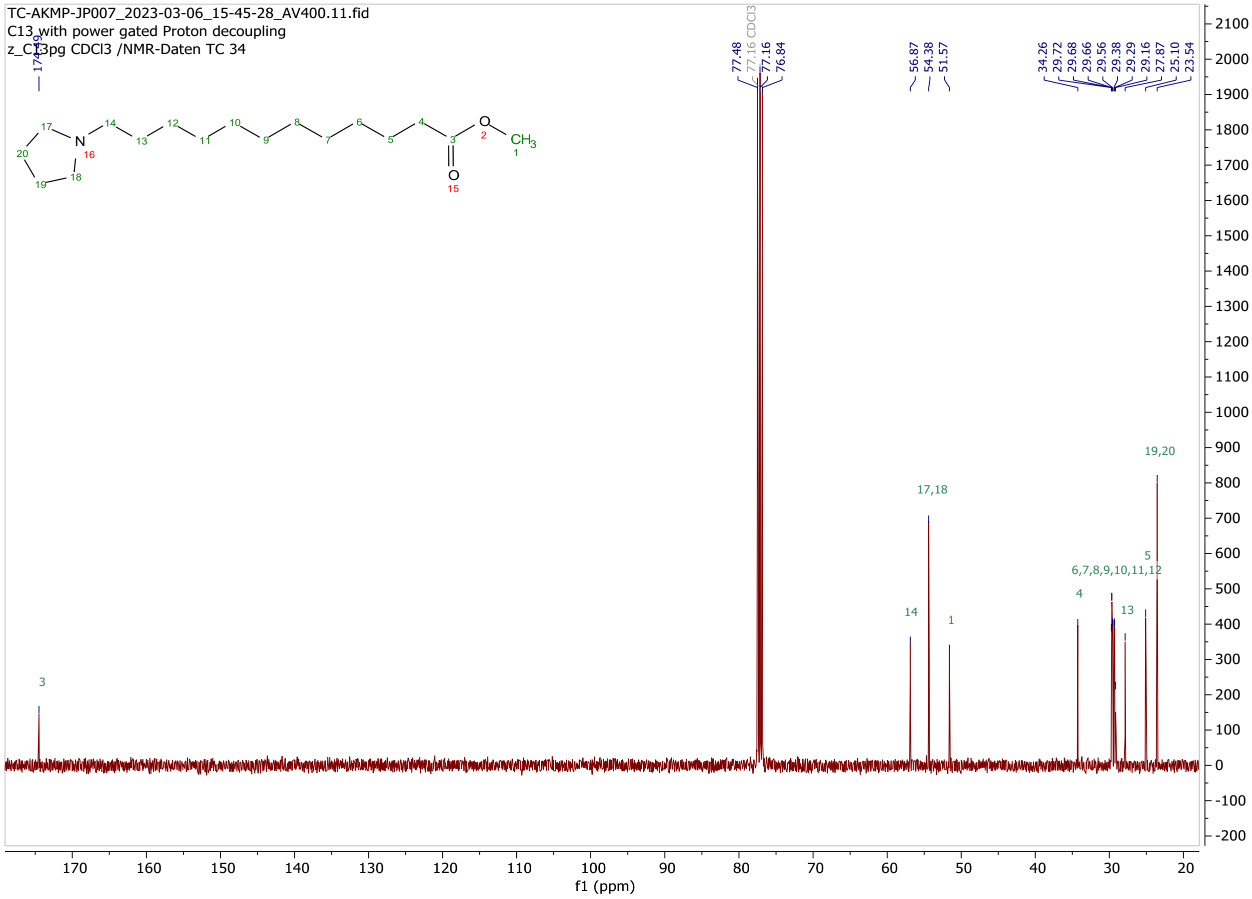


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

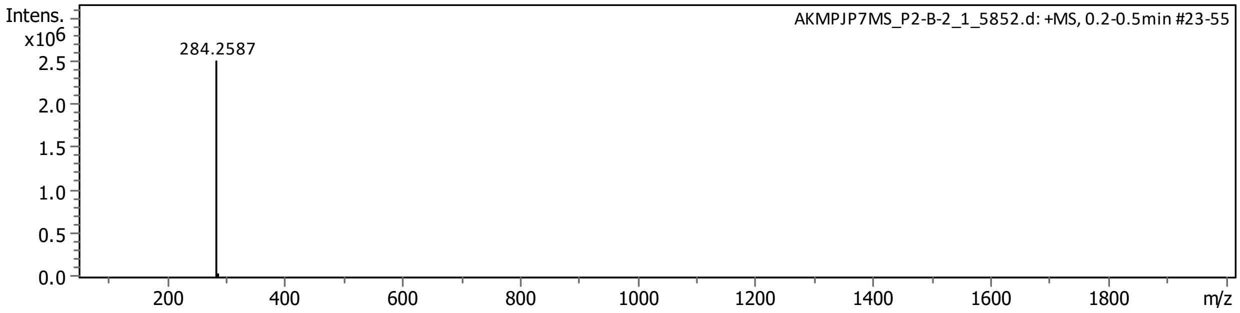
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.66 (s, 3H, **1**), 2.56–2.45 (m, 4H, **17-18**), 2.45–2.39 (m, 2H, **14**), 2.29 (t, J = 7.5 Hz, 2H, **4**), 1.83–1.72 (m, 4H, **19-20**), 1.61 (p, J = 7.2 Hz, 2H, **5**), 1.55–1.45 (m, 2H, **13**), 1.47–1.36 (m, 6H, **13, 19-20**), 1.32–1.23 (m, 14H, **6-12**).



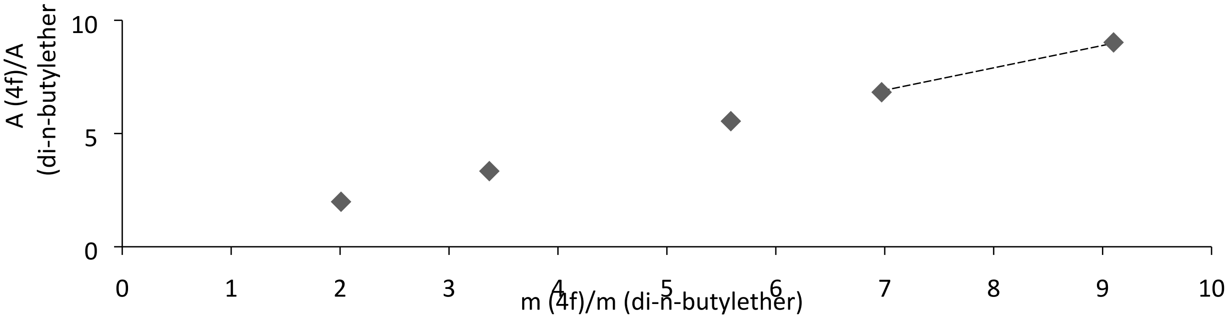
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 174.49 (C3), 56.87 (C14), 54.38 (C17-18), 51.57 (C1), 34.26 (C4), 29.72-29.16 (C6-C12), 27.87 (C13), 25.10 (C5), 23.54 (C19-20).



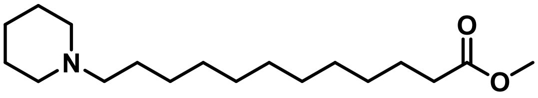
<u>HR-MS (ESI):</u> calcd. $[M+H]^+$ = 284.2585, found $[M+H]^+$ = 284.2587.



<u>GC-Calibration:</u>

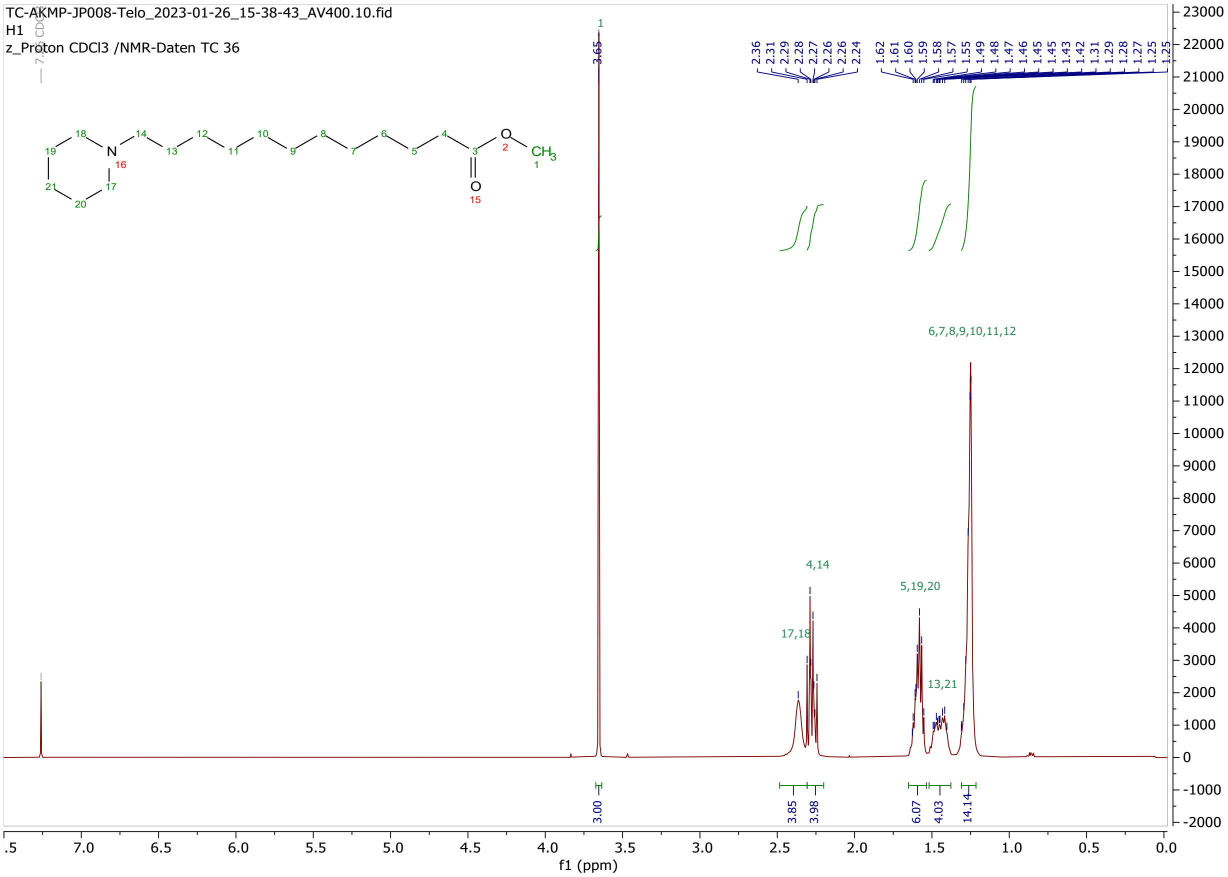


Methyl 12-(piperidin-1-yl)dodecanoate (*l*-4g)

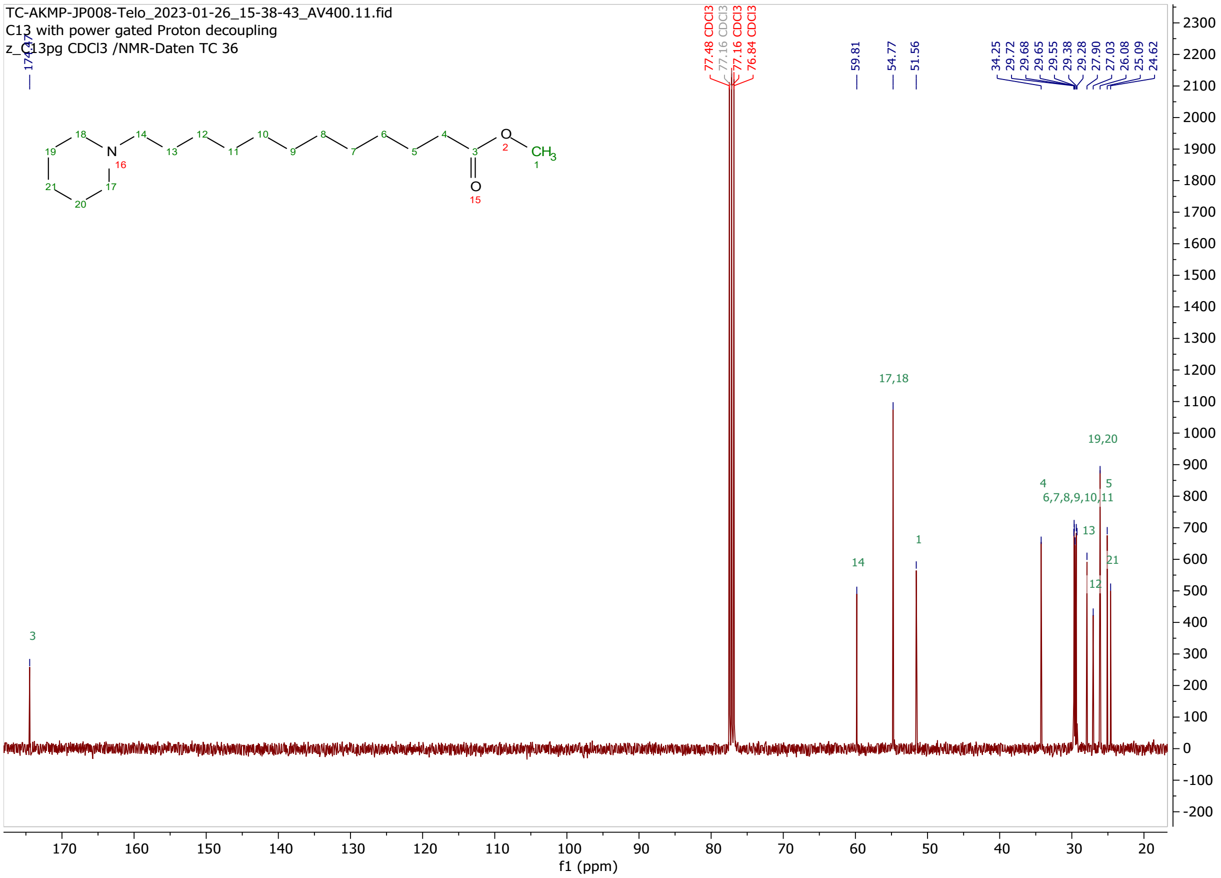


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.65 (s, 3H, **1**), 2.45–2.32 (m, 4H, **17-18**), 2.32–2.22 (m, 4H, **4, 14**), 1.65–1.53 (m, 4H, **5, 19-20**), 1.52–1.37 (m, 4H, **13, 21**), 1.32–1.21 (m, 14H, **6-12**).



^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 174.47 (C3), 59.81 (C14), 54.77 (C17-18), 51.56 (C1), 34.25 (C4), 29.72-29.28 (C6-C12), 27.90 (C13), 27.03 (C12), 26.08 (C19-20), 25.09 (C5), 24.62 (C21).



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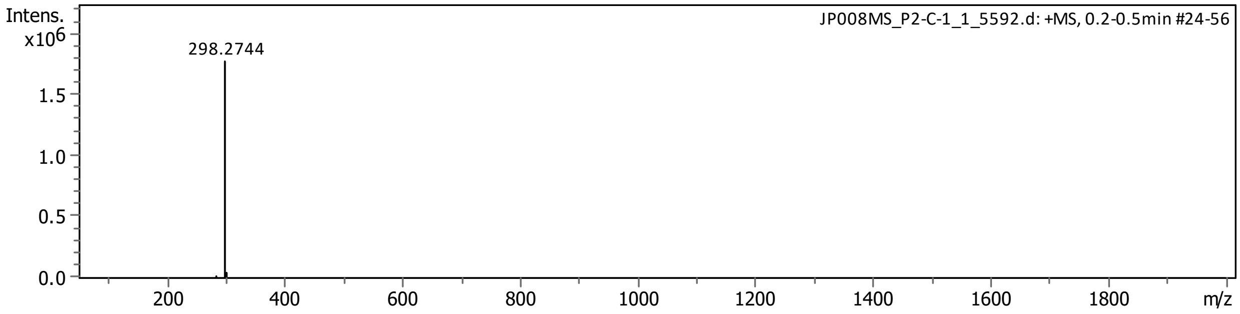

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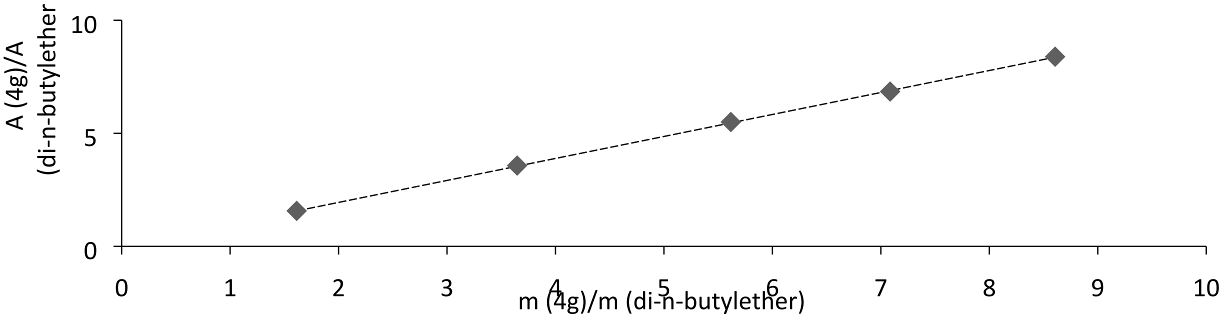
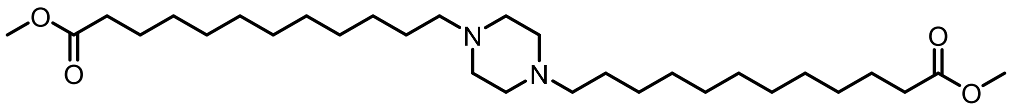
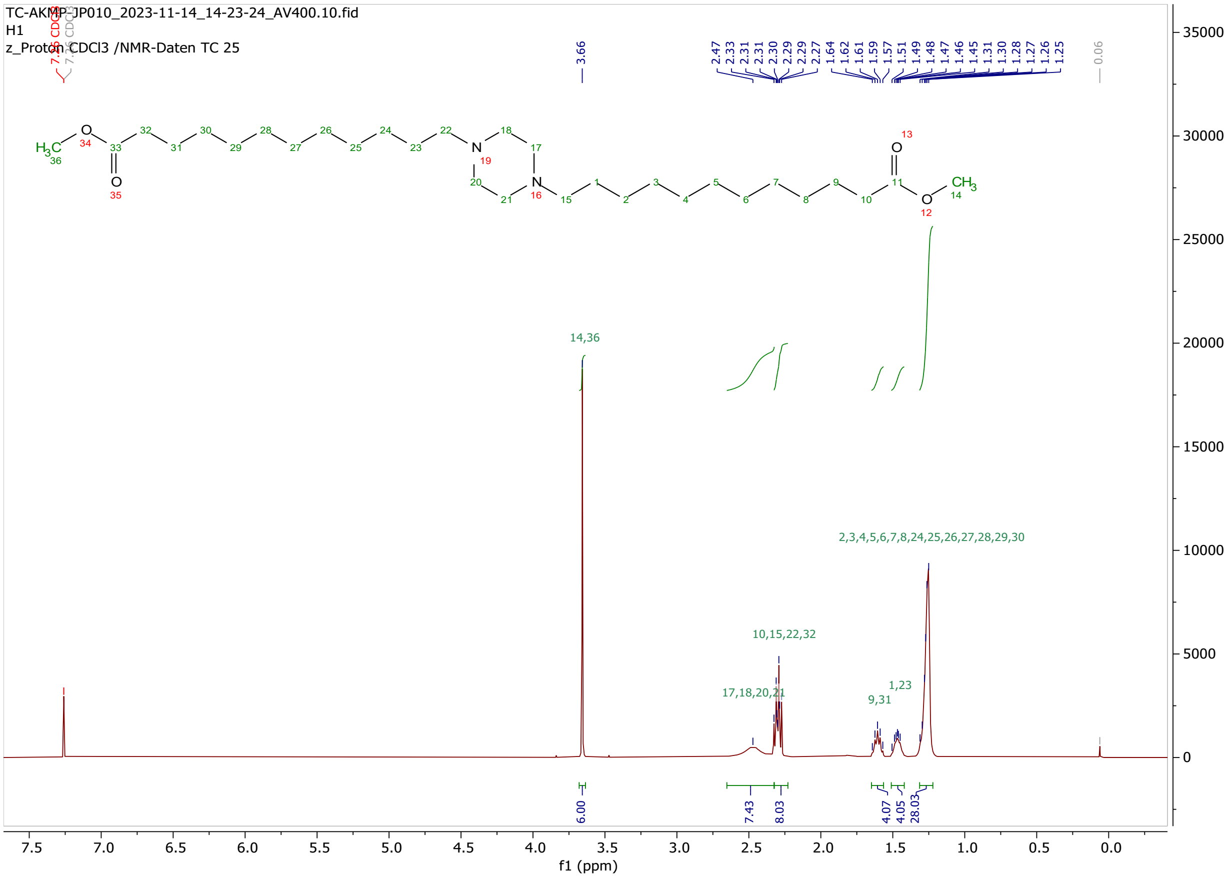


Dimethyl 12,12'-(piperazine-1,4-diyl)didodecanoate (*l*-4h)

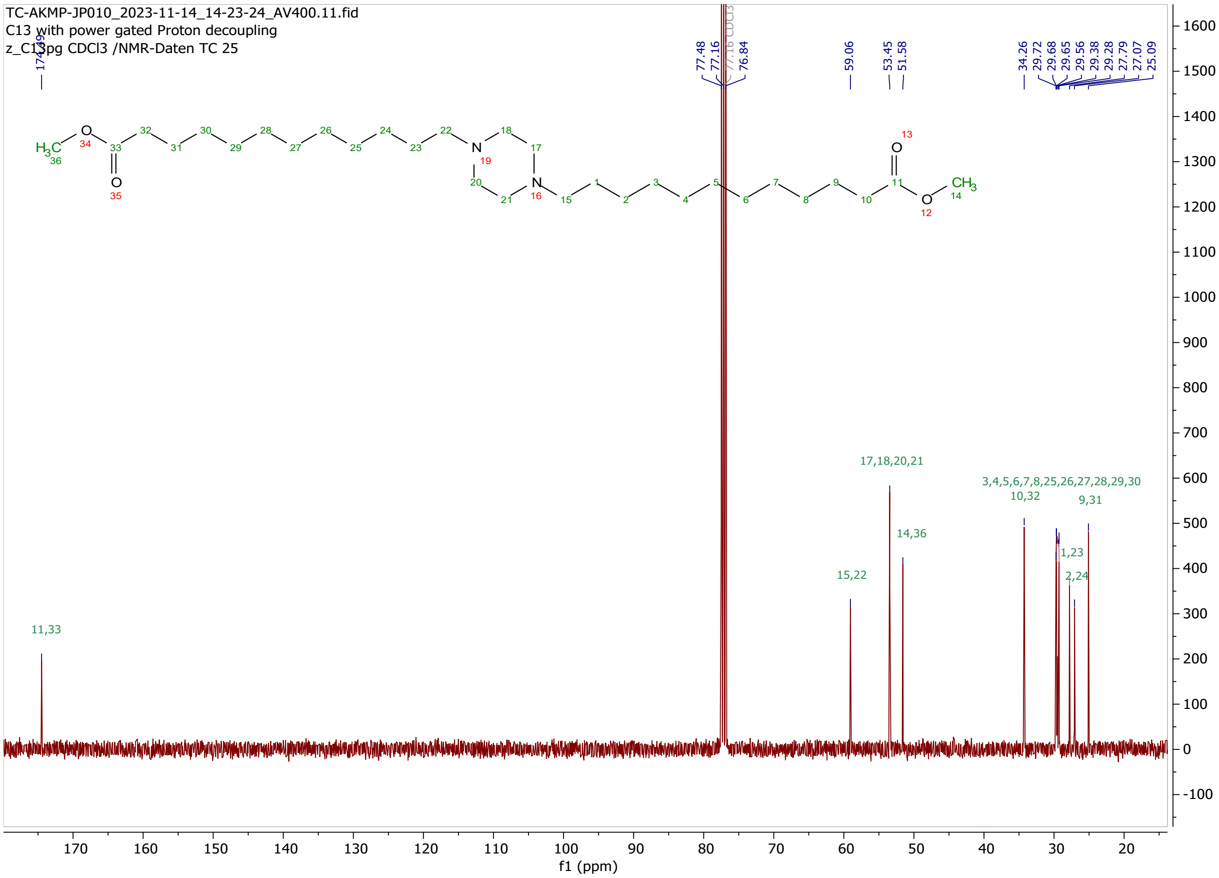


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to those previously reported in the literature.[2]

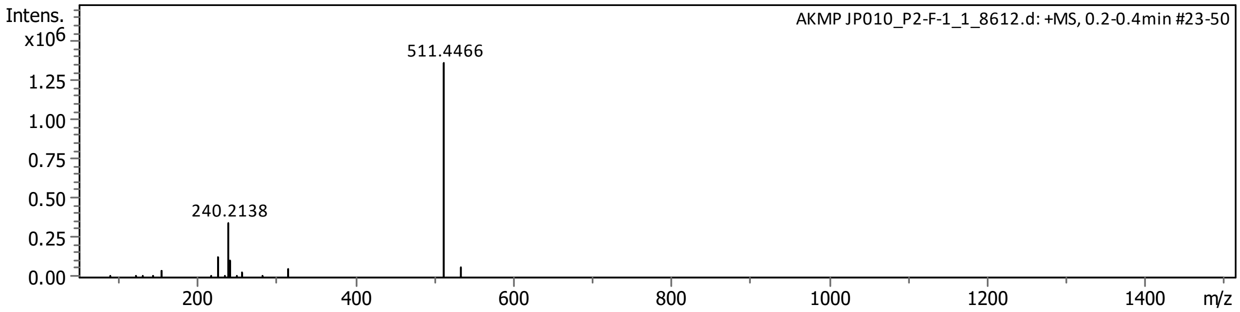
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.66 (s, 3H, **1**), 2.65–2.34 (m, 7H, **17-18, 20-21**), 2.33–2.23 (m, 8H, **10, 15, 22, 23**), 1.61 (p, J = 7.3 Hz, 4H, **9, 31**), 1.51–1.42 (m, 4H, **1, 23**), 1.32–1.20 (m, 28H, **2-8, 24-30**).



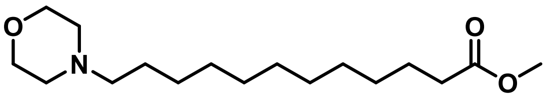
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 174.49 (C11, C33), 59.06 (C15, C22), 53.45 (C17-18, 20-21), 51.58 (C14, C36), 34.26 (C10, C32), 29.72-29.28 (C3-C8, C25-C30), 27.79 (C1, C23), 27.07 (C2, C24), 25.09 (C9, C31).



HR-MS (ESI): calcd. [M+H]$^+$ = 511.4470, found [M+H]$^+$ = 511.4466.

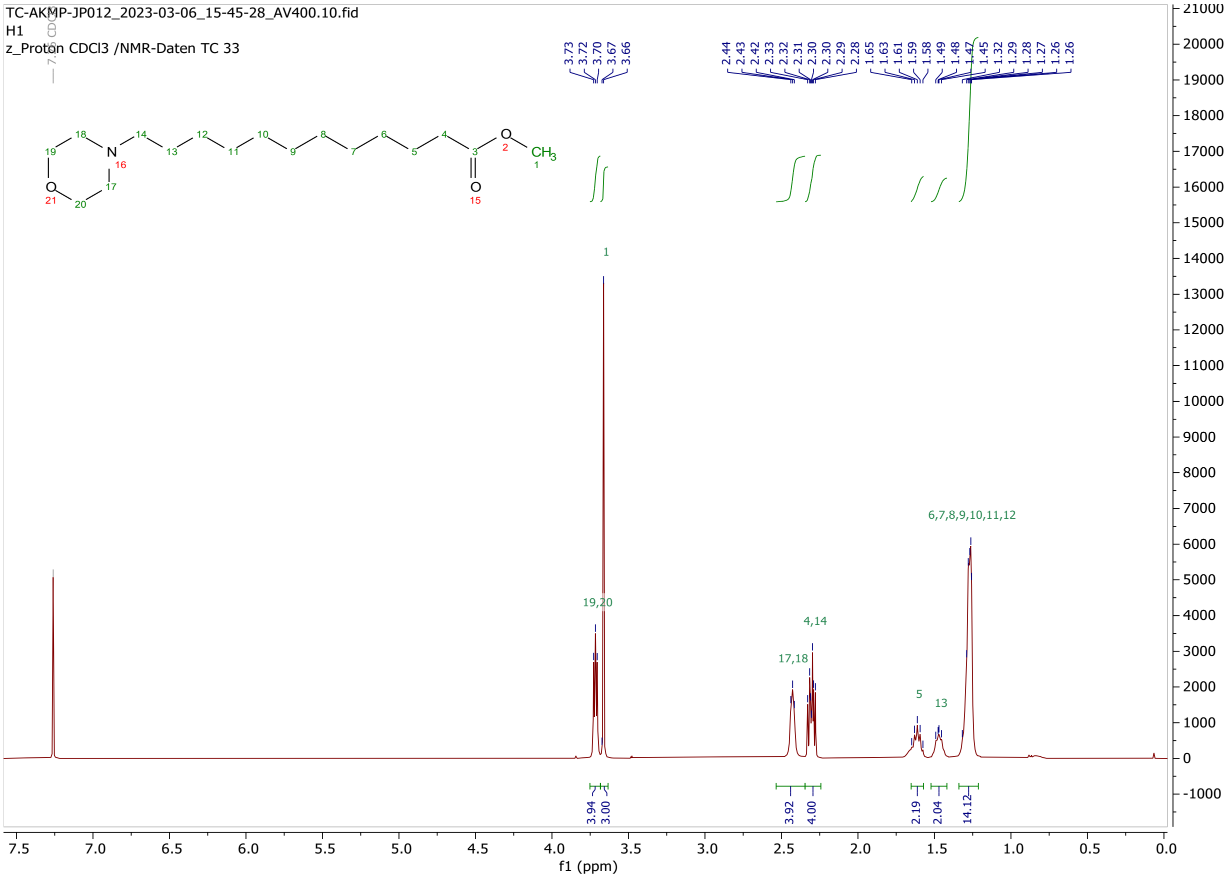


Methyl 12-morpholinododecanoate (*l*-4i)

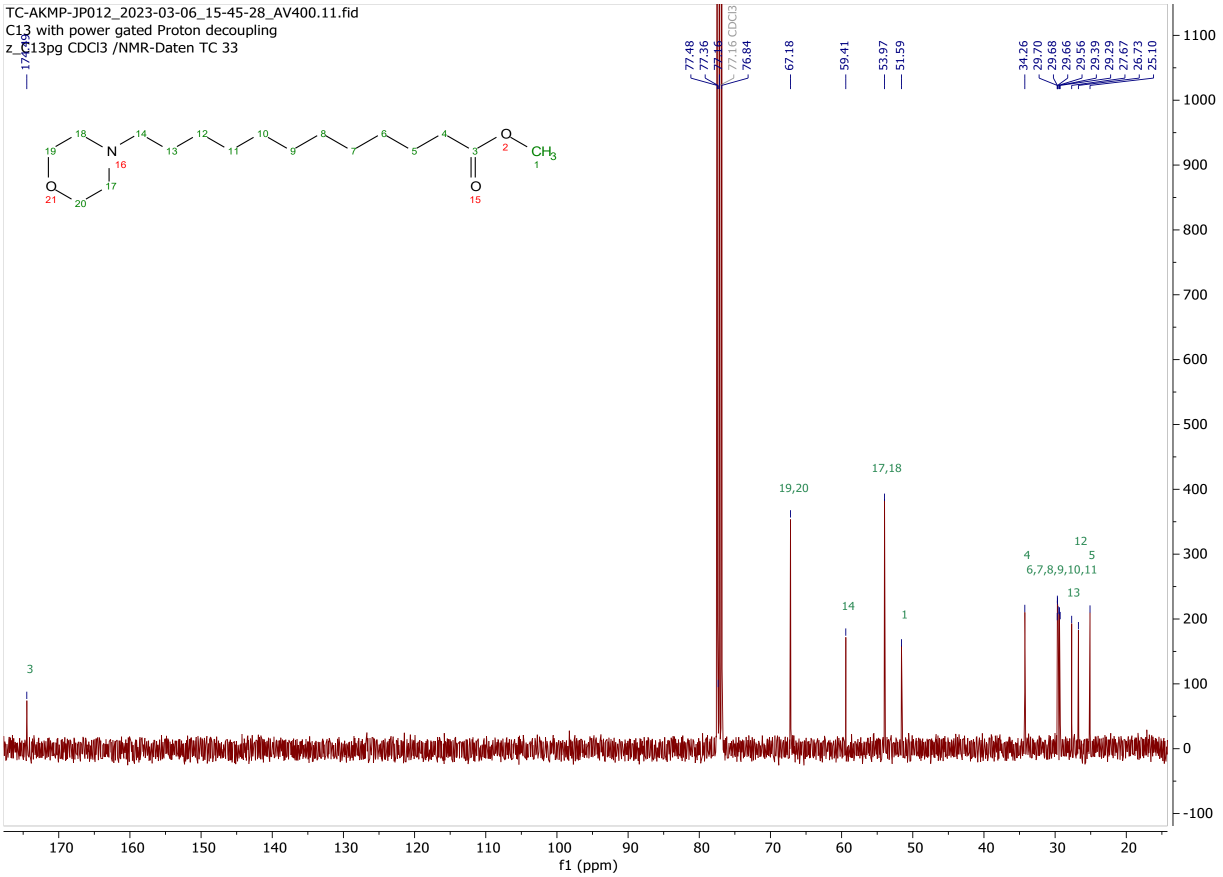


NMR Spectroscopy: The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

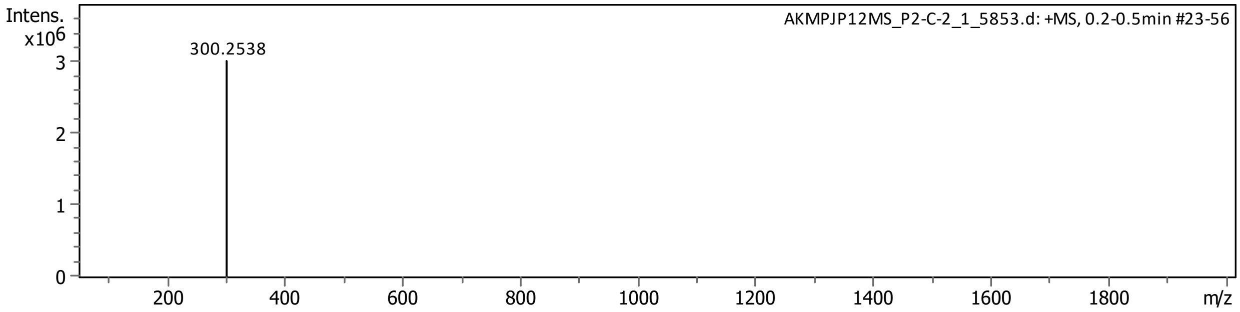
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) = 3.72 (t, J= 4.z6Hz, 4H, **19-20**), 3.66 (s, 3H, **1**), 2.5–2.34 (m, 4H, **17-18**), 2.34–2.24 (m, 4H, **4, 14**), 1.65–1.55 (m, 2H, **5**), 1.52–1.42 (m, 2H, **13**), 1.33–1.21 (m, 14H, **6-12**).



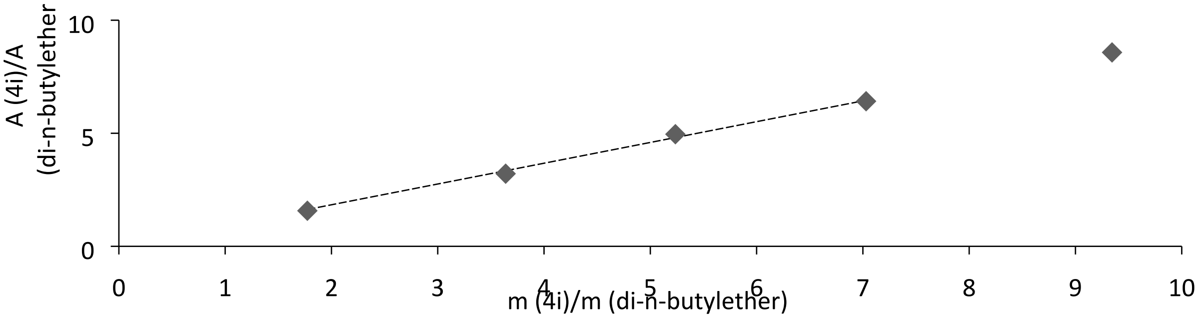
^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm) = 174.49 (C3), 67.18 (C19-20), 59.41 (C14), 53.97 (C17-18), 51.59 (C1), 34.26 (C4), 29.70-29.29 (C6-C12), 27.67 (C13), 26.73 (C12), 25.10 (C5).



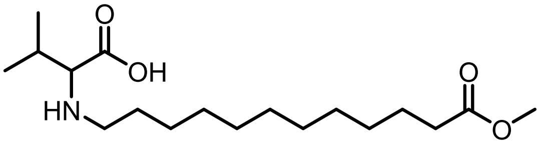
<u>HR-MS (ESI):</u> calcd. $[M+H]^+$ = 300.2534 , found $[M+H]^+$ = 300.2538.



<u>GC-Calibration:</u>

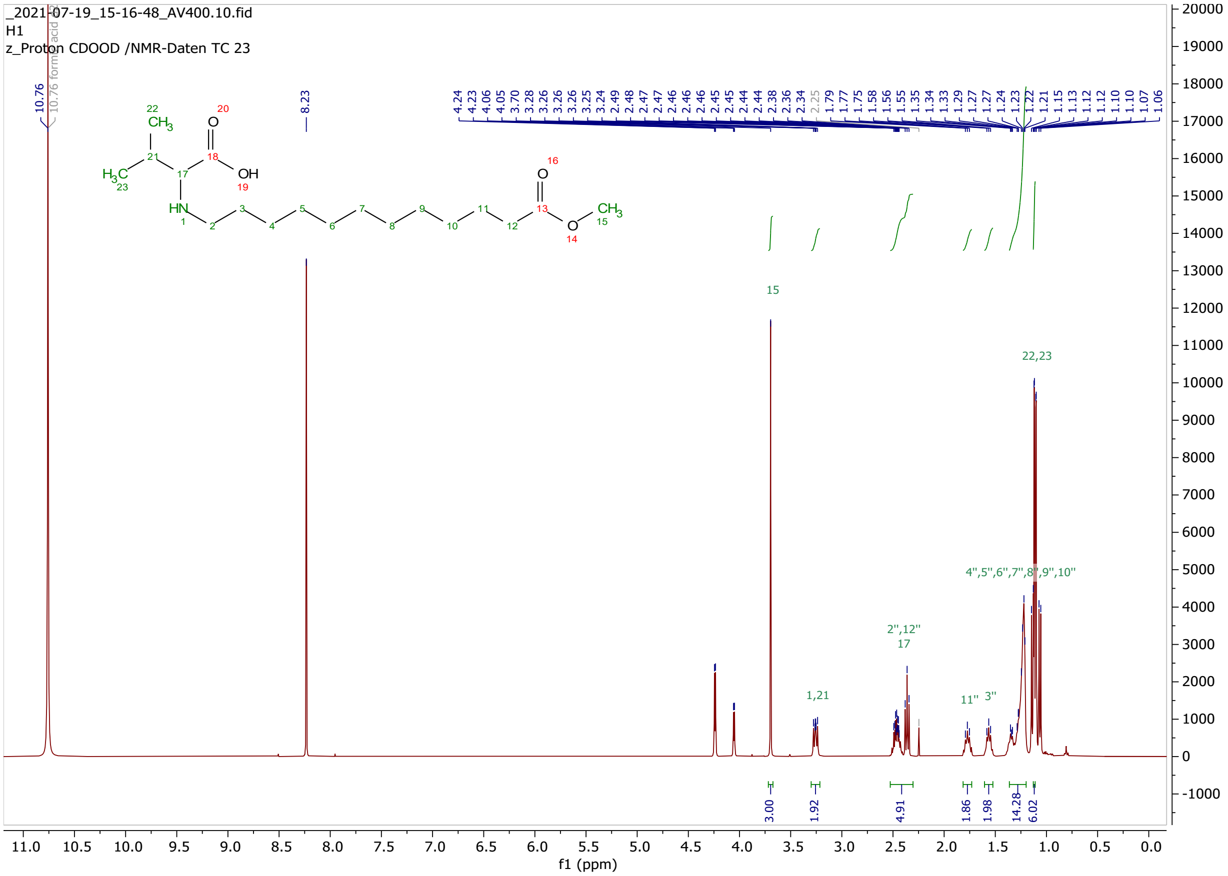


(12-methoxy-12-oxododecyl)valine (*l*-4l)

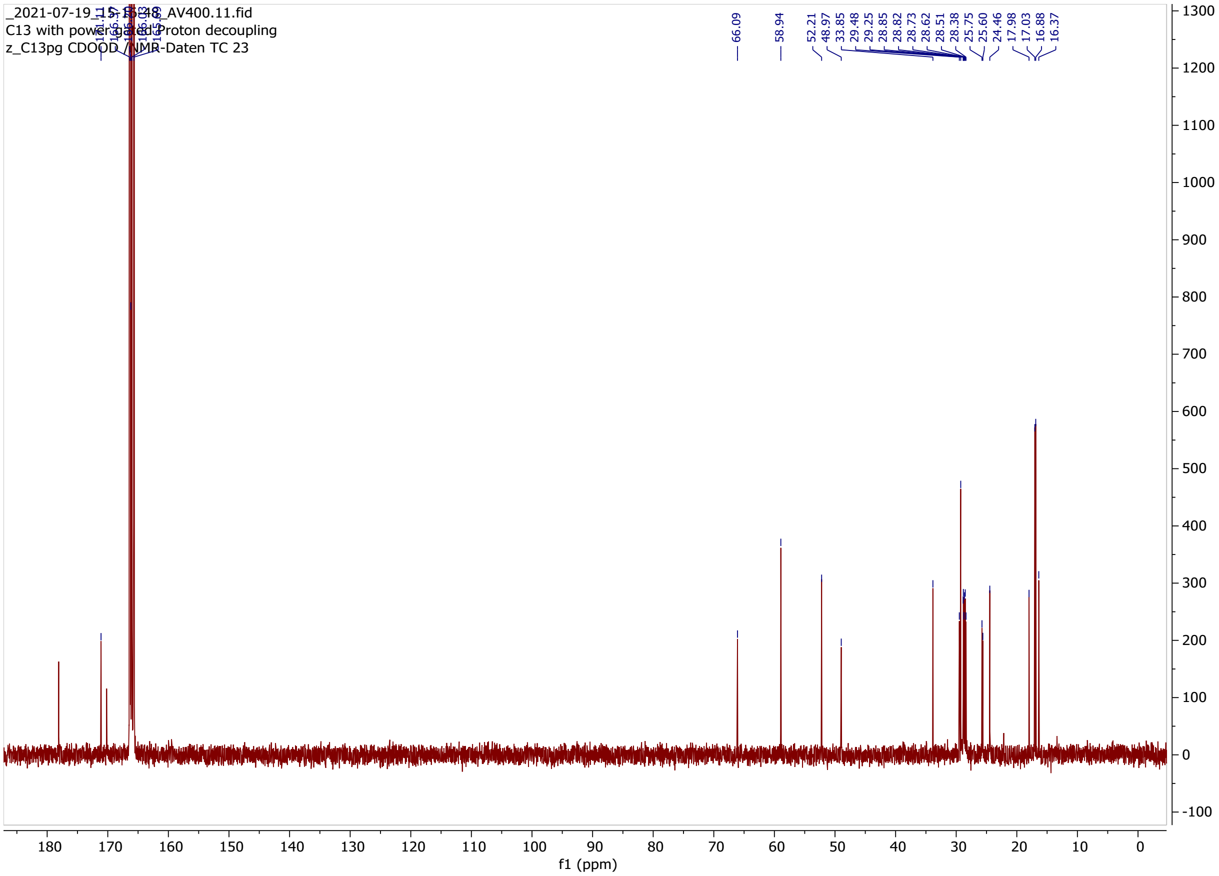


<u>NMR Spectroscopy:</u> The product precipitated as a white solid during the reaction. The NMR was carried out in deuterated formic acid and is still slightly contaminated by e.g. substrate.

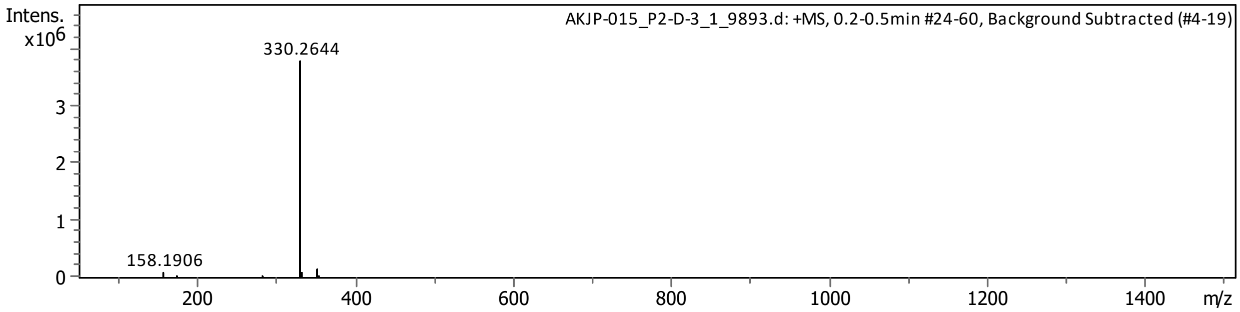
¹H-NMR (400 MHz, formic acid d2) δ (ppm):



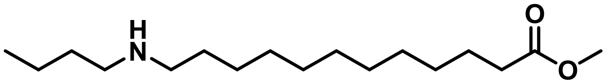
¹³C-NMR (100 MHz, formic acid d2) δ (ppm):



<u>HR-MS (ESI):</u> calcd. $[M+H]^+$ = 330.2639 , found $[M+H]^+$ = 330.2644.

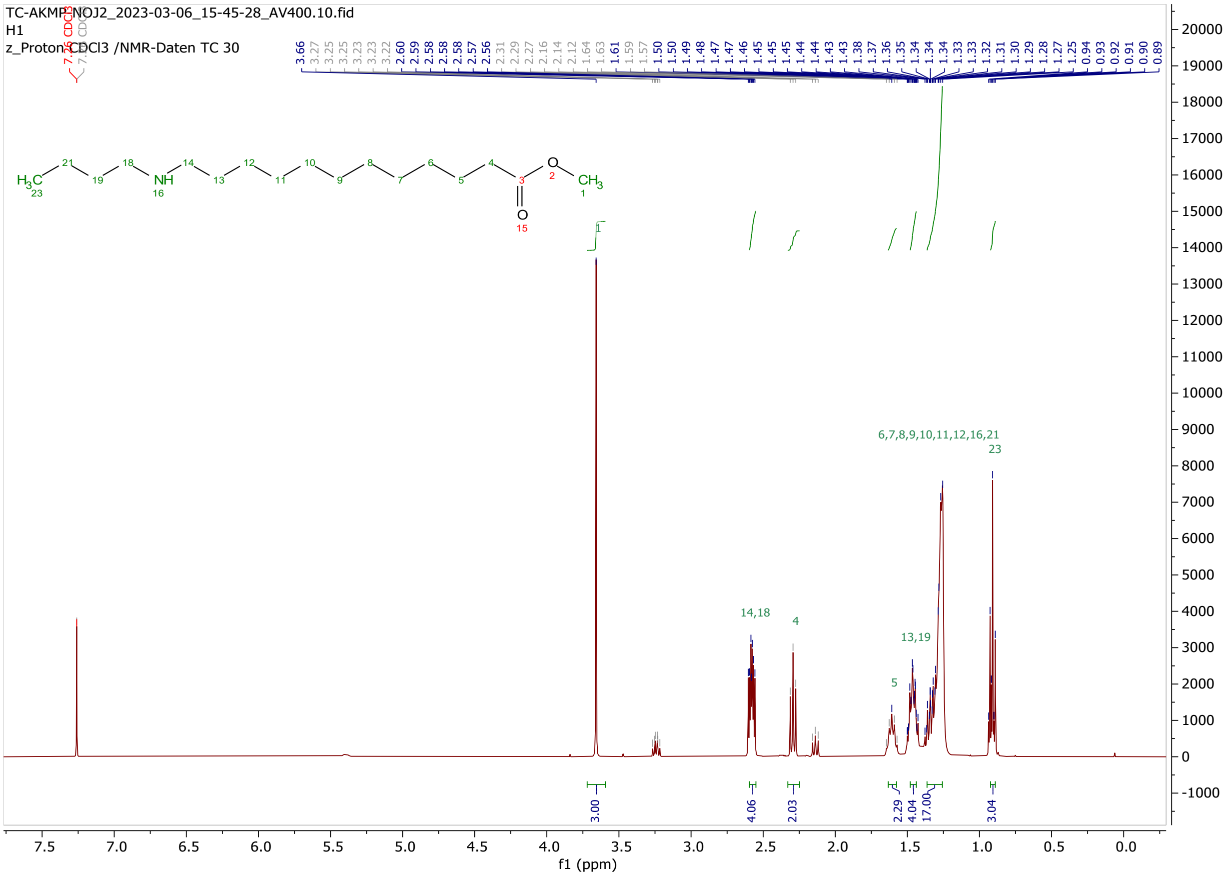


Methyl 12-(butylamino)dodecanoate (*l*-4n)

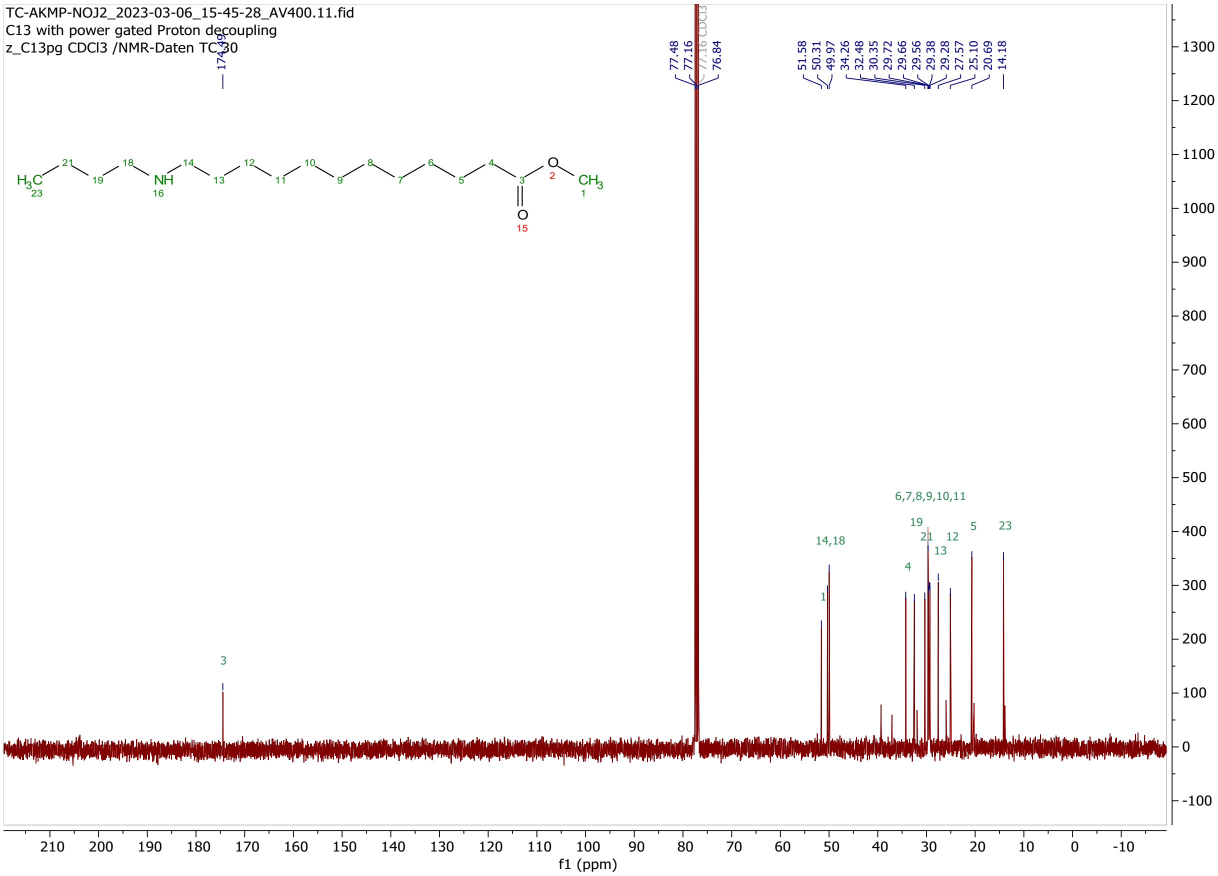


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

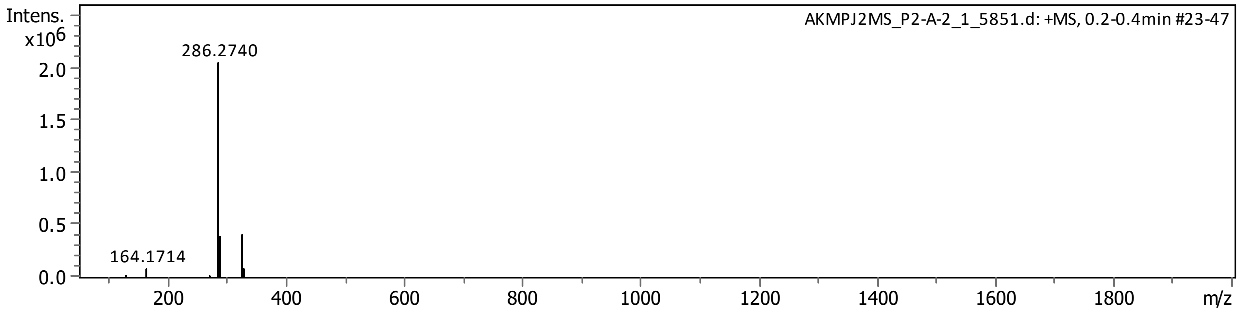
^{1}H-NMR (400 MHz, $CDCl_3$) δ (ppm) = 3.66 (s, 3H, **1**), 2.58 (dt, J = 7.3, 3.6 Hz, 4H, **14, 18**), 2.61 (t, J = 7.6 Hz, 2H, **4**), 1.65–1.55 (m, 2H, **5**), 1.48–1.44 (m, 4H, **13, 19**), 1.36–1.26 (m, 14H, **6-12, 21**), 0.92-0.89 (m, 3H, **23**).



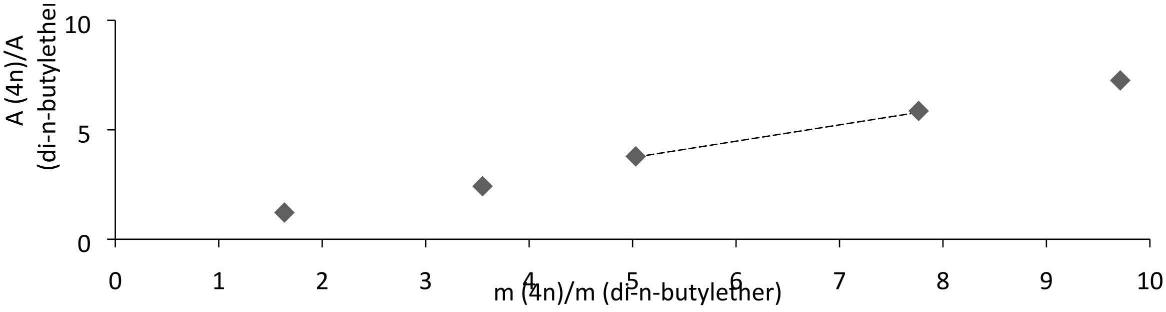
^{13}C-NMR (100 MHz, $CDCl_3$) δ (ppm) = 174.49 (C3), 51.58 (C1), 50.31-49.97 (C14, C18), 34.26 (C4), 32.48 (C19), 30.35 (C21), 29.72-29.28 (C6-C11), 27.57 (C13), 25.10 (C12), 20.69 (C5), 14.18 (C23).



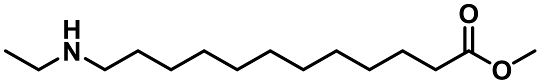
HR-MS (ESI): calcd. $[M+H]^+$ = 286.4795 , found $[M+H]^+$ = 286.2740.



GC-Calibration:

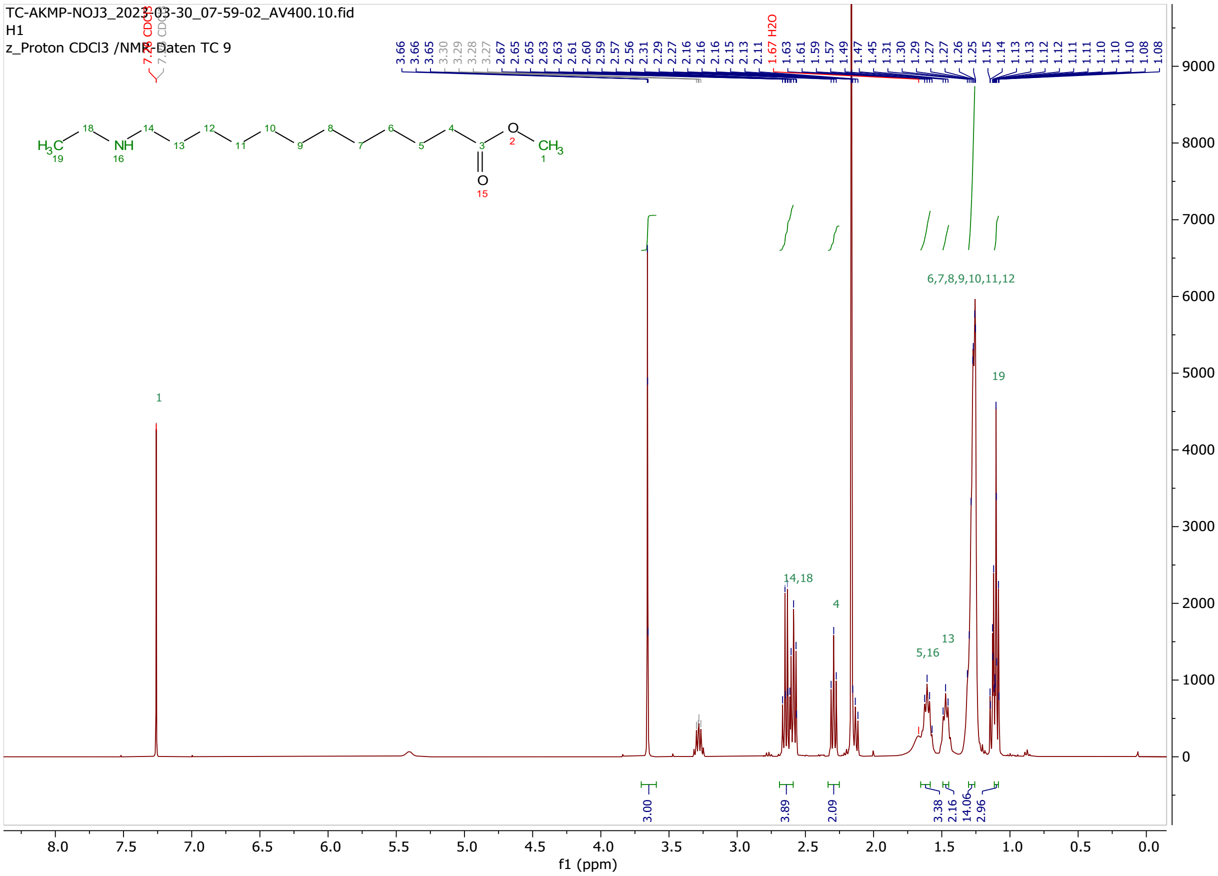


Methyl 12-(ethylamino)dodecanoate (*l*-4o)

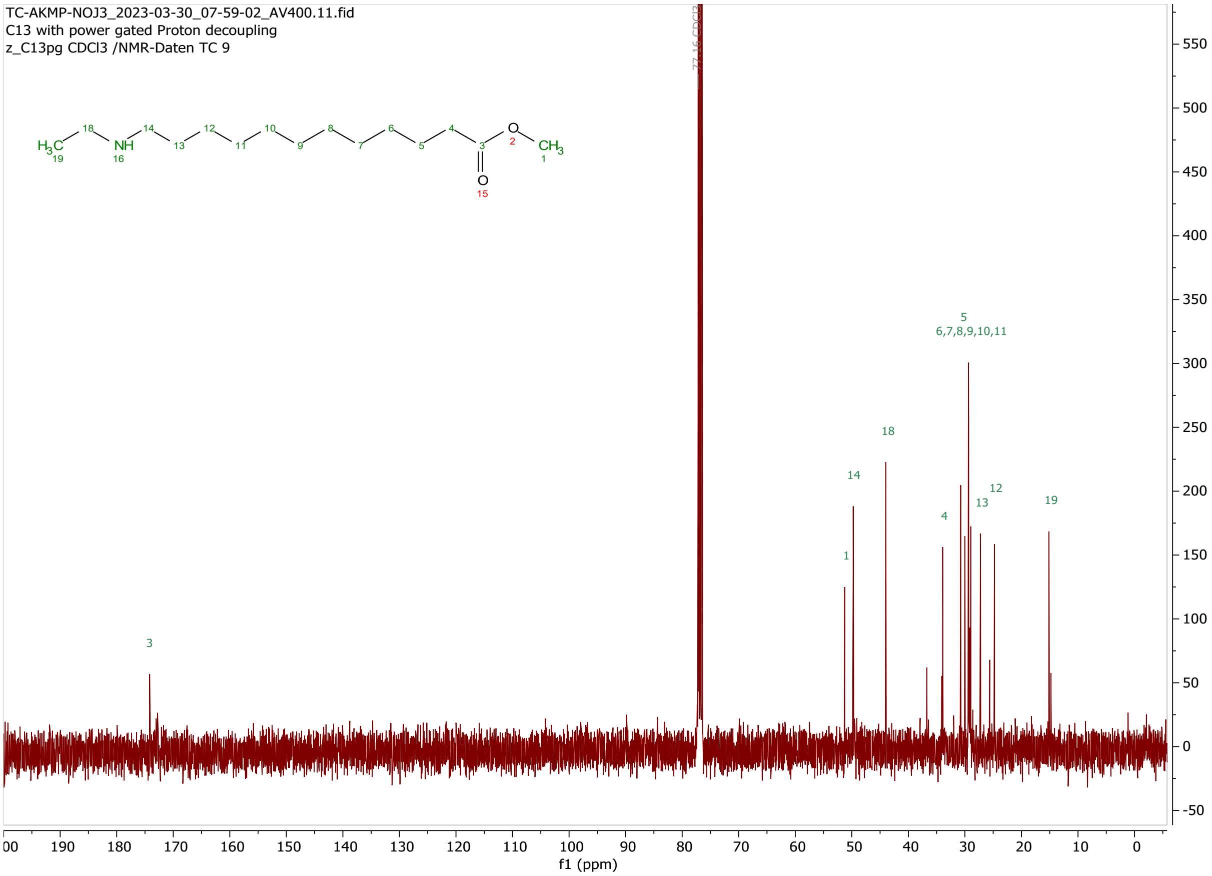


<u>NMR Spectroscopy:</u> The spectroscopic data correspond to a similar structure previously reported in the literature. [1]

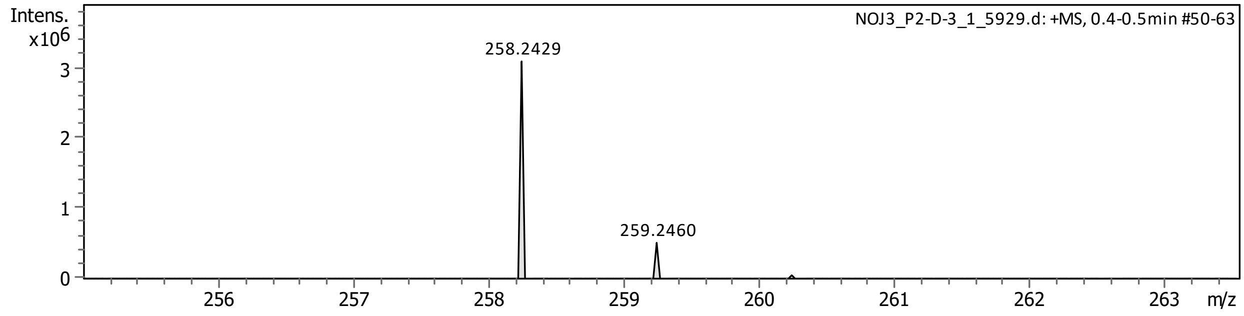
^{1}H-NMR (400 MHz, CDCl$_3$) δ (ppm) = 3.66 (s, 3H, **1**), 2.69-2.59 (m, 4H, **14-18**), 2.29 (t, J = 7.5 Hz, 2H, **4**), 1.65–1.55 (m, 3H, **5, 16**), 1.52–1.43 (m, 2H, **13**), 1.34–1.21 (m, 14H, **6-12**), 1.11-1.08 (m, 3H, **19**).



^{13}C-NMR (100 MHz, CDCl$_3$) δ (ppm) = 174.17 (C3), 51.26 (C1), 49.75 (C14), 43.99 (C18), 34.10 (C4), 33.94 (C5), 30.75-28.96 (C6-C11), 27.25 (C13), 25.61 (C12), 15.13 (C5).



<u>HR-MS (ESI):</u> calcd. $[M+H]^+$ = 258.4255 , found $[M+H]^+$ = 258.2429.



<u>GC-Calibration:</u>

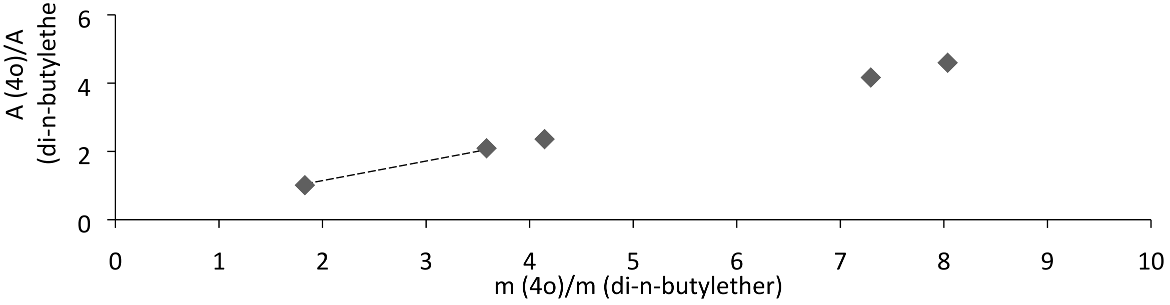


Table 2: Retention times and response factors for the GC analytic of the continuous miniplant operation. The branched species of the aldehydes, enamines, and tertiary amines were analyzed with the same calibration factor as their linear equivalents.

substance	Retention [min]	response factor
methanol	2.3	0.4056
diethylamine	2.63	0.9064
n-dodecane	6.66	1.3214
methyl undec-10-enoate	8.78	1.018
methyl undecanoate	8.87	0.9511
iso-methyl undec-10-enoate	8.92-9.07	1.018
methyl 12-oxododecanoate	13.59	0.8544
methyl 12-(diethylamino)dodecanoate	15.25	0.9555
methyl-12-(diethylamino)dodec-11-enoate	15.45	0.9555
UME aldol condensate	19.03-19.08	0.5991
Water*	2.48	1.0115

5. Further reaction experiments and results

Recycling experiment

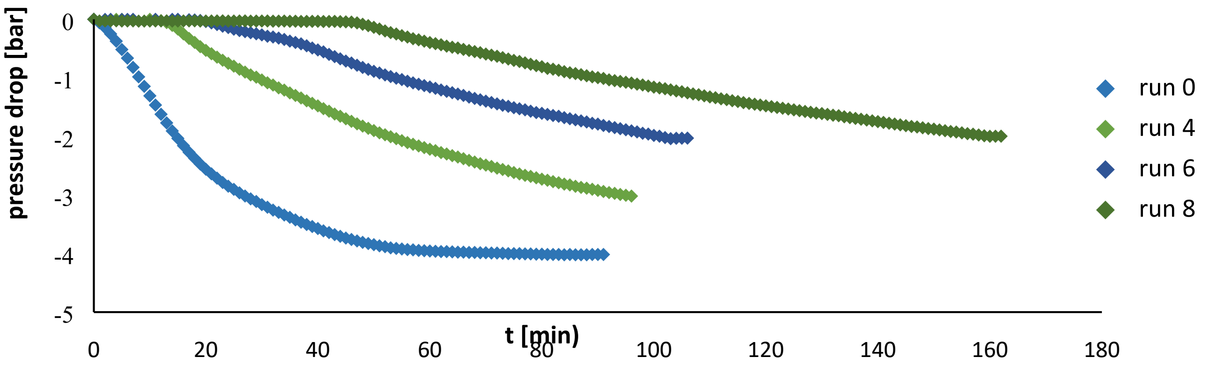
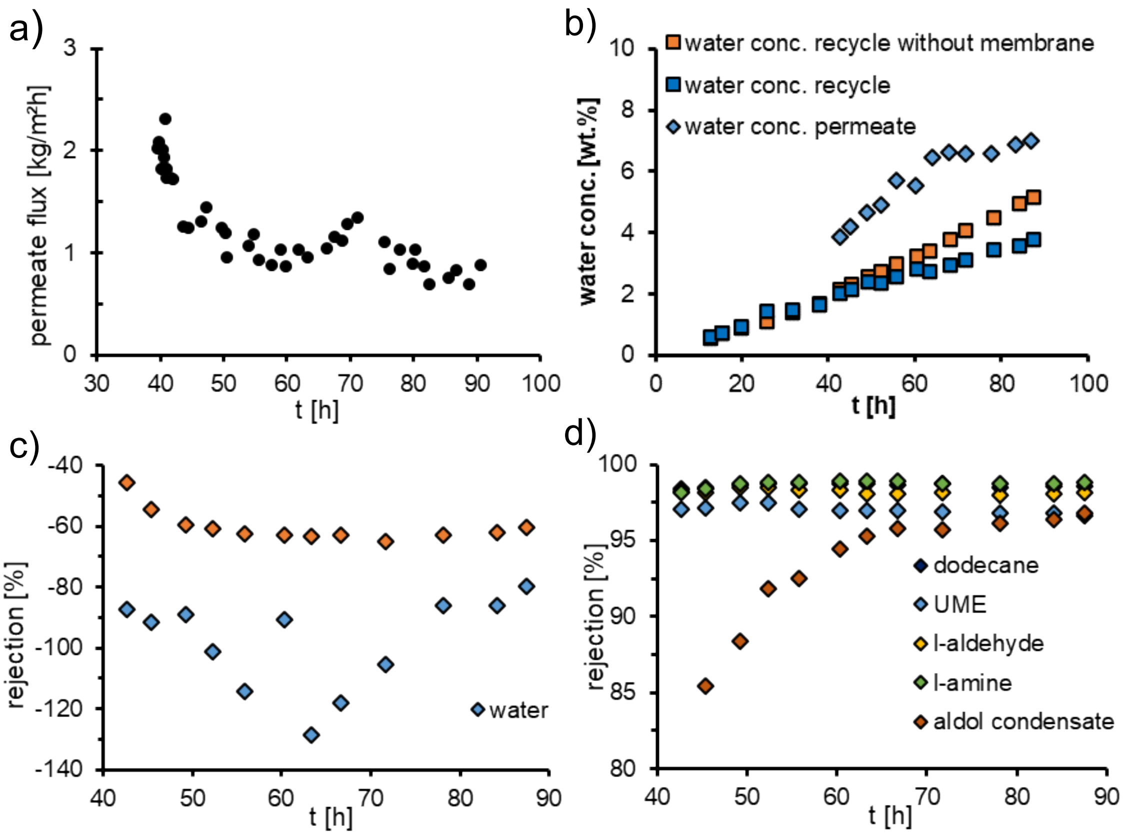


Figure 8: Pressure drop in the gas reservoir due to the usage of the gas for the reaction.



Membrane operation:

Figure 10: Membrane performance in the miniplant experiment. Figure a) shows the time progression of the permeate flux. In Figure b) the water concentration in the recycle and permeate streams of the miniplant experiment is displayed over time. The water concentration without membrane was calculated from the in the reaction theoretically produced

water. Figure c) and d) show the rejections of the nonpolar components over time. Separation conditions: Membrane: Nanopro S-3012, A_{mem} = 52 cm², T = 30 °C, p_{feed} = 36 bar, V_{feed} = 45-50 L h^{-1}. The compositions of feed and permeate were determined via GC-FID and GC-WLD measurements.

6. **Additional Literature**

[1] J. Bianga, N. Kopplin, J. Hülsmann, D. Vogt, T. Seidensticker, "Rhodium-Catalysed Reductive Amination for the Synthesis of Tertiary Amines", *Adv. Synth. Catal.* **2020**, *362*, 4415–4424.

[2] T. Seidensticker, J. M. Vosberg, K. A. Ostrowski, A. J. Vorholt, "Rhodium-Catalyzed Bis-Hydroaminomethylation of Linear Aliphatic Alkenes with Piperazine", *Adv. Synth. Catal.* **2016**, *358*, 610–621.