Supplementary Information

# Enantioselective Synthesis of Isocarbostyril Alkaloids and Analogs Using Catalytic Dearomative Functionalization of Benzene

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## 1. Experimental:

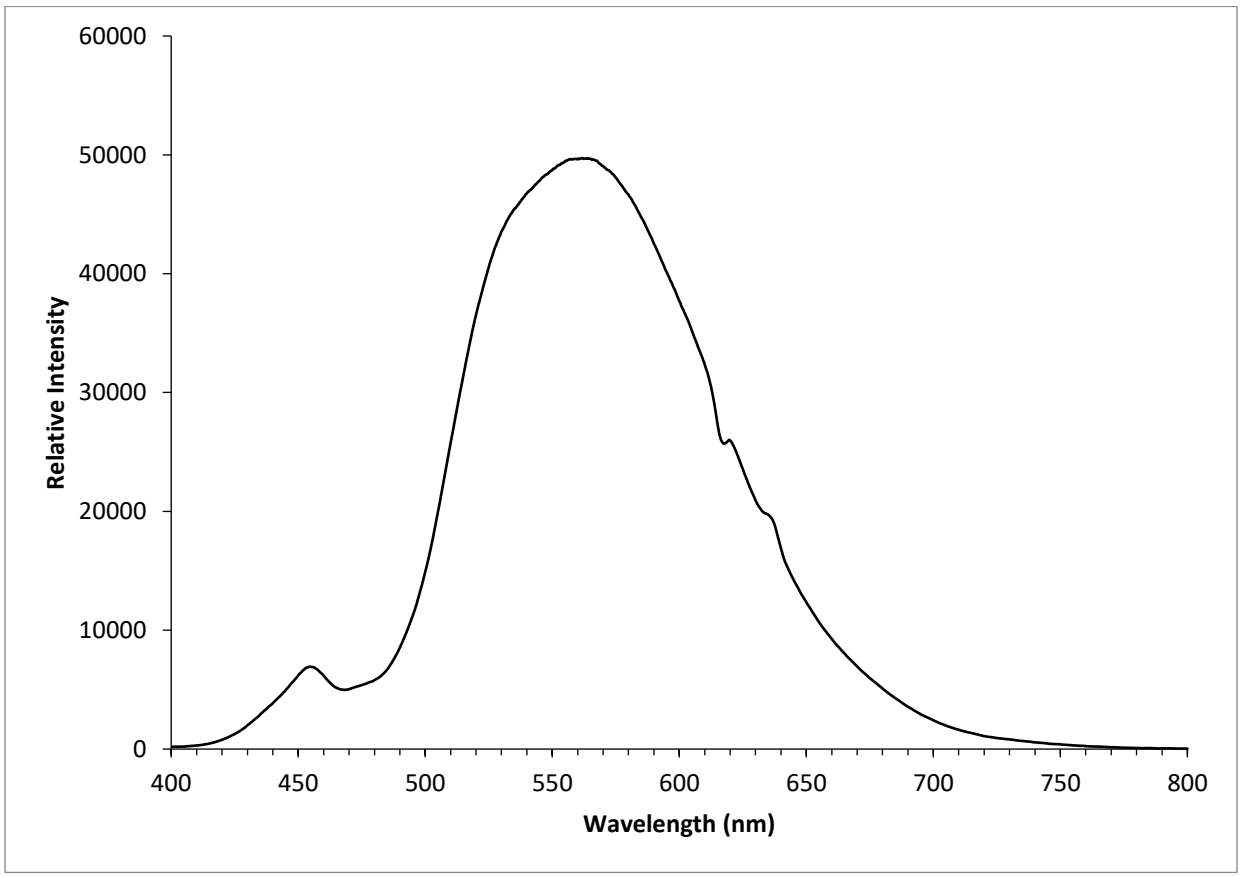
### General experimental:

Unless otherwise noted, all reactions were carried out under an ambient atmosphere. All chemicals were purchased from commercial suppliers and used as received. *N*-methyl-1,2,4-triazoline-3,5-dione (MTAD **12**) was prepared based on the literature procedures[1,2] and was resublimed before use. ($R,R_p$)- *i*Pr-Phosferrox was prepared based on the literature procedure[3,4] from D-valinol. $C_{18}$-derivatized $SiO_2$ was prepared according to the literature procedure.[5] Dry dichloromethane ($CH_2Cl_2$), and tetrahydrofuran (THF) were obtained by passing commercially available anhydrous, oxygen-free HPLC-grade solvents through activated alumina columns. Analytical thin-layer chromatography was performed on Merck silica gel 60 F254 aluminum plates. Visualization was accomplished with UV light and/or potassium permanganate ($KMnO_4$). Retention factor ($R_f$) values reported were measured using a 5 × 2 cm TLC plate in a developing chamber containing the solvent system described. Flash column chromatography was performed using Silicycle SiliaFlash® P60 ($SiO_2$, 40-63 μm particle size, 230-400 mesh). $^1$H and $^{13}$C NMR spectra were recorded on Bruker 500 (500 MHz, $^1$H; 126 MHz, $^{13}$C) or Varian Unity Inova 500 (500 MHz, $^1$H) spectrometers. Spectra are referenced to residual chloroform (δ = 7.26 ppm, $^1$H; 77.16 ppm, $^{13}$C), residual methanol (δ = 3.31 ppm, $^1$H; 49.00 ppm, $^{13}$C), residual benzene (δ = 7.16 ppm, $^1$H; 128.06 ppm, $^{13}$C), residual $H_2O$ (δ = 4.76 ppm, $^1$H) or residual dimethyl sulfoxide (δ = 2.50 ppm, $^1$H; 39.5 ppm, $^{13}$C). Chemical shifts are reported in parts per million (ppm). Multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants *J* are reported in Hertz (Hz). Mass spectrometry (MS) was performed by the University of Illinois Mass Spectrometry Laboratory. Electrospray ionization (ESI+) spectra were performed using a time-of-flight (TOF) mass analyzer. Data are reported in the form of m/z (intensity relative to the base peak = 100). For several compounds, Waters Q-TOF Ultima ESI and Agilent 6230 ESI TOF LC/MS spectrometers were used to obtain the high-resolution mass spectra. Infrared spectra were measured neat on a Perkin-Elmer spectrum BX FT-IR spectrometer. Peaks are reported in $cm^{-1}$ with indicated relative intensities: s (strong, 0–33% T); m (medium, 34–66% T), w (weak, 67–100% T), and br (broad). Visible-light spectrum of LED was recorded using an Avantes Sensline Avaspec-ULS TEC Spectrometer. Melting points of solids, compounds that solidified after chromatography, were measured on a Buchi B-540 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-2000 polarimeter at 589 nm, and are reported in units of $10^{-1}$ (deg $cm^2$ $g^{-1}$). HPLC was performed on a Shimadzu Prominence HPLC system with SPD-M20A UV/VIS Photodiode array detector (220 nm). LC-MS was performed on a Shimadzu Nexera XR UHPLC system with SPD-M30A UV/VIS Photodiode array detector and LC-MS 2020 mass spectrometer. Electrochemical reactions were run using an IKA ElectraSyn 2.0. Electrodes were purchased from IKA and used as received. The x-ray diffraction experiments were conducted using Bruker D8 Venture/Photon 100 diffractometer or Bruker APEX-II CCD diffractometer. Using Olex2,[6] the structure was solved with ShelXT[7] structure solution program using Intrinsic Phasing solution method, and the XL[8] refinement package using Least Squares minimization.

**LED light source:**

Generic cool white light LED corn bulbs were used for the photochemical experiments. These can be obtained from several manufactures over amazon.com and proved to give consistent results as well as identical visible spectra. Detailed info:

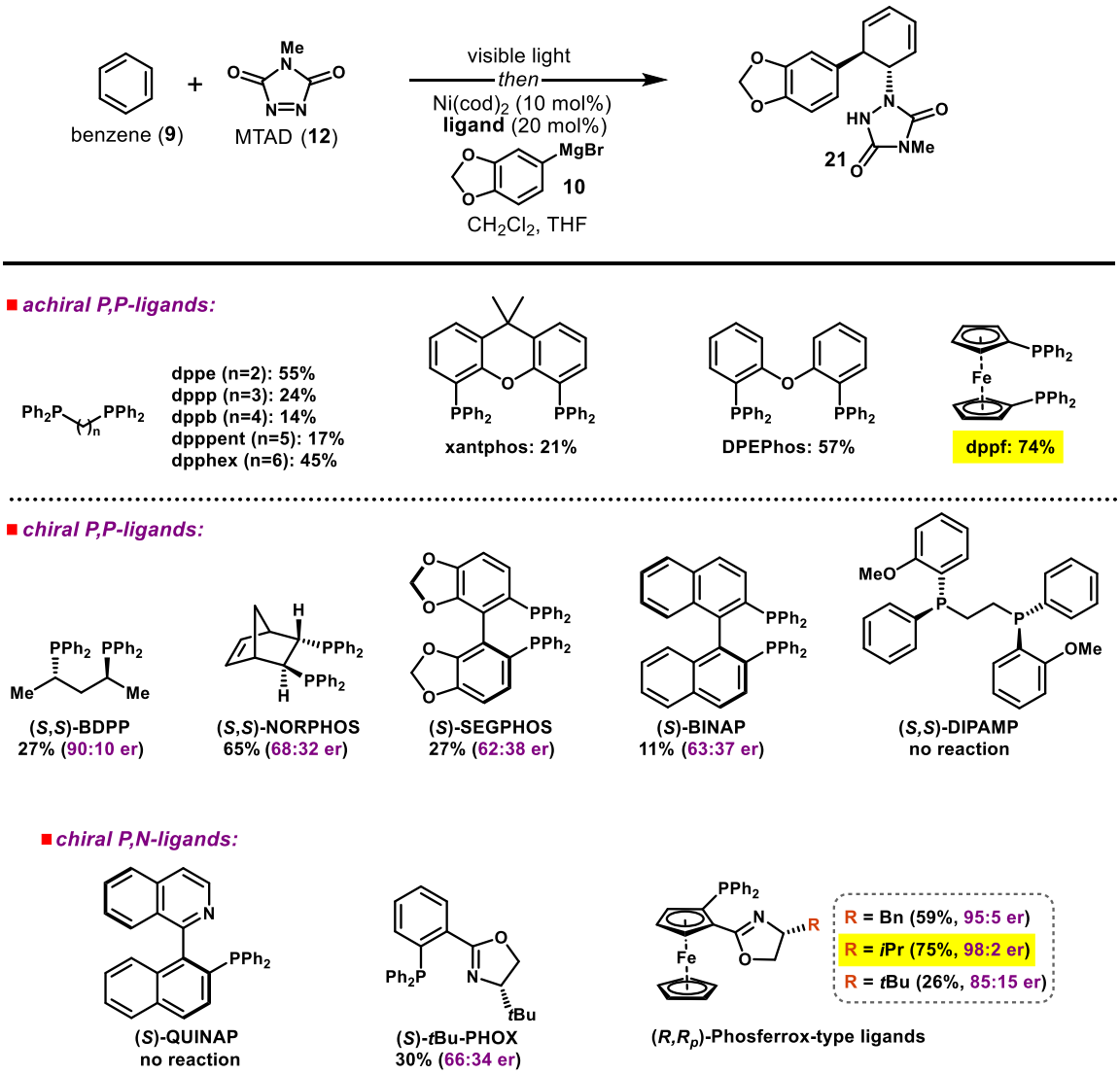
Socket: G4
LED Chip: 48 LEDs SMD 2835
Consume wattage: 4W
Input voltage: AC / DC 12V
Beam degree: 360 degrees
Color temperature: 6500K (Cool White)
Initial Lumens (lm): 290




**Spectra S1.** Spectrum of a LED bulb used.

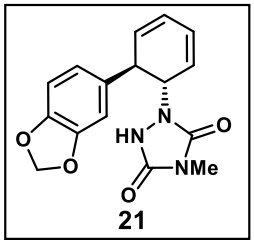
## 2. Ligand scope for Ni-catalyzed dearomative *trans*-1,2-carboamination

**Table S1: Survey of bidentate ligands.[a]**




[a]**Conditions:** MTAD (**12**, 45.2 mg, 0.4 mmol, 1.0 equiv.), benzene (**9**, 312.4 mg, 4.0 mmol, 10 equiv.), $CH_2Cl_2$ (4.0 mL), visible light, –78 °C; then $Ni(cod)_2$ (0.04 mmol, 11.0 mg, 10 mol%) and ligand (0.08 mmol, 20 mol%) added as a solution in $CH_2Cl_2$ (4.0 mL), **10** (0.4 mL, 3.0 M in THF, 1.2 mmol, 3.0 equiv.), –45 °C to rt over 3 h. Isolated yields shown after purification by flash chromatography. Enantiomeric ratio determined by HPLC analysis on a chiral stationary phase.

**Synthesis of diene 21:**[9] In an oven-dried test tube, MTAD (**12**, 45.2 mg, 0.40 mmol, 1.0 equiv.) was dissolved in anhydrous $CH_2Cl_2$ (4 mL) under nitrogen atmosphere and cooled to –78 °C. Benzene (**9**, 356 μL, 4.00 mmol, 10 equiv.) was slowly added and the solution was stirred for five minutes. The pink solution was irradiated with LED lights at –78 °C until complete loss of color. Upon decolorization, the LED lights were turned off and a pre-cooled (–78 °C) solution of $[Ni(cod)_2]$ (11.0 mg, 0.04 mmol, 10 mol%) and (*R*,$R_p$)-*i*Pr-Phosferrox (38.5 mg, 0.08 mmol, 20 mol%) in $CH_2Cl_2$ (4 mL) was added, followed by dropwise addition of 3,4-methylenedioxyphenylmagnesium bromide (**10**, 400 μL, 3.0 M in THF, 1.20 mmol, 3.0 equiv.) at the rate to keep the internal temperature below –65 °C. After addition, the cold bath temperature was warmed to –45 °C and allowed to slowly warm to 0 °C over 3 h. Reaction vessel was removed from the cold bath, stirred at room temperature for 15 min, and then aq. HCl (2 mL, 1 M) was added. The organic phase was separated and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 4 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 3:1 → 2:1) to give the desired compound as a colorless solid [94.4 mg, 0.39 mmol, 75%, 98:2 er].



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Enantiomeric ratio was determined with HPLC analysis using Diacel Chiracel® OJ-3 column, 25% *i*PrOH in hexanes, 0.8 mL/min $t_R$(minor) = 11.6 min, $t_R$(major) = 13.3 min.

$\boldsymbol{R_f}$ = 0.20 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +475.9 (*c* = 1.00 in $CHCl_3$)

**m.p.** = 160 – 161 °C

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 6.76 (d, *J* = 1.2 Hz, 1H), 6.72 (d, *J* = 1.2 Hz, 2H), 6.28 (ddt, *J* = 9.6, 5.4, 1.4 Hz, 1H), 6.13 (dddd, *J* = 9.6, 5.4, 2.0, 1.0 Hz, 1H), 5.96 – 5.88 (m, 3H), 5.60 (ddt, *J* = 9.6, 4.5, 1.0 Hz, 1H), 4.94 (ddd, *J* = 7.6, 4.5, 1.7 Hz, 1H), 3.68 (ddd, *J* = 7.6, 4.5, 2.0 Hz, 1H), 3.03 (s, 3H).

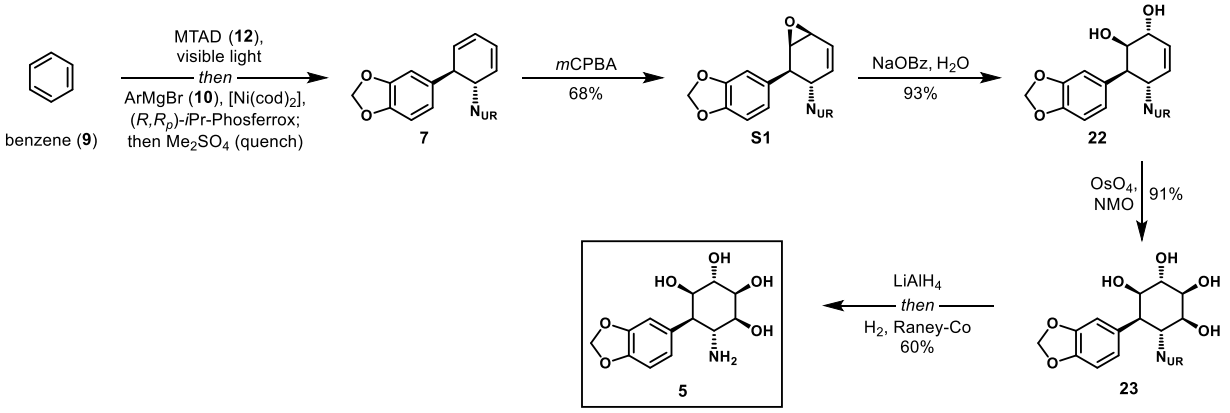
**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 155.1, 153.3, 148.0, 147.0, 133.9, 130.1, 128.7, 123.3, 121.3, 121.1, 108.5, 108.4, 101.2, 57.3, 44.5, 25.3.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{16}H_{15}N_3O_4$ $[M]^+$ calc.:313.1063; Found: 313.1071

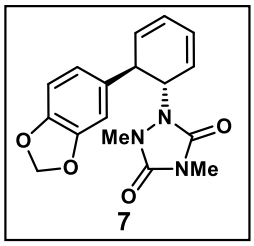
**IR** (ATR, neat, $cm^{-1}$): 3452 (w), 3158 (w), 2891 (w), 1765 (w), 1689 (s), 1502 (m), 1483 (m), 1246 (m), 1037 (m).

## 3. First generation approaches to (+)-7-deoxypancratistatin (1):

### 3-1. Synthesis of aminoteraol 5 via epoxidation:




**Synthesis of (+)-diene 7:** *[See page S7 for a detailed description of this photochemical set-up]* In an oven-dried 1 L media bottle, MTAD (**12**, 6.00 g, 53.1 mmol, 1.0 equiv.) was dissolved in anhydrous $CH_2Cl_2$ (265 mL) under nitrogen atmosphere and cooled to –78 °C. Benzene (**9**, 47.3 mL, 531 mmol, 10 equiv.) was slowly added and the solution was stirred for five minutes. The pink solution was irradiated with LED lights at –78 °C until complete loss of color. Upon decolorization, the LED lights were turned off and a solution of [Ni(cod)$_2$] (730 mg, 2.65 mmol, 5.0 mol%) and (*R*,*R*$_p$)-*i*Pr-Phosferrox (2.55 g, 5.31 mmol, 10 mol%) in $CH_2Cl_2$ (265 mL)was added, followed by dropwise addition of 3,4-methylenedioxyphenylmagnesium bromide (**10**, 53.1 mL, 3.0 M in THF, 159 mmol, 3.0 equiv.) at the rate to keep the internal temperature below –65 °C. After addition, the cold bath temperature was warmed to –45 °C and allowed to slowly warm to 0 °C over 3 h. Reaction vessel was removed from the cold bath and after stirring at room temperature for 15 min, $Me_2SO_4$ 50.2 mL, 531 mmol, 10 equiv.) and $K_2CO_3$ (22.0 g, 159 mmol, 3.0 equiv.) were added sequentially and the mixture was stirred at 35 °C for 8 h. The mixture was cooled to 0 °C and 5% aq. $NH_4OH$ (300 mL) was added, the phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 200 mL). The combined organic extracts were washed with water (2 × 200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid [11.4 g, 34.8 mmol, 65%, 98:2 er].




$\boldsymbol{R_f}$ = 0.36 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +275.9 (*c* = 0.78 in $CHCl_3$)

**m.p.** = 121 – 122 °C

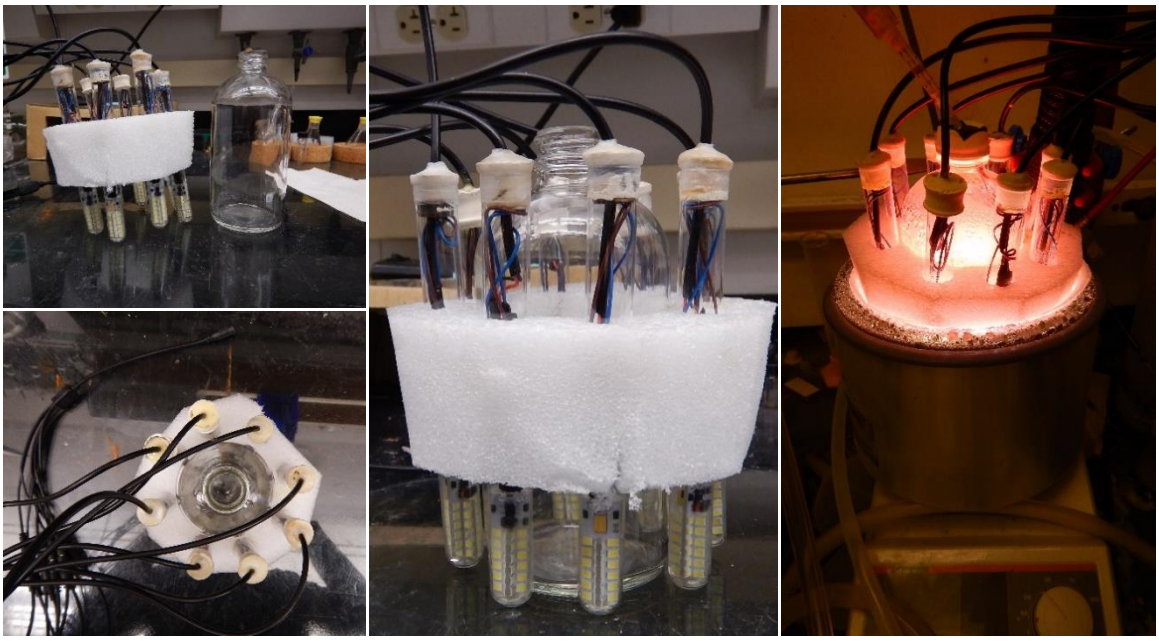
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.75 (d, *J* = 1.8 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.64 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.15 – 6.10 (m, 1H), 6.08 – 6.03 (m, 1H), 5.92 (d, *J* = 1.5 Hz, 1H), 5.91 (d, *J* = 1.5 Hz, 1H), 5.83 (ddt, *J* = 9.3, 3.1, 1.0 Hz, 1H), 5.68 (ddq, *J* = 9.7, 3.1, 1.0 Hz, 1H), 5.12 (dt, *J* = 13.6, 2.9 Hz, 1H), 3.89 (dt, *J* = 13.6, 3.1 Hz, 1H), 3.18 (s, 3H), 2.89 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.1, 155.1, 147.9, 147.0, 135.4, 130.9, 126.6, 125.5, 123.4, 121.5, 108.7, 108.2, 101.2, 61.0, 44.7, 35.1, 25.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{17}N_3O_4Na$ $[M+Na]^+$ calc.: 350.1117; Found: 350.1115.

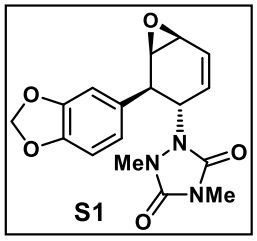
**IR** (ATR, neat, $cm^{-1}$): 2895 (m), 2250 (w), 1767 (w), 1700 (s), 1481 (m), 1035 (m), 912 (w), 725 (m).

**Set-up for dearomative *trans*-1,2-carboamination:** Eight 4W LED corn bulbs (12V, cool white light 6500K) were wired to a suitable 12V power supply, then sealed into test tubes and capped with septa (see Picture S1). Lights were arranged in a carousel fashion around a 1 L clear borosilicate glass media bottle (Picture S1). A normal reagent or media bottle can be used. The whole setup was kept submerged in a −78 °C bath during the photochemical reaction.



**Picture S1. Photochemical set-up for dearomative *trans*-1,2-carboamination.**

**Synthesis of epoxide S1:** To a stirred solution of diene **7** (627 mg, 1.92 mmol, 1.0 equiv.) in $CH_2Cl_2$ (19 mL) at 0 °C was added $NaHCO_3$ (1.61 g, 19.2 mmol, 10 equiv.) and *m*CPBA (880 mg, 75% w/w, 3.83 mmol, 2.0 equiv.). The resulting suspension was allowed to warm to room temperature and stirred overnight. Upon completion (TLC monitoring), the reagents were quenched with $Na_2S_2O_3$ (10% aq. 100 mL) and $NaHCO_3$ (sat. aq. 200 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 3:1 → 1:1) to give the desired compound as a colorless solid [447 mg, 1.30 mmol, 68%].




$\boldsymbol{R_f}$ = 0.22 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +154.9 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 154 – 156 °C

NMR analysis of epoxide **S1** revealed several conformational structures at 20 °C, which increased spectrum complexity. Therefore, a variable-temperature NMR spectroscopy was employed and a full coalescence of the peaks was observed at 100 °C.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 6.97 (d, *J* = 1.7 Hz, 0.05H), 6.94 (s, 0.05H), 6.84 (d, *J* = 7.9 Hz, 1H), 6.79 (d, *J* = 4.1 Hz, 1H), 6.72 – 6.66 (m, 1H), 6.53 (dd, *J* = 7.9, 1.8 Hz, 0.05H), 6.26 (dt, *J* = 10.2,

3.7 Hz, 1H), 6.06 (td, *J* = 7.6, 6.2, 3.7 Hz, 1H), 6.01 (d, *J* = 1.0 Hz, 1H), 5.97 (d, *J* = 1.1 Hz, 1H), 5.94 (dd, *J* = 2.7, 1.0 Hz, 0.05H), 4.95 (dt, *J* = 6.9, 3.1 Hz, 0.05H), 4.62 (br, 1H), 3.61 (d, *J* = 1.7 Hz, 0.05H), 3.55 (dd, *J* = 4.1, 1.0 Hz, 1H), 3.51 (td, *J* = 4.1, 1.7 Hz, 1H), 3.44 (dd, *J* = 4.1, 1.8 Hz, 0.05H), 3.39 (dd, *J* = 7.3, 1.8 Hz, 0.05H), 3.35 (t, *J* = 3.5 Hz, 0.05H), 3.22 (s, 0.05H), 3.00 (br, 3H), 2.77 (s, 0.15H), 2.64 (br, 3H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 6.84 – 6.78 (m, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.26 (dt, *J* = 7.6, 3.4 Hz, 1H), 6.04 (d, *J* = 9.8 Hz, 1H), 5.97 (d, *J* = 11.8 Hz, 2H), 4.55 (d, *J* = 11.0 Hz, 1H), 3.55 (d, *J* = 4.2 Hz, 1H), 3.50 (d, *J* = 4.2 Hz, 1H), 3.35 (d, *J* = 11.0 Hz, 1H), 2.95 (s, 3H), 2.73 (d, *J* = 2.0 Hz, 3H).

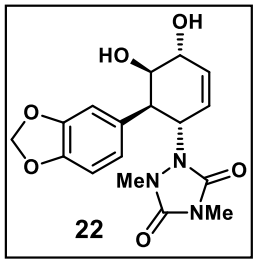
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 154.8, 154.1, 147.3, 146.5, 146.3, 134.3, 134.1, 133.6, 127.3, 125.8, 121.7, 121.6, 121.4, 108.5, 108.3, 108.1, 108.0, 107.7, 100.9, 60.4, 58.0, 57.2, 56.6, 46.5, 45.4, 44.7, 41.0, 34.8, 25.1, 24.9.

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 155.6, 154.9, 148.2, 147.4, 134.8, 134.4, 126.5, 122.4, 109.1, 108.7, 101.6, 58.0, 57.3, 47.4, 42.1, 34.6, 25.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{18}N_3O_5$ $[M+H]^+$ calc.: 344.1246; Found: 344.1245.

**IR** (ATR, neat, $cm^{-1}$): 2902 (w), 1767 (w), 1700 (s), 1484 (s), 1245 (m), 1037 (m), 932 (w), 775 (m).

**Synthesis of diol 22 from epoxide S1:** To a stirred solution of epoxide **S1** (816 mg, 2.38 mmol, 1.0 equiv.) in $H_2O$ (24 mL) was added NaOBz (24.0 mg, 0.17 mmol, 7.0 mol%) and the resulting mixture was then heated to 100 °C until judged complete by TLC. Upon completion, the aqueous phase was extracted with EtOAc (5 × 25 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 50:1 → 10:1) to give the desired compound as a colorless solid [799 mg, 2.21 mmol, 93%].



**22**

***R*$_f$** = 0.32 ($SiO_2$, $CH_2Cl_2$:MeOH = 9:1)

**$[\alpha]_D^{24}$** = +87.2 (*c* = 0.62 in EtOH)

**m.p.** = 187 – 188 °C

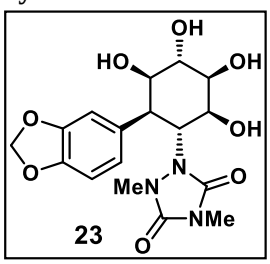
**$^1$H NMR** (500 MHz, $CD_3OD$) δ 7.02 (d, *J* = 1.7 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.7 Hz, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.03 (dd, *J* = 10.2, 1.9 Hz, 1H), 5.97 – 5.93 (m, 1H), 5.88 (m, 2H), 5.25 (d, *J* = 11.3 Hz, 1H), 4.03 – 3.99 (m, 1H), 3.87 – 3.83 (m, 1H), 3.35 (dd, *J* = 11.3, 1.9 Hz, 1H), 3.17 (s, 3H), 2.69 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 156.9, 156.8, 148.7, 148.2, 134.1, 132.9, 129.9, 123.9, 111.0, 108.4, 102.2, 75.9, 69.5, 57.6, 44.9, 35.1, 25.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{20}N_3O_6$ $[M+H]^+$ calc.: 362.1352; Found: 362.1352.

**IR** (ATR, neat, $cm^{-1}$): 3481 (m), 2902 (w), 1759 (w), 1689 (s), 1487 (s), 1251 (w), 1035 (m), 931 (w), 771 (w).

**Synthesis of tetraol 23:** To a stirred solution of diol **22** (7.15 g, 19.8 mmol, 1.0 equiv.) and NMO (3.48 g, 29.7 mmol, 1.5 equiv.) in *t*BuOH:$H_2O$ (80 mL, 1:1) at 25 °C was added $OsO_4$ (4.95 mL, 0.2 M in MeCN, 0.99 mmol, 5.0 mol%) and the resulting mixture was stirred overnight until complete conversion as judged by TLC. The reagents were quenched with excess $Na_2S_2O_3 \cdot 5H_2O$ (10 g), and the resulting solution was stirred for 30 min, and the solvent was completely removed under reduced pressure. The resulting residue was loaded onto silica and purified by flash chromatography (MeOH, $SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to give the desired compound as a colorless solid [7.13 g, 18.0 mmol, 91%].



**23**

$\boldsymbol{R_f}$ = 0.28 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +22.8 (*c* = 0.85 in EtOH)

**m.p.** = 148 – 150 °C

NMR analysis of tetraol **23** revealed several conformational structures at 20 °C, which increased spectrum complexity. Therefore, a variable-temperature NMR spectroscopy was employed and a full coalescence of the peaks was observed at 80 °C.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 6.98 (s, 0.2H), 6.86 (s, 0.8H), 6.79 (d, J = 8.0 Hz, 0.8H), 6.74 (d, J = 8.0 Hz, 0.2H), 6.70 (d, J = 8.0 Hz, 0.8H), 6.67 (d, J = 8.0 Hz, 0.2H), 5.94 (d, J = 5.7 Hz, 1.7H), 5.92 (d, J = 7.5 Hz, 0.3H), 4.77 (dd, J = 12.9, 10.5 Hz, 1.0H), 4.12 – 4.03 (m, 0.2H), 3.98 (dd, J = 10.6, 3.2 Hz, 0.8H), 3.92 – 3.87 (m, 1.0H), 3.87 – 3.81 (m, 1.0H), 3.59 (br, 1.0H), 3.40 – 3.31 (m, 1.0H), 3.02 (s, 2.3H), 2.92 (s, 0.7H), 2.78 (s, 2.3H), 2.73 (s, 0.7H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **80 °C**) δ 6.91 (s, 1H),6.75 (d, J = 8.0 Hz, 1H), 6.73 (dd, J = 8.0, 1.5 Hz, 1H), 5.94 – 5.91 (m, 2H), 4.79 (s, 1H), 4.08 (br, 1H), 3.94 (s, 1H), 3.90 (t, J = 3.3 Hz, 1H), 3.66 (s, 1H), 3.42 (br, 1H), 3.02 (s, 3H), 2.78 (s, 3H).

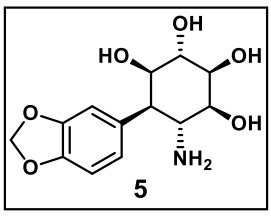
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 156.3, 155.5, 153.3, 152.2, 146.6, 146.5, 145.7, 145.6, 133.3, 133.1, 122.6, 122.3, 109.7, 107.6, 107.4, 100.6, 75.8, 75.7, 74.3, 70.0, 68.0, 67.9, 67.3, 57.2, 56.9, 45.2, 43.4, 35.4, 31.3, 25.2, 24.5.

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **80 °C**) δ 146.2, 145.3, 132.8, 122.0, 109.4, 107.0, 100.1, 75.3 74.1, 69.9, 67.6, 56.9, 24.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{22}N_3O_8$ $[M+H]^+$ calc.: 396.1407; found: 396.1390.

**IR** (ATR, neat, $cm^{-1}$): 3396 (br), 2971 (w), 2902 (w), 1758 (w), 1689 (s), 1489 (m), 1250 (w), 1039 (m), 877 (w).

**Synthesis of aminotetraol 5:** To a stirred, 0 °C solution of tetraol **23** (6.83 g, 17.3 mmol, 1.0 equiv.) in THF (345 mL) under an inert atmosphere was carefully added $LiAlH_4$ (13.1 g, 345 mmol, 20 equiv.) and the resulting mixture was heated to 60 °C and stirred for 24 h. The gray suspension was cooled to 0 °C, Rochelle salt (sat. aq. 345 mL) was carefully added and the resulting solution was stirred further 30 min at 25 °C. To this solution was added Raney®–Co (slurry in $H_2O$, 32.0 mL) and the mixture was stirred under hydrogen atmosphere (1 atm) at 60 °C until completion as judged by TLC analysis. The mixture was filtered through a pad of Celite® and the remaining solids were further washed with $H_2O$ (3 × 200 mL) and MeOH (3 × 200 mL). The combined filtrate was concentrated and the slurry was filtered again over $SiO_2$ using MeCN: $NH_4OH$ (aq. 35%) = 2:1. After removal of the solvent under reduced pressure, the resulting residue was purified by flash chromatography



**5**

($SiO_2$, $CH_2Cl_2$:MeOH:$NH_3$ (MeOH sat. sol.) = 10:1:0 → 6:1:0.1) to give the desired compound as a colorless solid [2.93 g, 10.3 mmol, 60%].

$\boldsymbol{R_f}$ = 0.10 ($SiO_2$, MeCN:MeOH = 9:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +29.1 (*c* = 0.83 in EtOH)

**m.p.** = 257 – 259 °C

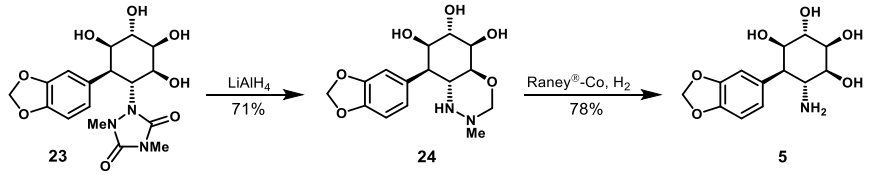
**$^1$H NMR** (500 MHz, $CD_3OD$) δ 6.97 (d, *J* = 1.5 Hz, 1H), 6.83 (dd, *J* = 8.1, 1.6 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 5.92 – 5.90 (m, 2H), 4.07 – 4.05 (m, 1H), 3.98 – 3.95 (m, 1H), 3.73 (dd, *J* = 9.9, 3.3 Hz, 1H), 3.69 – 3.67 (m, 1H), 3.58 (dd, *J* = 11.5, 10.0 Hz, 1H), 2.95 (dd, *J* = 11.6, 2.6 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 149.2, 148.0, 134.5, 123.8, 110.7, 109.0, 102.2, 76.7, 75.6, 74.4, 72.3, 50.1, 49.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{13}H_{18}NO_6$ $[M+H]^+$ calc.: 284.1134; found: 284.1137.

**IR** (ATR, neat, $cm^{-1}$): 3348 (m), 3292 (m), 2901 (m), 1501 (m), 1487 (m), 1248 (m), 1233 (m), 1034 (s), 925 (w).

**Control experiments showcasing that cyclic hydrazine 24 is an intermediate en-route to amine 5**




**Conversion of 23 → 24:** To a stirred, 0 °C solution of tetraol **23** (800 mg, 2.02 mmol, 1.0 equiv.) in THF (20 mL) under an inert atmosphere was carefully added $LiAlH_4$ (1.54 g, 40.5 mmol, 20 equiv.) and the resulting mixture was heated to 60 °C and stirred for 24 h. The gray suspension was cooled to 0 °C, Rochelle salt (sat. aq. 20 mL) was carefully added and the solution was stirred further 30 min at 25 °C. All solvents were removed under reduced pressure and the resulting residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to give the desired compound as a colorless solid [466 mg, 1.44 mmol, 71%]. This compound had a limited benchtop stability as noticeable decomposition (by TLC and $^1$H NMR) was observed within hours.

$\boldsymbol{R_f}$ = 0.47 ($SiO_2$, $CH_2Cl_2$:MeOH = 6:1)

$\boldsymbol{[\alpha]_D^{22}}$ = +33.4 (*c* = 0.67 in EtOH)

**m.p.** = 143 – 144 °C

**$^1$H NMR** (500 MHz, $CD_3OD$) δ 6.92 (d, *J* = 1.5 Hz, 1H), 6.78 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.75 (d, *J* = 8.0 Hz, 1H), 5.91 (d, *J* = 1.3 Hz, 1H), 5.90 (d, *J* = 1.3 Hz, 1H), 4.48 (d, *J* = 9.6 Hz, 1H), 4.42 (d, *J* = 9.6 Hz, 1H), 4.10 (dd, *J* = 11.8, 9.6 Hz, 1H), 4.06 – 4.04 (m, 1H), 4.02 – 3.98 (m, 1H), 3.72 (dd, *J* = 9.6, 2.8 Hz, 1H), 3.71 – 3.69 (m, 1H), 2.93 (dd, *J* = 11.8, 2.6 Hz, 1H), 2.62 (s, 3H).

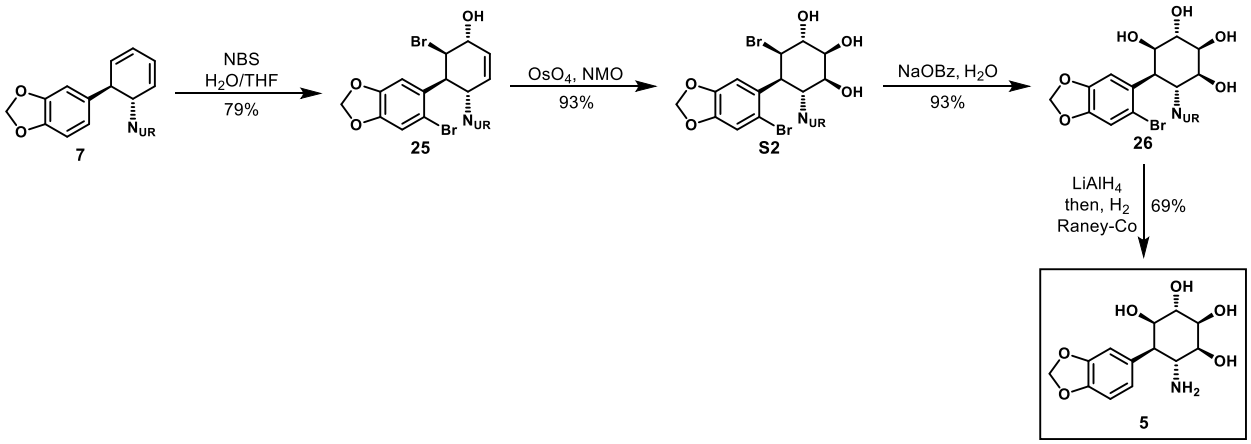
**$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 149.1, 148.0, 133.2, 123.6, 110.6, 109.0, 102.1, 87.1, 80.7, 77.3, 73.8, 72.4, 46.9, 46.4, 39.8.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{15}H_{21}N_2O_6$ $[M+H]^+$ calc.: 325.1400; found: 325.1398.

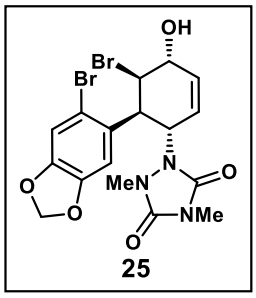
**IR** (ATR, neat, $cm^{-1}$): 3306 (br), 2906 (m), 1503 (m), 1489 (s), 1443 (m), 1251 (m), 1233 (m), 1038 (s), 929 (m), 809 (m).

**Conversion of 24 → 5:** To a stirred solution of cyclic hydrazine **24** (285 mg, 0.88 mmol) in THF (10 mL) was added Raney®-Co (slurry in $H_2O$, 4.0 mL) and the mixture was stirred under hydrogen atmosphere (1 atm) at 60 °C until completion as judged by TLC analysis. The black suspension was cooled to room temperature, filtered through a pad of Celite®, and the remaining solids were further washed with $H_2O$ (3 × 10 mL) and MeOH (3 × 10 mL). After removal of solvents under reduced pressure, the remaining residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH:$NH_3$ (MeOH sat. sol.) = 10:1:0 → 6:1:0.1) to give the desired amine as a colorless solid [195 mg, 0.69 mmol, 78%].

## 3-2. Synthesis of aminoteraol 5 via bromohydrin 25:




**Synthesis of bromohydrin 25:** To a stirred solution of (+)-diene **7** (22.5 g, 68.7 mmol, 1.00 equiv.) in THF:$H_2O$ (687 mL, 1:1) at 0 °C in the absence of light was added *N*-bromosuccinimide (27.48 g, 154.6 mmol, 2.25 equiv.), and the resulting mixture was stirred for 6 h. Upon completion (TLC monitoring), the reagents were quenched with 10% aq. $Na_2S_2O_3$ (200 ml), then the resulting solution was diluted with $H_2O$ (400 mL). The organic phase was separated, and the aqueous phase was extracted with $CHCl_3$ (2 × 600 mL). The combined organic layers were washed vigorously with sat. aq. $NaHCO_3$ (400 mL). The organic layer was dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 4:1 → 1:1) to give the desired compound as a colorless solid [27.3 g, 54.3 mmol, 79%].




$\boldsymbol{R_f}$ = 0.44 ($SiO_2$, hexanes:EtOAc = 1:3)

$\boldsymbol{[\alpha]_D^{23}}$ = +129.8 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 235 – 240 °C decomposition

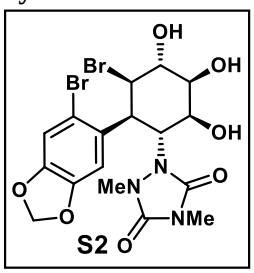
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.14 (s, 1H), 7.03 (s, 1H), 6.11 – 6.06 (m, 1H), 5.99 (s, 2H), 5.92 (d, *J* = 10.1 Hz, 1H), 5.30 – 5.10 (bs, 1H), 4.60 – 4.46 (m, 2H), 4.31 (s, 1H), 3.16 (s, 3H), 2.95 (s, 3H), 2.62 – 2.48 (bs, 1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 155.3, 155.2, 147.8, 147.1, 130.3, 128.8, 128.1, 115.8, 113.0, 110.0, 101.9, 69.2, 57.3, 55.6, 41.6, 34.6, 25.6.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{18}Br_2N_3O_5$ $[M+H]^+$ calc.: 501.9608; Found: 501.9605.

**IR** (ATR, neat, $cm^{-1}$): 3375 (br), 2904 (w), 1764 (m), 1694 (s), 1480 (s), 1231 (m), 1017 (m), 929 (w), 771 (w).

**Synthesis of dibromotriol S2:** To a stirred solution of (+)-bromohydrin **25** (350 mg, 0.696 mmol, 1.0 equiv.), *N*-methylmorpholine-*N*-oxide (123 mg, 1.04 mmol, 1.5 equiv.), and citric acid (292 mg, 1.39 mmol, 2.0 equiv.) in acetone:$H_2O$:*t*BuOH (5.6 mL, 1:1:2) at 25 °C was added $OsO_4$ (0.17 mL, 0.2 M in MeCN, 0.035 mmol, 5.0 mol%) and the resulting mixture was stirred overnight or until complete conversion as judged by TLC. The reagents were quenched with excess $Na_2S_2O_3 \cdot 5H_2O$ (10 g), the resulting solution was stirred for 30 min, and the solvent was completely removed under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 30:1 → 10:1) to give the desired compound as a colorless solid [348 mg, 0.648 mmol, 93%].




$\boldsymbol{R_f}$ = 0.45 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{23}}$ = –93.6 (*c* = 1.00 in $CHCl_3$)

**m.p.** = 165 – 167 °C

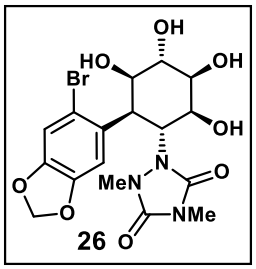
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.18 (s, 1H), 6.90 (s, 1H), 6.05 (s, 2H), 5.97 (d, *J* = 4.6 Hz, 1H), 5.01 (s, 1H), 4.82 (t, *J* = 11.4 Hz, 1H), 4.76 (d, *J* = 6.4 Hz, 1H), 4.25 (s, 1H), 4.18 (s, 1H), 4.15 (s, 1H), 4.06 – 4.00 (m, 2H), 3.93 (s, 1H), 2.90 (s, 3H), 2.87 (s, 3H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 156.6, 155.8, 147.2, 146.4, 130.2, 114.1, 112.0, 111.0, 102.0, 73.3, 72.6, 68.3, 56.6, 54.9, 43.3, 35.4, 25.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{20}N_3O_7Br_2$ $[M+H]^+$ calc.: 535.9668; found: 535.9674.

**IR** (ATR, neat, $cm^{-1}$): 3411 (br), 2910 (w), 1760 (w), 1689 (s), 1478 (s), 1400 (m), 1240 (m), 1036 (m), 729 (m).

**Synthesis of bromotetraol 26:** To a stirred solution of dibromotriol **S2** (250 mg, 0.47 mmol, 1.0 equiv.) in $H_2O$ (18 mL) was added NaOBz (134 mg, 0.93 mmol, 2.0 equiv.) and the resulting mixture was then heated at 100 °C for seven days. Upon completion, the solvent was completely removed under reduced pressure. The resulting residue was loaded onto silica and purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 1:2 → 0:1) to give the desired compound as a colorless solid [100 mg, 0.21 mmol, 45%].




$\boldsymbol{R_f}$ = 0.30 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{23}}$ = –6.23 (*c* = 1.00 in MeOH)

**m.p.** = 161 – 162 °C

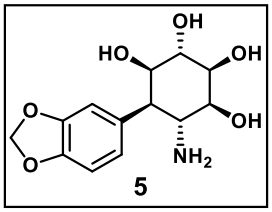
**$^1$H NMR** (500 MHz, $CD_3OD$) δ 7.08 (s, 1H), 7.02 (s, 1H), 5.98 – 5.90 (m, 2H), 5.00 (dd, *J* = 13.0, 10.5 Hz, 1H), 4.18 (dd, *J* = 10.5, 2.5 Hz, 1H), 4.13 (dd, *J* = 13.0, 2.7 Hz, 1H), 4.08 (d, *J* = 2.7 Hz, 2H), 3.87 (q, *J* = 2.5 Hz, 1H), 3.16 (s, 3H), 2.93 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 158.6, 157.6, 148.6, 148.5, 131.6, 115.8, 113.3, 112.4, 103.2, 76.1, 75.3, 71.6, 70.1, 58.4, 45.4, 36.2, 25.9.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{21}N_3O_8Br$ $[M+H]^+$ calc.: 474.0512; found: 472.0516.

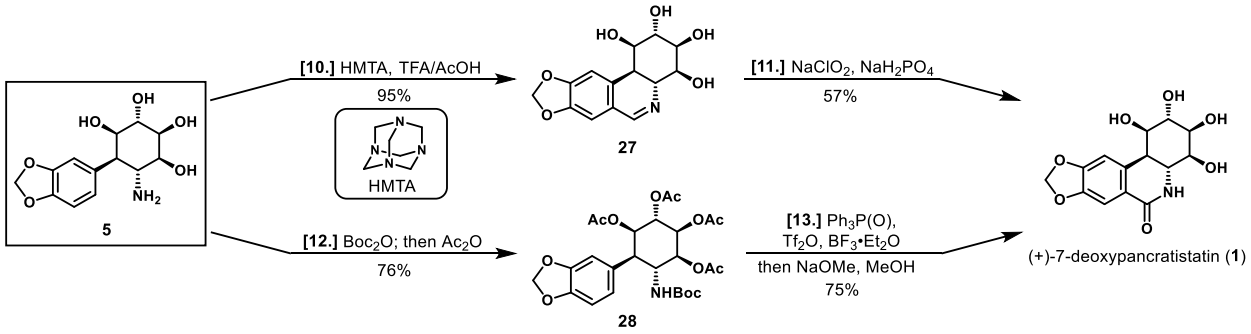
**IR** (ATR, neat, $cm^{-1}$): 3387 (br), 2907 (w), 1757 (w), 1683 (s), 1477 (s), 1401 (m), 1238 (w), 1035 (m), 845 (w).

**Synthesis of aminotetraol 5:** To a stirred, 0 °C solution of bromotetraol **26** (2.00 g, 4.22 mmol, 1.0 equiv.) in THF (42 mL) under an inert atmosphere was carefully added $LiAlH_4$ (3.20 g, 84.34 mmol, 20 equiv.) and the resulting mixture was heated to 60 °C and stirred for 24 h. The gray suspension was cooled to 0 °C, Rochelle salt (sat. aq. 42 mL) was carefully added and the resulting solution was stirred further 30 min at 25 °C. To this solution was added Raney®–Co (slurry in $H_2O$, 10.3 mL) and the mixture was stirred under hydrogen atmosphere (1 atm) at 60 °C until completion as judged by TLC analysis. The mixture was filtered through a pad of Celite® and the remaining solids were further washed with $H_2O$ (3 × 100 mL) and MeOH (3 × 100 mL). The combined filtrate was concentrated and the slurry was filtered again over $SiO_2$ using MeCN: $NH_4OH$ (aq. 35%) = 2:1. After removal of the solvent under reduced pressure, the resulting residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH:$NH_3$ (MeOH sat. sol.) = 10:1:0 → 6:1:0.1) to give the desired compound as a colorless solid [820 mg, 2.89 mmol, 69%]. Characterization data of this compound were in accordance with the values reported above.

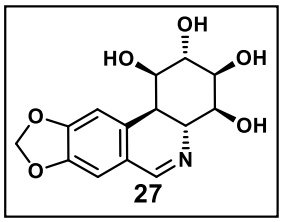


**5**

## 3-3. Conversion of aminotetraol 5 to (+)-7-deoxypancratistatin (1)




**Synthesis of dihydroisoquinoline 27:** To a stirred solution of amine **5** (100 mg, 0.35 mmol, 1.0 equiv.) in AcOH:TFA (1.2 mL, 3:1) at 25 °C was added hexamethylenetetramine (247 mg, 1.77 mmol, 5.0 equiv.) and the resulting mixture was heated to 90 °C and stirred overnight until complete conversion as judged by TLC. The reaction mixture was concentrated under reduced pressure and dissolved in MeOH (10 mL) and $NaHCO_3$ (2.50 g) was carefully added. The reaction mixture was then loaded onto Celite® and purified by flash chromatography ($C_{18}$ functionalized $SiO_2$, $H_2O$:MeOH = 5:1 → 3:1, and then $SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 6:1) to give the desired compound as a colorless solid [98.0 mg, 0.33 mmol, 95%].




$\boldsymbol{R_f}$ = 0.45 ($SiO_2$, $CH_2Cl_2$:MeOH:$NH_3$ (MeOH sat. sol.) = 6:1:0.1)

$[\alpha]_D^{23}$ = –7.0 (*c* = 0.62 in DMF)

**m.p.** = 222 – 224 °C decomposition

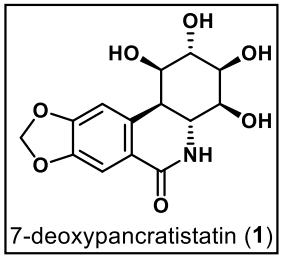
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 8.20 (d, *J* = 3.1 Hz, 1H), 7.04 (s, 1H), 6.91 (s, 1H), 6.05 (s, 2H), 5.34 – 4.58 (br, 4H), 4.34 (s, 1H), 4.03 – 3.84 (m, 2H), 3.76 (dd, *J* = 10.3, 2.9 Hz, 1H), 3.28 (d, *J* = 15.7 Hz, 1H), 2.73 (dd, *J* = 15.7, 2.6 Hz, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 158.2, 149.3, 145.5, 132.7, 123.5, 107.3, 105.7, 101.3, 74.2, 70.9, 70.0, 69.3, 55.9, 37.0.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{16}NO_6$ $[M+H]^+$ calc.: 294.0978; found: 294.0977.

**IR** (ATR, neat, $cm^{-1}$): 3280 (br), 2916 (w), 1656 (m), 1593 (m), 1485 (m), 1373 (m), 1264 (s), 1034 (s), 935 (m).

**Synthesis of (+)-7-deoxypancratistatin (1) from dihydroisoquinoline 27:** To a stirred solution of dihydroisoquinoline **27** (20.0 mg, 0.068 mmol, 1.0 equiv.) in THF (0.68 mL) and 2-methyl-2-butene (0.72 mL, 6.82 mmol, 100 equiv.) at 0 °C was added $NaClO_2$ (308 mg, 80% w/w, 2.73 mmol, 40 equiv.) and $NaH_2PO_4 \cdot 2H_2O$ (425 mg, 2.73 mmol, 40 equiv.) as a solution in $H_2O$ (0.27 mL) dropwise. The reaction was allowed to warm to 25 °C and was stirred until completion (TLC monitoring). If full conversion was not observed after 24 hours, another 20 equiv. of $NaClO_2$ and $NaH_2PO_4 \cdot 2H_2O$ would need to be added to drive the reaction to completion. Upon completion, the reagents were quenched with $Na_2S_2O_3 \cdot 5H_2O$ before the resulting solution was loaded onto silica gel and purified by flash chromatography ($C_{18}$ functionalized $SiO_2$,



$H_2O$:MeOH = 5:1 → 3:1, and then $SiO_2$, $CH_2Cl_2$:MeOH = 9:1 → 6:1) to give (+)-7-deoxypancratistatin (**1**) as a colorless solid [12.0 mg, 0.039 mmol, 57%]. Characterization data of this compound were in accordance with the literature values[10,11].

$\boldsymbol{R_f}$ = 0.30 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +75.5 (*c* = 0.75 in DMF);

Reported values:

lit.[7] $\boldsymbol{[\alpha]_D^{25}}$ = +78.5 (*c* = 0.75 in DMF)

lit.[8] $\boldsymbol{[\alpha]_D^{23}}$ = +72.7 (*c* = 2.3 in DMF)

**m.p.** = 310 – 312 °C

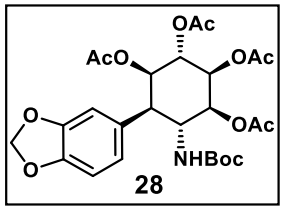
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.32 (s, 1H), 6.91 (s, 1H), 6.84 (s, 1H), 6.07 (s, 2H), 5.36 (d, *J* = 3.9 Hz, 1H), 5.07 (d, *J* = 5.7 Hz, 1H), 5.05 (d, *J* = 6.0 Hz, 1H), 4.78 (d, *J* = 7.5 Hz, 1H), 4.37 – 4.29 (m, 1H), 3.98 (q, *J* = 3.4 Hz, 1H), 3.91 – 3.83 (m, 1H), 3.79 – 3.66 (m, 2H), 2.99 (dd, *J* = 12.0, 2.0 Hz, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 164.0, 150.5, 145.8, 135.3, 123.8, 106.7, 105.5, 101.5, 73.4, 70.3, 70.2, 68.7, 50.4, 40.1, (39.8 observed by HSQC).

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{16}NO_7$ $[M+H]^+$ calc.: 310.0927; found: 310.0925.

**IR** (ATR, neat, $cm^{-1}$): 3347 (br), 2923 (w), 1650 (s), 1505 (w), 1469 (s), 1267 (m), 1203 (m), 1039 (s).

**Synthesis of protected aminotetraol 28:** To a stirred solution of amine **5** (1.20 g, 4.24 mmol, 1.0 equiv.) in dioxane:$H_2O$ (42 mL, 1:1) at 25 °C was added $Et_3N$ (1.80 mL, 12.7 mmol, 3.0 equiv.) and $Boc_2O$ (1.39 g, 6.35 mmol, 1.5 equiv.) and the reaction was stirred overnight at 25 °C until complete conversion as judged by TLC. Upon completion, the reaction was concentrated under reduced pressure and complete removal of water was achieved with azeotropic distillation using acetonitrile (3 × 2 mL). The crude residue was then suspended in $CH_2Cl_2$ (42 mL) and $Et_3N$ (2.90 mL, 21.2 mmol, 5.0 equiv.), DMAP (51.8 mg, 0.42 mmol, 10 mol%) and $Ac_2O$ (1.80 mL, 19.1 mmol, 4.5 equiv.) were added. The reaction was stirred at 25 °C until complete conversion as judged by TLC. Upon completion, the reagents were carefully quenched with $NaHCO_3$ and the resulting solution was stirred vigorously for 30 min. The phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organics were washed with aq. HCl (20 mL, 1M) and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The resulting residue was loaded onto silica and purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 3:1 → 1:1) to give the desired compound as a colorless solid [1.78 g, 3.22 mmol, 76%].



**28**

$\boldsymbol{R_f}$ = 0.38 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +20.6 (*c* = 1.00 in $CHCl_3$)

**m.p.** = 60 – 62 °C

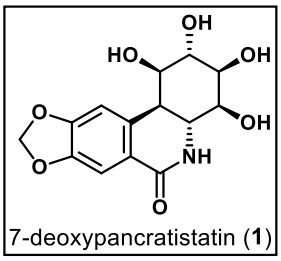
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 6.71 (s, 2H), 5.91 (dd, *J* = 13.9, 1.5 Hz, 2H), 5.33 (d, *J* = 3.5 Hz, 1H), 5.17 (dd, *J* = 10.5, 3.5 Hz, 1H), 5.10 (t, *J* = 3.0 Hz, 1H), 5.00 (td, *J* = 3.0, 1.5 Hz, 1H), 4.70 (q, *J* = 11.1 Hz, 1H), 4.16 (d, *J* = 10.5 Hz, 1H), 3.19 – 2.99 (m, 1H), 2.17 (s, 3H), 2.16 (s, 3H), 2.02 (s, 3H), 1.97 (s, 3H), 1.29 (s, 9H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.7, 169.6, 169.1, 168.4, 155.5, 147.8, 147.0, 129.9, 122.4, 109.4, 108.2, 101.1, 79.6, 72.3, 71.3, 68.9, 68.3, 47.6, 47.2, 28.2, 21.0*, 20.9, 20.8. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{26}H_{34}NO_{12}$ $[M+H]^+$ calc.: 552.2081; found: 552.2062.

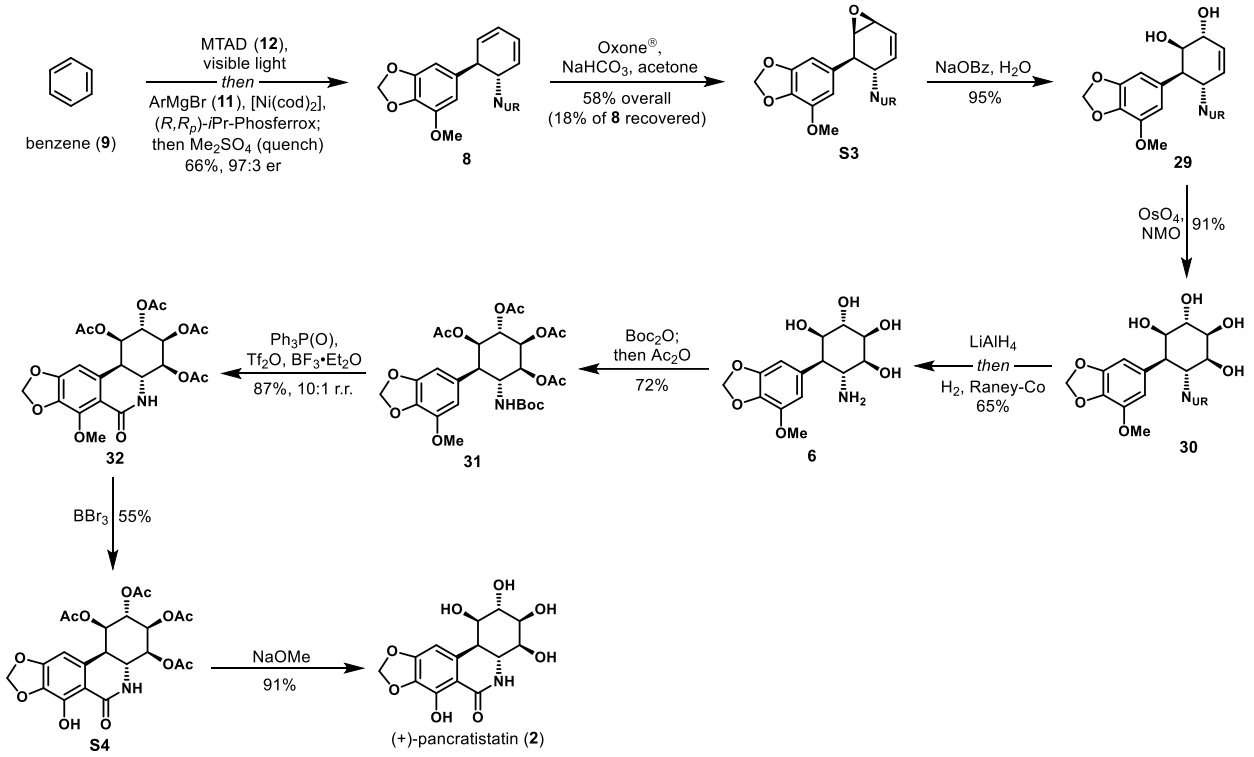
**IR** (ATR, neat, $cm^{-1}$): 3370 (w), 2977 (w), 1743 (s), 1712 (s), 1505 (m), 1492 (m), 1219 (s), 1039 (s), 730 (s).

**Synthesis of (+)-7-deoxypancratistatin (1) from protected amine 28:** To a stirred solution of $PPh_3O$ (2.15 g, 7.72 mmol, 2.4 equiv.) in $CH_2Cl_2$ (54 mL) at 0 °C under nitrogen atmosphere was added $Tf_2O$ (3.86 mL, 1.0 M in $CH_2Cl_2$, 3.86 mmol, 1.2 equiv.) dropwise. The reaction was stirred 30 min at the same temperature before the addition of protected amine **28** (1.78 g, 3.22 mmol, 1.0 equiv.) in $CH_2Cl_2$ (54 mL) dropwise. The mixture was stirred 15 min before the addition of $BF_3{\cdot}OEt_2$ (2.04 mL, 16.1 mmol, 5.0 equiv.). The reaction was stirred for 15 min before warming to 25 °C, then stirred another 45 min before $CH_2Cl_2$ (20 mL) was added and reagents were carefully quenched with sat. aq. $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The crude residue was then taken up in MeOH (32 mL) and NaOMe (3.58 mL, 25% w/w in MeOH, 16.1 mmol, 5.0 equiv.) was added. The reaction was stirred until completion by TLC before cooling to 0 °C and carefully neutralizing with HCl (1.34 mL, 12M), loading onto Celite® purification by flash chromatography ($C_{18}$ functionalized $SiO_2$, $H_2O$:MeOH = 5:1 → 3:1, and then $SiO_2$, $CH_2Cl_2$:MeOH = 9:1 → 6:1) to give (+)-7-deoxypancratistatin (**1**) as a colorless solid [743 mg, 2.40 mmol, 75% overall]. Characterization data of this compound were in accordance with the values reported above.

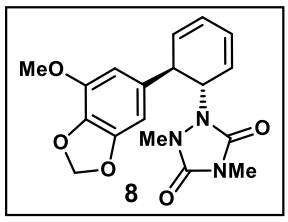


7-deoxypancratistatin (**1**)

## 4. First generation approach to (+)-pancratistatin (2)




**Synthesis of diene 8:** (+)-Diene **8** was prepared using the procedure to synthesize (+)-diene **7**, employing the Grignard reagent derived from 3,4-methylenedioxy-5-methoxy-phenyl bromide **11** (synthesized according to literature procedure[12]). The reaction was run on 53 mmol scale, with MTAD (6.00g) as the limiting reagent. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid [11.39g, 34.8 mmol, 66%, 97:3 er].




Enantiomeric ratio was determined with HPLC analysis using Daicel Chiracel® OJ-H column, 50% *i*PrOH in hexanes, 0.8 mL/min, $t_R$(minor) = 12.4 min, $t_R$(major) = 19.6 min.

$\boldsymbol{R_f}$ = 0.35 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +217.2 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 117 – 121 °C

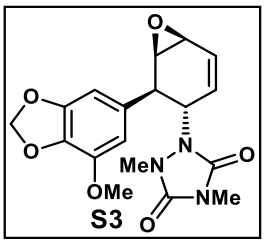
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.46 (d, *J* = 1.5 Hz, 1H), 6.38 (d, *J* = 1.5 Hz, 1H), 6.15 – 6.10 (m, 1H), 6.06 (ddd, *J* = 8.4, 5.3, 2.7 Hz, 1H), 5.94 (d, *J* = 1.6 Hz, 1H), 5.93 (d, *J* = 1.6 Hz, 1H), 5.85 (dd, *J* = 9.6, 3.1 Hz, 1H), 5.69 (dd, *J* = 9.6, 3.3 Hz, 1H), 5.16 (dt, *J* = 13.7, 3.1 Hz, 1H), 3.92 – 3.86 (m, 1H), 3.85 (s, 3H), 3.20 (s, 3H), 2.91 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.2, 155.1, 149.1, 143.5, 136.1, 134.6, 130.8, 126.5, 125.7, 123.5, 107.6, 102.4, 101.6, 61.0, 56.7, 45.1, 35.2, 25.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{19}N_3O_5Na$ $[M+Na]^+$ calc.: 380.1222; Found: 380.1218.

**IR** (ATR, neat, $cm^{-1}$): 2928 (m), 2244 (w), 1766 (w), 1706 (s), 1451 (m), 1093 (m), 963 (m), 723 (m).

**Synthesis of epoxide S3:** To a vigorously stirred solution of diene **8** (3.00 g, 8.39 mmol, 1.0 equiv.) and EDTA (31.2 mg, 83.9 µmol, 1.0 mol%) in a mixture of acetone, $CH_2Cl_2$, and sat. aq. $NaHCO_3$ (118 mL 1:10:20) was dropwise added Oxone® (10.3g, 16.8mmol. 2.0 equiv.) in water (46 mL) at 0 °C. The reaction was stirred at 0 °C for 30 minutes then was allowed to warm to 25 °C and stir for 8 hours. Then another aliquot of Oxone® (10.3g, 16.8mmol. 2.0 equiv.) in water (46 mL) at 0 °C and the reaction was stirred at 0 °C for another 30 minutes then was allowed to warm to 25 °C over 8 hours. The organic phase was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 4:1 → 1:1) to give the desired compound as a colorless solid [1.82 g, 4.88 mmol, 58%] as well as recovered starting material **8** [0.54 g, 1.52 mmol, 18%].



**S3**

$\boldsymbol{R_f}$ = 0.37 ($SiO_2$, hexanes:EtOAc = 1:3)

$\boldsymbol{[\alpha]_D^{23}}$ = +139.5 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 68 – 70 °C

NMR analysis of epoxide **S3** revealed several conformational structures at 20 °C, which increased spectrum complexity. Unfortunately, when variable-temperature NMR spectroscopy was employed full coalescence of the peaks was not observed.

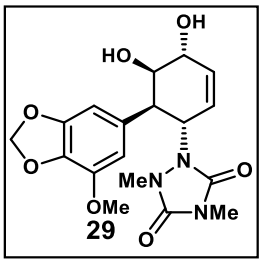
**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 6.54 – 6.50 (m, 2H), 6.50 – 6.49 (m, 0.8H), 6.28 – 6.24 (m, 1.4 H), 6.06 – 6.02 (m, 1.4 H), 5.96 (s, 1H), 5.95 (s, 0.4H), 5.94 (s, 1H), 5.92 (s, 0.4H), 4.66 (d, *J* = 10.9 Hz, 0.4H), 4.57 (d, *J* = 11.0 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 1.2H), 3.59 (t, *J* = 3.5 Hz, 0.4H), 3.56 (d, *J* = 4.2 Hz, 1H), 3.51 – 3.48 (m, 1H), 3.45 (d, *J* = 4.6 Hz, 0.4H), 3.32 (d, *J* = 11.1 Hz, 1H), 3.26 (d, *J* = 4.3 Hz, 0.4H), 3.20 (s, 1.2 H), 2.97 (s, 3. H), 2.74 (s, 3H), 2.67 (s, 1.2H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 155.0, 154.5, 154.0, 153.7, 148.3, 148.1, 142.7, 142.5, 134.1, 134.0, 133.8*, 125.3, 119.1 108.5, 108.4, 101.8, 101.7, 100.7*, 56.8, 56.2, 56.1, 55.9, 55.7, 54.7, 51.8, 49.4, 46.2, 41.2, 24.5, 24.4. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{20}N_3O_6$ $[M+H]^+$ calc.: 374.1352; Found: 374.1361.

**IR** (ATR, neat, $cm^{-1}$): 2902 (w), 1765 (w), 1698 (s), 1450 (s), 1234 (m), 1040 (m), 926 (w), 775 (m).

**Synthesis of diol 29:** Diol **29** was prepared using the procedure to synthesize diol **22**. Epoxide **S3** (1.70 g, 4.55 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 50:1 → 20:1) to give the desired compound as a colorless solid [1.69 g, 4.32 mmol, 95%].



**29**

$\boldsymbol{R_f}$ = 0.40 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +102.4 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 173 – 176 °C

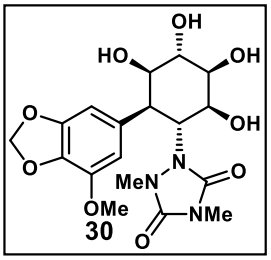
**$^1$H NMR** (500 MHz, $CD_3OD$) δ 6.65 (d, *J* = 1.5 Hz, 1H), 6.62 (d, *J* = 1.5 Hz, 1H), 6.03 (dd, *J* = 10.0, 1.9 Hz, 1H), 5.95 (ddd, *J* = 10.0, 4.5, 2.6 Hz, 1H), 5.87 (s, 2H), 5.25 (d, *J* = 11.0 Hz, 1H), 4.02 (ddd, *J* = 4.5, 2.6, 1.3 Hz, 1H), 3.87 (dd, *J* = 3.0, 1.3 Hz, 1H), 3.83 (s, 3H), 3.33 (s, 1H), 3.17 (s, 3H), 2.71 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 157.0, 156.9, 149.9, 144.3, 135.7, 134.7, 132.9, 129.8, 110.4, 104.6, 102.4, 75.9, 69.5, 57.6, 57.0, 45.2, 35.1, 25.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{21}N_3O_7Na$ $[M+Na]^+$ calc.: 414.1277; Found: 414.1287.

**IR** (ATR, neat, $cm^{-1}$): 3399 (br), 2911 (w), 1747 (w), 1682 (s), 1495 (m), 1452 (m), 1044 (m).

**Synthesis of tetraol 30:** Tetraol **30** was prepared using the procedure to synthesize tetraol **23**. Diol **29** (1.50 g, 3.83 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to give the desired compound as a colorless solid [1.48 g, 3.48mmol, 91%].




***R*$_f$** = 0.23 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

**$[\alpha]_D^{24}$** = +19.3 (*c* = 1.0 in MeOH)

**m.p.** = 134 – 138 °C

NMR analysis of tetraol **30** revealed several conformational structures at 20 °C, which increased spectrum complexity. Therefore, a variable-temperature NMR spectroscopy was employed and a full coalescence of the peaks was observed at 100 °C.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 6.60 (s, 0.25H), 6.57 – 6.54 (m, 1H), 6.53 (s, 1.25H), 5.95 – 5.87 (m, 2.5H), 5.41 (d, *J* = 3.7 Hz, 1H), 5.34 – 5.28 (m, 1.25H), 5.24 (d, *J* = 5.3 Hz, 0.25H), 4.96 (d, *J* = 7.4 Hz, 0.25H), 4.92 (d, *J* = 7.7 Hz, 1H), 4.82 – 4.70 (m, 2.25H), 4.35 (ddd, *J* = 9.9, 6.5, 3.0 Hz, 0.25H), 4.07 (t, *J* = 11.2 Hz, 0.25H), 4.00 (ddd, *J* = 10.2, 6.7, 3.1 Hz, 1H), 3.93 – 3.84 (m, 2.5H), 3.78 (s, 3H), 3.75 (s, 0.75H), 3.69 – 3.61 (m, 1H), 3.37 (s, 1H), 3.04 (s, 3H), 2.94 (s, 0.75H), 2.79 (s, 3H), 2.75 (s, 0.75H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 6.57 (s, 2H), 5.89 (s, 2H), 5.07 (s, 1H), 4.94 (s, 1H), 4.73 (s, 1H), 4.28 (s, 1H), 4.15 (s, 1H), 3.97 (s, 1H), 3.93 (d, *J* = 3.4 Hz, 1H), 3.81 (s, 3H), 3.71 (s, 1H), 3.49 (br, 1H), 3.04 (s, 3H), 2.98 (s, 1H), 2.79 (s, 3H).

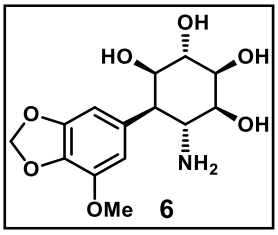
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 156.2, 155.5, 153.3, 152.2, 147.8, 147.7, 142.6, 142.3, 133.9*, 133.4, 133.2, 109.1, 108.8, 103.4, 103.2, 100.8*, 75.7, 75.2, 74.6, 74.4, 70.6, 70.2, 67.9, 67.5, 57.3, 56.9, 56.2*, 45.5, 43.7, 35.4, 31.2, 25.2, 24.5. (* Overlap of 2 peaks)

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 147.5, 142.2, 133.3, 133.2, 109.6, 103.0, 100.2, 75.2, 74.1, 70.0, 67.7, 56.9, 56.1, 24.3.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{24}N_3O_9$ $[M+H]^+$ calc.: 426.1513; found: 426.1510.

**IR** (ATR, neat, $cm^{-1}$): 3378 (br), 2910 (w), 1757 (w), 1686 (s), 1487 (m), 1244 (w), 1041 (m), 771 (w).

**Synthesis of amine 6:** Amine **6** was prepared using the procedure to synthesize amine **5**. Tetraol **30** (1.40 g, 3.54 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 10:1 → 4:1) to give the desired compound as a yellow solid [652 mg, 2.30 mmol, 65%].



**6**

$\boldsymbol{R_f}$ = 0.15 ($SiO_2$, $CH_2Cl_2$:$NH_3$ (MeOH sat. sol.) = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +18.9 (*c* = 0.5 in MeOH)

**m.p.** = 248 – 252 °C

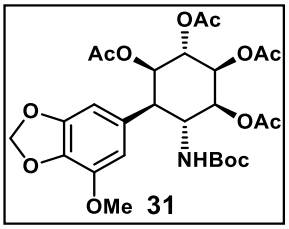
**$^1$H NMR** (500 MHz, $CD_3OD$) δ 6.68 (s, 1H), 6.66 (s, 1H), 6.01 – 5.85 (m, 2H), 4.09 (t, *J* = 3.2 Hz, 1H), 4.05 – 4.01 (m, 1H), 3.95 (dd, *J* = 10.3, 3.2 Hz, 1H), 3.91 (s, 3H), 3.81 (dd, *J* = 12.0, 10.3 Hz, 1H), 3.78 – 3.75 (m, 1H), 3.17 (dd, *J* = 12.0, 2.5 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $CD_3OD$) 150.8, 145.2, 136.5, 132.1, 110.9, 104.5, 102.7, 76.2, 75.1, 71.7, 71.1, 57.3, 52.8, 47.2.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{20}NO_7$ $[M+H]^+$ calc.: 314.1240; Found: 314.1237.

**IR** (ATR, neat, $cm^{-1}$): 3231 (br), 2906 (br), 1634 (w), 1512 (m), 1435 (s), 1256 (m), 1075 (s), 1038 (s).

**Synthesis of protected amine 31:** Protected amine **31** was prepared using the procedure to synthesize protected amine **28**. Amine **6** (600 mg, 2.12 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 3:1 → 1:1) to give the desired compound as a colorless solid [844 mg, 1.53 mmol, 72%].



**31**

$\boldsymbol{R_f}$ = 0.34 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +19.5 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 110 – 116 °C

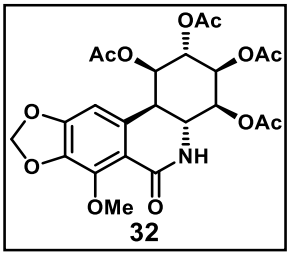
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.40 (s, 1H), 5.90 (s, 1H), 5.87 (s, 1H), 5.30 (d, *J* = 3.6 Hz, 1H), 5.13 (dd, *J* = 10.4, 3.6 Hz, 1H), 5.06 (t, *J* = 2.9 Hz, 1H), 4.98 (d, *J* = 2.9 Hz, 1H), 4.68 (q, *J* = 11.1 Hz, 1H), 4.28 (d, *J* = 10.4 Hz, 1H), 3.84 (s, 3H), 3.11 (dd, *J* = 11.1, 3.0 Hz, 1H), 2.13 (s, 6H), 1.98 (s, 3H), 1.93 (s, 3H), 1.27 (s, 9H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.5, 169.4, 168.8, 168.3, 155.5, 148.7, 143.3, 134.4, 130.4, 108.0, 103.1, 101.4, 79.5, 72.1, 71.1, 68.6, 68.0, 56.4, 47.5, 47.0, 28.1, 20.9, 20.8, 20.6, 20.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{27}H_{36}NO_{13}$ $[M+H]^+$ calc.: 582.2187; Found: 582.2161.

**IR** (ATR, neat, $cm^{-1}$): 2977 (w), 1744 (s), 1711 (m), 1367 (m), 1219 (s), 1041 (s), 927 (m).

**Synthesis of (+)-7-methoxy-pancratistatin tetraacetate 32:** To a stirred solution of $PPh_3O$ (861 mg, 3.10 mmol, 2.4 equiv.) in $CH_2Cl_2$ (21 mL) at 0 °C under nitrogen atmosphere was added $Tf_2O$ (1.55 mL, 1.0 M in $CH_2Cl_2$, 1.55 mmol, 1.2 equiv.) dropwise. The reaction was stirred 30 min at the same temperature before the addition of protected amine **31** (750 mg, 1.29 mmol, 1.0 equiv.) in $CH_2Cl_2$ (21 mL) dropwise. The mixture was stirred 15 min before the addition of $BF_3{\cdot}OEt_2$ (0.82 mL, 6.45 mmol, 5.0 equiv.). The reaction was stirred for 15 min before warming to 25 °C, then stirred another 45 min before $CH_2Cl_2$ (20 mL) was added and reagents were carefully quenched with sat. aq. $NaHCO_3$ (20 mL). The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 3:1 → 1:3) to give the desired compound as a mixture of constitutional isomers [569 mg, 1.12 mmol, 87%, 10:1 r.r]. Characterization data of (+)-7-methoxy-pancratistatin tetraacetate **32** were in accordance with the literature values.[12]



**32**

$\boldsymbol{R_f}$ = 0.38 ($SiO_2$, $CH_2Cl_2$:MeOH = 16:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +77.8 (*c* = 0.5 in MeOH)

For clarity, only the major constitutional isomer is described.

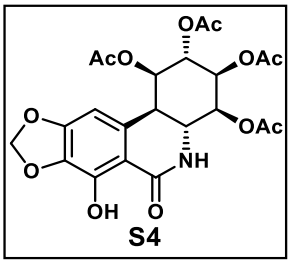
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.30 (s, 1H), 6.03 (d, *J* = 1.4 Hz, 1H), 5.98 (d, *J* = 1.4 Hz, 1H), 5.93 (s, 1H), 5.52 (d, *J* = 3.0 Hz, 1H), 5.45 (t, *J* = 3.2 Hz, 1H), 5.22 (t, *J* = 3.0 Hz, 1H), 5.13 (dd, *J* = 10.8, 3.2 Hz, 1H), 4.18 (dd, *J* = 12.8, 10.8 Hz, 1H), 4.09 – 4.04 (m, 3H), 3.37 (dd, *J* = 12.8, 2.9 Hz, 1H), 2.16 (s, 3H), 2.07 (s, 6H), 2.03 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.2, 169.7, 169.2, 168.4, 163.5, 152.6, 145.6, 137.7, 133.4, 115.9, 102.0, 99.1, 71.8, 67.8, 67.0, 66.7, 61.0, 47.7, 40.5, 21.0, 20.9, 20.8, 20.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{23}H_{26}NO_{12}$ $[M+H]^+$ calc.: 508.1455; Found: 508.1457.

**IR** (ATR, neat, $cm^{-1}$): 2923 (w), 1744 (s), 1667 (s), 1651 (w), 1481 (s), 1369 (m) 1212 (s), 1038 (s), 728 (w).

**Synthesis of (+)-pancratistatin tetraacetate S4:** (+)-pancratistatin tetraacetate **S4** was prepared according to literature procedure[12]. To the mixture of constitutional isomers **32** (500 mg, 985 μmol, 1.0 equiv.) in $CH_2Cl_2$ (49 mL) was added $BBr_3$ (985 μL, 985 μmol, 1.0 equiv.) at –78 °C. The reaction mixture was then warmed to 0 °C and stirred for 30 min. Then, 10% aq. $NH_4OH$ (20 mL) was added at 0 °C and stirred for 20 mins. The phases were separated and the aqueous phase was extracted with $CH_2Cl_2$ (5 × 100 mL). The combined organics were washed with brine (100 mL) and water (100 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 3:1 → 1:3) to give the desired compound as a colorless solid [269 mg, 541 μmol, 55%]. Characterization data of (+)-pancratistatin tetraacetate **S4** were in accordance with the literature values.[12]



**S4**

$\boldsymbol{R_f}$ = 0.32 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +32.8 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 239 – 242 °C

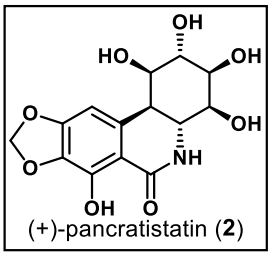
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 12.37 (s, 1H), 6.22 – 6.17 (m, 1H), 6.13 (s, 1H), 6.05 – 6.03 (m, 1H), 5.55 (d, *J* = 2.9 Hz, 1H), 5.46 (t, *J* = 3.4 Hz, 1H), 5.22 (t, *J* = 2.9 Hz, 1H), 5.17 (dd, *J* = 10.8, 3.4 Hz, 1H), 4.28 (dd, *J* = 13.2, 10.8 Hz, 1H), 3.48 – 3.38 (m, 1H), 2.16 (s, 3H), 2.09 (s, 6H), 2.04 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.1, 170.0, 169.7, 169.2, 168.4, 153.4, 146.9, 133.6, 131.8, 107.4, 102.6, 96.7, 71.8, 67.8, 67.0, 66.3, 48.4, 39.4, 21.0, 20.9, 20.8, 20.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{22}H_{24}NO_{12}$ $[M+H]^+$ calc.: 494.1299; Found: 494.1293.

**IR** (ATR, neat, $cm^{-1}$): 3351 (br), 2915 (w), 1741 (s), 1668 (w), 1370 (m), 1215 (s), 1081 (m), 1036 (s).

**Synthesis of (+)-pancratistatin 2 from (+)-pancratistatin tetraacetate S4:** To (+)-pancratistatin tetaacetate **S4** (250 mg, 507 μmol, 1.0 equiv.) in MeOH (5 mL) was added NaOMe (1.0 mL, 25% w/w in MeOH, 3.67 mmol, 7.5 equiv.). The reaction was stirred until completion by TLC before cooling to 0 °C and carefully neutralizing with HCl (313 μL, 12 M). The solution was then concentrated, and the residue was purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give the desired compound as a colorless solid [152 mg, 461 μmol, 91%].



(+)-pancratistatin (**2**)

$\boldsymbol{R_f}$ = 0.40 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{22}}$ = +37.0 (*c* = 1.0 in DMSO)

Reported values:

lit.[12] $\boldsymbol{[\alpha]_D^{23}}$ = + 38.0 (*c* = 1.08 in DMSO)
lit.[13] $\boldsymbol{[\alpha]_D^{25}}$ = + 44.0 (*c* = 1.0 in DMSO)
lit.[14] $\boldsymbol{[\alpha]_D^{26}}$ = + 41.0 (*c* = 1.0 in DMSO)
lit.[15] $\boldsymbol{[\alpha]_D^{25}}$ = + 45.0 (*c* = 0.7 in DMSO)
lit.[16] $\boldsymbol{[\alpha]_D^{20}}$ = + 46.0 (*c* = 1.0 in DMSO)
lit.[17] $\boldsymbol{[\alpha]_D^{28}}$ = + 36.8 (*c* = 1.0 in DMSO)
lit.[18] $\boldsymbol{[\alpha]_D^{34}}$ = + 48.0 (*c* = 1.0 in DMSO)
lit.[19] $\boldsymbol{[\alpha]_D^{21}}$ = + 37.0 (*c* = 1.0 in DMSO)

**m.p.** = 260 – 264 °C decomposition

**Note:** Due to large differences in reported optical rotations, we have prepared peracetylated (+)- and *rac*-pancratistatin using our synthetic blueprint and subject both to HPLC analysis on a chiral stationary phase. Accordingly, the enantiomeric ratio of our material was determined to be 98:2. See page S27 for detailed preparation and characterization of pentaacetate and page S68 for HPLC trace comparison.

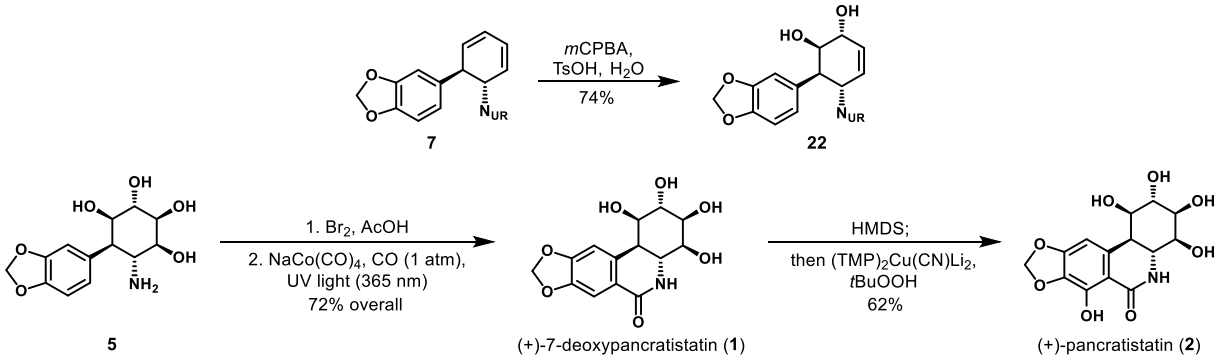
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 13.06 (s, 1H), 7.50 (s, 1H), 6.49 (s, 1H), 6.05 (s, 1H), 6.03 (s, 1H), 5.36 (d, *J* = 4.0 Hz, 1H), 5.08 (d, *J* = 5.7 Hz, 1H), 5.05 (d, *J* = 6.1 Hz, 1H), 4.83 (d, *J* = 7.5 Hz, 1H), 4.42 – 4.20 (m, 1H), 4.07 – 3.92 (m, 1H), 3.93 – 3.80 (m, 1H), 3.81 – 3.67 (m, 2H), 2.97 (d, *J* = 12.2 Hz, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 169.5, 152.1, 145.4, 135.7, 131.7, 107.5, 101.8, 97.7, 73.3, 70.2, 70.0, 68.5, 50.5, (39.5 observed by HSQC).

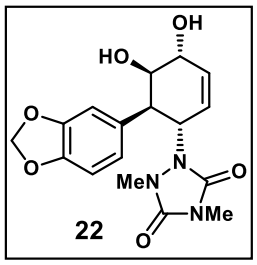
**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{16}NO_8$ $[M+H]^+$ calc.: 326.0876; found: 326.0872.

**IR** (ATR, neat, $cm^{-1}$): 3348 (m), 2926 (w), 1673 (m), 1615 (w), 1597 (w), 1462 (m), 1416 (m), 1347 (s), 1297 (m), 1228 (m), 1082 (s), 1065 (s), 1036 (s), 877 (m).

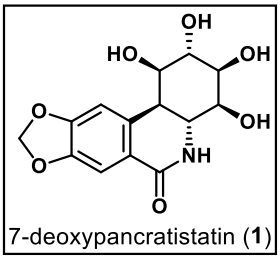
## 5. Streamlined synthesis of pancratistatins 1 and 2




**Synthesis of diol 22 from diene 7:** To a stirred solution of diene **7** (9.16 g, 28.0 mmol, 1.0 equiv.) in $CH_2Cl_2$:HFIP:$H_2O$ (110 mL, 8:3:1) at 0 °C was added *p*TsOH·$H_2O$ (532 mg, 2.80 mmol, 10 mol%) and *m*CPBA (7.84 g, 77% w/w, 35.0 mmol, 1.25 equiv.) and the resulting mixture was stirred for 10 min. The solution was then heated to 50 °C for 8 h. Upon completion (TLC monitoring), the reagents were quenched with $Na_2S_2O_3$ (10% aq. 100 mL) and $NaHCO_3$ (sat. aq. 200 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (5 × 250 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 50:1 → 10:1) to give the desired compound as a colorless solid [7.44 g, 20.6 mmol, 74%]. Characterization data of this compound were in accordance with the values reported above.

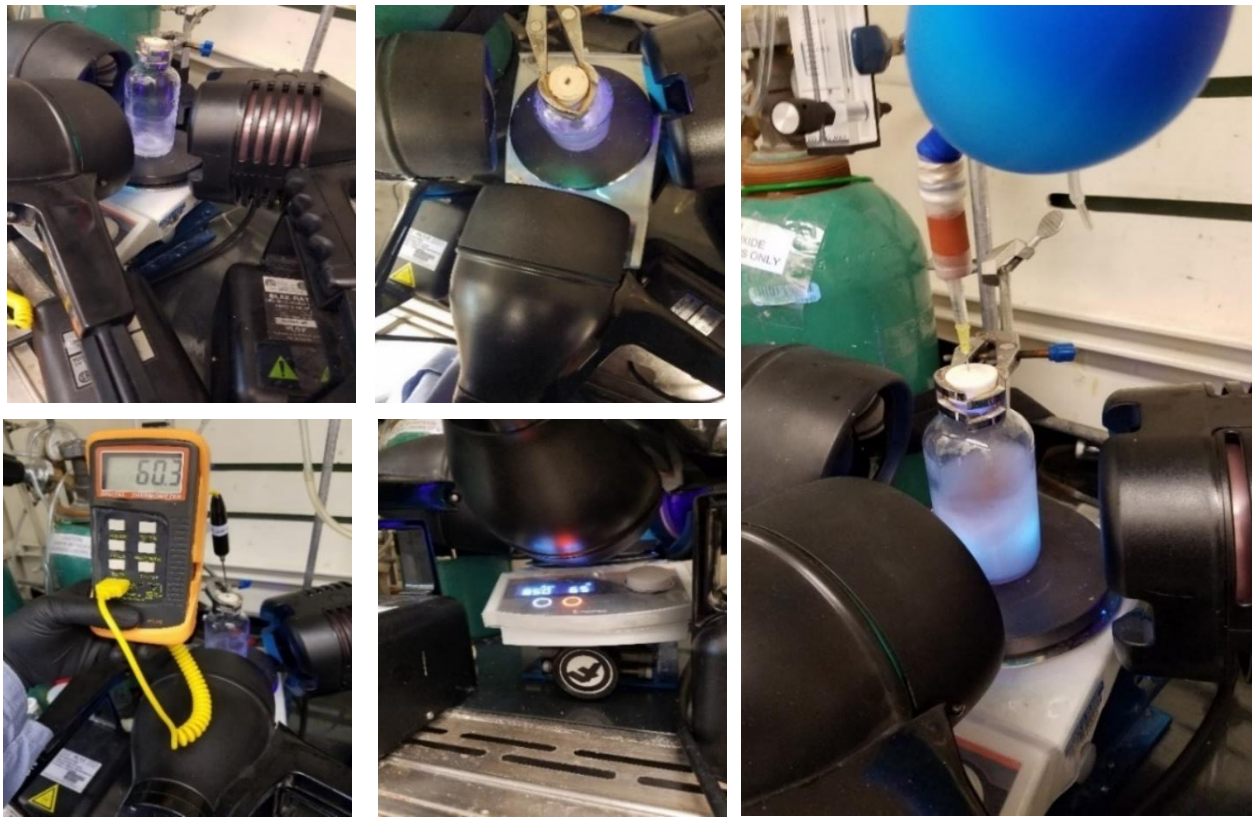



**Synthesis of (+)-7-deoxypancratistatin (1) from amine 5:** *[See page S25 for a detailed description of this photochemical set-up]*. To a stirred solution of amine **5** (2.1 g, 7.4 mmol, 1.0 equiv.) in AcOH (25 mL) was added $Br_2$ (9.63 mL, 1.0 M in AcOH, 9.63 mmol, 1.3 equiv.) dropwise. The resulting mixture was stirred in the dark at room temperature for 3 h. The solvent was removed under reduced pressure and the residual bromine was removed by co-evaporation with PhMe (3 × 5 mL) under reduced pressure. Then, *n*$Bu_4NBr$ (1.43 g, 4.45 mmol, 0.6 equiv.) and $NaCo(CO)_4$ (431 mg, 2.22 mmol, 30 mol%) were added followed by $NaHCO_3$ (sat. aq. 37 mL) and 1,4-dioxane (37 mL) and the flask was sealed with a septum. The suspension and reaction vessel were purged with CO and the reaction was stirred under a CO atmosphere (1 atm) at 60 °C under 365 nm irradiation for 8 h. Upon completion, the reaction was purged with $N_2$ and the solvent was removed under reduced pressure. The resulting residue was purified by flash chromatography ($C_{18}$ functionalized $SiO_2$, $H_2O$:MeOH = 5:1 → 3:1, and then $SiO_2$, $CH_2Cl_2$:MeOH = 9:1 → 6:1) to give (+)-7-deoxypancratistatin (**1**) as a colorless solid [1.64 g, 5.3 mmol, 72% overall]. Characterization data of this compound were in accordance with the values reported above.



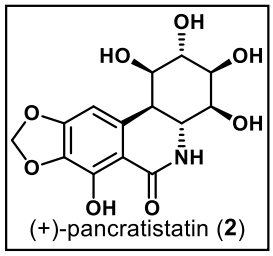
Set-up for carbonylation

Three commercial 100W UVP Blak-Ray™ B-100A UV Lamps (365 nm) were arranged around magnetic hot plate stirrer, which was lifted and adjusted to proper height for maximum light exposure (see Picture S2). Reaction vessel (250 mL reagent flask) containing 50 mL of water and magnetic stir bar was mounted on the plate, all three lights were turned on, and temperature sensor was inserted into the reaction media. The hot plate stirrer was turned on to stirring (850 rpm) and slow heating was applied until the internal temperature reached 60 °C. The plate temperature adjustment control was saved/recorded and this setting was used in further experiments involving carbonylation.



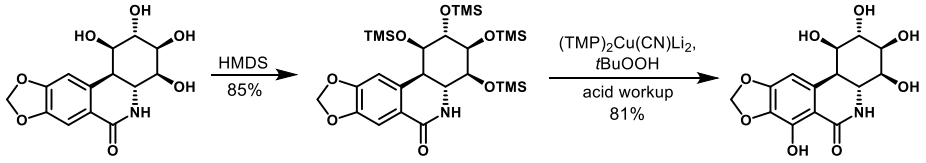
**Picture S2. Photochemical set-up for carbonylation**

**Synthesis of (+)-pancratistatin (2):** *[See page S28 for a detailed description of this protocol]* To (+)-7-deoxypancratistatin (**1**, 100 mg, 0.32 mmol) was added MeCN (2.0 mL), HMDS (2.03 mL, 9.70 mmol, 30 equiv.), and iodine (0.8 mg, 0.003 mmol, 1 mol%), and the resulting mixture was stirred at 80 °C for 12 h under an inert atmosphere. The resulting clear solution was cooled to room temperature and the volatiles were removed under reduced pressure. Trace amounts of HMDS were completely removed by azeotropic co-evaporation using toluene (3 × 2 mL). The flask containing leftover residue was flushed with nitrogen and sealed with rubber septa. THF (1.00 mL) was introduced and the resulting solution was cooled to –78 °C. Then freshly prepared $(TMP)_2Cu(CN)Li_2$[20] (3.73 mL, 0.195 M in THF, 0.73 mmol, 2.0 equiv.) was added and the mixture was warmed to 0 °C and stirred for 2 h at this temperature. The reaction was cooled again to –78 °C and *t*BuOOH (0.15 mL, 5.5 M in decane, 1.62 mmol, 2.5 equiv.) was added dropwise and solution was further stirred for 30 min before a mixture of sat. aq. $NH_4Cl$ and 10% aq. $Na_2S_2O_3$ (10 mL, 1:1) were added. After warming to room temperature, phases were separated and the aqueous phase was extracted with EtOAc (4 × 5 mL). A mixture of $CF_3COOH$:MeOH (20 mL, 1:1) was added to the combined organic extracts and volatiles were removed under reduced pressure. The residue was purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1; and then dry loaded using MeOH, $SiO_2$, $CHCl_3$:MeOH = 10:1 → 4:1) to give pancratistatin (**2**) as a colorless solid [65.0 mg, 0.20 mmol, 62%]. Characterization data of this compound were in accordance with the values reported above.



(+)-pancratistatin (**2**)

**Control experiments showcasing that tetra-*O*-TMS protected 7-deoxypancratisatin (33) is an intermediate en-route to pancratistatin (2)**



(+)-7-deoxypancratistatin (**1**) tetra-TMS-7-deoxypancratistatin (**33**) (+)-pancratistatin (**2**)

**Conversion of 1 → 33:** To (+)-7-deoxypancratistatin (**1**, 100 mg, 0.32 mmol, 1 equiv.) was added MeCN (2.0 mL), HMDS (2.03 mL, 9.70 mmol, 30 equiv.), and iodine (0.8 mg, 0.003 mmol, 1.0 mol%), and the resulting mixture was stirred at 80 °C for 12 h under an inert atmosphere. The resulting clear solution was cooled to room temperature and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc, containing 1% $Et_3N$ = 8:1 → 4:1) to give the desired compound as a colorless solid [165 mg, 0.28 mmol, 85%].

$\boldsymbol{R_f}$ = 0.40 ($SiO_2$, hexanes:EtOAc 1% TEA = 4:1)

$\boldsymbol{[\alpha]_D^{22}}$ = +104.7 (*c* = 1.0 in benzene)

**m.p.** = 56 – 57 °C

**$^1$H NMR** (500 MHz, $C_6D_6$) δ 8.16 – 8.11 (m, 1H), 6.71 (s, 1H), 6.10 – 5.93 (m, 1H), 5.31 – 5.19 (m, 2H), 4.56 – 4.43 (m, 1H), 4.38 (t, *J* = 2.9 Hz, 1H), 4.08 – 4.00 (m, 2H), 3.94 (td, *J* = 2.9, 1.0 Hz, 1H), 3.28 (dd, *J* = 12.7, 1.7 Hz, 1H), 0.21 (s, 9H), 0.17 – 0.14 (m, 18H), 0.11 (s, 9H).

**$^{13}$C NMR** (126 MHz, $C_6D_6$) δ 164.8, 151.1, 146.9, 134.5, 125.3, 108.9, 105.2, 101.4, 76.0, 74.8, 74.1, 71.9, 49.0, 42.1, 1.02, 1.01, 0.2, 0.0.

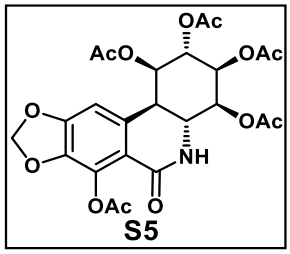
**HRMS** (ESI-TOF, m/z) calcd. For $C_{26}H_{48}NO_7Si_4$ $[M+H]^+$ calc.: 598.2502; found: 598.2508.

**IR** (ATR, neat, $cm^{-1}$): 3418 (w), 2955 (w), 2899 (w), 1669 (m), 1619 (w), 1483 (w), 1250 (m), 1133 (m), 1082 (m), 886 (m), 837 (s).

**Conversion of 33 → 2:** In an oven-dried vial, tetra-TMS-7-deoxypancratistatin (**33**, 39.0 mg, 0.065 mmol, 1 equiv.) was dissolved in THF (0.20 mL) and cooled to –78 °C. Then freshly prepared $(TMP)_2Cu(CN)Li_2$ (0.67 mL, 0.195 M in THF, 0.13 mmol, 2.0 equiv.) was added and the mixture was warmed to 0 °C and stirred for 2 h at this temperature. The reaction was cooled again to –78 °C and *t*BuOOH (0.03 mL, 5.5 M in decane, 0.16 mmol, 2.5 equiv.) was added dropwise and solution was further stirred for 30 min before a mixture of sat. aq. $NH_4Cl$ and 10% aq. $Na_2S_2O_3$ (2 mL, 1:1) were added. After warming to room temperature, phases were separated and the aqueous phase was extracted with EtOAc (4 × 2 mL). A mixture of $CF_3COOH$:MeOH (5 mL, 1:1) was added to the combined organic extracts and volatiles were removed under reduced pressure. The remaining residue was purified with two chromatographic separations (wet loaded with DMSO and purified using $C_{18}$ functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1; and then dry loaded with MeOH, $SiO_2$, $CHCl_3$:MeOH = 10:1 → 4:1) to give pancratistatin (**2**) as a colorless solid [17.0 mg, 0.05 mmol, 81%]. Characterization data of this compound were in accordance with the values reported above.

**Determination of optical purity of (+)-pancratistatin (2) by HPLC analysis of pancratistatin pentaacetate (S5)**

**Pancratistatin pentaacetate (S5):** To a stirred suspension of pancratistatin **2** (97.0 mg, 0.30 mmol, 1 equiv.) in THF (3.0 mL) was added DMAP (3.7 mg, 0.03mmol, 10 mol%), triethylamine (0.25 mL, 1.79 mmol, 6.0 equiv.), and acetic anhydride (0.17 mL, 1.79 mmol, 6.0 equiv.) and reaction was stirred at room temperature under inert atmosphere overnight. Upon completion, the reaction was partitioned between 1N HCl (5 mL) and EtOAc (5 mL). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic extracts were washed vigorously with $NaHCO_3$ (sat. aq. 10 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 2:1 → 1:2) to give pancratistatin pentaacetate as a colorless solid [145 mg, 0.27 mmol, 91%]. Characterization data for this compound were in accordance with the literature values[17].



S5

Enantioselectivity of 98:2 was determined with HPLC using Daicel Chiralpak® IA-3 column 50% *i*PrOH in hexanes, 0.8 mL/min, $t_R$(minor) = 7.7 min, $t_R$(major) = 16.8 min.

$\boldsymbol{R_f}$ = 0.37 ($SiO_2$, hexanes:EtOAc = 1:2)

$\boldsymbol{[\alpha]_D^{22}}$ = +64.6 (*c* = 1.0 in $CHCl_3$)

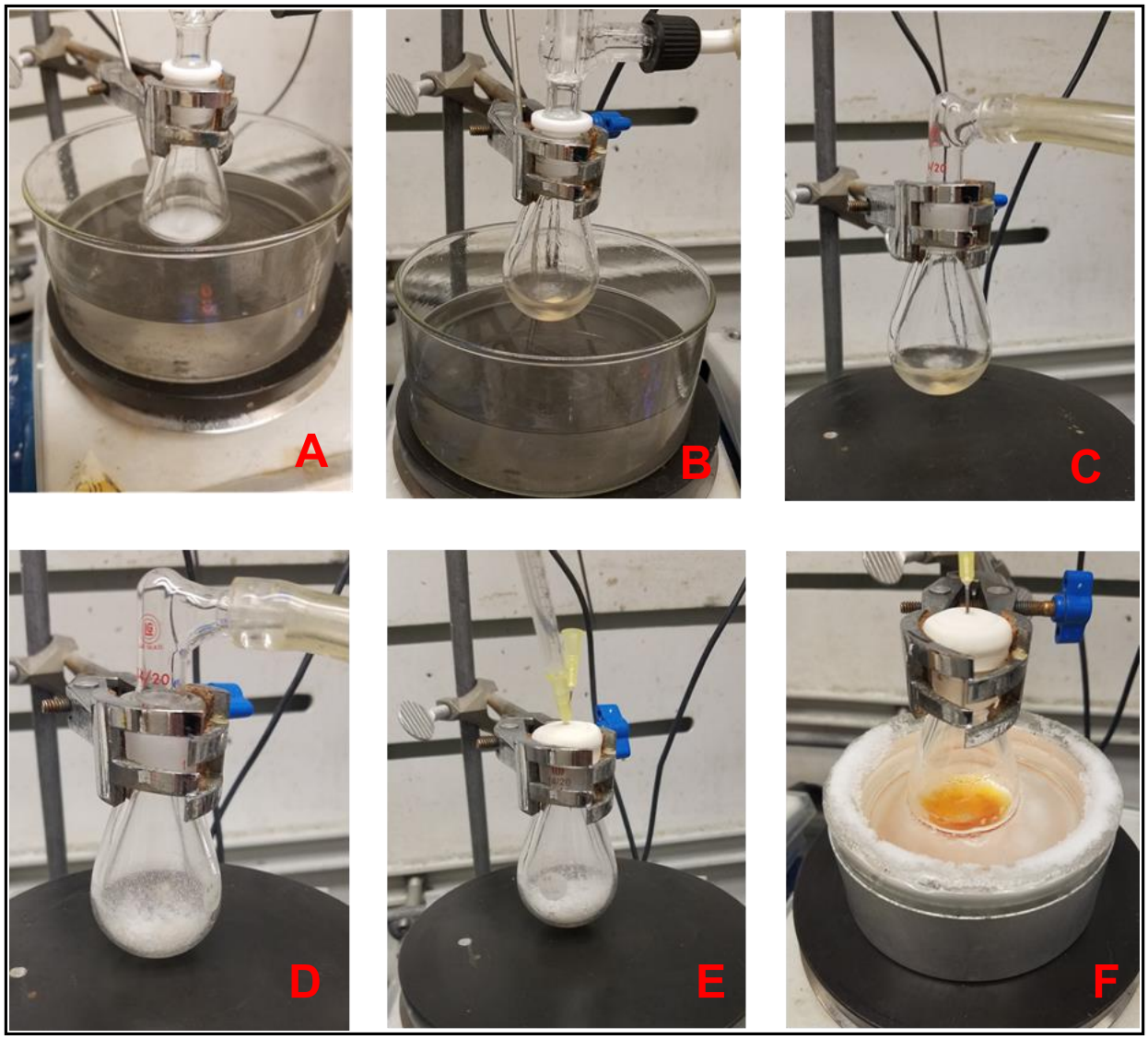
**m.p.** = 162 – 166 °C

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.10 – 6.02 (m, 2H), 5.83 (s, 1H), 5.60 – 5.51 (m, 1H), 5.50 – 5.40 (m, 1H), 5.23 – 5.17 (m, 1H), 5.12 (dd, *J* = 10.8, 3.5 Hz, 1H), 4.24 (dd, *J* = 12.9, 10.8 Hz, 1H), 3.43 (dd, *J* = 12.9, 2.9 Hz, 1H), 2.35 (s, 3H), 2.15 (s, 3H), 2.07 (s, 3H), 2.05 – 2.03 (m, 6H)

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 170.1, 169.8, 169.17, 169.16, 168.4, 163.0, 152.7, 139.9, 134.5, 132.9, 116.2, 103.1, 101.9, 71.7, 67.7, 66.9, 66.5, 47.9, 40.0, 21.0, 20.9, 20.85, 20.81, 20.7.

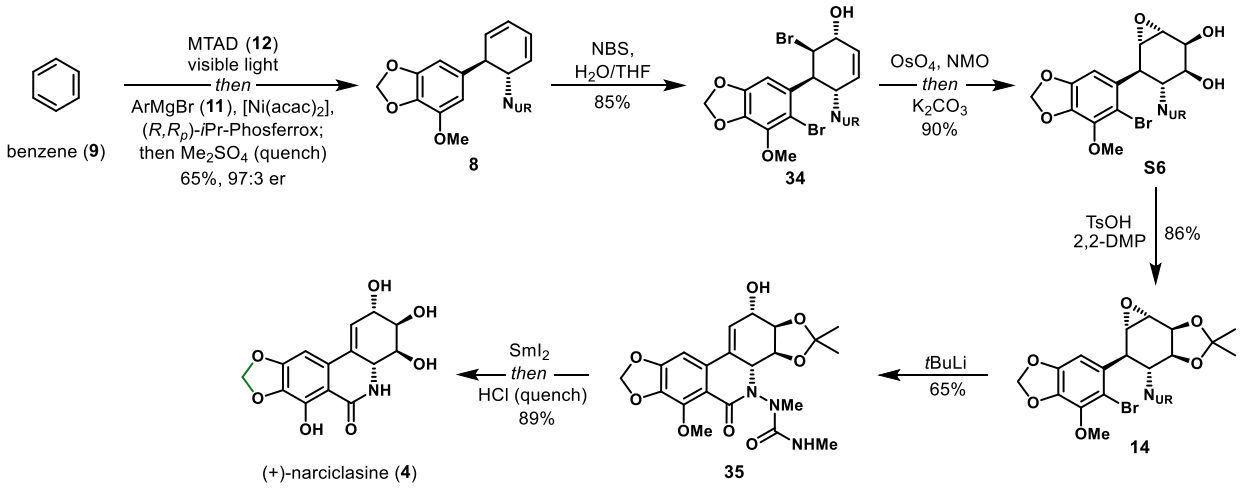
**HRMS** (ESI-TOF, m/z) calcd. For $C_{24}H_{26}NO_{13}$ $[M+H]^+$ calc.: 536.1404; found: 536.1411.

**IR** (ATR, neat, $cm^{-1}$): 3355 (w), 1745 (s), 1669 (s) 1634 (w), 1505 (w), 1484 (m), 1369 (m), 1340 (w), 1289 (w), 1247 (m), 1211 (s), 1176 (m), 1080 (m), 1042 (s), 949 (w), 925 (m), 861 (w), 815 (w), 754 (m), 639 (w).

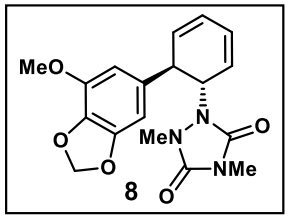



**Picture S3. Synthesis of pancratistatin.** (A) Initial suspension of (+)-7-deoxypancratistatin (**1**) in HMDS/MeCN. (B) Reaction mixture after 12 h at 80 °C. (C) Removal of volatiles under reduced pressure. (D) Leftover residue after azeotropic co-evaporation. (E) Nitrogen purge. (F) Reaction mixture after addition of $(TMP)_2Cu(CN)Li_2$.

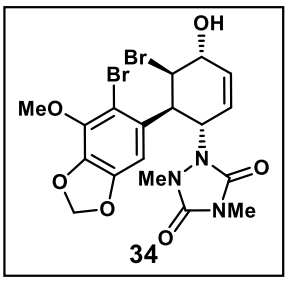
## 6. Total synthesis of (+)-narciclasine (4):




**Synthesis of diene 8:** In an oven-dried 1 L media bottle, MTAD (**12**, 6.00 g, 53 mmol, 1.0 equiv.) was dissolved in anhydrous $CH_2Cl_2$ (265 mL) under nitrogen atmosphere and cooled to –78 °C. Benzene (**9**) (47.3 mL, 0.53 mol, 10 equiv.) was slowly added and the solution was stirred for five minutes. The pink solution was irradiated with LED lights at –78 °C until complete loss of color. Upon decolorization, the LED lights were turned off and a solution of $[Ni(acac)_2]$ (204.5 mg, 0.79 mmol, 1.5 mol%) and (*R*,*R*$_p$)-*i*Pr-Phosferrox (501 mg, 1.06 mmol, 2.0 mol%) in $CH_2Cl_2$ (32 mL) (pre-stirred at 20 °C for 45 minutes then cooled to –78 °C) was added, followed by dropwise addition of 3,4-methylenedioxy-5-methoxy-phenyl bromide (**11**, 44.2 mL, 3.0 M in THF, 133 mmol, 2.5 equiv.) at the rate to keep the internal temperature below –65 °C. After addition, the cold bath temperature was warmed to –45 °C and allowed to slowly warm to 0 °C over 3 h. Reaction vessel was removed from the cold bath and after stirring at room temperature for 15 min, $Me_2SO_4$ (25.2 mL, 265 mmol, 5.0 equiv.) and $K_2CO_3$ (18.0 g, 133 mmol, 2.5 equiv.) were added sequentially and the mixture was stirred at 35 °C for 8 h. The mixture was cooled to 0 °C and 5% aq. $NH_4OH$ (300 mL) was added, the phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 200 mL). The combined organic extracts were washed with water (2 × 200 mL) and brine (200 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid [22.5 g, 68.7 mmol, 66% 97:3 er]. Characterization data of this compound were in accordance with the values reported above.




**Synthesis of bromohydrin 34:** Bromohydrin **34** was prepared using the procedure to synthesize bromohydrin **25**. Diene **8** (6.00 g, 16.8 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 4:1 → 1:1) to give the desired compound as a colorless solid [7.61 g, 14.3 mmol, 85%].




$\boldsymbol{R}_f$ = 0.56 ($SiO_2$, hexanes:EtOAc = 1:3)

$[\alpha]_D^{22}$ = +134.2 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 248 – 250 °C decomposition

NMR analysis of bromohydrin **34** revealed several conformational structures at 20 °C, which increased spectrum complexity. Unfortunately, when variable-temperature NMR spectroscopy was employed, no coalescence of the peaks was observed.

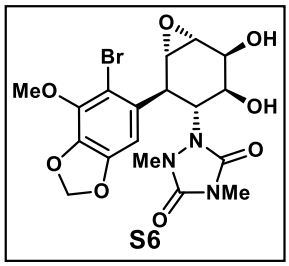
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.82 (s, 0.1H), 6.12 – 6.06 (m, 1H), 6.05 (s, 0.1H), 5.99 – 5.97 (m, 2.3H), 5.89 (d, *J* = 10.3, 1H), 5.35 (bs, 0.1H), 5.17 (bs, 1H), 4.68 – 4.51 (m, 2.2H), 4.34 (s, 1H), 4.30 (s, 0.1H), 4.03 (s, 3H), 3.94 (s, 0.3H), 3.17 (s, 0.3H), 3.15 (s, 3H), 2.97 (s, 3H), 2.92 (s, 0.3H), 2.76 – 2.55 (m, 1.1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 155.4, 155.3, 148.5, 140.6, 137.1, 130.1, 128.3, 110.4, 109.7, 104.5, 102.0, 69.5, 60.3, 57.3, 55.8, 41.9, 34.7, 25.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{20}Br_2N_3O_6$ $[M+H]^+$ calc.: 531.9719; Found: 531.9736.

**IR** (ATR, neat, $cm^{-1}$): 3404 (br), 2888 (w), 1763 (m), 1687 (s), 1482 (s), 1234 (m), 1054 (m), 935 (w), 774 (w).

**Synthesis of epoxydiol S6:** To a stirred solution of (+)-bromohydrin **34** (7.00 g, 13.1 mmol, 1.0 equiv.), *N*-methylmorpholine-*N*-oxide (2.33 g, 19.7 mmol, 1.5 equiv.), and citric acid (5.52 g, 26.3 mmol, 2.0 equiv.) in acetone:$H_2O$:*t*BuOH (105 mL, 1:1:2) at 25 °C was added $OsO_4$ (3.3 mL, 0.2 M in MeCN, 0.66 mmol, 5.0 mol%) and the resulting mixture was stirred overnight or until complete conversion as judged by TLC. The reagents were quenched with 10% aq. $Na_2S_2O_3$ (50 ml) and the resulting solution was stirred for 30 min, before diluting with $H_2O$ (100 mL), then $K_2CO_3$ (18.1 g, 131 mmol, 10 equiv.) was added and the reaction was stirred until complete conversion as judged by TLC. The organic phase was separated, and the aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 30:1 → 15:1) to give the desired compound as a colorless solid [5.72 g, 11.8 mmol, 90%].



**S6**

***R*$_f$** = 0.37 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

**[α]$_D^{22}$** = +62.9 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 163 – 165 °C

NMR analysis of epoxydiol **S6** revealed several conformational structures at 20 °C, which increased spectrum complexity. Therefore, a variable-temperature NMR spectroscopy was employed, and a full coalescence of the peaks was observed at 100 °C. For clarity only the two major conformers at 20 °C are described.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 6.94 (s, 1H), 6.79 (s, 0.8H), 6.11 (s, 1.8H), 6.08 – 6.04 (m, 1.8H), 5.71 (d, *J* = 4.5 Hz, 1H), 5.63 (d, *J* = 4.4 Hz, 0.8H), 4.93 – 4.88 (m, 1.8H), 4.49 (t, *J* = 10.3 Hz, 1H), 4.37 – 4.30 (m, 1.8H), 4.26 (d, *J* = 9.8 Hz, 0.8H), 4.08 (d, *J* = 9.9 Hz, 1H), 3.96 – 3.90 (m, 5.4H), 3.88 – 3.82 (m, 1.8H), 3.63 (t, *J* = 10.3 Hz, 0.8H), 3.36 (t, *J* = 3.3 Hz, 1.8H), 3.22 (s, 3H), 2.96 (s, 0.8H), 2.91 (s, 1H), 2.88 (s, 2.4H), 2.79 (s, 3H), 2.46 (s, 2.4H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 6.89 (s, 1H), 6.08 (s, 1H), 6.05 (s, 1H), 5.29 (s, 1H), 4.42 (d, *J* = 6.6 Hz, 1H), 4.39 – 4.37 (m, 1H), 4.29 – 4.05 (m, 2H), 3.94 (s, 3H), 3.01 – 2.93 (m, 3H), 3.01 – 2.81 (m, 1H) 2.84 (s, 3H).

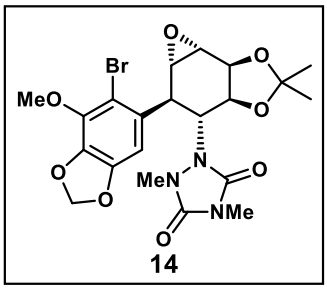
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 155.6, 155.1, 153.9, 152.8, 149.1, 148.8, 140.2, 139.5, 137.0, 136.6, 134.6, 133.6, 109.2, 108.9, 103.3, 102.6, 102.2*, 67.7, 67.4, 65.9, 64.7, 60.3, 60.1, 60.0, 59.9, 55.5, 55.2**, 47.1, 43.0, 34.9, 31.2, 25.2, 24.8. (* Overlap of 2 peaks, ** Overlap of 3 peaks)

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 148.5, 139.4, 136.4, 133.4, 108.8, 102.8, 101.6, 67.3, 65.2, 59.5, 59.3, 55.0*, 42.9, 24.3. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{21}BrN_3O_8$ $[M+H]^+$ calc.: 486.0512; Found: 486.0526.

**IR** (ATR, neat, $cm^{-1}$): 3414 (m), 2945 (w), 1747 (w), 1695 (s), 1477 (s), 1217 (m), 1085 (m), 922 (m), 728 (m).

**Synthesis of epoxyacetonide 14:** To a stirred solution of (+)-epoxydiol **S6** (5.00 g, 10.3 mmol, 1.0 equiv.) and 2,2-dimethoxypropane (2.5 mL, 20.6 mmol, 2.0 equiv.) in $CH_2Cl_2$ (59 mL) at 0 °C was added *p*TsOH·$H_2O$ (0.20 g, 1.0 mmol, 10 mol%) and the resulting mixture was stirred for 5 min before it was warmed to 25 °C and stirred for an additional 1 h or until complete conversion as judged by TLC. The reagents were quenched with aq. NaOH (20 ml, 2.0 M) and the resulting solution was stirred for 5 min, then diluted with $H_2O$ (100 mL). The phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 100 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 2:1 → 1:3) to give the desired compound as a colorless solid [4.65 g, 8.84 mmol, 86%].



**14**

***R*$_f$** = 0.36 ($SiO_2$, hexanes:EtOAc = 1:1)

**$[\alpha]_D^{23}$** = +190.7 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 209 – 213 °C

NMR analysis of epoxyacetonide **14** revealed several conformational and rotomeric structures at 20 °C, which increased spectrum complexity. Therefore, variable-temperature NMR spectroscopy was employed, and a full coalescence of the peaks was observed at 100 °C. For clarity only the two major conformers at 20 °C are described.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 6.82 (s, 1H), 6.79 (s, 0.2H), 6.11 – 6.06 (m, 2H), 6.05 – 6.04 (m, 0.4H), 5.01 (dd, *J* = 12.6, 10.4 Hz, 0.2H), 4.83 (dd, *J* = 11.8, 5.5 Hz, 1H), 4.44 (s, 1H), 4.25 (dd, *J* = 10.4, 5.2 Hz, 0.2H), 4.17 (dd, *J* = 12.1, 9.8 Hz, 0.2H), 3.93 (s, 3H), 3.91 (s, 0.6H), 3.83 – 3.72 (m, 1H), 3.66 – 3.61 (m, 0.2H), 3.51 – 3.46 (m, 1H), 3.16 (s, 0.2H), 3.13 (s, 1H), 2.94 (s, 3.6H), 2.84 (s, 0.6H), 2.82 (s, 3H), 2.71 (s, 0.2H), 2.68 (s, 1H), 1.47 (s, 0.6H), 1.44 (s, 3H), 1.35 (s, 0.6H), 1.32 (s, 3H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 6.79 (s, 1H), 6.06 (s, 1H), 6.05 (s, 1H), 4.83 (d, *J* = 5.5 Hz, 1H), 4.50 (s, 1H), 4.18 (s, 1H), 3.94 (s, 3H), 3.89 – 3.78 (m, 1H), 3.50 (s, 1H), 3.16 (s, 1H), 2.95 (s, 3H), 2.83 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H).

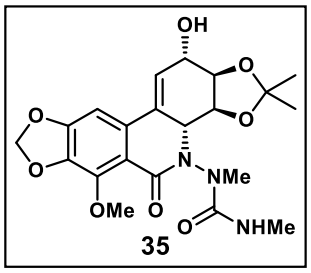
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 155.7, 155.5, 153.9, 153.2, 148.8, 147.8, 140.2, 139.8, 137.1, 136.7, 131.7, 130.8, 110.2, 110.0, 109.7, 109.5, 108.2, 103.1, 102.2*, 73.0, 72.9, 72.8, 72.6, 60.0, 59.9, 59.5, 58.5, 57.8, 57.5, 53.0, 51.6, 45.7, 43.4, 36.0, 32.1, 27.4, 27.2, 26.1, 25.7, 25.2, 24.7. (* Overlap of 2 peaks)

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 154.8, 154.5, 148.4, 139.7, 136.5, 131.4, 109.5, 109.3, 102.7, 101.7, 72.8, 72.4, 59.5, 59.3, 57.9, 51.3, 43.1, 34.2, 26.9, 25.2, 24.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{21}H_{25}BrN_3O_8$ $[M+H]^+$ calc.: 526.0825; Found: 526.0820.

**IR** (ATR, neat, $cm^{-1}$): 2986 (w), 1767 (w), 1704 (s), 1477 (s), 1249 (m), 1216 (s), 1077 (s), 921 (m), 774 (m).

**Synthesis of lactam 35:** *[See page S33 for a detailed description of the set-up]* To a stirred solution of (+)-epoxyacetonide **14** (4.00 g, 7.60 mmol, 1.0 equiv.), in THF (304 mL) at –78 °C was added a solution of *t*BuLi (25.5 mL, 0.7 M in hexanes, 17.9 mmol, 2.35 equiv.) over 3 h. The reagents were then quenched with sat. aq. $NH_4Cl$ (40 mL) at –78 °C then the reaction was warmed to 25 °C. The resulting mixture was diluted with $H_2O$ (100 mL) and the phases were separated. The aqueous phase was extracted with EtOAc (5 × 300 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 50:1 → 30:1) to give the desired compound as a colorless solid [2.21 g, 4.94 mmol, 65%].



**35**

$\boldsymbol{R_f}$ = 0.31 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{22}}$ = -5.9 (*c* = 0.5 in $CHCl_3$)

**m.p.** = 161 – 163 °C decomposition

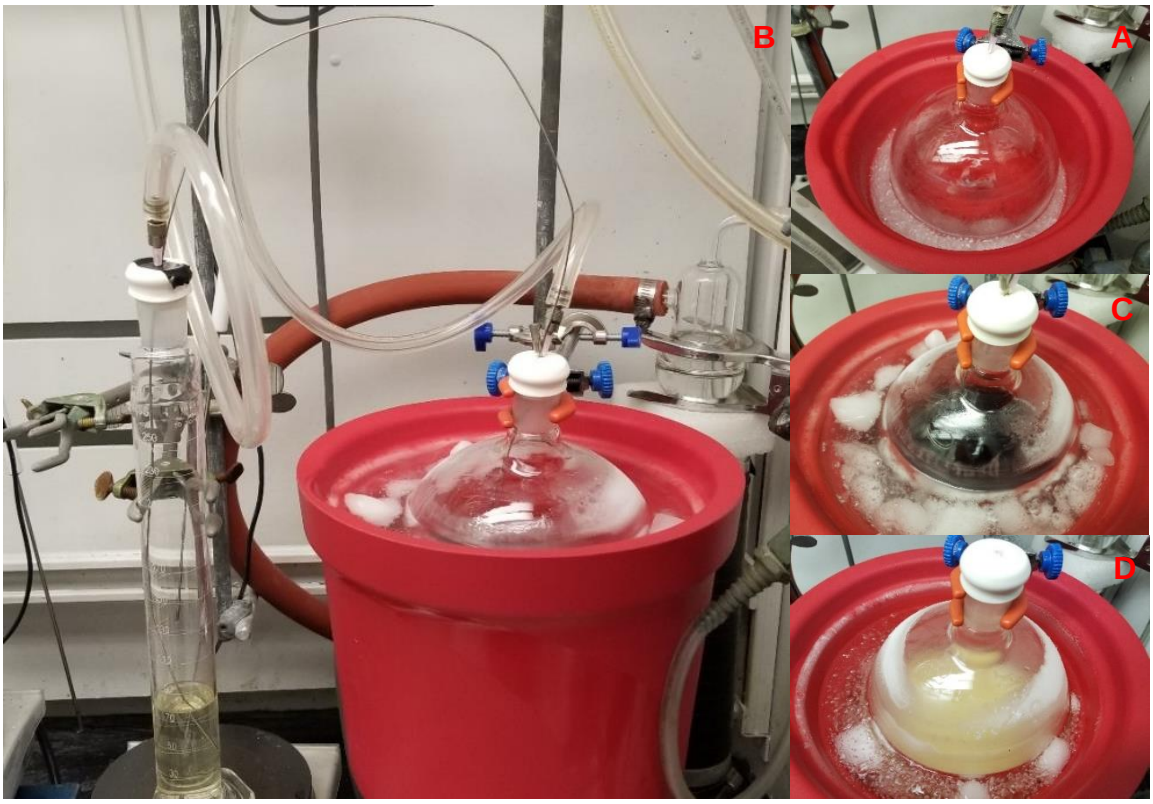
NMR analysis of lactam **35** revealed several conformational structures at 20 °C, which increased spectrum complexity. Unfortunately, when variable-temperature NMR spectroscopy was employed no coalescence of the peaks was observed.

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.81 (s, 0.4H), 6.40 (t, *J* = 3.1 Hz, 1H), 6.35 (t, *J* = 3.1 Hz, 0.4H), 6.04 (s, 2H), 6.02 – 6.00 (m, 1H), 5.05 (q, *J* = 4.8 Hz, 1H), 4.57 (bs, 0.4H), 4.55 – 4.49 (m, 1.4H), 4.45 – 4.40 (m, 1H), 4.35 – 4.26 (m, 2H), 4.06 – 4.01 (m, 1.4H), 4.04 (s, 3H), 4.02 (s, 1.2H), 3.28 (s, 1.2H), 3.13 (s, 3H), 3.06 (s, 0.4 H), 2.95 (s, 1H), 2.81 (d, *J* = 4.6 Hz, 1.2H), 2.76 (d, *J* = 4.8 Hz, 3H), 1.54 – 1.45 (m, 4.2H), 1.36 (s, 1.2H), 1.34 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 161.9*, 159.1, 157.7, 153.2, 152.8, 145.2, 145.2, 139.4, 139.2, 131.4, 130.4, 128.4, 128.4, 126.9*, 113.1*, 111.4, 110.3, 102.3, 102.2, 97.8, 97.2, 79.6, 78.8, 78.4, 76.1, 72.5, 71.0, 63.0, 61.1, 61.0, 60.5, 38.8, 31.9, 27.7, 27.6, 27.5, 27.2, 25.2, 24.9. (* Overlap of 2 peaks)

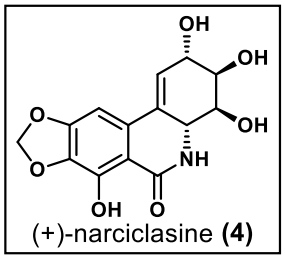
**HRMS** (ESI-TOF, m/z) calcd. For $C_{21}H_{26}N_3O_8$ $[M+H]^+$ calc.: 448.1720; Found: 448.1716.

**IR** (ATR, neat, $cm^{-1}$): 3397 (m), 2924 (w), 1661 (s), 1526 (m), 1480 (s), 1213 (s), 1049 (m), 932 (m), 771 (s).




**Picture S4. Synthesis of lactam 35.** (A) Initial solution of (+)-epoxyacetonide **14** in THF. (B) Cannulation of *t*BuLi into the reaction vessel. (C) Reaction mixture after addition of *t*BuLi. (D) Reaction mixture after addition of sat. aq. $NH_4Cl$.

**Synthesis of (+)-narciclasine 4:** To a stirred solution of (–)-lactam **35** (1.00 g, 2.23 mmol, 1.0 equiv.), in degassed MeOH (30 mL) at 0 °C was added dropwise a solution of $SmI_2$ (44.7 mL, 0.1 M in THF, 4.47 mmol, 2.0 equiv.)[21] over 30 min. The solution was then heated to 40 °C and was allowed to stir until complete conversion as judged by TLC. Then aq. HCl (40 mL, 6.0 M) was added and the resulting solution was stirred until complete conversion as judged by TLC. The solution was then carefully neutralized with solid $NaHCO_3$ (20 g). The resulting suspension was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeOH = 1:0 → 5:1) to give (+)-narciclasine as a colorless solid [610 mg, 1.99 mmol, 89%]. Characterization data of (+)-narciclasine (**4**) were in accordance with the literature values.[22,23]




$\boldsymbol{R_f}$ = 0.33 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +144.0 (*c* = 0.7 in MeOH)

$\boldsymbol{[\alpha]_D^{23}}$ = +165.2 (*c* = 1.0 in DMSO)

Reported Values:

**Lit**[22] $\boldsymbol{[\alpha]_D^{25}}$ = +141.8 (*c* = 0.7 in MeOH)

**Lit**[23] $\boldsymbol{[\alpha]_D^{25}}$ = +142.8 (*c* = 0.7 in MeOH)

**m.p.** = 200 – 216 °C decomposition

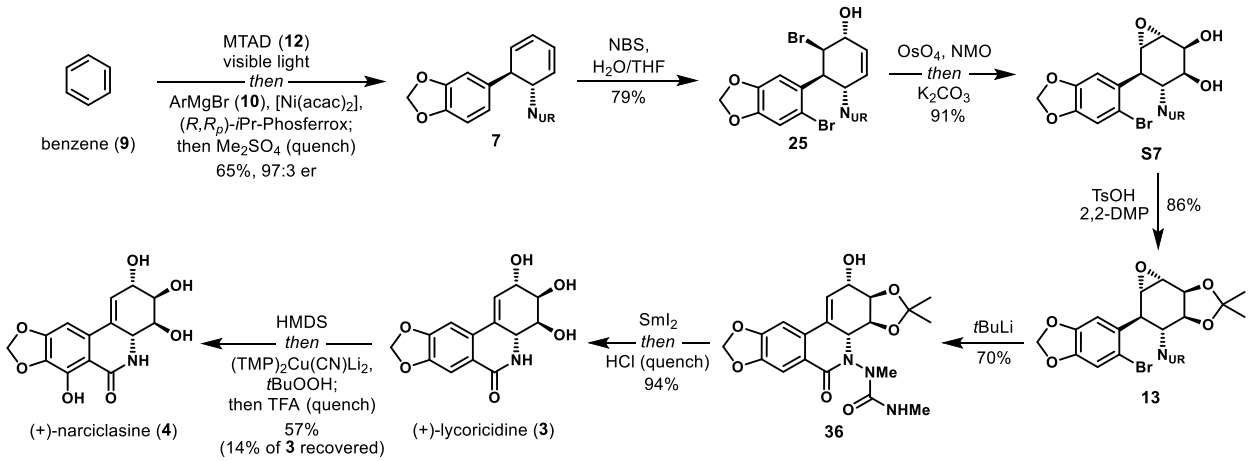
**$^{1}$H NMR** (500 MHz, DMSO-$d_6$) δ 13.26 (s, 1H), 7.89 (s, 1H), 6.86 (s, 1H), 6.16 – 6.14 (m, 1H), 6.11 – 6.07 (m, 2H), 5.20 – 5.18 (m, 2H), 5.02 (d, *J* = 3.7 Hz, 1H), 4.19 (ddd, *J* = 8.6, 2.6, 1.4 Hz, 1H), 4.03 – 3.99 (m, 1H), 3.80 (ddd, *J* = 8.6, 5.5, 2.2 Hz, 1H), 3.71 – 3.68 (m, 1H).

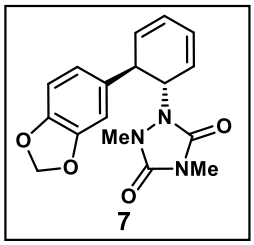
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 168.9, 152.3, 144.8, 133.4, 132.1, 129.2, 124.8, 105.6, 102.1, 95.8, 72.4, 69.1, 68.8, 52.9.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{17}N_2O_7$ $[M+NH_4]^+$ calc.: 325.1030; Found: 325.1039.

**IR** (ATR, neat, $cm^{-1}$): 3441 (br), 3205 (m), 2908 (m), 1666 (s), 1468 (s), 1355 (s), 1281 (m), 1079 (s), 1033 (s).

## 7. Scalable synthesis of (+)-lycoricidine (3) and (+)-narciclasine (4):



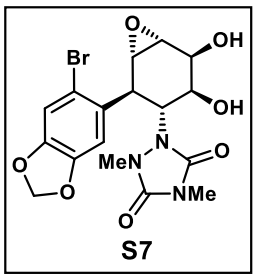

**Synthesis of (+)-diene 7:** In an oven-dried 1 L media bottle, MTAD (**12**, 12.00 g, 106 mmol, 1.0 equiv.) was dissolved in anhydrous $CH_2Cl_2$ (531 mL) under nitrogen atmosphere and cooled to –78 °C. Benzene (**9**) (94.6 mL, 1.06 mol, 10 equiv.) was slowly added and the solution was stirred for five minutes. The pink solution was irradiated with LED lights at –78 °C until complete loss of color. Upon decolorization, the LED lights were turned off and a solution of [Ni(acac)$_2$] (408.9 mg, 1.59 mmol, 1.5 mol%) and (*R*,*R*$_p$)-*i*Pr-Phosferrox (1.02 g, 2.12 mmol, 2.0 mol%) in $CH_2Cl_2$ (64 mL) (pre-stirred at 20 °C for 45 minutes then cooled to –78 °C) was added, followed by dropwise addition of 3,4-methylenedioxyphenylmagnesium bromide (**10**, 88.4 mL, 3.0 M in THF, 265 mmol, 2.5 equiv.) at the rate to keep the internal temperature below –65 °C. After addition, the cold bath temperature was warmed to –45 °C and allowed to slowly warm to 0 °C over 3 h. Reaction vessel was removed from the cold bath and after stirring at room temperature for 15 min, $Me_2SO_4$ (50.3 mL, 530 mmol, 5.0 equiv.) and $K_2CO_3$ (36.0 g, 265 mmol, 2.5 equiv.) were added sequentially and the mixture was stirred at 35 °C for 8 h. The mixture was cooled to 0 °C and 5% aq. $NH_4OH$ (600 mL) was added, the phases were separated, and the aqueous phase was extracted with $CH_2Cl_2$ (2 × 400 mL). The combined organic extracts were washed with water (2 × 400 mL) and brine (400 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid [22.5 g, 68.7 mmol, 65%]. Characterization data of this compound were in accordance with the values reported above.

### HPLC determination of enantioselectivity for carboamination reaction

A small sample of carboamination reaction mixture, before methylation with $Me_2SO_4$, was removed and hydrolyzed with aq. HCl (1M) and extracted with $CH_2Cl_2$. The organic extract was dried over $MgSO_4$, filtered, loaded onto silica and concentrated under reduced pressure. Purification by flash chromatography ($SiO_2$, hexanes:EtOAc = 3:1 → 2:1) afforded the product (**21**) as a colorless solid.

Enantiomeric ratio of 97:3 was determined by HPLC analysis using Daicel Chiracel® OJ-3 column, 25% *i*PrOH in hexanes, 0.8 mL/min, $t_R$(minor) = 11.3 min, $t_R$(major) = 12.8 min.

**Synthesis of epoxydiol S7:** Epoxydiol **S7** was prepared using the procedure to synthesize epoxydiol **S6**. Bromohydrin **25** (27.3 g, 54.3 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 30:1 → 15:1) to give the desired compound as a colorless solid [22.5 g, 49.3 mmol, 91%].



**S7**

$\boldsymbol{R}_f$ = 0.42 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$[\alpha]_D^{22}$ = +117.9 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 158 – 160 °C

NMR analysis of epoxydiol **S7** at 20 °C revealed several conformational isomers. Variable-temperature NMR spectroscopy was employed, and full coalescence of the peaks was observed at 100 °C.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 7.21 (s, 0.1H), 7.16 (s, 2H), 7.14 (s, 1H), 7.01 (s, 1H), 6.68 (s, 0.1H), 6.09 (s, 2H), 6.05 (m, 2.2H), 5.74 (d, *J* = 4.5 Hz, 1H), 5.64 (d, *J* = 4.5 Hz, 1H), 5.38 (d, *J* = 3.9 Hz, 0.1H), 4.93 (d, *J* = 6.4 Hz, 2H), 4.93 (d, *J* = 7.4 Hz, 0.1H), 4.46 (t, *J* = 10.3 Hz, 1H), 4.32 (m, 3H), 4.25 (t, *J* = 11.2 Hz, 0.1H), 4.13 (d, *J* = 9.9 Hz, 1H), 3.96 (d, *J* = 9.5 Hz, 1H), 3.84 (bs, 1H), 3.72 (d, *J* = 11.2 Hz, 0.1H), 3.60 (t, *J* = 10.3 Hz, 1H), 3.29 (m, 0.1H), 3.22 (s, 3H), 2.96 (bs, 1H), 2.91 (bs, 1H), 2.87 (s, 3H), 2.85 (s, 0.3H), 2.78 (s, 3H), 2.49 (s, 0.3H), 2.44 (s, 3H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 7.10 (s, 2H), 6.04 (d, *J* = 13.25, 2H), 5.28 (bs, 2H), 4.41 (s, 1H), 4.37 (d, *J* = 3.2 Hz, 1H), 4.08 (bs, 2H), 3.36 (t, *J* = 3.2 Hz, 1H), 3.03 – 2.77 (m, 7H).

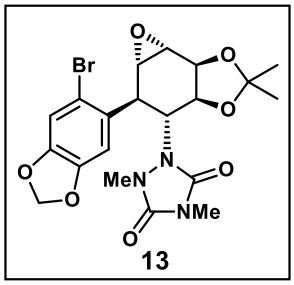
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 156.1, 155.6, 154.5, 153.7, 153.3, 148.4, 148.3, 148.1, 147.9, 147.8, 147.4, 133.5, 132.6, 131.2, 114.7, 114.4, 113.9, 113.7, 112.5, 112.4, 109.3, 108.6, 102.7, 68.3, 68.2, 67.9, 66.4, 65.7, 65.1, 60.8, 60.6, 57.1, 56.3, 55.9, 55.8, 55.7, 55.6, 47.1, 43.3, 35.3, 31.6, 25.6, 25.3, 25.2.

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 154.4, 154.3, 147.4, 147.1, 140.7 132.4, 113.7, 111.6, 108.4, 101.6, 67.3, 65.3, 59.5, 55.03, 55.00, 42.6, 24.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{18}BrN_3O_7K$ $[M+K]^+$ calc.: 495.9942; Found: 495.9944.

**IR** (ATR, neat, $cm^{-1}$): 3409 (br), 2893 (w), 1759 (w), 1691 (s), 1480 (s), 1234 (m), 1021 (m), 1035 (m), 928 (m), 775 (m).

**Synthesis of epoxyacetonide 13:** Epoxyacetonide **13** was prepared using the procedure to synthesize epoxyacetonide **14**. Epoxydiol **S7** (22.5 g, 49.3 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 2:1 → 1:3) to give the desired compound as a colorless solid [21.0 g, 42.2 mmol, 86%].



**13**

$\boldsymbol{R}_f$ = 0.52 ($SiO_2$, $CH_2Cl_2$:MeOH = 16:1)

$[\alpha]_D^{22}$ = +17.5 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 201 – 204 °C

NMR analysis of epoxyacetonide **13** at 20 °C revealed several conformational and rotomeric isomers. Variable-temperature NMR spectroscopy was employed, and a full coalescence of the peaks was observed at 80 °C.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 7.26 (s, 0.1H), 7.23 (bs, 1H), 7.20 (s, 0.2H), 7.12 – 7.01 (bs, 1H), 7.03 (s, 0.2H), 6.66 (s, 0.1H), 6.08 (d, *J* = 7.8 Hz, 2H), 6.04 (m, 0.6H), 4.96 (dd, *J* = 12.6, 10.4 Hz, 0.2H),

4.84 (d, *J* = 5.2 Hz, 1H), 4.82 (d, *J* = 5.9 Hz, 0.2H), 4.62 (m, 0.1H), 4.52 – 4.36 (bs, 1H), 4.25 (dd, *J* = 10.4, 5.9 Hz, 0.2H), 4.13 (dd, *J* = 12.2, 9.9 Hz, 0.1H), 3.75 – 3.62 (bs, 1H), 3.63 (m, 0.3H), 3.59 (s, 0.1H), 3.56 (s, 0.1H), 3.54 (s, 0.1H), 3.50 (bs, 1H), 3.47 (d, *J* = 3.4 Hz, 0.2H), 3.42 (s, 0.1H), 3.39 (s, 0.1H), 3.33 (s, 0.1H), 3.16 (s, 1H), 3.15 (bs, 1H), 3.00 – 2.89 (bs, 3H), 2.84 (s, 0.3H), 2.82 (s, 3H), 2.72 (s, 0.3H), 2.68 (s, 0.6H), 1.47 (s, 0.6H), 1.44 (m, 4H), 1.35 (s, 0.3H), 1.32 (s, 3H).

**$^1$H NMR** (500 MHz, DMSO-*d*$_6$, **80 °C**) δ 7.15 (s, 1H), 7.07 – 6.99 (bs, 1H), 6.04 (d, *J* = 6.0 Hz, 2H), 4.81 (d, *J* = 5.5 Hz, 1H), 4.52 – 4.43 (bs, 1H), 4.21 – 4.11 (bs, 1H), 3.75 – 3.66 (bs, 1H), 3.52 – 3.45 (bs, 1H), 3.20 – 3.10 (bs, 1H), 2.99 – 2.89 (bs, 3H), 2.81 (s, 3H), 1.47 (s, 3H), 1.34 (s, 3H).

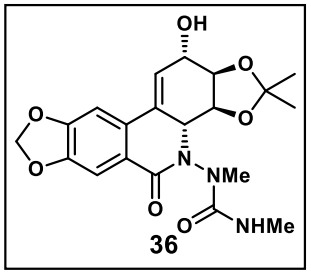
**$^{13}$C NMR** (126 MHz, DMSO-*d*$_6$, **20 °C**) δ 155.7, 155.5, 155.1, 154.0, 153.2, 153.3, 148.0, 147.7 147.6, 147.4, 147.1, 146.6, 130.6, 129.8, 129.7, 114.7, 113.6, 113.5, 113.1, 112.8, 112.4, 110.2, 109.9, 109.7, 108.6, 102.3, 102.2, 102.1, 73.0, 72.9, 72.8, 72.7, 72.6, 59.5, 58.6, 57.8, 57.6, 57.4, 57.3, 53.0, 52.8, 51.6, 45.2, 44.2, 43.3, 36.0, 32.1, 28.02, 27.5, 27.3, 26.2, 25.7, 25.2, 25.0, 24.8.

**$^{13}$C NMR** (126 MHz, DMSO-*d*$_6$, **80 °C**) δ 155.1, 154.8, 147.4, 147.2, 130.5, 112.1, 109.7, 108.4, 107.9, 101.9, 72.9, 72.5, 59.7, 58.2, 51.5, 43.1, 34.4, 27.1, 25.5, 24.8.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{20}H_{22}BrN_3O_7K$ $[M+K]^+$ calc.: 536.0255; Found: 536.0231.

**IR** (ATR, neat, cm$^{-1}$): 2924 (w), 1768 (w), 1704 (s), 1479 (s), 1235 (s), 1219 (s), 1034 (s), 927 (m), 774 (m).

**Synthesis of lactam 36:** Lactam **36** was prepared using the procedure to synthesize lactam **35**. Epoxyacetonide **13** (21.0 g, 42.2 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 50:1 → 30:1) to give the desired compound as a white solid [12.4 g, 29.8 mmol, 70%].



**36**

***R*$_f$** = 0.46 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

**$[\alpha]_D^{22}$** = –24.1 (*c* = 1.0 in EtOH)

**m.p.** = 150 – 155 °C decomposition

NMR analysis of lactam **36** at 20 °C revealed several conformational isomers. When variable-temperature NMR spectroscopy was employed no coalescence of the peaks was observed. Only the two major isomers are described for clarity.

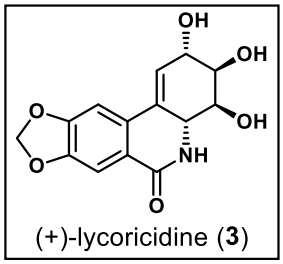
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.48 (s, 0.5H), 7.00 (s, 1H), 6.89 (s, 0.5H), 6.41 (t, *J* = 3.0 Hz, 1H), 6.34 (t, *J* = 3.2 Hz, 0.5H), 6.03 (s, 2H), 5.99 (d, *J* = 8.4 Hz, 1H), 5.10 (d, *J* = 4.9 Hz, 1H), 4.66 (d, *J* = 4.7 Hz, 0.5H), 4.62 (m, 0.5H), 4.51 (m, 2H), 4.33 (t, *J* = 7.7 Hz, 0.5H), 4.29 – 4.23 (m, 1.5H), 4.04 (m, 1.5H), 3.74 (s, 0.5H), 3.46 (s, 1H), 3.28 (s, 1.5H), 3.12 (s, 3H), 2.81 (d, *J* = 4.7 Hz, 1.5H), 2.76 (d, *J* = 4.9 Hz, 3H), 1.48 (s, 4.5H), 1.35 (s, 1.5H), 1.32 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 163.0, 162.2, 158.8, 157.5, 152.6, 152.1, 148.8, 148.5, 129.3, 128.6, 127.6, 127.4, 126.7, 126.3, 120.5, 120.3, 111.3, 110.4, 107.9, 107.8, 102.3, 102.2, 101.8, 101.3, 79.4, 78.6, 78.5, 76.6, 72.2, 71.4, 63.1, 61.0, 38.6, 31.9, 27.7, 27.5, 27.4, 27.2, 24.9, 24.8.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{20}H_{23}N_3O_7Na$ $[M+Na]^+$ calc.: 440.1428; Found: 440.1434.

**IR** (ATR, neat, cm$^{-1}$): 3380 (br), 2987 (w), 2916 (w), 1655 (s), 1535 (m), 1481 (s), 1259 (s), 1063 (m), 1035 (m), 764 (s), 750 (s).

**Synthesis of (+)-lycoricidine (3):** To a stirred solution of lactam **36** (12.4 g, 29.7 mmol, 1.0 equiv.), in degassed MeOH (400 mL) at 0 °C was added dropwise a solution of $SmI_2$ (595 mL, 0.1 M in THF, 59.5 mmol, 2.0 equiv.)[21] over 30 min. Then aq. HCl (500 mL, 6.0 M) was added and the resulting solution was stirred until complete conversion as judged by TLC. The solution was then carefully neutralized with solid $NaHCO_3$ (250 g). The resulting suspension was filtered and concentrated under reduced pressure. The residue was purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeOH = 1:0 → 5:1) to give lycoricidine as a colorless solid [8.10 g, 27.8 mmol, 94%]. Characterization data of (+)-lycoricidine (**3**) were in accordance with the literature values.[24,25]



(+)-lycoricidine (**3**)

$\boldsymbol{R_f}$ = 0.38 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{22}}$ = +178.2 (*c* = 0.45 in $C_5H_5N$)

$\boldsymbol{[\alpha]_D^{22}}$ = +157.2 (*c* = 1.0 in DMSO)

Reported Values:

**Lit[24]** $\boldsymbol{[\alpha]_D^{20}}$ = +180 (*c* = 0.45 in $C_5H_5N$)

**Lit[25]** $\boldsymbol{[\alpha]_D^{20}}$ = +182 (*c* = 0.45 in $C_5H_5N$)

**m.p.** = 216 – 218 °C decomposition

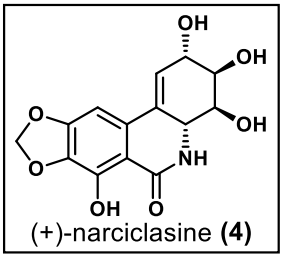
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.32 (s, 1H), 7.26 (s, 1H), 7.20 (s, 1H), 6.12 (m, 3H), 5.19 (m, 2H), 4.99 (d, *J* = 3.8 Hz, 1H), 4.19 (ddd, *J* = 8.6, 2.5, 1.3 Hz, 1H), 4.06 – 4.02 (bs, 1H), 3.79 (ddd, *J* = 8.6, 5.6, 2.2 Hz, 1H), 3.73 – 3.69 (bs, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 163.2, 151.0, 147.2, 131.8, 130.0, 123.7, 121.9, 106.2, 103.4, 101.9, 72.6, 69.3, 69.2, 52.8

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{14}NO_6$ $[M+H]^+$ calc.: 292.0816; Found: 292.0815.

**IR** (ATR, neat, $cm^{-1}$): 3274 (br), 2918 (m), 1661 (s), 1472 (s), 1392 (s), 1275 (m), 1086 (s), 1027 (s).

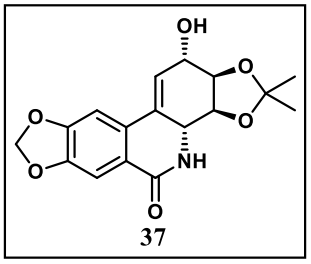
**Synthesis of (+)-narciclasine (4) from lycoricidine (3):** To (+)-lycoricidine (**3**) (3.00 g, 10.3 mmol, 1.0 equiv.) was added MeCN (60 mL), HMDS (65 mL, 309 mmol, 30 equiv.), and TFA (7.9 µL, 0.10 mmol, 1.0 mol%), and the resulting mixture was stirred at 25 °C for 2 h under an inert atmosphere. The volatiles were then removed under reduced pressure, and trace amounts of HMDS remaining were completely removed by azeotropic co-evaporation using toluene (3 × 60 mL). The flask containing leftover residue was flushed with nitrogen and sealed with rubber septa. THF (31 mL) was introduced and the resulting solution was cooled to –78 °C. Then, freshly prepared $(TMP)_2Cu(CN)Li_2$[20] (106 mL, 0.195 M in THF, 20.6 mmol, 2.0 equiv.) was added, and the mixture was warmed to 0 °C, and further stirred for 2 h at this temperature. The reaction was cooled again to –78 °C and *t*BuOOH (3.7 mL, 5.5 M in decane, 20.6 mmol, 2.0 equiv.) was added dropwise. After stirring the resulting mixture for 30 min, the reagents were quenched with mixture of sat. aq. $NH_4Cl$ and 10% aq. $Na_2S_2O_3$ (50 mL, 1:1), then warmed to room temperature. The phases were separated, and the aqueous phase was extracted with EtOAc (4 × 50 mL). A mixture of $CF_3COOH$:MeOH (100 mL, 1:1) was added to the combined organic extracts and volatiles were removed under reduced pressure. The residue was recrystallized from a $H_2O$ and MeOH mixture and then purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give (+)-narciclasine (**4**) as a colorless solid [1.80 g, 5.86 mmol, 57%], as well as recovered



(+)-narciclasine (**4**)

lycoricidine [**3**, 0.43 g, 1.47 mmol, 14%]. Characterization data of this compound were in accordance with the values reported above.

**Synthesis of (–)-lycoricidine 3,4-acetonide 37:** To a stirred solution of lactam **36** (1.00 g, 2.4 mmol, 1.0 equiv.), in degassed MeOH (32 mL) at 0 °C was added dropwise a solution of $SmI_2$ (48.0 mL, 0.1 M in THF, 4.8 mmol, 2.0 equiv.)[7] over 30 min. Then sat. aq. Rochelle's Salt (25 mL) was added and the resulting solution was diluted with $H_2O$ (100 mL). The phases were separated, and the aqueous phase was extracted with EtOAc (4 × 150 mL). The combined organic layers were dried over $Mg_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 60:1 → 40:1) to give the desired compound as a colorless solid [667 mg, 2.0 mmol, 83%]. Characterization data of (–)-lycoricidine 3,4-acetonide **37** were in accordance with the literature values.[26,27]



**37**

Optical purity of 97:3 was determined by HPLC analysis using Daicel Chiracel® OJ-3 column, 10% *i*PrOH in hexanes, 1.0 mL/min, $t_R$(major) = 22.3 min, $t_R$(minor) = 28.8 min.

$\boldsymbol{R_f}$ = 0.54 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{22}}$ = –33.3 (*c* = 0.76 in MeOH)

Reported Values:

**Lit[26]** $\boldsymbol{[\alpha]_D^{22}}$ = –34.3 (*c* = 0.76 in MeOH)

**Lit[27]** $\boldsymbol{[\alpha]_D^{25}}$ = –32.6 (*c* = 0.61 in MeOH)

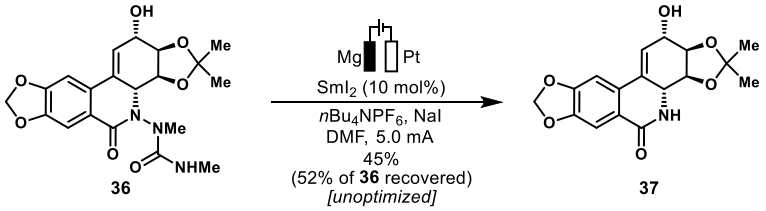
**m.p.** = 233 – 236 °C decomposition

**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 6.96 (s, 1H), 6.23 – 6.21 (m, 1H), 6.20 – 6.17 (m, 1H), 5.98 – 5.95 (m, 2H), 4.34 – 4.31 (m, 1H), 4.10 – 4.04 (m, 3H), 2.91 – 2.55 (bs, 1H), 1.46 (s, 3H), 1.32 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 162.5, 151.9, 148.8, 128.5, 127.7, 124.0, 121.0, 111.6, 107.8, 102.1, 101.6, 79.7, 79.0, 73.0, 56.1, 27.2, 24.9.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{18}NO_6$ $[M+H]^+$ calc.: 332.1129; Found: 332.1130.

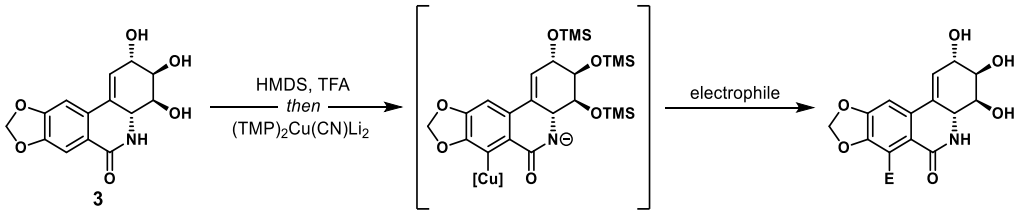
**IR** (ATR, neat, $cm^{-1}$): 3323 (br), 2904 (w), 1652 (s), 1614 (m), 1473 (s), 1378 (m), 1254 (s), 1023 (s), 878 (m), 772 (s).




**Electrochemical Cleavage of *N*-*N* bond:** For the catalytic $SmI_2$-mediated *N*-*N* bond cleavage, the following literature procedure was employed:[28] Lactam **36** (100 mg, 0.24 mmol, 1.0 equiv.), NaI (71.0 mg, 0.48 mmol, 2.0 equiv.) and $n$Bu$_4$NPF$_6$ (186 mg, 0.48 mmol, 2.0 equiv.) in degassed DMF (4.8 mL) were added to an undivided cell, with a magnesium anode (7 mm × 52 mm × 1 mm) and a platinum cathode (7 mm × 52 mm × 1 mm). Then $SmI_2$ (0.1 M in THF, 0.24 mL, 10 mol %) was added dropwise while stirring. At 25 °C, electrolysis was started with a constant current of 5.0 mA which was maintained for 3 days. Then, $H_2O$ (4.8 mL) was added to the mixture. The resulting slurry was filtrated through a celite pad, which was washed with EtOAc (40 mL × 3). The combined organic phases were washed with $H_2O$ (20.0 mL), brine (20.0 mL) then dried over $Mg_2SO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 60:1 → 40:1) to give the desired compound as a colorless solid [36.2 mg, 0.11 mmol, 45%] as well as recovered starting material **36** [51.9 mg, 0.12 mmol, 52%]. Characterization data of this compound were in accordance with the values reported above.

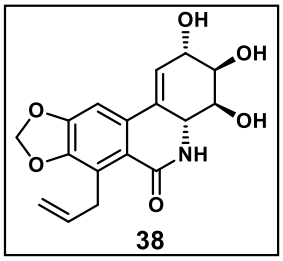
## 8. C-7 functionalization of (+)-lycoricidine (3):

**General procedure for the C-7 functionalization of (+)-lycoricidine (3):**




To (+)-lycoricidine (**3**) (100 mg, 343 μmol, 1.0 equiv.) was added MeCN (2.2 mL), HMDS (2.2 mL, 10.3 mmol, 30 equiv.), and TFA (2.6 μL, 34.3 μmol, 10 mol%), and the resulting mixture was stirred at 25 °C for 30 minutes under an inert atmosphere. The volatiles were then removed under reduced pressure, and trace amounts of HMDS remaining were completely removed by azeotropic co-evaporation using toluene (3 × 4.0 mL). The flask containing leftover residue was flushed with nitrogen and sealed with rubber septa. THF (1.0 mL) was introduced and the resulting solution was cooled to –78 °C. Then freshly prepared $(TMP)_2Cu(CN)Li_2$[20] (3.52 mL, 0.195 M in THF, 686 μmol, 2.0 equiv.) was added, and the mixture was warmed to 0 °C. After stirring the reaction mixture for 2 h at this temperature, the electrophile (1.7 mmol, 5.0 equiv.) was added dropwise and solution was stirred until complete conversion as judged by TLC, then a mixture of sat. aq. $NH_4Cl$ and 10% aq. $Na_2S_2O_3$ (3 mL, 1:1) was added. Upon warming to room temperature, the phases were separated and the aqueous phase was extracted with EtOAc (4 × 10 mL). A mixture of $CF_3COOH$:MeOH (10 mL, 1:1) was added to the combined organic extracts and volatiles were removed under reduced pressure. The product was purified by flash chromatography (either $SiO_2$ or $C_{18}$-functionalized $SiO_2$).

**7-allyl lycoricidine 38:** Following the general procedure, with allylbromide as an electrophile, the title compound was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a yellow solid [79.0 mg, 237 μmol, 69%].




$\boldsymbol{R_f}$ = 0.46 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +127.1 (*c* = 1.0 in MeOH)

**m.p.** = 88 – 91 °C decomposition

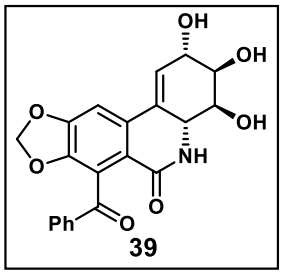
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.18 (s, 1H), 7.11 (s, 1H), 6.11 – 6.09 (m, 1H), 6.08 – 6.06 (m, 2H), 5.97 (ddt, *J* = 16.7, 10.1, 6.3 Hz, 1H), 5.17 (t, *J* = 6.3 Hz, 2H), 5.01 – 4.85 (m, 3H), 4.09 – 4.00 (m, 2H), 3.90 (dd, *J* = 13.7, 6.8 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.78 – 3.69 (m, 1H), 3.71 – 3.66 (m, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 164.1, 149.3, 147.0, 136.8, 133.3, 131.4, 123.4, 122.1, 119.6, 114.9, 102.4, 101.6, 72.5, 69.3, 69.2, 52.6, 30.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{18}NO_6$ $[M+H]^+$ calc.: 332.1134; Found: 332.1125.

**IR** (ATR, neat, $cm^{-1}$): 3277 (br), 2909 (w), 1638 (s), 1605 (m), 1466 (s), 1382 (m), 1224 (m), 1019 (s), 931 (m).

**7-oxophenyl lycoricidine 39:** Following the general procedure, with benzoylchloride as an electrophile, the title compound was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a colorless solid [114.0 mg, 289 µmol, 84%].



**39**

$\boldsymbol{R_f}$ = 0.43 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +138.2 (*c* = 1.0 in MeOH)

**m.p.** = 180 – 184 °C decomposition

NMR analysis of 7-oxophenyl lycoricidine **39** at 20 °C revealed two conformational isomers. When variable-temperature NMR spectroscopy was employed no coalescence of the peaks was observed.

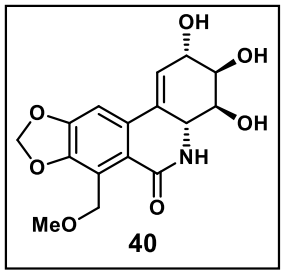
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.71 – 7.65 (m, 2H), 7.61 – 7.55 (m, 1H), 7.50 – 7.45 (m, 2H), 7.40 (s, 1H), 7.24 (s, 1H), 6.27 – 6.24 (m, 1H), 6.14 – 6.03 (m, 2H), 5.43 – 5.00 (m, 3H), 4.24 – 4.19 (m, 1H), 4.12 – 4.08 (m, 1H), 3.79 (d, *J* = 8.5 Hz, 1H), 3.75 – 3.72 (m, 1H)

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 192.6, 191.7, 162.8*, 151.5, 151.1, 145.8, 145.0, 137.5, 137.2, 133.2, 133.0, 132.9, 132.4, 130.2, 130.0, 128.8*, 128.6, 128.2, 125.1*, 121.4, 120.7, 120.7*, 104.2, 104.1 102.9*, 72.7*, 69.3*, 69.2*, 53.0, 52.8. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{21}H_{18}NO_7$ $[M+H]^+$ calc.: 396.1083; Found: 396.1095.

**IR** (ATR, neat, $cm^{-1}$): 3309 (br), 2921 (w), 1650 (s), 1596 (m), 1461 (m), 1391 (m), 1246 (s), 1032 (s), 1018 (s), 927 (m).

**7-methoxymethyl lycoricidine 40:** Following the general procedure, with chloromethyl methyl ether as an electrophile, the title compound was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a yellow solid [87.0 mg, 261 µmol, 76%].



**40**

$\boldsymbol{R_f}$ = 0.36 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{24}}$ = +75.5 (*c* = 1.0 in MeOH)

**m.p.** = 122 – 125 °C decomposition

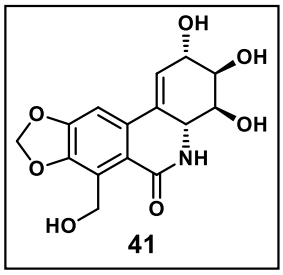
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.45 (s, 1H), 7.17 (s, 1H), 6.16 – 6.13 (m, 1H), 6.11 – 6.05 (m, 2H), 5.61 (d, *J* = 6.3 Hz, 1H), 5.30 (d, *J* = 5.5 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 5.06 (d, *J* = 3.4 Hz, 1H), 4.61 (d, *J* = 10.2 Hz, 1H), 4.06 – 4.01 (m, 2H), 3.82 – 3.74 (m, 1H), 3.71 – 3.69 (m, 1H), 3.22 (s, 3H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 163.1, 149.5, 147.8, 133.2, 131.4, 123.6, 120.5, 119.6, 103.7, 101.8, 72.6, 69.14, 69.11, 64.7, 57.6, 52.9.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{16}H_{18}NO_7$ $[M+H]^+$ calc.: 336.1083; Found: 336.1095.

**IR** (ATR, neat, $cm^{-1}$): 3380 (br), 3275 (br), 2922 (w), 1643 (s), 1608 (m), 1469 (s), 1395 (m), 1230 (m), 1016 (s), 927 (w).

**7-hydroxymethyl lycoricidine 41:** Following the general procedure, with 2-(trimethylsilyl) ethoxymethyl chloride as an electrophile, the crude material was stirred in neat TFA (5.0 mL) for 2 hours before concentration and purification by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a colorless solid [80.0 mg, 248 μmol, 72%].



41

$\boldsymbol{R_f}$ = 0.37 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +99.2 (*c* = 1.0 in MeOH)

**m.p.** = 157 – 162 °C decomposition

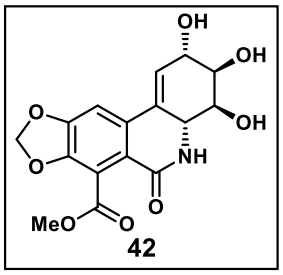
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.81 (s, 1H), 7.24 (s, 1H), 6.20 – 6.13 (m, 3H), 5.43 – 5.21 (m, 3H), 5.12 – 5.02 (bs, 1H), 4.68 – 4.58 (m, 2H), 4.13 (d, *J* = 8.5 Hz, 1H), 4.09 (m, 1H), 3.86 (d, *J* = 8.5 Hz, 1H), 3.77 – 3.74 (m, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 165.4, 150.0, 146.6, 133.7, 130.8, 124.2, 122.8, 120.3, 103.4, 101.8, 72.5, 69.1, 68.9, 55.5, 52.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{15}H_{16}NO_7$ $[M+H]^+$ calc.: 322.0927; Found: 322.0938.

**IR** (ATR, neat, $cm^{-1}$): 3265 (br), 2922 (m), 1646 (s), 1608 (m), 1464 (s), 1387 (m), 1228 (m), 1032 (s), 938 (w).

**7-carboxymethyl lycoricidine 42:** Following the general procedure, with methyl chloroformate as an electrophile, the title compound was purified by flash chromatography ($C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to yield a colorless solid [93.0 mg, 265 μmol, 77%].



42

$\boldsymbol{R_f}$ = 0.41 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +206.7 (*c* = 1.0 in DMSO)

**m.p.** = 201 – 205 °C decomposition

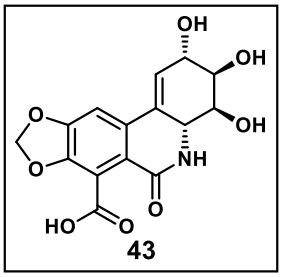
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.38 (s, 1H), 7.34 (s, 1H), 6.22 – 6.17 (m, 1H), 6.19 – 6.15 (m, 2H), 5.27 – 5.17 (m, 2H), 5.02 (s, 1H), 4.17 – 4.12 (m, 1H), 4.07 – 4.00 (m, 1H), 3.80 – 3.77 (m, 1H), 3.75 (s, 3H), 3.73 – 3.68 (m, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 165.6, 162.2, 150.9, 145.1, 132.4, 129.8, 124.9, 119.2, 114.8, 104.1, 102.8, 72.5, 69.1, 69.0, 52.7, 52.3.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{16}H_{16}NO_8$ $[M+H]^+$ calc.: 350.0876; Found: 350.0870.

**IR** (ATR, neat, $cm^{-1}$): 3379 (s), 3359 (s), 3228 (br), 2904 (w), 1716 (m), 1650 (m), 1607 (m), 1470 (m), 1398 (m), 1256 (m), 1030 (s), 1014 (s), 915 (w).

**lycoricidine-7-carboxylic acid 43:** To solution of **42** (25.0 mg, 71.6 µmol, 1.0 equiv.) in $H_2O$ (5.0 mL) was added aq. NaOH (5 mL, 2.0 M) and the reaction was stirred for 2 hours at 25 °C. The resulting solution was then neutralized to pH 7 with HCl (1.8 mL, 6.0 M) and was concentrated under reduced pressure. The residue was purified by flash chromatography (wet loaded with $H_2O$ and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give a yellow solid [13.0 mg, 39.9 µmol, 56%].



**43**

***R*f** = 0.75 ($C_{18}$-functionalized $SiO_2$, $H_2O$:MeOH = 2:1)

**[α]D22** = +169.5 (*c* = 0.5 in DMSO)

**m.p.** = 175 – 182 °C decomposition

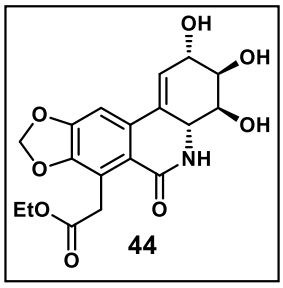
**$^1$H NMR** (500 MHz, $D_2O$) δ 7.08 (s, 1H), 6.20 – 6.14 (m, 1H), 6.04 (d, *J* = 8.9 Hz, 2H), 4.36 – 4.29 (m, 2H), 4.00 – 3.94 (m, 2H).

**$^{13}$C NMR** (126 MHz, $D_2O$) δ 173.5, 166.1, 152.2, 145.4, 132.97, 132.95, 122.4, 121.2, 117.8, 104.1, 103.5, 73.2, 69.8, 69.6, 52.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{15}H_{14}NO_8$ $[M+H]^+$ calc.: 336.0719; Found: 336.0718.

**IR** (ATR, neat, $cm^{-1}$): 3163 (br), 3047 (br), 2921 (m), 1645 (s), 1602 (m), 1569 (s), 1461 (s), 1391 (s), 1253 (m), 1080 (m), 1022 (s).

**ethyl 2-(7-lycoricidinyl)acetate 44:** Following the general procedure, with ethyl bromoacetate as an electrophile, the title compound was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a colorless solid [75.0 mg, 199.8 µmol, 58%].



**44**

***R*f** = 0.48 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

**[α]D23** = +128.0 (*c* = 1.0 in MeOH)

**m.p.** = 122 – 126 °C decomposition

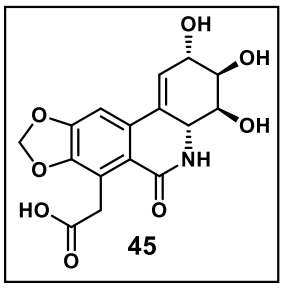
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.20 – 7.18 (m, 2H), 6.41 – 6.04 (m, 3H), 5.32 – 4.90 (m, 3H), 4.11 – 3.98 (m, 5H), 3.90 (d, *J* = 16.7 Hz, 1H), 3.80 – 3.76 (m, 1H), 3.72 – 3.70 (m, 1H), 1.17 (t, *J* = 7.1 Hz, 3H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 169.9, 164.2, 149.3, 147.5, 132.9, 130.9, 123.8, 119.9, 116.5, 102.9, 101.8, 72.5, 69.3, 69.2, 59.9, 52.6, 32.7, 14.1.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{20}NO_8$ $[M+H]^+$ calc.: 378.1189; Found: 378.1184.

**IR** (ATR, neat, $cm^{-1}$): 3303 (br), 2922 (m), 1716 (m), 1647 (m), 1608 (m), 1469 (m), 1386 (m), 1256 (m), 1053 (m), 1032 (s), 1017 (s), 931 (m).

**2-(7-lycoricidinyl)acetic acid 45:** To solution of **44** (25.0 mg, 68.8 μmol, 1.0 equiv.) in $H_2O$ (5 mL) was added was added aq. NaOH (5 mL, 2.0 M) and the reaction was stirred for 2 hours at 25 °C. The resulting solution was then neutralized to pH 7 with HCl (1.8 mL, 6.0 M) and was concentrated under reduced pressure. The residue was purified by flash chromatography (wet loaded with $H_2O$ and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give a colorless solid [14.2 mg, 44.5 μmol, 65%].




$\boldsymbol{R_f}$ = 0.69 ($C_{18}$-functionalized $SiO_2$, H2O:MeOH = 2:1)

**$[\alpha]_D^{22}$** = +46.2 (c = 0.5 in DMSO)

**m.p.** = 188 – 195 °C decomposition

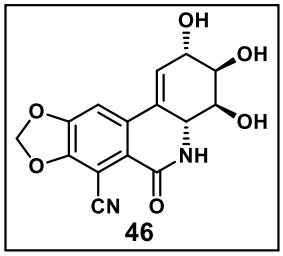
**$^1$H NMR** (500 MHz, $D_2O$) δ 7.11 (s, 1H), 6.29 – 6.16 (m, 1H), 6.13 – 6.05 (m, 2H), 4.41 – 4.38 (m, 1H), 4.34 (d, *J* = 8.5 Hz, 1H), 4.08 – 3.92 (m, 4H).

**$^{13}$C NMR** (126 MHz, $D_2O$) δ 177.0, 167.8, 151.0, 149.1, 133.8, 133.3, 122.2, 119.6, 117.3, 104.2, 103.1, 73.0, 69.8, 69.6, 52.7, 34.2.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{16}H_{14}NO_8$ $[M–H]^-$ calc.: 348.0719; Found: 348.0720.

**IR** (ATR, neat, $cm^{-1}$): 3270 (br), 2921 (m), 1645 (m), 1605 (m) 1469 (m), 1384 (m), 1287 (m), 1066 (s), 1027 (s).

**7-cyanolycoricidine 46:** Following the general procedure, with *N*-fluorobenzenesulfonimide as an oxidant in place of an electrophile, the title compound was purified by flash chromatography (wet loaded with $H_2O$ and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeOH = 1:0 → 5:1) to yield a yellow solid [14.6 mg, 46.2 μmol, 13%].




The nitrile is believed to come from the CuCN present in the reaction[29]

$\boldsymbol{R_f}$ = 0.21 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

**$[\alpha]_D^{22}$** = +169.9 (*c* = 0.5 in DMSO)

**m.p.** = 201 – 205 °C decomposition

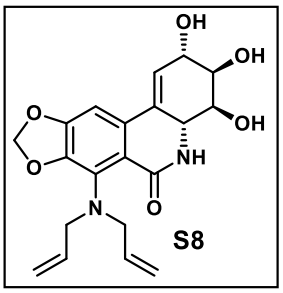
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 6.77 (s, 1H), 6.72 (s, 1H), 5.50 (d, *J* = 12.2 Hz, 2H), 5.44 – 5.39 (m, 1H), 4.42 (s, 2H), 4.24 (s, 1H), 3.34 (d, *J* = 8.1 Hz, 1H), 3.25 – 3.19 (m, 1H), 2.97 (dd, *J* = 8.1, 2.1 Hz, 1H), 2.88 (s, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 161.3, 153.4, 151.1, 133.2, 129.2, 125.9, 121.1, 113.5, 106.9, 104.0, 90.9, 72.4, 69.0, 68.9, 52.6.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{15}H_{13}N_2O_6$ $[M+H]^+$ calc.: 317.0774; Found: 317.0776.

**IR** (ATR, neat, $cm^{-1}$): 3314 (br), 2918 (m), 2228 (m), 1653 (s), 1614 (m), 1469 (s), 1399 (m), 1357 (m), 1096 (m), 1028 (s), 925 (w).

***N,N*-diallyl-7-aminolycoricidine S8:** Following the general procedure, with *O*-benzoyl-*N,N*-diallylhydroxylamine as an electrophile, the crude material was neutralized with sat. aq. $NaHCO_3$ (5 mL) before purification by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a yellow solid [87.2 mg, 226 μmol, 66%].




$\boldsymbol{R_f}$ = 0.42 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +100.6 (*c* = 1.0 in DMSO)

**m.p.** = 132 – 136 °C decomposition

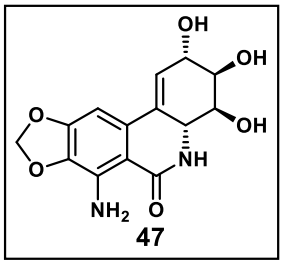
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.17 (s, 1H), 6.86 (s, 1H), 6.14 – 6.12 (m, 1H), 6.10 – 6.08 (m, 1H), 5.88 (s, 1H), 5.80 (ddt, *J* = 16.5, 10.1, 6.1 Hz, 2H), 5.15 (dd, *J* = 16.5, 2.0 Hz, 2H), 5.02 (dd, *J* = 10.1, 2.0 Hz, 2H), 5.23 – 4.87 (br, 3H), 4.03 – 4.01 (m, 1H), 3.94 (d, *J* = 7.9 Hz, 1H), 3.85 – 3.77 (m, 3H), 3.70 (d, *J* = 6.0 Hz, 1H), 3.69 – 3.65 (m, 2H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 163.6, 150.0, 141.6, 136.3, 133.8, 133.4, 132.6, 122.2, 116.9, 116.4, 100.7, 97.8, 72.5, 69.2, 69.2, 54.8, 52.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{20}H_{23}N_2O_6$ $[M+H]^+$ calc.: 387.1556; Found: 387.1552.

**IR** (ATR, neat, $cm^{-1}$): 3267 (br), 2891 (m), 1635 (s), 1594 (m), 1471 (m), 1344 (s), 1307 (m), 1222 (m), 1081 (s), 1031 (s), 919 (s).

**7-aminolycoricidine 47:** (+)-*N,N*-diallyl-7-aminolycoricidine **S8** (20.0 mg, 51.8 μmol, 1.0 equiv.), $Pd(PPh_3)_4$ (1.20 mg, 1.03 μmol, 2.0 mol%), and 1,3-dimethylbarbituric acid (48.5 mg, 311 μmol, 6.0 equiv.) were dissolved in $CH_2Cl_2$ (0.2 mL) and the resulting mixture was refluxed for 16 h. After, the solution was cooled to 25 °C and the solvent was removed under reduced pressure. The residue was purified by flash chromatography (wet loaded with $H_2O$ and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give a yellow solid [11.2 mg, 36.6 μmol, 71%].




$\boldsymbol{R_f}$ = 0.38 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +244.4 (*c* = 0.5 in DMSO)

**m.p.** = 129 – 132 °C decomposition

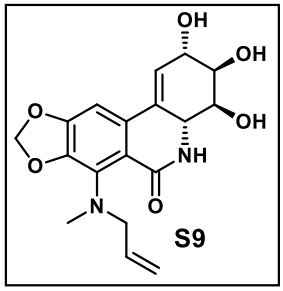
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 6.98 (s, 1H), 6.67 – 6.61 (bs, 2H), 6.54 (s, 1H), 6.05 – 6.01 (m, 3H), 5.26 – 4.93 (m, 3H), 4.06 (d, *J* = 8.3 Hz, 1H), 4.02 – 3.99 (m, *J* = 3.6 Hz, 1H), 3.74 (d, *J* = 8.3 Hz, 1H), 3.69 – 3.66 (m, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 167.0, 149.3, 134.8, 133.2, 133.1, 131.1, 123.0, 104.7, 101.2, 93.3, 72.4, 69.4, 69.3, 52.6.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{15}N_2O_6$ $[M+H]^+$ calc.: 307.0930; Found: 307.0931.

**IR** (ATR, neat, $cm^{-1}$): 3315 (br), 2903 (w), 1650 (s), 1556 (m), 1465 (w), 1395 (w), 1364 (s), 1235 (m), 1086 (m) 1023 (s), 925 (w).

***N*-methyl-*N*-allyl-7-aminolycoricidine S9:** Following the general procedure, with *O*-benzoyl-*N*-methyl-*N*-allylhydroxylamine as an electrophile, the crude material was neutralized with sat. aq. $NaHCO_3$ (5 mL) before purification by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a yellow solid [68.1 mg, 189 μmol, 55%].




$\boldsymbol{R_f}$ = 0.40 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +280.4 (*c* = 0.5 in DMSO)

**m.p.** = 113 – 117 °C decomposition

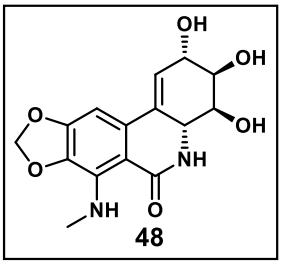
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.22 (s, 1H), 6.84 (s, 1H), 6.14 – 6.10 (m, 2H), 5.89 (d, *J* = 1.1 Hz, 1H), 5.88 – 5.79 (m, 1H), 5.23 (dd, *J* = 17.2, 1.8 Hz, 1H), 5.15 (d, *J* = 5.6 Hz, 1H), 5.12 – 5.06 (m, 1H), 5.04 (d, *J* = 5.6 Hz, 1H), 4.89 (d, *J* = 3.8 Hz, 1H), 4.02 (q, *J* = 4.6 Hz, 1H), 3.99 – 3.96 (m, 1H), 3.82 (ddd, *J* = 7.8, 5.4, 2.1 Hz, 1H), 3.71 (t, *J* = 6.9 Hz, 2H), 3.69 – 3.64 (m, 1H), 2.75 (s, 3H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 163.6, 149.9, 140.3, 136.2, 135.8, 133.6, 132.8, 122.0, 116.7, 115.8, 100.6, 96.9, 72.5, 69.2, 69.1, 57.2, 52.8, 40.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{21}N_2O_6$ $[M+H]^+$ calc.: 361.1400; Found: 361.1400.

**IR** (ATR, neat, $cm^{-1}$): 3285 (br), 2893 (m), 1636 (s), 1594 (m), 1490 (w), 1371 (m) 1344 (m), 1311 (m), 1225 (w), 1062 (m), 1021 (s), 934 (m).

***N*-methyl-7-aminolycoricidine 48:** Following the same procedure as compound **47**, using *N*-methyl-*N*-allyl-7-aminolycoricidine **S9** (60.1 mg, 166.8 μmol), the crude material was purified by flash chromatography (wet loaded with $H_2O$ and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give a yellow solid [31.2 mg, 97.4 μmol, 58%].




$\boldsymbol{R_f}$ = 0.42 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +200.2 (*c* = 1.0 in DMSO)

**m.p.** = 215 – 218 °C decomposition

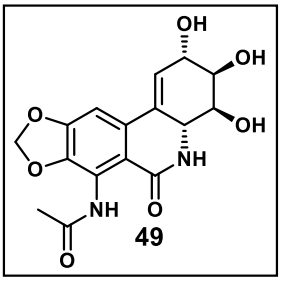
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 8.51 (q, *J* = 5.4 Hz, 1H), 7.08 (s, 1H), 6.53 (s, 1H), 6.04 (dd, *J* = 4.9, 2.3 Hz, 1H), 5.95 (dd, *J* = 7.3, 1.1 Hz, 2H), 5.18 (m, 2H), 4.96 (s, 1H), 4.04 (dt, *J* = 8.2, 1.8 Hz, 1H), 4.00 (q, *J* = 2.8 Hz, 1H), 3.74 (dd, *J* = 8.2, 2.3 Hz, 1H), 3.67 (d, *J* = 2.8 Hz, 1H), 3.01 (d, *J* = 5.4 Hz, 3H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 167.2, 150.6, 137.7, 133.8, 133.1, 131.1, 123.4, 105.2, 100.4, 93.6, 72.4, 69.3 69.2, 52.5, 31.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{15}H_{17}N_2O_6$ $[M+H]^+$ calc.: 321.1087; Found: 321.1084.

**IR** (ATR, neat, $cm^{-1}$): 3280 (br), 2897 (w), 1636 (s), 1594 (w), 1519 (m), 1454 (m), 1384 (m), 1292 (m), 1230 (m), 1075(m) 10005 (s), 935 (m).

**7-acetamidelycoricidine 49:** Following the general procedure, with *O*-benzoyl-*N*-hydroxylacetamide as an electrophile, the crude material was neutralized with sat. aq. $NaHCO_3$ (5 mL) before purification by flash chromatography (wet loaded with $H_2O$ and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to yield an colorless solid [67 mg, 190 μmol, 56%].




$\boldsymbol{R_f}$ = 0.35 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +187.6 (*c* = 0.5 in DMSO)

**m.p.** = 120 – 135 °C decomposition

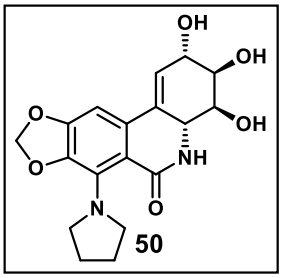
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 10.52 (s, 1H), 7.52 (s, 1H), 7.12 (s, 1H), 6.19 – 6.13 (m, 1H), 6.11 (s, 1H), 6.04 (s, 1H), 5.25 – 5.13 (m, 2H), 4.98 (s, 1H), 4.10 (dt, *J* = 8.3, 1.7 Hz, 1H), 4.04 (d, *J* = 4.3 Hz, 1H), 3.80 (d, *J* = 8.3 Hz, 1H), 3.70 (s, 1H), 2.04 (s, 3H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 167.0, 165.0, 151.0, 141.4, 132.7, 130.4, 124.3, 121.5, 113.1, 101.8, 100.6, 72.4, 69.1, 69.0, 52.7, 23.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{16}H_{17}N_2O_7$ $[M+H]^+$ calc.: 349.1036; Found: 349.1045.

**IR** (ATR, neat, $cm^{-1}$): 3278 (br), 2904 (w), 1648 (s), 1496 (m), 1476 (w), 1381 (s), 1229 (m), 1086 (m) 1026 (s), 930 (w).

**7-(1-pyrrolidinyl)lycoricidine 50:** Following the general procedure, with *O*-benzoyl-*N*-hydroxylpyrrolidine as an electrophile, the crude material was neutralized with sat. aq. $NaHCO_3$ (5 mL) before purification by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a yellow solid [108.0 mg, 299 μmol, 87%].




$\boldsymbol{R_f}$ = 0.37 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +559.0 (*c* = 1.0 in MeOH)

**m.p.** = 155 – 162 °C decomposition

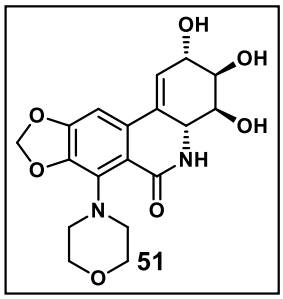
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.16 (s, 1H), 6.67 (s, 1H), 6.14 – 6.12 (m, 1H), 6.05 (s, 1H), 5.75 (s, 1H), 5.17 – 5.08 (bs, 1H), 5.05 – 4.98 (bs, 1H), 4.91 – 4.85 (bs, 1H), 4.05 – 4.01 (m, 1H), 3.96 (d, *J* = 7.9 Hz, 1H), 3.84 (d, *J* = 7.9 Hz, 1H), 3.77 (td, *J* = 9.7, 6.8 Hz, 2H), 3.69 – 3.65 (m, 1H), 3.06 (dd, *J* = 10.1, 6.8 Hz, 2H), 1.93 – 1.86 (m, 2H), 1.75 – 1.64 (m, 2H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 163.8, 149.4, 135.9, 134.1, 133.8, 133.3, 121.6, 112.5, 99.6, 93.8, 72.5, 69.2, 69.1, 52.9, 51.1, 25.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{21}N_2O_6$ $[M+H]^+$ calc.: 361.1400; Found: 361.1389.

**IR** (ATR, neat, $cm^{-1}$): 3278 (br), 2872 (m), 1629 (s), 1589 (m), 1456 (w), 1346 (m), 1303 (m), 1223 (m), 1081 (m), 1028 (s), 938 (w).

**7-(4-morpholinyl)lycoricidine 51:** Following the general procedure, with *O*-benzoyl-*N*-hydroxylmorpholine as an electrophile, the crude material was neutralized with sat. aq. $NaHCO_3$ (5 mL) before purification by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 20:1 → 8:1) to yield a yellow solid [107.0 mg, 286 µmol, 83%].




$\boldsymbol{R_f}$ = 0.44 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +269.9 (*c* = 1.0 in MeOH)

**m.p.** = 172 – 175 °C decomposition

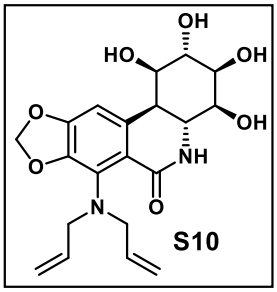
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.26 (s, 1H), 6.87 (s, 1H), 6.14 – 6.11 (m, 2H), 5.90 (s, 1H), 5.16 (s, 1H), 5.05 (s, 1H), 4.90 (s, 1H), 4.05 – 4.01 (bs, 1H), 3.98 (d, *J* = 8.1 Hz, 1H), 3.82 (d, *J* = 8.1 Hz, 1H), 3.70 – 3.64 (m, 3H), 3.63 – 3.57 (m, 2H), 3.36 – 3.30 (m, 2H), 2.99 – 2.94 (m, 2H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 163.6, 150.2, 140.2, 135.1, 133.9, 132.6, 122.3, 115.4, 100.8, 97.4, 72.5, 69.2, 69.1, 66.8, 52.8, 50.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{21}N_2O_7$ $[M+H]^+$ calc.: 377.1349; Found: 377.1338.

**IR** (ATR, neat, $cm^{-1}$): 3291 (br), 2886 (w), 1716 (w), 1637 (s), 1601 (m), 1469 (m), 1376 (m), 1262 (m), 1215 (m), 1096 (m) 1015 (s), 935 (w).

**Synthesis of *N*,*N*-diallylaminopancratistatin S10:** *N*,*N*-diallylaminopancratistatin **S10** was prepared using the procedure to synthesize *N*,*N*-diallylaminolycoricidine **S8**. (+)-7-deoxypancratistatin (**1**) (100 mg, 0.32 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 9:1) to give the desired compound as an orange solid [60.0 mg, 0.15 mmol, 46%].




$\boldsymbol{R_f}$ = 0.20 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{22}}$ = +69.9 (*c* = 0.5 in MeOH)

**m.p.** = 126 – 128 °C decomposition

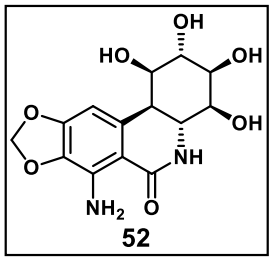
**$^1$H NMR** (500 MHz, $CD_3OD$) δ 6.59 (s, 1H), 6.03 (d, *J* = 1.2 Hz, 1H), 5.90 – 5.79 (m, 3H), 5.15 (dq, *J* = 17.2, 1.7 Hz, 2H), 5.02 (dt, *J* = 10.3, 1.7 Hz, 2H), 4.41 (t, *J* = 3.3 Hz, 1H), 4.17 (t, *J* = 3.3 Hz, 1H), 4.00 (d, *J* = 3.3 Hz, 1H), 3.89 (dd, *J* = 10.3, 3.3 Hz, 1H), 3.87 – 3.80 (m, 2H), 3.79 – 3.71 (m, 3H), 3.06 (dd, *J* = 12.6, 2.6 Hz, 1H).

**$^{13}$C NMR** (126 MHz, $CD_3OD$) δ 167.6, 152.3, 142.0, 138.6, 137.5*, 136.5, 119.3, 116.9*, 102.0, 100.8, 75.0, 71.9, 71.8, 70.9, 56.6*, 51.0, 43.6. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{20}H_{25}N_2O_7$ $[M+H]^+$ calc.: 405.1662; found: 405.1662.

**IR** (ATR, neat, $cm^{-1}$): 3305 (br), 2901 (w), 1635 (s), 1599 (m), 1476 (w), 1445 (w), 1324 (s), 1044 (s), 920 (m).

**Synthesis of 7-aminopancratistatin 52:** 7-Aminopancratistatin **52** was prepared using the procedure to synthesize 7-aminolycoricidine **47**. *N*,*N*-diallylaminopancratistatin **S10** (44.0 mg, 0.11 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography (wet loaded with $H_2O$ and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1; and then dry loaded using MeOH, $SiO_2$, $CHCl_3$:MeOH = 15:1 → 9:1) to give the desired compound as a yellow solid [23.0 mg, 0.07 mmol, 65%].



**52**

$\boldsymbol{R_f}$ = 0.36 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

**$[\alpha]_D^{22}$** = +59.4 (*c* = 1.0 in DMSO)

**m.p.** = 266 – 267 °C decomposition

**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 6.62 (s, 1H), 6.53 (s, 2H), 6.22 (s, 1H), 5.99 (d, *J* = 5.0 Hz, 2H), 5.32 (d, *J* = 3.9 Hz, 1H), 5.05 (t, *J* = 6.4 Hz, 2H), 4.78 (d, *J* = 7.6 Hz, 1H), 4.24 (dt, *J* = 6.8, 3.1 Hz, 1H), 3.96 (q, *J* = 3.5 Hz, 1H), 3.83 (dt, *J* = 6.1, 3.2 Hz, 1H), 3.69 (ddd, *J* = 9.7, 6.3, 3.0 Hz, 1H), 3.60 (dd, *J* = 12.9, 9.9 Hz, 1H), 2.88 (dd, *J* = 12.8, 2.6 Hz, 1H).

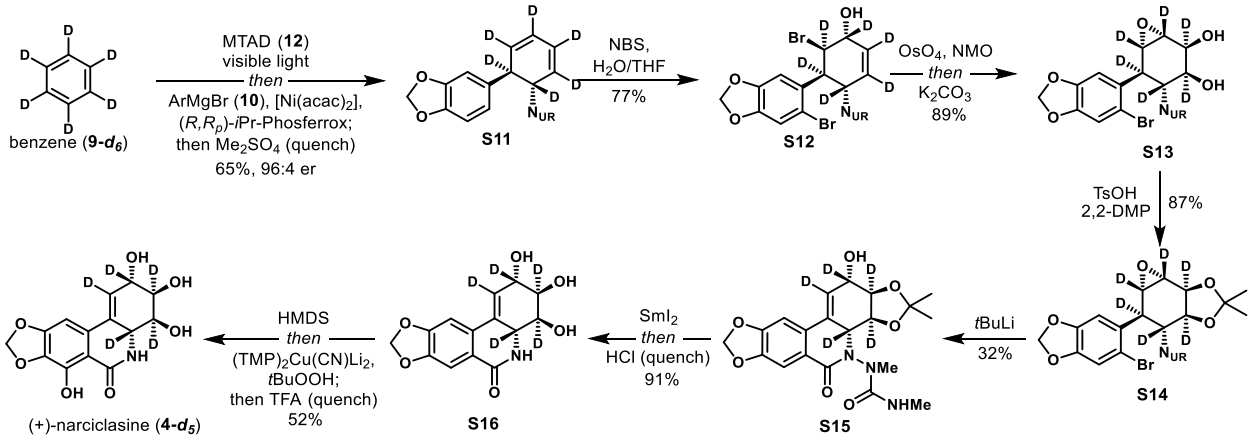
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 167.5, 149.1, 136.1, 135.3, 131.5, 106.7, 100.9, 94.8, 73.3, 70.4, 70.3, 68.8, 49.9, 40.3.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{17}N_2O_7$ $[M+H]^+$ calc.: 325.1036; found: 325.1029.

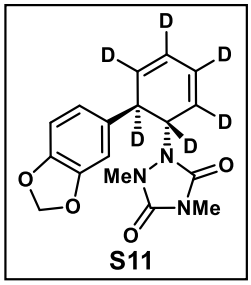
**IR** (ATR, neat, $cm^{-1}$): 3497 (w), 3387 (m), 3375 (m), 2910 (w), 1639 (s), 1564 (s), 1422 (m), 1029 (s), 921 (m).

## 9. Synthesis of differentially deuterated narciclasine analogs:

### 9-1. Synthesis of (+)-narciclasine 4-$d_5$




**Synthesis of diene S11:** Diene **S11** was prepared using the procedure to synthesize diene **7**, employing the Grignard reagent derived from 3,4-methylenedioxyphenyl bromide **10** and $d_6$-benzene **9-$d_6$**. The reaction was run on 27 mmol scale, with MTAD (**12**, 3.00 g) as the limiting reagent. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid [5.79g, 17.4 mmol, 65%, 96:4 er].




Enantiomeric ratio was determined with HPLC analysis using Daicel Chiracel® OJ-H column, 50% *i*PrOH in hexanes, 0.8 mL/min, $t_R$(minor) = 8.7 min, $t_R$(major) = 11.5 min.

$R_f$ = 0.36 ($SiO_2$, hexanes:EtOAc = 1:1)

$[\alpha]_D^{24}$ = +248.6 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 114 – 118 °C

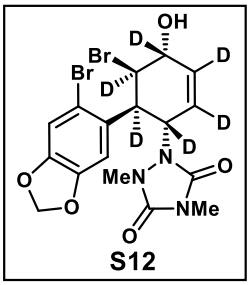
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.76 (d, *J* = 1.8 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.65 (dd, *J* = 8.0, 1.8 Hz, 1H), 6.15 – 6.10 (m, 1H), 6.08 – 6.03 (m, 1H), 3.19 (s, 3H), 2.90 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.1, 155.0, 147.9, 147.0, 135.3, 130.3 (t, *J* = 24.9 Hz), 126.2 (t, *J* = 24.6 Hz), 124.6 (t, *J* = 25.0 Hz), 122.8 (t, *J* = 24.8 Hz), 121.4, 108.6, 108.2, 101.1, 60.3 (t, *J* = 21.3 Hz), 44.0 (t, *J* = 19.6 Hz), 35.0, 25.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{11}D_6N_3O_4K$ $[M+K]^+$ calc.: 372.1227; Found: 372.1222.

**IR** (ATR, neat, $cm^{-1}$): 2886 (m), 2246 (w), 1763 (w), 1702 (s), 1482 (m), 1034 (m), 930 (m), 768 (m).

**Synthesis of bromohydrin S12:** Bromohydrin **S12** was prepared using the procedure to synthesize bromohydrin **25**. Diene **S11** (5.69 g, 17.1 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, hexanes: EtOAc = 4:1 → 1:1) to provide the desired compound as a colorless solid [6.71 g, 13.2 mmol, 77%].



**S12**

$\boldsymbol{R_f}$ = 0.44 ($SiO_2$, hexanes:EtOAc = 1:3)

$\boldsymbol{[\alpha]_D^{22}}$ = +109.6 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 226 – 229 °C decomposition

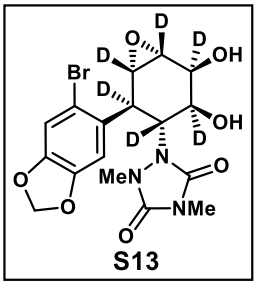
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.12 (s, 1H), 7.01 (s, 1H), 5.97 (s, 2H), 3.15 (s, 3H), 3.11 – 3.03 (m, 1H), 2.93 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 155.4, 155.3, 147.9, 147.2, 130.5 – 129.3 (m), 128.9, 127.9 (t, *J* = 23.3 Hz), 115.9, 113.1, 110.2, 102.1, 68.7 (t, *J* = 23.2 Hz), 57.0 (t, *J* = 25.2 Hz), 55.3 (t, *J* = 21.9 Hz), 41.2 (t, *J* = 19.2 Hz), 34.7, 25.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{15}D_6Br_2N_4O_5$ $[M+NH_4]^+$ calc.: 525.0250; Found: 525.0247.

**IR** (ATR, neat, $cm^{-1}$): 3334 (m), 2917 (w), 1767 (m), 1693 (s), 1478 (s), 1237 (m), 1034 (m), 916 (w), 771 (w).

**Synthesis of epoxydiol S13:** Epoxydiol **S13** was prepared using the procedure to synthesize (+)-epoxydiol **S6**. Bromohydrin **S12** (6.71 g, 13.2 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 30:1 → 15:1) to give the desired compound as a colorless solid [4.65 g, 10.1 mmol, 89%].



**S13**

$\boldsymbol{R_f}$ = 0.42 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{22}}$ = +110.1 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 155 – 157 °C

NMR analysis of epoxydiol **S13** revealed several conformational structures at 20 °C, which increased spectrum complexity. Therefore, a variable-temperature NMR spectroscopy was employed, and a full coalescence of the peaks was observed at 100 °C. For clarity only the two major conformers at 20 °C are described.

**$^1$H NMR** (500 MHz, DMSO-*d*$_6$, **20 °C**) δ 7.19 (s, 2H), 7.16 (s, 1H), 7.02 (s, 1H), 6.11 (s, 2H), 6.09 – 6.04 (m, 2H), 5.73 (s, 1H), 5.64 (s, 1H), 4.91 (s, 2H), 3.23 (s, 3H), 2.88 (s, 3H), 2.79 (s, 3H), 2.45 (s, 3H).

**$^1$H NMR** (500 MHz, DMSO-*d*$_6$, **100 °C**) δ 7.12 (s, 2H), 6.07 (s, 1H), 6.05 (s, 1H), 5.34 – 5.29 (m, 1H), 4.44 (s, 1H), 2.99 (s, 3H), 2.84 (s, 3H).

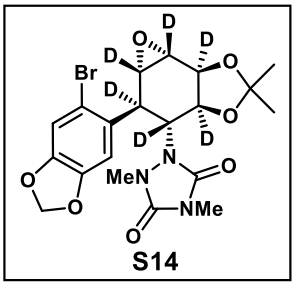
**$^{13}$C NMR** (126 MHz, DMSO-*d*$_6$, **20 °C**) δ 156.6, 155.8, 155.1, 147.9, 147.7, 147.2, 146.5, 133.4, 132.5, 129.5, 114.1, 112.1, 111.0, 108.8, 108.1, 102.2, 72.5, 71.9, 67.6, 66.9, 65.4, 64.2, 61.5, 59.7, 55.6 – 54.1 (m)*, 43.0, 42.3, 35.3, 34.8, 31.2, 25.3, 25.2, 24.8. (* Overlap of 2 peaks)

**$^{13}$C NMR** (126 MHz, DMSO-*d*$_6$, **100 °C**) δ 154.6 – 154.2 (m)*, 147.4, 147.1, 132.4, 113.6, 111.6, 108.3, 101.7, 66.9 – 66.5 (m), 65.2 – 64.5 (m), 59.5 – 58.8 (m), 54.8 – 54.1 (m)*, 42.6 – 41.8 (m), 24.4.* (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{17}H_{13}D_6BrN_3O_7$ $[M+H]^+$ calc.: 462.0777; Found: 462.0781.

**IR** (ATR, neat, $cm^{-1}$): 3410 (m), 2908 (w), 1760 (w), 1688 (s), 1477 (s), 1233 (m), 1035 (m), 915 (m), 725 (m).

**Synthesis of epoxyacetonide S14:** Epoxyacetonide **S14** was prepared using the procedure to synthesize epoxyacetonide **14**. Epoxydiol **S13** (4.65 g, 10.1 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 2:1 → 1:3) to give the desired compound as a colorless solid [4.40 g, 8.76 mmol, 87%].



**S14**

$\boldsymbol{R_f}$ = 0.52 ($SiO_2$, $CH_2Cl_2$:MeOH = 16:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +22.1 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 197 – 202 °C

NMR analysis of epoxyacetonide **S14** revealed several conformational structures at 20 °C, which increased spectrum complexity. Therefore, a variable-temperature NMR spectroscopy was employed, and a full coalescence of the peaks was observed at 80 °C. For clarity only the two major conformers at 20 °C are described.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 7.24 (s, 1H), 7.20 (s, 0.2H), 7.15 – 6.98 (m, 1.2H), 6.09 (s, 1H), 6.07 (s, 1H), 6.05 (s, 0.2H), 6.04 (s, 0.2H), 3.15 (s, 0.6H), 2.94 (s, 3H), 2.84 (s, 0.6H), 2.81 (s, 3H), 1.49 – 1.42 (m, 3.6H), 1.36 – 1.30 (m, 3.6H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **80 °C**) δ 7.17 (s, 1H), 7.03 (s, 1H), 6.06 (d, *J* = 5.8 Hz, 2H), 2.95 (s, 3H), 2.82 (s, 3H), 1.48 (s, 3H), 1.36 (s, 3H).

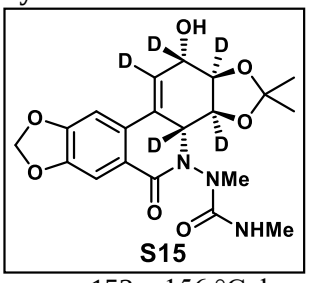
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 155.7, 155.5, 155.0, 154.0, 147.7 147.6, 147.4, 146.6, 130.6, 129.8, 114.6, 113.6, 113.4, 113.1, 112.8, 112.4, 110.2, 109.9, 108.6, 102.3, 102.2, 72.7 – 71.8 (m)***, 59.4 – 58.8 (m)*, 58.2 – 57.6 (m)*, 51.4 – 50.6 (m)*, 42.9 – 42.3 (m)*, 36.0, 32.1, 27.5, 27.3, 26.2, 25.7, 25.2, 25.1. (* Overlap of 2 peaks, *** Overlap of 4 peaks)

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **80 °C**) δ 155.0, 154.7, 147.3, 147.1, 130.4, 114.3, 112.0, 109.6, 108.3, 101.8, 72.6 – 71.6 (m)*, 59.1, 57.6, 50.8, 42.7, 34.3, 27.0, 25.4, 24.7. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{20}H_{20}D_6BrN4O_7$ $[M+NH_4]^+$ calc.: 521.1339; Found: 521.1339.

**IR** (ATR, neat, $cm^{-1}$): 2985 (w), 1769 (w), 1704 (s), 1478 (s), 1233 (s), 1218 (s), 1036 (s), 926 (m), 770 (m).

**Synthesis of lactam S15:** Lactam **S15** was prepared using the procedure to synthesize lactam **35**. Epoxyacetonide **S14** (3.85 g, 7.66 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 50:1 → 30:1) to give the desired compound as a colorless solid [1.04 g, 2.46 mmol, 32%].



**S15**

$\boldsymbol{R_f}$ = 0.46 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{22}}$ = -5.0 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 152 – 156 °C decomposition

NMR analysis of lactam **S15** at 20 °C revealed several conformational isomers. When variable-temperature NMR spectroscopy was employed no coalescence of the peaks was observed. Only the two major isomers are described for clarity.

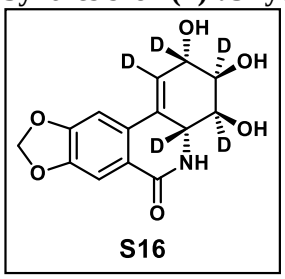
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.51 (s, 0.5H), 7.01 (s, 1H), 6.93 (s, 0.5H), 6.06 – 6.03 (m, 2H), 6.01 (s, 0.5H), 6.00 (s, 0.5H) 5.05 (q, *J* = 4.8 Hz, 1H), 4.61 (q, *J* = 4.7 Hz, 0.5H), 3.42 (s, .5H), 3.29 (s, 1.5H), 3.23 (s, 1H), 3.13 (s, 3H), 2.82 (d, *J* = 4.6 Hz, 1.5H), 2.77 (d, *J* = 4.7 Hz, 3H), 1.49 (s, 4.5H), 1.36 (s, 1.5H), 1.32 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 163.07, 162.17, 158.91, 157.54, 152.47, 152.06, 148.69, 148.40, 129.41, 128.59, 127.33, 127.1, 126.9 – 126.5 (m), 126.4– 126.1 (m), 120.40, 120.15, 111.14, 110.20, 107.76, 107.73, 102.29, 102.16, 101.82, 101.25, 79.23 – 78.36 (m), 78.32 – 77.53 (m)*, 75.99 (d, *J* = 20.8 Hz), 71.48 (t, *J* = 21.0, 17.6 Hz), 70.43 (t, *J* = 19.7, 10.9 Hz), 62.51 (t, *J* = 23.7, 19.7 Hz), 60.47 (t, *J* = 21.7, 17.0 Hz), 38.58, 31.91, 27.67, 27.45, 27.32, 27.10, 24.96, 24.77. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{20}H_{22}D_5N_4O_7$ $[M+NH_4]^+$ calc.: 440.2188; Found: 440.2192

**IR** (ATR, neat, $cm^{-1}$): 3353 (m), 2922 (w), 1650 (s), 1528 (m), 1478 (s), 1213 (s), 1035 (m), 933 (m), 757 (s).

**Synthesis of (+)-*d5*-lycoricidine S16:** (+)-*d5*-Lycoricidine **S16** was prepared using the procedure to synthesize (+)-lycoricidine **3**. Lactam **S15** (945.7 mg, 2.39 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeOH = 1:0 → 5:1) to give the desired compound as an colorless solid [606.7 mg, 2.048 mmol, 91%].



**S16**

$\boldsymbol{R_f}$ = 0.38 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +127.4 (*c* = 1.0 in DMSO)

**m.p.** = 213 – 216 °C decomposition

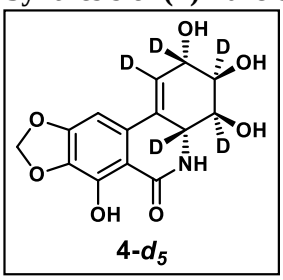
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 7.32 (s, 1H), 7.26 (s, 1H), 7.16 (s, 1H), 6.13 – 6.12 (m, 1H), 6.11 – 6.10 (m, 1H), 5.14 (s, 2H), 4.95 (s, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 163.2, 151.0, 147.2, 131.8, 130.0, 123.3 (t, *J* = 13.0 Hz), 121.9, 106.2, 103.4, 101.9, 72.0 (t, *J* = 23.1 Hz), 68.6 (t, *J* = 20.9 Hz), 68.5 (t, *J* = 20.8 Hz), 52.3 (t, *J* = 17.6 Hz)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{12}D_5N_2O_6$ $[M+NH_4]^+$ calc.: 314.1395; Found: 314.1381.

**IR** (ATR, neat, $cm^{-1}$): 3353 (s), 3273 (s), 2916 (m), 1649 (s), 1467 (s), 1382 (s), 1251 (m), 1102 (s), 1016 (s).

**Synthesis of (+)-narciclasine 4-*d*$_5$:** (+)-Narciclasine **4-*d*$_5$** was prepared using the procedure to synthesize (+)-narciclasine **4**. (+)-lycoricidine **S16** (100 mg, 337 μmol) was subjected to the reaction conditions. The residue was purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give (+)-narciclasine **4-*d*$_5$** as an colorless solid [55.2 mg, 177 μmol, 52%].



**4-*d*$_5$**

***R*$_f$** = 0.33 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

**[α]$_D^{22}$** = +159.3 (*c* = 1.0 in DMSO)

**m.p.** = 202 – 218 °C decomposition

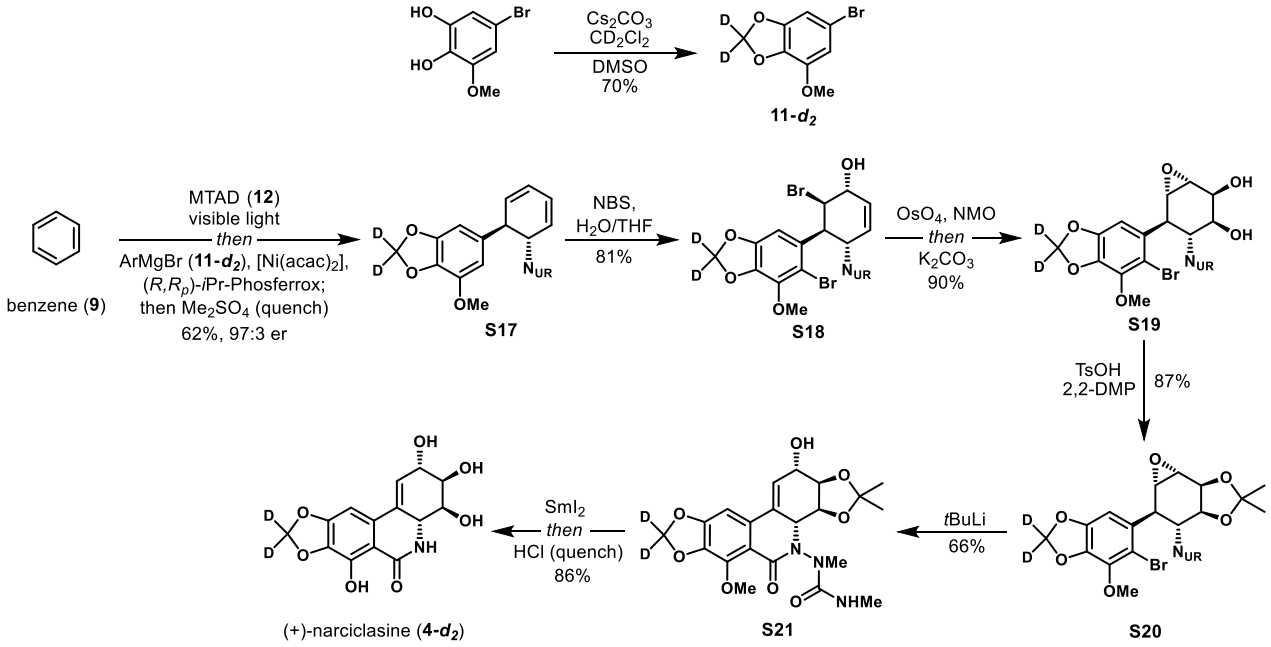
**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 13.25 (s, 1H), 7.86 (s, 1H), 6.86 (s, 1H), 6.10 – 6.07 (m, 2H), 5.16 (s, 1H), 5.13 (s, 1H), 4.98 (s, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 168.9, 152.3, 144.8, 133.4, 132.1, 129.2, 124.4 (t, *J* = 24.2 Hz), 105.5, 102.1, 95.8, 71.7 (t, *J* = 17.7 Hz), 68.4 (m), 68.3 (m), 52.4 (t, *J* = 20.8 Hz).

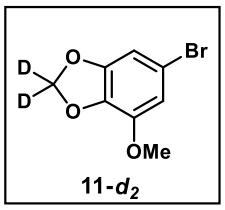
**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_9D_5NO_7$ $[M+H]^+$ calc.: 313.1084; Found: 313.1075.

**IR** (ATR, neat, $cm^{-1}$): 3442 (m), 3206 (m), 2912 (m), 1673 (s), 1428 (s), 1366 (s), 1229 (m), 1084 (s), 1015 (s).

## 9-2. Synthesis of (+)-narciclasine 4-$d_2$




**Synthesis of bromide 11-$d_2$:** In a round bottom flask equipped with a reflux condenser, a solution of 5-bromo-3-methoxy-1,2-benzenediol (prepared according to the literature procedure[12]) (28.4 g, 130 mmol, 1.0 equiv.) and $Cs_2CO_3$ (63.4 g, 194 mmol, 1.5 equiv.) in DMSO (259 mL) and $CD_2Cl_2$ (15 mL) was heated to 80 °C and stirred for 2 hours. Then, the solution was allowed to cool to 25 °C before being diluted with water (400 mL) and diethylether (400 mL). The phases were separated and the aqueous phase was extracted with diethylether (3 × 300 mL). The combined organics were washed with brine (500 mL) and water (500 mL), dried over $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 100:1 → 50:1) to give the desired compound as a colorless solid [21.2 g, 91 mmol, 70%].




$\boldsymbol{R_f}$ = 0.66 ($SiO_2$, hexanes:EtOAc = 5:1)

**m.p.** = 80 – 82 °C

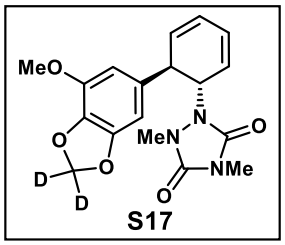
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.77 – 6.58 (m, 2H), 3.88 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 149.6, 144.3, 135.0, 113.4, 111.1, 106.3, 102.0 – 100.7 (m), 56.9.

**HRMS** (ESI-TOF, m/z) calcd. For $C_8H_5D_2O_3Br$ $[M]^+$ calc.: 231.9704; Found: 231.9695.

**IR** (ATR, neat, $cm^{-1}$): 3087 (w), 2975 (w), 2135 (w), 1625 (s), 1485 (s), 1420 (s), 1226 (s), 1129 (s), 987 (m), 814 (m).

**Synthesis of diene S17:** Diene **S17** was prepared using the procedure to synthesize diene **8**, employing the Grignard reagent derived from bromide **11-*d*₂**. The reaction was run on 25 mmol scale, with MTAD (**12**, 2.80g) as the limiting reagent. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 5:1 → 3:1) to give the desired compound as a colorless solid [5.52g, 15.4 mmol, 62%, 97:3 er].



**S17**

Enantiomeric ratio was determined with HPLC analysis using Daicel Chiracel® OJ-H column, 50% *i*PrOH in hexanes, 0.8 mL/min, $t_R$(minor) = 13.1 min, $t_R$(major) = 20.1 min.

$\boldsymbol{R_f}$ = 0.35 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{23}}$ = +200.3 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 119 – 121 °C

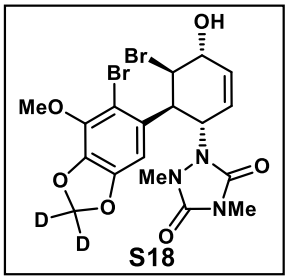
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.46 (s, 1H), 6.37 (s, 1H), 6.12 (ddd, *J* = 9.3, 5.2, 2.8 Hz, 1H), 6.08 – 6.03 (m, 1H), 5.85 (dd, *J* = 9.3, 3.2 Hz, 1H), 5.72 – 5.67 (m, 1H), 5.15 (dt, *J* = 13.8, 3.2 Hz, 1H), 3.91 – 3.86 (m, 1H), 3.85 (s, 3H), 3.20 (s, 3H), 2.91 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 156.2, 155.1, 149.1, 143.5, 136.1, 134.6, 130.8, 126.6, 125.7, 123.5, 107.6, 102.4, 101.5 – 100.6 (m), 61.0, 56.7, 45.1, 35.2, 25.5.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{17}D_2N_3O_5Na$ $[M+Na]^+$ calc.: 382.1348; Found: 382.1351.

**IR** (ATR, neat, $cm^{-1}$): 2932 (m), 2255 (w), 1766 (w), 1703 (s), 1452 (m), 1228 (m), 1129 (m), 946 (m), 758 (m).

**Synthesis of bromohydrin S18:** Bromohydrin **S18** was prepared using the procedure to synthesize bromohydrin **25**. Diene **S17** (5.32 g, 14.8 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, hexanes: EtOAc = 4:1 → 1:1) to provide the desired compound as a colorless solid [6.40 g, 12.0 mmol, 81%].



**S18**

$\boldsymbol{R_f}$ = 0.56 ($SiO_2$, hexanes:EtOAc = 1:3)

$\boldsymbol{[\alpha]_D^{20}}$ = +121.6 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 250 – 252 °C decomposition

NMR analysis of bromohydrin **S18** revealed several conformational structures at 20 °C, which increased spectrum complexity. Unfortunately, when variable-temperature NMR spectroscopy was employed no coalescence of the peaks was observed.

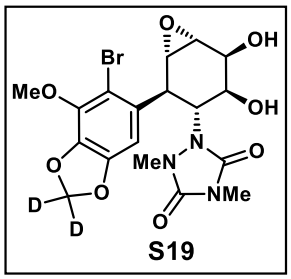
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 6.82 (s, 0.1H), 6.12 – 6.06 (m, 1.1H), 5.99 – 5.95 (m, 0.1H), 5.92 – 5.85 (m, 1H), 5.35 (bs, 0.1H), 5.17 (bs, 1H), 4.68 – 4.51 (m, 2.2H), 4.33 (s, 1H), 4.30 (s, 0.1H), 4.03 (s, 3H), 3.94 (s, 0.3H), 3.17 (s, 0.3H), 3.15 (s, 3H), 2.97 (s, 3H), 2.92 (s, 0.3H), 2.76 – 2.55 (m, 1.1H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 155.4, 155.3, 148.5, 140.6, 137.1, 130.0, 128.3, 110.4, 109.7, 104.5, 101.7 – 100.9 (m), 69.5, 60.3, 57.3, 55.8, 41.9, 34.7, 25.7.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{18}D_2Br_2N_3O_6$ $[M+H]^+$ calc.: 533.9844; Found: 533.9837.

**IR** (ATR, neat, $cm^{-1}$): 3407 (br), 2888 (w), 1763 (m), 1687 (s), 1483 (s), 1228 (m), 1169 (s), 1033 (m), 907 (w), 773 (w).

**Synthesis of epoxydiol S19:** Epoxydiol **S19** was prepared using the procedure to synthesize (+)-epoxydiol **S6**. Bromohydrin **S18** (6.30 g, 11.8 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 30:1 → 15:1) to give the desired compound as a colorless solid [5.81 g, 10.6 mmol, 90%].



**S19**

$\boldsymbol{R_f}$ = 0.37 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{21}}$ = +102.8 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 162 – 164 °C

NMR analysis of epoxydiol **S19** revealed several conformational structures at 20 °C, which increased spectrum complexity. Therefore, a variable-temperature NMR spectroscopy was employed, and a full coalescence of the peaks was observed at 100 °C. For clarity only the two major conformers at 20 °C are described.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 6.94 (s, 1H), 6.80 (s, 0.8H), 5.71 (d, *J* = 4.5 Hz, 1H), 5.63 (d, *J* = 4.4 Hz, 0.8H), 4.93 – 4.88 (m, 1.8H), 4.49 (t, *J* = 10.3 Hz, 1H), 4.38 – 4.30 (m, 1.8H), 4.26 (d, *J* = 9.7 Hz, 0.8H), 4.08 (d, *J* = 9.8 Hz, 1H), 3.96 – 3.90 (m, 5.4H), 3.88 – 3.82 (m, 1.8H), 3.63 (t, *J* = 10.4z Hz, 0.8H), 3.39 – 3.35 (m, 1.8H), 3.22 (s, 3H), 2.96 (s, 0.8H), 2.91 (s, 1H), 2.88 (s, 2.4H), 2.79 (s, 3H), 2.46 (s, 2.4H).

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 6.89 (s, 1H), 5.28 (s, 1H), 4.46 – 4.36 (m, 2H), 4.29 – 4.06 (m, 2H), 3.94 (s, 3H), 2.97 (br, 3H), 3.02 – 2.79 (m, 1H) 2.84 (s, 3H).

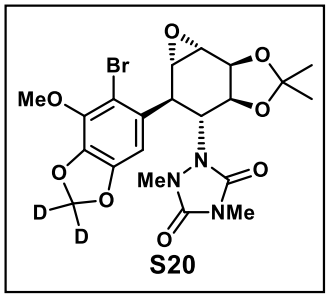
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 155.6, 155.1, 154.0, 152.8, 149.1, 148.9, 140.2, 139.5, 137.0, 136.6, 134.6, 133.6, 109.2, 108.9, 103.3, 102.6, 102.1 – 101.0 (m)*, 67.7, 67.4, 65.9, 64.7, 60.3, 60.1, 60.0, 59.9, 55.5, 55.2**, 47.1, 43.0, 34.9, 31.2, 25.2, 24.8. (* Overlap of 2 peaks, ** Overlap of 3 peaks)

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 154.2*, 148.5, 139.4, 136.5, 133.4, 108.8, 102.8, 101.3 – 100.7 (m), 100.9, 67.3, 65.2, 59.5, 59.3, 55.0*, 42.9, 24.3. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{18}H_{19}D_2BrN_3O_8$ $[M+H]^+$ calc.: 488.0638; Found: 488.0634.

**IR** (ATR, neat, $cm^{-1}$): 3412 (br), 2945 (w), 1761 (w), 1688 (s), 1478 (s), 1234 (m), 1107 (s), 1045 (m), 1007 (m), 771 (m).

**Synthesis of epoxyacetonide S20:** Epoxyacetonide **S20** was prepared using the procedure to synthesize epoxyacetonide **14**. Epoxydiol **S19** (5.00 g, 10.2 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, hexanes:EtOAc = 2:1 → 1:3) to give the desired compound as a colorless solid [4.71 g, 8.91 mmol, 87%].



**S20**

$\boldsymbol{R_f}$ = 0.36 ($SiO_2$, hexanes:EtOAc = 1:1)

$\boldsymbol{[\alpha]_D^{21}}$ = +21.5 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 213 – 214 °C

NMR analysis of epoxyacetonide **S20** revealed several conformational and rotomeric structures at 20 °C, which increased spectrum complexity. Therefore, variable-temperature NMR spectroscopy was employed, and a full coalescence of the peaks was observed at 100 °C. For clarity only the two major conformers at 20 °C are described.

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **20 °C**) δ 6.85 (s, 1H), 6.79 (s, 0.2H), 5.01 (dd, *J* = 12.6, 10.4 Hz, 0.2H), 4.83 (dd, *J* = 11.8, 5.5 Hz, 1H), 4.44 (s, 1H), 4.25 (dd, *J* = 10.4, 5.2 Hz, 0.2H), 4.17 (dd, *J* = 12.1, 9.8 Hz, 0.2H), 3.97 – 3.90 (m, 3.6H), 3.83 – 3.72 (m, 1H), 3.66 – 3.61 (m, 0.2H), 3.51 – 3.47 (m, 1H), 3.16 (s, 0.2H), 3.13 (s, 1H), 2.94 (bs, 3.6H), 2.85 – 2.80 (m, 3.6H), 2.71 (s, 0.2H), 2.68 (s, 1H), 1.49 – 1.39 (m, 3.6H), 1.36 – 1.25 (m, 3.6H)

**$^1$H NMR** (500 MHz, DMSO-$d_6$, **100 °C**) δ 6.79 (s, 1H), 4.82 (d, *J* = 5.5 Hz, 1H), 4.50 (s, 1H), 4.18 (s, 1H), 3.94 (s, 3H), 3.89 – 3.78 (m, 1H), 3.50 (s, 1H), 3.16 (s, 1H), 2.95 (s, 3H), 2.83 (s, 3H), 1.49 (s, 3H), 1.37 (s, 3H).

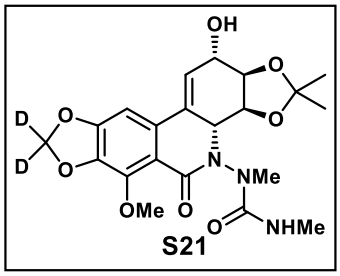
**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **20 °C**) δ 155.7, 155.5, 153.9, 153.2, 148.8, 147.9, 140.2, 139.8, 137.1, 136.7, 131.7, 130.8, 110.2, 110.0, 109.7, 109.5, 108.1, 103.1, 102.1 – 101.0 (m)*, 73.0, 72.9, 72.8, 72.6, 60.0, 59.9, 59.5, 58.5, 57.8, 57.5, 53.0, 51.6, 45.7, 43.4, 36.0, 32.1, 27.4, 27.2, 26.1, 25.7, 25.2, 24.7. (* Overlap of 2 peaks)

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$, **100 °C**) δ 154.8, 154.6, 148.4, 139.7, 136.6, 131.4, 109.5, 109.2, 102.7, 101.4 – 100.6 (m), 72.8, 72.4, 59.6, 59.4, 57.9, 51.3, 43.1, 34.2, 26.8, 25.2, 24.4.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{21}H_{23}D_2BrN_3O_8$ $[M+H]^+$ calc.: 528.0950; Found: 528.0935.

**IR** (ATR, neat, $cm^{-1}$): 2988 (w), 1767 (w), 1702 (s), 1479 (s), 1234 (s), 1217 (s), 1075 (s), 1001 (w), 774 (w).

**Synthesis of lactam S21:** Lactam **S21** was prepared using the procedure to synthesize lactam **35**. Epoxyacetonide **S20** (4.00 g, 7.57 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography ($SiO_2$, $CH_2Cl_2$:MeOH = 50:1 → 30:1) to give the desired compound as a colorless solid [2.23 g, 4.96 mmol, 66%].



**S21**

$\boldsymbol{R_f}$ = 0.31 ($SiO_2$, $CH_2Cl_2$:MeOH = 8:1)

$\boldsymbol{[\alpha]_D^{21}}$ = +3.1 (*c* = 1.0 in $CHCl_3$)

**m.p.** = 161 – 165 °C decomposition

NMR analysis of lactam **S21** revealed several conformational structures at 20 °C, which increased spectrum complexity. Unfortunately, when variable-temperature NMR spectroscopy was employed no coalescence of the peaks was observed.

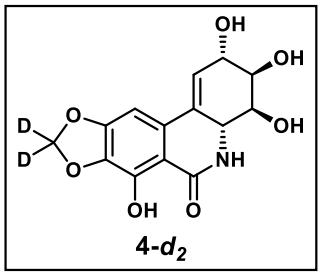
**$^1$H NMR** (500 MHz, $CDCl_3$) δ 6.79 (s, 1H), 6.73 (s, 0.5H), 6.41 – 6.36 (m, 1H), 6.37 – 6.32 (m, 0.5H), 5.20 (d, *J* = 4.9 Hz, 1H), 4.71 – 4.65 (m, 0.5H), 4.58 – 4.52 (m, 0.5H), 4.50 (t, *J* = 7.4 Hz, 1H), 4.43 – 4.36 (m, 1H), 4.33 – 4.23 (m, 2H), 4.08 (t, *J* = 6.9 Hz, 1H), 4.03 (t, *J* = 7.7 Hz, 0.5H), 4.00 (s, 3H), 3.98 (s, 1.5H), 3.87 – 3.80 (m, 0.5H), 3.69 – 3.59 (m, 1H), 3.25 (s, 1.5H), 3.10 (s, 3H), 2.79 (d, *J* = 4.6 Hz, 1.5H), 2.74 (d, *J* = 4.9 Hz, 3H), 1.48 – 1.43 (m, 4.5H), 1.34 (s, 1.5H), 1.32 (s, 3H).

**$^{13}$C NMR** (126 MHz, $CDCl_3$) δ 161.9, 160.8, 159.1, 157.7, 153.1, 152.7, 145.0*, 139.3, 139.2, 131.5, 130.4, 128.0*, 127.3*, 113.0, 112.9, 111.2, 110.0, 102.3 – 100.8 (m)*, 97.8, 97.2, 79.5, 78.7, 78.3, 76.0, 72.2, 70.6, 62.8, 61.0, 60.9, 60.4, 38.7, 31.8, 27.7, 27.5, 27.5, 27.2, 25.2, 24.9. (* Overlap of 2 peaks)

**HRMS** (ESI-TOF, m/z) calcd. For $C_{21}H_{24}D_2N_3O_8$ $[M+H]^+$ calc.: 450.1845; Found: 450.1841.

**IR** (ATR, neat, $cm^{-1}$): 3364 (br), 2937 (w), 1651 (s), 1529 (m), 1480 (s), 1210 (s), 1029 (m), 967 (m), 757 (s).

**Synthesis of (+)-narciclaisne 4-*d*$_2$:** (+)-narciclasine **4-*d*$_2$** was prepared using the procedure to synthesize (+)-narciclasine **4**. Lactam **S21** (1.00g, 2.23 mmol) was subjected to the reaction conditions. The residue was purified by flash chromatography (wet loaded with DMSO and purified using $C_{18}$-functionalized $SiO_2$, $H_2O$:MeCN = 1:0 → 5:1) to give (+)-narciclasine **4-*d*$_2$** as an colorless solid [589 mg, 1.92 mmol, 86%].



**4-*d*$_2$**

***R*$_f$** = 0.33 ($SiO_2$, $CHCl_3$:MeOH = 4:1)

**[α]$_D^{22}$** = +149.2 (*c* = 1.0 in DMSO)

**m.p.** = 202 – 216 °C decomposition

**$^1$H NMR** (500 MHz, DMSO-$d_6$) δ 13.26 (s, 1H), 7.89 (s, 1H), 6.86 (s, 1H), 6.16 – 6.14 (m, 1H), 5.21 (d, *J* = 5.9 Hz, 1H), 5.18 (d, *J* = 5.5 Hz, 1H), 5.02 (d, *J* = 3.7 Hz, 1H), 4.19 (ddd, *J* = 8.6, 2.6, 1.4 Hz, 1H), 4.02 (ddd, *J* = 5.9, 4.5, 2.2 Hz, 1H), 3.80 (ddd, *J* = 8.6, 5.5, 2.2 Hz, 1H), 3.72 – 3.69 (m, 1H).

**$^{13}$C NMR** (126 MHz, DMSO-$d_6$) δ 168.9, 152.4, 144.8, 133.4, 132.1, 129.3, 124.7, 105.6, 103.0 – 100.3 (m), 95.8, 72.4, 69.2, 68.8, 52.9.

**HRMS** (ESI-TOF, m/z) calcd. For $C_{14}H_{12}D_2N_2O_7$ $[M+H]^+$ calc.: 310.0896; Found: 310.0895.

**IR** (ATR, neat, $cm^{-1}$): 3367 (br), 3213(br), 2907 (m), 1669 (s), 1468 (s), 1372 (s), 1274 (m), 1131(s), 1003 (s).

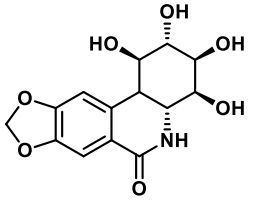
## 10. Cell viability assay

*Cell Culture and Reagents*

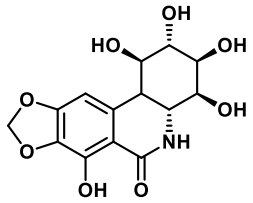
A549 and HCT116 cells were cultured in a 37 °C, 5% $CO_2$, humidified atmosphere in RPMI 1640 media supplemented with 1% penicillin/streptomycin and 10% fetal bovine serum. Lycoricidine, narciclasine, and derivatives were dissolved in DMSO and maintained as 10 mM stocks prior to use.

*Cell Viability Assay*

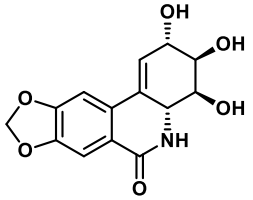
Cells were seeded in a 96 well plate and allowed to adhere for 3 h. Compounds were added in DMSO at varying concentrations (1% v/v final concentration of DMSO) before the cells were incubated for 72 h. After 72 h, cell viability was assessed via Alamar Blue assay. DMSO-treated cells served as live controls while raptinal-treated cells served as dead controls.



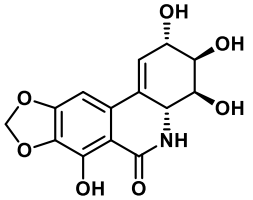
**(+)-7-deoxypancratistatin (1)**
**A549: 2.9 ± 0.6 μM**
**HCT116: 1.5 ± 0.1 μM**



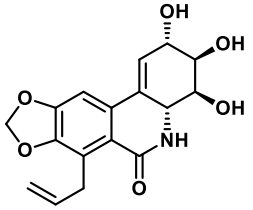
**(+)-pancratistatin (2)**
**A549: 0.75 ± 0.09 μM**
**HCT116: 0.44 ± 0.03 μM**



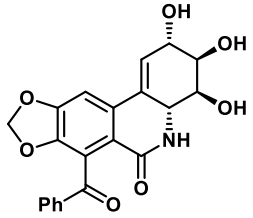
**(+)-lycoricidine (3)**
**A549: 0.73 ± 0.06 μM**
**HCT116: 0.54 ± 0.03 μM**



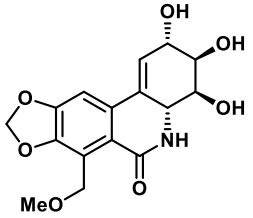
**(+)-narciclasine (4)**
**A549: 0.056 ± 0.004 μM**
**HCT116: 0.0324 ± 0.0004 μM**



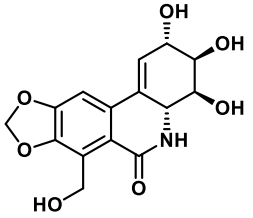
**38**
**A549: >100 μM**
**HCT116: >100 μM**



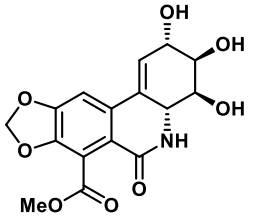
**39**
**A549: 44 ± 6 μM**
**HCT116: 35 ± 9 μM**



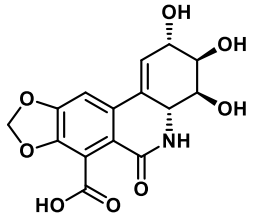
**40**
**A549: 48 ± 2 μM**
**HCT116: 50 ± 20 μM**



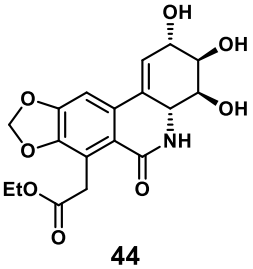
**41**
**A549: >100 μM**
**HCT116: >100 μM**



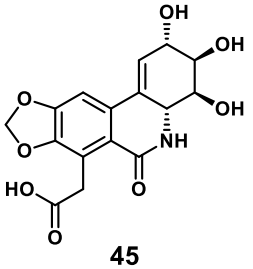
**42**
**A549: 39 ± 5 μM**
**HCT116: 29 ± 8 μM**



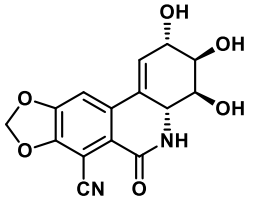
**43**
**A549: >100 μM**
**HCT116: 80 ± 20 μM**



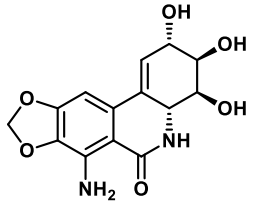
**44**
**A549: 74 ± 10 μM**
**HCT116: 80 ± 20 μM**



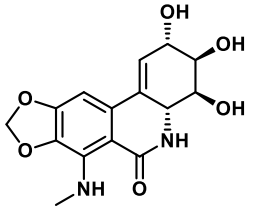
**45**
**A549: 89 ± 6 μM**
**HCT116: 70 ± 20 μM**



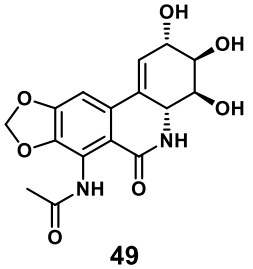
**46**
**A549: 1.2 ± 0.1 μM**
**HCT116: 0.48 ± 0.03 μM**



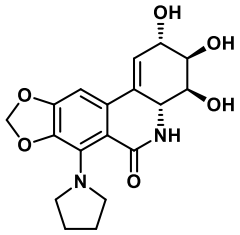
**47**
**A549: 0.38 ± 0.04 μM**
**HCT116: 0.39 ± 0.06 μM**



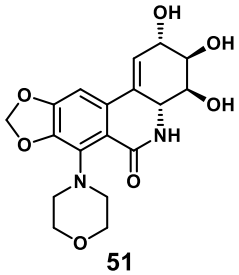
**48**
**A549: 28 ± 1 μM**
**HCT116: 12 ± 2 μM**



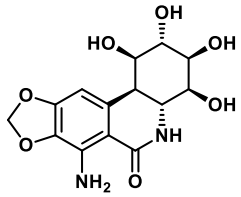
**49**
**A549: >100 μM**
**HCT116: >100 μM**



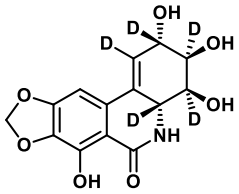
**50**
**A549: >100 μM**
**HCT116: >100 μM**



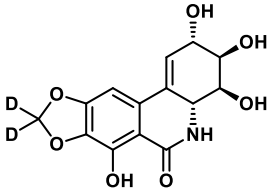
**51**
**A549: 39 ± 4 μM**
**HCT116: 33 ± 8 μM**



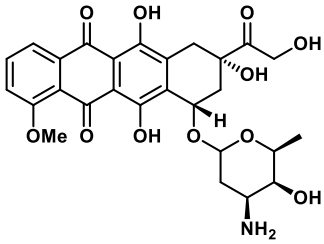
**52**
**A549: 9 ± 1 μM**
**HCT116: 3.4 ± 0.2 μM**



**4-$d_5$**
**A549: 0.066 ± 0.001 μM**
**HCT116: 0.043 ± 0.002 μM**



**4-$d_2$**
**A549: 0.07 ± 0.01 μM**
**HCT116: 0.04 ± 0.01 μM**

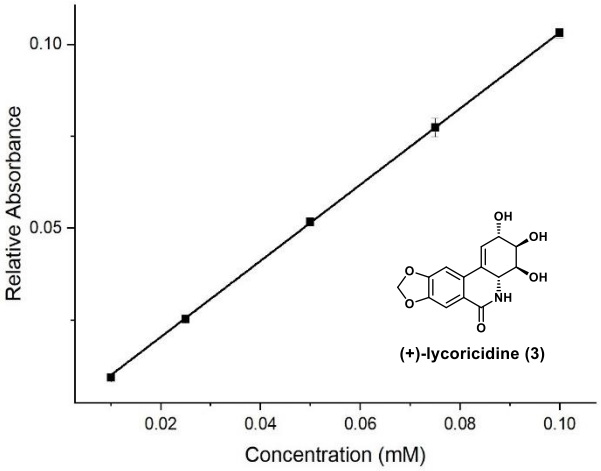


**doxorubicin**
**A549: 0.22 ± 0.03 μM**
**HCT116: 0.147 ± 0.009 μM**

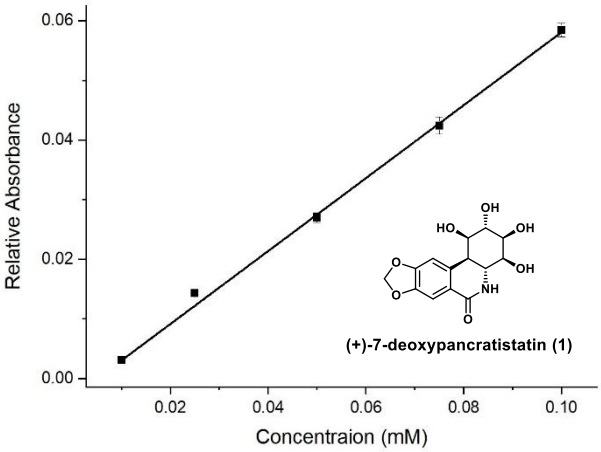
## 11. Solubility assay

A calibration was made for each compound by diluting a 1 mM DMSO solution to 10, 25, 50, 75, and 100 μM and then measuring their relative UV absorbance by LC-MS using a Kinetex® Evo C-18 50mm column running a gradient from 5% → 90% MeCN in water over 4 minutes at 0.4 mL/min.

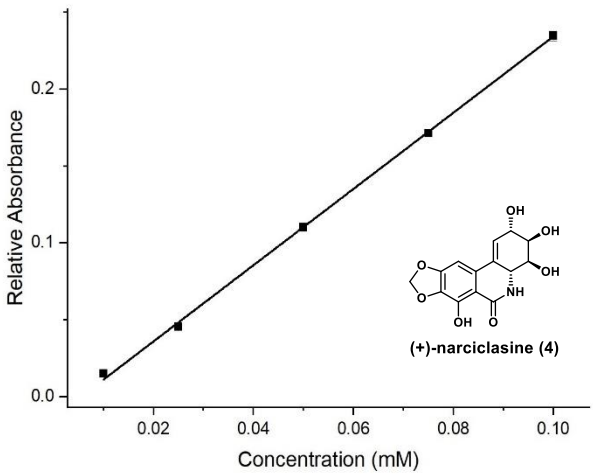
The aqueous solubility of each compound was measured using the shake-flask method. 1.0 mg of compound was diluted to 40 mM with water then stirred for 24 hours. Each solution was then filtered, diluted 10-fold, and analyzed by LCMS. The relative UV absorbance of each compound was then compared to its calibration curve to quantify its aqueous solubility.



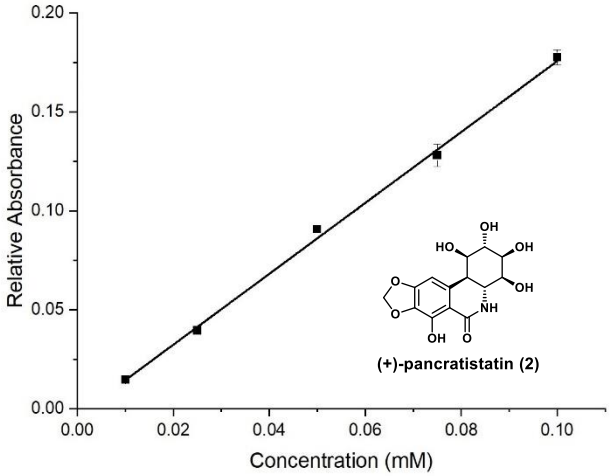

Calibration curve for **3**:
y = 1.0364 ± 0.0571x – 0.0004 ± 0.0004
$t_R$ = 1.732, λ = 254 nm
aq. Solubility = 0.56 ± 0.02 mg/ml



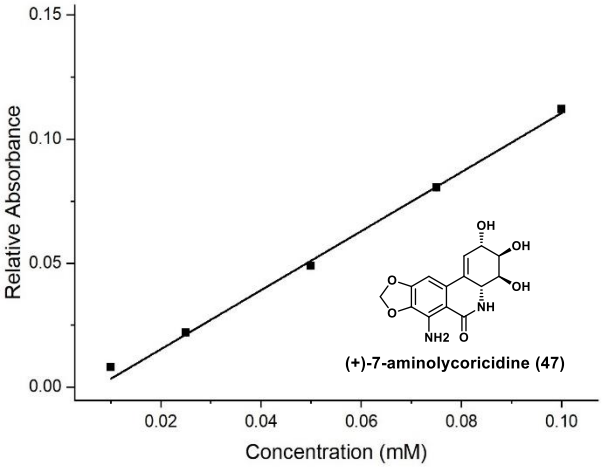

Calibration curve for **1**:
y = 0.6118 ± 0.0031x – 0. 0141 ± 0.0011
$t_R$ = 1.545, λ = 225 nm
aq. Solubility = 0.58 ± 0.02 mg/ml



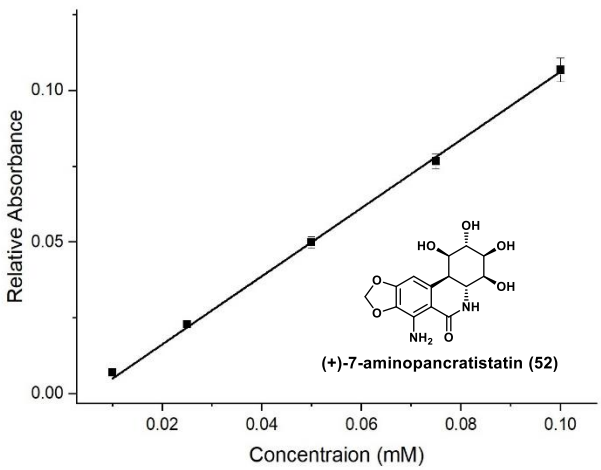

Calibration curve for **4**:
y = 2.4813 ± 0.0289x – 0.0139 ± 0.0021
$t_R$ = 1.914, λ = 254 nm
aq. Solubility = 0.34 ± 0.02 mg/ml




Calibration curve for **2**:
y = 1.7919 ± 0.0765x – 0.0036 ± 0.0060
$t_R$ = 1.840, λ = 235 nm
aq. Solubility = 0.56 ± 0.07 mg/ml




Calibration curve for **47**:
y = 1.1909 ± 0.0389x – 0.0086 ± 0.0026
$t_R$ = 1.775, λ = 254 nm
aq. Solubility = 3.74 ± 0.20 mg/ml



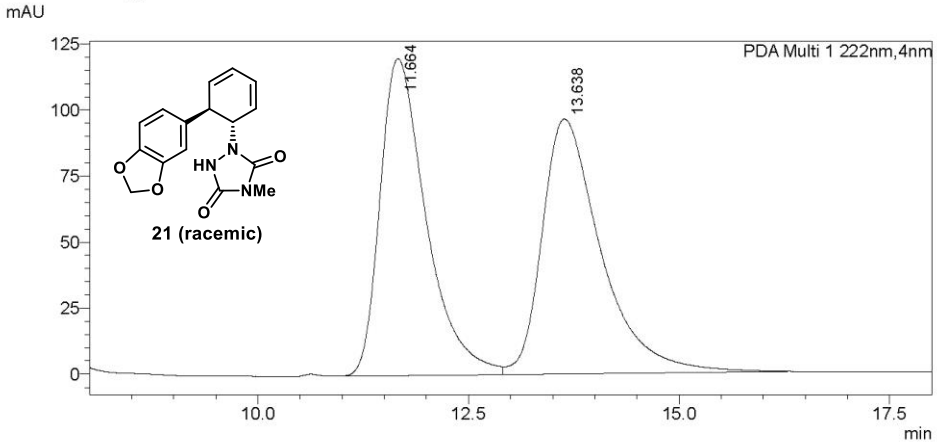

Calibration curve for **52**:
y = 1.1239 ± 0.0217x – 0.0063 ± 0.0017
$t_R$ = 1.682, λ = 235 nm
aq. Solubility = 3.46 ± 0.14 mg/ml

## 12. Mouse liver microsome assay

A mixture of PBS (pH 7.4), NADPH regenerating system solution A (Corning Life Sciences), and NADPH regenerating system solution B (Corning Life Sciences) was incubated at 37 ºC in a shaking incubator for 5 min. Next, compound was added in DMSO (final concentration 50 μM, 0.5% DMSO) before ice-cold mouse liver microsomes (Thermo Fisher, male CD-1 mice, pooled) were added (final protein concentration of 1 mg/mL). An aliquot was immediately removed, quenched with an equal volume of 100 μM internal standard in ice-cold acetonitrile, and centrifuged at 13,000 rcf for 3 min. The supernatant was diluted 1:5 in dd$H_2O$ and analyzed by LC-MS. The reactions were incubated at 37 ºC in a shaking incubator for 3 h. A second aliquot was removed, quenched and diluted as before and analyzed by LC-MS. The ratio of the areas of analyte: internal standard at 3 hours was compared to the ratio at $t_0$ to determine the percentage of compound remaining. Analysis was performed using a Kinetex® Evo C-18 50mm column running a gradient from 3% → 95% MeCN in water over 9 minutes at 0.4 mL/min. Internal standard = (+)-pancratistatin tetaacetate **S4**.

## 13. HPLC Spectra

**<Chromatogram>**

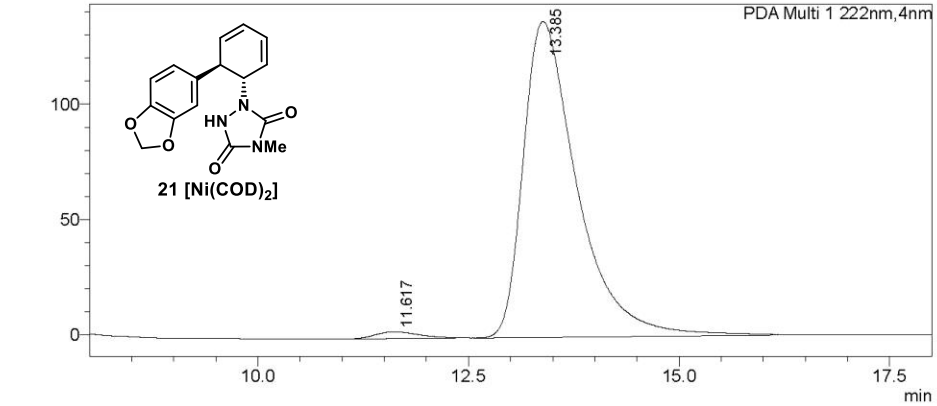



**<Peak Table>**

PDA Ch1 222nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 11.664 | 4561233 | 119984 | 49.272 | 55.421 | -- |
| 2 | 13.638 | 4696038 | 96513 | 50.728 | 44.579 | 1.815 |
| Total | | 9257271 | 216498 | 100.000 | 100.000 | |

**<Chromatogram>**

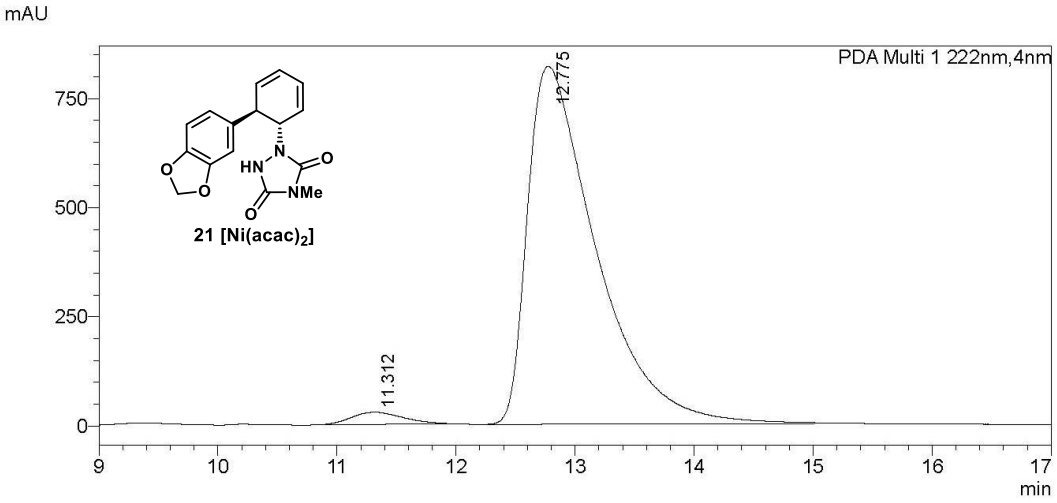



**<Peak Table>**

PDA Ch1 222nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 11.617 | 106472 | 2987 | 1.712 | 2.135 | -- |
| 2 | 13.385 | 6114141 | 136898 | 98.288 | 97.865 | 1.721 |
| Total | | 6220613 | 139885 | 100.000 | 100.000 | |

**<Chromatogram>**

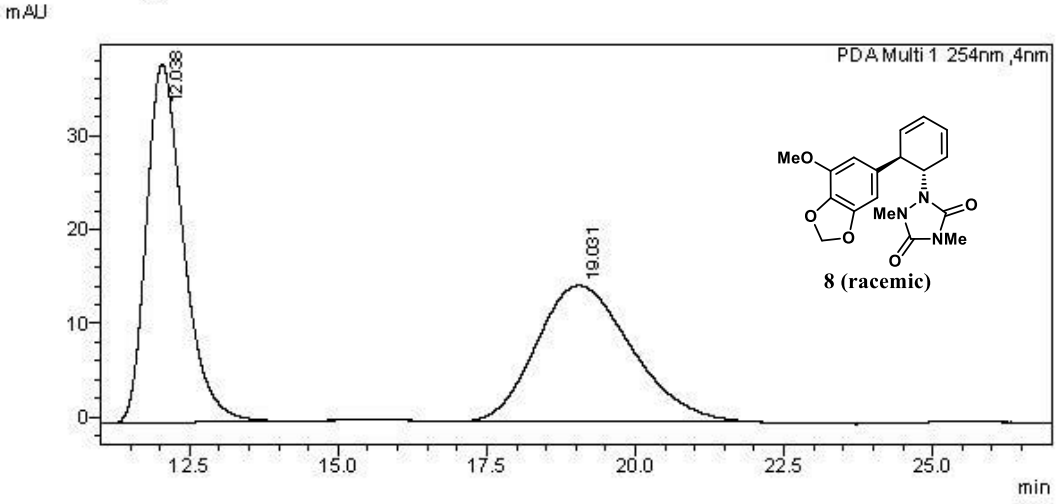



**<Peak Table>**

PDA Ch1 222nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 11.312 | 828369 | 27670 | 2.455 | 3.264 | -- |
| 2 | 12.775 | 32914647 | 820128 | 97.545 | 96.736 | 1.603 |
| Total | | 33743017 | 847798 | 100.000 | 100.000 | |

**<Chromatogram>**

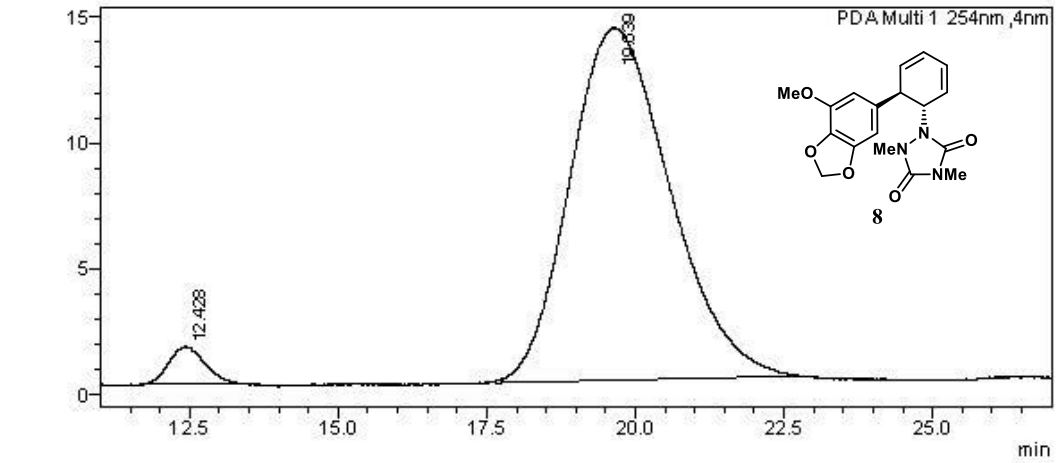



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 12.038 | 1650270 | 38102 | 50.781 | 72.517 | -- |
| 2 | 19.031 | 1599534 | 14440 | 49.219 | 27.483 | 3.460 |
| Total | | 3249804 | 52543 | 100.000 | 100.000 | |

**<Chromatogram>**

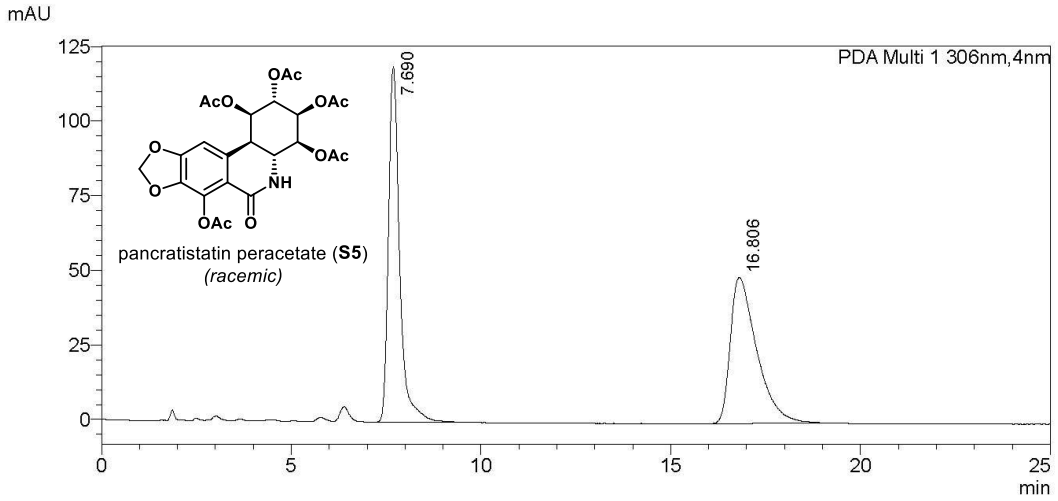



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 12.428 | 60774 | 1468 | 3.572 | 9.492 | -- |
| 2 | 19.639 | 1640639 | 13997 | 96.428 | 90.508 | 3.386 |
| Total | | 1701413 | 15465 | 100.000 | 100.000 | |

**<Chromatogram>**

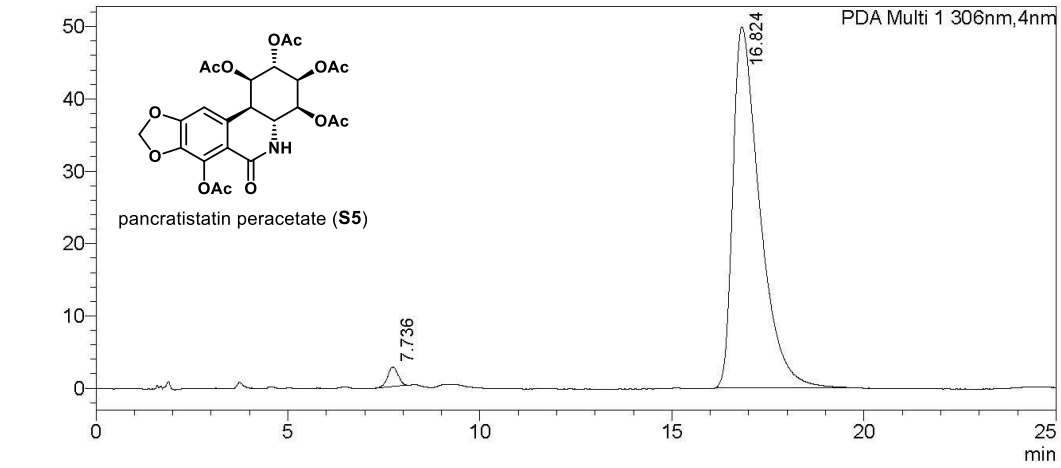



**<Peak Table>**

PDA Ch1 306nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 7.690 | 2427329 | 119295 | 50.730 | 70.895 | -- |
| 2 | 16.806 | 2357516 | 48974 | 49.270 | 29.105 | 9.941 |
| Total | | 4784845 | 168270 | 100.000 | 100.000 | |

**<Chromatogram>**



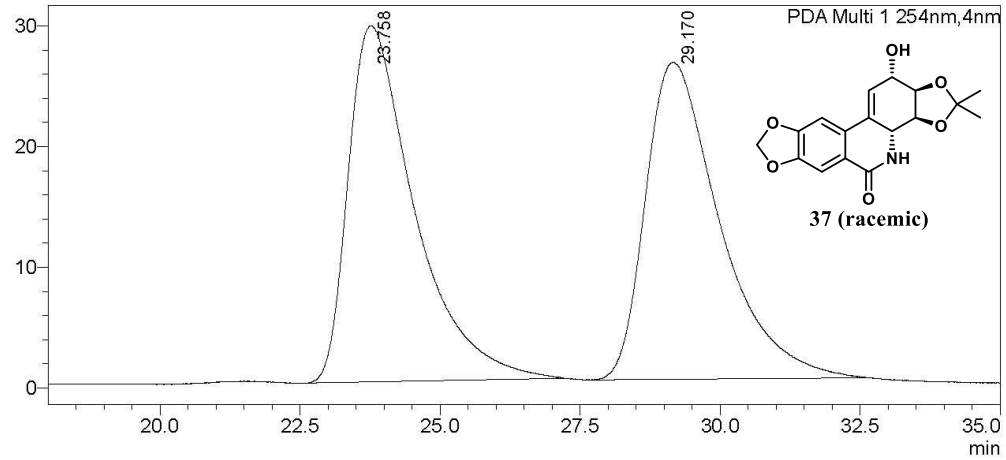

**<Peak Table>**

PDA Ch1 306nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 7.736 | 51200 | 2705 | 2.070 | 5.146 | -- |
| 2 | 16.824 | 2422004 | 49863 | 97.930 | 94.854 | 9.877 |
| Total | | 2473203 | 52568 | 100.000 | 100.000 | |

**<Chromatogram>**

mAU



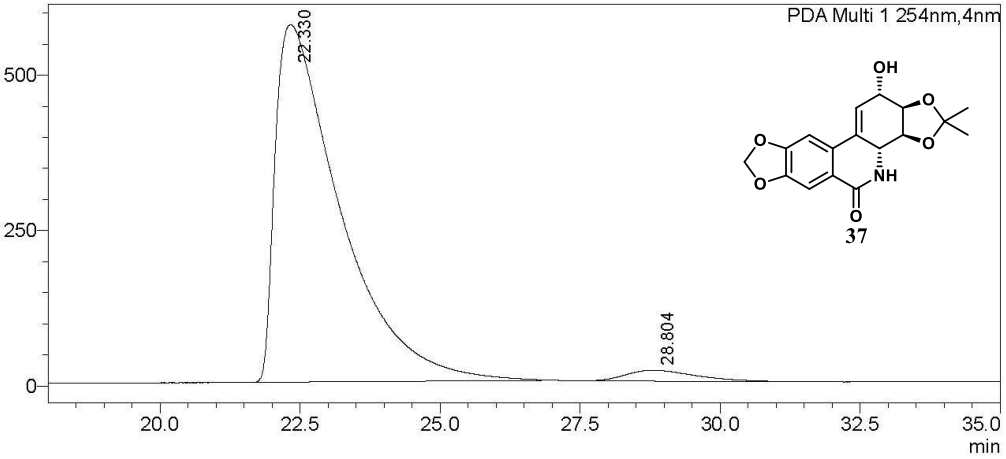

**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 23.758 | 2430388 | 29516 | 50.158 | 52.901 | -- |
| 2 | 29.170 | 2415064 | 26279 | 49.842 | 47.099 | 2.455 |
| Total | | 4845452 | 55795 | 100.000 | 100.000 | |

**<Chromatogram>**

mAU

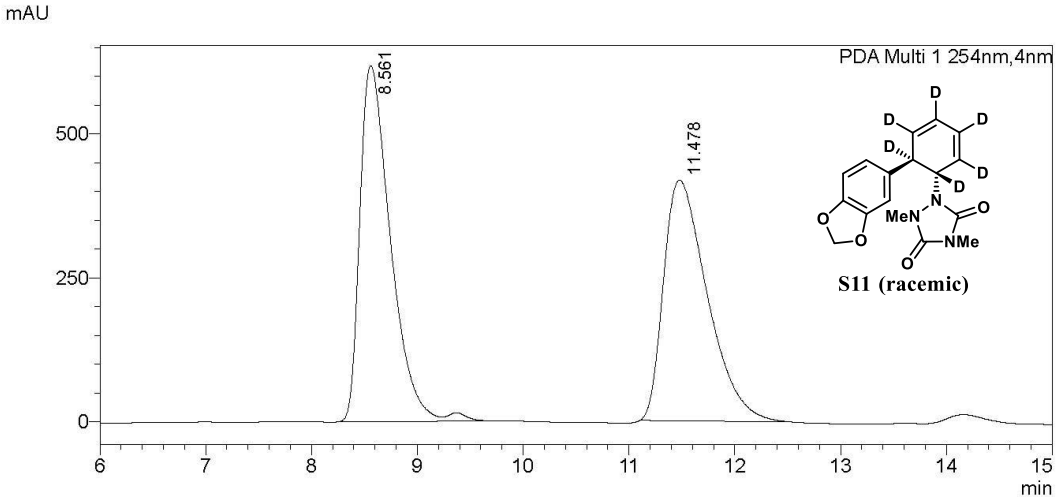



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 22.330 | 46650899 | 575662 | 96.862 | 97.066 | -- |
| 2 | 28.804 | 1511415 | 17398 | 3.138 | 2.934 | 3.009 |
| Total | | 48162314 | 593061 | 100.000 | 100.000 | |

**<Chromatogram>**

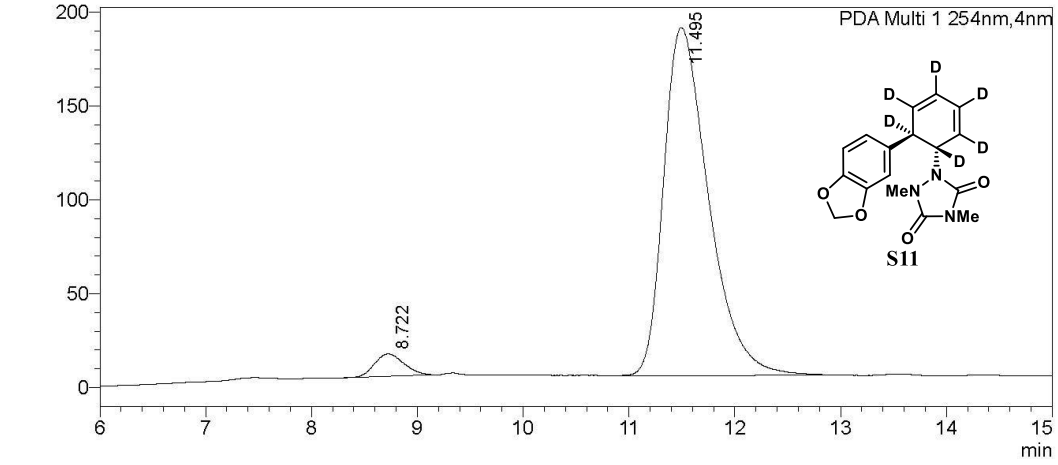



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 8.561 | 12501844 | 618355 | 50.971 | 59.659 | -- |
| 2 | 11.478 | 12025580 | 418124 | 49.029 | 40.341 | 4.527 |
| Total | | 24527424 | 1036479 | 100.000 | 100.000 | |

**<Chromatogram>**

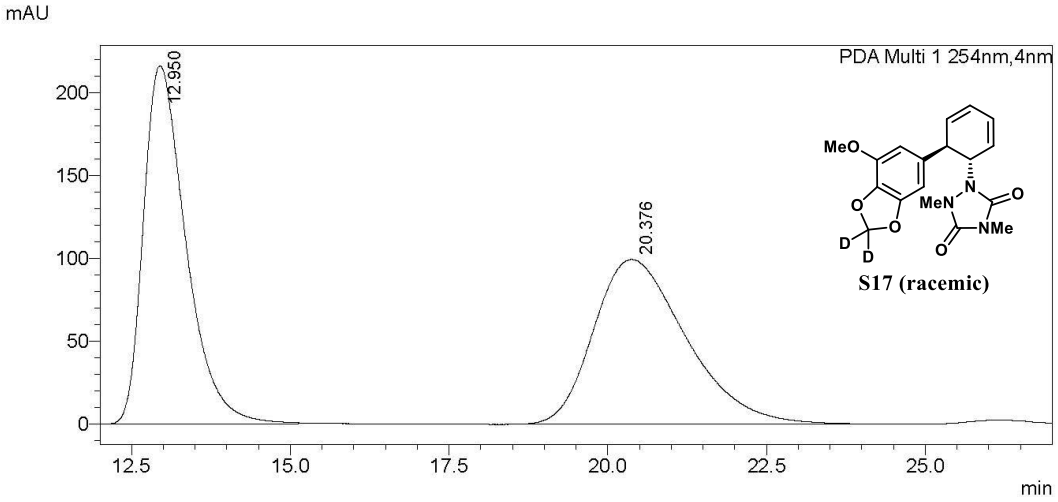



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 8.722 | 227358 | 11862 | 4.003 | 6.016 | -- |
| 2 | 11.495 | 5452786 | 185305 | 95.997 | 93.984 | 4.315 |
| Total | | 5680144 | 197167 | 100.000 | 100.000 | |

**<Chromatogram>**

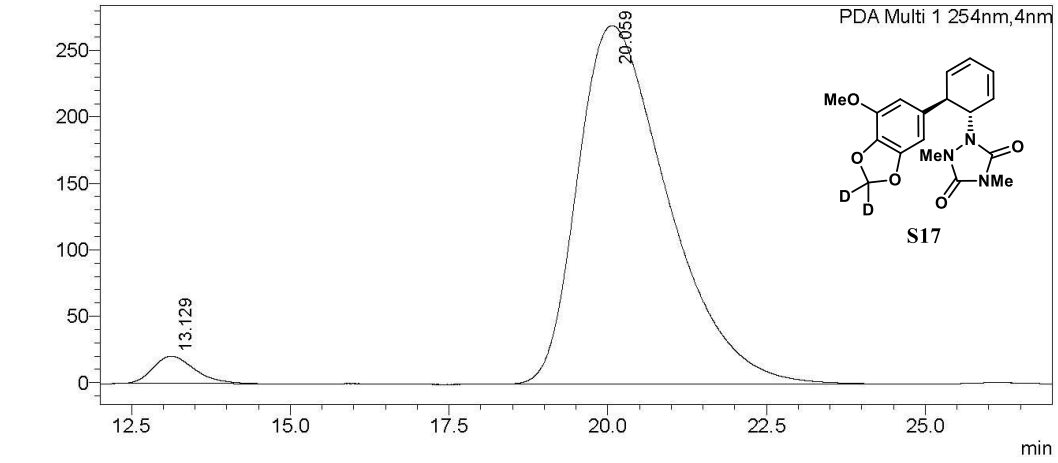



**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 12.950 | 10069319 | 216622 | 49.917 | 68.502 | -- |
| 2 | 20.376 | 10102868 | 99604 | 50.083 | 31.498 | 3.839 |
| Total | | 20172187 | 316227 | 100.000 | 100.000 | |

**<Chromatogram>**



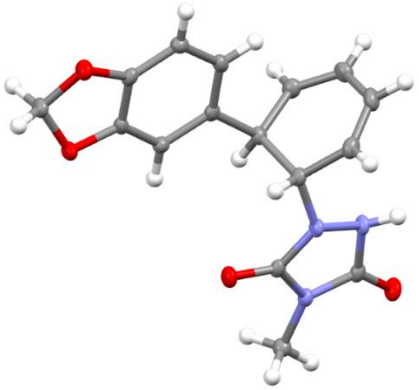

**<Peak Table>**

PDA Ch1 254nm

| Peak# | Ret. Time | Area | Height | Area% | Height% | Resolution(USP) |
|---|---|---|---|---|---|---|
| 1 | 13.129 | 923727 | 20497 | 3.343 | 7.059 | -- |
| 2 | 20.059 | 26704662 | 269887 | 96.657 | 92.941 | 3.678 |
| Total | | 27628389 | 290384 | 100.000 | 100.000 | |

## 14. Crystallographic Data

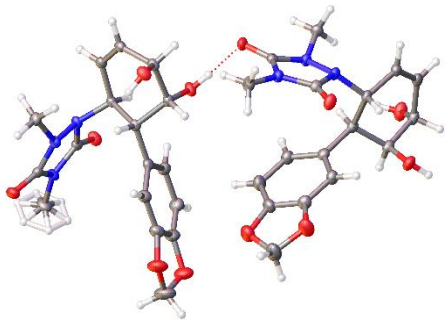
### Crystallographic data for diene 21



Single crystals of compound **21** were obtained by slow recrystallization from $CH_2Cl_2$/hexanes. A suitable crystal was selected and diffraction data were collected on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.15 K during data collection. Using Olex2[17], the structure was solved with the ShelXS structure solution program using Direct Methods and refined with the XL[18] refinement package using Least Squares minimization.

| | | |
|---|---|---|
| **Identification code** | CCDC 1545811 | |
| **Empirical formula** | $C_{16}H_{15}N_3O_4$ | |
| **Formula weight** | 313.31 | |
| **Temperature** | 100.15 K | |
| **Wavelength** | MoKα (λ = 0.71073 Å) | |
| **Crystal system** | triclinic | |
| **Space group** | P-1 | |
| **Unit cell dimensions** | **a** = 7.2463(5) Å | **α** = 72.6000(18)° |
| | **b** = 9.5480(7) Å | **β** = 72.9177(19)° |
| | **c** = 11.2269(8) Å | **γ** = 86.0255(18)° |
| **Volume** | 708.37(9) $Å^3$ | |
| **Z** | 2 | |
| **Density (calculated)** | 1.469 $Mg/m^3$ | |
| **Absorption coefficient** | 0.108 $mm^{-1}$ | |
| **F(000)** | 328.0 | |
| **Crystal size** | 0.267 × 0.252 × 0.138 $mm^3$ | |
| **Theta range for data collection** | 6.08 to 50.7°. | |
| **Index ranges** | $-8 \le h \le 8$, $-11 \le k \le 11$, $-13 \le l \le 13$ | |
| **Reflections collected** | 10076 | |
| **Independent reflections** | 2582 [$R_{int}$ = 0.0230, $R_{sigma}$ = 0.0184] | |
| **Completeness to theta = 25.242°** | 99.8 % | |
| **Refinement method** | Full-matrix least-squares on $F^2$ | |
| **Data / restraints / parameters** | 2582/0/215 | |
| **Goodness-of-fit on $F^2$** | 1.049 | |
| **Final R indices [I>2sigma(I)]** | R1 = 0.0304, wR2 = 0.0749 | |
| **R indices (all data)** | R1 = 0.0334, wR2 = 0.0771 | |
| **Extinction coefficient** | n/a | |
| **Largest diff. peak and hole** | 0.25 and -0.17 $e.Å^{-3}$ | |

**Crystallographic Data for diol 22**

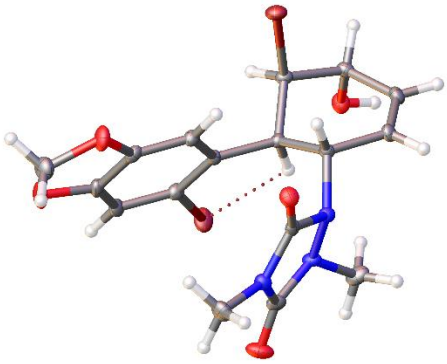


Twin crystals of compound **22** (racemate) were obtained by slow crystallization of the racemic mixtures from hexanes and ethyl acetate co-solvent. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 100.03 K during data collection.

| | |
|---|---|
| Identification code | CCDC 1876979 |
| Empirical formula | $C_{17}H_{19}N_3O_6$ |
| Formula weight | 361.35 |
| Temperature/K | 100.03 |
| Crystal system | trigonal |
| Space group | R3 |
| a/Å | 36.4159(9) |
| b/Å | 36.4159(9) |
| c/Å | 6.6637(2) |
| α/° | 90 |
| β/° | 90 |
| γ/° | 120 |
| Volume/Å$^3$ | 7652.9(4) |
| Z | 18 |
| $\rho_{calc}$g/cm$^3$ | 1.411 |
| μ/mm$^{-1}$ | 0.913 |
| F(000) | 3420.0 |
| Crystal size/mm$^3$ | 0.823 × 0.292 × 0.226 |
| Radiation | CuKα (λ = 1.54178) |
| 2Θ range for data collection/° | 4.854 to 136.658 |
| Index ranges | $-43 \leq h \leq 43$, $-42 \leq k \leq 43$, $-8 \leq l \leq 7$ |
| Reflections collected | 35277 |
| Independent reflections | 6229 [$R_{int}$ = 0.0292, $R_{sigma}$ = 0.0190] |
| Data/restraints/parameters | 6229/1/480 |
| Goodness-of-fit on F$^2$ | 1.077 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0261, $wR_2$ = 0.0669 |
| Final R indexes [all data] | $R_1$ = 0.0265, $wR_2$ = 0.0673 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.17/-0.20 |
| Flack parameter | 0.29(13) |

### 3. Crystallographic Data for bromohydrin 25

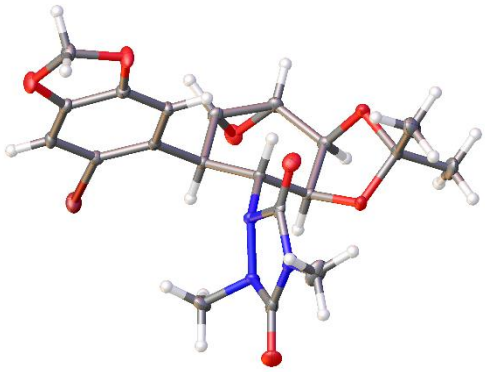
Single crystals of compound **25** were obtained by slow crystallization of the racemate from hexanes and ethyl acetate co-solvent. A suitable crystal was selected and diffraction data were collected on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.15 K during data collection.



| | |
|---|---|
| Identification code | CCDC 1876978 |
| Empirical formula | $C_{17}H_{17}Br_2N_3O_5$ |
| Formula weight | 503.15 |
| Temperature/K | 100.15 |
| Crystal system | monoclinic |
| Space group | $P2_1/c$ |
| a/Å | 8.6131(2) |
| b/Å | 13.0876(4) |
| c/Å | 16.5039(5) |
| α/° | 90 |
| β/° | 97.6830(10) |
| γ/° | 90 |
| Volume/Å$^3$ | 1843.70(9) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.813 |
| μ/mm$^{-1}$ | 4.432 |
| F(000) | 1000.0 |
| Crystal size/mm$^3$ | 0.418 × 0.224 × 0.136 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 5.698 to 56.682 |
| Index ranges | $-9 \le h \le 11$, $-17 \le k \le 17$, $-22 \le l \le 22$ |
| Reflections collected | 24215 |
| Independent reflections | 4592 [$R_{int}$ = 0.0246, $R_{sigma}$ = 0.0173] |
| Data/restraints/parameters | 4592/0/248 |
| Goodness-of-fit on $F^2$ | 1.028 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0203, $wR_2$ = 0.0491 |
| Final R indexes [all data] | $R_1$ = 0.0240, $wR_2$ = 0.0503 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.47/-0.37 |

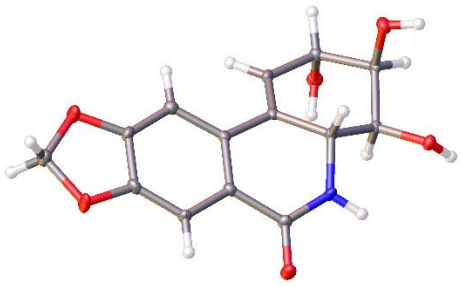
**Crystallographic data for epoxyacetonide 13**

Single crystals of epoxyacetonide **13** were obtained by slow crystallization of the racemic mixture **13** from dichloromethane and hexane co-solvent. A suitable crystal was selected and diffraction data were collected on a Bruker D8 Venture/Photon 100 diffractometer. The crystal was kept at 99.99 K during data collection.



| | |
|---|---|
| Identification code | CCDC 1846403 |
| Empirical formula | $C_{20}H_{22}BrN_3O_7$ |
| Formula weight | 496.31 |
| Temperature/K | 99.99 |
| Crystal system | monoclinic |
| Space group | $P2_1/n$ |
| a/Å | 10.4462(5) |
| b/Å | 16.5828(8) |
| c/Å | 12.4288(6) |
| α/° | 90 |
| β/° | 105.487(2) |
| γ/° | 90 |
| Volume/Å$^3$ | 2074.83(17) |
| Z | 4 |
| $\rho_{calc}$g/cm$^3$ | 1.589 |
| μ/mm$^{-1}$ | 2.030 |
| F(000) | 1016.0 |
| Crystal size/mm$^3$ | 0.614 × 0.569 × 0.521 |
| Radiation | MoKα (λ = 0.71073) |
| 2Θ range for data collection/° | 4.194 to 56.716 |
| Index ranges | $-13 \leq h \leq 13$, $-22 \leq k \leq 22$, $-16 \leq l \leq 16$ |
| Reflections collected | 70140 |
| Independent reflections | 5161 [$R_{int}$ = 0.0936, $R_{sigma}$ = 0.0292] |
| Data/restraints/parameters | 5161/0/285 |
| Goodness-of-fit on $F^2$ | 1.024 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0287, $wR_2$ = 0.0733 |
| Final R indexes [all data] | $R_1$ = 0.0315, $wR_2$ = 0.0749 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.46/-0.68 |

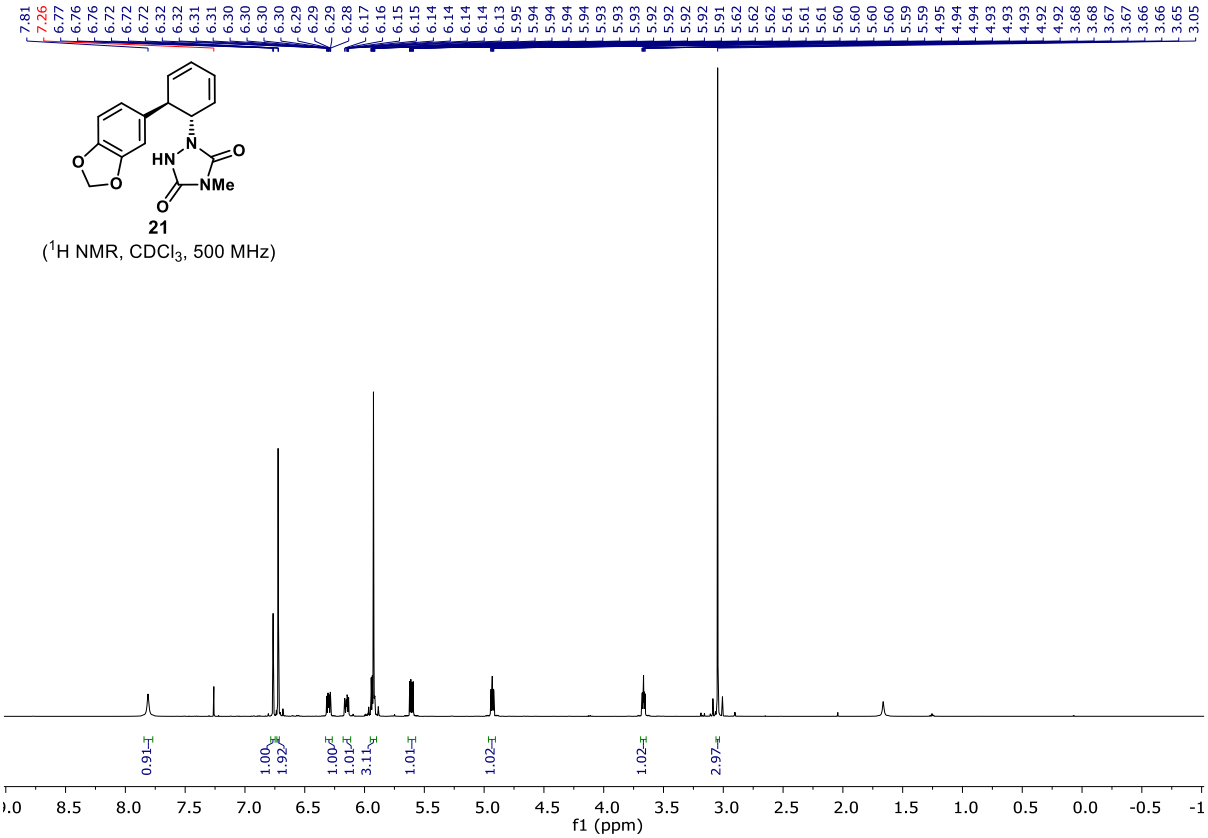
**Crystallographic data for (+)-lycoricidine (3)**

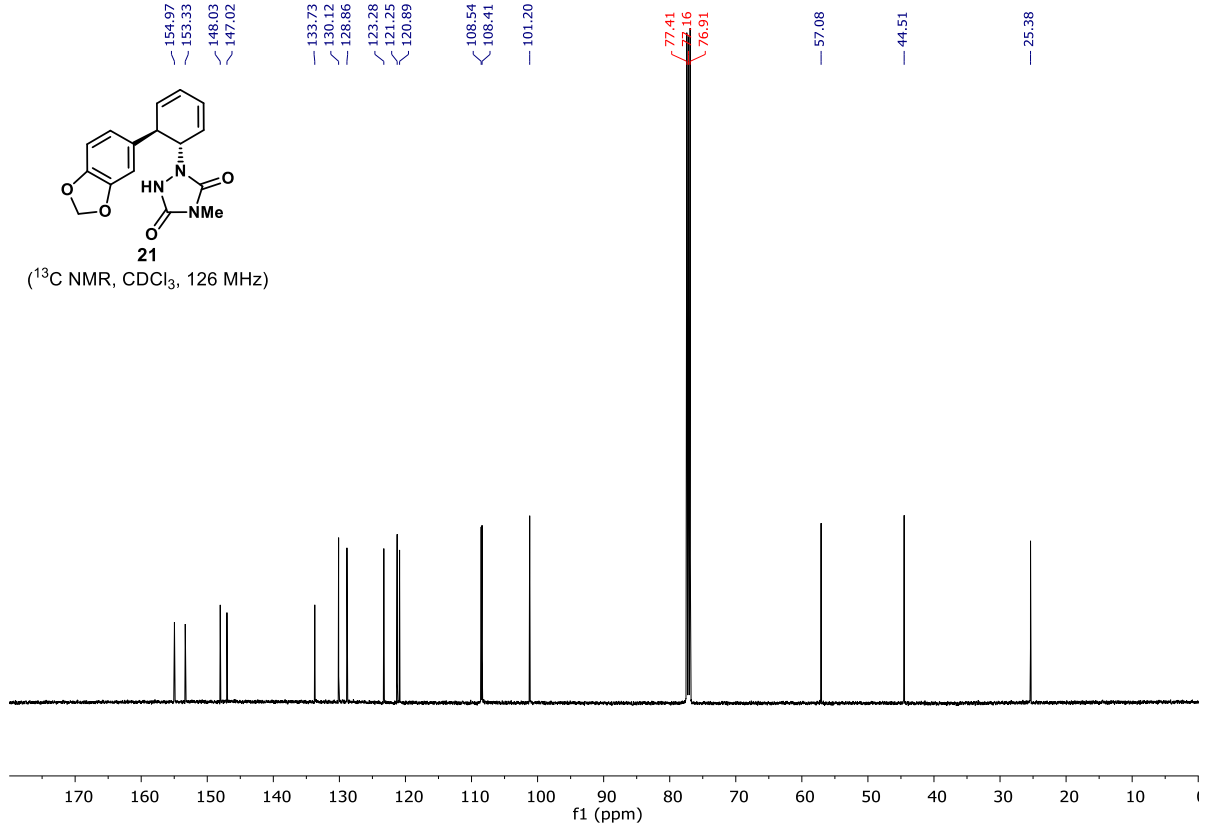


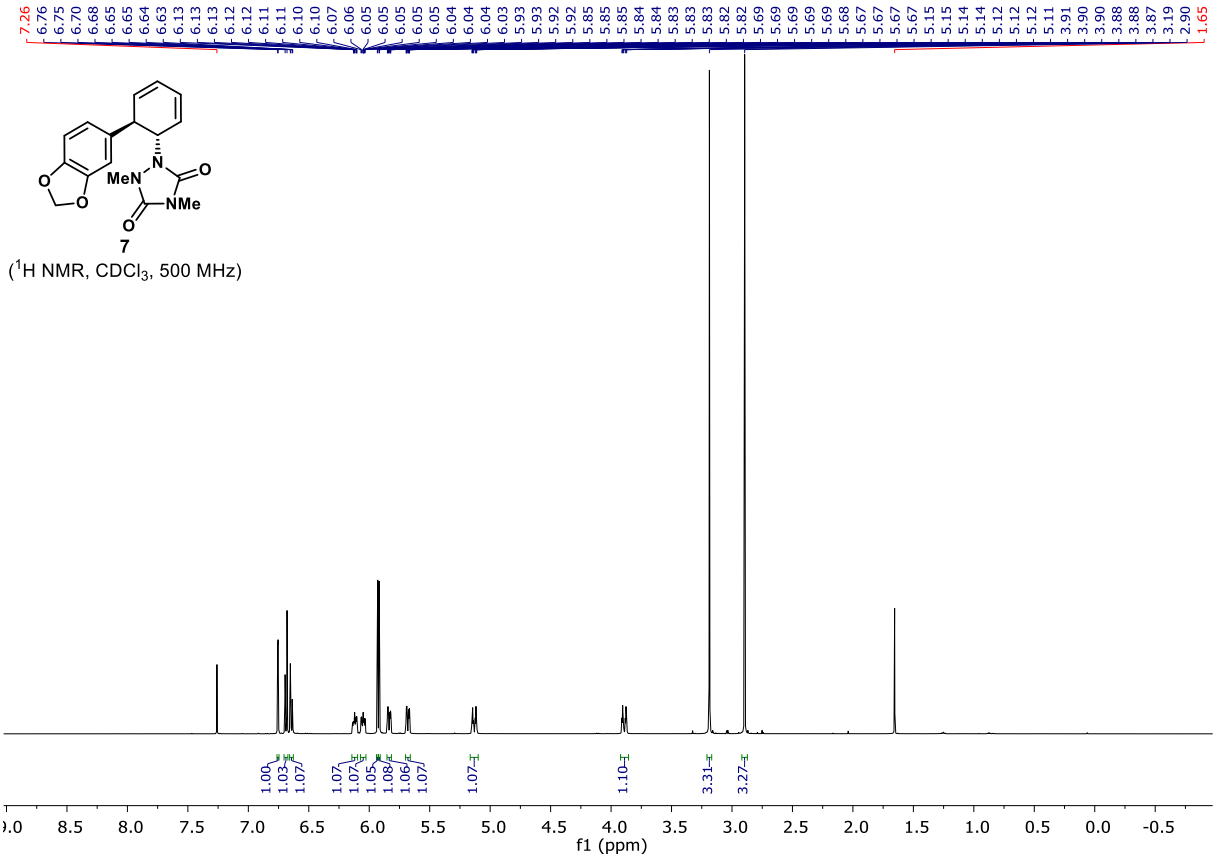
Single crystals of (+)-lycoricidine (**3**) were obtained by slow crystallization of the enantiopure (**3**) (>99% ee) from methanol and water co-solvent. A suitable crystal was selected and diffraction data were collected on a Bruker APEX-II CCD diffractometer. The crystal was kept at 100.01 K during data collection. The absolute stereochemistry at C2 (S), C3 (R), C4 (S), C5 (R), C16 (S), C17 (R), C18 (S), and C19 (R) were determined by calculating Hooft parameter.

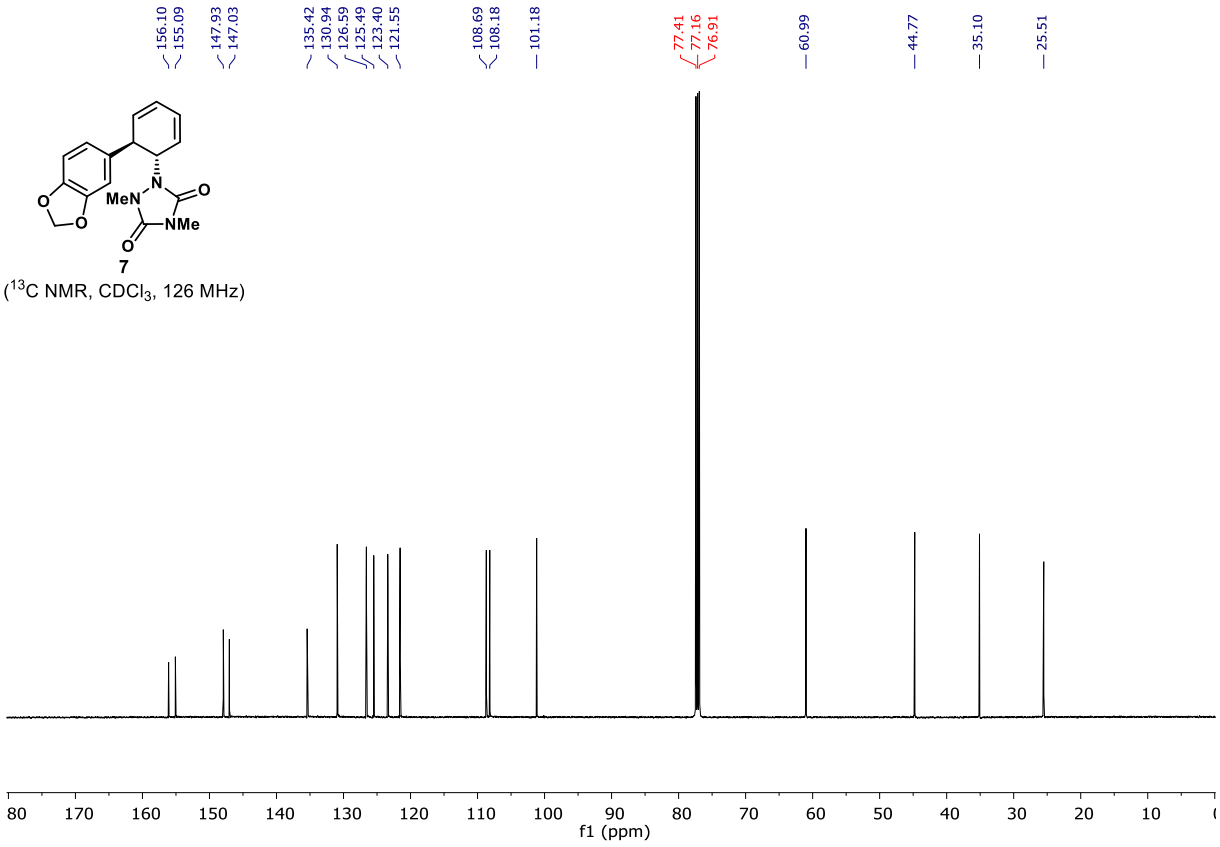
| | |
|---|---|
| Identification code | CCDC 1846404 |
| Empirical formula | $C_{14}H_{15}NO_7$ |
| Formula weight | 309.27 |
| Temperature/K | 100.01 |
| Crystal system | triclinic |
| Space group | P1 |
| a/Å | 7.2381(3) |
| b/Å | 9.3207(4) |
| c/Å | 11.0024(4) |
| α/° | 67.5140(10) |
| β/° | 89.8880(10) |
| γ/° | 75.5250(10) |
| Volume/Å$^3$ | 660.42(5) |
| Z | 2 |
| $\rho_{calc}$g/cm$^3$ | 1.555 |
| μ/mm$^{-1}$ | 1.081 |
| F(000) | 324.0 |
| Crystal size/mm$^3$ | 0.333 × 0.317 × 0.15 |
| Radiation | CuKα (λ = 1.54178) |
| 2Θ range for data collection/° | 8.746 to 136.46 |
| Index ranges | $-8 \le h \le 8$, $-11 \le k \le 11$, $-13 \le l \le 13$ |
| Reflections collected | 18788 |
| Independent reflections | 4675 [$R_{int}$ = 0.0293, $R_{sigma}$ = 0.0261] |
| Data/restraints/parameters | 4675/3/452 |
| Goodness-of-fit on $F^2$ | 1.074 |
| Final R indexes [I>=2σ (I)] | $R_1$ = 0.0303, $wR_2$ = 0.0776 |
| Final R indexes [all data] | $R_1$ = 0.0305, $wR_2$ = 0.0779 |
| Largest diff. peak/hole / e Å$^{-3}$ | 0.26/-0.28 |
| Flack parameter | -0.07(8) |
| Hooft parameter | 0.00(3) |

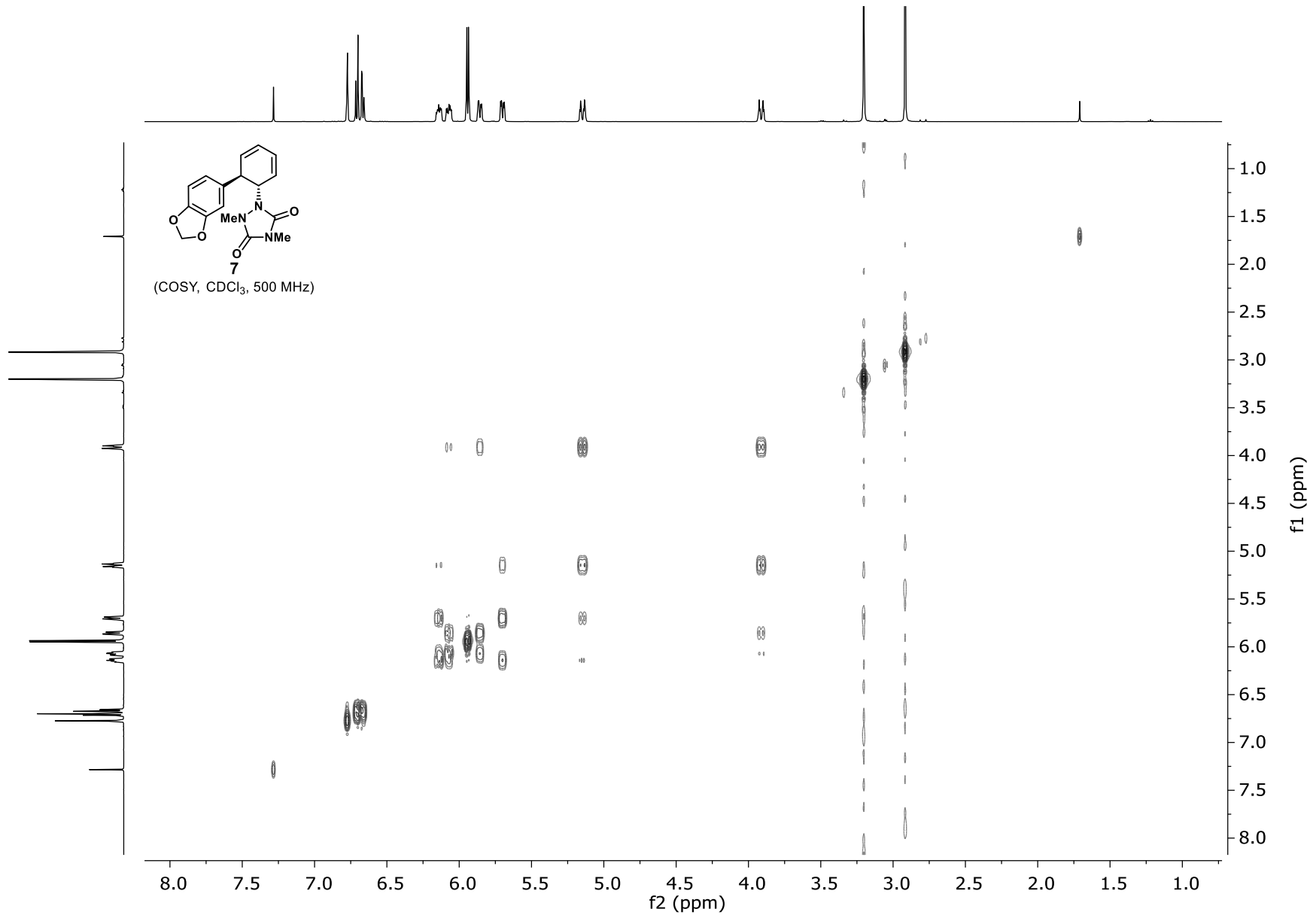
## 15. $^{1}H$ and $^{13}C$ NMR spectra

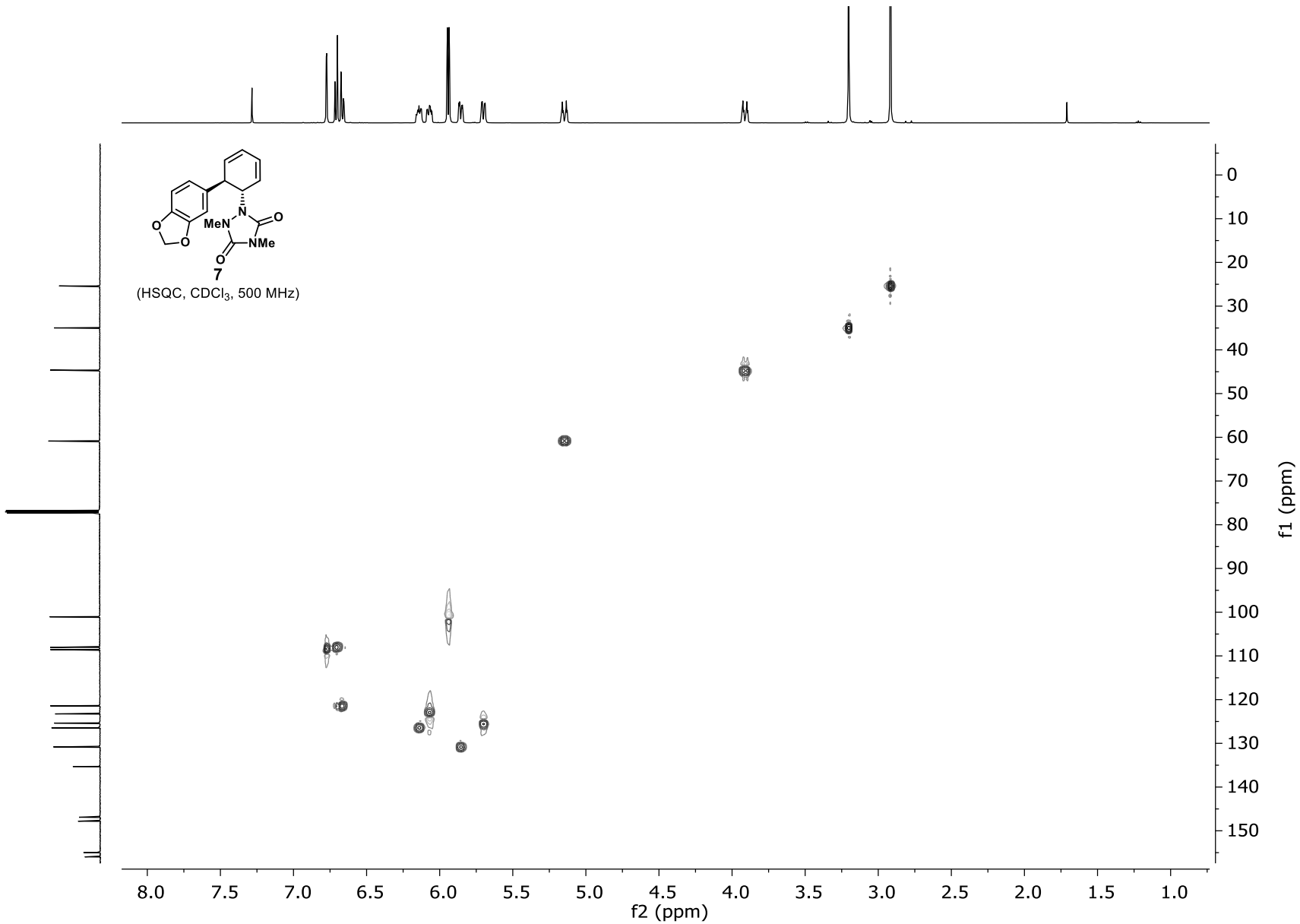


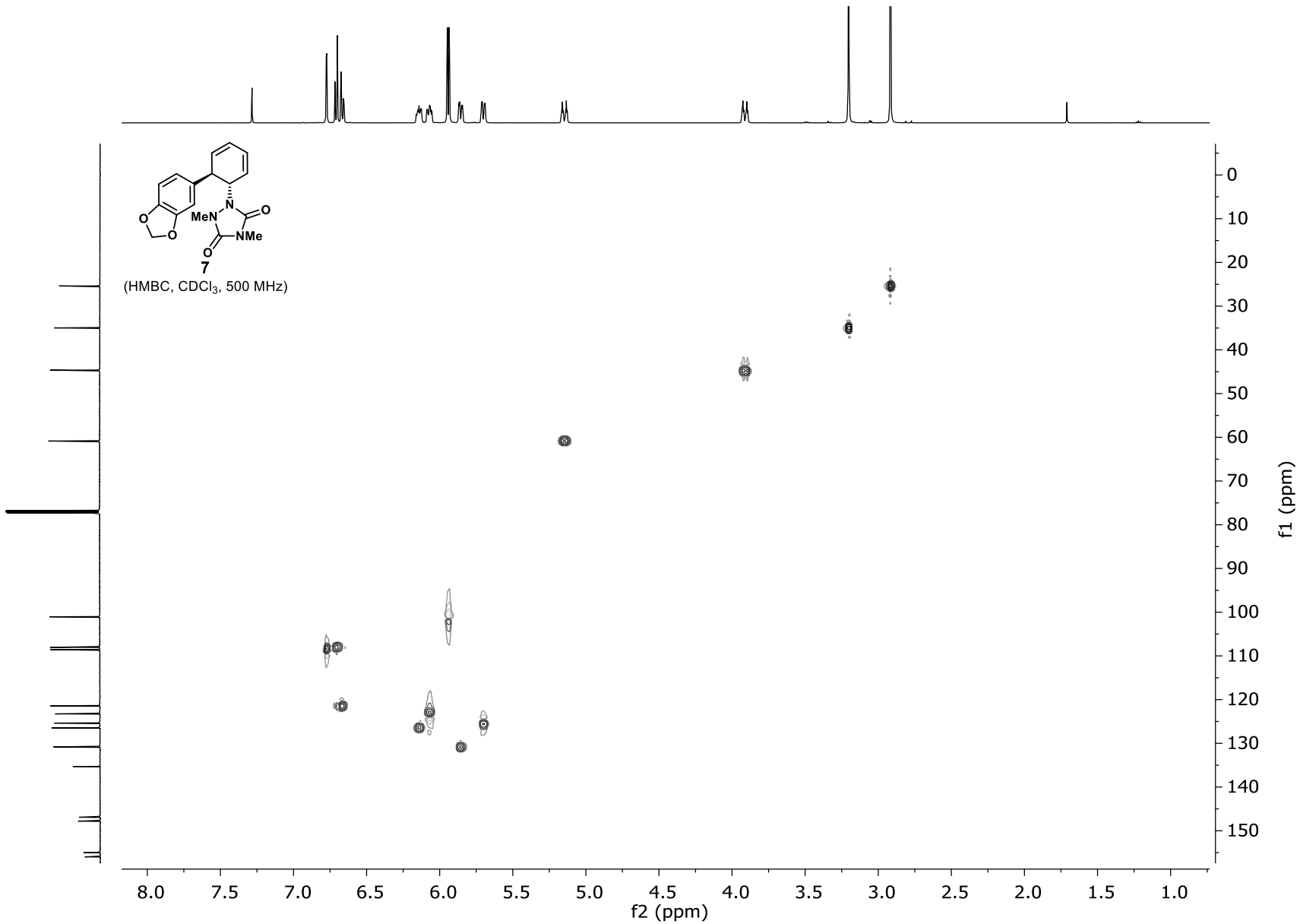



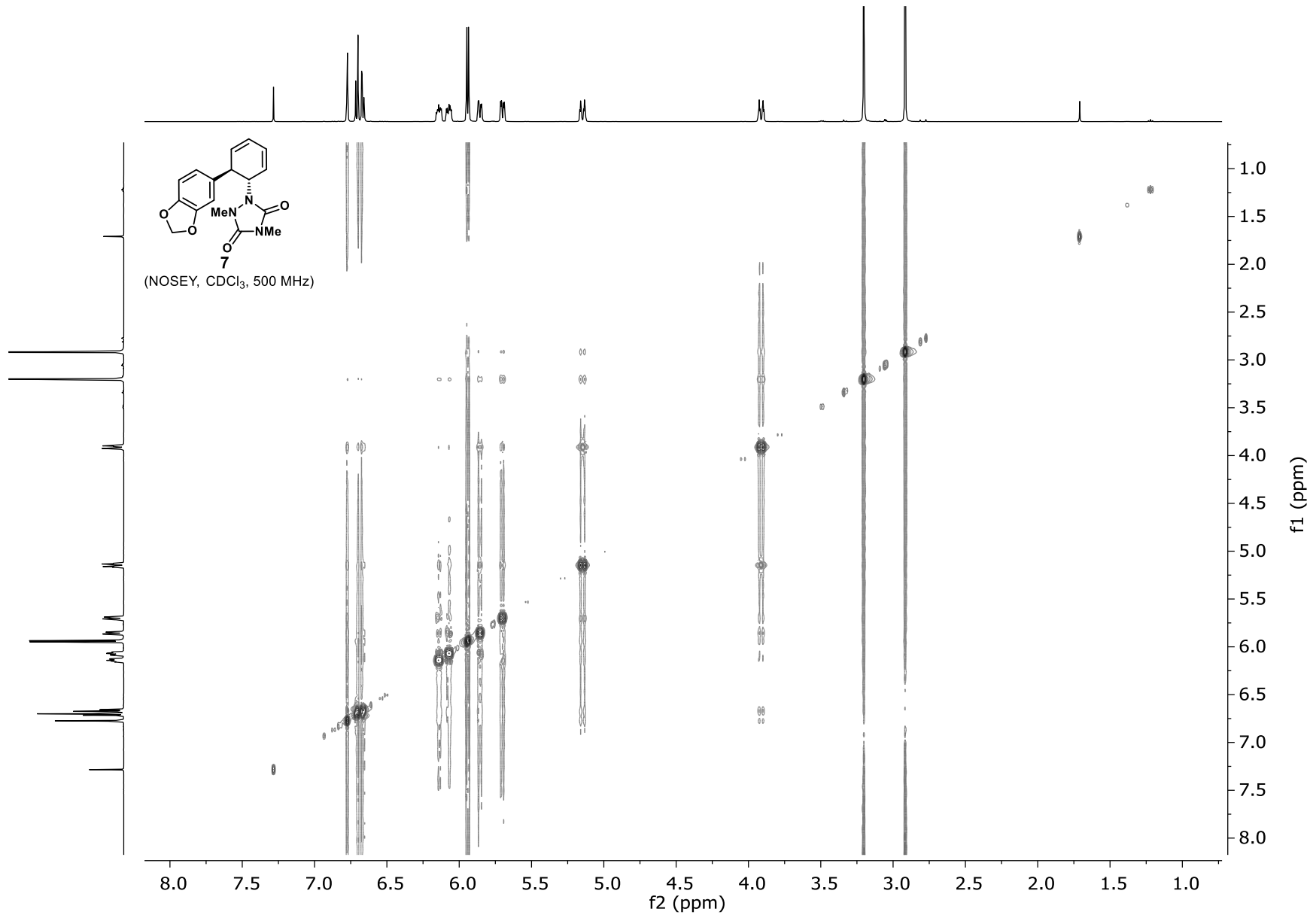

MeN
NMe
O
O
O
O
7
(1H NMR, CDCl3, 500 MHz)
f1 (ppm)

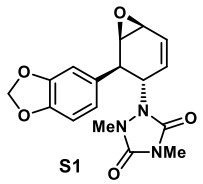

MeN
NMe
O
O
O
O
7
(13C NMR, CDCl3, 126 MHz)
f1 (ppm)


7
(COSY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)


MeN
NMe
O
O
O
O
7
(HSQC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150


MeN
N
O
O
O
NMe
O
7
(HMBC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

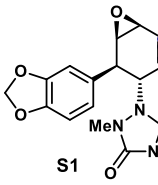

MeN
N
O
NMe
O
O
O
7
(NOSEY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)




S1

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

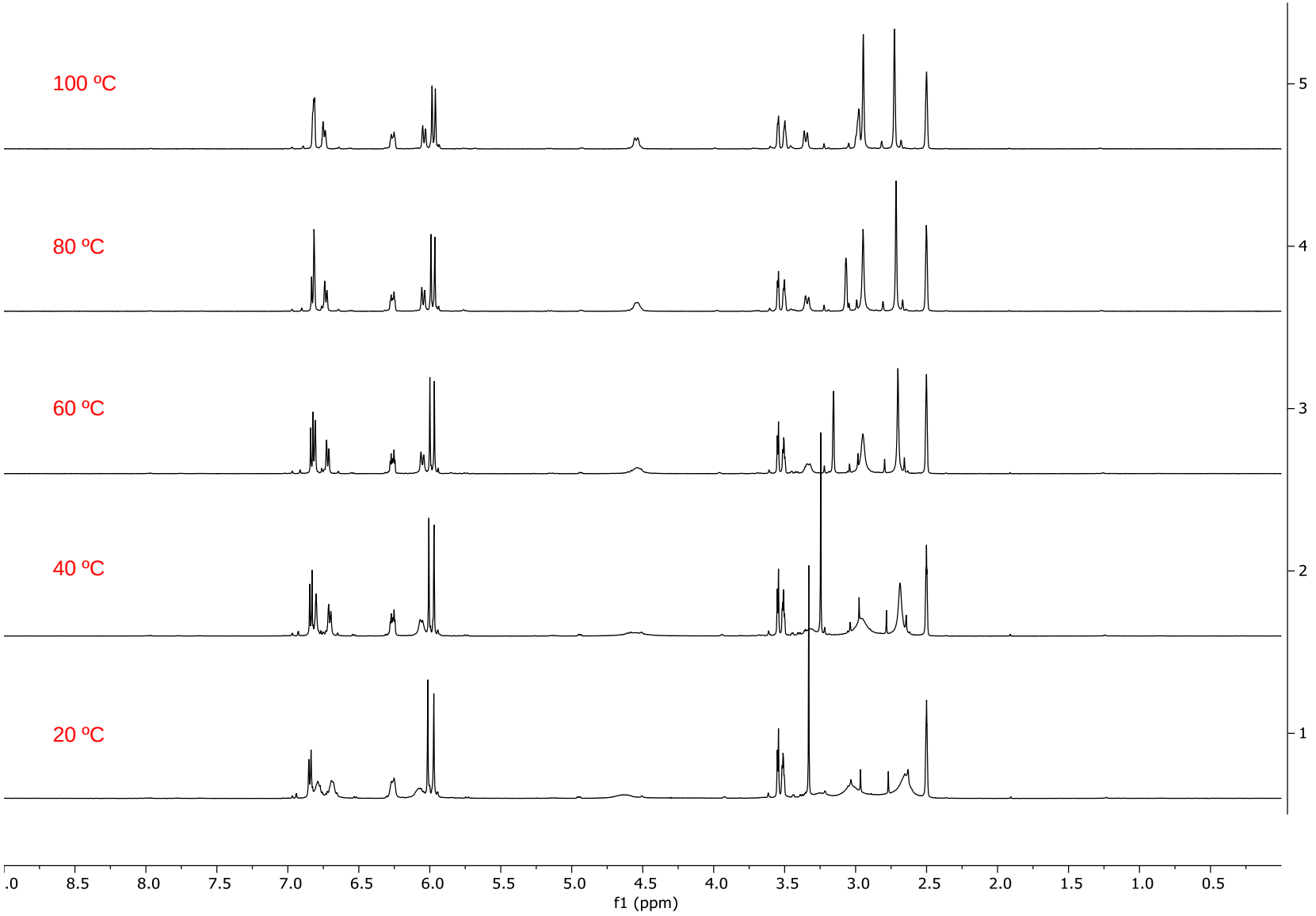


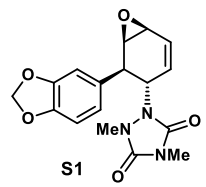




S1

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **S1** in DMSO, 500 MHz:

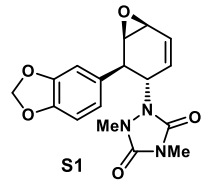





S1

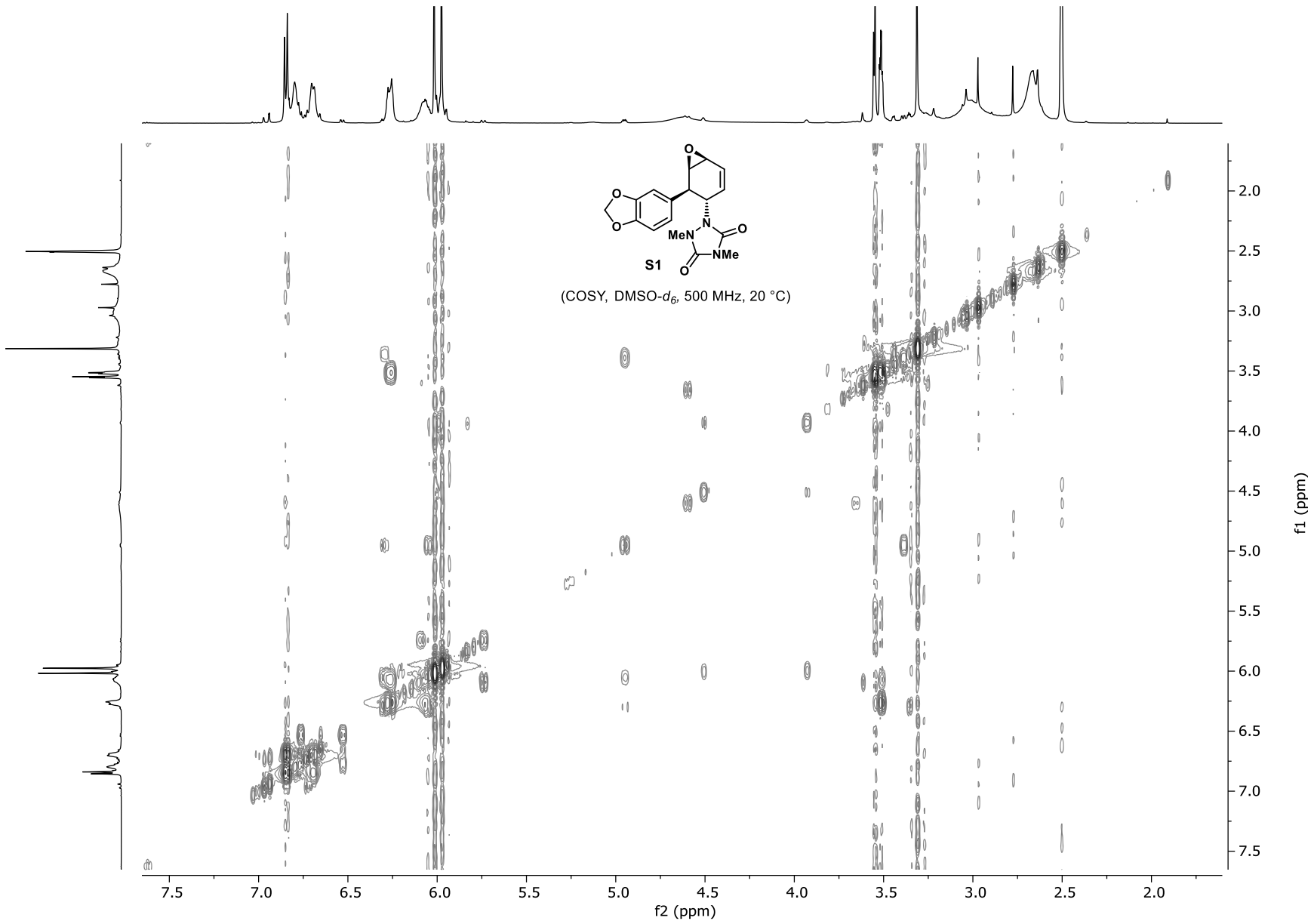
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)

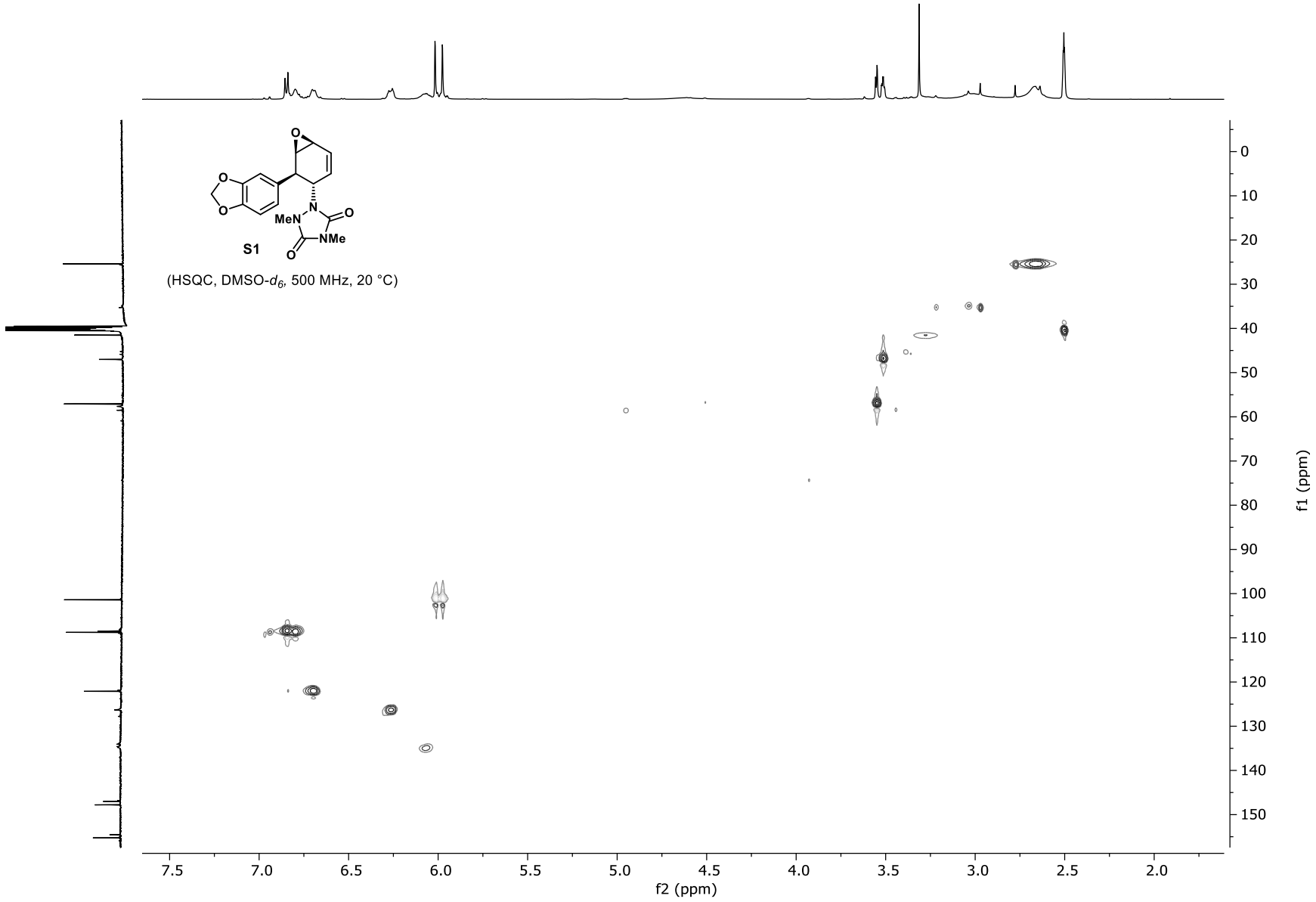


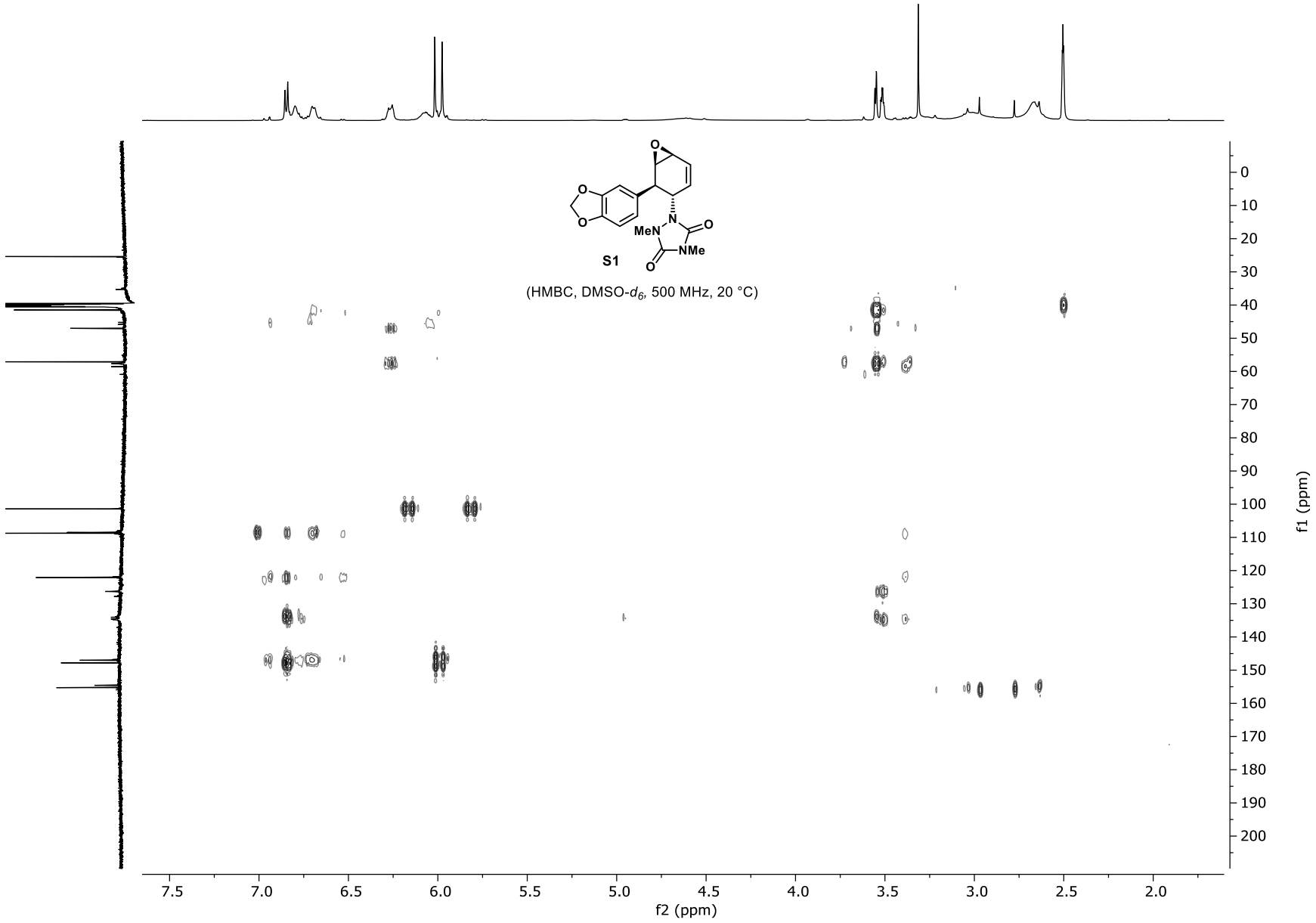



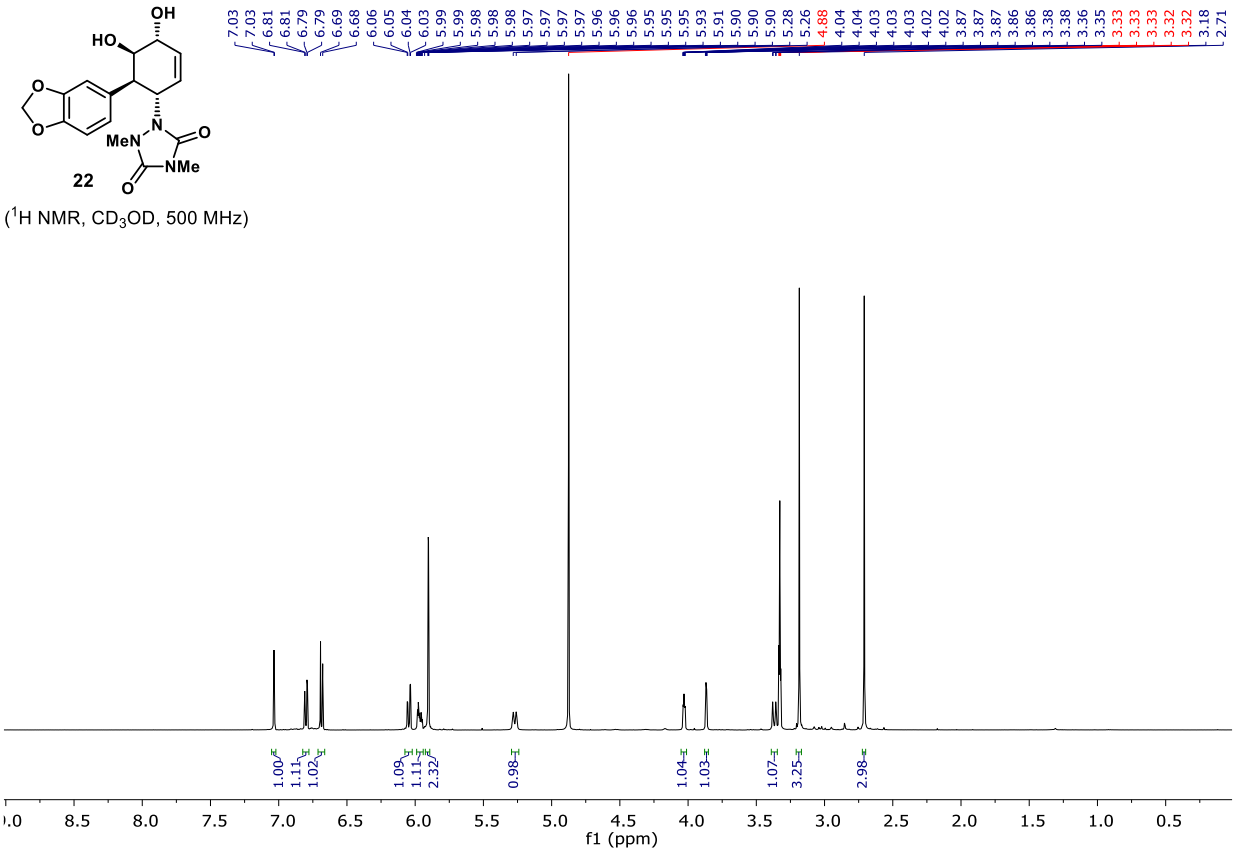

S1

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)

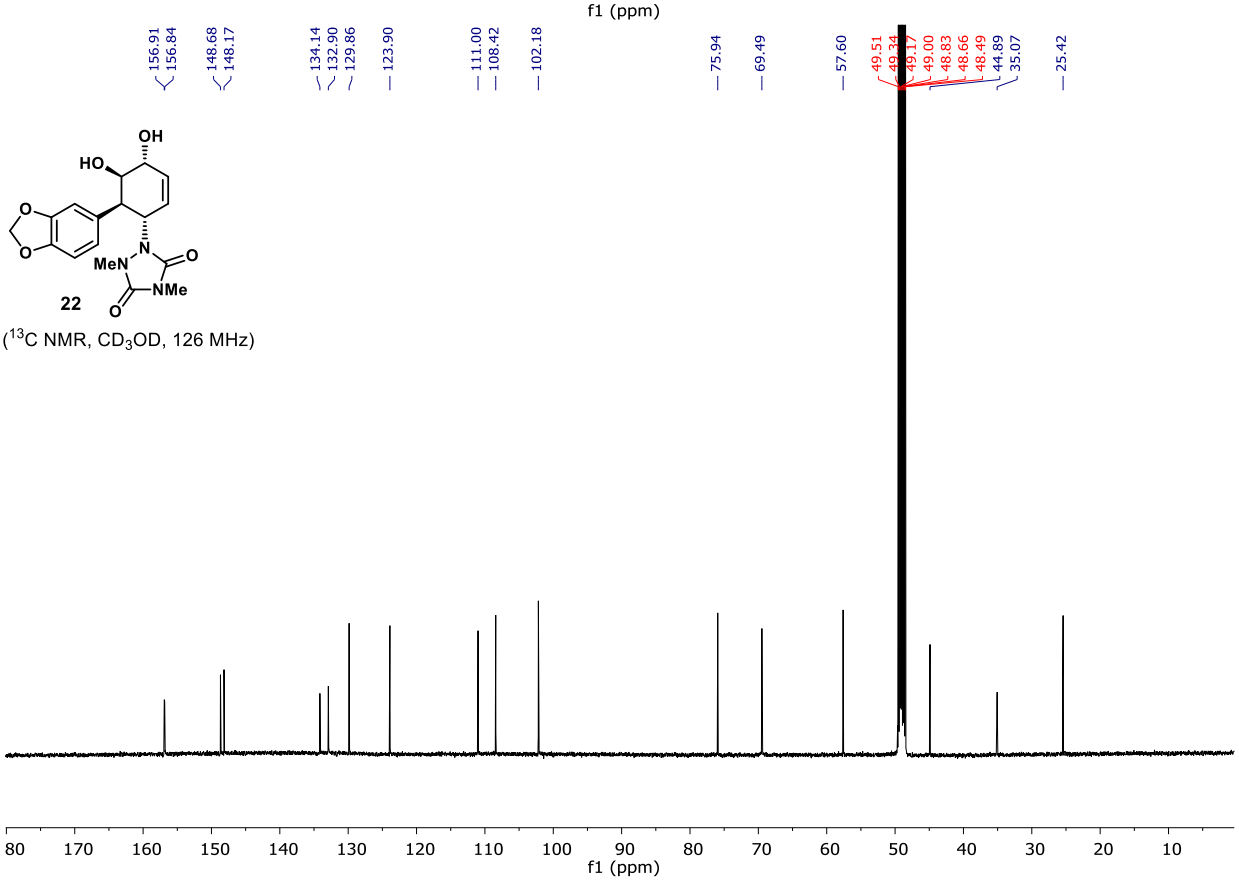

S1
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)


S1
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)

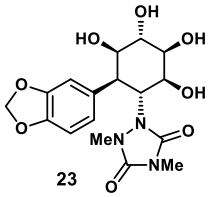

S1
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)




($^{1}$H NMR, $CD_3OD$, 500 MHz)



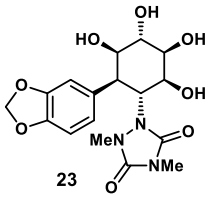

($^{13}$C NMR, $CD_3OD$, 126 MHz)




**23**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

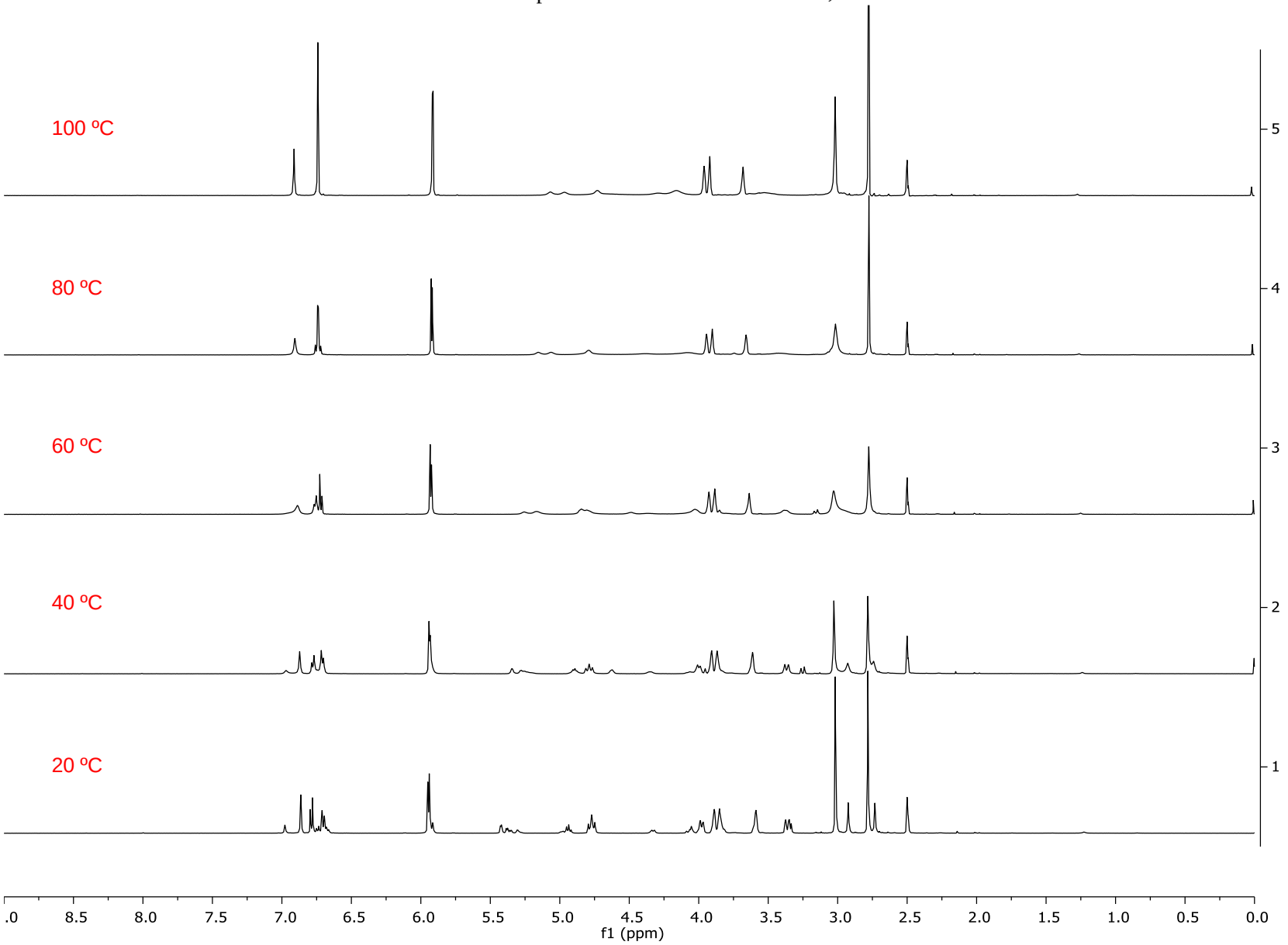


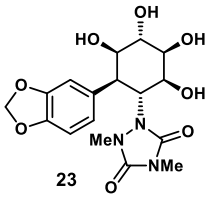




**23**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 80 °C)

$^{1}$H NMR temperature studies of **23** in DMSO, 500 MHz:

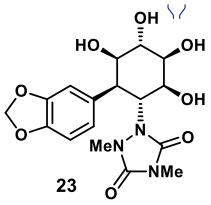





**23**

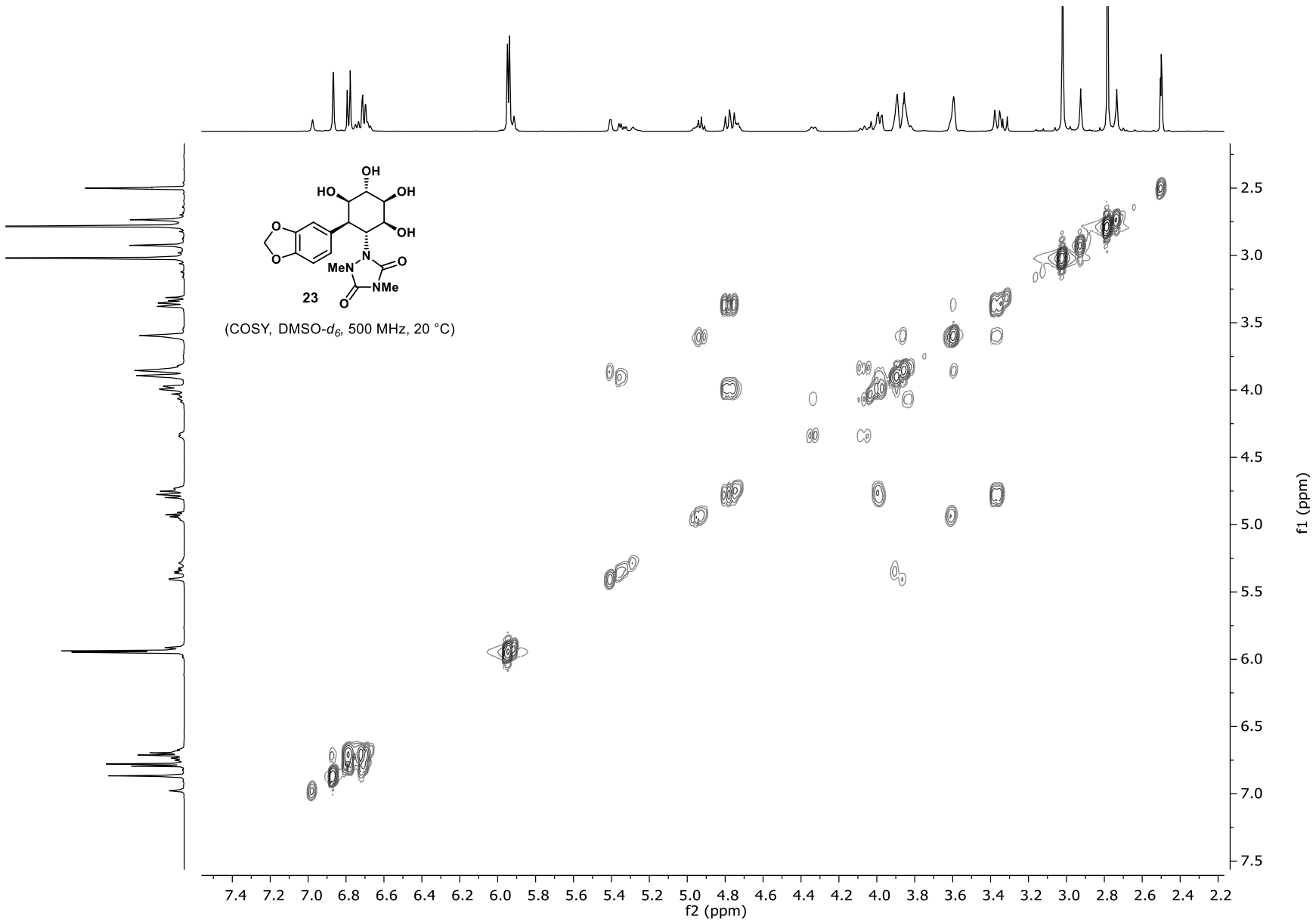
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)

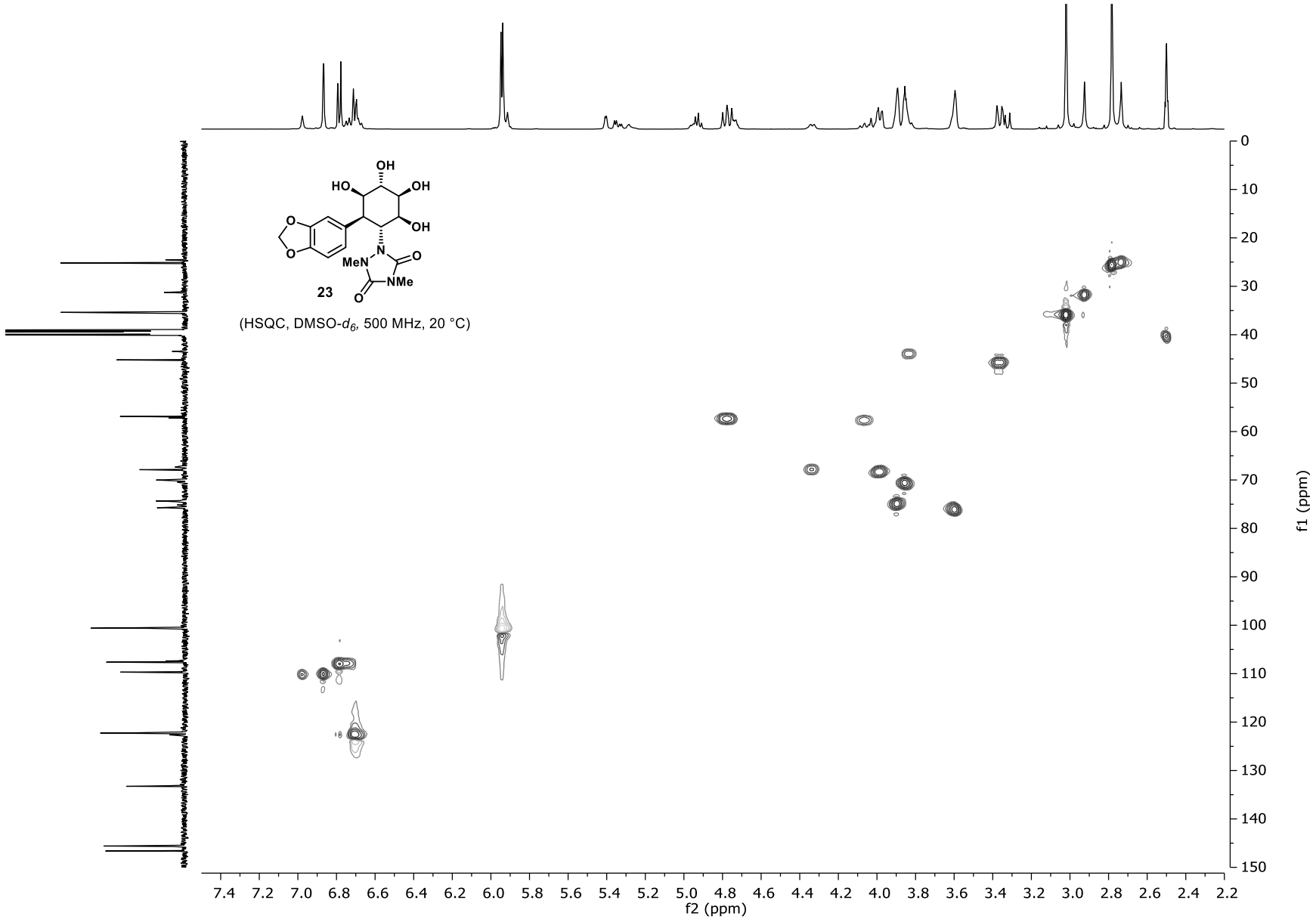


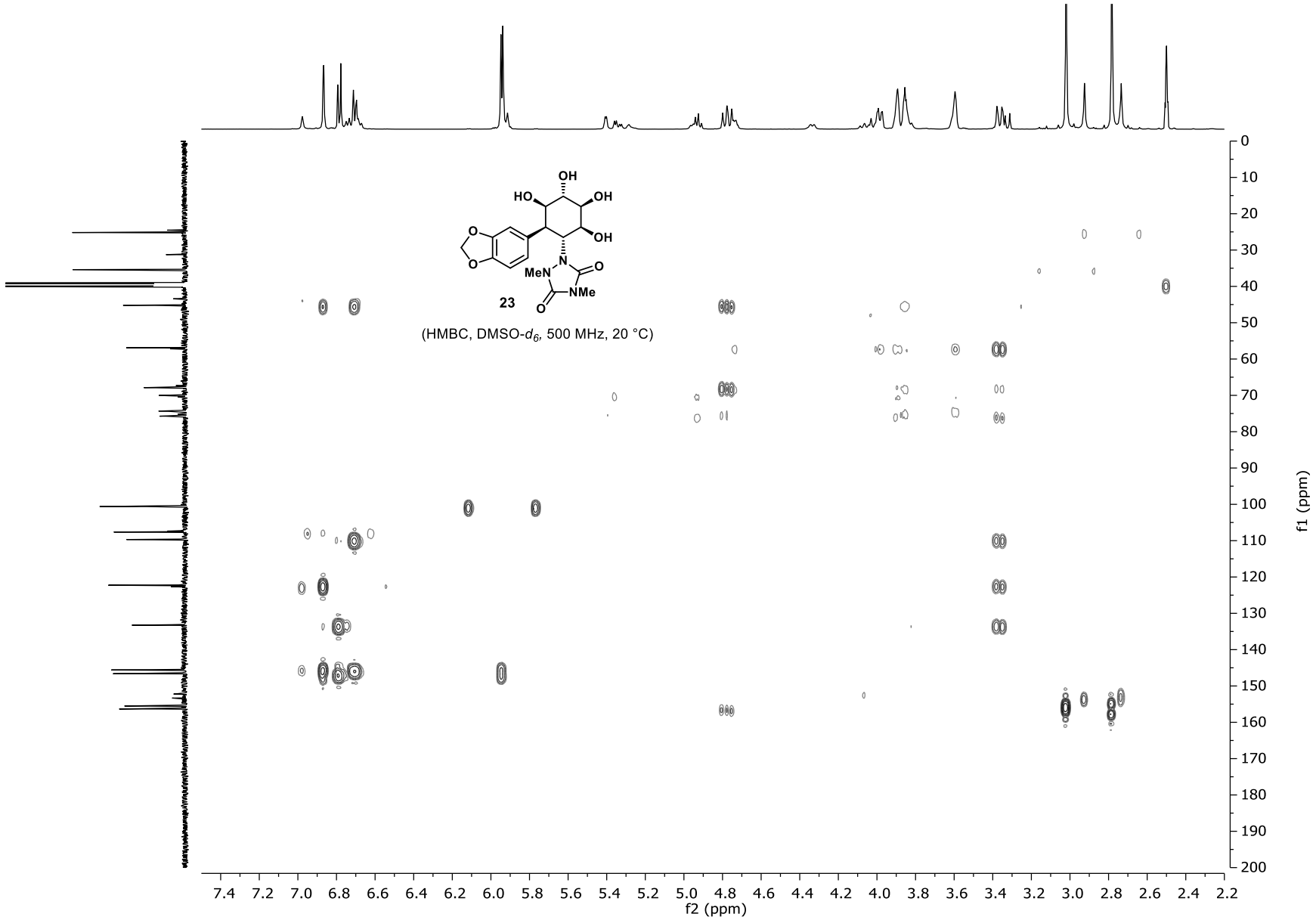



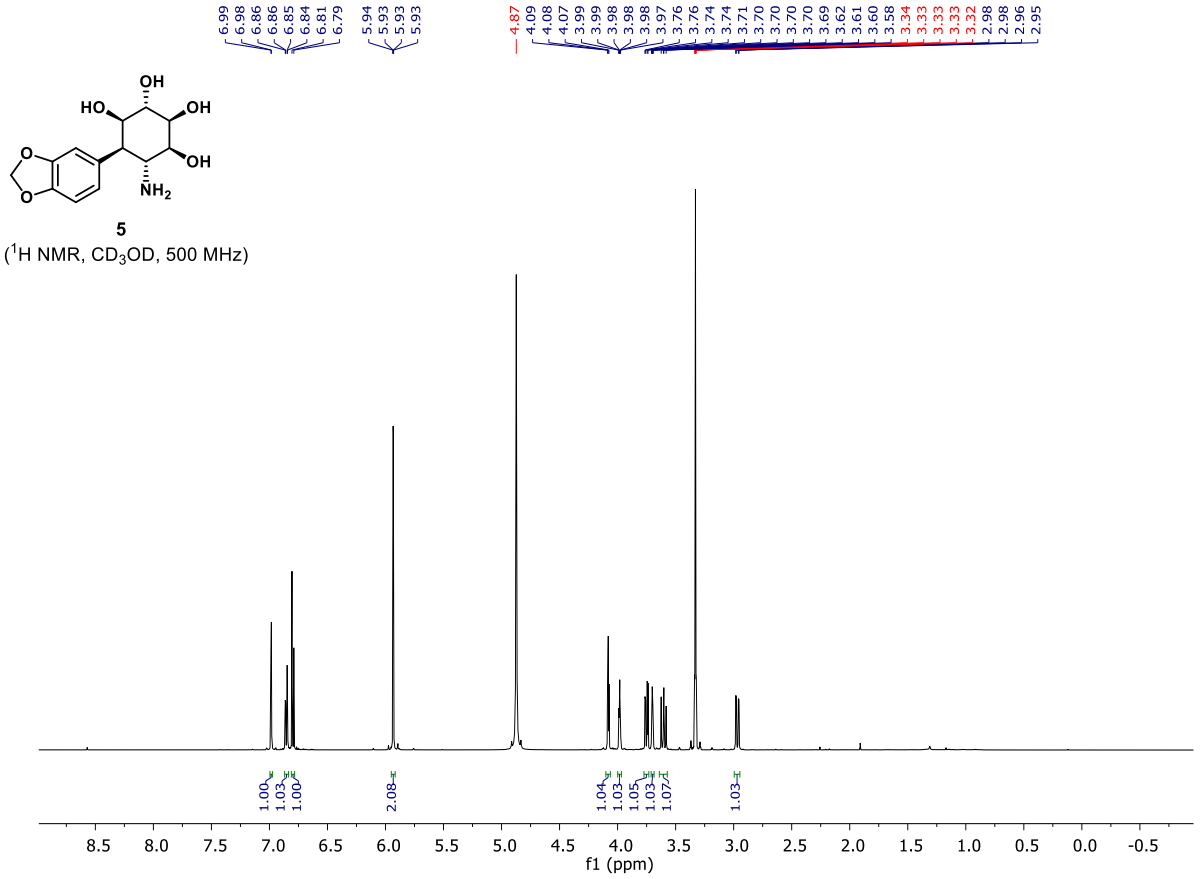

**23**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 80 °C)


OH
HO
OH
OH
O
O
N
MeN
O
NMe
O
23
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)

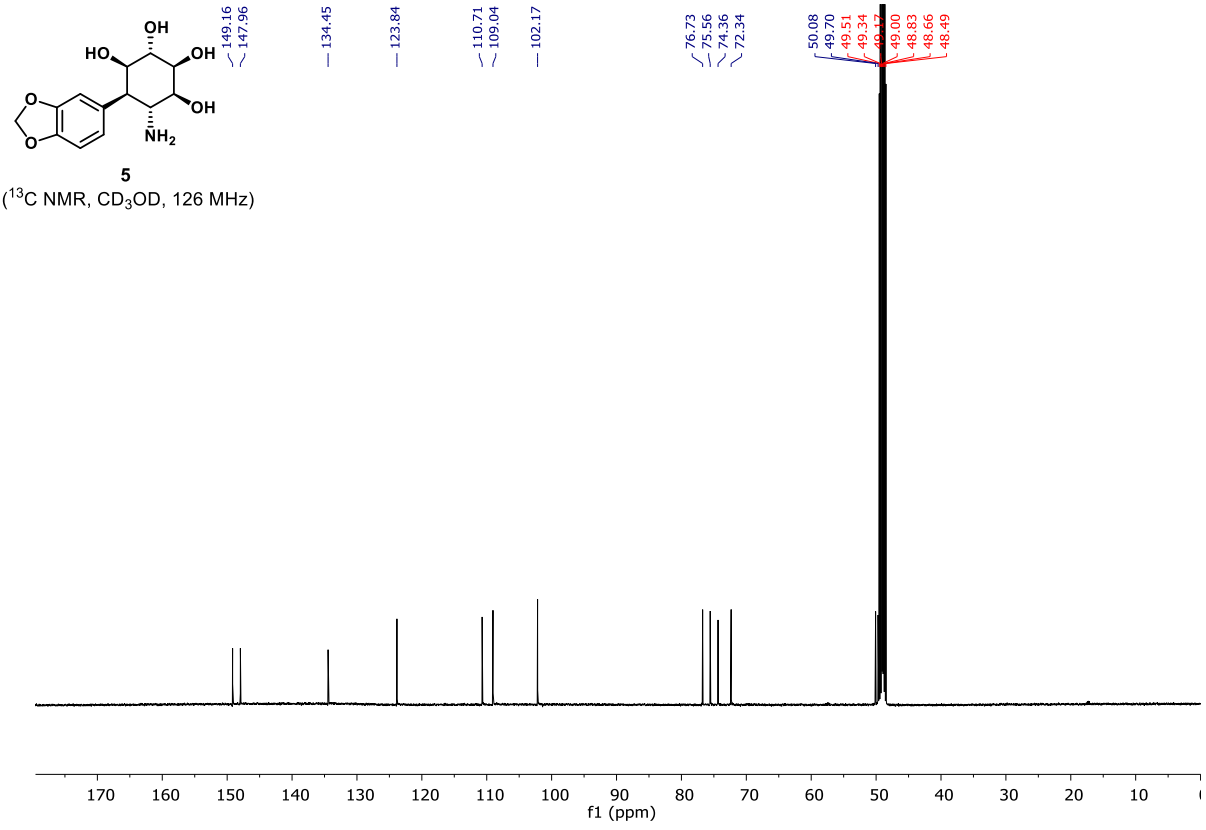

OH
HO
OH
OH
O
O
N
MeN
O
NMe
O
23
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)


OH
HO
OH
OH
O
O
MeN
N
O
NMe
O
23
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)



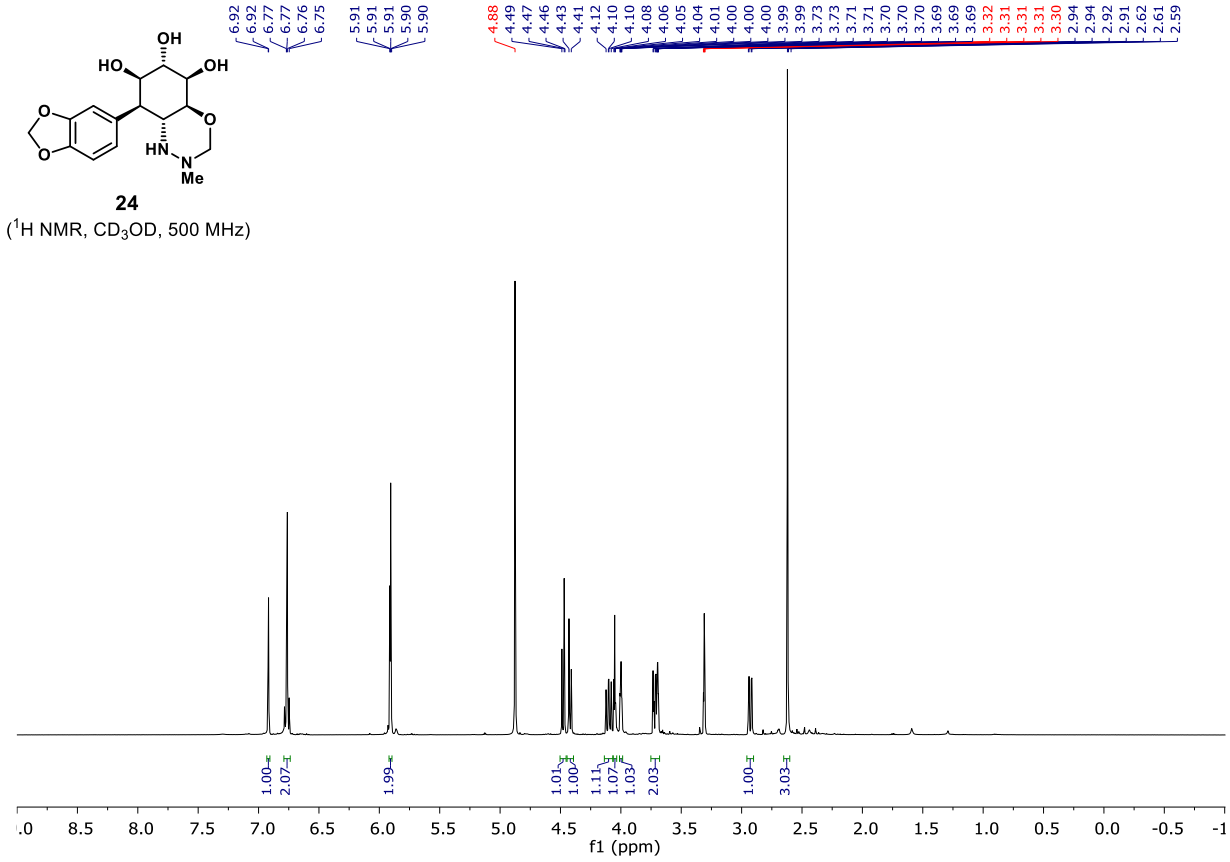

**5**

($^1$H NMR, $CD_3OD$, 500 MHz)



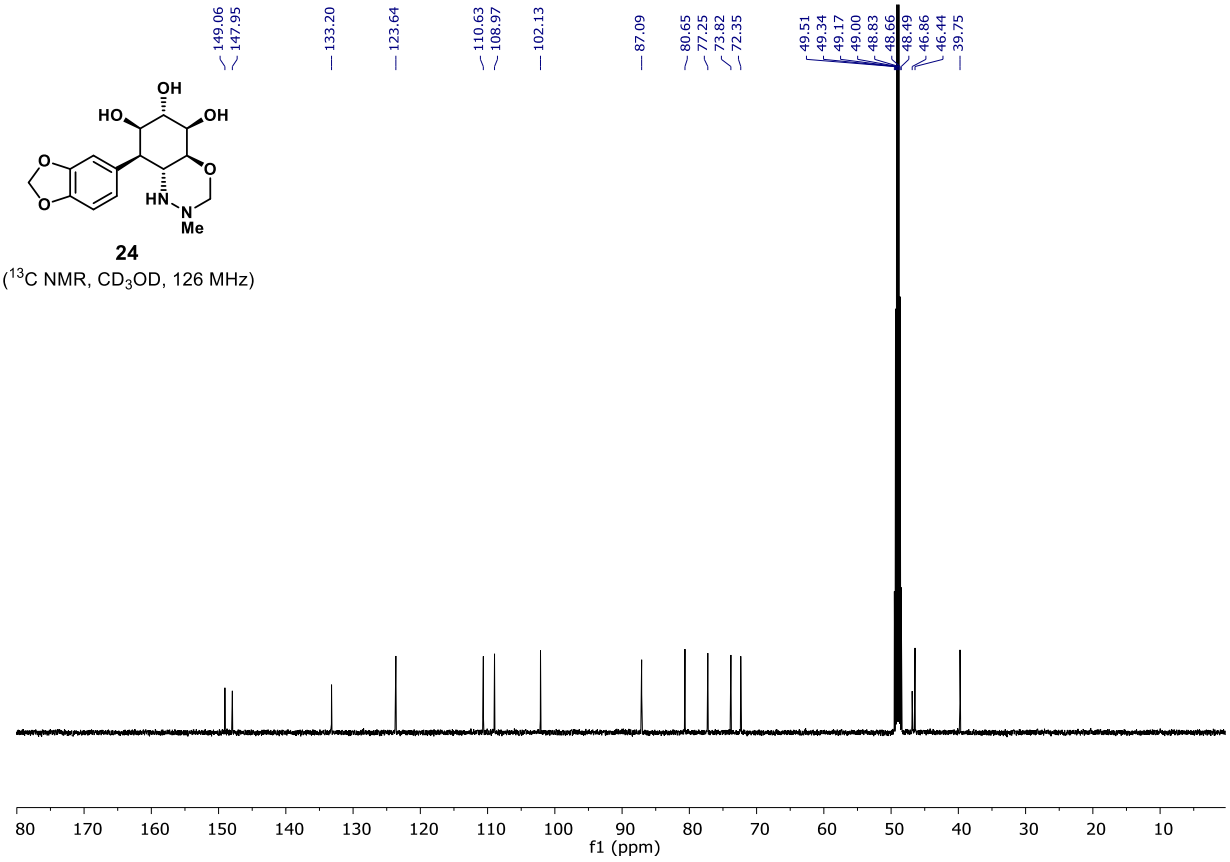

**5**

($^{13}$C NMR, $CD_3OD$, 126 MHz)



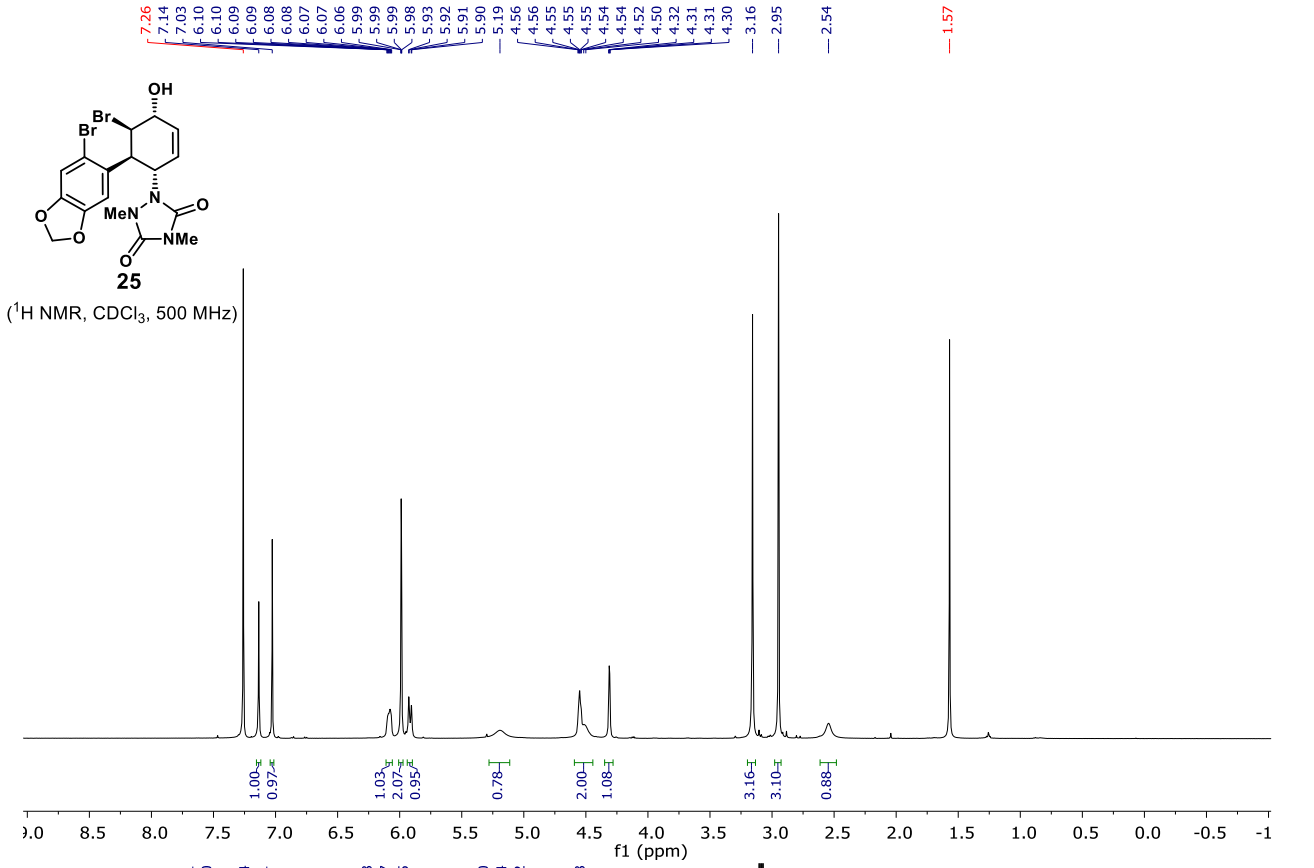

**24**

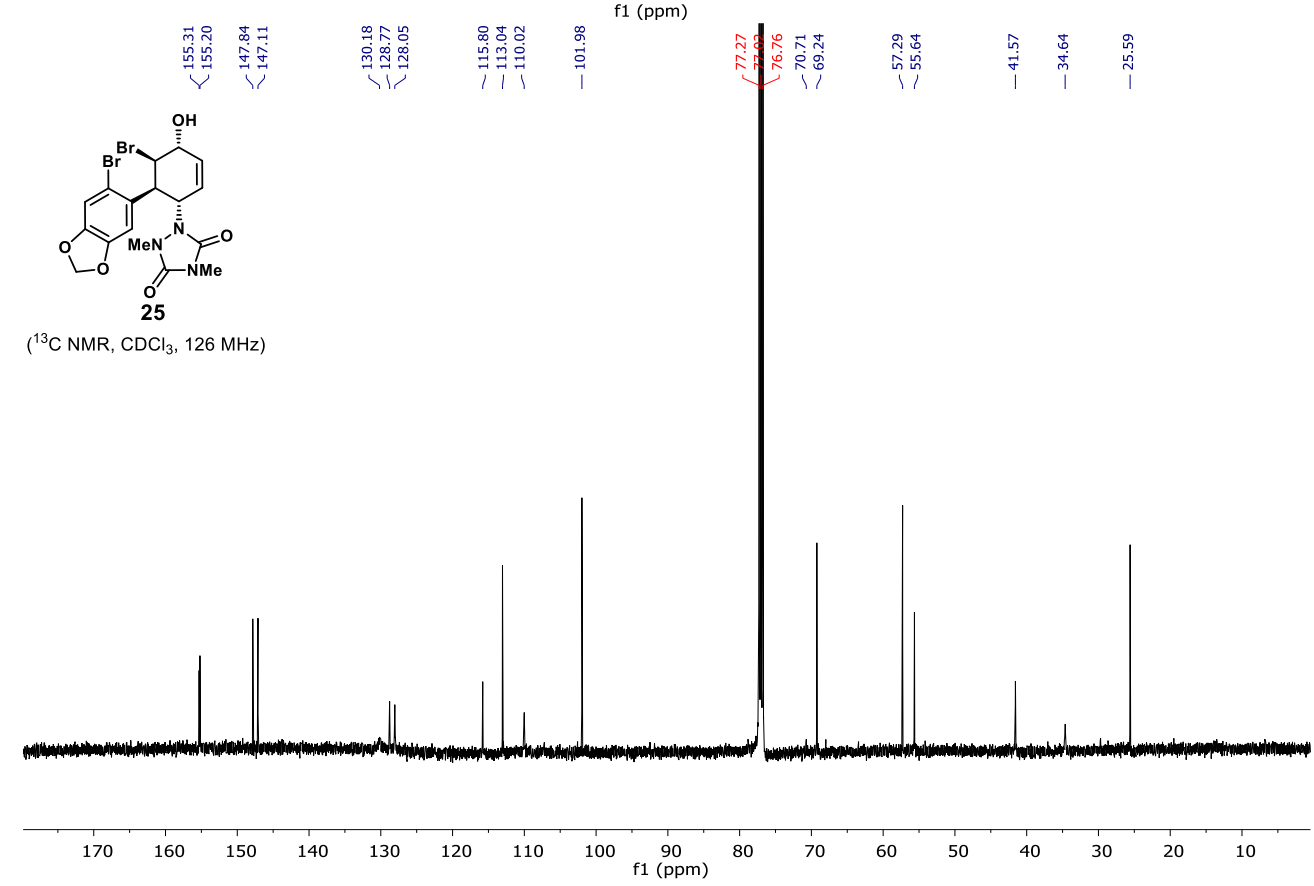
($^{1}$H NMR, $CD_3OD$, 500 MHz)

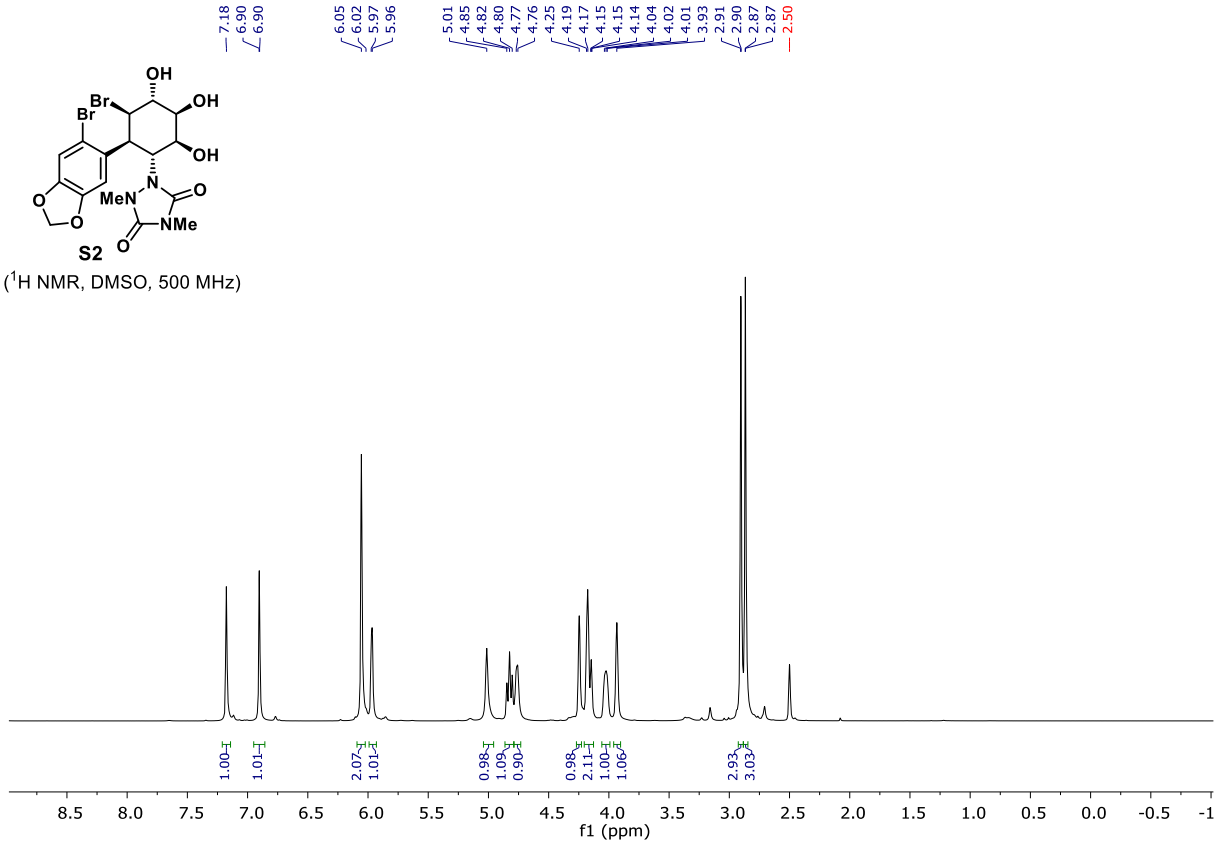



**24**

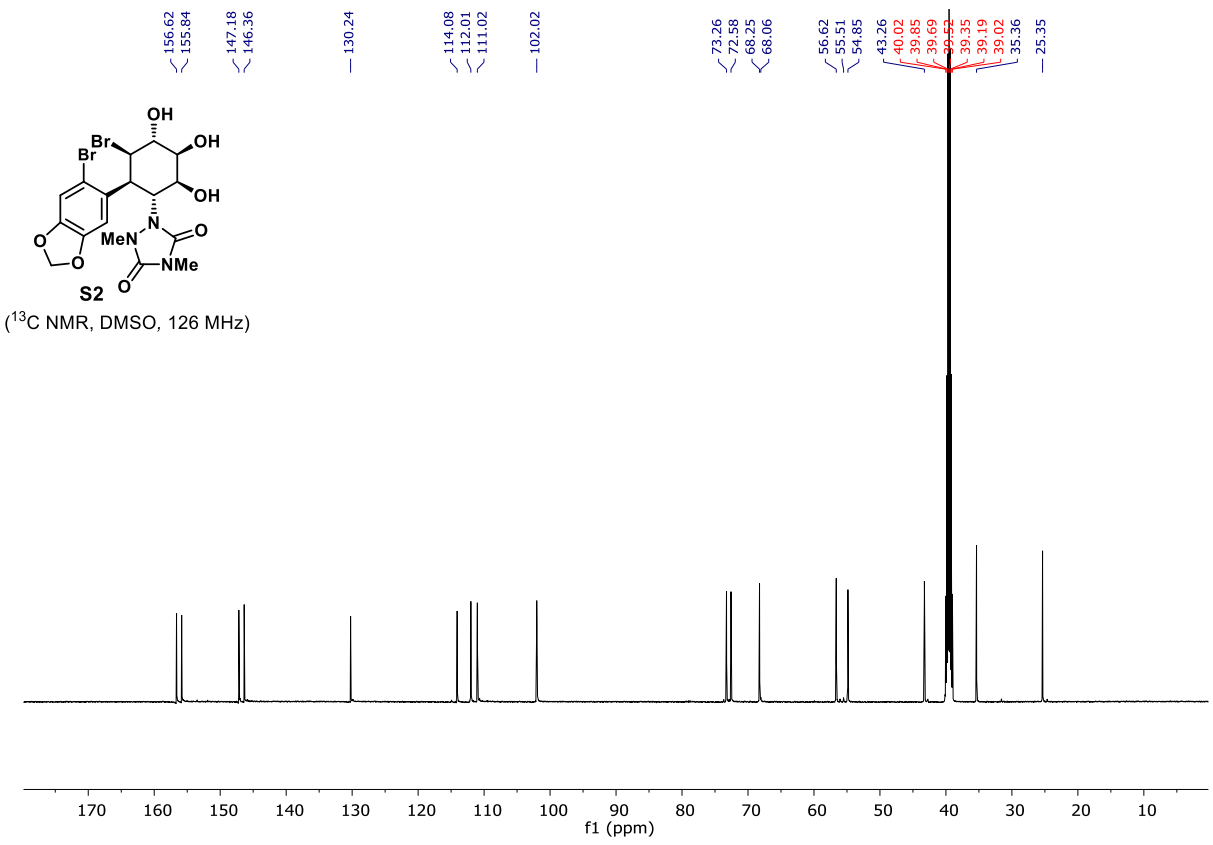
($^{13}$C NMR, $CD_3OD$, 126 MHz)


OH
Br
Br
O
O
MeN
N
O
NMe
O
25
(1H NMR, CDCl3, 500 MHz)
f1 (ppm)

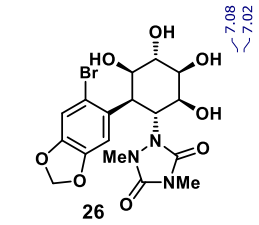

OH
Br
Br
O
O
MeN
N
O
NMe
O
25
(13C NMR, CDCl3, 126 MHz)
f1 (ppm)




($^1$H NMR, DMSO, 500 MHz)



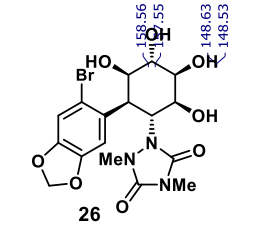

($^{13}$C NMR, DMSO, 126 MHz)




**26**

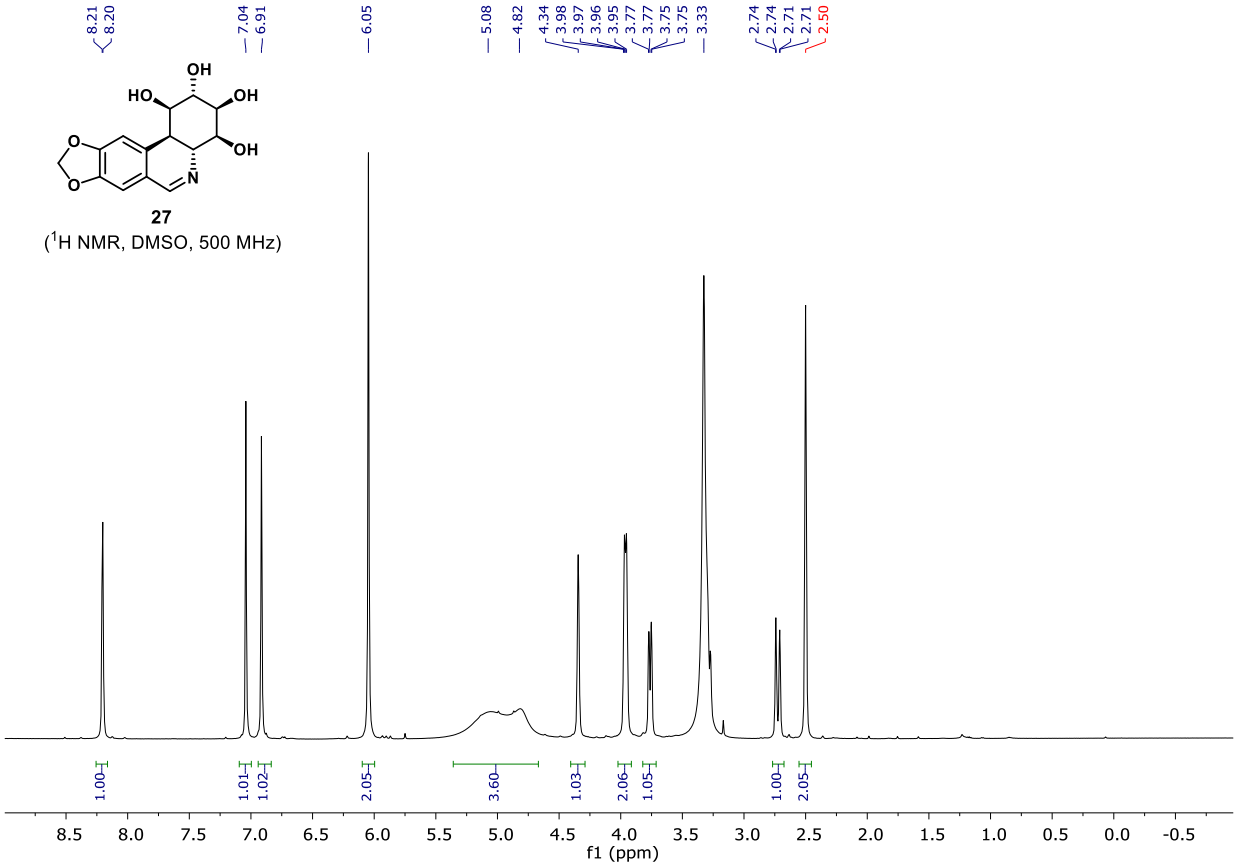
($^1$H NMR, $CD_3OD$, 500 MHz)



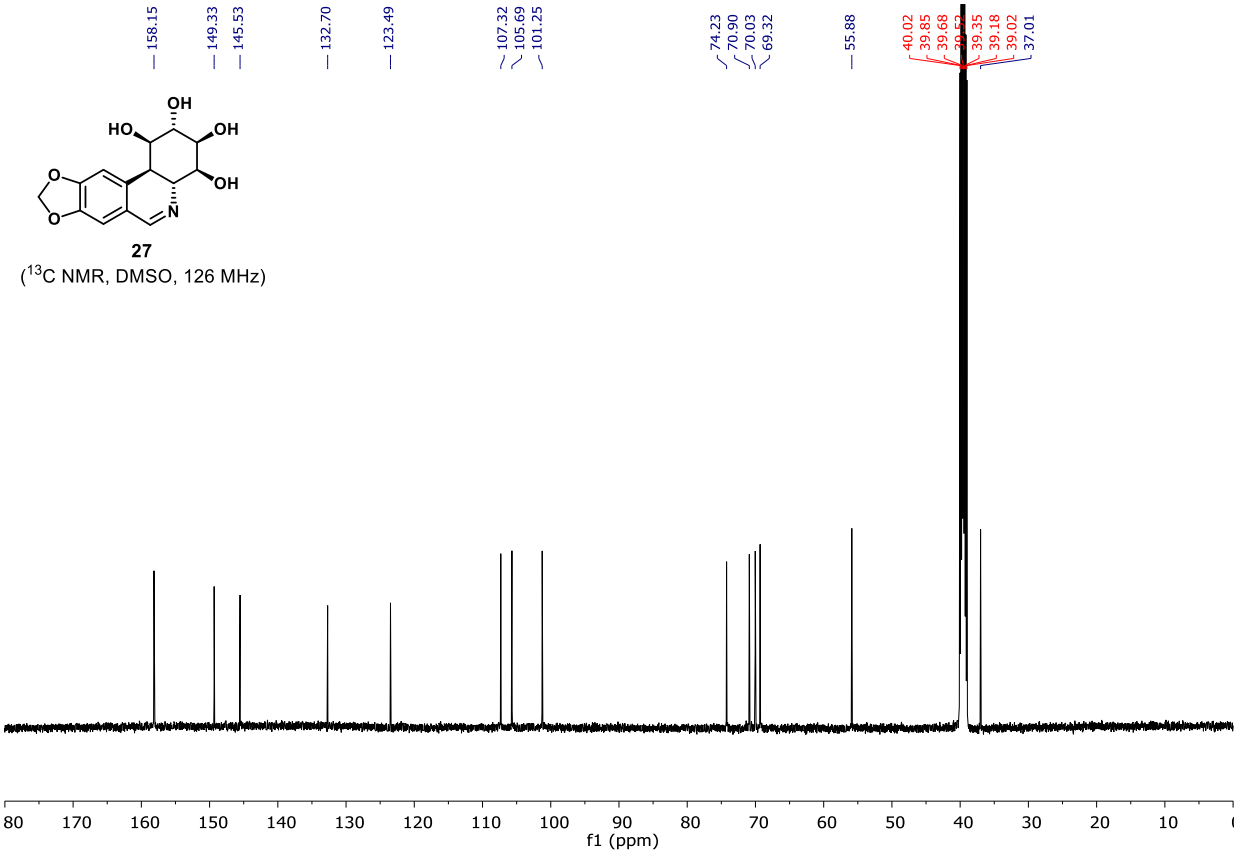

**26**

($^{13}$C NMR, $CD_3OD$, 126 MHz)



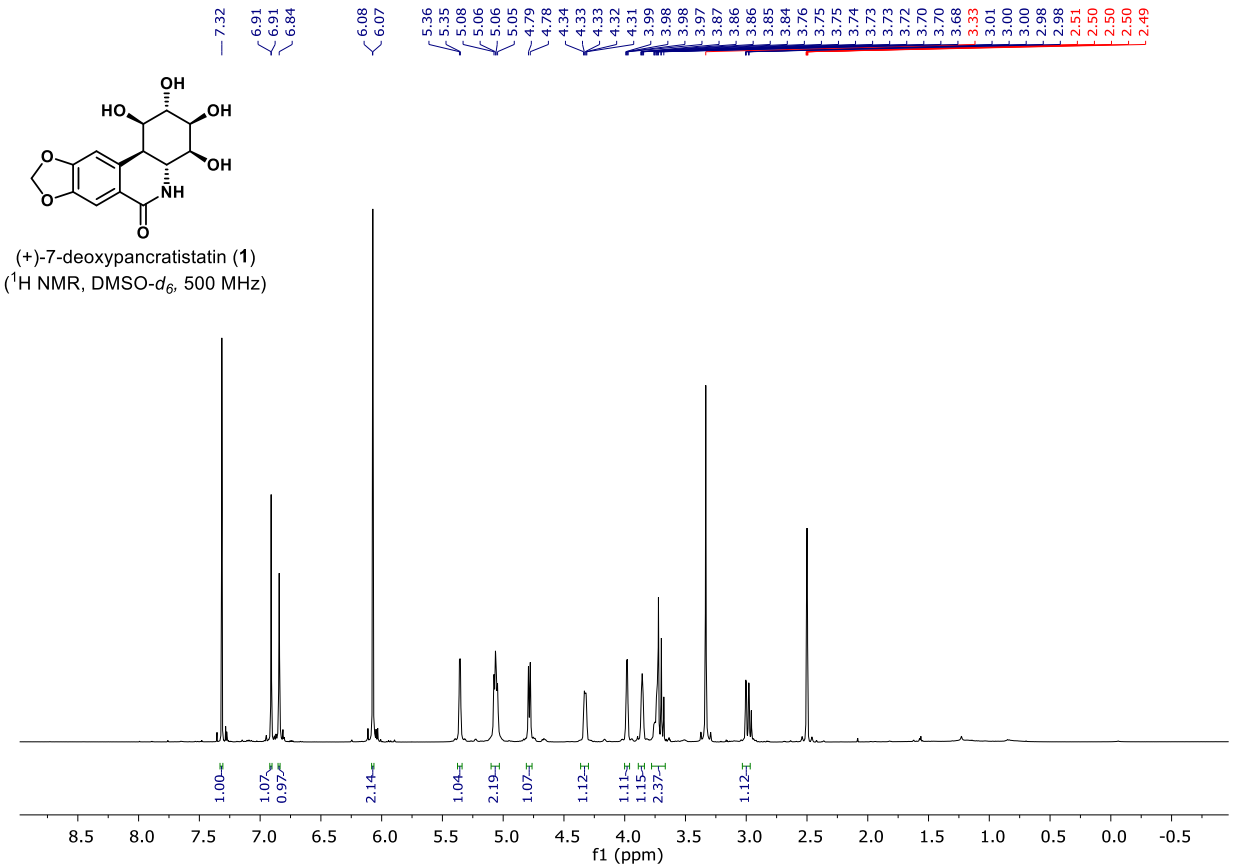

**27**

($^{1}$H NMR, DMSO, 500 MHz)

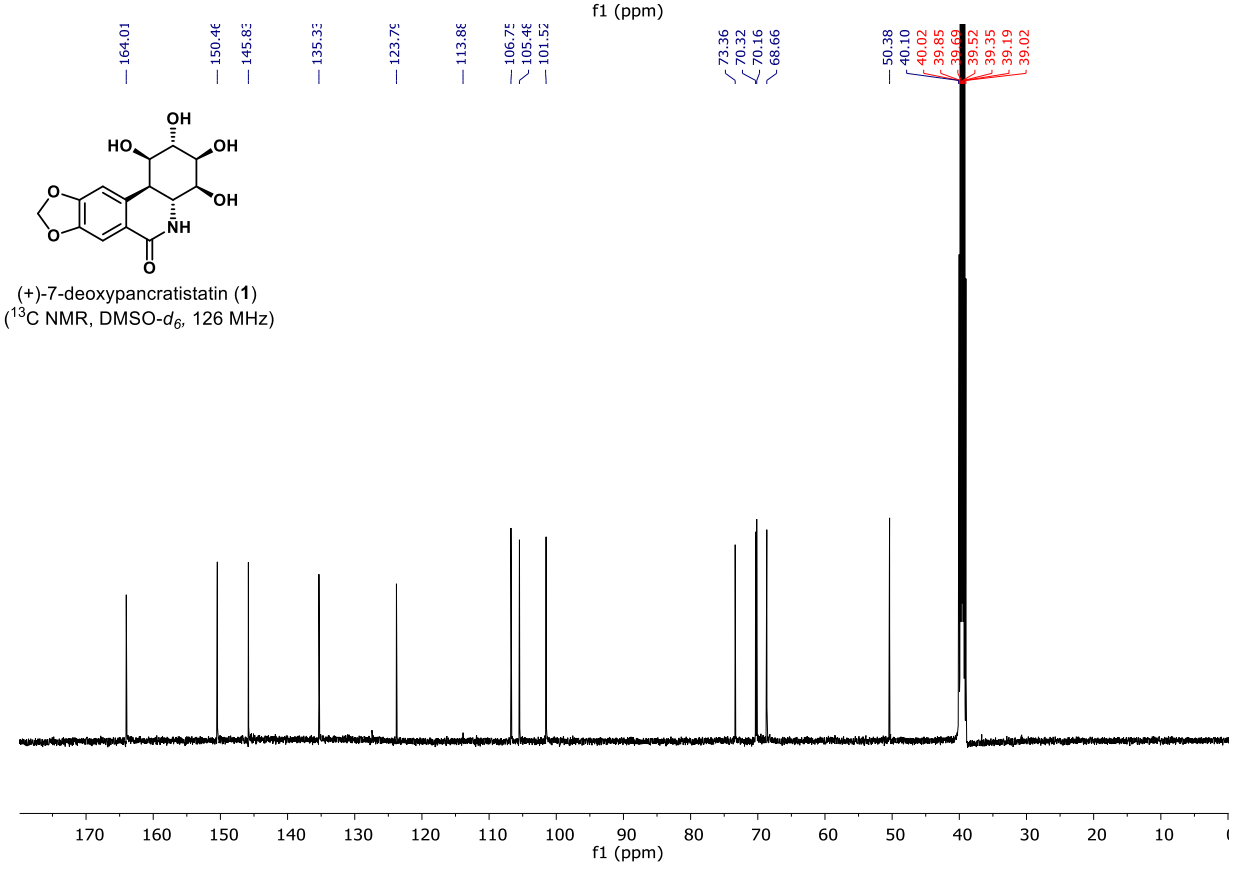



**27**

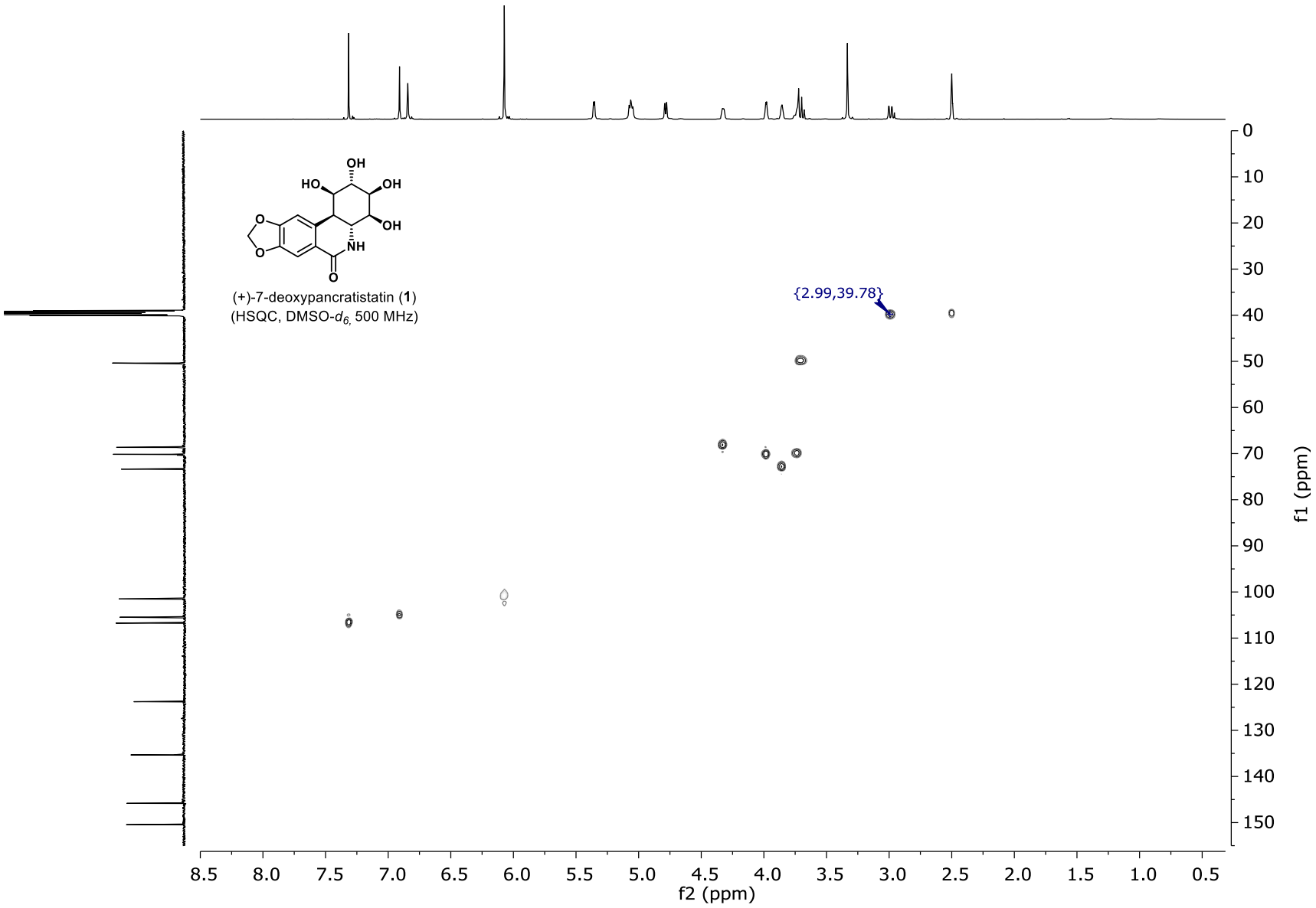
($^{13}$C NMR, DMSO, 126 MHz)

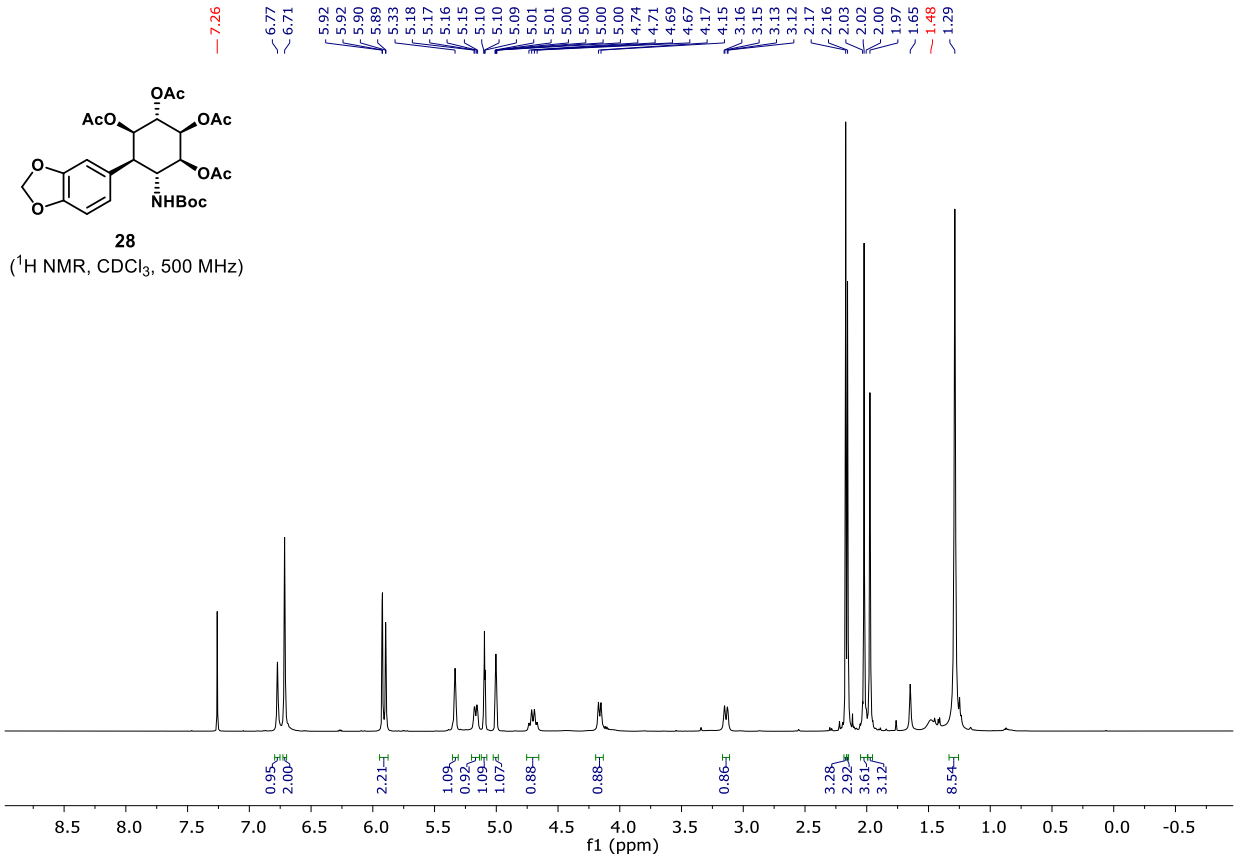



(+)-7-deoxypancratistatin (**1**)
($^{1}$H NMR, DMSO-$d_6$, 500 MHz)




(+)-7-deoxypancratistatin (**1**)
($^{13}$C NMR, DMSO-$d_6$, 126 MHz)

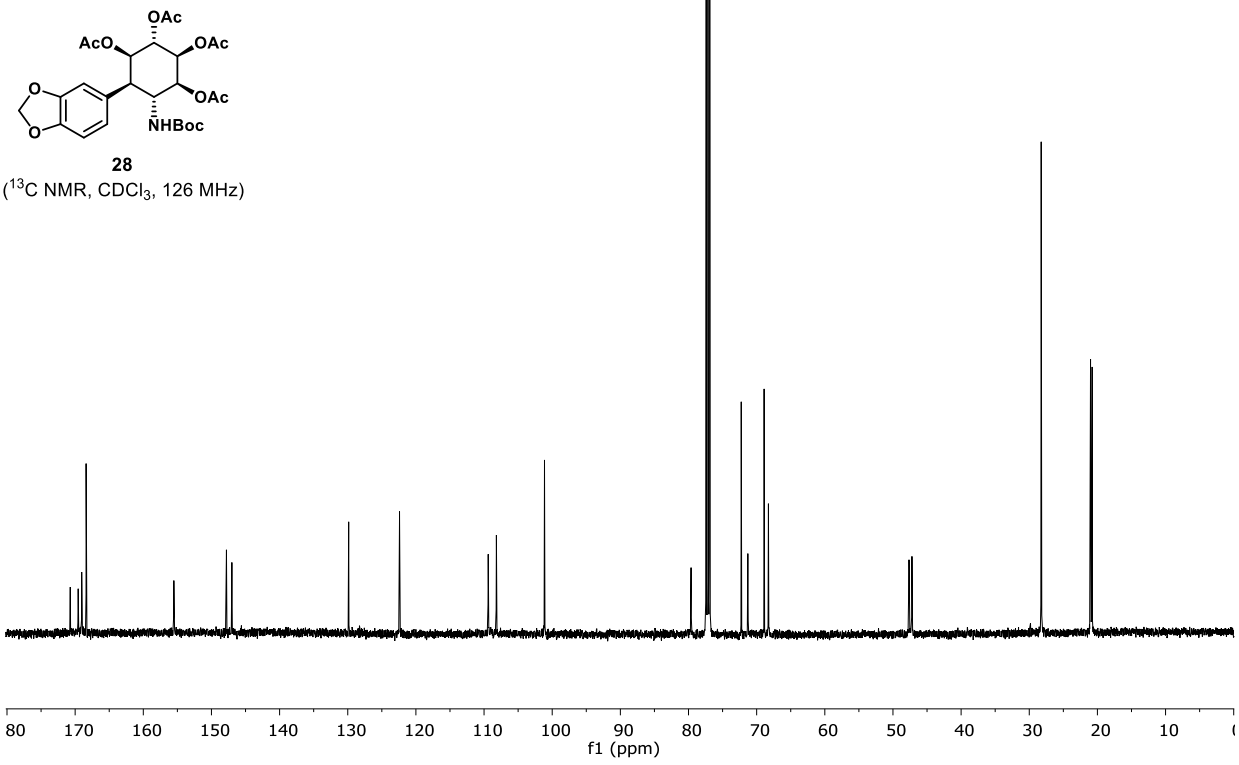

OH
HO
OH
OH
O
O
NH
O
(+)-7-deoxypancratistatin (1)
(HSQC, DMSO-d6, 500 MHz)
{2.99,39.78}
f1 (ppm)
f2 (ppm)




**28**

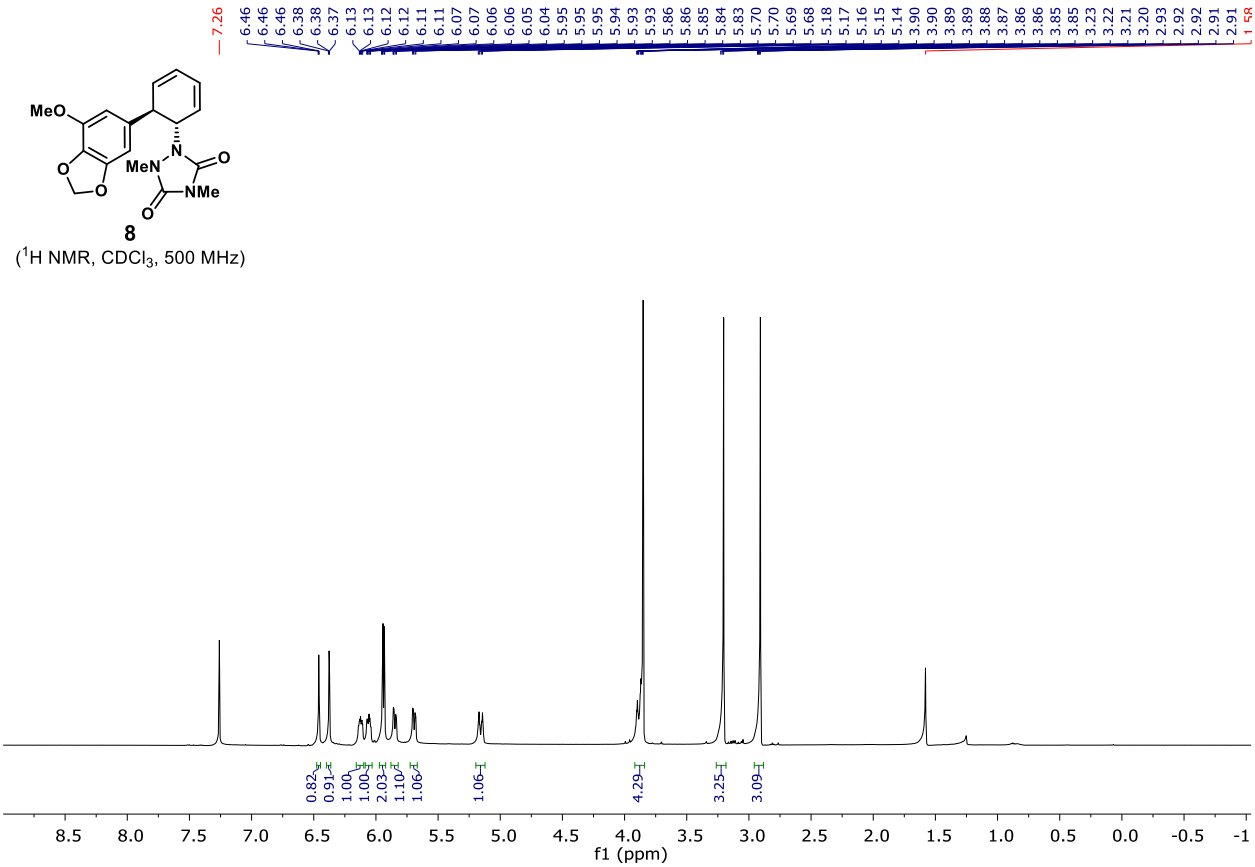
($^{1}$H NMR, $CDCl_3$, 500 MHz)

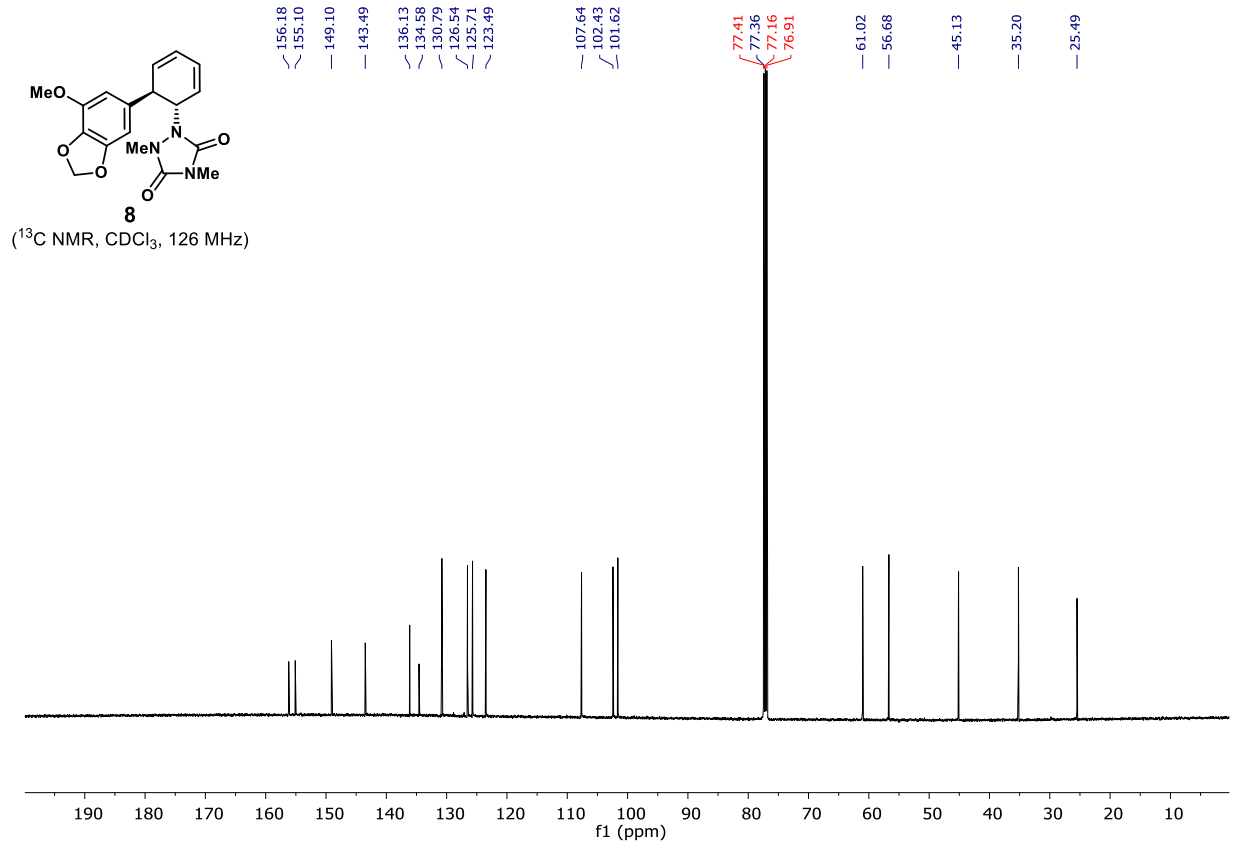


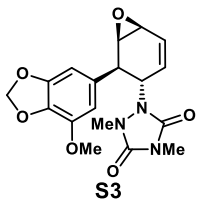




**28**

($^{13}$C NMR, $CDCl_3$, 126 MHz)


7.26
6.46 6.46 6.46 6.38 6.38 6.37 6.13 6.13 6.12 6.12 6.11 6.11 6.07 6.07 6.06 6.06 6.05 6.04 5.95 5.95 5.94 5.93 5.93 5.86 5.86 5.85 5.84 5.83 5.70 5.69 5.68 5.18 5.17 5.16 5.15 5.14 3.90 3.90 3.89 3.89 3.88 3.87 3.86 3.86 3.85 3.85 3.23 3.22 3.21 3.20 2.93 2.92 2.92 2.91 2.91
MeO
MeN
NMe
O
8
(1H NMR, CDCl3, 500 MHz)
0.82 0.91 1.00 1.00 2.03 1.10 1.06 1.06 4.29 3.25 3.09
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1
f1 (ppm)


156.18 155.10 149.10 143.49 136.13 134.58 130.79 126.54 125.71 123.49 107.64 102.43 101.62 77.41 77.36 77.16 76.91 61.02 56.68 45.13 35.20 25.49
MeO
MeN
NMe
O
8
(13C NMR, CDCl3, 126 MHz)
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

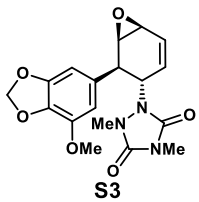



**S3**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)



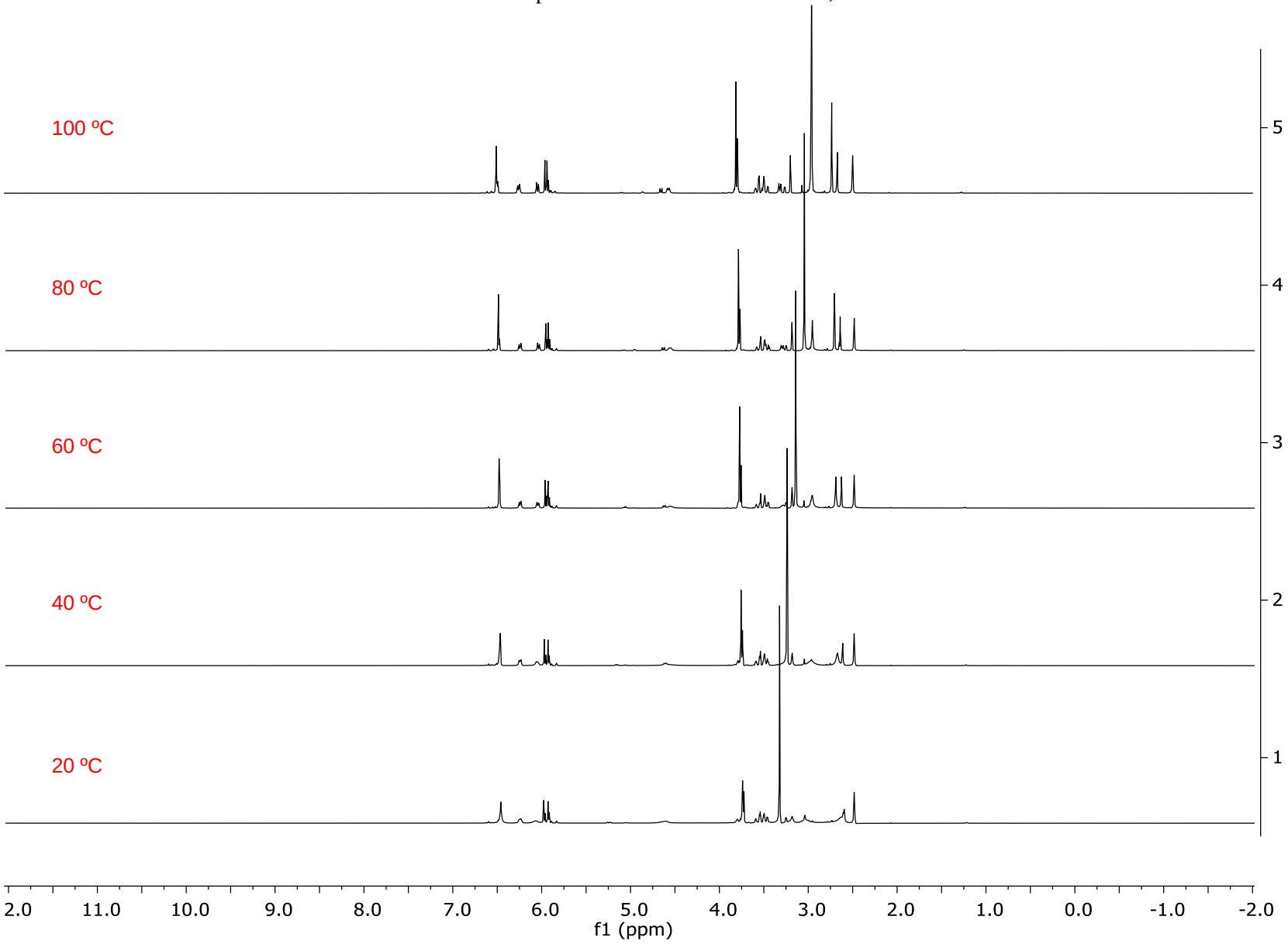


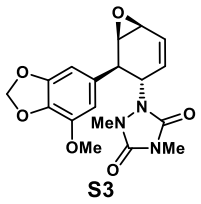



**S3**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **S3** in DMSO, 500 MHz:

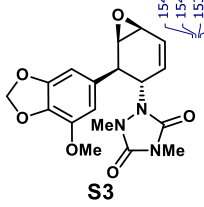





**S3**

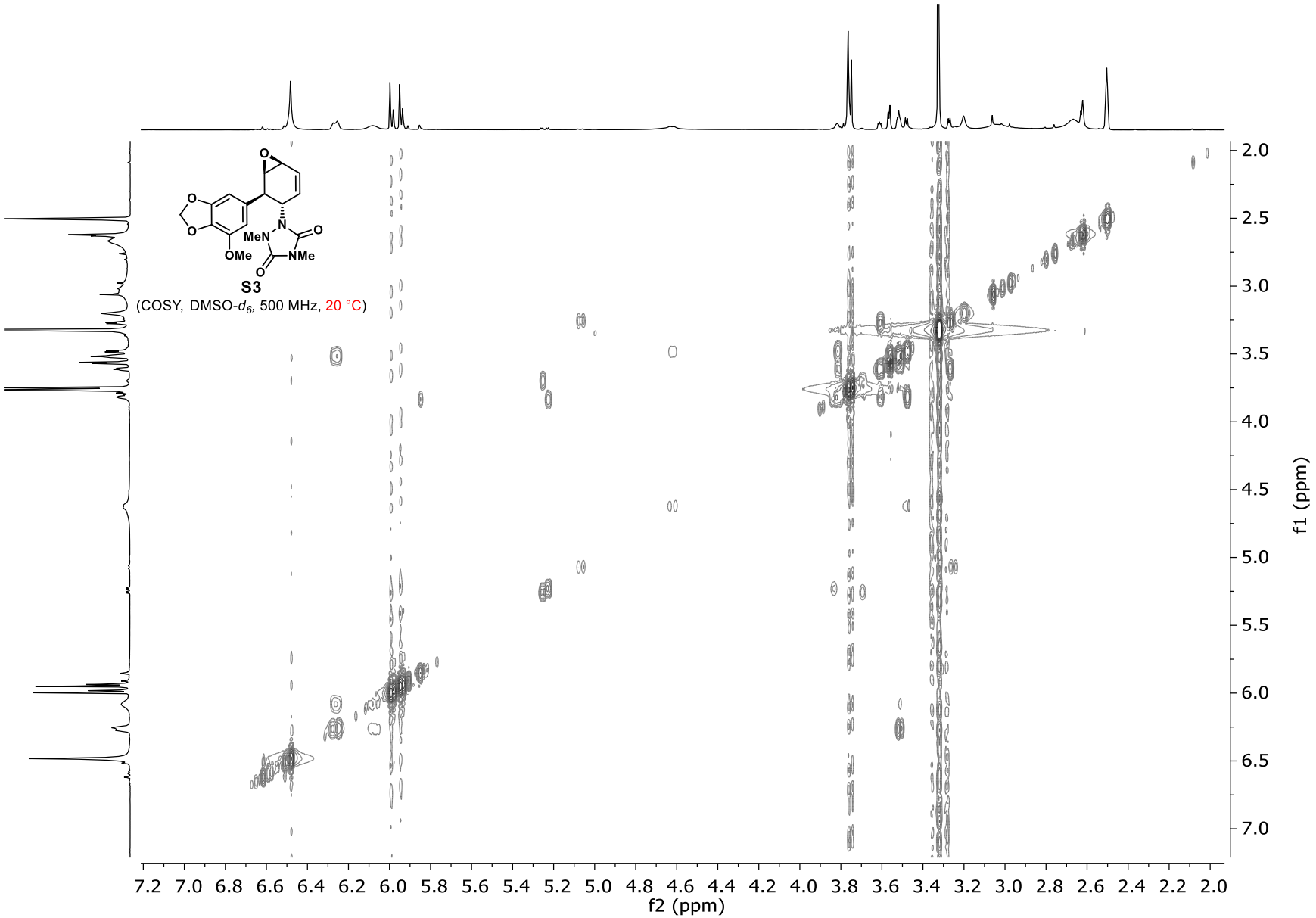
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)

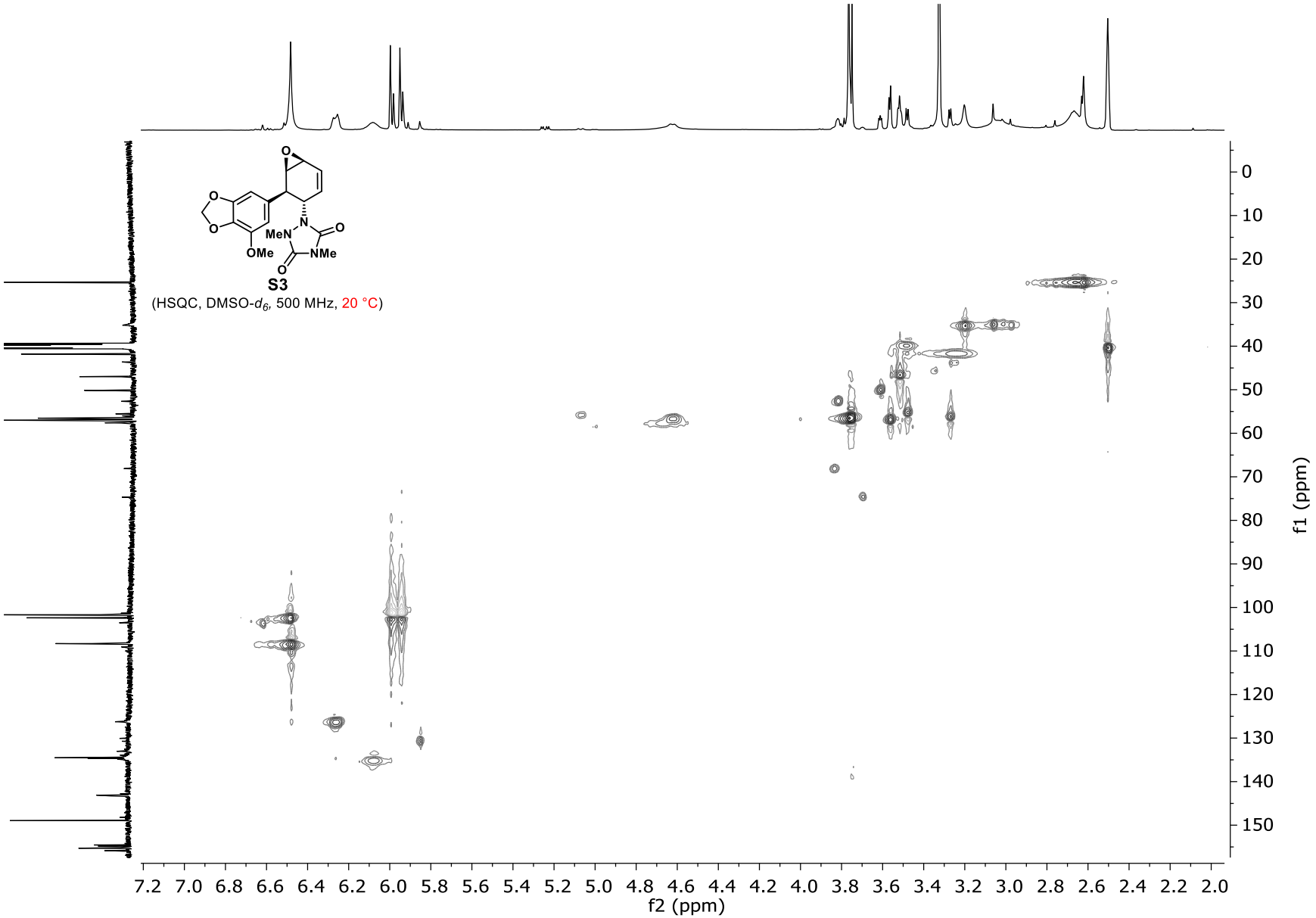


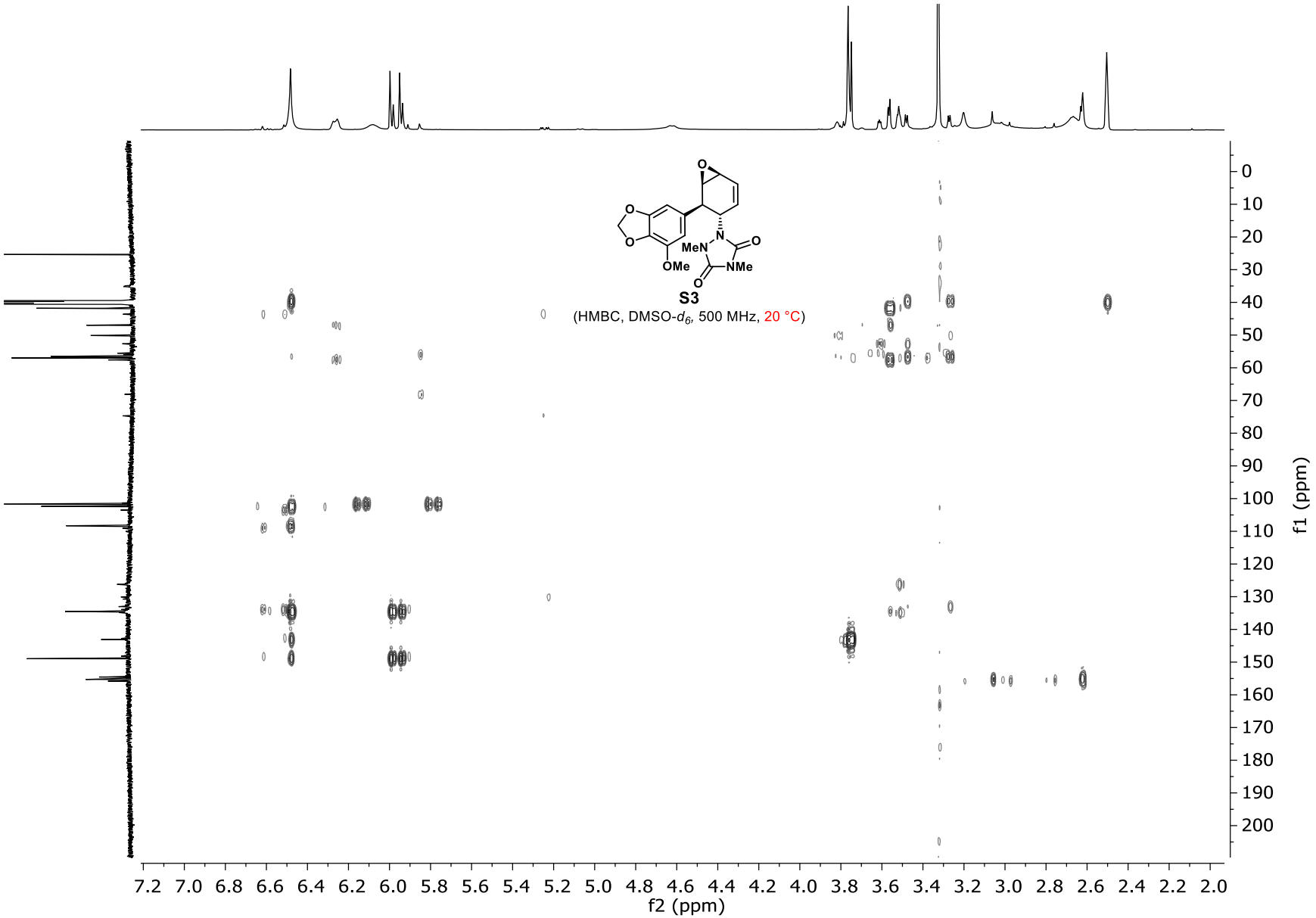



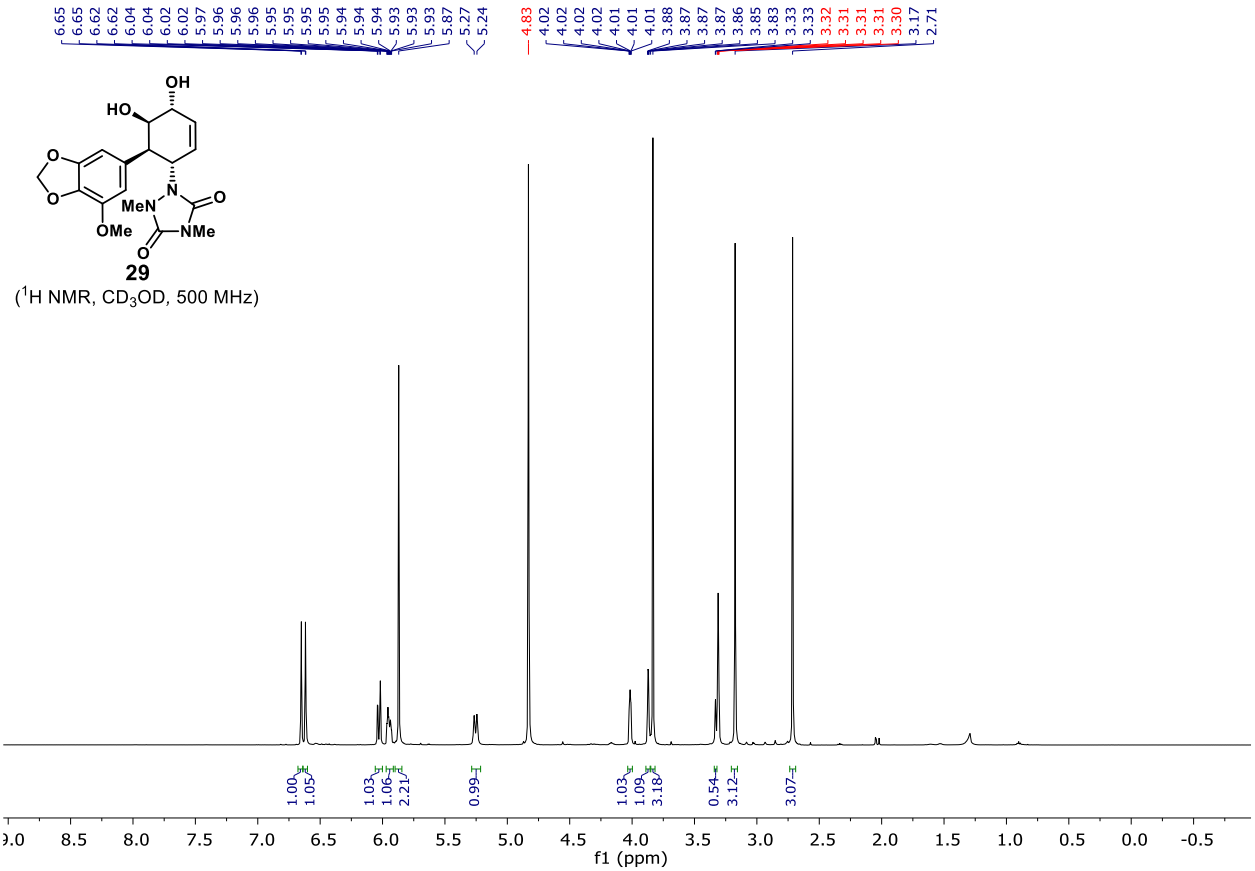

**S3**

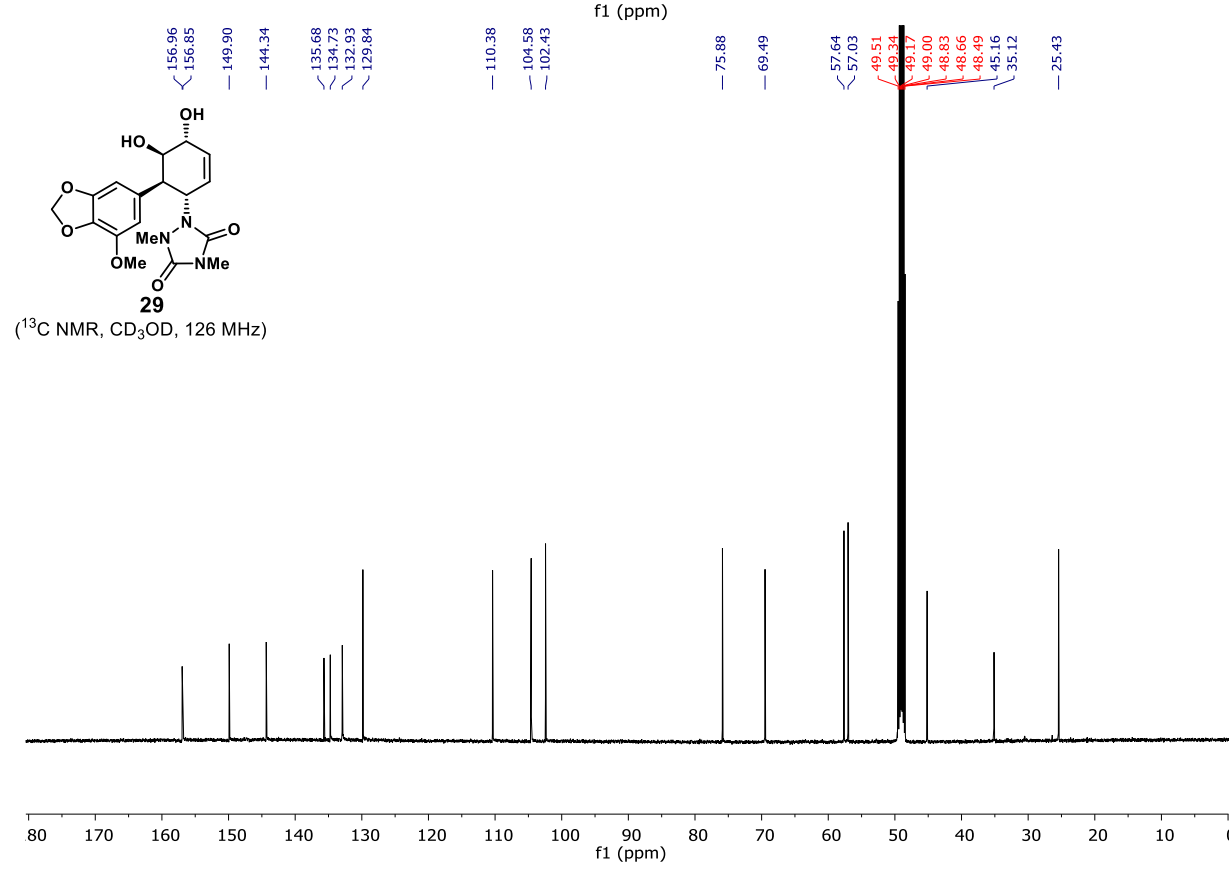
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)

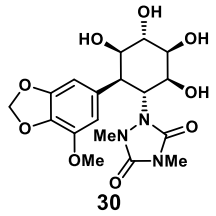

S3
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)


S3
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)


S3
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)


OH
HO
O
O
N
MeN
O
OMe
NMe
O
O
29
(1H NMR, CD3OD, 500 MHz)
f1 (ppm)

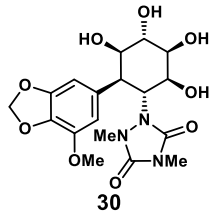

OH
HO
O
O
N
MeN
O
OMe
NMe
O
O
29
(13C NMR, CD3OD, 126 MHz)
f1 (ppm)




**30**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

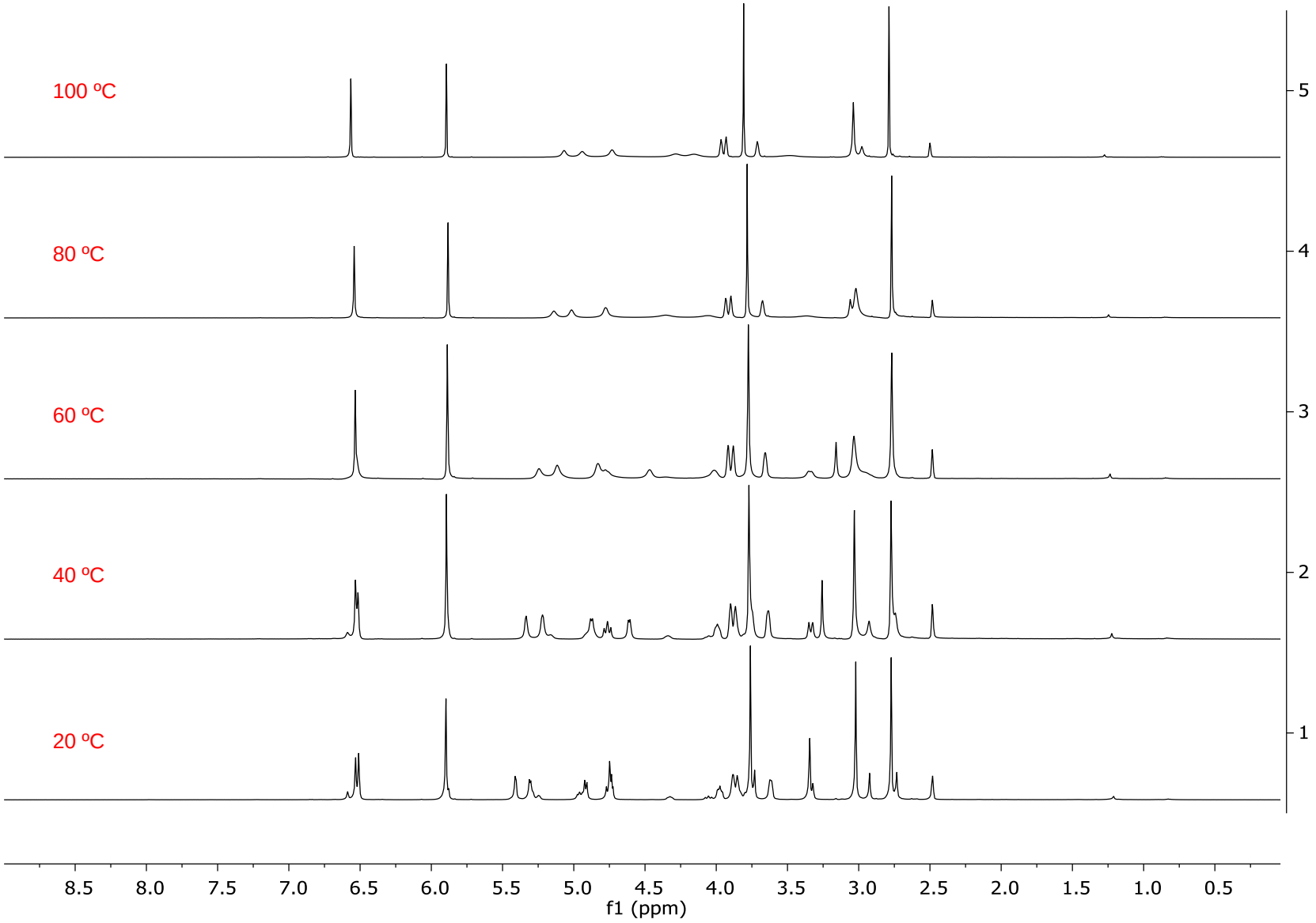


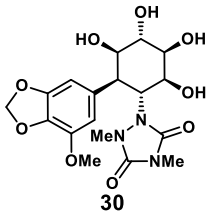




**30**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **30** in DMSO, 500 MHz:



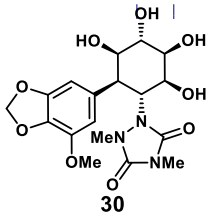



**30**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)

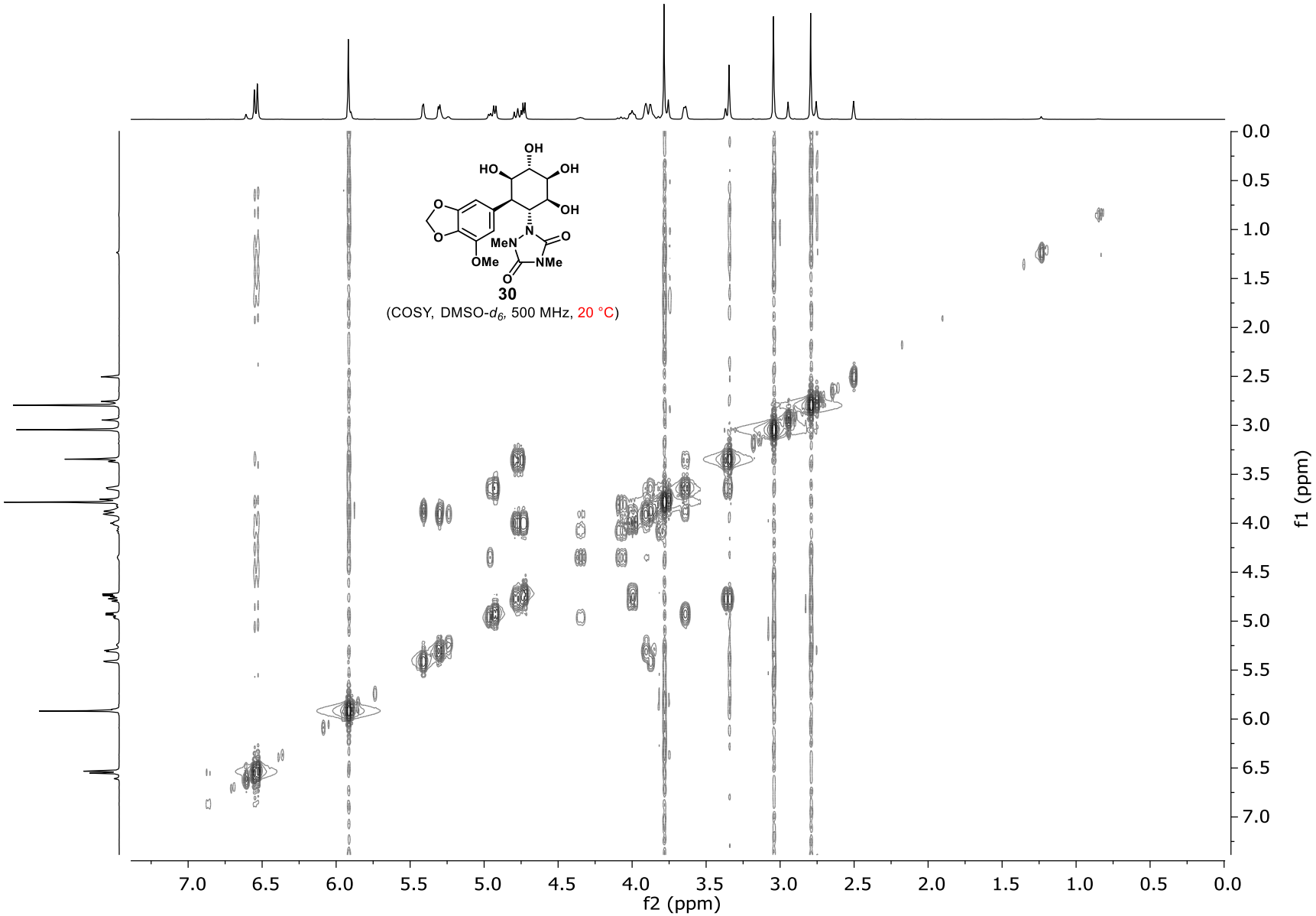


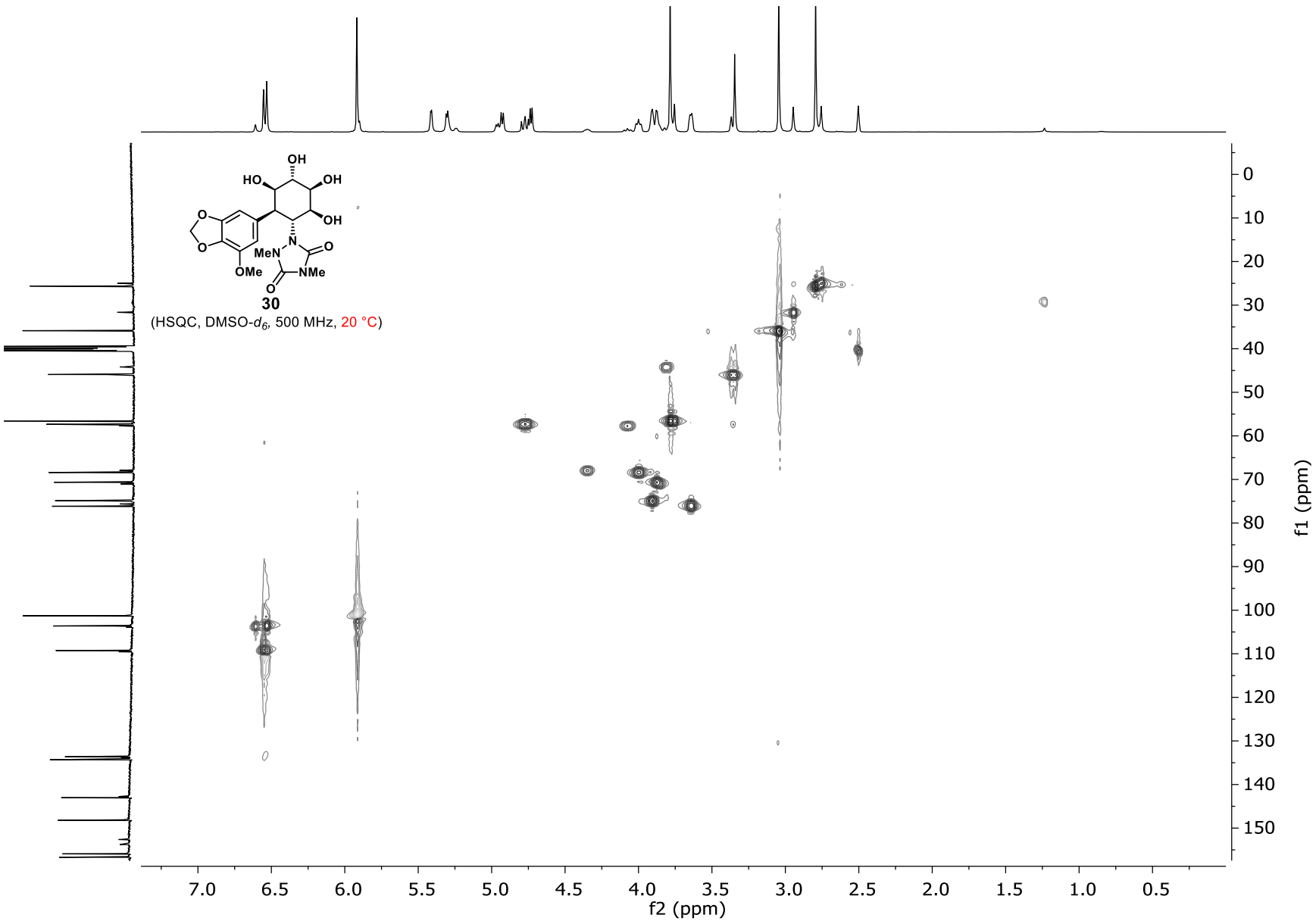

147.48
142.16
133.30
133.16
109.59
102.98
100.22
75.24
74.11
70.02
67.66
56.89
56.14
40.02
39.85
39.69
39.52
39.35
39.19
39.02
24.31

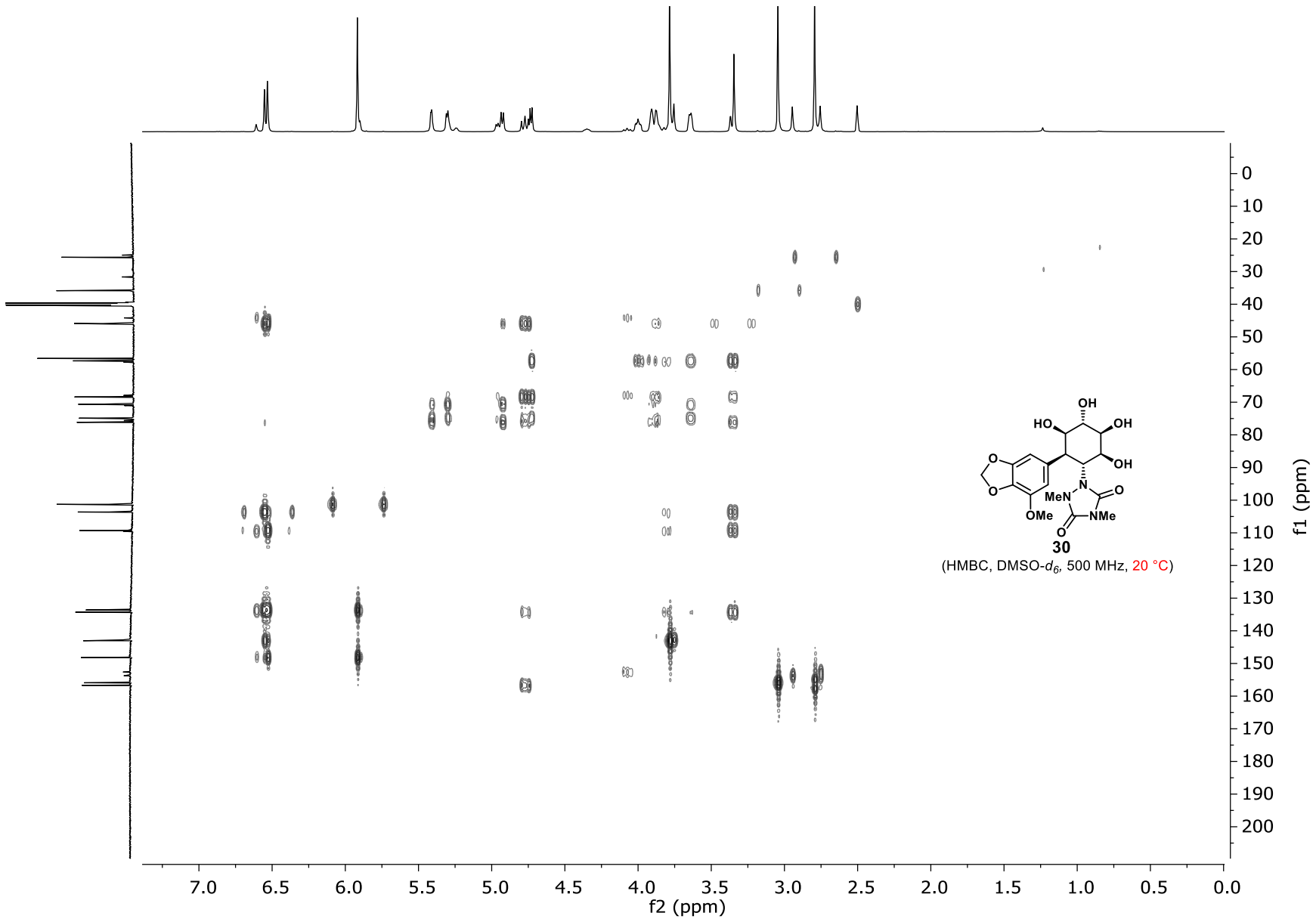


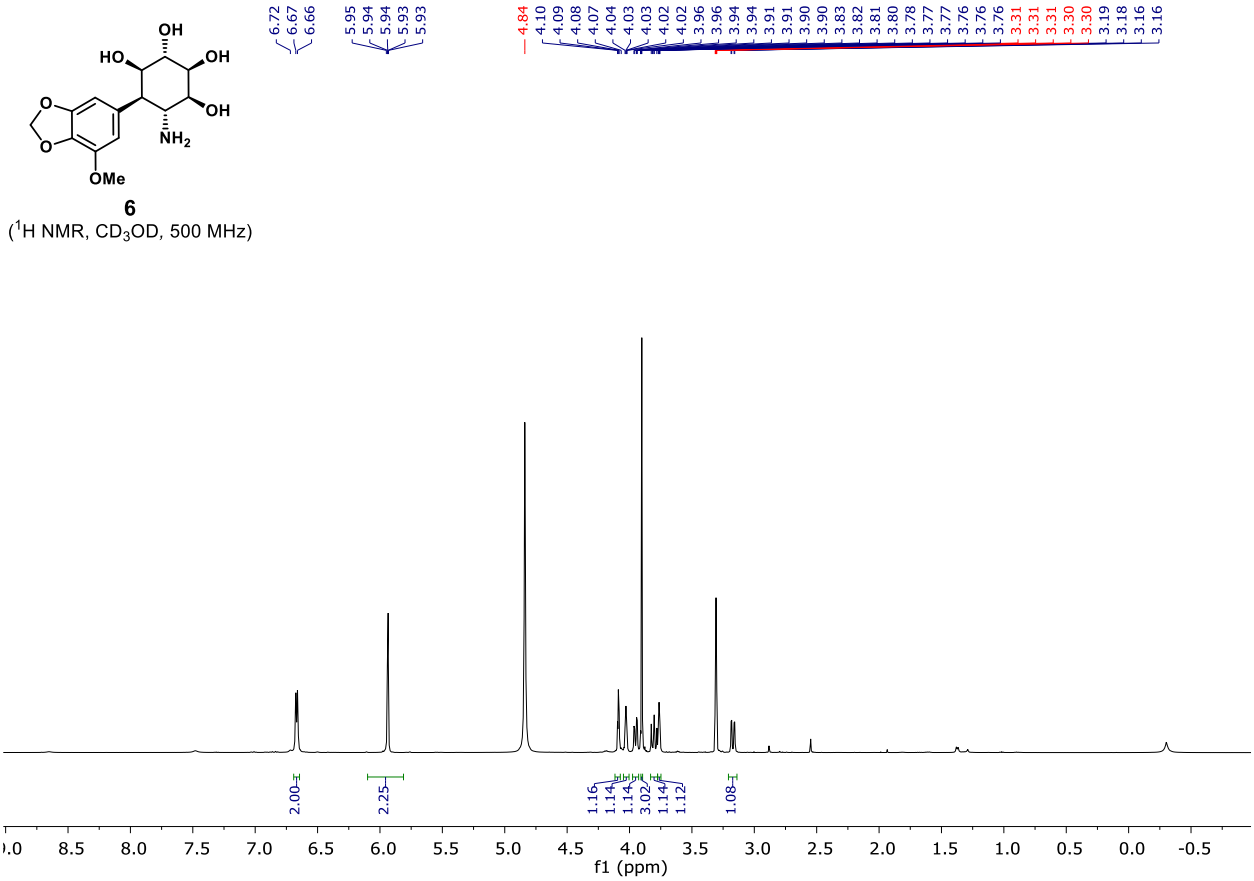

**30**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)


OH
HO
OH
OH
O
O
MeN
N
O
OMe
NMe
O
30
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0

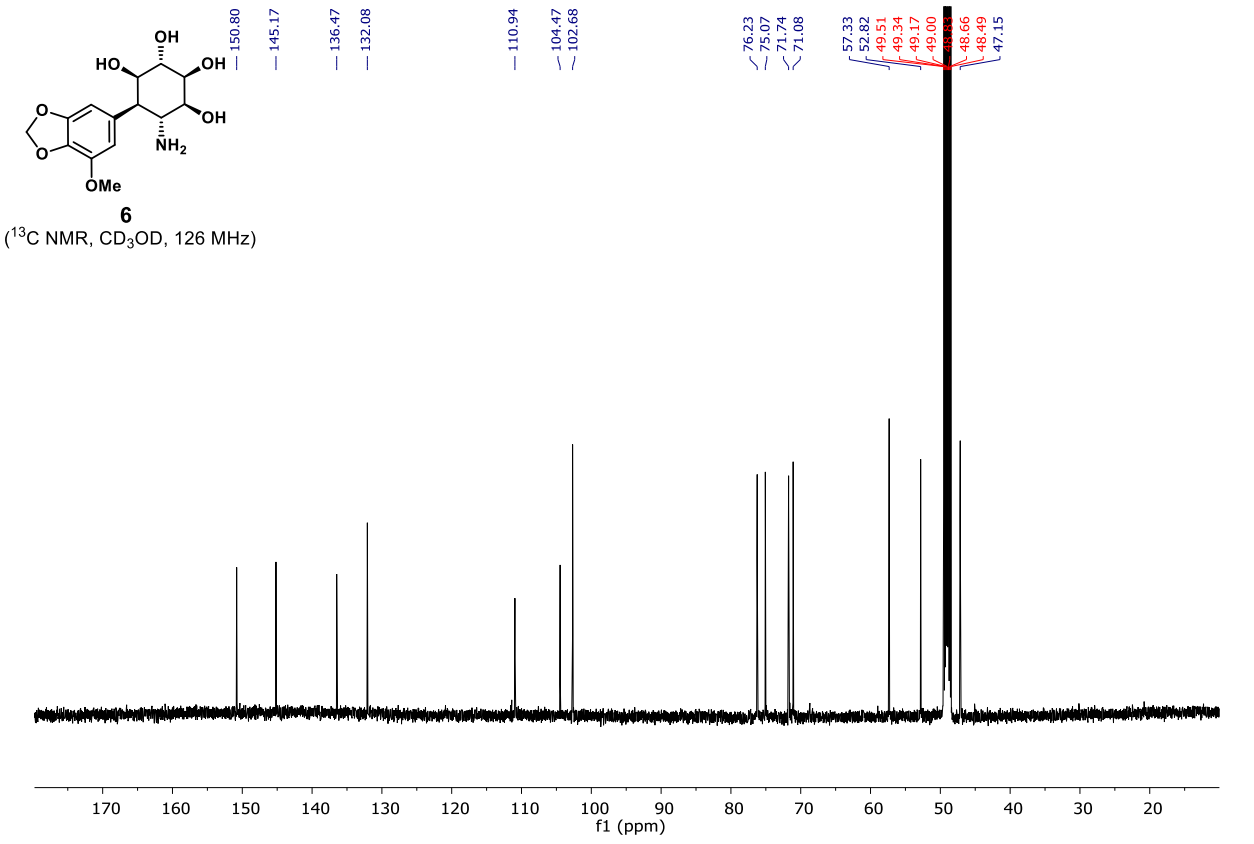

OH
HO
OH
OH
O
O
N
MeN
O
OMe
NMe
O
30
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)


f2 (ppm)
f1 (ppm)
30
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)



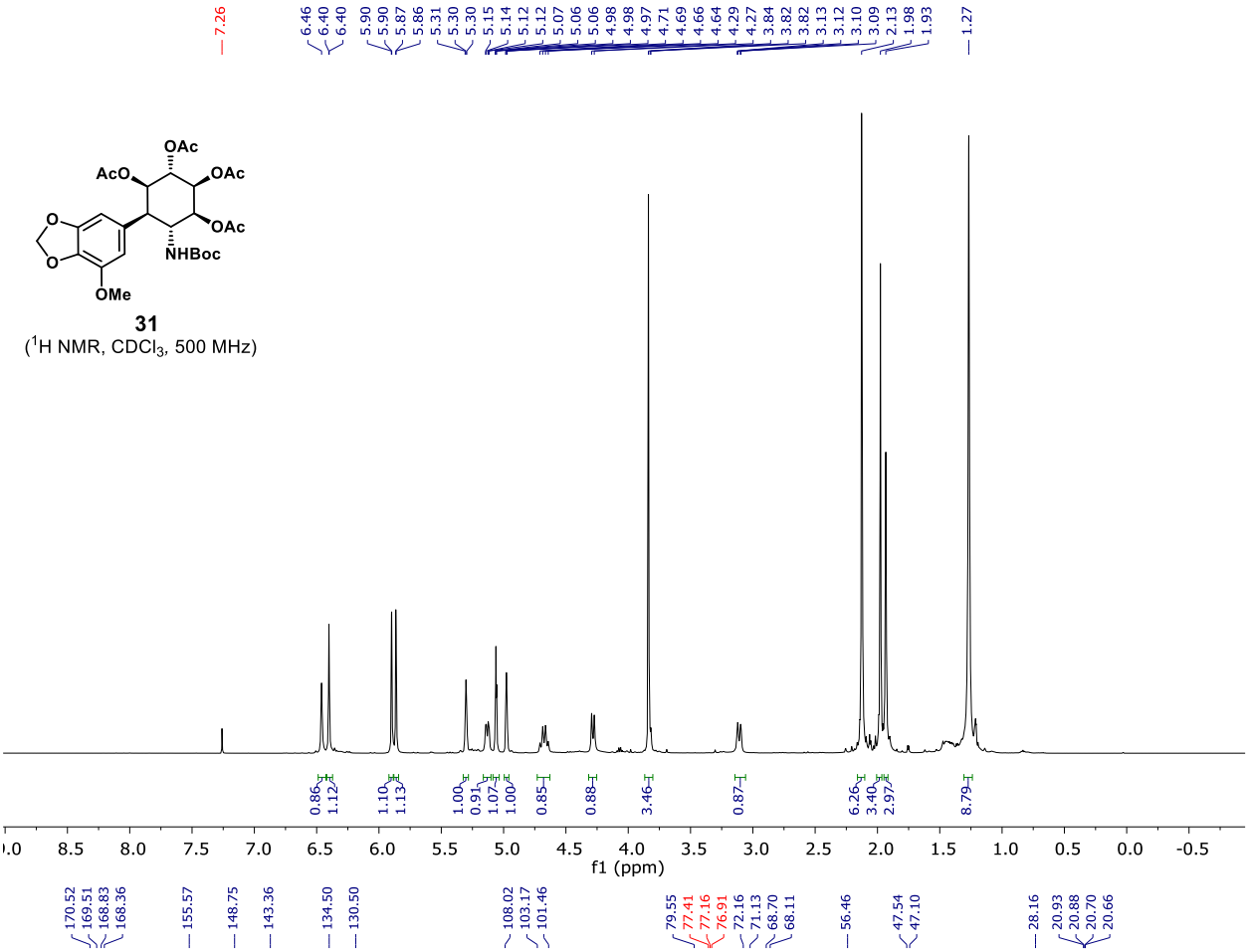

**6**

($^{1}$H NMR, $CD_3OD$, 500 MHz)



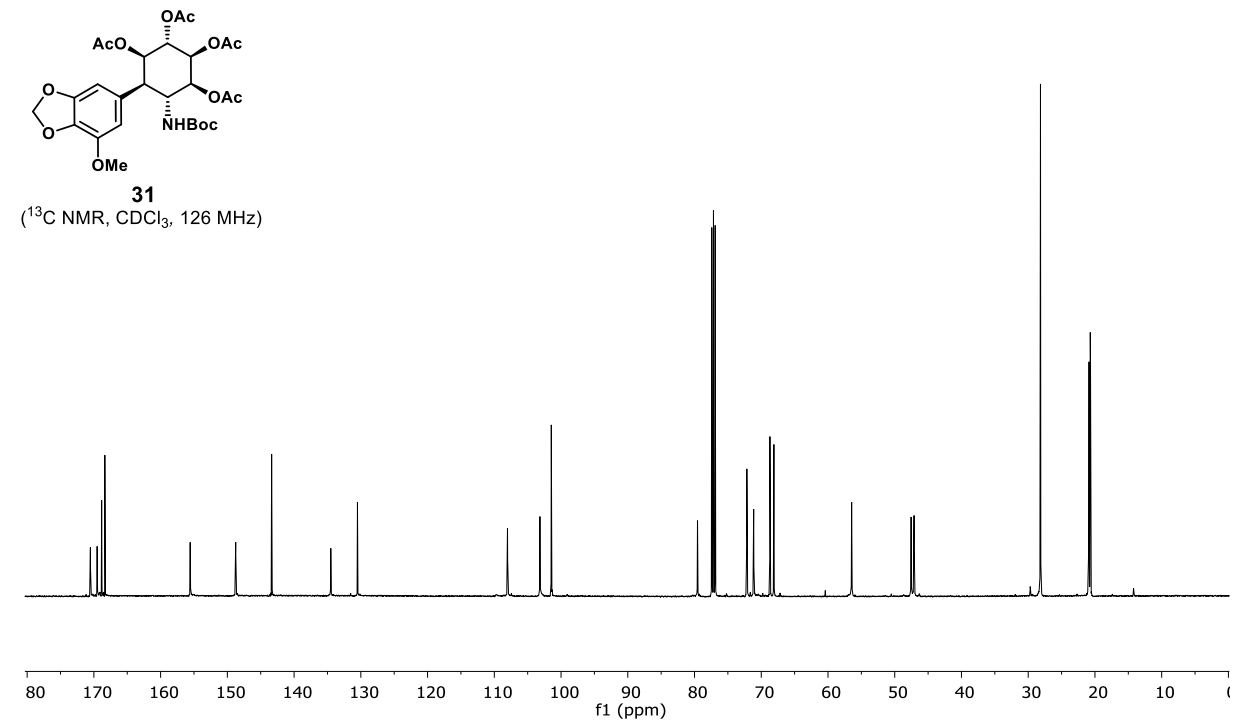

**6**

($^{13}$C NMR, $CD_3OD$, 126 MHz)



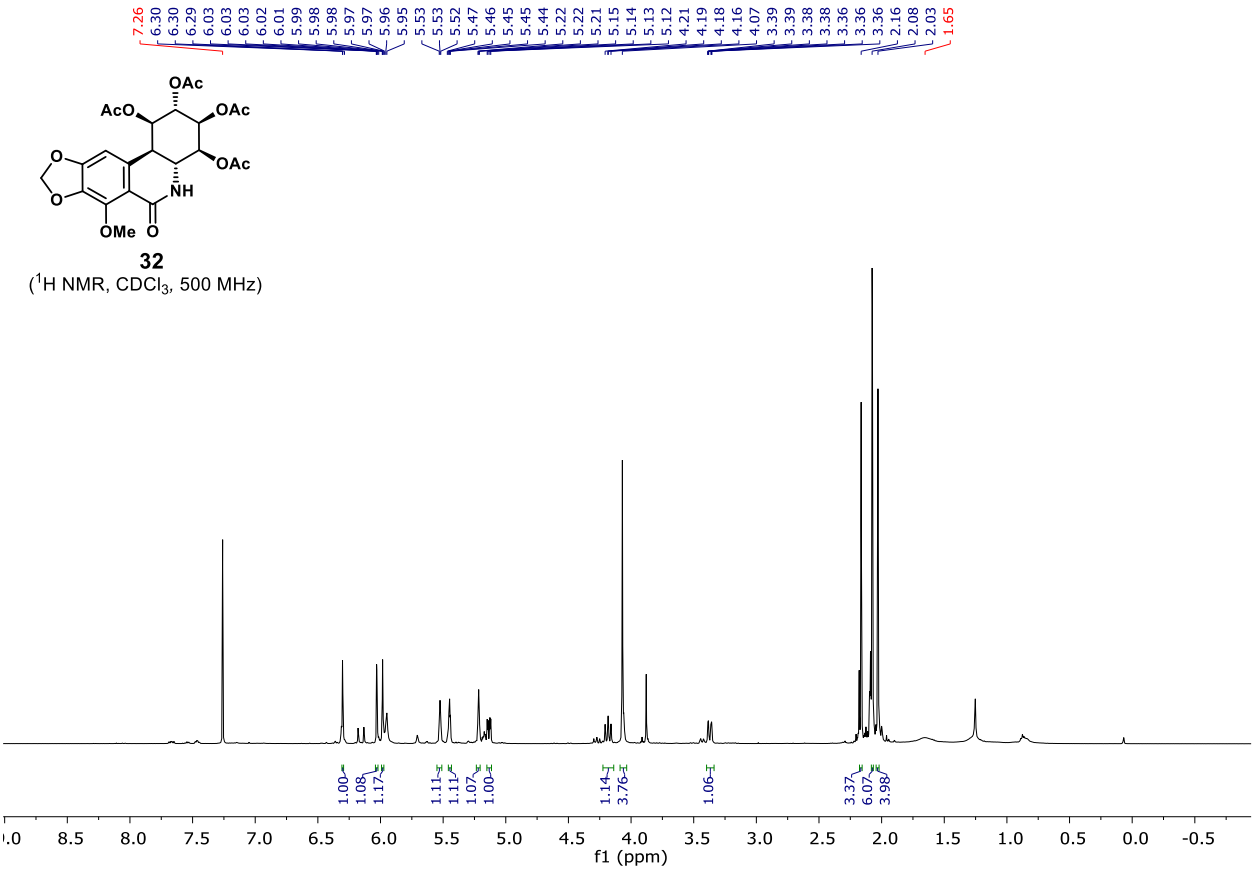

**31**

($^{1}$H NMR, $CDCl_3$, 500 MHz)



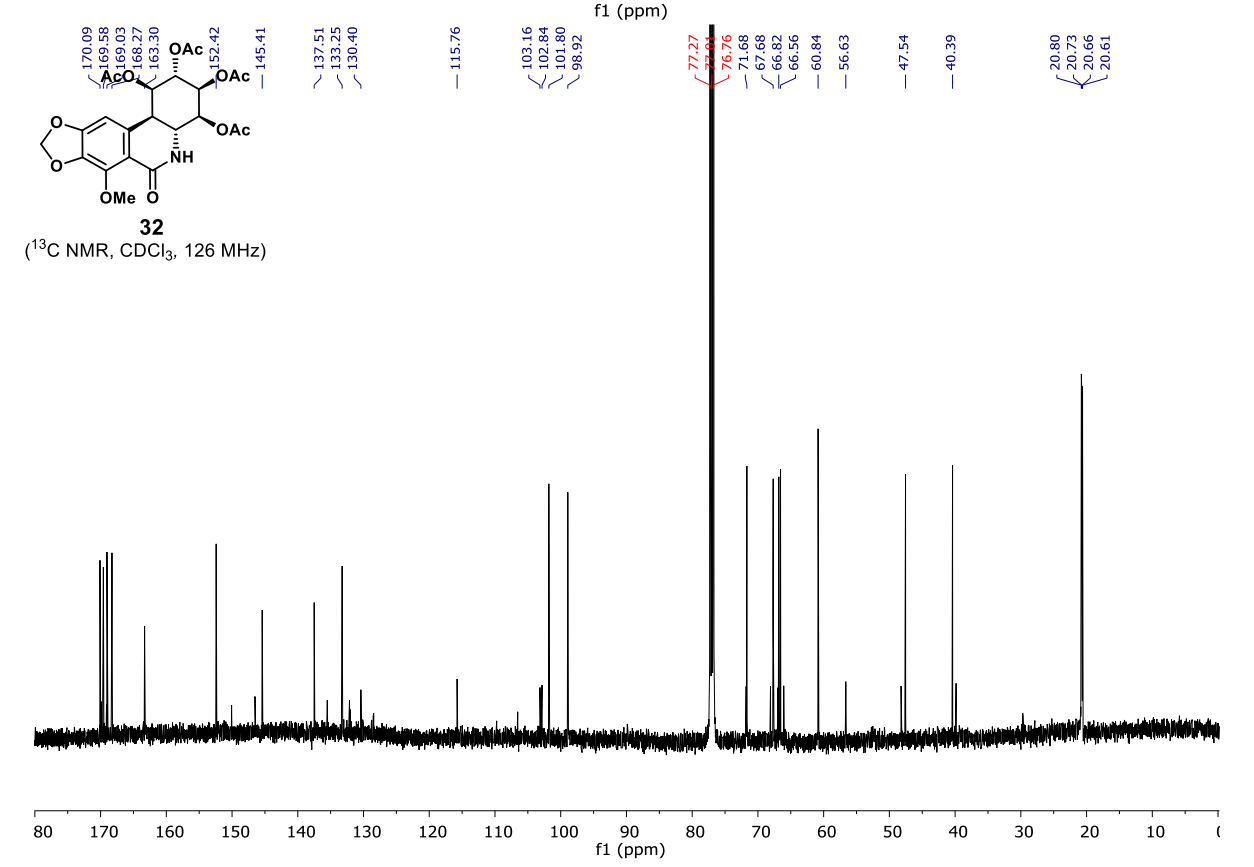

**31**

($^{13}$C NMR, $CDCl_3$, 126 MHz)



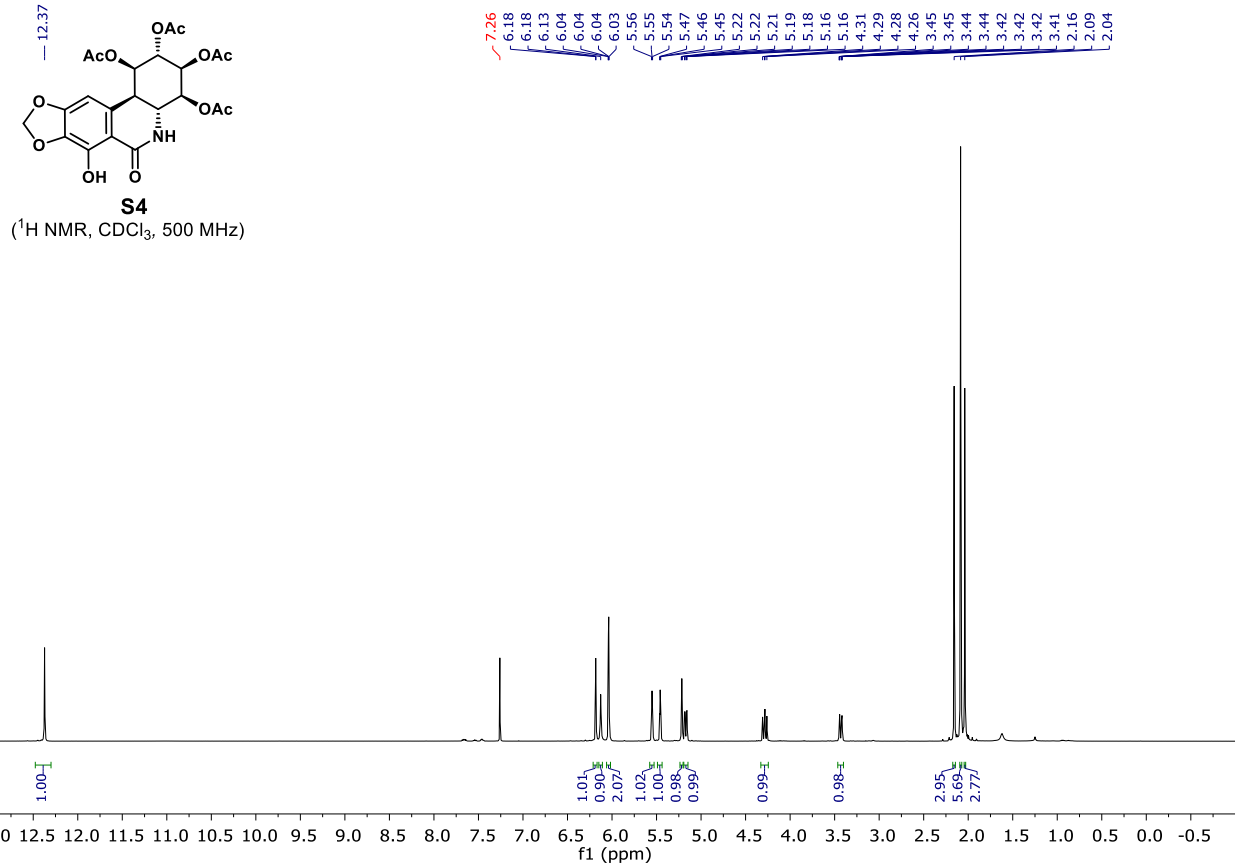

**32**

($^{1}$H NMR, $CDCl_3$, 500 MHz)

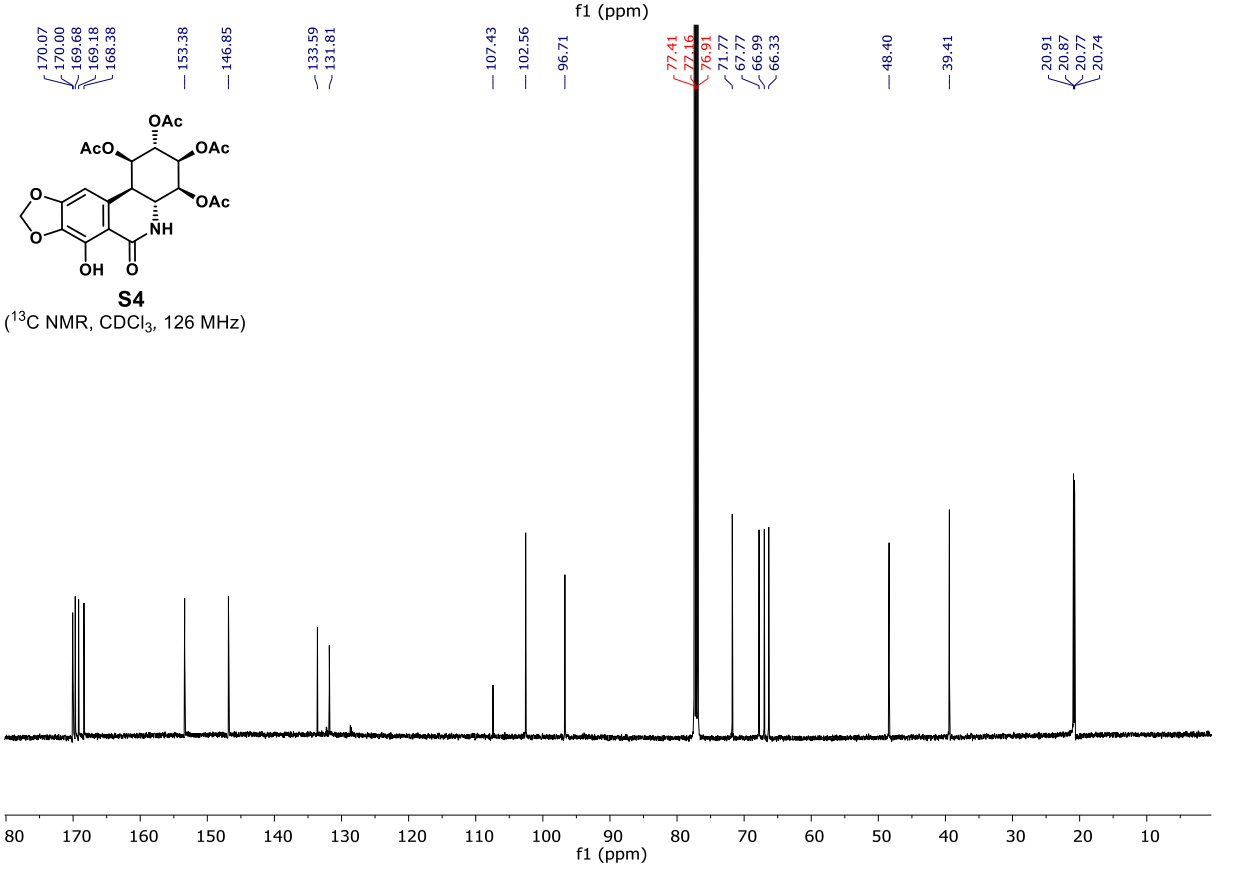



**32**

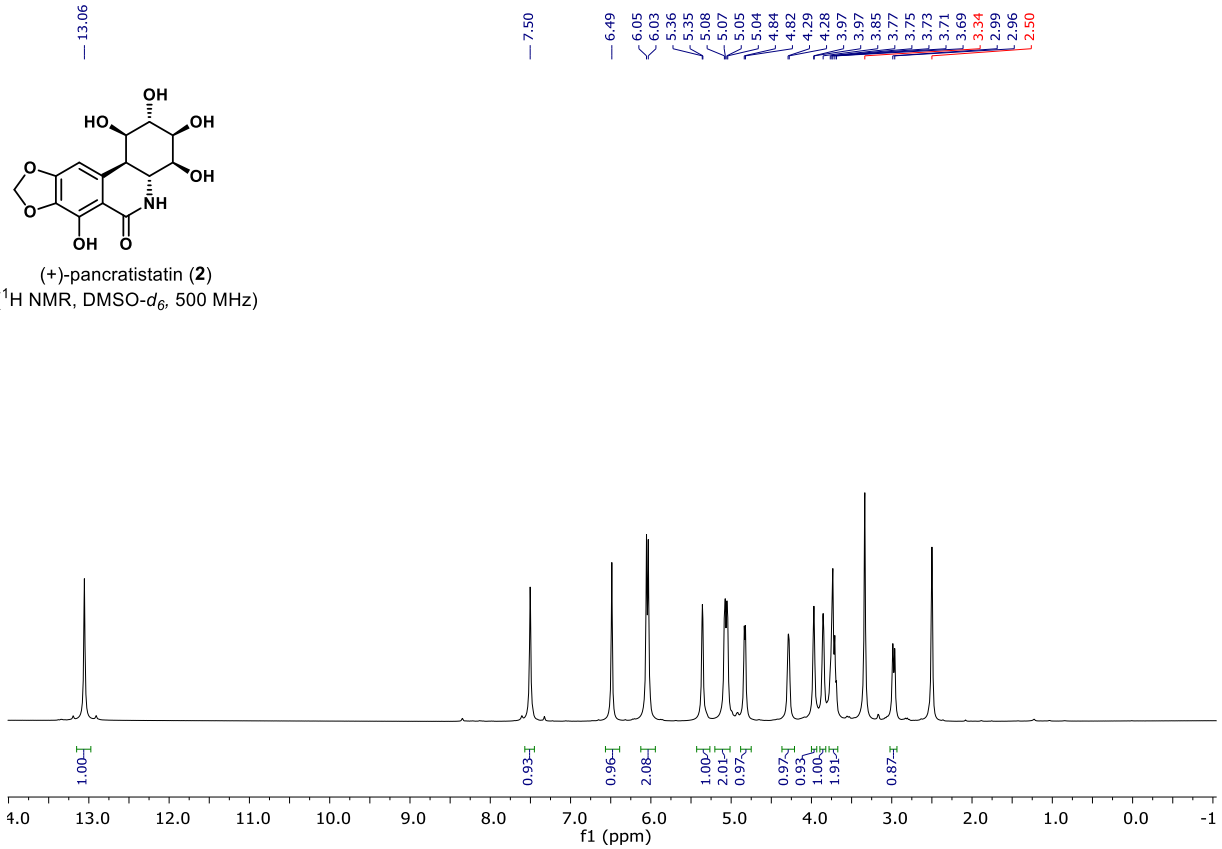
($^{13}$C NMR, $CDCl_3$, 126 MHz)



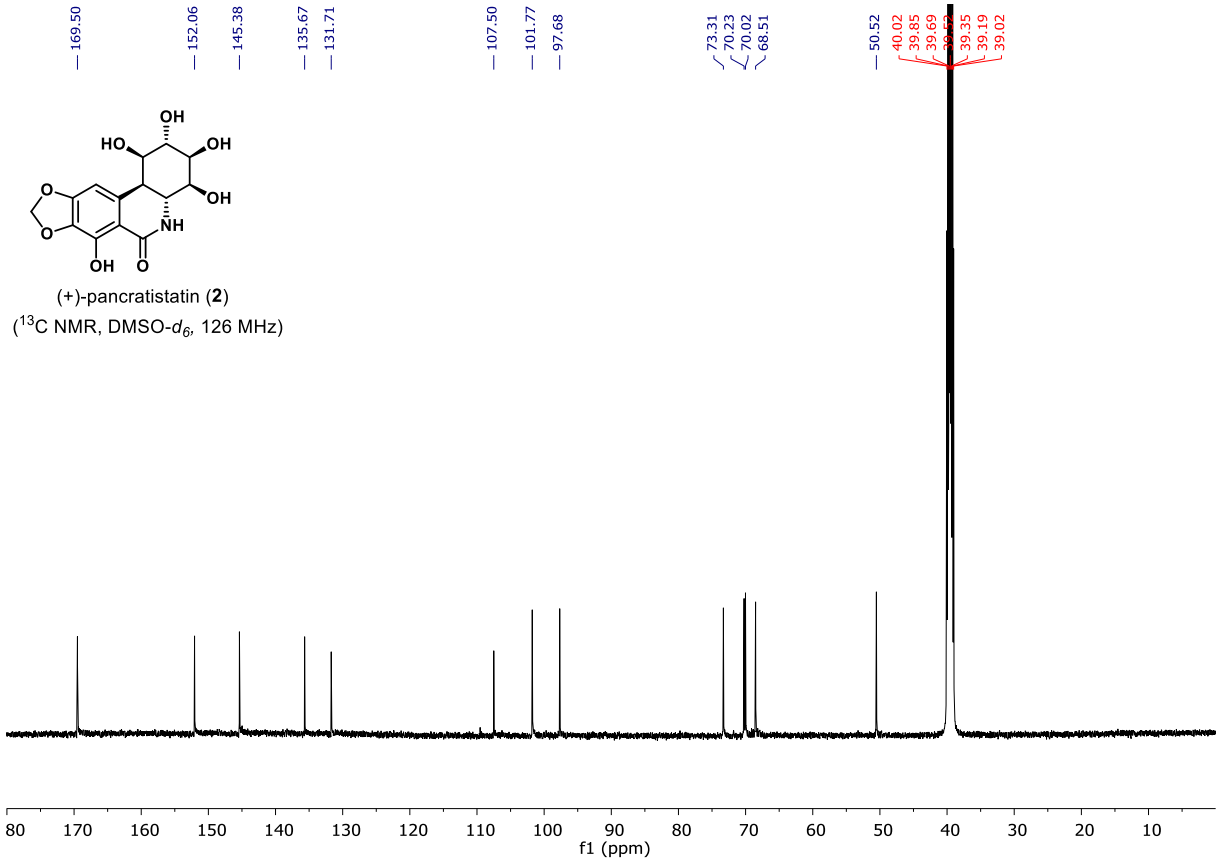

**S4**
($^1$H NMR, $CDCl_3$, 500 MHz)



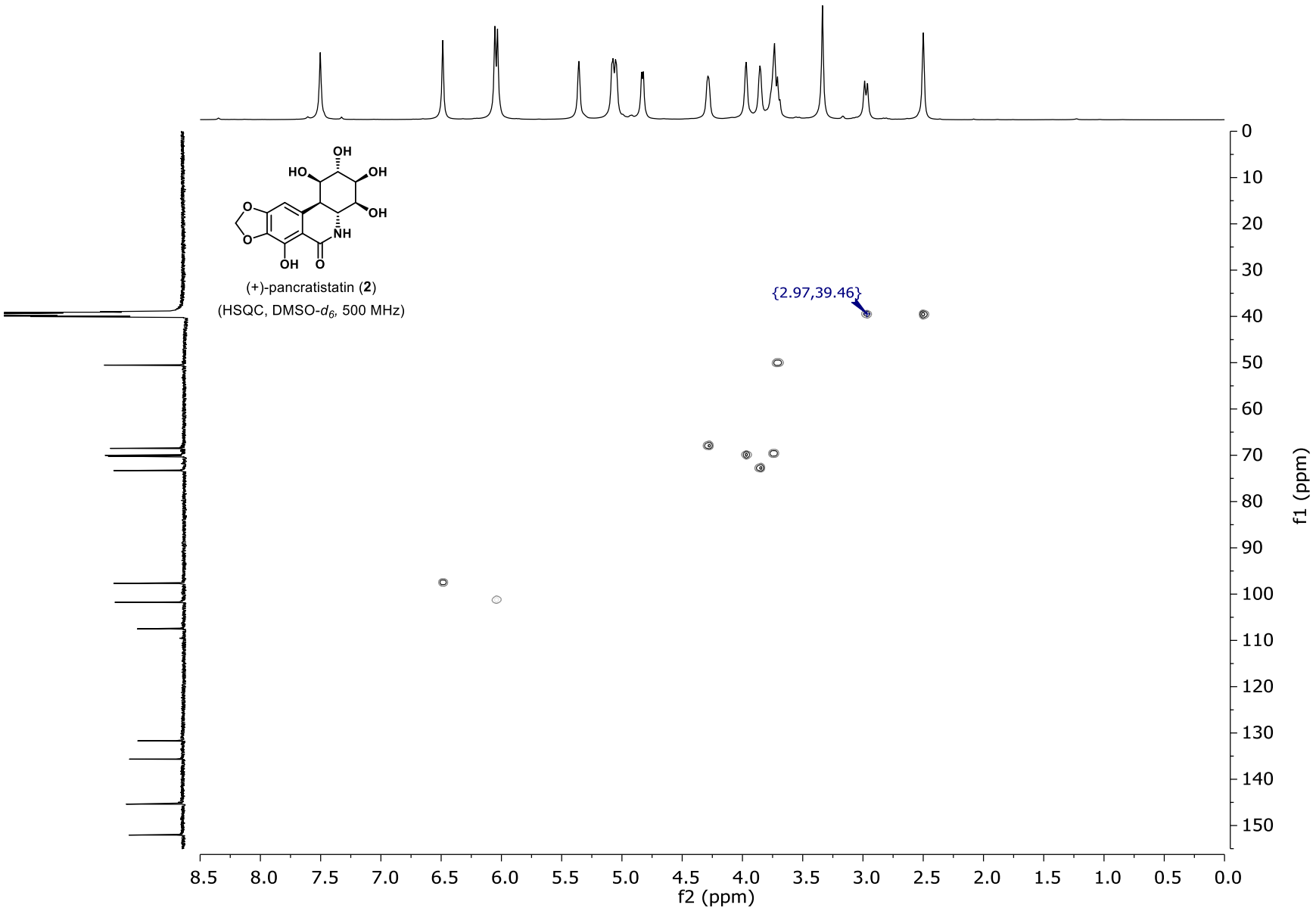

**S4**
($^{13}$C NMR, $CDCl_3$, 126 MHz)

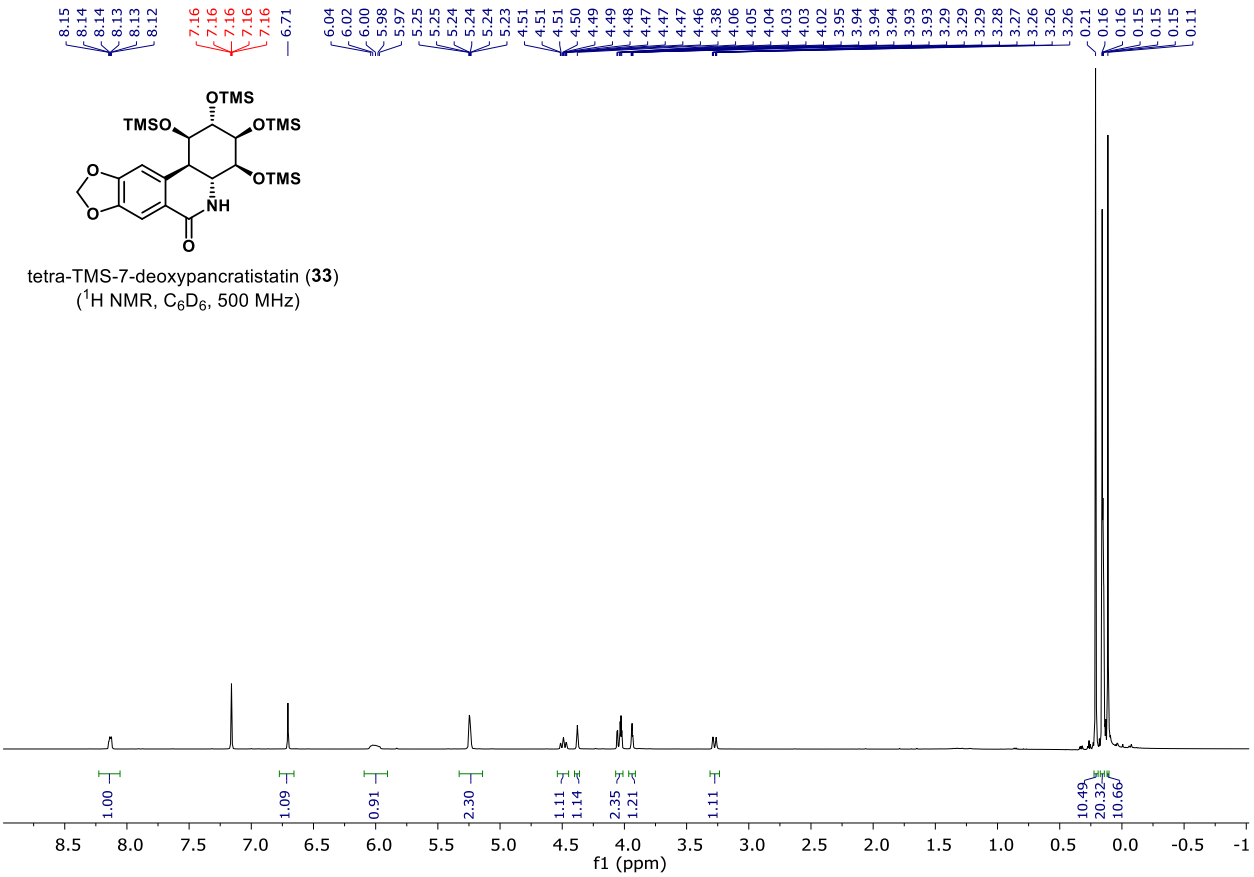



(+)-pancratistatin (**2**)
($^{1}$H NMR, DMSO-$d_6$, 500 MHz)

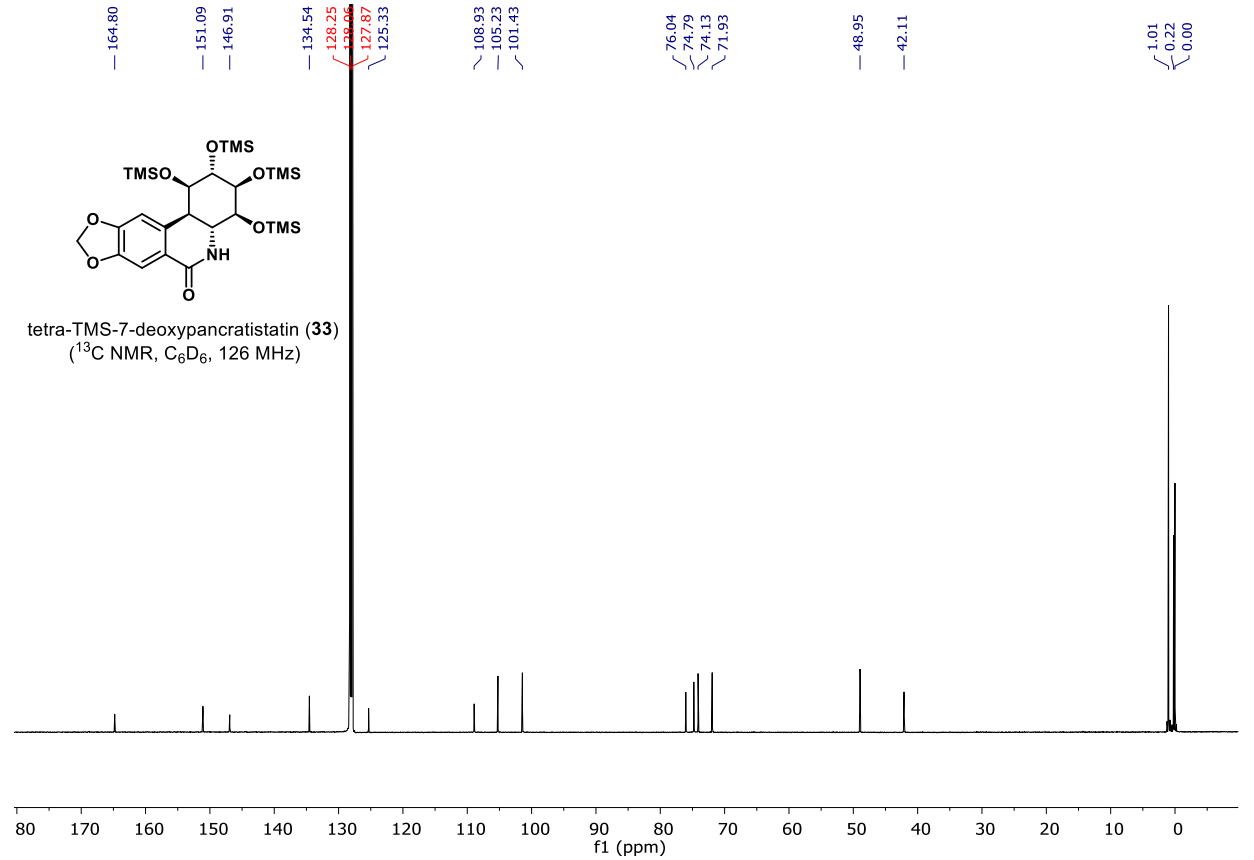



(+)-pancratistatin (**2**)
($^{13}$C NMR, DMSO-$d_6$, 126 MHz)

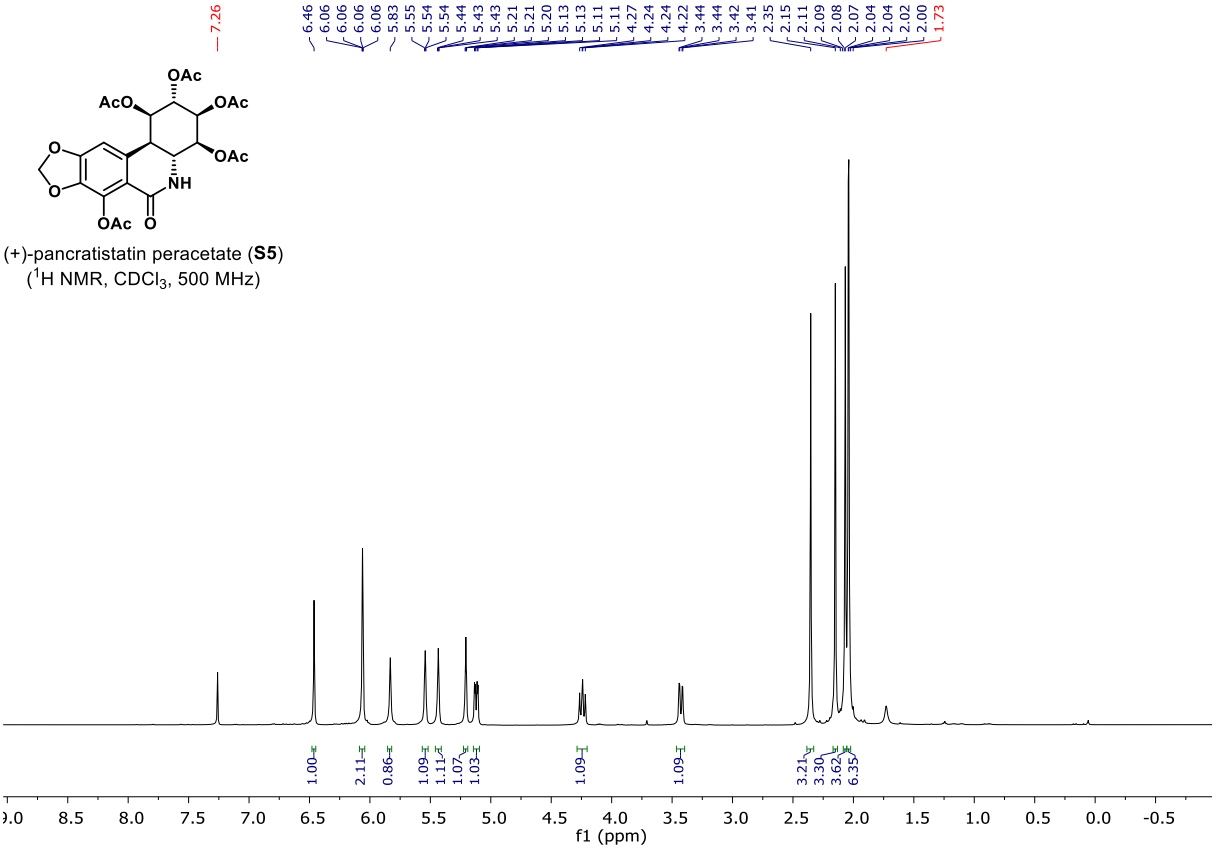

(+)-pancratistatin (2)
(HSQC, DMSO-d6, 500 MHz)
{2.97,39.46}
f2 (ppm)
f1 (ppm)



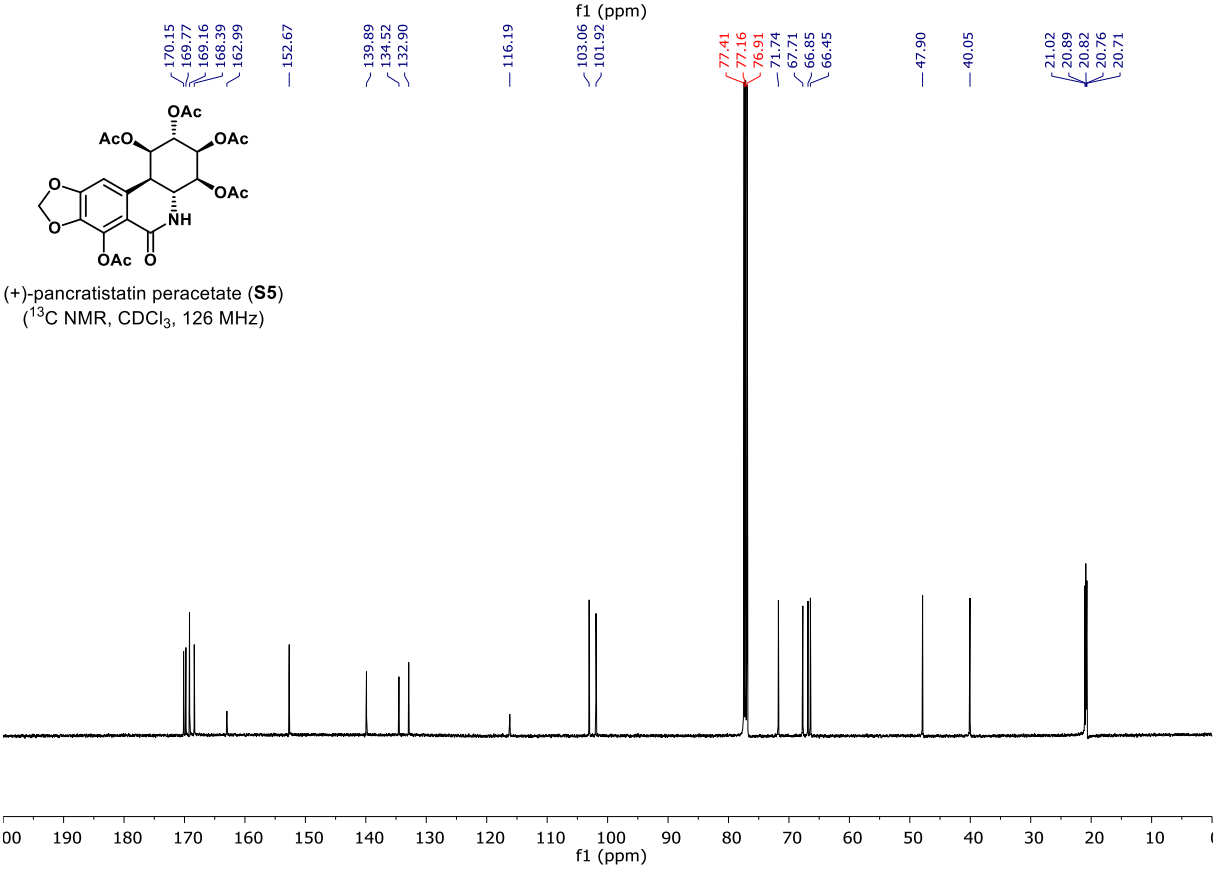

tetra-TMS-7-deoxypancratistatin (**33**)
($^{1}$H NMR, $C_6D_6$, 500 MHz)



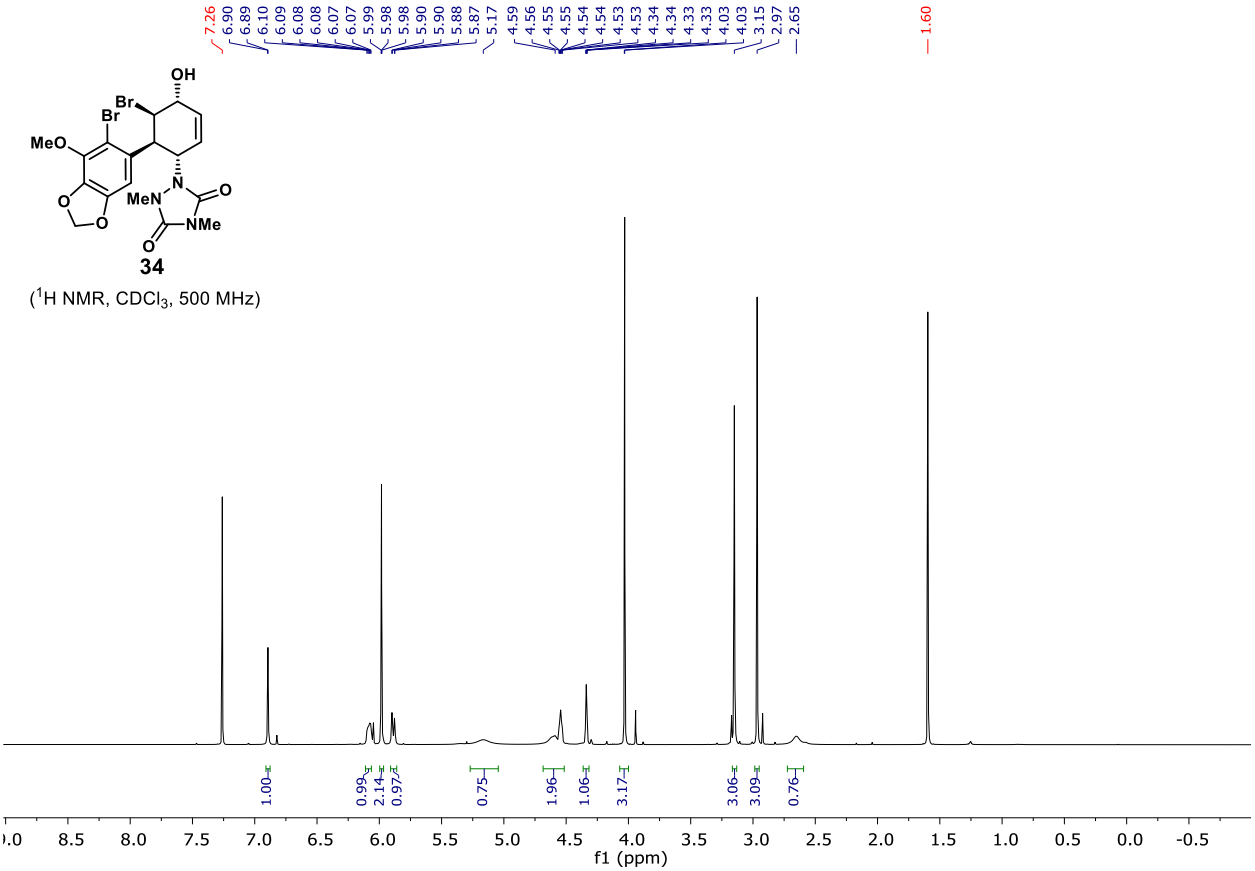

tetra-TMS-7-deoxypancratistatin (**33**)
($^{13}$C NMR, $C_6D_6$, 126 MHz)

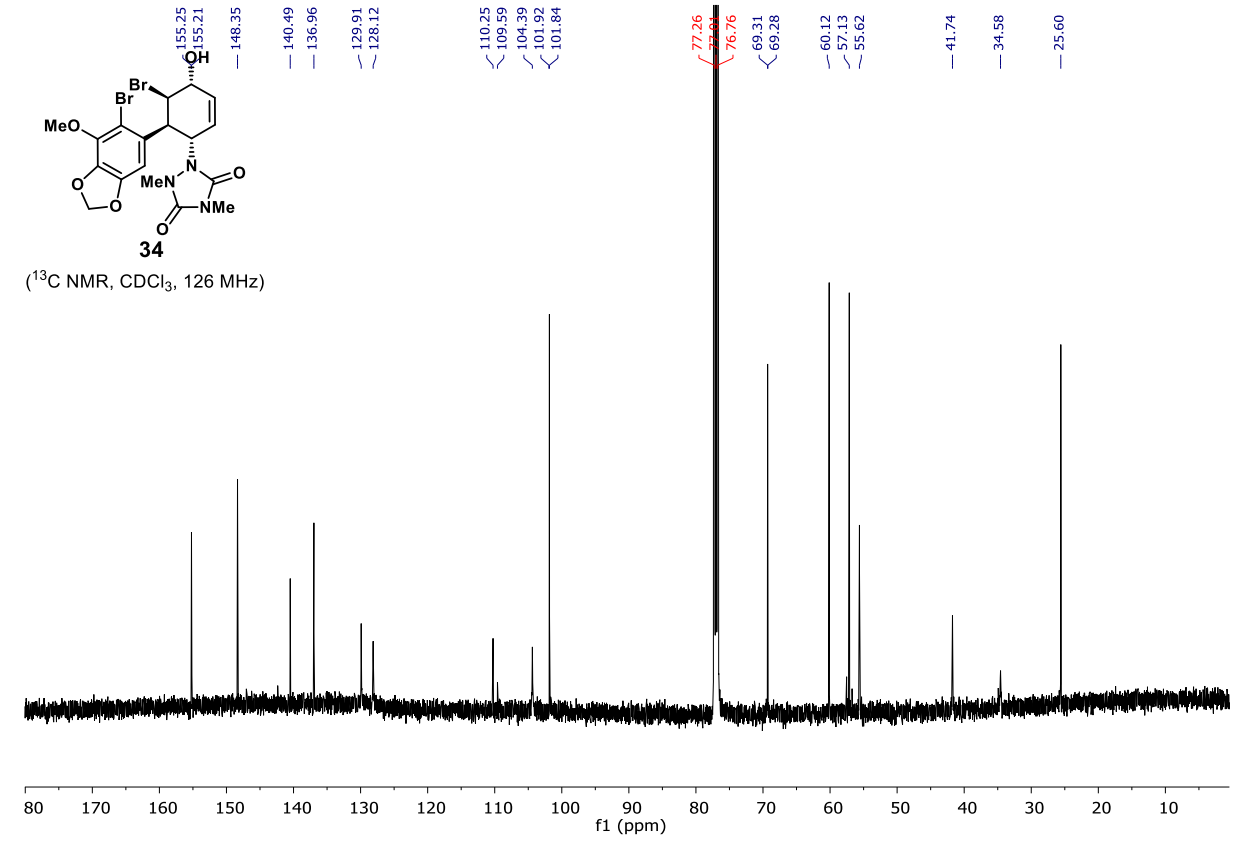


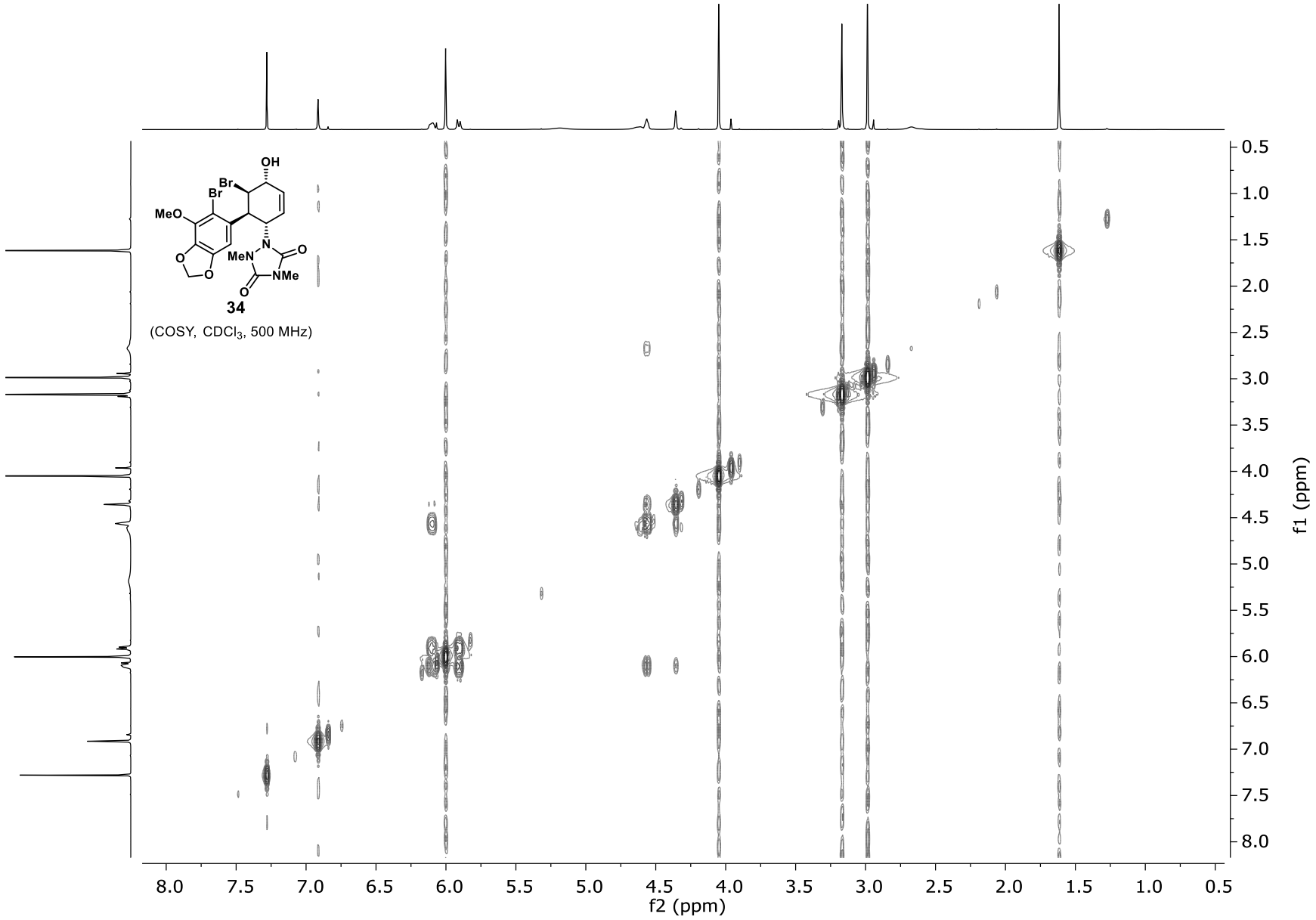

(+)-pancratistatin peracetate (**S5**)
($^{1}$H NMR, $CDCl_3$, 500 MHz)

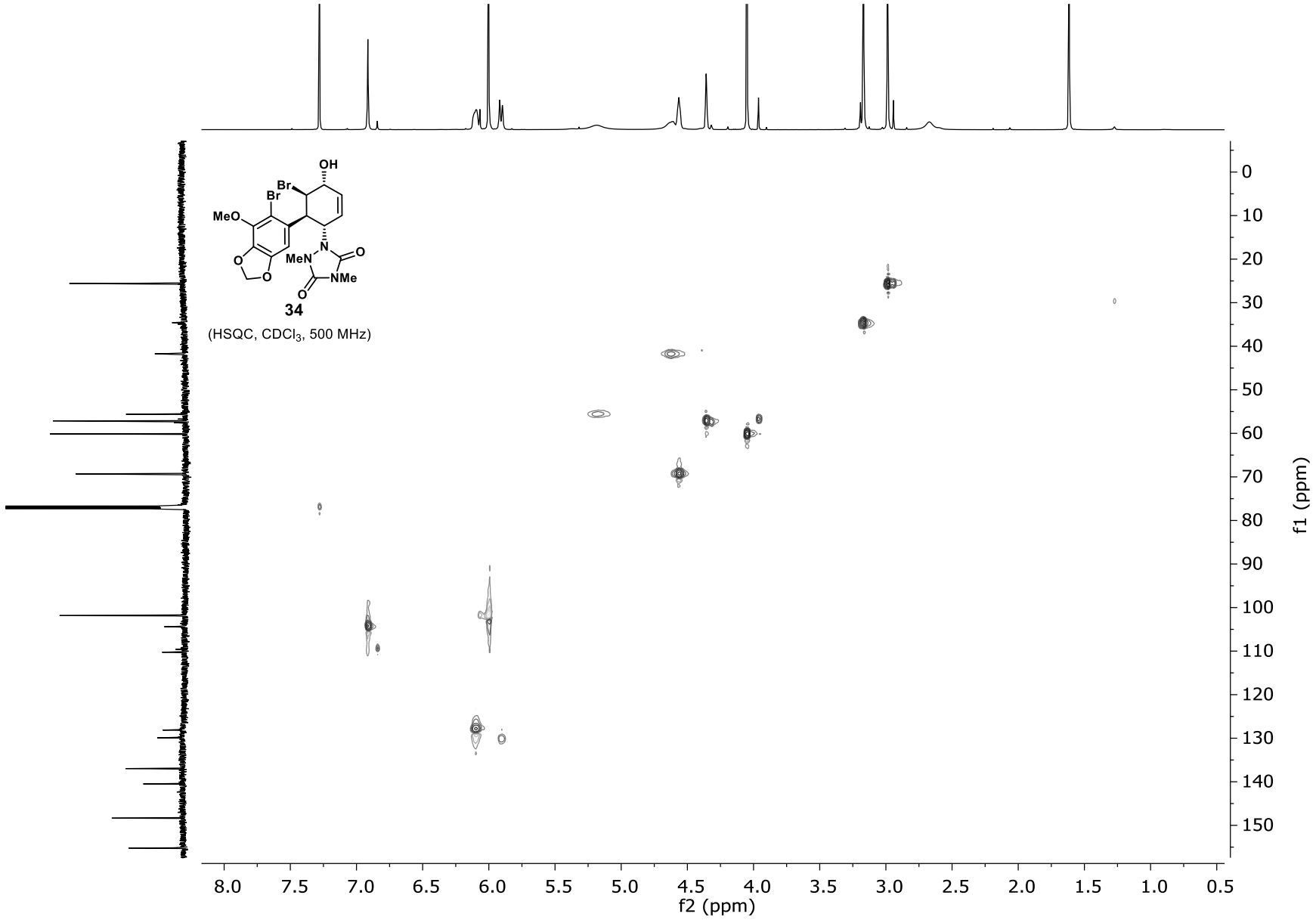


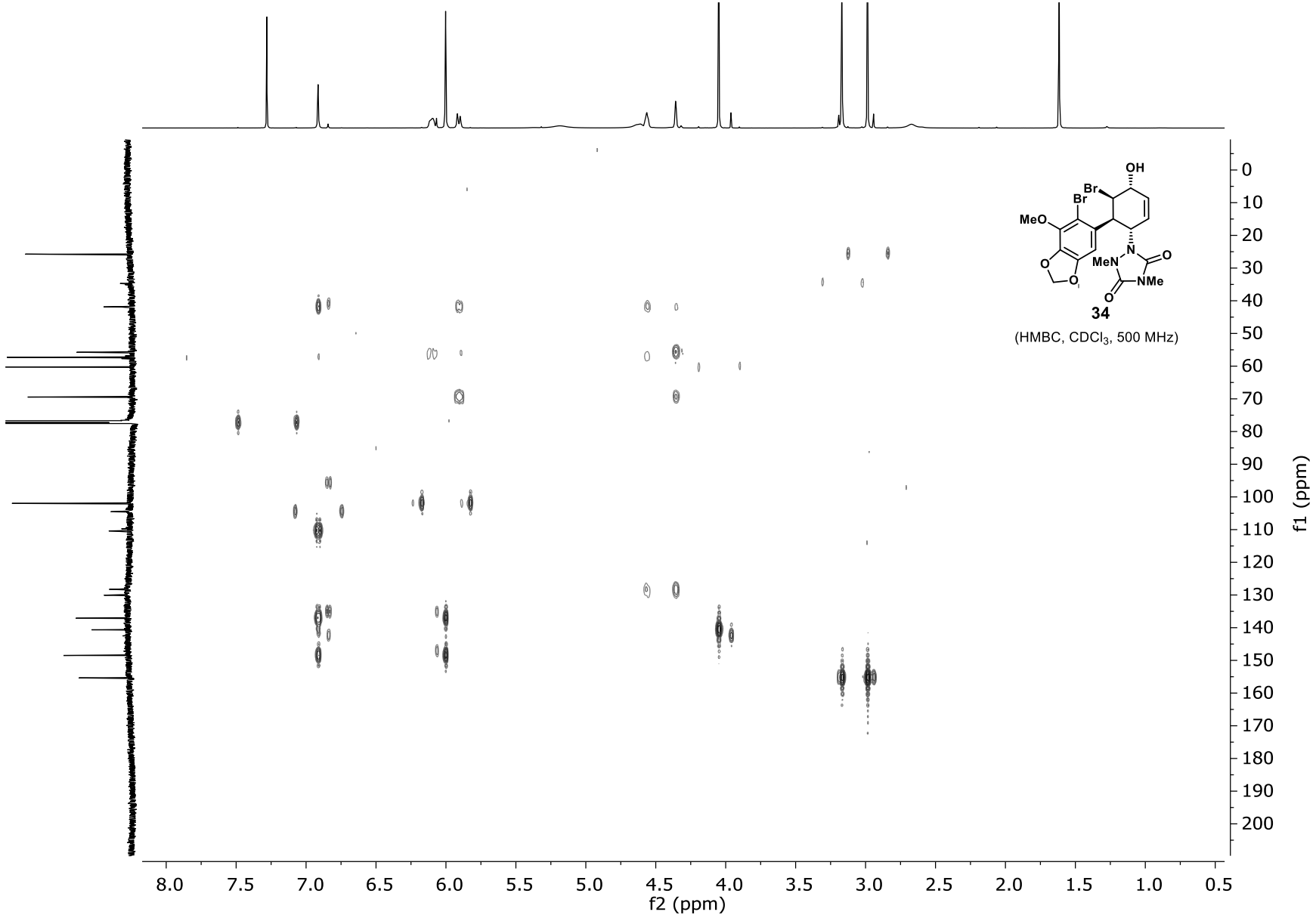

(+)-pancratistatin peracetate (**S5**)
($^{13}$C NMR, $CDCl_3$, 126 MHz)

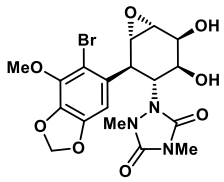

7.26
6.90
6.89
6.10
6.09
6.08
6.08
6.07
6.07
6.07
5.99
5.98
5.98
5.90
5.90
5.90
5.88
5.87
5.17
4.59
4.56
4.55
4.55
4.54
4.54
4.53
4.53
4.34
4.34
4.33
4.33
4.03
4.03
3.15
2.97
2.65
1.60
OH
Br
Br
MeO
MeN
NMe
O
O
O
O
O
34
(1H NMR, CDCl3, 500 MHz)
1.00
0.99
2.14
0.97
0.75
1.96
1.06
3.17
3.06
3.09
0.76
f1 (ppm)


155.25
155.21
148.35
140.49
136.96
129.91
128.12
110.25
109.59
104.39
101.92
101.84
77.26
76.76
69.31
69.28
60.12
57.13
55.62
41.74
34.58
25.60
OH
Br
Br
MeO
MeN
NMe
O
O
O
O
O
34
(13C NMR, CDCl3, 126 MHz)
f1 (ppm)


OH
Br
Br
MeO
O
O
MeN
N
O
NMe
O
34
(COSY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)


OH
Br
Br
MeO
O
O
MeN
N
O
NMe
O
34
(HSQC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

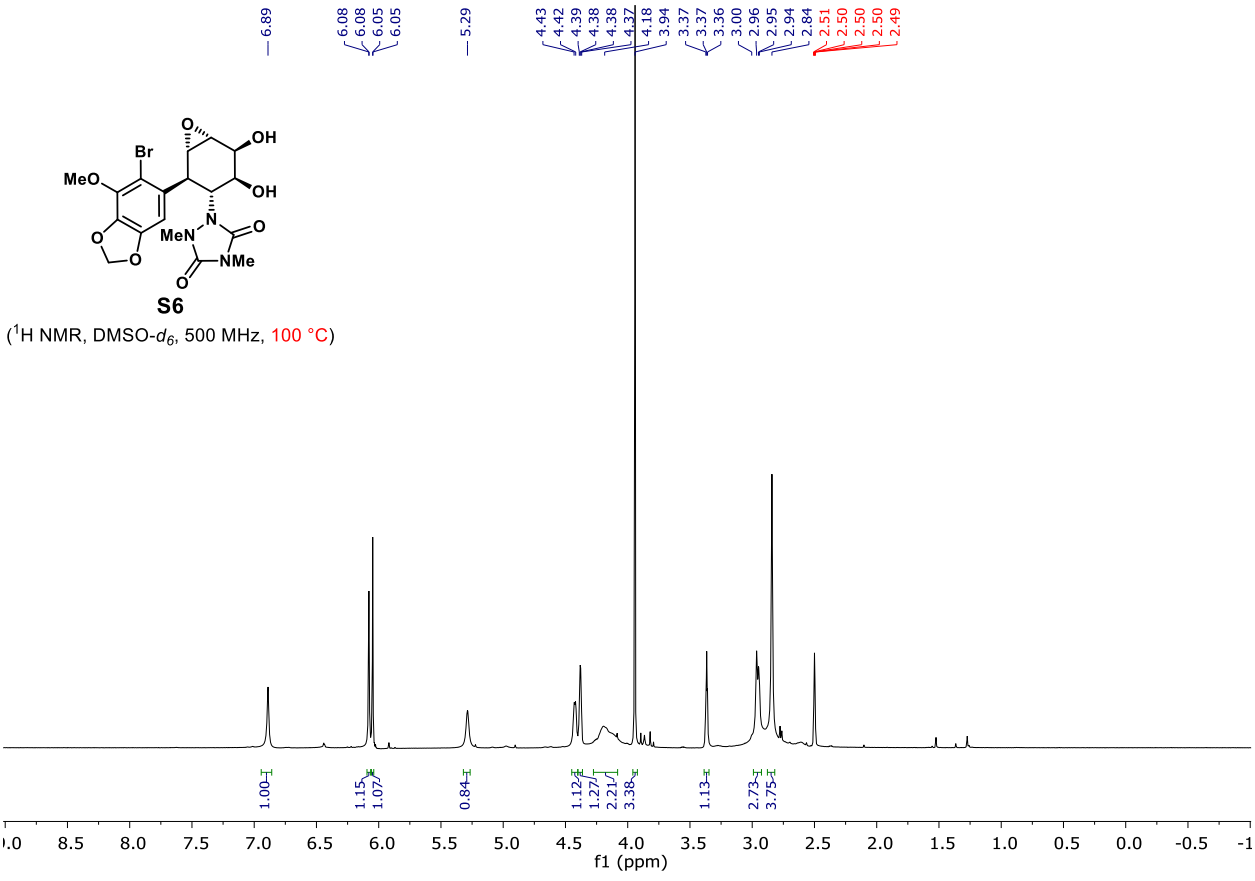

OH
Br
Br
MeO
O
O
MeN
N
O
NMe
O
34
(HMBC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)




**S6**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)



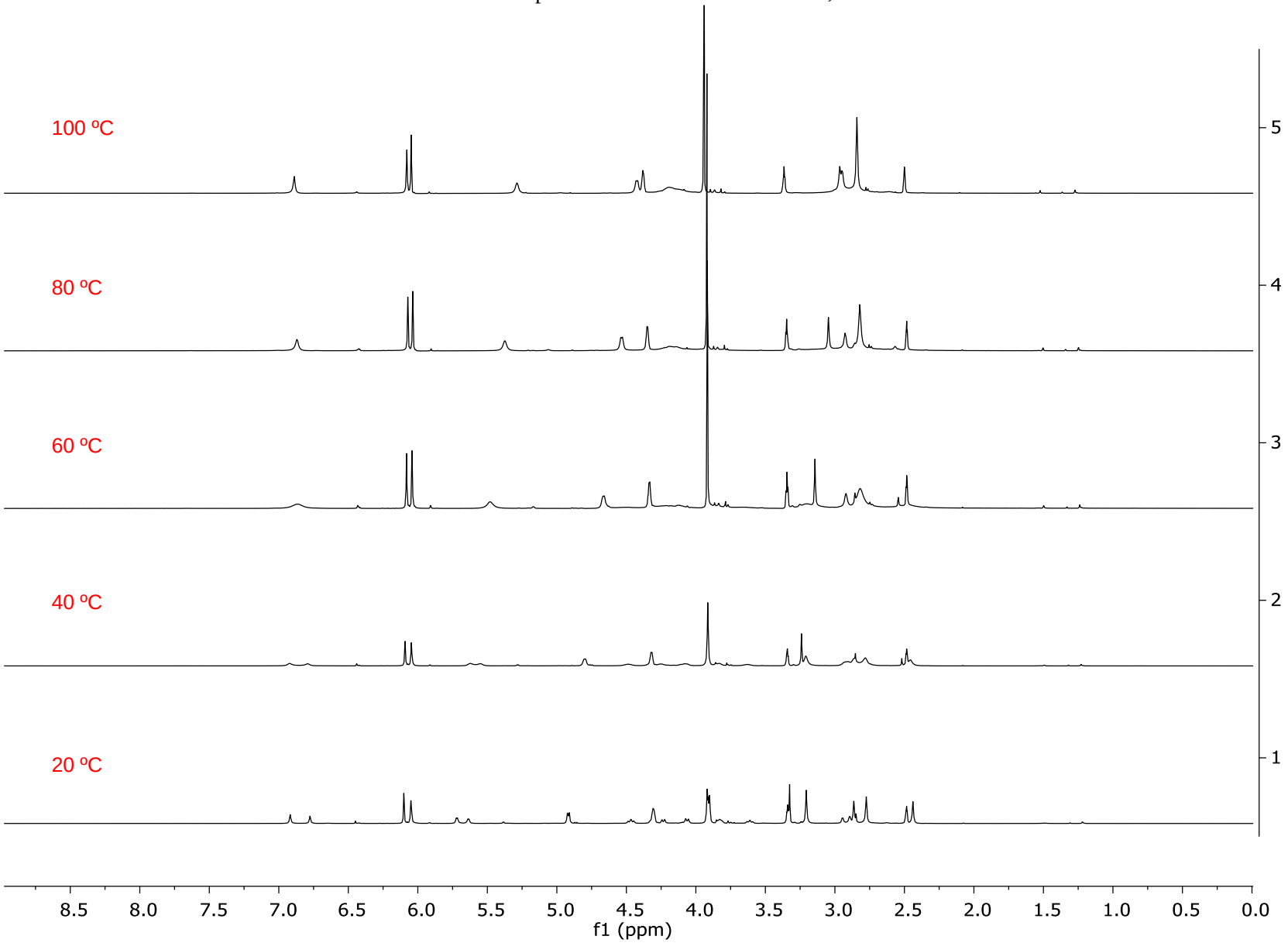


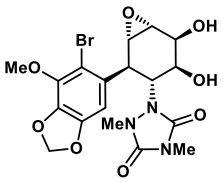


**S6**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **S6** in DMSO, 500 MHz:



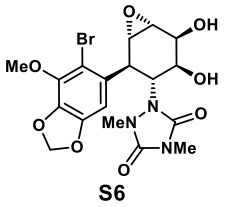



**S6**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)

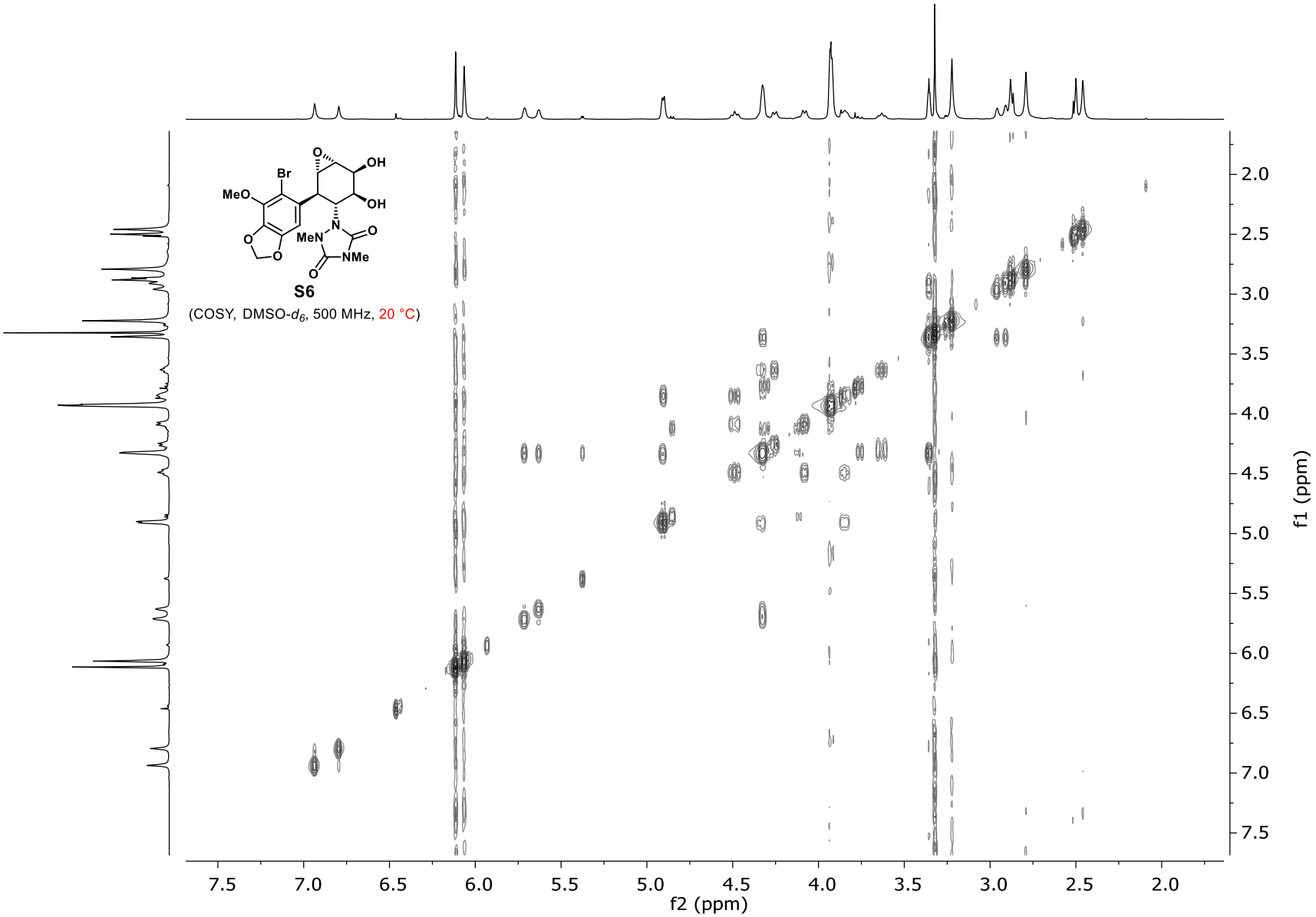


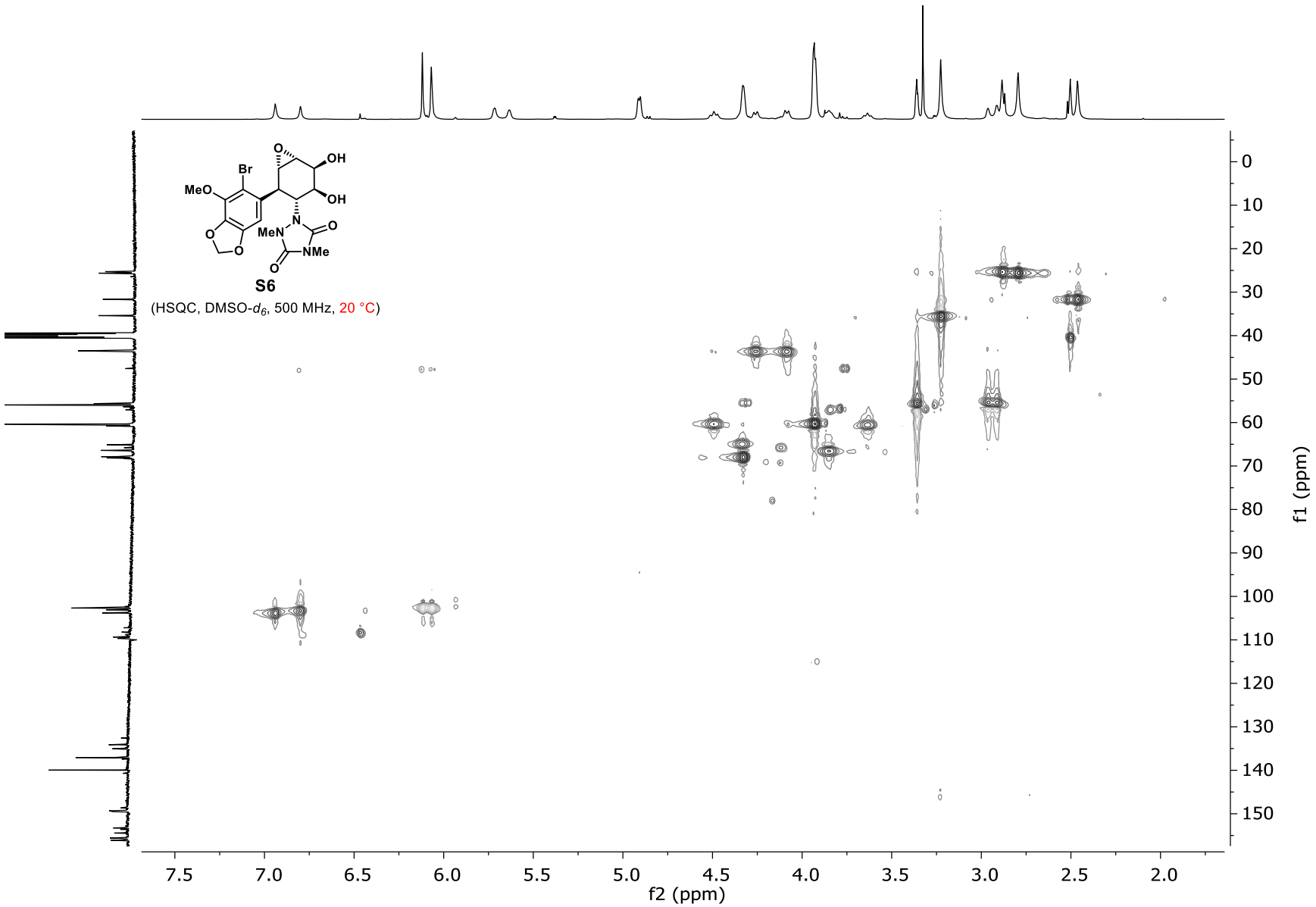

148.48
139.42
136.41
108.82
102.81
101.60
67.26
65.24
59.34
54.95
42.88
40.02
39.85
39.69
39.52
39.35
39.19
39.02
24.34

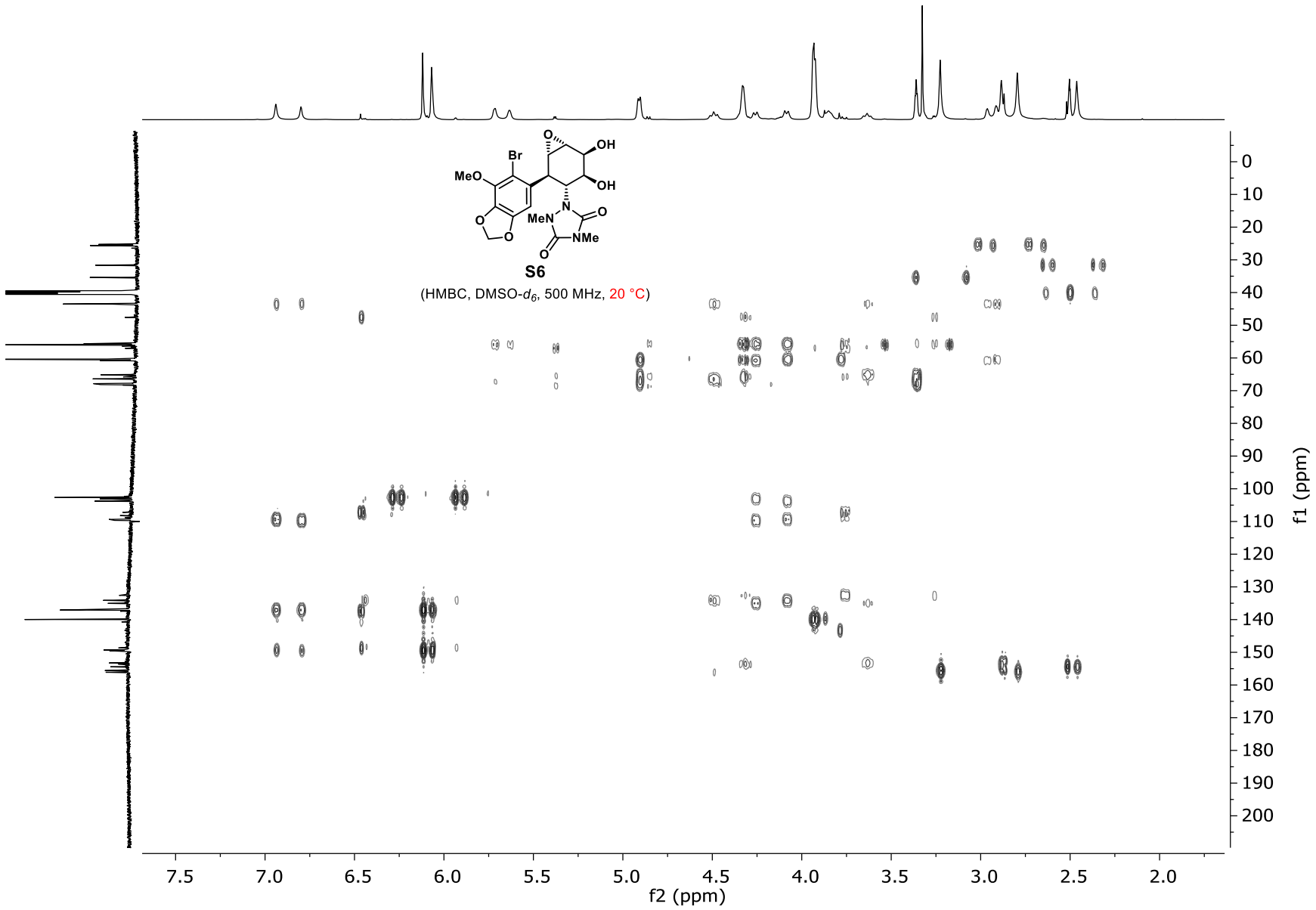


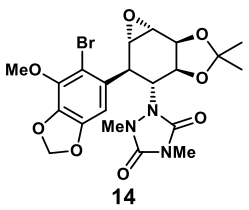

**S6**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)


Br
MeO
OH
OH
O
O
O
N
MeN
NMe
O
O
S6
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
f1 (ppm)


Br
MeO
OH
OH
MeN
NMe
S6
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)

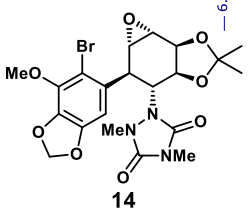

Br
MeO
O
OH
OH
N
MeN
O
NMe
O
O
O
S6
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)




**14**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

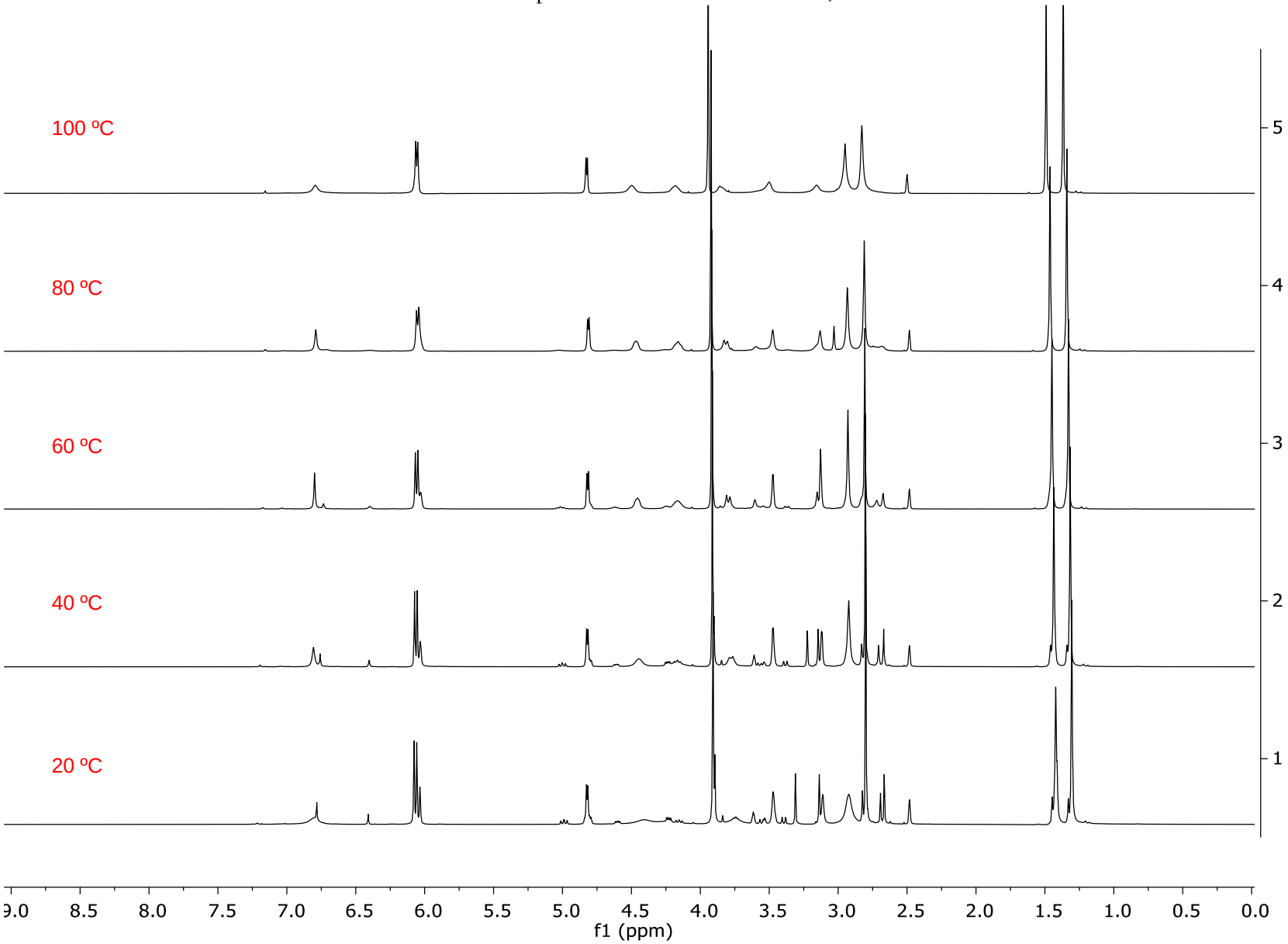


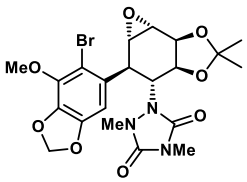




**14**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **14** in DMSO, 500 MHz:

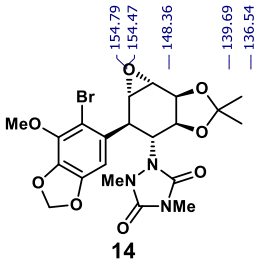





**14**

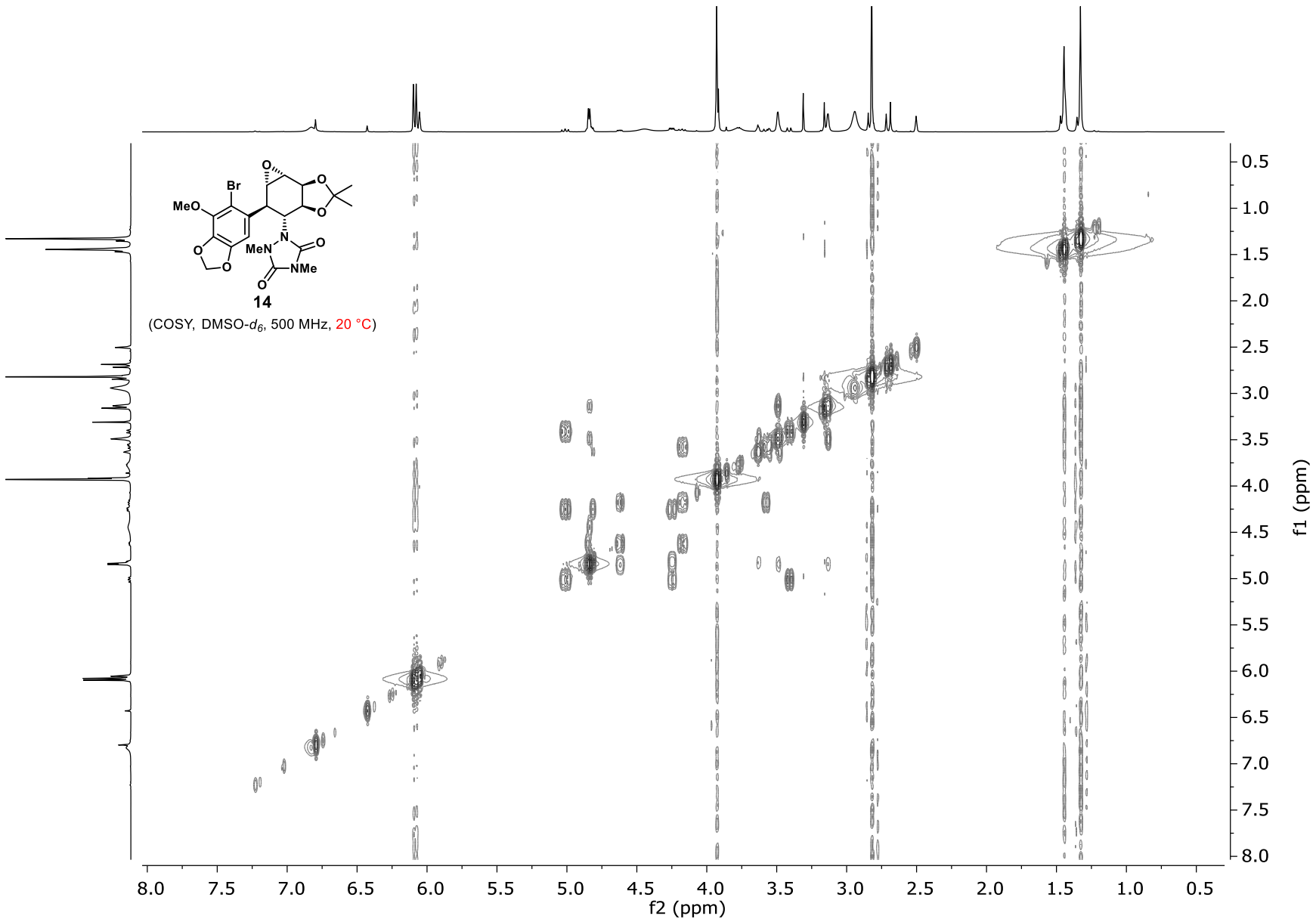
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)

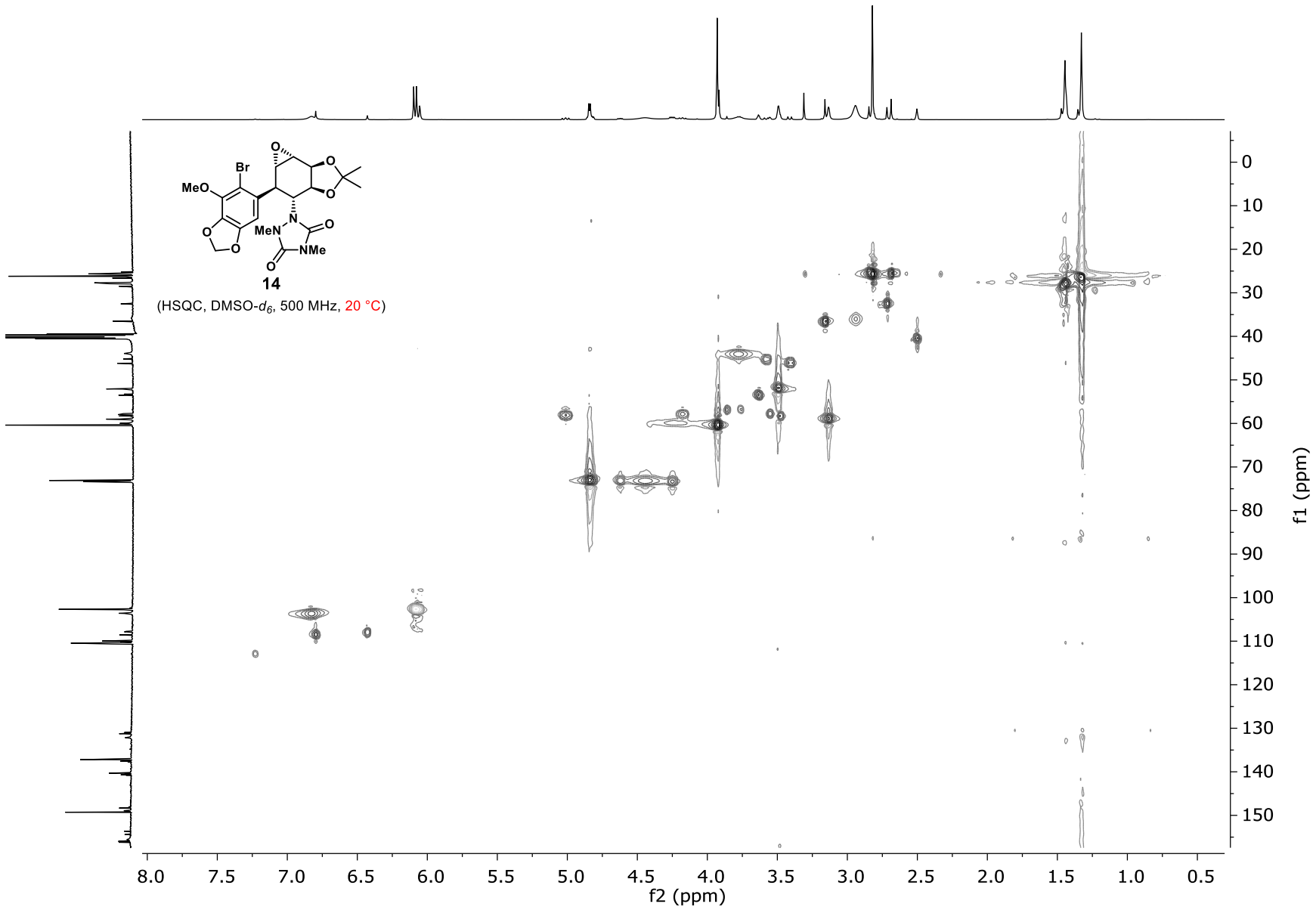


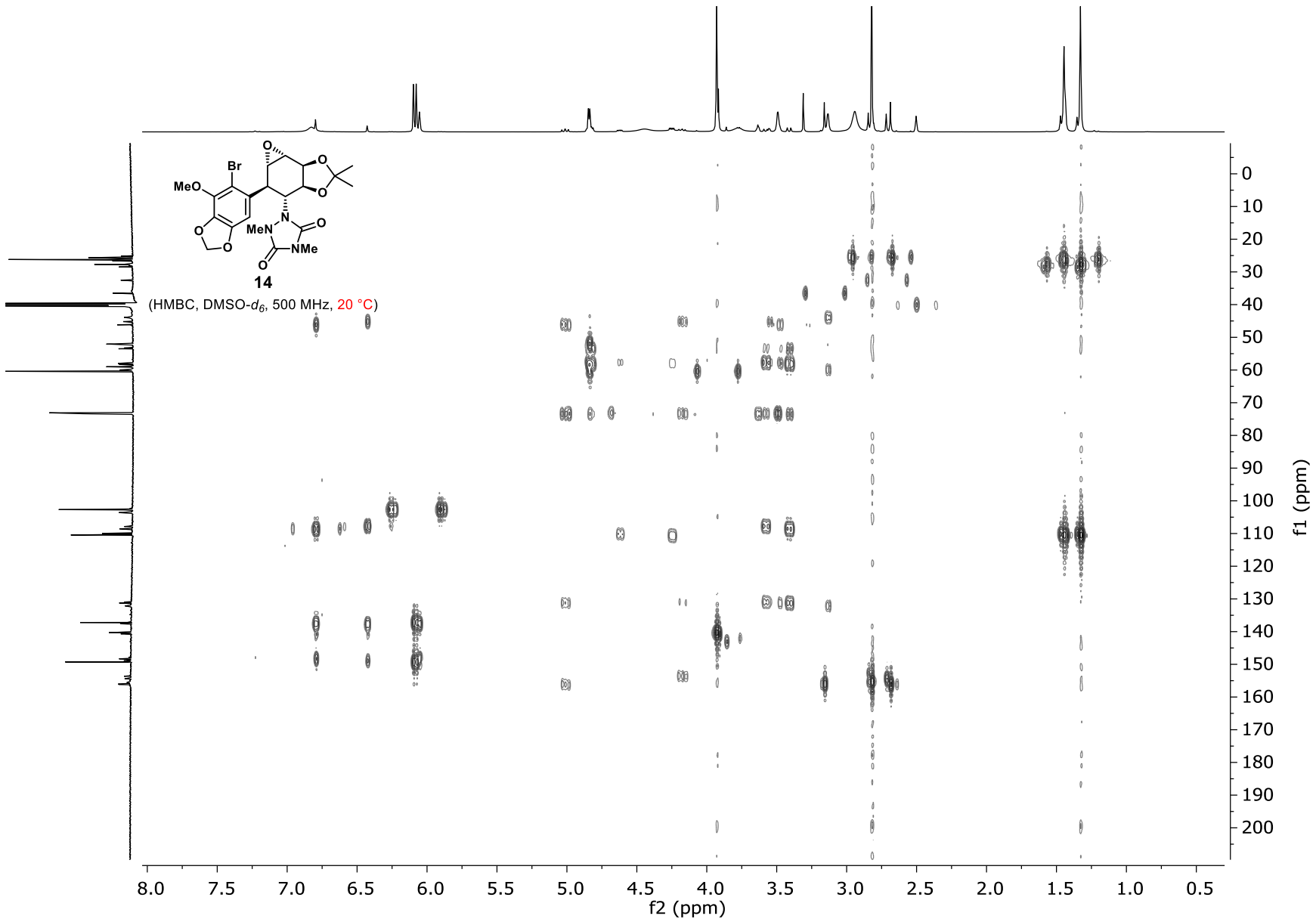



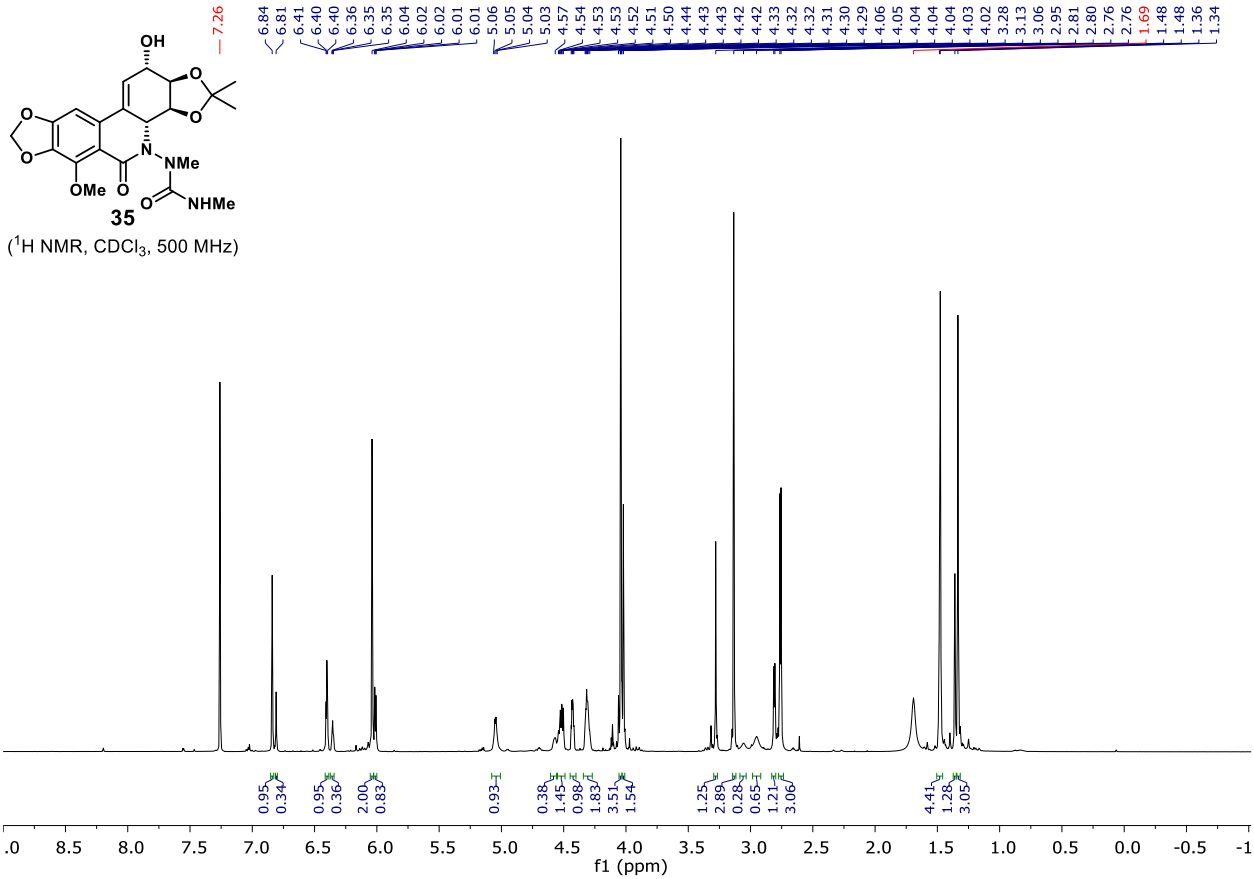

**14**

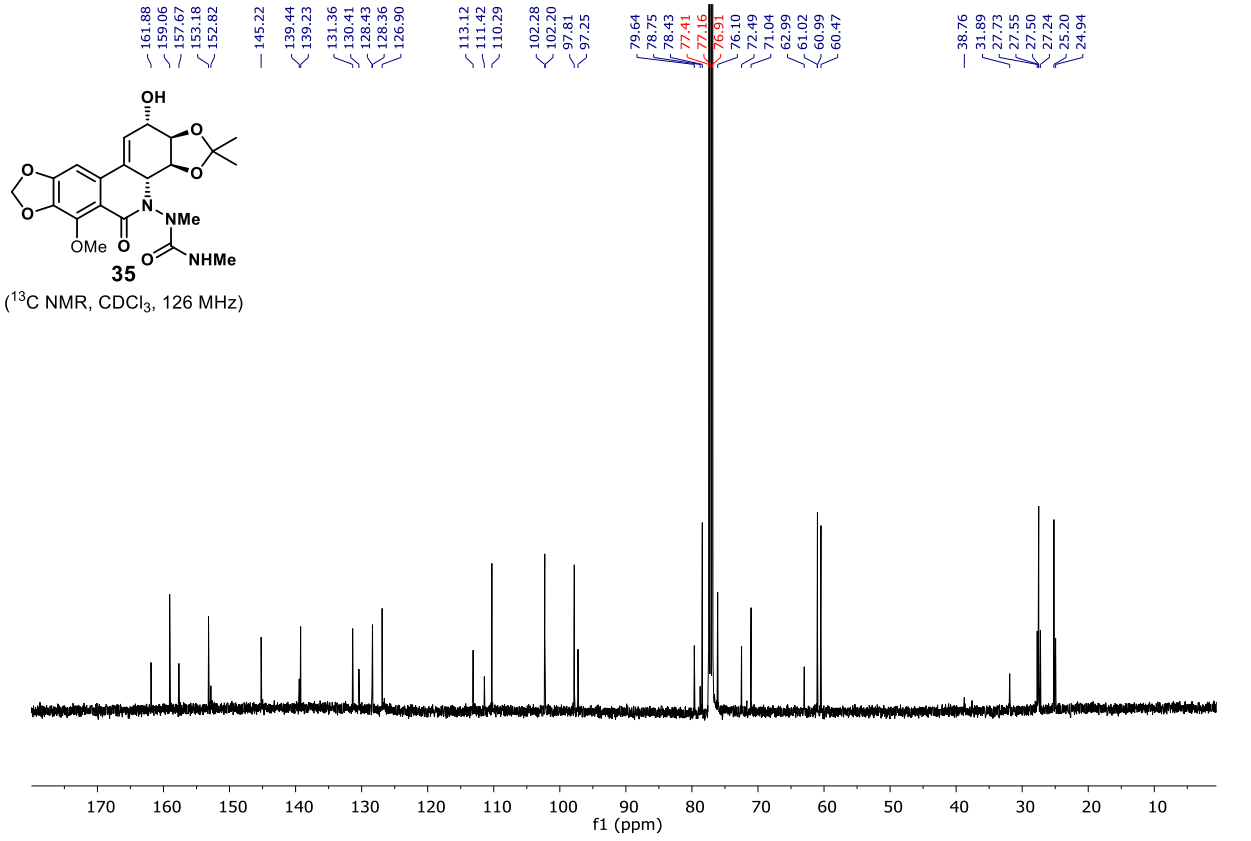
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)

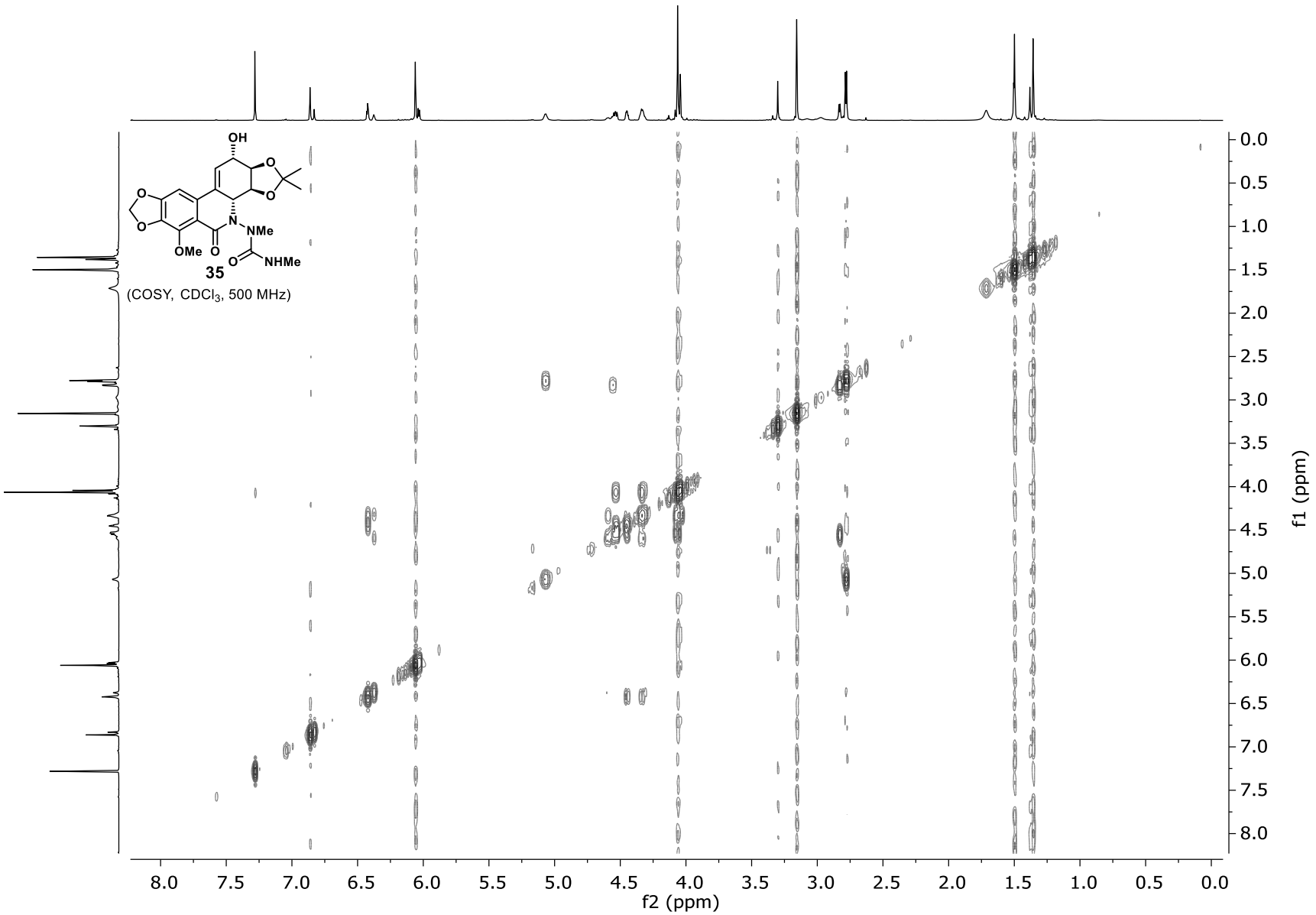

Br
MeO
O
O
O
O
O
MeN
N
O
NMe
O
14
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
f1 (ppm)

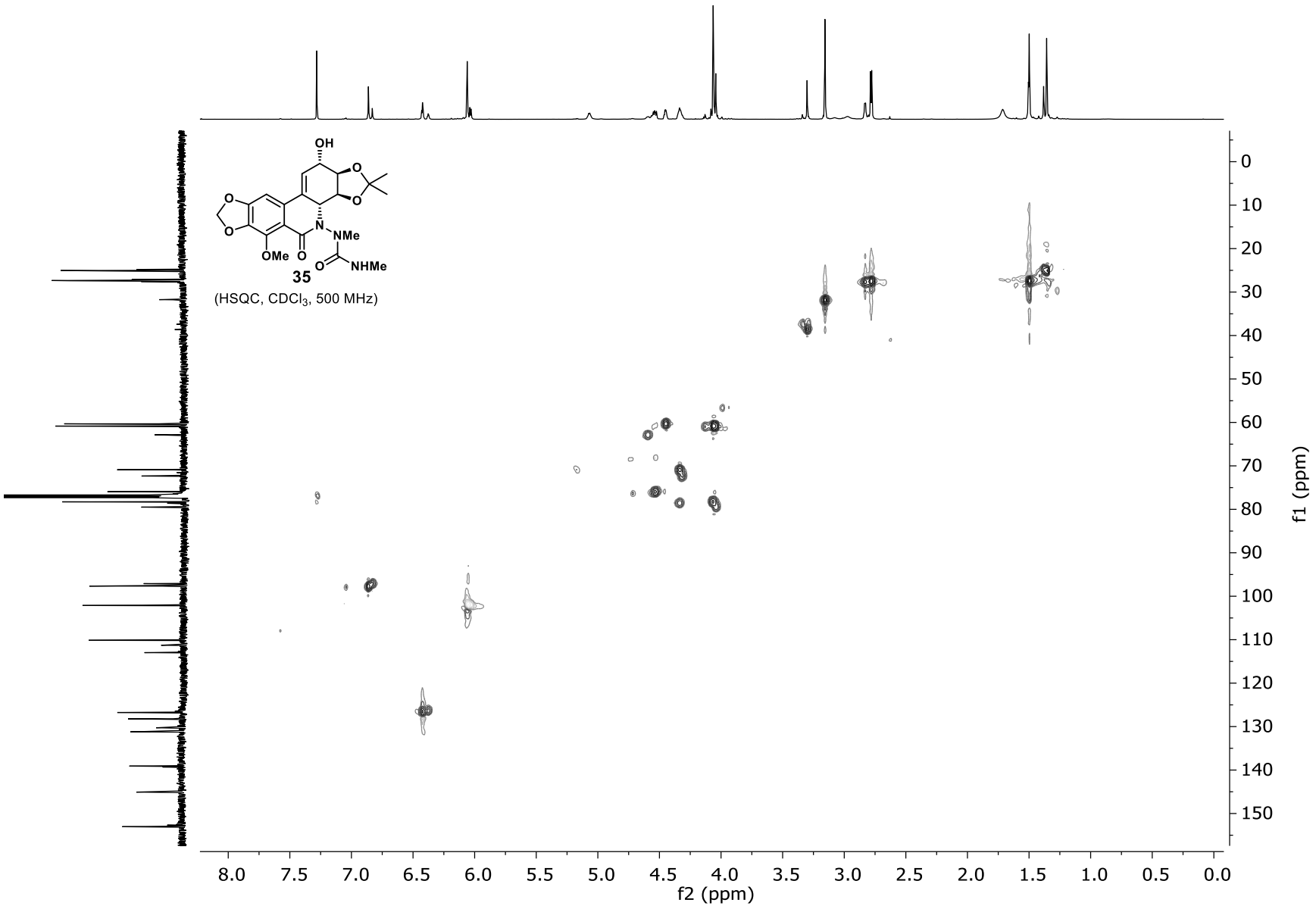

Br
MeO
O
O
O
O
MeN
N
O
NMe
O
14
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

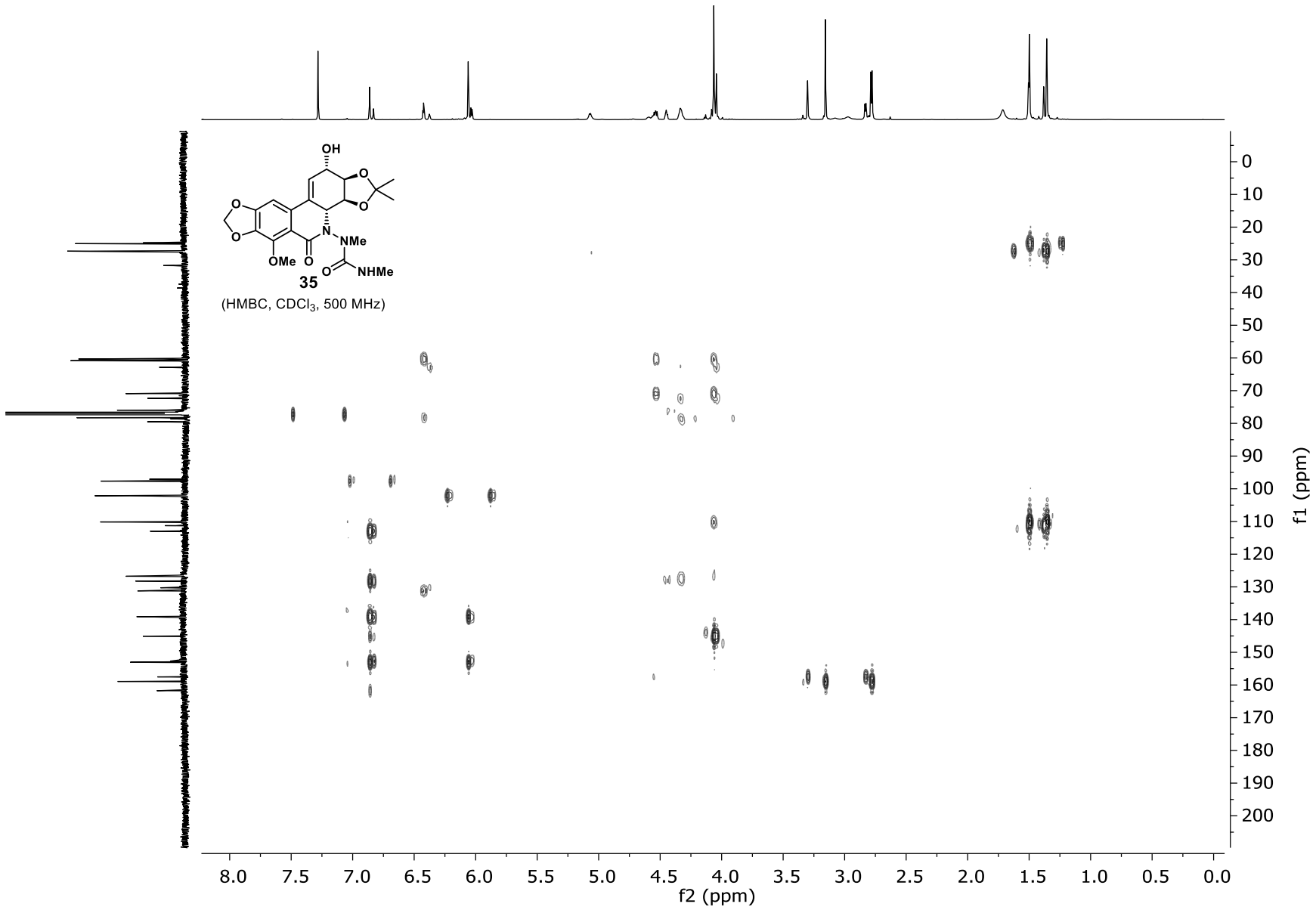

Br
MeO
O
O
O
O
O
MeN
N
O
NMe
O
14
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)

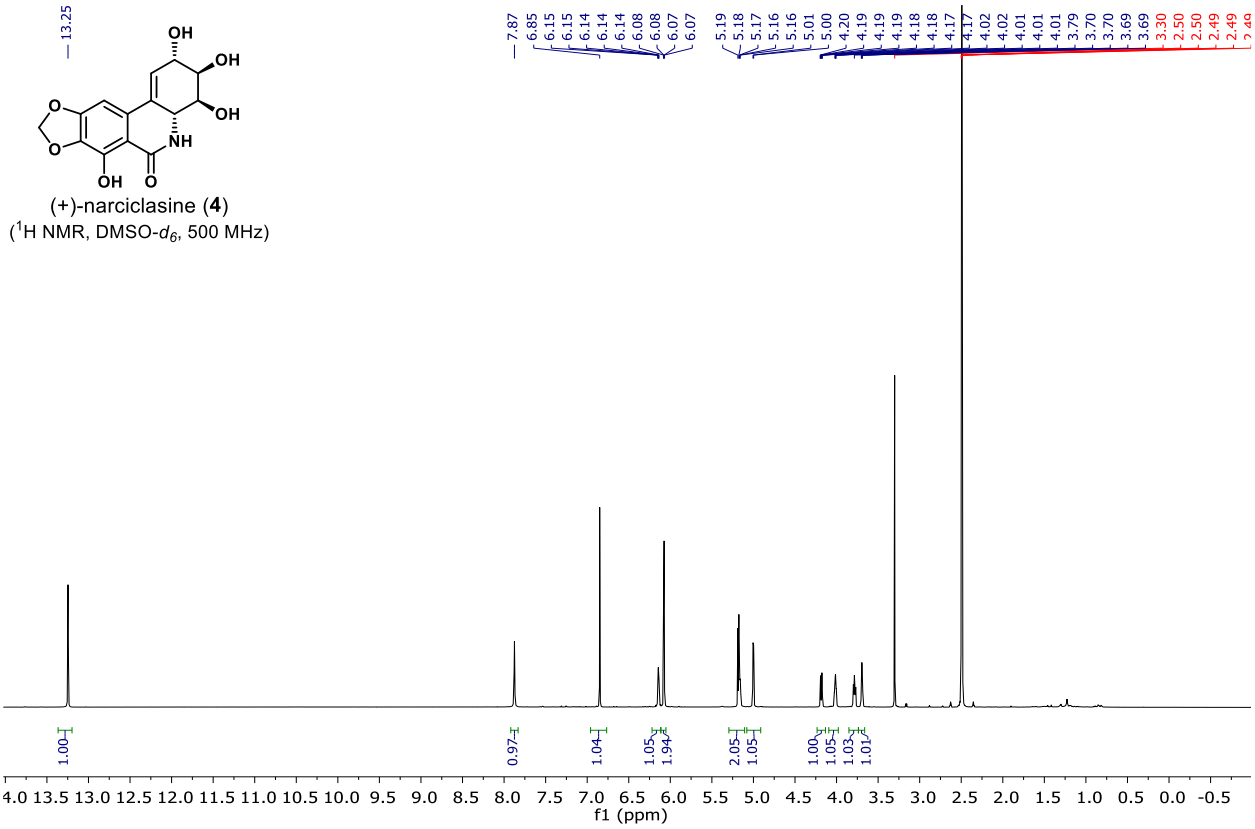

OH
O
O
O
O
N
NMe
OMe
O
O
NHMe
35
($^1$H NMR, $CDCl_3$, 500 MHz)
f1 (ppm)

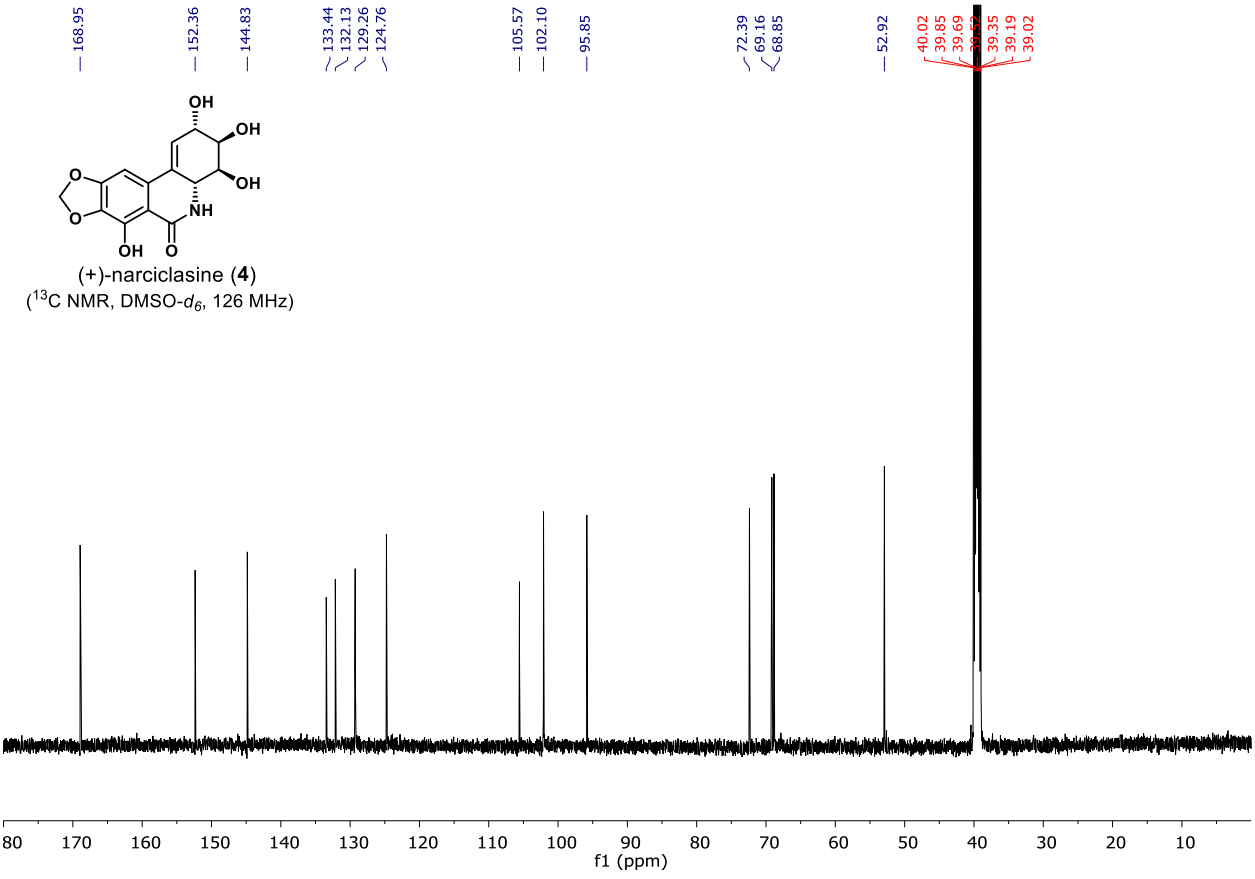

OH
O
O
O
O
N
NMe
OMe
O
O
NHMe
35
($^{13}$C NMR, $CDCl_3$, 126 MHz)
f1 (ppm)

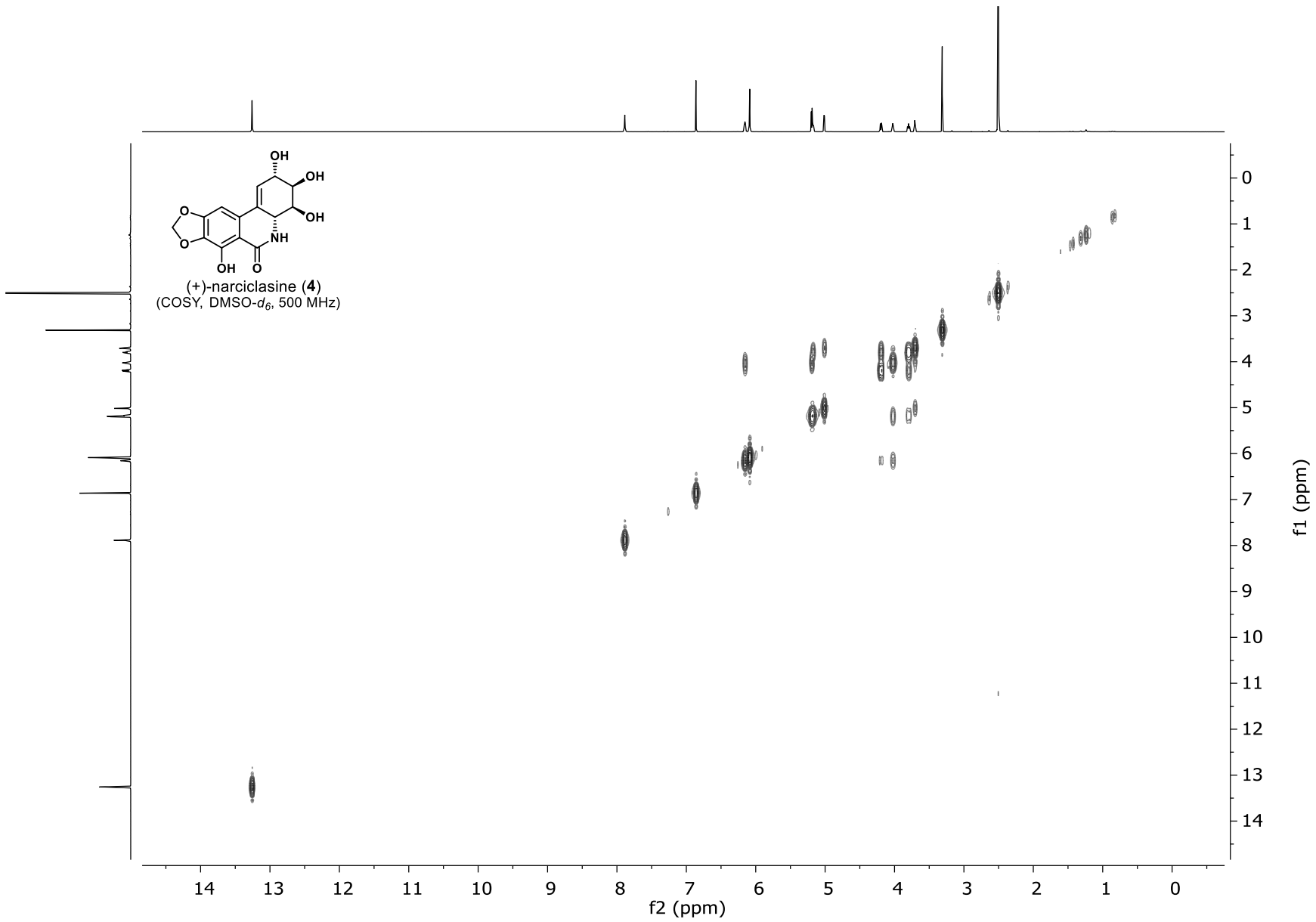

OH
O
O
O
O
N
NMe
OMe
O
O
NHMe
35
(COSY, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

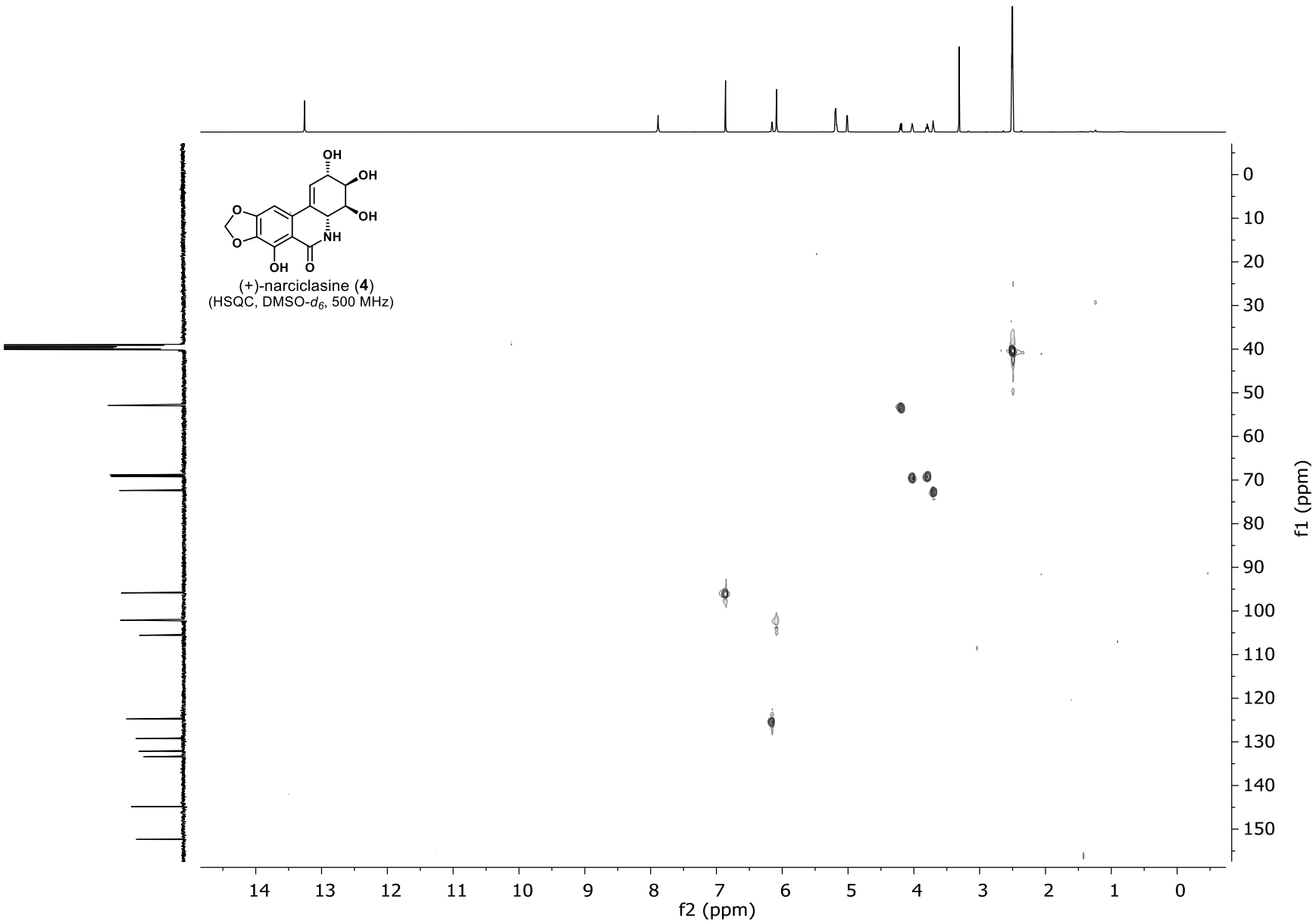

OH
O
O
O
O
N
NMe
OMe
O
O
NHMe
35
(HSQC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

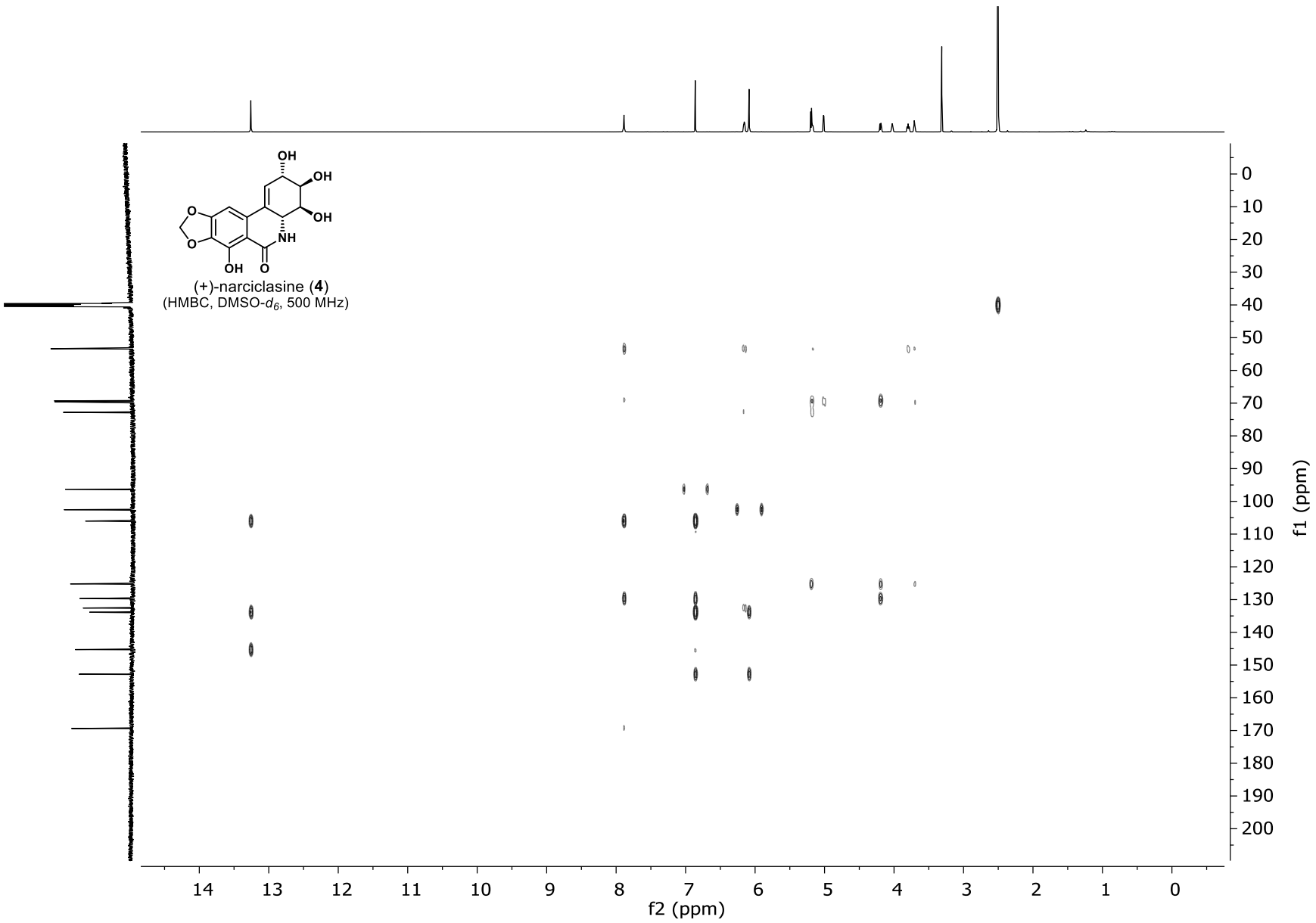

OH
O
O
O
O
N
NMe
OMe
O
O
NHMe
35
(HMBC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)

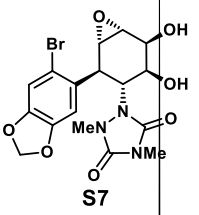

OH
OH
OH
O
O
NH
OH
O
(+)-narciclasine (4)
(1H NMR, DMSO-d6, 500 MHz)
f1 (ppm)


OH
OH
OH
O
O
NH
OH
O
(+)-narciclasine (4)
(13C NMR, DMSO-d6, 126 MHz)
f1 (ppm)


OH
OH
OH
O
O
NH
OH
O
(+)-narciclasine (4)
(COSY, DMSO-d6, 500 MHz)
f2 (ppm)
f1 (ppm)


OH
OH
OH
O
O
NH
OH
O
(+)-narciclasine (4)
(HSQC, DMSO-d6, 500 MHz)
f2 (ppm)
f1 (ppm)

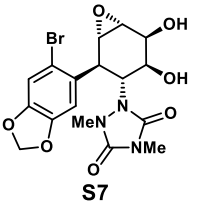

OH
OH
OH
O
O
NH
OH
O
(+)-narciclasine (4)
(HMBC, DMSO-d6, 500 MHz)
f2 (ppm)
f1 (ppm)




**S7**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

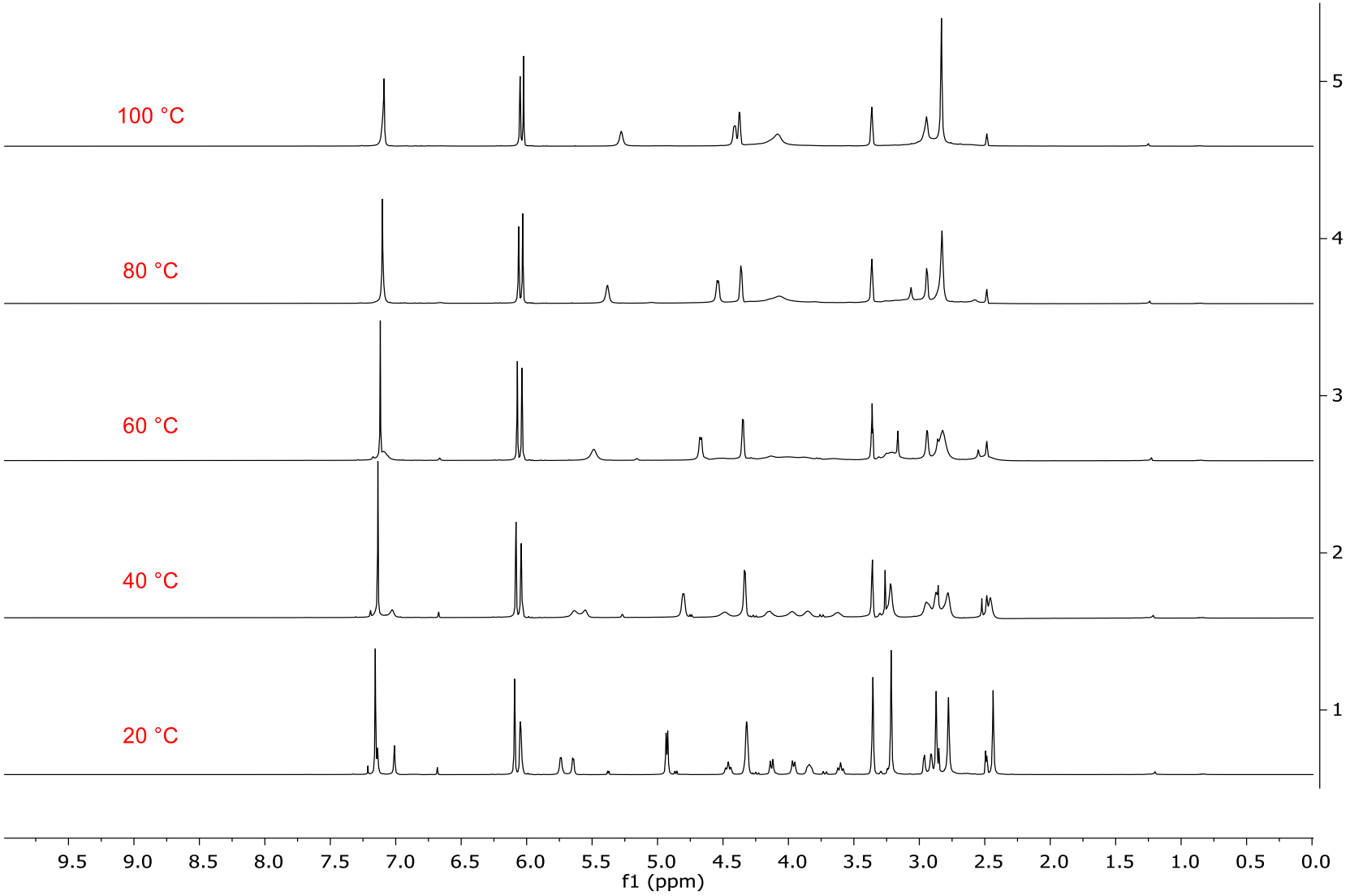


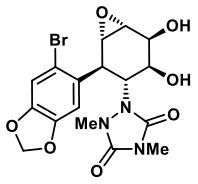




**S7**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H MNR temperature studies of **S7** in DMSO-$d_6$, 500 MHz

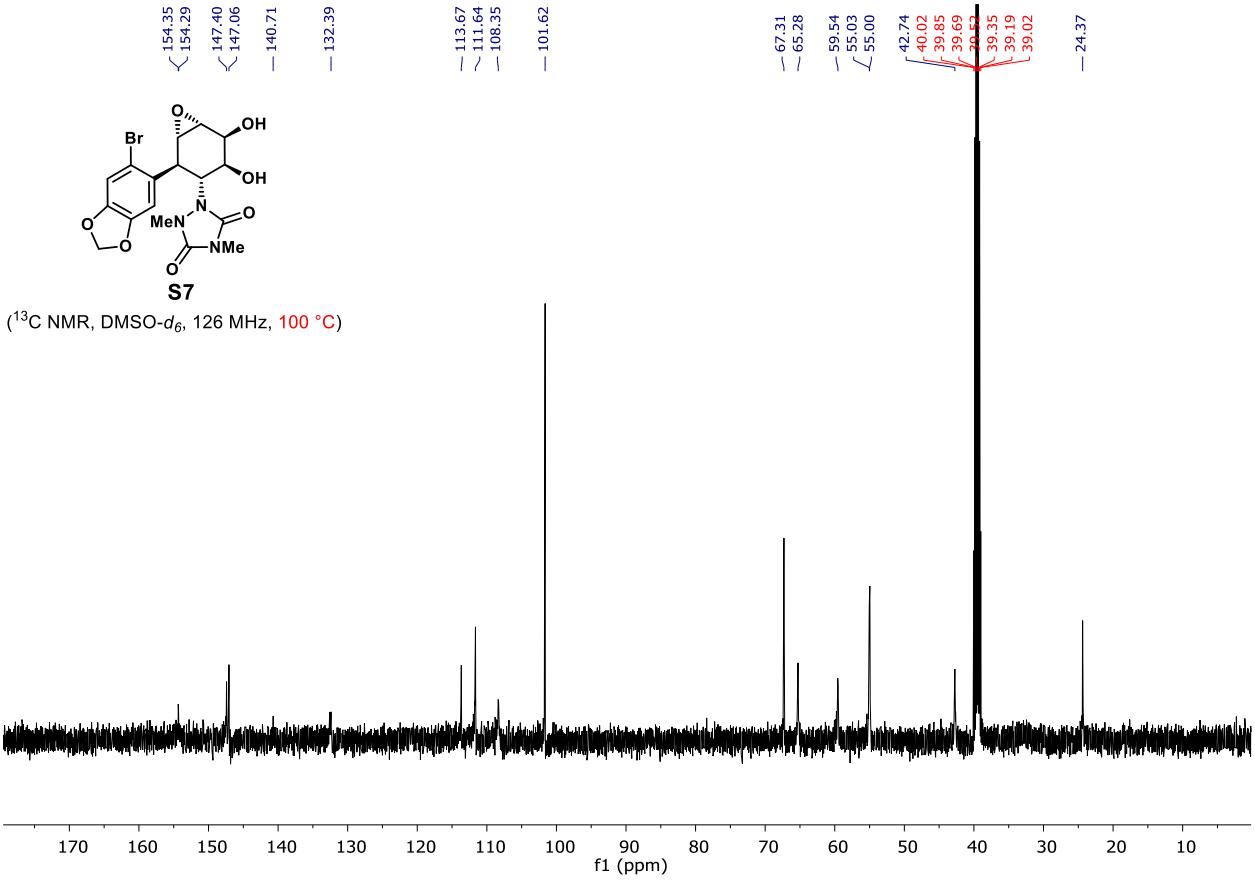





**S7**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)



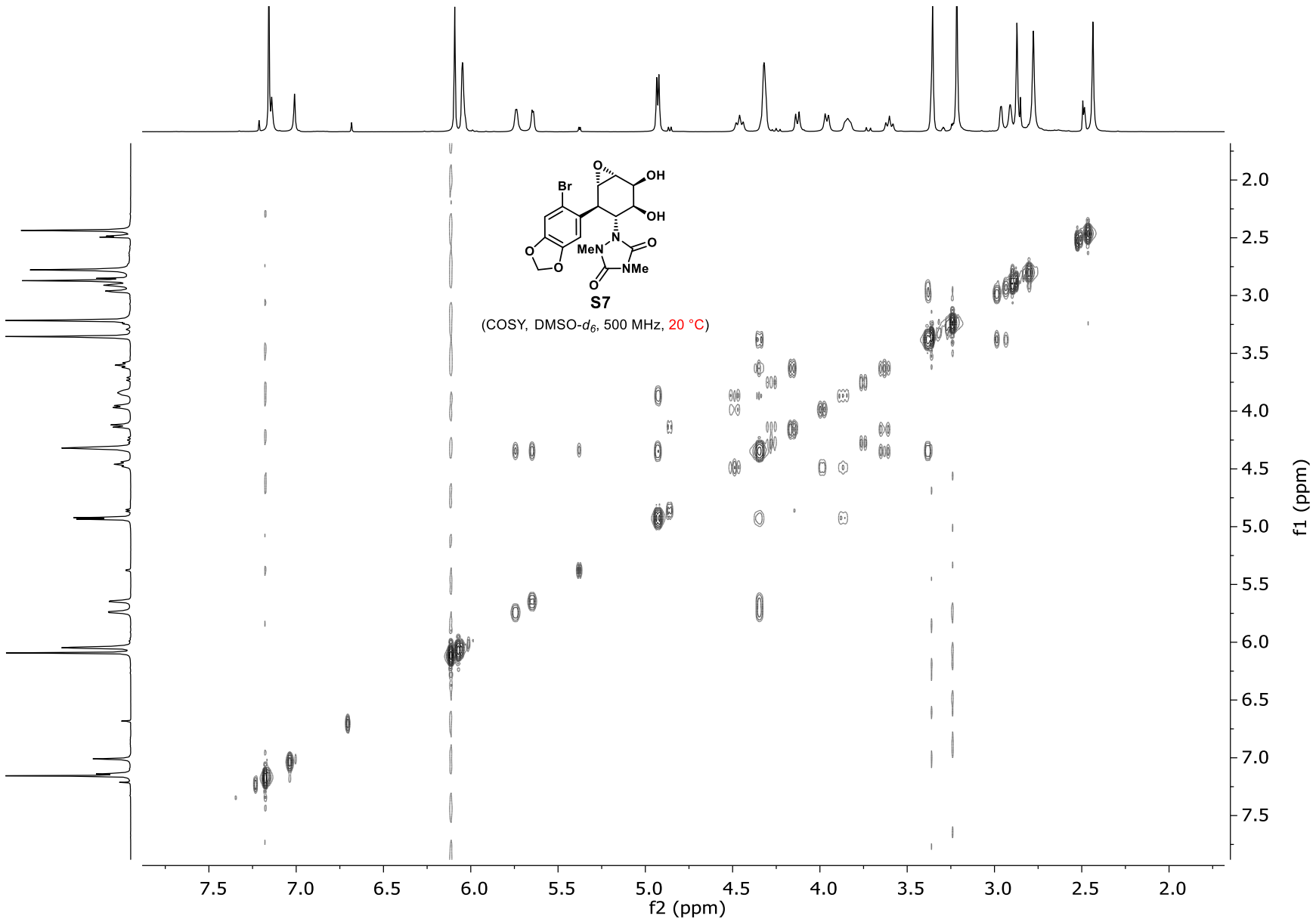



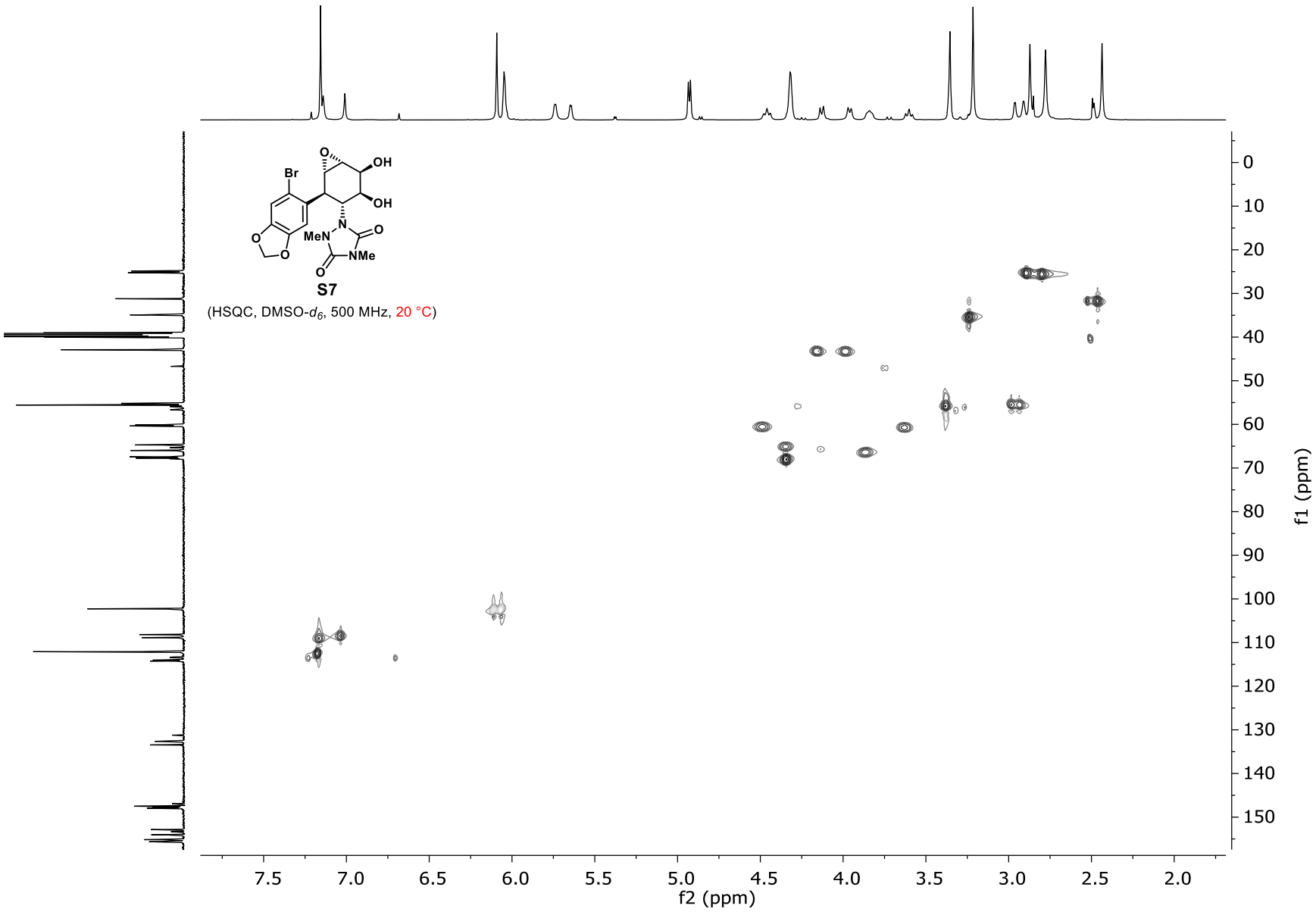


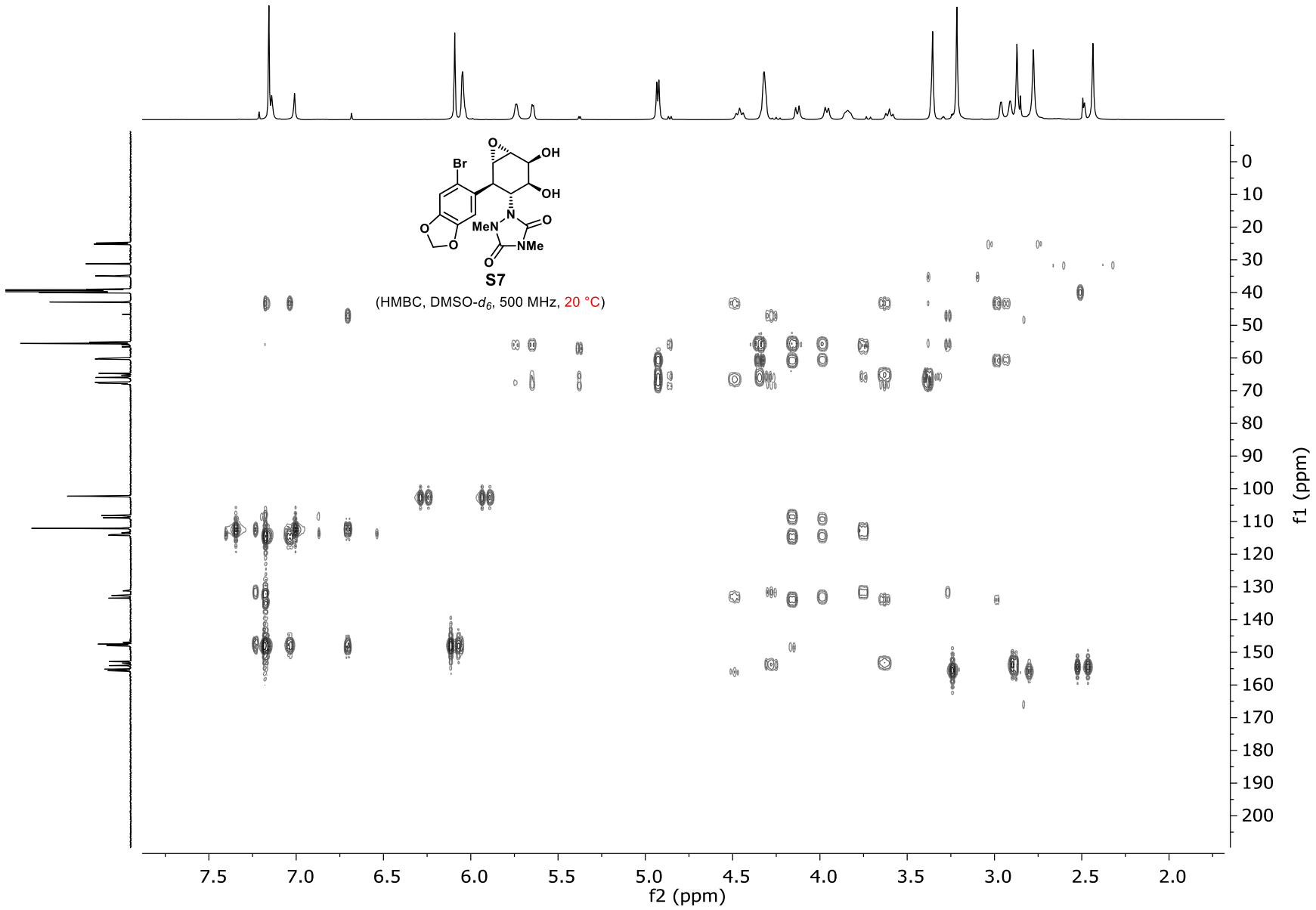


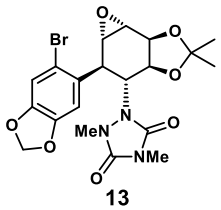
**S7**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)


Br
OH
OH
O
MeN
N
O
NMe
O
O
O
S7
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


Br
OH
OH
O
O
O
MeN
N
NMe
O
O
S7
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)

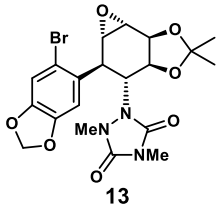

Br
OH
OH
MeN
N
O
NMe
O
O
O
O
S7
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)




**13**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

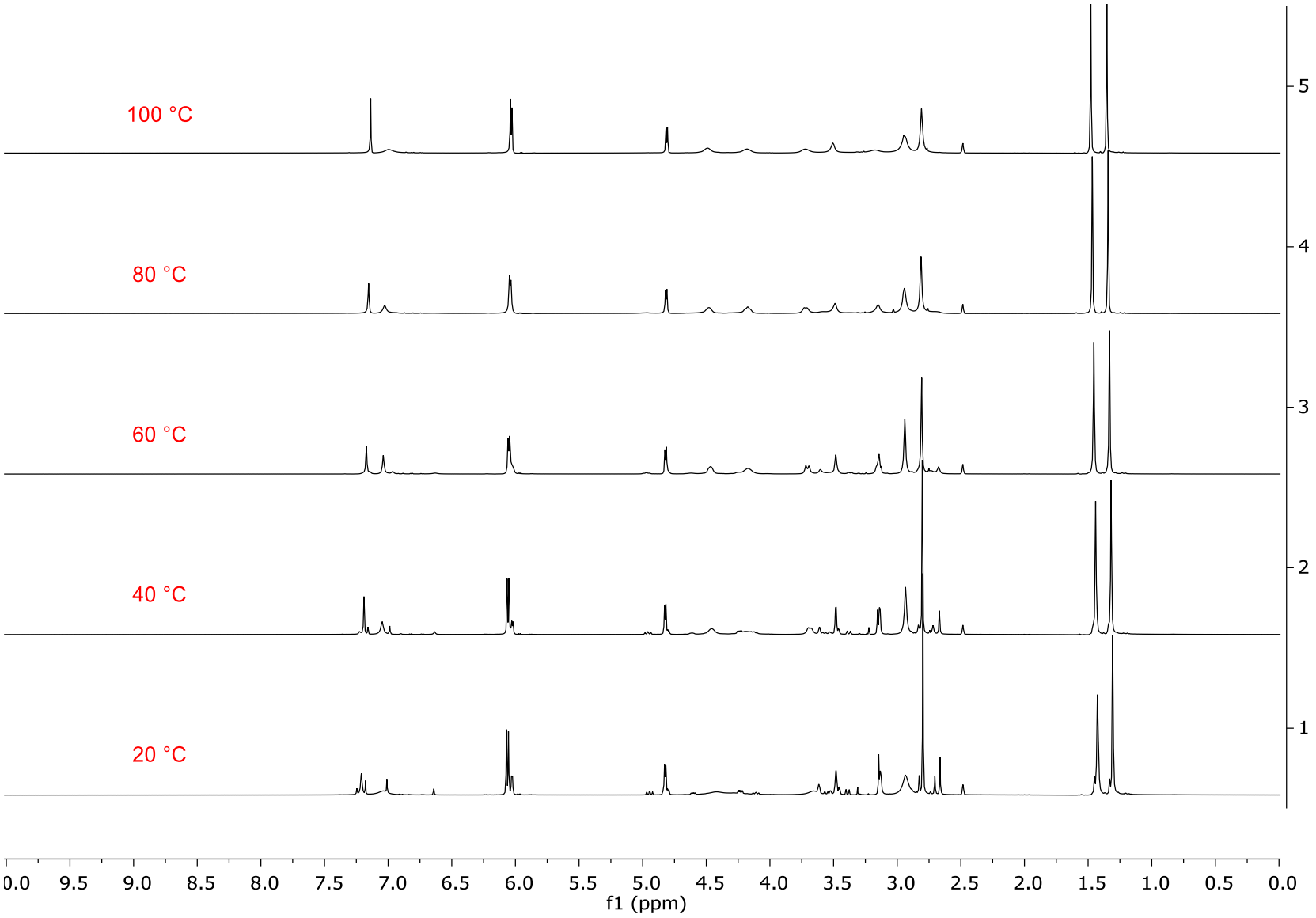


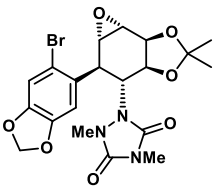




**13**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 80 °C)

$^{1}$H MNR temperature studies of **13** in DMSO-$d_6$, 500 MHz

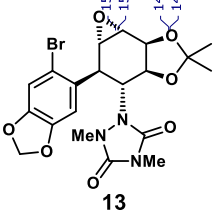





**13**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)

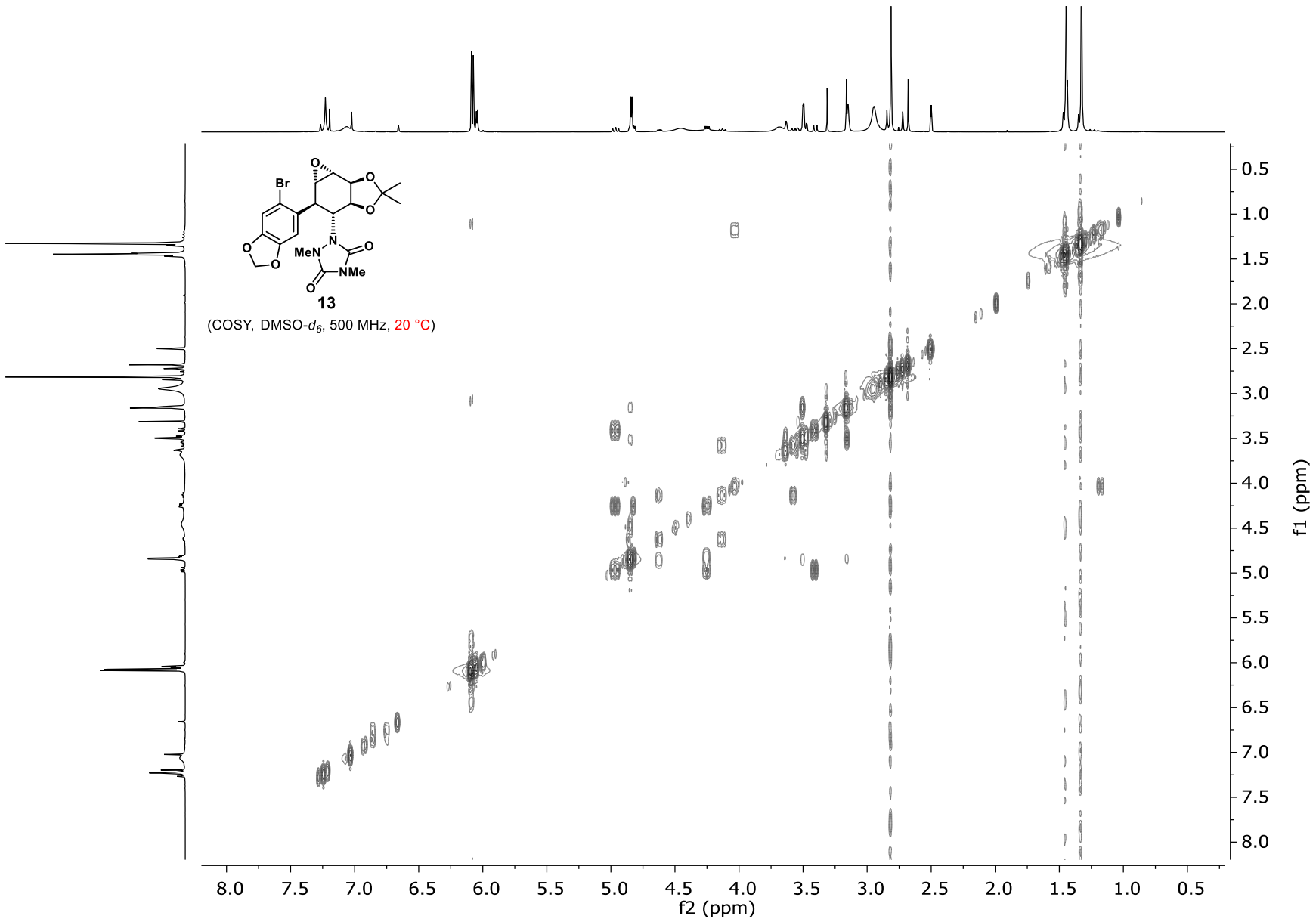


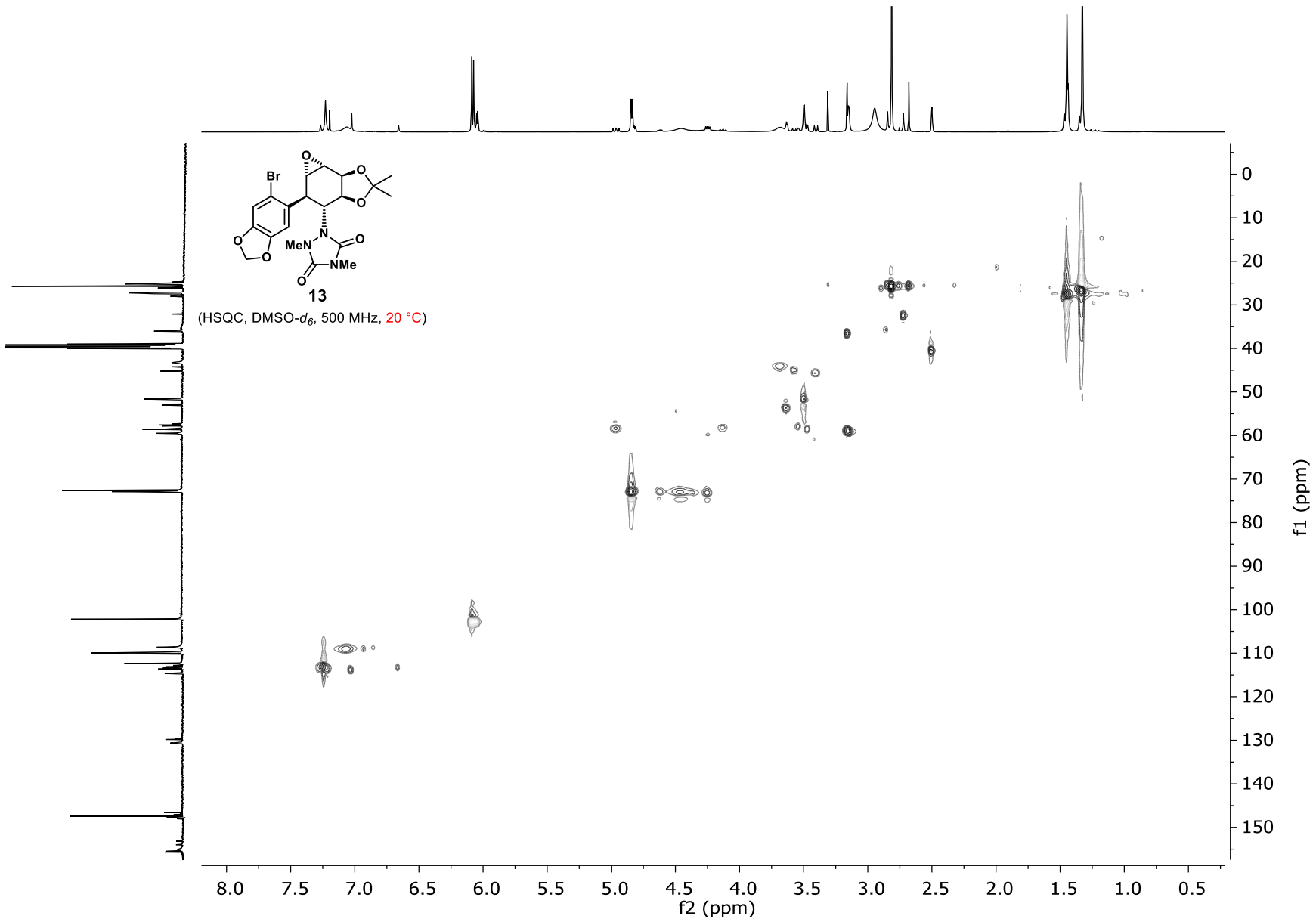



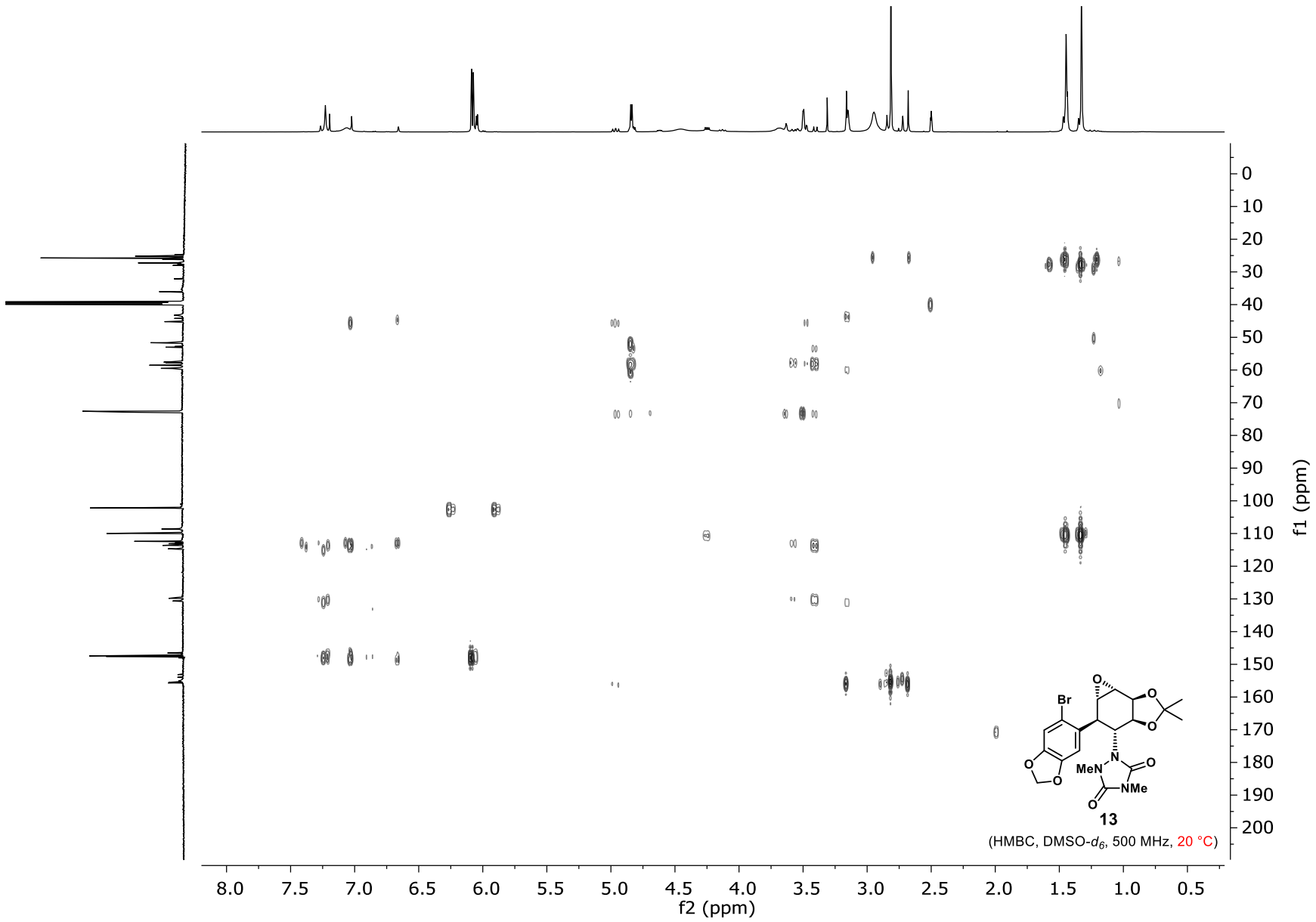

**13**

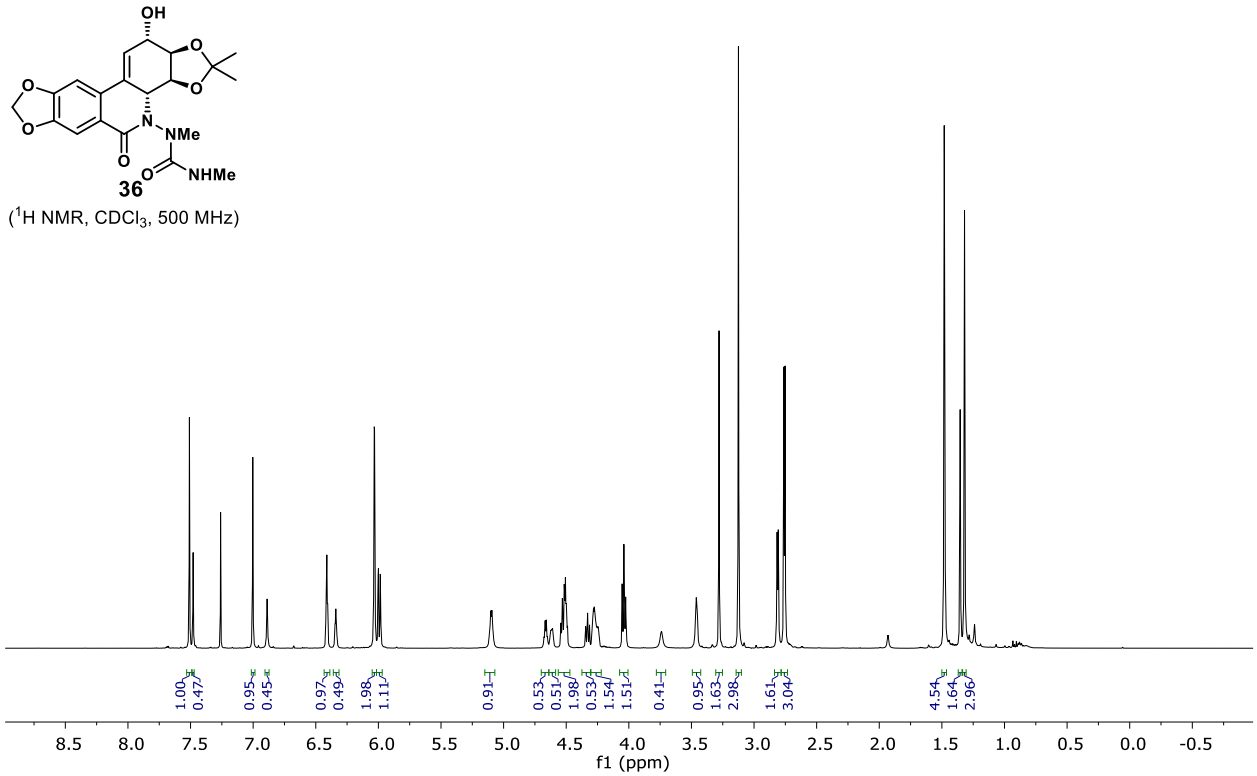
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 80 °C)

155.14
154.77
147.46
147.26
130.55
112.12
109.78
108.40
107.91
101.91
72.87
72.54
59.66
58.22
51.50
43.09
40.02
39.86
39.69
39.52
39.36
39.19
39.02
34.40
27.08
25.50
24.82

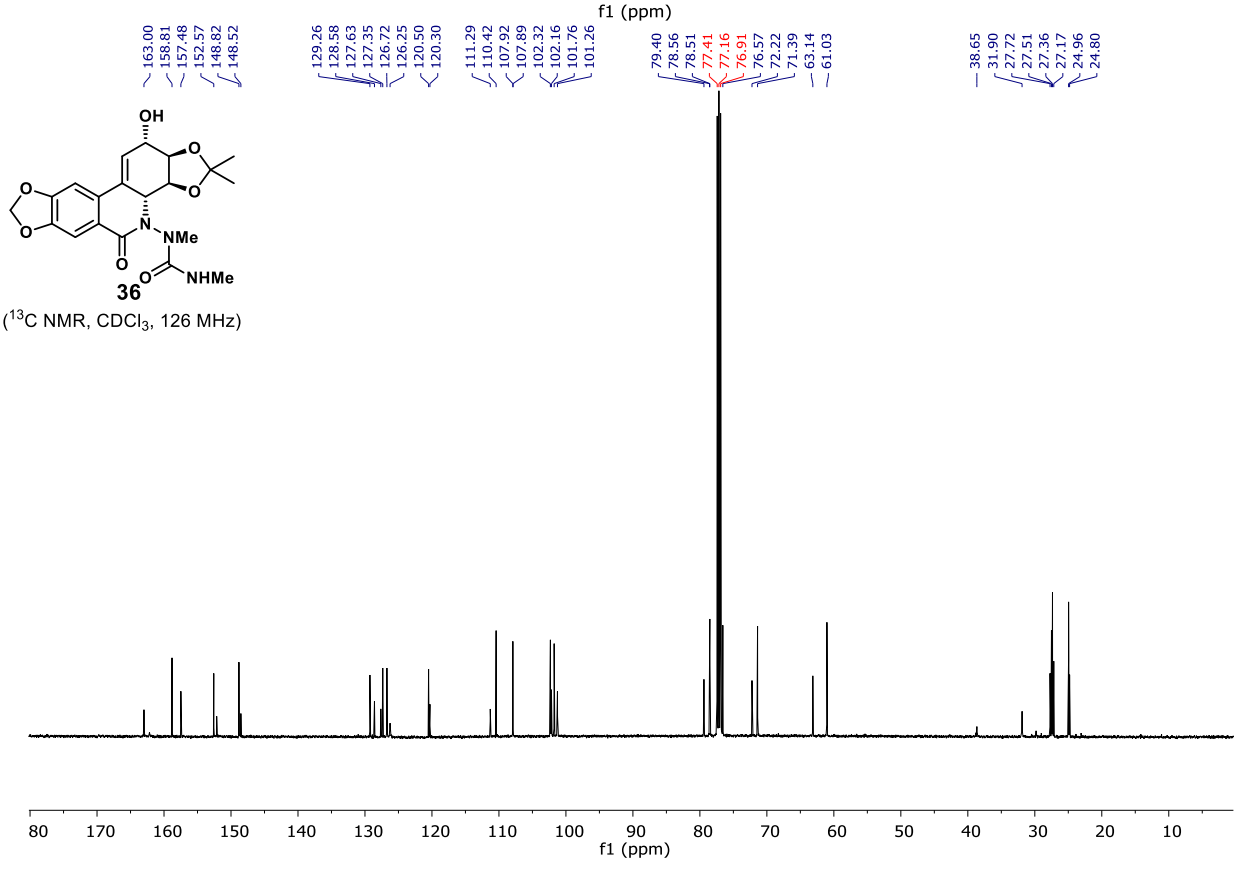

Br
O
O
O
O
O
MeN
N
O
NMe
O
13
(COSY, DMSO-$d_6$, 500 MHz, 20 °C)
f2 (ppm)
f1 (ppm)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


Br
O
O
O
O
O
MeN
N
O
NMe
O
13
(HSQC, DMSO-$d_6$, 500 MHz, 20 °C)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

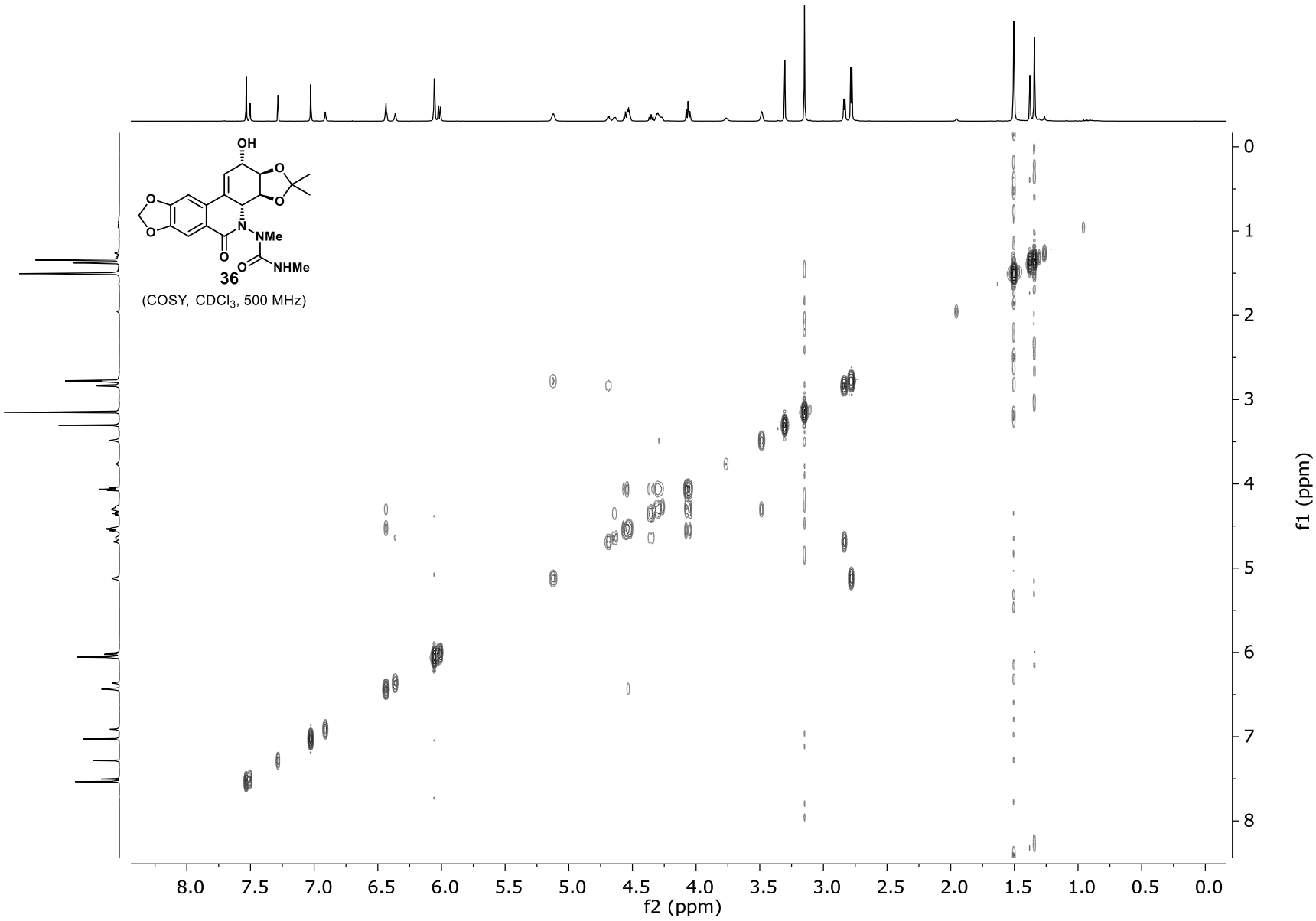

f2 (ppm)
f1 (ppm)
Br
MeN
NMe
13
(HMBC, DMSO-$d_6$, 500 MHz, 20 °C)

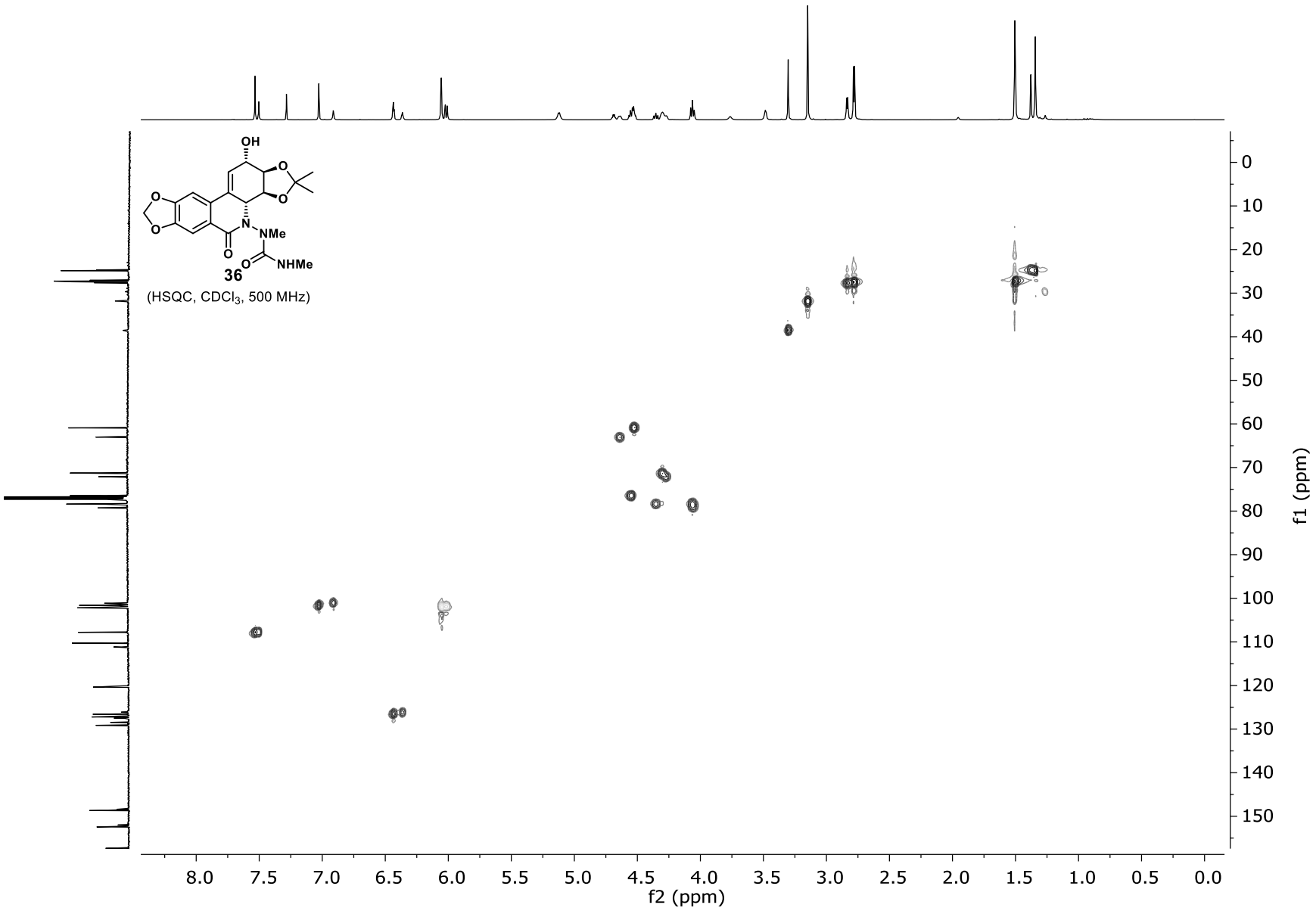


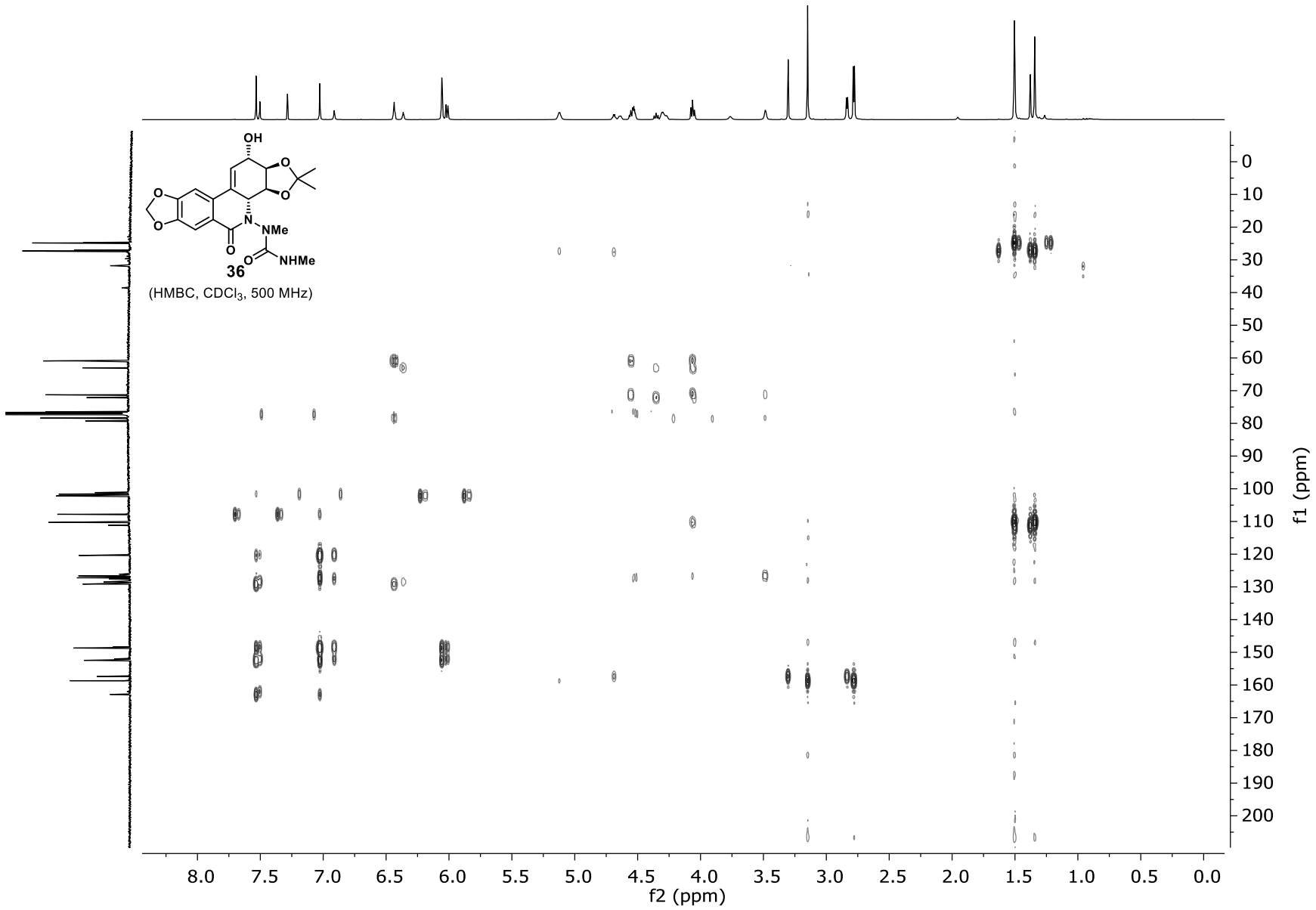

($^1$H NMR, $CDCl_3$, 500 MHz)

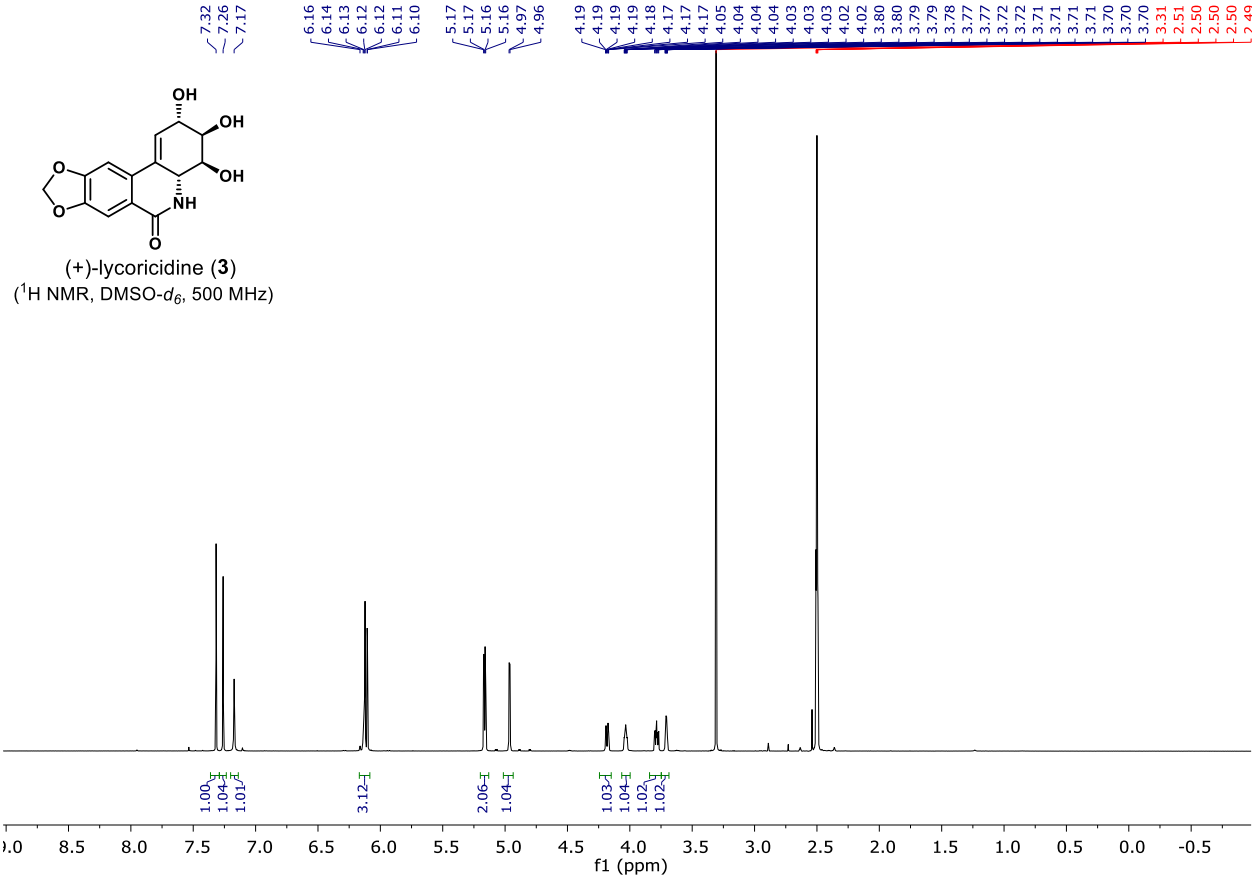


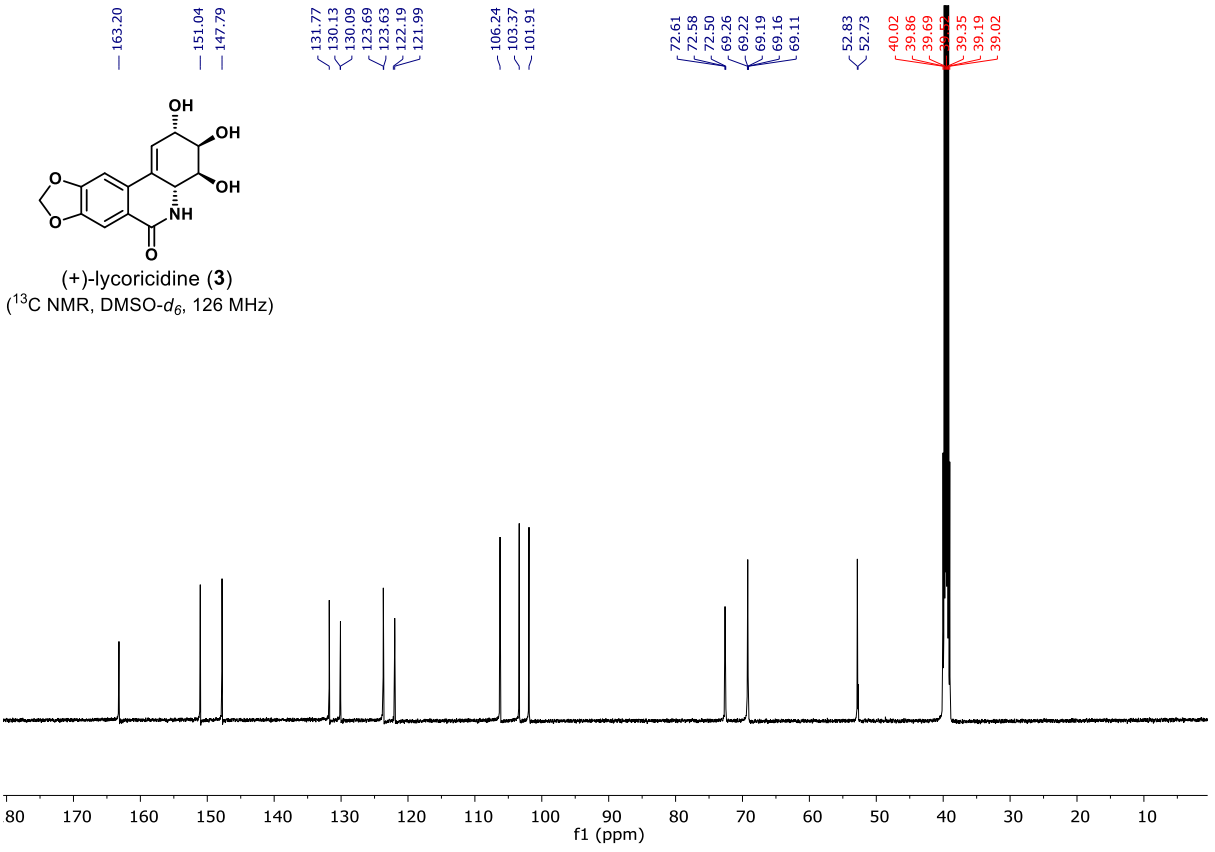

($^{13}$C NMR, $CDCl_3$, 126 MHz)

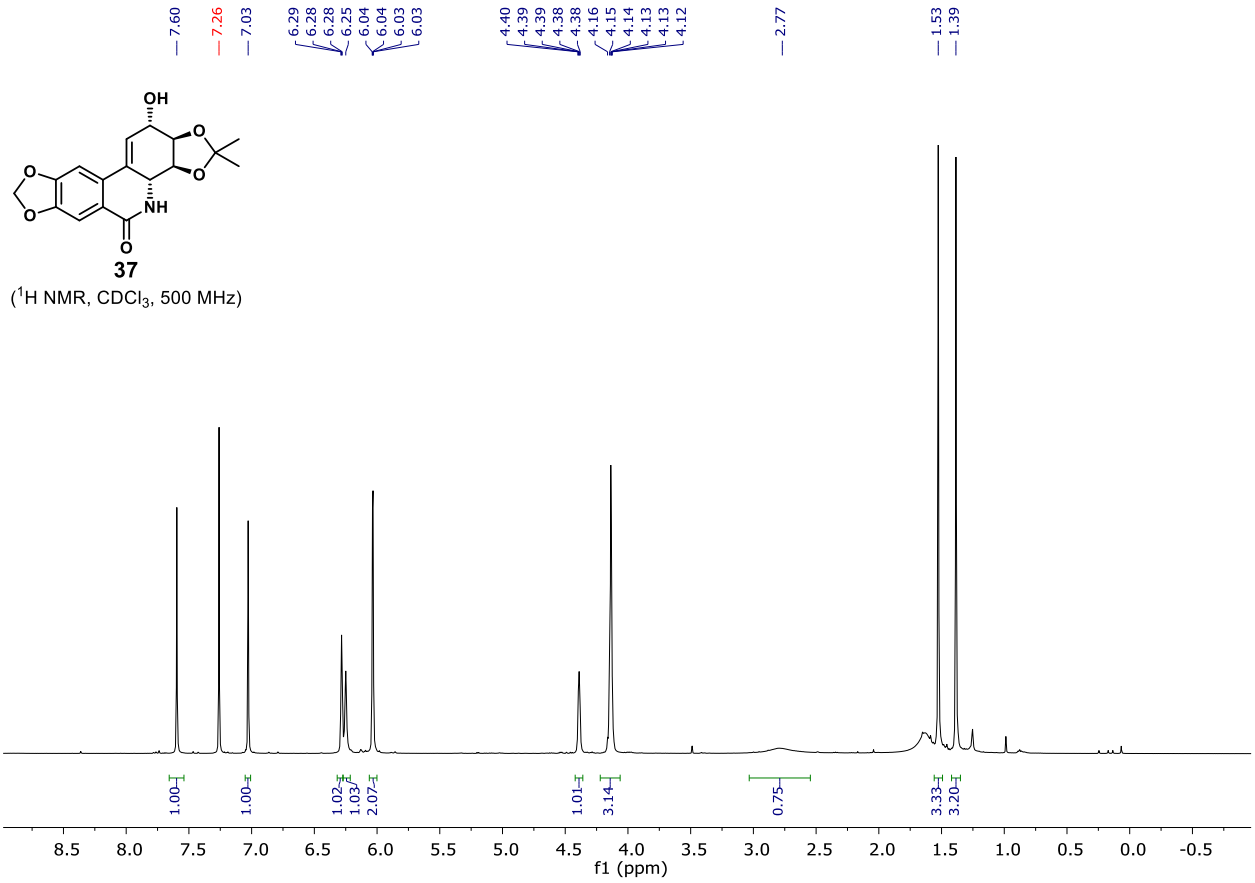

OH
O
O
O
O
N
NMe
O
O
NHMe
36
(COSY, CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
1
2
3
4
5
6
7
8
f1 (ppm)

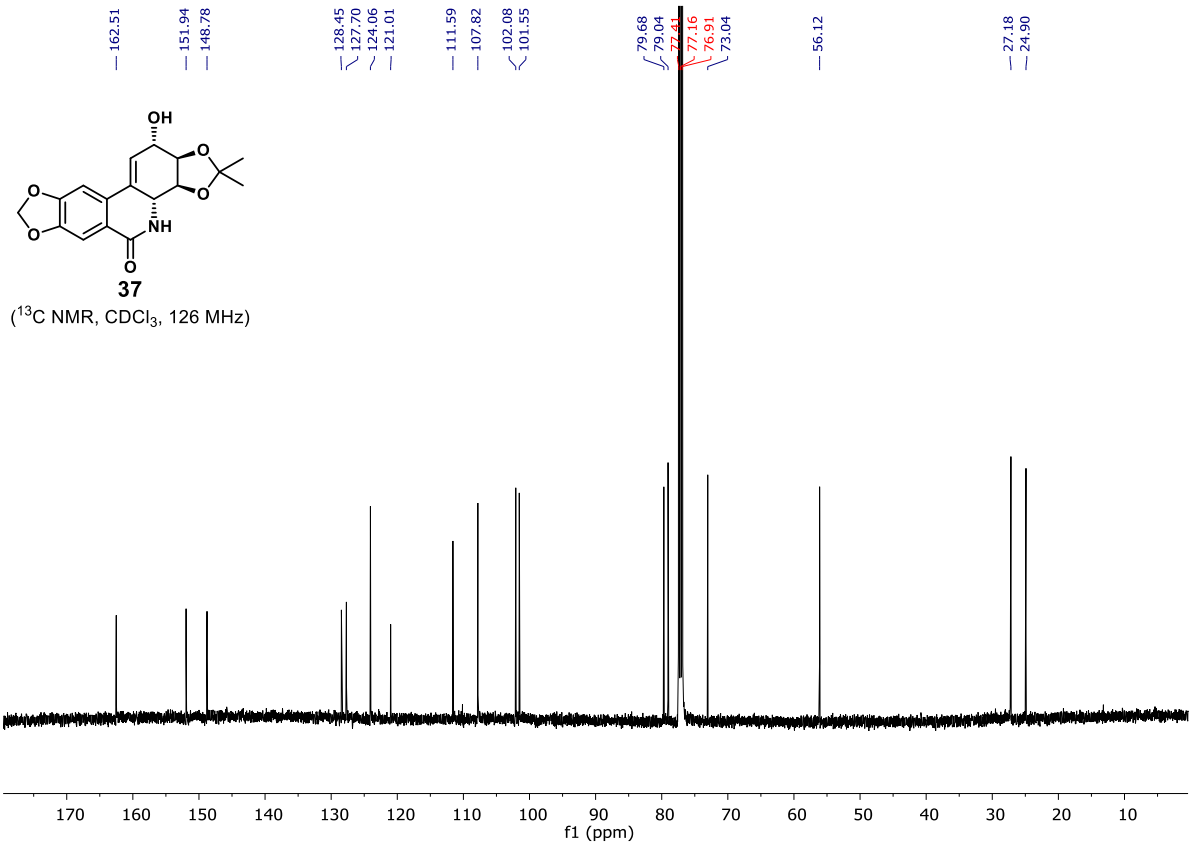

OH
O
O
O
O
N
NMe
O
O
NHMe
36
(HSQC, CDCl3, 500 MHz)
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f2 (ppm)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)

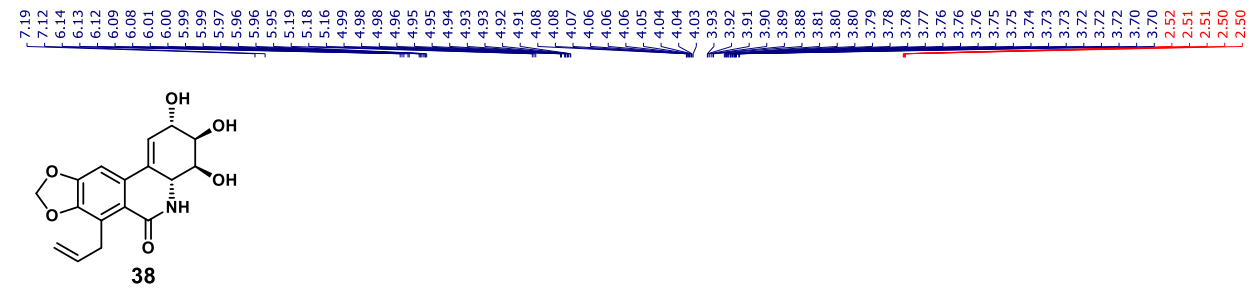

OH
O
O
O
O
N
NMe
O
O
NHMe
36
(HMBC, CDCl3, 500 MHz)
f2 (ppm)
f1 (ppm)


OH
OH
OH
O
O
NH
O
(+)-lycoricidine (3)
(1H NMR, DMSO-d6, 500 MHz)
f1 (ppm)


OH
OH
OH
O
O
NH
O
(+)-lycoricidine (3)
(13C NMR, DMSO-d6, 126 MHz)
f1 (ppm)


7.60
7.26
7.03
6.29
6.28
6.28
6.25
6.04
6.04
6.03
6.03
4.40
4.39
4.39
4.38
4.38
4.16
4.15
4.14
4.13
4.13
4.12
2.77
1.53
1.39
OH
O
O
O
O
NH
O
37
(1H NMR, CDCl3, 500 MHz)
1.00
1.00
1.02
1.03
2.07
1.01
3.14
0.75
3.33
3.20
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

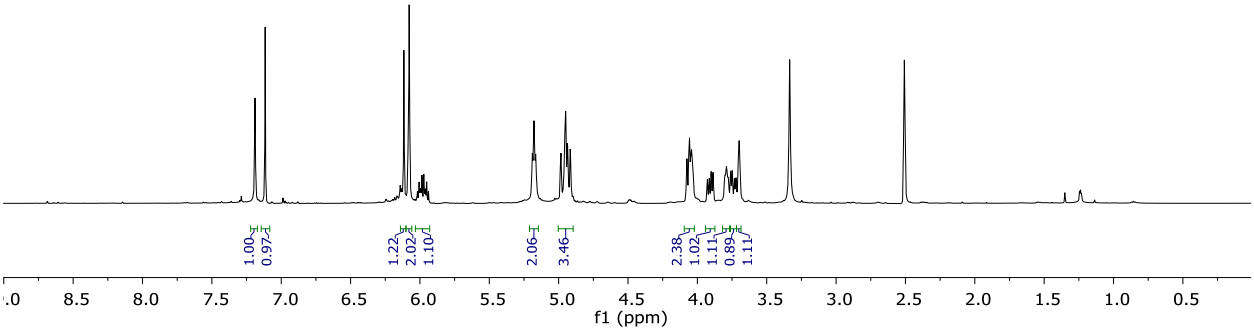

162.51
151.94
148.78
128.45
127.70
124.06
121.01
111.59
107.82
102.08
101.55
79.68
79.04
77.41
77.16
76.91
73.04
56.12
27.18
24.90
OH
O
O
O
O
NH
O
37
(13C NMR, CDCl3, 126 MHz)
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

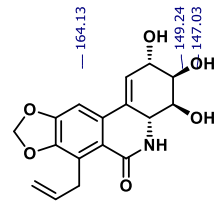




**38**

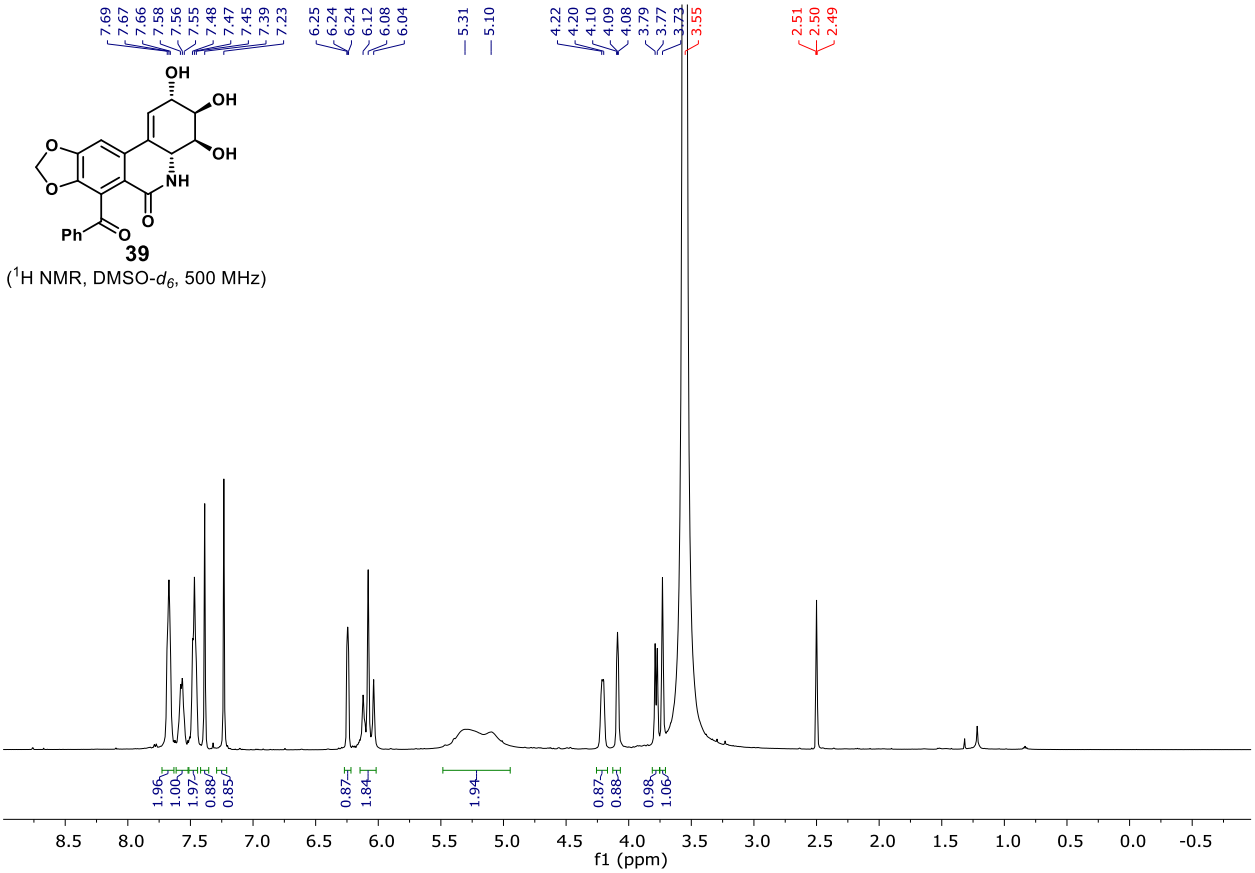
($^1$H NMR, DMSO-$d_6$, 500 MHz)

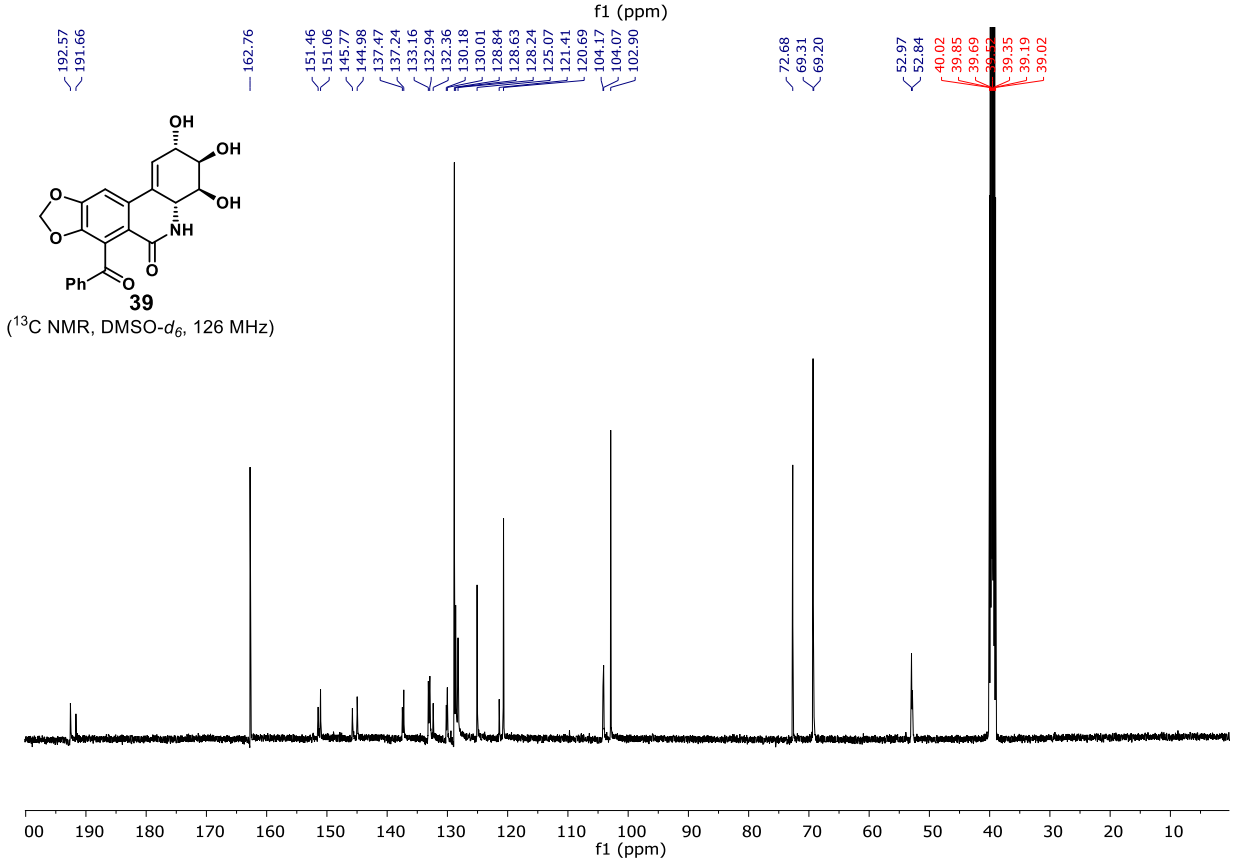


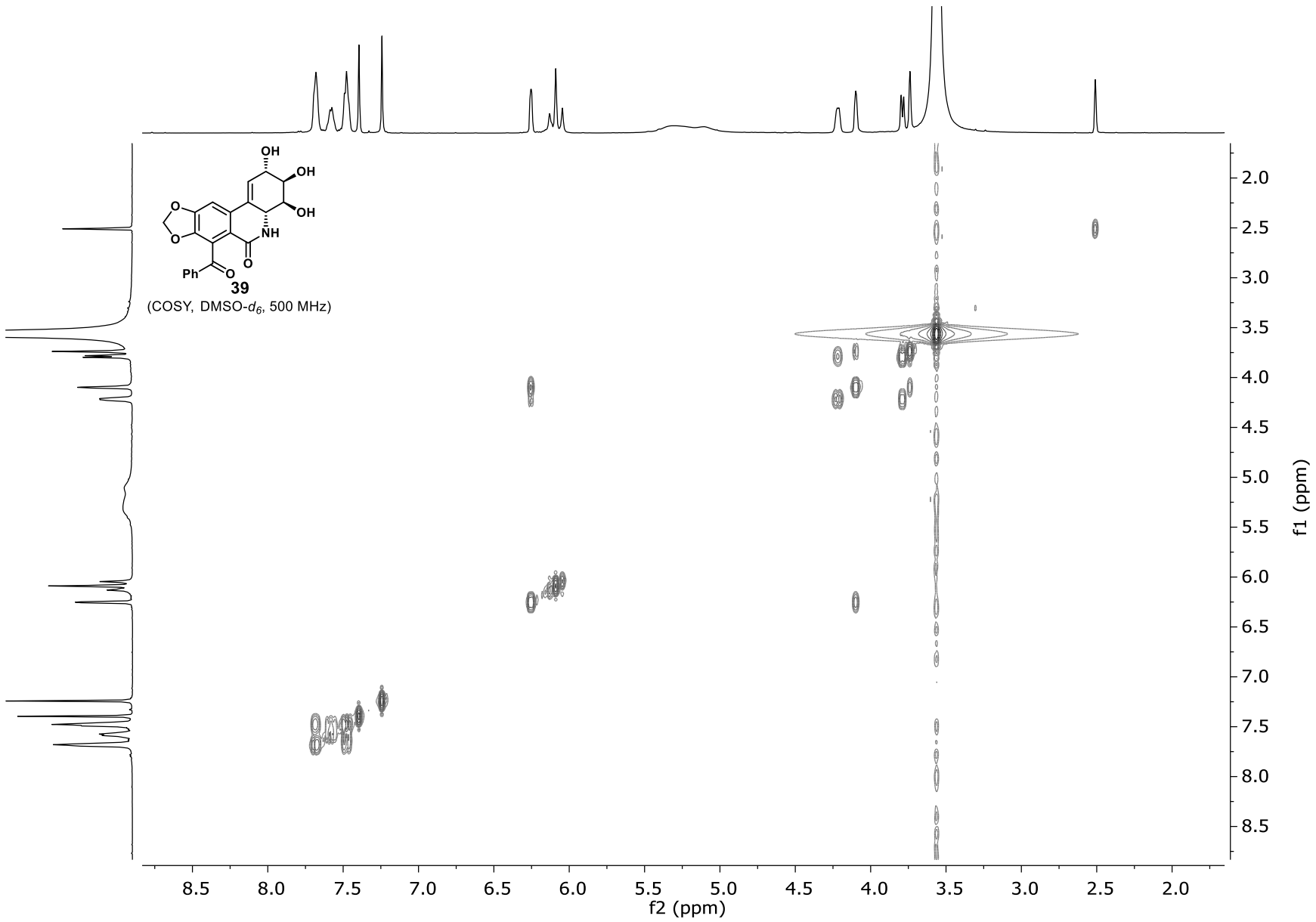


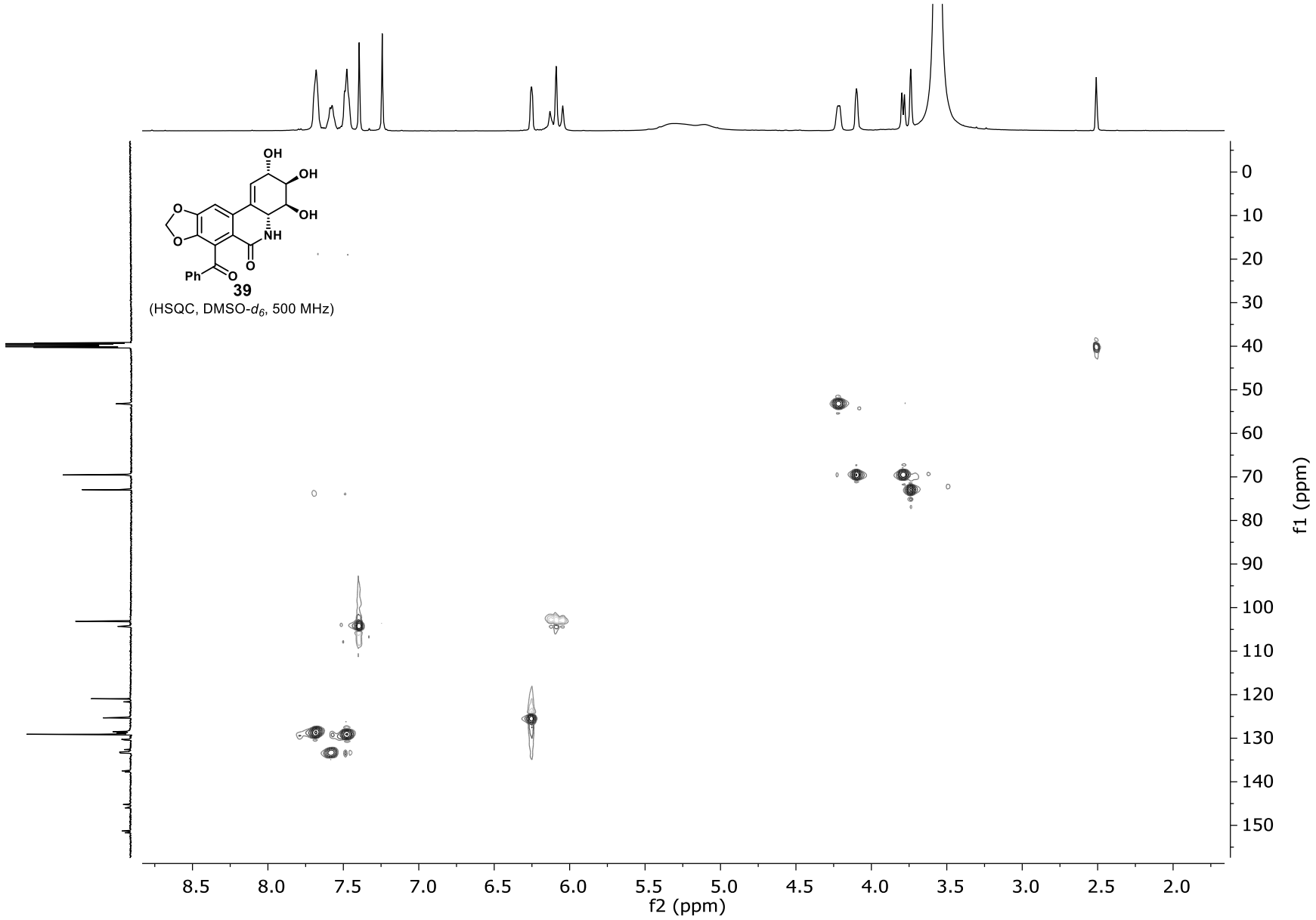
**38**

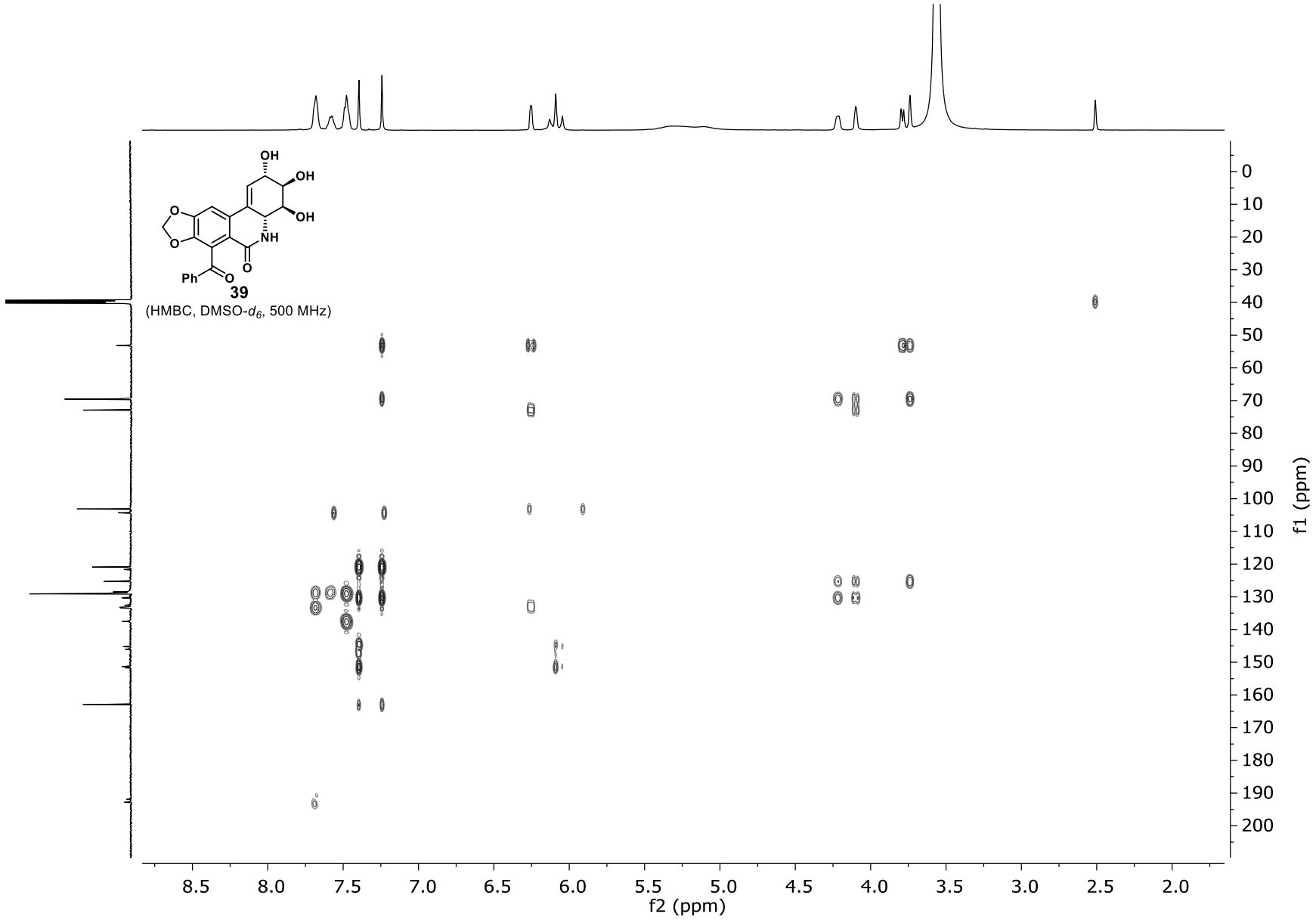
($^{13}$C NMR, DMSO-$d_6$, 126 MHz)

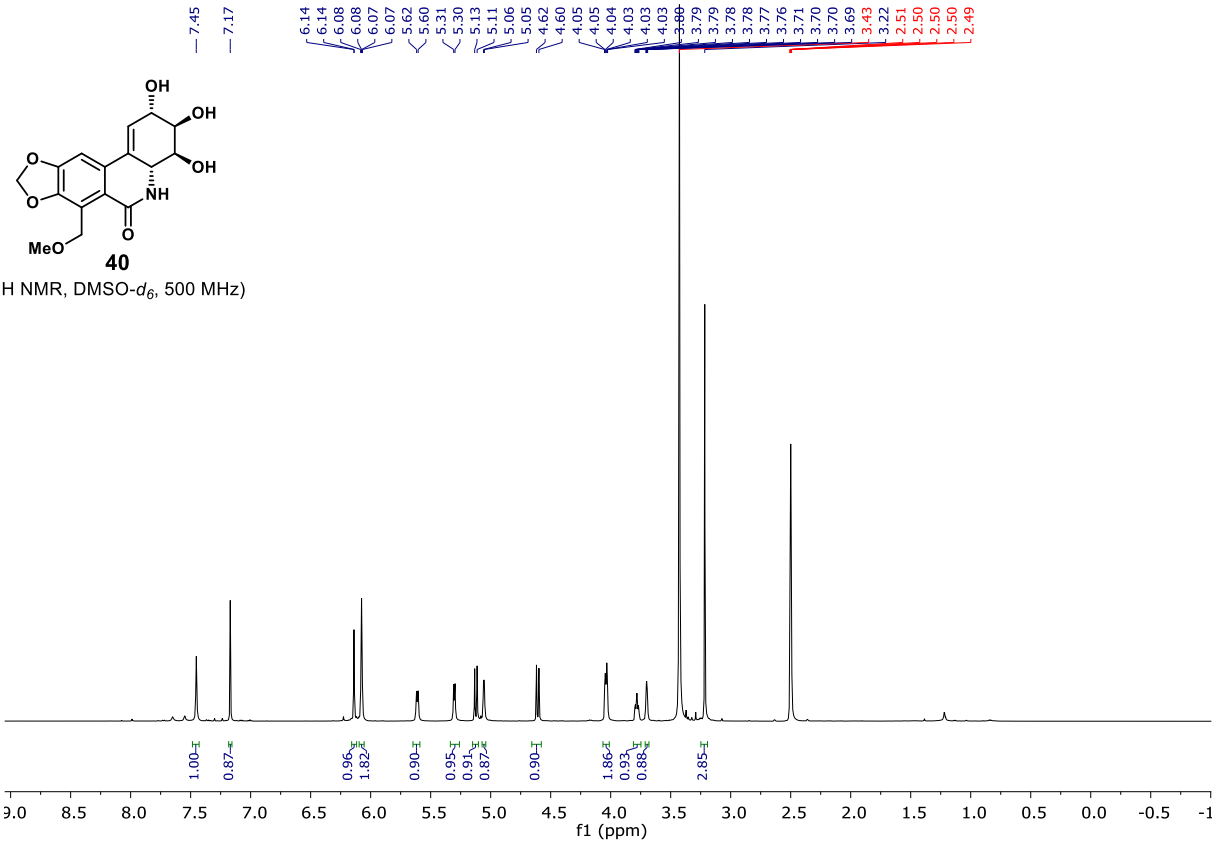

7.69
7.67
7.66
7.58
7.56
7.55
7.48
7.47
7.45
7.39
7.23
6.25
6.24
6.24
6.12
6.08
6.04
5.31
5.10
4.22
4.20
4.10
4.09
4.08
3.79
3.77
3.73
3.55
2.51
2.50
2.49
OH
OH
OH
O
O
NH
O
Ph
O
39
(1H NMR, DMSO-d6, 500 MHz)
1.96
1.00
1.97
0.88
0.85
0.87
1.84
1.94
0.87
0.88
0.98
1.06
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


192.57
191.66
162.76
151.46
151.06
145.77
144.98
137.47
137.24
133.16
132.94
132.36
130.18
130.01
128.84
128.63
128.24
125.07
121.41
120.69
104.17
104.07
102.90
72.68
69.31
69.20
52.97
52.84
40.02
39.85
39.69
39.52
39.35
39.19
39.02
OH
OH
OH
O
O
NH
O
Ph
O
39
(13C NMR, DMSO-d6, 126 MHz)
00 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)


OH
OH
OH
O
O
NH
O
Ph
O
39
(COSY, DMSO-$d_6$, 500 MHz)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)
f1 (ppm)

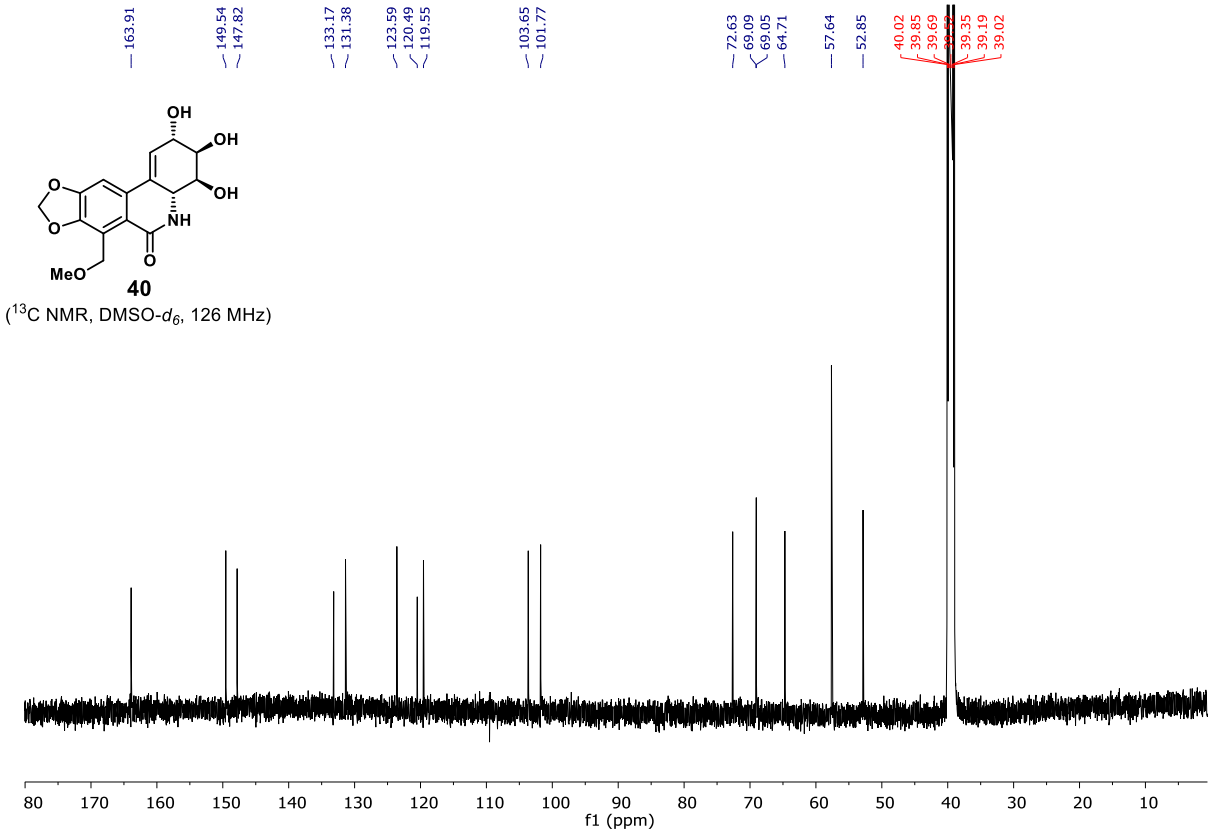

OH
OH
OH
O
O
NH
O
Ph
O
39
(HSQC, DMSO-$d_6$, 500 MHz)
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
f1 (ppm)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
f2 (ppm)


OH
OH
OH
O
O
NH
O
Ph
O
39
(HMBC, DMSO-$d_6$, 500 MHz)
f2 (ppm)
f1 (ppm)



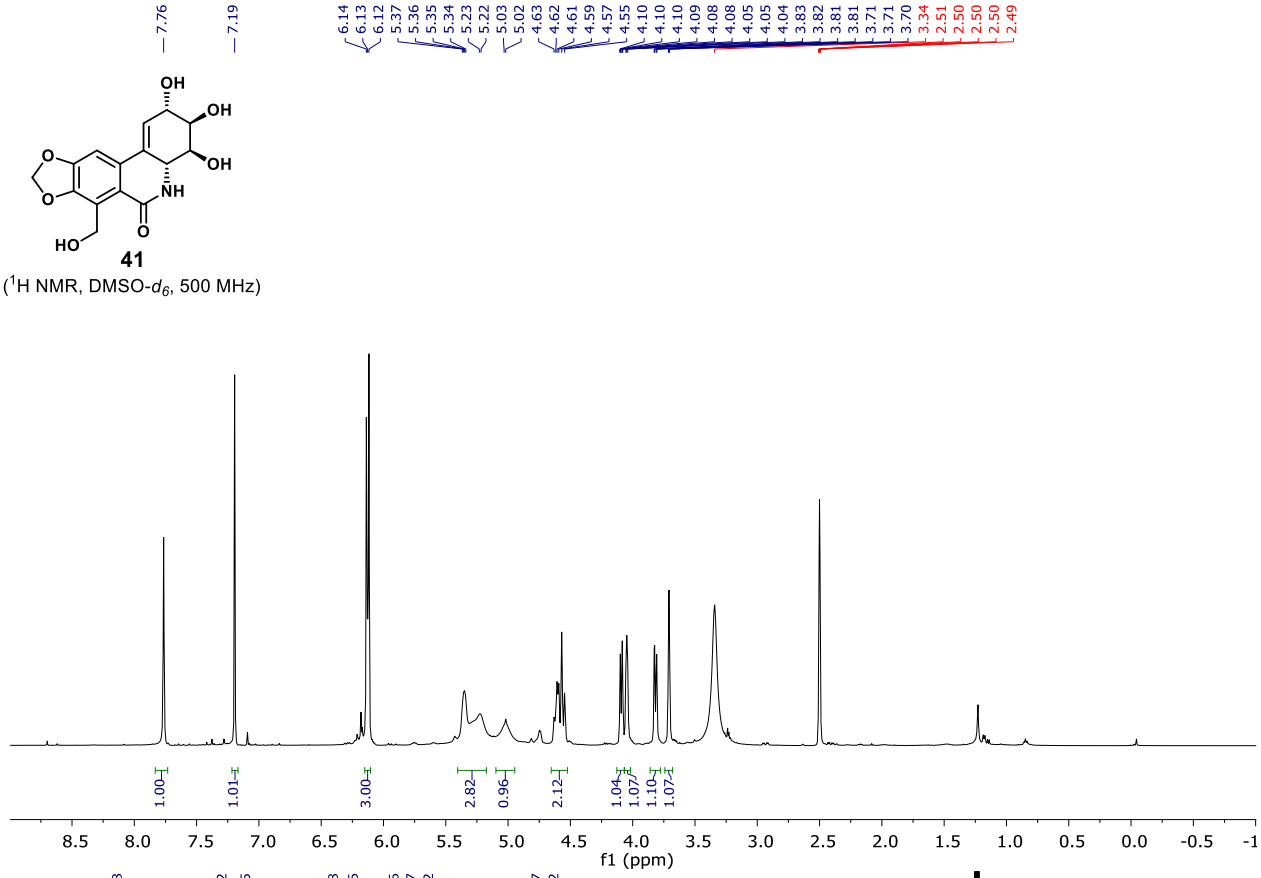

**40**

($^1$H NMR, DMSO-$d_6$, 500 MHz)



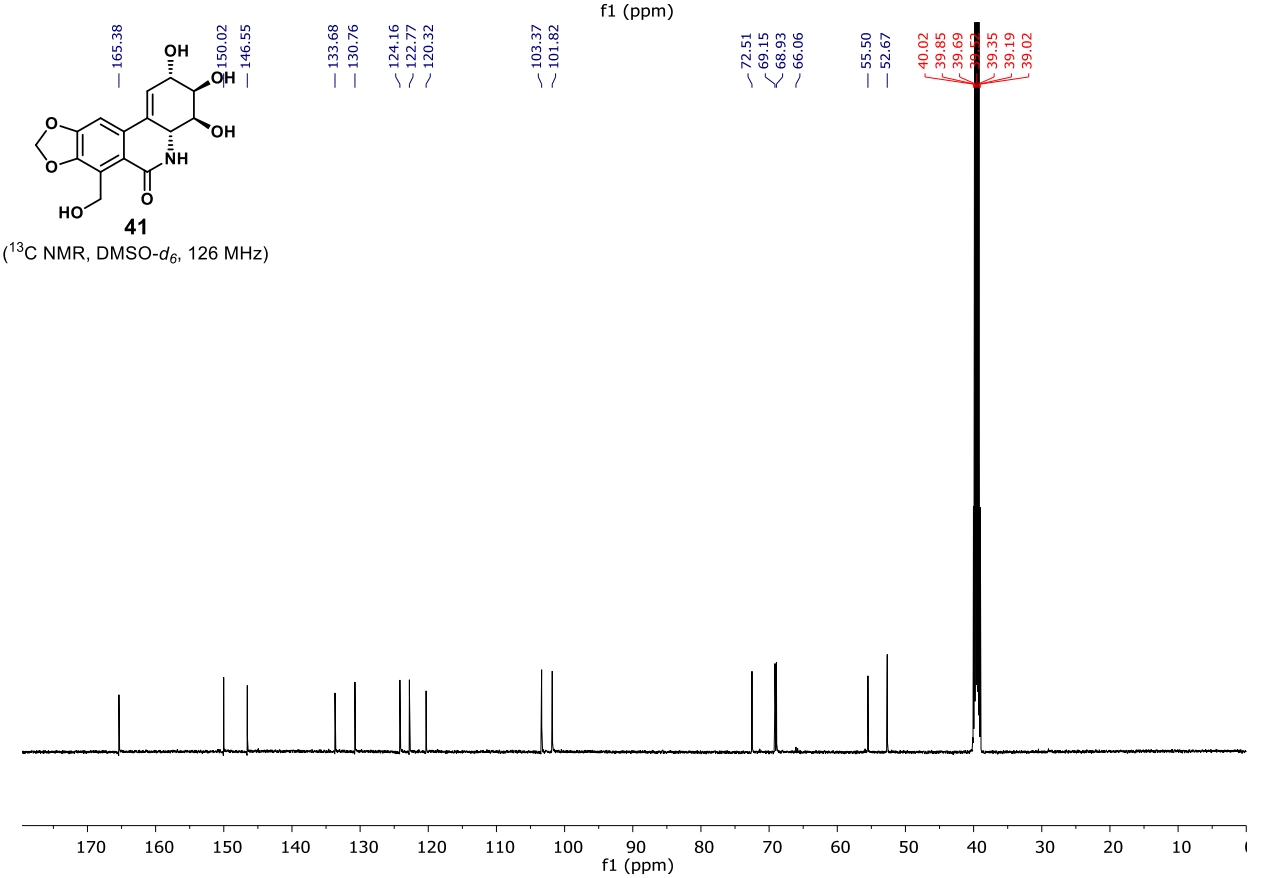

**40**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz)



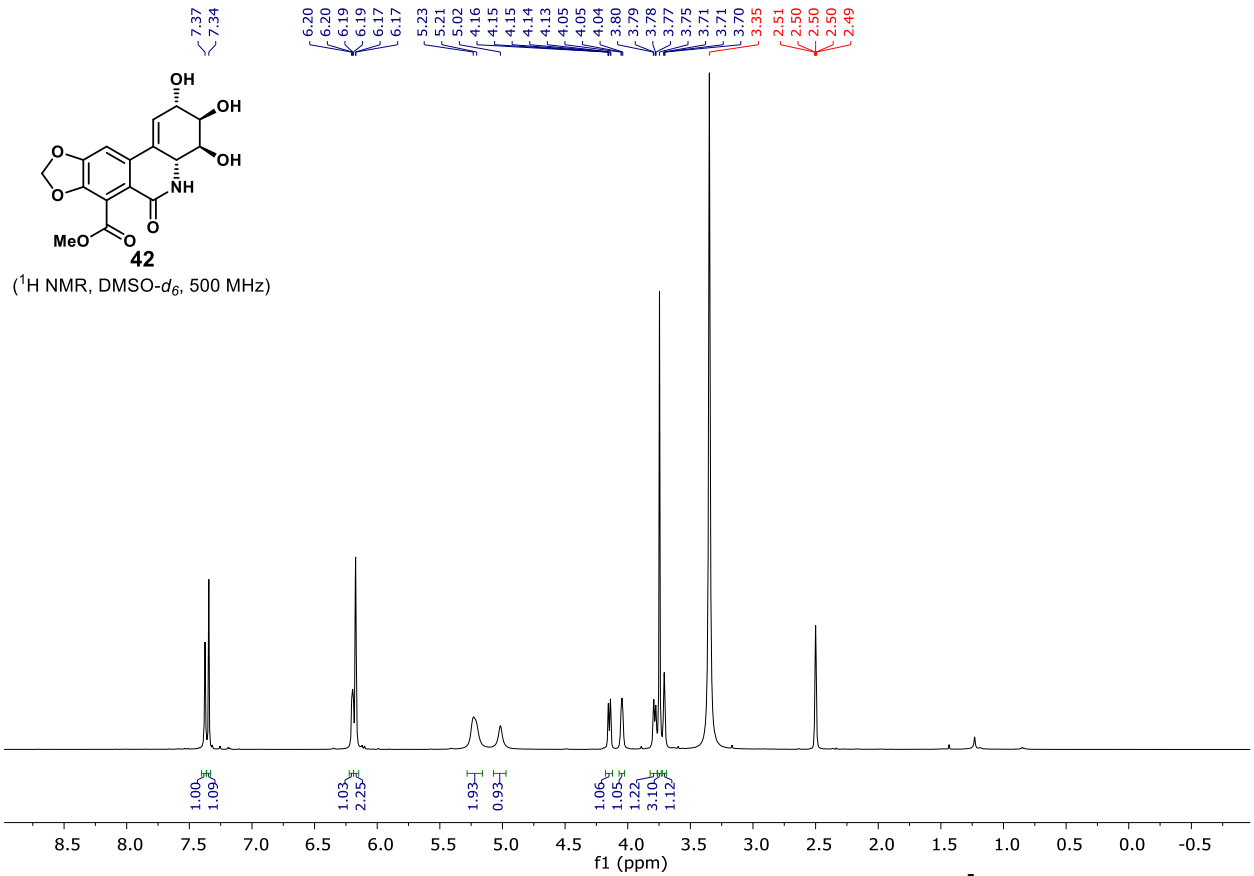

**41**

($^{1}$H NMR, DMSO-$d_6$, 500 MHz)



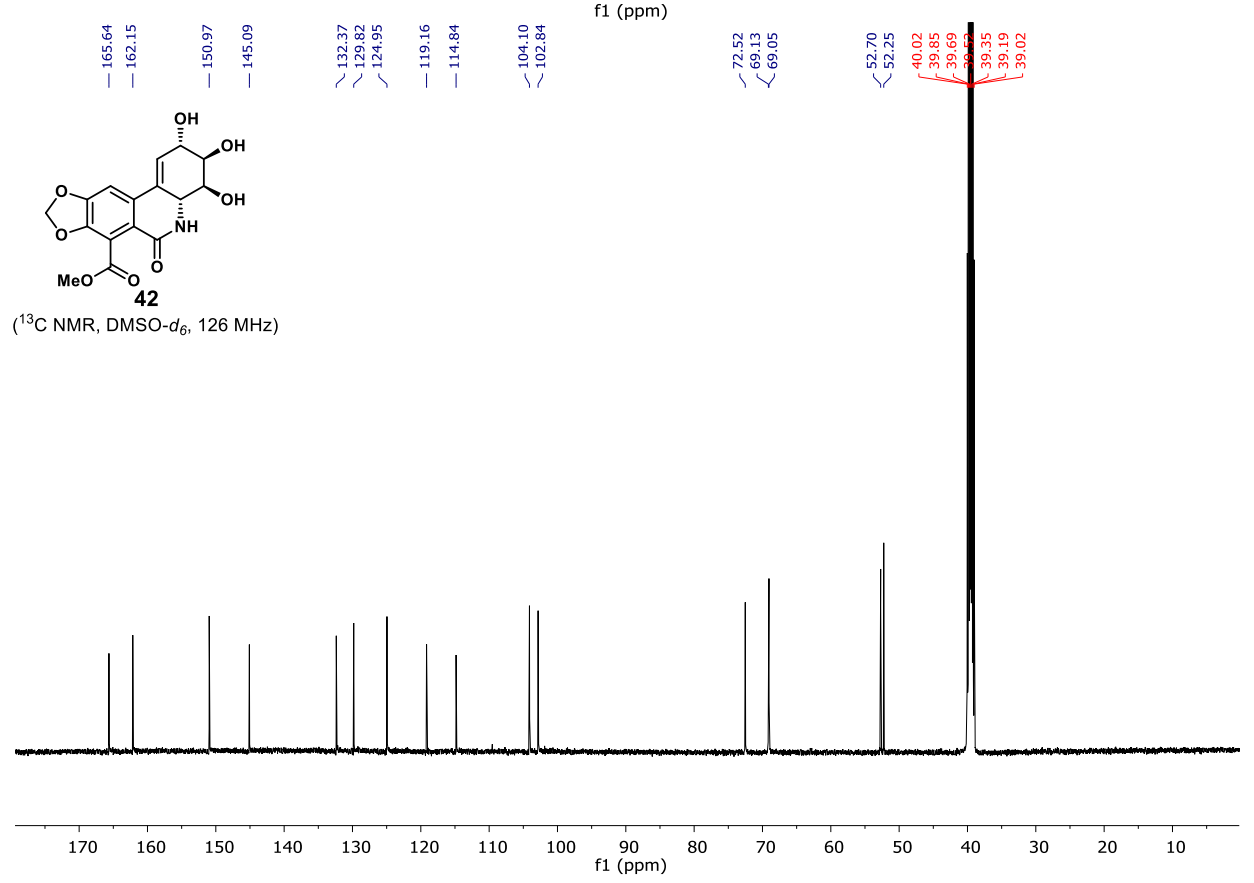

**41**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz)



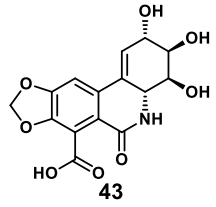

42

($^1$H NMR, DMSO-$d_6$, 500 MHz)




42

($^{13}$C NMR, DMSO-$d_6$, 126 MHz)

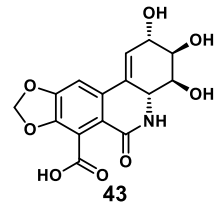



**43**

($^{1}$H NMR, $D_2O$, 500 MHz)

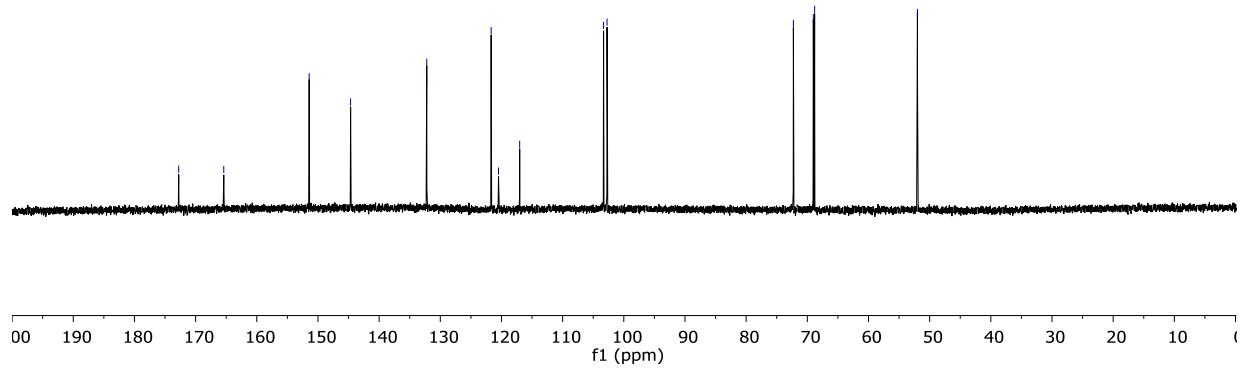


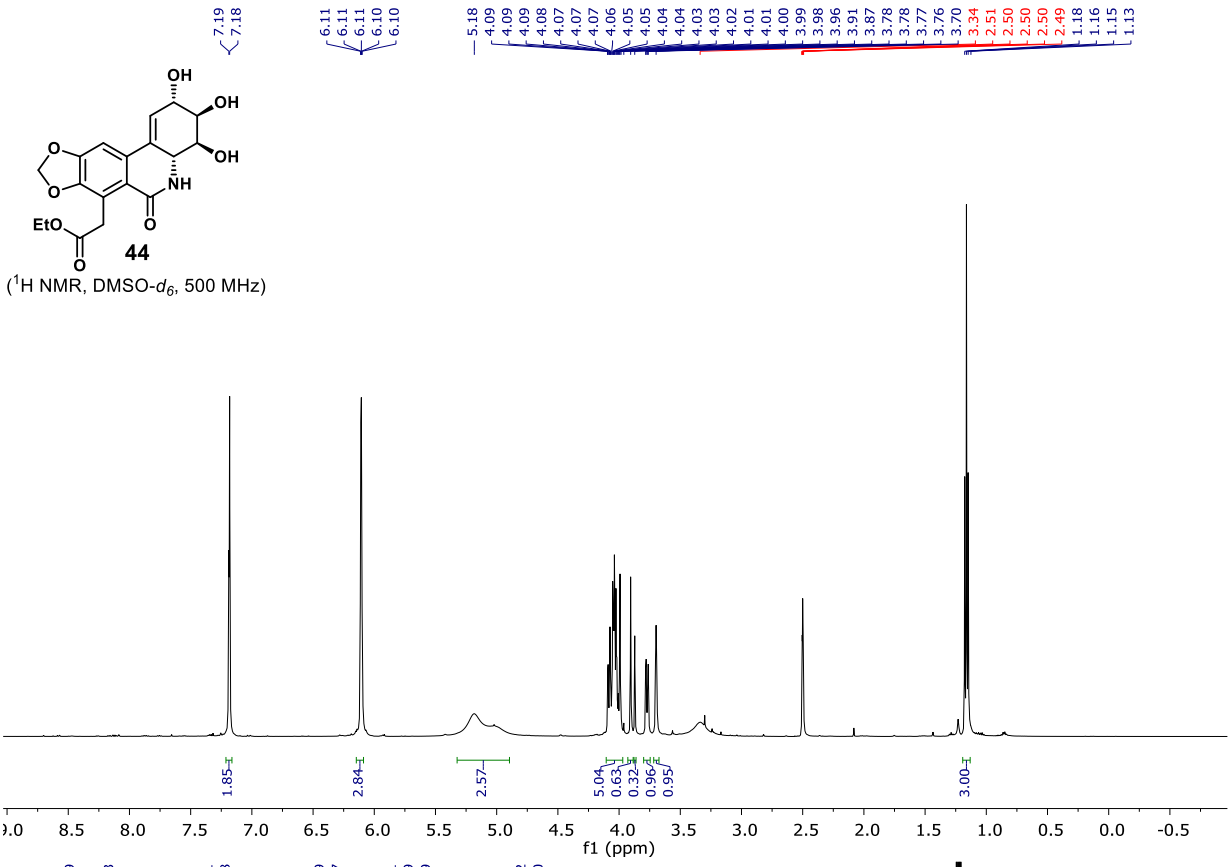


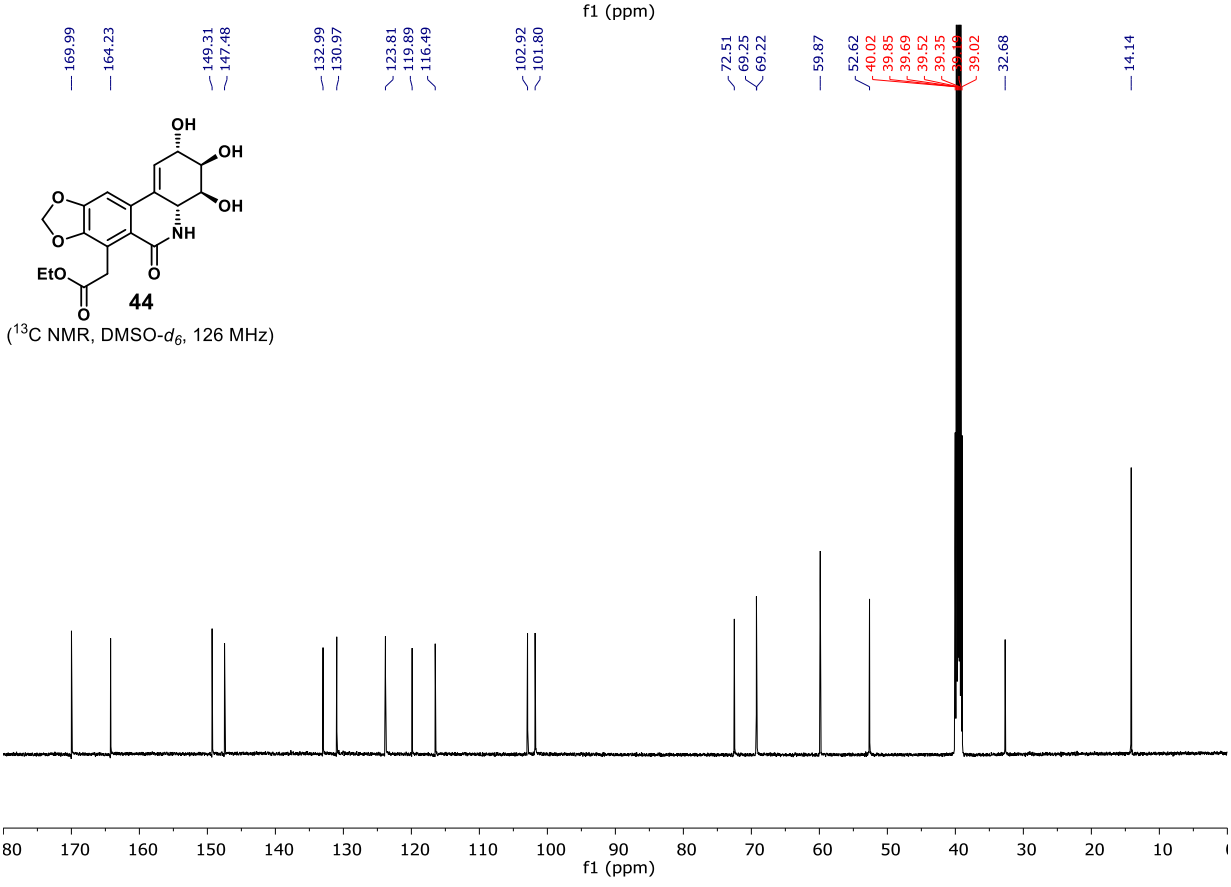


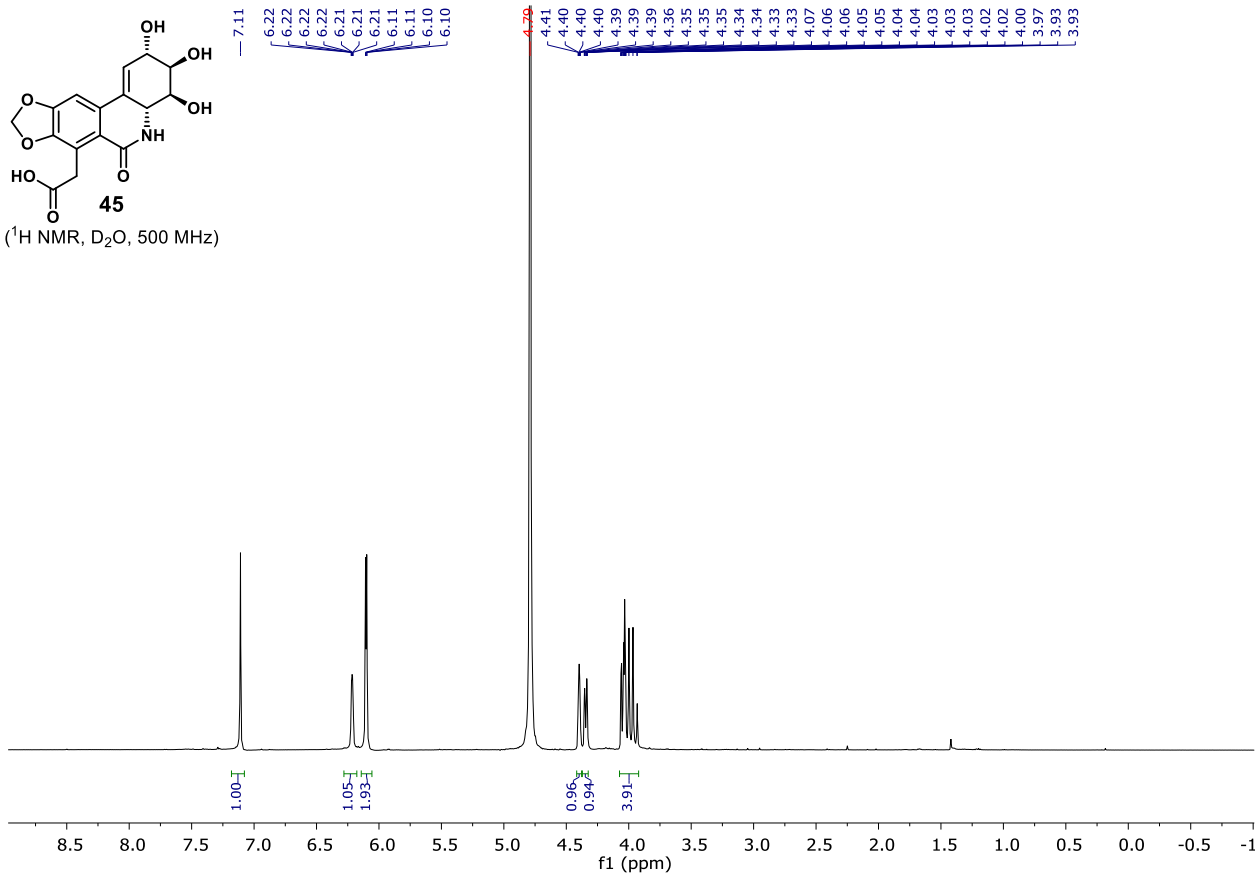

**43**

($^{13}$C NMR, $D_2O$, 126 MHz)

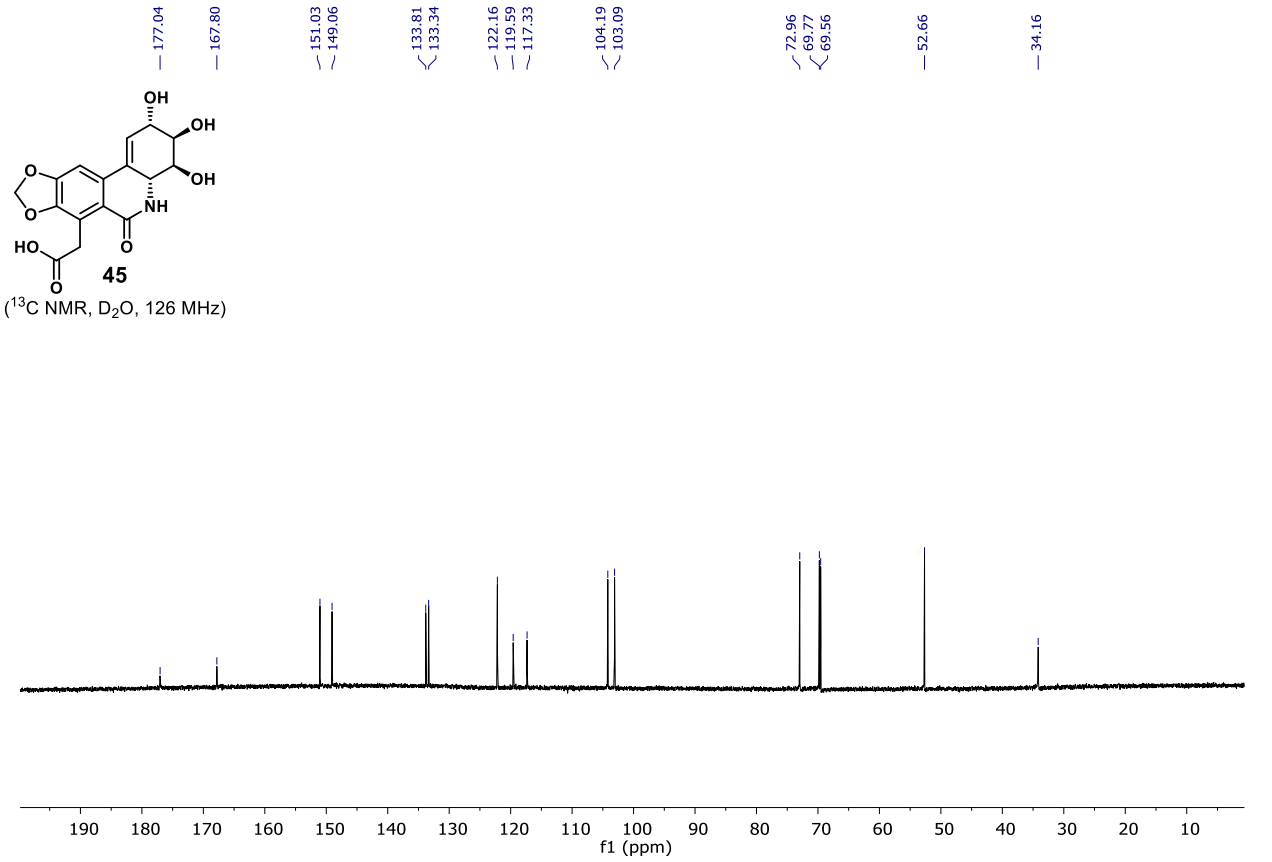



OH
OH
OH
O
O
NH
O
EtO
O
44
(1H NMR, DMSO-d6, 500 MHz)
f1 (ppm)

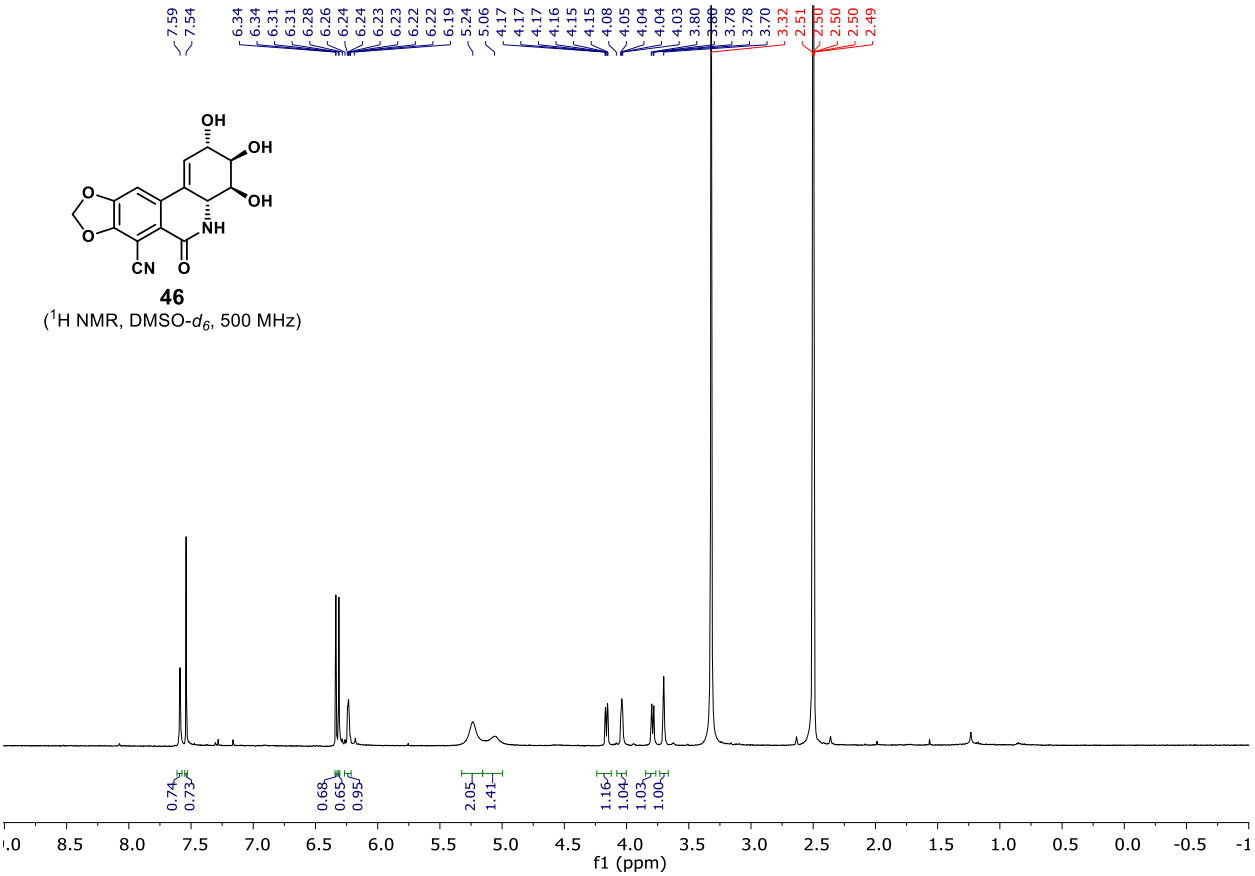

OH
OH
OH
O
O
NH
O
EtO
O
44
(13C NMR, DMSO-d6, 126 MHz)
f1 (ppm)




($^1$H NMR, $D_2O$, 500 MHz)

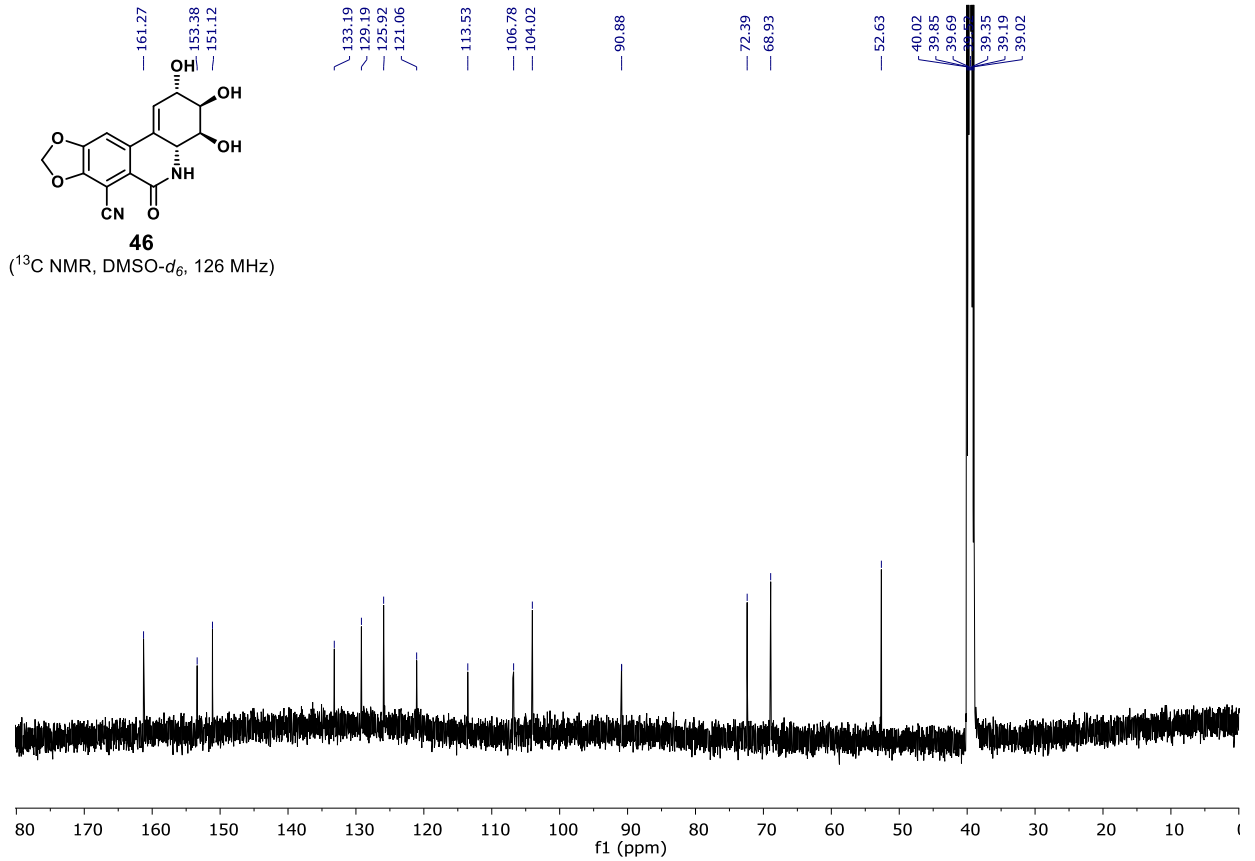



($^{13}$C NMR, $D_2O$, 126 MHz)



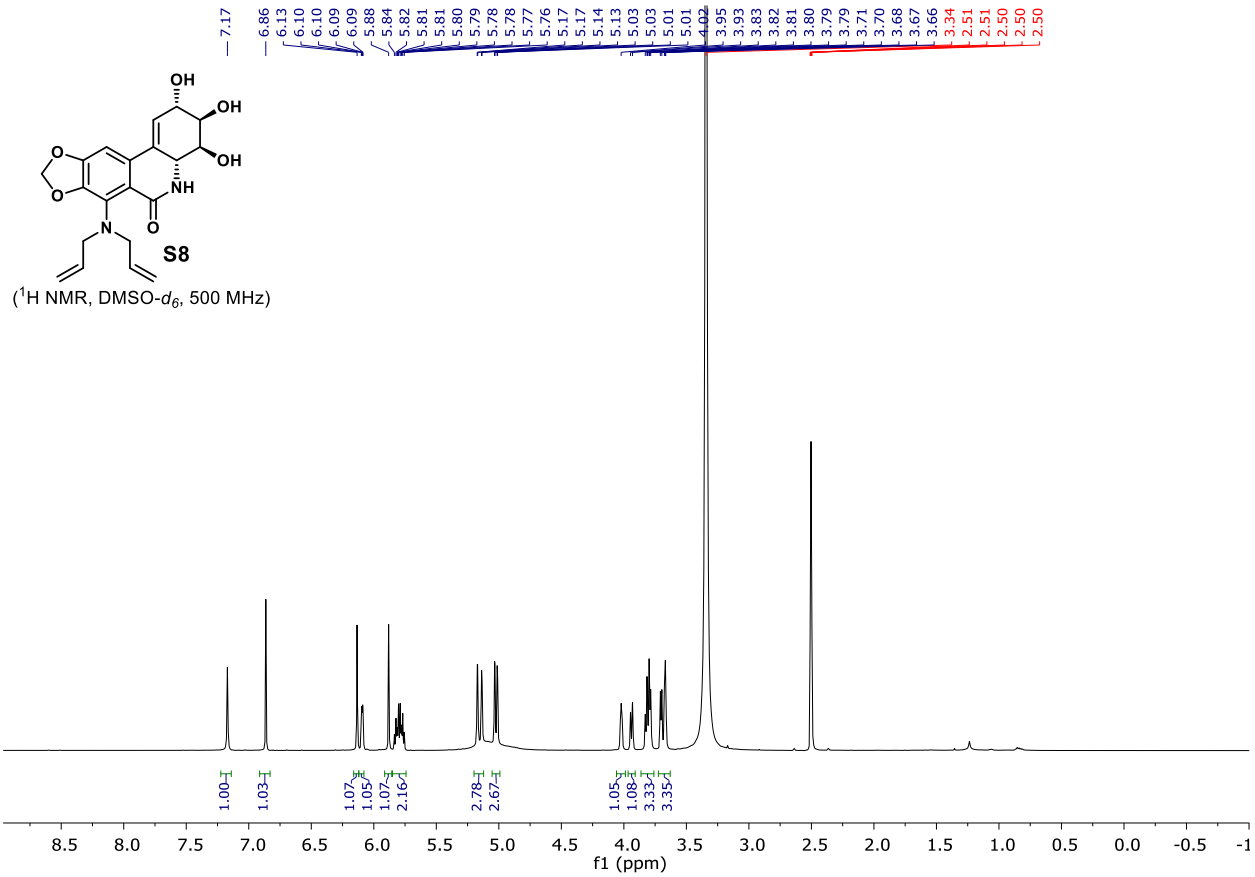

**46**

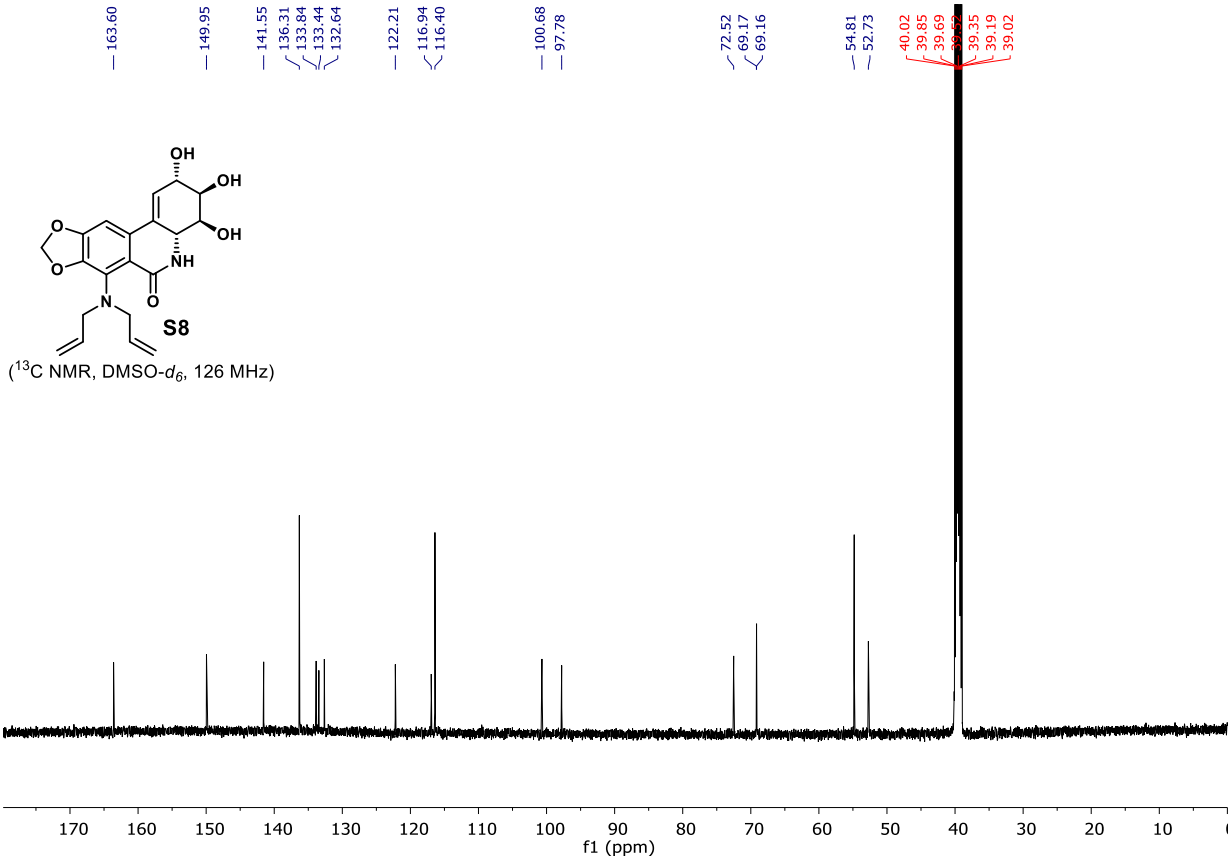
($^1$H NMR, DMSO-$d_6$, 500 MHz)

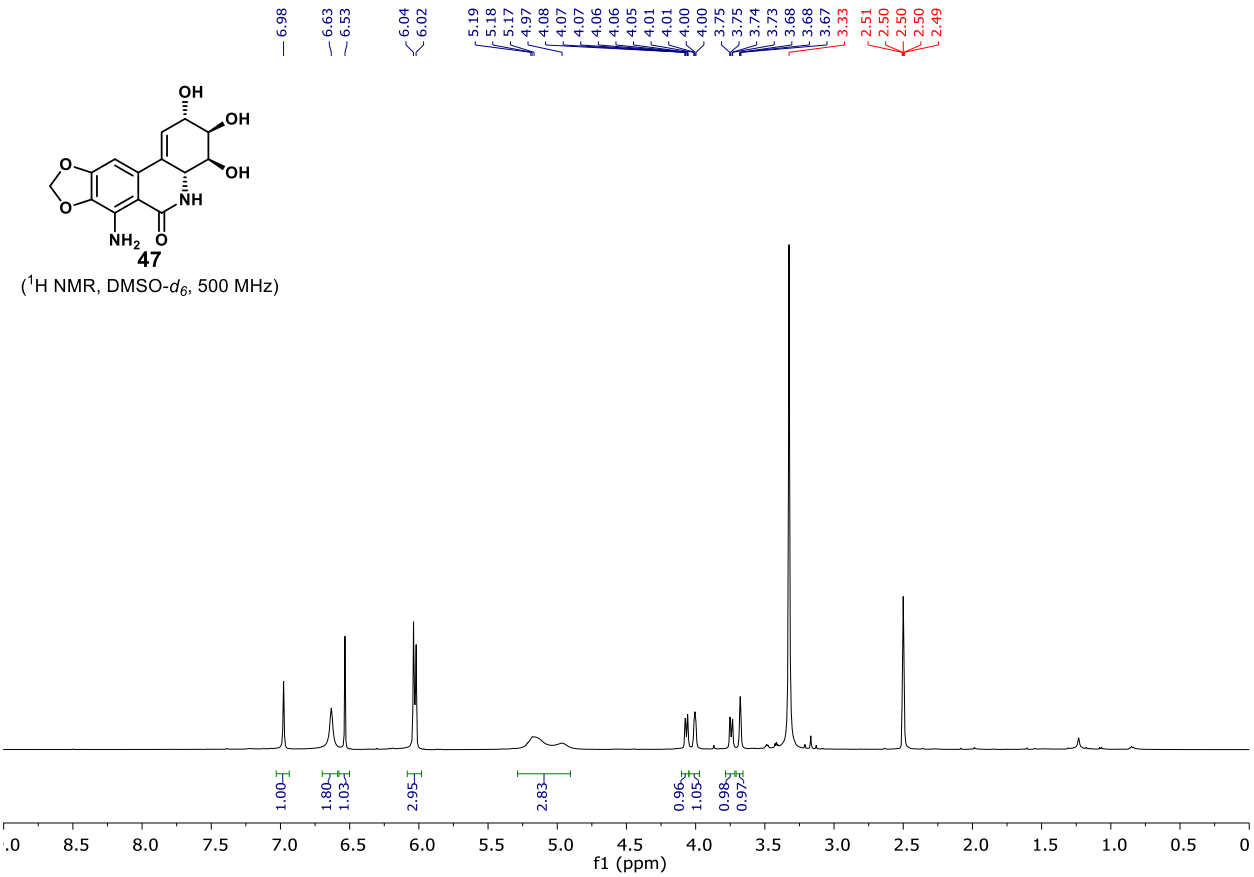



**46**

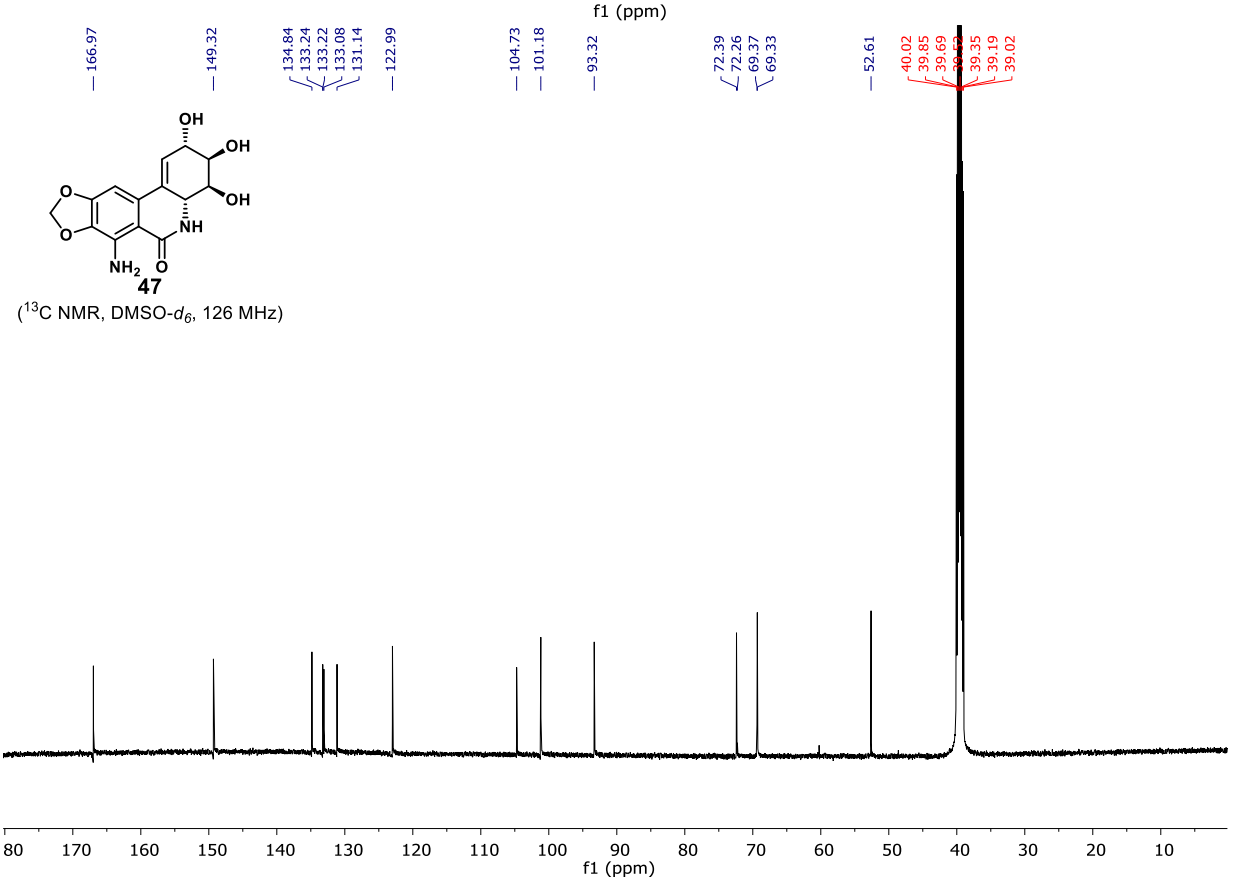
($^{13}$C NMR, DMSO-$d_6$, 126 MHz)


OH
OH
OH
O
O
NH
O
N
S8
(1H NMR, DMSO-d6, 500 MHz)
f1 (ppm)

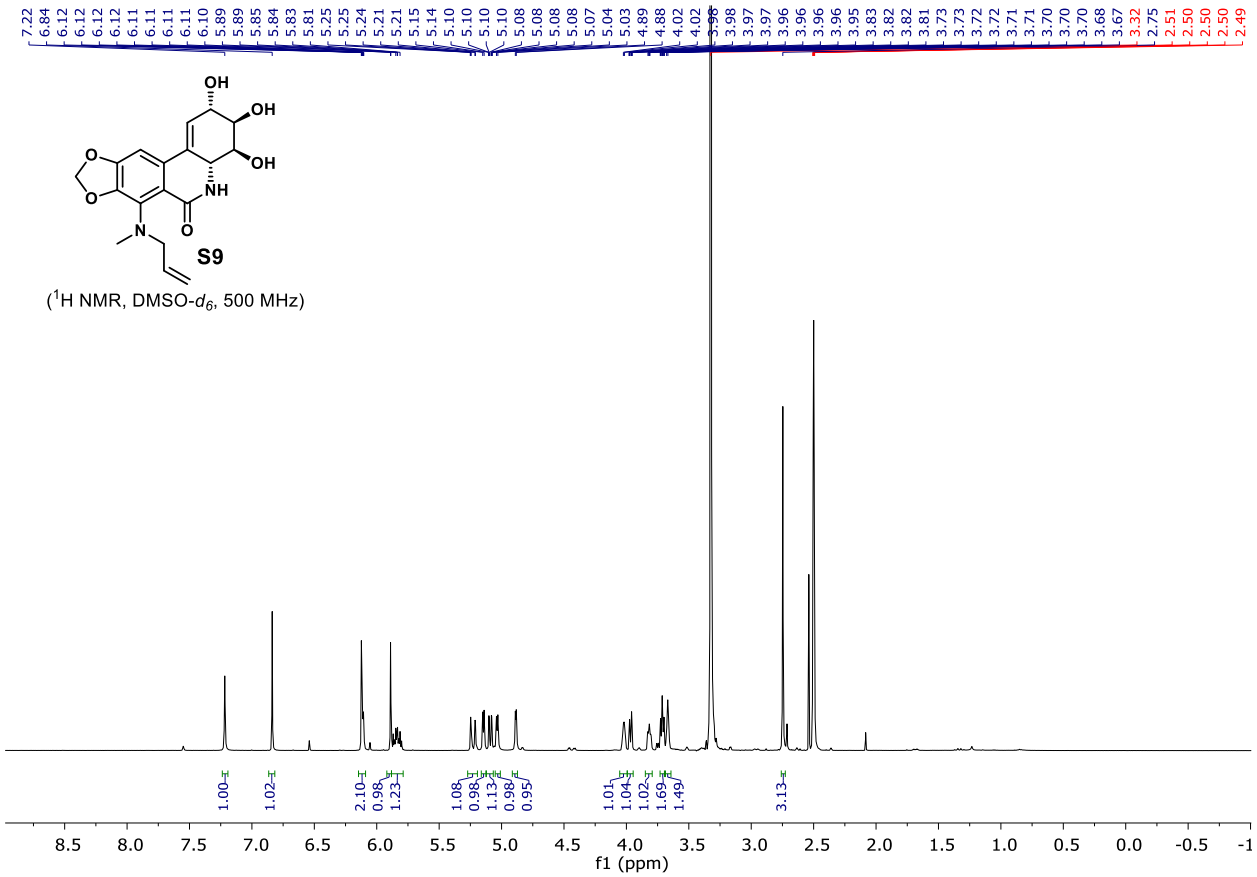

OH
OH
OH
O
O
NH
O
N
S8
(13C NMR, DMSO-d6, 126 MHz)
f1 (ppm)

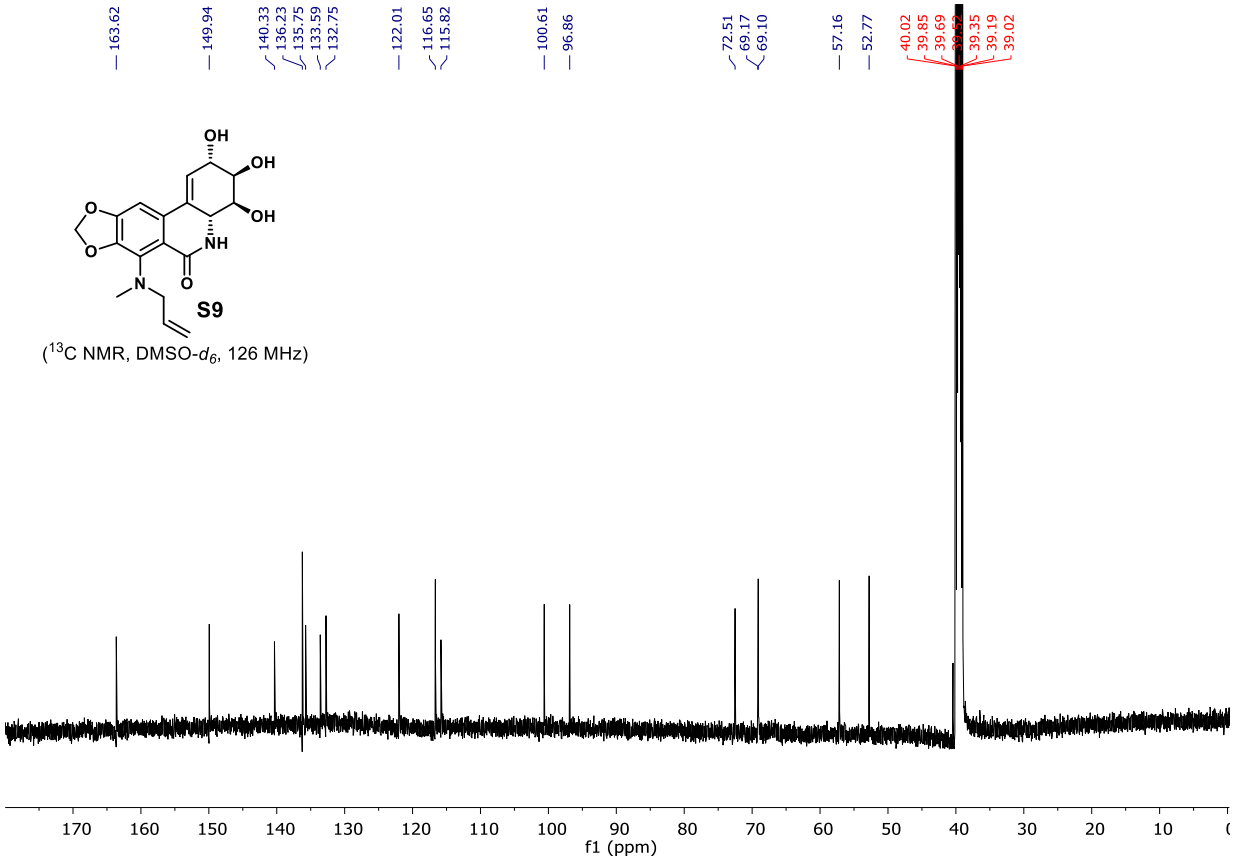


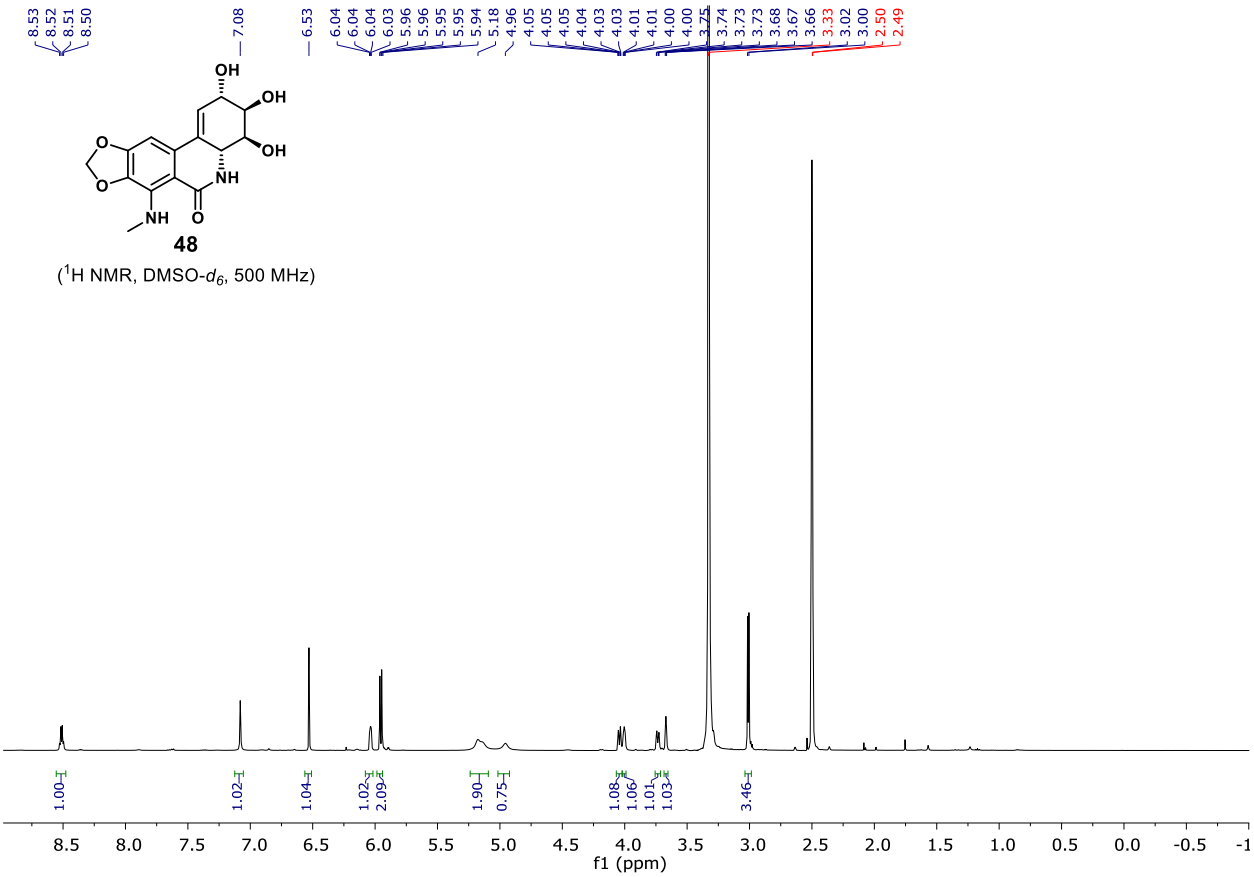

($^{1}$H NMR, DMSO-$d_6$, 500 MHz)



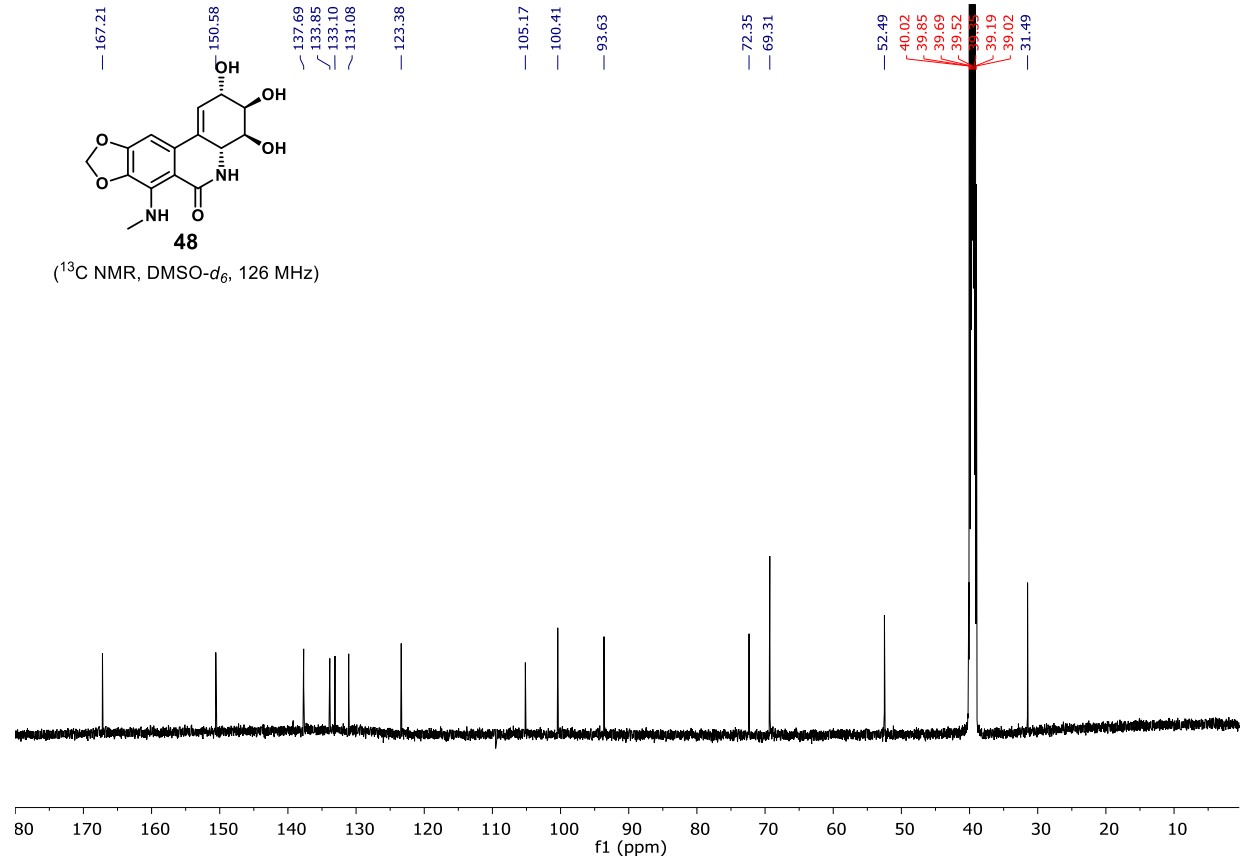

($^{13}$C NMR, DMSO-$d_6$, 126 MHz)


OH
OH
OH
O
O
NH
O
N
S9
(1H NMR, DMSO-d6, 500 MHz)
f1 (ppm)

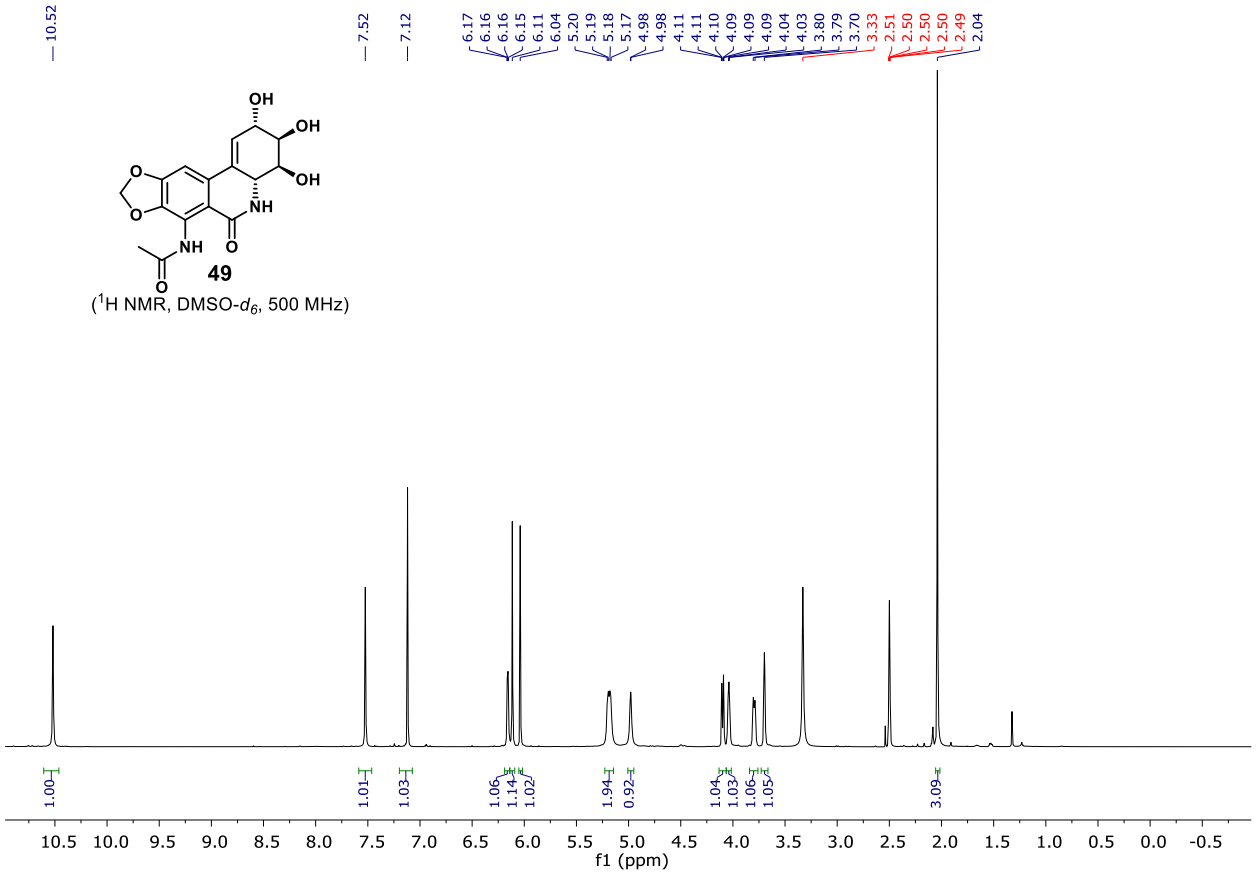

OH
OH
OH
O
O
NH
O
N
S9
(13C NMR, DMSO-d6, 126 MHz)
f1 (ppm)

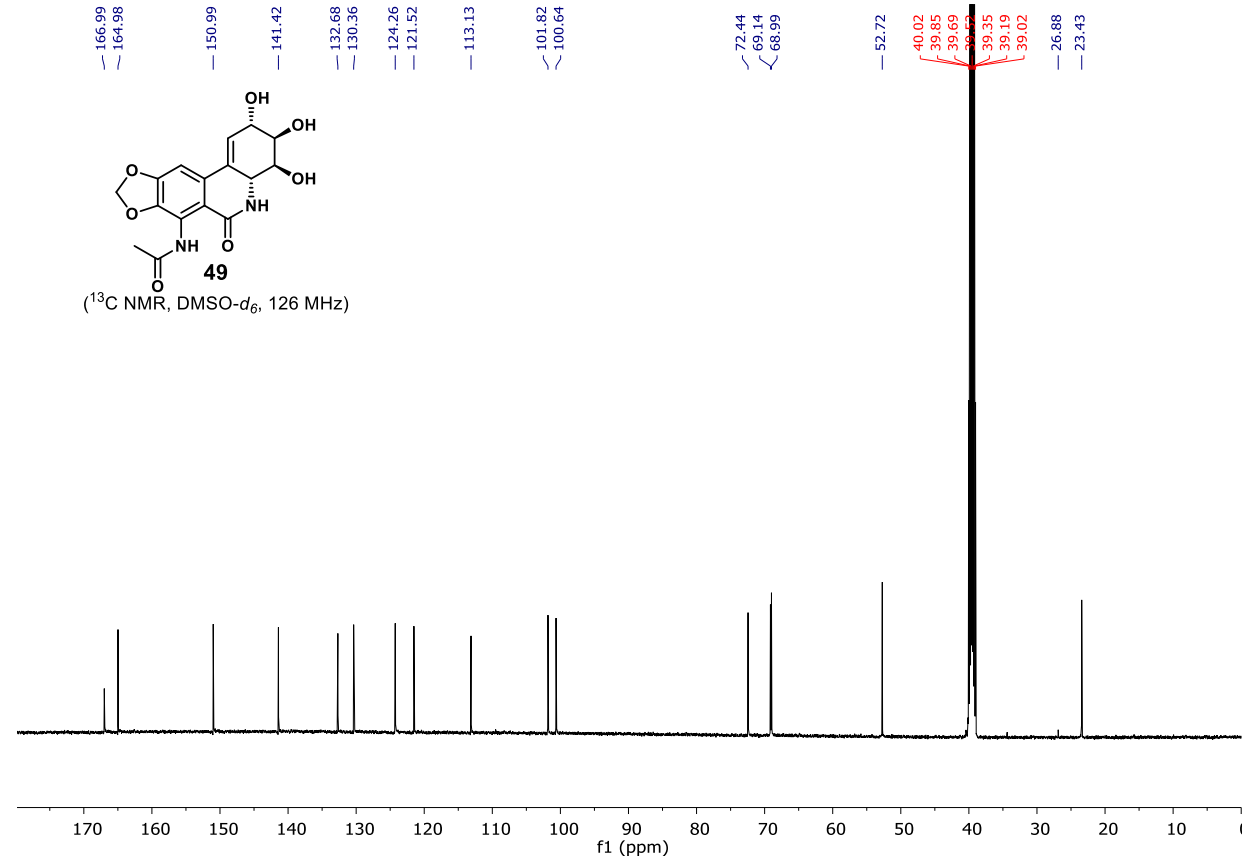


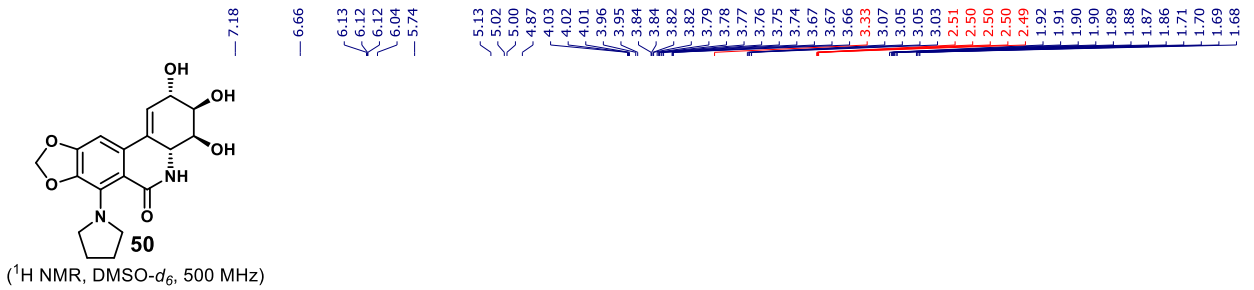

($^{1}$H NMR, DMSO-$d_6$, 500 MHz)




($^{13}$C NMR, DMSO-$d_6$, 126 MHz)


10.52
7.52
7.12
6.17
6.16
6.16
6.15
6.11
6.04
5.20
5.19
5.18
5.17
4.98
4.98
4.11
4.11
4.10
4.09
4.09
4.09
4.04
4.03
3.80
3.79
3.70
3.33
2.51
2.50
2.50
2.50
2.49
2.04
OH
OH
OH
O
O
NH
NH
O
O
49
(1H NMR, DMSO-d6, 500 MHz)
1.00
1.01
1.03
1.06
1.14
1.02
1.94
0.92
1.04
1.03
1.06
1.05
3.09
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


166.99
164.98
150.99
141.42
132.68
130.36
124.26
121.52
113.13
101.82
100.64
72.44
69.14
68.99
52.72
40.02
39.85
39.69
39.52
39.35
39.19
39.02
26.88
23.43
OH
OH
OH
O
O
NH
NH
O
O
49
(13C NMR, DMSO-d6, 126 MHz)
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
f1 (ppm)

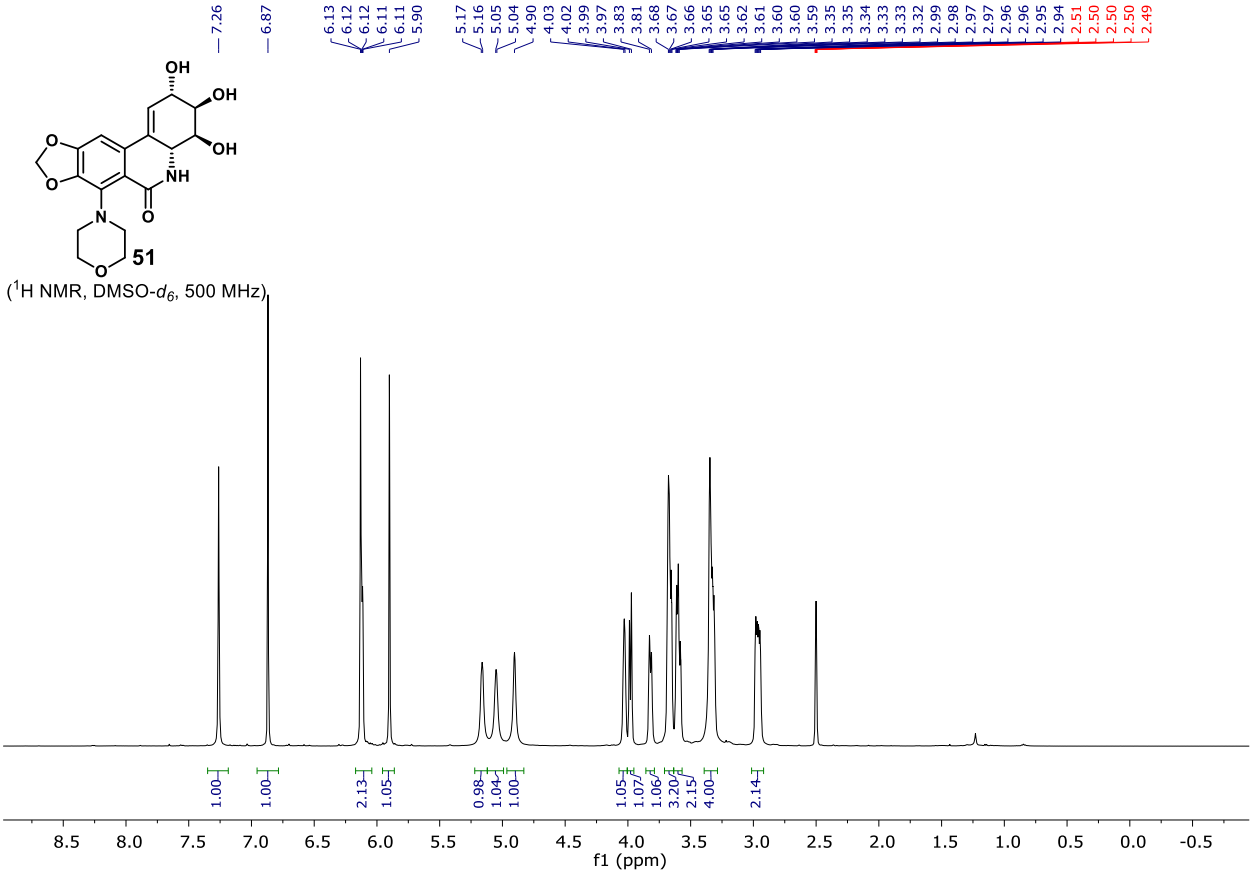


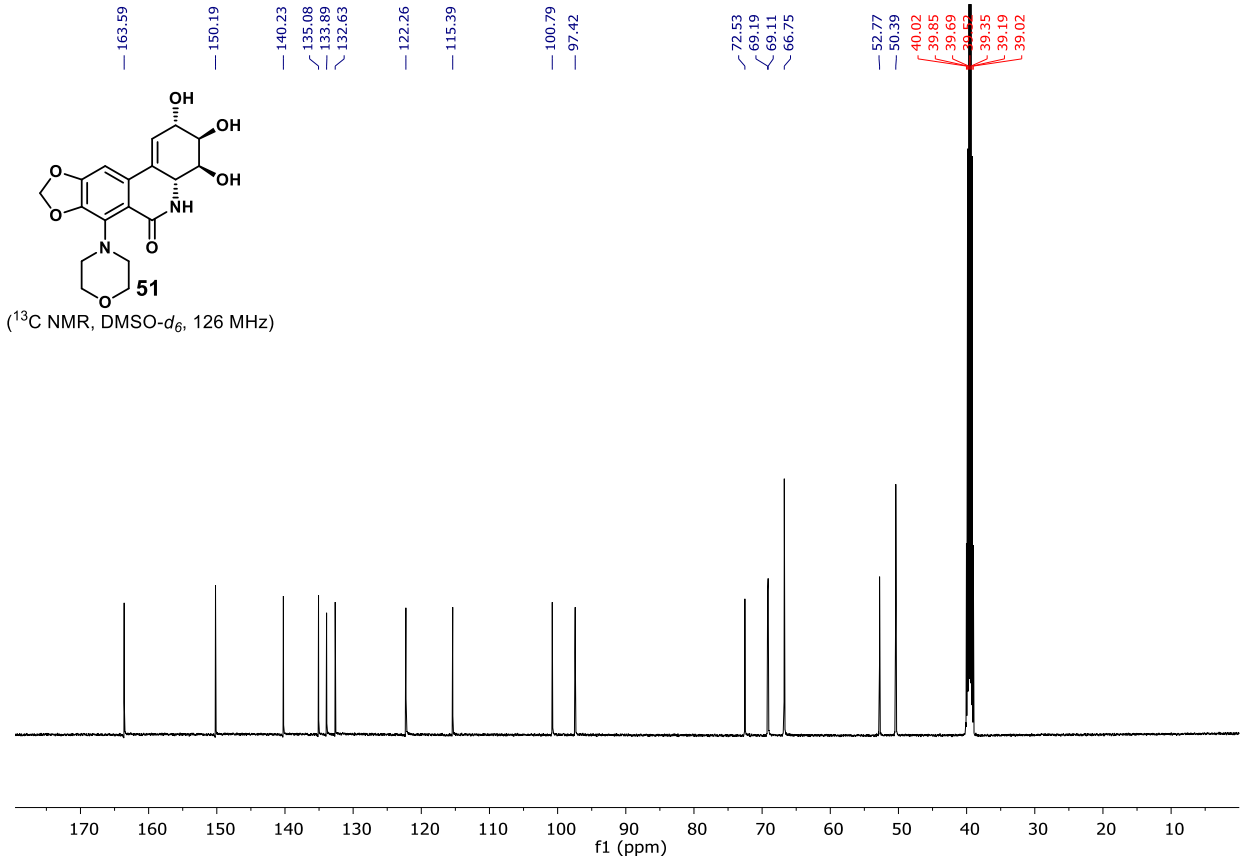

($^1$H NMR, DMSO-$d_6$, 500 MHz)

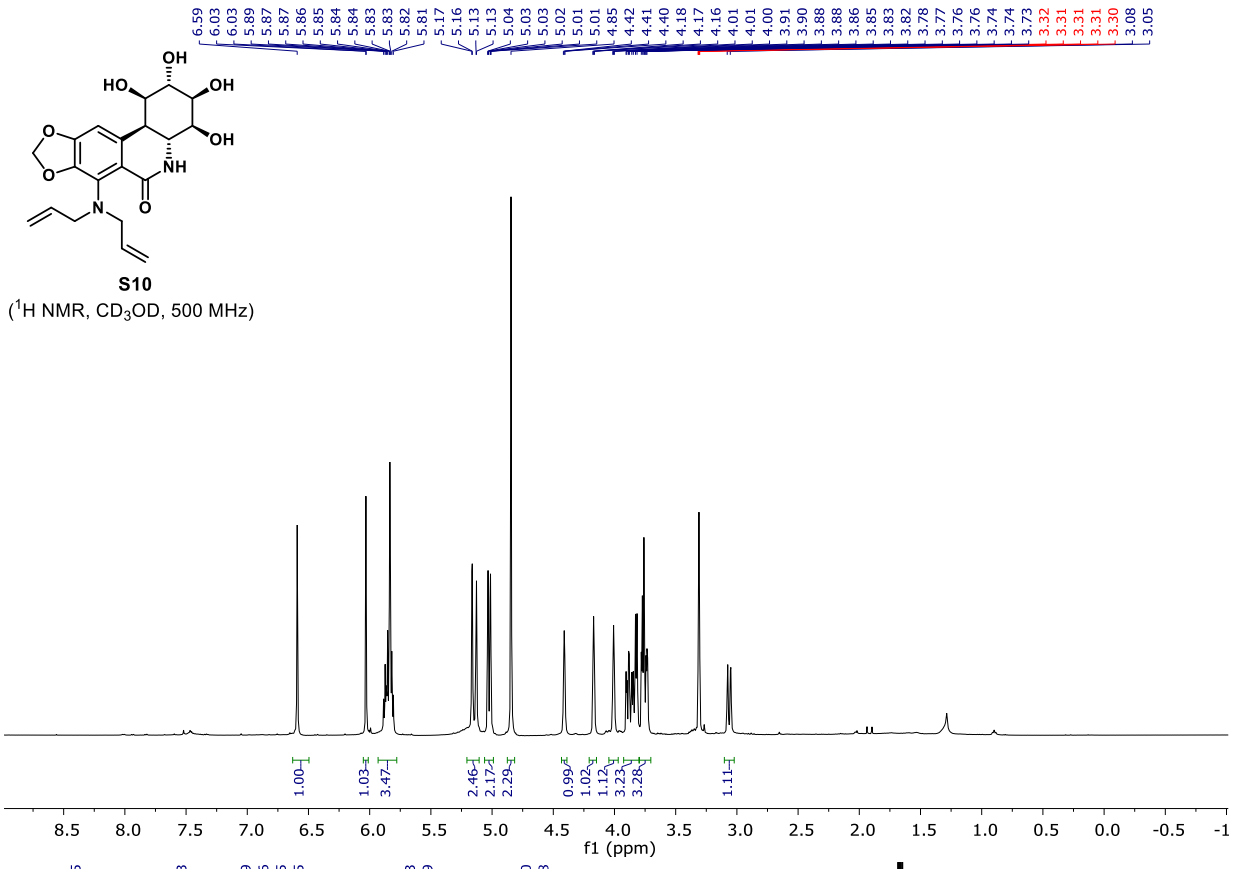




($^{13}$C NMR, DMSO-$d_6$, 126 MHz)

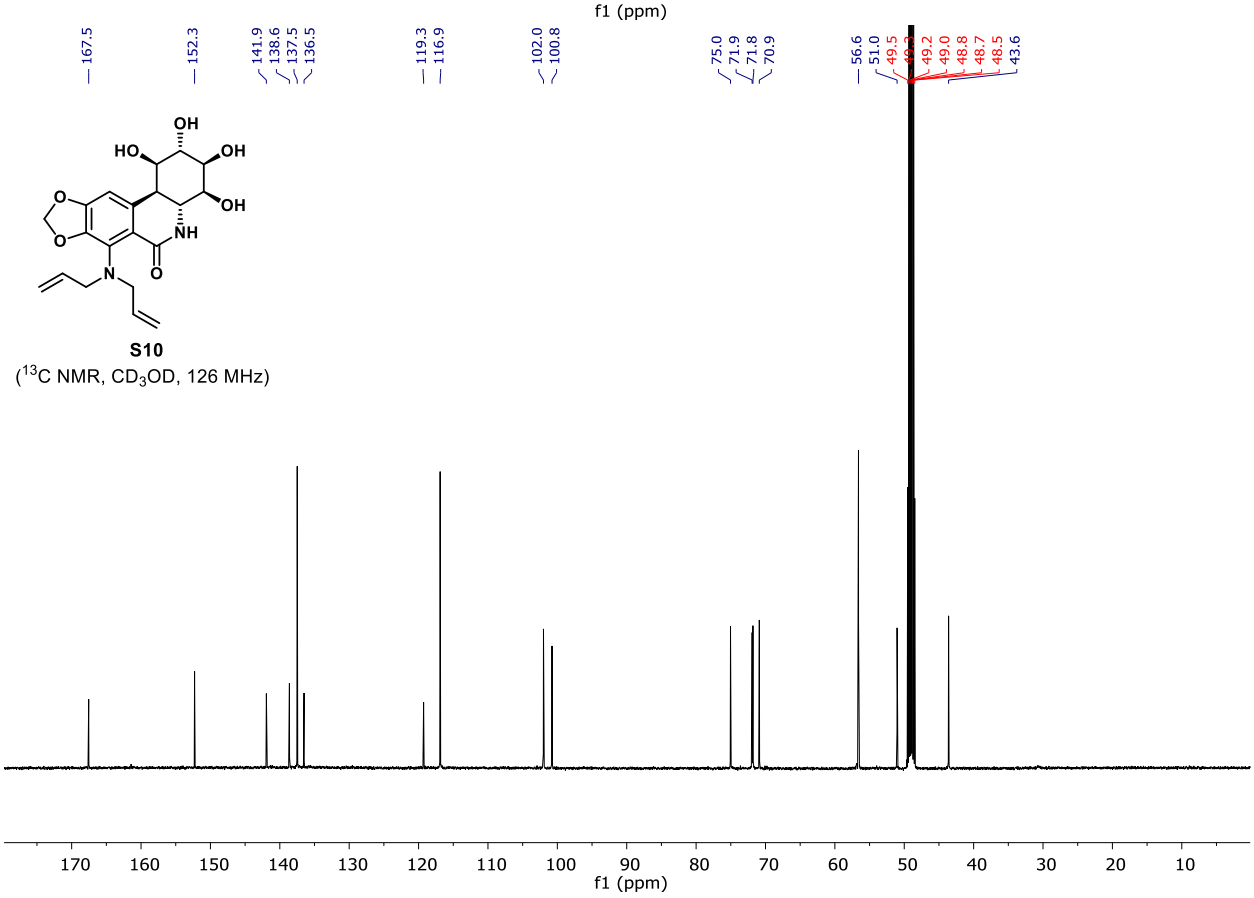

OH
OH
OH
O
O
NH
O
N
O
51
(1H NMR, DMSO-d6, 500 MHz)
f1 (ppm)


OH
OH
OH
O
O
NH
O
N
O
51
(13C NMR, DMSO-d6, 126 MHz)
f1 (ppm)



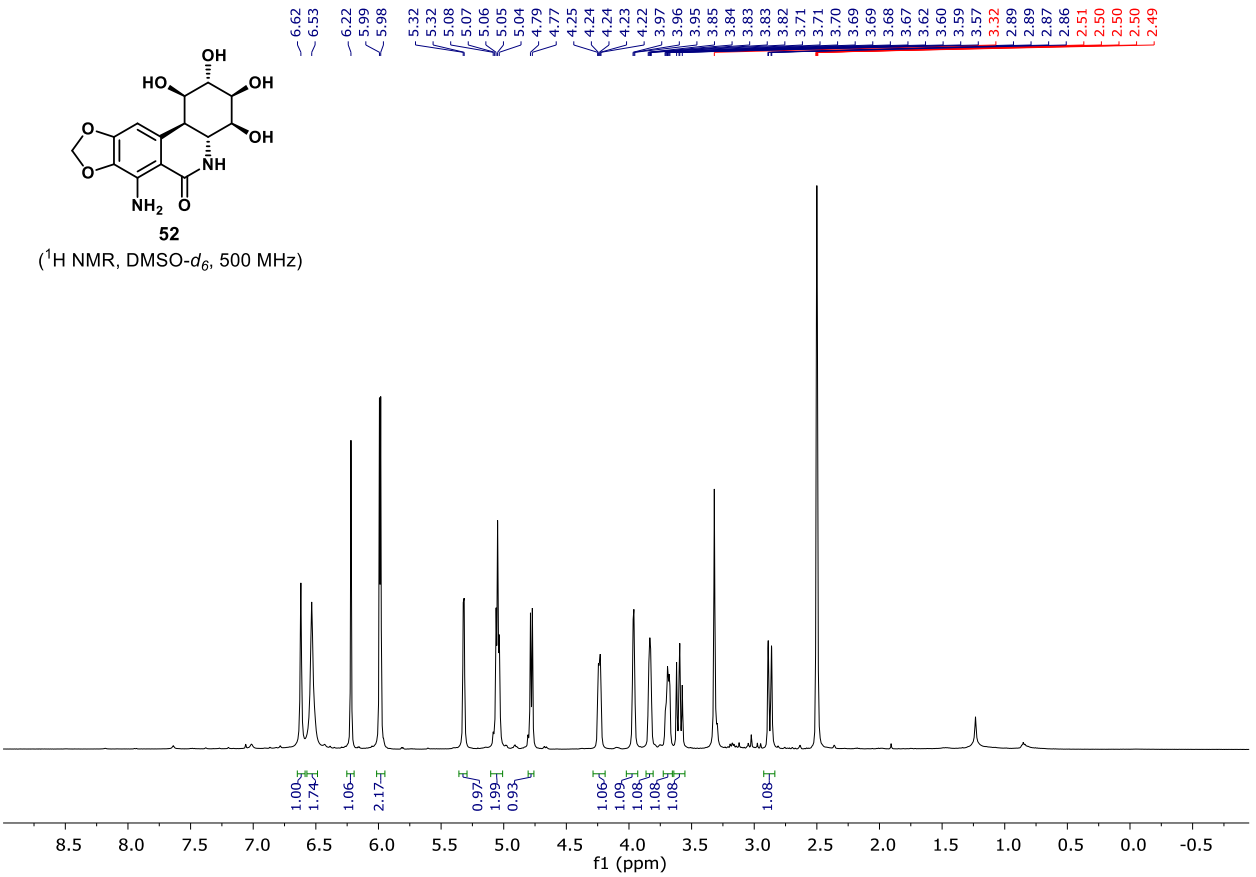

**S10**

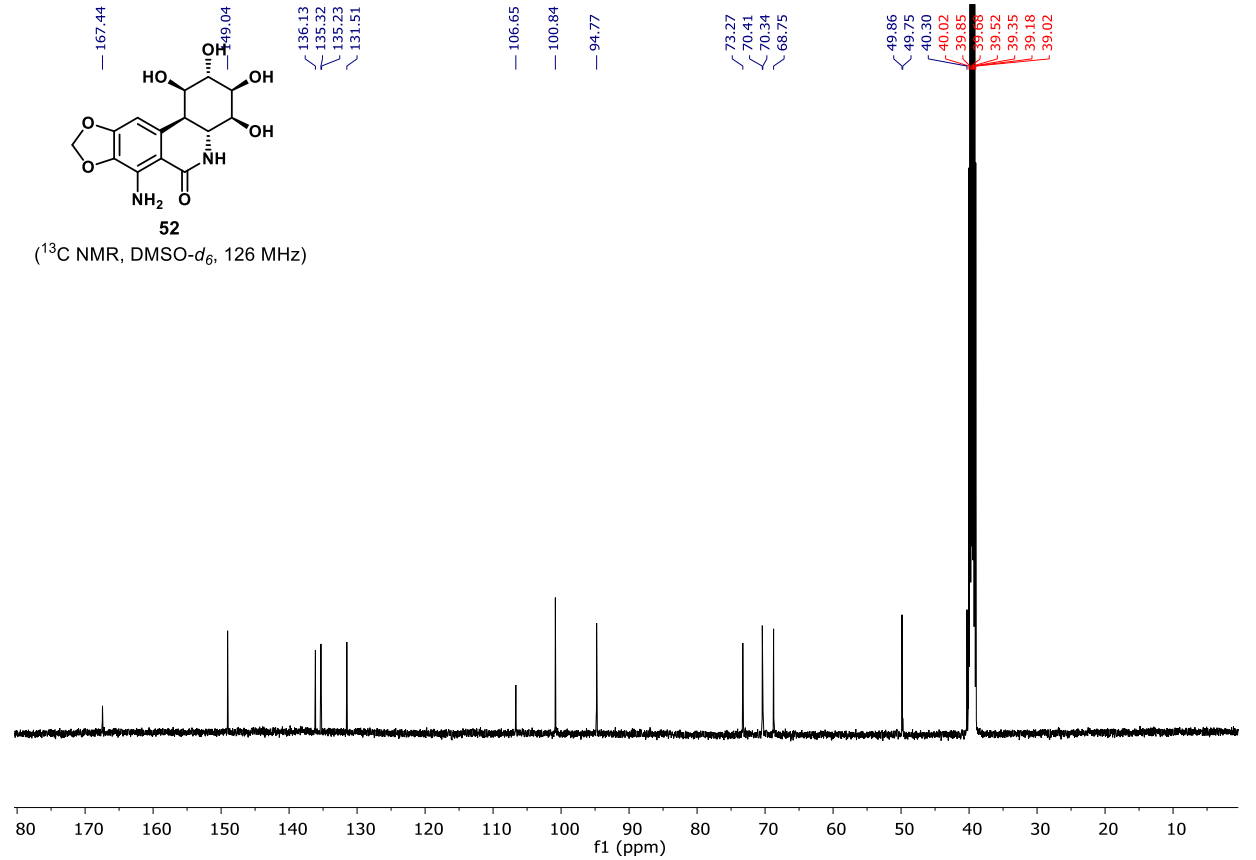
($^1$H NMR, $CD_3OD$, 500 MHz)

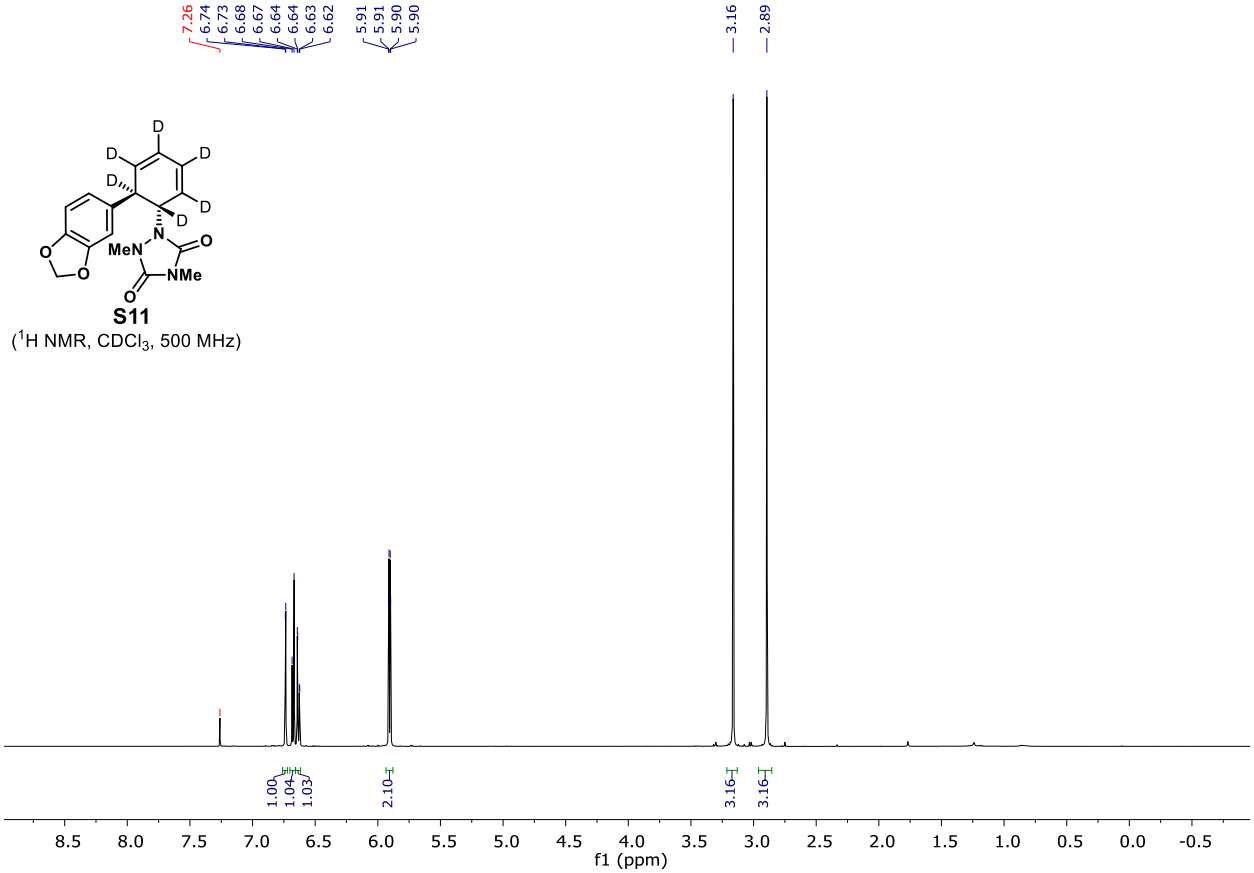



**S10**

($^{13}$C NMR, $CD_3OD$, 126 MHz)

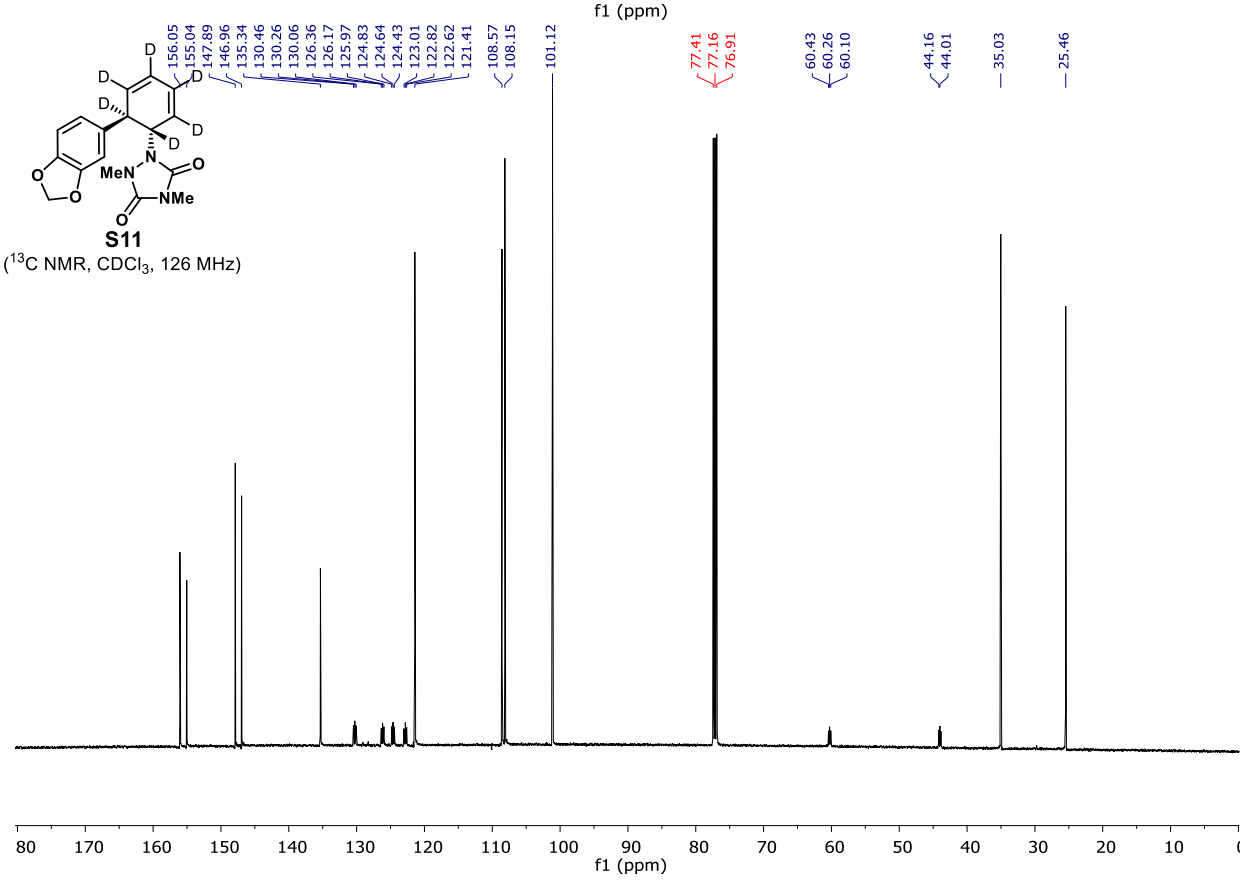

52
(1H NMR, DMSO-d6, 500 MHz)
f1 (ppm)


52
(13C NMR, DMSO-d6, 126 MHz)
f1 (ppm)



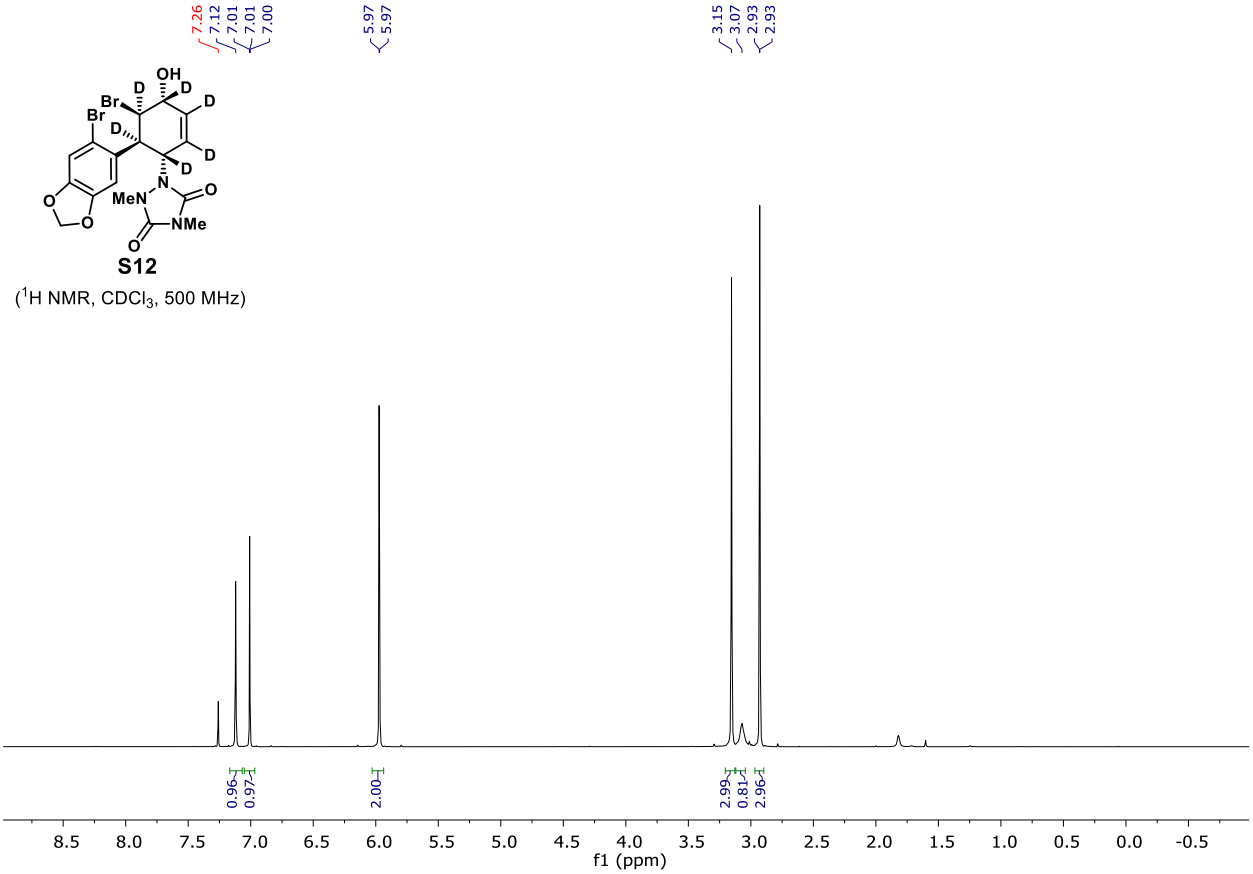

**S11**

($^1$H NMR, $CDCl_3$, 500 MHz)



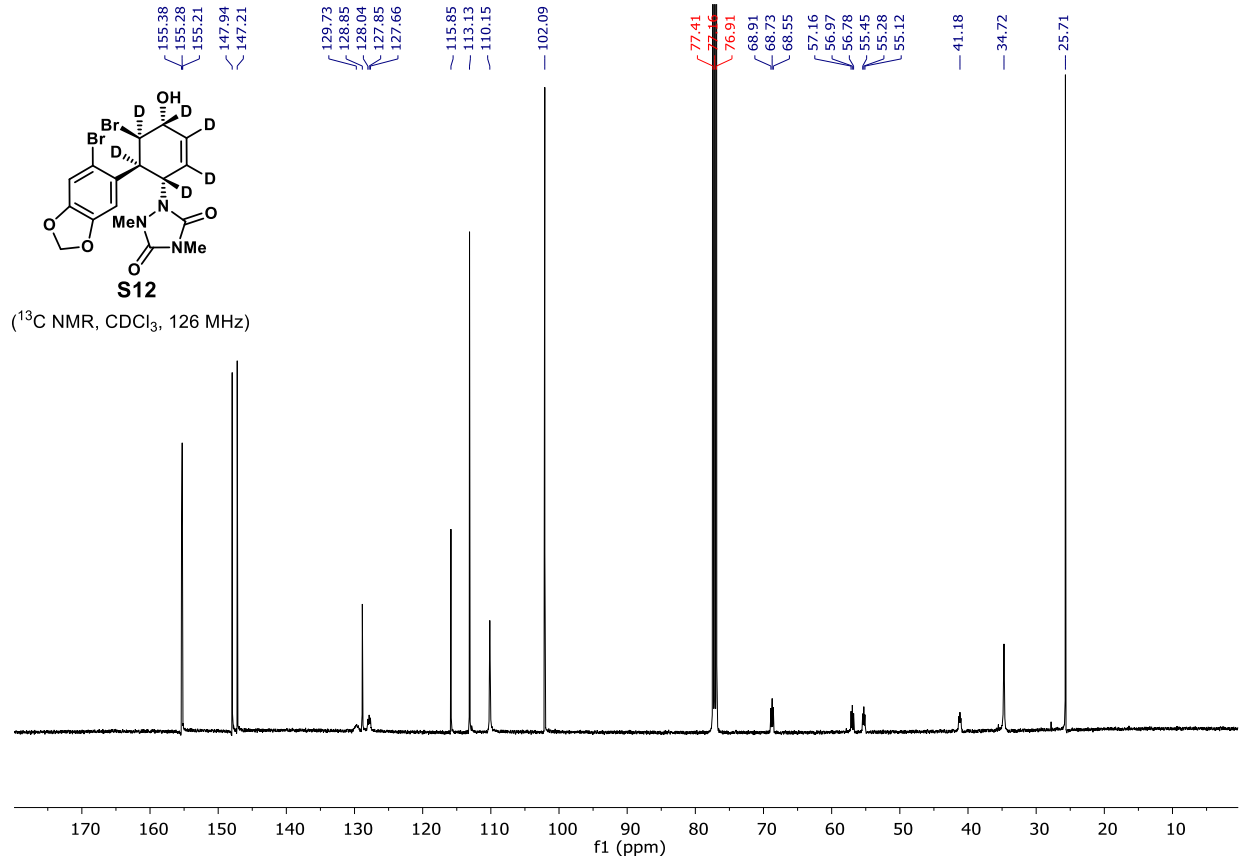

**S11**

($^{13}$C NMR, $CDCl_3$, 126 MHz)



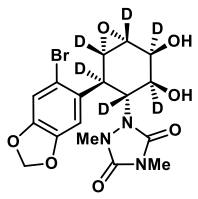

**S12**

($^1$H NMR, $CDCl_3$, 500 MHz)




**S12**

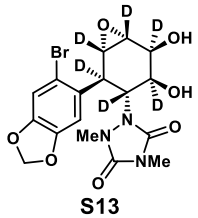
($^{13}$C NMR, $CDCl_3$, 126 MHz)




**S13**

($^1$H NMR, $CDCl_3$, 500 MHz, 20 °C)

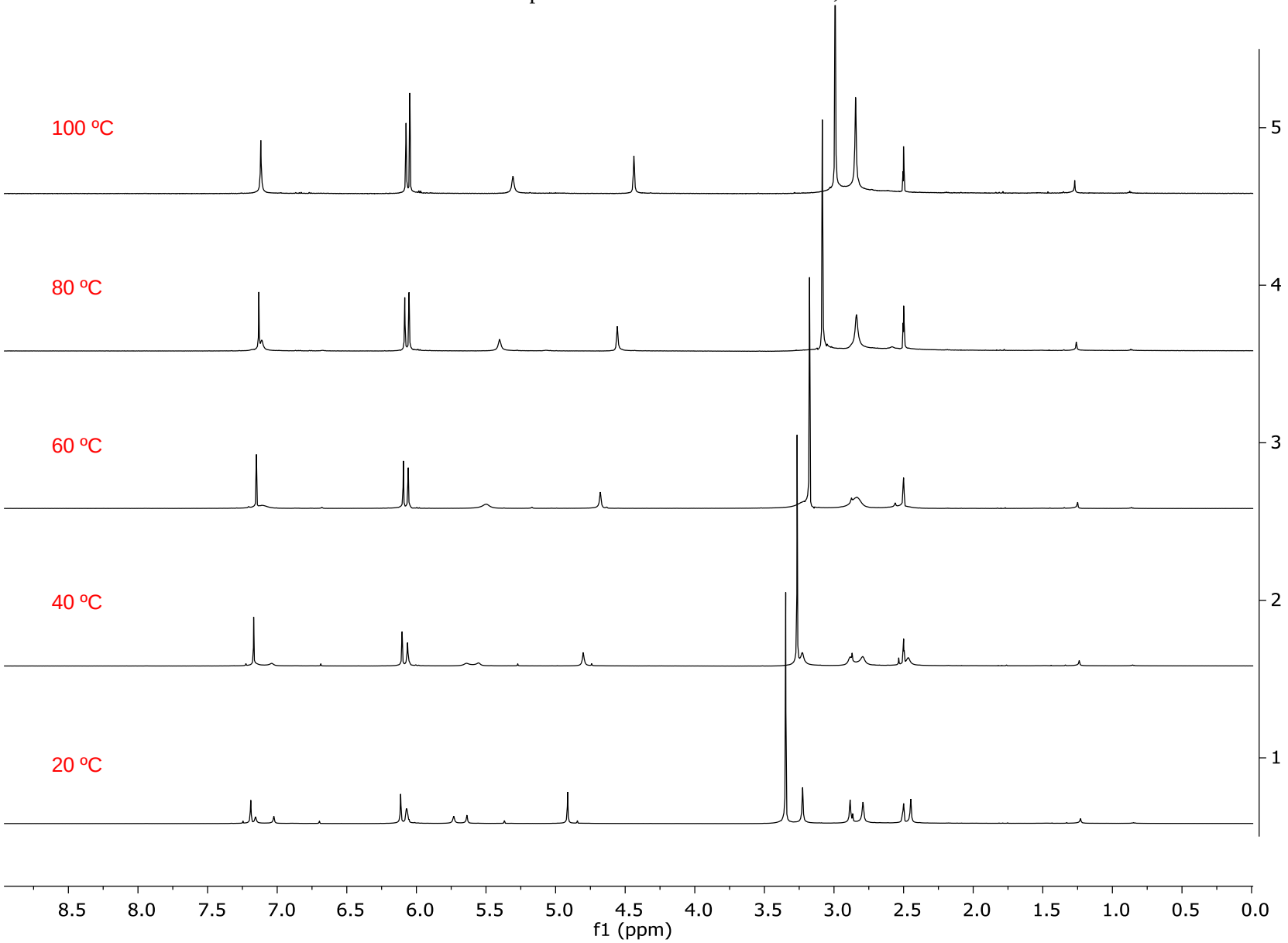


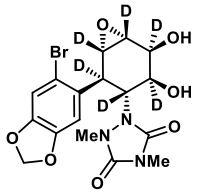




**S13**

($^1$H NMR, $CDCl_3$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **S13** in DMSO, 500 MHz:

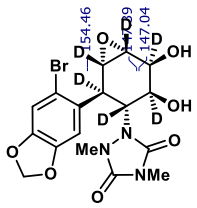




**S13**

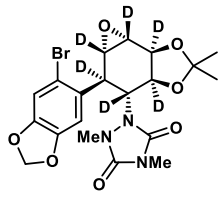
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)



**S13**

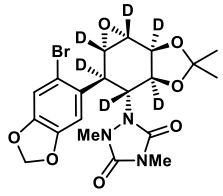
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)




**S14**

($^1$H NMR, $CDCl_3$, 500 MHz, 20 °C)

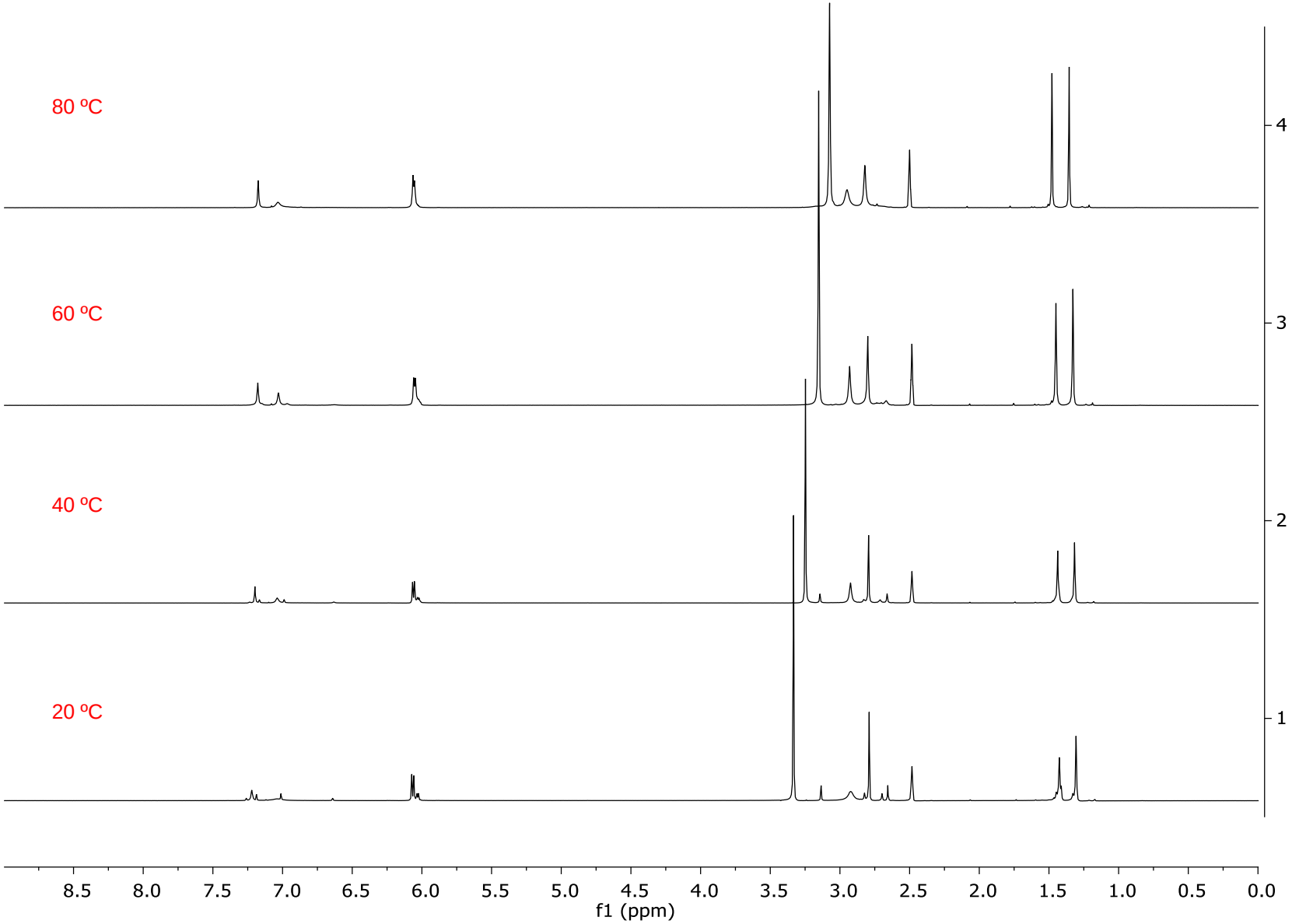


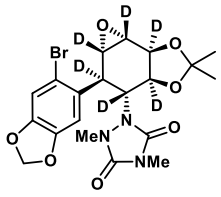




**S14**

($^1$H NMR, $CDCl_3$, 500 MHz, 80 °C)

$^{1}$H NMR temperature studies of **S14** in DMSO, 500 MHz:

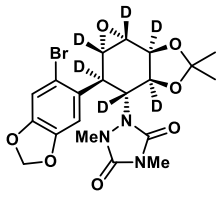




**S14**

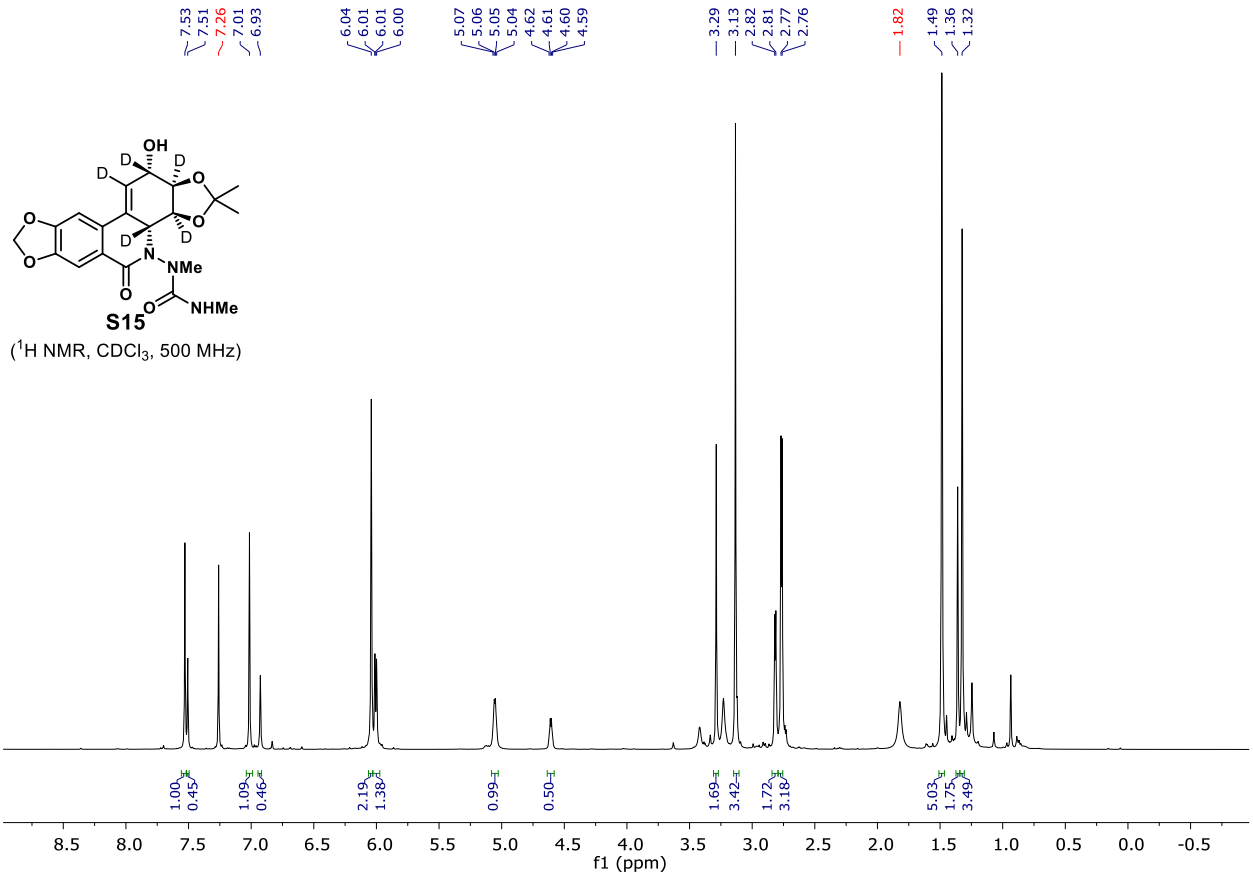
($^1$H NMR, $CDCl_3$, 500 MHz, 20 °C)

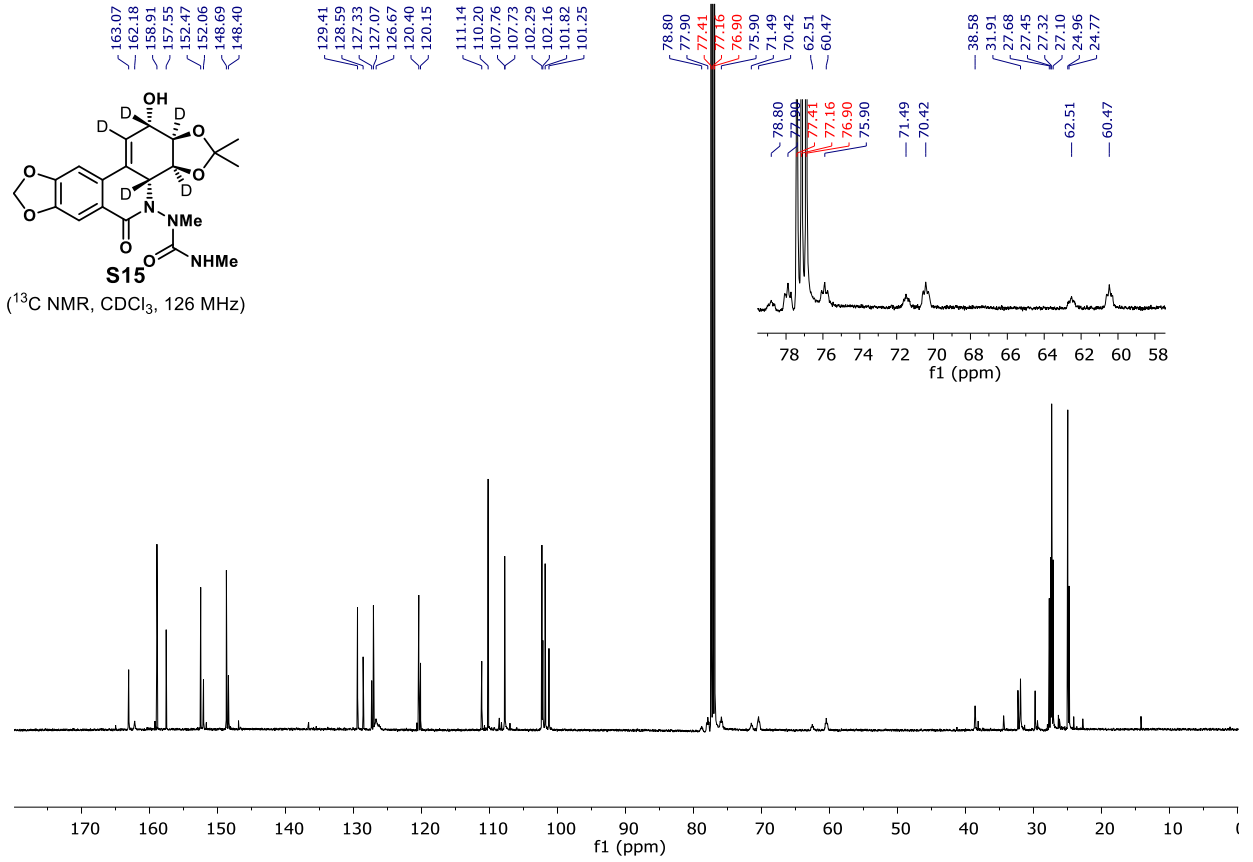


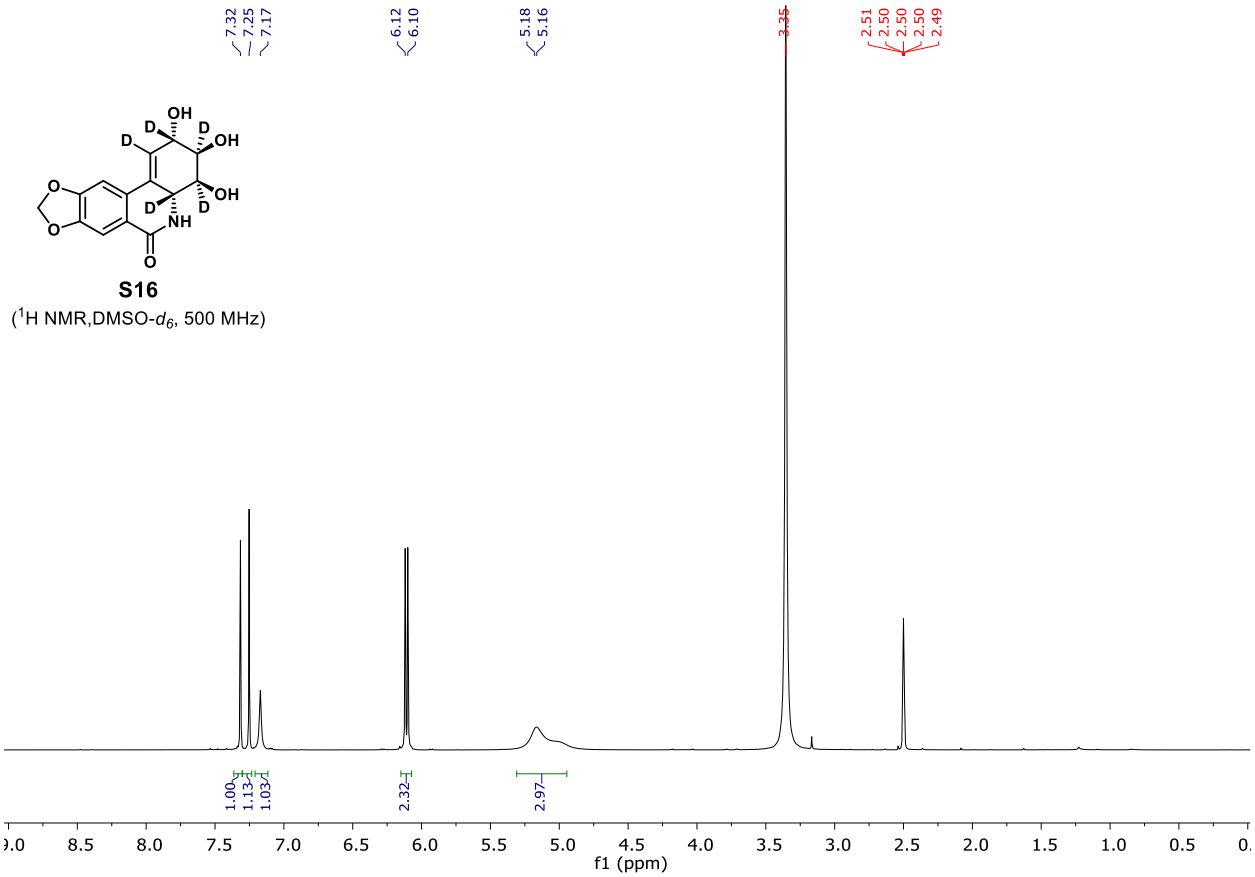



**S14**

($^1$H NMR, $CDCl_3$, 500 MHz, 80 °C)

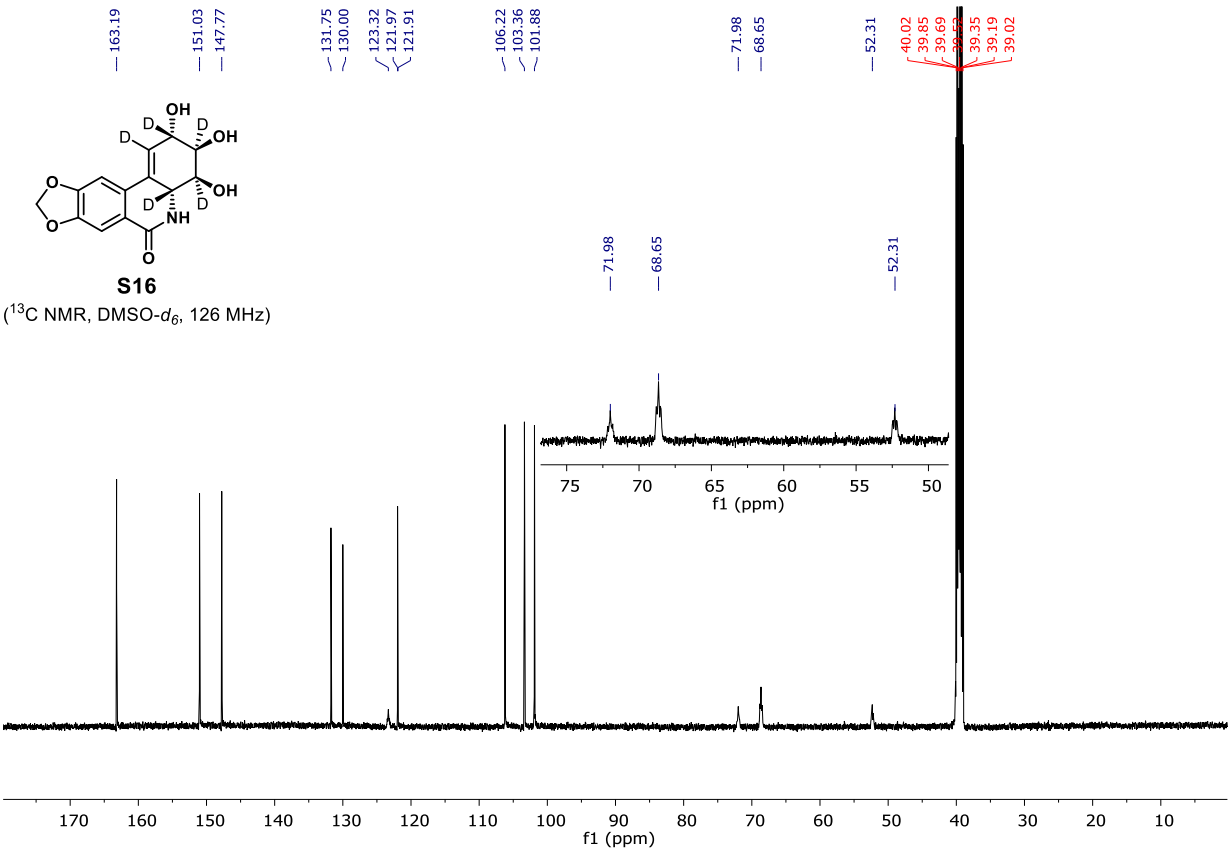

S15
($^1$H NMR, $CDCl_3$, 500 MHz)
f1 (ppm)


S15
($^{13}$C NMR, $CDCl_3$, 126 MHz)
f1 (ppm)



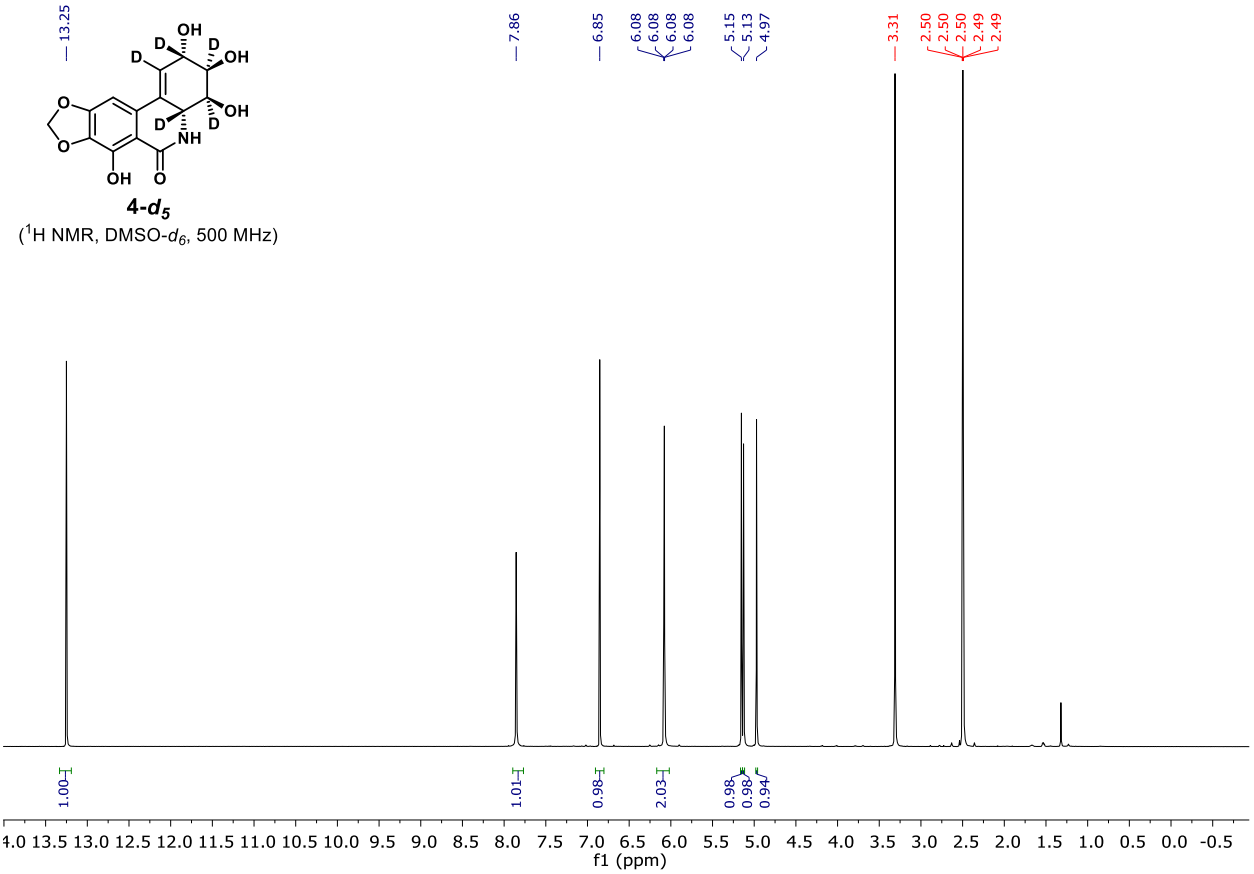

**S16**

($^1$H NMR,DMSO-$d_6$, 500 MHz)



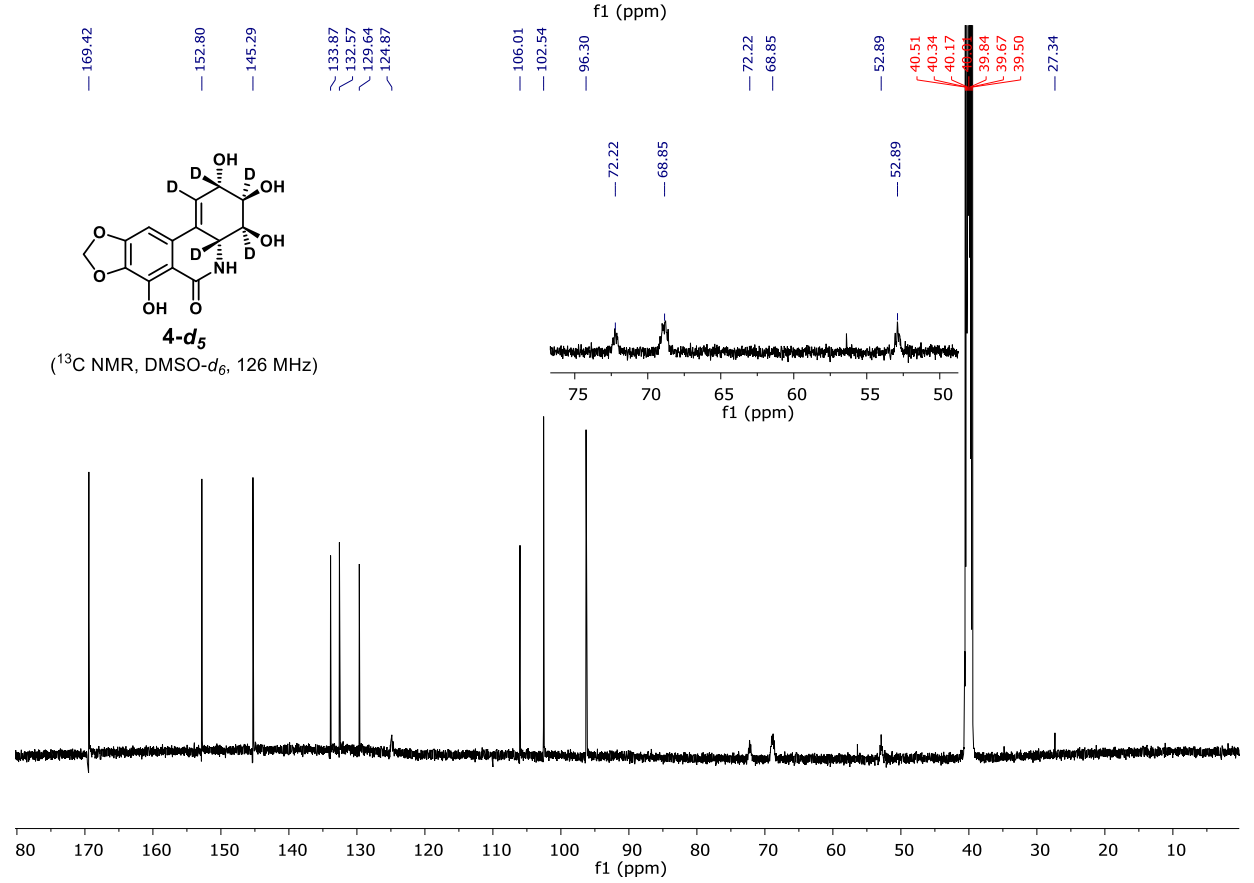

**S16**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz)



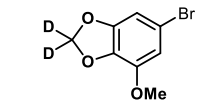

**4-$d_5$**

($^1$H NMR, DMSO-$d_6$, 500 MHz)




**4-$d_5$**

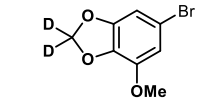
($^{13}$C NMR, DMSO-$d_6$, 126 MHz)




**11-$d_2$**

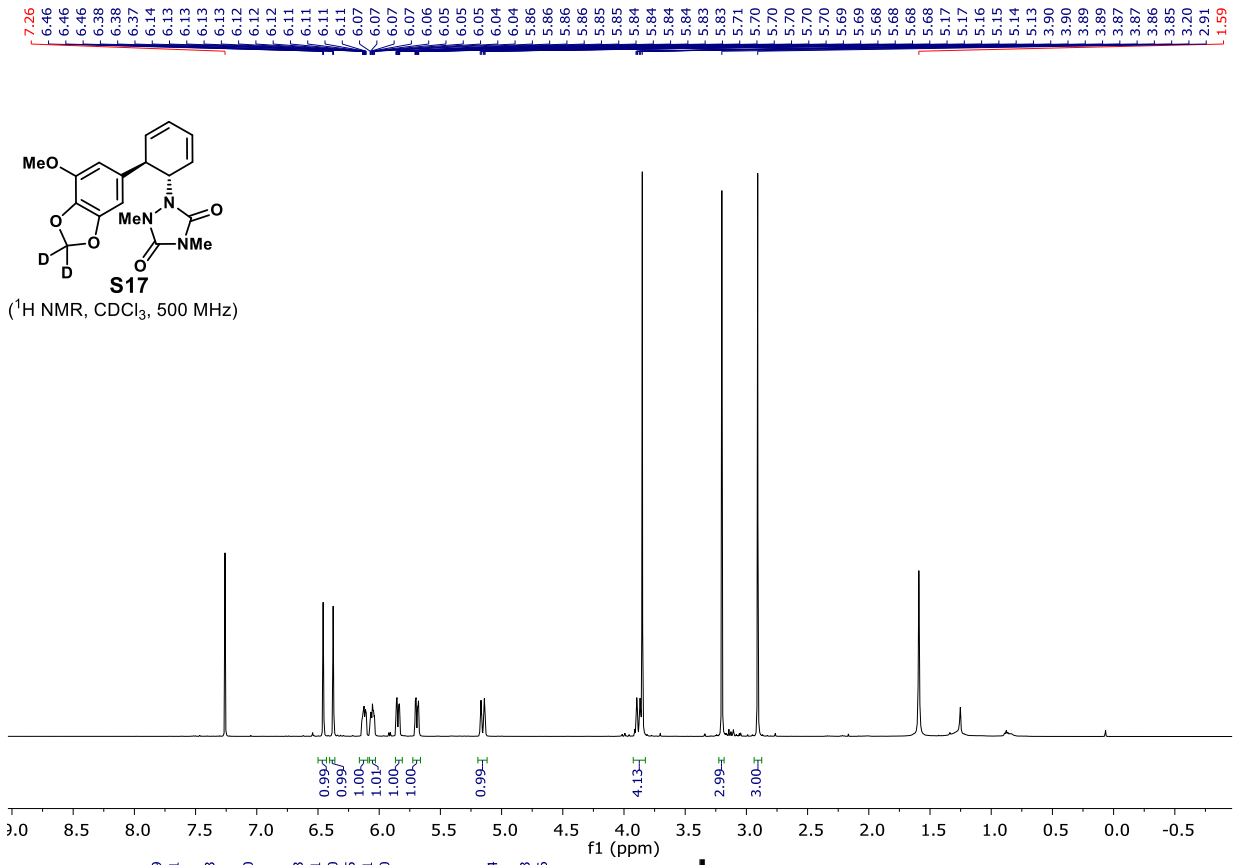
($^1$H NMR, $CDCl_3$, 500 MHz)



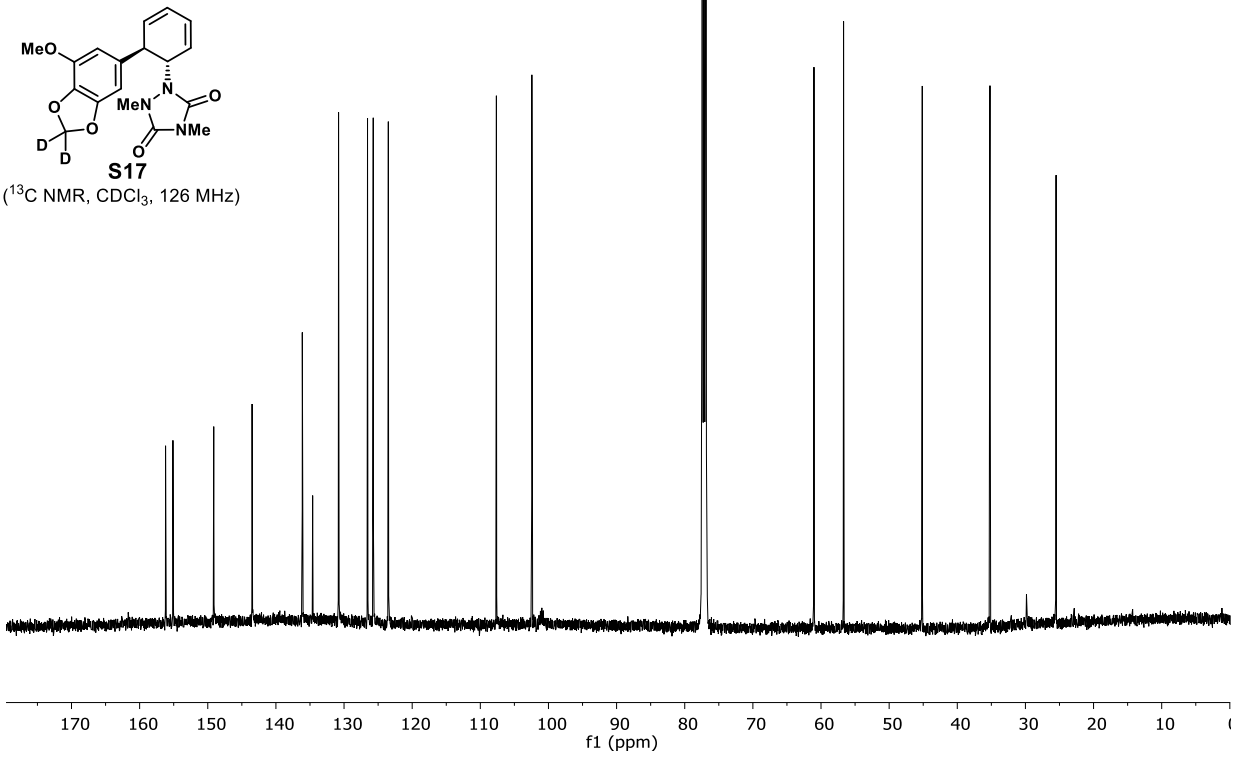

**11-$d_2$**

($^{13}$C NMR, $CDCl_3$, 126 MHz)

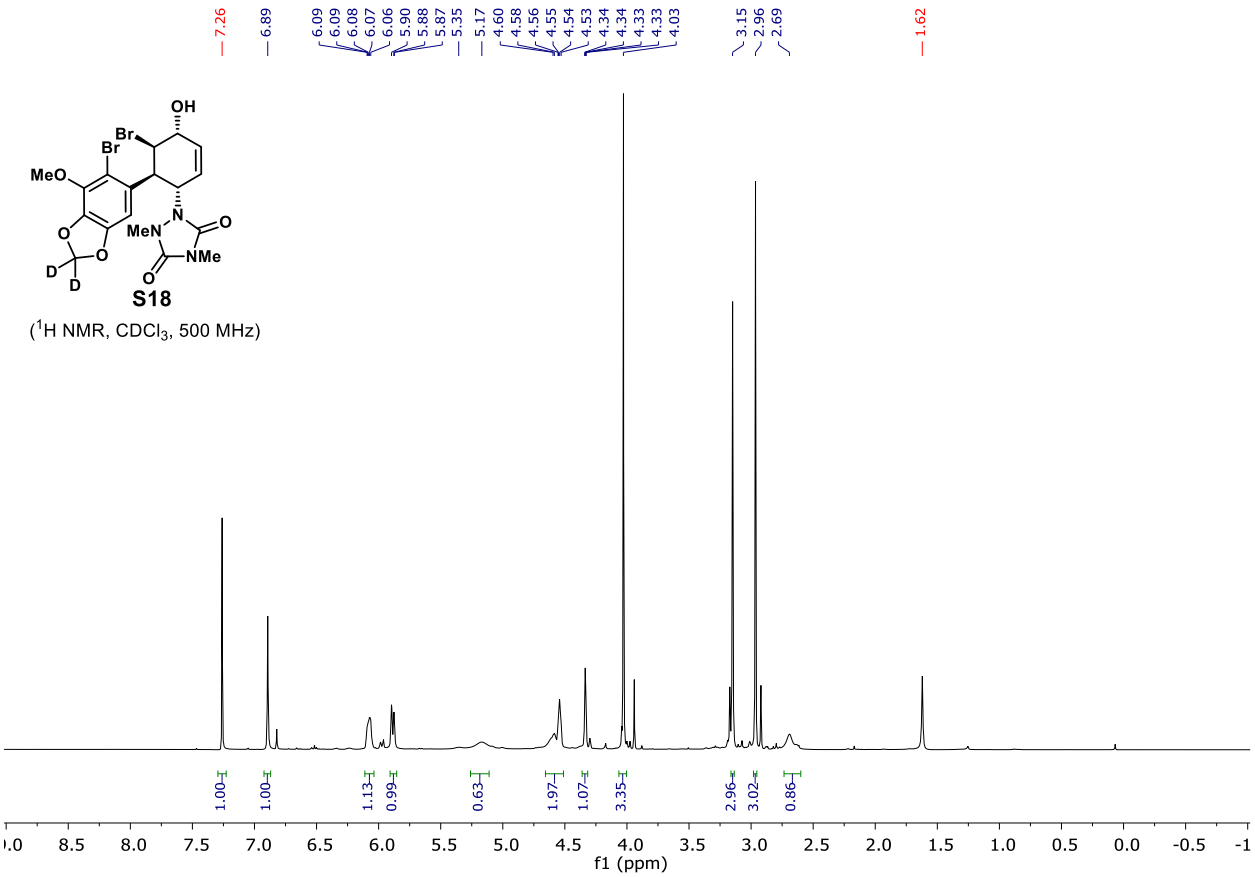


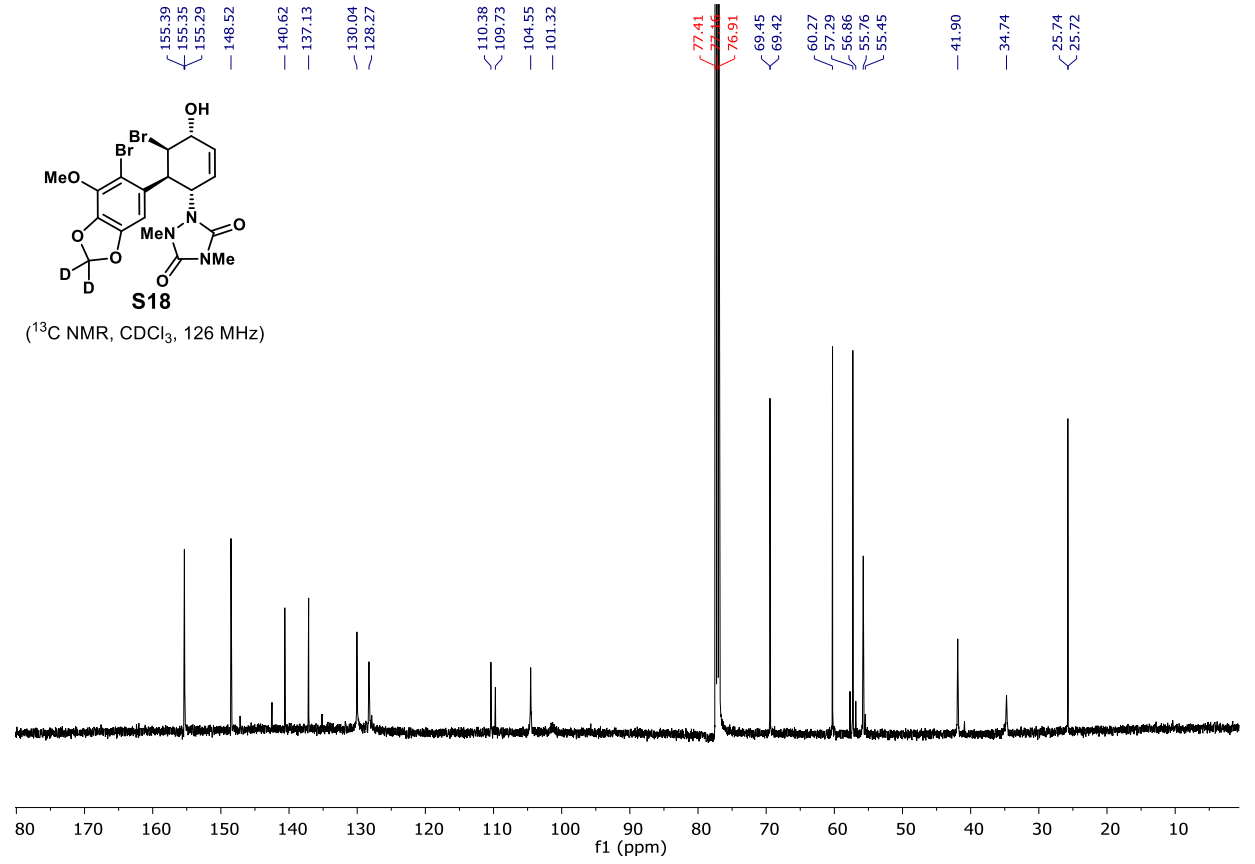

($^1$H NMR, $CDCl_3$, 500 MHz)






($^{13}$C NMR, $CDCl_3$, 126 MHz)


OH
Br
Br
MeO
O
O
D
D
MeN
N
O
NMe
O
S18
(1H NMR, CDCl3, 500 MHz)
7.26
6.89
6.09
6.09
6.08
6.07
6.06
5.90
5.88
5.87
5.35
5.17
4.60
4.58
4.56
4.55
4.54
4.53
4.34
4.34
4.33
4.33
4.03
3.15
2.96
2.69
1.62
1.00
1.00
1.13
0.99
0.63
1.97
1.07
3.35
2.96
3.02
0.86
f1 (ppm)


OH
Br
Br
MeO
O
O
D
D
MeN
N
O
NMe
O
S18
(13C NMR, CDCl3, 126 MHz)
155.39
155.35
155.29
148.52
140.62
137.13
130.04
128.27
110.38
109.73
104.55
101.32
77.41
77.16
76.91
69.45
69.42
60.27
57.29
56.86
55.76
55.45
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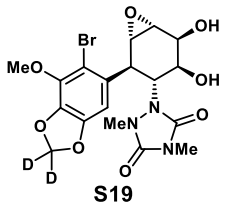
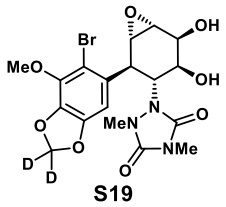
34.74
25.74
25.72
f1 (ppm)




**S19**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

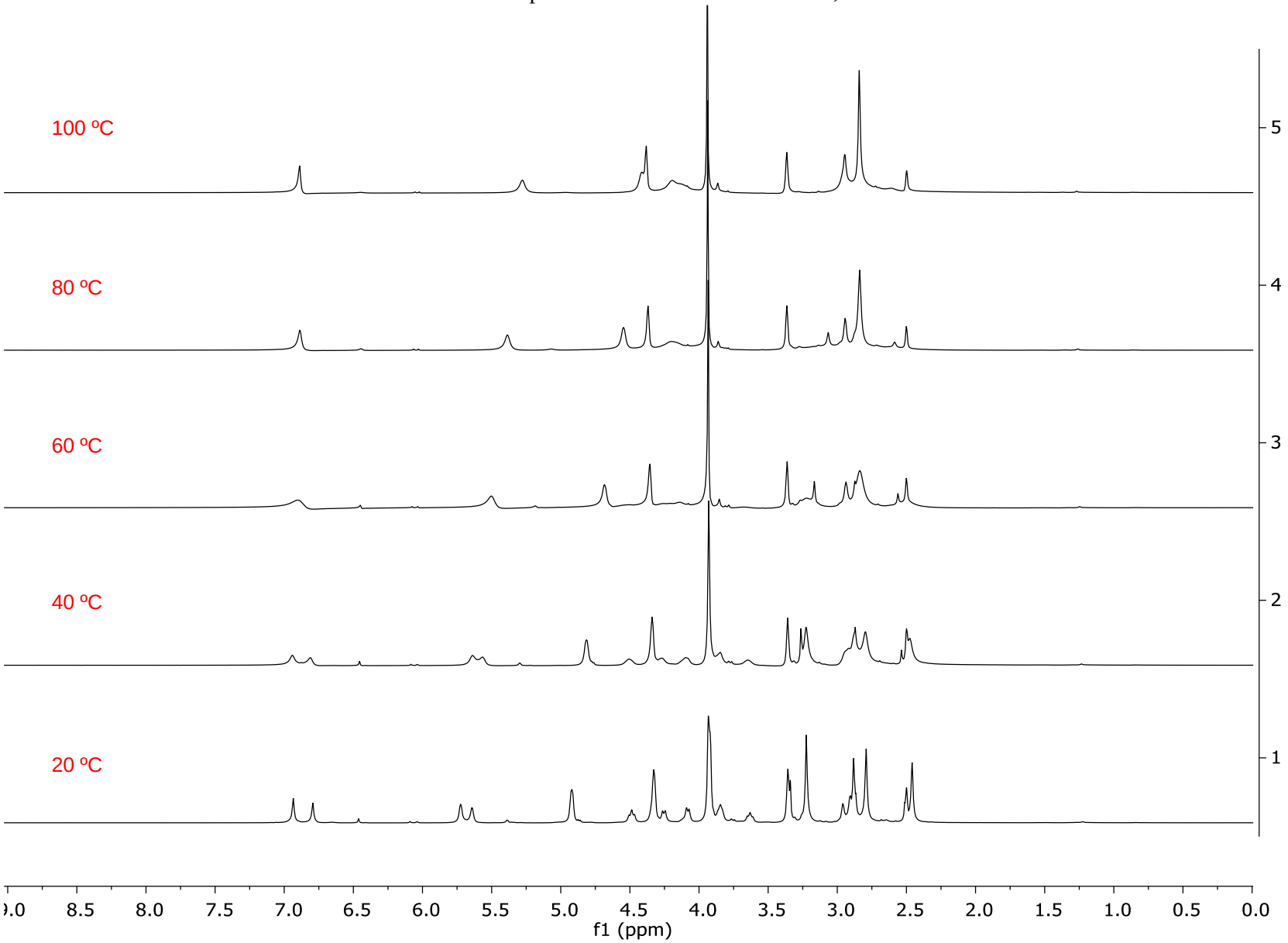


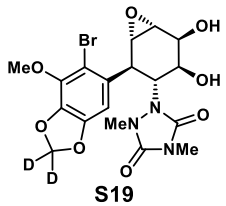




**S19**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **S19** in DMSO, 500 MHz:

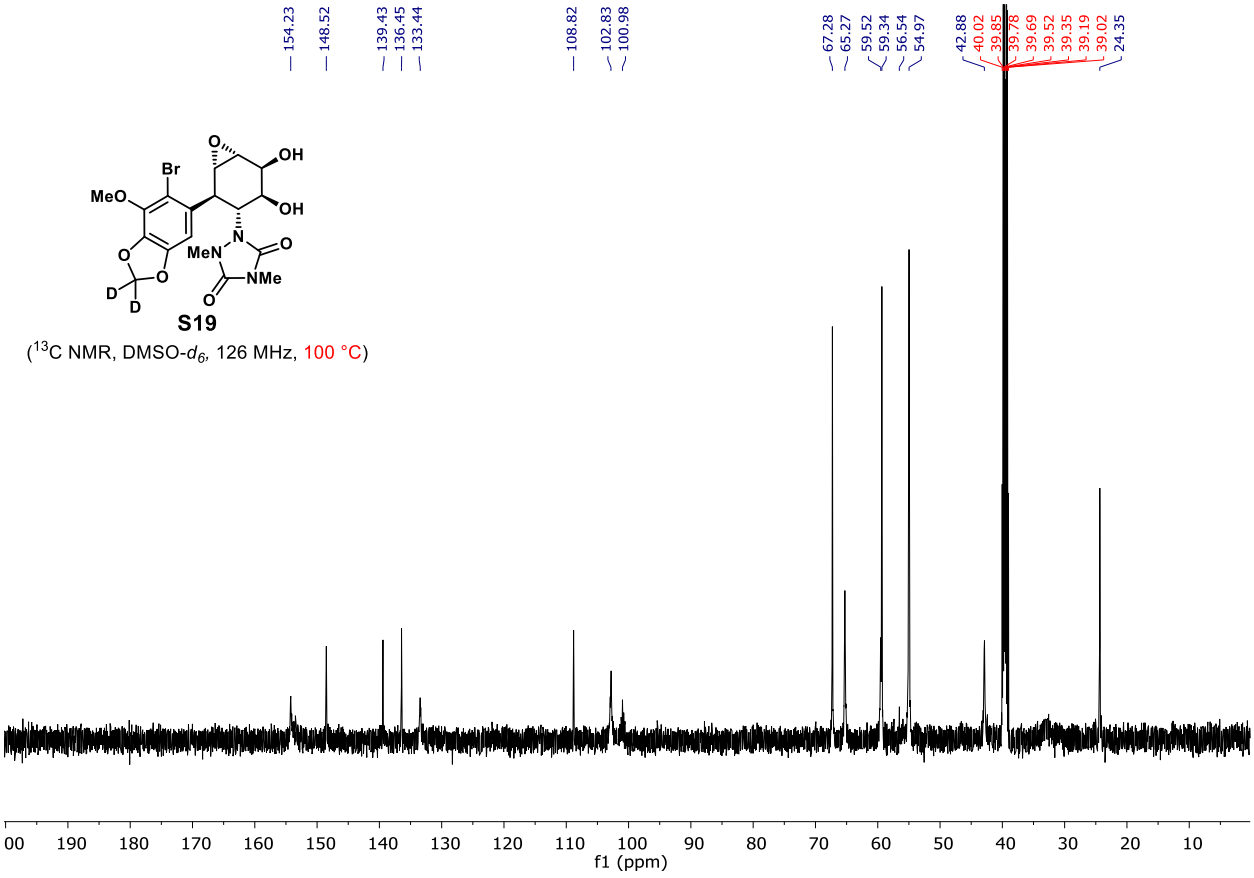





**S19**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)



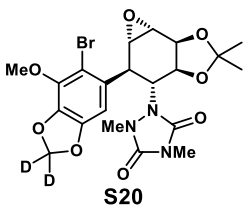







**S19**

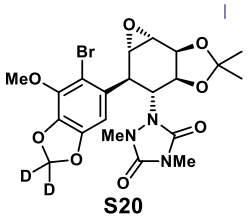
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)




**S20**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 20 °C)

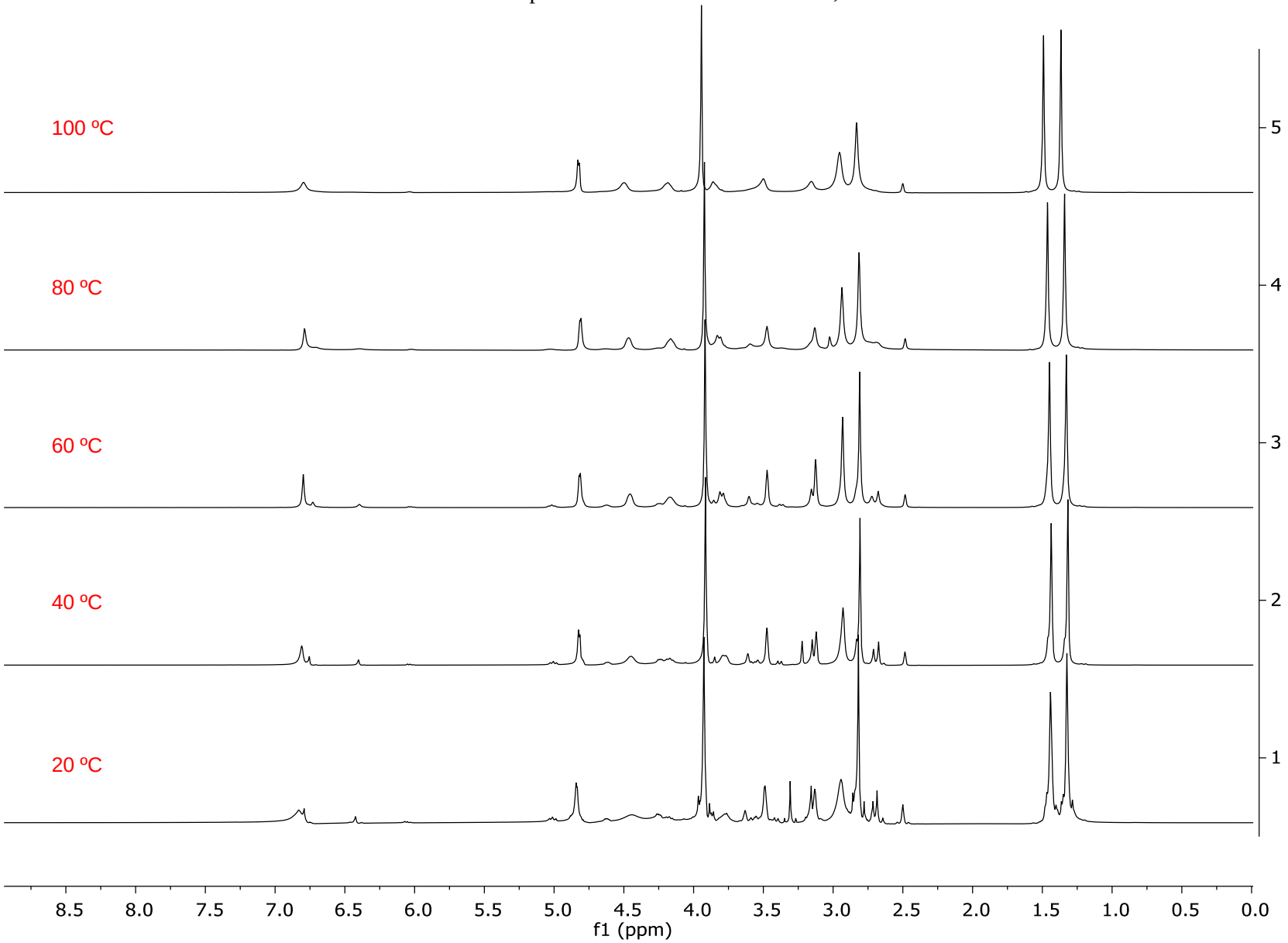


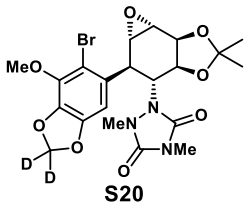




**S20**

($^1$H NMR, DMSO-$d_6$, 500 MHz, 100 °C)

$^{1}$H NMR temperature studies of **S20** in DMSO, 500 MHz:

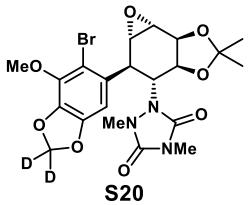





**S20**

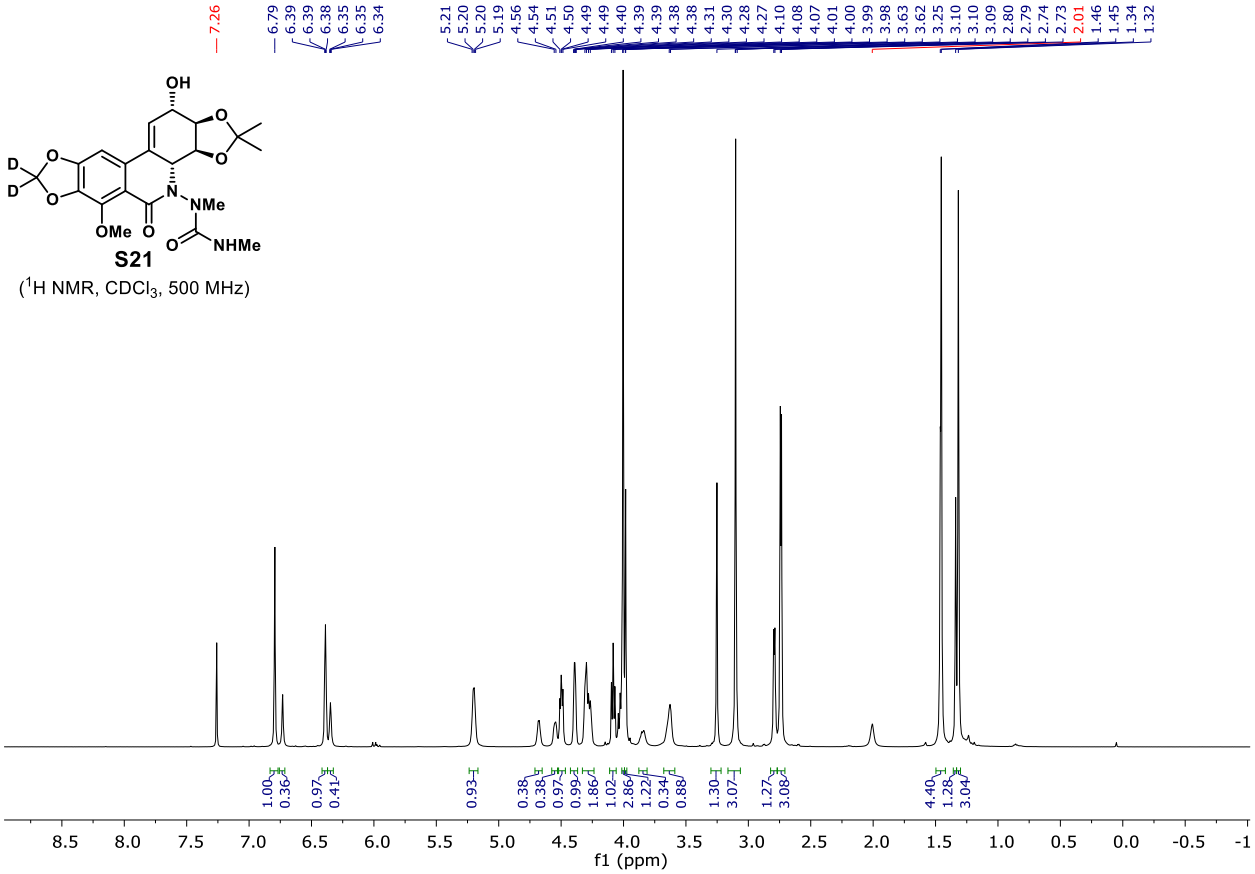
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 20 °C)



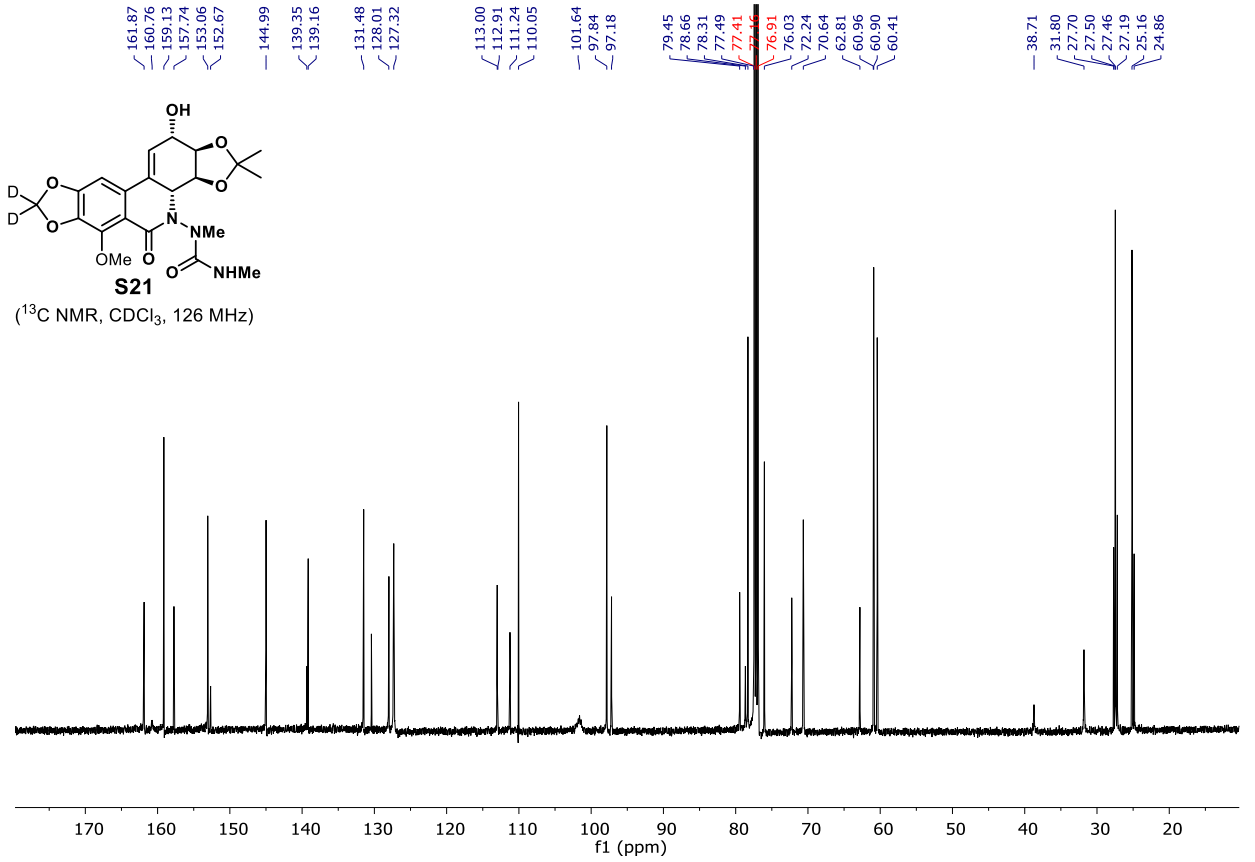




**S20**

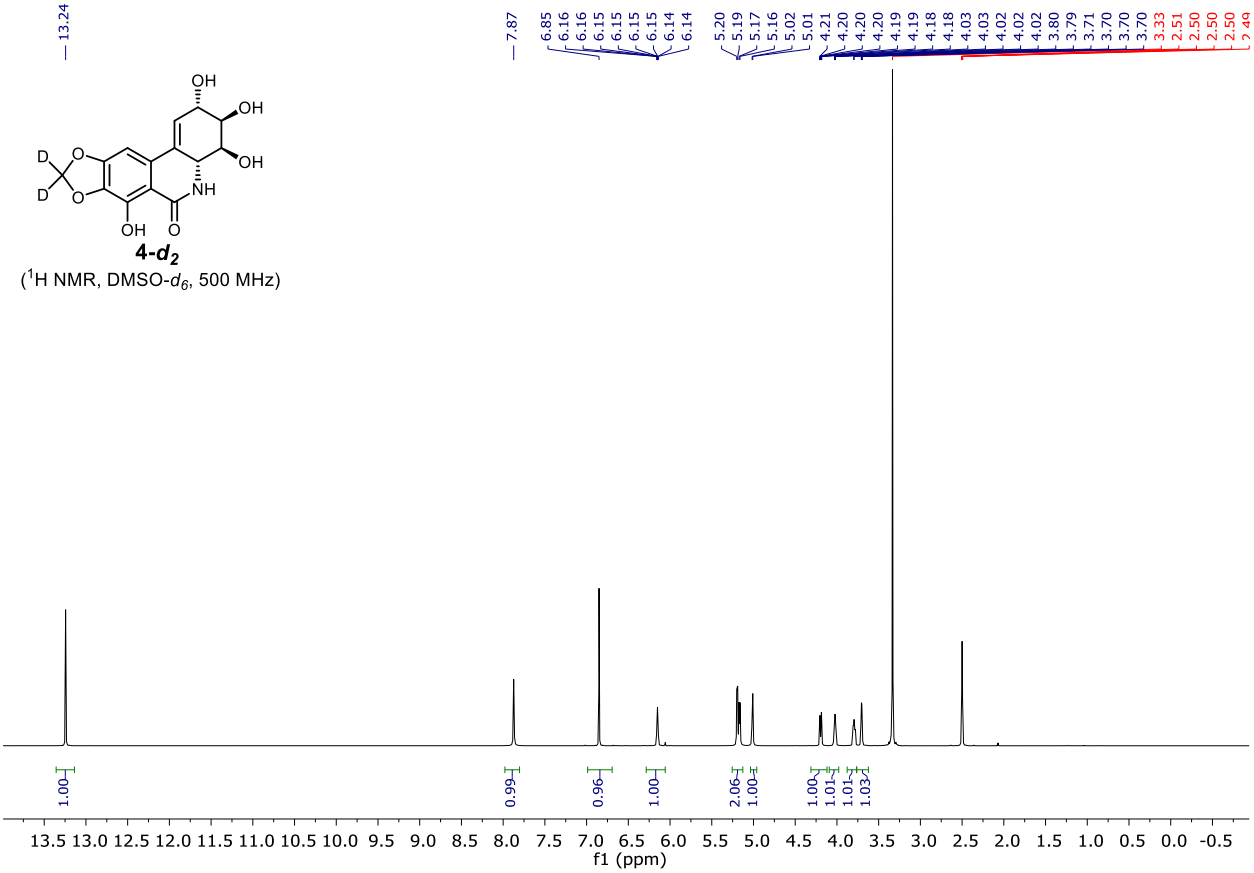
($^{13}$C NMR, DMSO-$d_6$, 126 MHz, 100 °C)




($^1$H NMR, $CDCl_3$, 500 MHz)




($^{13}$C NMR, $CDCl_3$, 126 MHz)

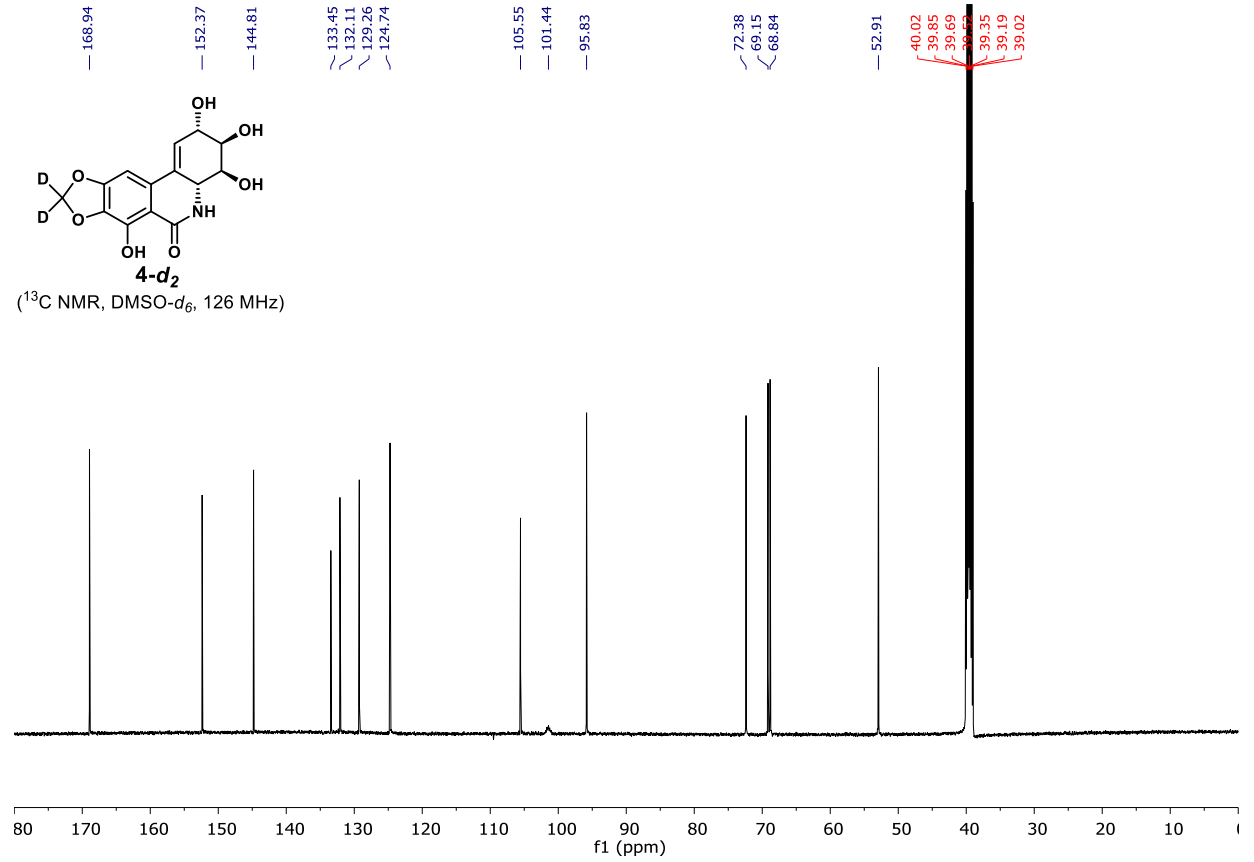






**4-$d_2$**

($^1$H NMR, DMSO-$d_6$, 500 MHz)







**4-$d_2$**

($^{13}$C NMR, DMSO-$d_6$, 126 MHz)

## 8. References


1) Breton, G. W.; Turlington, M. *Tetrahedron Lett.* **2014**, *55*, 4661.
2) Cookson, R. C.; Gupte, S. S.; Stevens, I. D. R.; Watts, C. T. *Org. Synth.* **1971**, *51*, 121.
3) Richards, C. J.; Mulvaney, A. W. *Tetrahedron: Asymmetry* **1996**, *7*, 1419.
4) Krout, M. R.; Mohr, J. T.; Stoltz, B. M. *Org. Synth.* **2009**, *86*, 181.
5) Edgell, W. F.; Lyford IV, J. *Inorg. Chem.* **1970**, *9*, 1932.
6) Dolomanov,O. V.; Bourhis, L. J.; Gildea, R. J.; Howard, J. A. K.; Puschmann, H. *J. Appl. Cryst.* **2009**, *42*, 339.
7) Sheldrick, G. M. *Acta Cryst.* **2015**, *A71*, 3.
8) Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.
9) Hernandez, L. W.; Pospech, J.; Klöckner, U.; Bingham, T. W.; Sarlah, D. *J. Am. Chem. Soc.*, **2017**, *139*, 15656
10) Hudlicky, T.; Tian, X.; Königsberger, K.; Maurya, R.; Rouden, J.; Fan, B. *J. Am. Chem. Soc.* **1996**, *118*, 10752.
11) Håkansson, A. E.; Palmelund, A.; Holm, H.; Madsen, R. *Chem. Eur. J.* **2006**, *12*, 3243).
12) Magnus, P.; Sebhat, I. K. *J. Am. Chem. Soc.* **1998**, *120*, 5341.
13) Trost, B. M.; Pulley, S. R. *J. Am. Chem. Soc.* **1995**, *117*, 10143.
14) Tian, X.; Hudlicky, T.; Koenigsberger, K. *J. Am. Chem. Soc.* **1995**, **117**, 3643.
15) Rigby, J. H.; Maharoof, U. S. M.; Mateo, M. E. *J. Am. Chem. Soc.* **2000**, *122*, 6624.
16) Fagin, F. C.; Garcia, O. N.; Santome H. L.; Alonso, R. *J. Org. Chem.*, **2012**, *77*, 11377.
17) Akai, S.; Kojima, M.; Yamauchi, S.; Kohji, T.; Nakamura, Y.; Sato, K.-i. *Asian J. Org. Chem.* **2013**, *2*, 299.
18) Dam, J. H.; Madsen, R. *Eur. J. Org. Chem.*, **2009**, 4666.
19) Pettit, G. R.; Gaddamidi, V.; Cragg, G. M.; Herald, D. L.; Sagawa, Y. *J. Chem. Soc., Chem. Commun.* **1984**, 1693.
20) Tezuka, N.; Shimojo, K.; Hirano, K.; Komagawa, S.; Yoshida, K.; Wang, C.; Miyamoto, K.; Saito, T.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2016**, *138*, 9166.
21) Girard, P.; Namy, J. L.; Kagan H. B. *J. Am. Chem. Soc.*, **1980**, *102*, 2693.
22) Rigby, J. H.; Mateo, M. E. *J. Am. Chem. Soc.*, **1997**, *119*, 12655.
23) Ghosal, S.; Lochan, R.; Kumar, A. Y.; Srivastava, R. S. *Phytochem.* **1985**, *24*, 1825.
24) Paulsen, H.; Stubbe, M. *Liebigs Ann. Chem.* **1983**, 535.
25) Yadav, J. S.; Satheesh, G.; Murthy, C. V. S. R. *Org. Lett.*, **2010**, *12*, 2544.
26) Keck, G. E.; Wager, T. T.; Rodriquez, J. F. D. *J. Am. Chem. Soc.*, **1999**, *121*, 5176
27) Pettit, G. R.; Eastham, S. A; Melody, N.; Orr, B.; Herald, D. L.; McGregor, J.; Knight, J. C.; Doubek, D. L.; Pettit, G. R. III; Garner, L. C.; Bell, J. A. *J. Nat. Prod.*, **2006**, *69*, 7
28) Mei, R.; Sauermann, N.; Oliveira, J. C. A.; Ackermann, L. *J. Am. Chem. Soc*. **2018**, *140*, 7913
29) Zhang, W.; Wang, F.; McCann, S. D.; Wang, D.; Chen, P.; Stahl, S. S.; Liu, G. *Science* **2016**, *353*, 1014.