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DIASTEREOSELECTIVE SYNTHESIS OF (±)-DEETHYLEBURNAMONINE USING A CATALYTIC CYCLOPROPANE RING-OPENING/FRIEDEL-CRAFTS ALKYLATION STRATEGY

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Abstract – A short, diastereoselective synthesis of (±)-deethyleburnamonine is reported with an overall yield of ~18% over six steps. The key synthetic step involves an indium(III)-catalyzed tandem ring-opening/Friedel-Crafts alkylation of a donor-acceptor-acceptor amino cyclopropane to generate the ABDE portion of the target.

The *eburnan*[1] alkaloids and the structurally-related *tacaman*[2] alkaloids represent a large group of biologically-active, naturally-occurring indole alkaloids that are isolated from several plants of the *Apocyanaceae* and *Tabernaemontana* genera (Figure 1). Each member of the *eburnan* and *tacaman* families is characterized by a common pentacyclic framework (**1**) that contains either a *cis*- or *trans*-fused D/E ring system.[3] While the vast majority of compounds have a *cis*-fused D/E ring system, several important biologically-active derivatives, such as vindeburnol (**2**), possess a *trans*-fused junction. The *eburnan* skeleton has an ethyl group at C*(20)*, while the *tacaman* skeleton has the ethyl group at C*(14)* instead.[4] Many of these compounds exhibit a variety of pharmacological activities, ranging from antitumor activity to muscle-stimulating activity.[5] Over the past 10 years, numerous efforts to fully understand the compounds' modulatory effects on brain circulation and neuronal homeostasis have been reported.[6] For example, vincamine (**3**) has been shown to have neuroprotective effects resulting from the blockage of voltage-gated sodium ion channels. Similarly, vinpocetine (**5**), the most extensively studied cogener of the *eburnan* class, is currently prescribed in Europe (tradename: Cavinton) for the treatment of disorders arising from cerebrovascular and cerebral neurodegenerative diseases.[7] This therapeutic potential has led to intense pharmacological and synthetic studies over the past several decades.[8]

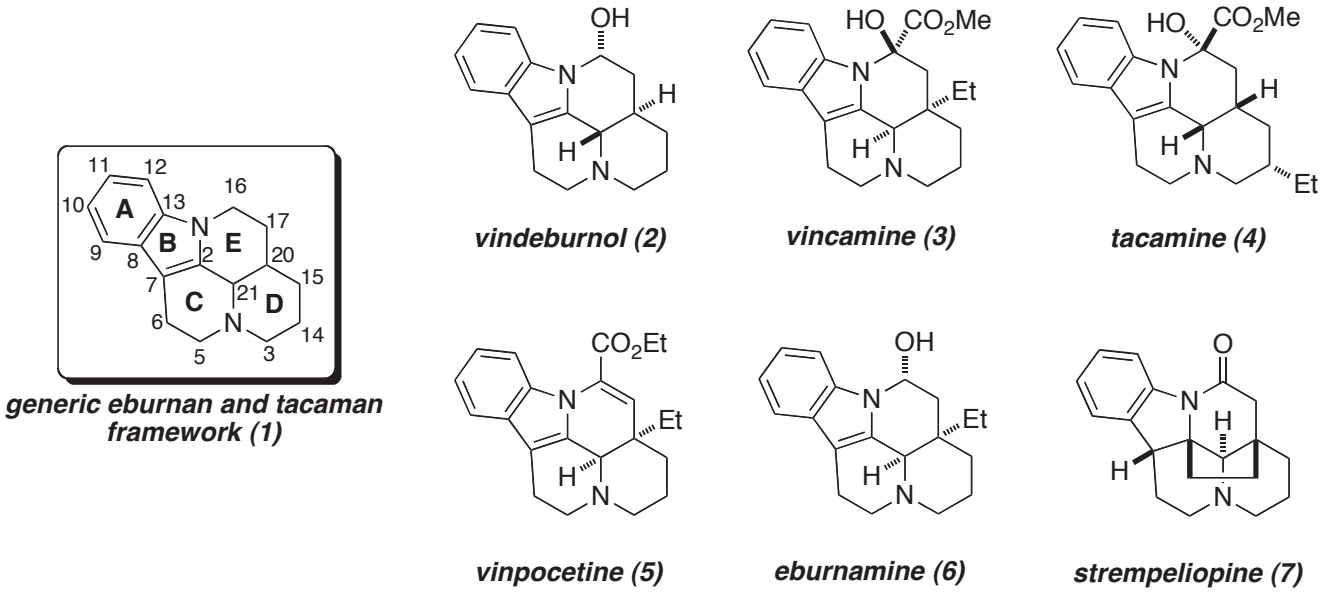
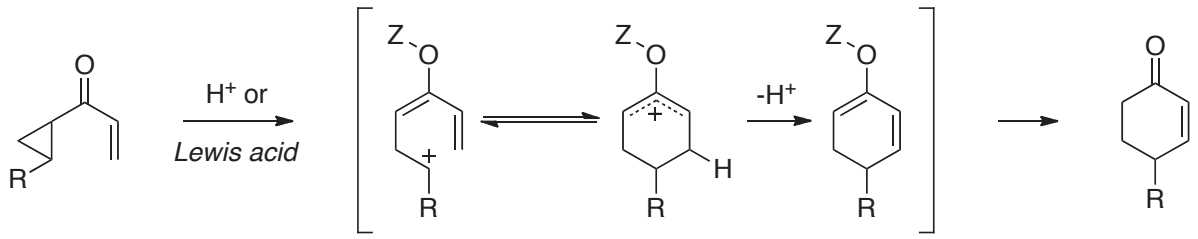


Figure 1. Representative *eburnan* and *tacaman* indole alkaloids

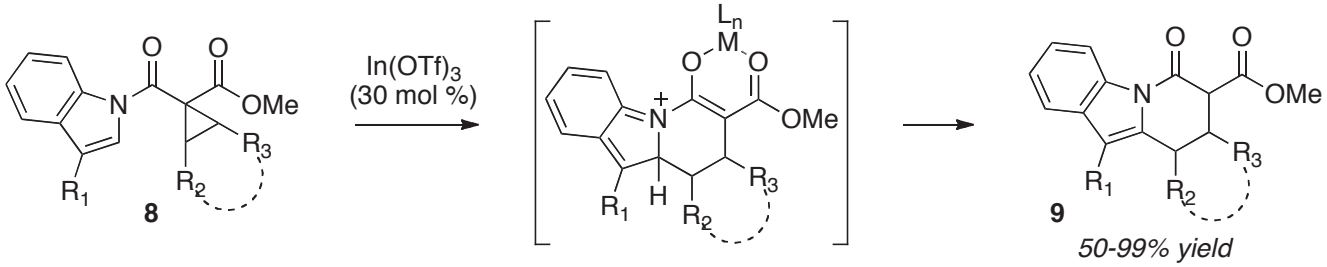
Of the synthetic strategies that have been reported for the assembly of the pentacyclic core, the most common approaches involve preparation of the ABCD ring system, with subsequent E-ring formation. The ABCD ring system is most often prepared by one of the following methods: (1) a Pictet-Spengler/Bischler-Napieralski cyclization;[9] (2) a Michael-type annulation;[10] or (3) annulation reactions of dihydro-β-carboline derivatives.[11] Recently, Padwa published an alternate route to the *eburnan* and *tacaman* alkaloids that involves a Rh(II)-catalyzed intramolecular dipolar cycloaddition of an α-diazo indoloamide, followed by reductive ring-opening and base-induced keto-amide ring contraction to build the full ADCDE skeleton.[12]



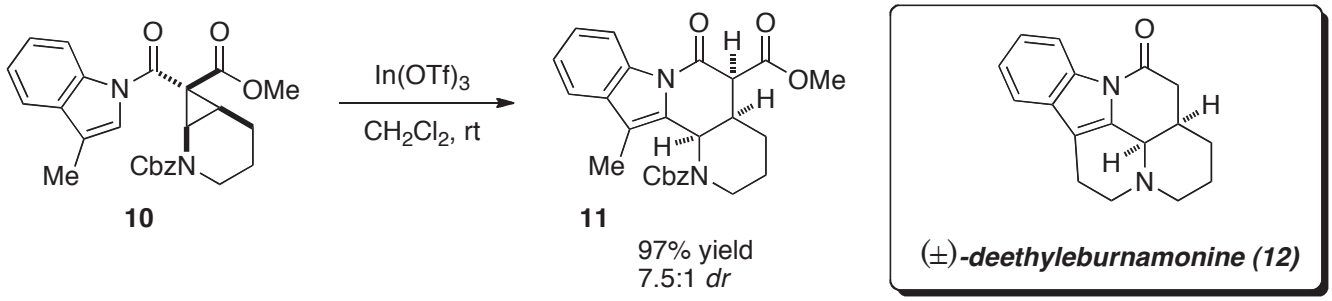
Scheme 1

In contrast to previous reports, our approach to the *eburnan* and *tacaman* alkaloids involves the initial assembly of the ABDE ring and stems from our recent success in the tandem ring-opening/intramolecular π cyclizations of donor-acceptor cyclopropanes, or homo-Nazarov cyclizations[13] (Scheme 1).[14] These reactions involve the acid-promoted heterolytic ring-opening of a donor-acceptor cyclopropane to

generate an acyclic cation, which is trapped intramolecularly by an adjacent π system to generate a six-membered cyclic oxyallyl cation. Deprotonation followed by tautomerization then affords the cyclohexenone product. We demonstrated that $In(OTf)_3$ (30 mol %) successfully catalyzes the cyclizations of alkenyl cyclopropyl ketones and cyclopropyl heteroaryl ketones to form the functionalized cyclohexyl rings.[15] The use of the donor-acceptor cyclopropanes bearing a secondary electron acceptor (an ester group) is essential, as it permits effective catalysis under mild reaction conditions. We recently disclosed an efficient method for the facile construction of 6,7,8,9-tetrahydropyrido[1,2-*a*]indole derivatives **9** in good to excellent yields (up to > 99%) using a tandem ring-opening/Friedel-Crafts alkylation strategy (Scheme 2).[16] The methodology is highly modular, operationally simple and amenable to a large variety of functional groups and substitution patterns.



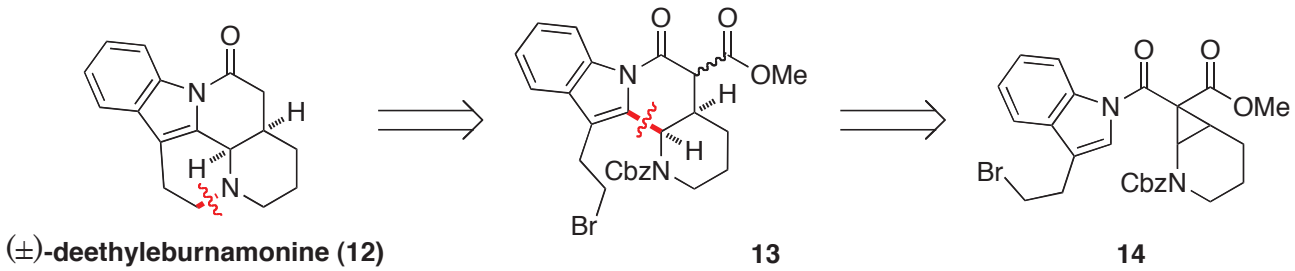
Scheme 2



Scheme 3

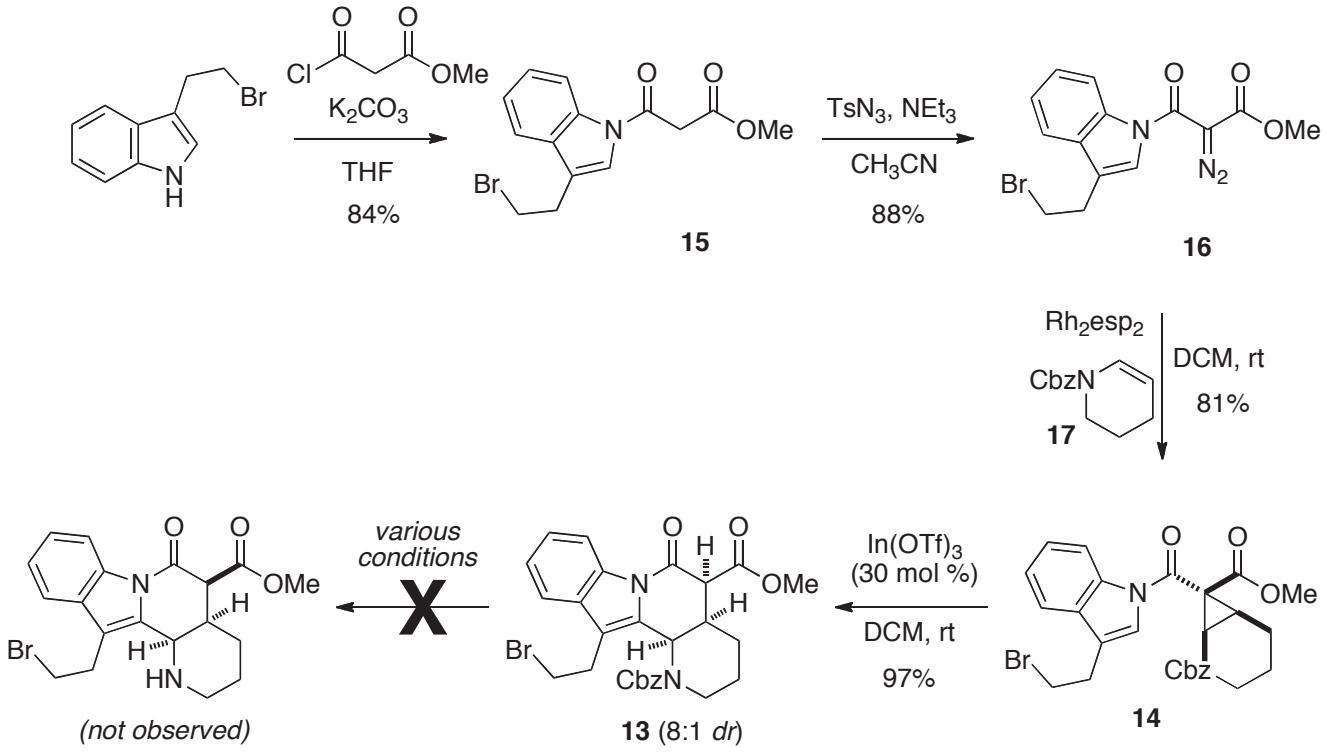
Encouraged by these results, we reasoned that the optimized method could be applied to the construction of the pentacyclic framework of the *eburnan* and *tacaman* classes of alkaloids, both of which possess the 6,7,8,9-tetrahydropyrido[1,2-*a*]indole ring system. For instance, the tetracyclic ABDE system was readily assembled from aminocyclopropane **10** using our method (Scheme 3). Under the standard reaction conditions, **10** provides the desired tetracyclic hydropyrido[1,2-*a*]indole based product **11** in 97% yield. It is important to note that the D/E ring contains only the 20,21-*cis*-ring junction with **11** being formed with a 7.5:1 diastereomeric preference for the all-*cis* isomer. This result led us to choose (±)-deethyleburnamonine (**12**) as an initial synthetic target because it represents the simplest example of

both the alkaloid classes (no ethyl group present). Moreover, the compound has interesting pharmacological properties.[17] (±)-Deethyleburnamonine was most recently synthesized by Lounasmaa in nine steps with an overall yield of ~18-20%.[18] In this report, we describe a short, diastereoselective approach to (±)-deethyleburnamonine using a catalytic tandem ring-opening/Friedel-Crafts alkylation protocol developed in our laboratory.



Scheme 4

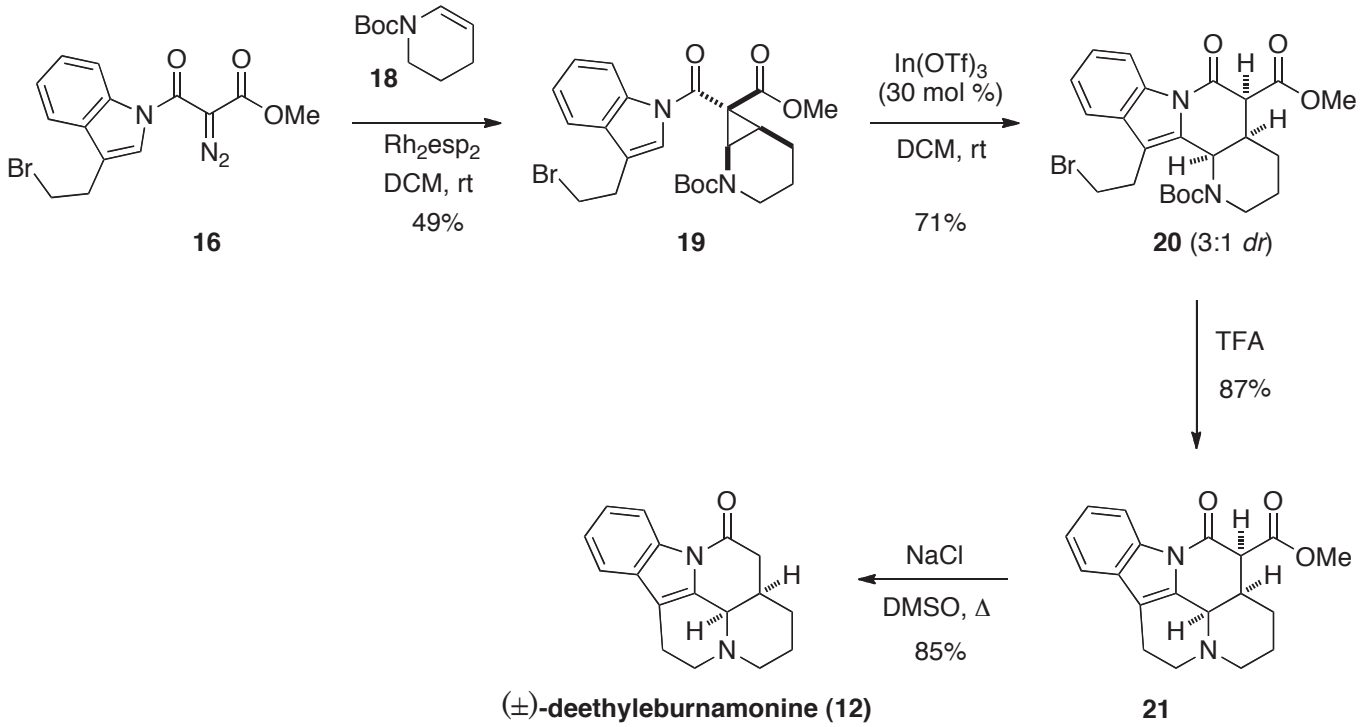
Our retrosynthetic approach is outlined in Scheme 4. We envisioned that (±)-dieethyleburnamonine would arise from the ABDE tetracycle **13** following *N*-deprotection, *N*-alkylation (C-ring formation), and decarbalkoxylation. Tetracycle **13** would be generated from the *N*-acylated indolyl cyclopropane **14** *via* our indium-catalyzed tandem cyclization.



Scheme 5

Success of the proposed route is predicated on facile access to cyclopropane **14**. Synthesis of **14** is readily achievable in three steps (Scheme 5). *N*-Acylation of commercially-available 3-(2-bromoethyl)-1*H*-indole provided the required β-ester amide **15** in 84% yield. Next, diazo transfer with tosyl azide provided the α-diazo ester **16** in 88% yield. Subsequent rhodium-catalyzed cyclopropanation in the presence of the Cbz-protected cyclic enamine **17** afforded the requisite cyclopropane **14** in 81% yield. Upon treatment with $In(OTf)_3$, cyclopropane **14** readily cyclized to form tetracycle **13** in 97% yield. The major product formed was the all-*cis* diastereomer with 8:1 *dr*. With **13** in hand, we anticipated that C-ring formation (*N*-alkylation) should be facile upon Cbz-deprotection. Unfortunately, the desired product was not observed when a variety of deprotection conditions were attempted, including hydrogenation.

To alleviate this issue, the Boc-protected enamine **18** was employed, which afforded cyclopropane **19** in 49% yield. The lower yield observed for the Boc-protected enamine is most likely due to the increased steric interference in the transition state between the *t*-Bu group of the enamine and the multi-dentate esp ligand of the rhodium carbenoid during cyclopropanation. Cyclization of **19** similarly provided the all-*cis* diasteromer **20** (~3:1 *dr*) but with less efficiency than the Cbz case (97% vs 71%), which may also be a result of the steric influence of the Boc *t*-butyl group. Fortunately, when **20** was subjected to TFA, both deprotection and C-ring closure occurred, generating **21** in 87% yield. Finally, Krapcho decarbalkoxylation[19] provided (±)-deethyleburnamonine (**12**) in 85% yield.



Scheme 6

In summary, we report a short, diastereoselective total synthesis of (±)-deethyleburnamonine. The key steps of the synthesis involve: (a) a tandem ring-opening/Friedel-Crafts alkylation to assemble the tetracyclic ABDE ring system with a *cis* D/E fused ring junction; (b) a TFA-promoted *N*-Boc deprotection/*N*-alkylation to generate the C-ring; and (3) a Krapcho decarbalkoxylation to generate the target. Using this protocol, (±)-deethyleburnamonine was obtained in 18% overall yield over six steps. Efforts towards the synthesis of other members of the *eburnan* and *tacaman* classes are currently underway and will be reported in due course.

EXPERIMENTAL

All reactions were carried out in pre-dried glassware from the oven where additional moisture was removed by flame drying the reaction vessel. Each reaction proceeded under a nitrogen atmosphere, and dry solvents were used, unless stated otherwise. Tetrahydrofuran and diethyl ether were distilled from a sodium/benzophenone ketyl under nitrogen and stored in a Schlenk flask. Acetonitrile and dichloromethane were purified by distillation from CaH_2 under N_2 prior to use. All other reagents were purchased from Acros, Sigma-Aldrich, Fluka, VWR, Merck, Alfa Aesar, TCI and Strem (for metal catalysts) and used without further purification. Chromatographic purification was performed as flash chromatography with Dynamic Adsorbents silica gel (32-65 μm) and solvents indicated as eluent with 0.1-0.5 bar pressure. For quantitative flash chromatography, technical grade solvents were utilized. Analytical thin-layer chromatography (TLC) was performed on EMD silica gel 60 F254 TLC glass plates. Visualization was accomplished with UV light, aqueous basic potassium permanganate ($KMnO_4$) solution, iodine, aqueous acidic dinitrophenylhydrazine (DNP) solution, aqueous acidic *p*-anisaldehyde (PAA) solution, and ethanol solution of phosphomolybdic acid (PMA) followed by heating. Each yield refers to isolated analytically pure material. Infrared (IR) spectra were obtained using a Nicolet 4700 FTIR with an ATR attachment from SmartOrbit Thermoelectronic Corp. The IR bands are characterized as weak (w), medium (m), and strong (s). Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded on a Varian Mercury Vx 300 spectrometer or a Varian Mercury Vx 400 spectrometer with solvent resonances as the internal standard (^{1}H NMR: $CDCl_3$ at 7.26 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm). ^{1}H NMR data are reported as follows: chemical shift (ppm), multiplicity (s = singlet, d = doublet, dd = doublet of doublets, dt = doublet of triplets, ddd = doublet of doublet of doublets, t = triplet, m = multiplet), coupling constants (Hz), and integration. Mass spectra were obtained using a VG-70SE instrument.

Preparation of N-Cbz-protected aminocyclopropane (14)

In a round bottom flask charged with a magnetic stir bar, Rh_2esp_2 (1.4 mg, 1.87 μmol) was dissolved in CH_2Cl_2 (6 mL). The reaction vessel was cooled to 0 ˚C and benzyl 3,4-dihydropyridine-1(2*H*)-

carboxylate (**17**, 0.037 g, 0.187 mmol) was added. After 10 min, 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-2-diazo-3-oxopropanoate (**16**, 0.085 g, 0.243 mmol) was dissolved in CH_2Cl_2 (2 mL) and syringed into the reaction mixture. After 10 min, the ice bath was removed and the reaction proceeded at room temperature. After 12 h, the solution was quenched with saturated thiourea and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (30% EtOAc/Hexanes, R_f 0.25) to afford **14** as a light brown oil (0.081 g, 81%). (Rotamers!!!) **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.2 Hz, 1H), 7.57 – 7.28 (m, 8H), 7.05 (d, *J* = 43.0 Hz, 1H), 5.19 (d, *J* = 3.2 Hz, 2H), 4.74 (d, *J* = 21.7 Hz, 1H), 3.79 (d, *J* = 3.3 Hz, 3H), 3.71 – 3.51 (m, 4H), 3.35 – 3.10 (m, 3H), 2.46 – 2.25 (m, 1H), 2.25 – 2.01 (m, 1H), 2.00 – 1.76 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.4, 168.3, 167.3, 167.2, 165.7, 165.7, 165.6, 165.5, 153.5, 152.9, 136.0, 135.9, 130.3, 130.1, 130.0, 128.5, 128.3, 128.2, 128.1, 128.0, 127.9, 126.8, 126.5, 126.3, 125.9, 125.7, 124.3, 124.1, 123.3, 123.1, 122.9, 122.4, 122.2, 120.4, 119.7, 119.2, 119.1, 118.6, 117.4, 117.1, 116.9, 116.7, 111.4, 111.3, 110.7, 110.6, 67.8, 67.7, 58.0, 57.9, 57.7, 53.4, 52.9, 52.9, 52.8, 43.3, 42.1, 41.9, 38.8, 38.7, 31.3, 30.9, 28.6, 28.4, 23.7, 23.2, 23.0, 22.9, 21.2, 19.3, 19.2. **IR**: 2951.9 (w), 2928.1 (w), 2847.1 (w), 1761.3 (s), 1703.26 (s), 1451.7 (s), 1370.7 (m), 1275.5 (m), 1218.3 (m), 1170.7 (m), 742.1 (s) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 538.1103, Obs. 538.1094.

Preparation of *N*-Cbz-protected ABDE tetracycle (13)

2-Benzyl 7-methyl 7-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (**15**, 0.045 g, 0.083 mmol) was added to a solution of $In(OTf)_3$ (0.014 g, 0.025 mmol) in CH_2Cl_2 (3 mL) at room temperature. Upon completion as monitored by TLC, the reaction mixture was quenched with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (25% EtOAc/Hexanes, R_f 0.25) to afford **13** as a pale brown oil (0.098 g, 98%) after 2 h. Diastereomeric ratio: (8:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 (dd, *J* = 14.5, 6.9 Hz, 1.07), 7.50 – 7.19 (m, 9.14), 5.93 (dd, *J* = 17.0, 4.6 Hz, 1), 5.30 – 5.06 (m, 2.54), 4.09 (d, *J* = 13.2 Hz, 1.16), 3.92 – 3.57 (m, 4.64), 3.56 – 2.76 (m, 5.17), 2.75 – 2.48 (m, 2.28), 1.77 (d, *J* = 10.4 Hz, 1.25), 1.53 (s, 2.17), 1.43 – 1.26 (m, 1.08). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.1, 162.8, 155.1, 136.0, 134.7, 130.2, 130.0, 129.1, 129.0, 128.5, 128.2, 128.1, 125.6, 125.5, 124.4, 124.3, 117.9, 117.8, 117.0, 116.7, 116.5, 68.2, 68.1, 55.9, 53.1, 52.5, 48.3, 42.5, 39.7, 37.7, 30.0, 27.2, 27.5, 26.6, 24.6. **IR**: 2950.4 (w), 2910.7 (w), 2880.6 (w), 1755.7 (s), 1719.2 (s), 1442.8 (m), 1275.6 (m), 758.2 (s) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 538.1103, Obs. 538.1105.

Preparation of N-Boc-protected aminocyclopropane (19)

In a round bottom flask charged with a magnetic stir bar, Rh_2esp_2 (1.0 mg, 1.319 μmol) was dissolved in CH_2Cl_2 (15 mL). The reaction vessel was cooled to 0 ˚C and *tert*-butyl 3,4-dihydropyridine-1(2*H*)-carboxylate (**17**, 0.201 g, 1.098 mmol) was added. After 10 min, methyl 3-(3-(2-bromoethyl)-1*H*-indol-1-yl)-2-diazo-3-oxopropanoate (**16**, 0.500 g, 1.422 mmol) was dissolved in CH_2Cl_2 (5 mL) and syringed into the reaction mixture. After 10 min, the ice bath was removed and the reaction proceeded at room temperature. After 12 h, the solution was quenched with saturated aqueous thiourea and stirred for 30 min. The organic layer was separated and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (30% EtOAc/Hexanes, R_f 0.25) afforded **19** as a colorless oil (0.271 g, 49%). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.47 (d, *J* = 8.1 Hz, 1H), 7.56 – 7.45 (m, 1H), 7.43 – 7.28 (m, 2H), 6.98 (d, *J* = 66.6 Hz, 1H), 4.74 (d, *J* = 9.4 Hz, 1H), 3.79 (d, *J* = 3.8 Hz, 3H), 3.70 – 3.35 (m, 4H), 3.27 (t, *J* = 6.9 Hz, 2H), 3.17 (t, *J* = 6.8 Hz, 1H), 2.45 – 2.04 (m, 2H), 1.93 – 1.76 (m, 2H), 1.47 (d, *J* = 7.5 Hz, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6, 165.8, 152.6, 151.8, 136.1, 129.9, 129.8, 127.9, 126.9, 126.7, 125.8, 124.1, 122.2, 121.9, 120.3, 119.6, 118.4, 117.1, 110.1, 109.3, 81.2, 81.1, 58.2, 52.9, 43.3, 42.2, 41.1, 34.6, 31.6, 31.2, 28.5, 28.4, 28.2, 25.3, 23.7, 23.0, 22.6, 21.4, 14.1. **IR**: 2998 (w), 2942.3 (w), 1725.2 (s), 1628.9 (s), 1468.9 (s), 1342.1 (s), 1185.6 (s), 760.4 (s) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 504.1300, Obs. 504.1251.

Preparation of *N*-Boc-protected ABDE tetracycle (20)

2-*tert*-Butyl 7-methyl 7-(3-(2-bromoethyl)-1*H*-indole-1-carbonyl)-2-azabicyclo[4.1.0]heptane-2,7-dicarboxylate (**19**, 0.075 g, 0.148 mmol) was added to a solution of $In(OTf)_3$ (0.030 g, 0.053 mmol) in CH_2Cl_2 (10 mL) at room temperature. Upon completion as determined by TLC, the reaction mixture was quenched with water and extracted three times with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel flash column chromatography (25% EtOAc/Hexanes, R_f 0.30) to afford **20** as a colorless oil (0.053 g, 71%) after 3 h. Diastereomeric ratio: (3.2:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.55 – 8.43 (m, 1.11H), 7.57 – 7.49 (m, 1.16), 7.42 – 7.30 (m, 2.5), 5.97 (s, 1), 4.05 (t, *J* = 11.6 Hz, 090), 3.84 (s, 1), 3.76 (d, *J* = 3.9 Hz, 2.87), 3.73 – 3.63 (m, 1.17), 3.52 (dt, *J* = 20.5, 12.0 Hz, 2.33), 3.33 – 3.05 (m, 2.64), 2.65 (d, *J* = 12.1 Hz, 2.39), 2.29 (d, *J* = 10.6 Hz, 0.22), 1.86 (d, *J* = 13.0 Hz, 1), 1.69 – 1.49 (m, 13.63). **^{13}C NMR** (75 MHz, $CDCl_3$) 168.2, 167.5, 163.0, 154.6, 154.3, 134.7, 134.5, 130.3, 130.1, 130.0, 129.7, 129.5, 125.4, 124.4, 124.2, 118.0, 117.9, 117.8, 116.7, 116.5, 81.1, 81.1, 56.0, 53.6, 53.1, 52.5, 50.2, 42.5, 40.3, 39.9, 37.6, 29.9, 28.4, 28.3, 27.5, 26.8, 24.7, 24.4, 22.8. **IR**: 2997.9 (w), 2961.3 (w), 1766.3 (m), 1726.7 (s), 1469.1 (s), 1186.1 (m), 760.3 (s), 663.1 (m) cm^{-1}. **HRMS** (ESI) M/Z^+ Calc. 504.1300, Obs. 504.1255.

Preparation of *N*-Boc-protected pentacycle (21)

Tetracycle **20** (0.030 g, 0.059 mmol) was dissolved in trifluoroacetic acid (2 mL) and stirred for 2 h. Saturated aqueous $NaHCO_3$ was slowly added to quench the reaction. The resulting mixture was extracted three times with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (1.5% MeOH/CH_2Cl_2, R_f 0.40) to afford **21** as a colorless oil (0.0168 g, 87% yield). Diastereomeric ratio: (5:1). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 – 8.30 (m, 1.11), 7.46 – 7.40 (m, 1.27), 7.36 – 7.25 (m, 2.45), 4.46 – 4.34 (m, 1.11), 3.84 (s, 0.60), 3.75 (d, *J* = 3.8 Hz, 3.24), 3.68 – 3.59 (m, 9.42), 3.36 – 3.28 (m, 2.61), 2.98 – 2.74 (m, 3.24), 2.68 – 2.33 (m, 4.88), 1.65 (ddd, *J* = 10.6, 9.2, 7.6 Hz, 4.01). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 168.6, 167.4, 164.0, 160.9, 135.3, 135.0, 128.4, 128.3, 127.7, 127.5, 126.9, 126.4, 124.8, 124.0, 122.1, 120.9, 120.3, 118.8, 117.2, 116.7, 112.6, 104.9, 77.4, 77.0, 76.6, 70.3, 55.3, 53.6, 53.1, 49.5, 48.4, 44.2, 35.8, 33.8, 32.4, 29.6, 27.0, 24.8, 16.1, 14.6. **HRMS** (ESI) M/Z^+ Calc. 324.1434, Obs. 324.1470.

Preparation of (±)-deethyleburnamonine (12)

To a 10 mL round bottom flask equipped with a stir bar, β-amide ester (**21**, 0.050 g, 0.154 mmol), NaCl (9.46 mg, 0.161 mmol), water (5.55 μL, 0.308 mmol) and DMSO (3 mL) were added at room temperature. The flask was fitted with a reflux condenser and heated to 150 ˚C with vigorous stirring. After heating for 16 h, TLC analysis indicated consumption of starting material. The reaction was cooled and diluted with 7:3 Hexanes/Et_2O (25 mL) and washed three times with water. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography (1.5% MeOH/CH_2Cl_2, R_f 0.40) to afford **12** as a white solid (0.0349 g, 85% yield). **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 1H), 7.36 – 7.27 (m, 2H), 4.40 – 4.30 (m, 1H), 3.39 – 3.29 (m, 2H), 3.02 – 2.83 (m, 2H), 2.72 – 2.57 (m, 3H), 2.46 (qdd, *J* = 10.9, 5.3, 3.1 Hz, 3H), 1.69 – 1.55 (m, 3H), 1.00 – 0.81 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.3, 134.3, 131.3, 129.8, 124.3, 123.8, 118.0, 116.2, 112.7, 53.4, 50.4, 44.5, 39.7, 34.3, 25.3, 24.7, 16.3. The physical characterization of the product matches the previously reported data in the literature (see ref. 17).

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