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Stereochemical Complexity in Oxocarbenium-Ion-Initiated Cascade Annulations for the Synthesis of the ABCD Core of Mattogrossine

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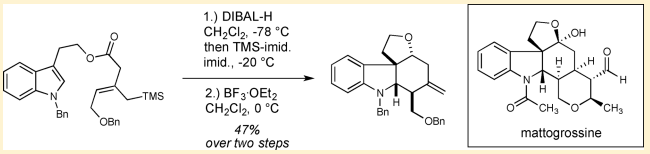
Supporting Information

ABSTRACT: Mattogrossine is an indole alkaloid isolated from *Strychnos mattogrossensis* that contains an unusual tetrahydrofuran ring with a concomitant hemiacetal in its structure. While tetrahydrofuran intermediates have been used in the synthesis of other strychnos alkaloids, no investigations have been performed into the synthesis of alkaloids containing this structure. We have developed an oxocarbenium-ion-initiated cascade annulation that provides us access to the ABCD ring structure of mattogrossine.



Challenged by the structural diversity of indole alkaloid natural products, many of which exhibit potent biological activities, we have pursued a research program aimed at developing a synthetic strategy that employs divergent cascade annulation reactions to efficiently access the core structures of these compounds.[1] In our initial investigation, we focused on developing an iminium-ion-initiated cascade for the synthesis of the Malagasy alkaloids, including malagashanine (**1**) and myrtoidine (**2**) (Figure 1A).[1a] During these studies, we became aware of the structural similarity between the Malagasy alkaloids, isolated from the Madagascan shrub *Strychnos myrtoides*, and mattogrossine (**3**), isolated from *Strychnos mattogrossensis*.[2] In nature, mattogrossine and malagashanine are postulated to arise from the common synthetic precursor strychnobrasiline (**4**), although the biosynthetic pathways have yet to be unambiguously established. Both possess a common pentacyclic framework with seven consecutive stereocenters. Intriguingly, mattogrossine possesses an unusual C ring tetrahydrofuran containing a C3 hemiacetal, in place of the more common C ring pyrrolidine typically found in strychnos alkaloids. Although indole alkaloid structures with C ring tetrahydrofurans have been synthesized as intermediates en route to traditional pyrrolidine containing natural products, there are no studies specifically addressing this motif in natural product synthesis.[3] Herein we outline a strategy for the synthesis of the ABCD core of mattogrossine by an oxocarbenium-ion-initiated cascade annulation reaction.

Based upon our previous studies toward related alkaloids,[1c] we envisioned that mattogrossine could be synthesized by elaboration of an ABCD core **5** (Figure 1B) and that this core could be accessed by cascade annulation of oxocarbenium ion intermediate **6** generated by Lewis acid mediated decomposition of a mixed acetal **7**. Initial reaction of the generated oxocarbenium ion with the tethered indole at the 3-position leads to formation of an indolenium ion, which upon trapping with a pendant allylsilane nucleophile would provide the ABCD core of mattogrossine in a single step. The requisite mixed acetal intermediate could be readily accessed by selective reduction and trapping of a simple ester intermediate. An analogous iminium ion cascade annulation was used by our group in the synthesis of the natural product malagashanine, providing the core of the natural product with high

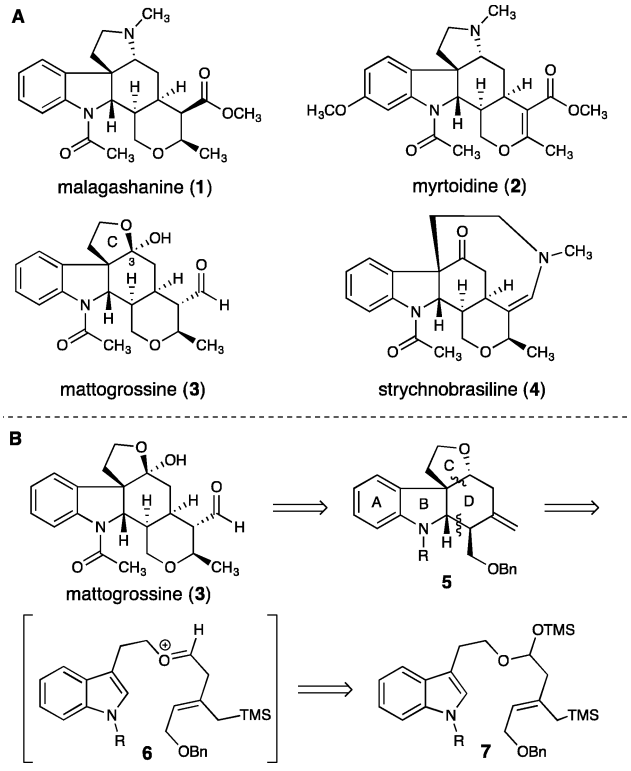


Figure 1. (A) Malagasy alkaloids and their proposed biosynthetic precursor, strychnobrasiline. (B) Retrosynthetic analysis for the synthesis of mattogrossine.

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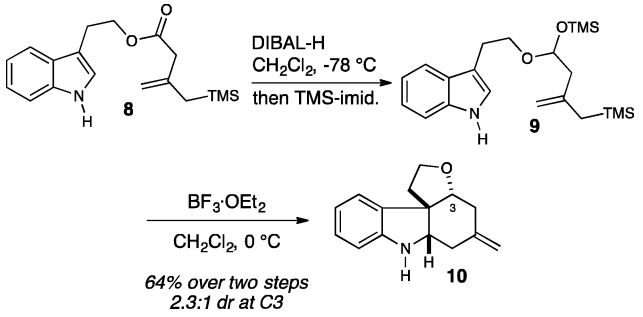
diastereoselectivity, with allylsilane geometry translating directly into stereochemistry observed in the formed alkaloid core.[1c] Unclear to us was whether this high level of diastereoselectivity would also translate into an oxocarbenium ion cascade annulation necessary for the synthesis of a mattogrossine core.

In our preliminary studies focused on cascade annulation reactions of iminium ions,[1a] we had demonstrated that this reaction could be extended to the cyclization of analogous oxocarbenium ion intermediates.[4] Tryptophol-derived ester **8** was reduced with DIBAL-H and in situ trapped by TMS-imidazole to form the sensitive mixed acetal **9** (Scheme 1).

Scheme 1. Synthesis and Cyclization of Mixed Acetal Intermediate 9 to Mattogrossine Core 10

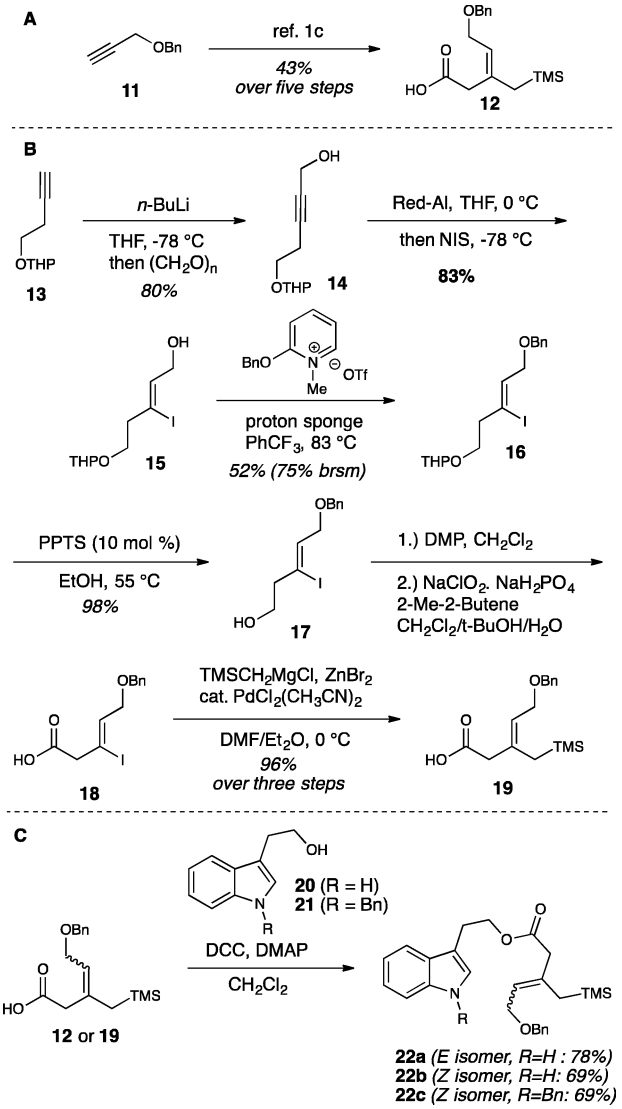


Subsequent decomposition of the mixed acetal with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 at 0 °C provided the tetrahydrofuran analog **10** in 64% yield with a 2.3:1 diastereoselectivity at the C3 position. Although this study demonstrated that the ABCD ring system of mattogrossine could be constructed by a cascade annulation, it did not address the feasibility of using trisubstituted allylsilanes necessary to introduce a required C16 substituent with the appropriate relative stereochemistry for the synthesis of mattogrossine.

Our investigations into the effect of trisubstituted allylsilanes on the cascade commenced with the synthesis of the *E*-allylsilane **12** and the *Z*-allylsilane **19**.[5] We have previously reported the synthesis of *E*-allylsilane **12**, readily available from benzyl propargyl ether **11** in five steps (43% yield), during our investigations into the synthesis of malagashanine (Scheme 2A).[1c] The complementary *Z*-allylsilane **19** can be prepared in seven steps from the THP acetal of 3-butyn-1-ol **13** (Scheme 2B). Deprotonation of the terminal alkyne in **13** with *n*-butyllithium followed by reaction with paraformaldehyde provided the propargyl alcohol **14** in 80% yield. The required alkene stereochemistry was set by *trans*-selective reduction of the propargyl alcohol **14** with Red-Al followed by trapping with *N*-iodosuccinimide, providing *Z*-vinyl iodide **15** in 83% yield.[6] This vinyl iodide proved particularly sensitive to elimination under even mildly basic conditions, proving problematic in the subsequent benzylation step. Ultimately, the use of Dudley's reagent[7] in the presence of a proton sponge provided acceptable yields (52%, 75% brsm) of benzyl ether **16** to continue the synthesis. Subsequent deprotection of the THP acetal with PPTS provided homoallylic alcohol **17** in 98% yield, which underwent oxidation[8] to the carboxylic acid **18** followed by Negishi cross-coupling which provided the *Z*-allylsilane **19** in 96% yield over three steps.[9]

With carboxylic acid substituted allylsilanes **12** and **19** in hand, we proceeded to synthesize the requisite oxocarbenium ion precursors (Scheme 2C). Each isomer was subjected to

Scheme 2. (A) Synthesis of *E*-Allylsilane 12; (B) Synthesis of *Z*-allylsilane 19; (C) Synthesis of Esters 22a–c



standard DCC-promoted esterification with tryptophol **20**, providing esters **22a** and **22b** in 78% and 69% yield, respectively.[10] To investigate the impact of indole protection on the cascade annulation reaction, an *N*-benzyl tryptophol ester **22c**, formed by DCC coupling of *Z*-allylsilane **12** and *N*-benzyl tryptophol[11] **21**, was also synthesized (69% yield). All three esters **22a–c** were reduced with DIBAL-H at −78 °C, and the resulting hemiacetal aluminates were subjected to transmetalation with trimethylsilylimidazole in the presence of excess imidazole, providing TMS acetals **23a–c** (Figure 2A). We note that additional imidazole promoted the transmetalation reaction and resulted in uniformly reproducible syntheses of the TMS acetals. In its absence, transmetalation was capricious, and yields of the TMS acetals were routinely inferior. In all cases, the TMS acetals were not stable to silica gel, and crude reaction mixtures were immediately subjected to the cyclization reactions.

When each TMS acetal substrate was subjected to $BF_3{\cdot}OEt_2$-mediated cyclization, a mixture of cyclization products was always observed (Figure 2B). For TMS acetal **23a** with a free indole and *E*-allylsilane geometry, the total isolated yield of

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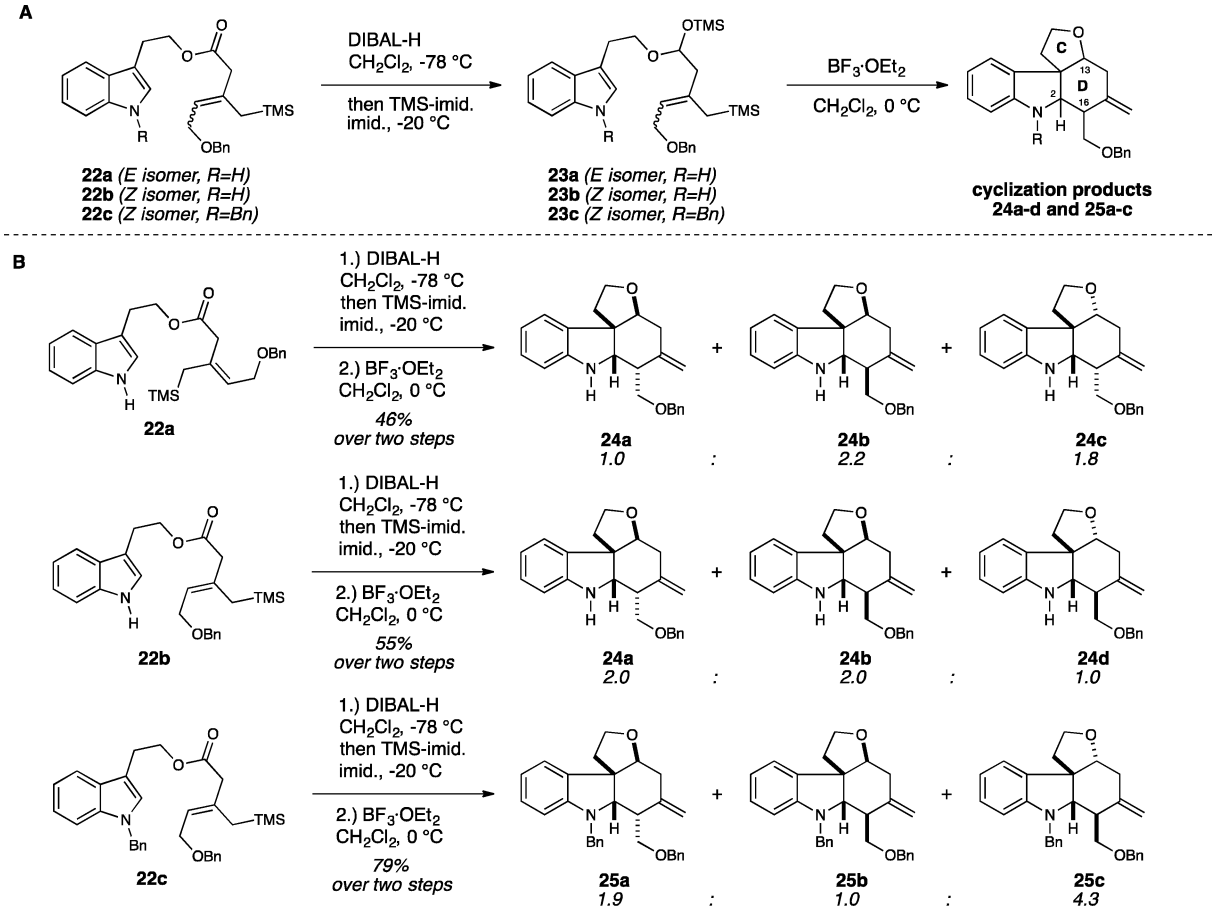

Figure 2. Cyclization reactions leading to the synthesis of mattogrossine cores.

three products was 46% from ester **22a** with a product ratio of **24a**:**24b**:**24c** = 1:2.2:1.8. For TMS acetal **23b** with a free indole and *Z*-allylsilane geometry, the total isolated yield of three products was 55% from ester **22b** with a product ratio of **24a**:**24b**:**24d** = 2:2:1. In both cases, an unprotected indole substrate provided predominantly products containing a *cis* C/D ring fusion as a mixture of C16 epimers. In contrast, with benzyl protection of the indole nitrogen in TMS acetal **23c**, this trend reversed and the *Z*-allylsilane isomer provided three products in 79% yield from ester **22c** with a product ratio of **25a**:**25b**:**25c** = 1.9:1:4.3. In all cases, the products containing a C/D *trans* fusion (**24c**, **24d**, and **25c**) were isolated as single diastereomers. Based on the observation that a fixed *cis* iminium ion geometry in the Corey group's synthesis of aspidophytine led to the selective formation of a *cis* fused C/D ring system[12] and our own observations that reversing the iminium ion geometry results in selective formation of the *trans* fused system,[1a] we postulate that the mixture of C/D ring fusion diastereomers reflects the ratio of oxocarbenium ion *E*/*Z* isomers trapped by each substrate under the reaction conditions.

The specific range of products observed for each cascade cyclization correspond to specific transition states for the allylsilane addition step (Figure 3). For substrates that lead to a *cis* C/D ring fusion (**24a**–**b** and **25a**–**b**), the mixture of diastereomers formed regardless of allylsilane geometry reflects a small energetic difference between boat- (**26a**) and chairlike (**26b**) transition states for the allylsilane addition step. For substrates that lead to a *trans* C/D ring fusion (**24c**–**d** and **25c**), single diastereomers that reflect the geometry of the starting allylsilane and are consistent with a chair transition state are isolated. This suggests a greater energy difference for the boat- and chairlike (**26c**) transition state for products with *trans* C/D ring fusions.

CONCLUSION

We have demonstrated herein the feasibility of an oxocarbenium-ion-initiated cascade cyclization for the formation of tetracyclic cores of the natural product mattogrossine. However, they are inherently more complicated than the analogous iminium ion cascades we have used previously for other alkaloid natural products, providing mixtures of diastereomeric products due to lower selectivity for discrete oxocarbenium geometries. Nevertheless, we have discovered reaction conditions that lead to the formation of a tetracyclic intermediate **25c** in 47% yield with the appropriate stereochemistry for use in a total synthesis of mattogrossine.

EXPERIMENTAL SECTION

General Information. Reactions were performed under a dry nitrogen atmosphere with anhydrous solvents using standard Schlenk techniques unless otherwise stated. Glassware was dried in an oven at 120 °C for a minimum of 6 h prior to use. Anhydrous tetrahydrofuran (THF), diethyl ether (Et_2O), and dichloromethane (CH_2Cl_2) were obtained by passage through activated alumina using a *Glass Contours* solvent purification system. Anhydrous *N*,*N*-dimethylformamide (DMF) was obtained from EMD Millipore and stored over dry 4 Å molecular sieves. Boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) was distilled under vacuum from calcium hydride directly before use.

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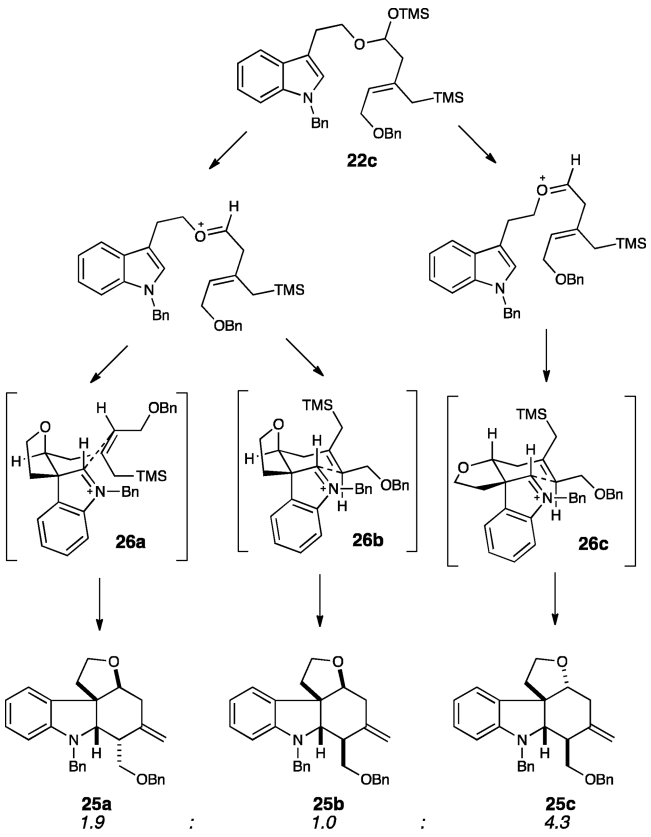

Figure 3. Stereochemical rationale for mattogrossine core cyclization products.

Schwartz reagent (Cp_2ZrHCl) was stored and weighed in a nitrogen-filled glovebox. $Pd(MeCN)_2Cl_2$[13] and Dess-Martin Periodinane (DMP)[14] were synthesized according to previously reported methods. All other reagents and solvents were obtained from commercial suppliers and used as received. Analytical thin layer chromatography (TLC) was performed on precoated glass backed Silicycle SiliaPure 0.25 mm silica gel 60 plates. Visualization was accomplished with UV light, ethanolic *p*-anisaldehyde, ethanolic phosphomolybdic acid, or aqueous potassium permanganate. Flash column chromatography was performed using Silicycle SilaFlash F60 silica gel (40–63 μm). Preparatory thin layer chromatography was performed on precoated glass backed Silicycle SiliaPure 1.0 mm silica gel 60 plates. ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Varian Inova 600 spectrometer (600 MHz ^1H, 151 MHz ^{13}C) and a Varian Inova 400 spectrometer (400 MHz + H, 100 MHz ^{13}C) at room temperature in $CDCl_3$ (neutralized and dried over anhydrous K_2CO_3) with internal $CHCl_3$ as the reference (7.26 ppm for ^1H and 77.23 ppm for ^{13}C), unless otherwise stated. Chemical shifts were reported in parts per million (ppm), and coupling constants (J values), in Hz. Multiplicity was indicated using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, b = broad. Infrared (IR) spectra were recorded using a Thermo Electron Corporation Nicolet 380 FT-IR spectrometer. High resolution mass spectra (HRMS) were obtained using a Thermo Electron Corporation Finigan LTQFTMS (at the Mass Spectrometry Facility, Emory University). We acknowledge the use of shared instrumentation provided by grants from the NIH and the NSF.

THP Acetal ***13****.* PPTS (110.0 mg, 0.44 mmol, 0.005 equiv) was added to a solution of 3-butyn-1-ol (6.3 g, 90.0 mmol, 1.0 equiv) and DHP (6.3 g, 90.0 mmol, 1.0 equiv) in CH_2Cl_2 (150.0 mL) at 23 °C, and the resulting mixture was stirred for 12 h. The reaction mixture was quenched with water (150.0 mL), and the organic layer was separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 30.0 mL). The combined organic layer was washed with brine (2 × 50.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by vacuum distillation (84–84.5 °C/14 mmHg) provided THP acetal **13** (13.5 g, 97%) as a colorless oil. Spectral data matched those previously reported in the literature.[15] R_f = 0.45 (5:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 4.66 (t, J = 3.6 Hz, 1H), 3.92–3.81 (m, 2H), 3.61–3.49 (m, 2H), 2.50 (td, J = 6.8, 2.4 Hz, 2H), 1.99 (t, J = 2.4 Hz, 1H), 1.85–1.80 (m, 1H), 1.78–1.69 (m, 1H), 1.65–1.50 (m, 4H) ppm.

Propargylic Alcohol ***14****.* A solution of THP acetal **13** (7.7 g, 50.0 mmol, 1.0 equiv) in THF (150.0 mL) was cooled to −78 °C. *n*-BuLi (2.5 M in hexanes, 22.0 mL, 55.0 mmol, 1.1 equiv) was slowly added over 30 min, and the resulting solution was stirred at −78 °C for 1 h. Paraformaldehyde (3.8 g, 125.0 mmol, 2.5 equiv) was added, and the resulting mixture was gradually warmed to room temperature and stirred for 14 h. The reaction was quenched with saturated aqueous NH_4Cl (45.0 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 100.0 mL). The combined organic layer was washed with brine (2 × 100.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (3:1 hexanes/EtOAc) afforded propargylic alcohol **14** (7.3 g, 80%) as a colorless oil. Spectral data matched those previously reported in the literature.[16] R_f = 0.20 (2:1 hexanes/EtOAc); ^1H NMR (400 MHz, CDCl3) δ 4.64 (t, J = 3.2 Hz, 1H), 4.24 (t, J = 2.0 Hz, 2H), 3.91–3.79 (m, 2H), 3.59–3.49 (m, 2H), 2.53 (tt, J = 6.8, 2.4 Hz, 2H), 1.99 (s, 1H), 1.86–1.78 (m, 1H), 1.73–1.69 (m, 1H), 1.63–1.50 (m, 4H) ppm.

Vinyl Iodide ***15****.* A solution of propargylic alcohol **14** (3.6 g, 19.2 mmol, 1.0 equiv) in THF (60.0 mL) was cooled to 0 °C. Red-Al (60 wt % in toluene, 9.8 mL, 32.6 mmol, 1.7 equiv) was slowly added over 15 min. The reaction mixture was stirred for 1 h at 0 °C and then was cooled to −78 °C. A solution of NIS (7.3 g, 32.6 mmol, 1.7 equiv) in THF (20.0 mL) was added. After 20 min at −78 °C, the reaction was quenched by slow addition of aqueous 15% Rochelle's salt solution (110.0 mL) and Na_2SO_3 aqueous solution (40.0 mL). The resulting mixture was gradually warmed to room temperature and stirred until both layers were clear. The layers were separated, and the aqueous phase was extracted with Et_2O (2 × 50.0 mL). The combined organic layer was washed with brine (2 × 30.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash column chromatography on silica gel (3:1 hexanes/EtOAc) afforded vinyl iodide **15** (5.0 g, 83%) as a colorless oil. Spectral data matched those previously reported in the literature.[17] R_f = 0.30 (2:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 5.95 (t, J = 6.0 Hz, 1H), 4.60 (t, J = 2.4 Hz, 1H), 4.18 (t, J = 4.2 Hz, 2H), 3.89–3.82 (m, 2H), 3.59–3.48 (m, 2H), 2.80 (t, J = 6.0 Hz, 2H), 2.12 (br s, 1H), 1.83–1.76 (m, 1H), 1.73–1.66 (m, 1H), 1.60–1.48 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 105.0, 99.1, 67.5, 66.1, 62.6, 45.5, 30.7, 25.6, 19.6 ppm.

Benzyl Ether ***16****.* A suspension of vinyl iodide **15** (5.4 g, 17.3 mmol, 1.0 equiv), Dudley's Reagent (12.1 g, 34.6 mmol, 2.0 equiv), and proton sponge (7.4 g, 34.6 mmol, 2.0 equiv) in $PhCF_3$ (35.0 mL) was heated to 83 °C for 24 h. After cooling to room temperature, the reaction mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. Purification by flash column chromatography on silica gel (10:1 hexanes/EtOAc) afforded benzyl ether **16** (3.6 g, 52%) as a colorless oil, in addition to 31% recovered starting material. R_f = 0.45 (9:1 hexanes/EtOAc); ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.29 (m, 5H), 5.97 (t, J = 6.0 Hz, 1H), 4.63 (t, J = 2.8 Hz, 1H), 4.54 (s, 2H), 4.12 (d, J = 4.2 Hz, 2H), 3.91–3.84 (m, 2H), 3.60–3.51 (m, 2H), 2.83 (t, J = 6.8 Hz, 2H), 1.85–1.77 (m, 1H), 1.74–1.67 (m, 1H), 1.63–1.50 (m, 4H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 134.0, 128.5, 128.0, 127.8, 105.5, 98.9, 74.6, 72.5, 66.0, 62.4, 45.6, 30.7, 25.6, 19.5 ppm; HRMS (+APCI) calculated for $C_{17}H_{24}I_1O_3$ $[M + H]^+$ 403.0770, found 403.0773.

Homoallylic Alcohol ***17****.* A solution of benzyl ether **16** (2.1 g, 5.3 mmol, 1.0 equiv) and PPTS (131.9 mg, 0.53 mmol, 0.1 equiv) in EtOH (90.0 mL) was heated to 55 °C for 90 min. The mixture was concentrated, and additional EtOH (30.0 mL) was added. The mixture was heated to 55 °C for 30 min. This procedure was repeated three times until the substrate was consumed, upon which the reaction mixture was concentrated under reduced pressure. Purification by flash

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column chromatography on silica gel (5:2 hexanes/EtOAc) afforded homoallylic alcohol **17** (1.6 g, 98%) as a colorless oil. R_f = 0.50 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 5H), 6.00 (t, J = 6.0 Hz, 1H), 4.55 (s, 2H), 4.12 (d, J = 5.6 Hz, 2H), 3.74 (t, J = 6.0 Hz, 2H), 2.74 (t, J = 6.0 Hz, 2H), 1.86 (br s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 134.9, 128.6, 128.1, 128.0, 105.8, 74.6, 72.9, 61.0, 48.2 ppm; IR (thin film, cm^{-1}) 3380, 2859, 1644, 1453, 1356, 1092, 1048, 1028, 735, 696; HRMS (+APCI) calculated for $C_{12}H_{14}O_1I_1$ [M − OH]$^+$ 301.0084, found 301.0085.

Carboxylic Acid ***19***. Dess-Martin periodinane (1.77 g, 4.16 mmol, 1.5 equiv) was added to a solution of homoallylic alcohol **17** (880 mg, 2.77 mmol, 1.0 equiv) in CH_2Cl_2 (30.0 mL), and the resulting suspension was stirred at room temperature for 5 h. The reaction was quenched with saturated aqueous $NaHCO_3$/20% aqueous Na_2SO_3 (1:1, 40.0 mL), and the resulting biphasic mixture was stirred for 15 min. The two layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (4 × 30.0 mL). The combined organic layer was washed with brine (50.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (4.2 mL) and *t*-BuOH (23.0 mL). 2-Methyl-2-butene (12.6 mL) was added, and the resulting mixture was stirred for 5 min. A solution of $NaClO_2$ (2.48 g, 27.4 mmol, 9.9 equiv) and NaH_2PO_4 (2.98 g, 24.8 mmol, 9.0 equiv) in H_2O (24.6 mL) was added, and the resulting mixture was stirred for 1 h. The reaction was quenched with brine (40.0 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 30.0 mL). The combined organic layer was washed with brine (50.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was azeotroped with benzene (3 × 30.0 mL) to thoroughly remove residual *t*-BuOH, providing crude carboxylic acid **18**, which was used without further purification.

To a flask charged with anhydrous $ZnBr_2$ (1.94 g, 8.6 mmol, 3.2 equiv) was added $TMSCH_2MgCl$ solution (1.0 M in Et_2O, 8.1 mL, 8.1 mmol, 3 equiv), and the resultant mixture was stirred at room temperature for 12 h. DMF (6.0 mL) and Et_2O (2.0 mL) were added, and the reaction was cooled to 0 °C. A solution of crude carboxylic acid **18** in DMF (5.0 mL) was added via cannula to the zinc suspension, and the reaction mixture was stirred for 5 min. A solution of $Pd(CH_3CN)_2Cl_2$ (70 mg, 0.27 mmol, 0.1 equiv) in DMF (1.0 mL) was added over 5 min, and the reaction mixture was warmed to room temperature and stirred for 4 h. The reaction was quenched with saturated aqueous NH_4Cl (20.0 mL) and EtOAc (40.0 mL), and the layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was filtered through Celite and rinsed with Et_2O (3 × 20.0 mL). The filtrate was washed with 10% aqueous LiCl (3 × 50.0 mL) and brine (3 × 50.0 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide carboxylic acid (744.9 mg, 94%) as a yellow oil, which was subsequently used without further purification. R_f = 0.09 (7:3 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.28 (m, 5H), 5.48 (t, J = 6.4 Hz, 1H), 4.51 (s, 2H), 4.99 (d, J = 6.4 Hz, 2H), 3.04 (s, 2H), 1.67 (s, 2H), 0.02 (s, 9H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.2, 137.3, 128.7, 128.3, 127.9, 121.9, 72.6, 66.0, 40.0, 29.8, 27.9, −1.2 ppm; IR (thin film, cm^{-1}) 3550−2560, 2952, 1707, 1657, 1247, 840; HRMS (+NSI) calculated for $C_{16}H_{25}O_3Si$ [M + H]$^+$ 293.1568, found 293.1566.

General Procedure for the Synthesis of Esters ***22a−c***. A solution of acid **12** or **19** (1.0 equiv) and tryptophol **20** or **21** (1.2 equiv) in CH_2Cl_2 (0.17 M in acid) was cooled to 0 °C. A solution of DCC (1.2 equiv) and DMAP (0.05 equiv) in CH_2Cl_2 (0.2 M in DCC) was slowly added to the acid solution. The resulting mixture was warmed to room temperature and stirred for 14 h. The reaction mixture was filtered through Celite, and the pad was rinsed twice with Et_2O. The filtrate was washed twice with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. Subsequent purification provided the desired esters **22a−c**.

Ester ***22a***. Purification by flash column chromatography on silica gel (10:1 to 5:1 hexanes/EtOAc) provided ester **22a** (338.9 mg, 78%) as a colorless oil. R_f = 0.65 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.39−7.28 (m, 6H), 7.21 (t, J = 7.2 Hz, 1H), 7.16−7.12 (m, 1H), 7.01 (t, J = 2.0 Hz, 1H), 5.44 (t, J = 7.2 Hz, 1H), 4.49 (s, 2H), 4.36 (t, J = 7.2 Hz, 2H), 4.05 (d, J = 6.8 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 3.05 (s, 2H), 0.06 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.7, 136.3, 135.1, 128.6, 127.9, 127.7, 127.6, 123.2, 122.3, 122.2, 119.6, 118.9, 112.0, 111.3, 71.8, 66.7, 65.0, 38.6, 28.3, 24.9, −1.1 ppm; IR (thin film, cm^{-1}) 3412, 2952, 1731, 1456, 1248, 1160, 1095, 850, 740, 698; HRMS (+NSI) calculated for $C_{26}H_{34}O_3N_1Si_1$ [M + H]$^+$ 436.2303, found 436.2300.

Ester ***22b***. Purification by flash column chromatography on silica gel (6:1 hexanes/EtOAc) provided ester **22b** (300.4 mg, 69%) as a colorless oil. %). R_f = 0.20 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.27−7.21 (m, 5H), 7.15 (td, J = 8.0, 0.8 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 7.6 Hz, 1H), 6.90 (d, J = 1.6 Hz, 1H), 5.34 (t, J = 6.4 Hz, 1H), 4.41 (s, 2H), 4.26 (t, J = 6.8 Hz, 2H), 3.90 (d, J = 6.4 Hz, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.89 (s, 2H), 1.52 (s, 2H), −0.09 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 138.5, 136.2, 135.2, 128.6, 128.3, 127.9, 127.5, 122.8, 122.6, 122.1, 119.5, 118.8, 111.9, 111.3, 72.5, 67.1, 64.9, 45.1, 24.8, 22.5, −0.8 ppm; IR (thin film, cm^{-1}) 3420, 2952, 1731, 1456, 1249, 1165, 1092, 1007, 853, 740; HRMS (+NSI) calculated for $C_{26}H_{33}O_3N_1Na_1Si_1$ [M + Na]$^+$ 458.2122, found 458.2120.

Ester ***22c***. Purification by flash column chromatography on silica gel (20:1 to 10:1 hexanes/EtOAc) provided ester **22c** (361.3 mg, 69%) as a colorless oil. R_f = 0.40 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 7.6 Hz, 1H), 7.33−7.23 (m, 10H), 7.18−7.07 (m, 3H), 6.96 (s, 1H), 5.42 (t, J = 6.4 Hz, 1H), 5.25 (s, 2H), 4.48 (s, 2H), 4.35 (t, J = 7.6 Hz, 2H), 3.96 (d, J = 6.8 Hz, 2H), 3.09 (t, J = 7.2 Hz, 2H), 2.98 (s, 2H), 1.61 (s, 2H), 0.00 (s, 9H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 138.7, 137.8, 136.8, 135.1, 129.0, 128.6, 128.4, 128.1, 127.8, 127.7, 127.0, 126.5, 123.0, 122.1, 119.4, 119.2, 111.3, 109.9, 72.3, 67.0, 65.0, 50.1, 45.1, 25.0, 22.6, −0.7 ppm; IR (thin film, cm^{-1}) 3029, 2952, 1731, 1467, 1454, 1249, 1163, 853, 738, 698; HRMS (+NSI) (m/z): calculated for $C_{33}H_{39}O_3N_1Na_1Si_1$ [M + Na]$^+$ 548.2591, found 548.2591.

General Procedure for the Synthesis of TMS Acetals ***23a−c*** *and Subsequent Cyclization Reactions*. A solution of ester **22a−c** (1.0 equiv) in CH_2Cl_2 (0.07 M) was cooled to −78 °C, and DIBAL-H (1.0 M in CH_2Cl_2 or hexanes, 3.0 equiv) was added over 10 min. The reaction was stirred for 45 min at −78 °C, and then imidazole (1.2 equiv) and TMS-imidazole (4.0 equiv) were added. The reaction mixture was warmed to −25 °C and stirred for 16 h, and then was further warmed to 0 °C and stirred for 3 h. The reaction was quenched with aqueous 15% Rochelle's salt and Et_2O, and the biphasic mixture was stirred vigorously until both layers were clear. The layers were separated, and the aqueous phase was extracted twice with Et_2O. The combined organic layer was washed with saturated aqueous $CuSO_4$ and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to provide the crude TMS acetals **23a−c**. These compounds were used without further purification due to their instability.

A solution of TMS acetal **23a−c** (1.0 equiv) in CH_2Cl_2 (0.04 M) was cooled to 0 °C. $BF_3{\cdot}OEt_2$ (3.0 equiv) was added, and the reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with saturated aqueous $NaHCO_3$, and the biphasic mixture was stirred for 15 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 three times. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure.

The crude mixture of reaction products formed from TMS acetal **23a** was purified by flash column chromatography on silica gel (10:1 to 3:1 hexanes/EtOAc), providing **24a**:**24b**:**24c** (82.2 mg, 46%) in a 1:2.2:1.8 ratio.

Mattogrossine Core ***24a***. R_f = 0.40 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.41−7.34 (m, 5H), 7.11 (d, J = 7.2 Hz, 1H), 7.06 (t, J = 7.2 Hz, 1H), 6.78 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 7.2 Hz, 1H), 4.98 (s, 1H), 4.88 (s, 1H), 4.66 (d, J = 12.6 Hz, 1H), 4.52 (d, J = 12.6 Hz, 1H), 4.15 (td, J = 9.0, 4.8 Hz, 1H), 4.05 (d, J = 3.6 Hz,

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1H), 4.01 (q, J = 8.4 Hz, 1H), 3.91 (dd, J = 9.6, 4.8 Hz, 1H), 3.69 (t, J = 9.0 Hz, 1H), 3.68 (t, J = 4.2 Hz, 1H), 2.97 (br s, 1H), 2.57 (ddd, J = 13.2, 8.4, 4.8 Hz, 1H), 2.53−2.52 (m, 2H), 2.14 (dt, J = 13.2, 8.4 Hz, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 150.3, 142.0, 138.3, 133.7, 128.8, 128.3, 128.2, 123.0, 119.4, 111.2, 110.1, 84.3, 73.4, 70.1, 67.5, 66.5, 53.6, 40.0, 38.3, 34.0 ppm; IR (thin film, cm^{-1}) 3360, 2927, 2862, 1699, 1652, 1558, 1486, 1457, 1076, 741; HRMS (+APCI) calculated for $C_{23}H_{26}O_2N$ $[M + H]^+$ 348.1958, found 348.1954.

Mattogrossine Core ***24b***. R_f = 0.35 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42−7.33 (m, 5H), 7.10 (d, J = 7.8 Hz, 1H), 7.09 (t, J = 7.8 Hz, 1H), 6.78 (t, J = 7.8 Hz, 1H), 6.65 (d, J = 7.8 Hz, 1H), 4.94 (s, 1H), 4.62 (s, 1H), 4.60−4.59 (m, 2H), 4.44 (t, J = 3.0 Hz, 1H), 4.02 (td, J = 9.0, 3.0 Hz, 1H), 3.94 (td, J = 9.0, 6.6 Hz, 1H), 3.89 (dd, J = 9.6, 4.2 Hz, 1H), 3.77 (t, J = 9.0 Hz, 1H), 3.45 (d, J = 8.4 Hz, 1H), 2.57 (dd, J = 13.8, 3.0 Hz, 1H), 2.43−2.40 (m, 1H), 2.39−2.33 (m, 2H), 1.91 (td, J = 12.6, 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.0, 141.7, 138.0, 131.2, 128.8, 128.5, 128.1, 128.0, 122.2, 119.1, 110.5, 80.2, 76.7, 73.9, 71.8, 67.0, 54.5, 43.3, 40.9, 37.6; IR (thin film, cm^{-1}) 3360, 2924, 2856, 2031, 1670, 1575, 1558, 1473, 1071, 743; HRMS [+ APCI] (m/z): calcd for $C_{23}H_{26}O_2N$ $[M + H]^+$: 348.1958, found 348.1953.

Mattogrossine Core ***24c***. R_f = 0.34 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42−7.33 (m, 6H), 7.13 (t, J = 7.8 Hz, 1H), 6.92−6.84 (m, 2H), 4.89 (s, 1H), 4.61 (s, 2H), 4.55 (s, 1H), 4.14−4.01 (m, 2H), 3.88 (dd, J = 9.0, 4.8 Hz, 1H), 3.69−3.64 (m, 2H), 3.59−3.54 (m, 1H), 2.64 (dd, J = 12.0, 4.2 Hz, 1H), 2.41 (t, J = 12.6 Hz, 1H), 2.34−2.29 (m, 1H), 2.20−2.14 (m, 1H), 2.04−2.18 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.5, 137.8, 128.8, 128.7, 128.2, 128.1, 127.9, 125.5, 111.1, 81.1, 74.0, 72.7, 68.6, 66.1, 55.9, 44.3, 38.7, 37.4 ppm; IR (thin film, cm^{-1}) 3374, 2922, 2879, 1736, 1604, 1477, 1462, 1101, 1052, 749; HRMS (+NSI) calculated for $C_{23}H_{26}O_2N$ $[M + H]^+$ 348.1958, found 348.1953.

The crude mixture of reaction products formed from TMS acetal **23b** was purified by flash column chromatography on silica gel (5:1 hexanes/EtOAc) and then preparatory thin layer chromatography (5:1 hexanes/EtOAc, deactivated with 6% Et_3N), providing **24a**:**24b**:**24d** (52.1 mg, 55%) in a 2:2:1 ratio.

Mattogrossine Core ***24d***. R_f = 0.34 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.43−7.35 (m, 5H), 7.09 (d, J = 7.2 Hz, 1H), 6.97 (t, J = 7.2 Hz, 1H), 6.63 (t, J = 7.2 Hz, 1H), 6.39 (d, J = 7.2 Hz, 1H), 4.65 (d, J = 12.0 Hz, 1H), 4.58 (s, 1H), 4.52 (d, J = 12.0 Hz, 1H), 4.42 (s, 1H), 4.22 (dd, J = 11.5, 7.2 Hz, 1H), 4.19−4.14 (m, 3H), 3.70−3.69 (m, 2H), 2.81−2.76 (m, 1H), 2.69−2.67 (m, 1H), 2.31 (dd, J = 15.6, 11.4 Hz, 1H), 2.25−2.19 (m, 1H), 2.16−2.12 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$, 150 MHz) δ 141.9, 138.1, 132.0, 128.8, 128.12, 128.10, 125.3, 118.2, 111.1, 73.7, 68.2, 67.3, 62.3, 55.7, 41.6, 40.1, 33.4 ppm; IR (thin film, cm^{-1}) 3360, 2924, 1993, 1698, 1652, 1558, 1540, 1456, 1081, 749; HRMS (+APCI) calculatedd for $C_{23}H_{26}O_2N$ $[M + H]^+$ 348.1958, found 348.1955.

The crude mixture of reaction products formed from TMS acetal **23c** was purified by flash column chromatography on silica gel (20:1 to 5:1 hexanes/EtOAc), providing **25a**:**25b**:**25c** (103.4 mg, 79%) in a 1.9:1:4.3 ratio.

Mattogrossine Core ***25a***. R_f = 0.50 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.22 (m, 10H), 7.08 (dd, J = 7.6, 1.2 Hz, 1H), 7.03 (td, J = 7.6, 1.2 Hz, 1H), 6.74 (td, J = 7.6, 0.8 Hz, 1H), 6.37 (d, J = 8.0 Hz, 1H), 5.05 (s, 1H), 4.94 (s, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.46−4.42 (m, 2H), 4.14 (d, J = 16.4 Hz, 1H), 3.96−3.91 (m, 2H), 3.88 (d, J = 4.8 Hz, 1H), 3.78 (t, J = 9.6 Hz, 1H), 3.74 (t, J = 4.0 Hz, 1H), 3.58 (dd, J = 9.6, 6.0 Hz, 1H), 3.17−3.13 (m, 1H), 2.64−2.54 (m, 2H), 2.38 (ddd, J = 13.2, 7.6, 4.4 Hz, 1H), 2.06 (dt, J = 13.2, 8.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9, 141.8, 139.3, 138.3, 134.9, 128.6, 128.5, 128.3, 128.1, 127.9, 127.4, 127.1, 122.5, 118.7, 114.5, 108.4, 84.4, 73.1, 72.5, 70.7, 67.3, 52.4, 51.9, 41.4, 41.3, 33.0 ppm; IR (thin film, cm^{-1}) 2929, 2853, 1604, 1484, 1453, 1354, 1100, 1074, 739, 698; HRMS (+NSI) calculated for $C_{30}H_{31}O_2N$ $[M]^+$ 437.2349, found 437.2348.

Mattogrossine Core ***25b***. R_f = 0.48 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.21 (m, 10H), 7.11−7.02 (m, 2H), 6.75 (t, J = 7.6 Hz, 1H), 6.26 (d, J = 8.0 Hz, 1H), 4.93 (s, 1H), 4.74 (s, 1H), 4.49 (t, J = 6.8 Hz, 1H), 4.45−4.41 (m, 2H), 4.14−4.06 (m, 2H), 3.98 (td, J = 8.4, 6.8 Hz, 1H), 3.93−3.88 (m, 2H), 3.72 (dd, J = 9.2, 7.2 Hz, 1H), 3.49 (t, J = 9.2 Hz, 1H), 3.20−3.12 (m, 1H), 2.70−2.56 (m, 2H), 2.50 (ddd, J = 13.2, 8.4, 5.6 Hz, 1H), 2.23−2.16 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 153.8, 142.1, 139.8, 138.4, 134.7, 132.5, 128.63, 128.60, 127.9, 127.8, 126.9, 126.8, 122.0, 118.7, 111.1, 107.9, 83.5, 73.3, 71.8, 69.2, 67.3, 54.5, 53.7, 42.1, 40.7, 32.5 ppm; IR (thin film, cm^{-1}) 2925, 2855, 1603, 1485, 1077, 738, 698 ppm; HRMS (+APCI) calculated for $C_{30}H_{32}O_2N$ $[M + H]^+$ 438.2428, found 438.2423.

Mattogrossine Core ***25c***. R_f = 0.46 (5:1 hexanes/EtOAc); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42−7.35 (m, 5H), 7.26−7.22 (m, 3H), 7.16−7.14 (m, 2H), 7.10 (dd, J = 7.2, 1.2 Hz, 1H), 7.08 (td, J = 7.2, 1.8 Hz, 1H), 6.67 (t, J = 7.2 Hz, 1H), 6.56 (d, J = 7.2 Hz, 1H), 4.72 (d, J = 15.6 Hz, 1H), 4.66 (s, 1H), 4.56−4.49 (m, 3H), 4.28 (d, J = 15.6 Hz, 1H), 4.22 (dd, J = 11.4, 6.6 Hz, 1H), 4.12−4.01 (m, 3H), 3.87−3.84 (m, 1H), 3.65 (dd, J = 9.0, 4.2 Hz, 1H), 2.82−2.77 (m, 2H), 2.34 (dd, J = 15.6, 11.4 Hz, 1H), 1.81 (dt, J = 11.4, 10.2 Hz, 1H), 1.69−1.66 (m, 1H) ppm; ^{13}C NMR (150 MHz, $CDCl_3$) δ 152.4, 142.2, 139.1, 138.2, 134.0, 128.7, 128.4, 128.2, 128.1, 128.0, 127.9, 127.2, 125.3, 118.1, 111.2, 108.9, 77.6, 73.6, 68.9, 66.8, 65.9, 55.8, 53.9, 42.9, 40.8, 33.2 ppm; IR (thin film, cm^{-1}) 3028, 2871, 1599, 1481, 1452, 1126, 1074, 1025, 742, 698; HRMS (+NSI) calculated for $C_{30}H_{31}O_2N$ $[M]^+$ 437.2349, found 437.2347.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00503.

Structural elucidation of mattogrossine cores **24a−d** and **25a−c**; NMR spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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