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Total Synthesis of (±)-Quebrachamine via [3+2] Cycloaddition and Efficient Chloroacetamide Photocyclization

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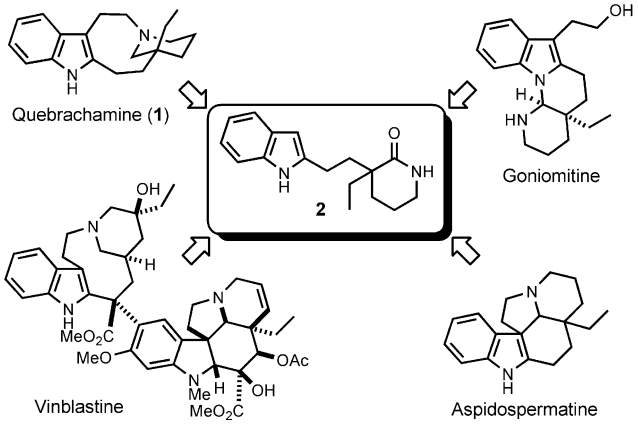
The total synthesis of (±)-quebrachamine has been completed in 13 linear steps and 17.8 % overall yield. The indole core was constructed via a formal [3+2] dipolar cycloaddition between a functionalized nitrile and donor-acceptor cyclopropane, and the synthetically challenging nine-membered ring was secured by an efficient chloroacetamide photocyclization.

Introduction

Dipolar cycloadditions are widely utilized in the formation of functionalized heterocycles involving donor-acceptor (DA) cyclopropanes with nitriles,[1] indoles,[2] and other reaction partners.[3] Part of our research efforts have focused on developing efficient [3+2] annulation methodology with nitriles to afford highly substituted pyrroles with absolute regiochemical control. It was envisioned that this powerful strategy could lead to indole **2**, and subsequently allow access to natural products such as quebrachamine (**1**), goniomitine, aspidospermatine, and vinblastine (Scheme 1).



Scheme 1. Potential natural product targets from **2**.

The utility of the dipolar methodology was recently illustrated by us with the total synthesis of (±)-goniomitine, which featured a [3+2] annulation reaction between a functionalized nitrile and DA cyclopropane to afford a substituted tetrahydroindole.[4] Building on these initial discoveries, we report here the total synthesis of (±)-quebrachamine (**1**). This work further illustrates the value of indole **2** as a synthetic precursor to several natural products, which was first utilized by Takano and co-workers in the synthesis of (–)-goniomitine.[5]

Quebrachamine (**1**), which was first isolated over a century ago by Hesse from Aspidosperma quebracho tree bark, is an intriguing tetracyclic indole alkaloid featuring a synthetically challenging nine-membered ring.[6] This natural product belongs to a large family of Aspidosperma alkaloids possessing diverse biological activity,[7] including α-adrenergic blocking behavior in urogenital tissue.[8] Attractive pharmacological properties along with its complex framework have inspired considerable and sustained synthetic efforts, with the first reported total synthesis of quebrachamine in 1963 by Stork and Dolfini.[9] Interestingly, the majority of previous syntheses feature a reductive ring-opening of a 5–6 system to access the nine-membered ring, presumably due to the notorious difficulty associated with the formation of medium-sized rings.[10]

In light of these pioneering efforts, we envisioned a novel approach to (±)-quebrachamine (**1**) that confronts formation of the nine-membered ring through an early retrosynthetic disconnection that identified two strategic bonds (Scheme 2). Either of these disconnections would allow for a variety of Friedel–Crafts acylation or *N*-alkylation type strategies to be explored, while greatly simplifying the synthetic target to advanced key intermediate **2**. Our previous work on the (±)-goniomitine synthesis provided a route to **2**, by oxidation and decarboxylation of the tetra-substituted

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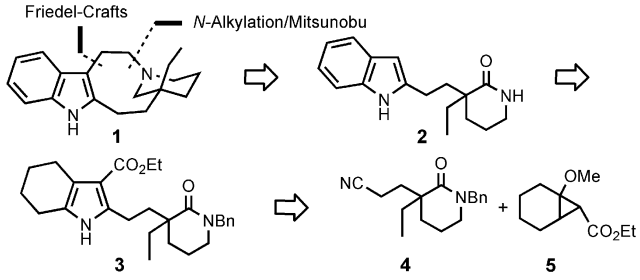
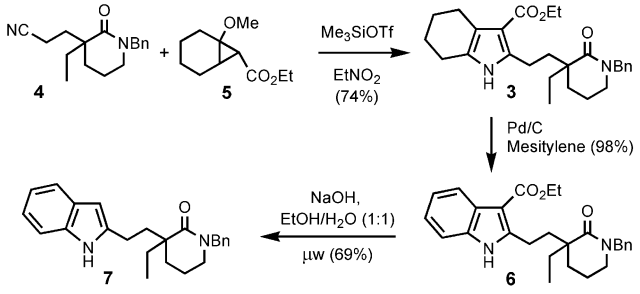
pyrrole **3**, which in turn is generated from the [3+2] cycloaddition involving functionalized nitrile **4** and cyclopropane **5**.



Scheme 2. Retrosynthetic strategy.

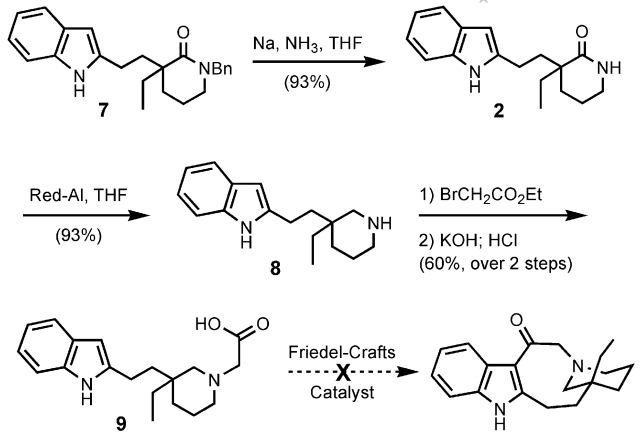
Results and Discussion

The synthesis began with the preparation of nitrile **4**, which was completed in five steps from commercially available δ-valerolactam as described previously.[4] The cycloaddition reaction between functionalized nitrile **4** and DA cyclopropane **5** (Me_3SiOTf, $EtNO_2$, –30 °C) proceeded smoothly to afford cycloadduct **3** in 74% yield (Scheme 3). Oxidation of the tetra-substituted pyrrole **3** with catalytic palladium on carbon in refluxing mesitylene provided the indole core in an excellent 98% yield. In lieu of enforcing an ungainly transformation on the ester group to convert it into a precursor suitable for constructing the two-carbon bridge of the nine-membered ring, it was deemed expendable and discarded by microwave-assisted decarboxylation (NaOH, $EtOH/H_2O$, 150 °C, 69%), thereby clearing the field for exploring methods for ring closure.



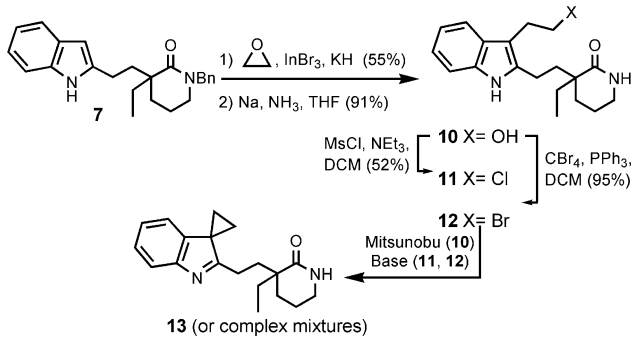
Scheme 3. Synthesis of intermediate **7**.

Our initial approach sought to enlist a Friedel–Crafts reaction to form the nine-membered ring in the penultimate step of the synthesis. The sequence began with deprotection of tertiary lactam **7** (Na, NH_3, THF) giving **2** in 93% yield (Scheme 4). The cyclization precursor **9** was prepared by Red-Al® reduction of lactam **2**, *N*-alkylation of the resulting amine **8** with ethyl bromoacetate, and saponification. The key carboxylic acid **9** (as well as related acid chlorides and mixed anhydrides) was then subjected to a wide variety of established Friedel–Crafts acylation conditions,[11] but the substrates were unresponsive to these efforts, and decomposed when forcing conditions were applied.



Scheme 4. Friedel–Crafts cyclization approach.

Faced with an apparently unnavigable Friedel–Crafts pathway, we retreated to an earlier position in **7**, as a substrate upon which to build the two carbon linker at the vacant C3 position of the indole (Scheme 5). The effort began by installation of a β-hydroxyethyl side-chain using ethylene oxide under In^{III} catalysis conditions. Optimization experiments for this reaction led us to 1 equiv. $InBr_3$ and 4 equiv. of KH, conditions that are likely generating $KInH_4$ in situ as the active Lewis acid in this process.[12] Aluminum and gallium trihydrides are known to form stable N-, P-, and O-donor complexes,[13] but the corresponding indium hydride complexes have remained relatively unexplored.[14] This novel method for indole β-hydroxyethyl alkylation at C3 provides an alternative strategy to methods employing strong bases for indole deprotonation and oxoester intermediates where selective reduction can be difficult in the presence of other carbonyl substituents.[15]

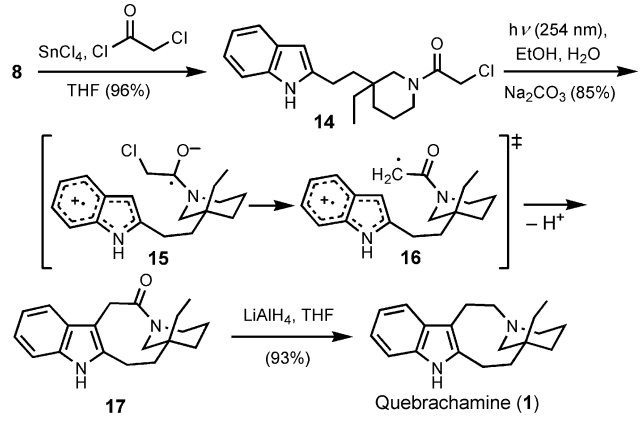


Scheme 5. Mitsunobu/*N*-alkylation cyclization approach.

After removal of the benzylic group, the secondary lactam **10** was subjected to Mitsunobu reaction conditions. Additionally, the halide derivatives **11** and **12** were treated with a variety of bases with the expectation that a slow intramolecular alkylation would ensue; however, both Mitsunobu and S_N2 strategies proved futile. We then moved away from anionic alkylation conditions in favor of a neutral amine nucleophile prepared by reduction of the lactam, but after generation of the β-haloethyl side-chain the material became too unstable for further investigation. In some

cases it appears that the nucleophilicity of the indole was interfering with the desired cyclization, generating either complex mixtures or the three-membered spirocycle **13**. Attempts to attenuate the indole nucleophilicity by installing a TMS or Boc protecting group on several advanced intermediates proved surprisingly elusive, perhaps due to the steric hindrance from the side chain.

After extensive exploration of these classic alkylation and acylation strategies, our successful route turned to a photo-induced ring closure (Scheme 6). Chloroacetamide Witkop photocyclizations[16] are important yet perhaps underutilized synthetic processes that have been employed in the formation of medium-sized lactams,[17] and in the synthesis of Vinca and Strychnos alkaloids.[18] We were initially apprehensive about the potential efficiency of this process because while simple substrates, such as isotryptamine,[18d] cyclize in high yield, substrates with complexity comparable to that of quebrachamine reportedly do so in low to modest yields (15–55%).[18]



Scheme 6. Cyclization and completion.

Preparation of the photocyclization precursor began with acylation of piperidine **8** with chloroacetyl chloride. Upon irradiation of chloroacetylated amine **14** (254 nm, Na_2CO_3, EtOH/H_2O), we were delighted to find the desired cyclization product **17** in an unprecedented 85% yield. The photocyclization mechanism likely involves photo-excitation and electron-transfer steps leading to an initial diradical species **15**.[17] After chloride ionization, intramolecular cyclization of **16** occurs at C3 of the indole, which is likely the most favorable position for attack based on geometric considerations and calculated spin density.[19] To complete the synthesis, treatment of tetracyclic lactam **17** with $LiAlH_4$ secured (±)-quebrachamine (**1**) in 93% yield.

Conclusions

In summary, the total synthesis of (±)-quebrachamine (**1**) has been accomplished in 13 steps and 17.8% overall yield starting from commercially available δ-valerolactam. This work highlights the utility of indole synthesis by the formal [3+2] cycloaddition reaction between donor-acceptor cyclopropanes and nitriles. Additionally, it features a nine-membered ring synthesis by a remarkably efficient photo-induced cyclization strategy. Studies are underway to develop an asymmetric synthesis of nitrile **4**.

Experimental Section

Ethyl 2-[2-(1-Benzyl-3-ethyl-2-oxopiperidin-3-yl)ethyl]-1*H*-indole-3-carboxylate (6): Tetra-substituted pyrrole **3** (4.38 g, 10.0 mmol) was added to a suspension of palladium on carbon (5% Pd/C, 665 mg) in mesitylene (100 mL) and refluxed for 1 d. The palladium was removed by filtration through a pad of silica gel and Celite. After the solution was concentrated under reduced pressure, purification by flash chromatography on silica gel using EtOAc/hexanes for elution, which provided the title compound as a white solid (98%, 4.24 g). R_f = 0.18 (33% EtOAc in hexanes); m.p. 134–136 °C (hexanes/EtOAc crystal). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.69 (br. s, 1 H), 8.07 (d, J = 8.2 Hz, 1 H), 7.30–7.12 (m, 8 H), 4.69 (d, J = 14.6 Hz, 1 H), 4.54 (d, J = 14.6 Hz, 1 H), 4.39 (q, J = 7.0 Hz, 2 H), 3.62 (ddd, J = 6.4, 9.9, 14.0 Hz, 1 H), 3.29–3.19 (m, 2 H), 2.82 (ddd, J = 5.3, 9.9, 14.6 Hz, 1 H), 2.17 (ddd, J = 5.3, 9.9, 14.6 Hz, 1 H), 1.93–1.80 (m, 6 H), 1.66 (dq, J = 7.5, 15.0 Hz, 1 H), 1.45 (t, J = 7.0 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.4, 166.1, 149.0, 137.1, 134.8, 128.6, 127.7, 127.3, 126.9, 122.1, 121.2, 111.0, 103.4, 59.3, 50.7, 47.9, 45.8, 37.4, 31.6, 28.8, 22.9, 19.5, 14.6, 8.5 ppm. HRMS: *m*/*z* 432.2419 (calcd. for $C_{27}H_{32}N_2O_3$, 432.2413).

1-Benzyl-3-ethyl-3-[2-(1*H*-indol-2-yl)ethyl]piperidin-2-one (7): Indole **6** (4.32 g, 10.0 mmol) was dissolved in ethanol (85 mL) and a solution of sodium hydroxide (4.00 g, 100 mmol) in water (85 mL) was added. The mixture was heated to 150 °C in a microwave reactor for 3 h (900 rpm stirring). The mixture was cooled and neutralized with 1 M HCl. The volatiles were removed under reduced pressure and the residue was dissolved in 60 mL of EtOAc. The solution was extracted with EtOAc (3 × 60 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as yellow solid (69%, 2.49 g). R_f = 0.27 (33% EtOAc in hexanes); m.p. 96–98 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (br. s, 1 H), 7.50 (d, J = 8.2 Hz, 1 H), 7.32–7.22 (m, 6 H), 7.09 (app. t, J = 7.6 Hz, 1 H), 7.04 (app. t, J = 7.6 Hz, 1 H), 6.20 (s, 1 H), 4.66 (d, J = 14.6 Hz, 1 H), 4.53 (d, J = 14.6 Hz, 1 H), 3.22 (t, J = 5.3 Hz, 2 H), 2.86 (ddd, J = 5.8, 10.5, 15.2 Hz, 1 H), 2.66 (ddd, J = 4.7, 10.5, 15.2 Hz, 1 H), 2.19 (ddd, J = 4.1, 10.5, 13.5 Hz, 1 H), 1.88–1.77 (m, 6 H), 1.68 (dq, J = 7.5, 15.0 Hz, 1 H), 0.90 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.8, 140.0, 137.5, 136.0, 128.6, 127.9, 127.3, 120.8, 119.6, 119.3, 110.5, 99.1, 50.6, 47.7, 45.5, 37.8, 31.4, 29.1, 23.8, 19.6, 8.5 ppm. HRMS: *m*/*z* 360.2203 (calcd. for $C_{24}H_{28}N_2O$, 360.2202).

3-Ethyl-3-[2-(1*H*-indol-2-yl)ethyl]piperidin-2-one (2): A solution of lactam **7** (100 mg, 0.28 mmol) in THF (7.0 mL) and *tert*-butyl alcohol (0.30 mL) was cooled to –78 °C and liquid ammonia (5.0 mL) was added to the solution. Sodium metal (33 mg, 1.4 mmol) was cut into small portions, washed with dry hexanes and added to the ammonia mixture. The reaction mixture was stirred at –78 °C for 10 min and then solid NH_4Cl (200 mg) was added. The reaction was warmed to room temperature while the ammonia evaporated completely. Water (10 mL) was added and the heterogeneous mixture was separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash

chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as white solid (93% yield, 70.0 mg). R_f = 0.12 (80% EtOAc in hexanes); m.p. 170–172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.44 (br. s, 1 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.27 (d, J = 8.2 Hz, 1 H), 7.08 (app. t, J = 7.6 Hz, 1 H), 7.03 (app. t, J = 7.6 Hz, 1 H), 6.20 (s, 1 H), 5.91 (br. s, 1 H), 3.32–3.29 (m, 2 H), 2.86 (ddd, J = 5.8, 11.1, 15.2 Hz, 1 H), 2.68 (ddd, J = 4.1, 11.1, 14.6 Hz, 1 H), 2.13 (ddd, J = 4.7, 11.7, 14.0 Hz, 1 H), 1.86–1.75 (m, 6 H), 1.64 (dq, J = 7.5, 15.0 Hz, 1 H), 0.91 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.0, 139.9, 136.0, 128.6, 120.8, 119.6, 119.3, 110.5, 99.0, 45.0, 42.7, 37.7, 31.1, 29.0, 23.7, 19.6, 8.4 ppm. HRMS: *m*/*z* 270.1726 (calcd. for $C_{17}H_{22}N_2O$, 270.1732).

2-[2-(3-Ethylpiperidin-3-yl)ethyl]-1*H*-indole (8): A solution of lactam **2** (100 mg, 0.28 mmol) in THF (15 mL) was cooled to 0 °C and Red-Al® (0.55 mL, 2.80 mmol of 65 wt% in toluene) was added dropwise. The flask was fitted with a reflux condenser and the ice bath removed. The solution was warmed to room temperature slowly and was heated at reflux for 12 h. The mixture was cooled to 0 °C and poured into a saturated solution of sodium potassium tartrate (15 mL). After stirring for 1 h at room temperature, the heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using a MeOH/EtOAc gradient solvent system, which provided the title compound as an orange oil (93% yield, 67.0 mg). R_f = 0.03 (10% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.01 (br. s, 1 H), 7.51 (dd, J = 1.5, 7.0 Hz, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.09 (dt, J = 1.9, 7.6 Hz, 1 H), 7.04 (dt, J = 1.4, 7.3 Hz, 1 H), 6.23 (s, 1 H), 4.22 (br. s, 1 H), 2.96–2.90 (m, 1 H), 2.75–2.69 (m, 2 H), 2.67–2.62 (m, 2 H), 2.50 (d, J = 12.4 Hz, 1 H), 1.94 (ddd, J = 6.5, 10.2, 14.1 Hz, 1 H), 1.66 (ddd, J = 6.7, 10.2, 14.1 Hz, 2 H), 1.55–1.25 (m, 6 H), 0.85 (t, J = 5.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.2, 136.0, 128.7, 120.7, 119.5, 119.3, 110.4, 98.9, 54.0, 46.5, 34.6, 33.8, 32.9, 28.2, 21.8, 21.4, 7.1 ppm. HRMS: *m*/*z* 256.1931 (calcd. for $C_{17}H_{24}N_2$, 256.1939).

Ethyl {3-Ethyl-3-[2-(1*H*-indol-2-yl)ethyl]piperidin-1-yl}acetate (18): Amine **8** (109 mg, 0.42 mmol) was dissolved in MeCN (30 mL) and then diisopropylethylamine (96 μL, 0.55 mmol) was added slowly dropwise followed by ethyl bromoacetate (62 μL, 0.55). After 14 h, the solution was poured into 15 mL of 1 M HCl. The heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as a colourless oil (82% yield, 119 mg). R_f = 0.67 (10% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.79 (br. s, 1 H), 7.53 (d, J = 7.5 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.11 (td, J = 7.4, 1.5 Hz, 1 H), 7.07 (td, J = 7.3, 1.2 Hz, 1 H), 7.25 (d, J = 1.2 Hz, 1 H), 4.26 (d, J = 8.0 Hz, 1 H), 4.22 (d, J = 8.0 Hz, 1 H), 3.17 (q, J = 16.0 Hz, 2 H), 2.74–2.64 (m, 3 H), 2.51 (d, J = 11.0 Hz, 1 H), 2.31–2.27 (m, 1 H), 2.18–2.11 (m, 1 H), 1.99 (d, J = 11.0 Hz, 1 H), 1.81–1.71 (m, 1 H), 1.68–1.56 (m, 2 H), 1.52–1.43 (m, 2 H), 1.31 (t, J = 7.1 Hz, 3 H), 1.28–1.18 (m, 2 H), 0.90 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 140.9, 136.1, 128.8, 120.5, 119.5, 119.2, 110.4, 98.8, 62.0, 60.5, 60.0, 54.8, 35.9, 33.6, 33.1, 29.0, 22.1, 21.7, 14.2, 7.2 ppm. HRMS: *m*/*z* 342.2358 (calcd. for $C_{21}H_{30}N_2O_2$, 342.2307).

{3-Ethyl-3-[2-(1*H*-indol-2-yl)ethyl]piperidin-1-yl}acetic Acid (9): Ester **18** (85 mg, 0.25 mmol) was dissolved in EtOH (5.0 mL) and 2 M NaOH (0.25 mL, 0.5 mmol) was added slowly dropwise. After 8 h, the solution was neutralized with 1 M HCl and concentrated under reduced pressure. The residue was dissolved in EtOAc and water (20 mL, 1:1) and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as colourless oil (73% yield, 57.0 mg). R_f = 0.05 (10% MeOH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.67 (br. s, 1 H), 7.45 (d, J = 7.2 Hz, 1 H), 7.33 (br. s, 1 H), 7.05–6.94 (m, 2 H), 6.12 (br. s, 1 H), 3.80–2.62 (m, 1 H), 3.58–3.45 (m, 1 H), 3.42–2.13 (m, 2 H), 2.95–2.76 (m, 1 H), 2.54–2.41 (m, 1 H), 2.39–2.25 (m, 1 H), 2.18–1.82 (m, 2 H), 1.16–1.35 (m, 3 H), 1.34–1.16 (m, 3 H), 0.99–0.83 (m, 2 H), 0.75 (br. s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.2, 139.9, 136.4, 128.4, 120.5, 119.4, 119.0, 111.0, 98.6, 59.5, 58.7, 53.9, 35.7, 31.6, 30.8, 29.6, 21.6, 18.9, 6.7 ppm. HRMS: *m*/*z* 314.1988 (calcd. for $C_{19}H_{26}N_2O_2$, 314.1994).

1-Benzyl-3-ethyl-3-{2-[3-(2-hydroxyethyl)-1*H*-indol-2-yl]ethyl}-piperidin-2-one (19): Indole **7** (25.0 mg, 0.06 mmol) was dissolved in 0.20 mL of methyl *tert*-butyl ether (MTBE) and cooled to –25 °C. A solution of KH (9.6 mg, 0.24 mmol) in 0.50 mL of MTBE was then added. $InBr_3$ (21.0 mg, 0.06 mmol) and butylated hydroxytoluene (1.00 mg, 0.005 mmol) were then added, followed by ethylene oxide (45 μL, 0.9 mmol) as a solution in 0.30 mL of MTBE. The flask was capped an the solution was held at 0 °C for 12 h. The solution was warmed to room temperature until the ethylene oxide evaporated. The solution was poured into 10 mL of water and the heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as yellow oil (55% yield, 13.0 mg). R_f = 0.55 (100% EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (br. s, 1 H), 7.49 (d, J = 7.6 Hz, 1 H), 7.32–2.23 (m, 6 H), 7.11 (td, J = 7.5, 1.3 Hz, 1 H), 7.08 (td, J = 6.6, 1.2 Hz, 1 H), 4.68 (d, J = 14.0 Hz, 1 H), 4.55 (d, J = 14.0 Hz, 1 H), 3.83 (t, J = 6.4 Hz, 1 H), 3.29–3.21 (m, 2 H), 2.96 (td, J = 2.2, 6.4 Hz, 2 H), 2.92–2.85 (m, 1 H), 2.53 (ddd, J = 4.0, 10.0, 14.0 Hz, 1 H), 2.17 (ddd, J = 3.9, 10.0, 14.0 Hz, 1 H), 1.85–1.65 (m, 8 H), 0.89 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.1, 137.3, 135.5, 128.6, 127.9, 127.3, 121.1, 119.0, 117.9, 110.6, 106.5, 62.8, 50.7, 47.8, 45.8, 38.3, 31.6, 28.9, 27.7, 21.6, 19.5, 8.4 ppm. HRMS: *m*/*z* 404.2474 (calcd. for $C_{26}H_{32}N_2O_2$, 404.2464).

3-Ethyl-3-{2-[3-(2-hydroxyethyl)-1*H*-indol-2-yl]ethyl}piperidin-2-one (10): The title compound was prepared from indole **19** using the same procedure as the deprotection of compound **7** and isolated as a colourless oil (91% yield). R_f = 0.19 (5% MeoH in EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.85 (br. s, 1 H), 7.50 (d, J = 7.4 Hz, 1 H), 7.26–7.24 (m, 1 H), 7.10–7.02 (m, 2 H), 6.10 (br. s, 1 H), 3.84 (t, J = 6.4 Hz, 2 H), 3.24–3.20 (m, 2 H), 2.99–2.94 (m, 2 H), 2.83 (ddd, J = 5.9, 12.0, 14.0 Hz, 1 H), 2.49 (ddd, J = 2.3, 12.0, 16.0 Hz, 1 H), 2.42 (br. s, 1 H), 2.10–2.02 (m, 1 H), 1.80–1.68 (m, 5 H), 1.65–1.54 (m, 2 H), 0.86 (t, J = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.2, 137.2, 135.5, 128.3, 120.9, 118.8, 117.9, 110.6, 106.6, 62.6, 45.1, 42.6, 38.2, 31.4, 28.7, 27.8, 21.4, 19.6, 8.3 ppm. HRMS: *m*/*z* 314.1985 (calcd. for $C_{19}H_{26}N_2O_2$, 314.1994).

3-{2-[3-(2-Chloroethyl)-1*H*-indol-2-yl]ethyl}-3-ethylpiperidin-2-one (11): Alcohol **10** (30 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (1.0 mL) and cooled to 0 °C. Methanesulfonyl chloride (10 μL,

0.13) and then Et_3N (40 μL, 028 mmol) were added dropwise. After 3 h at room temperature, the solution was poured into a saturated solution of $NaHCO_3$ (10 mL). The heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as yellow oil (52% yield, 48.0 mg). R_f = 0.41 (5% MeOH in EtOAc). Due to the instability of this compound, $^{13}C/^1H$ NMR and HRMS were not obtained. TLC analysis was the primary means of identification and it was used immediately.

3-{2-[3-(2-Bromoethyl)-1*H*-indol-2-yl]ethyl}-3-ethylpiperidin-2-one (12): CBr_4 (68 mg, 0.2 mmol) and PPh_3 (52.0 mg, 0.2 mmol) were added to a solution of alcohol **10** (43 mg, 0.13 mmol) in CH_2Cl_2 (0.60 mL). After 3 h, the solution was concentrated under reduced pressure. The residue was purification by flash chromatography on silica gel using EtOAc/hexanes for elution. The semi-pure product was triturated with cyclohexane to provide the title compound as colourless oil (95% yield, 48.0 mg). R_f = 0.29 (5% MeOH in EtOAc). Due to the instability of this compound, $^{13}C/^1H$ NMR and HRMS were not obtained. TLC analysis was the primary means of identification and it was used immediately.

3-Ethyl-3-{3-[(*E*)-2-(1-methylcyclopropyl)phenylimino]propyl}-piperidin-2-one (13): A solution of PPh_3 (25.0 mg, 0.095 mmol) and diisopropyl azodicarboxylate (19.0 mg, 0.09 mmol) in 2.0 mL of THF was maintained at room temperature for 30 min and then cooled to 0 °C. A solution of indole **10** (20 mg, 0.063 mmol) in THF (0.75 mL) was added and stirred for 12 h at room temperature. The heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as yellow oil (50–56% yield). R_f = 0.18 (5% MeOH in EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.4 Hz, 1 H), 7.30 (t, J = 7.7 Hz, 1 H), 7.15 (t, J = 7.4 Hz, 1 H), 6.95 (d, J = 6.8 Hz, 1 H), 5.61 (br. s, 1 H), 3.29 (dt, J = 5.8, 1.9 Hz, 2 H), 2.48 (ddd, J = 5.9, 11.2, 15.1 Hz, 1 H), 2.25 (ddd, J = 5.4, 11.0, 16.0 Hz, 1 H), 2.07–2.01 (m, 2 H), 1.97–1.93 (m, 1 H), 1.90–1.68 (m, 7 H), 1.63–1.54 (m, 2 H), 0.89 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.1, 137.0, 135.3, 127.8, 127.1, 119.1, 117.5, 110.7, 107.0, 45.3, 44.7, 42.7, 37.8, 31.2, 28.9, 28.2, 21.4, 19.5, 8.4 ppm.

The title compound can also be prepared by adding a solution of indole **11** or **12** (0.05 mmol) in THF (8.0 mL) to a slurry of NaH in 1.6 mL of THF. The solution was heated to reflux for 30 min, cooled and then poured into 10 mL of water. The heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as yellow oil.

2-Chloro-1-{3-ethyl-3-[2-(1*H*-indol-2-yl)ethyl]piperidin-1-yl}-ethanone (14): A tin(IV) chloride solution (0.34 mL, 0.34 mmol, 1 M in CH_2Cl_2) was added slowly dropwise to a solution of amine **8** (40 mg, 0.16 mmol) in CH_2Cl_2 (8.0 mL) at 0 °C and stirred for 10 min. Chloroacetyl chloride (12 μL, 0.16 mmol) and 0.80 mL of $EtNO_2$ were then added. After 12 h at room temperature, the solution was poured into 15 mL of water and the heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 15 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as colourless oil (96% yield, 51.0 mg). R_f = 0.57 (100% EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 8.70 (br. s, 1 H), 7.49 (d, J = 7.8 Hz, 1 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.08 (td, J = 1.2, 7.5 Hz, 1 H), 7.02 (td, J = 1.1, 7.4 Hz, 1 H), 6.18 (s, 1 H), 4.24 (d, J = 13.3 Hz, 1 H), 4.18 (d, J = 12.0 Hz, 1 H), 4.13 (d, J = 12.0 Hz, 1 H), 3.69 (ddd, J = 3.7, 13.1 Hz, 1 H), 3.18 (ddd, J = 3.5, 10.2, 13.8 Hz, 1 H), 2.77 (dt, J = 3.1, 12.0 Hz, 1 H), 2.70–2.62 (m, 2 H), 1.69–1.58 (m, 5 H), 1.53–1.36 (m, 3 H), 0.92 (t, J = 7.5 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 140.3, 136.1, 128.6, 120.6, 119.5, 119.1, 110.6, 98.8, 50.3, 47.7, 41.1, 37.1, 34.5, 32.9, 28.5, 22.6, 22.0, 7.1 ppm. HRMS: *m/z* 332.1647 (calcd. for $C_{19}H_{25}ClN_2O$, 332.1655).

(±)-Quebrachamine (1): Lactam **17** (9.0 mg, 0.03 mmol) in THF (2.0 mL) was added to a cooled (0 °C) suspension of $LiAlH_4$ (6.0 mg, 0.15 mmol) in THF (1.0 mL). The solution was warmed to room temperature slowly and heated to refluxe for 3 h. The mixture was cooled to 0 °C and poured into a saturated solution of sodium potassium tartrate (15 mL). After 1 h at room temperature, the heterogeneous mixture was separated and the aqueous layer was extracted with EtOAc (5 × 10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel using EtOAc/hexanes for elution provided the title compound as a white solid (93% yield, 8.0 mg). R_f = 0.39 (100% EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (br. s, 1 H), 7.47 (d, J = 7.0 Hz, 1 H), 7.26 (dd, J = 7.0, 1.5 Hz, 1 H), 7.08 (td, J = 7.0, 1.5 Hz, 1 H), 7.05 (td, J = 7.0, 1.5 Hz, 1 H), 3.24 (br. d, J = 11.7 Hz, 1 H), 2.92 (ddd, J = 4.4, 11.4, 16.0 Hz, 1 H), 2.83 (ddd, J = 2.9, 4.4, 15.0 Hz, 1 H), 2.75–2.64 (m, 2 H), 2.46–2.44 (m, 1 H), 2.41 (ddd, J = 2.9, 4.4, 11.4 Hz, 1 H), 2.32 (td, J = 11.5, 4.4 Hz, 1 H), 2.23 (td, J = 11.3, 3.2 Hz, 1 H), 1.91 (dd, J = 7.0, 14.0 Hz, 1 H), 1.62–1.54 (m, 2 H), 1.49 (d, J = 11.7 Hz, 1 H), 1.32–1.27 (m, 2 H), 1.23–1.20 (m, 1 H), 1.17–1.08 (m, 2 H), 0.84 (t, J = 7.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.8, 134.7, 128.9, 120.1, 118.6, 117.3, 109.9, 108.7, 56.7, 55.0, 53.2, 37.1, 34.7, 33.4, 32.0, 22.6, 22.4, 21.9, 7.7 ppm. HRMS: *m/z* 282.2085 (calcd. for $C_{19}H_{26}N_2$, 282.2096).

Supporting Information (see also the footnote on the first page of this article): All spectroscopic data and general experimental procedures.

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