Electronic Supplementary Material (ESI) for Chemical Science

Atom Economic Macrolactonization and Lactonization via Redox-Neutral Rhodium-Catalyzed Coupling of Terminal Alkynes with Carboxylic Acids

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Supporting Information

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General

Chromatographic purification of products was accomplished using Machery-Nagel silica gel 60® (230-400 mesh). Thin layer chromatography was performed on aluminum plates pre-coated with silica gel (Merk, $60F_{254}$), which were visualized by quenching of UV fluorescence (λmax = 254 nm), and/or by staining with 1% w/v $KMnO_4$ in 0.5 M aqueous K_2CO_3, followed by heating.

Nuclear magnetic resonance spectra were acquired on a Bruker Avance 400 spectrometer (400 MHz and 100.6 MHz for ^1H and ^{13}C respectively) and on a Varian Mercury (300 MHz and 75.5 MHz for ^1H and ^{13}C respectively). All ^1H NMR spectra are reported in parts per million (ppm) downfield of TMS and were measured relative to the signals at 7.26 ppm ($CHCl_3$). All ^{13}C NMR spectra were reported in ppm relative to residual $CHCl_3$ (77.16 ppm) and were obtained with ^1H decoupling. Data for ^1H NMR are described as follow: chemical shift (δ in ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; sx, sextuplet; m, multiplet; app, apparent; br, broad signal), coupling constant (Hz), integration. Data for ^{13}C NMR spectra are described in terms of chemical shift (δ in ppm).

High resolution mass spectra were obtained on a Finnigan MAT 8200 instrument (CI/NH_3: 110 eV; EI: 70 eV).

The analytical HPLC analyses were performed on an MERCK HITACHI chromatograph (column type: 250/4 Nucleosil 100-5, Macherey-Nagel; eluent: *n*-Heptan/Dioxan 80/20; Wavelength: 215 nm; rate: 1 mL/min).

The preparative HPLC was performed on an K1800 KNAUER chromatograph (column type: ET 250/1"/20 Nucleosil 100-7, Macherey-Nagel; eluent: *n*-Heptan/Dioxan 80/20; Wavelength: 210 nm; rate: 22 mL/min).

The melting points were determined with a Totolli apparatus.

If not specified, the exocyclic enol (macro)lactone **M** (Markovnikov product, **1M**-**19M**) was not separated from the ω-vinyl (macro)lactone **L** (**1**-**19**) by chromatography on silica gel. The ^1H and ^{13}C spectra were recorded as a mixture of isomers and due to the overlapping of most of the NMR signals (^1H and ^{13}C) between the two products (**L**/**M**), only the data of ω-vinyl (macro)lactones **L** (**1**-**19**) were reported (*see characterization data of the lactones and macrolactones*).

The dimer of the Markovnikov product was never detected in the crude reaction mixture (product **1** to **19**). Due to the very low isolated yields and the overlapping of most of the ^1H NMR signals between the two diastereomers of the dimers **5d**, **6d** and **7d**, the diastereomeric ratios (d.r.) were not determined.

Materials

1,2-Dichloroethane (DCE) was freshly distilled over CaH_2 and degassed by three Freeze-Pump-Thaw cycles prior to use. DPEphos was purchased from Acros organics. $[(COD)RhCl]_2$ was prepared from $RhCl_3(H_2O)_x$ and 1,5-cyclooctadiene following the procedure described by Bosnich and co-workers.[1] Ethylenediamine, propargyl alcohol, alkyl bromide, *n*-buthyllithium (1.6 or 2.5 M solution in hexanes), chromium (VI) oxyde, were purchased from Acros organics. 2-Bromobenzyl bromide, 1-trimethylsilyl-1-propyne, 5-amino-1-pentanol, *N*-Boc-*L*-valine, *L*-proline (esterified using $SOCl_2$ in MeOH) were purchased from AlfaAesar. Glycinmethylester hydrochloride and *L*-valine methyl ester hydrochloride were purchased from Aldrich.

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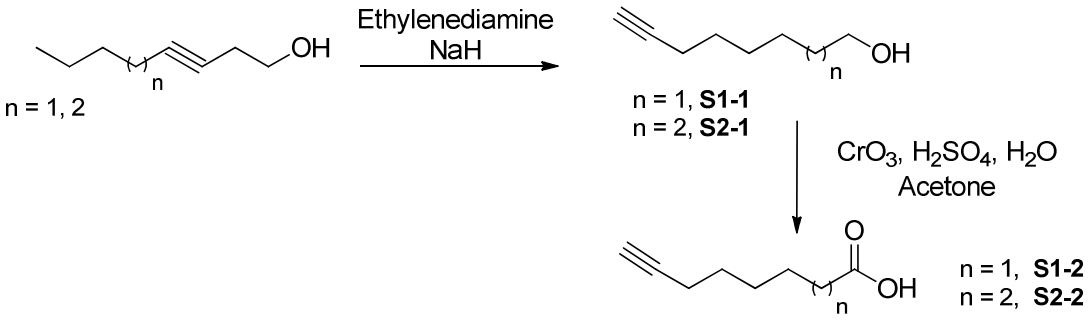
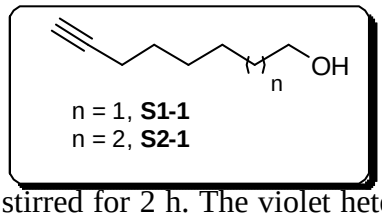
Synthesis of the starting materials

Alkynoic acids S1-2, S2-2

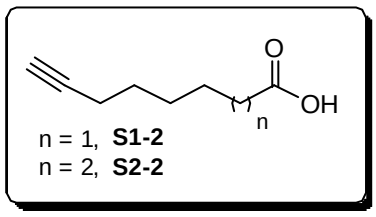


Scheme 1. Preparation of the alkynoic acids **S1-2** and **S2-2**



General procedure 1 (acetylene-zipper reaction, Scheme 1)
Following the procedure described by S. E. Denmark and co-workers,[2] 5.75 g (144 mmol) of NaH (60% in mineral oil) was added to a cooled solution (0°C) of ethylene-1,2-diamine (35 mL) under argon and allowed to warm to room temperature and stirred for 2 h. The violet heterogeneous mixture was then heated at 60°C and stirred for 1 h. The blue-green reaction mixture was then cooled down to 40°C, the alkynyl alcohol (24 mmol) was added and the solution was stirred at 70°C for 1.5 h. After cooling to 0°C, H_2O (50 mL) and HCl_{aq} (1 M, 50 mL) were added carefully. The yellow-orange mixture was then poured into a separatory funnel and HCl_{aq} (1M, 100 mL) was added. The mixture was extracted with Et_2O (3 x 100 mL) and the combined organic layer were washed with HCl_{aq} (1M, 150 mL), brine (150 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by chromatography on silica gel (eluent hexanes/EtOAc 5/1 to 3/1).

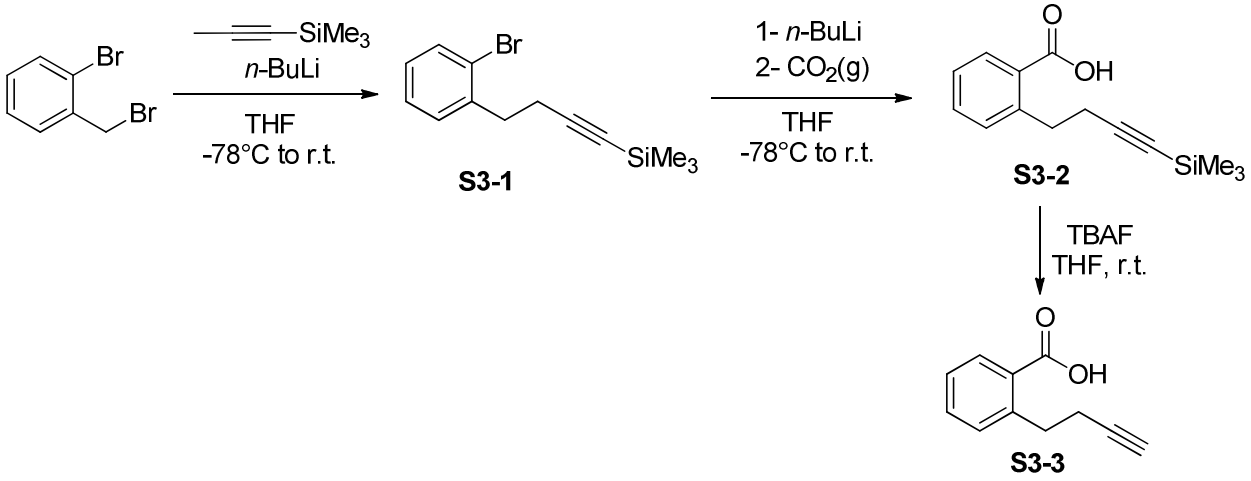
7-Octyn-1-ol (**S1-1**) and 8-Nonyn-1-ol (**S2-1**) were obtained each as colorless oils in 65% and 75% yield respectively and the analytical data were in complete agreement with those reported.[2]



General procedure 2 (Scheme 1)
Following a modified procedure described by Tron and co-workers,[3] a solution of alcohol (15 mmol) in acetone was added dropwise to a cooled (0°C) solution of Jones' reagent (CrO_3, 22 mmol, 2.3 g ; H_2SO_4, 30 mmol, 1.60 mL ; H_2O, 24 mL) and the mixture was stirred for 8 h. The mixture was diluted with EtOAc (50 mL) and water (50 mL) and the aqueous layer was extracted with EtOAc (4 x 30 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude mixture was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 5/1 then 2/1).

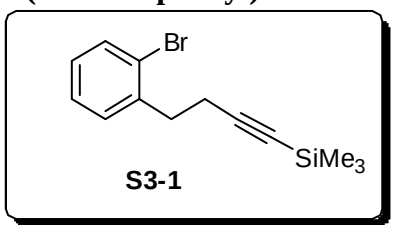
7-Octynoic acid (**S1-2**) and 8-Nonynoic acid (**S2-2**) were obtained as pure white solids in 45% and 48% yields respectively and the analytical data were in complete agreement with those reported.[3]

2-Butynyl benzoic acid acid S3-3



Scheme 2. Preparation of the 2-butynyl benzoic acid **S3-3**

4-(2-Bromophenyl)-1-trimethylsilylbut-1-yne (S3-1)



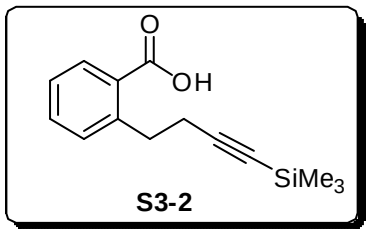
To a solution of 1-(trimethylsilyl)propyne (44.5 mmol, 5 g) in THF (0.3M, 150 mL) was added *n*-BuLi (2.5M in hexanes, 44.5, 17.8 mL) dropwise at -78°C. After stirring at this temperature for 3 h, a solution of 2-bromobenzylbromide (42.8 mmol, 10.7 g) in THF (15 mL) was added dropwise over 20 min. After complete addition, the cooling bath was removed and the reaction mixture allowed to warm to room temperature and stirred for 16 h. The solvent was removed under reduced pressure and the crude mixture was filtered through a pad of silica gel and then distilled (115°C, 0.15 mbar). The title compound **S3-1** was isolated as a colorless oil in 68% yield (8.2 g).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.53 (dd, *J* = 7.9, 1.0, 1H), 7.31-7.20 (m, 2H), 7.08 (td, *J* = 7.7, 2.1, 1H), 2.96 (t, *J* = 7.4, 2H), 2.54 t, *J* = 7.4, 2H), 0.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 139.8, 132.9, 131.1, 128.2, 127.4, 124.5, 106.2, 85.7, 35.4, 20.4, 0.21.

CI-HRMS: *m/z* calcd for $C_{13}H_{21}N^{79}BrSi$ $[M+NH_4]^+$ 298.0627 found 298.0624.

2-(4-(Trimethylsilyl)but-3-yn-1-yl)benzoic acid (S3-2)



To a solution of **S3-1** (0.5 g, 1.78 mmol) in THF (0.2M, 8.9 mL) was added dropwise *n*-BuLi (2.5M in hexanes, 1.78 mmol, 0.71 mL) at -78°C. After 15 min at this temperature, CO_2(g) was bubbled through the solution for 1 min. The mixture was then allowed to warm to room temperature over 20 min and HCl (1M, 20 mL) was added. The mixture was diluted with EtOAc and the aqueous layer extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 5/1) afforded **S3-2** as a white solid in 60% yield (0.26 g).

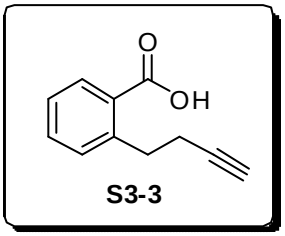
m.p. 88-89 °C

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.06 (dd, *J* = 7.8, 1.3, 1H), 7.49 (td, *J* = 7.5, 1.3, 1H), 7.40-7.29 (m, 2H), 3.25 (t, *J* = 7.3, 2H), 2.60 (t, *J* = 7.3, 2H), 0.12 (s, 9H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.0, 143.4, 132.9, 132.2, 131.9, 128.1, 126.7, 106.8, 85.8, 33.7, 21.8, 0.2,

CI-HRMS: *m/z* calcd for $C_{14}H_{17}O_2Si$ [M-H] 245.0998 found 245.1001.

2-(But-3-yn-1-yl)benzoic acid (S3-3)



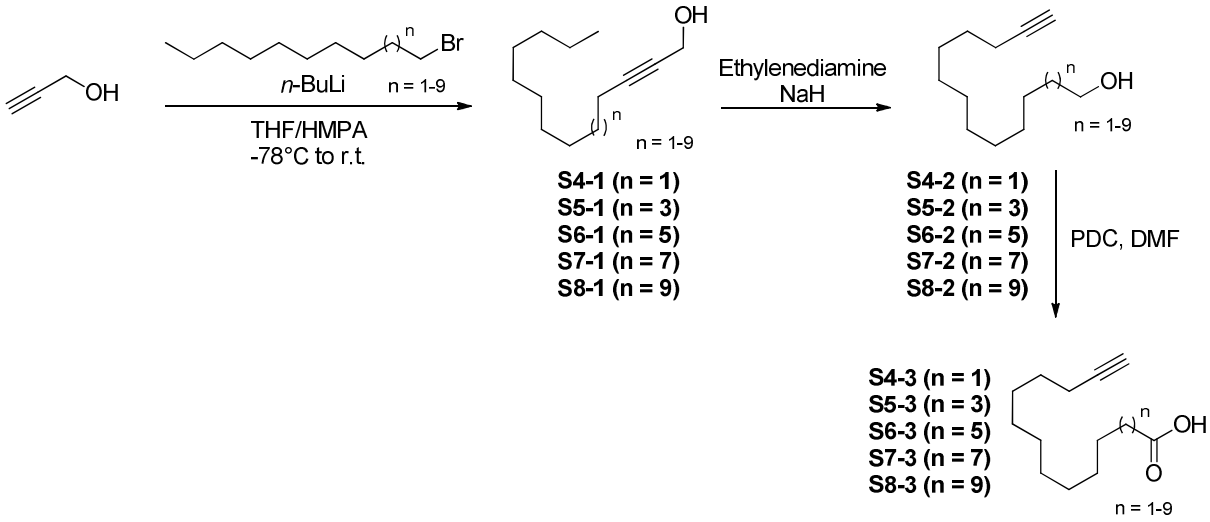
To a solution of **S3-2** (0.26 g, 1.05 mmol) in THF (2.0 mL) was added TBAF (1M in THF, 2.10 mmol, 2.10 mL) at room temperature. After 1 h, the solution was diluted with EtOAc (10 mL) and HCl (1M, 10 mL) was added. The aqueous layer was extracted with EtOAc (3 x 10 mL) and the combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1) afforded **S3-3** as a white solid in 71% yield (0.13 g).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.08 (dd, *J* = 7.8, 1.2, 1H), 7.52 (td, *J* = 7.8, 1.2, 1H), 7.41-7.31 (m, 2H), 3.27 (t, *J* =7.4, 2H), 2.58 (td, *J* = 7.4, 2.7, 2H), 1.98 (bt, *J* = 2.7, 1H).

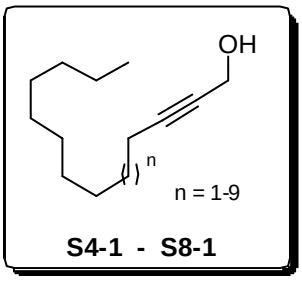
^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.2, 143.3, 133.1, 132.0, 131.9, 128.1, 126.8, 84.0, 69.3, 33.7, 20.4.

CI-HRMS: *m/z* calcd for $C_{11}H_{14}O_2N$ $[M+NH_4]^+$ 192.1024 found 192.1020.

Alkynoic acids S4-3 - S8-3



Scheme 3. Preparation of the alkynoic acids **S4-3 - S8-3**



***General procedure 3 (Scheme 3)*[4]**

To a solution of freshly distilled propargyl alcohol (3.2 g, 57.1 mmol) in THF (90 mL) and HMPA (24 mL) was added *n*-BuLi (2.5M in hexanes, 114.1 mmol, 45.6 mL) at -78°C over 40 min. The reaction mixture was then warmed to -30°C and the alkyl bromide (43.9 mmol) was added dropwise. After complete addition, the cooling bath was removed and the solution was allowed to warm to room temperature and stirred overnight (16 h). NH_4Cl_{sat} was added (150 mL) and the aqueous layer was extracted with EtOAc (2 x 100 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/AcOEt 10/1 to 3/1) afforded the alcohol **SX-1** (*vide infra*).

Tridec-2-yn-1-ol (n = 1, S4-1, yield = 68%, white solid)

m.p. 44-45 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.23 (bt, *J* = 2.23, 2H), 2.19 (m, 2H), 1.49 (m, 2H), 1.41-1.17 (m, 14H), 0.87 (bt, *J* = 7.0, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 86.7, 78.4, 51.5, 32.0, 29.7, 29.6, 29.4, 29.3, 29.0, 28.7, 22.8, 18.8, 14.2.
CI-HRMS: *m/z* calcd for $C_{13}H_{28}ON$ $[M+NH_4]^+$ 214.2171 found 241.2170.

Pentadec-2-yn-1-ol (n = 3, S5-1, yield = 79%, white solid)

m.p. 47-48 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.24 (t, *J* = 2.2, 2H), 2.20 (tt, *J* = 7.1, 2.2, 2H), 1.50 (m, 2H), 1.41-1.19 (m, 19H), 0.88 (t, *J* = 6.6, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 86.8, 78.4, 51.6, 32.0, 29.80, 29.77 (2C), 29.7, 29.5, 29.3, 29.0, 28.8, 22.8, 18.9, 14.2.
CI-HRMS: *m/z* calcd for $C_{15}H_{32}ON$ $[M+NH_4]^+$ 242.2484 found 242.2485.

Heptadec-2-yn-1-ol (n = 5, S6-1, yield = 69%, white solid)

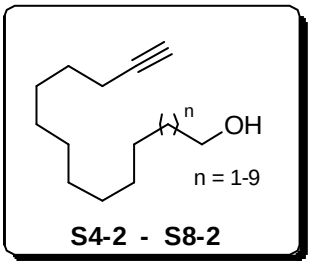
m.p. 60-61 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.25 (t, *J* = 2.2, 2H), 2.21 (tt, J = 7.1, 2.2, 2H), 1.57-1.42 (m, 2H), 1.41-1.20 (m, 23H), 0.88 (bt, J = 6.8, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 86.8, 78.4, 51.6, 32.1, 29.84, 29.83, 29.81 (2C), 29.80, 29.7, 29.5, 29.3, 29.0, 28.8, 22.8, 18.9, 14.2,
CI-HRMS: *m/z* calcd for $C_{17}H_{36}ON$ $[M+NH_4]^+$ 270.2797 found 270.2800.

Nonadec-2-yn-1-ol (n = 7, S7-1, yield = 81%, white solid)

m.p. 69-70 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.25 (t, *J* = 2.2, 2H), 2.20 (tt, *J* = 7.2, 2.2, 2H), 1.53-1.49 (m, 2H), 1.42-1.20 (m, 27H), 0.88 (bt, *J* = 7.1, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 86.8, 78.4, 51.6, 32.1, 29.84 (3C), 29.80 (2C), 29.78, 29.7, 29.5, 29.3, 29.0, 28.8, 22.8, 18.9, 14.2.
CI-HRMS: *m/z* calcd for $C_{19}H_{40}ON$ $[M+NH_4]^+$ 298.3110 found 298.3111.

Henicos-2-yn-1-ol (n = 9, S8-1, yield = 78%, white solid)

m.p. 73-74 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.25 (t, *J* = 2.3, 2H), 2.21 (tt, *J* =7.1, 2.3, 2H), 1.52-1.44 (m, 2H), 1.40-1.21 (m, 31H), 0.88 (bt, *J* = 6.9, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 86.9, 78.4, 51.6, 32.1, 29.84 (6C), 29.80 (2C), 29.77, 29.7, 29.5, 29.3, 29.0, 28.8, 22.8, 18.9, 14.2.
CI-HRMS: *m/z* calcd for $C_{21}H_{44}ON$ $[M+NH_4]^+$ 326.3423 found 326.3425.



S4-2 - S8-2

The alcohols **S4-2** to **S8-2** were prepared from the alcohols **S4-1** to **S8-1**, respectively using the acetylene zipper reaction described in the *general procedure 1 (vide supra).*

Tridec-12-yn-1-ol (n = 1, S4-2, yield = 71%, white solid)

m.p. 43-44 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.62 (t, *J* = 6.5, 2H), 2.17 (td, *J* = 6.9, 2.6, 2H), 1.92 (t, *J* = 2.6, 1H), 1.61-1.44 (m, 4H), 1.42-1.20 (m, 14H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 84.9, 68.2, 63.2, 32.9, 29.7, 29.64, 29.59, 29.5, 29.2, 28.9, 28.6, 25.9, 18.5
CI-HRMS: *m/z* calcd for $C_{13}H_{28}ON$ $[M+NH_4]^+$ 214.2171 found 214.2167.

Pentadec-14-yn-1-ol (n = 3, S5-2, yield = 55%, white solid)

m.p. 47-48 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64 (t, *J* = 6.7, 2H), 2.18 (td, *J* = 6.9, 2.6, 2H), 1.93 (t, *J* = 2.6, 1H), 1.62-1.46 (m, 4H), 1.44-1.21 (m, 19H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 85.0, 68.2, 63.2, 33.0, 29.75 (2C), 29.72 (2C), 29.63, 29.57, 29.2, 28.9, 28.6, 25.9, 18.5.
CI-HRMS: *m/z* calcd for $C_{15}H_{32}ON$ $[M+NH_4]^+$ 242.2484 found 242.2483.

Heptadec-16-yn-1-ol (n = 5, S6-2, yield = 59%, white solid)

m.p. 55-56 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.61 (t, *J* = 6.7, 2H), 2.15 (td, *J* = 6.9, 2.6, 2H), 1.91 (t, *J* = 2.6, 1H), 1.67-1.15 (m, 27H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 84.9, 68.1, 63.1, 32.9, 29.75 (3C), 29.72, 29.71 (2C), 29.6, 29.5, 29.2, 28.9, 28.6, 25.9, 18.5.
CI-HRMS: *m/z* calcd for $C_{17}H_{36}ON$ $[M+NH_4]^+$ 270.2797 found 270.2793.

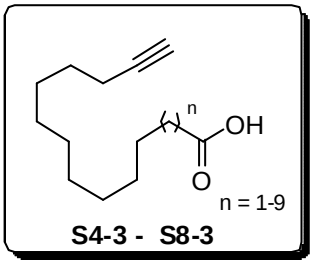
Nonadec-18-yn-1-ol (n = 7, S7-2, yield = 78%, white solid)

m.p. 65-67 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.63 (t, *J* = 6.6, 2H), 2.17 (td, *J* = 7.0, 2.6, 2H), 1.93 (t, *J* = 2.6, 1H), 1.62-1.45 (m, 4H), 1.44-1.19 (m, 27H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 85.0, 68.1, 63.2, 33.0, 29.8 (6C), 29.7 (3C), 29.64, 29.57, 29.2, 28.9, 28.6, 25.9.
CI-HRMS: *m/z* calcd for $C_{19}H_{40}ON$ $[M+NH_4]^+$ 298.3110 found 298.3107.

Henicos-20-yn-1-ol (n = 9, S8-2, yield = 77%, white solid)

m.p. 71-73 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.64 (t, *J* = 6.6, 2H), 2.18 (td, *J* = 7.0, 2.7, 2H), 1.93 (t, *J* = 2.7, 1H), 1.63-1.45 (m, 4H), 1.44-1.20 (m, 31H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 85.0, 68.1, 63.3, 33.0, 29.83 (5C), 29.80 (2C), 29.76 (3C), 29.65, 29.58, 29.3, 28.9, 28.6, 25.9, 18.5.
CI-HRMS: *m/z* calcd for $C_{21}H_{44}ON\,[M+NH_4]^+$ 326.3427 found 326.3423.



***General procedure 4 (Scheme 3)*[5]**
To a solution of alcohol **S4-2** – **S8-2** (23.2 mmol, 5.2 g) in DMF (90 mL) was added pyridinium dichromate (70.0 mmol, 26.5 g). The mixture was stirred overnight, diluted with HCl (1M, 100 mL) and extracted with EtOAc (3 x 100 mL) . The combined organic extracts were washed with brine (300 mL), dried over MgSO4 and purified by flash chromatography on silica gel (eluent hexanes/AcOEt 2/1).

Tridec-12-ynoic acid (n = 1, S4-3, yield = 58%, white solid)

m.p. 63-65 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (t, *J* = 7.4, 2H), 2.17 (td, *J* = 7.1, 2.7, 2H), 1.93 (t, *J* = 2.7, 1H), 1.67-1.58 (m, 2H), 1.56-1.47 (m, 2H), 1.43-1.24 (m, 12H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.2, 84.9, 68.2, 34.2, 29.54, 29.48, 29.3, 29.20, 29.18, 28.9, 28.6, 24.8, 18.5.
CI-HRMS: *m/z* calcd for $C_{13}H_{26}O_2N\,[M+NH_4]^+$ 228.1963 found 228.1964.

Pentadec-14-ynoic acid (n = 3, S5-3, yield = 90%, white solid)

m.p. 70-72 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (t, *J* = 7.3, 2H), 2.18 (td, *J* = 7.0, 2.7, 2H), 1.93 (t, *J* = 2.7, 1H), 1.68-1.59 (m, 2H), 1.57-1.47 (m, 2H), 1.43-1.23 (m, 16H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.7, 85.0, 68.2, 34.1, 29.7 (2C), 29.6, 29.5, 29.4, 29.24, 29.20, 28.9, 28.6, 24.8, 18.5.
CI-HRMS: *m/z* calcd for $C_{15}H_{30}O_2N\,[M+NH_4]^+$ 256.2276 found 256.2277.

Heptadec-16-ynoic acid (n = 5, S6-3, yield = 70%, white solid)

m.p. 75-77 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.34 (t, *J* = 7.2, 2H), 2.20 (td, *J* = 7.0, 2.6, 2H), 1.93 (t, *J* = 2.6, 1H), 1.68-1.58 (m, 2H), 1.57-1.47 (m, 2H), 1.43-1.22 (m, 20H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.9, 85.0, 68.2, 34.1, 29.8 (2C), 29.74, 29.72, 29.65, 29.57, 29.4, 29.3, 29.2, 28.9, 28.6, 24.8, 18.5.
CI-HRMS: *m/z* calcd for $C_{17}H_{34}O_2N\,[M+NH_4]^+$ 284.2589 found 284.2586.

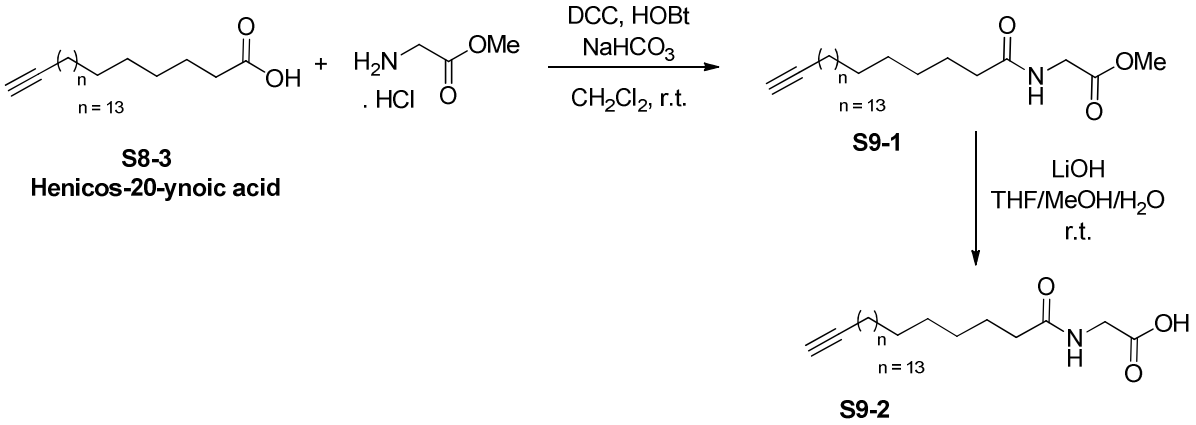
Nonadec-18-ynoic acid (n = 7, S7-3, yield = 72%, white solid)

m.p. 81-83 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (t, *J* = 7.5, 2H), 2.18 (td, *J* = 7.1, 2.5, 2H), 1.93 (t, *J* = 2.5, 1H), 1.67-1.60 (m, 2H), 1.56-1.48 (m, 2H), 1.43-1.22 (m, 24H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 178.5, 85.0, 68.2, 33.9, 29.80 (3C), 29.78, 29.76, 29.74, 29.70, 29.6, 29.4, 29.3, 29.2, 28.9, 28.6, 24.8, 18.5.
CI-HRMS: *m/z* calcd for $C_{19}H_{38}O_2N\,[M+NH_4]^+$ 312.2902 found 312.2904.

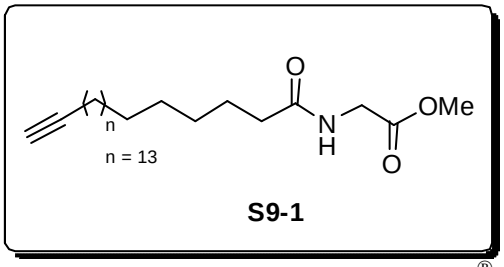
Henicos-20-ynoic acid (n = 9, S8-3, yield = 61%, white solid)

m.p. 95-98 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (t, *J* = 7.5, 2H), 2.20 (td, *J* = 7.1, 2.7, 2H), 1.93 (t, *J* = 2.7, 1H), 1.67-1.59 (m, 2H), 1.56-1.48 (m, 2H), 1.43-1.21 (m, 28H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 179.6, 85.0, 68.1, 34.1, 29.82 (4C), 29.80, 29.79, 29.76, 29.7, 29.65, 29.58, 29.4, 29.3, 29.2, 28.9, 28.7, 24.8, 18.5.
CI-HRMS: *m/z* calcd for $C_{21}H_{42}O_2N$ $[M+NH_4]^+$ 340.3215 found 340.3213.

2-(Henicos-20-ynamido)acetic acid S9-2

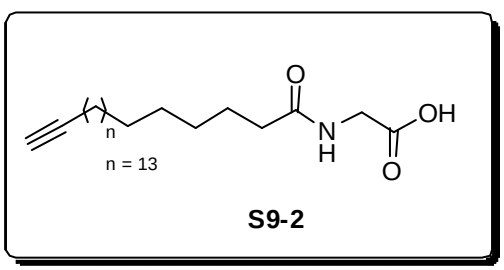


Scheme 4. Preparation of the 2-(henicos-20-ynamido)acetic acid **S9-2**



To a solution of the carboxylic acid **S8-3** (1.83 mmol, 0.59 g) in dichloromethane (15 mL) was added glycine methyl ester (hydrochloride) (2.74 mmol, 0.34 g), $NaHCO_3$ (2.74 mmol, 0.23 g), HOBt (3.66 mmol, 0.46 g) and DCC (3.66 mmol, 0.75 g) and the heterogeneous mixture was stirred for 20 h at room temperature. The reaction mixture was then filtered through a pad of Celite® and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/3) afforded **S9-1** as a white solid in 88% yield (0.64 g).

m.p. 103-105 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.93 (bs, 1H), 4.04 (d, *J* = 5.3, 2H), 3.76 (s, 3H), 2.29-2.10 (m, 4H), 1.73-1.13 (m, 33H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 170.7, 85.0, 68.1, 52.5, 41.3, 36.6, 29.81 (4C), 29.78 (2C), 29.7 (2C), 29.64, 29.61, 29.5, 29.4, 29.2, 28.9, 28.6, 25.7, 18.5.
CI-HRMS: *m/z* calcd for $C_{24}H_{44}O_3N$ $[M+H]^+$ 394.3321 found 394.3321.

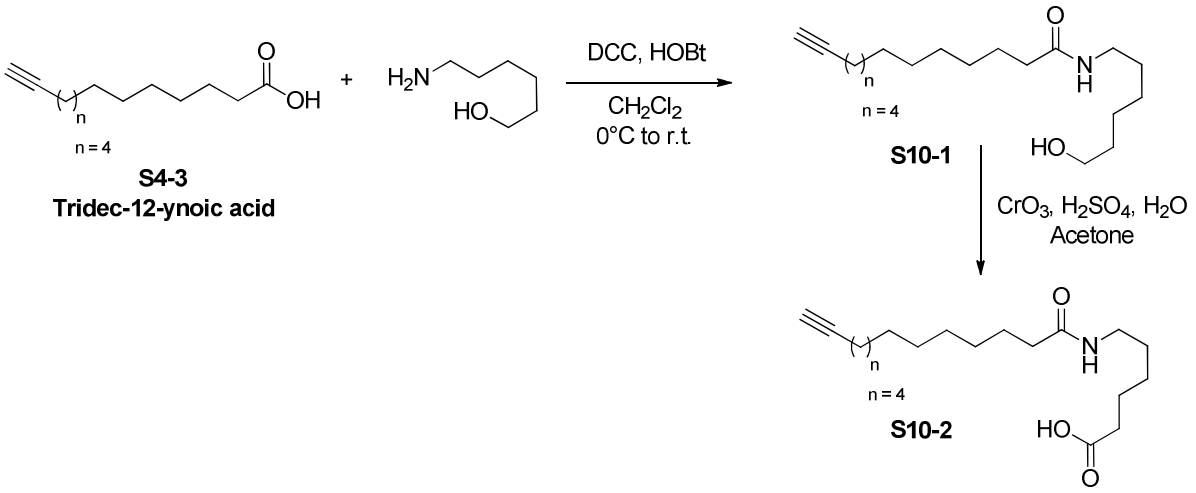


To a solution of methyl ester **S9-1** (1.0 mmol) in 8:2:1 THF/water/MeOH (35 mL) was added LiOH (3.1 mmol, 0.13 g) at 0°C and the reaction mixture was stirred at room temperature for 4 h. HCl (1M, 15 mL) was added to the heterogeneous mixture followed by EtOAc (80 mL). The aqueous layer was

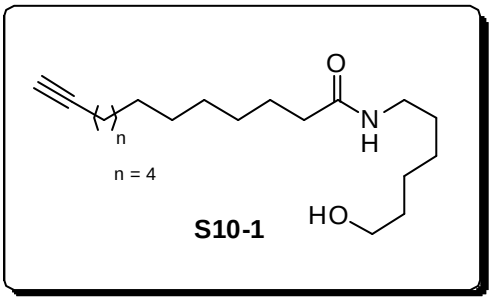
extracted with EtOAc (1 x 50 mL) and combined organic extracts were washed with brine, dried over $MgSO_4$ and concentrated under vacuum. The carboxylic acid **S9-2** was used for the macrolactonization reaction without further purification (quantitative yield).

m.p. 125-130 °C
^{1}H NMR (MeOD, 300 MHz): δ 3.87 (bs, 2H), 2.24 (t, *J* = 7.1, 2H), 2.19-2.12 (m, 2H), 1.67-1.02 (m, 35H).
^{13}C NMR (MeOD, 100 MHz): δ 176.7, 172.3, 85.1, 69.3, 36.9, 34.7, 30.74 (5C), 30.72 (2C), 30.69, 30.63, 30.61, 30.45, 30.3, 30.2, 29.8, 29.7, 26.8, 19.0.
CI-HRMS: *m/z* calcd for $C_{23}H_{42}O_3N$ $[M+H]^+$ 380.3165 found 380.3157.

6-(Tridec-12-ynamido)hexanoic acid S10-2

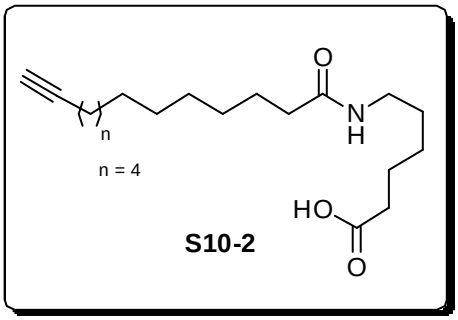


Scheme 5. Preparation of the 6-(tridec-12-ynamido)hexanoic acid **S10-2**



To a solution of the carboxylic acid **S4-3** (2.42 mmol, 0.51 g) in dichloromethane (5 mL) was added HOBt (2.42 mmol, 0.34 g). The reaction mixture was cooled to 0°C and DCC was added (2.42 mmol, 0.50 g). After stirring for 1 h at this temperature, 6-aminohexan-1-ol was added (2.90 mmol, 0.34 g) and the heterogeneous mixture was stirred overnight (14 h) at room temperature, filtered through a pad of Celite® and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent CH_2Cl_2/MeOH 90/10) afforded **S10-1** as a white solid in quantitative yield (750 mg).

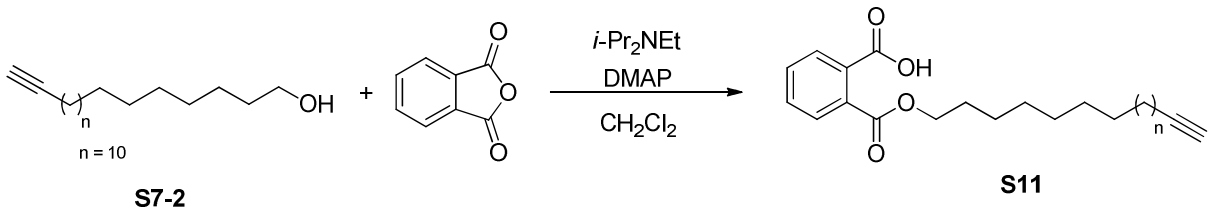
m.p. 85-86 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.45 (bs, 1H), 3.63 (t, *J* = 6.2, 2H), 3.24 (app q, *J* = 6.7, 2H), 2.23-2.08 (m, 4H), 1.93 (bt, *J* = 2.6, 1H), 1.68-1.17 (m, 25H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 84.9, 68.2, 62.8, 39.4, 37.1, 32.7, 29.8, 29.5 (2C), 29.45, 29.43, 29.2, 28.9, 28.6, 26.6, 25.9, 25.4, 18.5.
CI-HRMS: *m/z* calcd for $C_{19}H_{36}O_2N$ $[M+H]^+$ 310.2746 found 310.2742.



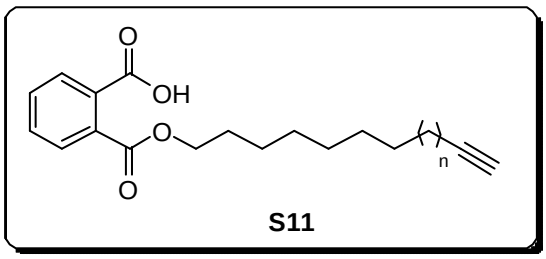
Following a modified procedure described by Holmes and co-workers,[6] to a solution of the alcohol **S10-1** (2.1 mmol, 650 mg) in acetone (90mL) was added Jones' reagent (CrO_3, 3.08 mmol, 0.32 g ; H_2SO_4, 4.2 mmol, 0.22 mL ; H_2O, 3.40 mL) at 0°C. After 8 h, the mixture was diluted with EtOAc (50 mL) and water (50 mL) and the aqueous layer was extracted with EtOAc (6 x 30 mL). The combined organic extracts were washed with brine (80 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/3 to EtOAc 100%) afforded **S10-2** as a white solid in 25 % yield (170 mg).

m.p. 95-97 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.46 (bs, 1H), 3.26 (app q, *J* = 6.7, 2H), 2.36 (t, *J* = 7.3, 2H), 2.22-2.10 (m, 4H), 1.93 (t, *J* = 2.6, 1H), 1.74-1.20 (m, 22H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.5, 173.4, 84.9, 68.2, 39.3, 37.0, 33.7, 29.57, 29.55, 29.45 (2C), 29.43, 29.21, 28.9, 28.6, 26.4, 25.9, 24.4, 18.5
CI-HRMS: *m/z* calcd for $C_{19}H_{34}O_3N$ $[M+H]^+$ 324.2539 found 324.2531.

2-((Nonadec-18-yn-1-yloxy)carbonyl)benzoic acid S11



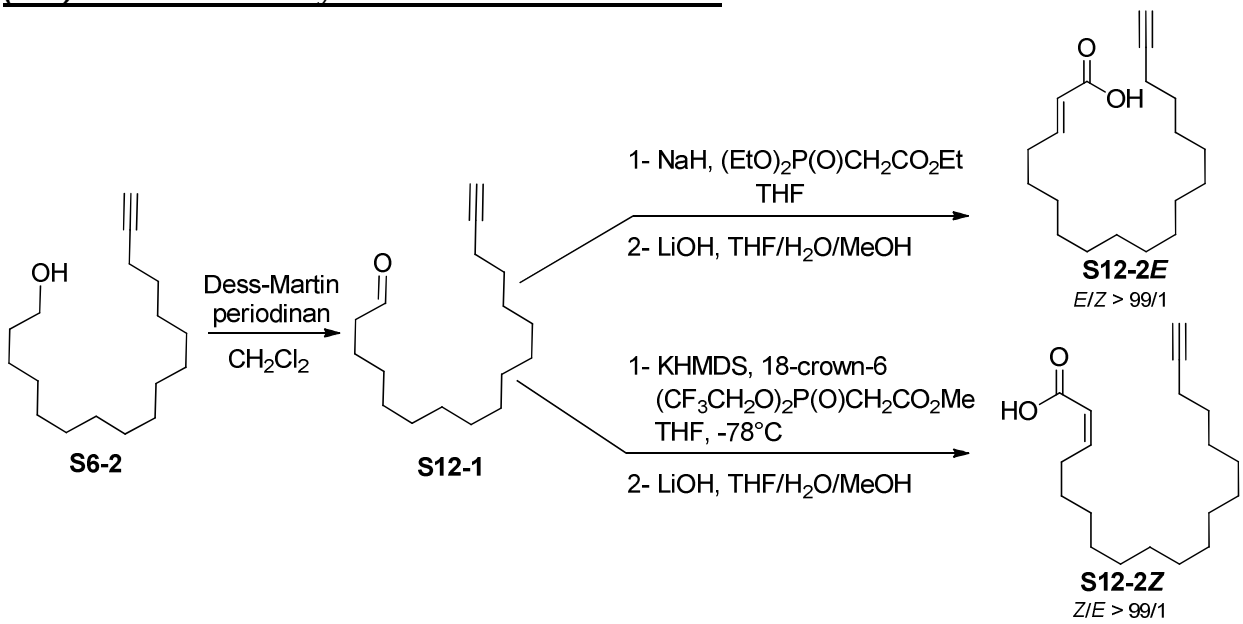
Scheme 6. Preparation of the 2-((nonadec-18-yn-1-yloxy)carbonyl)benzoic acid **S11**



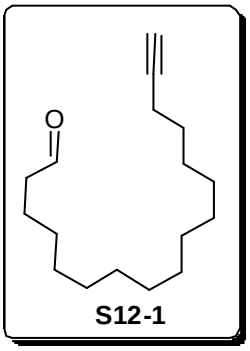
To a solution of phthalic anhydride (6.65 mmol, 0.99 g) in dichloromethane (13 mL) was added **S7-2** (6.34 mmol, 1.60 g) and *i*-Pr_2NEt (9.5 mmol, 1.6 mL) at room temperature. A solution of DMAP (1.58 mmol, 0.19 g) in dichloromethane (3 mL) was then added dropwise and the solution was stirred for 16 h. After dilution with dichloromethane (20 mL), the reaction mixture was washed with HCl (1M, 3x 15 mL), H_2O (1 x 20 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1) afforded **S11** as a white solid in 69% yield (1.87 g).

m.p. 86-87 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.92 (dd, *J* = 7.3, 1.8, 1H), 7.71 (dd, *J* =7.4, 1.6, 1H), 7.60 (td, *J* = 7.3, 1.6, 1H), 7.56 (td, *J* = 7.4, 1.6, 1H), 4.32 (t, *J* = 6.8, 2H), 2.17 (td, *J* = 7.2, 2.7, 2H), 1.92 (t, *J* = 2.7, 1H), 1.74 (m, 2H), 1.52 (m, 2H), 1.44-1.18 (m, 28H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.1, 168.3, 133.6, 132.3, 131.0, 130.2, 130.1, 129.0, 84.9, 68.2, 66.4, 29.82 (3C), 29.80, 29.78, 29.75 (2C), 29.67, 29.65, 29.4, 29.3, 28.9, 28.7, 28.6, 26.1, 18.5.
CI-HRMS: *m/z* calcd for $C_{27}H_{41}O_4$ $[M+H]^+$ 429.3005 found 429.2999.

(E/Z)-nonadec-2-en-18-ynoic acid S12-2E and S12-2Z

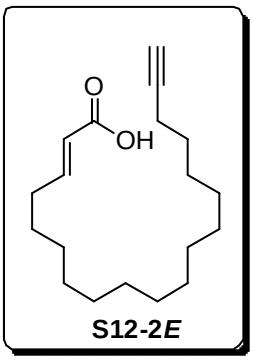


Scheme 7. Preparation of the (*E/Z*)-nonadec-2-en-18-ynoic acid **S12-2*E*/*Z***



To a solution of **S6-2** (16.20 mmol, 4.10 g) in CH_2Cl_2 (160 mL) was added the Dess-Martin periodinan (21.06 mmol, 8.90 g) at room temperature and the heterogeneous mixture (white precipitate) was stirred for 3 h. $NaHCO_{3sat}$ (120 mL) and then carefully $Na_2S_2O_5$ (26 g) were added and the mixture was stirred for 1 h filtered through a pad of Celite®, extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 5/1) afforded **S12-1** as a white solid in 51% yield (2.07 g).

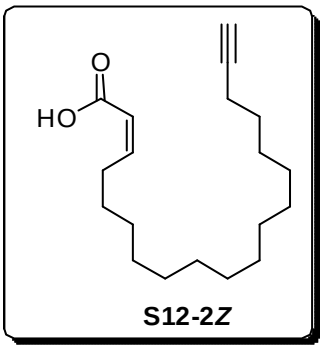
m.p. 62-64 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.75 (bs, 1H), 2.40 (td, *J* = 7.3, 1.6, 2H), 2.16 (td, *J* = 7.2, 2.7, 2H), 1.92 (bt, *J* = 2.7, 1H), 1.69-1.12 (m, 24H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 203.0, 84.9, 68.1, 44.0, 29.74 (2C), 29.72 and 29.70, 29.6, 29.55 and 29.48, 29.3, 29.2, 28.9, 28.6, 22.2, 18.5.
CI-HRMS: *m/z* calcd for $C_{17}H_{34}NO$ $[M+NH_4]^+$ 268.2640 found 268.2635.



To a suspension of NaH (16.20 mmol, 0.65 g, 60% in mineral oil) in THF (30 mL)was added dropwise triethyl phosphonoacetate (18.90 mmol, 3.70 mL) at 0°C.[7] After 30 min, the mixture was allowed to warm slowly to room temperature and **S12-1** (10.80 mmol, 2.70 g) was added by small portion. After 3 h, NH_4Cl_{sat} (30 mL) was added and the aqueous layer was extracted with EtOAc (2 x 70 mL). The combined organic extracts were washed with brine (1 x 70 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/AcOEt 25/1, *E*/*Z* > 99/1) afforded the unsaturated ester as a white solid in 60% yield (1.98 g). The ester was then hydrolyzed to the

corresponding carboxylic acid using the procedure described for **S9-2** and **S12-2*E*** was obtained as a white solid after purification by flash chromatography on silica gel (eluent hexanes/AcOEt 3/1) in 75% yield (1.42 g).

m.p. 68-70 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.08 (dt, *J* = 15.7, 7.1, 1H), 5.82 (d, *J* = 15.7, 1H), 2.28-2.10 (m, 4H), 1.93 (bt, *J* = 2.4, 1H), 1.58-1.17 (m, 25H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 152.6, 120.8, 84.9, 68.2, 32.4, 29.75 (2C) and 29.73 (2C), 29.6 (2C), 29.5, 29.3, 29.2, 28.9, 28.6, 28.0, 18.5.
CI-HRMS: *m/z* calcd for $C_{19}H_{36}NO_2$ $[M+NH_4]^+$ 310.2746 found 310.2750.

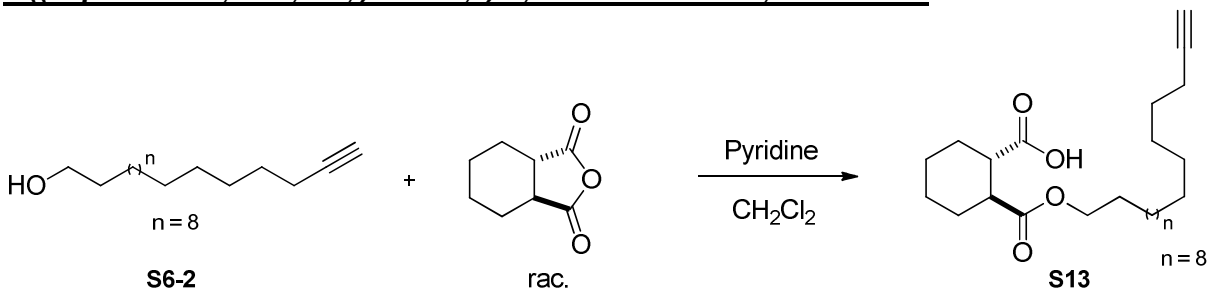


S12-2*Z*

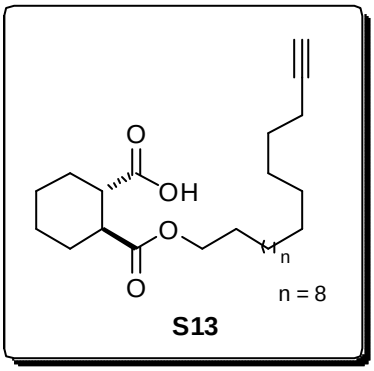
To a cooled solution (-78°C) of 18-crown-6 (43.2 mmol, 11.4 g) and bis(2,2,2-trifluoromethyl) (methoxycarbonyl methyl)-phosphate (15.12 mmol, 3.2 mL) in THF (150 mL) was added dropwise KHMDS (10.53 mmol, 21 mL, 0.5M in toluene) and the reaction mixture was stirred for 30 min. Then a solution of aldehyde **S12-1** (10.80 mmol, 2.7 g) in THF (16 mL) at -10°C was cannulated. After 1.5 h at -78°C, NH_4Cl_{sat} (120 mL) was added. The aqueous layer was extracted with AcOEt (2 x 100 mL) and the combined organic layers were washed with H_2O (1 x 150 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent pentane/Et_2O 50/1) afforded the unsaturated ester as a white solid in 14% yield (0.46 g, *Z*/*E* > 99/1). The ester was then hydrolyzed to the corresponding carboxylic acid using the procedure described for **S9-2** and **S12-2*Z*** was obtained as a white solid after purification by flash chromatography on silica gel (eluent hexanes/AcOEt 5/1) in 57% yield (0.25 g).

m.p. 72-74 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.35 (dt, J = 11.6, 6.4, 1H), 5.79 (app dt, J = 11.6, 1.8, 1H), 2.65 (m, 2H), 2.18 (td, J = 6.9, 2.6, 2H), 1.93 (t, J = 2.6, 1H), 1.61-1.17 (m, 25H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0, 153.7, 118.8, 85.0, 68.2, 29.78 (3C), 29.75, 29.70, 29.65, 29.57, 29.42, 29.37, 29.3, 29.1, 28.9, 28.7, 18.5.
CI-HRMS: *m/z* calcd for $C_{19}H_{36}NO_2$ $[M+NH_4]^+$ 310.2746 found 310.2747.

2-((heptadec-16-yn-1-yloxy)carbonyl)-cyclohexanecarboxylic acid S13



Scheme 8. Preparation of the 2-((heptadec-16-yn-1-yloxy)carbonyl)-cyclohexanecarboxylic acid **S13**



S13

To a solution of trans-1,2-cyclohexanedicarboxylic anhydride (7.50 mmol, 1.15 g) in dichloromethane (16 mL) was added **S6-2** (7.10 mmol, 1.80 g) and pyridine (10.60 mmol, 0.85 mL) at room temperature and the mixture was then stirred for 16 h. After dilution with dichloromethane (40 mL), the reaction mixture was washed with HCl (1M, 3x 25 mL), H_2O (1 x 20 mL), dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1) afforded **S13** as a white solid in 45% yield (1.30 g).

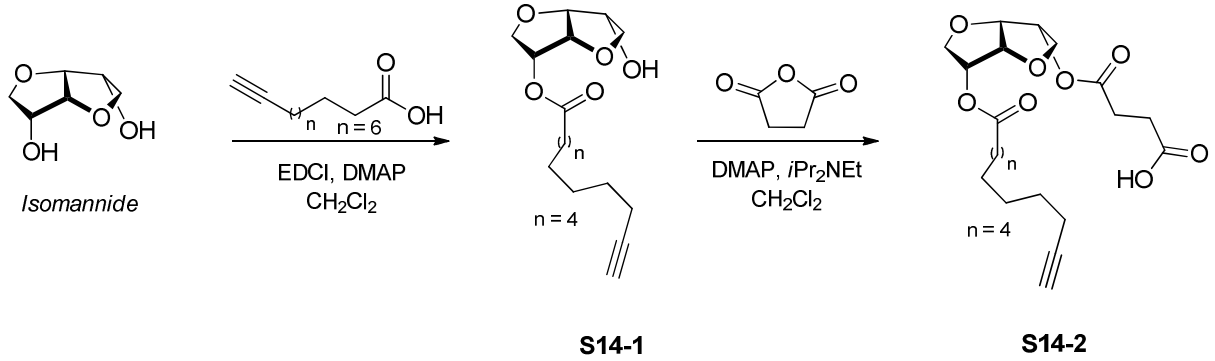
m.p. 55-58 °C

^{1}H NMR ($CDCl_3$, 300 MHz): δ 4.06 (m, 2H), 2.70-2.49 (m, 2H), 2.18 (td, *J* = 6.9, 2.4, 2H), 2.10 (bt, 2H), 1.93 (t, *J* = 2.4, 1H), 1.87-1.70 (m, 2H), 1.66-1.16 (m, 30H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 180.1, 175.1, 85.0, 68.2, 64.9, 44.8, 44.5, 29.82, 29.80 (2C) and 29.76 (2C), 29.7 (2C), 29.4, 29.3, 29.0 (2C), 28.9, 28.72 (2C) and 28.66, 26.0, 25.3, 18.5.

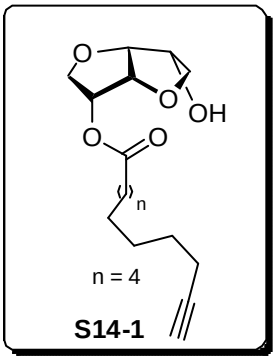
CI-HRMS: *m/z* calcd for $C_{25}H_{46}NO_4$ $[M+NH_4]^+$ 424.3427 found 424.3423.

4-oxo-4-(((3S,3aR)-6-(undec-10-ynoyloxy)hexahydrofuro[3,2-b]furan-3-yl)oxy)butanoic acid S14-2



S14-1 **S14-2**

Scheme 9. Preparation of the 4-oxo-4-(((3*S*,3a*R*)-6-(undec-10-ynoyloxy)hexahydrofuro[3,2-b]furan-3-yl)oxy)butanoic acid **S14-2**



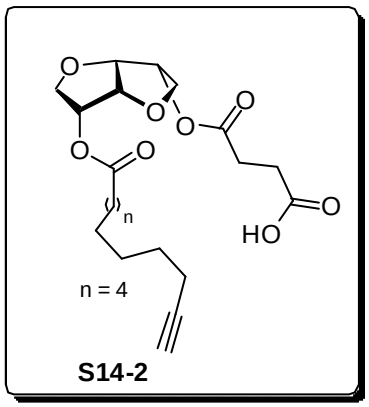
S14-1

To a solution of isomannide (44.2 mmol, 6.5 g) in CH_2Cl_2 (50 mL) at 0°C was added 10-undecynoic acid (19.2 mmol, 3.5 g), EDCI (44.2 mmol, 6 g) and DMAP (1.92 mmol, 0.23 g) and the homogeneous mixture was stirred at room temperature for 24 h.[8] The solution was diluted with CH_2Cl_2 (100 mL) and washed with HCl (2M, 2 x 50 mL) and H_2O (1 x 50 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/5) afforded **S14-1** as a viscous colorless oil in 67% yield (4.0 g).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.14 (app q, *J* = 6.2, 1H), 4.69 (t, *J* = 5.2, 1H), 4.47 (t, *J* = 5.2, 1H), 4.29 (m, 1H), 4.10 (dd, *J* = 9.3, 6.2, 1H), 3.96 (dd, *J* = 9.2, 6.2, 1H), 3.83 (dd, *J* = 9.3, 6.5, 1H), 3.57 (dd, *J* = 9.2, 7.0, 1H), 2.58 (bd, 1H), 2.37 (t, *J* = 7.8, 2H), 2.17 (td, *J* = 6.9, 2.6, 2H), 1.93 (t, *J* = 2.6, 1H), 1.70-1.22 (m, 12H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 84.8, 81.7, 80.6, 74.1, 74.0, 72.4, 71.0, 68.2, 34.0, 29.2, 29.1, 29.0, 28.8, 28.5, 24.9, 18.5.

CI-HRMS: *m/z* calcd for $C_{17}H_{30}NO_5$ $[M+NH_4]^+$ 328.2124 found 328.2126.
$[\alpha]_D^{19}$ = +88.2 (c = 1, $CHCl_3$).

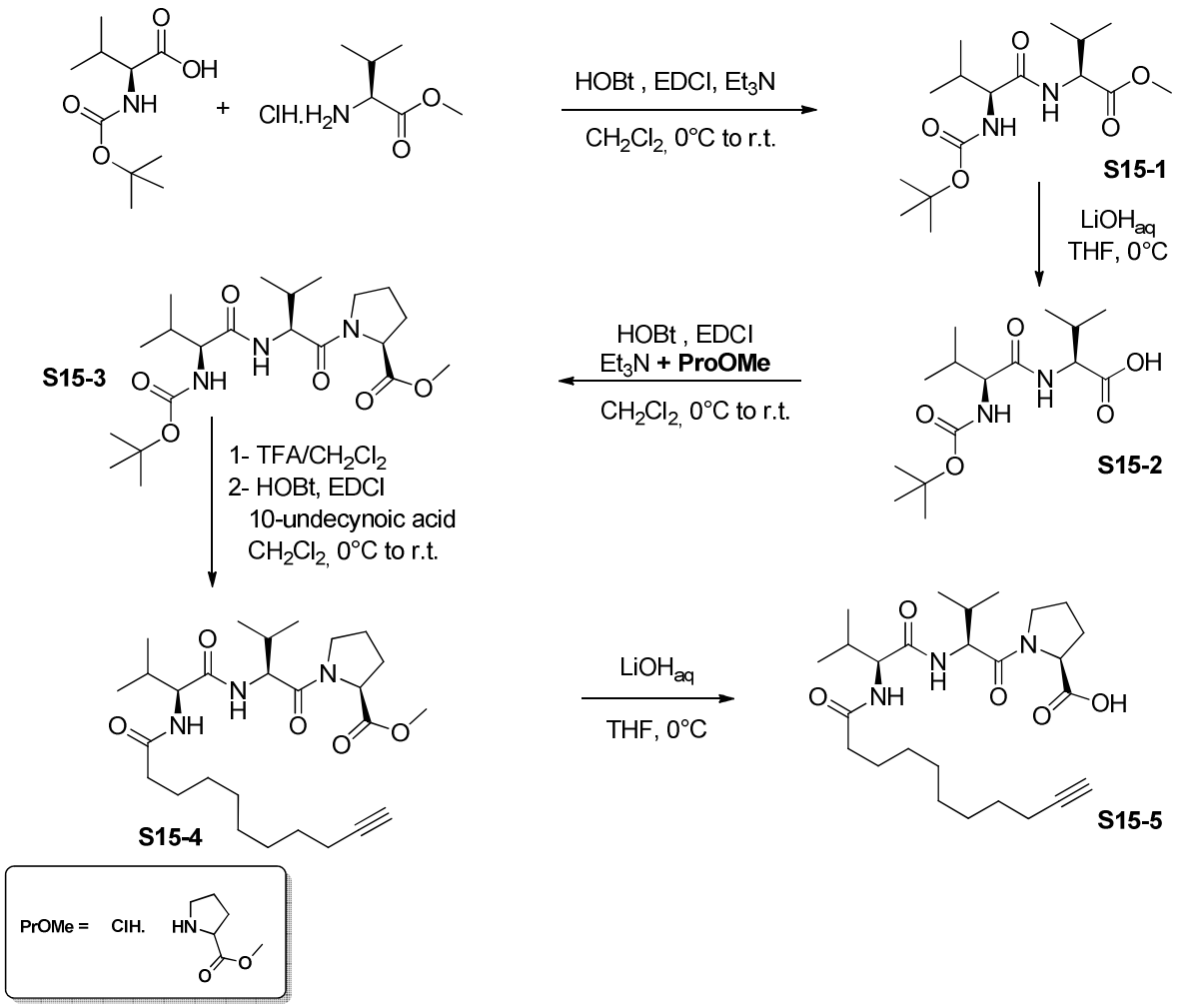


S14-2

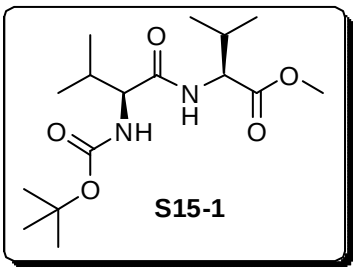
To a solution of **S14-1** (8.7 mmol, 2.7 g) in CH_2Cl_2 (25 mL) at 0°C was added succinic anhydride (10.0 mmol, 1.0 g), *i*Pr_2NEt (13.0 mmol, 2.3 mL) and a solution of DMAP (1.3 mmol, 0.16 g) in CH_2Cl_2 (2.5 mL) dropwise and the mixture was stirred at room temperature for 48 h.[9] The solution was diluted with CH_2Cl_2 (50 mL) and washed with HCl (1M, 3 x 25 mL) and H_2O (1 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent EtOAc 100% to EtOAc/MeOH 95/5) afforded **S14-2** as a white solid (after 2 days at -30°C) in 55% yield (2.0 g).

m.p. 60-65 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.10 (m, 2H), 4.68 (m, 2H), 4.03 (dd, *J* = 9.3, 6.5, 1H), 4.02 (dd, *J* = 9.3, 6.4, 1H), 3.81 (dd, *J* = 9.3, 6.8, 1H), 3.78 (dd, *J* = 9.3, 7.1, 1H), 2.78-2.63 (m, 4H), 2.37 (t, *J* = 7.6, 2H), 2.17 (td, *J* = 7.0, 2.7, 2H), 1.93 (t, *J* = 2.7, 1H), 1.70-1.22 (m, 12H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.0, 173.4, 171.7, 84.8, 80.51 and 80.47, 74.2, 73.6, 70.55 and 70.51, 68.3, 34.0, 29.2, 29.1, 29.0, 28.82 and 28.78, 28.7, 28.6, 24.9, 18.5.
CI-HRMS: *m/z* calcd for $C_{21}H_{34}NO_8$ $[M+NH_4]^+$ 428.2284 found 428.2287.
$[\alpha]_D^{19}$ = +109.0 (c = 1, $CHCl_3$).

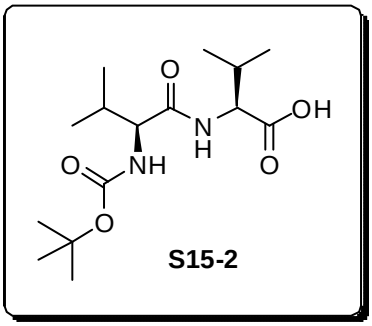
10-Undecyne-Val-Val-Pro-OH S15-5



Scheme 10. Preparation of the 10-Undecyne-Val-Val-Pro-OH **S15-5**

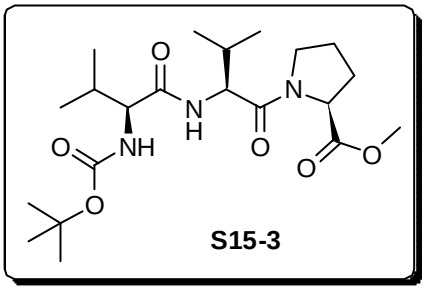


N-(*tert*-Butoxycarbonyl)-*L*-valine (9.90 mmol, 2.15 g) and *L*-valine methyl ester hydrochloride (11.88 mmol, 2.0 g) were dissolved in CH_2Cl_2 (37 mL) under argon at 0°C. Triethylamine (11.88 mmol, 1.7 mL) was added dropwise to the mixture and after 10 min, hydroxybenzotriazole (14.85 mmol, 2.0 g). After 15 min, EDCI (14.85 mmol, 2.3 g) was added and the yellowish solution was allowed to warm to room temperature and stirred for 15 h. The mixture was diluted with CH_2Cl_2 (30 mL) and washed with citric acid solution (5%, 35 mL) and $NaHCO_{3sat.}$ (35 mL). The organic layer was dried over $MgSO_4$ and concentrated under vacuum. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1 to 1/3) afforded the dipeptide **S15-1** as a white solid in 90% yield (2.94 g) and the analytical data were in complete agreement with those reported.[10,11]



S15-2

To a solution of dipeptide **S15-1** (7.60 mmol, 2.5 g) in THF (110 mL) at 0°C was added slowly over 10 min $LiOH_{aq}$ (0.2 N, 75 mL). After 3 h at 0°C, $NaHSO_4$ was added (0.2 N) until pH 2-3 was reached and the aqueous phase was subsequently extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, concentrated under vacuumand **S15-2** was isolated as a pure white solid in quantitative yield (2.4 g). The analytical data were in complete agreement with those reported.[12,13]

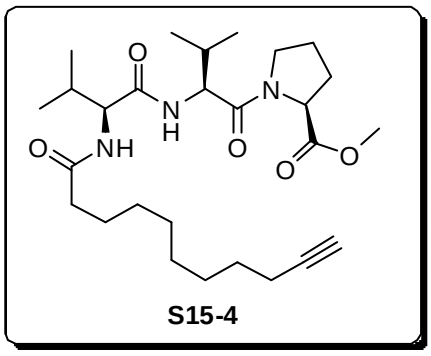


S15-3

Following the procedure described for the preparation of **S15-1** using **S15-2** (7.60 mmol, 2.5 g) and *L*-proline methyl ester hydrochloride (9.12 mmol, 1.5 g), **S15-3** was obtained as a viscous colorless oil (79% yield, 2.57 g) after purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1 to EtOAc 100%).

*^{1}H and ^{13}C NMR data of **S15-3** were recorded as a mixture of two rotamers (Note - Only the signals of the major rotamer are reported.)*

m.p. 88-90 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.66 (d, *J* = 8.9, 1H), 5.12-5.00 (m, 1H), 4.57 (dd, *J* = 8.9, 6.8, 1H), 4.46 (dd, *J* = 8.9, 5.2, 1H), 3.97-3.85 (m, 1H), 3.84-3.74 (m, 1H), 3.69-3.59 (m, 1H) and 3.68 (s, 3H), 2.24-1.83 (m, 6H), 1.40 (s, 9H), 1.01-0.81 (m, 12H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.5, 171.7, 170.4, 155.8, 79.8, 60.1, 58.9, 55.6, 52.2, 47.3, 31.3, 30.9, 29.1, 28.4 (3C), 25.0, 19.4 and 19.3, 17.8 and 17.7.
CI-HRMS: *m/z* calcd for $C_{21}H_{38}O_6N_3$ $[M+H]^+$ 428.2761 found 428.2766.
$[\alpha]_D^{19}$ = -51.3 (c = 2.30, $CHCl_3$)

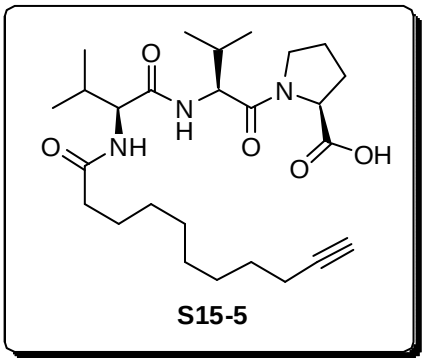


S15-4

The tripeptide **S15-3** (6.00 mmol, 2.56 g) was dissolved in a solution of TFA/CH_2Cl_2 (1:1, 20 mL) and stirred at room temperature for 3 h. The solvents were then evaporated under vacuum and the crude yellow oil was dissolved in dichloromethane, washed with $NaHCO_{3sat}$ (3 x 30 mL), dried over $MgSO_4$ and concentrated under vacuum. The deprotected tripeptide was isolated as a yellowish oil and used for the coupling reaction without further purification following the procedure described for **S15-1** using 10-undecynoic acid (7.20 mmol, 1.31 g, HOBt (9 mmol, 1.22 g) and EDCI (9 mmol, 1.39). Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1 to EtOAc 100%) afforded **S15-4** as a viscous colorless oil (yield = 65%, 1.92 g, calculated for two steps).

*^{1}H and ^{13}C NMR data of **S15-4** were recorded as a mixture of two rotamers (Note - Only the signals of the major rotamer are reported.)*

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.42 (d, *J* = 9.0, 1H), 6.00 (d, *J* = 8.6, 1H), 4.59 (dd, *J* = 9.0, 6.4, 1H), 4.51 (dd, *J* = 8.8, 5.4, 1H), 4.30 (dd, *J* = 8.6, 6.4, 1H), 3.91-3.75 (m, 1H), 3.72 (s, 3H), 3.70-3.51 (m, 1H), 2.28-1.94 (m, 8H), 1.93 (t, *J* = 2.6, 1H), 1.72-1.56 (m, 4H), 1.51 (m, 2H), 1.43-1.24 (m, 8H), 1.03-0.86 (m, 12H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 172.5, 171.4, 170.3, 84.9, 68.2, 58.9, 58.4, 55.7, 52.3, 47.4, 36.9, 31.4, 31.3, 29.3 (2C), 29.2, 28.6, 25.8, 25.2, 19.9, 19.5, 19.4, 18.5, 18.2, 17.8, 17.7.
CI-HRMS: *m/z* calcd for $C_{27}H_{46}O_5N_3$ $[M+H]^+$ 492.3437 found 492.3432.
$[\alpha]_D^{19}$ = -54.8 (c = 0.33, $CHCl_3$)



S15-5

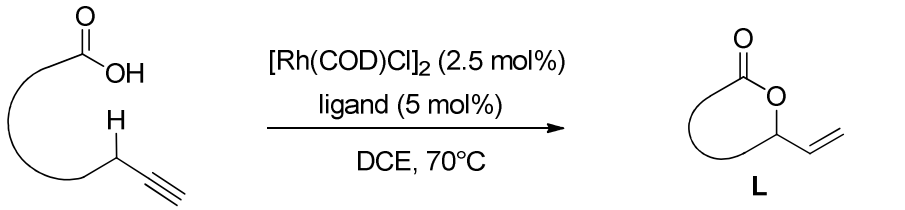
Following the procedure described for the preparation of **S15-2** using **S15-4** (3.6 mmol, 1.77 g), aqueous $LiOH_{aq}$ (0.2 N, 72 mL), **S15-5** was isolated as a white solid (yield = 89%, 1.53 g).

*^{1}H and ^{13}C NMR data of **S15-5** were recorded as a mixture of two rotamers (Note - Only the signals of the major rotamer are reported.)*

m.p. 105-106 °C
^{1}H NMR ($CDCl_3$, 400 MHz): δ 10.51 (bs, 1H), 7.74 (d, J = 8.6, 1H), 6.72 (d, J = 8.7, 1H), 4.57 (m, 1H), 4.48-4.37 (m, 2H), 4.00-3.78 (m, 1H), 3.88-3.78 (m, 1H), 3.72-3.62 (m, 1H), 2.30-1.83 (m, 11H), 1.62-1.51 (m, 2H), 1.51-1.42 (m, 2H), 1.38-1.19 (m, 8H), 0.98-0.78 (m, 12H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.9, 173.7, 172.0, 171.1, 84.7, 68.2, 59.3, 58.0, 56.0, 47.7, 36.7, 31.6, 31.2, 29.25, 29.23, 29.0, 28.7, 28.5, 25.8, 25.1, 19.5, 19.2, 19.1, 18.4, 18.2, 18.0.
CI-HRMS: *m/z* calcd for $C_{26}H_{44}O_5N_3$ $[M+H]^+$ 478.3281 found 478.3285.
$[\alpha]_D^{19}$ = -50.8 (c = 1, $CHCl_3$)

Lactonization and macrolactonization reactions

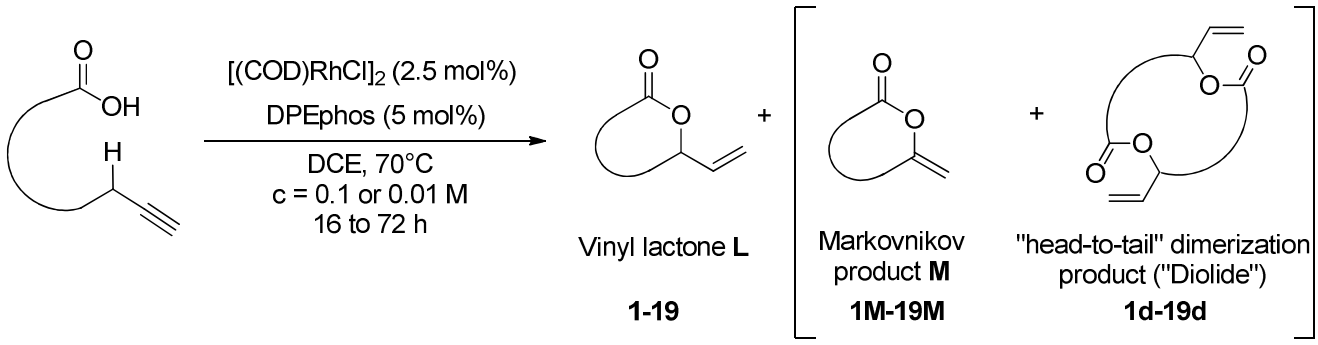
Optimization of the lactonization and macrolactonization reaction conditions:



entry	L	ligand	time (h)	[c][a]	yield (%)[b]	observations
1	**3**	DPEphos	16	0.1	53	yellow precipitate
2	**3**	DPEphos	16	0.01	26	yellow precipitate and complex mixture of by-products
3	**3**	DPEphos	16	0.5	22	yellow precipitate
4	**3**	DPPB[c]	16	0.1	49	complex mixture of by-products
5	**3**	DPPF[d]	16	0.1	44	yellow precipitate
6	**3**	DPPP[e]	16	0.1	34	complex mixture of by-products
7	**8**	DPEphos	16	0.01	18	27% conv.
8[f]	**8**	DPEphos	40	0.01	40	less than 10% of dimer (diolide)
9	**8**	DPEphos	40	0.01	55	less than 10% of dimer (diolide)
10	**8**	DPEphos	40	1	n.d.[g]	product/dimer (diolide) = 1/1

[a] Concentration in mol/L. [b] Isolated yield after purification by flash chromatography. [c] 1,4-Bis(diphenylphosphino)butane. [d] 1,1'-Bis-(diphenylphosphino)-ferrocene. [e] 1,3-Bis(diphenylphosphino)propane. [f] Syringe pump was used (addition over 6 hours). [g] Not determined.

General procedure for the lactonization and macrolactonization reactions



Scheme 11. Lactonization and macrolactonization *via* redox-neutral rhodium-catalyzed coupling of terminal alkynes with carboxylic acids.

General procedure 5: lactonization reaction (5 to 8-membered lactones).

A 10 ml Schlenk flask was flame-dried under vacuum, backfilled with argon (Argon 5.0 from Sauerstoffwerke Friedrichshafen) and cooled to room temperature using a standard Schlenk

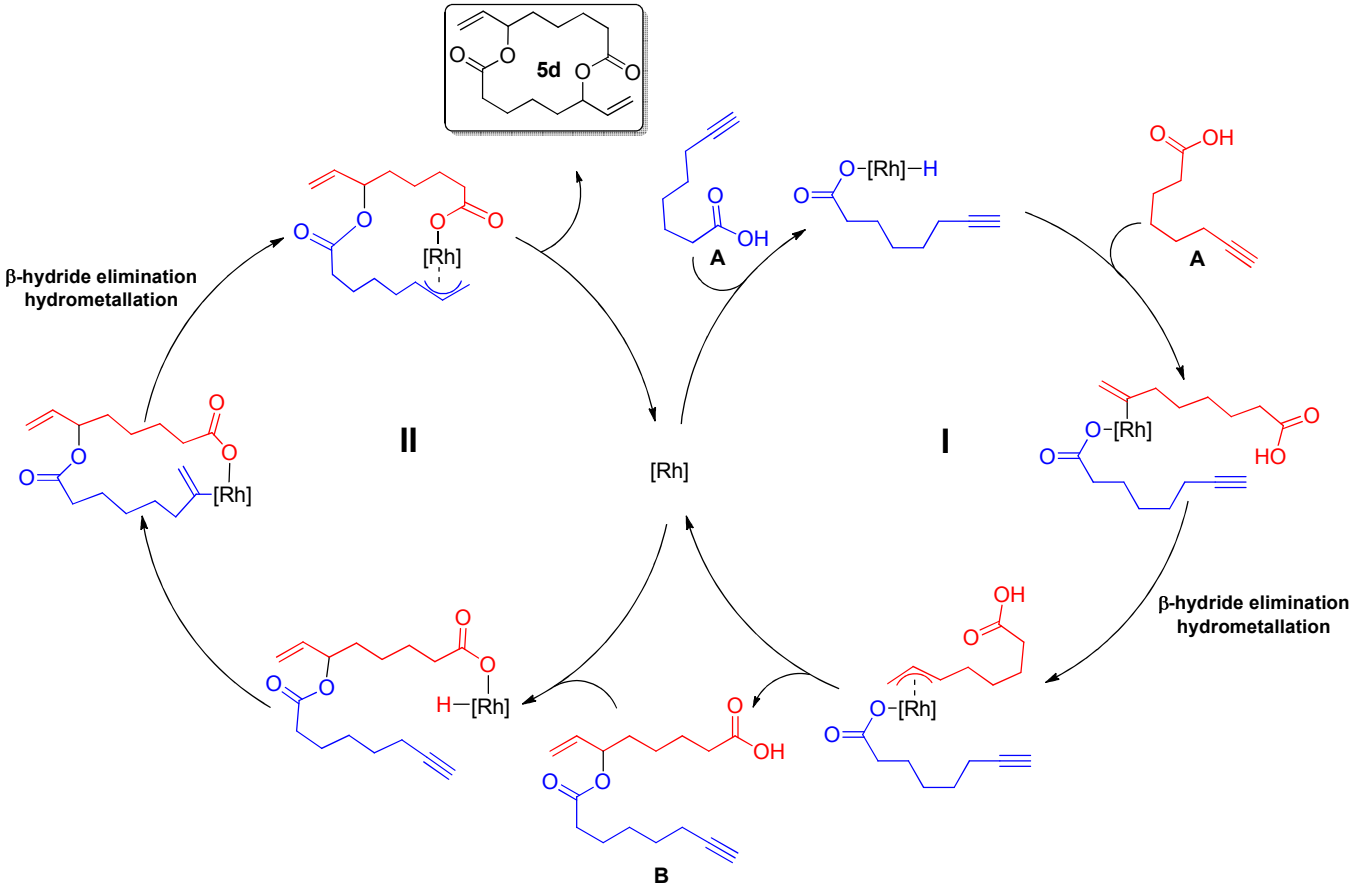
line apparatus. The Schlenk flask was then charged with 0.011 mmol (5.4 mg) of $[(COD)RhCl]_2$, 0.022 mmol (11.8 mg) of DPEphos, 0.44 mmol of alkynoic acid and 4.4 mL of freshly distilled 1,2-dichloroethane were then added under a flow of argon. The Schlenk flask was then sealed and the mixture stirred for 16 hours in a pre-heated oil bath at 70°C. After cooling to room temperature, the mixture was flushed through a plug of silica gel with dichloromethane and ethyl acetate. The solution was concentrated under vacuum and the crude mixture analysed by ^{1}H NMR and purified by flash chromatography on silica gel.

General procedure 6: macrolactonization reaction (12 to 23-membered macrolactones).

A 250 ml Schlenk flask was flame-dried under vacuum, backfilled with argon (Argon 5.0 from Sauerstoffwerke Friedrichshafen) and cooled to room temperature using a standard Schlenk line apparatus. The Schlenk flask was then charged with 0.022 mmol (10.8 mg) of $[(COD)RhCl]_2$, 0.044 mmol (23.6 mg) of DPEphos and 88 mL of freshly distilled 1,2-dichloroethane were then added under a flow of argon. The solution was allowed to stir for 30 min at room temperature. Subsequently, 0.88 mmol of alkynoic acid was added. The Schlenk flask was sealed and the mixture stirred for 40 or 72 hours in a pre-heated oil bath at 70°C. After cooling to room temperature, the mixture was flushed through a plug of silica gel with dichloromethane and ethyl acetate. The solution was concentrated under vacuum and the crude mixture analysed by ^{1}H NMR and purified by flash chromatography on silica gel.

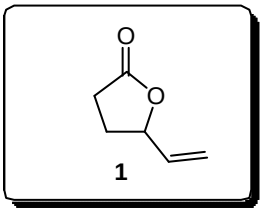
Formation of the dimer (diolide):

The formation of the dimer or diolide (e.g. for the formation of the 14-membered diolide **5d** see Scheme 12) occurs by an intermolecular redox-neutral rhodium-catalyzed coupling between two alkynoic acids (**A**) leading to a branched allylic ester **B** (catalytic cycle **I**). The remaining alkyne and carboxylic acid functions of **B** react in an intramolecular manner (macrolactonization reaction, catalytic cycle **II**) to finally furnish the dimer or diolide (14-membered macrocycle **5d**).



Scheme 12. Proposed mechanism for the formation of the 14-membered diolide **5d**.

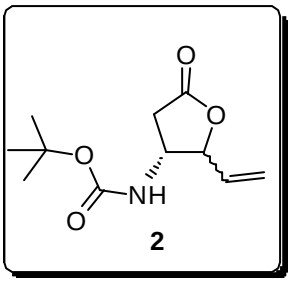
Characterization data of the lactones



1 was prepared according to the *general procedure 5* starting from hex-5-ynoic acid (0.44 mmol, 49.3 mg). The crude reaction mixture (**1**/**1d** > 98/2, **1**/**1M** = 85/15) was purified by flash chromatography on silica gel (pentane/Et_2O 1/1) and the γ-vinyl lactone **1** was separated from the corresponding exocyclic enol lactone **1M** and obtained as a colorless oil (yield = 62%, 30.6 mg, conversion > 98%).

Note – Product volatile.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.89 (ddd, *J* = 17.0, 10.5, 5.9, 1H), 5.37 (m, *J* = 17.0, 1H), 5.26 (dt, *J* = 10.5, 1.1, 1H), 4.94 (m, 1H), 2.58-2.49 (m, 2H), 2.42 (m, 1H), 2.07-1.93 (m, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 177.0, 135.7, 117.6, 80.6, 28.44 and 28.39.
CI-HRMS: *m/z* calcd for $C_6H_{12}O_2N\,[M+NH_4]^+$ 130.0868 found 130.0870.



2 was prepared according to the *general procedure 5* (using 0.016 mmol of $[Rh(COD)Cl]_2$ and 0.032 mmol of DPEphos) starting from (*S*)-3-(Boc-amino)-5-hexynoic acid (0.44 mmol, 100 mg). The crude reaction mixture (**2-A/B**/**2d** > 98/2, **2-A/B/2M** > 98/2) was purified by flash chromatography on silica gel (eluent hexanes/AcOEt 5/1) and the γ-vinyl lactones **2-A** and **2-B** were separated and obtained as pure colorless oils (yield (**2-A** and **2-B**) = 71%, 71 mg, **2-A/2-B** = 83/17, conversion > 98%).

γ-vinyl lactone 2-A *(major diastereomer (R,S) / first eluted)*

$[\alpha]_D^{19}$ = -6.0 (c = 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ 5.92 (ddd, *J* = 17.2, 10.5, 5.1, 1H), 5.42 (bd, *J* = 17.2, 1H), 5.31 (bd, *J* = 10.5, 1H), 5.00-4.88 (m, 1H), 4.84-4.72 (m, 1H), 4.21-4.05 (m, 1H_1), 2.87 (dd, *J* = 17.8, 7.9, 1H), 2.43 (dd, *J* = 17.8, 4.9, 1H), 1.44 (s, 9H).
^{13}C NMR ($CDCl_3$, 100 MHz, 263 K): δ 175.1, 155.1, 133.0, 118.3, 85.4, 80.7, 52.3, 34.0, 28.3 (3C).
CI-HRMS: *m/z* calcd for $C_{11}H_{21}N_2O_4\,[M+NH_4]^+$ 245.1501 found 245.1502.

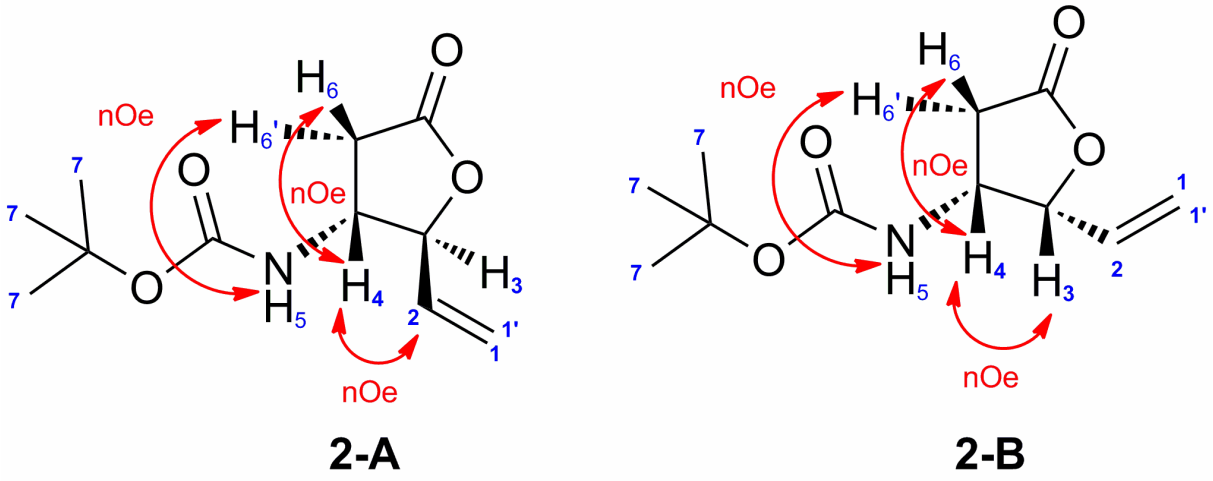
γ-vinyl lactone 2-B *(minor diastereomer (R,R) / second eluted)*

$[\alpha]_D^{19}$ = +67.0 (c = 0.66, $CHCl_3$)

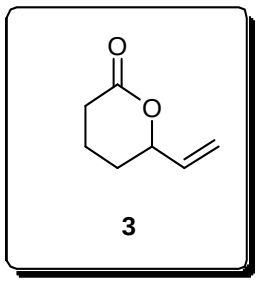
^{1}H NMR ($CDCl_3$, 300 MHz, 298 K): δ 5.82 (ddd, *J* = 17.2, 10.8, 5.2, 1H_2), 5.52 (app dt, *J* = 17.2, 1.3, 1H_1), 5.44 (app dt, *J* = 10.8, 1.3, 1$H_{1'}$), 5.12-5.01 (m, 1H_3), 4.77-4.62 (m, 1H_5), 4.60-4.45 (m, 1H_4), 2.86 (dd, *J* = 17.7, 7.5, 1H_6), 2.51 (dd, *J* = 17.7, 4.8, 1$H_{6'}$), 1.43 (s, 9H_7).
^{13}C NMR ($CDCl_3$, 100 MHz, 263 K): δ 174.8, 155.0, 130.0, 119.9, 81.9, 80.6, 50.0, 35.8, 28.3 (3C).
CI-HRMS: *m/z* calcd for $C_{11}H_{21}N_2O_4\,[M+NH_4]^+$ 245.1501 found 245.1504.

Determination of the aboslute configuration of the γ-vinyl lactones 2-A and 2-B by nOe experiments.

nOe experiments of 2-A and 2-B (recorded at 263K)



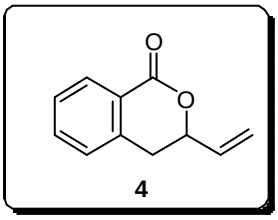
The nOe signal between **H_2-H_4**, H_4-H_6 and H_5-$H_{6'}$ for the γ-vinyl lactone **2-A** led to the assignment of the absolute configuration as the (*R*,*S*)-diastereomer. In reverse conclusion, the nOe signals between **H_3-H_4**, H_4-H_6 and H_5-$H_{6'}$ for the γ-vinyl lactone **2-B** led to the assignment of the absolute configuration as the (*R*,*R*)-diastereomer.



3 was prepared according to the *general procedure 5* starting from hept-6-ynoic acid (0.44 mmol, 55.5 mg). The crude reaction mixture (**3**/**3d** > 98/2, **3**/3**M** = 95/5) was purified by flash chromatography on desactivated silica gel (eluent hexanes/Et_2O 1/1 + 5% Et_3N) and **3** was obtained as a colorless oil and as a mixture of isomers (**3**/**3M** = 95/5, yield = 53%, 29.5 mg, conversion > 90%).[14] [Note – A yellow precipitate was formed after 16 h of reaction time but characterization of this solid failed due to its insolubility)

Note – Product unstable (stored at -30°C).

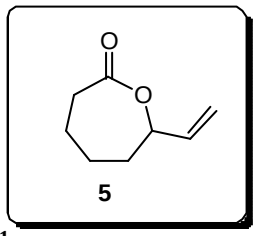
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.86 (ddd, *J* = 17.2, 10.6, 5.5, 1H), 5.33 (dt, *J* = 17.2, 1.3, 1H), 5.22 (dt, *J* = 10.6, 1.3, 1H), 4.85-4.77 (m, 1H), 2.64-2.40 (m, 2H), 2.04-1.79 (m, 3H), 1.71-1.58 (m, 1H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.2, 136.2, 116.9, 80.3, 29.6, 28.0, 18.1.



4 was prepared according to the *general procedure 5* starting from **S3-3** (0.44 mmol, 76.6 mg). The crude reaction mixture (**4**/**4d** > 98/2, **4**/**4M** > 98/2) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1) and **3** was obtained as a colorless oil (yield = 47%, 36.0 mg, conversion = 84%). [Note – A yellow precipitate was formed after 8h of reaction time but characterization of this solid failed due to its insolubility).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.11 (dd, *J* = 7.6, 1.2, 1H), 7.54 (td, *J* = 7.6, 1.5, 1H), 7.40 (t, *J* = 7.6, 1H), 7.25 (d, *J* = 7.6, 1H), 6.02 (ddd, *J* = 17.2, 10.7, 5.6, 1H), 4.46 (app dt, *J* = 17.2, 1.0, 1H), 5.32 (app dt, *J* = 10.7, 1.0, 1H), 5.04 (m, 1H), 3.10-3.03 (m, 2H).

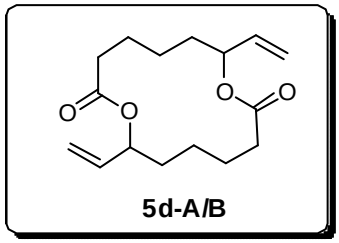
^{13}C NMR ($CDCl_3$, 100 MHz): δ 165.2, 138.6, 135.2, 134.0, 130.5, 127.9, 127.5, 125.3, 118.3, 78.7, 33.4.
EI-HRMS: *m/z* calcd for $C_{11}H_{10}O_2$ [M]$^+$ 174.0681 found 174.0681.



5

5 was prepared according to the *general procedure 5* starting from 7-Octynoic acid **S1-2** (0.44 mmol, 61.7 mg). The crude reaction mixture (**5**/**5M** > 98/2 + **5d**) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 5/1) and pure **5** was obtained as a colorless oil (yield = 34%, 21 mg, conversion > 98%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.90 (ddd, *J* = 17.1, 10.5, 5.8, 1H), 5.35 (dt, *J* = 17.1, 1.3, 1H), 5.18 (dt, *J* = 10.5, 1.3, 1H), 4.74 (m, 1H), 2.77-2.55 (m, 2H), 2.06-1.86 (m, 3H), 1.81-1.49 (m, 4H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.0, 136.9, 116.1, 80.6, 35.2, 35.1, 28.3, 22.9.
CI-HRMS: *m/z* calcd for $C_8H_{13}O_2$ [M+H]$^+$ 141.0915 found 141.0913.

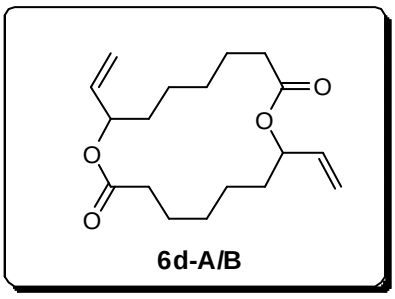


5d-A/B

5d (1st eluted) was separated from **5** (2nd eluted) by flash chromatography (eluent hexanes/EtOAc 5/1) and obtained as a colorless oil and as a mixture of two diastereomers [**5d-A** and **5d-B** (*d.r. not determined*)] (22% yield, 13.6 mg).

*^{1}H and ^{13}C NMR data of **5d** were recorded as a mixture of two diastereomers (**5d-A** and **5d-B**) (^{1}H NMR data reported for only one diastereomer-**5d-A**).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.89-5.71 (m, 2H), 5.44-5.27 (m, 2H), 5.22 (bd, *J* = 17.1, 1H), 5.14 (m, 1H), 2.51-2.25 (m, 4H), 1.79-1.30 (m, 12H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.1, 136.5, 116.1, 73.3, 35.1, 33.8, 25.3, 23.6.
^{13}C NMR ($CDCl_3$, 100 MHz): (*second diastereomer*) δ 172.8, 137.0, 115.9, 74.1, 34.5, 34.2, 25.0, 24.8.
CI-HRMS: *m/z* calcd for $C_{16}H_{28}O_4N$ [M+NH_4]$^+$ 298.2018 found 298.2017.



6d-A/B

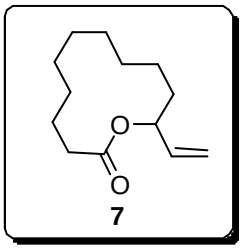
6d was obtained from 8-nonynoic acid **S2-2** (0.44 mmol, 67.8 mg) using the *general procedure 5*. The crude reaction mixture was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 10/1). and **6d** was isolated as a colorless oil and as a mixture of two diastereomers [**6d-A** and **6d-B** (*d.r. not determined*)] (yield = 42%, 28.5 mg, conversion = 74%). *(No trace of the 8-membered lactone **6** was detected in the crude ^{1}H NMR spectrum).*

*^{1}H and ^{13}C NMR data of **6d** were recorded as a mixture of two diastereomers (**6d-A** and **6d-B**) (^{1}H NMR data reported for only one diastereomer-**6d-A**).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.79 (m, 2H), 5.36-5.21 (m, 2H), 5.13 (dt, *J* = 17.3, 1.3, 2H), 5.12 (dt, *J* = 10.6, 1.3, 1H), 2.46-2.24 (m, 4H), 1.85-1.56 (m, 5H), 1.46-1.19 (m, 11H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 136.9, 115.94, 74.4, 34.4, 34.13, 28.7, 25.0, 24.4.
^{13}C NMR ($CDCl_3$, 100 MHz): (*second diastereomer*) δ 172.9, 136.8, 115.90, 73.6, 34.2, 34.08, 28.4, 24.8, 24.1.
CI-HRMS: *m/z* calcd for $C_{18}H_{32}O_4N$ $[M+NH_4]^+$ 326.2331 found 326.2334.

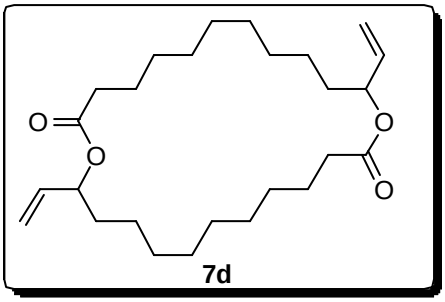
Characterization data of the macrolactones



7 was prepared according to the *general procedure 6* starting from tridec-12-ynoic acid **S4-3** (0.88 mmol, 185 mg). The crude mixture (**7**/7**M** = 92/8 + **7d**) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 25/1) and **7** was obtained as a colorless oil and as a mixture of isomers (**7**/**7M** = 92/8, yield = 30%, 55.5 mg, conversion > 98%).

*^{1}H and ^{13}C NMR data of **7** were recorded as a mixture of **L** (**7**) and **M** (**7M**).*

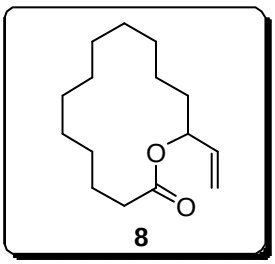
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.84 (ddd, *J* = 17.2, 10.6, 5.6, 1H), 5.50-5.42 (m, 1H), 5.23 (app dt, *J* = 17.2, 1.4, 1H), 5.14 (app dt, *J* = 10.6, 1.4, 1H), 2.57-2.45 (m, 1H), 2.33-2.19 (m, 1H), 1.88-1.55 (m, 4H), 1.50-1.19 (m, 12H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.6, 136.6, 115.7, 73.7, 35.1, 31.2, 25.7, 25.0, 24.9, 23.90, 23.87, 23.6, 20.9.
CI-HRMS: *m/z* calcd for $C_{13}H_{26}O_2N$ $[M+NH_4]^+$ 228.1963 found 228.1962.



7d (2nd eluted) was separated from **7** (1st eluted) by flash chromatography (eluent hexanes/EtOAc 25/1) and obtained as colorless oil and as a mixture of two diastereomers [**7d-A** and **7d-B** (*d.r. not determined*)] (yield = 24%, 44.4 mg).

*^{1}H and ^{13}C NMR data of **7d** were recorded as a mixture of two diastereomers (**7d-A** and **7d-B**) (^{1}H NMR data reported for only one diastereomer-**7d-A**).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.80 (ddd, *J* = 17.1, 10.5, 6.0, 2H), 5.30 (m, 2H), 5.21 (app dt, *J* = 17.1, 1.3, 2H), 5.12 (app dt, *J* = 10.5, 1.3, 2H), 2.37-2.27 (m, 4H), 1.73-1.54 (m, 6H), 1.41-1.17 (m, 26H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 137.1, 116.0, 74.0, 34.8, 34.3, 29.5, 29.4 (2C), 29.3, 28.9, 25.3, 25.0
CI-HRMS: *m/z* calcd for $C_{26}H_{45}O_4$ $[M+H]^+$ 421.3318 found 421.3312.

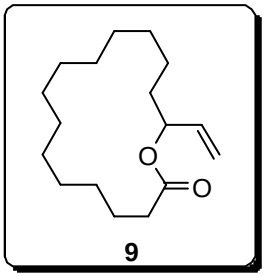


8 was prepared according to the *general procedure 6* starting from pentadec-14-ynoic acid **S5-3** (0.88 mmol, 210 mg). The crude mixture (**8**/**8d** > 90/10, **8**/**8M** = 98/2) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 25/1) and **8** was obtained as a

colorless oil and as a mixture of isomers (**8**/**8M** = 98/2, yield = 55%, 115 mg, conversion = 80%).

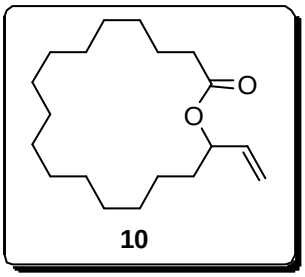
*^{1}H and ^{13}C NMR data of **8** were recorded as a mixture of **L** (**8**) and **M** (**8M**).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.82 (ddd, *J* = 17.1, 10.6, 5.7, 1H), 5.36 (m, 1H), 5.22 (app, dt, *J* = 17.1, 1.4, 1H), 5.12 (app dt, *J* = 10.6, 1.4, 1H), 2.53-2.40 (m, 1H), 2.36-2.25 (m, 1H), 1.80-1.16 (m, 20H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 137.1, 115.7, 73.7, 34.5, 33.6, 26.5, 26.2, 26.0, 25.7, 25.6, 25.0, 24.04, 24.02, 22.0,
CI-HRMS: *m/z* calcd for $C_{15}H_{30}O_2N$ $[M+NH_4]^+$ 256.2276 found 256.2272.



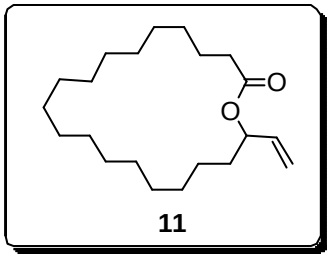
9 was prepared according to the *general procedure 6* starting from heptadec-16-ynoic acid **S6-3** (0.88 mmol, 234 mg). The crude mixture (**9**/**9d** > 95/5, **9**/**9M** > 98/2) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 25/1) and **9** was obtained as a colorless oil (yield = 74%, 173 mg, conversion > 98%).

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.81 (ddd, *J* = 17.1, 10.6, 5.8, 1H), 5.32 (m, 1H), 5.21 (app dt, *J* = 17.1, 1.3, 1H), 5.12 (app dt, *J* = 10.6, 1.3, 1H), 2.44-2.24 (m, 2H), 1.81-1.53 (m, 4H), 1.47-1.19 (m, 20H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 137.1, 115.8, 74.3, 34.8, 34.3, 27.9, 27.6, 27.4, 27.3, 26.8, 26.4, 26.2, 25.88, 25.86, 25.1, 24.1,
CI-HRMS: *m/z* calcd for $C_{17}H_{34}O_2N$ $[M+NH_4]^+$ 284.2589 found 284.2592.



10 was prepared according to the *general procedure 6* starting from nonadec-18-ynoic acid **S7-3** (0.88 mmol, 259 mg). The crude mixture (**10**/**10d** > 95/5, **10**/**10M** > 98/2) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 25/1) and **10** was obtained as a colorless oil (yield = 69%, 178mg, conversion > 98%).

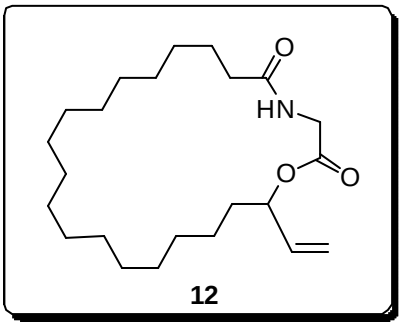
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.81 (ddd, *J* = 17.1, 10.6, 6.0, 1H), 5.29 (m, 1H), 5.21 (app dt, *J* = 17.1, 1.4, 1H), 5.13 (app dt, *J* = 10.6, 1.4, 1H), 2.43-2.23 (m, 2H), 1.78-1.48 (m, 4H), 1.44-1.16 (m, 24H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 137.0, 116.0, 74.4, 35.0, 34.4, 28.6, 28.5, 28.3, 28.1, 27.6, 27.35, 27.27, 27.19, 27.17, 26.7, 26.3, 25.2, 24.5.
EI-HRMS: *m/z* calcd for $C_{19}H_{34}O_2$ $[M]^+$ 294.2559 found 294.2564.



11 was prepared according to the *general procedure 6* starting from henicos-20-ynoic acid **S8-3** (0.88 mmol, 284 mg). The crude mixture (**11**/**11d** > 90/10, **11**/**11M** > 98/2) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 50/1) and **11**

was obtained as a colorless oil (yield = 67%, 190 mg, conversion > 98%).

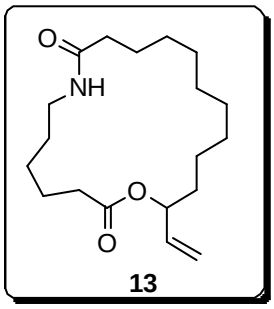
^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.79 (ddd, *J* = 17.2, 10.6, 6.0, 1H), 5.28 (m, 1H), 5.21 (app dt, *J* = 17.2, 1.4, 1H), 5.12 (app dt, *J* = 10.6, 1.4, 1H), 2.39-2.25 (m, 2H), 1.74-1.53 (m, 4H), 1.42-1.21 (m, 28H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 137.1, 116.0, 74.4, 34.9, 34.3, 29.0, 28.78, 28.76, 28.7, 28.3, 28.12 (2C), 28.10, 27.7, 27.44, 27.37, 27.3, 27.1, 25.2, 24.9.
EI-HRMS: *m/z* calcd for $C_{21}H_{38}O_2$ $[M]^+$ 322.2872 found 322.2868.



12 was prepared according to the *general procedure 6* starting from **S9-2** (0.88 mmol, 334mg). The crude mixture (**12**/**12d** > 98/2, **12**/**12M** = 80/20) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 2/1) and **12** was obtained as a white solid and as a mixture of isomers (**12**/**12M** = 80/20, yield = 65%, 217 mg, conversion > 98%).

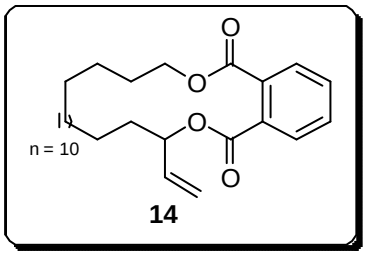
*^{1}H and ^{13}C NMR data of **12** were recorded as a mixture of **L (12)** and **M (12M)**.*

m.p. 94-95 °C
^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.00-5.87 (m, 1H), 5.79 (ddd, *J* = 17.0, 10.6, 6.5, 1H), 5.36 (m, 1H), 5.24 (app dt, *J* = 17.0, 1.1, 1H), 5.17 (app dt, *J* = 10.6, 1.1, 1H), 4.15 (dd, *J* = 18.3, 5.3, 1H), 3.97 (dd, *J* = 18.3, 4.4, 1H), 2.35-2.13 (m, 2H), 1.80-1.15 (m, 32H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 169.5, 136.2, 117.1, 76.1, 41.7, 36.6, 34.1, 28.9, 28.83, 28.81, 28.78, 28.75, 28.71, 28.67 (2C), 28.57, 28.51, 28.48, 28.3, 28.2, 25.6, 24.8.
EI-HRMS: *m/z* calcd for $C_{23}H_{41}O_3N$ $[M]^+$ 379.3092 found 379.3086.



13 was prepared according to the *general procedure 6* starting from **S10-2** (0.22 mmol, 71.2 mg). The crude mixture (**13**/**13d** > 98/2, **13**/**13M** > 98/2) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 1/3) and **13** was obtained as a white solid (yield = 71%, 50.5 mg, conversion > 98%).

m.p. 90-92 °C
^{1}H NMR ($CDCl_3$, 400MHz): δ 5.79 (ddd, *J* = 17.1, 10.5, 6.0, 1H), 5.63-5.52 (m, 1H), 5.36-5.27 (m, 1H), 5.21 (app dt, *J* = 17.1, 1.4, 1H), 5.13 (app dt, *J* = 10.5, 1.4, 1H), 3.53-3.41 (m, 1H), 3.22-3.08 (m, 1H), 2.43-2.28 (m, 2H), 2.22-2.10 (m, 2H), 1.70-1.17 (m, 22H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.5, 173.2, 137.0, 116.2, 74.2, 39.0, 37.0, 34.2, 33.8, 28.9, 28.35, 28.31, 28.10, 28.06, 28.0, 26.1, 25.7, 24.2, 24.1,
CI-HRMS: *m/z* calcd for $C_{19}H_{34}O_3N$ $[M+H]^+$ 324.2539 found 324.2532.

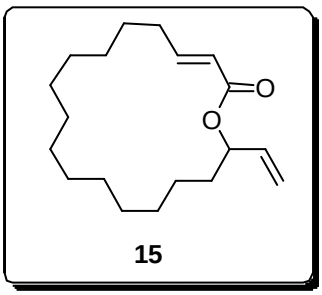


14

14 was prepared according to the *general procedure 6* starting from **S11** (0.88 mmol, 377 mg). The crude mixture (**14**/**14d** > 98/2, **14**/**14M** > 91/9) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 1/1) and **14** was obtained as a colorless oil and as a mixture of isomers (yield = 61%, 230 mg, conversion > 98%).

*^{1}H and ^{13}C NMR data of **14** were recorded as a mixture of **L** (**14**) and **M** (**14M**).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.77-7.65 (m, 2H), 7.59-7.47 (m, 2H), 5.88 (ddd, *J* = 17.2, 10.6, 6.8, 1H), 5.45 (m, 1H), 5.33 (bd, *J* = 17.2, 1H), 5.22 (bd, *J* = 10.6, 1H), 4.35-4.20 (m, 2H), 1.86-1.60 (m, 4H), 1.47-1.18 (m, 26H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.0, 166.7, 136.4, 132.7, 132.3, 131.1, 130.9, 129.1, 128.9, 117.3, 76.5, 66.0, 34.3, 29.1, 28.7, 28.6, 28.54, 28.50, 28.3, 28.1, 27.7, 27.5, 27.4, 27.3, 27.2, 25.8, 25.1.
CI-HRMS: *m/z* calcd for $C_{27}H_{41}O_4$ $[M+H]^+$ 429.3005 found 429.3006.

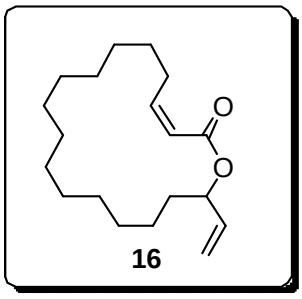


15

15 was prepared according to the *general procedure 6* starting from **S12-2*E*** (0.88 mmol, 257 mg). The crude mixture [**15**/**15d** > 85/15, **15**/**15M** = 98/2 (< 2% of (*Z*)-*anti*-Markovnikov isomer detected)] was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 25/1) and **15** was obtained as a colorless oil and as a mixture of isomers (**15**/**15M** = 98/2, yield = 51%, 131 mg, conversion = 90%).

*^{1}H and ^{13}C NMR data of **15** were recorded as a mixture of **L** (**15**) and **M** (**15M**). Due to the presence of conformers in $CDCl_3$, the ^{1}H and ^{13}C NMR spectra of **15** were recorded in C_6D_6.*

^{1}H NMR (C_6D_6, 300 MHz): δ 6.95 (dt, *J* = 15.5, 7.7, 1H), 5.85 (app dt, *J* = 15.5, 1.3, 1H), 5.79 (ddd, *J* = 17.2, 10.5, 5.5, 1H), 5.67-5.58 (m, 1H), 5.26 (app dt, *J* = 17.2, 1.3, 1H), 5.01 (app dt, *J* = 10.5, 1.3, 1H), 1.93-1.78 (m, 2H), 1.60-1.01 (m, 24H).
^{13}C NMR (C_6D_6, 100 MHz): δ 165.4, 149.0, 137.8, 122.9, 115.3, 73.4, 34.5, 31.5, 28.5 (2C), 28.4, 28.2, 28.0, 27.6, 27.2, 27.1, 26.8, 26.3, 23.9,
CI-HRMS: *m/z* calcd for $C_{19}H_{36}NO_2$ $[M+NH_4]^+$ 310.2746 found 310.2748.

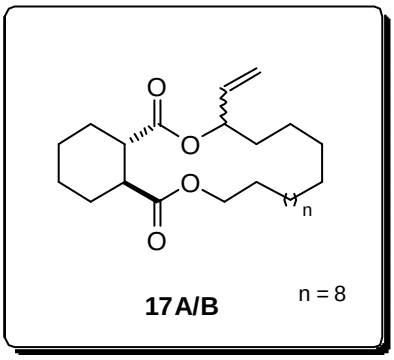


16

16 was prepared according to the *general procedure 6* (using 0.0094 mmol of $[Rh(COD)Cl]_2$ and 0.019 mmol of DPEphos) starting from **S12-2*Z*** (0.25 mmol, 73.1 mg). The crude mixture **16**/**16d** > 95/5, **16**/**16M** = 97/3) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 25/1) and **16** was obtained as a colorless oil and as a mixture of isomers (**16**/**16M** = 97/3, yield = 64%, 46.9 mg, conversion > 95%).

*^{1}H and ^{13}C NMR data of **16** were recorded as a mixture of **L** (**16**) and **M** (**16M**).*

^{1}H NMR (C_6D_6, 300 MHz): δ 6.19 (ddd, *J* = 11.5, 9.8, 6.2, 1H), 5.89-5.76 (m, 2H), 5.44-5.36 (m, 1H), 5.24 (app dt, *J* = 17.3, 1.3, 1H), 5.13 (app dt, *J* = 10.51.3, 1H), 3.17-3.02 (m, 1H), 2.37-2.22 (m, 1H), 1.76-1.15 (m, 24H).
^{13}C NMR (C_6D_6, 100 MHz): δ 166.1, 150.3, 137.2, 120.4, 116.1, 73.8, 34.4, 28.7, 28.4, 28.2, 27.98, 27.93, 27.87, 27.6, 27.1, 26.8, 26.5, 26.4, 24.5.
CI-HRMS: *m/z* calcd for $C_{19}H_{36}NO_2$ $[M+NH_4]^+$ 310.2746 found 310.2750.

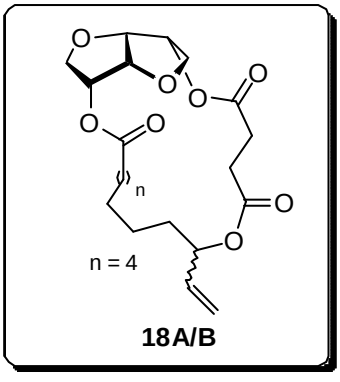


17A/B

17 was prepared according to the *general procedure 6* starting from **S13** (0.88 mmol, 358 mg). The crude mixture **17**/**17d** > 98/2, **17**/**17M** = 98/2, **d.r** (**17A**/**17B**) = 57/43) was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 5/1) and **17** was obtained as a colorless oil and as a mixture of two diastereomers (**17A** and **17B**) together with **17M** (**17**/**17M** = 98/2, **d.r** (**17A**/**17B**) = 57/43, yield = 69%, 247 mg, conversion > 98%). (Note - *The diastereomeric ratio was obtained by integration of ethylenic proton in the crude ^{1}H NMR spectrum.)*

*^{1}H and ^{13}C NMR data of **17** were recorded as a mixture of **L** (two diastereomers: **17A** and **17B**) and **M** (**17M**) (^{1}H NMR data reported for only one diastereomer-**17A**).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.75 (ddd, *J* = 17.5, 10.6, 6.3, 1H), 5.27-5.09 (m, 3H), 4.21-3.91 (m, 2H), 2.68-2.53 (m, 2H), 2.12-1.98 (m, 2H), 1.83-1.71 (m, 2H), 1.68-1.46 and 1.43-1.16 (m, 30H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 175.10, 173.6, 136.7, 116.6, 74.6, 64.8, 45.7, 45.2, 33.8, 29.4-26.9 (13C), 25.5-24.5 (3C).
^{13}C NMR ($CDCl_3$, 100 MHz): (*second diastereomer*) δ 175.07, 174.6, 137.0, 116.3, 74.6, 64.5, 45.0, 44.9, 34.3, 29.4-26.9 (13C), 25.5-24.5 (3C).
CI-HRMS: *m/z* calcd for $C_{25}H_{46}NO_4$ $[M+NH_4]^+$ 424.3427 found 424.3415.



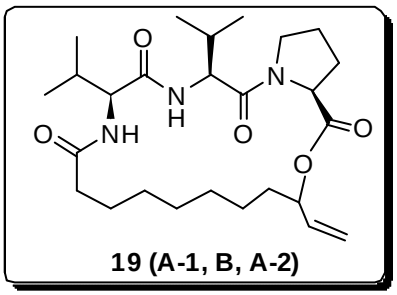
18A/B

18 was prepared according to the *general procedure 6* (using 0.033 mmol of $[Rh(COD)Cl]_2$ and 0.066 mmol of DPEphos) starting from **S14-2** [0.88 mmol, 361 mg). The crude mixture [**18**/**18d** > 95/5, **18**/**18M** = 96/4, **d.r** (**18A**/**18B**) = 65/35, (< 4% of (*Z*)-*anti*-Markovnikov isomer **18AM-Z** detected)] was purified by flash chromatography on silica gel (eluent hexanes/EtOAc 2/1) and **18** was obtained as a yellowish oil and as a mixture of two diastereomers (**18A** and **18B**) together with **18M** and **18AM-Z** [**18**/**18M** = 96/4 (< 4% of **18AM-Z**), **d.r** (**18A**/**18B**) = 65/35, yield = 65%, 234 mg, conversion = 90%].

*^{1}H and ^{13}C NMR data of **18** were recorded as a mixture of **L** (two diastereomers: **18A** and **18B**) and **M** (**18M**) (^{1}H NMR data reported for only one diastereomer-**18A**).*

^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.77 (ddd, *J* = 17.1, 10.5, 6.2, 1H), 5.30-4.99 (m, 5H), 4.76-4.62 (m, 2H), 4.07-3.93 (m, 2H), 3.90-3.72 (m, 2H), 2.89-2.51 (m, 4H), 2.45-2.31 (m, 2H), 1.78-1.48 (m, 4H), 1.46-1.19 (m, 8H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.4, 171.5, 171.0, 136.5, 116.6, 80.9, 80.7, 75.4, 73.6, 73.3, 71.6, 71.2, 34.4, 33.9, 29.9-27.9 (5C), 25.3, 24.6.
^{13}C NMR ($CDCl_3$, 100 MHz): (*second diastereomer*) δ 173.3, 171.4, 171.2, 136.5, 116.8, 80.8, 80.7, 75.5, 73.8, 73.1, 71.6, 71.5, 34.2, 34.1, 29.9-27.9 (5C), 25.1, 24.5.
CI-HRMS: *m/z* calcd for $C_{21}H_{34}NO_8$ $[M+NH_4]^+$ 428.2284 found 428.2286.



19 (A-1, B, A-2)

19 was prepared according to the *general procedure 6* starting from **S12-5** (0.88 mmol, 420 mg). The crude mixture (see HPLC chromatogram) was purified by flash chromatography on silica gel (eluent EtOAc 100%) and **19** was isolated as a mixture of isomers (**19A-1**, **19B**, **19M** and **19A-2**) (yield = 52%, 218 mg, conversion > 98%).

Due to the complexity of the ^{1}H and ^{13}C NMR spectra of the mixture of isomers (**19A-1**, **19B**, **19M** and **19A-2**) *(see scanned images of ^{1}H and ^{13}C NMR spectra), only the high resolution mass data is reported.*

CI-HRMS: *m/z* calcd for $C_{26}H_{44}O_5N_3$ $[M+H]^+$ 478.3281 found 478.3281.

The isomers **19A-1** (32%; RT = 14.4 min), **19B** (36%; RT = 18.3 min) and **19A-2** (27%; RT = 30.3 min) were separated by preparative HPLC (column type: ET 250/1"/20 Nucleosil 100-7; elution: *n*-Heptan/Dioxan 80/20; rate: 22 mL/min) and fully characterized. The minor Markovnikov product **19M** (RT = 16.2 min) was not characterized by NMR due to the very small amount of this isomer (5 %, calculated by HPLC and by integration in the crude ^{1}H NMR spectrum).

*Analytical data of **19A-1** ; **19B** and **19A-2***

19A-1 *(32%; RT = 14.4 min)*

^{1}H NMR ($CDCl_3$, 400MHz): δ 6.57 (d, *J* = 9.0, 1H), 5.94 (d, 1H, *J* = 8.8), 5.75 (ddd, *J* = 17.2, 10.5, 6.1, 1H), **5.32 (m, 1H)**, 5.21 (app dt, *J* = 17.2, 1.3, 1H), 5.13 (app dt, *J* = 10.5, 1.3, 1H), 4.62 (dd, *J* = 9.0, 6.4, 1H), 4.44 (bdd, *J* = 8.4, 2.9, 1H), 4.39 (dd, *J* = 8.8, 5.8, 1H), 3.93-3.85 (m, 1H), 3.60-3.52 (m, 1H), 2.37-2.25 (m, 2H), 2.24-1.92 (m, 5H), 1.89-1.46 (m, 6H), 1.46-1.18 (m, 7H), 0.96 (d, *J* = 6.7, 6H), 0.92 (d, *J* = 6.8, 3H), 0.91 (d, *J* = 6.7, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.6, 171.7, 171.0, 170.3, 136.8, 116.4, 74.5, 59.1, 58.1, 55.8, 47.3, 36.5, 34.2, 31.3, 30.0, 29.3, 28.5, 28.3, 28.1, 25.4, 24.7, 24.0, 19.8, 19.7, 17.82, 17.77.
EI-HRMS: *m/z* calcd for $C_{26}H_{43}O_5N_3$ $[M]^+$ 477.3203 found 477.3200.
$[\alpha]_D^{19}$ = -68.7 (c = 0.16, $CHCl_3$)

19B (*36%; RT = 18.3 min)*

^{1}H NMR ($CDCl_3$, 400MHz): δ 6.55 (d, *J* = 9.0, 1H), 6.25 (d, *J* = 8.5, 1H), 5.70 (ddd, *J* = 17.3, 10.5, 6.7, 1H), 5.21 (app dt, *J* = 17.3, 1.3, 1H), 5.15 (app dt, *J* = 10.5, 1.3, 1H), **5.08 (app q, *J* = 6.7, 1H)**, 4.72 (dd, *J* = 9.0, 5.1, 1H), 4.45 (dd, *J* = 8.5, 5.3, 1H), 4.42 (dd, *J* = 9.0,

3.5, 1H), 3.86-3.79 (m, 1H), 3.61-3.54 (m, 1H), 2.38-2.29 (m, 1H), 2.25-1.94 (m, 6H), 1.94-1-82 (m, 1H), 1.62-1.07 (m, 12H), 0.99 (d, *J* = 6.6, 3H), 0.98 (d, *J* = 6.6, 3H), 0.94 (d, *J* = 6.9, 3H), 0.89 (d, *J* = 6.6, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.3, 171.2, 170.8, 169.9, 136.4, 117.4, 75.9, 60.1, 58.0, 55.5, 47.2, 36.6, 33.9, 32.5, 31.2, 29.4, 29.3, 29.1, 27.8, 24.9, 24.7, 24.6, 20.2, 19.4, 18.0, 17.2,
EI-HRMS: *m/z* calcd for $C_{26}H_{43}O_5N_3$ $[M]^+$ 477.3203 found 477.3209
$[\alpha]_D^{19}$ = -32.5 (c = 0.20, $CHCl_3$)

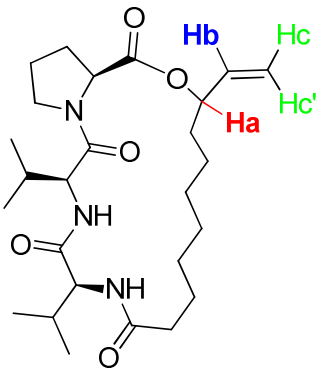
19A-2 (*27%; RT = 30.3 min)*

^{1}H NMR ($CDCl_3$, 400MHz): δ 7.23 (d, *J* = 7.8, 1H), 5.80 (ddd, *J* = 17.3, 10.6, 5.7, 1H), 5.58 (d, *J* = 8.0, 1H), **5.30 (m, 1H)**, 5.16 (app dt, *J* = 17.3, 1.4, 1H), 5.09 (app dt, *J* = 10.6, 1.4, 1H), 4.60 (dd, *J* = 8.0, 4.1, 1H), 4.31 (app bt, *J* = 7.8, 1H), 4.28 (dd, *J* = 7.8, 4.5, 1H), 3.73-3.55 (m, 1H), 3.63-3.55 (m, 1H), 2.63-2.54 (m, 1H), 2.40-2.21 (m, 3H), 2.19-2.03 (m, 2H), 2.00-1.79 (m, 3H), 1.71-1.23 (m, 11H), 1.00 (d, *J* = 6.6, 3H), 0.98 (d, *J* = 7.0, 3H), 0.92 (d, *J* = 6.8, 3H), 0.84 (d, *J* = 6.7, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.9, 172.3, 171.1, 169.6, 137.2, 115.5, 75.3, 60.0, 59.7, 55.1, 47.2, 36.9, 34.4, 31.2, 30.5, 29.04, 29.03, 28.9, 28.4, 26.0, 25.9, 25.4, 20.2, 19.8, 17.4, 16.8.
CI-HRMS: *m/z* calcd for $C_{26}H_{43}O_5N_3$ $[M]^+$ 477.3203 found 477.3204
$[\alpha]_D^{19}$ = -60.5 (c = 0.19, $CHCl_3$)

- All of the compounds **19A-1/2, 19B** and **19M** display the same mass, number of ^{13}C resonances with very similar chemical shifts indicating that they are isomers. The products **19A-1**, **19A-2** and **19B** were assigned as two diastereomers (**19A-1/2** and **19B**) of the 19-membered ω-vinyl macrolactone **19** because of the highly characteristic ^{1}H NMR signals of **Ha**, **Hb** and **Hc/c'**. The product **19M** (not isolated as a pure compound) was assigned to the Markovnikov product by analysis of a HSQC spectra (2D, correlation ^{1}H-^{13}C) regarding the characteristic correlation between **Hd/d'** (4.67 and 4.61 ppm in $CDCl_3$) (**Figure 2**) and the corresponding terminal vinylic ^{13}C (101.2 ppm in $CDCl_3$).

- **19A-1** and **19A-2** are presumably two proline amide rotamers (*trans*/*cis*) of the diastereomer **A**,[15] because of the similarities of the NMR spectroscopical properties of the two isomers regarding the chemical shift and the multiplicity for **Ha** as well as similarity of the optical rotatory power (**Figure 1**). The isomer **19B** is the second diastereomer named **B** (d.r. **A/B** = 62/38).

- The proposed structures of **19A-1/2**, **19B** and **19M** are depicted in **Figure 2**. For more clarity, the stereochemistry of the new chiral center formed (allylic position a*) was assigned arbitrarily. Due to the absence of information on the nature of the proline amide rotamer isolated, both isomer *cis* and *trans* of **19B** and **19M** are represented.



Ha	δ (ppm)	multiplicity	optical rotatory power
19A-1	5.32	Very complex multiplet	-68.7
19B	5.08	apparent quadruplet	-32.5
19A-2	5.30	Very complex multiplet	-60.5

Figure 1. ^{1}H NMR data and optical rotation of **19A-1**, **19B** and **19A-2**

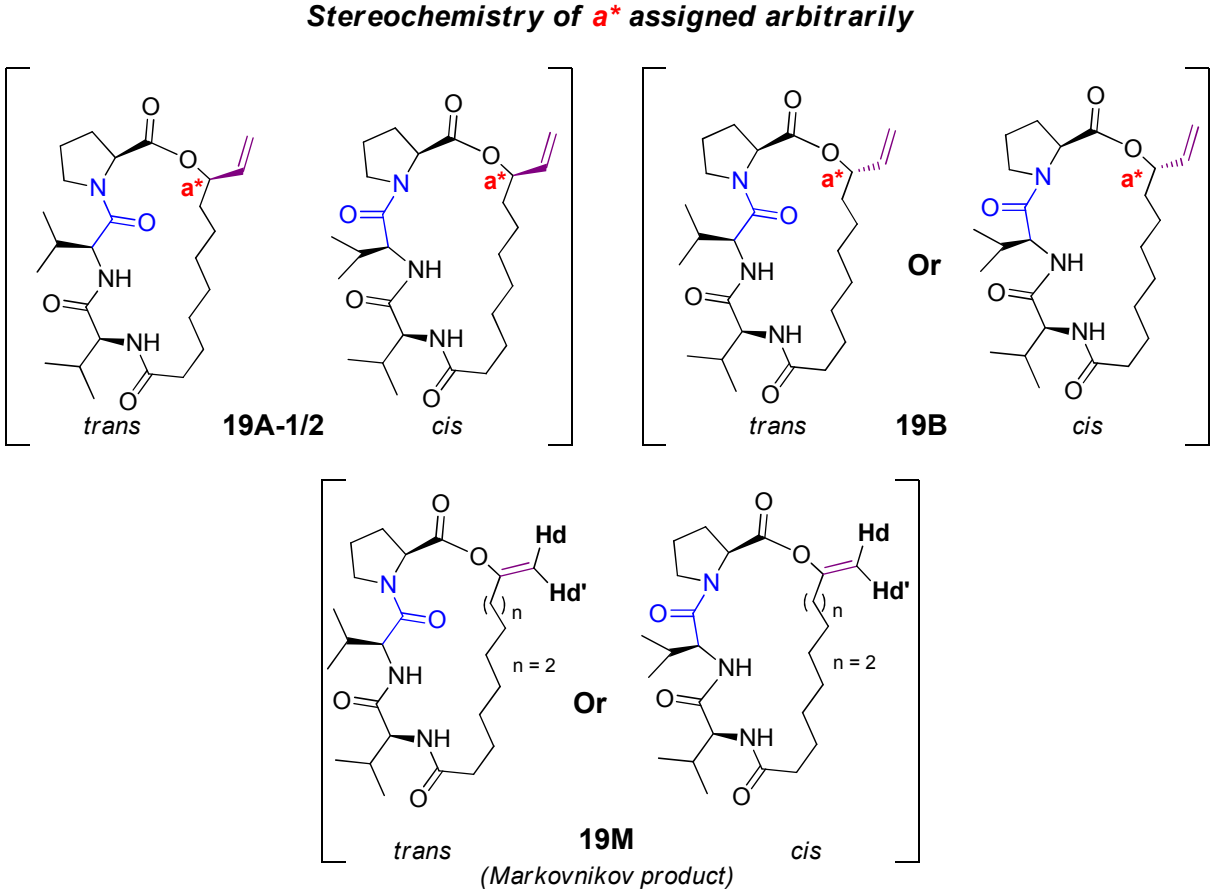
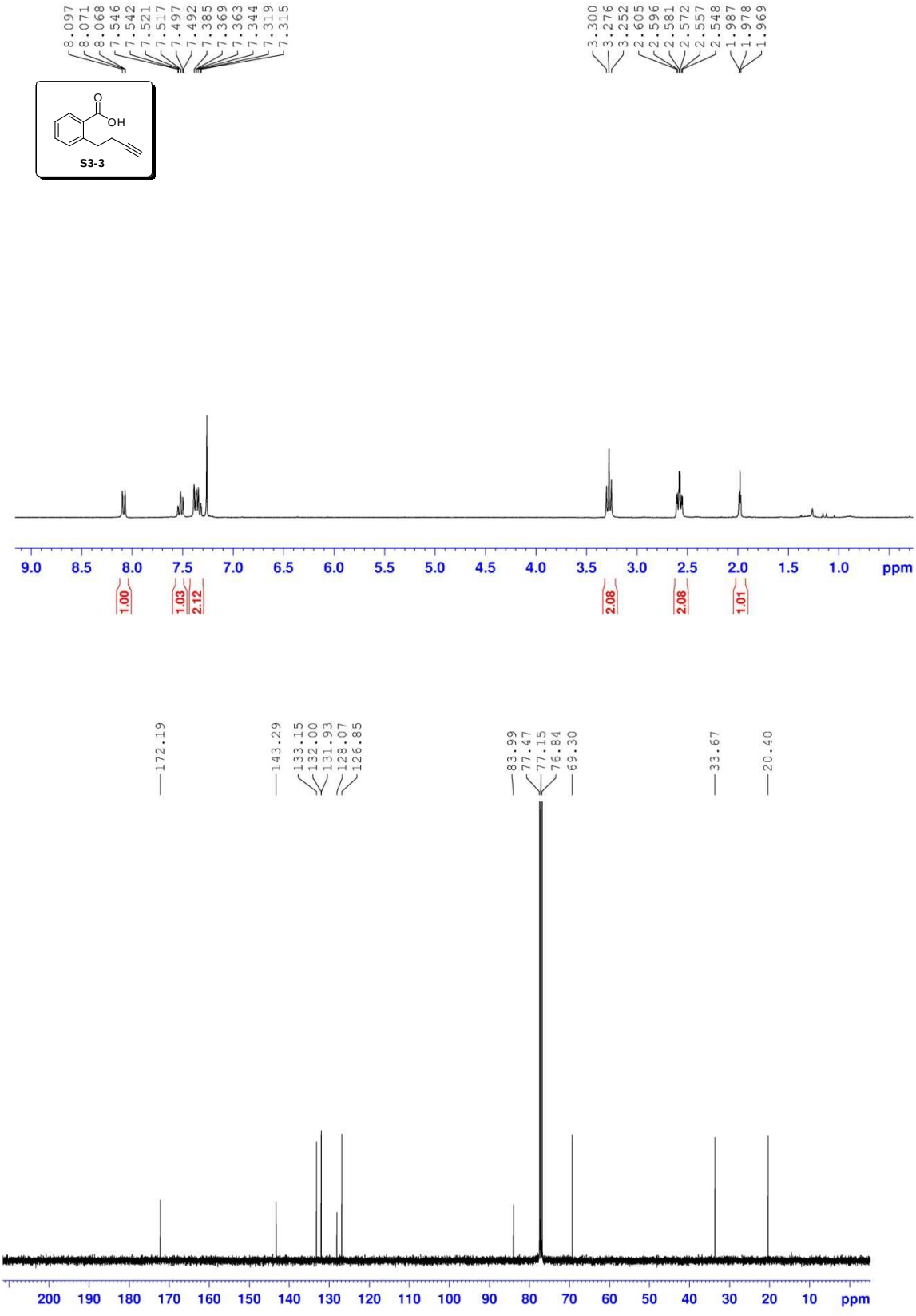
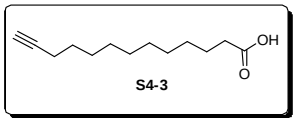


Figure 2. Proposed structures of **19A-1/2**, **19B** and **19M**

^{1}H NMR and ^{13}C NMR spectra of the carboxylic acids

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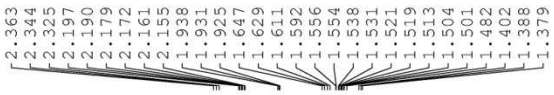
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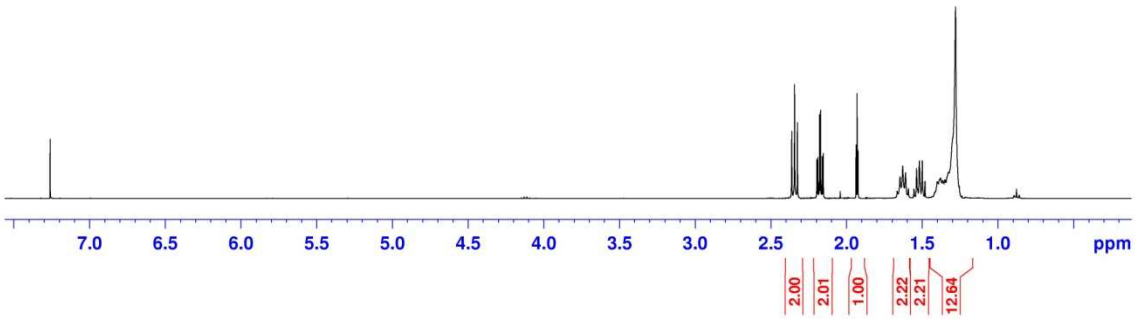
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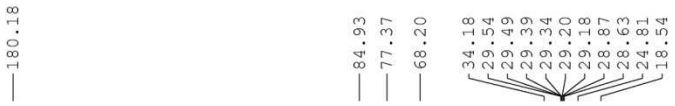
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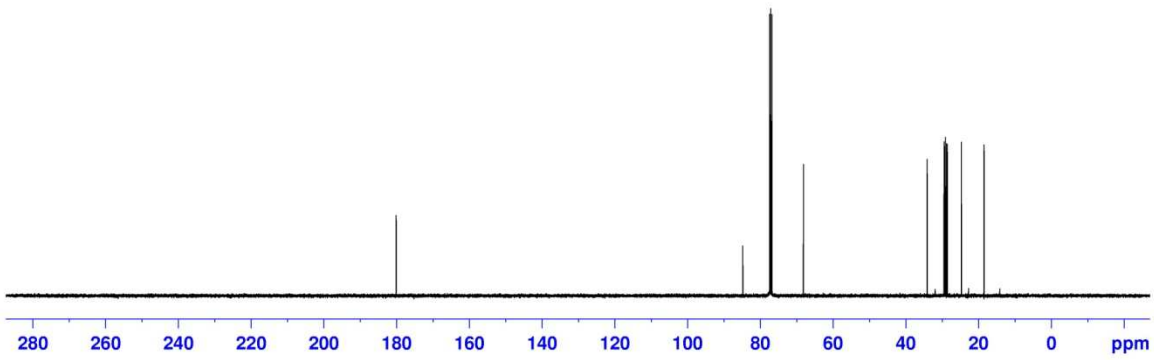
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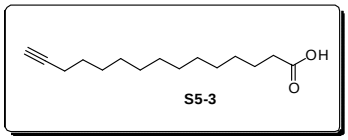
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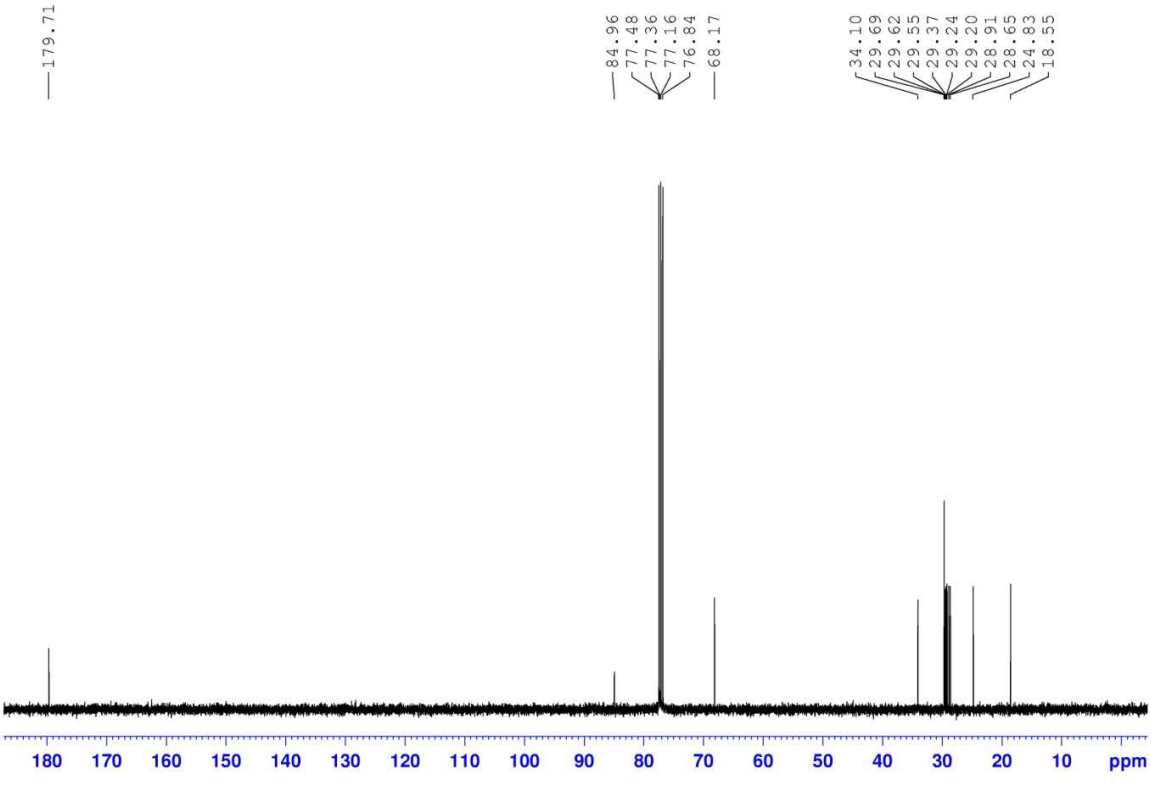
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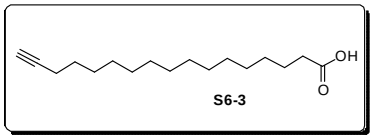
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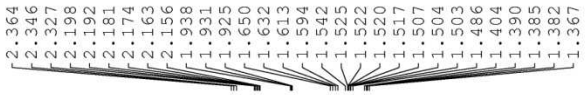
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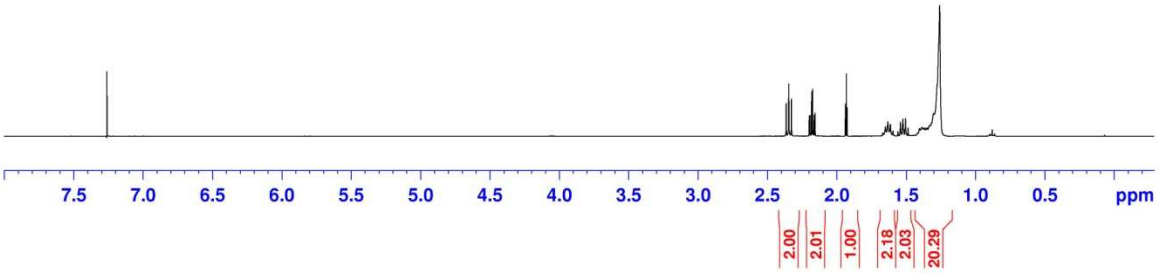
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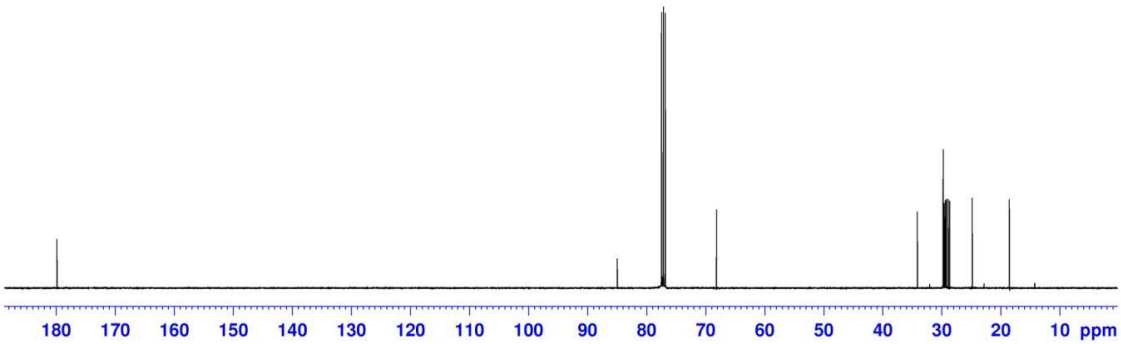
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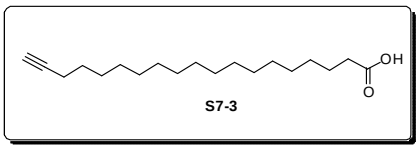
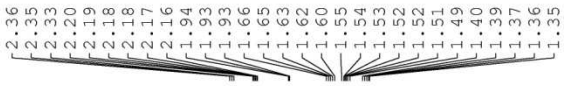
20
10 ppm


OH
O
S7-3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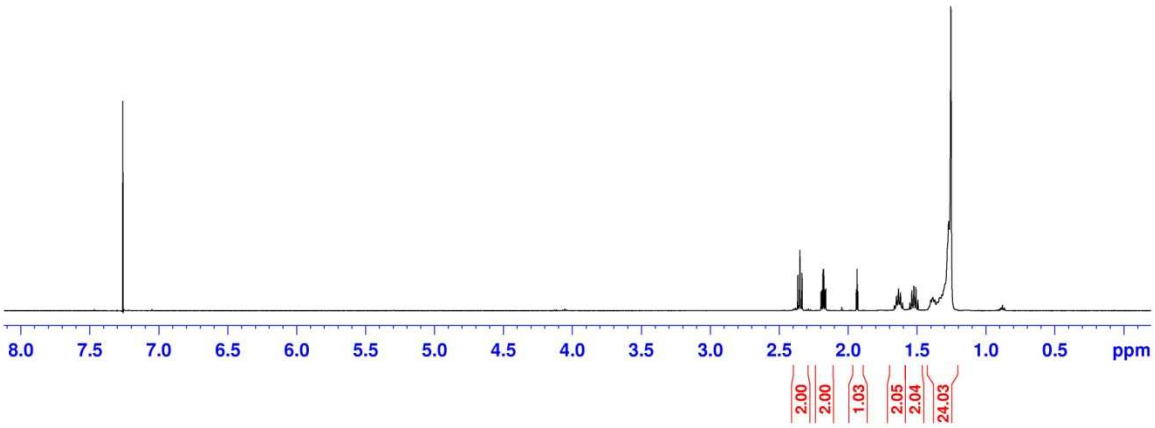
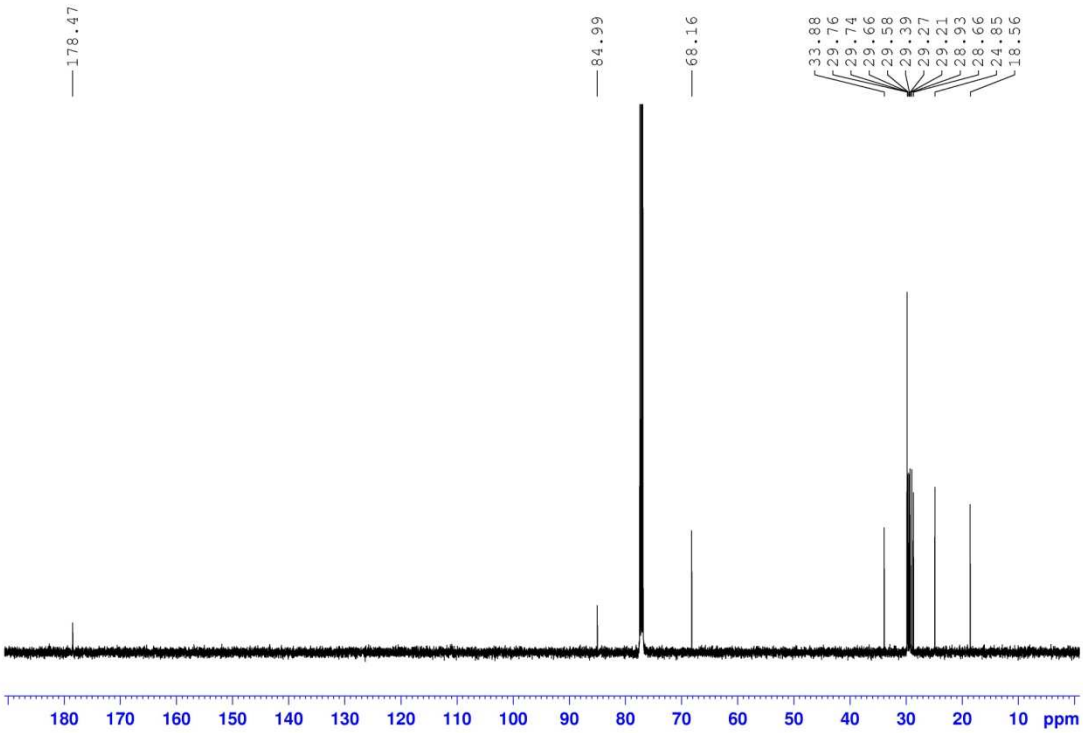
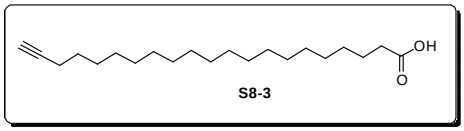
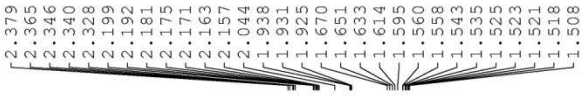
2.35
2.33
2.20
2.19
2.18
2.18
2.17
2.16
1.94
1.93
1.93
1.66
1.65
1.63
1.62
1.60
1.55
1.54
1.53
1.52
1.52
1.51
1.49
1.40
1.39
1.37
1.36
1.35


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
2.00
1.03
2.05
2.04
24.03


178.47
84.99
68.16
33.88
29.76
29.74
29.66
29.58
29.39
29.27
29.21
28.93
28.66
24.85
18.56
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


OH
O
S8-3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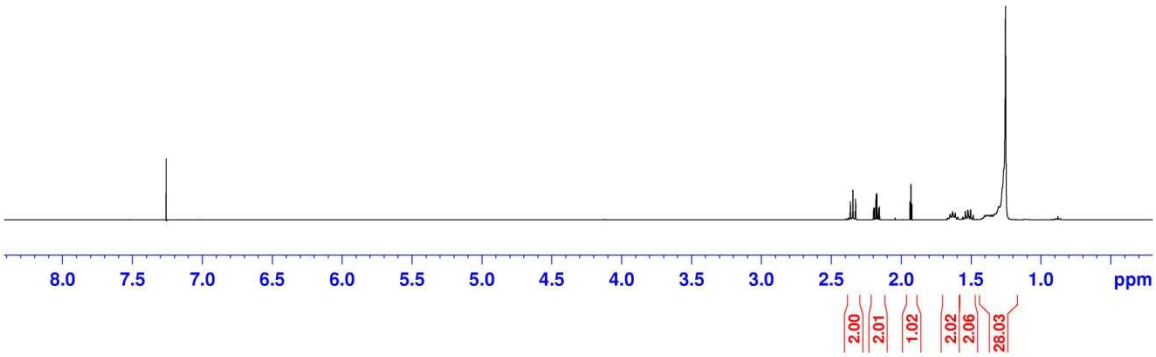
2.365
2.346
2.340
2.328
2.199
2.192
2.181
2.175
2.171
2.163
2.157
2.044
1.938
1.931
1.925
1.670
1.651
1.633
1.614
1.595
1.560
1.558
1.543
1.535
1.525
1.523
1.521
1.518
1.508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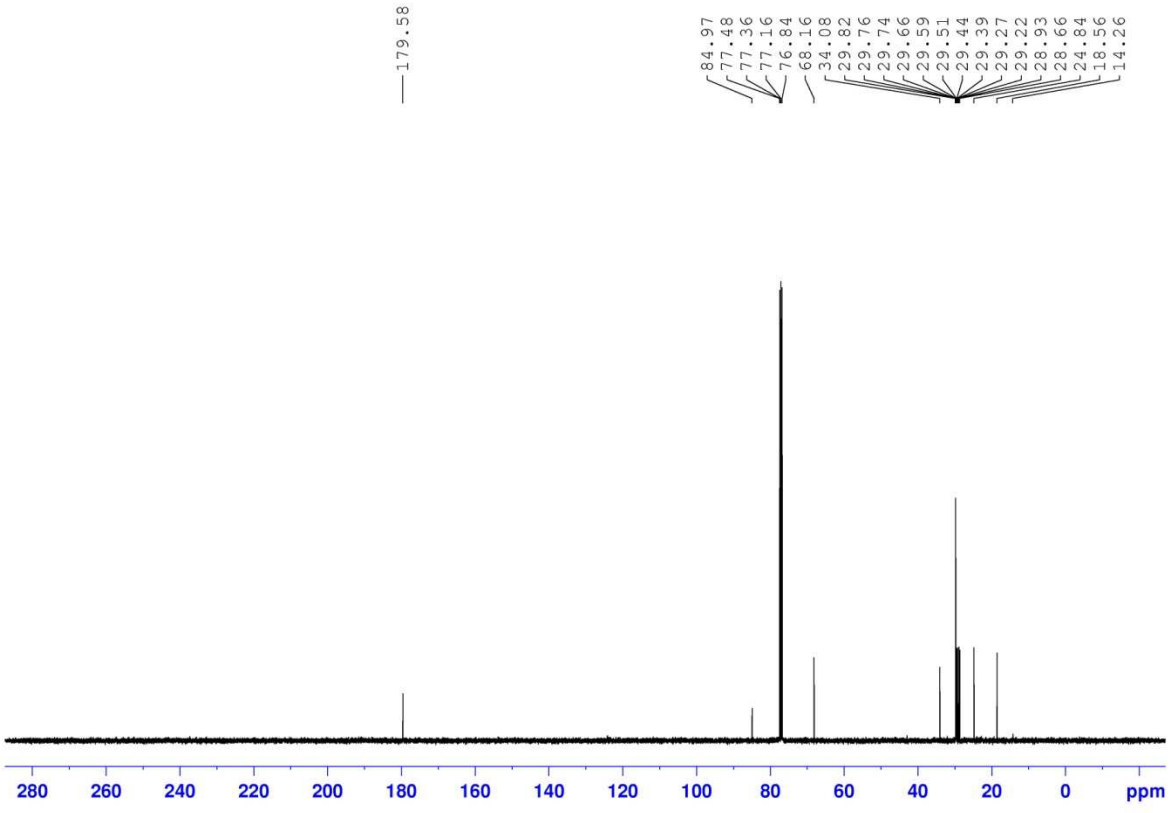
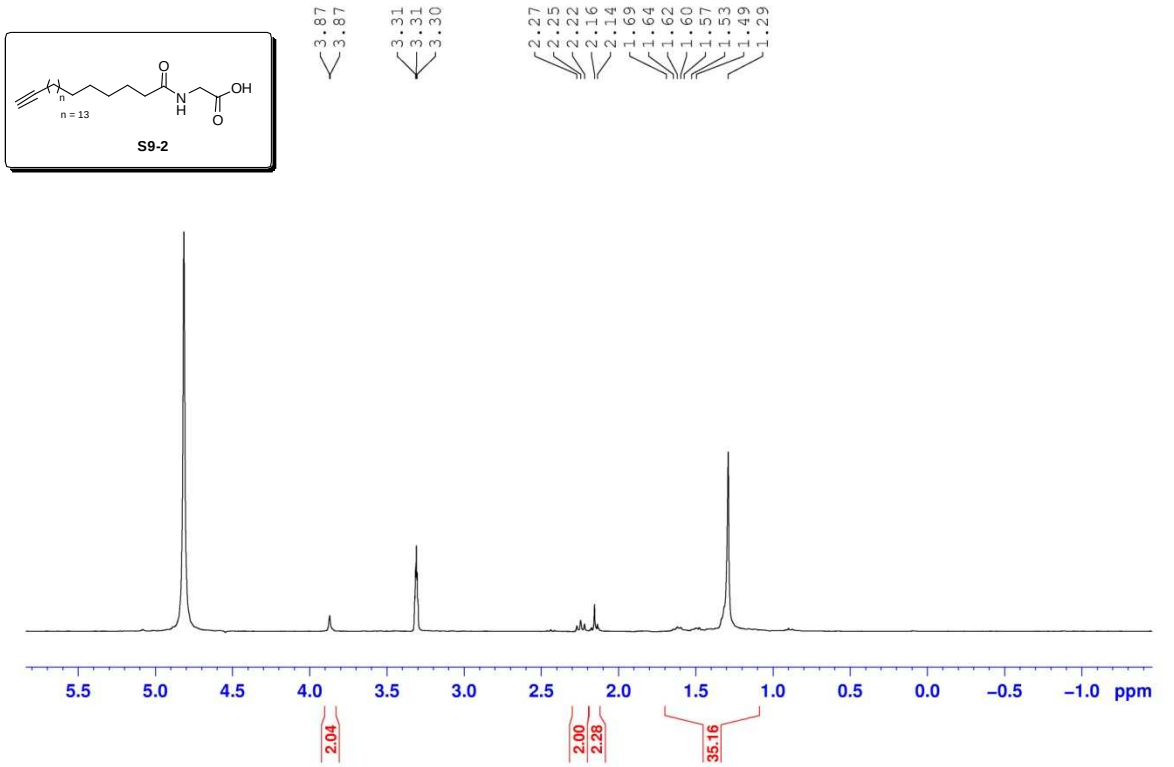
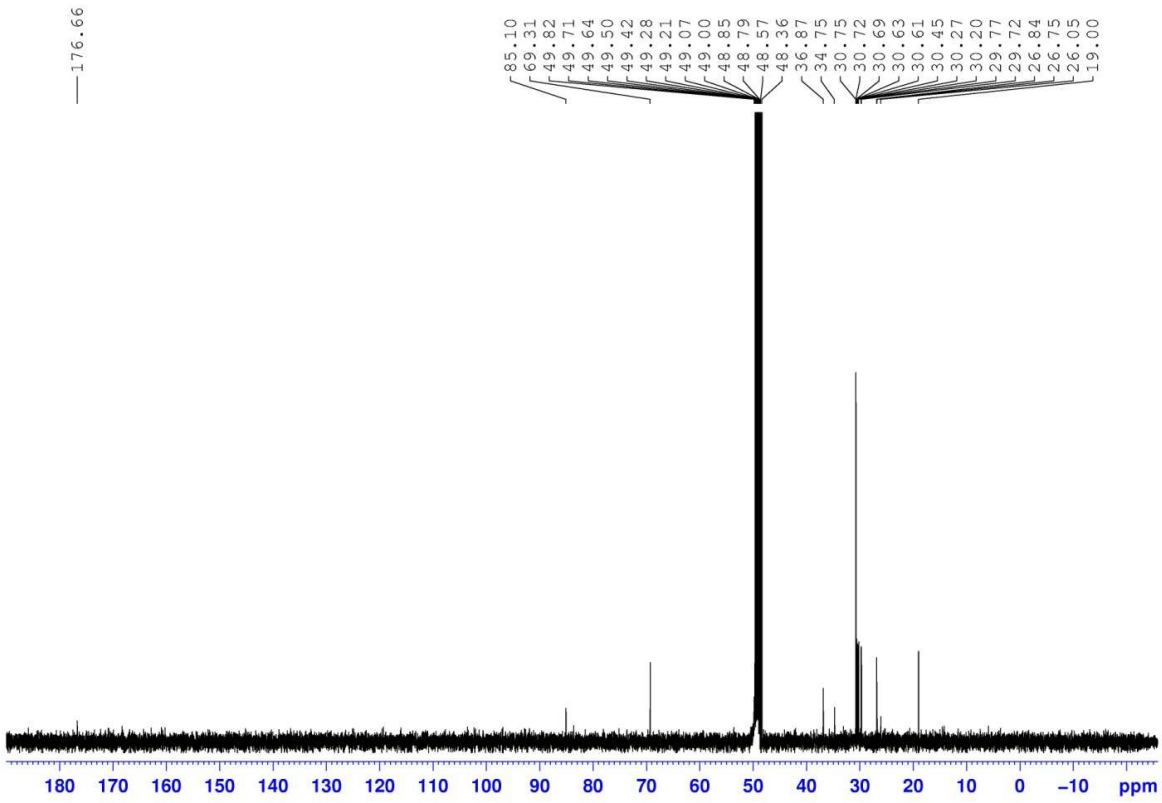
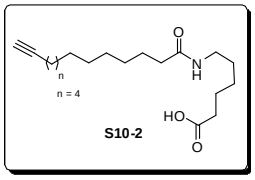
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
2.00
2.01
1.02
2.02
2.06
28.03

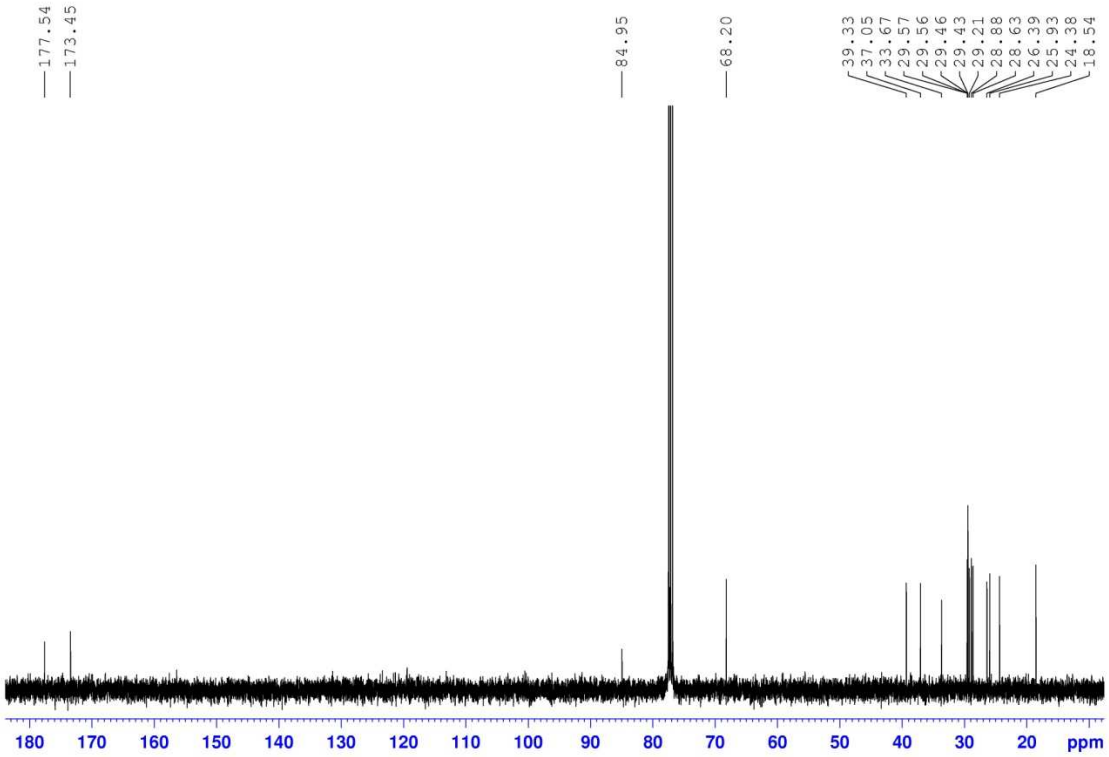

179.58
84.97
77.48
77.36
77.16
76.84
68.16
34.08
29.82
29.76
29.74
29.66
29.59
29.51
29.44
29.39
29.27
29.22
28.93
28.66
24.84
18.56
14.26
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

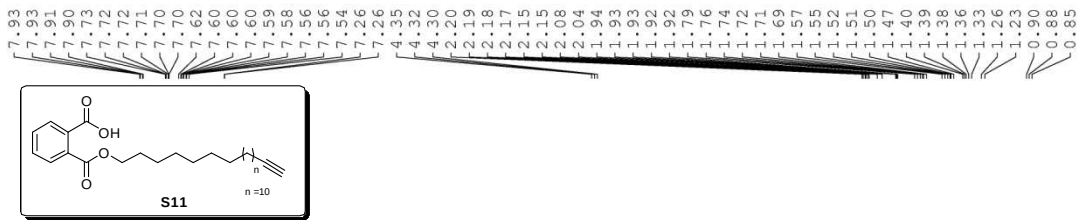

n = 13
S9-2
3.87
3.87
3.31
3.31
3.30
2.27
2.25
2.22
2.16
2.14
1.69
1.64
1.62
1.60
1.57
1.53
1.49
1.29
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
−0.5
−1.0
ppm
2.04
2.00
2.28
35.16


176.66
85.10
69.31
49.82
49.71
49.64
49.50
49.42
49.28
49.21
49.07
49.00
48.85
48.79
48.57
48.36
36.87
34.75
30.75
30.72
30.69
30.63
30.61
30.45
30.27
30.20
29.77
29.72
26.84
26.75
26.05
19.00
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
ppm

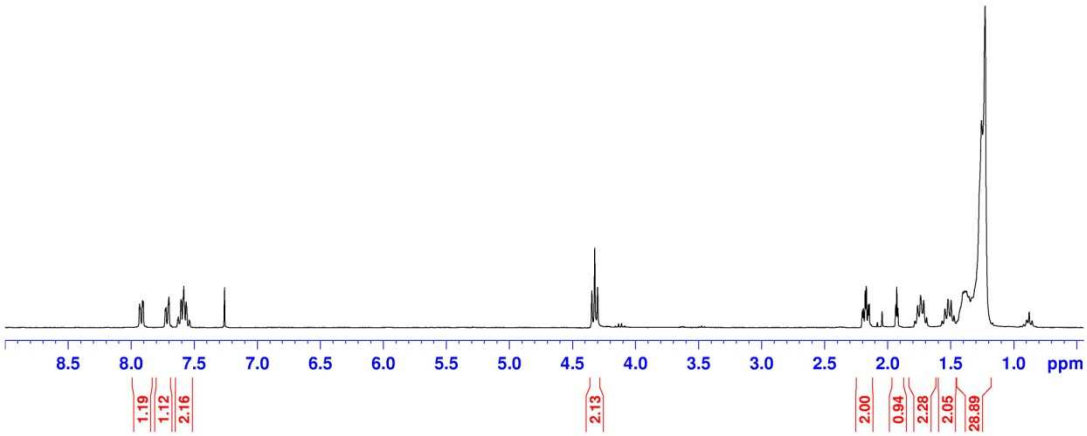

O
N
H
n
n = 4
HO
O
S10-2

5.463
3.291
3.268
3.247
3.224
2.384
2.360
2.335
2.204
2.195
2.180
2.172
2.155
2.149
2.128
1.941
1.932
1.924
1.689
1.664
1.638
1.614
1.588
1.546
1.524
1.497
1.425
1.400
1.389
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
0.96
2.00
2.08
4.15
1.10
22.24


177.54
173.45
84.95
68.20
39.33
37.05
33.67
29.57
29.56
29.46
29.43
29.21
28.88
28.63
26.39
25.93
24.38
18.54
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


7.93
7.93
7.91
7.90
7.73
7.72
7.72
7.71
7.70
7.70
7.62
7.60
7.60
7.59
7.58
7.56
7.56
7.54
7.26
7.26
4.35
4.32
4.30
2.20
2.19
2.18
2.17
2.15
2.15
2.08
2.04
1.94
1.93
1.93
1.92
1.92
1.79
1.76
1.74
1.72
1.71
1.69
1.57
1.55
1.52
1.51
1.50
1.47
1.40
1.39
1.38
1.36
1.33
1.26
1.23
0.90
0.88
0.85

OH
O
O
O
n
n =10
S11


8.5
8.0
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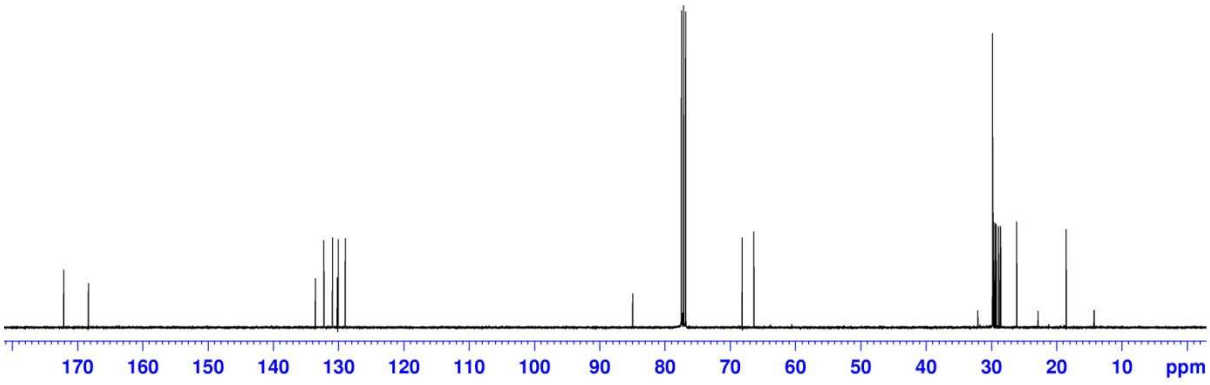
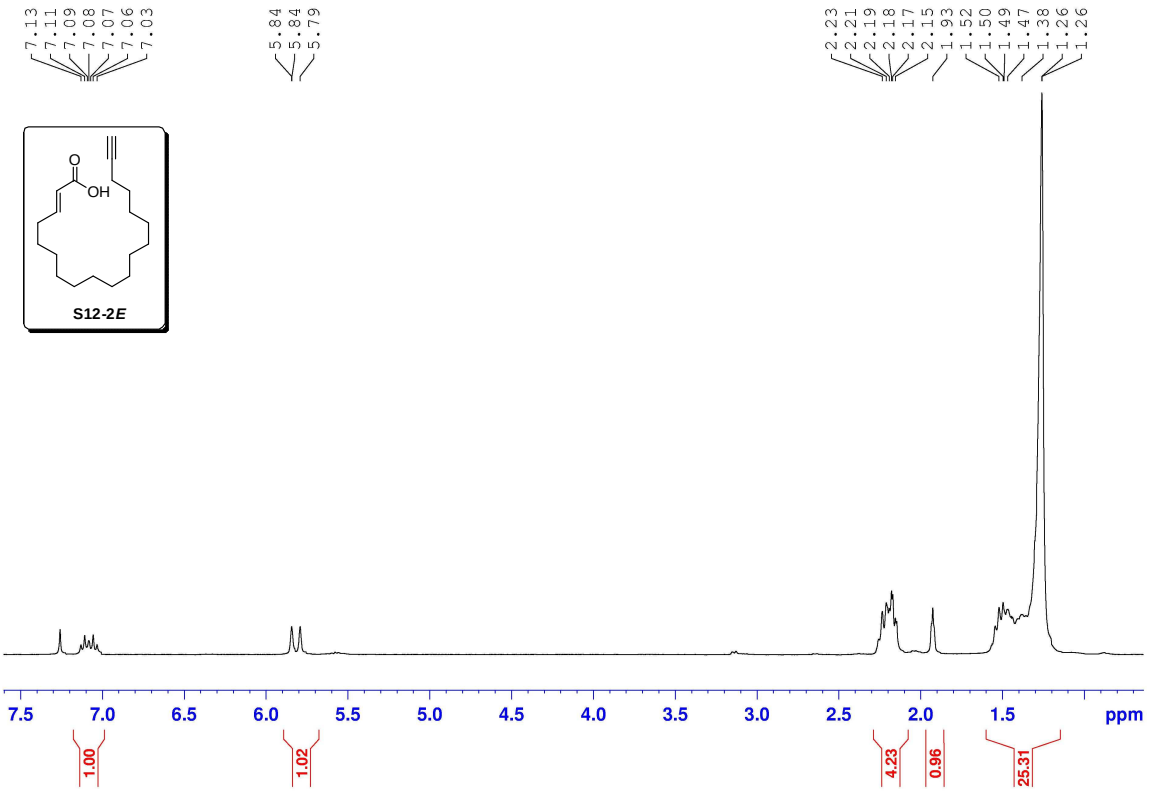
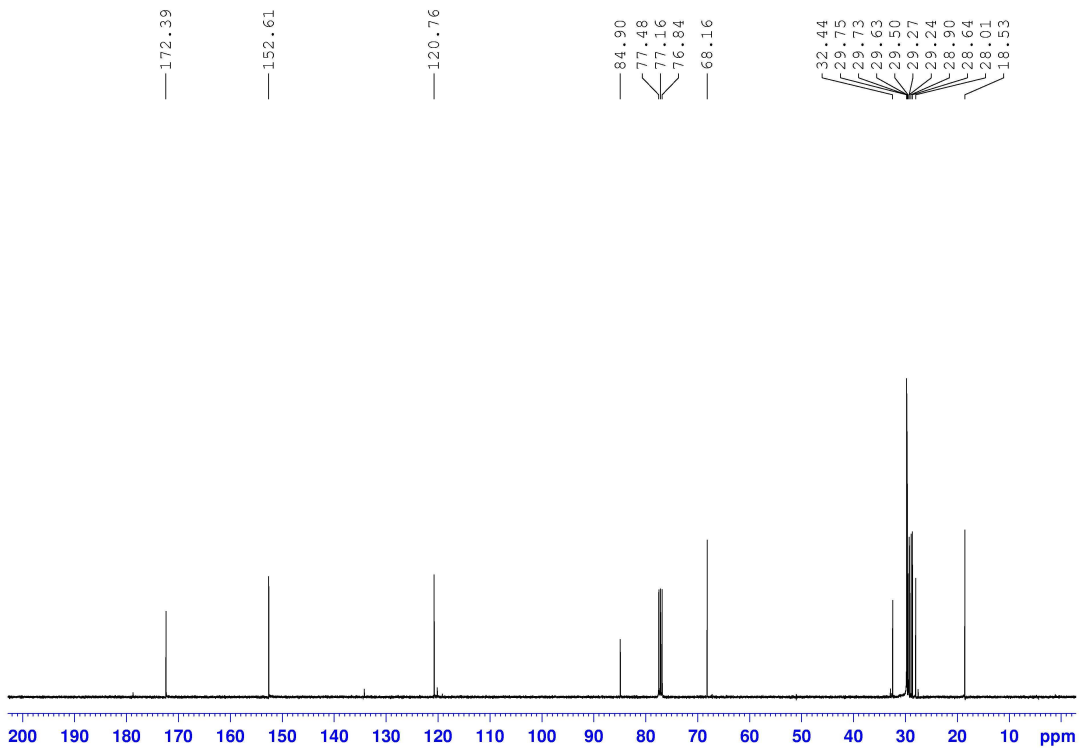
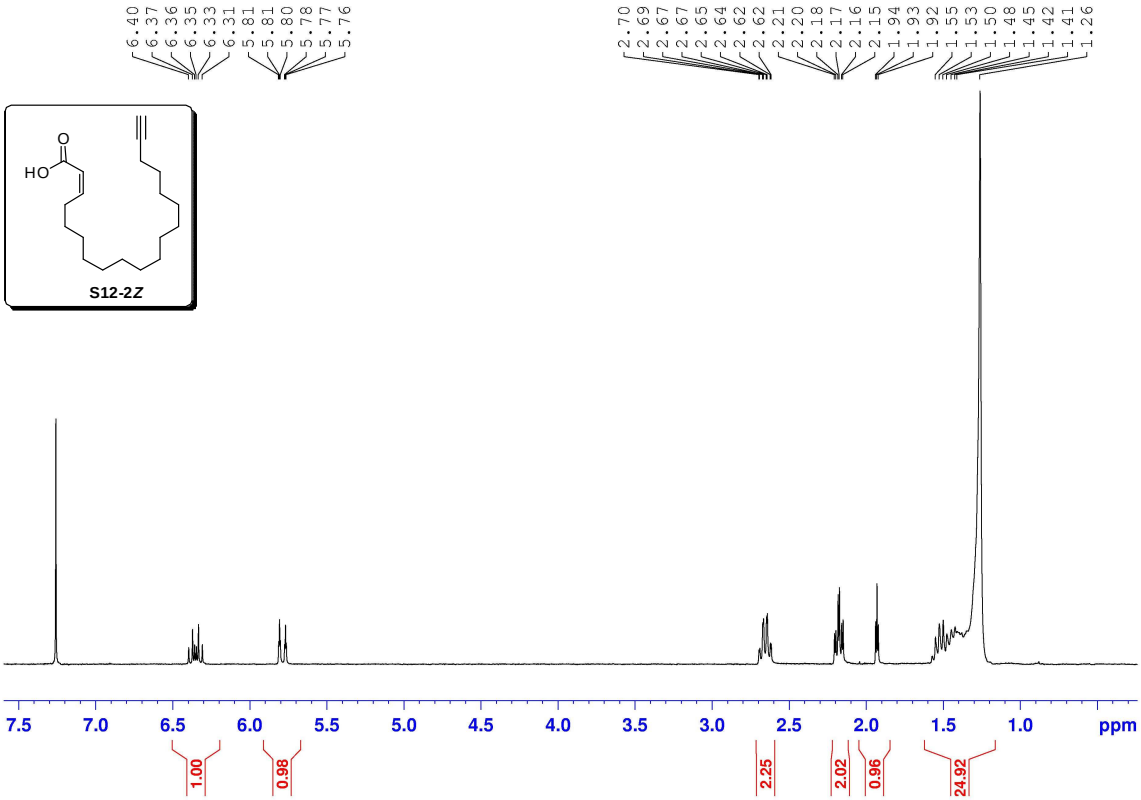
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.19
1.12
2.16
2.13
2.00
0.94
2.28
2.05
28.89


172.08
168.35
133.58
132.27
130.96
130.22
130.08
129.01
84.95
77.47
77.36
77.16
76.84
68.16
66.39
32.07
29.81
29.80
29.77
29.75
29.67
29.65
29.50
29.43
29.26
28.91
28.65
28.56
26.12
22.83
18.54
14.33
14.25


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


7.13
7.11
7.09
7.08
7.07
7.06
7.03
5.84
5.84
5.79
2.23
2.21
2.19
2.18
2.17
2.15
1.93
1.52
1.50
1.49
1.47
1.38
1.26
1.26
O
OH
S12-2E
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.00
1.02
4.23
0.96
25.31


172.39
152.61
120.76
84.90
77.48
77.16
76.84
68.16
32.44
29.75
29.73
29.63
29.50
29.27
29.24
28.90
28.64
28.01
18.53
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm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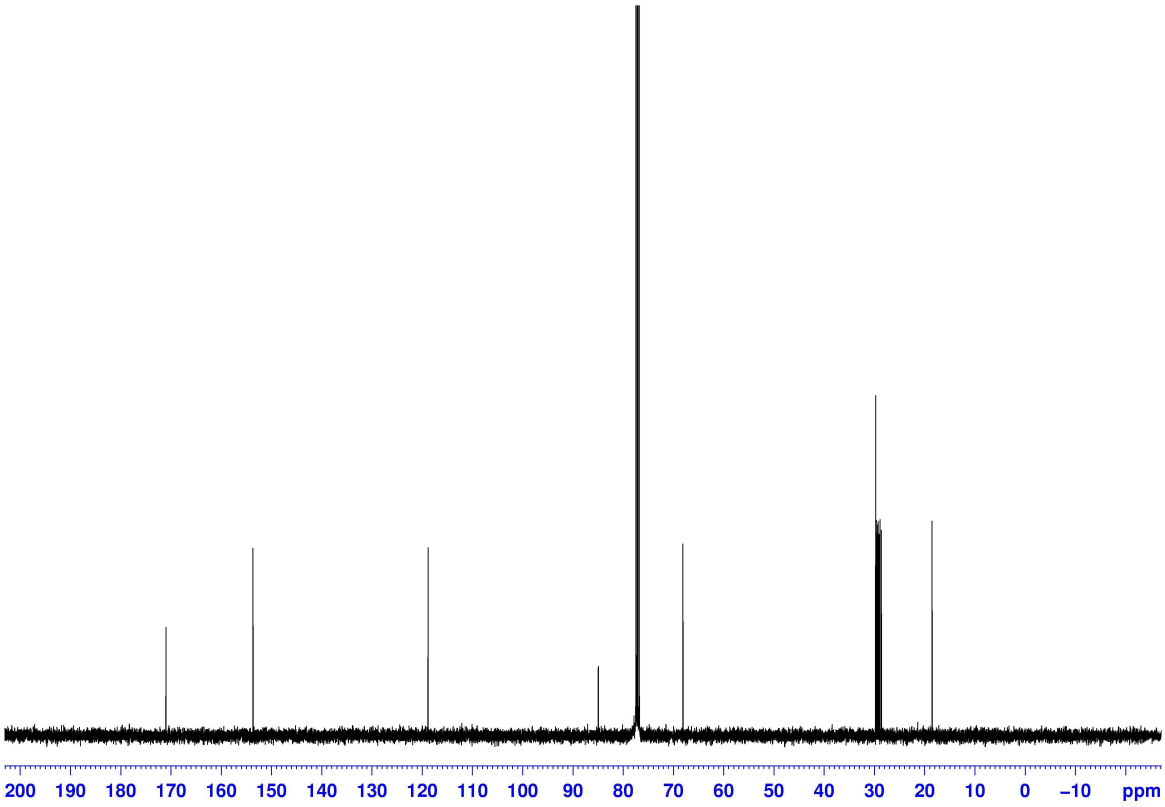
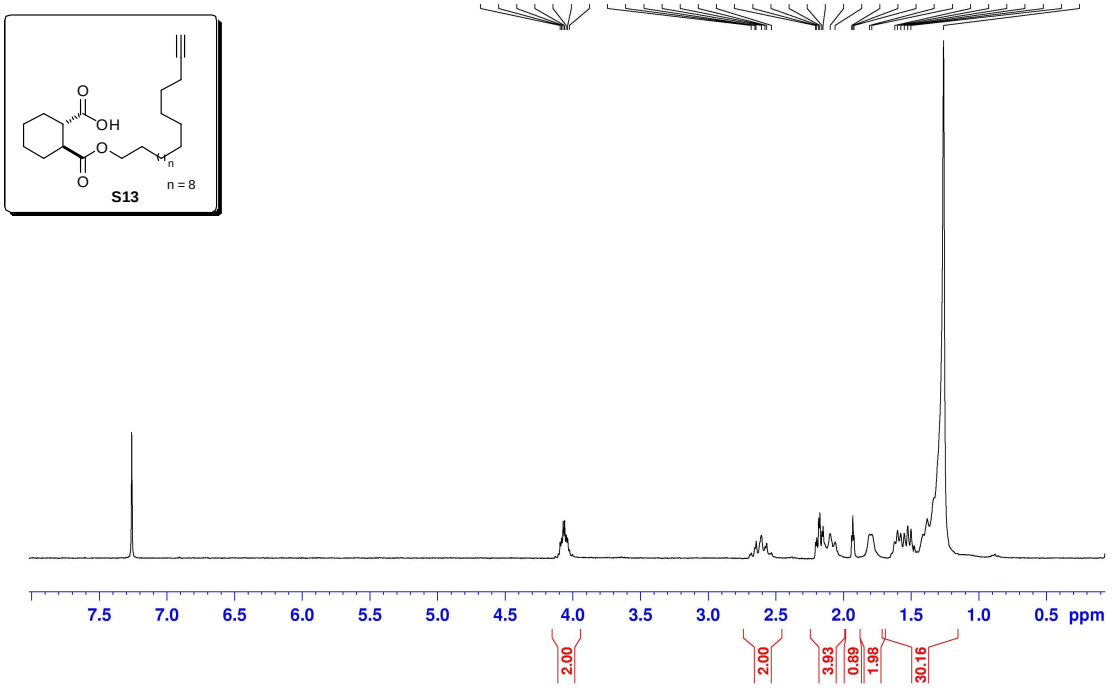
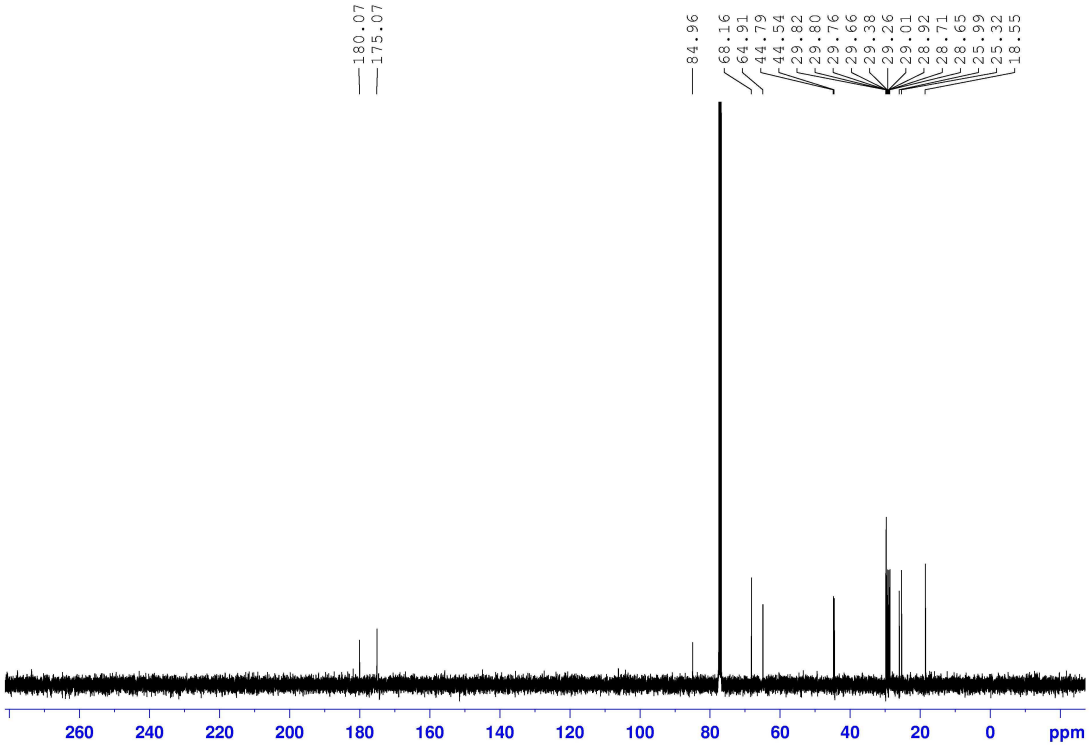
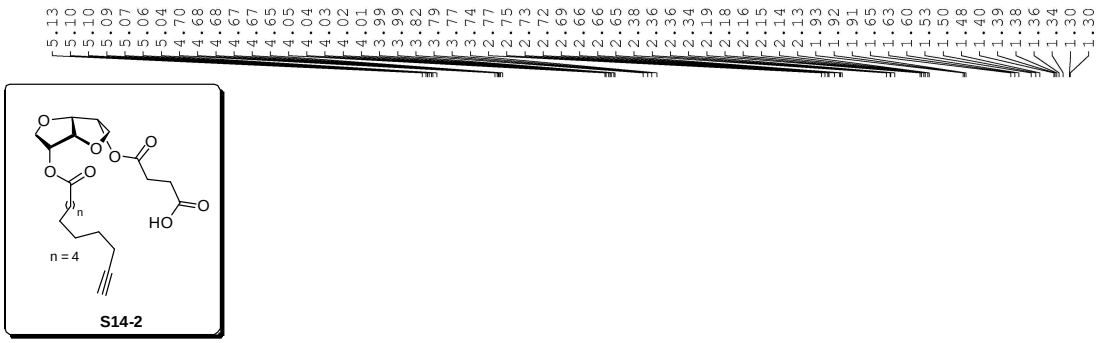
6.37
6.36
6.35
6.33
6.31
5.81
5.81
5.80
5.78
5.77
5.76
2.70
2.69
2.67
2.67
2.65
2.64
2.62
2.62
2.21
2.20
2.18
2.17
2.16
2.15
1.94
1.93
1.92
1.55
1.53
1.50
1.48
1.45
1.42
1.41
1.26
HO
O
S12-2Z
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
0.98
2.25
2.02
0.96
24.92


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−10
ppm

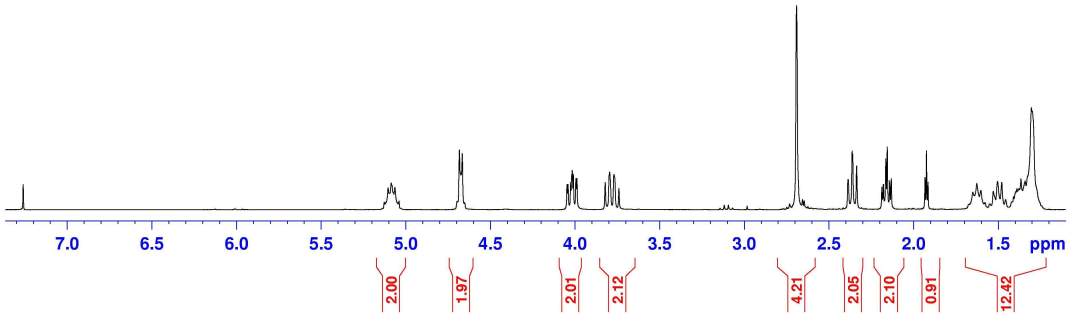

4.09
4.08
4.07
4.06
4.05
4.04
4.02
2.68
2.65
2.64
2.61
2.58
2.57
2.53
2.21
2.20
2.18
2.17
2.16
2.15
2.10
2.06
1.94
1.93
1.92
1.81
1.79
1.62
1.60
1.58
1.55
1.52
1.50
1.26
OH
O
O
O
n
n = 8
S13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
2.00
3.93
0.89
1.98
30.16

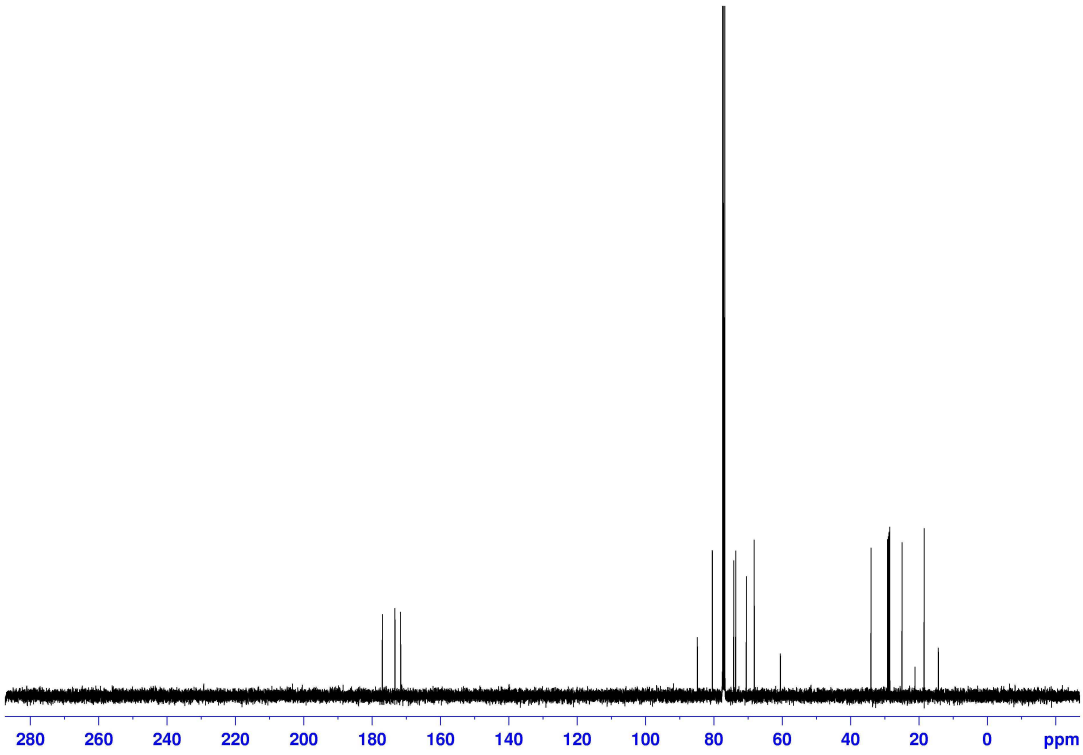

180.07
175.07
84.96
68.16
64.91
44.79
44.54
29.82
29.80
29.76
29.66
29.38
29.26
29.01
28.92
28.71
28.65
25.99
25.32
18.55
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm

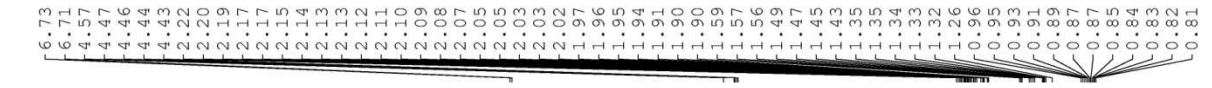

5.13 5.10 5.10 5.09 5.07 5.06 5.04 4.70 4.68 4.68 4.67 4.67 4.65 4.05 4.04 4.03 4.02 4.01 3.99 3.99 3.82 3.79 3.77 3.74 2.77 2.75 2.73 2.72 2.69 2.66 2.66 2.65 2.38 2.36 2.36 2.34 2.19 2.18 2.16 2.15 2.14 2.13 1.93 1.92 1.91 1.65 1.63 1.60 1.53 1.50 1.48 1.40 1.39 1.38 1.36 1.34 1.30 1.30

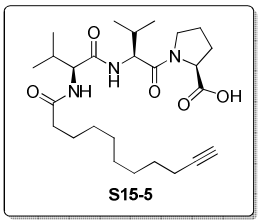
O
O
O
O
O
O
n
HO
n = 4

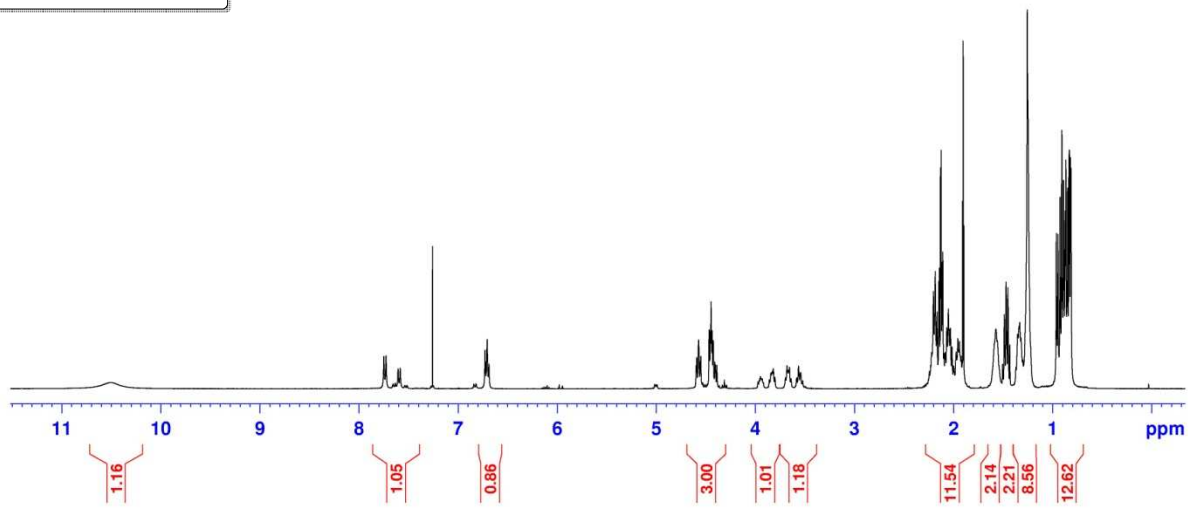
S14-2

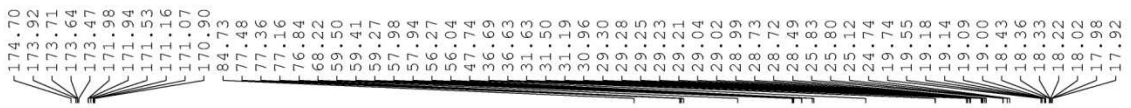

7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 ppm
2.00 1.97 2.01 2.12 4.21 2.05 2.10 0.91 12.42

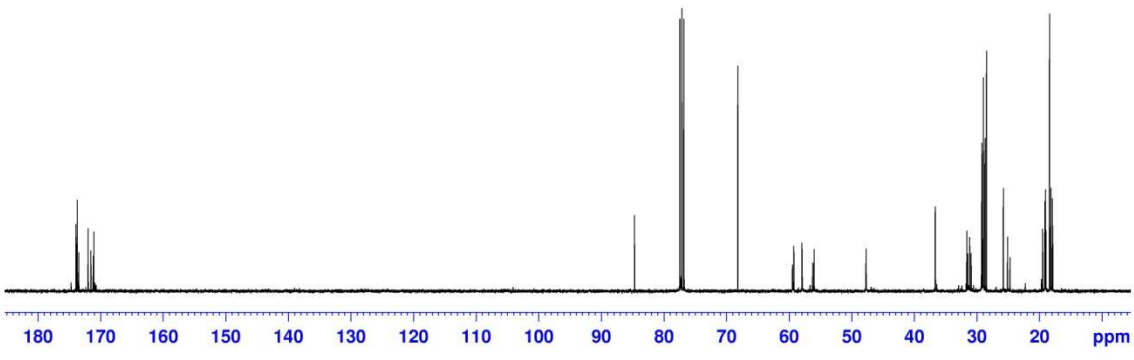

280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 ppm



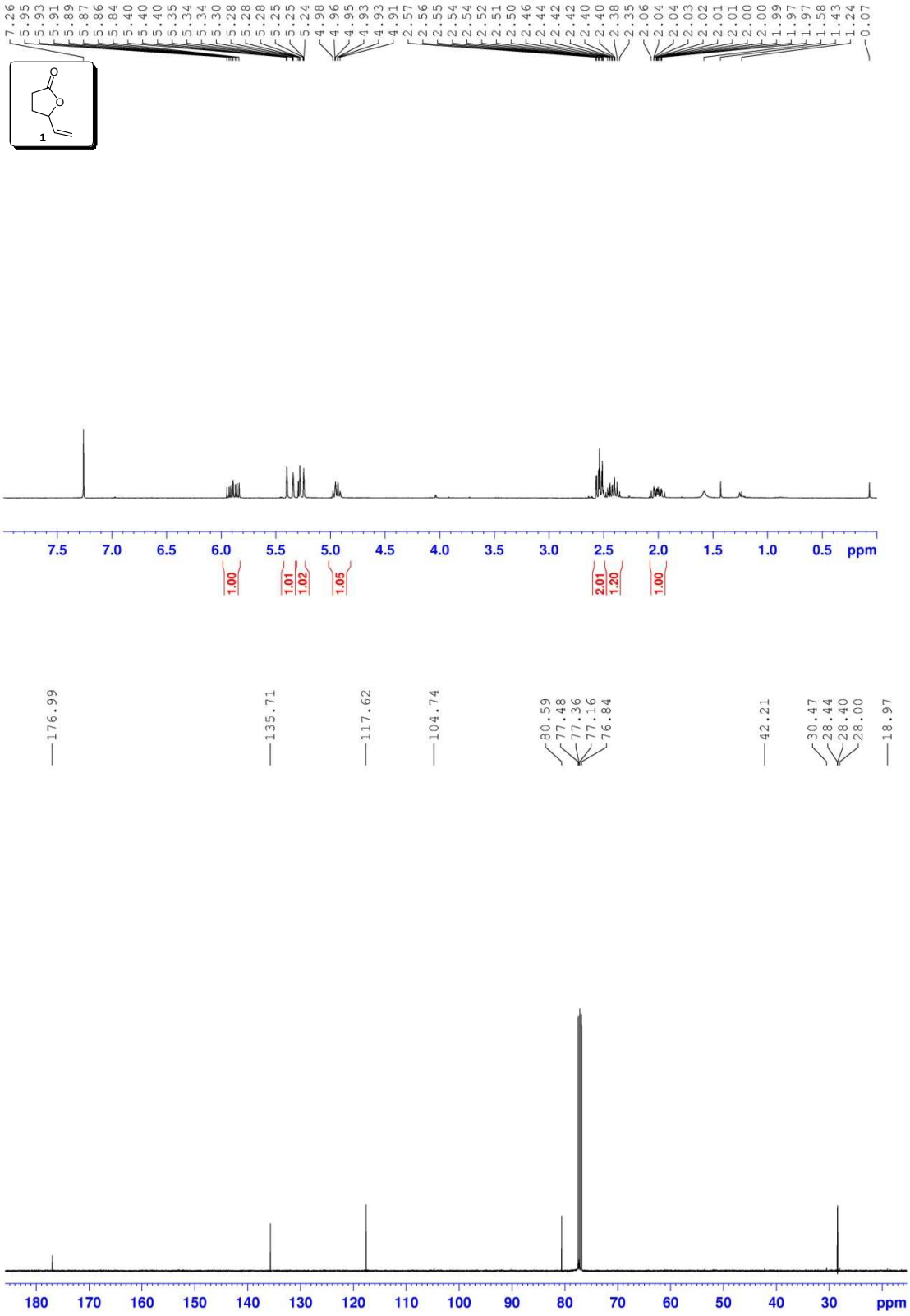

S15-5

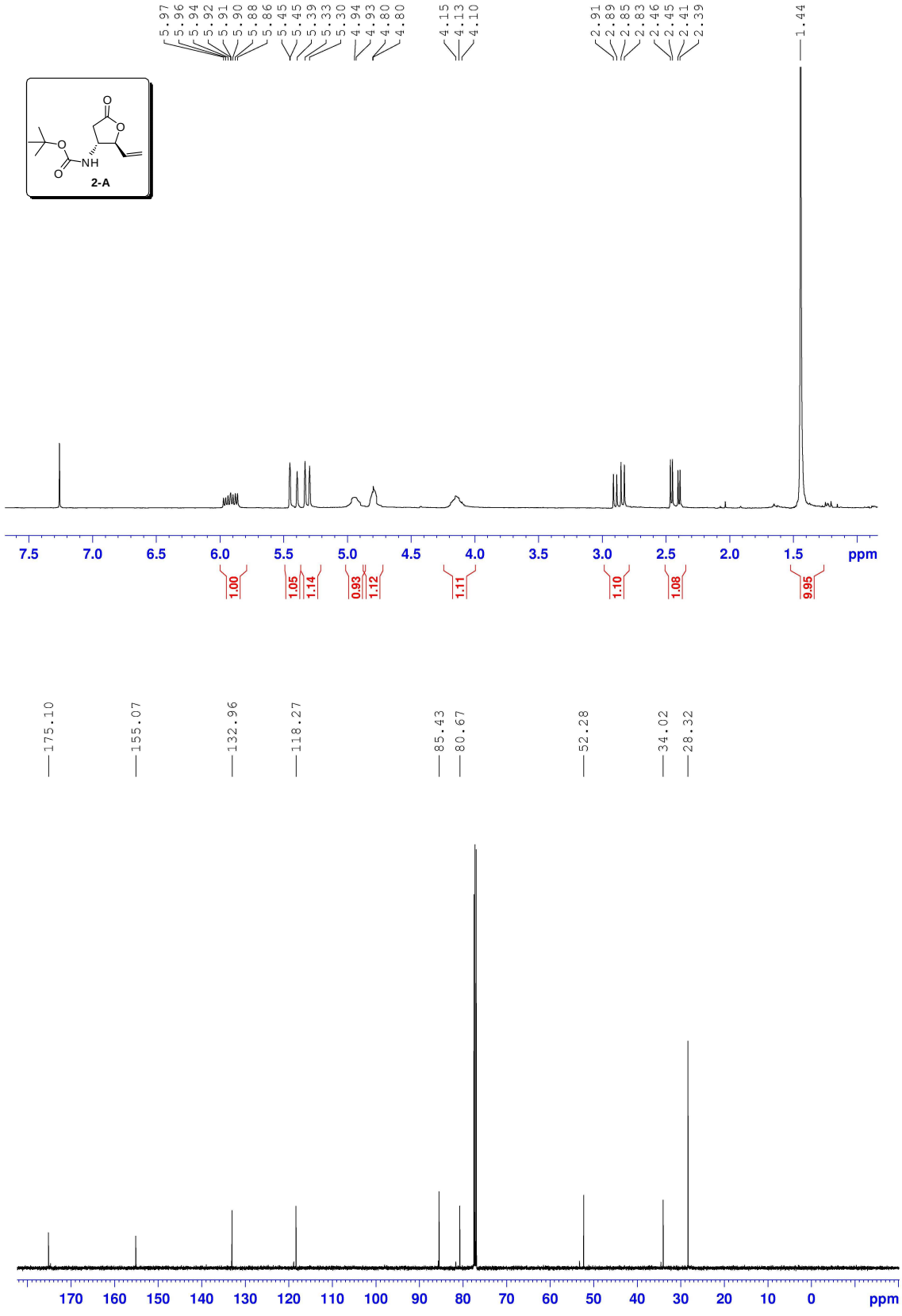

ppm
1.16
1.05
0.86
3.00
1.01
1.18
11.54
2.14
2.21
8.56
12.62




ppm

^{1}H NMR and ^{13}C NMR spectra of the lactones and macrolactones




5.97
5.96
5.94
5.92
5.91
5.90
5.88
5.86
5.45
5.45
5.39
5.33
5.30
4.94
4.93
4.80
4.80
4.15
4.13
4.10
2.91
2.89
2.85
2.83
2.46
2.45
2.41
2.39
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1.08
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85.43
80.67
52.28
34.02
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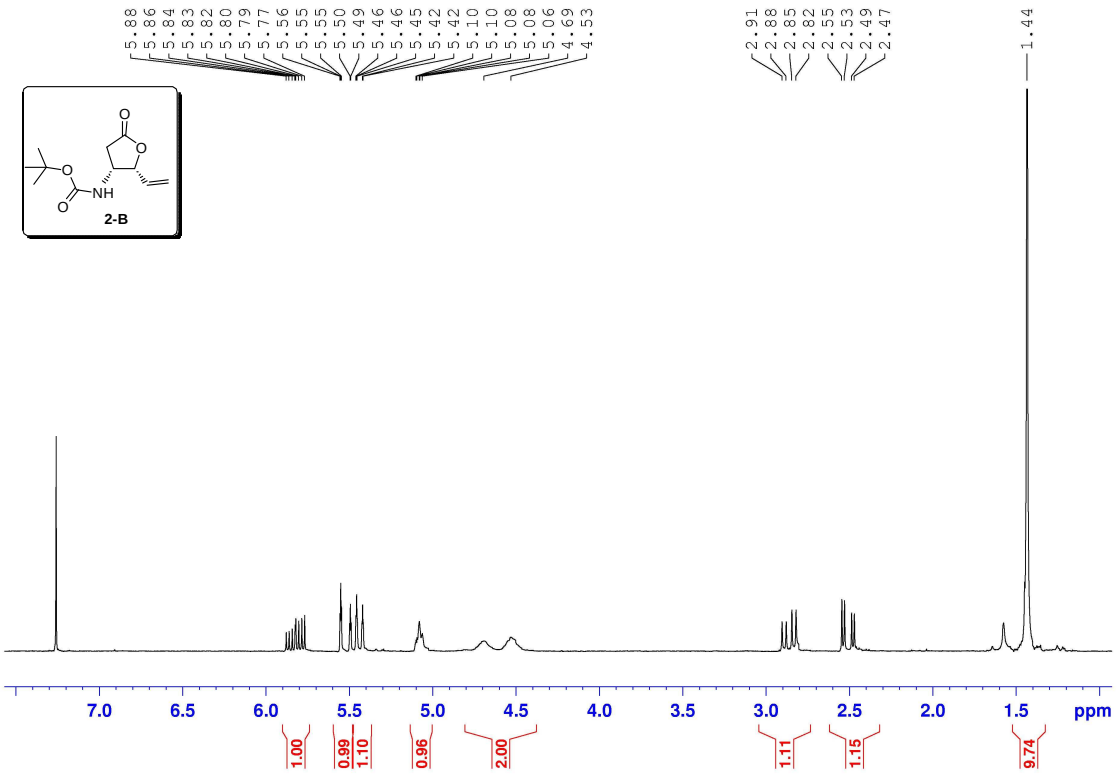
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5.42
5.10
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2.82
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2.49
2.47
1.44
O
O
O
NH
O
2-B
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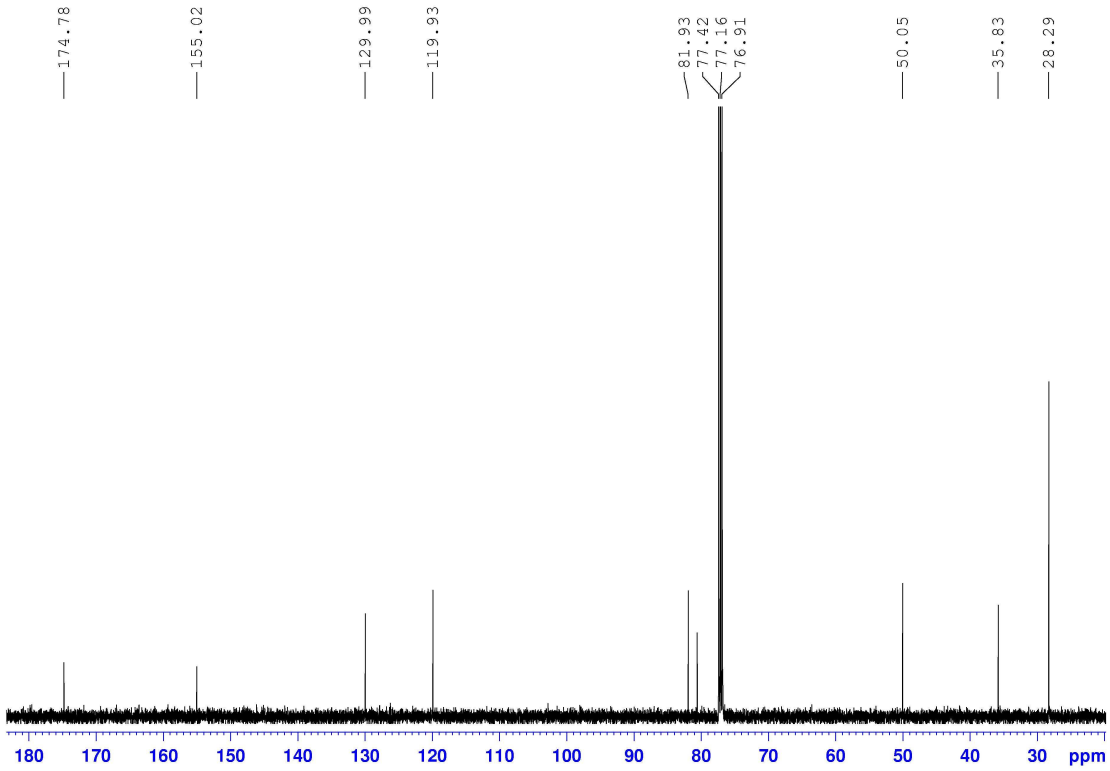
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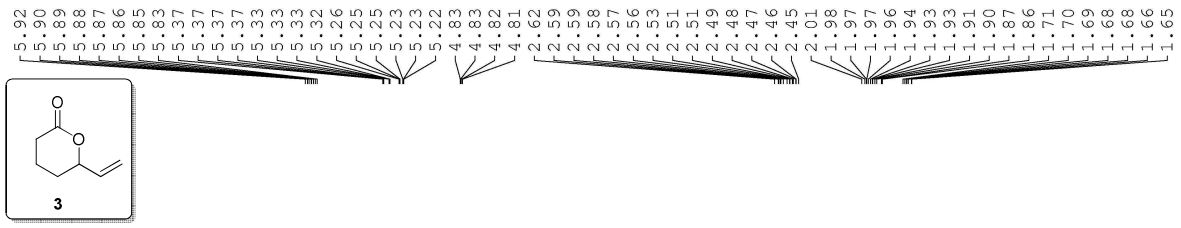
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5.32
5.26
5.25
5.23
5.23
5.22
4.83
4.83
4.82
4.81
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2.59
2.58
2.57
2.56
2.53
2.51
2.51
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2.45
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1.97
1.96
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1.91
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1.68
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1.65

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O
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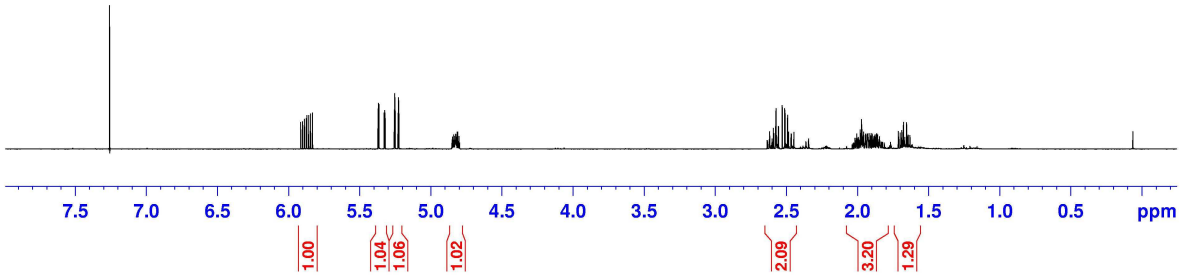
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1.06
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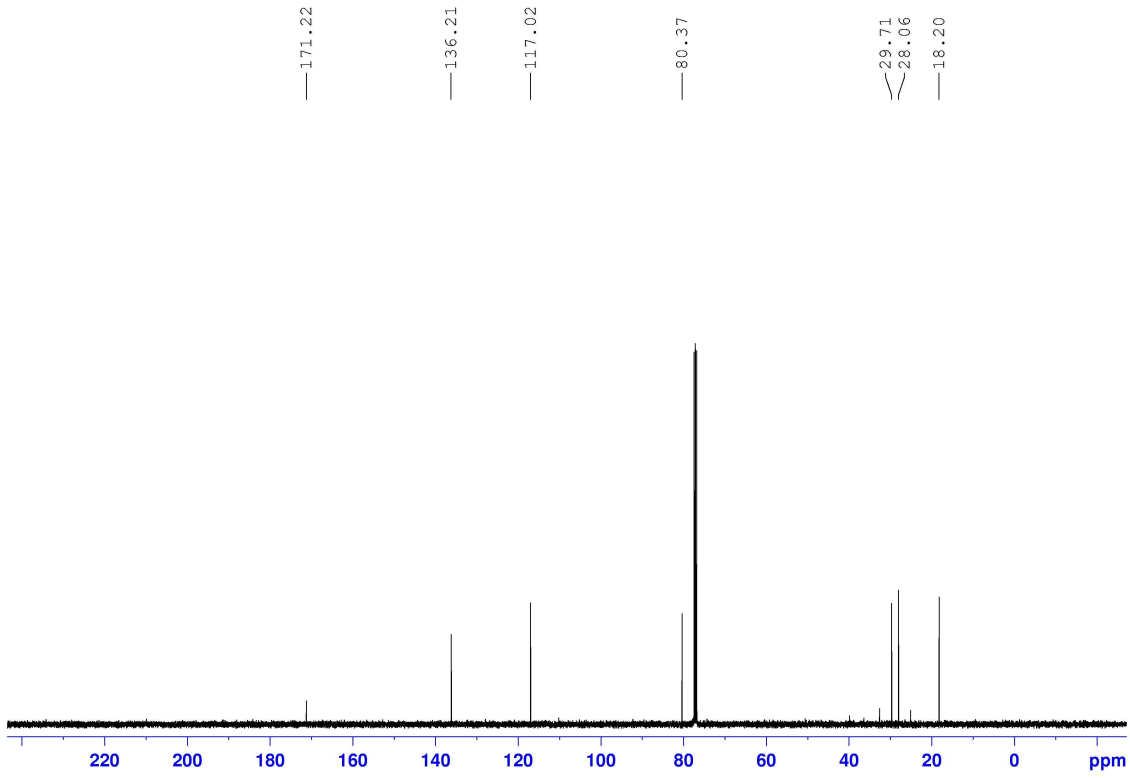
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120
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60
40
20
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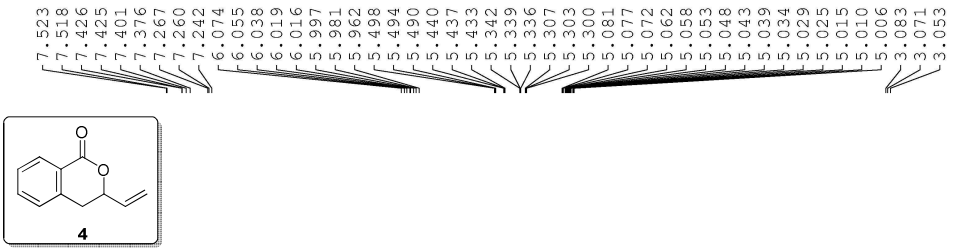
ppm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6.038
6.019
6.016
5.997
5.981
5.962
5.498
5.494
5.490
5.440
5.437
5.433
5.342
5.339
5.336
5.307
5.303
5.300
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5.077
5.072
5.062
5.058
5.053
5.048
5.043
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5.010
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3.083
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3.053

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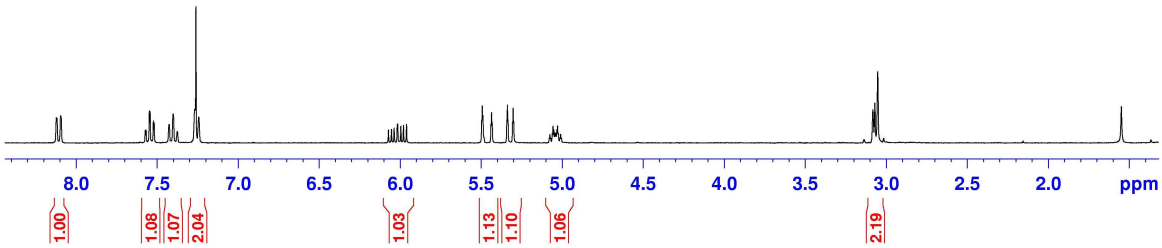
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1.03
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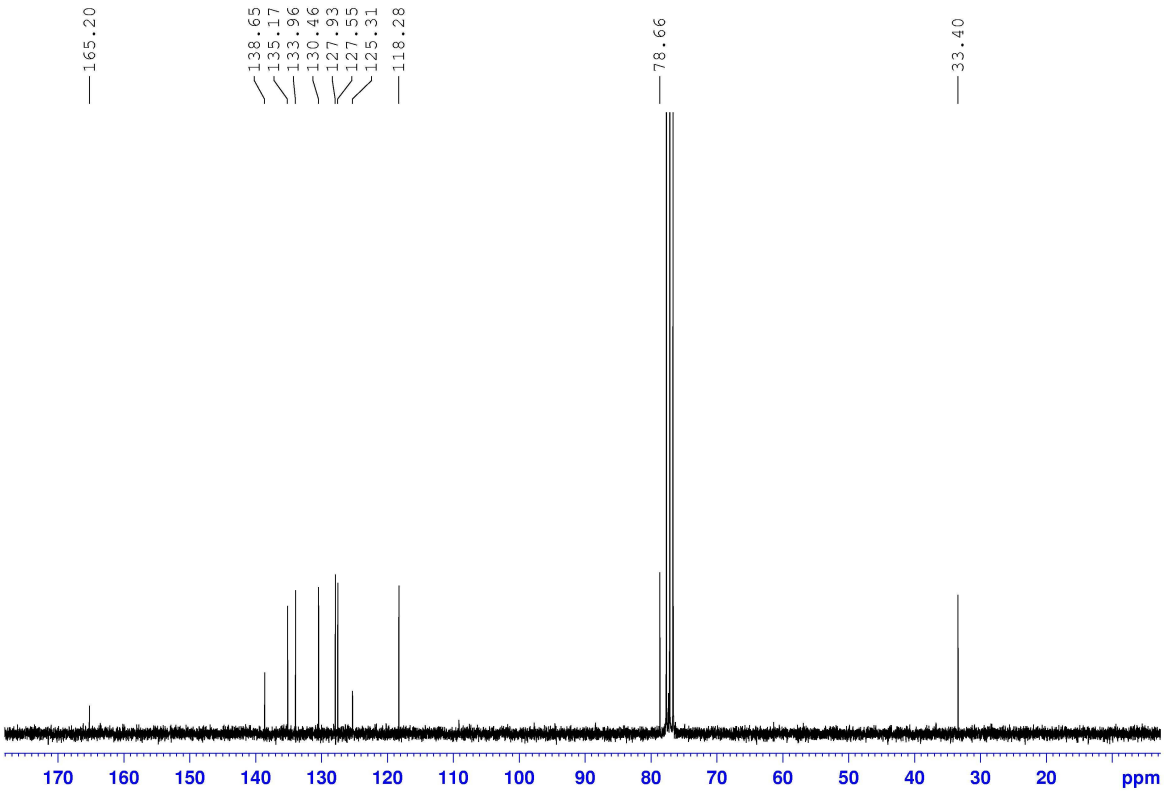
1.10
1.06
2.19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125.31
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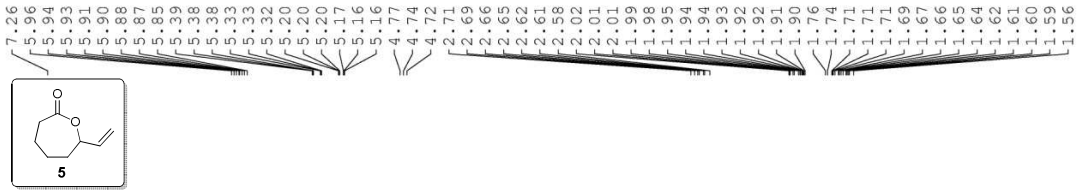
ppm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5.87
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5.38
5.33
5.33
5.32
5.20
5.20
5.20
5.17
5.16
5.16
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4.74
4.72
2.71
2.69
2.66
2.65
2.62
2.61
2.58
2.02
2.01
2.01
1.99
1.98
1.95
1.94
1.94
1.93
1.92
1.92
1.91
1.90
1.76
1.74
1.71
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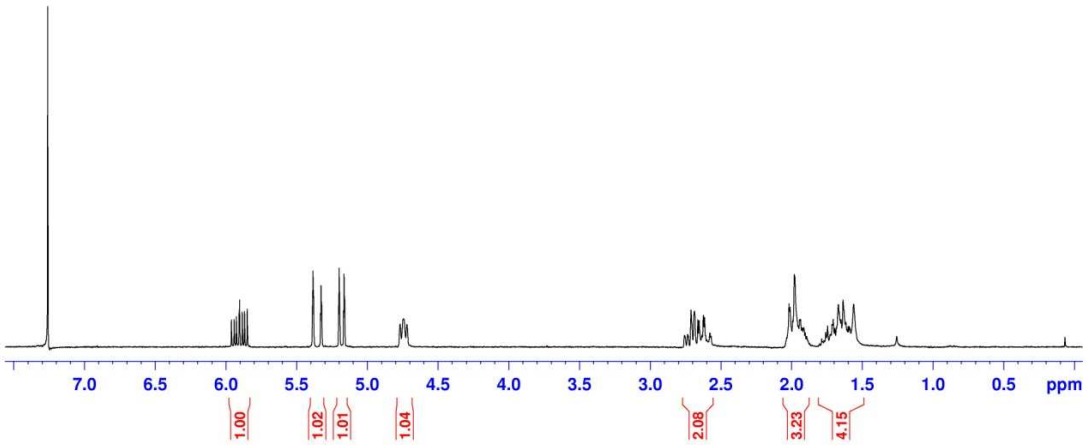
1.59
1.56

5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4.0
3.5
3.0
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2.0
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1.0
0.5
ppm
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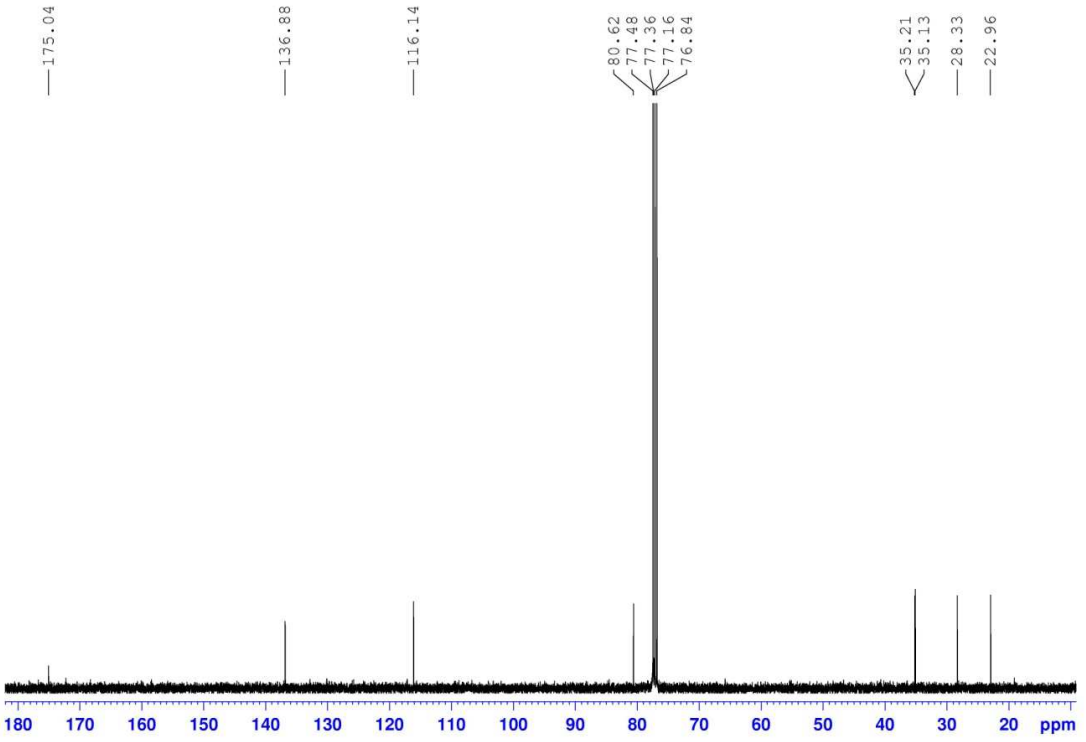
1.02
1.01
1.04
2.08
3.23
4.15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28.33
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150
140
130
120
110
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80
70
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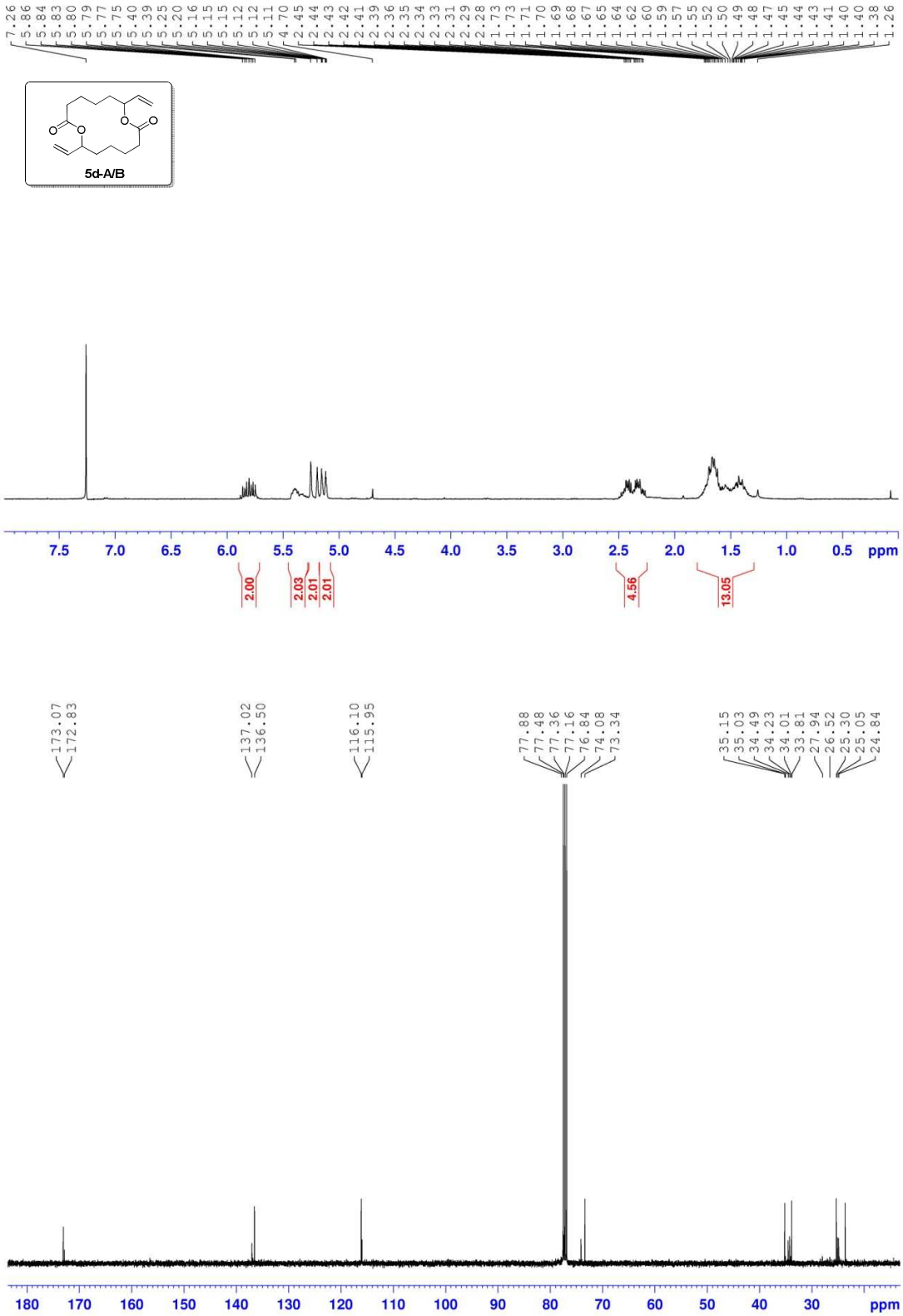
50
40
30
20
ppm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5.16
5.15
5.12
5.11
4.70
2.45
2.44
2.43
2.42
2.41
2.39
2.36
2.35
2.34
2.33
2.31
2.29
2.28
1.73
1.73
1.71
1.70
1.69
1.68
1.67
1.65
1.64
1.62
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1.59
1.57
1.55
1.52
1.50
1.49
1.48
1.47
1.45
1.44
1.43
1.41
1.40
1.40
1.38
1.26
5d-A/B
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
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2.03
2.01
2.01
4.56
13.05
173.07
172.83
137.02
136.50
116.10
115.95
77.88
77.48
77.36
77.16
76.84
74.08
73.34
35.15
35.03
34.49
34.23
34.01
33.81
27.94
26.52
25.30
25.05
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170
160
150
140
130
120
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90
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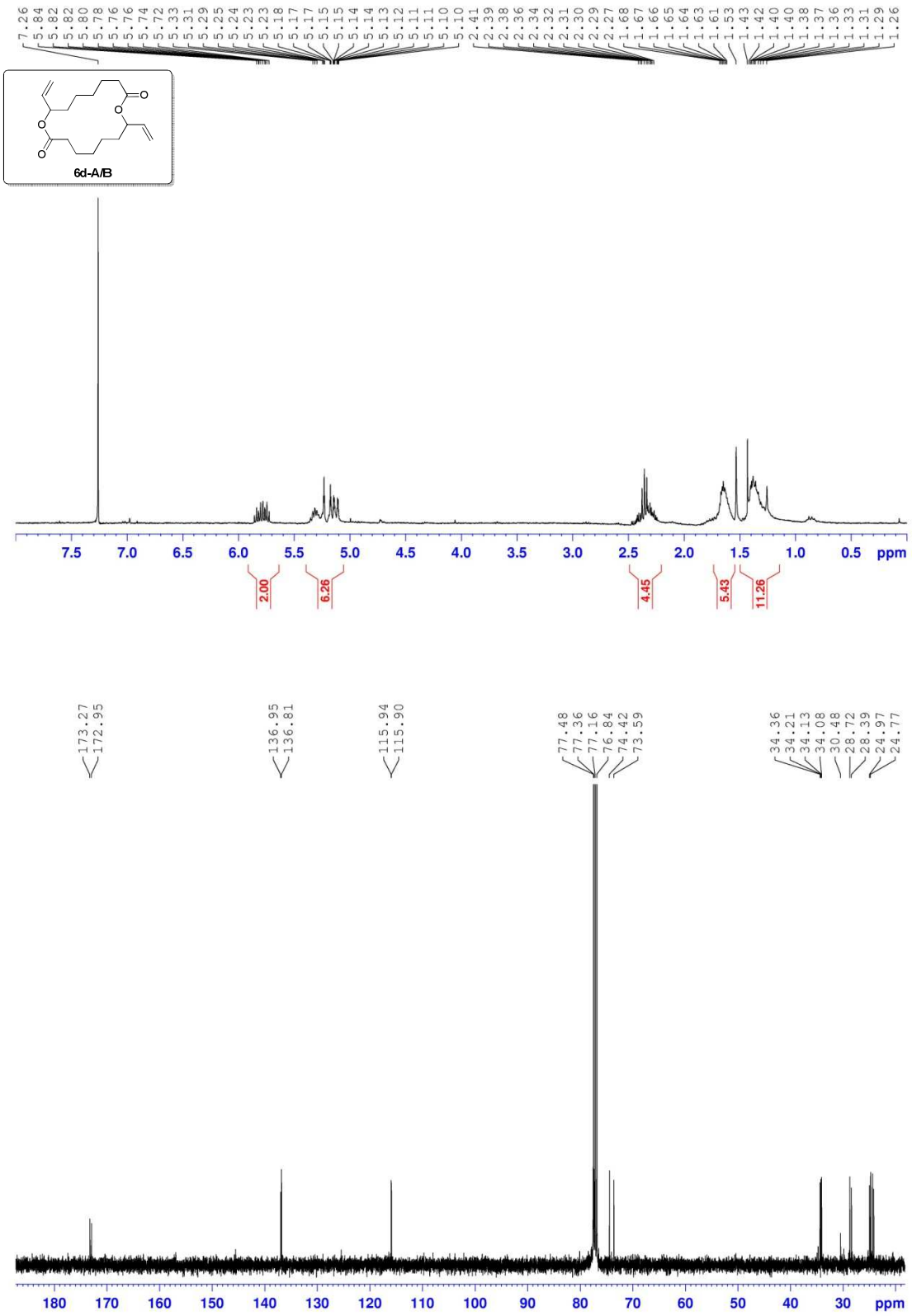
50
40
30
ppm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5.25
5.24
5.23
5.23
5.18
5.17
5.17
5.15
5.15
5.14
5.14
5.13
5.12
5.11
5.11
5.10
5.10
2.41
2.39
2.38
2.36
2.34
2.32
2.31
2.30
2.29
2.27
1.68
1.67
1.66
1.65
1.64
1.63
1.61
1.53
1.43
1.42
1.40
1.40
1.38
1.37
1.36
1.33
1.31
1.29
1.26
6d-A/B
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.00
6.26
4.45
5.43
11.26
173.27
172.95
136.95
136.81
115.94
115.90
77.48
77.36
77.16
76.84
74.42
73.59
34.36
34.21
34.13
34.08
30.48
28.72
28.39
24.97
24.77
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170
160
150
140
130
120
110
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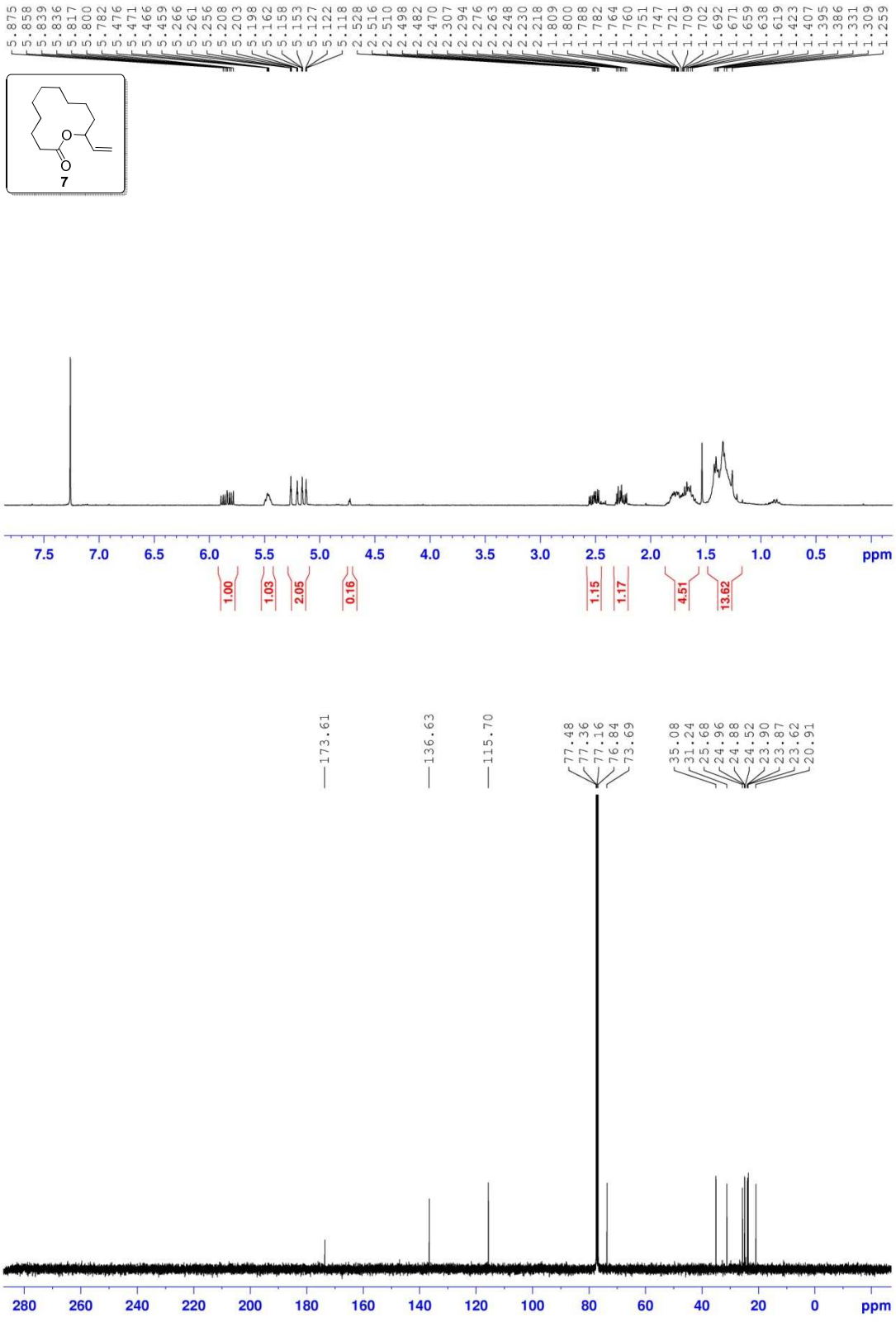
90
80
70
60
50
40
30
ppm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5.208
5.203
5.198
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5.127
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2.510
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2.263
2.248
2.230
2.218
1.809
1.800
1.788
1.782
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1.751
1.747
1.721
1.709
1.702
1.692
1.671
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1.638
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1.423
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1.386
1.331
1.309
1.259
O
O
7
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5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
1.03
2.05
0.16
1.15
1.17
4.51
13.62
173.61
136.63
115.70
77.48
77.36
77.16
76.84
73.69
35.08
31.24
25.68
24.96
24.88
24.52
23.90
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260
240
220
200
180
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120
100
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40
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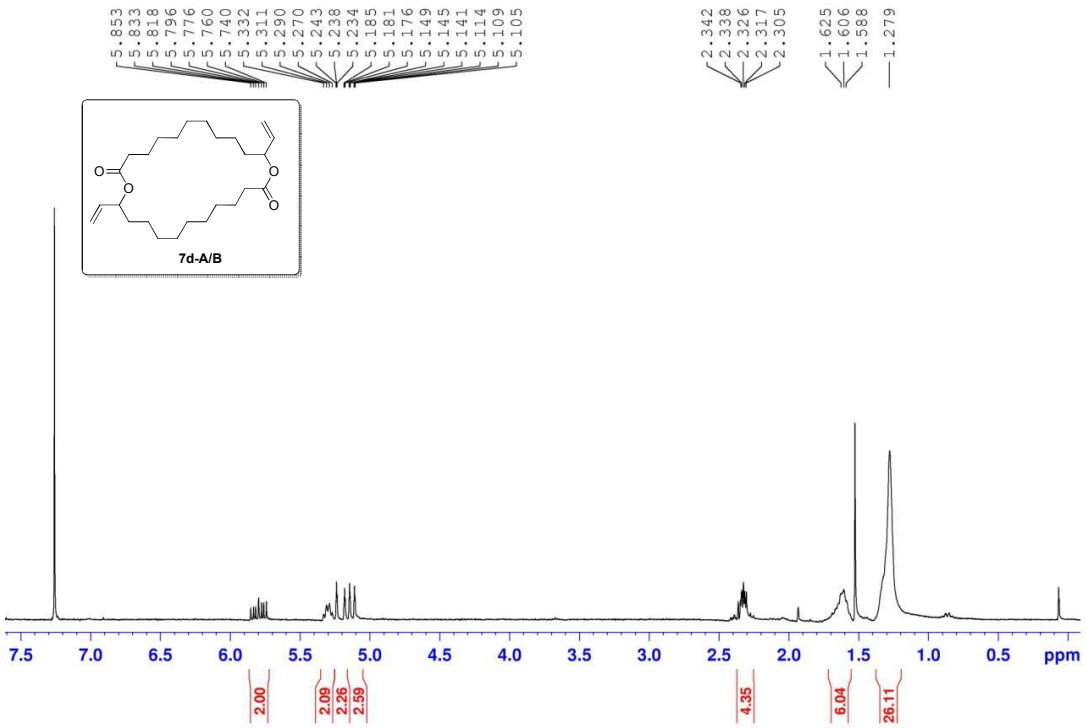
0
ppm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5.270
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5.238
5.234
5.185
5.181
5.176
5.149
5.145
5.141
5.114
5.109
5.105
2.342
2.338
2.326
2.317
2.305
1.625
1.606
1.588
1.279
7d-A/B
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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0.5
ppm
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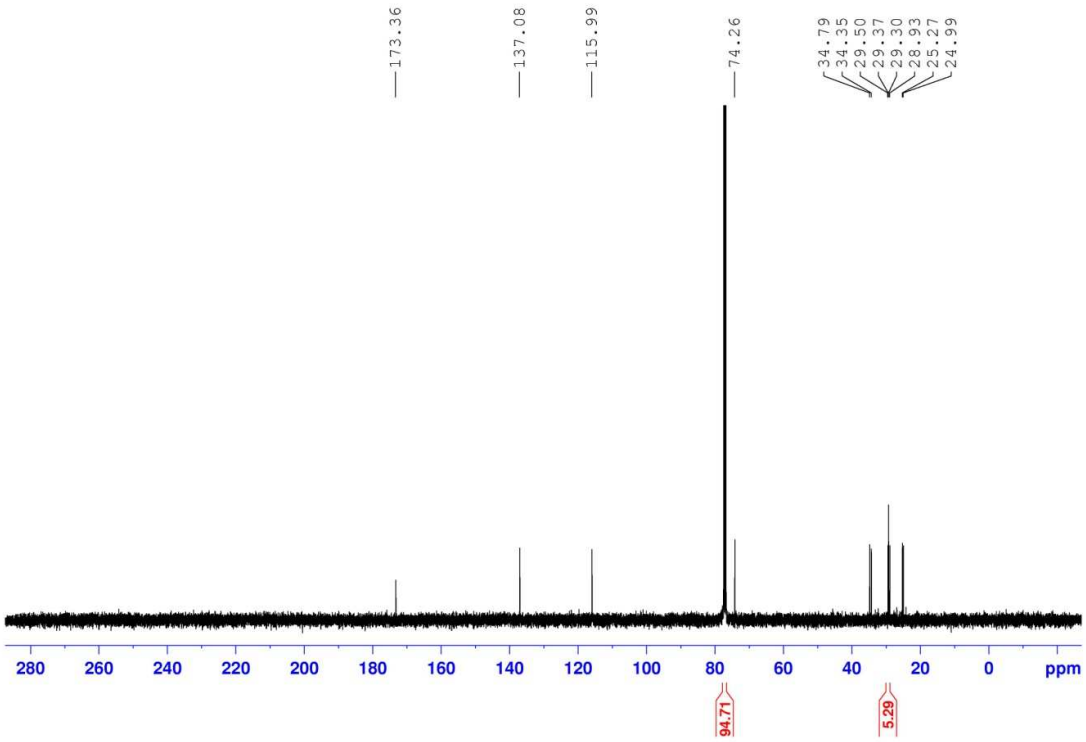
2.26
2.59
4.35
6.04
26.11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29.37
29.30
28.93
25.27
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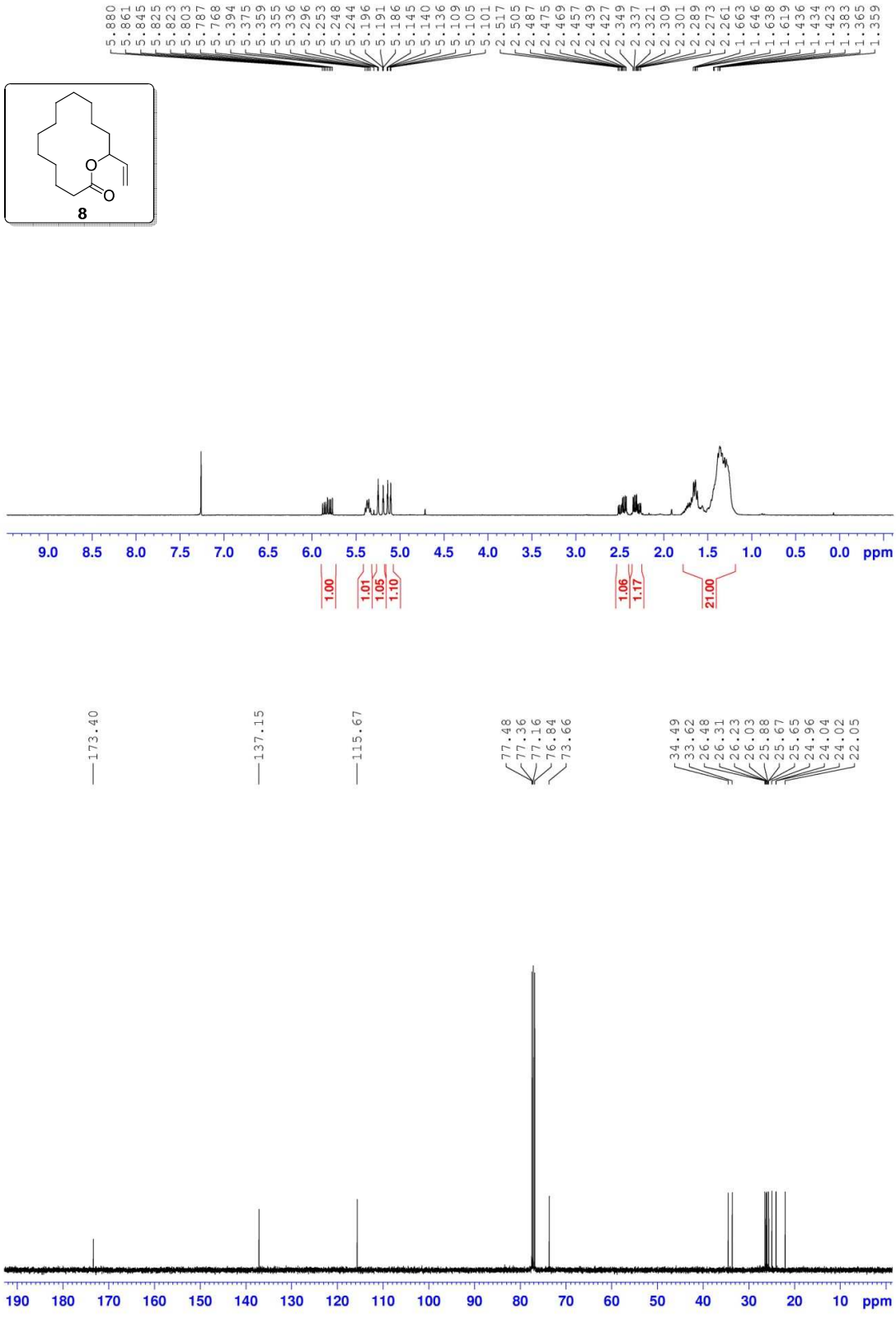
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm
94.71
5.29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5.355
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5.244
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5.186
5.145
5.140
5.136
5.109
5.105
5.101
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2.487
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2.469
2.457
2.439
2.427
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2.337
2.321
2.309
2.301
2.289
2.273
2.261
1.663
1.646
1.638
1.619
1.436
1.434
1.423
1.383
1.365
1.359
O
O
8
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.00
1.01
1.05
1.10
1.06
1.17
21.00
173.40
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115.67
77.48
77.36
77.16
76.84
73.66
34.49
33.62
26.48
26.31
26.23
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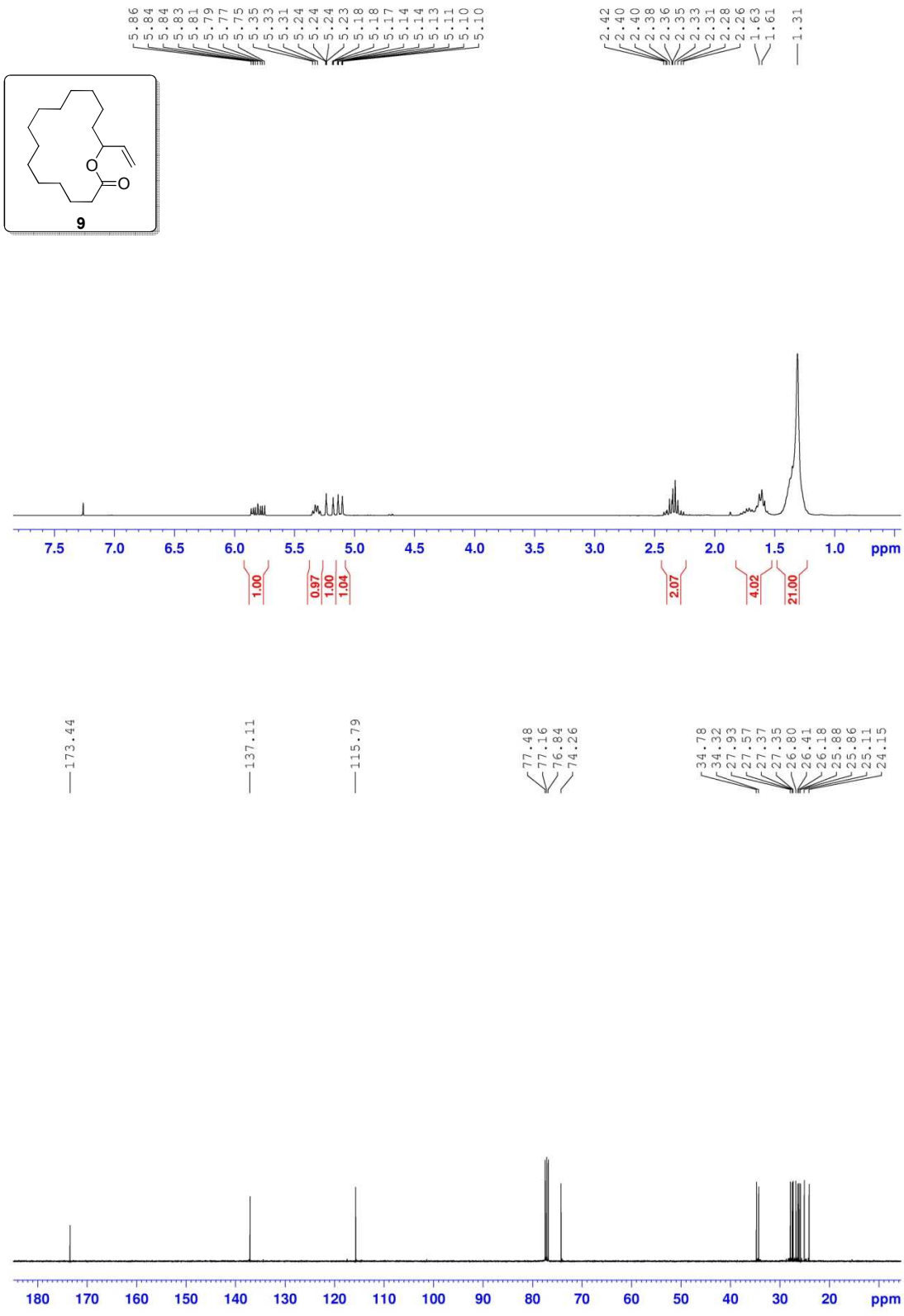
25.65
24.96
24.04
24.02
22.05
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm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5.24
5.24
5.23
5.18
5.18
5.17
5.14
5.14
5.13
5.11
5.10
5.10
2.42
2.40
2.40
2.38
2.36
2.35
2.33
2.31
2.28
2.26
1.63
1.61
1.31
O
O
9
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
ppm
1.00
0.97
1.00
1.04
2.07
4.02
21.00
173.44
137.11
115.79
77.48
77.16
76.84
74.26
34.78
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27.93
27.57
27.37
27.35
26.80
26.41
26.18
25.88
25.86
25.11
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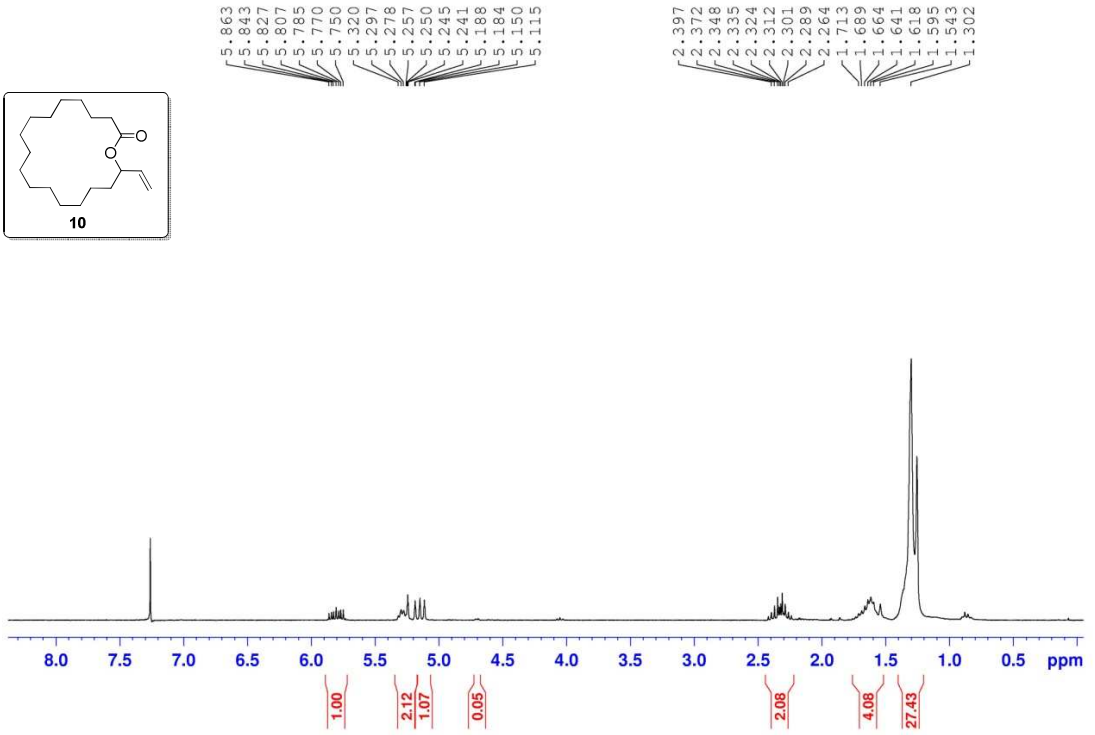
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm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5.245
5.241
5.188
5.184
5.150
5.115
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2.312
2.301
2.289
2.264
1.713
1.689
1.664
1.641
1.618
1.595
1.543
1.302
10
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7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
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1.0
0.5
ppm
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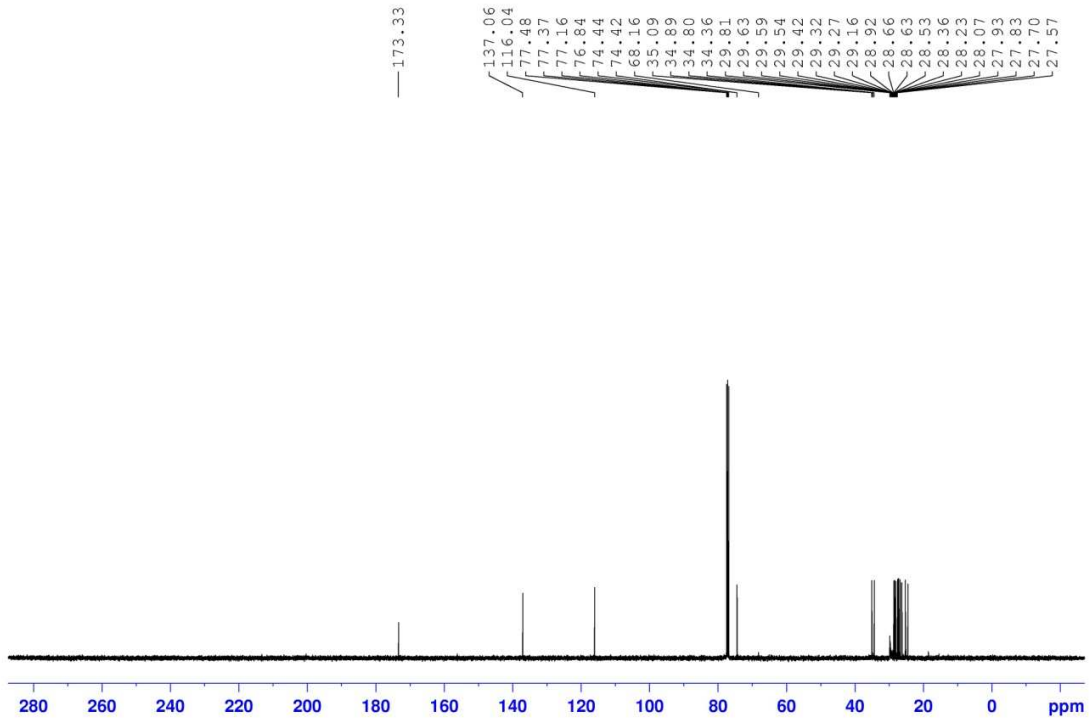
2.08
4.08
27.43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74.44
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68.16
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34.80
34.36
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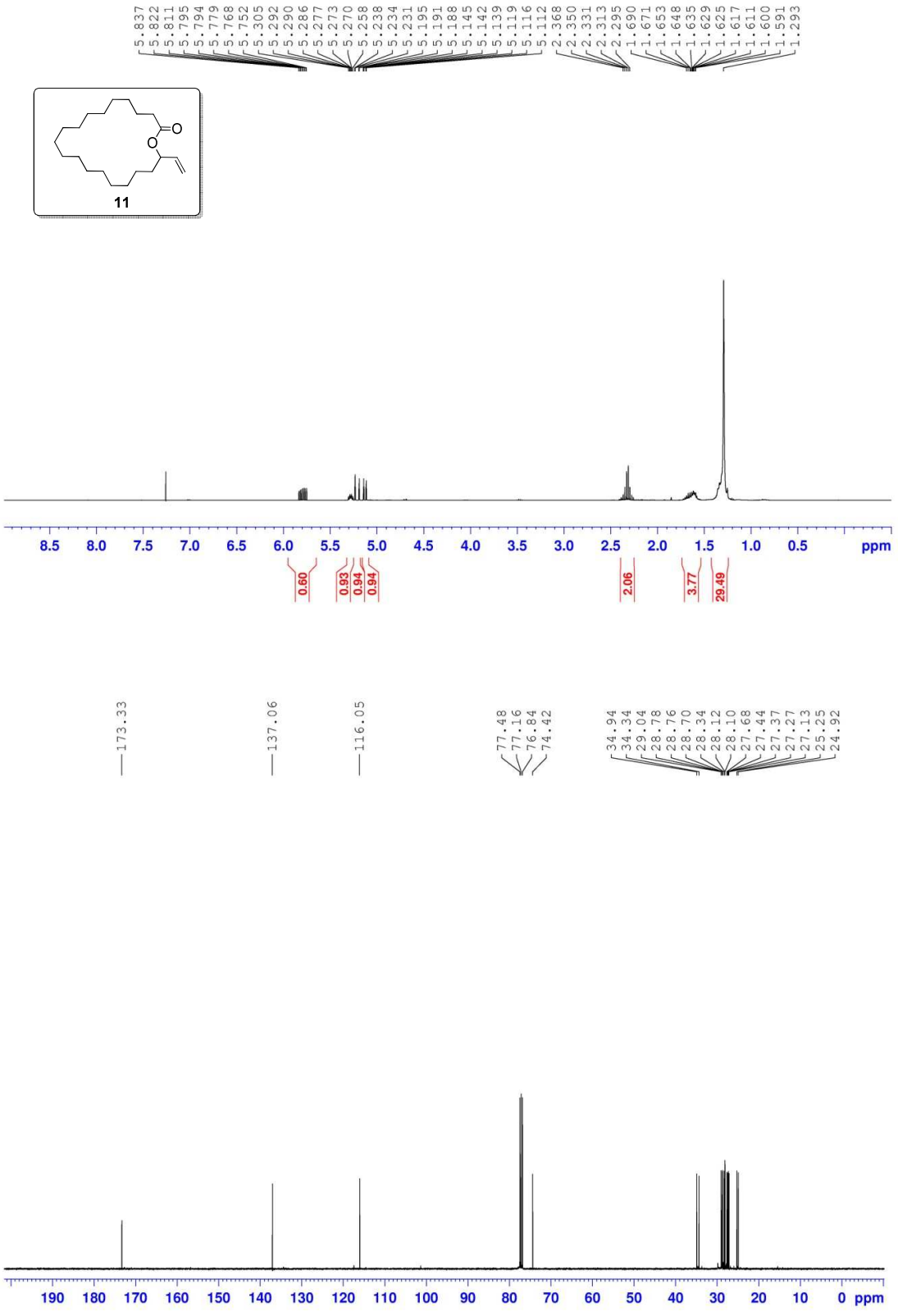
29.63
29.59
29.54
29.42
29.32
29.27
29.16
28.92
28.66
28.63
28.53
28.36
28.23
28.07
27.93
27.83
27.70
27.57
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
ppm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5.811
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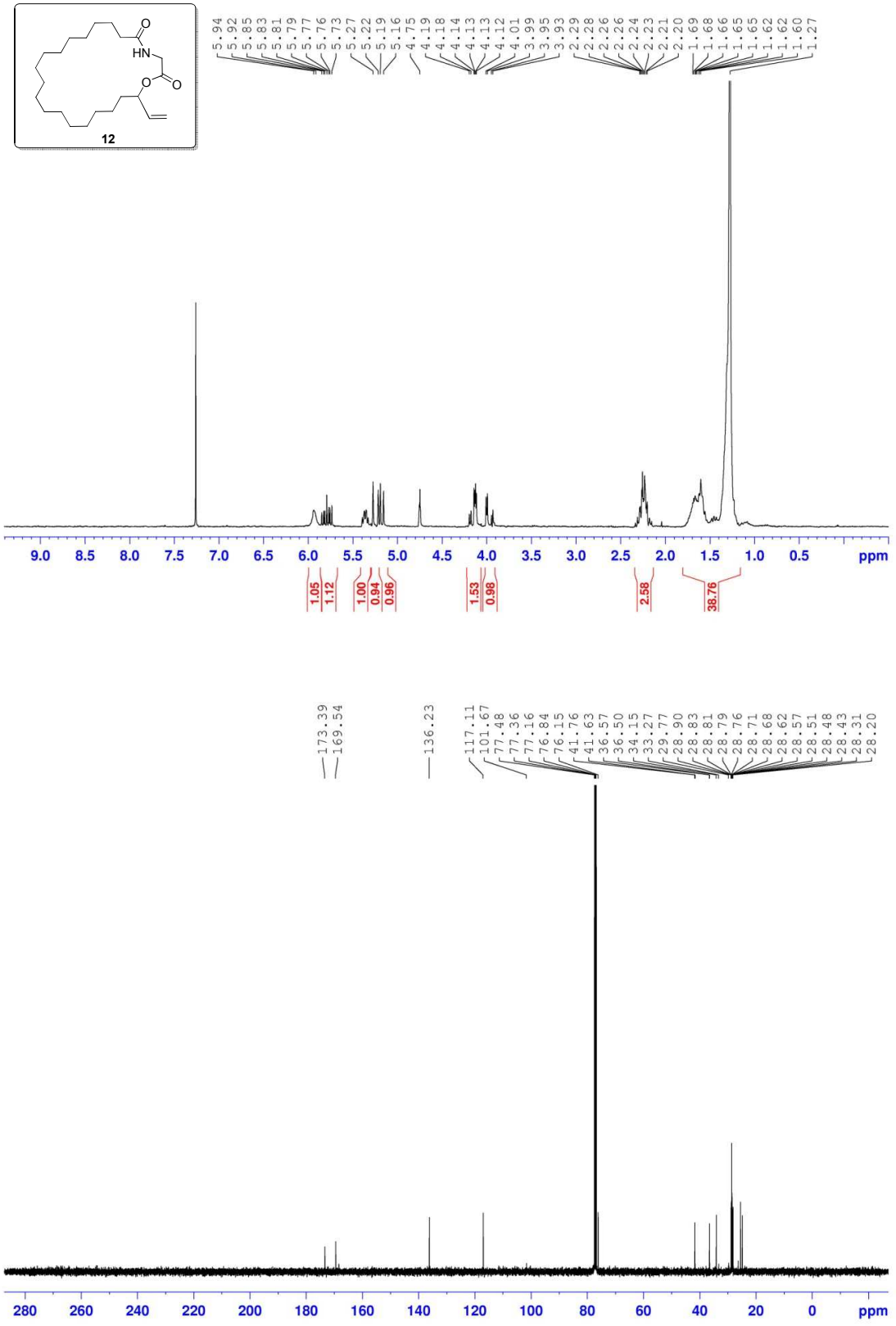
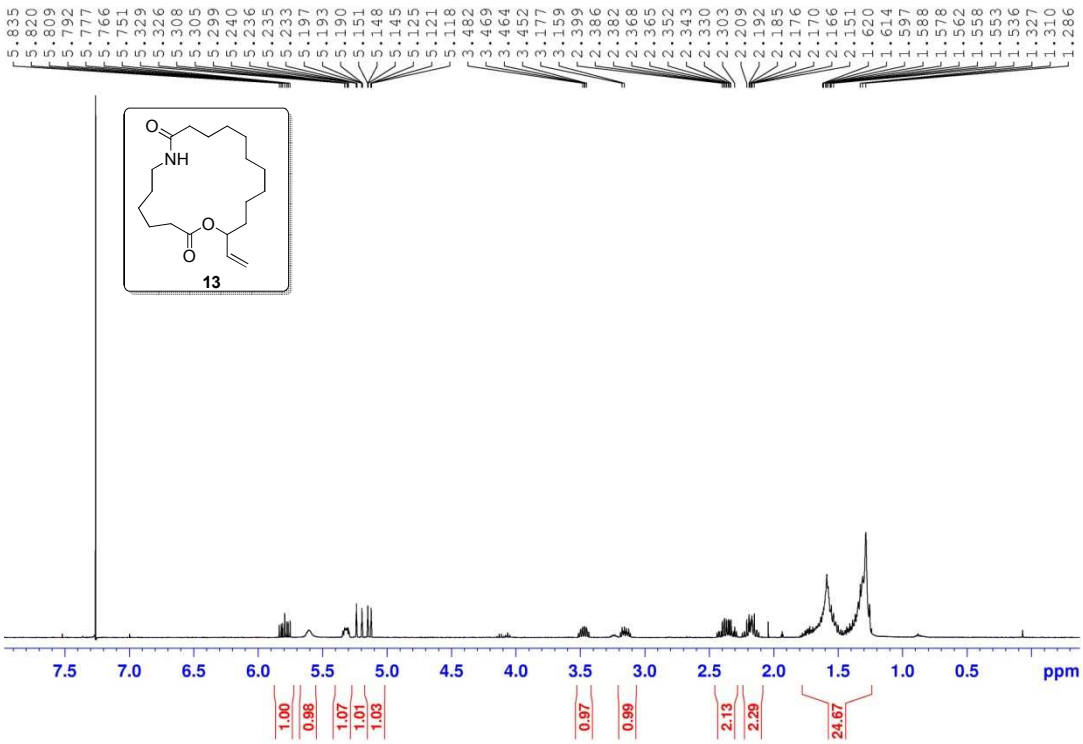
5.794
5.779
5.768
5.752
5.305
5.292
5.290
5.286
5.277
5.273
5.270
5.258
5.238
5.234
5.231
5.195
5.191
5.188
5.145
5.142
5.139
5.119
5.116
5.112
2.368
2.350
2.331
2.313
2.295
1.690
1.671
1.653
1.648
1.635
1.629
1.625
1.617
1.611
1.600
1.591
1.293
O
O
11
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
0.60
0.93
0.94
0.94
2.06
3.77
29.49
173.33
137.06
116.05
77.48
77.16
76.84
74.42
34.94
34.34
29.04
28.78
28.76
28.70
28.34
28.12
28.10
27.68
27.44
27.37
27.27
27.13
25.25
24.92
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


12
5.94
5.92
5.85
5.83
5.81
5.79
5.77
5.76
5.73
5.27
5.22
5.19
5.16
4.75
4.19
4.18
4.14
4.13
4.13
4.12
4.01
3.99
3.95
3.93
2.29
2.28
2.26
2.26
2.24
2.23
2.21
2.20
1.69
1.68
1.66
1.65
1.65
1.62
1.62
1.60
1.27
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.05
1.12
1.00
0.94
0.96
1.53
0.98
2.58
38.76
173.39
169.54
136.23
117.11
101.67
77.48
77.36
77.16
76.84
76.15
41.76
41.63
36.57
36.50
34.15
33.27
29.77
28.90
28.83
28.81
28.79
28.76
28.71
28.68
28.62
28.57
28.51
28.48
28.43
28.31
28.20
280 260 240 220 200 180 160 140 120 100 80 60 40 20 0 ppm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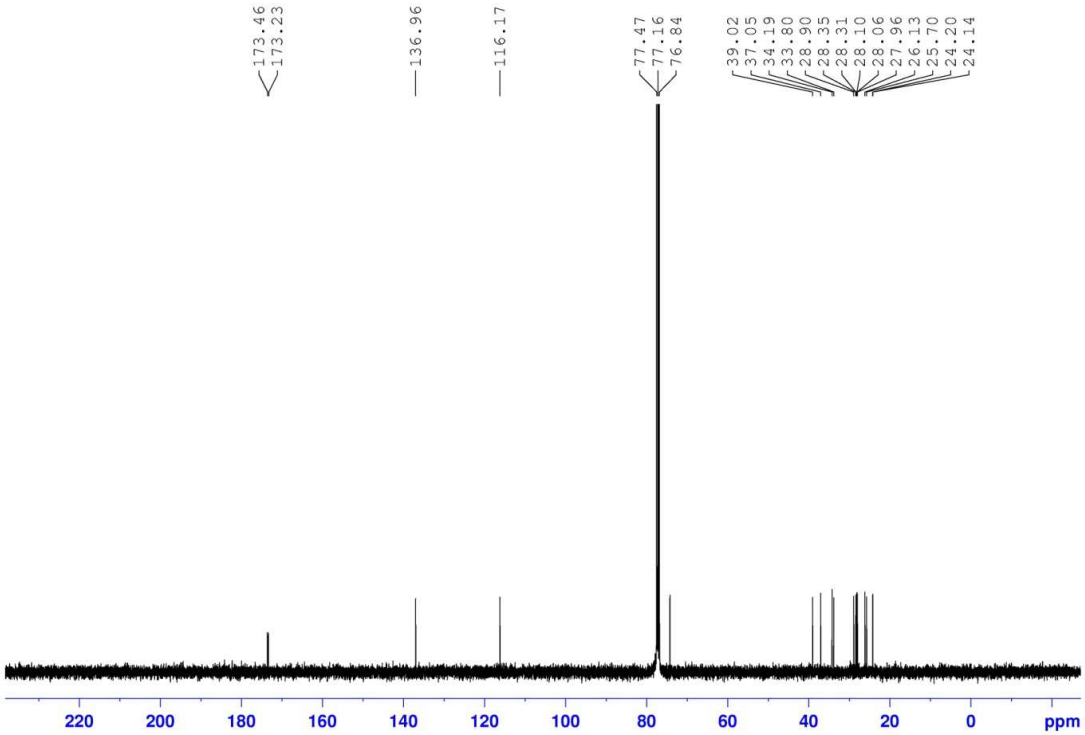
5.820
5.809
5.792
5.777
5.766
5.751
5.329
5.326
5.308
5.305
5.299
5.240
5.236
5.235
5.233
5.197
5.193
5.190
5.151
5.148
5.145
5.125
5.121
5.118
3.482
3.469
3.464
3.452
3.177
3.159
2.399
2.386
2.382
2.368
2.365
2.352
2.343
2.330
2.303
2.209
2.192
2.185
2.176
2.170
2.166
2.151
1.620
1.614
1.597
1.588
1.578
1.562
1.558
1.553
1.536
1.327
1.310
1.286
O
NH
O
O
13
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
0.98
1.07
1.01
1.03
0.97
0.99
2.13
2.29
24.67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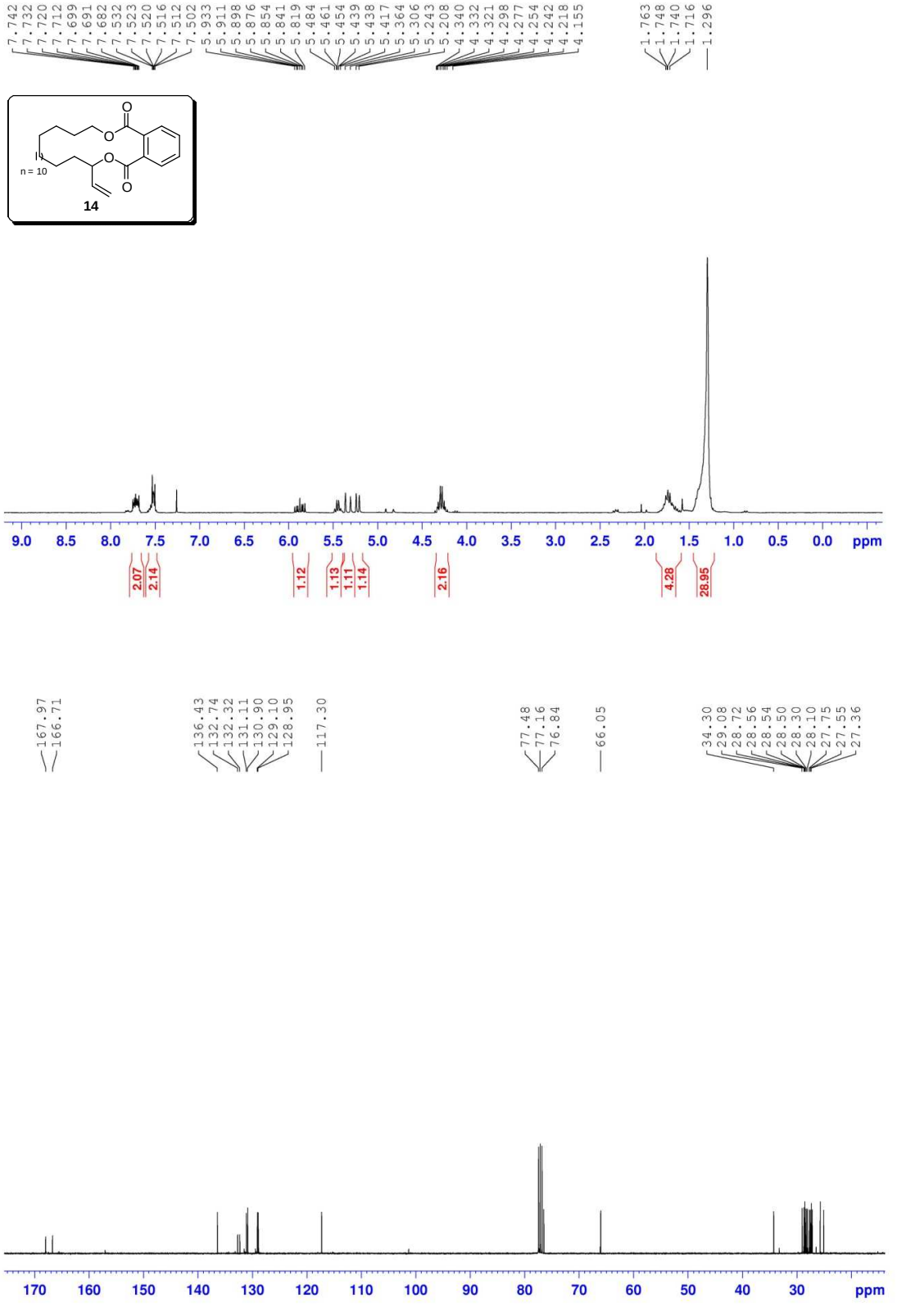
173.23
136.96
116.17
77.47
77.16
76.84
39.02
37.05
34.19
33.80
28.90
28.35
28.31
28.10
28.06
27.96
26.13
25.70
24.20
24.14
220
200
180
160
140
120
100
80
60
40
20
0
ppm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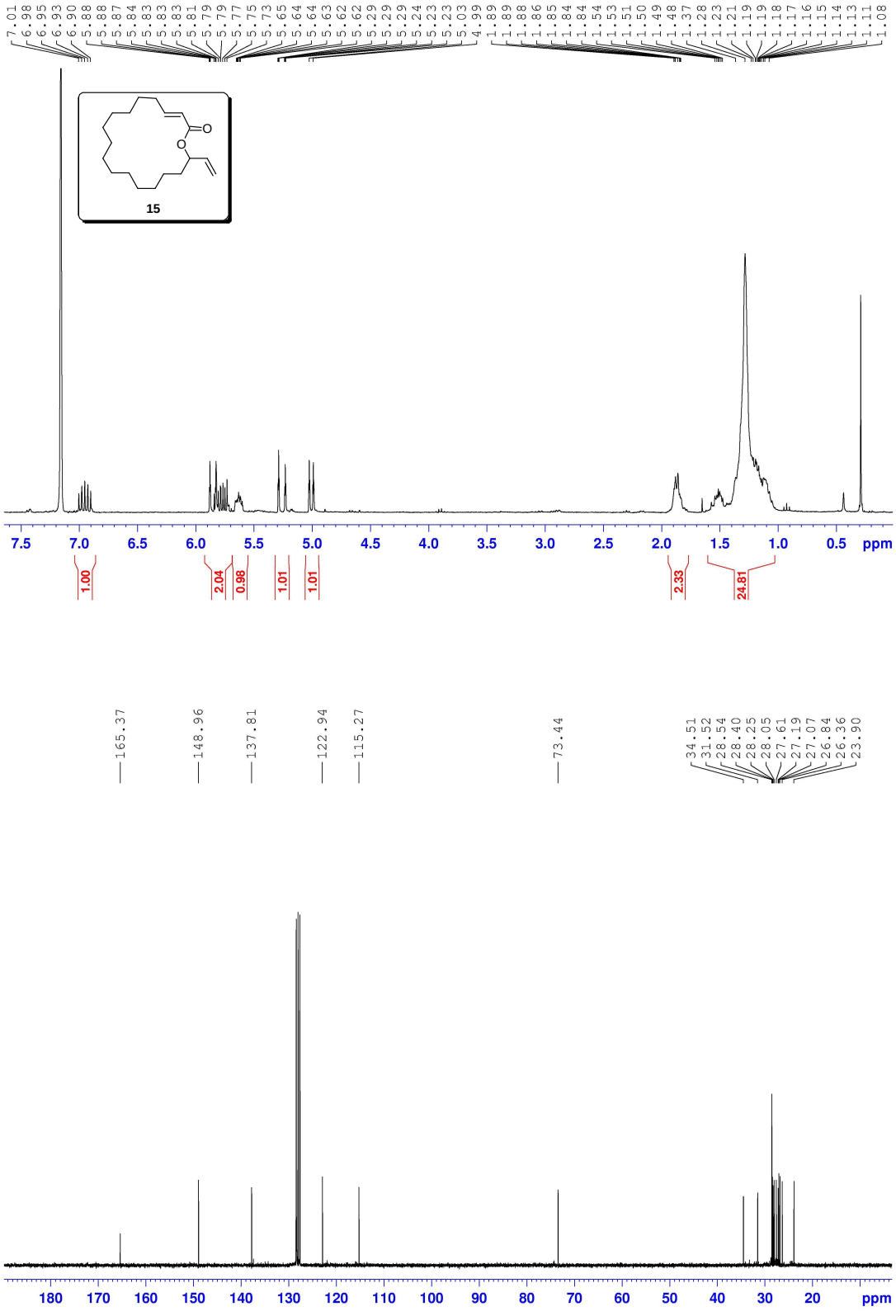
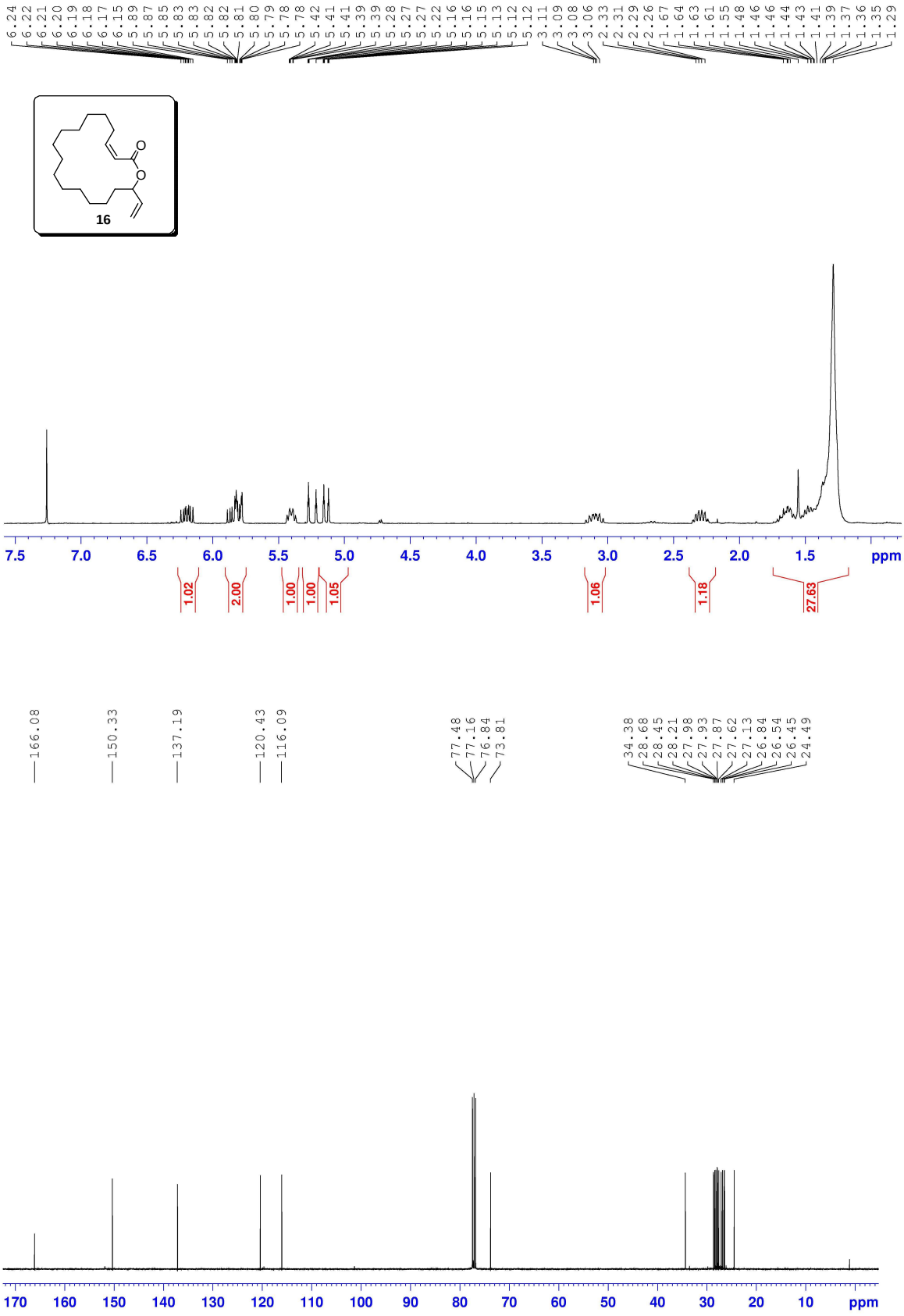
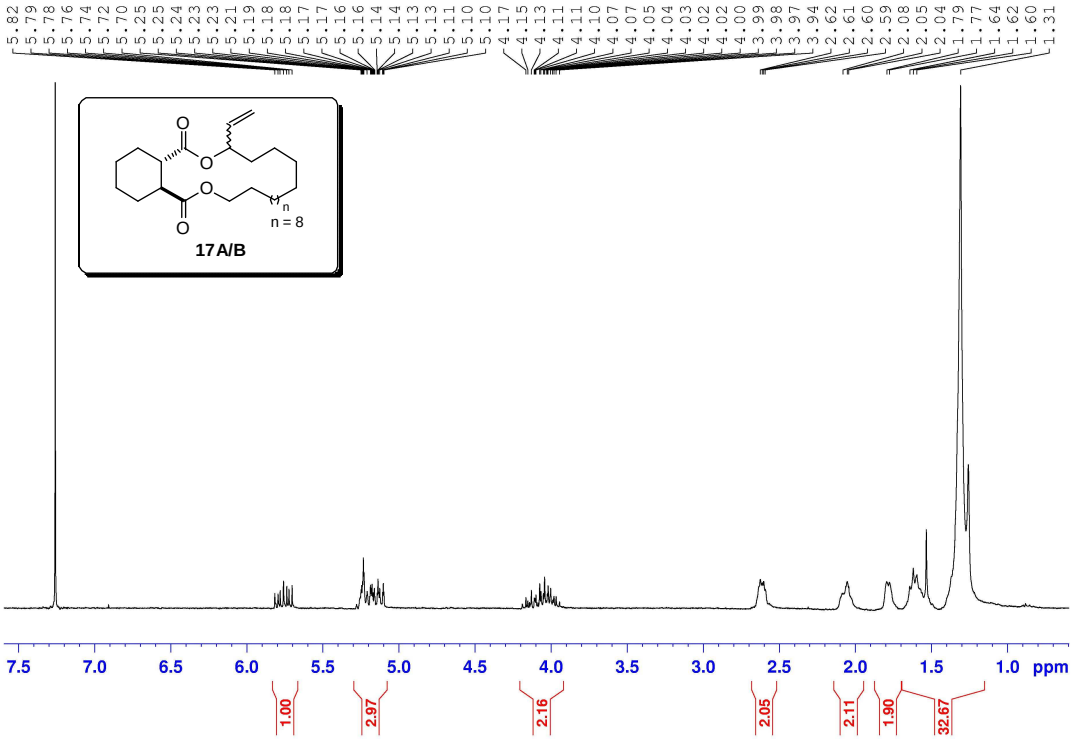
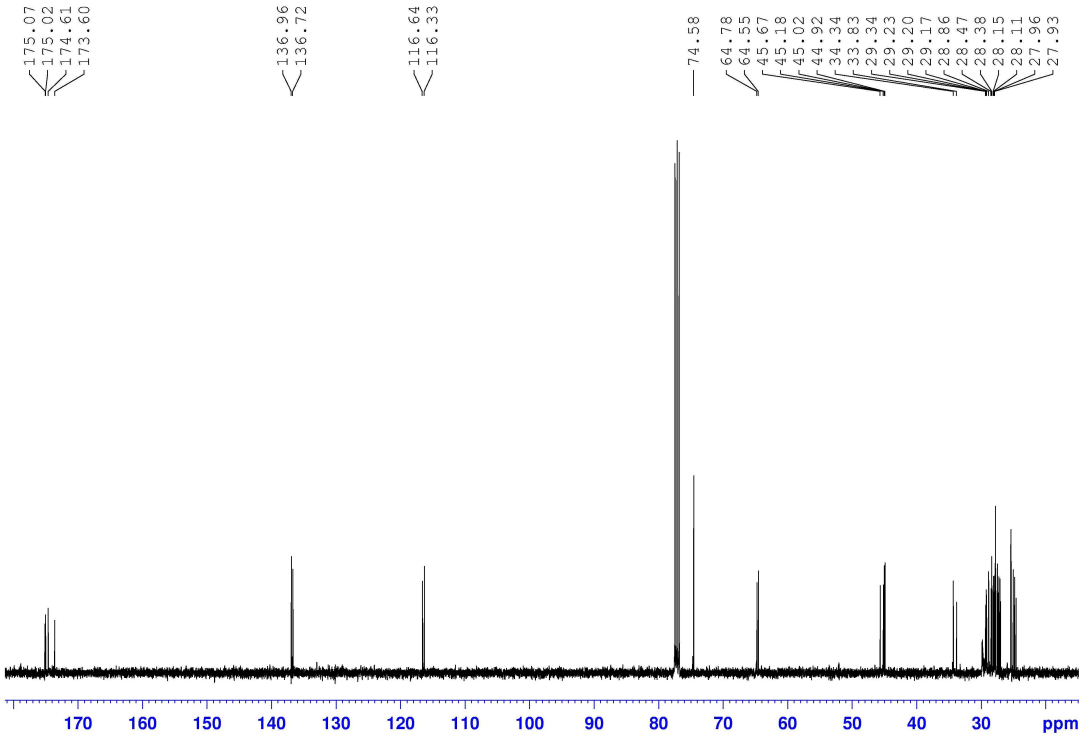
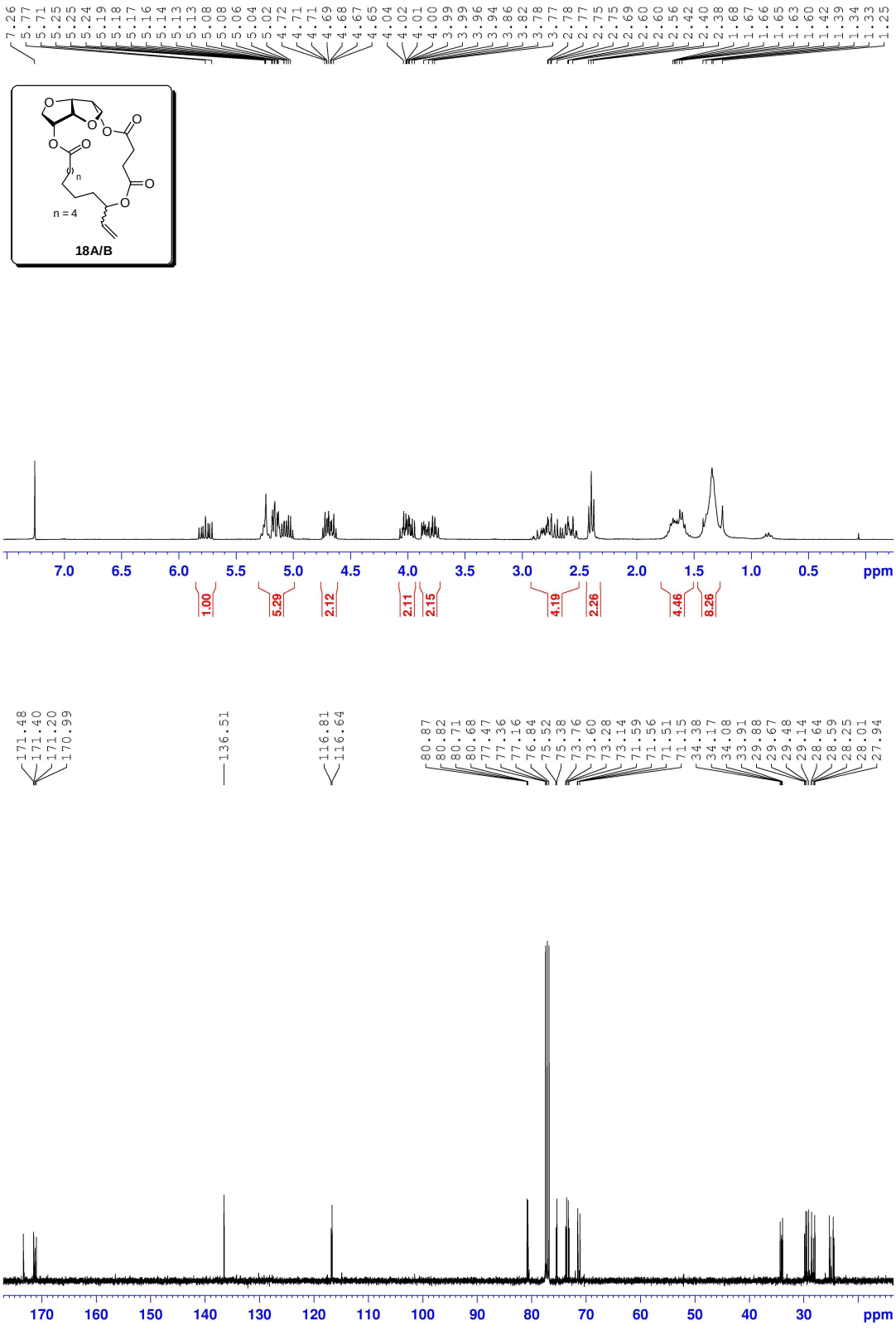
7.732
7.720
7.712
7.699
7.691
7.682
7.532
7.523
7.520
7.516
7.512
7.502
5.933
5.911
5.898
5.876
5.854
5.841
5.819
5.484
5.461
5.454
5.439
5.438
5.417
5.364
5.306
5.243
5.208
4.340
4.332
4.321
4.298
4.277
4.254
4.242
4.218
4.155
1.763
1.748
1.740
1.716
1.296
n = 10
14
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
2.07
2.14
1.12
1.13
1.11
1.14
2.16
4.28
28.95
167.97
166.71
136.43
132.74
132.32
131.11
130.90
129.10
128.95
117.30
77.48
77.16
76.84
66.05
34.30
29.08
28.72
28.56
28.54
28.50
28.30
28.10
27.75
27.55
27.36
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm


7.01
6.98
6.95
6.93
6.90
5.88
5.87
5.84
5.83
5.83
5.81
5.79
5.79
5.77
5.75
5.73
5.65
5.64
5.63
5.62
5.29
5.29
5.24
5.23
5.03
4.99
1.89
1.89
1.88
1.86
1.85
1.84
1.84
1.54
1.53
1.51
1.50
1.49
1.48
1.37
1.28
1.23
1.21
1.19
1.19
1.18
1.17
1.16
1.15
1.14
1.13
1.11
1.08
O
O
15
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
2.04
0.98
1.01
1.01
2.33
24.81
165.37
148.96
137.81
122.94
115.27
73.44
34.51
31.52
28.54
28.40
28.25
28.05
27.61
27.19
27.07
26.84
26.36
23.90
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm


6.24
6.22
6.21
6.20
6.19
6.18
6.17
6.15
5.89
5.87
5.85
5.83
5.83
5.82
5.81
5.80
5.79
5.78
5.78
5.42
5.41
5.41
5.39
5.39
5.28
5.27
5.27
5.22
5.16
5.16
5.15
5.13
5.12
5.12
3.11
3.09
3.08
3.06
2.33
2.31
2.29
2.26
1.67
1.64
1.63
1.61
1.55
1.48
1.46
1.46
1.44
1.43
1.41
1.39
1.37
1.36
1.35
1.29
O
O
16
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
ppm
1.02
2.00
1.00
1.00
1.05
1.06
1.18
27.63
166.08
150.33
137.19
120.43
116.09
77.48
77.16
76.84
73.81
34.38
28.68
28.45
28.21
27.98
27.93
27.87
27.62
27.13
26.84
26.54
26.45
24.49
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm


5.82 5.79 5.78 5.76 5.74 5.72 5.70 5.25 5.25 5.24 5.23 5.21 5.19 5.18 5.17 5.17 5.16 5.16 5.14 5.14 5.13 5.13 5.11 5.10 5.10
4.17 4.15 4.13 4.11 4.11 4.10 4.07 4.07 4.05 4.04 4.03 4.02 4.02 4.00 3.99 3.98 3.97 3.94 2.62 2.61 2.60 2.59 2.08 2.05 2.04 1.79 1.77 1.64 1.62 1.60 1.31
O
O
O
O
n
n = 8
17A/B
7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 ppm
1.00
2.97
2.16
2.05
2.11
1.90
32.67


175.07 175.02 174.61 173.60
136.96 136.72
116.64 116.33
74.58
64.78 64.55 45.67 45.18 45.02 44.92 34.34 33.83 29.34 29.23 29.20 29.17 28.86 28.47 28.38 28.15 28.11 27.96 27.93
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm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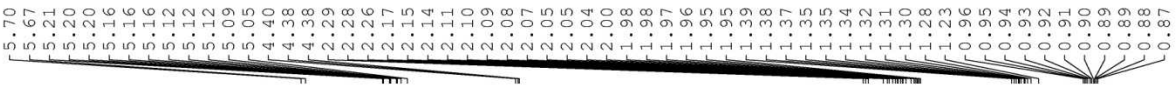
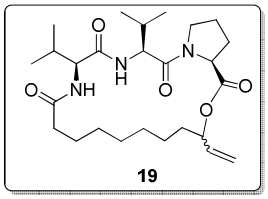
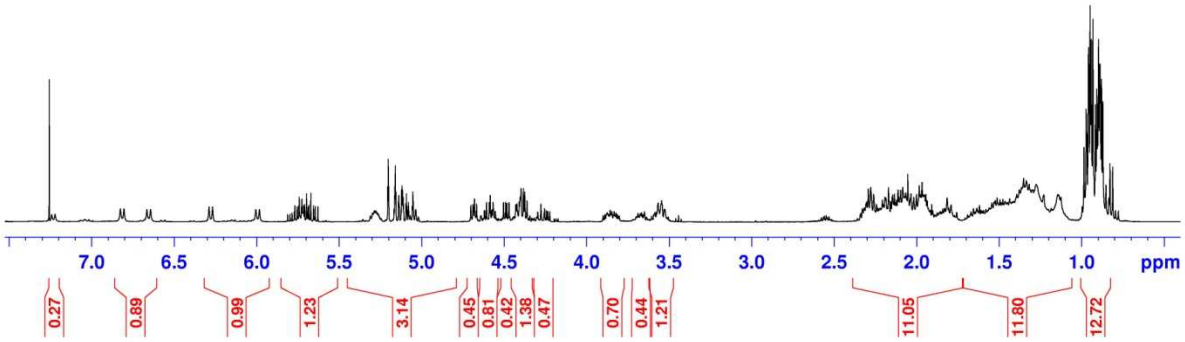
5.77
5.71
5.25
5.25
5.24
5.19
5.18
5.17
5.16
5.14
5.13
5.13
5.08
5.08
5.06
5.04
5.02
4.72
4.71
4.71
4.69
4.68
4.67
4.65
4.04
4.02
4.01
4.00
3.99
3.99
3.96
3.94
3.86
3.82
3.78
3.77
2.78
2.77
2.75
2.75
2.69
2.60
2.60
2.56
2.42
2.40
2.38
1.68
1.67
1.66
1.65
1.63
1.60
1.42
1.39
1.34
1.33
1.25
n = 4
18A/B
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.00
5.29
2.12
2.11
2.15
4.19
2.26
4.46
8.26
171.48
171.40
171.20
170.99
136.51
116.81
116.64
80.87
80.82
80.71
80.68
77.47
77.36
77.16
76.84
75.52
75.38
73.76
73.60
73.28
73.14
71.59
71.56
71.51
71.15
34.38
34.17
34.08
33.91
29.88
29.67
29.48
29.14
28.64
28.59
28.25
28.01
27.94
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm

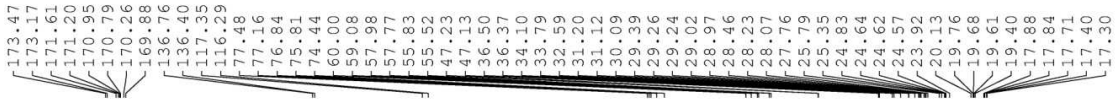


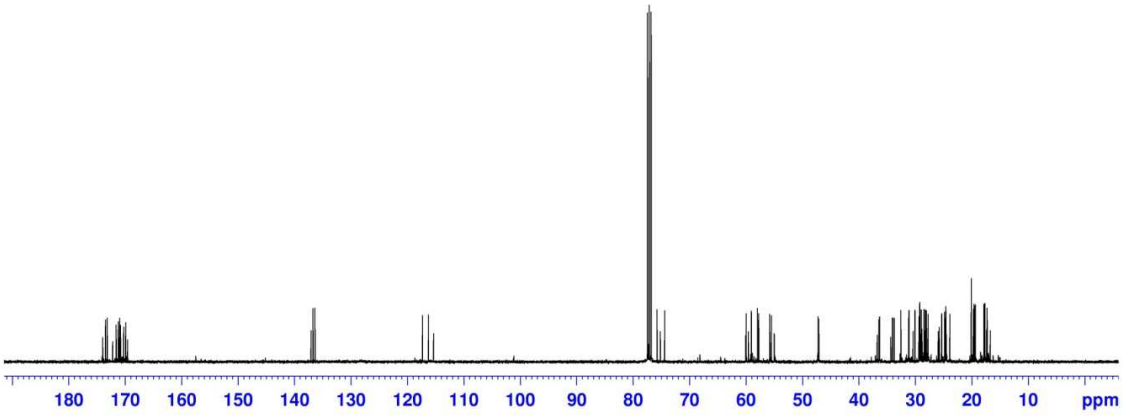


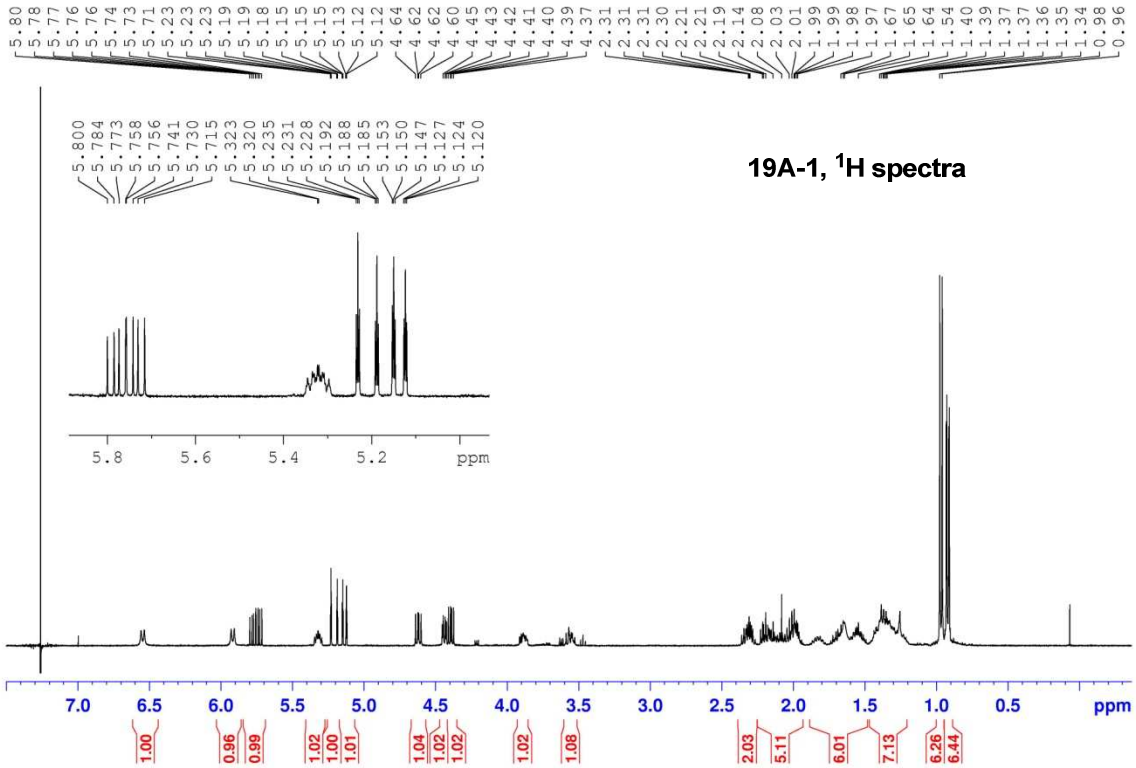
19

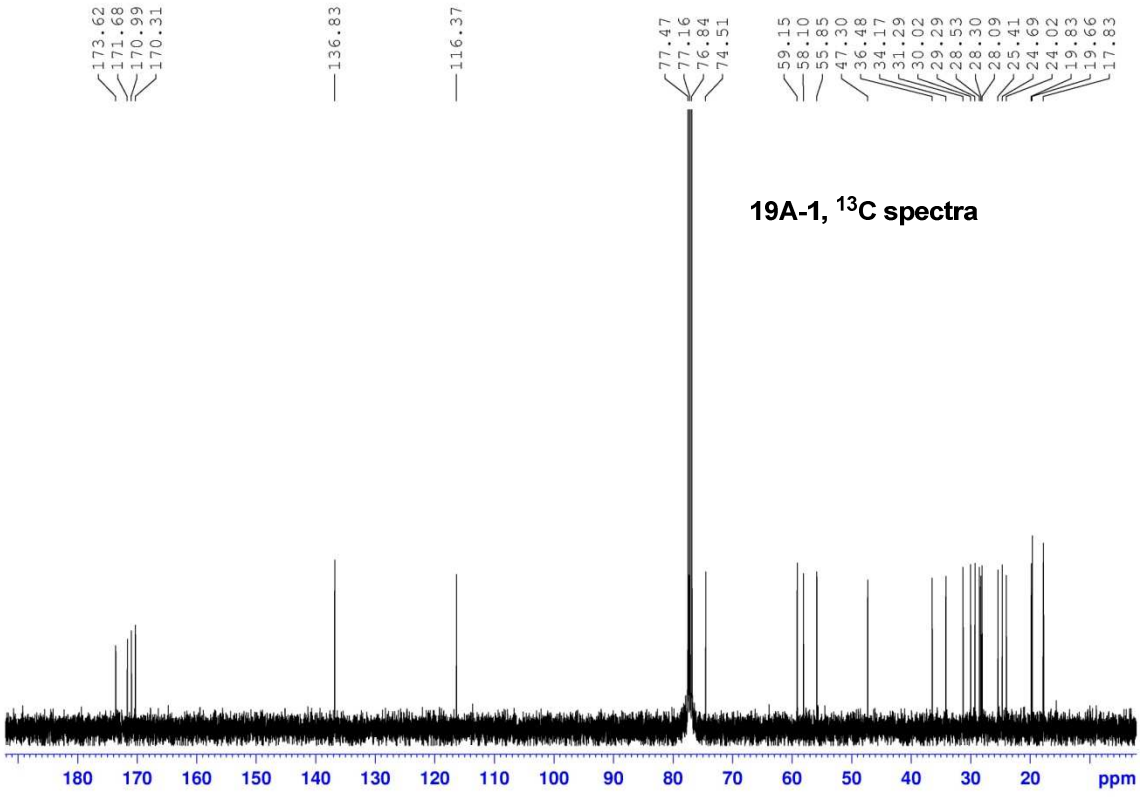
Mixture of **19A-1**; **19B**; **19A-2**

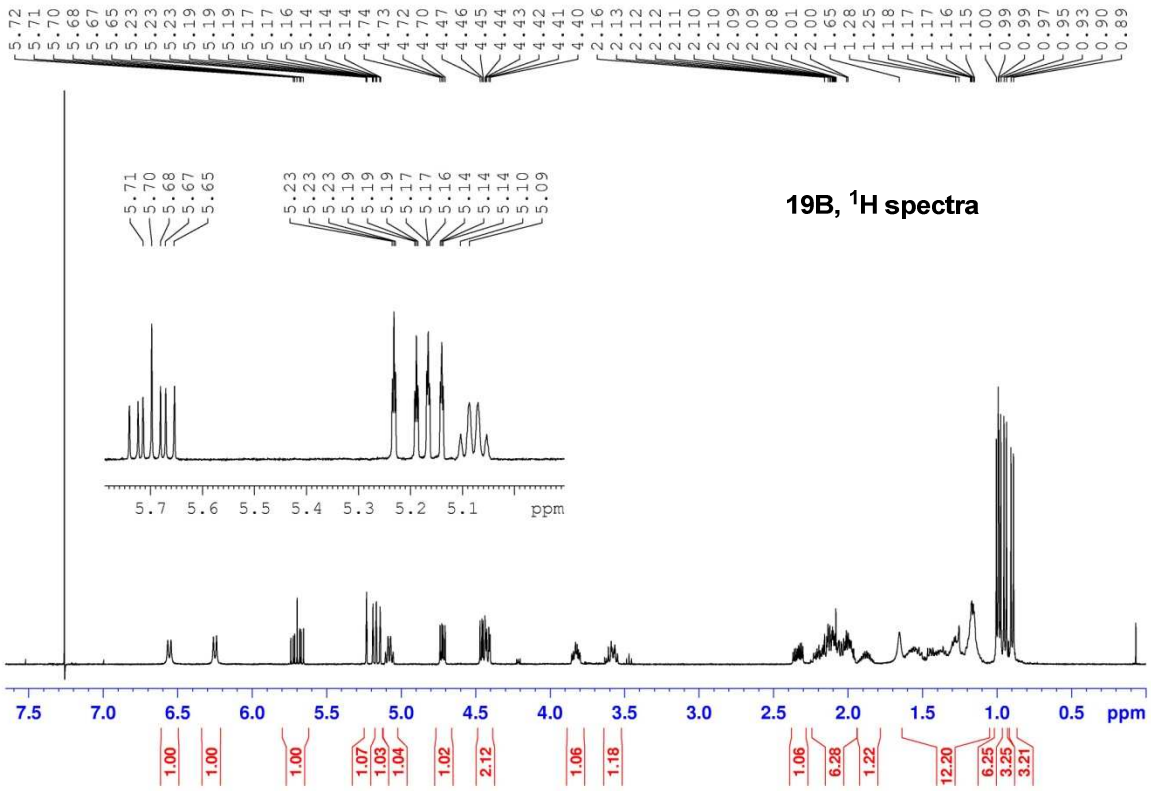


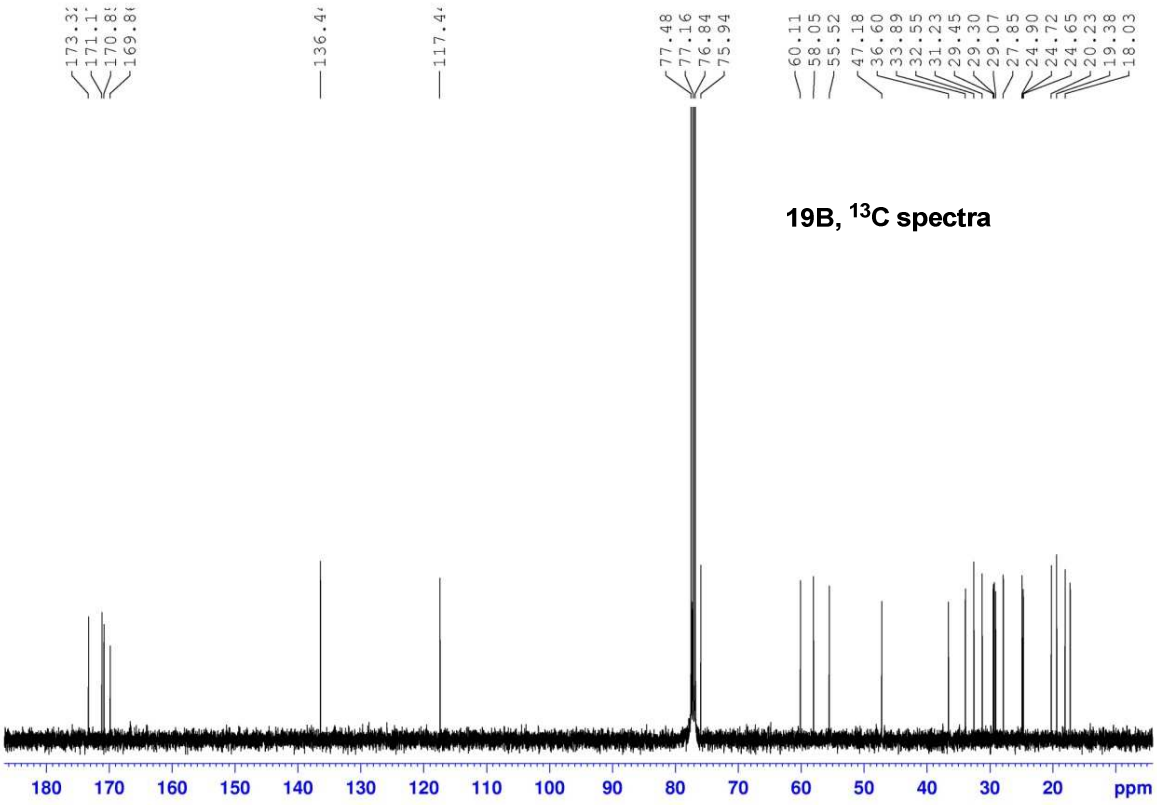


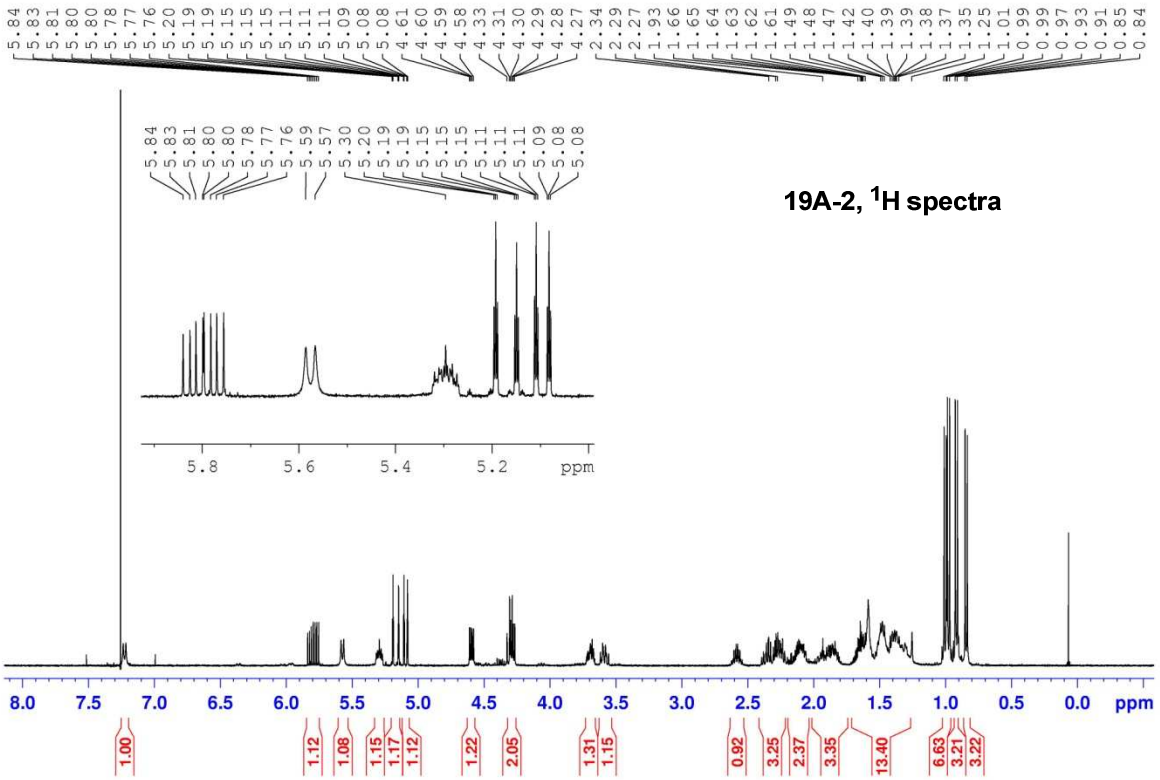


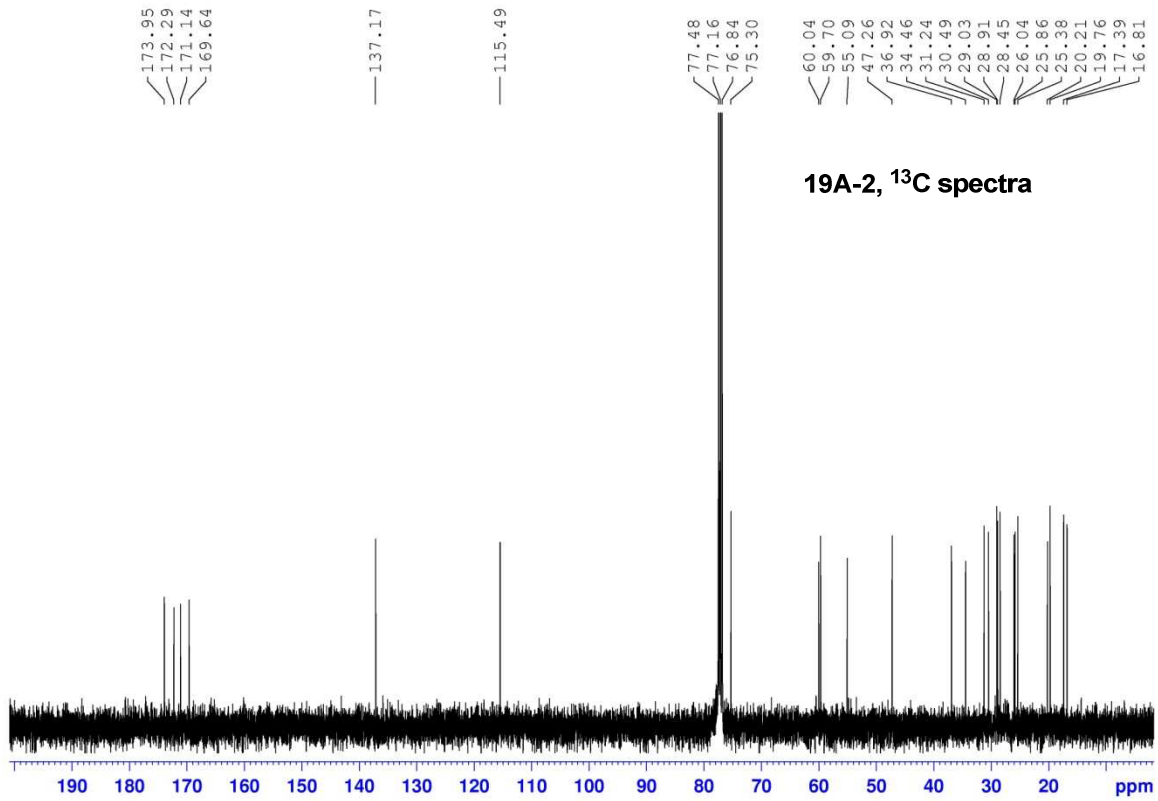

19A-1, 1H spectra
ppm


19A-1, 13C spectra
ppm


19B, 1H spectra
ppm


19B, 13C spectra
ppm

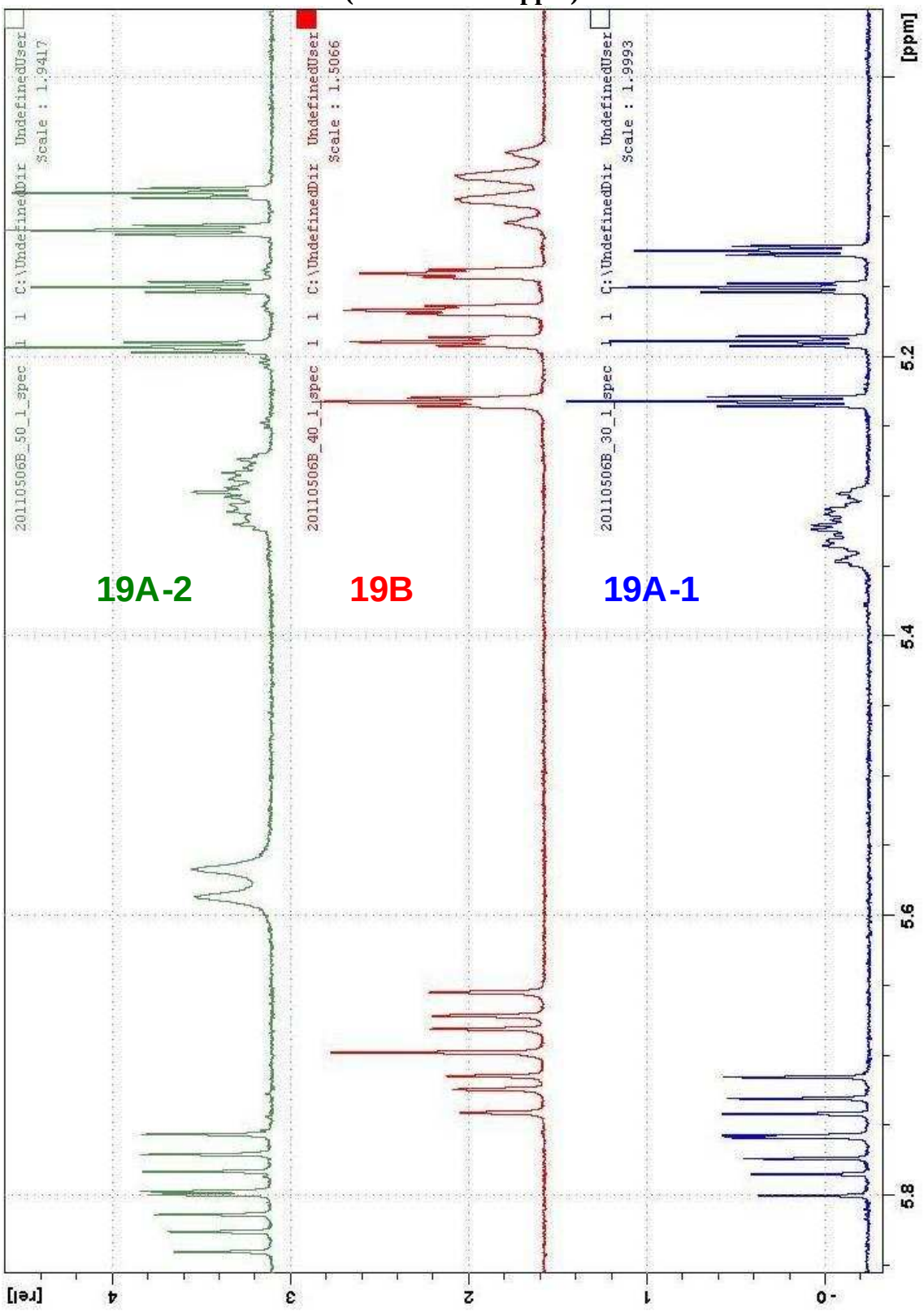

19A-2, ^{1}H spectra
ppm


19A-2, ^{13}C spectra
ppm

*Alexandre Lumbroso, Nacim Abermil and Bernhard Breit**

Scanned images of ^{1}H NMR spectra of the isomers (19A-1, 19B, 19A-2) and HPLC chromatogram of the crude mixture.

^{1}H NMR spectra of the isomers (19A-1, 19B, 19A-2)
(5.85 < δ < 5.00 ppm)



HPLC chromatogram of 19 (crude reaction mixture)

D-7000 HSM: Fehrenbach Series: 0941 Report: original System: Sys 2

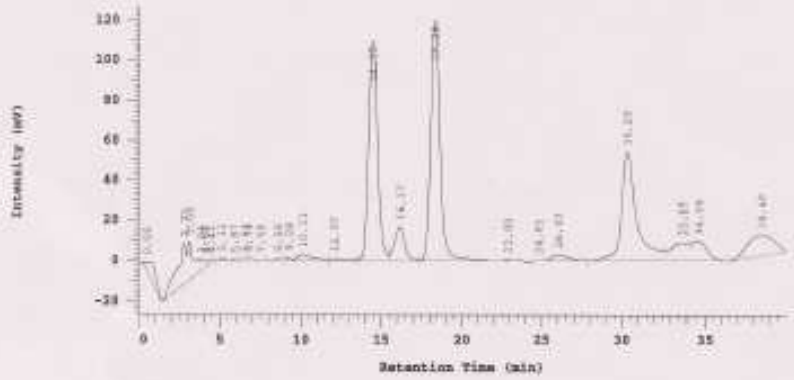
Universität Freiburg
Inst. für Organische Chemie und
Biochemie

Analyzed: 03.05.11 08:20 Reported: 03.05.11 09:00
Processed: 03.05.11 09:00

Data Path: D:\hsm\Fehrenbach\DATA\0941\
Processing Method: MN100-5 n-HeptanDioxan80/20

System(acquisition): Sys 2 Series:0941
Application: Fehrenbach Vial Number: 1
Sample Name: AL0418 Vial Type: UNK
Injection from this vial: 1 of 1 Volume: 1.0 ul
Sample Description:

Chrom Type: HPLC Channel : 1



Acquisition Method: MN100-5 n-HeptanDioxan80/20
Column Type: Si60 Developed by: fehrenbach
Pump A Type: L-7100
Solvent A: Heptan Solvent B: i-Propanol
Solvent C: Dioxan Solvent D: Äthanol
Method Description: n-Heptan/Dioxan 80/20, 215nm, 1ml/min

Chrom Type: HPLC Channel : 1

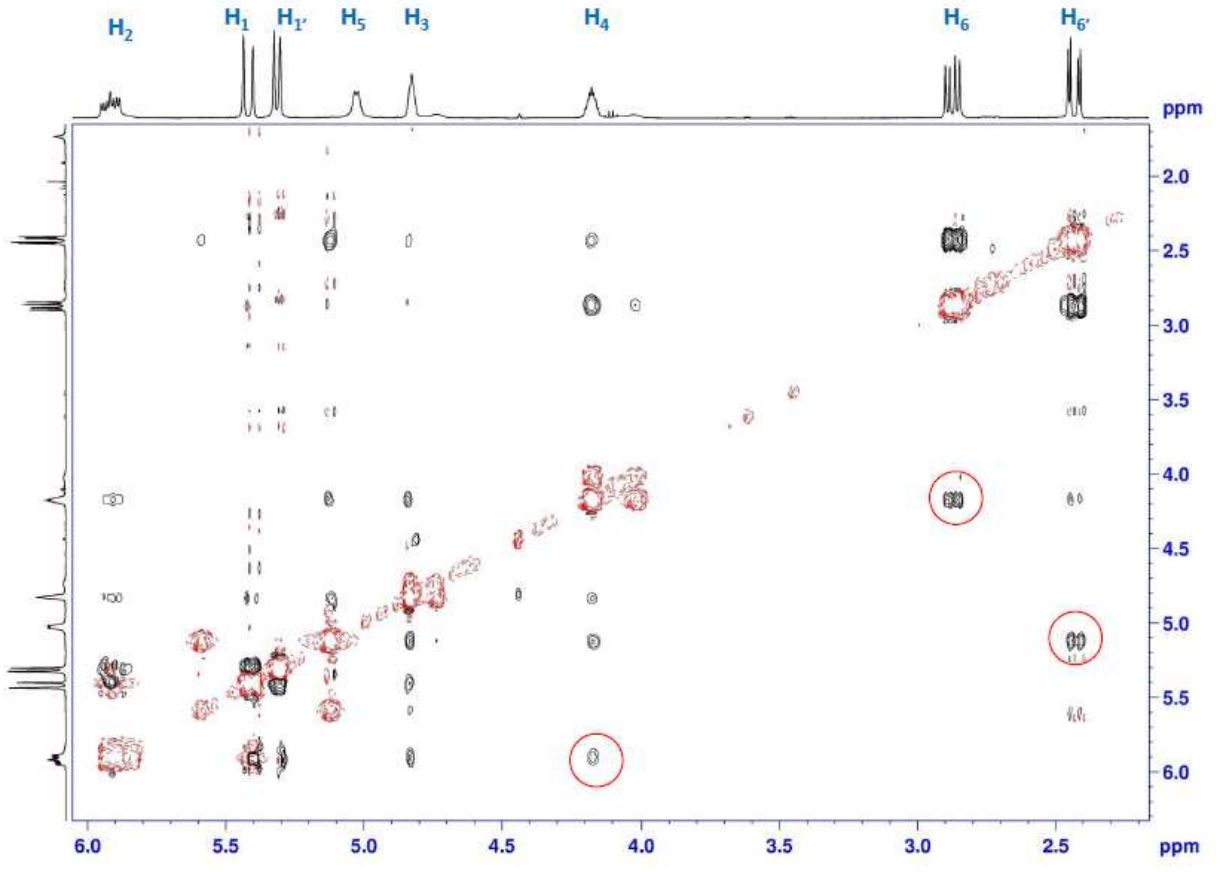
Peak Quantitation: AREA
Calculation Method: AREA%

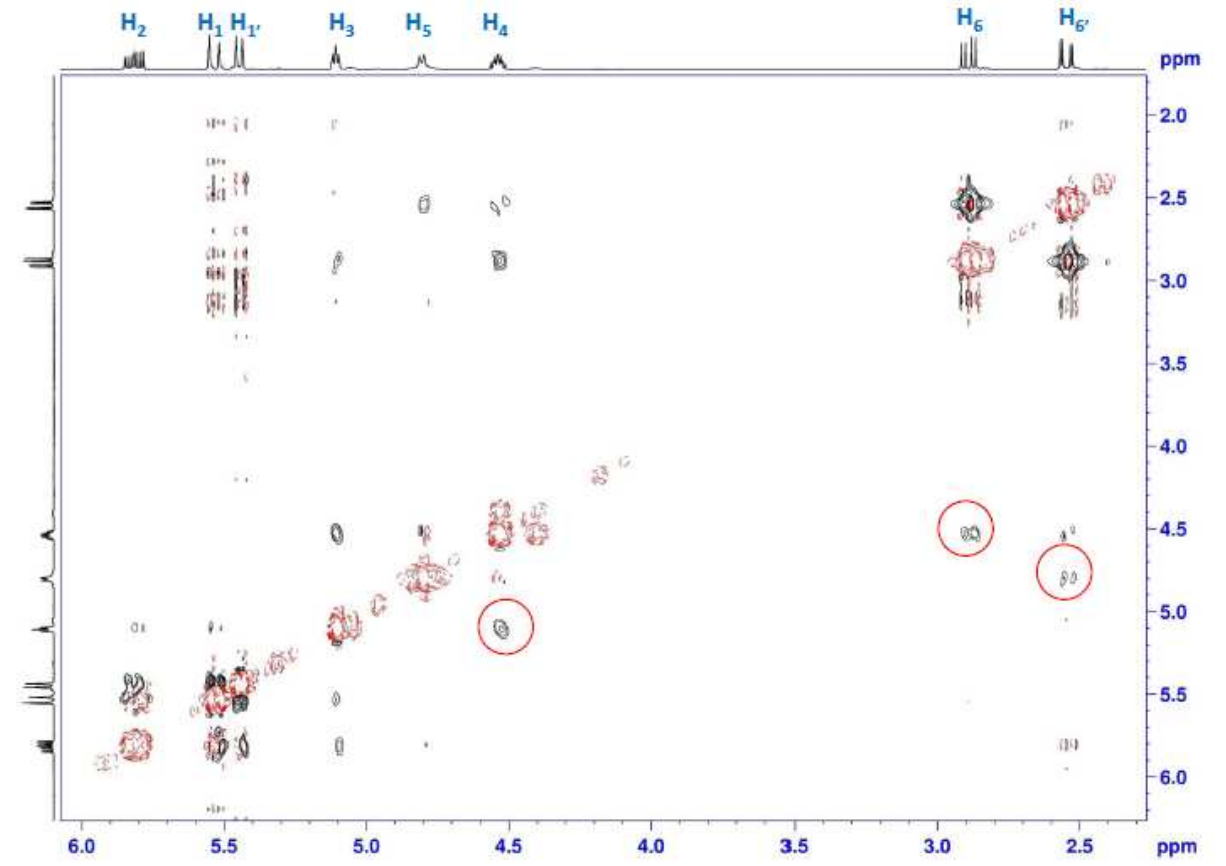
No.	RT	Area %	Area	BC
1	0,50	1,810	308725	BB
2	2,77	4,441	757491	BV
3	3,09	2,796	476903	VV
4	3,84	0,413	70468	VV
5	4,08	0,401	68338	VV
6	4,41	0,182	30968	VB
7	5,11	0,113	19276	BB
8	5,87	0,014	2457	BB
9	6,53	0,012	2006	BB
10	6,74	0,005	882	BB
11	7,50	0,009	1588	BB
12	8,58	0,035	5948	BV
13	9,24	0,066	11233	VV
14	10,11	0,899	153257	VB

D-7000 HSM: Fehrenbach Series: 0941 Report: original System: Sys 2

15	12,07	0,298	50886	BV
16	14,43	23,442	3998496	VV
17	16,17	4,039	688877	VV
18	18,29	26,460	4513325	VV
19	22,89	0,091	15439	TBB
20	24,81	0,023	3850	BB
21	26,03	1,110	189394	BB
22	30,29	19,727	3364785	BV
23	33,69	3,522	600691	VV
24	34,58	3,585	611571	VB
25	38,48	6,508	1110104	BB
		100,000	17056948	

Scanned images of nOe spectra (2D) of 2-A and 2-B

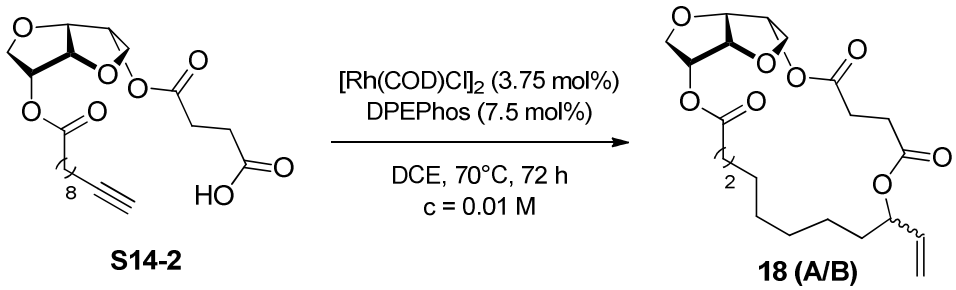




Macrolactonization using (–) and (+)-DIOP:

To investigate whether the use of chiral ligands can influence the diastereoselectivity of the macrolactonization process, the reaction of **S14-2** has been tested with (–) and (+)-DIOP.

Procedure:
A 250 ml Schlenk flask was flame-dried under vacuum, backfilled with argon (Argon 5.0 from Sauerstoffwerke Friedrichshafen) and cooled to room temperature using a standard Schlenk line apparatus. The Schlenk flask was then charged with 0.033 mmol (16.3 mg) of $[(COD)RhCl]_2$, 0.066 mmol (32.9 mg) of (–) or (+)-DIOP and 88 mL of freshly distilled 1,2-dichloroethane were then added under a flow of argon. The solution was allowed to stir for 30 min at room temperature. Subsequently, 0.88 mmol of alkynoic acid **S14-2** (360.8 mg) was added. The Schlenk flask was sealed and the mixture stirred for 72 hours in a pre-heated oil bath at 70°C. After cooling to room temperature, the mixture was flushed through a plug of silica gel with dichloromethane and ethyl acetate. The yellow solution was concentrated under vacuum and the crude mixture analysed by ^{1}H NMR. Purification by flash chromatography on silica gel (eluent hexanes/EtOAc 2/1) afforded **18** as a yellow oil and as a mixture of isomers (**18A/B** and **18M**) (yields = 4 and 6%, 14.3 and 21.6 mg).



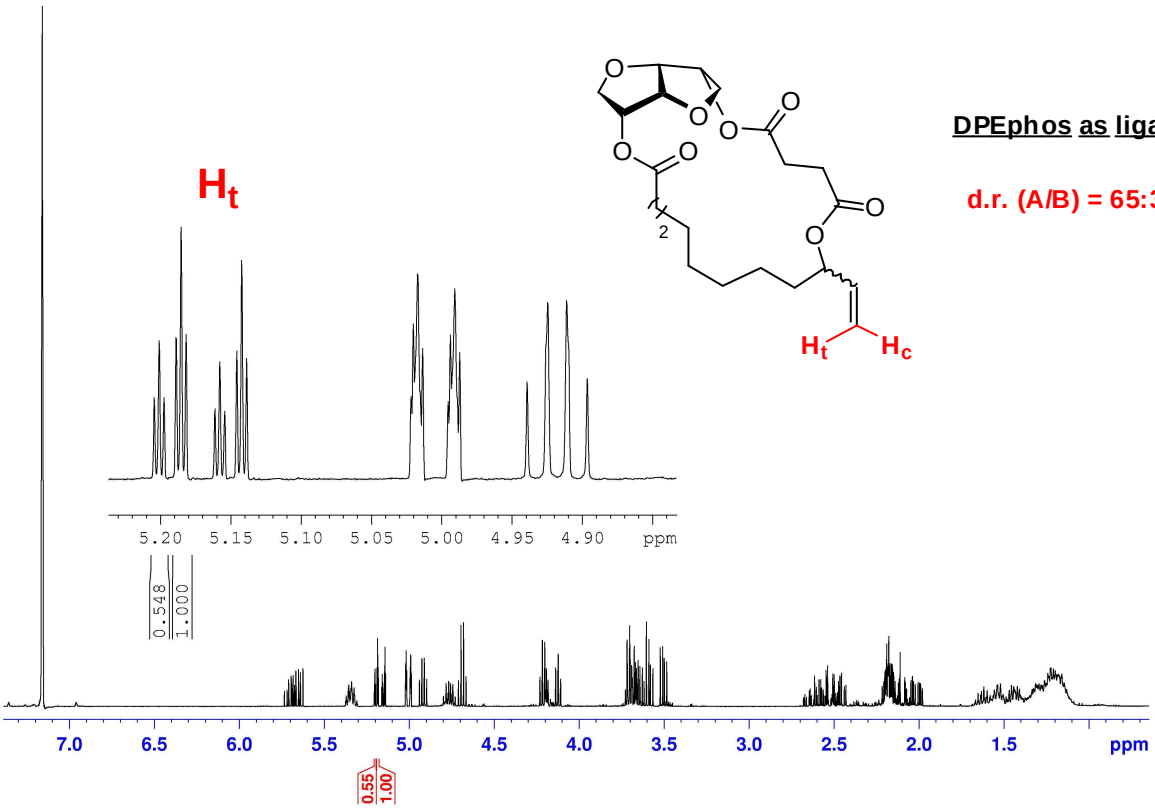
S14-2 **18 (A/B)**

entry	ligand	yield (%)[a]	d.r. 18(A/B)[b]
1	DPEphos[c]	65	65:35
2	(–)-DIOP	4	72:28
3	(+)-DIOP	6	40:60

[a] Isolated yields. [b] Determined by integration of ethylenic protons in the ^{1}H NMR spectrum (recorded in C_6D_6). [c] For the experimental procedure see *general procedure 6* p. S19

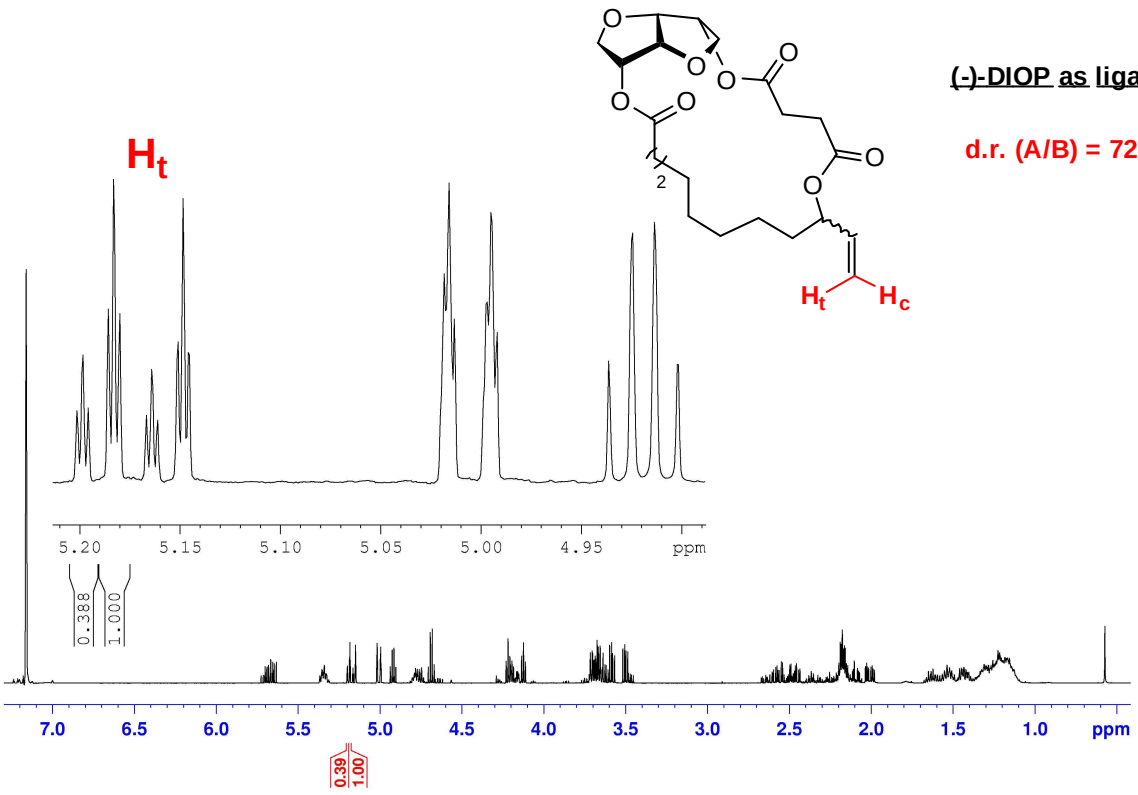
These results show that employing (–)-DIOP as the ligand, the diastereomeric ratio of the reaction is slightly improved (matched case, entry 2). Interestingly, using (+)-DIOP, the opposite diastereoselectivity was observed (mismatched case, entry 3). However, yields of these reactions (entries 2 and 3) are dramatically reduced when compared with standard conditions (DPEphos, entry 1). This exploratory study shows that a stereoselective induction can be obtained using a chiral catalyst system.

Scanned images of ^{1}H NMR spectra:



DPEphos as ligand

d.r. (A/B) = 65:35



(-)-DIOP as ligand

d.r. (A/B) = 72:28

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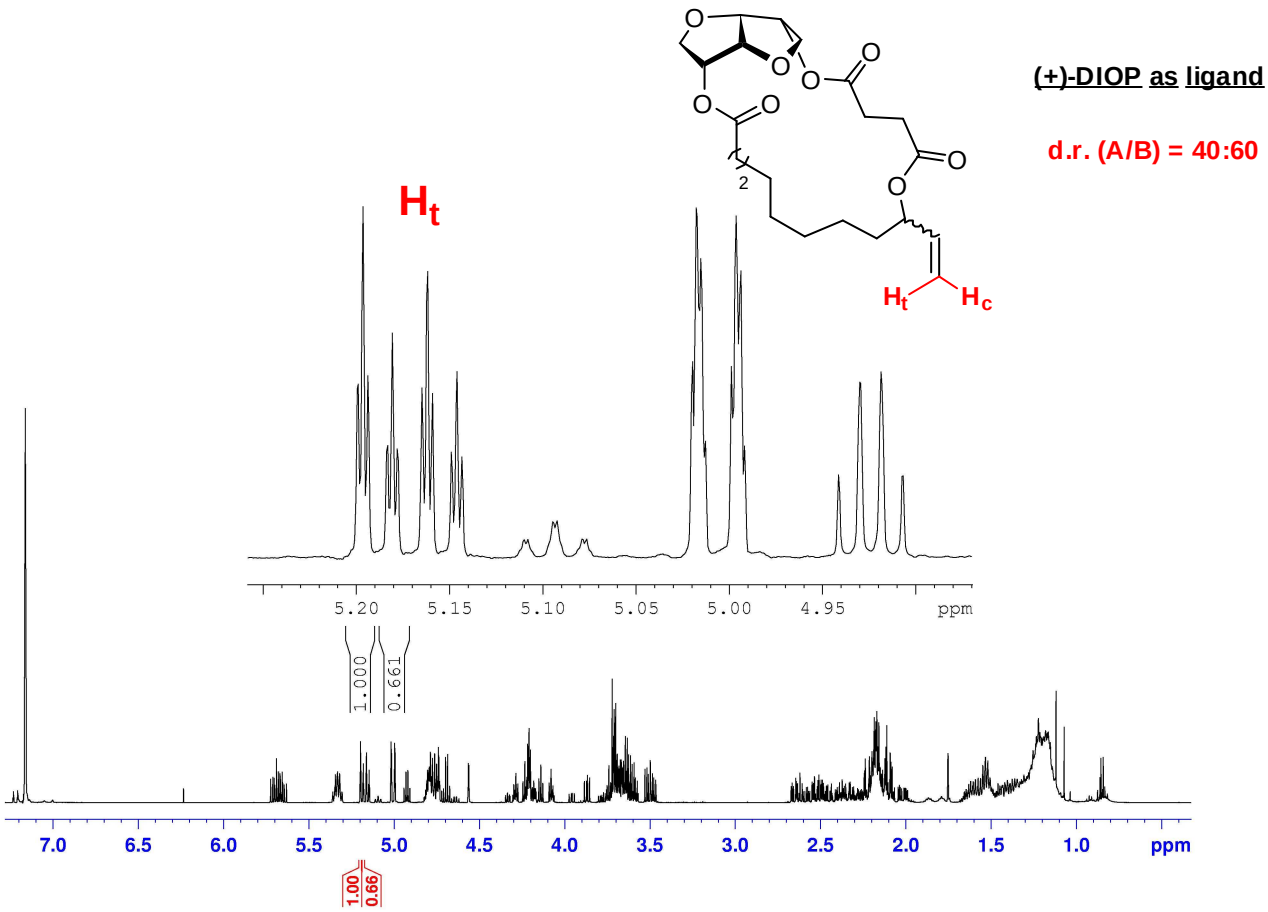

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