The Pyridoacridine Family Tree: A Useful Scheme for Designing Synthesis and Predicting Undiscovered Natural Products

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The Pyridoacridine Family Tree: A Useful Scheme for Designing Synthesis and Predicting Undiscovered Natural Products

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The pyridoacridine natural products represent a large and growing class and serve here to illustrate the wealth of information that can be extracted by comparing natural products on the basis of structure and occurrence.

The pyridoacridines are a group of highly colored, polycyclic aromatic natural products isolated from marine organisms. They have shown a wide range of biological activity that has been summarized elsewhere.[1]

It has been suggested that the unusual cross-phyletic distribution of the pyridoacridine natural products is due to symbiotic marine microorganisms. However, there does not appear to be solid evidence to support this conjecture.[1] It appears at least as likely that the same oxidative pathway that leads from the ubiquitous amino acids to the pyridoacridine core has been conserved evolutionarily.

The development of new biochemistry can be viewed as occurring by a mutational process, as does biological evolution. Small changes in the starting point (starting material) of a pathway maintaining the same set of rules can give rise to emergent properties (unexpected product structures).

We believe that by looking for the simplest pathway that could give rise to all the natural products of a series, it is possible both to devise a synthesis/possible biosynthesis and to predict natural products that may be as of yet undiscovered.

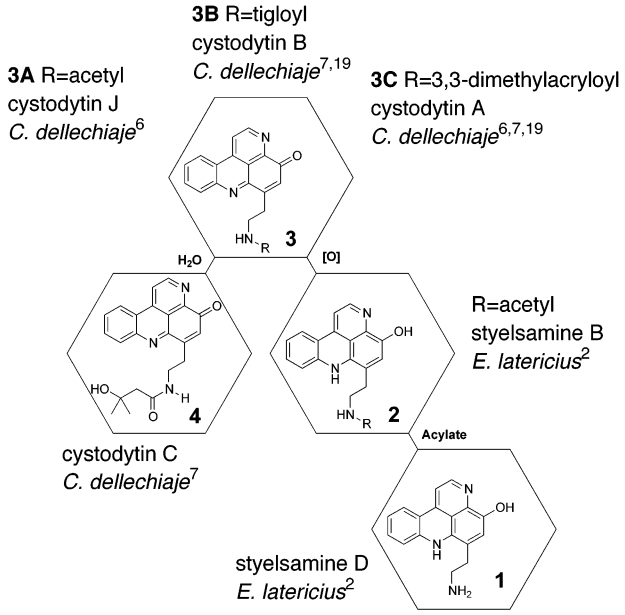
A natural product may arise by any number of pathways, and in fact, multiple pathways can exist within the same organism. For this reason, the existence of one pathway cannot disprove the existence of another. Furthermore, the incredible diversity of the world ecology makes it likely that a large number of the natural products that would arise by simple diversion from a well-established pathway will exist somewhere, in some organism, as an intermediate or as a natural product.

The Pyridoacridine Family Tree

The simplest of the dopamine-based pyridoacridines can be seen as deriving from the parent free amine styelsamine D (**1**, Schemes 1 and 4). Styelsamine B (**2**, Figure 1, Scheme 1) and D (**1**) were isolated from the extract of the Indonesian ascidian *Eusynstyela latericius* along with the higher oxidation state relatives styelsamines A (**33**, Scheme 7) and C (**46**, Scheme 11). In the same study, the racemic styelsamine A was shown to oxidize to the corresponding iminoquinone (**34**, Scheme 7) upon standing in DMSO-d_6.[2]

With an appropriate starting point in the pyridoacridine family it is possible to synthesize numerous natural products/natural product analogues with ease. We have taken styelsamine B (**2**, Figure 1, Scheme 1) as our starting point.

Scheme 1. Simple Dopamine-Derived Pyridoacridines (Total Synthesis of Styelsamine D, Cystodytin A/B)



In a recent publication we demonstrated the biomimetic synthesis of styelsamine B (2) from kynuramine and *N*-acetyl dopamine. Styelsamine B (**2**) was further oxidized to the quinonimine cystodytin J (**3A**, Scheme 1).[3] Thiol addition to quinonimines such as **3A** occurs unambiguously at the 9 position, as is the case in the reported conversion of cystodytin J (**3A**) to diplamine (**44B**, Scheme 10) with methanethiol.[4] The reaction of dopaquinone with cysteine is known to yield predominantly 5-*S*-cysteinyl dopamine,[5] which is not a viable intermediate in the synthesis of the sulfur-containing pyridoacridines. It appears likely that all the dopamine-derived pyridoacridines are prepared by modifying simple C9 unsubstituted pyridoacridines such as **2**.

As shown in Scheme 1, acetylation of styelsamine D (**1**) should yield styelsamine B (**2**), which may be oxidized to cystodytin J (**3A**), as we have previously reported.[3] Cystodytin J (**3A**) was isolated, along with cystodytin A (**3C**, Scheme 1), kuanoniamine D (**39D**, Scheme 9), dehydrokuanoniamine B (**39A**), shermilamine B (**38B**, Scheme 8) and C (**38C**), and eilatin, from a Fijian *Cystodytes* ascidian.[6]

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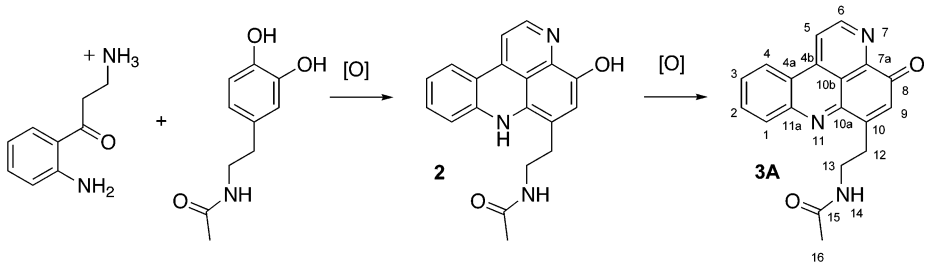
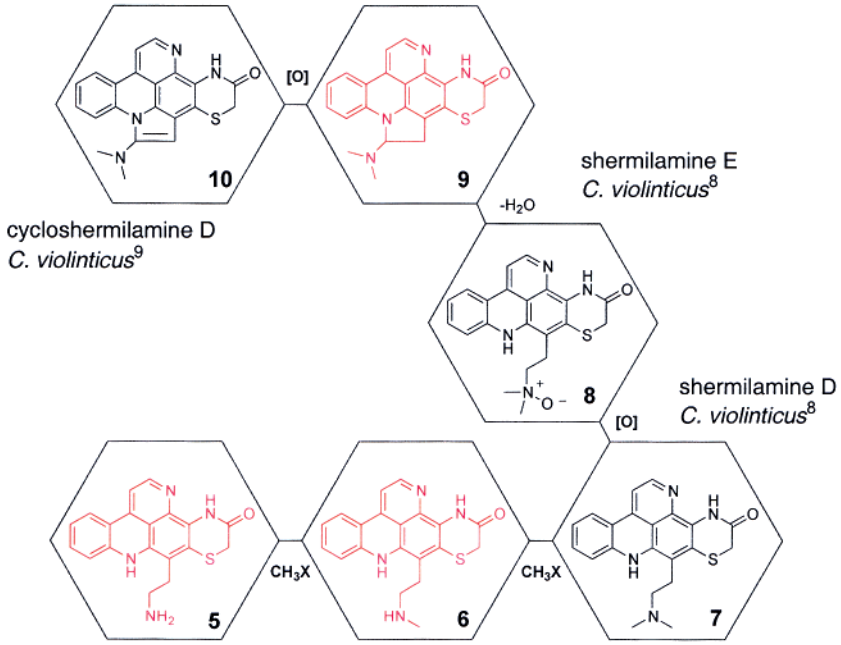
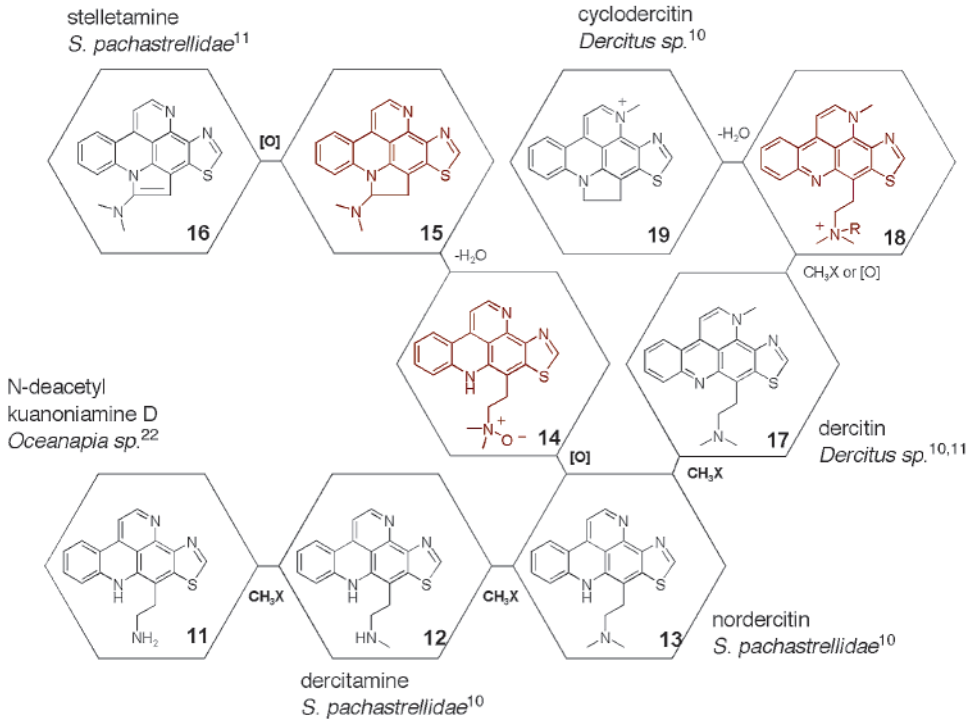


Figure 1. Biomimetic synthesis of styelsamine B and cystodytin J.

Scheme 2. Cysteine Derived Pyridoacridines (Methylation Pathway)



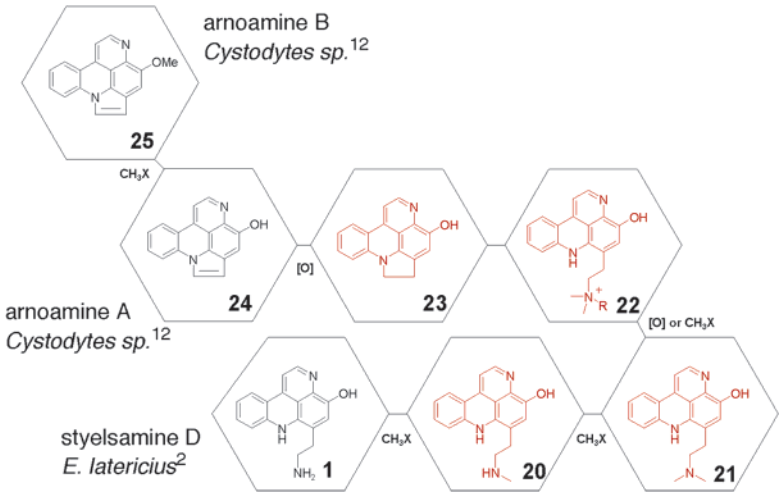
Scheme 3. Thiazole Containing Pyridoacridines (Methylation Pathway)



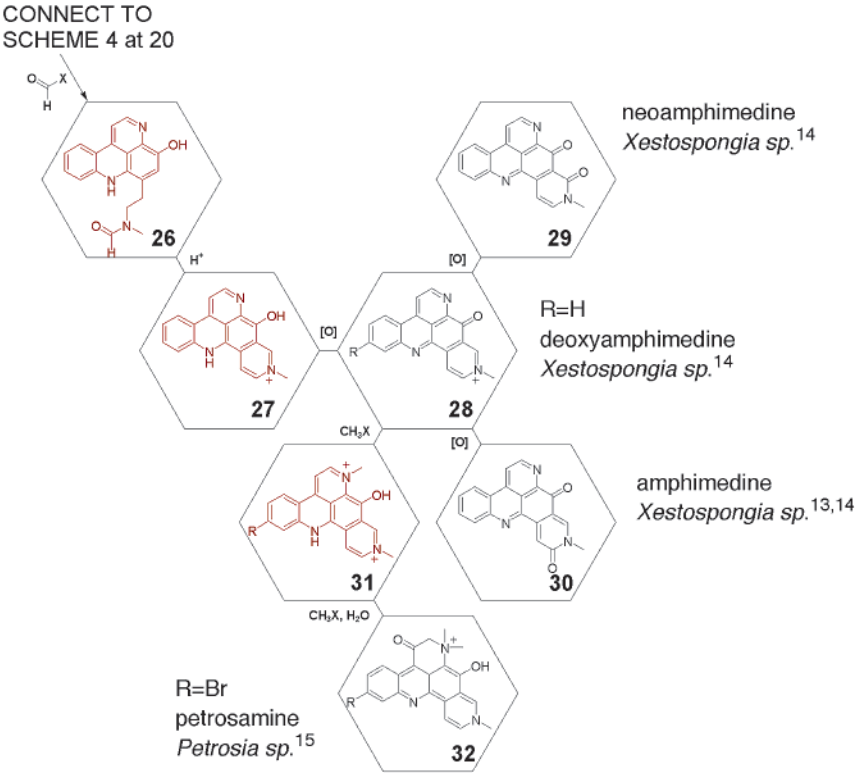
Cystodytins A−C (**3C**, **3B**, **4**) have also been isolated from the Okinawan tunicate *Cystodytes dellechiajei*.[7] Cystodytin C (**4**) is easily recognizable as hydrated cystodytin A (**3C**).

We have found that styelsamine B (**2**, Scheme 1) may be hydrolyzed to the primary amine styelsamine D (**1**) in quantitative yield. Acylation under basic conditions, open

Scheme 4. Pentacyclic Pyridoacridines (Methylation Pathway)



Scheme 5. Pentacyclic Pyridoacridines (Methylation Pathway cont.)



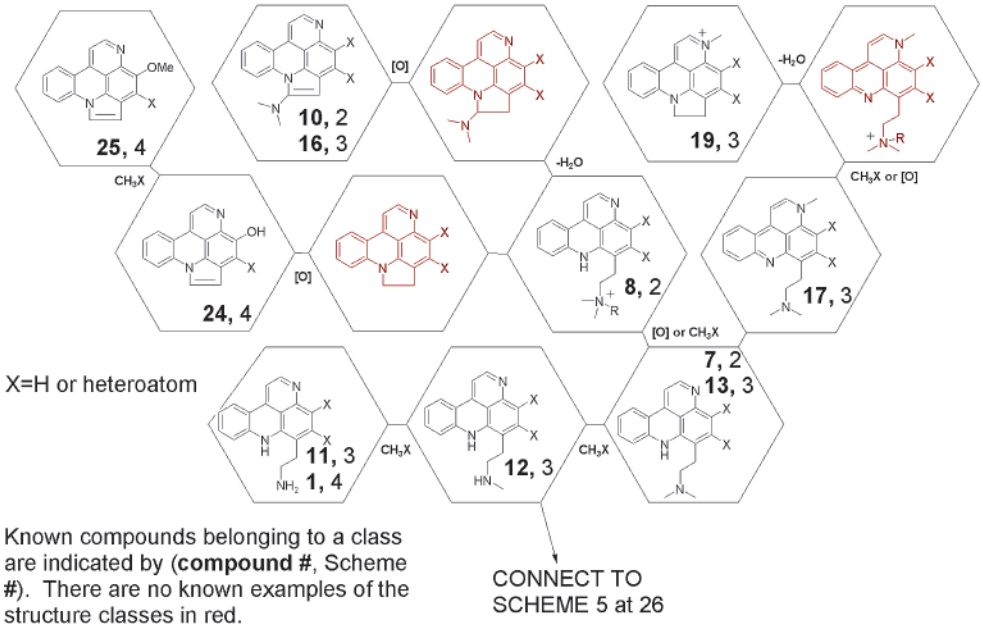
to air, allow cystodytins A (**3C**, Scheme 1) and B (**3B**) to be prepared rather efficiently. The hydration of cystodytin A (**3C**) to form cystodytin C (**4**, Scheme 1) has been demonstrated by others.[7] Taken together, the five reactions we have reported in this area constitute the total synthesis of five natural products (**1**, **2**, **3A**, **3B**, **3C**, Scheme 1) and the formal synthesis of two (**4**, Scheme 1; **44B**, Scheme 10). Such efficiency is a natural consequence of the interconnectivity of the natural products. Instructions for the rest of the known dopamine-derived pyridoacridines may be found in the schemes that populate the rest of this paper.

General Instructions. Many of the compounds indicated throughout this article are likely to exist in protonated form, but this has been disregarded in drawing the structures for the sake of simplicity. Similar transformations in schemes are oriented such that they may be superimposed. When two schemes are superimposed, any spot where one scheme contains a natural product, and the other does not, implies the possibility of an undiscovered natural product in that scheme. The unlabeled, red structures are compounds that have not been isolated as natural products, but are likely precursors of a known natural product. These are compounds considered likely to be isolated in the future. The reaction type indicated next to the lines serves purely as a guide to identify the transformation occurring. The connections necessary to assemble the full map are included in the schemes themselves.

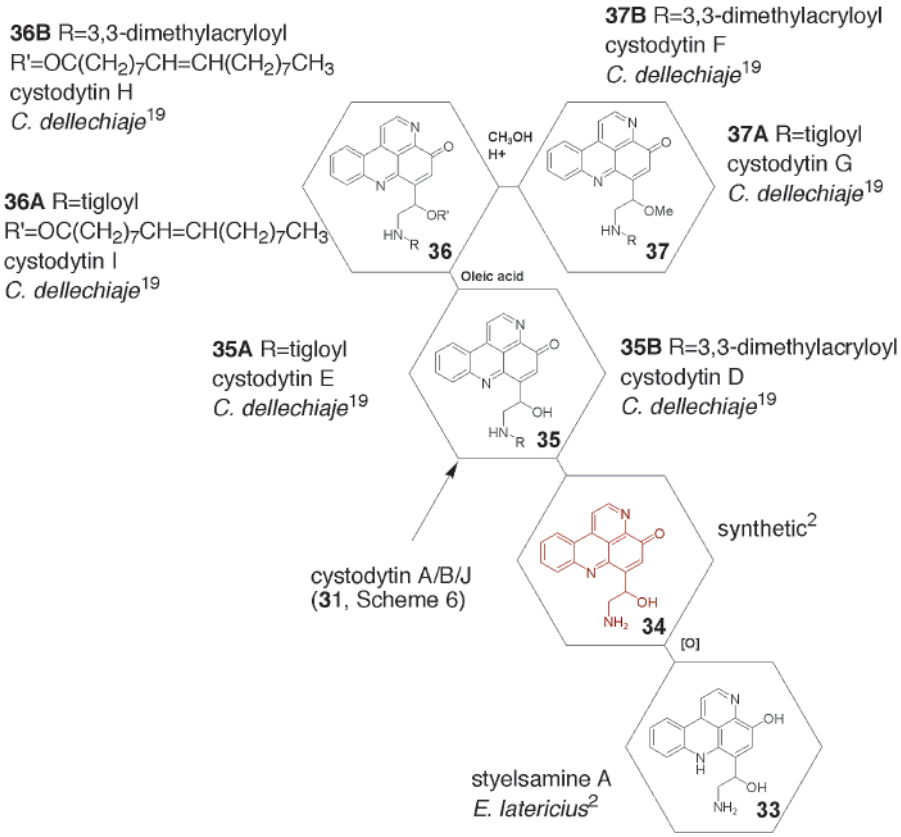
Before moving on to the bulk of the pyridoacridines we will first address those that are likely to involve side chain methylation since they provide a clear example of how information may be extracted from the schemes.

Pathways Involving Ethylamine Side Chain Methylation. Shermilamines D (**8**, Scheme 2) and E (**9**) were isolated together from the tunicate *Cystodytes violatinctus* collected at the Mayotte Lagoon, Comoros Islands.[8] In a later publication, the isolation of cycloshermilamine D (**10**)

Scheme 6. General Map Generated by Overlaying Schemes 2−4



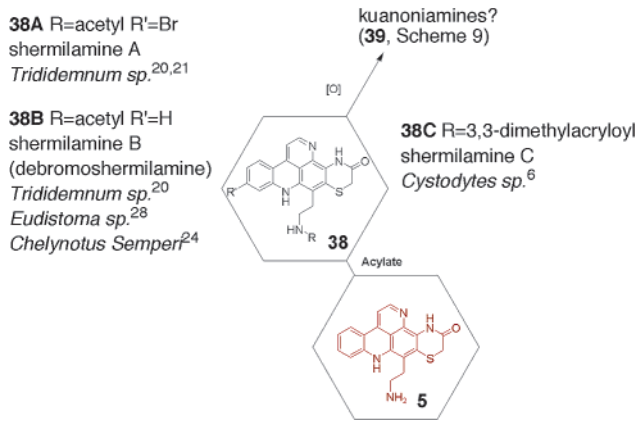
Scheme 7. Pyridoacridines Hydroxylated at C-12 (Acylation Pathway)



from the same organism and location was reported.[9] The methylation/N-oxidation/cyclization pathway proposed to connect shermilamines D (**8**) and E (**9**) and cycloshermilamine D (**10**) is shown in Scheme 2. The hypothetical *N*,*N*-didesmethyl (**5**) and *N*-desmethylated (**6**) shermilamines are shown in red since they are as yet unknown. The co-isolation of the corresponding *N*-methyl (**12**) and dimethyl (**13**) compounds from the thiazole series (Scheme 3) strengthens the case for sequential methylation.[10] The possibility that methylation could occur at an earlier stage [i.e., shermilamine D (**7**) could arise from dimethyl dopamine] cannot be excluded.

A similar pathway may be imagined as connecting nordercitin (**13**, Scheme 3) to stelletamine (**16**) through the hypothetical *N*-oxide (**14**) and a cyclized but unoxidized intermediate (**15**). The pyridoacridines dercitin (**17**, Scheme 3) and cyclodercitin (**19**) have been isolated from *Dercitus* sp. collected in the Bahamas. This publication also claims isolation of dercitamide/kuanoniamine C (**39C**, Scheme 9) and two related *N*-oxides: N-14 (**14**, Scheme 3) and N-7

Scheme 8. Cysteine Derived Pyridoacridines (Acylation Pathway)



(**18**, Scheme 3). Since no spectral information is provided for these compounds, we treat them as unknown. Cyclodercitin (**19**) was reported to oxidize to its fully unsaturated analogue upon standing in TFA-*d* in air.[10]

The deep water sponge *Stelleta* sp. has also yielded the hexacyclic stelletamine (**16**, Scheme 3), the structure of which was assigned by X-ray crystallography.[11] It has been proposed that the five-membered ring common to the arnoamines (**24/25**, Scheme 4), cyclodercitin (**19**, Scheme 3), and stelletamine (**16**, Scheme 3) may arise from the ethylamine side chain present in most of the pyridoacridines.[12] We propose stelletamine (**16**) and cycloshermilamine D (**10**, Scheme 2) may be formed via the hypothetical *N*-oxide as shown in Figure 2. An extract of *Stelleta* sp. collected in the same area yielded dercitamine (**12**, Scheme 3), nordercitin (**13**, Scheme 3), and dercitamide/kuanoniamine C (**39C**, Scheme 9).[10]

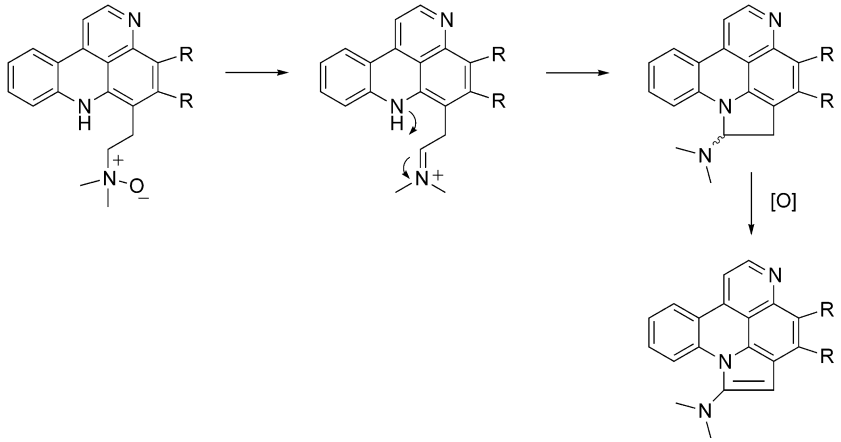


Figure 2. Proposed mechanism for the formation of stelletamine (**16**)/cycloshermilamine D (**10**).

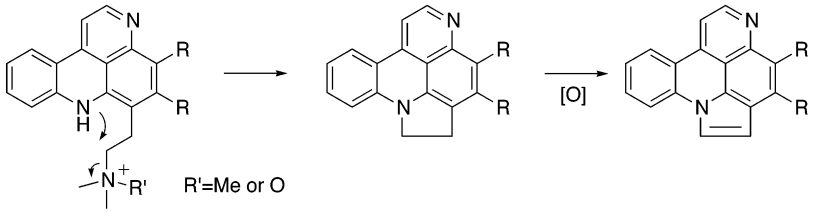
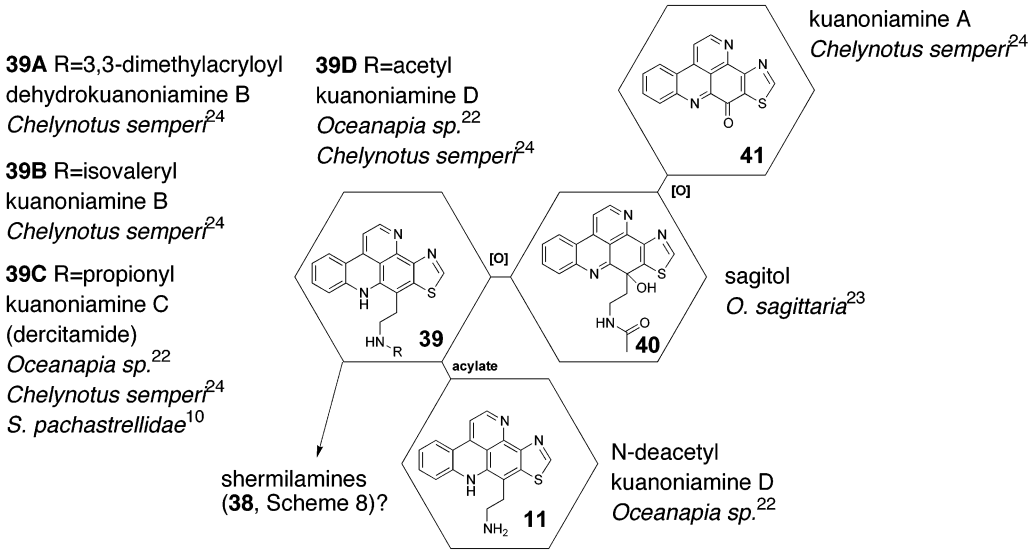
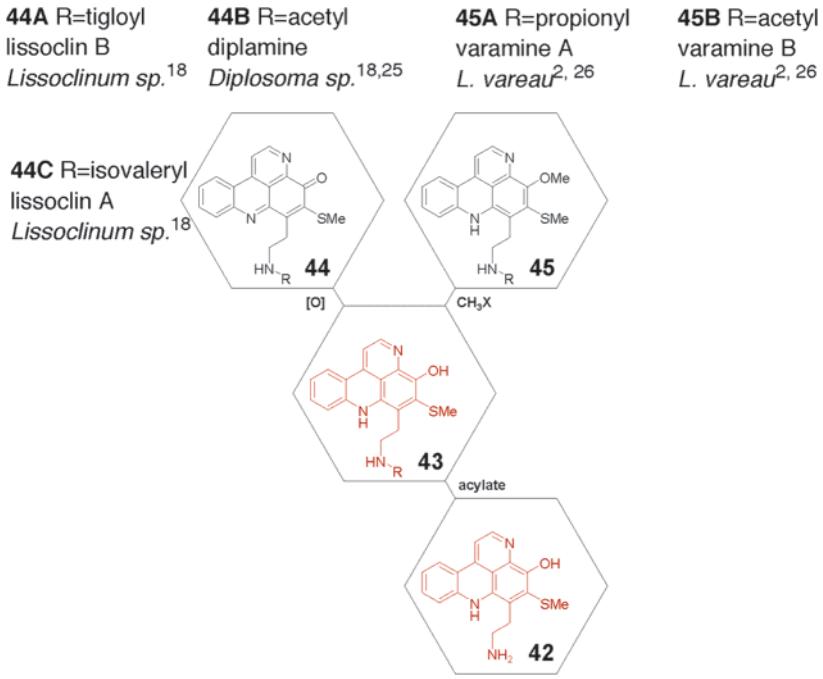


Figure 3. Proposed mechanism for the formation of arnoamine A (**24**)/cyclodercitin (**19**).

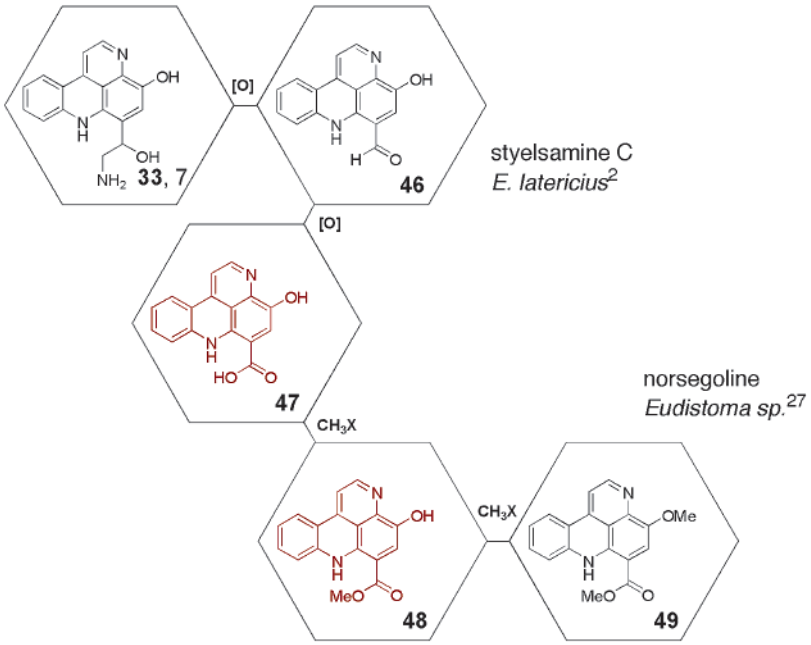
Scheme 9. Thiazole Containing Pyridoacridines (Acylation Pathway)



Scheme 10. S-Methylated Pyridoacridines (Acylation Pathway)



Scheme 11. Further Oxidation Products of Styelsamine A



Styelsamine D (**1**, Schemes 1 and 4) was isolated from an extract of the ascidian *Eusynstyela latericius* collected in Indonesia along with styelsamines A−C (**33**, **2**, **46**).[2] The arnoamines (**24/25**, Scheme 4) were isolated from a collection of *Cystodytes* sp. made near Arno Atoll, Republic of the Marshall Islands.[12]

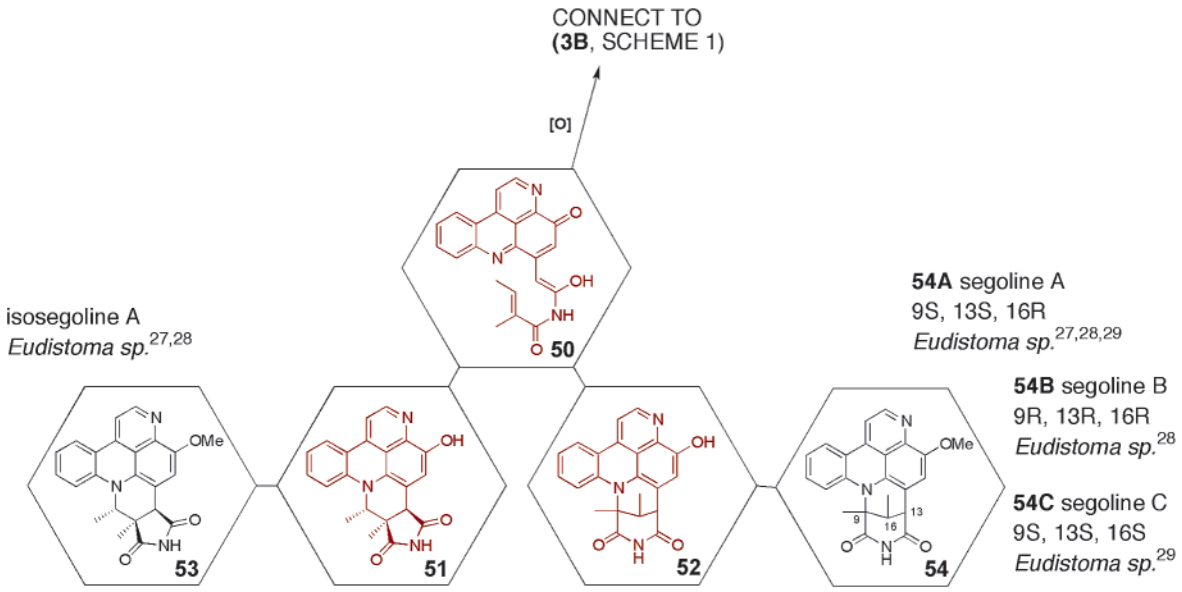
The connection between arnoamine A (**24**) and styelsamine D (**1**) through hypothetical intermediates **20**−**23** (Scheme 4) has been made by analogy to the apparent path connecting *N*-deacetyl kuanoniamine D (**11**, Scheme 3) and cyclodercitin (**19**). It seems the simplest reaction pathway would involve further extension of the existing methylation pathway to the quaternary ammonium, which could serve as a leaving group in the cyclization (Figure 3).

Special Case. A possible connection between styelsamine D (**1**) and the pentacyclic amphimedine (**30**) may be seen in Scheme 5. Formylation of the proposed *N*-methyl styelsamine D derivative (**20**, Scheme 4) should provide an intermediate (**26**, Scheme 5) capable of a Bischler-Naperialski cyclization that would set up the *N*-methyl isoquinoline ring system (**27**, Scheme 5) common to the natural products found in Scheme 5. Oxidation of this proposed intermediate (**27**) connects to deoxyamphimedine (**28**), the simplest of the compounds in this series.

Deoxyamphimedine (**28**) was isolated along with neoamphimedine (**29**) and amphimedine[13] (**30**) from two specimens of a *Xestospongia* sp. collected from the Phillipines and Palau.[14] Selective oxidation of deoxyamphimedine (**28**) at position 9 or 11 should give rise to neoamphimedine (**29**) and amphimedine (**30**) as in Scheme 5.

Petrosamine (**32**, Scheme 5) is a natural product sharing the amphimedine skeleton isolated from a specimen of the

Scheme 12. Possible Pathway to the Segolines/Isosegoline A



sponge *Petrosia* sp. collected in Belize.[15] Bromination of petrosamine (**32**) could occur at virtually any point, as is the case for other brominated pyridoacridines such as shermilamine A (**38A**, Scheme 8). The ascidian *Lissoclinum* sp. has been found to produce 6-bromotryptamine,[16] potential precursor of 6-bromokynuramine and, therefore, the bromopyridoacridines (**32/38A**). Also isolated from this creature were the pyridoacridines lissoclin A/B (**44C/44A**, Scheme 10).[17] For simplicity, we therefore presume that the brominated pyridoacridines arise by a parallel pathway using bromokynuramine as starting material.

By overlaying Schemes 2−4 we can construct a hypothetical map (Scheme 6) of what types of structures may be expected to occur and how they might be prepared. Some compounds may be missing for practical reasons. For instance, it is notable that the N-7 methylated cyclodercitin (**19**, Scheme 3) is known, but the related arnoamine intermediate (**23**, Scheme 4) is not. This may simply be due to the excessive oxidizability of the latter. The compounds of Scheme 5 have been excluded since they represent a special case (only pyridoacridines unsubstituted at C-9 may undergo the requisite cyclization).

Pathways Beginning with Side Chain Acylation. The acylation/oxidation pathway proposed to connect styelsamine D (**1**) to cystodytin A (**3C**, Scheme 1) may be invoked to connect styelsamine A (**33**) to cystodytin D (**35B**, Scheme 7). Replacement of the benzylic hydroxyl group of cystodytins D/E (**35B/35A**) with an oleate ester connects them to cystodytins H and I (**36A/36B**, Scheme 7), respectively. The conversion of the oleate ester natural products to the methyl ethers (**36** → **37**) with acidic methanol was demonstrated in the isolation paper.[18] The methyl ether natural products (**37A/37B**) may be an artifact of isolation.

It is possible that styelsamine A (**33**, Scheme 7) is derived from styelsamine D (**1**, Scheme 1) by selective hydroxylation at C12. It seems equally likely that styelsamine A (**33**) and the other pyridoacridines represented in Scheme 7 arise by a parallel pathway involving the reaction of kynuramine with norepinephrine.

Shermilamine A (**38A**, Scheme 8) and its unbrominated analogue shermilamine B (**38B**) have been isolated from the colonial tunicate *Trididemnum* sp. from Pago Bay, Guam.[19,20] Shermilamine B (**38B**) has also been isolated from several other sources including a *Cystodytes* sp. ascidian, where it was found occurring with shermilamine C (**38C**) and other pyridoacridines.[6] The unacylated shermilamine precursor (**5**) is as of yet undiscovered.

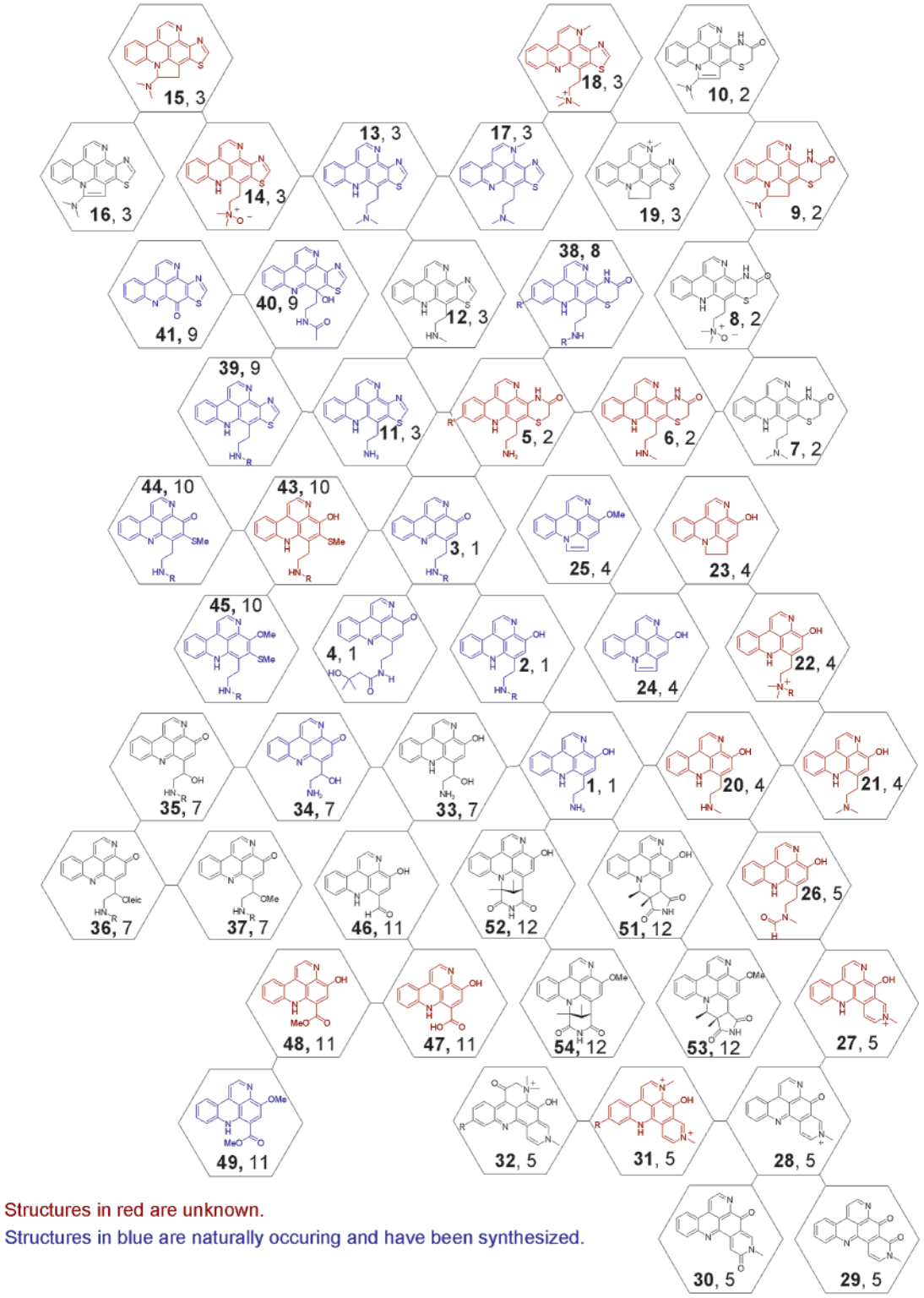
The Micronesian sponge *Oceanapia* sp. has yielded the primary amine *N*-deacetyl kuanoniamine D (**11**, Scheme 3) along with its acylated relatives kuanoniamine C/D (**39C/39D**, Scheme 9).[21] The acidic hydrolysis of kuanoniamine C (**39C**) to form *N*-deacetyl kuanoniamine D (**11**) was demonstrated in the isolation paper. Acylation of this primary amine connects it to kuanoniamines B−D (**39B−D**), and oxidation of kuanoniamine D (**39D**) has been shown to yield sagitol (**40**).[22]

Kuanoniamines C and D (**39C/39D**) were also isolated from an undescribed tunicate and its predator mollusk *Chelynotus semperi* along with kuanoniamines A/B (**39A, 41**) and shermilamine B (**38B**, Scheme 8).[23] The isolation of the shermilamines and the kuanoniamines from the same source makes it likely either that they share a common precursor or that there exists an oxidative process capable of converting the shermilamines to the kuanoniamines. Kuanoniamine C (**39C**) has also been isolated from the deep water sponge *Stelleta* under the name dercitamide.[10] Both kuanoniamines A and B (**39A/41**, Scheme 9) have been isolated from a *Cystodytes* ascidian.[11] It is possible that further oxidation of a pyridoacridine similar to sagitol (**40**) may lead to kuanoniamine A (**41**).

The colonial ascidian *Lissoclinum* sp. has yielded the pyridoacridines lissoclins A and B (**44C**/**44A**, Scheme 10).[17] Lissoclins A and B may derive from the unknown parent amine (**42**) by acylation to form the unknown intermediate (**43**) followed by oxidation. Diplamine (**44B**), the *N*-acetyl analogue of lissoclin B (**44A**), was isolated from a collection of the tunicate *Diplosoma* sp. in the Fiji Islands. It has been demonstrated that varamine A (**45A**) can be oxidatively demethylated to form diplamine (**44B**).[24] Varamines A (**45A**) and B (**45B**) were isolated from a collection of the tunicate *Lissoclinum vareau* made in the Fiji islands.[25]

Miscellaneous Transformations. The styelsamines A−D were isolated from the ascidian *Eusynstyela latericius* collected by scuba in Ujung Pandang, Indonesia.[2] As shown in Scheme 11, oxidative degradation of the ethanolamine side chain of styelsamine A (**33**) should provide the alde-

Scheme 13. A Global Map of the Dopamine-Derived Pyridoacridines



hyde styelsamine C (**46**). Oxidation of styelsamine C (**46**) to the unknown acid (**47**) and subsequent methylation provide a connection to norsegoline (**49**).

Norsegoline (**49**) has been isolated from the purple tunicate *Eudistoma* sp. along with the pyridoacridines segoline A and isosegoline A (**54A/53**, Scheme 12).[26] Segoline B (**54B**), segoline A (**54A**), isosegoline A (**53**), norsegoline (**49**, Scheme 11), shermilamine B (**38B**, Scheme 8), and eilatin were found in another collection of *Eudistoma* sp. from the same area.[27] Segoline C (**54C**, Scheme 12), the enantiomer of segoline B (**54B**), has been isolated from the Indian Ocean tunicate *Eudistoma bituminis* where it was found occurring with segoline A and norsegoline.[28] The remaining possible configuration (9*R*,13*R*,16*S*) has yet to be isolated. The isolation paper suggests that this may be due to reactivity; however, since the missing segoline is the enantiomer of the stable compound segoline A (**54A**), this does not seem possible. The origin of the segolines is unclear; however, it is interesting to note that the carbon skeleton of these natural products would be consistent with biosynthesis from a tiglic amide such as cystodytin B (**3B**, Scheme 1).

Conclusion

To see the overall picture generated by the above treatment of the pyridoacridines, it is necessary to generate a complete map of the natural product family such as the one seen in Scheme 13. Note that additional connections between natural product types may exist. A mapping exercise of this type may be performed on any sufficiently large family of natural products. Given the amount of information such an exercise may yield, we recommend the reader apply this analysis to their area of interest.

Experimental Section

General Experimental Procedures. Materials were obtained from commercial suppliers and were used without further purification. Styelsamine B was prepared as reported previously.[3] For analytical thin-layer chromatography, Merck Kieselgel 60 F254 (250 micron thickness) plates were used. Column chromatography was performed with EM silica gel 60 (230−400 mesh). IR spectra were determined as KBr pellets. Elemental analyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

Styelsamine D (1). Styelsamine B (**2**, 25 mg, 0.07 mmol) was dissolved in 1:1 MeOH/4 N HCl (10 mL) and heated to 80 °C for 48 h. Removal of solvent under reduced pressure provided styelsamine D as a purple solid (24 mg, 0.07 mmol, 100%). Mp > 300 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 13.52 (br s, 1); 11.55 (br s, 1); 10.99 (br s, 1); 8.25 (m, 4); 8.19 (d, 1, J = 8.5); 8.14 (d, 1, J = 8.4); 7.63 (t, 1, J = 7.6); 7.53 (m, 2); 7.17 (t, 1, J = 7.7); 3.33 (m, 2); 2.99 (m, 2). ^{13}C NMR (125 MHz): δ 148.9, 143.0, 141.1, 136.9, 134.4, 128.2, 126.2, 125.0, 122.3, 121.9, 120.2, 117.8, 114.0, 113.6, 104.9, 38.1, 28.4. IR: 3390, 3067, 1652, 1620, 1580, 1474, 1360, 1222, 1129 cm^{-1}.

Cystodytin A (3C). To a solution of styelsamine D (**1**, 20 mg, 0.06 mmol) in a stirring 1:1 EtOAc/H_2O biphase was added NEt_3 (500 L) followed by 3,3-dimethylacryloyl chloride (10 equiv, 69 mg, 0.58 mmol) at 25 °C. The color of the purple aqueous layer quickly faded, and the organics became red-orange. After stirring at room temperature open to air 30 min the layers were separated and the organics were dried with sodium sulfate. Hexanes were added until persistent cloudiness appeared, and the solution was let stand overnight. The orange precipitate was purified by silica gel column chromatography (9:1 EtOAc/MeOH) and concentrated under reduced pressure to yield cystodytin A (**3C**, 7 mg, 0.02 mmol, 33%). Mp: 189−190 °C. ^{1}H NMR (500 MHz, 2:1 $CDCl_3$/CD_3OD): δ 9.02 (br s, 1); 8.47 (d, 1, J = 7.3); 8.41 (br s, 1); 8.23 (d, 1, J = 7.4); 7.88 (t, 1, J = 7.0); 7.78 (t, 1, J = 7.2); 6.82 (s, 1); 5.53 (s, 1); 3.70 (t, 2, J = 6.8); 3.29 (m, 2); 2.01 (s, 3); 1.73 (s, 3). ^{13}C NMR (125 MHz, $CDCl_3$/CD_3OD): δ 183.5, 167.7, 152.6, 151.2, 150.1, 149.5, 146.3, 145.3, 137.1, 132.4, 131.8, 129.9, 122.9, 121.7, 119.6, 118.1, 117.9, 115.2, 38.6, 31.5, 27.0, 19.6. IR: 3411, 1656, 1635, 1625, 1588, 1540, 1520, 1332, 1301, 1181 cm^{-1}. MS: 359 (M^+ + 2), 273, 272, 260, 247, 218, 83. HRMS: calcd for $C_{22}H_{21}N_3O_2$ 359.1634, obsd 359.1645.

Cystodytin B (3B). 3B was prepared as described for cystodytin A. The product was isolated as a yellow powder (13 mg, 0.036 mmol, 63%), mp 180−181 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.15 (d, 1, J = 4.9); 8.53 (d, 1, J = 7.9); 8.48 (d, 1, J = 5.1); 8.27 (d, 1, J = 8.1); 7.91 (t, 1, J = 7.6); 7.82 (t, 1, J = 7.6); 6.87 (s, 1); 6.37 (br s, 1); 6.31 (q, 1, J = 6.9); 3.80 (m, 2); 3.30 (t, 2, J = 6.3); 1.74 (s, 1); 1.65 (d, 3, J = 6.8). ^{13}C NMR (125 MHz, $CDCl_3$): δ 183.4, 169.5, 152.3, 150.5, 149.9, 146.7, 145.2, 137.1, 132.7, 131.9, 131.8, 131.7, 130.5, 129.8, 122.9, 121.8, 119.3, 118.0, 39.7, 31.3, 13.8, 12.4. IR: 3452, 3283, 1657, 1617, 1587, 1532, 1332, 1301, 1181 cm^{-1}. MS: 359 (M^+ + 2), 272, 260, 247, 218, 83. HRMS: calcd for $C_{22}H_{21}N_3O_2$ 359.1634, obsd 359.1638.

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Supporting Information Available: Spectra for styelsamine D, cystodytin A, and cystodytin B. This material is available free of charge via the Internet at http://pubs.acs.org.

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