Asymmetric Total Synthesis and Absolute Stereochemistry of the Neuroactive Marine Macrolide Palmyrolide A

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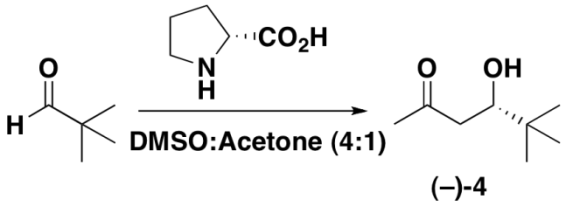
Supporting Information

Materials and Methods

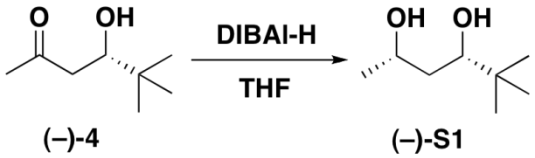
Unless otherwise noted, reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Reaction solvents (CH_2Cl_2, THF, and Et_2O) were purified before use in a Glass Contour Solvent Purification System under a flow of dry nitrogen. Dimethylsulfoxide (DMSO) and toluene were distilled from CaH_2. All other solvents and reagents were purchased from Sigma-Aldrich and used as received, unless otherwise specified. Thin-layer chromatography (TLC) was performed using plates precoated with silica gel 60 Å F-254 (250 μm) purchased from Silicycle and visualized by UV light, $KMnO_4$, or anisaldehyde stains, followed by heating. Silicycle SilicaFlash ® P60 silica gel (particle size 40-63 μm) was used for flash chromatography. ^1H and ^{13}C NMR spectra were recorded on a Varian Oxford 300 (operating at 300 MHz and 75 MHz respectively) or Varian Unity 400 (operating at 400 MHz and 100 MHz, respectively), and are reported relative to residual solvent peak (δ 7.26 and δ 77.0 for ^1H and ^{13}C in $CDCl_3$. Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Spectra obtained are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR spectra were recorded on a Perkin Elmer Spectrum One FTIR Spectrometer and samples were prepared by evaporation from $CHCl_3$ or CH_2Cl_2 on NaCl plates. High-resolution mass spectra were obtained using positive electrospray ionization on a Bruker 12 Tesla APEX –Qe FTICR-MS with and Apollo II ion source at the COSMIC Laboratory facility at Old Dominion University, VA.

Experimental Procedures and Compound Characterization Data:



(*S*)-4-hydroxy-5,5-dimethylhexan-2-one [(–)-**4**)]. Was prepared following the literature procedure of Cavelier and coworkers.[1] A screw-top flask was charged with pivaldehyde (5.89 mL, 54.3 mmol) and D-Proline (2.50 g, 21.7 mmol) dissolved in DMSO (183.0 mL) and reagent grade acetone (51.0 mL). The reaction flask was then sealed, and the mixture was allowed to stir for 5 days at room temperature before being quenching with a half-saturated NH_4Cl solution (100 mL). The reaction mixture was then extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated to afford crude aldol product (–)-**4**, which was purified by flash column chromatography (4:1 hexanes:EtOAc) to afford 5.28 g (68% yield) of a slightly yellow oil.

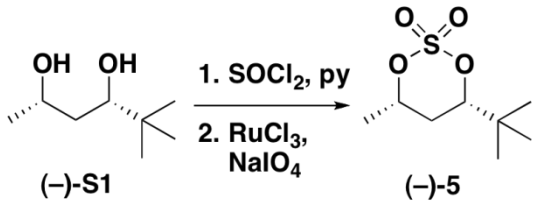
^{1}H, ^{13}C and optical rotation data was in agreement with literature values. See SI Footnote 1.



***syn*-Diol (–)-S1**. A solution of (–)-**4** (1.63 g, 11.3 mmol) in dry THF (220.0 mL) was cooled to –78 °C and treated with a solution of DIBAl-H (1.0 M in heptane, 28.36 mL, 28.4 mmol) slowly, allowing each drop to run down the side of the flask. The reaction mixture was allowed to stir at –78 °C for 3.5 h before being quenched by the addition of a 10% HCl aqueous solution (30 mL). After the cooling bath was removed, the contents of the flask were warmed to room temperature, and allowed to stir for an additional 3 h. The crude reaction mixture was then partitioned between ether (50 mL) and brine (50 mL), and the aqueous phase was re-extracted with additional ether washes. The combined organic phases were then dried over $MgSO_4$, filtered, and concentrated to afford crude diol as a 10:1 mixture of diastereomers, which were purified by flash column chromatography (9:1→8:2 hexanes:EtOAc) to afford 1.38 g (83% yield) of clean *syn*-diol (–)-**S1**.

^{1}H, ^{13}C and optical rotation data was in agreement with literature values. See SI Footnote 1.

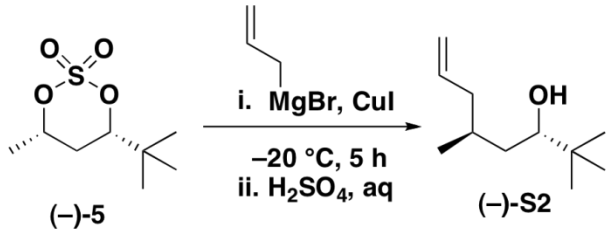
[1] Gilles, A.; Martinez, J.; Cavelier, F. *J. Org. Chem.* **2009**, *74*, 4298–4304



***syn*-Cyclic Sulfate (–)-5**. Was prepared following the literature procedure of Cavelier and coworkers.[1] A solution of diol (–)-**S1** (0.403 g, 2.76 mmol) in dry pyridine (12.5 mL) was cooled to 0 °C and treated with $SOCl_2$ (1.00 mL, 13.8 mmol). The reaction mixture was allowed to stir at 0 °C for 45 min before being quenched by the addition of water. The contents of the flask were then extracted with CH_2Cl_2, washed with a saturated aqueous $KHSO_4$ solution, followed by a saturated aqueous $NaHCO_3$ solution. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated to afford the crude sulfite which was taken on to the next step without further purification.

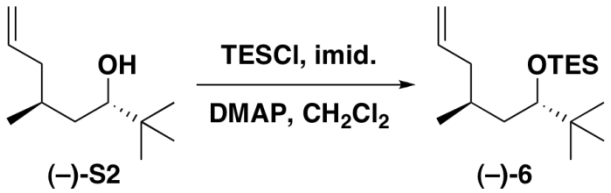
The crude sulfite was then dissolved a 2:1:1 mixture of water:MeCN:CCl_4 (22 mL : 22 mL : 11 mL), and treated with $RuCl_3$•xH_2O (0.030 g) and $NaIO_4$ (0.884 g, 4.14 mmol). The biphasic reaction mixture was then vigorously stirred at room temperature for 2 h before being diluted with Et_2O and extracted from a saturated aqueous $NaHCO_3$ solution. The crude sulfate was purified by flash column chromatography (8:2 hexanes:EtOAc) to afford 0.491 g (85% yield over two steps) of *syn*-Cyclic Sulfate (–)-**5** as a white solid.

^{1}H, ^{13}C and optical rotation data was in agreement with literature values. See SI Footnote 1.



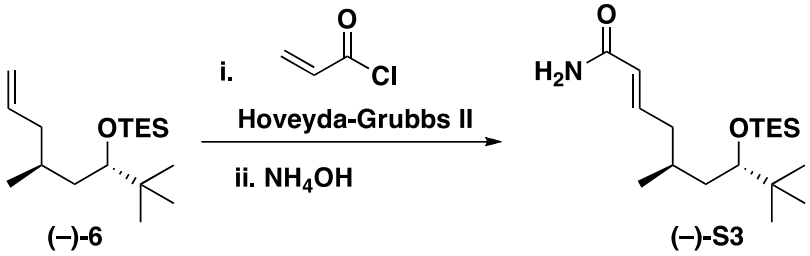
Alcohol (–)-S2. Was prepared following the literature procedure of Cavelier and coworkers.[1] To a flask containing a solution of cyclic sulfate (–)-**5** (0.057 g, 0.27 mmol) and CuI (0.063 g, 0.32 mmol) in dry THF (0.5 mL) at –25 °C was added allylmagnesium bromide (1.0 M in ether, 1.36 mL, 1.36 mmol). The purple-colored reaction mixture was allowed to stir at –25 °C for 5 h before being warmed to room temperature and then concentrated *in vacuo*. The solid residue was dissolved in ether (10 mL), and treated with a 20% aqueous H_2SO_4 solution (2 mL). The contents of the flask were then stirred vigorously for 12 h before the phases were separated and aqueous layer extracted with ether, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (8:2 hexanes:EtOAc) to afford 0.036 g (76% yield) of alcohol (–)-**S2**.

^{1}H, ^{13}C and optical rotation data was in agreement with literature values. See SI Footnote 1.

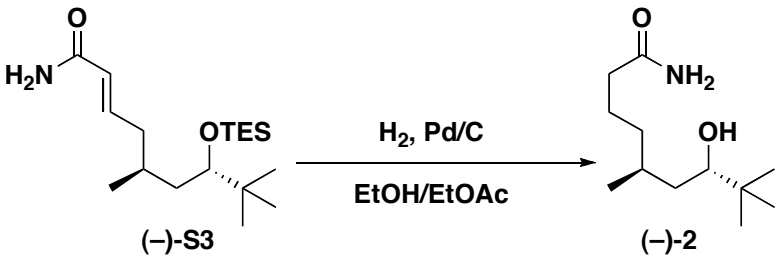


Silyl ether (–)-6. Alcohol (–)-**S2** (0.713 g, 4.18 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and treated with imidazole (1.14 g, 16.7 mmol), DMAP (0.051 g, 0.4 mmol), and triethylsilyl chloride (0.84 mL, 5.02 mmol). The reaction mixture was allowed to stir overnight at room temperature before being diluted with CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$ solution and brine. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (95:5 hexanes:EtOAc) to afford 1.16 g (98% yield) of silyl ether (–)-**6**.

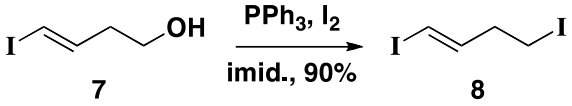
^{1}H, ^{13}C and optical rotation data was in agreement with literature values. See SI Footnote 1.



Amide (–)-S3. To a solution of silyl ether (–)-**6** (0.049 g, 0.17 mmol) in dry CH_2Cl_2 (1 mL) was added freshly distilled acryloyl chloride (0.021 mL, 0.25 mmol) followed by the Hoveyda-Grubbs II precatalyst (0.0054 g, 0.0086 mmol). The flask was flushed with nitrogen and the reaction mixture was allowed to stir overnight at room temperature. After the disappearance of starting material was noted by TLC, NH_4OH (1 mL) was added in a single portion. The contents of the flask were stirred vigorously for 1 h before the phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 → 2:1 EtOAc:hexanes) to afford 0.033 g (58% yield) of amide (–)-**S3**. $[\alpha]_D^{21.5}$ = – 118.94 (c = 1.12, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 300 MHz) 6.88-6.78 (m, 1H), 5.83 (d, *J* = 15 Hz, 1H), 3.33 (dd, *J* = 2.1, 8.1 Hz, 1H), 2.39-2.30 (m, 1H), 1.93-1.69 (m, 2H), 1.42-1.21 (m, 2H), 0.96 (t, *J* = 8.1 Hz, 9 H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.84 (s, 9H), 0.60 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 167.6, 144.9, 124.1, 78.6, 40.7, 38.4, 35.6, 29.5, 26.2, 21.0, 7.2, 5.8; IR (neat, thin film) ν 3348, 3183, 2956, 2913, 2876, 1674, 1646, 1617, 1414, 1107, 1086, 977, 737 cm^{-1}; HRMS *m/z* calc'd for $C_{18}H_{37}NO_2SiNa$ [M+Na]$^+$: 350.2486, found 350.2485.



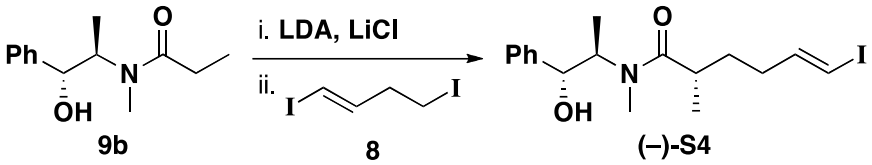
Amide (–)-2. A solution of amide (–)-**S3** (0.026 g, 0.074 mmol) was dissolved in a 1:1 mixture of EtOH:EtOAc (2 mL) and treated with Pd/C (0.025 g). The reaction mixture was then flushed with hydrogen gas and allowed to stir overnight under an atmosphere of hydrogen (using a balloon). After TLC showed the complete consumption of starting material, the reaction mixture was diluted with EtOAc and filtered through a short plug of celite, rinsing several times with fresh EtOAc. The filtrate was concentrated *in vacuo* and purified by flash column chromatography (100:1 EtOAc:Et_3N) to afford 0.014 g (89% yield) of amide (–)-**2**. $[\alpha]_D^{24.1}$= –54.88 (c = 1.01, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 5.64 (bs, 2H), 3.28 (dd, *J* = 2.0, 10.4 Hz, 1H), 2.22 (t, *J* = 7.2 Hz, 2H), 1.87-1.48 (m, 5H), 1.39-1.32 (m, 1H), 1.26-1.19 (m, 1H), 1.11-1.02 (m, 1H), 0.94 (d, *J* = 6.4 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 100 MHz) 175.7, 77.2, 39.0, 35.9, 34.9, 34.6, 29.4, 25.7, 22.8, 20.9; IR (neat, thin film) ν 3352, 3195, 2953, 2870, 1667, 1615, 1479, 1463, 1394, 1364, 1072 cm^{-1}; HRMS *m/z* calc'd for $C_{15}H_{25}NO_2Na$ $[M+Na]^+$: 238.1778, found 238.1776.



Diiodide 8. Triphenylphosphine (2.15 g, 8.21 mmol) and imidazole (0.559 g, 8.21 mmol) were dissolved in dry CH_2Cl_2 (25 mL) and cooled to 0 °C. To this, was added iodine crystals (2.08 g, 8.21 mmol), and the contents of the flask were allowed to stir at 0°C for 15 min before a solution of alcohol **7**[2] (1.55 g, 7.82 mmol) in dry CH_2Cl_2 (15 mL) was added via cannula. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 4 h. The mixture was concentrated *in vacuo* and redissolved in ether. The triphenylphosphine oxide which precipitated was filtered over celite and the filtrate washed several times with ether. The combined ether layers were again concentrated *in vacuo* and purified directly by flash column chromatography (100% hexanes) to afford 2.18 g (90% yield) of diiodide **8**. ^{1}H NMR (δ, ppm, $CDCl_3$, 300 MHz) 6.52-6.43 (m, 1H), 6.21 (d, *J* = 14.4, 1H), 3.15 (t, *J* = 6.0 Hz, 2H), 2.62 (q, *J* =

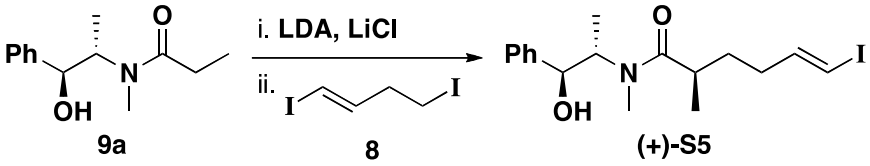
[2] Trend, R.M.; Ramtohul, Y.K.; Stoltz, B.M. *J. Am. Chem. Soc.* **2005**, *127*, 17778-17788.

6.9 Hz, 2H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 143.9, 78.0, 39.5, 2.9; IR (neat, thin film) ν 3045, 2956, 1602, 1419, 1246, 1199, 1167, 1117, 945; Due to volatility, we were not able to obtain an HRMS for diiodide **8**.

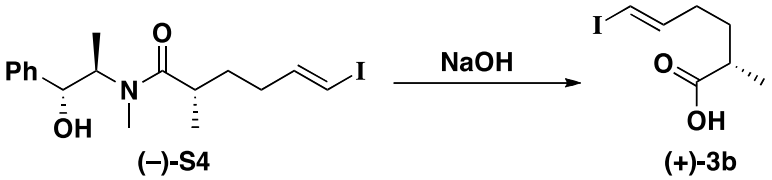


Vinyl iodide (–)-S4. Lithium chloride (1.23 g, 29.1 mmol) was placed in a round-bottom flask under vacuum and flame-dried before use. Once cooled, the flask was placed under an atmosphere of nitrogen and charged with diisopropylamide (1.53 mL, 10.9 mmol) and dry THF (5 mL). The contents of the flask were cooled to 0 °C and treated with *n*BuLi (2.5 M in hexanes, 4.37 mL, 10.9 mmol) dropwise. After 20 min, the LDA solution was cooled to –78 °C before a solution of amide **9b**[3] (1.07 g, 4.85 mmol) in dry THF (10 mL) was added dropwise via cannula. After 1 h at –78 °C, the flask was allowed to warm up to 0 °C for 15 min, and then room temperature for 5 min. The flask was then cooled back down to 0 °C, and a solution of diiodide **8** (2.18 g, 7.09 mmol) in dry THF (5 mL) was added slowly via cannula. The reaction mixture was allowed to stir at 0 °C for 30 min before being quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The phases were separated, and the aqueous phase extracted with CH_2Cl_2, followed by EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 EtOAc:hexanes) to afford 0.969 g [49.6% yield (77% borsm)] of vinyl amide (–)-**S4** as a pair of rotamers (~3:1 ratio). $[\alpha]_D^{23.8} = -35.05$ (c = 1.23, $CHCl_3$); ^{1}H NMR (mixture of rotamers, δ, ppm, $CDCl_3$, 400 MHz) 7.40-7.24 (m, 8H), 6.51 (minor, quintet, *J* = 6.8 Hz, 0.3H), 6.40 (major, quintet, *J* = 7.6 Hz, 1H), 6.02 (minor, d, *J* = 14.8 Hz, 0.3H), 5.8 (major, d, *J* = 14.4 Hz, 1H), 4.63-4.55 (m, 2H), 4.42 (bs, 1H), 4.07-4.00 (minor, m, 0.3H), 2.90 (minor, s, 1H), 2.84 (major, s, 3H), 2.67-2.53 (m, 1.4H), 2.07-1.85 (m, 3.3H), 1.80-1.72 (m, 1H), 1.45-1.33 (m, 1.5H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 4H), 1.01 (d, *J* = 6.8 Hz, 1.3H); ^{13}C NMR (mixture of rotamers, δ, ppm, $CDCl_3$, 100 MHz) 177.9, 176.9, 146.4, 145.8, 142.5, 141.4, 128.7, 128.3, 127.5, 126.9, 126.1, 76.1, 75.4, 75.0, 57.7, 35.5, 34.7, 33.7, 32.2, 27.1, 18.0, 17.4, 15.6, 14.3; IR (neat, thin film) ν 3377, 3061, 3029, 2968, 2933, 2873, 1616, 1453, 1409, 1374, 1108. 1082, 1050, 1027, 701 cm^{-1}; HRMS *m/z* calc'd for $C_{17}H_{24}INO_2Na$ $[M+Na]^+$: 424.0744, found 424.0738.

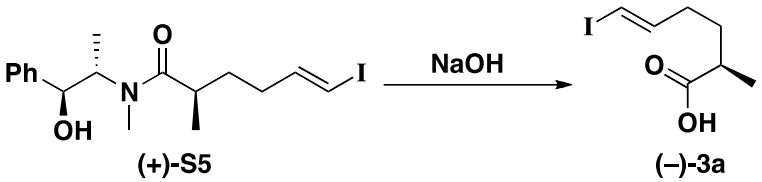
[3] Myers, A.G.; Yang, B.H.; Chen, H.; McKinstry, L.; Kopecky, D.J.; Gleason, J.L. *J. Am. Chem. Soc.* **1997**, *119*, 6496-6511.



Vinyl iodide (+)-S5. Was prepared in an analogous manner as vinyl iodide (–)-**S4**. $[\alpha]_D^{23.1}$= + 39.30 (c = 1.90, $CHCl_3$); ^{1}H NMR (mixture of rotamers, δ, ppm, $CDCl_3$, 400 MHz) 7.40-7.24 (m, 8H), 6.51 (minor, quintet, *J* = 6.8 Hz, 0.3H), 6.40 (major, quintet, *J* = 7.6 Hz, 1H), 6.02 (minor, d, *J* = 14.8 Hz, 0.3H), 5.8 (major, d, *J* = 14.4 Hz, 1H), 4.63-4.55 (m, 2H), 4.42 (bs, 1H), 4.07-4.00 (minor, m, 0.3H), 2.90 (minor, s, 1H), 2.84 (major, s, 3H), 2.67-2.53 (m, 1.4H), 2.07-1.85 (m, 3.3H), 1.80-1.72 (m, 1H), 1.45-1.33 (m, 1.5H), 1.14 (d, *J* = 6.8 Hz, 3H), 1.05 (d, *J* = 6.8 Hz, 4H), 1.01 (d, *J* = 6.8 Hz, 1.3H); ^{13}C NMR was identical to that obtained for (–)-**S4**; IR (neat, thin film) ν 3377, 3061, 3029, 2968, 2933, 2873, 1616, 1453, 1409, 1374, 1108. 1082, 1050, 1027, 701 cm^{-1}; HRMS *m/z* calc'd for $C_{17}H_{24}INO_2Na$ $[M+Na]^+$: 424.0744, found 424.0738.

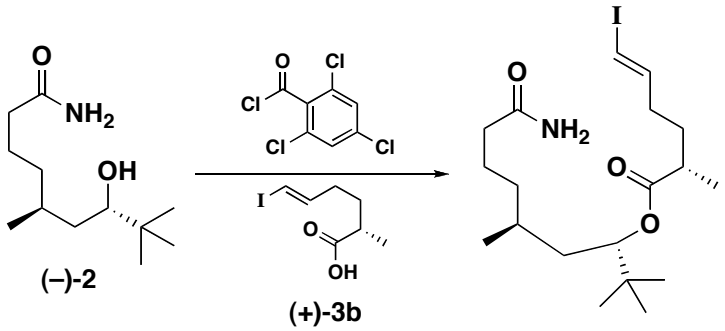


Vinyl iodide (+)-3b. A solution of vinyl amide (–)-**S4** (0.030 g, 0.074 mmol) in *t*BuOH (0.6 mL) and MeOH (0.6 mL) was treated with an aqueous NaOH solution (3.22 N, 1.2 mL). A condenser was attached, and the mixture was heated to 85 °C for 24 h. The flask was allowed to cool before the contents were concentrated *in vacuo*. The aqueous residue was diluted with water, and washed with CH_2Cl_2. The aqueous layer was acidified with concentrated HCl solution and again extracted with CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated to afford 0.012 g of vinyl iodide (+)-**3b** (65%) which would used directly in the next step without further purification. $[\alpha]_D^{25.1}$ = + 20.98 (c = 1.06, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 6.54-6.44 (m, 1H), 6.06 (td, *J* = 1.2, 14.4 Hz, 1H), 2.48 (sextet, *J* = 6.9 Hz, 1H), 2.12 (dq, *J* = 1.2, 7.5 Hz, 2H) 1.87-1.75 (m, 1H), 1.62-1.48 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (δ, ppm, $CDCl_3$, 100 MHz) 182.3, 145.2, 75.6, 38.4, 33.6, 31.9, 16.8; IR (neat, thin film) ν 3049, 2967, 2930, 1702 cm^{-1}; HRMS *m/z* calc'd for $C_7H_{11}IO_2Na$ $[M+Na]^+$: 276.9696, found 276.9699.



(+)-S5 (–)-3a

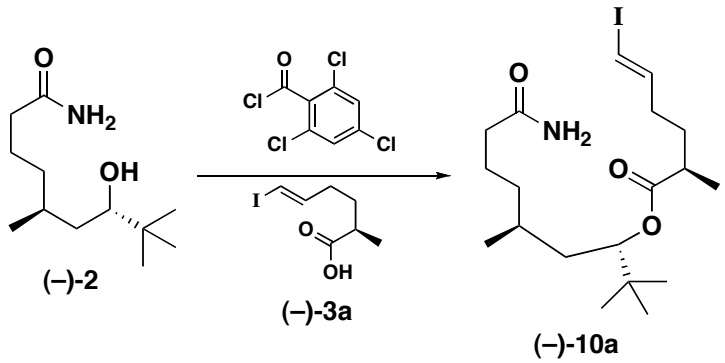
Vinyl iodide (–)-3a. Was prepared in an analogous manner as vinyl iodide (+)-**3b**. $[\alpha]_D^{21.9}$ = – 18.82 (c = 0.82, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 6.54-6.44 (m, 1H), 6.06 (td, *J* = 1.2, 14.4 Hz, 1H), 2.48 (sextet, *J* = 6.9 Hz, 1H), 2.12 (dq, *J* = 1.2, 7.5 Hz, 2H) 1.87-1.75 (m, 1H), 1.62-1.48 (m, 1H), 1.20 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR was identical to that obtained for (+)-**3b**; IR (neat, thin film) ν 3049, 2967, 2930, 1702 cm^{-1}; HRMS *m/z* calc'd for $C_7H_{11}IO_2Na$ $[M+Na]^+$: 276.9696, found 276.9694.



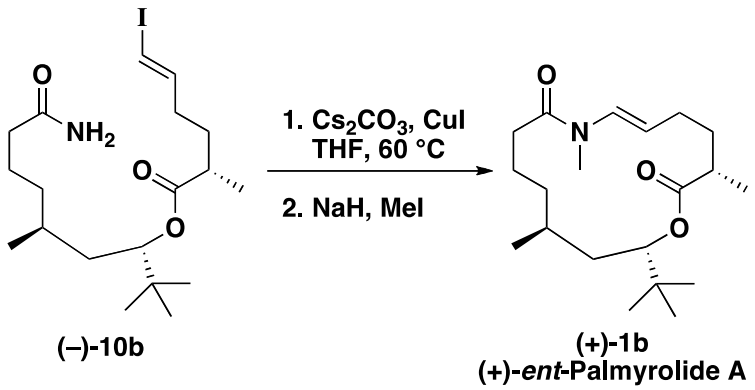
(–)-2 (+)-3b (–)-10b

Amide (–)-10b. A solution of vinyl iodide (+)-**3b** (0.058 g, 0.23 mmol) in dry THF (1.3 mL) was treated with freshly distilled DIPEA (64.1 μL, 0.36 mmol) followed by 2,4,6-trichlorobenzoyl chloride (43.1 μL, 0.27 mmol). The mixture was stirred at room temperature for 3 h, and the resulting mixed anhydride was then concentrated *in vacuo*. The residue was dissolved in dry toluene (3.6 mL) and was added, via cannula, to a separate flask containing amide (–)-**2** (0.028 g, 0.13 mmol) and DMAP (0.028 g, 0.23 mmol). The reaction mixture was allowed to stir at room temperature for 18 h before CH_2Cl_2 (20 mL) was added, and the mixture washed with a saturated aqueous solution of $NaHCO_3$ (20 mL). The phases were separated, and the aqueous layer extracted with additional CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 EtOAc:hexanes) to afford 0.098 g (74 % yield) of amide (–)-**10b**. $[\alpha]_D^{23.2}$ = – 20.50 (c = 1.01, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 6.52-6.44 (m, 1H), 6.02 (d on top of a bs, *J* = 14.4 Hz, 3H), 4.78 (dd, *J* = 3.6, 8.4 Hz, 1H), 2.49-2.42 (m, 1H), 2.23-2.05 (m, 4H), 1.85-1.71 (m, 2H), 1.55-1.43 (m, 3H), 1.41-1.37 (m 1H), 1.31-1.20 (m, 1H), 1.16 (d, *J* = 6.8 Hz, 3H), 1.10-0.99

(m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 100 MHz) 176.3 (2C), 145.4, 78.8, 75.3, 39.2, 37.5, 34.6, 34.5, 33.7, 33.6, 32.1, 28.9, 25.9, 22.6, 20.8, 17.4; IR (neat, thin film) ν 3423, 3350, 3200, 2964, 2872, 1724, 1667, 1607, 1462, 1397, 1379, 1366, 1222, 1186, 1123, 1065, 957 cm^{-1}; HRMS *m/z* calc'd for $C_{19}H_{34}INO_3Na$ $[M+Na]^+$: 474.1476, found 474.1463.

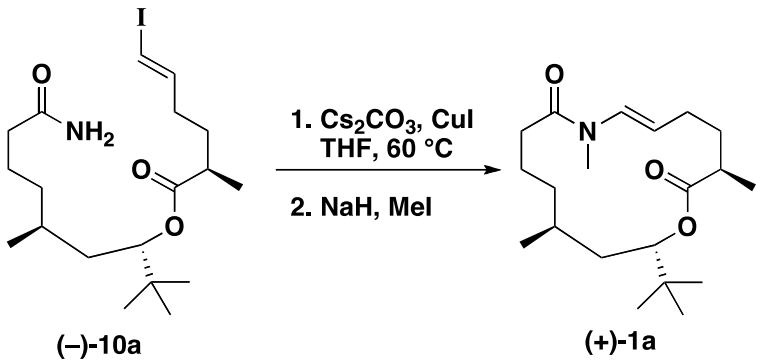


Amide (–)-10a. Was prepared in an analogous manner as amide (–)-**10b**. $[\alpha]_D^{21.4}$ = – 42.06 (c = 1.075, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 300 MHz) 6.49 (dt, J = 7.2, 14.4 Hz, 1H), 6.02 (d, J = 14.4 Hz, 1H), 5.88 (bs, 1H), 5.46 (bs, 1H), 4.79 (dd, J = 4.5, 6.3 Hz, 1H), 2.45 (sextet, J = 6.9 Hz, 1H), 2.23-2.15 (m, 2H), 2.12-2.05 (m, 2H), 1.86-1.69 (m, 2H), 1.61-1.25 (m, 6H), 1.17 (d, J = 7.2 Hz, 3H), 1.11-0.99 (m, 1H), 0.91-0.87 (doublet / singlet overlapping, 12H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 176.5, 175.8, 145.6, 79.0, 75.5, 39.3, 37.7, 35.7, 34.79, 34.77, 33.9, 32.3, 29.2, 26.1, 22.8, 21.1, 17.5; IR (neat, thin film) ν 3429, 3351, 3203, 2962, 2934, 2868, 1725, 1665, 1607, 1461, 1380, 1366, 1259, 1181, 1119, 1067, 957, 935 cm^{-1}; HRMS *m/z* calc'd for $C_{19}H_{34}INO_3Na$ $[M+Na]^+$: 474.1476, found 474.1471.

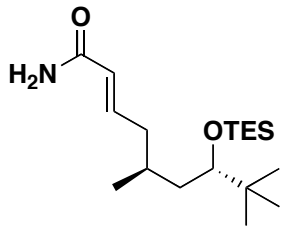


(+)-*ent*-Palmyrolide A (1b). A mixture of amide (–)-**10b** (0.042 g, 0.093 mmol), copper iodide (0.003 g, 0.013 mmol) and cesium carbonate (0.050 g, 3.07 mmol) was suspended in dry THF (9.3 mL). *N*,*N*'-Dimethylethylenediamine (25 μL, 2.32 mmol) was added, and the reaction flask was degassed by bubbling dry nitrogen gas for 10 min. The septum was quickly removed, and replaced with a glass stopper. The contents of the flask were then heated at 60 °C overnight. The flask was allowed to cool to room temperature before being diluted with EtOAc 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 (7:3 hexanes:EtOAc) to afford 0.013 g [45 % yield (71 % borsm)] of enamide **S6** which was used in the next step without extensive characterization.

Enamide **S6** (0.013 g, 0.042 mmol) was dissolved in dry THF (0.5 mL), cooled to 0 °C and treated with sodium hydride (60% dispersion, 0.008 g, 0.2 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 20 min, the reaction mixture was diluted with EtOAc and quenched with water. The phases were separated, and the aqueous phase extracted with additional EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (8:2 hexanes:EtOAc) to afford 0.013 g (89 % yield) of (+)-*ent*-Palmyrolide A **(1b)**. $[\alpha]_D^{22.9}$ = + 23.44 (c = 0.65, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 6.47 (d, *J* = 14 Hz, 1H), 5.27 (dt, *J* = 7.2, 14 Hz, 1H), 4.88 (dd, *J* = 2.0, 10.8 Hz, 1H), 3.04 (s, 3H), 2.52-2.43 (m, 1H), 2.42-2.34 (m, 2H), 2.33-2.24 (m, 2H), 1.86-1.71 (m, 3H), 1.70-1.45 (m, 3H), 1.41-1.31 (m, 2H), 1.21 (d, *J* = 7.2 Hz, 3H), 1.11-1.02 (m, 1H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 100 MHz) 175.3, 172.9, 130.7, 117.3, 38.9, 35.8, 35.2, 34.5, 32.8, 31.7, 29.3, 27.0, 26.1, 24.3, 20.6, 16.8 (**Note**: At 100 MHz, we did not observe the C(7) CH signal at δ 76.9 ppm. At this frequency, the peak is buried under the $CDCl_3$ peak. Pleasingly, the peak is visible in the HMQC spectra, a scan of which has been included); IR (neat, thin film) ν 2963, 2873, 1725, 1676, 1649, 1465, 1366, 1250, 1180, 1127, 1072, 936 cm^{-1}; HRMS *m*/*z* calc'd for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$: 360.2509, found 360.2503.



Macrolide (+)-1a. Was prepared in an analogous manner as (+)-*ent*-Palmyrolide A (**1b**). $[\alpha]_D^{21.4}$ = + 2.67 (c = 0.39, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 6.63 (d, *J* = 13.6 Hz, 1H), 4.92 (ddd, *J* = 5.2, 8.8, 13.6 Hz, 1H), 4.85 (dd, *J* = 2.0, 9.6, 1H), 3.05 (s, 3H), 2.60-2.42 (m, 3H), 2.32 (dt, *J* = 7.2, 13.6 Hz, 1H), 2.24-2.17 (m, 1H), 2.03-1.95 (m, 1H), 1.84-1.74 (m, 1H), 1.68-1.54 (m, 2H), 1.49-1.30 (m, 4H), 1.26 (d, *J* = 7.2 Hz, 3H), 1.03-0.93 (m, 1H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 100 MHz) 175.4, 172.8, 129.8, 110.2, 76.5, 37.2, 36.6, 35.4, 34.3, 33.6, 31.0, 29.8, 29.5, 27.3, 25.9, 24.9, 20.0, 19.2; IR (neat, thin film) ν 2959, 2927, 2873, 1728, 1675, 1646, 1466, 1413, 1384, 1366, 1333, 1298, 1240, 1205, 1193, 1171, 1121, 933 cm^{-1}; HRMS *m/z* calc'd for $C_{20}H_{35}NO_3Na$ $[M+Na]^+$: 360.2509, found 360.2503.



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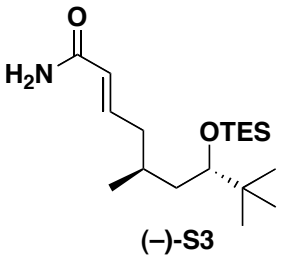
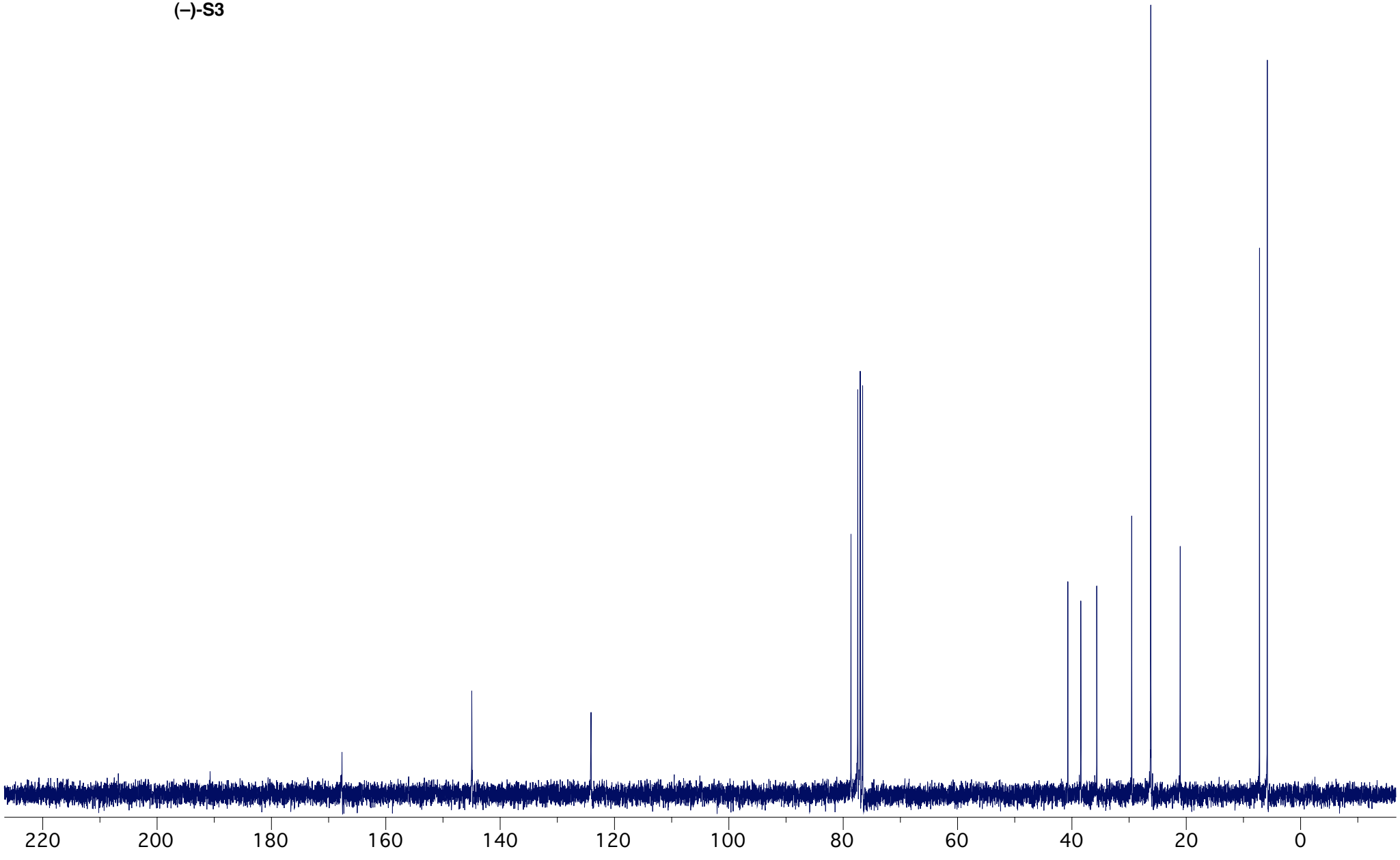
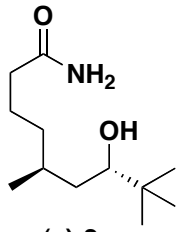
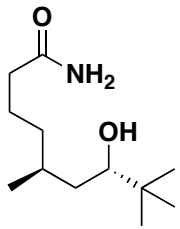


(–)-S3

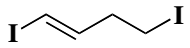




(–)-2



(–)-2



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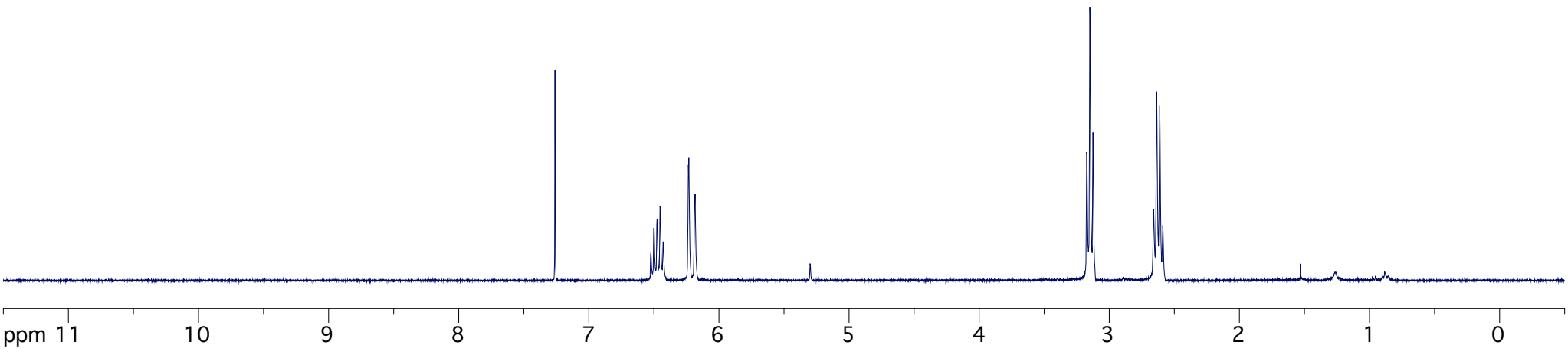

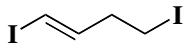

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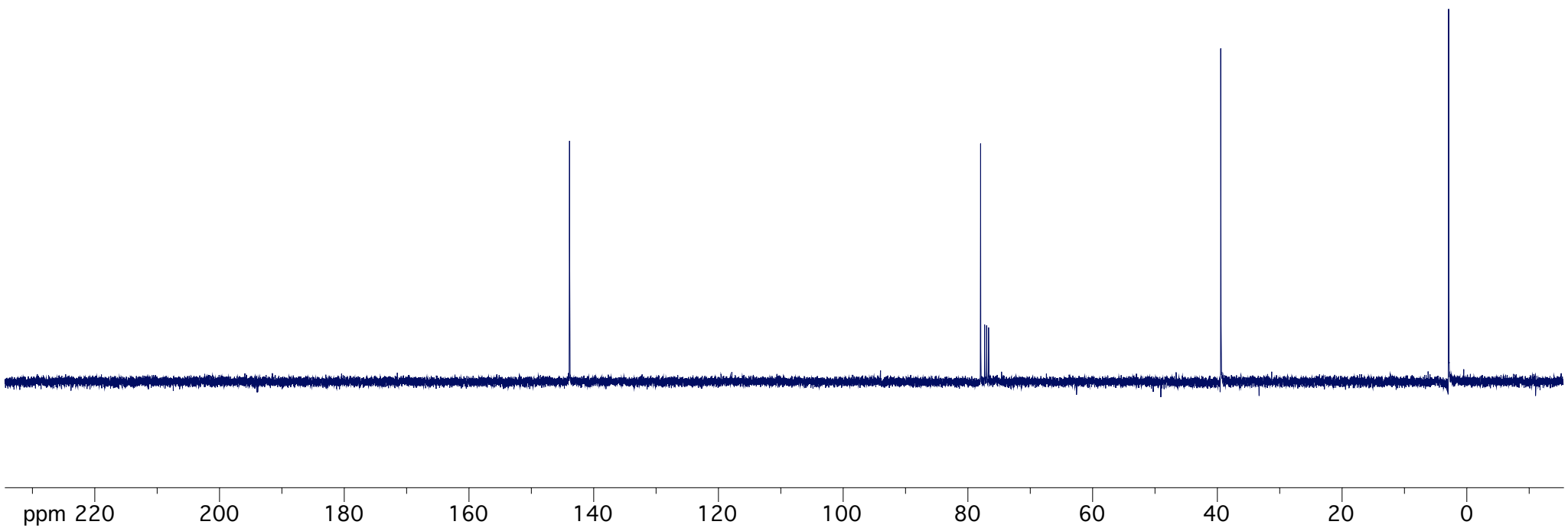

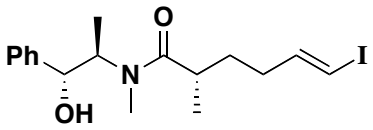

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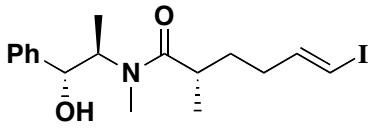
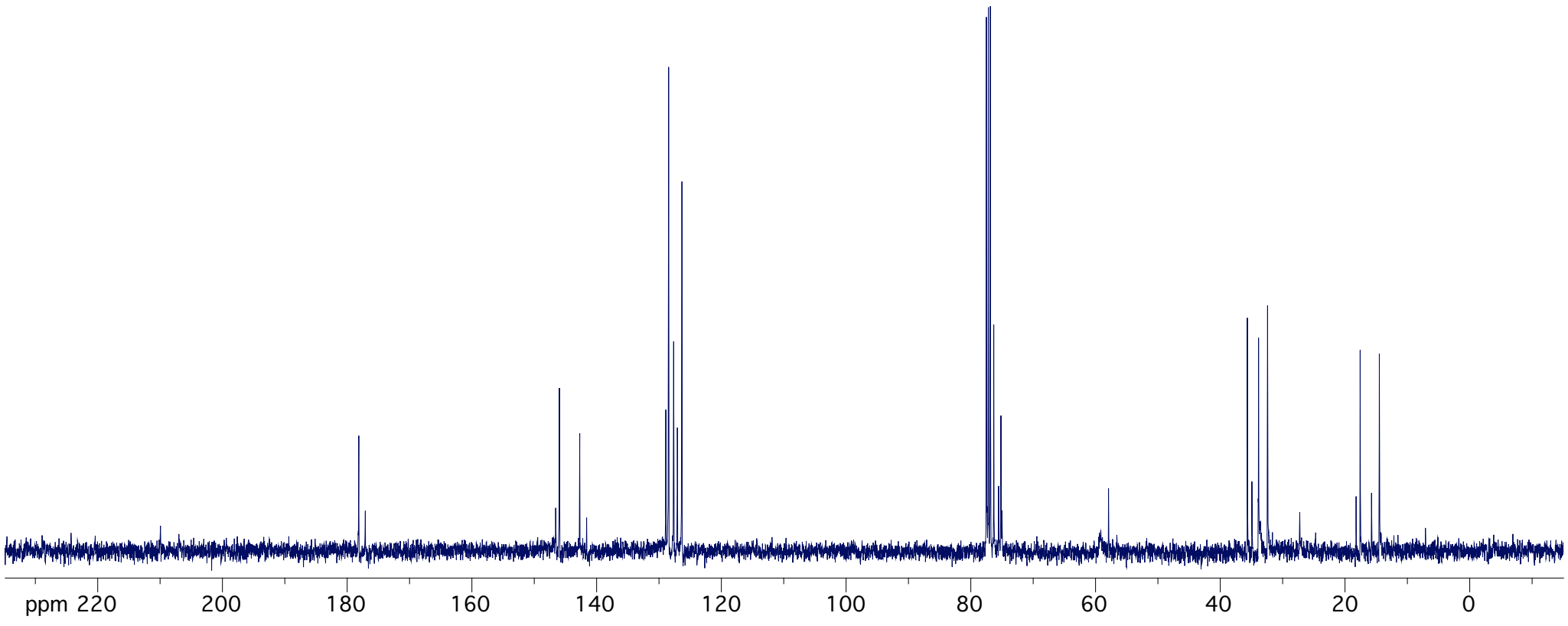
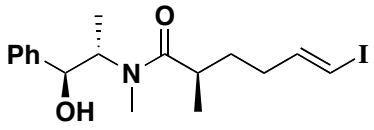
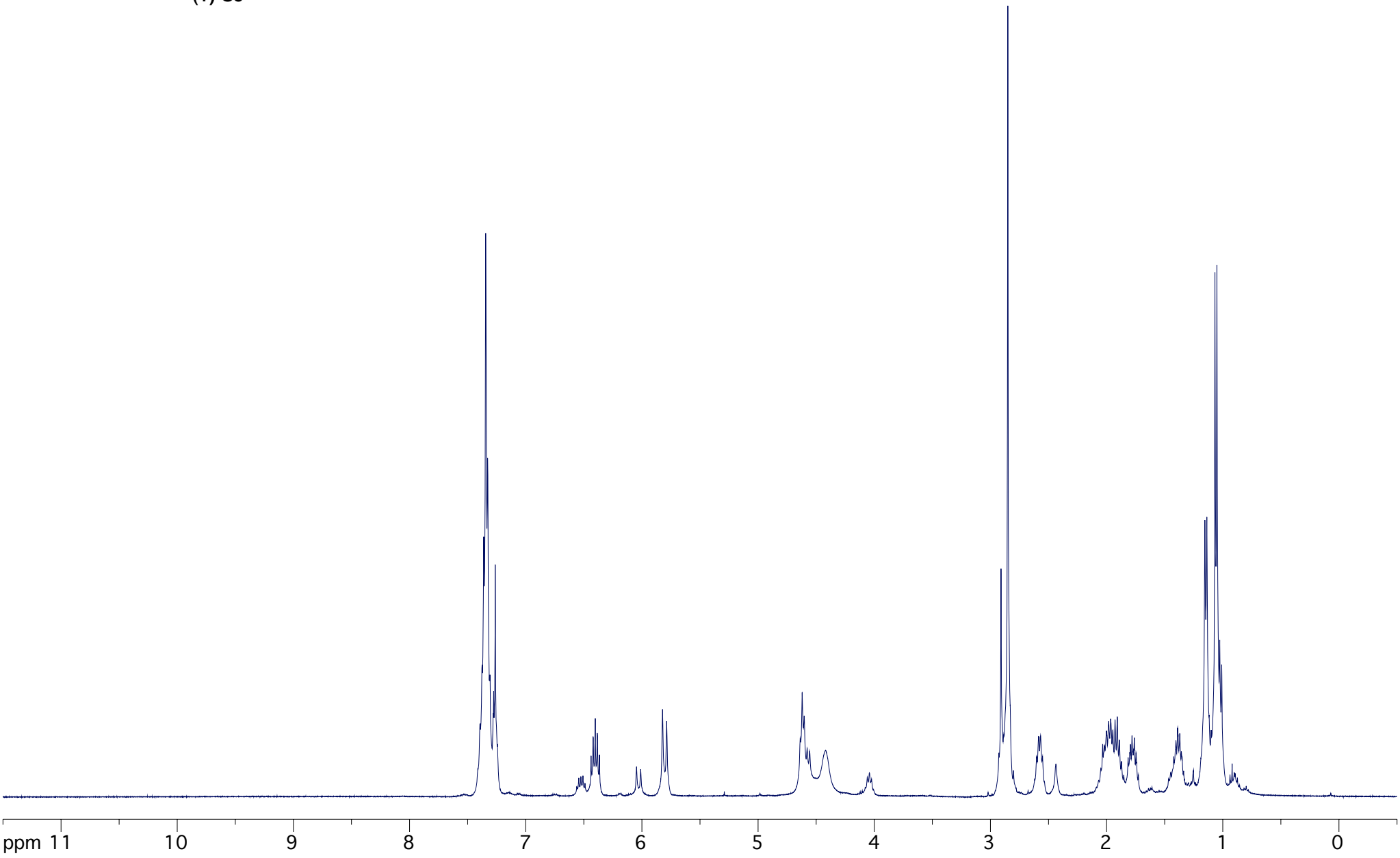


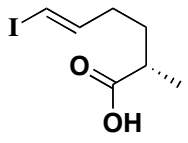
(–)-S4



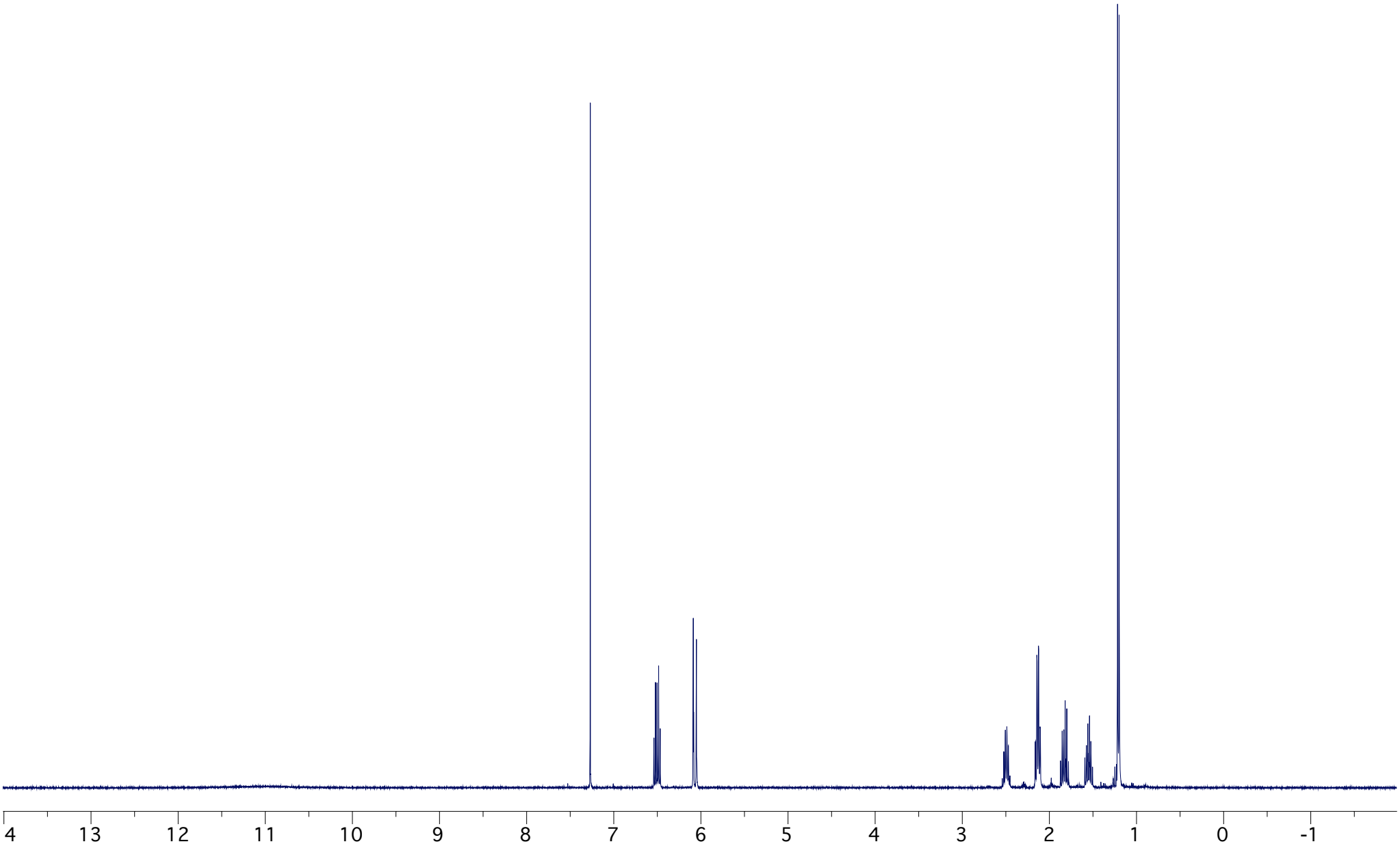


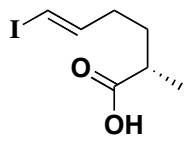
(+)-S5



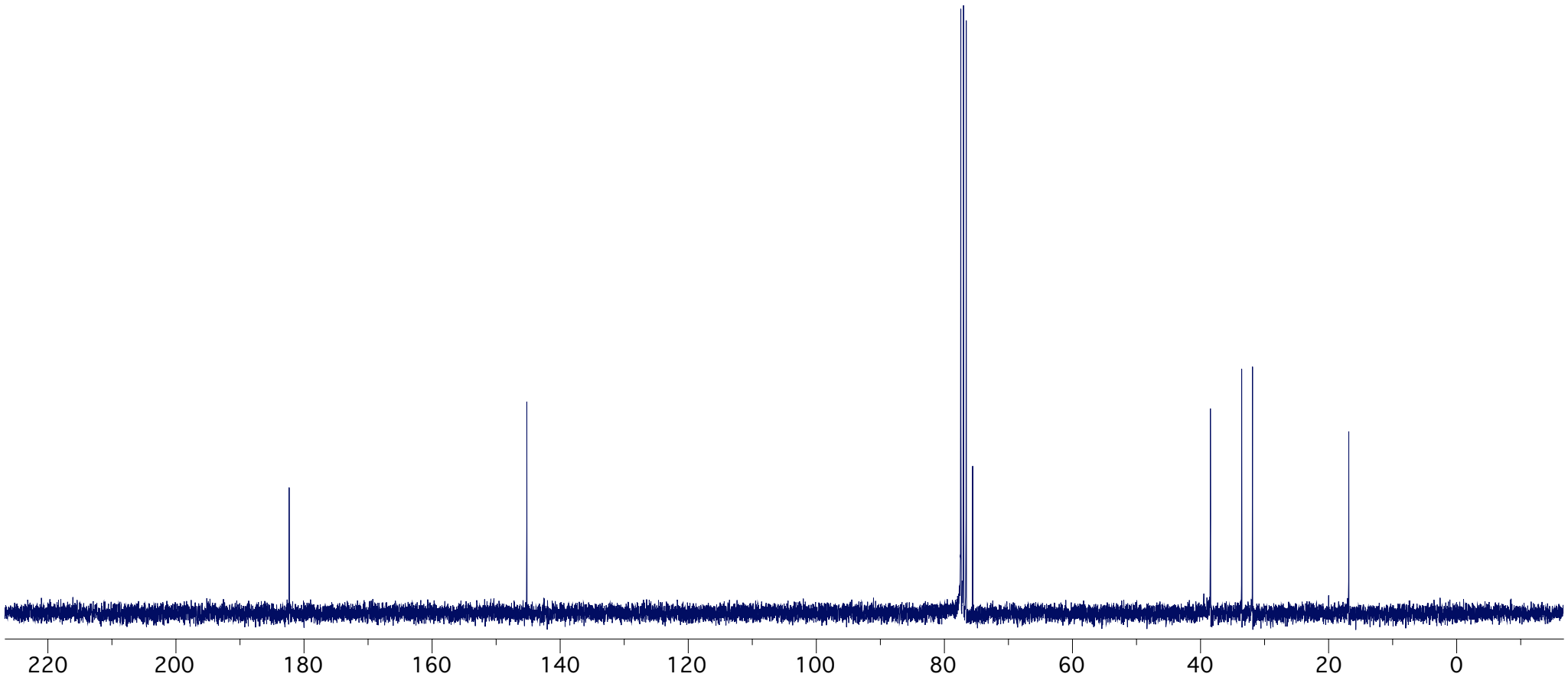


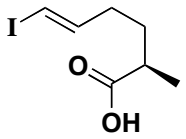
(+)-3b





(+)-3b





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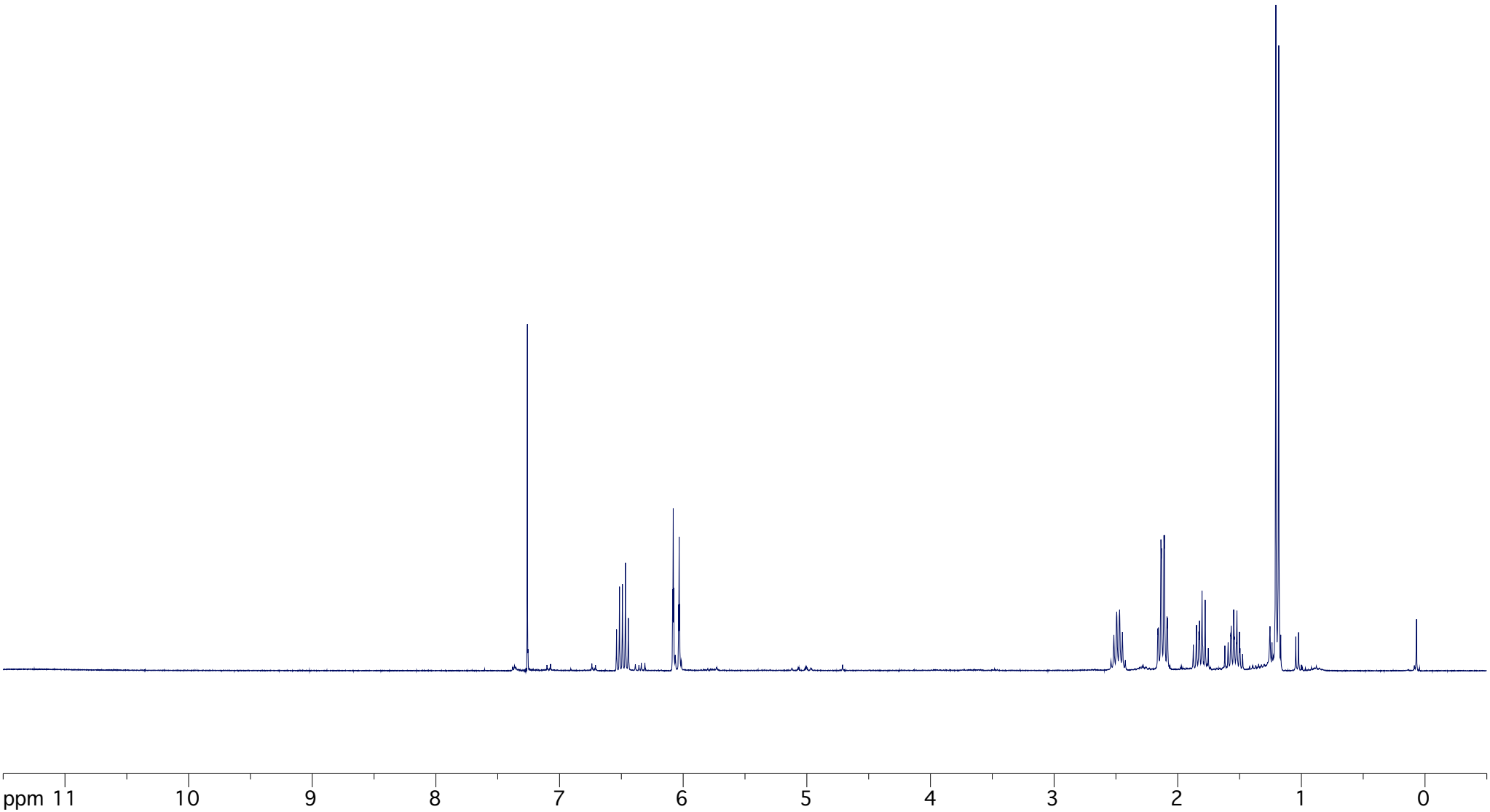
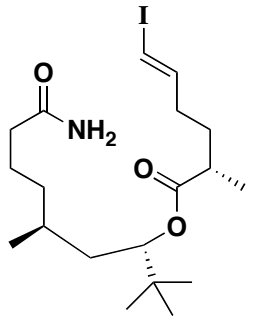
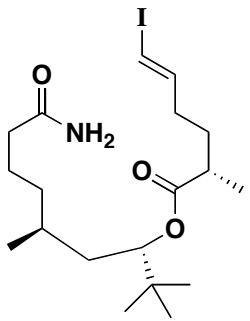
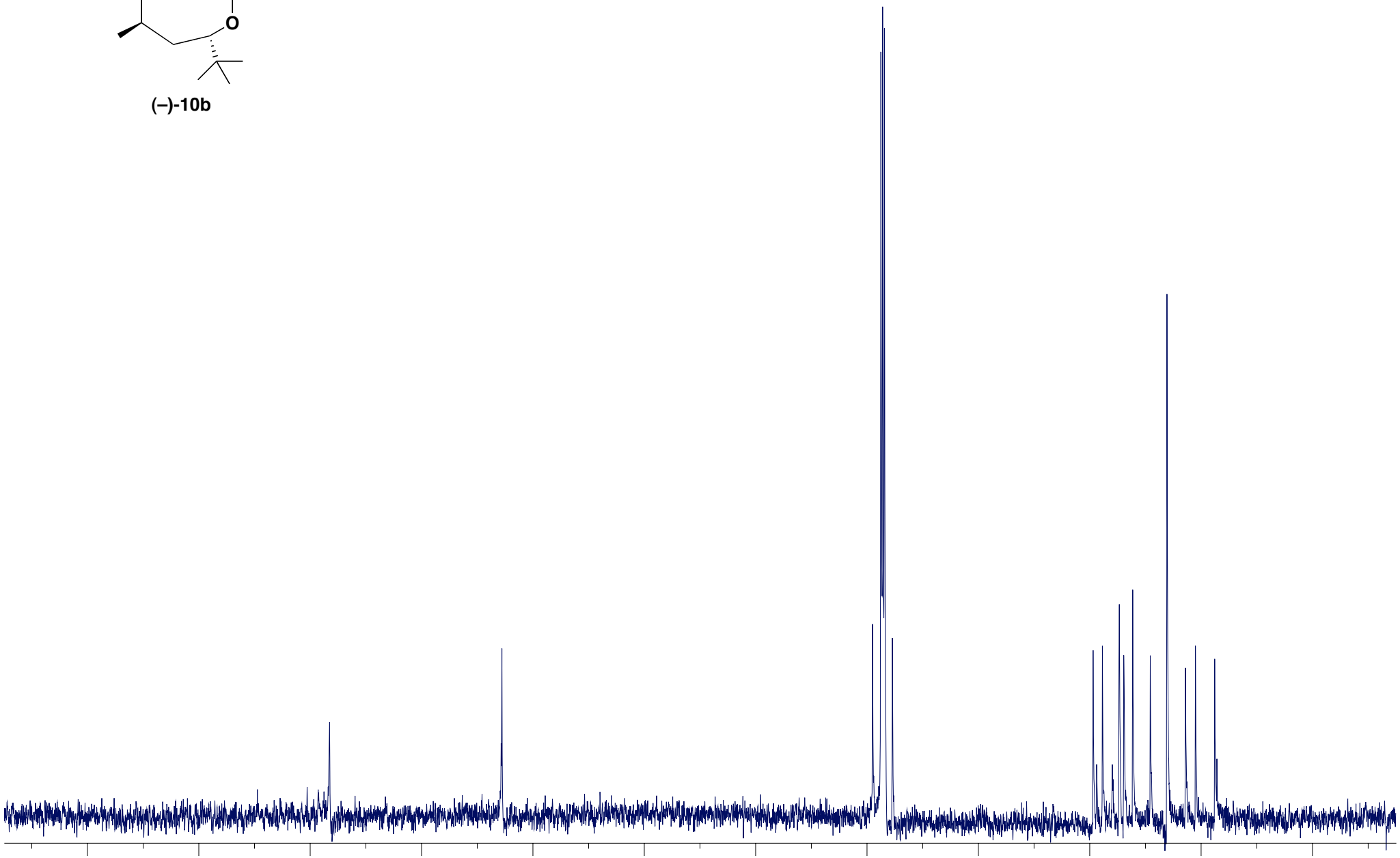


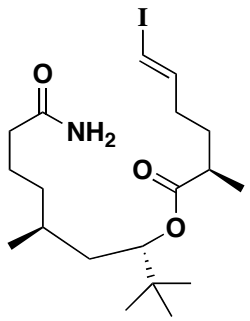


(–)-10b



(–)-10b





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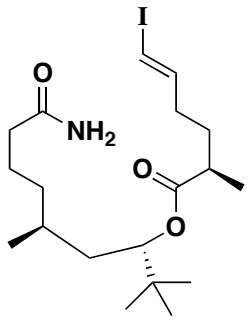

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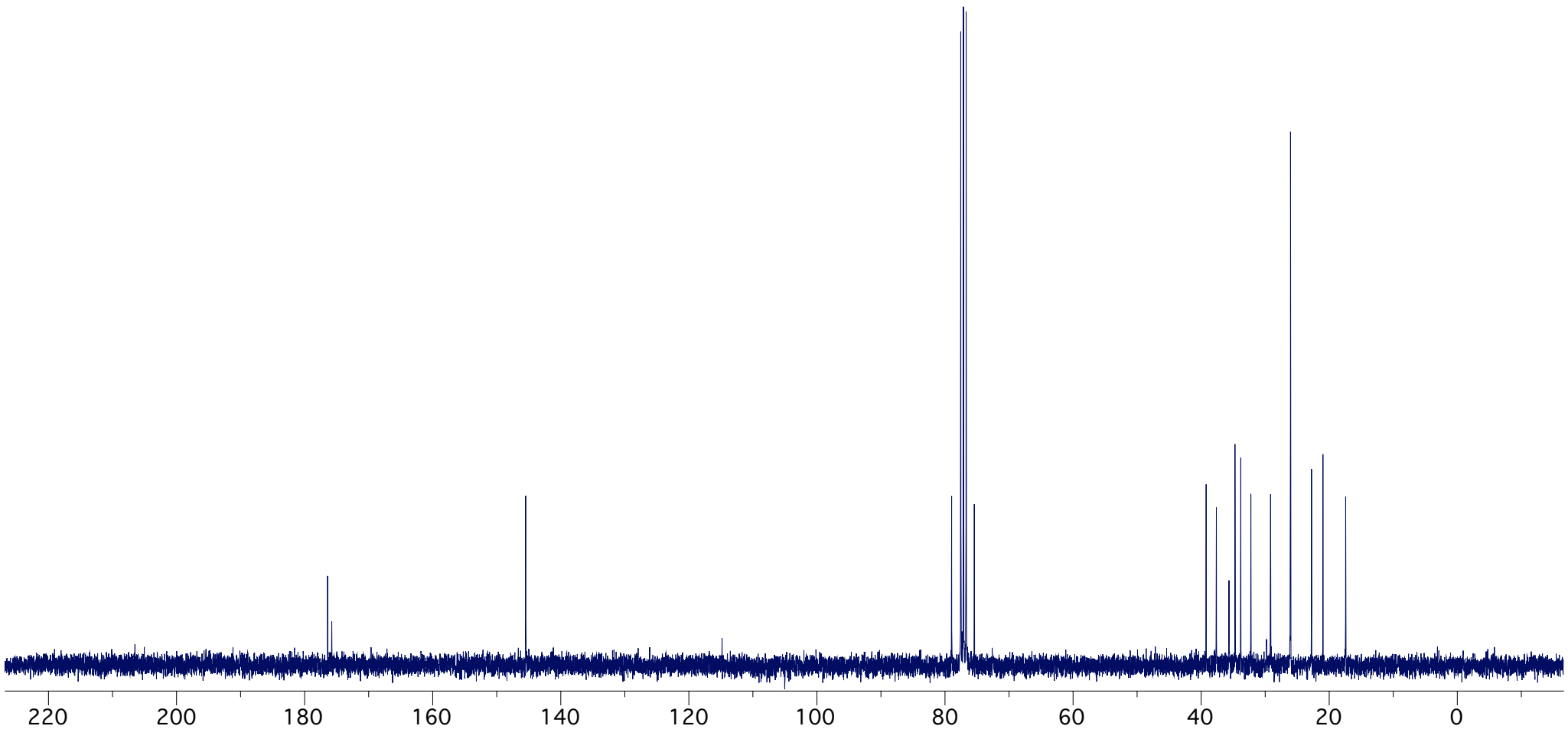
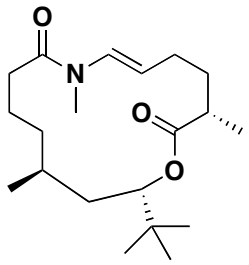
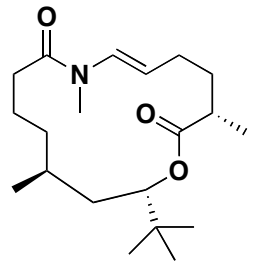
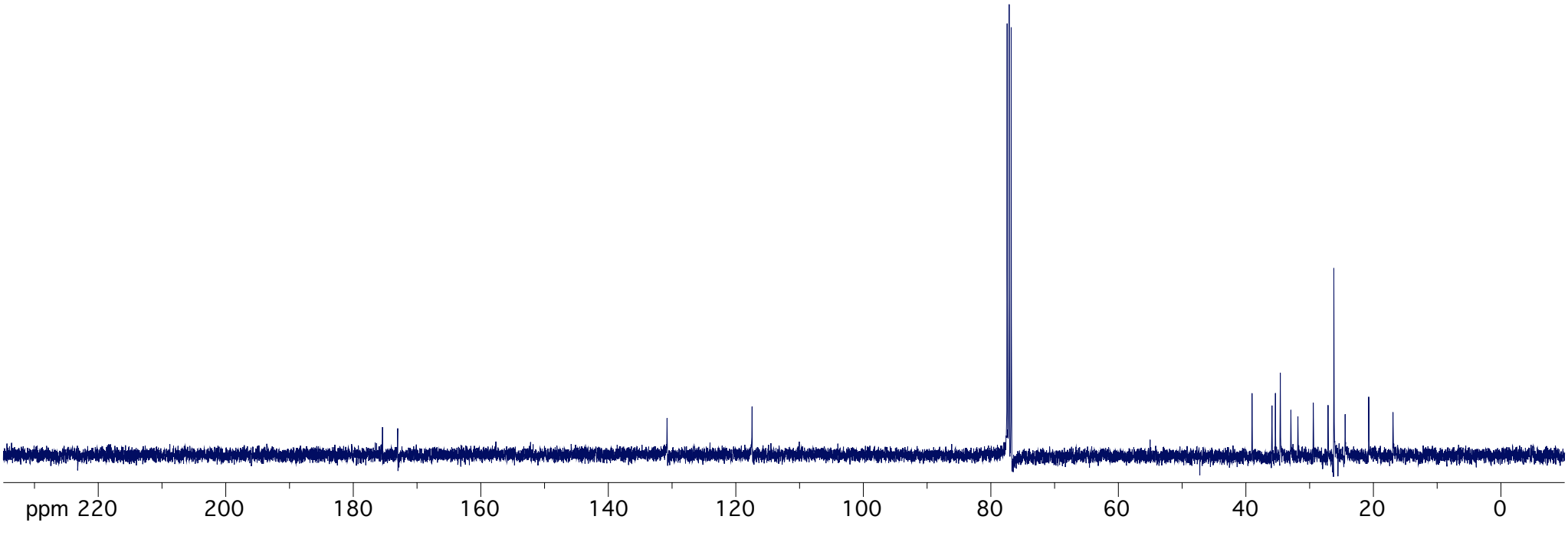


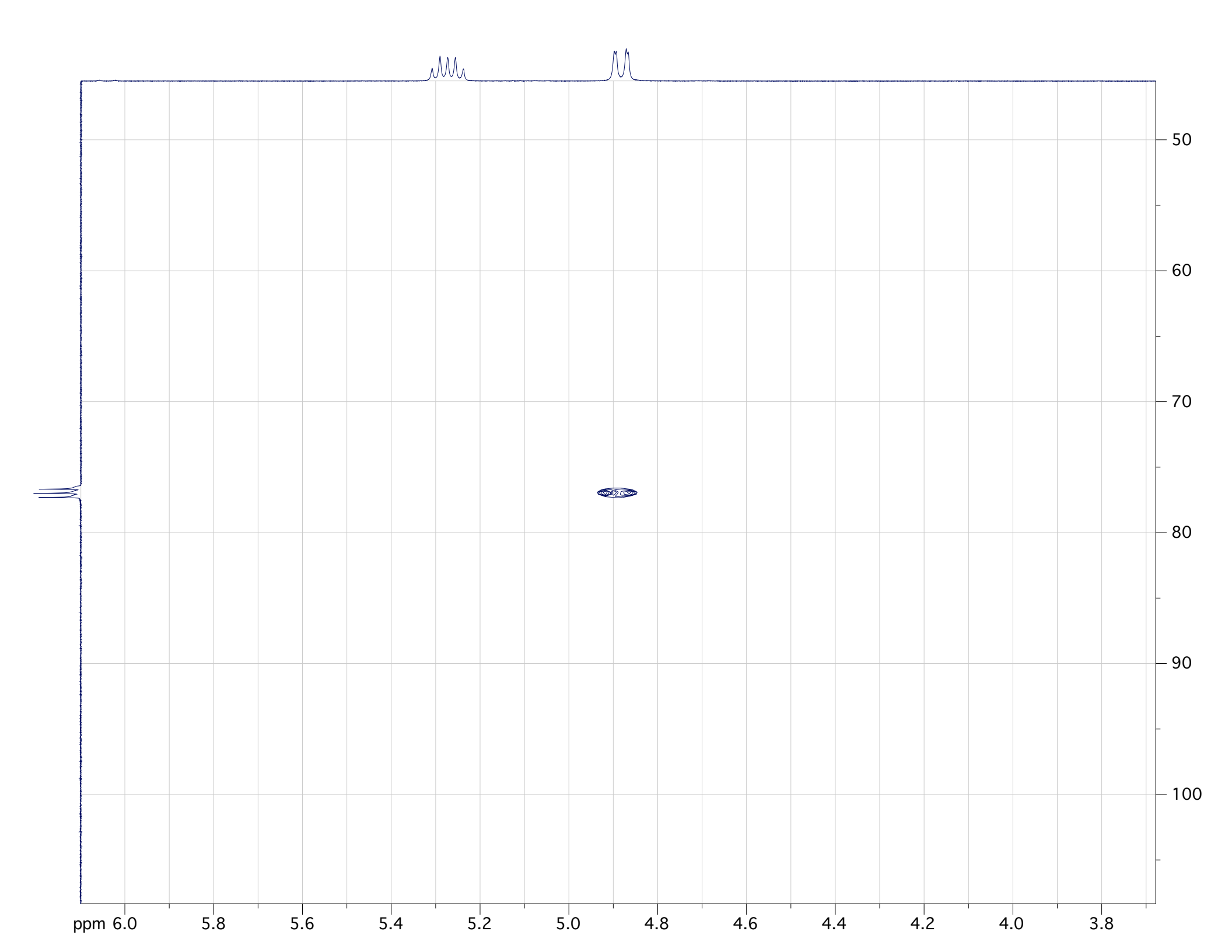


(+)-1b
(+)-*ent*-Palmyrolide A



(+)-1b
(+)-*ent*-Palmyrolide A

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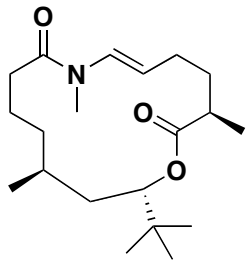
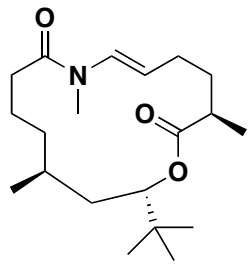
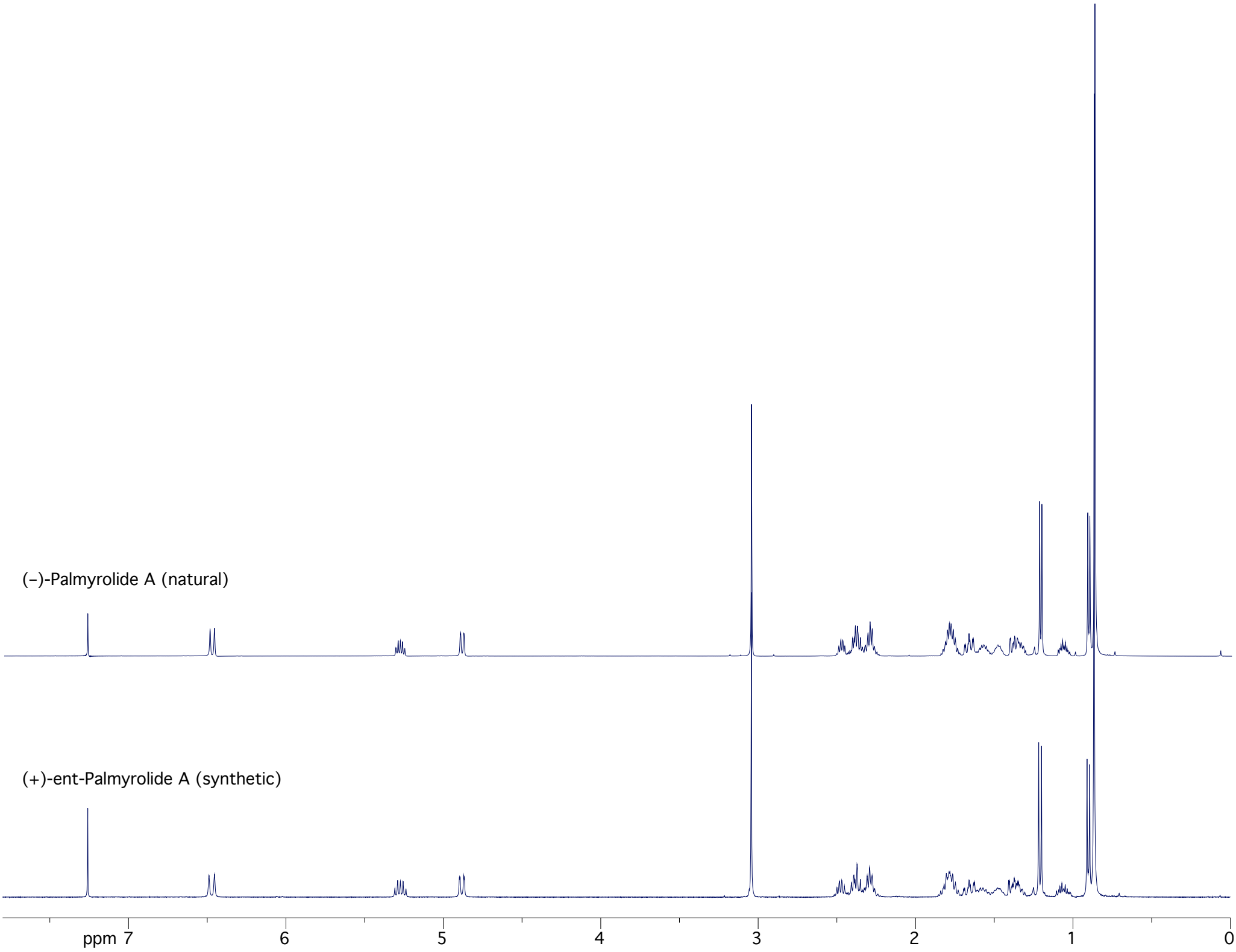
3.8



(+)-1a



(–)-1a


(–)-Palmyrolide A (natural)
(+)-ent-Palmyrolide A (synthetic)
ppm 7
6
5
4
3
2
1
0