Electronic Supplementary Information (ESI)

for

Large-ring lactones from plant oils

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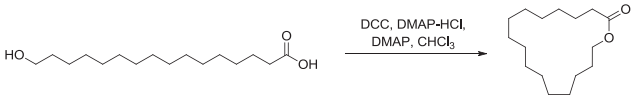
Content

General procedures for macrolactonisation

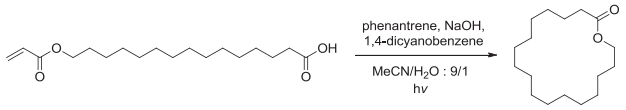
There are various reports for the cyclisation of ω-hydroxy carboxylic compounds. Keck macrolactonisation [1], an intramolecular variation of the Steglich esterification with dicyclohexylcarbodiimide (DCC) and N,N-dimethyl-4-aminopyridine (DMAP) is one prominent example for converting acyclic compounds into the corresponding lactones (cf. **Scheme S1**).



Scheme S1. Keck macrolactonisation of 16-hydroxyhexadecanoic acid

Using this procedure, macrolactones with a ring size of up to 17 have been prepared by Keck and co-workers.[2] However, low solubility of the acyclic compound in combination with the high dilution required for the monomeric cyclisation is a major drawback of this route.

Photochemical approaches to macrocycles have been reported by Yoshimi *et al.* for macrolactones with ring sizes of up to 20 carbon atoms (cf. **Scheme S2**).[3]



Scheme S2. Photochemical strategy to heptadecalactone.

Although this route provides access to a wide range of ring sizes of macrocyclic lactones by simply repeating the cyclisation step after ring-opening of the lactone, this strategy requires high dilution (1 mM) and therefore again a large quantity of solvents. Another drawback is the loss of one carbon atom during the cyclisation, which is converted into CO_2.

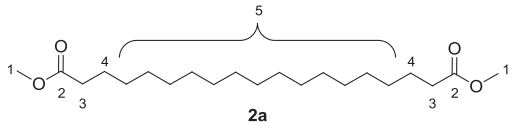
Experimental Section

General

All reactions and manipulation of moisture and air sensitive substances were performed under an inert gas atmosphere using standard Schlenk or glove box techniques. Solvents were dried under an inert atmosphere as follows: Xylene and toluene were distilled from sodium prior to use. CH_2Cl_2 was distilled from CaH_2, and MeOH was distilled from magnesium turnings. All dry solvents were stored under an inert atmosphere Carbon monoxide (3.7) for isomerising alkoxycarbonylation experiments was supplied by Air Liquide. Methyl oleate (92.5 %) supplied by Dako AG was degassed prior to use. [Pd(dtbpx)$(OTf)_2$] was prepared by a reported procedure.[4] ROP catalysts [Al(salen)Et] and [Al(salen)OBn], and the salen ligand were prepared according to reported procedures.[5,7] Isomerising alkoxycarbonylation experiments were run in stainless steel high pressure reactors (Büchi miniclave (300 mL) with a mechanical stirrer and a heating/cooling mantle controlled by a temperature sensor dipping directly in the reaction mixture). All deuterated solvents for NMR spectroscopy were supplied by Euriotop. Organic syntheses were monitored by TLC on Merck TLC silica gel 60 F254 plates on plastic sheets with F254 fluorescent indicator. The TLC plates were stained in an ethanolic phosphomolybdic acid solution for spot analysis. NMR spectra were recorded on a Varian Inova 400 or a Bruker Avance 400 spectrometer. ^{1}H and ^{13}C chemical shifts were referenced to the solvent signals. NMR spectroscopy of polymers was performed in 1,1,2,2-tetrachloroethane-d_2 at 130 °C. GPC analyses of polymers were performed with a Polymer-Laboratories GPC220 instrument equipped with PLgel Olexis columns using the refractive index detector. Molecular weights were determined by calibration with PE standards at 160 °C in 1,2,4-trichlorobenzene (Flow rate: 1.0 mL per minute). GC analysis were performed using a Perkin Elmer Clarus 500 instrument with an autosampler equipped with an Elite-5 crossbond 5 % diphenyl- 95 % dimethyl polysiloxane column of 30 m length, 0.25 mm inner diameter and 0.25 µm film thickness. The temperature of the oven was kept at 100 °C for 1 min, then heated from 100 °C to 300 °C with a heating rate of 15 °C per minute. The final temperature was held for 5 min. The injector was kept at 270 °C and the detector at 280 °C. The injection volume was 1.0 µl. Analysis of the retention times and peak areas were performed using the TotalChrom software of Perkin Elmer. DSC analysis was performed on a Netzsch DSC 204 F1 at a heating rate of 10 °C per minute in a temperature range from -50 °C to 160 °C. All data reported are from second heating cycles. ESI mass spectrometry was performed on a Bruker Esquire 3000+. About 100 µl of the sample solution in MeOH or THF, saturated with NaCl, were injected. All elemental analysis were performed on a Heraeus CHN-O-RAPID elemental analyser.

Synthetic procedures

Dimethyl 1,19-nonadecanedioate (2a)

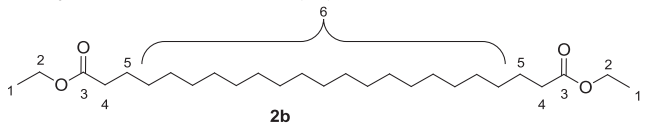


2a

Dimethyl ester **2a** was synthesised according to [1]. In a glove box a Schlenk tube was charged with 0.189 g (0.236 mmol) of [Pd(dtbpx)$(OTf)_2$]. Outside the glove box 40.0 mL (35.04 g, 118.18 mmol) of methyl oleate and 110.0 mL (86.9 g, 2.71 mol) of MeOH were added. The yellow solution was cannula transferred into the pressure reactor under an inert atmosphere and the reactor was pressurised with 20 bar of CO, heated to 90 °C and stirred for 90 h. The reactor was cooled to room temperature, vented and the crude product was dissolved in CH_2Cl_2. The solution was filtrated to remove Pd black particles before the solvent was removed by rotary evaporation. Multiple recrystallisations from MeOH yielded 35.69 g (100.10 mmol, 85 %) of pure diester **2a** as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 3.66 (s, 6H, H-1), 2.30 (t, $^3J_{HH}$ = 7.5 Hz, 4H, H-3), 1.65 - 1.57 (m, 4H, H-4), 1.35 - 1.23 (m, 26H, H-5) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ = 174.5 (C-2), 51.6 (C-1), 34.3 (C-3), 29.8 - 29.3 (C-5), 25.1 (C-4) ppm.

Diethyl 1,23-tricosanedioate (2b)



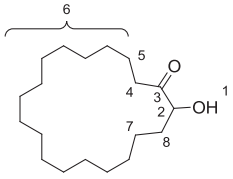
2b

Diethyl ester **2b** was synthesised according to [1]. In a glove box a Schlenk tube was charged with 0.205 g (0.256 mmol) of [Pd(dtbpx)$(OTf)_2$]. Outside the glove box 40.5 mL (35.20 g, 96.00 mmol) of ethyl erucate and 100.0 mL (78.9 g, 1.71 mol) of EtOH were added. The yellow solution was cannula transferred into the pressure reactor under an inert atmosphere and the

reactor was pressurised with 20 bar of CO, heated to 90 °C and stirred for 90 h. The reactor was cooled to room temperature, vented, and the crude product was dissolved in CH_2Cl_2. The solution was filtrated to remove Pd black particles before the solvent was removed by rotary evaporation. Multiple recrystallisations from EtOH yielded 35.40 g (78.05 mmol, 81 %) of pure diester **2b** as a white solid.

^{1}H-NMR ($CDCl_3$, 400 MHz, 25 °C): δ = 4.12 (q, $^3J_{HH}$ = 7.1 Hz, 6H, H-2), 2.28 (t, $^3J_{HH}$ = 7.6 Hz, 4H, H-4), 1.65 - 1.57 (m, 4H, H-5), 1.31 - 1.19 (m, 38H, H-1/H-6) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ = 174.5 (C-3), 60.3 (C-2), 34.5 (C-4), 29.8 - 29.3 (C-5), 14.3 (C-1) ppm.

2-Hydroxycyclononadecanone (3a)

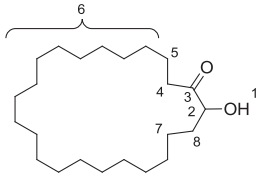


3a

According to [8], 2.71 g (117.80 mmol) of sodium were suspended in 350 mL of dry xylene at 150 °C in a flame dried three-necked 1 L flask with argon inlet, reflux condenser (equipped with a gas bubbler) and a septum stopper, using a magnetic stir bar. To this slurry a solution of 6.00 g (16.83 mmol) of dimethyl 1,19-nonadecanedioate (**2a**) in 100 mL of dry xylene was added over a period of 4 h by means of a syringe pump. The yellow turbid mixture was stirred for another hour after the addition was completed. The mixture was cooled in an ice bath and quenched with 2 mL of MeOH and 10 mL of water, sequentially. The off-white slurry was acidified with 50 ml of 2.4 N HCl to pH 5 and diluted with 200 mL of Et_2O. After separating the phases, the aqueous phase was extracted with 100 mL of Et_2O and the combined organic layer was then washed sequentially with water and brine. The organic phase was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. Purification of the yellow residue by flash column chromatography (300 g silica gel, pentane/Et_2O 5/2) yielded 4.21 g (14.20 mmol, 84 %) of a colorless waxy solid.

R_f (pentane/Et_2O : 5/2): 0.38; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ =4.22 (dd, $^3J_{HH}$ =5.8Hz, $^3J_{HH}$ =4.6Hz, 1H, H-2), 3.51 (s, 1H, H-1), 2.59 - 2.31 (m, 2H, H-4), 1.89 - 1.42 (m, 6H, H-5, H-7, H-8), 1.39 - 1.19 (m, 26H, H-6) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =212.8 (C-3), 76.4 (C-2), 37.7 (C-4), 33.2 (C-8), 28.7 - 27.5 (C-6), 23.7 - 23.4 (C-5, C-7) ppm; **ESI-MS**: m/z = 319.5 (M^++Na).

2-Hydroxycyclotricosanone (3b)

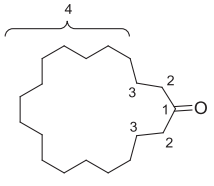


3b

The C_{23}-acyloin was prepared as described for compound **3a** in 51 % yield.

R_f (pentane/Et_2O : 5/2): 0.38; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ =4.20 (dd, $^3J_{HH}$ =6.4Hz, $^3J_{HH}$ =4.1Hz, 1H, H-2), 3.34 (s, 1H, H-1), 2.57 - 2.32 (m, 2H, H-4), 1.88 - 1.40 (m, 6H, H-5, H-7, H-8), 1.38 - 1.18 (m, 34H, H-6) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =212.8 (C-3), 76.3 (C-2), 37.7 (C-4), 33.4 (C-8), 29.1 - 28.0 (C-6), 24.1 - 23.5 (C-5, C-7) ppm; **ESI-MS**: m/z = 375.4 (M^++Na).

Cyclononadecanone (4a)



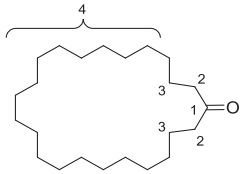
4a

The dehydroxylation of acyloin **4a** was performed according to [9] for the dehydroxylation of acyclic butyroin. To a solution of 1.00 g (3.37 mmol) acyloin **3a** in 30 mL of dry CH_2Cl_2, 1.20 mL (1.69 g, 8.43 mmol) of trimethylsilyl iodide were added. The dark brown solution was allowed to stand at room temperature for 21 h before it was
quenched with aqueous sodium ascorbate solution to reduce formed iodine. After separating the layers, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was washed sequentially with water and brine, dried over $MgSO_4$ before the solvent was removed by rotary evaporation. The white-yellowish crude product was purified by flash column

chromatography (200 g, gradient from pentane to pentane/EtOAc 9/1) to yield 0.73 g (2.60 mmol, 77 %) of a colorless waxy solid.

R_f (pentane/EtOAc : 9/1): 0.65; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ =2.36 (t, $^3J_{HH}$ =7.0Hz, 4H, H-2), 1.62 - 1.53 (m, 4H, H-3), 1.31 - 1.21 (m, 28H, H-4) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =212.3 (C-1), 42.6 (C-2), 28.5 - 27.6 (C-4), 23.9 (C-3) ppm; **ESI-MS**: m/z = 303.4 (M^++Na).

Cyclotricosanone (4b)

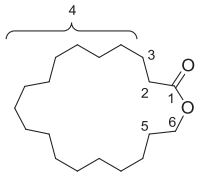


4b

Cyclotricosanone (**4b**) was prepared as described for cycloketone **4a**. Column chromatography (gradient from CH_2Cl_2/EtOAc 99/1 to CH_2Cl_2/EtOAc 49/1) yielded the desired compound as a colorless solid in 71 % yield.

R_f (pentane/EtOAc : 49/1): 0.23; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ =2.39 (t, $^3J_{HH}$ =7.1Hz, 4H, H-2), 1.63 - 1.55 (m, 4H, H-3), 1.32 - 1.24 (m, 36H, H-4) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =212.3 (C-1), 42.6 (C-2), 28.5 - 27.6 (C-4), 23.9 (C-3) ppm; **ESI-MS**: m/z = 335.1 (M^--H).

Nonadecalactone (5a)

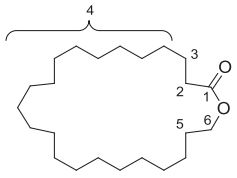


5a

The Baeyer-Villiger oxidation was performed in a flame-dried 250 mL round bottom flask with an argon inlet and septum stopper, according to [10] for the synthesis of a C_{14} lactone. 3.70 g (39.37 mmol) of urea hydrogen peroxide, 6.52 g (45.93 mmol) of Na_2HPO_4 and 1.84 g (6.56 mmol) of cycloketone **4a** were suspended in 100 mL of dry CH_2Cl_2 and cooled in an ice bath. To the cooled slurry 6.47 mL (9.45 g, 45.93 mmol) of trifluoroacetic anhydride were added slowly via syringe and the resulting light yellow mixture was stirred for 18 h with slow warming to room temperature. The slurry was washed twice with aqueous $NaHCO_3$ solution, sodium ascorbate solution and brine, dried over $MgSO_4$ and the solvent was removed by rotary evaporation. Purification of the light yellow oil via flash column chromatography (250 g silica gel, pentane/CH_2Cl_2 1/1) yielded 1.65 g (5.53 mmol, 84 %) of a light yellow oil. Polymerisation grade purity was obtained by another flash column chromatography with pure CH_2Cl_2.

R_f (pentane/CH_2Cl_2 : 1/1): 0.45; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ =4.09 (t, $^3J_{HH}$ =6.0Hz, 2H, H-6), 2.30 (t, $^3J_{HH}$ =7.2Hz, 2H, H-2), 1.68 - 1.57 (m, 4H, H-3, H-5), 1.43 - 1.23 (m, 28H, H-4) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =174.1 (C-1), 64.3 (C-6), 34.8 (C-2), 28.7 - 27.2 (C-4), 25.9 (C-5), 25.2 (C-3) ppm; **ESI-MS**: m/z = 319.4 (M^++Na); **Elemental analysis** (%): *calcd*: 76.97 % (C); 12.24 % (H) *found*: 77.09 % (C); 12.31 % (H).

Tricosalactone (5b)

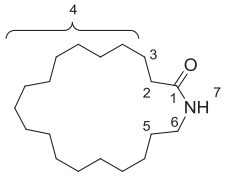


5b

TCL was prepared as described for NDL (**5b**). Column chromatography afforded TCL as colorless solid in 71 % yield.

R_f (pentane/CH_2Cl_2 : 1/1): 0.35; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ =4.09 (t, $^3J_{HH}$ =6.1 Hz, 2H, H-6), 2.31 (t, $^3J_{HH}$ =7.3Hz, 2H, H-2), 1.68 - 1.58 (m, 4H, H-3, H-5), 1.41 - 1.25 (m, 36H, H-4) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =174.2 (C-1), 64.4 (C-6), 34.7 (C-2), 29.2 - 28.0 (C-4), 26.1 (C-5), 25.3 (C-3) ppm; **ESI-MS**: m/z = 375.4 (M^++Na); **Elemental analysis** (%): *calcd*: 78.35 % (C); 12.58 % (H) *found*: 78.32 % (C); 12.31 % (H).

Nonadecalactam (6a)

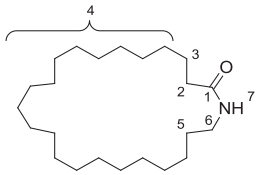


6a

According to a procedure for the preparation of laurolactam [11], 0.10 g (0.36 mmol) of cycloketone **4a** were dissolved in 10 mL of formic acid. 0.06 g (0.53 mmol) of hydroxylamine-*O*-sulfonic acid, dissolved in 5 mL of formic acid, were added drop wise to the stirred solution. The mixture was refluxed at 110 °C for 16.5 h and quenched by pouring the mixture in ice water. After neutralising the slurry with saturated sodium carbonate solution, the slurry was extracted with chloroform, the organic phase was washed subsequently with water and brine and dried over $MgSO_4$. Removing the solvent by rotary evaporation yielded the brown crude product, which was purified by flash column chromatography (50 g, pentane/EtOAc 1/1). In this way 50 mg (48 %) of lactam **6a** as a colorless solid were obtained.

R_f (pentane/EtOAc : 6/4): 0.20; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ = 5.67 (s, 1H, H-7), 3.26 (vq, $^3J_{HH}$ =6.2 Hz, 2H, H-6), 2.16 (t, $^3J_{HH}$ =7.0Hz, 2H, H-2), 1.66 - 1.57 (m, 2H, H-5), 1.51 - 1.43 (m, 2H, H-3), 1.33 - 1.22 (m, 28H, H-4) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =173.3 (C-1), 39.3 (C-6), 37.1 (C-2), 29.5 (C-5), 28.9 - 26.5 (C-4), 26.0 (C-3) ppm; **ESI-MS**: m/z = 318.2 (M^++Na).

Tricosalactam (6b)



6b

Tricosalactam (**6b**) was prepared as described for nonadecalactam (**6a**). After flash column chromatography, the lactam was obtained as a colorless solid in 87 % yield.

R_f (pentane/EtOAc : 6/4): 0.31; **^{1}H-NMR** ($CDCl_3$, 400 MHz, 25 °C): δ = 5.60 (s, 1H, H-7), 3.26 (pq, $^3J_{HH}$ =6.3 Hz, 2H, H-6), 2.16 (t, $^3J_{HH}$ =7.1 Hz, 2H, H-2), 1.66 - 1.58 (m, 2H, H-5), 1.52 - 1.44 (m, 2H, H-3), 1.34 - 1.23 (m, 36H, H-4) ppm; **^{13}C{^{1}H}-NMR** ($CDCl_3$, 100 MHz, 25 °C): δ =173.3 (C-1), 39.4 (C-6), 37.0 (C-2), 29.6 (C-5), 29.2 - 26.7 (C-4), 26.0 (C-3) ppm; **ESI-MS**: m/z = 374.4 (M^++Na).

ESI mass spectra

2-Hydroxycyclononadecanone (3a)

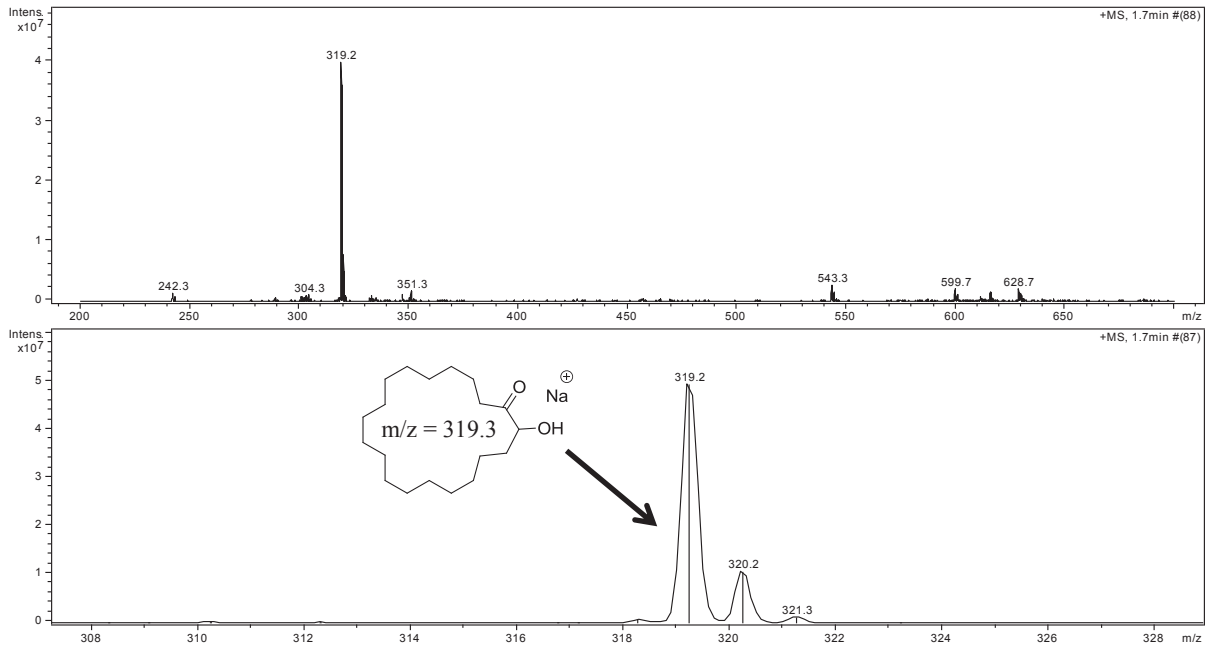


Figure S1. ESI mass spectrum of 2-hydroxycyclononadecanone (**3a**) in MeOH saturated with NaCl.

2-Hydroxycyclotricosanone (3b)

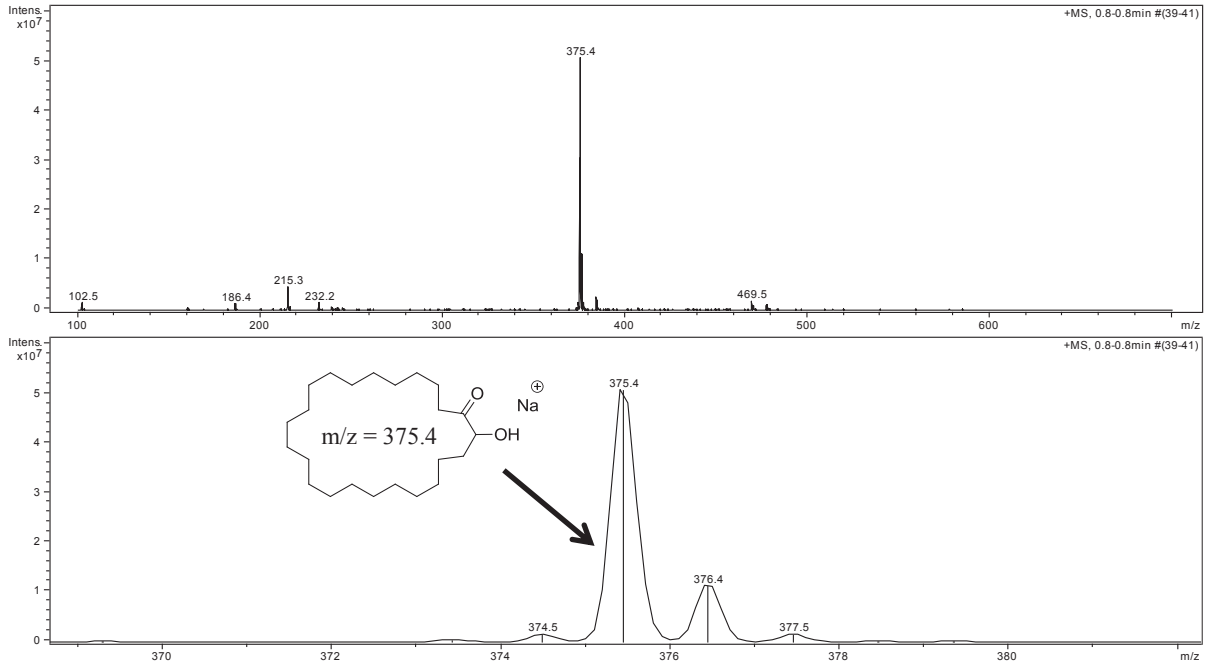


Figure S2. ESI mass spectrum of 2-hydroxycyclotricosanone (**3b**) in MeOH saturated with NaCl.

Gas chromatograms

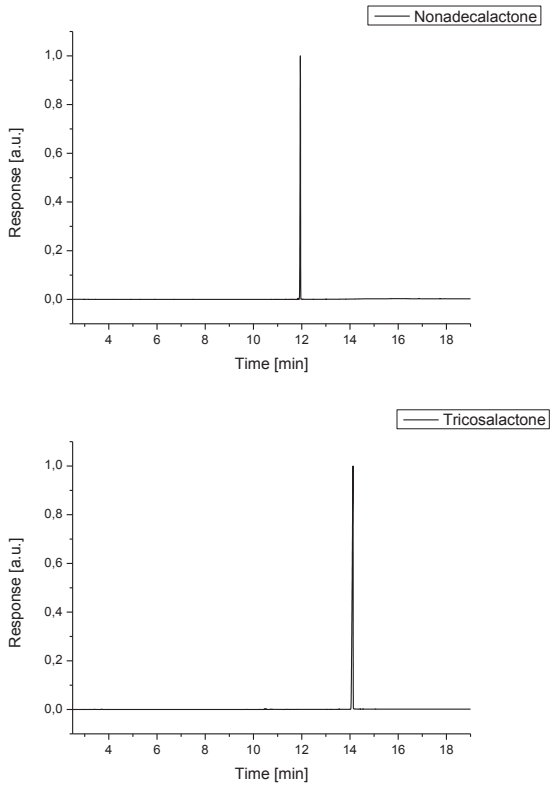


Figure S3. Gas chromatograms of NDL (**5a**) and TCL (**5b**) illustrating a purity > 99 %.

NMR spectra

Nonadecalactone (5a)

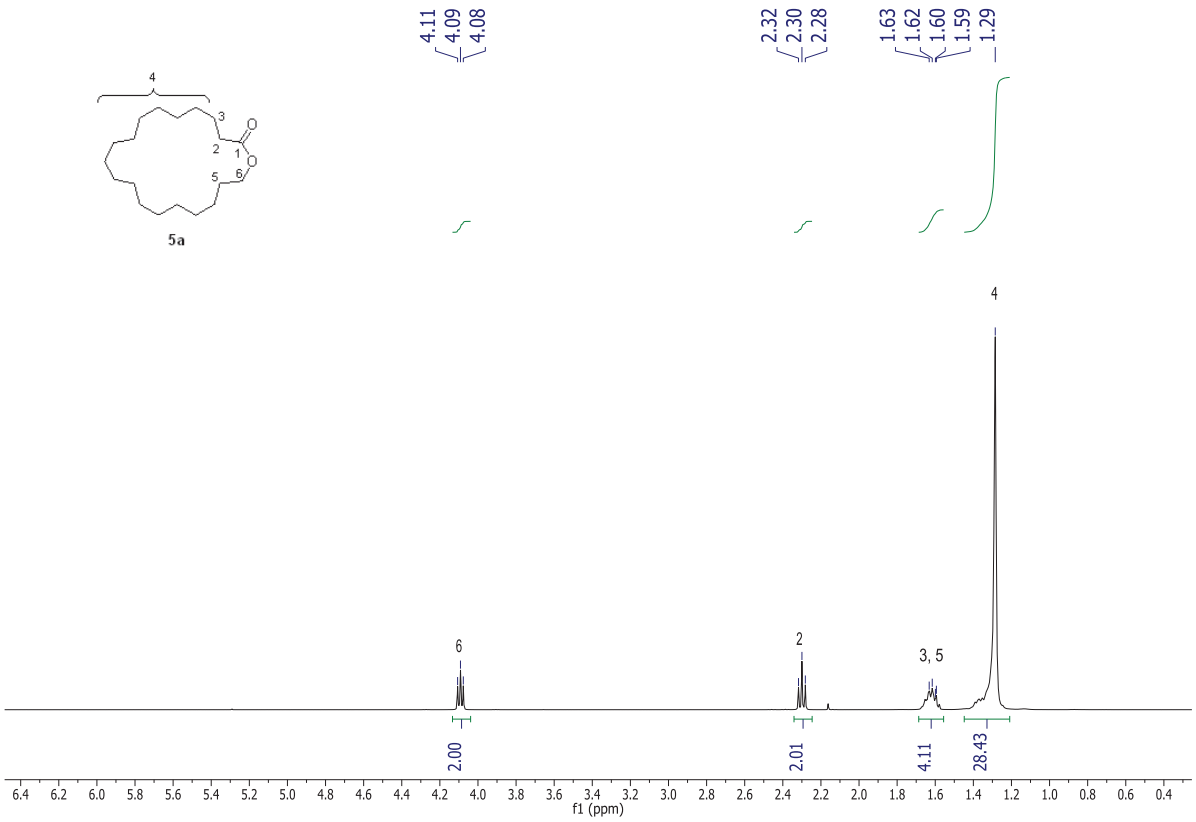


Figure S4. ^{1}H-NMR spectrum of nonadecalactone in chloroform-d_1.

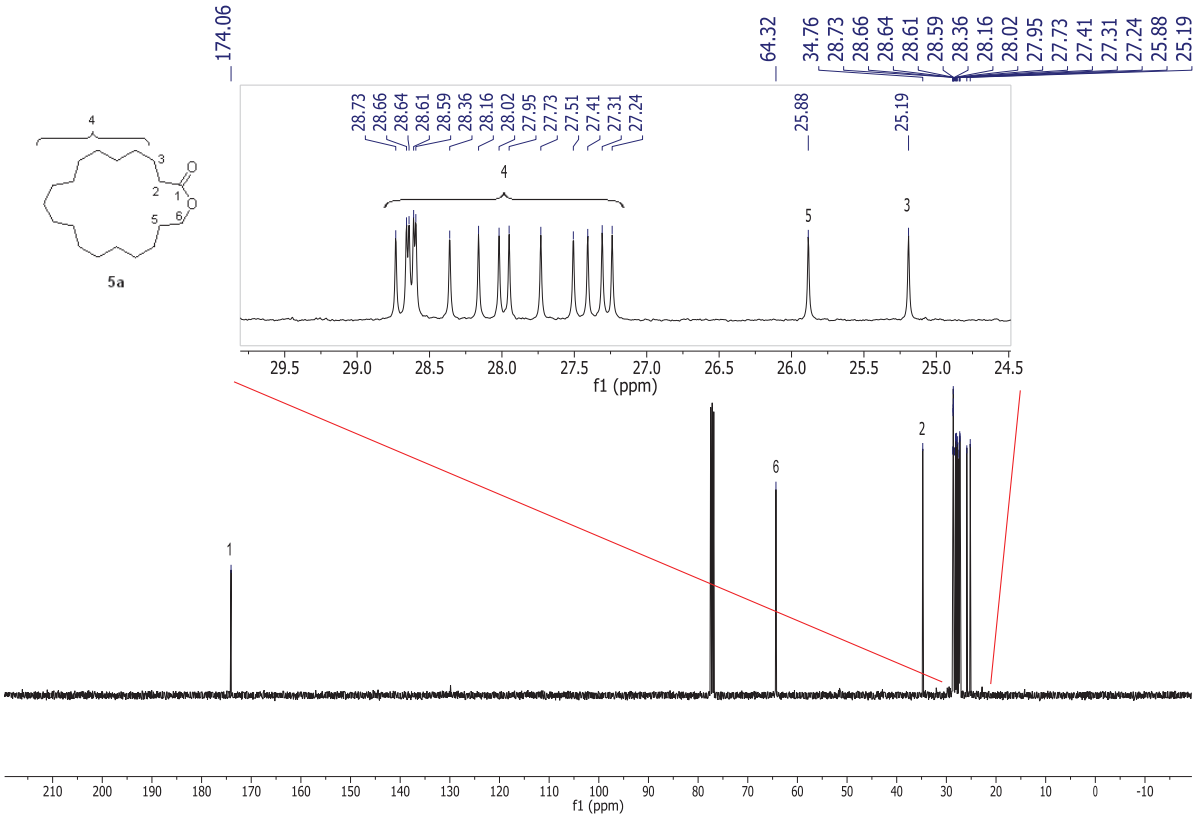


Figure S5. ^{13}C-NMR spectrum of nonadecalactone in chloroform-d_1.

Tricosalactone (5b)

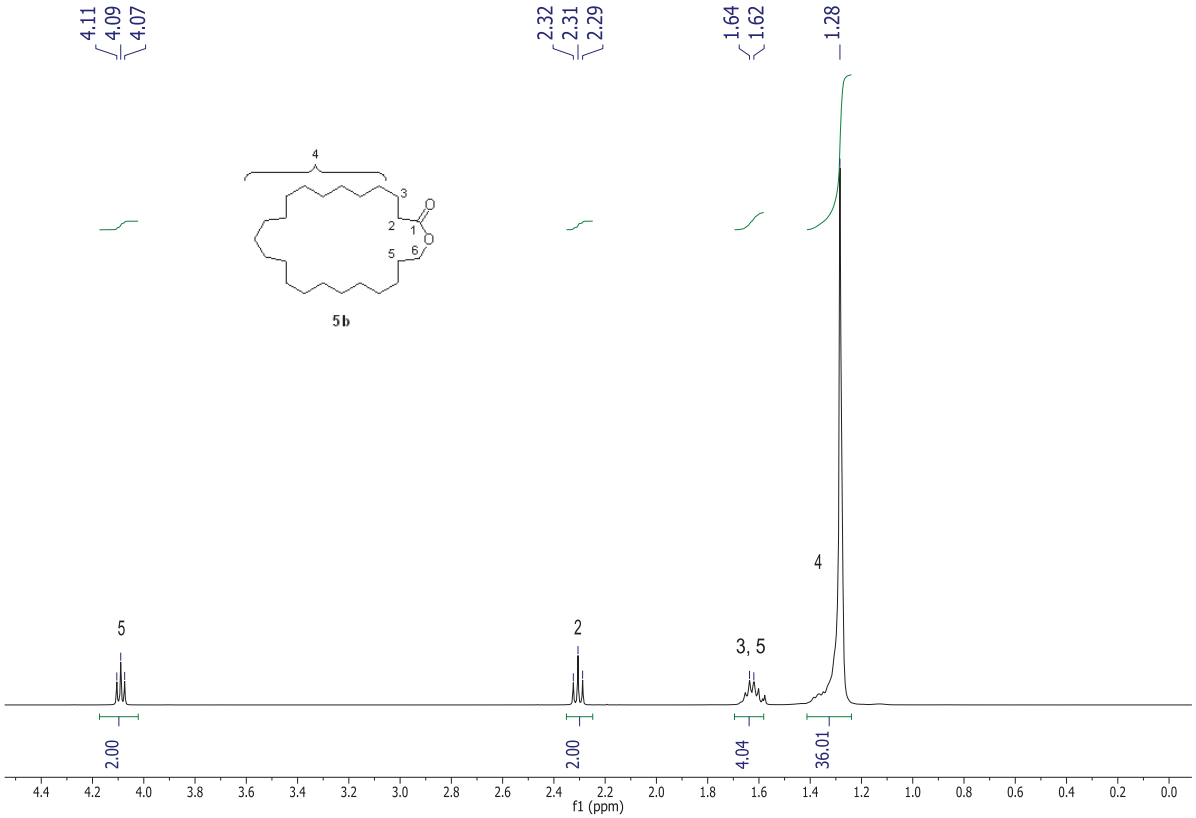


Figure S6. ^{1}H-NMR spectrum of tricosalactone in chloroform-d_1.

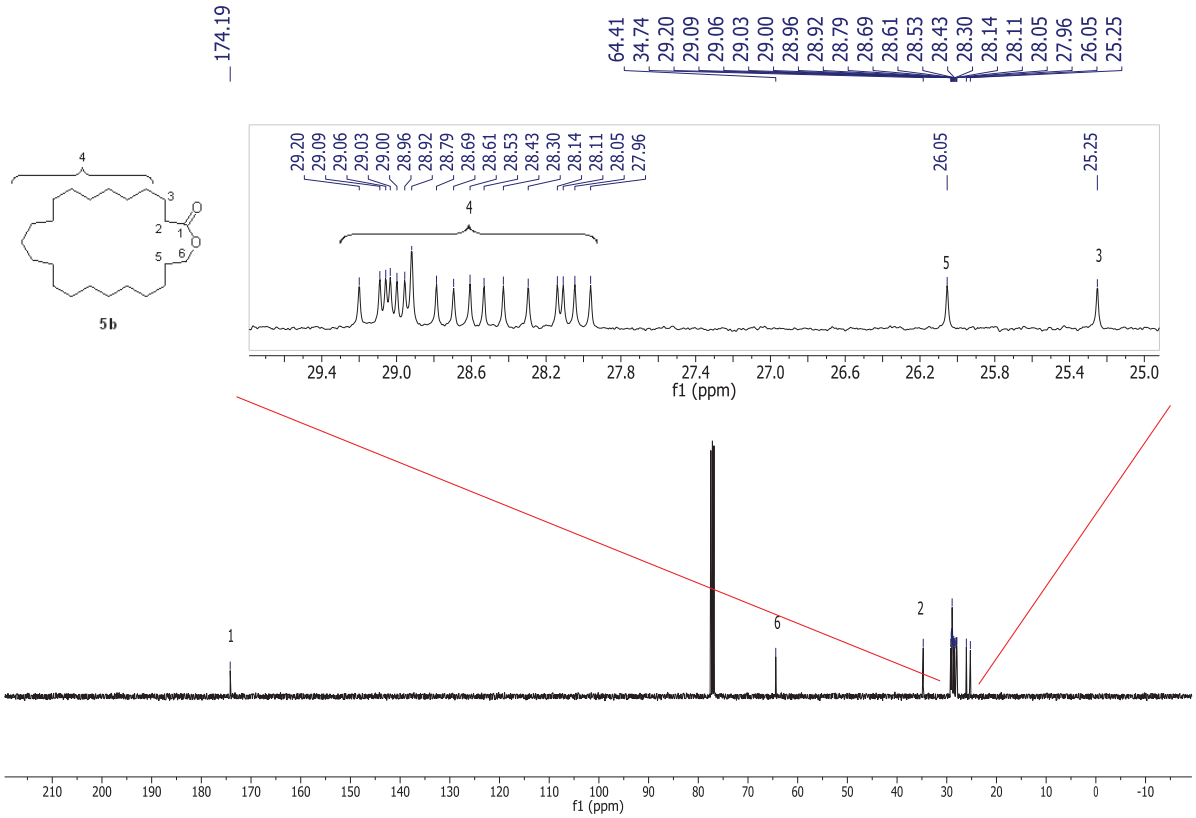


Figure S7. ^{13}C-NMR spectrum of tricosalactone in chloroform-d_1.

Nonadecalactam (6a)

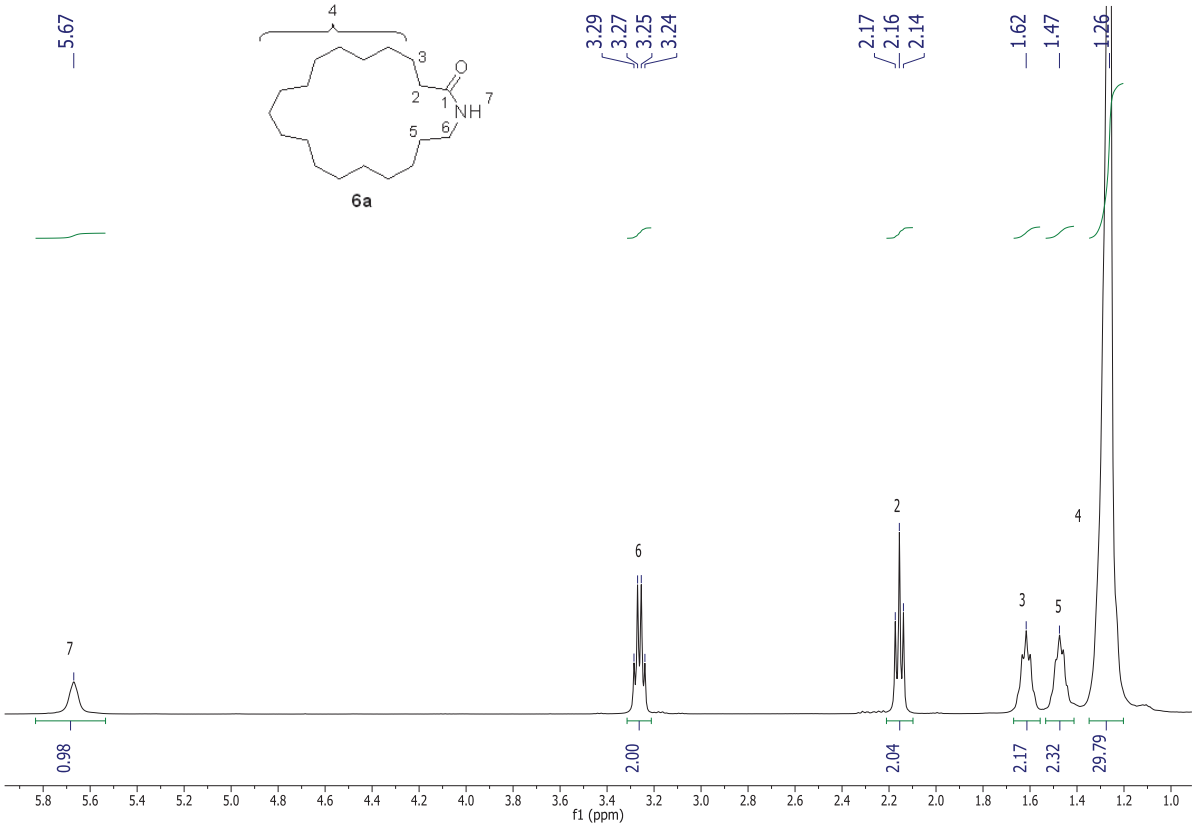


Figure S8. ^{1}H-NMR spectrum of nonadecalactam in chloroform-d_1.

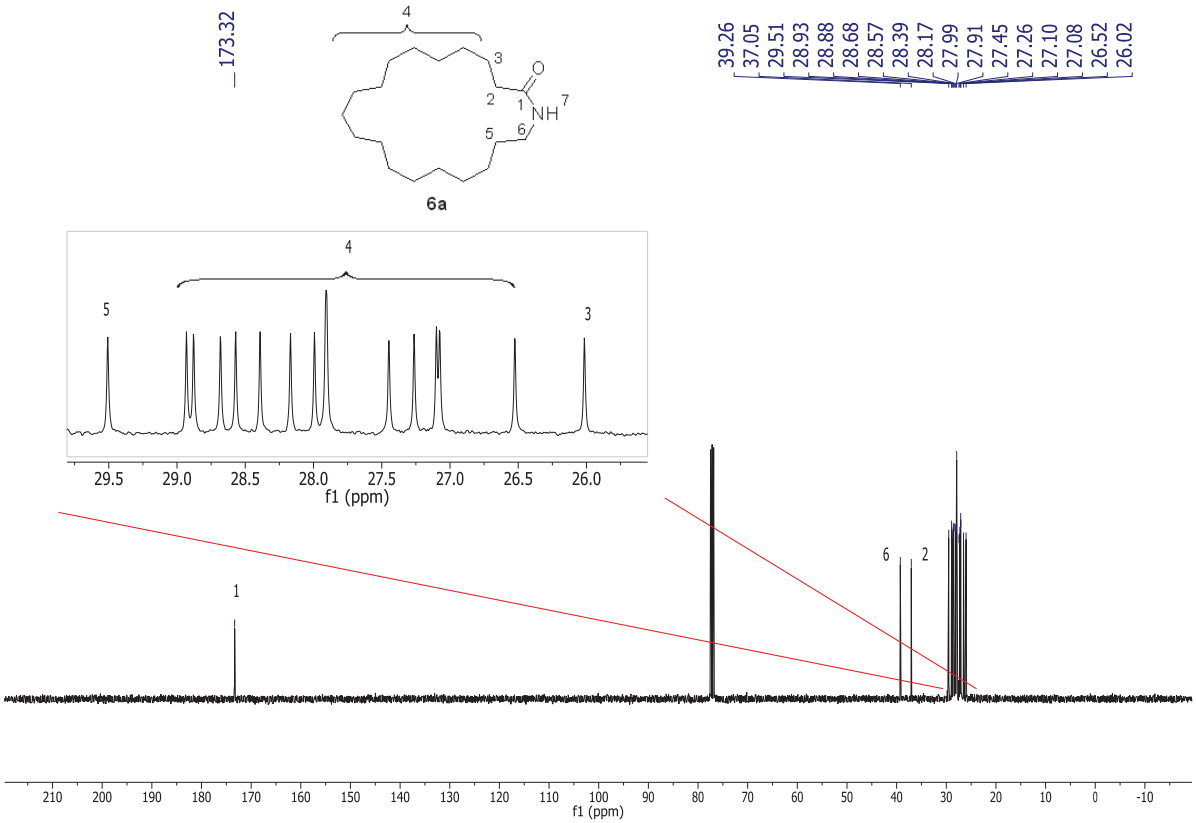


Figure S9. ^{13}C-NMR spectrum of nonadecalactam in chloroform-d_1.

Tricosalactam (6b)

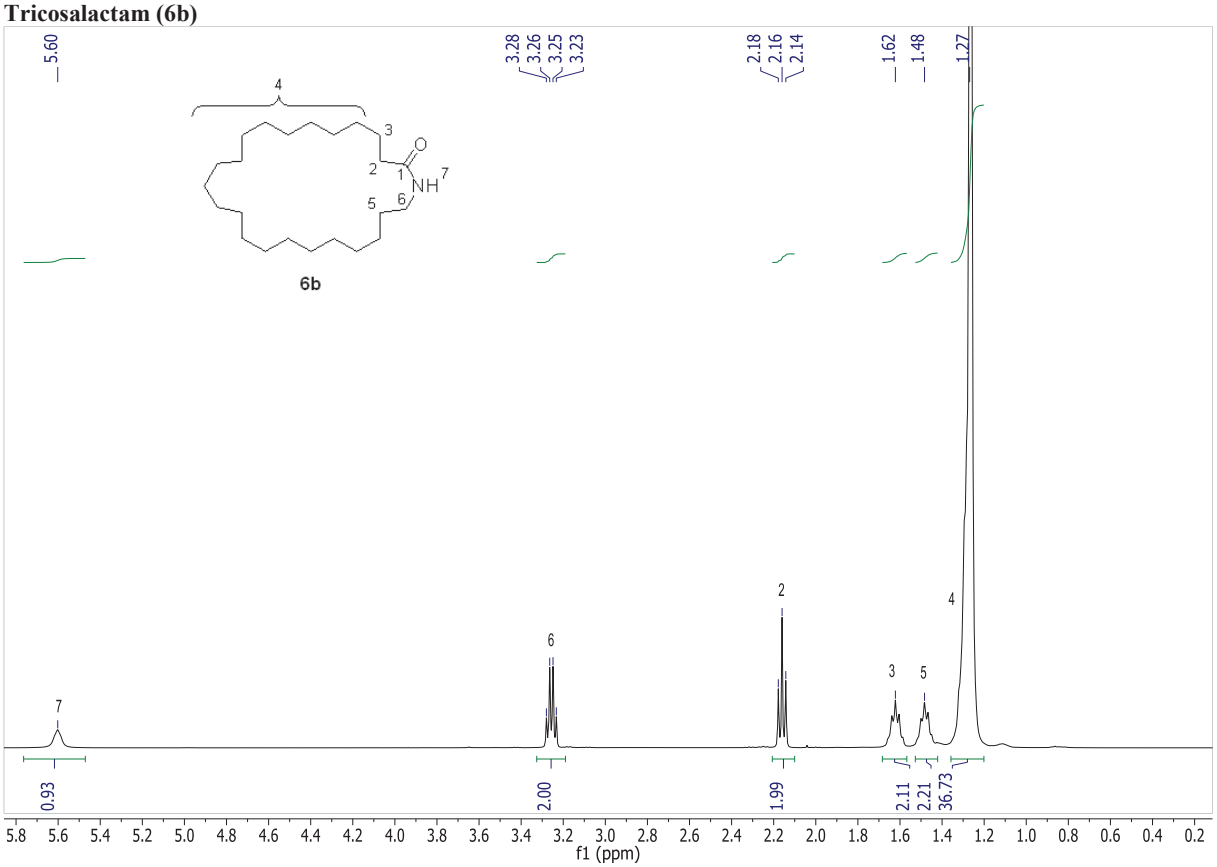


Figure S10. ^{1}H-NMR spectrum of tricosalactam in chloroform-d_1.

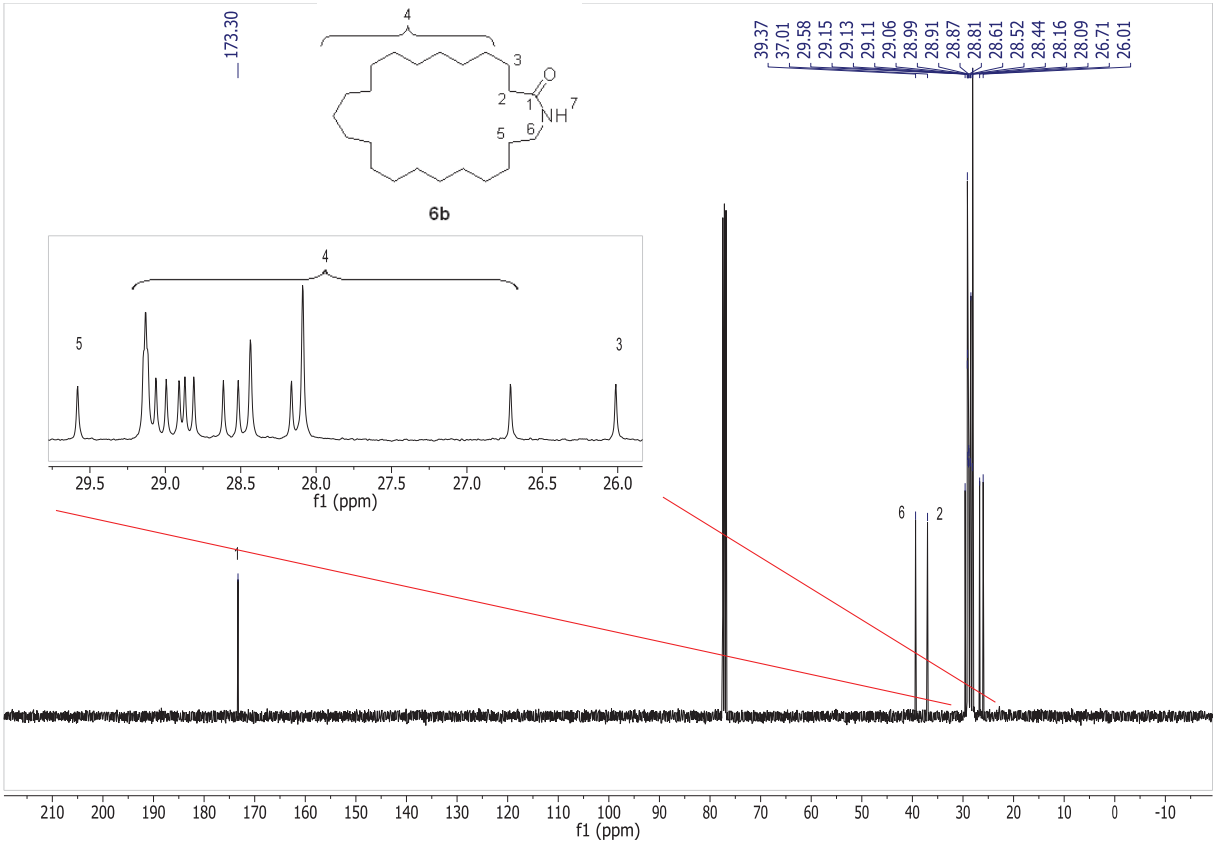


Figure S11. ^{13}C-NMR spectrum of tricosalactam in chloroform-d_1.

Notes and references

(1) Boden, E. P.; Keck, G. E., *J. Org. Chem.* **1985,** *50* (13), 2394-2395.

(2) This strategy has also been explored for the preparation of macrocyclic lactones from plant oils, however we were not able to perform this reaction on a practical scale without using excessive amounts of halogenated solvents.

(3) Yoshimi, Y.; Masuda, M.; Mizunashi, T.; Nishikawa, K.; Maeda, K.; Koshida, N.; Itou, T.; Morita, T.; Hatanaka, M., *Org. Lett.* **2009,** *11* (20), 4652-4655.

(4) F. Stempfle, D. Quinzler, I. Heckler and S. Mecking, *Macromolecules*, 2011, **44**, 4159-4166.

(5) E. A. Karakhanov, A. L. Maximov, Y. S. Kardasheva, V. A. Skorkin, S. V. Kardashev, E. A. Ivanova, E. Lurie-Luke, J. A. Seeley and S. L. Cron, *Ind. Eng. Chem. Res.*, 2010, **49**, 4607-4613.

(6) S. J. Dzugan and V. L. Goedken, *Inorg. Chem.*, 1986, **25**, 2858-2864.

(7) I. van der Meulen, E. Gubbels, S. Huijser, R. l. Sablong, C. E. Koning, A. Heise and R. Duchateau, *Macromolecules*, 2011, **44**, 4301-4305.

(8) A. Weiper-Idelmann, M. aus dem Kahmen, H. J. Schäfer and M. Gockeln, *Acta Chem. Scand.*, 1998, **52**, 672-682.

(9) T.-L. Ho, *Syn. Comm.*, 1979, **9**, 665-668.

(10) D. S. Clyne and L. Weiler, *Tetrahedron*, 1999, **55**, 13659-13682.

(11) G. A. Olah and A. P. Fung, *Synthesis*, 1979, **1979**, 537-538.