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Supporting Information

Total Synthesis of Crocagin A

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1 General Experimental

Unless otherwise specified, all reactions were carried out under Ar atmosphere in oven-dried glassware.

Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled over sodium and benzophenone, triethylamine (NEt_3) and *N*,*N*-diisopropylamine (DIPA) over calcium hydride. All other solvents as well as starting materials and reagents were obtained from commercial sources and used without further purification.

Flash column chromatography was performed using the analytical grade solvents indicated and Merck silica gel (40–63 µm, 60 Å) as the stationary phase. Reactions and chromatography fractions were monitored with Merck silica gel 60 F254 glass plates and visualized using a 254 nm UV lamp and/or by treatment with a suitable dip (potassium permanganate, ceric ammonium molybdate or anisaldehyde) followed by heating.

Proton (^1H) and carbon (^{13}C) NMR spectra were recorded at 23 °C (unless otherwise stated) on Bruker 400 or Bruker Avance III 500 or Varian 600 instrument. The spectral analysis of crocagin A (**1**) and the mixed NMR experiments were performed with Bruker Avance III 700 spectrometer with a 5 mm TCI cryoprobe (1H 700 MHz, 13C 175 MHz). Chemical shifts (δ) are expressed in parts per million (ppm) and are calibrated using residual protic solvent as an internal reference for proton ($CHCl_3$: δ = 7.26 ppm, CH_3OH: δ = 3.31 ppm, DMSO-d_6: δ = 2.50 ppm), and for carbon the central carbon resonance of the solvent ($CDCl_3$: δ = 77.16 ppm, CD_3OD: δ = 49.00 ppm, DMSO-d_6: δ = 39.52 ppm). Multiplicity is defined as: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet, br = broad or combinations of the above. To assign proton and carbon spectra, a range of 2D-NMR experiments (COSY, HSQC, HMBC, NOESY) were used. The numbering of atoms in the molecules does not correspond to the IUPAC nomenclature.

Infrared spectra were recorded on a Perkin-Elmer BXII-FTIR spectrometer. Samples were analyzed as neat materials.

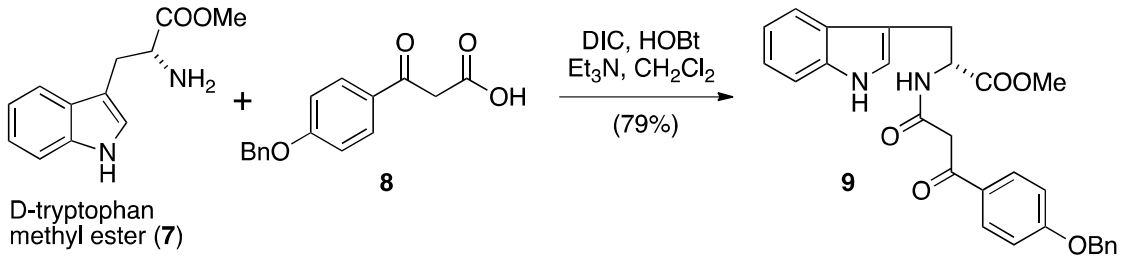
Mass spectrometry experiments were performed on a Thermo Finnigan MAT 95 (Electron Ionisation, EI) and on a Thermo Finnigan LTQ FT (Electrospray Ionisation, ESI) instrument.

Melting points were measured on a Büchi melting point B-540 system and are uncorrected.

Optical rotations were measured at the given temperature (T in [°C]) on a Perkin-Elmer 241 or Krüss P8000-T polarimeter using a sodium lamp (Na D-line, 589 nm). Measurements were carried out in a cell with path length (l) of 0.5 dm. Concentrations are given in g/100 mL

2 Experimental Procedures

2.1 (*R*)-Methyl 2-(3-(4-(benzyloxy)phenyl)-3-oxopropanamido)-3-(1*H*-indol-3-yl)propanoate (9)



Diisopropylcarbodiimide (4.90 mL, 31.5 mmol; 1.5 eq) was added portionwise to a suspension of amine **7** (5.35 g; 21.0 mmol), β-ketoacid **8**[1] (6.24 g; 23.1 mmol; 1.1 eq), HOBt (4.54 g; 33.6 mmol; 1.6 eq) and triethylamine (6.50 mL; 46.2 mmol; 2.2 eq) in dry dichloromethane (135 mL). After stirring for 40 h, the reaction mixture was diluted with dichloromethane and washed with 1M HCl, saturated $NaHCO_3$ and brine. The extract was dried over anhydrous Na_2SO_4, concentrated in *vacuo* and purified by flash chromatography (50% EtOAc/hexanes → 70% EtOAc/hexanes), to afford 7.83 g (79%) of the pure β-ketoamide **9**, as a yellowish foam.

R_f = 0.20 (40% EtOAc in hexanes).

$[\alpha]_D^{26}$ = −49.3° (c = 0.75, $CHCl_3$).

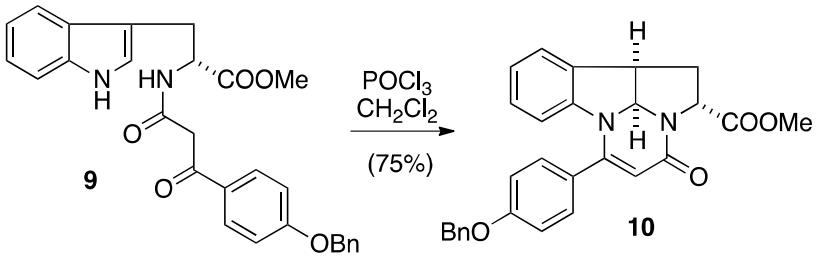
^{1}H NMR (600 MHz, $CDCl_3$): δ 8.08 (s, 1H), 7.92 (d, *J* = 9.0, 2H), 7.53 (d, *J* = 8.0, 1H), 7.50 (d, *J* = 7.6, 1H), 7.42 – 7.31 (m, 5H), 7.32 (d, *J* = 8.9, 1H), 7.18 – 7.13 (m, 1H), 7.10 – 7.05 (m, 1H), 7.03 (d, *J* = 2.4, 1H), 7.00 (d, *J* = 9.0, 2H), 5.14 (s, 2H), 4.94 (dt, J_1 = 5.7, J_2 = 7.7, 1H), 3.84 (dd, J_1 = 16.3, J_2 = 34.8 Hz, 2H), 3.65 (s, 3H), 3.33 (d, *J* = 5.7, 2H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 193.7, 172.2, 165.9, 163.4, 136.2, 136.1, 131.2, 129.5, 128.9, 128.5, 127.6, 127.6, 123.1, 122.3, 119.7, 118.7, 115.0, 111.3, 110.1, 70.4, 53.2, 52.5, 45.4, 27.8.

IR ($\tilde{\nu}$ /cm^{-1}): 3318, 2950, 1737, 1646, 1597, 1573, 1509, 1455, 1421, 1321, 1254, 1211, 1167, 1115, 999, 910, 829.

HRMS (ESI): calcd. for $C_{28}H_{27}N_2O_5$ $(M+H)^+$ 471.1914; found: 471.1917.

2.2 (2*R*,2a1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-3-oxo-2,2a1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (10)



Phosphorus oxychloride (10.2 mL; 108 mmol; 15 eq) was added dropwise to a solution of β-ketoamide **9** (3.40 g; 7.27 mmol) in dry dichloromethane (66 mL) and the mixture was stirred at room temperature for 22 h. The reaction mixture was diluted with dichloromethane and carefully quenched with 5% ammonia solution (300 mL), while cooling in an ice bath. The extract was dried over anhydrous Na_2SO_4, filtered and concentrated in *vacuo*. After flash chromatography (80 % EtOAc in hexanes → 100 % EtOAc), 2.45 g (75 %) of the pure product **10** was isolated, in form of a yellow foam.

R_f = 0.70 (80% EtOAc in hexanes).

$[\alpha]_D^{26}$ = −248.7° (c = 0.79, $CHCl_3$).

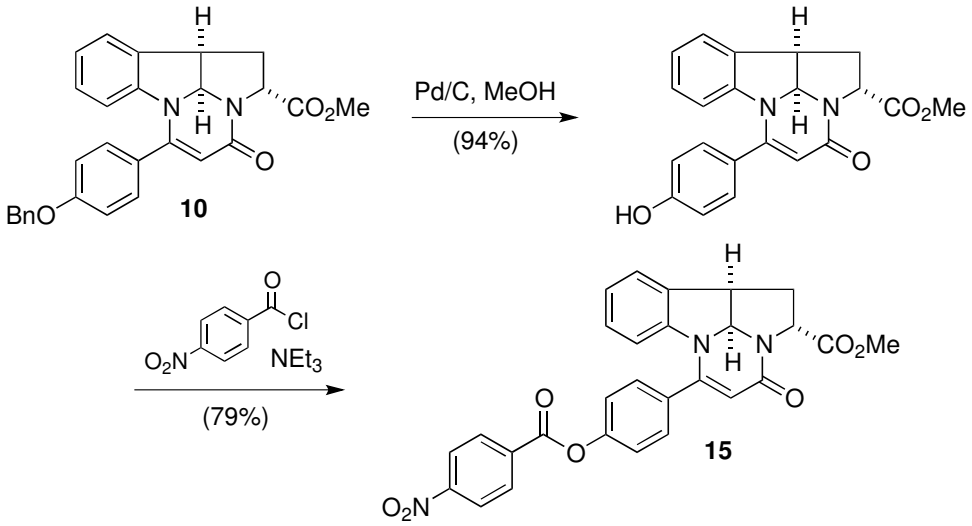
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.8, 2H), 7.46 (d, *J* = 7.3, 2H), 7.42 (t, *J* = 7.5, 2H), 7.36 (t, *J* = 7.3, 1H), 7.19 (d, *J* = 6.3, 1H), 7.06 (d, *J* = 8.8, 2H), 6.92 – 6.87 (m, 2H), 6.02 (d, *J* = 7.4, 1H), 5.93 (d, *J* = 7.2, 1H), 5.84 (s, 1H), 5.14 (s, 2H), 4.48 (dd, J_1 = 5.8, J_2 = 8.7, 1H), 4.20 (td, J_1 = 3.6, J_2 = 8.1, 1H), 3.80 (s, 3H), 2.64 (ddd, J_1 = 5.7, J_2 = 8.7, J_3 = 14.3, 1H), 2.58 – 2.52 (m, 1H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 172.5, 162.6, 161.4, 152.1, 145.9, 136.5, 133.3, 130.1, 128.8, 128.5, 128.4, 127.7, 126.8, 124.9, 122.2, 115.4, 112.8, 105.8, 80.2, 70.4, 56.8, 52.7, 44.8, 35.5.

IR ($\tilde{\nu}$ /cm^{-1}): 3008, 2952, 1738, 1642,1506, 1477, 1427, 1369, 1296, 1240, 1218, 1202, 1171, 1113, 1023, 1007, 826.

HRMS (ESI): calcd. for $C_{28}H_{25}N_2O_4$ $[M+H]^+$ 453.1809; found: 453.1814.

2.3 (2*R*,2a^1*R*,9b*R*)-methyl 5-(4-((4-nitrobenzoyl)oxy)phenyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (15)



10% Palladium on charcoal (20.0 mg) was added to a solution of tetracyclic compound **10** (100 mg; 0.220 mmol) in methanol (3 mL), and the mixture was stirred for 2 h under 1 atm of hydrogen. The mixture was filtered through a plug of celite and the solvent was removed in *vacuo*, to yield 78.0 mg (94%) of the virtually pure phenol, as a colorless oil.

p-Nitrobenzoyl chloride (42.0 mg; 0.228 mmol; 1.1 eq) was added to a solution of phenol (75.0 mg; 0.207 mmol) and triethylamine (38.0 µL; 0.269 mmol; 1.3 eq) in dichloromethane (3 mL), and the solution was stirred for 5 minutes. The reaction mixture was diluted with dichloromethane, washed with 1M HCl and brine and the organic extract was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the filtrate was concentrated in *vacuo*, to give a yellowish-white solid (59.0 mg; 79%). The crude ester **15** was recrystallized from methanol and crystals suitable for X-ray analysis were obtained.

R_f = 0.20 (60% EtOAc in hexanes).

$[\alpha]_D^{22}$ = −320.9 ° (*c* = 0.24, $CHCl_3$).

m.p.: 192 – 194 °C (MeOH).

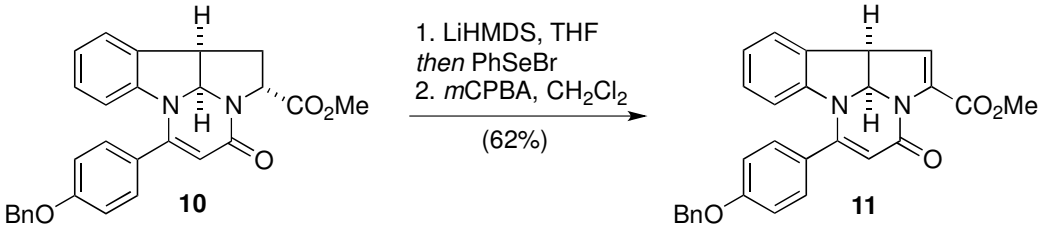
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 1.9, 4H), 7.80 (d, *J* = 8.7, 2H), 7.38 (d, *J* = 8.7, 2H), 7.22 (d, *J* = 6.6, 1H), 7.00 – 6.88 (m, 2H), 6.07 – 6.01 (m, 1H), 6.00 – 5.94 (m, 2H), 4.51 (dd, J_1 = 8.7, J_2 = 5.8, 1H), 4.23 (t, *J* = 5.9, 1H), 3.81 (s, 3H), 2.73 – 2.51 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 163.1, 162.2, 152.7, 151.2, 151.2, 145.6, 134.6, 133.3, 132.3, 131.5, 129.9, 128.7, 125.1, 124.0, 122.5, 122.4, 112.7, 107.8, 80.3, 56.8, 52.8, 44.8, 35.5.

IR ($\tilde{\nu}$ /cm^{-1}): 2948, 2357, 1736, 1723, 1652, 1600, 1524, 1504, 1477, 1460, 1423, 1406, 1345, 1321, 1292, 1266, 1209, 1166, 1108, 1083, 1027.

HRMS (ESI): calcd. for $C_{28}H_{21}O_7N_3Na$ $[M+Na]^+$ 534.1272; found 534.1272.

2.4 (2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-3-oxo-3,9b-dihydro-2a^{1}H-2a,5a-diazacyclopenta[*jk*] fluorene-2-carboxylate (11)



n-Butyl lithium (1.6 M; 11.0 mL; 17.7 mmol; 2 eq) was added to a cold (-30 °C) solution of hexamethyldisilazane (3.9 mL; 18.6 mmol; 2.2 eq) in dry THF (50 mL) and the mixture was stirred at 0 °C for 30 minutes. The resulting solution of LiHMDS was added to a cold (-60 °C) solution of ester **10** (4.00 g; 8.85 mmol) in dry THF (100 mL). After 20 minutes of stirring, a solution of PhSeBr (4.59 g; 19.5 mmol; 2.2 eq) in THF (50 mL) was added and the mixture was stirred for additional 20 minutes. The reaction mixture was diluted with ethyl acetate and washed with saturated NH_4Cl and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude mixture was dissolved in dichloromethane (50 mL), and treated with *m*CPBA (77%; 2.58 g; 11.5 mmol; 1.3 eq) at 0 °C. After 15 minutes, the mixture was washed with 5% sodium thiosulfate, saturated $NaHCO_3$ and brine, the organic extract was dried over anhydrous $MgSO_4$ and filtered. The solvent was removed in *vacuo*, and the residue was purified by flash chromatography (50% EtOAc in hexanes) to yield 2.45 g (62%) of the unsaturated ester **11**, as a yellow foam.

R_f = 0.30 (20% Et_2O in DCM).

$[\alpha]_D^{24}$ = −397.8 ° (c = 0.45, $CHCl_3$).

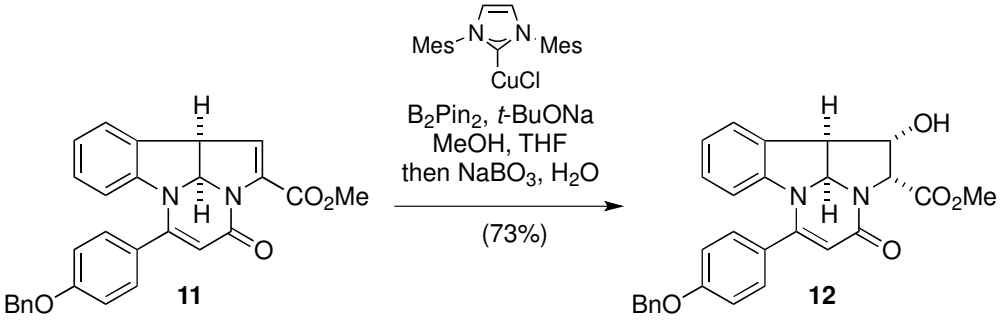
^{1}H NMR (600 MHz, $CDCl_3$): δ 7.64 (d, *J* = 8.9, 2H), 7.47 – 7.46 (m, 2H), 7.43 – 7.41 (m, 2H), 7.37 – 7.36 (m, 1H), 7.25 – 7.20 (m, 1H), 7.07 (d, *J* = 8.9, 2H), 6.94 – 6.89 (m, 2H), 6.15 – 6.10 (m, 1H), 6.00 (d, *J* = 3.6, 1H), 5.94 (d, *J* = 9.8, 1H), 5.91 (s, 1H), 5.15 (s, 2H), 4.61 (dd, J_1 = 9.8, J_1 = 3.6, 1H), 3.88 (s, 3H).

^{13}C NMR (150 MHz, $CDCl_3$): δ 162.3, 161.6, 160.1, 151.8, 145.2, 137.1, 136.4, 130.3, 128.8, 128.5, 128.4, 127.7, 127.2, 126.4, 125.2, 122.6, 116.1, 115.6, 112.5, 105.8, 80.2, 70.4, 52.9, 48.4.

IR ($\tilde{\nu}$ /cm^{-1}): 2922, 1736, 1649, 1600, 1505, 1476, 1459, 1423, 1409, 1360, 1287, 1244, 1227, 1171, 1120, 1020, 1000, 907, 819.

HRMS (ESI): calcd. for $C_{28}H_{23}N_2O_4$ $[M+H]^+$ 451.1652; found: 451.1661.

2.5 (1*S*,2*R*,2a^{1}R,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-1-hydroxy-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (12)



Bis(pinacolato)diboron (1.40 g; 5.52 mmol; 1.2 eq) was added to a solution of chloro[1,3-bis(2,4,6-trimethylphenyl)imidazol-2-ylidene]copper(I) (223 mg; 12 mol%) and *t*-BuONa (79.6 mg; 18 mol%) in dry THF (10 mL), under nitrogen. After 5 minutes, a solution of unsaturated ester **11** (2.07 g; 4.60 mmol) in dry THF (32 mL) was added, followed by methanol (240 µL; 5.98 mmol; 1.3 eq). After 40 minutes, a solution of sodium perborate tetrahydrate (1.42 g; 9.20 mmol; 2 eq) in water (20 mL) was added and stirring was continued for 30 minutes. The reaction mixture was partitioned between ether and brine, and the organic extract was dried over anhydrous Na_2SO_4. After filtration, the solvent was removed in *vacuo* and the residue was purified by flash chromatography (80% EtOAc in hexanes), to afford 1.57 g (73%) of the pure alcohol **12**, as a pale yellow foam.

R_f = 0.30 (80% EtOAc in hexanes).

$[\alpha]_D^{24}$ = −209.7 ° (c = 0.33, $CHCl_3$).

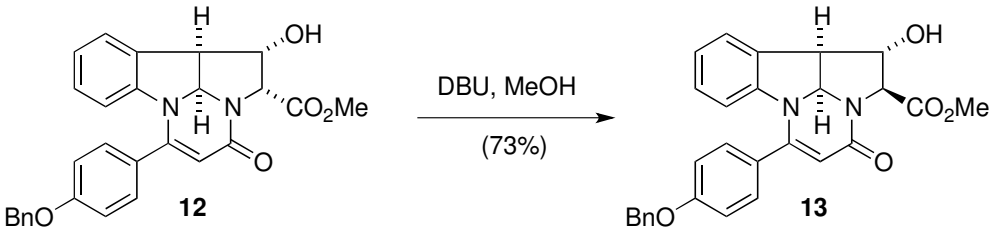
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.8, 2H), 7.51 – 7.29 (m, 6H), 7.05 (d, *J* = 8.8, 2H), 6.98 – 6.83 (m, 2H), 6.11 (d, *J* = 7.2, 1H), 6.02 (d, *J* = 8.5, 1H), 5.84 (s, 1H), 5.13 (s, 2H), 4.74 (dd, J_1 = 6.8, J_2 = 2.7 Hz, 1H), 4.61 (d, *J* = 6.8, 1H), 4.12 (d, *J* = 7.2, 1H), 3.79 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7, 163.2, 161.4, 152.5, 145.9, 136.4, 130.7, 130.1, 128.8, 128.8, 128.4, 127.7, 126.4, 125.2, 122.2, 115.4, 112.9, 105.4, 79.2, 77.5, 70.3, 62.8, 54.5, 52.6.

IR ($\tilde{\nu}$ /cm^{-1}): 3339, 2975, 1741, 1626, 1601, 1506, 1477, 1433, 1368, 1299, 1248, 1170, 1114, 1076, 1005.

HRMS (ESI): calcd. for $C_{28}H_{25}N_2O_5$ $[M+H]^+$ 469.1758; found: 469.1758.

2.6 (1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-1-hydroxy-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (13)



A solution of ester **12** (2.00 g; 4.27 mmol) and DBU (3.2 mL; 21.4 mmol; 5 eq) in dry methanol (20 mL) was heated at 70 °C for 2 h, under nitrogen. The reaction mixture was cooled to room temperature and quenched by addition of 1M HCl (to pH=5). The reaction mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The residual mixture of diastereomeric esters (ca. 1:1) was purified by flash chromatography (100% EtOAc), to afford separated diastereomeric esters. The total of 1.46 g (73%) of ester **13** was obtained through two isomerisation cycles as a colorless foam.

R_f = 0.30 (100% EtOAc).

$[\alpha]_D^{24}$ = −86.7 ° (c = 0.24, MeOH).

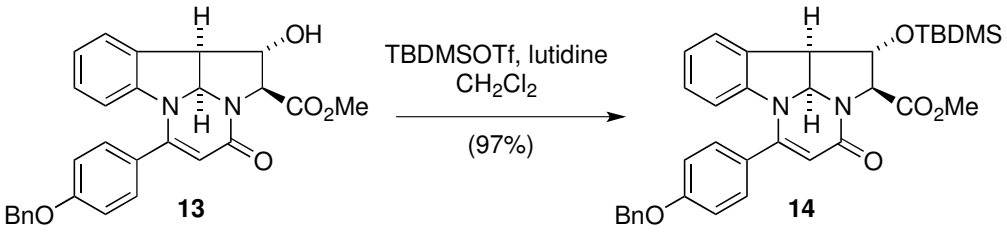
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, *J* = 8.8, 2H), 7.47 – 7.36 (m, 5H), 7.17 (d, *J* = 7.4, 1H), 7.07 (d, *J* = 8.8, 2H), 6.91 (t, *J* = 7.7, 1H), 6.82 (t, *J* = 7.4, 1H), 6.08 (d, *J* = 8.0, 1H), 5.96 (s, 1H), 5.91 (d, *J* = 6.7, 1H), 5.15 (s, 2H), 4.86 (d, *J* = 4.3, 1H), 4.71 (s, 1H), 4.15 (d, *J* = 6.7, 1H), 3.15 (s, 3H), 3.07 (d, *J* = 4.6, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.7, 164.9, 161.6, 153.6, 147.4, 136.5, 130.4, 129.4, 129.1, 128.8, 128.4, 127.7, 126.6, 125.1, 121.9, 115.5, 112.8, 106.4, 80.5, 80.1, 70.4, 68.6, 53.6, 52.4.

IR ($\tilde{\nu}$ /cm^{-1}): 3262, 2933, 1733, 1625, 1600, 1504, 1475, 1428, 1333, 1300, 1247, 1171, 1009, 821.

HRMS (ESI): calcd. for $C_{28}H_{25}N_2O_5$ $[M+H]^+$ 469.1758; found: 469.1758.

2.7 (1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (14)



TBDMSOTf (668 µL; 2.91 mmol; 1.5 eq) was added dropwise to a solution of alcohol **13** (0.910 g; 1.94 mmol) and 2,6-lutidine (550 µL; 4.85 mmol; 2.5 eq) in dry dichloromethane (3 mL). After 45 minutes of stirring, the reaction mixture was diluted with dichloromethane, washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The residue was purified by flash chromatography (100% EtOAc) to yield 1.10 g (97%) of the TBDMS-protected product **14**, as a colorless oil.

R_f = 0.30 (50% EtOAc in hexanes).

$[\alpha]_D^{24}$ = −185.8 ° (c = 0.30, $CHCl_3$).

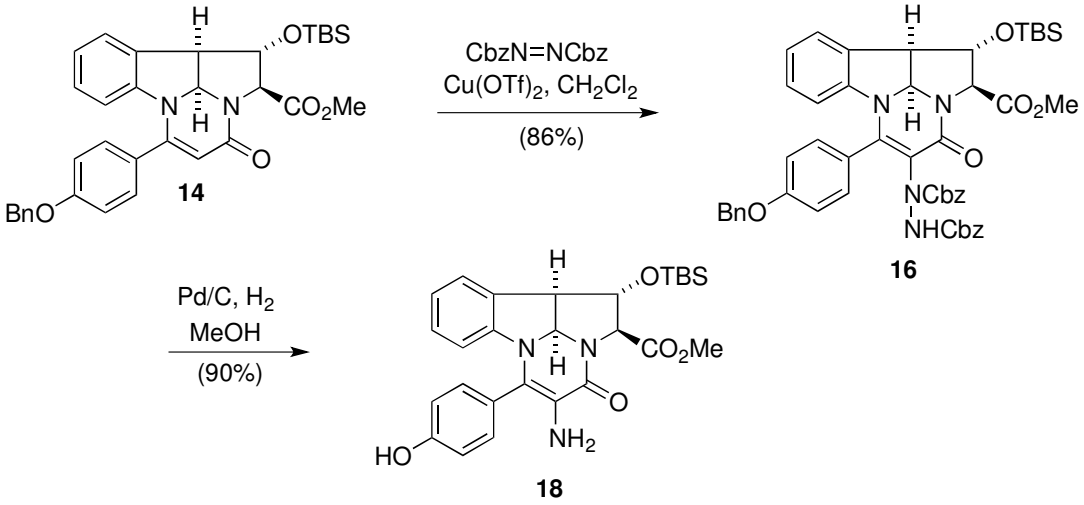
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 8.9, 2H), 7.48 – 7.34 (m, 5H), 7.11 (d, *J* = 7.4, 1H), 7.07 (d, *J* = 8.9, 2H), 6.91 (t, *J* = 7.7, 1H), 6.81 (t, *J* = 7.4, 1H), 6.08 (d, *J* = 8.0, 1H), 5.96 (s, 1H), 5.91 (d, *J* = 6.7, 1H), 5.15 (s, 2H), 4.77 (s, 1H), 4.59 (s, 1H), 4.01 (d, *J* = 6.7, 1H), 3.18 (s, 3H), 0.98 (s, 9H), 0.26 (s, 3H), 0.24 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.9, 164.4, 161.5, 153.1, 147.4, 136.5, 130.3, 129.6 , 129.0, 128.8, 128.4, 127.7, 126.8, 124.8, 121.7, 115.4, 112.8, 106.7, 81.0, 80.6, 70.4, 68.7, 54.8, 52.2, 25.9, 18.3, -4.6, -4.8.

IR ($\tilde{\nu}$ /cm^{-1}): 2951, 2927, 2360, 1757, 1736, 1644, 1602, 1505, 1476, 1460, 1423, 1409, 1300, 1250, 1171, 1081.

HRMS (ESI): calcd. for $C_{34}H_{39}N_2O_5Si$ $[M+H]^+$ 583.2623; found: 583.2620.

2.8 (1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 4-amino-1-((*tert*-butyldimethylsilyl)oxy)-5-(4-hydroxyphenyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (18)



Copper(II) trifluoromethanesulfonate (342 mg; 50 mol%) was added to a solution of tetracycle **14** (1.10 g; 1.89 mmol) and dibenzyl azodicarboxylate (880 mg; 2.83 mmol; 1.5 eq) in dry dichloromethane (25 mL). The reaction mixture was stirred at room temperature for 4 h and the mixture was partitioned between ether and water and the organic layer was washed with 5% ammonia solution and brine. The organic extract was dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude material was purified by flash chromatography (30% EtOAc/hexanes), to afford 1.42 g (86%) of the pure product, as a yellowish foam.

10% palladium on charcoal (450 mg) was added to a solution of hydrazine **16** (1.05 g; 1.19 mmol) in methanol (35 mL) and the reaction mixture was stirred under hydrogen (balloon pressure) for 1 h. The reaction mixture was filtered through a pad of celite, the celite was washed with methanol and the filtrate was concentrated. The residue was purified by flash chromatography (60% EtOAc in hexanes), to afford 545 mg (90%) of the pure amine **18**, as a yellowish oil.

R_f = 0.50 (80% EtOAc in hexane).

$[\alpha]_D^{24}$ = −246.7° (c = 0.33, MeOH).

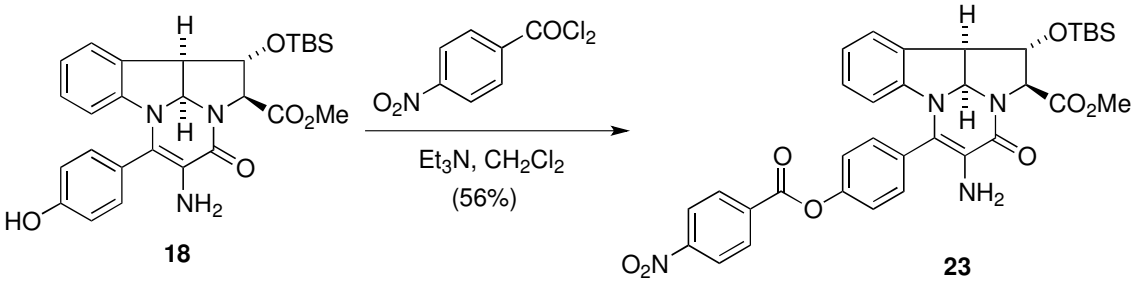
^{1}H NMR (400 MHz, CD_3OD): δ 7.65 (d, *J* = 8.8, 2H), 7.10 (d, *J* = 7.4, 1H), 6.91 (d, *J* = 8.8, 2H), 6.86 (t, *J* = 7.7, 1H), 6.74 (t, *J* = 7.9, 1H), 5.90 (d, *J* = 8.0, 1H), 5.80 (d, *J* = 6.2, 1H), 4.88 (s, 1H), 4.51 (s, 1H), 3.99 (d, *J* = 6.2, 1H), 3.70 (s, 2H), 3.17 (s, 3H), 1.01 (s, 9H), 0.30 (s, 3H), 0.28 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD): δ 169.5, 164.1, 159.5, 150.3, 131.6, 129.8, 129.8, 128.2, 126.6, 125.5, 125.3, 121.9, 117.0, 113.3, 81.9, 80.9, 70.0, 55.7, 52.7, 26.2, 19.0, -4.7, -4.8.

IR ($\tilde{\nu}$ /cm^{-1}): 3301, 2949, 2855, 1736, 1639, 1602, 1511, 1476, 1459, 1434, 1360, 1300, 1260, 1168, 1088.

HRMS (ESI): calcd. for $C_{27}H_{34}N_3O_5Si$ $[M+H]^+$ 508.2262; found: 508.2260.

2.9 (2*R*,2a^1*R*,9b*R*)-Methyl 4-amino-1-((*tert*-butyldimethylsilyl)oxy) 5-(4-((4-nitrobenzoyl)oxy)phenyl)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (23)



p-Nitrobenzoyl chloride (18.2 mg; 0.098 mmol; 1.1 eq) was added to a solution of phenol **18** (45 mg; 0.0891 mmol) and triethylamine (16.0 µL; 0.116 mmol; 1.3 eq) in dichloromethane (2 mL), and the solution was stirred for 5 minutes. The reaction mixture was diluted with dichloromethane, washed with brine, and the organic extract was dried over anhydrous Na_2SO_4. The drying agent was filtered off and the filtrate was concentrated in *vacuo*, to give a red solid (33.0 mg; 56%). The crude ester **23** was recrystallized from methanol and red crystals suitable for X-ray analysis were obtained.

R_f = 0.20 (30% EtOAc in hexanes).

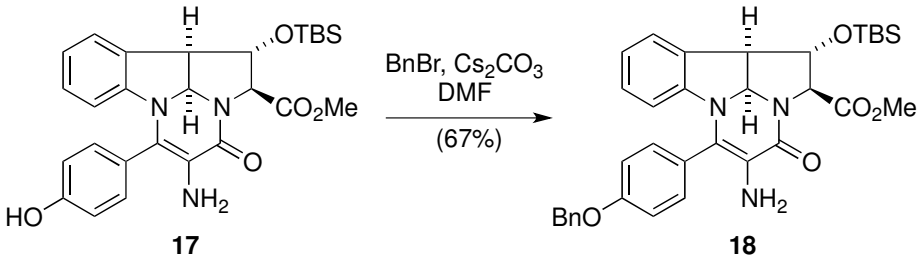
^{1}H NMR (400 MHz, CD_3OD): δ 8.14 – 8.12 (m, 2H), 8.03 (d, *J* = 8.9, 1H), 7.74 (d, *J* = 8.7, 2H), 7.46 (dd, *J* = 12.9, 8.7, 1H), 7.22 (d, *J* = 8.8, 2H), 6.93 (d, *J* = 7.4, 1H), 6.69 (t, *J* = 7.2, 1H), 6.57 (t, *J* = 7.2, 1H), 5.76 (d, *J* = 7.9, 1H), 5.66 (d, *J* = 6.1, 1H), 4.70 (s, 1H), 4.31 (s, 1H), 3.81 (d, *J* = 6.1, 1H), 3.76 (s, 1H), 2.99 (s, 3H), 0.80 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H).

^{13}C NMR (101 MHz, CD_3OD): δ 167.46, 165.54 (HMBC), 163.80 (HMBC), 160.95 (HMBC), 157.53, 149.92, 148.33, 135.79 (HMBC), 133.45, 133.27 (HMBC), 130.45, 129.79, 129.66, 127.99, 122.90, 122.69, 119.91, 115.05, 111.35, 79.90, 78.87, 68.05, 53.70, 50.70, 24.24, 17.00, -6.72, -6.80.

IR ($\tilde{\nu}$ /cm^{-1}): 2948, 2929, 1729, 1650, 1599, 1523, 1457, 1429, 1347, 1260, 1194, 1157, 1081, 1011.

HRMS (ESI): calcd. for $C_{34}H_{37}N_4O_8Si$ $[M+H]^+$ 657.2375; found 657.2373.

2.10 (1*S*,2*S*,2a^1*R*,9b*R*)-Methyl 4-amino-5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,9b-tetrahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (18)



17 **18**

To a solution of phenol **17** (545 mg; 1.07 mmol) in dry DMF were added Cs_2CO_3 (523 mg; 1.60 mmol; 1.5 eq), benzyl bromide (140 µL; 1.18 mmol; 1.1 eq) and TBAI (80.0 mg; 20 mol%). The reaction mixture was stirred at room temperature for 30 minutes. The mixture was diluted with ether, washed with water and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by flash chromatography, to yield (428 mg; 67%) of benzyl ether **18**, as a yellowish foam.

R_f = 0.30 (30% EtOAc in hexanes).

$[\alpha]_D^{23}$ = −166.9° (c = 0.35, MeOH).

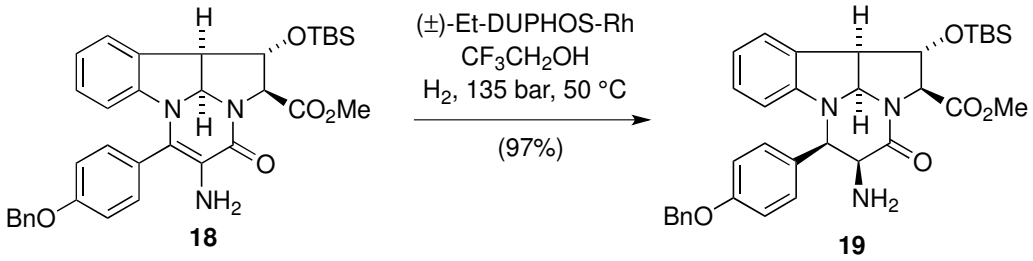
^{1}H NMR (400 MHz, CD_3OD): δ 7.75 (d, *J* = 8.9, 2H), 7.47 (d, *J* = 8.5, 2H), 7.39 (t, *J* = 7.9, 2H), 7.35 – 7.30 (m, 1H), 7.14 – 7.10 (m, 3H), 6.85 (t, *J* = 7.7, 1H), 6.75 (t, *J* = 7.8, 1H), 5.88 (d, *J* = 7.9, 1H), 5.81 (d, *J* = 6.2, 1H), 5.16 (s, 2H), 4.89 (s, 1H), 4.51 (s, 1H), 3.99 (d, *J* = 6.2, 1H), 3.66 (s, 1H) 3.17 (s, 3H), 1.01 (s, 9H), 0.30 (s, 3H), 0.28 (s, 3H).

^{13}C NMR (100 MHz, CD_3OD): δ 169.4, 164.0, 160.6, 150.3, 138.4, 131.5, 129.8, 129.7, 129.6, 129.0, 128.7, 128.3, 127.2, 126.1, 125.5, 121.9, 116.6, 113.2, 81.9, 80.9, 71.1, 70.0, 55.7, 52.7, 26.2, 19.0, -4.7, -4.8.

IR ($\tilde{\nu}$ /cm^{-1}): 3357, 2950, 2925, 2853, 1758, 1731, 1656, 1601, 1573, 1507, 1475, 1459, 1432, 1361, 1299, 1245, 1222, 1169, 1086, 1005.

HRMS (ESI): calcd. for $C_{34}H_{40}N_3O_5Si$ $[M+H]^+$ 598.2732; found 598.2726.

2.11 (1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-Methyl 4-amino-5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (19)



A solution of enamine **18** (100 mg; 0.168 mmol) in trifluoroethanol (5 mL) was degassed with argon and (±)-1,2-bis(2,5-diethylphospholano)benzene)1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (11.1 mg; 10 mol%) was added. After additional 5 minutes of argon bubbling, the mixture was transferred in a high pressure autoclave. The reaction mixture was stirred for 10 h under hydrogen (125 bar), at 50 °C. The solvent was removed on rotovap and the residue was purified by column chromatography (100% EtOAc → 5% MeOH in EtOAc), to give 98.0 mg (97%) of amine **19**, as a colorless oil.

R_f = 0.10 (100% EtOAc).

$[\alpha]_D^{23}$ = 79.0° (c = 0.20, MeOH).

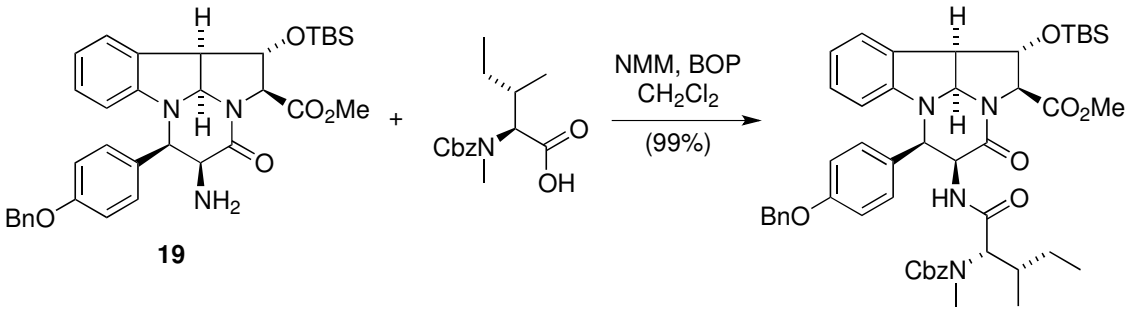
^{1}H NMR (500 MHz, CD_3OD): δ 7.42 (d, *J* = 8.8, 2H), 7.36 (t, *J* = 7.8, 2H), 7.32 – 7.26 (m, 3H), 7.10 (d, *J* = 7.4, 1H), 6.92 (d, *J* = 7.8, 2H), 6.71 (t, *J* = 7.5, 1H), 6.57 (t, *J* = 7.8, 1H), 5.90 (d, *J* = 8.3, 1H), 5.47 (d, *J* = 8.0, 1H), 5.11 (d, *J* = 7.4, 1H), 5.06 (s, 2H), 4.76 – 4.73 (m, 1H), 4.28 (d, *J* = 4.3, 1H), 4.23 (d, *J* = 7.4, 1H), 3.82 (dd, J_1 = 8.2, J_2 = 3.3, 1H), 3.66 (s, 3H), 0.99 (s, 9H), 0.22 (s, 3H), 0.15 (s, 3H).

^{13}C NMR (125 MHz, CD_3OD): δ 171.5, 170.5, 160.4, 149.1, 138.6, 129.6, 129.5, 129.0, 128.9, 128.6, 128.0, 127.6, 125.1, 118.9, 115.8, 112.2, 84.5, 78.1, 71.0, 68.4, 63.3, 56.5, 55.9, 53.0, 26.2, 18.8, -4.5, -4.6.

IR ($\tilde{\nu}$ /cm^{-1}): 3360, 3033, 2953, 2930, 2857, 1746, 1687, 1606, 1510, 1481, 1463, 1431, 1363, 1251, 1174, 1090, 1022.

HRMS (ESI): calcd. for $C_{34}H_{42}N_3O_5Si$ $[M+H]^+$ 600.2888; found 600.2889.

2.12 (1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-Methyl 4-((2*S*,3*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3-methylpentan amido)-5-(4-(benzyloxy)phenyl)-1-((*tert*-butyldimethylsilyl)oxy)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (20)



N-methymorpholine (150 µL; 1.33 mmol; 3 eq) was added to a solution of amine **19** (267 mg; 0.445 mmol), Cbz-*N*-Me-Ile-OH (162 mg; 0.579 mmol; 1.3 eq) and BOP (315 mg; 0.712 mmol; 1.6 eq) in dry dichloromethane (5 mL) and the mixture was stirred at room temperature for 3 h. The mixture was diluted with ether, washed with 1M HCl, saturated $NaHCO_3$ and brine. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (20% EtOAc in hexanes), to afford 379 mg (99%) of the peptide **20**, as a colorless viscous oil.

R_f = 0.30 (40% EtOAc in hexanes).

$[\alpha]_D^{23}$ = 113.3° (c = 0.10, MeOH).

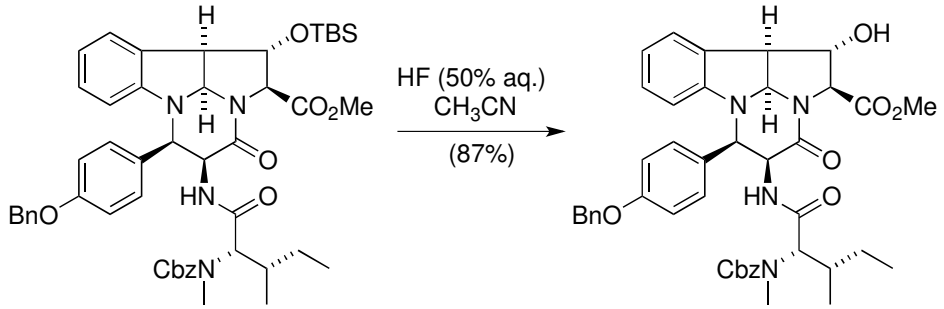
^{1}H NMR (500 MHz, DMSO-d_6, 333 K): δ 7.44 – 7.18 (m, 10H), 7.11 (d, *J* = 7.4, 1H), 7.04 (d, *J* = 8.8, 2H), 6.81 (d, *J* = 8.7, 2H), 6.73 (t, *J* = 7.6, 1H), 6.61 – 6.49 (m, 2H), 6.01 (d, *J* = 8.6, 1H), 5.47 (d, *J* = 7.9, 1H), 5.31 (d, *J* = 7.5, 1H), 5.23 (t, *J* = 7.0, 1H), 5.10 – 4.89 (m, 4H), 4.68 – 4.62 (m, 1H), 4.19 (d, *J* = 5.0, 1H), 4.16 (d, *J* = 10.9, 1H), 3.83 (dd, J_1 = 8.5, J_2 = 3.8 Hz, 1H), 3.64 (s, 3H), 2.82 (s, 3H), 2.04 – 1.90 (m, 1H), 1.38 – 1.14 (m, 2H), 0.96 (s, 9H), 0.84 – 0.73 (m, 6H), 0.18 (s, 3H), 0.11 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6, 333 K): δ 168.8, 168.4, 164.6, 158.0, 155.6, 147.2, 136.8, 136.5, 130.1, 128.0, 127.5, 127.4, 127.3, 127.2, 126.8, 126.8, 126.4, 123.7, 117.2, 114.1, 109.9, 83.0, 75.8, 69.1, 66.2, 66.2, 61.8, 58.0, 53.6, 53.0, 51.9, 31.4, 29.4, 25.3, 23.9, 17.3, 14.9, 9.7, -5.0, -5.2.

IR ($\tilde{\nu}$ /cm^{-1}): 3398, 3060, 3033, 2956, 2931, 2892, 2858, 1748, 1698, 1607, 1511, 1481, 1435, 1366, 1306, 1250.

HRMS (ESI): calcd. for $C_{49}H_{61}N_4O_8Si$ $[M+H]^+$ 861.4253; found 861.4261.

2.13 (1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-Methyl 4-((2*S*,3*S*)-2-(((benzyloxy)carbonyl)(methyl)amino)-3-methylpentan amido)-5-(4-(benzyloxy)phenyl)-1-hydroxy-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylate (21)



20 **21**

50% HF (1.5 mL) was added to a solution of peptide **20** (380 mg; 0.441 mmol) in MeCN (4 mL) in a polyethylene vessel, and the reaction mixture was stirred 1h at 45 °C. The reaction mixture was diluted with ether, washed with saturated $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, filtered and concentrated in *vacuo*. The crude product was purified by column chromatography (50% EtOAc in hexanes), to afford 292 mg (87%) of alcohol **21**, as a colorless oil.

R_f = 0.30 (50% EtOAc in hexanes).

$[\alpha]_D^{23}$ = 149.2° (c = 0.50, MeOH).

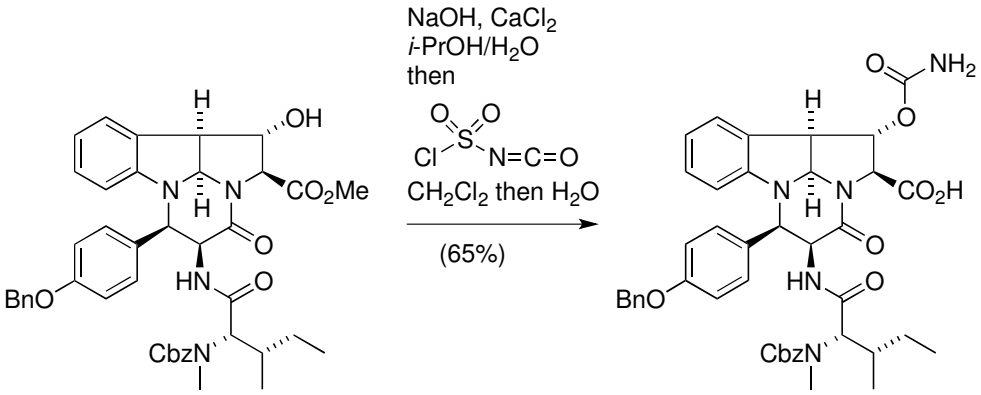
^{1}H NMR (500 MHz, DMSO-d_6, 333 K): δ 7.44 – 7.23 (m, 10H), 7.17 (d, *J* = 7.2, 1H), 7.05 (d, *J* = 8.6, 2H), 6.80 (d, *J* = 8.5, 2H), 6.71 (t, *J* = 7.6, 1H), 6.54 (t, *J* = 7.3, 2H), 6.20 (d, *J* = 5.3, 1H), 5.97 (d, *J* = 8.6, 1H), 5.47 (d, *J* = 7.5, 1H), 5.32 (d, *J* = 7.3, 1H), 5.21 (t, *J* = 6.8, 1H), 4.99 (s, 3H), 4.50 (d, *J* = 4.7, 1H), 4.16 (d, *J* = 5.5, 2H), 3.78 (dd, J_1 = 8.4, J_2 = 4.3, 1H), 3.63 (s, 3H), 2.83 (s, 3H), 1.98 (br s, 1H), 1.35 – 1.27 (m, 1H), 1.00 – 0.91 (m, 1H), 0.86 – 0.75 (m, 6H).

^{13}C NMR (125 MHz, DMSO-d_6, 333 K): δ 168.9, 168.6, 164.5, 157.9, 155.4 (detected by HMBC), 146.9, 136.8, 136.5, 130.1, 128.0 (2 signals), 127.8, 127.4, 127.3, 127.2, 126.8 (2 signals), 126.5, 123.8, 117.1, 114.0, 109.6, 82.0, 75.7, 69.1, 66.2, 65.5, 61.8, 58.0, 53.0, 52.9, 51.8, 31.5, 29.4, 23.9, 14.9, 9.7.

IR ($\tilde{\nu}$ /cm^{-1}): 3395, 2962, 1748, 1692, 1671, 1607, 1512, 1480, 1439, 1401, 1370, 1308, 1242, 1175, 1114.

HRMS (ESI): calcd. for $C_{43}H_{46}N_4O_8Si$ $[M+Na]^+$ 769.3208; found 769.3189.

2.14 (1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-4-((2*S*,3*S*)-2-(((Benzyloxy)carbonyl)(methyl)amino)-3-methylpentanamido)-5-(4-(benzyloxy)phenyl)-1-(carbamoyloxy)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta[*jk*]fluorene-2-carboxylic acid (22)



A solution of NaOH (13.4 mg/1 mL H_2O; 0.335 mmol; 2.5 eq) was added to methylester **21** (100 mg; 0.134 mmol), dissolved in $CaCl_2$ solution (0.8 M $CaCl_2$ in *i*-PrOH/H_2O 7:3; 10 mL). The mixture was stirred for 4 h, before it was acidified with 1M HCl solution and extracted with EtOAc (50 mL). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated, to give free acid as a colorless solid (90.5 mg; 92%). The crude acid was dissolved in CH_2Cl_2 (6 mL), chlorosulfonylisocyanate (21.5 µL; 0.250 mmol) was added and the mixture was stirred for 15 min at room temperature. THF (10 mL) and H_2O (10 mL) were added and the mixture was stirred for 10 min at room temperature. The product was extracted with EtOAc (10 mL), washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by three column chromatographies (1. 0.4 % formic acid in EtOAc; 2. 100 % EtOAc→ 0.4 % formic acid in EtOAc; 3. 50% EtOAc in hexanes → 0.4 % formic acid in EtOAc), to yield 62 mg (65%) of carbamate **22**, as a white solid.

$[\alpha]_D^{23}$ = 95.6° (c = 0.52, MeOH).

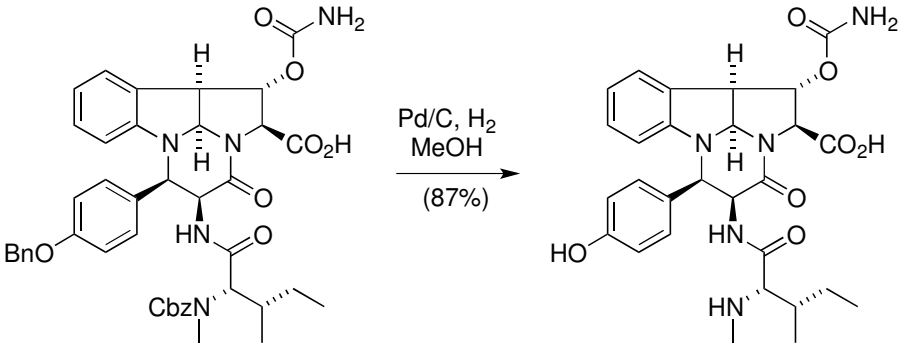
^{1}H NMR (500 MHz, DMSO-d_6, 333 K): δ 7.41 – 7.22 (m, 10H), 7.24 (d, *J* = 7.2, 1H), 7.17 (d, *J* = 8.5, 2H), 6.75 (d, *J* = 7.4, 2H), 6.68 (t, *J* = 7.7, 1H), 6.55 (t, *J* = 7.2, 1H), 6.48 (d, *J* = 5.8, 1H), 5.99 (d, *J* = 8.5, 1H), 5.46 – 5.32 (m, 3H), 5.27 (t, *J* = 6.9, 1H), 5.01 – 4.96 (m, 4H), 4.28 (d, *J* = 3.9, 1H), 4.14 (d, *J* = 10.3, 1H), 3.98 (d, *J* = 8.3, 1H), 2.80 (s, 3H), 1.98 – 1.94 (m, 1H), 1.33 – 1.26 (m, 1H), 0.96 – 0.92 (m, 1H), 0.82 – 0.76 (m, 6H).

^{13}C NMR (125 MHz, DMSO, 333 K): δ 168.9, 168.8, 164.8, 157.9, 156.8, 155.2, 147.6, 136.8, 136.5, 130.6, 128.0, 128.0, 127.4, 127.4, 127.2, 127.2, 126.8, 126.2, 126.0, 124.5, 117.5, 113.9, 110.5, 81.8, 75.8, 69.1, 66.2, 64.1, 61.9, 58.6, 53.2, 51.7, 31.4, 29.4, 23.9, 14.9, 9.7.

IR ($\tilde{\nu}$ /cm^{-1}): 3394, 3193, 3063, 3034, 2964, 2931, 2878, 2502, 2257, 2127, 1736, 1693, 1607, 1512, 1480, 1441, 1390, 1311, 1244, 1180, 1154.

HRMS (ESI): calcd. for $C_{43}H_{45}N_5O_9Na$ [M+Na]$^+$ 798.3109; found 798.3093.

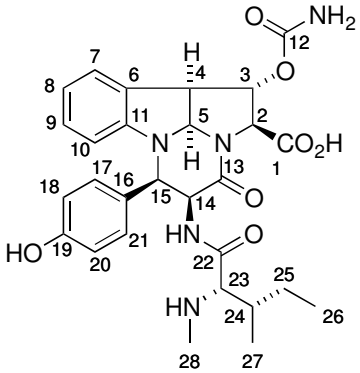
2.15 (1*S*,2*S*,2a^1*R*,4*S*,5*R*,9b*R*)-1-(Carbamoyloxy)-5-(4-hydroxyphenyl)-4-((2*S*,3*S*)-3-methyl-2-(methylamino)pentanamido)-3-oxo-2,2a^1,3,4,5,9b-hexahydro-1*H*-2a,5a-diazacyclopenta [*jk*]fluorene-2-carboxylic acid (Crocagin A, 1)



22 **1**

10 % palladium on charcoal (16.5 mg) was added to a solution of benzylether **22** (30.0 mg; 0.0387 mmol) in methanol (3 mL) and the mixture was stirred for 1.5 h under 1 atm of hydrogen. The mixture was diluted with EtOAc (15 mL) and filtered through a pad of celite. The filtrate was evaporated to dryness, to afford 18.2 mg (87%) of crocagin A (**1**) in a virtually pure form (white amorphous solid).

$[\alpha]_D^{24}$ = +93.6° (c = 0.16, MeOH).[1]



^{1}H NMR (700 MHz, DMSO-*d*$_6$)*: δ 9.30 (br s, 1H, phenolic OH), 8.04 (br s, 1H, N*H*Me), 7.24 (d, *J* = 6.7, 1H, N*H*CO), 7.18 (d, *J* = 7.3, 1H, H-7), 6.96 (br s, 2H, CON*H*$_2$), 6.58 (br s, 2H, H-18/20), 6.56 (t, *J* = 7.3, 1H, H-9), 6.46 (br s, 2H, H-17/21), 6.44 (t, *J* = 7.5, 1H, H-8), 5.82 (d, *J* = 8.3, 1H, H-5), 5.26 (s, 1H, H-3), 5.23 (d, *J* = 8.1, 1H, H-10), 5.09 (d, *J*

[1] The previously reported optical rotation value of the isolated crocagin A (K. Viehrig, F. Surup, C. Volz, J. Herrmann, A. A. Fayad, S. Adam, J. Köhnke, D. Trauner, R. Müller, *Angew. Chem. Int. Ed.* **2017**, *56*, 7407-7410.) turned out to be incorrect, due to minor impurities present in the isolated material. After thorough purification of the natural sample, $[\alpha]_D^{24}$ is +92.3° (c = 0.27, MeOH).

= 7.8, 1H, H-15), 5.06 (t, *J* = 6.9, 1H, H-14), 4.03 (s, 1H, H-2), 3.7 (d, *J* = 7.7, 1H, H-4), 2.59 (d, *J* = 5.0, 1H, H-23), 2.13 (s, 3H, H-28), 1.44 (m, 1H, H-24), 1.20 (m, 1H, H-25), 0.93 (m, 1H, H-25), 0.77 (t, *J* = 7.7, 3H, H-26), 0.71 (d, *J* = 6.9, 3H, H-27).

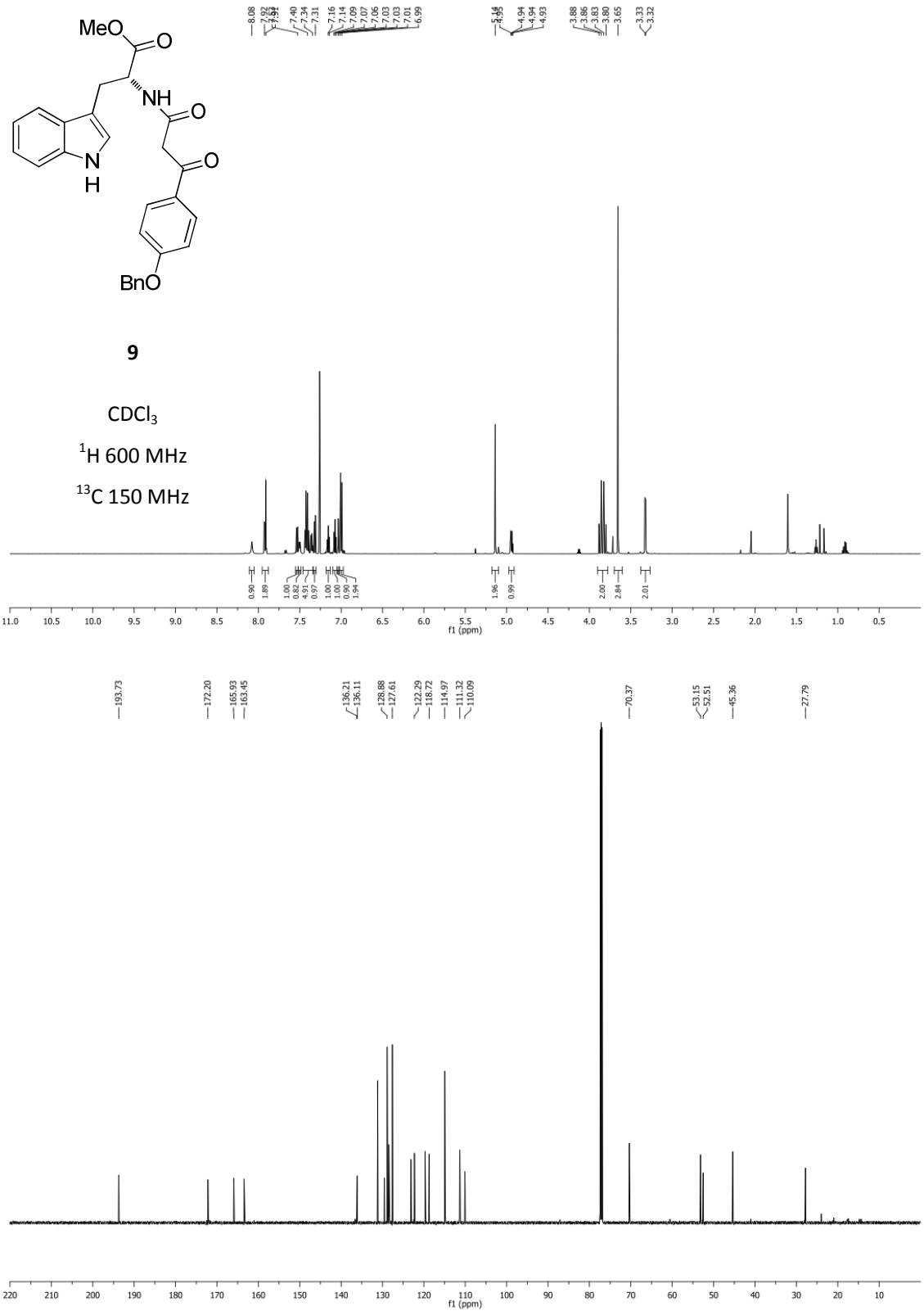
^{13}C NMR (175 MHz, DMSO-*d*$_6$)*: δ 172.4 (C-1), 169.0 (C-22), 164.7 (C-13), 156.7 (C-19), 156.2 (C-12), 148.6 (C-11), 132.1 (C-17/21), 126.8 (C-9), 126.7 (C-6), 124.9 (C-7), 124.6 (C-16), 116.9 (C-8), 115.7 (C-18/21), 110.5 (C-10), 83.7 (C-3), 75.9 (C-5), 69.6 (C-23), 67.9 (C-2), 60.4 (C-15), 53.1 (C-14), 52.3 (C-4), 37.5 (C-24), 35.5 (C-28), 24.3 (C-25), 15.6 (C-27), 11.8 (C-26).

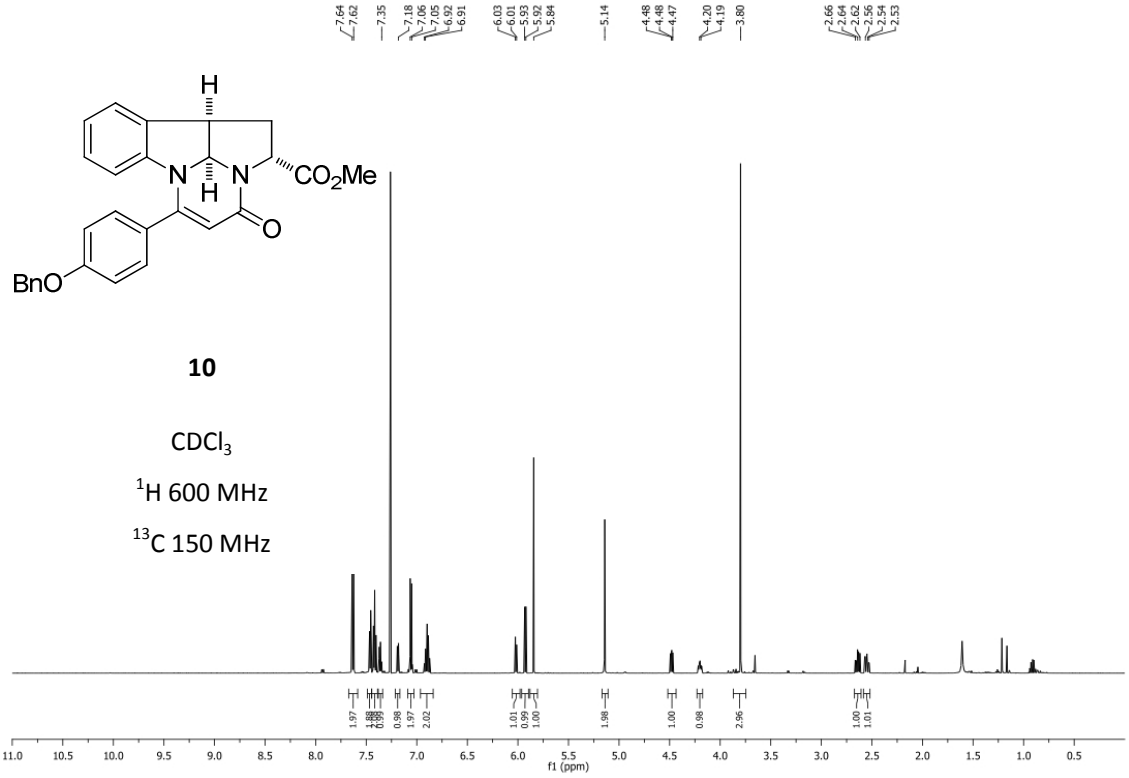
*Some chemical shifts in both ^{1}H and ^{13}C NMR spectra of the synthesized (see spectra on the page S34) and natural crocagin A (**1**) are not exactly the same (see the superposed spectra of the synthesized and natural product on the page S35), most probably due to slightly different pH values of the two samples (see the superposed spectra of the synthesized crocagin A in neutral, acidic and basic conditions on the page S36). However, no new signals (or signal duplication) appear after mixing the synthetic sample with natural crocagin A (**1**) (in 2:1 ratio), proofing that these two samples have the identical chemical structures (see the mixed NMR spectra on the page S37).

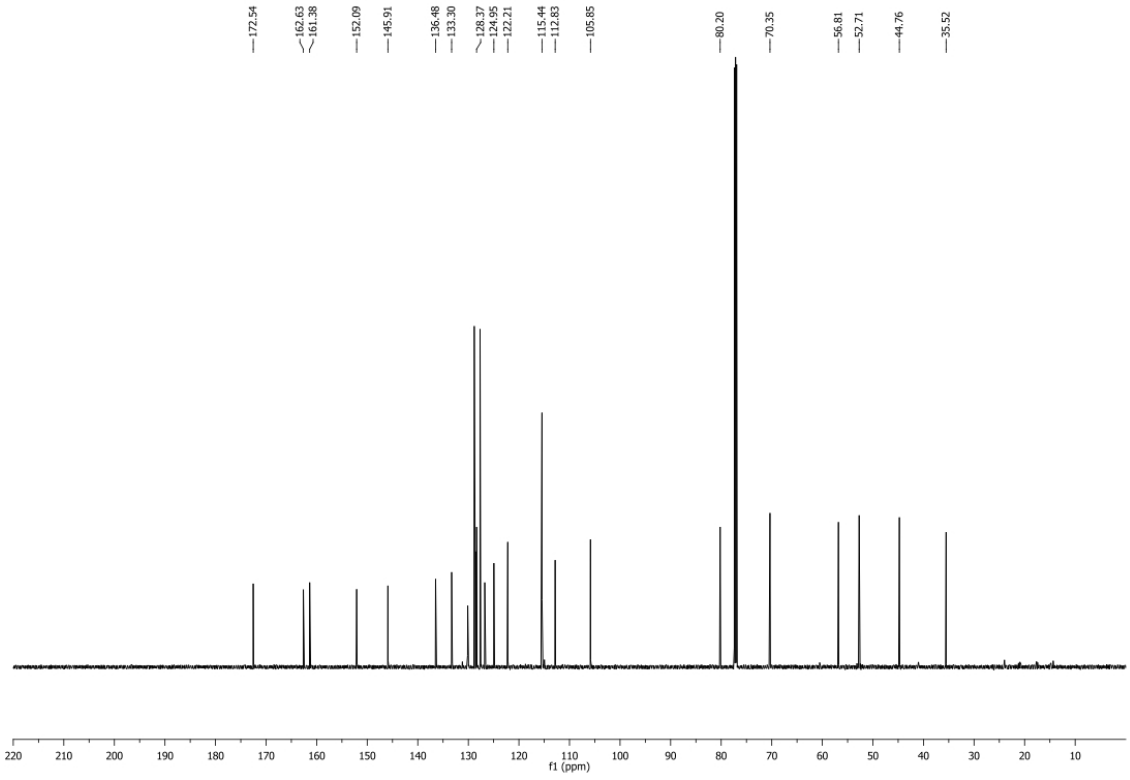
IR ($\tilde{\nu}$ /cm^{-1}): 3276, 3179, 2962, 2361, 1717, 1664, 1597, 1516, 1477, 1461, 1386, 1366, 1331, 1270, 1242, 1180, 1050.

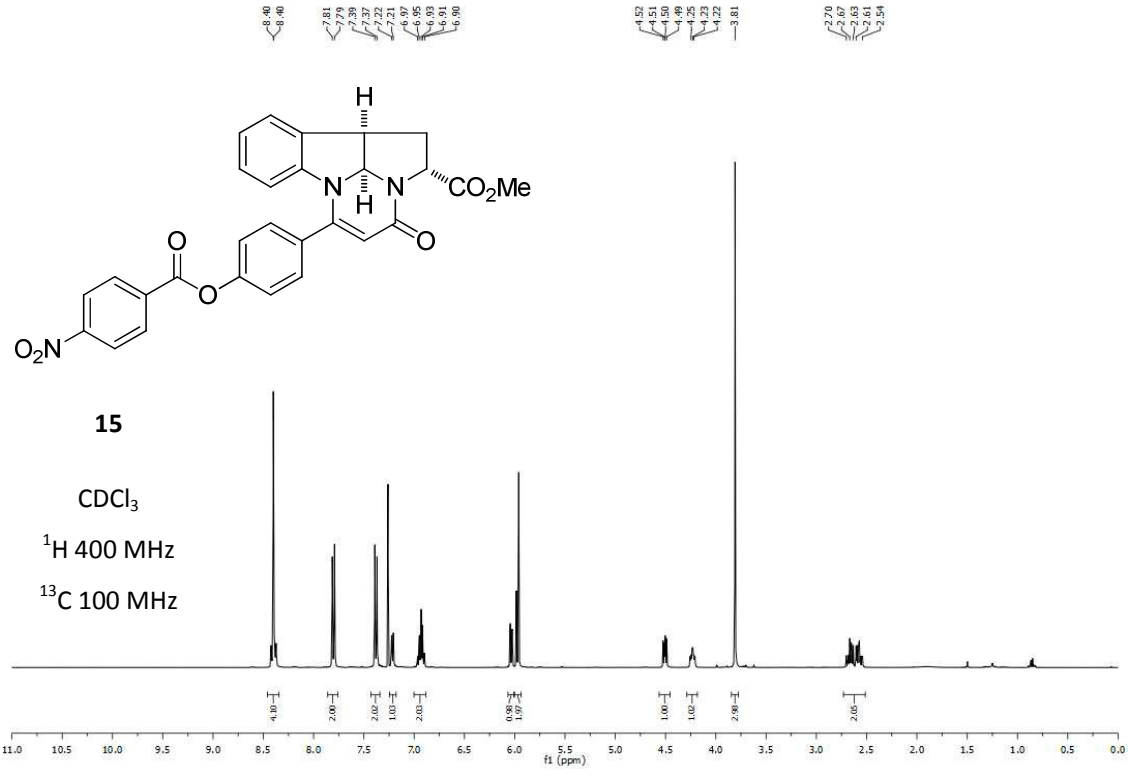
HRMS (ESI): calcd. for $C_{28}H_{34}N_5O_7$ $[M+H]^+$ 552.2453; found 552.2441.

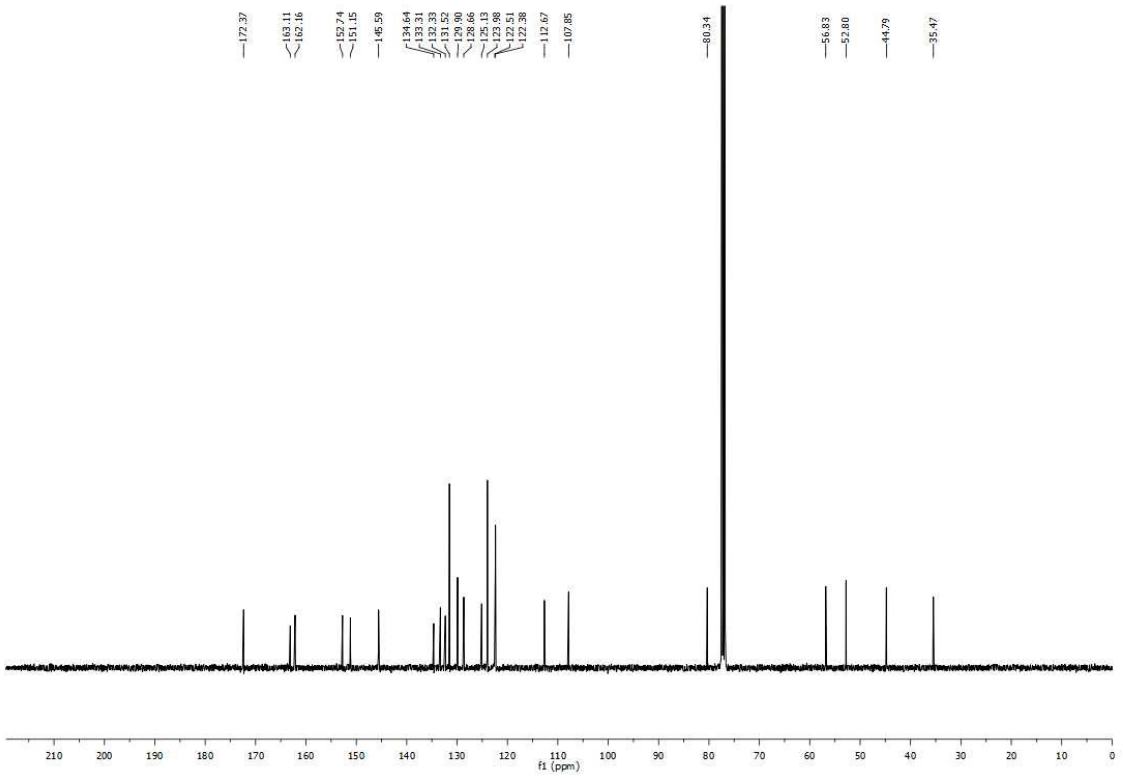
3 NMR Spectra

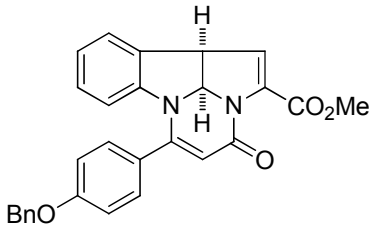



7.64
7.62
7.35
7.18
7.06
7.05
6.92
6.91
6.03
6.01
5.93
5.92
5.84
5.14
4.48
4.48
4.47
4.20
4.19
3.80
2.66
2.64
2.64
2.62
2.56
2.54
2.53
H
N
H
N
CO2Me
O
BnO
10
CDCl3
1H 600 MHz
13C 150 MHz
f1 (ppm)


172.54
162.63
161.38
152.09
145.91
136.48
133.30
128.37
124.95
122.21
115.44
112.83
105.85
80.20
70.35
56.81
52.71
44.76
35.52
f1 (ppm)


H
N
H
N
CO2Me
O
O
O
O2N
15
CDCl3
1H 400 MHz
13C 100 MHz
f1 (ppm)


f1 (ppm)

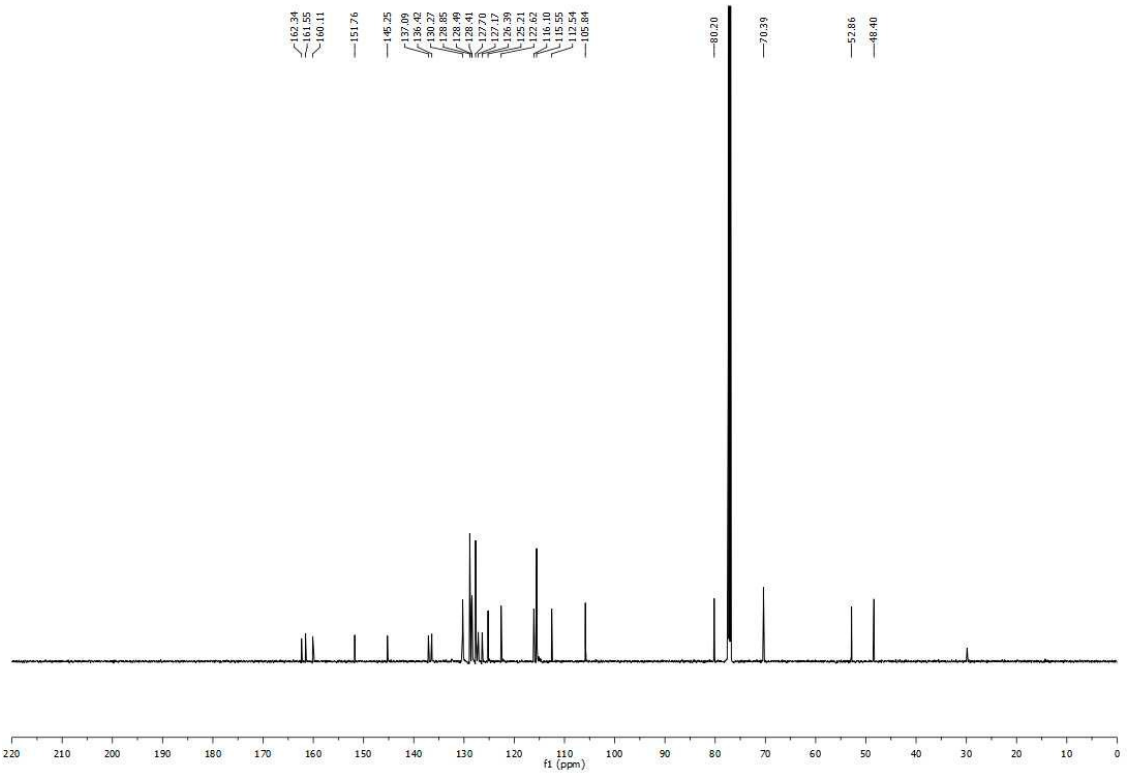


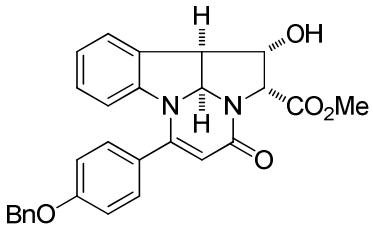
11

$CDCl_3$

^{1}H 600 MHz

^{13}C 150 MHz



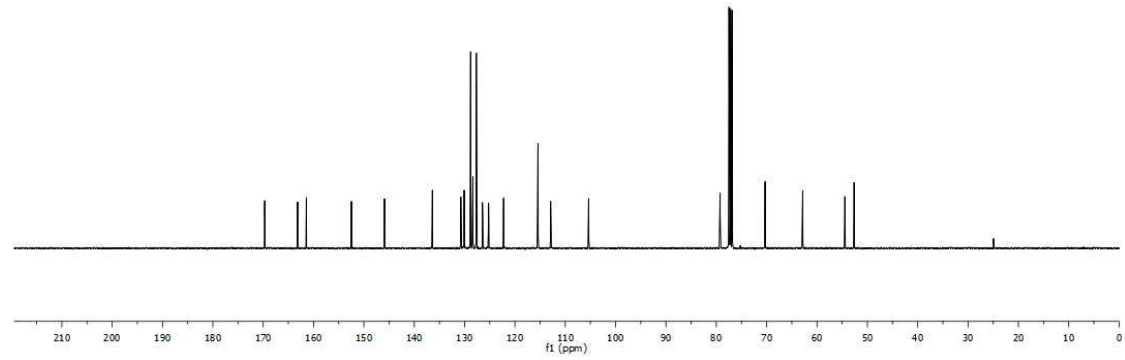


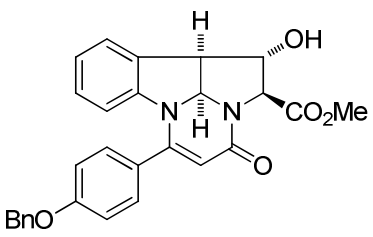
12

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



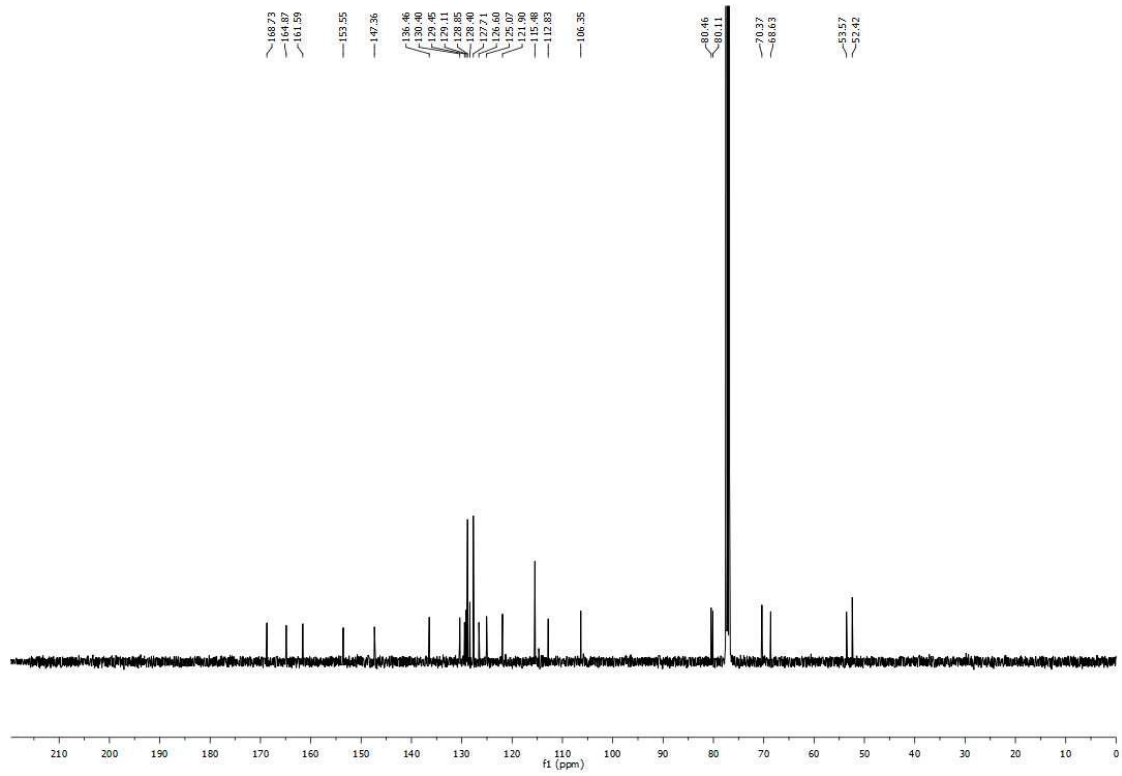


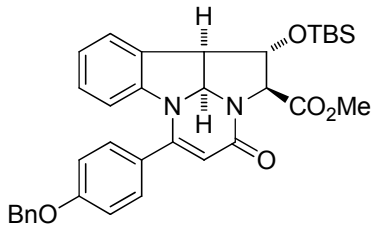
13

$CDCl_3$

^{1}H 400 MHz

^{13}C 100 MHz



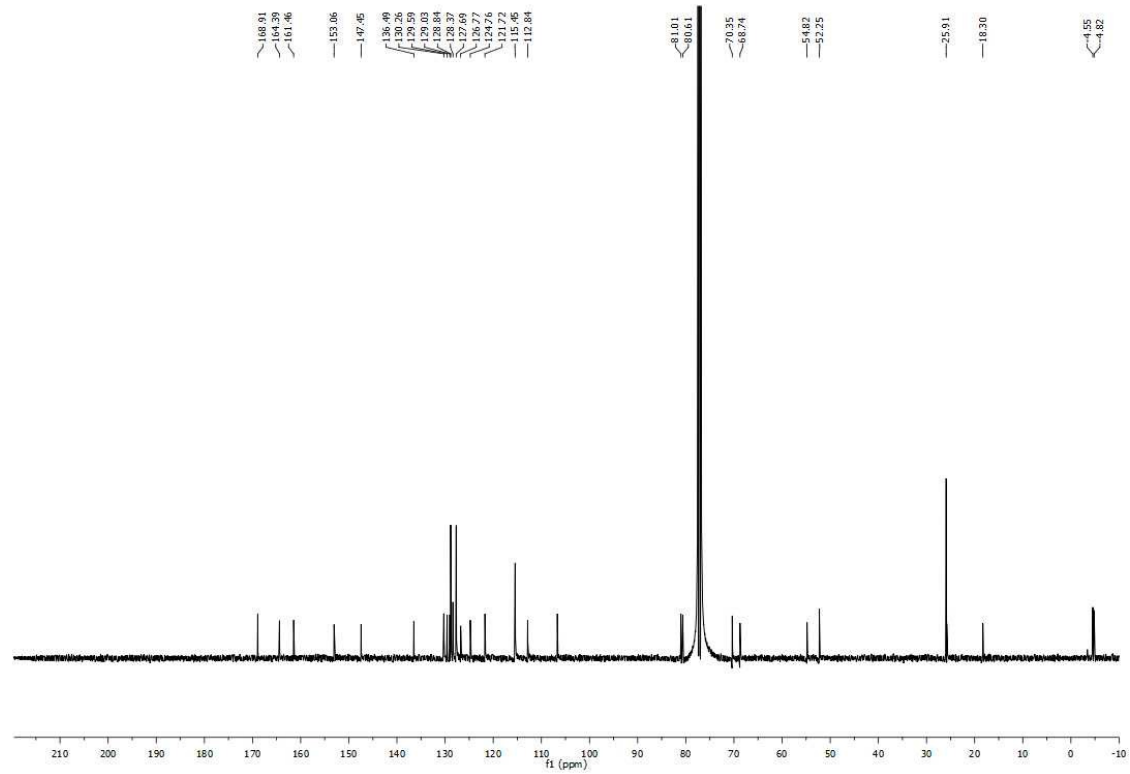


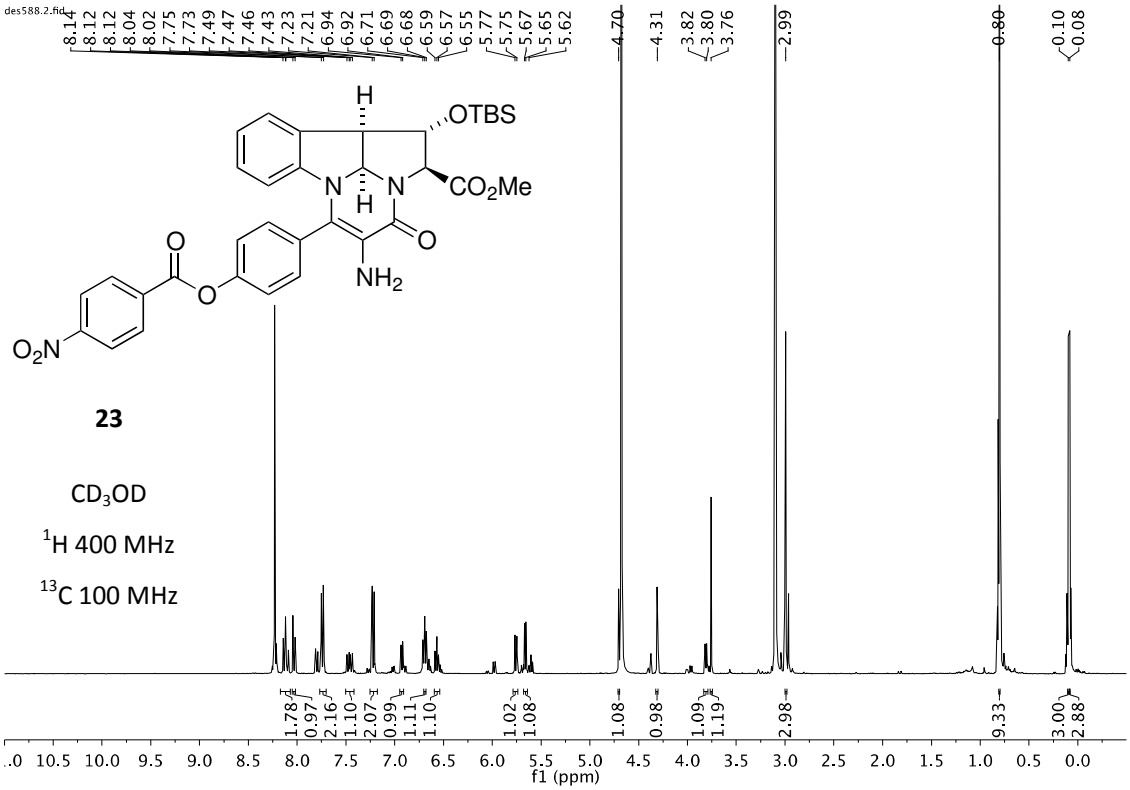
14

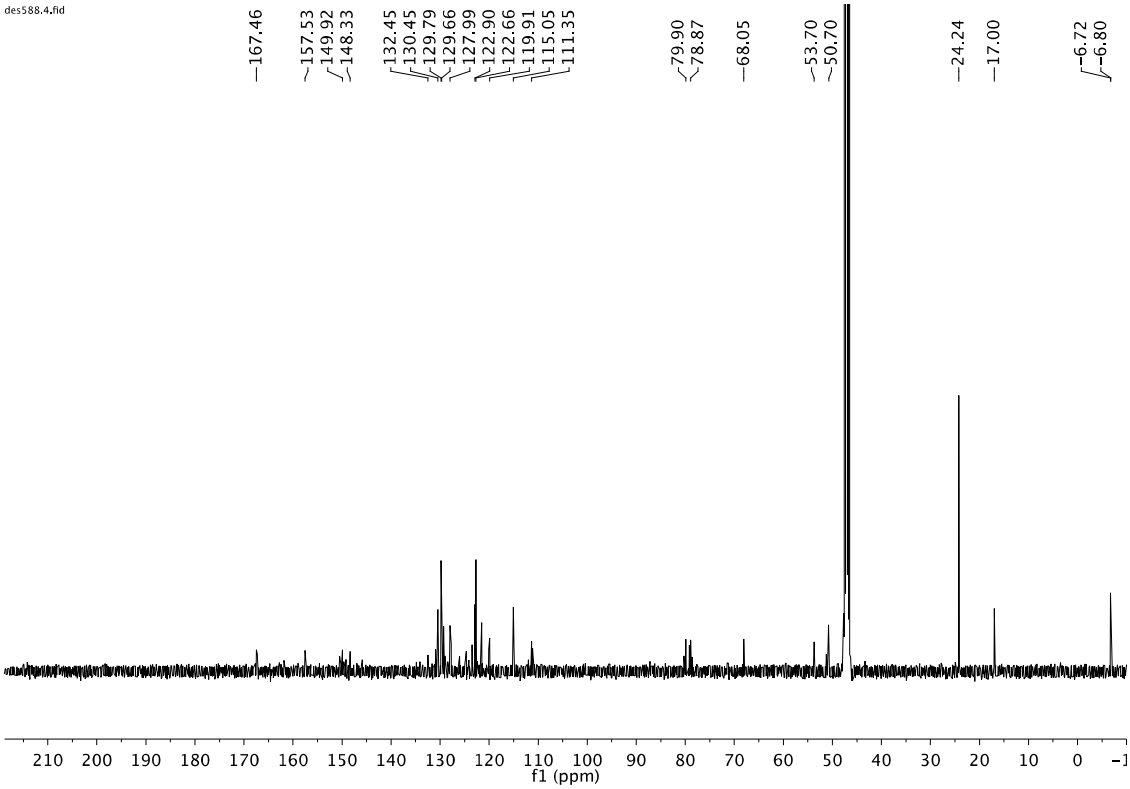
$CDCl_3$

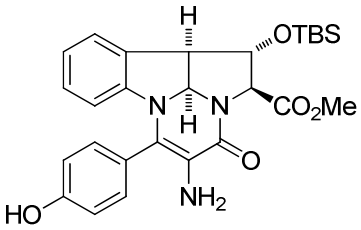
^{1}H 400 MHz

^{13}C 100 MHz




des588.2.fid
8.14
8.12
8.12
8.04
8.02
7.75
7.73
7.49
7.47
7.46
7.43
7.23
7.21
6.94
6.92
6.71
6.69
6.68
6.59
6.57
6.55
5.77
5.75
5.67
5.65
5.62
4.70
4.31
3.82
3.80
3.76
2.99
0.80
0.10
0.08
H
OTBS
N
N
H
CO2Me
O
O
NH2
O
O
O2N
23
CD3OD
1H 400 MHz
13C 100 MHz
1.78
0.97
2.16
1.10
2.07
0.99
1.11
1.10
1.02
1.08
1.08
0.98
1.09
1.19
2.98
9.33
3.00
2.88
f1 (ppm)


des588.4.fid
167.46
157.53
149.92
148.33
132.45
130.45
129.79
129.66
127.99
122.90
122.66
119.91
115.05
111.35
79.90
78.87
68.05
53.70
50.70
24.24
17.00
6.72
6.80
f1 (ppm)

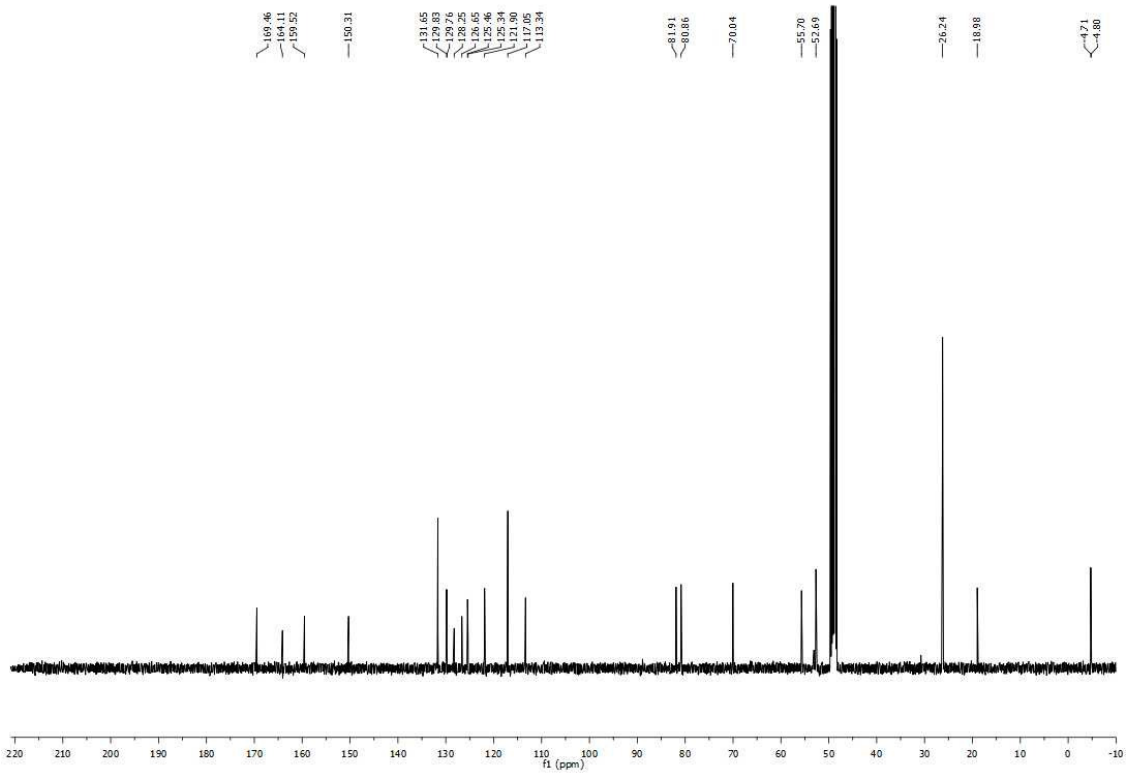


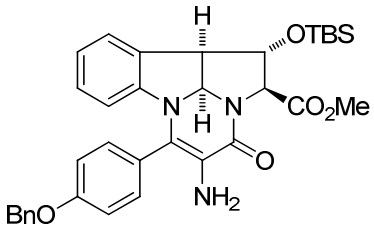
17

CD_3OD

^{1}H 400 MHz

^{13}C 100 MHz



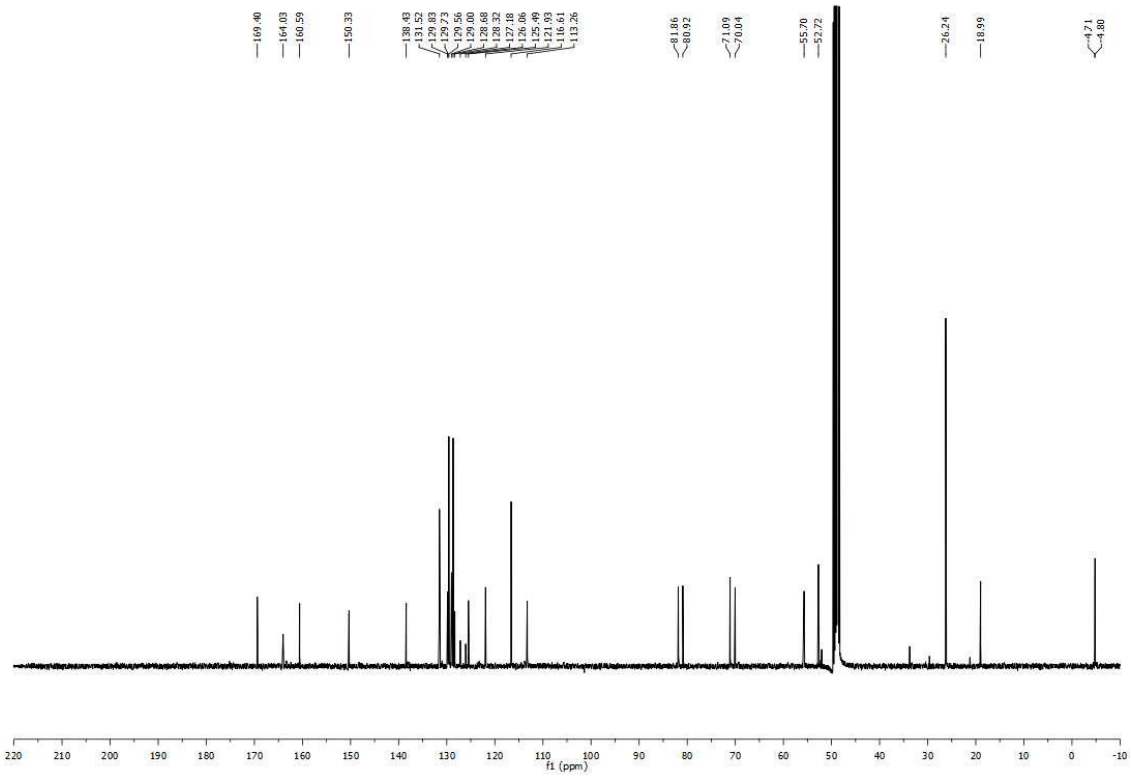


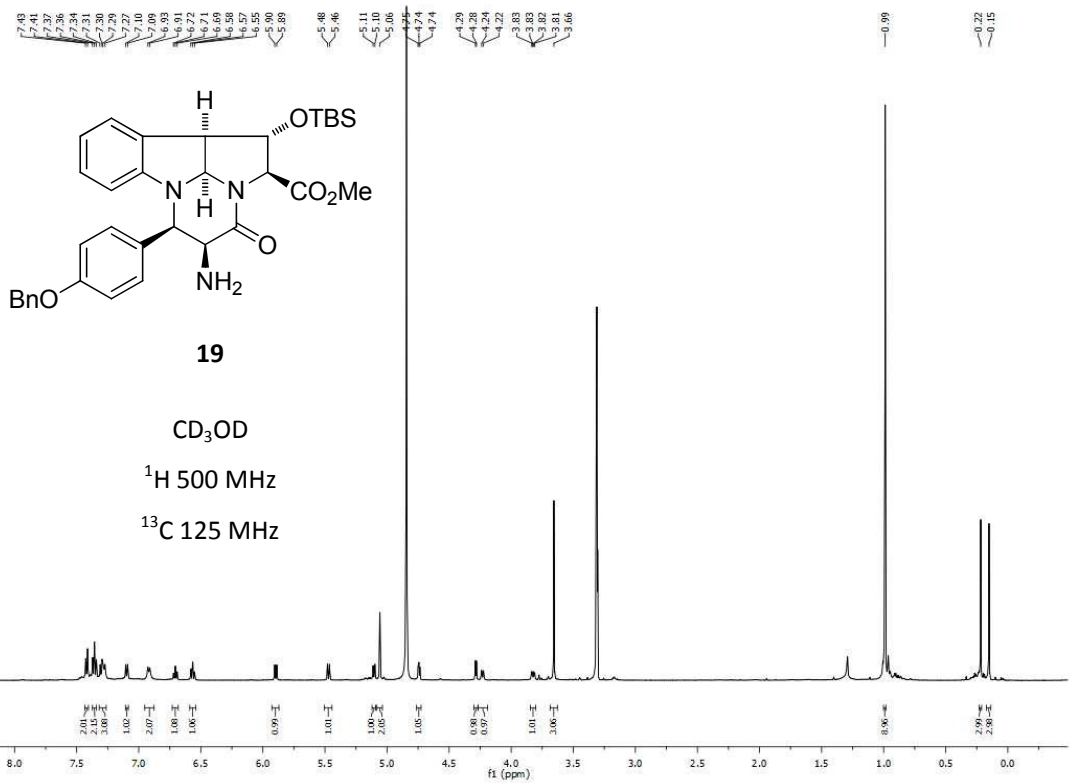
18

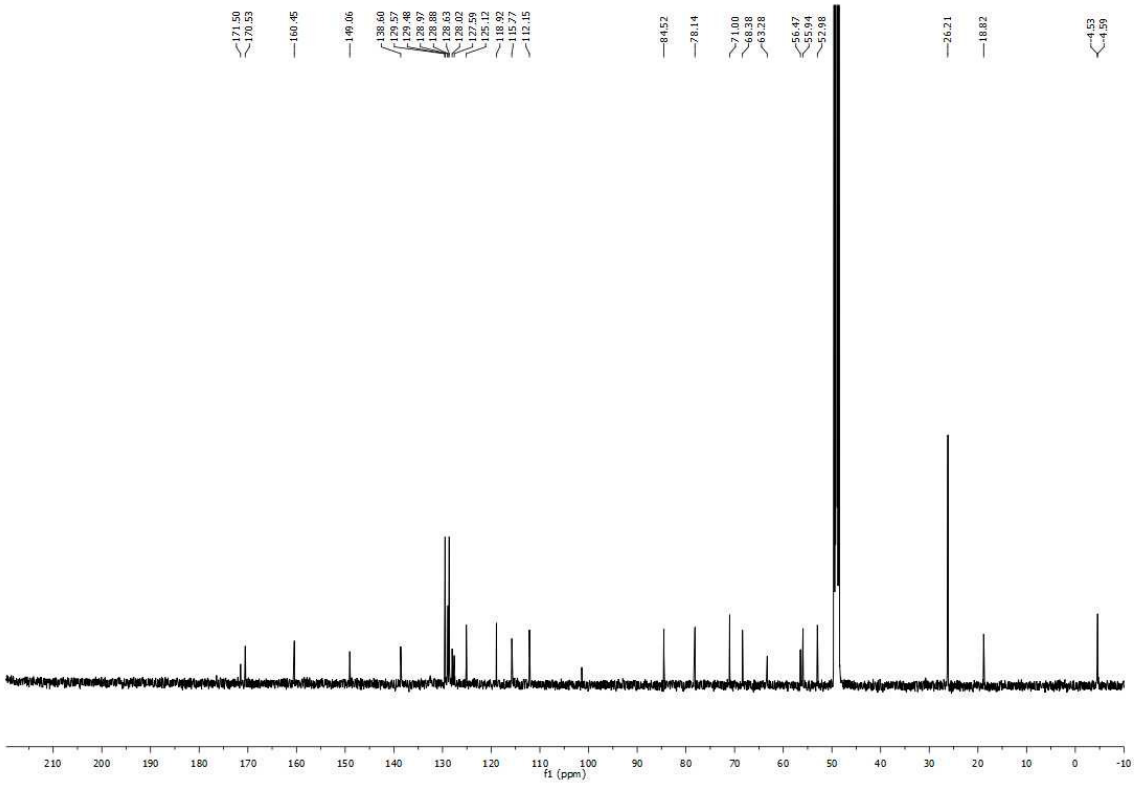
CD_3OD

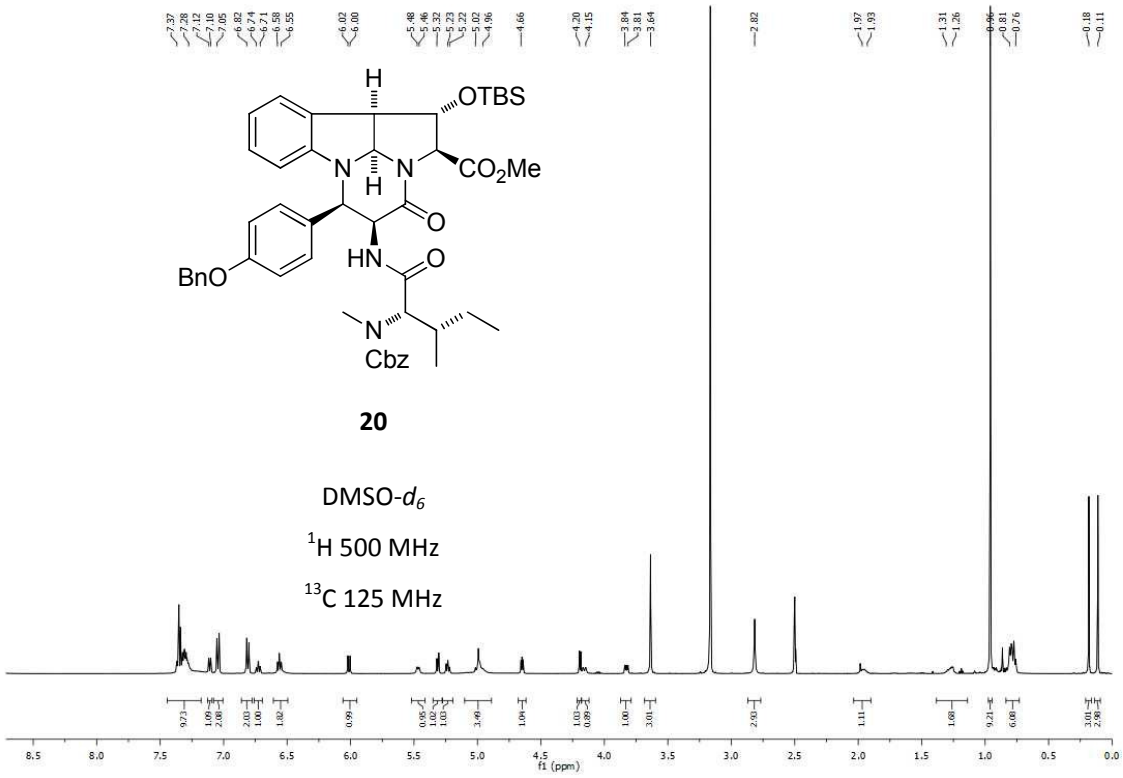
^{1}H 400 MHz

^{13}C 100 MHz




OTBS
CO2Me
NH2
BnO
19
CD3OD
1H 500 MHz
13C 125 MHz
f1 (ppm)


f1 (ppm)

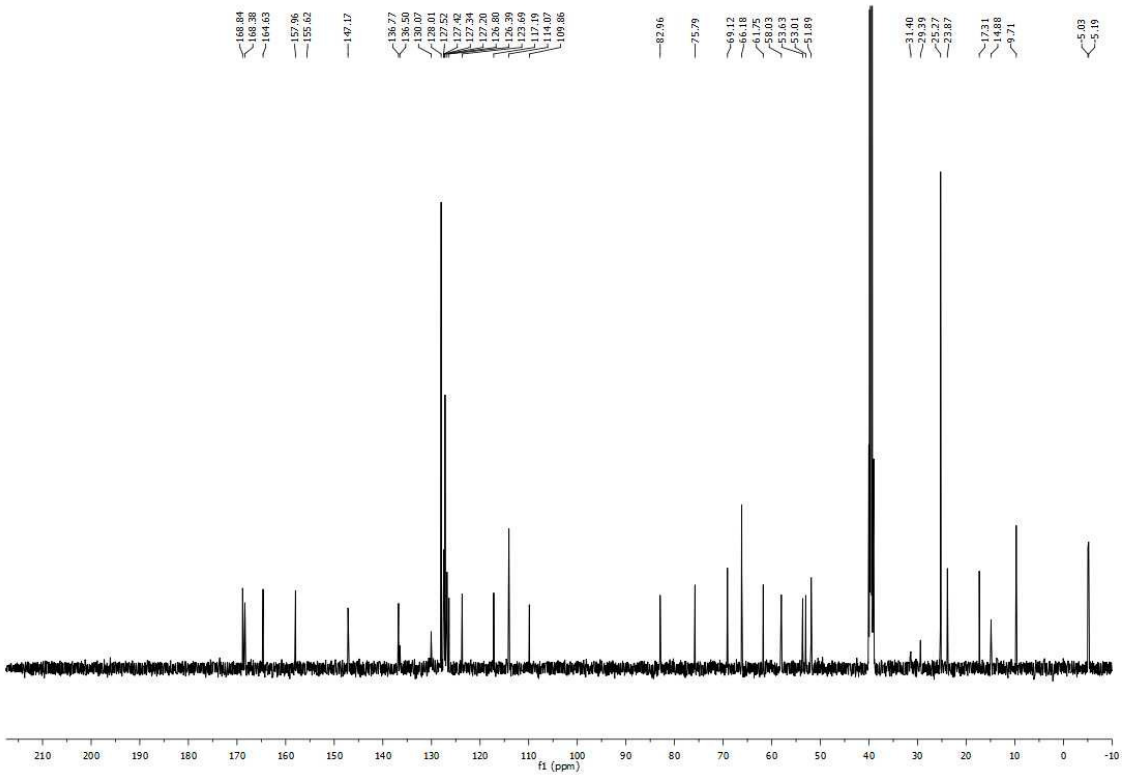


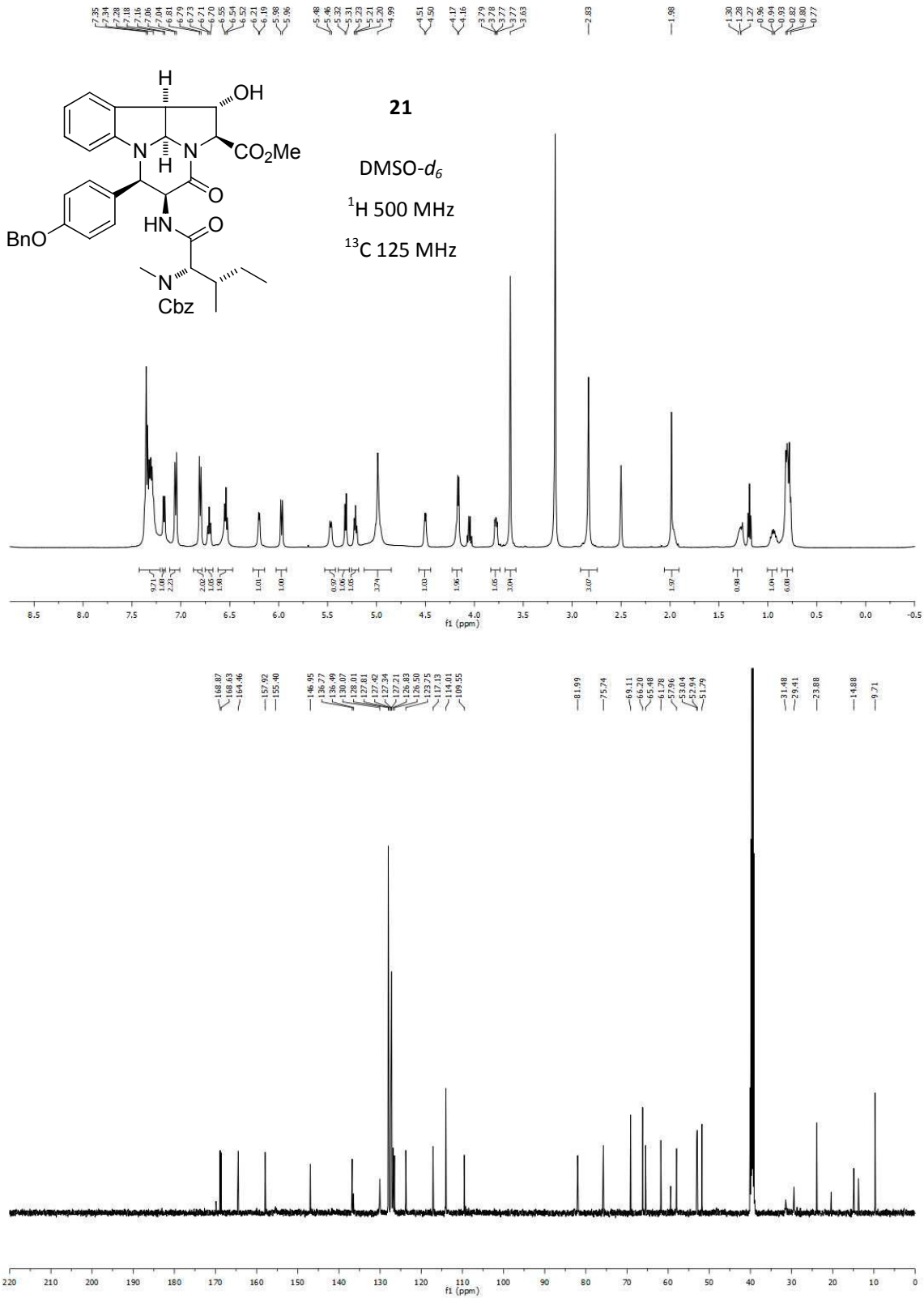
20

DMSO-d_6

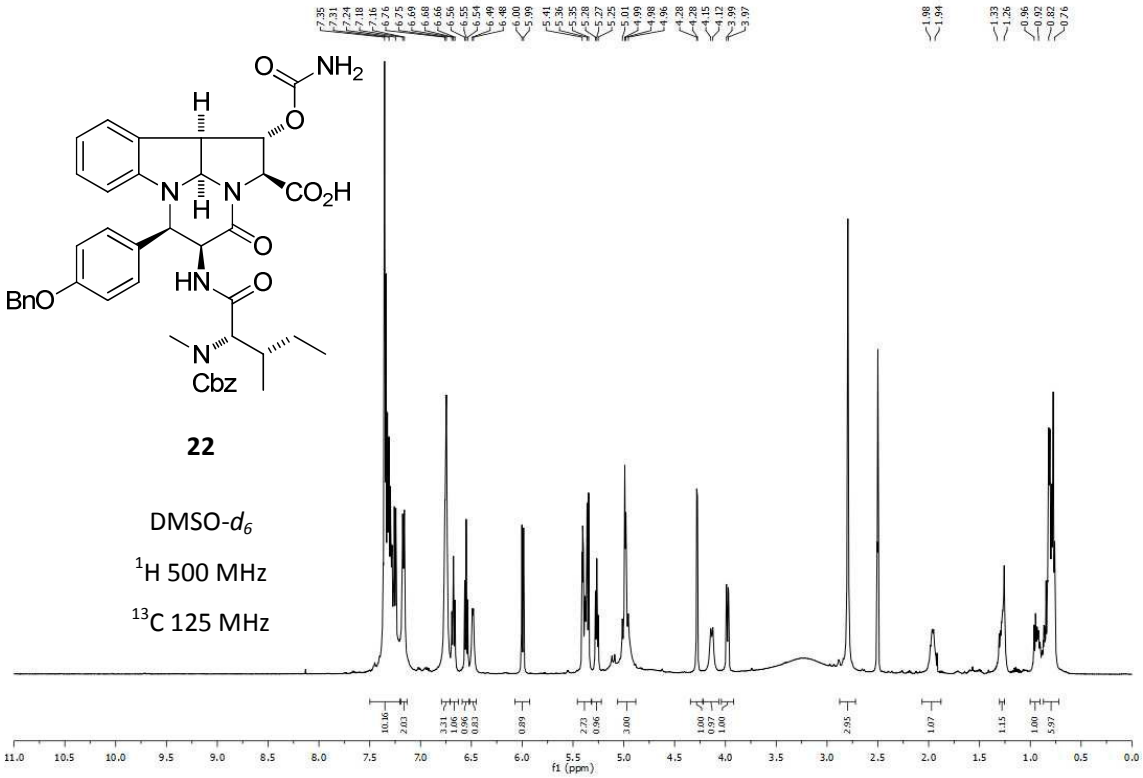
^{1}H 500 MHz

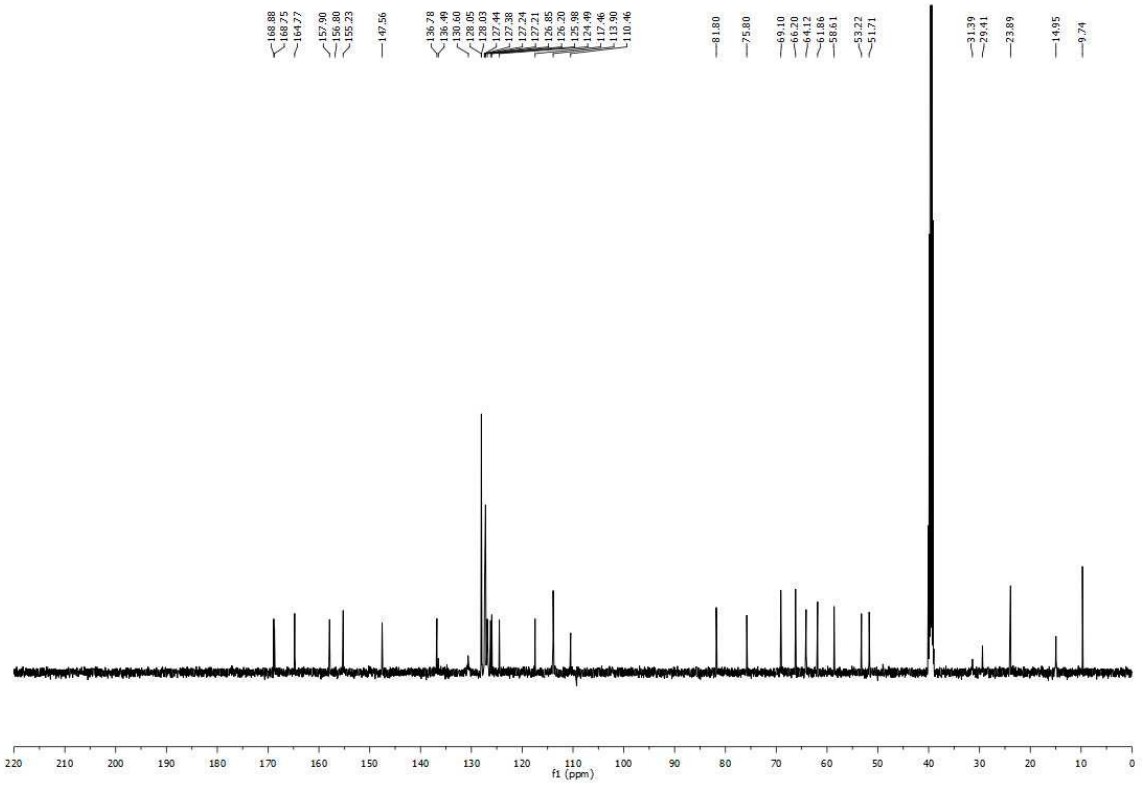
^{13}C 125 MHz





Inseparable from EtOAc, even after 2 days under vacuum of 10^{-3} mbar and coevaporation with toluene.

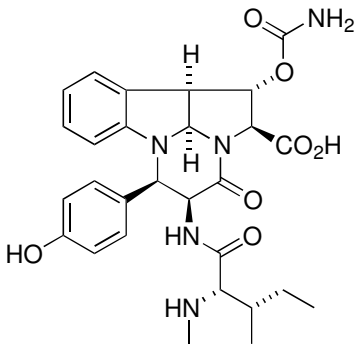

22
DMSO-d_6
^{1}H 500 MHz
^{13}C 125 MHz
f1 (ppm)

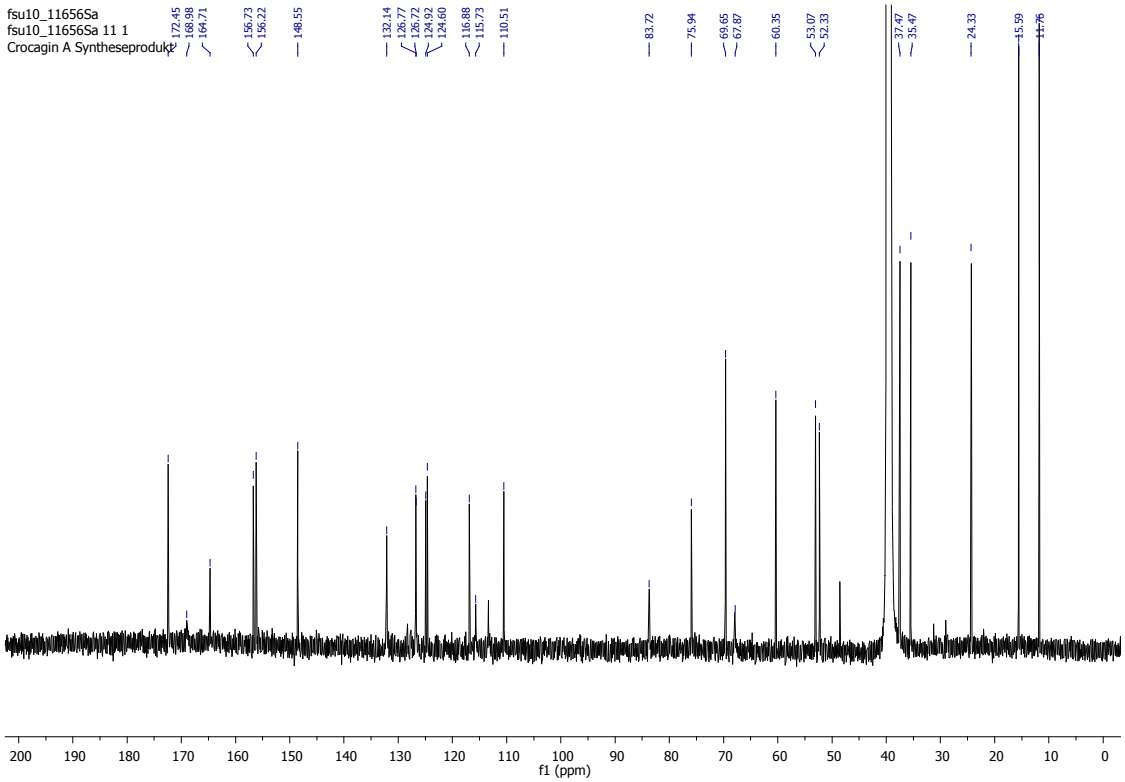

f1 (ppm)

Crocagin A (1)
(synthesized)
DMSO-d_6

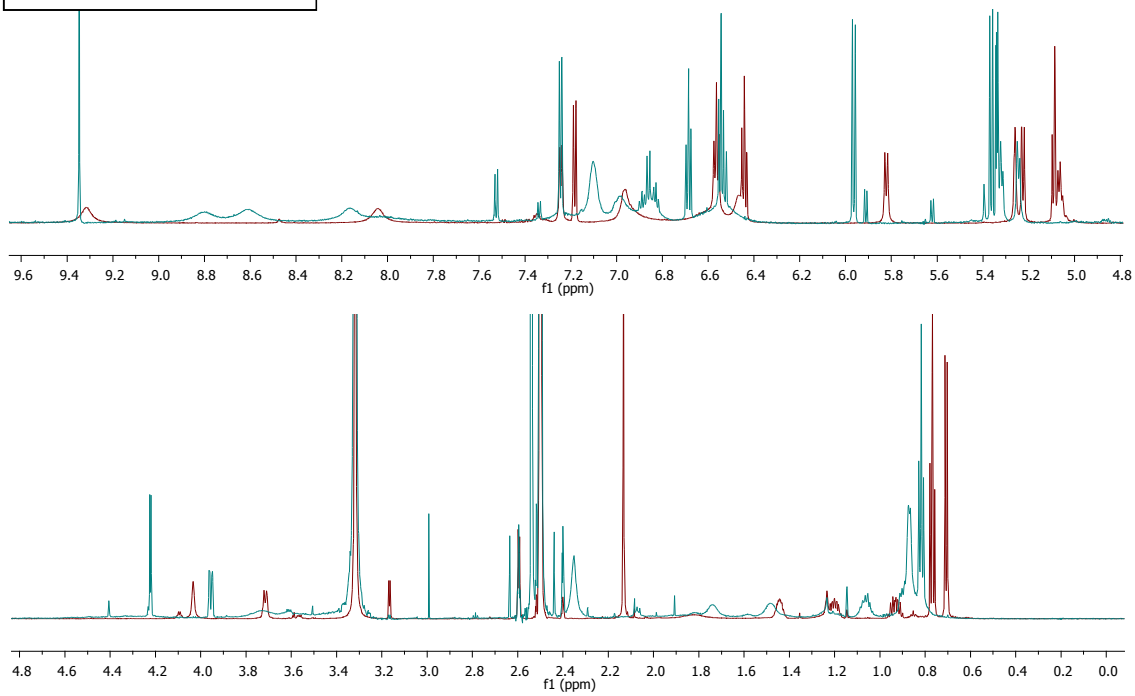
^{1}H 700 MHz

^{13}C 175 MHz

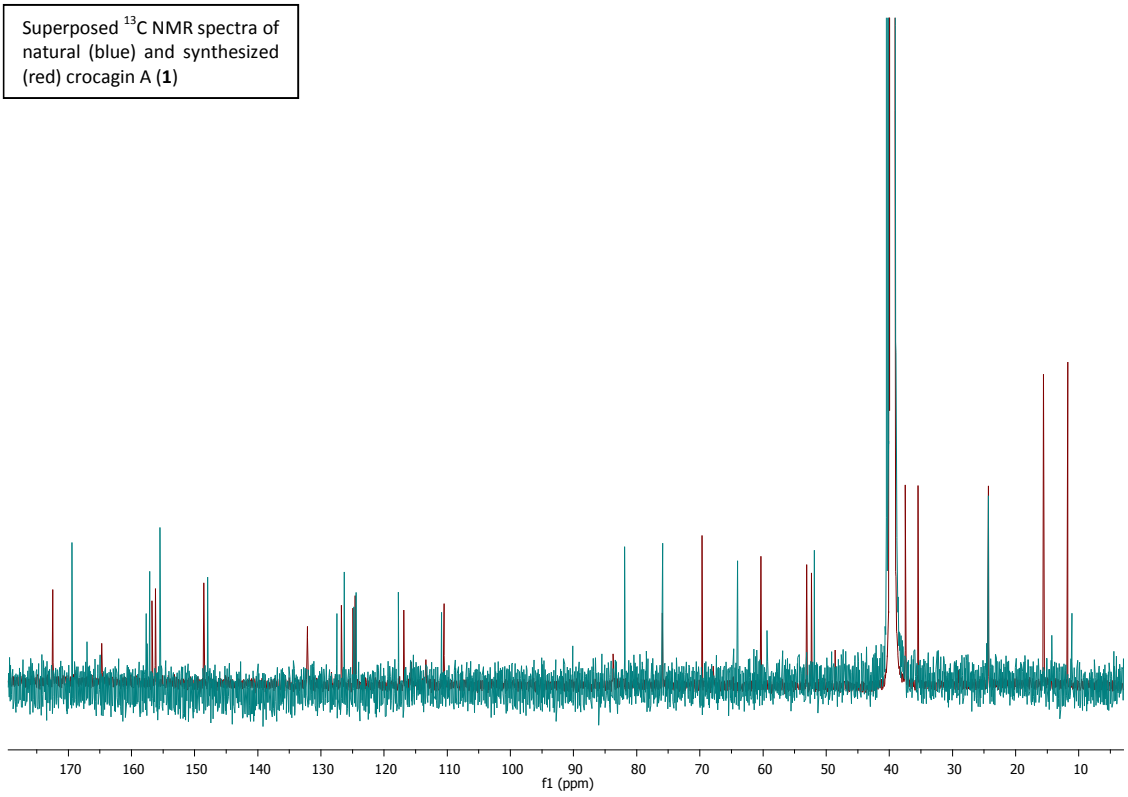




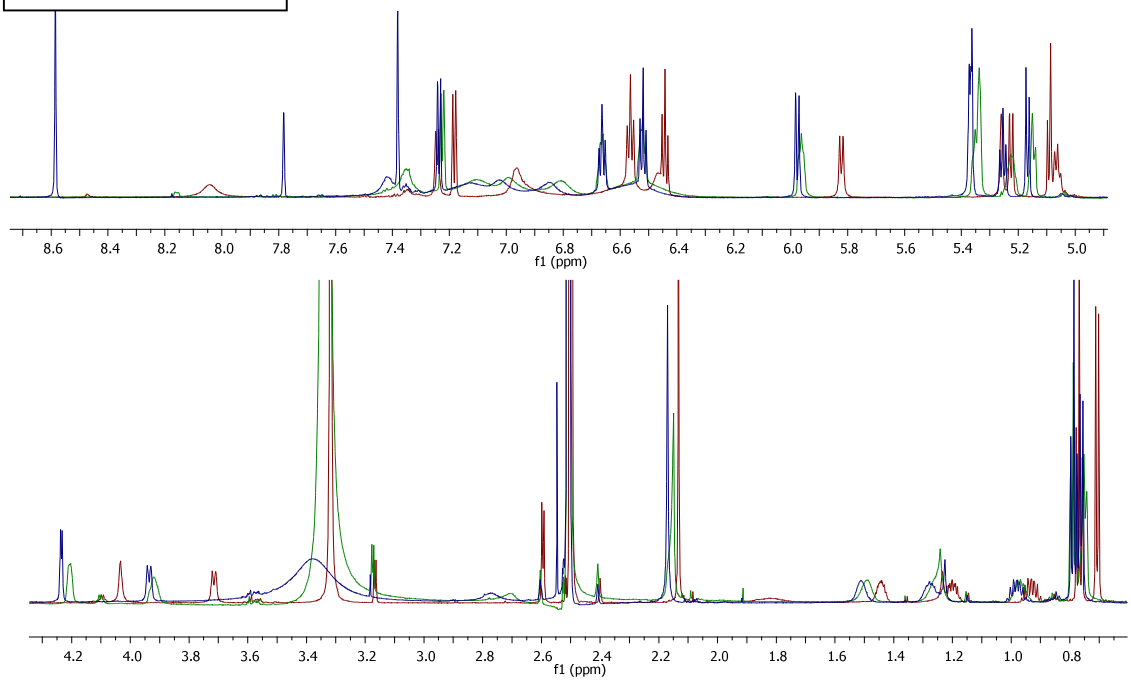
Superposed ^{1}H NMR spectra of natural (blue) and synthesized (red) crocagin A (**1**)



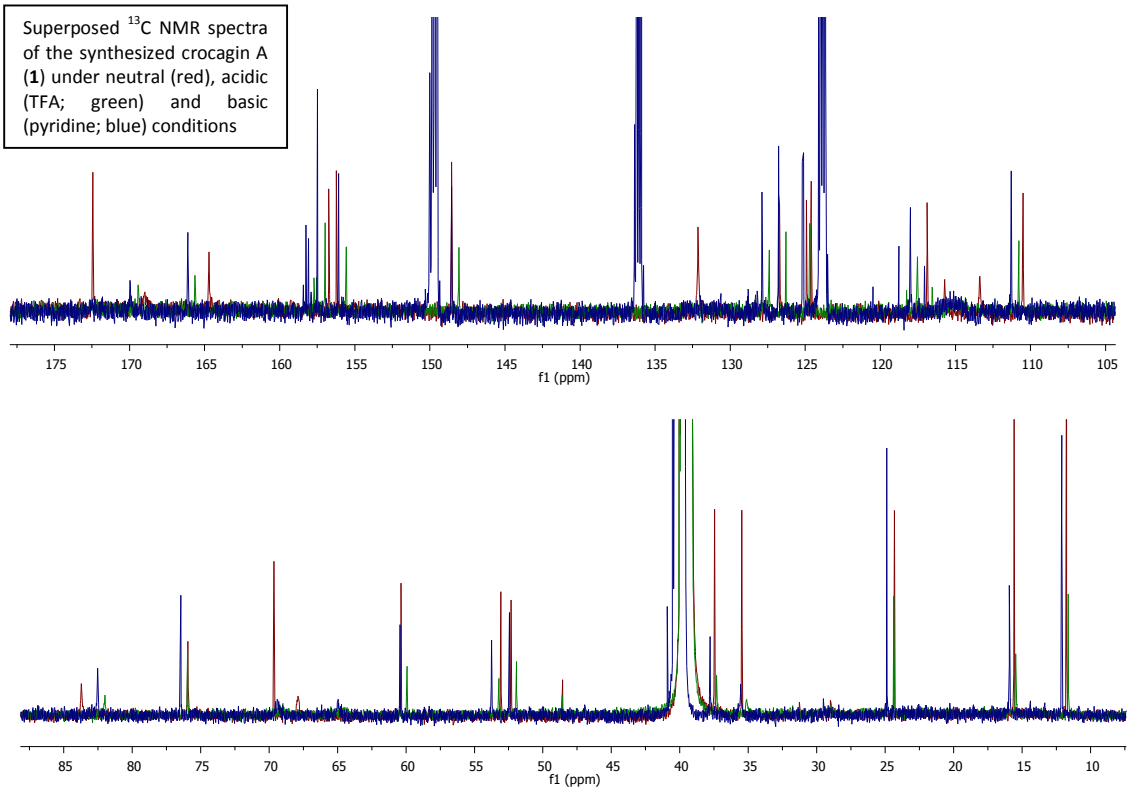
Superposed ^{13}C NMR spectra of natural (blue) and synthesized (red) crocagin A (**1**)



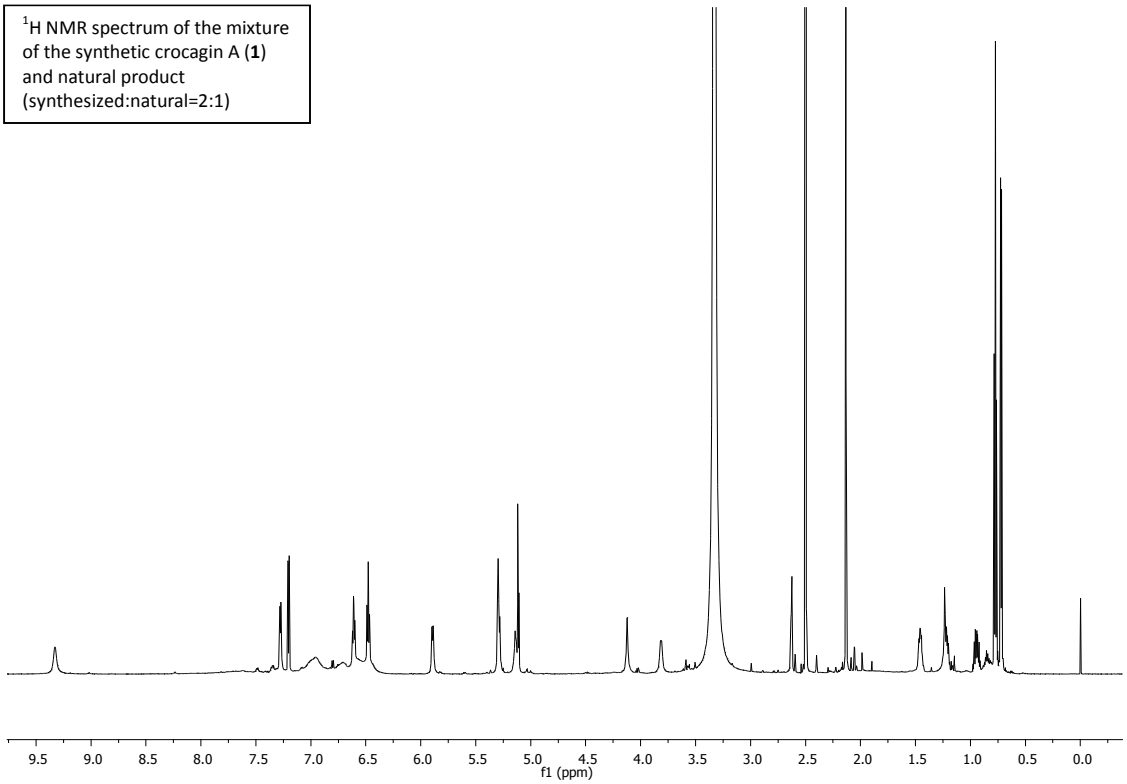
Superposed ^{1}H NMR spectra of the synthesized crocagin A (**1**) under neutral (red), acidic (TFA; green) and basic (pyridine; blue) conditions



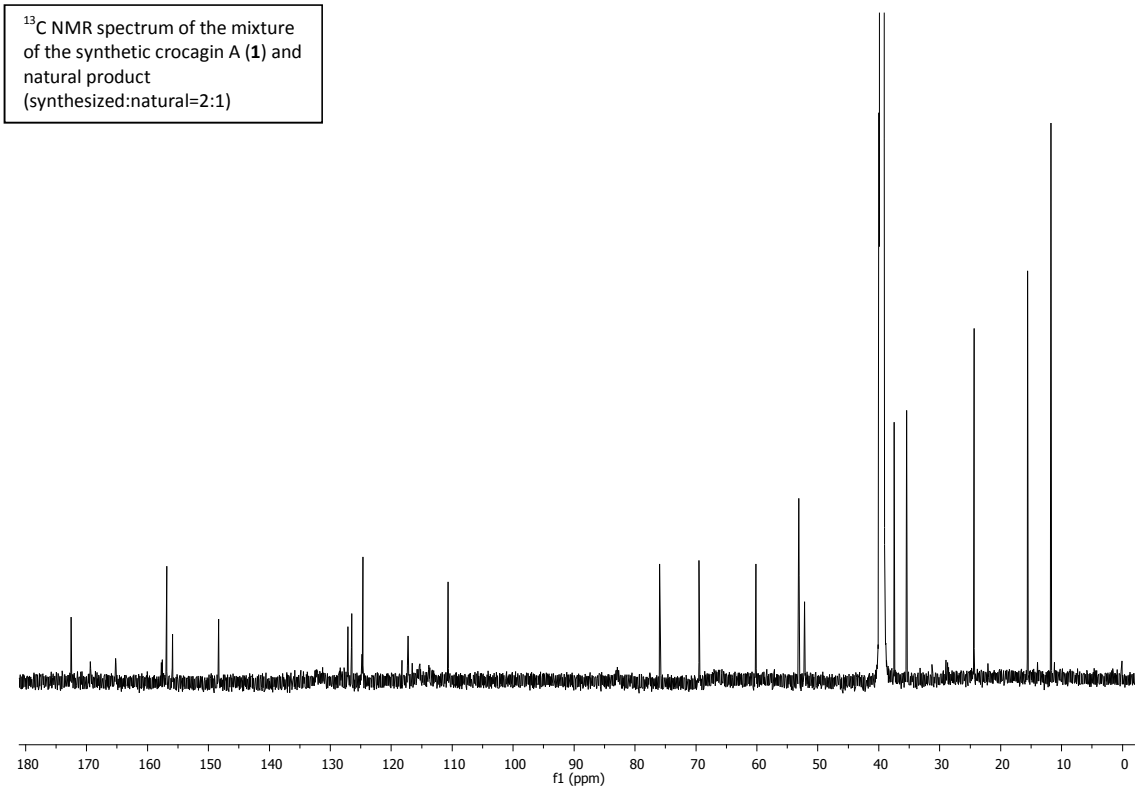
Superposed ^{13}C NMR spectra of the synthesized crocagin A (**1**) under neutral (red), acidic (TFA; green) and basic (pyridine; blue) conditions



^{1}H NMR spectrum of the mixture of the synthetic crocagin A (**1**) and natural product (synthesized:natural=2:1)



^{13}C NMR spectrum of the mixture of the synthetic crocagin A (**1**) and natural product (synthesized:natural=2:1)



4 X-ray Crystallographic Data

Single-Crystal X-ray Analysis of tetracyclic compound 15

Crystallographic data for compound **15** are deposited at the Cambridge Crystallographic Data Centre, the deposition number: CCDC 1524710

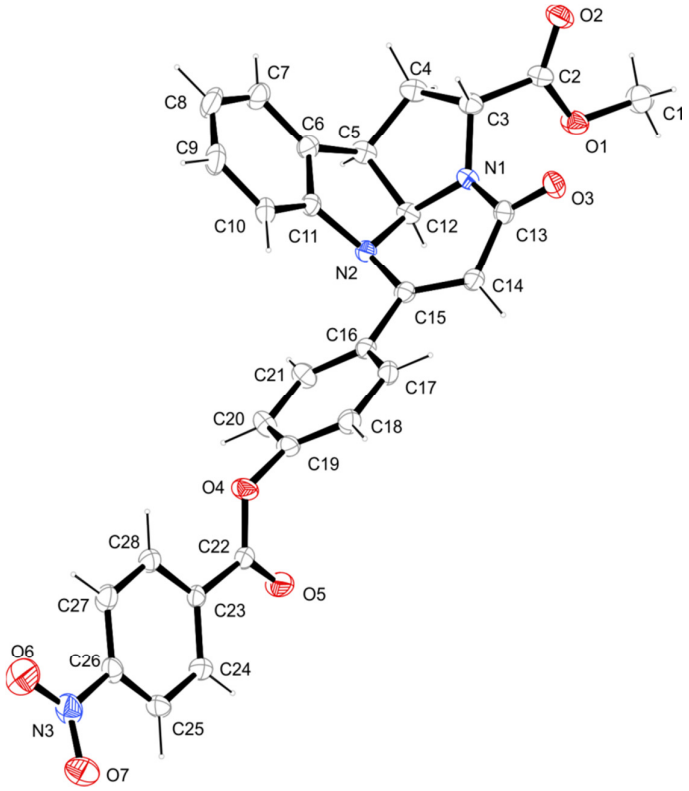


Figure 1 Molecular structure of **15** (one molecule out of asymmetric unit).

Table 1 Crystallographic data for **15**.

	15
net formula	$C_{28}H_{21}N_3O_7$
M_r/g mol^{-1}	511.482
crystal size/mm	0.120 × 0.100 × 0.080
T/K	173(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	orthorhombic
space group	$P2_12_12_1$
a/Å	4.7688(2)
b/Å	20.4417(11)
c/Å	24.2942(11)

α/°	90
β/°	90
γ/°	90
V/Å^3	2368.26(19)
Z	4
calc. density/g cm^{-3}	1.43455(12)
μ/mm^{-1}	0.105
absorption correction	multi-scan
transmission factor range	0.9231–0.9580
refls. measured	12832
R_{int}	0.0307
mean σ(I)/I	0.0367
θ range	3.10–25.38
observed refls.	3658
x, y (weighting scheme)	0.0371, 0.4195
hydrogen refinement	constr
Flack parameter	0.7(9)
refls in refinement	4290
parameters	344
restraints	0
$R(F_{obs})$	0.0342
$R_w(F^2)$	0.0792
S	1.021
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.188
min electron density/e Å^{-3}	−0.127

Single-Crystal X-ray Analysis of tetracyclic compound 23

Crystallographic data for compound **23** are deposited at the Cambridge Crystallographic Data Centre, the deposition number: CCDC 1524711

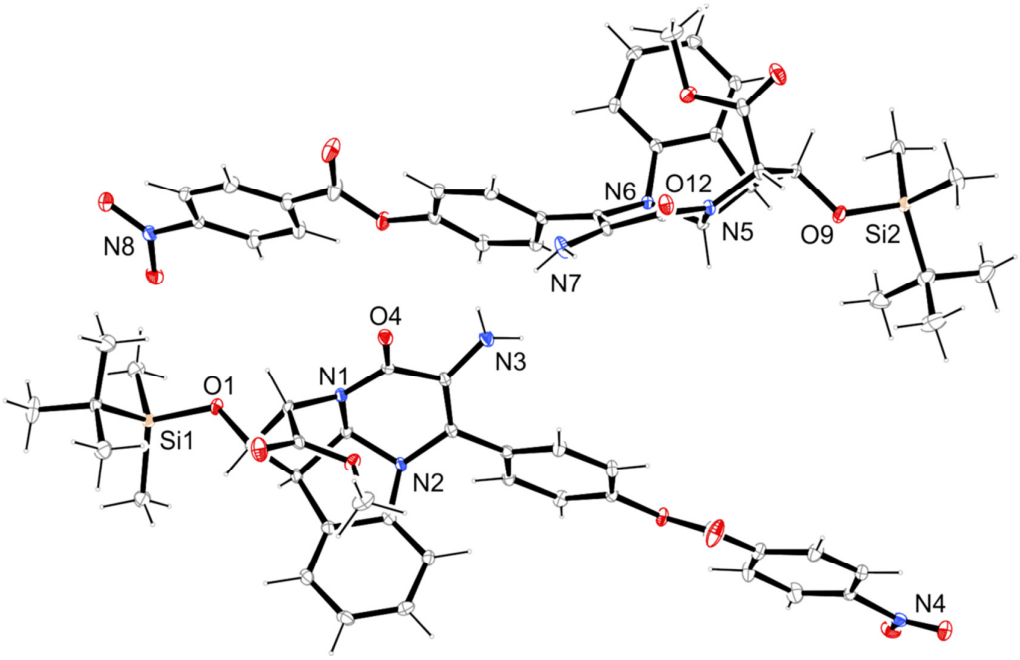


Figure 2 Molecular structure of **23** (two molecules out of assymetric unit).

Table 2 Crystallographic data for **23**.

	23
net formula	$C_{34}H_{36}N_4O_8Si$
M_r/g mol^{-1}	656.757
crystal size/mm	0.200 × 0.050 × 0.020
T/K	100(2)
radiation	'Mo Kα
diffractometer	'Bruker D8Venture'
crystal system	triclinic
space group	*P*1
a/Å	7.0977(6)
b/Å	12.5914(11)
c/Å	19.2902(16)
α/°	76.810(2)
β/°	86.395(2)
γ/°	75.068(2)
V/Å^3	1621.8(2)

Z	2
calc. density/g cm^{-3}	1.34491(17)
μ/mm^{-1}	0.131
absorption correction	multi-scan
transmission factor range	0.8145–0.9585
refls. measured	59648
R_{int}	0.0717
mean σ(I)/I	0.0687
θ range	3.04–26.37
observed refls.	10470
x, y (weighting scheme)	0.0407, 0.4337
hydrogen refinement	mixed
Flack parameter	0.07(9)
refls in refinement	13003
parameters	885
restraints	7
$R(F_{obs})$	0.0450
$R_w(F^2)$	0.0972
S	1.032
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.492
min electron density/e Å^{-3}	−0.268

5 Literature

[1] J. Zeng, Y. Tan, J. Ma, M. Leow, D. Tirtorahardjo, X. Liu *Chemistry – A European Journal* **2014**, *20*, 405 – 409.