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Bioinspired Syntheses of the Pyridoacridine Marine Alkaloids Demethyldeoxyamphimedine, Deoxyamphimedine, and Amphimedine

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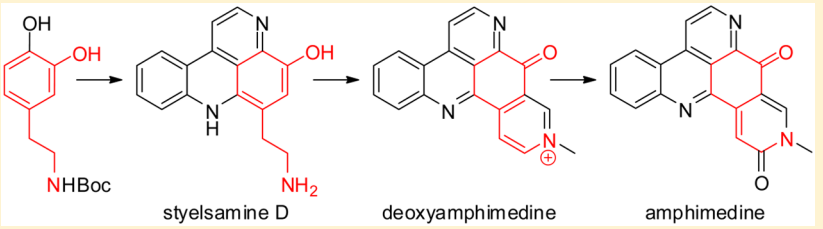
Supporting Information



ABSTRACT: Efficient bioinspired syntheses of the biologically active pyridoacridine marine alkaloids demethyldeoxyamphimedine, deoxyamphimedine, and amphimedine are reported. Reaction of styelsamine D, prepared via an optimized route starting from Boc-dopamine, with paraformaldehyde afforded demethyldeoxyamphimedine and deoxyamphimedine. Oxidation of the latter using either $K_3[Fe(CN)_6]$ or DMSO/conc. HCl gave amphimedine in 8 steps from tryptamine with an overall yield of 14%. The versatility of the method was demonstrated by the synthesis of non-natural ethyl and benzyl congeners of deoxyamphimedine and amphimedine.

Amphimedine (**1**), reported in 1983 from an *Amphimedon* sp. sponge, was the first example of a natural product bearing a new alkaloid skeleton.[1] Related dopamine-based pyridoacridines, encapsulating the 11*H*-pyrido[4,3,2-*mn*]-acridine skeleton, now number greater than 40.[2,3] Alkaloids belonging to this family typically exhibit significant biological activities, including cytotoxicity.[4] For example, of the pentacyclic pyridoacridine analogues amphimedine (**1**), neoamphimedine (**2**),[5] deoxyamphimedine (**3**),[6] and demethyldeoxyamphimedine (**4**)[7] (Figure 1), **1** induces specific developmental effects in zebrafish embryos,[8] **2** is cytotoxic and stimulates topoisomerase II to catenate DNA,[5,9,10] and **3** causes damage to DNA via the production of reactive oxygen species.[11] A number of syntheses of amphimedine (**1**)[12−15] and demethyldeoxyamphimedine (**4**)[16,17] have been reported, all relying upon either hetero-Diels−Alder or Pd- or Li-metalation reactions to construct the core skeleton. In the case of amphimedine, total syntheses have been reported that incorporate a longest linear sequence of up to 13 steps. Syntheses of demethyldeoxyamphimedine on the other hand are considerably shorter with the recent report by Bracher of a 4 step, 6.4% yield sequence being the most efficient to date.[17] None of the syntheses, however, can be considered bioinspired or biomimetic. Several groups have speculated that styelsamine D (**5**), itself a natural product isolated from the ascidian *Eusynstyela latericius*,[18] could be a biosynthetic intermediate to a large subset of pyridoacridine alkaloids, including **1**−**4**.[3,7] Preliminary experiments by Bry et al. observed that addition of formaldehyde to a marine organism extract that contains both styelsamine D (**5**) and demethyldeoxyamphimedine (**4**) led to the disappearance of the former with time and a concomitant increase in detectable quantities of the latter.[7]

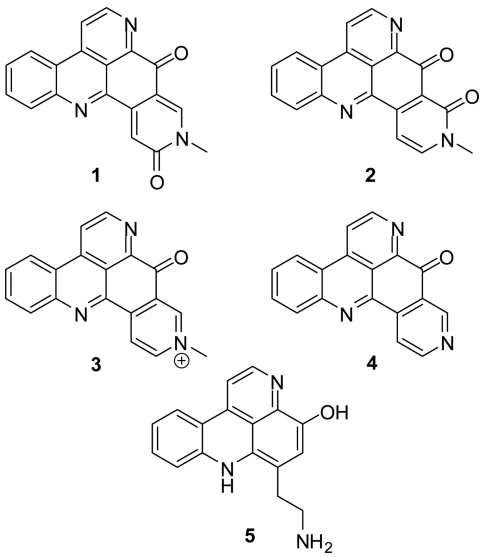


Figure 1. Structures of marine pyridoacridine alkaloids amphimedine (**1**), neoamphimedine (**2**), deoxyamphimedine (**3**), demethyldeoxyamphimedine (**4**), and styelsamine D (**5**).

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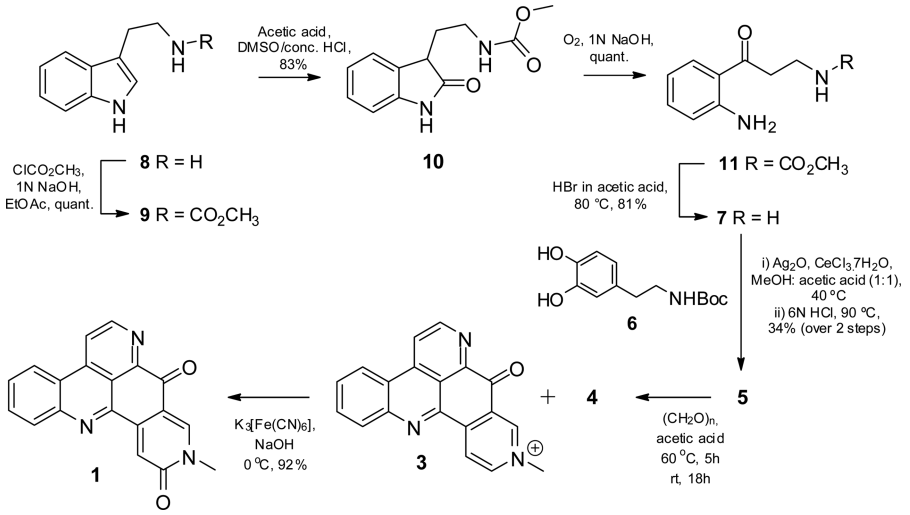
Scheme 1. Synthesis of Demethyldeoxyamphimedine (4), Deoxyamphimedine (3), and Amphimedine (1)



We report herein an improved synthesis of styelsamine D, efficient bioinspired conversion of styelsamine D (**5**) to demethyldeoxyamphimedine (**4**) and deoxyamphimedine (**3**), and subsequent oxidation of the latter to amphimedine (**1**). The versatility of the approach is demonstrated by the synthesis of non-natural analogues of **1** and **3**. In addition, an alternative route to amphimedine via the anticipated natural product *N*-methyl styelsamine D is also demonstrated.

Skyler and Heathcock have previously reported the development of a biomimetic synthesis of styelsamine B (*N*-acetyl styelsamine D), where oxidative coupling of *N*-acetyl dopamine with kynuramine followed by in situ acid-mediated ring closure led to the formation of the required pyridoacridine skeleton.[19] This procedure required the product to undergo subsequent acid hydrolysis (MeOH/4 N HCl (1:1), 80 °C, 2 d) to afford styelsamine D (**5**).[3,20] We have modified this reaction process to more specifically target the synthesis of styelsamine D by utilizing *tert*-butyl 2-(3,4-dihydroxyphenyl) ethylcarbamate (Boc-dopamine, **6**) as starting material and by optimizing the synthesis of the coupling partner kynuramine (**7**). The modified synthesis of kynuramine (**7**) began by protection of tryptamine (**8**) to give carbamate **9** (Scheme 1). Oxidation of the protected tryptamine (**9**) yielded oxindole **10**,[21] which upon treatment with O_2 in basic conditions[21,22] afforded protected kynuramine (**11**) in quantitative yield. Removal of the carbamate protecting group gave kynuramine (**7**) in 81% yield (Scheme 1). This synthetic route circumvents the use of ozone as the ring opening reagent and affords kynuramine with an improved overall yield of 67% (previous overall yield was 57%).[19] With kynuramine in hand, coupling of **7** with **6**[23] using a two-step sequence afforded styelsamine D (**5**) in 34% yield (Scheme 1). Reaction of **5** with paraformaldehyde (5 equiv) in acetic acid[24] gratifyingly afforded the two pentacyclic natural products deoxyamphimedine (**3**) in 48% yield and demethyldeoxyamphimedine (**4**) in 52% yield. Repeating our reaction with an increasing number of equivalents of paraformaldehyde gave a corresponding increase in the yield of **3** vs **4** (9.1 equiv, 58 and 34%, respectively; 15 equiv, 66 and 34%, respectively). This represents the first reported synthesis of deoxyamphimedine and the highest yielding synthesis of demethyldeoxyamphimedine reported to date.

With an optimized synthesis of styelsamine D and with the successful reaction with paraformaldehyde, our attention then turned to oxidation of deoxyamphimedine. We were interested in not only achieving oxidation but also discerning whether one or both of amphimedine (**1**) or neoamphimedine (**2**) were the product(s). The reagent of choice for oxidation of a methylpyridinium to an *N*-methylpyridone is $K_3[Fe(CN)_6]$ in aq NaOH.[14,25,26] In the present study, oxidation of deoxyamphimedine **3** using alkaline ferricyanide yielded exclusively amphimedine (**1**) in 92% yield. A range of other oxidants were subsequently explored (data not shown), and it was found that the reaction of deoxyamphimedine (**3**) in DMSO/conc. HCl[21,22] (9:1) afforded amphimedine in 75% yield in addition to trace amounts of demethylated starting material **4**. Changing the relative ratio of DMSO/conc. HCl used in the reaction from 9:1 to 11:1 afforded demethyldeoxyamphimedine (**4**) in 14.5% yield and only trace amounts of amphimedine. This is the first apparent report of *N*-methylpyridone formation using such a mild oxidant system. Neither of these successful oxidants ($K_3[Fe(CN)_6]$ or DMSO/conc. HCl) afforded detectable quantities of the isomeric neoamphimedine (**2**) natural product.

Among the pyridoacridine alkaloids, deoxyamphimedine (**3**) and ascididemin are unique in their ability to induce damage in DNA via the generation of reactive oxygen species,[11,27] whereas amphimedine appears to be unique in inducing a specific but mechanistically undefined developmental phenotype in zebrafish.[8] To facilitate future structure−activity relationship studies, we investigated whether our new methodology could be used to synthesize new non-natural ethyl and benzyl analogues of both deoxyamphimedine and amphimedine (Scheme 2).

Alkylation of *N*-(3,4-dimethoxyphenethyl)acetamide (**12**)[20] proceeded smoothly to give **13**−**15** (96−99%), which were then de-*O*-methylated (BBr_3, CH_2Cl_2) to give catechols **16**−**18** (61−99%). Subsequent oxidative coupling with kynuramine (**7**) afforded the alkylated styelsamine B analogues **19**−**21** (10−12%), which upon hydrolysis in aq HCl, gave the corresponding *N*-alkyl styelsamine D analogues **22**−**24** (51−71%). Ring closure of the anticipated natural product *N*-methylstyelsamine D (**22**)[3] using paraformaldehyde in acetic acid afforded deoxyamphimedine (**3**) in 91% yield, and the reaction of ethyl (**23**) and benzyl (**24**) analogues of styelsamine D gave the corresponding deoxyamphimedine analogues **25** and **26** in good yields (83 and 91%, respectively).[28] Finally, oxidation of the latter two products using $K_3[Fe(CN)_6]$/NaOH

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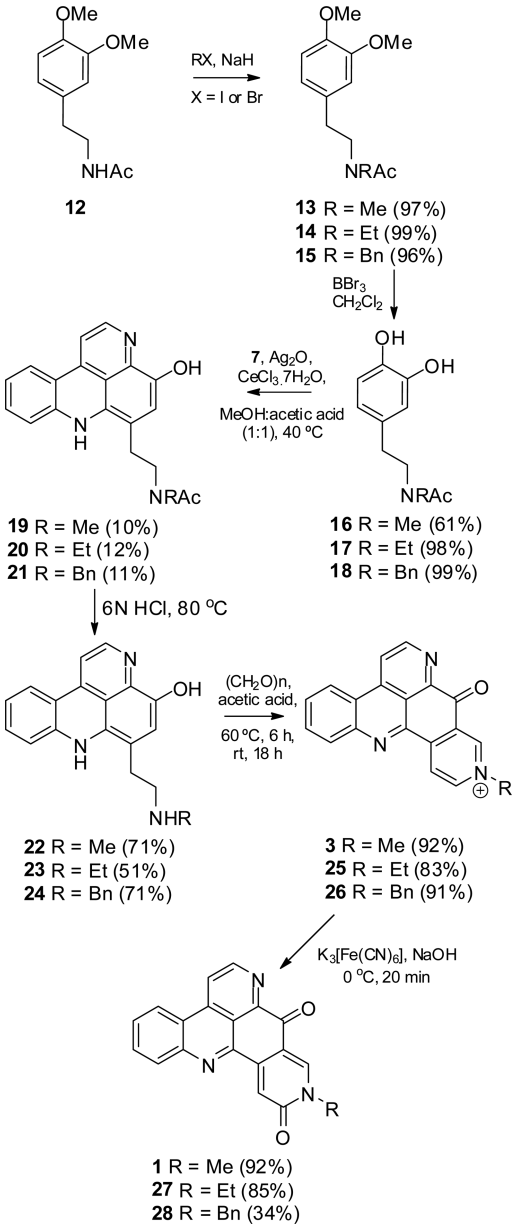
Scheme 2. Synthesis of Deoxyamphimedine Analogues 25 and 26 and Amphimedine Analogues 27 and 28



afforded the non-natural amphimedine analogues **27** (85% yield) and **28** (34% yield).

The observed conversion of styelsamine D (**5**) to both demethyldeoxyamphimedine and deoxyamphimedine suggests a mechanism whereby the first mole of formaldehyde achieves a Pictet–Spengler-type ring closure[29] to form **29** (Scheme 3). Pentacycle **29** can then either undergo in situ oxidation to demethyldeoxyamphimedine (**4**) or alternatively react with a second equivalent of formaldehyde to give **30** with subsequent tautomerization and oxidation affording deoxyamphimedine (**3**). Observation of elevated yields of **3**, at the expense of **4**, upon reaction of styelsamine D with increasing equivalents of paraformaldehyde provides support for this mechanism.

In summary, we have described a versatile bioinspired approach to the synthesis of the marine natural products demethyldeoxyamphimedine (**4**), deoxyamphimedine (**3**), and amphimedine (**1**) and used the methodology to prepare novel analogues. It is anticipated that this protocol will be useful for the synthesis of other structurally related biologically active pyridoacridine natural products.

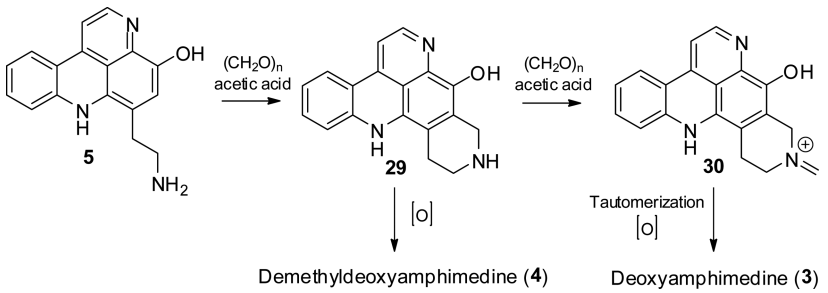
EXPERIMENTAL SECTION

General Procedures. NMR spectra were recorded at either 500 or 400 MHz for ^{1}H nuclei and 125 or 100 MHz for ^{13}C nuclei. Residual solvent signals or TMS (when present) were used as reference (CD_3OD: δ_H 3.31, δ_C 49.0; $CDCl_3$: δ_H TMS 0, δ_C 77.16; TFA-*d*/$CDCl_3$: δ_H TMS 0, δ_C 77.16; DMSO-d_6: δ_H 2.50, δ_C 39.52). Assignments were based on 2D NMR data using standard COSY, multiplicity edited HSQC, HMBC, and where appropriate NOESY pulse sequences. ESI-MS (including high resolution) data were acquired on a micrOTOF Q II mass spectrometer. Analytical reversed-phase HPLC was run using a C_8 column (3 μm, 7 × 33 mm) and eluted with a linear gradient of H_2O (0.05% TFA) to MeCN over 13.5 min at 2 mL/min. Reversed-phase flash column chromatography was carried out on C_2 (40–63 μm) or LH-20 solid support. Silica gel column chromatography was carried out on silica media with either 40–63 or 15–40 μm particle sizes. All solvents used were distilled at analytical grade or better. Chemical reagents used were purchased from standard chemical suppliers.

*Typtamine-Methyl Carbamate (**9**).* A solution of tryptamine hydrochloride (15 g, 0.090 mol), EtOAc (150 mL), and NaOH (1 N, 95 mL) was degassed and stirred followed by dropwise addition of methyl chloroformate (11.5 g, 9.40 mL, 0.12 mol) under N_2 atmosphere. The mixture was stirred for 45 min at rt and then washed with water (2 × 50 mL) and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude reaction product was then dissolved in EtOAc (10 mL) and added to *n*-hexane (100 mL) to yield **9** as a brown solid (20.4 g, quant.) after filtration. ^{1}H and ^{13}C NMR data matched literature values.[19]

*Oxindole (**10**).* A solution of tryptamine methyl carbamate (**9**, 2.33 g, 10.7 mmol) in glacial acetic acid (50 mL) was added slowly to a solution of DMSO (2.1 mL) and concd HCl (10.7 mL) and stirred for 1 h and 15 min. The reaction was then poured into saturated aqueous Na_2CO_3 (180 mL) and extracted with EtOAc (3 × 80 mL). The

Scheme 3. Proposed Mechanism for the Conversion of Styelsamine D (5) to Demethyldeoxyamphimedine (4) and Deoxyamphimedine (3)



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combined organic layers were washed with brine (180 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. Purification by silica gel column chromatography (*n*-hexane/EtOAc) gave oxindole **10** as a dark yellow oil (2.1 g, 83%). R_f (100% CH_2Cl_2) 0.15; (+)-HRESIMS *m*/*z* 235.1077 $[M + H]^+$ (calcd for $C_{12}H_{15}N_2O_3$, 235.1077). ^1H and ^{13}C NMR data matched literature values.[21]

*Kynuramine-Methyl Carbamate (**11**).* Oxygen was bubbled into a stirred solution of the oxindole **10** (0.2 g, 0.85 mmol) in 1 N NaOH (10 mL). The resulting mixture was stirred for a further 3 h and 45 min at rt after which 10% HCl was added to adjust the pH to 7. The mixture was then extracted with EtOAc (3 × 20 mL); the combined organic extracts were dried over $MgSO_4$, and the solvent was removed under reduced pressure to yield **11** as a yellow solid (0.19 g, quant.). ^1H and ^{13}C NMR data matched literature values.[19]

*Kynuramine Dihydrobromide (**7**).* A solution of **11** (0.19 g, 0.65 mmol) in HBr in acetic acid (7 mL) was stirred and heated at 80 °C under N_2 atmosphere overnight. After the solution was cooled to rt, THF was added (15 mL), and the mixture was stirred at 0 °C for 30 min. The brown solid was then triturated (THF) to yield **7** as an off-white solid (0.19 g, 81.1%). ^1H and ^{13}C NMR data matched literature values.[19]

*N-(3,4-Dimethoxyphenethyl)acetamide (**12**).* A solution of 2-(3,4-dimethyoxyphenyl)ethyl amine (0.2 g, 0.19 mL, 1.10 mmol) in Et_3N (0.24 mL, 0.20 g, 1.99 mmol) and acetic anhydride (0.38 mL, 0.41 g, 3.97 mmol) was stirred at rt under N_2 atmosphere for 45 min. Dichloromethane (5 mL) was then added, and the mixture was washed with H_2O (10 mL). The organic phase was then dried ($MgSO_4$), and the solvent was removed under reduced pressure to afford **12** as a dark yellow oil (0.24 g, 97.6%). ^1H and ^{13}C NMR data matched literature values.[20]

*N-Boc-Dopamine (**6**).* Boc_2O (1.09 g, 5.00 mmol) was added to a solution of dopamine hydrochloride (0.86 g, 4.53 mmol) in a mixture of THF (9.4 mL) and sat. aq $NaHCO_3$ (5.6 mL). The reaction mixture was stirred at rt for 2 h after which the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to yield **6** as a white solid (1.15 g, quant.). ^1H and ^{13}C NMR data matched literature values.[23]

*Styelsamine D (**5**).* Kynuramine dihydrobromide (**7**) (0.10 g, 0.41 mmol) was added to a stirred solution of *tert*-butyl 2-(3,4-dihydroxyphenyl)ethylcarbamate[4] (**6**, 0.13 g, 0.39 mmol) in MeOH/acetic acid (2:1, 6 mL) under a N_2 atmosphere followed by the addition of $CeCl_3{\cdot}7H_2O$ (0.022 g, 0.054 mmol) and Ag_2O (0.20 g, 0.99 mmol). The mixture was stirred at 40 °C for 1 h and 30 min after which the solution was filtered through Celite and added dropwise to a solution of 6 N HCl (15 mL) at 90 °C. The solution was stirred for a further 2 h, and then the solvent was removed in vacuo. The product mixture was purified using C_2 reversed-phase chromatography (MeOH/H_2O/TFA) to give styelsamine D ditrifluoroacetate as a purple oil (0.068 g, 34%). ^1H, ^{13}C, and HRMS data agreed with literature values.[20]

*Deoxyamphimedine (**3**) and Demethyldeoxyamphimedine (**4**).* Paraformaldehyde (4.79 mg, 0.16 mmol) was added to a solution of styelsamine D ditrifluoroacetate (16.1 mg, 0.032 mmol) in acetic acid (2 mL) and stirred for 5 h at 60 °C and then left stirring overnight at rt. The acetic acid was then removed in vacuo, and the product mixture was purified using Sephadex LH-20 column chromatography (MeOH/TFA) to give, in order of elution, deoxyamphimedine (**3**, 13.1 mg, 48%) as a brown/yellow oil and demethyldeoxyamphimedine (**4**, 9.1 mg, 52%) as a brown oil. Repeating the reaction in the presence of increasing equivalents of paraformaldehyde gave **3** (58%) and **4** (34%) with 9.1 equiv of paraformaldehyde and **3** (66%), **4** (34%) with 15 equiv of paraformaldehyde.

*Deoxyamphimedine (**3**).* ^1H NMR (CD_3OD, 400 MHz) δ 9.88 (1H, s, H-9), 9.42 (1H, d, *J* = 5.5 Hz, H-12), 9.33−9.25 (2H, m, H-6, 11), 9.08 (1H, br s, H-5), 8.93 (1H, d, *J* = 7.56 Hz, H-4), 8.47 (1H, d, *J* = 7.6 Hz, H-1), 8.11 (1H, t, *J* = 7.6 Hz, H-2), 8.04 (1H, t, *J* = 7.7 Hz, H-3), 4.66 (3H, s, H_3-14); ^{13}C NMR (CD_3OD, 100 MHz) δ 179.2 (C-8), 151.4 (C-6), 149.4 (C-11), 149.4 (C-12a), 147.9 (C-9), 147.2 (C-7a), 146.6 (C-13a), 145.4 (C-12b), 139.8 (C-4b), 134.0 (C-2), 133.3 (C-1), 132.9 (C-3), 131.5 (C-8a), 125.2 (C-4), 124.5 (C-12), 124.2 (C-4a), 122.9 (C-5), 120.9 (C-12c), 49.0 (C-14); (+)-HRESIMS *m*/*z* 298.0966 [M] (calcd for $C_{19}H_{12}N_3O$, 298.0975).

*Demethyldeoxyamphimedine (**4**).* ^1H NMR (TFA-*d*/$CDCl_3$ (2:1), 400 MHz) δ 9.87 (1H, s, H-9), 9.72 (1H, br s, H-12), 9.63 (1H, br s, H-5), 9.49 (1H, br s, H-6), 9.40 (1H, br s, H-11), 9.05 (1H, d, *J* = 7.7 Hz, H-4), 8.80 (1H, d, *J* = 7.7 Hz, H-1), 8.47 (1H, t, *J* = 7.7 Hz, H-3), 8.33 (1H, t, *J* = 7.7 Hz, H-2); ^{13}C NMR (TFA-*d*/$CDCl_3$ (2:1), 100 MHz) δ 173.7 (C-8), 150.6 (C-12a), 148.0 (C-13a), 146.5 (C-4b), 146.4 (C-11), 144.1 (C-9), 143.4 (C-12b), 141.5 (C-6), 138.2 (C-2), 138.1 (C-7a), 135.4 (C-3), 134.9 (C-1), 128.7 (C-8a), 126.8 (C-5), 126.2 (C-4), 125.0 (C-12), 121.3 (C-4a), signal due to C-12c was obscured by TFA-*d* peaks; ^1H NMR ($CDCl_3$, 500 MHz) δ 9.72 (1H, s, H-9), 9.38 (1H, d, *J* = 5.4 Hz, H-6), 9.12 (1H, d, *J* = 5.5 Hz, H-12), 8.84 (1H, d, *J* = 5.5 Hz, H-11), 8.71 (1H, d, *J* = 5.4 Hz, H-5), 8.68 (1H, dd, *J* = 8.4, 1.3 Hz, H-4), 8.43 (1H, dd, *J* = 8.4, 1.3 Hz, H-1), 8.01 (1H, dt, *J* = 8.4, 1.3 Hz, H-2), 7.90 (1H, dt, *J* = 8.4, 1.3 Hz, H-3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 154.8, 150.7, 150.5, 147.3, 147.0, 145.7, 142.2, 138.3, 132.2, 132.0, 130.0, 126.6, 123.0, 122.4, 120.0, 119.2, 118.5 (one resonance not observed); (+)-HRESIMS *m*/*z* 306.0647 $[M + Na]^+$ (calcd for $C_{18}H_9N_3NaO$, 306.0638).

*Amphimedine (**1**).* A solution of NaOH (1.02 mg, 0.025 mmol) in water (200 μL) and a solution of potassium ferricyanide (4.18 mg, 0.013 mmol) in water (200 μL) were added simultaneously to a stirred solution of deoxyamphimedine (**3**, 2.61 mg, 6.4 μmol) in water (500 μL) at 0 °C over a period of 10 min. After the dropwise addition, the reaction mixture was stirred for 25 min after which it was diluted with water (1 mL) and extracted with CH_2Cl_2 (5 × 3 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The product mixture was purified using silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) to give amphimedine (**1**) as a bright yellow powder (1.82 mg, 92%). Alternatively, deoxyamphimedine (1.41 mg, 3.4 μmol) was dissolved in DMSO (90 μL), and concd HCl (10 μL) was added. The solution was stirred at rt for 2 h. The solution was then neutralized by the addition of sat. aq $NaHCO_3$ and extracted with CH_2Cl_2 (5 × 3 mL), and the crude product was purified by LH-20 column chromatography (MeOH) to give amphimedine (**1**) (1.07 mg, 75%). R_f (CH_2Cl_2/MeOH, 9:1) 0.21; ^1H NMR (TFA-*d*/$CDCl_3$ (2:1), 400 MHz) δ 9.39 (1H, s, H-9), 9.30 (1H, d, *J* = 5.5 Hz, H-12), 9.10 (2H, m, H-6, 11), 8.88 (1H, br s, H-5), 8.64 (1H, d, *J* = 7.56 Hz, H-4), 8.35 (1H, d, *J* = 7.6 Hz, H-1), 8.35 (1H, t, *J* = 7.6 Hz, H-2), 8.18 (1H, t, *J* = 7.7 Hz, H-3), 3.98 (3H, s, H_3-14); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.30 (1H, d, *J* = 5.5 Hz, H-6), 8.80 (1H, s, H-9), 8.77−8.63 (2H, m, H-4, 5), 8.37 (1H, dd, *J* = 8.1, 1.1 Hz, H-1), 8.06 (1H, s, H-12), 7.99 (1H, dt, *J* = 8.1, 1.1 Hz, H-2), 7.87 (1H, dt, *J* = 8.1, 1.1 Hz, H-3), 3.80 (3H, s, H_3-14); ^{13}C NMR (TFA-*d*/$CDCl_3$ (2:1), 100 MHz) δ 172.8 (C-8), 165.6 (C-11), 147.7 (C-13a), 147.3 (C-9), 145.8 (C-4b), 145.3 (C-12b), 143.5 (C-12a), 139.5 (C-6, C-7), 137.4 (C-2), 133.5 (C-1), 133.0 (C-3), 125.3 (C-4), 124.9 (C-5), 120.4 (C-4a), 118.7 (C-12c), 114.9 (C-12), 113.5 (C-12c), 40.0 (C-14); (+)-HRESIMS *m*/*z* 314.0931 $[M + H]^+$ (calcd for $C_{19}H_{12}N_3O_2$, 314.0924).

*General Procedure A: Alkylation of N-(3,4-Dimethoxyphenethyl)-acetamide (**12**).* The relevant alkyl halide (2−4 equiv) is added dropwise to a solution of *N*-(3,4-dimethoxyphenethyl)acetamide (1 equiv) and sodium hydride (2 equiv) in THF/DMF (10:1, 5 mL). The reaction was allowed to stir at rt under N_2 atmosphere for 10 min after which the mixture was heated at reflux overnight. The solvent was then removed in vacuo, and the product mixture was dissolved in EtOAc and washed with sat. aq $Na_2S_2O_3$ and then dried ($MgSO_4$). The solvent was then removed in vacuo to yield the alkylated product.

General Procedure B: De-O-methylation of N-Alkyl-dimethoxyphenethylacetamides. To a stirred solution of the alkylated acetamide (1 equiv) in CH_2Cl_2 was added a solution of BBr_3 (9 equiv) in CH_2Cl_2 dropwise at 0 °C under a N_2 atmosphere. The mixture was stirred for 5−6 h after which MeOH was added followed by washing with brine and water. The aqueous layer was extracted with EtOAc, and the organic extract was dried ($MgSO_4$) followed by removal of the solvent in vacuo to yield the demethylated product.

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J. Org. Chem. XXXX, XXX, XXX−XXX

General Procedure C: Preparation of N-Alkyl Analogues of Styelsamine B. Kynuramine dihydrobromide (**7**, 1.05 equiv) was added to a stirred solution of the relevant *N*-dihydroxyphenylethyl-*N*-alkylacetamide (1 equiv) in MeOH-HOAc (2:1, 5 mL) under N_2 atmosphere followed by the addition of $CeCl_3{\cdot}7H_2O$ (0.15 equiv) and Ag_2O (2.2 equiv). The mixture was stirred at 40 °C for 2 h after which the solution was filtered through Celite and added dropwise to a solution of 6 N HCl (20 mL) at 90 °C. The solution was stirred for a further 30 min and then dried in vacuo. The product mixture was purified using C_2 reversed-phase flash (MeOH/H_2O/0.05% TFA) and Sephadex LH-20 column chromatography (MeOH/0.05% TFA) to yield styelsamine B analogues as the TFA salts.

General Procedure D: Preparation of N-Alkyl Analogues of Styelsamine D. A solution of *N*-alkyl styelsamine B and 6 N HCl was stirred for 30−50 h at 80 °C. Concentration of the reaction mixture under reduced pressure was followed by purification using C_{18} reversed-phase flash column chromatography (MeOH/H_2O/0.05% TFA) to yield the styelsamine D analogues as di-TFA salts.

General Procedure E: Synthesis of N-alkyl Analogues of Demethyldeoxyamphimedine. Paraformaldehyde (5 equiv) was added to a solution of *N*-alkyl-styelsamine D (1 equiv) in acetic acid and stirred for 5−6 h at 60 °C and then left stirring overnight at rt. The acetic acid was then removed in vacuo, and the product mixture was purified using Sephadex LH-20 column chromatography (MeOH + 0.05% TFA) to yield *N*-alkyl analogues of demethyldeoxyamphimedine.

General Procedure F: Synthesis of N-Alkyl Analogues of Demethylamphimedine. A solution of NaOH (4 equiv) in water and a solution of potassium ferricyanide (2 equiv) in water were added dropwise simultaneously to a stirred solution of *N*-alkyl-demethyldeoxyamphimedine in water at 0 °C over a period of 10 min. After the addition, the reaction mixture was stirred for 20 min after which it was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and the solvent was removed in vacuo. The product mixture was purified using silica gel column chromatography (CH_2Cl_2/MeOH, 9:1) to yield *N*-alkyl analogues of demethylamphimedine.

*N-(3,4-Dimethoxyphenethyl)-N-methylacetamide (**13**).* Using general procedure A, *N*-(3,4-dimethoxyphenethyl)acetamide (**12**, 0.3 g, 1.34 mmol), methyl iodide (0.67 g, 0.29 mL, 4.7 mmol), and sodium hydride (64.5 mg, 2.69 mmol) afforded **13** as a yellow oil (0.31 g, 97%) in a 1:1 mixture of rotamers. R_f (100% CH_2Cl_2) 0.17; IR (ATR) ν_{max} 2933, 1514, 1626, 1261, 1236 cm^{-1}. Rotamer 1: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.81 (1H, d, J = 8.2 Hz, H-8), 6.76 (1H, obscured, H-5), 6.69 (1H, dd, J = 1.9, 8.2 Hz, H-9), 3.86 (3H, s, H_3-13), 3.85 (3H, s, H_3-14), 3.49 (2H, t, J = 7.0 Hz, H_2-2), 2.93 (3H, s, H_3-10), 2.81−2.78 (2H, m, H_2-3), 1.84 (3H, s, H_3-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5 (C-11), 148.9 (C-6), 147.7 (C-7), 130.6 (C-4), 120.5 (C-9), 111.9 (C-5), 111.4 (C-8), 55.7 (C-13, 14), 52.4 (C-2), 34.0 (C-3), 33.1 (C-10), 20.7 (C-12). Rotamer 2: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.80 (1H, d, J = 7.9 Hz, H-8), 6.75 (1H, dd, J = 7.9, 2.0 Hz, H-9), 6.66 (1H, d, J = 2.0 Hz, H-9), 3.86 (3H, s, H_3-13), 3.84 (3H, s, H_3-14), 3.56 (2H, t, J = 7.8 Hz, H_2-2), 2.89 (2H, s, H_3-10), 2.78−2.76 (2H, m, H_2-3), 2.06 (3H, s, H_3-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (C-11), 148.7 (C-6), 147.3 (C-7), 131.5 (C-4), 120.6 (C-9), 111.8 (C-5), 111.2 (C-8), 55.7 (C-13, 14), 49.5 (C-2), 36.6 (C-10), 33.1 (C-3), 21.7 (C-12); (+)-HRESIMS m/z 260.1262 $[M + Na]^+$ (calcd for $C_{13}H_{19}NNaO_3$, 260.1257). ^1H and ^{13}C signals could not be assigned to specific rotamers.

*N-(3,4-Dihydroxyphenethyl)-N-methylacetamide (**16**).* Using general procedure B, *N*-(3,4-dimethoxyphenethyl)-*N*-methylacetamide (**13**, 50.0 mg. 0.21 mmol) and BBr_3 (0.48 g, 1.90 mmol. 0.18 mL) afforded **16** as a yellow oil (27.0 mg, 61%) in a 1:1 mixture of rotamers. IR (ATR) ν_{max} 3187, 1583, 1440, 1408, 1233, 1113 cm^{-1}. Rotamer 1: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.70 (1H, d, J = 8.1 Hz, H-8), 6.65−6.64 (1H, m, H-5), 6.54−6.52 (1H, m, H-9), 3.50−3.46 (2H, m, H_2-2), 2.91 (3H, s, H_3-10), 2.66 (2H, t, J = 7.1 Hz, H_2-3), 2.04 (3H, s, H_3-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.2 (C-11), 146.4 (C-6), 145.1 (C-7), 131.9 (C-4), 121.2 (C-9), 117.1 (C-5), 116.5 (C-8), 51.1 (C-2), 37.3 (C-10), 33.84 (C-3), 21.7 (C-12). Rotamer 2: ^1H NMR ($CDCl_3$, 400 MHz) δ 6.68 (1H, d, J = 8.0 Hz, H-8), 6.64−6.63 (1H, m, H-5), 6.52−6.50 (1H, m, H-9), 3.53−3.50 (2H, m, H_2-2), 2.89 (3H, s, H_3-10), 2.71 (2H, t, J = 6.7 Hz, H_2-3), 1.76 (3H, s, H_3-12); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5 (C-11), 146.2 (C-6), 144.8 (C-7), 131.3 (C-4), 121.1 (C-9), 116.9 (C-5), 116.4 (C-8), 53.8 (C-2), 34.6 (C-3), 33.79 (C-10), 20.8 (C-12); (+)-HRESIMS m/z 232.0948 $[M + Na]^+$ (calcd for $C_{11}H_{15}NNaO_3$, 232.0944). ^1H and ^{13}C signals could not be assigned to specific rotamers.

*N-(3,4-Dimethoxyphenethyl)-N-ethylacetamide (**14**).* Using general procedure A, *N*-(3,4-dimethoxyphenethyl)acetamide (**12**, 0.46 g, 1.80 mmol), ethyl bromide (0.39 g, 0.27 mL, 3.6 mmol), and sodium hydride (0.14 g, 3.6 mmol) afforded **14** as a pale yellow oil (0.52 g, quantitative yield) in a mixture of rotamers. R_f (30% EtOAc/Hex) 0.12; IR (ATR) ν_{max} 2935, 1623, 1515, 1420, 1261, 1236 cm^{-1}. Rotamer 1: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.82 (1H, d, J = 7.8 Hz, H-8), 6.70 (1H, dd, J = 7.8, 2.0 Hz, H-9), 6.66 (1H, d, J = 2.0 Hz, H-5), 3.88 (3H, s, H_3-14), 3.86 (3H, s, H_3-15), 3.45 (2H, t, J = 7.3 Hz, H_2-2), 3.40 (2H, q, J = 7.3 Hz, H_2-10), 2.79−2.76 (2H, m, H_2-3), 1.91 (3H, s, H_3-13), 1.16−1.11 (3H, m, H_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.2 (C-12), 149.2 (C-6), 148.0 (C-7), 130.9 (C-4), 120.9 (C-9), 112.2 (C-5), 111.4 (C-8), 56.0 (C-13, 14), 50.2 (C-2), 40.5 (C-10), 35.1 (C-3), 21.6 (C-13), 13.0 (C-11). Rotamer 2: ^1H NMR ($CDCl_3$, 500 MHz) δ 6.80−6.78 (1H, m, H-5), 6.77−6.74 (2H, m, H-8, 9), 3.88 (3H, s, H_3-14), 3.86 (3H, s, H_3-15), 3.50 (2H, t, J = 7.4 Hz, H_2-2), 3.20 (2H, q, J = 7.1 Hz, H_2-10), 2.82−2.79 (2H, m, H_2-3), 2.10 (3H, s, H_3-13), 1.16−1.11 (3H, m, H_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.1 (C-12), 149.0 (C-6), 147.6 (C-7), 132.1 (C-4), 120.8 (C-9), 112.1 (C-5), 111.6 (C-8), 56.0 (C-13, 14), 47.8 (C-2), 44.1 (C-10), 33.9 (C-3), 21.5 (C-13), 14.1 (C-11); (+)-HRESIMS m/z 274.1414 $[M + Na]^+$ (calcd for $C_{14}H_{21}NNaO_3$, 274.1414). ^1H and ^{13}C signals could not be assigned to specific rotamers.

*N-(3,4-Dihydroxyphenethyl)-N-ethylacetamide (**17**).* Using general procedure B, *N*-(3,4-dimethoxyphenethyl)-*N*-ethylacetamide (**14**, 0.38 g. 1.5 mmol) and BBr_3 (3.0 g, 12.1 mmol. 1.10 mL) afforded **17** as a pale brown gum (0.33 g, 98% yield) in a mixture of rotamers. IR (ATR) ν_{max} 3179, 2977, 1588, 1441, 1280 cm^{-1}. Rotamer 1: ^1H NMR (CD_3OD, 500 MHz) δ 6.71−6.67 (1H, m, H-8), 6.66−6.62 (1H, m, H-5), 6.54−6.49 (1H, m, H-9), 3.48 (2H, t, J = 7.1, H_2-2), 3.36 (2H, q, J = 7.2 Hz, H_2-10), 2.72 (2H, obscured, H_2-3), 2.08 (3H, s, H_3-13), 1.11−1.08 (3H, m, H_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.1 (C-12), 146.5 (C-6)[f], 145.1 (C-7), 131.3 (C-4), 121.3 (C-9), 117.1 (C-5), 116.5 (C-8), 51.4 (C-2), 41.7 (C-10), 35.2 (C-3), 21.2 (C-13), 12.9 (C-11). Rotamer 2: ^1H NMR (CD_3OD, 500 MHz) δ 6.71−6.67 (1H, m, H-8), 6.66−6.62 (1H, m, H-5), 6.54−6.49 (1H, m, H-9), 3.44 (2H, t, J = 6.8, H_2-2), 3.25 (2H, q, J = 7.2 Hz, H_2-10), 2.67 (2H, obscured, H_2-3), 1.81 (3H, s, H_3-13), 1.14−1.11 (3H, m, H_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 172.8 (C-12), 146.3 (C-6), 144.8 (C-7), 132.1 (C-4), 121.1 (C-9), 116.9 (C-5), 116.4 (C-8), 49.1 (C-2), 45.2 (C-10), 34.3 (C-3), 21.2 (C-13), 14.0 (C-11); (+)-HRESIMS m/z 224.1283 $[M + H]^+$ (calcd for $C_{12}H_{18}NO_3$, 224.1281). ^1H and ^{13}C signals could not be assigned to specific rotamers.

*N-(3,4-Dimethoxyphenethyl)-N-benzylacetamide (**15**).* Using general procedure A, *N*-(3,4-dimethoxyphenethyl)acetamide (**12**, 0.54 g, 2.42 mmol), benzyl bromide (0.83 g, 0.58 mL, 4.8 mmol), and sodium hydride (0.19 g, 4.8 mmol) afforded **15** as a pale yellow oil (0.73 g, 96%) in a mixture of rotamers. R_f (50% EtOAc/Hex) 0.16; IR (ATR) ν_{max} 2934, 1634, 1515, 1419, 1261, 1027 cm^{-1}. Rotamer 1: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.34 (2H, m, H-17, 19), 7.31−7.27 (2H, m, H-16, 20), 7.26−7.23 (1H, m, H-18), 6.81−6.76 (1H, m, H-8), 6.65 (1H, dd, J = 8.5, 1.9 Hz, H-9), 6.58 (1H, d, J = 1.9 Hz, H-5), 4.60 (2H, s, H_2-14), 3.85 (6H, s, H_3-12, 13), 3.42 (2H, t, J = 7.2 Hz, H_2-2), 2.74 (2H, t, J = 7.2 Hz, H_2-3), 2.02 (3H, s, CH_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8 (C-10), 149.0 (C-6), 148.0 (C-7), 137.8 (C-15), 130.9 (C-4), 129.0 (C-17, 18), 128.3 (C-16, 20), 127.7 (C-18), 120.8 (C-9), 112.1 (C-5), 111.6 (C-8), 56.0 (C-12, 13), 49.7 (C-2), 48.3 (C-14), 33.7 (C-3), 21.4 (C-11). Rotamer 2: ^1H NMR ($CDCl_3$, 500 MHz) δ 7.37−7.34 (2H, m, H-17, 19), 7.26−7.23 (1H, m, H-18), 7.13 (2H, d, J = 7.6 Hz, H-16, 20), 6.81−6.76 (1H, m, H-8), 6.72−6.69 (2H, m, H-5, 9), 6.58 (1H, d, J = 1.9 Hz, H-5), 4.36 (2H, s, H_2-14), 3.85 (6H, s, OCH_3-12, 13), 3.56 (2H, t, J = 7.3 Hz, H_2-2),

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J. Org. Chem. XXXX, XXX, XXX−XXX

2.80 (2H, t, J = 7.3 Hz, H_2-3), 2.12 (3H, s, CH_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.0 (C-10), 149.2 (C-6), 147.6 (C-7), 136.9 (C-15), 131.9 (C-4), 129.0 (C-17, 18), 127.5 (C-18), 126.4 (C-16, 20), 120.8 (C-9), 112.0 (C-5), 111.4 (C-8), 56.0 (C-12, 13), 52.9 (C-14), 48.4 (C-2), 34.6 (C-3), 22.0 (C-11); (+)-HRESIMS m/z 336.1563 $[M + Na]^+$ (calcd for $C_{19}H_{23}NNaO_3$, 336.1570). ^{1}H and ^{13}C signals could not be assigned to specific rotamers.

*N-(3,4-Dihydroxyphenethyl)-N-benzylacetamide (**18**).* Using general procedure B, *N*-(3,4-dimethoxyphenethyl)-*N*-benzylacetamide (**15**, 0.41 g. 1.31 mmol) and BBr_3 (2.62 g, 10.0 mmol. 0.97 mL) afforded **18** as a white gum (0.36 g, 97%) in a mixture of rotamers. IR (ATR) ν_{max} 3207, 1596, 1440, 1419, 1363, 1194 cm^{-1}. Rotamer 1: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.41−7.34 (2H, m, H-15, 17), 7.29−7.25 (1H, m, H-16), 7.16 (2H, d, J = 8.0 Hz H-14, 18), 6.72−6.66 (1H, m, H-8), 6.62−6.59 (1H, m, H-5), 6.51−6.45 (1H, m, H-9), 4.43 (2H, s, H_2-12), 3.46 (2H, t, J = 7.5 Hz, H_2-2), 2.66 (2H, t, J = 7.5 Hz, H_2-3), 1.94 (3H, s, CH_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6 (C-10), 146.5 (C-6), 145.1 (C-7), 138.2 (C-13), 132.0 (C-4), 129.9 (C-15, 17), 128.6 (C-16), 127.7 (C-14, 18), 121.3 (C-9), 117.0 (C-5), 116.5 (C-8), 53.8 (C-12), 49.8 (C-2), 34.1 (C-3), 21.2 (C-11). Rotamer 2: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.30 (2H, m, H-15, 17), 7.29−7.25 (1H, m, H-16), 7.23−7.22 (2H, m, H-14, 18), 6.72−6.66 (1H, m, H-8), 6.62−6.59 (1H, m, H-5), 6.51−6.45 (1H, m, H-9), 4.57 (2H, s, H_2-12), 3.43 (2H, t, J = 7.2 Hz, H_2-2), 2.68 (2H, t, J = 7.2 Hz, H_2-3), 2.11 (3H, s, CH_3-11); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 173.6 (C-10), 146.3 (C-6), 144.8 (C-7), 138.8 (C-13), 131.3 (C-4), 129.6 (C-15, 17), 129.0 (C-14, 18), 128.4 (C-16), 121.1 (C-9), 116.9 (C-5)[i], 116.4 (C-8), 51.0 (C-2), 49.0 (C-12), 34.8 (C-3), 21.8 (C-11); (+)-HRESIMS m/z 308.1253 $[M + Na]^+$ (calcd for $C_{17}H_{19}NNaO_3$, 308.1257). ^{1}H and ^{13}C signals could not be assigned to specific rotamers.

*N-Methyl-styelsamine B (**19**).* Using general procedure C, kynuramine dihydrobromide (**7**, 0.11 g, 0.35 mmol), *N*-(3,4-dihydroxyphenethyl)-*N*-methylacetamide (**16**, 0.075 g, 0.33 mmol), $CeCl_3\cdot 7H_2O$ (0.019 g, 0.005 mmol), and Ag_2O (0.17 g, 0.73 mmol) afforded **19** as a purple oil (TFA salt, 15.1 mg, 10% yield). R_t = 8.27 min; IR (ATR) ν_{max} 3098, 1677, 1619, 1582, 1197, 1132 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.99−7.94 (1H, m, H-2), 7.90−7.85 (1H, m, H-4), 7.60−7.54 (1H, m, H-6), 7.53−7.47 (1H, m, H-7), 7.27−7.24 (1H, s, H-10), 7.23−7.11 (1H, m, H-3), 7.17−7.11 (1H, m, H-5), 3.40−3.34 (2H, m, H_2-14), 3.19 (3H, s, H_3-17), 2.91−2.82 (2H, m, H_2-13), 2.20 (3H, m, H_3-16); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.5 (C-15), 151.3 (C-3a), 143.5 (C-2), 142.6 (C-7a), 138.1 (C-11), 136.3 (C-6), 130.3 (C-8a), 127.6 (C-11a), 126.2 (C-4), 124.0 (C-5), 122.7 (C-10), 121.9 (C-11b), 119.1 (C-7), 116.9 (C-9), 11.5 (C-3b), 105.7 (C-3), 48.4 (C-13), 37.9 (C-16), 30.3 (C-12), 21.6 (C-15); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 13.47 (1H, br s, NH-1), 11.54 (1H, br s, NH-8), 10.83 (1H, br s, OH-12), 8.24 (1H, d, J = 6.6 Hz, H-2), 8.20 (1H, d, J = 8.6 Hz, H-4), 7.70 (1H, t, J = 8.6 Hz, H-6), 7.63 (1H, d, J = 8.6 Hz, H-7), 7.54 (1H, d, J = 6.6 Hz, H-3), 7.42 (1H, s, H-10), 7.23 (1H, t, J = 8.6 Hz, H-5), 3.47−3.41 (2H, m, H_2-14), 3.10 (3H, s, H_3-17), 3.05−2.98 (2H, m, H_2-13), 2.10 (3H, s, H_3-16); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 171.7 (C-15), 149.3 (C-3a), 143.4 (C-2), 141.0 (C-7a), 136.6 (C-11), 135.1 (C-6), 128.5 (C-8a), 125.9 (C-11a), 125.6 (C-4), 122.5 (C-5), 121.4 (C-10), 120.3 (C-11b), 117.7 (C-7), 115.7 (C-9), 113.9 (C-3b), 105.0 (C-3), 46.5 (C-14), 37.0 (C-17), 28.6 (C-13), 21.5 (C-16); (+)-HRESIMS m/z 334.1562 $[M + H]^+$ (calcd for $C_{20}H_{20}N_3O_2$, 334.1550).

*N-Ethyl-styelsamine B (**20**).* Using general procedure C, kynuramine dihydrobromide (**7**, 0.16 g, 0.50 mmol), *N*-(3,4-dihydroxyphenethyl)-*N*-ethylacetamide (**17**, 0.11 g, 0.48 mmol), $CeCl_3\cdot 7H_2O$ (0.027 g, 0.072 mmol), and Ag_2O (0.24 g, 1.10 mmol) afforded **20** as a purple oil (TFA salt, 27.2 mg, 12% yield).

R_t = 8.98 min; IR (ATR) ν_{max} 3140, 2980, 1586, 1506, 1426, 1194 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.92 (1H, d, J = 6.7 Hz, H-2), 7.82 (1H, d, J = 8.3 Hz, H-4), 7.54 (1H, dt, J = 7.4, 1.2 Hz, H-6), 7.45 (1H, d, J = 7.4 Hz, H-7), 7.21 (1H, s, H-10), 7.15−7.11 (2H, m, H-3, 5), 3.52 (2H, q, J = 7.1 Hz, H_2-16), 3.29 (2H, obscured, H_2-13), 2.79 (2H, t, J = 7.0 Hz, H_2-12), 2.23 (3H, s, H_3-15), 1.28 (3H, t, J = 7.1 Hz, H_3-17); ^{13}C NMR (CD_3OD, 125 MHz) δ 173.9 (C-14), 150.8 (C-3a), 143.3 (C-2), 142.3 (C-7a), 137.9 (C-11), 136.1 (C-6), 129.9 (C-8a), 127.2 (C-11a), 126.0 (C-4), 123.8 (C-5), 122.6 (C-10), 121.5 (C-11b), 119.0 (C-7), 116.8 (C-9), 115.2 (C-3b), 105.5 (C-3), 46.4 (C-16), 46.3 (C-13), 31.5 (C-12), 21.2 (C-15), 14.7 (C-17); (+)-HRESIMS m/z 348.1716 $[M + H]^+$ (calcd for $C_{21}H_{22}N_3O_2$, 348.1707).

*N-Benzyl-styelsamine B (**21**).* Using general procedure C, kynuramine dihydrobromide (**7**, 0.12 g, 0.37 mmol), *N*-(3,4-dihydroxyphenethyl)-*N*-benzylacetamide (**18**, 0.10 g, 0.35 mmol), $CeCl_3\cdot 7H_2O$ (0.020 g, 0.05 mmol), and Ag_2O (0.18 g, 0.77 mmol) afforded **21** as a purple oil (TFA salt, 20.5 mg, 11% yield). R_t = 9.53 min; IR (ATR) ν_{max} 3423, 2949, 1661, 1582, 1250, 1130 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 7.93 (1H, br s, H-2), 7.89−7.83 (1H, m, H-4), 7.58−7.52 (1H, m, H-6), 7.53−7.47 (1H, m, H-7), 7.42 (2H, t, J = 7.7, H-19, 21), 7.35 (1H, d, J = 7.7 Hz, H-20), 7.30 (2H, d, J = 7.7 Hz, H-18, 22) 7.19−7.12 (2H, m, H-3, 5), 7.04 (1H, s, H-10), 4.72 (2H, s, H_2-16), 3.36−3.31 (2H, m, H_2-13), 2.74−2.64 (2H, m, H_2-12), 2.30 (3H, s, H_3-15); ^{13}C NMR (CD_3OD, 125 MHz) δ 174.7 (C-14), 150.9 (C-3a), 143.3 (C-2), 142.3 (C-7a), 138.0 (C-11)[a], 137.9 (C-17)[a], 136.2 (C-6), 130.1 (C-19, 21), 129.9 (C-8a), 129.0 (C-20), 128.2 (C-18, 22), 127.3 (C-11a), 126.0 (C-4), 123.9 (C-5), 122.5 (C-10), 121.5 (C-11b), 119.0 (C-7), 116.7 (C-9), 115.3 (C-3b), 105.5 (C-3), 54.8 (C-16), 47.0 (C-13), 31.0 (C-12), 21.8 (C-15); (+)-HRESIMS m/z 410.1859 $[M + H]^+$ (calcd for $C_{26}H_{24}N_3O_2$, 410.1863).

*N-Methyl-styelsamine D (**22**).* Using general procedure D, *N*-methyl-styelsamine B (**19**, 15.1 mg, 0.03 mmol) and 6 N HCl (8 mL) afforded **22** as a purple oil (bis-TFA salt, 7.07 mg, 41% [71% yield based on recovered starting material]). R_t = 7.01 min; IR (ATR) ν_{max} 3098, 1677, 1619, 1582, 1197, 1132 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 8.19 (1H, d, J = 6.6 Hz, H-2), 8.12 (1H, d, J = 8.2 Hz, H-4), 7.90 (1H, d, J = 8.2 Hz, H-7), 7.67 (1H, t, J = 8.2 Hz, H-6), 7.53 (1H, d, J = 6.3 Hz, H-3), 7.49 (1H, s, H-10), 7.26 (1H, t, J = 8.2 Hz, H-5), 3.41−3.36 (2H, m, H_2-12), 3.27−3.31 (2H, m, H_2-13), 2.78 (3H, s, H_3-15); ^{13}C NMR (CD_3OD, 125 MHz) δ 151.5 (C-3a), 143.9 (C-2), 142.7 (C-7a), 138.6 (C-11), 136.4 (C-6), 130.3 (C-8a), 128.7 (C-11a), 126.3 (C-4), 124.2 (C-5), 122.8 (C-10), 122.2 (C-11b), 119.2 (C-7), 115.7 (C-3b), 114.4 (C-9), 106.5 (C-3), 49.0 (C-13), 33.8 (C-15), 28.7 (C-12); ^{1}H NMR (DMSO-d_6, 500 MHz) δ 10.98 (2H, br s, NH-8), 8.70 (2H, br s, NH-14), 8.32 (1H, d, J = 6.3 Hz, H-2), 8.25 (1H, d, J = 8.2 Hz, H-4), 7.81 (1H, d, J = 8.7 Hz, H-7), 7.71 (1H, t, J = 8.7 Hz, H-6), 7.62 (1H, d, J = 6.3 Hz, H-3), 7.49 (1H, s, H-10), 7.25 (1H, t, J = 8.2 Hz, H-5), 3.28 (2H, t, J = 6.9 Hz, H_2-12), 3.22−3.18 (2H, m, H_2-13), 2.62 (3H, t, J = 4.7 Hz, H_3-15); ^{13}C NMR (DMSO-d_6, 125 MHz) δ 150.0 (C-3a), 143.6 (C-2), 141.1 (C-7a), 137.1 (C-11), 135.0 (C-6), 128.5 (C-8a), 126.8 (C-11a), 125.5 (−4), 122.7 (C-5), 121.9 (C-10), 120.6 (C-11b), 117.9 (C-7), 113.6 (C-9), 115.5 (C-3b), 105.4 (C-3), 47.0 (C-13), 32.7 (C-15), 27.1 (C-12); (+)-HRESIMS m/z 292.1448 $[M + H]^+$ (calcd for $C_{18}H_{18}N_3O$, 292.1444).

*N-Ethyl-styelsamine D (**23**).* Using general procedure D, *N*-ethyl-styelsamine B (**20**, 11.9 mg, 0.03 mmol) and 6 N HCl (8 mL) afforded **23** as a purple oil (bis-TFA salt, 3.95 mg, 29% [51% based on recovered starting material]). R_t = 7.47 min; IR (ATR) ν_{max} 3403, 2949, 1672, 1583, 1250, 1132 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 8.10 (1H, br s, H-2), 8.02 (1H, d, J = 7.8 Hz, H-4), 7.68 (1H, d, J = 7.8 Hz, H-7), 7.63 (1H, t, J = 7.8 Hz, H-6), 7.42−4.38 (2H, m, H-3, 10), 7.22 (1H, t, J = 7.8 Hz, H-5), 3.28−3.24 (4H, m, H_2-12, 13), 3.12 (2H, q, J = 7.3 Hz, H_2-15), 1.34 (3H, t, J = 7.3 Hz, H_3-16); ^{13}C NMR (CD_3OD, 125 MHz) δ 151.3 (C-3a), 143.7 (C-2), 142.5 (C-7a), 138.6 (C-11), 136.4 (C-6), 130.0 (C-8a), 128.4 (C-11a), 126.1 (C-4), 124.2 (C-5), 122.8 (C-10), 122.0 (C-11b), 119.1 (C-7), 115.5 (C-3b), 114.5 (C-9), 106.2 (C-3), 47.1 (C-13), 44.3 (C-13), 28.7 (C-12), 11.4 (C-16); (+)-HRESIMS m/z 306.1597 $[M + H]^+$ (calcd for $C_{19}H_{20}N_3O$, 306.1601).

*N-Benzyl-styelsamine D (**24**).* Using general procedure D, *N*-benzyl-styelsamine B (**21**, 20.4 mg, 0.04 mmol) and 6 N HCl (8 mL) afforded **24** as a purple oil (bis-TFA salt, 9.44 mg, 41% [71% based upon recovered starting material]). R_t = 8.52 min; IR (ATR) ν_{max} 3402, 2949, 1679, 1584, 1250, 1141, 1030 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 8.12 (1H, d, J = 6.5 Hz, H-2), 8.00 (1H, d, J = 8.2 Hz, H-4), 7.87 (1H, d, J = 8.0 Hz, H-7), 7.61 (1H, t, J = 8.0 Hz, H-6), 7.59−

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J. Org. Chem. XXXX, XXX, XXX−XXX

7.57 (2H, m, H-16, 20), 7.46−7.43 (3H, m, H-17, 18, 19), 7.41 (1H, d, J = 6.5 Hz, H-3), 7.39 (1H, s, H-10), 7.20 (1H, t, J = 8.2 Hz, H-5), 4.28 (2H, s, H_2-14), 3.36−3.34 (2H, m, H_2-12), 3.34−3.32 (2H, m, H_2-13); ^{13}C NMR (CD_3OD, 125 MHz) δ 151.2 (C-3a), 143.7 (C-2), 142.5 (C-7a), 138.5 (C-11), 136.3 (C-6), 132.5 (C-15), 131.1 (C-16, 20), 130.7 (C-18), 130.3 (C-17, 19), 129.9 (C-8a), 128.3 (C-11a), 126.1 (C-4), 124.2 (C-5), 122.7 (C-10), 121.9 (C-11b), 119.1 (C-7), 115.5 (C-3b), 114.5 (C-9), 106.3 (C-3), 52.5 (C-14), 47.2 (C-13), 28.8 (C-12); (+)-HRESIMS m/z 368.1754 $[M + H]^+$ (calcd for $C_{24}H_{22}N_3O$, 368.1757).

*N-Ethyl-demethyldeoxyamphimedine (**25**).* Using general procedure E, *N*-ethyl-styelsamine D (**23**, 11.5 mg, 0.02 mmol), paraformaldehyde (4.1 mg, 0.14 mmol), and acetic acid (2 mL) afforded **25** as a dark yellow powder (TFA salt, 7.61 mg, 83% yield). R_t = 8.28 min; IR (ATR) ν_{max} 3401, 1671, 1427, 1183, 1110, 1032 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 9.95 (1H, s, H-9), 9.46 (1H, d, J = 5.5 Hz, H-12), 9.39 (1H, d, J = 5.5 Hz, H-11), 9.31 (1H, d, J = 4.9 Hz, H-6), 9.10 (1H, d, J = 4.9 Hz, H-5), 8.94 (1H, d, J = 8.0 Hz, H-4), 8.49 (1H, d, J = 8.0 Hz, H-1), 8.12 (1H, t, J = 8.0 Hz, H-2), 8.04 (1H, t, J = 8.0 Hz, H-3), 4.94 (2H, q, J = 7.2 Hz, H_2-14), 1.82 (3H, t, J = 7.2 Hz, H_3-15); ^{13}C NMR (CD_3OD, 125 MHz) δ 179.2 (C-8), 151.4 (C-6), 149.7 (C-12a), 148.2 (C-11), 147.2 (C-7a), 146.8 (C-9), 146.7 (C-13a), 145.5 (C-12b), 139.8 (C-4b), 134.0 (C-2), 133.3 (C-1), 133.0 (C-3), 132.0 (C-8a), 125.2 (C-4), 125.0 (C-12), 124.2 (C-4a), 122.9 (C-5), 120.9 (C-12c), 59.1 (C-14), 16.8 (C-15); (+)-HRESIMS m/z 312.1125 $[M]^+$ (calcd for $C_{20}H_{14}N_3O$, 312.1131).

*N-Benzyl-demethyldeoxyamphimedine (**26**).* Using general procedure E, *N*-benzyl-styelsamine D (**24**, 8.1 mg, 0.02 mmol), paraformaldehyde (2.5 mg, 0.08 mmol), and acetic acid (1.5 mL) afforded **26** as a dark yellow powder (TFA salt, 6.04 mg, 74%). R_t = 9.07 min; IR (ATR) ν_{max} 3408, 1691, 1636, 1250, 1129 cm^{-1}; ^{1}H NMR (CD_3OD, 500 MHz) δ 10.02 (1H, s, H-9), 9.49 (1H, d, J = 6.5 Hz, H-12), 9.38 (1H, d, J = 6.5 Hz, H-11), 9.36 (1H, d, J = 5.3 Hz, H-6), 9.16 (1H, d, J = 5.3 Hz, H-5), 9.00 (1H, d, J = 8.0 Hz, H-4), 8.53 (1H, d, J = 8.0 Hz, H-1), 8.14 (1H, t, J = 8.0 Hz, H-2), 8.08 (1H, t, J = 8.0 Hz, H-3), 7.69−7.63 (2H, m, H-16, 20), 7.56−7.51 (3H, 17, 18, 19), 6.09 (2H, s, H_2-14); ^{13}C NMR (CD_3OD, 125 MHz) δ 179.2 (C-8), 151.4 (C-6), 150.2 (C-12a), 148.2 (C-11), 147.3 (C-7a)[a], 146.8 (C-9, 13a), 145.6 (C-12b)[a], 139.9 (C-4b), 134.3 (C-15), 134.0 (C-2), 133.3 (C-1), 133.0 (C-3), 132.4 (C-8a), 131.3 (C-18), 130.9 (C-17, 19), 130.5 (C-16, 20), 125.3 (C-4, 12), 124.4 (C-4a), 122.9 (C-5), 121.1 (C-12c), 66.1 (C-14); (+)-HRESIMS m/z 374.1275 [M] (calcd for $C_{25}H_{16}N_3O$, 374.1288).

*N-Ethyl-demethylamphimedine (**27**).* Using general procedure F, *N*-ethyl-demethyldeoxyamphimedine (**25**, 4.61 mg, 0.011 mmol), NaOH (1.73 mg, 0.043 mmol, in 0.3 mL of water), and potassium ferricyanide (7.14 mg, 0.022 mmol, in 0.3 mL of water) afforded **27** as a yellow powder (3.01 mg, 85%). R_f (CH_2Cl_2/MeOH, 9:1) 0.18; IR (ATR) ν_{max} 3408, 2924, 1738, 1638, 1217, 1090 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.29 (1H, br s, H-6), 8.79 (1H, s, H-9), 8.67−8.57 (2H, m, H-4, 5), 8.35 (1H, d, J = 7.8 Hz, H-1), 8.01 (1H, s, H-12), 7.98 (1H, t, J = 7.8 Hz, H-2), 7.86 (1H, t, J = 7.8 Hz, H-3), 4.24 (2H, q, J = 7.4 Hz, H_2-14), 1.54 (3H, t, J = 7.4 Hz, H_3-15); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 179.1 (C-8), 162.5 (C-11), 150.0 (C-6), 147.7 (C-7a), 146.7 (C-12b), 145.4 (C-13a), 144.0 (C-9), 142.9 (C-12a), 138.4 (C-4b), 132.1 (C-2), 131.9 (C-1), 129.6 (C-3), 123.0 (C-4), 122.3 (C-4a), 119.9 (C-12c), 119.4 (C-5), 114.6 (C-12), 113.8 (C-8a), 46.2 (C-14), 14.9 (C-15); (+)-HRESIMS m/z 350.0890 $[M + Na]^+$ (calcd for $C_{20}H_{13}N_3NaO_2$, 350.0900).

*N-Benzyl-demethylamphimedine (**28**).* Using general procedure F, *N*-benzyl-demethyldeoxyamphimedine (**26**, 7.65 mg, 0.016 mmol), NaOH (2.51 mg, 0.063 mmol, in 0.4 mL of water), and potassium ferricyanide (10.3 mg, 0.031 mmol, in 0.4 mL of water) afforded **28** as a poorly soluble yellow powder (2.10 mg, 34%). Benzyl derivative **28** is poorly soluble in most solvents and thus characterization was limited to ^{1}H NMR and HRESIMS. R_f (CH_2Cl_2/MeOH, 9:1) 0.26; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.30 (1H, d, J = 5.6 Hz, H-6), 8.82 (1H, s, H-9), 8.67−8.63 (2H, m, H-4, 5), 8.39 (1H, d, J = 8.3 Hz, H-1), 8.11 (1H, s, H-12), 7.99 (1H, t, J = 8.3 Hz, H-2), 7.87 (1H, t, J = 8.3 Hz, H-3), 7.46−7.43 (2H, m, H-16, 20), 7.42−7.37 (3H, m, H-17, 18, 19), 5.37 (2H, s, H_2-14); (+)-HRESIMS m/z 412.1055 $[M + Na]^+$ (calcd for $C_{25}H_{15}N_3NaO_2$, 412.1056).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02312.

^{1}H and ^{13}C NMR spectra for **1**, **3**−**5**, and **13**−**27** and ^{1}H spectra of **11** and **28** (PDF)

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Notes

The authors declare no competing financial interest.

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