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Synthesis of Reported and Revised Structures of Amathamide D and Synthesis of Convolutamine F, H and Lutamide A, C

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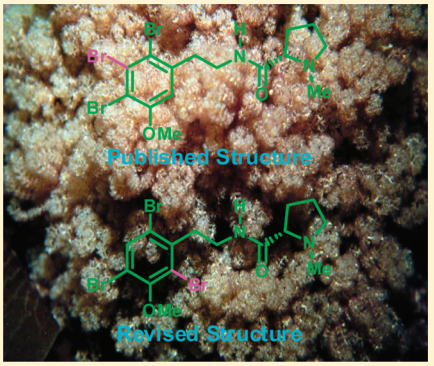
Supporting Information

ABSTRACT: Total synthesis of the published structure of amathamide D is described. Methyl 2,3,4-tribromo-5-hydroxybenzoate was selected as starting compound because it is readily accessible *via* acid-mediated Grob fragmentation−aromatization reaction of 1,4,5,6-tetrabromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one. The aforementioned ester was transformed into the reported structure of amathamide D through methylation of a hydroxyl group and conversion of the ester moiety to a *β*-aminoethyl side chain. The NMR data of the synthetic compound did not conform to the reported natural product structure possessing contiguously positioned *β*-aminoethyl side chain, a set of three adjacent bromines, and a methyl ether linkage on the phenyl ring. This prompted us to redefine the natural product structure by synthesizing a product whose spectral data exactly matched with the reported data of amathamide D. The convolutamine H, with completely substituted phenyl ring adorned with an extra methyl ether functional group, has also been synthesized by application of Grob fragmentation−aromatization strategy to 3-(benzyloxy)-1,4,5,6-tetrabromo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one. This approach furnished directly methyl 2,3,4-tribromo-5,6-dimethoxybenzoate, which was converted straightforwardly into convolutamine H. Further, synthesis of convolutamine F and lutamide A and C is also described.



INTRODUCTION

The hunt for new structural entities as potential pharmaceutical agents is a never ending endeavor, and marine organisms have been one among the most promising sources of natural products as a result of their wide ranging biological activity profile. They are relatively less explored compared to other traditional sources, though the number of new marine natural products being discovered is continuously growing. Organohalogens constitute about 15−20% of all newly discovered marine natural products.[1] Amathamides are brominated alkaloids and were isolated from the bryozoan *Amathia* genus (**1**−**8**, Figure 1).[2] The biological activities of isolated amathamides were not investigated extensively, while amathamide C and H were found to possess moderate antimalarial and antitrypanosomal activity.

Convolutamines A−H were isolated from Floridian marine bryozoan *Amathia convoluta*.[3] They resemble amathamides in having a *β*-nitrogen functionality and bromine(s) as well as a methyl ether linkage on the aryl moiety. Convolutamine F (**9**) displayed the biological activity against human epidermoid carcinoma KB cells and its vincristine-resistant KB/VJ-300 cells and also showed inhibitory effects for cell division of fertilized sea urchin eggs.[3b] Until now, only one synthesis of convolutamine F is reported in the literature, which involves 7 steps with 44% overall yield from 3-hydroxyphenylacetic acid.[4] We herein report a straightforward synthesis of convolutamine F from readily available 3-hydroxybenzaldehyde in 5 steps with an overall yield of 53%. Convolutamine H (**11**) is a nematocidal brominated marine alkaloid.[3c] It was found to be more potent than levamisole, a commercially available anthelmintic. Convolutamine H might be a precursor in biosynthesis of amathamide G, a tribrominated proline derived alkaloid. It was also suggested that *β*-phenylethyl amine, isolated from *Amathia wilsoni*, could be a biosynthetic precursor for various amathamides.[2c]

The presence of three contiguous bromines on the phenyl ring in some members of amathamides and convolutamines was a particularly striking feature that attracted our attention. The construction of aryl derivatives with three adjacent bromine atoms poses a formidable challenge since a straightforward installation through aromatic electrophilic substitution reactions is not a viable method to access them. The presence of a strong activating methoxy group is another major deterrent. A very interesting and noteworthy strategy reported by Weinreb's group for the synthesis of chartelline A (**12**) involves an indirect installation of three bromines,[5] the most difficult central bromine substituent being installed by utilizing an amine group as surrogate for bromine *via* modified Sandmeyer reaction. The activating amine functionality on the aryl ring in which the *para* position is already blocked facilitated the *ortho* bromination at two free adjacent positions. This strategy cannot

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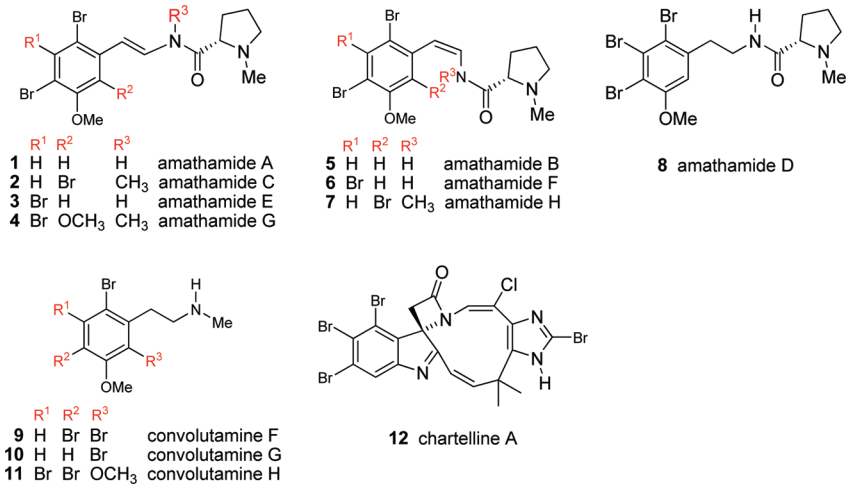
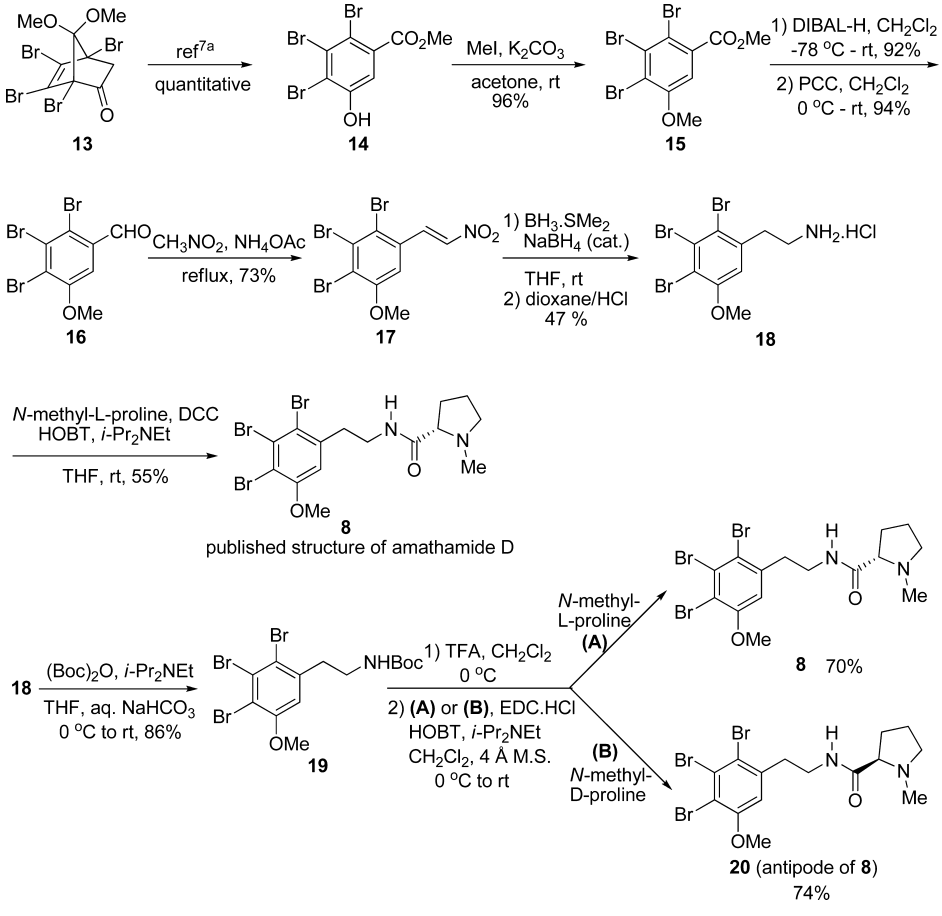


Figure 1. Structures of some marine-originated alkaloids.

Scheme 1. Synthesis of Amathamide D (8) (Structure As Published in the Literature) and Its Antipode (20)



be extended to amathamides and convolutamines due to lack of a blocking *para* substituent. Second, the presence of a methoxy unit is a further complicating factor. Recently, methods that build up the aromatic ring starting from aliphatic precursors (benzannulation methods) have been developed.[6] These methods, although offering better regiochemical control in certain cases, are not completely unrestrictive.

In order to explore the synthetic efficacy of our previously discovered methodology of synthesizing substituted bromophenol derivatives starting from differently substituted 1,4,5,6-tetrabromo-7,7-dimethoxy norbornene skeleton, we became interested in synthesis of some of these brominated alkaloids of marine origin. Herein we report synthesis and structure revision of amathamide D along with the synthesis of some other marine alkaloids.

RESULTS AND DISCUSSION

Methyl 2,3,4-tribromo-5-hydroxybenzoate **14** is easily accessible *via* acid-mediated Grob fragmentation aromatization reaction from 1,4,5,6-tetrabromo-7,7-dimethoxybicyclo[2.2.1]-

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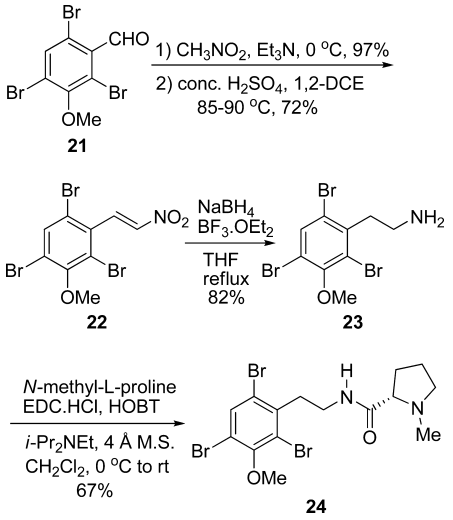
hept-5-en-2-one **13** in quantitative yield by our previously reported methodology.[7] The ester group in **14** could be conveniently converted in the desired substituted β-aminoethyl side chain. First, hydroxyl group in **14** was methylated using MeI. Since a direct conversion of ester to aldehyde group was problematic due to over-reduction, a two-step procedure involving a reduction (DIBAL-H)−oxidation (PCC) sequence was used to obtain **16**.[8] Aldehyde **16** was converted into α,β-unsaturated nitro compound **17** by refluxing with CH_3NO_2 in presence of NH_4OAc.[8,9] Our initial attempts for the reduction of nitroethylene moiety of **17** with reagents such as $LiAlH_4$, Fe/HCl, Pd−C/H_2, PtO_2/H_2, and Na_2S/$NaHCO_3$ failed to yield the desired saturated amine. Finally we succeeded in obtaining the amine as hydrochloride salt **18** using BH_3·SMe_2.[10] Because the free amine was not stable, it was converted into hydrochloride salt by using a saturated solution of anhydrous HCl in dioxane. Coupling reaction between **18** and *N*-methyl-L-proline[11a] was performed using DCC to get amide **8**. Otherwise when the Boc-protected amine **19** was utilized directly we obtained the amide **8** with enhanced yield *via* a protocol comprising deprotection with TFA, followed by coupling[12] with *N*-methyl-L-proline. The product **8** (Scheme 1), thus obtained should correspond to the published structure of amathamide D. However, a comparison of ^{1}H and ^{13}C NMR values revealed that it is not in conformity with published data, indicating the need for a revision of the structure for amathamide D. The most prominent difference in ^{1}H NMR was for Ar−H with a 0.93 ppm variation, while in ^{13}C NMR, peaks in the aromatic region displayed variations ranging between 2 and 6 ppm. Since optical rotation data for amathamide D was not reported in the literature, we determined the specific rotation for **8**. Further, we synthesized its antipode **20** by coupling *N*-methyl-D-proline[11b] with Boc amine **19** and measured its specific rotation as well. This exercise was done keeping in mind the fact that the assignment of absolute configuration for the published structure of amathamide D was based on the extrapolation of circular dichroism (CD) studies carried out for amathamide A and B.

In order to determine the correct structure for amathamide D, we looked at some of the closely related aromatic derivatives possessing bromine substituents at the 1,3,5-positions relative to each other. The reported chemical shift value for Ar−H at δ 7.75 ppm in the ^{1}H NMR spectrum strongly pointed out that the three bromines could be symmetrically substituted instead of being contiguous as proposed. In order to prove this unambiguously, we thought of synthesizing the molecule with symmetrically substituted bromines. For this purpose we chose 2,4,6-tribromo-3-methoxybenzaldehyde **21** (Scheme 2) as our starting material for the structure revision of amathamide D, which was prepared according to the literature method.[13] Attempts to synthesize (*E*)-1,3,5-tribromo-2-methoxy-4-(2-nitrovinyl)benzene **22** according to literature procedure using CH_3NO_2 and AcOH/NH_4OAc under reflux condition always furnished, in our hands, a mixture of **21** and **22** (based on ^{1}H NMR). We then followed a two-step protocol for the synthesis of **22** *via* Henry reaction followed by dehydration with conc H_2SO_4.[8] The requisite 2-(2,4,6-tribromo-3-methoxyphenyl)-ethanamine **23** was obtained by the reduction of unsaturated nitro compound **22** with BH_3·THF (generated *in situ* with BF_3·OEt_2 and $NaBH_4$) at reflux temperature.[10] Initially observed moderate to poor yield could be substantially improved to 82% on slight modification in workup procedure.

Scheme 2. Synthesis of Amathamide D (24) for Structure Revision



The so obtained 2-(2,4,6-tribromo-3-methoxyphenyl)-ethanamine **23** was coupled with *N*-methyl-L-proline using DCC as a coupling reagent. The reaction proceeded slowly and gave poor yield. Changing the coupling reagent to EDC·HCl furnished 67% yield of the amide **24**. The spectroscopic data (^{1}H and ^{13}C NMR) of **24** was found to be in accordance with the literature reported values of natural amathamide D. Figure 2 represents a ^{1}H NMR comparison of published and revised structures of amathamide D.

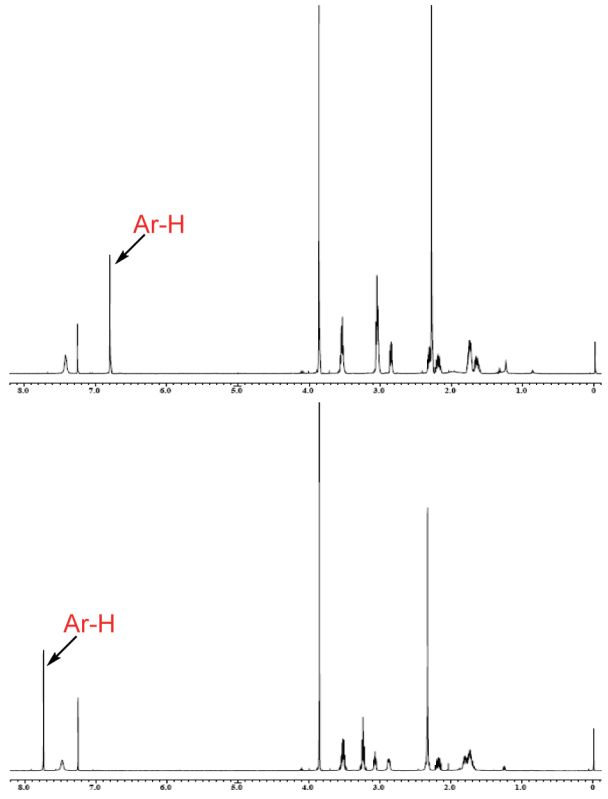


Figure 2. ^{1}H NMR comparison of proposed structure of amathamide D (**8**) and revised structure of (synthetic) amathamide D (**24**).

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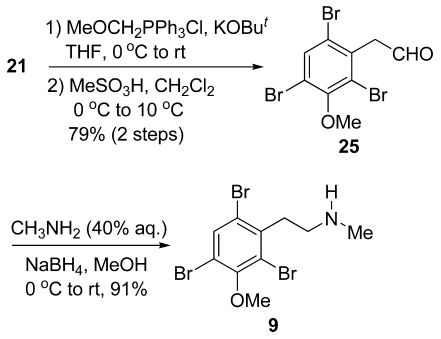
Since convolutamine F (**9**) has three symmetrical bromines on an aromatic system with methyl ether substituent and *β*-aminoethyl moiety, 2,4,6-tribromo-3-methoxybenzaldehyde **21** is a suitable substrate for convolutamine F synthesis. One-carbon homologation of 2,4,6-tribromo-3-methoxybenzaldehyde **21** *via* Wittig reaction followed by hydrolysis of vinyl ether with $MeSO_3H$ furnished 2-(2,4,6-tribromo-3-methoxyphenyl)acetaldehyde **25** (Scheme 3). Finally, aldehyde

Scheme 3. Synthesis of Convolutamine F (9)

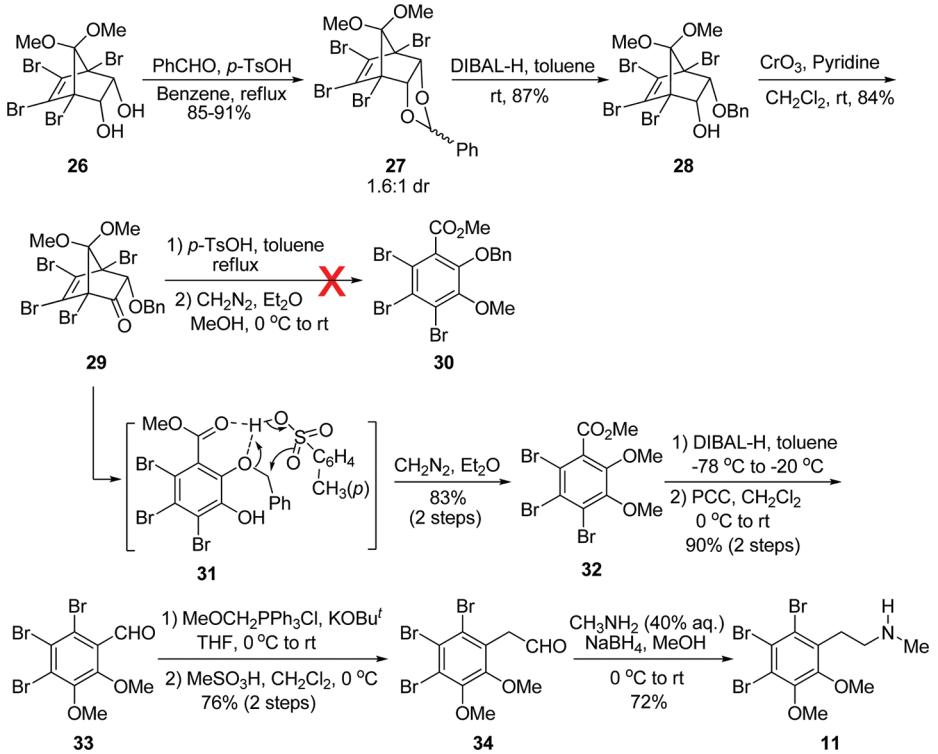


25 on reductive amination with methylamine (40% aq)/$NaBH_4$[14] gave the title compound convolutamine F (**9**) in excellent yield. Synthetic **9** was found to be identical to the natural convolutamine F as proved by ^1H and ^{13}C NMR data and high-resolution mass spectrometry.

Our next target was to synthesize convolutamine H (**11**), which is even more demanding. Indeed a pair of contiguous methyl ether and a set of three adjoining bromines have to be installed. For that purpose 1,4,5,6-tetrabromo-7,7-dimethoxybicyclo[2.2.1]hept-5-ene-2,3-diol **26** was prepared according to literature protocol.[15] Our original plan was to selectively monomethylate one of the hydroxyl groups and then oxidize the remaining hydroxyl group to ketone to set up Grob fragmentation to obtain monomethylated catechol derivative. Unfortunately, monomethylation of diol **26** was not successful perhaps due to its instability under basic conditions. Therefore we followed an indirect strategy for monoprotection. The diol **26** on treatment with benzaldehyde/*p*-TsOH[16] under reflux condition gave product **27** as 1.6:1 diastereomeric mixture (diastereomeric ratio was determined by the integration of benzylidene proton). A diastereomeric mixture of benzylidene acetals **27** on hydrogenolysis with DIBAL-H[17] in toluene furnished monobenzyl ether **28**. Compound **28** was oxidized into monoketonorbornene **29** with pyridinium dichromate (PDC).[7]

The monoketonorbornene **29** was subjected to Grob fragmentation−aromatization reaction in refluxing toluene using *p*-toluenesulfonic acid monohydrate (*p*-TsOH.H_2O). The crude phenolic product was methylated with diazomethane to obtain the methyl ether of phenol. To our pleasant surprise, we found that the benzyl ether group, present in the starting material, was replaced by a methyl ether group in the product obtained. A dimethylated catechol derivative **32** was obtained instead of the expected **30**, saving us from two extra steps. It appears that *in situ* debenzylation of **30** is taking place during the reaction. A literature search revealed that debenzylation of *ortho*-substituted phenol would take place in acidic medium.[18] A plausible mechanism *via* intermediate **31** is depicted in Scheme 4. The ester **32** was converted into aldehyde **33** by reduction with DIBAL-H followed by oxidation with PCC. One-carbon homologation of aldehyde **33** was achieved by Wittig reaction followed by acidic hydrolysis of vinyl ether with $MeSO_3H$. The homologated aldehyde **34** on reductive amination with methylamine (40% aq)/$NaBH_4$ gave title compound convolutamine H (**11**). Synthetic **11** was confirmed

Scheme 4. Synthesis of Convolutamine H (11)



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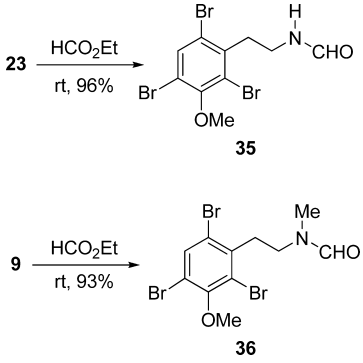
to be identical to natural convolutamine H by ^{1}H and ^{13}C NMR data and high-resolution mass spectrometry.

In order to exploit the synthon **23** and **9**, we focused our attention on lutamide synthesis. Lutamides are another class of formylated alkaloids and were isolated from a Floridian bryozoan.[4] Lutamide C showed cell growth inhibitory activity against the human monocyte, such as lymphocytic leukemia U937 cells. Phenylethylamine **23**, synthesized during amathamide D synthesis, was cleanly transformed into formylated product **35** with ethyl formate[19] at room temperature (Scheme 5). Compound **35** is lutamide A and has all spectroscopic data

Scheme 5. Synthesis of Lutamide A (35) and C (36)



in accordance with those reported. Convolutamine F (**9**) was also formylated with ethyl formate to give product **36**. Formylation using HCO_2NH_4 in CH_3CN under reflux condition[20] gave only 75% of the desired product. Compound **36** is lutamide C and has all spectroscopic data in accordance with those reported.

CONCLUSION

In conclusion, we have synthesized amathamide D according to the published structure and redefined its structure *via* synthesis. We found that natural amathamide D has symmetrical substitution of bromines on the aromatic ring and not contiguous as published. Convolutamine H, having a completely substituted phenyl ring, has been synthesized *via* an interesting pathway. We have also synthesized convolutamine F with improved overall yield as well as fewer steps. Lutamide A and C have also been synthesized.

EXPERIMENTAL SECTION

General Methods. All reactions were performed in oven-dried apparatus. Commercial grade solvents were distilled before use. Melting points were obtained in open capillary tubes and are uncorrected. Infrared spectra were recorded as KBr pellets (solids) or as thin films on NaCl flats (liquids). ^{1}H NMR was recorded at 400 or 500 MHz. Proton decoupled ^{13}C NMR was recorded at 100 or 125 MHz. HRMS were recorded using electron spray ionization (ESI) or electron ionization (EI) mode. Optical rotations were measured using a 2-mL cell with a 1-dm path length and are reported as $[\alpha]^{22}_D$ (*c* g/100 mL, solvent).

Methyl 2,3,4-Tribromo-5-methoxybenzoate (15). To a well-stirred partially soluble mixture of methyl 2,3,4-tribromo-5-hydroxybenzoate **14** (1.57 g, 4.04 mmol) in dry acetone (20 mL) was added anhydrous K_2CO_3 (668.4 mg, 4.84 mmol, 1.2 equiv) followed by MeI (1.3 mL, ~5 equiv). The reaction was then stirred at room temperature for 4 h. After completion of starting material (monitored by TLC), the reaction mixture was concentrated under *vacuo* to remove the volatiles. Water was added to the crude residue, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by silica gel column chromatography (20% EtOAc/hexane) to give methyl ether **15** (1.56 g, 96%) as a white crystalline solid. Mp 112−114 °C (lit.[7a] 116−118 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 3.95 (s, 3H), 3.93 (s, 3H).

2,3,4-Tribromo-5-methoxybenzaldehyde (16). To a cooled (−78 °C) magnetically stirred solution of ester **15** (1.5 g, 3.73 mmol) in CH_2Cl_2 (20 mL) was added a solution of DIBAL-H (8.76 mmol, 7.3 mL of 20 wt % solution in toluene) dropwise over a period of 10 min under argon atmosphere. The resulting solution was allowed to warm to room temperature and stirred for 70 h. After completion of starting material (monitored by TLC) the reaction was taken at −78 °C and quenched by dropwise addition of MeOH (2.5 mL) followed by saturated aqueous Rochelle salt solution (2.5 mL). The mixture was then allowed to warm to room temperature, diluted with EtOAc (20 mL), and subjected to vigorous stirring for 1 h. The resulting solidified mass settled at the bottom, and the organic layer was decanted. The solid residue was washed with EtOAc (3 × 5 mL). 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 column chromatography (60−80% EtOAc/hexane) to give the alcohol (1.3 g, 92%) as a white solid. Mp 136−138 °C. ^{1}H NMR (400 MHz, $CDCl_3$/DMSO-d_6 = 3:1) δ 7.12 (s, 1H), 4.50 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$/DMSO-d_6 = 3:1) δ 156.0, 142.9, 128.3, 114.1, 113.2, 109.4, 64.6, 56.5; IR (KBr) 3300−2700 (OH), 1580, 1440, 1400, 1340, 1245, 1180, 1060 cm^{-1}. Anal. Calcd for $C_8H_7Br_3O_2$: C, 25.63; H, 1.88. Found: C, 25.69; H, 1.76.

To a cooled (0−5 °C) solution of the alcohol (obtained above) (1.2 g, 3.20 mmol) in CH_2Cl_2 (60 mL) was added PCC (702 mg, 3.26 mmol). The resulting solution was allowed to warm to room temperature and stirred for 60 h. It was then filtered through a small silica gel pad to remove the inorganic impurities and washed with CH_2Cl_2 (10 mL). The filtrate was concentrated, and then the residue was purified by silica gel column chromatography (30−50% EtOAc/hexane) to give aldehyde **16** (1.12 g, 94%) as a white solid. Mp 138−140 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.27 (s, 1H), 7.38 (s, 1H), 3.94 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.8, 156.8, 134.5, 131.1, 123.6, 121.1, 109.6, 57.0; IR (KBr) 3070, 2878, 1685, 1566, 1365, 1064, 860 cm^{-1}. Anal. Calcd for $C_8H_5Br_3O_2$: C, 25.77; H, 1.35. Found: C, 25.78; H, 1.26.

(*E*)-2,3,4-Tribromo-1-methoxy-5-(2-nitrovinyl)benzene (17). To a solution of aldehyde **16** (900 mg, 2.41 mmol) in anhydrous nitromethane (12 mL) was added ammonium acetate (185.8 mg, 2.41 mmol). The reaction was refluxed for 5 h. After completion of starting material (monitored by TLC), the reaction was allowed to cool to room temperature, and the solvent was evaporated *in vacuo*. The residue was taken up in EtOAc (20 mL) and washed with water (7 mL). The aqueous phase was extracted again with EtOAc (3 × 8 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5−30% CH_2Cl_2/hexane) to give **17** (734 mg, 73%) as a yellow solid. Mp 191−193 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, 1H, J = 13.4 Hz), 7.48 (d, 1H, J = 13.4 Hz), 6.95 (s, 1H), 3.95 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6, 139.8, 138.7, 131.6, 131.4, 120.5, 120.1, 108.9, 57.1; IR (KBr) 3108, 1628, 1571, 1342, 1247, 1198, 1074, 967, 835 cm^{-1}; HRMS (ESI) calcd for $C_9H_{10}Br_3N_2O_3$ (M + NH_4), 430.8242; found, 430.8240.

2-(2,3,4-Tribromo-5-methoxyphenyl)ethanamine Hydrochloride (18). To a cooled (0 °C) solution of BH_3·SMe_2 (236.7 mg, 3.12 mmol) in anhydrous THF (1 mL) was added *via* cannula a solution of compound **17** (216 mg, 0.52 mmol) dissolved in anhydrous THF (5 mL). The reaction was stirred for 20 min at 0 °C and then allowed to warm to room temperature, and $NaBH_4$ (5.2 mg, 0.14 mmol) was added. The mixture was stirred at room temperature for 6.5 days, then distilled water ice (3 g) followed by 10% HCl solution (2.6 mL) was added, and the mixture was stirred at 60−65 °C for 2 h. All THF was removed *in vacuo*, and then water (8 mL) was added to the residue, which was extracted with Et_2O (3 × 8

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mL). The aqueous phase was made basic to pH 9−10 with 25% aqueous NH_3 solution, and then solid NaCl was added until saturation of the aqueous layer. The aqueous phase was then extracted with $CHCl_3$ (3 × 15 mL). The combined $CHCl_3$ extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was then dissolved in $CHCl_3$ (0.8 mL) and cooled to 0 °C, and then saturated dioxane/HCl was added dropwise until the appearance of white precipitate. The obtained white solid was washed with $CHCl_3$ and dried in vacuum, to give amine hydrochloride salt **18** (103.1 mg, 47%) as a white crystalline solid. Mp 245−250 °C (decomposed).

Synthesis of Amide 8 from Amine Hydrochloride Salt 18. To a cooled (0 °C) solution of *N*-methyl-L-proline (6.2 mg, 0.048 mmol) in anhydrous CH_2Cl_2 (1 mL) were added DCC (7.2 mg, 0.035 mmol) and HOBT (5.6 mg, 0.04 mmol). The mixture was then stirred for 30 min at 0 °C, and then a solution of amine hydrochloride salt **18** (13.5 mg, 0.03 mmol) in anhydrous THF (0.5 mL) followed by *i*-Pr_2NEt (8.2 mg, 0.06 mmol) was added. The mixture was stirred for 20 min at 0 °C and then allowed to warm to room temperature. After stirring for 12 h at room temperature (monitored by TLC), the reaction was then quenched with 5% citric acid (0.5 mL), and all volatiles were removed under reduced pressure. EtOAc (10 mL) was added and the organic phase was washed with saturated aqueous $NaHCO_3$ solution (1 mL) and brine (1 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5−10% MeOH/EtOAc) to give **8** (8.7 mg, 55%) as a light brown solid. Mp 134−136 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 7.47 (br s, 1H), 6.82 (s, 1H), 3.88 (s, 3H), 3.56 (q, 2H, J = 6.7 Hz), 3.07 (t, 3H, J = 7.1 Hz), 2.90 (br s, 1H), 2.31 (br s, 4H), 2.21−2.19 (m, 1H), 1.76−1.71 (m, 3H).

Synthesis of Boc-Protected Amine 19. To a cooled (0 °C) solution of amine hydrochloride salt **18** (65 mg, 0.15 mmol) in THF (2.2 mL) were added di-*tert*-butyl dicarbonate $(Boc)_2O$ (40 mg, 0.18 mmol), *i*-Pr_2NEt (29.6 mg, 0.23 mmol), and saturated aqueous $NaHCO_3$ solution (1 mL). The mixture was then allowed to warm to room temperature and stirred overnight. All volatiles were removed under reduced pressure, and the residue was taken up in EtOAc (10 mL), washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15−25% EtOAc/hexane) to give **19** (64.2 mg, 86%) as a white crystalline solid. Mp 112−114 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 6.77 (s, 1H), 4.61 (br s, 1H), 3.88 (s, 3H), 3.38 (q, 2H, J = 6.7 Hz), 3.03 (t, 2H, J = 6.9 Hz), 1.43 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.1, 156.0, 140.1, 129.6, 118.4, 114.2, 112.6, 79.6, 56.9, 39.9, 38.8, 28.5; IR (KBr) 3368, 3074, 2977, 1678, 1528, 1453, 1273, 1165, 1067, 850, 657 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}Br_3NO_3$ (M + H), 485.8915; found, 485.8915.

Synthesis of Amide 8 from Boc-Protected Amine 19. To a cooled (0 °C) solution of compound **19** (39 mg, 0.08 mmol) in anhydrous CH_2Cl_2 (0.7 mL) was added TFA (0.1 mL). The resultant solution was then stirred for 25 min at 0 °C, and then all volatiles were removed in vacuum until the appearance of yellowish solid. The obtained yellowish solid was dissolved in anhydrous THF (1 mL). In another two-necked round-bottom flask containing a solution of *N*-methyl-L-proline (12.4 mg, 0.096 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C were added HOBT (17.3 mg, 0.13 mmol), EDC·HCl (21.5 mg, 0.11 mmol), *i*-Pr_2NEt (23.7 mg, 0.18 mmol), and 4 Å molecular sieves. The mixture was then stirred for 30 min at 0 °C, and to this was added *via* cannula a solution of the TFA salt from compound **19**. The mixture was then allowed to warm to room temperature and stirred for 8 h. CH_2Cl_2 (10 mL) was added, and the reaction was quenched with 5% citric acid (1 mL). The solution was then washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% MeOH/$CHCl_3$) to give **8** (27.7 mg, 70%) as a light brown solid. Mp 135−137 °C; $[\alpha]^{22}_D$ −38.9 (c 0.86, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.42 (br s, 1H), 6.80 (s, 1H), 3.86 (s, 3H), 3.56−3.52 (m, 2H), 3.06−3.02 (m, 3H), 2.85 (dd, 1H, J = 5.2, 10.3 Hz), 2.34−2.28 (m, 4H), 2.21−2.17 (m, 1H), 1.77−1.75 (m, 2H), 1.67−1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 156.2, 140.2, 129.6, 118.5, 114.4, 112.5, 69.0, 56.9, 56.7, 41.9, 38.4, 38.2, 31.2, 24.4; IR (KBr) 3248, 3060, 2939, 1640, 1358, 1065, 900, 681 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}Br_3N_2O_2$ (M + H), 496.9075; found, 496.9073.

Synthesis of Amide 20. To a cooled (0 °C) solution of compound **19** (35.3 mg, 0.07 mmol) in anhydrous CH_2Cl_2 (0.7 mL) was added TFA (0.1 mL). The solution was then stirred for 25 min at 0 °C, and then all volatiles were removed in vacuum until the appearance of yellowish solid. The obtained yellowish solid was dissolved in anhydrous THF (1 mL). In another two-necked round-bottom flask containing a solution of *N*-methyl-D-proline (11.2 mg, 0.087 mmol) in anhydrous CH_2Cl_2 (0.8 mL) at 0 °C were added HOBT (15.6 mg, 0.12 mmol), EDC·HCl (19.4 mg, 0.10 mmol), *i*-Pr_2NEt (21.5 mg, 0.17 mmol), and 4 Å molecular sieves. The mixture was then stirred for 30 min at 0 °C and to this was added *via* cannula a solution of the TFA salt from compound **19**. The mixture was then allowed to warm to room temperature and stirred for 12 h. CH_2Cl_2 (10 mL) was added, and the reaction was quenched with 5% citric acid (1 mL). The solution was then washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (1% MeOH/$CHCl_3$) to give **20** (26.6 mg, 74%) as a light yellow solid. Mp 141−143 °C; $[\alpha]^{22}_D$ +37.8 (c 0.9, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.43 (br s, 1H), 6.80 (s, 1H), 3.86 (s, 3H), 3.56−3.52 (m, 2H), 3.05 (t, 3H, J = 7.0 Hz), 2.88 (dd, 1H, J = 4.7, 9.6 Hz), 2.34−2.28 (m, 4H), 2.23−2.15 (m, 1H), 1.77−1.73 (m, 2H), 1.68−1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 156.1, 140.0, 129.5, 118.4, 114.2, 112.3, 68.8, 56.8, 56.6, 41.7, 38.2, 38.1, 31.0, 24.3; IR (KBr) 3249, 3060, 2939, 2775, 1640, 1358, 1065, 860, 681 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}Br_3N_2O_2$ (M + H), 496.9075; found, 496.9073.

(*E*)-1,3,5-Tribromo-2-methoxy-4-(2-nitrovinyl)benzene (22). To a solution of aldehyde **21** (800 mg, 2.14 mmol) in anhydrous nitromethane (6.4 mL) at 0 °C was added Et_3N (216.6 mg, 2.14 mmol). The reaction was then stirred for 40 min at 0 °C, and then the solvent was evaporated *in vacuo*. The residue was purified by silica gel column chromatography (6−15% EtOAc/hexane) to furnish β-nitro alcohol (901.6 mg, 97%) as a colorless sticky oil that solidified on cooling. Mp 99−102 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.82 (s, 1H), 6.24−6.20 (m, 1H), 5.17 (dd, 1H, J = 10.4, 13.2 Hz), 4.52 (dd, 1H, J = 3.2, 13.3 Hz), 3.88 (s, 3H), 3.36 (d, 1H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 137.3, 135.6, 121.1, 119.2, 118.5, 72.6, 60.7, 53.4; IR (KBr) 3522, 2950, 1556, 1360, 1026, 897, 692 cm^{-1}; HRMS (ESI) calcd for $C_9H_{12}Br_3N_2O_4$ (M + NH_4), 448.8347; found, 448.8348.

To a solution of β-nitro alcohol (obtained above) (800 mg, 1.84 mmol) in 1,2-dichloroethane (7.2 mL) was added conc H_2SO_4 (541.9 mg, 5.53 mmol). The resulting solution was heated at 85−90 °C for 80 min (monitored by TLC). The reaction was then allowed to cool to room temperature, and EtOAc (15 mL) was added. The organic phase was washed with saturated aqueous $NaHCO_3$ solution (5 mL), and the aqueous phase was then extracted again with EtOAc (3 × 6 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5−25% CH_2Cl_2/hexane) to give **22** (551 mg, 72%) as a yellow crystalline solid. Mp 112−114 °C (lit.[13] 93 °C); ^1H NMR (500 MHz, $CDCl_3$) δ 7.98 (d, 1H, J = 13.7 Hz), 7.88 (s, 1H), 7.56 (d, 1H, J = 13.7 Hz), 3.89 (s, 3H).

2-(2,4,6-Tribromo-3-methoxyphenyl)ethanamine (23). To a cooled (0 °C) solution of the $NaBH_4$ (238.6 mg, 6.28 mmol) in anhydrous THF (8 mL) was added BF_3·OEt_2 (1.13 g, 7.93 mmol). The resultant solution was then stirred for 10 min at 0 °C and for 15 min at room temperature. Then a solution of nitro compound **22** (550 mg, 1.32 mmol) in anhydrous THF (5.2 mL) was added *via* cannula. The reaction was refluxed for 7.5 h and then allowed to cool to room temperature. Water (17 mL) was added dropwise, followed by 1 N HCl (17 mL). The reaction was heated again to 80−85 °C for 2 h. After cooling at room temperature, the mixture was then extracted with Et_2O (2 × 10 mL). The aqueous layer was made basic with (20% w/w) aqueous NaOH to pH 10, then solid NaCl was added, and the

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aqueous mixture was extracted with Et_2O (3 × 20 mL). Previous Et_2O extracts also were basified with (20% w/w) aqueous NaOH to pH 10 and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography over silica gel (5−20% MeOH/$CHCl_3$) to give **23** (419.2 mg, 82%) as a colorless sticky liquid that solidified on standing. Mp 56−58 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (s, 1H), 3.85 (s, 3H), 3.15−3.12 (m, 2H), 2.91 (t, 2H, J = 7.6 Hz), 1.42 (br s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 139.7, 135.4, 121.9, 120.0, 116.0, 60.6, 41.5, 40.7; IR (KBr) 3359, 3287, 3014, 2935, 1557, 1448, 1355, 1018, 930, 639 cm^{-1}; HRMS (ESI) calcd for $C_9H_{11}Br_3NO$ (M + H), 385.8391; found, 385.8398.

Synthesis of Amide 24. To a cooled (0 °C) solution of *N*-methyl-L-proline (19.9 mg, 0.16 mmol) in anhydrous CH_2Cl_2 (1 mL) were added HOBT (27.8 mg, 0.21 mmol), EDC·HCl (34.6 mg, 0.18 mmol), *i*-Pr_2NEt (23.3 mg, 0.18 mmol), and 4 Å molecular sieves. The mixture was then stirred for 30 min at 0 °C, and then a solution of amine **23** (50 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (0.6 mL) was added. The reaction solution was then allowed to warm to room temperature and stirred 12 h. After completion of starting material (monitored by TLC), the reaction was diluted with CH_2Cl_2 (7 mL) and quenched with 5% citric acid (0.8 mL). The solution was then washed with saturated aqueous $NaHCO_3$ solution and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% MeOH/$CHCl_3$) to give **24** (43.2 mg, 67%) as a colorless liquid which solidified on cooling. Mp 89−91 °C; $[\alpha]^{23}_D$ −39.8 (c 0.49, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.48 (br s, 1H), 3.85 (s, 3H), 3.54−3.50 (m, 2H), 3.24 (dt, 2H, J = 2.1, 7.3 Hz), 3.08−3.05 (m, 1H), 2.89 (dd, 1H, J = 4.9, 10.1 Hz), 2.33 (s, 4H), 2.20−2.14 (m, 1H), 1.83−1.76 (m, 1H), 1.74−1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.8, 154.1, 139.0, 135.5, 122.2, 120.2, 116.5, 69.0, 60.6, 56.8, 42.0, 37.1, 37.0, 31.0, 24.5; IR (KBr) 3309, 2967, 2939, 1650, 1529, 1448, 1360, 1264, 1050, 861, 746 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}Br_3N_2O_2$ (M + H), 496.9075; found, 496.9078.

2-(2,4,6-Tribromo-3-methoxyphenyl)acetaldehyde (25). To a cooled (0 °C) solution of methoxymethyltriphenylphosphonium chloride (10.36 g, 30.23 mmol) in anhydrous THF (30 mL) was added potassium *tert*-butoxide (3.30 g, 29.49 mmol). The mixture was stirred for 20 min at 0 °C and then for 1.5 h at room temperature, and a solution of aldehyde **21** (5.5 g, 14.74 mmol) in anhydrous THF (45 mL) was added *via* cannula at 0 °C. The reaction was allowed to warm to room temperature and stirred overnight. The reaction was filtered through a short silica pad, and the filtrate was then washed with water (30 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3% EtOAc/hexane) as eluent to furnish the enol ether, which was used as such in the next reaction.

To a cooled (0−10 °C) solution of the enol ether (obtained above) in anhydrous CH_2Cl_2 (220 mL) was added methanesulphonic acid ($MeSO_3H$, 4.3 g, 44.8 mmol) dropwise. After 3 h, the reaction was poured in saturated aqueous $NaHCO_3$ solution (50 mL), and then organic phase was separated and washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (5% EtOAc/hexane) to give **25** (4.53 g, 79%) as a white solid. Mp 108−110 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (s, 1H), 7.80 (s, 1H), 4.21 (s, 2H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.1, 154.2, 135.5, 134.1, 122.5, 120.5, 117.7, 60.7, 51.6; IR (KBr) 3073, 2939, 2850, 2724, 1714, 1561, 1452, 1038, 659 cm^{-1}; HRMS (ESI) calcd for $C_9H_8Br_3O_2$ (M + H), 384.8074; found, 384.8091.

Convolutamine F (9). To a solution of aldehyde **25** (200 mg, 0.52 mmol) in anhydrous MeOH (3 mL) was added a 40% aqueous solution of methylamine (100.1 mg, 1.29 mmol). The reaction was stirred for 30 min at room temperatureand then cooled to 0 °C, and $NaBH_4$ (15.7 mg, 0.41 mmol) was added in three portions over a period of 10 min. The reaction was stirred for 24 h at room temperature, then water (2.5 mL) was added, and all MeOH was removed under reduced pressure. The obtained aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (10−25% MeOH/$CHCl_3$) to give **9** (188 mg, 91%) as a colorless viscous liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 3.85 (s, 3H), 3.16 (t, 2H, J = 7.8 Hz), 2.76 (t, 2H, J = 7.9 Hz), 2.49 (s, 3H), 1.45 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.0, 139.9, 135.4, 121.8, 120.0, 116.0, 60.6, 49.7, 37.7, 36.4; IR (Neat) 3331, 2934, 2842, 1558, 1451, 1358, 1075, 864 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{13}Br_3NO$ (M + H), 399.8547; found, 399.8540.

Synthesis of Benzylidene Acetal 27. To a solution of diol **26** (13.45 g, 26.79 mmol) in anhydrous benzene (428 mL) were added *p*-toluenesulfonic acid monohydrate (509 mg, 2.68 mmol) and benzaldehyde (3.98 g, 37.55 mmol). The reaction was refluxed for 11 h with azeotropic removal of water with a Dean−Stark condenser (monitored by TLC). The reaction was allowed to cool to room temperature, poured into saturated aqueous $NaHCO_3$ solution (60 mL), and then extracted with Et_2O (3 × 70 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (3% EtOAc/hexane) to give **27** (13.38 g, 85%) in 1.6:1 diastereomeric mixture as a white crystalline solid. Mp 113−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50−7.48 (m, 2H), 7.39−7.34 (m, 8H), 6.01 (s, 1H), 5.81 (s, 1H), 5.07 (s, 2H), 4.98 (s, 2H), 3.65 (s, 3H), 3.62 (s, 3H), 3.60 (2 s, partially merged, due to two -OMe, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.7, 134.1, 130.3, 129.6, 128.5, 128.4, 127.8, 126.2, 125.4, 124.8, 115.4, 113.7, 109.2, 107.7, 88.1, 87.1, 70.3, 69.8, 53.1, 52.1, 52.0; IR (KBr) 3039, 2946, 1608, 1461, 1187, 1039, 931, 702 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}Br_4NO_4$ (M + NH_4), 603.7969; found, 603.7974.

3-(Benzyloxy)-1,4,5,6-tetrabromo-7,7-dimethoxybicyclo-[2.2.1]hept-5-en-2-ol (28). To a cooled (−10 °C) solution of benzylidene acetal **27** (12.6 g, 21.34 mmol) in anhydrous toluene (22 mL) was added DIBAL-H (25% in toluene, 36.4 g, 64.02 mmol). The reaction was allowed to warm to room temperature and stirred for 14 h (monitored by TLC). The reaction was cooled to −20 °C, and MeOH (30 mL) was added dropwise followed by 10% aq NaOH (30 mL). The mixture was then extracted with Et_2O (5 × 30 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2−5% EtOAc/hexane) to give **28** (10.95 g, 87%) as a colorless viscous liquid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37−7.33 (m, 5H), 4.87 (d, 1H, J = 11.5 Hz), 4.75 (d, 1H, J = 11.5 Hz), 4.51 (t, 1H, J = 7.4 Hz), 4.40 (d, 1H, J = 7.4 Hz), 3.59 (s, 3H), 3.57 (s, 3H), 2.76 (d, 1H, J = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 128.5, 128.3, 128.0, 124.3, 110.1, 84.0, 78.1, 75.3, 73.0, 71.8, 53.1, 51.8; IR (Neat) 3501, 2948, 1571, 1455, 1139, 1105, 1030, 739 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}Br_4NO_4$ (M + NH_4), 605.8126; found, 605.8128.

3-(Benzyloxy)-1,4,5,6-tetrabromo-7,7-dimethoxybicyclo-[2.2.1]hept-5-en-2-one (29). To a solution of pyridine (576.5 mg, 7.30 mmol) in CH_2Cl_2 (11.6 mL) was added CrO_3 (365 mg, 3.65 mmol). The resultant solution was stirred at room temperature for 30−40 min, and then to this a solution of alcohol **28** (320 mg, 0.54 mmol) in CH_2Cl_2 (10 mL) was added and stirred for 90 h at room temperature. The reaction solution was then filtered through a small silica gel pad, and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (2% EtOAc/hexane) to give **29** (267 mg, 84%) as a white crystalline solid. Mp 94−96 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 4.95 (d, 1H, J = 12.2 Hz), 4.85 (d, 1H, J = 12.2 Hz), 4.09 (s, 1H), 3.57 (s, 3H), 3.49 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 136.6, 130.2, 128.4, 128.0, 127.8, 119.0, 112.4, 79.8, 74.4, 69.4, 53.4, 52.1; IR (KBr) 2993, 1780, 1561, 1453, 1121, 1026, 745 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{15}Br_4O_4$ (M + H), 586.7704; found, 586.7701.

Methyl 2,3,4-Tribromo-5,6-dimethoxybenzoate (32). To a solution of ketone **29** (2.0 g, 3.39 mmol) in anhydrous toluene (11.9 mL) was added *p*-toluenesulfonic acid monohydrate (322 mg, 1.69 mmol). The resultant solution was refluxed for 3.5 h and then allowed to cool to room temperature. The reaction was poured into saturated aqueous $NaHCO_3$ solution (8 mL) and then extracted with EtOAc (3

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× 25 mL). The combined organic phases were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was dissolved in MeOH (3 mL) and then treated with diazomethane at 0 °C. All volatiles were removed under reduced pressure, and the residue was purified by silica gel column chromatography (2% EtOAc/hexane) to give **32** (1.22 g, 83%) as a white crystalline solid. Mp 77−78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.96 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 151.0, 149.8, 132.6, 123.8, 123.6, 116.5, 61.9, 60.7, 53.0; IR (KBr) 2943, 2860, 1746, 1550, 1455, 1280, 1029, 656 cm^{-1}; HRMS (EI) calcd for $C_{10}H_9Br_3O_4$, 429.8051; found, 429.8055.

2,3,4-Tribromo-5,6-dimethoxybenzaldehyde (33). To a cooled (−78 °C) solution of ester **32** (910 mg, 2.10 mmol) in anhydrous toluene (12.6 mL) was added DIBAL-H (1.0 M in toluene, 6.3 mL, 6.30 mmol). The resulting solution was allowed to warm to −20 °C in 2 h (monitored by TLC). The reaction solution was cooled again to −78 °C, and MeOH (1.5 mL) was added dropwise followed by saturated aqueous Rochelle salt solution (1.5 mL). The mixture was then allowed to warm to room temperature, diluted with EtOAc (15 mL), and subjected to vigorous stirring for 1 h. The resulting solidified mass settled at the bottom, and the organic layer was decanted. The solid residue was washed with EtOAc (2 × 5 mL). The combined organic phases were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (15−30% EtOAc/hexane as eluent) to furnish the alcohol, which was used as such for the next reaction.

To a cooled (0 °C) solution of PCC (476.6 mg, 2.21 mmol) in anhydrous CH_2Cl_2 (2 mL) was added a solution of alcohol (obtained above) in anhydrous CH_2Cl_2 (12 mL). The resulting solution was allowed to warm to room temperature and stirred for 44 h. It was then filtered through a small silica gel pad to remove the inorganic impurities and washed with CH_2Cl_2, and the filtrate was concentrated. The residue was purified by silica gel column chromatography (2−4% EtOAc/hexane) to furnish aldehyde **33** (759.3 mg, 90%) as a white crystalline solid. Mp 105−107 °C (lit.[2d] 102−104 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 3.96 (s, 3H), 3.91 (s, 3H).

2-(2,3,4-Tribromo-5,6-dimethoxyphenyl)acetaldehyde (34). Experimental procedure is similar to that for compound **25**. After column purification the compound **34** (579.6 mg, 76%) was obtained as a white solid. Mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 4.06 (s, 2H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 151.7, 150.6, 129.3, 123.3, 123.0, 121.8, 61.1, 60.5, 46.9; IR (KBr) 2976, 2838, 2731, 1713, 1455, 1370, 1061, 897 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{10}Br_3O_3$ (M + H), 414.8180; found, 414.8184.

Convolutamine H (11). Experimental procedure is similar to that for compound **9**. After column purification the product **11** (24.7 mg, 72%) was obtained as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.88 (s, 3H), 3.84 (s, 3H), 3.07 (t, 2H, J = 7.7 Hz), 2.76 (t, 2H, J = 7.7 Hz), 2.49 (s, 3H), 1.79 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 150.7, 135.5, 123.1, 122.8, 120.2, 61.1, 60.4, 50.6, 36.2, 32.7; IR (Neat) 3350, 2936, 2851, 1623, 1449, 1388, 1009, 750 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{15}Br_3NO_2$ (M + H), 429.8653; found, 429.8654.

Lutamide A (35). A solution of amine **23** (52 mg, 0.13 mmol) in ethyl formate (0.5 mL) was stirred at room temperature for 10 h. The excess ethyl formate was removed under reduced pressure, and the residue was purified by silica gel column chromatography (60−70% EtOAc/hexane) to give product **35** (53.4 mg, 96%) as a white solid. Mp 100−101 °C (lit.[4] 105 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17, 7.99, and 7.96 (each s, due to geometrical isomer, 1H), 7.78 and 7.76 (each s, due to geometrical isomer, 1H), 5.85 (br s, 1H), 3.87 (s, 3H), 3.57 and 3.47 (each q, due to geometrical isomer, 2H, J = 6.6 and 7.0 Hz), 3.26 (t, 2H, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2 and 161.3 (due to geometrical isomer), 154.2 and 154.0 (due to geometrical isomer), 138.4 and 137.3 (due to geometrical isomer), 135.6 and 135.5 (due to geometrical isomer), 122.0 and 121.9 (due to geometrical isomer), 120.0 and 119.9 (due to geometrical isomer), 117.0 and 116.6 (due to geometrical isomer), 60.6 and 60.5 (due to geometrical isomer), 39.6 and 38.7 (due to geometrical isomer), 36.7 and 36.2 (due to geometrical isomer); IR (KBr) 3268, 3067, 2936, 2877, 1738, 1651, 1454, 1026, 871 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{11}Br_3NO_2$ (M + H), 413.8340; found, 413.8340.

Lutamide C (36). Experimental procedure is similar to that for compound **35**. After column purification the product **36** (44.6 mg, 93%) was obtained as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.78 and 7.76 (each s, due to geometrical isomer, 1H), 3.88 and 3.87 (each s, due to geometrical isomer, 3H), 3.55−3.51 and 3.44−3.40 (each m, due to geometrical isomer, 2H), 3.27−3.23 (m, 2H), 3.00 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6 and 162.4 (due to geometrical isomer), 154.2 and 154.0 (due to geometrical isomer), 138.5 and 137.4 (due to geometrical isomer), 135.6 and 135.4 (due to geometrical isomer), 121.9 and 121.8 (due to geometrical isomer), 119.9 and 119.8 (due to geometrical isomer), 116.9 and 116.5 (due to geometrical isomer), 60.6 and 60.5 (due to geometrical isomer), 47.2 and 42.2 (due to geometrical isomer), 36.6, 34.9, 34.6, 30.1; IR (Neat) 2935, 2849, 1678, 1452, 1075, 865 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{13}Br_3NO_2$ (M + H), 427.8496; found, 427.8496.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H NMR, ^{13}C NMR, and HRMS spectra for products. 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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