Total Synthesis of Incargranine A

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1.2 GENERAL EXPERIMENTAL CONDITIONS

NMR spectra
$^1$H NMR spectra were recorded at 600 MHz, 500 MHz, and 400 MHz using a, Bruker AVANCE 600, Bruker AVANCE 500, Bruker PRO 500 or Bruker AVANCE 400 spectrometer. Residual solvent peaks were used as an internal reference for $^1$H NMR spectra (CDCl$_3$ δ 7.26 ppm, CD$_2$Cl$_2$ δ 5.32 ppm, CD$_3$OD δ 3.31 ppm). Coupling constants ($J$) are quoted to the nearest 0.1 Hz. Assignment of proton signals was assisted by $^1$H-$^1$H COSY, HSQC and HMBC experiments. $^{13}$C NMR spectra were recorded at 150 MHz or 125 MHz, using a Bruker AVANCE 600, or Bruker AVANCE 500 spectrometer. Solvent peaks were used as an internal reference for $^{13}$C NMR spectra (CDCl$_3$ δ 77.16 ppm, CD$_2$Cl$_2$ δ 54.00 ppm CD$_3$OD δ 49.00 ppm). $^{13}$C NMR peaks are generally reported to 1 decimal place. For compounds with several very close $^{13}$C NMR signals, however, peaks are reported to 2 decimal places. Assignment of carbon signals was assisted by $^1$H-$^1$H COSY, HSQC, HMBC and NOESY experiments.

IR spectra
IR spectra of solids and liquids were recorded as neat samples on a Shimadzu IRAffinity-1 FTIR spectrometer fitted with an ATR attachment.

Melting Point
Melting points were measured on a Gallenkamp Melting Point System.

Mass spectrometry
High resolution mass spectra were recorded either on a Bruker microTOF instrument using Electrospray Ionisation (ESI+) or on VG Autospec mass spectrometer using electron impact (EI+) ionization, operating at 70 eV.

Analytical TLC
Analytical TLC was performed with Merck silica gel plates, precoated with silica gel 60 F254 (0.2 mm). Visualisation was effected by quenching of UV fluorescence ($\lambda_{max} = 254$ nm) and by staining with $p$-anisaldehyde or KMnO$_4$ standard TLC stain solutions, followed by heating.

Flash chromatography
Flash chromatography employed Merck Kiesegel 60 (230–400 mesh) silica gel, or Merck aluminium oxide 90, active, neutral (70-230 mesh, activity I).

Experimental procedures, reagents and glassware
Reactions were conducted under a positive pressure of dry nitrogen in oven-dried glassware. Anhydrous solvents were either obtained from commercial sources or dried according to the procedure outlined by Grubbs and co-workers. Commercially available chemicals were used as purchased. The yields reported in this paper are shown as a range of isolated yields obtained on various scales, we herein provide experimental details for the largest scale procedures conducted (note: the stated scale corresponds to the quantity of product isolated).
1.3 SPECIFIC EXPERIMENTAL CONDITIONS

1.3.1 Experimental Procedure for Compound 13

2-(4-aminophenyl)ethanol 12 (5.00 g, 36.5 mmol), iPr₂NEt (13.2 mL, 76.0 mmol), NaI (2.28 g, 15.2 mmol) and a trace quantity of BHT were dissolved in anhydrous CH₃CN (200 mL) at room temperature under a N₂ atmosphere. Cis-1,4-dichlorobut-2-ene (3.20 mL, 30.4 mmol) was added and the mixture heated to 60 °C with stirring. After 1.5 hours when TLC analysis indicated complete consumption of starting material, the reaction mixture was cooled to room temperature, water (250 mL) added and extracted with EtOAc (4 × 150 mL). The organic layers were combined, washed with brine, dried with Na₂SO₄ and concentrated under reduced pressure to give a brown solid. Flash chromatography (silica gel neutralised with Et₃N, CH₂Cl₂ + trace BHT) gave 2-(4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl)ethan-1-ol 37 13 as pale yellow solid (5.00 g, 26.3 mmol, 87% yield).

Rf 0.20 (CH₂Cl₂);

¹H NMR (500 MHz, CDCl₃); δ 7.12 (d, J = 8.6 Hz, 2H), 6.51 (d, J = 8.6 Hz, 2H), 5.95 (s, 2H), 4.10 (s, 4H), 3.81 (q, J = 6.5 Hz, 2H), 2.78 (t, J = 6.5 Hz, 2H), 1.39 (t, J = 6.0 Hz, 1H) ppm;

¹³C NMR (126 MHz, CDCl₃); δ 146.1, 130.1, 126.6, 125.0, 111.5, 64.2, 54.7, 38.4 ppm;

IR (cm⁻¹) 3302(br), 2922, 2849, 2824, 1626, 1612, 1522, 1474, 1362, 1188, 1043, 1015, 1003;

HRMS (ESI⁺) 190.1240 (calculated [M+H]⁺ 190.1226);

M.p. 121-123 °C.
1.3.2 Experimental Procedure for Compound 14

2-(4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl)ethan-1-ol 13 (0.200 g, 1.06 mmol) and imidazole (0.080 g, 1.16 mmol) were dissolved in anhydrous THF (3 mL) at room temperature under an N₂ atmosphere. TBSCI (0.175 g, 1.16 mmol) was added with stirring at room temperature. After 1.5 hours, additional imidazole (0.014 g) and TBSCI (0.032 g) were added. After 2.5 hours, when TLC analysis showed complete consumption of starting material, Et₂O (10 mL) and saturated aqueous NH₄Cl (5 mL) were added, the organic fraction separated and the aqueous fraction extracted with Et₂O (2 × 10 mL). The organic fractions were combined, dried over Na₂SO₄ and concentrated under reduced pressure to give a pale yellow solid. Flash chromatography (silica gel, 19:1 petroleum ether/Et₂O) gave OTBS 2-(4-(2,5-dihydro-1H-pyrrol-1-yl)phenyl)ethanol 14 as a white solid (0.270 g, 0.890 mmol, 84% yield).

1H NMR (500 MHz, CD₂Cl₂) δ 7.07 (d, J = 8.5 Hz, 2H), 6.46 (d, J = 8.5 Hz, 2H), 5.96 (s, 2H), 4.07 (s, 4H), 3.73 (t, J = 7.2 Hz, 2H), 2.70 (t, J = 7.2 Hz, 2H), 0.89 (s, 9H), 0.02 (s, 6H) ppm;

13C NMR (126 MHz, CD₂Cl₂) δ 146.4, 130.4, 127.0, 126.5, 111.6, 65.6, 55.1, 39.3, 26.3, 18.8, −5.1 ppm;

IR (cm⁻¹) 2953, 2928, 2855, 2822, 1626, 1614, 1524, 1472, 1373, 1361, 1254, 1188, 1088;

HRMS (ESI⁺) 304.2127 (calculated [M+H]⁺ 304.2091);

M.p. 63-65 °C.
Experimental Procedure for Compound 16

Dihydropyrrole 14 (42 mg, 0.14 mmol), durene (18 mg, 0.14 mmol) and a trace quantity of BHT were placed into an NMR tube fitted with a J Young valve. The tube was evacuated and flushed with N₂ three times, then anhydrous, degassed CD₂Cl₂ (0.5 mL) was added, followed by Rh(H)(CO)(PPh₃)₃ (6 mg, 7 µmol). The tube was sealed and heated to 40 °C for 30 minutes, then cooled to room temperature, pyrrolidine (7 µL, 93 µmol) was added. After 16 hours, when ¹H NMR analysis showed complete consumption of starting material (giving a 66 % yield of aminal 15), (±)-rengyolone 6 (49 mg, 0.31 mmol) was added. After 10 days at room temperature, when ¹H NMR analysis showed complete consumption of aminal 15, the reaction mixture was concentrated under reduced pressure and purified. Flash chromatography (silica gel, 19:1 CH₂Cl₂/MeOH) gave the cross-dimer 16 (7 mg, 15 µmol, 12 % yield) as a yellow oil.

¹H NMR (601 MHz, CD₂Cl₂) δ 7.08 (d, J = 8.6 Hz, 2H, H-2', H-6'), 6.74 (d, J = 8.6 Hz, 2H, H-3’, H-5’), 5.58 (d, J = 6.4 Hz, 1H, H-1’'), 4.15 (dd, J = 9.3, 5.5 Hz, 1H, H-6), 4.02 – 3.95 (m, 2H, CH₂-7), 3.73 (td, J = 7.4, 1.6 Hz, 2H, CH₂-8’), 3.46 – 3.38 (m, 2H, CH₂-4’’), 3.27 – 3.21 (m, 1H, H-2’''), 2.71 (t, J = 7.2 Hz, 2H, CH₂-7’), 2.68 – 2.63 (m, 2H, H-5a, H-2), 2.47 (dd, J = 16.1, 5.8 Hz, 1H, H-3a), 2.35 (dd, J = 16.1, 9.7 Hz, 1H, H-3b), 2.31 – 2.24 (m, 2H, H-5b, H-8a), 2.08 – 1.98 (m, 2H, H-8b, H-3”a), 1.89 (ddt, J = 13.0, 7.4, 5.5 Hz, 1H, H-3”b), 0.89 (s, 9H, OTBS), 0.02 (s, 6H, OTBS) ppm;

¹³C NMR (151 MHz, CD₂Cl₂) δ 209.39 (C-4), 144.92 (C-4’), 130.20 (C-2’, C-6’), 129.13 (C-1’), 113.77 (C-3’, C-5’), 94.68 (C-1’’), 91.41 (C-1), 80.24 (C-6), 67.00 (C-7), 65.45 (C-8’), 49.46 (C-4”’), 46.97 (C-2”’), 44.31 (C-5), 42.94 (C-2), 39.48 (C-3), 39.27 (C-7’), 38.56 (C-8), 26.29 (3 × CH₃ OTBS), 24.82 (C-3”’), 18.78 (C OTBS), −5.05 (2 × CH₃ OTBS) ppm;

IR (cm⁻¹) 2951, 2928, 2884, 2855, 1717, 1614, 1518, 1462, 1377, 1254, 1188;

HRMS (ESI⁺) 458.2785 (calculated [M+H]⁺ 458.272
1.3.4 Experimental Procedure for Compound 20

Compound 20 was prepared according to the previously reported procedure.²

a) Tyrosol 20a (15.0 g, 108.9 mmol) was dissolved in anhydrous THF (60 mL) at room temperature under an N₂ atmosphere. The solution was cooled to 0 °C and a solution of tert-butyldimethylsilylchloride (14.8 g, 98.1 mmol) in anhydrous THF (60 mL) was added dropwise over 45 minutes with vigorous stirring. The mixture was stirred at 0 °C until TLC analysis indicated complete consumption of the starting material (50 minutes). The reaction mixture was then diluted with Et₂O (150 mL) and saturated aqueous NH₄Cl (100 mL) added. The aqueous layer was separated and extracted with Et₂O (3 × 100mL). The organic layers were combined, dried with MgSO₄, filtered and concentrated under reduced pressure to give a white crystalline solid. Flash chromatography (silica gel, 3:1 Petroleum Ether 40-60/EtOAc) gave 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)phenol 20b as a white crystalline solid (25.0 g, 99.1 mmol, 91% yield); All data matched that previously reported.²

¹H NMR (400 MHz, CDCl₃) δ 7.11 - 7.04 (m, 2H), 6.78 - 6.72 (m, 2H), 3.76 (t, J = 7.1 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H), 0.87 (s, 9H), −0.01 (s, 6H) ppm;

¹³C NMR (101 MHz, CDCl₃) δ 154.0, 131.4, 130.2, 115.2, 65.0, 38.8, 26.1, 18.5, −5.2 ppm;

b) Phenol 20b (24.4 g, 96.7 mmol) was dissolved in CH₃CN (480 mL) and H₂O (120 mL) at room temperature. The solution was cooled in an ice-water bath to an internal temperature of 2-3 °C and PhI(OAc)₂ (37.5 g, 116.4 mmol) was added portion-wise over 3 minutes with vigorous stirring. The mixture was stirred at 2-3 °C until TLC analysis indicated complete consumption of the starting material (20 minutes), then saturated aqueous Na₂SO₃ (300 mL) was added followed by Et₂O (300 mL). The organic layer was separated and the aqueous layer extracted with Et₂O (2 × 200 mL). The organic layers were combined, dried with MgSO₄ and concentrated under reduced pressure, giving a dark green/black oil. Flash chromatography (silica gel, gradient 9:1 Petroleum Ether 40-60/EtOAc to neat EtOAc) gave 4-(2-((tert-butyldimethylsilyl)oxy)ethyl)-4-hydroxycyclohexa-2,5-dienone 20 (15.1 g, 56.3 mmol, 58% yield) as a pale yellow crystalline solid; All data matched that previously reported.²
$^1$H NMR (400 MHz, CDCl₃) δ 6.97 (d, $J = 10.1$ Hz, 2H), 6.15 (d, $J = 10.1$ Hz, 2H), 4.41 (s, 1H), 3.94 (t, $J = 5.7$ Hz, 2H), 1.94 (t, $J = 5.7$ Hz, 2H), 0.91 (s, 9H), 0.11 (s, 6H) ppm;

$^{13}$C NMR (101 MHz, CDCl₃) δ 185.7, 151.2, 127.5, 69.8, 60.9, 41.4, 25.9, 18.2, −5.3 ppm;
1.3.5 Experimental Procedure for Compound 6

(±)-Rengyolone (6) was prepared according to the previously reported procedure.\(^2\)

para-quinol 20 (10.5 g, 39.2 mmol) was dissolved in anhydrous THF (80 mL) at room temperature under an N\(_2\) atmosphere. TBAF (1 M in THF, 78.4 mL, 78.4 mmol) was added with stirring over 10 minutes. The resulting mixture was stirred at room temperature until TLC analysis indicated complete consumption of the starting material (25 minutes), then cooled to 0 °C and saturated aqueous NH\(_4\)Cl (40 mL) and H\(_2\)O (20 mL) were added. The organic layer was separated and the aqueous layer extracted with EtOAc (10 \(\times\) 50mL). The organic layers were combined, dried over Na\(_2\)SO\(_4\) and concentrated under reduced pressure to give a pale yellow oil. Flash chromatography (silica gel 230-400 mesh, gradient 1:1 Petroleum Ether 40-60/EtOAc to neat EtOAc) gave (±)-rengyolone (2) as a pale yellow oil, that later solidified in the fridge (4.8 g, 31.4 mmol, 80 % yield);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.76 (dd, \(J = 10.2, 1.4\) Hz, 1H), 6.02 (d, \(J = 10.2\) Hz, 1H), 4.24 (ddd, \(J \approx 6.0, 4.8, 1.4\) Hz, 1H), 4.08 (apparent td, \(J \approx 8.5, 6.5\) Hz, 1H), 3.96 (apparent td, \(J \approx 8.5, 6.3\) Hz, 1H), 2.78 (dd, \(J = 16.9, 4.8\) Hz, 1H), 2.61 (dd, \(J = 16.9, 5.8\) Hz, 1H), 2.33 (ddd, \(J = 13.0, 8.3, 6.4\) Hz, 1H), 2.23 (ddd, \(J = 13.0, 8.2, 6.5\) Hz, 1H), 2.01 (br. s, 1H);

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 196.8, 147.8, 129.1, 81.8, 75.9, 66.4, 40.4, 39.7.
2,5-dihydropyrrole 13 (1.51 g, 7.96 mmol) was placed in a single neck Schlenk flask. The flask was evacuated and flushed with N₂ three times. Anhydrous CH₂Cl₂ (20 mL) was added and the resulting solution degassed by three freeze-pump-thaw cycles. Anhydrous, degassed pyrrolidine (0.730 mL, 8.76 mmol) was added, followed by Rh(H)(CO)(PPh₃)₃ (5 mol%, 0.368 g, 0.398 mmol). The tube was sealed and heated to 40 °C with stirring. After 2 hours, when ¹H-NMR analysis showed complete conversion of starting material to aminal 19, (for an example of ¹H NMR monitoring of this reaction, see 1.4.5) the solution was cooled to room temperature, water (0.3 mL) added followed by p-quinol 20 (5.36 g, 19.9 mmol). The flask was re-sealed and stirred at room temperature. After 20 hours at room temperature, when ¹H-NMR analysis indicated consumption of starting material, the solvent was removed under reduced pressure to give a brown oil. Flash chromatography (silica gel neutralised with Et₃N, 4:1 → 1:1 petroleum ether/EtOAc) gave the desired compound 21 (2.81 g, 6.13 mmol, 77% yield) as a brown oil. The stereochemistry of dimer 21 was assigned as cis-syn-cis based on NOESY data, in particular NOESY cross-peaks between H(3b)-H(3'b) and H(1'″)-H(2).

Rᶠ 0.26 (1:1 petroleum ether:EtOAc);

¹H NMR (500 MHz, CD₂Cl₂); δ 7.09 (d, J = 8.6 Hz, 2H, H-2', H-6'), 6.75 (d, J = 8.6 Hz, 2H, H-3', H-5'), 6.50 (dd, J = 10.3, 1.7 Hz, 1H, H-6), 5.87 (dd, J = 10.3, 1.0 Hz, 1H, H-5), 5.69 (d, J = 6.2 Hz, 1H, H-1'″), 3.90 – 3.84 (m, 1H, H-8a), 3.80 – 3.73 (m, 3H, H-8b, H-8'a, H-8'b), 3.26 (td, J = 8.9, 5.2 Hz, 1H, H-4''a), 3.19 – 3.11 (m, 2H, H-2'', H-4''b), 3.00 (ddt, J = 9.3, 7.2, 1.8 Hz, 1H, H-2), 2.80 – 2.73 (m, 3H, H-3a, CH₂-7'), 2.62 (dt, J = 18.2, 1.4 Hz, 1H, H-3b), 2.03 – 1.93 (m, 2H, H-3''a, H-H-7a), 1.93 – 1.87 (m, 1H, H-7b), 1.84 – 1.76 (m, 1H, H-3''b), 1.44 (d, J = 5.5 Hz, 1H, OH), 0.88 (s, 9H, OTBS), 0.05 (d, J = 6.2 Hz, 6H, OTBS) ppm;

¹³C NMR (126 MHz, CD₂Cl₂); δ 192.9 (C-4), 149.3 (C-6), 140.1 (C-4''), 125.1 (C-2', C-6'), 122.3 (C-1'), 109.1 (C-3', C-5'), 89.3 (C-1″), 75.7 (C-1), 59.4 (C-8), 54.2 (C-8), 43.6 (C-4'″),
43.0 (C-2''), 39.3 (C-2), 37.7 (C-7), 33.9 (C-7'), 31.2 (C-3), 21.2 (3C OTBS), 19.8 (C-3''), 13.6 (C OTBS), −10.1 (2C OTBS) ppm;

**IR (cm⁻¹)** 3495, 2953, 2930, 2893, 2843, 1670, 1614, 1518, 1485, 1462, 1369, 1248, 1088;

**HRMS (ESI⁺)** 458.2742 (calculated [M+H]⁺ 458.2721);
OTBS dimer 21 (0.810 g, 1.77 mmol) was dissolved in anhydrous THF (20 mL) at room temperature. TBAF (2.65 mL, 1.0 M in THF, 2.65 mmol) was added with stirring at room temperature. After 3 hours, additional TBAF (0.885 mL, 1.0 M in THF, 0.885 mmol) was added and mixture stirred at room temperature for a further 30 minutes. When TLC analysis showed complete consumption of starting material (3.5 hours total), saturated NH₄Cl (25 mL) was added and the resulting mixture extracted with CHCl₃ (3 × 30 mL). The organic layers were combined, washed with brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a dark yellow oil. Flash chromatography (silica gel 230-400 mesh 96:4 → 95:5 CHCl₃/MeOH) gave the ring closed product 22 (0.344 g, 1.00 mmol, 56 % yield) along with the ring opened product 18 (0.0628 g, 0.183 mmol, 10 % yield).

Ring-closed 22

Rf 0.30 (96:4 CH₂Cl₂:MeOH);

¹H NMR (500 MHz, CD₂Cl₂) δ 7.09 (d, J = 8.5 Hz, 2H, H-2’, H-6’), 6.77 (d, J = 8.6 Hz, 2H, H-3’, H-5’), 5.59 (d, J = 6.4 Hz, 1H, H-1”), 4.14 (dd, J = 9.4, 5.5 Hz, 1H, H-6), 4.01 – 3.93 (m, 2H, CH₂-8), 3.74 (td, J = 6.5, 3.1 Hz, 2H, CH₂-8’), 3.47 – 3.38 (m, 2H, CH₂-4’), 3.28-3.20 (m, 1H, H-2”), 2.74 (t, J = 6.7 Hz, 2H, CH₂-7’), 2.68 – 2.61 (m, 2H, H-5a, H-2), 2.47 (dd, J = 16.2, 5.8 Hz, 1H, H-3a), 2.34 (dd, J = 16.2, 9.7 Hz, 1H, H-3b), 2.31 – 2.22 (m, 2H, H-5b, H-7a), 2.10 – 1.97 (m, 2H, H-7b, H-3”a), 1.89 (ddt, J = 12.9, 7.3, 5.5 Hz, 1H, H-3”b), 1.58 (d, J = 5.2 Hz, 1H, OH) ppm;

¹³C NMR (126 MHz, CD₂Cl₂) δ 209.4 (C-4), 145.1 (C-4’), 130.1 (C-2’, C-6’), 128.5 (C-1’), 114.0 (C-3’, C-5’), 94.6 (C-1”), 91.5 (C-1), 80.2 (C-6), 67.0 (C-8), 64.4 (C-8’), 49.4 (C-4”), 46.9 (C-2”), 44.3 (C-5), 42.9 (C-2), 39.4 (C-3), 38.9 (C-7’), 38.5 (C-7), 24.8 (3”) ppm;

IR (cm⁻¹) 3439, 2938, 2874, 1711, 1614, 1518, 1377, 1346, 1186, 1043;

HRMS (ESI’); 366.1678 (calculated [M+Na]⁺ 366.1676);
Ring-open 18

**Rr** 0.20 (96:4 CH₂Cl₂:MeOH);

**¹H NMR** (601 MHz, CD₃OD) δ 7.09 – 7.04 (m, 2H, H-2’, H-6’), 6.77 – 6.73 (m, 2H, H-3’, H-5’), 6.57 (dd, J = 10.4, 1.7 Hz, 1H, H-6’), 5.91 (dd, J = 10.3, 1.0 Hz, 1H, H-6), 5.72 (d, J = 6.2 Hz, 1H, H-5), 3.82 – 3.71 (m, 2H, CH₂-8), 3.68 (t, J = 7.3 Hz, 2H, CH₂-8’), 3.27 (td, J = 9.0, 5.0 Hz, 1H, H-4”a), 3.21 (tt, J = 10.3, 5.6 Hz, 1H, H-2”), 3.12 (td, J = 8.5, 6.4 Hz, 1H, H-4”b), 2.96 (ddt, J = 9.5, 7.5, 1.7 Hz, 1H, H-2), 2.84 (dd, J = 18.4, 7.3 Hz, 1H, H-3a), 2.72 (t, J = 7.3 Hz, 2H, CH₂-7'), 2.69 – 2.63 (m, 1H, H-3b), 2.06 (dt, J = 13.8, 6.8 Hz, 1H, H-7a), 2.02 – 1.97 (m, 1H, H-3”a), 1.94 (dt, J = 14.2, 6.4 Hz, 1H, H-7b), 1.77 (ddt, J = 13.4, 8.1, 5.1 Hz, 1H, H-3”b) ppm;

**¹³C NMR** (151 MHz, CD₃OD) δ 200.3 (C-4), 155.9 (C-6), 145.7 (C-4’), 130.4 (C-2’, C-6’), 129.3 (C-1’), 127.5 (C-5’), 114.7 (C-3’, C-5’), 95.1 (C-1”), 81.3 (C-1), 64.7 (C-8’), 58.7 (C-8), 49.3, 49.1 (C-3” and C-2” overlap with solvent), 45.3 (C-2), 42.9 (C-7), 39.4 (C-7’), 36.5 (C-3), 25.2 (C-3”) ppm;

**IR** (cm⁻¹) 3374, 2920, 2857, 1665, 1614, 1518, 1371, 1348, 1045, 1005;

**HRMS** (ESI⁺); 344.1849 (calculated [M+H]⁺ 344.1856).
1.3.8  Experimental Procedure for Incargranine A 1

Ring-open pre-incargranine A 18 (7 mg, 20 µmol) was dissolved in CD$_3$OD (0.6 mL) in an NMR tube. The resulting solution was heated to 40 °C and monitored by $^1$H NMR. After 55 hours the reaction mixture was cooled to room temperature and purified by flash chromatography (silica gel 230-400 mesh 96:4 CHCl$_3$/MeOH) to give incargranine A (1) (2 mg, 7 µmol) in a 33% yield (43% brsm) along with unreacted starting material 18 (1 mg, 4 µmol). For characterisation data for incargranine A (1) see below.
**1.3.9 Alternative Experimental Procedure for incargranine A 1**

Compound **21** (2.10 g, 4.58 mmol) was dissolved in anhydrous MeOH (50 mL) at room temperature. I$_2$ (1 % w/v in MeOH, 11.6 mL, 0.459 mmol) was added and the resulting solution stirred at room temperature. After 22 hours, when TLC analysis showed complete consumption of starting material, saturated aqueous Na$_2$S$_2$O$_3$ (9 mL) was added. The resulting suspension was concentrated under reduced pressure to remove the majority of the MeOH, then the aqueous residue was extracted with CHCl$_3$ ($10 \times 30$ mL). The organic fractions were combined, washed with brine, dried with Na$_2$SO$_4$ and concentrated under reduced pressure to give a brown foaming oil. Flash chromatography (silica gel, CHCl$_3$ + 5% MeOH $\rightarrow$ 7% MeOH) gave incargranine A (1) (1.33 g, 3.87 mmol, 84% yield) as a pale yellow, foaming amorphous solid. All data matched that previously reported for isolated incargranine A.$^3$

$R_f$ 0.15 (19:1 CHCl$_3$:MeOH);

$^1$H NMR (600 MHz, CD$_3$OD); $\delta$ 7.06 (d, $J = 8.6$ Hz, 2H), 6.63 (d, $J = 8.6$ Hz, 2H), 4.06 (dd, $J = 9.7$, 3.0 Hz, 1H), 3.92 (td, $J = 8.4$, 1.7 Hz, 1H), 3.86 – 3.84 (m, 1H), 3.84 – 3.80 (m, 1H), 3.68 (t, $J = 7.2$ Hz, 2H), 3.44 (ddd, $J = 9.4$, 7.9, 5.5 Hz, 1H), 3.35 (dddd, $J = 9.7$, 8.1, 5.9, 1.9 Hz, 1H), 3.22 (dd, $J = 3.9$, 3.0 Hz, 1H), 3.14 (ddd, $J = 9.5$, 8.3, 6.4 Hz, 1H), 2.71 (t, $J = 7.2$ Hz, 2H), 2.49 (dd, $J = 20.0$, 3.4 Hz, 1H), 2.39 – 2.35 (m, 1H), 2.35 – 2.26 (m, 2H), 2.19 (dddd, $J = 13.5$, 10.1, 8.3, 5.5 Hz, 1H), 2.00 – 1.89 (m, 2H ppm);

$^{13}$C NMR (151 MHz, CD$_3$OD); $\delta$ 213.9, 146.8, 130.6, 129.1, 115.4, 86.8, 81.7, 68.1, 64.6, 60.1, 53.9, 51.2, 42.8, 39.7, 39.4, 36.7, 36.1, 27.4 ppm;

IR (cm$^{-1}$); 3387(br), 2953, 2860, 1720, 1614, 1516, 1361, 1302, 1221, 1159, 1105, 1047;

HRMS (ESI$^+$); 344.1844 (calculated [M+H]$^+$ 344.1856);

M.p. 78-80 °C (no lit. value available).
1.3.9.1 Comparison of NMR Spectra of Synthetic and Isolated Incargranine A (1)

Professor Zhang kindly provided the pdf copies of $^1$H and $^{13}$C spectra shown below. A comparison of $^1$H and $^{13}$C NMR data reported for synthetic incargranine A (1) (in CD$_3$OD) with the data for natural incargranine A (1)\(^3\) is shown below. Note that the spectrometer frequency differs between the tabulated data (as published 600MHz, 150MHz)\(^3\) and spectra provided in pdf form (300MHz, 75MHz).

<table>
<thead>
<tr>
<th>Atom #</th>
<th>Synthetic incargranine A (CD$_3$OD)</th>
<th>Natural incargranine A (CD$_3$OD)$^3$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta$ $^1$H (600MHz) m, J (Hz)</td>
<td>$\delta$ $^{13}$C (150MHz) m, J (Hz)</td>
</tr>
<tr>
<td>1</td>
<td>--</td>
<td>81.7</td>
</tr>
<tr>
<td>2</td>
<td>2.39-2.35 m</td>
<td>2.39-2.37 m</td>
</tr>
<tr>
<td>3a</td>
<td>2.49 dd (20.0, 3.4)</td>
<td>2.49 dd (18.9, 3.3)</td>
</tr>
<tr>
<td>3b</td>
<td>2.35-2.26 m (overlap)</td>
<td>2.31 dd (18.9, 3.1)</td>
</tr>
<tr>
<td>4</td>
<td>--</td>
<td>213.9</td>
</tr>
<tr>
<td>5</td>
<td>3.22 dd (3.9, 3.0)</td>
<td>3.21 dd (3.6, 3.3)</td>
</tr>
<tr>
<td>6</td>
<td>3.86-3.84 m</td>
<td>3.83 d (3.6)</td>
</tr>
<tr>
<td>7a</td>
<td>2.35-2.26 m (overlap)</td>
<td>2.00-1.97 m</td>
</tr>
<tr>
<td>7b</td>
<td>2.00-1.89 m (overlap)</td>
<td>39.7</td>
</tr>
<tr>
<td>8a</td>
<td>3.92 app. td (8.4, 1.7)</td>
<td>3.95-3.89 m</td>
</tr>
<tr>
<td>8b</td>
<td>3.84-3.80 m</td>
<td>3.83-3.78 m</td>
</tr>
<tr>
<td>1’</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>2’, 6’</td>
<td>7.06 d (8.6)</td>
<td>7.05 d (8.4)</td>
</tr>
<tr>
<td>3’, 5’</td>
<td>6.63 d (8.6)</td>
<td>6.61 d (8.4)</td>
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<tr>
<td>4’</td>
<td>--</td>
<td>146.8</td>
</tr>
<tr>
<td>7’(CH$_2$)</td>
<td>2.71 d (7.2)</td>
<td>2.70 t (7.2)</td>
</tr>
<tr>
<td>8’ CH$_2$</td>
<td>3.68 t (7.2)</td>
<td>3.67 t(7.2)</td>
</tr>
<tr>
<td>1’’</td>
<td>4.06 dd (9.7, 3.0)</td>
<td>4.06 dd (8.6, 3.0)</td>
</tr>
<tr>
<td>2’’</td>
<td>3.39-3.32 m</td>
<td>3.36-3.34 m</td>
</tr>
<tr>
<td>3’’a</td>
<td>2.22-2.14 m</td>
<td>2.21-2.15 m</td>
</tr>
<tr>
<td>3’’b</td>
<td>2.00-1.89 m (overlap)</td>
<td>1.95-1.92 m</td>
</tr>
<tr>
<td>4’’a</td>
<td>3.44 ddd (9.4, 7.9, 5.5)</td>
<td>3.48-3.40 m</td>
</tr>
<tr>
<td>4’’b</td>
<td>3.14 ddd(9.5, 8.3, 6.4)</td>
<td>3.18-3.13 m</td>
</tr>
</tbody>
</table>
Comparison of $^1$H NMR spectra of isolated and synthetic incarganine A

$^1$H NMR (300 MHz, CD$_3$OD) isolated incarganine A

$^1$H NMR (600 MHz, CD$_3$OD) synthetic incarganine A
Comparison of $^{13}$C NMR spectra of isolated and synthetic incarganine A

$^{13}$C NMR (75 MHz, CD$_3$OD) isolated incarganine A

$^{13}$C NMR (150 MHz, CD$_3$OD) synthetic incarganine A
1.4.1 $^1$H NMR Spectrum of Compound 13

$^1$H NMR (500 MHz, CDCl₃)
1.4.2 $^{13}$C NMR Spectrum of Compound 13
1.4.3 $^1$H NMR Spectrum of Compound 14
1.4.4 $^{13}$C NMR Spectrum of Compound 14
1.4.5 $^1$H NMR Spectrum of Compound 16

\[ \text{\includegraphics[width=\textwidth]{nmr_spectrum.png}} \]
1.4.6 $^{13}$C NMR Spectrum of Compound 16
In-situ monitoring of the formation of aminal \textbf{19} by \textsuperscript{1}H NMR Spectroscopy.
1.4.8 $^1$H NMR Spectrum of Compound 21
1.4.9 $^{13}$C NMR Spectrum of Compound 21
1.4.10 NOESY Spectrum of Compound 21
$^1\text{H NMR (500 MHz, CD}_2\text{Cl}_2$)

1.4.11  $^1\text{H NMR Spectrum of Compound 22}$
1.4.12 $^{13}$C NMR Spectrum of Compound 22
1.4.13 $^1$H NMR Spectrum of Compound 18
1.4.14 $^{13}$C NMR Spectrum of Compound 18
$^1$H NMR (601 MHz, CD$_2$OD) incargranine A
1.4.16 $^{13}$C NMR Spectrum of Incargranine A
1.4.17 $^1$H-$^1$H COSY Spectrum of Incargranine A 1
1.4.18 $^1$H-$^{13}$C HSQC Spectrum of Incargranine A 1

(undf) 1
1.4.19 $^1$H-$^{13}$C HMBC Spectrum of Incargranine A 1
1.4.20 NOESY Spectrum of Incargranine A 1
1.5 REFERENCES

