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Total Synthesis of Microtubule-Stabilizing Agent Ceratamine A

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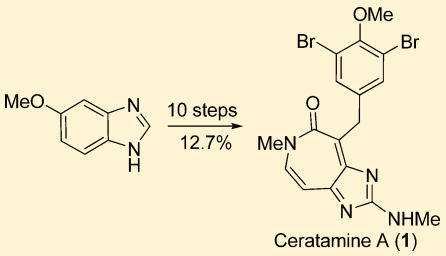
Supporting Information

ABSTRACT: The total synthesis of ceratamine A, a natural microtubule-stabilizing agent with unusual cellular effects, has been accomplished starting from 5-methoxybenzimidazole in 10 steps in an overall yield of 12.7%. The key steps in the synthesis involved the Schmidt rearrangement to construct the azepine ring, the alkylation of lactam to introduce the C-5 benzylic side chain, and the highly economical S_NAr reaction to install the C-2 methylamine residue.

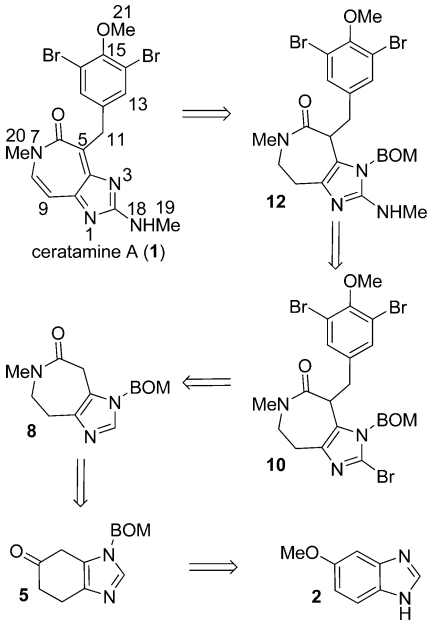


The first promoter of tubulin polymerization ever discovered was paclitaxel, which arguably represents one of the major milestones in the history of cancer treatment after its successful development into an effective anticancer drug.[1] The taxanes such as paclitaxel and docetaxel are the most successful class of anticancer drugs currently used in clinics. Drug resistance and cross resistance with other chemotherapeutic agents are the major common drawbacks of these drugs. Despite the appearance of many cancer-specific targets over the past several decades, investigation of new tubulin inhibitors still represents an important sphere of modern anticancer drug discovery and development, especially for multidrug resistance cancer cells.[2] So far, a number of structurally diversified natural products with microtubule-stabilizing activity have been found, and the epothilone derivative, ixabepilone, was successfully launched in 2007 for the treatment of breast cancer.[3]

Ceratamine A (**1**), originally isolated from marine sponge *Pseudoceratina* sp. collected in Papua New Guinea, is an antimitotic heterocyclic alkaloid with a novel imidazo[4,5-*d*]azepine core.[4] Structurally, ceratamine A has a novel but simple chemical structure without chiral centers. Functionally, mechanistic studies have shown that ceratamine A is a microtubule-stabilizing agent, which has a tubulin-binding site totally different from that of paclitaxel.[5] While blocking the cancer cell division cycle by promoting tubulin polymerization, ceratamine A exhibits an unprecedented mitotic arrest phenotype that is distinct from those of all the other tubulin-stabilizing agents described to date. The unique mechanism of action implies that ceratamine A may show a different spectrum of toxicity and anticancer activity, particularly against multidrug resistance cancers. Thus, ceratamine A is a promising anticancer leading compound. One total synthesis by Coleman and one synthetic study by Andersen have been reported.[6] However, investigations of systematic structural modification and SAR have not been reported, because of the limitation of these synthetic routes. The purpose of this paper is to report a flexible approach to this natural product suitable for analogue synthesis. Herein, we report the second total synthesis of ceratamine A, which follows a different strategy.

We envisioned that, for the synthetic route to be suitable for the efficient synthesis of ceratamine A derivatives, introduction of the 2-methylamino group and 5-benzylic side chain at a later stage would be the best choice. The retrosynthetic analysis of ceratamine A is shown in Scheme 1. Ceratamine A (**1**) could be transformed from compound **12** via dehydrogenation. 2-Methylaminoimidazole **12** could be accessed from C-2 functionalization of bromide compound **10** with methylamine.

Scheme 1. Retrosynthetic Analysis of Ceratamine A



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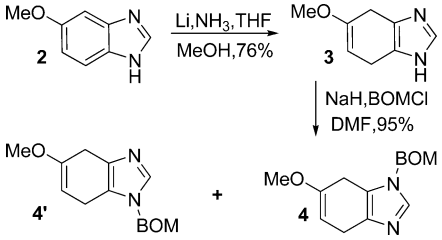
Compound **10** could in turn be prepared through the α-benzylation of the carbonyl group of lactam **8** and the ensuing C-2 bromination. Lactam **8** could be constructed through the pivotal Schmidt rearrangement of ketone **5**. Compound **5** could be prepared through several steps from 5-methoxybenzimidazole (**2**).

The entire synthesis started from the preparation of key intermediate **4** and its regioisomer **4′** (Scheme 2), both of which could be applied for the total synthesis of ceratamine A by this synthetic approach.

Scheme 2. Synthesis of Key Intermediates 4 and 4′

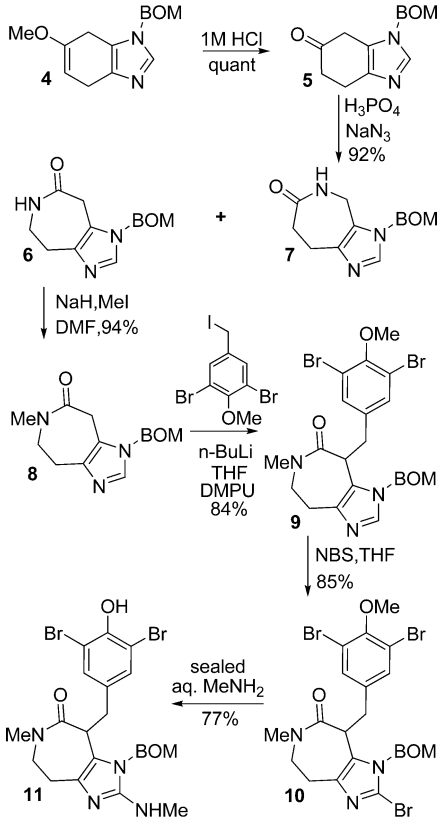


Compounds **4** and **4′** were thus synthesized in satisfactory yields through an efficient two-step transformation starting from the commercially available 5-methoxybenzimidazole (**2**). Birch-type reduction of methoxybenzimidazole **2** with lithium in liquid ammonia yielded methyl enol ether **3** in a fairly good yield.[7] Treatment of **3** with sodium hydride and BOMCl in DMF provided a mixture of compounds **4** and **4′** in a ratio of 1:1, which was successfully separated to give two pure compounds. The structures of compounds **4** and **4′** were identified by NOE correlations.

Acid-promoted hydrolysis of **4** (25 °C, 2 h) gave ketone **5** in an almost quantitative yield (Scheme 3). Construction of the azepine ring of lactam **6** is the key step in this synthetic route, which was realized through the Schmidt rearrangement reaction.[8] First, treatment of **5** with sodium azide in TFA afforded two isomeric mixtures of lactam **6** and undesired lactam **7** in a ratio of 3:1 (determined by ^{1}H NMR). Fortunately, if ketone **5** was treated with 2 equiv of sodium azide in phosphoric acid, products **6** and **7** were obtained in a 7:1 ratio. Methylation of the nitrogen of lactam **6** with sodium hydride and iodomethane afforded **8** in an excellent yield. For the benzylation of lactam **8**, LHDMS and LDA were initially investigated as the bases. However, the desired product **9** was not observed either in THF or in a THF/DMPU (10:1) cosolvent. We were pleased to find that deprotonation of *N*-methyllactam **8** with *n*-BuLi in the presence of DMPU and 1,3-dibromo-5-(iodomethyl)-2-methoxybenzene[9] furnished benzylated product **9** in 84% yield, which was subsequently brominated at C-2 using NBS[10] to give bromide compound **10** in 85% yield.

Functionalization of C-2 of compound **10** with the methylamine group proved to be unexpectedly complicated. First, the copper(I)- and Pd-catalyzed methods developed for the synthesis of the 2-aminoimidazole were tested.[11,12] Unfortunately, both methods gave only the major byproduct of phenol **11**.[13,14] Next, we returned to the S_NAr reaction, which was used in the transformation of 2-bromo-azoles into diversified 2-aminoimidazoles, for the introduction of the C-2 methylamine group.[15] However, treatment of **10** with aqueous methylamine in a sealed tube also yielded undesired byproduct **11** (Scheme 3). After several conditions had been tested,

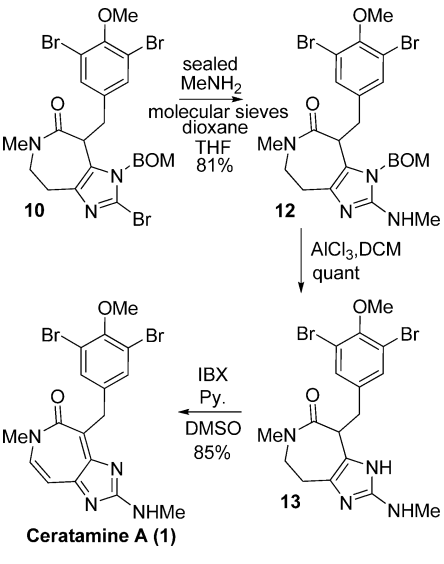
Scheme 3. Construction of the Imidazo[4,5-*d*]azepine System



treatment of **10** with methylamine in a mixed solvent of dioxane and THF with the addition of activated molecular sieves in a sealed tube yielded the desired compound **12** as the major product (Scheme 4).[13]

Then exposure of **12** to anhydrous $AlCl_3$ in CH_2Cl_2 cleanly yielded 2-aminoimidazole **13** in an almost quantitative yield. Finally, oxidation of **13** with IBX afforded ceratamine A according to the method developed by Coleman's group.[6c] The

Scheme 4. Completion of the Total Synthesis of Ceratamine A



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spectral data (^{1}H and ^{13}C NMR) of the synthetic compound **1** are identical with those reported for the natural ceratamine A.

In summary, we have accomplished an efficient synthesis of ceratamine A starting from the readily available 5-methoxybenzimidazole in 10 steps in an overall yield of 12.7%. Our synthetic approach features a highly effective Schmidt rearrangement to form the azepine ring. Other key steps include the successful isolation of the regioisomeric mixtures of compound **4** and **4′**, the benzylation of lactam **8** to introduce the C-5 side chain, and a highly economical S_NAr reaction to install the C-2 methylamine group at an advanced stage that would facilitate the structural modification of ceratamine A to a great extent. Thus, this synthetic route is amenable to the synthesis of structural variants of ceratamine A. The further structural modification and biological studies of ceratamine A are currently in progress and will be reported in due course.

EXPERIMENTAL SECTION

Compound 3. A solution of compound **2** (3.4 g, 22.9 mmol) in THF (30 mL) and MeOH (10 mL) was added dropwise to liquid ammonia (200 mL) at −78 °C. The resulting solution was treated portionwise with lithium (1.4 g, 201.7 mmol). The mixture was stirred at −78 °C for 6 h and treated dropwise with MeOH. After evaporation of the ammonia and removal of the MeOH and THF under reduced pressure, the residue was treated with DCM (100 mL) and H_2O (50 mL). The organic layer was separated and the aqueous phase extracted with DCM (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to yield compound **3** (2.6 g, 17.3 mmol, 76%) as a brown solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (br s, NH), 7.66 (s, 1H), 4.81 (br s, 1H), 3.61 (s, 3H), 3.35 (br s, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 133.8, 127.2, 126.6, 90.9, 54.8, 27.3, 22.5; HRMS (ESI) m/z calcd for $C_8H_{11}N_2O$ $(M + H)^+$ 151.08659, found 151.08606.

Compound 4 and Compound 4′. NaH (0.68 g, 60% in oil, 17.00 mmol) was added to a solution of compound **3** (2.05 g, 13.65 mmol) in DMF (60 mL) at −18 °C. The resulting solution was stirred for 1 h at 0 °C, and BOM-Cl (2.18 mL, 15.70 mmol) was added dropwise at −18 °C. The mixture was stirred at 0 °C for 2 h and at room temperature for 2 h. The reaction was quenched by the addition of H_2O (100 mL) and the mixture extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with brine (100 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to yield compound **4′** (1.72 g, 6.36 mmol, 47.4%) as a colorless oil: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.72 (s, 1H), 7.35−7.27 (m, 5H), 5.37 (s, 2H), 4.86 (t, J = 3.3 Hz, 1H), 4.43 (s, 2H), 3.55 (s, 3H), 3.29 (m, 2H), 3.19 (d, J = 6.5 Hz, 1H), 3.18 (d, J = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8, 137.1, 136.5, 134.8, 128.8, 128.4, 128.1, 123.5, 89.5, 73.6, 69.8, 54.8, 29.1, 21.1; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_2$ $(M + H)^+$ 271.14410, found 271.14412. Compound **4** (1.79 g, 6.62 mmol, 47.6%) was obtained as a colorless oil: ^{1}H NMR (600 MHz, DMSO-d_6) δ 7.71 (s, 1H), 7.35−7.27 (m, 5H), 5.37 (s, 2H), 4.89 (m, 1H), 4.43 (s, 2H), 3.55 (s, 3H), 3.32 (d, J = 6.5 Hz, 1H), 3.31 (d, J = 6.5 Hz, 1H), 3.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.0, 137.1, 136.5, 135.5, 128.8, 128.4, 128.0, 122.8, 92.4, 73.5, 69.8, 54.9, 25.6, 24.6; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_2$ $(M + H)^+$ 271.14410, found 271.14304.

Compound 5. To a solution of compound **4** (1.61 g, 5.95 mmol) in 1,4-dioxane (200 mL) was added hydrochloric acid (1 M, 20 mL). The solution was stirred overnight at room temperature and carefully neutralized by the addition of 2 M sodium hydroxide under vigorous stirring and cooling with an ice/water bath. The mixture was extracted with EtOAc (3 × 100 mL), and the combined organic layers were washed with water (100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to yield compound **5** (1.52 g, 5.93 mmol, 100%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.38−7.26 (m, 5H), 5.21 (s, 2H), 4.45 (s, 2H), 3.46 (s, 2H), 2.98 (t, J = 6.8 Hz, 2H), 2.70 (t, J = 6.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 206.8, 137.9, 136.7, 136.1, 128.8, 128.5, 128.0, 122.5, 73.5, 70.1, 39.5, 35.9, 22.9; HRMS (ESI) m/z calcd for $C_{15}H_{17}N_2O_2$ $(M + H)^+$ 257.12845, found 257.12848.

Compound 6. To a solution of compound **5** (1.43 g, 5.58 mmol) in THF (5 mL) and phosphoric acid (85% solution in water, 35 mL) was added portionwise sodium azide (0.73 g, 11.23 mmol) over a period of 1 h. The reaction mixture was stirred for 3 h at 60 °C and carefully neutralized by the addition of ammonium hydroxide (28−30% solution in water) under vigorous stirring and cooling with an ice/water bath. The mixture was extracted with DCM (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to yield compound **6** (0.82 g, 2.99 mmol, 54%) as a foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.38−7.27 (m, 5H), 6.36 (t, J = 6.6 Hz, 1H), 5.39 (s, 2H), 4.51 (s, 2H), 3.72 (s, 2H), 3.56 (dt, J = 6.6, 5.0 Hz, 2H), 2.92 (t, J = 5.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 136.6, 136.1, 135.6, 128.9, 128.6, 128.2, 119.5, 74.3, 70.7, 39.7, 31.2, 28.9; HRMS (ESI) m/z calcd for $C_{15}H_{18}N_3O_2$ $(M + H)^+$ 272.13935, found 272.13934.

Compound 8. NaH (0.20 g, 60% in oil, 5.00 mmol) was added to a solution of compound **6** (1.19 g, 4.39 mmol) in DMF (40 mL) at −5 °C. The resulting solution was stirred for 30 min at this temperature, and iodomethane (0.33 mL, 5.27 mmol) was added dropwise. The mixture was stirred at room temperature for 2 h. The reaction was quenched by the addition of MeOH (5 mL) and H_2O (30 mL) and the mixture extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to yield compound **8** (1.18 g, 4.14 mmol, 94%) as a foam: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.37−7.28 (m, 5H), 5.25 (s, 2H), 4.44 (s, 2H), 3.73 (s, 2H), 3.68 (m, 2H), 3.05 (s, 3H), 2.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 137.7, 137.0, 136.3, 128.8, 128.4, 128.1, 119.5, 73.3, 69.9, 48.3, 34.6, 31.9, 27.2; HRMS (ESI) m/z calcd for $C_{16}H_{20}N_3O_2$ $(M + H)^+$ 286.15500, found 286.15507.

Compound 9. To a stirred solution of compound **8** (0.88 g, 3.08 mmol) in THF (45 mL) and DMPU (3 mL) cooled to −78 °C was added dropwise a solution of *n*-BuLi (2.5 M in hexane, 1.36 mL, 3.39 mmol) via syringe. The resulting solution was stirred at −78 °C for 100 min. A solution of 1,3-dibromo-5-(iodomethyl)-2-methoxybenzene (1.50 g, 3.70 mmol) in THF (10 mL) was added dropwise via syringe. The reaction mixture was warmed to −18 °C and stirred at this temperature for 3 h, 0 °C for 2 h, room temperature for 2 h, and 70 °C for 2 h, diluted with DCM (400 mL), washed with H_2O (3 × 200 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to afford compound **9** (1.46 g, 2.59 mmol, 84%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.39−7.29 (m, 5H), 7.25 (s, 2H), 5.16 (d, J = 11.2 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 4.47 (d, J = 12.1 Hz, 1H), 4.43 (d, J = 12.1 Hz, 1H), 4.17 (ddd, J = 15.0, 12.7, 1.9 Hz, 1H), 4.08 (m, 1H), 3.85 (s, 3H), 3.48 (dt, J = 15.0, 3.0 Hz, 1H), 3.12 (m, 2H), 3.09 (s, 3H), 2.99 (ddd, J = 16.2, 12.7, 3.0 Hz, 1H), 2.89 (d, J = 16.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 153.2, 138.8, 137.9, 137.0, 135.9, 133.2, 128.9, 128.6, 128.1, 123.1, 118.2, 73.3, 70.0, 60.8, 47.5, 47.3, 39.5, 36.6, 27.7; HRMS (ESI) m/z calcd for $C_{24}H_{26}Br_2N_3O_3$ $(M + H)^+$ 562.03354, found 562.03253.

Compound 10. To a solution of compound **9** (1.30 g, 2.31 mmol) in THF (50 mL) was added NBS (0.62 g, 3.48 mmol) at 0 °C. The reaction mixture was stirred overnight at this temperature, and saturated aqueous Na_2SO_3 (20 mL) and H_2O (20 mL) were added. The mixture was extracted with EtOAc (3 × 50 mL), and the combined organic layers were washed with brine (60 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to yield compound **10** (1.26 g, 1.96 mmol, 85%) as a foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.30 (m, 5H), 7.22 (s, 2H), 5.22 (d, J = 11.2 Hz, 1H), 4.93 (d, J = 11.2 Hz, 1H), 4.56 (d, J = 11.6 Hz, 1H), 4.52 (d, J = 11.6 Hz, 1H), 4.13 (t, J = 13.0 Hz, 1H), 4.06 (t, J = 7.6 Hz, 1H), 3.85 (s, 3H), 3.45 (d, J = 13.0 Hz, 1H), 3.08 (brs, 5H), 2.97−2.83 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4,

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153.4, 139.3, 136.7, 136.2, 133.2, 128.9, 128.6, 128.0, 126.3, 120.6, 118.3, 73.8, 70.9, 60.9, 48.1, 47.3, 39.5, 36.8, 27.8; HRMS (ESI) m/z calcd for $C_{24}H_{25}Br_3N_3O_3$ $(M + H)^+$ 639.94406, found 639.94348.

Compound 11. A mixture of compound **10** (102 mg, 0.160 mmol) and methylamine [40% (w/w) aqueous, 5 mL] was heated for 36 h at 120 °C in a sealed tube. The reaction mixture was concentrated, and the residue was purified by column chromatography (C-18 reverse-phase silica, 60% MeOH/H_2O mixture) to afford compound **11** (71 mg, 0.123 mmol, 77%) as a colorless oil: ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.37−7.28 (m, 5H), 7.28 (s, 2H), 5.85 (m, NH), 5.17 (d, J = 11.6 Hz, 1H), 4.95 (d, J = 11.6 Hz, 1H), 4.47 (d, J = 12.2 Hz, 1H), 4.44 (d, J = 12.2 Hz, 1H), 4.12 (t, J = 13.5 Hz, 1H), 3.77 (dd, J = 9.9, 6.7 Hz, 1H), 3.40 (dt, J = 15.2, 3 Hz, 1H), 2.99 (m, 2H), 2.88 (s, 3H), 2.74 (d, J = 4.2 Hz, 3H), 2.66 (m, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.2, 150.6, 149.6, 137.4, 132.7, 132.6, 132.4, 128.3, 127.6, 127.5, 116.8, 111.8, 70.3, 69.1, 46.8, 46.5, 38.2, 35.5, 29.6, 27.1; HRMS (ESI) m/z calcd for $C_{24}H_{27}Br_2N_4O_3$ $(M + H)^+$ 577.04444, found 577.04453.

Compound 12. A mixture of compound **10** (150 mg, 0.234 mmol), methylamine (2 M in THF, 3 mL, 6.000 mmol), 1,4-dioxane (20 mL), and activated molecular sieves (3A, powder, 5 g) was heated for 12 h at 120 °C in a sealed tube. The reaction mixture was filtered, the filtrate concentrated, and the residue purified by column chromatography (C-18 reverse-phase silica, 70% MeOH/H_2O mixture) to afford compound **12** (112 mg, 0.189 mmol, 81%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.34 (m, 3H), 7.30 (d, J = 6.8 Hz, 2H), 7.13 (s, 2H), 4.64 (d, J = 11.3 Hz, 1H), 4.45 (d, J = 12.2 Hz, 1H), 4.36 (d, J = 12.2 Hz, 1H), 4.30 (d, J = 11.3 Hz, 1H), 4.11 (m, 2H), 3.85 (s, 3H), 3.73 (t, J = 7.7 Hz, 1H), 3.42 (dt, J = 15.2, 3.3 Hz, 1H), 3.08 (s, 3H), 3.03 (t, J = 7.7 Hz, 1H), 2.95 (d, J = 5.2 Hz, 3H), 2.90 (m, 2H), 2.79 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 153.2, 151.5, 137.1, 136.2, 133.2, 133.0, 129.0, 128.7, 128.2, 118.3, 117.2, 70.1, 69.6, 60.8, 47.6, 47.5, 40.1, 36.5, 30.3, 27.7; HRMS (ESI) m/z calcd for $C_{25}H_{29}Br_2N_4O_3$ $(M + H)^+$ 591.06009, found 591.06110.

Compound 13. To compound **12** (90 mg, 0.152 mmol) in DCM (5 mL) was added anhydrous $AlCl_3$ (203 mg, 1.52 mmol) in one portion, and the reaction mixture was stirred for 1 h at room temperature. The resulting blood red slurry was quenched by the addition of methanol and filtered, and the filtrate was concentrated. The residue was purified by column chromatography (C-18 reverse-phase silica, 60% MeOH/H_2O mixture) to afford compound **13** (72 mg, 0.152 mmol, 100%) as a pale yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (m, NH), 7.74 (m, NH), 7.61 (s, 2H), 4.11 (m, 1H), 3.78 (br s, 5H), 3.14 (m, 2H), 2.89 (s, 3H), 2.85 (d, J = 4.6 Hz, 3H), 2.67 (m, 2H); ^{13}C NMR for **13**·HCl (75 MHz, DMSO-d_6) δ 169.6, 151.7, 146.9, 138.4, 133.4, 121.2, 117.7, 116.9, 60.3, 45.6, 40.2, 38.8, 34.9, 29.5, 23.0; HRMS (ESI) m/z calcd for $C_{17}H_{21}Br_2N_4O_2$ $(M + H)^+$ 471.00258, found 471.00278.

Ceratamine A (1). Compound **13** (68 mg, 0.144 mmol) was dissolved in DMSO (0.6 mL). Pyridine (58 μL, 0.720 mmol) and IBX (162 mg, 0.576 mmol) were added, and the mixture was stirred for 1 h at 35 °C. The resulting dark yellow solution was quenched by the addition of saturated aqueous $Na_2S_2O_4$ (9 mL) and saturated $NaHCO_3$ (5 mL). The reaction mixture was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, and concentrated. The crude product was purified by column chromatography to yield ceratamine A (**1**) (56 mg, 0.120 mmol, 85%) as a yellow solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.68 (m, NH), 7.74 (d, J = 9.9 Hz, 1H), 7.66 (s, 2H), 6.42 (d, J = 9.9 Hz, 1H), 4.23 (s, 2H), 3.72 (s, 3H), 3.55 (s, 3H), 3.07 (d, J = 4.9 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.6, 169.7, 164.1, 160.5, 151.4, 142.9, 140.2, 133.1, 121.3, 116.6, 100.4, 60.3, 43.7, 35.0, 29.2; HRMS (ESI) m/z calcd for $C_{17}H_{17}Br_2N_4O_2$ $(M + H)^+$ 466.9713, found 466.9716.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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