

## Electronic Supporting Information

# Enantioselective Total Synthesis of Antibiotic CJ-16,264, Synthesis and Biological Evaluation of Designed Analogues and Discovery of Highly Potent and Simpler Antibacterial Agents

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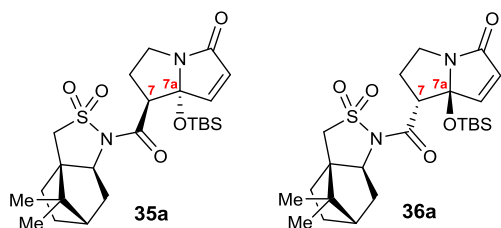
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## I. General Information

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, diethyl ether (Et<sub>2</sub>O), acetonitrile (MeCN), methylene chloride (CH<sub>2</sub>Cl<sub>2</sub>), triethylamine (Et<sub>3</sub>N), diisopropylamine, and pyridine were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (<sup>1</sup>H NMR) homogeneous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F<sub>254</sub>) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate or an aqueous solution of potassium permanganate and heat as developing agents. Acros Organics silica gel (60 Å, particle size 0.035–0.070 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 mm E. Merck silica gel plates (60F<sub>254</sub>). NMR spectra were recorded on a Bruker Avance III HD 600 MHz equipped with a 5 mm DCH cryoprobe, a Bruker Avance III 500 MHz, and a Bruker 400 MHz instrument, calibrated using residual undeuterated solvent for <sup>1</sup>H NMR [ $\delta_{\text{H}}=7.26$  (CHCl<sub>3</sub>), 7.16 (C<sub>6</sub>D<sub>5</sub>H), 2.05 (acetone-*d*<sub>5</sub>), and 2.50 (DMSO-*d*<sub>5</sub>) ppm] and deuterated solvent for <sup>13</sup>C NMR [ $\delta_{\text{C}}=77.16$  (CDCl<sub>3</sub>), 128.06 (C<sub>6</sub>D<sub>6</sub>), 39.52 (acetone-*d*<sub>5</sub>), and 39.52 (DMSO-*d*<sub>6</sub>) ppm] as an internal reference at 298 K. The following abbreviations were used to indicate the multiplicities: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sept = septet, and m = multiplet. IR spectra were recorded on a Perkin–Elmer Spectrum 100 FT-IR spectrometer. High resolution mass spectrometric measurements (HRMS) were performed on a Waters Micromass AutoSpec Ultima GC/MS, Agilent Technologies 6530 Accurate Mass QToF LC/MS (ESI) or Agilent 1200 HPLC-6130 MSD (ESI) instrument. Optical rotations were measured on a Schmidt+Haensch Polartronic M100 polarimeter at 589.44 nm using 100 mm cells and the solvent and concentration indicated [in units of 10<sup>-1</sup> (deg cm<sup>2</sup> g<sup>-1</sup>)]. UV-vis spectra were recorded on a Varian Cary 5000 UV-vis-NIR-spectrometer and a Beckman DU 7500 spectrophotometer using 10 mm quartz-cells and the solvent and concentration indicated.

## II. Experimental Procedures and Characterization Data

**(7*S*,7*aR*)-7a-[[*tert*-Butyl(dimethyl)silyl]oxy]-7-[[*(3aR,6S,7aS)*-8,8-dimethyl-2,2-dioxidotetrahydro-3*a*,6-methano-2,1-benzothiazol-1(3*H*,4*H*)-yl]carbonyl]-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one** and **(7*S*,7*aR*)-7a-[[*tert*-butyl(dimethyl)silyl]oxy]-7-[[*(3aR,6S,7aS)*-8,8-dimethyl-2,2-dioxidotetrahydro-3*a*,6-methano-2,1-benzothiazol-1(3*H*,4*H*)-yl]carbonyl]-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one** (**35a** and **36a**):



To a stirred solution of carboxylic acid ( $\pm$ )-**29** (1.00 g, 3.30 mmol, 1.0 equiv) in THF (10 mL) at  $-20\text{ }^{\circ}\text{C}$  was added  $\text{Et}_3\text{N}$  (1.67 mL, 8.25 mmol, 2.5 equiv) and PivCl (660  $\mu\text{L}$ , 4.95 mmol, 1.05 equiv). After stirring for 1 h at this temperature, LiCl (360 mg, 5.61 mmol, 1.7 equiv) followed by (*R*)-

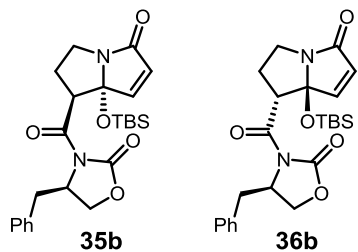
camphor sultam **34a** (1.20 g, 3.96 mmol, 1.2 equiv) was added. After stirring the resulting solution for an additional 6 h at  $-20\text{ }^{\circ}\text{C}$ , the reaction mixture was then quenched by the addition of sat. aq.  $\text{NH}_4\text{Cl}$  solution (10 mL) and diluted with EtOAc (50 mL). The phases were separated, the aqueous layer was extracted with EtOAc ( $2 \times 50\text{ mL}$ ). The combined organic extracts were washed with  $\text{H}_2\text{O}$  (10 mL), brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ , gradient from 10% EtOAc in hexanes  $\rightarrow$  20% EtOAc in hexanes) gave pure title compounds (**35a** and **36a**, 623 mg, 1.26 mmol, 38% yield; 714 mg, 1.44 mmol, 44% yield) as white amorphous solids.

The absolute configuration of the C7 and C7*a* stereocenters at the tetrahydropyrrolo[1,2-*a*]pyrrol-3-one within these compounds (**35a** and **36a**) was not discernable from their NMR spectral data and, therefore, the depicted structures should be considered interchangeable.

**35a** or **36a**:  $R_f=0.40$  (hexanes:EtOAc, 3:2);  $[\alpha]_D^{25}=+42$  ( $c=1.5$  in  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}=3274, 2956, 2886, 1716, 1594, 1462, 1268, 1195, 1076, 779\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  6.99 (d,  $J=5.7\text{ Hz}$ , 1H), 5.92 (d,  $J=5.7\text{ Hz}$ , 1H), 3.83–3.73 (m, 3H), 3.50 (d,  $J=13.8\text{ Hz}$ , 1H), 3.44 (d,  $J=13.8\text{ Hz}$ , 1H), 3.28–3.25 (m, 1H), 2.68–2.61 (m, 1H), 2.54–2.50 (m, 1H), 1.96–1.81 (m, 5H), 1.49–1.42 (m, 1H), 1.40–1.23 (m, 1H), 1.13 (s, 3H), 0.96 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.01 (s, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  172.87, 170.05, 147.62, 128.21, 101.37, 65.52, 53.14, 52.49, 48.29, 47.77, 44.48, 42.21, 38.03, 33.03, 31.71, 26.44, 25.50, 20.73, 19.96, 17.94,  $-3.42, -3.97$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{24}\text{H}_{38}\text{N}_2\text{O}_5\text{SSiNa}^+$   $[\text{M}+\text{Na}]^+$ : 517.2163, found: 517.2161.

**35a** or **36a**:  $R_f=0.45$  (hexanes:EtOAc, 3:2);  $[\alpha]_D^{25}=+64$  ( $c=0.8$  in  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}=2957$ , 2858, 1705, 1447, 1310, 1281  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.00 (d,  $J=5.8$  Hz, 1 H), 5.97 (d,  $J=5.7$  Hz, 1 H), 3.77–3.73 (m, 3 H), 3.51 (d,  $J=13.8$  Hz, 1 H), 3.43 (d,  $J=13.8$  Hz, 1 H), 3.30 (ddd,  $J=11.0, 9.1, 2.1$  Hz, 1 H), 2.77 (dtd,  $J=13.1, 9.2, 7.1$  Hz, 1 H), 2.38–2.34 (m, 1 H), 2.03–1.97 (m, 2 H), 1.95–1.83 (m, 3 H), 1.38 (ddd,  $J=11.2, 9.1, 2.3$  Hz, 1 H), 1.30 (ddd,  $J=11.2, 9.1, 4.0$  Hz, 1 H), 1.12 (s, 3 H), 0.96 (s, 3 H), 0.86 (s, 9 H), 0.06 (s, 3 H), 0.02 (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  173.74, 170.57, 147.43, 128.73, 101.07, 65.36, 53.37, 51.61, 48.39, 47.84, 44.75, 41.99, 38.52, 33.69, 33.02, 26.41, 25.54, 21.08, 19.92, 17.96,  $-3.37, -3.89$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{24}\text{H}_{38}\text{N}_2\text{O}_5\text{SSiNa}^+$   $[\text{M}+\text{Na}]^+$ : 517.2163, found: 517.2161.

**(7S,7aR)-7-[[*(4S)*-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl]-7a-[[*tert*-butyl(dimethyl)silyl]oxy]-5,6,7,7a-tetrahydro-3H-pyrrolo[1,2-*a*]pyrrol-3-one** and **(7R,7aR)-7-[[*(4S)*-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl]-7a-[[*tert*-butyl(dimethyl)silyl]oxy]-5,6,7,7a-tetrahydro-3H-pyrrolo[1,2-*a*]pyrrol-3-one (**35b** and **36b**):**



To a stirred solution of carboxylic acid ( $\pm$ )-**29** (600 mg, 2.00 mmol, 1.0 equiv) in THF (6 mL) at  $-20^\circ\text{C}$  was added  $\text{Et}_3\text{N}$  (693  $\mu\text{L}$ , 5.00 mmol, 2.5 equiv) and  $\text{PivCl}$  (257  $\mu\text{L}$ , 2.10 mmol, 1.05 equiv). After stirring for 1 h at this temperature,  $\text{LiCl}$  (144 mg, 3.4 mmol, 1.7 equiv) followed by (*R*)-oxazolidinone **34b** (425 mg, 2.40 mmol, 1.2 equiv) was added. After stirring the resulting

solution for an additional 6 h at  $-20^\circ\text{C}$ , the reaction mixture was then quenched by the addition of sat. aq.  $\text{NH}_4\text{Cl}$  solution (10 mL) and diluted with EtOAc (50 mL). The phases were separated, the aqueous layer was extracted with EtOAc ( $2 \times 50$  mL). The combined organic extracts were washed with  $\text{H}_2\text{O}$  (10 mL), brine (10 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated under reduced pressure. Purification by flash column chromatography ( $\text{SiO}_2$ , gradient from 10% EtOAc in hexanes  $\rightarrow$  20% EtOAc in hexanes) gave the pure title compounds (**35b**; 392 mg, 859  $\mu\text{mol}$ , 43% yield; **36b**; 406 mg, 889  $\mu\text{mol}$ , 44% yield) as colorless oils.

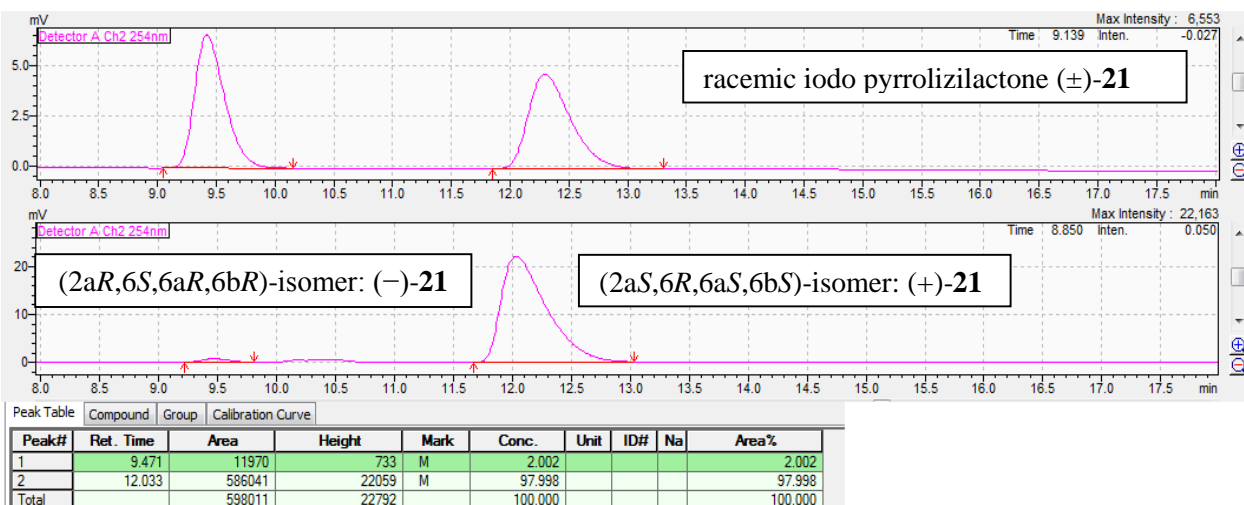
**35b**:  $R_f=0.60$  (hexanes:EtOAc, 3:2);  $[\alpha]_D^{25}=+28$  ( $c=1.3$  in  $\text{CHCl}_3$ ); IR (film)  $\nu_{\text{max}}=2956, 2930, 2858, 1781, 1715, 1384, 1250, 1093, 834, 780$   $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.32 (t,  $J=7.2$  Hz, 2 H), 7.28–7.24 (t,  $J=7.2$  Hz, 1 H), 7.19–7.15 (m, 2 H), 7.02 (d,  $J=5.8$  Hz, 1 H), 6.00 (d,  $J=5.7$  Hz, 1 H), 4.52 (ddt,  $J=9.9, 6.7, 3.4$  Hz, 1 H), 4.33 (d,  $J=6.5$  Hz, 1 H), 4.16–4.10 (m, 2 H), 3.91 (q,  $J=9.3$  Hz, 1 H), 3.33 (ddd,  $J=10.8, 9.6, 1.9$  Hz, 1 H), 3.21 (dd,  $J=13.2, 3.3$  Hz, 1 H), 2.69 (dtd,  $J=13.0, 9.4, 6.6$  Hz, 1 H), 2.57 (ddd,  $J=13.2, 8.8, 1.9$  Hz, 1 H), 2.42 (dd,  $J=13.2, 10.9$  Hz, 1 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  172.61, 170.90,

153.43, 147.25, 135.18, 129.40, 129.08, 128.94, 127.47, 101.23, 66.33, 55.75, 51.33, 42.03, 37.65, 31.52, 25.52, 17.97, -3.34, -3.91 ppm; HRMS (ESI-TOF): calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup>: 479.1973, found: 479.1981.

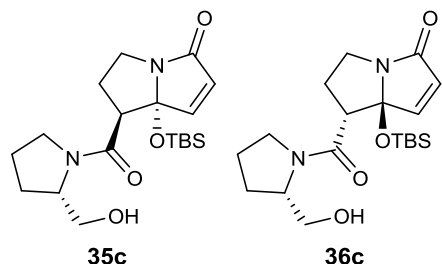
**36b**: R<sub>f</sub>=0.50 (hexanes:EtOAc, 3:2); [α]<sub>D</sub><sup>25</sup> = +19 (*c* = 3.0 in CHCl<sub>3</sub>); IR (film) ν<sub>max</sub> = 2955, 2857, 1778, 1713, 1381, 1248, 1093, 834 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.31 (dd, *J* = 8.1, 6.6 Hz, 2H), 7.27–7.24 (m, 1H), 7.15–7.14 (m, 2H), 6.88 (d, *J* = 5.8 Hz, 1H), 5.99 (d, *J* = 5.7 Hz, 1H), 4.53 (dtd, *J* = 9.3, 5.5, 3.5 Hz, 1H), 4.45 (d, *J* = 6.6 Hz, 1H), 4.15 (s, 1H), 4.14 (s, 1H), 3.88–3.84 (m, 1H), 3.32 (ddd, *J* = 11.0, 9.4, 1.9 Hz, 1H), 3.23 (dd, *J* = 13.4, 3.5 Hz, 1H), 2.75–2.68 (m, 2H), 2.54 (ddd, *J* = 13.2, 10.8, 1.9 Hz, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 172.70, 171.22, 153.43, 146.69, 134.89, 129.42, 129.04, 127.50, 101.03, 66.28, 55.09, 51.57, 42.03, 37.82, 31.97, 25.50, 17.93, -3.38, -3.95 ppm; HRMS (ESI-TOF): calcd for C<sub>24</sub>H<sub>32</sub>N<sub>2</sub>O<sub>5</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup>: 479.1973, found: 479.1974.

**(2a*S*,6*R*,6a*S*,6b*S*)-6b-{{*tert*-Butyl(dimethyl)silyloxy}-6-iodohexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**21**]**: To a stirred solution of amide **35b** (90 mg, 0.20 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub>:MeOH:H<sub>2</sub>O (1:1:0.05 v/v/v, 5 mL) at 25 °C was added I(*sym*-collidine)<sub>2</sub>ClO<sub>4</sub> (480 mg, 1.0 mmol, 5.0 equiv). After stirring in the dark for 7 d at 25 °C, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The reaction mixture was washed sequentially with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 × 30 mL), aq. HCl (0.5 M; 2 × 30 mL), and brine (30 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. Purification by flash column chromatography (SiO<sub>2</sub>, gradient from 10% EtOAc in hexanes → 20% EtOAc in hexanes) gave pure title compound [(+)-**21**; 2.6 mg, 6.1 μmol, 3% yield, 98:2 *er*; enantiomeric ratio was determined by HPLC using CHIRAL-PAK (OD-H, 250 × 4.6 mm, 13% *i*-PrOH:hexanes, flow rate 17 mL/min); (2a*R*,6*S*,6a*R*,6b*R*)-isomer: 9.47 min; (2a*S*,6*R*,6a*S*,6b*S*)-isomer: 12.03 min] as a light yellow solid.

**(+)-21**: R<sub>f</sub>=0.50 (hexanes:EtOAc, 2:1); [α]<sub>D</sub><sup>25</sup> = +21 (*c* = 0.2 in CHCl<sub>3</sub>); IR (film) ν<sub>max</sub> = 3007, 2954, 2887, 2859, 1794, 1718, 1472, 1361, 1257, 1164, 1137, 1012, 889, 840, 780 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.97 (s, 1H), 4.44 (s, 1H), 3.96–3.91 (m, 1H), 3.34–3.29 (m, 1H), 3.12 (dd, *J* = 9.4, 2.4 Hz, 1H), 2.69–2.54 (m, 2H), 0.95 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 174.26, 172.39, 102.15, 86.16, 49.42, 42.98, 30.06, 25.63, 18.04, 12.68, -3.19, -3.26 ppm; HRMS (ESI-TOF): calcd for C<sub>14</sub>H<sub>22</sub>INO<sub>4</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup>: 446.0255, found: 446.0262.



**(7*S*,7*aR*)-7*a*-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-[[*(2R)*-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl]-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one and (7*R*,7*aR*)-7*a*-{[*tert*-butyl-(dimethyl)silyl]oxy}-7-[[*(2R)*-2-(hydroxymethyl)pyrrolidin-1-yl]carbonyl]-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one (35c and 36c):** To a stirred solution of carboxylic acid

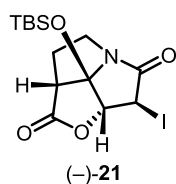


(±)-**29** (450 mg, 1.50 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (6 mL) at 0 °C was added EDCI (431 mg, 2.25 mmol, 1.5 equiv) and 1-hydroxy-7-azabenzotriazole (204 mg, 1.50 mmol, 1.0 equiv). After stirring for 20 min at this temperature, (*S*)-prolinol (**34c**; 152 mg, 3.00 mmol, 2.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) followed by *i*-Pr<sub>2</sub>NEt (0.76 mL, 4.5 mmol, 3.0 equiv) was added. After stirring the resulting solution for an additional 16 h at 25 °C, the reaction mixture was then quenched by the addition of sat. aq. NH<sub>4</sub>Cl solution (5 mL) and diluted with CH<sub>2</sub>Cl<sub>2</sub> (20 mL). The phases were separated, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2 × 15 mL). The combined organic extracts were washed with sat. aq. NaHCO<sub>3</sub> (2 × 10 mL), brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>, gradient from CH<sub>2</sub>Cl<sub>2</sub> → 2% MeOH in CH<sub>2</sub>Cl<sub>2</sub>) gave pure title compounds (**35c** and **36c**, 386 mg, 1.02 mmol, 68% yield, 1:1 *dr*) as a colorless oil.

**35c** and **36c**: *R*<sub>f</sub> = 0.10 (EtOAc); IR (film)  $\nu_{\text{max}}$  = 3422, 2954, 2886, 2857, 1713, 1622, 1472, 1277, 1197, 1087 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 1:1 mixture of diastereomers, \*Indicates inclusion of signals of both diastereomers)  $\delta$  6.81 (d, *J* = 5.7 Hz, 1 H), 6.70 (d, *J* = 5.7 Hz, 1 H), 6.03 (d, *J* = 5.8 Hz, 1 H), 6.02 (d, *J* = 5.7 Hz, 1 H), 4.21–4.17 (m, 1 H), 4.07–4.03 (m, 1 H), 3.92–3.88\* (m,

2H), 3.77 (ddd,  $J = 10.3, 7.5, 5.0$  Hz, 1H), 3.68–3.45\* (m, 7H), 3.25–3.21\* (m, 2H), 2.50–2.42\* (m, 2H), 2.08–1.83\* (m, 6H), 1.67–1.57\* (m, 2H), 0.87\* (s, 18H), 0.09\* (s, 6H), 0.02\* (s, 6H), 0.01\* (s, 6H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ , 1:1 mixture of diastereomers)  $\delta$  174.11, 173.96, 171.90, 171.89, 146.99, 146.78, 129.11, 129.02, 101.42, 101.21, 67.04, 66.85, 61.30, 60.81, 52.37, 51.94, 48.60, 48.39, 42.78, 32.06, 31.44, 28.42, 28.09, 25.59, 24.58, 17.91, –3.40, –3.87 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{19}\text{H}_{32}\text{N}_2\text{O}_4\text{SiNa}^+ [\text{M}+\text{Na}]^+$ : 403.2024, found: 403.2023.

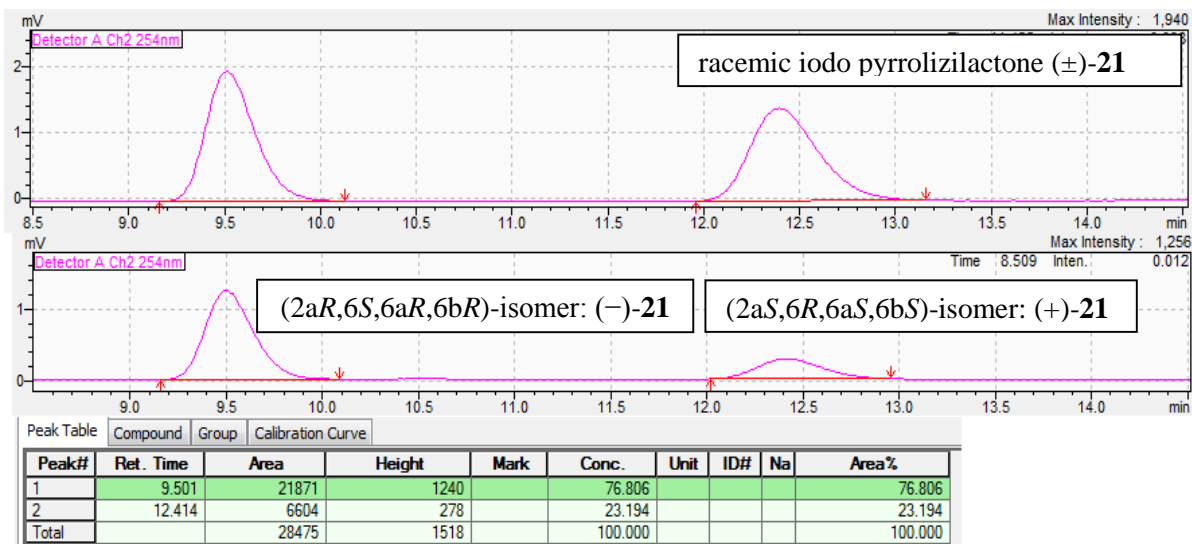
**(2aR,6S,6aR,6bR)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-iodohexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(–)-21]:** To a stirred solution of amide **35c** and **36c** (1:1 mixture



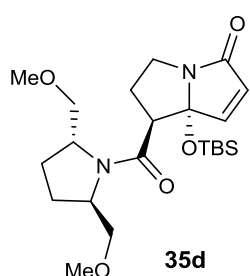
of diastereomers, 60 mg, 0.16 mmol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$ :MeOH:H $_2\text{O}$  (1:1:0.05 v/v/v, 5 mL) at 25 °C was added I(*sym*-collidine) $_2\text{ClO}_4$  (380 mg, 0.80 mmol, 5.0 equiv). After stirring in the dark for 72 h at 25 °C, the reaction mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (50 mL). The reaction mixture was washed sequentially with

sat. aq.  $\text{Na}_2\text{S}_2\text{O}_3$  (2  $\times$  10 mL), aq. HCl (0.5 M; 2  $\times$  10 mL), and brine (10 mL). The organic layer was dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated. Purification by flash column chromatography ( $\text{SiO}_2$ , gradient from 10% EtOAc in hexanes  $\rightarrow$  20% EtOAc in hexanes) gave pure title compound [(–)-21; 19 mg, 0.045 mmol, 28% yield, 23:77 *er*; enantiomeric ratio was determined by HPLC using CHIRAL-PAK (OD-H, 250  $\times$  4.6 mm, 13% *i*-PrOH:hexanes, flow rate 17 mL/min); (2aR,6S,6aR,6bR)-isomer: 9.5 min; (2aS,6R,6aS,6bS)-isomer: 12.4 min] as a light yellow solid.

(–)-21: The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data of (–)-21 matched those of (+)-21.  $[\alpha]_{\text{D}}^{25} = -10$  ( $c = 0.5$  in  $\text{CHCl}_3$ ).



**(7*S*,7*aR*)-7-[[*(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]carbonyl]-7*a*-[[*tert*-butyl(dimethyl)silyl]oxy]-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one (35d)***: To a stirred



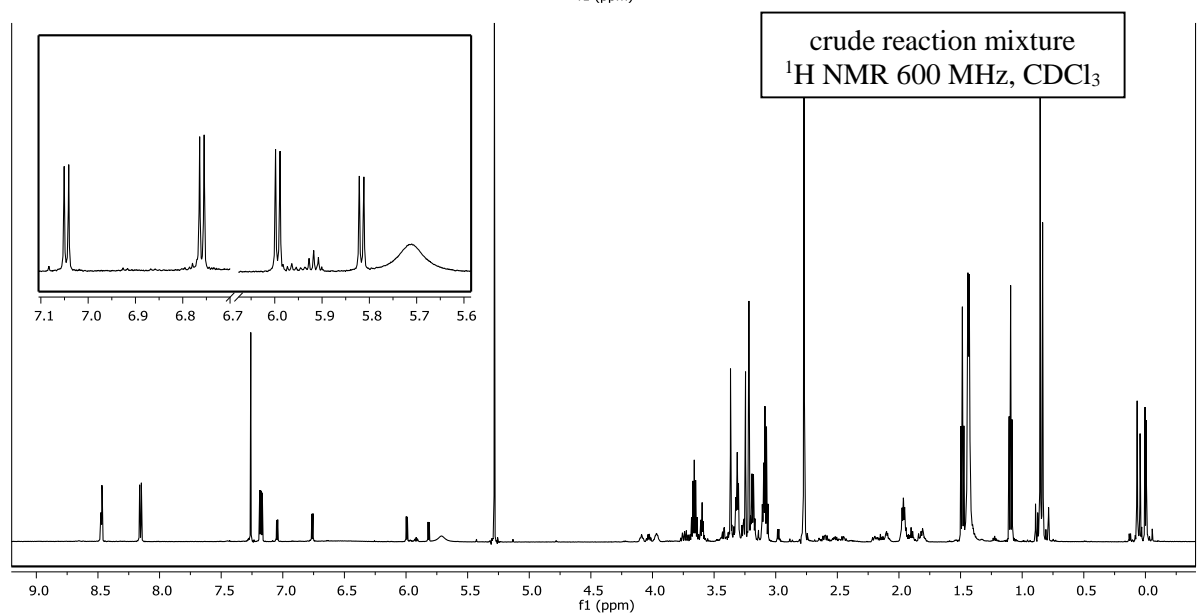
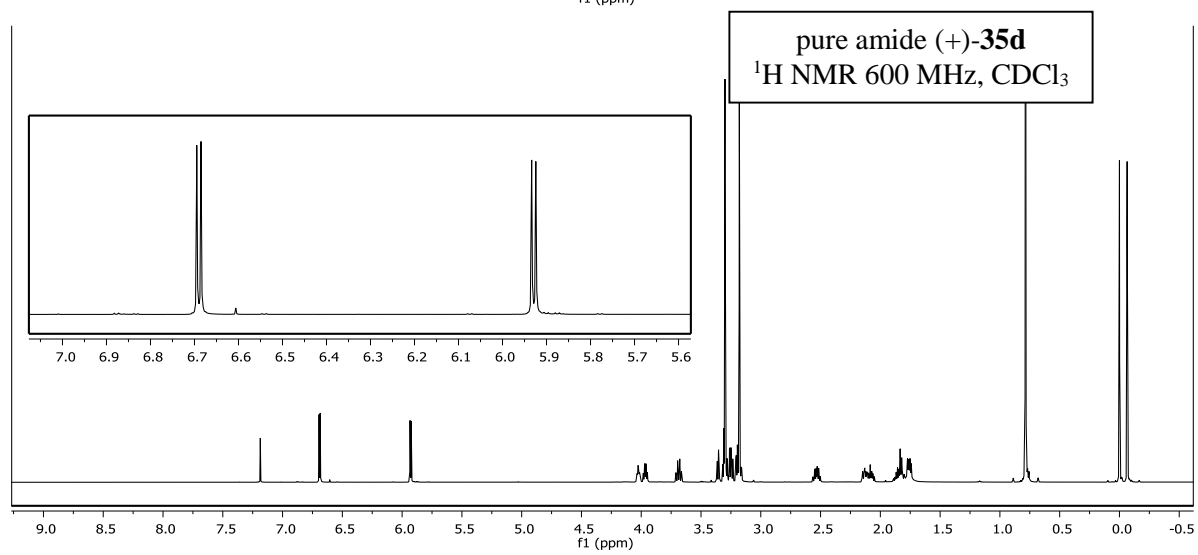
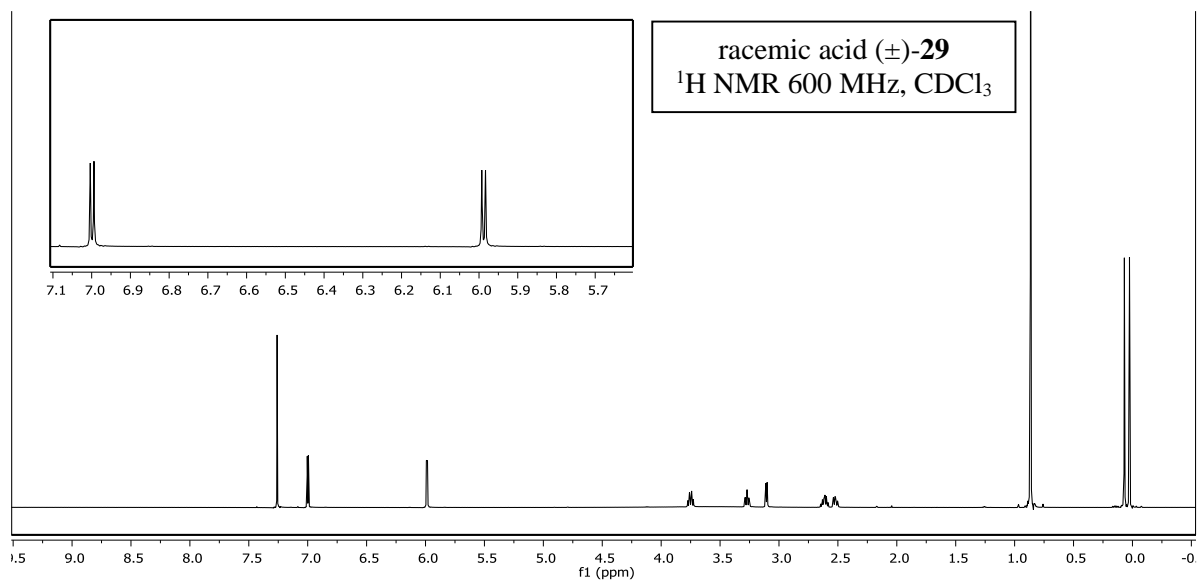
solution of carboxylic acid ( $\pm$ )-**29** (297 mg, 1.00 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (3 mL) at 0 °C was added EDCI (287 mg, 1.50 mmol, 1.5 equiv) and 1-hydroxy-7-azabenzotriazole (136 mg, 1.00 mmol, 1.0 equiv). After stirring for 20 min at this temperature, amine **34d** (96.0 mg, 600  $\mu$ mol, 0.6 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (1 mL) followed by *i*-Pr<sub>2</sub>NEt (423  $\mu$ L, 3.00 mmol, 3.0 equiv) was added. After stirring the resulting solution for an additional 48 h at 0 °C, the

reaction mixture was then quenched by the addition of aq. HCl solution (1.0 M; 5 mL) and diluted with CH<sub>2</sub>Cl<sub>2</sub> (50 mL). The phases were separated, the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (2  $\times$  10 mL). The combined organic extracts were washed with aq. HCl solution (1.0 M; 2  $\times$  5 mL), H<sub>2</sub>O (10 mL), brine (10 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO<sub>2</sub>, gradient from 40% hexanes in EtOAc  $\rightarrow$  60% hexanes in EtOAc  $\rightarrow$  100% EtOAc) gave pure title compound (**35d**; 197 mg, 0.450 mmol, 45% yield) as a colorless oil and ( $-$ )-**29** (124 mg, 0.420 mmol, 42% yield) as a white amorphous solid.

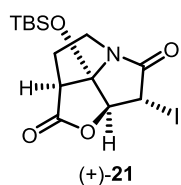
**35d**:  $R_f$  = 0.40 (EtOAc);  $[\alpha]_D^{25} = +26$  ( $c = 1.0$  in C<sub>6</sub>H<sub>6</sub>); IR (film)  $\nu_{\max} = 2954, 2892, 2858, 1718, 1638, 1423, 1322, 1251, 1112, 1073, 834, 810, 778$  cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  6.76 (d,  $J = 5.7$  Hz, 1H), 6.00 (d,  $J = 5.7$  Hz, 1H), 4.11–4.08 (m, 1H), 4.06–4.01 (m, 1H), 3.76 (dt,  $J = 10.7, 8.6$  Hz, 1H), 3.43 (dd,  $J = 9.2, 3.0$  Hz, 1H), 3.40–3.35 (m, 5H), 3.32 (dd,  $J = 9.4, 7.0$  Hz, 1H), 3.29–3.22 (m, 5H), 2.61 (dtd,  $J = 12.8, 8.8, 7.3$  Hz, 1H), 2.23–2.12 (m, 2H), 1.97–1.87 (m, 2H), 1.86–1.81 (m, 1H), 0.86 (s, 9H), 0.07 (s, 3H), 0.01 (s, 3H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  174.72, 170.97, 147.30, 128.71, 101.49, 75.29, 71.21, 59.09, 59.03, 57.82, 57.16, 50.54, 42.57, 33.67, 27.51, 25.73, 25.61, 17.92, -3.37, -3.98 ppm; HRMS (ESI-TOF): calcd for C<sub>22</sub>H<sub>38</sub>N<sub>2</sub>O<sub>5</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup>: 461.2442, found: 461.2418.

( $-$ )-**29**: The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral data of ( $-$ )-**29** matched those of previously reported by the Danishefsky group.<sup>1</sup>  $[\alpha]_D^{25} = -27$  ( $c = 1.0$  in CHCl<sub>3</sub>).



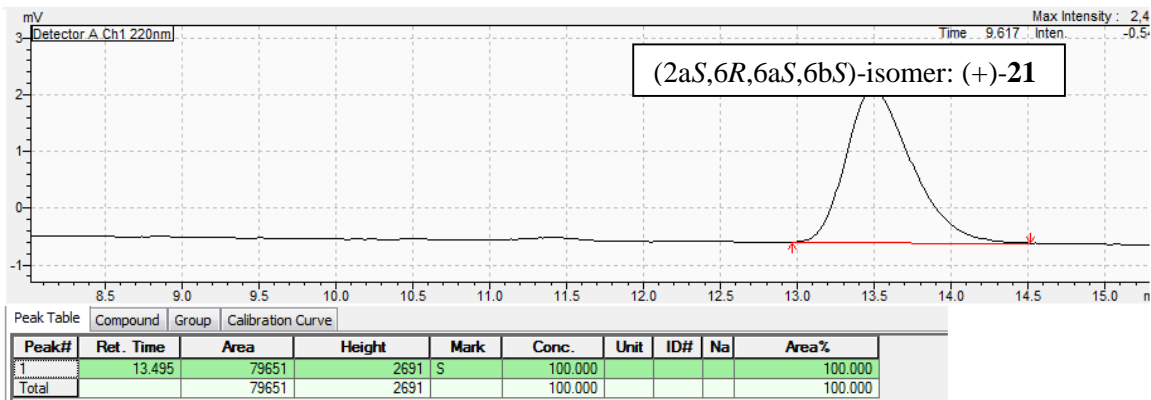
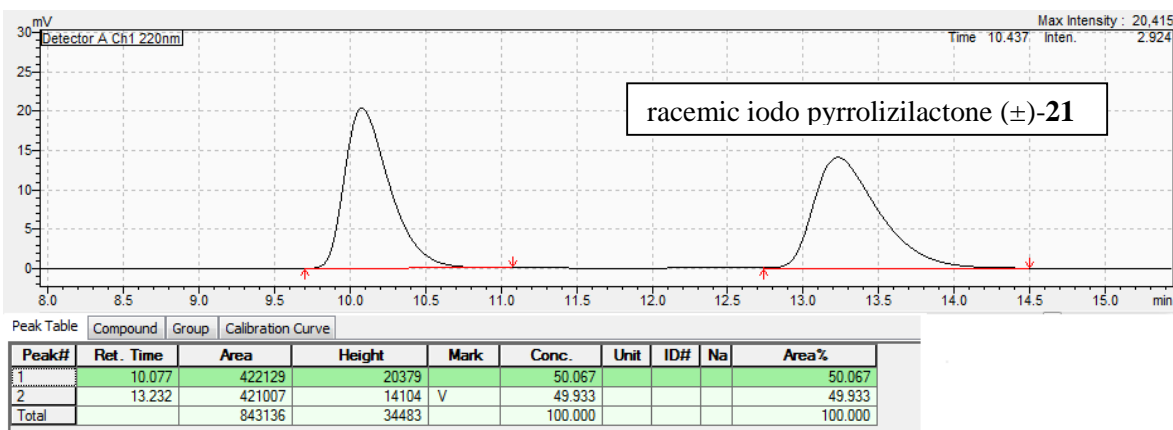


**(2a*S*,6*R*,6a*S*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-iodohexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**21**]:**

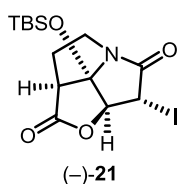


To a stirred solution of amide **35d** (1.50 g, 3.42 mmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub>:MeOH:H<sub>2</sub>O (1:1:0.05 v/v/v, 75 mL) at 25 °C was added I(*sym*-collidine)<sub>2</sub>ClO<sub>4</sub> (8.12 g, 17.1 mmol, 5.0 equiv). After stirring in the dark for 72 h at 25 °C, the reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The reaction mixture was washed sequentially with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2 × 30 mL), aq. HCl (1 M; 2 × 10 mL), H<sub>2</sub>O (10 mL) and brine (10 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. Purification by flash column chromatography (SiO<sub>2</sub>, gradient from 10% EtOAc in hexanes → 20% EtOAc in hexanes) gave pure title compound [(+)-**21**; 677 mg, 1.60 mmol, 47% yield, >99:1 *er*; enantiomeric ratio was determined by HPLC using CHIRAL-PAK (OD-H, 250 × 4.6 mm, 13% *i*-PrOH:hexanes, flow rate 17 mL/min); (2a*R*,6*S*,6a*R*,6b*R*)-isomer: 10.07 min; (2a*S*,6*R*,6a*S*,6b*S*)-isomer: 13.49 min] as a light yellow solid and amide **35d** (389 mg, 0.891 mmol) was recovered.

(+)-**21**: The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral data of (+)-**21** matched those of previously synthesized (+)-**21**. [α]<sub>D</sub><sup>25</sup> = +25 (*c* = 1.0 in CHCl<sub>3</sub>).

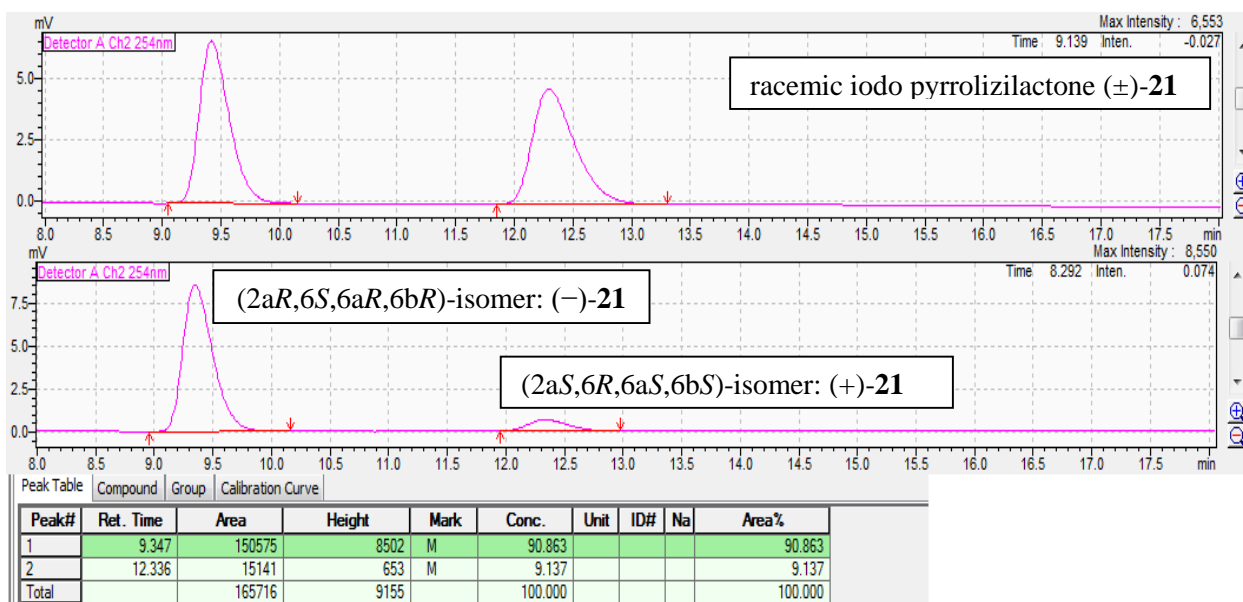


**(2aR,6S,6aR,6bR)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-iodohexahydro-1-oxa-4a-azacyclo-penta[*cd*]pentalene-2,5-dione [(-)-**21**]:** To a stirred solution of acid (-)-**29** (124 mg, 418  $\mu$ mol,

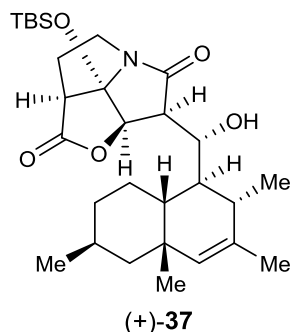


1.0 equiv) in Et<sub>2</sub>O:sat. aq. NaHCO<sub>3</sub> (1:1 v/v, 10 mL) at 25 °C was added I<sub>2</sub> (317 mg, 1.25 mmol, 3.0 equiv). After stirring in the dark for 24 h at 25 °C, the reaction mixture was diluted with Et<sub>2</sub>O (50 mL). The reaction mixture was washed sequentially with sat. aq. Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (2  $\times$  5 mL), H<sub>2</sub>O (10 mL) and brine (10 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated. Purification by flash column chromatography (SiO<sub>2</sub>, gradient from 10% EtOAc in hexanes  $\rightarrow$  20% EtOAc in hexanes) gave pure title compound [(-)-**21**, 131 mg, 309  $\mu$ mol, 74% yield, 91:9 *er*, enantiomeric ratio was determined by HPLC using CHIRAL-PAK (OD-H, 250  $\times$  4.6 mm, 13% *i*-PrOH:hexanes, flow rate 17 mL/min); (2aR,6S,6aR,6bR)-isomer: 9.3 min; (2aS,6R,6aS,6bS)-isomer: 12.3 min] as a light yellow solid.

(-)-**21**: The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectral data of (-)-**21** matched those of previously reported by the Danishefsky group.<sup>1</sup> [ $\alpha$ ]<sub>D</sub><sup>25</sup> = -22 (*c* = 1.0 in CHCl<sub>3</sub>).



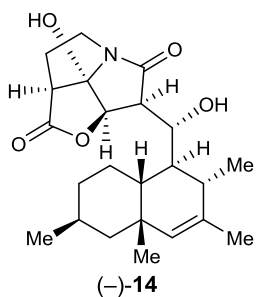
**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(*R*)-hydroxy[(1*S*,4a*R*,6*S*,8a*R*)-2,3,4a,6-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**37**]:**



(50 mg, 0.23 mmol, 2.0 equiv) and iodide (+)-**21** (48 mg, 0.11 mmol, 1.0 equiv) in toluene (4 mL) at  $-78^{\circ}\text{C}$  was added  $\text{BEt}_3$  (1.0 M in hexanes, 0.12 mL, 0.12 mmol, 1.1 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (1 mL). The reaction mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 100% hexanes  $\rightarrow$  20%  $\text{EtOAc}$  in hexanes) providing pure title compound [(+)-**37**; 48 mg, 93  $\mu\text{mol}$ , 82% yield] as a colorless oil.

(+)-**37**:  $R_f=0.40$  (hexanes: $\text{EtOAc}$ , 4:1);  $[\alpha]_D^{25}=+12$  ( $c=1.0$ ,  $\text{C}_6\text{H}_6$ ); IR (film)  $\nu_{\text{max}}$  3471, 2929, 2860, 1794, 1702, 1374, 1141, 838, 780  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.20 (s, 1 H), 4.76 (d,  $J=2.2$  Hz, 1 H), 4.48 (d,  $J=3.9$  Hz, 1 H), 4.38–4.36 (m, 1 H), 3.44–3.39 (m, 1 H), 3.22 (dd,  $J=8.6$ , 3.8 Hz, 1 H), 2.82–2.49 (m, 1 H), 2.69–2.64 (m, 1 H), 2.37 (dd,  $J=8.8$ , 1.2 Hz, 1 H), 2.07–2.02 (m, 1 H), 1.78 (s, 3 H), 1.76–1.72 (m, 1 H), 1.68 (br s, 1 H), 1.66–1.59 (m, 5 H), 1.46–1.40 (m, 1 H), 1.31 (s, 3 H), 1.25 (d,  $J=7.5$  Hz, 3 H), 0.97–0.87 (m, 5 H), 0.79 (s, 9 H),  $-0.11$  (s, 3 H),  $-0.21$  (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  177.0, 173.7, 134.6, 131.5, 100.4, 82.6, 73.0, 51.7, 51.3, 50.9, 49.2, 45.9, 42.5, 36.3, 35.4, 33.7, 30.7, 30.1, 29.4, 28.7, 25.4, 23.2, 22.8, 22.6, 17.8,  $-3.6$ ,  $-4.0$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{29}\text{H}_{47}\text{NO}_5\text{SiNa}^+$   $[\text{M}+\text{Na}]^+$  540.3116 found 540.3124.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-{hydroxy[(1*S*,2*S*,4a*R*,6*S*,8a*R*)-2,3,4a,6-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]methyl}hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(–)-**14**]:**

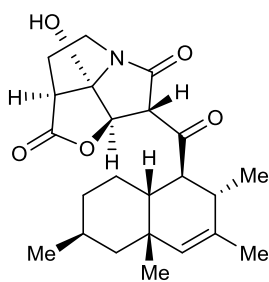


(1.0 M in THF, 12  $\mu\text{L}$ , 12  $\mu\text{mol}$ , 1.0 equiv) and acetic acid (7.0  $\mu\text{L}$ , 12  $\mu\text{mol}$ , 1.05 equiv) in THF (2 mL) was added TBS ether (+)-**37** (10 mg, 12  $\mu\text{mol}$ , 1.0 equiv) in THF (1 mL) at  $0^{\circ}\text{C}$  and the resulting mixture was stirred for 30 min at the same temperature before it was quenched by the addition of sat. aq.  $\text{NH}_4\text{Cl}$  (2 mL). The resulting mixture was extracted with  $\text{EtOAc}$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$ , and concentrated under reduced

pressure. The resulting crude product was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) providing pure title compound [(–)-**14**; 4.1 mg, 10 μmol, 88% yield] as a colorless oil.

(–)-**14**: R<sub>f</sub>=0.30 (hexanes:EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> = –15 (*c*=0.5, acetone); IR (film) ν<sub>max</sub> 3339, 2919, 1789, 1693, 1446, 1382, 1022 cm<sup>–1</sup>; <sup>1</sup>H NMR (600 MHz, acetone-d<sub>6</sub>) δ 6.25 (br s, 1 H), 5.07 (d, *J*=3.5 Hz, 1 H), 5.06 (s, 1 H), 4.54 (d, *J*=2.5 Hz, 1 H), 4.07–4.03 (m, 1 H), 3.77 (ddd, *J*=11.4, 9.6, 6.3 Hz, 1 H), 3.36 (dd, *J*=8.0, 4.0 Hz, 1 H), 3.33–3.28 (m, 2 H), 2.79 (br s, 1 H), 2.70 (dtd, *J*=15.6, 9.5, 6.2 Hz, 1 H), 2.55 (dd, *J*=14.5, 7.2 Hz, 1 H), 2.43 (dddd, *J*=13.8, 9.2, 4.7, 1.7 Hz, 1 H), 1.69 (s, 3 H), 1.65 (br s, 1 H), 1.58–1.53 (m, 1 H), 1.48–1.40 (m, 3 H), 1.35–1.28 (m, 1 H), 1.18 (d, *J*=7.5 Hz, 3 H), 1.08 (s, 3 H), 0.90 (d, *J*=13.2, 11.8 Hz, 1 H), 0.86–0.79 (m, 4 H) ppm; <sup>13</sup>C NMR (151 MHz, acetone-d<sub>6</sub>) δ 176.7, 175.9, 135.6, 131.1, 100.2, 83.1, 73.4, 52.2, 51.6, 51.5, 49.1, 46.0, 42.2, 36.7, 36.1, 33.9, 30.6, 29.9, 29.6, 29.4, 23.3, 22.9, 22.6 ppm; HRMS (ESI-TOF): calcd for C<sub>23</sub>H<sub>33</sub>NO<sub>5</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 426.2251 found 426.2259.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*S*,2*S*,4a*R*,6*S*,8a*R*)-2,3,4a,6-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]carbonyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**1**]:** To a stirred solution of diol (–)-**14** (6.0 mg, 15 μmol, 1.0 equiv) in EtOAc (1 mL)



at 70 °C was added IBX (21 mg, 74 μmol, 5.0 equiv) and the resulting mixture was stirred for 9 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with Et<sub>2</sub>O (15 mL) and passed through a plug of Celite. The solvent was removed under reduced pressure and the obtained residue was purified by passing it through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes)

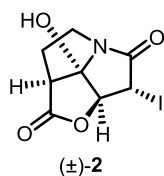
furnishing title compound [(+)-**1**; 4.1 mg, 10 μmol, 68% yield] as a colorless oil.

(+)-**1**: R<sub>f</sub>=0.30 (hexanes:EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> = +8 (*c*=0.3, MeOH); IR (film) ν<sub>max</sub> 3446, 2924, 2854, 1793, 1719, 1690, 1555, 1456, 1336, 1260, 1161, 1024, 798 cm<sup>–1</sup>; <sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 5.09 (s, 1 H), 5.01 (s, 1 H), 4.16 (s, 1 H), 4.03 (s, 1 H), 3.53 (ddd, *J*=11.9, 9.4, 6.1 Hz, 1 H), 2.98 (br s, 1 H), 2.78 (ddd, *J*=11.9, 9.9, 4.8 Hz, 1 H), 2.72 (dd, *J*=9.2, 1.7 Hz, 1 H), 2.55 (br d, *J*=11.0 Hz, 1 H), 2.14 (dd, *J*=3.9, 3.0 Hz, 1 H), 2.12–2.04 (m, 1 H), 1.97–1.88 (m, 1 H), 1.68 (s, 3 H), 1.62–1.56 (m, 1 H), 1.46–1.32 (m, 4 H), 1.09–1.00 (m, 2 H), 0.95 (d, *J*=7.4 Hz, 3 H), 0.93 (s, 3 H), 0.89 (d, *J*=6.5 Hz, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 209.8, 173.9, 167.6, 133.1, 131.4, 100.9,

81.1, 63.7, 63.6, 48.8, 47.5, 41.8, 38.9, 37.0, 34.2, 31.9, 29.7, 29.7, 29.1, 28.8, 22.3, 21.6, 21.0 ppm; HRMS (ESI-TOF): calcd for C<sub>23</sub>H<sub>31</sub>NO<sub>5</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 424.2094 found 424.2101.

***rel*-(2a*S*,6*R*,6a*S*,6b*S*)-6b-Hydroxy-6-iodohexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-**

**2,5-dione [(±)-2]:** To a stirred solution of iodide (±)-**21** (20 mg, 47 μmol, 1.0 equiv) in THF

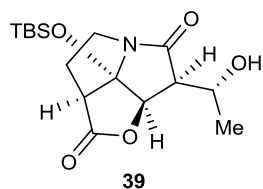


(1 mL) at 0 °C was added TASF (23 mg, 85 μmol, 1.8 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by addition of H<sub>2</sub>O (2 mL). The reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over MgSO<sub>4</sub> and

concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) providing pure title compound [(±)-**2**; 5.0 mg, 16 μmol, 35% yield] as a colorless oil.

(±)-**2**: R<sub>f</sub> = 0.20 (hexanes:EtOAc, 1:1); IR (film) ν<sub>max</sub> 2928, 1792, 1706, 1378, 1329, 1156, 1008, 838 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.12 (s, 1 H), 4.41 (s, 1 H), 3.91 (ddd, *J*=12.2, 9.4, 5.9 Hz, 1 H), 3.41 (ddd, *J*=12.1, 9.8, 5.2 Hz, 1 H), 3.25 (dd, *J*=9.3, 1.9 Hz, 1 H), 2.94 (br s, 1 H), 2.76–2.67 (m, 1 H), 2.62–2.54 (m, 1 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 173.6, 172.1, 101.2, 84.8, 48.9, 42.7, 25.8, 14.0 ppm; HRMS (ESI-TOF): calcd for C<sub>8</sub>H<sub>9</sub>NO<sub>4</sub>I<sup>+</sup> [M+H]<sup>+</sup> 309.9571 found 309.9578.

***rel*-(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(1*R*)-1-hydroxyethyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (39):** To a stirred solution of acetaldehyde **38**



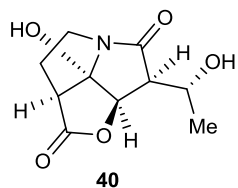
(20 μL, 360 μmol, 5.0 equiv) and iodide (±)-**21** (30 mg, 71 μmol, 1.0 equiv) in toluene (4 mL) at -78 °C was added BEt<sub>3</sub> (1.0 M in hexanes, 71 μL, 71 μmol, 1.0 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H<sub>2</sub>O (1 mL). The

reaction mixture was extracted with Et<sub>2</sub>O (3 × 10 mL) and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 100% hexanes→20% EtOAc in hexanes) providing pure title compound (**39**; 20 mg, 59 μmol, 83% yield) as a colorless oil.

**39**: R<sub>f</sub> = 0.30 (hexanes:EtOAc, 4:1); IR (film) ν<sub>max</sub> 3495, 2955, 2931, 2858, 1789, 1700, 1371, 1304, 1250, 1102, 1057, 893, 778 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.74 (d, *J*=4.0 Hz, 1 H), 4.24 (s, 1 H), 4.16–4.09 (m, 1 H), 3.81 (ddd, *J*=11.8, 9.1, 7.3 Hz, 1 H), 3.33–3.26 (m, 1 H), 3.11–3.03 (m, 1 H), 2.90 (dd, *J*=9.4, 4.0 Hz, 1 H), 2.66–2.52 (m, 2 H), 1.30 (d, *J*=6.1 Hz, 3 H), 0.89 (s,

9H), 0.16 (s, 3H), 0.14 (s, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  176.9, 174.9, 101.1, 82.1, 65.0, 53.4, 49.4, 42.5, 29.1, 25.5, 20.5, 17.9, -3.1, -3.5 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{16}\text{H}_{27}\text{NO}_5\text{SiNa}^+$   $[\text{M}+\text{Na}]^+$  364.1551 found 364.1562.

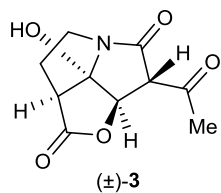
***rel*-(2*aS*,6*S*,6*aR*,6*bS*)-6*b*-Hydroxy-6-[(1*R*)-1-hydroxyethyl]hexahydro-1-oxa-4*a*-azacyclo-penta[*cd*]pentalene-2,5-dione (**40**):**



To a stirred solution of TBS ether **39** (17 mg, 50  $\mu\text{mol}$ , 1.0 equiv) in THF (2 mL) at 0  $^\circ\text{C}$  was added TASF (21 mg, 75  $\mu\text{mol}$ , 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 25$  mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 30% EtOAc in hexanes  $\rightarrow$  60% EtOAc in hexanes) providing pure title compound (**40**; 12 mg, 44  $\mu\text{mol}$ , 88% yield) as a white amorphous solid.

**40**:  $R_f = 0.20$  (hexanes:EtOAc, 3:2); IR (film)  $\nu_{\text{max}}$  3406, 2926, 1781, 1682, 1378, 1332, 1305, 1167, 1095, 1053  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz, MeOD)  $\delta$  4.90 (d,  $J=3.9$  Hz, 1H), 4.05 (dq,  $J=9.1, 6.3$  Hz, 1H), 3.73 (ddd,  $J=11.7, 9.4, 6.4$  Hz, 1H), 3.30–3.26 (m, 1H), 3.21 (dd,  $J=9.1, 1.6$  Hz, 1H), 3.10 (dd,  $J=9.0, 3.9$  Hz, 1H), 2.71–2.61 (m, 1H), 2.46–2.39 (m, 1H), 1.29 (d,  $J=6.3$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz, MeOD)  $\delta$  177.3, 177.2, 100.6, 83.0, 66.0, 54.2, 49.4, 42.2, 29.8, 20.9 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{10}\text{H}_{13}\text{NO}_5\text{Na}^+$   $[\text{M}+\text{Na}]^+$  250.0686 found 250.0678.

***rel*-(2*aS*,6*S*,6*aR*,6*bS*)-6-Acetyl-6*b*-hydroxyhexahydro-1-oxa-4*a*-azacyclo-penta[*cd*]pentalene-2,5-dione [( $\pm$ )-**3**]:**

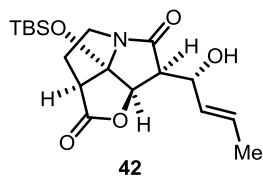


at 70  $^\circ\text{C}$  was added IBX (38 mg, 130  $\mu\text{mol}$ , 5.0 equiv) and the resulting mixture was stirred for 6 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with  $\text{Et}_2\text{O}$  (15 mL) and passed through a plug of Celite. The solvent was removed under reduced pressure and the obtained residue was purified by passing it through a short plug of silica (gradient from 10% EtOAc in hexanes  $\rightarrow$  70% EtOAc in hexanes) furnishing title compound [( $\pm$ )-**3**; 3.4 mg, 15  $\mu\text{mol}$ , 57% yield] as a colorless oil.

( $\pm$ )-**3**:  $R_f = 0.20$  (hexanes:EtOAc, 1:2); IR (film)  $\nu_{\text{max}}$  3394, 2962, 2917, 1787, 1699, 1413, 1362, 1166, 1034  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.12 (s, 1H), 4.77 (s, 1H), 3.90–3.82 (m, 1H),

3.58 (br s, 1 H), 3.40–3.29 (m, 2 H), 2.72–2.63 (m, 1 H), 2.51 (s, 3 H), 2.49–2.40 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  204.48, 174.75, 166.81, 101.07, 80.08, 65.57, 47.88, 41.88, 30.85, 30.10 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{10}\text{H}_{11}\text{NO}_5\text{Na}^+$   $[\text{M}+\text{Na}]^+$  248.0529 found 248.0532.

***rel*-(2*aS*,6*S*,6*aR*,6*bS*)-6*b*-{*tert*-Butyl(dimethyl)silyloxy}-6-[(1*R*,2*E*)-1-hydroxybut-2-en-1-yl]hexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalene-2,5-dione (42)**: To a stirred solution of crotonaldehyde (**41**; 87  $\mu\text{L}$ , 1.1 mmol, 3.0 equiv) and iodide ( $\pm$ )-**21** (150 mg, 350  $\mu\text{mol}$ , 1.0 equiv)

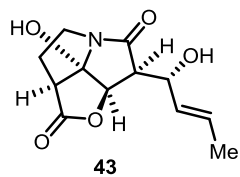


in toluene (8 mL) at  $-78^\circ\text{C}$  was added  $\text{BET}_3$  (1.0 M in hexanes, 0.39 mL, 0.39 mmol, 1.1 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (1 mL). The reaction mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined

organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 100% hexanes  $\rightarrow$  20%  $\text{EtOAc}$  in hexanes) providing pure title compound [**42**; 94 mg, 260  $\mu\text{mol}$ ,  $\sim$ 10:1 (*E*)/(*Z*) mixture, 72% yield] as a colorless oil.

**42**:  $R_f=0.50$  (hexanes: $\text{EtOAc}$ , 2:1);  $[\alpha]_D^{25} = +21$  ( $c=1.0$  in  $\text{C}_6\text{H}_6$ ); IR (film)  $\nu_{\text{max}}$  3480, 2955, 2931, 2858, 1790, 1701, 1472, 1374, 1303, 1252, 1142, 1087, 1062, 893, 838, 780  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR [600 MHz,  $\text{CDCl}_3$ , data for (*E*)-isomer]  $\delta$  5.92 (dq,  $J=15.4, 6.6, 1.0$  Hz, 1 H), 5.49 (ddq,  $J=15.3, 7.3, 1.6$  Hz, 1 H), 4.66 (d,  $J=3.9$  Hz, 1 H), 4.45 (dd,  $J=9.7, 7.3$  Hz, 1 H), 4.35 (s, 1 H), 3.80 (dt,  $J=11.9, 8.2$  Hz, 1 H), 3.35–3.27 (m, 1 H), 3.07–3.04 (m, 1 H), 3.01 (dd,  $J=9.8, 3.9$  Hz, 1 H), 2.64–2.56 (m, 2 H), 1.75 (dd,  $J=6.4, 1.6$  Hz, 3 H), 0.89 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H) ppm;  $^{13}\text{C}$  NMR [151 MHz,  $\text{CDCl}_3$ , data for (*E*)-isomer]  $\delta$  176.54, 174.83, 130.50, 128.82, 128.08, 100.82, 82.04, 69.54, 52.05, 49.28, 42.32, 28.97, 25.44, 17.95,  $-3.26$ ,  $-3.65$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{18}\text{H}_{29}\text{NO}_5\text{SiNa}^+$   $[\text{M}+\text{Na}]^+$ : 390.1707, found: 390.1712.

***rel*-(2*aS*,6*S*,6*aR*,6*bS*)-6*b*-Hydroxy-6-[(1*R*,2*E*)-1-hydroxybut-2-en-1-yl]hexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalene-2,5-dione (43)**: To a stirred solution of TBS ether **42** (50 mg,



0.14 mmol, 1.0 equiv) in THF (2 mL) at  $0^\circ\text{C}$  was added TBAF (1.0 M in THF, 0.14 mL, 0.14 mmol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of sat. aq.  $\text{NH}_4\text{Cl}$  solution (2 mL) and  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was

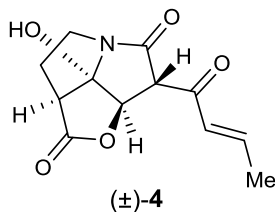
extracted with  $\text{EtOAc}$  ( $3 \times 5$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and



concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 30% EtOAc in hexanes→70% EtOAc in hexanes) providing pure title compound [**43**; 31 mg, 120 μmol, 10:1 (*E*)/(*Z*) mixture, 90% yield] as a white amorphous solid.

**43**: R<sub>f</sub>=0.20 (hexanes:EtOAc, 2:3); IR (film) ν<sub>max</sub> 3316, 2960, 2918, 2856, 1787, 1685, 1383, 1331, 1304, 1162, 1082, 1060, 1008, 969, 731 cm<sup>-1</sup>; <sup>1</sup>H NMR [600 MHz, CDCl<sub>3</sub>, data for (*E*)-isomer] δ 5.93 (dq, *J*=14.0, 6.6, 0.9 Hz, 1 H), 5.47 (ddq, *J*=15.3, 7.4, 1.7 Hz, 1 H), 4.77 (d, *J*=4.0 Hz, 1 H), 4.48 (dd, *J*=9.8, 7.5 Hz, 2 H), 3.84 (ddd, *J*=11.9, 9.3, 6.4 Hz, 1 H), 3.72 (s, 1 H), 3.36 (dddd, *J*=11.6, 10.0, 4.7, 1.2 Hz, 1 H), 3.12 (dd, *J*=9.1, 1.9 Hz, 1 H), 3.10 (dd, *J*=9.8, 4.0 Hz, 1 H), 2.69 (dtd, *J*=13.9, 9.3, 6.5 Hz, 1 H), 2.58 (dddd, *J*=13.9, 9.3, 4.6, 1.9 Hz, 1 H), 1.79–1.70 (m, 3 H) ppm; <sup>13</sup>C NMR [151 MHz, CDCl<sub>3</sub>, data for (*E*)-isomer] δ 176.01, 174.76, 130.92, 128.62, 99.70, 81.10, 69.69, 51.77, 48.25, 41.92, 29.03, 17.94 ppm; HRMS (ESI-TOF): calcd for C<sub>12</sub>H<sub>15</sub>NO<sub>5</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 276.0842, found: 276.0843.

***rel*-(2*aS*,6*S*,6*aR*,6*bS*)-6-[(2*E*)-But-2-enoyl]-6*b*-hydroxyhexahydro-1-oxa-4*a*-azacyclopenta-*[cd]*pentalene-2,5-dione [(±)-**4**]**: To a stirred solution of diol **43** (6.0 mg, 24 μmol, 1.0 equiv) in

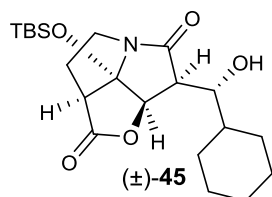


EtOAc (3 mL) at 70 °C was added IBX (40 mg, 140 μmol, 6.0 equiv) and the resulting mixture was stirred for 6 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with Et<sub>2</sub>O (15 mL) and passed through a plug of Celite. The solvent was removed under reduced pressure and the obtained residue was purified by passing

it through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing title compound [(±)-**4**; 3.2 mg, 13 μmol, 54% yield] as a colorless oil.

(±)-**4**: R<sub>f</sub>=0.30 (hexanes:EtOAc, 1:1); IR (film) ν<sub>max</sub> 3422, 2921, 1793, 1721, 1676, 1615, 1424, 1303, 1144, 1114, 1033, 903, 693 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.26 (dq, *J*=15.8, 6.8 Hz, 1 H), 6.33 (dq, *J*=15.8, 1.6 Hz, 1 H), 4.88 (s, 2 H), 4.33 (s, 1 H), 3.83 (ddd, *J*=12.0, 9.4, 5.6 Hz, 1 H), 3.33 (ddd, *J*=12.0, 9.8, 5.2 Hz, 1 H), 3.28 (dd, *J*=9.4, 2.0 Hz, 1 H), 2.74 (dtd, *J*=13.8, 9.6, 5.6 Hz, 1 H), 2.57 (dddd, *J*=14.1, 9.4, 5.2, 2.0 Hz, 1 H), 2.06 (dd, *J*=6.8, 1.6 Hz, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 194.45, 174.95, 167.36, 152.16, 130.72, 100.97, 80.91, 61.42, 47.87, 41.71, 30.07, 19.25 ppm; HRMS (ESI-TOF): calcd for C<sub>12</sub>H<sub>13</sub>NO<sub>5</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 274.0686, found: 274.0687.

***rel*-(2a*S*,6*S*,6a*R*,6b*S*)-6b-*tert*-Butyl(dimethyl)silyloxy-6-[(*S*)-cyclohexyl(hydroxy)methyl]-hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-45]:** To a stirred solution of

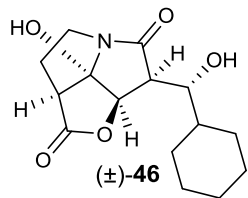


cyclohexane carboxaldehyde (**44**; 54  $\mu$ L, 450  $\mu$ mol, 5.0 equiv) and iodide (±)-**21** (40 mg, 95  $\mu$ mol, 1.0 equiv) in toluene (4 mL) at  $-78^{\circ}\text{C}$  was added  $\text{BET}_3$  (1.0 M in hexanes, 95  $\mu$ L, 95  $\mu$ mol, 1.0 equiv). The resulting mixture

was stirred for 6 h at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (1 mL). The reaction mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 100% hexanes $\rightarrow$ 20% EtOAc in hexanes) providing pure title compound [(±)-**45**; 38 mg, 95  $\mu$ mol, quantitative yield] as a colorless oil.

(±)-**45**:  $R_f = 0.50$  (hexanes:EtOAc, 1:4); IR (film)  $\nu_{\text{max}}$  3502, 2928, 2856, 1792, 1701, 1374, 1306, 1140, 1110, 893  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  4.73 (d,  $J=3.9$  Hz, 1 H), 4.02 (br s, 1 H), 3.88 (d,  $J=9.6$  Hz, 1 H), 3.82–3.75 (m, 1 H), 3.31–3.25 (m, 1 H), 3.15 (dd,  $J=9.7, 3.8$  Hz, 1 H), 3.06 (dd,  $J=8.4, 2.1$  Hz, 1 H), 2.65–2.52 (m, 2 H), 1.83 (d,  $J=12.0$  Hz, 1 H), 1.77 (d,  $J=12.5$  Hz, 1 H), 1.67 (d,  $J=11.6$  Hz, 1 H), 1.62–1.43 (m, 3 H), 1.38 (ddd,  $J=15.2, 10.4, 3.8$  Hz, 1 H), 1.26–1.11 (m, 4 H), 0.89 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  177.7, 175.0, 101.0, 82.0, 71.8, 49.5, 49.2, 42.4, 40.1, 30.0, 29.1, 26.7, 26.61, 26.56, 25.5, 25.3, 17.9,  $-3.2, -3.5$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{21}\text{H}_{35}\text{NO}_5\text{SiNa}^+$   $[\text{M}+\text{Na}]^+$  432.2177 found 432.2169.

***rel*-(2a*S*,6*S*,6a*R*,6b*S*)-6-[(*R*)-Cyclohexyl(hydroxy)methyl]-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-46]:** To a stirred solution of TBS ether (±)-**45** (40 mg,



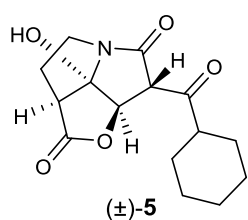
98  $\mu$ mol, 1.0 equiv) in THF (2 mL) at  $0^{\circ}\text{C}$  was added TASF (40 mg, 150  $\mu$ mol, 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 15$  mL) and the combined

organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 30% EtOAc in

hexanes→60% EtOAc in hexanes) providing pure title compound [(±)-**46**; 19 mg, 64 μmol, 66% yield] as a colorless oil.

(±)-**46**:  $R_f = 0.20$  (hexanes:EtOAc, 1:1); IR (film)  $\nu_{\max}$  3385, 2926, 2854, 1788, 1692, 1391, 1332, 1105, 1056  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz, acetone- $d_6$ )  $\delta$  6.19 (s, 1 H), 4.98 (d,  $J = 3.9$  Hz, 1 H), 4.23 (s, 1 H), 3.78–3.67 (m, 2 H), 3.32–3.23 (m, 3 H), 2.73–2.64 (m, 1 H), 2.47–2.38 (m, 1 H), 1.81–1.72 (m, 2 H), 1.72–1.61 (m, 2 H), 1.56–1.46 (m, 3 H), 1.39–1.23 (m, 3 H), 1.18–1.11 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (151 MHz, acetone- $d_6$ )  $\delta$  177.8, 176.0, 100.5, 81.9, 72.5, 49.5, 49.0, 42.0, 40.9, 30.9, 29.7, 27.4, 27.3, 27.0, 25.7 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{15}\text{H}_{21}\text{NO}_5\text{Na}^+$   $[\text{M}+\text{Na}]^+$  318.1312 found 318.1300.

**rel-(2a*S*,6*S*,6a*R*,6b*S*)-6-(Cyclohexylcarbonyl)-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-**5**]**: To a stirred solution of diol (±)-**46** (8.0 mg, 27 μmol,

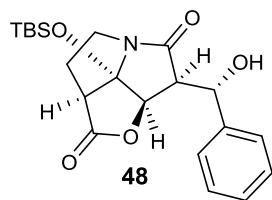


1.0 equiv) in degassed  $\text{CH}_2\text{Cl}_2$  (1 mL) at  $0^\circ\text{C}$  was added an ice cooled solution of DMP (0.1 M solution in  $\text{CH}_2\text{Cl}_2$ , 0.41 mL, 41 μmol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with  $\text{Et}_2\text{O}$  (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica

(gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing pure title compound [(±)-**5**; 5.0 mg, 17 μmol, 63% yield] as a colorless oil.

(±)-**5**:  $R_f = 0.40$  (hexanes:EtOAc, 1:1); IR (film)  $\nu_{\max}$  3442, 2931, 2856, 1790, 1687, 1334, 1310, 1162, 1114, 1025  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  4.75 (s, 1 H), 4.20 (s, 1 H), 3.83 (ddd,  $J = 12.0, 9.5, 5.6$  Hz, 1 H), 3.34 (ddd,  $J = 12.0, 9.8, 5.3$  Hz, 1 H), 3.26 (dd,  $J = 9.4, 1.9$  Hz, 1 H), 2.79–2.68 (m, 2 H), 2.59–2.51 (m, 1 H), 2.02 (d,  $J = 12.2$  Hz, 1 H), 1.95 (d,  $J = 13.1$  Hz, 1 H), 1.86–1.75 (m, 2 H), 1.74–1.66 (m, 1 H), 1.45–1.16 (m, 6 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  209.8, 174.9, 167.3, 101.1, 80.8, 62.9, 51.5, 47.9, 41.9, 30.2, 28.5, 27.1, 25.8, 25.7, 25.1 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{15}\text{H}_{19}\text{NO}_5\text{Na}^+$   $[\text{M}+\text{Na}]^+$  316.1155 found 316.1162.

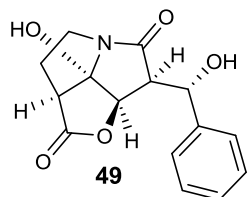
**rel-(2a*S*,6*S*,6a*R*,6b*S*)-6b-{*tert*-Butyl(dimethyl)silyl}oxy}-6-[(*R*)-hydroxy(phenyl)methyl]-hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**48**)**: To a stirred solution of benzaldehyde (**47**; 22 μL, 210 μmol, 3.0 equiv) and iodide (±)-**21** (30 mg, 71 μmol, 1.0 equiv) in toluene (4 mL) at  $-78^\circ\text{C}$  was added  $\text{BEt}_3$  (0.12 mL, 1.0 M in hexanes, 0.12 mmol, 1.1 equiv). The



resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H<sub>2</sub>O (1 mL). The reaction mixture was extracted with Et<sub>2</sub>O (3 × 10 mL) and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 100% hexanes→20% EtOAc in hexanes) providing pure title compound **48** (29 mg, 71 μmol, quantitative yield) as a colorless oil.

**48**: R<sub>f</sub> = 0.30 (hexanes:EtOAc, 4:1); IR (film) ν<sub>max</sub> 3476, 2954, 2901, 2930, 2858, 1790, 1699, 1376, 1301, 1141, 1066, 897, 770 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 7.50 (d, *J* = 7.3 Hz, 2 H), 7.39 (t, *J* = 7.4 Hz, 2 H), 7.34 (t, *J* = 7.3 Hz, 1 H), 5.05 (d, *J* = 9.9 Hz, 1 H), 4.72 (s, 1 H), 4.28 (d, *J* = 3.8 Hz, 1 H), 3.84 (dt, *J* = 11.8, 8.3 Hz, 1 H), 3.26–3.29 (m, 1 H), 3.24 (dd, *J* = 9.9, 3.7 Hz, 1 H), 3.02–2.97 (m, 1 H), 2.64–2.57 (m, 2 H), 0.83 (s, 9 H), 0.10 (s, 3 H), 0.10 (s, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 176.3, 174.8, 140.1, 128.9, 128.6, 126.9, 100.8, 81.9, 71.1, 54.0, 49.3, 42.3, 29.1, 25.5, 17.9, -3.2, -3.5 ppm; HRMS (ESI-TOF): calcd for C<sub>21</sub>H<sub>29</sub>NO<sub>5</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup> 426.1707 found 426.1698.

**rel-(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(*S*)-hydroxy(phenyl)methyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (49)**: To a stirred solution of TBS ether **48** (30 mg, 74 μmol,

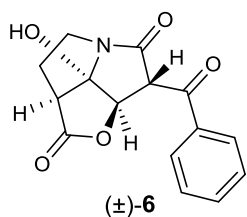


1.0 equiv) in THF (2 mL) at 0 °C was added TASF (40 mg, 150 μmol, 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of H<sub>2</sub>O (2 mL). The reaction mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 30% EtOAc in hexanes→60% EtOAc in hexanes) providing pure title compound (**49**, 12 mg, 41 μmol, 56% yield) as a colorless oil.

**49**: R<sub>f</sub> = 0.11 (hexanes:EtOAc, 1:1); IR (film) ν<sub>max</sub> 3388, 2965, 2904, 1788, 1694, 1394, 1332, 1304, 1162, 1064 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, acetone-*d*<sub>6</sub>) δ 7.48 (d, *J* = 7.2 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 2 H), 7.33 (t, *J* = 7.3 Hz, 1 H), 6.17 (s, 1 H), 4.95 (s, 1 H), 4.94 (t, *J* = 5.0 Hz, 1 H), 4.39 (d, *J* = 3.7 Hz, 1 H), 3.78 (ddd, *J* = 11.5, 9.4, 6.7 Hz, 1 H), 3.42 (dd, *J* = 9.8, 3.6 Hz, 1 H), 3.33 (td, *J* = 10.8, 4.3 Hz, 1 H), 3.25 (d, *J* = 8.9 Hz, 1 H), 2.74–2.63 (m, 1 H), 2.51–2.40 (m, 1 H) ppm; <sup>13</sup>C

NMR (151 MHz, acetone- $d_6$ )  $\delta$  176.4, 175.8, 142.1, 129.2, 128.8, 127.6, 100.2, 81.9, 71.7, 71.6, 54.2, 48.9, 41.9 ppm; HRMS (ESI-TOF): calcd for  $C_{15}H_{15}NO_5Na^+$   $[M+Na]^+$  312.0842 found 312.0837.

***rel*-(2a*S*,6*S*,6a*R*,6b*S*)-6-Benzoyl-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-**6**]**: To a stirred solution of diol **49** (5.0 mg, 17  $\mu$ mol, 1.0 equiv) in degassed  $CH_2Cl_2$

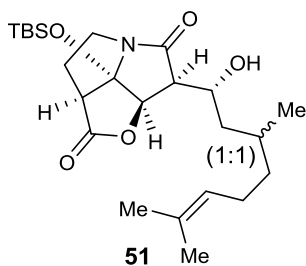


(1 ml) at 0 °C was added an ice cooled solution of DMP (0.1 M solution in  $CH_2Cl_2$ , 0.25 mL, 0.025 mmol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with  $Et_2O$  (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10%  $EtOAc$

in hexanes  $\rightarrow$  50%  $EtOAc$  in hexanes) furnishing pure title compound [(±)-**6**; 3.1 mg, 10  $\mu$ mol, 61% yield] as a colorless oil.

(±)-**6**:  $R_f$  = 0.30 (hexanes: $EtOAc$ , 2:3); IR (film)  $\nu_{max}$  3455, 2631, 1789, 1715, 1663, 1290, 1020  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  8.18 (d,  $J=7.3$  Hz, 2 H), 7.70 (t,  $J=7.4$  Hz, 1 H), 7.57 (t,  $J=7.9$  Hz, 2 H), 5.03 (s, 1 H), 4.98 (s, 1 H), 4.86 (s, 1 H), 3.88 (ddd,  $J=12.1, 9.4, 5.6$  Hz, 1 H), 3.40–3.28 (m, 2 H), 2.78 (tdd,  $J=15.2, 9.7, 5.6$  Hz, 1 H), 2.65–2.53 (m, 1 H) ppm;  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  195.4, 175.1, 167.3, 135.6, 134.7, 130.3, 129.4, 101.1, 81.5, 61.0, 48.1, 42.0, 30.2 ppm; HRMS (ESI-TOF): calcd for  $C_{15}H_{13}NO_5Na^+$   $[M+Na]^+$  310.0686 found 310.0691.

***rel*-(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(1*R*)-1-hydroxy-3,7-dimethyloct-6-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**51**)**: To a stirred

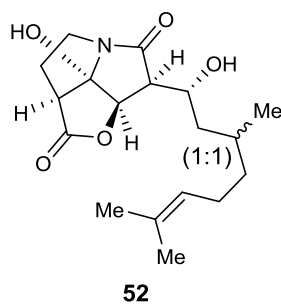


solution of (±)-citronellal (±)-**50** (33 mg, 210  $\mu$ mol, 3.0 equiv) and iodide (±)-**21** (30 mg, 71  $\mu$ mol, 1.0 equiv) in toluene (4 mL) at  $-78$  °C was added  $BEt_3$  (0.12 mL, 1.0 M in hexanes, 0.12 mmol, 1.0 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of  $H_2O$  (1 mL). The reaction mixture was extracted with  $Et_2O$  ( $3 \times 10$  mL) and the combined organic layers were

dried over  $MgSO_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $SiO_2$ , gradient from 100% hexanes  $\rightarrow$  20%  $EtOAc$  in hexanes) providing pure title compound (**51**; 26 mg, 58  $\mu$ mol, 81% yield, ca. 1:1 *dr*) as a colorless oil.

**51:**  $R_f = 0.50$  (hexanes:EtOAc, 1:4); IR (film)  $\nu_{\max}$  3503, 2956, 2930, 2859, 1793, 1702, 1376, 1304, 1141, 839  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , ca. 1:1 *dr*, \*Indicates inclusion of signals of both diastereomers)  $\delta$  5.13–5.08\* (m, 2H), 4.73\* (d,  $J=4.0$  Hz, 2H), 4.19\* (d,  $J=8.3$  Hz, 2H), 4.13–4.06\* (m, 2H), 3.85–3.76\* (m, 2H), 3.33–3.26\* (m, 2H), 3.07\* (dt,  $J=8.1, 2.3$  Hz, 2H), 2.95–2.90\* (m, 2H), 2.64–2.53\* (m, 4H), 2.08–1.81\* (m, 6H), 1.67\* (s, 6H), 1.60\* (s, 6H), 1.57–1.53 (m 1H), 1.50 (tdd,  $J=11.4, 7.8, 4.7$  Hz 1H), 1.44\* (t,  $J=6.6$  Hz, 2H), 1.35–1.18\* (m, 3H), 1.13–1.05 (m, 1H), 0.97 (d,  $J=6.7$  Hz, 3H), 0.93 (d,  $J=6.6$  Hz, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.15 (s, 3H), 0.15 (s, 3H), 0.14 (s, 6H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ , ca. 1:1 *dr*)  $\delta$  177.21, 177.20, 174.9, 174.8, 131.4, 131.3, 125.04, 124.98, 101.0, 100.9, 82.1, 82.0, 66.7, 66.4, 52.7, 52.6, 49.47, 49.46, 42.4, 42.2, 41.8, 38.5, 35.7, 29.1, 28.8, 28.4, 25.9, 25.8, 25.6, 25.5, 20.9, 18.7, 18.0, 17.9, –3.1, –3.5 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{24}\text{H}_{41}\text{NO}_5\text{SiNa}^+$  [ $\text{M}+\text{Na}$ ] $^+$  474.2646 found 474.2644.

***rel*-(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*R*)-1-hydroxy-3,7-dimethyloct-6-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (52):** To a stirred solution of TBS ether **52**

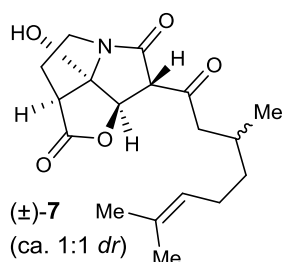


(16 mg, 35  $\mu\text{mol}$ , 1.0 equiv) in THF (2 mL) at 0  $^\circ\text{C}$  was added TASF (14 mg, 53  $\mu\text{mol}$ , 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 15$  mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 30% EtOAc in hexanes  $\rightarrow$  60% EtOAc in hexanes) providing pure title compound (**52**; 8.0 mg, 24  $\mu\text{mol}$ , 68% yield, ca. 1:1 *dr*) as a colorless oil.

**52:**  $R_f = 0.20$  (hexanes:EtOAc, 1:1); IR (film)  $\nu_{\max}$  3363, 2960, 2923, 2854, 1789, 1689, 1379, 1332, 1305, 1072, 1059  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ , ca. 1:1 *dr*, \*Indicates inclusion of signals of both diastereomers)  $\delta$  5.10\* (d,  $J=6.5$  Hz, 2H), 4.84\* (s, 2H), 4.30\* (d,  $J=20.7$  Hz, 2H), 4.11\* (t,  $J=9.5$  Hz, 2H), 4.07\* (br s, 2H), 3.81\* (br s, 2H), 3.35\* (br s, 2H), 3.18\* (d,  $J=9.0$  Hz, 2H), 3.04\* (t,  $J=9.7$  Hz, 2H), 2.69\* (dt,  $J=15.5, 8.8$  Hz, 2H), 2.56\* (t,  $J=9.0$  Hz, 2H), 2.07–1.94\* (m, 3H), 1.91 (dd,  $J=15.0, 8.0$  Hz, 1H), 1.86–1.81\* (m, 2H), 1.68\* (s, 6H), 1.57\* (s, 6H), 1.58–1.50 (m, 1H), 1.52–1.34\* (m, 2H), 1.34–1.16\* (m, 4H), 1.13–1.03 (m, 1H), 0.96 (d,  $J=6.7$  Hz, 3H), 0.92 (d,  $J=6.5$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ , ca. 1:1 *dr*)  $\delta$  176.79,

176.76, 174.94, 174.85, 131.51, 131.46, 124.92, 124.86, 99.88, 99.84, 81.21, 81.17, 66.9, 66.6, 52.45, 52.42, 48.37, 48.36, 42.2, 42.1, 41.7, 38.4, 35.7, 29.2, 28.8, 28.4, 25.9, 25.7, 25.4, 20.8, 18.7, 17.9 ppm; HRMS (ESI-TOF): calcd for C<sub>18</sub>H<sub>27</sub>NO<sub>5</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 360.1781 found 360.1789.

**rel-(2a*S*,6*S*,6a*R*,6b*S*)-6-(3,7-Dimethyloct-6-enoyl)-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-7]:** To a stirred solution of diol (±)-**52** (4.0 mg, 12 μmol,

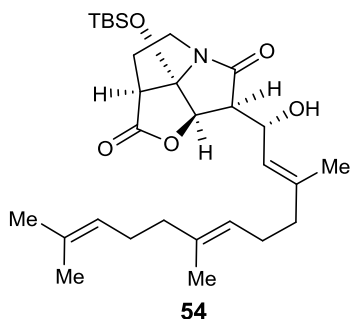


1.0 equiv) in degassed CH<sub>2</sub>Cl<sub>2</sub> (1 ml) at 0 °C was added an ice cooled solution of DMP (0.1 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 0.18 mL, 18 μmol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with Et<sub>2</sub>O (5 mL) and passed through a plug of Celite.

The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing pure title compound [(±)-**7**; 2.5 mg, 7.0 μmol, 63% yield, ca. 1:1 *dr*] as a colorless oil.

(±)-**7**: R<sub>f</sub> = 0.40 (hexanes:EtOAc, 1:1); IR (film) ν<sub>max</sub> 3420, 2962, 2924, 2854, 1794, 1696, 1455, 1377, 1163, 1024 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, ca. 1:1 *dr*, \*Indicates inclusion of signals of both diastereomers) δ 5.07\* (m, 2H), 4.82 (s, 1H), 4.81 (s, 1H), 4.59\* (br s, 2H), 4.04 (s, 1H), 4.03 (s, 1H), 3.83\* (ddd, *J*=12.0, 9.5, 5.5 Hz, 2H), 3.34\* (ddd, *J*=12.1, 9.9, 5.3 Hz, 2H), 3.27\* (dd, *J*=9.4, 1.9 Hz, 2H), 2.87 (dd, *J*=17.7, 6.1 Hz, 1H), 2.80–2.65\* (m, 4H), 2.62–2.52\* (m, 3H), 2.09–1.90\* (m, 6H), 1.69 (s, 3H), 1.68 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H), 1.38–1.30 (m, 1H), 1.30–1.17\* (m, 3H), 0.97 (d, *J*=6.7 Hz, 3H), 0.90 (d, *J*=6.7 Hz, 3H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>, ca. 1:1 *dr*) δ 206.8, 174.9, 167.14, 167.06, 132.21, 132.18, 124.1, 101.2, 80.4, 65.2, 51.3, 51.0, 48.0, 42.0, 36.9, 36.7, 30.2, 28.4, 28.3, 25.93, 25.92, 25.6, 25.5, 19.9, 19.6, 17.91, 17.88 ppm; HRMS (ESI-TOF): calcd for C<sub>18</sub>H<sub>25</sub>NO<sub>5</sub>Na<sup>+</sup> [M+Na]<sup>+</sup> 358.1625 found 358.1631.

**rel-(2a*S*,6*S*,6a*R*,6b*S*)-6b-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(1*R*,2*E*,6*E*)-1-hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-di-**

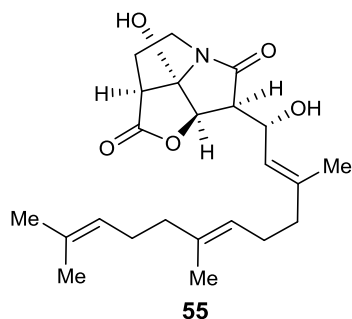


**one (54):** To a stirred solution of aldehyde **53** (220 mg, 1.0 mmol, 3.0 equiv) and iodide (±)-**21** (140 mg, 330 μmol, 1.0 equiv) in toluene (10 mL) at -78 °C was added BEt<sub>3</sub> (330 μL, 1.0 M in hexanes, 330 μmol, 1.0 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H<sub>2</sub>O (1 mL). The reaction mixture was extracted with Et<sub>2</sub>O

(3 × 10 mL) and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 100% hexanes→20% EtOAc in hexanes) providing pure title compound (**54**; 140 mg, 280 μmol, 84% yield) as a colorless oil.

**54**: R<sub>f</sub> = 0.50 (hexanes:EtOAc, 3:7); IR (film) ν<sub>max</sub> 3488, 2955, 2929, 2857, 1792, 1705, 1472, 1375, 1300, 1138, 1069, 892, 837, 779 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.16 (d, *J* = 8.7 Hz, 1H), 5.10–5.06 (m, 2H), 4.74 (t, *J* = 9.4 Hz, 1H), 4.56 (d, *J* = 3.9 Hz, 1H), 4.25 (s, 1H), 3.79 (dt, *J* = 11.8, 8.3 Hz, 1H), 3.32–3.28 (m, 1H), 3.03 (ddd, *J* = 10.5, 7.9, 4.5 Hz, 2H), 2.58 (dd, *J* = 12.7, 5.9 Hz, 2H), 2.17–2.00 (m, 6H), 1.97–1.95 (m, 2H), 1.75 (d, *J* = 0.8 Hz, 3H), 1.67 (s, 3H), 1.59 (s, 3H), 1.59 (s, 3H), 0.88 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 176.9, 174.9, 142.9, 135.6, 131.6, 124.4, 123.9, 122.6, 100.8, 82.3, 65.7, 52.3, 49.4, 42.4, 40.1, 40.0, 29.0, 27.0, 26.4, 25.9, 25.5, 17.92, 17.88, 17.2, 16.2, -3.2, -3.6 ppm; HRMS (ESI-TOF): calcd for C<sub>29</sub>H<sub>47</sub>NO<sub>5</sub>SiNa<sup>+</sup> [M+Na]<sup>+</sup>: 540.3107, found: 540.3116.

**rel-(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*R*,2*E*,6*E*)-1-hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**55**):** To a stirred



solution of TBS ether **54** (80 mg, 150 μmol, 1.0 equiv) in THF (2 mL) at 0 °C was added TBAF (1.0 M in THF, 150 μL, 150 μmol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of sat. aq. NH<sub>4</sub>Cl (1 mL) and H<sub>2</sub>O (2 mL). The reaction mixture was extracted with EtOAc (3 × 25 mL) and the combined organic layers were dried over Na<sub>2</sub>SO<sub>4</sub> and concentrated under reduced pressure. The resulting

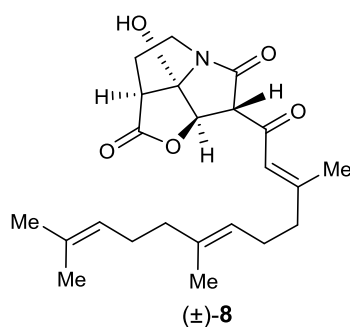
crude product was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 30% EtOAc in hexanes→60% EtOAc in hexanes) providing pure title compound (**55**; 43 mg, 110 μmol, 72% yield) as a colorless oil.

**55**: R<sub>f</sub> = 0.10 (hexanes:EtOAc, 1:1); IR (film) ν<sub>max</sub> 3294, 2964, 2920, 2854, 1792, 1697, 1437, 1384, 1304, 1305, 1064, 1009 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.14–5.05 (m, 3H), 4.76 (t, *J* = 9.5 Hz, 1H), 4.66 (d, *J* = 3.8 Hz, 1H), 4.60 (br s, 1H), 4.57 (s, 1H), 3.80 (ddd, *J* = 11.4, 9.3, 6.8 Hz, 1H), 3.35–3.28 (m, 1H), 3.20 (dd, *J* = 9.7, 3.6 Hz, 1H), 3.12 (d, *J* = 8.1 Hz, 1H), 2.68 (ddd, *J* = 19.0, 12.6, 8.0 Hz, 1H), 2.58–2.50 (m, 1H), 2.15–2.09 (m, 2H), 2.08–2.01 (m, 4H), 1.97 (t, *J* = 7.6 Hz, 2H),



1.76 (s, 3H), 1.68 (s, 3H), 1.60 (s, 6H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  176.3, 175.1, 143.8, 135.8, 131.7, 124.4, 123.7, 122.1, 99.7, 81.5, 66.0, 52.0, 48.3, 41.9, 40.1, 40.0, 29.2, 26.9, 26.6, 25.9, 17.9, 17.2, 16.3 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{23}\text{H}_{33}\text{NO}_5\text{Na}^+$   $[\text{M}+\text{Na}]^+$  426.2251 found 426.2234.

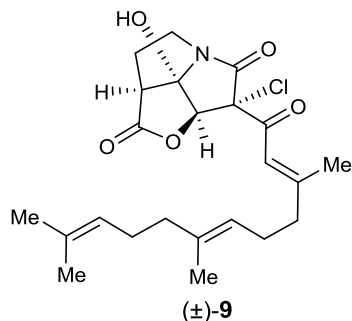
***rel*-(2*aS*,6*S*,6*aR*,6*bS*)-6b-Hydroxy-6-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienoyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-8] and *rel*-(2*aS*,6*S*,6*aS*,6*bS*)-6-chloro-6b-hydroxy-6-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienoyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-9]:** To a stirred solution of diol **55** (10 mg, 25  $\mu\text{mol}$ ,



1.0 equiv) in degassed  $\text{CH}_2\text{Cl}_2$  (1 ml) at  $0^\circ\text{C}$  was added an ice cooled solution of DMP (0.1 M solution in  $\text{CH}_2\text{Cl}_2$ , 370  $\mu\text{L}$ , 37  $\mu\text{mol}$ , 1.5 equiv) and the resulting mixture was stirred for 1.5 h at the same temperature before it was diluted with  $\text{Et}_2\text{O}$  (5 mL) and passed through a plug of Celite. The resulting crude product was purified by preparative TLC ( $\text{SiO}_2$ , 50%  $\text{EtOAc}$  in hexanes) furnishing pure

1,3-dicarbonyl derivative [(±)-8; 2.4 mg, 6.0  $\mu\text{mol}$ , 24% yield] as a colorless oil and chloro-1,3-dicarbonyl compound [(±)-9; 1.2 mg, 3.0  $\mu\text{mol}$ , 11% yield] as a white amorphous solid.

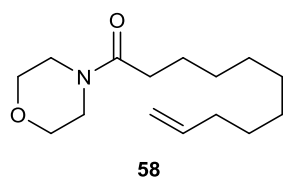
(±)-8:  $R_f=0.30$  (hexanes: $\text{EtOAc}$ , 1:1); IR (film)  $\nu_{\text{max}}$  3426, 2954, 2923, 2854, 1793, 1717, 1666, 1606, 1456, 1377, 1274, 1112, 1024  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.12 (s, 1 H), 5.24–5.21 (m, 1 H), 5.06–5.03 (m, 1 H), 5.00 (br s, 1 H), 4.33 (s, 1 H), 3.70 (s, 1 H), 3.45 (ddd,  $J=11.9, 9.3, 5.8\text{ Hz}$ , 1 H), 2.69 (ddd,  $J=11.9, 9.8, 4.9\text{ Hz}$ , 1 H), 2.65 (dd,  $J=9.3, 1.9\text{ Hz}$ , 1 H), 2.17 (q,  $J=7.4\text{ Hz}$ , 2H), 2.09–2.00 (m, 3H), 1.99–1.92 (m, 5H), 1.88 (dtd,  $J=13.7, 9.6, 5.9\text{ Hz}$ , 1H), 1.82 (t,  $J=7.6\text{ Hz}$ , 2H), 1.70 (d,  $J=1.4\text{ Hz}$ , 3H), 1.59 (d,  $J=1.3\text{ Hz}$ , 3H), 1.52 (d,  $J=1.3\text{ Hz}$ , 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  194.53, 174.42, 167.82, 167.07, 136.63, 131.44, 124.72, 122.96, 122.26, 100.96, 80.54, 66.16, 47.83, 41.63, 40.09, 29.90, 27.12, 26.19, 25.90, 20.32, 17.80, 16.11 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{23}\text{H}_{31}\text{NO}_5\text{Na}^+$   $[\text{M}+\text{Na}]^+$  424.2101 found 424.2085.



(±)-**9**:  $R_f = 0.20$  (hexanes:EtOAc, 1:1); IR (film)  $\nu_{\max}$  3386, 2964, 2854, 1793, 1721, 1646, 1586, 1312, 1262, 1024  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  6.90 (q,  $J = 1.3$  Hz, 1 H), 5.23–1.56 (m, 1 H), 5.09–5.07 (tq,  $J = 7.1, 1.4$  Hz, 1 H), 4.63 (s, 1 H), 3.39 (ddd,  $J = 11.9, 9.3, 5.9$  Hz, 1 H), 2.67 (ddd,  $J = 11.8, 9.8, 5.0$  Hz, 1 H), 2.65 (br s, 1 H), 2.36 (dd,  $J = 9.2, 2.0$  Hz, 1 H), 2.15 (q,  $J = 7.6$  Hz, 2 H), 2.10 (d,  $J = 1.2$  Hz, 3 H), 2.06 (p,  $J = 7.6$  Hz, 4 H), 1.95 (dd,  $J = 8.8, 6.2$  Hz, 2 H), 1.88 (tdd,  $J = 9.3, 4.7, 2.1$  Hz, 1 H), 1.75–1.66 (m, 4 H), 1.58 (s, 3 H), 1.52 (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  185.62, 172.78, 167.67, 165.87, 136.28, 131.25, 124.93, 123.28, 120.19, 98.50, 83.96, 68.03, 48.09, 42.42, 41.87, 40.11, 28.69, 27.20, 26.25, 25.90, 20.75, 17.80, 16.13 ppm; ESI-TOF: calcd for  $\text{C}_{23}\text{H}_{30}\text{ClNO}_5\text{Na}^+ [\text{M}+\text{Na}]^+$ : 458.1705, found: 458.1707.

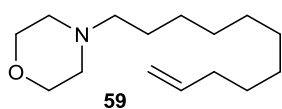
**IBX-oxidation of diol (55)**: To a stirred solution of diol **55** (20 mg, 50  $\mu\text{mol}$ , 1.0 equiv) in EtOAc (3 mL) at 70 °C was added IBX (69 mg, 250  $\mu\text{mol}$ , 5.0 equiv) and the resulting mixture was stirred for 5 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with  $\text{Et}_2\text{O}$  (15 mL) and passed through a plug of Celite. The solvent was removed under reduced pressure and the obtained residue was purified by passing it through a short plug of silica (gradient from 10% EtOAc in hexanes  $\rightarrow$  50% EtOAc in hexanes) furnishing title compound [(±)-**4**; 12 mg, 29  $\mu\text{mol}$ , 58% yield] as a colorless oil.

**1-(Morpholin-4-yl)undec-10-en-1-one (58)**: To a stirred solution of acid **57** (5.00 g, 27.1 mmol, 10 equiv) in  $\text{CH}_2\text{Cl}_2$  (100 mL) at 0 °C was added oxalyl chloride (4.66 mL, 54.3 mmol, 2.0 equiv) and the resulting mixture was slowly warmed to 25 °C. After stirring for 3 h at 25 °C the volatiles were removed and the crude residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (100 mL) was added  $\text{NEt}_3$  (11.3 mL, 81.3 mmol, 3.0 equiv) and morpholine (4.75 mL, 54.3 mmol, 2.0 equiv) at 0 °C. The resulting mixture was stirred at 25 °C for 9 h before it was quenched by the addition of dropwise addition of aq. HCl solution (1 N, 50 mL). The reaction mixture was extracted with EtOAc (3  $\times$  100 mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 10% EtOAc in hexanes  $\rightarrow$  20% EtOAc in hexanes) providing pure title compound (**58**; 5.20 g, 20.5 mmol, 75% yield) as a colorless oil.



**58:**  $R_f=0.60$  (hexanes:EtOAc, 3:2); IR (film)  $\nu_{\max}$  3075, 2923, 2852, 1640, 1427, 1271, 1230, 1115, 909  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.80 (ddt,  $J=16.9, 10.2, 6.7$  Hz, 1 H), 4.98 (dq,  $J=17.1, 1.9$  Hz, 1 H), 4.93–4.91 (m, 1 H), 3.66–3.65 (m, 4 H), 3.61–3.60 (m, 2 H), 3.45 (t,  $J=4.8$  Hz, 2 H), 2.32–2.26 (m, 2 H), 2.07–1.97 (m, 2 H), 1.62 (p,  $J=7.6$  Hz, 2 H), 1.41–1.22 (m, 10 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  171.95, 139.24, 114.21, 67.04, 66.77, 46.14, 41.94, 33.85, 33.20, 29.52, 29.43, 29.40, 29.14, 28.96, 25.32 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{15}\text{H}_{28}\text{NO}_2^+$   $[\text{M}+\text{H}]^+$ : 254.2120, found: 254.2117.

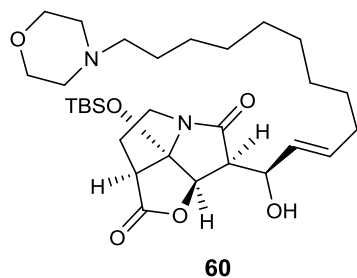
**4-(Undec-10-en-1-yl)morpholine (59):** To a stirred solution of amide **58** (5.00 g, 19.7 mmol,



1.0 equiv) in THF (60 mL) at 0 °C was added  $\text{LiAlH}_4$  (1.0 M in THF, 39.4 mL, 39.4 mmol, 2.0 equiv) and the resulting mixture was removed from the ice bath and slowly warmed to 85 °C. After stirring for 12 h at the same temperature, the resulting mixture was cooled to 0 °C and carefully quenched by the addition of water (5 mL) and aq. 15% NaOH solution (5 mL). The mixture was filtered through Celite and the precipitated salts were washed with EtOAc. The organic layer was dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 30% EtOAc in hexanes→50% EtOAc in hexanes) providing pure amine **59** (3.80 g, 15.8 mmol, 80% yield) as a colorless oil.

**59:**  $R_f=0.30$  (hexanes:EtOAc, 2:3); IR (film)  $\nu_{\max}$  3076, 2925, 2853, 2807, 1640, 1456, 1357, 1119, 910, 866  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.80 (ddt,  $J=16.9, 10.2, 6.7$  Hz, 1 H), 4.98 (dq,  $J=17.1, 1.8$  Hz, 1 H), 4.92 (dq,  $J=10.4, 2.2$  Hz, 1 H), 3.71 (t,  $J=4.7$  Hz, 5 H), 2.43 (t,  $J=4.7$  Hz, 4 H), 2.34–2.27 (m, 2 H), 2.03 (q,  $J=7.1$  Hz, 2 H), 1.51–1.43 (m, 2 H), 1.38–1.34 (m, 2 H), 1.27–1.29 (m, 10 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  139.30, 114.19, 67.10, 59.34, 53.90, 33.89, 29.64, 29.60, 29.52, 29.20, 29.01, 27.61, 26.65 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{15}\text{H}_{30}\text{NO}^+$   $[\text{M}+\text{H}]^+$ : 240.2322, found: 240.2325.

**(2*a*S,6*S*,6*a*R,6*b*S)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(1*R*,2*E*)-1-hydroxy-12-(morpholin-4-yl)dodec-2-en-1-yl]hexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalene-2,5-dione (**60**):** To a

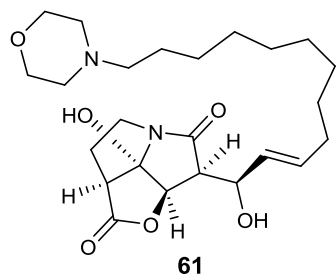


stirred solution of allylic alcohol **42** (100 mg, 270  $\mu\text{mol}$ , 1.0 equiv) and alkene **59** (170 mg, 810  $\mu\text{mol}$ , 6.0 equiv) in dry  $\text{CH}_2\text{Cl}_2$  (5 mL) at 25  $^\circ\text{C}$  was added Grubbs 2<sup>nd</sup> generation catalyst **56** (23 mg, 27  $\mu\text{mol}$ , 0.1 equiv). The resulting reddish-brown mixture was heated to 40  $^\circ\text{C}$ . After 24 h of stirring the volatiles were removed and the crude mixture was purified by flash column chromatography

( $\text{SiO}_2$ , gradient from 20% hexanes $\rightarrow$ 80% EtOAc in hexanes) providing alcohol (**60**; 73 mg, 130  $\mu\text{mol}$ , 48% yield) as a brown oil and allylic alcohol **42** (36 mg, 0.10 mmol) was recovered.

**60**:  $R_f=0.10$  (hexanes:EtOAc, 2:3); IR (film)  $\nu_{\text{max}}$  3481, 2927, 2855, 1791, 1702, 1463, 1301, 116, 837, 780  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.89 (dt,  $J=15.5, 6.8$  Hz, 1 H), 5.45 (ddt,  $J=15.3, 7.2, 1.5$  Hz, 1 H), 4.63 (d,  $J=3.9$  Hz, 1 H), 4.46 (dd,  $J=9.7, 7.2$  Hz, 1 H), 3.80 (dt,  $J=12.0, 8.1$  Hz, 1 H), 3.71 (t,  $J=4.7$  Hz, 4 H), 3.31 (ddd,  $J=12.6, 8.3, 5.4$  Hz, 1 H), 3.05 (dt,  $J=10.8, 5.4$  Hz, 1 H), 3.00 (dd,  $J=9.8, 3.9$  Hz, 1 H), 2.64–2.56 (m, 2 H), 2.43 (s, 4 H), 2.32–2.29 (m, 2 H), 2.06 (q,  $J=7.3$  Hz, 2 H), 1.46 (q,  $J=7.2$  Hz, 2 H), 1.38 (q,  $J=7.4$  Hz, 2 H), 1.27 (br s, 11 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  176.46, 174.81, 135.57, 127.51, 100.78, 82.05, 69.50, 67.07, 59.31, 53.87, 52.15, 49.28, 42.28, 32.37, 29.64, 29.60, 29.48, 29.24, 29.00, 28.95, 27.60, 26.62, 25.43, 17.83,  $-3.27, -3.65$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{30}\text{H}_{53}\text{N}_2\text{O}_6^+$   $[\text{M}+\text{H}]^+$ : 565.3667, found: 565.3675.

**(2*a*S,6*S*,6*a*R,6*b*S)-6b-Hydroxy-6-[(1*R*,2*E*)-1-hydroxy-12-(morpholin-4-yl)dodec-2-en-1-yl]-hexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalene-2,5-dione (**61**):** To a stirred solution of TBS

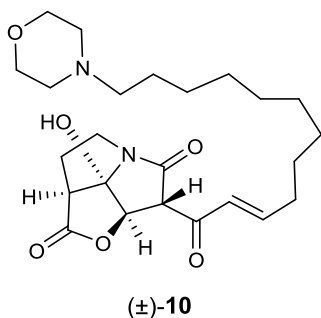


ether **60** (54 mg, 100  $\mu\text{mol}$ , 1.0 equiv) in THF 3 mL at 0  $^\circ\text{C}$  was added TBAF (1.0 M in THF, 100  $\mu\text{L}$ , 100  $\mu\text{mol}$ , 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  solution (2 mL) and  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with EtOAc (3 $\times$ 5 mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and

concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 30% EtOAc in hexanes $\rightarrow$ 100% EtOAc) providing pure title compound (**61**; 27 mg, 62  $\mu\text{mol}$ , 62% yield) as a colorless oil.

**61**:  $R_f=0.50$  (MeOH:CH<sub>2</sub>Cl<sub>2</sub>, 1:9); IR (film)  $\nu_{\max}$  3384, 2924, 2855, 1786, 1688, 1637, 1387, 1114, 1056, 1033, 733 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  5.87 (dd,  $J=15.0, 7.4$  Hz, 1 H), 5.44 (dd,  $J=15.4, 7.3$  Hz, 1 H), 4.71 (d,  $J=3.8$  Hz, 1 H), 4.52–4.45 (m, 2 H), 3.87 (ddd,  $J=11.8, 9.2, 6.0$  Hz, 1 H), 3.71 (t,  $J=4.6$  Hz, 4 H), 3.39–3.30 (m, 1 H), 3.14 (d,  $J=9.0$  Hz, 1 H), 3.02 (dd,  $J=9.9, 3.8$  Hz, 1 H), 2.75–2.64 (m, 2 H), 2.61–2.28 (m, 7 H), 2.10 (hept,  $J=7.3$  Hz, 2 H), 1.59–1.38 (m, 2 H), 1.44–1.46 (m, 2 H), 1.38–1.24 (m, 10 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  175.60, 175.02, 135.34, 128.09, 99.49, 81.63, 69.64, 66.39, 59.30, 53.72, 51.97, 48.45, 41.83, 31.51, 29.19, 28.78, 28.72, 28.14, 27.97, 27.88, 26.73, 26.08 ppm; HRMS (ESI-TOF): calcd for C<sub>24</sub>H<sub>39</sub>N<sub>2</sub>O<sub>6</sub><sup>+</sup> [M+H]<sup>+</sup>: 451.2803, found: 451.2807.

**rel-(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(2*E*)-12-(morpholin-4-yl)dodec-2-enoyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-10]**: To a stirred solution of diol **61** (5.0 mg,



11  $\mu$ mol, 1.0 equiv) in EtOAc (2 ml) at 25 °C was added IBX (15 mg, 55  $\mu$ mol, 5.0 equiv) and the resulting mixture was heated at 70 °C for 2 h. The reaction mixture was filtered through Celite and washed with EtOAc. The solvent was removed under reduced pressure and the obtained residue was purified by preparative TLC using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> furnishing morpholine analog [(±)-**10**, 1.2 mg, 2.6  $\mu$ mol, 24%

yield, ~90% purity] as a colorless oil.

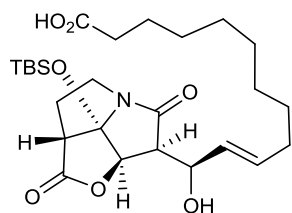
(±)-**10**:  $R_f=0.61$  (MeOH:CH<sub>2</sub>Cl<sub>2</sub>, 1:9); IR (film)  $\nu_{\max}$  3433, 2923, 2852, 2766, 1790, 1699, 1457, 1118, 866 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$  7.28 (dt,  $J=15.9, 6.6$  Hz, 1 H), 6.29 (d,  $J=15.9$  Hz, 1 H), 4.89 (s, 1 H), 4.33 (s, 1 H), 3.83 (ddd,  $J=12.1, 9.4, 5.6$  Hz, 1 H), 3.74 (t,  $J=4.7$  Hz, 5 H), 3.33 (ddd,  $J=12.0, 9.7, 5.1$  Hz, 1 H), 3.28 (dd,  $J=9.4, 2.0$  Hz, 1 H), 2.77–2.71 (m, 1 H), 2.57 (dddd,  $J=11.3, 7.1, 5.4, 2.0$  Hz, 1 H), 2.49 (s, 4 H), 2.35 (p,  $J=7.3$  Hz, 4 H), 1.54–1.49 (m, 2 H), 1.37–1.25 (m, 12 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  194.61, 174.96, 167.39, 157.04, 129.02, 100.96, 80.94, 66.81, 61.46, 59.16, 53.68, 47.89, 41.73, 33.29, 30.07, 29.79, 29.54, 29.45, 29.33, 29.22, 27.82, 27.52 ppm; HRMS (ESI-TOF): calcd for C<sub>24</sub>H<sub>37</sub>N<sub>2</sub>O<sub>6</sub><sup>+</sup> [M+H]<sup>+</sup>: 435.2490, found: 435.2501.

**Trimethylsilyl undec-10-enoate (62)**: To a stirred solution of undec-10-enoic acid (5.27 g, 28.6  $\mu$ mol, 1.0 equiv) in dry THF (30 mL) was added Et<sub>3</sub>N (3.99 mL, 2.90 g, 28.6  $\mu$ mol, 1.0 equiv) and the reaction mixture was cooled to 0 °C. TMSCl (3.63 mL, 3.11 g, 28.6  $\mu$ mol, 1.0 equiv) was added and the reaction was allowed to warm to 25 °C

and stirred for 1 h at this temperature. Then, the resulting mixture was filtered through a sintered funnel under argon atmosphere, the filtrate was washed with dry THF (10 mL) and the residue was concentrated under reduced pressure. Distillation under reduced pressure (120 °C, 5.3 mbar) gave product **62** (6.07 g, 23.7 mmol, 83% yield) as a colorless liquid.

**62**: IR (film)  $\nu_{\max}$  = 2926, 2855, 1717, 1641, 1252, 1188, 909, 846, 762, 729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.81 (ddt,  $J$  = 17.0, 10.2, 6.7 Hz, 1 H), 4.99 (dq,  $J$  = 17.0, 1.8 Hz, 1 H), 4.92 (ddt,  $J$  = 10.2, 2.3, 1.2 Hz, 1 H), 2.29 (t,  $J$  = 7.5 Hz, 2 H), 2.03 (tdd,  $J$  = 8.0, 6.1, 1.4 Hz, 2 H), 1.58 (p,  $J$  = 6.9 Hz, 2 H), 1.37 (p,  $J$  = 6.9 Hz, 2 H), 1.34–1.21 (m, 8 H), 0.28 (s, 9 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  174.65, 139.33, 114.28, 36.08, 33.94, 29.45, 29.39, 29.22, 29.21, 29.05, 25.12, –0.07 ppm; HRMS (CI): calcd for  $\text{C}_{14}\text{H}_{29}\text{O}_2\text{Si}^+$  [ $\text{M}$ ] $^+$ : 257.1937, found: 257.1930.

**(10E,12R)-12-[(2aR,6S,6aR,6bS)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-2,5-dioxooctahydro-1-oxa-4a-azacyclopenta[*cd*]pentalen-6-yl]-12-hydroxydodec-10-enoic acid (**63**):** To a stirred



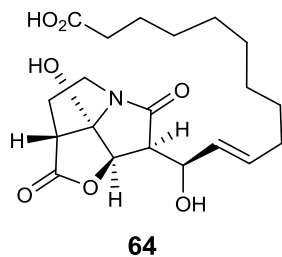
**63**

solution of ( $\pm$ )-**42** (300 mg, 709  $\mu\text{mol}$ , 1.0 equiv) in dry  $\text{CH}_2\text{Cl}_2$  was added **62** (546 mg, 2.13 mmol, 3.0 equiv), the reaction mixture was degassed by purging with Ar for 10 min, followed by the addition of Grubbs II catalyst (60.0 mg, 0.142 mmol, 0.20 equiv) and heated to 40 °C for 16 h. The crude reaction mixture was then concentrated under reduced

pressure and purification of the residue by flash column chromatography ( $\text{SiO}_2$ , hexanes:EtOAc, 8:2 $\rightarrow$ 1:1) gave product **63** (229 mg, 449  $\mu\text{mol}$ , 63% yield) as a colorless liquid.

**63**:  $R_f$  = 0.55 (hexanes:EtOAc, 1:1); IR (film)  $\nu_{\max}$  = 3475, 2929, 2856, 1793, 1706, 1463, 1378, 1303, 1253, 1142, 1094, 839, 781  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.89 (dtd,  $J$  = 14.9, 6.8, 0.9 Hz, 1 H), 5.46 (ddt,  $J$  = 15.4, 7.3, 1.5 Hz, 1 H), 4.64 (d,  $J$  = 3.9 Hz, 1 H), 4.51–4.39 (m, 1 H), 3.81 (dt,  $J$  = 12.1, 8.0 Hz, 1 H), 3.37–3.23 (m, 1 H), 3.10–3.05 (m, 1 H), 3.02 (dd,  $J$  = 9.8, 3.9 Hz, 1 H), 2.65–2.54 (m, 2 H), 2.34 (t,  $J$  = 7.4 Hz, 2 H), 2.11–2.03 (m, 2 H), 1.62 (p,  $J$  = 7.4 Hz, 2 H), 1.45–1.22 (m, 13 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  178.71, 176.52, 174.94, 135.71, 127.55, 100.86, 82.11, 69.64, 52.16, 49.35, 42.34, 34.00, 32.37, 29.20, 29.16, 29.03, 29.02, 29.00, 28.94, 25.49, 24.76, 17.89, –3.21, –3.58 ppm; HRMS (ESI): calcd for  $\text{C}_{26}\text{H}_{43}\text{NO}_7\text{SiNa}^+$  [ $\text{M}+\text{Na}$ ] $^+$ : 532.2701, found: 532.2704.

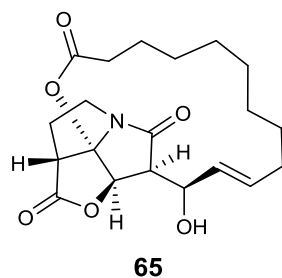
**(10*E*,12*R*)-12-Hydroxy-12-[(2*aR*,6*S*,6*aR*,6*bS*)-6*b*-hydroxy-2,5-dioxooctahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalen-6-yl]dodec-10-enoic acid (**64**):**



0.432 mmol, 1.0 equiv) in THF (11 mL) at 0 °C was added AcOH (50  $\mu$ L, 0.864 mmol, 2.0 equiv) followed by TBAF (1 M in THF, 430  $\mu$ L, 0.432 mmol, 1.0 equiv) and the reaction was stirred for 6 h at 0 °C before it was quenched by addition of satd. aq.  $\text{NH}_4\text{Cl}$  (10 mL), and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic extracts were dried over anhyd.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography ( $\text{SiO}_2$ , hexanes:EtOAc, 1:1  $\rightarrow$  0:1  $\rightarrow$  EtOAc with 1% HCOOH) to yield product **64** (140 mg, 354  $\mu$ mol, 82% yield) as a colorless oil.

**64**:  $R_f = 0.35$  (EtOAc); IR (film)  $\nu_{\text{max}} = 3375, 2924, 2852, 1792, 1702, 1388, 1333, 1305, 1163, 1092, 1060, 1010 \text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.87 (dt,  $J = 15.8, 6.9$  Hz, 1 H), 5.44 (ddt,  $J = 15.3, 7.4, 1.5$  Hz, 1 H), 4.73 (d,  $J = 4.0$  Hz, 1 H), 4.49 (dd,  $J = 9.9, 7.4$  Hz, 1 H), 3.83 (ddd,  $J = 11.9, 9.3, 6.2$  Hz, 1 H), 3.42–3.28 (m, 1 H), 3.24 (dd,  $J = 10.0, 4.0$  Hz, 1 H), 3.22–3.15 (m, 1 H), 2.69 (dtd,  $J = 13.7, 9.5, 6.2$  Hz, 1 H), 2.55 (dddd,  $J = 13.9, 9.4, 4.8, 2.0$  Hz, 1 H), 2.42–2.24 (m, 2 H), 2.14–2.01 (m, 2 H), 1.67–1.56 (m, 2 H), 1.40 (pd,  $J = 6.9, 2.5$  Hz, 2 H), 1.36–1.19 (m, 10 H) ppm;  $^{13}\text{C NMR}$  (151 MHz,  $\text{CDCl}_3$ )  $\delta$  178.35, 175.98, 175.24, 135.99, 127.63, 99.74, 81.41, 69.99, 51.78, 48.32, 41.83, 33.97, 31.95, 29.16, 28.80, 28.61, 28.37, 28.27, 28.12, 24.72 ppm; HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{29}\text{NO}_7\text{Na}^+$  [ $\text{M}+\text{Na}$ ] $^+$ : 418.1836, found: 418.1836.

**(3*aR*,5*aR*,6*S*,7*R*,8*E*,19*aS*)-7-Hydroxy-3,3*a*,6,7,10,11,12,13,14,15,16,17-dodecahydro-1,6-methanooxacyclohexadecino[3',2':2,3]furo[3,4-*b*]pyrrole-4,18,20(2*H*,5*aH*)-trione (**65**):**

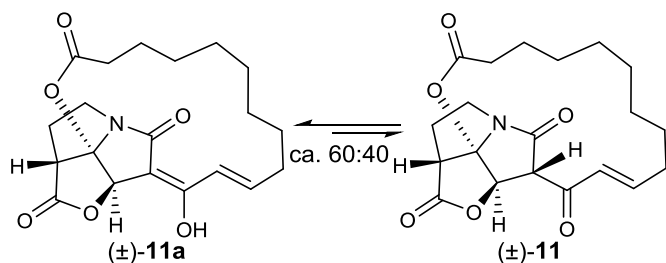


0.432 mmol, 1.0 equiv) in THF (11 mL) at 0 °C was added AcOH (50  $\mu$ L, 0.864 mmol, 2.0 equiv) followed by TBAF (1 M in THF, 430  $\mu$ L, 0.432 mmol, 1.0 equiv) and the reaction was stirred for 6 h at 0 °C before it was quenched by addition of satd. aq.  $\text{NH}_4\text{Cl}$  (10 mL), and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 50$  mL). The combined organic extracts were dried over anhyd.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography ( $\text{SiO}_2$ , hexanes:EtOAc, 1:1  $\rightarrow$  0:1  $\rightarrow$  EtOAc with 1% HCOOH) to yield product **64** (140 mg, 354  $\mu$ mol, 82% yield) as a colorless oil.

stirred solution of 2-methyl-6-nitrobenzoic anhydride (31 mg, 88  $\mu$ mol, 1.4 equiv) and 4-dimethylaminopyridine (23 mg, 190  $\mu$ mol, 3.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (40 mL) at 25 °C was added dropwise a solution of **64** (25 mg, 63  $\mu$ mol, 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (20 mL) over 10 h and the reaction mixture was stirred for further 1 h. Then, it was washed sequentially with satd. aq.  $\text{NaHCO}_3$  (20 mL), aq. HCl (0.2 M; 20 mL) and brine (20 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered and concentrated under reduced pressure. Flash column chromatography of the residue ( $\text{SiO}_2$ , hexanes:EtOAc, 7:3  $\rightarrow$  1:1) gave product **65** (20 mg, 53  $\mu$ mol, 84% yield) as colorless liquid.

**65**:  $R_f=0.63$  (EtOAc); IR (film)  $\nu_{\max}=3493, 2927, 2854, 1795, 1713, 1459, 1376, 1339, 1220, 1157, 1103, 1057, 1027, 731\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  (600 MHz,  $\text{CDCl}_3$ )  $\delta$  5.89 (dddd,  $J=15.2, 10.1, 4.9, 1.4\text{ Hz}$ , 1H), 5.62 (dd,  $J=15.6, 4.5\text{ Hz}$ , 1H), 5.05 (d,  $J=4.0\text{ Hz}$ , 1H), 4.54 (ddt,  $J=9.1, 4.3, 1.4\text{ Hz}$ , 1H), 4.24 (t,  $J=1.3\text{ Hz}$ , 1H), 3.98–3.85 (m, 2H), 3.33 (dddd,  $J=11.8, 9.3, 5.3, 1.1\text{ Hz}$ , 1H), 2.90 (dd,  $J=9.7, 4.0\text{ Hz}$ , 1H), 2.68–2.50 (m, 2H), 2.45 (ddd,  $J=14.2, 6.2, 4.0\text{ Hz}$ , 1H), 2.40–2.25 (m, 2H), 1.93 (dtd,  $J=13.6, 10.7, 3.1\text{ Hz}$ , 1H), 1.76–1.61 (m, 2H), 1.53–1.45 (m, 1H), 1.41 (hept,  $J=5.7\text{ Hz}$ , 2H), 1.34–1.12 (m, 3H), 1.02 (ddt,  $J=18.5, 13.2, 6.2\text{ Hz}$ , 1H) ppm;  $^{13}\text{C NMR}$  (151 MHz,  $\text{CDCl}_3$ )  $\delta$  175.41, 174.11, 174.09, 131.95, 129.93, 103.03, 77.86, 66.71, 54.23, 46.04, 42.26, 34.55, 31.99, 29.12, 29.11, 28.42, 27.91, 27.54, 27.33, 25.73 ppm; HRMS (ESI): calcd for  $\text{C}_{20}\text{H}_{27}\text{NO}_6\text{SiNa}^+ [\text{M}+\text{Na}]^+$ : 400.1731, found: 400.1733.

**rel-(3aR,5aR,6S,8E,19aS)-3,3a,5a,6,10,11,12,13,14,15,16,17-Dodecahydro-1,6-methanooxacyclohexadecino[3',2':2,3]furo[3,4-b]pyrrole-4,7,18,20(2H)-tetrone [(±)-11] and rel-(3aR,5aR,6E,8E,19aS)-7-hydroxy-3,3a,10,11,12,13,14,15,16,17-decahydro-1,6-methanooxacyclohexadecino[3',2':2,3]furo[3,4-b]pyrrole-4,18,20(2H,5aH)-trione [(±)-11a]**: To a stirred



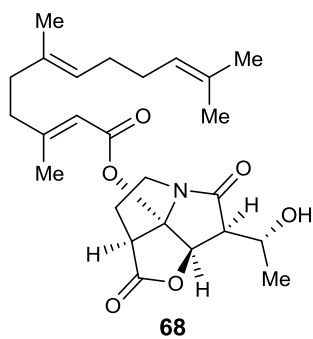
solution of diol **65** (5.0 mg, 13  $\mu\text{mol}$ , 1.0 equiv) in EtOAc (1 ml) at 25  $^{\circ}\text{C}$  was added IBX (19 mg, 67  $\mu\text{mol}$ , 5.0 equiv) and the resulting mixture was heated at 70  $^{\circ}\text{C}$  for 7 h. The reaction mixture was filtered

through Celite and washed with EtOAc. The solvent was removed under reduced pressure and the obtained residue was purified by preparative TLC using 2% MeOH in  $\text{CH}_2\text{Cl}_2$  furnishing morpholine analog [(±)-**11** and (±)-**11a**]; 2.4 mg, 6.4  $\mu\text{mol}$ , 48% yield, ~90% purity, ~60:40 mixture of enol and diketone] as a colorless oil.

(±)-**11** and (±)-**11a**:  $R_f=0.30$  (hexanes:EtOAc, 2:3); IR (film)  $\nu_{\max} 2928, 2855, 1791, 1732, 1684, 1619, 1389, 1336, 1128, 1038, 800\text{ cm}^{-1}$ ;  $^1\text{H NMR}$  [600 MHz,  $\text{C}_6\text{D}_6$ , ~60:40 mixture of enol and 1,3-diketone, \*Indicates signals corresponding to the enol compound (±)-**11a**]  $\delta$  11.44\* (br s, 0.6H), 6.97 (ddd,  $J=15.2, 10.3, 4.7\text{ Hz}$ , 0.4H), 6.63\* (dd,  $J=15.3, 1.8\text{ Hz}$ , 0.4H), 6.44\* (ddd,  $J=15.3, 10.1, 5.9\text{ Hz}$ , 0.6H), 5.77\* (d,  $J=15.7\text{ Hz}$ , 0.6H), 5.49\* (s, 0.6H), 5.24 (s, 0.4H), 3.61 (ddd,  $J=11.3, 9.6, 4.8\text{ Hz}$ , 0.4H), 3.56\* (dd,  $J=9.9, 4.2\text{ Hz}$ , 0.6H), 3.47–3.40\* (m, 0.6H), 3.39 (s, 0.4H), 3.02–2.95\* (m, 0.4H), 2.77–2.66 (m, 1H), 2.22–1.54 (m, 7H), 1.33–0.86 (m, 10H), 0.72–0.66 (m, 1H) ppm;  $^{13}\text{C NMR}$  (151 MHz,  $\text{C}_6\text{D}_6$ , ~60:40 mixture of enol and 1,3-diketone)  $\delta$  187.92,



174.34, 174.02, 173.88, 171.93, 165.99, 151.86, 143.15, 125.78, 123.16, 105.27, 103.69, 100.21, 80.85, 77.16, 63.26, 47.95, 46.75, 45.78, 44.28, 34.52, 34.31, 32.11, 31.52, 31.32, 29.36, 28.09, 28.03, 27.73, 27.36, 26.66, 26.55, 26.32, 26.26, 26.11, 25.93, 24.53 ppm; HRMS (ESI-TOF): calcd for C<sub>20</sub>H<sub>25</sub>NO<sub>6</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 398.1574, found: 398.1576.

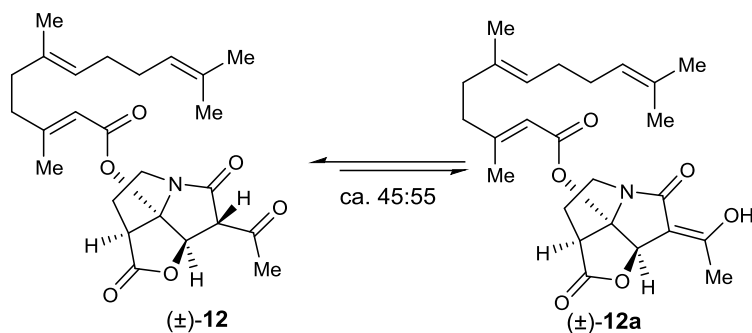


**(2a*S*,6*S*,6a*R*,6b*S*)-6-[(1*R*)-1-Hydroxyethyl]-2,5-dioxohexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalen-6b(5*H*)-yl (2*E*,6*E*)-3,6,11-trimethyldodeca-2,6,10-trienoate (68):** To a stirred solution of diol **40** (22.5 mg, 100 μmol, 1.0 equiv) and farnesoic acid **66** (23.9 mg, 100 μmol, 1.0 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at 0 °C was added Et<sub>3</sub>N (45.0 μL, 300 μmol, 3.0 equiv), 2,4,6-trichlorobenzoic anhydride (15.6 μL, 100 μmol, 1.0 equiv) and 4-dimethylaminopyridine (24.4 mg,

200 μmol, 2.0 equiv). After stirring for an additional 3 h, the reaction mixture was washed sequentially with sat. aq. NaHCO<sub>3</sub> solution (5 mL), sat. aq. NH<sub>4</sub>Cl (0.5 M; 3 mL), and brine (5 mL). The organic layer was dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated under reduced pressure. The resultant crude product was purified by flash column chromatography (SiO<sub>2</sub>; hexanes:EtOAc: 3:1) yielded pure title compound (**68**; 17.4 mg, 39.1 μmol, 39% yield) as a colorless oil.

**68:** R<sub>f</sub>=0.60 (hexanes:EtOAc, 2:1); IR (film) ν<sub>max</sub> 3502, 2971, 2915, 2856, 1791, 1705, 1638, 1476, 1051 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 5.67 (s, 1 H), 5.15 (d, *J*=4.6 Hz, 1 H), 5.11–5.01 (m, 2 H), 4.25 (s, 1 H), 4.13 (dq, *J*=9.6, 6.1 Hz, 1 H), 3.99 (ddd, *J*=11.5, 9.5, 4.8 Hz, 1 H), 3.57 (dd, *J*=9.9, 2.6 Hz, 1 H), 3.40 (td, *J*=10.4, 5.8 Hz, 1 H), 3.17 (dd, *J*=9.6, 4.6 Hz, 1 H), 2.80 (dtd, *J*=14.3, 9.7, 4.8 Hz, 1 H), 2.48 (dtd, *J*=13.2, 6.2, 3.0 Hz, 1 H), 2.28–2.13 (m, 7 H), 2.06 (q, *J*=7.3 Hz, 2 H), 1.99 (dd, *J*=9.1, 6.2 Hz, 2 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.59 (s, 3 H), 1.32 (d, *J*=6.1 Hz, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 177.11, 174.69, 165.88, 164.66, 136.73, 131.61, 124.15, 122.46, 113.70, 102.31, 79.43, 64.98, 52.81, 47.77, 43.86, 41.34, 39.74, 30.54, 26.75, 25.92, 25.78, 20.49, 19.39, 17.77, 16.14 ppm; HRMS (ESI-TOF): calcd for C<sub>25</sub>H<sub>35</sub>NO<sub>6</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 468.2357, found: 468.2361.

*rel*-(2*aS*,6*S*,6*aR*,6*bS*)-6-Acetyl-2,5-dioxohexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalen-6*b*-(5*H*)-yl (2*E*,6*E*)-3,6,11-trimethyldodeca-2,6,10-trienoate [(±)-**12**] and *rel*-(2*aS*,6*Z*,6*aR*,6*bS*)-6-(1-Hydroxyethylidene)-2,5-dioxohexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalen-6*b*(5*H*)-yl (2*E*,6*E*)-3,6,11-trimethyldodeca-2,6,10-trienoate [(±)-**12a**]: To a stirred solution of diol **68**

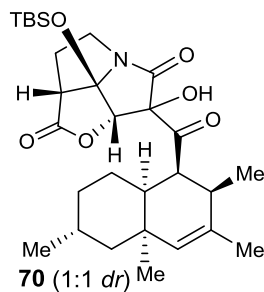


(3 mg, 8  $\mu$ mol, 1.0 equiv) in EtOAc (1 ml) at 25 °C was added IBX (10 mg, 40  $\mu$ mol, 5.0 equiv) and the resulting mixture was heated at 70 °C for 6 h. The reaction mixture was filtered through Celite and washed with EtOAc. The solvent was

removed under reduced pressure and the obtained residue was purified by preparative TLC using 5% MeOH in CH<sub>2</sub>Cl<sub>2</sub> furnishing analog (±)-**12** and (±)-**12a** (1.4 mg, 3.7  $\mu$ mol, 47% yield, ~90% purity, ~55:45 mixture of enol and 1,3-diketone, ~90% purity) as a colorless oil.

(±)-**12** and (±)-**12a**:  $R_f$ =0.40 (hexanes:EtOAc, 1:2); IR (film)  $\nu_{\max}$  2966, 2921, 2856, 1790, 1716, 1682, 1643, 1361, 1125, 1054 cm<sup>-1</sup>; <sup>1</sup>H NMR [600 MHz, CDCl<sub>3</sub>, ~55:45 mixture of enol and 1,3-diketone, \*Indicates inclusion of signals corresponding to the (±)-**12** and (±)-**12a**]  $\delta$  11.66 (s, 1H), 5.67\* (s, 2H), 5.56 (s, 1H), 5.53 (s, 1H), 5.09–5.06\* (m, 4H), 4.03–3.97\* (m, 2H), 3.75 (s, 1H), 3.69–3.60\* (m, 2H), 3.50 (dt,  $J$ =11.6, 8.3 Hz, 1H), 3.40 (ddd,  $J$ =11.8, 9.2, 6.6 Hz, 1H), 2.82–2.70\* (m, 2H), 2.52–2.34\* (m, 6H), 2.26–2.14\* (m, 16H), 2.14–1.92\* (m, 8H), 1.68\* (s, 6H), 1.61\* (s, 6H), 1.60\* (s, 6H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>, ~55:45 mixture of enol and 1,3-diketone)  $\delta$  <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$  197.87, 175.49, 175.03, 174.63, 169.82, 165.52, 165.10, 164.92, 136.66, 136.65, 136.41, 131.60, 131.56, 131.54, 124.26, 124.22, 124.18, 122.78, 122.54, 114.60, 114.05, 113.80, 103.74, 103.45, 101.38, 79.34, 78.45, 64.77, 48.38, 47.53, 46.49, 44.76, 41.34, 41.30, 41.23, 39.75, 32.38, 31.03, 28.68, 26.75, 26.01, 25.97, 25.93, 25.77, 19.39, 19.34, 19.16, 18.91, 17.77, 16.12 ppm; HRMS (ESI-TOF): calcd for C<sub>25</sub>H<sub>33</sub>NO<sub>6</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 466.2200, found: 466.2212.

**(2aR,6aS,6bR)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-hydroxy-6-[(1S,2R,4aS,6R,8aS)-2,3,4a,6-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]carbonyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**70**):**

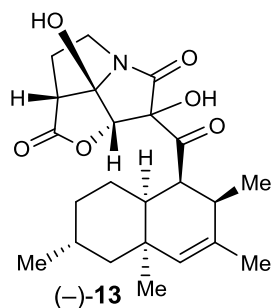


(16 mg, 31  $\mu\text{mol}$ , 1.0 equiv) in  $\text{CH}_2\text{Cl}_2$  (1.6 mL) at  $0^\circ\text{C}$  was added DMP (40 mg, 93  $\mu\text{mol}$ , 3.0 equiv) and the resulting mixture was stirred for 45 min at  $25^\circ\text{C}$  before it was diluted with  $\text{Et}_2\text{O}$  (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes  $\rightarrow$  50% EtOAc in hexanes) furnishing pure hydroxy TBS ether **70** (10 mg, 19  $\mu\text{mol}$ , 61%, ca.

1:1 *dr*) as a colorless oil.

**70:**  $R_f = 0.27$  (hexanes:EtOAc, 1:4); IR (film)  $\nu_{\text{max}}$  3378, 2951, 2927, 2859, 1795, 1722, 1462, 1376, 1331, 1253, 1134, 840  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{C}_6\text{D}_6$ , ca. 1:1 *dr*, \*Indicates signals for the other diastereomer)  $\delta$  5.16 (s, 1 H), 5.11 (s, 1 H), 4.89 (s, 1 H), 4.47 (dd,  $J = 6.9, 2.2$  Hz, 1 H), 3.97 (s, 1 H), 3.83 (ddd,  $J = 12.1, 9.8, 5.4$  Hz, 1 H), 3.70 (s, 1 H), 3.50 (ddd,  $J = 12.1, 9.5, 6.0$  Hz, 1 H), 3.21 (dt,  $J = 14.2, 7.0$  Hz, 1 H), 2.90–2.84 (m, 1 H), 2.84–2.74\* (m, 2 H), 2.71 (dd,  $J = 9.5, 1.9$  Hz, 1 H), 2.56–2.46\* (m, 2 H), 2.41 (dd,  $J = 9.3, 1.7$  Hz, 1 H), 2.12–1.98\* (m, 3 H), 1.92–1.79\* (m, 3 H), 1.76\* (s, 3 H), 1.71\* (s, 3 H), 1.71–1.64\* (m, 2 H), 1.63–1.42\* (m, 4 H), 1.49 (s, 3 H), 1.40 (d,  $J = 7.5$  Hz, 3 H), 1.28 (d,  $J = 7.5$  Hz, 3 H), 1.21 (s, 3 H), 1.16–0.90\* (m, 8 H), 1.00 (s, 9 H), 0.96 (s, 9 H), 0.92 (d,  $J = 6.7$  Hz, 3 H), 0.91 (d,  $J = 8.0$  Hz, 3 H), 0.19 (s, 3 H), 0.09 (s, 3 H), 0.07 (s, 3 H), 0.04 (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{C}_6\text{D}_6$ , ca. 1:1 *dr*)  $\delta$  208.3, 205.9, 173.9, 173.6, 171.9, 170.4, 135.5, 135.1, 131.2, 130.9, 101.8, 99.6, 86.5, 85.8, 84.6, 82.5, 50.73, 50.69, 50.3, 49.3, 48.5, 44.9, 43.1, 42.9, 42.5, 41.6, 37.6, 37.4, 35.9, 35.8, 34.4, 34.1, 31.8, 31.2, 29.9, 29.8, 29.4, 27.9, 26.0, 26.0, 25.8, 25.7, 22.9, 22.8, 22.6, 22.2, 18.24, 18.22, 16.9, 16.8,  $-3.4, -3.5, -3.7, -3.9$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{29}\text{H}_{45}\text{NO}_6\text{SiNa}^+$   $[\text{M}+\text{Na}]^+$  554.2908 found 554.2920.

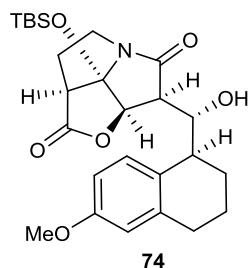
**(2aR,6aS,6bR)-6,6b-Dihydroxy-6-[(1S,2R,4aS,6R,8aS)-2,3,4a,6-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl]carbonyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(–)-**13**]:** To a stirred solution of hydroxy TBS ether **70** (4.0 mg, 7.8  $\mu\text{mol}$ , 1.0 equiv) in THF (0.5 mL) at  $25^\circ\text{C}$  was added a drop of DMF and TASF (21 mg, 78  $\mu\text{mol}$ , 10 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 5$  mL) and the



combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 10% EtOAc in hexanes  $\rightarrow$  50% EtOAc in hexanes) providing pure hydroxy-1,3-carbonyl derivative [(-)-**13**; 1.0 mg, 2.6  $\mu\text{mol}$ , 33% yield] as a colorless oil.

(-)-**13**:  $R_f = 0.14$  (hexanes:EtOAc, 1:1);  $[\alpha]_D^{25} = -0.1$  ( $c = 0.1$ ,  $\text{C}_6\text{D}_6$ ); IR (film)  $\nu_{\text{max}}$  3381, 2924, 1800, 1721, 1377, 1033  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.03 (s, 1H), 4.81 (br s, 1H), 3.95 (dd,  $J = 7.1, 2.0$  Hz, 1H), 3.62 (s, 1H), 3.29–3.21 (m, 1H), 3.12–3.04 (m, 1H), 2.65–2.57 (m, 1H), 2.38–2.29 (m, 2H), 1.89–1.65 (m, 5H), 1.64 (s, 3H), 1.49–1.43 (m, 2H), 1.37 (s, 3H), 1.33 (d,  $J = 7.5$  Hz, 3H), 1.05–0.85 (m, 3H), 0.82 (d,  $J = 6.5$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  207.6, 173.3, 169.4, 135.0, 131.0, 100.6, 84.8, 83.9, 50.7, 47.8, 46.8, 41.7, 41.2, 37.5, 35.9, 33.8, 31.7, 29.8, 29.3, 25.9, 22.8, 22.6, 16.7 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{23}\text{H}_{31}\text{NO}_6\text{Na}^+$   $[\text{M}+\text{Na}]^+$  418.2224 found 418.2209.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-{hydroxy[(1*R*)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]methyl}hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**74**):** To a stirred solution of aldehyde **71** (114 mg, 0.6 mmol, 3.0 equiv) and iodide (+)-**21**



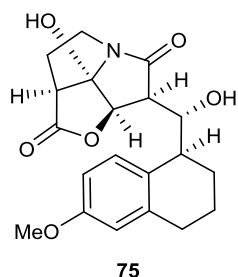
(84 mg, 200  $\mu\text{mol}$ , 1.0 equiv) in dry toluene 3 mL at  $-78^\circ\text{C}$  was added  $\text{BEt}_3$  (1.0 M in hexanes, 0.26 mL, 0.26 mmol, 1.3 equiv) dropwise and the resulting reaction mixture was stirred for 6 h at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (2 mL) at cold. The reaction mixture was brought to  $25^\circ\text{C}$  and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced

pressure. The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 100% hexanes  $\rightarrow$  20% EtOAc in hexanes) providing pure title compound (**74**; 64 mg, 130  $\mu\text{mol}$ , 66% yield) as a colorless oil.

**74**:  $R_f = 0.30$  (hexanes:EtOAc, 1:4);  $[\alpha]_D^{25} = +24$  ( $c = 1.0$  in  $\text{C}_6\text{H}_6$ ); IR (film)  $\nu_{\text{max}}$  3481, 3065, 2931, 2859, 1787, 1699, 1584, 1468, 1376, 1332, 1252, 1140, 1095, 890, 837, 779, 731  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (t,  $J = 7.9$  Hz, 1H), 6.73 (dd,  $J = 7.6, 1.1$  Hz, 1H), 6.68 (dd,  $J = 8.2, 1.0$  Hz, 1H), 4.55 (dd,  $J = 9.8, 3.5$  Hz, 1H), 4.51 (d,  $J = 3.9$  Hz, 1H), 4.16 (s, 1H), 3.83–3.79 (m, 4H), 3.39 (dt,  $J = 7.6, 3.9$  Hz, 1H), 3.34–3.27 (m, 2H), 3.04 (dd,  $J = 7.4, 3.4$  Hz, 1H), 2.81 (dt,  $J = 16.3, 6.2$  Hz,

1 H), 2.68 (dt,  $J=16.3, 4.1$  Hz, 1 H), 2.61–2.56 (m, 2 H), 2.19–2.12 (m, 2 H), 1.75–1.70 (m, 1 H), 1.69–1.59 (m, 1 H), 0.91 (s, 9H), 0.18 (s, 3H), 0.15 (s, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  177.63, 174.80, 157.41, 141.14, 126.87, 125.69, 121.43, 107.65, 100.78, 82.21, 70.29, 55.19, 49.43, 42.30, 35.08, 29.50, 28.95, 25.46, 23.02, 20.75, 17.86,  $-3.30, -3.63$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{26}\text{H}_{37}\text{NO}_6\text{SiNa}^+ [\text{M}+\text{Na}]^+$ : 510.2282, found: 510.2293.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-{hydroxy[(1*S*)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]methyl}hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (75):** To a stirred

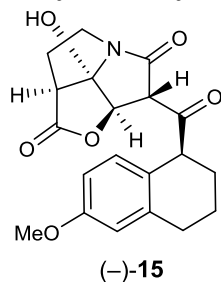


solution of TBS ether **74** (60 mg, 120  $\mu\text{mol}$ , 1.0 equiv) in THF (2 mL) at  $0^\circ\text{C}$  was added TBAF (1.0 M in THF, 120  $\mu\text{L}$ , 120  $\mu\text{mol}$ , 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  solution (2 mL) and  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 5$  mL) and

the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 30% EtOAc in hexanes  $\rightarrow$  50% EtOAc in hexanes) providing pure title compound (**75**; 31 mg, 83  $\mu\text{mol}$ , 67% yield) as a colorless oil.

**75:**  $R_f=0.30$  (hexanes:EtOAc, 3:2);  $[\alpha]_D^{25} = +3$  ( $c=0.7$  in EtOH); IR (film)  $\nu_{\text{max}}$  3304, 1938, 2868, 2836, 1784, 1684, 1583, 1460, 1393, 1331, 1256, 1086, 910, 793, 729  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )  $\delta$  7.11 (t,  $J=7.9$  Hz, 1 H), 6.72 (dd,  $J=7.6, 1.1$  Hz, 1 H), 6.69 (dd,  $J=8.2, 1.1$  Hz, 1 H), 4.72 (d,  $J=4.0$  Hz, 1 H), 4.60 (dd,  $J=9.9, 3.1$  Hz, 1 H), 4.12 (q,  $J=7.1$  Hz, 2 H), 3.86–3.81 (m, 4 H), 3.41–3.31 (m, 2 H), 3.35–3.27 (m, 1 H), 3.14 (dd,  $J=9.1, 1.9$  Hz, 1 H), 2.79 (dt,  $J=16.2, 7.5$  Hz, 1 H), 2.70–2.64 (m, 2 H), 2.57 (dddd,  $J=13.9, 9.3, 4.7, 2.0$  Hz, 1 H), 2.18–2.13 (m, 2 H), 1.79–1.74 (m, 1 H), 1.62–1.56 (m, 1 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  177.33, 174.94, 157.43, 141.26, 126.96, 125.28, 121.40, 107.68, 99.71, 81.32, 70.34, 55.10, 49.31, 48.29, 41.94, 34.79, 29.72, 29.03, 22.75, 21.07 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{20}\text{H}_{23}\text{NO}_6\text{Na}^+ [\text{M}+\text{Na}]^+$ : 396.1418, found: 396.1423.

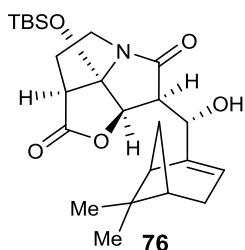
**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*S*)-6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl]carbonyl}hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(-)-**15**]:** To a stirred solution of diol **75** (13 mg, 35  $\mu$ mol, 1.0 equiv) in degassed CH<sub>2</sub>Cl<sub>2</sub> (1 ml) at 0 °C was added an ice cooled solution of DMP (22 mg, 53  $\mu$ mol, 1.5 equiv) and the resulting mixture was stirred for 1.5 h at the same temperature before it was diluted with Et<sub>2</sub>O (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing pure title compound [(-)-**15**; 7.0 mg, 19  $\mu$ mol, 55% yield] as a colorless oil.



(-)-**15**:  $R_f$ =0.30 (hexanes:EtOAc, 1:1);  $[\alpha]_D^{25} = -28$  ( $c=0.1$  in C<sub>6</sub>H<sub>6</sub>); IR (film)  $\nu_{\max}$  3452, 2938, 1790, 1698, 1587, 1468, 1259, 1161, 1094, 1027, 772 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  6.99 (t,  $J=7.9$  Hz, 1 H), 6.63 (d,  $J=8.1$  Hz, 1 H), 6.30 (d,  $J=8.1$  Hz, 1 H), 4.85 (s, 1 H), 4.42 (s, 1 H), 4.09 (t,  $J=7.4$  Hz, 1 H), 3.98 (s, 1 H), 3.52 (ddd,  $J=11.9, 9.3, 6.0$  Hz, 1 H), 3.25 (s, 3 H), 2.77 (ddd,  $J=11.8, 9.7, 4.9$  Hz, 1 H), 2.69 (dd,  $J=9.3, 2.0$  Hz, 1 H), 2.55 (ddd,  $J=16.6, 8.4, 4.9$  Hz, 1 H), 2.38 (dt,  $J=16.5, 5.7$  Hz, 1 H), 2.06 (dddd,  $J=14.0, 9.3, 4.9, 2.0$  Hz, 1 H), 1.93 (dtd,  $J=13.7, 9.5, 6.0$  Hz, 1 H), 1.73–1.67 (m, 1 H), 1.69–1.53 (m, 1 H), 1.50–1.45 (m, 1 H), 1.25–1.19 (m, 1 H) ppm; <sup>13</sup>C NMR (151 MHz, C<sub>6</sub>D<sub>6</sub>)  $\delta$  208.66, 174.26, 167.79, 156.93, 139.51, 122.56, 122.23, 107.88, 101.03, 81.33, 62.10, 54.70, 48.64, 47.83, 41.84, 29.92, 29.56, 25.15, 20.94 ppm; HRMS (ESI-TOF): calcd for C<sub>20</sub>H<sub>21</sub>NO<sub>6</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 394.1261, found: 394.1264.

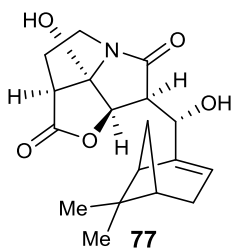
**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(*S*)-(6,6-dimethylbicyclo[3.1.1]hept-2-en-2-yl)(hydroxy)methyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**76**):**

To a stirred solution of aldehyde **72** (90 mg, 600  $\mu$ mol, 3.0 equiv) and iodide (+)-**21** (84 mg, 200  $\mu$ mol, 1.0 equiv) in dry toluene (3 mL) at -78 °C was added BEt<sub>3</sub> (1.0 M in hexanes, 260  $\mu$ L, 260  $\mu$ mol, 1.3 equiv) dropwise and the resulting reaction mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H<sub>2</sub>O (~2 mL) at cold. The reaction mixture was extracted with Et<sub>2</sub>O (3  $\times$  10 mL) and the combined organic layers were dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 100% hexanes→20% EtOAc in hexanes) providing pure title compound (**76**; 69 mg, 160  $\mu$ mol, 81% yield) as a colorless oil.



**76:**  $R_f=0.60$  (hexanes:EtOAc, 3:7);  $[\alpha]_D^{25}=+37$  ( $c=1.0$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3477, 2983, 2951, 2833, 1791, 1701, 1464, 1365, 1300, 1252, 1141, 1070, 865, 837, 780, 733, 674  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  5.65–5.67 (m, 1 H), 4.58 (d,  $J=3.7$  Hz, 1 H), 4.49 (d,  $J=10.0$  Hz, 1 H), 4.33 (s, 1 H), 3.80 (dt,  $J=11.9, 8.2$  Hz, 1 H), 3.32–3.26 (m, 1 H), 3.15 (dd,  $J=10.0, 3.7$  Hz, 1 H), 3.07–3.03 (m, 1 H), 2.62–2.58 (m, 2 H), 2.47 (dt,  $J=8.4, 5.6$  Hz, 1 H), 2.42 (td,  $J=5.6, 1.5$  Hz, 1 H), 2.32 (t,  $J=3.0$  Hz, 2 H), 2.17–2.14 (m, 1 H), 1.34 (s, 3 H), 1.10 (d,  $J=8.5$  Hz, 1 H), 0.91 (s, 3 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.14 (s, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  176.57, 174.86, 145.43, 122.41, 100.59, 82.08, 71.11, 49.63, 49.32, 41.97, 41.31, 41.11, 38.36, 31.92, 31.42, 28.88, 26.24, 25.38, 21.44, 17.86,  $-3.32, -3.61$  ppm; HRMS (ESI-TOF): calcd for  $C_{24}H_{37}NO_5SiNa^+$   $[M+Na]^+$ : 470.2333, found: 470.2338.

**(2a*S*,6*S*,6a*R*,6b*S*)-6-[(*S*)-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)(hydroxy)methyl]-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**77**):**



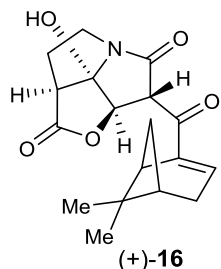
of TBS ether **76** (50 mg, 110  $\mu$ mol, 10 equiv) in THF (3 mL) at 0 °C was added TBAF (1.0 M in THF, 110  $\mu$ L, 110  $\mu$ mol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous  $NH_4Cl$  solution (2 mL) and  $H_2O$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 5$  mL) and the combined

organic layers were dried over  $MgSO_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $SiO_2$ , gradient from 30% EtOAc in hexanes  $\rightarrow$  50% EtOAc in hexanes) providing pure title compound (**77**; 24 mg, 72  $\mu$ mol, 64% yield) as a colorless oil.

**77:**  $R_f=0.30$  (hexanes:EtOAc, 3:2);  $[\alpha]_D^{25}=+51$  ( $c=0.3$  in EtOH); IR (film)  $\nu_{max}$  3331, 2983, 2934, 2917, 2832, 1788, 1690, 1476, 1383, 1305, 1160, 1064, 1010, 911, 732  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  5.70–5.61 (m, 1 H), 4.67 (d,  $J=3.9$  Hz, 1 H), 4.47 (d,  $J=9.9$  Hz, 1 H), 4.29 (br s, 1 H), 3.81 (ddd,  $J=11.9, 9.3, 6.6$  Hz, 1 H), 3.61 (s, 1 H), 3.37–3.33 (m, 1 H), 3.26 (dd,  $J=10.0, 3.9$  Hz, 1 H), 3.16 (dd,  $J=8.9, 1.8$  Hz, 1 H), 2.69 (dddd,  $J=13.8, 9.8, 9.0, 6.6$  Hz, 1 H), 2.58 (dddd,  $J=13.8, 9.3, 4.5, 1.9$  Hz, 1 H), 2.48 (dt,  $J=8.5, 5.6$  Hz, 1 H), 2.41 (td,  $J=5.6, 1.5$  Hz, 1 H), 2.32 (td,  $J=2.9, 1.3$  Hz, 2 H), 2.17–2.14 (m, 1 H), 1.34 (s, 3 H), 1.11 (d,  $J=8.5$  Hz, 1 H), 0.90 (s, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  176.63, 174.81, 145.03, 123.07, 99.60, 81.37, 71.38, 49.47, 48.24, 41.96,

41.21, 41.17, 38.36, 32.09, 31.43, 28.97, 26.21, 21.41 ppm; HRMS (ESI-TOF): calcd for  $C_{18}H_{23}NO_5SiNa^+$   $[M+Na]^+$ : 356.1468, found: 356.1476.

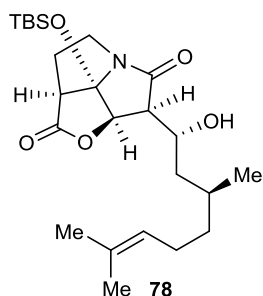
**(2a*S*,6*S*,6a*R*,6b*S*)-6-[(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)carbonyl]-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**16**]**: To a stirred solution of diol **77**



(10 mg, 30  $\mu$ mol, 1.0 equiv) in degassed  $CH_2Cl_2$  (1 mL) at 0 °C was added an ice cooled solution of DMP (19 mg, 45  $\mu$ mol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with  $Et_2O$  (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10%  $EtOAc$  in hexanes  $\rightarrow$  50%  $EtOAc$  in hexanes) furnishing pure title compound [(+)-**16**; 6.0 mg, 18  $\mu$ mol, 60% yield] as a colorless oil.

(+)-**16**:  $R_f$  = 0.50 (hexanes: $EtOAc$ , 3:2);  $[\alpha]_D^{25}$  = +63 ( $c$  = 0.3 in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3433, 2935, 1792, 1716, 1634, 1607, 1416, 1280, 1031, 926  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $C_6D_6$ )  $\delta$  6.85–6.83 (m, 1H), 5.12 (s, 1H), 4.30 (s, 1H), 4.18 (s, 1H), 3.43 (ddd,  $J$  = 12.0, 9.3, 5.8 Hz, 1H), 3.04 (td,  $J$  = 5.7, 1.6 Hz, 1H), 2.66–2.61 (m, 2H), 2.22 (dt,  $J$  = 9.3, 5.7 Hz, 1H), 2.07–1.98 (m, 3H), 1.85 (dtd,  $J$  = 13.7, 9.6, 5.8 Hz, 1H), 1.72–1.70 (tt,  $J$  = 6.2, 2.8 Hz, 1H), 1.08 (s, 3H), 0.82 (d,  $J$  = 9.2 Hz, 1H), 0.59 (s, 3H) ppm;  $^{13}C$  NMR (151 MHz,  $C_6D_6$ )  $\delta$  193.06, 174.46, 167.67, 147.60, 147.02, 100.87, 81.13, 59.87, 47.80, 41.66, 40.18, 39.49, 37.88, 33.28, 30.79, 29.86, 25.69, 20.63 ppm; HRMS (ESI-TOF): calcd for  $C_{18}H_{21}NO_5Na^+$   $[M+Na]^+$ : 354.1312, found: 354.1317.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[(*tert*-Butyl(dimethyl)silyl)oxy]-6-[(1*R*,3*S*)-1-hydroxy-3,7-dimethyloct-6-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**78**)**: To a stirred

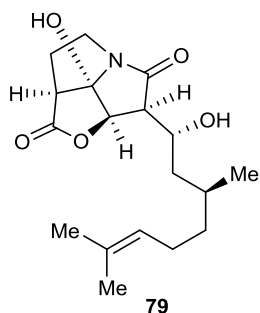


solution of aldehyde **73** (76 mg, 490  $\mu$ mol, 3.0 equiv) and iodide (+)-**21** (70 mg, 160  $\mu$ mol, 1.0 equiv) in dry toluene 3 mL at  $-78$  °C was added  $BEt_3$  (1.0 M in hexanes, 210  $\mu$ L, 210  $\mu$ mol, 1.3 equiv) dropwise and the resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of  $H_2O$  (2 mL) at cold. The reaction mixture was brought to 25 °C and extracted with  $Et_2O$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $MgSO_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $SiO_2$ , gradient from 100% hexanes  $\rightarrow$  10%  $EtOAc$  in hexanes) providing title compound (**78**; 52 mg, 120  $\mu$ mol, 70% yield) as a colorless oil.



**78:**  $R_f=0.50$  (hexanes:EtOAc,1:4);  $[\alpha]_D^{25}=+40$  ( $c=0.4$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3498, 2956, 2930, 2859, 1794, 1705, 1472, 1377, 1305, 1253, 1143, 1060, 894, 839, 781  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $C_6D_6$ )  $\delta$  5.29–5.25 (m, 1 H), 4.58 (t,  $J=1.8$  Hz, 1 H), 4.33 (tt,  $J=10.0, 1.9$  Hz, 1 H), 4.23 (d,  $J=4.0$  Hz, 1 H), 3.41 (ddd,  $J=12.0, 9.2, 7.3$  Hz, 1 H), 2.91 (dd,  $J=9.5, 4.0$  Hz, 1 H), 2.67 (ddd,  $J=12.6, 9.9, 3.9$  Hz, 1 H), 2.33 (dd,  $J=9.0, 1.6$  Hz, 1 H), 2.19–2.07 (m, 3 H), 2.03 (dddd,  $J=13.4, 9.3, 3.9, 1.6$  Hz, 1 H), 1.78–1.75 (m, 5 H), 1.69 (s, 3 H), 1.48 (ddt,  $J=12.7, 9.6, 6.2$  Hz, 1 H), 1.38–1.31 (m, 2 H), 1.05 (d,  $J=6.6$  Hz, 3 H), 0.77 (s, 9 H),  $-0.17$  (s, 3 H),  $-0.23$  (s, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $C_6D_6$ )  $\delta$  177.51, 173.75, 130.99, 125.50, 100.83, 81.57, 66.72, 52.94, 49.18, 42.50, 42.22, 38.81, 28.78, 28.76, 26.17, 25.92, 25.46, 19.14, 17.80, 17.77,  $-3.62$ ,  $-4.03$  ppm; HRMS (ESI-TOF): calcd for  $C_{24}H_{42}NO_5Si^+$   $[M+H]^+$ : 452.2827, found: 452.2832.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*R*,3*S*)-1-hydroxy-3,7-dimethyloct-6-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (79):** To a stirred solution of TBS ether **78**

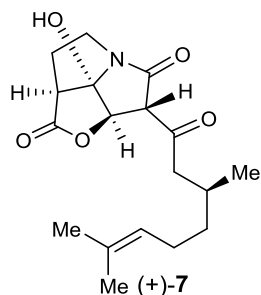


(46 mg, 100  $\mu$ mol, 1.0 equiv) in THF (2 mL) at 0 °C was added TBAF (1.0 M in THF, 100  $\mu$ L, 100  $\mu$ mol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous  $NH_4Cl$  solution (2 mL) and  $H_2O$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 5$  mL) and the combined organic layers were dried over  $MgSO_4$  and concentrated under reduced pressure. The

resulting crude product was purified by flash column chromatography ( $SiO_2$ , gradient from 30% EtOAc in hexanes  $\rightarrow$  50% EtOAc in hexanes) providing pure title compound (**79**; 26 mg, 77  $\mu$ mol, 77% yield) as a colorless oil.

**79:**  $R_f=0.20$  (hexanes:EtOAc, 1:1);  $[\alpha]_D^{25}=+40$  ( $c=0.2$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3229, 2966, 2923, 2865, 2844, 1787, 1677, 1455, 1055, 1033, 1013  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $C_6D_6$ )  $\delta$  5.31–5.28 (m, 1 H), 4.56 (s, 1 H), 4.25–4.22 (m, 1 H), 4.03 (d,  $J=4.1$  Hz, 1 H), 3.37 (ddd,  $J=11.8, 9.3, 6.4$  Hz, 1 H), 2.60–2.55 (m, 2 H), 2.31 (dd,  $J=9.2, 1.9$  Hz, 1 H), 2.19–2.07 (m, 3 H), 1.96–1.92 (m, 2 H), 1.74–1.68 (m, 4 H), 1.62–1.57 (m, 4 H), 1.48 (ddt,  $J=12.7, 9.4, 6.3$  Hz, 1 H), 1.36 (dddd,  $J=13.5, 9.4, 7.6, 6.2$  Hz, 1 H), 1.25–1.20 (m, 1 H), 1.01 (d,  $J=6.6$  Hz, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $C_6D_6$ )  $\delta$  176.69, 173.71, 131.06, 125.48, 99.31, 80.54, 66.56, 52.40, 47.97, 42.19, 41.79, 38.81, 28.82, 28.66, 26.16, 25.93, 19.03, 17.82 ppm; HRMS (ESI-TOF): calcd for  $C_{18}H_{27}NO_5Na^+$   $[M+Na]^+$ : 360.1781, found: 360.1782.

**(2a*S*,6*S*,6a*R*,6b*S*)-6-[(3*S*)-3,7-Dimethyloct-6-enoyl]-6b-hydroxyhexahydro-1-oxa-4a-aza-cyclopenta[*cd*]pentalene-2,5-dione [(+)-**7**]:** To a stirred solution of diol **79** (14 mg, 41  $\mu$ mol,

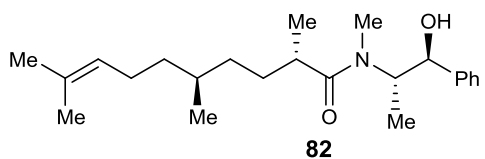


1.0 equiv) in degassed  $\text{CH}_2\text{Cl}_2$  (1 ml) at 0  $^\circ\text{C}$  was added an ice cooled solution of DMP (28 mg, 66  $\mu$ mol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with  $\text{Et}_2\text{O}$  (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 25%  $\text{EtOAc}$  in hexanes  $\rightarrow$  50%  $\text{EtOAc}$  in hexanes) furnishing pure title compound

[(+)-**7**; 8.3 mg, 25  $\mu$ mol, 60% yield] as a colorless oil.

(+)-**7**:  $R_f = 0.40$  (hexanes: $\text{EtOAc}$ , 1:1);  $[\alpha]_D^{25} = +85$  ( $c = 0.2$  in  $\text{C}_6\text{H}_6$ ); IR (film)  $\nu_{\text{max}}$  3435, 2961, 2924, 2856, 1790, 1720, 1695, 1456, 1378, 1270, 1115, 1023, 732  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.15–5.13 (m, 1H), 4.52 (s, 1H), 4.21 (s, 1H), 3.60 (s, 1H), 3.40 (ddd,  $J = 11.9, 9.3, 5.8$  Hz, 1H), 2.68–2.61 (m, 2H), 2.38 (dd,  $J = 17.9, 8.4$  Hz, 1H), 2.07 (dd,  $J = 17.9, 4.9$  Hz, 1H), 1.98 (dddd,  $J = 14.1, 9.3, 5.1, 2.1$  Hz, 1H), 1.94–1.80 (m, 4H), 1.68 (s, 3H), 1.55 (s, 3H), 1.15 (ddt,  $J = 12.8, 9.2, 6.3$  Hz, 1H), 1.03 (dddd,  $J = 13.7, 9.2, 7.8, 6.3$  Hz, 1H), 0.71 (d,  $J = 6.6$  Hz, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  206.72, 174.15, 166.87, 131.63, 124.64, 100.95, 79.97, 65.47, 50.31, 47.75, 41.82, 36.77, 29.88, 28.10, 25.87, 25.82, 19.35, 17.75 ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{18}\text{H}_{25}\text{NO}_5\text{Na}^+$   $[\text{M}+\text{Na}]^+$ : 358.1625, found: 358.1623.

**(2*S*,5*S*)-*N*-[(1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl]-*N*,2,5,9-tetramethyldec-8-enamide (**82**):**

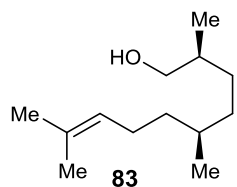


A solution of *n*-butyllithium in hexanes (2.5 M; 27.4 mL, 70.0 mmol, 4.0 equiv) was added to a suspension of lithium chloride (9.40 g, 222 mmol, 12.7 equiv) and diisopropylamine (10.6 mL, 75.3 mmol, 4.3 equiv) in THF (50 mL) at  $-78^\circ\text{C}$ . The resulting suspension was warmed to 0  $^\circ\text{C}$  and then re-cooled to  $-78^\circ\text{C}$ . An ice cooled solution of amide **81** (8.12 g, 36.7 mmol, 2.1 equiv) in THF (110 mL) was added and the mixture was stirred at  $-78^\circ\text{C}$  for 1 h, at 0  $^\circ\text{C}$  for 15 min, and at 25  $^\circ\text{C}$  for 5 min. The mixture was cooled to 0  $^\circ\text{C}$ , and iodide **80** (4.66 g, 17.5 mmol, 1.0 equiv) was added neat to the reaction mixture. After being stirred for 24 h at 0  $^\circ\text{C}$ , the resulting mixture was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  solution (200 mL), and the resulting mixture was extracted with ethyl acetate ( $4 \times 100$  mL), and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The resulting crude

product was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 20% EtOAc in hexanes→40% EtOAc in hexanes) providing pure title compound (**82**; 5.36 g, 14.9 mmol, 85% yield) as a colorless oil.

**82**: R<sub>f</sub>=0.40 (hexanes:EtOAc, 2:3); [α]<sub>D</sub><sup>25</sup> = -78 (c=2.0 in C<sub>6</sub>H<sub>6</sub>); IR (film) ν<sub>max</sub> 3377, 3087, 2964, 2926, 2855, 1618, 1452, 1408, 1376, 1110, 1050, 701 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>, 4:1 rotamer ratio, \*indicates minor rotamer peaks) δ 7.38–7.31 (m, 5 H), 5.10–5.07 (m, 1 H), 4.62 (d, J=7.5 Hz, 0.8 H), 4.59\* (d, J=7.5 Hz, 0.2 H), 4.39 (br s, 0.8 H), 4.06–4.10\* (br s, 0.2 H), 2.84 (s, 2.5 H), 2.92\* (s, 0.6 H), 2.78–1.72\* (m, 0.2 H), 2.54 (quint, J=6.8 Hz, 0.8 H), 2.00–1.99 (m, 2 H), 1.68\* (s, 3 H), 1.66–1.60 (m, 4 H), 1.38–1.00 (m, 13 H), 0.90\* (d, J=6.6 Hz, 0.6 H), 0.87\* (d, J=6.6 Hz, 2.5 H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>, 4:1 rotamer ratio, \*indicates minor rotamer peaks) δ 179.37, 177.97\*, 142.73, 131.20, 128.85\*, 128.40, 127.61, 127.01\*, 126.37, 125.13\*, 124.96, 76.68, 37.11, 37.00, 34.99\*, 34.77, 32.84\*, 32.63, 31.69\*, 31.58, 25.82, 25.61, 19.67\*, 19.58, 18.22\*, 17.74, 17.50, 15.56\*, 14.61 ppm; HRMS (ESI-TOF): calcd for C<sub>23</sub>H<sub>38</sub>NO<sub>2</sub><sup>+</sup> [M+H]<sup>+</sup>: 360.2897, found: 575.2888.

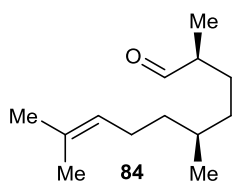
**(2S,5S)-2,5,9-Trimethyldec-8-en-1-ol (83)**: A solution of *n*-butyllithium in hexanes (2.5 M;



10% EtOAc in hexanes→20% EtOAc in hexanes) provided pure title compound (**83**; 1.71 g, 8.60 mmol, 72% yield) as a colorless oil.

**83**:  $R_f=0.40$  (hexanes:EtOAc, 1:4);  $[\alpha]_D^{25} = -9$  ( $c=2.0$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3340, 2956, 2915, 2856, 1456, 1377, 1033  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  5.12–5.09 (m, 1 H), 3.52 (dd,  $J=10.5$ , 5.7 Hz, 1 H), 3.42 (dd,  $J=10.5$ , 6.5 Hz, 1 H), 2.04–1.90 (m, 2 H), 1.68 (q,  $J=1.3$  Hz, 3 H), 1.60–1.55 (m, 4 H), 1.45–1.31 (m, 5 H), 1.17–1.03 (m, 3 H), 0.97 (d,  $J=6.4$  Hz, 3 H), 0.87 (d,  $J=6.4$  Hz, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  131.13, 125.07, 68.47, 37.03, 36.25, 34.34, 32.85, 30.61, 25.81, 25.63, 19.76, 17.72, 16.82 ppm; HRMS (CI): calcd for  $C_{13}H_{26}O^+$   $[M]^+$ : 198.1984, found: 198.1980.

**(2S,5S)-2,5,9-Trimethyldec-8-enal (84)**: To a stirred solution of alcohol **83** (400 mg, 2.00 mmol,

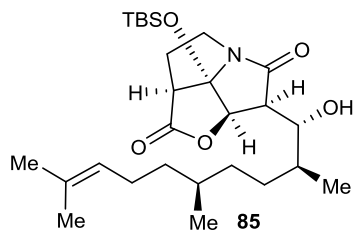


1.0 equiv) in  $CH_2Cl_2$  10 mL at 0 °C was added DMP (1.27 g, 3.00 mmol, 1.5 equiv) and  $NaHCO_3$  (756 mg, 9.00 mmol, 3.0 equiv). The resulting mixture was stirred for 1 h at 25 °C before it was quenched by the addition of saturated aq.  $NaHCO_3$  (5 mL) and saturated aq.  $Na_2S_2O_3$  (5 mL). The reaction

mixture was extracted with ether ( $3 \times 10$  mL) and the combined organic layers were dried over  $Na_2SO_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $SiO_2$ , gradient from 100% hexanes→5% EtOAc in hexanes) providing pure title compound (**84**; 323 mg, 1.65 mmol, 82% yield) as a colorless oil.

**84**:  $R_f=0.70$  (hexanes:EtOAc, 1:4);  $[\alpha]_D^{25} = +20$  ( $c=1.0$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  2963, 2924, 2856, 1727, 1458, 1377, 1259, 1119, 924, 825, 752  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  9.61 (d,  $J=2.1$  Hz, 1 H), 5.10–5.07 (m, 1 H), 2.30 (hd,  $J=6.8$ , 2.1 Hz, 1 H), 2.02–1.92 (m, 2 H), 1.77–1.71 (m, 1 H), 1.68 (s, 3 H), 1.60 (s, 3 H), 1.45–1.30 (m, 4 H), 1.18–1.11 (m, 2 H), 1.09 (d,  $J=7.0$  Hz, 3 H), 0.89 (d,  $J=6.6$  Hz, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  205.44, 131.30, 124.84, 46.70, 36.91, 34.22, 32.62, 28.15, 25.81, 25.56, 19.57, 17.73, 13.55 ppm; HRMS (CI): calcd for  $C_{13}H_{24}O^+$   $[M]^+$ : 196.1834, found: 196.1827.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(1*R*,2*S*,5*S*)-1-hydroxy-2,5,9-trimethyldec-8-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (85):** To a

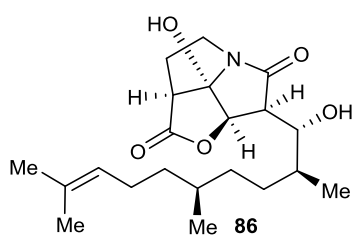


stirred solution of aldehyde **84** (98 mg, 0.50 mmol, 3.0 equiv) and iodide (+)-**21** (70 mg, 170  $\mu$ mol, 1.0 equiv) in dry toluene (3 mL) at  $-78$   $^{\circ}$ C was added  $\text{BEt}_3$  (1.0 M in hexanes, 210  $\mu$ L, 210  $\mu$ mol, 1.3 equiv) dropwise and the resulting reaction mixture was stirred for 6 h at the same temperature before it was quenched by the addition

of  $\text{H}_2\text{O}$  (2 mL) at cold. The reaction mixture was brought to  $25$   $^{\circ}$ C and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 5% hexanes  $\rightarrow$  10%  $\text{EtOAc}$  in hexanes) providing pure title compound (**85**; 51 mg, 100  $\mu$ mol, 63% yield) as a colorless oil.

**85**:  $R_f=0.50$  (hexanes: $\text{EtOAc}$ , 1:4);  $[\alpha]_D^{25} = +27$  ( $c=0.5$  in  $\text{C}_6\text{H}_6$ ); IR (film)  $\nu_{\text{max}}$  3422, 2956, 2929, 2859, 1794, 1705, 1462, 1377, 1305, 1142, 1057, 1033, 1012, 895, 839, 780  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  5.29–5.26 (m, 1 H), 4.39 (t,  $J=1.6$  Hz, 1 H), 4.30 (dt,  $J=9.8, 1.9$  Hz, 1 H), 4.17 (d,  $J=3.9$  Hz, 1 H), 3.41 (ddd,  $J=12.0, 9.2, 7.2$  Hz, 1 H), 3.14 (dd,  $J=9.8, 3.9$  Hz, 1 H), 2.66 (ddd,  $J=12.8, 7.1, 3.6$  Hz, 1 H), 2.33 (dd,  $J=8.9, 1.6$  Hz, 1 H), 2.18–2.00 (m, 3 H), 1.86–1.68 (m, 5 H), 1.68–1.60 (m, 4 H), 1.56–1.44 (m, 4 H), 1.35–1.21 (m, 2 H), 1.08 (d,  $J=6.8$  Hz, 3 H), 0.95 (d,  $J=6.2$  Hz, 3 H), 0.78 (s, 9 H),  $-0.14$  (s, 3 H),  $-0.21$  (s, 3 H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{C}_6\text{D}_6$ )  $\delta$  177.88, 173.76, 130.74, 125.76, 100.86, 81.37, 70.02, 49.97, 49.17, 42.34, 37.55, 35.50, 34.90, 32.98, 31.56, 28.79, 26.19, 25.95, 25.43, 19.83, 17.79, 13.22,  $-3.62$ ,  $-4.01$  ppm; HRMS (ESI-TOF): calcd for  $\text{C}_{27}\text{H}_{48}\text{NO}_5\text{Si}^+$   $[\text{M}+\text{H}]^+$ : 494.3296, found: 494.3308.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*R*,2*S*,5*S*)-1-hydroxy-2,5,9-trimethyldec-8-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (86):** To a stirred solution of TBS ether



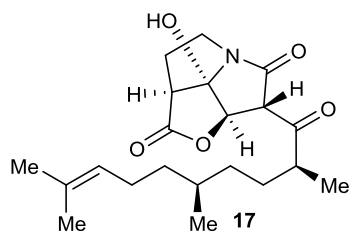
**85** (43 mg, 87  $\mu$ mol, 10 equiv) in THF (2 mL) at  $0$   $^{\circ}$ C was added TBAF (1.0 M in THF, 110  $\mu$ L, 110  $\mu$ mol, 1.3 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous  $\text{NH}_4\text{Cl}$  solution (2 mL) and  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with

$\text{EtOAc}$  ( $3 \times 5$  mL) and the combined organic layers were dried over  $\text{NaSO}_4$  and concentrated under

reduced pressure. The resulting crude product was purified by flash column chromatography (SiO<sub>2</sub>, gradient from 30% EtOAc in hexanes→50% EtOAc in hexanes) providing pure title compound (**86**; 28 mg, 74 μmol, 85% yield) as a colorless oil.

**86**: R<sub>f</sub>=0.20 (hexanes:EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> = +34 (c=0.4 in C<sub>6</sub>H<sub>6</sub>); IR (film) ν<sub>max</sub> 3257, 2965, 2924, 2858, 1790, 1682, 1441, 1334, 1310, 1062, 1033, 773 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 5.28–5.26 (m, 1 H), 4.37 (br s, 1 H), 4.20 (dt, *J*=9.9, 1.8 Hz, 1 H), 4.04 (d, *J*=4.0 Hz, 1 H), 3.37 (ddd, *J*=11.8, 9.3, 6.4 Hz, 1 H), 2.92 (dd, *J*=9.9, 4.0 Hz, 1 H), 2.62 (dddd, *J*=11.3, 9.9, 4.6, 1.1 Hz, 1 H), 2.49 (s, 1 H), 2.36 (dd, *J*=9.2, 1.9 Hz, 1 H), 2.17–2.05 (m, 2 H), 1.97 (dddd, *J*=13.8, 9.3, 4.6, 2.0 Hz, 1 H), 1.80–1.73 (m, 2 H), 1.71 (d, *J*=1.4 Hz, 3 H), 1.63–1.56 (m, 4 H), 1.54–1.42 (m, 4 H), 1.32–1.19 (m, 2 H), 1.03 (d, *J*=6.8 Hz, 3 H), 0.94 (d, *J*=6.2 Hz, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 177.42, 173.82, 130.78, 125.72, 99.50, 80.54, 70.18, 49.60, 47.91, 41.81, 37.54, 35.42, 34.87, 32.98, 31.61, 28.90, 26.17, 25.94, 19.82, 17.79, 13.23 ppm; HRMS (ESI-TOF): calcd for C<sub>21</sub>H<sub>33</sub>NO<sub>5</sub>Na<sup>+</sup> [M+Na]<sup>+</sup>: 402.2257, found: 402.2251.

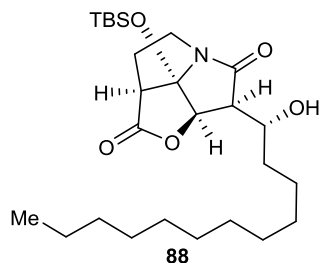
**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(2*S*,5*S*)-2,5,9-trimethyldec-8-enoyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**17**]**: To a stirred solution of diol **86** (10 mg, 26 μmol, 1.0 equiv) in degassed CH<sub>2</sub>Cl<sub>2</sub> (1 ml) at 0 °C was added an ice cooled solution of DMP (17 mg, 40 μmol 1.5 equiv) and the resulting mixture was stirred for 2 h at the same temperature before it was diluted with Et<sub>2</sub>O (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 25% EtOAc in hexanes→50% EtOAc in hexanes) furnishing pure title compound [(+)-**17**; 6.0 mg, 16 μmol, 61% yield)] as a colorless oil.



(+)-**17**: R<sub>f</sub>=0.40 (hexanes:EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> = +21 (c=0.2 in C<sub>6</sub>H<sub>6</sub>); IR (film) ν<sub>max</sub> 3448, 2963, 2924, 2856, 1793, 1719, 1692, 1456, 1376, 1335, 1162, 1115, 1021 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, C<sub>6</sub>D<sub>6</sub>) δ 5.20 (t, *J*=7.3 Hz, 1 H), 4.69 (s, 1 H), 4.18 (s, 1 H), 3.85 (s, 1 H), 3.43 (ddd, *J*=12.0, 9.3, 5.8 Hz, 1 H), 2.68 (ddd, *J*=11.9, 9.8, 5.0 Hz, 1 H), 2.62 (dd, *J*=9.3, 2.1 Hz, 1 H), 2.49 (h, *J*=7.0 Hz, 1 H), 2.13–1.94 (m, 3 H), 1.89–1.80 (m, 1 H), 1.75–1.70 (s, 4 H), 1.59 (s, 3 H), 1.37–1.31 (m, 2 H), 1.24–1.07 (m, 3 H), 0.93–0.91 (m, 1 H), 0.83 (d, *J*=6.4 Hz, 3 H), 0.76 (d, *J*=7.1 Hz, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, C<sub>6</sub>D<sub>6</sub>) δ 209.47, 173.11, 165.97, 130.02, 124.41, 99.96, 79.35, 62.72, 46.70,

46.64, 40.83, 36.24, 33.34, 31.67, 28.85, 27.92, 25.00, 24.92, 18.55, 16.75, 14.69 ppm; HRMS (ESI-TOF): calcd for  $C_{21}H_{31}NO_5Na^+$   $[M+Na]^+$ : 400.2094, found: 400.2093.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(1*R*)-1-hydroxydodecyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**88**):** To a stirred solution of aldehyde **87**

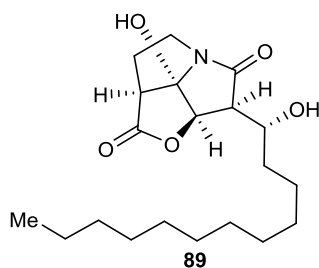


(235 mg, 1.27 mmol, 3.0 equiv) and iodide (+)-**21** (180 mg, 423  $\mu$ mol, 1.0 equiv) in dry toluene (3 mL) at  $-78^\circ\text{C}$  was added  $\text{BEt}_3$  (1.0 M in hexanes, 423  $\mu$ L, 423  $\mu$ mol, 1.0 equiv) dropwise and the resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (4 mL) at cold. The reaction mixture

was brought to  $25^\circ\text{C}$  and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 100% hexanes  $\rightarrow$  20% EtOAc in hexanes) providing pure title compound (**88**; 169 mg, 351  $\mu$ mol, 83% yield) as a colorless oil.

**88**:  $R_f = 0.50$  (hexanes:EtOAc, 1:2);  $[\alpha]_D^{25} = +28$  ( $c = 0.8$  in  $\text{C}_6\text{H}_6$ ); IR (film)  $\nu_{\text{max}}$  3505, 2953, 2925, 2855, 1792, 1702, 1463, 1375, 1303, 1251, 1142, 1061, 837, 779, 675  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ ) 4.74 (d,  $J = 4.0$  Hz, 1 H), 4.19 (s, 1 H), 4.01–3.97 (m, 1 H), 3.83–3.78 (m, 1 H), 3.32–3.27 (m, 1 H), 3.08–3.06 (m, 1 H), 2.96 (dd,  $J = 9.5, 4.0$  Hz, 1 H), 2.64–2.54 (m, 2 H), 1.62–1.25 (m, 20H), 0.89–0.86 (m, 12H), 0.15 (s, 3H), 0.14 (s, 3H) ppm;  $^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )  $\delta$  177.02, 174.80, 100.87, 81.93, 68.22, 51.92, 49.34, 42.29, 34.28, 32.00, 29.73, 29.71, 29.67, 29.42, 29.00, 25.41, 24.82, 22.76, 17.82, 14.20,  $-3.28$ ,  $-3.65$  ppm; HRMS (ESI-TOF): calcd for  $C_{26}H_{47}NO_5\text{SiNa}^+$   $[M+Na]^+$ : 504.3116, found: 504.3124.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*R*)-1-hydroxydodecyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**89**):** To a stirred solution of TBAF (1.0 M in THF, 590  $\mu$ L,



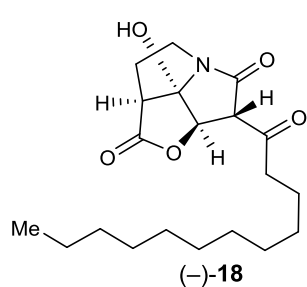
590  $\mu$ mol, 1.1 equiv) and acetic acid (36  $\mu$ L, 590  $\mu$ mol, 1.1 equiv) in THF (3 mL) was added TBS ether **88** (260 mg, 540  $\mu$ mol, 1.0 equiv) in THF (1 mL) at  $0^\circ\text{C}$  and the resulting mixture was stirred for 15 min at the same temperature before it was quenched by the addition of sat. aq.  $\text{NH}_4\text{Cl}$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$ ,

and concentrated under reduced pressure. The resulting crude product was purified by flash

column chromatography (SiO<sub>2</sub>, gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) providing pure title compound (**89**; 170 mg, 470 μmol, 87% yield) as a colorless oil.

**89**: R<sub>f</sub>=0.30 (hexanes:EtOAc, 2:3); [α]<sub>D</sub><sup>25</sup> = +49 (*c* = 0.5 in C<sub>6</sub>H<sub>6</sub>); IR (film) ν<sub>max</sub> 3336, 2954, 2922, 2853, 1788, 1685, 1388, 1332, 1305, 1163, 1087, 1058, 1010, 946, 771, 706 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.84 (d, *J* = 4.1 Hz, 1 H), 4.48 (s, 1 H), 4.38 (s, 1 H), 4.01 (td, *J* = 9.1, 2.6 Hz, 1 H), 3.81 (ddd, *J* = 11.8, 9.3, 6.2 Hz, 1 H), 3.37–3.32 (m, 1 H), 3.18 (dd, *J* = 9.2, 1.9 Hz, 1 H), 3.07 (dd, *J* = 9.5, 4.0 Hz, 1 H), 2.69 (dtd, *J* = 13.8, 9.5, 6.2 Hz, 1 H), 2.55 (dddd, *J* = 13.9, 9.4, 4.8, 2.0 Hz, 1 H), 1.63–1.26 (m, 20 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 176.60, 174.95, 99.76, 81.14, 68.59, 51.71, 48.23, 41.88, 34.31, 32.01, 29.76, 29.73, 29.72, 29.70, 29.66, 29.44, 29.12, 24.89, 22.78, 14.20 ppm; HRMS (ESI-TOF): calcd for C<sub>20</sub>H<sub>33</sub>NO<sub>5</sub>Na<sup>+</sup> [*M*+Na]<sup>+</sup>: 390.2251, found: 390.2258.

**(2a*S*,6*S*,6a*R*,6b*S*)-6-Dodecanoyl-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(-)-**18**] and (2a*S*,6a*R*,6b*S*)-6-Dodecanoyl-6,6b-dihydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**19**]**: To a stirred solution of diol **89** (10 mg,



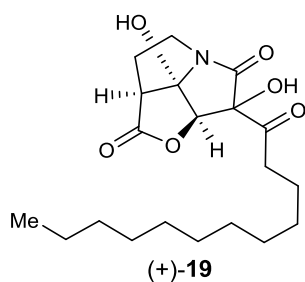
27 μmol, 1.0 equiv) in degassed CH<sub>2</sub>Cl<sub>2</sub> (1 ml) at 0 °C was added DMP (23 mg, 55 μmol, 2.0 equiv) and the resulting mixture was stirred for 3 h at 25 °C before it was diluted with Et<sub>2</sub>O (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing pure 1,3-dicarbonyl

analog [(-)-**18**; 4.6 mg, 13 μmol, 46% yield] and hydroxy-1,3-dicarbonyl analog [(+)-**19**; 1.1 mg, 3.0 μmol, 11% yield] as white amorphous solids.

(-)-**18**: R<sub>f</sub> = 0.40 (hexanes:EtOAc, 1:1); [α]<sub>D</sub><sup>25</sup> = -7 (*c* = 1.0 in C<sub>6</sub>H<sub>6</sub>); IR (film) ν<sub>max</sub> 3418, 2963, 2917, 2852, 1785, 1711, 1671, 1649, 1407, 1330, 1174, 1027 cm<sup>-1</sup>; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>) δ 4.82 (s, 1 H), 4.58 (s, 1 H), 4.05 (s, 1 H), 3.83 (ddd, *J* = 12.0, 9.4, 5.5 Hz, 1 H), 3.34 (ddd, *J* = 12.0, 9.8, 5.3 Hz, 1 H), 3.27 (dd, *J* = 9.4, 2.1 Hz, 1 H), 2.95–2.89 (m, 1 H), 2.78–2.70 (m, 2 H), 2.57 (dd, *J* = 14.0, 9.4 Hz, 1 H), 1.65–1.58 (m, 2 H), 1.31–1.26 (m, 16 H), 0.88 (t, *J* = 7.0 Hz, 3 H) ppm; <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>) δ 206.88, 174.79, 167.02, 101.06, 80.27, 64.83, 47.84, 43.82, 41.84, 31.99, 30.11, 29.67, 29.65, 29.47, 29.41, 29.36, 28.88, 22.87, 22.78, 14.21 ppm; HRMS (ESI-TOF): calcd for C<sub>20</sub>H<sub>31</sub>NO<sub>5</sub>Na<sup>+</sup> [*M*+Na]<sup>+</sup>: 388.2094, found: 388.2099.



(+)-**19**:  $R_f=0.45$  (hexanes:EtOAc,1:1);  $[\alpha]_D^{25}=+3$  ( $c=0.1$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3425, 2924, 2854,



1794, 1698, 1332, 1305, 1163, 1114, 1025  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $C_6D_6$ )  $\delta$  5.23 (s, 1H), 4.14 (s, 1H), 3.44 (ddd,  $J=12.0, 9.3, 6.0$ Hz, 2H), 2.75–2.60 (m, 4H), 2.06 (t,  $J=7.1$  Hz, 1H), 1.89 (dddd,  $J=14.0, 9.3, 4.9, 2.0$  Hz, 1H), 1.81–1.74 (m, 1H), 1.52–1.47 (m, 17H), 0.92 (t,  $J=7.0$  Hz, 3H) ppm;  $^{13}C$  NMR (151 MHz,  $C_6D_6$ )  $\delta$  212.49, 173.39, 169.08, 97.51, 87.01, 81.44, 48.19, 41.67, 38.65, 31.97, 29.69, 29.64,

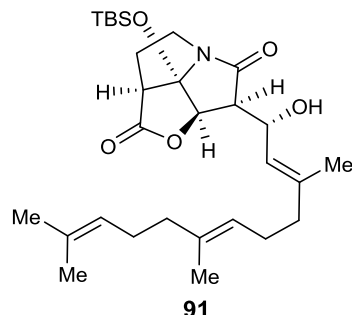
29.48, 29.43, 29.34, 28.72, 27.26, 22.76, 22.38, 14.01 ppm; HRMS (ESI-TOF): calcd for  $C_{20}H_{31}NO_6Na^+$   $[M+Na]^+$ : 404.2044, found: 404.2049.

**IBX-oxidation of diol (89)**: To a stirred solution of diol **89** (140 mg, 380  $\mu$ mol, 1.0 equiv) in EtOAc (10 mL) at 70 °C was added IBX (530 mg, 1.90 mmol, 5.0 equiv) and the resulting mixture was stirred for 7 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with Et<sub>2</sub>O (15 mL) and passed through a plug of Celite. The resulting crude product was purified by passing it through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing title compound [(–)-**18**; 120 mg, 320  $\mu$ mol, 83% yield] as an amorphous solid.

**(2a*S*,6a*R*,6b*S*)-6-Dodecanoyl-6,6b-dihydroxyhexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**19**] from (–)-**18****: To a stirred solution of 1,3-dicarbonyl compound (–)-**18** (3.0 mg, 8.2  $\mu$ mol, 1.0 equiv) in  $CH_2Cl_2$  (1 ml) at 25 °C was added DMP (21 mg, 49  $\mu$ mol, 6.0 equiv) and the resulting mixture was stirred for 6 h at 25 °C before it was diluted with Et<sub>2</sub>O (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing hydroxy 1,3-dicarbonyl derivative [(+)-**19**; 1.8 mg, 4.7  $\mu$ mol, 58% yield] as a white amorphous solid.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-butyl(dimethyl)silyl]oxy]-6-[(1*R*,2*E*,6*E*)-1-hydroxy-3,7,11-trimethyl**

**(91):** To a stirred solution of aldehyde **53** (73 mg, 330  $\mu$ mol, 2.0 equiv) and iodide (+)-**21** (70 mg,



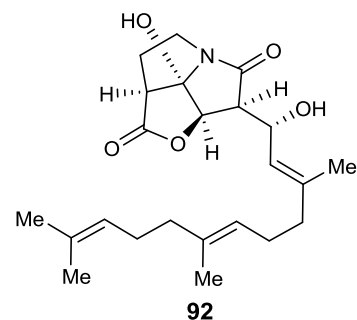
160  $\mu$ mol, 1.0 equiv) in toluene (3 mL) at  $-78$   $^{\circ}$ C was added  $\text{BEt}_3$  (210  $\mu$ L, 1.0 M in hexanes, 210  $\mu$ mol, 1.3 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by addition of  $\text{H}_2\text{O}$  (1 mL). The reaction mixture was extracted with  $\text{Et}_2\text{O}$  ( $3 \times 10$  mL) and the combined organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure.

The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 100% hexanes $\rightarrow$ 20% EtOAc in hexanes) providing pure title compound (**91**; 64 mg, 120  $\mu$ mol, 77% yield) as a colorless oil.

**91:** The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data of **91** matched those of previously synthesized racemic **54**.  $[\alpha]_{\text{D}}^{25} = +57.2$  ( $c = 1.0$  in  $\text{C}_6\text{H}_6$ ).

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-hydroxy-6-[(1*R*,2*E*,6*E*)-1-hydroxy-3,7,11-trimethyl**

**(92):** To a stirred solution



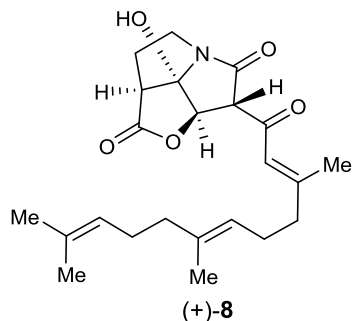
of TBS ether **91** (80 mg, 150  $\mu$ mol, 1.0 equiv) in THF (2 mL) at  $-10$   $^{\circ}$ C was added TBAF (1.0 M in THF, 150  $\mu$ L, 150  $\mu$ mol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by addition of saturated aq.  $\text{NH}_4\text{Cl}$  (1 mL) and  $\text{H}_2\text{O}$  (2 mL). The reaction mixture was extracted with EtOAc ( $3 \times 25$  mL) and the combined organic layers were dried over  $\text{Na}_2\text{SO}_4$  and concentrated under reduced pressure. The resulting

crude product was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 30% EtOAc in

hexanes→60% EtOAc in hexanes) providing pure title compound (**92**; 41 mg, 100 μmol, 66% yield) as a colorless oil.

**92**: The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data of **92** matched those of previously synthesized racemic **55**.  $[\alpha]_{\text{D}}^{25} = +69$  ( $c = 0.5$  in  $\text{C}_6\text{H}_6$ ).

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(2*E*,6*E*)-3,7,11-trimethyldodeca-2,6,10-trienoyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**8**]**: To a stirred solution of diol **92**

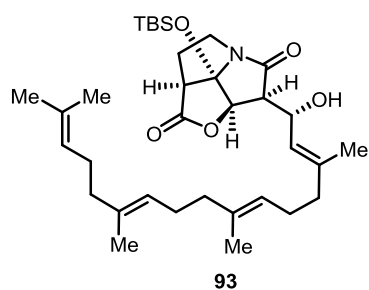


(13 mg, 32 μmol, 1.0 equiv) in degassed  $\text{CH}_2\text{Cl}_2$  (3 ml) at 25 °C was added activated  $\text{MnO}_2$  (140 mg, 1.3 mmol, 40 equiv) in four portions every 2 h and the resulting mixture was stirred for an additional 2 h at the same temperature. Then, the resulting mixture was diluted with  $\text{CH}_2\text{Cl}_2$  (10 ml), passed through a plug of Celite and the filtrate was concentrated under reduced pressure. The resulting

crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes→50% EtOAc in hexanes) furnishing pure title compound (+)-**8** (5.0 mg, 12 μmol, 39% yield) as a colorless oil and diol **92** (6.2 mg, 15 μmol).

(+)-**8**: The  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectral data of (+)-**8** matched those of previously synthesized racemic ( $\pm$ )-**8**.  $[\alpha]_{\text{D}}^{25} = +7$  ( $c = 0.3$  in  $\text{C}_6\text{H}_6$ ).

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-[[*tert*-Butyl(dimethyl)silyl]oxy]-6-[(1*R*,2*E*,6*E*,10*E*)-1-hydroxy-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**93**)**: To a stirred solution of aldehyde **90** (100 mg, 350 μmol, 2.0 equiv) and iodide

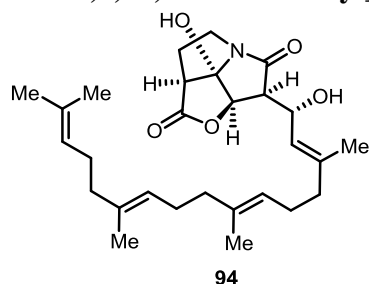


(+)-**21** (74 mg, 180 μmol, 1.0 equiv) in dry toluene (3 mL) at -78 °C was added  $\text{BET}_3$  (1.0 M in hexanes, 230 μL, 230 μmol, 1.3 equiv) dropwise and the resulting reaction mixture was stirred for 4 h at the same temperature before it was quenched by the addition of  $\text{H}_2\text{O}$  (3 mL) at cold. The reaction mixture was brought to 25 °C and extracted with  $\text{Et}_2\text{O}$  ( $3 \times 30$  mL) and the combined

organic layers were dried over  $\text{MgSO}_4$  and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography ( $\text{SiO}_2$ , gradient from 10% hexanes→20% EtOAc in hexanes) providing pure title compound (**93**; 71 mg, 120 μmol, 69% yield) as a colorless oil.

**93**:  $R_f=0.50$  (hexanes:EtOAc, 3:7);  $[\alpha]_D^{25} = +51$  ( $c=1.0$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3479, 2955, 2929, 2857, 1793, 1707, 1472, 1376, 1301, 1253, 1186, 839  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  5.18–5.16 (m, 1 H), 5.12–5.08 (m, 3 H), 4.75 (t,  $J=9.4$  Hz, 1 H), 4.57 (d,  $J=3.9$  Hz, 1 H), 4.25 (s, 1 H), 3.80 (dt,  $J=11.9, 8.3$  Hz, 1 H), 3.33–3.29 (m, 1 H), 3.07–3.02 (m, 2 H), 2.61–2.57 (m, 2 H), 2.17–2.11 (m, 2 H), 2.11–2.04 (m, 6 H), 1.97 (dt,  $J=10.7, 6.1$  Hz, 4 H), 1.76 (d,  $J=1.4$  Hz, 3 H), 1.68 (q,  $J=1.3$  Hz, 3 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.59 (d,  $J=1.2$  Hz, 3 H), 0.89 (s, 9 H), 0.16 (s, 3 H), 0.14 (s, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  176.77, 174.75, 142.87, 135.53, 135.14, 131.35, 124.45, 124.17, 123.85, 122.41, 100.74, 82.23, 65.60, 52.19, 49.28, 42.28, 39.93, 39.82, 28.94, 26.86, 26.76, 26.43, 25.79, 25.44, 17.83, 17.78, 17.12, 16.11,  $-3.25, -3.65$  ppm; HRMS (ESI-TOF): calcd for  $C_{34}H_{55}NO_5SiNa^+$   $[M+Na]^+$ : 608.3742, found: 608.3751.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*R*,2*E*,6*E*,10*E*)-1-hydroxy-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraen-1-yl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (**94**):**



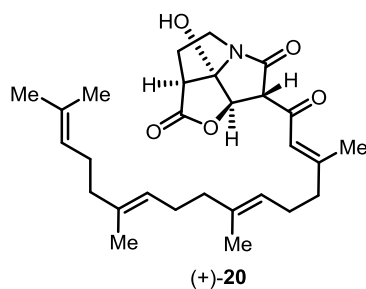
To a stirred solution of TBS ether **93** (70 mg, 120  $\mu$ mol, 1.0 equiv) in THF (2 mL) at 0  $^{\circ}C$  was added TBAF (1.0 M in THF, 120  $\mu$ L, 120  $\mu$ mol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aq.  $NH_4Cl$  (2 mL) and  $H_2O$  (2 mL). The reaction mixture

was extracted with EtOAc ( $3 \times 10$  mL) and the combined organic layers were dried over  $Na_2SO_4$  and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography ( $SiO_2$ , gradient from 30% EtOAc in hexanes  $\rightarrow$  60% EtOAc in hexanes) providing pure title compound (**94**; 38 mg, 81  $\mu$ mol, 67% yield) as a colorless oil.

**94**:  $R_f=0.10$  (hexanes:EtOAc, 1:1);  $[\alpha]_D^{25} = +74$  ( $c=1.0$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3270, 2965, 2917, 2854, 1785, 1681, 1440, 1382, 1307, 1064, 1009, 770, 707  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $CDCl_3$ )  $\delta$  5.18–5.16 (m, 1 H), 5.12–5.08 (m, 3 H), 4.76 (t,  $J=9.5$  Hz, 1 H), 4.67 (d,  $J=3.9$  Hz, 1 H), 4.43 (br s, 1 H), 3.96 (s, 1 H), 3.81 (ddd,  $J=11.8, 9.2, 6.5$  Hz, 1 H), 3.36–3.32 (m, 1 H), 3.18 (dd,  $J=9.7, 3.9$  Hz, 1 H), 3.13 (dd,  $J=9.1, 1.8$  Hz, 1 H), 2.68 (dtd,  $J=13.7, 9.4, 6.5$  Hz, 1 H), 2.57 (dddd,  $J=13.8, 9.3, 4.6, 1.9$  Hz, 1 H), 2.16–2.04 (m, 8 H), 1.98 (dt,  $J=11.1, 5.7$  Hz, 4 H), 1.76 (d,  $J=1.3$  Hz, 3 H), 1.68 (d,  $J=1.5$  Hz, 3 H), 1.61 (s, 3 H), 1.60 (s, 3 H), 1.60 (s, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $CDCl_3$ )  $\delta$  176.23, 174.74, 143.45, 135.69, 135.22, 131.40, 124.44, 124.16, 123.63, 122.11, 99.60, 81.31, 65.78, 51.90, 48.21, 41.85, 39.96, 39.84, 39.82, 29.00, 26.86, 26.74, 26.49, 25.79, 17.79, 17.09,

16.18, 16.12 ppm; HRMS (ESI-TOF): calcd for  $C_{28}H_{41}NO_5Na^+$   $[M+Na]^+$ : 494.2877, found: 494.2879.

**(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(2*E*,6*E*,10*E*)-3,7,11,15-tetramethylhexadeca-2,6,10,14-tetraenoyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(+)-**20**]:**



To a stirred solution of diol **94** (6.0 mg, 13  $\mu$ mol, 1.0 equiv) in degassed  $CH_2Cl_2$  (3 ml) at 25  $^\circ C$  was added activated  $MnO_2$  (55 mg, 510  $\mu$ mol, 40 equiv) in four portions every 2 h and the resulting mixture was stirred for an additional 2 h at the same temperature. Then, the mixture was diluted with  $CH_2Cl_2$  (10 ml), passed through a plug of Celite and the filtrate was concentrated under reduced pressure. The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes  $\rightarrow$  50% EtOAc in hexanes) furnishing pure title compound (+)-**20** (2.6 mg, 5.5  $\mu$ mol, 44% yield) as a colorless oil and diol **94** (2.1 mg, 4.4  $\mu$ mol).

(+)-**20**:  $R_f = 0.50$  (hexanes:EtOAc, 1:1);  $[\alpha]_D^{25} = +35$  ( $c = 0.1$  in  $C_6H_6$ ); IR (film)  $\nu_{max}$  3399, 2918, 1795, 1719, 1605, 1427, 1161, 1117, 1025  $cm^{-1}$ ;  $^1H$  NMR (600 MHz,  $C_6D_6$ )  $\delta$  6.13–6.12 (m, 1 H), 5.30–5.24 (m, 2 H), 5.07–5.04 (m, 1 H), 5.00 (s, 1 H), 4.33 (s, 1 H), 3.70 (s, 1 H), 3.45 (ddd,  $J = 11.9, 9.3, 5.9$  Hz, 1 H), 2.69 (ddd,  $J = 11.9, 9.8, 5.0$  Hz, 1 H), 2.65 (dd,  $J = 9.3, 2.0$  Hz, 1 H), 2.22–2.17 (m, 4 H), 2.12–1.99 (m, 6 H), 1.98–1.94 (m, 4 H), 1.91–1.81 (m, 3 H), 1.69 (s, 3 H), 1.63 (s, 3 H), 1.58 (s, 3 H), 1.53 (s, 3 H) ppm;  $^{13}C$  NMR (151 MHz,  $C_6D_6$ )  $\delta$  194.53, 174.41, 167.81, 167.07, 136.68, 135.32, 131.29, 124.89, 124.61, 122.96, 122.25, 100.95, 80.56, 66.16, 47.83, 41.67, 41.64, 40.28, 40.09, 29.90, 27.28, 27.06, 26.21, 25.90, 20.33, 17.80, 16.18, 16.14 ppm; HRMS (ESI-TOF): calcd for  $C_{28}H_{39}NO_5Na^+$   $[M+Na]^+$ : 492.2720, found: 492.2722.

### III. Biological Materials and Methods for Evaluation of CJ-16,264 and Analogues

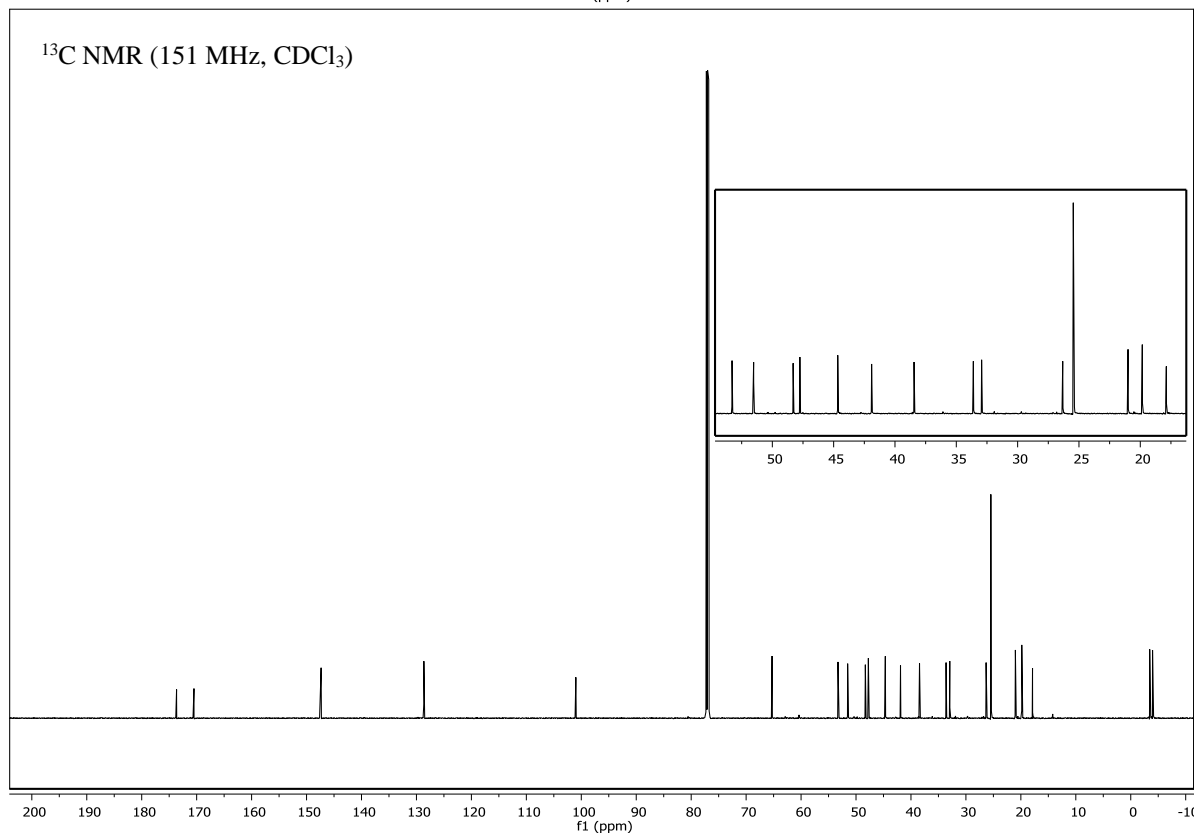
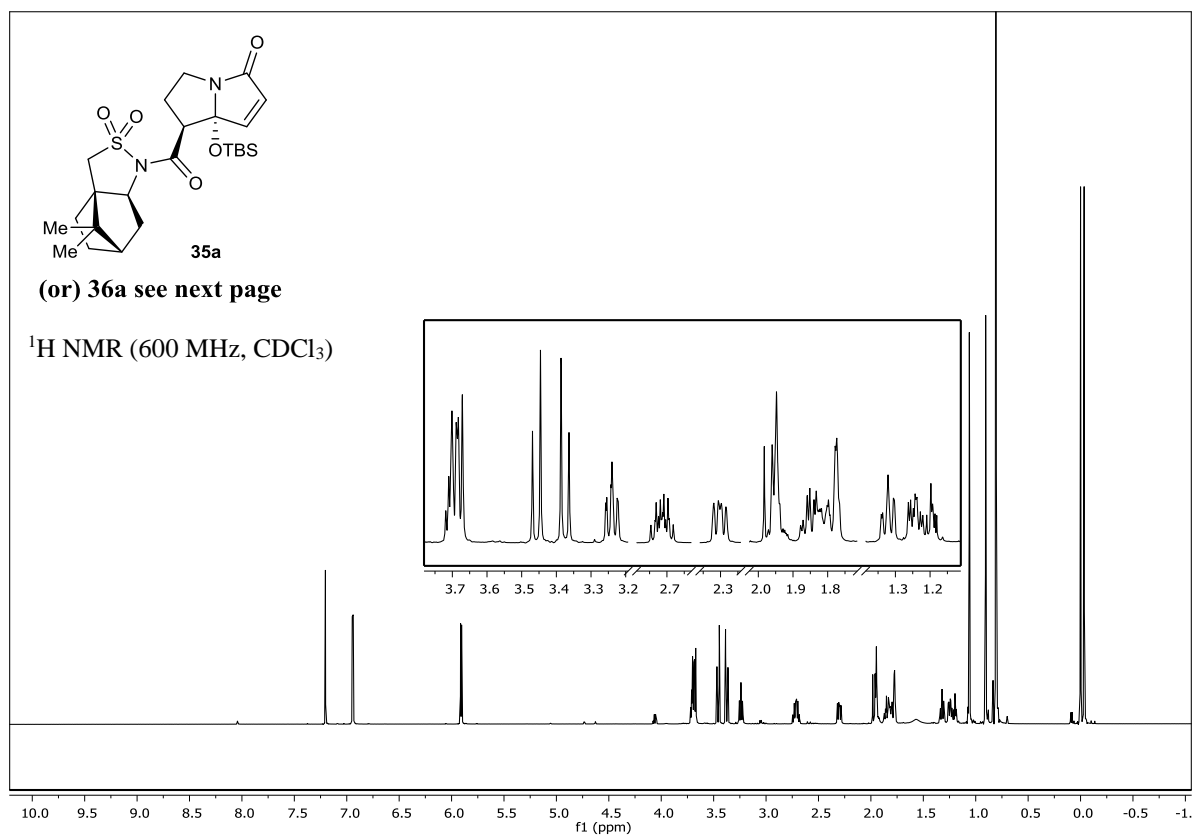
For these studies we used three clinical strains: *Enterococcus faecalis* S613, *Enterococcus faecium* isolate 105, and Methicillin-resistant *Staphylococcus aureus* MRA 371. Additionally, we also used one laboratory strain, *Bacillus subtilis* 168. We cultured the two enterococci strains in a mix of 80% Lysogeny Broth (LB) and 20% Brain Heart Infusion (BHI) and the MRSA 371 and *B. subtilis* 168 strains in 100% LB media.

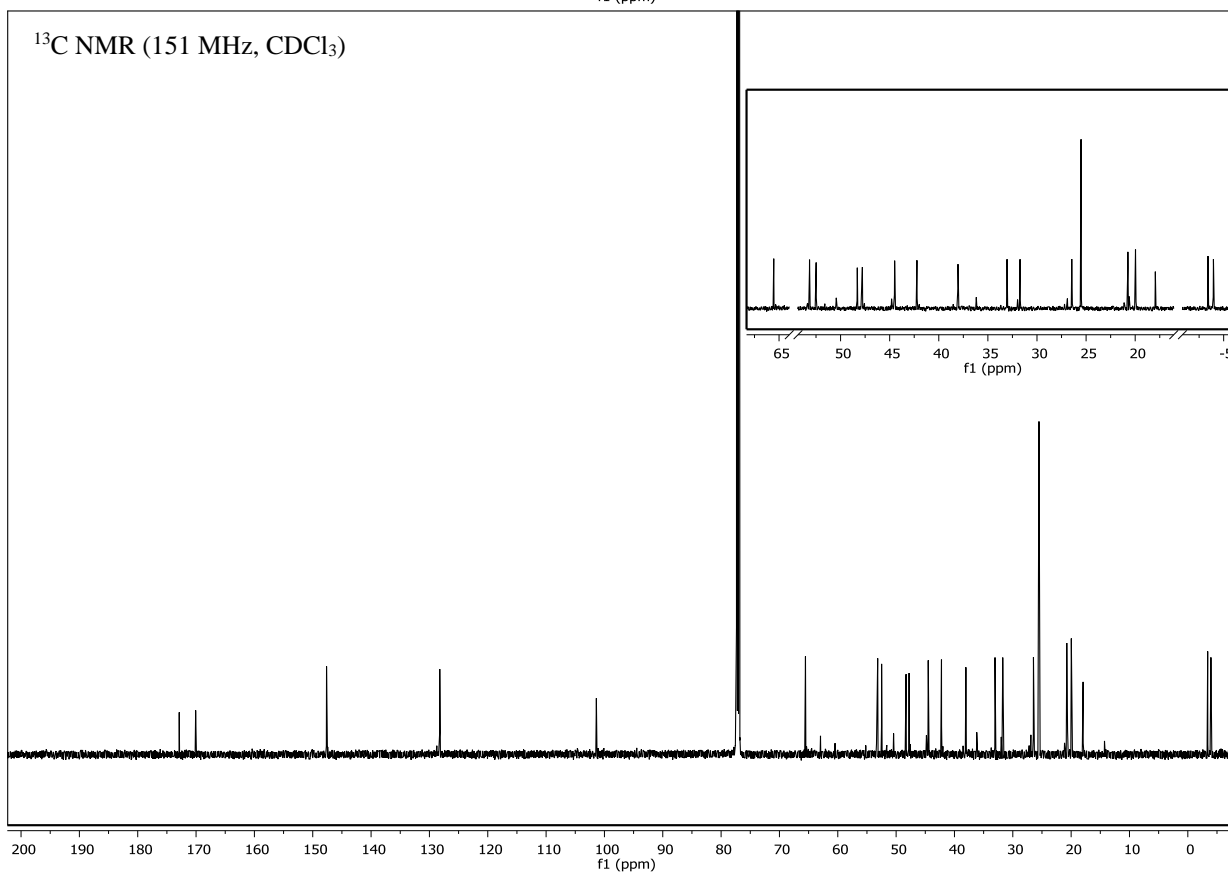
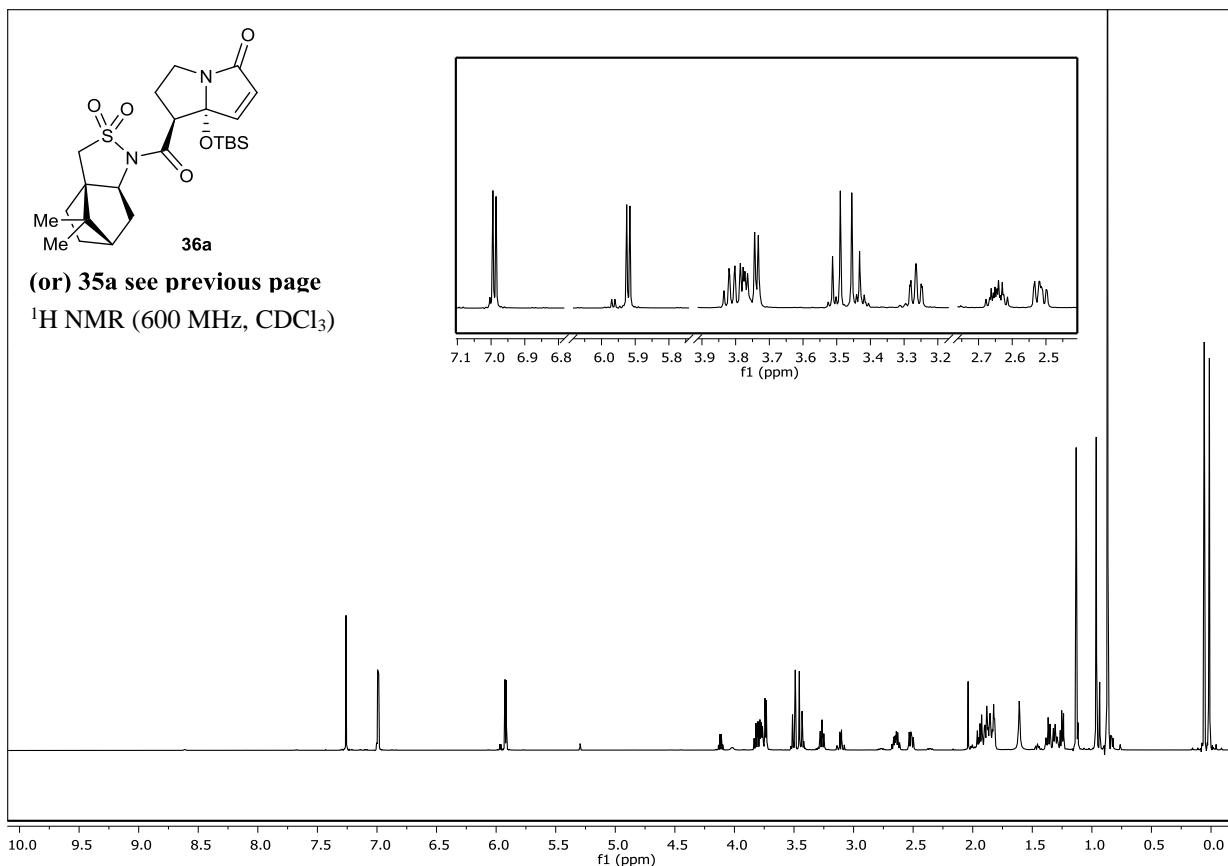
For the minimal inhibitory concentration (MIC) assays we performed standard micro-broth MIC assays in triplicate using 96-well plates. We filled wells with 100  $\mu$ L of broth media and then used 1  $\mu$ L of overnight stationary phase culture to inoculate the wells. CJ-16,264 and analogues were tested at concentrations that increased in two-fold increments and spanned 0.125–64  $\mu$ g/mL. We incubated the 96-well plates overnight at 37 °C. After 16–24 h we inspected the plates and defined MICs as the lowest drug concentration that had no visible growth in the well.

### IV. References

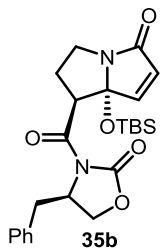
- (1) Lambert, T. H.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2006**, *128*, 426–427.

## V. $^1\text{H}$ and $^{13}\text{C}$ NMR Spectra of Compounds

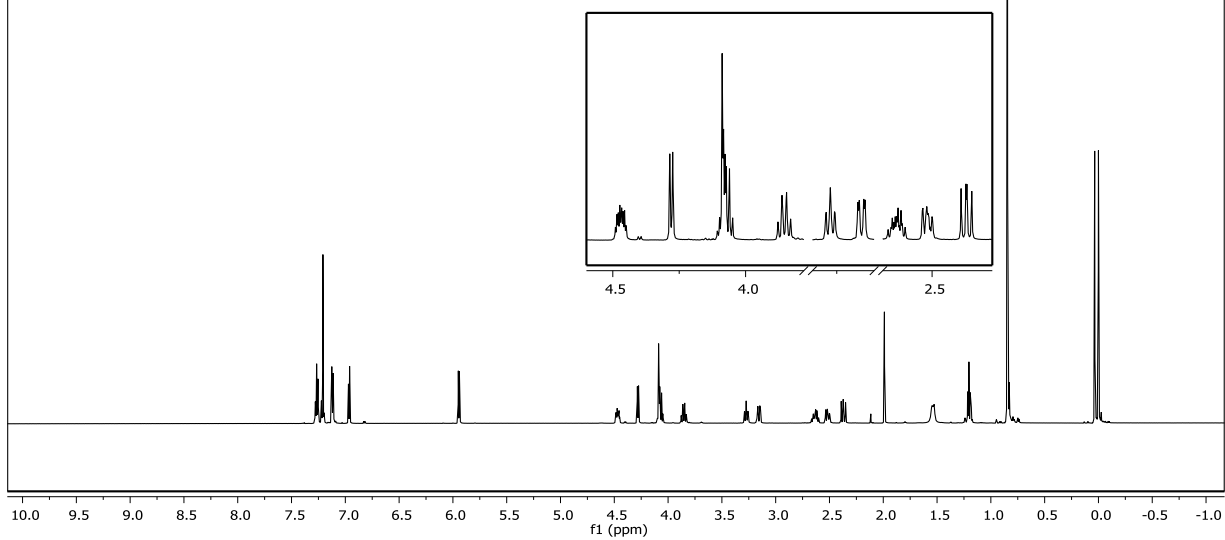




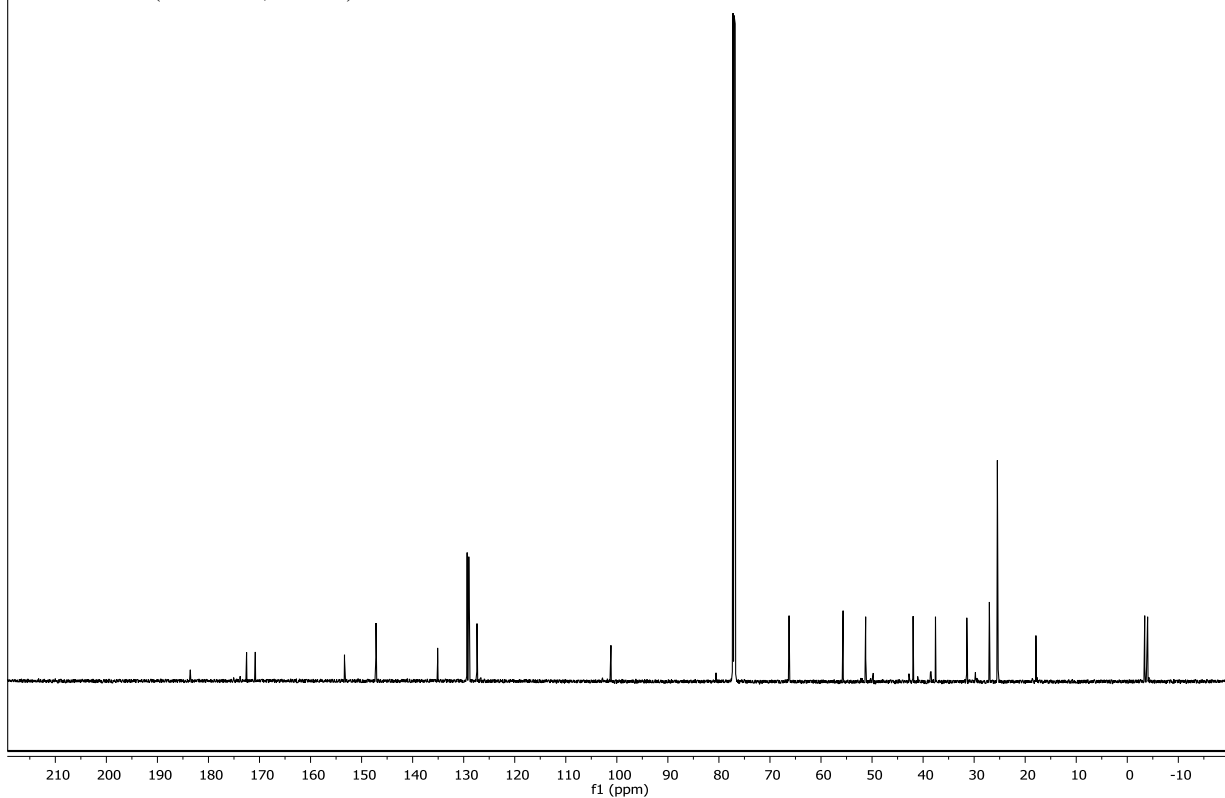


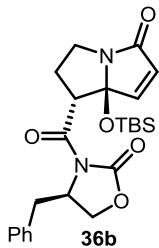


$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )

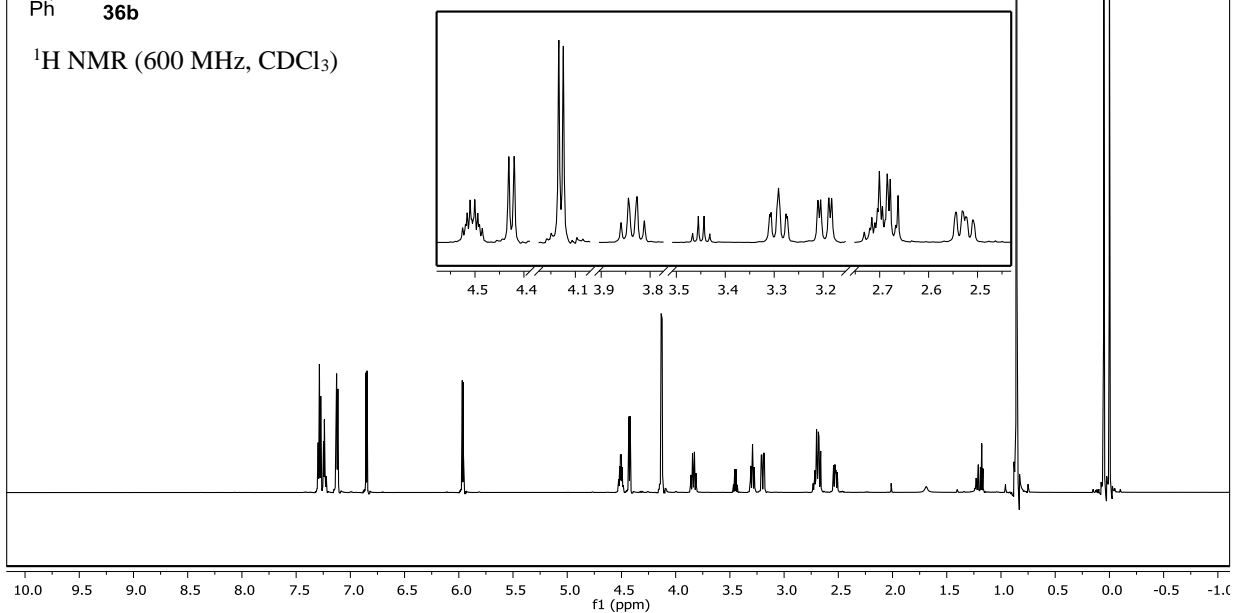


$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )

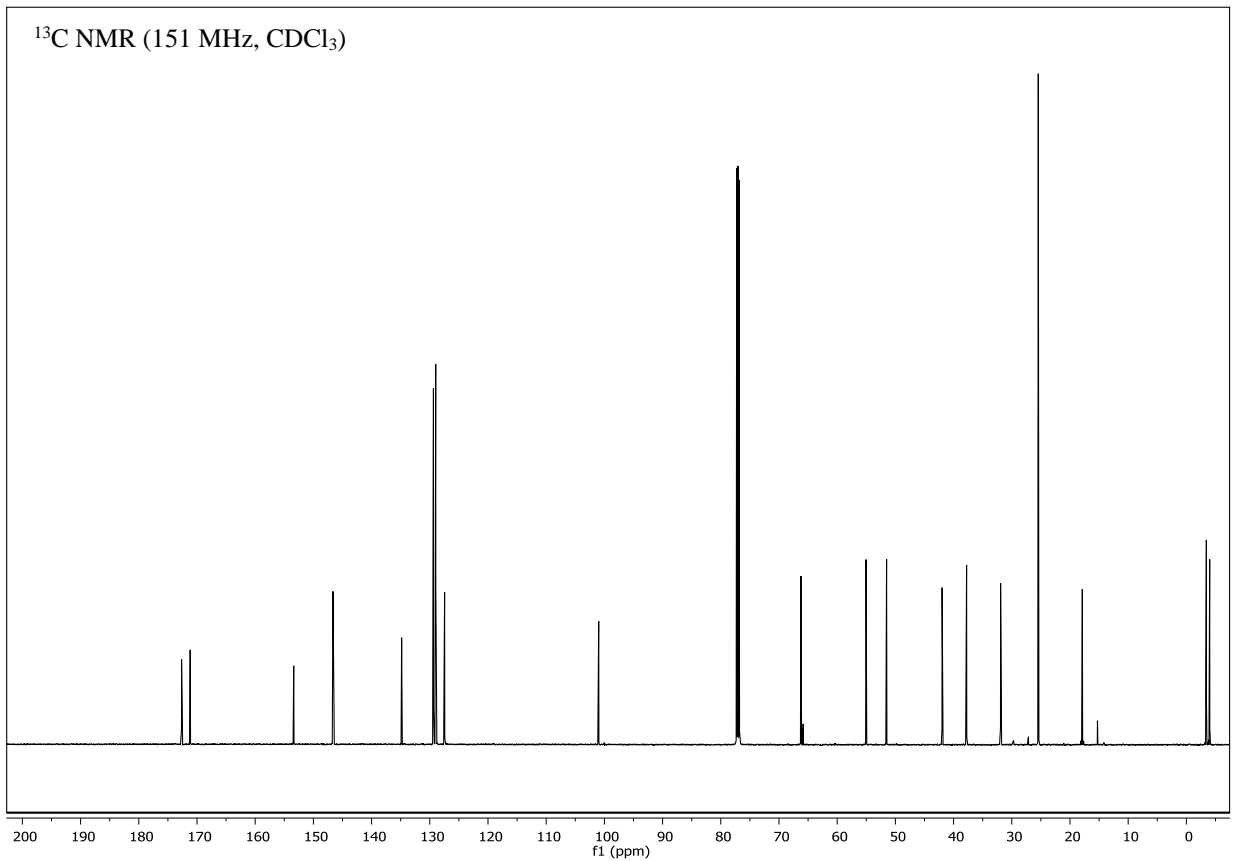




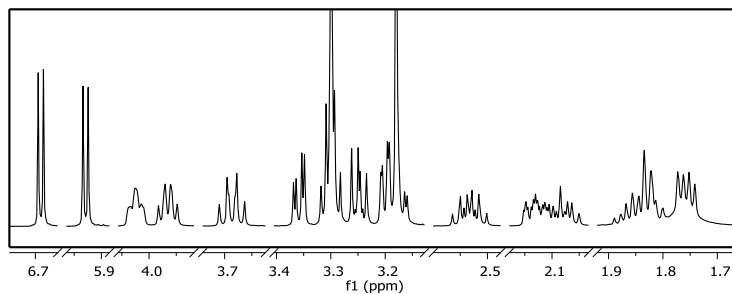
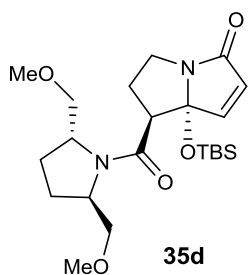
<sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)



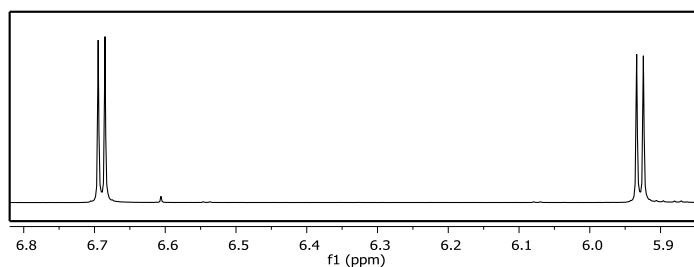
<sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)



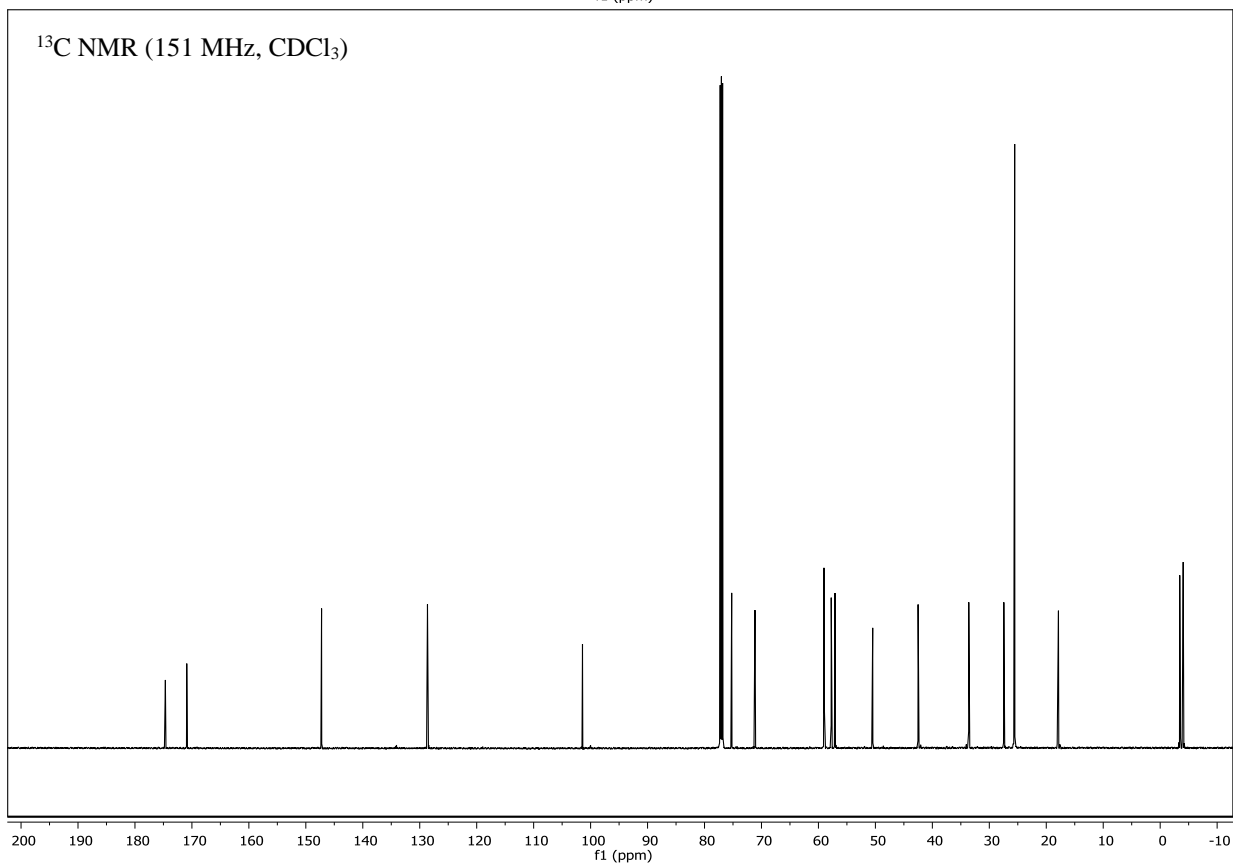


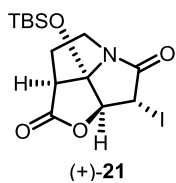


$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )

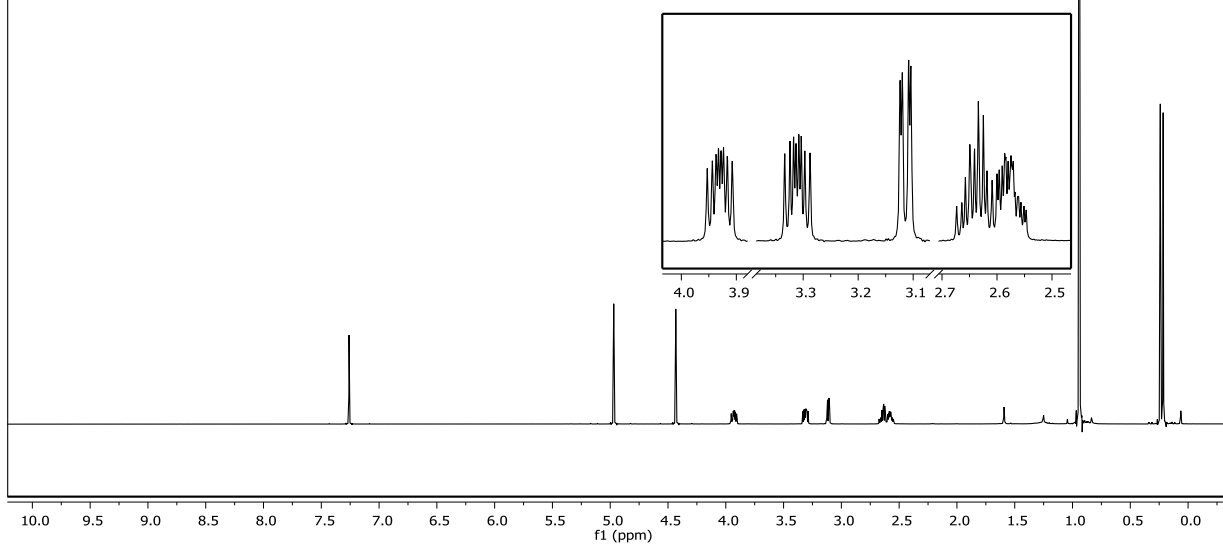


$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )

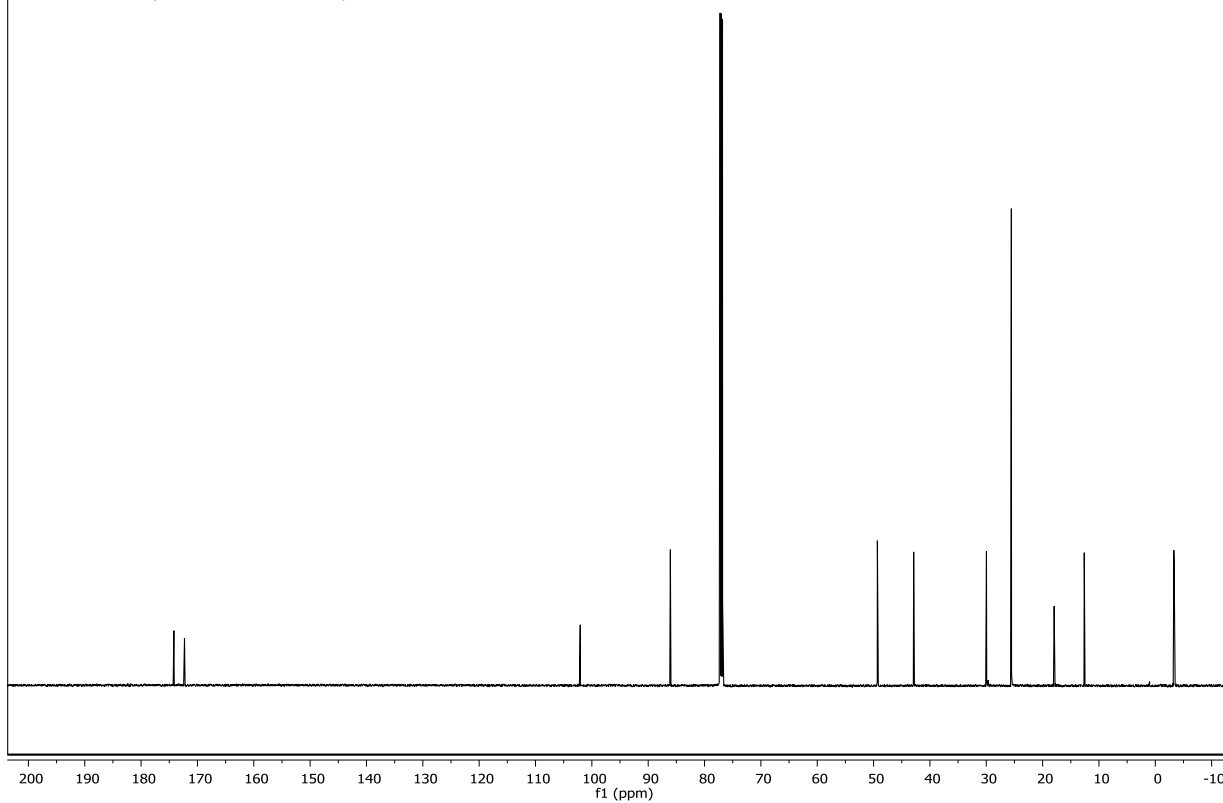


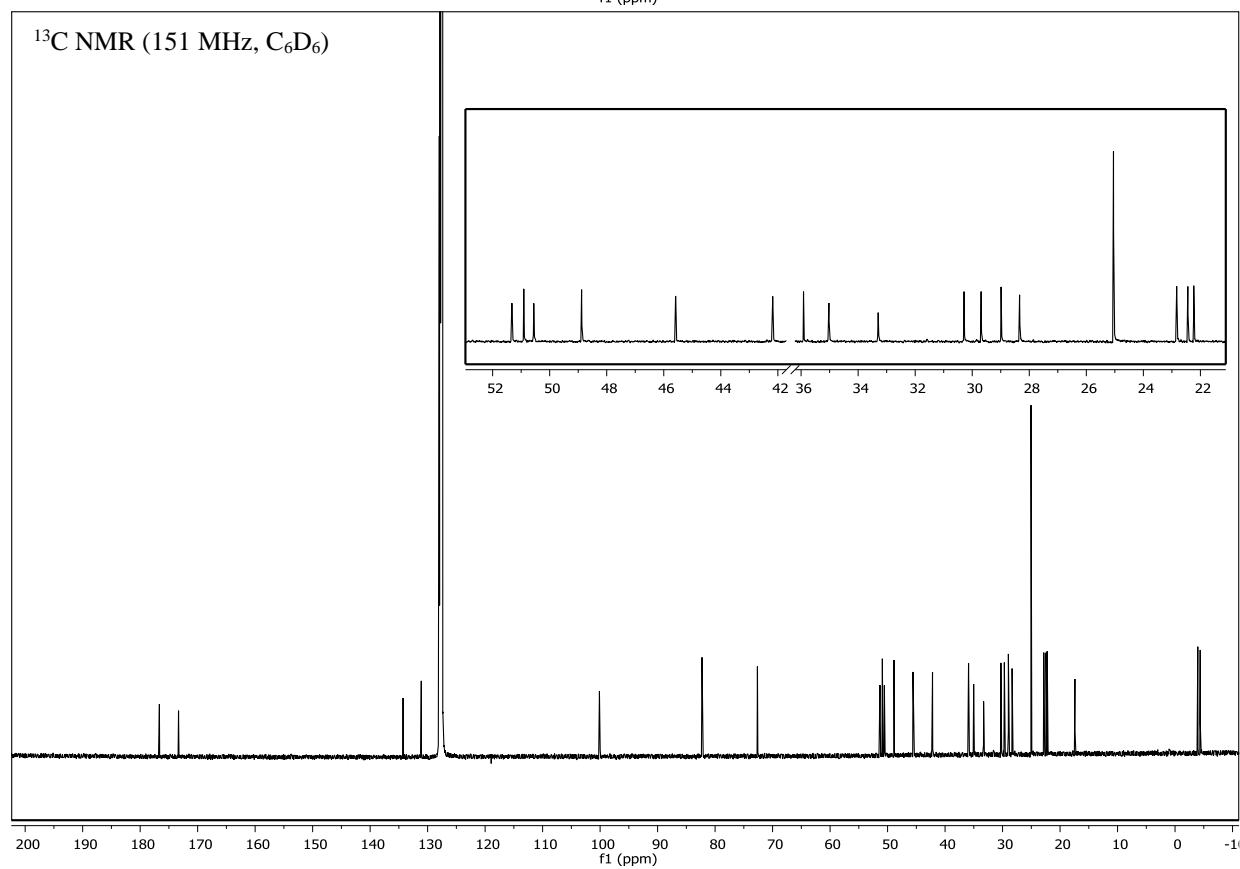
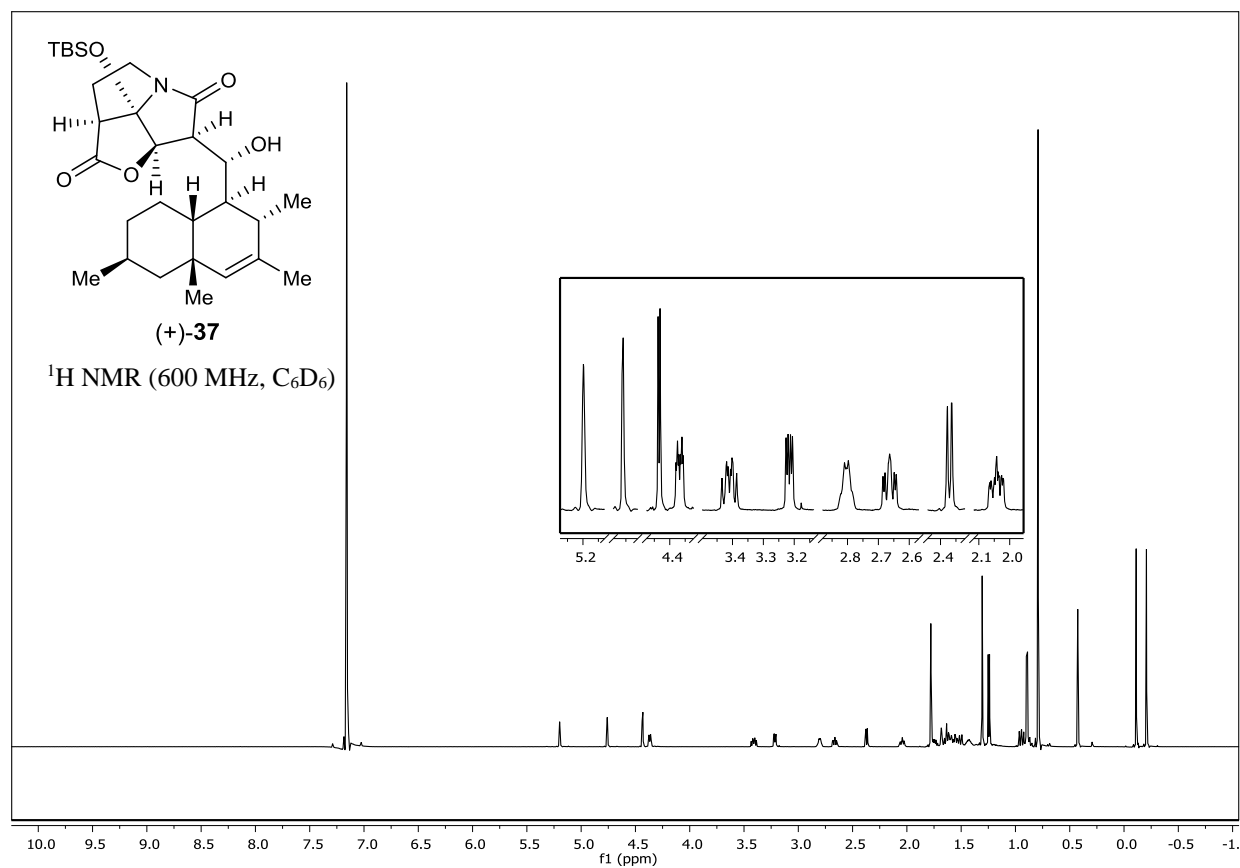


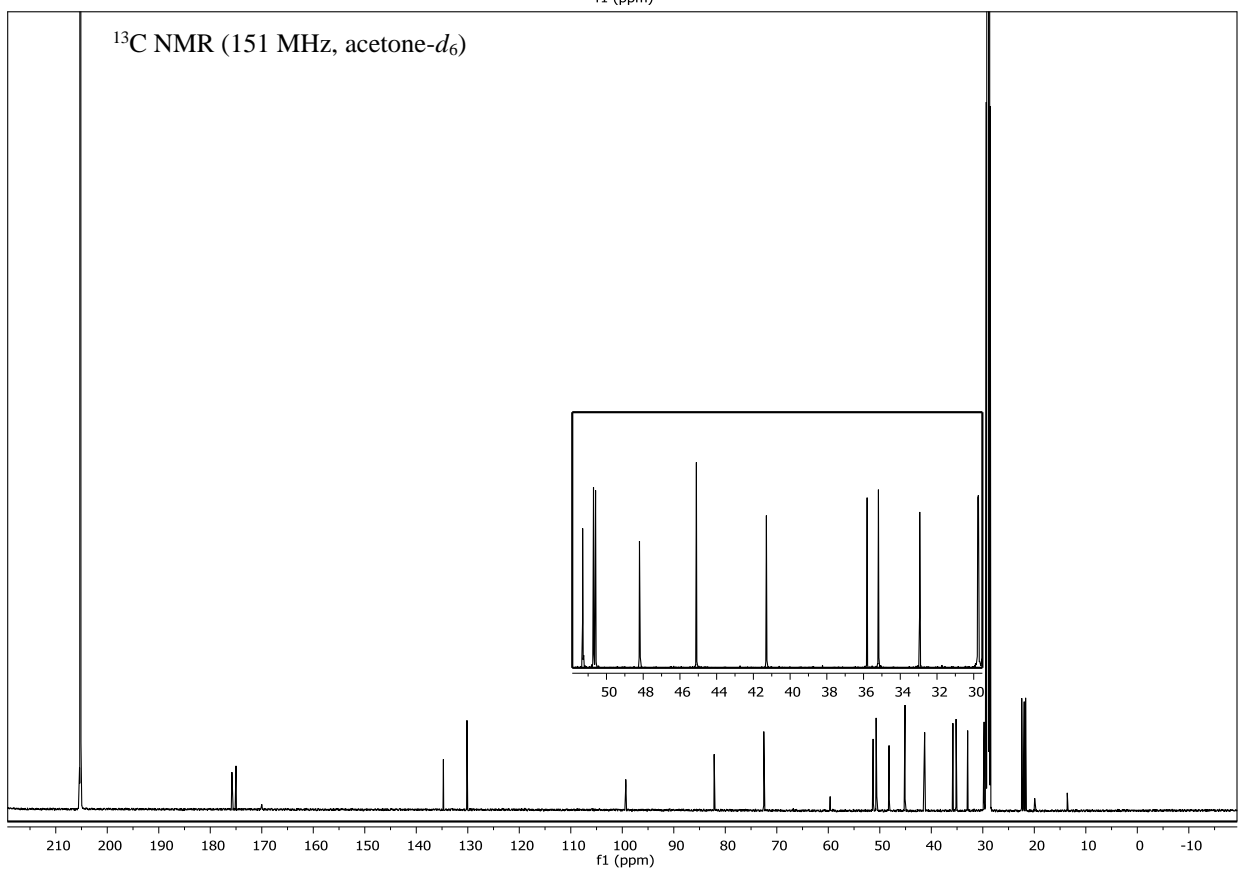
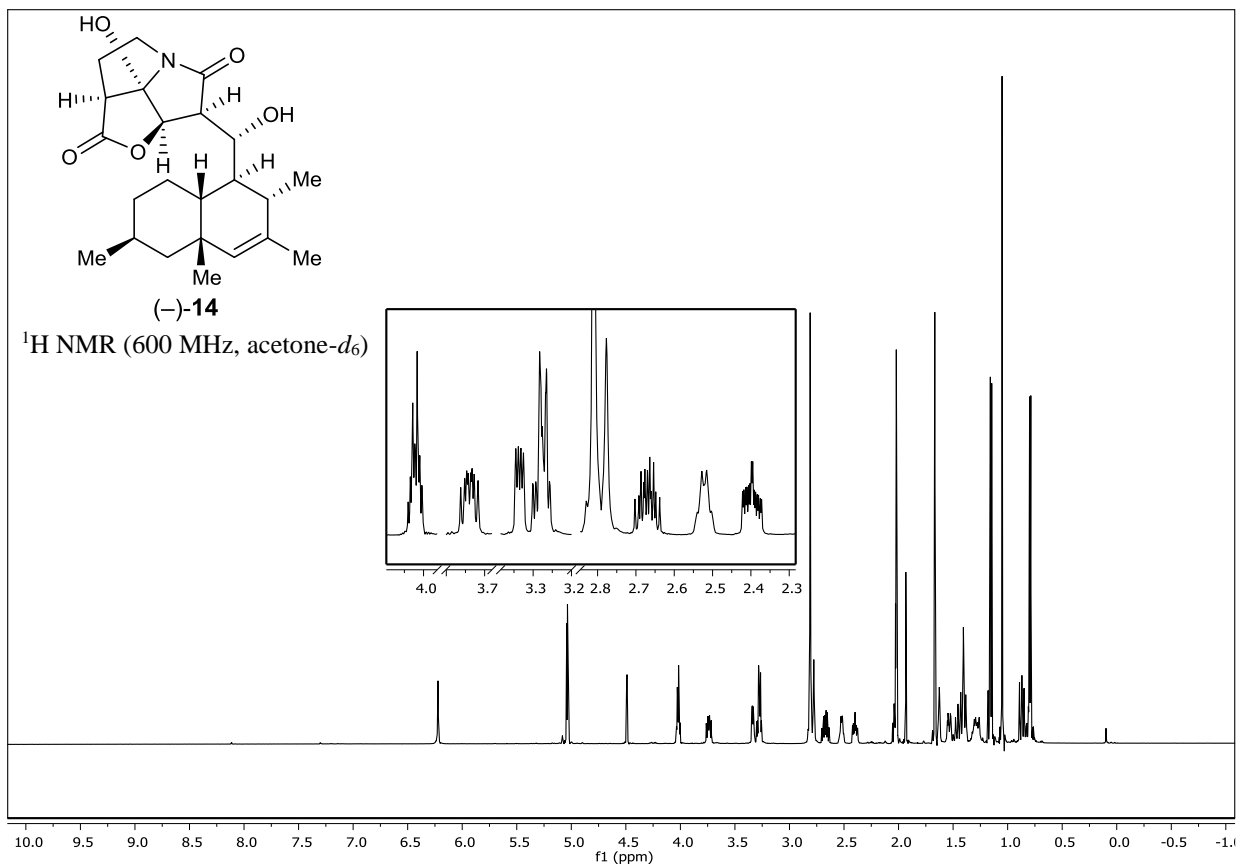
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )

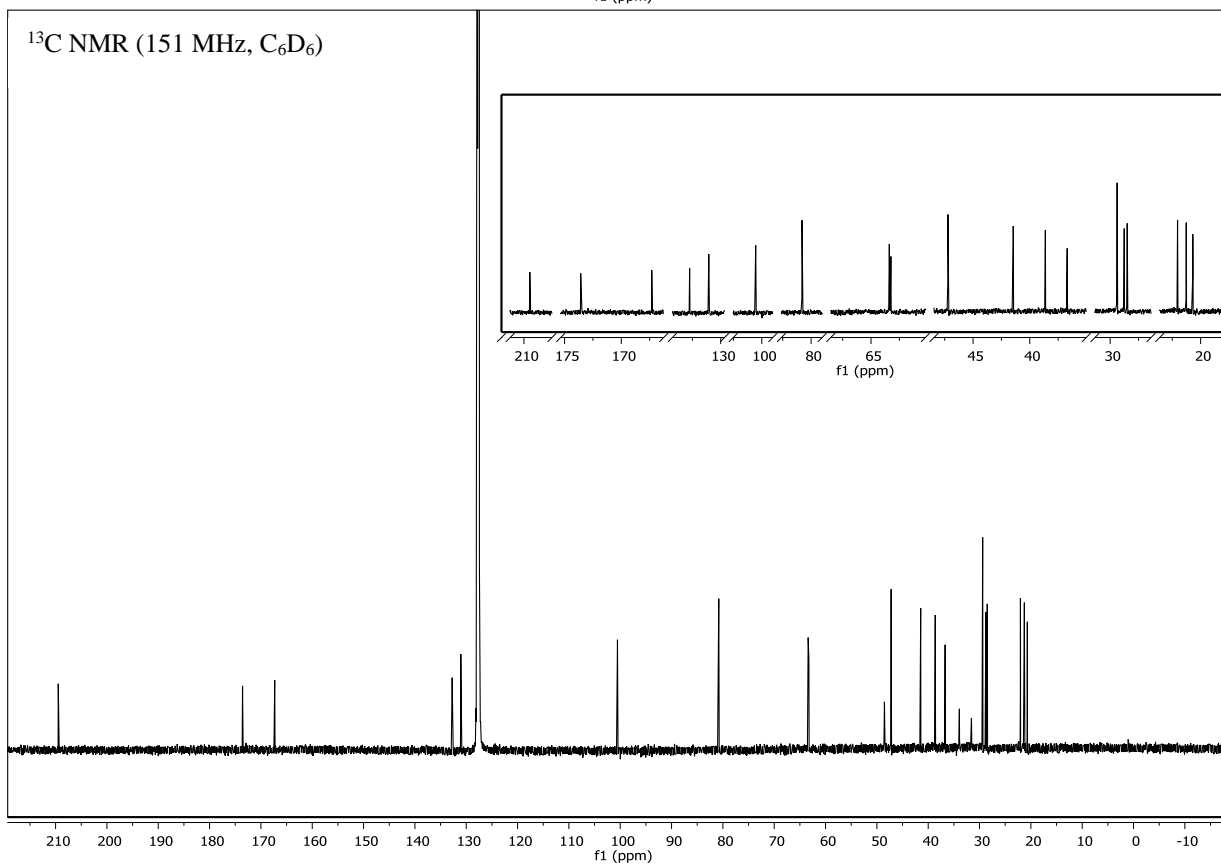
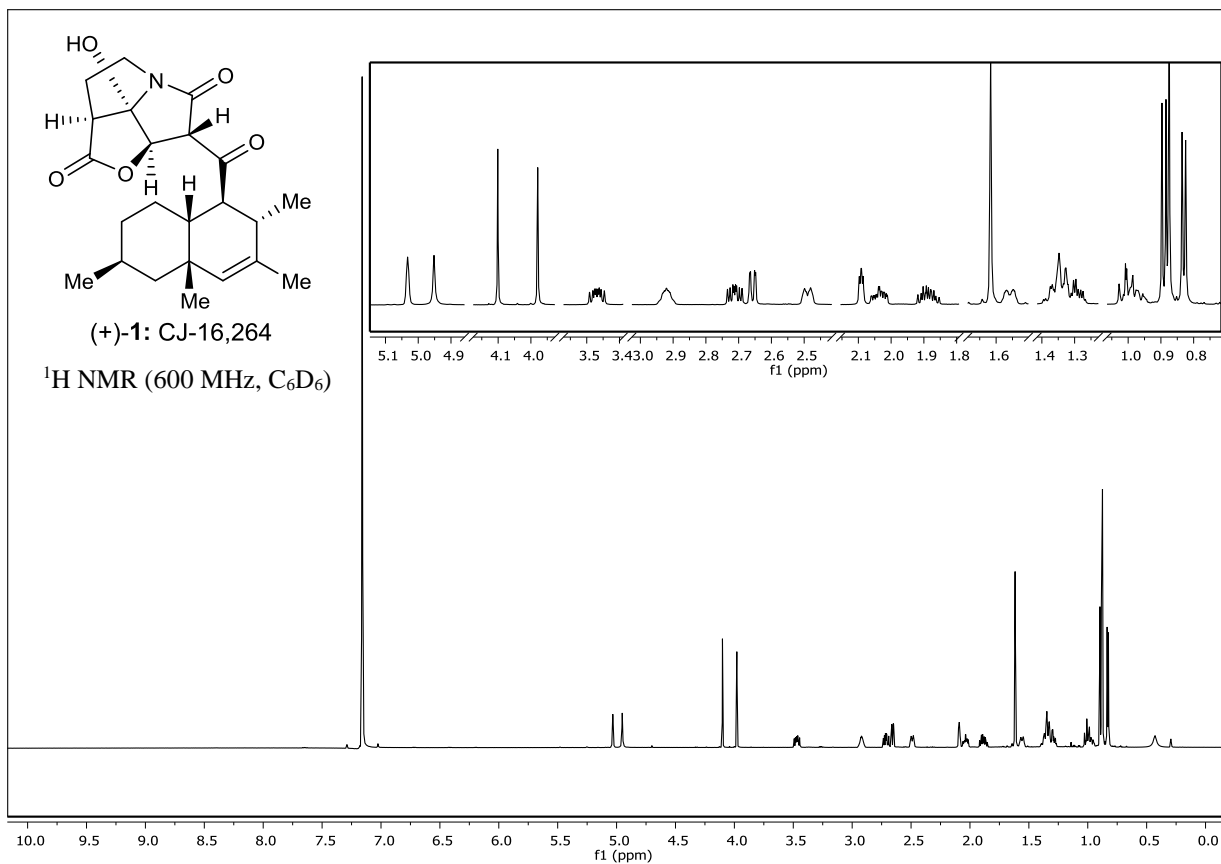


$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )

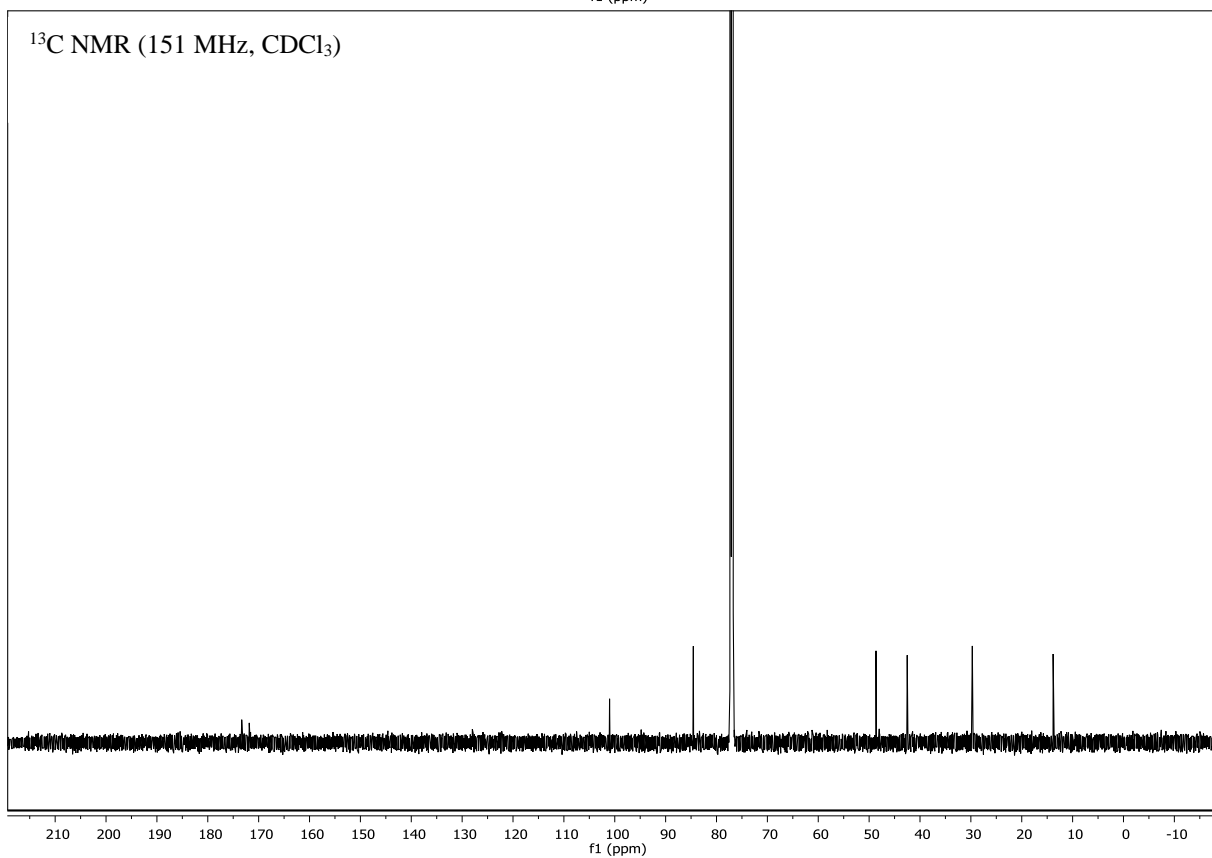
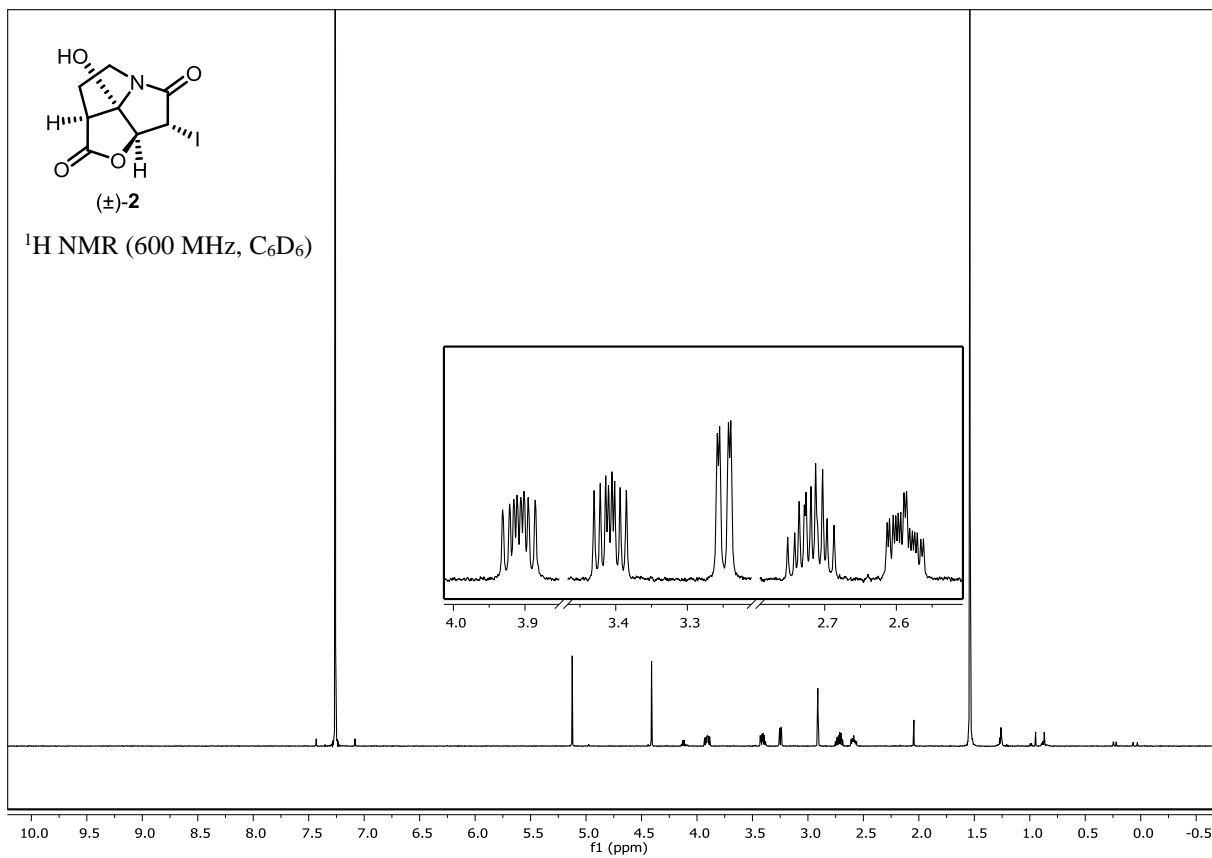




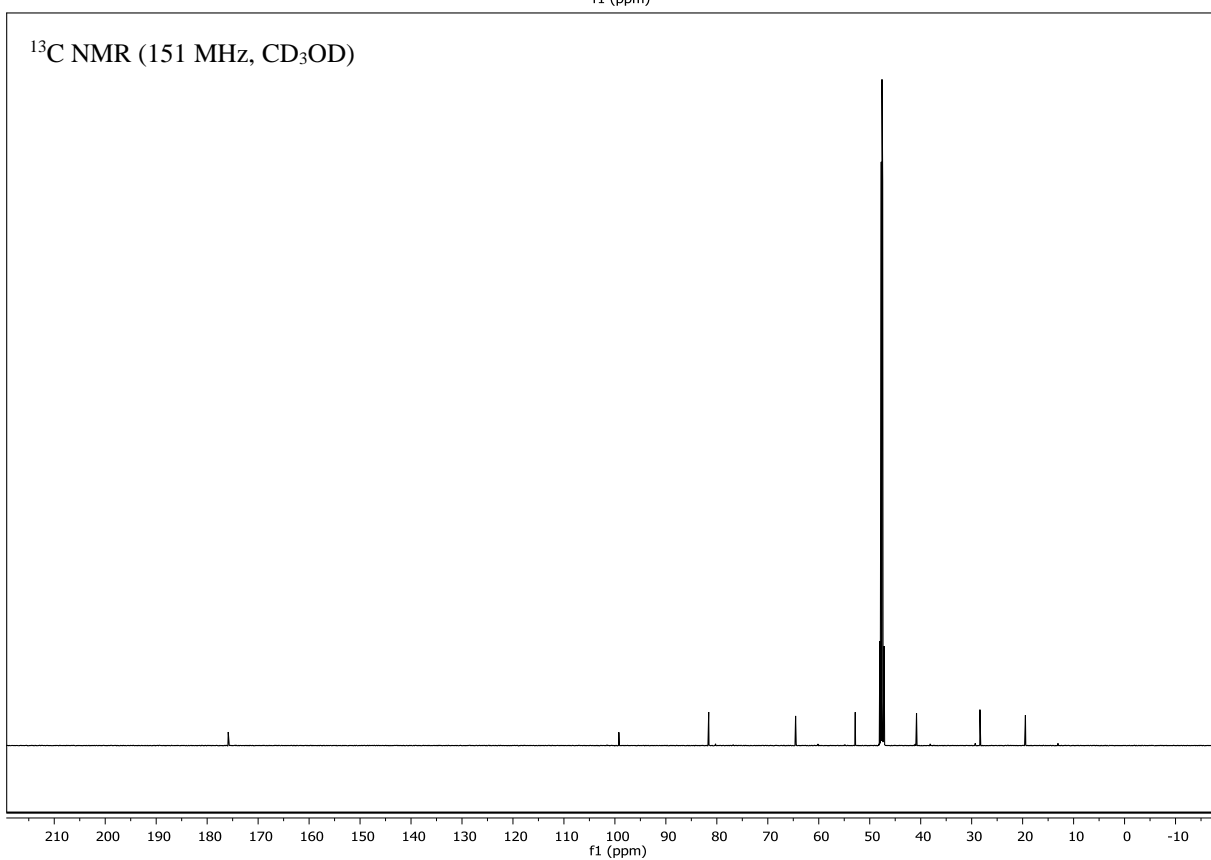
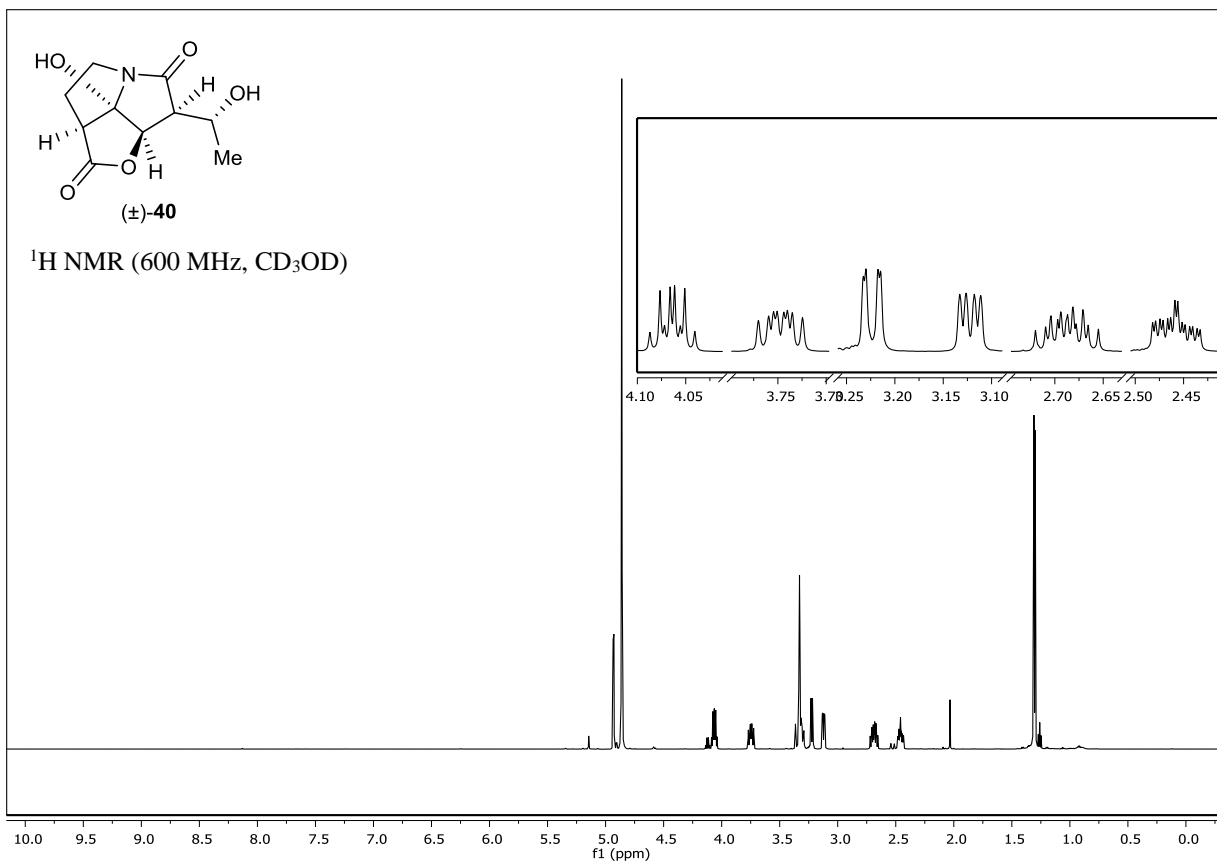


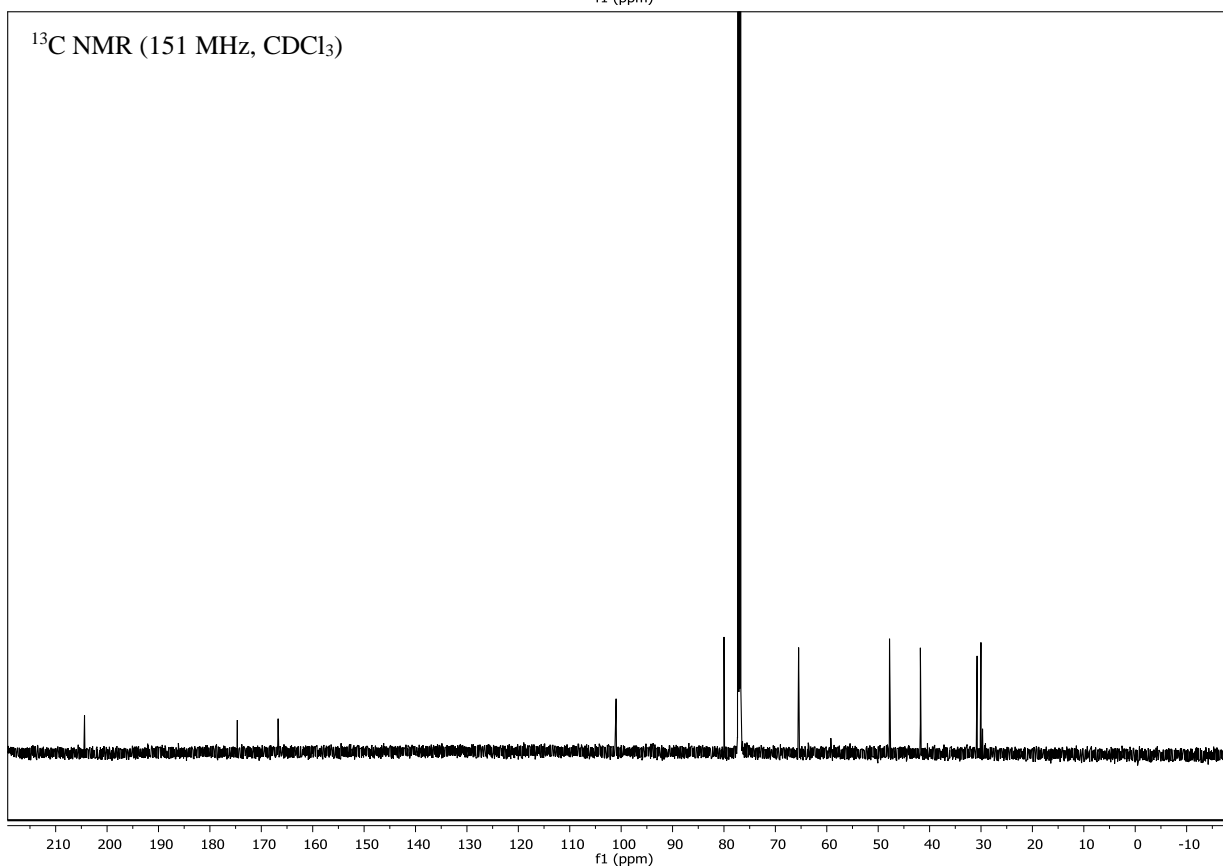
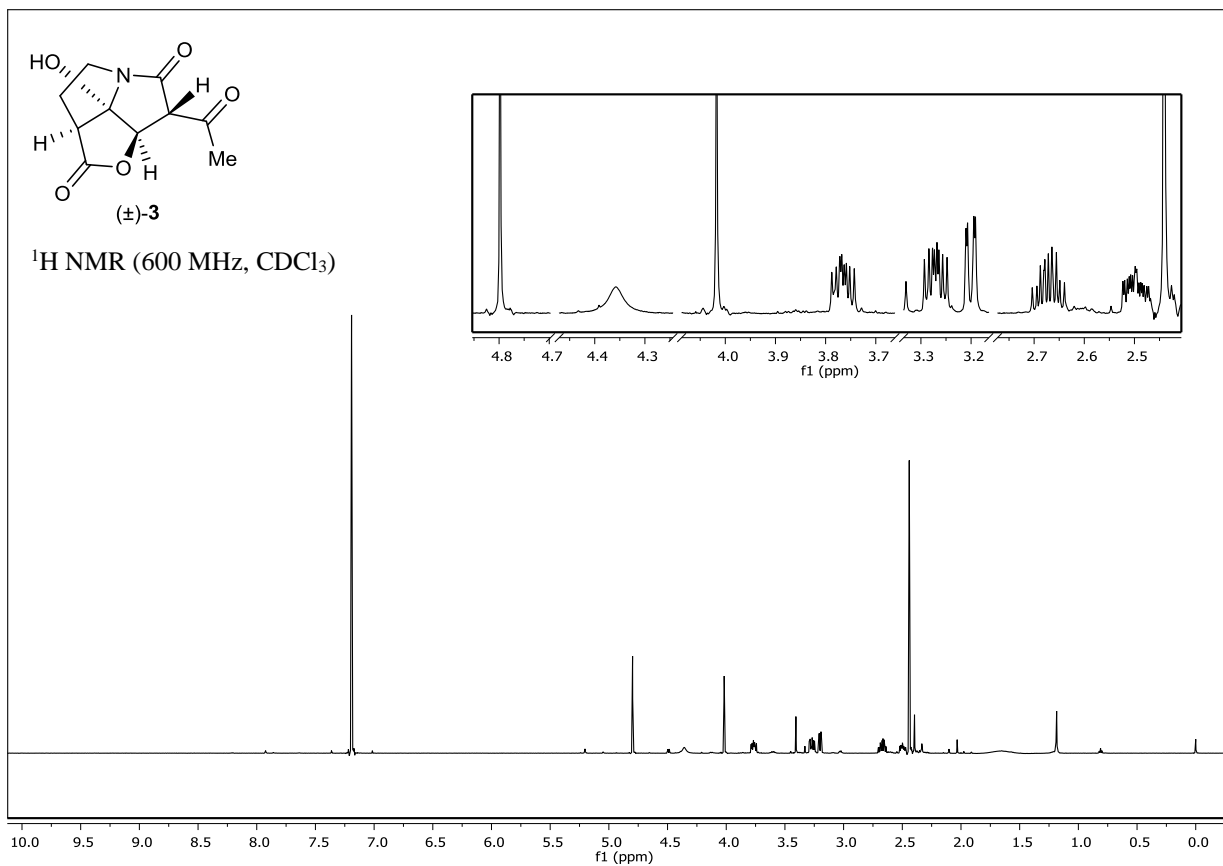




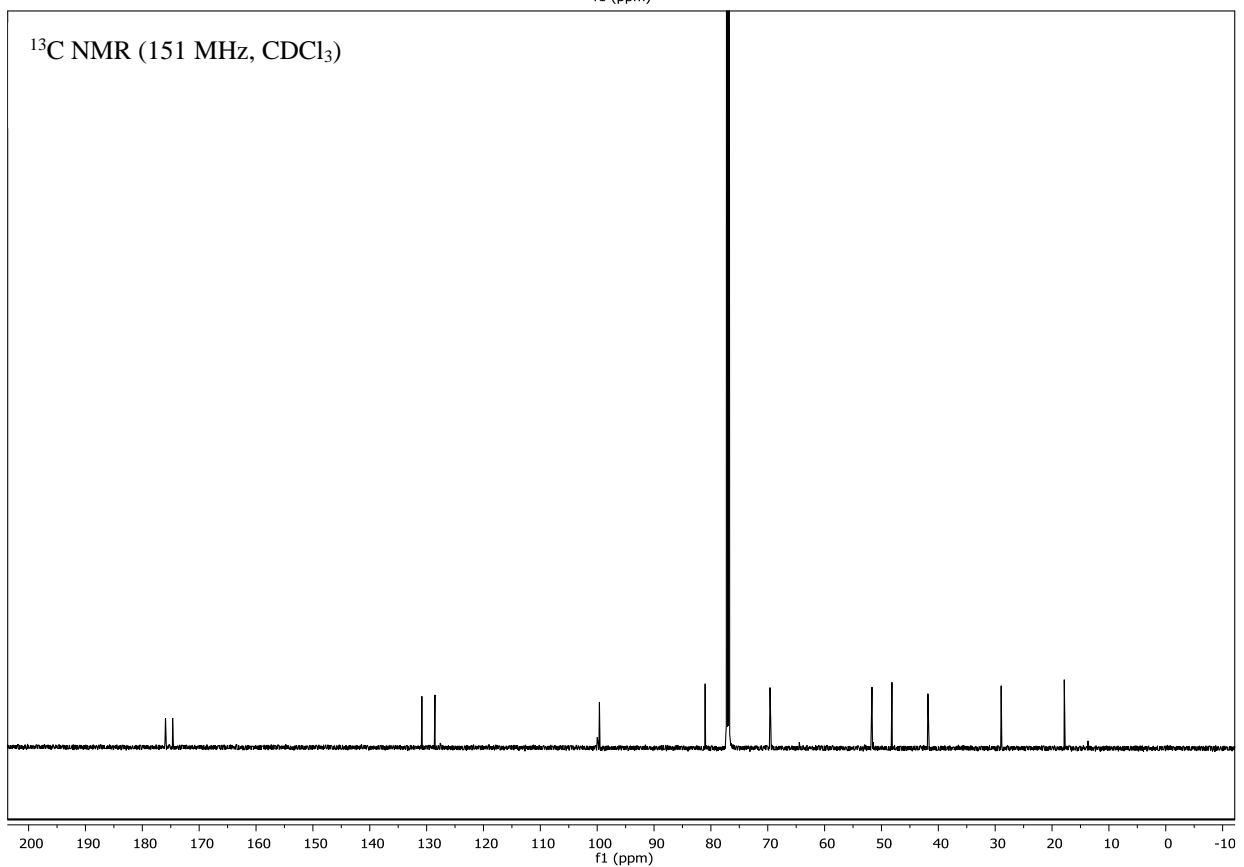
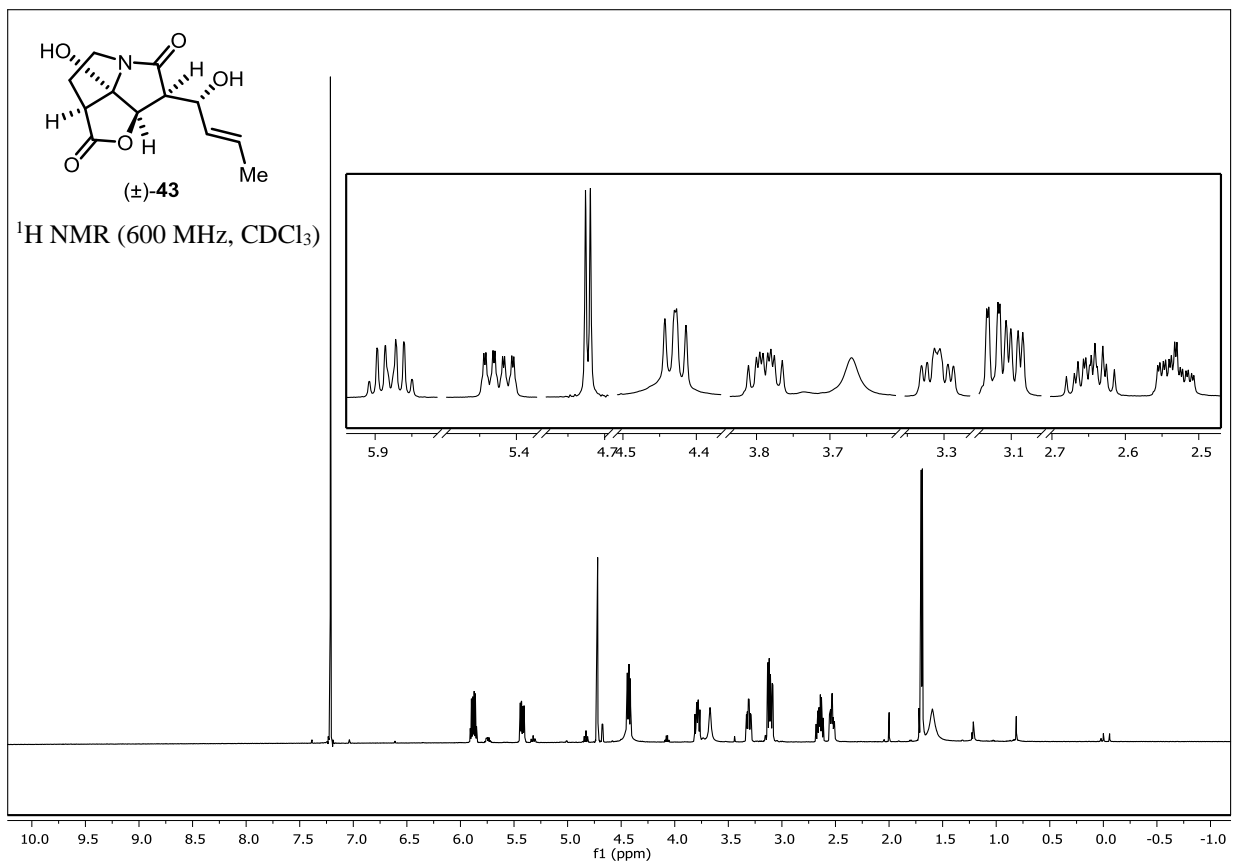


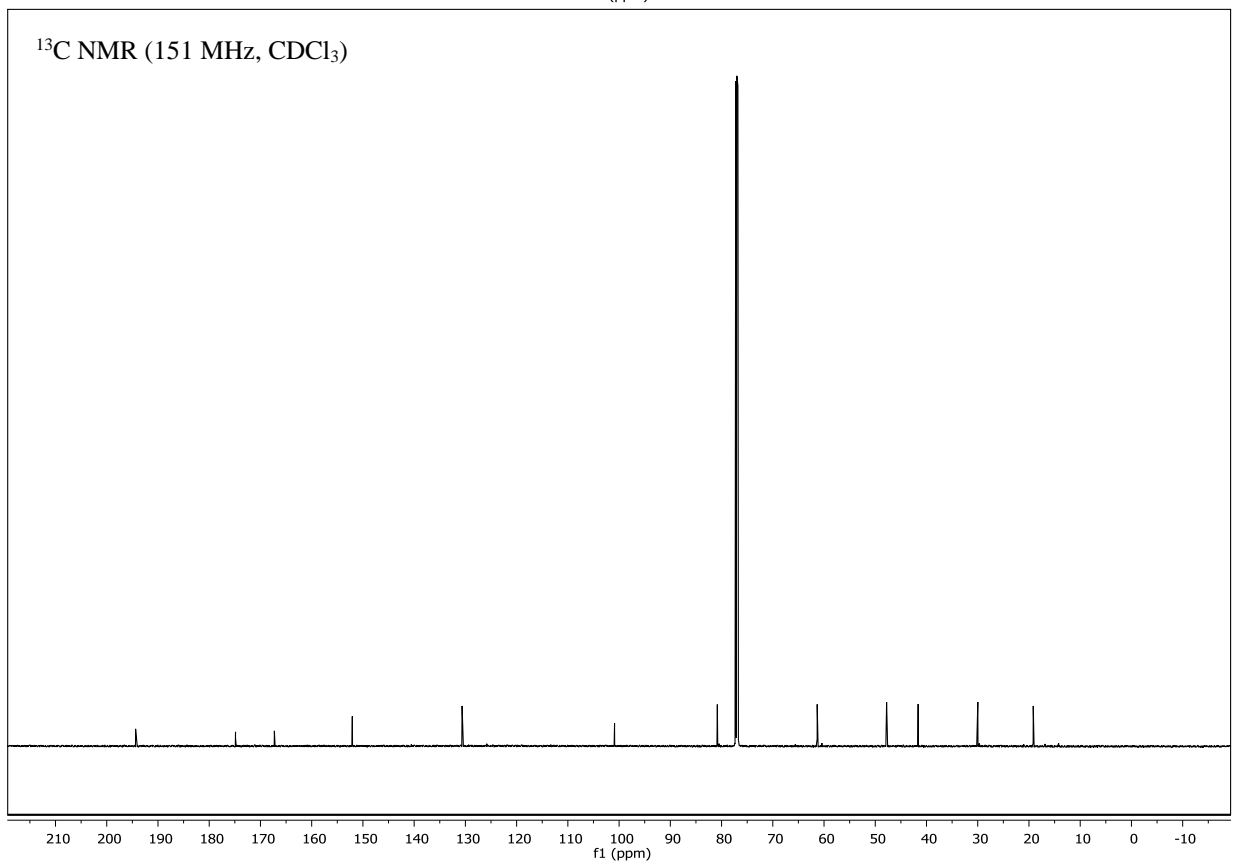
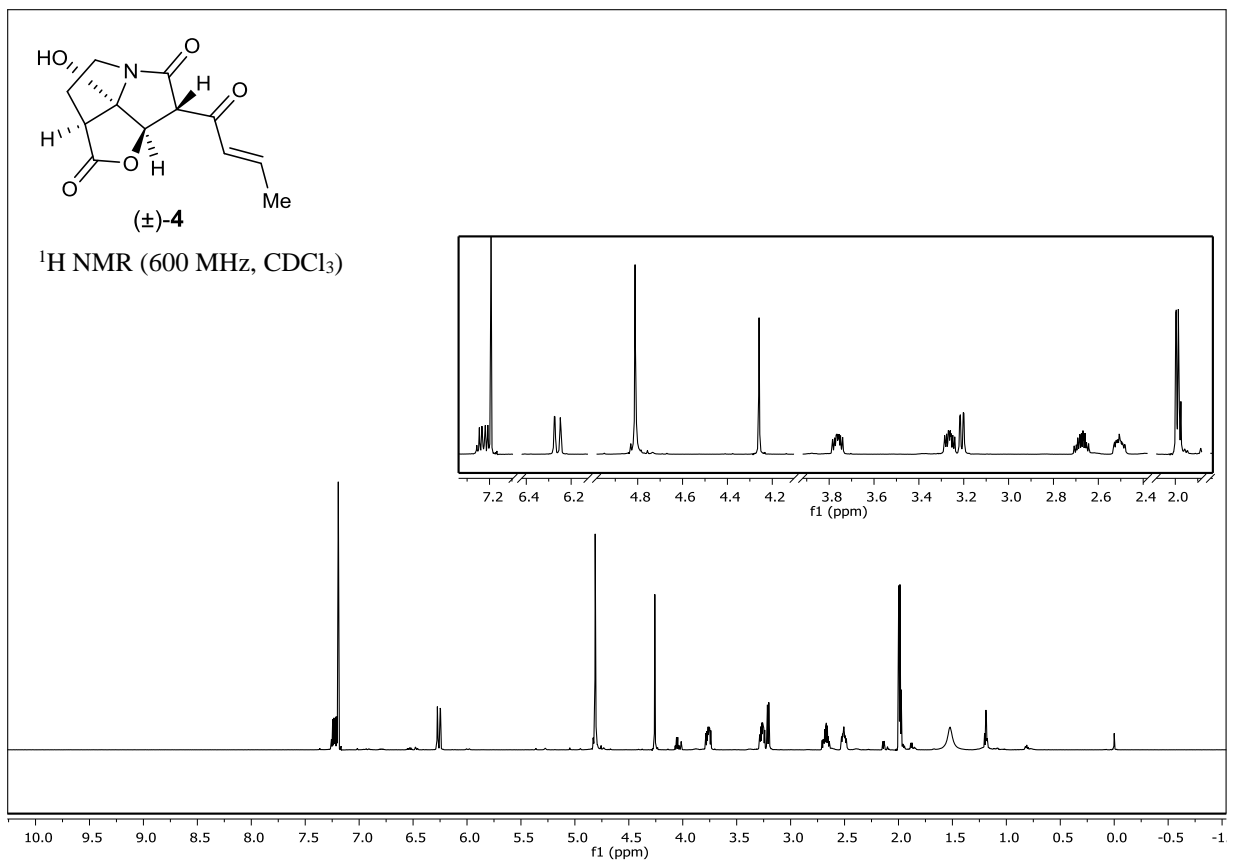






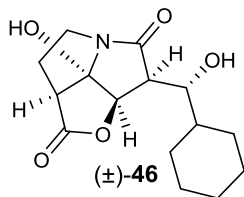




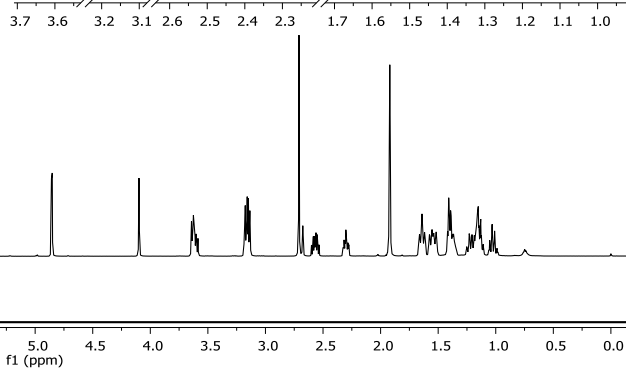
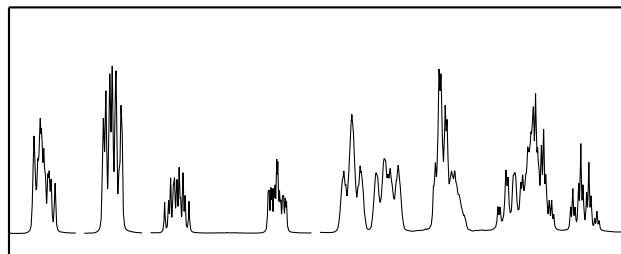




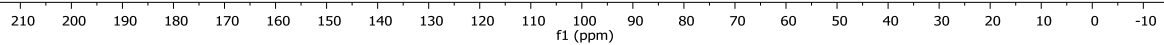
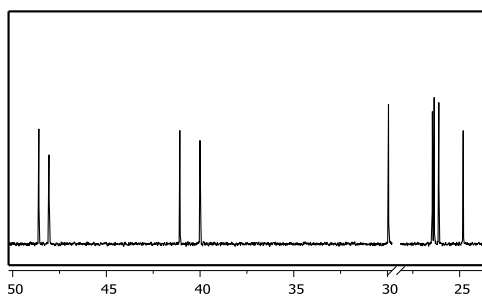


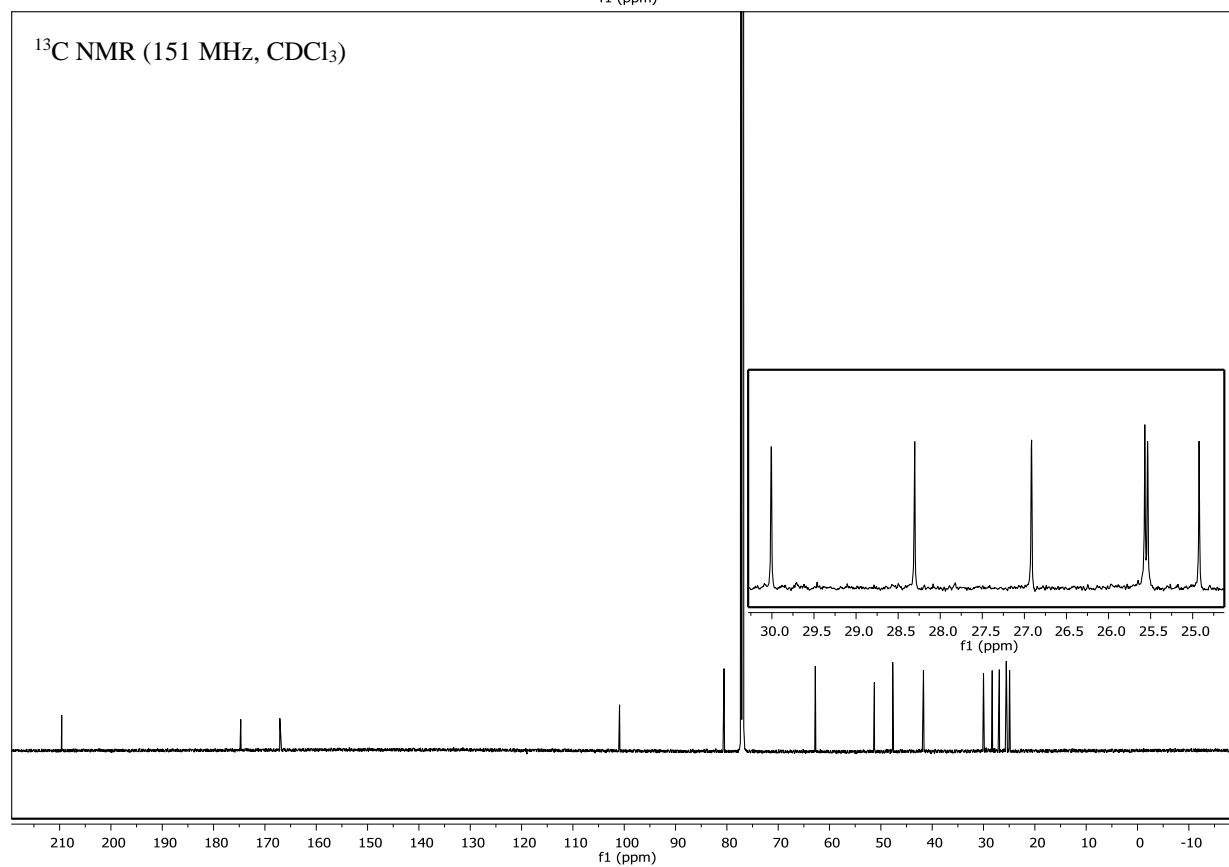
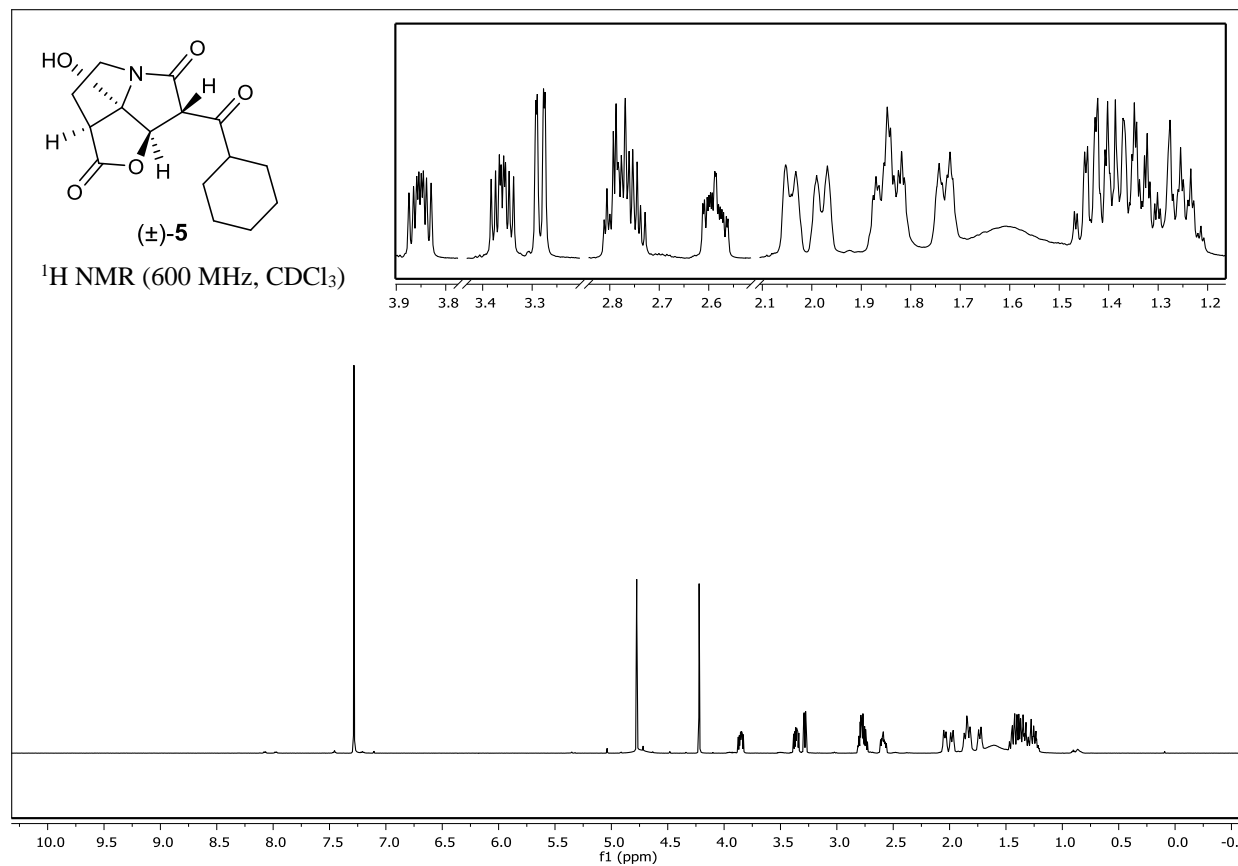


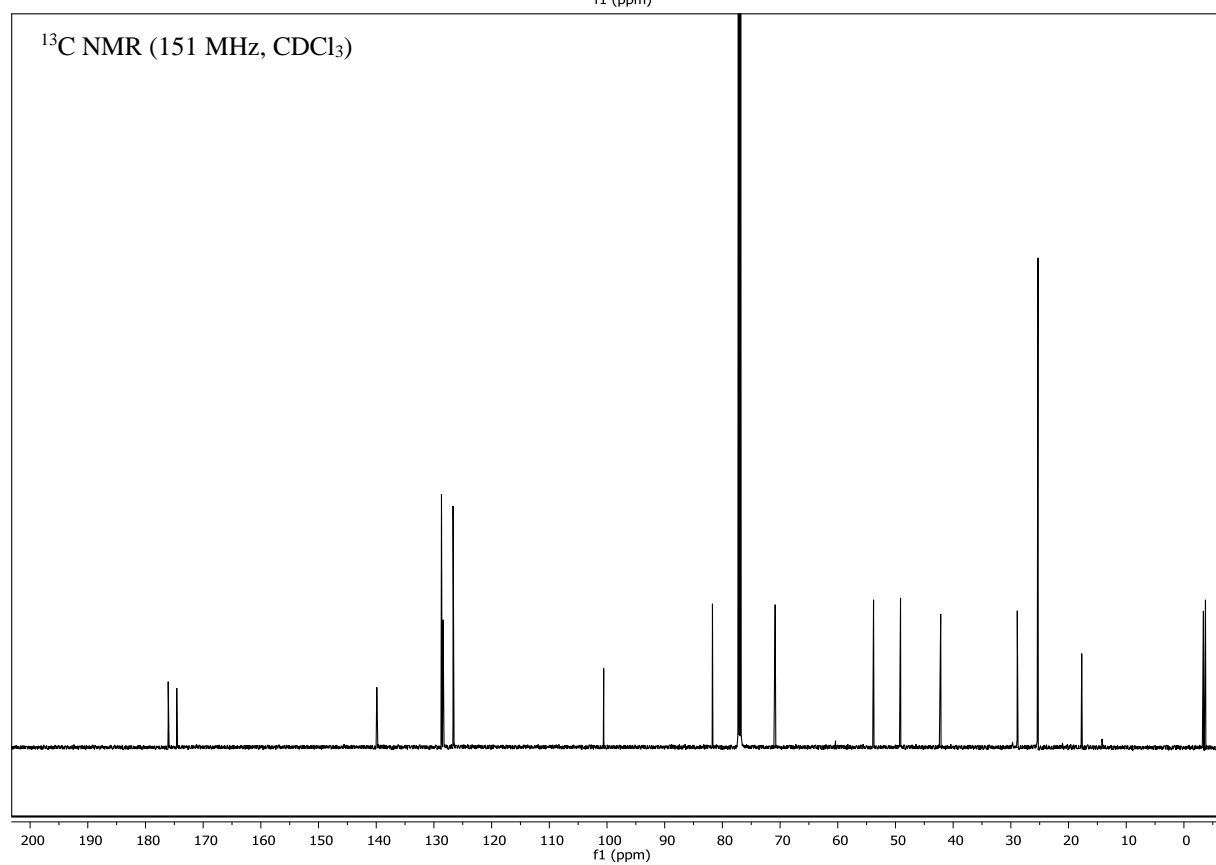
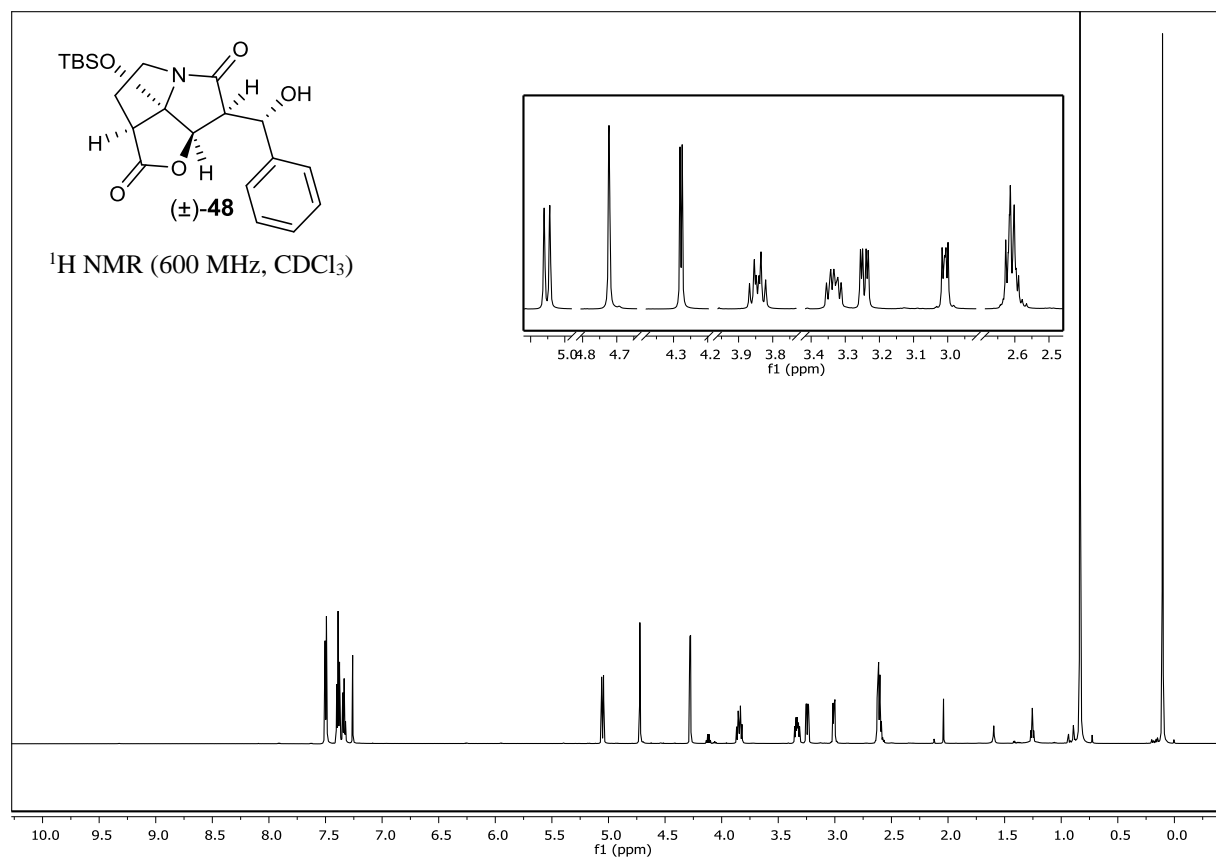
<sup>1</sup>H NMR (600 MHz, acetone-*d*<sub>6</sub>)

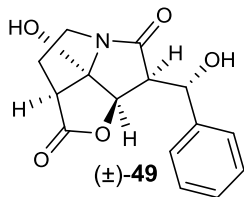


<sup>13</sup>C NMR (151 MHz, acetone-*d*<sub>6</sub>)

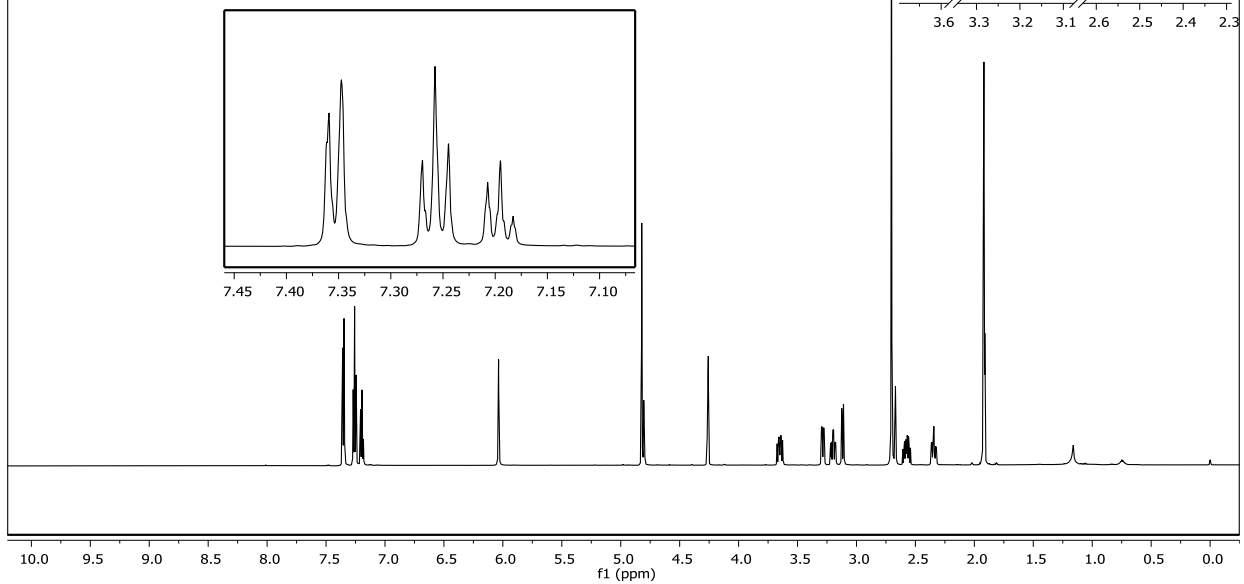




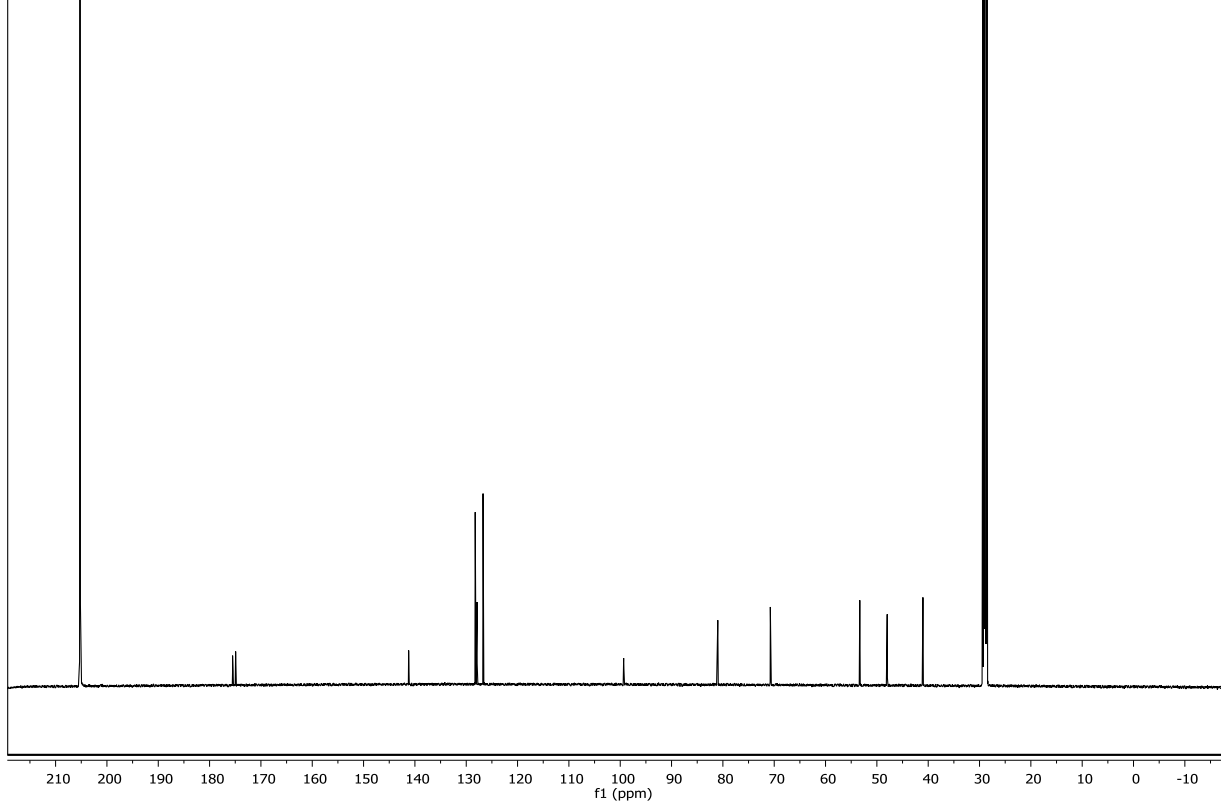


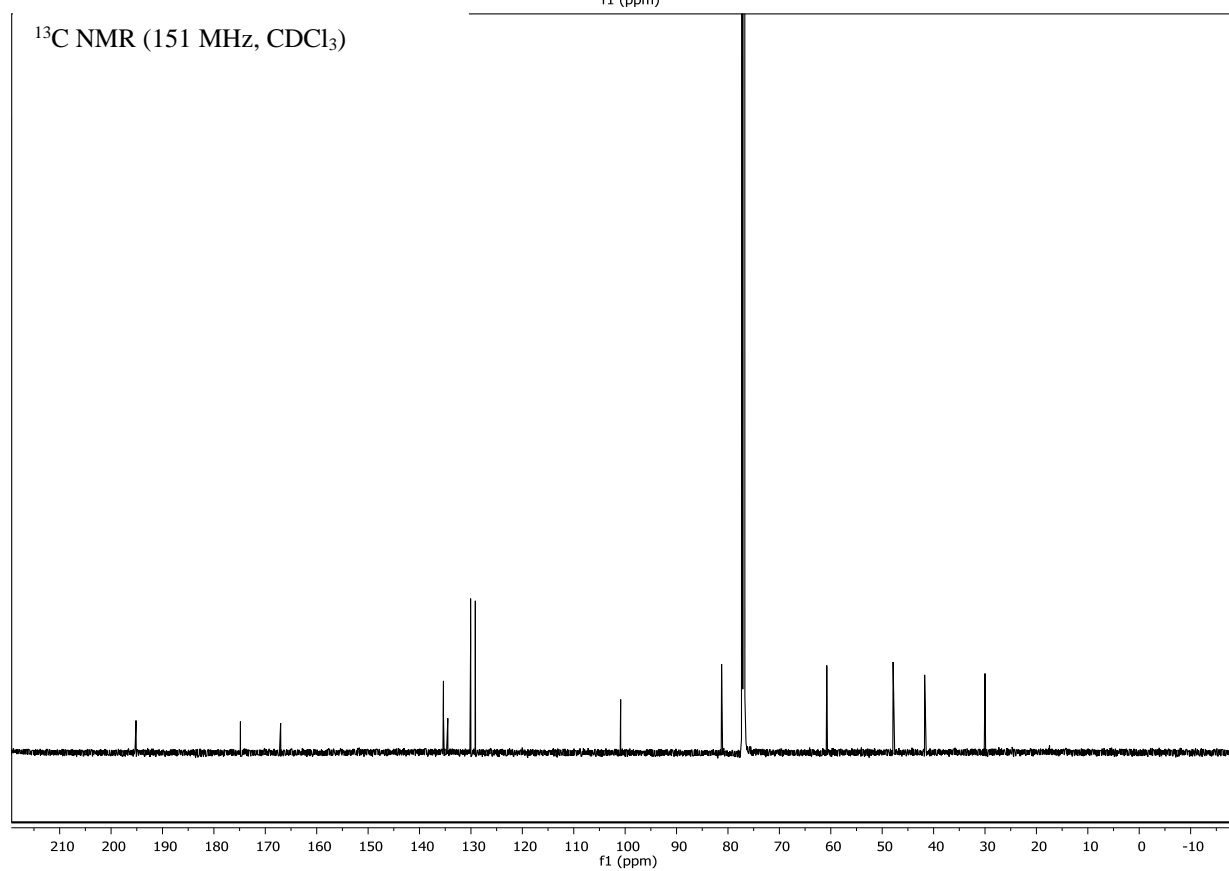
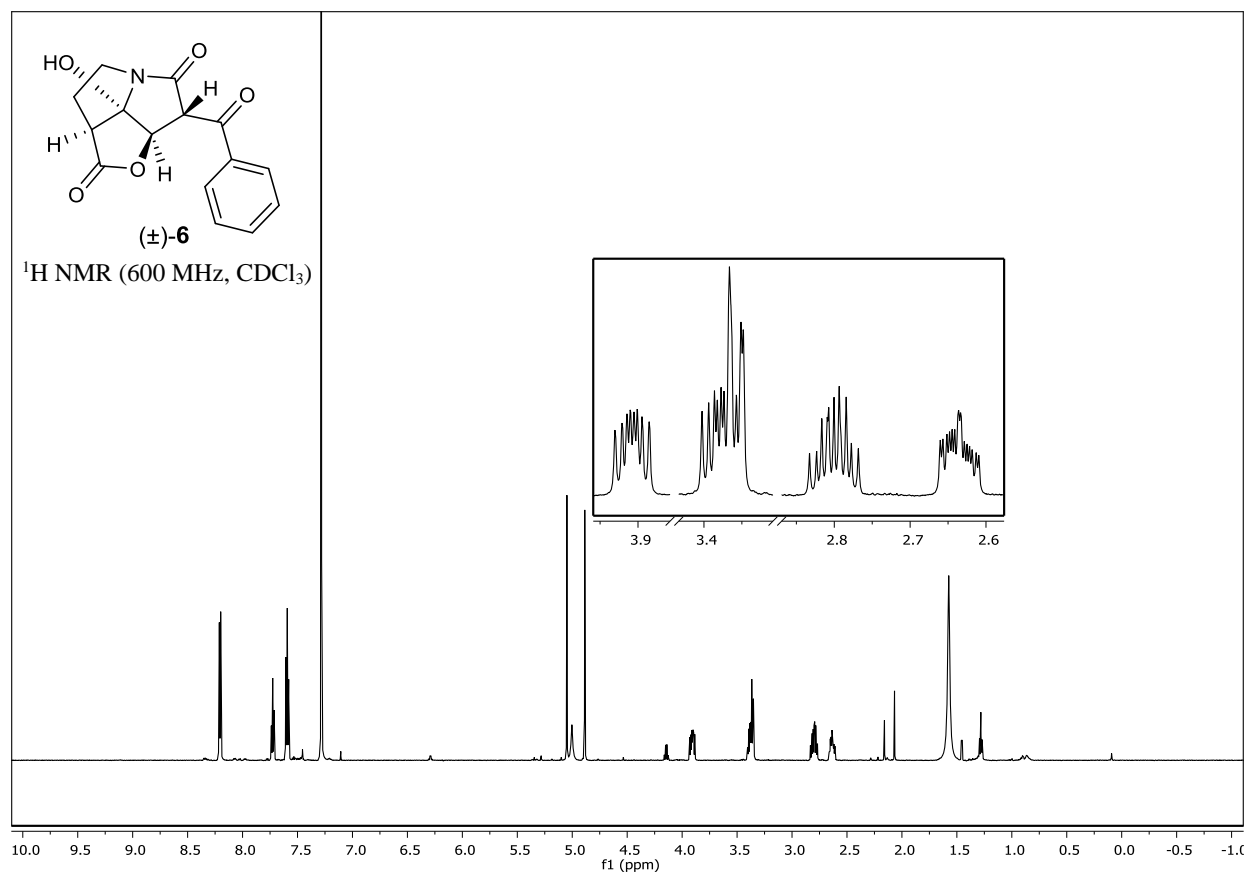


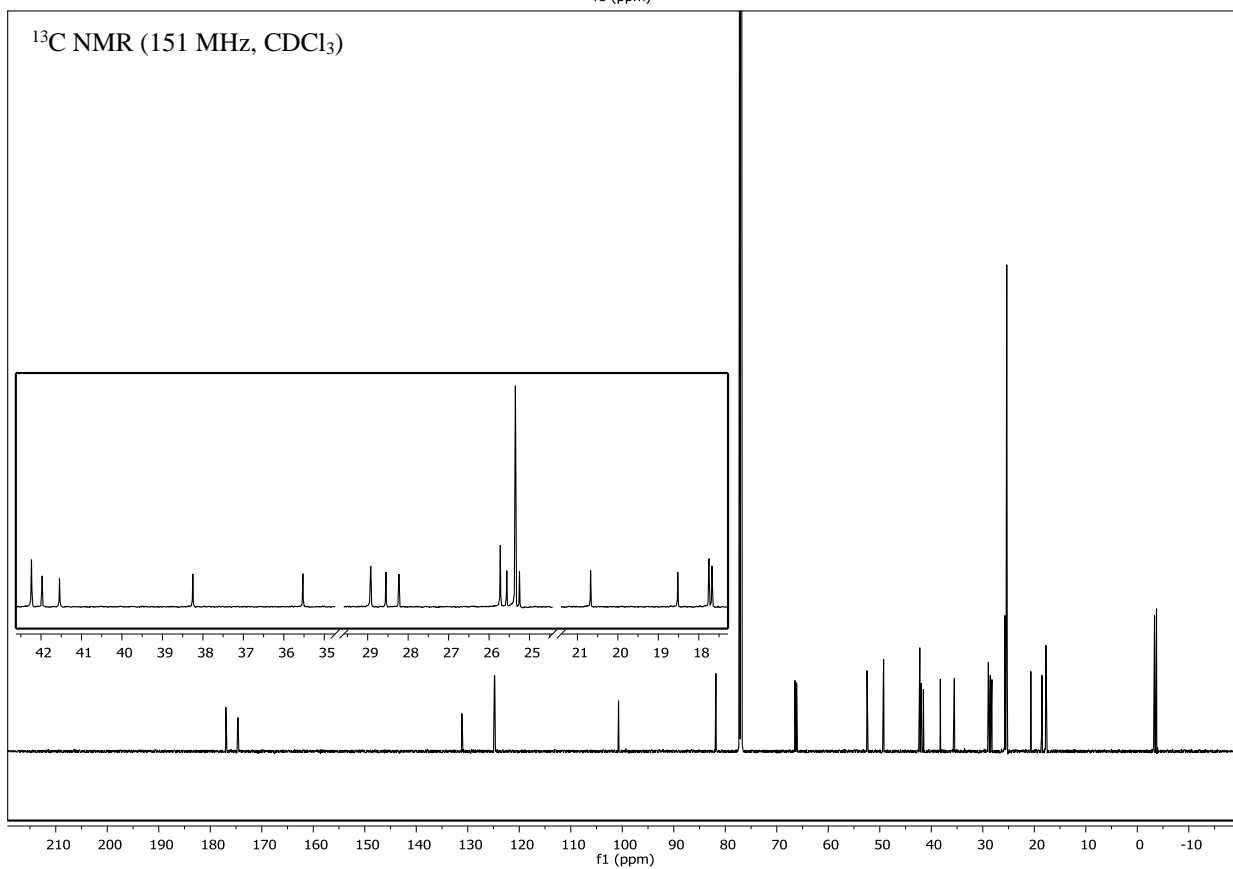
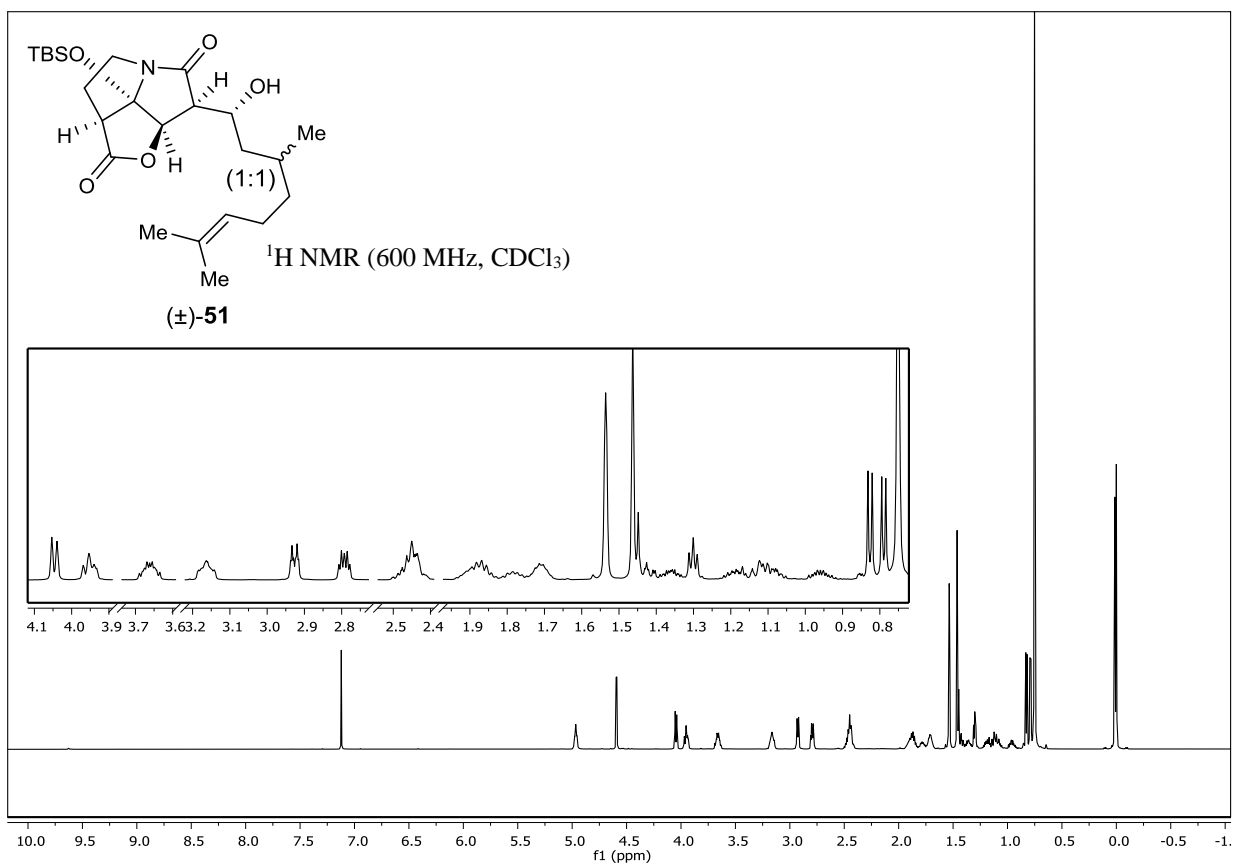
$^1\text{H}$  NMR (600 MHz, acetone- $d_6$ )

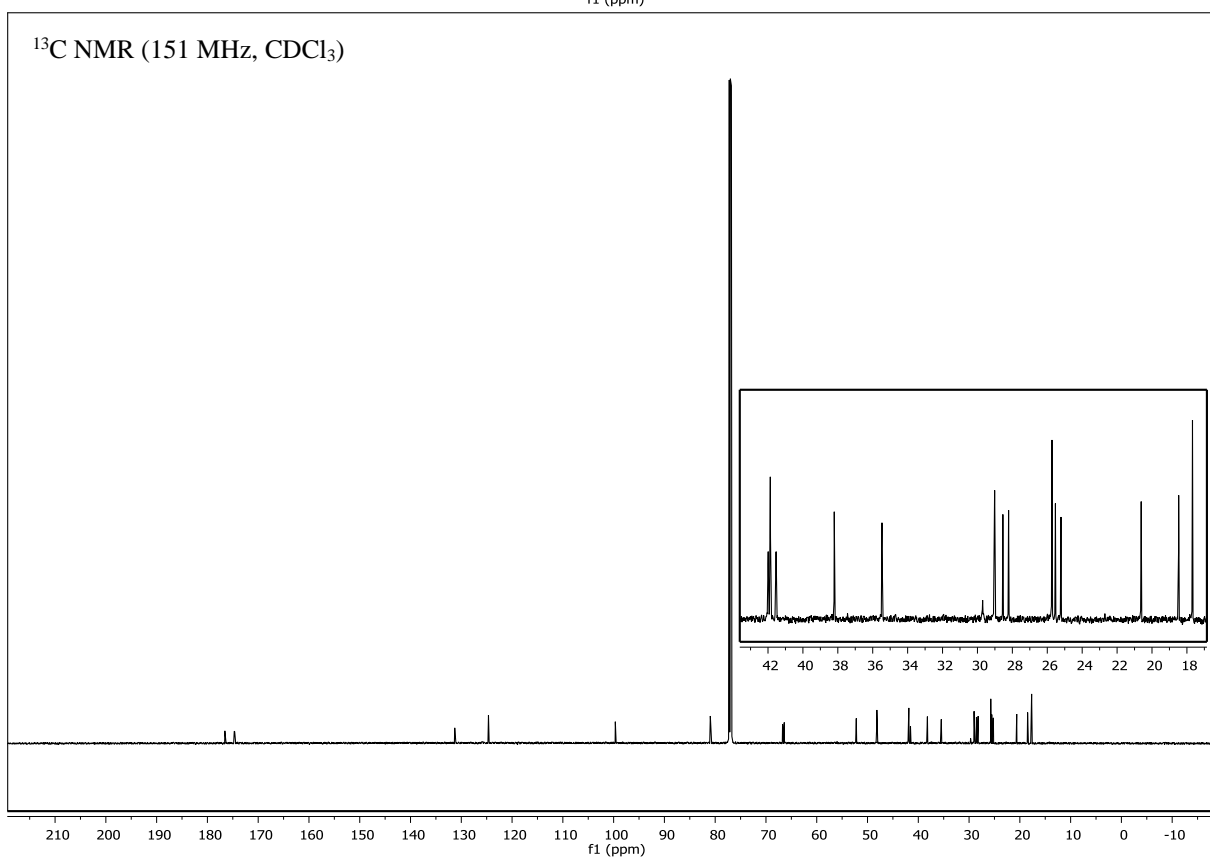
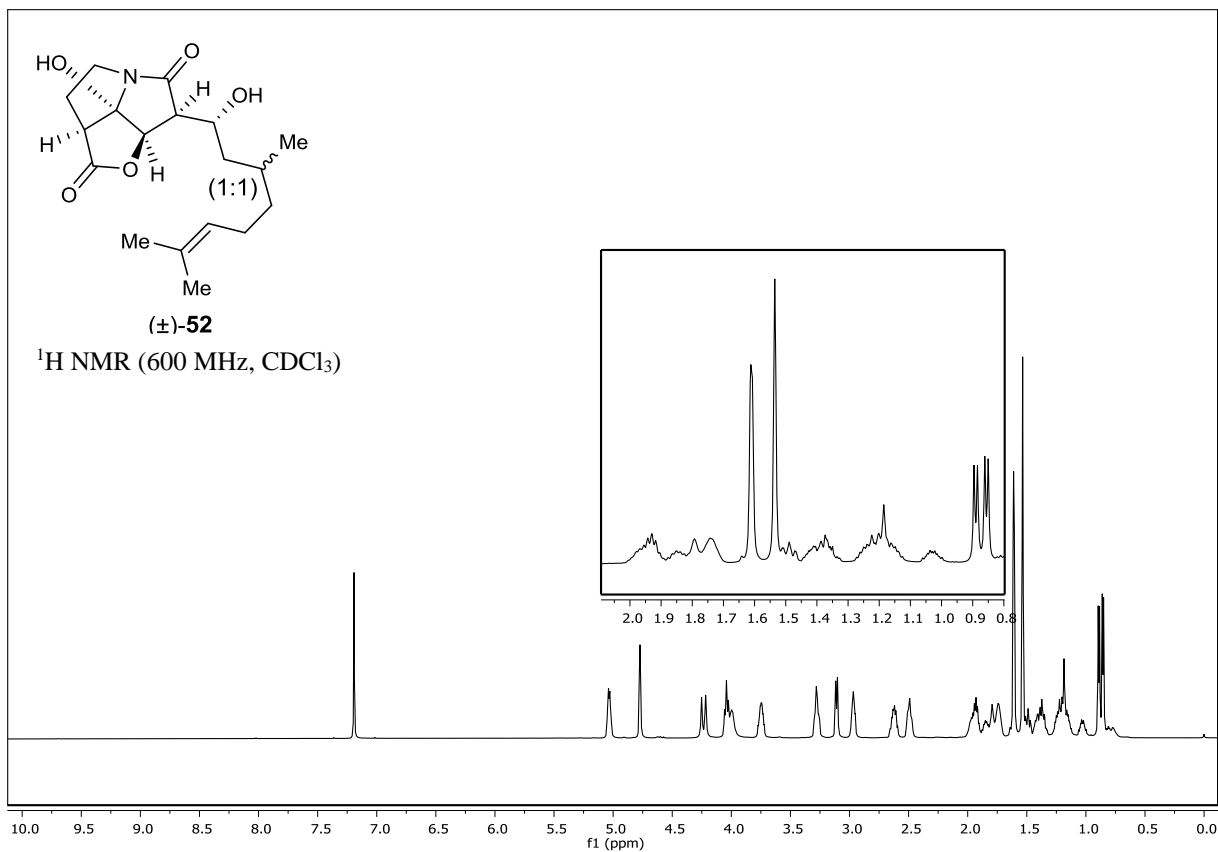


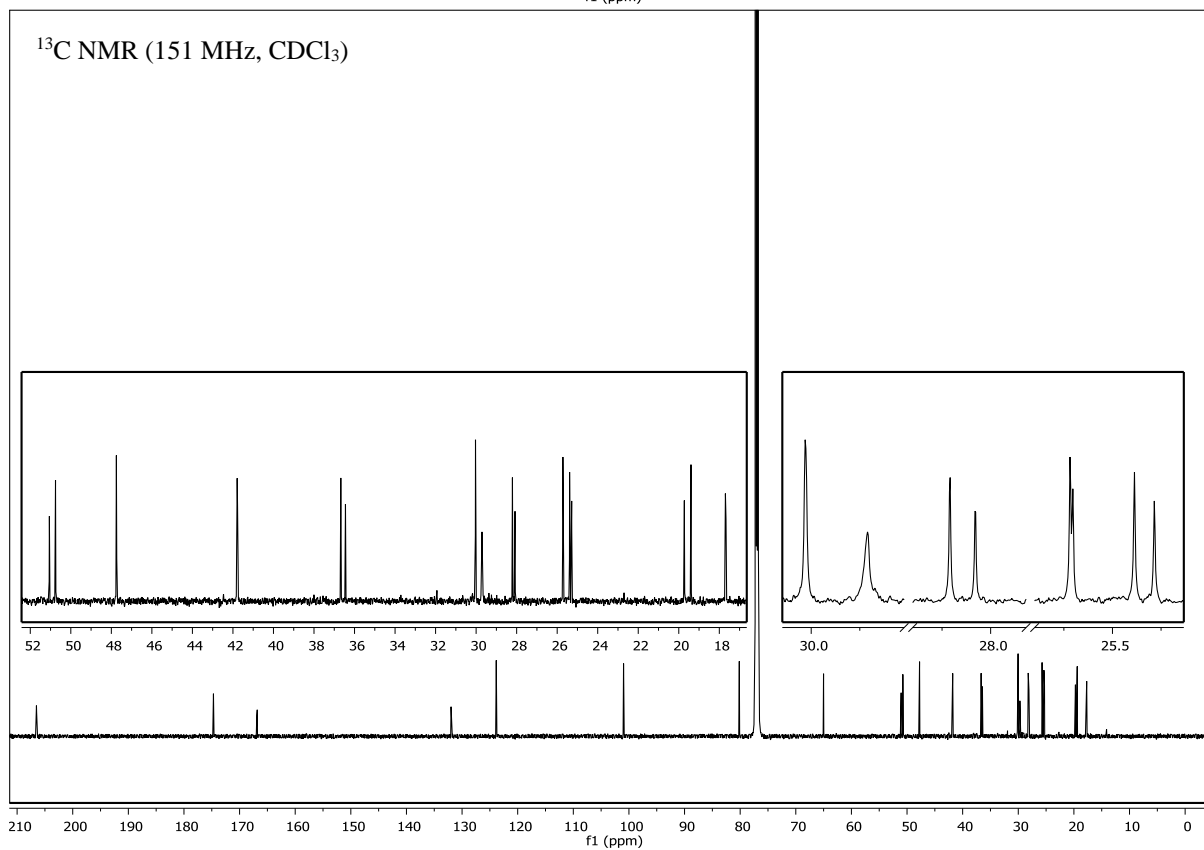
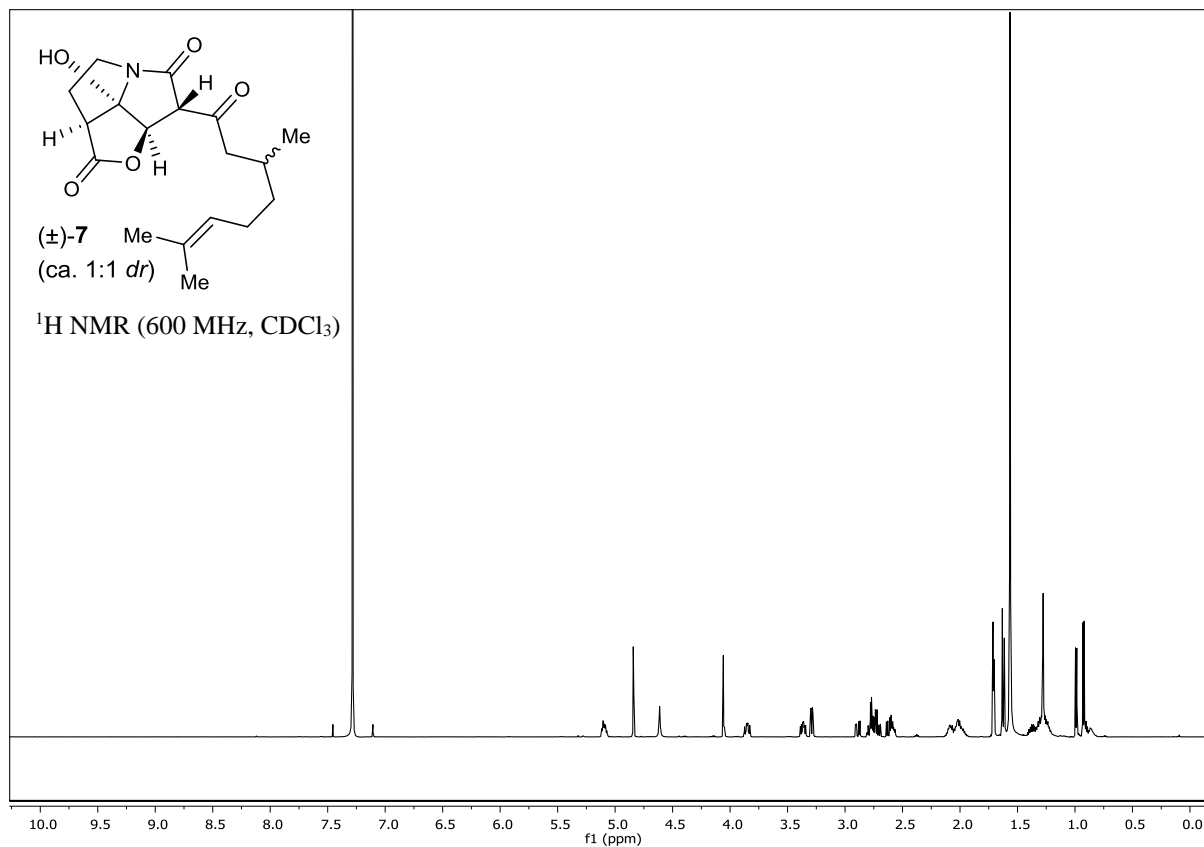
$^{13}\text{C}$  NMR (151 MHz, acetone- $d_6$ )



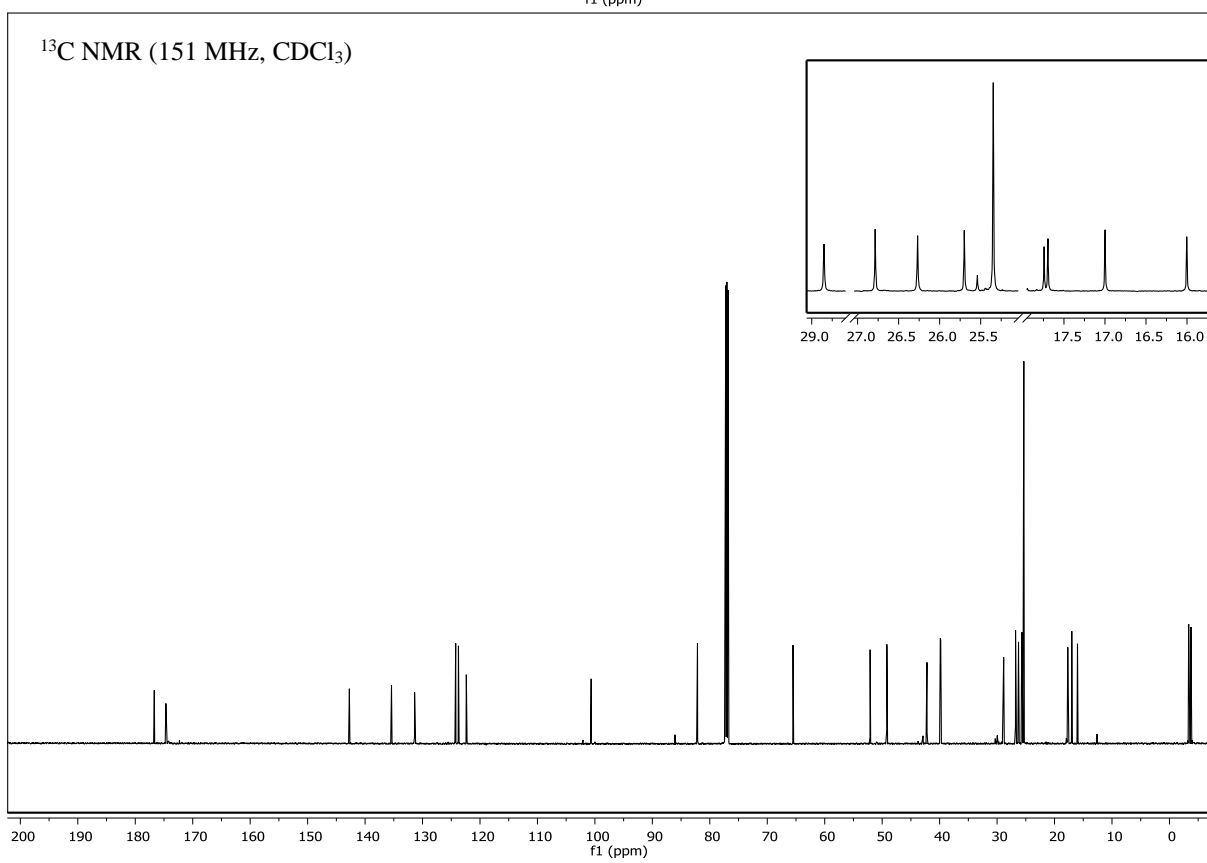
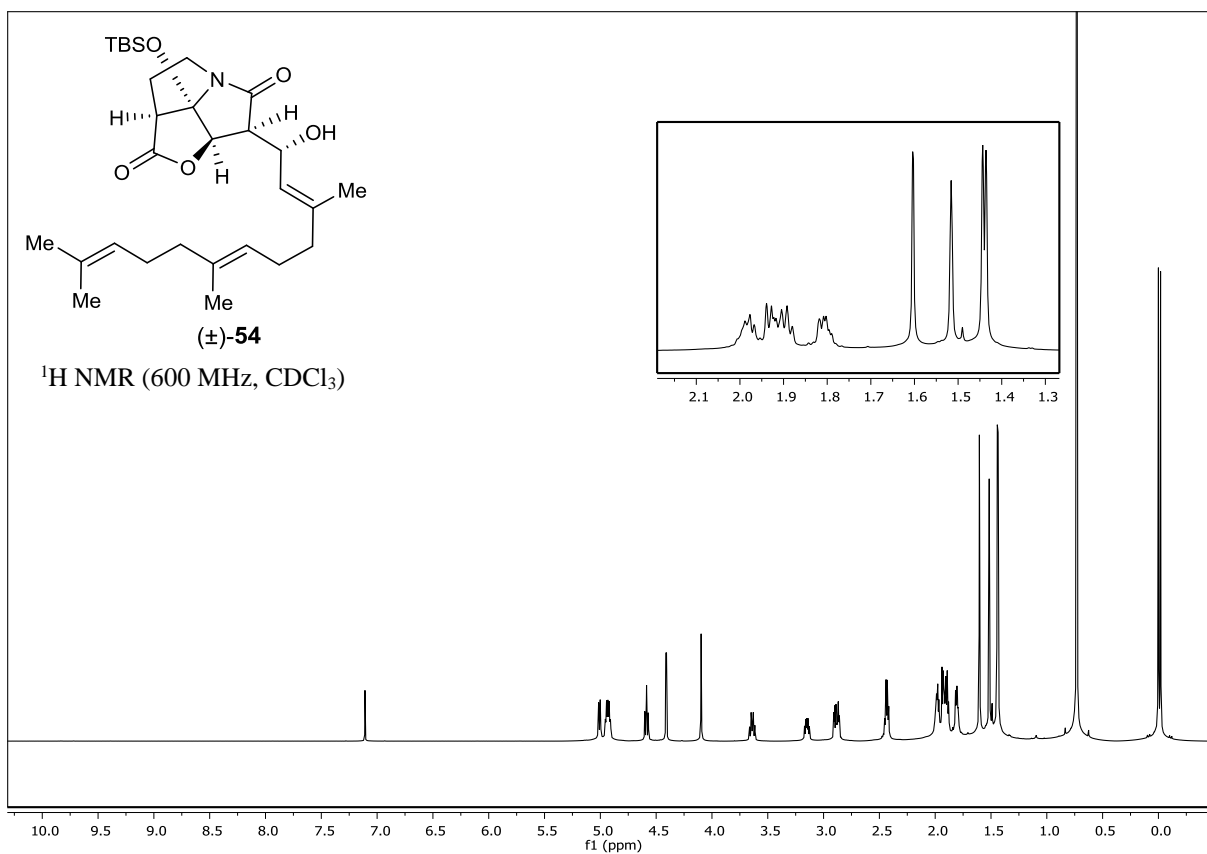


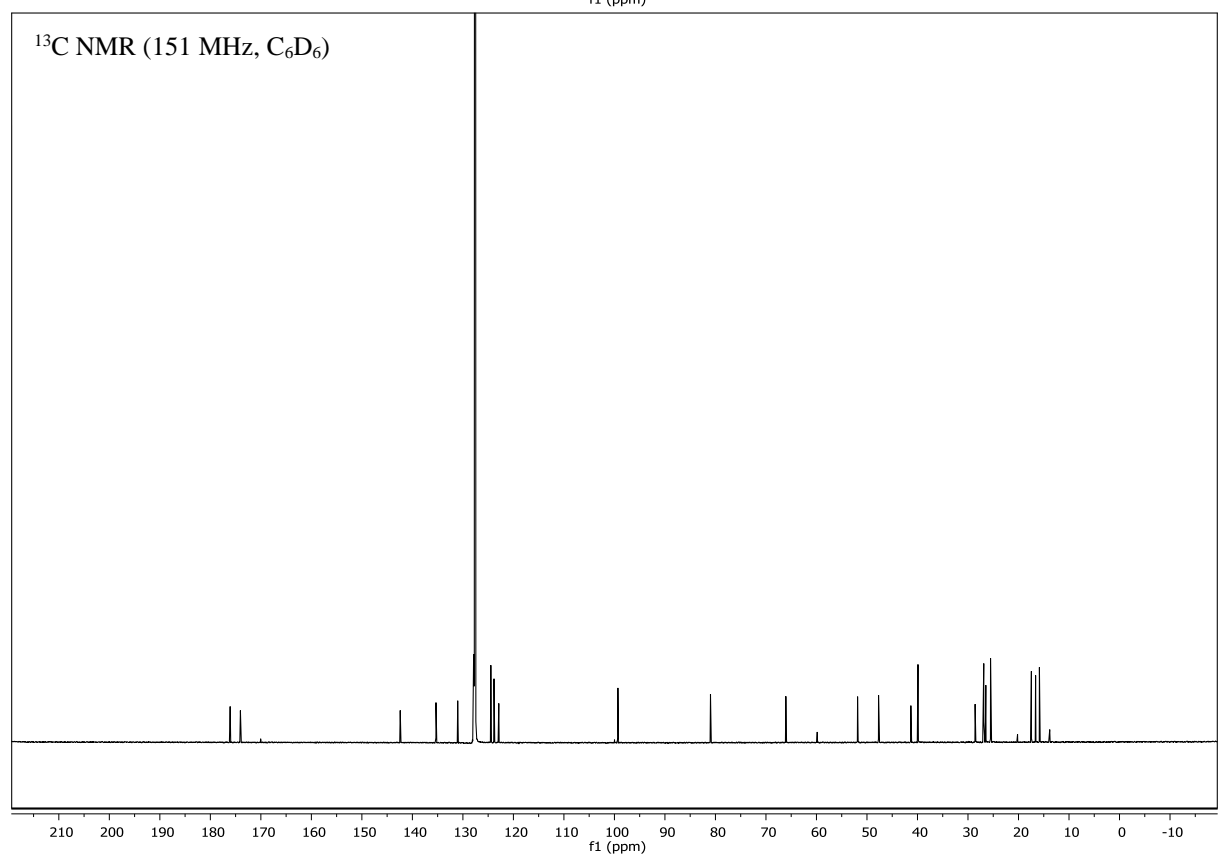
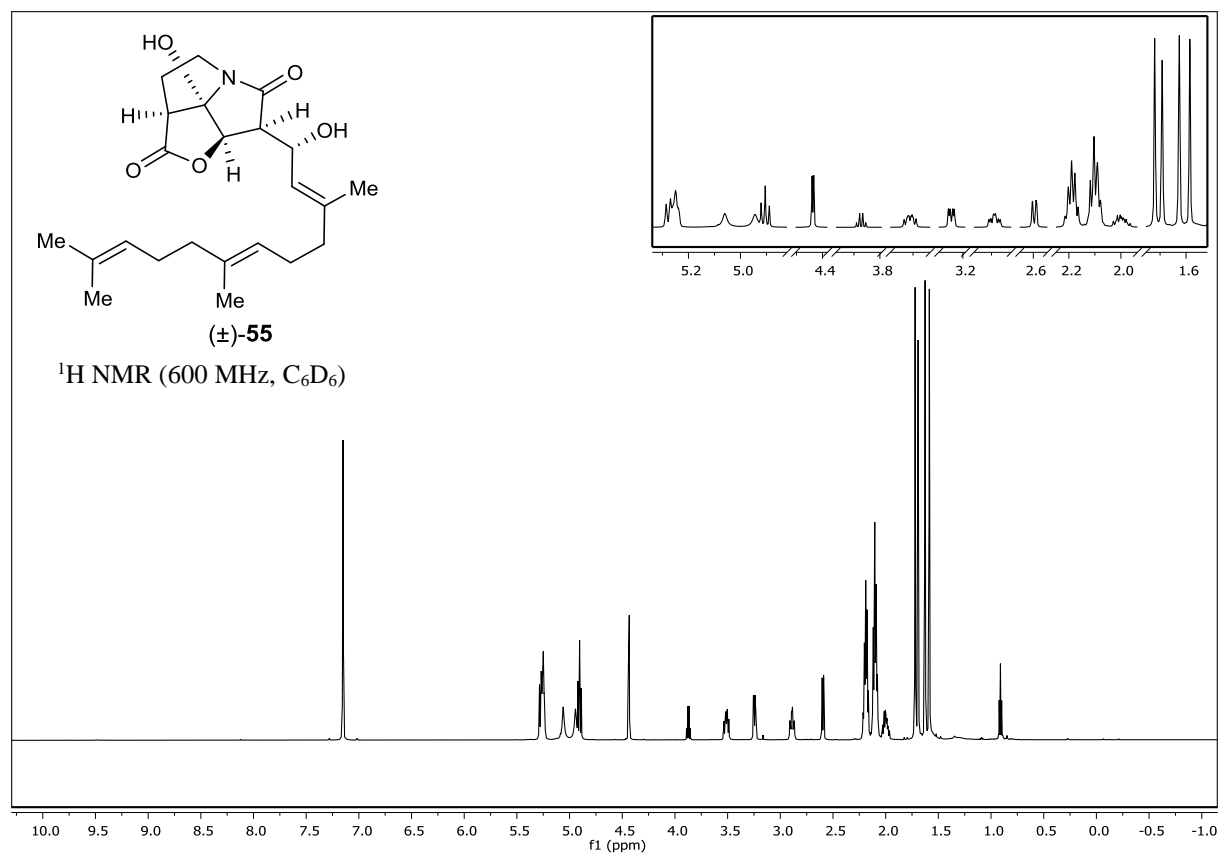




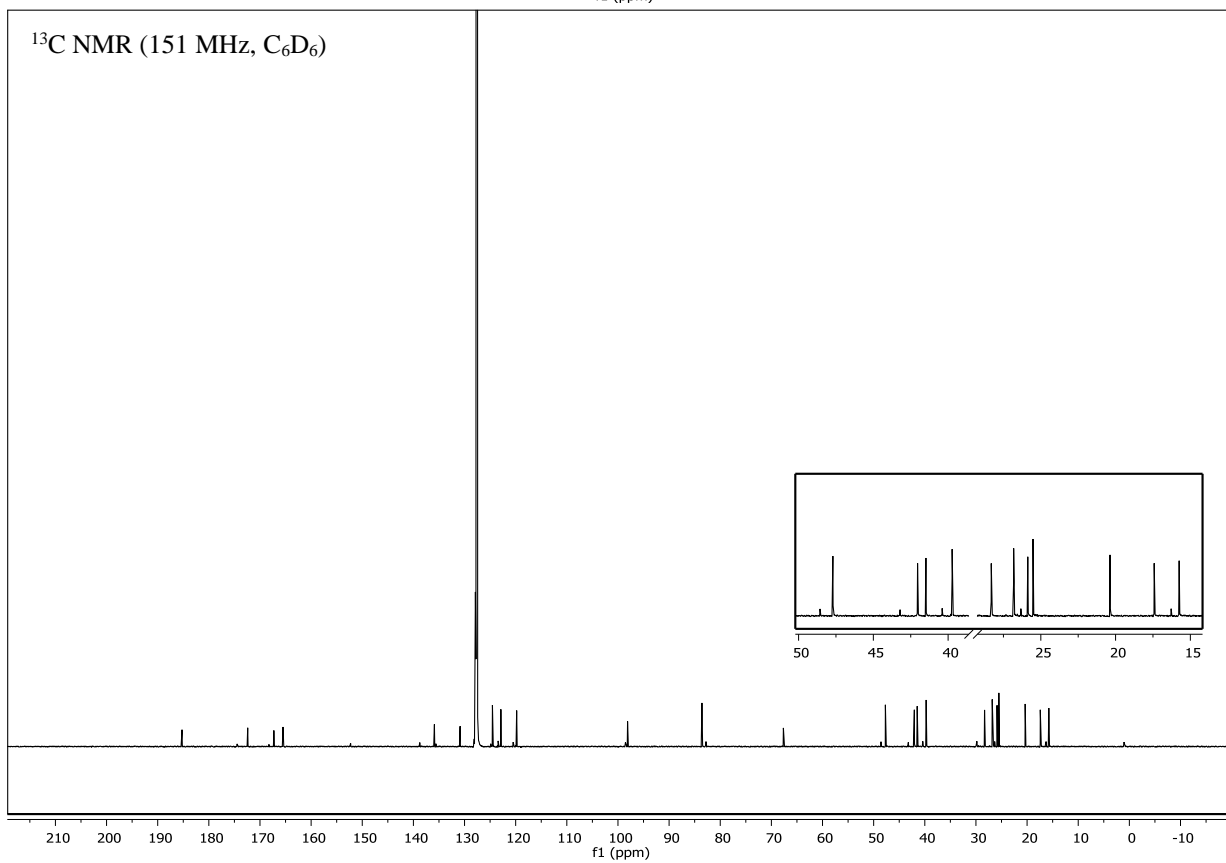
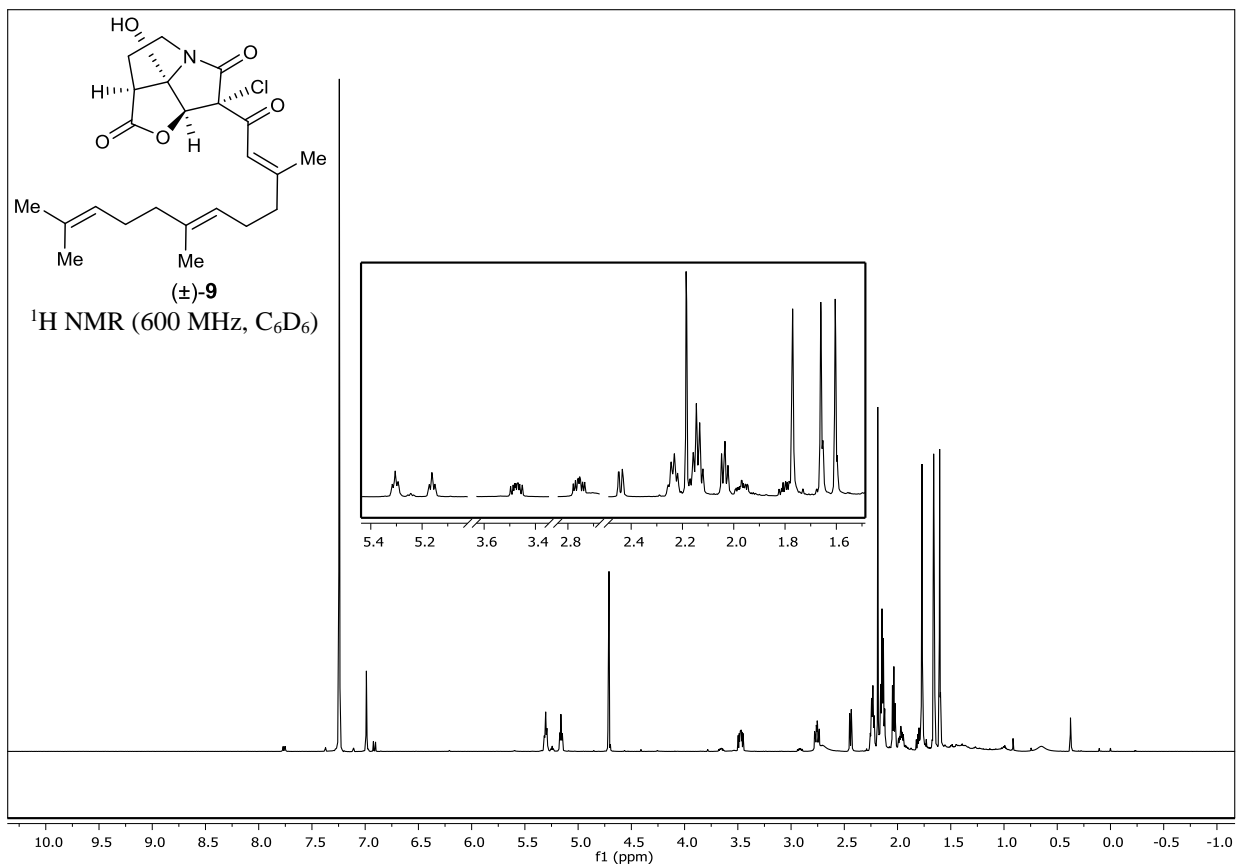


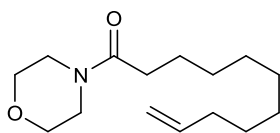






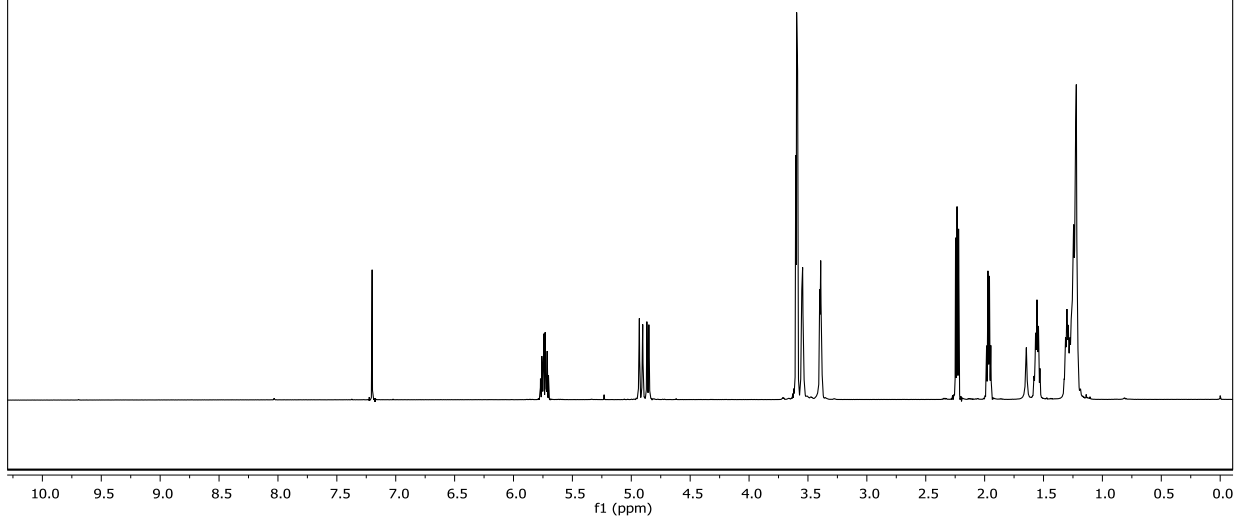




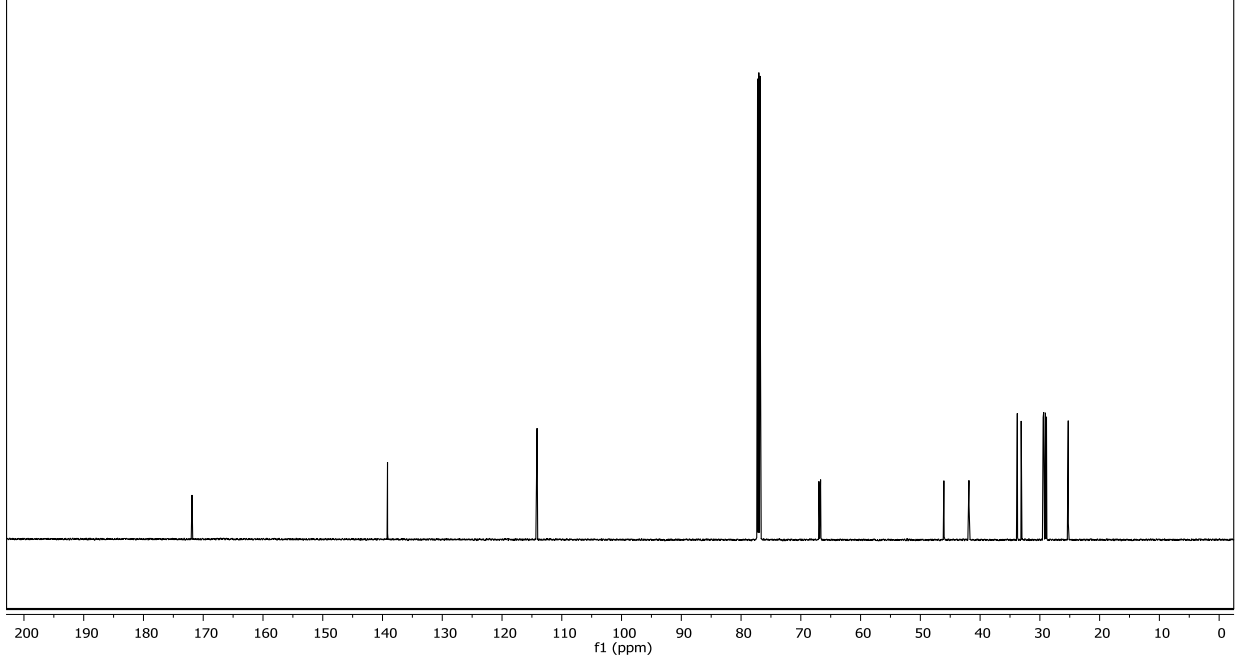


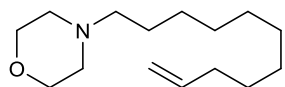
**58**

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )



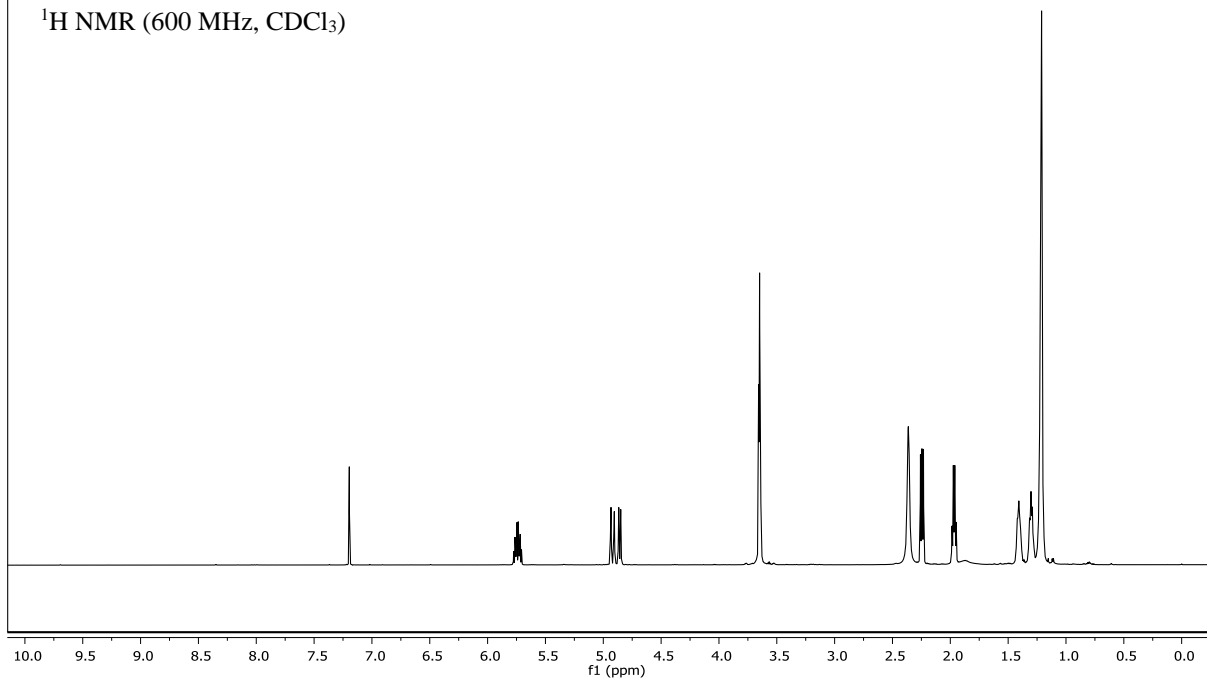
$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )



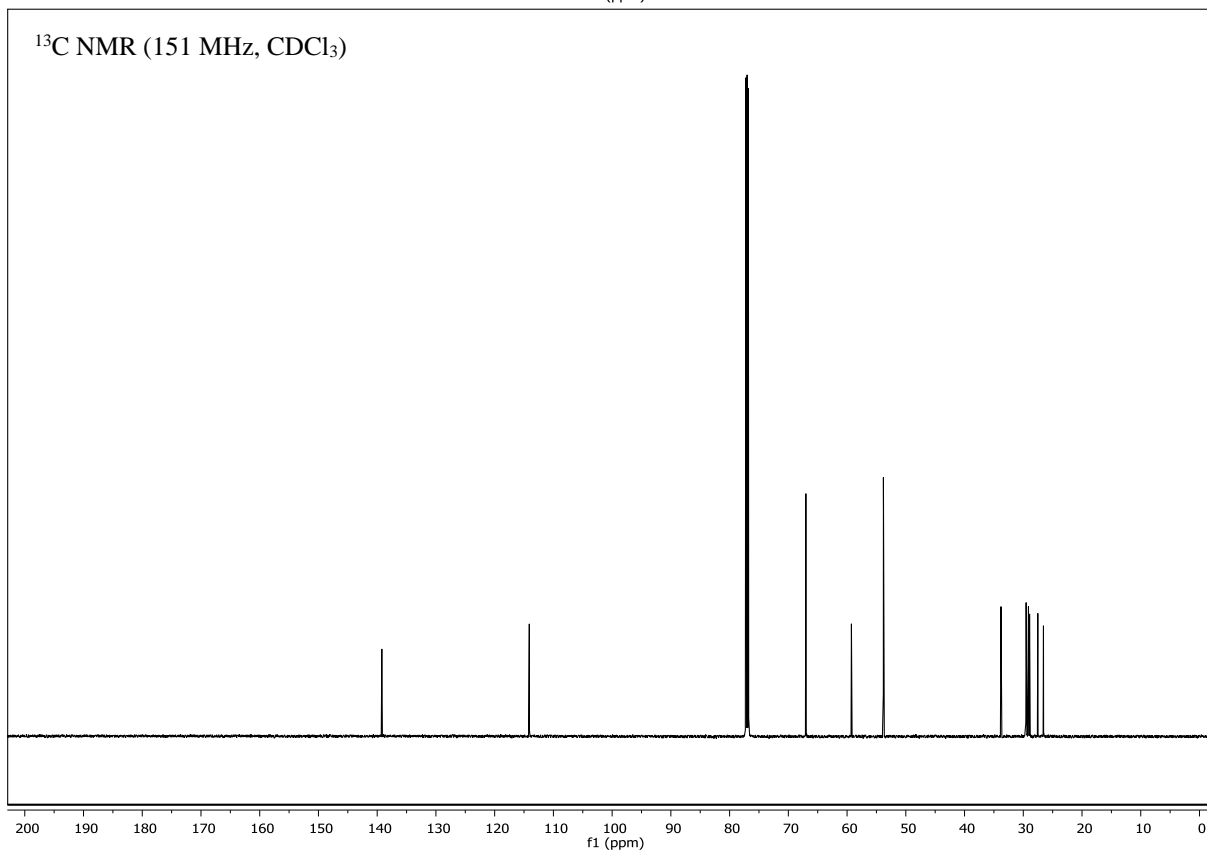


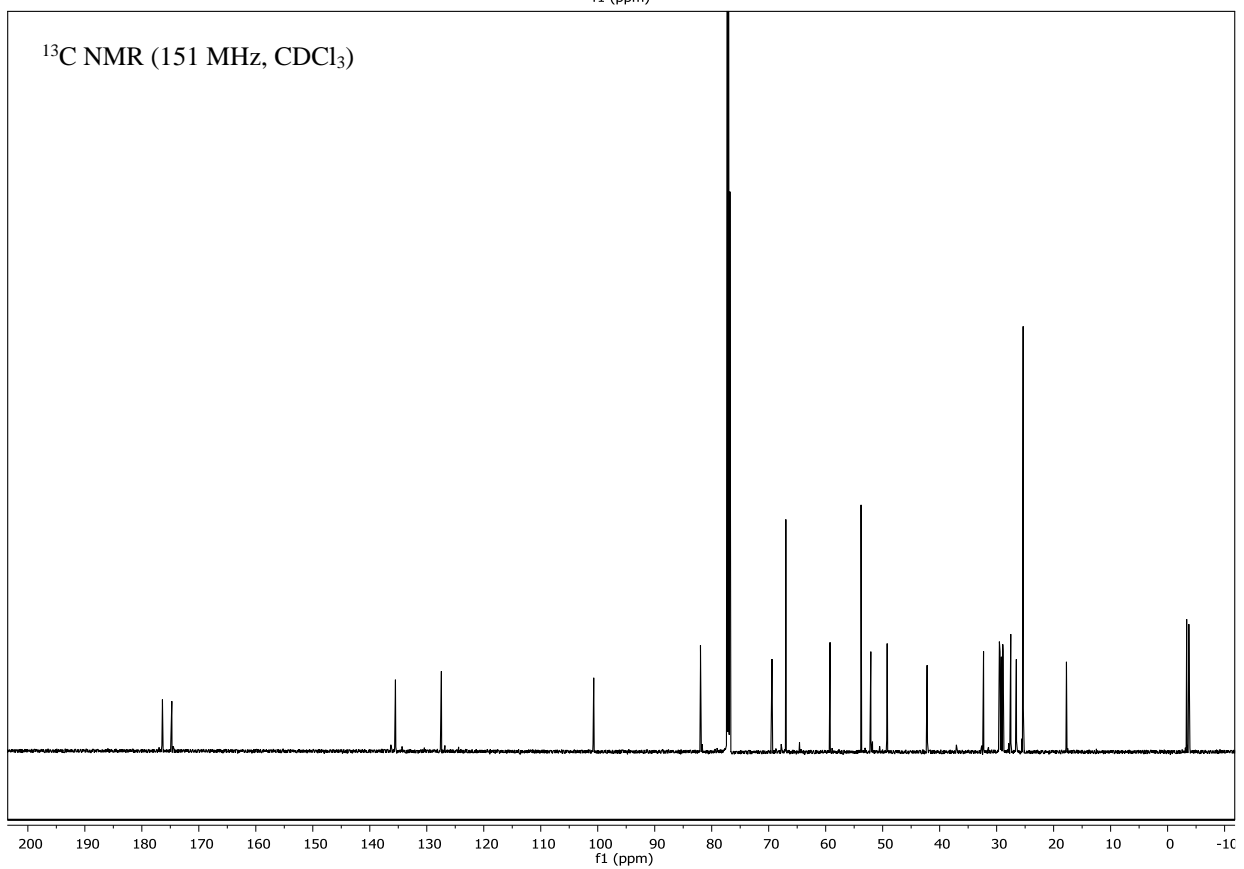
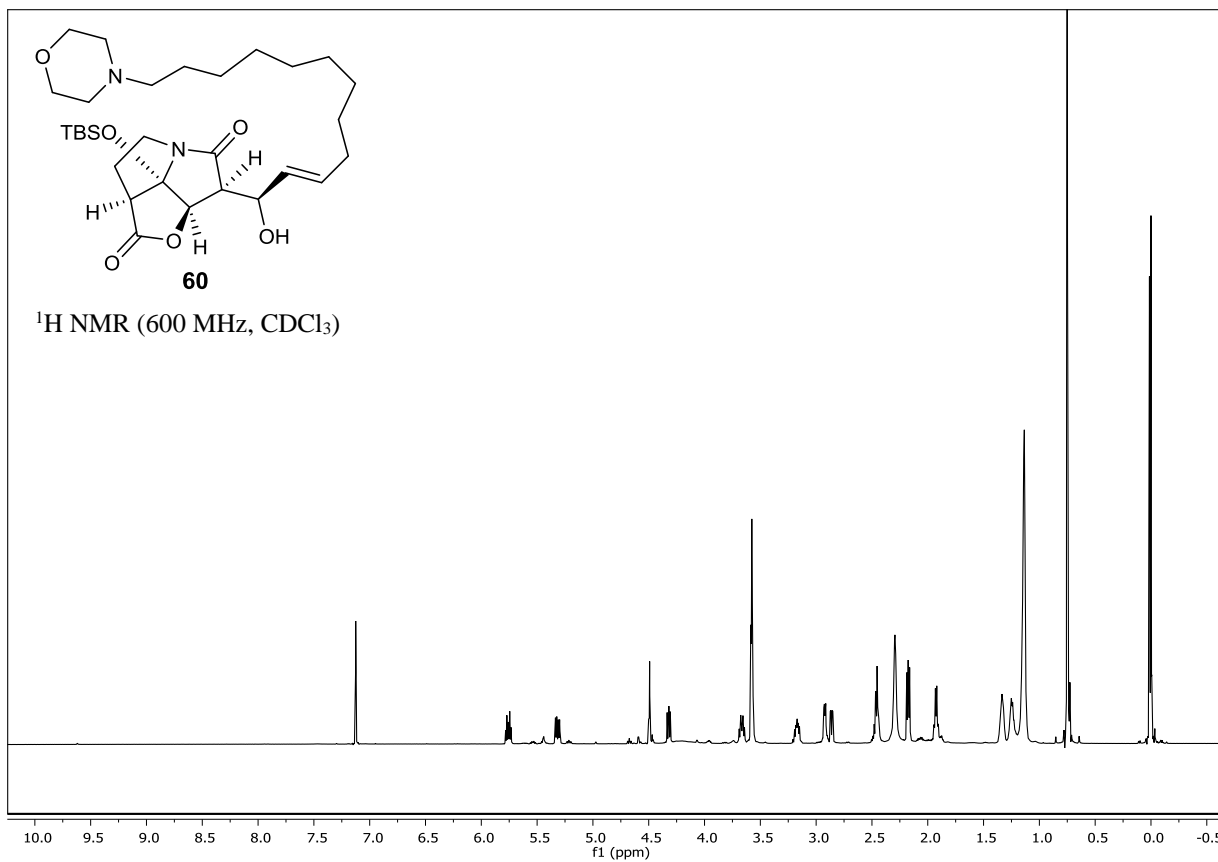
**59**

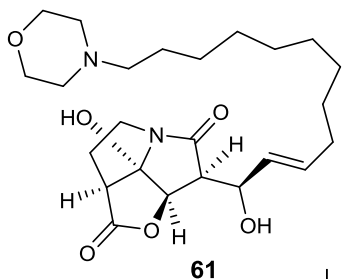
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )



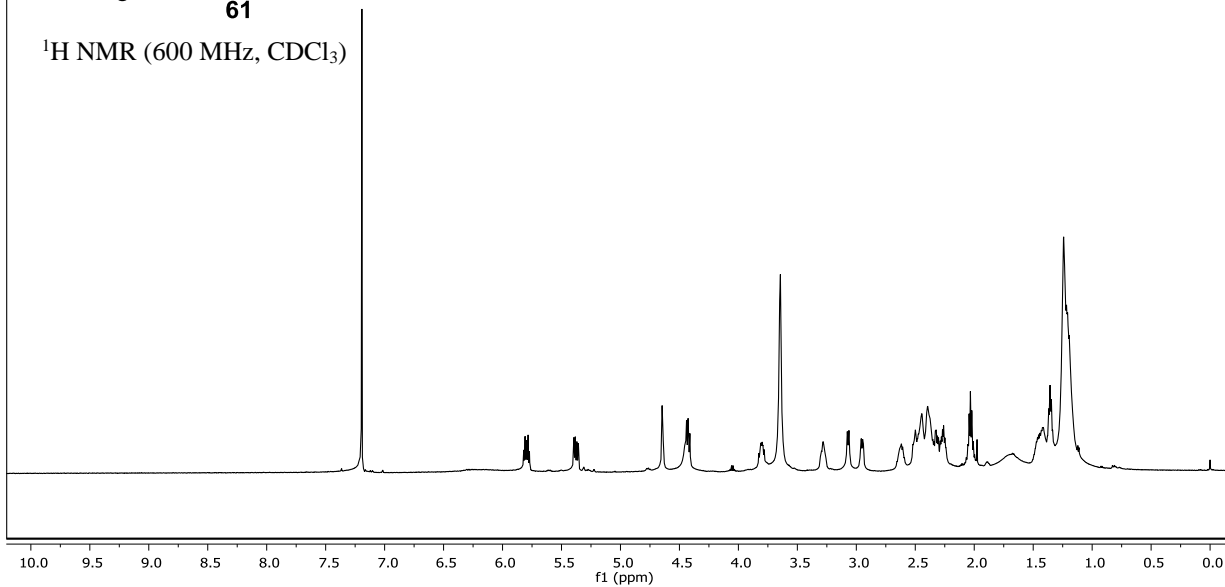
$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )



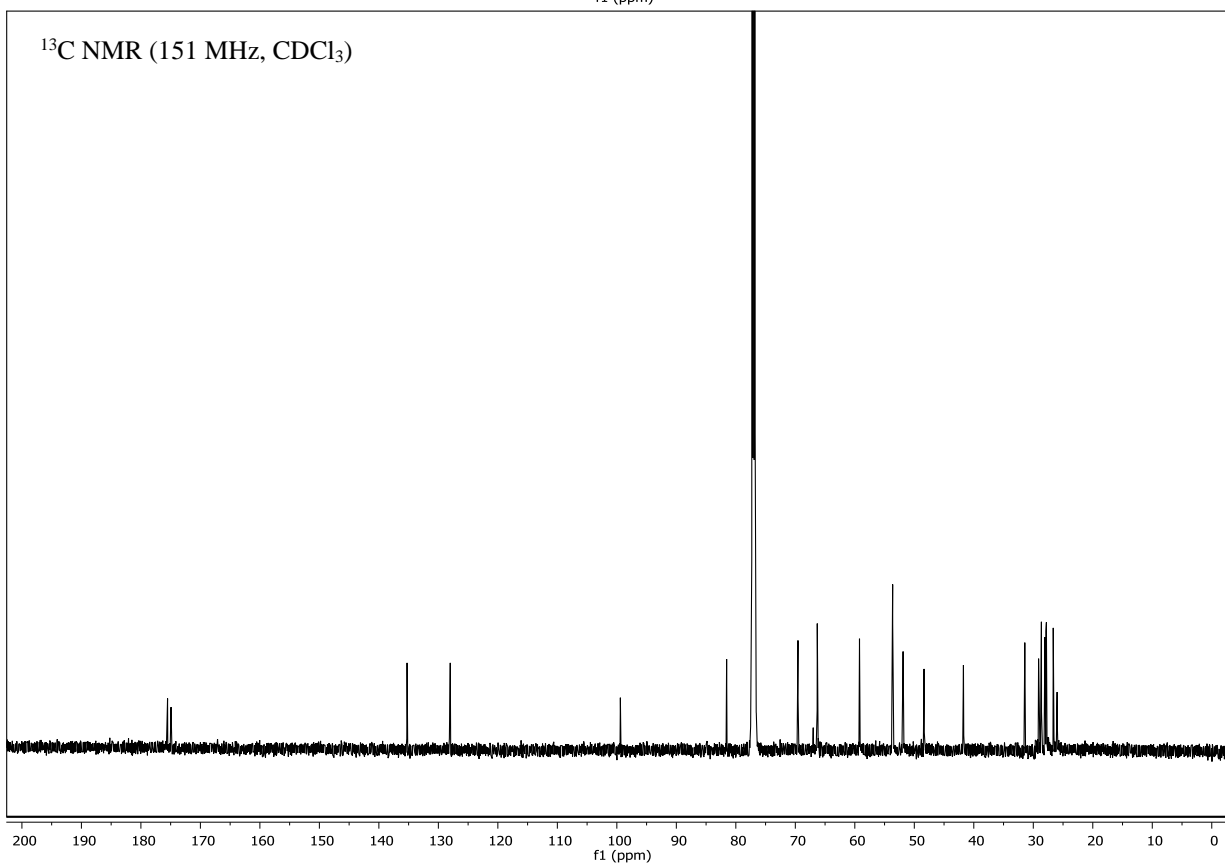




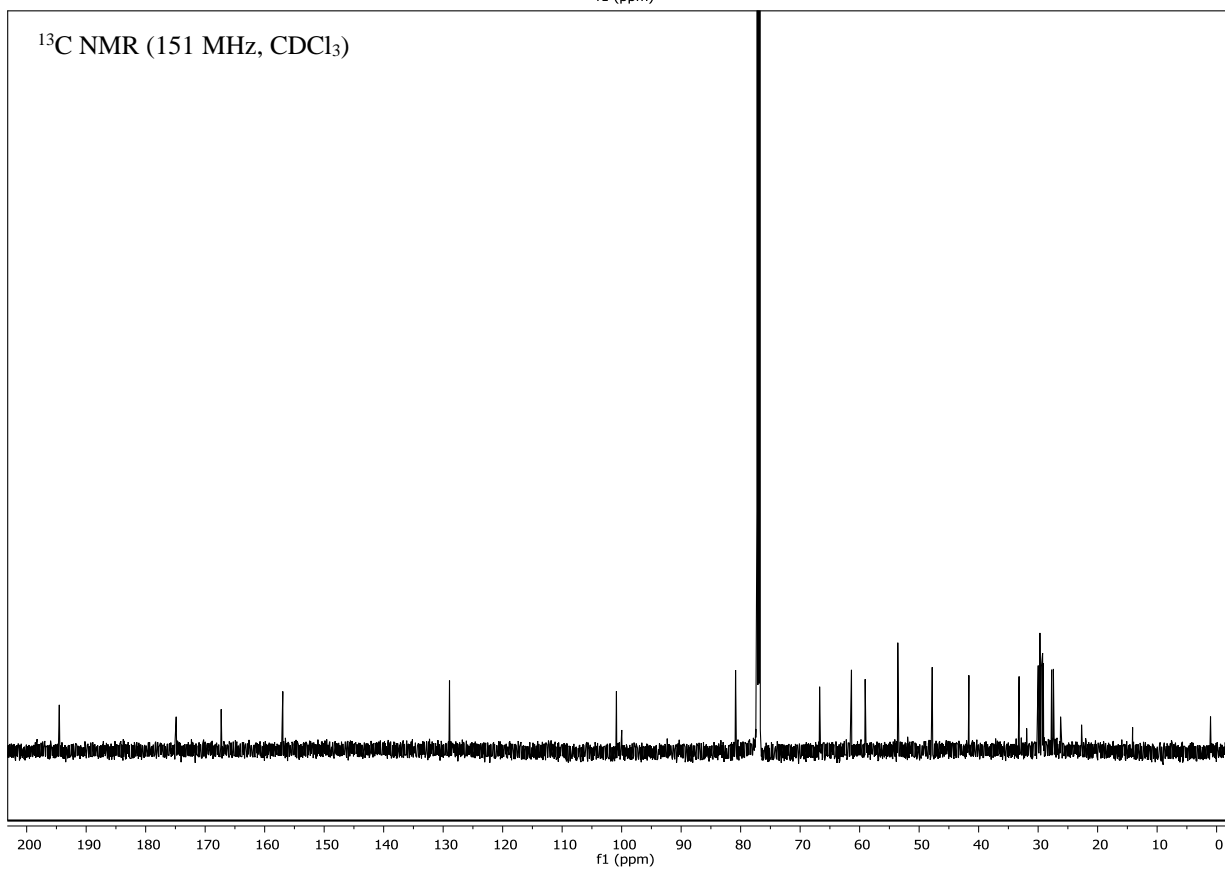
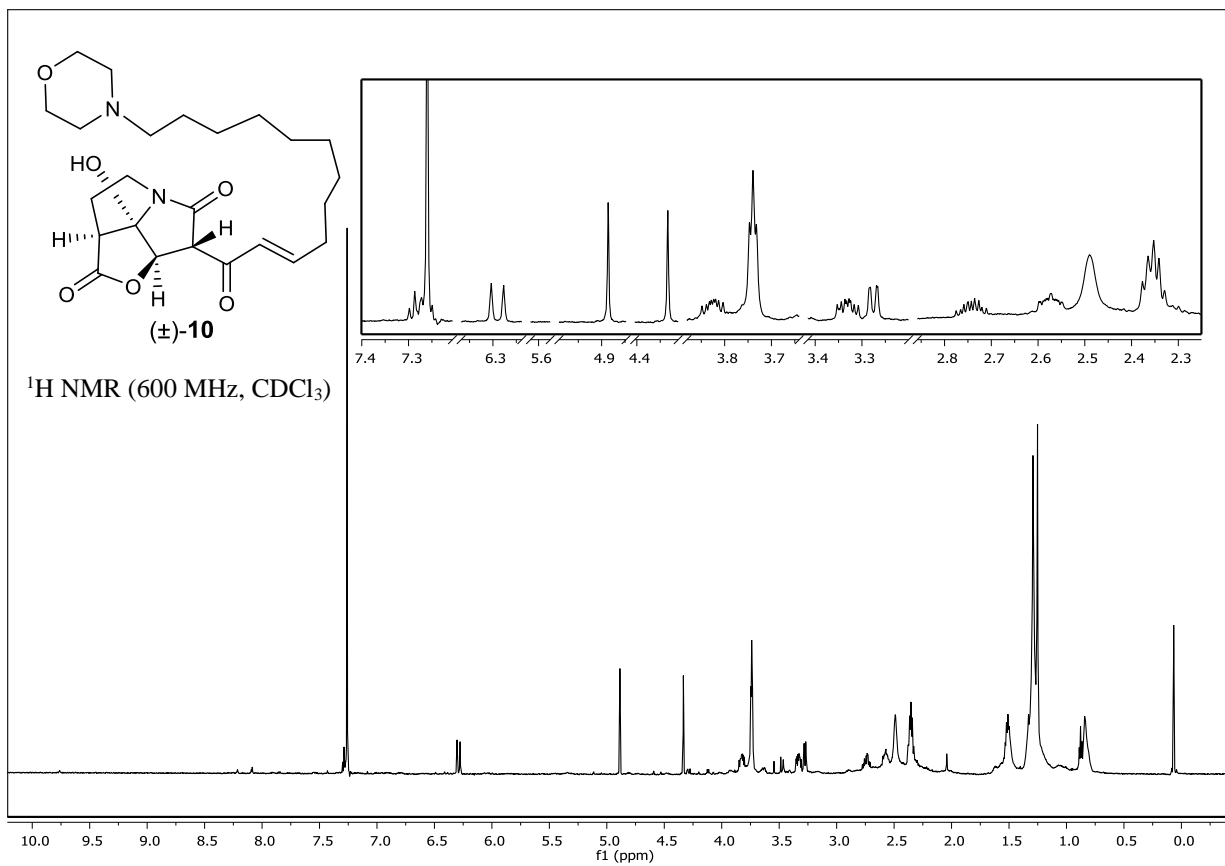
$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )

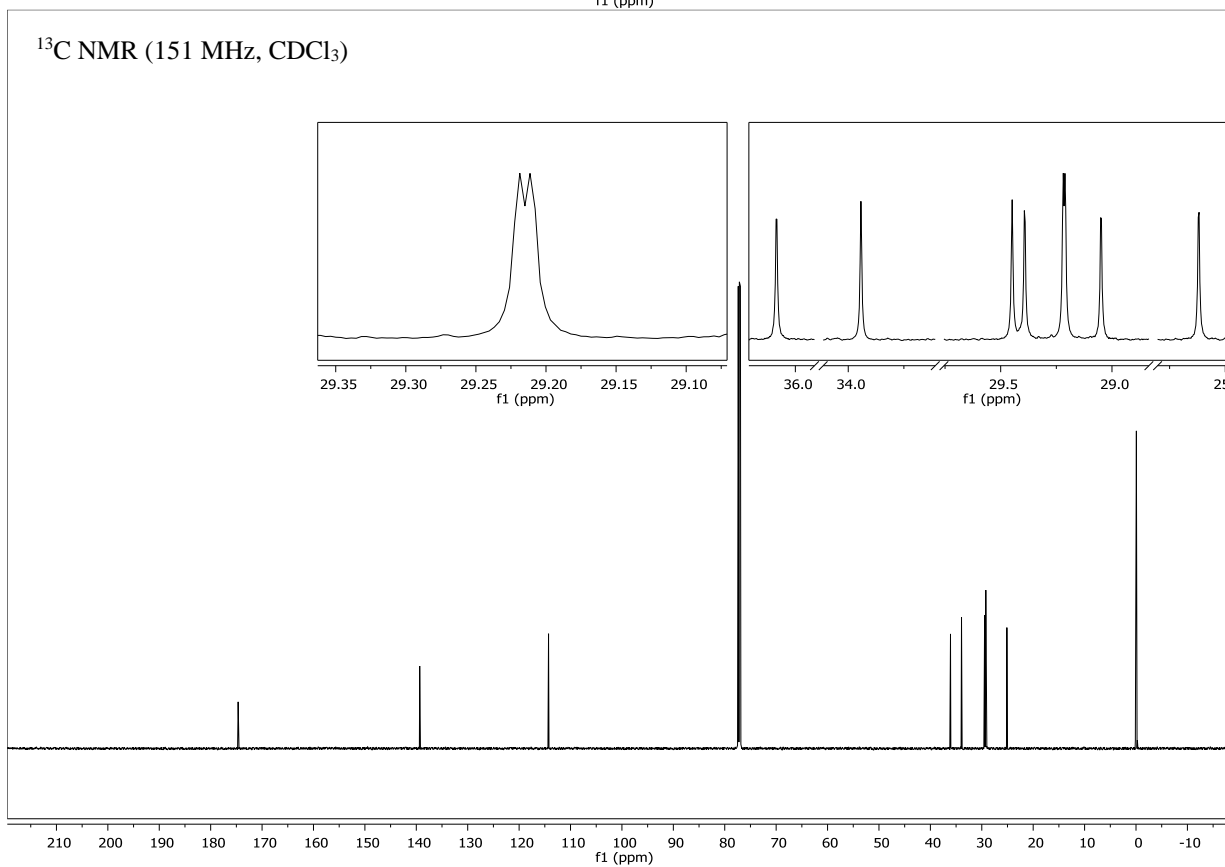
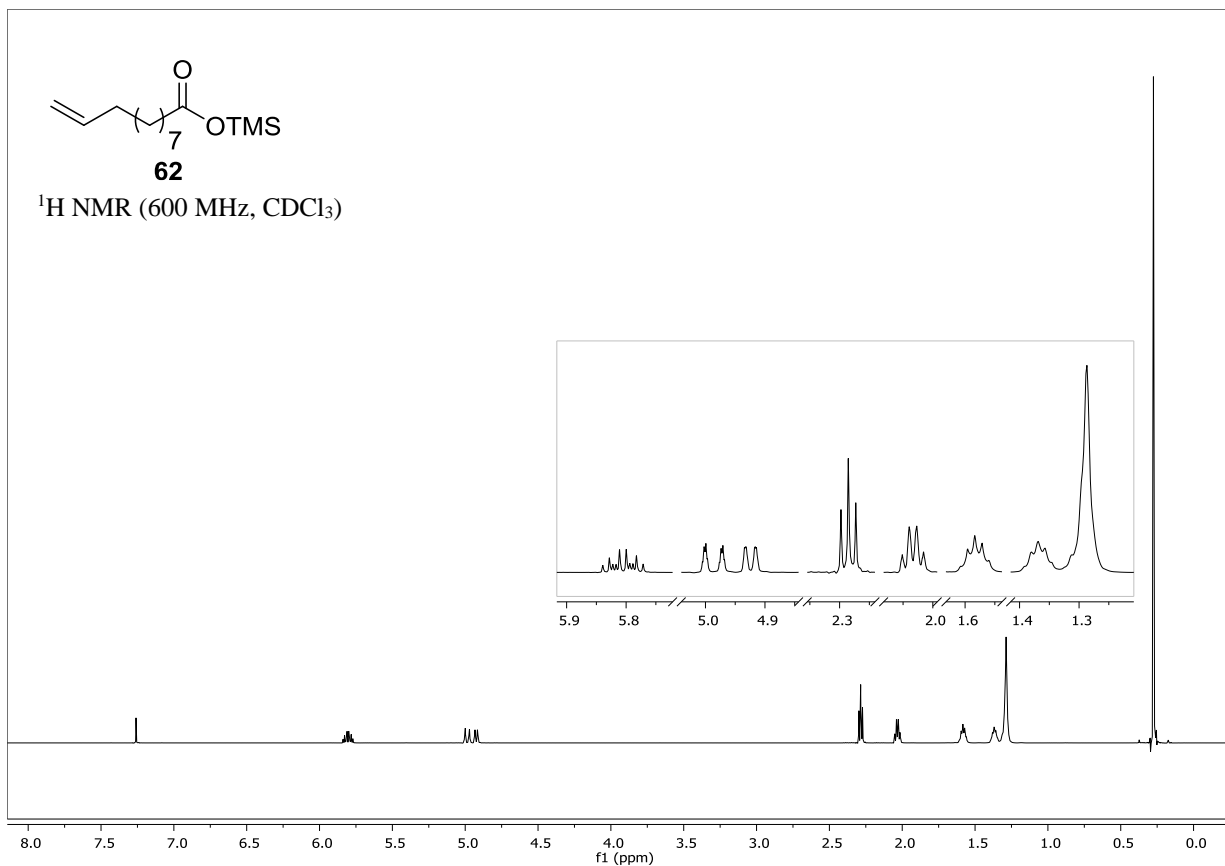


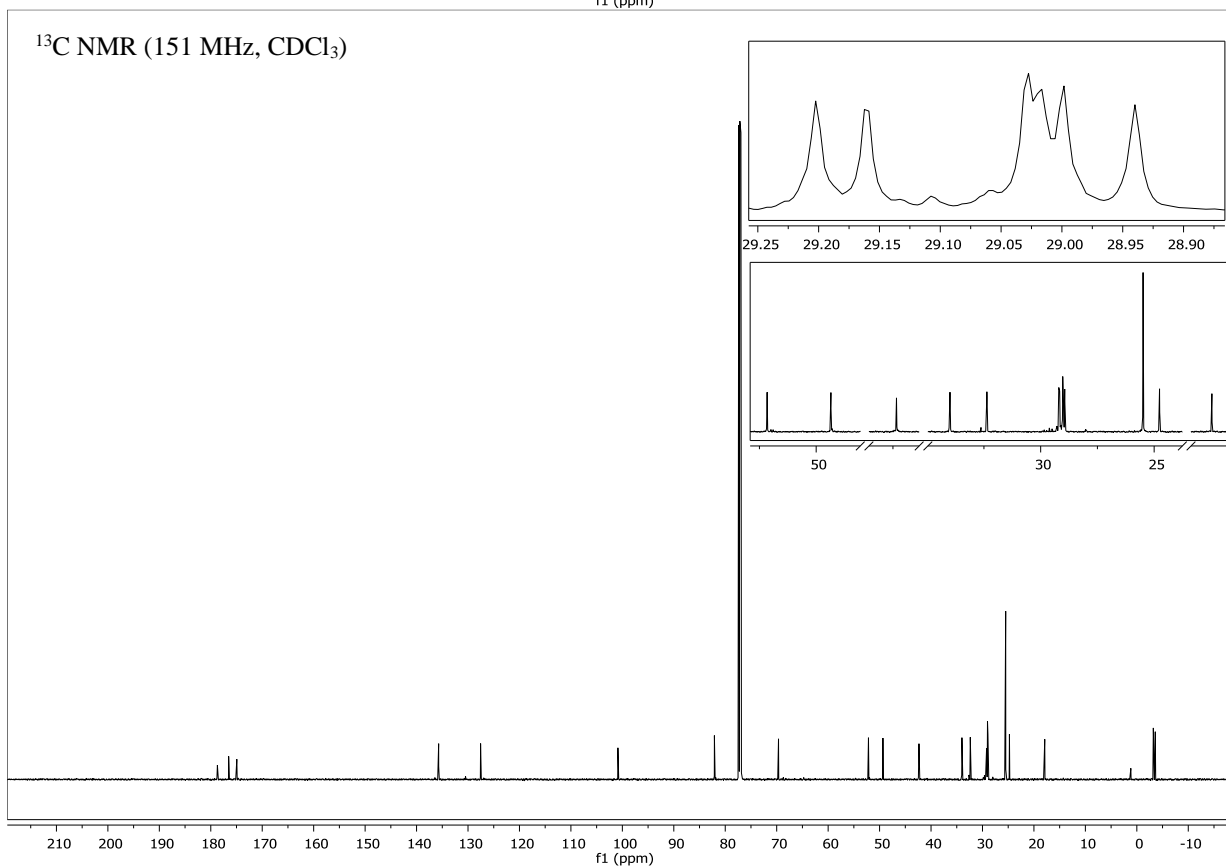
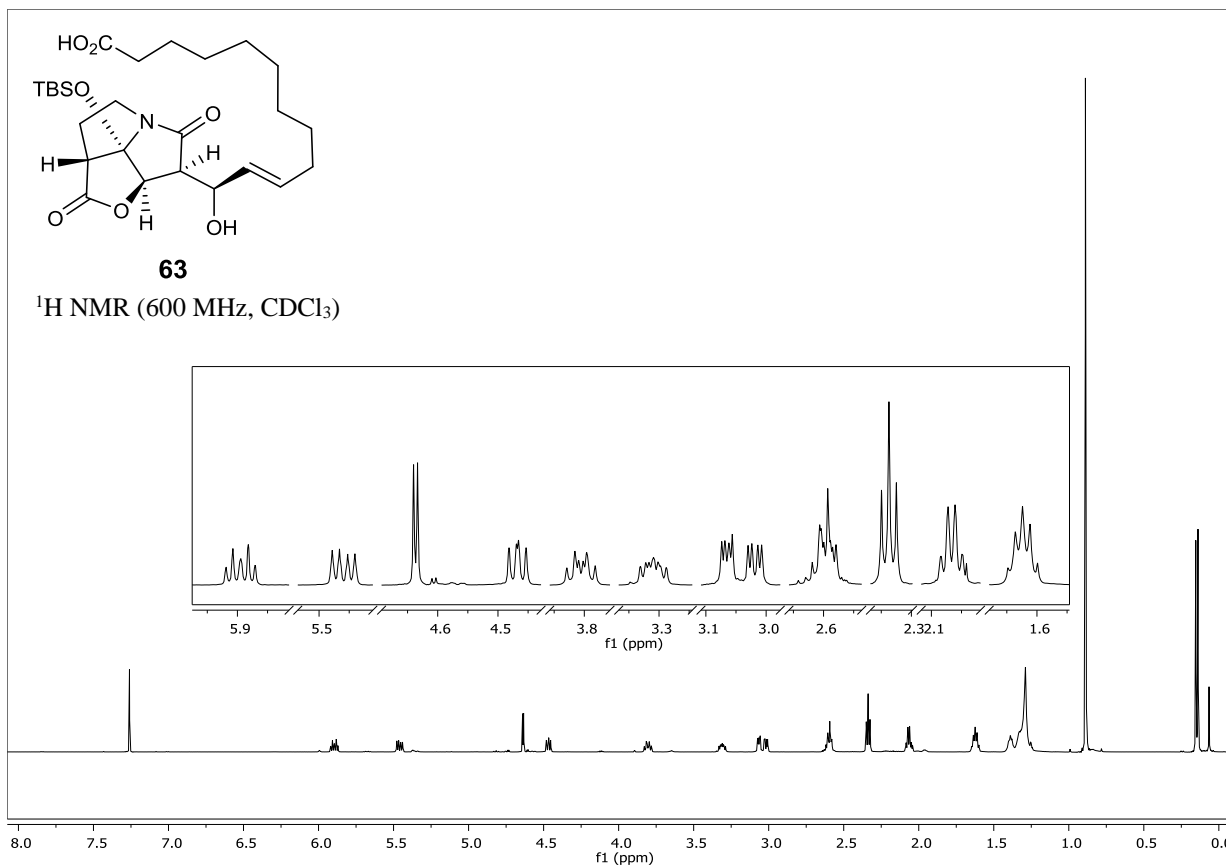
$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )

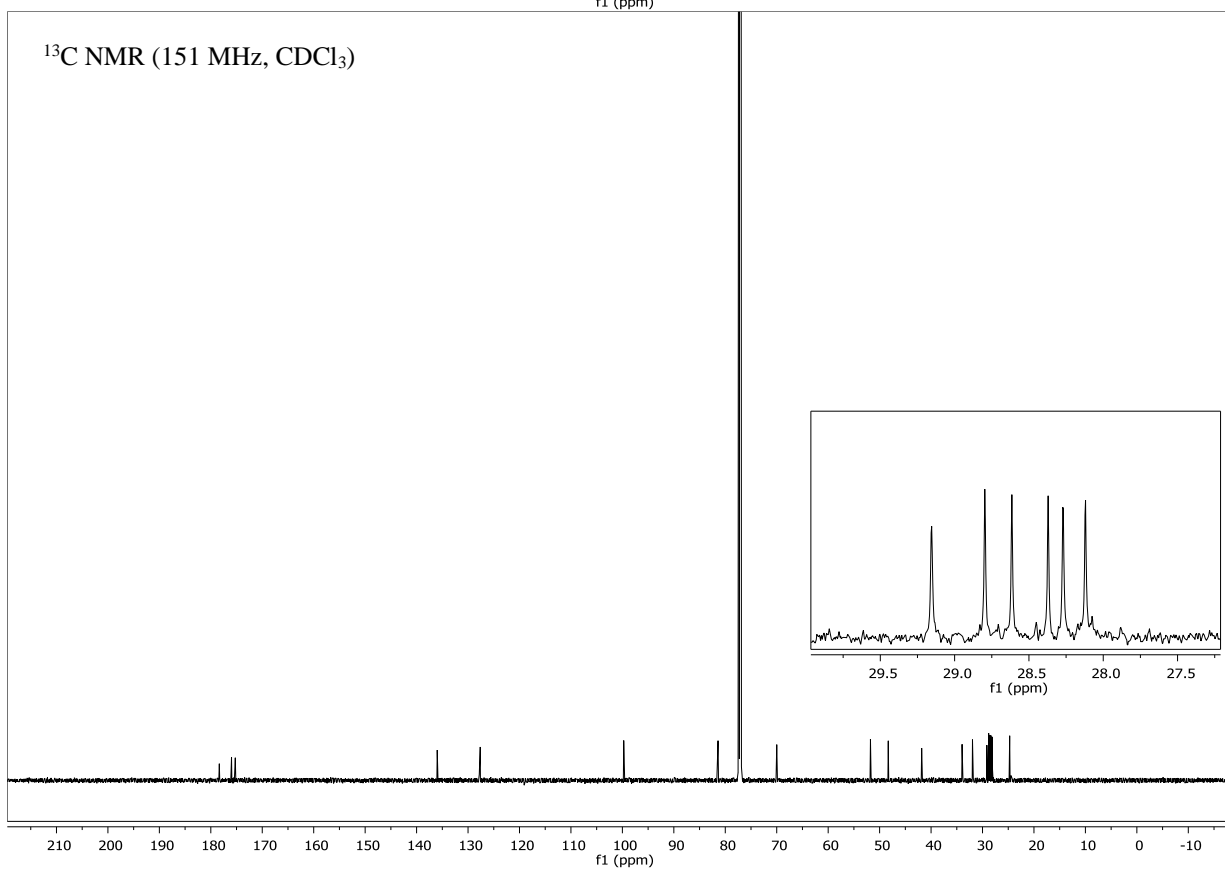
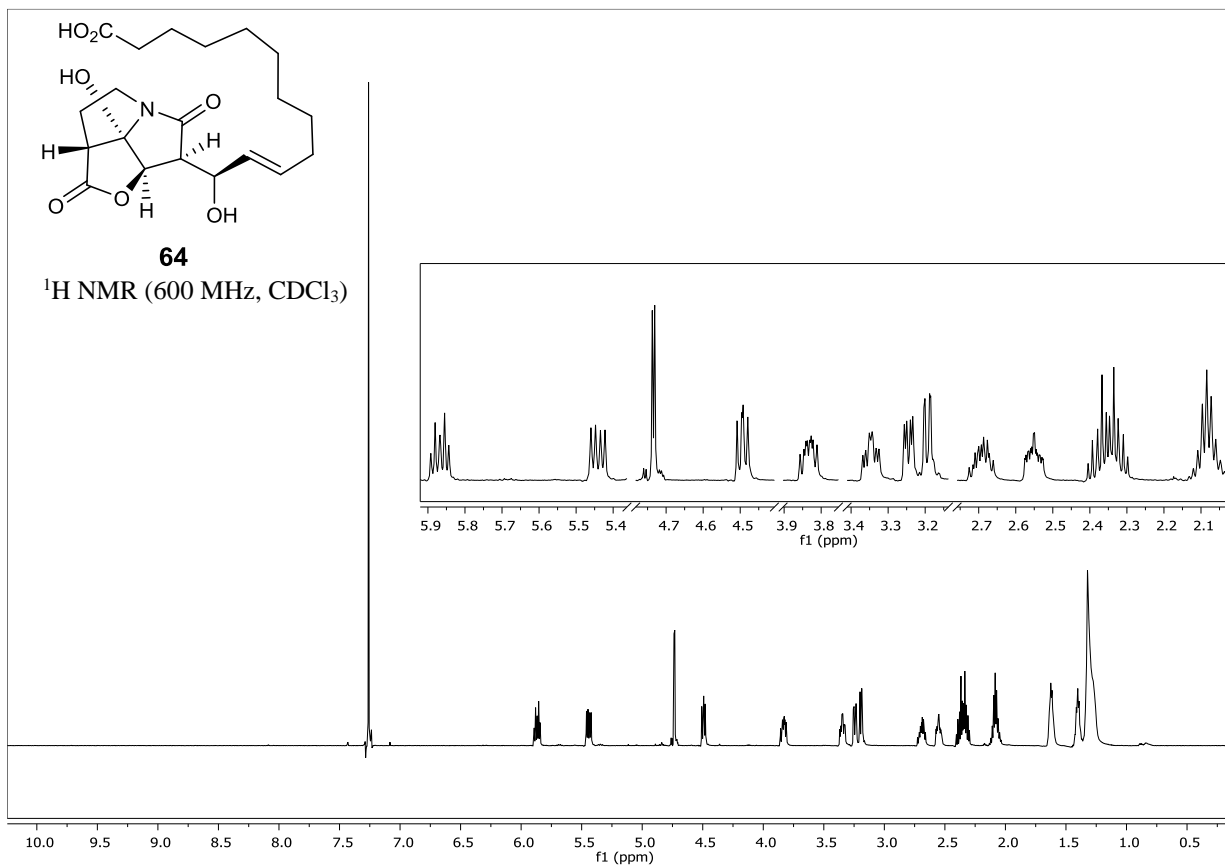


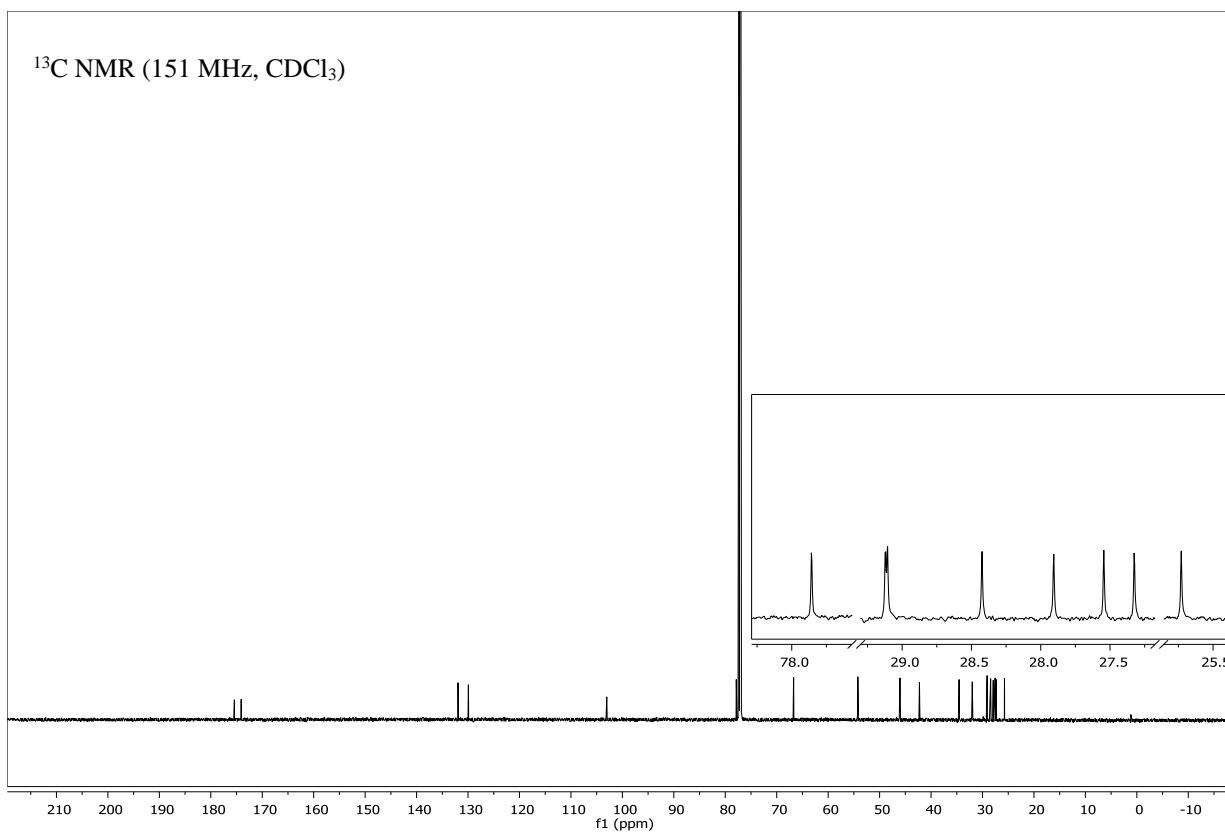
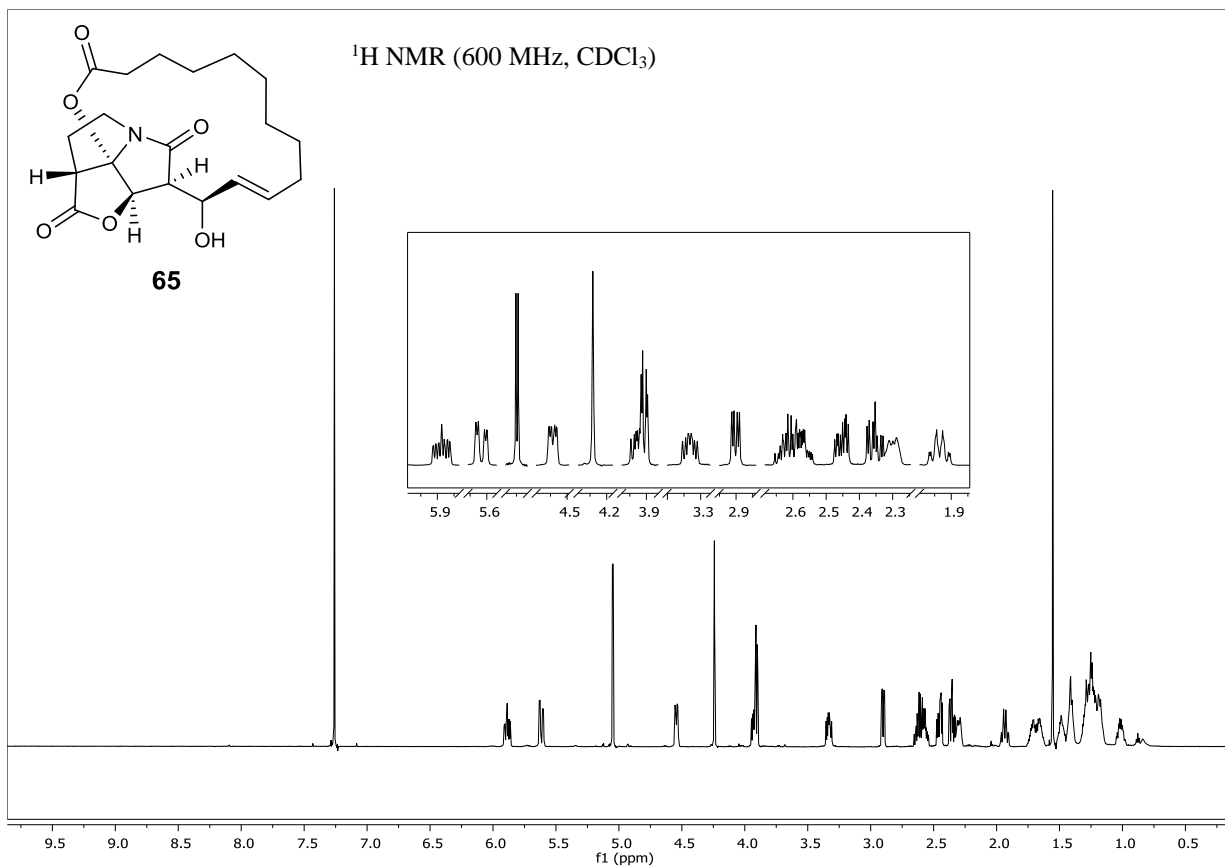


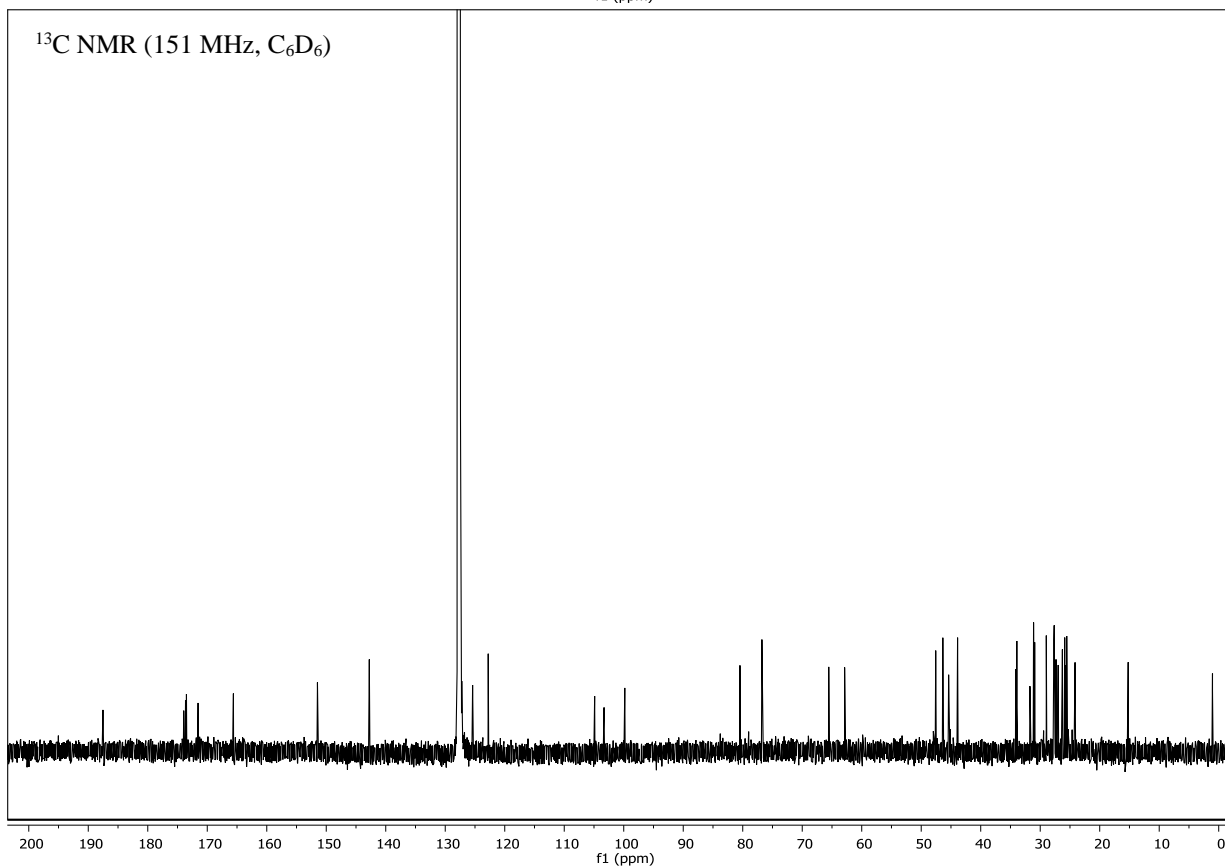
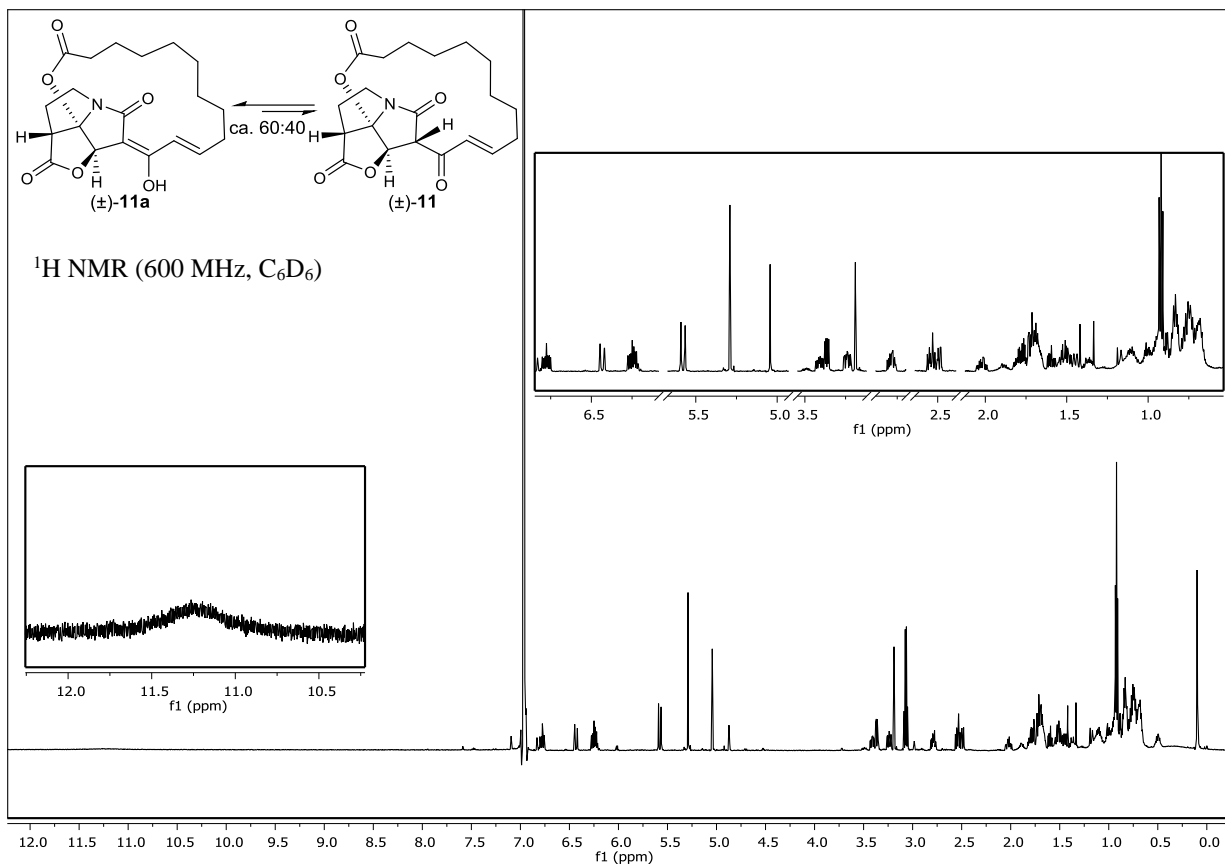


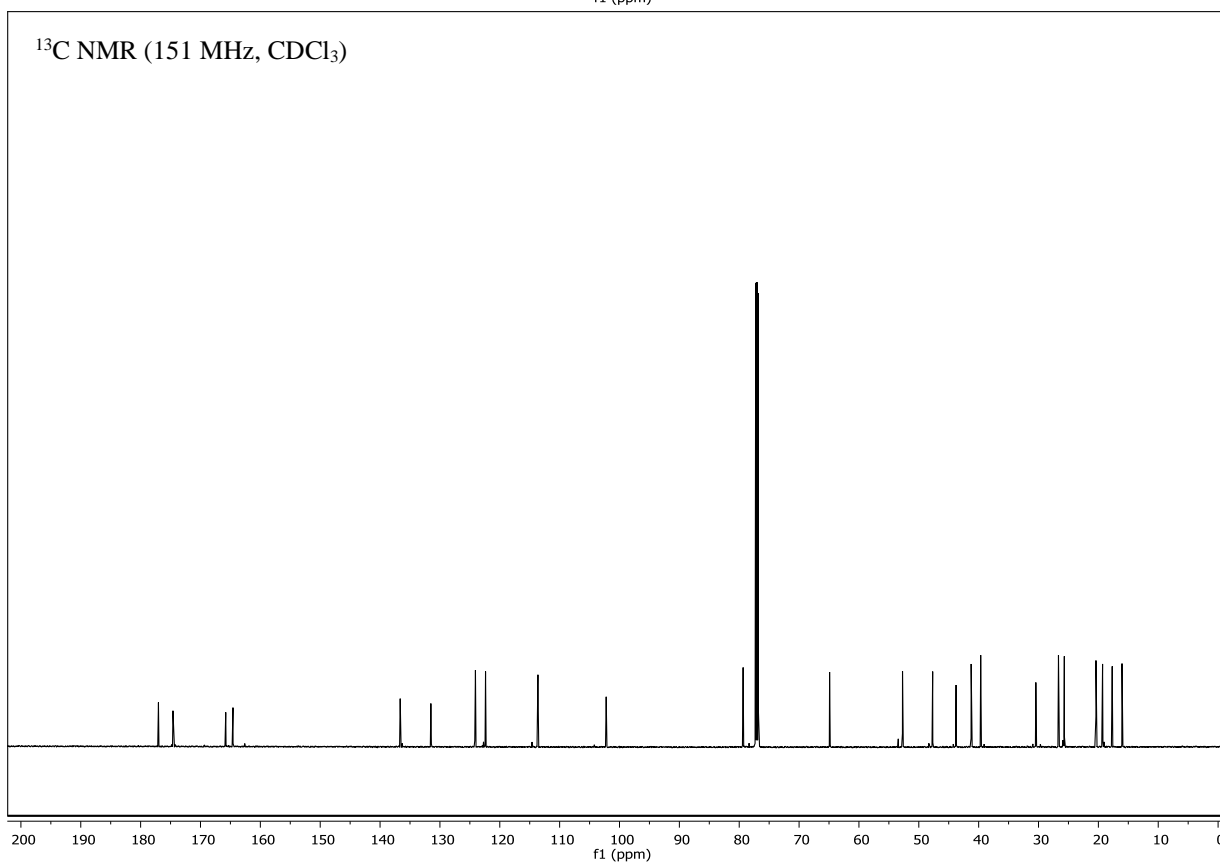
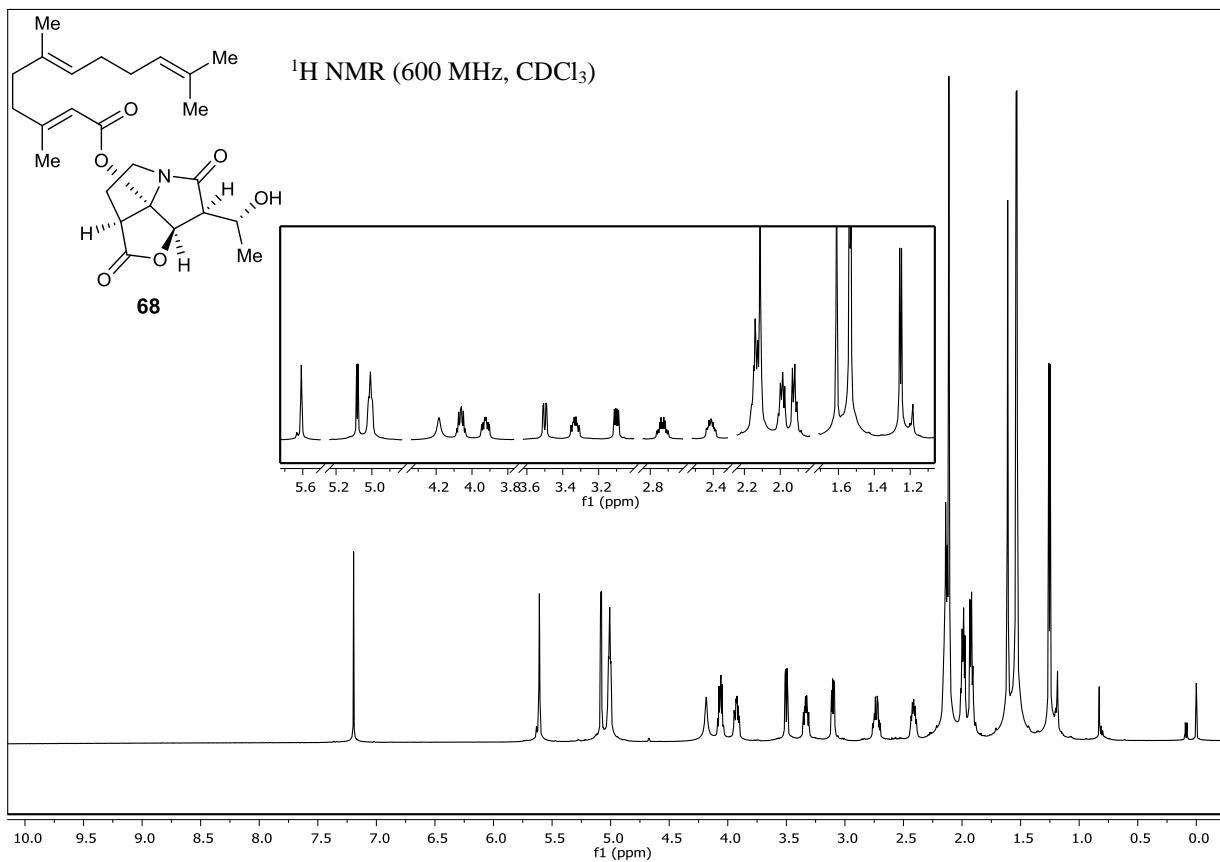


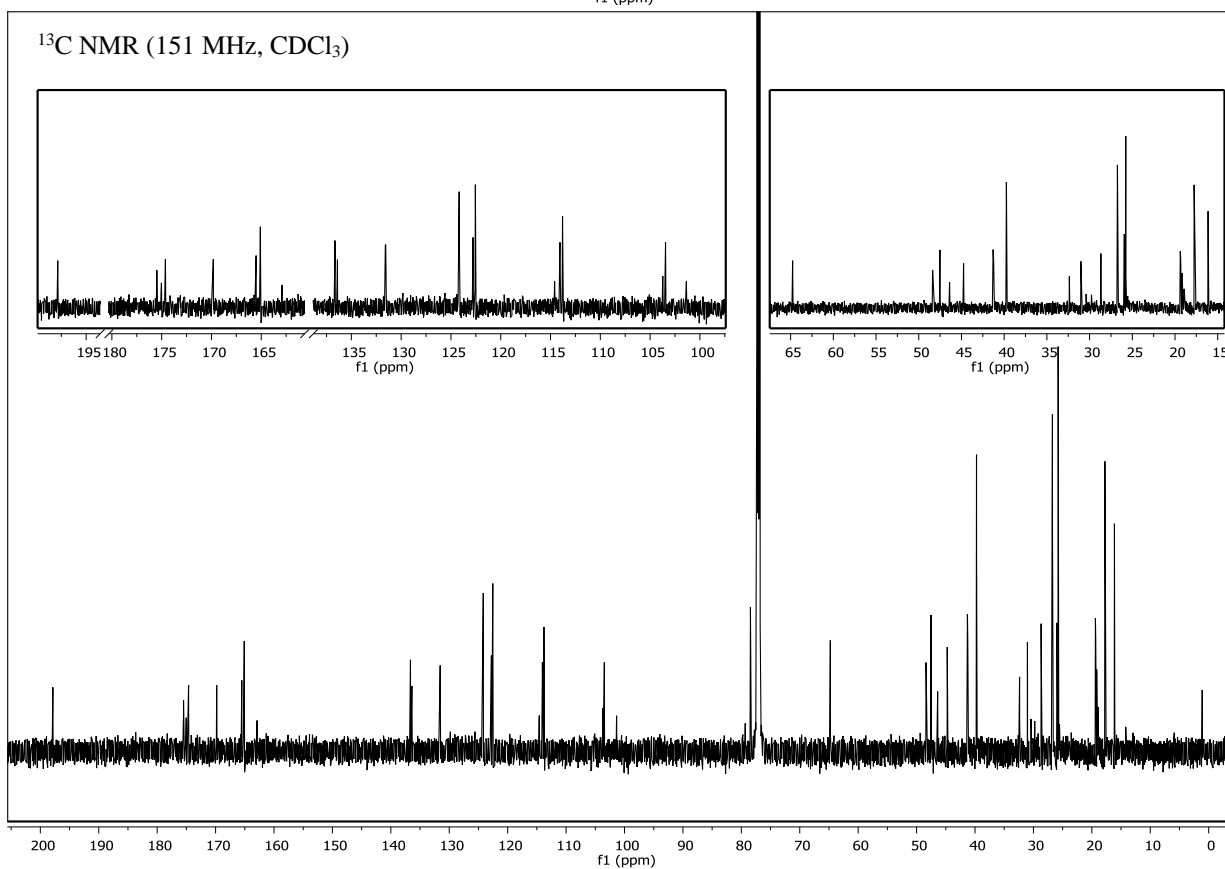
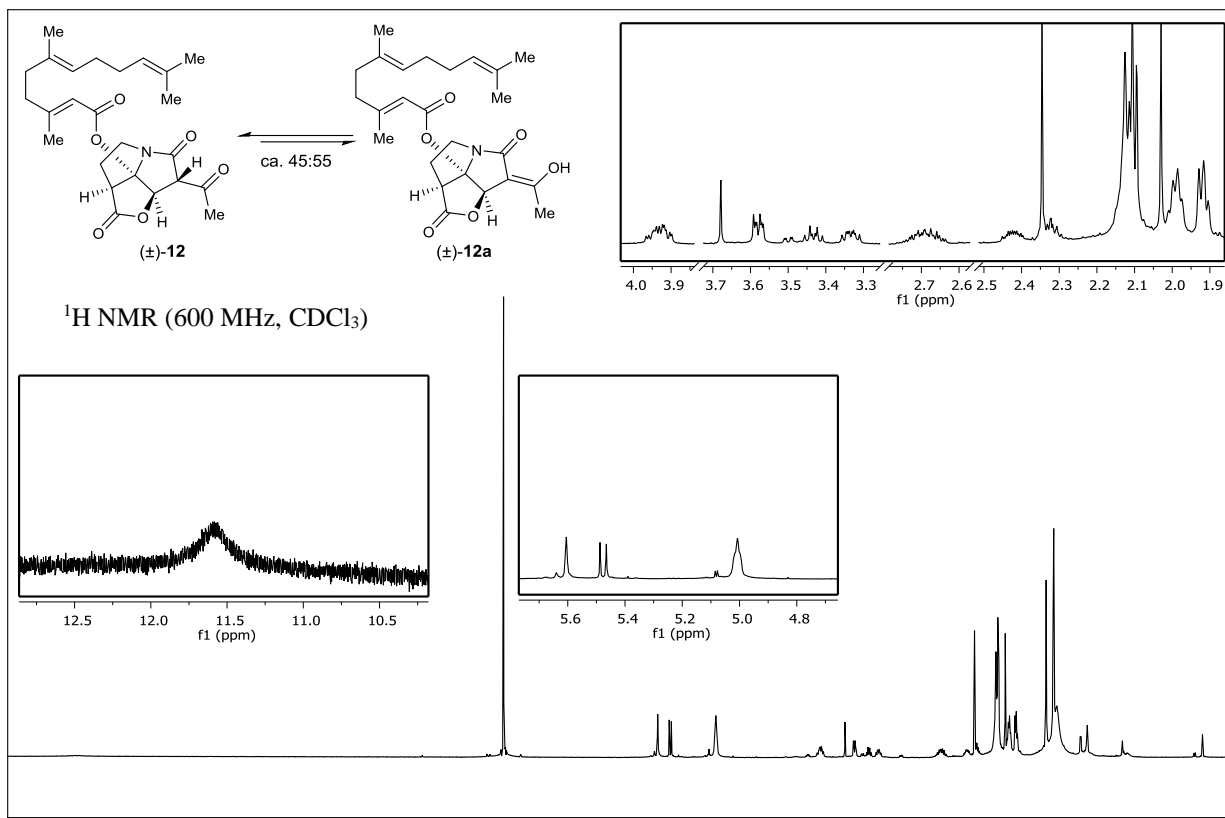




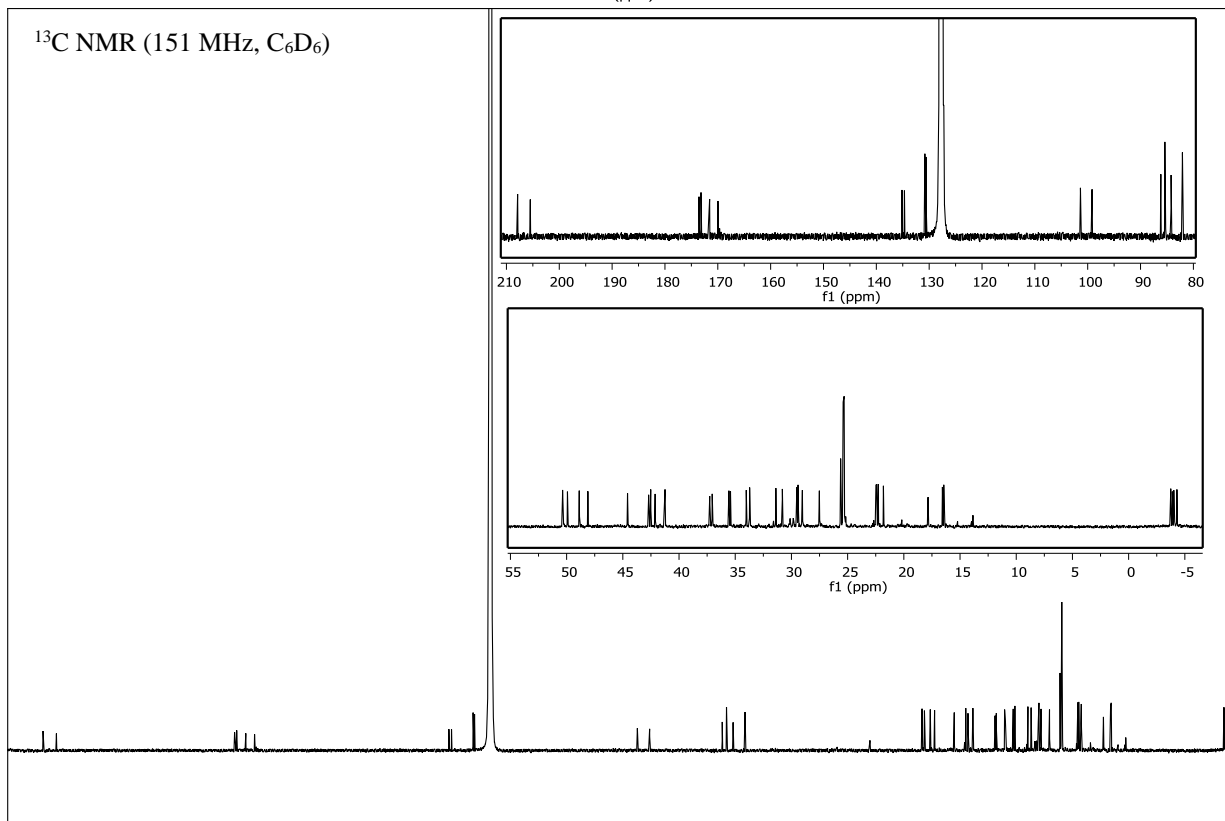
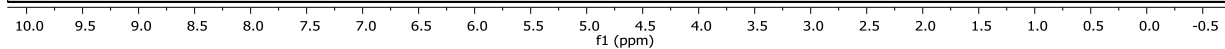
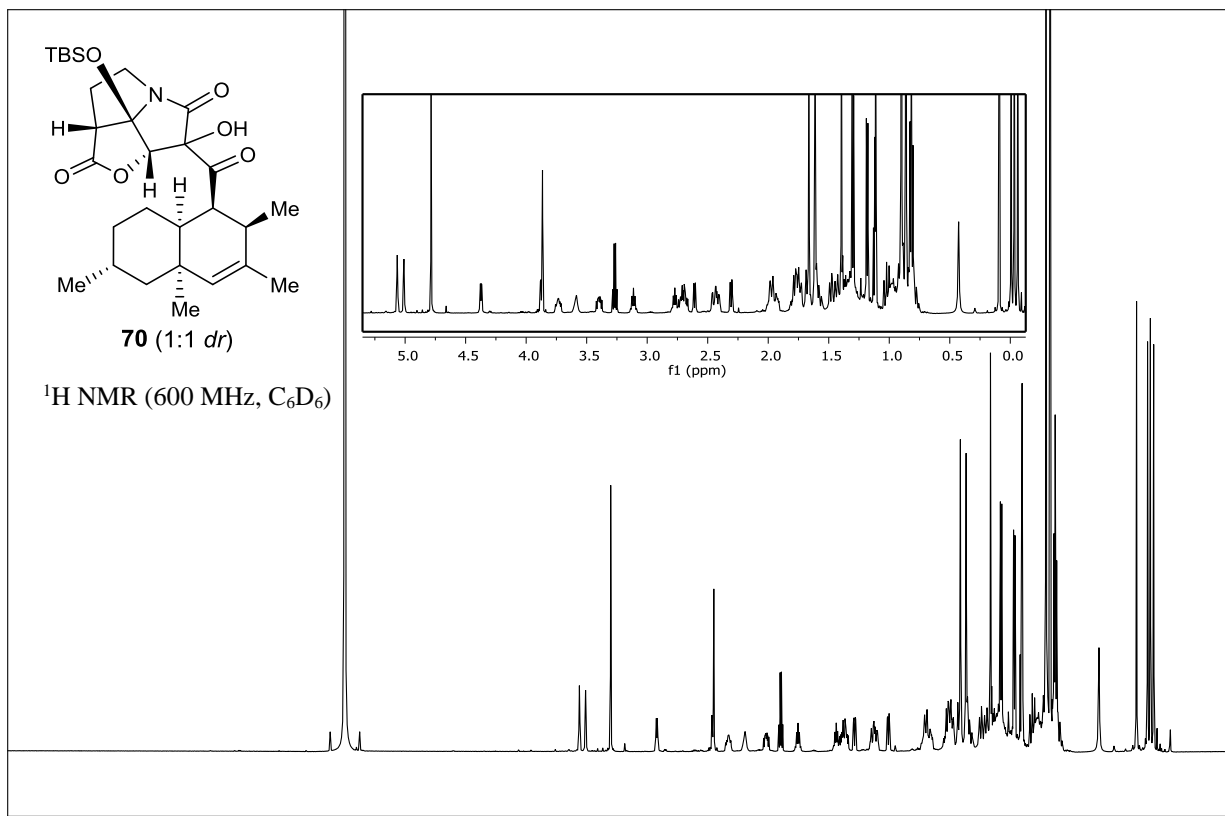


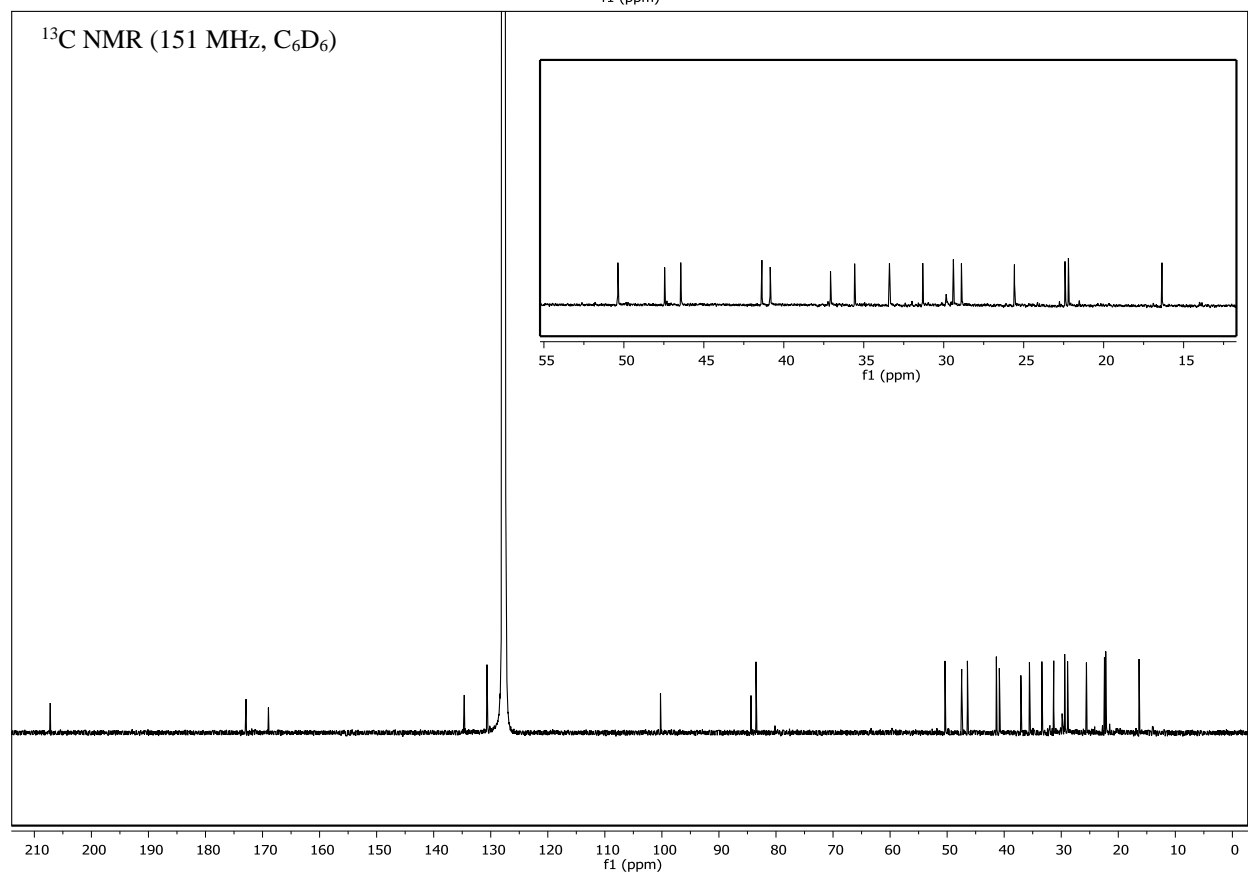
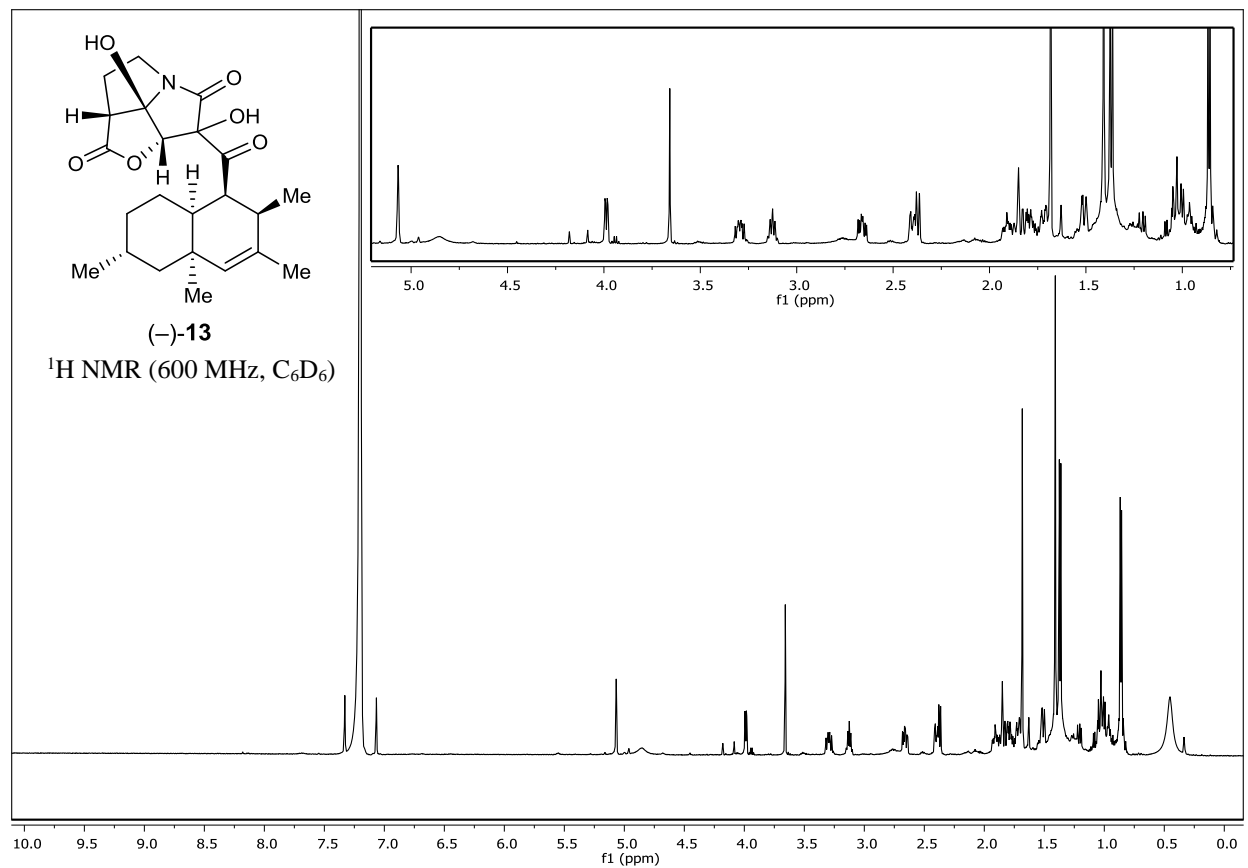


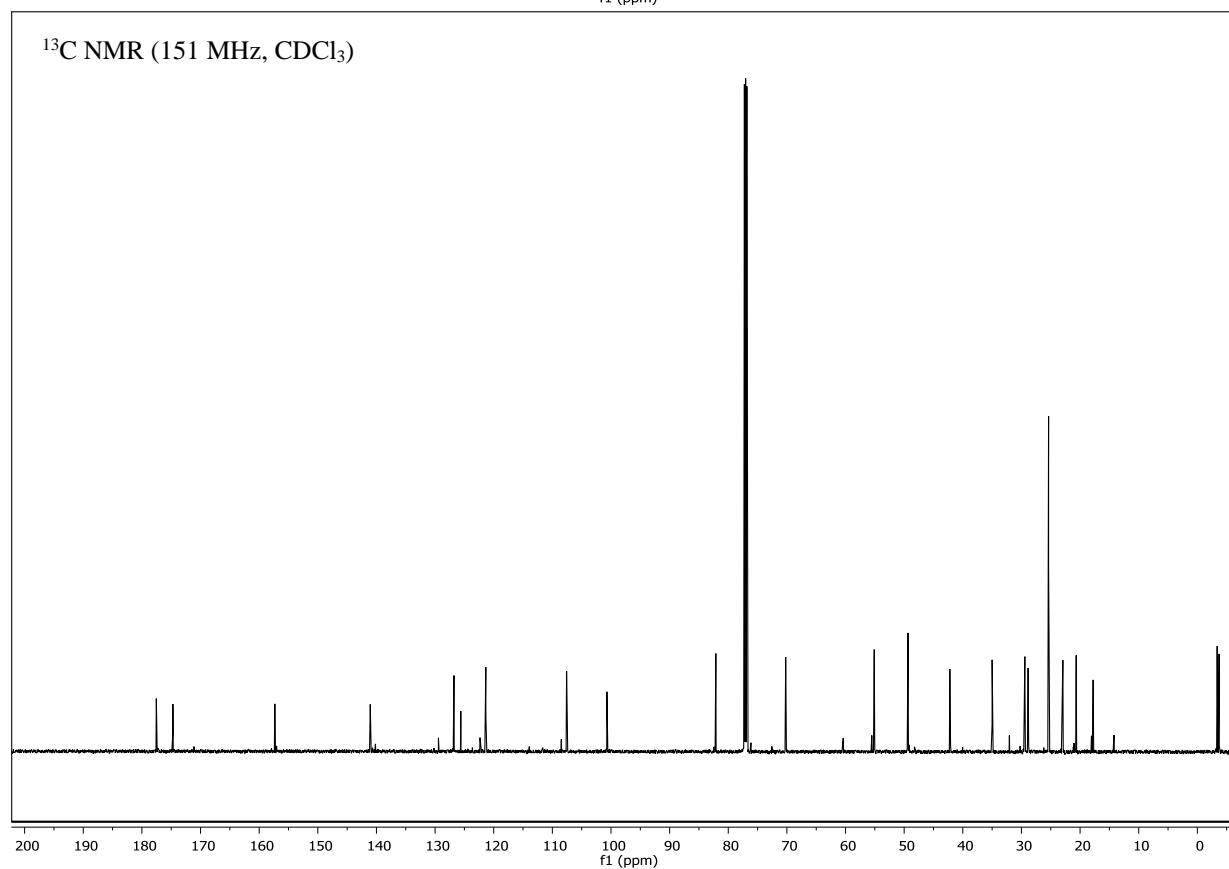
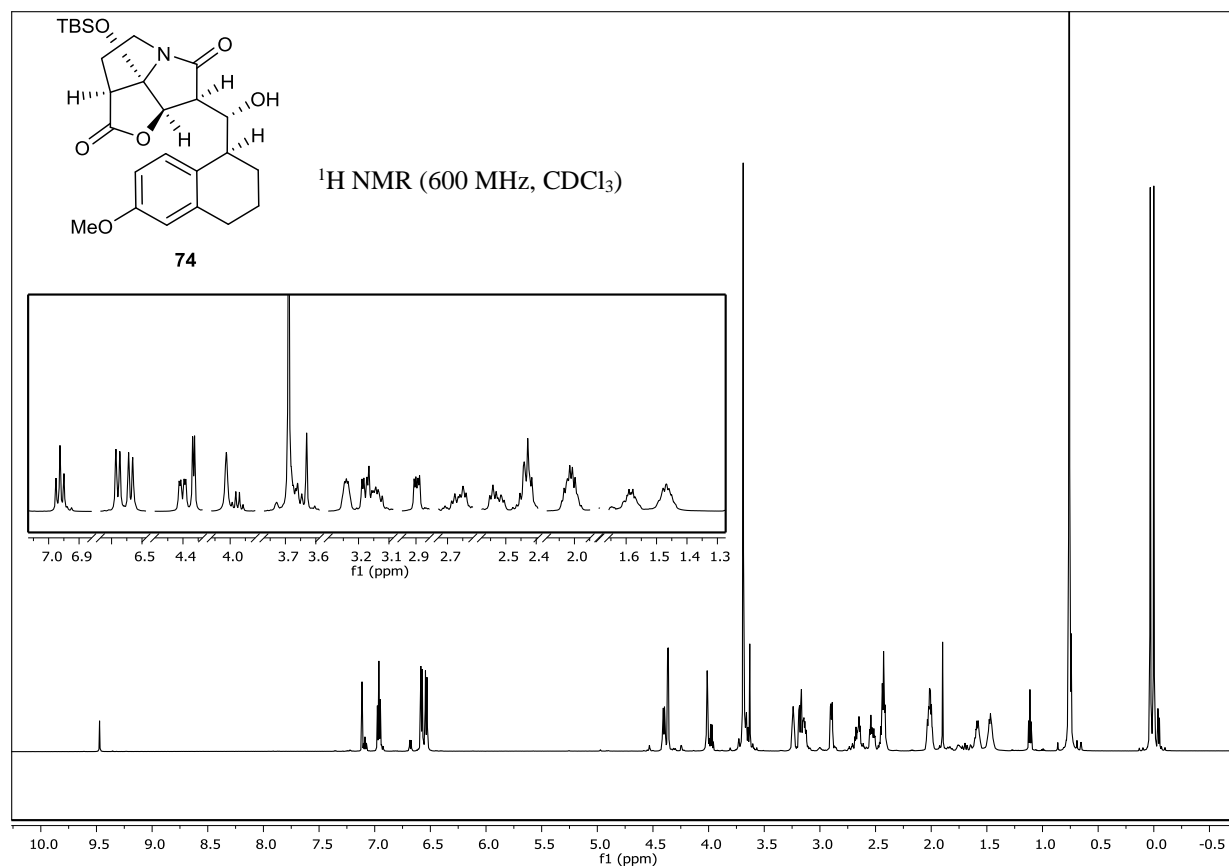


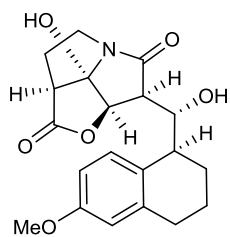






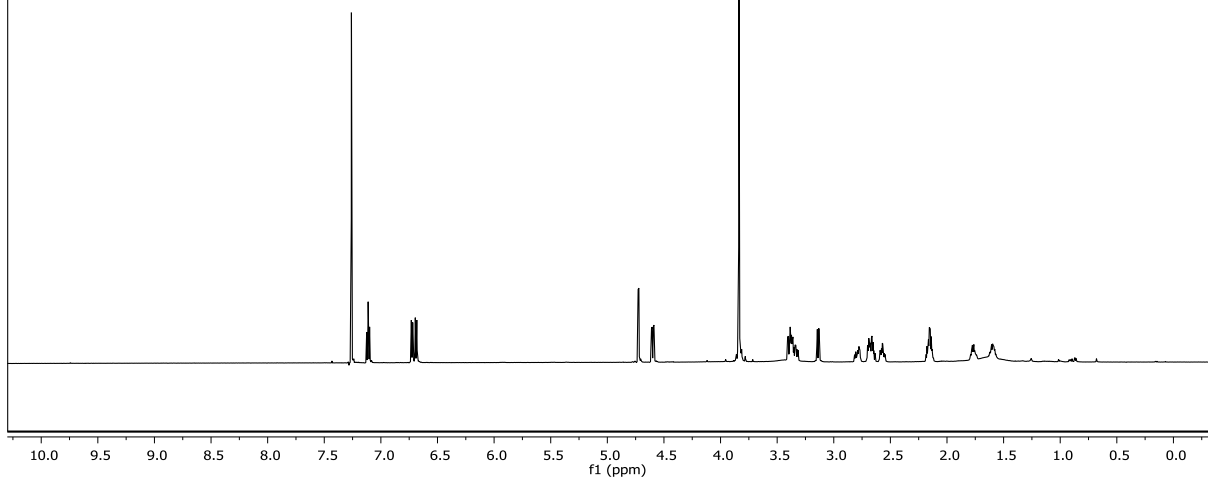
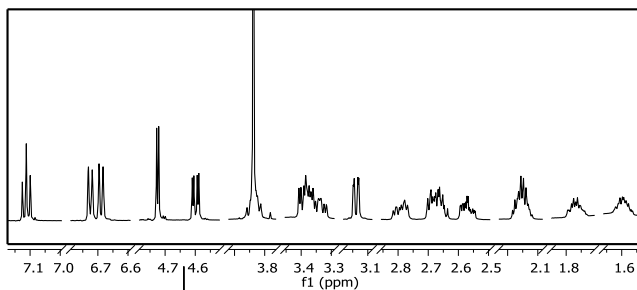






75

$^1\text{H}$  NMR (600 MHz,  $\text{CDCl}_3$ )



$^{13}\text{C}$  NMR (151 MHz,  $\text{CDCl}_3$ )

