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THE CONCISE AND VERSATILE SYNTHESIS OF EPI-MALBRANCHEAMIDE AND STRUCTURALLY RELATED ANALOGS

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Abstract - The synthesis of C-19-*epi*-malbrancheamide and several structurally related analogs is reported.

INTRODUCTION

The unique family of prenylated indole alkaloids containing the characteristic bicyclo[2.2.2]diazaoctane core has grown quite significantly since the birth of the family in 1969, when brevianamides A and B (**1** and **2**, Figure 1) were isolated from *Penicillium brevicompactum* by Birch and co-workers.[1] While the brevianamides display insecticidal activity, other members of the family such as the paraherquamides, marcfortines, sclerotamides, VM55599 and the asperparalines have shown potential for use in veterinary medicine with their anthelmintic and antinematodal activity.[2] The most recent additions to the family, stephacidins A and B (**3** and **5**), avrainvillamide (**4**), and malbrancheamide (**6**), have brought about renewed interest in these compounds, due to their unique pharmacological profiles.[3,4,5,6] While avrainvillamide has antibiotic activity towards several Gram-positive bacteria, both the stephacidins and avrainvillamide show *in vitro* cytotoxicity against numerous human tumor cell lines.[3a, 4a] Stephacidin B displays good selectivity for prostate carcinoma (IC_{50} = 0.06 μM in LNCaP cell lines). Very interestingly, the stephacidins are thought to operate with a novel mechanism of action which has yet to be elucidated.[3a, 3c] Malbrancheamide is the first alkaloid in this family to possess a chlorinated indole, and its major difference from stephacidin A is the reduced tertiary lactam in the bicyclic core. Malbrancheamide has been shown to be a novel type of calmodulin (CaM) inhibitor, where the compound competes with the formation of the CaM-PDE1 active complex.[5] Calmodulin is a calcium-binding protein that can bind to and regulate a multitude of different protein targets, affecting many different cellular functions. Due to

this multifunctional role, CaM inhibitors have been proposed as potential pharmaceutical targets for a wide range of uses, including MDR (multi-drug resistance) modifying agents and tumor metastasis inhibition.[7] Therefore, this new natural product could have other pharmacological properties yet to be discovered.[5]

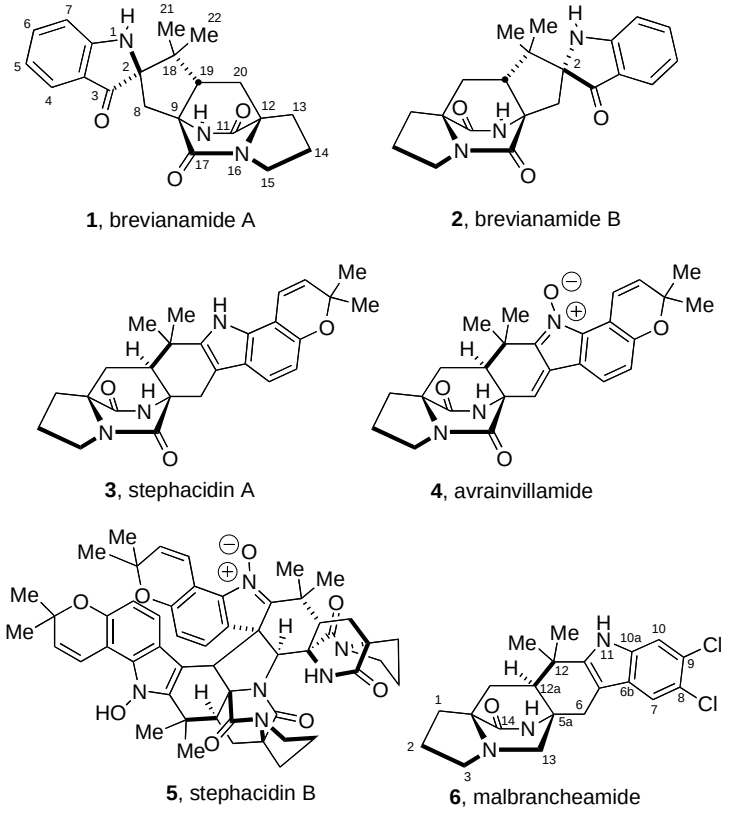


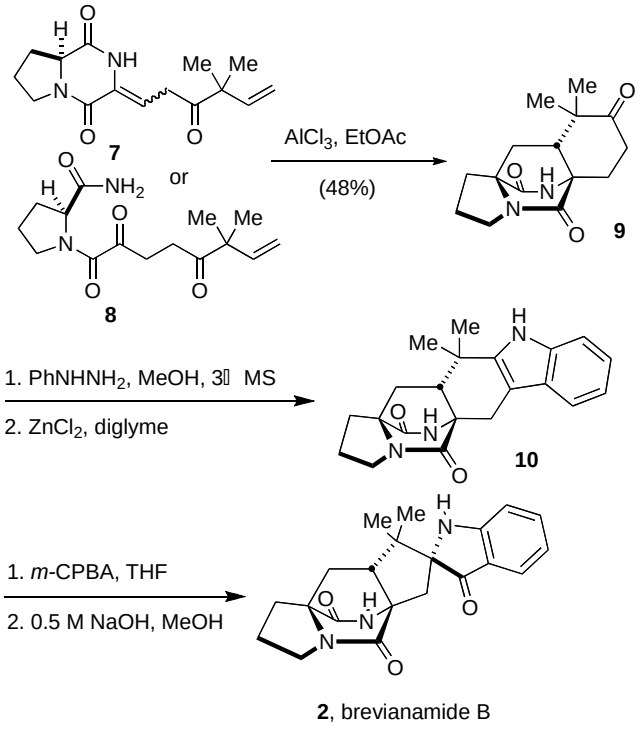
Figure 1. Structures of some of the bicyclo[2.2.2] indole alkaloids.

Recently, we have reported a concise synthesis of brevianamide B (**2**) through a key diastereoselective Diels-Alder reaction that establishes the characteristic bicyclo[2.2.2]diazaoctane core of **9** as the *anti*-diastereomer (Scheme 1).[8] Tricyclic ketone (**9**) was converted into brevianamide B through a Fischer indole reaction with phenyl hydrazine. The 2,3-disubstituted indole (**10**) has the same structural core as stephacidin A, yet is diastereomeric at C-12a (or C-19, brevianamide numbering) of the bicycle-[2.2.2]diazaoctane core. Herein, we have deployed this convergent strategy to access C-12a-*epi*-malbrancheamide (**18**) and *epi*-stephacidin-like derivatives that might prove to possess biological activities.

RESULTS AND DISCUSSION

The Fischer indole reaction was carried out with the hydrazones formed from the condensation of ketone (**9**) and various commercially available substituted hydrazines (Table 1). All of these reactions produced

the desired indole products but were somewhat lower yielding than the reaction that formed **10** from **9** with phenyl hydrazine. From these various Fischer indole reactions, some interesting trends in substitution patterns were observed and are discussed below.



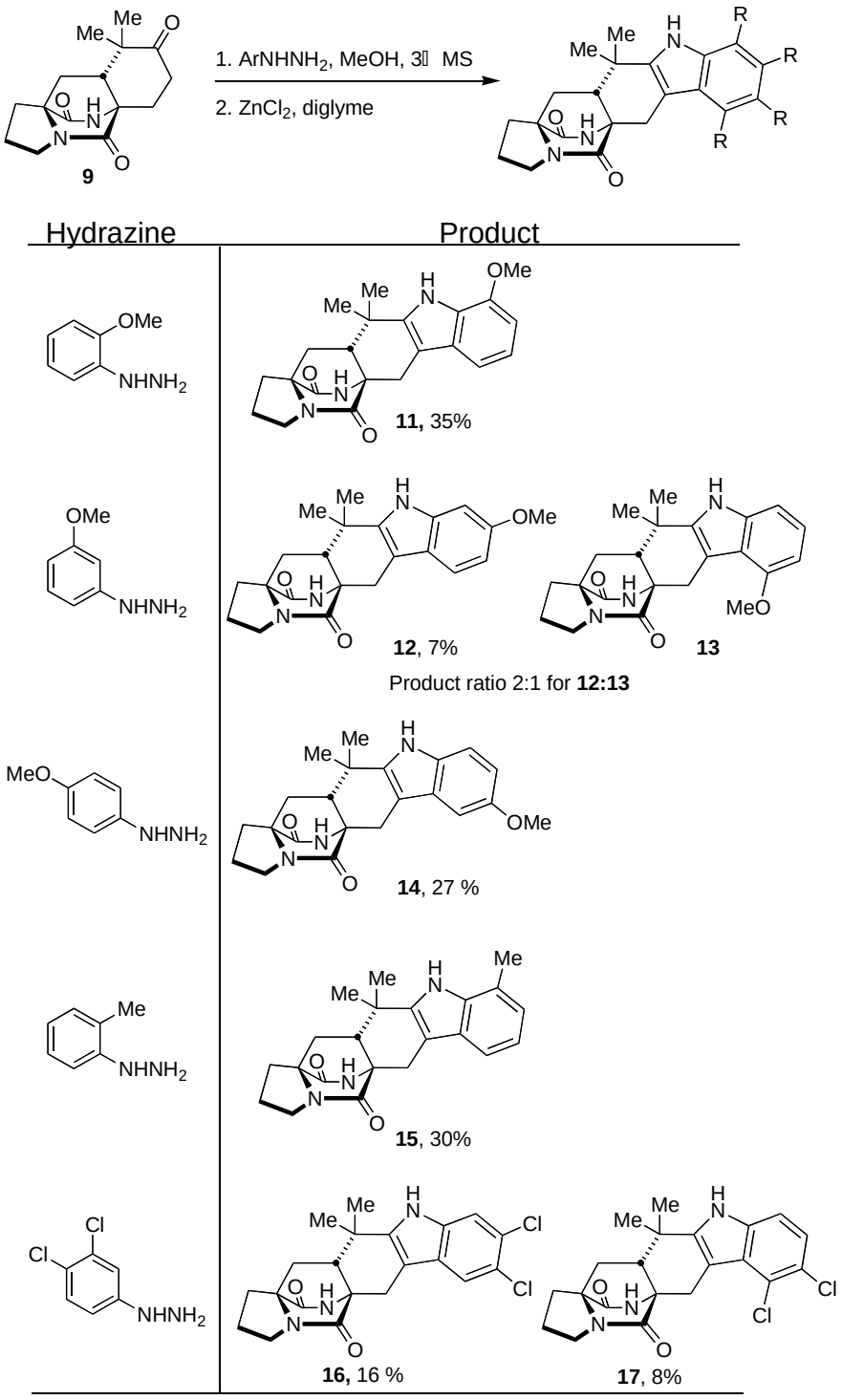
Scheme 1. The concise synthesis of brevianamide B (**2**).

The methoxy-substituted hydrazines were chosen to make indole derivatives that resemble the oxygen substitution of stephacidin A. Indole (**12**) contains the corresponding 6-oxo substitution pattern of stephacidin, however it was much more difficult to obtain than indoles (**11**) and (**14**). In general, it was observed that the electron donating groups in the *ortho* and *para* position gave higher yielding reactions than the *meta*-methoxyphenyl derivatives. Interestingly, when 3-methoxyphenylhydrazine was exchanged for the electron-withdrawing 1-(3-triflouromethoxy) phenylhydrazine, the Fischer reaction failed altogether. The major difficulty in obtaining **12** was due to the difficulty in separating the two regioisomers formed in the reaction. The same difficulty was observed in the isolation of indoles (**16**) and (**17**). In both cases, the products were isolated only after tedious and repetitive preparative thin layer chromatography separations under very specific solvent elution conditions. While the 6-methoxyindole (**12**) could be obtained in pure form in only 7 % yield, the regioisomer (**13**) was never obtained in pure form from the mixture.

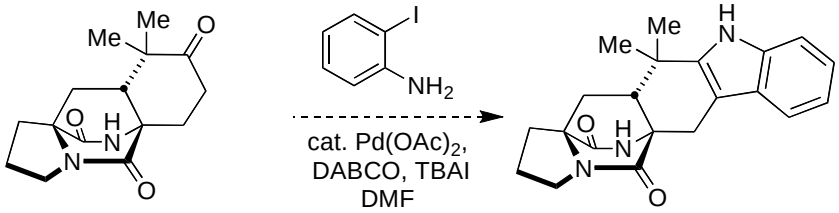
The 1-(2-methylphenyl)hydrazine was chosen as a less polar alternative to the methoxy derivatives and the desired indole (**15)** was obtained in 30 % yield. When 1-(2-chlorophenyl)hydrazine was used instead, the condensation with ketone (**9**) did not occur. The bulky chlorine on the hydrazine and the *gem*-dimethyl group *alpha* to the ketone presumably provides steric congestion that hindered the condensation.

Due to the initial shortcomings with the separation of the regioisomers formed from the Fischer indole reactions, we investigated the regioselective palladium-catalyzed annulation of *o*-iodoanaline and the ketone (**9**) (Scheme 2).[9,6c] However, ketone (**9**) failed to react with the aniline, despite various conditions and modifications that were investigated.

Table 1. Synthesis of *epi*-stephacidin A derivatives.



Once the two dichloro indole regioisomers (**16** and **17**) were separated, the final reduction of the tertiary lactam was required to give *epi*-malbrancheamide (**18**) and its corresponding regioisomer. In our synthesis of paraherquamide A, the tertiary lactam could be selectively reduced in the presence of the secondary lactam by treatment with excess DIBAL-H.[10]



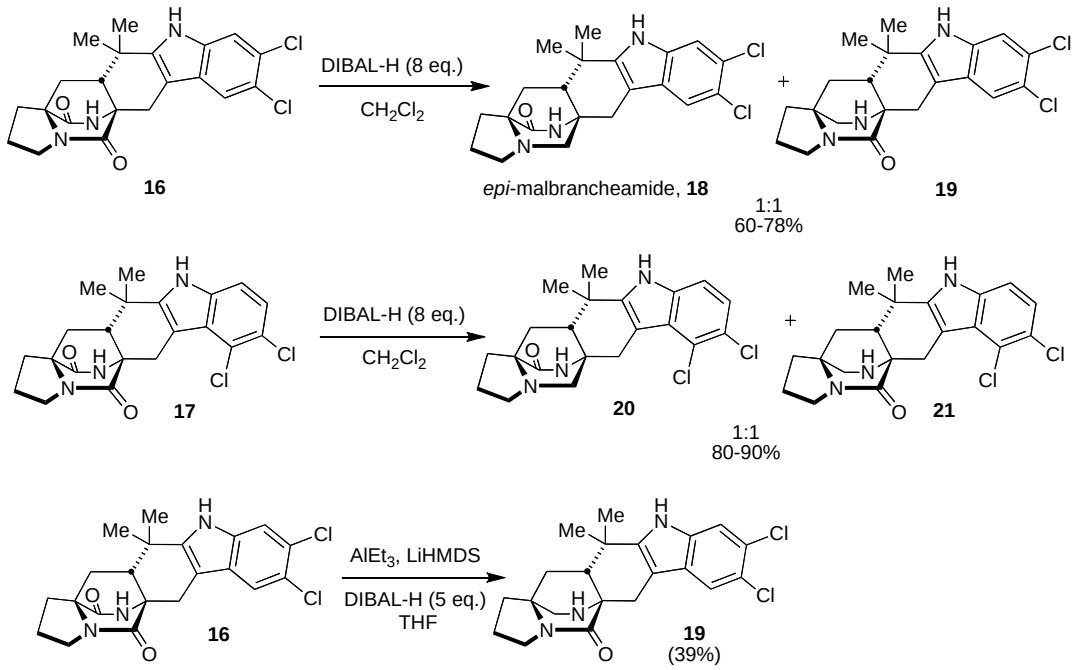
9 **10**

Scheme 2. Attempted Pd-catalyzed annulation.

The reduction of either regioisomer (**16**) or (**17**) with DIBAL-H gave a ~1:1 mixture of both the reduced tertiary lactam (**18** and **20**) and the reduced secondary lactam (**19** and **21**) in good yields (Scheme 3). While the reduced secondary lactam derivatives are intriguing compounds for biological activity studies, we were interested to see if pre-complexation with $AlEt_3$ would change the selectivity of the reduction. In our laboratory's earlier synthesis of paraherquamide B, selective reduction of the tertiary lactam was achieved by pre-complexation of the secondary lactam with $AlEt_3$.[11] Interestingly, this reaction with the *anti*-diastereomer (**16**) led to the opposite selectivity observed with paraherquamide B, which has the same *syn*-orientation (C-19, brevianamide numbering) as the stephacidins and malbrancheamide. In the present case, only the secondary lactam was reduced, and no *epi*-malbrancheamide product was observed. Examination of models of the two C-19 diastereomers reveals a plausible reason for the observed selectivities observed. The *syn*-diastereomer assumes a geometry wherein the *gem*-dimethyl groups effectively block one face of the tertiary amide, thus leaving the secondary amide more exposed for coordination with alane. In contrast, the geometry of the *anti*-diastereomer orients the *gem*-dimethyl groups on top of the secondary amide, thereby leaving the tertiary amide free for complexation.

CONCLUSION

We have demonstrated that the versatile ketone (**9**), can be utilized to prepare several malbrancheamide or stephacidin A analogs by deployment of the Fischer indole synthesis. While the yields for the Fischer indole reactions themselves are characteristically modest, the concise and convergent nature of the approach that we have employed provides ready access to these hexacyclic substances in a straightforward manner. We have submitted the derivatives reported here for biological evaluation and the results of those studies will be reported elsewhere.



Scheme 3. Reduction of the lactam and synthesis of *epi*-malbrancheamide (**18**).

EXPERIMENTAL

General Considerations. Commercially available reagents were used as received without further purification. Thin layer chromatography was performed using 0.25 mm silica gel 60 (F254, Merck) plates visualizing at 254 nm, or developed with potassium permanganate solutions by heating with a hot-air gun. Specified products were purified by flash column chromatography using silica gel 60 (230-400 mesh, Merck). IR absorptions on NaCl plates were run on a Perkin Elmer FT-IR 1600. ^{1}H NMR spectral data was obtained using Varian 300, 400 or 500 MHz instruments. ^{13}C NMR spectral data was obtained using a Varian 100 or 125 MHz spectrometer. Mass spectra were obtained at Colorado State University's Central Instrument Facility. Chemical shifts are reported in ppm relative to $CHCl_3$ at δ 7.27 (^{1}H NMR) and δ77.23 (^{13}C NMR). Chemical shifts are reported in ppm relative to CD_3OD at δ 3.31 (^{1}H NMR) and δ49.15 (^{13}C NMR). For all NMR spectra, δ values are given in ppm and *J* values in Hz.

*General Procedure for the synthesis of indoles (**11-17**) from ketone (**9**) with various commercial hydrazines:*

To a solution of cyclic ketone (**9**) (1 mol equiv.) in anhydrous methanol (20 % vol/wt.), under argon, was added activated 3 Å molecular sieves (1 vol. equiv.) followed by phenylhydrazine (1.5 mol equiv.). The mixture was heated at 90 ^{o}C in a sealed reaction vessel for 18 h, then it was allowed to cool to rt and the solvent was evaporated under reduced pressure to give the crude hydrazone that was taken on without further purification. The crude oil was dissolved in anhydrous 2-methoxyethyl ether (20 % vol/wt.) under

argon, and anhydrous zinc chloride (2 mol equiv.) was added. The reaction mixture was heated at 172 ^{o}C in a sealed reaction vessel for 24 h. The reaction mixture was filtered through celite, the filter was washed with toluene and the solvent was removed by short path distillation to leave a crude residue that was brought up in EtOAc (10 mL) and washed with water (10 mL). The aqueous phase was extracted with EtOAc (3 x 5 mL) and the combined organics were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Concentration under reduced pressure gave the crude indole, which was purified by column chromatography on silica using (EtOAc) as eluent to give the product. The regioisomers (**12/13**) and (**16/17**) were separated by preparative TLC, using 10:6:1 hexanes, ethyl acetate, and methanol. The plate was subjected to the chamber's solvent 3 times, allowing the plate to dry in between runs.

7-Methoxyindole (11). (from 54 mg of **9** and 50 mg of (2-methoxyphenyl)hydrazine: 35 %, 26 mg, brown oil) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.21 (3H, s), 1.30 (3H, s), 1.89 (1H, ddd, *J* = 12.9, 7.5, 7.5 Hz), 1.96-2.13 (4H, m), 2.38 (1H, dd, *J* = 9.6, 4.2 Hz), 2.77 (1H, ddd, *J* = 12.6, 6.9, 6.0 Hz), 2.88 (1H, d, *J* = 18.0 Hz), 3.51 (2H, t, *J* = 6.9 Hz), 3.88 (1H, d, *J* = 18.9 Hz), 3.92 (3H, s), 6.34 (1H, br s), 6.62 (1H, d, *J* = 7.8 Hz), 7.01 (1H, t, *J* = 7.8 Hz), 7.12 (1H, d, *J* = 7.8 Hz), 8.16 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.23, 24.68, 25.43, 29.15, 29.35, 32.84, 34.75, 44.37, 45.94, 55.52, 61.84, 67.26, 102.49, 104.29, 111.45, 120.32, 126.73, 128.62, 139.53, 145.89, 169.31, 173.02. IR (NaCl): 3583, 3244, 2957, 2359, 1683, 1576, 1397, 1305, 1256, 1075, 776, 729, 666 cm^{-1}. HRMS (FAB+): Calcd for $C_{22}H_{25}N_3O_3$ (MH^+): 380.19295. Found: 380.195818 (MH^+).

6-Methoxyindole (12). (from 141 mg of **9** and 106 mg of (3-methoxyphenyl)hydrazine: 7 %, 14 mg, yellow oil) ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (3H, s), 1.32 (3H, s), 1.88 (1H, ddd, *J* = 12.4, 8.4, 8.0 Hz), 2.05-2.16 (4H, m), 2.35 (1H, dd, *J* = 9.6, 5.2 Hz), 2.83 (1H, ddd, *J* = 14.0, 7.2, 6.8 Hz), 2.88 (1H, d, *J* = 14.0 Hz), 3.56 (2H, t, *J* = 7.6 Hz), 3.85 (3H, s), 3.92 (1H, d, *J* = 9.2 Hz), 5.73 (1H, br s), 6.80 (1H, d, *J* = 8.8 Hz), 6.86 (1H, s), 7.39 (1H, d, *J* = 9.6 Hz), 7.72 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 24.36, 24.85, 25.65, 29.61, 33.01, 34.85, 44.52, 46.03, 56.14, 60.75, 62.04, 67.45, 91.88, 94.79, 95.35, 100.07, 104.30, 109.34, 119.25, 121.91, 156.93, 173.01. IR (NaCl): 3583, 3284, 2957, 2360, 1685, 1457, 1404, 1258, 1158, 1107, 1031, 665 cm^{-1}. HRMS (FAB+): Calcd for $C_{22}H_{25}N_3O_3$ (MH^+): 380.19295. Found: 380.195779 (MH^+).

5-Methoxyindole (14). (from 70 mg of **9** and 88 mg of (4-methoxyphenyl)hydrazine: 27 %, 26 mg, yellow oil) ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.22 (3H, s), 1.28 (3H, s), 1.89 (1H, ddd, *J* = 13.2, 7.5, 5.7 Hz), 1.96-2.09 (4H, m), 2.28 (1H, dd, *J* = 9.6, 4.2 Hz), 2.76 (1H, ddd, *J* = 12.9, 7.2, 6.3 Hz), 2.85 (1H, d, *J* = 18.0 Hz), 3.50 (2H, t, *J* = 6.6 Hz), 3.77 (1H, d, *J* = 6.3 Hz), 3.83 (3H, s), 6.28 (1H, br s), 6.79 (1H, dd, *J* = 8.7, 2.7 Hz), 6.95 (1H, d, *J* = 2.4 Hz), 7.17 (1H, d, *J* = 8.7 Hz), 7.99 (1H, br s). ^{13}C NMR (100 MHz,

$CDCl_3$) δ: 24.13, 24.81, 25.48, 29.12, 29.46, 32.91, 34.91, 44.49, 46.02, 56.24, 61.86, 67.33, 100.65, 103.66, 111.65, 112.05, 127.76, 131.57, 132.34, 140.73, 154.18, 169.26. IR (NaCl): 3583, 3318, 2960, 2360, 1683, 1457, 1404, 1288, 1203, 1171, 1092, 1030, 734, 665 cm^{-1}. HRMS (FAB+): Calcd for $C_{22}H_{25}N_3O_3$ (MH^+): 380.19295. Found: 380.196995 (MH^+).

7-Methylindole (15). (from 64 mg of **9** and 50 mg of (2-methylphenyl)hydrazine: 30 %, 25 mg, yellow oil) ^1H NMR (500 MHz, $CDCl_3$) δ: 1.33 (3H, s), 1.37 (3H, s), 1.88 (1H, ddd, *J* = 12.5, 8.0, 7.0 Hz), 2.03-2.20(4H, m), 2.37 (1H, dd, *J* = 10.0, 4.0 Hz), 2.50 (3H, s), 2.83 (1H, ddd, *J* = 12.5, 6.5, 6.0 Hz), 2.91 (1H, d, *J* = 17.5 Hz), 3.56 (2H, t, *J* = 7.0 Hz), 3.94 (1H, d, *J* = 18.0 Hz), 5.77 (1H, br s), 7.02 (1H, d, *J* = 7.5 Hz), 7.08 (1H, t, *J* = 7.5 Hz), 7.40 (1H, d, *J* = 7.5 Hz), 7.66 (1H, br s). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 16.95, 24.12, 24.68, 25.44, 28.49, 29.36, 32.85, 34.75, 44.38, 45.99, 61.79, 67.26, 104.42, 116.29, 120.11, 122.98, 126.96, 136.08, 139.55, 169.32, 173.05. IR (NaCl): 3583, 3317, 2958, 1674, 1440, 1405, 1337, 1181, 1083, 775, 665 cm^{-1}. HRMS (FAB+): Calcd for $C_{22}H_{25}N_3O_2$ (MH^+): 364.19803. Found: 364.198917 (MH^+).

5,6-Dichloroindole (16). (from 70 mg of **9** and 81 mg of 3,4-dichlorophenylhydrazine hydrochloride: 16 %, 17 mg, yellow oil) ^1H NMR (400 MHz, $CDCl_3$) δ: 1.31 (3H, s), 1.34 (3H, s), 1.88 (1H, ddd, *J* = 15.6, 8.8, 6.8 Hz), 2.04-2.21 (4H, m), 2.45 (1H, dd, *J* = 9.6, 4.4 Hz), 2.80-2.86 (2H, m), 3.56 (2H, t, *J* = 7.2 Hz), 3.91 (1H, d, *J* = 18 Hz), 5.82 (1H, br s), 7.41 (1H, s), 7.58 (1H, s), 7.87 (1H, br s). ^{13}C NMR (100 MHz, CD_3OD) δ: 23.89, 24.85, 25.51, 28.75, 30.05, 33.41, 36.13, 45.36, 47.35, 62.77, 68.77, 104.13, 113.35, 120.02, 123.48, 125.63, 128.72, 137.46, 144.57, 171.76, 175.53. IR (NaCl): 3583, 3272, 2923, 1669, 1404, 665 cm^{-1}. HRMS (FAB+): Calcd for $C_{21}H_{21}N_3O_2Cl_2$ (MH^+): 418.108908. Found: 418.106941 (MH^+).

4,5-Dichloroindole (17). (from 70 mg of **9** and 81 mg of 3,4-dichlorophenylhydrazine hydrochloride: 8 %, 8 mg, white residue) ^1H NMR (300 MHz, $CDCl_3$) δ: 1.32 (3H, s), 1.34 (3H, s), 1.89 (1H, dd, *J* = 13.5, 7.2), 2.04-2.17 (4H, m), 2.34 (1H, dd, *J* = 10.2, 4.2 Hz), 2.84 (1H, ddd, *J* = 13.2, 6.9, 6.3), 3.39 (1H, d, *J* = 19.2 Hz), 3.56 (2H, t, *J* = 6.9 Hz), 4.19 (1H, d, *J* = 18.6 Hz), 5.77 (1H, br s), 7.17 (2H AB, *J* = 8.7 Hz, Δν = 22.94 Hz), 7.96 (1H, br s). ^{13}C NMR (100 MHz, CD_3OD) δ: 25.62, 26.22, 26.93, 29.57, 30.76, 34.16, 36.71, 46.07, 47.51, 63.52, 69.44, 105.52, 112.51, 120.73, 124.35, 127.83, 138.63, 145.06, 172.52, 176.29. IR (NaCl): 3583, 3273, 2923, 2360, 1674, 1429, 1314, 1249, 794, 665 cm^{-1}. HRMS (FAB+): Calcd for $C_{21}H_{21}N_3O_2Cl_2$ (MH^+): 418.108908. Found: 418.106941 (MH^+).

*General procedure for the reduction of the tertiary and secondary lactams of **16** and **17**:*

To a solution of the indole (1 equiv) in dichloromethane (10% vol/wt.) at 0 °C, was added 5 equiv. of DIBAL-H (1M in dichloromethane). The solution was stirred at 0 °C for 1 h, then at rt for 1 h. The solution was cooled to 0 °C so that another portion of DIBAL-H (3.2 equiv.) could be added. The solution was again stirred at 0 °C for 1 h and at rt for 1 h. After being brought back to 0 °C, the reaction was quenched by the addition of saturated aq. NH_4Cl. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The organic layer was washed with brine, dried with Na_2SO_4, and concentrated *in vacuo* to give the crude product. The product was purified by preparative TLC, using 10:6:1 hexanes, ethyl acetate, and methanol. The plate was eluted three times, allowing the plate to dry in-between elution runs. The secondary reduced lactam product was obtained from the band with the lowest R_f, (0.2), and the tertiary reduced lactam product was obtained from the band with the higher R_f (0.5).

***Epi*-malbrancheamide (18).** (from 8 mg of **16**: 39 %, 3 mg, colorless oil) ^{1}H NMR (500 MHz, CD_3OD) δ: 1.33 (3H, s), 1.42 (3H, s), 1.44-1.48 (1H, m), 1.84-1.90 (2H, m), 1.93-2.03 (2H, m), 2.13-2.19 (2H, m), 2.26 (1H, dd, *J* = 10.0, 1.5), 2.50-2.55 (1H, m), 2.84 (2H, m), 3.04-3.08 (1H, m), 3.43 (1H, d, *J* = 10.5 Hz), 7.39 (1H, s), 7.48 (1H, s). ^{13}C NMR (125 MHz, CD_3OD) δ: 23.62, 24.23, 28.17, 30.06, 30.67, 32.51, 35.56, 47.95, 55.36, 57.45, 59.40, 66.08, 104.70, 113.02, 119.48, 123.27, 125.25, 128.10, 137.16, 145.03, 176.47. IR (NaCl): 3583, 3313, 2922, 1653, 1471, 1260, 1260 cm^{-1}. HRMS (FAB+): Calcd for $C_{21}H_{23}N_3OCl_2$ (MH^+): 404.129643. Found: 404.128497 (MH^+).

Indole (19). (from 8 mg of **16**: 39 %, 3 mg colorless oil) ^{1}H NMR (500 MHz, CD_3OD) δ: 1.17 (3H, s), 1.29 (3H, s), 1.42-1.48 (1H, m), 1.89-1.94 (3H, m), 2.10-2.19 (2H, m), 2.37 (1H, q, *J* = 17.0, 9.0), 2.47-2.52 (1H, m), 2.66 (1H, d, *J* = 10.5 Hz), 2.86 (2H AB, *J* = 8.7 Hz, Δν = 60.99 Hz), 3.08-3.11 (2H, m), 7.38 (1H, s), 7.49 (1H, s). ^{13}C NMR (100 MHz, CD_3OD) δ: 23.43, 24.53, 27.99, 28.15, 28.79, 31.76, 35.87, 47.40, 54.40, 56.73, 62.23, 66.78, 104.15, 113.30, 119.91, 123.37, 125.37, 128.56, 137.39, 145.70, 175.73. IR (NaCl): 3583, 2927, 1718, 1558, 1457, 1363, 1226, 665 cm^{-1}. HRMS (FAB+): Calcd for $C_{21}H_{23}N_3OCl_2$ (MH^+): 404.129643. Found: 404.129725 (MH^+).

Indole (20). (from 6 mg of **17**: 35 %, 2 mg, colorless oil) ^{1}H NMR (400 MHz, CD_3OD) δ: 1.34 (3H, s), 1.45 (3H, s), 1.47-1.50 (1H, m), 1.85-1.94 (2H, m), 1.96-2.04 (2H, m), 2.12-2.19 (2H, m), 2.27 (1H, d, *J* = 10.0), 2.50-2.57 (1H, m), 2.85 (2H, m), 3.10 (1H, m), 3.49 (1H, d, *J* = 10.0 Hz), 7.15 (2H AB, *J* = 8.8 Hz, Δν = 26.44 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ: 23.73, 24.40, 28.28, 30.18, 30.79, 32.60, 35.55, 48.10, 55.52, 57.61, 59.74, 66.25, 105.56, 111.73, 113.26, 119.73, 123.54, 137.45, 137.93, 145.22, 176.82. IR (NaCl): 3583, 3259, 2924, 2853, 2360, 1670, 1456, 1315 cm^{-1}. HRMS (FAB+): Calcd for

$C_{21}H_{23}N_3OCl_2$ (MH^+): 404.129643. Found: 404.128609 (MH^+).

Indole (21). (from 6 mg of **17**: 53 %, 3 mg colorless oil) ^{1}H NMR (400 MHz, CD_3OD) δ: 1.18 (3H, s), 1.29 (3H, s), 1.41-1.48 (1H, m), 1.86-1.93 (3H, m), 1.99 (1H, d, *J* = 2.0 Hz), 2.09-2.18 (2H, m), 2.37 (1H, q, *J* = 17.2, 8.8 Hz), 2.46-2.52 (1H, m), 2.66 (1H, d, *J* = 10.4 Hz), 3.08-3.13 (3H, m), 3.45 (1H, d, *J* = 17.6 Hz), 7.11 (2H AB, *J* = 8.4 Hz, Δν = 29.78 Hz). ^{13}C NMR (125 MHz, CD_3OD) δ: 23.50, 24.61, 28.08, 28.21, 31.38, 31.96, 35.78, 46.87, 54.42, 56.82, 62.56, 66.64, 104.82, 111.77, 123.48, 123.60, 124.10, 126.98, 137.88, 145.56, 176.02. IR (NaCl): 3583, 3264, 2925, 2853, 1668, 1456, 1315, 1247, 665 cm^{-1}. HRMS (FAB+): Calcd for $C_{21}H_{23}N_3OCl_2$ (MH^+): 404.129643. Found: 404.129383 (MH^+).

*Procedure to selectively reduce the secondary lactam of **16**:*

To a solution of the indole (**16**) (4 mg, 0.0096 mmol) in THF (0.8 mL) at -78 °C, was added LiHMDS (1M in THF, 0.019 mmol). After the solution was stirred for 30 min, Et_3Al (1M in hexanes, 0.020 mmol) was added and the solution was stirred at -78 °C for 15 min. DIBAL-H (1M in toluene, 0.029 mmol) was added, and the mixture was stirred at -78 °C for 10 min, then at 0 °C for 3 h. The solution was allowed to warm to rt and was quenched with MeOH (0.1 mL) and taken up in EtOAc (10 mL). The organics were washed with saturated aqueous NH_4Cl, followed by brine, then dried over Na_2SO_4. The solvent was removed *in vacuo*, and the crude product was purified by preparative TLC, using 10:6:1 hexanes, ethyl acetate, and methanol. The plate was eluted three times, allowing the plate to dry in between elution runs. The secondary reduced lactam (**19**) product (1.5 mg) was obtained from the band with the R_f, (0.2) in 39 % yield.

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