Electronic Supplementary Material (ESI) for Chemical Communications

Synthesis of palmyrolide A and its *cis* isomer and mechanistic insight into *trans-cis* isomerization of enamide macrocycle

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Supporting Information

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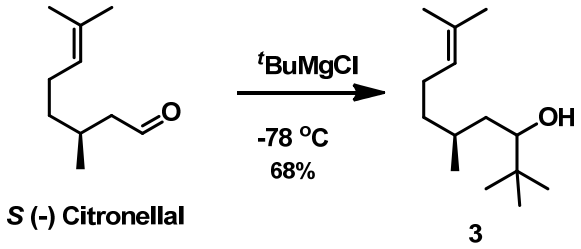
General:

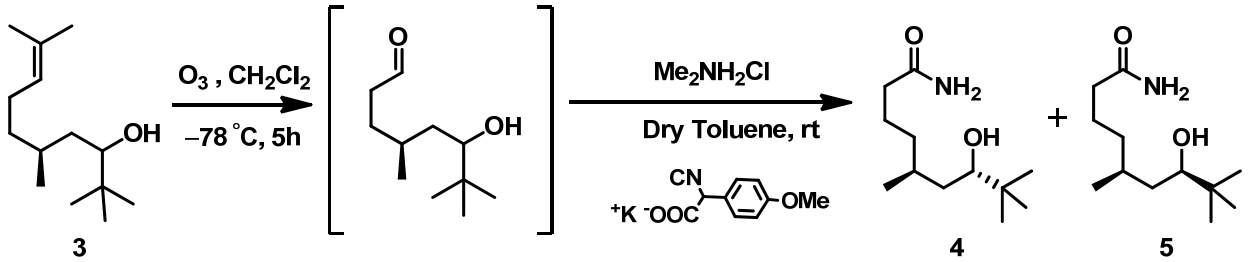
All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus *via* rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F254). Visualization was accomplished with either UV light, or by immersion in ethanolic solution of phosphomolybdic acid (PMA), *para*-anisaldehyde, 2,4-DNP strain, $KMnO_4$, Ninhydrinsoln, Iodine adsorbed on silica gel followed by heating on a heat gun for ~15 sec. Column chromatography was performed on silica gel (100-200 or 230-400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^{1}H NMR and ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, or 500 MHz spectrometer. Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to $CDCl_3$, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS (ESI) were recorded on ORBITRAP mass analyser (Thermo Scientific, Q Exactive). Mass spectra were measured with ESI ionization in MSQ LCMS mass spectrometer .Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Chemical nomenclature was generated using ChemDraw. Melting points of solids

were measured in melting point apparatus. Optical rotation values were recorded on P-2000 polarimeter at 589 nm.

Experimental Procedures:



(5*S*)-2,2,5,9-tetramethyldec-8-en-3-ol(3): *t*-Butylmagnesium chloride (2.0 M in THF 12.9 mL, 25.97 mmol) was added dropwise to a solution of commercial *S*-citronellal (2.00 g, 12.98 mmol) in dry THF (20 mL) at –78 °C. The reaction mixture was stirred at same temperature for 2 h. Then the reaction mixture was quenched with saturated aqueous ammonium chloride (50 mL) and extracted with EtOAc (3 x 20 mL).The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by flash chromatography over silica gel (1–5% EtOAc/hexanes) to afford alcohol **3** (1.83 g, 68% yield, ~ 1:1 diasteromeric mixture) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 (t, *J* = 7.0 Hz, 1 H), 3.28 (d, *J* = 12.0 Hz, 1 H), 1.85–2.08 (m, 2 H), 1.67 (s, 3 H), 1.60 (s, 3 H), 1.43–1.51 (m, 0.58 H), 1.17–1.36 (m, 4 H), 1.00–1.09 (m, 0.58 H), 0.94 (d, *J* = 6.7 Hz, 1.5 H), 0.89 (d, overlapped, 1.5 H), 0.88 (s, 9 H);^{13}C NMR(400 MHz, $CDCl_3$) δ 131.3, 125.0, 124.9, 77.7, 77.3, 39.4, 39.0, 38.5, 35.7, 35.0, 34.9, 29.8, 29.3, 25.9, 25.8, 25.7, 25.7, 25.4, 21.0, 18.9, 17.8; IRυ_{max}(film): 3349, 2964, 2874, 1670, 1512 cm^{-1}; HRMS (ESI): *m*/*z* calculated for $C_{14}H_{29}O$ $[M+H]^+$ 213.2213, found 213.2211.



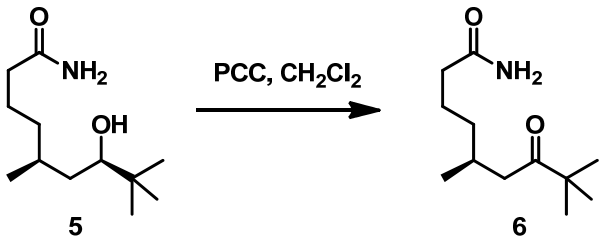
(5*S*,7*S*)-7-Hydroxy-5,8,8-trimethylnonanamide (4) and (5*S*,7*R*)-7-hydroxy-5,8,8-trimethylnonanamide (5)[1]: A stream of ozone was bubbled through a cold (–78 °C) solution ofthe alcohol **3** (0.3 g, 1.41 mmol) in CH_2Cl_2 (10 mL) until the distinctive blue color of ozone was clearly observed. Ozonolysis was then terminated, and excess ozone was displaced by passing a stream of nitrogen through the solution for 5–10 min, and then neat Me_2S (0.2 mL, 2.82 mmol) was added dropwise. The resulting reaction mixture was allowed to warm to room temperature and stirred for 8 h. The reaction mixture was concentrated *in vacuo.*The crude product obtained was filtered by short silica gel column chromatography to get aldehyde (290 mg) as colorless oil. It was forwarded for next step without taking any extensive characterization. IRυ_{max}(film): 3446, 2954, 1723, 1458 cm^{-1}.

Dimethylamine hydrochloride (137 mg,1.69 mmol) was added to a solution of above aldehyde taken in dry toluene (2.0 mL) and stirred at room temperature for 10 minutes. The resultant suspension was transferred via syringe to a solution of freshly prepared potassium 2-isocyano-2-(4-methoxyphenyl) acetate (485 mg, 2.12 mmol) and dimethylamine hydrochloride (137 mg, 1.69 mmol) in dry toluene (6.0 mL). Then it was allowed to stir at room temperature for 24 h. The reaction mixture was then evaporated to dryness. The crude product obtained was dissolved in EtOAc (5.0 mL), washed with water (3.0 mL), dried over anhydrous Na_2SO_4, filtered and concentrated *in vacuo*. The resulting light yellow oil was dissolved in THF (4.0 mL), treated with 1N HCl (10.6 mL, 7.05 mmol), and the reaction mixture was allowed to stir at room temperature for 5 h. The reaction mixture was basified with aqueous saturated $NaHCO_3$ (about 15 mL, pH~10), and extracted with EtOAc (3 x 20 mL). The combined organic extracts were washed with brine (5.0ml), dried over Na_2SO_4, filtered and concentrated *in vacuo* and subjected to flash chromatography over silica gel (1.5% MeOH/CH_2Cl_2) afforded two separable alcohols **4** (85 mg, 28%) as a colorless oil and **5** (80mg, 26% yield) as a white solid respectively.

Data for **4**, $[\alpha]_D^{25.3}$= – 41.5 (*c* = 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (bs, 1 H), 5.79 (bs, 1 H), 3.26 (dd, *J* = 1.7, 10.3 Hz, 1 H), 2.20 (t, *J* = 7.2 Hz, 2 H), 1.46-1.78 (m, 5 H), 1.29–1.36 (m, 1 H), 1.18–1.25 (m, 1 H), 0.99–1.08 (m, 1 H), 0.92 (d, *J* = 6.5 Hz, 3 H), 0.86

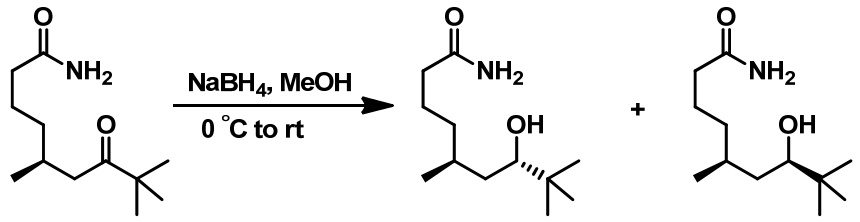
(s, 9 H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 176.3, 77.4, 39.1, 36.0, 35.0, 34.6, 29.4, 26.0, 23.0, 21.0; IRυ_{max}(film): 3353, 3196, 2953, 1667, 1463, 1403 cm^{-1}; HRMS (ESI):*m*/*z* calculated for $C_{12}H_{25}NO_2Na$ $[M+Na]^+$ 238.1778, found 238.1774.

Data for **5**, Mp = 95 - 97°C; $[\alpha]_D^{26.5}$ = + 26.9 (*c* = 0.43, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.46 (bs, 1 H), 5.38 (bs, 1 H), 3.28 (dd, *J* = 2.0, 10.5 Hz,1 H), 2.22 (dt, *J* = 2.0, 8.0 Hz, 2 H), 1.63–1.72 (m, 3 H), 1.15–1.35 (m, 5 H), 0.90 (d, overlapped, 3 H), 0.88 (s, 9 H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 176.03, 77.49, 38.7, 37.8, 36.1, 35.0, 29.4, 25.8, 23.0, 19.1; IRυ_{max}(film): 3356,2953, 1655, 1512, 1459, 1406 cm^{-1}; HRMS (ESI):*m*/*z* calculated for $C_{12}H_{26}NO_2$ $[M+H]^+$ 216.1958, found 216.1953.



5 6

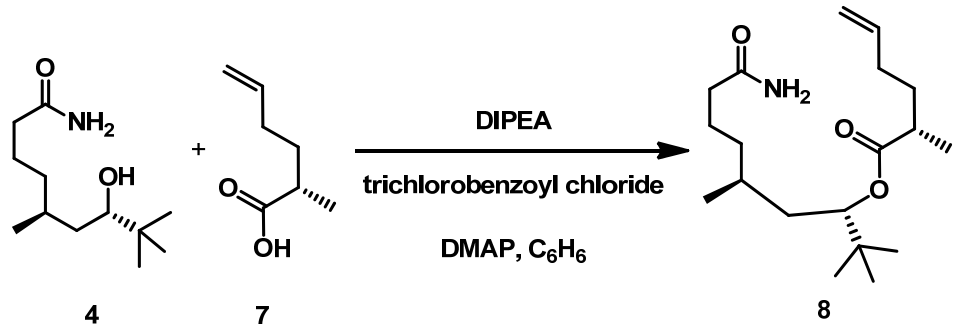
(*S*)-5,8,8-Trimethyl-7-oxononanamide (6): A solution of alcohol **5** (50.0 mg, 0.24mmol) in dry CH_2Cl_2(5.0 mL) at 0 °C was treated with PCC (80 mg, 0.37 mmol) and stirred at room temperature for 2 h. The reaction mixture was filtered through celite pad, and the pad was washed thoroughly with diethyl ether(15mL). Combined washings were concentrated *in vacuo*. Purification by flash chromatography over silica gel (50–80% EtOAc/hexanes) afforded keto compound **6** (26.0 mg, 53% yield) as white solid: Mp = 64-67 °C; $[\alpha]_D^{25.0}$= – 4.6 (*c* = 0.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (bs, 1 H), 5.83 (bs, 1 H), 2.28–2.41 (m, 2 H),2.18 (t, *J* = 7.2 Hz, 2 H), 1.98–2.06 (m, 1 H), 1.51–1.69 (m, 2 H), 1.21–1.31 (m, 1 H), 1.07–1.18 (m, overlapped,1 H), 1.07 (s, 9 H), 0.83 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 216.0, 176.1, 44.26, 43.8, 36.1, 35.9, 28.1, 26.3, 23.0, 19.8; IRυ_{max}(film): 3359, 3193, 2952, 1698, 1661, 1633 cm^{-1}; HRMS (ESI):*m*/*z* calculated for $C_{12}H_{24}NO_2$ $[M+H]^+$ 214.1802, found 214.1799.



6 4 5

Reduction of Keto to alcohols 4 and 5:

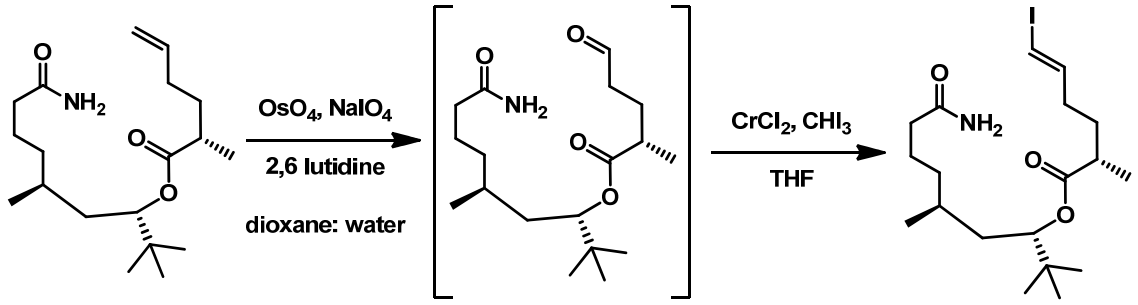
A solution of keto compound **6** (20.0 mg, 0.1 mmol) in MeOH (3.0 mL) at 0 °C was treated with $NaBH_4$ (8.0 mg, 0.2 mmol) and stirred at room temperature for 1 h. The reaction mixture concentrated *in vacuo*. Purification by flash chromatography over silica gel (50-80% EtOAc/hexanes) afforded alcohols **4** and **5** (16.5 mg, 82% yield, 1:1 mixture of diastereomers) as a colorless oil.



4 7 8

(*S*)-(3*S*,5*S*)-9-Amino-2,2,5-trimethyl-9-oxononan-3-yl 2-methylhex-5-enoate (8)[4]: To a solution of acid **7**[6] (100 mg, 0.78 mmol) in benzene (3.0 mL), was added 2,4,6-trichlorobenzylchloride (0.17 mL, 1.12 mmol), followed by Hunigs base (0.16 mL, 0.95 mmol), alcohol **4** (120 mg, 0.56 mmol) and DMAP (170 mg, 1.40 mmol). The reaction mixture was stirred at room temperature for 12 h before being diluted with EtOAc (10 mL). Then the organic layer was washed with water (3 x 5.0 mL), brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography over silica gel (50–60% EtOAc/hexanes) afforded **8** (146 mg, 80% yield) as a colorless oil:$[\alpha]_D^{25.3}$= –26.44 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.10 (bs, 1 H),5.96 (bs, 1 H), 5.69-5.79 (m, 1 H), 4.92–4.99 (m, 2 H), 4.74–4.77 (m, 1 H), 2.39–2.47 (m, 1 H), 2.01–2.16 (m, 4 H), 1.67–1.81 (m, 2 H), 1.24–1.46 (m, 6 H), 1.13 (d, *J* = 6.8 Hz, 3 H), 0.90–1.04 (m, 1 H), 0.86 (d, overlapped, 3 H), 0.84 (s, 9 H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 176.8, 175.9, 137.9,

115.1, 78.6,39.5, 37.6, 35.4, 34.5, 34.5, 32.8, 31.5, 28.8, 26.0, 22.7, 20.9, 17.4; IRυ_{max}(film): 3349, 3197, 2961, 2872, 1729, 1668 cm^{-1}; HRMS (ESI):*m*/*z* calculated for $C_{19}H_{36}NO_3$ $[M+H]^+$326.2690, found 326.2688.

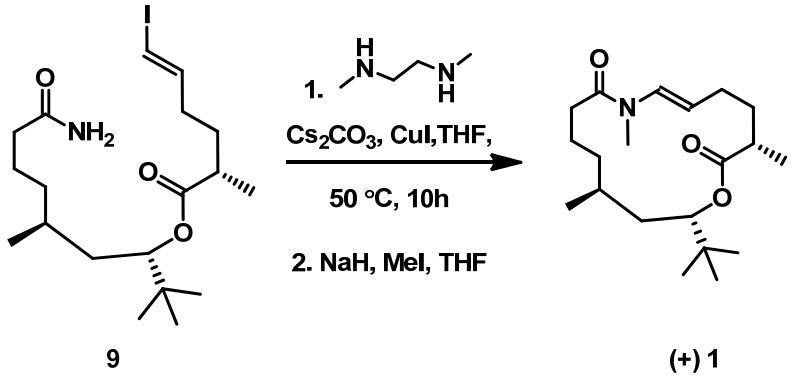


8 9

(*S*,*E*)-(3*S*,5*S*)-9-Amino-2,2,5-trimethyl-9-oxononan-3-yl 6-iodo-2-methylhex-5-enoate (9)[3, 5]**:** A solution of alcohol **13** (90 mg, 0.276 mmol) in dioxane-water (4.0 mL, 3:1) was treated with 2,6-lutidine (65 µL, 0.55 mmol), followed by OsO_4 (2.5 % solution in *t*-BuOH, 30 µL, 0.03 mmol) and $NaIO_4$ (234 mg, 1.10 mmol). The reaction mixture was stirred at room temperature and monitored by TLC. When starting material was completely consumed, water (5.0mL) and EtOAc (5.0 mL) were added and the aqueous layer was extracted with EtOAc (3 x 5 mL). The combined organic extracts were washed with saturated aqueous solution of $Na_2S_2O_3$ (5.0 mL), brine (5.0 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Crude was partly purified by short silica gel column chromatography to get aldehyde (70 mg, 77% yield) as colorless oil:^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.26 Hz, 1 H), 5.88 (bs, 1 H), 5.34 (bs, 1 H), 4.80 (dd, *J* = 9.0, 2.5 Hz, 1 H), 2.45–2.56 (m, 3 H), 2.11–2.25 (m, 2 H), 1.94–2.03 (m, 1 H), 1.71–1.82 (m, 2 H), 1.45–1.56 (m, 2 H), 1.38–1.43 (m, 2 H), 1.20 (d, *J* = 7.0 Hz, 3 H), 0.90 (d, overlapped, 3 H), 0.87 (s, 9 H); HRMS (ESI):*m*/*z* calculated for $C_{18}H_{34}NO_4$ $[M+H]^+$328.2479, found 328.2482.

To a slurry of anhydrous $CrCl_2$ (134 mg, 1.10 mmol) in dry THF (2.0 mL) at 0 °C, was added dropwise a solution of above aldehyde (60.0 mg, 0.18 mmol) and CHI_3 (144 mg, 0.36 mmol) in dry THF (3.0 mL). The reaction mixture was stirred at 0 °C for 10 h and then quenched with water (5.0mL). The mixture was extracted with Diethyl ether (5 x 8mL) and the combined organic extracts were dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by flash chromatography over silica gel (60–80% EtOAc/hexanes) afforded **9** (43

mg, 53% yield) as a colorless oil: $[\alpha]_D^{25.3}$= – 23.29 (*c* = 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.44–6.51 (m, 1 H), 6.02 (d, *J* = 14.5 Hz, 1 H), 5.93 (bs, 1 H), 5.52 (bs, 1 H), 4.78 (dd, *J* = 3.4, 8.6 Hz, 1 H), 2.40–2.49 (m, 1 H), 2.11–2.23 (m, 2 H), 2.04–2.10 (m, 2 H), 1.71-1.85 (m, 3 H), 1.43–1.54 (m, 3 H), 1.33–1.42 (m, 2 H),1.16 (d, *J* = 6.1 Hz, 3 H), 1.00–1.08 (m, 1 H), 0.89 (d, overlapped, 3 H), 0.86 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5, 175.8, 145.5, 78.9, 75.5, 39.4, 37.7, 35.6, 34.6, 33.9, 32.2, 29.0, 26.1, 22.8, 21.0, 17.6; IRυ_{max}(film): 3349, 3197, 2960, 2871, 1725, 1669 cm^{-1}; HRMS (ESI):*m*/*z* calculated for $C_{19}H_{34}INO_4Na$ $[M+Na]^+$474.1472, found 474.1476.

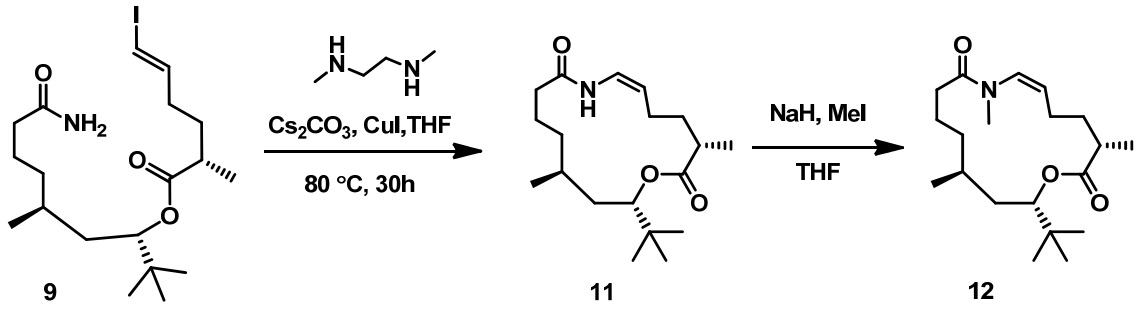


9 (+) 1

(3*S*,13*S*,15*S*,*E*)-15-(*tert*-butyl)-3,8,13-Trimethyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (+)1[2]: A mixture of amide **9** (38mg, 0.084 mmol), copper iodide (8.0mg, 0.042 mmol), and caesium carbonate (52mg, 0.159mmol) were suspended in dry THF(5.0mL). N,N′ Dimethylethylenediamine (34 μL, 0.30 mmol) was added, and the reaction flask was degassed by bubbling dry argon gas for 10 min. The septum was quickly removed and replaced with a Teflon stopper. The contents of the flask were then heated at 50 °C for 10h.The flask was allowed to cool to room temperature, diluted with EtOAc (5.0 mL) and filtered through a short plug of silica gel. The crude N-H macrolide was then concentrated in vacuo and purified by flash column chromatography over silica gel (20–25% EtOAc/hexane) to afford enamide **10** (15 mg, 65% brsm) as colorless oil, which was used in the next step without extensive characterization.

Enamide **10** (8.0 mg, 0.024 mmol) was dissolved in dry THF (1.0 mL), cooled to 0 °C, and treated with sodium hydride (60% dispersion, 3.0 mg, 0.072 mmol). The cooling bath was removed, and the flask was allowed to warm to room temperature and stir for 20 min. Iodomethane (0.1 mL, 1.61 mmol) was then added. After 30 min, the reaction mixture was

diluted with EtOAc (5.0 mL) and quenched with water. The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 3.0 mL). The combined organic extracts were then dried over Na_2SO_4, filtered and concentrated. The crude product was purified by flash column chromatography over silica gel (15–20% EtOAc/hexanes) to afford (+)- Palmyrolide A, **(+) 1,** (8.0 mg, 95%) as a colorless oil : $[\alpha]_D^{25}$= + 24.55 (*c* = 0.49, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (d, *J* = 13.7 Hz, 1 H), 5.28 (dt,*J* = 7.02, 13.7 Hz, 1 H), 4.88 (dd, *J* = 2.0, 9.76 Hz, 1 H), 3.05 (s, 3 H), 2.46-2.49 (m, 1 H), 2.34-2.42 (m, 2 H), 2.25-2.33 (m, 2 H), 1.72-1.84 (m, 3 H), 1.64-1.69 (m, 2 H), 1.45-1.51 (m, 1 H), 1.31-1.40 (m, 2 H), 1.21 (d, *J* = 7.02 Hz, 3 H), 1.03-1.10 (m, 1 H), 0.90 (d, *J* = 6.70 Hz, 3 H), 0.87 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 173.08, 130.8, 117.5, 77.0, 39.0, 35.9, 35.4, 34.7, 34.6, 33.0, 31.9, 29.5, 27.1, 26.2, 24.5, 20.8, 16.9; IRυ_{max}(film): 2959, 2930, 1726, 1650 cm^{-1}; HRMS (ESI):*m*/*z* calculated for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$360.2509, found 360.2503.

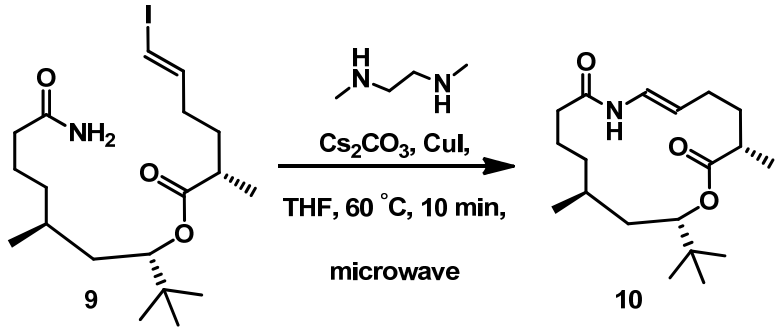


(3S,13S,15S,Z)-15-(tert-butyl)-3,13-dimethyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (11): A mixture of amide **9** (33 mg, 0.073 mmol), copper iodide (6.9 mg, 0.09 mmol), and caesium carbonate (45 mg, 0.138 mmol) were suspended in dry THF (5.0 mL). N,N′ Dimethylethylenediamine (30μL, 0.306 mmol) was added, and the reaction flask was degassed by bubbling dry argon gas for 10 min. The septum was quickly removed and replaced with a teflon stopper. The contents of the flask were then heated at 80 °C for 24–30h. The flask was allowed to cool to room temperature, diluted with EtOAc (5.0 mL) and filtered through a short plug of silica gel. The crude N-H macrolide was then concentrated in vacuo and purified by flash column chromatography (20–25% EtOAc/hexane) to afford cis enamide **11** (10 mg, 43%) as a colorless oil: $[\alpha]_D^{25.7}$ = – 72.66 (*c* = 0.248, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.0 Hz, 1 H), 6.59 (t, *J* = 8.04 Hz, 1 H), 4.97 (q, *J* = 8.00 Hz, 1 H), 4.90 (d, *J* = 8.00 Hz, 1 H), 2.47–2.57 (m, 2 H), 2.37–2.43 (m, 1 H), 2.06–2.12 (m, 1

H), 1.94–2.01 (m, 1 H), 1.67–1.88 (m, 4 H), 1.28–1.53 (m, 4 H), 1.21 (d, *J* = 8.00 Hz, 3 H), 1.05–1.13 (m, 1 H), 0.89 (s, 9 H), 0.85 (d, *J* = 6.27 Hz, 3 H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 177.4, 172.1, 122.8, 113.0, 79.1, 39.9, 38.6, 37.3, 36.9, 34.8, 34.4, 28.2, 26.2, 26.0, 23.5, 22.2, 20.2, 17.3;IRυ_{max}(film): 3361, 3019, 2967, 1658, 1501, 1215 cm^{-1}; HRMS (ESI):*m*/*z* calculated for $C_{20}H_{33}NO_3Na$ $[M+Na]^+$ 346.2353, found 346.2350.

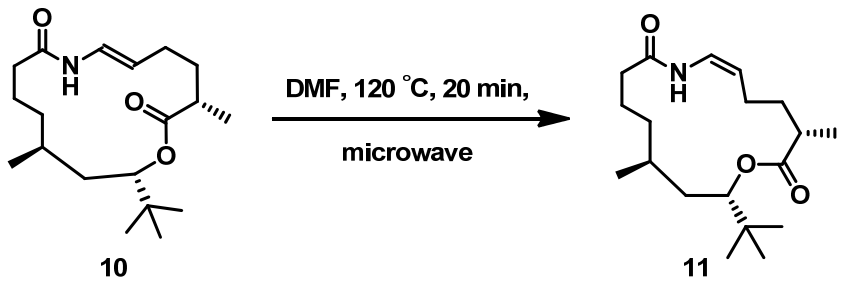
(3*S*,13*S*,15*S*,*Z*)-15-(*tert*-butyl)-3,8,13-trimethyl-1-oxa-8-azacyclopentadec-6-ene-2,9-dione (12): Enamide(10mg, 0.03 mmol) was dissolved in dry THF (1.0 mL), cooled to 0 °C, and treated with sodium hydride (60% dispersion, 6.0 mg, 0.15 mmol). The cooling bath was removed, and the flask was allowed to warm to room temperature and stir for 20 min. Iodomethane (0.1 mL, 1.61 mmol) was then added. After 3 h, the reaction mixture was diluted with EtOAc (5.0 mL) and quenched with water. The phases were separated, and the aqueous phase was extracted with EtOAc (3 x 3.0 mL). The combined organic layers were then dried over Na_2SO4, filtered, and concentrated. The crude product was purified by flash column chromatography over silica gel (15–20% EtOAc/hexanes) to afford *cis*-(–)-Palmyrolide –A **12** (9.0 mg, 86%) of as a white solid. $[\alpha]_D^{25.8}$= – 6.65 (*c* = 0.497, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.11 (d, *J* = 7.5 Hz, 1 H), 5.36–5.41 (m, 1 H), 4.87 (d, *J* = 10.54 Hz, 1 H), 2.99 (s, 3 H), 2.29–2.48 (m, 3 H), 1.91- 2.11 (m, 3 H), 1.65-1.72 (m, 1 H), 1.29-1.51 (m, 6 H), 1.20 (d, J = 7.03 Hz, 3 H), 0.94 (m, 1 H), 0.89 (d, *J* = 6.0 Hz, 3 H), 0.85 (s, 9 H);^{13}C NMR(100 MHz, $CDCl_3$) δ 174.5, 172.7, 130.4, 130.2, 41.0, 35.4, 33.7, 33.4, 32.0,28.4, 26.2, 24.5, 22.4, 19.9, 17.6; IRυ_{max}(film): 3019, 2966, 1715, 1635, 1522, 1215 cm^{-1}; HRMS (ESI): *m*/*z* calculated for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$ 360.2509, found 360.2505.

Microwave assisted macrocylization:



A mixture of amide **9** (8.0 mg, 0.017 mmol), copper iodide (3.3 mg, 0.017 mmol), and caesium carbonate (15 mg, 0.046 mmol) was suspended in dry THF (3.0 mL). N,N′ Dimethylethylenediamine (10 μL, 0.069 mmol) was added, and the reaction flask was degassed by bubbling dry argon gas for 10 min and then heated in a microwave reactor at 60 °C for 10-12 min, The flask was allowed to cool to room temperature, diluted with EtOAc (5.0 mL) and filtered through a short plug of silica gel. The crude N-Hmacrolide was then concentrated in vacuo and purified by flash column chromatography over silica gel (20–25% EtOAc/hexane) to afford enamide **10** (3.0mg, 70% brsm) as colorless oil.

Conversion of trans enamide to cis enamide via microwave heating:



10 11

The trans enamide **10** (3.0 mg), obtained in above reaction was taken in dry DMF (2.0 mL), and heated in microwave reactor at 120 °C for 20 min, the trans enamide was converted to cis enamide **11** (compared on TLC with authentic *cis* enamide sample).

Computational Studies :

The DFT calculations have been done with the Turbomole suite of programs, using Turbomole 6.0.[7] The TZVP basis set[8] and the PBE functional[9] have been employed in all the calculations. The resolution of identity (RI)[10], along with the multipole accelerated resolution of identity (marij)[11] approximations were employed for an accurate and efficient treatment of the electronic Coulomb term in the DFT calculations. Dispersion corrections have been incorporated through single point calculations. Solvent effects have been included for the solvent dimethyl formamide (DMF) (ε = 38.71) through single point calculations with the Conductor Like Screening Model – COSMO[12]. Frequency calculations have been done at the DFT level at 298.15 K in order to obtain the zero point energy, internal energy and entropic contributions. Care was taken to ensure that the obtained transition state structures possessed only one imaginary frequency corresponding to the correct normal mode. Hence the numbers reported are ΔG values.

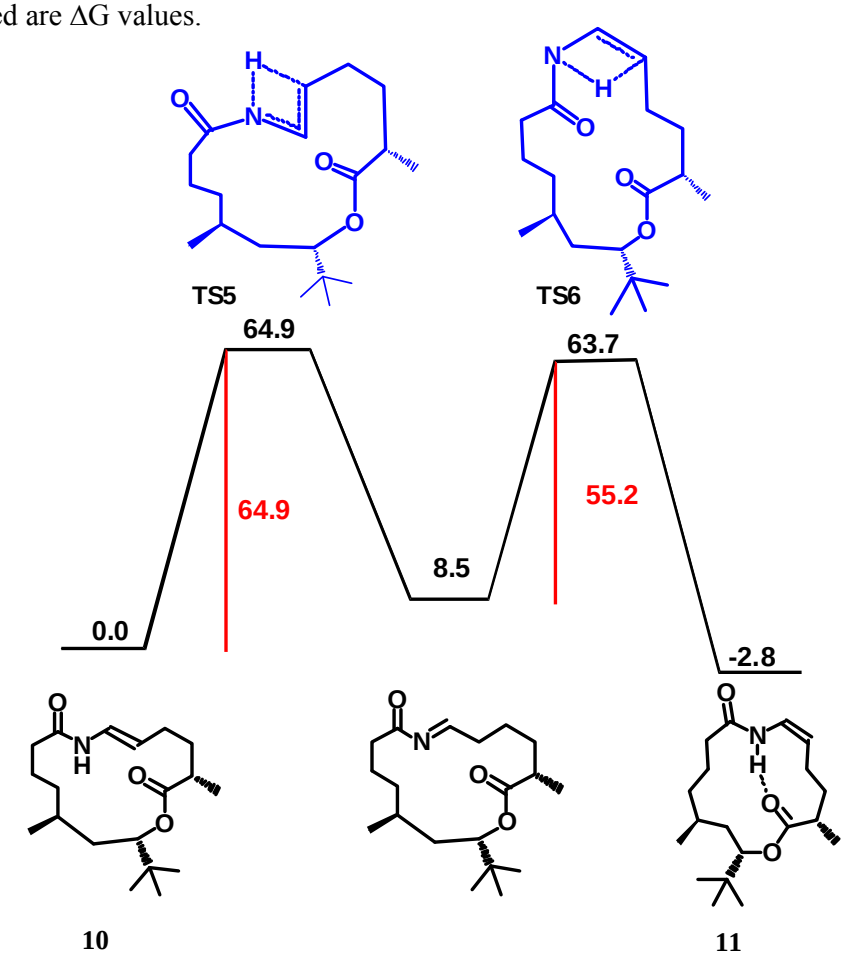


Figure S1: The energy profile for the direct conversion from *trans* to *cis* without tranfer of proton to the oxygen atom.

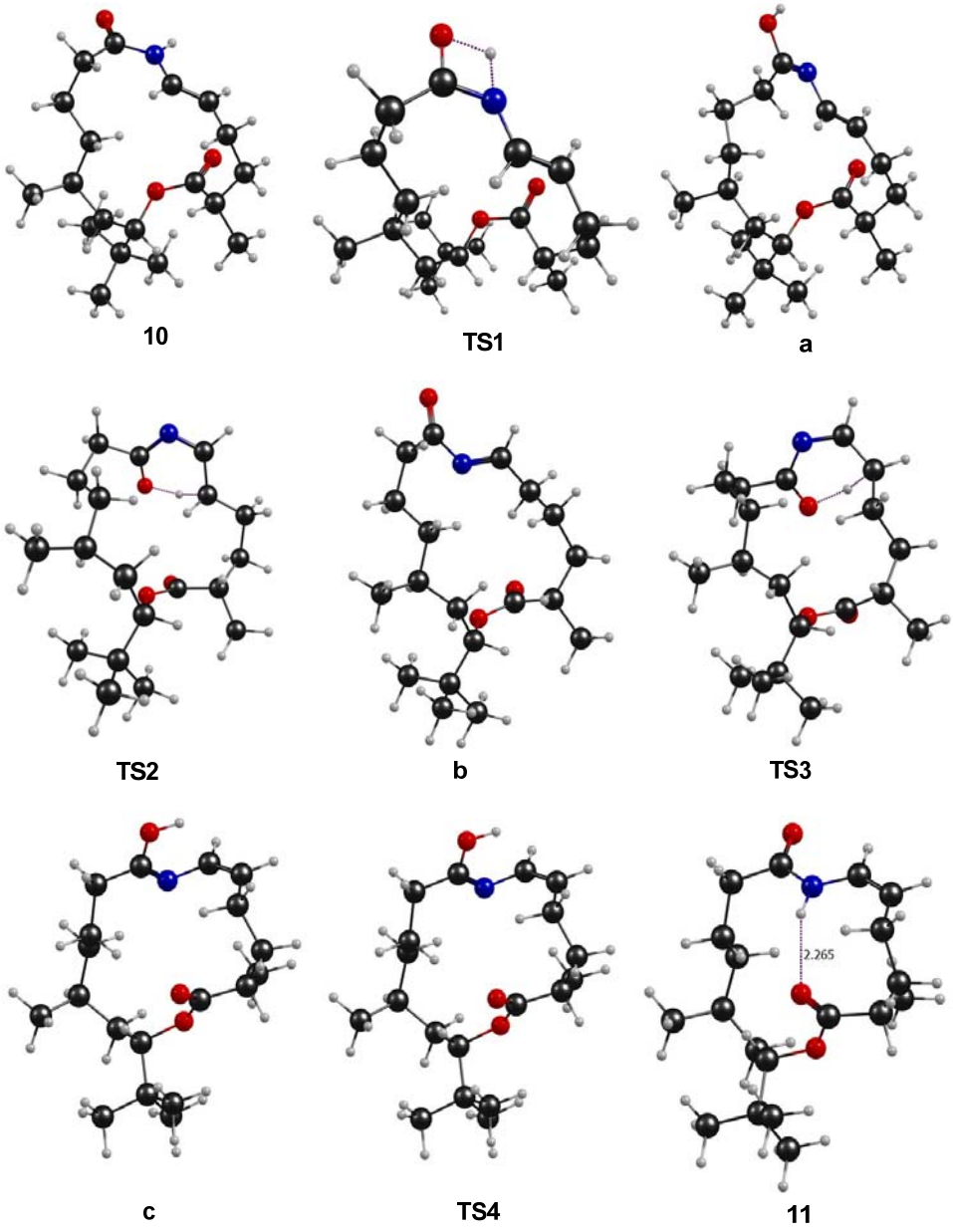
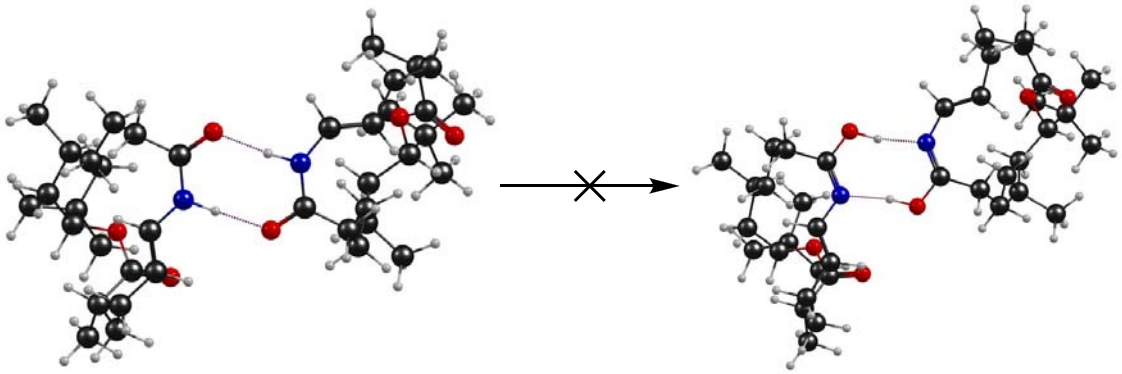


Figure S2: The structures, optimized with DFT, for the reactants, intermediates and transition states that have been discussed in the manuscript

Mechanistic Studies: Solvent Assisted Mechanisms and Intermolecular Processes :

- Shown in Figure S3 below is an attempt to probe the possibility of an intermolecular process where the transfer of the hydrogen from the nitrogen to the oxygen could happen through the presence of a second "**10**" species in the vicinity. What was observed was that, in all attempts where the hydrogens were transferred to the oxygen atoms from the nitrogens, the oxygens reverted hydrogens back to the original nitrogen atoms, re-forming the species "**13**". In other words, no stable intermediate existed with the hydrogens shifted to the oxygen atoms. This result suggests that an intermolecular process of hydrogen transfer from the nitrogen to the oxygen is unlikely.

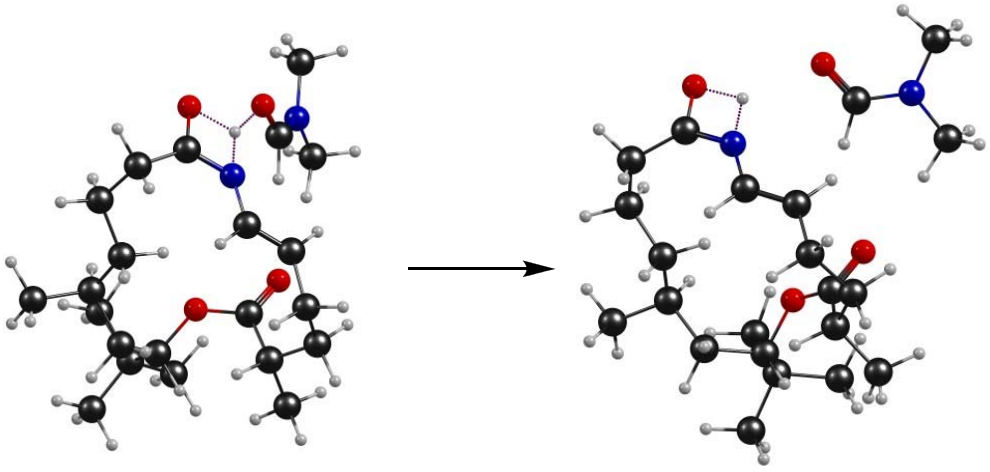


13 **14**

Figure S3: The results of attempt made to transfer hydrogens from the nitrogens to the oxygens in the intermolecular process. "**13**" would be the structure formed by the intermolecular interaction between the two "**10**" moieties. All attempts to form the species denoted as "**14**" below failed, in every instance. Even with increased basis set, the hydrogens were found to revert back to the nitrogens, that is, re-form the structure **13**.

- Shown in Figure S4 below are the results of an attempt to include an explicit solvent molecule (DMF) in the vicinity of the hydrogen which is being transferred intramolecularly. It was observed that in the final transition state obtained, the solvent molecule had shifted away from the region of the four centered transition state. Moreover, no change was seen in the barrier height by the explicit inclusion of the solvent molecule. In other words, explicit inclusion of the solvent molecule does not lead to any change in the nature of the transition state, or in the barrier for the

intramolecular transfer reaction. It is also to be noted that a full transition state search was done with the COSMO incorporated, instead of a single point COSMO calculation after a gas phase calculation. This, too, did not lead to a change in the barrier (of 35.7 kcal/mol) that had been obtained earlier from the gas phase transition state calculations for the intramolecular hydrogen transfer from nitrogen to the oxygen.



TS7 **TS7'**

Figure S4 : The result of the attempts to optimize the transition state with the solvent present in the vicinity of the hydrogen being transferred: "**TS7**" is the input structure provided to Turbomole, and "**TS7'**" is the structure that was obtained as the final transition state structure.

Coordinates:-

Cartesian coordinates of the optimized structures using DFT for the structures shown in figure **2** of manuscript and figure **S1** of supporting information.

Structure **10**

C	-0.014802	-3.905587	-0.007507
C	0.586247	-2.466124	0.111844
O	-0.129435	-1.621666	-0.845519
C	0.473785	-0.943307	-1.874270
C	1.964802	-0.592056	-1.787634
C	2.259971	0.781289	-2.426519
C	1.753766	2.038413	-1.692238
C	0.264438	2.208134	-1.711480
C	-0.480293	2.455226	-0.622040

N	-1.872131	2.580624	-0.630567
C	-2.770244	2.497332	0.422129
O	-3.979330	2.491964	0.191307
C	-2.235108	2.392926	1.844107
C	-2.084685	0.930089	2.323313
C	-0.848048	0.225280	1.757066
C	-0.661377	-1.249570	2.156207
C	-0.592818	-1.436037	3.678873
C	0.628753	-1.817249	1.505947
O	-0.212818	-0.638343	-2.828741
H	-1.282164	2.929919	1.973870
H	-2.985655	2.899965	2.465535
H	-2.999871	0.376008	2.055045
H	-2.039441	0.944565	3.423234
H	0.053710	0.783615	2.076363
H	-0.869633	0.270494	0.659265
H	-1.535242	-1.803471	1.782435
H	1.072975	-2.568411	2.177934
H	1.369461	-0.998324	1.466238
H	1.633177	-2.561311	-0.218535
C	0.173499	-4.387129	-1.460071
C	-1.514024	-3.970618	0.331667
C	0.764959	-4.856046	0.920105
H	-0.471445	-2.497862	3.942770
H	-1.501814	-1.075592	4.180571
H	0.264599	-0.887740	4.103989
C	2.780688	-1.668024	-2.537526
H	2.278691	-0.570438	-0.730742
H	1.854238	0.772173	-3.450551
H	3.355622	0.860382	-2.520833
H	2.232454	2.904309	-2.186800
H	2.121443	2.044498	-0.650918
H	-0.230691	2.076851	-2.679363
H	-0.016843	2.558365	0.359423
H	-2.336372	2.560430	-1.540013
H	-0.208110	-5.413646	-1.565318
H	-0.370013	-3.749897	-2.170705
H	1.237099	-4.401391	-1.746167
H	0.449105	-5.893907	0.736221
H	1.850614	-4.803332	0.738028
H	0.584299	-4.643136	1.983535
H	-1.907450	-4.963657	0.065346
H	-1.703192	-3.824420	1.404306
H	-2.082666	-3.220051	-0.234476
H	3.852073	-1.424297	-2.494564
H	2.645456	-2.674484	-2.119429
H	2.476863	-1.700437	-3.593687

Structure **a**

N	-0.269087	-3.528726	0.507408
C	0.619857	-2.454672	0.503830
C	0.623028	-1.402373	-0.336348
C	1.422348	-0.155396	-0.075393
C	2.006496	0.561950	-1.302529

C	3.158543	-0.139764	-2.042146
C	2.642753	-1.253929	-2.957595
O	1.547355	-1.219056	-3.483299
C	3.913842	0.888751	-2.912553
O	3.451193	-2.312697	-3.274102
C	4.814602	-2.527366	-2.792400
C	5.667014	-2.940958	-4.034477
C	5.803367	-1.709548	-4.953159
C	7.076712	-3.348279	-3.570950
C	5.026348	-4.070598	-4.860403
C	4.767834	-3.450051	-1.557494
C	3.983404	-4.782728	-1.678597
C	4.908447	-6.004855	-1.784977
C	3.000239	-5.006036	-0.501686
C	1.752310	-5.803180	-0.920985
H	2.676002	-4.037472	-0.090824
H	3.530302	-5.524585	0.315338
H	3.372883	-4.717891	-2.594639
H	4.328132	-6.936290	-1.873081
H	5.584403	-5.959011	-2.649802
H	5.532060	-6.088998	-0.879871
H	4.935518	-5.007816	-4.298691
H	5.650294	-4.275274	-5.744131
H	4.026035	-3.781038	-5.207820
H	4.309011	-2.847338	-0.755762
H	5.802858	-3.633383	-1.225859
H	5.234386	-1.566271	-2.452530
H	4.820758	-1.344616	-5.284007
H	6.382277	-1.972626	-5.851189
H	6.333216	-0.886661	-4.447479
H	7.537349	-2.566930	-2.944576
H	7.727327	-3.494684	-4.446204
H	7.074588	-4.285717	-2.998438
H	1.269413	-2.428219	1.390301
H	-0.062724	-1.389435	-1.189150
H	0.762484	0.579630	0.424730
H	2.224964	-0.372072	0.652361
H	1.205152	0.764124	-2.030125
H	2.385550	1.541166	-0.967446
H	3.856631	-0.558777	-1.297832
H	4.739081	0.439053	-3.479518
H	4.328730	1.684050	-2.276828
H	3.222840	1.350881	-3.632807
H	1.370477	-6.407109	-0.083461
C	0.613678	-4.885169	-1.443132
H	2.023647	-6.523370	-1.709432
H	0.014924	-5.407387	-2.202119
C	-0.311319	-4.501480	-0.317304
H	1.031425	-3.981872	-1.908844
O	-1.293154	-5.438114	-0.147112
H	-1.799870	-5.138929	0.637280

Structure **b**

C	-0.117625	-3.464614	0.594256
C	0.718954	-2.242105	0.191242
C	0.013952	-1.410186	-0.917848
C	-0.468204	0.012581	-0.586346

O	0.621838	0.767498	0.034194
C	1.440742	1.644134	-0.616940
O	2.172559	2.339998	0.060671
C	-1.717312	0.203986	0.327984
C	-2.891724	-0.607255	-0.247862
C	-2.098541	1.698089	0.298411
C	-1.463264	-0.201839	1.790293
C	1.411955	1.749663	-2.145579
C	0.538699	2.959757	-2.532079
C	2.834642	1.907107	-2.721557
C	3.750781	0.676116	-2.559388
C	4.693644	0.738546	-1.332060
C	5.292955	-0.604023	-1.060401
N	4.943806	-1.293558	-0.045770
C	5.460490	-2.562435	0.250228
C	4.429087	-3.687476	0.269317
C	3.007671	-3.344558	0.759668
C	2.126454	-2.653634	-0.285995
O	6.634305	-2.738717	0.550741
H	4.374700	-4.085539	-0.761806
H	4.875500	-4.484580	0.880665
H	3.074822	-2.710303	1.658894
H	2.535532	-4.287743	1.077520
H	2.025562	-3.312954	-1.170032
H	2.644544	-1.745632	-0.627441
H	0.856319	-1.598000	1.074824
H	-0.843962	-1.968078	-1.325526
H	0.711744	-1.303440	-1.766478
H	-0.732803	0.492713	-1.543996
H	-1.137689	-3.183933	0.894622
H	0.331022	-4.008593	1.437745
H	-0.205304	-4.168949	-0.250008
H	0.971218	0.839077	-2.581474
H	3.302520	2.793711	-2.265789
H	2.714315	2.127779	-3.794255
H	4.360880	0.548705	-3.468080
H	3.126381	-0.231400	-2.491466
H	6.003347	-1.011373	-1.806894
H	-2.991815	1.871312	0.916461
H	-1.288323	2.326549	0.693301
H	-2.333909	2.032188	-0.725239
H	-3.814071	-0.363220	0.299986
H	-3.065668	-0.371400	-1.310304
H	-2.732652	-1.691154	-0.159809
H	-2.347366	0.044029	2.398142
H	-1.280633	-1.278946	1.898014
H	-0.603273	0.340171	2.206164
H	0.503137	3.066789	-3.626065
H	-0.492677	2.860060	-2.165179
H	0.961035	3.881163	-2.106791
H	5.494510	1.469339	-1.538022
H	4.151677	1.073948	-0.438979

Structure **c**

C	-5.296243	2.787369	4.336002
C	-5.460437	3.911255	3.297438
C	-4.111562	4.636186	3.128422

C	-6.492094	4.938235	3.798151
C	-5.934394	3.350731	1.920502
O	-4.896435	2.434264	1.418022
C	-4.030183	2.856977	0.461566
C	-2.932796	1.817966	0.218300
C	-2.167950	2.081233	-1.097528
C	-2.976562	2.092810	-2.413314
C	-3.566992	0.777772	-2.835269
C	-4.886951	0.492523	-2.893198
N	-5.921766	1.350010	-2.489632
C	-6.275481	2.335449	-3.228138
O	-5.744680	2.608535	-4.458911
C	-7.247422	2.540719	1.960782
C	-8.398983	2.885599	0.983205
C	-8.967197	4.293065	1.210667
C	-8.138157	2.576738	-0.511839
C	-7.418238	3.651845	-1.336582
C	-7.331457	3.334759	-2.839116
O	-4.090180	3.944633	-0.088520
H	-5.992836	4.193707	1.216024
H	-6.247892	2.281308	4.555732
H	-4.918785	3.204347	5.281846
H	-4.579289	2.030271	3.988158
H	-4.165410	5.411768	2.350253
H	-3.305978	3.939063	2.858111
H	-3.825351	5.117664	4.075815
H	-6.620362	5.761592	3.078832
H	-7.478250	4.487961	3.979202
H	-6.148450	5.374681	4.748067
H	-6.976831	1.482707	1.819391
H	-7.669514	2.603932	2.976012
H	-9.198097	2.180357	1.276906
H	-9.324875	4.412722	2.244467
H	-9.819130	4.484987	0.539983
H	-8.222045	5.081533	1.027358
H	-9.124085	2.408149	-0.984206
H	-7.589545	1.627230	-0.600350
H	-6.402025	3.835379	-0.957387
H	-7.962409	4.605301	-1.243249
H	-8.305587	2.963931	-3.206589
H	-7.124031	4.253052	-3.407835
C	-3.392233	0.365217	0.420516
H	-1.677051	3.062768	-1.014233
H	-1.362031	1.330669	-1.164663
H	-3.756683	2.862530	-2.334024
H	-2.285296	2.436796	-3.203655
H	-2.871359	-0.033397	-3.073310
H	-5.211679	-0.519984	-3.160763
H	-5.054975	1.924962	-4.623638
H	-2.555220	-0.319048	0.217371
H	-3.728740	0.199164	1.451661
H	-4.215907	0.103908	-0.253785
H	-2.207232	2.034784	1.027593

Structure **11**

C	-5.235565	2.832887	4.203819

C	-5.478223	4.003229	3.235228
C	-4.182853	4.816363	3.065806
C	-6.605501	4.947624	3.750567
C	-6.386914	5.564666	5.148281
C	-6.447509	7.102229	5.330807
C	-7.814302	7.777027	5.043065
C	-8.107176	8.210575	3.599852
C	-9.372762	9.081283	3.484255
C	-10.677424	8.434463	3.938425
O	-11.405942	8.931356	4.794540
O	-7.841709	4.144296	3.834469
C	-8.854703	4.355315	2.962770
O	-8.844240	5.226162	2.101802
C	-5.876556	3.442486	1.856652
C	-5.279549	7.829741	4.651506
C	-9.975802	3.347107	3.206594
C	-11.090070	3.378512	2.137603
C	-11.825313	4.705796	1.832437
C	-12.530979	5.381346	2.973968
C	-12.155602	6.524274	3.579036
N	-10.999476	7.250504	3.291069
H	-6.773120	5.720669	2.987361
H	-4.883122	3.174692	5.187931
H	-4.465470	2.161498	3.794422
H	-6.152744	2.246117	4.354094
H	-6.114354	4.249422	1.147639
H	-6.750602	2.779311	1.925131
H	-5.047457	2.853009	1.437334
H	-4.320411	5.651860	2.362068
H	-3.820356	5.229375	4.017653
H	-3.390189	4.168084	2.663297
H	-7.133090	5.109381	5.817964
H	-5.409455	5.236312	5.535788
H	-6.296518	7.231536	6.417884
H	-4.314310	7.460361	5.028550
H	-5.322165	8.911604	4.851056
H	-5.278377	7.697184	3.559249
H	-7.867662	8.682306	5.672908
H	-8.624214	7.120670	5.406031
H	-8.185953	7.338486	2.932974
H	-7.266950	8.810883	3.216386
H	-9.265968	9.990738	4.092138
H	-9.496591	9.403429	2.435946
C	-10.489495	3.410592	4.659897
H	-10.663348	3.023364	1.185272
H	-11.831312	2.619611	2.439891
H	-11.114385	5.391615	1.352386
H	-12.577426	4.466885	1.060002
H	-13.454521	4.921793	3.336342
H	-12.745980	6.980590	4.374687
H	-10.326328	6.854752	2.633363
H	-11.245124	2.626718	4.814266
H	-9.670622	3.242994	5.370963
H	-10.960536	4.376235	4.879152
H	-9.478274	2.365154	3.100698

Structure **TS1**

C	-1.192270	-1.505975	3.655460
C	-1.002374	-1.194086	2.164075
C	0.398377	-1.677146	1.696067
C	0.560548	-2.331463	0.314361
O	-0.090900	-1.526087	-0.716708
C	0.580037	-0.830710	-1.694521
O	-0.030462	-0.552280	-2.705682
C	0.059949	-3.804508	0.145905
C	0.801524	-4.704676	1.151828
C	0.412732	-4.279854	-1.277542
C	-1.458192	-3.959561	0.342308
C	2.048455	-0.435540	-1.482366
C	2.957648	-1.505679	-2.126174
C	2.366818	0.928726	-2.130154
C	1.812622	2.192542	-1.443523
C	0.328054	2.357191	-1.542988
C	-0.476056	2.588844	-0.490001
N	-1.855086	2.700836	-0.582039
C	-2.777938	2.627292	0.368905
C	-2.630913	2.418448	1.842420
C	-2.521222	0.921994	2.226162
C	-1.170282	0.304107	1.853779
O	-3.934742	2.716977	-0.221901
H	-1.740206	2.955930	2.207820
H	-3.512455	2.863104	2.324317
H	-3.342122	0.367748	1.742364
H	-2.687727	0.849702	3.312152
H	-0.369444	0.860505	2.378299
H	-0.992020	0.440258	0.777748
H	-1.778980	-1.729621	1.598998
H	0.802515	-2.392699	2.429262
H	1.084693	-0.813070	1.732928
H	1.642500	-2.365287	0.106443
H	-1.081918	-2.583493	3.852209
H	-2.186016	-1.207458	4.017774
H	-0.440114	-0.978575	4.265638
H	2.264185	-0.379330	-0.402237
H	2.016716	0.898030	-3.173976
H	3.465281	1.016521	-2.165898
H	2.311225	3.054269	-1.926285
H	2.125944	2.216369	-0.384670
H	-0.125360	2.244974	-2.532279
H	-0.050368	2.678726	0.518257
H	-3.049447	2.778634	-1.201301
H	0.090441	-5.323241	-1.412684
H	-0.086539	-3.670085	-2.042635
H	1.498578	-4.246613	-1.457535
H	0.568106	-5.760268	0.946274
H	1.894597	-4.586486	1.075491
H	0.506178	-4.501383	2.191339
H	-1.761286	-4.979691	0.061027
H	-1.758193	-3.808609	1.388650
H	-2.015108	-3.256186	-0.292293
H	4.013585	-1.230930	-1.989692
H	2.810712	-2.506117	-1.698120
H	2.755505	-1.569784	-3.205107

Structure **TS2**

C	4.730256	0.133423	-2.500715
C	3.678227	-0.780331	-1.838229
C	2.936390	-1.557352	-2.942204
O	3.344669	-2.808711	-3.329352
C	4.617237	-3.464863	-3.035700
C	4.355082	-4.676324	-2.116300
C	3.170276	-5.623933	-2.477509
C	2.079703	-5.567529	-1.387737
C	0.658996	-5.930669	-1.847603
C	-0.423893	-5.506933	-0.819118
C	-0.178698	-4.069544	-0.454024
C	2.683673	0.086351	-1.018866
C	2.129159	-0.558568	0.261672
C	1.457180	-1.891904	0.031613
C	0.726617	-2.576062	1.027758
N	0.191337	-3.778701	0.810342
O	1.969290	-1.095706	-3.512478
C	5.327218	-3.741316	-4.402442
C	4.457330	-4.560505	-5.372041
C	5.652700	-2.394261	-5.075514
C	6.654452	-4.477985	-4.144062
C	3.638460	-7.067293	-2.708229
H	2.056299	-4.537855	-1.005576
H	2.378064	-6.193793	-0.527148
H	2.707636	-5.250788	-3.404169
H	2.796449	-7.724917	-2.971806
H	4.378728	-7.140827	-3.519408
H	4.105194	-7.473161	-1.795905
H	4.274072	-5.579508	-5.007571
H	4.971664	-4.645983	-6.341532
H	3.488713	-4.071239	-5.543067
H	4.186775	-4.275820	-1.102546
H	5.294214	-5.246224	-2.043677
H	5.269252	-2.764969	-2.485231
H	4.746600	-1.798139	-5.251745
H	6.129980	-2.570633	-6.051263
H	6.355996	-1.800919	-4.470513
H	7.270930	-3.954840	-3.394981
H	7.237306	-4.526211	-5.075910
H	6.500308	-5.510457	-3.799936
H	1.430124	0.148516	0.737086
H	2.964343	-0.690395	0.976237
H	1.860783	0.376414	-1.689147
H	3.202068	1.014388	-0.730714
H	4.197271	-1.484613	-1.165452
H	5.461390	-0.426250	-3.097328
H	5.276548	0.693120	-1.727922
H	4.235154	0.857833	-3.163968
H	0.563394	-7.010105	-2.044884
H	0.450951	-5.406787	-2.794193
H	-0.371140	-6.108592	0.098860
H	-1.423272	-5.626688	-1.265404
H	0.456942	-2.071243	1.968788
O	-0.268669	-3.184520	-1.378699
H	2.047460	-2.556289	-0.618007
H	0.404462	-2.153952	-0.809528

Structure **TS3**

C	-0.230530	-2.941181	1.819155
C	0.597209	-1.943586	0.995149
C	1.886230	-2.638486	0.494075
C	3.003916	-2.859683	1.525626
C	3.683601	-1.563767	2.009307
C	4.235807	-0.749696	0.862773
C	-0.192354	-1.361917	-0.210669
C	-0.778578	0.063474	-0.119860
C	-2.093332	0.324832	0.683053
C	-1.872648	0.339725	2.205545
O	0.225223	0.967889	0.430138
C	0.929260	1.909470	-0.268919
C	1.077545	1.819646	-1.795806
C	2.587637	1.814817	-2.129639
C	3.232913	0.432362	-1.936118
C	4.732280	0.468236	-1.629371
C	5.426078	-0.640379	-1.083261
N	4.965530	-1.389301	-0.078730
O	1.457053	2.800357	0.363793
C	-3.146300	-0.731133	0.305655
C	-2.622168	1.712692	0.265175
C	0.363212	3.022813	-2.434042
H	1.606788	-3.614784	0.058784
H	2.313334	-2.060643	-0.340470
H	0.888377	-1.097872	1.639242
H	-1.002132	-2.048794	-0.505997
H	0.488714	-1.336629	-1.078134
H	-1.006662	0.367813	-1.155915
H	-1.161365	-2.506893	2.207403
H	0.337367	-3.316939	2.683598
H	-0.504754	-3.810813	1.199373
H	0.630514	0.889916	-2.181701
H	3.073939	2.563947	-1.486709
H	2.722835	2.149497	-3.171119
H	3.079340	-0.174286	-2.845393
H	2.713005	-0.095041	-1.125993
H	6.481315	-0.796524	-1.356074
H	-3.549312	1.946518	0.809737
H	-1.893785	2.503618	0.493909
H	-2.851085	1.746959	-0.812559
H	-4.119597	-0.456386	0.739487
H	-3.279533	-0.800300	-0.786225
H	-2.885785	-1.730600	0.681495
H	-2.826946	0.549600	2.712826
H	-1.500273	-0.619457	2.585690
H	-1.153584	1.119125	2.488584
H	0.467429	2.989600	-3.528416
H	-0.710049	3.037625	-2.193302
H	0.804727	3.960306	-2.068172
H	5.317363	1.068475	-2.334936
H	4.589931	0.866134	-0.336747
O	4.037737	0.515866	0.858054
H	2.991750	-0.921040	2.570321
H	4.511619	-1.821078	2.689569
H	2.625324	-3.402953	2.406578

H	3.771927	-3.501710	1.068299

Structure **TS4**

C	-4.183200	9.595659	5.053485
C	-4.251484	9.635390	3.517038
C	-3.405338	8.489941	2.875240
C	-3.754854	7.082674	3.391628
C	-3.815348	5.871860	2.410853
C	-2.503182	5.070105	2.267706
C	-1.400839	5.715406	1.425716
C	-0.057509	4.943486	1.434839
C	0.656792	5.004473	2.746992
O	0.202320	4.408842	3.816993
C	-3.737775	11.003223	3.028160
C	-5.712078	9.488215	3.048608
O	-1.983631	8.744698	3.171699
C	-1.205526	9.278111	2.190576
O	-1.580113	9.458194	1.043577
C	0.189090	9.664757	2.700007
C	1.214888	9.529846	1.555979
C	1.459095	8.070267	1.088827
C	2.678696	7.420261	1.668535
C	2.788994	6.353975	2.489478
N	1.808827	5.566632	3.092463
C	-4.457706	6.212262	1.059515
H	-3.520299	8.563782	1.784703
H	-4.617743	8.673353	5.465733
H	-4.743541	10.442924	5.477333
H	-3.143195	9.669060	5.403433
H	-3.712873	11.055598	1.930157
H	-2.727224	11.216541	3.404978
H	-4.399783	11.801527	3.396107
H	-5.784038	9.521643	1.950136
H	-6.174995	8.551766	3.391932
H	-6.315178	10.317285	3.448392
H	-3.069966	6.841181	4.220262
H	-4.752647	7.150347	3.849359
H	-4.503723	5.166516	2.910135
H	-5.438654	6.694433	1.192208
H	-4.615704	5.297528	0.467671
H	-3.836796	6.890137	0.455209
H	-2.751010	4.088922	1.823001
H	-2.111313	4.854041	3.273549
H	-1.227699	6.741861	1.776268
H	-1.721730	5.801037	0.376069
H	-0.252069	3.879440	1.221581
H	0.607254	5.324076	0.646746
C	0.612361	8.985037	4.006829
H	0.848357	10.121704	0.706031
H	2.163933	9.983601	1.883575
H	0.561781	7.475989	1.293839
H	1.562469	8.075472	-0.009640
H	3.631200	7.886555	1.393312
H	3.791409	6.082414	2.835527
H	1.339752	4.940914	4.193500
H	1.603390	9.352262	4.309943
H	-0.097865	9.196537	4.815785

H	0.680219	7.894246	3.899240
H	0.088898	10.749089	2.903291

Structure **TS5**

C	-0.716391	-2.654670	3.361835
C	-0.400979	-1.874162	2.079318
C	1.099175	-2.040990	1.695915
C	1.475185	-2.335906	0.233051
O	0.711636	-1.467612	-0.663305
C	1.221762	-0.428195	-1.393680
O	0.544016	-0.015483	-2.315625
C	1.291493	-3.804964	-0.268737
C	2.180054	-4.735123	0.579208
C	1.763834	-3.893417	-1.732998
C	-0.167937	-4.284577	-0.199387
C	2.589952	0.178627	-1.043227
C	3.687347	-0.569010	-1.833375
C	2.654187	1.678828	-1.416911
C	1.969695	2.684446	-0.475212
C	0.469783	2.531222	-0.347558
C	-0.217409	2.417181	0.877959
N	-1.493848	2.800766	0.687717
C	-2.589333	2.232162	1.368605
C	-2.359119	1.551215	2.722053
C	-2.146185	0.019388	2.610458
C	-0.721483	-0.373736	2.209766
O	-3.708359	2.282327	0.876322
H	-1.517495	2.004987	3.271566
H	-3.274042	1.744610	3.299468
H	-2.879520	-0.392530	1.897673
H	-2.386054	-0.417247	3.592548
H	-0.020698	0.060078	2.950140
H	-0.472774	0.084084	1.239869
H	-1.028659	-2.271666	1.267433
H	1.550591	-2.836741	2.307708
H	1.631488	-1.119742	1.990839
H	2.547776	-2.110470	0.119404
H	-0.470464	-3.721334	3.247015
H	-1.780127	-2.591608	3.631808
H	-0.130737	-2.268262	4.212562
H	2.779132	0.059220	0.037672
H	2.239784	1.786727	-2.431733
H	3.720443	1.949946	-1.482247
H	2.214548	3.696783	-0.841886
H	2.425167	2.625081	0.530576
H	0.199771	2.124214	1.849156
H	1.652626	-4.925672	-2.097481
H	1.174824	-3.238793	-2.389504
H	2.827120	-3.624826	-1.833085
H	2.169967	-5.747873	0.149923
H	3.227180	-4.392703	0.595984
H	1.829513	-4.817503	1.617973
H	-0.248867	-5.281501	-0.658979
H	-0.526197	-4.372764	0.835866
H	-0.836159	-3.605915	-0.747677
H	4.674275	-0.153808	-1.584740
H	3.709435	-1.645600	-1.621956

H	3.524181	-0.442654	-2.913605
H	0.014615	1.908480	-1.135226
H	-0.814341	3.189271	-0.516384

Structure **TS6**

C	-0.485264	-2.946967	0.241185
C	0.302976	-1.634618	0.132618
C	1.822600	-1.864360	0.056713
C	2.457265	-2.559607	1.265801
C	4.000541	-2.662465	1.198004
C	4.699286	-1.334561	1.502193
O	5.126424	-1.061049	2.616950
C	-0.167550	-0.814733	-1.101894
C	-0.413569	0.695371	-0.938621
C	-1.726981	1.138561	-0.214390
C	-1.798790	0.680798	1.252448
O	0.708441	1.309887	-0.230732
C	1.671070	2.100885	-0.806707
C	1.803920	2.164127	-2.333848
C	3.263559	2.379621	-2.787384
C	4.209536	1.159581	-2.750701
C	4.759904	0.827453	-1.381579
C	4.784755	-0.484903	-0.829945
N	4.648505	-0.374796	0.484047
O	2.378763	2.749219	-0.063287
C	-2.935929	0.577345	-0.986446
C	-1.809389	2.677443	-0.245764
C	0.946423	3.342857	-2.845772
H	4.298383	-3.055810	0.211685
H	4.358391	-3.367047	1.960697
H	2.177617	-2.032022	2.193329
H	2.061991	-3.583686	1.359983
H	2.048161	-2.450256	-0.856087
H	2.288693	-0.879504	-0.076274
H	0.119173	-1.045744	1.043139
H	-1.094625	-1.248610	-1.506783
H	0.580691	-0.940657	-1.904233
H	-0.477309	1.127031	-1.950998
H	-1.567050	-2.756397	0.315986
H	-0.194333	-3.530668	1.126483
H	-0.319606	-3.579174	-0.646537
H	1.429517	1.228004	-2.781419
H	3.692963	3.200787	-2.192861
H	3.216400	2.732154	-3.830906
H	5.033882	1.370800	-3.455484
H	3.677368	0.283324	-3.160905
H	4.832106	-1.446264	-1.360545
H	-2.730896	3.011541	0.254093
H	-0.957666	3.139277	0.271418
H	-1.841318	3.058622	-1.278629
H	-3.865227	1.000535	-0.577062
H	-2.894057	0.840997	-2.055533
H	-3.011790	-0.516679	-0.906209
H	-2.681974	1.129401	1.732542
H	-1.898697	-0.409819	1.342635
H	-0.910336	1.002719	1.813687
H	1.003865	3.401030	-3.942275

H	-0.110701	3.251651	-2.564531
H	1.323499	4.288269	-2.430070
H	5.611020	1.443223	-1.056459
H	4.427758	0.924969	0.078850

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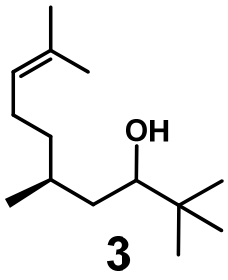

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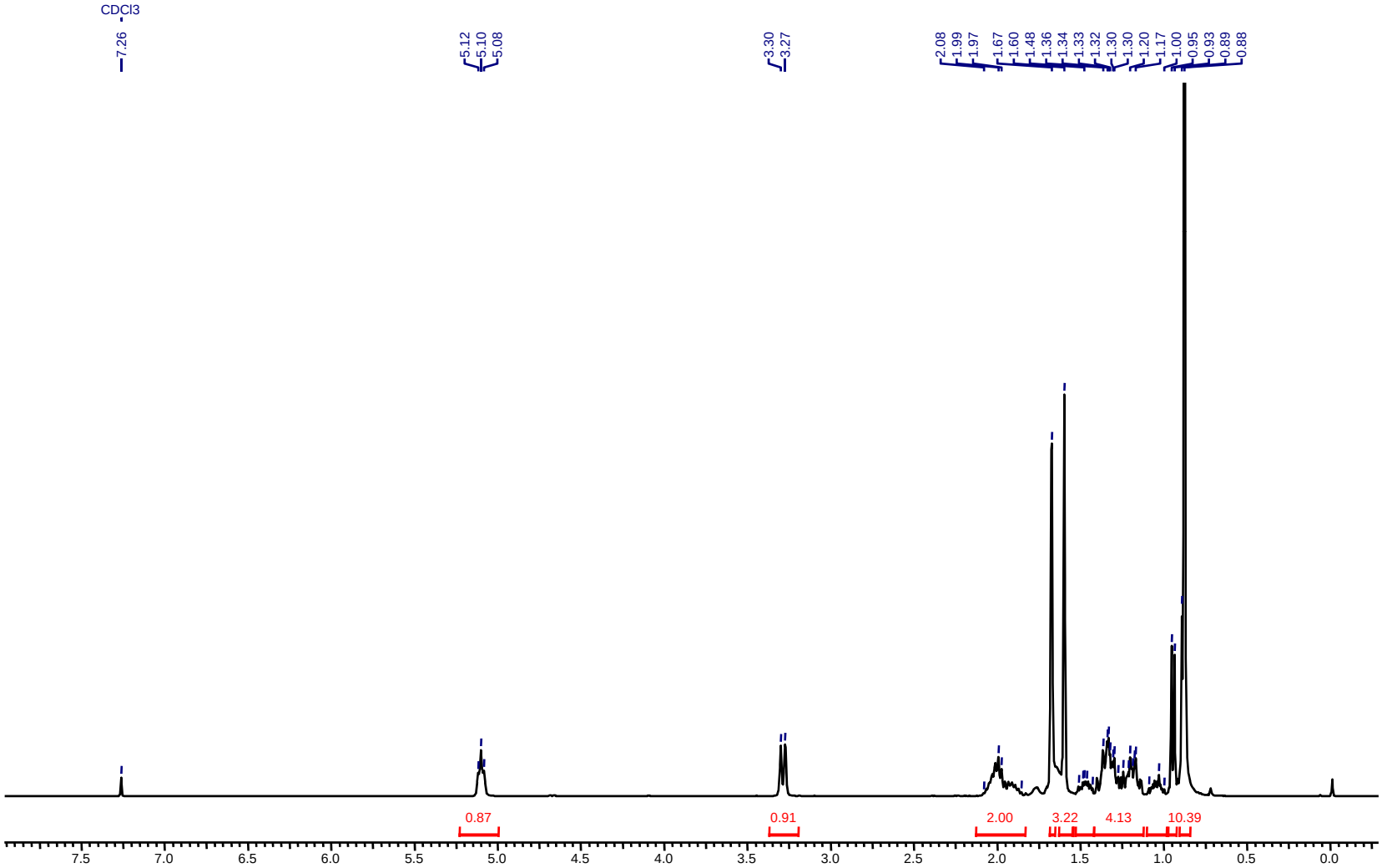

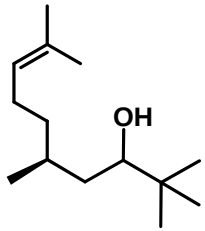

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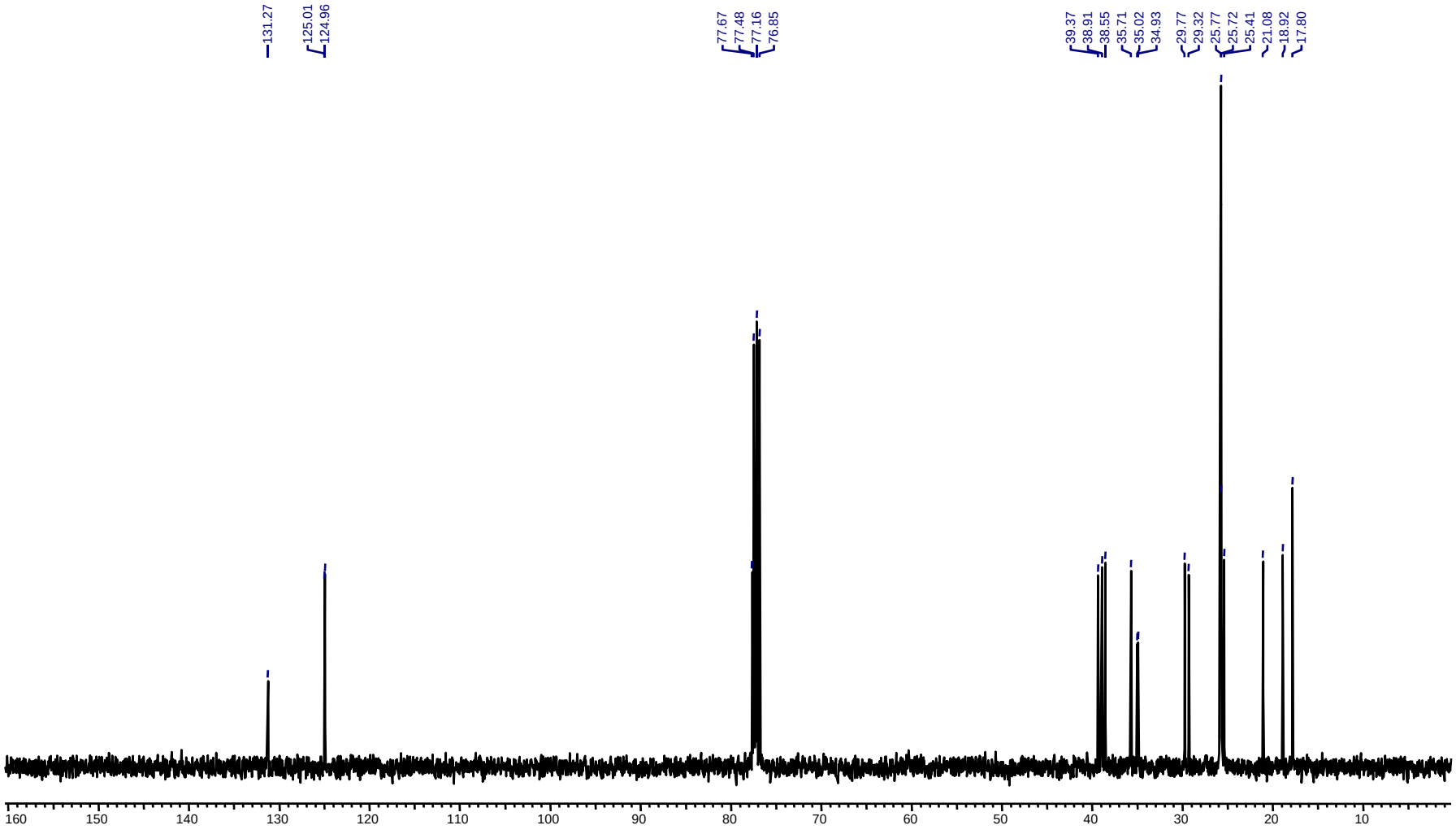

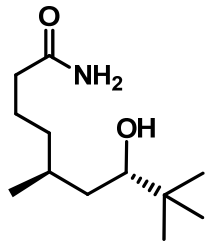

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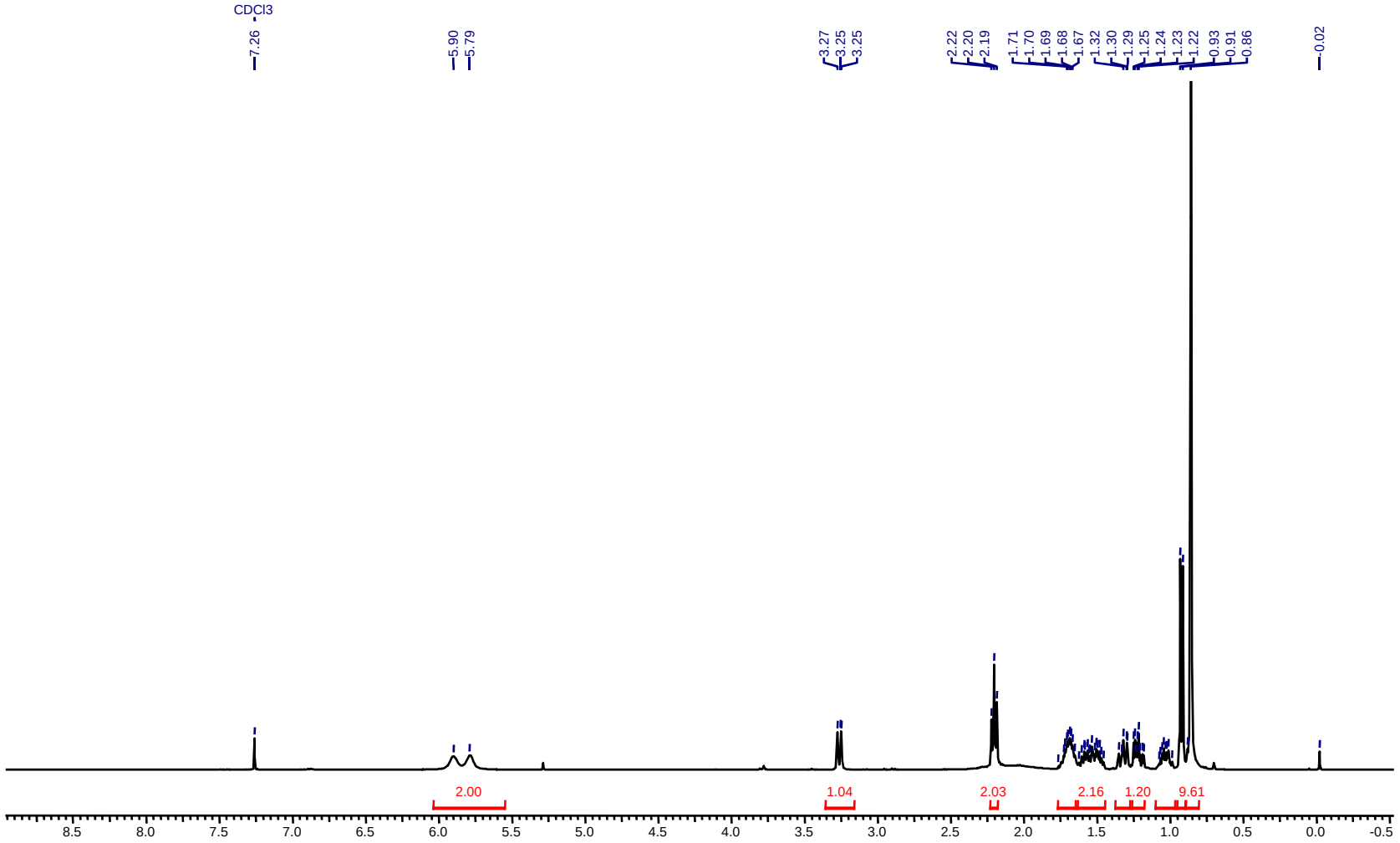

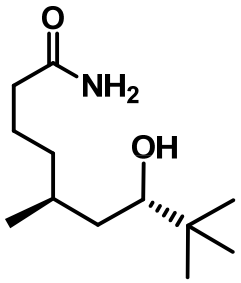

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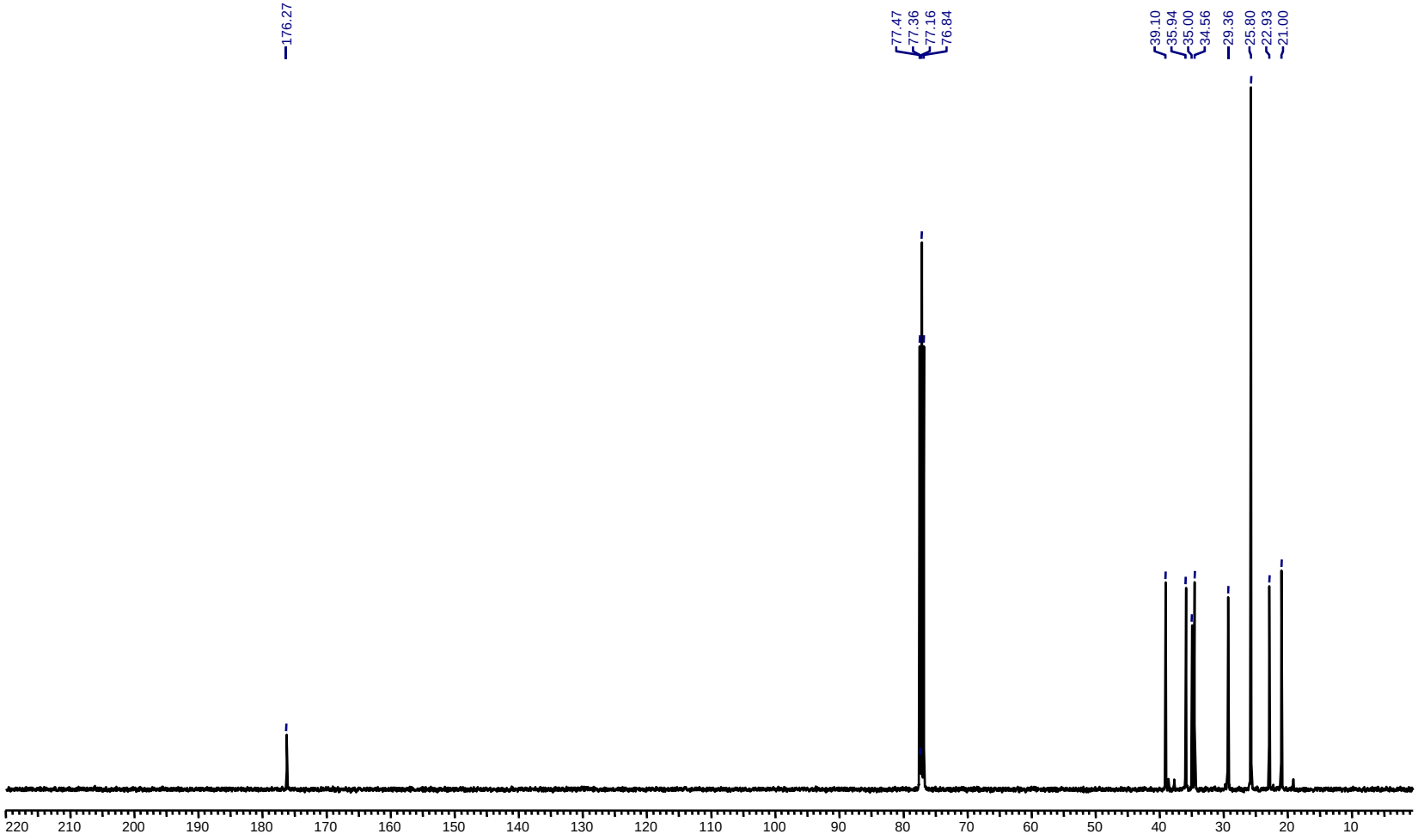

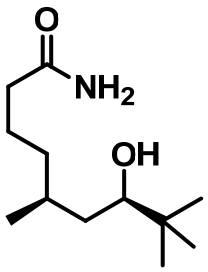

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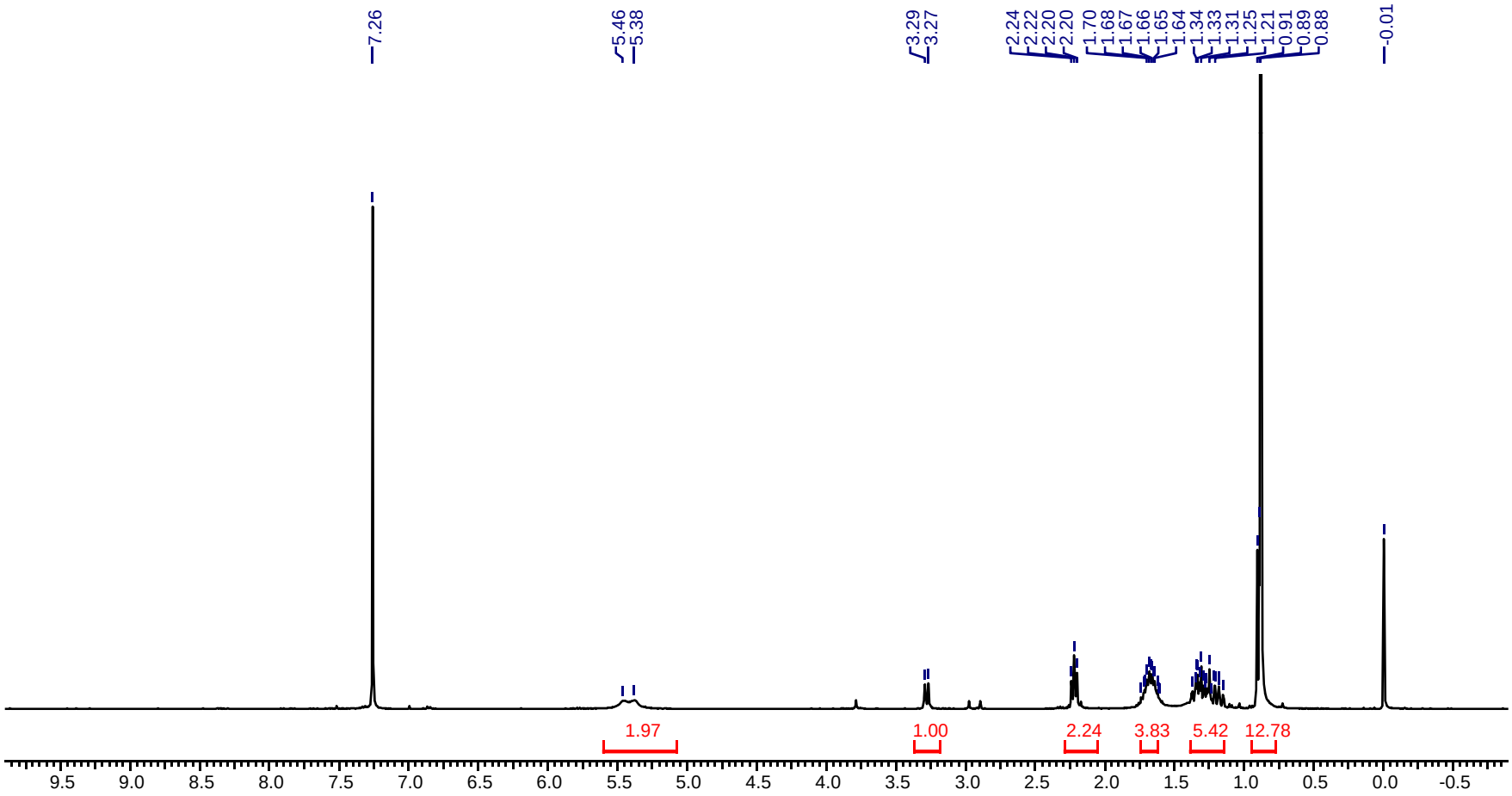

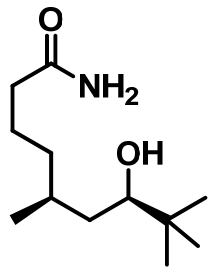

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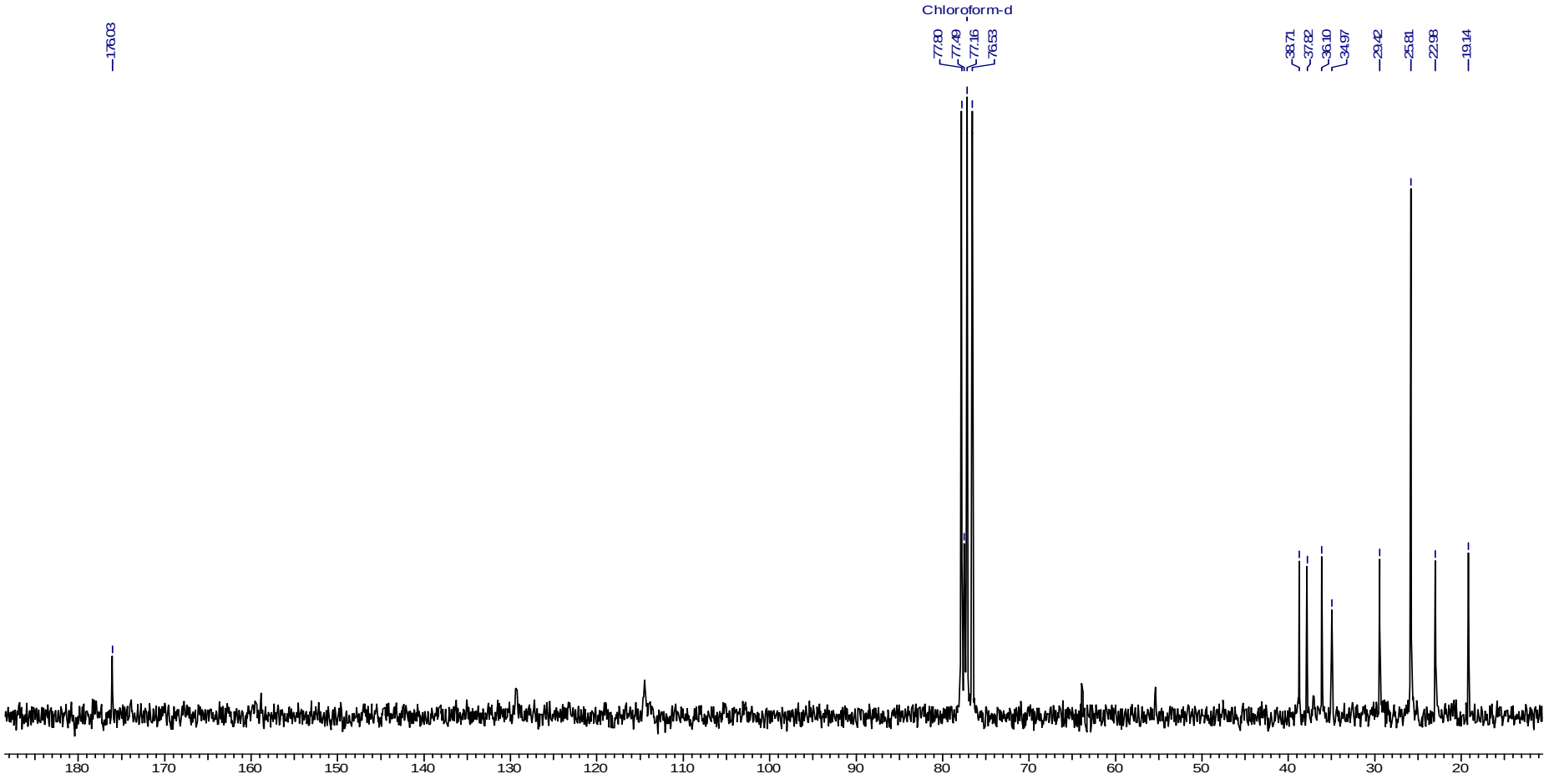

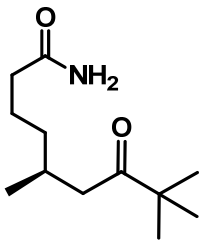

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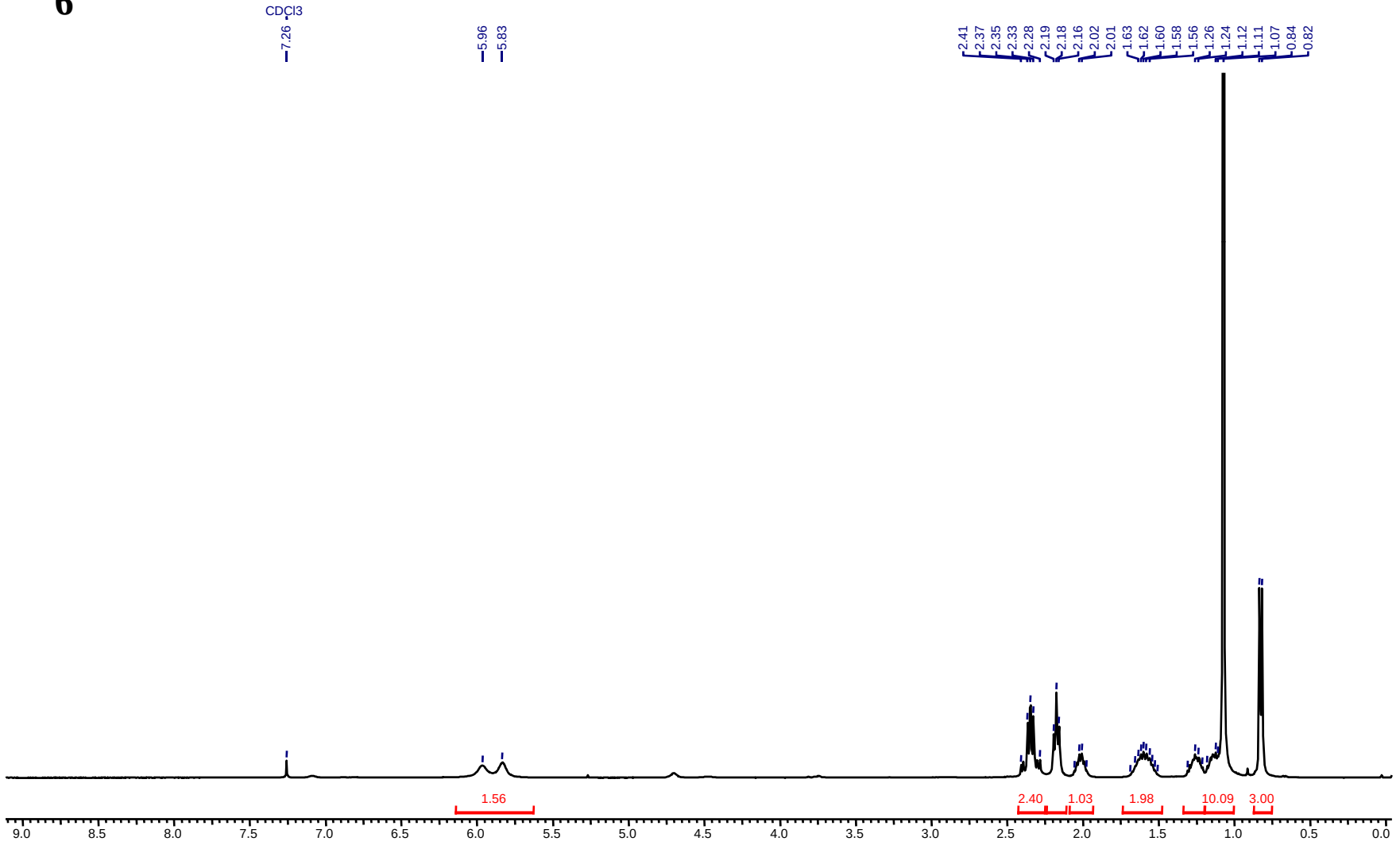

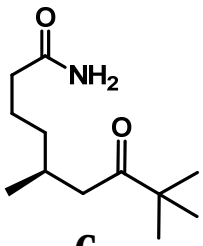

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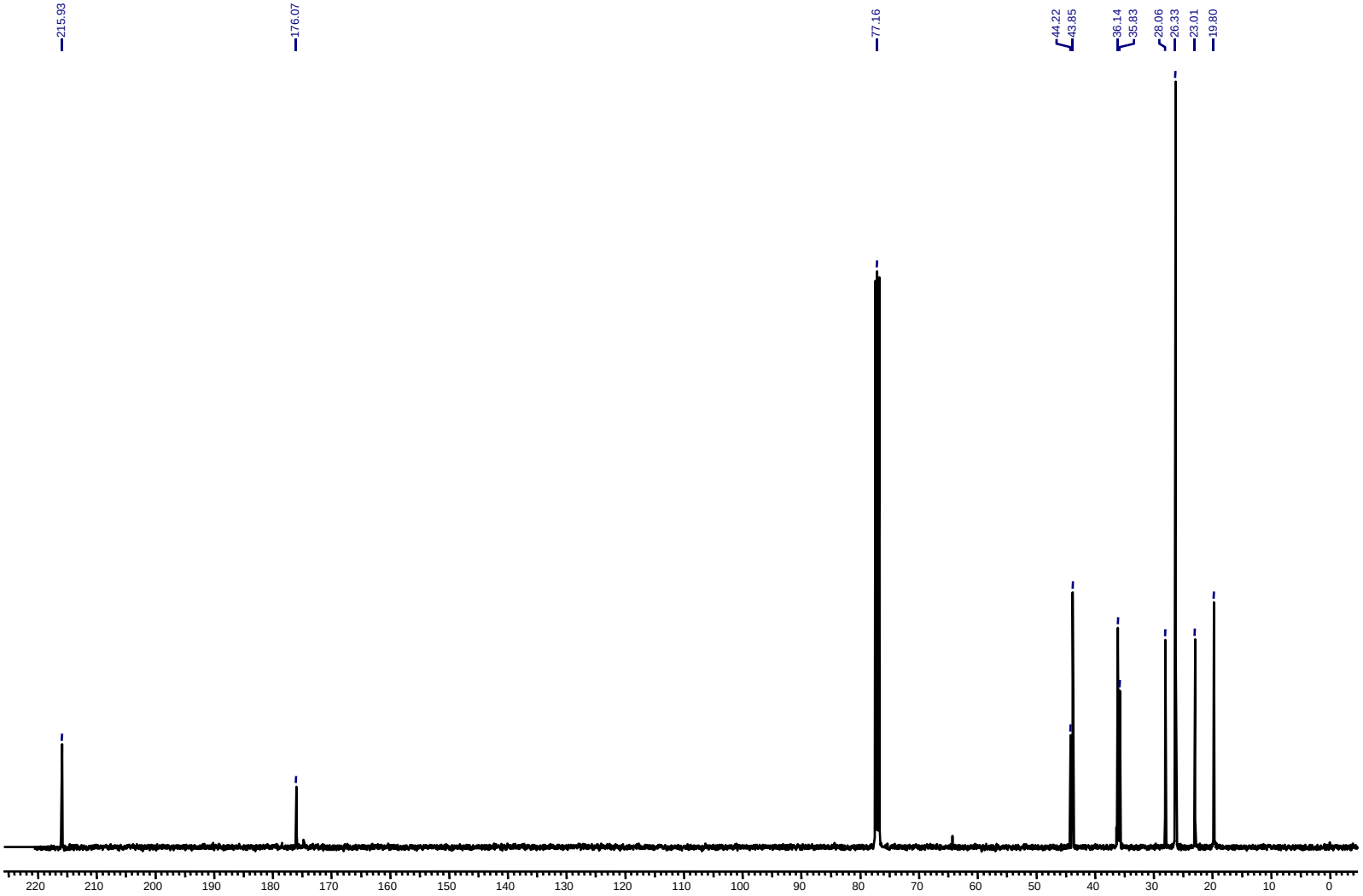

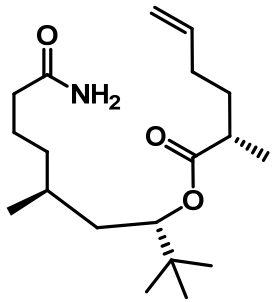

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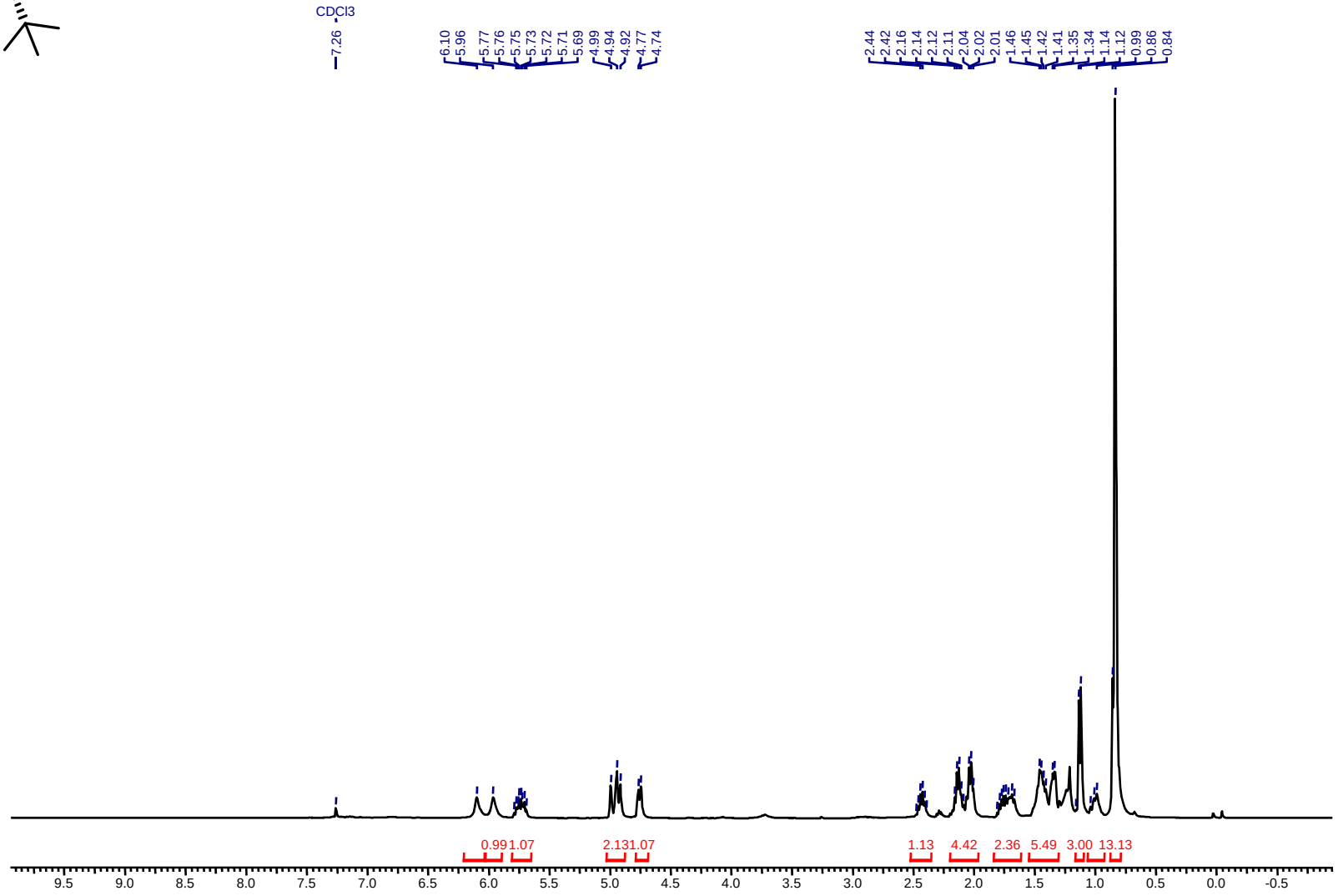

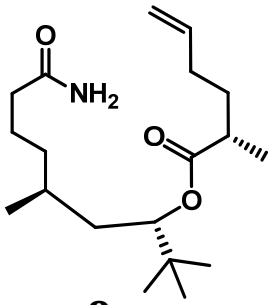

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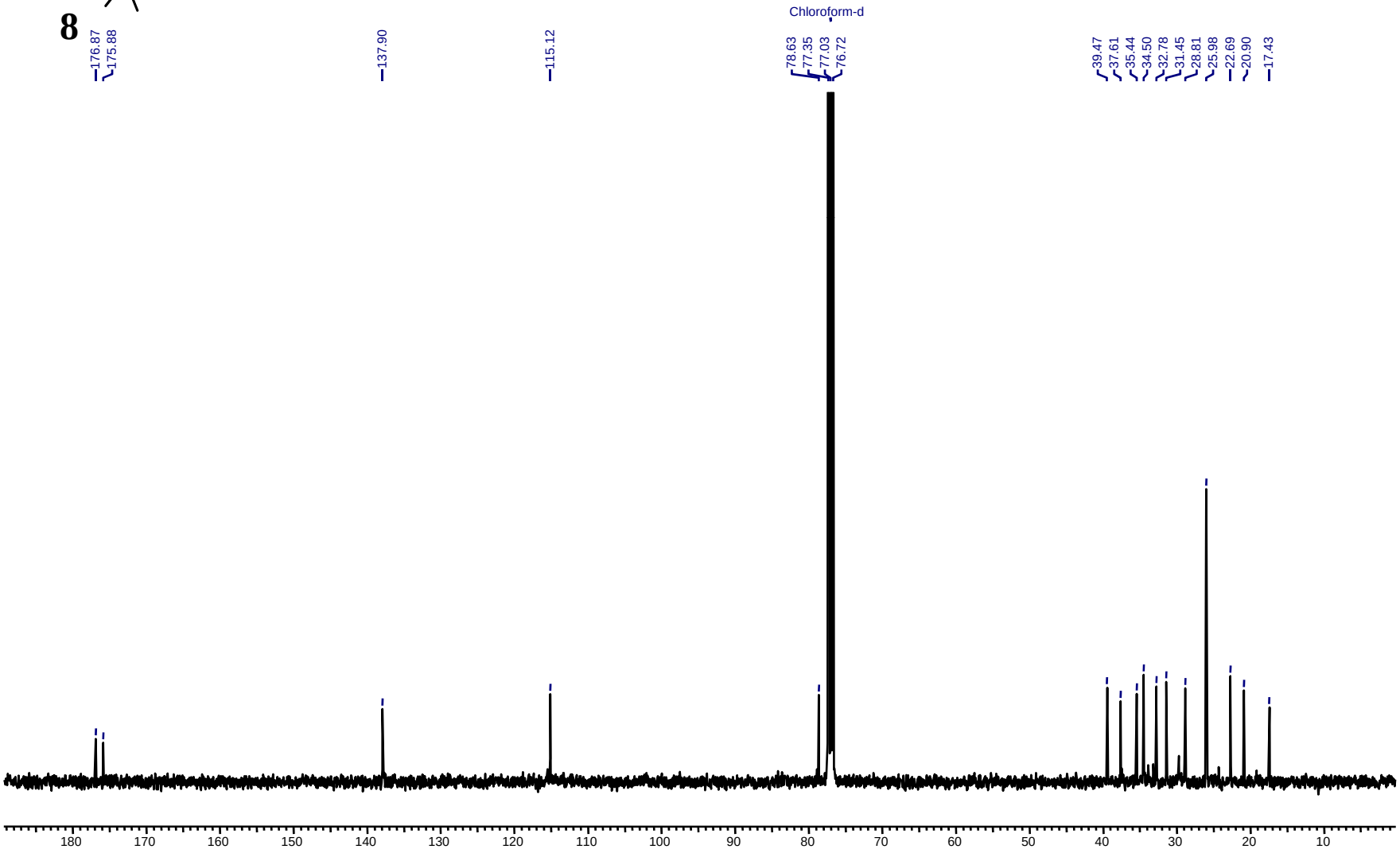

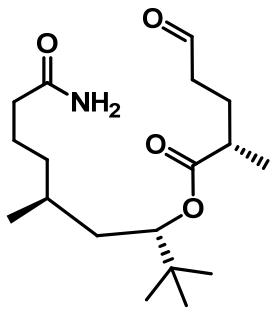

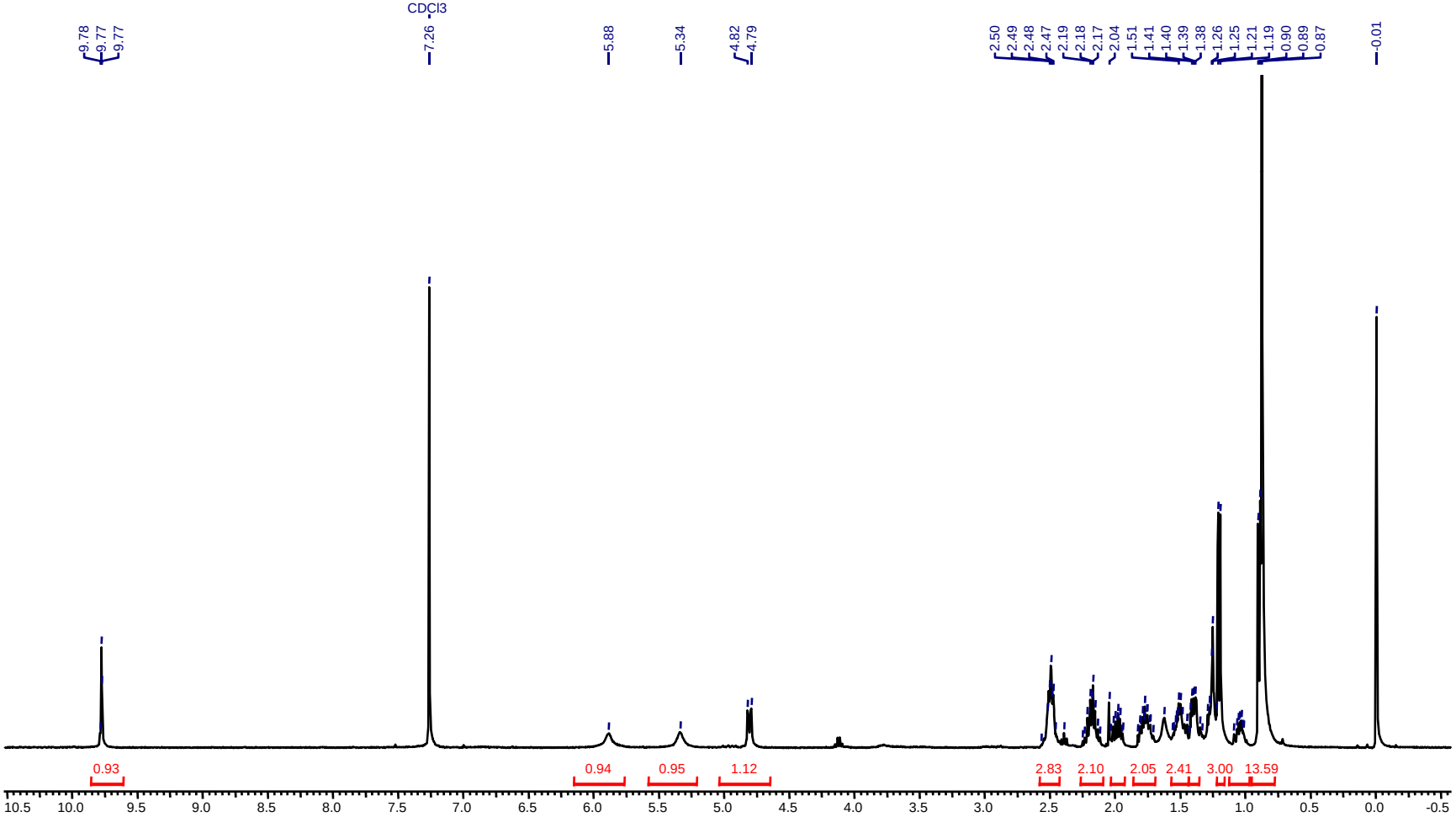

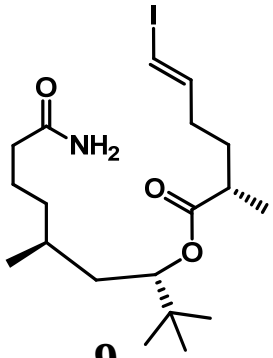

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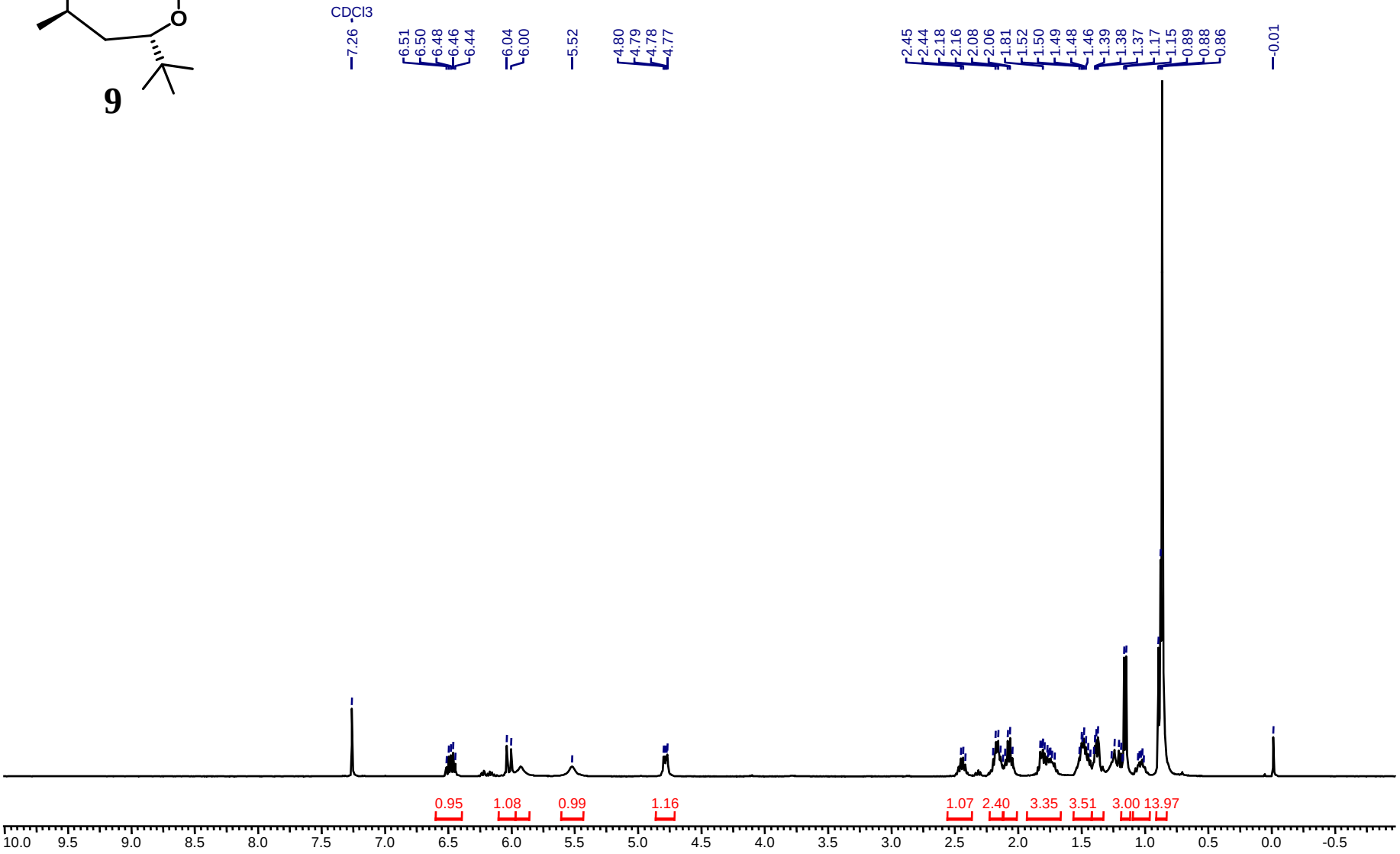

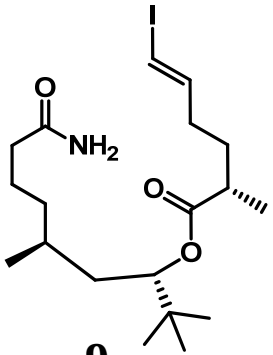

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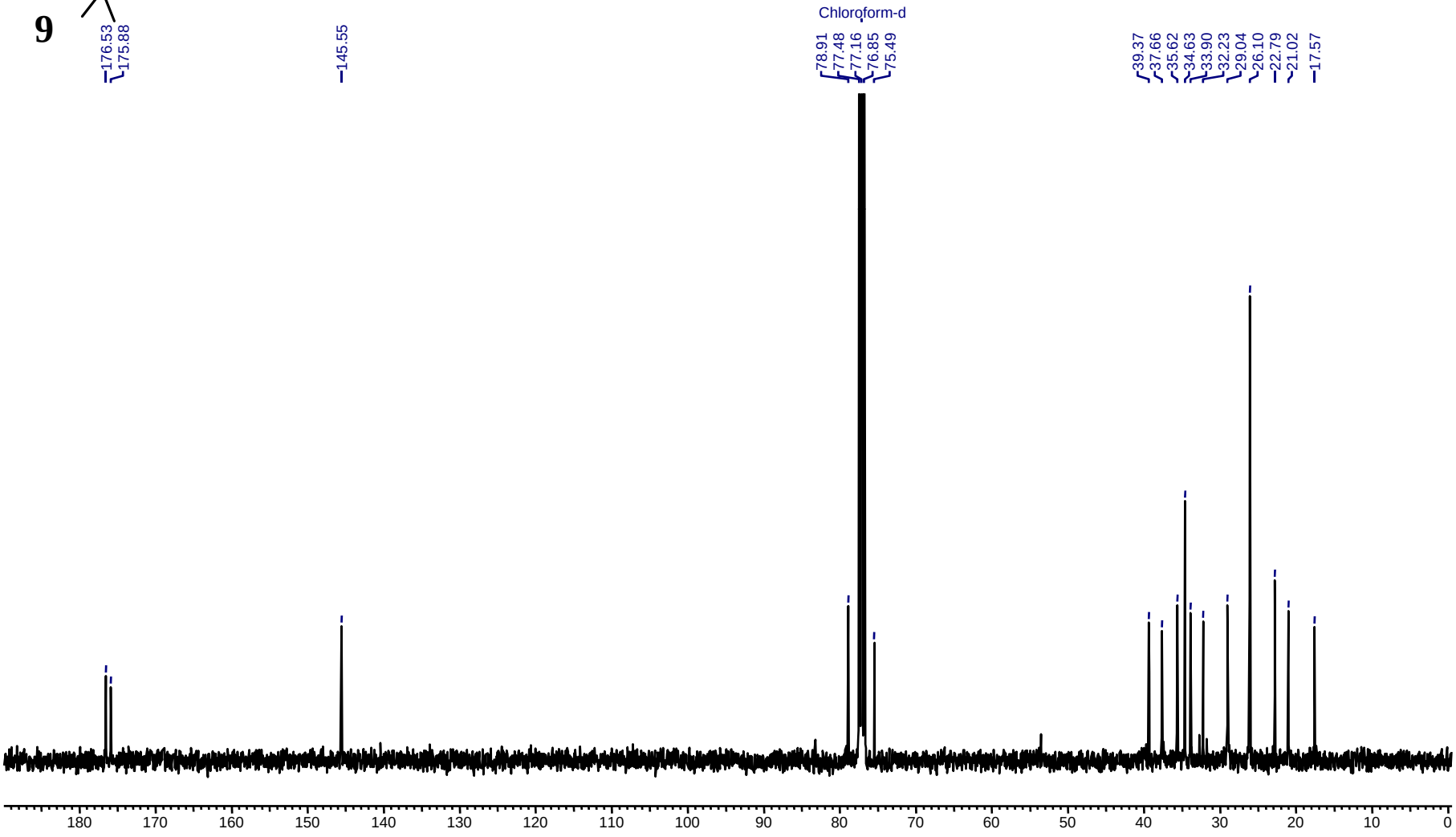

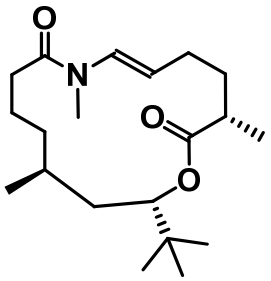

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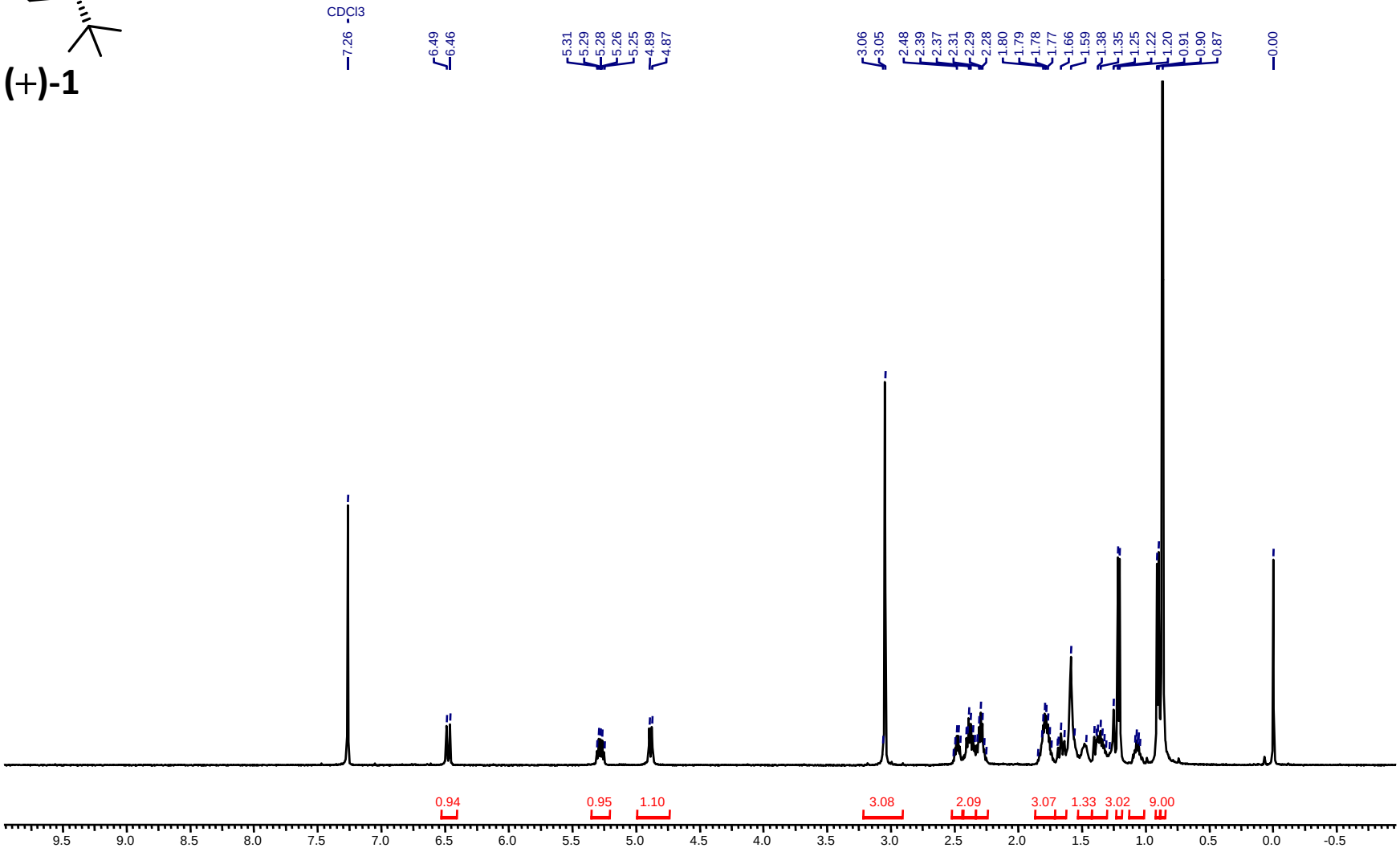

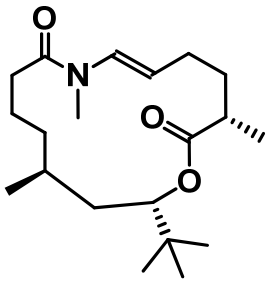

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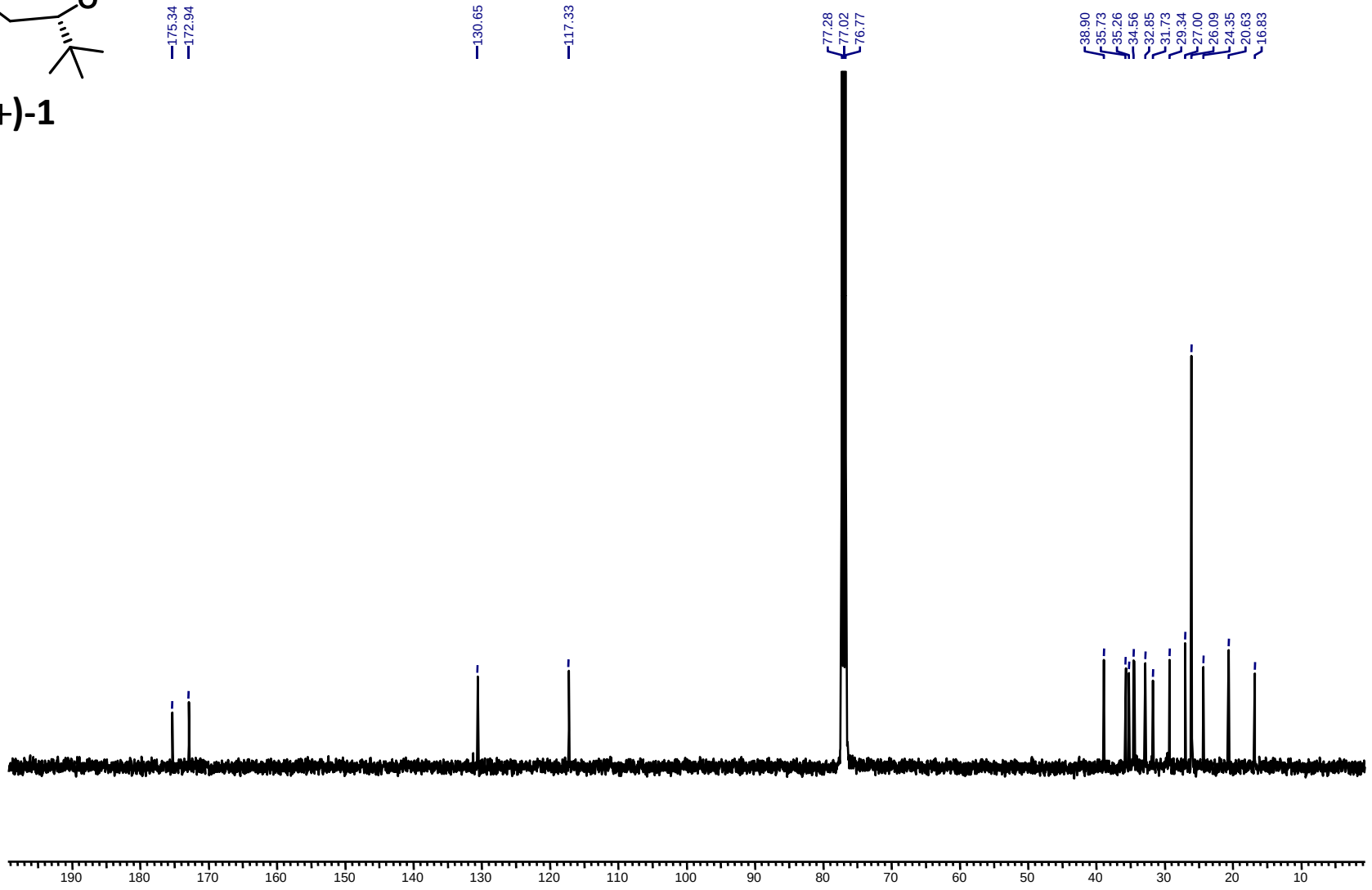

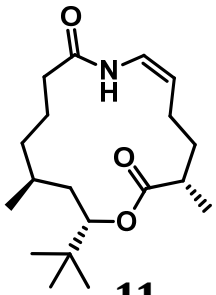

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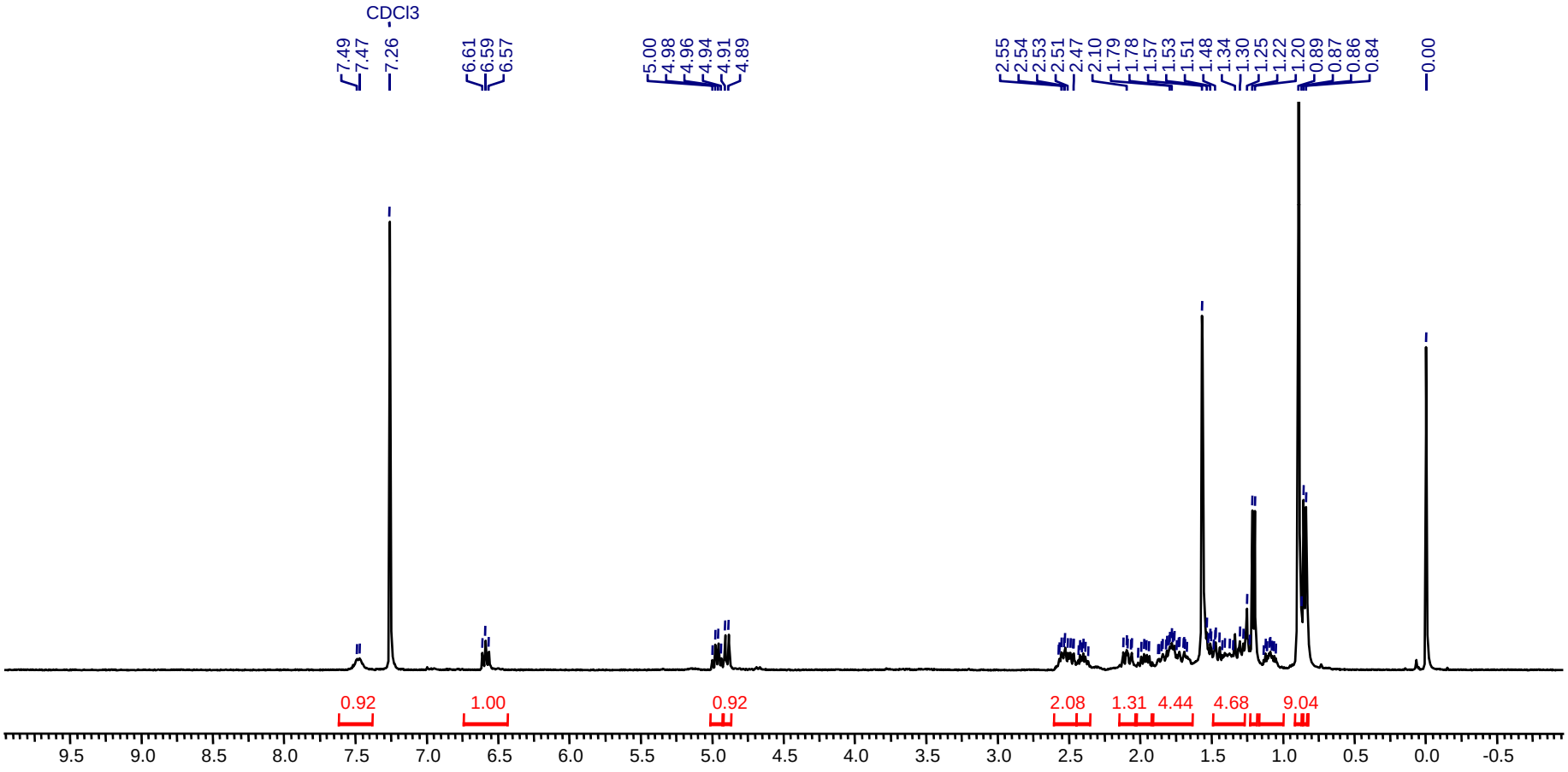

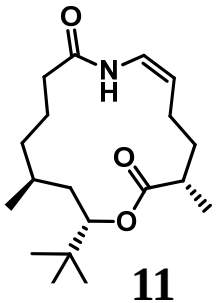

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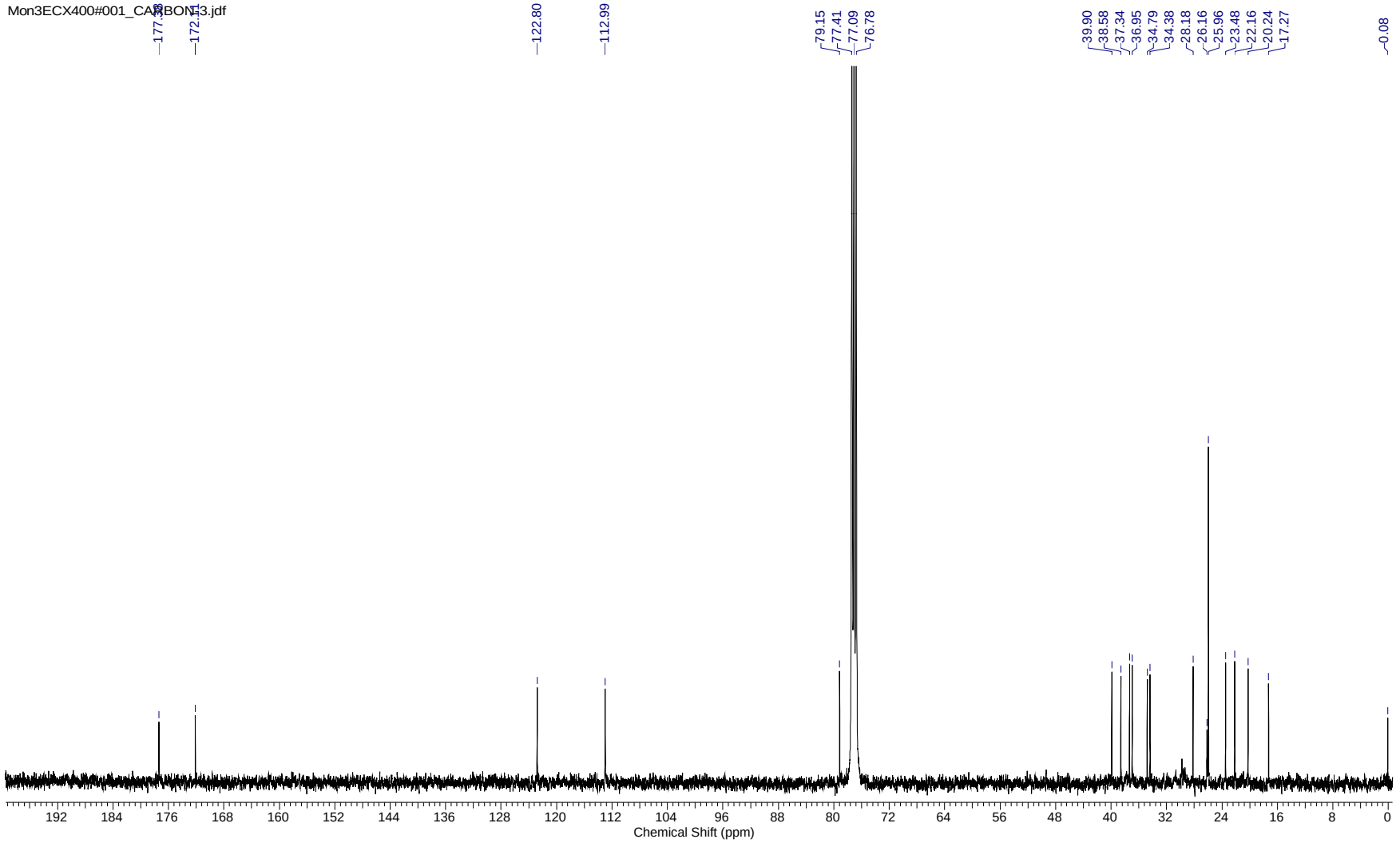

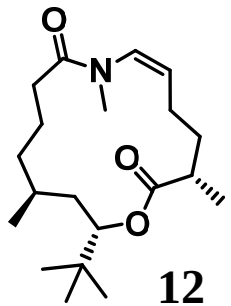

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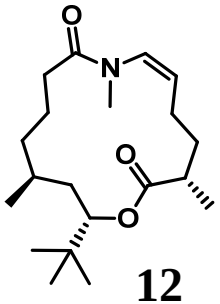

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