

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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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 (Et₂O), acetonitrile (MeCN), methylene chloride (CH₂Cl₂), triethylamine (Et₃N), diisopropylamine, and pyridine were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H 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 (60F₂₅₄) 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 (60F₂₅₄). 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 ¹H NMR [$\delta_{\text{H}} = 7.26$ (CHCl₃), 7.16 (C₆D₅H), 2.05 (acetone-*d*₅), and 2.50 (DMSO-*d*₅) ppm] and deuterated solvent for ¹³C NMR [$\delta_{\text{C}} = 77.16$ (CDCl₃), 128.06 (C₆D₆), 39.52 (acetone-*d*₅), and 39.52 (DMSO-*d*₆) 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 10⁻¹ (deg cm² g⁻¹)]. 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.

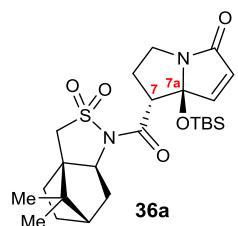
II. Experimental Procedures and Characterization Data

(7*S*,7*aR*)-7*a*-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-{[(3*aR*,6*S*,7*aS*)-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*)-7*a*-{[*tert*-butyl(dimethyl)silyl]oxy}-7-{[(3*aR*,6*S*,7*aS*)-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 Et₃N (1.67 mL, 8.25 mmol, 2.5 equiv) and PivCl (660 μL , 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. NH₄Cl 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 H₂O (10 mL), brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, 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.

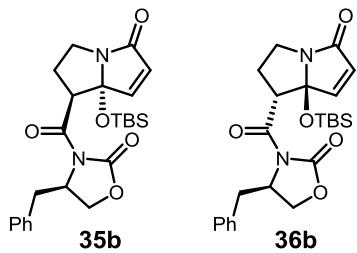
The absolute configuration of the C7 and C7*a* stereocenters at the tetrahydropyrrolo[1,2-*a*]pyrrol-3-one within these compounds (**35a** and **36a**) was not discernable from their NMR spectral data and, therefore, the depicted structures should be considered interchangeable.

35a or 36a: R_f=0.40 (hexanes:EtOAc, 3:2); [α]_D²⁵=+42 (*c*=1.5 in CHCl₃); IR (film) ν_{max}=3274, 2956, 2886, 1716, 1594, 1462, 1268, 1195, 1076, 779 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 6.99 (d, *J*=5.7 Hz, 1 H), 5.92 (d, *J*=5.7 Hz, 1 H), 3.83–3.73 (m, 3 H), 3.50 (d, *J*=13.8 Hz, 1 H), 3.44 (d, *J*=13.8 Hz, 1 H), 3.28–3.25 (m, 1 H), 2.68–2.61 (m, 1 H), 2.54–2.50 (m, 1 H), 1.96–1.81 (m, 5 H), 1.49–1.42 (m, 1 H), 1.40–1.23 (m, 1 H), 1.13 (s, 3 H), 0.96 (s, 3 H), 0.87 (s, 9 H), 0.05 (s, 3 H), 0.01 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃) δ 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 C₂₄H₃₈N₂O₅SSiNa⁺ [M+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 CHCl_3); IR (film) $\nu_{\text{max}} = 2957, 2858, 1705, 1447, 1310, 1281 \text{ cm}^{-1}$; ^1H NMR (600 MHz, CDCl_3) δ 7.00 (d, $J = 5.8 \text{ Hz}$, 1 H), 5.97 (d, $J = 5.7 \text{ Hz}$, 1 H), 3.77–3.73 (m, 3 H), 3.51 (d, $J = 13.8 \text{ Hz}$, 1 H), 3.43 (d, $J = 13.8 \text{ Hz}$, 1 H), 3.30 (ddd, $J = 11.0, 9.1, 2.1 \text{ Hz}$, 1 H), 2.77 (dtd, $J = 13.1, 9.2, 7.1 \text{ Hz}$, 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, $J = 11.2, 9.1, 2.3 \text{ Hz}$, 1 H), 1.30 (ddd, $J = 11.2, 9.1, 4.0 \text{ Hz}$, 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}C NMR (151 MHz, CDCl_3) δ 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.

(7*S*,7*aR*)-7-{[(4*S*)-4-Benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-7*a*-{[tert-butyl(dimethyl)silyloxy]-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one and (7*R*,7*aR*)-7-{[(4*S*)-4-benzyl-2-oxo-1,3-oxazolidin-3-yl]carbonyl}-7*a*-{[tert-butyl(dimethyl)silyl]oxy}-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one (35b and 36b): To a stirred solution of carboxylic acid (\pm)-29



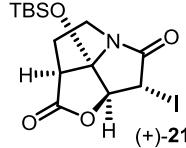
(600 mg, 2.00 mmol, 1.0 equiv) in THF (6 mL) at -20°C was added Et_3N (693 μL , 5.00 mmol, 2.5 equiv) and PivCl (257 μL , 2.10 mmol, 1.05 equiv). After stirring for 1 h at this temperature, LiCl (144 mg, 3.4 mmol, 1.7 equiv) followed by (*R*)-oxazolidinone **34b** (425 mg, 2.40 mmol, 1.2 equiv) was added. After stirring the resulting

solution for an additional 6 h at -20°C , the reaction mixture was then quenched by the addition of sat. aq. NH_4Cl solution (10 mL) and diluted with EtOAc (50 mL). The phases were separated, the aqueous layer was extracted with EtOAc (2×50 mL). The combined organic extracts were washed with H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , gradient from 10% EtOAc in hexanes \rightarrow 20% EtOAc in hexanes) gave the pure title compounds (**35b**; 392 mg, 859 μmol , 43% yield; **36b**; 406 mg, 889 μmol , 44% yield) as colorless oils.

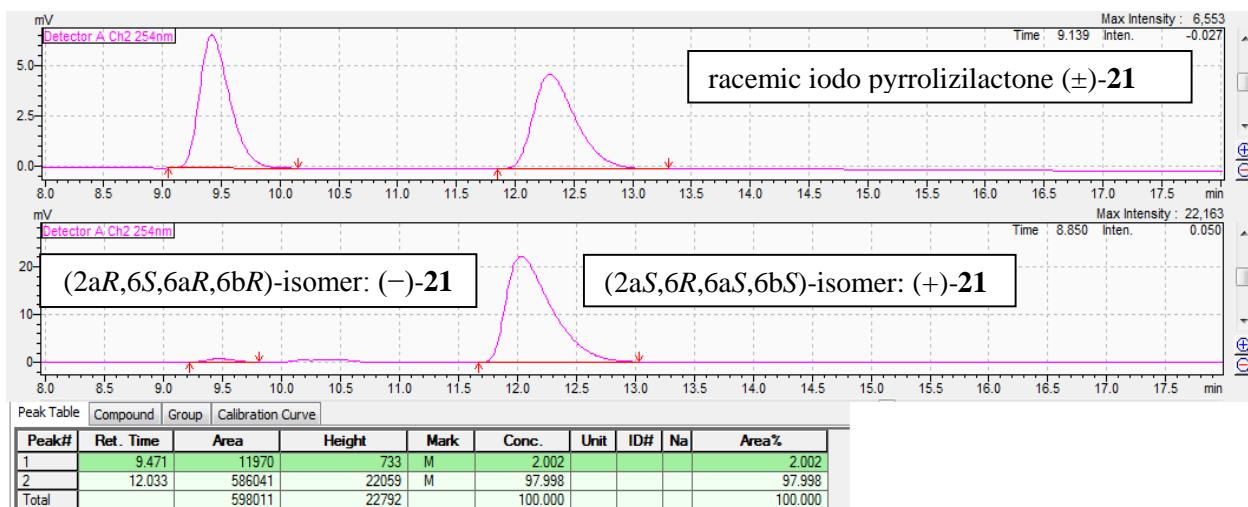
35b: $R_f = 0.60$ (hexanes:EtOAc, 3:2); $[\alpha]_D^{25} = +28$ ($c = 1.3$ in CHCl_3); IR (film) $\nu_{\text{max}} = 2956, 2930, 2858, 1781, 1715, 1384, 1250, 1093, 834, 780 \text{ cm}^{-1}$; ^1H NMR (600 MHz, CDCl_3) δ 7.32 (t, $J = 7.2 \text{ Hz}$, 2 H), 7.28–7.24 (t, $J = 7.2 \text{ Hz}$, 1 H), 7.19–7.15 (m, 2 H), 7.02 (d, $J = 5.8 \text{ Hz}$, 1 H), 6.00 (d, $J = 5.7 \text{ Hz}$, 1 H), 4.52 (ddt, $J = 9.9, 6.7, 3.4 \text{ Hz}$, 1 H), 4.33 (d, $J = 6.5 \text{ Hz}$, 1 H), 4.16–4.10 (m, 2 H), 3.91 (q, $J = 9.3 \text{ Hz}$, 1 H), 3.33 (ddd, $J = 10.8, 9.6, 1.9 \text{ Hz}$, 1 H), 3.21 (dd, $J = 13.2, 3.3 \text{ Hz}$, 1 H), 2.69 (dtd, $J = 13.0, 9.4, 6.6 \text{ Hz}$, 1 H), 2.57 (ddd, $J = 13.2, 8.8, 1.9 \text{ Hz}$, 1 H), 2.42 (dd, $J = 13.2, 10.9 \text{ Hz}$, 1 H), 0.90 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 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 $C_{24}H_{32}N_2O_5SiNa^+$ [M+Na]⁺: 479.1973, found: 479.1981.

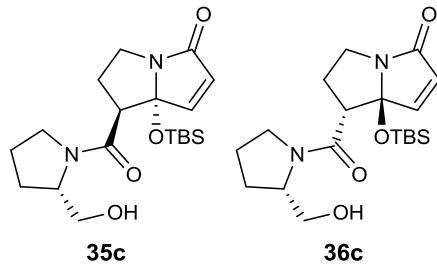
36b: $R_f=0.50$ (hexanes:EtOAc, 3:2); $[\alpha]_D^{25}=+19$ ($c=3.0$ in $CHCl_3$); IR (film) $\nu_{max}=2955, 2857, 1778, 1713, 1381, 1248, 1093, 834\text{ cm}^{-1}$; 1H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, $J=8.1, 6.6\text{ Hz}$, 2H), 7.27–7.24 (m, 1H), 7.15–7.14 (m, 2H), 6.88 (d, $J=5.8\text{ Hz}$, 1H), 5.99 (d, $J=5.7\text{ Hz}$, 1H), 4.53 (td, $J=9.3, 5.5, 3.5\text{ Hz}$, 1H), 4.45 (d, $J=6.6\text{ Hz}$, 1H), 4.15 (s, 1H), 4.14 (s, 1H), 3.88–3.84 (m, 1H), 3.32 (ddd, $J=11.0, 9.4, 1.9\text{ Hz}$, 1H), 3.23 (dd, $J=13.4, 3.5\text{ Hz}$, 1H), 2.75–2.68 (m, 2H), 2.54 (ddd, $J=13.2, 10.8, 1.9\text{ Hz}$, 1H), 0.88 (s, 9H), 0.08 (s, 3H), 0.03 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{24}H_{32}N_2O_5SiNa^+$ [M+Na]⁺: 479.1973, found: 479.1974.

(2aS,6R,6aS,6bS)-6b-{[tert-Butyl(dimethyl)silyl]oxy}-6-iodohexahydro-1-oxa-4a-azacyclo-penta[cd]pentalene-2,5-dione [(+)-21]: To a stirred solution of amide **35b** (90 mg, 0.20 mmol, TBSO(1.0 equiv) in $CH_2Cl_2:MeOH:H_2O$ (1:1:0.05 v/v/v, 5 mL) at 25 °C was added I(*sym*-collidine)₂ClO₄ (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_2Cl_2 (50 mL). The reaction mixture was washed sequentially with sat. aq. Na₂S₂O₃ (2 × 30 mL), aq. HCl (0.5 M; 2 × 30 mL), and brine (30 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated. Purification by flash column chromatography (SiO₂, 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); (2aR,6S,6aR,6bR)-isomer: 9.47 min; (2aS,6R,6aS,6bS)-isomer: 12.03 min] as a light yellow solid.

(+)-21: $R_f=0.50$ (hexanes:EtOAc, 2:1); $[\alpha]_D^{25}=+21$ ($c=0.2$ in $CHCl_3$); IR (film) $\nu_{max}=3007, 2954, 2887, 2859, 1794, 1718, 1472, 1361, 1257, 1164, 1137, 1012, 889, 840, 780\text{ cm}^{-1}$; 1H NMR (600 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.44 (s, 1H), 3.96–3.91 (m, 1H), 3.34–3.29 (m, 1H), 3.12 (dd, $J=9.4, 2.4\text{ Hz}$, 1H), 2.69–2.54 (m, 2H), 0.95 (s, 9H), 0.24 (s, 3H), 0.22 (s, 3H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) 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 $C_{14}H_{22}INO_4SiNa^+$ [M+Na]⁺: 446.0255, found: 446.0262.



(7*S*,7*aR*)-7*a*-{[*tert*-Butyl(dimethyl)silyl]oxy}-7-{[(2*R*)-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*a**R*)-7*a*-{[*tert*-butyl-(dimethyl)silyl]oxy}-7-{[(2*R*)-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



(\pm)-29 (450 mg, 1.50 mmol, 1.0 equiv) in CH_2Cl_2 (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_2Cl_2 (1 mL) followed by *i*-Pr₂NEt (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. NH₄Cl solution (5 mL) and diluted with CH_2Cl_2 (20 mL). The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ (2 × 10 mL), brine (10 mL), dried (Na₂SO₄), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, gradient from CH_2Cl_2 → 2% MeOH in CH_2Cl_2) gave pure title compounds (35c and 36c, 386 mg, 1.02 mmol, 68% yield, 1:1 *dr*) as a colorless oil.

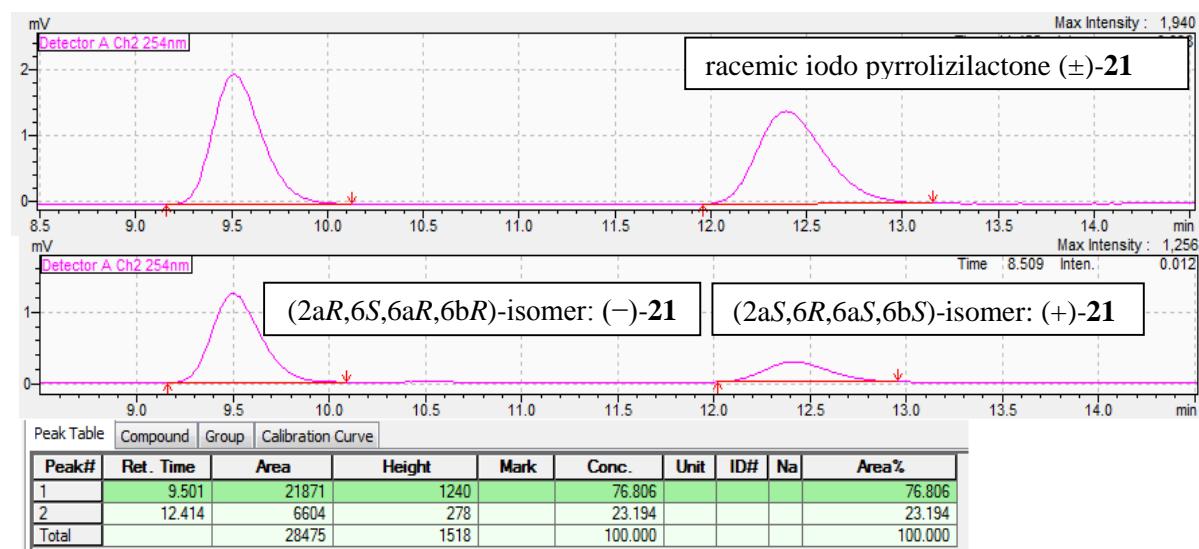
35c and 36c: R_f=0.10 (EtOAc); IR (film) ν_{max} =3422, 2954, 2886, 2857, 1713, 1622, 1472, 1277, 1197, 1087 cm⁻¹; ¹H NMR (600 MHz, CDCl₃, 1:1 mixture of diastereomers, *Indicates inclusion of signals of both diastereomers) δ 6.81 (d, *J*=5.7 Hz, 1 H), 6.70 (d, *J*=5.7 Hz, 1 H), 6.03 (d, *J*=5.8 Hz, 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,

2 H), 3.77 (ddd, $J = 10.3, 7.5, 5.0$ Hz, 1 H), 3.68–3.45* (m, 7 H), 3.25–3.21* (m, 2 H), 2.50–2.42* (m, 2 H), 2.08–1.83* (m, 6 H), 1.67–1.57* (m, 2 H), 0.87* (s, 18 H), 0.09* (s, 6 H), 0.02* (s, 6 H), 0.01* (s, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3 , 1:1 mixture of diastereomers) δ 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.

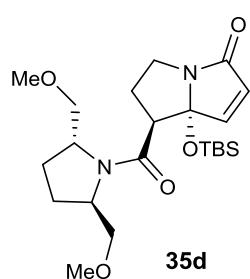
(2a*R*,6*S*,6a*R*,6b*R*)-6b-{{[tert-Butyl(dimethyl)silyl]oxy}-6-iodohexahydro-1-oxa-4a-azacyclo-penta[cd]pentalene-2,5-dione [(-)-21]: To a stirred solution of amide **35c** and **36c** (1:1 mixture

of diastereomers, 60 mg, 0.16 mmol, 1.0 equiv) in $\text{CH}_2\text{Cl}_2:\text{MeOH:H}_2\text{O}$ (1:1:0.05 v/v/v, 5 mL) at 25 °C was added $\text{I}(\text{sym-collidine})_2\text{ClO}_4$ (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 CH_2Cl_2 (50 mL). The reaction mixture was washed sequentially with sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (2×10 mL), aq. HCl (0.5 M; 2×10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. Purification by flash column chromatography (SiO_2 , gradient from 10% EtOAc in hexanes→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 × 4.6 mm, 13% *i*-PrOH:hexanes, flow rate 17 mL/min); (2a*R*,6*S*,6a*R*,6b*R*)-isomer: 9.5 min; (2a*S*,6*R*,6a*S*,6b*S*)-isomer: 12.4 min] as a light yellow solid.

(-)–**21**: The ^1H NMR and ^{13}C NMR spectral data of (–)-**21** matched those of (+)-**21**. $[\alpha]_D^{25} = -10$ ($c = 0.5$ in CHCl_3).



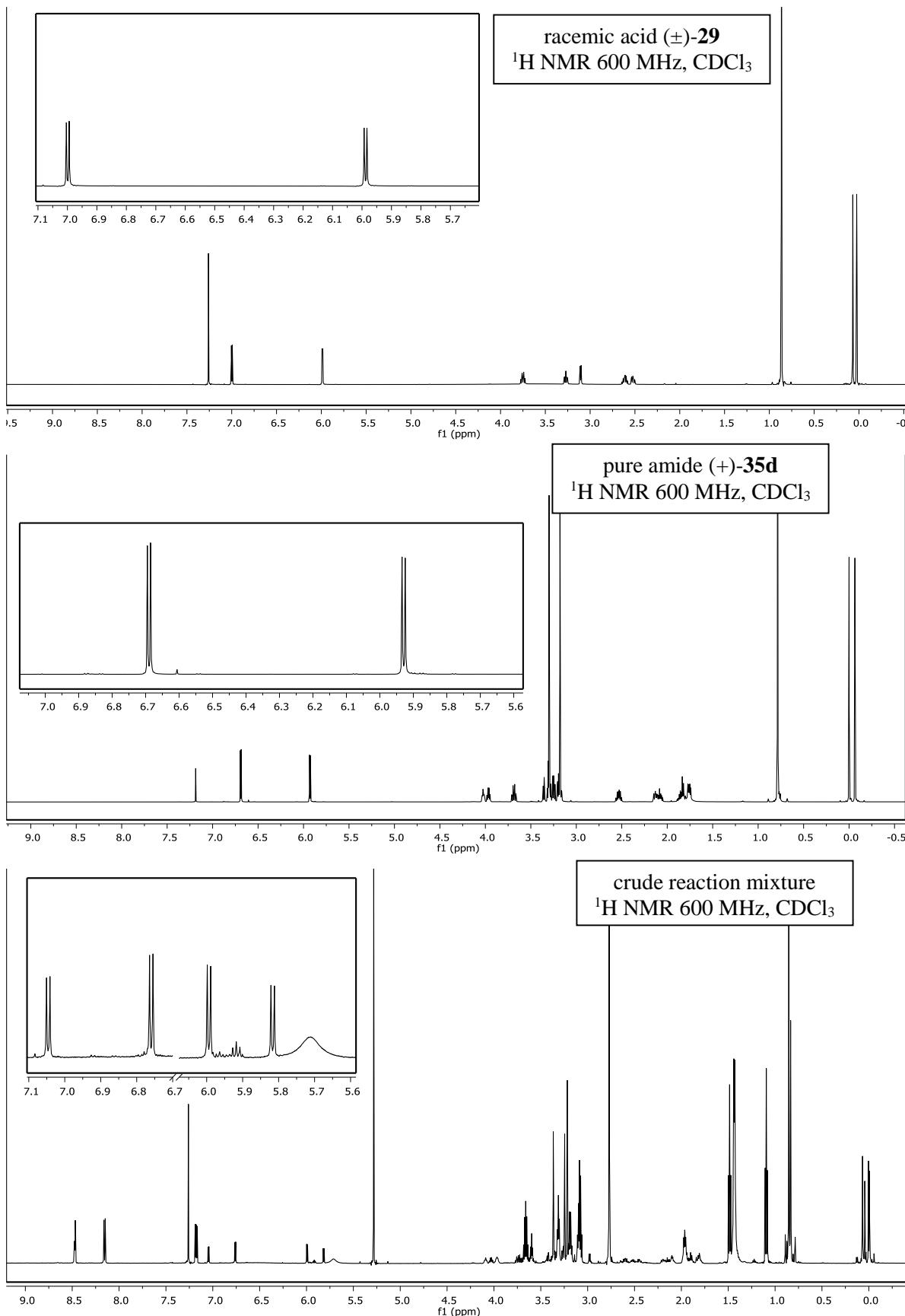
(7*S*,7*aR*)-7-[(2*S*,5*S*)-2,5-Bis(methoxymethyl)pyrrolidin-1-yl]carbonyl]-7*a*-{[*tert*-butyl(di-methyl)silyl]oxy}-5,6,7,7*a*-tetrahydro-3*H*-pyrrolo[1,2-*a*]pyrrol-3-one (35d**):**



To a stirred solution of carboxylic acid (\pm)-**29** (297 mg, 1.00 mmol, 1.0 equiv) in CH_2Cl_2 (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 μ mol, 0.6 equiv) in CH_2Cl_2 (1 mL) followed by *i*-Pr₂NEt (423 μ 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_2Cl_2 (50 mL). The phases were separated, the aqueous layer was extracted with CH_2Cl_2 (2 \times 10 mL). The combined organic extracts were washed with aq. HCl solution (1.0 M; 2 \times 5 mL), H_2O (10 mL), brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (SiO_2 , 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.

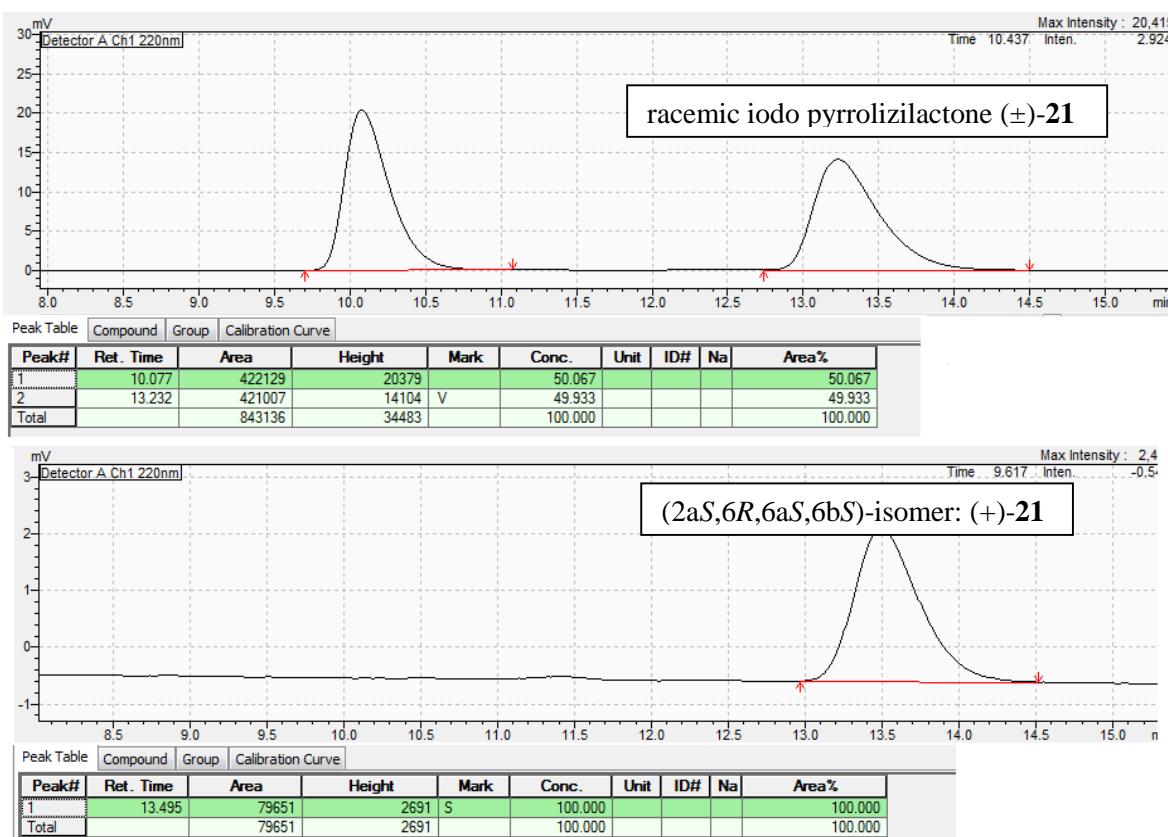
35d: R_f = 0.40 (EtOAc); $[\alpha]_D^{25} = +26$ ($c = 1.0$ in C_6H_6); IR (film) $\nu_{\text{max}} = 2954, 2892, 2858, 1718, 1638, 1423, 1322, 1251, 1112, 1073, 834, 810, 778 \text{ cm}^{-1}$; ¹H NMR (600 MHz, CDCl_3) δ 6.76 (d, $J = 5.7 \text{ Hz}$, 1 H), 6.00 (d, $J = 5.7 \text{ Hz}$, 1 H), 4.11–4.08 (m, 1 H), 4.06–4.01 (m, 1 H), 3.76 (dt, $J = 10.7, 8.6 \text{ Hz}$, 1 H), 3.43 (dd, $J = 9.2, 3.0 \text{ Hz}$, 1 H), 3.40–3.35 (m, 5 H), 3.32 (dd, $J = 9.4, 7.0 \text{ Hz}$, 1 H), 3.29–3.22 (m, 5 H), 2.61 (dt, $J = 12.8, 8.8, 7.3 \text{ Hz}$, 1 H), 2.23–2.12 (m, 2 H), 1.97–1.87 (m, 2 H), 1.86–1.81 (m, 1 H), 0.86 (s, 9 H), 0.07 (s, 3 H), 0.01 (s, 3 H) ppm; ¹³C NMR (151 MHz, CDCl_3) δ 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 $\text{C}_{22}\text{H}_{38}\text{N}_2\text{O}_5\text{SiNa}^+$ [M+Na]⁺: 461.2442, found: 461.2418.

(*-*)-29: The ¹H NMR and ¹³C NMR spectral data of (*-*)-**29** matched those of previously reported by the Danishefsky group.¹ $[\alpha]_D^{25} = -27$ ($c = 1.0$ in CHCl_3).



(2aS,6R,6aS,6bS)-6b-{[tert-Butyl(dimethyl)silyl]oxy}-6-iodohexahydro-1-oxa-4a-azacyclo-penta[cd]pentalene-2,5-dione [(+)-21]: To a stirred solution of amide **35d** (1.50 g, 3.42 mmol, 1.0 equiv) in CH₂Cl₂:MeOH:H₂O (1:1:0.05 v/v/v, 75 mL) at 25 °C was added I(sym-collidine)₂ClO₄ (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 CH₂Cl₂ (100 mL). The reaction mixture was washed sequentially with sat. aq. Na₂S₂O₃ (2×30 mL), aq. HCl (1 M; 2×10 mL), H₂O (10 mL) and brine (10 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated. Purification by flash column chromatography (SiO₂, 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*,6*bR*)-isomer: 10.07 min; (2a*S*,6*R*,6*aS*,6*bS*)-isomer: 13.49 min] as a light yellow solid and amide **35d** (389 mg, 0.891 mmol) was recovered.

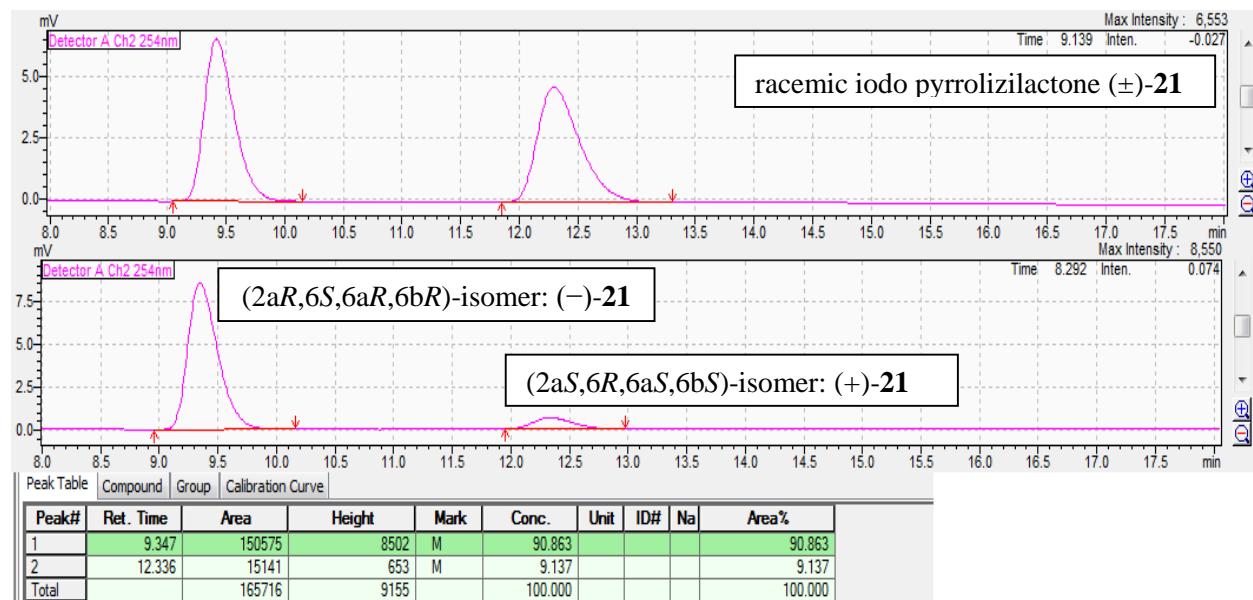
(+)-**21**: The ¹H NMR and ¹³C NMR spectral data of (+)-**21** matched those of previously synthesized (+)-**21**. [α]_D²⁵ = +25 (*c* = 1.0 in CHCl₃).



(2a*R*,6*S*,6a*R*,6b*R*)-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 µmol,

1.0 equiv) in Et₂O:sat. aq. NaHCO₃ (1:1 *v/v*, 10 mL) at 25 °C was added I₂ (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 Et₂O (50 mL). The reaction mixture was washed sequentially with sat. aq. Na₂S₂O₃ (2 × 5 mL), H₂O (10 mL) and brine (10 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated. Purification by flash column chromatography (SiO₂, gradient from 10% EtOAc in hexanes→20% EtOAc in hexanes) gave pure title compound [(-)-**21**, 131 mg, 309 µmol, 74% yield, 91:9 *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: 9.3 min; (2a*S*,6*R*,6a*S*,6b*S*)-isomer: 12.3 min] as a light yellow solid.

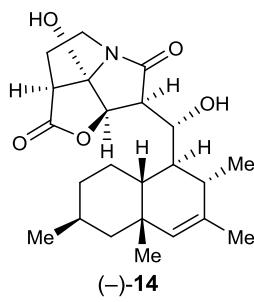
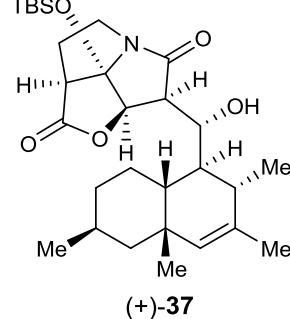
(-)-**21**: The ¹H NMR and ¹³C NMR spectral data of (-)-**21** matched those of previously reported by the Danishefsky group.¹ [α]_D²⁵ = -22 (*c*=1.0 in CHCl₃).



(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]: To a stirred solution of aldehyde (−)-22 (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 °C was added BEt₃ (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 H₂O (1 mL). The reaction mixture was extracted with Et₂O (3 × 10 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO₂, gradient from 100% hexanes→20% EtOAc in hexanes) providing pure title compound [(+)-37; 48 mg, 93 μmol, 82% yield] as a colorless oil.

(+)-37: R_f=0.40 (hexanes:EtOAc, 4:1); [α]_D²⁵=+12 (c=1.0, C₆H₆); IR (film) ν_{max} 3471, 2929, 2860, 1794, 1702, 1374, 1141, 838, 780 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ 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; ¹³C NMR (151 MHz, C₆D₆) δ 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 C₂₉H₄₇NO₅SiNa⁺ [M+Na]⁺ 540.3116 found 540.3124.

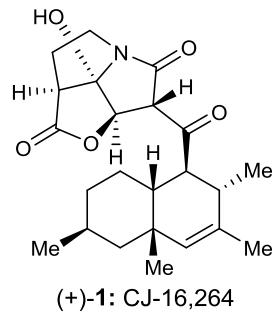
(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-{hydroxy[(1*S*,2*S*,4a*R*,6*S*,8a*R*)-2,3,4a,6-tetramethyl-1,2,4a,5,6,7,8,8a-octahydronaphthalen-1-yl)methyl}hexahydro-1-oxa-4a-azacyclopenta[cd]-pentalene-2,5-dione [(-)-14]: To a stirred solution of TBAF (1.0 M in THF, 12 μL, 12 μmol, 1.0 equiv) and acetic acid (7.0 μL, 12 μmol, 1.05 equiv) in THF (2 mL) was added TBS ether (+)-37 (10 mg, 12 μmol, 1.0 equiv) in THF (1 mL) at 0 °C and the resulting mixture was stirred for 30 min at the same temperature before it was quenched by the addition of sat. aq. NH₄Cl (2 mL). The resulting mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried over MgSO₄, and concentrated under reduced



pressure. The resulting crude product was purified by flash column chromatography (SiO_2 , gradient from 10% EtOAc in hexanes \rightarrow 50% EtOAc in hexanes) providing pure title compound [(-)-**14**; 4.1 mg, 10 μmol , 88% yield] as a colorless oil.

(-)-**14**: $R_f=0.30$ (hexanes:EtOAc, 1:1); $[\alpha]_D^{25}=-15$ ($c=0.5$, acetone); IR (film) ν_{max} 3339, 2919, 1789, 1693, 1446, 1382, 1022 cm^{-1} ; ^1H NMR (600 MHz, acetone- d_6) 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; ^{13}C NMR (151 MHz, acetone- d_6) 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 $\text{C}_{23}\text{H}_{33}\text{NO}_5\text{Na}^+$ $[\text{M}+\text{Na}]^+$ 426.2251 found 426.2259.

(2aS,6aR,6bS)-6b-Hydroxy-6-{{[(1S,2S,4aR,6S,8aR)-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)



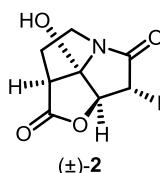
at 70 °C was added IBX (21 mg, 74 μmol , 5.0 equiv) and the resulting mixture was stirred for 9 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with Et_2O (15 mL) and passed through a plug of Celite. The solvent was removed under reduced pressure and the obtained 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 [(+)-**1**; 4.1 mg, 10 μmol , 68% yield] as a colorless oil.

(+)-**1**: $R_f=0.30$ (hexanes:EtOAc, 1:1); $[\alpha]_D^{25}=+8$ ($c=0.3$, MeOH); IR (film) ν_{max} 3446, 2924, 2854, 1793, 1719, 1690, 1555, 1456, 1336, 1260, 1161, 1024, 798 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) 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; ^{13}C NMR (151 MHz, C_6D_6) 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, 29.1, 28.8, 22.3, 21.6, 21.0 ppm; HRMS (ESI-TOF): calcd for $C_{23}H_{31}NO_5Na^+$ [M+Na]⁺ 424.2094 found 424.2101.

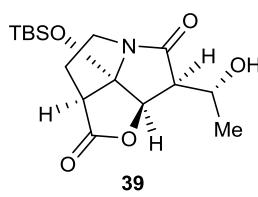
***rel*-(2a*S*,6*R*,6a*S*,6b*S*)-6b-Hydroxy-6-iodohexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione [(±)-2]:** To a stirred solution of iodide (±)-21 (20 mg, 47 µmol, 1.0 equiv) in THF



(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 H₂O (2 mL). The reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO₂, 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_f = 0.20 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 2928, 1792, 1706, 1378, 1329, 1156, 1008, 838 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (151 MHz, CDCl₃) δ 173.6, 172.1, 101.2, 84.8, 48.9, 42.7, 25.8, 14.0 ppm; HRMS (ESI-TOF): calcd for C₈H₉NO₄I⁺ [M+H]⁺ 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 BEt₃ (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 H₂O (1 mL). The reaction mixture was extracted with Et₂O (3×10 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO₂, 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_f = 0.30 (hexanes:EtOAc, 4:1); IR (film) ν_{max} 3495, 2955, 2931, 2858, 1789, 1700, 1371, 1304, 1250, 1102, 1057, 893, 778 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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,

9 H), 0.16 (s, 3 H), 0.14 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 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*-(2a*S*,6*S*,6a*R*,6b*S*)-6b-Hydroxy-6-[(1*R*)-1-hydroxyethyl]hexahydro-1-oxa-4a-azacyclo-penta[cd]pentalene-2,5-dione (**40**):**

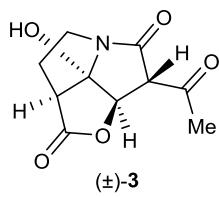
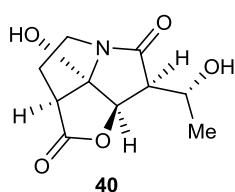
To a stirred solution of TBS ether **39** (17 mg, 50 μmol , 1.0 equiv) in THF (2 mL) at 0 °C was added TASF (21 mg, 75 μmol , 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×25 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 → 60% EtOAc in hexanes) providing pure title compound (**40**; 12 mg, 44 μmol , 88% yield) as a white amorphous solid.

40: $R_f = 0.20$ (hexanes:EtOAc, 3:2); IR (film) ν_{max} 3406, 2926, 1781, 1682, 1378, 1332, 1305, 1167, 1095, 1053 cm^{-1} ; ^1H NMR (600 MHz, MeOD) δ 4.90 (d, $J=3.9$ Hz, 1 H), 4.05 (dq, $J=9.1$, 6.3 Hz, 1 H), 3.73 (ddd, $J=11.7$, 9.4, 6.4 Hz, 1 H), 3.30–3.26 (m, 1 H), 3.21 (dd, $J=9.1$, 1.6 Hz, 1 H), 3.10 (dd, $J=9.0$, 3.9 Hz, 1 H), 2.71–2.61 (m, 1 H), 2.46–2.39 (m, 1 H), 1.29 (d, $J=6.3$ Hz, 3 H) ppm; ^{13}C NMR (151 MHz, MeOD) δ 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*-(2a*S*,6*S*,6a*R*,6b*S*)-6-Acetyl-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione [(\pm)-**3**]:**

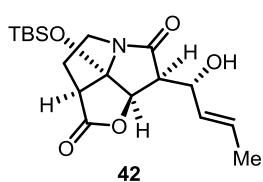
To a stirred solution of diol **40** (6.0 mg, 27 μmol , 1.0 equiv) in EtOAc (3 mL) at 70 °C was added IBX (38 mg, 130 μmol , 5.0 equiv) and the resulting mixture was stirred for 6 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with Et_2O (15 mL) and passed through 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 → 70% EtOAc in hexanes) furnishing title compound [(\pm)-**3**; 3.4 mg, 15 mmol, 57% yield] as a colorless oil.

(\pm)-**3:** $R_f = 0.20$ (hexanes:EtOAc, 1:2); IR (film) ν_{max} 3394, 2962, 2917, 1787, 1699, 1413, 1362, 1166, 1034 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.12 (s, 1 H), 4.77 (s, 1 H), 3.90–3.82 (m, 1 H),



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}C NMR (151 MHz, CDCl_3) δ 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-(2aS,6S,6aR,6bS)-6b-{{[tert-Butyl(dimethyl)silyl]oxy}-6-[(1R,2E)-1-hydroxybut-2-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (42): To a stirred solution of crotonaldehyde (**41**; 87 μL , 1.1 mmol, 3.0 equiv) and iodide (\pm)-**21** (150 mg, 350 μmol , 1.0 equiv)

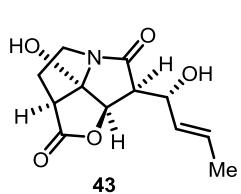


in toluene (8 mL) at -78°C was added BET_3 (1.0 M in hexanes, 0.39 mL, 0.39 mmol, 1.1 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H_2O (1 mL). The reaction mixture was extracted with Et_2O (3×10 mL) and the combined

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 [**42**; 94 mg, 260 μmol , \sim 10:1 (*E*)/(*Z*) mixture, 72% yield] as a colorless oil.

42: R_f =0.50 (hexanes: EtOAc , 2:1); $[\alpha]_D^{25}=+21$ ($c=1.0$ in C_6H_6); IR (film) ν_{max} 3480, 2955, 2931, 2858, 1790, 1701, 1472, 1374, 1303, 1252, 1142, 1087, 1062, 893, 838, 780 cm^{-1} ; ^1H NMR [600 MHz, CDCl_3 , data for (*E*)-isomer] δ 5.92 (dqd, $J=15.4, 6.6, 1.0$ 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}C NMR [151 MHz, CDCl_3 , data for (*E*)-isomer] δ 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-(2aS,6S,6aR,6bS)-6b-Hydroxy-6-[(1R,2E)-1-hydroxybut-2-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (43): To a stirred solution of TBS ether **42** (50 mg,

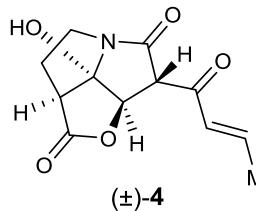


0.14 mmol, 1.0 equiv) in THF (2 mL) at 0°C was added TBAF (1.0 M in THF, 0.14 mL, 0.14 mmol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of sat. aq. NH_4Cl solution (2 mL) and H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×5 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 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: $R_f=0.20$ (hexanes:EtOAc, 2:3); IR (film) ν_{max} 3316, 2960, 2918, 2856, 1787, 1685, 1383, 1331, 1304, 1162, 1082, 1060, 1008, 969, 731 cm^{-1} ; ^1H NMR [600 MHz, CDCl_3 , data for (*E*)-isomer] δ 5.93 (dqd, $J=14.0, 6.6, 0.9$ 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; ^{13}C NMR [151 MHz, CDCl_3 , 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 $\text{C}_{12}\text{H}_{15}\text{NO}_5\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 276.0842, found: 276.0843.

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

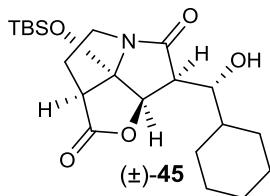


EtOAc (3 mL) at 70 °C was added IBX (40 mg, 140 μmol , 6.0 equiv) and the resulting mixture was stirred for 6 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with Et_2O (15 mL) and passed through a plug of Celite. The solvent was removed under reduced pressure 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 [(\pm)-4; 3.2 mg, 13 μmol , 54% yield] as a colorless oil.

(\pm)-**4:** $R_f=0.30$ (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3422, 2921, 1793, 1721, 1676, 1615, 1424, 1303, 1144, 1114, 1033, 903, 693 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) 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; ^{13}C NMR (151 MHz, CDCl_3) 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 $\text{C}_{12}\text{H}_{13}\text{NO}_5\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 274.0686, found: 274.0687.

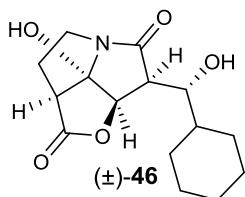
rel-(2aS,6S,6aR,6bS)-6b-{[tert-Butyl(dimethyl)silyl]oxy}-6-[(S)-cyclohexyl(hydroxy)methyl]-hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione [(±)-45]: To a stirred solution of



cyclohexane carboxaldehyde (**44**; 54 µL, 450 µmol, 5.0 equiv) and iodide (\pm)-**21** (40 mg, 95 µmol, 1.0 equiv) in toluene (4 mL) at -78°C was added BET_3 (1.0 M in hexanes, 95 µL, 95 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_2O (1 mL). The reaction mixture was extracted with Et_2O (3×10 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 [\pm]-**45**; 38 mg, 95 µmol, quantitative yield] as a colorless oil.

(±)-45: $R_f = 0.50$ (hexanes: EtOAc , 1:4); IR (film) ν_{max} 3502, 2928, 2856, 1792, 1701, 1374, 1306, 1140, 1110, 893 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 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}C NMR (151 MHz, CDCl_3) δ 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-(2aS,6S,6aR,6bS)-6-[(R)-Cyclohexyl(hydroxy)methyl]-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione [(±)-46]: To a stirred solution of TBS ether (\pm)-**45** (40 mg,

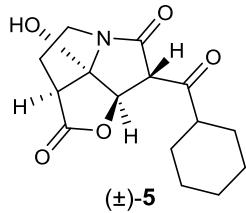


98 µmol, 1.0 equiv) in THF (2 mL) at 0°C was added TASF (40 mg, 150 µmol, 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×15 mL) and the combined organic layers were 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 [(\pm)-**46**; 19 mg, 64 μ mol, 66% yield] as a colorless oil.

(\pm)-**46**: R_f = 0.20 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3385, 2926, 2854, 1788, 1692, 1391, 1332, 1105, 1056 cm^{-1} ; ^1H NMR (600 MHz, acetone- d_6) δ 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}C NMR (151 MHz, acetone- d_6) δ 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 $\text{C}_{15}\text{H}_{21}\text{NO}_5\text{Na}^+$ [M+Na] $^+$ 318.1312 found 318.1300.

rel-(2aS,6S,6aR,6bS)-6-(Cyclohexylcarbonyl)-6b-hydroxyhexahydro-1-oxa-4a-azacyclo-penta[cd]pentalene-2,5-dione [(\pm) -**5**]: To a stirred solution of diol (\pm)-**46** (8.0 mg, 27 μ mol,

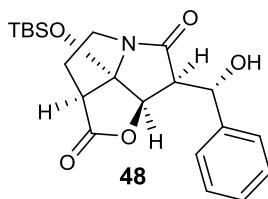


1.0 equiv) in degassed CH_2Cl_2 (1 ml) at 0 °C was added an ice cooled solution of DMP (0.1 M solution in CH_2Cl_2 , 0.41 mL, 41 μ mol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with Et_2O (5 mL) and passed through a plug of Celite. The 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 [(\pm) -**5**; 5.0 mg, 17 μ mol, 63% yield] as a colorless oil.

(\pm)-**5**: R_f = 0.40 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3442, 2931, 2856, 1790, 1687, 1334, 1310, 1162, 1114, 1025 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 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}C NMR (151 MHz, CDCl_3) δ 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 $\text{C}_{15}\text{H}_{19}\text{NO}_5\text{Na}^+$ [M+Na] $^+$ 316.1155 found 316.1162.

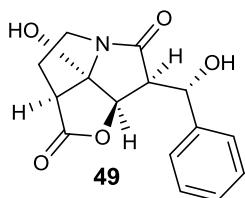
rel-(2aS,6S,6aR,6bS)-6b-{{[tert-Butyl(dimethyl)silyl]oxy}-6-[*(R*)-hydroxy(phenyl)methyl]-hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (**48**): To a stirred solution of benzaldehyde (**47**; 22 μ L, 210 μ mol, 3.0 equiv) and iodide (\pm)-**21** (30 mg, 71 μ mol, 1.0 equiv) in toluene (4 mL) at -78 °C was added BET_3 (0.12 mL, 1.0 M in hexanes, 0.12 mmol, 1.1 equiv). The



resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H₂O (1 mL). The reaction mixture was extracted with Et₂O (3 × 10 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO₂, 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_f = 0.30 (hexanes:EtOAc, 4:1); IR (film) ν_{max} 3476, 2954, 2901, 2930, 2858, 1790, 1699, 1376, 1301, 1141, 1066, 897, 770 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (151 MHz, CDCl₃) 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 C₂₁H₂₉NO₅SiNa⁺ [M+Na]⁺ 426.1707 found 426.1698.

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

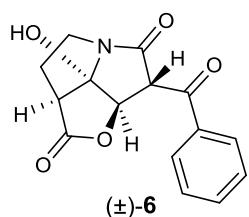


1.0 equiv) in THF (2 mL) at 0 °C was added TASF (40 mg, 150 μmol, 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of H₂O (2 mL). The reaction mixture was extracted with EtOAc (3 × 15 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO₂, 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_f = 0.11 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3388, 2965, 2904, 1788, 1694, 1394, 1332, 1304, 1162, 1064 cm⁻¹; ¹H NMR (600 MHz, acetone-*d*₆) 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; ¹³C

NMR (151 MHz, acetone-*d*₆) δ 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 C₁₅H₁₅NO₅Na⁺ [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 μmol, 1.0 equiv) in degassed CH₂Cl₂

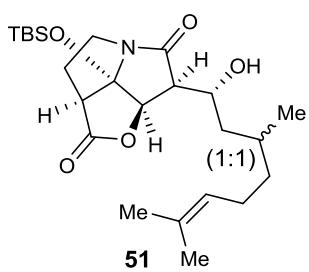


(1 ml) at 0 °C was added an ice cooled solution of DMP (0.1 M solution in CH₂Cl₂, 0.25 mL, 0.025 mmol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with Et₂O (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc

in hexanes→50% EtOAc in hexanes) furnishing pure title compound [(±)-6; 3.1 mg, 10 μmol, 61% yield] as a colorless oil.

(±)-6: R_f = 0.30 (hexanes:EtOAc, 2:3); IR (film) ν_{max} 3455, 2631, 1789, 1715, 1663, 1290, 1020 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 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; ¹³C NMR (151 MHz, CDCl₃) δ 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 C₁₅H₁₃NO₅Na⁺ [M+Na]⁺ 310.0686 found 310.0691.

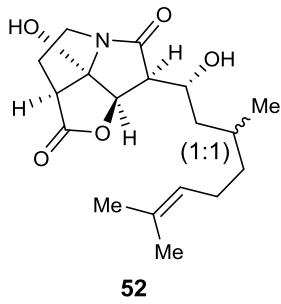
***rel*-(2a*S*,6*S*,6a*R*,6b*S*)-6b-{[tert-Butyl(dimethyl)silyl]oxy}-6-[(1*R*)-1-hydroxy-3,7-dimethyl-oct-6-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (51):** To a stirred



solution of (±)-citronellal (±)-**50** (33 mg, 210 μmol, 3.0 equiv) and iodide (±)-**21** (30 mg, 71 μmol, 1.0 equiv) in toluene (4 mL) at -78 °C was added BEt₃ (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 H₂O (1 mL). The reaction mixture was extracted with Et₂O (3 × 10 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO₂, gradient from 100% hexanes→20% EtOAc in hexanes) providing pure title compound (**51**; 26 mg, 58 μmol, 81% yield, ca. 1:1 *dr*) as a colorless oil.

51: $R_f = 0.50$ (hexanes:EtOAc, 1:4); IR (film) ν_{max} 3503, 2956, 2930, 2859, 1793, 1702, 1376, 1304, 1141, 839 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , ca. 1:1 *dr*, *Indicates inclusion of signals of both diastereomers) δ 5.13–5.08* (m, 2 H), 4.73* (d, $J=4.0$ Hz, 2 H), 4.19* (d, $J=8.3$ Hz, 2 H), 4.13–4.06* (m, 2 H), 3.85–3.76* (m, 2 H), 3.33–3.26* (m, 2 H), 3.07* (dt, $J=8.1, 2.3$ Hz, 2 H), 2.95–2.90* (m, 2 H), 2.64–2.53* (m, 4 H), 2.08–1.81* (m, 6 H), 1.67* (s, 6 H), 1.60* (s, 6 H), 1.57–1.53 (m, 1 H), 1.50 (tdd, $J=11.4, 7.8, 4.7$ Hz, 1 H), 1.44* (t, $J=6.6$ Hz, 2 H), 1.35–1.18* (m, 3 H), 1.13–1.05 (m, 1 H), 0.97 (d, $J=6.7$ Hz, 3 H), 0.93 (d, $J=6.6$ Hz, 3 H), 0.89 (s, 9 H), 0.89 (s, 9 H), 0.15 (s, 3 H), 0.15 (s, 3 H), 0.14 (s, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3 , ca. 1:1 *dr*) δ 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-(2aS,6S,6aR,6bS)-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**

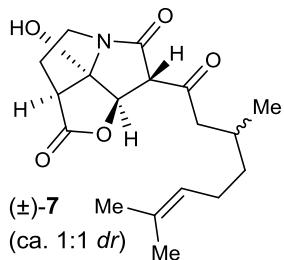


(16 mg, 35 μmol , 1.0 equiv) in THF (2 mL) at 0 $^\circ\text{C}$ was added TASF (14 mg, 53 μmol , 1.5 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×15 mL) and the combined 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 (**52**; 8.0 mg, 24 μmol , 68% yield, ca. 1:1 *dr*) as a colorless oil.

52: $R_f = 0.20$ (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3363, 2960, 2923, 2854, 1789, 1689, 1379, 1332, 1305, 1072, 1059 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , ca. 1:1 *dr*, *Indicates inclusion of signals of both diastereomers) δ 5.10* (d, $J=6.5$ Hz, 2 H), 4.84* (s, 2 H), 4.30* (d, $J=20.7$ Hz, 2 H), 4.11* (t, $J=9.5$ Hz, 2 H), 4.07* (br s, 2 H), 3.81* (br s, 2 H), 3.35* (br s, 2 H), 3.18* (d, $J=9.0$ Hz, 2 H), 3.04* (t, $J=9.7$ Hz, 2 H), 2.69* (dt, $J=15.5, 8.8$ Hz, 2 H), 2.56* (t, $J=9.0$ Hz, 2 H), 2.07–1.94* (m, 3 H), 1.91 (dd, $J=15.0, 8.0$ Hz, 1 H), 1.86–1.81* (m, 2 H), 1.68* (s, 6 H), 1.57* (s, 6 H), 1.58–1.50 (m, 1 H), 1.52–1.34* (m, 2 H), 1.34–1.16* (m, 4 H), 1.13–1.03 (m, 1 H), 0.96 (d, $J=6.7$ Hz, 3 H), 0.92 (d, $J=6.5$ Hz, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3 , ca. 1:1 *dr*) δ 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 $C_{18}H_{27}NO_5Na^+$ [M+Na]⁺ 360.1781 found 360.1789.

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

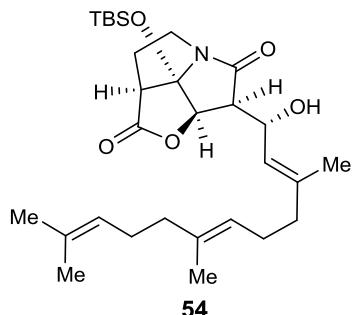


1.0 equiv) in degassed CH₂Cl₂ (1 ml) at 0 °C was added an ice cooled solution of DMP (0.1 M solution in CH₂Cl₂, 0.18 mL, 18 µmol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with Et₂O (5 mL) and passed through a plug of Celite.

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_f = 0.40 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3420, 2962, 2924, 2854, 1794, 1696, 1455, 1377, 1163, 1024 cm⁻¹; ¹H NMR (600 MHz, CDCl₃, ca. 1:1 *dr*, *Indicates inclusion of signals of both diastereomers) δ 5.07* (m, 2 H), 4.82 (s, 1 H), 4.81 (s, 1 H), 4.59* (br s, 2 H), 4.04 (s, 1 H), 4.03 (s, 1 H), 3.83* (ddd, J=12.0, 9.5, 5.5 Hz, 2 H), 3.34* (ddd, J=12.1, 9.9, 5.3 Hz, 2 H), 3.27* (dd, J=9.4, 1.9 Hz, 2 H), 2.87 (dd, J=17.7, 6.1 Hz, 1 H), 2.80–2.65* (m, 4 H), 2.62–2.52* (m, 3 H), 2.09–1.90* (m, 6 H), 1.69 (s, 3 H), 1.68 (s, 3 H), 1.61 (s, 3 H), 1.59 (s, 3 H), 1.38–1.30 (m, 1 H), 1.30–1.17* (m, 3 H), 0.97 (d, J=6.7 Hz, 3 H), 0.90 (d, J=6.7 Hz, 3 H) ppm; ¹³C NMR (151 MHz, CDCl₃, 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 $C_{18}H_{25}NO_5Na^+$ [M+Na]⁺ 358.1625 found 358.1631.

rel-(2aS,6S,6aR,6bS)-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-dione (54): To a stirred solution of aldehyde **53** (220 mg, 1.0 mmol,

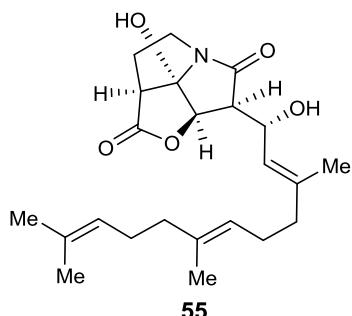


3.0 equiv) and iodide (±)-**21** (140 mg, 330 µmol, 1.0 equiv) in toluene (10 mL) at -78 °C was added BEt₃ (330 µL, 1.0 M in hexanes, 330 µmol, 1.0 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H₂O (1 mL). The reaction mixture was extracted with Et₂O

(3×10 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 → 20% EtOAc in hexanes) providing pure title compound (**54**; 140 mg, 280 mmol, 84% yield) as a colorless oil.

54: $R_f = 0.50$ (hexanes:EtOAc, 3:7); IR (film) ν_{max} 3488, 2955, 2929, 2857, 1792, 1705, 1472, 1375, 1300, 1138, 1069, 892, 837, 779 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.16 (d, $J = 8.7\text{ Hz}$, 1 H), 5.10–5.06 (m, 2 H), 4.74 (t, $J = 9.4\text{ Hz}$, 1 H), 4.56 (d, $J = 3.9\text{ Hz}$, 1 H), 4.25 (s, 1 H), 3.79 (dt, $J = 11.8$, 8.3 Hz, 1 H), 3.32–3.28 (m, 1 H), 3.03 (ddd, $J = 10.5$, 7.9, 4.5 Hz, 2 H), 2.58 (dd, $J = 12.7$, 5.9 Hz, 2 H), 2.17–2.00 (m, 6 H), 1.97–1.95 (m, 2 H), 1.75 (d, $J = 0.8\text{ Hz}$, 3 H), 1.67 (s, 3 H), 1.59 (s, 3 H), 1.59 (s, 3 H), 0.88 (s, 9 H), 0.15 (s, 3 H), 0.13 (s, 3 H); ^{13}C NMR (151 MHz, CDCl_3) 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 $\text{C}_{29}\text{H}_{47}\text{NO}_5\text{SiNa}^+$ [$\text{M}+\text{Na}]^+$: 540.3107, found: 540.3116.

rel-(2aS,6S,6aR,6bS)-6b-Hydroxy-6-[(1R,2E,6E)-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



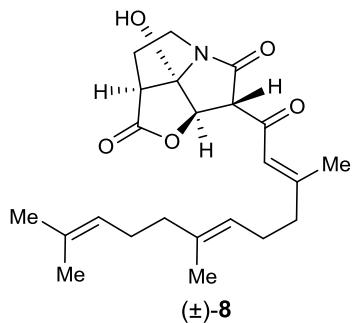
solution of TBS ether **54** (80 mg, 150 μmol , 1.0 equiv) in THF (2 mL) at 0°C was added TBAF (1.0 M in THF, 150 μL , 150 μmol , 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of sat. aq. NH_4Cl (1 mL) and H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×25 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 → 60% EtOAc in hexanes) providing pure title compound (**55**; 43 mg, 110 μmol , 72% yield) as a colorless oil.

55: $R_f = 0.10$ (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3294, 2964, 2920, 2854, 1792, 1697, 1437, 1384, 1304, 1305, 1064, 1009 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 5.14–5.05 (m, 3 H), 4.76 (t, $J = 9.5\text{ Hz}$, 1 H), 4.66 (d, $J = 3.8\text{ Hz}$, 1 H), 4.60 (br s, 1 H), 4.57 (s, 1 H), 3.80 (ddd, $J = 11.4$, 9.3, 6.8 Hz, 1 H), 3.35–3.28 (m, 1 H), 3.20 (dd, $J = 9.7$, 3.6 Hz, 1 H), 3.12 (d, $J = 8.1\text{ Hz}$, 1 H), 2.68 (ddd, $J = 19.0$, 12.6, 8.0 Hz, 1 H), 2.58–2.50 (m, 1 H), 2.15–2.09 (m, 2 H), 2.08–2.01 (m, 4 H), 1.97 (t, $J = 7.6\text{ Hz}$, 2 H),

1.76 (s, 3 H), 1.68 (s, 3 H), 1.60 (s, 6 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 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.

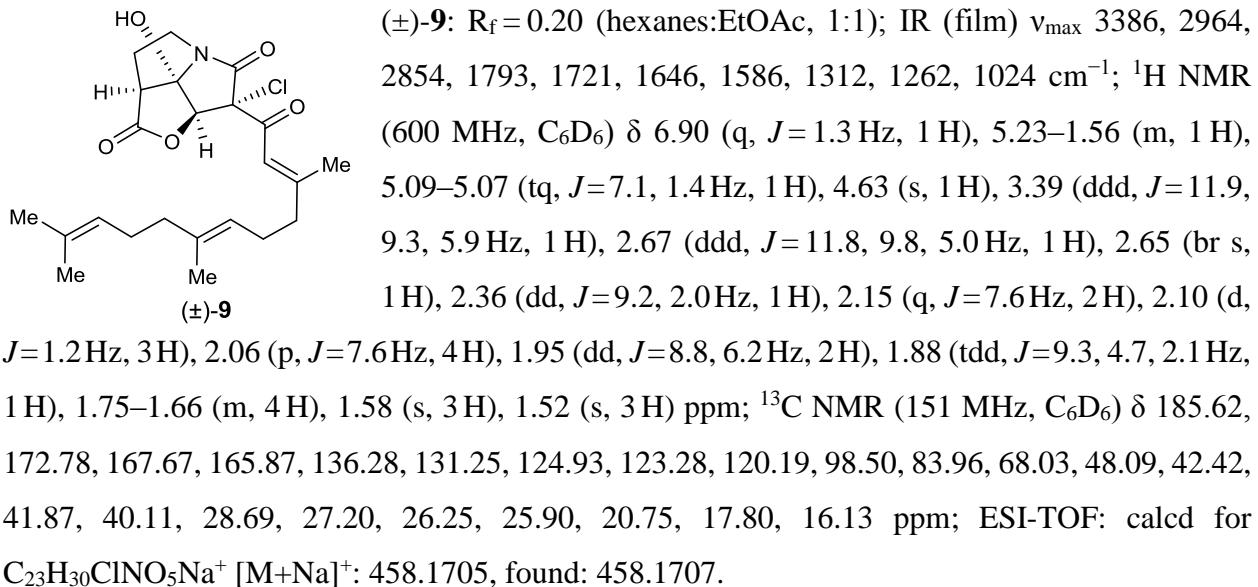
rel-(2aS,6S,6aR,6bS)-6b-Hydroxy-6-[(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienoyl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione [(\pm)-8] and rel-(2aS,6S,6aS,6bS)-6-chloro-6b-hydroxy-6-[(2E,6E)-3,7,11-trimethyldodeca-2,6,10-trienoyl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione [(\pm)-9]: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



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 , 370 μL , 37 μmol , 1.5 equiv) and the resulting mixture was stirred for 1.5 h 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 preparative TLC (SiO_2 , 50% EtOAc in hexanes) furnishing pure

1,3-dicarbonyl derivative [(\pm)-8; 2.4 mg, 6.0 μmol , 24% yield] as a colorless oil and chloro-1,3-dicarbonyl compound [(\pm)-9; 1.2 mg, 3.0 μmol , 11% yield] as a white amorphous solid.

(±)-8: R_f =0.30 (hexanes:EtOAc, 1:1); IR (film) ν_{max} 3426, 2954, 2923, 2854, 1793, 1717, 1666, 1606, 1456, 1377, 1274, 1112, 1024 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) δ 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 Hz, 1 H), 2.69 (ddd, J =11.9, 9.8, 4.9 Hz, 1 H), 2.65 (dd, J =9.3, 1.9 Hz, 1 H), 2.17 (q, J =7.4 Hz, 2 H), 2.09–2.00 (m, 3 H), 1.99–1.92 (m, 5 H), 1.88 (dtd, J =13.7, 9.6, 5.9 Hz, 1 H), 1.82 (t, J =7.6 Hz, 2 H), 1.70 (d, J =1.4 Hz, 3 H), 1.59 (d, J =1.3 Hz, 3 H), 1.52 (d, J =1.3 Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ 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.



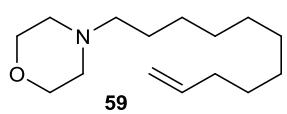
IBX-oxidation of diol (55): To a stirred solution of diol **55** (20 mg, 50 μmol , 1.0 equiv) in EtOAc (3 mL) at 70 $^\circ\text{C}$ was added IBX (69 mg, 250 μmol , 5.0 equiv) and the resulting mixture was stirred for 5 h at the same temperature. The resulting mixture was cooled to room temperature, diluted with Et_2O (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 [(\pm) -**4**; 12 mg, 29 μmol , 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 CH_2Cl_2 (100 mL) at 0 $^\circ\text{C}$ was added oxalyl chloride (4.66 mL, 54.3 mmol, 2.0 equiv) and the resulting mixture was slowly warmed to 25 $^\circ\text{C}$. After stirring for 3 h at 25 $^\circ\text{C}$ the volatiles were removed and the crude residue was dissolved in CH_2Cl_2 (100 mL) was added NEt_3 (11.3 mL, 81.3 mmol, 3.0 equiv) and morpholine (4.75 mL, 54.3 mmol, 2.0 equiv) at 0 $^\circ\text{C}$. The resulting mixture was stirred at 25 $^\circ\text{C}$ 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 (3×100 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 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.

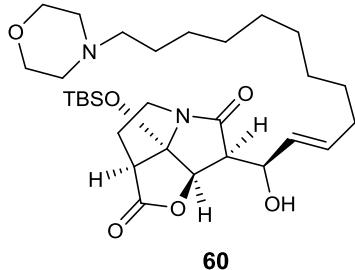
58: R_f =0.60 (hexanes:EtOAc, 3:2); IR (film) ν_{max} 3075, 2923, 2852, 1640, 1427, 1271, 1230, 1115, 909 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 5.80 (ddt, J =16.9, 10.2, 6.7 Hz, 1 H), 4.98 (dq, J =17.1, 1.9 Hz, 1 H), 4.93–4.91 (m, 1 H), 3.66–3.65 (m, 4 H), 3.61–3.60 (m, 2 H), 3.45 (t, J =4.8 Hz, 2 H), 2.32–2.26 (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; ¹³C NMR (151 MHz, CDCl₃) δ 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 C₁₅H₂₈NO₂⁺ [M+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 LiAlH₄ (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 MgSO₄ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO₂, 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) ν_{max} 3076, 2925, 2853, 2807, 1640, 1456, 1357, 1119, 910, 866 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 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; ¹³C NMR (151 MHz, CDCl₃) δ 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 C₁₅H₃₀NO⁺ [M+H]⁺: 240.2322, found: 240.2325.



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

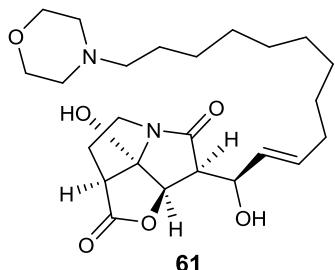


To a stirred solution of allylic alcohol **42** (100 mg, 270 μ mol, 1.0 equiv) and alkene **59** (170 mg, 810 μ mol, 6.0 equiv) in dry CH_2Cl_2 (5 mL) at 25 °C was added Grubbs 2nd generation catalyst **56** (23 mg, 27 μ mol, 0.1 equiv). The resulting reddish-brown mixture was heated to 40 °C. After 24 h of stirring the volatiles were removed and the crude mixture was purified by flash column chromatography

(SiO_2 , gradient from 20% hexanes→80% EtOAc in hexanes) providing alcohol (**60**; 73 mg, 130 μ 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) ν_{max} 3481, 2927, 2855, 1791, 1702, 1463, 1301, 116, 837, 780 cm^{-1} ; ¹H NMR (600 MHz, CDCl_3) δ 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; ¹³C NMR (151 MHz, CDCl_3) δ 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 $\text{C}_{30}\text{H}_{53}\text{N}_2\text{O}_6^+$ [M+H]⁺: 565.3667, found: 565.3675.

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

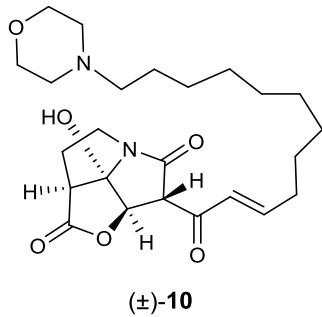


ether **60** (54 mg, 100 μ mol, 1.0 equiv) in THF 3 mL at 0 °C was added TBAF (1.0 M in THF, 100 μ L, 100 μ mol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL) and H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×5 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→100% EtOAc) providing pure title compound (**61**; 27 mg, 62 μ mol, 62% yield) as a colorless oil.

61: $R_f = 0.50$ (MeOH:CH₂Cl₂, 1:9); IR (film) ν_{max} 3384, 2924, 2855, 1786, 1688, 1637, 1387, 1114, 1056, 1033, 733 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 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; ¹³C NMR (151 MHz, CDCl₃) δ 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 C₂₄H₃₉N₂O₆⁺ [M+H]⁺: 451.2803, found: 451.2807.

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



11 μ mol, 1.0 equiv) in EtOAc (2 ml) at 25 °C was added IBX (15 mg, 55 μ 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 CH₂Cl₂ furnishing morpholine analog [(\pm)-**10**, 1.2 mg, 2.6 mmol, 24% yield, ~90% purity] as a colorless oil.

(\pm)-10: $R_f = 0.61$ (MeOH:CH₂Cl₂, 1:9); IR (film) ν_{max} 3433, 2923, 2852, 2766, 1790, 1699, 1457, 1118, 866 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 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; ¹³C NMR (151 MHz, CDCl₃) δ 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 C₂₄H₃₇N₂O₆⁺ [M+H]⁺: 435.2490, found: 435.2501.

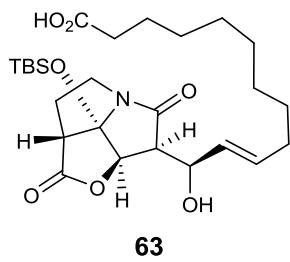
Trimethylsilyl undec-10-enoate (62): To a stirred solution of undec-10-enoic acid (5.27 g,

28.6 mmol, 1.0 equiv) in dry THF (30 mL) was added Et₃N (3.99 mL, 2.90 g, 28.6 mmol, 1.0 equiv) and the reaction mixture was cooled to 0 °C. TMSCl (3.63 mL, 3.11 g., 28.6 mmol, 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) $\nu_{\text{max}} = 2926, 2855, 1717, 1641, 1252, 1188, 909, 846, 762, 729 \text{ cm}^{-1}$; ^1H NMR (600 MHz, CDCl_3) δ 5.81 (ddt, $J=17.0, 10.2, 6.7 \text{ Hz}$, 1 H), 4.99 (dq, $J=17.0, 1.8 \text{ Hz}$, 1 H), 4.92 (ddt, $J=10.2, 2.3, 1.2 \text{ Hz}$, 1 H), 2.29 (t, $J=7.5 \text{ Hz}$, 2 H), 2.03 (tdd, $J=8.0, 6.1, 1.4 \text{ Hz}$, 2 H), 1.58 (p, $J=6.9 \text{ Hz}$, 2 H), 1.37 (p, $J=6.9 \text{ Hz}$, 2 H), 1.34–1.21 (m, 8 H), 0.28 (s, 9 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 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 $\text{C}_{14}\text{H}_{29}\text{O}_2\text{Si}^+$ [M] $^+$: 257.1937, found: 257.1930.

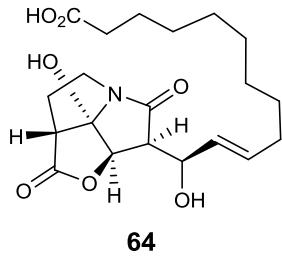
(10*E*,12*R*)-12-[*(2aR,6S,6aR,6bS)-6b*-{[tert-Butyl(dimethyl)silyl]oxy}-2,5-dioxooctahydro-1-oxa-4a-azacyclopenta[cd]pentalen-6-yl]-12-hydroxydodec-10-enoic acid (63**):**



To a stirred solution of (\pm)-**42** (300 mg, 709 μmol , 1.0 equiv) in dry CH_2Cl_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 (SiO_2 , hexanes:EtOAc, 8:2→1:1) gave product **63** (229 mg, 449 μmol , 63% yield) as a colorless liquid.

63: $R_f = 0.55$ (hexanes:EtOAc, 1:1); IR (film) $\nu_{\text{max}} = 3475, 2929, 2856, 1793, 1706, 1463, 1378, 1303, 1253, 1142, 1094, 839, 781 \text{ cm}^{-1}$; ^1H NMR (600 MHz, CDCl_3) δ 5.89 (dtd, $J=14.9, 6.8, 0.9 \text{ Hz}$, 1 H), 5.46 (ddt, $J=15.4, 7.3, 1.5 \text{ Hz}$, 1 H), 4.64 (d, $J=3.9 \text{ Hz}$, 1 H), 4.51–4.39 (m, 1 H), 3.81 (dt, $J=12.1, 8.0 \text{ Hz}$, 1 H), 3.37–3.23 (m, 1 H), 3.10–3.05 (m, 1 H), 3.02 (dd, $J=9.8, 3.9 \text{ Hz}$, 1 H), 2.65–2.54 (m, 2 H), 2.34 (t, $J=7.4 \text{ Hz}$, 2 H), 2.11–2.03 (m, 2 H), 1.62 (p, $J=7.4 \text{ Hz}$, 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}C NMR (151 MHz, CDCl_3) δ 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 $\text{C}_{26}\text{H}_{43}\text{NO}_7\text{SiNa}^+$ [M+Na] $^+$: 532.2701, found: 532.2704.

(10*E*,12*R*)-12-Hydroxy-12-[(2a*R*,6*S*,6a*R*,6b*S*)-6b-hydroxy-2,5-dioxooctahydro-1-oxa-4a-azacyclopenta[cd]pentalen-6-yl]dodec-10-enoic acid (64): To a stirred solution of **63** (220 mg,



0.432 mmol, 1.0 equiv) in THF (11 mL) at 0 °C was added AcOH (50 µL, 0.864 mmol, 2.0 equiv) followed by TBAF (1 M in THF, 430 µL, 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. NH4Cl (10 mL), and extracted with Et2O (3 × 50 mL). The combined organic extracts were dried over anh. MgSO4, filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (SiO2, hexanes:EtOAc, 1:1→0:1→EtOAc with 1% HCOOH) to yield product **64** (140 mg, 354 µmol, 82% yield) as a colorless oil.

64: R_f=0.35 (EtOAc); IR (film) ν_{max}=3375, 2924, 2852, 1792, 1702, 1388, 1333, 1305, 1163, 1092, 1060, 1010 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 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; ¹³C NMR (151 MHz, CDCl₃) δ 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 C₂₀H₂₉NO₇Na⁺ [M+Na]⁺: 418.1836, found: 418.1836.

(3a*R*,5a*R*,6*S*,7*R*,8*E*,19a*S*)-7-Hydroxy-3,3a,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*,5a*H*)-trione (65): To a

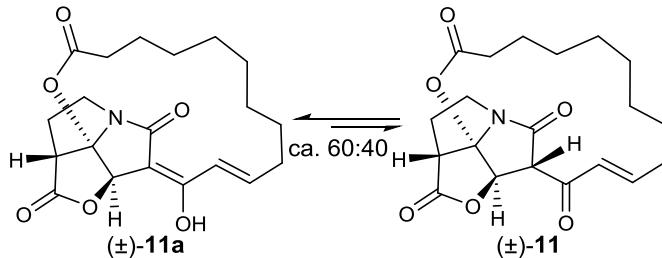
stirred solution of 2-methyl-6-nitrobenzoic anhydride (31 mg, 88 µmol, 1.4 equiv) and 4-dimethylaminopyridine (23 mg, 190 µmol, 3.0 equiv) in CH₂Cl₂ (40 mL) at 25 °C was added dropwise a solution of **64** (25 mg, 63 µmol, 1.0 equiv) in CH₂Cl₂ (20 mL) over 10 h and the reaction mixture was stirred for further 1 h. Then, it was washed sequentially with satd. aq. NaHCO₃ (20 mL), aq. HCl (0.2 M; 20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Flash column chromatography of the residue (SiO₂, hexanes:EtOAc, 7:3→1:1) gave product **65** (20 mg, 53 µmol, 84% yield) as colorless liquid.

65: $R_f = 0.63$ (EtOAc); IR (film) $\nu_{\text{max}} = 3493, 2927, 2854, 1795, 1713, 1459, 1376, 1339, 1220, 1157, 1103, 1057, 1027, 731 \text{ cm}^{-1}$; ^1H NMR (600 MHz, CDCl_3) δ 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 (td, $J = 13.6, 10.7, 3.1 \text{ Hz}$, 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}C NMR (151 MHz, CDCl_3) δ 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-methanooxa-cyclohexadecino[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-methanooxa-cyclohexadecino[3',2':2,3]furo[3,4-b]pyrrole-4,18,20(2H,5aH)-trione [(±)-11a]:**

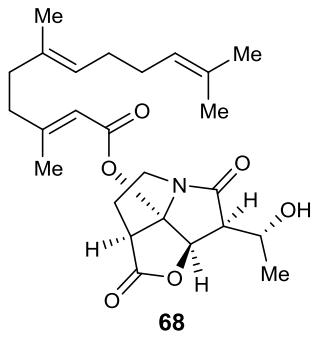
To a stirred solution of diol **65** (5.0 mg, 13 μmol , 1.0 equiv) in EtOAc (1 ml) at 25 °C was added IBX (19 mg, 67 μmol , 5.0 equiv) and the resulting mixture was heated at 70 °C for 7 h. The reaction mixture was filtered through Celite and washed with EtOAc. The solvent was removed under reduced pressure and the obtained residue was purified by preparative TLC using 2% MeOH in CH_2Cl_2 furnishing morpholine analog [(±)-**11** and (±)-**11a**; 2.4 mg, 6.4 mmol, 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) ν_{max} 2928, 2855, 1791, 1732, 1684, 1619, 1389, 1336, 1128, 1038, 800 cm^{-1} ; ^1H NMR [600 MHz, C_6D_6 , ~60:40 mixture of enol and 1,3-diketone, *Indicates signals corresponding to the enol compound (±)-**11a**] δ 11.44* (br s, 0.6 H), 6.97 (ddd, $J = 15.2, 10.3, 4.7 \text{ Hz}$, 0.4 H), 6.63* (dd, $J = 15.3, 1.8 \text{ Hz}$, 0.4 H), 6.44* (ddd, $J = 15.3, 10.1, 5.9 \text{ Hz}$, 0.6 H), 5.77* (d, $J = 15.7 \text{ Hz}$, 0.6 H), 5.49* (s, 0.6 H), 5.24 (s, 0.4 H), 3.61 (ddd, $J = 11.3, 9.6, 4.8 \text{ Hz}$, 0.4 H), 3.56* (dd, $J = 9.9, 4.2 \text{ Hz}$, 0.6 H), 3.47–3.40* (m, 0.6 H), 3.39 (s, 0.4 H), 3.02–2.95* (m, 0.4 H), 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}C NMR (151 MHz, C_6D_6 , ~60:40 mixture of enol and 1,3-diketone) δ 187.92,



solution of diol **65** (5.0 mg, 13 μmol , 1.0 equiv) in EtOAc (1 ml) at 25 °C was added IBX (19 mg, 67 μmol , 5.0 equiv) and the resulting mixture was heated at 70 °C for 7 h. The reaction mixture was filtered

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 $C_{20}H_{25}NO_6Na^+$ [M+Na]⁺: 398.1574, found: 398.1576.

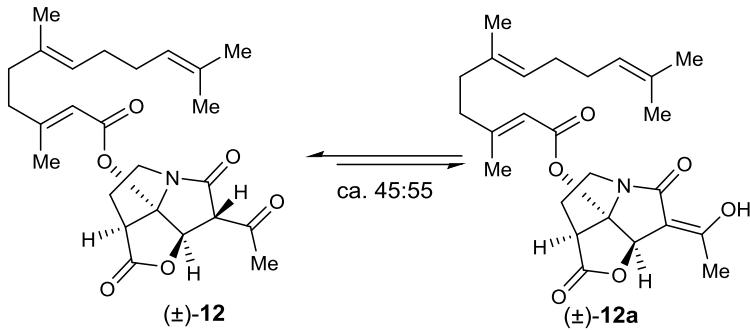


(2a*S*,6*S*,6a*R*,6b*S*)-6-[(1*R*)-1-Hydroxyethyl]-2,5-dioxohexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalen-6b(5*H*)-yl (2*E*,6*E*)-3,6,11-trimethyldodeca-2,6,10-trienoate (68):

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 CH₂Cl₂ (2 mL) at 0 °C was added Et₃N (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. NaHCO₃ solution (5 mL), sat. aq. NH₄Cl (0.5 M; 3 mL), and brine (5 mL). The organic layer was dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The resultant crude product was purified by flash column chromatography (SiO₂; hexanes:EtOAc: 3:1) yielded pure title compound (**68**; 17.4 mg, 39.1 µmol, 39% yield) as a colorless oil.

68: R_f=0.60 (hexanes:EtOAc, 2:1); IR (film) ν_{max} 3502, 2971, 2915, 2856, 1791, 1705, 1638, 1476, 1051 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) 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; ¹³C NMR (151 MHz, CDCl₃) 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 $C_{25}H_{35}NO_6Na^+$ [M+Na]⁺: 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 (*2E,6E*)-3,6,11-trimethyldodeca-2,6,10-trienoate [(\pm)-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 (*2E,6E*)-3,6,11-trimethyldodeca-2,6,10-trienoate [(\pm)-12a]: To a stirred solution of diol **68**



(3 mg, 8 μ mol, 1.0 equiv) in EtOAc (1 ml) at 25 $^{\circ}$ C was added IBX (10 mg, 40 μ mol, 5.0 equiv) and the resulting mixture was heated at 70 $^{\circ}$ 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 CH₂Cl₂ furnishing analog (\pm)-12 and (\pm)-12a (1.4 mg, 3.7 μ mol, 47% yield, ~90% purity, ~55:45 mixture of enol and 1,3-diketone, ~90% purity) as a colorless oil.

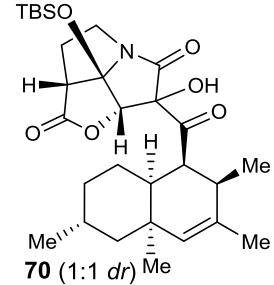
(\pm)-12 and (\pm)-12a: R_f=0.40 (hexanes:EtOAc, 1:2); IR (film) ν_{max} 2966, 2921, 2856, 1790, 1716, 1682, 1643, 1361, 1125, 1054 cm⁻¹; ¹H NMR [600 MHz, CDCl₃, ~55:45 mixture of enol and 1,3-diketone, *Indicates inclusion of signals corresponding to the (\pm)-12 and (\pm)-12a] δ 11.66 (s, 1 H), 5.67* (s, 2 H), 5.56 (s, 1 H), 5.53 (s, 1 H), 5.09–5.06* (m, 4 H), 4.03–3.97* (m, 2 H), 3.75 (s, 1 H), 3.69–3.60* (m, 2 H), 3.50 (dt, *J*=11.6, 8.3 Hz, 1 H), 3.40 (ddd, *J*=11.8, 9.2, 6.6 Hz, 1 H), 2.82–2.70* (m, 2 H), 2.52–2.34* (m, 6 H), 2.26–2.14* (m, 16 H), 2.14–1.92* (m, 8 H), 1.68* (s, 6 H), 1.61* (s, 6 H), 1.60* (s, 6 H) ppm; ¹³C NMR (151 MHz, CDCl₃, ~55:45 mixture of enol and 1,3-diketone) δ ¹³C NMR (151 MHz, CDCl₃) δ 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 C₂₅H₃₃NO₆Na⁺ [M+Na]⁺: 466.2200, found: 466.2212.

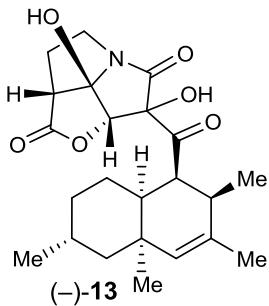
(2a*R*,6a*S*,6b*R*)-6b-{{[tert-Butyl(dimethyl)silyl]oxy}-6-hydroxy-6-{{[(1*S*,2*R*,4*aS*,6*R*,8*aS*)-2,3,4*a*,6-tetramethyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl]carbonyl}hexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalene-2,5-dione (70):

To a stirred solution of TBS ether **69** (16 mg, 31 μ mol, 1.0 equiv) in CH_2Cl_2 (1.6 mL) at 0 $^{\circ}$ C was added DMP (40 mg, 93 μ mol, 3.0 equiv) and the resulting mixture was stirred for 45 min at 25 $^{\circ}$ C 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 hydroxy TBS ether **70** (10 mg, 19 μ mol, 61%, ca. 1:1 *dr*) as a colorless oil.

70: R_f = 0.27 (hexanes:EtOAc, 1:4); IR (film) ν_{max} 3378, 2951, 2927, 2859, 1795, 1722, 1462, 1376, 1331, 1253, 1134, 840 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6 , ca. 1:1 *dr*, *Indicates signals for the other diastereomer) δ 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}C NMR (151 MHz, C_6D_6 , ca. 1:1 *dr*) δ 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 $\text{C}_{29}\text{H}_{45}\text{NO}_6\text{SiNa}^+$ [M+Na]⁺ 554.2908 found 554.2920.

(2a*R*,6a*S*,6b*R*)-6,6b-Dihydroxy-6-{{[(1*S*,2*R*,4*aS*,6*R*,8*aS*)-2,3,4*a*,6-tetramethyl-1,2,4*a*,5,6,7,8,8*a*-octahydronaphthalen-1-yl]carbonyl}hexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentalene-2,5-dione [−]-13]: To a stirred solution of hydroxy TBS ether **70** (4.0 mg, 7.8 μ mol, 1.0 equiv) in THF (0.5 mL) at 25 $^{\circ}$ C was added a drop of DMF and TASF (21 mg, 78 μ mol, 10 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was quenched by the addition of H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×5 mL) and the

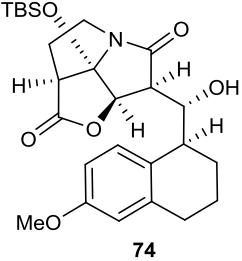




combined organic layers were dried over MgSO_4 and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO_2 , gradient from 10% EtOAc in hexanes \rightarrow 50% EtOAc in hexanes) providing pure hydroxy-1,3-carbonyl derivative [(-)-13; 1.0 mg, 2.6 μmol , 33% yield] as a colorless oil.

(-)-13: $R_f = 0.14$ (hexanes:EtOAc, 1:1); $[\alpha]_D^{25} = -0.1$ ($c = 0.1$, C_6D_6); IR (film) ν_{max} 3381, 2924, 1800, 1721, 1377, 1033 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) δ 5.03 (s, 1 H), 4.81 (br s, 1 H), 3.95 (dd, $J = 7.1, 2.0$ Hz, 1 H), 3.62 (s, 1 H), 3.29–3.21 (m, 1 H), 3.12–3.04 (m 1 H), 2.65–2.57 (m, 1 H), 2.38–2.29 (m, 2 H), 1.89–1.65 (m, 5 H), 1.64 (s, 3 H), 1.49–1.43 (m, 2 H), 1.37 (s, 3 H), 1.33 (d, $J = 7.5$ Hz, 3 H), 1.05–0.85 (m, 3 H), 0.82 (d, $J = 6.5$ Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ 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**

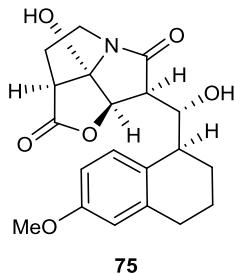


(84 mg, 200 μmol , 1.0 equiv) in dry toluene 3 mL at -78°C was added BET_3 (1.0 M in hexanes, 0.26 mL, 0.26 mmol, 1.3 equiv) dropwise and the resulting reaction mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H_2O (2 mL) at cold. The reaction mixture was brought to 25°C and extracted with Et_2O (3×10 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 (**74**; 64 mg, 130 μmol , 66% yield) as a colorless oil.

74: $R_f = 0.30$ (hexanes:EtOAc, 1:4); $[\alpha]_D^{25} = +24$ ($c = 1.0$ in C_6H_6); IR (film) ν_{max} 3481, 3065, 2931, 2859, 1787, 1699, 1584, 1468, 1376, 1332, 1252, 1140, 1095, 890, 837, 779, 731 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.11 (t, $J = 7.9$ Hz, 1 H), 6.73 (dd, $J = 7.6, 1.1$ Hz, 1 H), 6.68 (dd, $J = 8.2, 1.0$ Hz, 1 H), 4.55 (dd, $J = 9.8, 3.5$ Hz, 1 H), 4.51 (d, $J = 3.9$ Hz, 1 H), 4.16 (s, 1 H), 3.83–3.79 (m, 4 H), 3.39 (dt, $J = 7.6, 3.9$ Hz, 1 H), 3.34–3.27 (m, 2 H), 3.04 (dd, $J = 7.4, 3.4$ Hz, 1 H), 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, 9 H), 0.18 (s, 3 H), 0.15 (s, 3 H) ppm; ^{13}C NMR (151 MHz, CDCl_3) δ 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 μmol , 1.0 equiv) in THF (2 mL) at 0 °C was added TBAF (1.0 M in THF, 120 μL , 120 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 saturated aqueous NH_4Cl solution (2 mL) and H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×5 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 → 50% EtOAc in hexanes) providing pure title compound (**75**; 31 mg, 83 μmol , 67% yield) as a colorless oil.

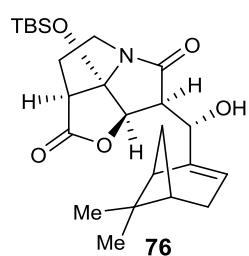
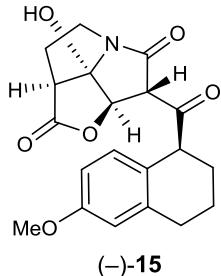
75: $R_f=0.30$ (hexanes:EtOAc, 3:2); $[\alpha]_D^{25}=+3$ ($c=0.7$ in EtOH); IR (film) ν_{max} 3304, 1938, 2868, 2836, 1784, 1684, 1583, 1460, 1393, 1331, 1256, 1086, 910, 793, 729 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.11 (t, $J=7.9$ Hz, 1 H), 6.72 (dd, $J=7.6$, 1.1 Hz, 1 H), 6.69 (dd, $J=8.2$, 1.1 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 (dd, $J=13.9$, 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}C NMR (151 MHz, CDCl_3) δ 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 μ mol, 1.0 equiv) in degassed CH₂Cl₂ (1 mL) at 0 °C was added an ice cooled solution of DMP (22 mg, 53 μ mol, 1.5 equiv) and the resulting mixture was stirred for 1.5 h at the same temperature before it was diluted with Et₂O (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 μ mol, 55% yield] as a colorless oil.

(-)-15: R_f=0.30 (hexanes:EtOAc, 1:1); [α]_D²⁵=−28 (*c*=0.1 in C₆H₆); IR (film) ν_{max} 3452, 2938, 1790, 1698, 1587, 1468, 1259, 1161, 1094, 1027, 772 cm^{−1}; ¹H NMR (600 MHz, C₆D₆) δ 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; ¹³C NMR (151 MHz, C₆D₆) δ 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 C₂₀H₂₁NO₆Na⁺ [M+Na]⁺: 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):

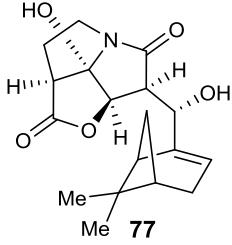
To a stirred solution of aldehyde **72** (90 mg, 600 μ mol, 3.0 equiv) and iodide (+)-**21** (84 mg, 200 μ mol, 1.0 equiv) in dry toluene (3 mL) at −78 °C was added BEt₃ (1.0 M in hexanes, 260 μ L, 260 μ mol, 1.3 equiv) dropwise and the resulting reaction mixture was stirred for 6 h at the same temperature before it was quenched by the addition of H₂O (~2 mL) at cold. The reaction mixture was extracted with Et₂O (3 × 10 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO₂, gradient from 100% hexanes→20% EtOAc in hexanes) providing pure title compound (**76**; 69 mg, 160 μ 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) ν_{max} 3477, 2983, 2951, 2833, 1791, 1701, 1464, 1365, 1300, 1252, 1141, 1070, 865, 837, 780, 733, 674 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

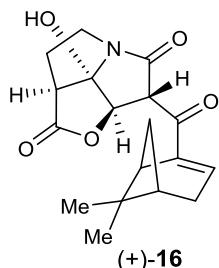
(2a*S*,6*S*,6a*R*,6b*S*)-6-[(*S*)-(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)(hydroxy)methyl]-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[cd]pentale-2,5-dione (77): To a stirred solution of TBS ether **76** (50 mg, 110 μ mol, 10 equiv) in THF (3 mL) at 0 $^\circ$ C was added TBAF (1.0 M in THF, 110 μ L, 110 μ 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 (3×5 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 μ 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) ν_{max} 3331, 2983, 2934, 2917, 2832, 1788, 1690, 1476, 1383, 1305, 1160, 1064, 1010, 911, 732 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

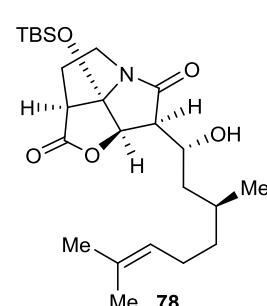
(2a*S*,6*S*,6a*R*,6b*S*)-6-[(6,6-Dimethylbicyclo[3.1.1]hept-2-en-2-yl)carbonyl]-6b-hydroxyhexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione [(+)-16]: To a stirred solution of diol **77**



(10 mg, 30 μ mol, 1.0 equiv) in degassed CH₂Cl₂ (1 mL) at 0 °C was added an ice cooled solution of DMP (19 mg, 45 μ mol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with Et₂O (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 [(+)-**16**; 6.0 mg, 18 μ mol, 60% yield] as a colorless oil.

(+)-**16**: $R_f = 0.50$ (hexanes:EtOAc, 3:2); $[\alpha]_D^{25} = +63$ ($c = 0.3$ in C₆H₆); IR (film) ν_{max} 3433, 2935, 1792, 1716, 1634, 1607, 1416, 1280, 1031, 926 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ 6.85–6.83 (m, 1 H), 5.12 (s, 1 H), 4.30 (s, 1 H), 4.18 (s, 1 H), 3.43 (ddd, $J = 12.0, 9.3, 5.8$ Hz, 1 H), 3.04 (td, $J = 5.7, 1.6$ Hz, 1 H), 2.66–2.61 (m, 2 H), 2.22 (dt, $J = 9.3, 5.7$ Hz, 1 H), 2.07–1.98 (m, 3 H), 1.85 (dtd, $J = 13.7, 9.6, 5.8$ Hz, 1 H), 1.72–1.70 (tt, $J = 6.2, 2.8$ Hz, 1 H), 1.08 (s, 3 H), 0.82 (d, $J = 9.2$ Hz, 1 H), 0.59 (s, 3 H) ppm; ¹³C NMR (151 MHz, C₆D₆) δ 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.

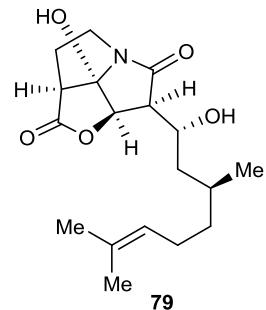
(2a*S*,6*S*,6a*R*,6b*S*)-6b-{[tert-Butyl(dimethyl)silyl]oxy}-6-[(1*R*,3*S*)-1-hydroxy-3,7-dimethyloct-6-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (78): To a stirred



solution of aldehyde **73** (76 mg, 490 μ mol, 3.0 equiv) and iodide (+)-**21** (70 mg, 160 μ mol, 1.0 equiv) in dry toluene 3 mL at -78 °C was added BEt₃ (1.0 M in hexanes, 210 μ L, 210 μ 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 H₂O (2 mL) at cold. The reaction mixture was brought to 25 °C and extracted with Et₂O (3 × 10 mL) and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO₂, gradient from 100% hexanes→10% EtOAc in hexanes) providing title compound (**78**; 52 mg, 120 μ 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) ν_{\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) δ 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) δ 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**

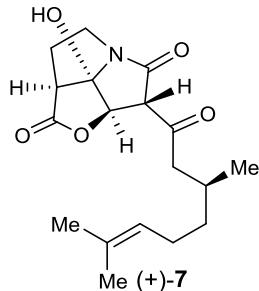


(46 mg, 100 μmol , 1.0 equiv) in THF (2 mL) at 0 $^\circ\text{C}$ was added TBAF (1.0 M in THF, 100 μL , 100 μmol , 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL) and H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×5 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 → 50% EtOAc in hexanes) providing pure title compound (**79**; 26 mg, 77 μmol , 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) ν_{\max} 3229, 2966, 2923, 2865, 2844, 1787, 1677, 1455, 1055, 1033, 1013 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) δ 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) δ 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.

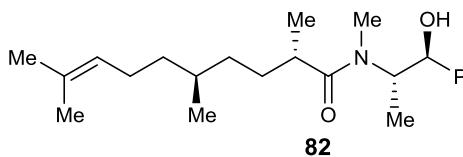
(2a*S*,6*S*,6a*R*,6b*S*)-6-[(3*S*)-3,7-Dimethyloct-6-enoyl]-6*b*-hydroxyhexahydro-1-oxa-4a-aza-cyclopenta[cd]pentalene-2,5-dione [(+)-7]: To a stirred solution of diol **79** (14 mg, 41 µmol,



1.0 equiv) in degassed CH₂Cl₂ (1 ml) at 0 °C was added an ice cooled solution of DMP (28 mg, 66 µmol, 1.5 equiv) and the resulting mixture was stirred for 30 min at the same temperature before it was diluted with Et₂O (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 [(+)-**7**; 8.3 mg, 25 µmol, 60% yield] as a colorless oil.

(+)-7: R_f=0.40 (hexanes:EtOAc, 1:1); [α]_D²⁵=+85 (*c*=0.2 in C₆H₆); IR (film) ν_{max} 3435, 2961, 2924, 2856, 1790, 1720, 1695, 1456, 1378, 1270, 1115, 1023, 732 cm⁻¹; ¹H NMR (600 MHz, C₆D₆) δ 5.15–5.13 (m, 1 H), 4.52 (s, 1 H), 4.21 (s, 1 H), 3.60 (s, 1 H), 3.40 (ddd, *J*=11.9, 9.3, 5.8 Hz, 1 H), 2.68–2.61 (m, 2 H), 2.38 (dd, *J*=17.9, 8.4 Hz, 1 H), 2.07 (dd, *J*=17.9, 4.9 Hz, 1 H), 1.98 (dd, *J*=14.1, 9.3, 5.1, 2.1 Hz, 1 H), 1.94–1.80 (m, 4 H), 1.68 (s, 3 H), 1.55 (s, 3 H), 1.15 (ddt, *J*=12.8, 9.2, 6.3 Hz, 1 H), 1.03 (dd, *J*=13.7, 9.2, 7.8, 6.3 Hz, 1 H), 0.71 (d, *J*=6.6 Hz, 3 H) ppm; ¹³C NMR (151 MHz, C₆D₆) δ 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 C₁₈H₂₅NO₅Na⁺ [M+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):

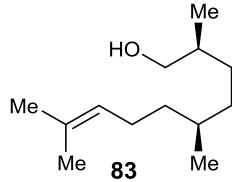


A solution of *n*-butyllithium in hexanes (2.5 M; 27.4 mL, 70.0 mmol, 4.0 equiv) was added to a suspension of lithium chloride (9.40 g, 222 mmol, 12.7 equiv) and diisopropylamine (10.6 mL, 75.3 mmol, 4.3 equiv) in THF (50 mL) at -78 °C. The resulting suspension was warmed to 0 °C and then recooled to -78 °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 °C for 1 h, at 0 °C for 15 min, and at 25 °C for 5 min. The mixture was cooled to 0 °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 °C, the resulting mixture was quenched by the addition of saturated aqueous NH₄Cl solution (200 mL), and the resulting mixture was extracted with ethyl acetate (4×100 mL), and the combined organic layers were dried over MgSO₄ and concentrated under reduced pressure. The resulting crude

product was purified by flash column chromatography (SiO_2 , 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: $R_f=0.40$ (hexanes:EtOAc, 2:3); $[\alpha]_D^{25}=-78$ ($c=2.0$ in C_6H_6); IR (film) ν_{max} 3377, 3087, 2964, 2926, 2855, 1618, 1452, 1408, 1376, 1110, 1050, 701 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3 , 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). ^{13}C NMR (151 MHz, CDCl_3 , 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 $\text{C}_{23}\text{H}_{38}\text{NO}_2^+ [\text{M}+\text{H}]^+$: 360.2897, found: 575.2888.

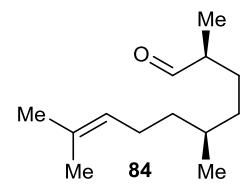
(2S,5S)-2,5,9-Trimethyldec-8-en-1-ol (83): A solution of *n*-butyllithium in hexanes (2.5 M; 20.0 mL, 46.5 mmol, 3.9 equiv) was added to a solution of diisopropylamine (7.02 mL, 50.1 mmol, 4.2 equiv) in THF (50 mL) at -78°C . The resulting solution was stirred at -78°C for 10 min, then warmed to 0°C , and held at that temperature for 10 min. $\text{BH}_3\cdot\text{NH}_3$ complex (90%, 1.64 g, 47.7 mmol, 4.0 equiv) was added in one portion, and the suspension was stirred at 0°C for 15 min and then was warmed to 23°C . After 15 min, the suspension was cooled to 0°C . A solution of amide **82** (4.27 g, 11.9 mmol, 1.0 equiv) in THF (30 mL, followed by a 10 mL rinse) was added. The reaction mixture was continued at the same temperature for 24 h, and then cooled to 0°C where excess hydride was quenched by the careful addition of aqueous HCl (3 N, 120 mL). The mixture was stirred for 30 min at 0°C and then extracted with four 45 mL portions of ether. The combined organic extracts were washed sequentially with aqueous hydrochloric acid solution (3 N, 20 mL), aqueous NaOH (2 N, 20 mL), and brine (20 mL). The organic extracts were dried over Na_2SO_4 and concentrated. Purification of the residue by flash column chromatography (SiO_2 , gradient from



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) ν_{\max} 3340, 2956, 2915, 2856, 1456, 1377, 1033 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 × 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) ν_{\max} 2963, 2924, 2856, 1727, 1458, 1377, 1259, 1119, 924, 825, 752 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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.

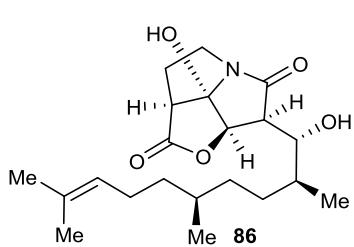
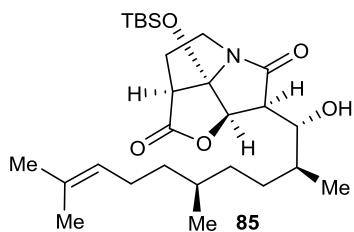
(2a*S*,6*S*,6a*R*,6b*S*)-6b-{[*tert*-Butyl(dimethyl)silyl]oxy}-6-[(1*R*,2*S*,5*S*)-1-hydroxy-2,5,9-trimethyldec-8-en-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (85):

To a stirred solution of aldehyde **84** (98 mg, 0.50 mmol, 3.0 equiv) and iodide (+)-**21** (70 mg, 170 μ mol, 1.0 equiv) in dry toluene (3 mL) at -78°C was added BET_3 (1.0 M in hexanes, 210 μL , 210 μmol , 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_2O (2 mL) at cold. The reaction mixture was brought to 25°C and extracted with Et_2O (3×10 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (SiO_2 , gradient from 5% hexanes \rightarrow 10% EtOAc in hexanes) providing pure title compound (**85**; 51 mg, 100 μmol , 63% yield) as a colorless oil.

85: $R_f = 0.50$ (hexanes: EtOAc , 1:4); $[\alpha]_D^{25} = +27$ ($c = 0.5$ in C_6H_6); IR (film) ν_{max} 3422, 2956, 2929, 2859, 1794, 1705, 1462, 1377, 1305, 1142, 1057, 1033, 1012, 895, 839, 780 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) δ 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}C NMR (151 MHz, C_6D_6) δ 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

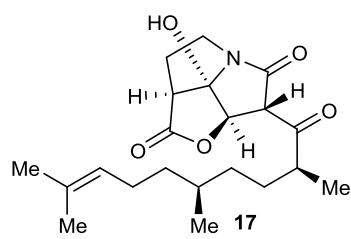
85 (43 mg, 87 μmol , 10 equiv) in THF (2 mL) at 0°C was added TBAF (1.0 M in THF, 110 μL , 110 μmol , 1.3 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aqueous NH_4Cl solution (2 mL) and H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×5 mL) and the combined organic layers were dried over NaSO_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 (**86**; 28 mg, 74 μmol , 85% yield) as a colorless oil.

86: $R_f=0.20$ (hexanes:EtOAc, 1:1); $[\alpha]_D^{25}=+34$ ($c=0.4$ in C_6H_6); IR (film) ν_{max} 3257, 2965, 2924, 2858, 1790, 1682, 1441, 1334, 1310, 1062, 1033, 773 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) 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; ^{13}C NMR (151 MHz, C_6D_6) 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 $\text{C}_{21}\text{H}_{33}\text{NO}_5\text{Na}^+$ [$\text{M}+\text{Na}]^+$: 402.2257, found: 402.2251.

(2a*S*,6*S*,6*aR*,6*bS*)-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_2Cl_2 (1 ml) at 0 $^\circ\text{C}$ 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_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 25% EtOAc in hexanes \rightarrow 50% EtOAc in hexanes) furnishing pure title compound [(+)-**17**; 6.0 mg, 16 μmol , 61% yield)] as a colorless oil.

(+)-**17:** $R_f=0.40$ (hexanes:EtOAc, 1:1); $[\alpha]_D^{25}=+21$ ($c=0.2$ in C_6H_6); IR (film) ν_{max} 3448, 2963, 2924, 2856, 1793, 1719, 1692, 1456, 1376, 1335, 1162, 1115, 1021 cm^{-1} ; ^1H NMR (600 MHz, C_6D_6) 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; ^{13}C NMR (151 MHz, C_6D_6) 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.

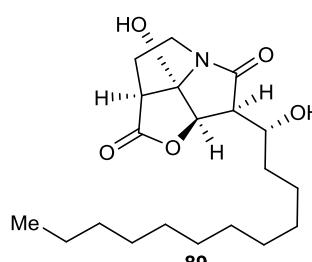
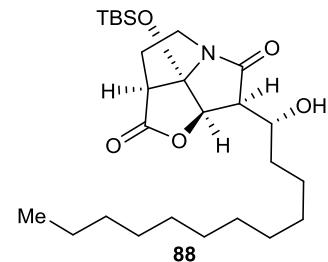
(2a*S*,6*S*,6a*R*,6b*S*)-6b-{{[tert-Butyl(dimethyl)silyl]oxy}-6-[(1*R*)-1-hydroxydodecyl]hexahydro-1-oxa-4a-azacyclopenta[*cd*]pentalene-2,5-dione (88):

To a stirred solution of aldehyde **87** (235 mg, 1.27 mmol, 3.0 equiv) and iodide (+)-**21** (180 mg, 423 μ mol, 1.0 equiv) in dry toluene (3 mL) at $-78^\circ C$ was added BEt_3 (1.0 M in hexanes, 423 μ L, 423 μ 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 H_2O (4 mL) at cold. The reaction mixture was brought to $25^\circ C$ and extracted with Et_2O (3×10 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 (**88**; 169 mg, 351 μ mol, 83% yield) as a colorless oil.

88: $R_f = 0.50$ (hexanes: $EtOAc$, 1:2); $[\alpha]_D^{25} = +28$ ($c = 0.8$ in C_6H_6); IR (film) ν_{max} 3505, 2953, 2925, 2855, 1792, 1702, 1463, 1375, 1303, 1251, 1142, 1061, 837, 779, 675 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) 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, 20 H), 0.89–0.86 (m, 12 H), 0.15 (s, 3 H), 0.14 (s, 3 H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 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 $C_{26}H_{47}NO_5SiNa^+$ $[M+Na]^+$: 504.3116, found: 504.3124.

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

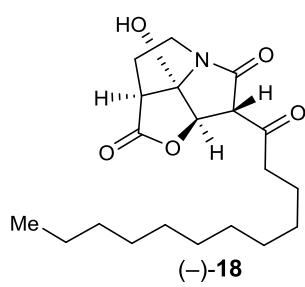
590 μ mol, 1.1 equiv) and acetic acid (36 μ L, 590 μ mol, 1.1 equiv) in THF (3 mL) was added TBS ether **88** (260 mg, 540 μ mol, 1.0 equiv) in THF (1 mL) at $0^\circ C$ and the resulting mixture was stirred for 15 min at the same temperature before it was quenched by the addition of sat. aq. NH_4Cl (2 mL). The reaction mixture was extracted with $EtOAc$ (3×10 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 10% EtOAc in hexanes \rightarrow 50% EtOAc in hexanes) providing pure title compound (**89**; 170 mg, 470 μmol , 87% yield) as a colorless oil.

89: $R_f=0.30$ (hexanes:EtOAc, 2:3); $[\alpha]_D^{25}=+49$ ($c=0.5$ in C_6H_6); IR (film) ν_{max} 3336, 2954, 2922, 2853, 1788, 1685, 1388, 1332, 1305, 1163, 1087, 1058, 1010, 946, 771, 706 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) 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 (td, $J=13.8, 9.5, 6.2$ 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; ^{13}C NMR (151 MHz, CDCl_3) 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 $\text{C}_{20}\text{H}_{33}\text{NO}_5\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 390.2251, found: 390.2258.

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

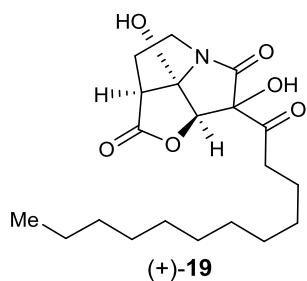


27 μmol , 1.0 equiv) in degassed CH_2Cl_2 (1 ml) at 0 $^\circ\text{C}$ was added DMP (23 mg, 55 μmol , 2.0 equiv) and the resulting mixture was stirred for 3 h at 25 $^\circ\text{C}$ before it was diluted with Et_2O (5 mL) and passed through a plug of Celite. The resulting crude product was purified by passing through a short plug of silica (gradient from 10% EtOAc in hexanes \rightarrow 50% EtOAc in hexanes) furnishing pure 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: $R_f=0.40$ (hexanes:EtOAc, 1:1); $[\alpha]_D^{25}=-7$ ($c=1.0$ in C_6H_6); IR (film) ν_{max} 3418, 2963, 2917, 2852, 1785, 1711, 1671, 1649, 1407, 1330, 1174, 1027 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) 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; ^{13}C NMR (151 MHz, CDCl_3) 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 $\text{C}_{20}\text{H}_{31}\text{NO}_5\text{Na}^+$ $[\text{M}+\text{Na}]^+$: 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) ν_{max} 3425, 2924, 2854,



1794, 1698, 1332, 1305, 1163, 1114, 1025 cm^{-1} ; 1H NMR (600 MHz, C_6D_6) δ 5.23 (s, 1 H), 4.14 (s, 1 H), 3.44 (ddd, $J = 12.0, 9.3, 6.0$ Hz, 2 H), 2.75–2.60 (m, 4 H), 2.06 (t, $J = 7.1$ Hz, 1 H), 1.89 (dddd, $J = 14.0, 9.3, 4.9, 2.0$ Hz, 1 H), 1.81–1.74 (m, 1 H), 1.52–1.47 (m, 17 H), 0.92 (t, $J = 7.0$ Hz, 3 H) ppm; ^{13}C NMR (151 MHz, C_6D_6) δ 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 μ 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_2O (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 μ mol, 83% yield] as an amorphous solid.

(2a*S*,6*aR*,6*bS*)-6-Dodecanoyl-6*b*-dihydroxyhexahydro-1-oxa-4*a*-azacyclopenta[*cd*]pentene-2,5-dione [(+)-19**] from (-)-**18**:** To a stirred solution of 1,3-dicarbonyl compound (-)-**18** (3.0 mg, 8.2 μ mol, 1.0 equiv) in CH_2Cl_2 (1 ml) at 25 °C was added DMP (21 mg, 49 μ mol, 6.0 equiv) and the resulting mixture was stirred for 6 h at 25 °C 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 → 50% EtOAc in hexanes) furnishing hydroxy 1,3-dicarbonyl derivative [(+)-**19**; 1.8 mg, 4.7 μ mol, 58% yield] as a white amorphous solid.

(2a*S*,6*S*,6a*R*,6b*S*)-6b-{{[tert-butyl(dimethyl)silyl]oxy}-6-[*(1R,2E,6E)*-1-hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (91):

To a stirred solution of aldehyde **53** (73 mg, 330 μ mol, 2.0 equiv) and iodide (+)-**21** (70 mg,

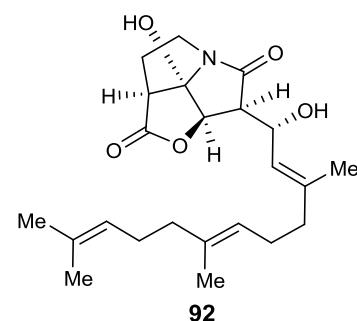
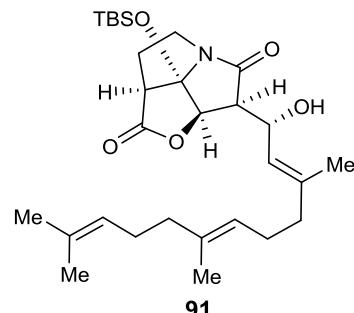
160 μ mol, 1.0 equiv) in toluene (3 mL) at -78°C was added BET_3 (210 μL , 1.0 M in hexanes, 210 μ mol, 1.3 equiv). The resulting mixture was stirred for 6 h at the same temperature before it was quenched by addition of H_2O (1 mL). The reaction mixture was extracted with Et_2O (3×10 mL) and the combined 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 **91**; 64 mg, 120 μ mol, 77% yield) as a colorless oil.

91: The ^1H NMR and ^{13}C NMR spectral data of **91** matched those of previously synthesized racemic **54**. $[\alpha]_D^{25} = +57.2$ ($c = 1.0$ in C_6H_6).

(2a*S*,6*S*,6a*R*,6b*S*)-6b-hydroxy-6-[*(1R,2E,6E)*-1-hydroxy-3,7,11-trimethyldodeca-2,6,10-trien-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (92):

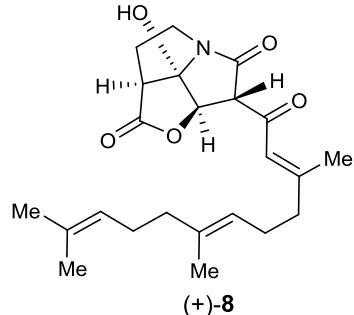
To a stirred solution of TBS ether **91** (80 mg, 150 μ mol, 1.0 equiv) in THF (2 mL) at -10°C was added TBAF (1.0 M in THF, 150 μL , 150 μ mol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by addition of saturated aq. NH_4Cl (1 mL) and H_2O (2 mL). The reaction mixture was extracted with EtOAc (3×25 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 → 60% EtOAc in hexanes) providing pure title compound (**92**; 41 mg, 100 µmol, 66% yield) as a colorless oil.

92: The ^1H NMR and ^{13}C NMR spectral data of **92** matched those of previously synthesized racemic **55**. $[\alpha]_D^{25} = +69$ ($c = 0.5$ in C_6H_6).

(2a*S*,6*S*,6*aR*,6*bS*)-6b-Hydroxy-6-[*(2E,6E)*-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**

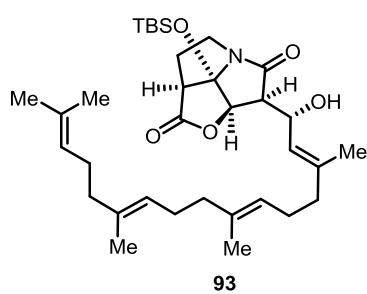


(13 mg, 32 µmol, 1.0 equiv) in degassed CH_2Cl_2 (3 ml) at 25 °C was added activated MnO_2 (140 mg, 1.3 mmol, 40 equiv) in four portions every 2 h and the resulting mixture was stirred for an additional 2 h at the same temperature. Then, the resulting mixture was diluted with CH_2Cl_2 (10 ml), passed 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 → 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 ^1H NMR and ^{13}C NMR spectral data of (+)-**8** matched those of previously synthesized racemic (\pm) -**8**. $[\alpha]_D^{25} = +7$ ($c = 0.3$ in C_6H_6).

(2a*S*,6*S*,6*aR*,6*bS*)-6b-{{[tert-Butyl(dimethyl)silyl]oxy}-6-[*(1R,2E,6E,10E)*-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

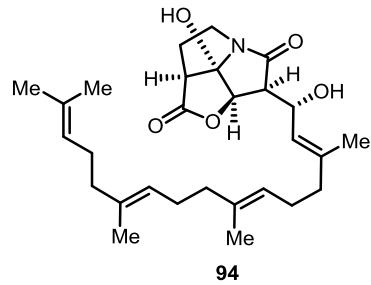


(+)-**21** (74 mg, 180 µmol, 1.0 equiv) in dry toluene (3 mL) at -78 °C was added BEt_3 (1.0 M in hexanes, 230 µL, 230 µmol, 1.3 equiv) dropwise and the resulting reaction mixture was stirred for 4 h at the same temperature before it was quenched by the addition of H_2O (3 mL) at cold. The reaction mixture was brought to 25 °C and extracted with Et_2O (3×30 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 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) ν_{max} 3479, 2955, 2929, 2857, 1793, 1707, 1472, 1376, 1301, 1253, 1186, 839 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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-tetramethylhexa-deca-2,6,10,14-tetraen-1-yl]hexahydro-1-oxa-4a-azacyclopenta[cd]pentalene-2,5-dione (94):



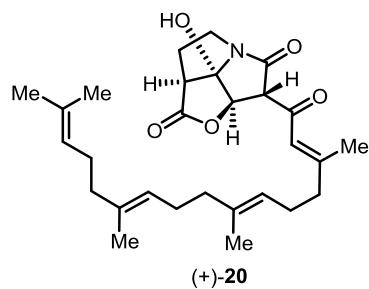
To a stirred solution of TBS ether **93** (70 mg, 120 μ mol, 1.0 equiv) in THF (2 mL) at 0 °C was added TBAF (1.0 M in THF, 120 μ L, 120 μ mol, 1.0 equiv) and the resulting mixture was stirred for 5 min at the same temperature before it was quenched by the addition of saturated aq. NH₄Cl (2 mL) and H₂O (2 mL). The reaction mixture

was extracted with EtOAc (3 \times 10 mL) and the combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure. The resulting crude product was purified by flash column chromatography (SiO₂, gradient from 30% EtOAc in hexanes \rightarrow 60% EtOAc in hexanes) providing pure title compound (**94**; 38 mg, 81 μ 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) ν_{max} 3270, 2965, 2917, 2854, 1785, 1681, 1440, 1382, 1307, 1064, 1009, 770, 707 cm^{-1} ; 1H NMR (600 MHz, $CDCl_3$) δ 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, $CDCl_3$) δ 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 μ mol, 1.0 equiv) in degassed CH_2Cl_2 (3 ml) at 25 °C was added activated MnO_2 (55 mg, 510 μ 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→50% EtOAc in hexanes) furnishing pure title compound **(+)-20** (2.6 mg, 5.5 μ mol, 44% yield) as a colorless oil and diol **94** (2.1 mg, 4.4 μ mol).

(+)-20: $R_f = 0.50$ (hexanes:EtOAc,1:1); $[\alpha]_D^{25} = +35$ ($c = 0.1$ in C_6H_6); IR (film) ν_{max} 3399, 2918, 1795, 1719, 1605, 1427, 1161, 1117, 1025 cm^{-1} ; 1H NMR (600 MHz, C_6D_6) δ 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) δ 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

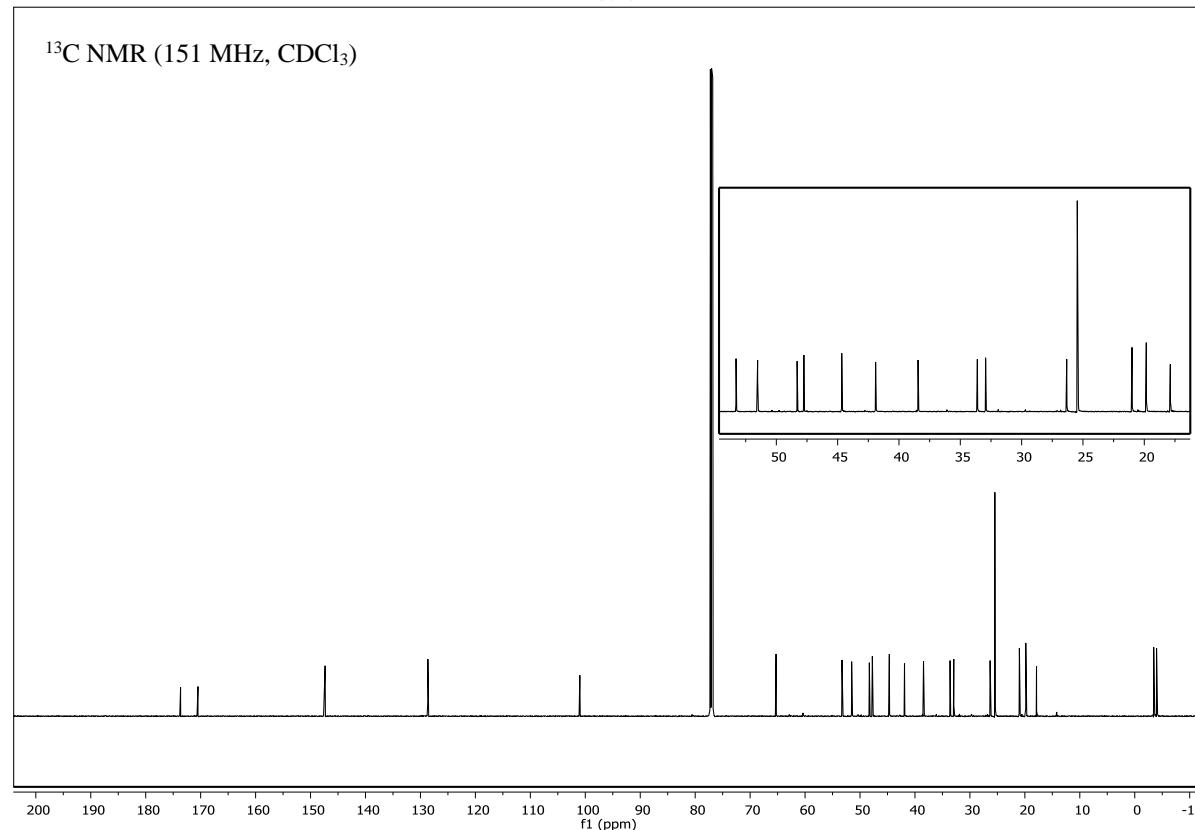
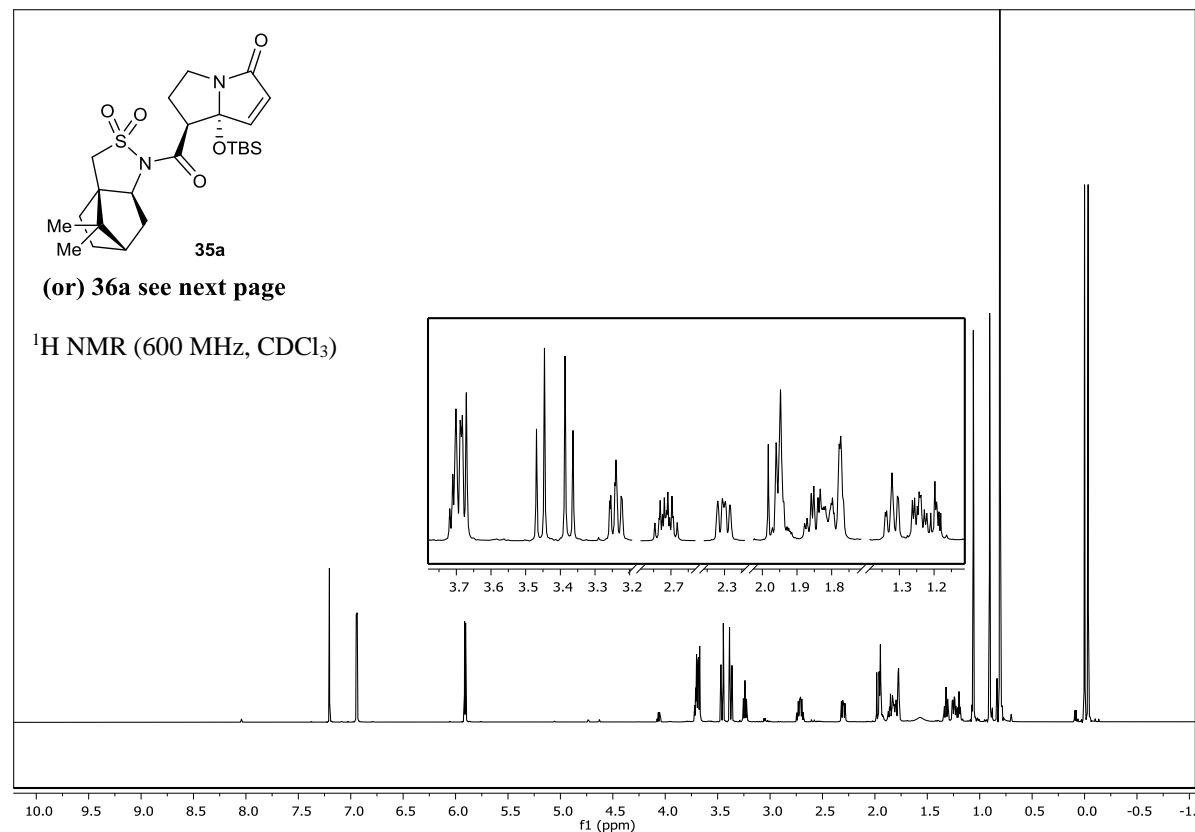
For these studies we used three clinical strains: *Enterococcus faecalis* S613, *Enterococcus faecium* isolate 105, and Methicillin-resistant *Staphylococcus aureus* MRA 371. Additionally, we also used one laboratory strain, *Bacillus subtilis* 168. We cultured the two enterococci strains in a mix of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

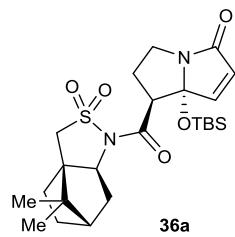
For the minimal inhibitory concentration (MIC) assays we performed standard micro-broth MIC assays in triplicate using 96-well plates. We filled wells with 100 µL of broth media and then used 1 µL of overnight stationary phase culture to inoculate the wells. CJ-16,264 and analogues were tested at concentrations that increased in two-fold increments and spanned 0.125–64 µg/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.

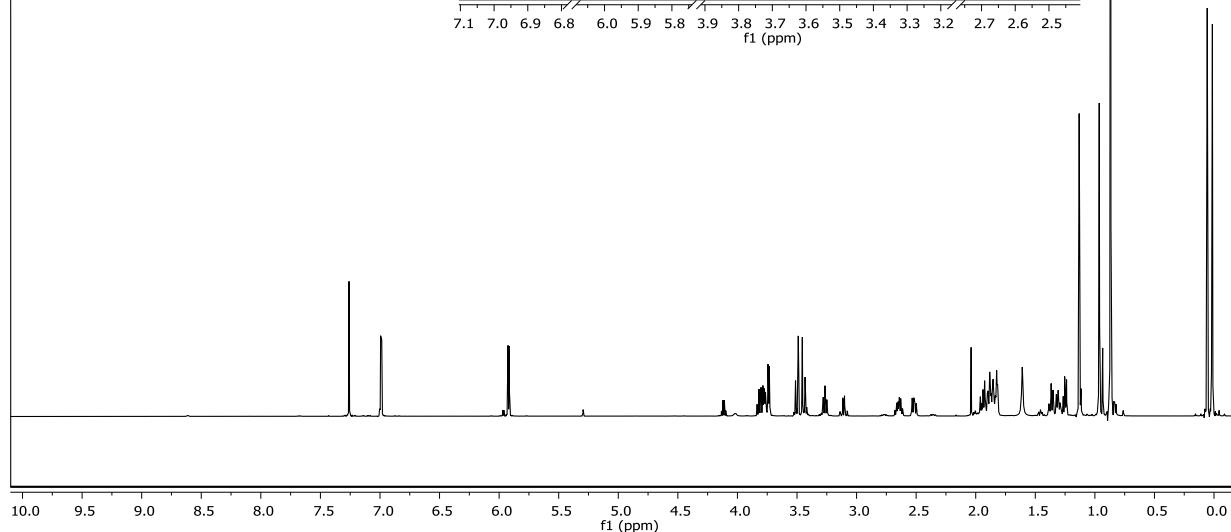
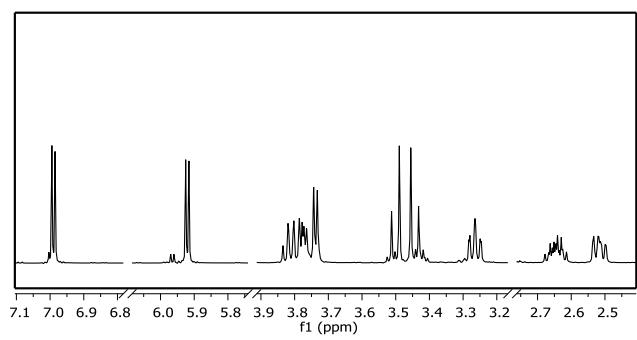
V. ^1H and ^{13}C NMR Spectra of Compounds



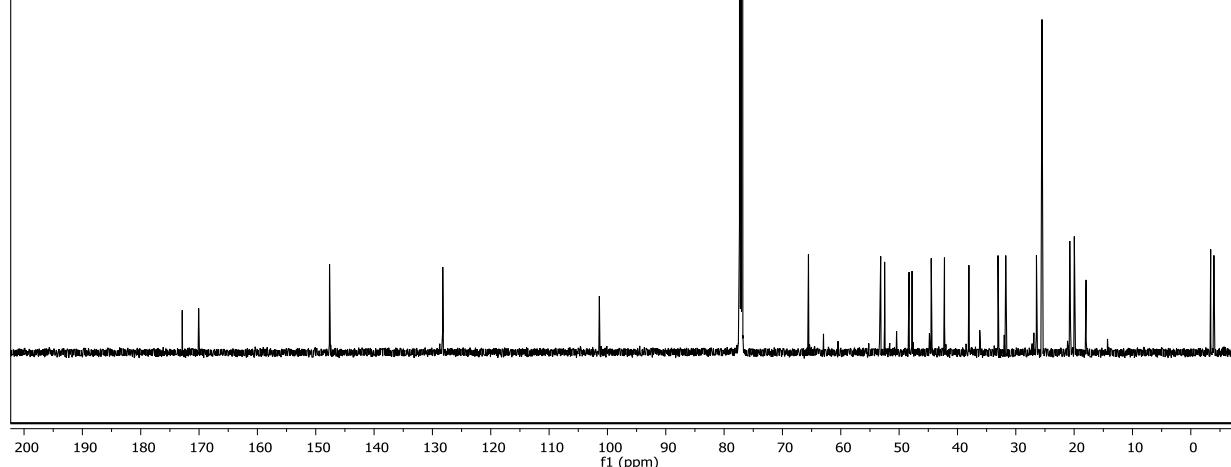
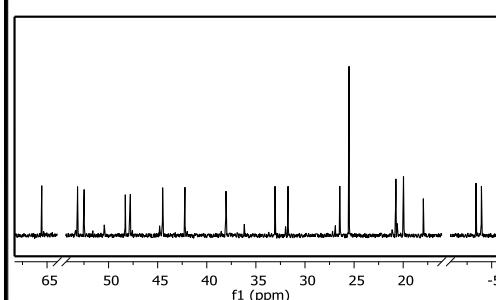


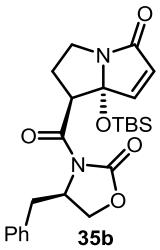
(or) **35a** see previous page

¹H NMR (600 MHz, CDCl₃)

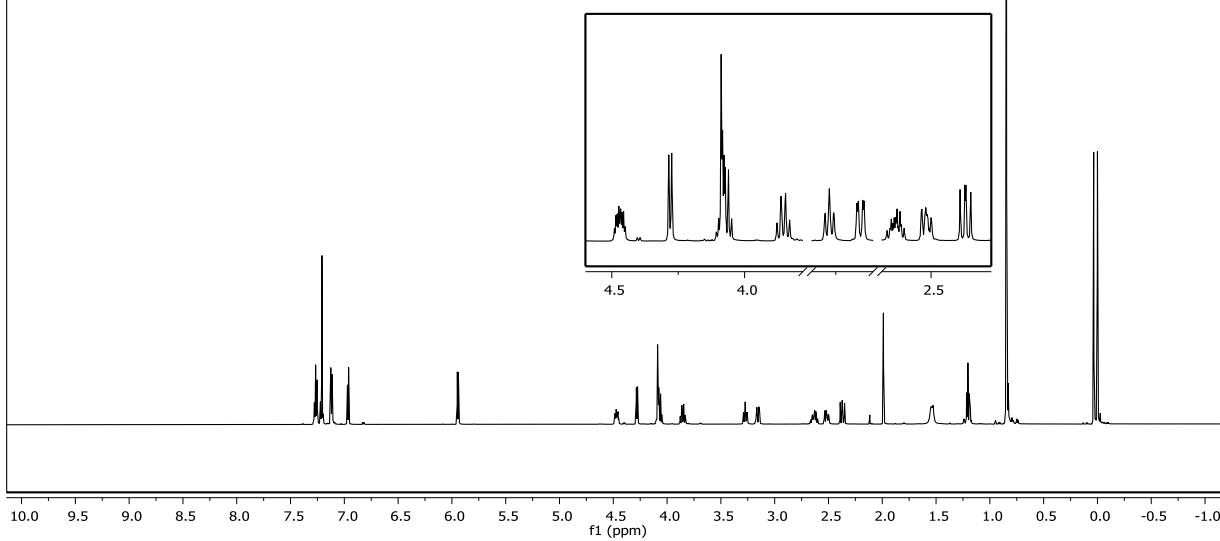


¹³C NMR (151 MHz, CDCl₃)

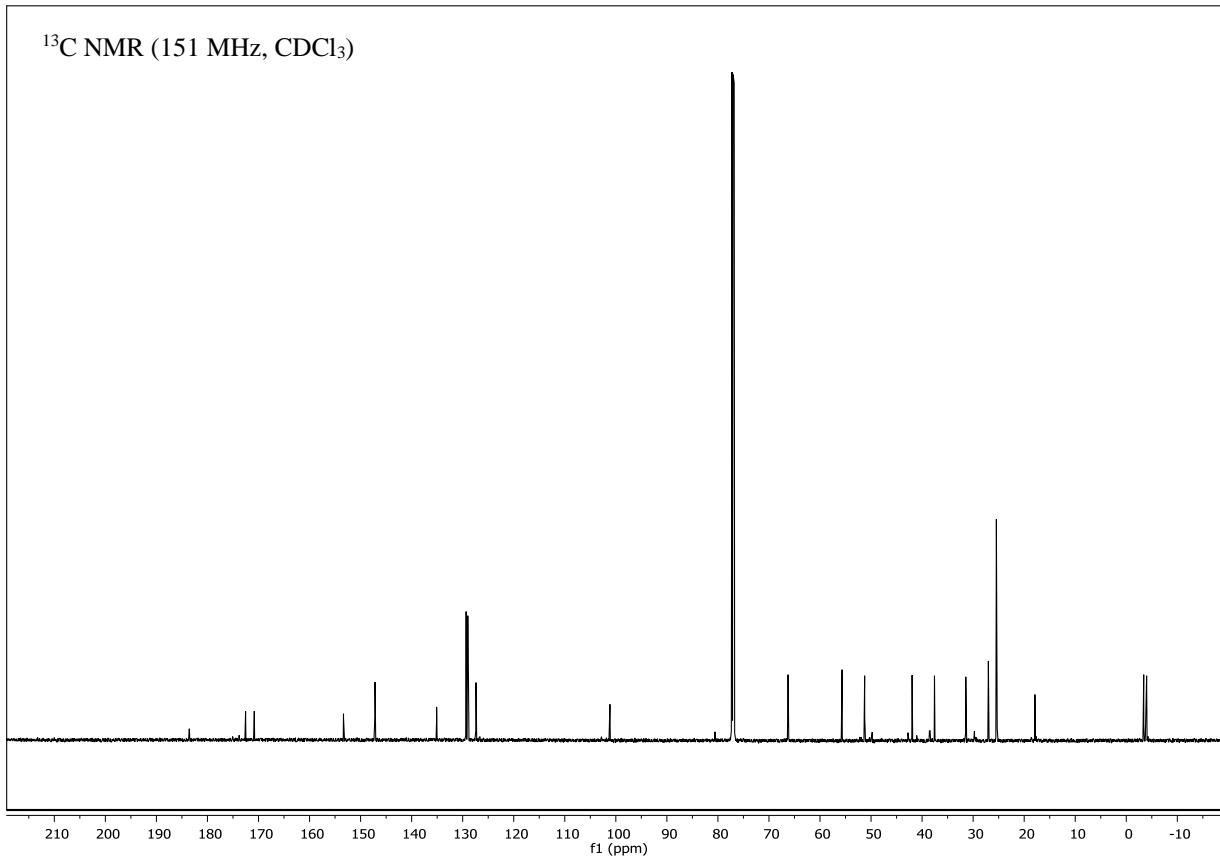


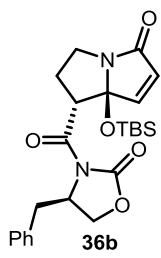


¹H NMR (600 MHz, CDCl₃)

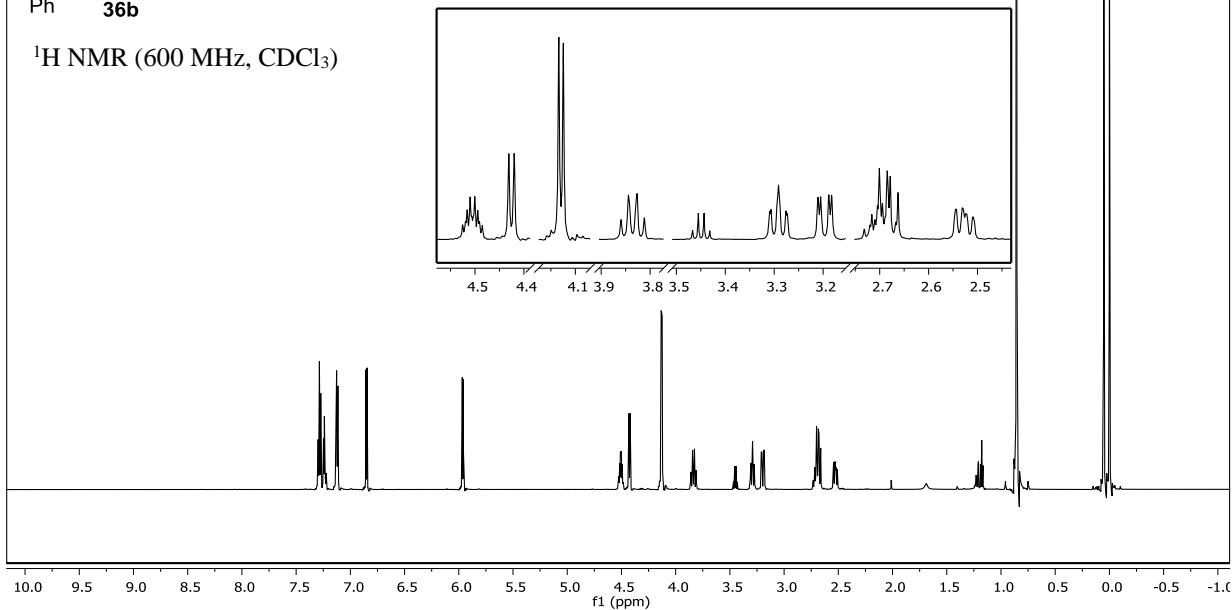


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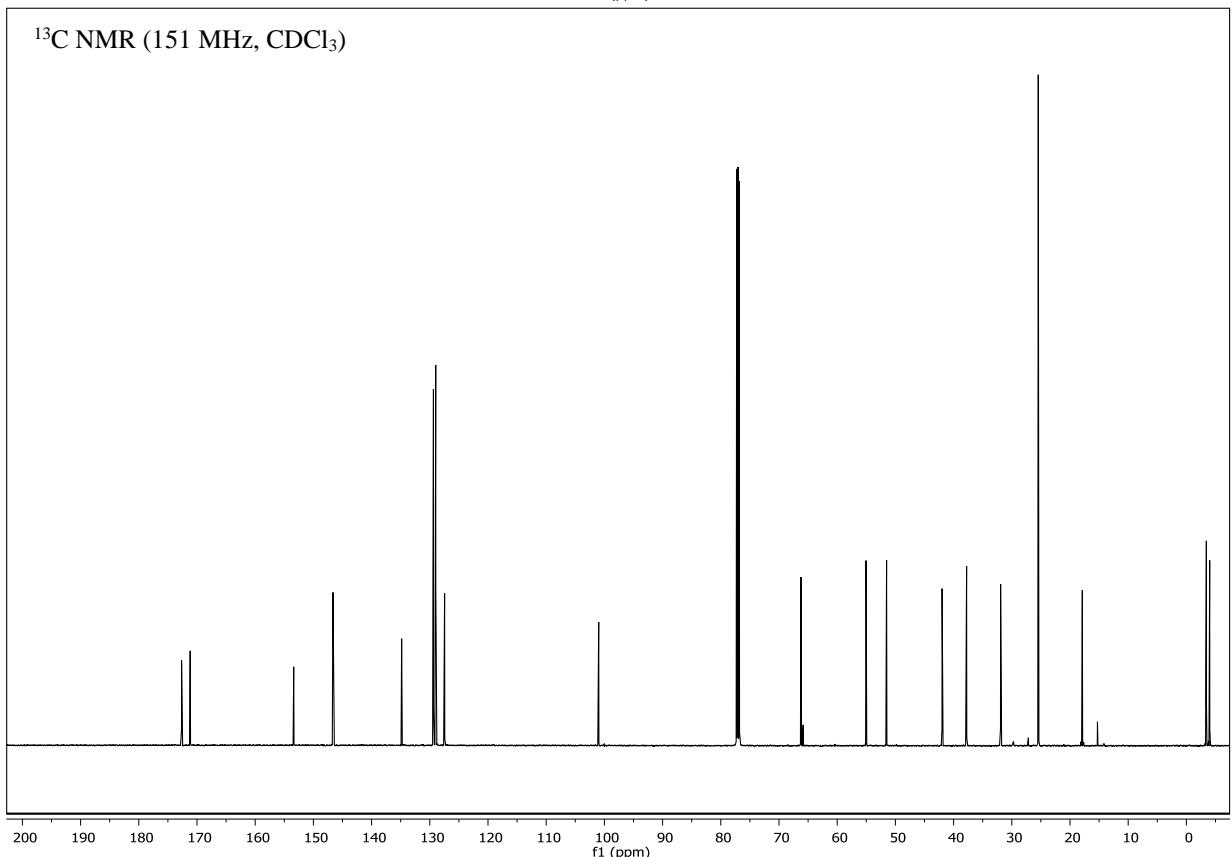


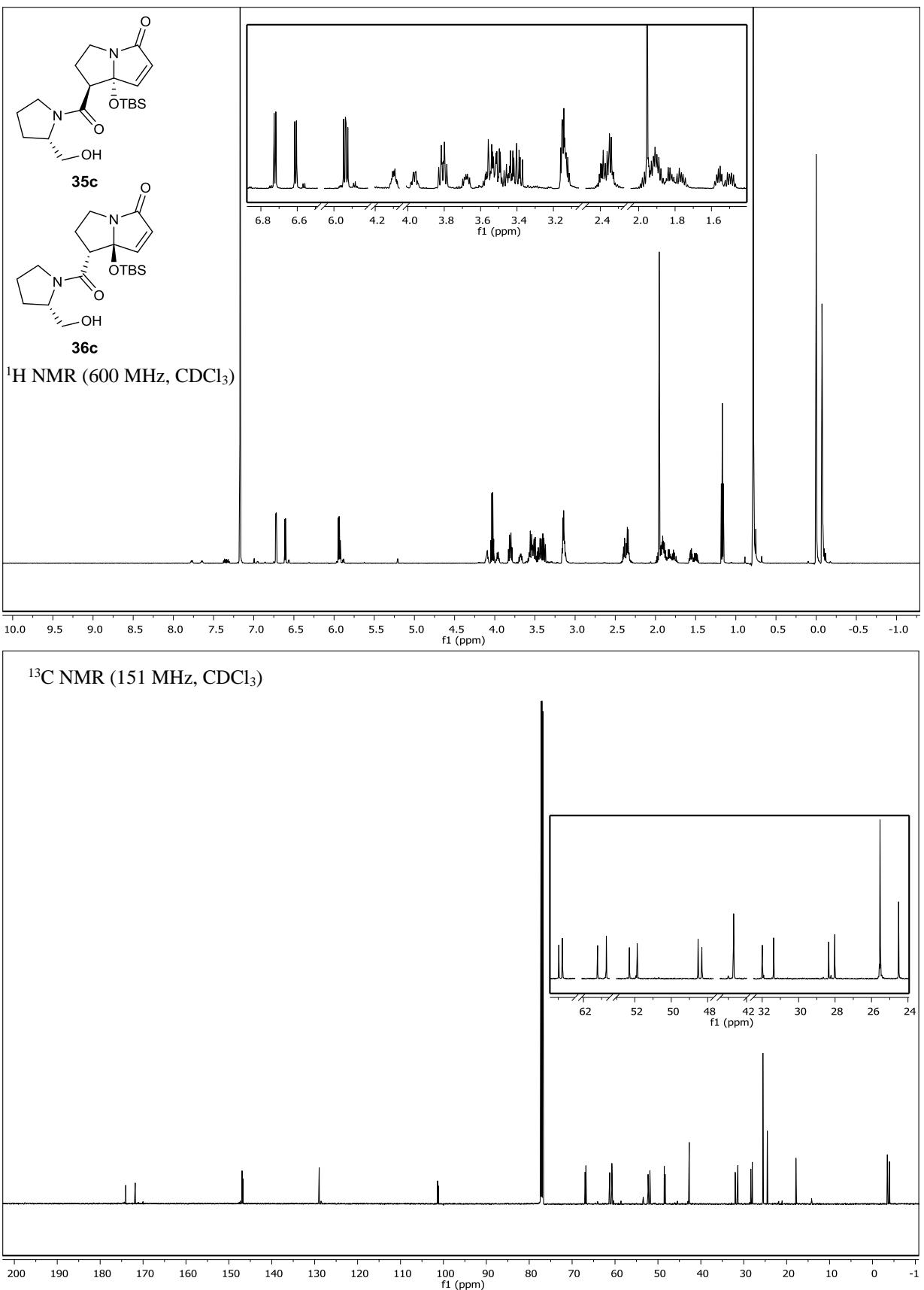


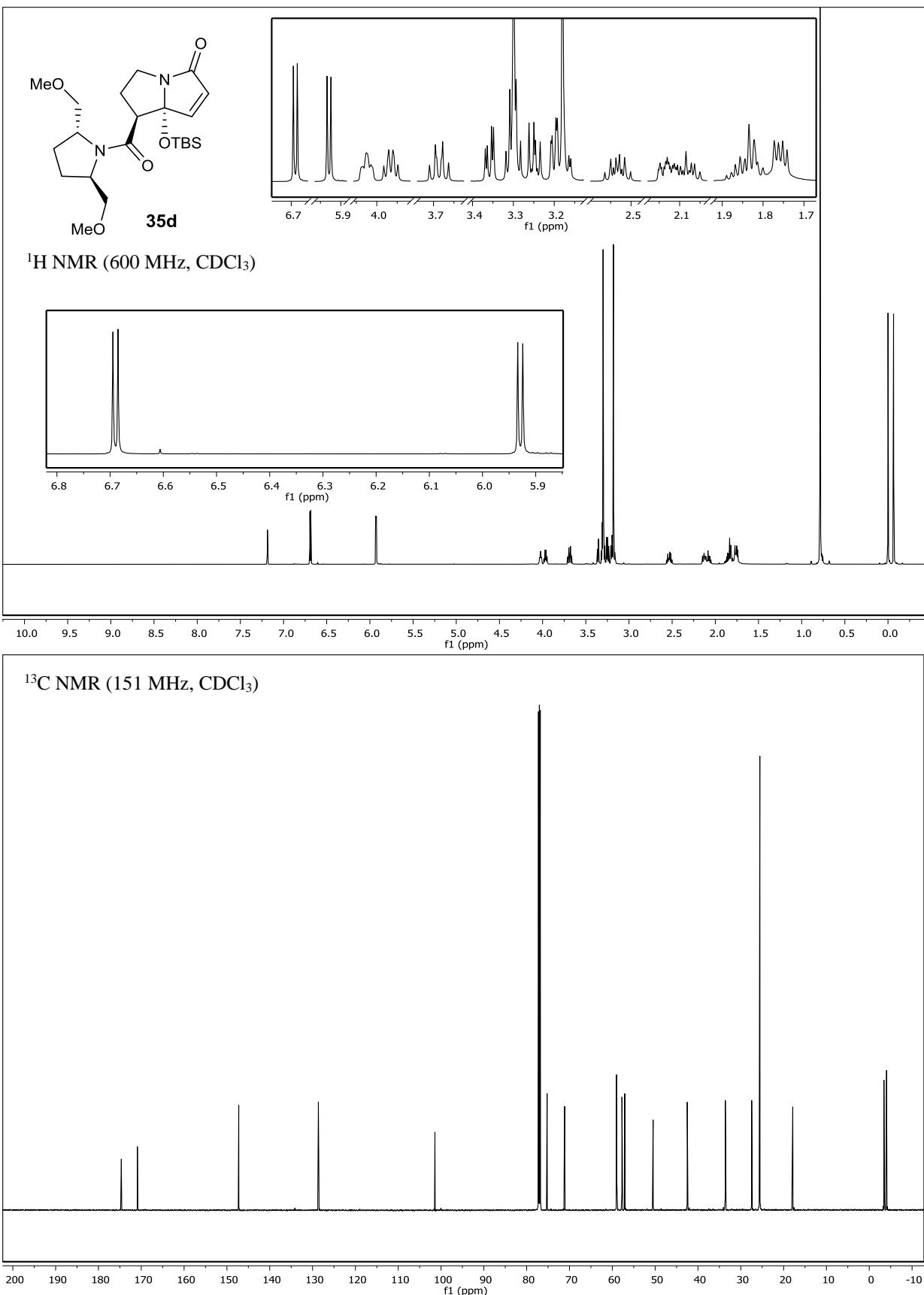
¹H NMR (600 MHz, CDCl₃)

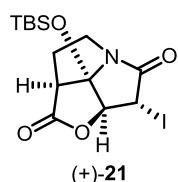


¹³C NMR (151 MHz, CDCl₃)

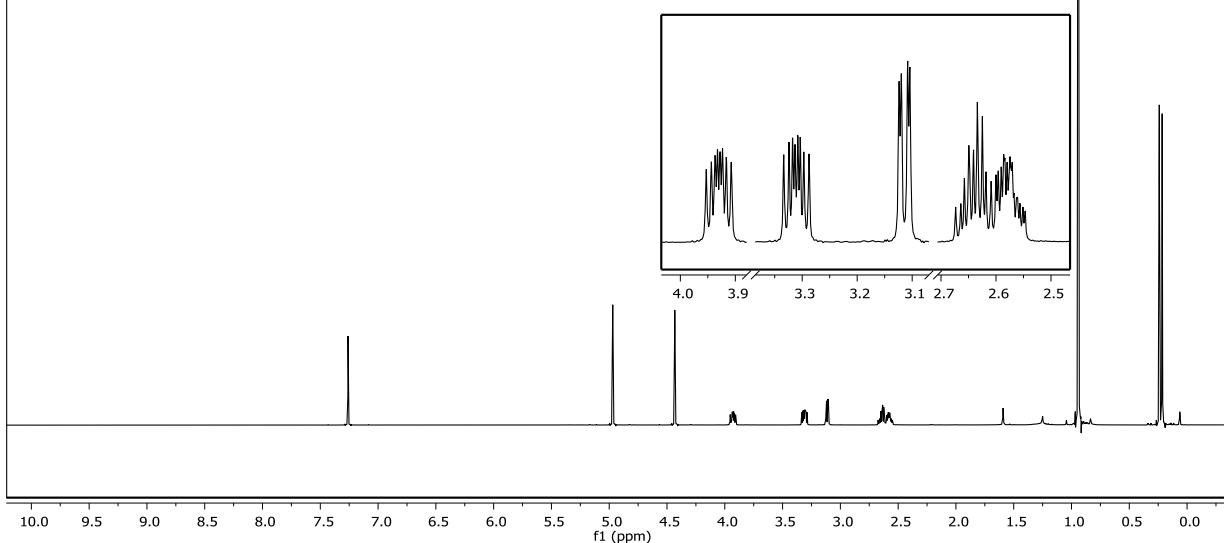




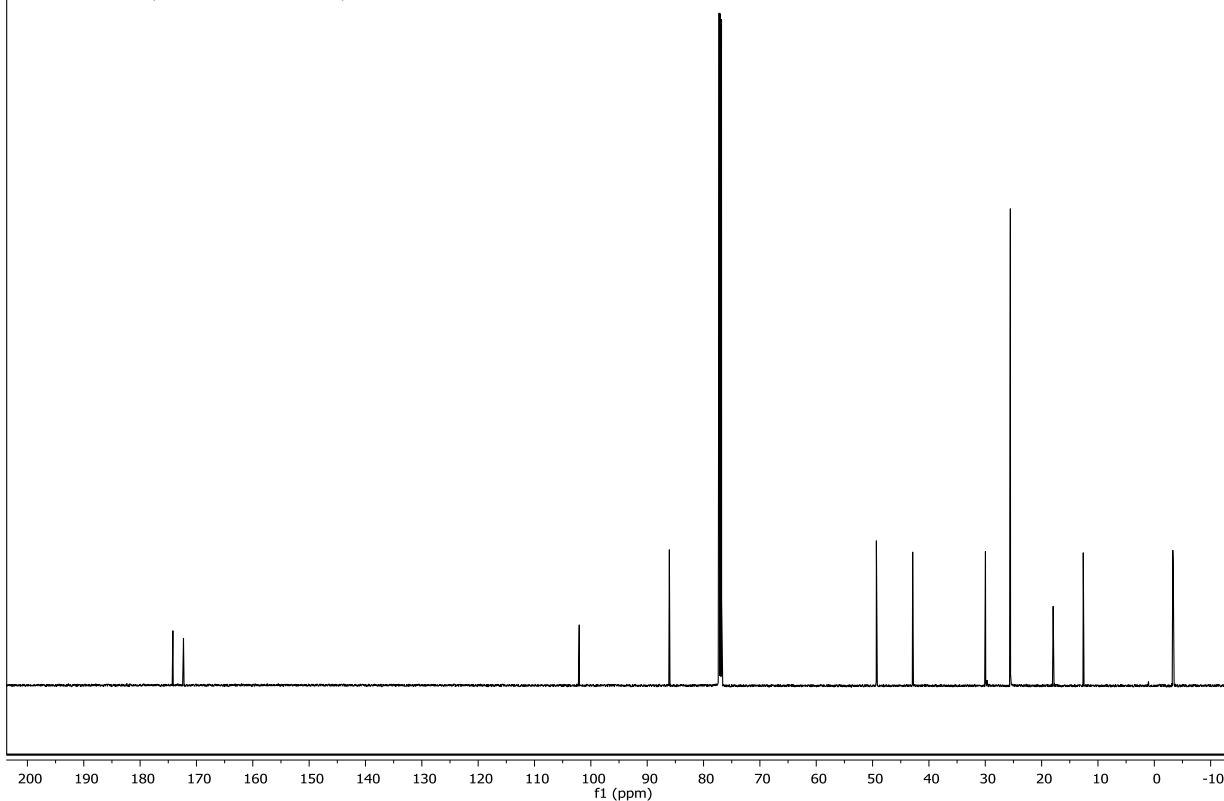


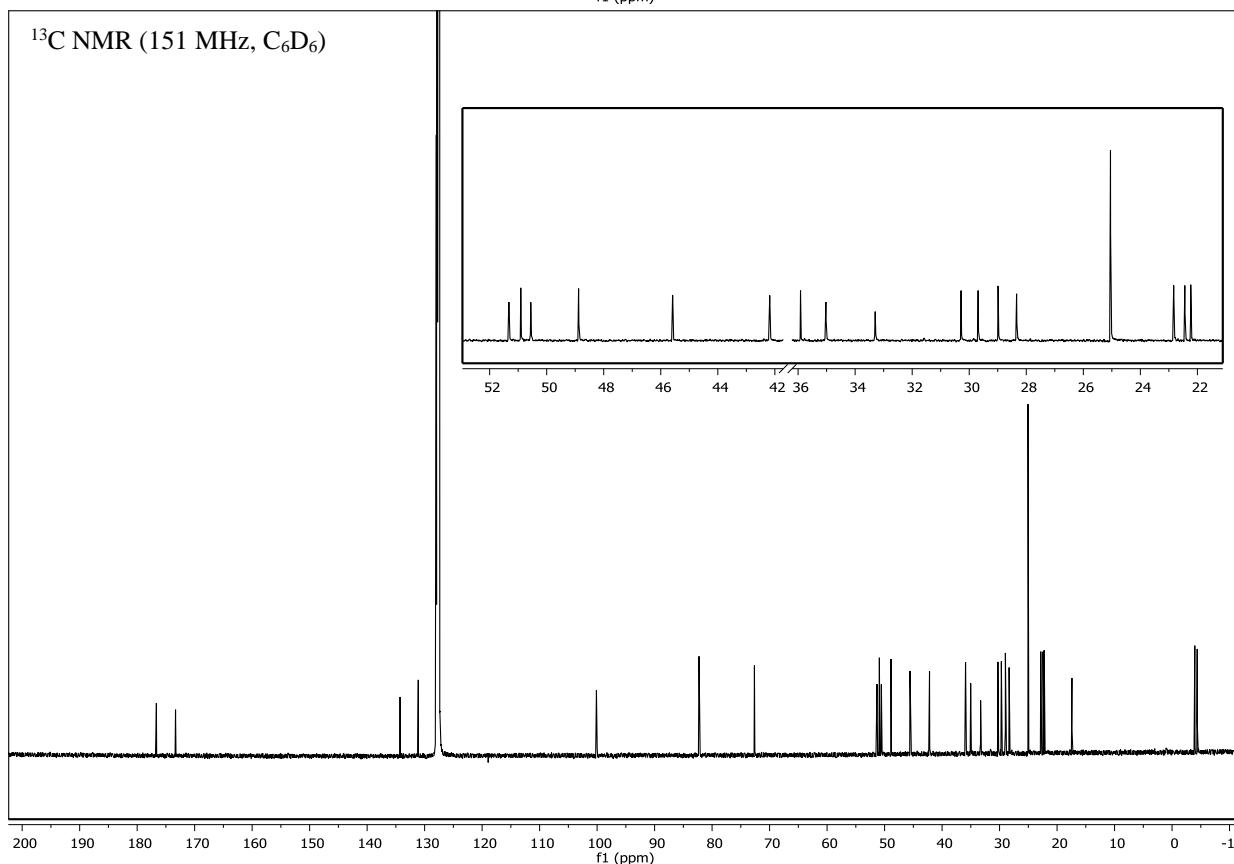
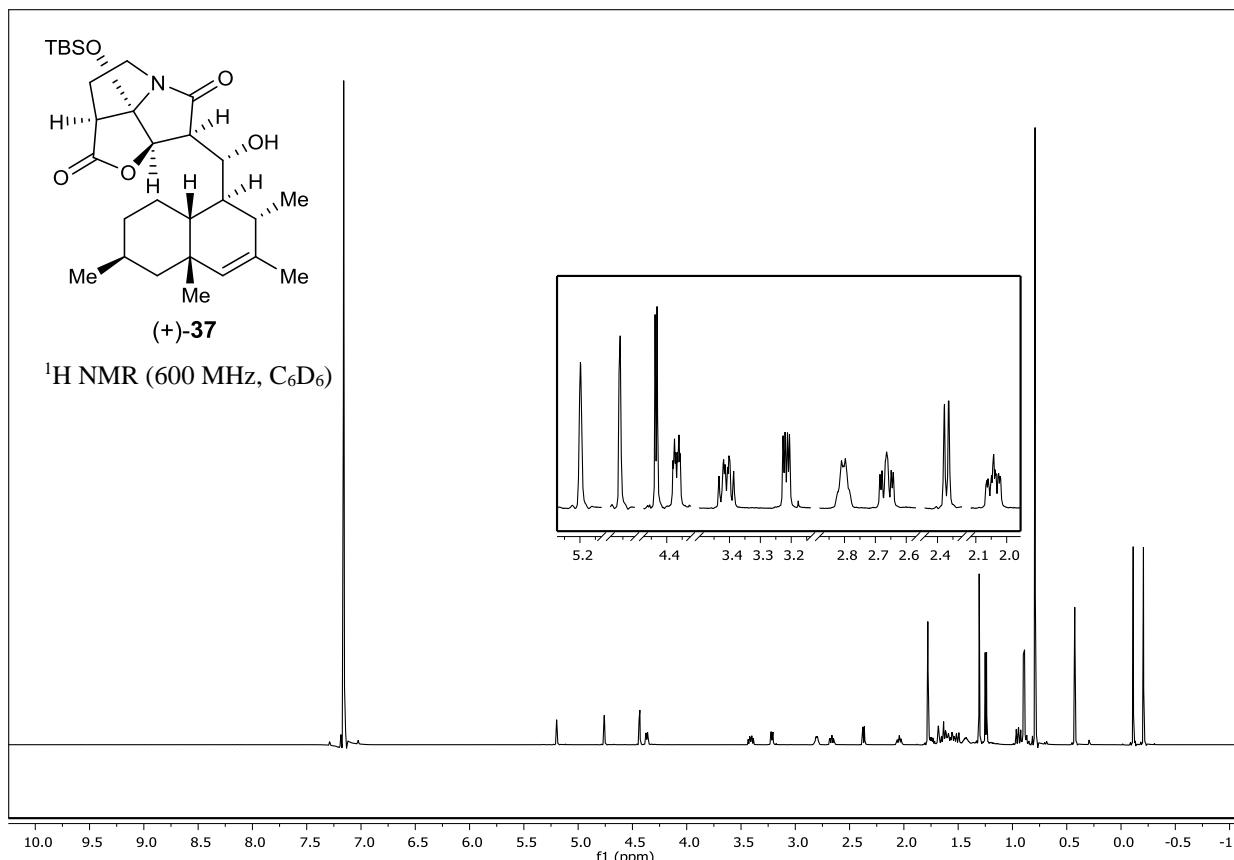


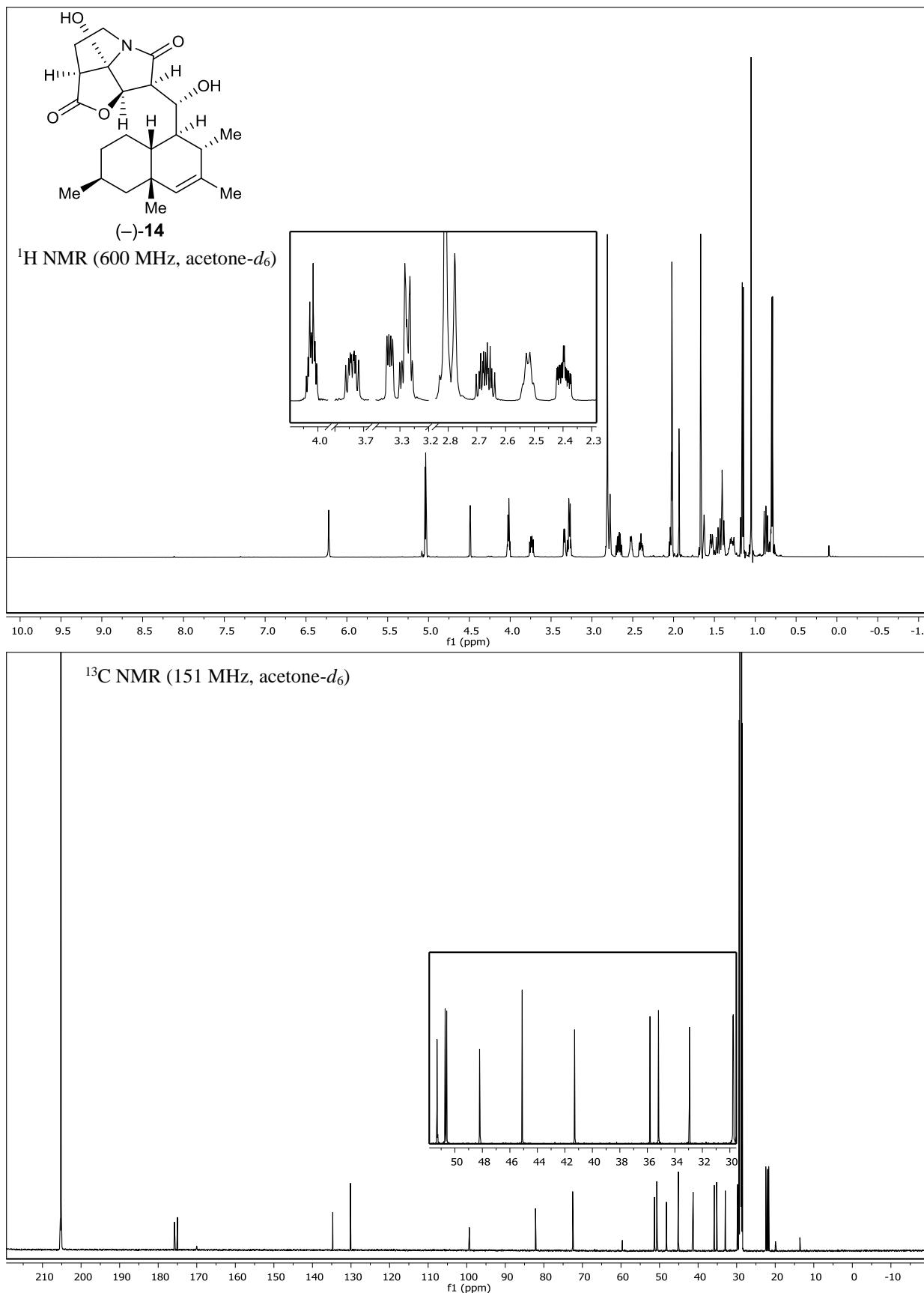
¹H NMR (600 MHz, CDCl₃)

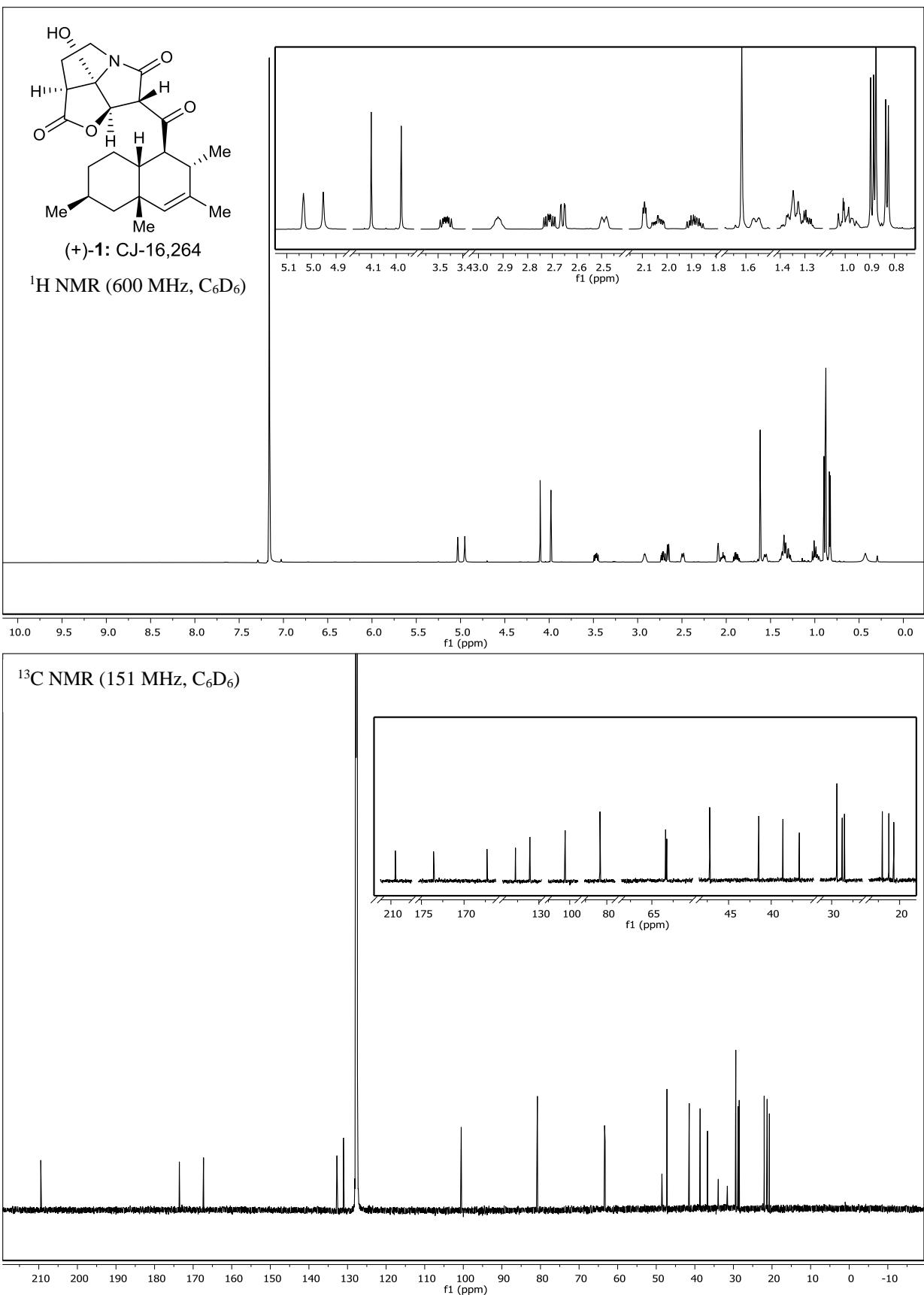


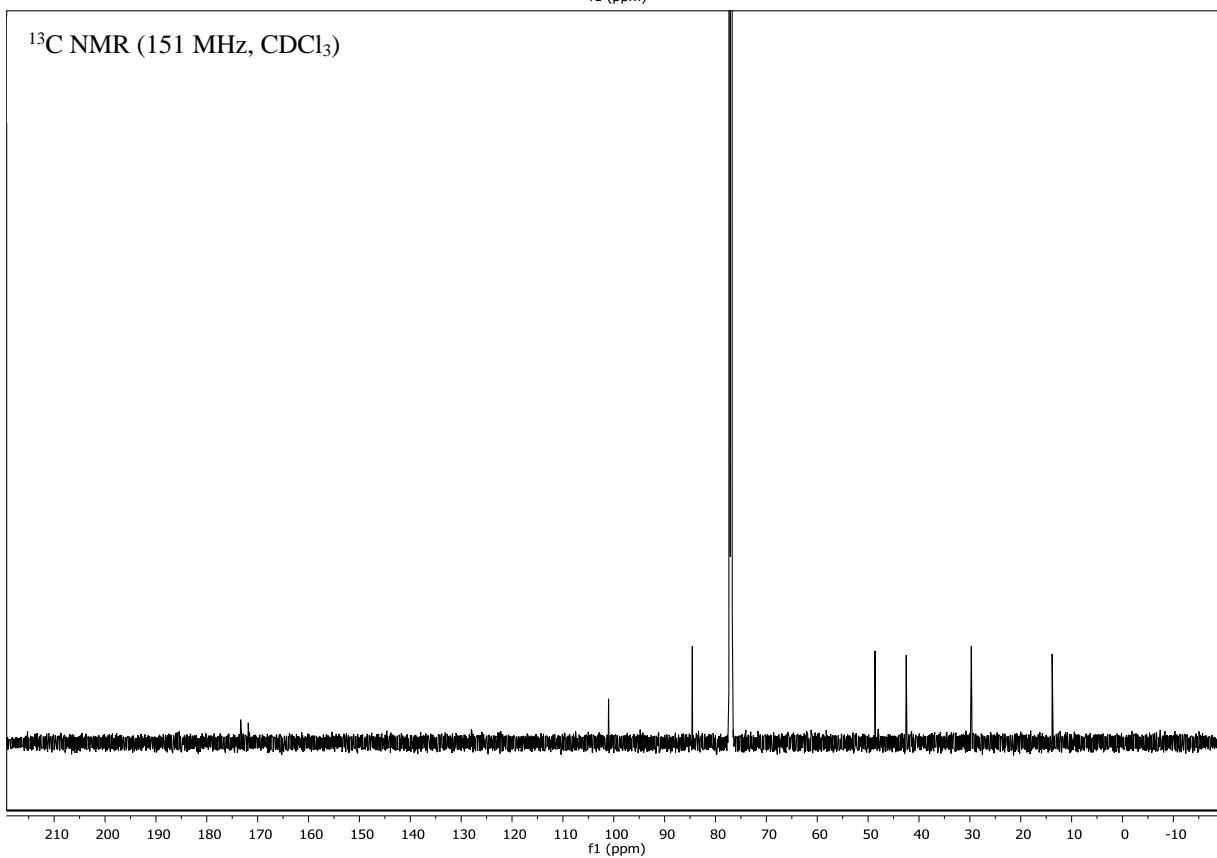
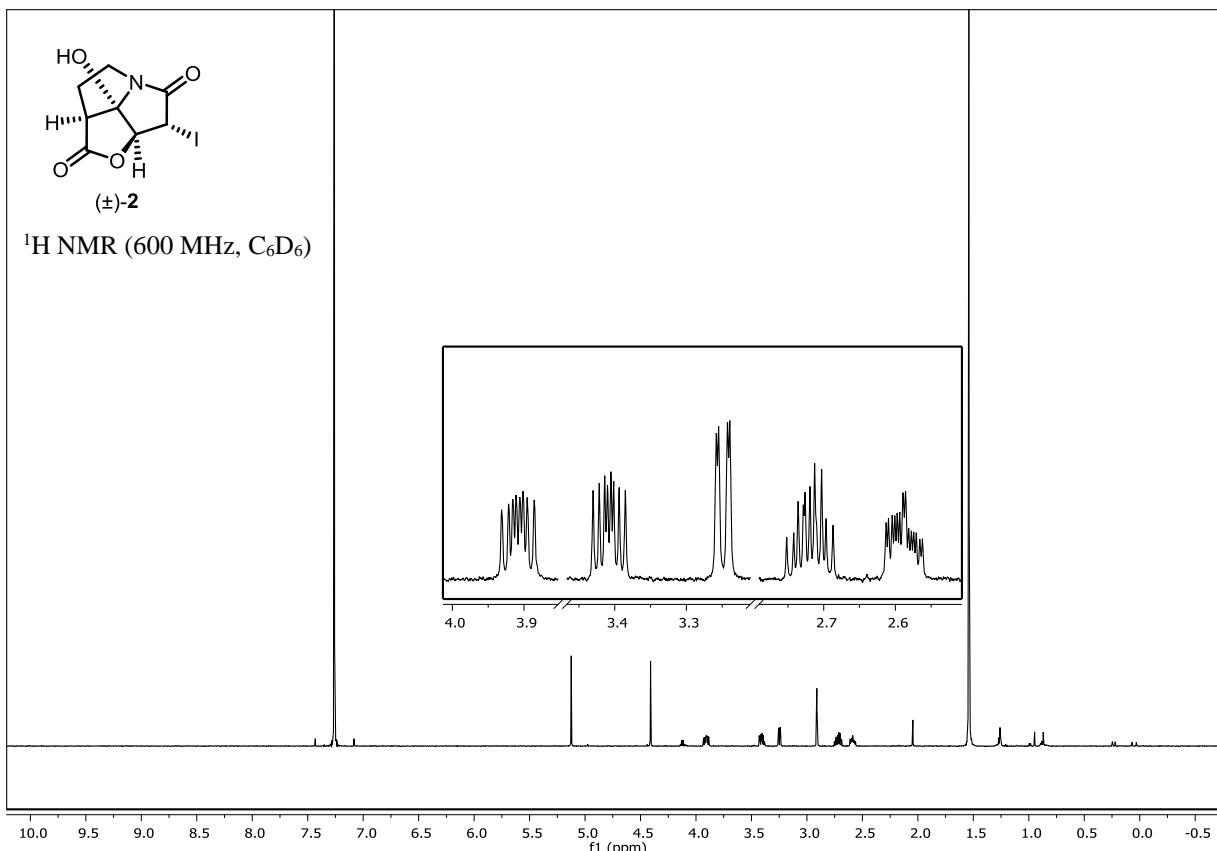
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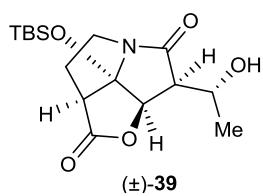




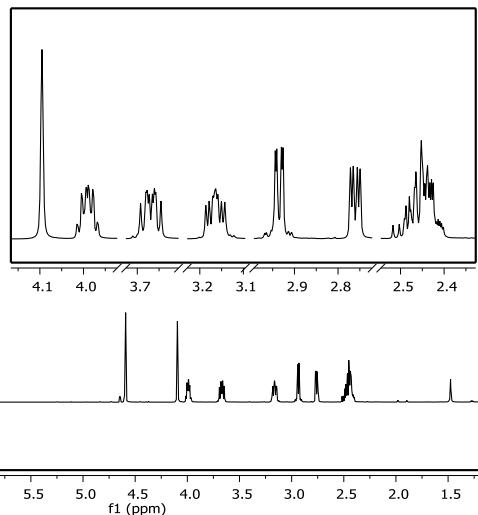




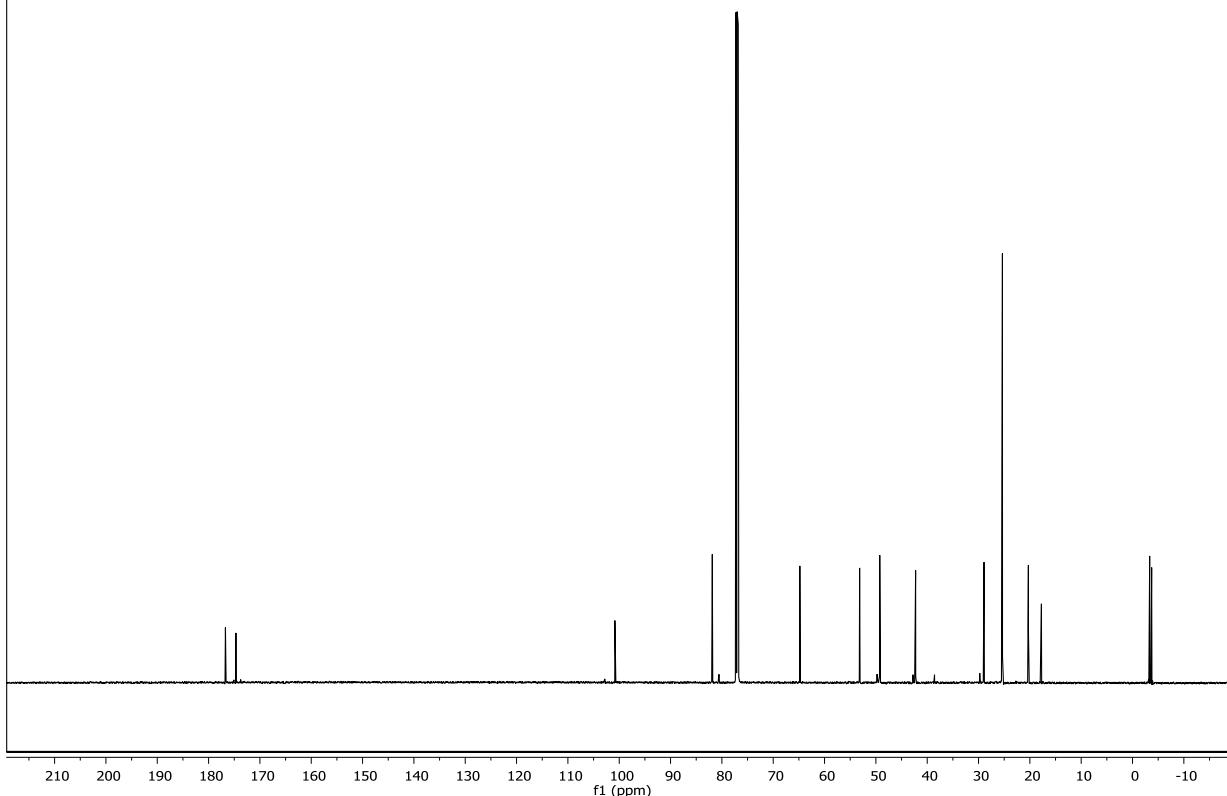


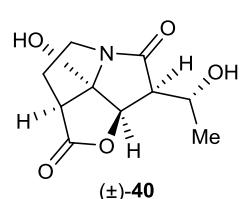


^1H NMR (600 MHz, CDCl_3)

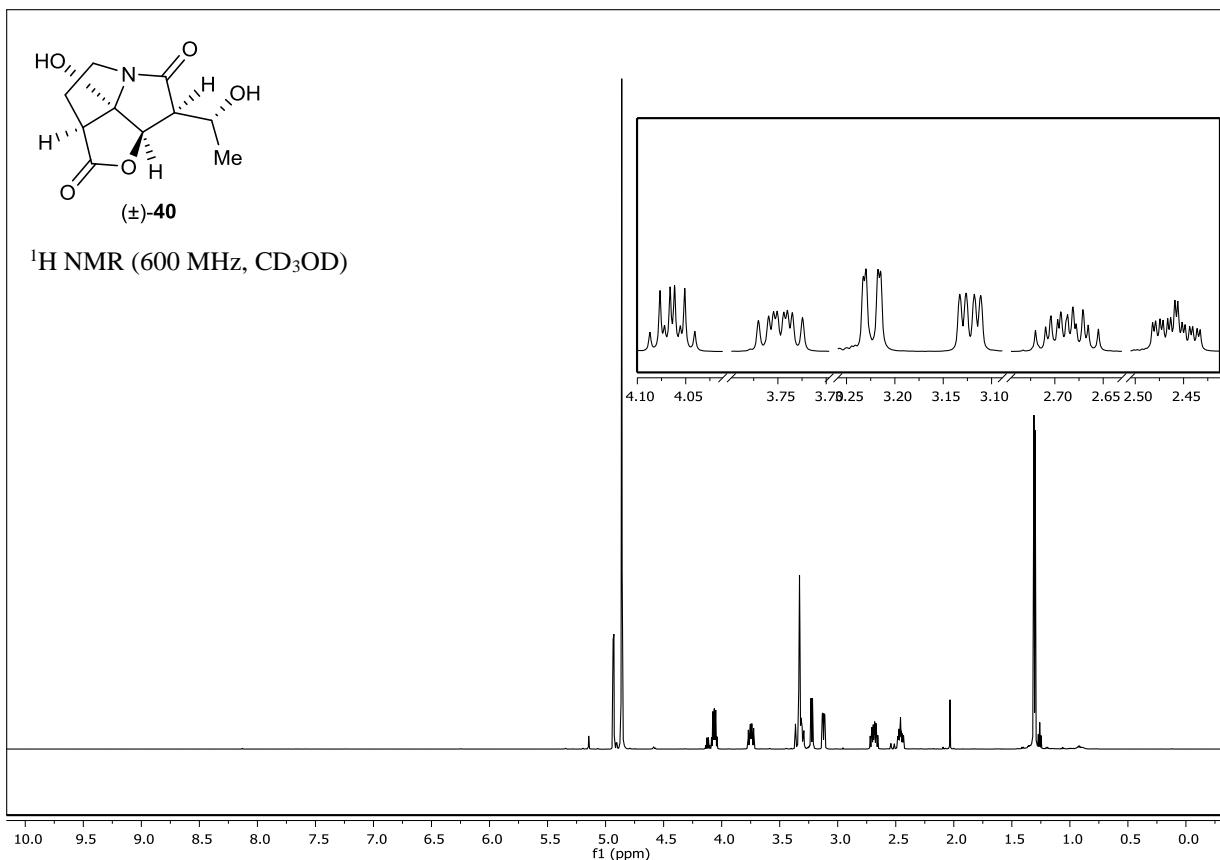


^{13}C NMR (151 MHz, CDCl_3)

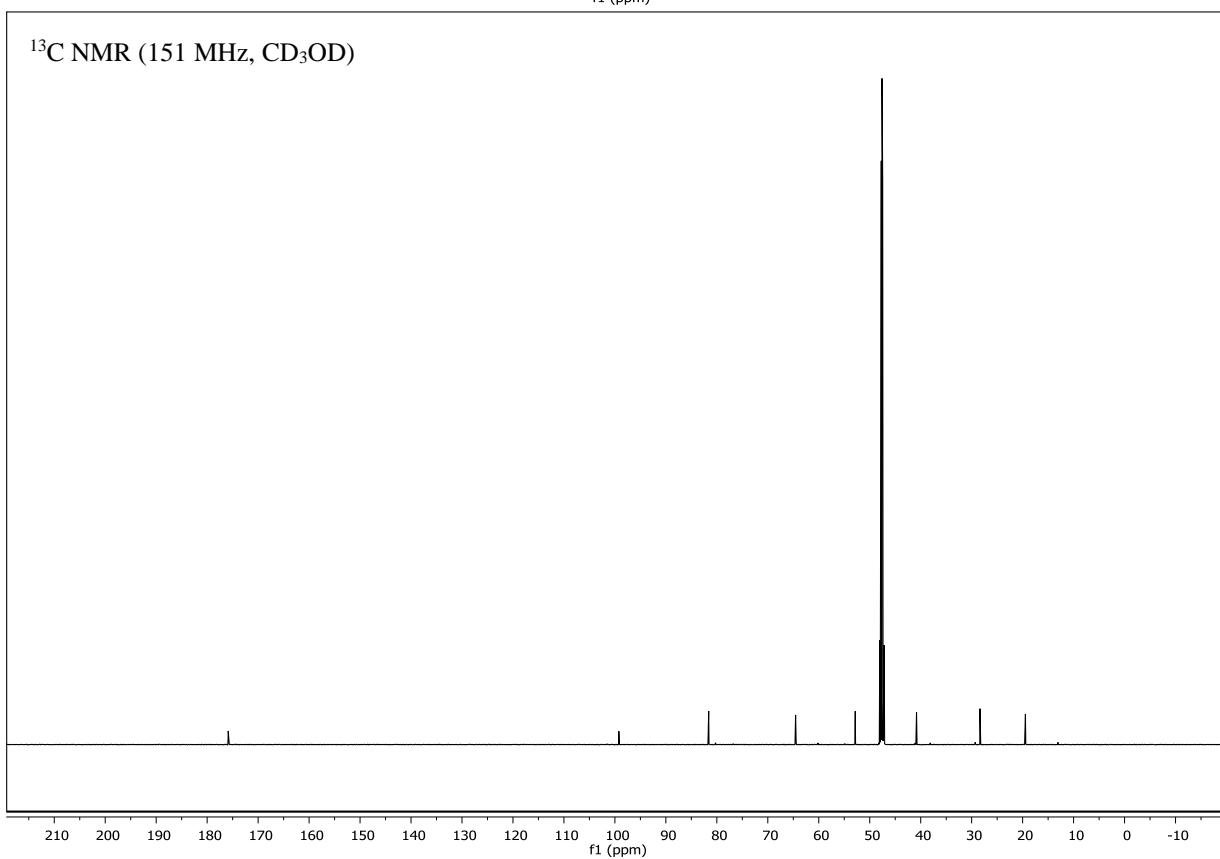


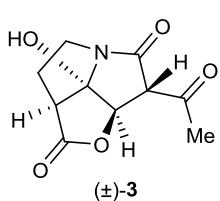


^1H NMR (600 MHz, CD_3OD)

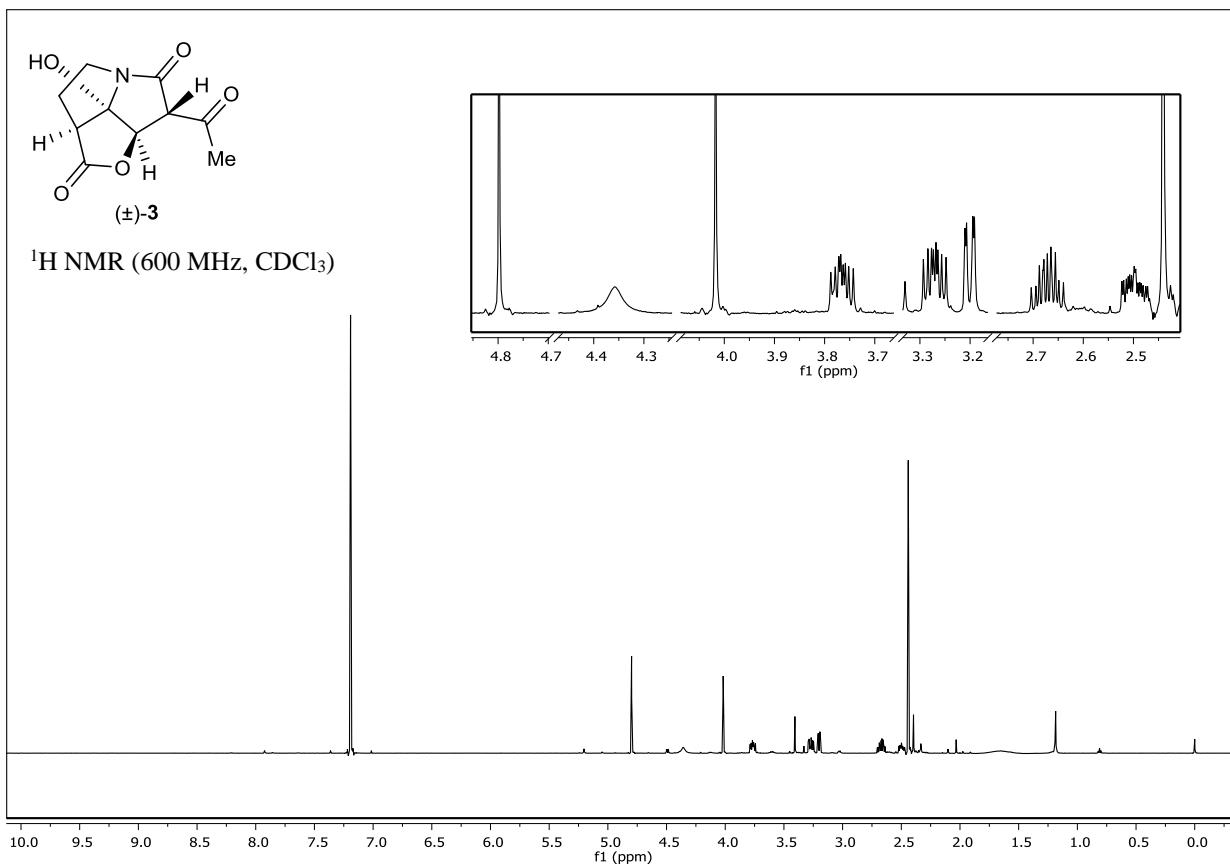


^{13}C NMR (151 MHz, CD_3OD)

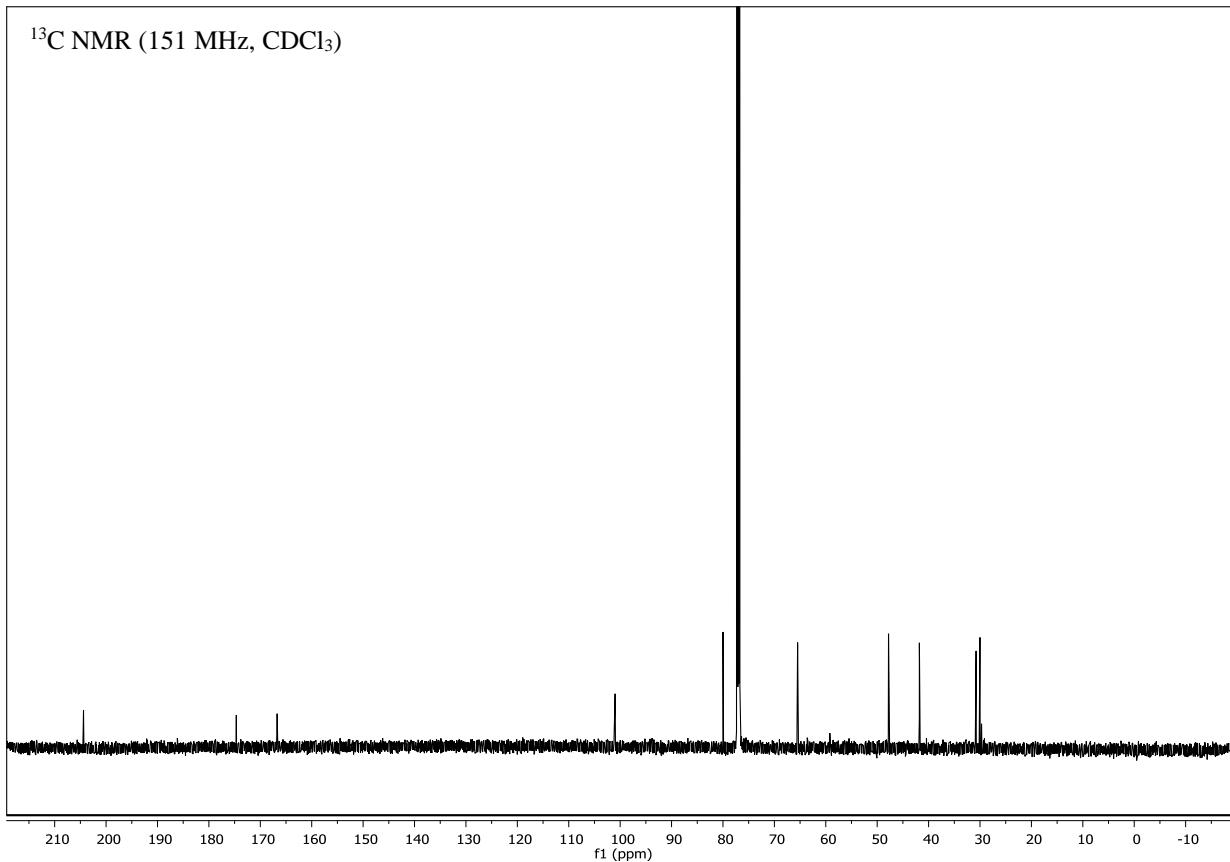


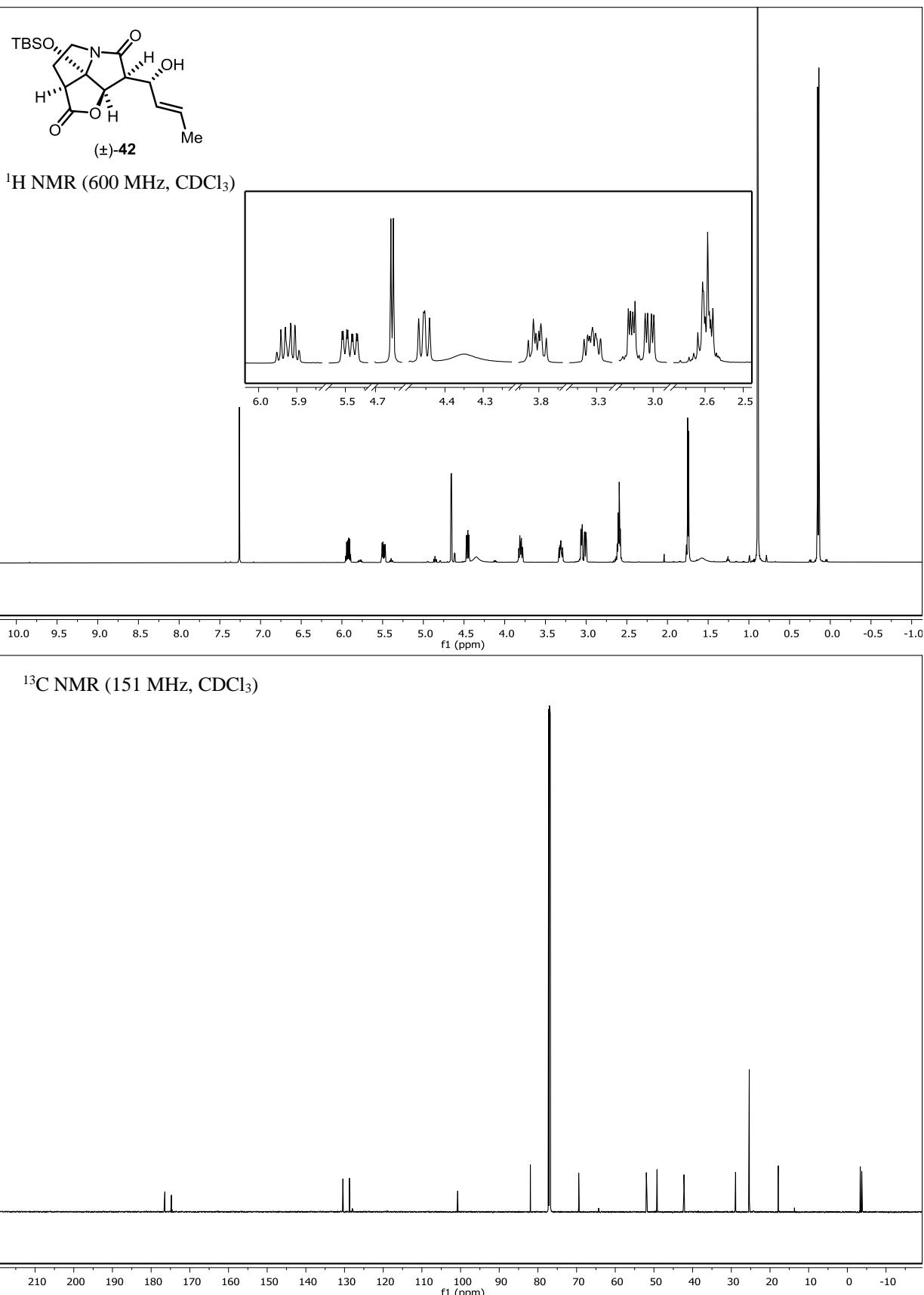


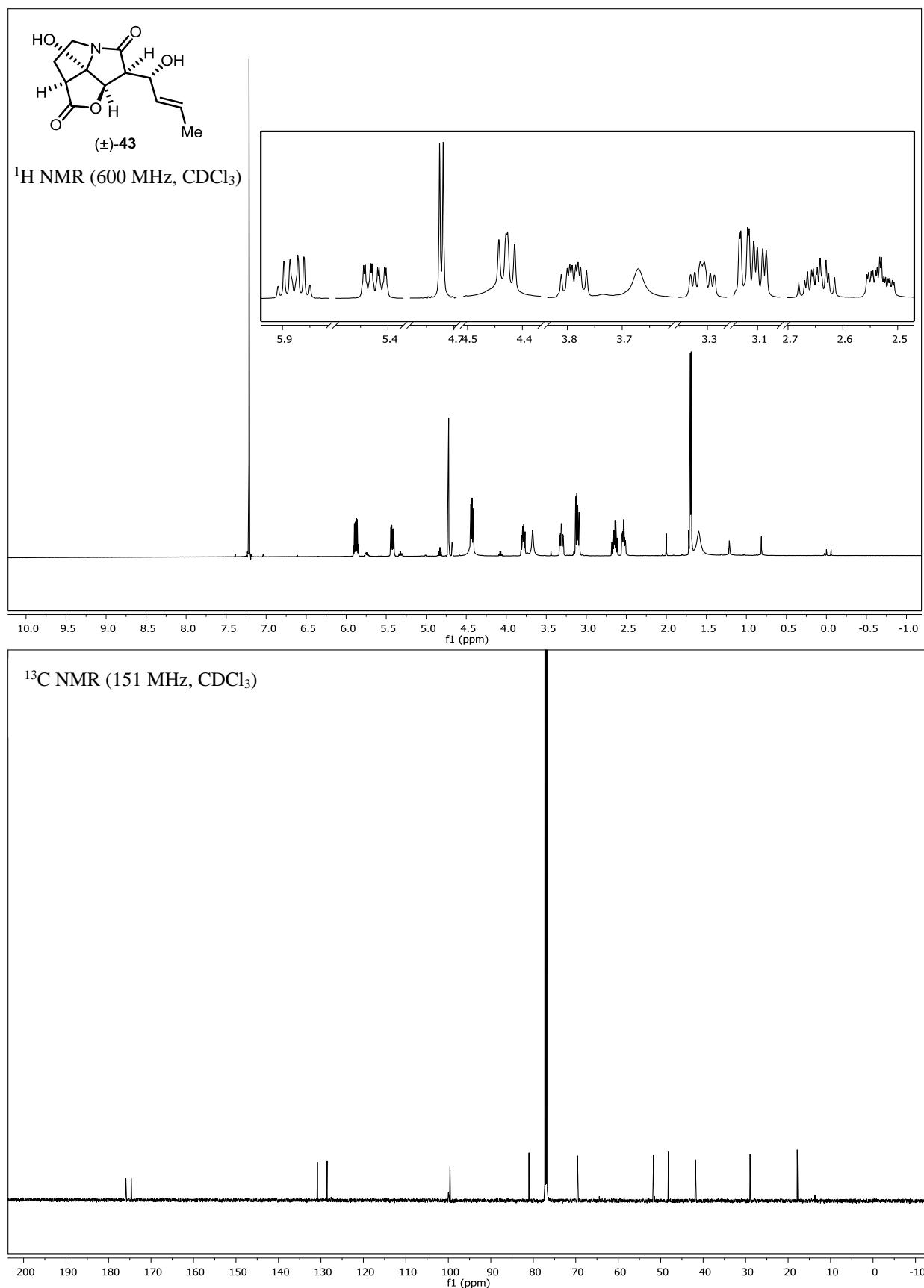
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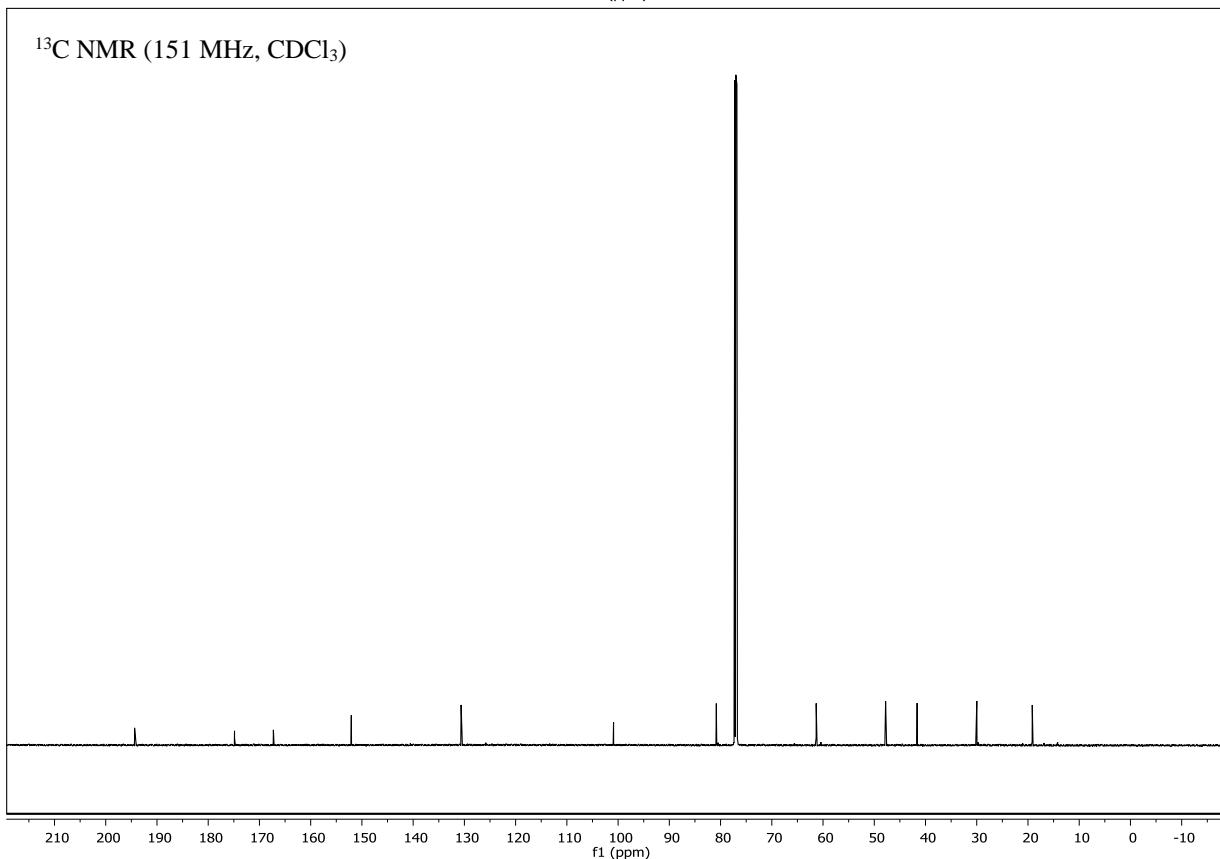
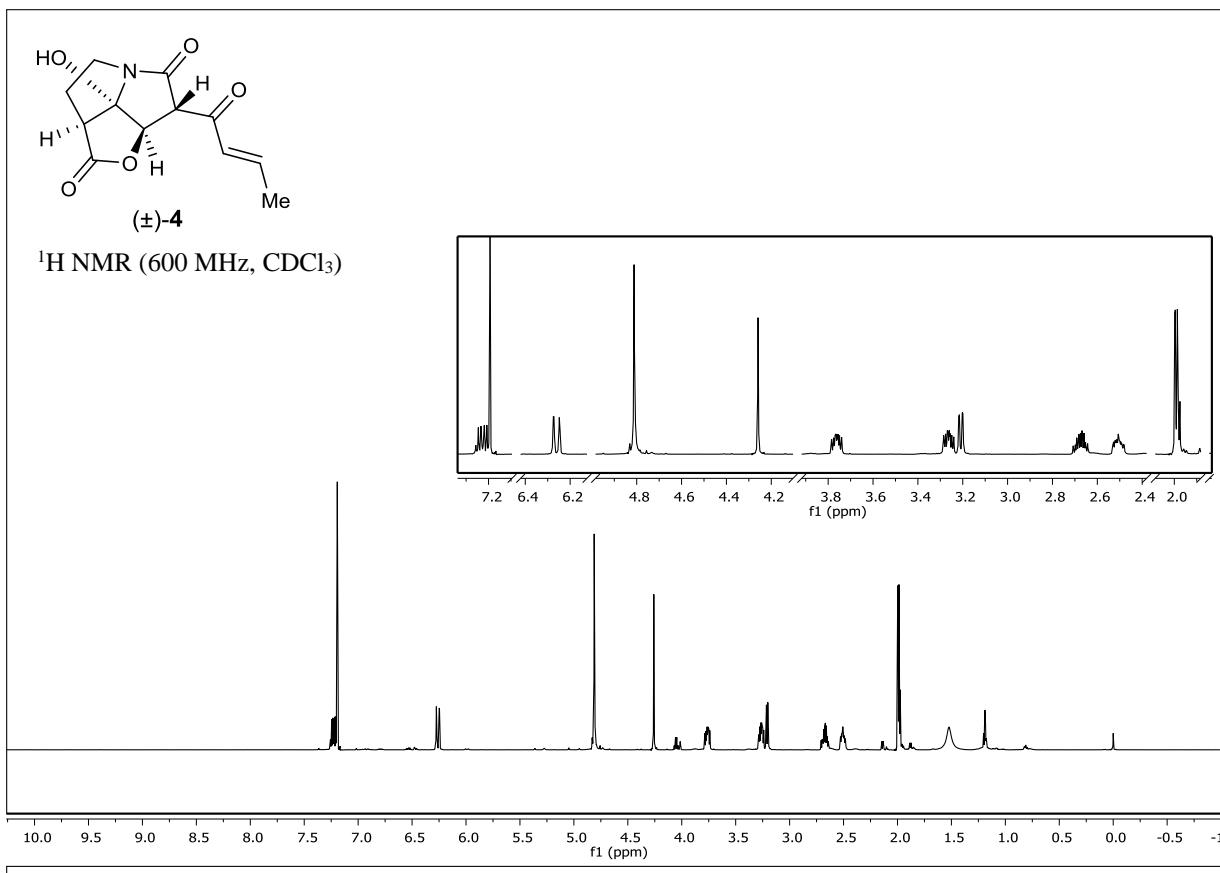


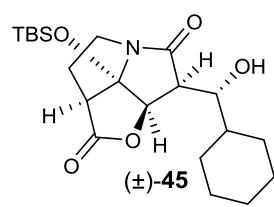
^{13}C NMR (151 MHz, CDCl_3)



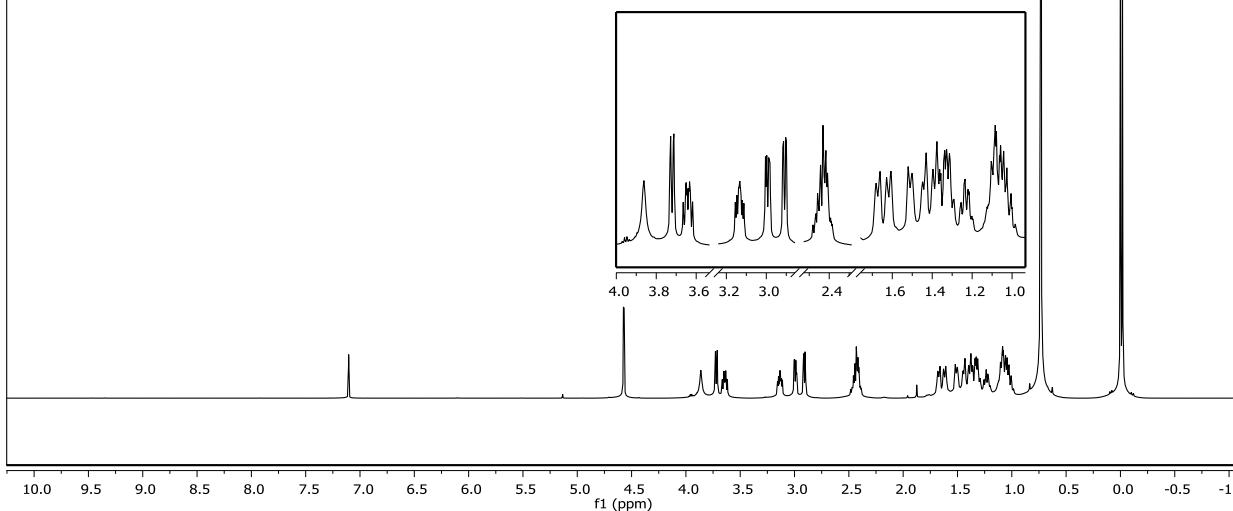




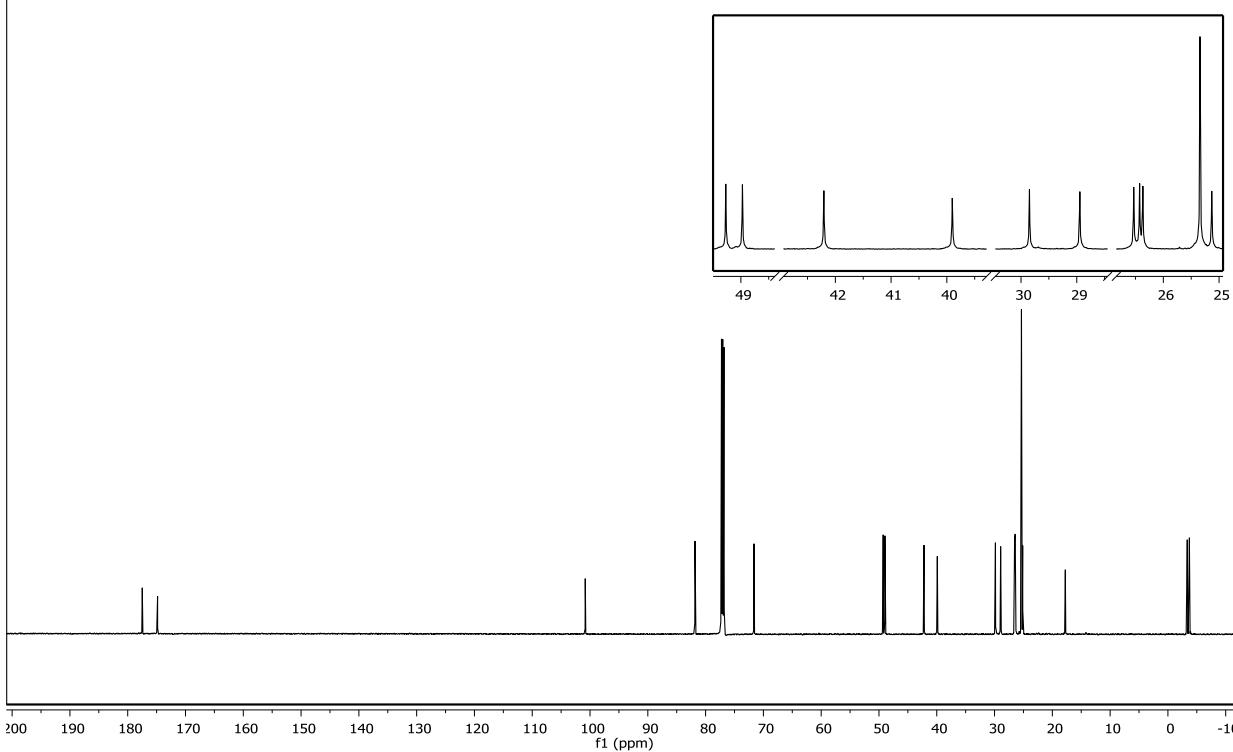


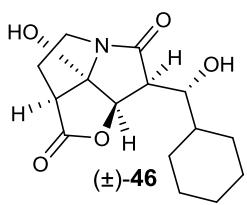


^1H NMR (600 MHz, CDCl_3)

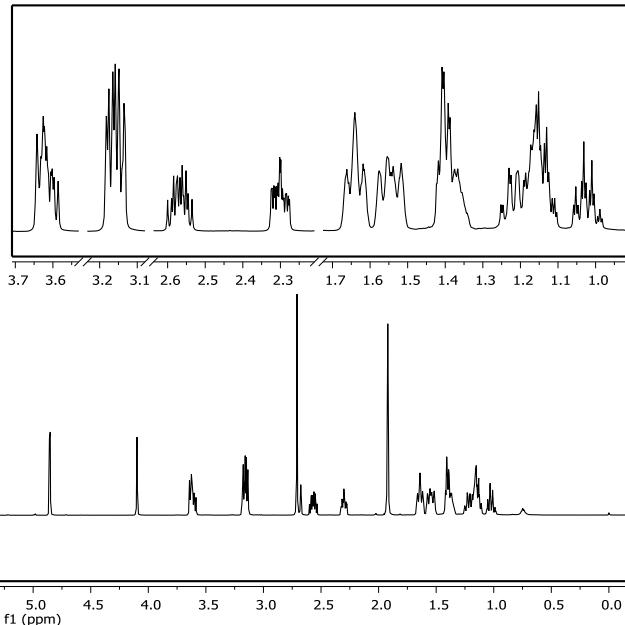


^{13}C NMR (151 MHz, CDCl_3)



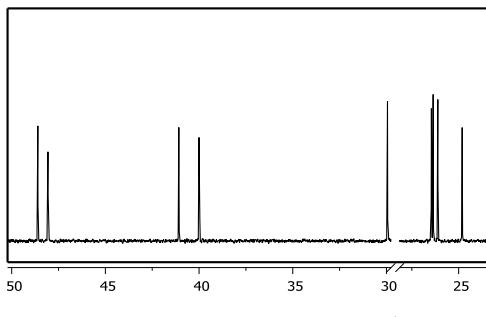


^1H NMR (600 MHz, acetone- d_6)

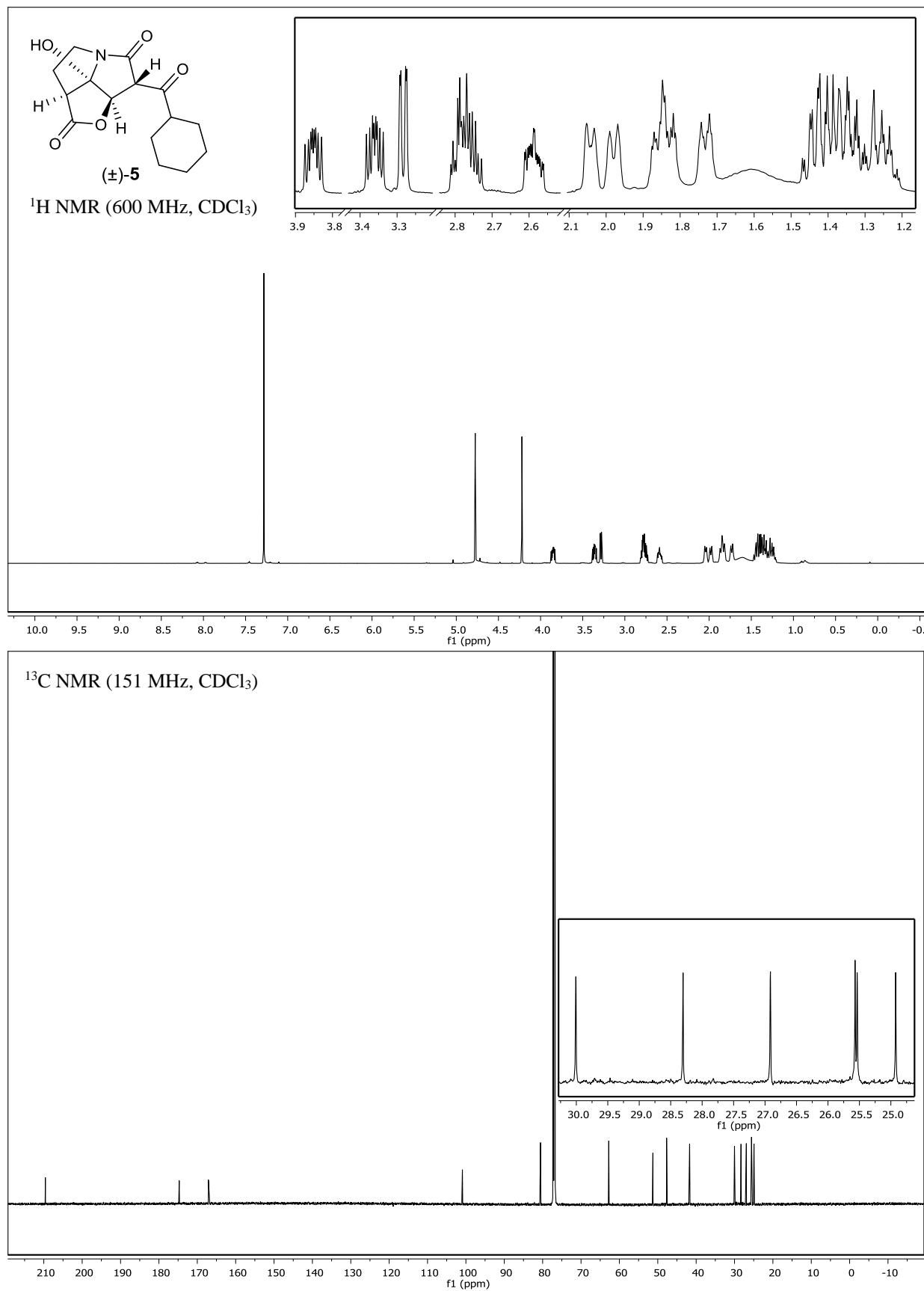


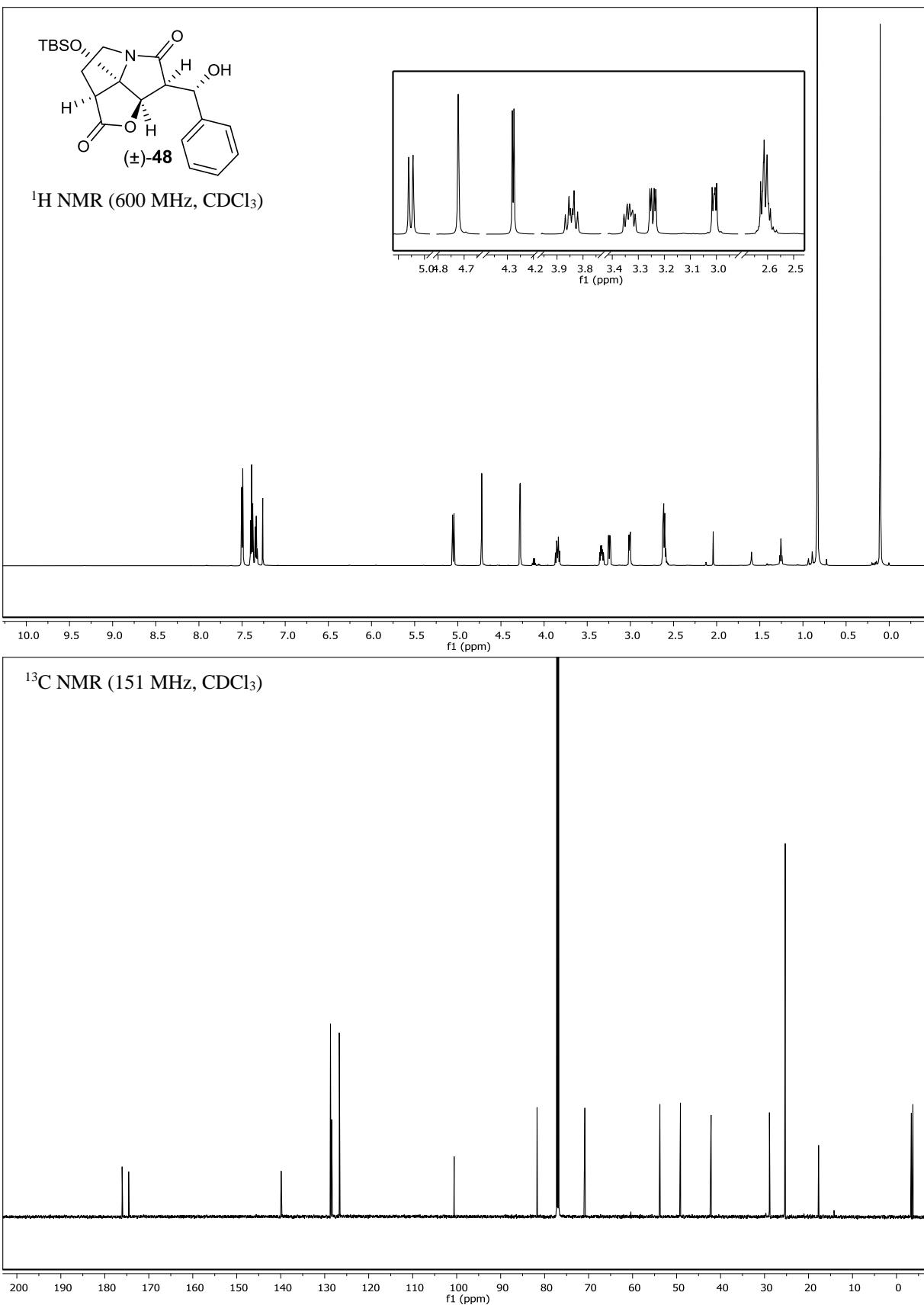
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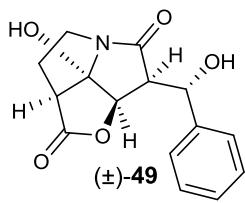
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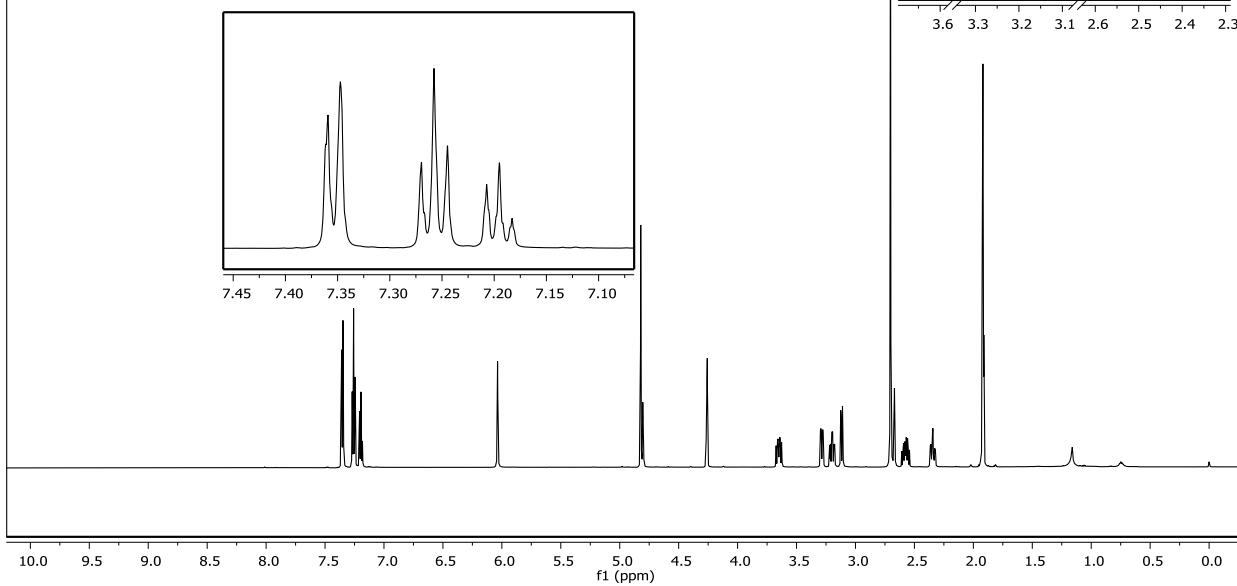
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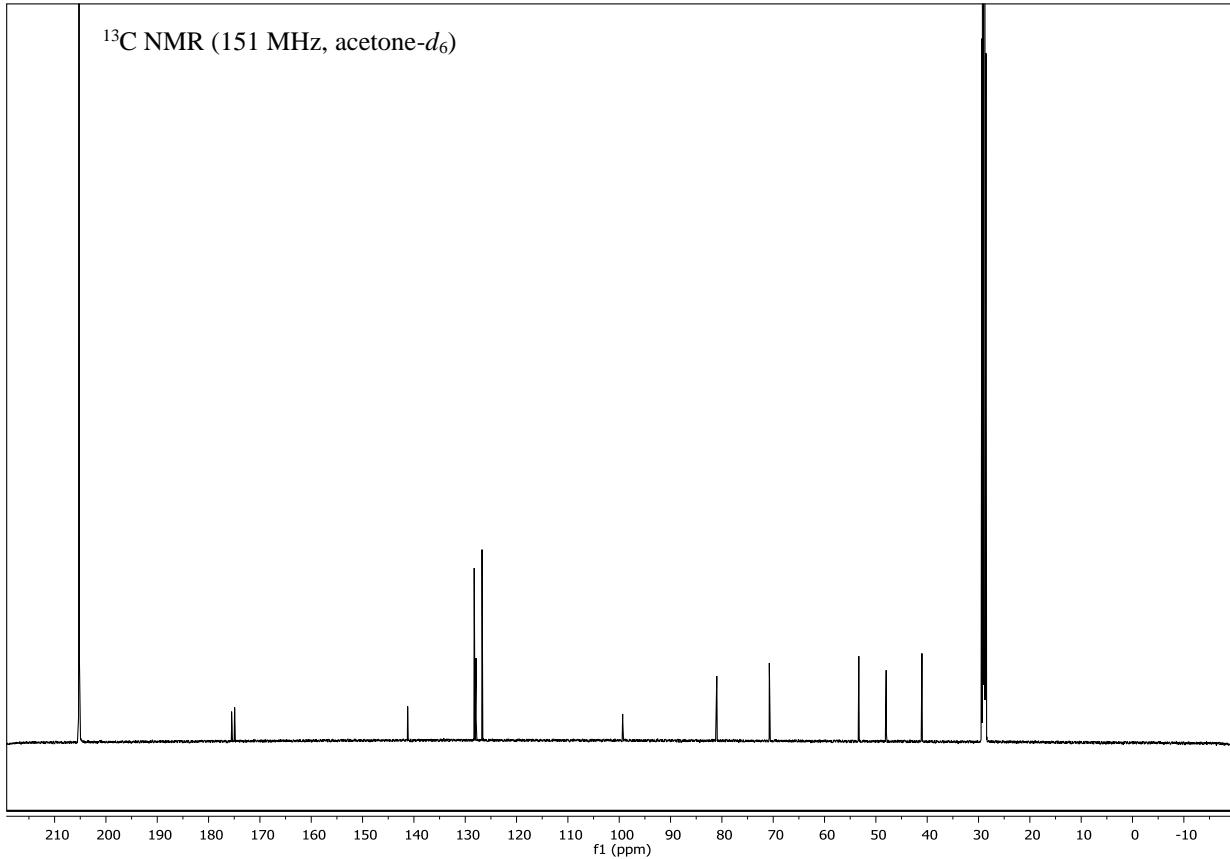


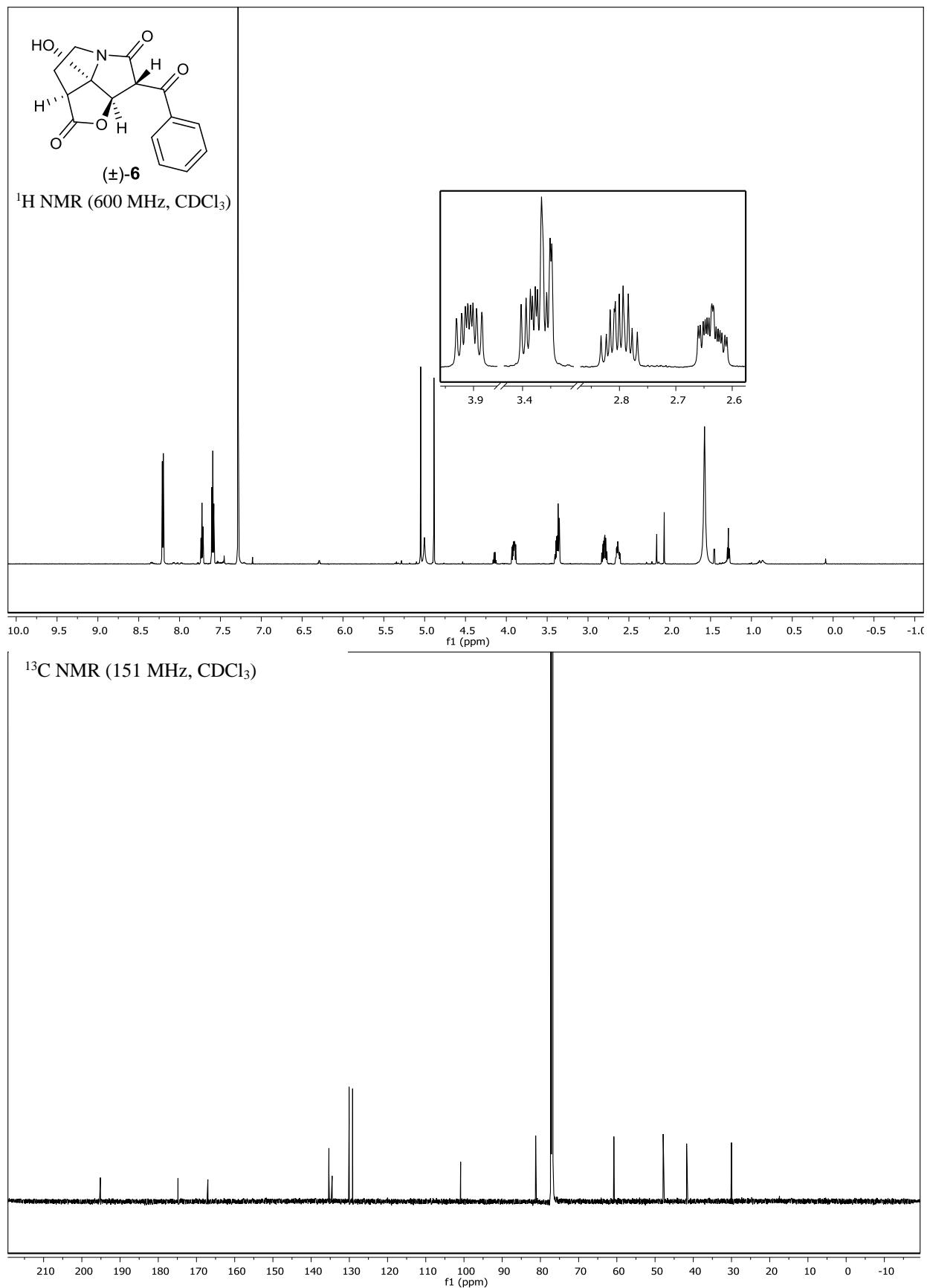


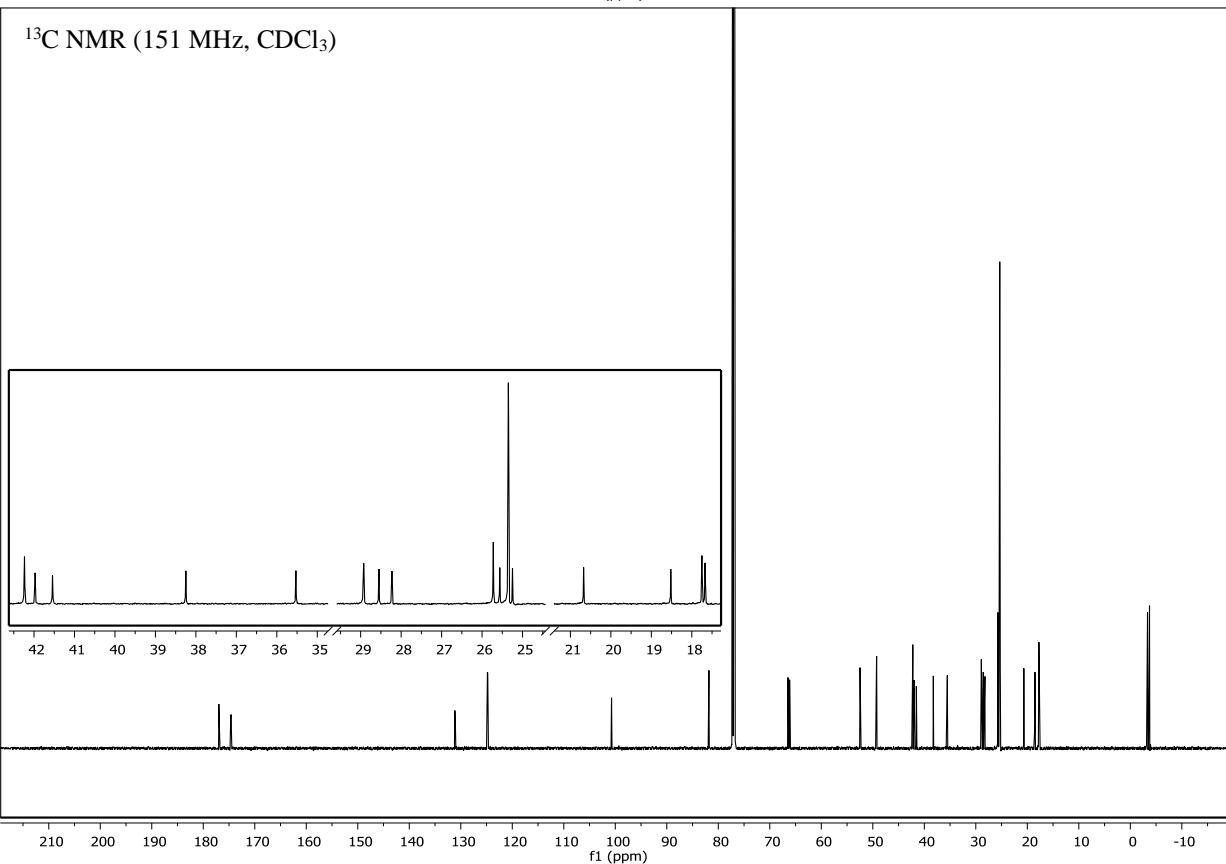
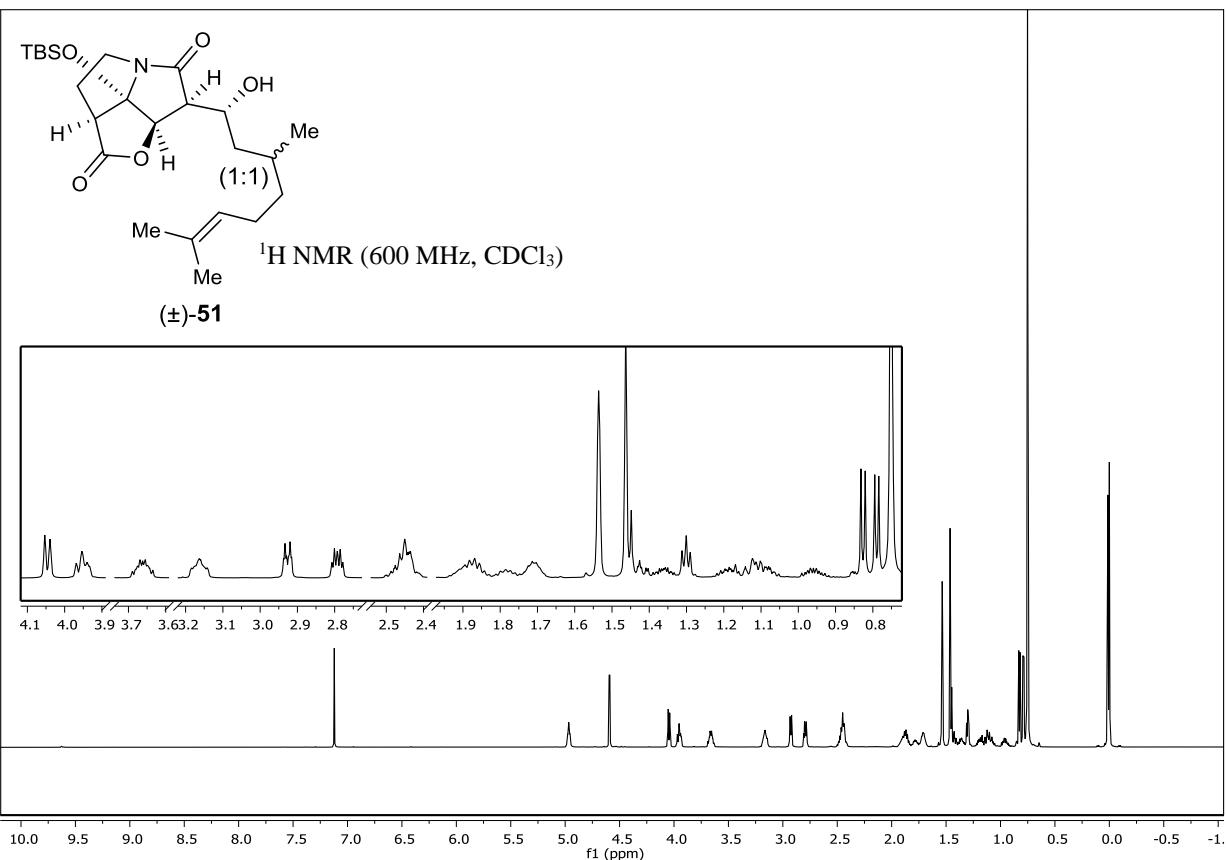
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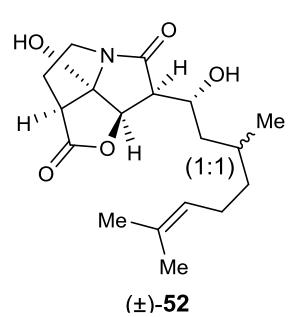


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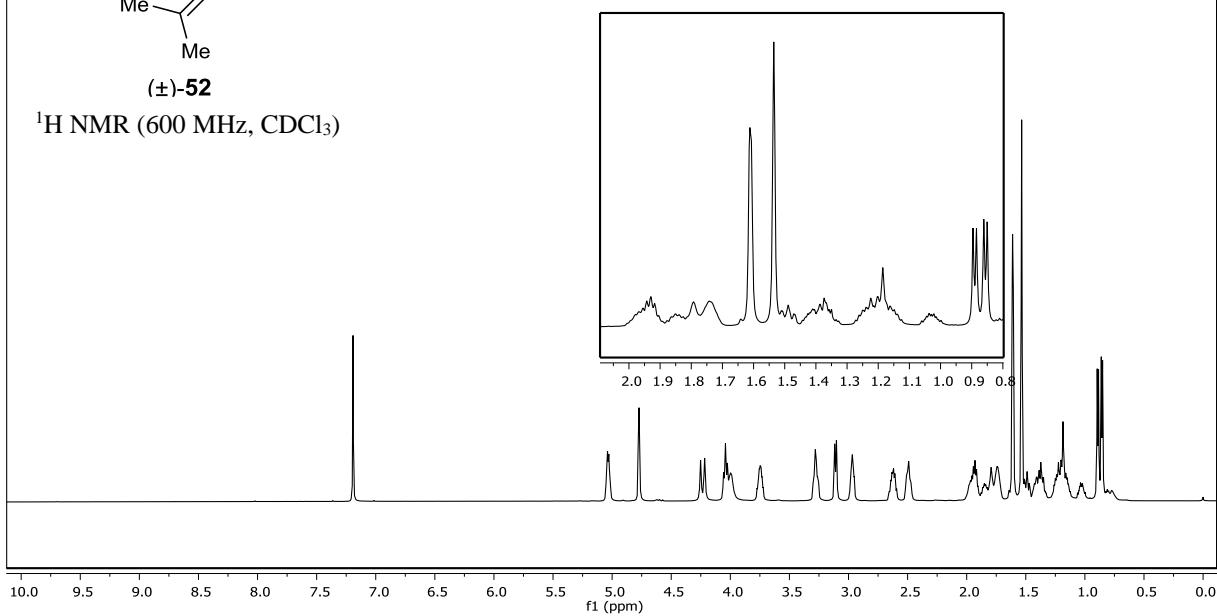




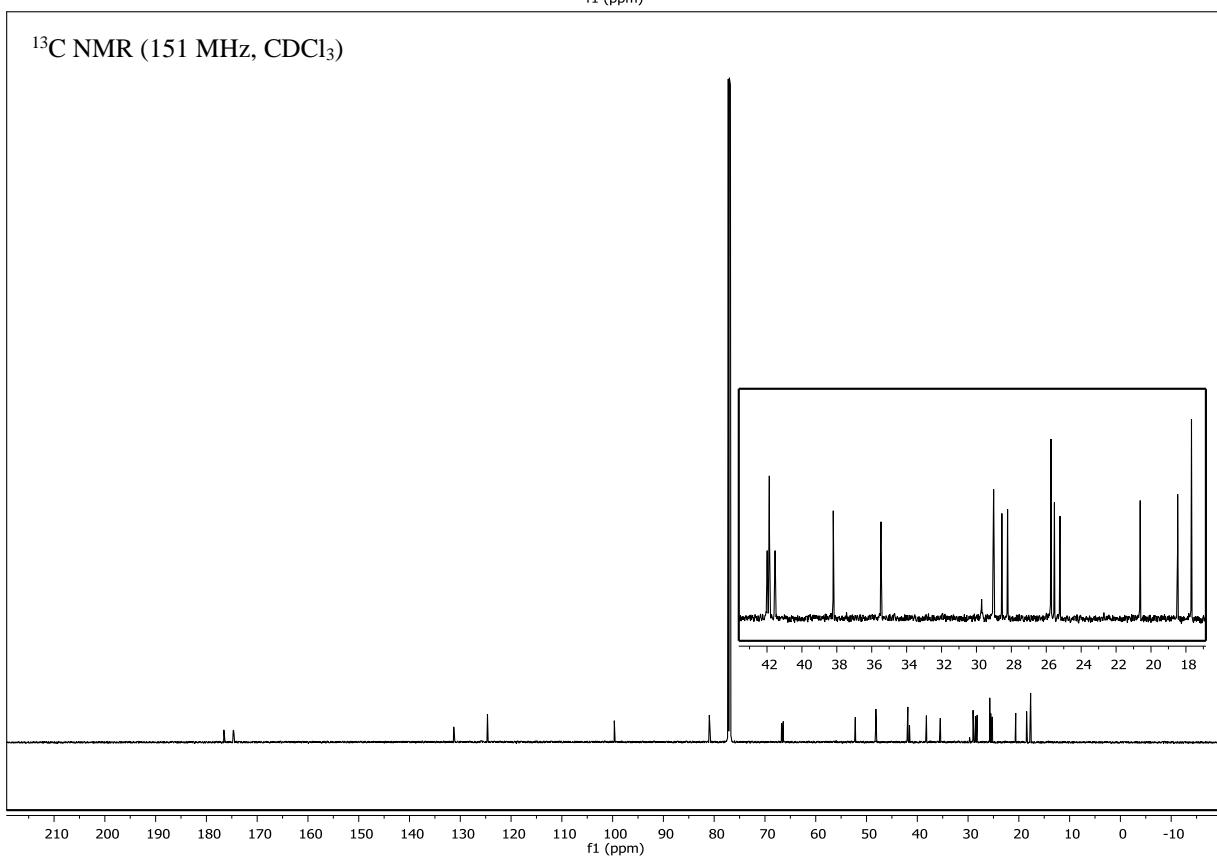


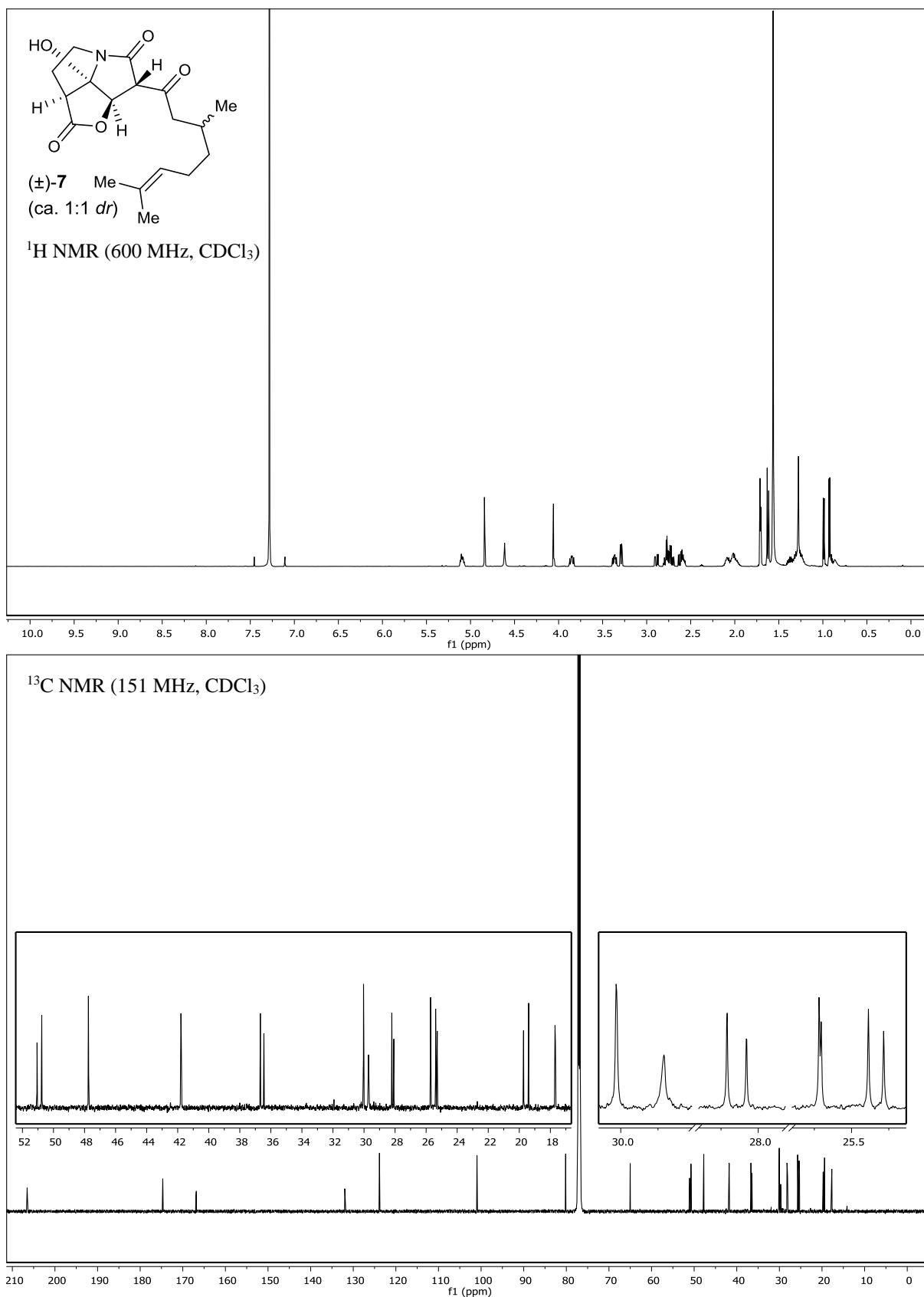


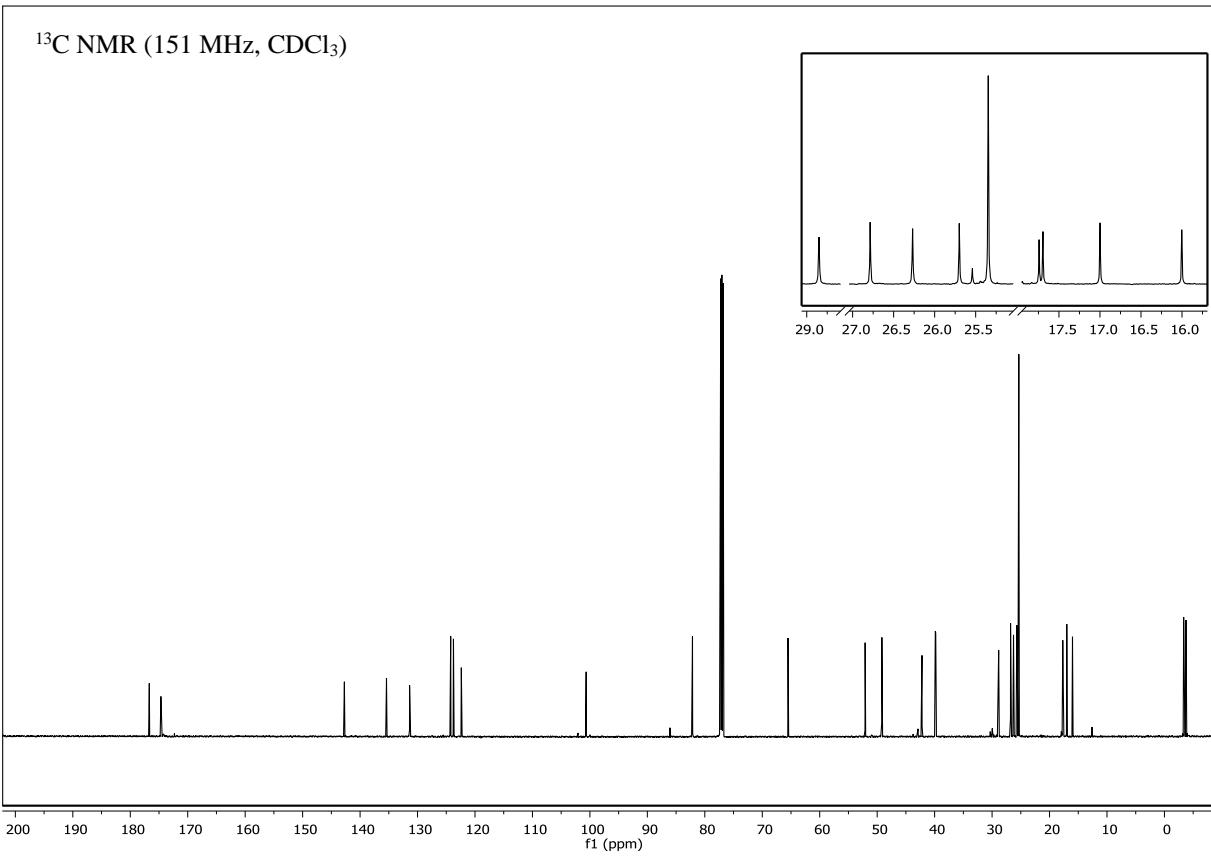
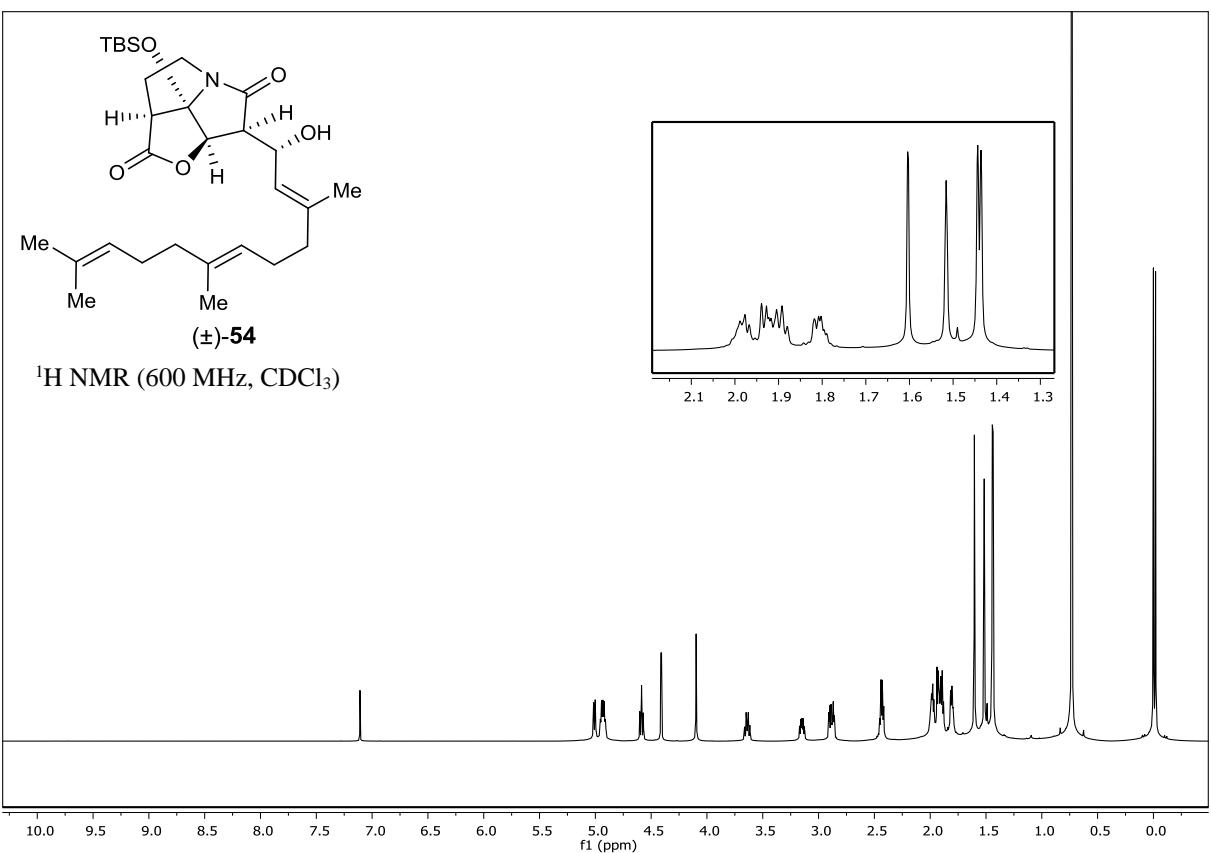
^1H NMR (600 MHz, CDCl_3)

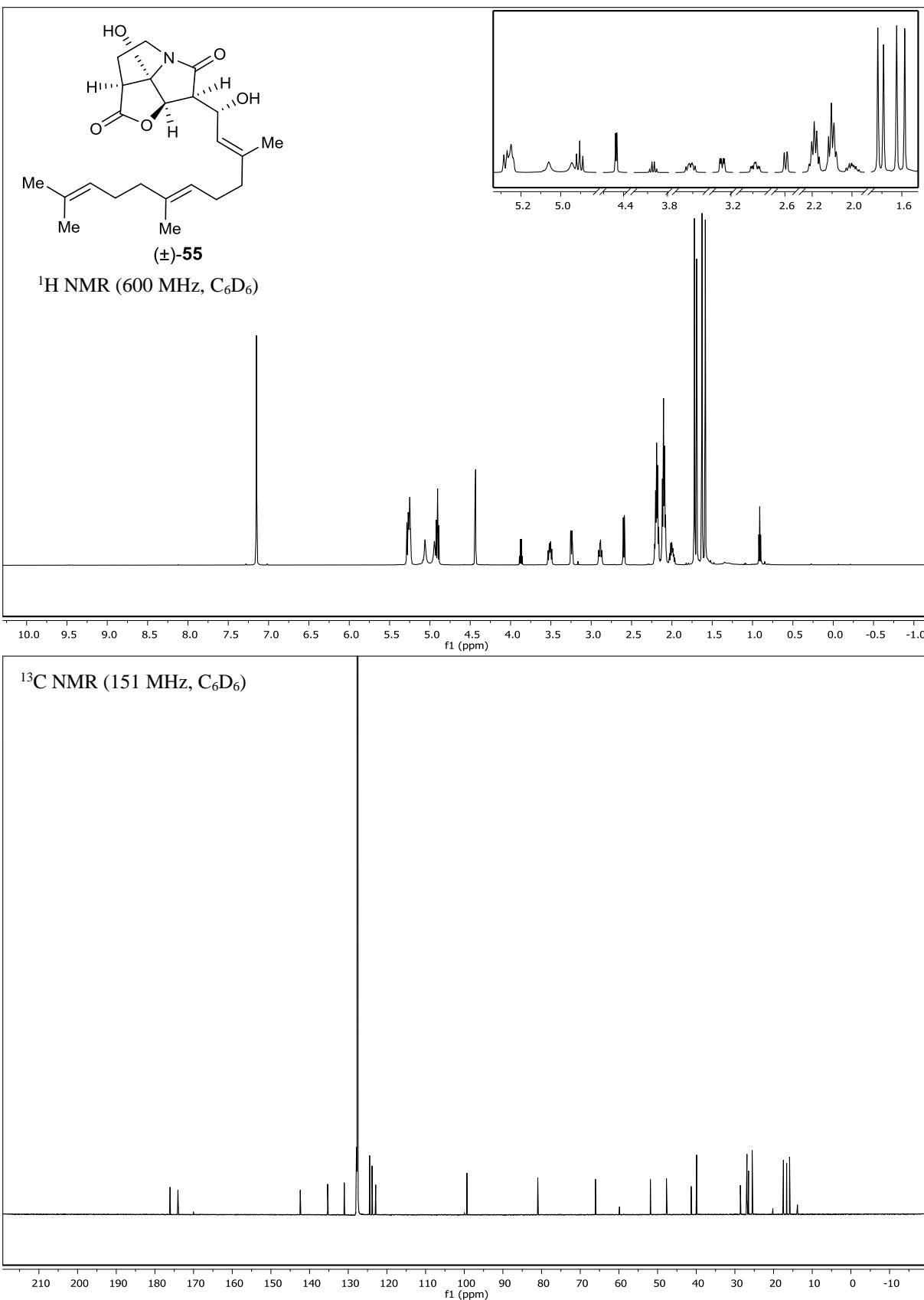


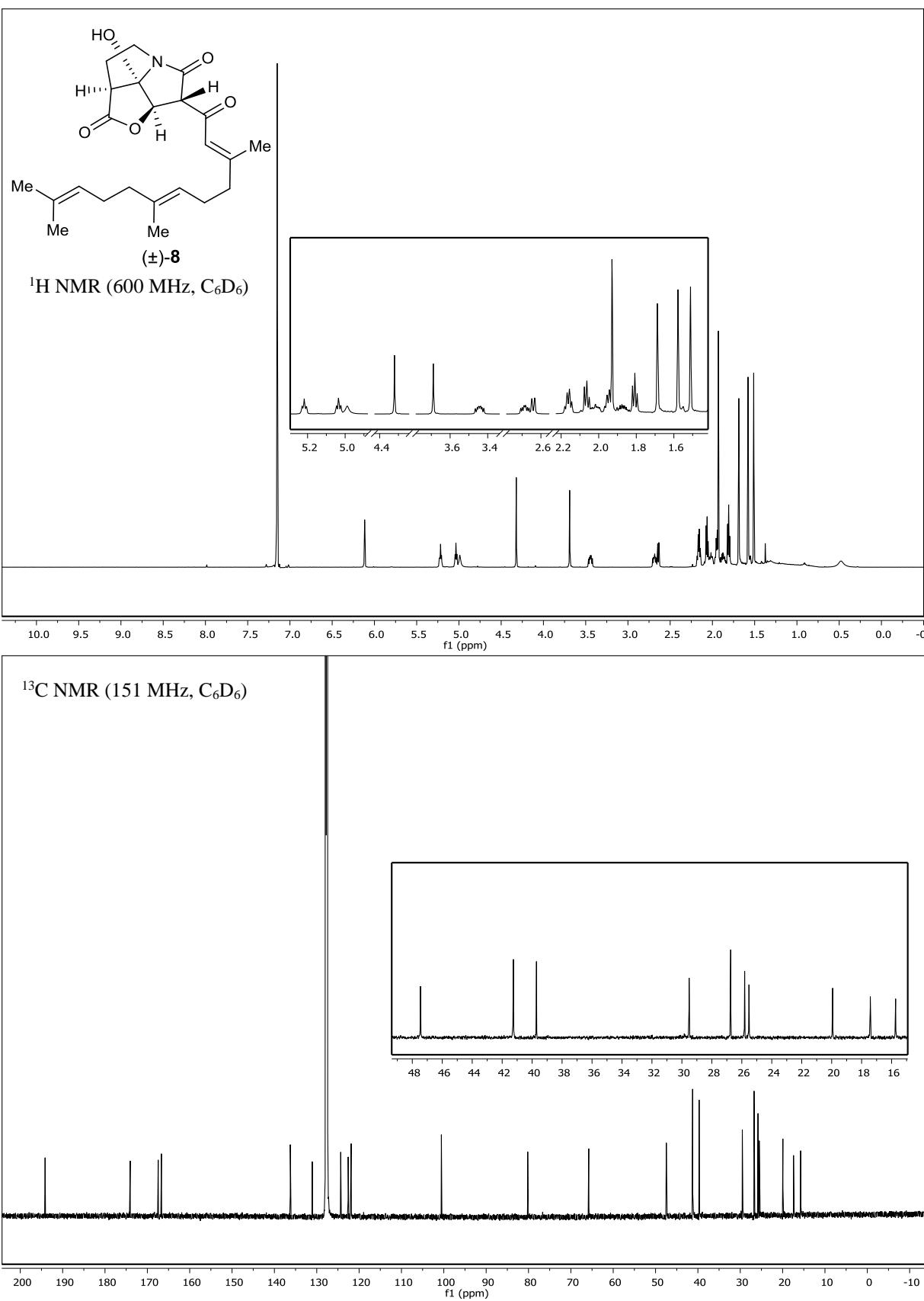
^{13}C NMR (151 MHz, CDCl_3)

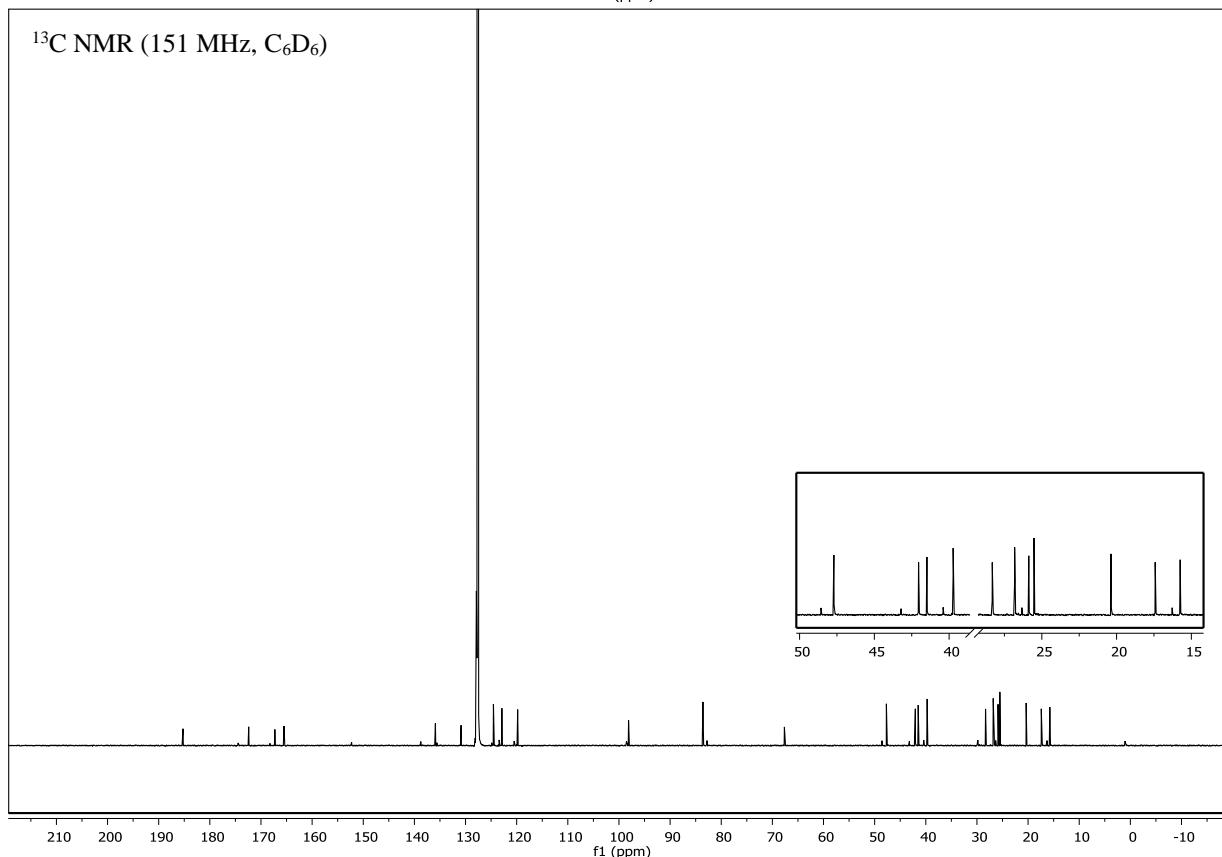
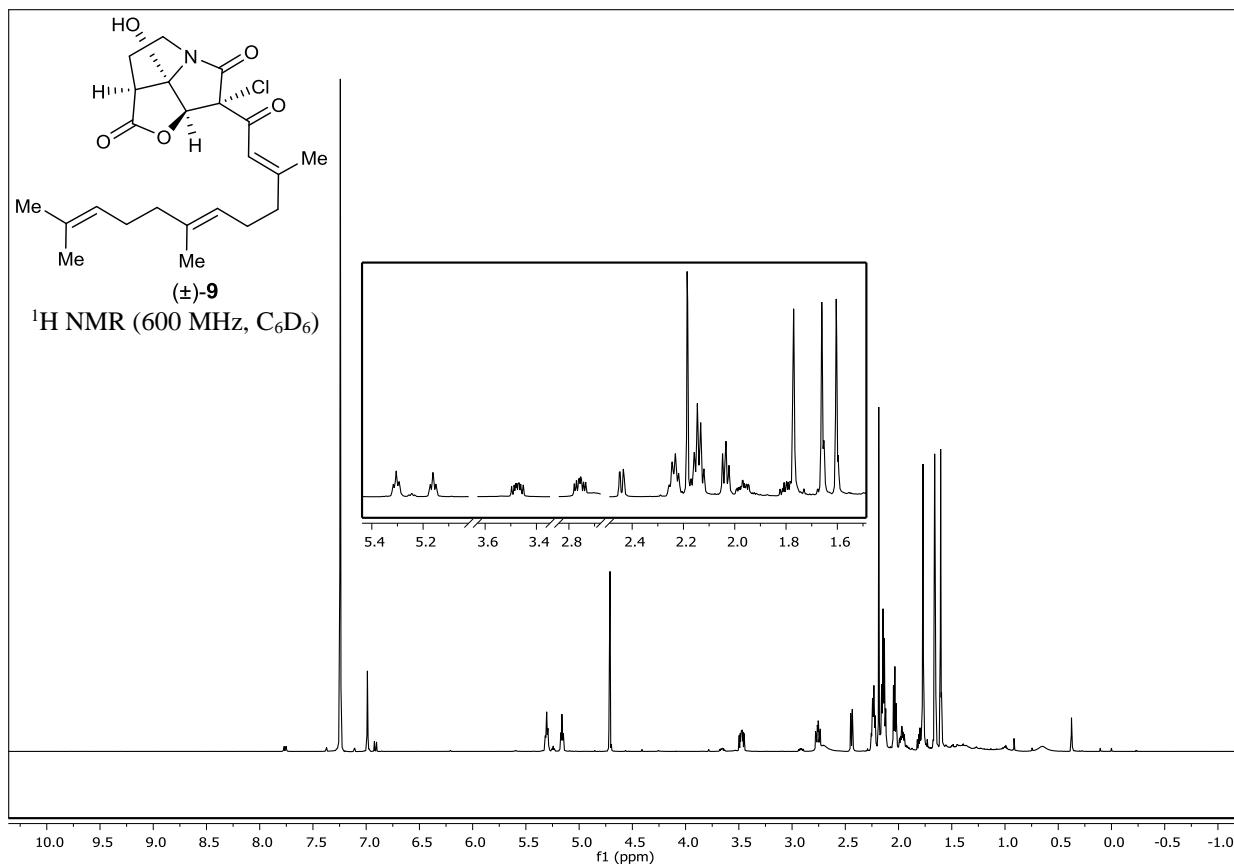


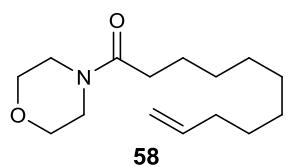






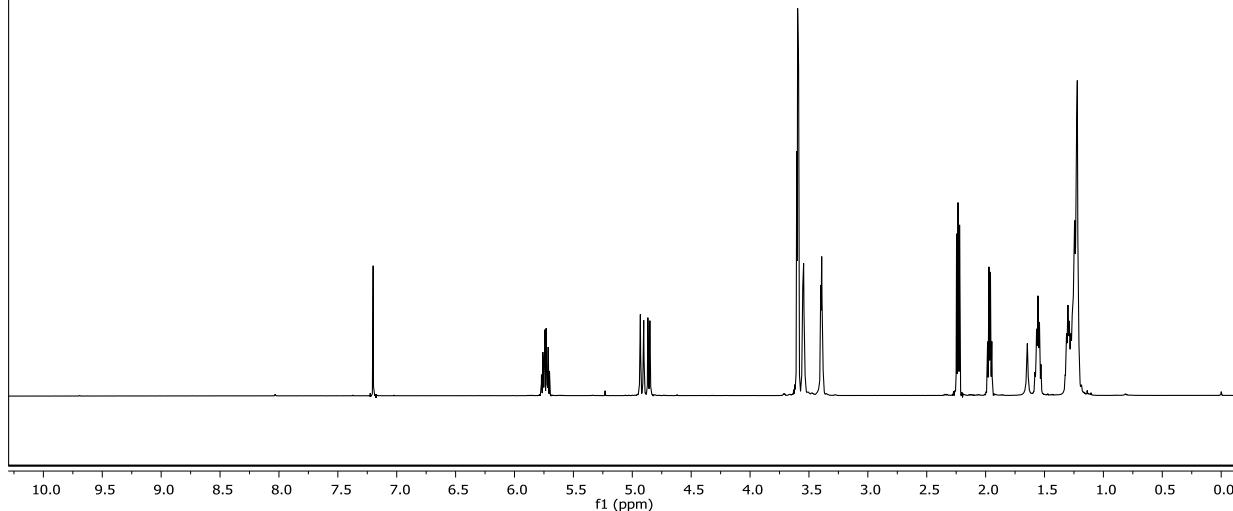




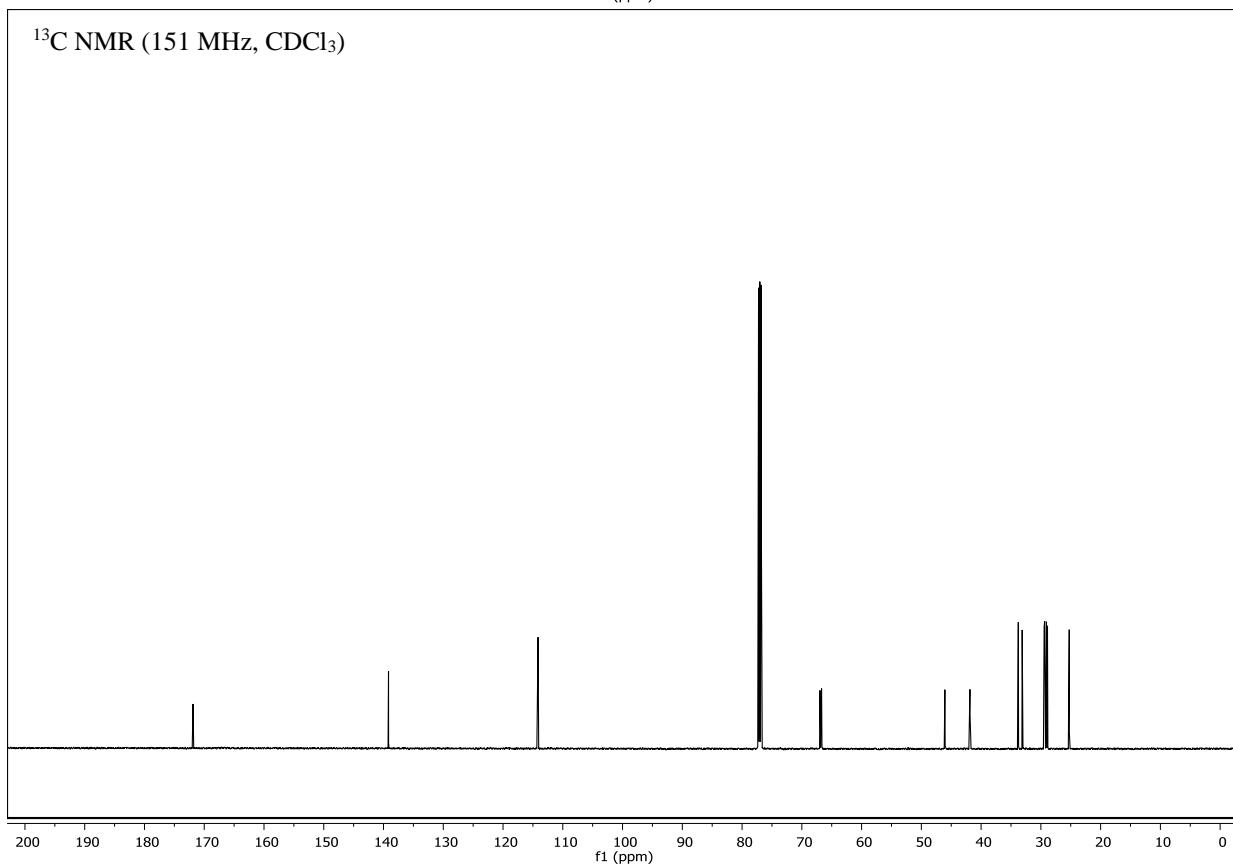


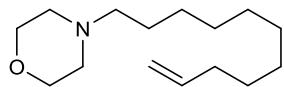
58

¹H NMR (600 MHz, CDCl₃)



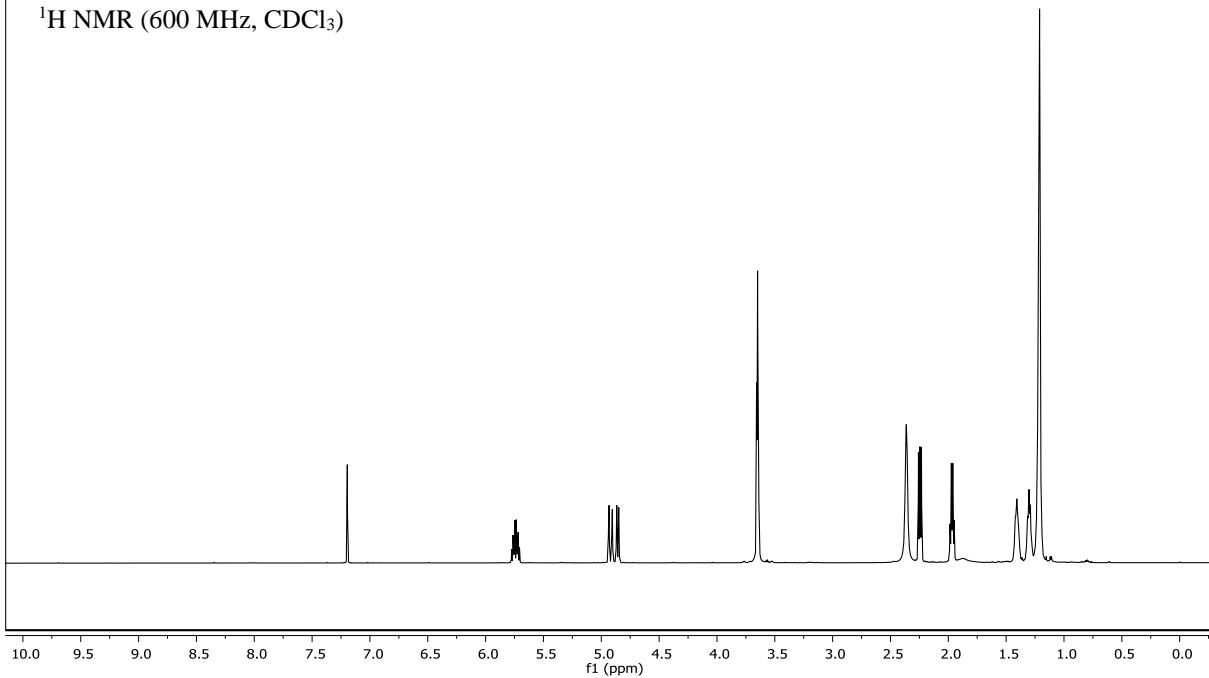
¹³C NMR (151 MHz, CDCl₃)



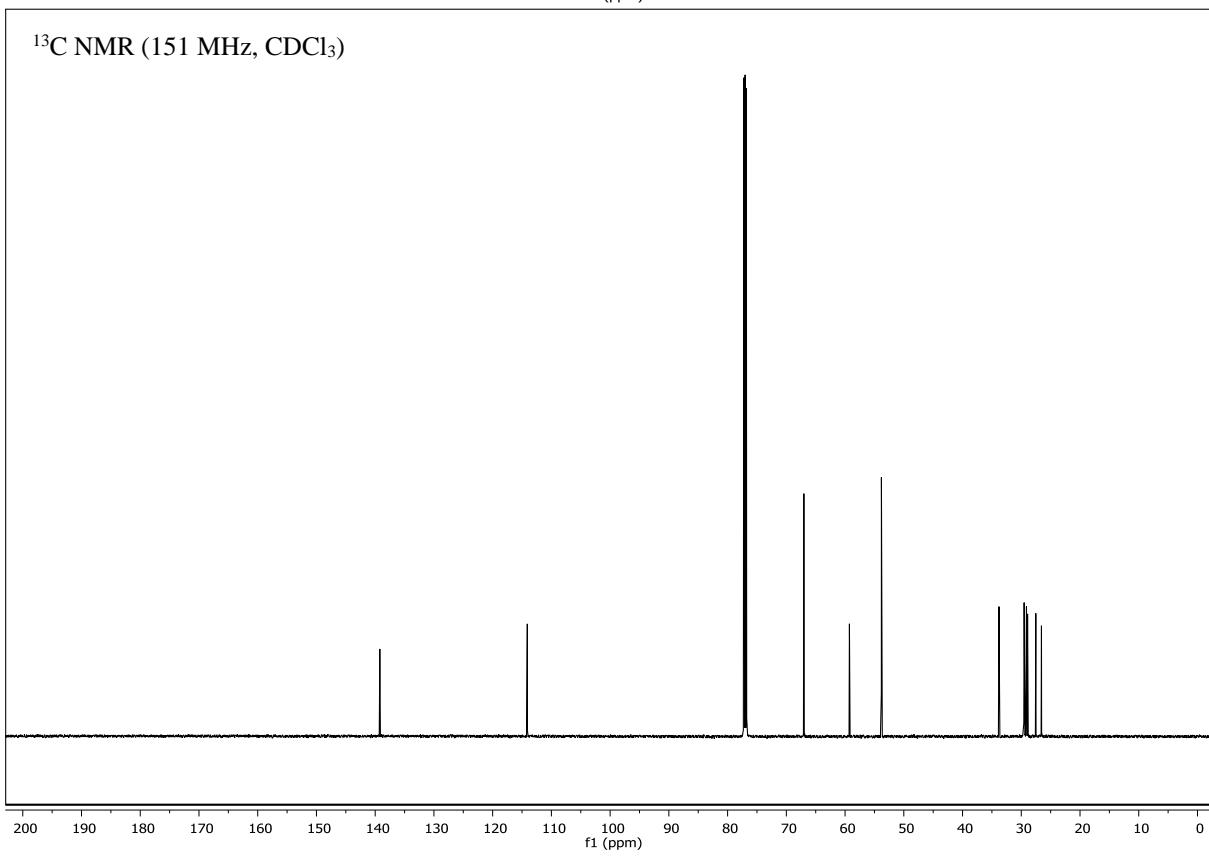


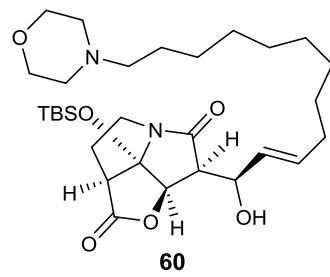
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¹H NMR (600 MHz, CDCl₃)

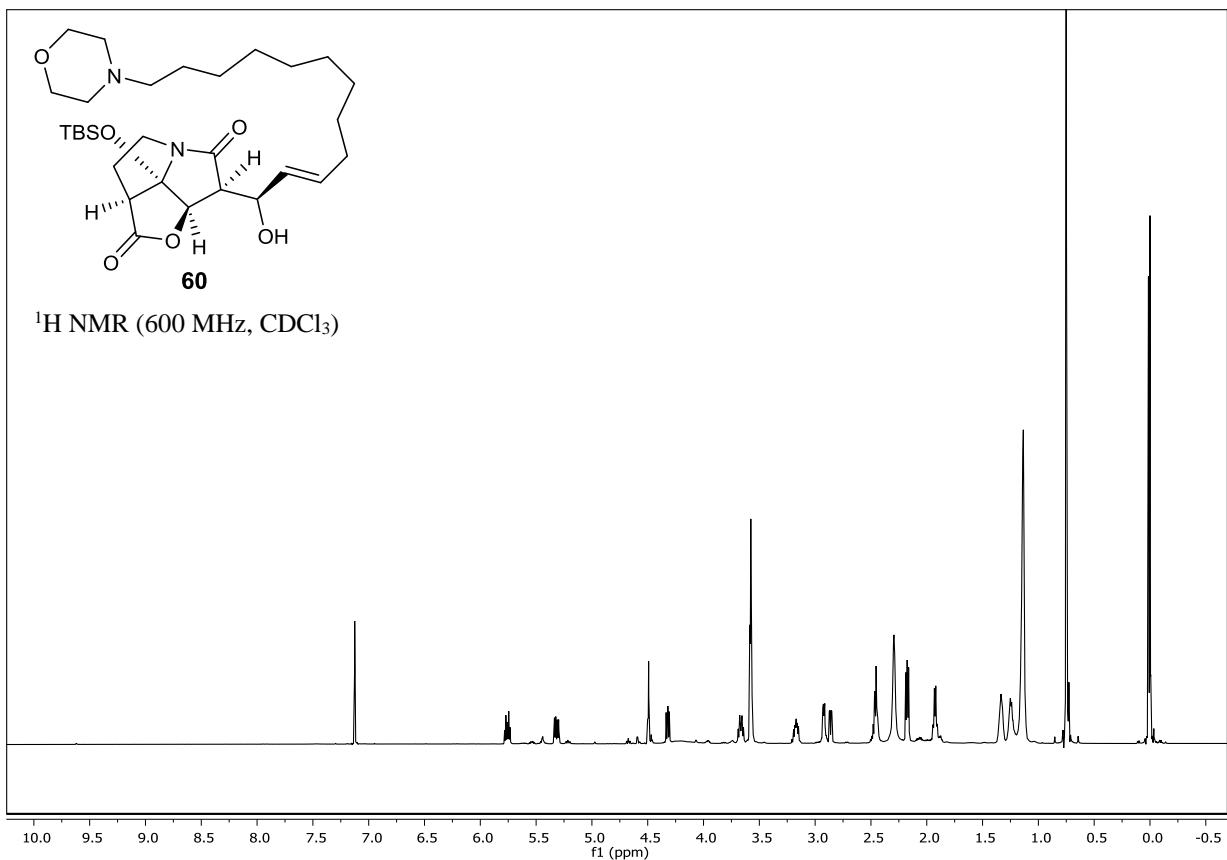


¹³C NMR (151 MHz, CDCl₃)

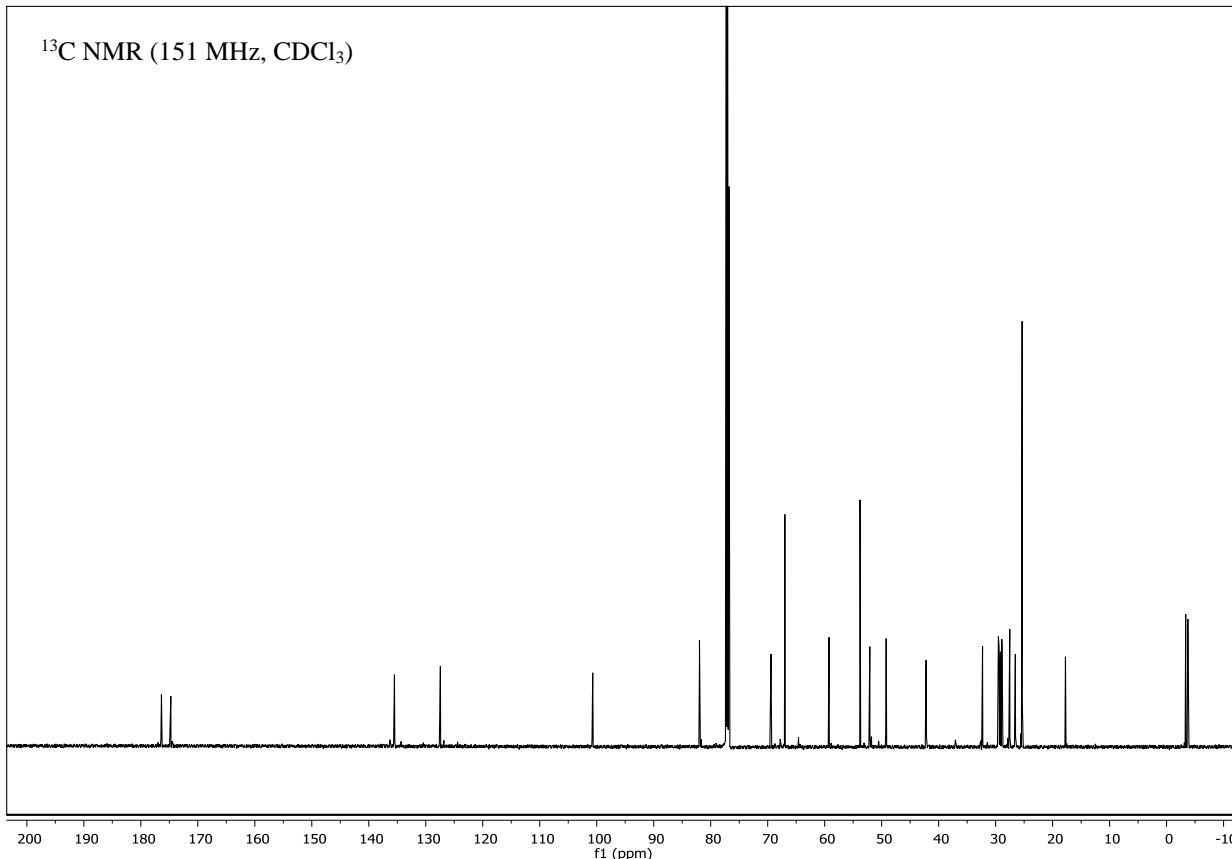


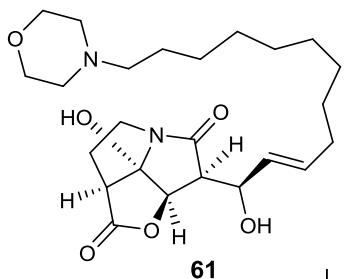


^1H NMR (600 MHz, CDCl_3)



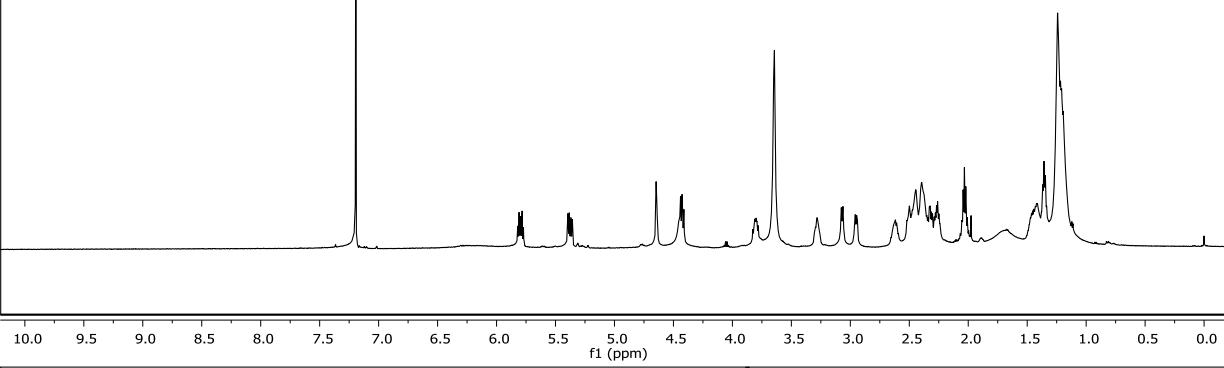
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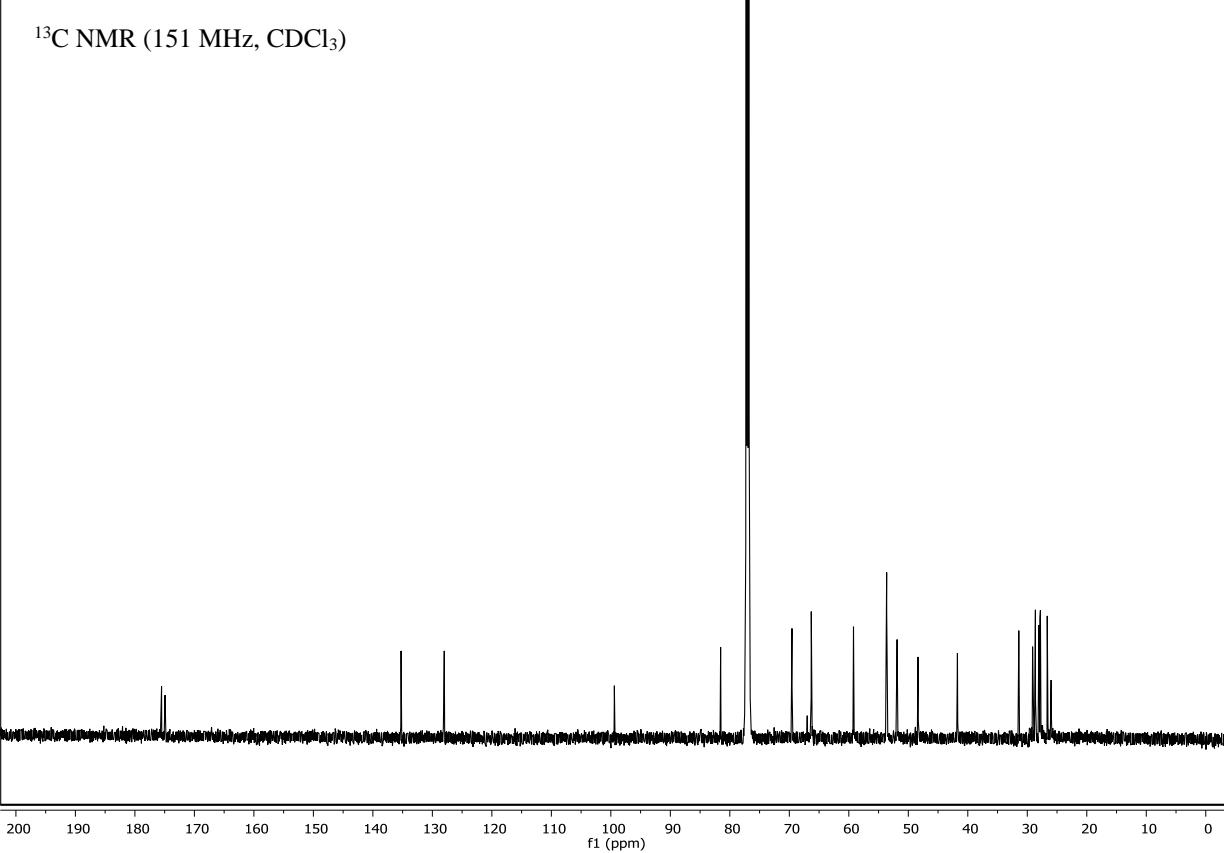


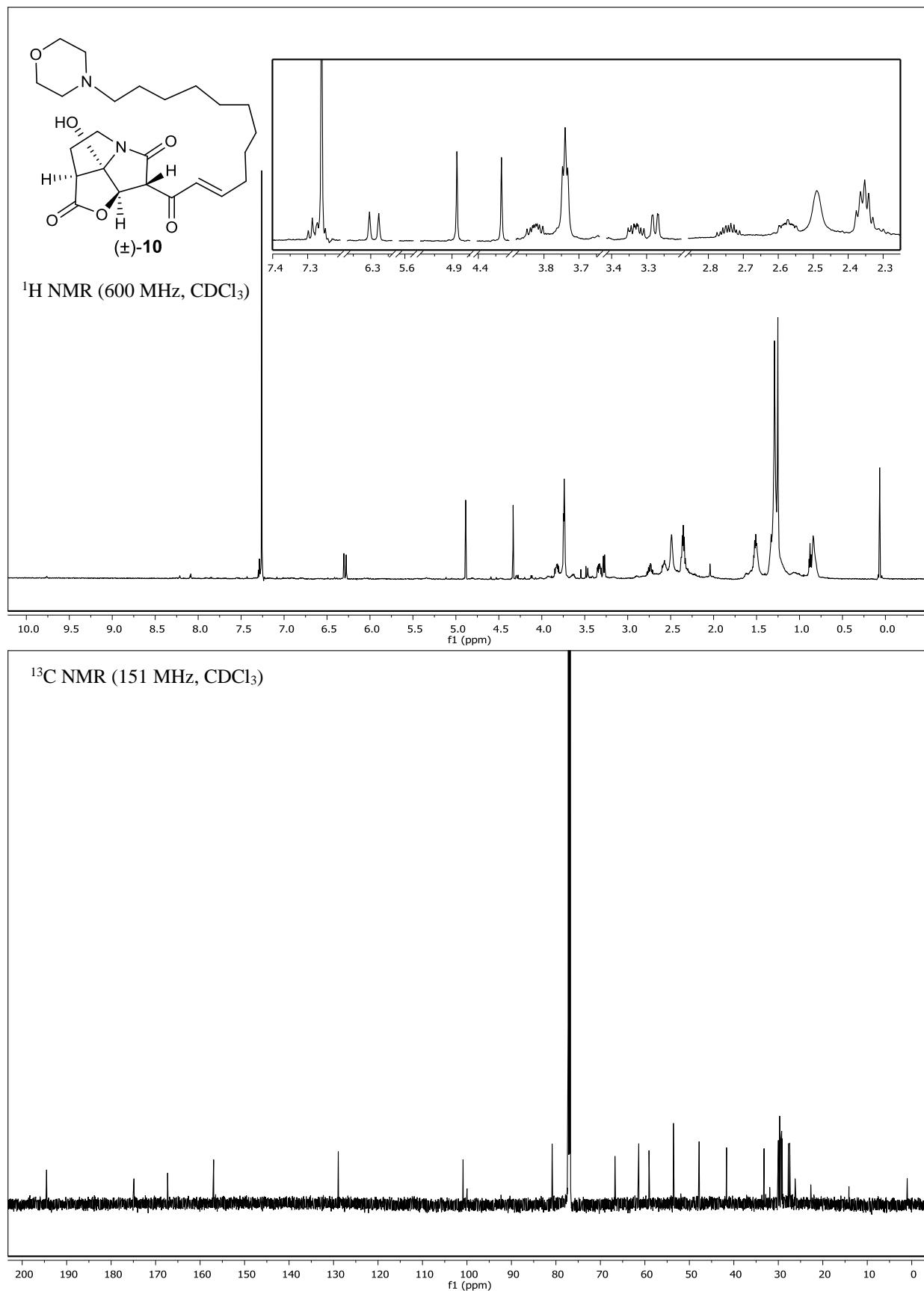
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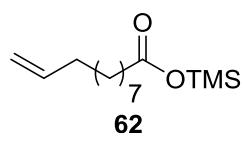
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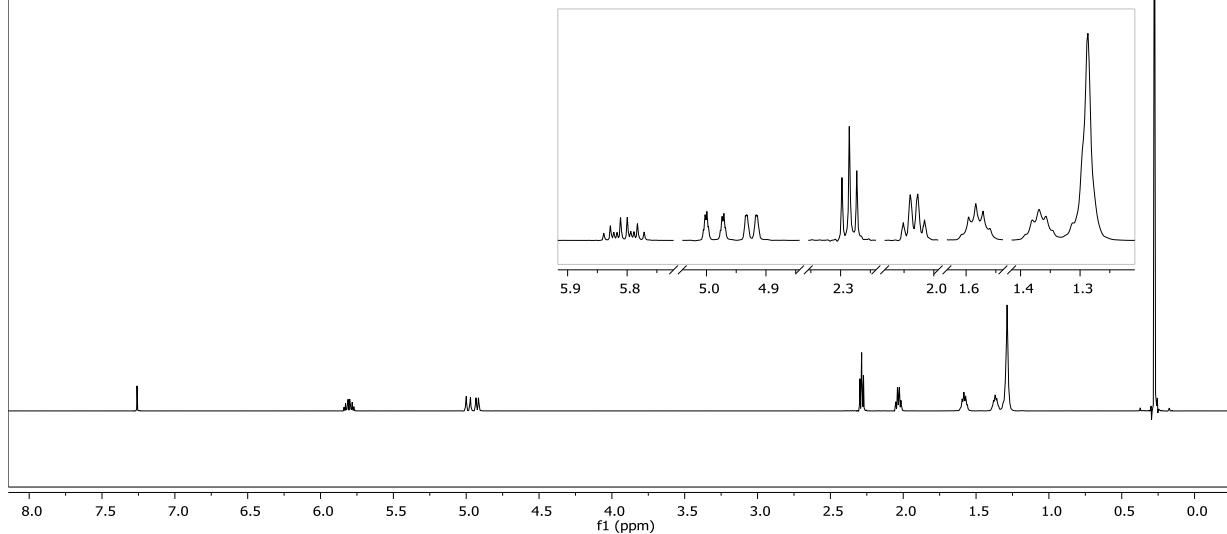
^{13}C NMR (151 MHz, CDCl_3)



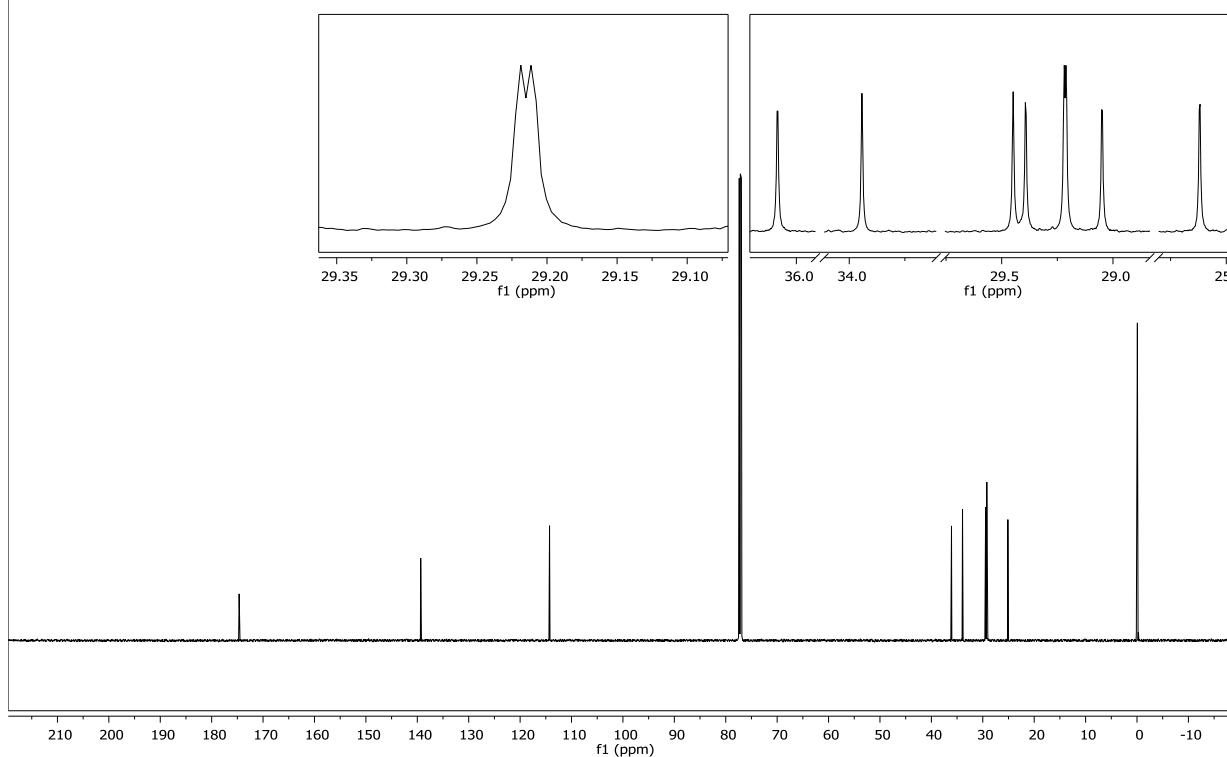


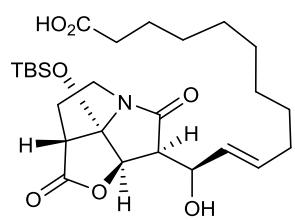


¹H NMR (600 MHz, CDCl₃)



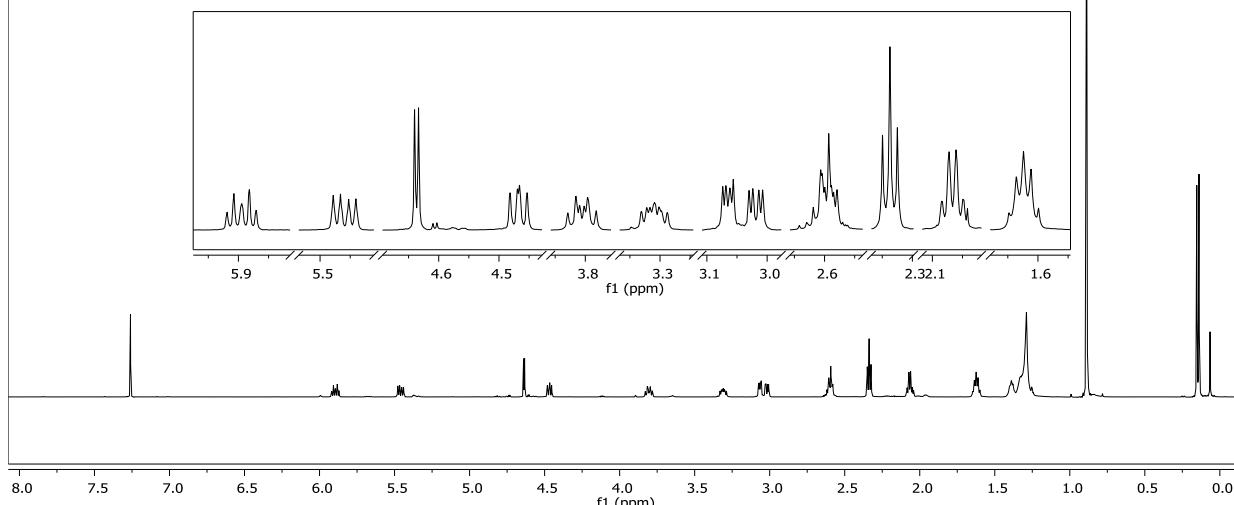
¹³C NMR (151 MHz, CDCl₃)



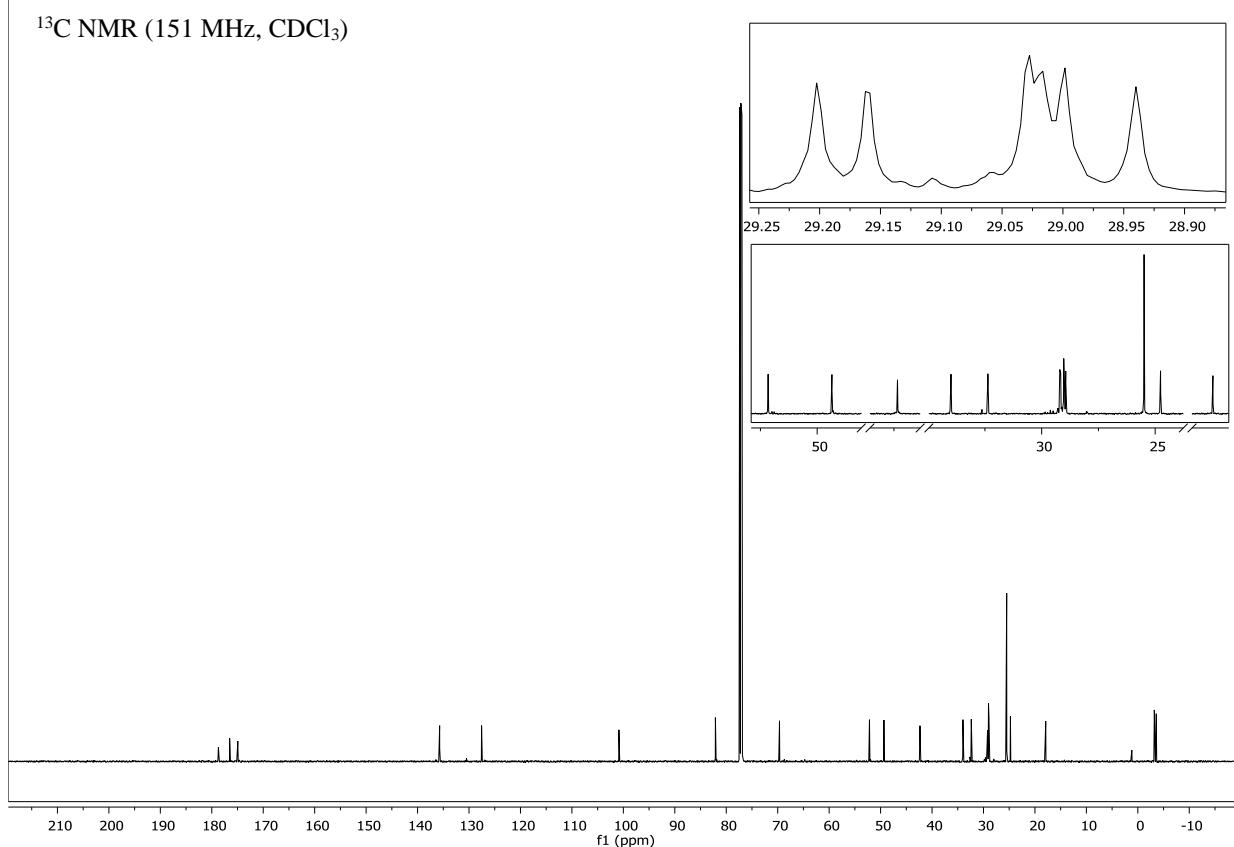


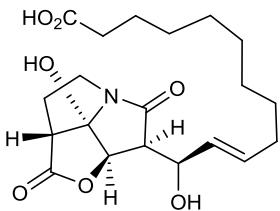
63

^1H NMR (600 MHz, CDCl_3)



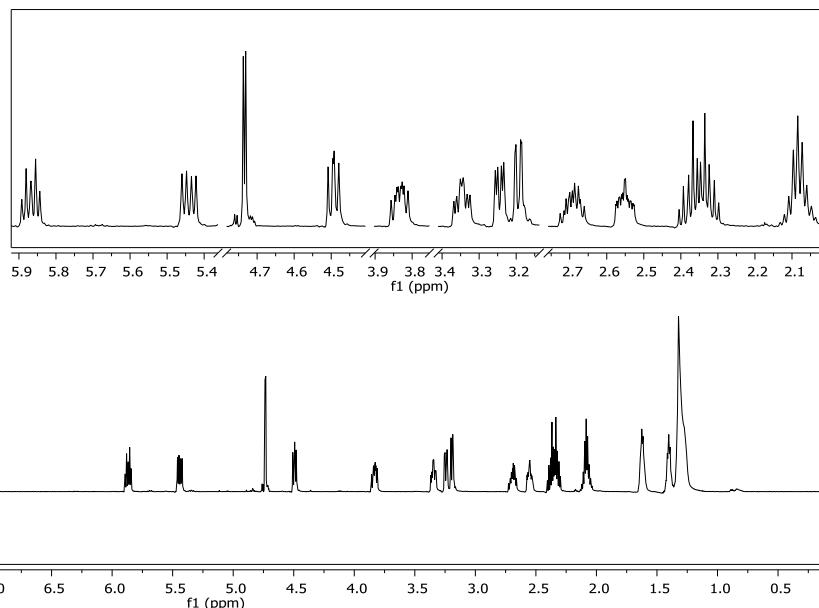
^{13}C NMR (151 MHz, CDCl_3)



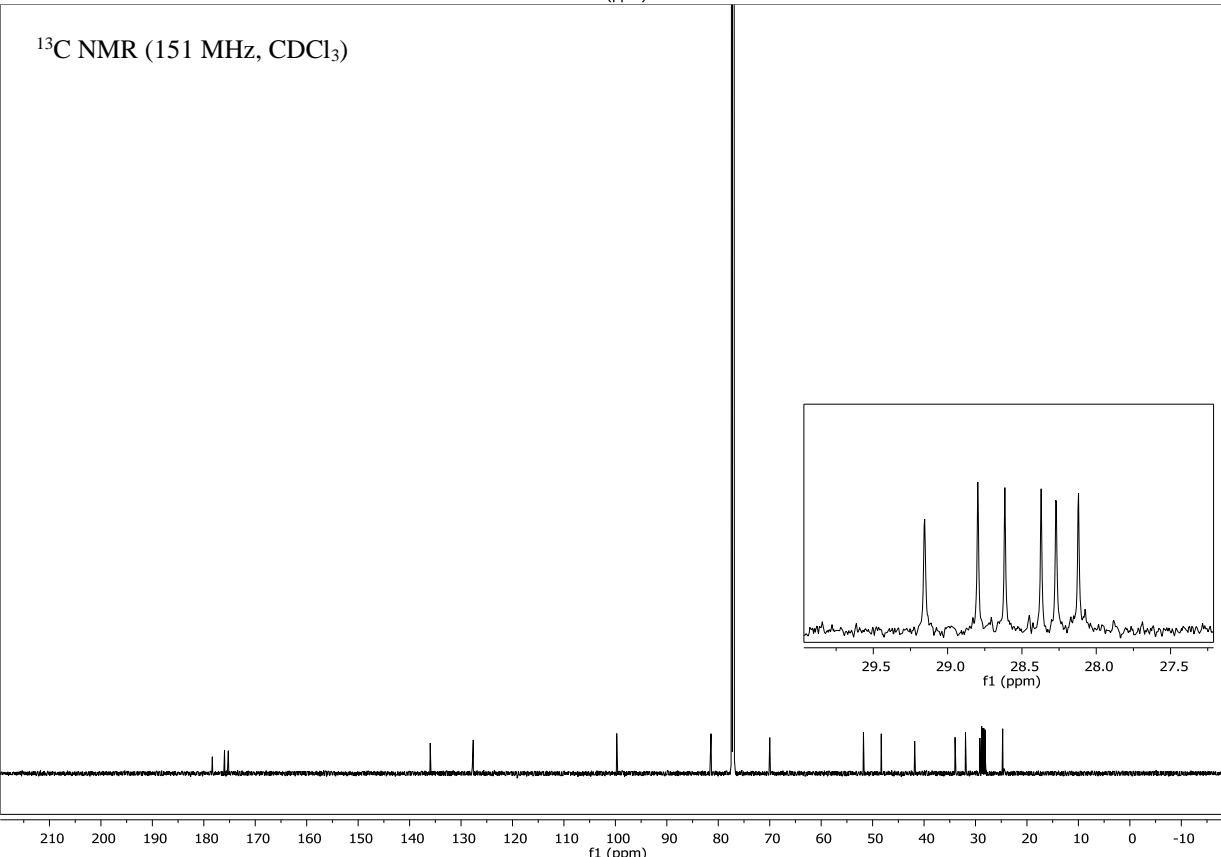


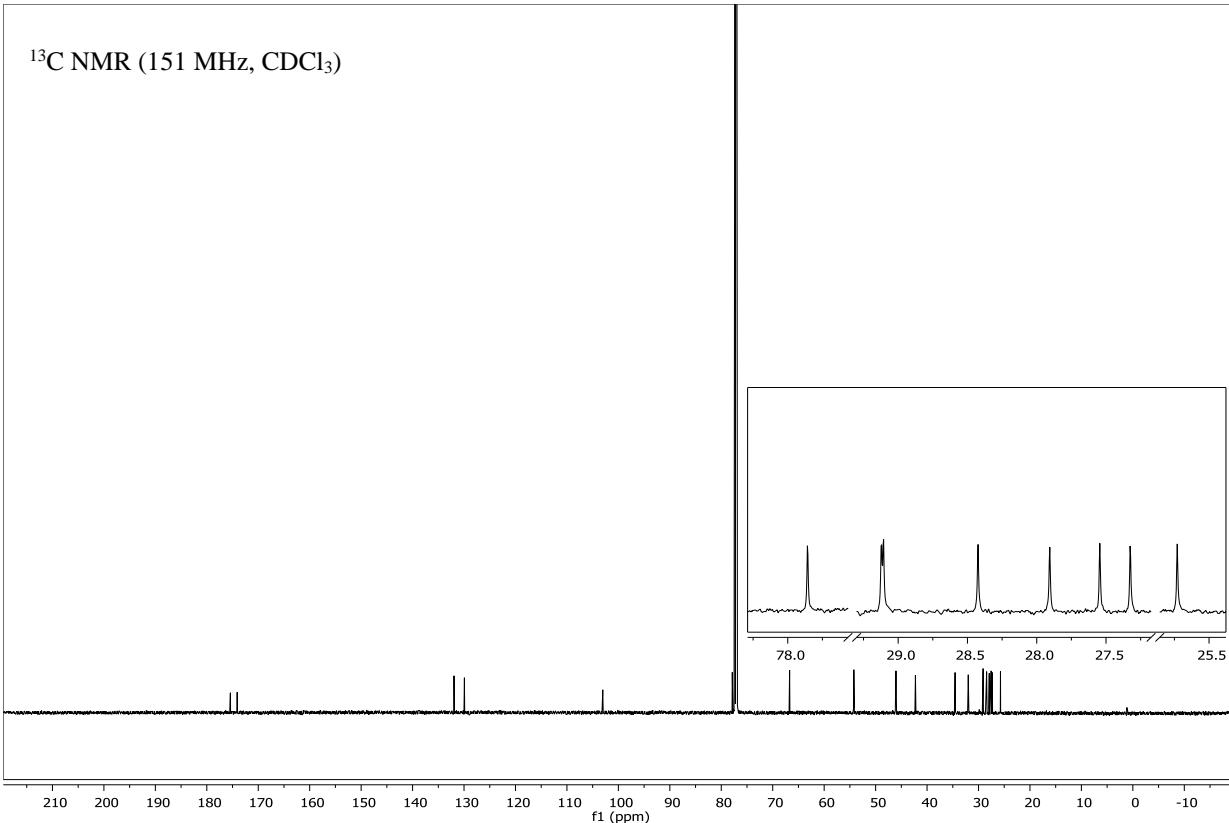
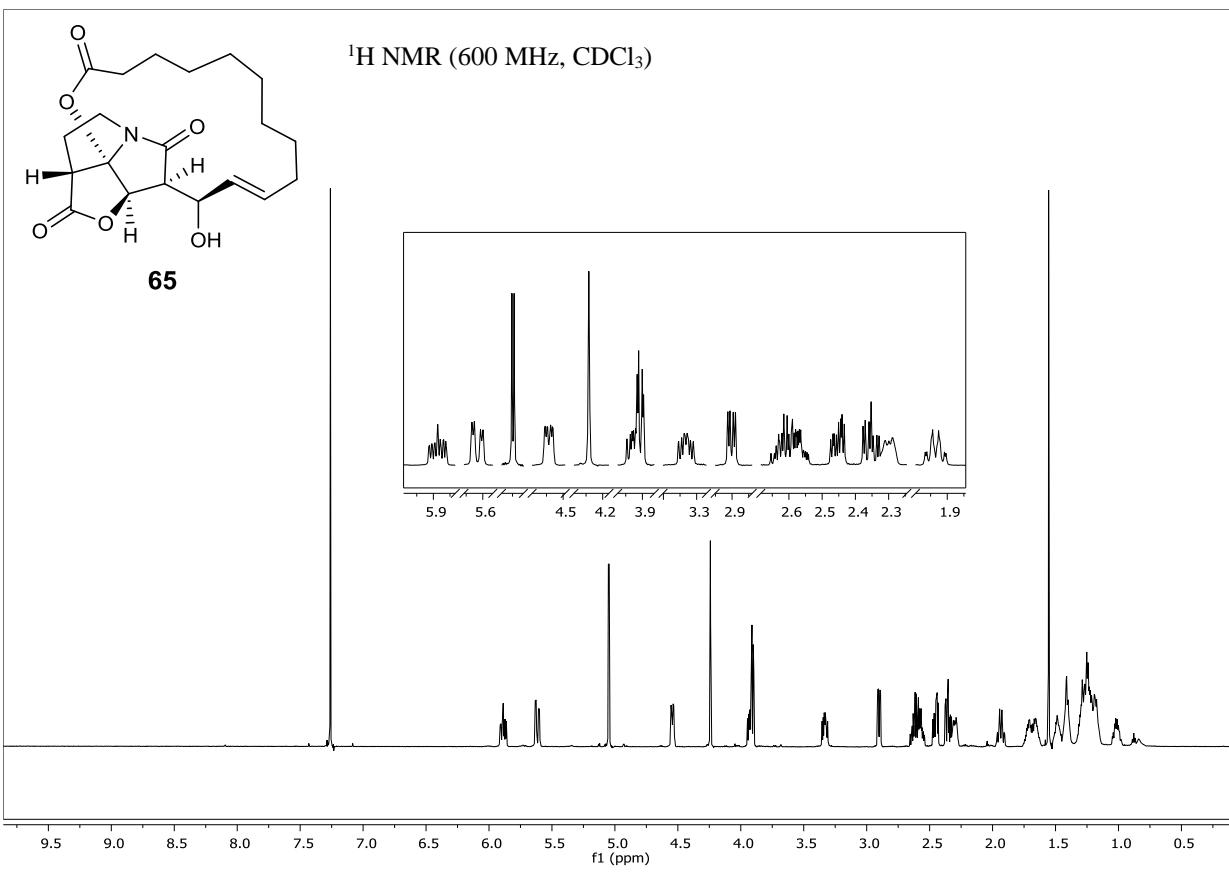
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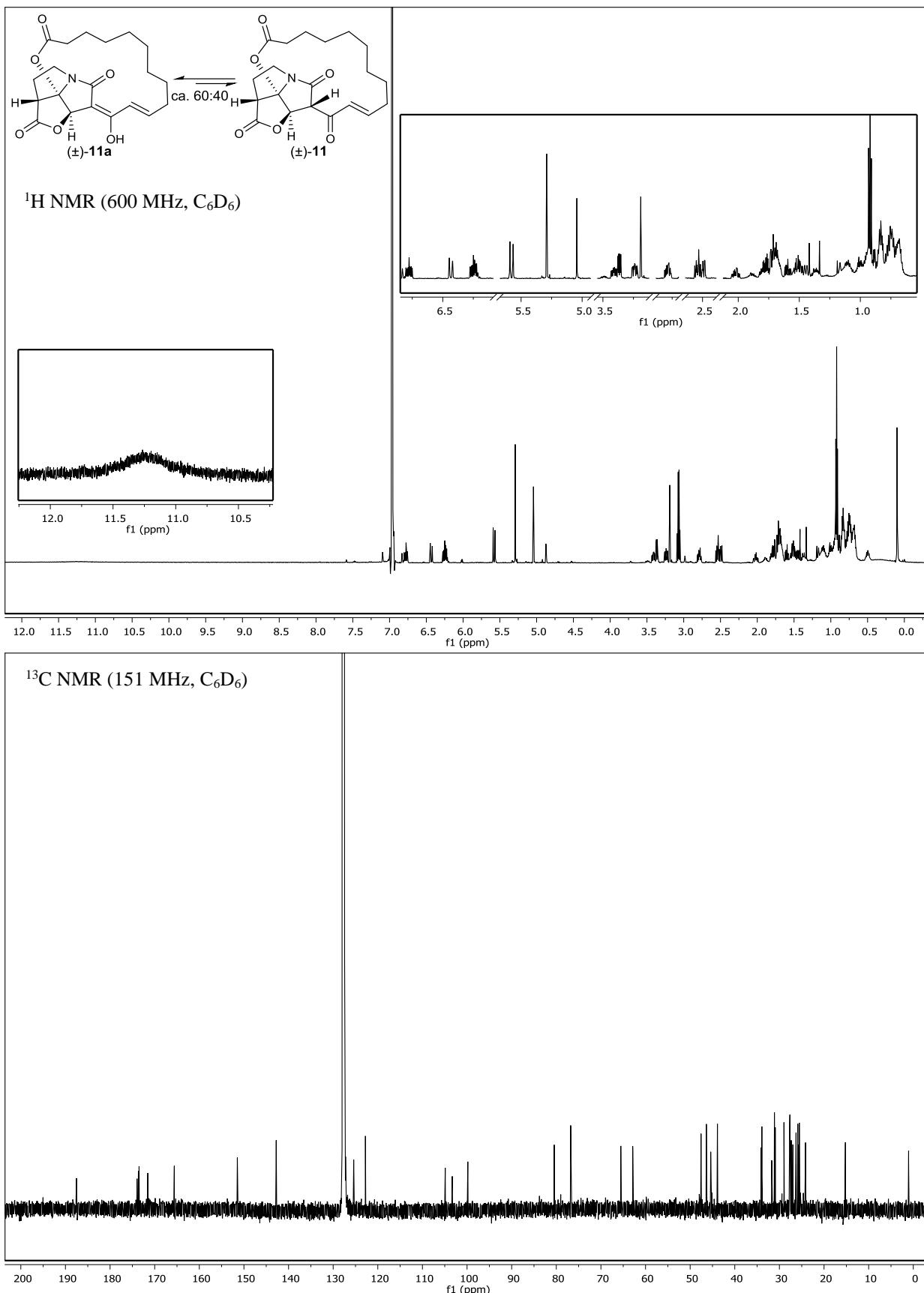
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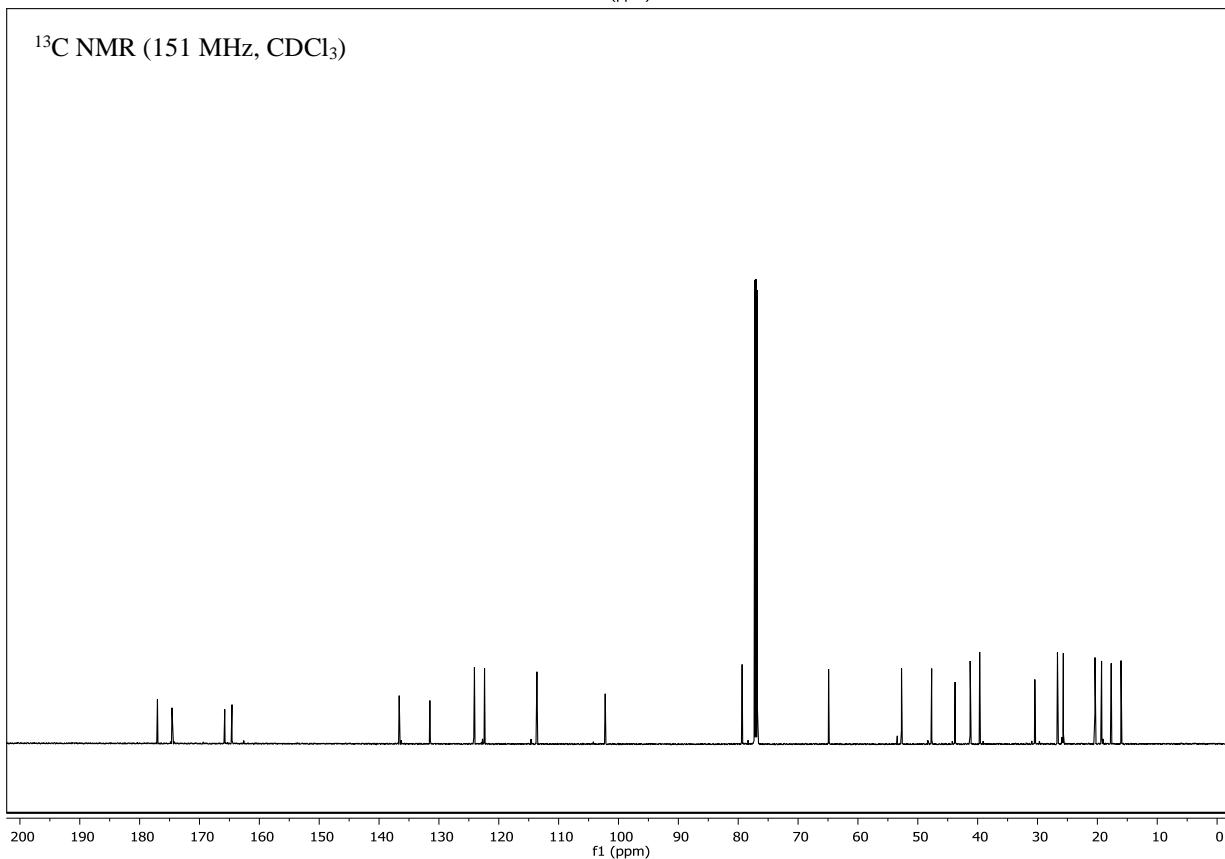
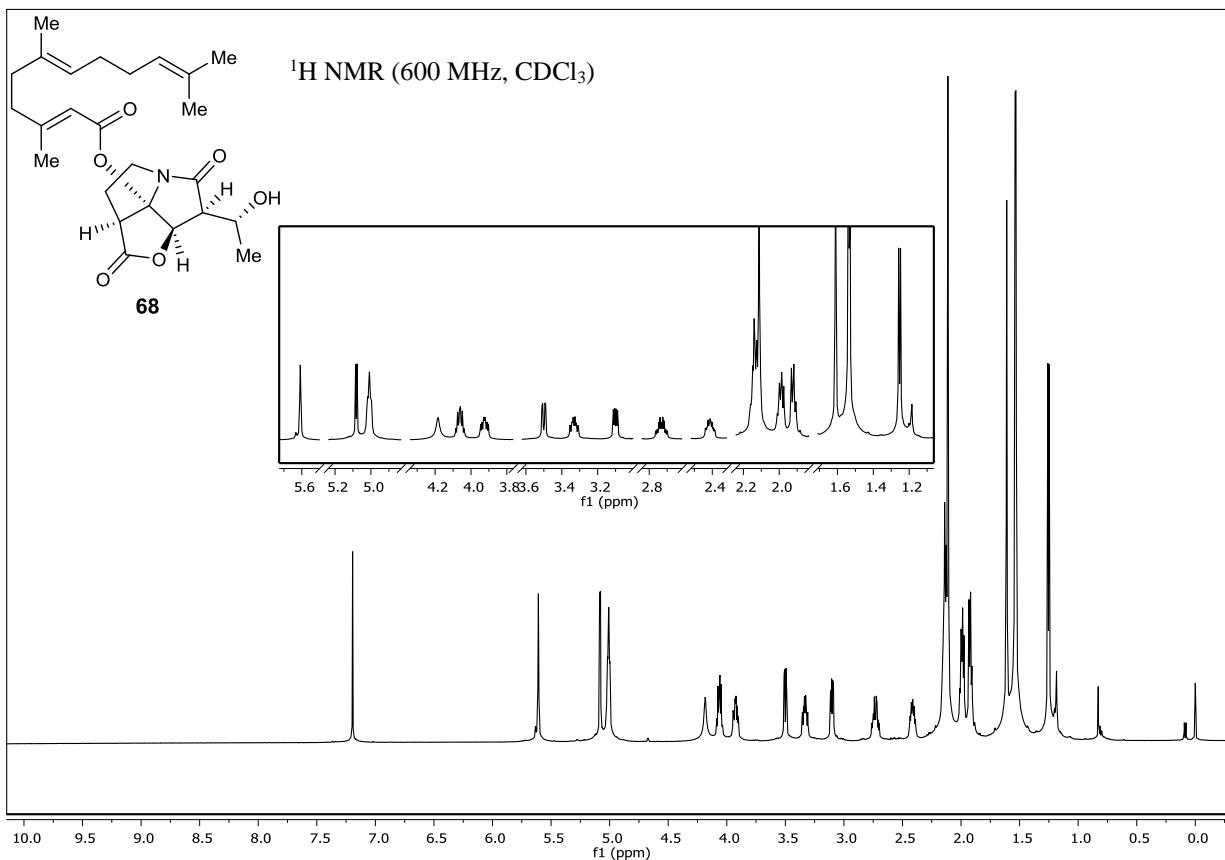


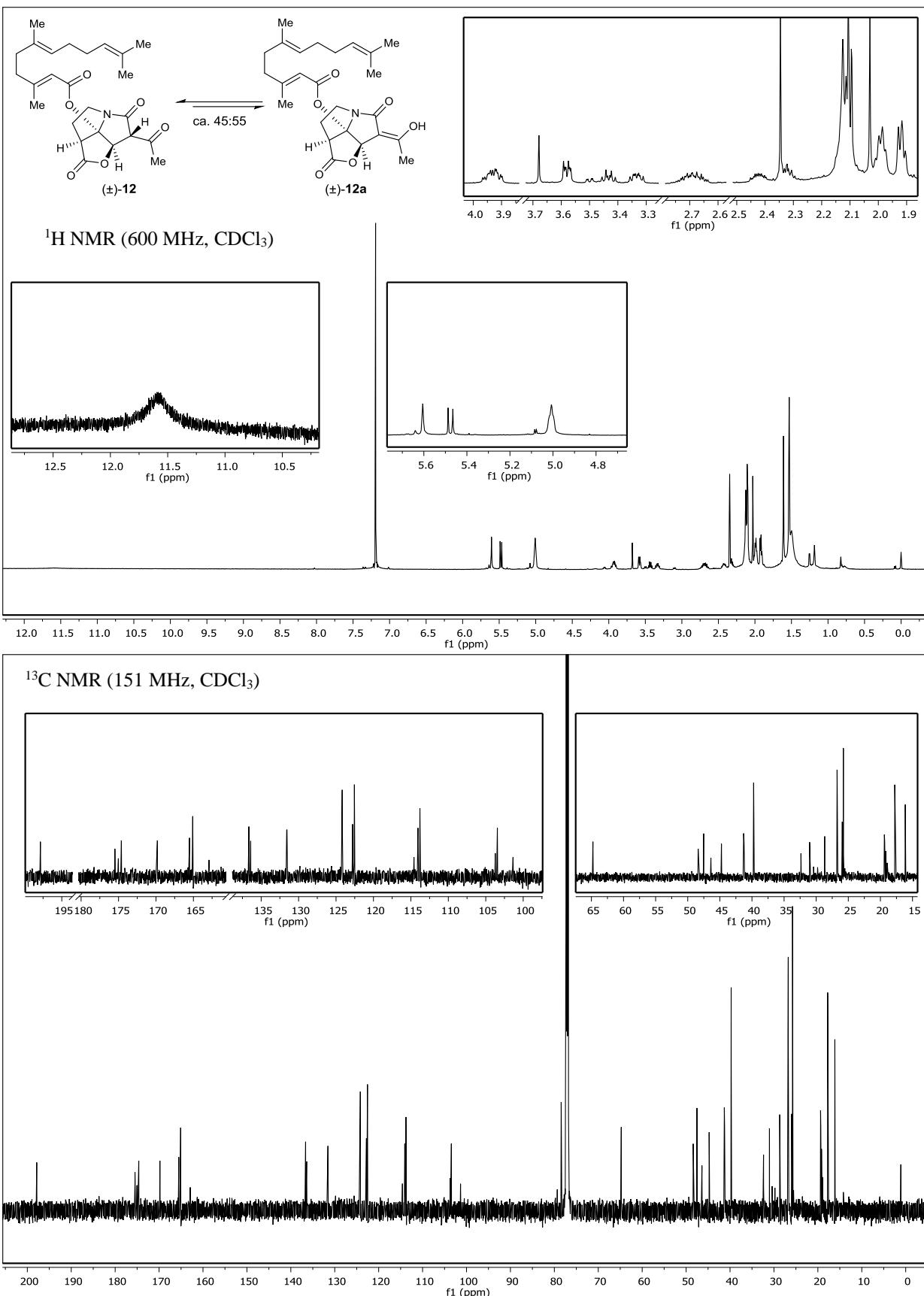
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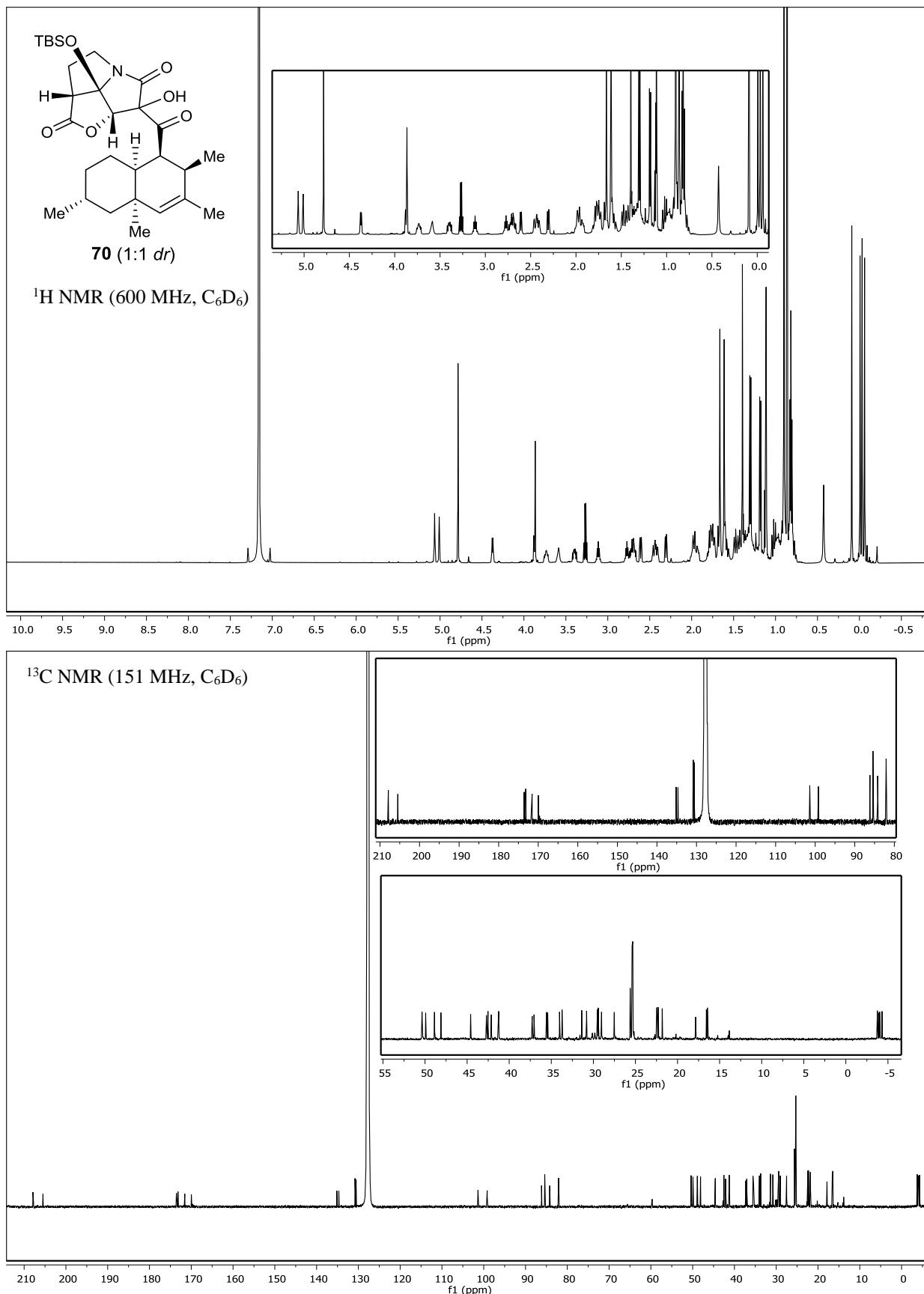


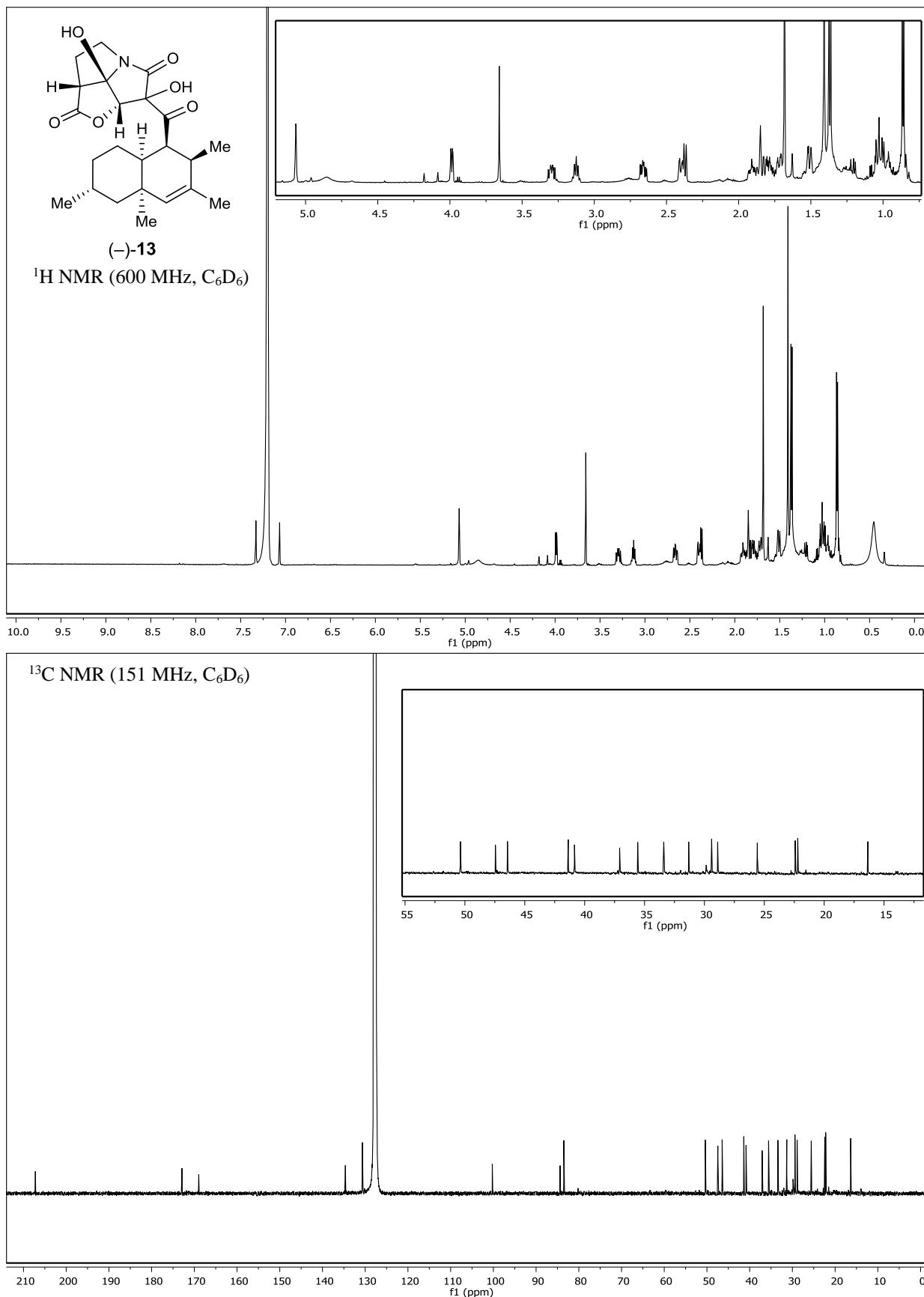


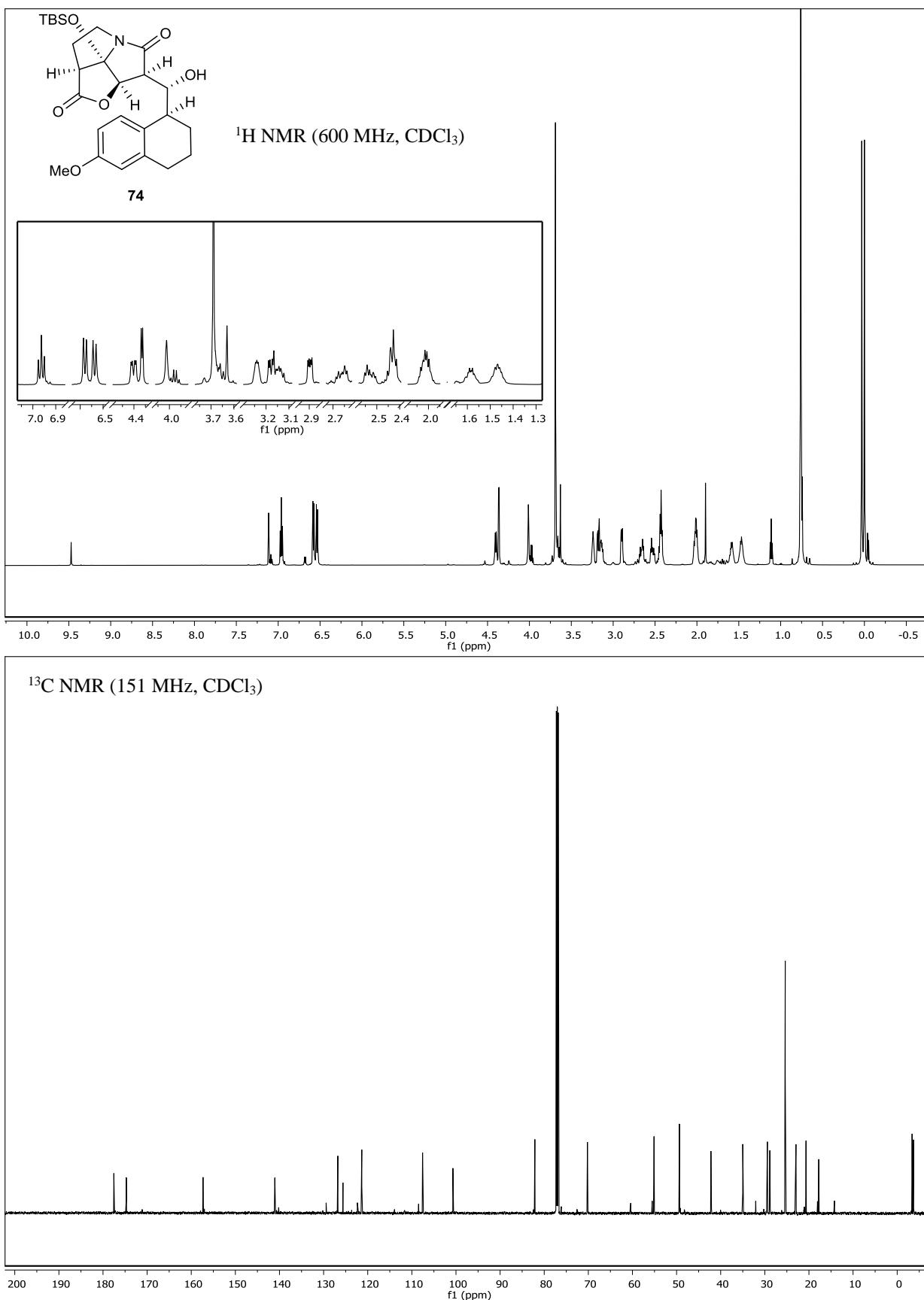


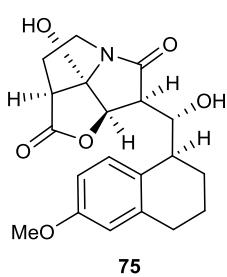




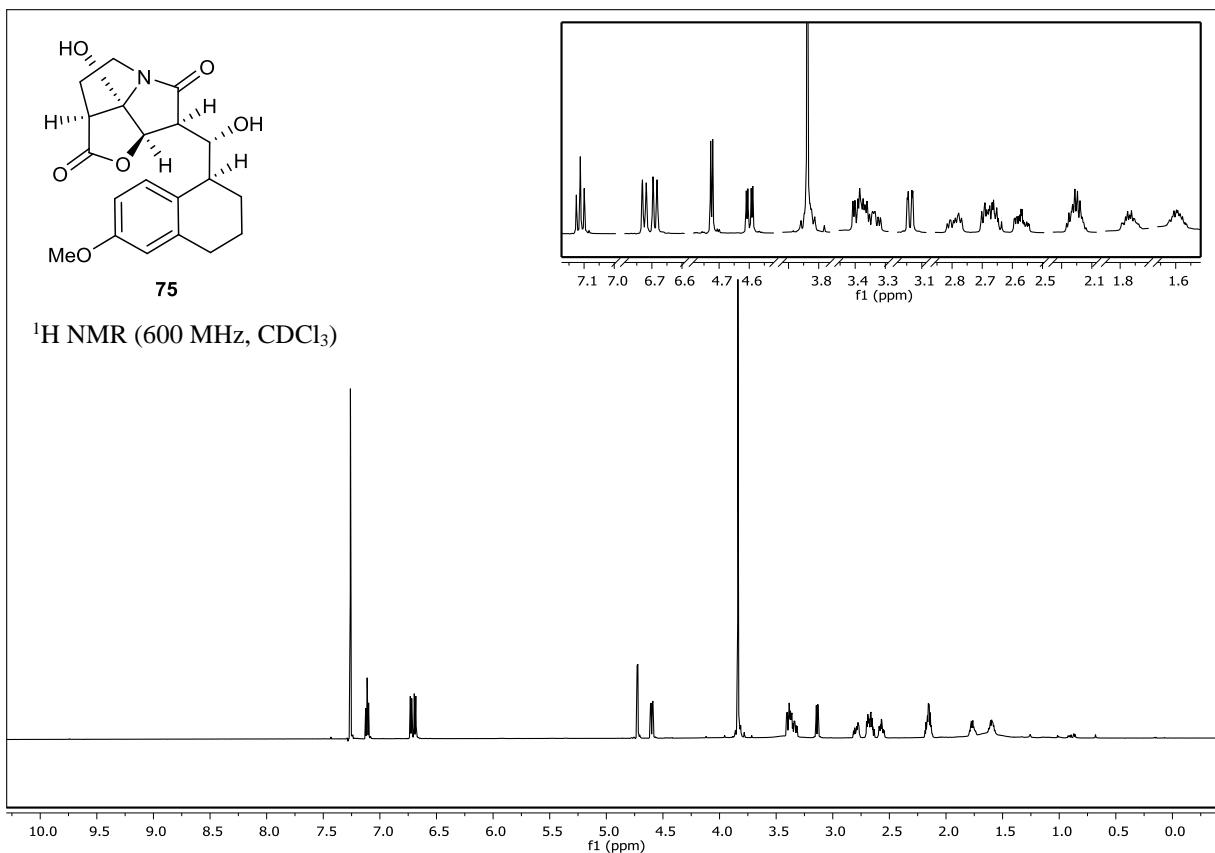




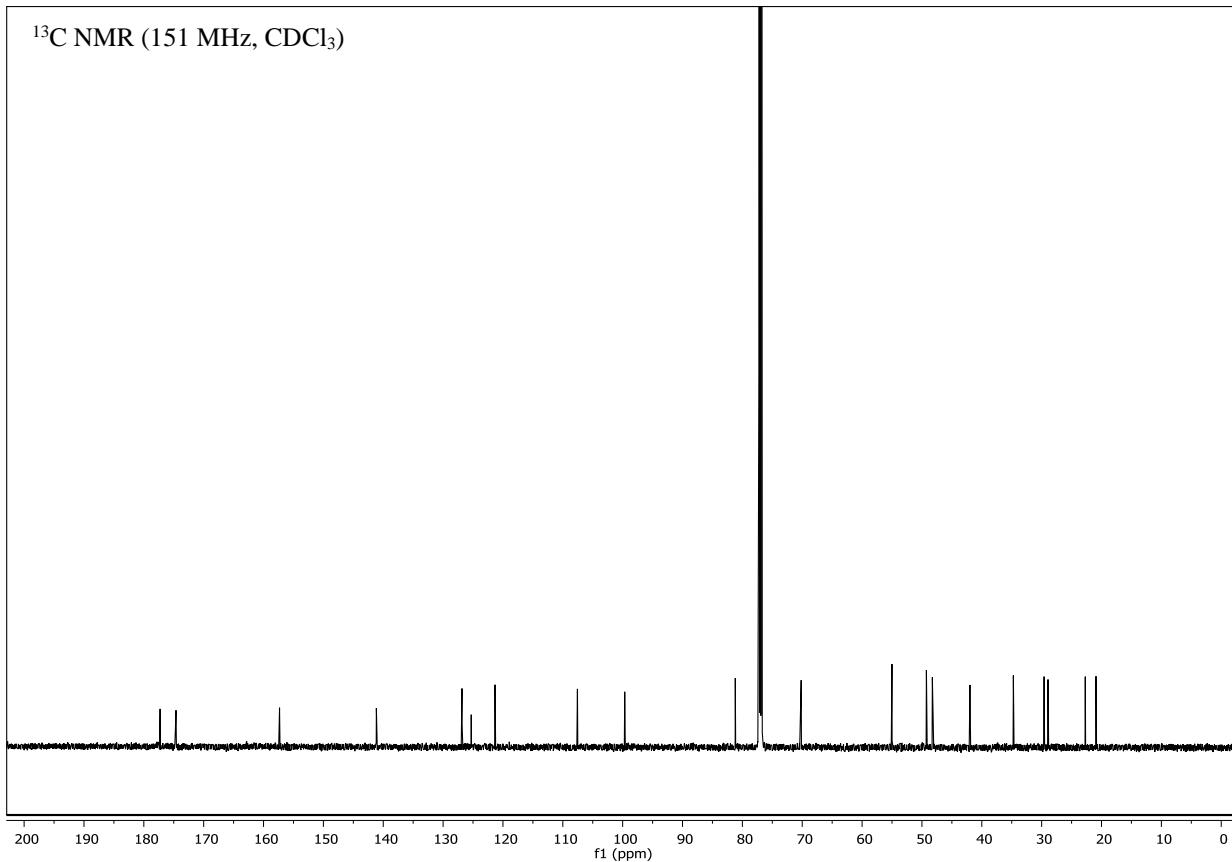


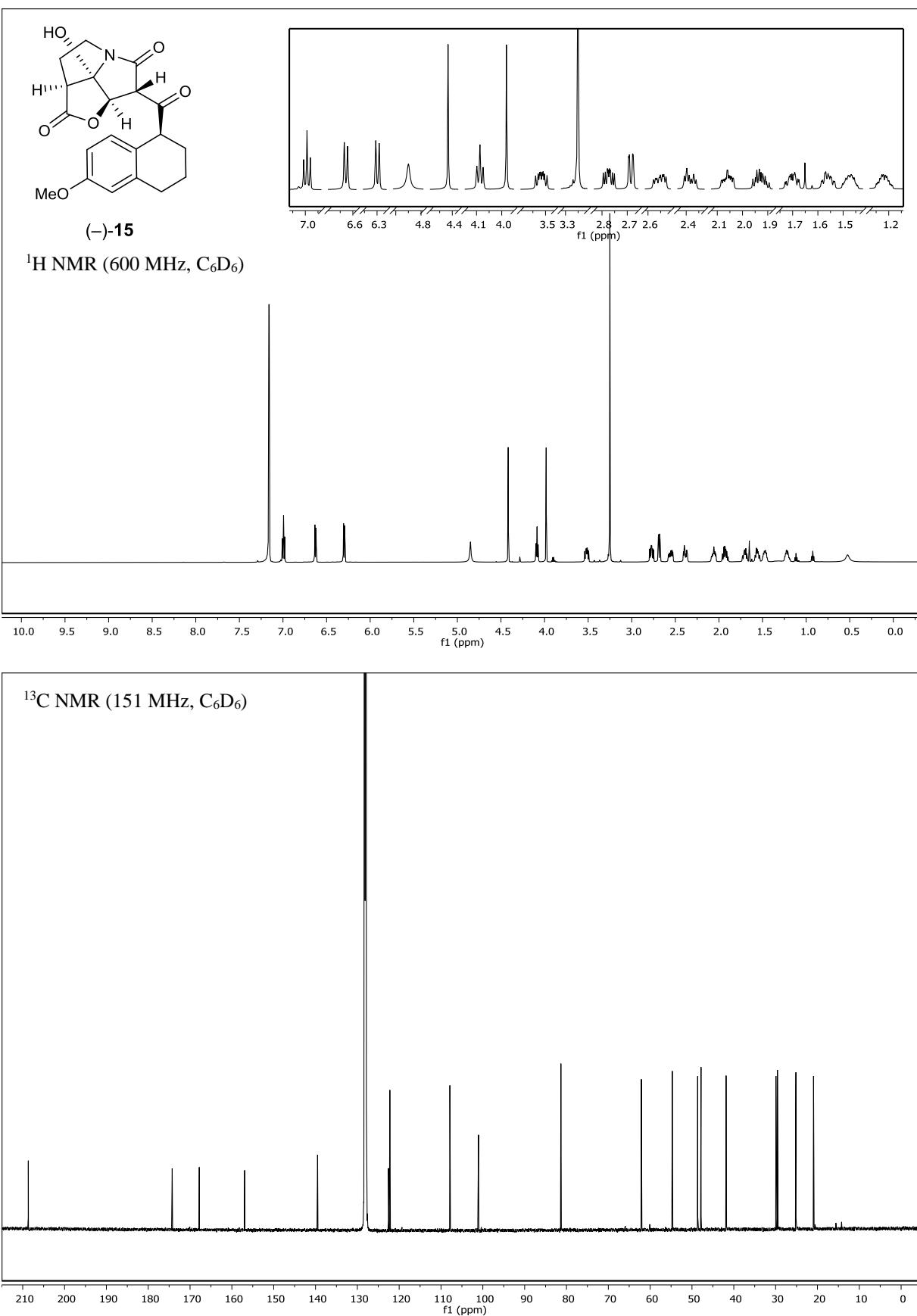


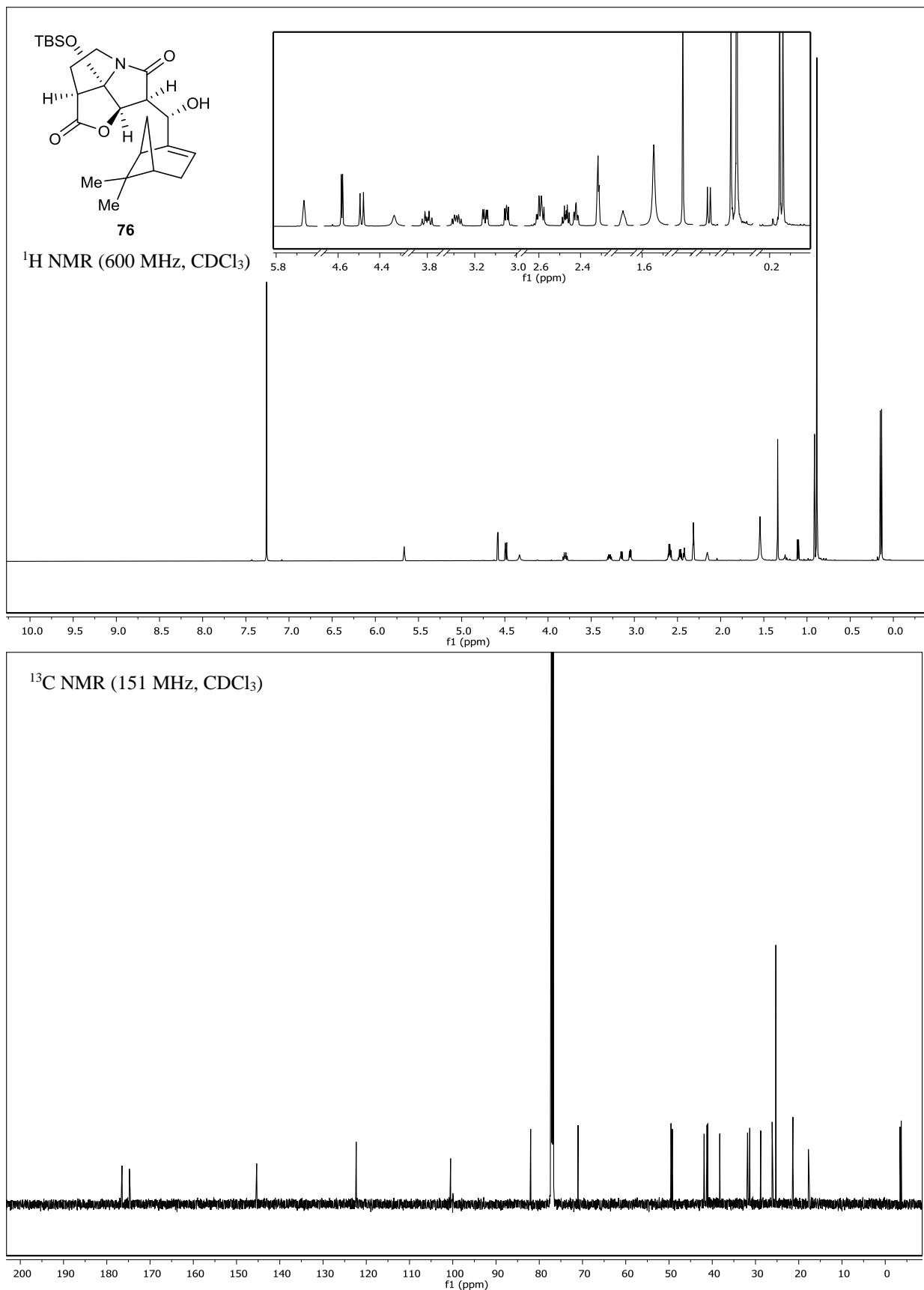
^1H NMR (600 MHz, CDCl_3)

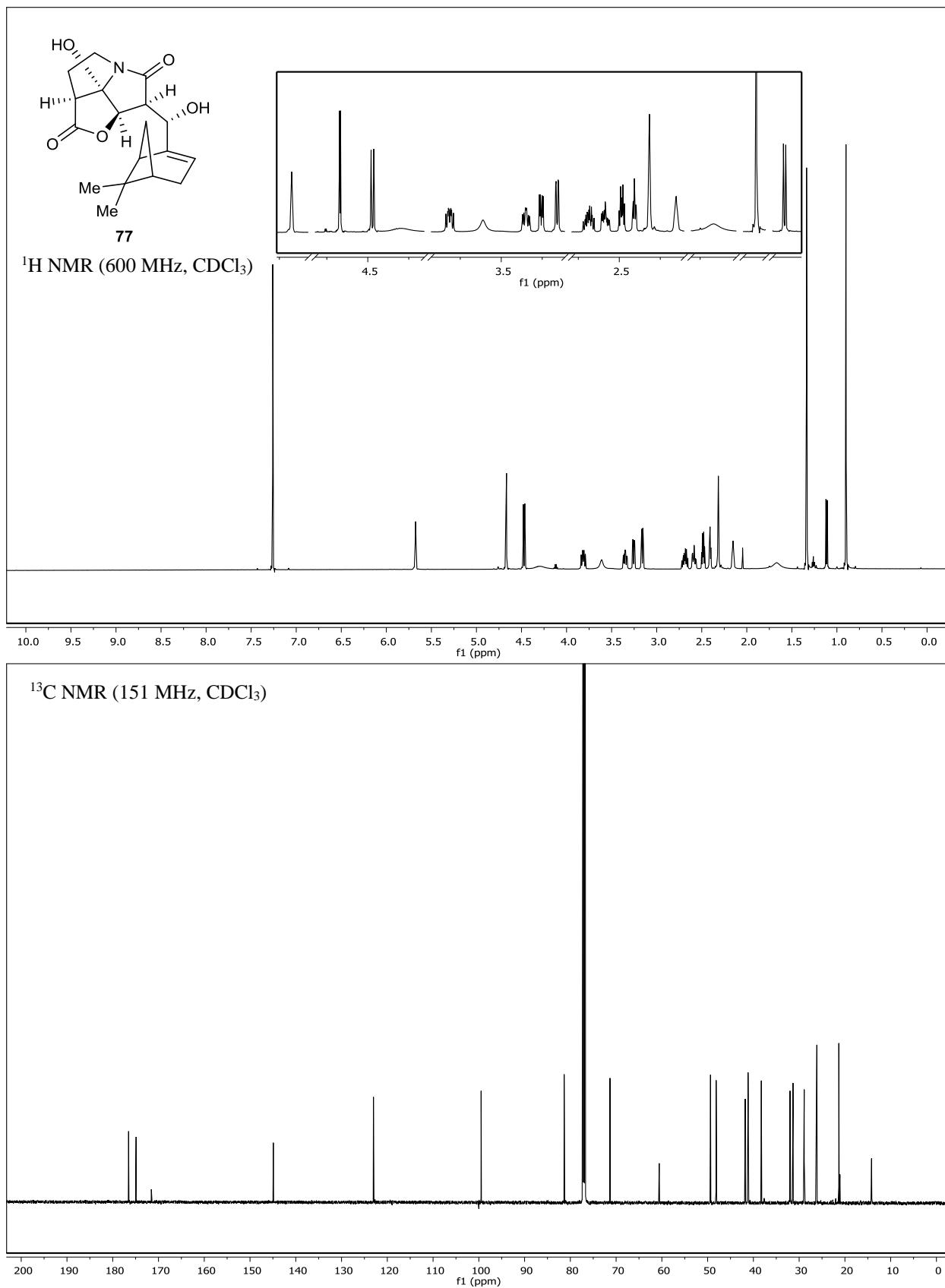


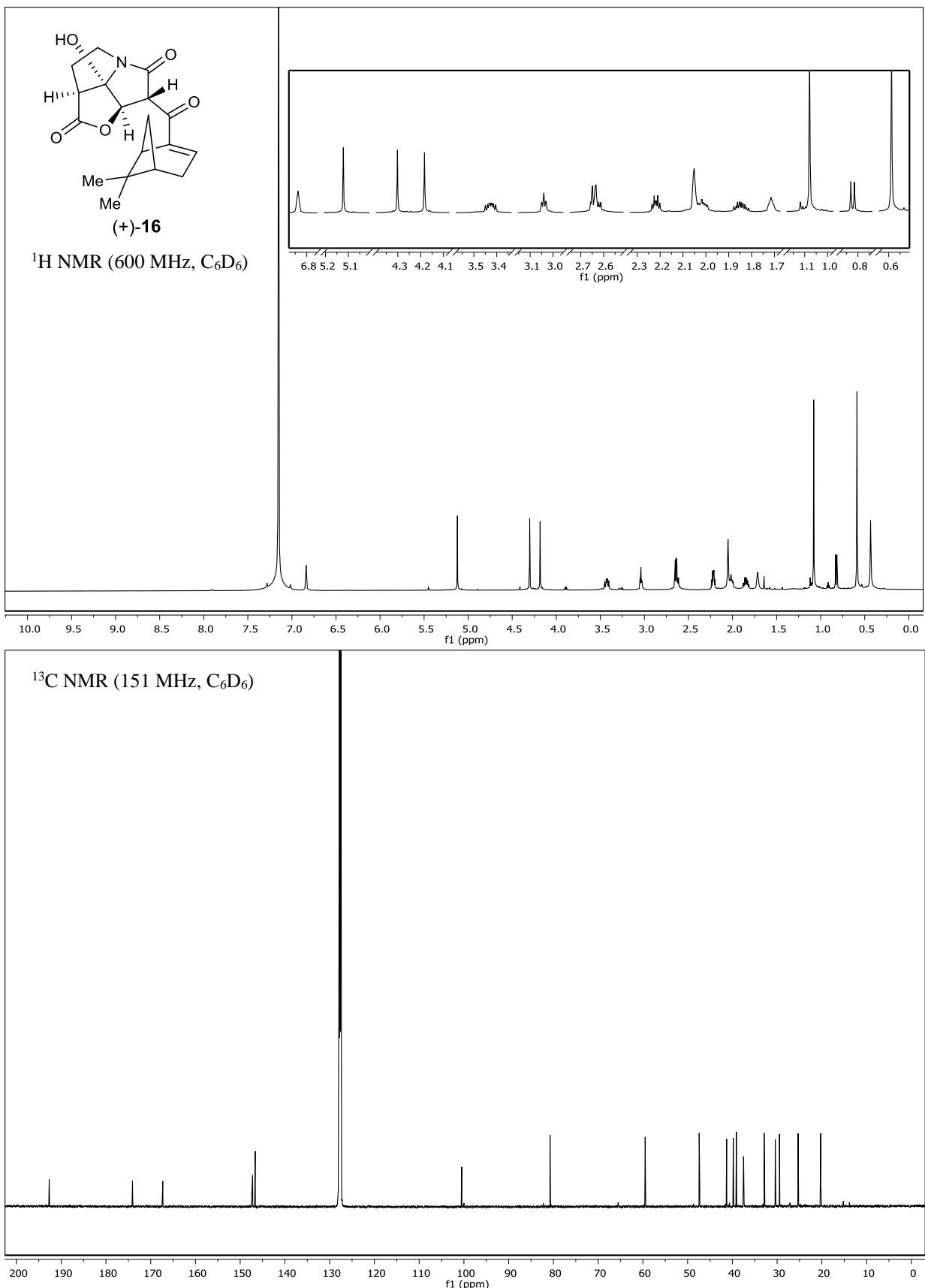
^{13}C NMR (151 MHz, CDCl_3)

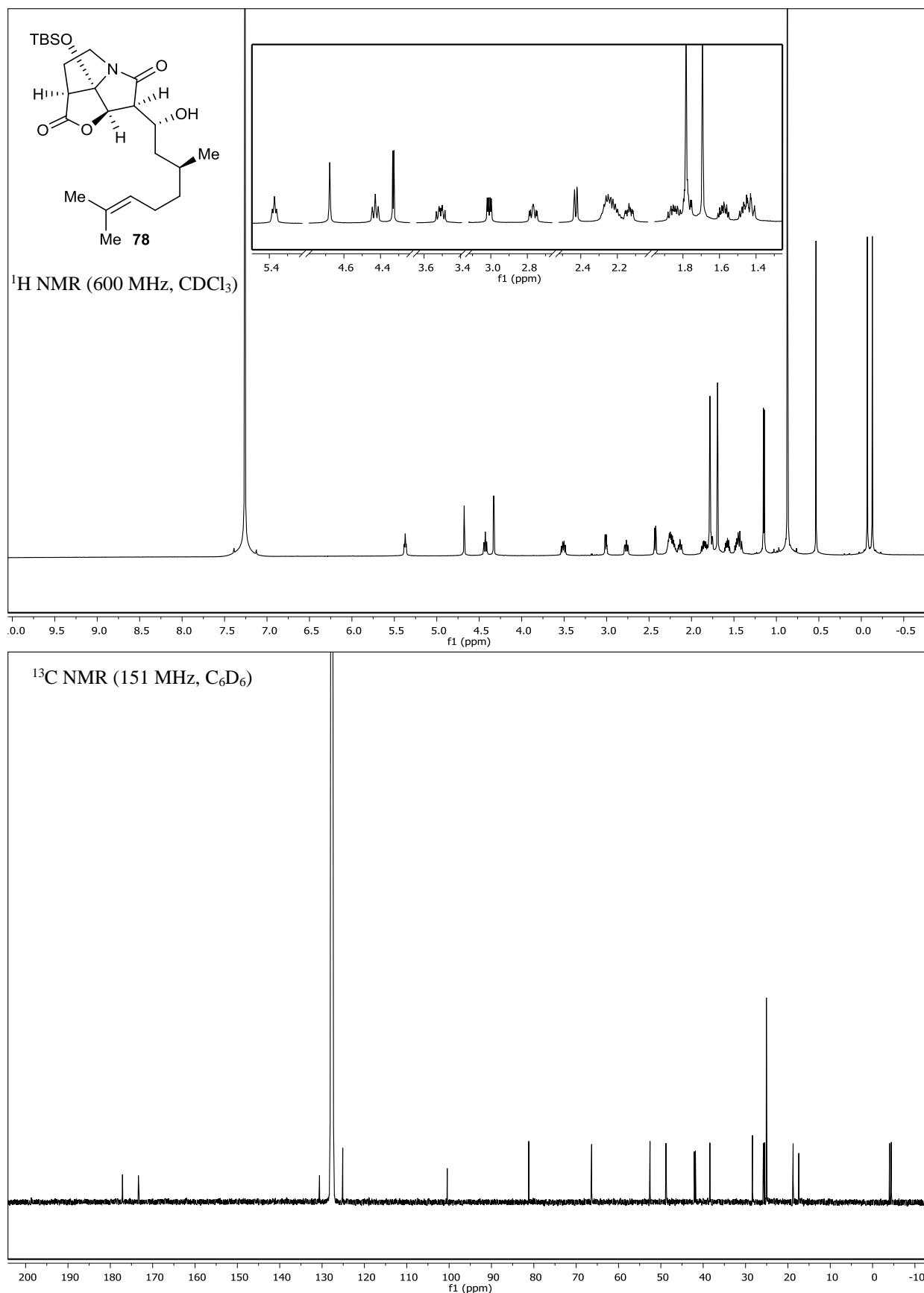


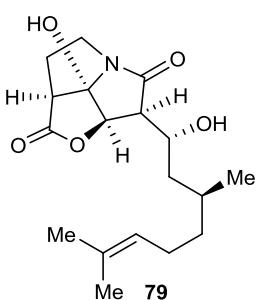




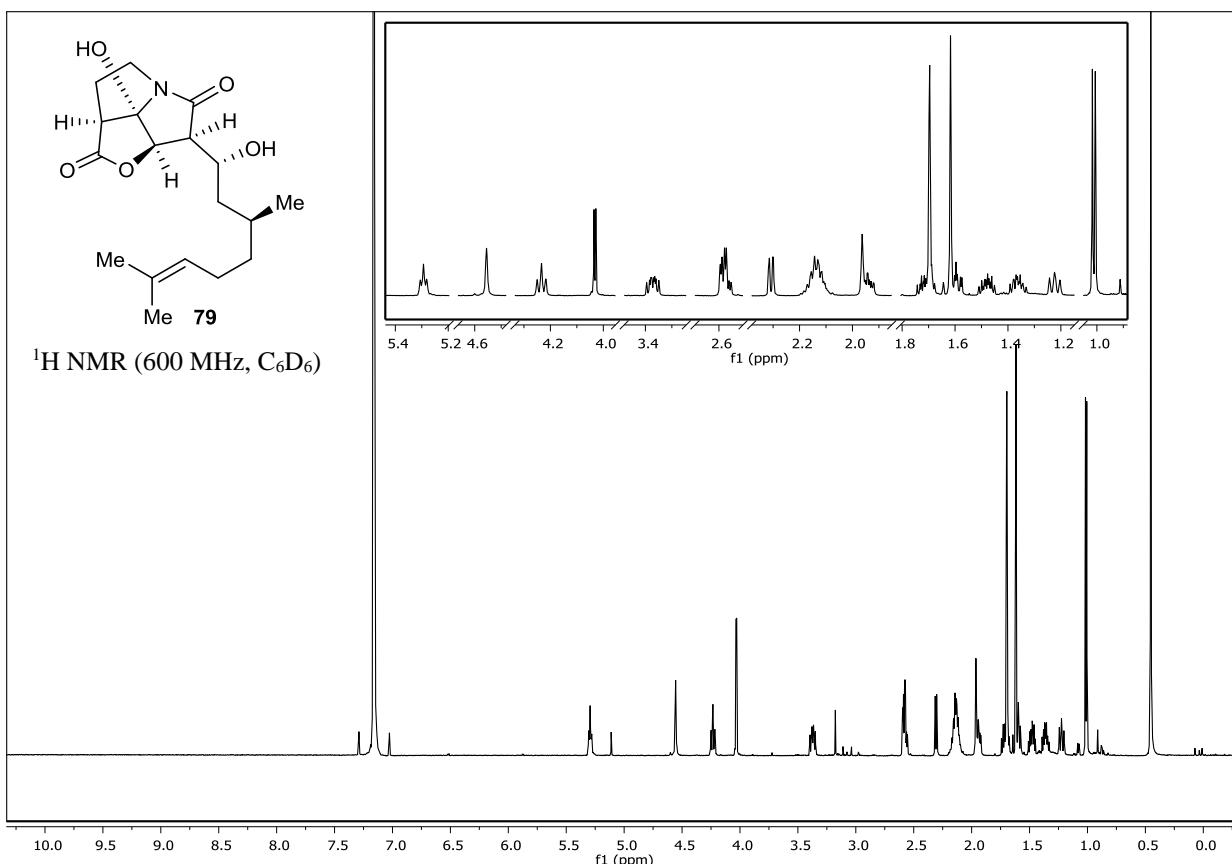




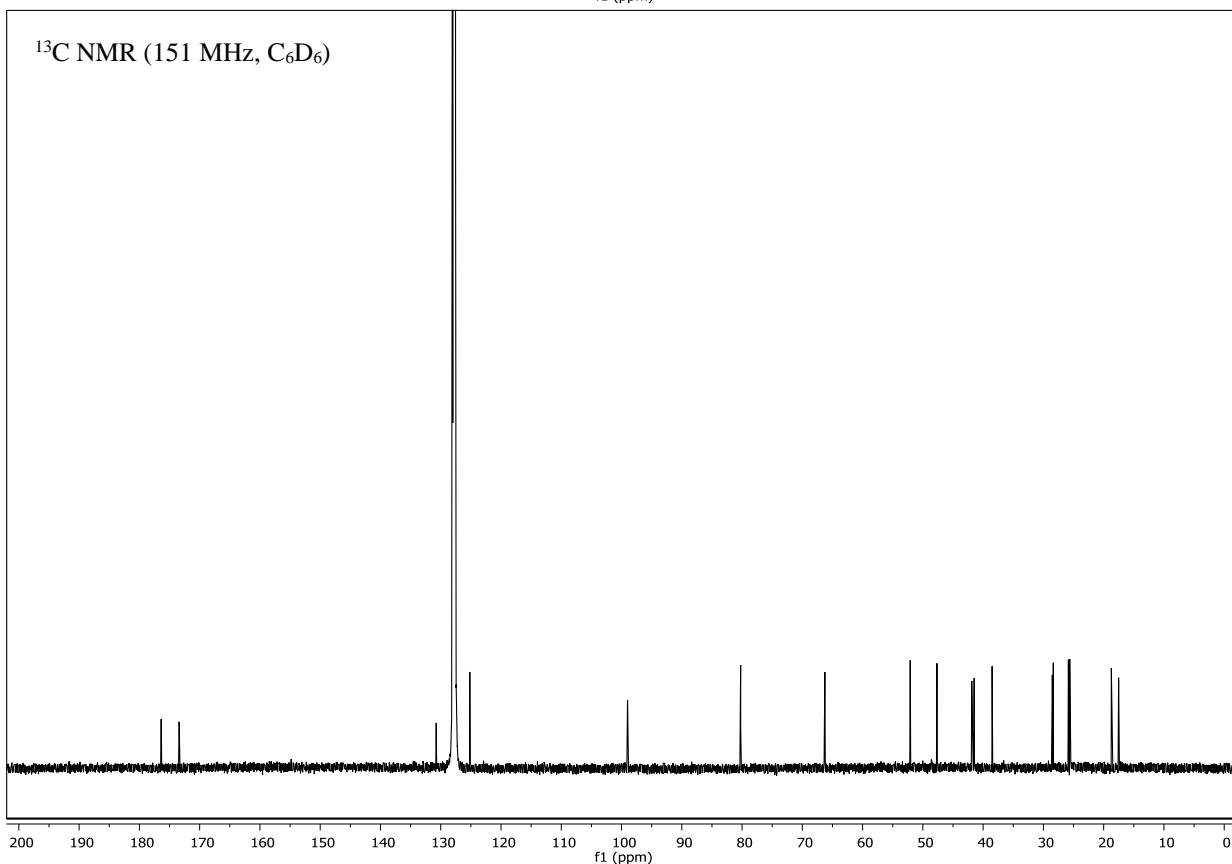


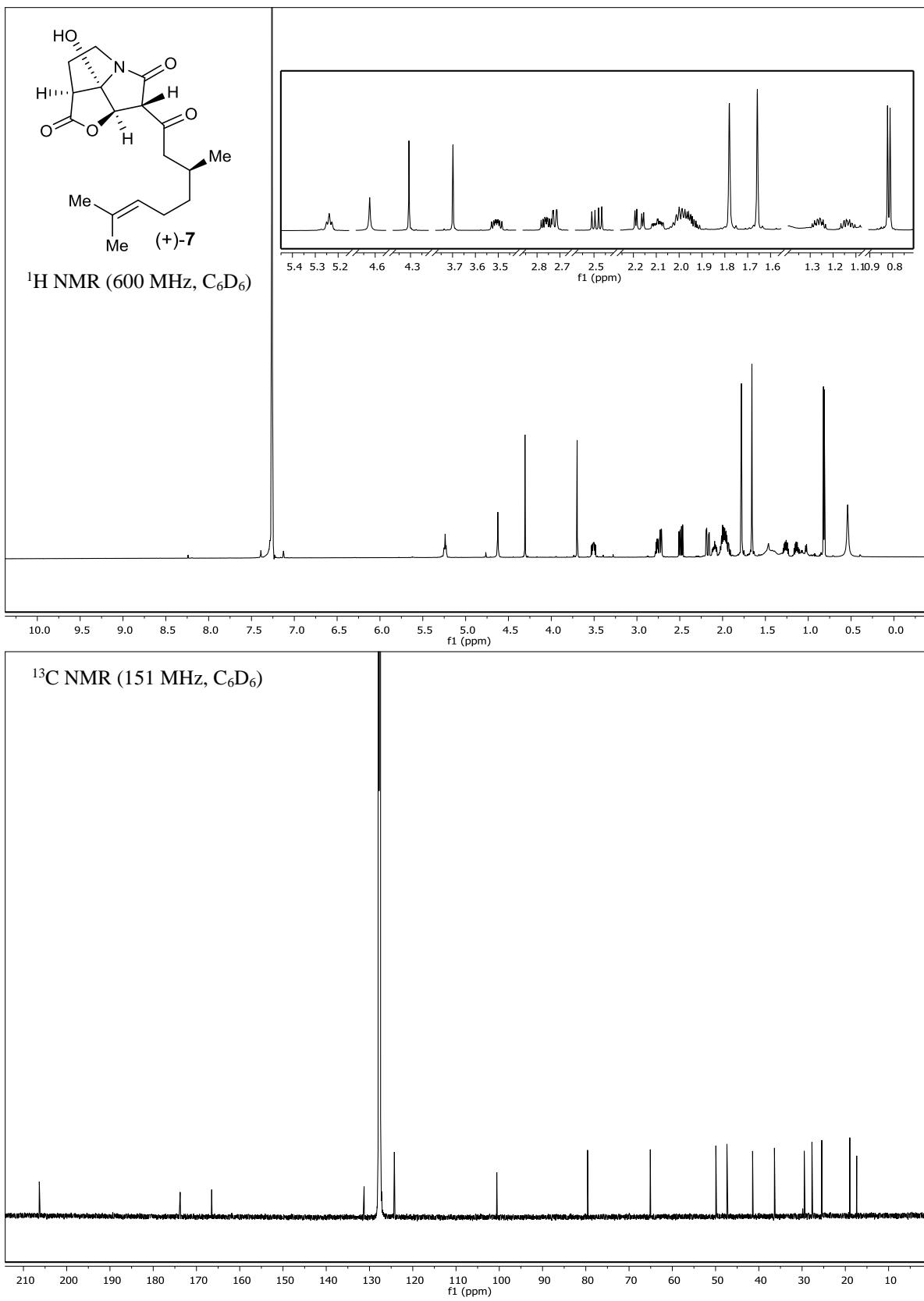


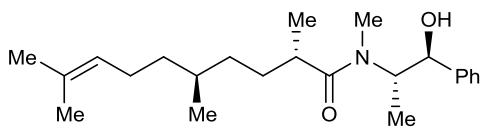
^1H NMR (600 MHz, C_6D_6)



^{13}C NMR (151 MHz, C_6D_6)

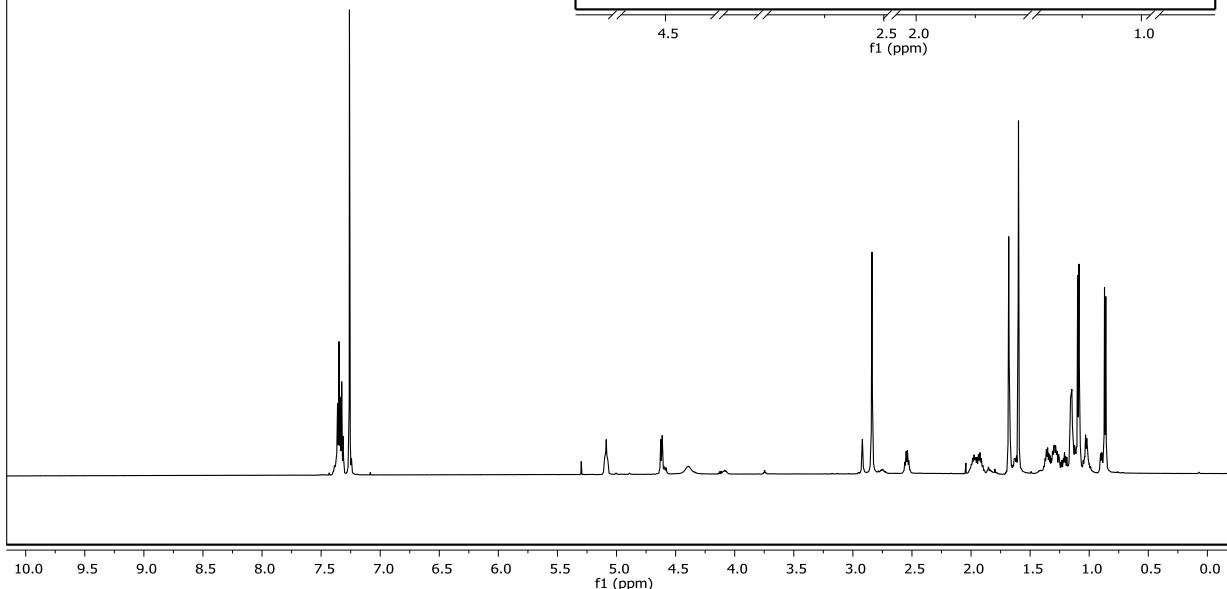
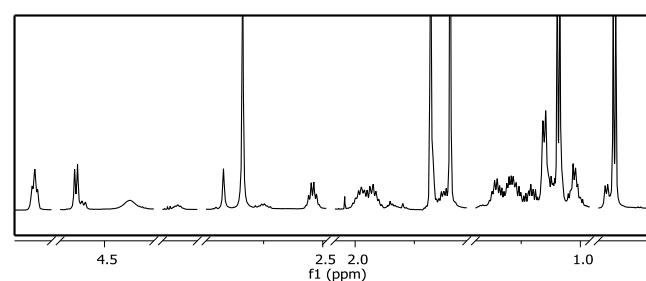




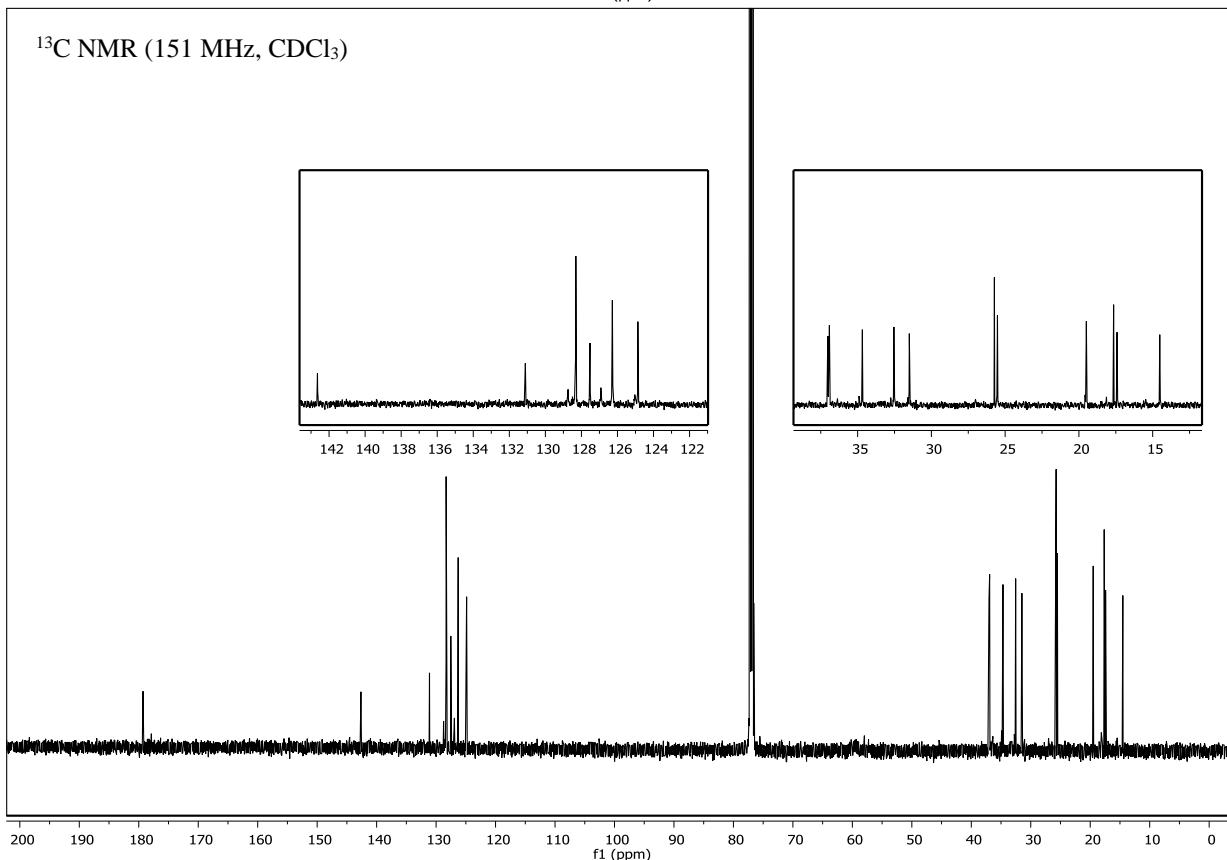


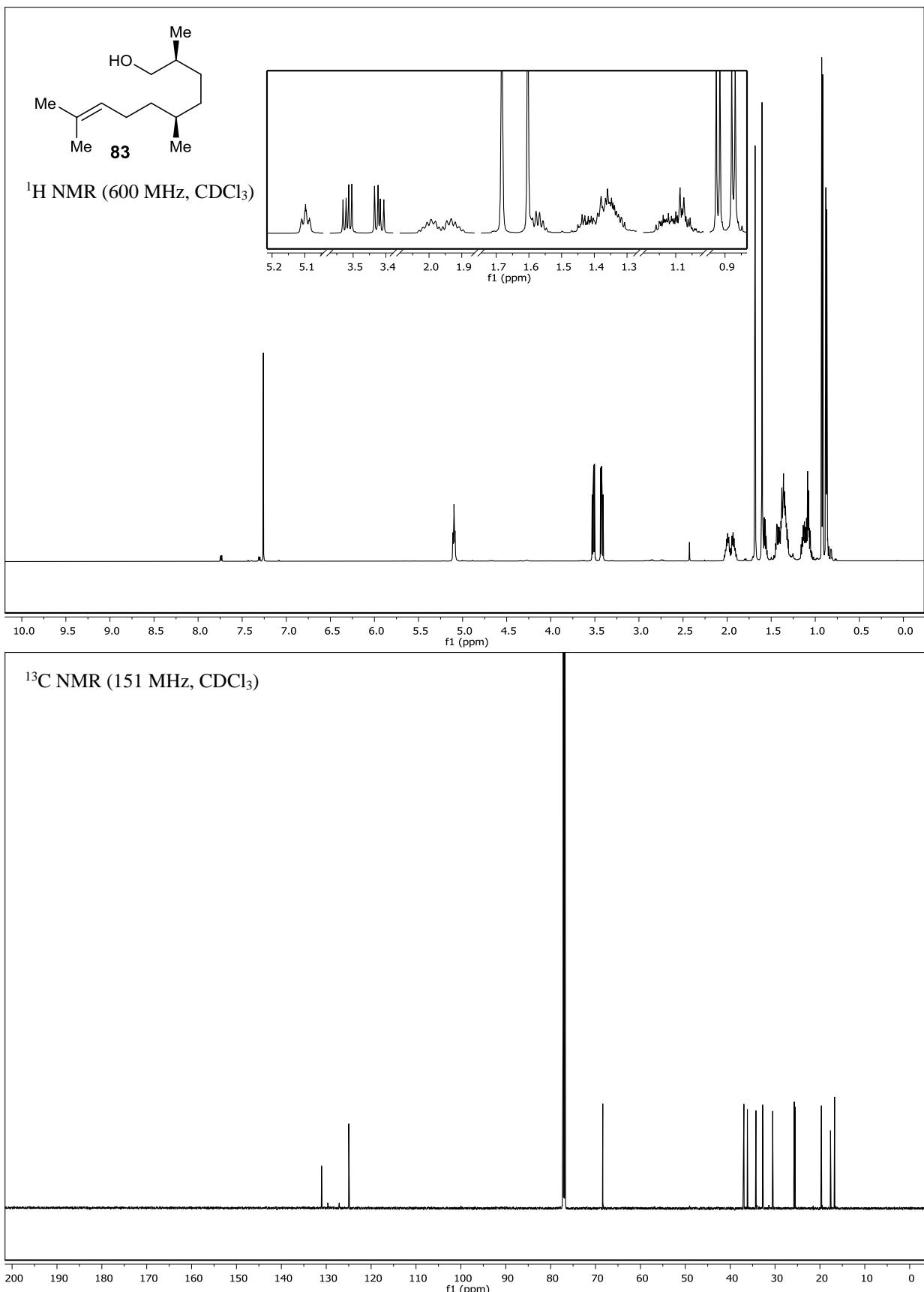
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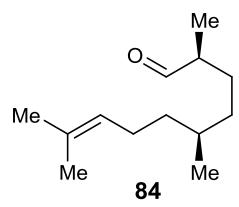
^1H NMR (600 MHz, CDCl_3)



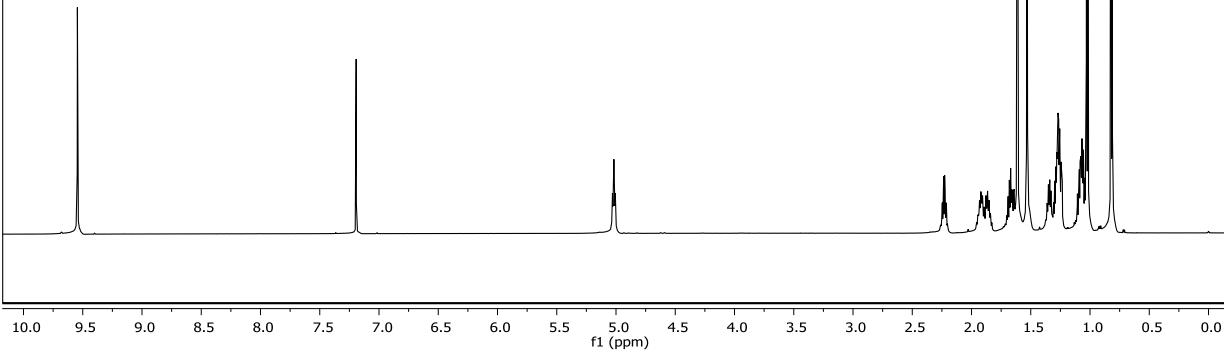
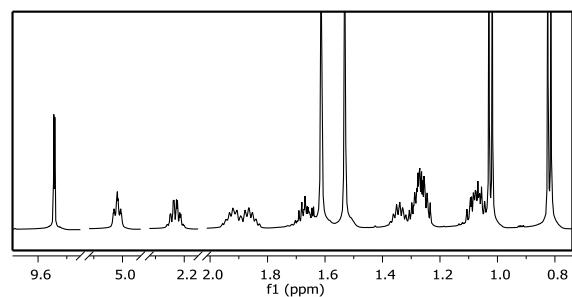
^{13}C NMR (151 MHz, CDCl_3)







¹H NMR (600 MHz, CDCl₃)



¹³C NMR (151 MHz, CDCl₃)

