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Supporting Information for:

A unified strategy to reverse-prenylated indole alkaloids: total syntheses of preparaherquamide, premalbrancheamide, and (+)-VM-55599.

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Table of Contents

1.General Considerations

1.1. Solvents and Reagents

Unless noted below, commercial reagents were purchased from Millipore Sigma, Acros Organics, Chem-Impex, Combi-blocks, TCI, and/or Alfa Aesar, and used without additional purification. Solvents were purchased from Fisher Scientific, Acros Organics, Alfa Aesar, and Sigma Aldrich. Tetrahydrofuran (THF), and triethylamine (Et_3N) were sparged with argon and dried by passing through alumina columns using argon in a Glass Contour solvent purification system. Dichloromethane (CH_2Cl_2) and toluene (PhMe) was freshly distilled over calcium hydride under a N_2 atmosphere prior to each use. Acetone was degassed via freeze-pump-thaw (3 cycles), and stored over 4 Å molecular sieves in a Schlenk flask under N_2. All other solvents and reagents were used as received unless otherwise noted.

1.2. Experimental Procedures

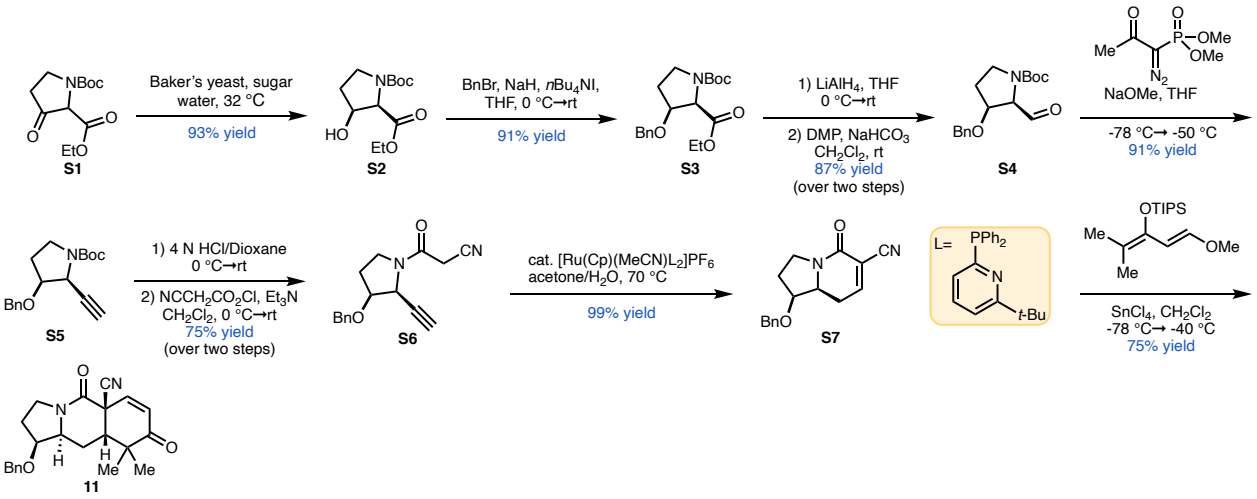
Unless otherwise noted in the experimental procedures, reactions were carried out in flame or oven-dried glassware under a positive pressure of N_2 in anhydrous solvents using standard Schlenk techniques. Reaction temperatures above room temperature (22–23 °C) were controlled by an IKA® temperature modulator and monitored using liquid-in-glass thermometers. Reaction progress was monitored using a combination of LC/MS analysis (using a Shimadzu LCMS-2020 (UFLC) equipped with the LC-20AD solvent delivery system, a SPD-20AV prominence UV/Vis detector (SPD-M20A Photo Diode Array), and a Thermo Scientific Hypersil GOLD HPLC column (5 μm particle size, 4.6 × 50 mm)), and thin-layer chromatography (TLC) on SiliCycle Siliaplates (glass-backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator). Flash column chromatography was performed with either glass columns using Silicycle silica gel (40–63 μm particle size) or with a Yamazen Smart Flash EPCLC W-Prep 2XY (dual channel) automated flash chromatography system on prefilled, premium, universal columns using ACS grade solvents.[1] Preparative thin layer chromatography was performed on SiliCycle Siliaplates (glass-backed, extra hard layer, 60 Å, 250 μm thickness, F254 indicator).

1.3. Analytical Instrumentation

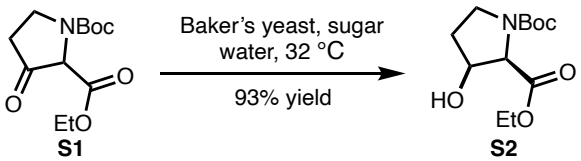
^{1}H NMR and ^{13}C NMR data were recorded on Bruker AVQ-400, AVB-400, RDX-500, AV-600 and AV-700 spectrometers using $CDCl_3$ and DMSO-d_6 as solvents, typically at 20–23 °C. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ 7.26 for ^{1}H NMR, δ 77.16 for ^{13}C NMR in $CDCl_3$ and δ 2.50 for ^{1}H NMR, δ 39.52 for ^{13}C NMR in DMSO-d_6). Data for ^{1}H and ^{13}C spectroscopy are reported as follows; chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, hept = heptet, m = multiplet, br = broad), coupling constant (Hz), integration. Melting points were determined using a MEL-TEMP™ apparatus and are uncorrected. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. High-resolution mass spectra (HRMS) were obtained from the Catalysis Facility of the Lawrence Berkeley National Laboratory (supported by the Director, Office of Science, of the US Department of Energy under contract no. DE-AC02-05CH11231) using a PerkinElmer AxION 2 TOF-MS.

2. Synthesis of Tricycle 11

Enone **11** was synthesized from commercially available 1-tert-butyl 2-ethyl 3-oxopyrrolidine-1,2-dicarboxylate (**S1**) (CAS 170123-25-8) according to a published procedure.[2a] Gram-scale quantities of **11** were prepared in one pass. **S1** can also be synthesized on decagram-scale.[2b-d]

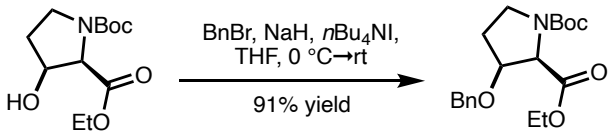


Scheme S1. Synthesis of tricycle **11**.[2]



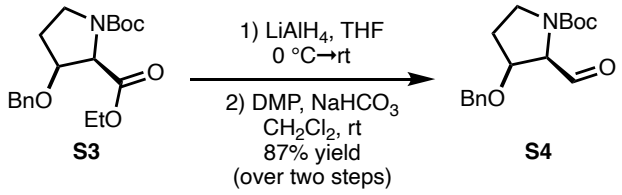
1-(Tert-butyl) 2-ethyl (2R,3S)-3-hydroxypyrrolidine-1,2-dicarboxylate (**S2**).

This procedure was adapted from the reported literature procedure.[2a] To a 2 L Erlenmeyer flask charged with **S1** (24.3 g, 94.6 mmol, 1.00 equiv) and sugar (Trader Joe's Organic brand, 208 g, 1.15 mol, 22.0 equiv) was added water (1.90 L, 0.05M). The reaction mixture was heated to 32 °C and allowed to stir at this temperature until all the sugar had dissolved. At this point dry Baker's yeast (243 g, Red Star™) was added in one portion. The resulting mixture was stirred at 32 °C for 24 h, filtered and extracted with EtOAc (5 x 700 mL). The combined organic extracts were dried over Na_2SO_4 , filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (300 mL SiO_2, 2:3 EtOAc/hexanes) to give **S2** (22.6 g, 88.0 mmol, 86%) as a clear, colorless oil. [α] D^{25}+ 21.6 (c 1.21, CH_2Cl_2). Spectral data were in full agreement with reported literature values.[2a]



S2 **S3**

1-(tert-butyl) 2-ethyl (2R,3S)-3-(benzyloxy)pyrrolidine-1,2-dicarboxylate (**S3**). This procedure was adapted from the reported literature procedure.[2a] 1 To a solution of **S2** (5.73 g, 22.1 mmol, 1.00 equiv), tetrabutylammonium iodide (2.20 g, 6.63 mmol, 0.30 equiv), and benzyl bromide (3.96 mL, 55.9 mmol, 1.50 equiv) in THF (150 mL, 0.15M) at 0 °C was added NaH (60% dispersion in mineral oil, 0.97 g, 24.2 mmol, 1.10 equiv) in three equal portions. The reaction mixture was slowly warmed to room temperature and allowed to stir for 15 h, at which time the reacting mixture was quenched by the addition of ice-cold water (60 mL). The aqueous layer was extracted with EtOAc (4 x 90 mL) and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (150 mL SiO_2, 1:9 EtOAc/hexanes) to yield **S3** (7.02 g, 20.1 mmol, 91 %) as a clear, colorless oil. Spectral data and yield were in full agreement with the reported values.[2a]

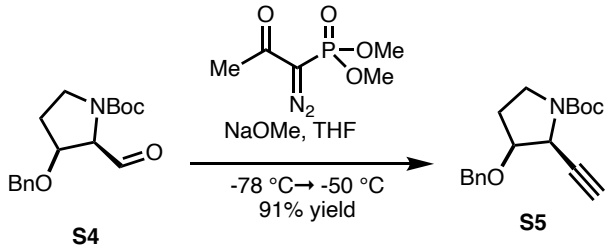


S3 **S4**

tert-butyl (2R,3S)-3-(benzyloxy)-2formylpyrrolidine-1-carboxylate (S4)

This procedure was adapted from the reported literature procedure.[2a] To a solution of 1-(tert-butyl) 2-ethyl (2R,3S)-3-(benzyloxy)pyrrolidine-1,2-dicarboxylate (**S3**) (13.7 g, 39.2 mmol, 1.0 equiv) in THF (325mL, 0.1M) cooled to 0 °C was added $LiAlH_4$ (3.71 g, 97.8 mmol, 2.5 equiv) in four equal portions. The resulting solution was stirred at 0 °C for 50 min then diluted with Et_2O (325 mL). The solution was cooled to 0 °C, then 5.5 mL of distilled water was added dropwise, followed by 5.5 mL of 15% aqueous NaOH. After 5 min, 16.3 mL of distilled water was added and the solution was warmed to room temperature and stirred for 30 min. $MgSO_4$ (65 g) was then added and the solution was stirred at room temperature for 1.5 h, then filtered, and concentrated in vacuo. The crude oil was dissolved in CH_2Cl_2 (221 mL, 0.18M) and $NaHCO_3$ (16.4 g, 195.4 mmol, 5.0 equiv) was added. The resulting solution was cooled to 0 °C and Dess-Martin periodinane (DMP) (18.2

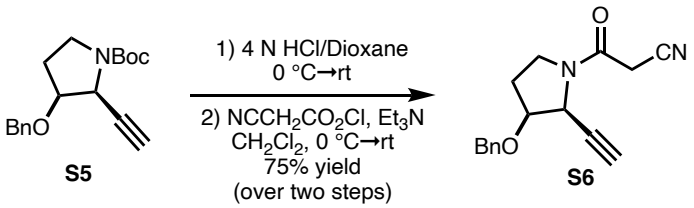
g, 43.0 mmol, 1.1 equiv) was added in three equal portions. After 2.5 h, the resulting yellow solution was warmed to room temperature then poured into a separatory funnel containing 800 mL (1:1 v/v) saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 400 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude oil was purified by silica gel chromatography (250 mL SiO 2 with 1:4 ethyl acetate:hexanes) to yield **S4** (10.4 g, 34.1 mmol, 87% over 2 steps) as a clear, colorless oil. Spectral data and yield were in full agreement with the reported values.[2a]



S4 **S5**

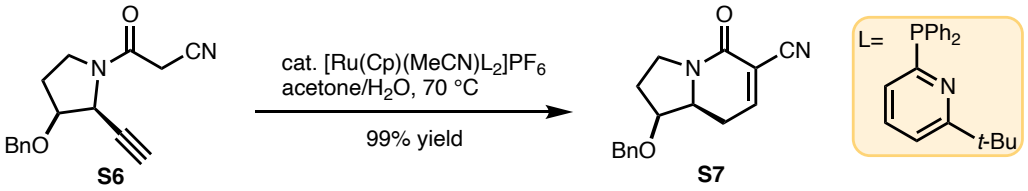
tert-butyl (2S,3S)-3-(benzyloxy)-2-ethynylpyrrolidine-1-carboxylate (S5)

This procedure was adapted from the reported literature procedure.[2a] A solution of dimethyl (1-diazo-2-oxopropyl)phosphonate[3] (15.04 g, 78.3 mmol, 1.5 equiv) in THF (200 mL, 0.39M) was added via cannula to a stirring suspension of NaOMe (13.5 g, 261 mmol, 5.0 equiv) in THF (200 mL, 1.30M) at –78 °C (dry ice/acetone) and stirred for 30 min. To this solution was added a cooled solution (–78 °C) of tert-butyl (2R,3S)-3-(benzyloxy)-2formylpyrrolidine-1-carboxylate (**S4**) (15.93 g, 52.2 mmol, 1.0 equiv) in THF (200 mL, 0.26M) via cannula along the side of the flask. The resulting solution was slowly warmed to –50 °C by allowing the dry ice/acetone bath to expire. Dry ice was added as needed to maintain a temperature of ≤ –50 °C. After TLC analysis indicated complete consumption of the starting material, saturated aqueous $NaHCO_3$ (400 mL) was added followed by Et_2O (500 mL). The solution was warmed to room temperature, the layers were separated, and the aqueous layer was extracted with Et_2O (3 x 500 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude yellow oil was purified by silica gel chromatography (300 mL SiO_2 with 1:9 ethyl acetate:hexanes) to yield **S5** (14.27 g, 47.4 mmol, 91%) as a white solid. Spectral data and yield were in full agreement with the reported values.[2a]



3((2S,3S)-3-(benzyloxy)-2-ethynylpyrrolidin-1-yl)-3-oxopropanenitrile (S6)

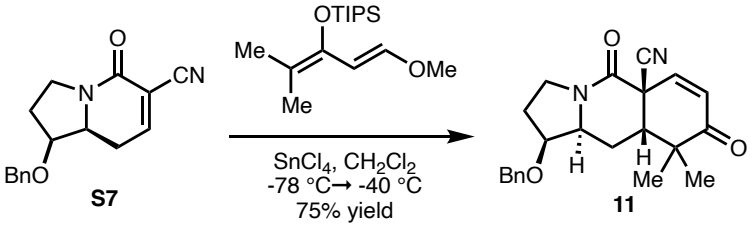
This procedure was adapted from the reported literature procedure.[2a] To a flask charged with tert-butyl (2S,3S)-3-(benzyloxy)-2-ethynylpyrrolidine-1-carboxylate (**S5**) (14.2 g, 47.2 mmol, 1.0 equiv) was added 4 N HCl/dioxane (60 mL, 236 mmol, 5.0 equiv) dropwise at 0 °C. The resulting solution was then warmed to room temperature and stirred for 30 min at which point the solvent was removed in vacuo. The excess HCl/dioxane was removed by azeotropic distillation with Et_2O (2 x 100 mL) and then hexanes (2 x 100 mL) to give a beige solid which was dried in vacuo overnight. The resulting crude mixture was suspended in CH_2Cl_2 (100 mL) and Et_3N (16.5 mL, 118 mmol, 2.5 equiv) was added dropwise at 0 °C, followed by the dropwise addition of cyanoacetylchloride (12.2 g, 118 mmol, 2.5 equiv) as a solution in CH_2Cl_2 (60 mL, 1.97 M). The resulting red solution was stirred at 0 °C for 2 h then warmed to room temperature and stirred for an additional 1 h. Saturated aqueous $NaHCO_3$ (200 mL) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (4 x 250 mL) and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude red oil was purified by silica gel chromatography (400 mL SiO_2 with 2:3 to 3:2 ethyl acetate:hexanes) to yield **S6** (9.52 g, 35.5 mmol, 75% over 2 steps) as an orange solid. Spectral data and yield were in full agreement with the reported values.[2a]



(1S,8aS)-1-(benzyloxy)-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-6-carbonitrile (S7)

This procedure was adapted from a known procedure.[2a,4] In a nitrogen atmosphere glove box, to a Schlenk flask charged with 3((2S,3S)-3-(benzyloxy)-2-ethynylpyrrolidin-1-yl)-3-oxopropanenitrile (**S6**) (832 mg, 3.10 mmol, 1.0 equiv) and a stir bar was added acetonitrilebis[2diphenylphosphino-6-t-butylpyridine]cyclopentadienylruthenium(II)

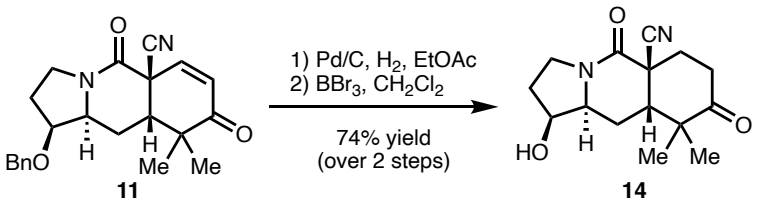
hexafluorophosphate[4] (248 mg, 0.250 mmol, 0.08 equiv). A degassed solution of acetone (6.3 mL) and HPLC grade water (0.280 mL) was added to the Schlenk flask in the glove box via syringe. The reaction vessel was then capped and removed from the glove box and the resulting yellow solution was placed in a preheated oil bath and stirred at 70 °C for 24 h, at which time the reaction mixture was diluted with ethyl acetate (10 mL) and concentrated in vacuo. The resulting yellow oil was purified by silica gel chromatography (40 mL SiO_2 with 1:1 to 2:1 ethyl acetate:hexanes) to yield **S7** (823 mg, 3.07 mmol, 99%) as a yellow solid. Spectral data and yield were in full agreement with the reported values.[2a]



(1S,5aR,9aS,10aS)-1-(benzyloxy)-9,9-dimethyl-5,8-dioxo1,2,3,8,9,9a,10,10a-octahydropyrrolo[1,2-b]isoquinoline-5a(5H)-carbonitrile (11)

This procedure was adapted from the reported literature procedure.[2a] A solution of (1S,8aS)-1-(benzyloxy)-5-oxo-1,2,3,5,8,8a-hexahydroindolizine-6-carbonitrile (**S7**) (2.82 g, 10.52 mmol, 1.0 equiv) and (E)-triisopropyl((1-methoxy-4-methylpenta-1,3-dien-3yl)oxy)silane[5] (5.97 g, 21.0 mmol, 2.0 equiv) in CH_2Cl_2 (105 mL, 0.1M) was cooled to –78 °C and then $SnCl_4$ (1.0 M in CH_2Cl_2 , 12.6 mL, 12.62 mmol, 1.2 equiv) was added dropwise. The resulting red solution was then warmed to –42 °C (MeCN/dry ice) and after 40 min, additional (E)-triisopropyl((1-methoxy-4-methylpenta-1,3-dien-3-yl)oxy)silane (17) (2.0 g, 7.03 mmol, 0.66 equiv) was added and the MeCN/dry ice bath removed. The solution was allowed to warm to room temperature and stirred for 30 min, then saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was stirred vigorously for 3 h. The resulting mixture was vacuum filtered through a fritted funnel and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL), and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated in vacuo. The resulting oil was purified by silica gel chromatography (200 mL SiO 2 with 3:7 to 7:3 ethyl acetate:hexanes) to yield 11 (2.86 g, 7.85 mmol, 75%) as a yellow foam. Spectral data and yield were in full agreement with the reported values.[2a]

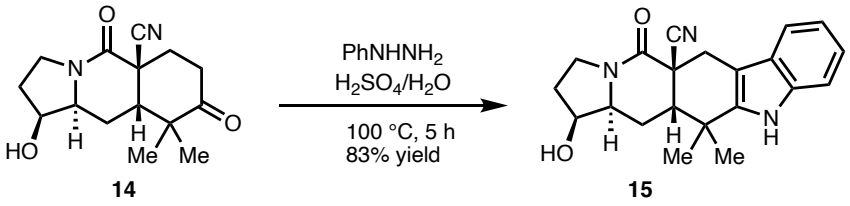
3. Experimental Procedures and Characterization Data



(1*S*,5a*R*,9a*S*,10a*S*)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-*b*]isoquinoline-5a(5*H*)-carbonitrile (14)

This procedure was adapted from the reported literature.[2a] To a round-bottomed flask containing (1*S*,5a*R*,9a*S*,10a*S*)-1-(benzyloxy)-9,9-dimethyl-5,8-dioxo-1,2,3,8,9,9a,10,10a-octahydropyrrolo[1,2-*b*]isoquinoline-5a(5*H*)-carbonitrile (**11**) (930 mg, 2.55 mmol, 1.0 equiv) was added Pd/C (93 mg, 10 wt%) and ethyl acetate (2 mL) and the atmosphere replaced with H_2 (three cycles of evacuation/backfill). Additional ethyl acetate (45 mL, 0.06M) was added and the resulting mixture was stirred at room temperature overnight. After 16 h, the reaction mixture was filtered through Celite and washed with ethyl acetate. The solvent was removed *in vacuo* and the resulting pale yellow oil was used without further purification. The crude oil was dissolved in CH_2Cl_2 (78 mL, 0.033M) and cooled to –78 °C. BBr_3 (1.10 mL, 11.7 mmol, 4.6 equiv) was then added dropwise along the side of the flask and stirred for 15 min at which point saturated aqueous $NaHCO_3$ (80 mL) was added and the mixture allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 80 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography (40 mL SiO_2 with 2% to 5% methanol:dichloromethane) to yield **14** (524 mg, 1.89 mmol, 74% over 2 steps) as a white solid. **m.p.** 167–169 °C. TLC (methanol:dichloromethane, 1:9 v/v): R_f=0.60; **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 4.24 – 4.14 (m, 1H), 3.93 (dt, *J* = 12.5, 9.0 Hz, 1H), 3.56 – 3.49 (m, 1H), 3.48 – 3.41 (m, 1H), 3.34 (ddd, *J* = 12.8, 7.7, 5.2 Hz, 1H), 2.73 – 2.63 (m, 2H), 2.60 – 2.36 (m, 4H), 2.00 (td, *J* = 8.5, 8.1, 3.3 Hz, 2H), 1.91 (dt, *J* = 14.7, 6.3 Hz, 1H), 1.37 (s, 3H), 1.12 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 212.3, 164.2, 121.5, 72.3, 60.1, 48.0, 46.1, 43.9, 43.0, 34.3, 31.4, 29.8, 26.3, 22.8, 21.9; **IR** (NaCl, thin film) ν_{max}: 3413, 2927, 2360, 1712, 1647, 1456 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{20}O_3N_2Na$ ($[M+Na]^+$):

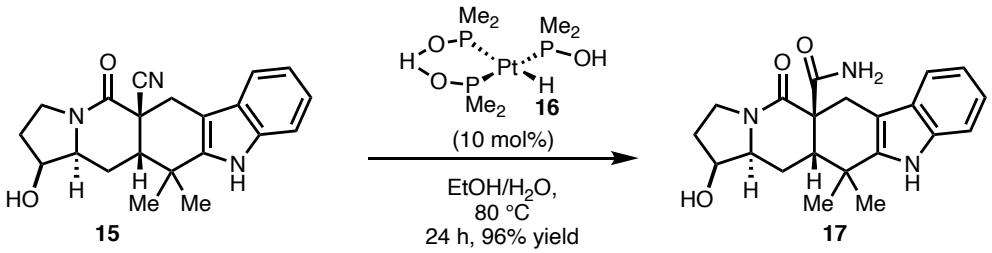
299.1366, found 299.1367. Spectral data and yield were in full agreement with the reported values.[2a]



14 15

(1*S*,5a*R*,12a*S*,13a*S*)-1-hydroxy-12,12-dimethyl-5-oxo-2,3,6,11,12,12a,13,13a-octahydro-1*H*-indolizino[7,6-*b*]carbazole-5a(5*H*)-carbonitrile (15)

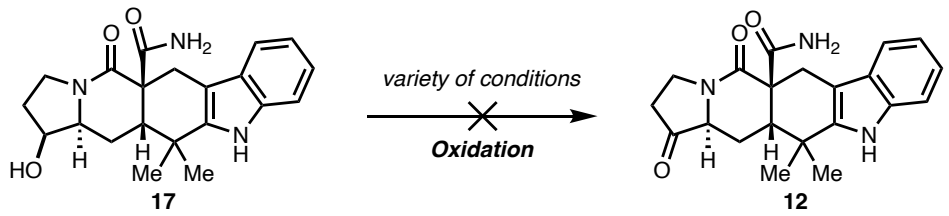
To a suspension of (1S,5aR,9aS,10aS)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-b]isoquinoline-5a(5H)-carbonitrile (**14**) (524 mg, 1.90 mmol, 1.0 equiv) in aqueous H_2SO_4 (5%v/v, 32 mL, 0.06M) was added phenylhydrazine (0.75 mL, 7.60 mmol, 4.0 equiv) at room temperature and the resulting mixture was heated to 100 °C and held at this temperature. After 14 h, the resulting reaction mixture was cooled to room temperature and then filtered through a Büchner funnel, layered with a medium porosity filter paper, and washed with water (30 mL) and then diethyl ether (2 x 30 mL). The beige solid was collected and dried *in vacuo* overnight to yield **15** (550 mg, 1.58 mmol, 83%) as a beige solid. **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ = 11.02 (s, 1H), 7.44 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 6.98 (t, J = 7.5 Hz, 1H), 5.16 (d, J = 4.8 Hz, 1H), 4.00 (q, J = 3.8 Hz, 1H), 3.72 (dt, J = 11.9, 8.9 Hz, 1H), 3.55 (d, J = 9.2 Hz, 1H), 3.24 – 3.16 (m, 2H), 3.05 (d, J = 15.8 Hz, 1H), 2.41 (dd, J = 13.0, 6.0 Hz, 1H), 2.26 (ddd, J =14.3, 6.2, 2.2 Hz, 1H), 1.93 (dtd, J = 13.8, 9.6, 4.4 Hz, 1H), 1.78 (ddd, J = 12.7, 8.9, 2.6 Hz, 1H), 1.72 – 1.66 (m, 1H), 1.65 (s, 3H), 1.39 (s, 3H); **^{13}C NMR** (150 MHz, (CD3)2SO) δ = 165.3, 139.6, 136.2, 126.3, 122.4, 120.9, 118.5, 117.8, 110.9, 101.9, 72.1, 57.9, 45.1, 43.1, 42.8, 34.7, 30.5, 29.6, 27.3, 26.3, 20.4.; **HRMS** (ESI) calcd for $C_{21}H_{23}O_2N_3Na$ ($[M+Na]^+$): 372.1682, found 372.1682.



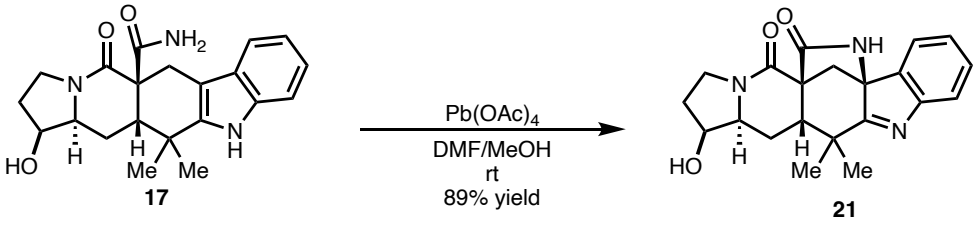
(1*S*,5a*R*,12a*S*,13a*S*)-1-hydroxy-12,12-dimethyl-5-oxo-2,3,6,11,12,12a,13,13a-octahydro-1*H*-indolizino[7,6-*b*]carbazole-5a(5*H*)-carboxamide (17)

$(Me_2POH)_2Pt(H)(Me_2PO)$(**16**)[6] (3.74) (43 mg, 0.10 mmol, 0.1 equiv) was added in one portion to a solution of (1S,5aR,12aS,13aS)-1-hydroxy-12,12-dimethyl-5-oxo-2,3,6,11,12,12a,13,13a-octahydro-1H-indolizino[7,6-b]carbazole-5a(5H)-carbonitrile (**15**) (350 mg, 1.0 mmol, 1.0 equiv) in a mixture of EtOH/H_2O (4:1 v/v, 10.0 mL, 0.10M). The reaction mixture was heated to 80 °C for 12 hours and then cooled to room temperature. The resulting solution was then diluted with CH_2Cl_2 (10 mL) and passed through a short column containing silica gel (10 mL) layered with Na_2SO_4 (20 mL) and washed with 20% MeOH/CH_2Cl_2 (50 mL). The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (20 mL SiO_2 with 10% to 20% methanol:dichloromethane) to yield **17** (358 mg, 0.97 mmol, 97%) as a white foam. TLC (methanol:dichloromethane, 1:9 v/v): Rf= 0.20; **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ = 10.68 (s, 1H), 7.37 (d, J = 7.7 Hz, 1H), 7.25 (d, J = 7.7 Hz, 1H), 7.00 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H), 6.97 (s, 1H), 6.94 – 6.90 (m, 1H), 6.84 (s, 1H), 3.95 (dd, J = 4.8, 2.9 Hz, 1H), 3.67 (dt, J = 11.9, 8.6 Hz, 1H), 3.51 – 3.45 (m, 1H), 3.18 (d, J = 15.9 Hz, 1H), 3.09 (ddd, J = 11.9, 10.6, 3.2 Hz, 1H), 2.90 (d, J = 15.9 Hz, 1H), 2.66 (dd, J = 9.6, 5.9 Hz, 1H), 2.22 (dt, J = 14.0, 5.6 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.79 – 1.63 (m, 2H), 1.48 – 1.39 (m, 1H), 1.34 (s, 3H), 1.33 (s, 3H).; **^{13}C NMR** (150 MHz, (CD3)2SO) δ = 174.6, 170.5, 140.0, 136.1, 126.6, 120.2, 117.9, 117.7, 110.6, 104.0, 71.6, 58.8, 53.2, 43.1, 42.1, 34.7, 31.2, 30.1, 26.7, 24.4, 20.8.; IR (neat) νmax: 3276, 3187, 2951, 2883, 1665, 1613, 1460, 1297, 1196 cm–1; **HRMS** (ESI) calcd for $C_{21}H_{25}O_3N_3Na$ ($[M+Na]^+$): 390.1788, found 390.1790.

Table S1. Oxidation of **17**.



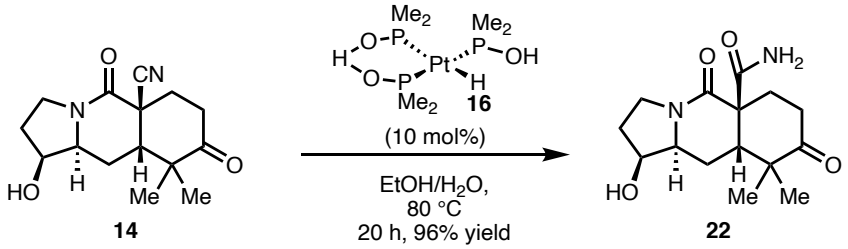
Entry	Conditions	Result
1	DMP, $NaHCO_3$, CH_2Cl_2, rt	Decomposition
2	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt, 1.5 h	Decomposition
3	$(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C to rt, 0.5 h	~22% yield, messy
4	TPAP (10 mol%), NMO, 4Å MS, CH_2Cl_2, rt	Decomposition
5	PCC, NaOAc, CH_2Cl_2, rt	Starting Material
6	SO_3●pyr, Et_3N, DMSO/CH_2Cl_2, rt	Starting Material
7	Al(*i*OPr)$_3$, acetone/toluene, 90 °C	Starting Material
8	Zr(*i*OBu)$_4$, acetone/toluene, 90 °C	Starting Material



(1*S*,5a*R*,7a*S*,13a*S*,14a*S*)-1-hydroxy-13,13-dimethyl-2,3,13,13a,14,14a-hexahydro-1*H*,5*H*-5a,7a-methanoindolizino[7',6':5,6]azepino[3,2-*b*]indole-5,6(7*H*)-dione (21)

To a solution of (1S,5aR,12aS,13aS)-1-hydroxy-12,12-dimethyl-5-oxo-2,3,6,11,12,12a,13,13a-octahydro-1H-indolizino[7,6-b]carbazole-5a(5H)-carboxamide (**17**) (100 mg, 0.272 mmol, 1.0 equiv) in a mixture of DMF/MeOH (1:1 v/v, 9.1 mL, 0.03M) was added $Pb(OAc)_4$ (241 mg, 0.545 mmol, 2.0 equiv) at room temperature. The resulting brown-red mixture was stirred at room temperature for 2 h at which time sat. aq. $NaHCO_3$ (20 mL) was added. The biphasic mixture was then transferred to a 100 mL separatory funnel and the aqueous layer was extracted with ethyl

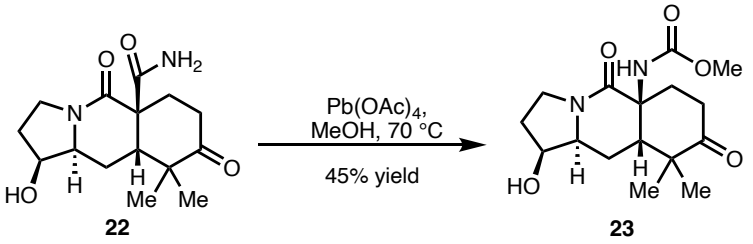
acetate (5 x 40 mL). The combined organic layers were dried over Na_2SO_4, then filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (10 mL SiO_2 with 1% to 2% to 5% methanol:dichloromethane) to yield **21** (88 mg, 0.241 mmol, 89%) as a white foam. TLC (ethyl acetate:hexanes, 1:9 v/v): R_f= 0.27; **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ = 8.26 (s, 1H), 7.55 (d, J = 7.3 Hz, 1H), 7.53 (d, J = 7.3 Hz, 1H), 7.42 (td, J = 7.4, 1.3 Hz, 1H), 7.27 (td, J = 7.4, 1.3 Hz, 1H), 5.08 (s, 1H), 4.01 (s, 1H), 3.65 (dt, J = 11.7, 8.4 Hz, 1H), 3.22 (d, J = 9.6 Hz, 1H), 3.05 (td, J = 11.2, 3.5 Hz, 1H), 2.39 (dd, J = 13.6, 5.2 Hz, 1H), 2.22 (dd, J = 13.9, 5.7 Hz, 1H), 2.11 (dd, J = 11.3, 1.7 Hz, 1H), 1.95 – 1.88 (m, 1H), 1.82 (td, J = 13.9, 9.5 Hz, 1H), 1.70 (ddd, J = 13.2, 9.1, 3.6 Hz, 1H), 1.37 (s, 3H), 1.32 (s, 3H); **^{13}C NMR** (150 MHz, $(CD_3)_2SO$) δ = 190.3, 177.0, 167.0, 154.7, 135.0, 129.7, 125.7, 123.2, 120.4, 71.8, 69.3, 58.1, 54.4, 41.7, 41.4, 38.5, 32.0, 30.7, 24.9, 21.5.; **HRMS** (ESI) calcd for $C_{21}H_{24}O_3N_3$ ($[M+H]^+$): 366.1812, found 366.1818.



(1*S*,5a*R*,9a*S*,10a*S*)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-*b*]isoquinoline-5a(5*H*)-carboxamide (22)

$(Me_2POH)_2Pt(H)(Me_2PO)$ (**16**)[6] (68 mg, 0.16 mmol, 0.1 equiv) was added in one portion to a solution of (1*S*,5a*R*,9a*S*,10a*S*)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-*b*]isoquinoline-5a(5*H*)-carbonitrile (**14**) (440 mg, 1.59 mmol, 1.0 equiv) in a mixture of EtOH/H_2O (4:1 v/v, 10.6 mL, 0.15M). The reaction mixture was heated to 80 °C and held at this temperature for 16 hours and then cooled to room temperature. The resulting solution was then diluted with CH_2Cl_2 (10 mL) and passed through a short column containing silica gel (10 mL) layered with Na_2SO_4 (20 mL) and washed with 10% MeOH/CH_2Cl_2 (50 mL). The filtrate was concentrated *in vacuo* and purified by silica gel chromatography (20 mL SiO_2 with 5% to 10% methanol:dichloromethane) to yield **22** (451 mg, 1.53 mmol, 96%) as a white solid. **m.p.** 236–238 °C; TLC (methanol:dichloromethane, 1:9 v/v): R_f= 0.24; **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.14 (s, 1H), 6.32 (s, 1H), 4.17 (s, 1H), 3.86 (dt, *J* = 11.5, 9.2 Hz, 1H), 3.52 (dd, *J* = 11.9, 5.7 Hz, 1H), 3.38 (ddd, *J* = 12.7, 8.7, 4.1 Hz, 1H), 3.06 – 3.00 (m, 1H), 2.62 (dt, *J* = 14.0, 6.4 Hz, 1H), 2.43 (t, *J* =

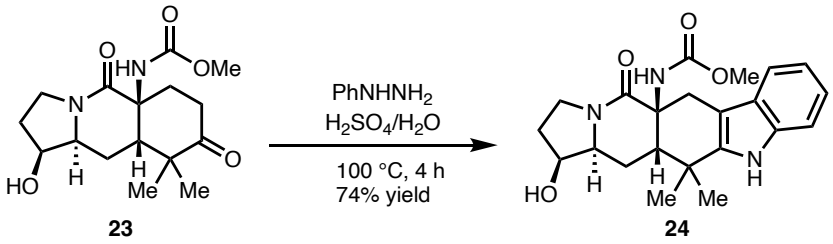
6.9 Hz, 2H), 2.23 (dt, *J* = 14.0, 6.9 Hz, 1H), 2.02 – 1.88 (m, 4H), 1.23 (s, 3H), 1.14 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 214.6, 174.3, 171.2, 71.6, 61.2, 52.5, 46.9, 43.6, 41.4, 35.1, 31.4, 30.9, 25.2, 22.7, 21.4. **IR** (neat) ν_{max}: 3409, 2920, 2850, 1674, 1624, 1466 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{23}O_4N_2$ ($[M+H]^+$): 295.1652, found 295.1652.



Methyl (1*S*,5a*S*,9a*S*,10a*S*)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-*b*]isoquinolin-5a(5*H*)-yl)carbamate (23)

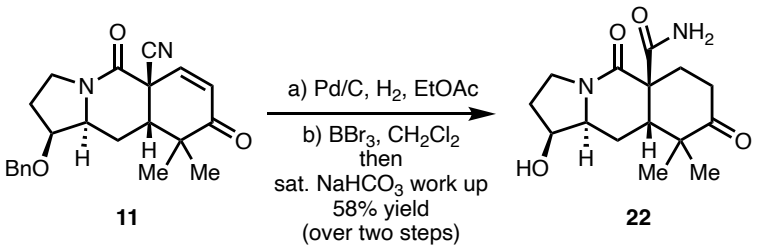
To a solution of (1S,5aR,9aS,10aS)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-b]isoquinoline-5a(5H)-carboxamide (**22**) (224 mg, 0.761 mmol, 1.0 equiv) in anhydrous MeOH (7.6 mL, 0.10M) was added $Pb(OAc)_4$ (844 mg, 1.90 mmol, 2.5 equiv) in one portion at room temperature. The resulting mixture was heated to 70 °C for 3.5 h at which time the reaction mixture was cooled to room temperature. Additional $Pb(OAc)_4$ (844 mg, 1.90 mmol, 2.5 equiv) was added in one portion at room temperature and then the resulting mixture was heated to 70 °C and held at this temperature for 2 h. The resulting reaction mixture was then cooled to room temperature and additional $Pb(OAc)_4$ (844 mg, 1.90 mmol, 2.5 equiv) was added in one portion at room temperature and then the resulting mixture heated to 70 °C for 1.5 h. The reaction mixture was then cooled to room temperature and poured into a 250 mL separatory funnel containing sat. aq. $NaHCO_3$ (60 mL). The aqueous layer was extracted with ethyl acetate (5 x 60 mL) and the combined organic layers were dried over Na_2SO_4, then filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (20 mL SiO_2 with 2% to 5% to 10%methanol:dichloromethane) to yield **23** (110 mg, 0.339 mmol, 45%) as a white foam and recovered **22** (17 mg, 0.0578 mmol, 7.6% recovery). TLC (methanol:dichloromethane, 1:9 v/v): R_f= 0.37; **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 5.32 (s, 1H), 4.17 (s, 1H), 3.98 (q, J = 9.5 Hz, 1H), 3.67 (s, 3H), 3.43 – 3.35 (m, 1H), 3.27 (t, J = 11.3 Hz, 1H), 3.09 (t, J = 7.3 Hz, 1H), 2.75 –2.65 (m, 1H), 2.41 – 2.25 (m, 3H), 2.09 – 2.00 (m, 1H), 1.99 – 1.91 (m, 1H), 1.80 (dt, J = 15.1, 7.6 Hz, 1H), 1.42

(s, 3H), 1.14 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 214.7, 170.8, 157.1, 73.3, 59.6, 58.5, 52.4, 47.9, 45.3, 43.3, 33.5, 32.1, 31.0, 27.9, 23.3, 22.6.; **HRMS** (ESI) calcd for C16H25O5N2 ([M+H]+): 325.1758, found 325.1761; calcd for $C_{16}H_{24}O_5N_2Na$ ($[M+Na]^+$): 347.1577, found 347.1578.



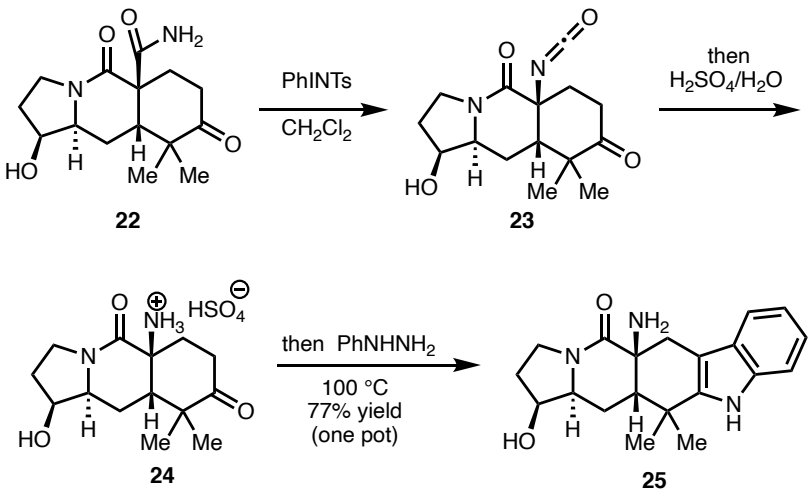
methyl ((1*S*,5a*S*,12a*S*,13a*S*)-1-hydroxy-12,12-dimethyl-5-oxo-2,3,6,11,12,12a,13,13a-octahydro-1*H*-indolizino[7,6-*b*]carbazol-5a(5*H*)-yl)carbamate (**24**)

To a suspension of methyl ((1S,5aS,9aS,10aS)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-b]isoquinolin-5a(5H)-yl)carbamate (**23**) (110 mg, 0.339 mmol, 1.0 equiv) in aqueous H_2SO_4 (5% v/v, 5.7 mL, 0.06M) was added phenylhydrazine (0.140 mL, 1.36 mmol, 4.0 equiv) at room temperature and the resulting mixture was heated to 100 °C. After 3.5 h, the resulting reaction mixture was cooled to room temperature and slowly poured into a 250 mL separatory funnel containing sat. aq. $NaHCO_3$ (60 mL) and stirred gently until bubbling ceased. The aqueous layer was then extracted with ethyl acetate (5 x 60 mL) and the combined organic layers were dried over Na_2SO_4, then filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (20 mL SiO_2 with 2% to 5% to 10% methanol:dichloromethane) to yield **24** (100 mg, 0.252 mmol, 74%) as a yellow solid. TLC (methanol:dichloromethane, 1:9 v/v): R_f= 0.30; **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.92 (s, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 5.03 (s, 1H), 4.16 – 4.09 (m, 2H), 3.61 (s, 3H), 3.43 (d, J = 9.0 Hz, 1H), 3.31 – 3.24 (m, 1H), 3.17 (dd, J = 13.9, 5.5 Hz, 1H), 3.12 (d, J = 16.6 Hz, 1H), 2.95 (d, J = 16.6 Hz, 1H), 2.45 (dd, J = 14.6, 5.5 Hz, 1H), 2.16 – 2.08 (m, 1H), 2.01 – 1.94 (m, 1H), 1.87 – 1.80 (m, 2H), 1.47 (s, 3H), 1.41 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 171.6, 156.6, 140.1, 136.4, 127.1, 121.8, 119.7, 117.8, 111.0, 101.9, 74.3, 59.2, 58.7, 52.3, 42.5, 40.9, 34.7, 32.0, 30.7, 28.7, 28.0, 22.2; **HRMS** (ESI) calcd for $C_{22}H_{28}O_4N_3$ ($[M+H]^+$): 398.2074, found 398.2077.



(1*S*,5a*R*,9a*S*,10a*S*)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-*b*]isoquinoline-5a(5*H*)-carboxamide (22)

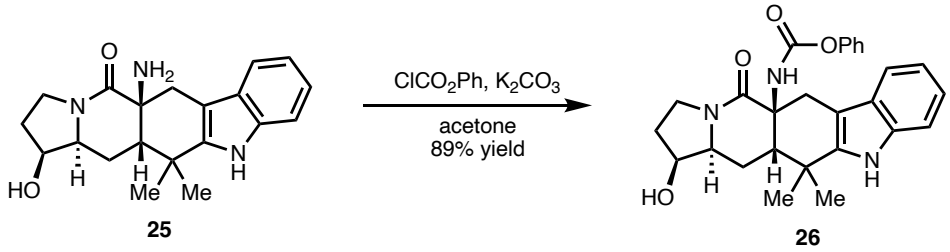
To a round-bottomed flask containing (1*S*,5a*R*,9a*S*,10a*S*)-1-(benzyloxy)-9,9-dimethyl-5,8-dioxo-1,2,3,8,9,9a,10,10a-octahydropyrrolo[1,2-*b*]isoquinoline-5a(5*H*)-carbonitrile (**11**) (710 mg, 1.95 mmol, 1.0 equiv) was added Pd/C (71 mg, 10 wt%) and ethyl acetate (2 mL) and the atmosphere replaced with H_2 (three cycles of evacuation/backfill). Additional ethyl acetate (32 mL, 0.06M) was added and the resulting mixture was stirred at room temperature overnight. After 16 h, the reaction mixture was filtered through Celite and washed with ethyl acetate. The solvent was removed *in vacuo* and the resulting pale yellow oil was used without further purification. The crude oil was dissolved in CH_2Cl_2 (78 mL, 0.024M) and cooled to –78 °C. BBr_3 (1.32 mL, 13.9 mmol, 7.1 equiv) was then added dropwise along the side of the flask and stirred for 15 min at which point saturated aqueous $NaHCO_3$ (80 mL) was added and the mixture allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (4 x 80 mL). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil was purified by silica gel chromatography (40 mL SiO_2 with 2% to 5% methanol:dichloromethane) to yield **22** (330 mg, 1.12 mmol, 58% over 2 steps) as a white solid. **m.p.** 236–238 °C; TLC (methanol:dichloromethane, 1:9 v/v): R_f= 0.24; **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.14 (s, 1H), 6.32 (s, 1H), 4.17 (s, 1H), 3.86 (dt, *J* = 11.5, 9.2 Hz, 1H), 3.52 (dd, *J* = 11.9, 5.7 Hz, 1H), 3.38 (ddd, *J* = 12.7, 8.7, 4.1 Hz, 1H), 3.06 – 3.00 (m, 1H), 2.62 (dt, *J* = 14.0, 6.4 Hz, 1H), 2.43 (t, *J* = 6.9 Hz, 2H), 2.23 (dt, *J* = 14.0, 6.9 Hz, 1H), 2.02 – 1.88 (m, 4H), 1.23 (s, 3H), 1.14 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 214.6, 174.3, 171.2, 71.6, 61.2, 52.5, 46.9, 43.6, 41.4, 35.1, 31.4, 30.9, 25.2, 22.7, 21.4. **IR** (neat) ν_{max}: 3409, 2920, 2850, 1674, 1624, 1466 cm^{-1}; **HRMS** (ESI) calcd for $C_{15}H_{23}O_4N_2$ ($[M+H]^+$): 295.1652, found 295.1652.



(1*S*,5a*S*,12a*S*,13a*S*)-5a-amino-1-hydroxy-12,12-dimethyl-1,2,3,5a,6,11,12,12a,13,13a-decahydro-5*H*-indolizino[7,6-*b*]carbazol-5-one (25)

To a solution of (1*S*,5a*R*,9a*S*,10a*S*)-1-hydroxy-9,9-dimethyl-5,8-dioxodecahydropyrrolo[1,2-*b*]isoquinoline-5a(5*H*)-carboxamide (**22**) (500 mg, 1.70 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (34 mL, 0.05M) was added (tosylimio)-phenyl-λ^3-iodane[7] (PhINTs) (760 mg, 2.04 mmol, 1.2 equiv) in one portion at room temperature. The resulting solution was stirred at room temperature for 2 h, until TLC indicated complete consumption of starting material, and then aqueous H_2SO_4 (5% v/v, 34 mL) was added and the resulting solution was heated to 50 °C and held at this temperature for 1 h. The biphasic reaction mixture was then cooled to room temperature and the organic layer was removed by pipette. To the remaining aqueous layer was added phenylhydrazine (0.67 mL, 6.80 mmol, 4.0 equiv) and the solution was then heated to 100 °C and held at this temperature for 16 h. The solution was then cooled to 0 °C and solid K_2CO_3 was added portion-wise until bubbling ceased, followed by aqueous NaOH (5% w/v, 3 mL) to ensure a pH ≥ 12. The resulting reaction mixture was transferred to a 100 mL separatory funnel and the aqueous layer was extracted with ethyl acetate (5 x 40 mL). The combined organic layers were dried over Na_2SO_4, then filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (50 mL SiO_2 with 5% to 10% to 20% methanol:dichloromethane) to yield **25** (443 mg, 1.31 mmol, 77%) as an orange/brownish solid. TLC (methanol:dichloromethane, 1:9 v/v): R_f= 0.07; **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ = 10.79 (s, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 3.97 (d, *J* = 3.5 Hz, 1H), 3.67 (q, *J* = 9.7 Hz, 1H), 3.47 (d, *J* = 9.7 Hz, 1H), 3.16 (t, *J* = 11.1 Hz, 1H), 2.93 (d, *J* = 15.4 Hz, 1H), 2.49 (d, *J* = 15.4 Hz, 1H), 2.25

(ddd, J = 14.0, 6.6, 3.1 Hz, 1H), 1.96 – 1.85 (m, 2H), 1.80 – 1.74 (m, 1H), 1.63 – 1.57 (m, 1H), 1.55 (s, 3H), 1.35 (s, 3H); **^{13}C NMR** (150 MHz, $(CD_3)_2SO$) δ = 173.6, 140.0, 136.3, 127.3, 120.2, 118.0, 117.4, 110.6, 103.0, 71.9, 58.0, 56.4, 45.4, 42.6, 34.8, 30.9, 30.5, 30.0, 27.4, 21.8; **IR** (neat) ν_{max}: 3286, 2951, 2926, 2894, 1625, 1554, 1465, 1302, 1203, 1130 cm^{-1}; **HRMS** (ESI) calcd for $C_{20}H_{26}O_2N_3$ ($[M+H]^+$): 340.2020, found 340.2016.

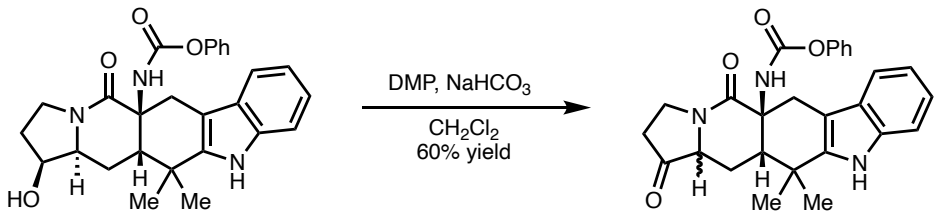


25 26

((1*S*,5a*S*,12a*S*,13a*S*)-1-hydroxy-12,12-dimethyl-5-oxo-2,3,6,11,12,12a,13,13a-octahydro-1*H*-indolizino[7,6-*b*]carbazol-5a(5*H*)-yl)carbamate (26)

To a solution of (1*S*,5a*S*,12a*S*,13a*S*)-5a-amino-1-hydroxy-12,12-dimethyl-1,2,3,5a,6,11,12,12a,13,13a-decahydro-5*H*-indolizino[7,6-*b*]carbazol-5-one (**25**) (100 mg, 0.295 mmol, 1.0 equiv), and K_2CO_3 (81 mg, 0.59 mmol, 2.0 equiv) in anhydrous acetone (5.9 mL, 0.05M) was added phenyl chloroformate (45 µL, 0.354 mmol, 1.2 equiv) by syringe and stirred at room temperature. After 3.5 h, additional phenyl chloroformate (45 µL, 0.354 mmol, 1.2 equiv) was added by syringe and the mixture was stirred for an additional 3.5 h at which point water (6 mL) was added slowly. The resulting aqueous layer was extracted with ethyl acetate (4 x 8 mL) and the combined organic layers were dried over Na_2SO_4, then filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (10 mL SiO_2 with 2% to 5% to 10% methanol:dichloromethane) to yield **26** (120 mg, 0.261 mmol, 89%) as an orange foam. TLC (methanol:dichloromethane, 1:9 v/v): R_f= 0.52; **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.39 (s, 1H), 7.45 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.24 (t, J = 7.8 Hz, 2H), 7.19 (t, J = 7.6 Hz, 1H), 7.14 – 7.08 (m, 2H), 7.02 (d, J = 7.9 Hz, 2H), 5.43 (s, 1H), 4.09 – 4.00 (m, 2H), 3.40 (d, J = 10.0 Hz, 1H), 3.28 (td, J = 11.5, 3.5 Hz, 1H), 3.22 – 3.14 (m, 2H), 3.03 (d, J = 16.5 Hz, 1H), 2.45 – 2.39 (m, 1H), 2.05 – 1.97 (m, 1H), 1.89 (ddd, J = 13.7, 9.3, 3.5 Hz, 1H), 1.79 (td, J = 14.0, 9.5 Hz, 1H), 1.59 (s, 3H), 1.42 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 171.1, 154.4, 150.9, 140.0, 136.4, 129.2, 127.1, 125.3, 121.92, 121.89, 119.8, 117.9, 111.1, 102.0, 74.3, 59.5, 58.6, 42.5, 40.8, 34.8,

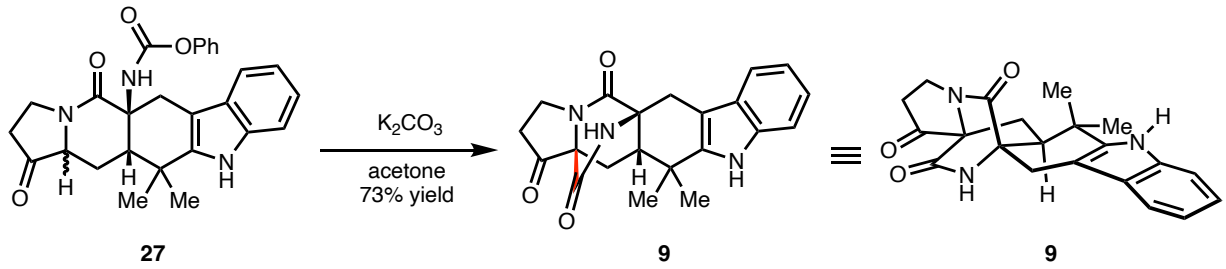
31.9, 30.8, 28.7, 28.0, 22.2; **IR** (neat) ν_{max}: 3416, 3269, 2924, 2972, 1726, 1634, 1463, 1127 cm^{-1}; **HRMS** (ESI) calcd for $C_{27}H_{30}O_4N_3$ ($[M+H]^+$): 460.2231, found 460.2238.



phenyl ((5a*S*,12a*S*)-12,12-dimethyl-1,5-dioxo-2,3,6,11,12,12a,13,13a-octahydro-1*H*-indolizino[7,6-*b*]carbazol-5a(5*H*)-yl)carbamate (27)

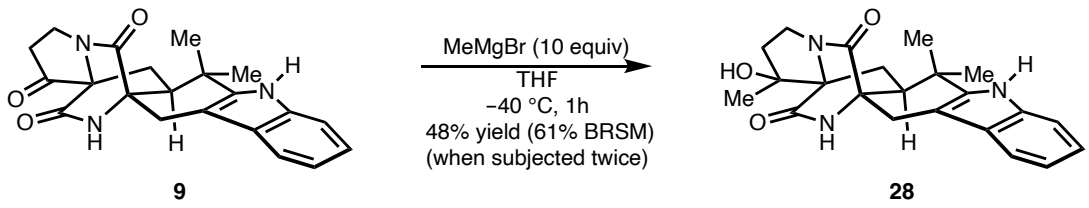
To a solution of phenyl ((1*S*,5a*S*,12a*S*,13a*S*)-1-hydroxy-12,12-dimethyl-5-oxo-2,3,6,11,12,12a,13,13a-octahydro-1*H*-indolizino[7,6-*b*]carbazol-5a(5*H*)-yl)carbamate (**26**) (57.8 mg, 0.126 mmol, 1.0 equiv) in reagent grade CH_2Cl_2 (2.5 mL, 0.05M) was added Dess-Martin periodinane (DMP) (85.6 mg, 0.201 mmol, 1.6 equiv) in eight portions (8 x 10.7 mg) at 10 minute intervals at room temperature. After 20 minutes at room temperature, sat. aq. $NaHCO_3$ (5.0 mL) was added and the biphasic mixture was stirred until the organic layer was no longer cloudy. The layers were separated and the aqueous layer was extracted with ethyl acetate (4 x 3 mL). The combined organic extracts were dried over Na_2SO_4, then filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (10 mL SiO_2 with 20% to 40% to 60% ethyl acetate:hexanes) to yield **27** (35 mg, 0.0765 mmol, 60%) as an orange foam. TLC (methanol:dichloromethane, 1:19 v/v): R_f= 0.32; **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 8.26 (s, 1H), 7.45 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 7.5 Hz, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.15 – 7.11 (m, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 5.43 (s, 1H), 4.64 (t, *J* = 10.7 Hz, 1H), 3.55 (d, *J* = 9.7 Hz, 1H), 3.31 (dt, *J* = 11.7, 8.6 Hz, 1H), 3.21 (d, *J* = 16.6 Hz, 1H), 3.04 (d, *J* = 16.6 Hz, 1H), 2.88 (dd, *J* = 13.9, 5.6 Hz, 1H), 2.57 – 2.39 (m, 3H), 1.90 (td, *J* = 14.2, 9.7 Hz, 1H), 1.57 (s, 3H), 1.42 (s, 3H); **^{13}C NMR** (150 MHz, $CDCl_3$) δ = 210.4, 171.2, 154.1, 150.8, 139.7, 136.4, 129.3, 127.0, 125.5, 122.2, 121.8, 120.0, 118.0, 111.1, 101.9, 60.0, 59.6, 41.0, 40.3, 35.8, 34.7, 30.4, 28.3,

28.2, 22.0; **IR** (neat) ν_{max}: 3338, 2959, 2924, 1727, 1652, 1469, 1202 cm^{-1}; **HRMS** (ESI) calcd for $C_{27}H_{28}O_4N_3$ ($[M+H]^+$): 458.2074, found 458.2075.



(5a*S*,12a*S*,13a*R*)-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-1,5,14-trione (9)

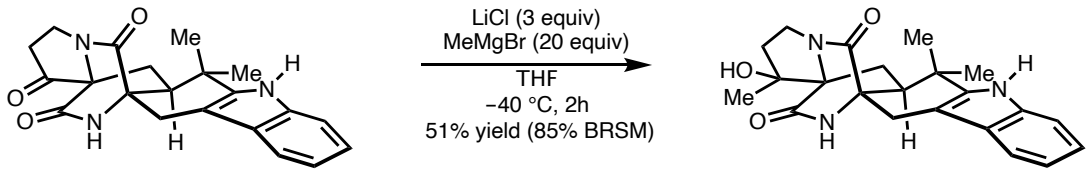
This procedure was adapted and modified from the reported literature.[2a,8] A solution of phenyl ((5a*S*,12a*S*,13a*S*)-12,12-dimethyl-1,5-dioxo-2,3,6,11,12,12a,13,13a-octahydro-1*H*-indolizino[7,6-*b*]carbazol-5a(5*H*)-yl)carbamate (**27**) (43.8 mg, 0.0958 mmol, 1.0 equiv), and K_2CO_3 (26.5 mg, 0.192 mmol, 2.0 equiv) in anhydrous acetone (3.8 mL, 0.025M) was heated to 50 °C and held at this temperature for 2 h. After the reaction mixture was allowed to cool to room temperature, sat. aq. NH_4Cl (4.0 mL) was added and the aqueous layer was extracted with ethyl acetate (4 x 4 mL). The combined organic extracts were dried over Na_2SO_4, and then filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (5 mL SiO_2 with 1% to 2% to 5% methanol:dichloromethane) to yield **9** (25.5 mg, 0.0702 mmol, 73%) as a white powder. TLC (methanol:dichloromethane, 1:19 v/v): R_f= 0.31; **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ = 10.78 (s, 1H), 8.98 (s, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.28 (d, *J* = 8.0 Hz, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.3 Hz, 1H), 3.74 (td, *J* = 10.6, 4.1 Hz, 1H), 3.52 (q, *J* = 8.9 Hz, 1H), 3.47 (d, *J* = 15.4 Hz, 1H), 2.82 (q, *J* = 9.6 Hz, 1H), 2.78 – 2.71 (m, 2H), 2.56 (dd, *J* = 10.3, 4.8 Hz, 1H), 2.24 (dd, *J* = 13.4, 10.3 Hz, 1H), 2.17 (dd, *J* = 13.5, 4.8 Hz, 1H), 1.27 (s, 3H), 1.01 (s, 3H); **^{13}C NMR** (150 MHz, $(CD_3)_2SO$) δ = 205.6, 169.3, 169.0, 140.7, 136.4, 126.4, 120.7, 118.3, 117.5, 110.8, 103.0, 66.8, 60.5, 48.5, 38.2, 36.3, 34.6, 27.8, 27.1, 23.6, 21.9; **IR** (neat) ν_{max}: 3349, 2957, 2918, 1767, 1688, 1393 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{22}O_3N_3$ ($[M+H]^+$): 364.1656, found 364.1656.



9 28

(5aS,12aS,13aR)-1-hydroxy-1,12,12-trimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-5,14-dione (28):

(5aS,12aS,13aR)-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-1,5,14-trione (**9**) (11.2 mg, 30.0 μmol, 1.0 equiv) was dissolved in THF (1.0 mL) and then cooled to −40 °C. A solution of MeMgBr in THF (1.0 M, 0.30 mL, 0.30 mmol, 10 equiv) was added dropwise at −40 °C and the resulting mixture stirred for 1 hour at which point the reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (1.0 mL). H_2O (0.5 mL) was added and the phases were separated. The aqueous phase was extracted with $CHCl_3$/EtOH 2:1 (3 × 1.5 mL) andthe combined organics were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The procedure above was repeated with the crude mixture. The resulting residue was purified by silica gel chromatography (3 mL SiO_2 with 1% to 3% to 5% methanol:dichloromethane) to yield (5aS,12aS,13aR)-1-hydroxy-1,12,12-trimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-5,14-dione (**28**) (5.6 mg, 18 μmol, 48%) as an amorphous solid and **9** (2.4 mg, 6.6 μmol, 21%). TLC (methanol:dichloromethane, 1:19 v/v): R_f = 0.22. **^{1}H NMR** (500 MHz, CD_3OD) δ = 7.41 (d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.03 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.99 – 6.93 (m, 1H), 3.60 (d, *J* = 15.3 Hz, 1H), 3.52 – 3.37 (m, 2H), 2.73 (d, *J* = 15.3 Hz, 1H), 2.61 (dd, *J* = 10.7, 4.4 Hz, 1H), 2.52 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.11 – 1.95 (m, 3H), 1.75 (s, 3H), 1.37 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, CD_3OD) δ 175.5, 173.3, 141.6, 138.4, 128.2, 122.0, 119.5, 118.7, 111.6, 104.5, 78.5, 72.1, 61.5, 50.5, 43.2, 40.0, 36.3, 28.7, 25.7, 25.3, 22.8, 22.3; **IR** (ATR) ν_{max}: 3428, 2963, 2930, 1675, 1458, 745 cm^{-1}; **HRMS** (ESI): calcd for $C_{22}H_{25}N_3NaO_3$ ($[M+Na]^+$): 402.1788, found: 402.1784.

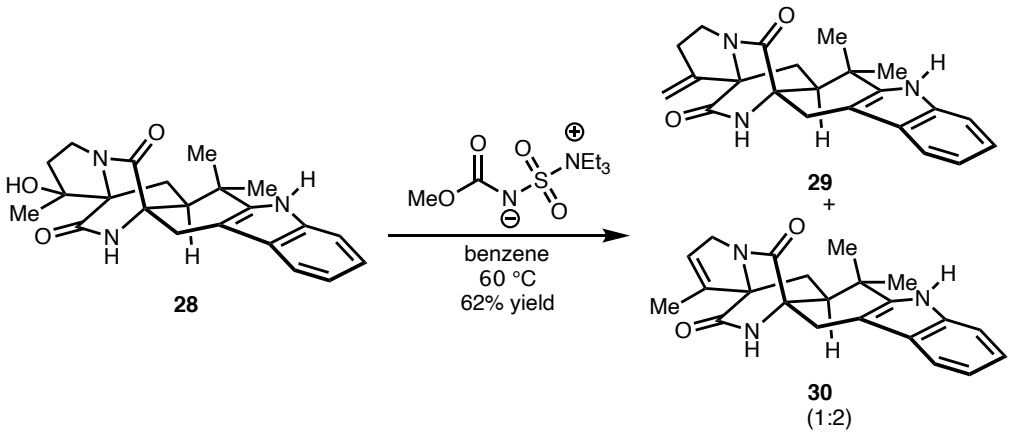


9 **28**

(5aS,12aS,13aR)-1-hydroxy-1,12,12-trimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-5,14-dione (28):

(5aS,12aS,13aR)-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-1,5,14-trione (**9)** (3.0 mg, 8.0 μmol, 1.0 equiv) and LiCl (1.0 mg, 24.0 μmol, 3.0 equiv) were dissolved in THF (0.3 mL) and the solution was cooled to −40 °C. A solution of MeMgBr in THF (1.0 M, 0.16 mL, 0.16 mmol, 20 equiv) was added dropwise at that temperature. The reaction mixture was stirred for 2 h. The reaction was quenched by addition of a saturated aqueous solution of NH_4Cl (1.0 mL). H_2O (0.5 mL) was added and the phases were separated. The aqueous phase was extracted with $CHCl_3$/EtOH 2:1 (3 × 1.5 mL). The combined organic phases were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (3 mL SiO_2 with 1% to 3% to 5% methanol:dichloromethane) to yield (5aS,12aS,13aR)-1-hydroxy-1,12,12-trimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-5,14-dione **28** (1.6 mg, 4.2 μmol, 51%) as an amorphous solid and **9** (1.2 mg, 3.16 μmol, 40%).

^{1}H NMR (500 MHz, CD_3OD) δ = 7.41 (apparent d, *J* = 7.7 Hz, 1H), 7.24 (d, *J* = 8.1 Hz, 1H), 7.03 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 6.99 – 6.93 (m, 1H), 3.60 (d, *J* = 15.3 Hz, 1H), 3.52 – 3.37 (m, 2H), 2.73 (d, *J* = 15.3 Hz, 1H), 2.61 (dd, *J* = 10.7, 4.4 Hz, 1H), 2.52 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.11 – 1.95 (m, 2H), 1.75 (s, 3H), 1.37 (s, 3H), 1.10 (s, 3H). **^{13}C NMR** (101 MHz, CD_3OD) δ 175.5, 173.3, 141.6, 138.4, 128.2, 122.0, 119.5, 118.7, 111.6, 104.5, 78.5, 72.1, 61.5, 50.5, 43.2, 40.0, 36.3, 28.7, 25.7, 25.3, 22.8, 22.3; **IR** (ATR) ν_{max}: 3428, 2963, 2930, 1675, 1458, 745 cm^{-1}; **HRMS** (ESI): calcd for $C_{22}H_{25}N_3NaO_3$ ($[M+Na]^+$): 402.1788, found: 402.1784.



(5a*S*,12a*S*,13a*R*)-12,12-dimethyl-1-methylene-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (29) and (5a*S*,12a*S*,13a*R*)-1,12,12-trimethyl-11,12,12a,13-tetrahydro-3*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (30)

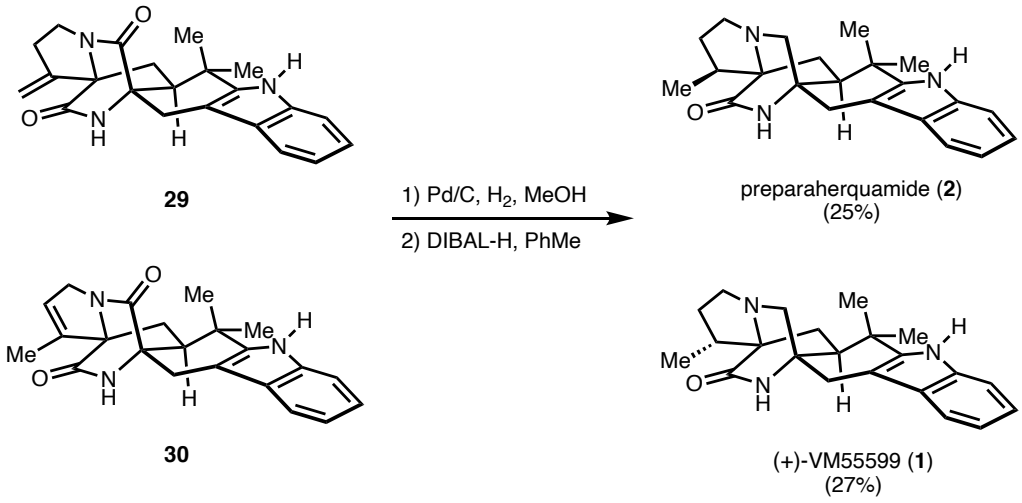
To a 4 mL vial was added (5aS,12aS,13aR)-1-hydroxy-1,12,12-trimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-5,14-dione (**28**) (3.8 mg, 10 μmol, 1.0 equiv) and Burgess reagent[9] (24 mg, 0.10 mmol, 10 equiv) under N2. benzene (0.4 mL) was added and the resulting solution was placed in a 70 °C preheated oil bath. The reaction mixture was stirred and held at that temperature for 90 min. Then the reaction mixture was allowed to cool down to room temperature. The solvent was removed under reduced pressure. Purification by column chromatography (silica) using 2% methanol in DCM yielded a 1:2 mixture (determined by 1H NMR integration of crude mixture) of (5a*S*,12a*S*,13a*R*)-12,12-dimethyl-1-methylene-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (**29**) and (5a*S*,12a*S*,13a*R*)-1,12,12-trimethyl-11,12,12a,13-tetrahydro-3*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (**30**) (2.4 mg, 6.2 μmol, 62%). TLC (methanol:dichloromethane, 1:19 v/v): $R_f = 0.35$; **IR** (ATR) ν_{max}: 3264, 2949, 1614, 1426, 1334, 1216, 1110, 1056 cm^{-1}

HRMS (ESI) calcd for $C_{22}H_{24}N_3O_2$ ($[M+H]^+$): 384.1682, found 384.1679.

Characterization from isolated band containing 0.7:1.0 ratio of **29** to **30**

^{1}H NMR (700 MHz, CD_3OD) δ 10.31 (s, 1+.07H), 7.52 – 7.43 (m, 1+0.7H), 7.29 (d, *J* = 8.0 Hz, 1+0.7H), 7.11 – 7.05 (m, 1+0.7H), 7.04 – 6.98 (m, 1+0.7H), 5.84 – 5.76 (m, 1H), 5.51 – 5.48 (m, 0.7H), 5.37 – 5.34 (m, 0.7H), 4.08 (d, *J* = 14.4 Hz, 2H), 3.72 – 3.63 (m, 2+1.4H), 2.87 – 2.79 (m, 3H), 2.76 – 2.68 (m, 1+0.7H), 2.56 (dd, *J* = 13.3, 10.4 Hz, 1H), 2.14 (dd, *J* = 13.6, 4.8 Hz, 0.7H), 2.09 (d, *J* = 2.0 Hz, 3H), 2.01 (dd, *J* = 13.4, 4.6 Hz, 1H), 1.39 (s, 6H), 1.36 – 1.31 (m, 1.4 H) 1.12 (s, 2.1H), 1.10 (s, 3H).

^{13}C NMR (176 MHz, CD_3OD) δ 175.6, 174.5, 171.7, 171.1, 145.1, 141.3, 138.4, 137.6, 128.1, 123.1, 122.1, 119.6, 118.7, 112.8, 111.7, 104.5, 74.4, 69.5, 61.9, 61.8, 51.2, 50.5, 50.0, 43.1, 36.2, 36.1, 32.6, 32.1, 30.6, 28.8, 25.2, 22.6, 22.4, 13.5 (Isomers have overlapping ^{13}C signals)



Preparaherquamide (2) and (+)-VM55599 (1)

To a 4 mL vial containing a solution of (5a*S*,12a*S*,13a*R*)-12,12-dimethyl-1-methylene-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (**29**) and (5a*S*,12a*S*,13a*R*)-1,12,12-trimethyl-11,12,12a,13-tetrahydro-3*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (**30**) (3.4 mg, 9.4 μmol, 1.0 equiv) in MeOH (0.4 mL) was added palladium on charcoal (10 wt% Pd, 3.4 mg) and the vial was placed in a Parr steel bomb reactor. The reactor was purged with H_2 three times and then pressurized to 450 psi with H_2. The reaction mixture was stirred overnight at room temperature. Then the reaction mixture was filtered through Celite and rinsed with methanol. Solvents were removed under reduced pressure and the resulting solid was dissolved in toluene (1.75 mL) and

cooled to 0°C. To the resulting solution was added DIBAL-H (1 M in hexanes, 0.18 mL, 0.18 mmol, 19 equiv) dropwise, and then the resulting solution was warmed to room temperature. After the reaction mixture was stirred for 19 h, the resulting solution was quenched by portion-wise addition of solid $Na_2SO_4 \cdot 10\ H_2O$ (74 mg, 0.23 mmol, 24 equiv) and stirred at room temperature for 1 h. The mixture was filtered through celite, washed with methanol:dichloromethane 1:9 v/v, and concentrated under reduced pressure. Column chromatography on silica using 1% methanol in DCM to 2% methanol in DCM yielded a mixture of preparaherquamide (**2**) and (+)-VM55599 (**1**) (1.8 mg, 1:1 mixture based on ^{1}H integration) as a colorless solid. TLC (methanol:dichloromethane, 1:19 v/v): R_f = 0.34. The mixture was separated by preparative thin layer chromatography (acetone:dichloromethane, 1:19 v/v) to provide preparaherquamide (**2)** (0.82 mg, 2.5 μmol, 25%) and (+)-VM55599 (**1**) (0.88 mg, 2.5 μmol, 27%).

(+)-VM55599 (**1**): $[\alpha]^{22}_D$ = +23.3 degrees (*c* = 0.03, MeOH)

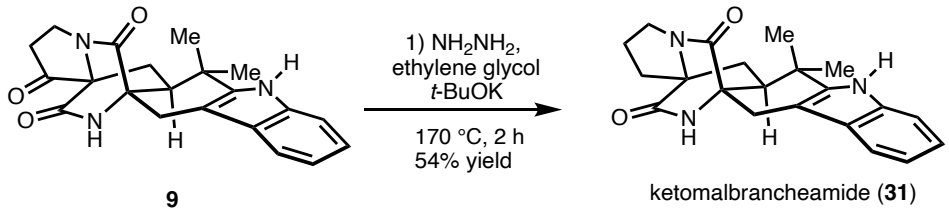
Literature value for (–)-VM55599 $[\alpha]^{22}_D$ = -23 (*c* = 1.1 g L^{-1} in MeOH)[10]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.17 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.23 (s, 1H), 3.49 (d, *J* = 10.3 Hz, 1H), 3.00 (m, 2H), 2.95 (d, *J* = 15.0 Hz, 1H), 2.80 (d, *J* = 15.0 Hz, 1H), 2.30 (dd, *J* = 10.3, 1.9 Hz, 1H), 2.17 (m, 3H), 2.00 (dd, *J* = 13.2, 4.3 Hz, 1H), 1.78 (dd, *J* = 13.2, 11.4 Hz, 1H), 1.43 (m, 3H), 1.41 (m, 1H), 1.35 (s, 3H), 1.04 (d, *J* = 7.2 Hz, 3H).

Preparaherquamide (**2**): $[\alpha]^{22}_D$ = +33.3 degrees (*c* = 0.03 $CHCl_3$);

Literature value for preparaherquamide: $[\alpha]^{23}_D$ +31.2 (c 0.026, $CHCl_3$)[11]

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (1H, brs), 7.43 (d, *J* = 7.8 Hz, 1H), δ 7.32 (d, *J* = 7.9 Hz,1H), 7.17 (ddd, 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.00 (s, 1H), 3.47 (d, *J* = 10.4 Hz, 1H), 3.21 (td, *J* = 8.8, 5.0 Hz, 1H), 2.91 (d, *J* = 15.0 Hz, 1H), 2.81 (d, *J* = 15.0 Hz, 1H), 2.30 (td, *J* = 10.0, 4.4 Hz, 1H), 2.21 (d, *J* = 9.2 Hz, 1H), 2.20 (m, 2H), 2.02 (m, 2H), 1.97 (m, 1H), 1.69 (m, 1H), 1.41 (d, *J* = 8.0 Hz, 3H), 1.40 (s, 3H), 1.33 (s, 3H).

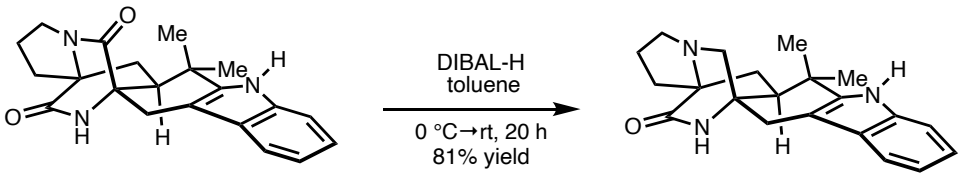


9 ketomalbrancheamide (**31**)

(12a*S*,13a*S*)-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (31)

To a solution of (12a*S*,13a*S*)-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-1,5,14-trione (**9**) (39.0 mg, 0.107 mmol, 1.0 equiv) in deoxygenated (three cycles of freeze/pump/thaw) anhydrous ethylene glycol (4.3 mL, 0.025M) was added hydrazine (3.4 μL, 0.107 mmol, 1.0 equiv) under a nitrogen atmosphere . The solution was then heated to and held at 70 °C for 17 h, at which time the solution was cooled to room temperature and *t*BuOK (36.0 mg, 0.321 mmol, 3.0 equiv) was added in one portion at room temperature. The solution was then placed in a preheated heating block at 170 °C. After 2 h, the reaction mixture was allowed to cool to room temperature, and saturated aqueous NH_4Cl (10 mL) was added. The aqueous layer was extracted with ethyl acetate (4 x 8 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting residue was purified by silica gel chromatography (3 mL SiO_2 with 1% to 3% to 5% methanol:dichloromethane) to yield **31** (20.0 mg, 0.0573 mmol, 54%) as a beige powder. TLC (methanol:dichloromethane, 1:19 v/v): R_f = 0.29; **^{1}H NMR** (600 MHz, $(CD_3)_2SO$) δ = 10.74 (s, 1H), 8.70 (s, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 7.9 Hz, 1H), 7.04 (td, *J* = 7.7, 3.2 Hz, 1H), 6.97 (td, *J* = 7.5, 3.3 Hz, 1H), 3.44 (dd, *J* = 15.4, 3.4 Hz, 1H), 3.28 – 3.22 (m, 1H), 2.70 (dd, *J* = 15.5, 3.5 Hz, 1H), 2.57 – 2.52 (m, 1H), 2.46 (dd, *J* = 9.9, 4.7 Hz, 1H), 2.06 (td, *J* = 11.7, 10.0, 3.4 Hz, 1H), 2.02 – 1.94 (m, 2H),

1.89 – 1.79 (m, 2H), 1.28 (s, 3H), 1.00 (s, 3H); **^{13}C NMR** (150 MHz, $(CD_3)_2SO$) δ = 173.0, 168.5, 140.7, 136.4, 126.5, 120.6, 118.1, 117.5, 110.7, 103.3, 66.0, 59.7, 49.1, 43.5, 34.5, 30.1, 28.7, 27.9, 24.0, 23.8, 21.6; **IR** (neat) ν_{max}: 3302, 2912, 1676, 1555, 1459, 1259, 1087 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{22}O_2N_3$ ($[M+H]^+$): 348.1718, found 348.1715.

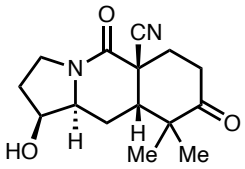


ketomalbrancheamide (**31**) premalbrancheamide (**32**)

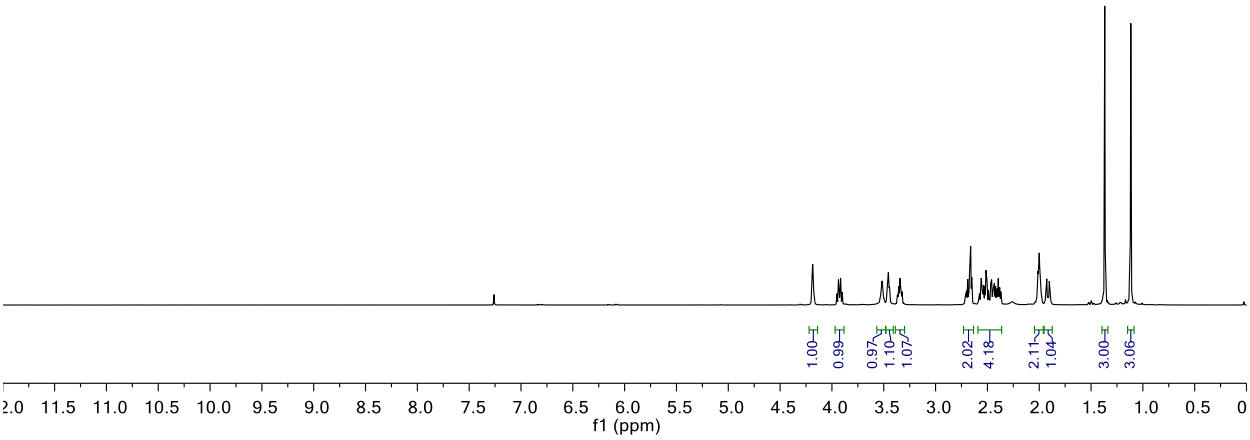
Premalbrancheamide (32)

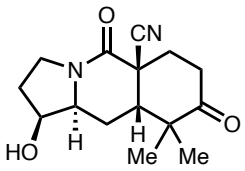
To a solution of (12a*S*,13a*S*)-12,12-dimethyl-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (**31**) (4.6 mg, 0.013 mmol, 1.0 equiv) in toluene (2.7 mL, 0.005M) at 0 ºC was added DIBAL-H (1M in hexanes, 0.26 mL, 0.26 mmol, 20 equiv) dropwise, and then the resulting solution was allowed to warm to room temperature. After 20 h, the resulting solution was quenched by portionwise addition of solid $Na_2SO_4.10H_2O$ (110 mg, 0. 0.34 mmol, 26 equiv) and stirred at room temperature for 1 h. The mixture was filtered, washed with methanol:dichloromethane 1:9 v/v, and concentrated. The resulting residue was purified by preparative-TLC (methanol:dichloromethane 1:24 v/v developed three times) to yield premalbrancheamide (**32**) (3.6 mg, 0.011 mmol, 81%) as a white powder. $[\alpha]^{22}_D$ = +12.7 degrees (*c* = 0.3, MeOH); TLC (methanol:dichloromethane, 1:19 v/v): R_f= 0.30; **^{1}H NMR** (600 MHz, CD_3OD): δ = 7.38 (d, *J* = 7.8 Hz, 1H), 7.30 (d, *J* = 8.1 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.99 (t, *J* = 7.4 Hz, 1H), 3.51 (d, *J* = 10.3 Hz, 1H), 3.13 – 3.05 (m, 1H), 2.92 (d, *J* = 3.2 Hz, 2H), 2.57 (ddd, *J* = 13.5, 8.2, 5.5 Hz, 1H), 2.30 (dd, *J* = 10.3, 2.0 Hz, 1H), 2.25 – 2.13 (m, 2H), 2.04 (t, *J* = 12.1 Hz, 1H), 1.99 (dd, *J* = 13.2, 5.0 Hz, 1H), 1.92 (qd, *J* = 8.4, 5.6, 3.4 Hz, 2H), 1.58 – 1.50 (m, 1H), 1.47 (s, 3H), 1.38 (s, 3H). **^{13}C NMR** (150 MHz, CD_3OD): δ = 176.7, 142.2, 138.5, 128.2, 122.0, 119.5, 118.3, 111.6, 104.5, 66.2, 59.5, 57.7, 55.4, 48.8, 35.4, 32.5, 30.9, 30.5, 28.2, 24.4, 23.6; **IR** (neat) ν_{max}: 3287, 2959, 2924, 1667, 1459 cm^{-1}; **HRMS** (ESI) calcd for $C_{21}H_{26}O_1N_3$ ($[M+H]^+$): 336.2070, found 336.2066.

4. ^{1}H & ^{13}C NMR Spectra

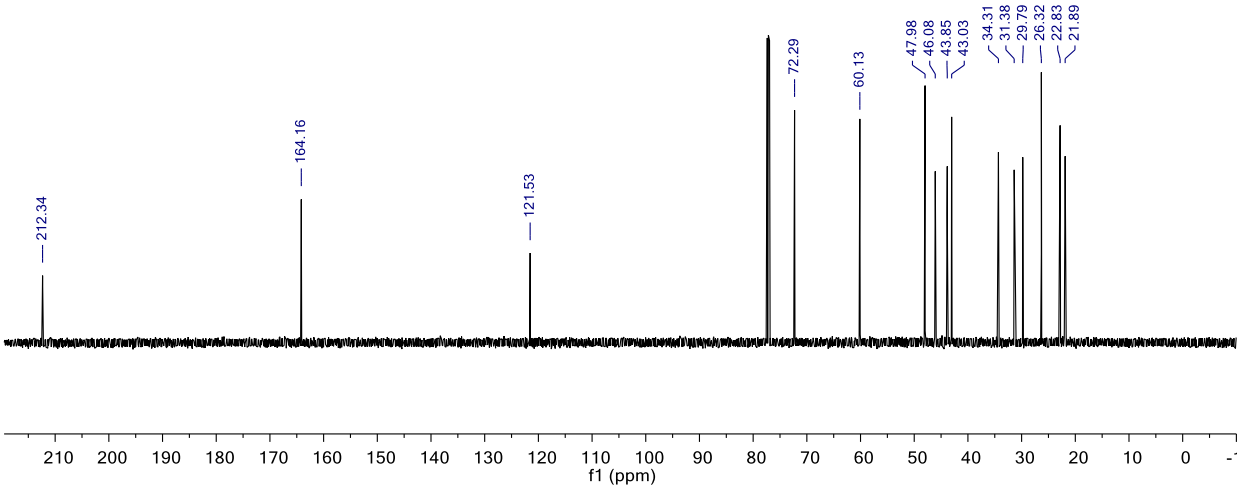


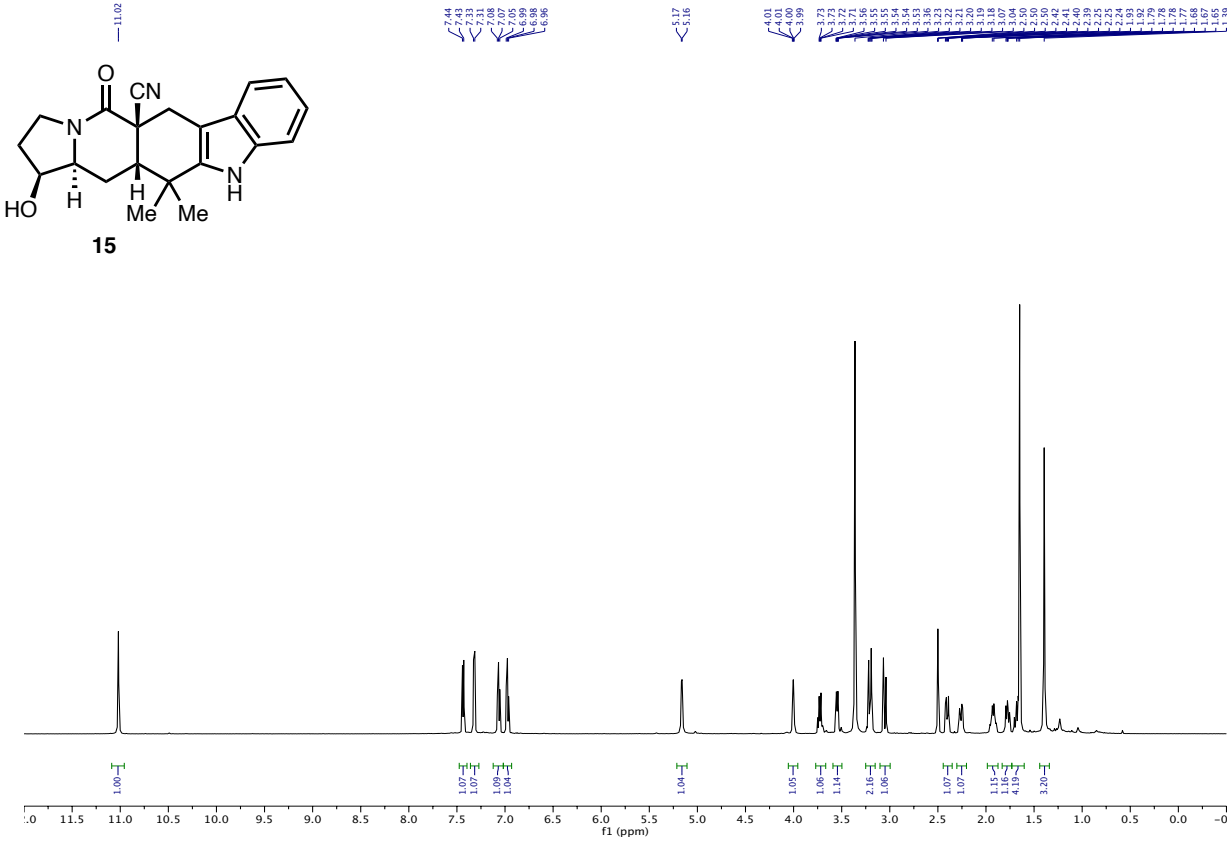
14




O
CN
N
HO
H
H
Me
Me
O

14


212.34
164.16
121.53
72.29
60.13
47.98
46.08
43.85
43.03
34.31
31.38
29.79
26.32
22.83
21.89
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



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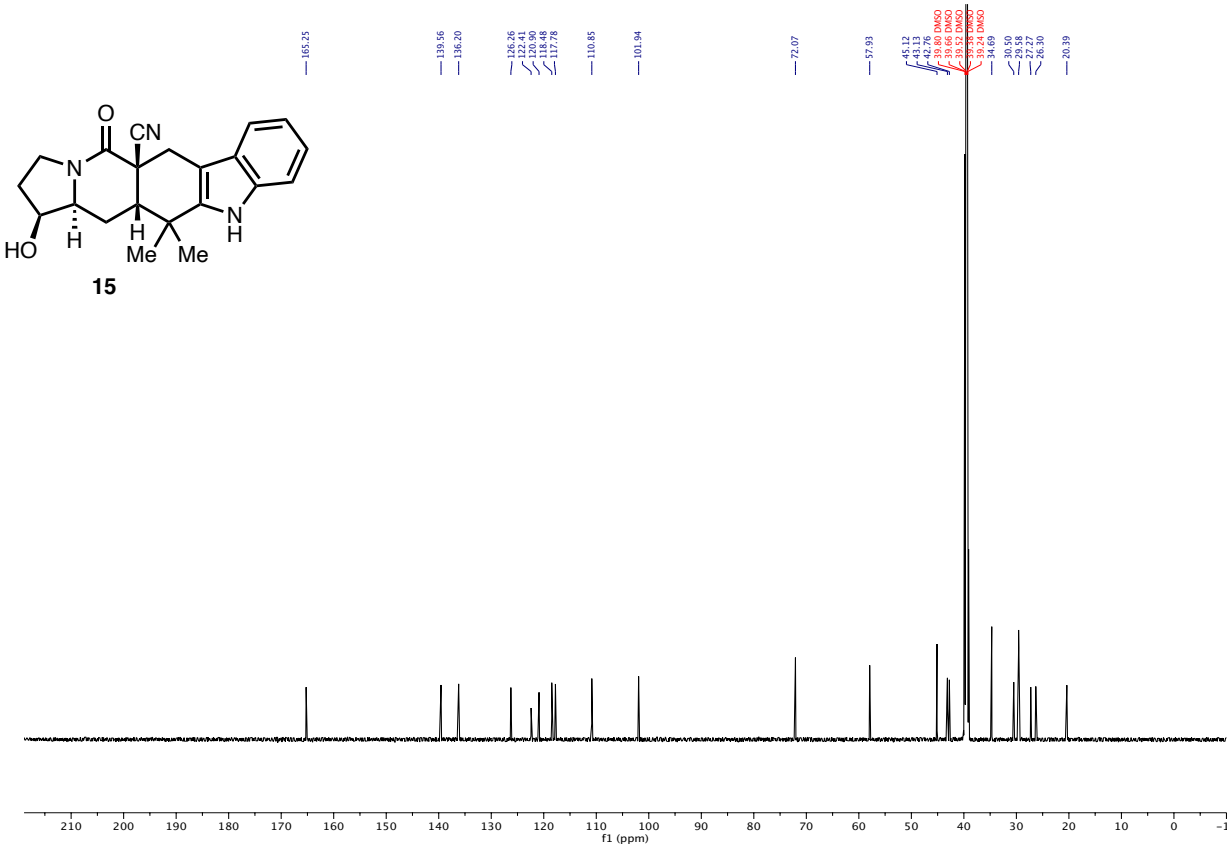
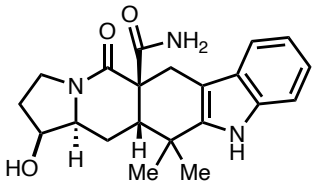
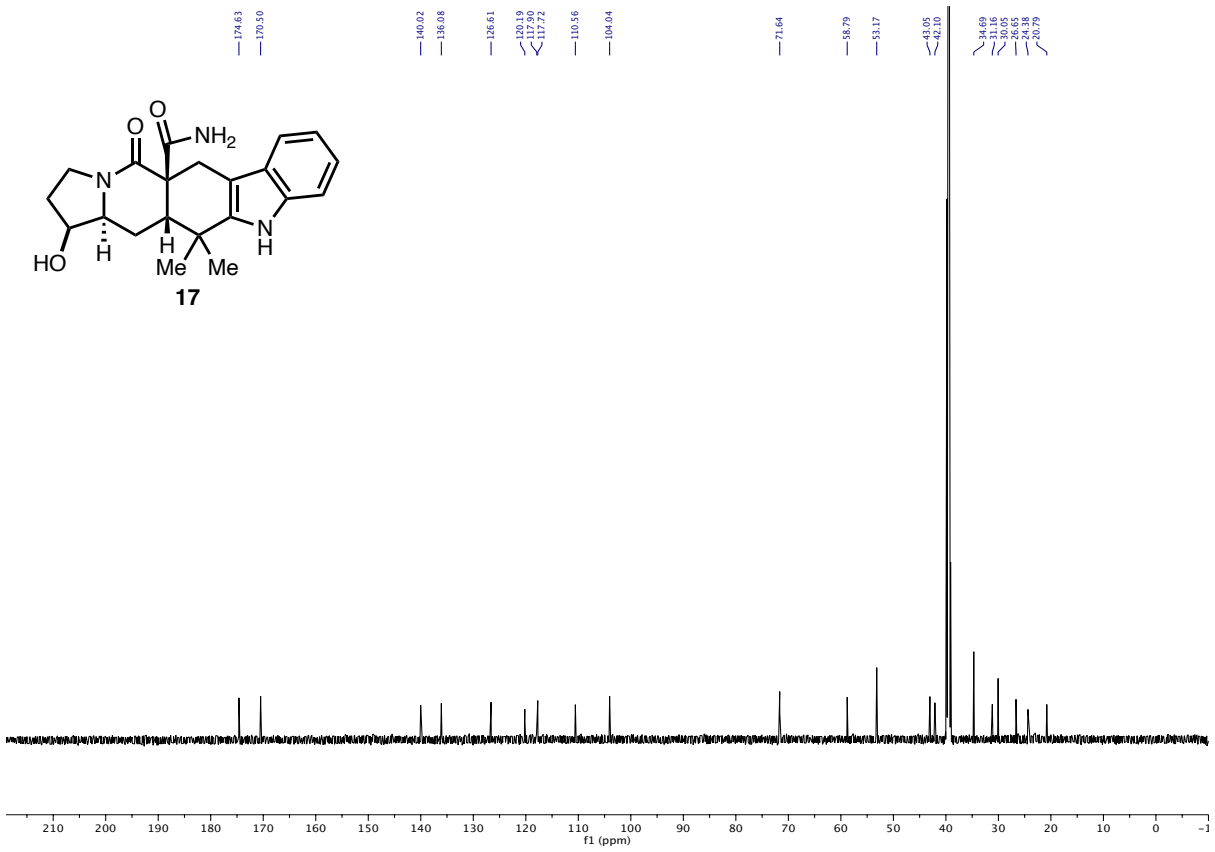
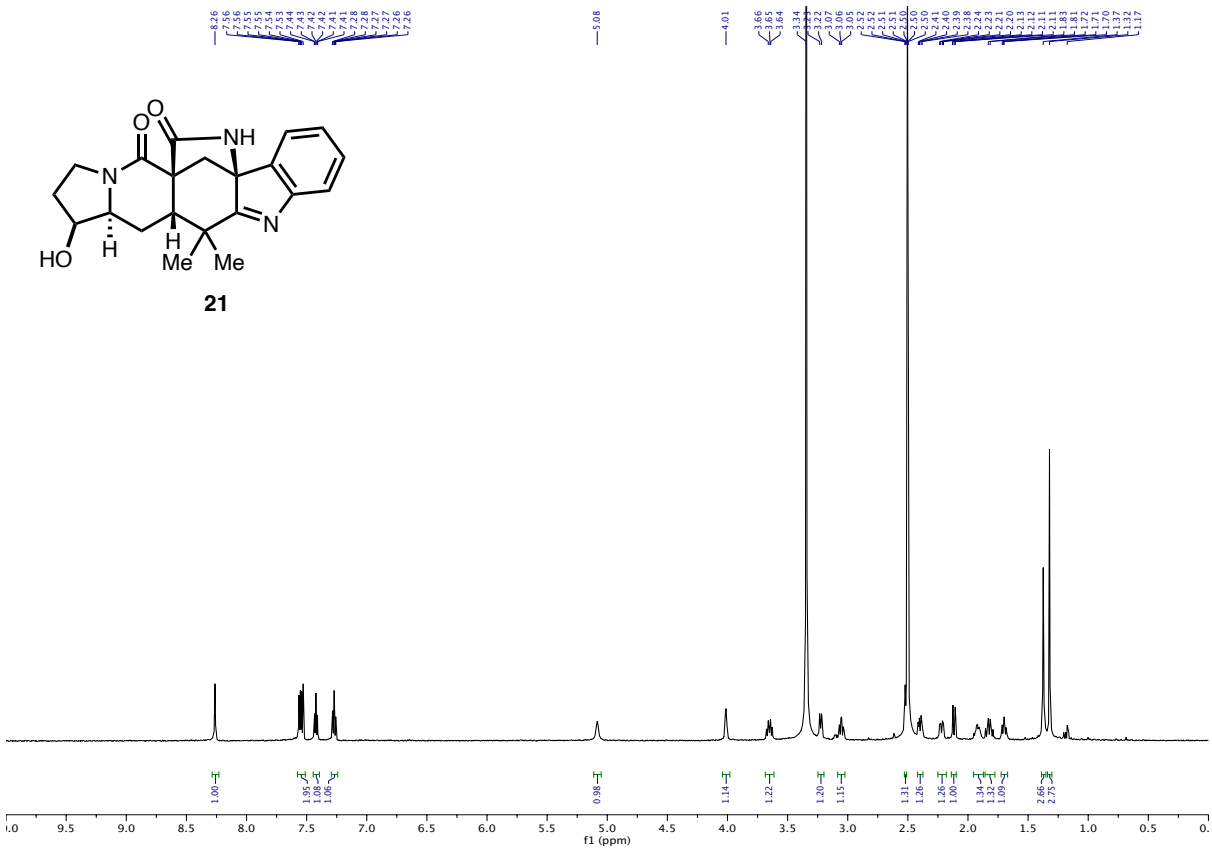

O
CN
N
H
HO
H
Me
Me
N
H
15
165.25
139.56
136.20
126.26
125.41
120.90
118.48
117.78
110.85
101.94
72.07
57.93
45.12
43.33
42.76
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
34.69
30.50
29.58
27.27
26.30
20.39
f1 (ppm)

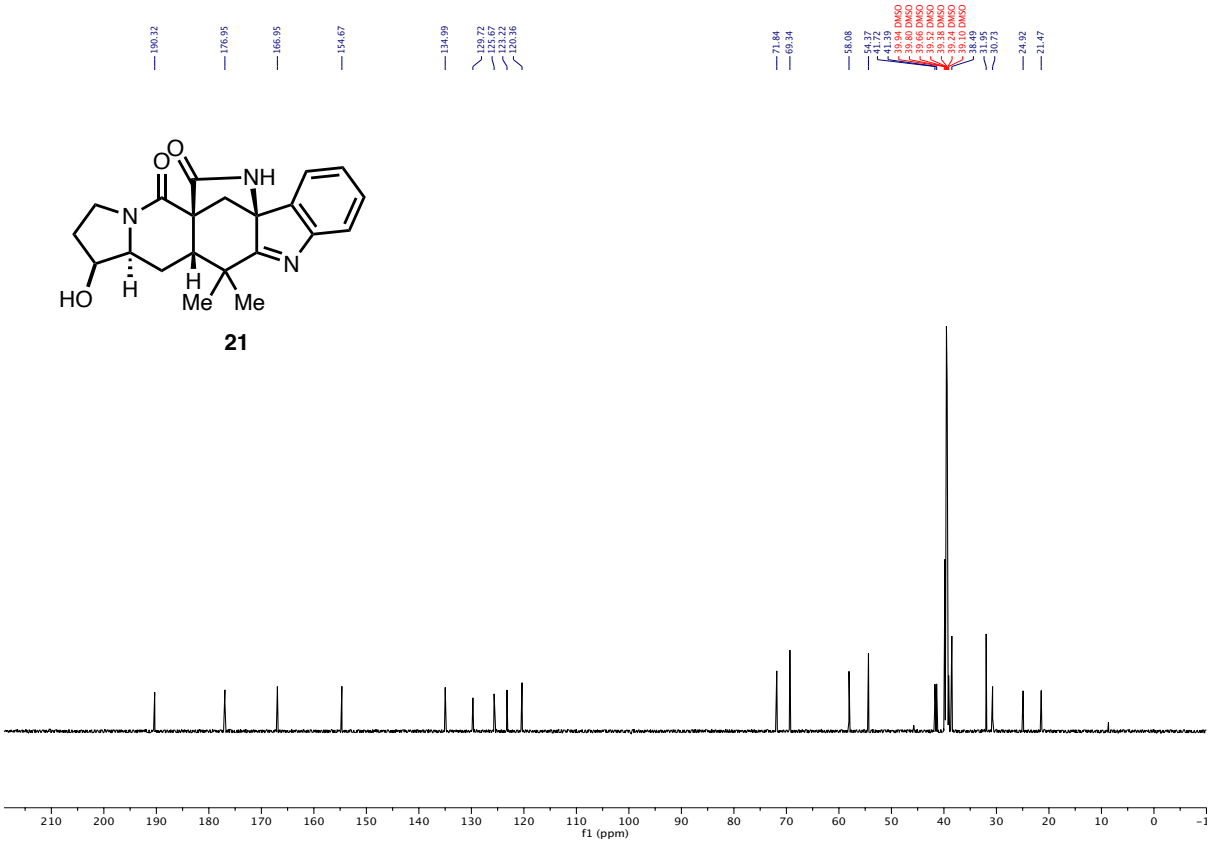

O
O
NH2
N
HO
H
H
Me
Me
N
H

17

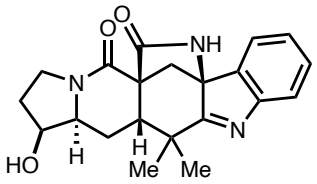
10.68
7.37
7.36
7.26
7.24
7.01
7.00
6.98
6.97
6.93
6.92
6.91
6.84
3.95
3.95
3.95
3.94
3.68
3.66
3.48
3.42
3.19
3.17
3.09
2.92
2.89
2.67
2.66
2.65
2.64
2.51
2.50
2.50
2.50
2.49
2.23
2.21
1.77
1.75
1.74
1.69
1.67
1.34
1.33
1.11
1.09
1.00
1.02
1.03
1.88
1.15
0.91
1.05
1.31
2.92
1.21
1.13
1.02
1.02
1.04
1.14
2.73
1.28
6.02
1.26
f1 (ppm)


174.63
170.50
140.02
136.08
126.61
120.19
117.90
117.72
110.56
104.04
71.64
58.79
53.17
43.05
42.10
34.69
31.16
30.05
26.65
24.38
20.79
O
O
NH2
N
HO
H
H
Me
Me
N
H
17
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−1
f1 (ppm)


O
O
NH
N
N
H
HO
H
Me
Me
21
f1 (ppm)


190.32
176.95
166.95
154.67
134.99
129.72
125.67
121.22
120.36
71.84
69.34
58.08
54.37
41.72
41.39
39.94 DMSO
39.80 DMSO
39.66 DMSO
39.52 DMSO
39.38 DMSO
39.24 DMSO
39.10 DMSO
38.49
31.95
30.73
24.92
21.47
O
O
NH
N
N
H
HO
H
Me
Me
21
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
−1
f1 (ppm)

DEPT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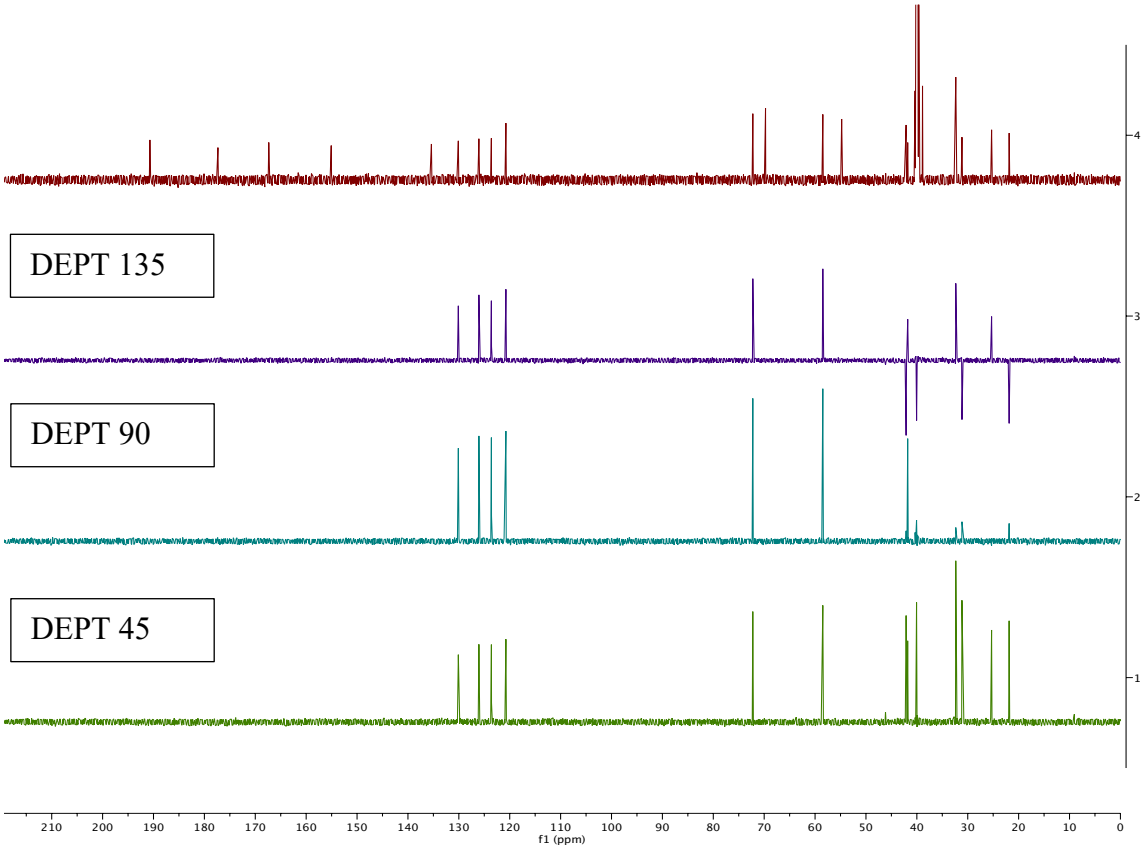
O
NH
N
N
HO
H
H
Me
Me

21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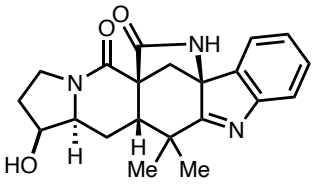
DEPT 90
DEPT 45
4
3
2
1
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

COSY



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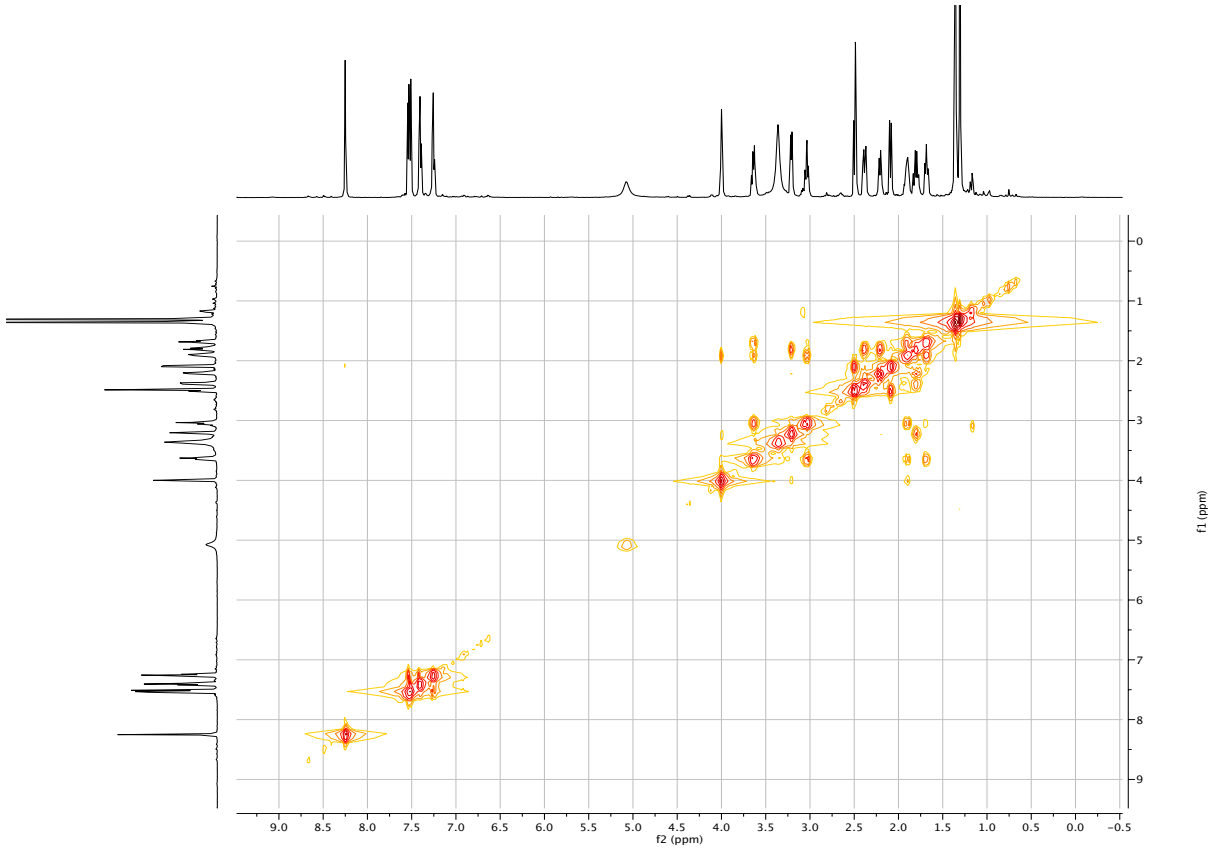
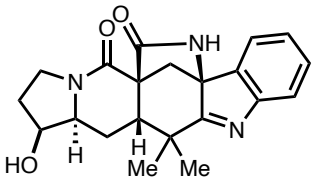


HSQC



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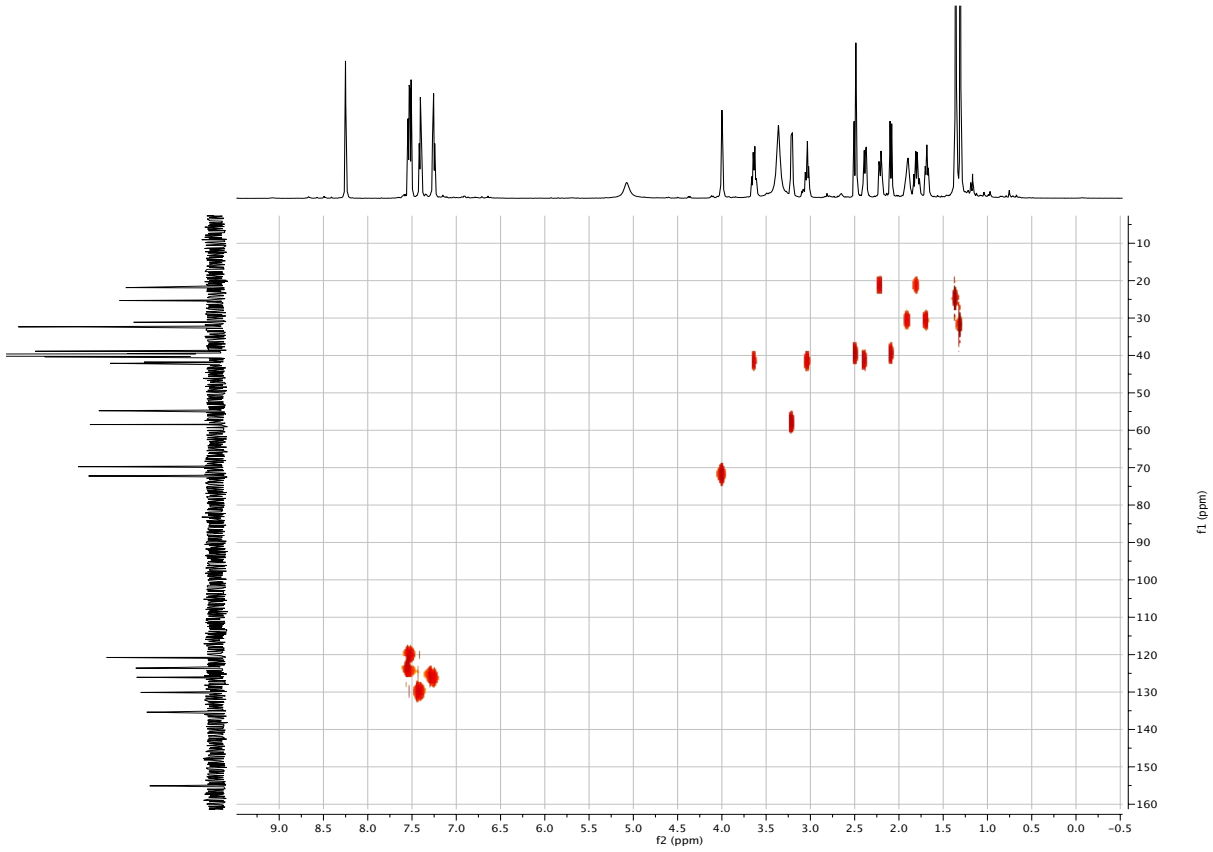
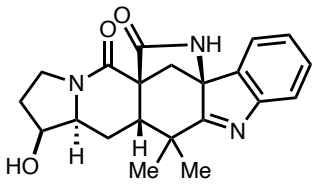


HMBC



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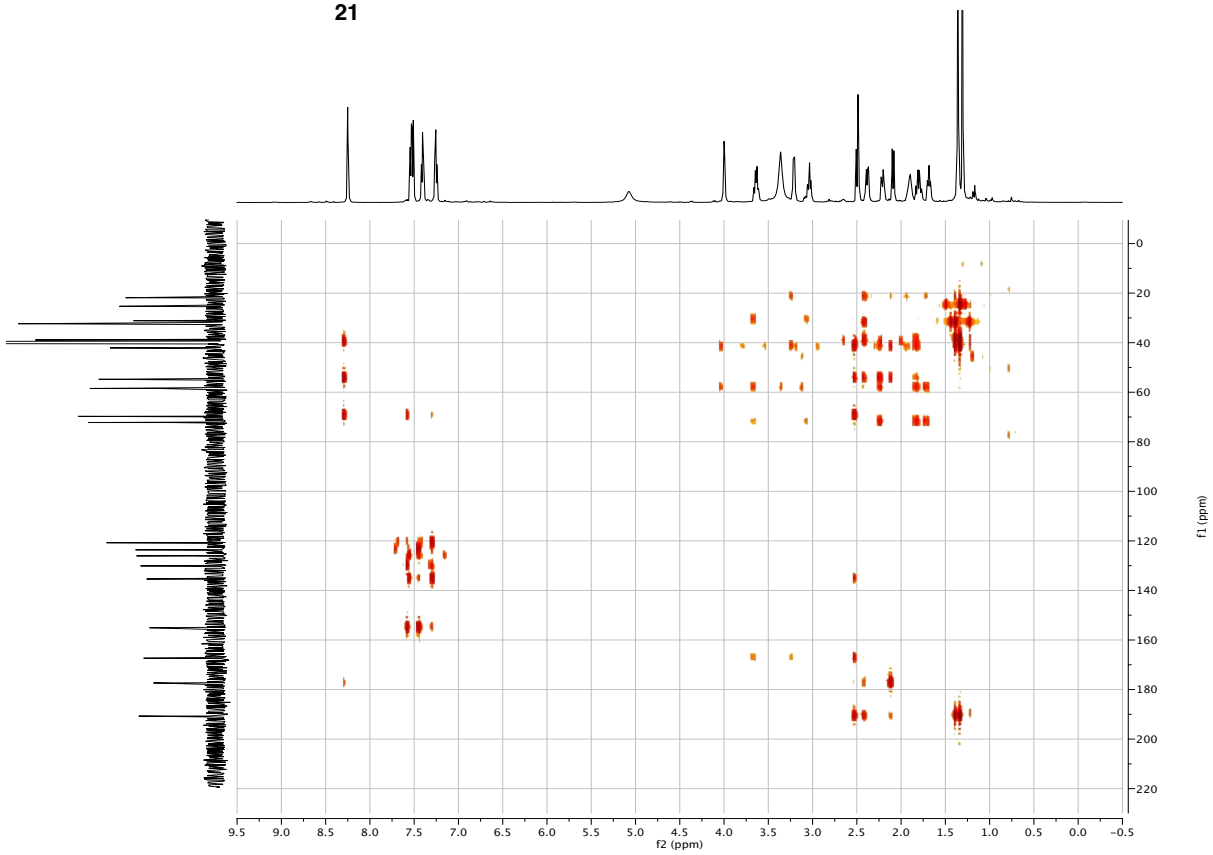
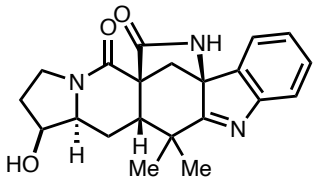


NOESY



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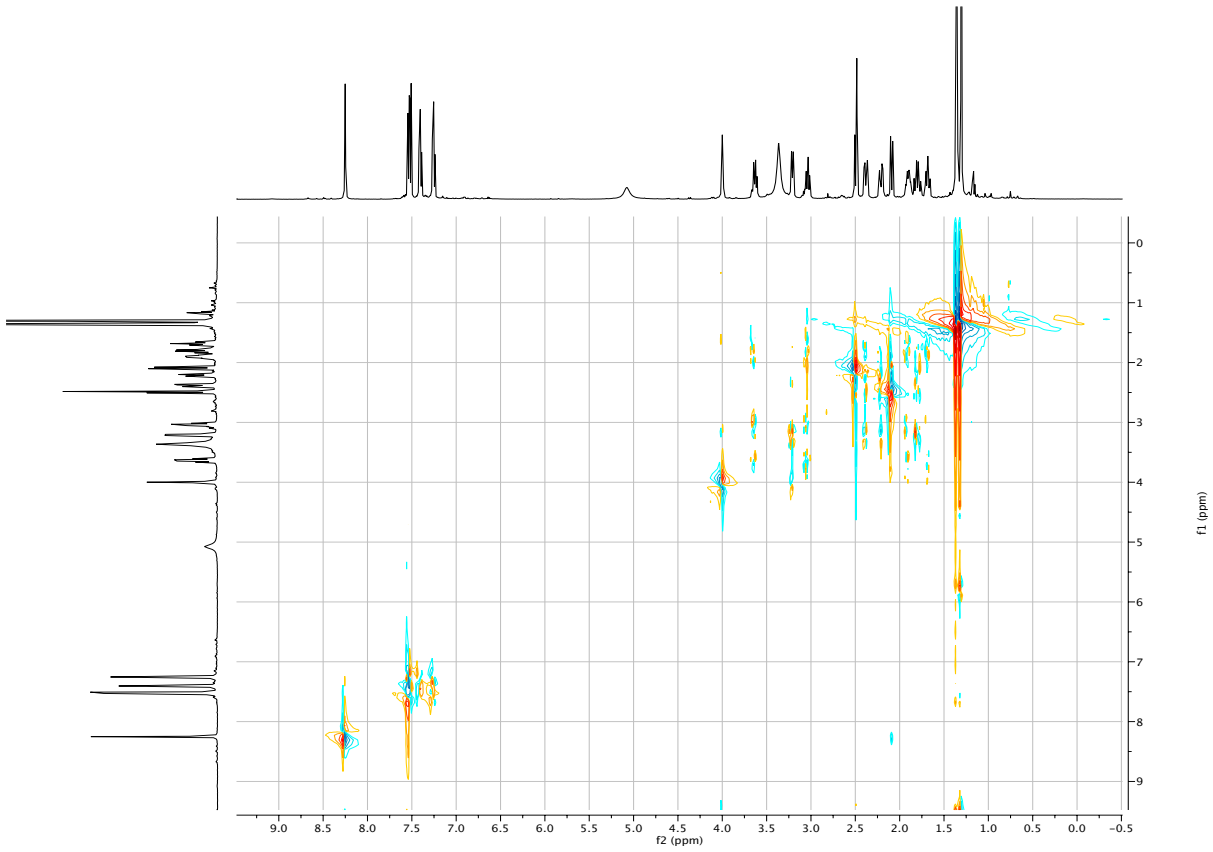
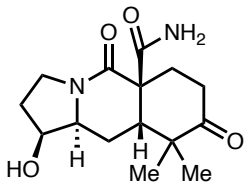
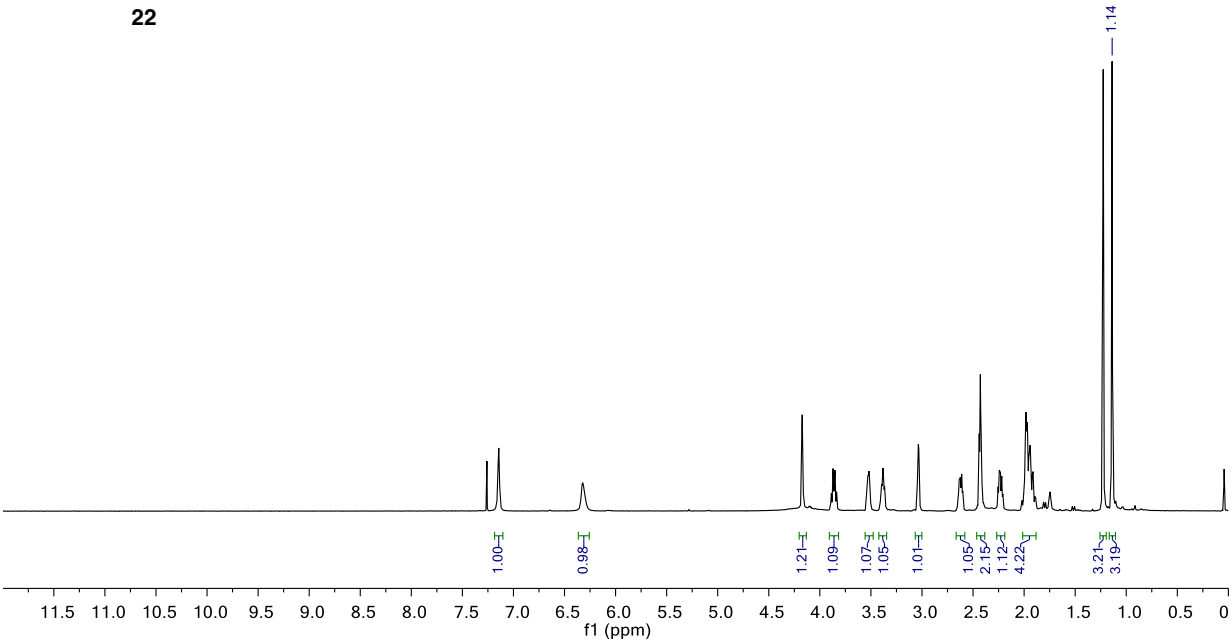
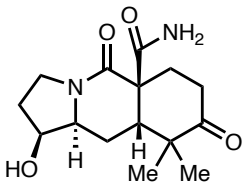


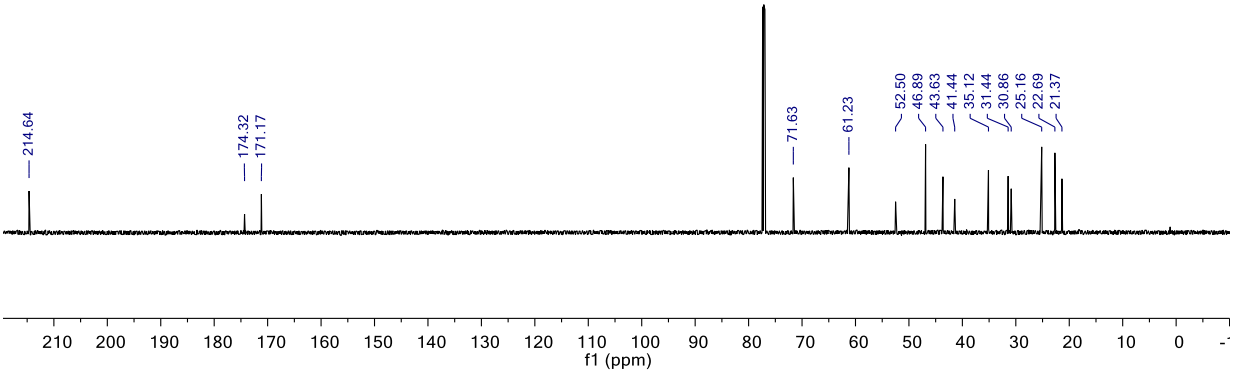

O
O
NH2
N
O
HO
H
H
Me
Me

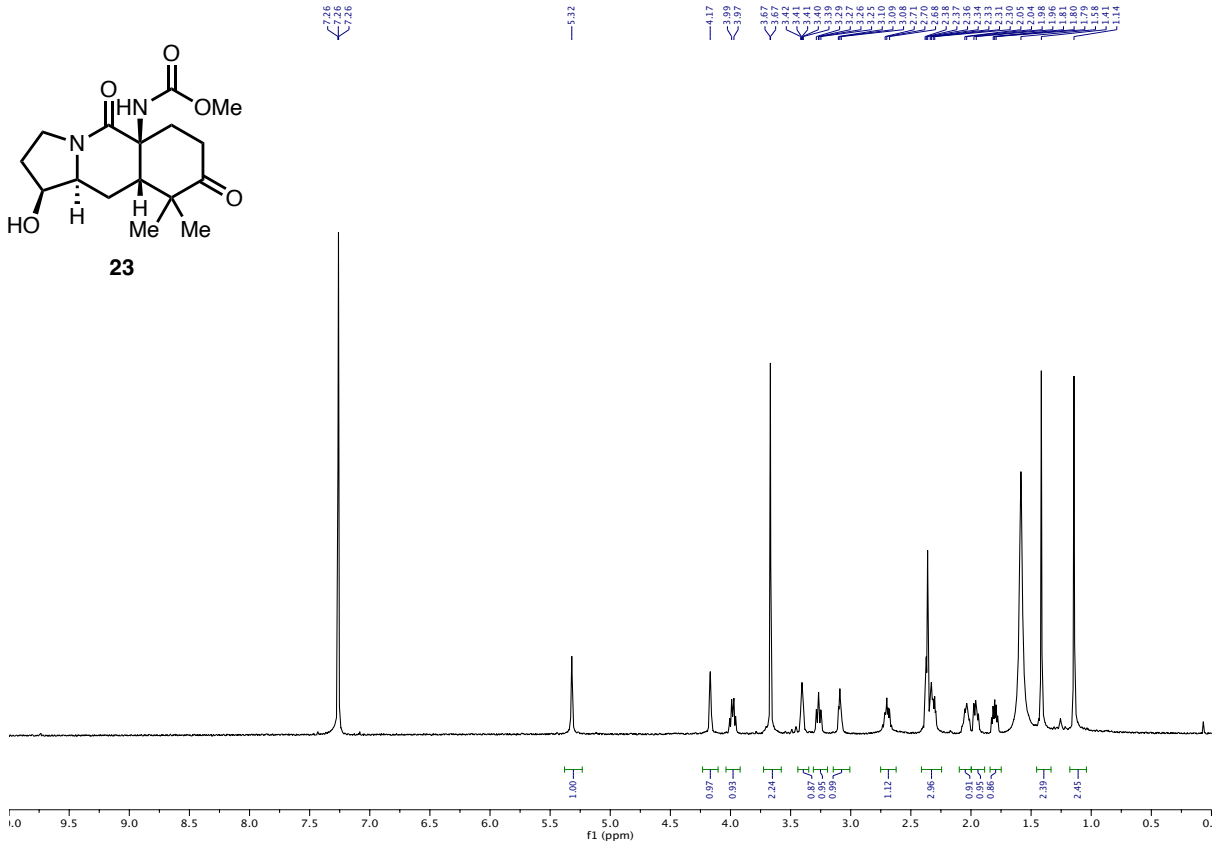
22

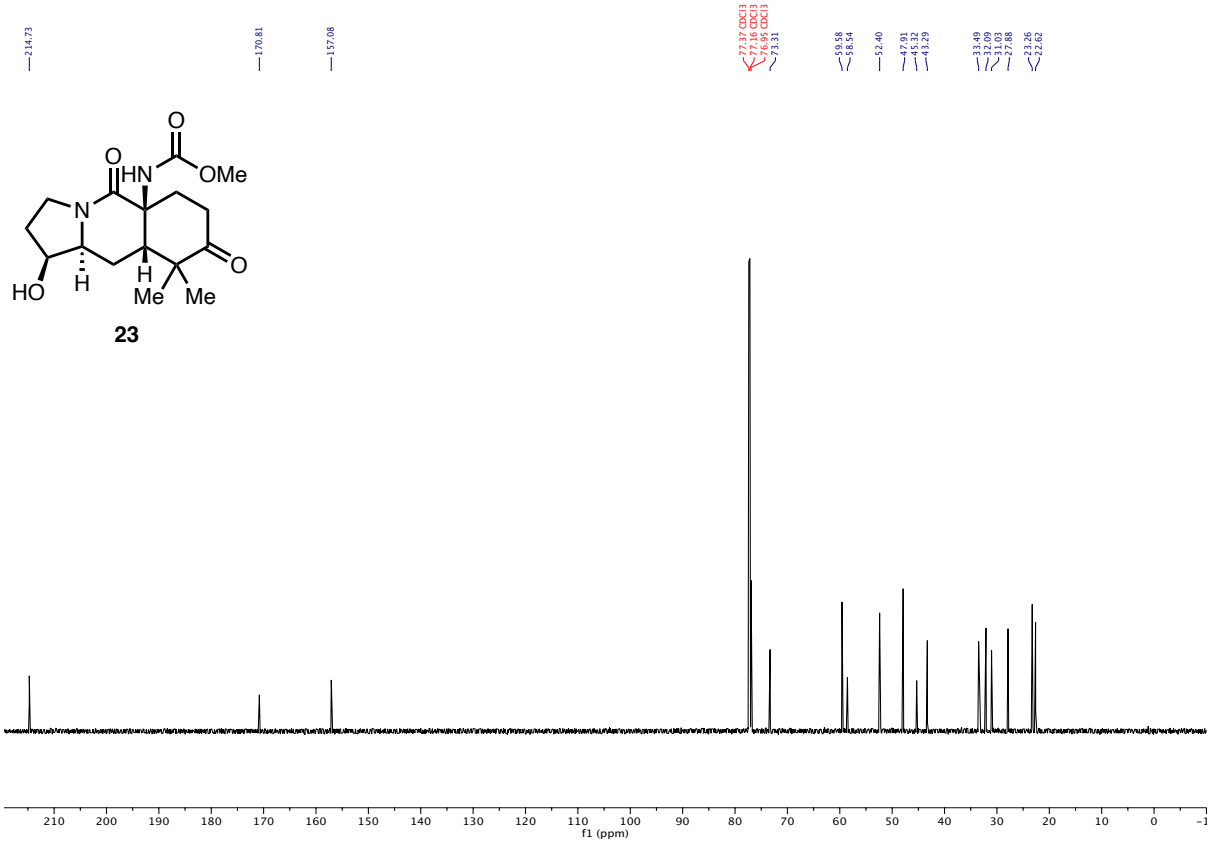

1.14
1.00
0.98
1.21
1.09
1.07
1.05
1.01
1.05
2.15
1.12
4.22
3.21
3.19
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0
f1 (ppm)


O
O
NH2
N
HO
H
H
Me
Me
O

22


214.64
174.32
171.17
71.63
61.23
52.50
46.89
43.63
41.44
35.12
31.44
30.86
25.16
22.69
21.37
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


O
O
HN
OMe
N
O
HO
H
H
Me
Me
23
f1 (ppm)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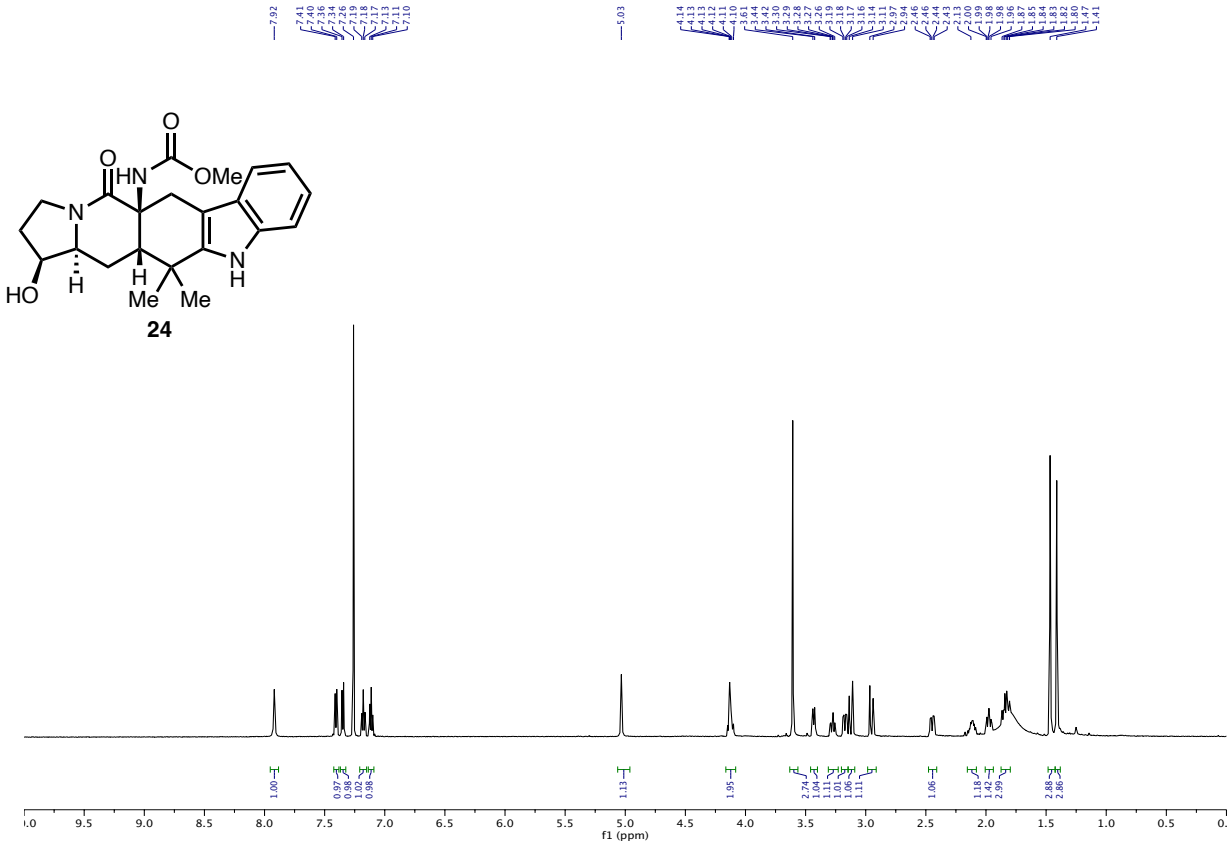
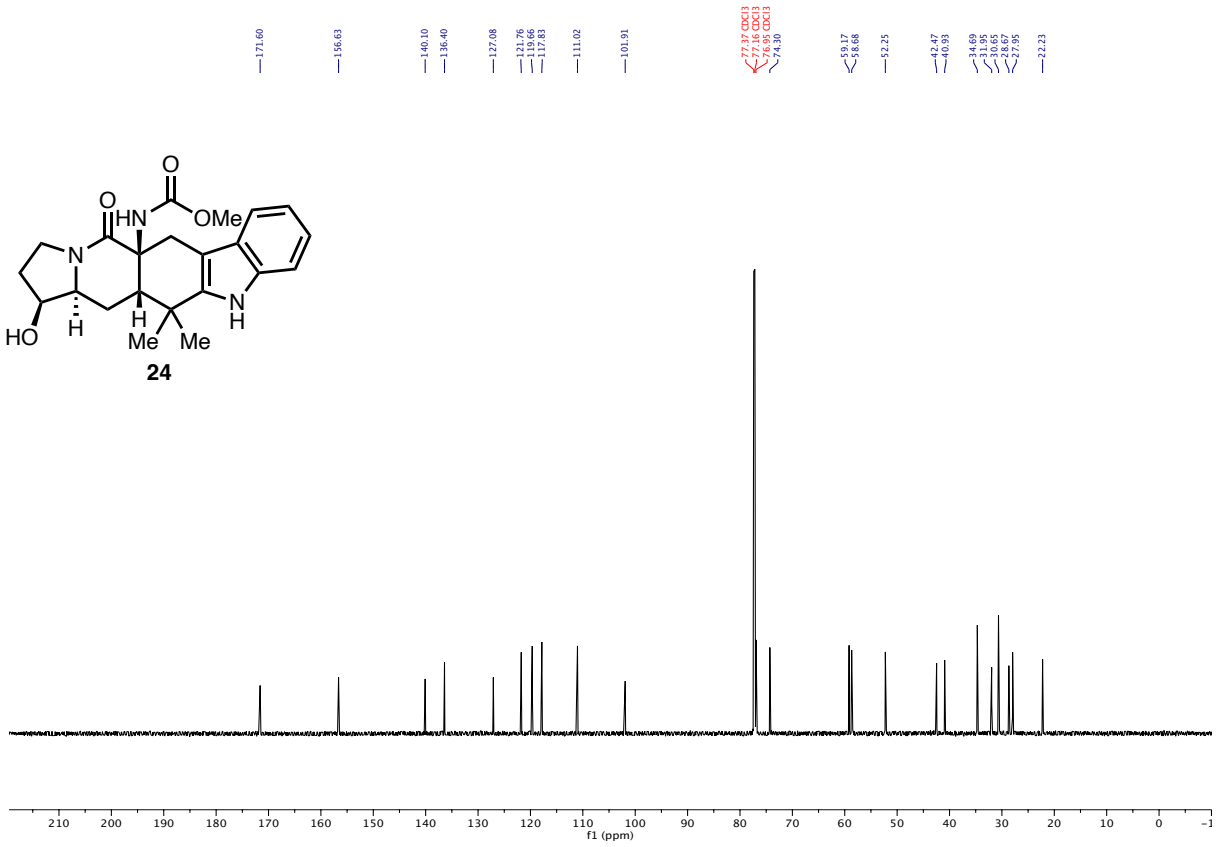
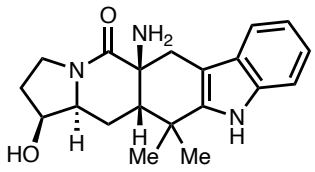
170.81
157.08
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
73.31
59.58
58.54
52.40
47.91
45.32
43.29
33.49
32.09
31.03
27.88
23.26
22.62
O
O
HN
OMe
N
HO
H
H
Me
Me
O
23
f1 (ppm)

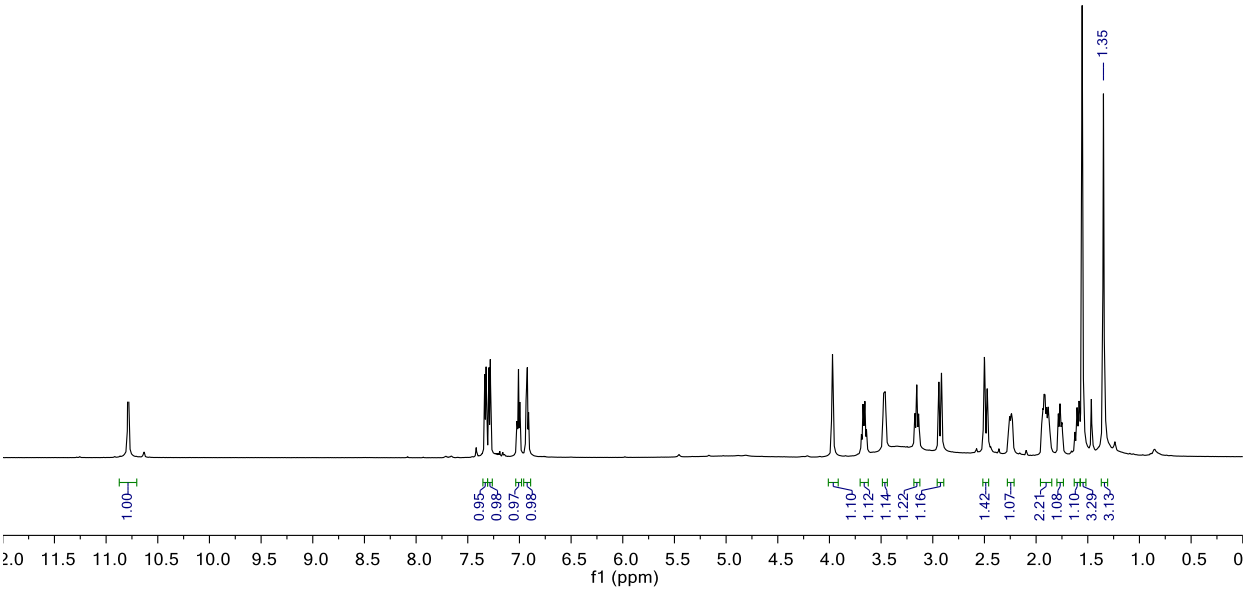

O
O
HN
OMe
N
N
H
HO
H
H
Me
Me
24
f1 (ppm)

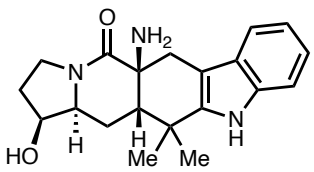

171.60
156.63
140.10
136.40
127.08
121.76
119.66
117.83
111.02
101.91
77.37 CDCl3
77.16 CDCl3
76.95 CDCl3
74.30
59.17
58.68
52.25
42.47
40.93
34.69
31.95
30.65
28.67
27.95
22.23
O
O
HN
OMe
N
HO
H
H
Me
Me
N
H
f1 (ppm)

24

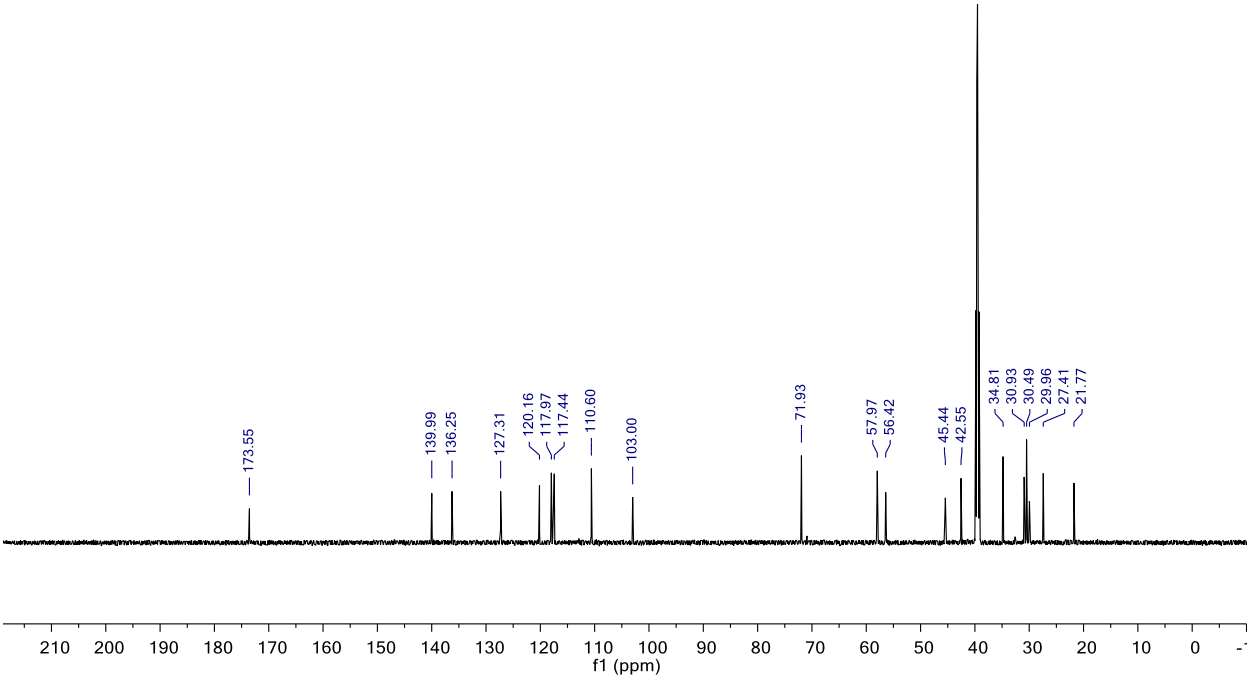

O
NH2
N
HO
H
H
Me
Me
N
H

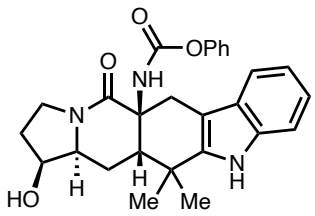
25


1.35
1.00
0.95
0.98
0.97
0.98
1.10
1.12
1.14
1.22
1.16
1.42
1.07
2.21
1.08
1.10
3.29
3.13
2.0 11.5 11.0 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
f1 (ppm)

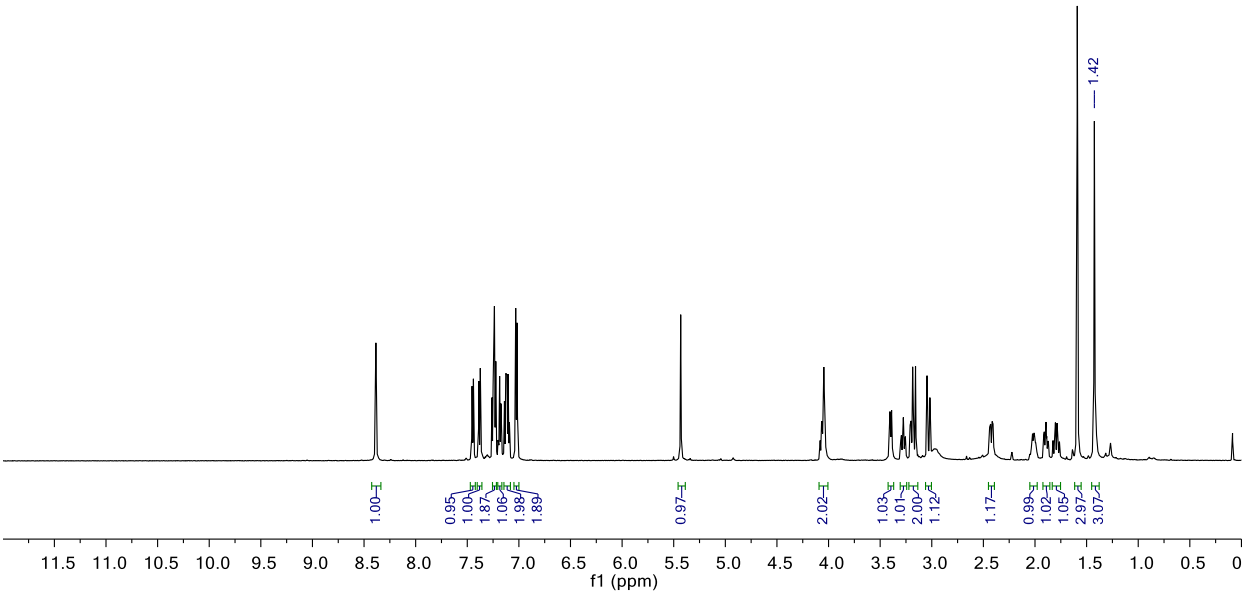

O
NH2
N
H
HO
H
Me
Me
N
H

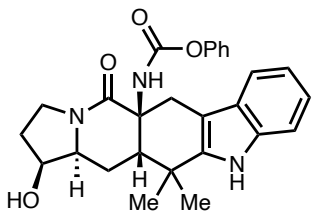
25


173.55
139.99
136.25
127.31
120.16
117.97
117.44
110.60
103.00
71.93
57.97
56.42
45.44
42.55
34.81
30.93
30.49
29.96
27.41
21.77
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

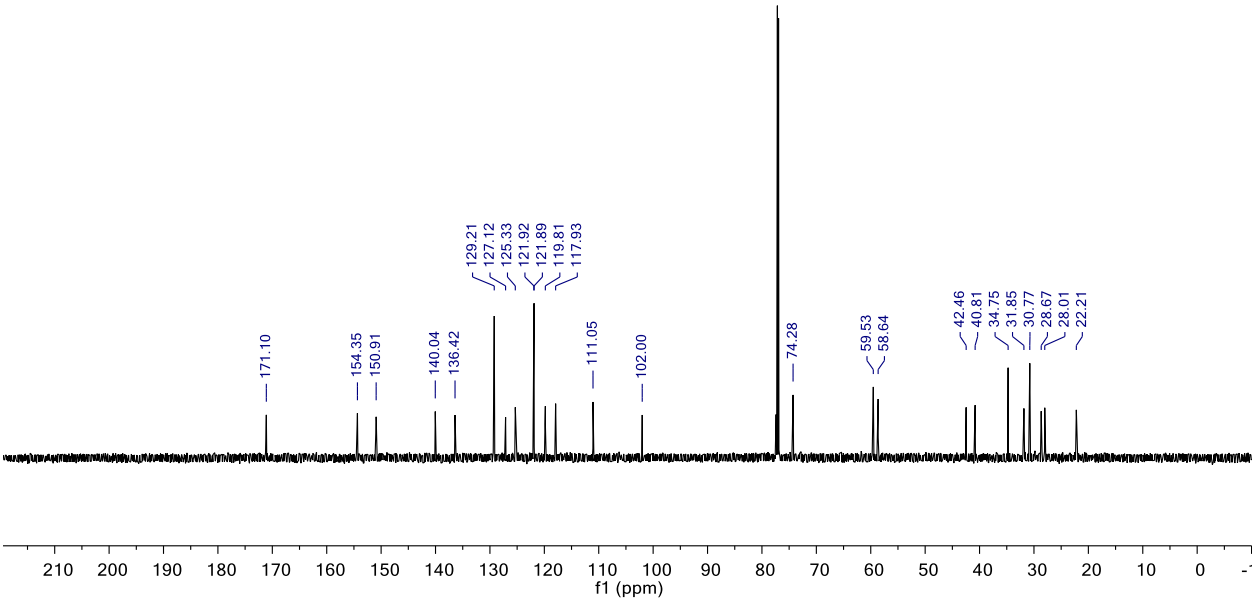

O
OPh
O
NH
N
H
HO
H
Me
Me
N
H

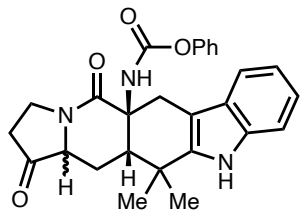
26


1.42
1.00
0.95
1.00
1.87
1.06
1.98
1.89
0.97
2.02
1.03
1.01
2.00
1.12
1.17
0.99
1.02
1.05
2.97
3.07
11.5 11.0 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
f1 (ppm)

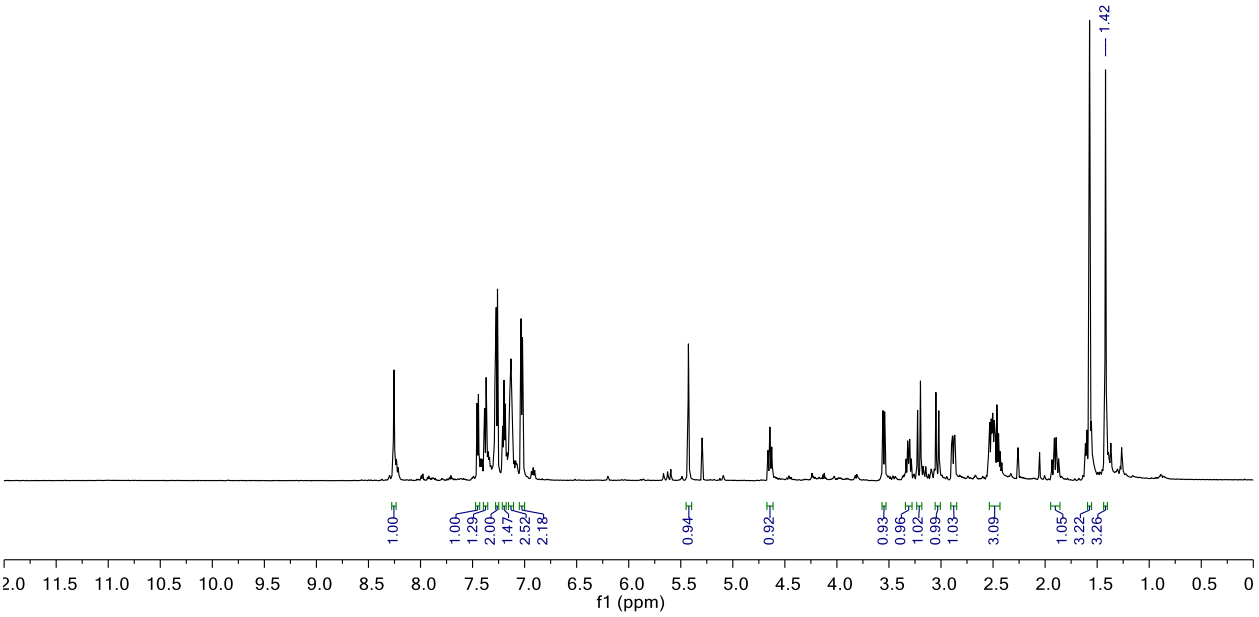

O
OPh
O
NH
N
HO
H
H
Me
Me
N
H

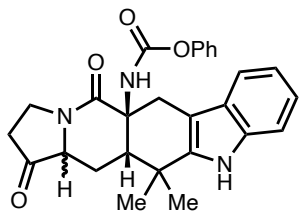
26


171.10
154.35
150.91
140.04
136.42
129.21
127.12
125.33
121.92
121.89
119.81
117.93
111.05
102.00
74.28
59.53
58.64
42.46
40.81
34.75
31.85
30.77
28.67
28.01
22.21
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

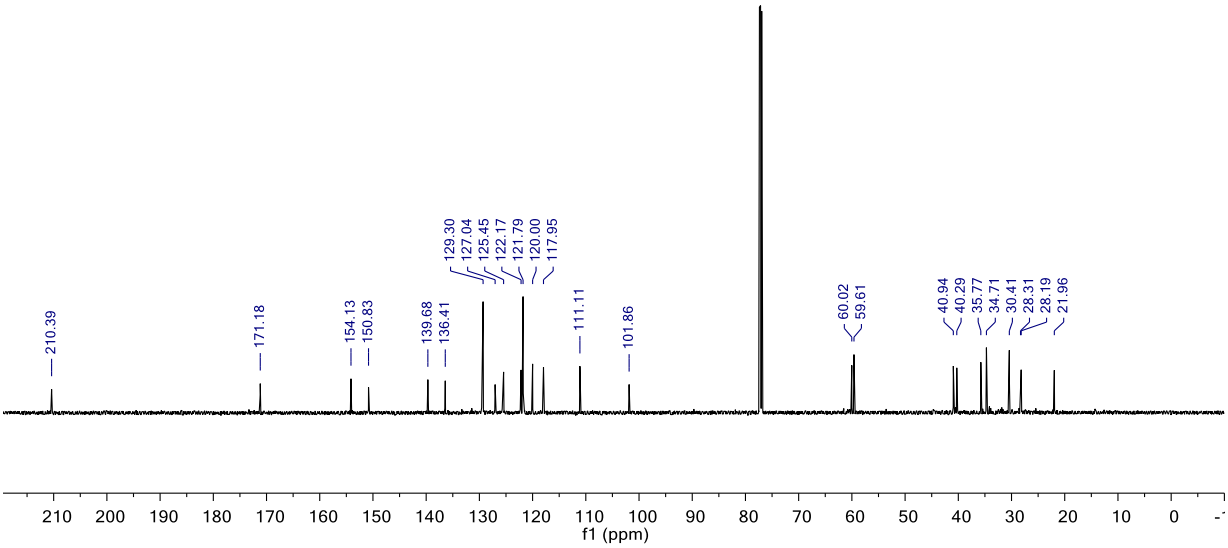

O
OPh
O
NH
N
H
H
Me
Me
O
N
H

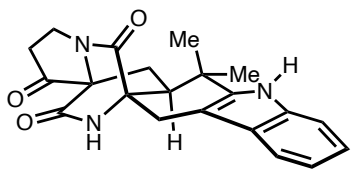
27


1.42
1.00
1.00
1.29
2.00
1.47
2.52
2.18
0.94
0.92
0.93
0.96
1.02
0.99
1.03
3.09
1.05
3.22
3.26
2.0 11.5 11.0 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
f1 (ppm)

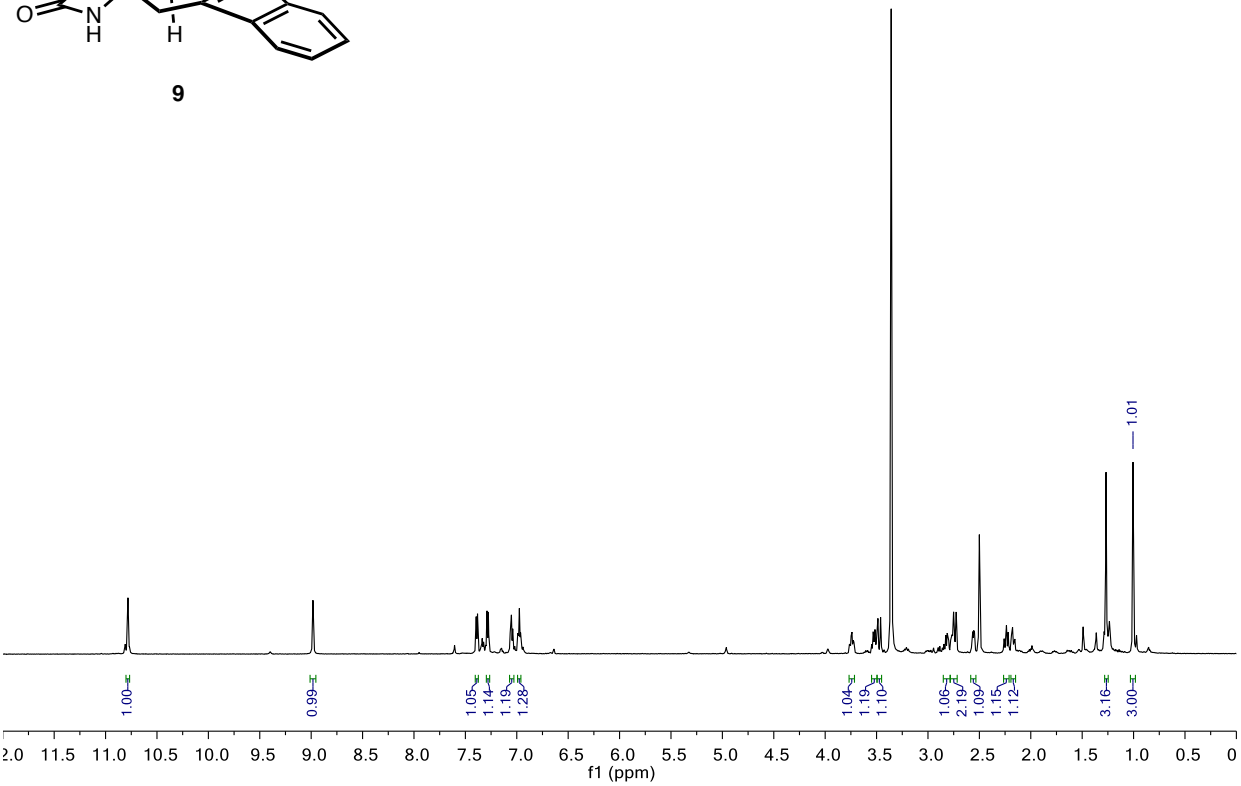

O
OPh
O
NH
N
H
O
H
Me
Me
N
H

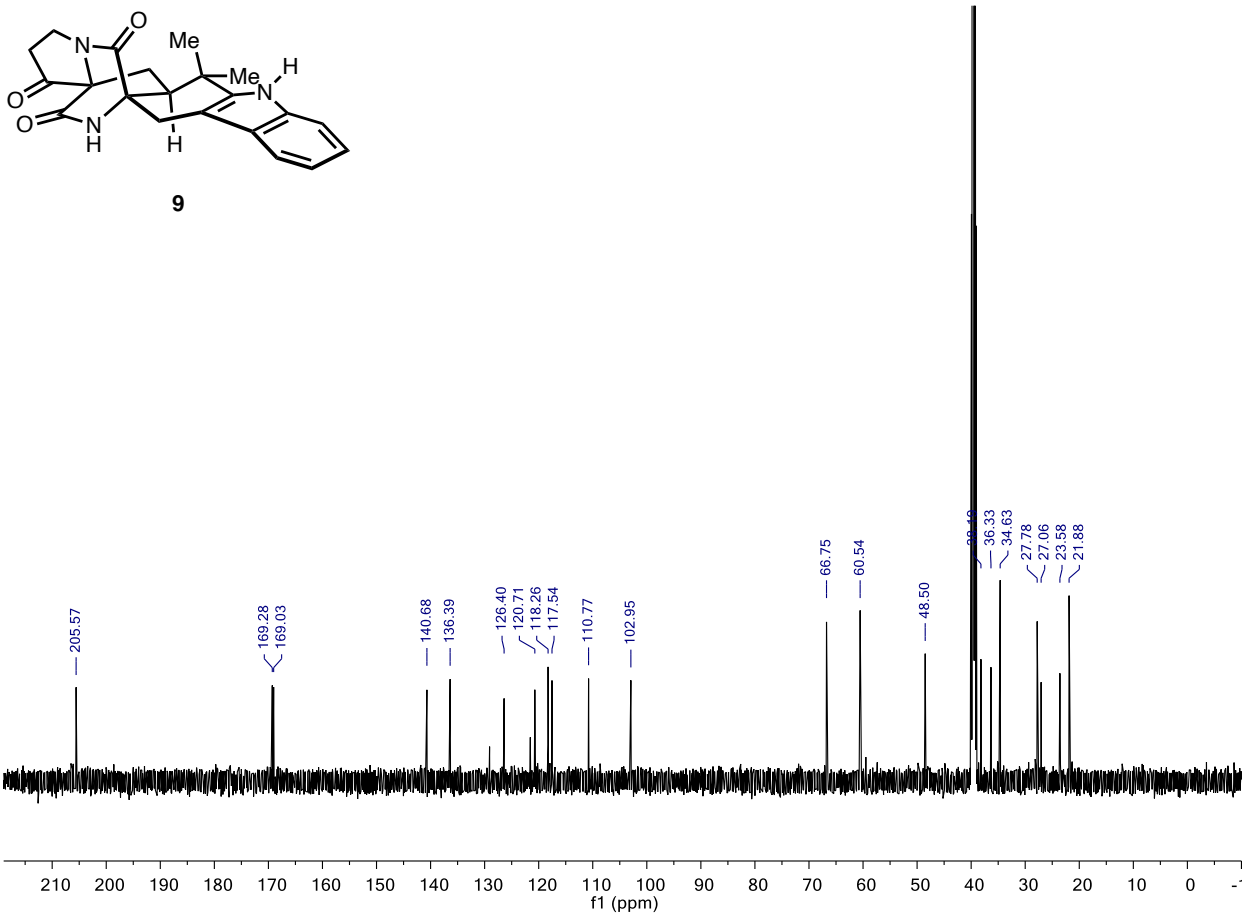
27


210.39
171.18
154.13
150.83
139.68
136.41
129.30
127.04
125.45
122.17
121.79
120.00
117.95
111.11
101.86
60.02
59.61
40.94
40.29
35.77
34.71
30.41
28.31
28.19
21.96
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

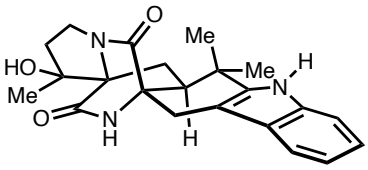

O
N
Me
Me
H
N
O
O
N
H
H

9


1.01
1.00
0.99
1.05
1.14
1.19
1.28
1.04
1.19
1.10
1.06
2.19
1.09
1.15
1.12
3.16
3.00
2.0 11.5 11.0 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
f1 (ppm)

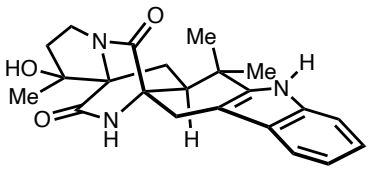

O
N
Me
Me
H
N
O
O
N
H
H
205.57
169.28
169.03
140.68
136.39
126.40
120.71
118.26
117.54
110.77
102.95
66.75
60.54
48.50
36.33
34.63
27.78
27.06
23.58
21.88
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

9

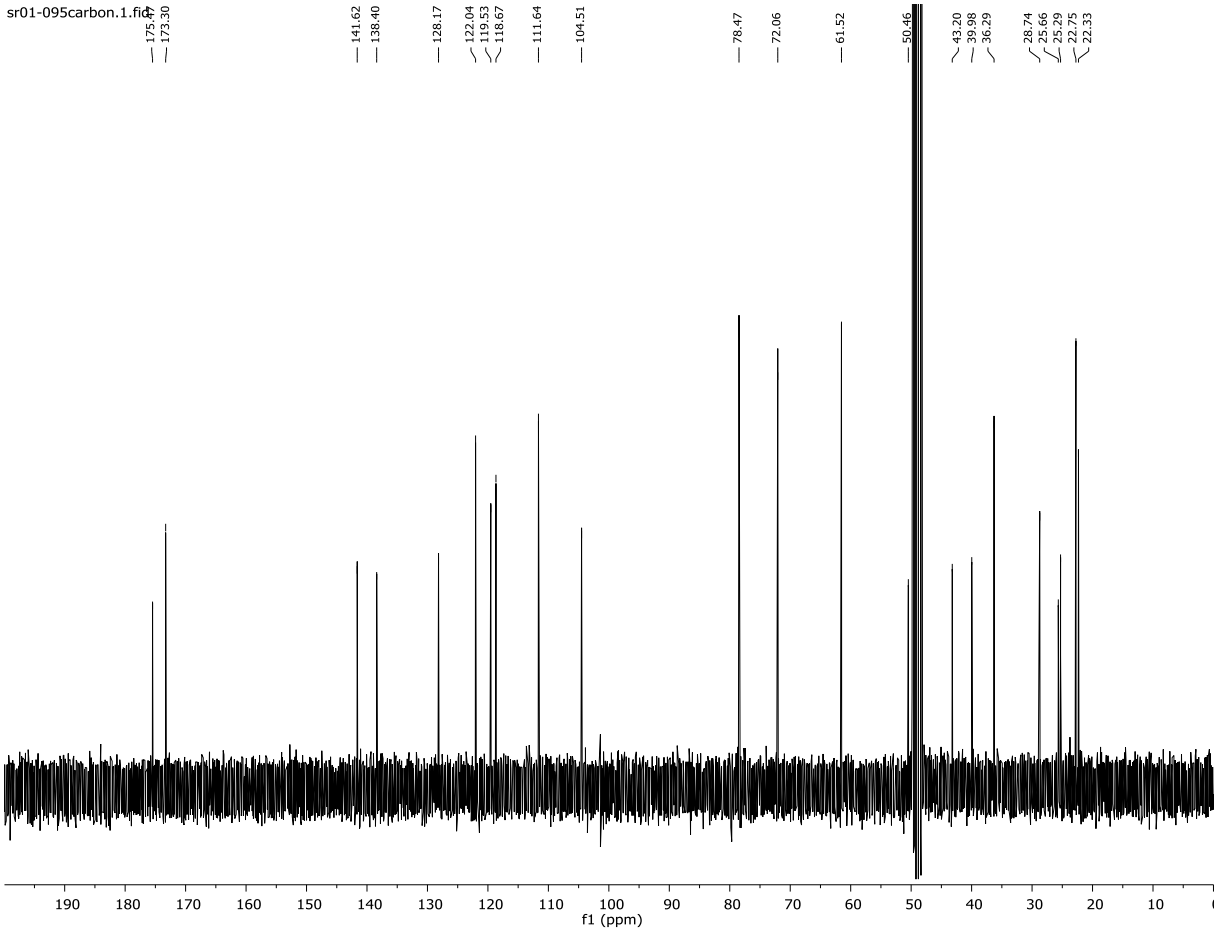

O
N
Me
HO
Me
Me
H
N
O
N
H
H

28

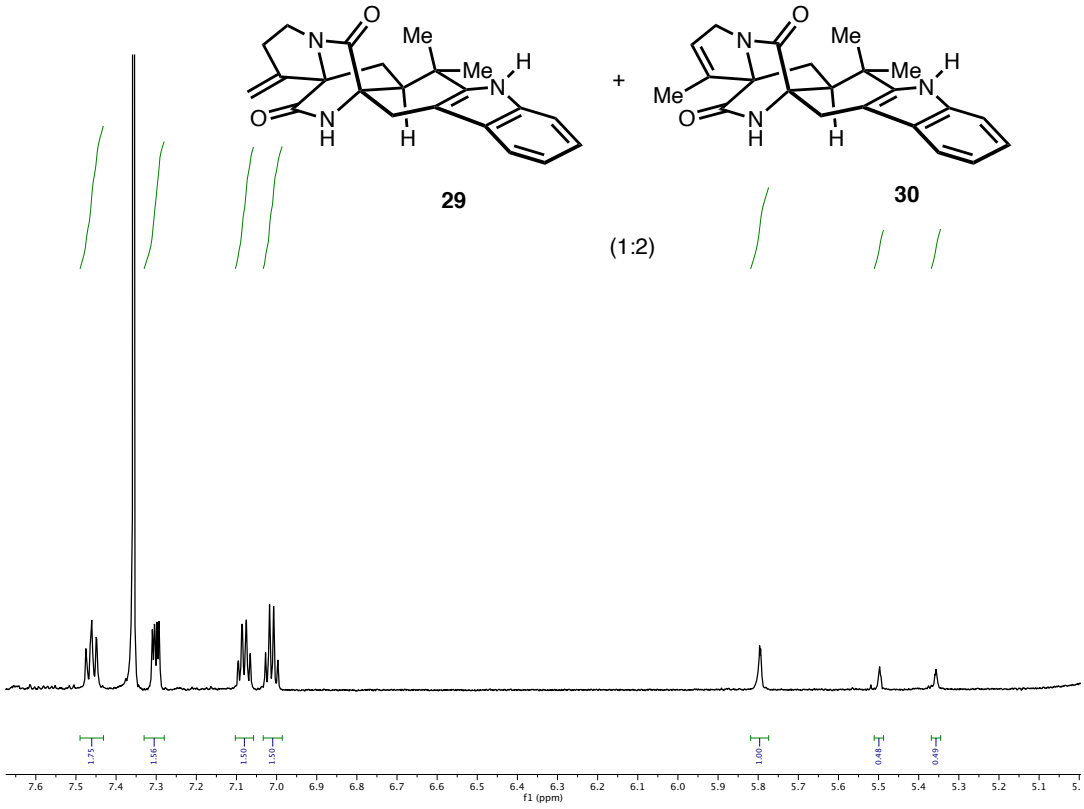
1.00
1.00
0.99
1.01
1.07
2.16
1.02
1.05
1.01
3.11
3.09
3.08
3.02
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


O
N
Me
HO
Me
Me
H
N
O
N
H
H

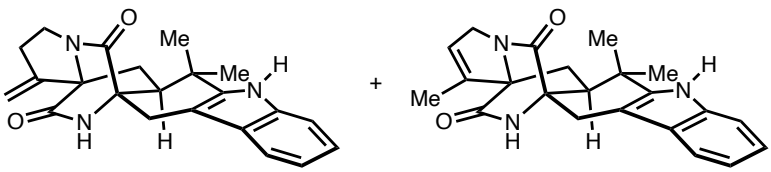
28


sr01-095carbon.1.fid
175.47
173.30
141.62
138.40
128.17
122.04
119.53
118.67
111.64
104.51
78.47
72.06
61.52
50.46
43.20
39.98
36.29
28.74
25.66
25.29
22.75
22.33
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

Crude ^{1}H (In $CDCl_3$) NMR (1:2 ratio of **29** to **30**)

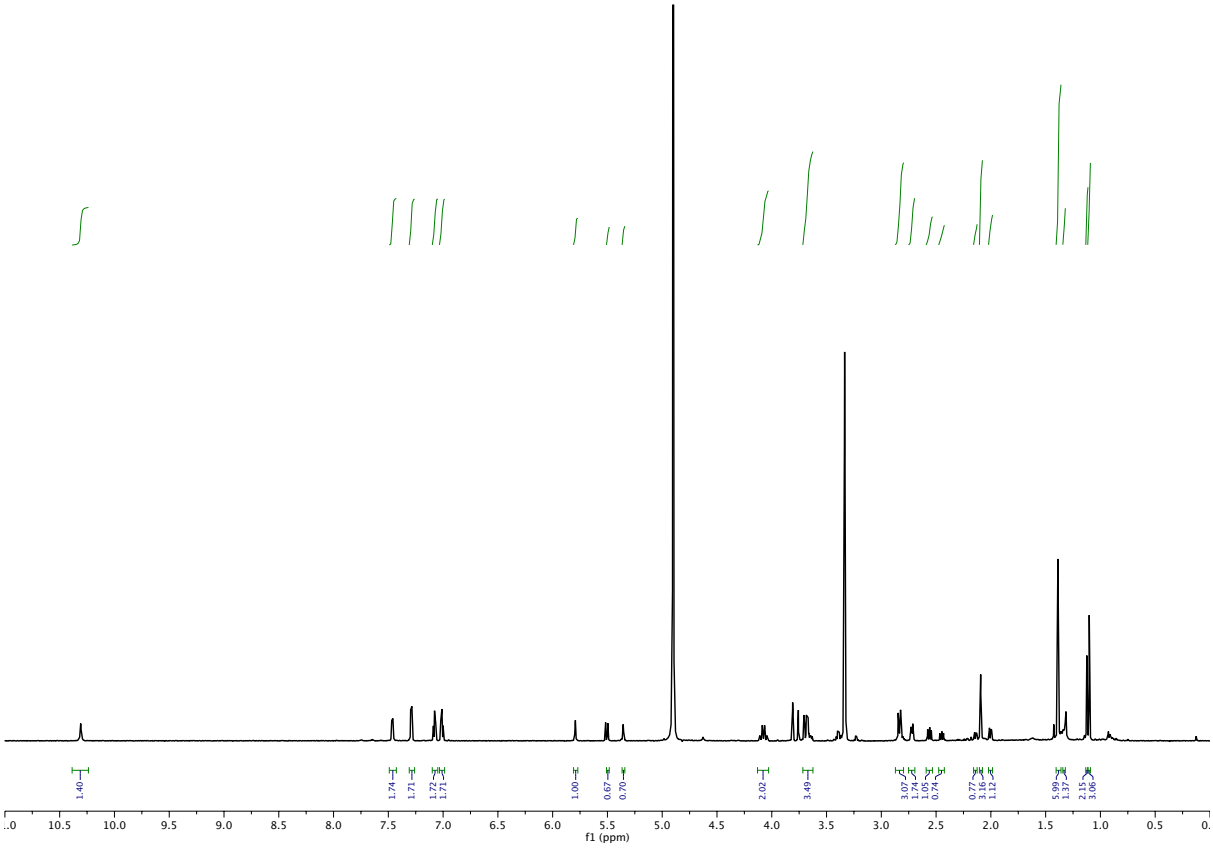


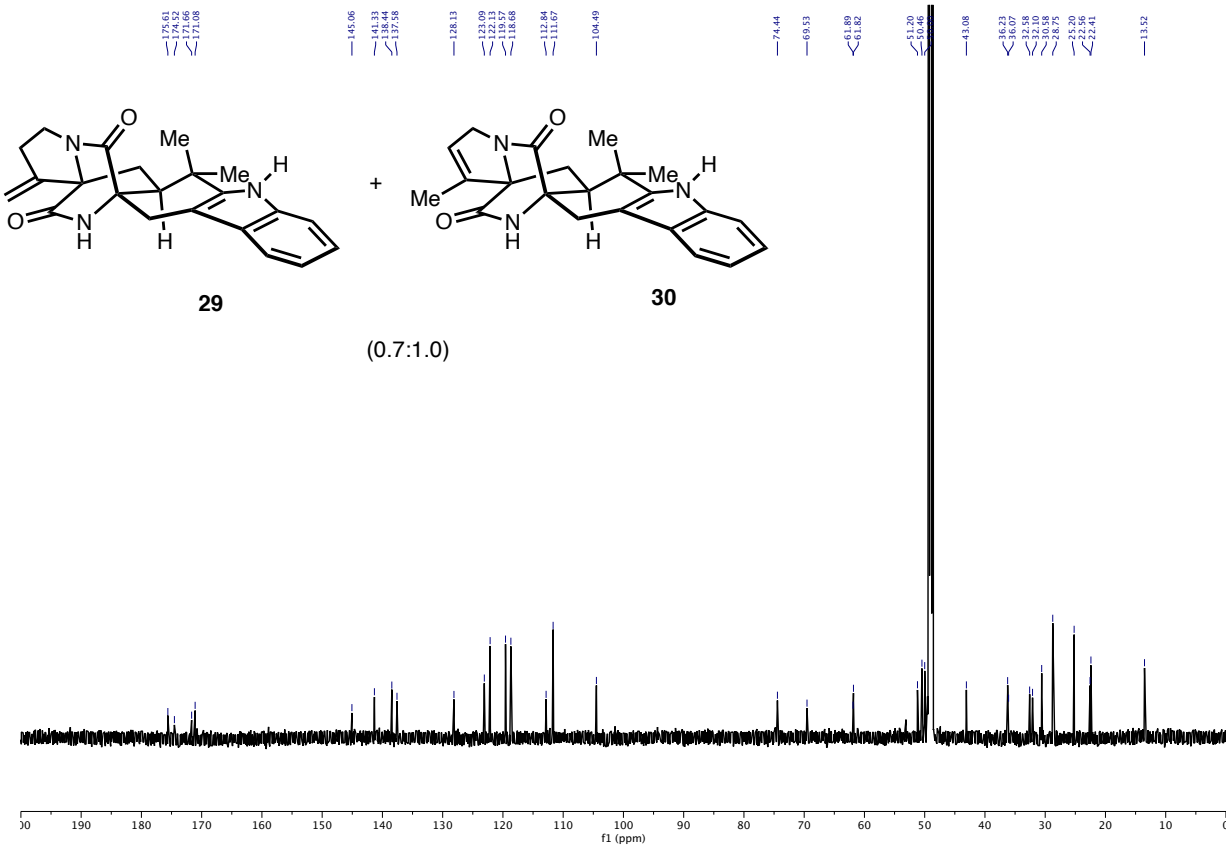
Isolated band containing 0.7:1.0 ratio of **29** to **30**



29 + **30**

(0.7:1.0)




175.61
174.52
173.66
171.08
145.06
141.33
138.44
137.58
128.13
123.09
121.15
119.57
118.68
112.84
111.67
104.49
74.44
69.53
61.89
61.82
51.20
50.46
43.08
36.23
35.07
33.58
32.10
30.58
28.75
25.20
23.55
22.41
13.52
O
N
Me
Me
N
H
O
N
H
H
+
Me
O
N
H
H
f1 (ppm)

29

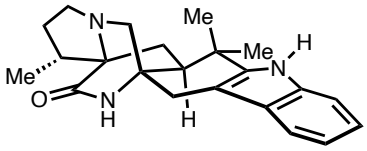
(0.7:1.0)

30

5. Natural product spectra and comparisons.

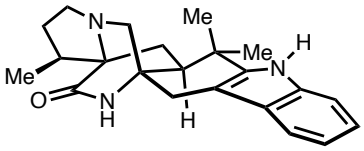
Analysis of initial mixture of (+)-VM55599 (1) and preparaherquamide (2) prior to preparative thin layer chromatography

A ^{1}H and ^{13}C NMR of this mixture is provided. Careful analysis of the ^{1}H and ^{13}C NMR and comparison to previously reported spectra allows for determination of structures (See below).

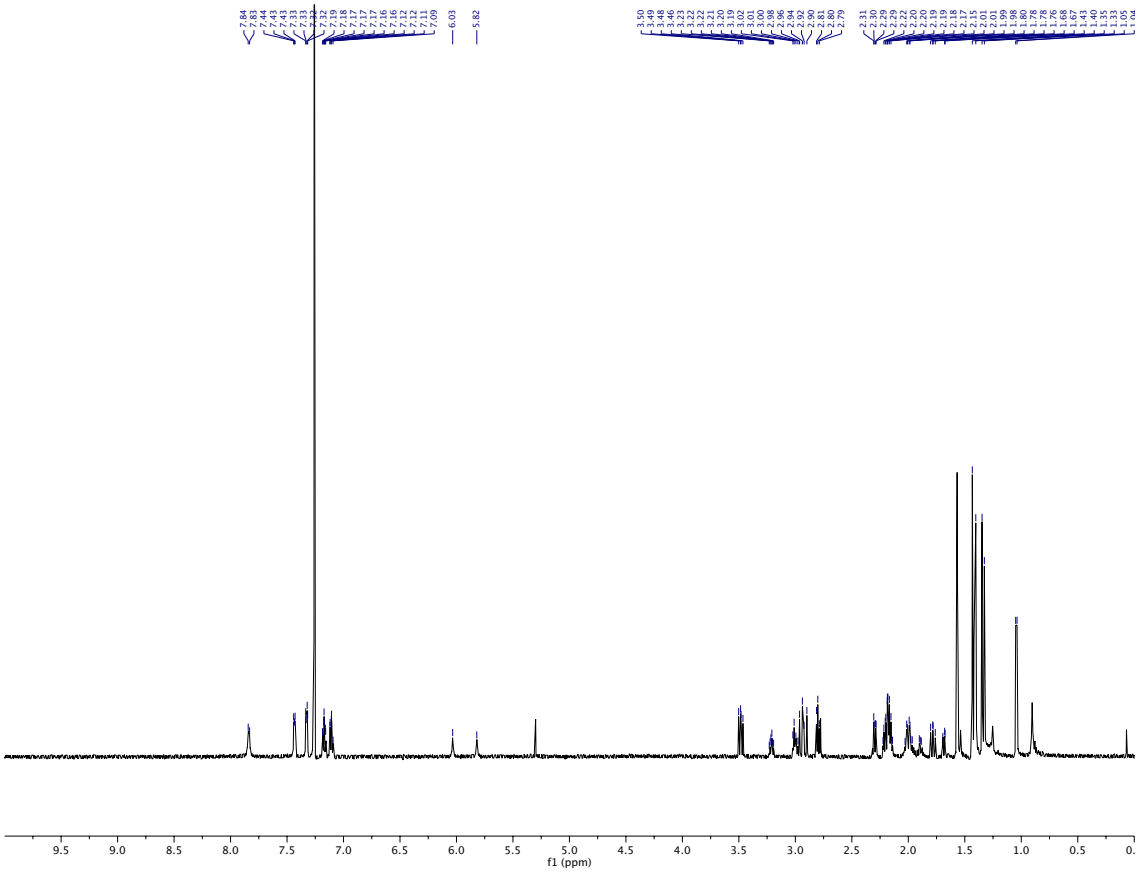


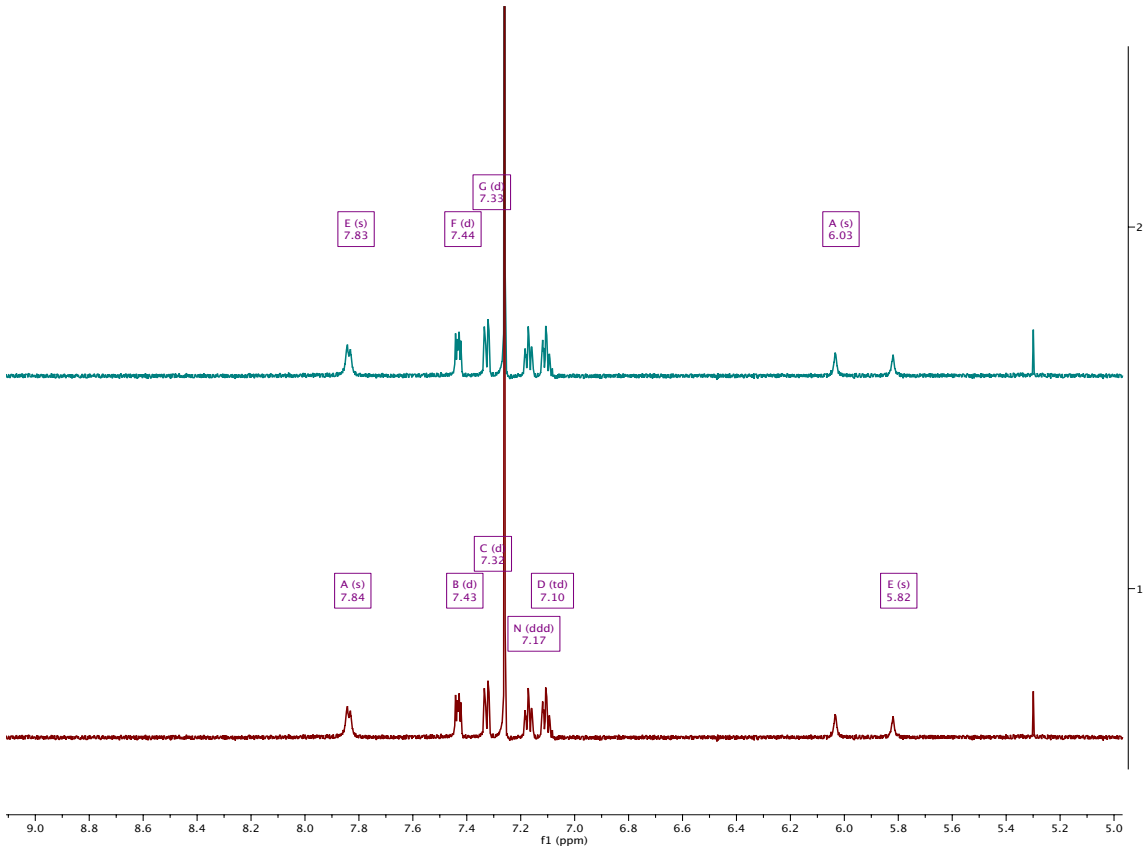
VM55599 (**1**)

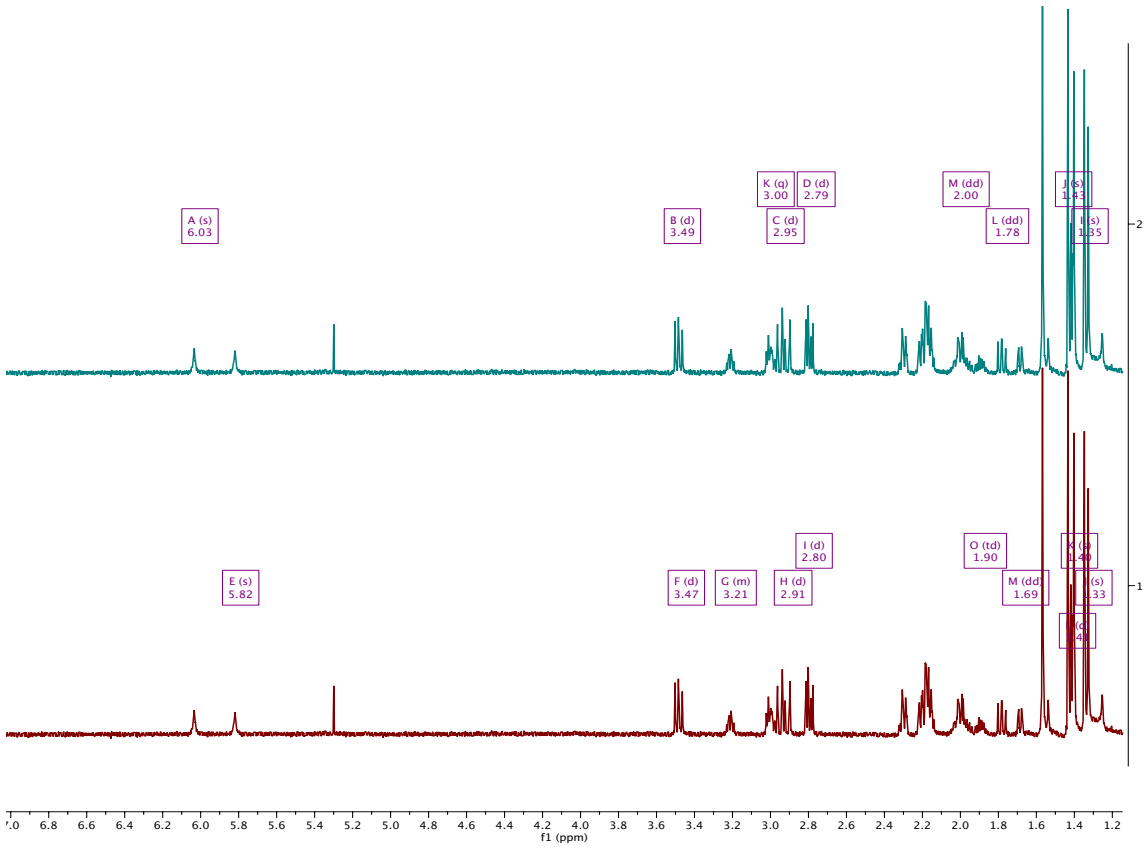
+



preparaherquamide (**2**)




G (d)
7.33
E (s)
7.83
F (d)
7.44
A (s)
6.03
2
C (d)
7.32
A (s)
7.84
B (d)
7.43
D (td)
7.10
E (s)
5.82
N (ddd)
7.17
1
9.0
8.8
8.6
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
5.8
5.6
5.4
5.2
5.0
f1 (ppm)

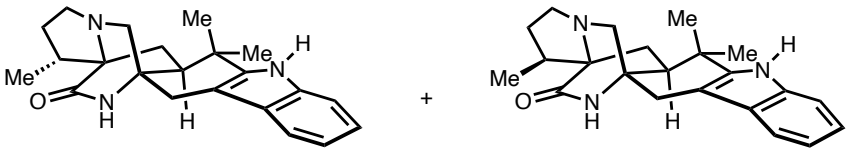


From Mixture:

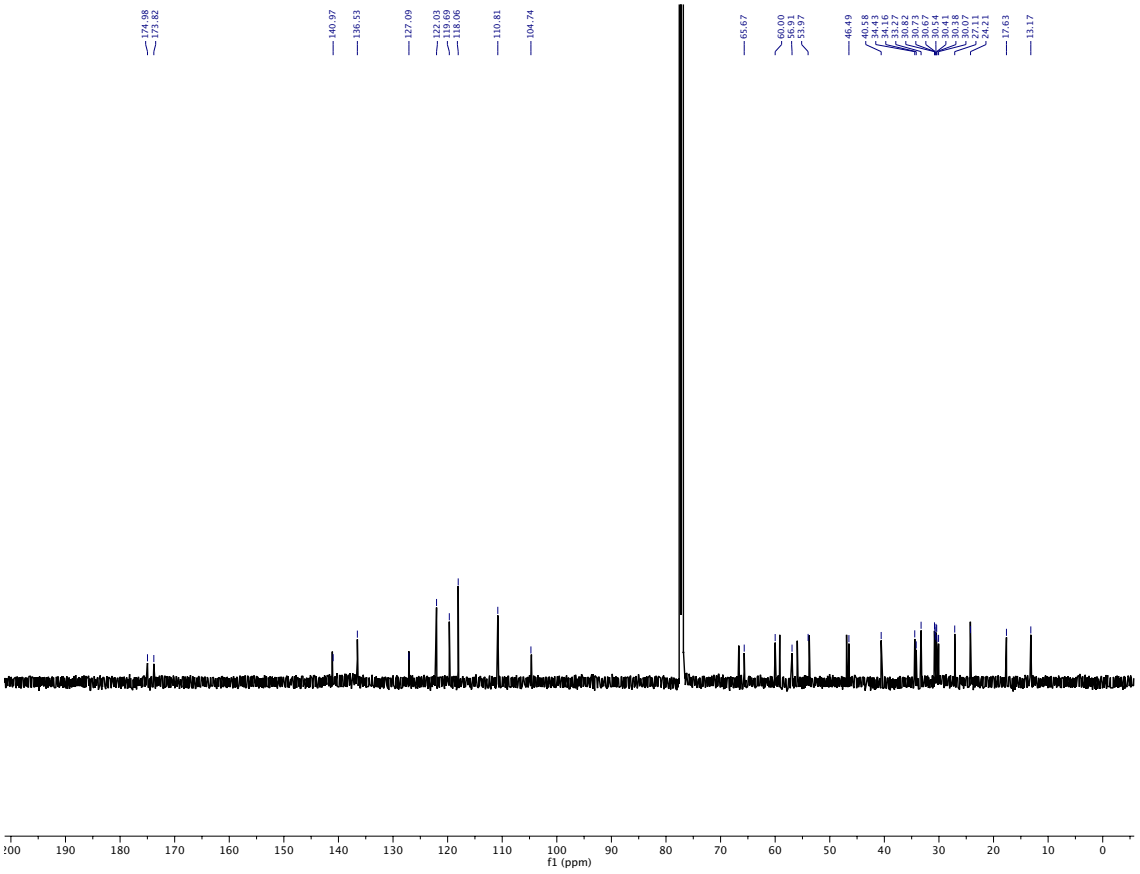
(+)-VM55599 (**1**): **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.83 (brs, 1H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.34-7.30 (m, 1H), 7.19-7.15 (m, 1H), 7.12-7.09 (m, 1H), 6.03 (brs, 1H), 3.49 (d, *J* = 10.4 Hz), 3.06-3.00 (m, 2H), 2.95 (d, *J* = 15.2 Hz, 1H), 2.79(d, *J* = 15.2 Hz, 1H), 2.33-2.27 (m, 1H), 2.23-2.13 (m, 3H), 1.93-1.87 (m, 1H), 1.78 (dd, d, *J* = 13.2, 11.7 Hz), 1.43 (s, 3H), 1.41 (m, 1H), 1.35 (s, 3H), 1.04 (d, *J* = 7.1 Hz).

Preparaherquamide (**2**): **^{1}H NMR** (600 MHz, $CDCl_3$) δ = 7.84 (brs, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.19-7.15 (m, 1H), 7.12-7.09 (m, 1H), 5.82 (brs, 1H), 3.47 (d, *J* = 10.3 Hz), 3.23-3.18 (m, 1H), 2.91 (d, *J* = 15.1 Hz, 1H), 2.80 (d, *J* = 15.1 Hz, 1H), 2.33-2.27(m, 1H), 2.23-2.13 (m, 3H), 2.05-1.93 (m, 3H), 1.69 (dd, *J* = 11.2, 2.1 Hz, 1H), 1.41 (d, *J* = 7.1 Hz, 3H), 1.40 (s, 3H), 1.33 (s, 3H).

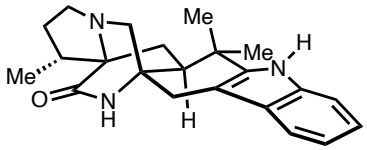
^{13}C NMR of mixture



VM55599 (**1**) + preparaherquamide (**2**)



^{13}C NMR Signals corresponding to (+)-VM55599 (**1**) from mixture.



VM55599 (**1**)

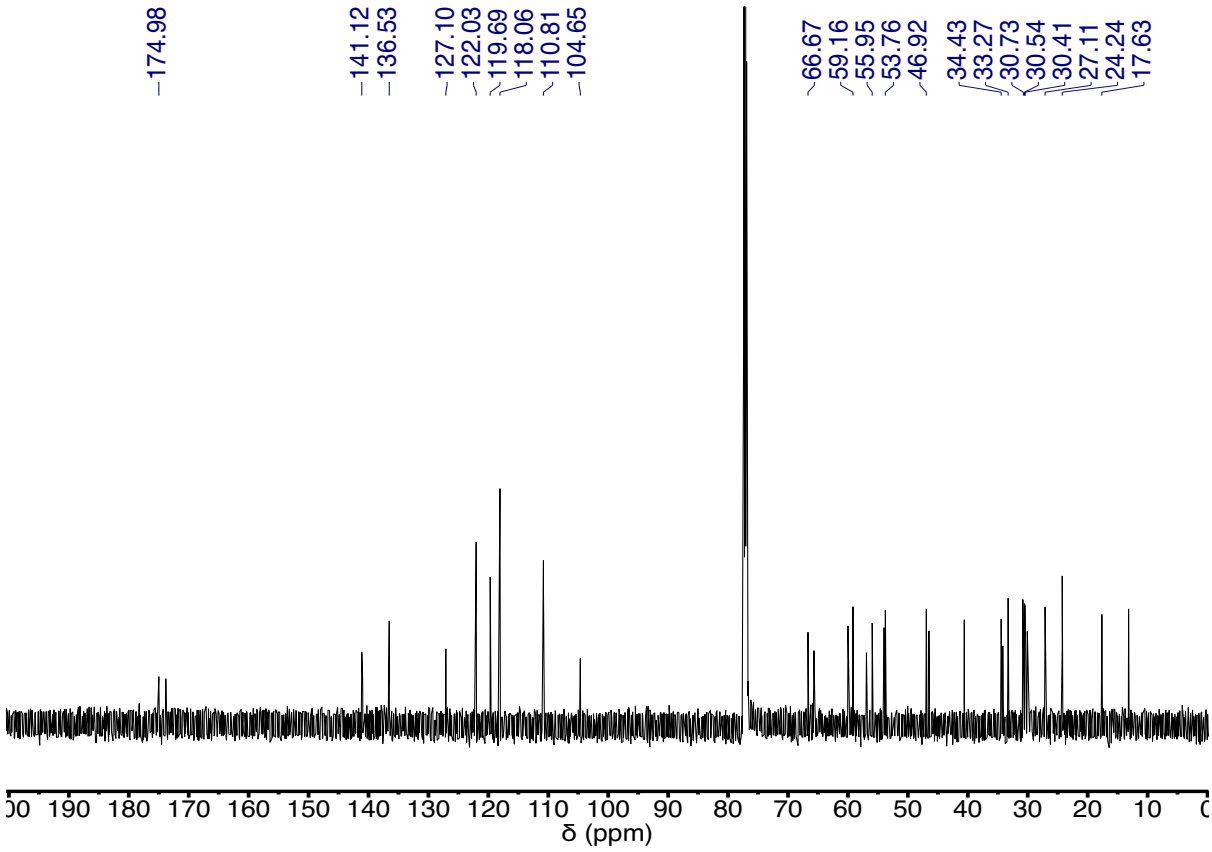


Table S2. ^{13}C NMR in $CDCl_3$ (plus one drop of DMSO)[a,b] for (+)-VM55599 (**1**) in mixture: Comparison of spectral data. [a]*rac*-VM55599: S. E. Blanchflower, R. M. Banks, M. Everett and C. Reading, *J. Antibiot.,* 1993, **46**, 1355-1363. [a] rac-VM55599: E.M. Stocking, J. F. Sanz-Cervera and R. M. Williams, *J. Am. Chem. Soc.,* 2000, **122**,1675-1683. Both reports used $CDCl_3$ with a drop of DMSO to aid in solubility instead of pure $CDCl_3$, this can explain some minor shifts

a) Reading[a] (δ)	b)Williams[b] (δ)	Found (δ)	Δ_1	Δ_2
174.8	174.8	175.0	0.2	0.2
141.2	141.1	141.1	0.0	0.1
136.5	136.4	136.5	0.1	0
126.8	126.8	127.1	0.3	0.3
121.3	121.5	122.0	0.5	0.7
119.0	119.2	119.7	0.5	0.7
117.7	117.7	118.1	0.4	0.4
110.6	110.6	110.8	0.2	0.2
104.0	104.1	104.7	0.6	0.7
66.3	66.4	66.7	0.3	0.4
58.9	58.9	59.2	0.3	0.3
55.6	55.7	56.0	0.3	0.4
53.5	53.6	53.8	0.2	0.3
46.7	46.6	47.0	0.4	0.3
34.2	34.2	34.4	0.2	0.2
33.0	33.0	33.3	0.3	0.3
30.5	30.5	30.7	0.2	0.2
30.2	30.2	30.5	0.3	0.3
30.0	30.1	30.4	0.3	0.4
26.8	26.8	27.1	0.3	0.3
23.9	24.0	24.2	0.2	0.3
17.4	17.5	17.6	0.1	0.2

^{13}C NMR Signals corresponding to preparaherquamide (**2**) from mixture.

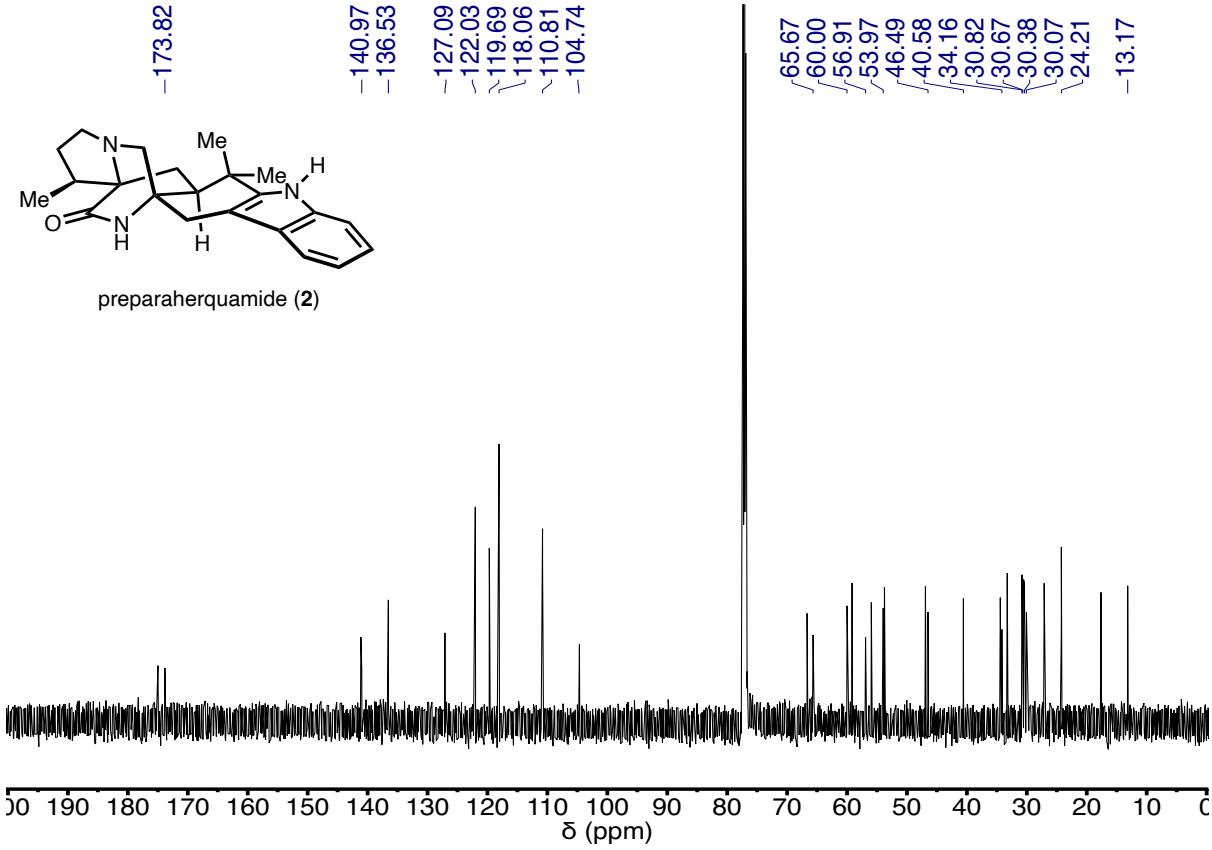


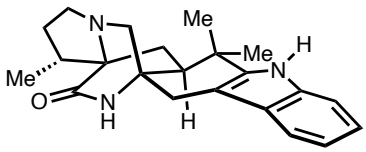
Table S3. ^{13}C NMR in $CDCl_3$ for preparaherquamide (**2**) in mixture: Comparison of spectral data.[a] S. Nishikori, K. Takemoto, S. Kamisuki, S. Nakajima, K. Kuramochi, S. Tsukuda, S, M. Iwamoto, Y. Katayama, T. Suzuki, S. Kobayashi, K. Watashi and F. Sugawara, *J. Nat. Prod.,* 2016, **79**, 442−446.

Sugawara[a] (δ)	Found	Δ
173.7	173.8	0.1
140.8	141.0	0.2
136.3	136.5	0.2
126.9	127.1	0.2
121.9	122.0	0.1
119.5	119.7	0.2
117.9	118.1	0.2
110.6	110.8	0.2
104.6	104.7	0.1
65.5	65.7	0.2
59.8	60.0	0.2
56.7	56.9	0.2
53.8	54.0	0.2
46.3	46.5	0.2
40.4	40.6	0.2
34.0	34.2	0.2
30.6	30.8	0.2
30.5	30.7	0.2
30.2	30.4	0.2
29.9	30.1	0.2
24.0	24.2	0.2
13.0	13.2	0.2

The mixture was separated by preparative thin layer chromatography (5% acetone:dichloromethane) to afford (+)-VM55599 (**1**) and preparaherquamide (**2**).

Analysis of VM55599 (1) and preparaherquamide (2) after preparative thin layer chromatography

(+)-**VM55599** (**1**)

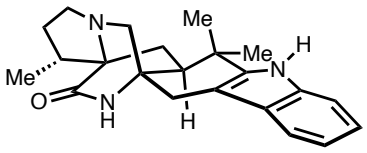


(+)-VM55599 (**1**)

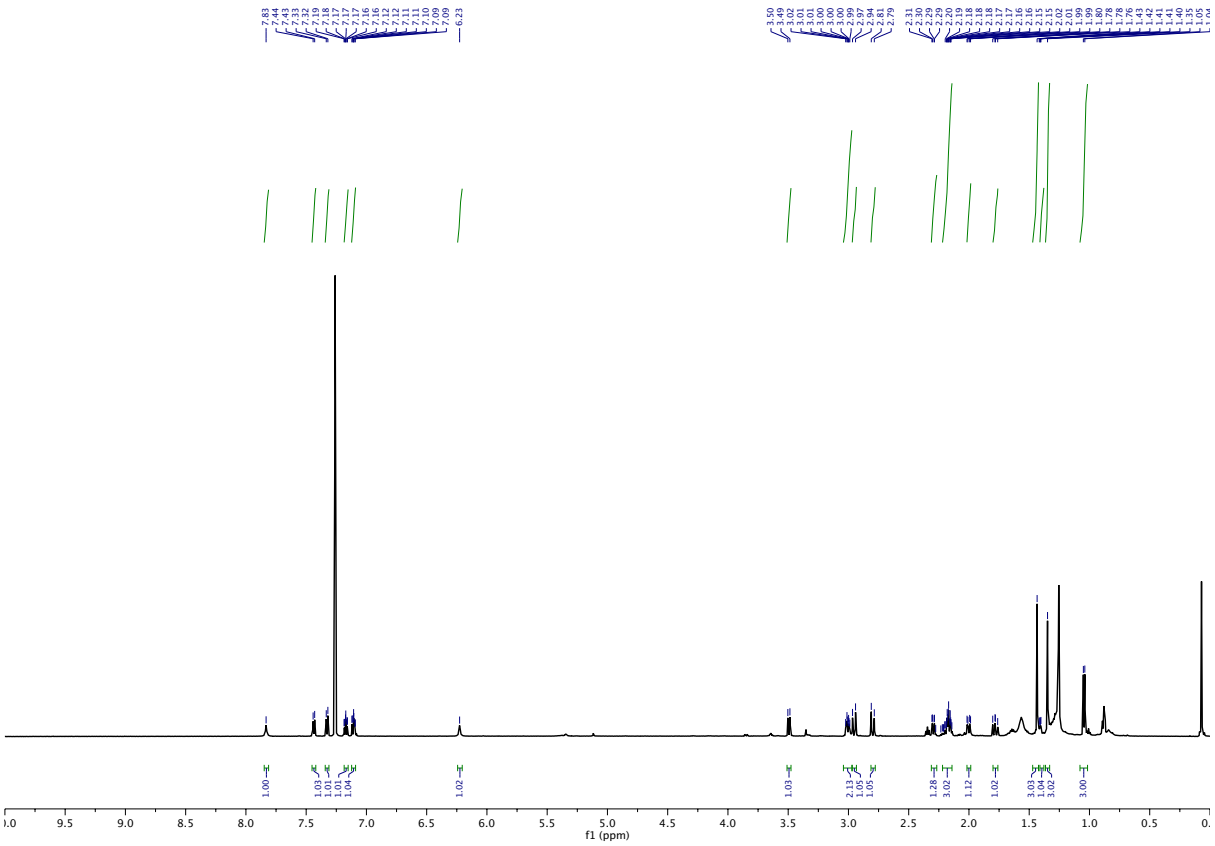
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.44 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 7.9 Hz, 1H), 7.17 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.23 (s, 1H), 3.49 (d, *J* = 10.3 Hz, 1H), 3.00 (m, 2H), 2.95 (d, *J* = 15.0 Hz, 1H), 2.80 (d, *J* = 15.0 Hz, 1H), 2.30 (dd, *J* = 10.3, 1.9 Hz, 1H), 2.17 (m, 3H), 2.00 (dd, *J* = 13.2, 4.3 Hz, 1H), 1.78 (dd, *J* = 13.2, 11.4 Hz, 1H), 1.43 (m, 3H), 1.41 (m, 1H), 1.35 (s, 3H), 1.04 (d, *J* = 7.2 Hz, 3H).

Table S4. ^{1}H NMR in $CDCl_3$ (plus one drop of DMSO)[a,b] for isolated VM55599 (**1**): Comparison of spectral data. [a] *rac*-VM55599: E.M. Stocking, J. F. Sanz-Cervera and R. M. Williams, *J. Am. Chem. Soc.,* 2000, **122**,1675-1683. [b]VM55599 S. E. Blanchflower, R. M. Banks, M. Everett and C. Reading, *J. Antibiot.,* 1993, **46**, 1355-1363. Numbering for proton-proton coupling constants is based on reported literature.[b]

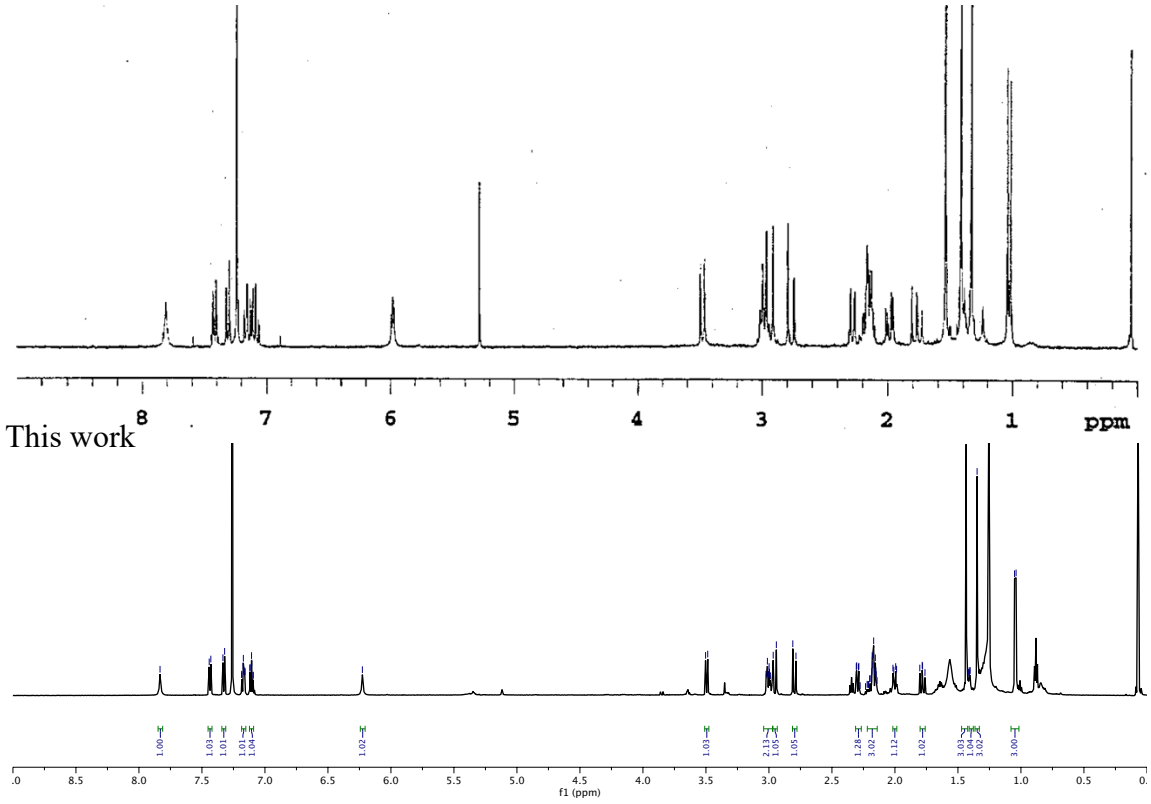
Literature[a]	Found
δ 8.40 (brs, 1H)	δ 7.83 (brs, 1H)
δ 7.39 (d, J = 7.8 Hz, 1H) or δ 7.43 (d, $J_{4,5}$ = 7.7 Hz, 1H)[b]	δ 7.44 (d, J = 7.6 Hz, 1H)
δ 7.29 (d, J = 7.3 Hz,1H) or δ 7.33 (d, $J_{6,7}$ = 8.1 Hz, 1H)[b]	δ 7.33 (d, J = 7.9 Hz, 1H)
δ 7.11 (ddd, J = 7.0, 7.0, 1.2 Hz, 1H) or δ 7.15 (ddd, 8.1,7.0, 1.1 Hz,1H)[b]	δ 7.17 (ddd, 8.1, 7.1, 1.2 Hz, 1H)
δ 7.04 (ddd, J = 7.8, 7.8, 0.8 Hz, 1H) or δ 7.07 (ddd, J = 7.7, 7.0 ,1.1Hz, 1H)[b]	δ 7.11 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H)
δ 6.28 (brs, 1H)	δ 6.23 (s, 1H)
δ 3.45 (d, J = 10.1 Hz, 1H) or δ 3.49 (d, J = 10.2 Hz, 1H)[b]	δ 3.49 (d, J = 10.3 Hz, 1H)
δ 2.96 (m, 2H) or δ 3.00 (m, 2H)[b]	δ 3.00 (m, 2H)
δ 2.90 (d, J = 15.2 Hz, 1H) or δ 2.94 (d, J = 15.1 Hz, 1H)[b]	δ 2.95 (d, J = 15.0 Hz, 1H)
δ 2.76 (d, J = 15.2 Hz, 1H) or δ 2.82 (d, J = 15.1 Hz, 1H)[b]	δ 2.80 (d, J = 15.0 Hz, 1H)
δ 2.24 (dd, 10.1, 1.6 Hz 1H) or δ 2.29 (dd, J = 10.2, 1.9 Hz, 1H)[b]	δ 2.30 (dd, J = 10.3, 1.9 Hz, 1H)
δ 2.13 (m, 3H) or δ 2.15 (m, 3H)[b]	δ 2.17 (m, 3H)
δ 1.96 (dd, 13.2, 4.3 Hz 1H) or δ 2.00 (dd, 13.2, 4.3 Hz 1H)[b]	δ 2.00 (dd, J = 13.2, 4.3 Hz, 1H)
δ 1.73 (dd, 13.2, 11.7 Hz 1H) or δ 1.78 (dd, 13.2, 11.4 Hz 1H)[b]	δ 1.78 (dd, J = 13.2, 11.4 Hz, 1H)
δ 1.39 (s, 3H) or δ 1.44 (s, 3H)[b]	δ 1.43 (m, 3H)
δ 1.37 (m, 1H) or δ 1.42 (m, 1H)	δ 1.41 (m, 1H)
δ 1.31 (s, 3H) or δ 1.35 (s, 3H)[b]	δ 1.35 (s, 3H)
δ 1.00 (d, J = 7.0 Hz, 3H) or 1.05 (d, J = 7.0 Hz, 3H)[b]	δ 1.04 (d, J = 7.2 Hz, 3H)



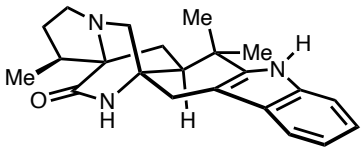
(+)-VM55599 (**1**)



J. Am. Chem. Soc., 2000, **122**, 1675-1683.



Preparaherquamide (**2**)



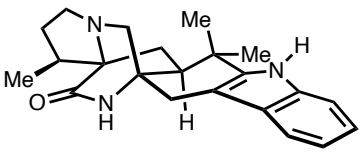
preparaherquamide (**2**)

Formula: $C_{22}H_{27}N_3O$

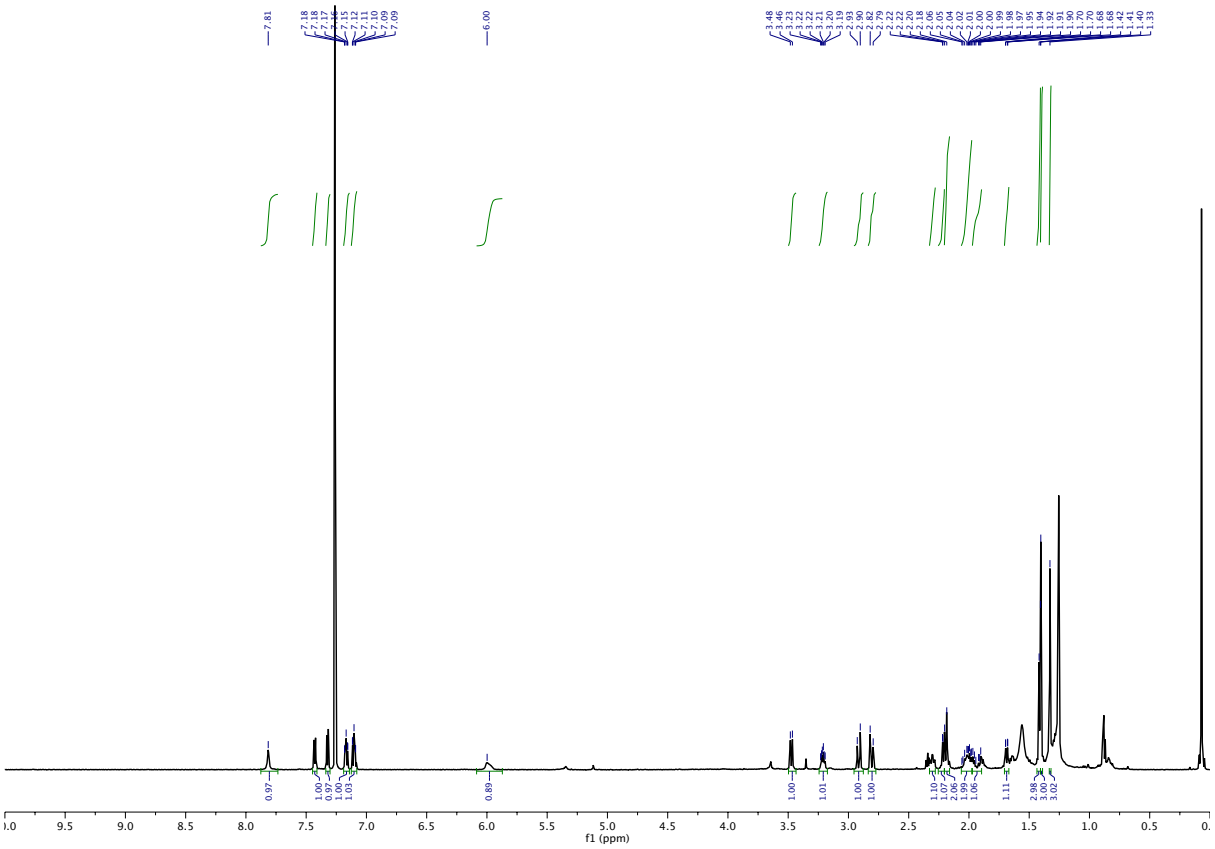
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.81 (1H, brs), 7.43 (d, *J* = 7.8 Hz, 1H), δ 7.32 (d, *J* = 7.9 Hz,1H), 7.17 (ddd, 8.2, 7.1, 1.2 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 6.00 (s, 1H), 3.47 (d, *J* = 10.4 Hz, 1H), 3.21 (td, *J* = 8.8, 5.0 Hz, 1H), 2.91 (d, *J* = 15.0 Hz, 1H), 2.81 (d, *J* = 15.0 Hz, 1H), 2.30 (td, *J* = 10.0, 4.4 Hz, 1H), 2.21 (d, *J* = 9.2 Hz, 1H), 2.20 (m, 2H), 2.02 (m, 2H), 1.97 (m, 1H), 1.69 (m, 1H), 1.41 (d, *J* = 8.0 Hz, 3H), 1.40 (s, 3H), 1.33 (s, 3H).

Table S5. ^{1}H NMR in $CDCl_3$ isolated preparaherquamide (**1**): Comparison of spectral data. [a] S. Nishikori, K. Takemoto, S. Kamisuki, S. Nakajima, K. Kuramochi, S. Tsukuda, S, M. Iwamoto, Y. Katayama, T. Suzuki, S. Kobayashi, K. Watashi and F. Sugawara, *J. Nat. Prod.,* 2016, **79**, 442−446. [b] E.M. Stocking, J. F. Sanz-Cervera and R. M. Williams, *J. Am. Chem. Soc.,* 2000, **122**,1675-1683.

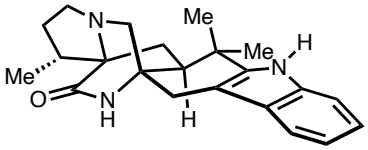
Literature[a]	Found
δ 7.85 (1H, brs)	δ 7.81 (1H, brs)
δ 7.43 (d, *J* = 7.7 Hz, 1H)	δ 7.43 (d, *J* = 7.8 Hz, 1H)
δ 7.32 (d, *J* = 8.0 Hz,1H)	δ 7.32 (d, *J* = 7.9 Hz,1H)
δ 7.17 (dd, *J* = 8.0,7.0 Hz,1H) or δ 7.15 (1H, ddd, *J* = 7.8, 7.8, 1.0 Hz)[b]	δ 7.17 (ddd, 8.2, 7.1, 1.2 Hz, 1H)
δ 7.10(dd, *J* = 7.7,7.0 Hz, 1H) or δ 7.08 (ddd, *J* = 7.4, 7.4, 1.2 Hz, 1H)[b]	δ 7.10 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H)
δ 5.87 (brs, 1H)	δ 6.00 (s, 1H)
δ 3.47 (d, *J* = 10.5 Hz, 1H)	δ 3.47 (d, *J* = 10.4 Hz, 1H)
δ 3.21 (m, 1H)	δ 3.21 (td, *J* = 8.8, 5.0 Hz, 1H)
δ 2.91 (d, *J* = 15.1 Hz, 1H)	δ 2.91 (d, *J* = 15.0 Hz, 1H)
δ 2.80 (d, *J* = 15.1 Hz, 1H)	δ 2.81 (d, *J* = 15.0 Hz, 1H)
δ 2.30 (ddd, 9.4, 9.4, 4.5, 1H)	δ 2.30 (td, *J* = 10.0, 4.4 Hz, 1H)
δ 2.21 (d, *J* = 9.2 Hz, 1H)	δ 2.21 (d, *J* = 9.2 Hz, 1H)
δ 2.20 (m, 2H)	δ 2.20 (m, 2H)
δ 2.02 (m, 2H)	δ 2.02 (m, 2H)
δ 1.97 (m, 1H)	δ 1.97 (m, 1H)
δ 1.69 (m, 1H)	δ 1.69 (m, 1H)
δ 1.41 (d, *J* = 7.7 Hz, 3H)	δ 1.41 (d, *J* = 8.0 Hz, 3H)
δ 1.40 (s, 3H)	δ 1.40 (s, 3H)
δ 1.33 (s, 3H)	δ 1.33 (s, 3H)



preparaherquamide (**2**)

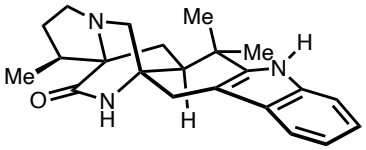


Stacked ^{1}H NMR spectra



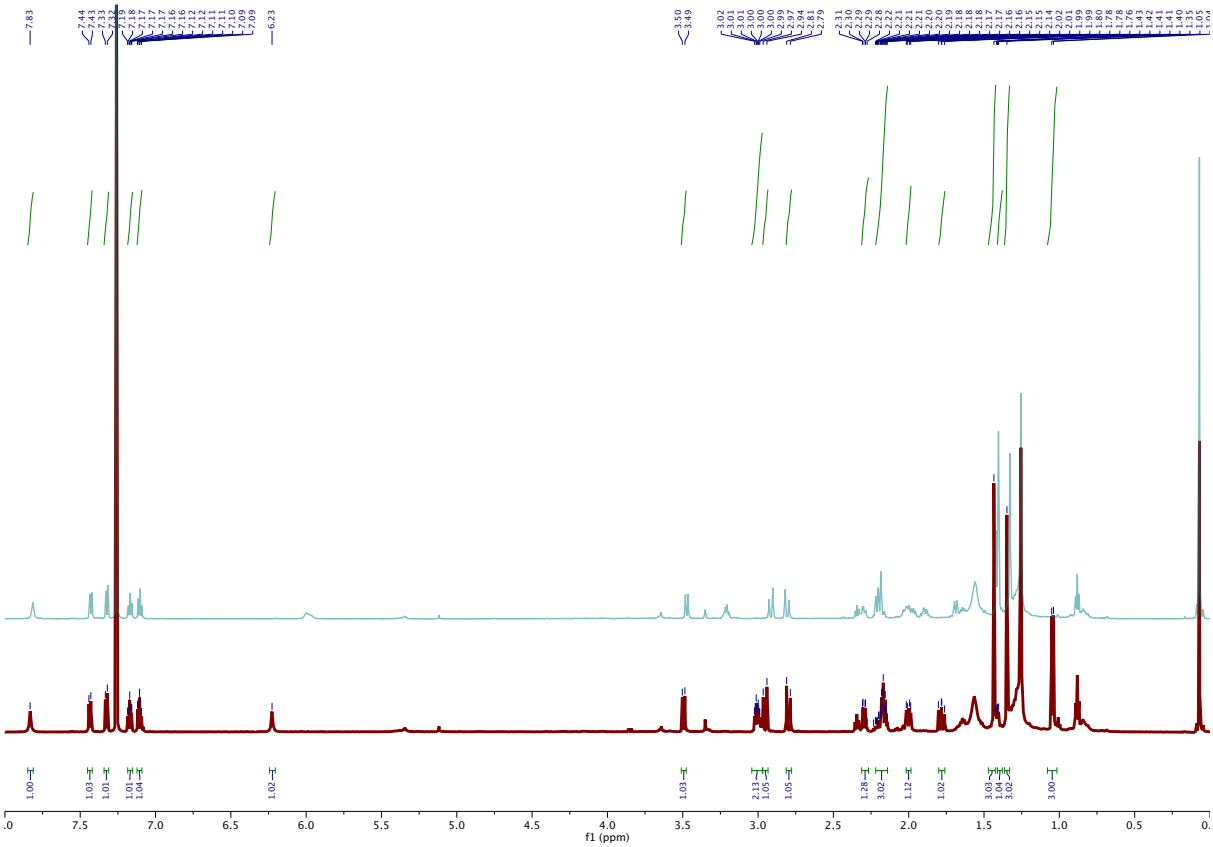
(+)-VM55599 (**1**)

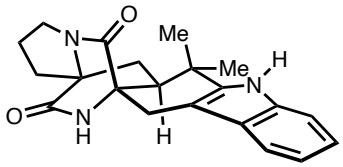
Bottom



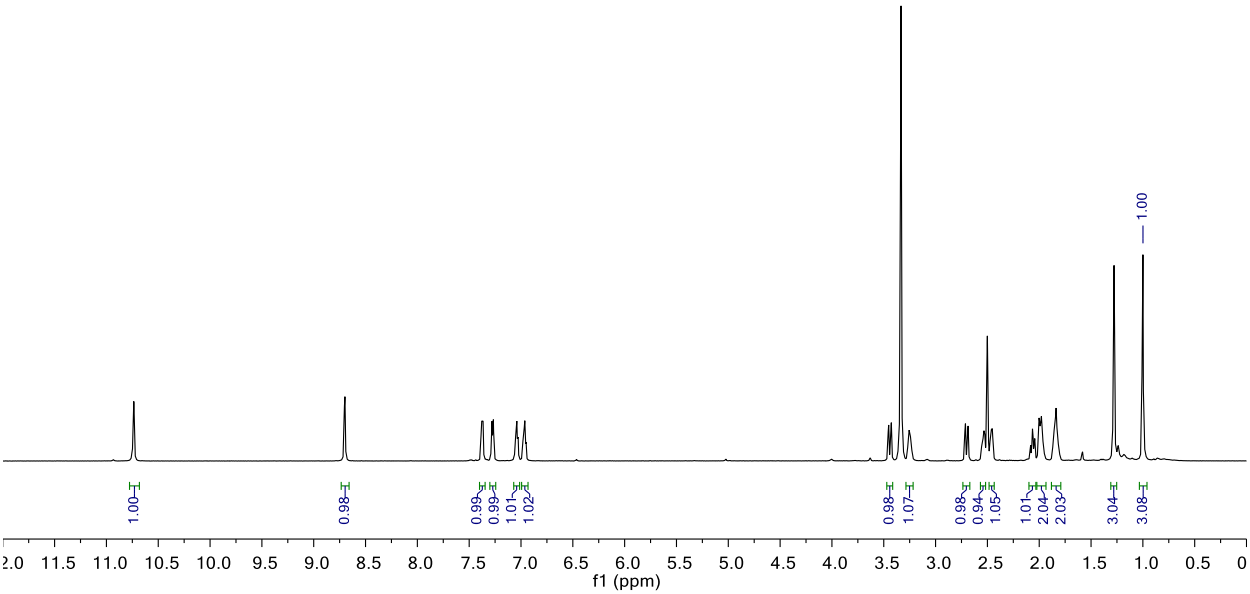
preparaherquamide (**2**)

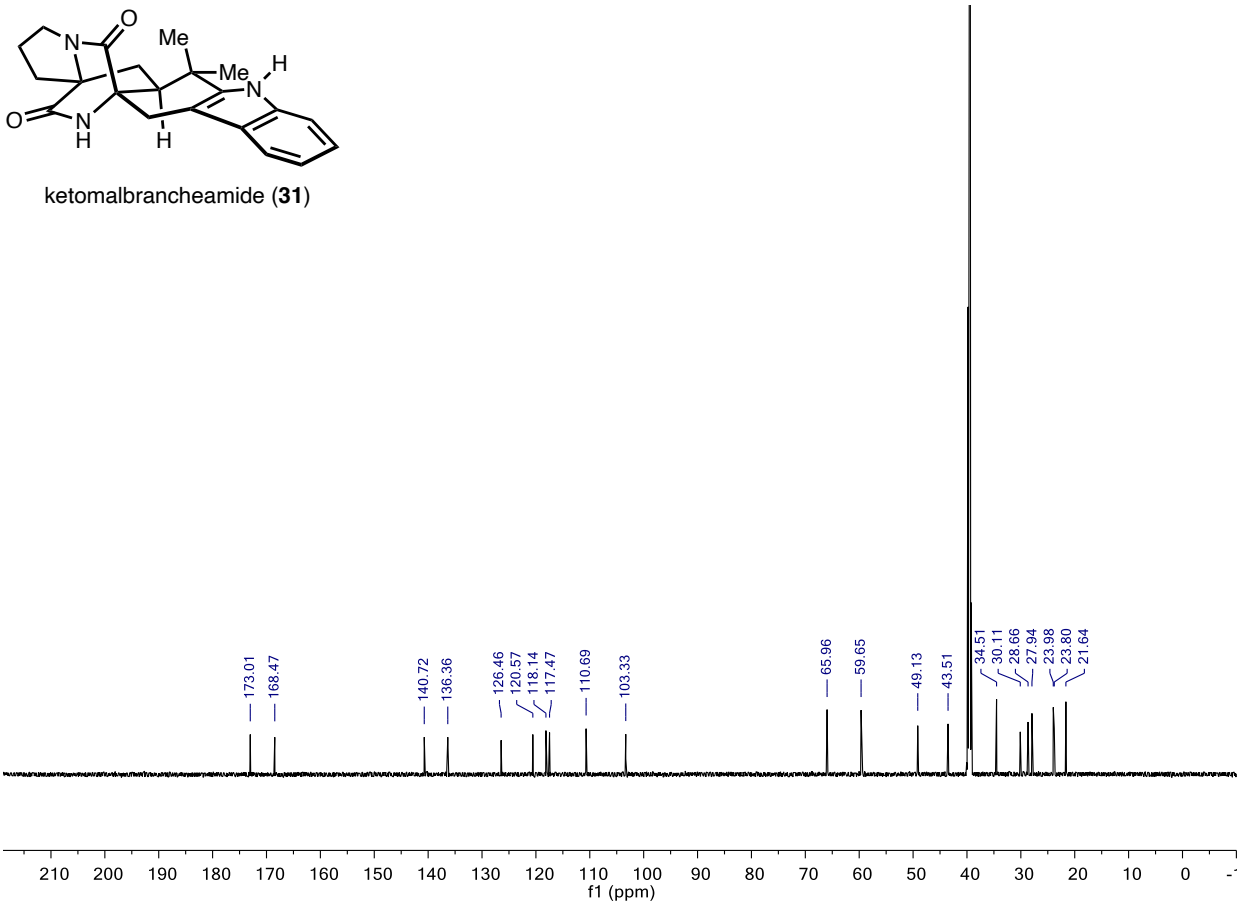
Top

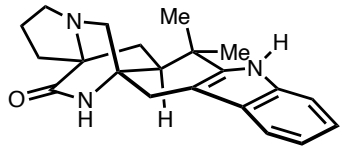




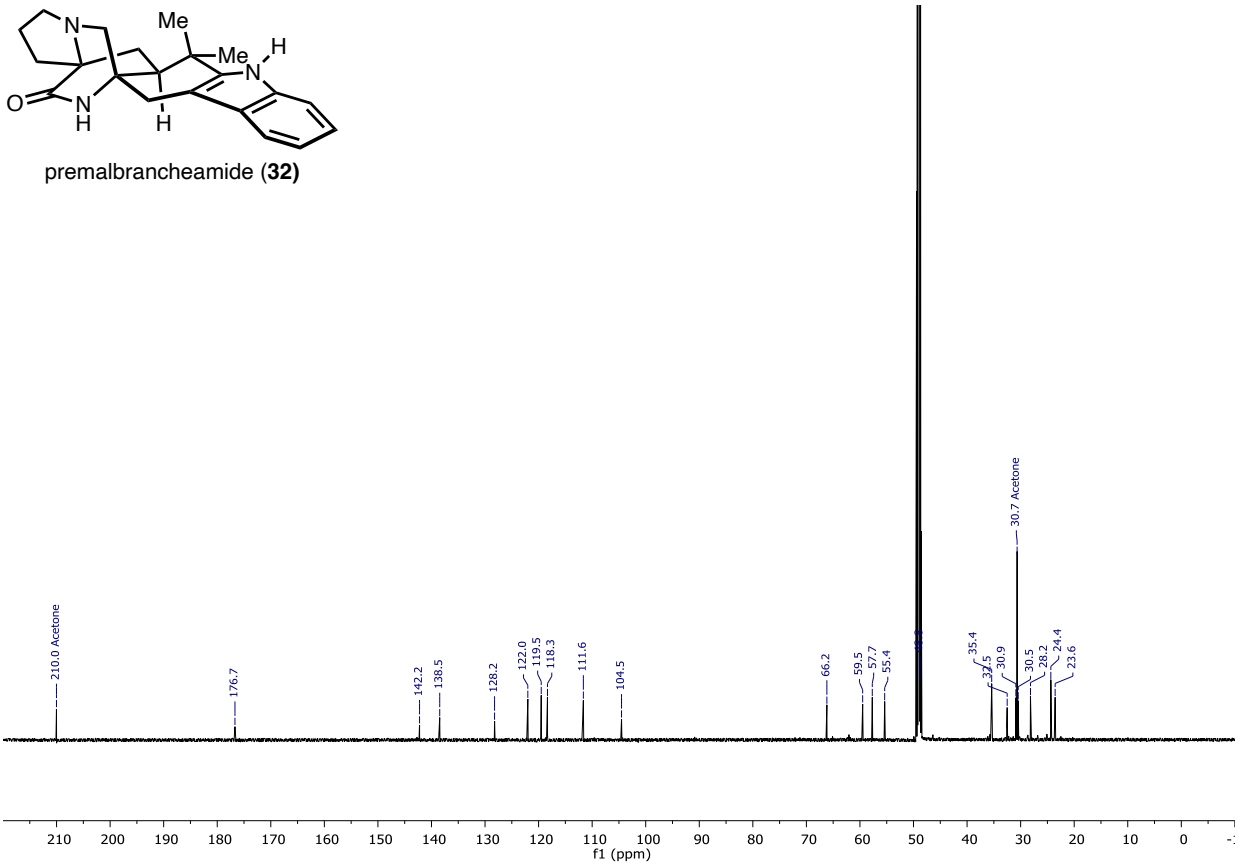
ketomalbrancheamide (**31**)




O
N
Me
Me
H
N
O
N
H
H
ketomalbrancheamide (31)
173.01
168.47
140.72
136.36
126.46
120.57
118.14
117.47
110.69
103.33
65.96
59.65
49.13
43.51
34.51
30.11
28.66
27.94
23.98
23.80
21.64
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)



premalbrancheamide (**32)**



premalbrancheamide (**32**)

5. References

1) W. C. Still, M. Kahn and A. J. Mitra, *J. Org. Chem.,* 1978, **43**, 2923–2925.

2) A) For the synthesis of **11**, see: E. V. Mercado-Marin and R. Sarpong, *Chem. Sci.*, 2015, **6**, 5048–5052. For the synthesis of **S1**, see: B) R. M. Williams, J. Cao, H and Tsujishima, R. J. Cox, *J. Am. Chem. Soc.,* 2003, **125**, 12172. C) J. Cooper, P. T. Gallagher and D. W. Knight, *J. Chem. Soc. Chem. Commun.,* 1988, **8**, 509. D) **S1** can also be accessed on large scale by substituting methyl potassium malonate for ethyl potassium malonate in the procedure developed by Sorensen and co-workers (R. Moreau and E. J. Sorensen, *Tetrahedron*, 2007, **63**, 6446).

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10) J. F, Sanz-Cervera and R. M. Williams, *J. Am. Chem. Soc.,* 2002, **124**, 2556–2559.

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