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Studies on Difficult Intramolecular Hydroaminations in the Context of Four Syntheses of Alkaloid Natural Products

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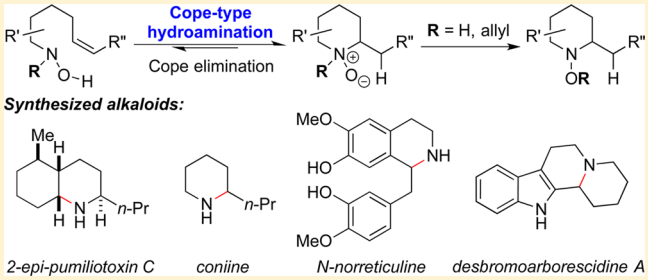
Supporting Information

ABSTRACT: Examples of intramolecular alkene hydroaminations forming six-membered ring systems are rare, especially for systems in which the double bond is disubstituted. Such cyclizations have important synthetic relevance. Herein we report a systematic study of these cyclizations using recently developed Cope-type hydroamination methodologies. Difficult intramolecular alkene hydroaminations were used as key steps in syntheses of 2-*epi*-pumiliotoxin C, coniine, *N*-norreticuline and desbromoarborescidine A. This effort required the development of optimized hydroamination conditions to improve the efficiency of the cyclizations. Collectively, our results show that Cope-type cyclizations can be achieved on a variety of challenging substrates and proceed under similar conditions for both *N*-H and *N*-substituted hydroxylamines.



INTRODUCTION

The development of broadly applicable intramolecular C−N bond-forming reactions is of major importance, as nitrogen heterocycles are omnipresent in both natural and synthetic biologically active molecules. A variety of transformations have thus been elaborated for the synthesis of nitrogen heterocycles. Among those, the hydroamination of C−C π-bonds has recently emerged as a versatile strategy.[1] Intramolecular hydroaminations can provide saturated or unsaturated nitrogen-containing heterocycles from simple precursors, and stereoselective variants are emerging to access enantioenriched products.[2]

Various approaches have been used to overcome the high activation energy arising from a destabilizing interaction between the electron-rich nitrogen atom and the C−C π-bond.[1] Catalytic methodologies requiring the use of Brønsted or Lewis acids,[3] strong bases,[4] or transition-metal complexes (actinides, lanthanides, early or late transition metals)[5−7] have resulted in the formation of a variety of heterocyclic ring systems. Reactions of alkynes are generally quite versatile, but cyclizations of alkene precursors are often limited to specific ring systems. Even if alkene hydroamination is more challenging than alkyne hydroamination, the formation of five-membered ring systems is generally facile with terminal alkenes.

In contrast, related cyclizations of internal alkenes or homologues leading to six-membered ring systems are usually challenging. To achieve such cyclizations, substrates benefiting from a conformational bias (e.g., the Thorpe−Ingold effect) or terminal alkenes are typically reported, thus suggesting limited synthetic applicability in unbiased systems.[8] Indeed, apparently minor changes in substrate structure can dramatically change the potential energy surface of intramolecular hydroaminations. Changing the ring size can significantly impact the nature of the transition state: for example, a *syn*-amino metalation event can require an unfavorable *boat* conformation in six-membered ring systems, in contrast to a favorable *envelope* conformation in five-membered ring systems.[9] Changing the alkene substitution pattern also inherently impacts the stability and reactivity of reaction intermediates: for example, 2° metal−alkyl intermediates are formed upon insertion onto internal alkenes, while 1° metal−alkyl intermediates are formed from terminal alkenes. Such considerations likely account for the limited number of examples of intramolecular *alkene* hydroaminations forming complex six-membered ring systems. Herein we report a systematic study of such difficult cyclizations performed in the context of alkaloid synthesis and describe improved conditions that led to syntheses of 2-*epi*-pumiliotoxin C, coniine, *N*-norreticuline, and desbromoarborescidine A.

Known for over 35 years,[10,11] Cope-type hydroamination has become a convenient approach for the formation of saturated nitrogen heterocycles (Scheme 1).[12] Cyclization of hydroxylamines onto both alkenes and alkynes is possible under mild conditions: reactions occur below room temperature in favorable systems. This thermal hydroamination reactivity occurs via a concerted, five-membered transition state (i.e., the reverse of a Cope elimination[13]) under neutral conditions that are inherently compatible with a variety of functional groups.[14] The general features of Cope-type cyclizations of

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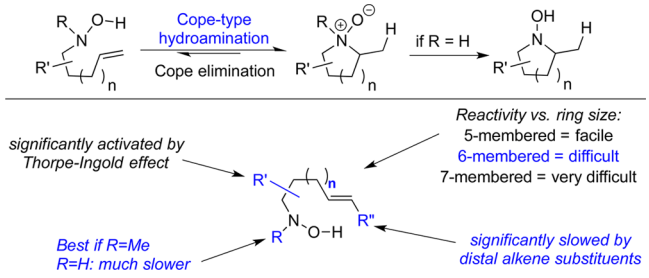
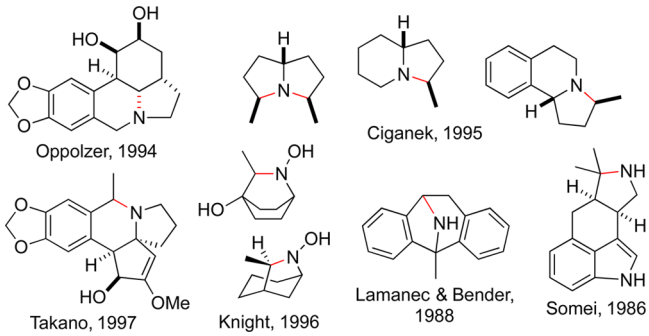
Scheme 1. General Trends of Intramolecular Cope-Type Hydroaminations[12]



alkenes are presented in Scheme 1, which also outlines some of the limitations associated with this approach.[12]

As shown in Scheme 1, the formation of six-membered ring systems and cyclizations on internal alkenes are also typically more challenging Cope-type hydroaminations. Much synthetic work has been performed to understand and demonstrate the applicability of this reactivity. The scope of the reaction has been broadened over the years, and while the cyclization of five-membered rings remains the most encountered intramolecular transformation, several challenging intramolecular Cope-type cyclizations have been used to form complex nitrogen heterocycles (Scheme 2).[12,15] Recently, Krenske, Holmes, and Houk have also provided a wealth of computational insight on these cyclizations.[16]

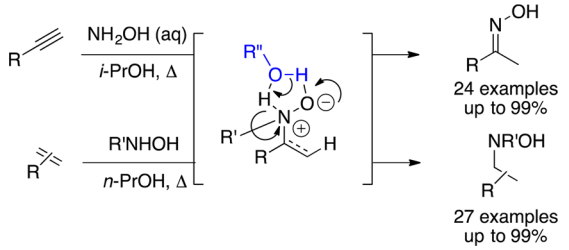
Scheme 2. Examples of Complex Heterocycles Synthesized Using Intramolecular Cope-Type Hydroamination of Alkenes[17]



Over the past few years, our group has reinvestigated Cope-type hydroamination reactions.[18] Our early efforts to develop intermolecular reactions unveiled remarkable solvent effects: alcoholic solvents are *necessary* for intermolecular alkene hydroaminations to occur in high yields.[19] We also provided computational evidence for stabilization of the *N*-oxide intermediate and for a solvent-assisted proton transfer process leading to the hydroamination products (Scheme 3).[19b] In subsequent studies, *t*-BuOH emerged as a superior solvent for the thermolysis of primary *N*-alkylhydroxylamines.[20] Under these conditions, various substrates, substitution patterns, electronic biases, and functional groups are well-tolerated. The efficiency achievable under the conditions optimized for intermolecular reactivity suggested that difficult cyclizations and thus novel heterocyclic syntheses could be enabled under improved conditions.

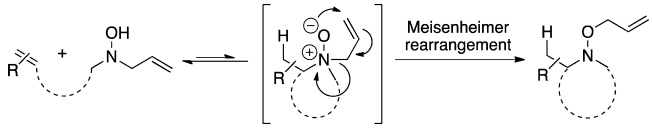
In parallel to this work, a novel reaction sequence was developed to overcome thermal instability associated with primary *N*-alkylhydroxylamines. We were first drawn toward

Scheme 3. Intermolecular Cope-Type Hydroamination in the Presence of Alcoholic Solvents



reaction sequences to address the challenging issue of thermoneutrality associated with (intermolecular) alkene hydroamination.[21] Indeed, reaction sequences in which a second step follows a hydroamination event allow the formation of more stable "hydroamination" products and thus minimize the possible reversibility that could result in synthetic limitations. The Cope-type hydroamination/Meisenheimer rearrangement (CHMR) sequence (Scheme 4) was thus

Scheme 4. Cope-Type Hydroamination/Meisenheimer Rearrangement Sequence



developed, building on the propensity of the *N*-oxide intermediate (formed via a Cope-type hydroamination) to engage in a [2,3]-Meisenheimer rearrangement.[22] This sequence provides access to neutral hydroamination products that are more stable than their *N*-oxide intermediates and also obviates the need for a proton transfer step. Another attractive feature of this approach is that it benefits from the improved reactivity reported for *N*-substituted hydroxylamines in cyclization reactions (N–Me vs N–H, Scheme 1).[12] In addition, *N*,*N*-disubstituted hydroxylamine reagents proved in our hands to be more thermally stable than the parent N–H primary hydroxylamines.

The scope of the Cope-type hydroamination methodologies illustrated in Schemes 3 and 4 had been explored mostly in intermolecular systems. Given that the majority of published Cope-type cyclizations formed five-membered ring systems,[12,15] we embarked on a systematic study to evaluate our two methodologies in the context of difficult cyclizations forming six-membered ring systems and compare them with established Cope-type cyclization protocols. At the center of these efforts was our desire to explore the reported beneficial effect of nitrogen substitution (R = Me ≫ R = H; Scheme 1),[12] since we felt that this reactivity trend could be *different* in the presence of alcohols as solvents. Herein we present our results in the context of the syntheses of four alkaloids: 2-*epi*-pumiliotoxin C, coniine, *N*-norreticuline, and desbromoarborescidine A. Collectively, our results provide two different approaches and improved reaction conditions to perform challenging intramolecular alkene hydroamination reactions.

RESULTS AND DISCUSSION

Building on encouraging results obtained in intermolecular Cope-type hydroamination reactions, we initiated synthetic studies on the pumiliotoxin C system.[23] Pumiliotoxin C is a

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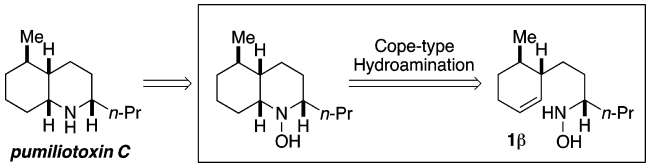
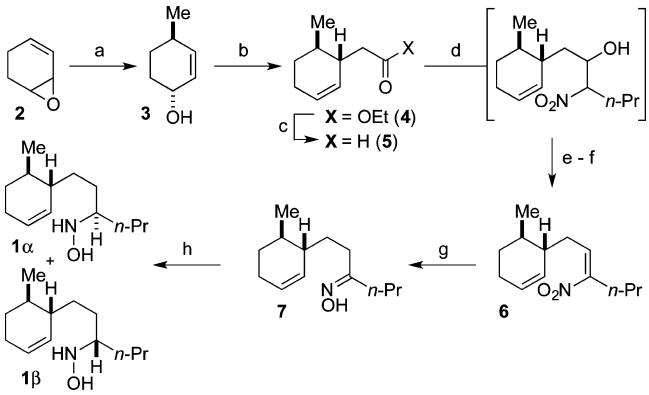
potent toxin found in the skin secretions of the poison Dendrobatidae frogs and is structurally characterized by a *cis*-decahydroquinoline backbone with minimal substitution.[24] This natural product and ring system has also been a popular synthetic target, and several epimeric structures are also present in the alkaloid literature.[25] Our retrosynthetic analysis of pumiliotoxin C, illustrated in Scheme 5, features a difficult intramolecular alkene hydroamination step.

Scheme 5. Retrosynthetic Analysis of Pumiliotoxin C Featuring an Alkene Hydroamination Reaction



It was speculated that pumiliotoxin C could be obtained via an intramolecular Cope-type hydroamination to close the cis junction of the decalin under kinetic control, followed by reduction to provide the desired alkaloid. This approach could be readily tested since it required a cyclization precursor of moderate complexity (**1**). Substrate **1** was thus synthesized in eight steps from 3,4-epoxy-1-cyclohexene (Scheme 6). First,

Scheme 6. Pumiliotoxin C System: Synthesis of the Cyclization Precursor[a]

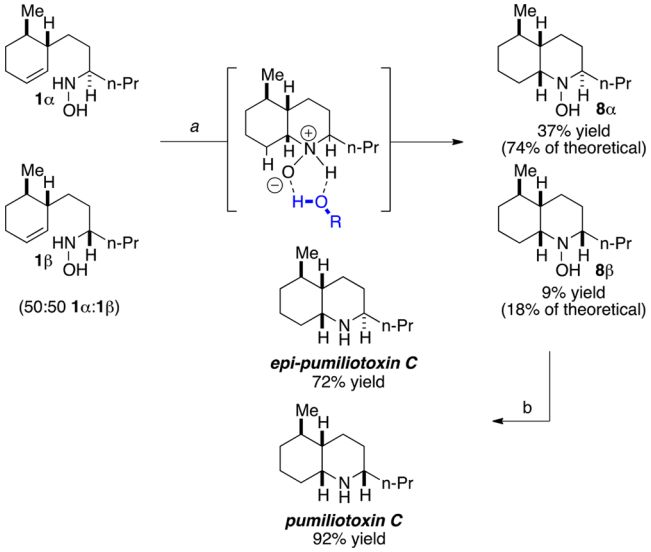


[a]Reagents and conditions: (a) MeLi, CuCN, Et_2O, −78 °C, 88%. (b) $MeC(OEt)_3$, *o*-$O_2NC_6H_4OH$ (cat.), 170 °C, 74%. (c) DIBAL, CH_2Cl_2, −78 °C, 77% (95% brsm). (d) 1-Nitrobutane, KO*t*-Bu, THF/*t*-BuOH (1:1), 0 °C to RT, 78%. (e) Ac_2O, DMAP, Et_2O, RT. (f) K_2CO_3, Et_2O, 35 °C, >99%, two steps. (g) Zn, AcOH, THF, RT, 70%. (h) $NaBH_3CN$, HCl, MeOH, 95%.

cuprate-mediated opening of conjugated epoxide **2** provided the allylic alcohol **3** necessary for the following Johnson orthoester Claisen rearrangement.[26,27] With the key diastereomeric relationship installed, reduction afforded aldehyde **5**, and installation of the complete carbon backbone was performed using an approach based on the Henry reaction.[28] Zinc reduction of nitroalkene **6** afforded oxime **7**,[29] which was reduced upon treatment with $NaCNBH_3$ under acidic conditions to afford two hydroxylamine epimers of the cyclization precursor (**1*α*** and **1*β***).

The use of the Cope-type hydroamination conditions previously reported by Oppolzer (benzene, 180 °C, sealed tube) did not yield any of the desired cyclization product.[14b] However, in agreement with the strong solvent effects observed for intermolecular variants of the reaction (vide supra),[19,20] we explored the use of alcohols as solvents. Gratifyingly, the use of an *n*-PrOH/H_2O solvent mixture allowed the cyclization of both epimers in yields of 37% (**1*α*** → **8*α***) and 9% (**1*β*** → **8*β***) (Scheme 7). Since this reaction was performed on a 50:50

Scheme 7. Pumiliotoxin C System: Key Cope-Type Hydroamination and Final Step[a]



[a]Reagents and conditions: (a) *n*-PrOH/H_2O, *μ*W, 180 °C. (b) Zn, AcOH.

mixture of epimers, this result indicates that the cyclization of **1*α*** was quite efficient despite the forcing conditions (74% of the theoretical yield). The epimeric products were separated and then then independently subjected to Zn/AcOH reduction conditions to effect cleavage of the N−O bond, providing 2-*epi*-pumiliotoxin C (**9**, from **8*α***) and pumiliotoxin C (from **8*β***). Comparison with literature data allowed unambiguous assignation of each product, consequently allowing rationalization of the stereochemical outcome of the key hydroamination step.

The faster cyclization observed for epimer **1*α*** under the Cope-type hydroamination conditions suggests a more stable transition state for the cyclization of **1*α*** relative to **1*β***. This observation is consistent with a boat conformation for the six-membered ring system being formed in the Cope-type hydroamination transition state. Indeed, in the cyclization of **1*α*** the *n*-propyl substituent is in a pseudoequatorial position (R = H, Figure 1), whereas for epimer **1*β*** it must adopt a disfavored pseudoaxial orientation.[23] Support for this hypothesis was recently provided in the computational work of Krenske, Holmes, and Houk,[16] which showed that cyclizations of six-membered rings occur via a boat conformation. Indeed,

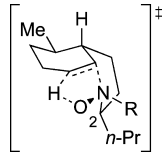


Figure 1. 2-*epi*-Pumiliotoxin C: Proposed boat Cope-type hydroamination TS.

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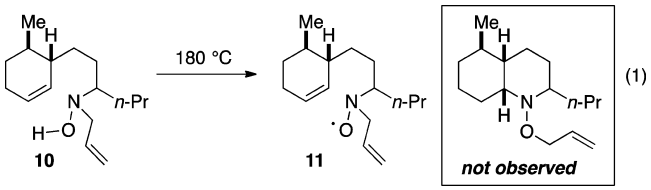
this allows the required planar orientation between the alkene and hydroxylamine functionalities during the hydroamination event.

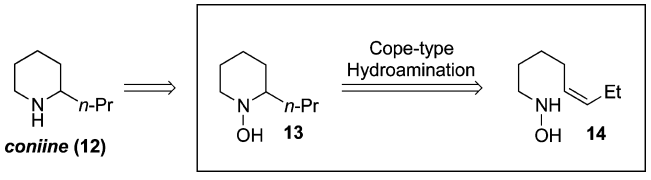
These adapted protic reaction conditions allowed for a difficult intramolecular Cope-type hydroamination of unprecedented complexity. In contrast, the attempted cyclization of precursor **10** using the CHMR sequence did not provide any of the desired product, even under forcing reaction conditions (eq 1). This failure to cyclize is consistent with steric destabilization



associated with the nitrogen substituent being eclipsed with the *n*-Pr side chain in the proposed tricyclic transition-state structure (R = allyl, Figure 1). The only product that could be isolated was nitroxide radical **11**, which was likely formed via reaction with adventitious oxygen at high temperature.[30] Nitroxide **11** could be purified by silica gel chromatography and showed ^{1}H and ^{13}C NMR spectral data nearly identical to those of hydroxylamine **10**. However, an OH stretch was not present in the IR spectrum, and nitroxide **11** was significantly more polar (TLC analysis). Further support for the structure of **11** was acquired by electron paramagnetic resonance spectroscopy (see the Supporting Information for the EPR spectrum).

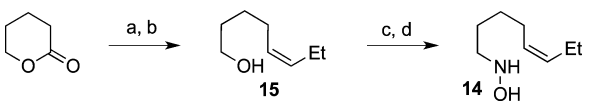
Coniine was then selected for further development on the basis of the general features of the intramolecular Cope-type hydroamination reactivity of alkenes. It presented itself as the ideal target for the optimization of a difficult six-membered-ring cyclization, as the requisite precursor would combine all of the known challenges to this reactivity (see Scheme 1): N–H substitution, cyclization to form a six-membered ring system, and the presence of an alkyl substituent at the distal position of the alkene. In addition, it called for the synthesis of a simple cyclization precursor, as shown in Scheme 8.[31,32]

Scheme 8. Retrosynthetic Analysis of Coniine Featuring an Alkene Hydroamination Reaction



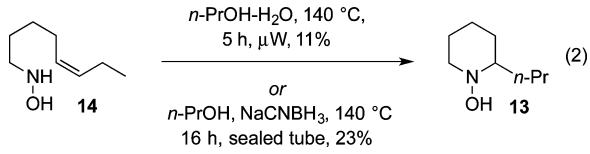
Preparation of the coniine cyclization precursor was accomplished in four steps (Scheme 9). A one-pot DIBAL reduction/Wittig olefination provided alcohol **15** in 74% yield, and the cis and trans isomers (*Z*:*E* = 7:1) were separated by column chromatography over $AgNO_3$-impregnated silica gel.[33] A Mitsunobu reaction using BocNHOBoc was then performed on **15** to introduce the hydroxylamine functionality,[34] and subsequent deprotection using TFA afforded cyclization precursor **14**.

Scheme 9. Coniine: Formation of the Cyclization Precursor[a]



[a]Reagents and conditions: (a, b) DIBAL-H, toluene, −60 °C, 6 h; then *n*-PrPPh$_3$Br, *n*-BuLi, THF, reflux, 1 h, 74% (*Z*:*E* = 7:1). (c) BocNHOBoc, PPh$_3$, DIAD, THF, 0 °C, 1 h, 83%. (d) TFA/CH_2Cl_2, 30 min, quant.

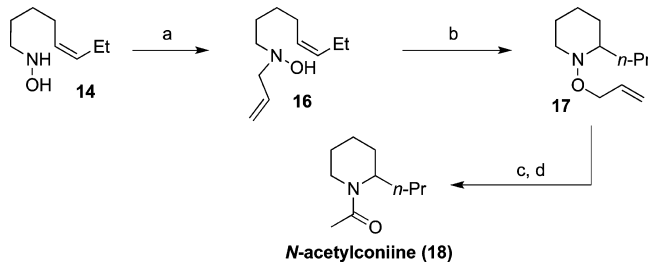
Lacking a Thorpe–Ingold effect and possessing distal alkene substitution, substrate **14** failed to cyclize under standard literature conditions, and decomposition of the hydroxylamine occurred upon heating.[14] With the conditions developed for the pumiliotoxin C system, the cyclization precursor was heated using microwave irradiation at 140 °C in *n*-propanol/H_2O. Unfortunately, only an 11% yield of the desired product was isolated (eq 2). Sodium cyanoborohydride was added to



increase the yield of the cyclization, as a beneficial effect of this additive has been observed in intermolecular Cope-type hydroamination reactions.[19a] This additive allowed the formation of coniine hydroxylamine (**13**) in 23% yield, a 2-fold increase from the original microwave cyclization attempts. In contrast to the previous system, coniine precursor **14** is a terminal primary hydroxylamine, whereas the pumiliotoxin precursors **1** are internal hydroxylamines (i.e., branching is present on the carbon). As also observed in our intermolecular alkene hydroamination work,[19] terminal primary hydroxylamines are more sensitive under thermolysis conditions. Despite considerable experimentation, degradation and dimerization[35] were the main outcomes when coniine precursor **14** was submitted to a variety of reaction conditions.

As discussed before, we speculated that reaction sequences of *N*,*N*-dialkylhydroxylamines such as the CHMR cascade could be useful for challenging cyclizations because of the increased stability of hydroxylamine precursors and a more favorable thermodynamic profile. The allylation of hydroxylamine **14** was therefore accomplished using potassium carbonate and allyl bromide in THF, affording the desired product **16** in 68% yield (Scheme 10). With the allylated precursor in hand, the cyclization was attempted under various conditions. No significant solvent effect was gathered from the use of protic

Scheme 10. Coniine: Optimized CHMR Sequence and Final Step[a]



[a]Reagents and conditions: (a) Allyl-Br, K_2CO_3, THF (0.25 M), RT, 4 h, 68%. (b) H_2O (10 equiv), benzene (0.01 M), 150 °C, 16 h, sealed tube, 42% (+15% SM). (c) Zn (dust), 10 M AcOH, 55 °C, 4 h. (d) Ac_2O, pyridine, RT, 16 h, 10%.

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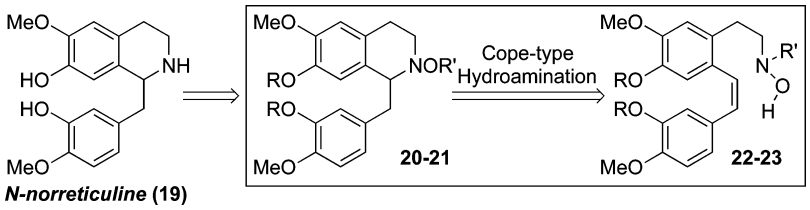
Scheme 11. Retrosynthetic Analysis of *N*-Norreticuline Featuring an Alkene Hydroamination Reaction



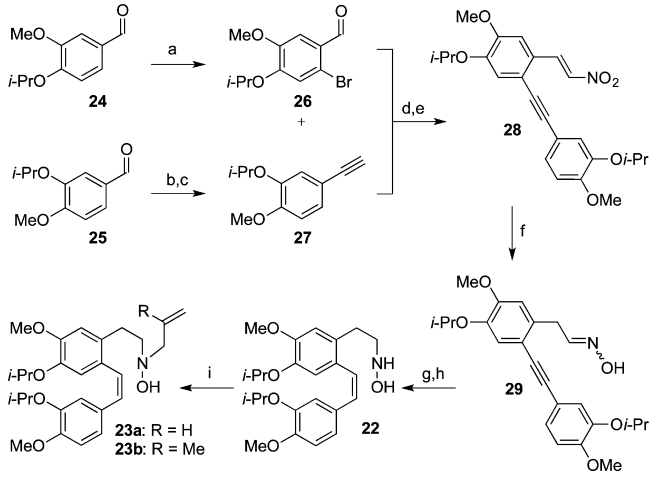
solvents, as could be expected since no proton transfer step was necessary. The highest yield was obtained in deoxygenated nonpolar solvents such as benzene. The addition of water to the system did not improve the reaction yield but helped prevent degradation of the starting material. Diluted reactions proved more efficient, as the main side reactions were dimerization and deallylation of the cyclized product.[36] Under improved conditions, a modest but reliable 42% yield could be isolated, along with 15% of unreacted starting material **16**. With the cyclized product in hand, the synthesis of coniine was completed upon cleavage of N−O bond using zinc dust in a solution of acetic acid.[37] Because of the toxicity associated with coniine, this reaction was only performed on a small scale, and the product obtained was then quickly reacted with acetic anhydride in pyridine to successfully afford the protected *N*-acetyl-(±)-coniine **18** in an unoptimized 10% yield over two steps.[38]

The CHMR sequence was required for the synthesis of coniine as it capitalized on more robust starting materials and more stable hydroamination products. Given the success of this challenging cyclization, we felt that more complex synthetic targets were now within reach. We selected *N*-norreticuline for further exploration of difficult cyclizations. Part of the family of benzyltetrahydroisoquinolines, reticuline is an intermediate in the biosynthetic pathway of morphinan, aporphine, protoberberine, and pavinan alkaloids.[39] From an alkene hydroamination perspective,[40] we speculated that such cyclization would be slightly more facile because of favorable conformational effects and the activating effect of aromatic groups at the distal alkene position.[14b] Retrosynthetic analysis of *N*-norreticuline (Scheme 11) called for the synthesis of two types of cyclization precursors (**22** and **23**) required for comparison of the two Cope-type hydroamination methodologies.

The synthesis of the cyclization precursors from aldehydes **24** and **25** is shown in Scheme 12. Bromination of protected vanillin derivative **24** afforded the Sonogashira precursor **26** in good yield.[41] A Corey−Fuchs reaction sequence was performed on protected *iso*-vanillin derivative **25**, affording alkyne **27** in 80% yield.[42] The two fragments were then combined using a Sonogashira reaction to provide the disubstituted alkyne (not shown).[43] A modified Henry reaction sequence then proceeded smoothly to provide nitroalkene **28**, and tin-mediated reduction afforded oxime **29**.[44] With the desired structural elements in place, partial hydrogenation of the alkyne was effected with Lindlar's catalyst in the presence of a sacrificial alkene, providing the *cis*-alkene (**30**, not shown) in 87% yield. The oxime was then reduced with sodium cyanoborohydride to give the somewhat labile hydroxylamine **22**, which was rapidly allylated or methallylated to provide the cyclization precursors **23a** and **23b**.

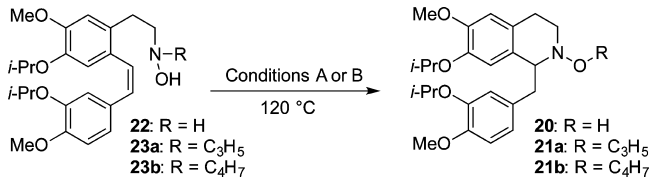
We then tested the key hydroamination step, and the results are shown in Table 1. In agreement with our previous results, the attempted cyclization of **22** under literature conditions

Scheme 12. *N*-Norreticuline: Synthesis of the Cyclization Precursors[a]



[a]Reagents and conditions: (a) Br_2, MeOH, 0 °C, 2 h, 76%. (b) PPh_3, CBr_4, Zn (dust), CH_2Cl_2, RT, 1 h, quant. (c) *n*-BuLi, THF, −78 °C, 2 h, 80%. (d) $PdCl_2(PPh_3)_2$, CuI, Et_3N, RT, 24 h, 87%. (e) NH_4OAc, $MeNO_2$, AcOH, 100 °C, 4 h, 82%. (f) $SnCl_2{\cdot}H_2O$, EtOAc, RT, 10 h, 59%. (g) Lindlar catalyst, H_2 (1 atm), EtOAc/1-hexene (1:1), 5 h, 87%. (h) $NaCNBH_3$, pH ∼3, MeOH, RT, 1 h. (i) R = Me: 2-methallyl chloride, DBU, DMF/THF (1:5), reflux, 2 h, 87%; R = H: K_2CO_3, allyl-Br, THF, RT, 4 h, 50%.

Table 1. *N*- Norreticuline: Optimization of the Key Cyclization



entry	substrate	R	conditions[a]	yield (%)
1	**22**	H	A	27
2	**22**	H	A	51[b]
3	**23a**	allyl	B	45
4	**23b**	allyl	B	57
5	**23b**	methallyl	B	54[c]

[a]Conditions A: *n*-PrOH (0.01 M), 120 °C, 16 h, sealed tube. Conditions B: H_2O (10 equiv), benzene (0.01 M), 120 °C, 18−24 h, sealed tube. [b]$NaCNBH_3$ (1 equiv). [c]32% of the *E* isomer of the starting material was also isolated.

(benzene, 120 °C, sealed tube) afforded <7% yield of the desired product.[14] However, in contrast to our previous results, no desired product could be obtained under similar conditions upon heating in *n*-PrOH/H_2O. Thus, we performed the Cope-type cyclizations on the free hydroxylamine **22** simply by heating in *n*-PrOH:[19a] this provided lower yields than those

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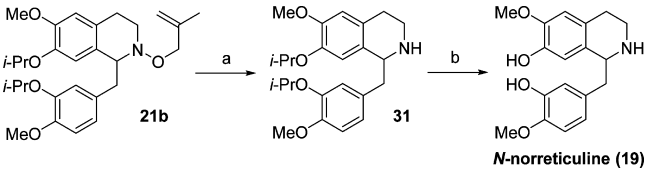
obtained from the CHMR sequence, which is consistent with the trends observed with coniine (Table 1, entries 1 and 2 vs 3−5). Interestingly, we again observed a beneficial effect using $NaCNBH_3$ as an additive (entry 1 vs 2).[19a] The CHMR sequence afforded *N*-norreticuline precursor **21** in modest but reliable yields (entries 3−5). The slightly higher yields observed with methallyl substrate **23b** can be attributed to the increased stability of the methallyl substituent, which is less prone to degradation and side reactions.[45] Interestingly, with this substrate the *E* isomer of the starting material was also recovered in 32% yield after the reaction, confirming that the intramolecular Cope-type hydroamination is reversible under the reaction conditions.[46] It should be noted that all of the sequential reactions were performed at lower temperatures than those used for the synthesis of coniine (120 vs 140 °C), which supports the hypothesis that a slightly beneficial conformational effect is present in the *N*-norreticuline system.

The synthesis of *N*-norreticuline was completed by reduction of the N−O bond followed by partial deprotection of the phenols (Scheme 13).[47] This provided the desired product in a total of 11 steps and 11% yield.[48]

Scheme 13. *N*-Norreticuline: Final Steps[a]



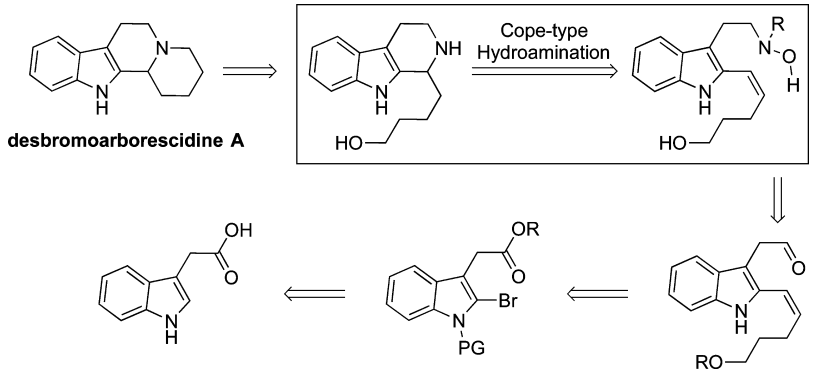
[a]Reagents and conditions: (a) Zn (dust), $AcOH/H_2O$, RT, 5 h, 78%. (b) BCl_3, CH_2Cl_2, −10 °C to RT, > 99%.

Finally, a similar study leading toward the synthesis of desbromoarborescidine A was undertaken. We selected this simple bioactive natural product as a representative member of the family of *β*-carboline alkaloids.[49] The retrosynthetic analysis is shown in Scheme 14. It was planned that the final cyclization to give desbromoarborescidine A would come from a reductive amination, while the key intramolecular hydroamination step would allow the formation of the internal six-membered ring. The alkene necessary for this reaction would be installed via a palladium-catalyzed cross-coupling on a suitable brominated indole.

The synthesis of the hydroamination precursors was performed as shown in Scheme 15. The acid was first esterified in acidified *n*-propanol, after which the indole was protected. Bromination at the 2-position[50,51] allowed the formation of the heteroaryl halide necessary for the ensuing Sonogashira reaction.[52] Hydrogenation using Lindlar's catalyst in the presence of a sacrificial alkene afforded the *cis*-alkene needed for the key step. However, this procedure proved to be scale-sensitive, with little product formation occurring when the reaction was performed on more than 500 mg. Thus, we opted to perform partial hydrogenation of the alkyne using Rosenmund's catalyst, and the desired alkene was obtained in 97% yield.[53] The ester reduction provided alcohol **37** in 77% yield.[54] Oxidation under Parikh−Doering conditions afforded aldehyde **38**.[55] The hydroxylamine moiety was then incorporated via reductive amination, and the desired hydroamination precursor **40** was produced in 61% yield over two steps. Deprotection of the alcohol was also observed during the reduction step, thus obviating the need for an additional deprotection step. Hydroxylamine **40** was also derivatized to afford the allylated and methallylated substrates in 48% and 38% yield, respectively.

As for the previous syntheses, the key cyclization step was attempted on the free hydroxylamine and on its allyl and methallyl derivatives (Table 2). In these experiments, we again observed a beneficial effect of using $NaCNBH_3$ as an additive.[19a] Indeed, the attempted cyclization in *n*-PrOH led only to degradation of the starting material (entry 1), while a modest 40% yield was obtained in the presence of $NaCNBH_3$ (entry 2). Significantly higher yields were obtained using a combination of two changes. First, we performed the reaction using tertiary alcohols as solvents, in agreement with our recent observation that decomposition of linear, primary hydroxylamines is minimized when the heating is performed in *t*-BuOH.[20] Heating was also performed using microwave irradiation, which provided increased yields of the Cope-type hydroamination product over the sealed-tube conditions both in the presence and in the absence of $NaCNBH_3$ (entries 3 and 4 vs 5 and 6). Gratifyingly, the desired product **42** was obtained in 87% yield with the use of *t*-BuOH as the solvent, $NaCNBH_3$ as the additive, and microwave irradiation. The use of structurally similar *t*-amyl alcohol provided similar results under microwave irradiation (entry 6 vs 8). The CHMR sequence also afforded the desired cyclization products reliably but in modest yields. The methallyl substrate **41b** provided the cyclized product **43b** in 53% yield, while the allyl substrate **41a** provided the cyclized product **43a** in 64% yield. Again, we believe this is due to the increased steric hindrance associated with the methallyl substituent, which prevents the Meisenheimer rearrangement from occurring easily. This result is in contrast to what was observed in the synthesis of *N*-

Scheme 14. Desbromoarborescidine A: Retrosynthetic Analysis



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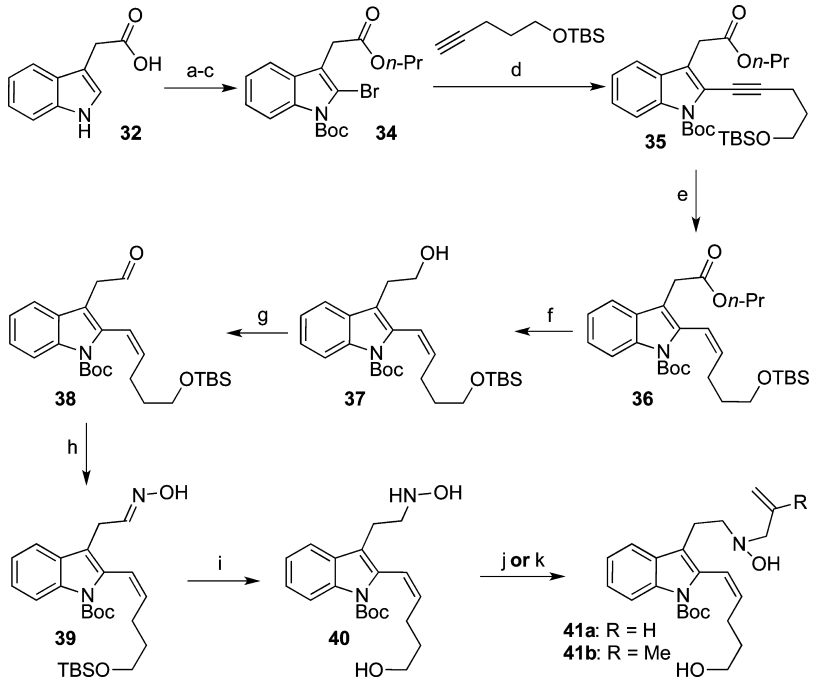
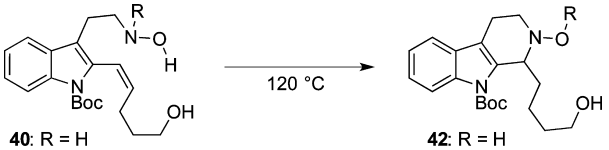
Scheme 15. Desbromoarborescidine A: Synthesis of the Common Aldehyde[a]



[a]Reagents and conditions: (a) HCl (g), *n*-PrOH, reflux, 3 h, quant. (b) NBS, CH_2Cl_2, 0 °C, 2 h. (c) Boc_2O, DMAP, CH_2Cl_2, RT, 0.5 h, 61% over two steps. (d) $Pd(PPh_3)_4$, CuI, *i*-$PrNH_2$, DME, 70 °C, 3.5 h, quant. (e) H_2, $Pd/BaSO_4$, quinoline, EtOH, RT, 7 h, 97%. (f) $LiAlH_4$, THF, 0 °C, 20 min, 77%. (g) SO_3·pyr, Et_3N, DMSO, CH_2Cl_2, 0 °C, 1.5 h, 69%. (h) NH_2OH·HCl, NaOAc, *i*-PrOH, RT, 1.5 h, 88%. (i) $NaCNBH_3$, pH ∼3, MeOH, RT, 1 h, 69%. (j) Allyl-Br, K_2CO_3, THF, RT, 6 h, 48%. (k) 2-Methallyl chloride, DBU, DMF/THF (1:5), reflux, 4 h, 38%

Table 2. Desbromoarborescidine A: Optimization of the Hydroamination Step[a]



entry	substrate	solvent	additive	yield (%)
1	**40**	*n*-PrOH	–	0
2	**40**	*n*-PrOH	$NaCNBH_3$	40
3	**40**	*t*-BuOH	–	48
4	**40**	*t*-BuOH	$NaCNBH_3$	77
5	**40**	*t*-BuOH[b]	–	70
6	**40**	*t*-BuOH[c]	$NaCNBH_3$	87
7	**40**	*t*-AmOH	–	44
8	**40**	*t*-AmOH[b]	$NaCNBH_3$	80
9	**41a**	C_6H_6	H_2O[d]	64
10	**41b**	C_6H_6	H_2O[d]	53

[a]Conditions: additive (1 equiv), solvent (0.01 M), 120 °C, 16 h, sealed tube. [b]μW irradiation, 4 h. [c]μW irradiation, 16 h. [d]10 equiv.

norreticuline, where the methallylated substrate provided the best results.

In order to complete the total synthesis of desbromoarborescidine A, the indole nitrogen was deprotected under acidic conditions (Scheme 16). The N–O bond was then cleaved using zinc dust, affording amino alcohol **43** in 73% yield for the one-pot procedure. The primary alcohol was then activated using $SOCl_2$, and the cyclization was effected under basic conditions, providing desbromoarborescidine A in a total of 13 steps and 8% overall yield.[56,57]

■ CONCLUSION

This study allowed the comparison of novel methodologies in the context of difficult intramolecular hydroaminations forming six-membered ring systems. Cyclizations using Cope-type hydroamination methodologies were achieved as key steps in the syntheses of 2-*epi*-pumiliotoxin C, coniine, *N*-norreticuline, and desbromoarborescidine A. Cyclizations of N–H hydroxylamines in alcoholic solvents using $NaCNBH_3$ as additive or cyclizations of *N*-allyl (or *N*-methallyl) precursors using the Cope-type hydroamination/Meisenheimer rearrangement (CHMR) sequence proved to be reliable synthetic tools for the difficult cyclizations leading to six-membered ring systems. In addition, cyclization of both N–H hydroxylamine and *N*-allyl (or *N*-methallyl) precursors occurred under similar reaction conditions, suggesting that the important beneficial effect of nitrogen substitution previously reported for intramolecular Cope-type hydroaminations depends on the reaction conditions employed. Overall, these studies show that two approaches can be utilized to minimize hydroxylamine decomposition under thermolysis and consequently represent intramolecular alkene hydroamination procedures of broad applicability for the synthesis of alkaloid natural products.

■ EXPERIMENTAL SECTION

General Information. All of the reactions were performed in flame-dried or oven-dried glass round-bottom flasks or 15–48 mL sealed tubes under argon. Purification of the reaction products was carried out by flash column chromatography using silica gel (40–63 μm). Analytical thin-layer chromatography (TLC) was performed on aluminum sheets precoated with silica gel 60 F_{254}, cut to size.

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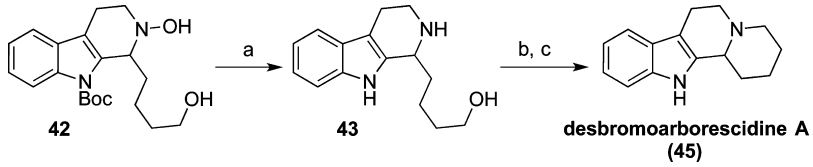
Scheme 16. Desbromoarborescidine A: Final Steps[a]



[a]Reagents and conditions: (a) TFA, CH_2Cl_2, RT, 12 h; then H_2O, Zn (dust), 16 h, 73%. (b) $SOCl_2$, CH_2Cl_2, sealed tube, 40 °C, 3 h. (c) 2 M NaOH, CH_2Cl_2, RT, 16 h, 55% over two steps.

Visualization was accomplished with UV light followed by dipping in a potassium permanganate solution and/or heating, unless otherwise noted. Microwave reactions were run in a Biotage microwave reactor using appropriate glassware and monitoring the temperature with an external sensor.

^{1}H and ^{13}C NMR spectra were recorded on 300 or 400 MHz and 75 or 100 MHz spectrometers, respectively, at ambient temperature. Spectra are reported in parts per million using solvent as the internal standard ($CDCl_3$ at 7.26 ppm or C_6D_6 at 7.15 ppm for ^{1}H NMR and $CDCl_3$ at 77.0 ppm or C_6D_6 at 128.1 ppm for ^{13}C NMR). ^{1}H NMR data are reported as follows: multiplicity (ap = apparent, br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant(s) in hertz. High-resolution mass spectroscopy (HRMS) was performed on a mass spectrometer (magnetic sector) with an electron beam of 70 eV. Infrared (IR) spectra were obtained using neat thin films on a sodium chloride disk. Melting points were determined using a melting point apparatus.

Materials. Dichloromethane, isopropanol, DME, and toluene were dried by distillation over calcium hydride. Tetrahydrofuran and diethyl ether were dried by distillation over sodium/benzophenone ketyl. DMSO and DMF were dried over activated 3 Å molecular sieves. Triethylamine was dried by distillation over calcium hydride, while diisopropylamine and diethylamine were dried by distillation over KOH pellets. Unless otherwise noted, all commercial materials were used without further purification. Most of the procedures for compounds **13**–**16** (coniine) and **19**–**31** (norreticuline) have been reported previously.[22]

3,4-Epoxycyclohexene (2). Prepared according to a literature procedure.[58] To a stirring mixture of 1,3-cyclohexadiene (12.7 g, 15.1 mL, 159 mmol) and anhydrous sodium carbonate (86 g, 635 mmol, 4.0 equiv) in dichloromethane (0.900 M, 174 mL) at −1 °C was added dropwise a commercially available 32% solution of peracetic acid (12.6 g, 35.1 mL, 167 mmol, 1.05 equiv) in dilute acetic acid that had been pretreated with a small amount of sodium acetate. The mixture was stirred at room temperature until a negative peroxide test was obtained with starch–iodide paper. By TLC, the reaction looked done after 3 h. The solid salts were removed by filtration and were washed well with additional solvent. Distillation through a Vigreux column permitted the separation of the solvent from the subsequent collection of the product in an ice-cold collecting flask as a light-yellow liquid (7.7 g, 80 mmol, 50%). TLC: R_f 0.57 (20% EtOAc/hexanes). The ^{1}H NMR spectral data were found to be in good agreement with those in the literature.[59]

(±)-(1*S,4*S**)-4-Methylcyclohex-2-enol (3).** Prepared according to a literature procedure[26] using copper cyanide azeotroped with dry toluene (2 mL of toluene for each 100 mg of copper cyanide) before use in the reaction.[60] *The salt content of the starting methyllithium ether solution was said to be very important. A common ion effect seems to cause the cyanocuprate to be quite insoluble, to the extent that the reaction may not take place at all in some instances when the solutions are not salt-free. The amount of organocuprate could be lowered to 2 equiv without affecting the yield.* Copper cyanide (3.8 g, 42 mmol, 3.0 equiv) was gently flame-dried under vacuum in the reaction flask. It was then suspended in dried ether (0.070 M, 210 mL) under an inert atmosphere before being cooled to −40 °C. An equimolar amount of freshly titrated methyllithium solution (28 mL, 42 mmol, 3.0 equiv, 1.5 M in diethyl ether) was slowly added. The suspension was then stirred at the same temperature until no copper cyanide remained visible at the bottom of the light-beige solution, which took about 1 h. The solution was cooled to −78 °C, and an ether solution (0.40 M, 40 mL) of 3,4-epoxycyclohexene **2** (1.4 g, 14 mmol) was added via cannula. The bright-yellow mixture was allowed to slowly warm to room temperature over 5 h, and then the reaction was quenched with 130 mL of a saturated NH_4Cl solution. After filtration through a Celite pad and washing of the ether layer with a brine solution, the organic phase was dried over sodium sulfate and carefully concentrated in vacuo because of its volatility. The product was isolated as a colorless liquid (1.38 g, 12.3 mmol, 88% yield) after column chromatography (30–40% Et_2O/hexanes). The product was sometimes even used without purification directly in the next step. TLC: R_f 0.14 (20% EtOAc/hexanes). The ^{1}H and ^{13}C NMR spectral data were found to be in good agreement with those in the literature[61] except that an extra peak at 2.72 ppm (s, 1H) was found in the ^{1}H NMR spectrum. The trans stereochemistry was confirmed by comparing the obtained ^{13}C NMR data with those for the trans and cis stereoisomers reported in the literature.[62]

(±)-Ethyl 2-((1*R,6*S**)-6-Methylcyclohex-2-enyl)acetate (4).** Prepared according to a literature procedure.[27] A mixture of allylic alcohol **3** (4.8 g, 42 mmol, 1.0 equiv), 2-nitrophenol (0.55 g, 3.9 mmol, 0.090 equiv), and triethyl orthoacetate (0.100 M, 434 mL) was heated at 170 °C for a period of 6 h with a Dean–Stark apparatus. The Dean–Stark trap was emptied every hour. After completion of the reaction, the triethyl orthoacetate was then distilled through a Vigreux column under vacuum at 65 °C. The distillate was purified by column chromatography (3% ether/hexanes) to give a colorless liquid with a flowery smell (5.7 g, 31 mmol, 74% yield). TLC: R_f 0.71 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.68 (ddd, J = 9.0, 5.1, and 3.4 Hz, 1H), 5.50 (ddd, J = 10.1, 4.2, and 2.1 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.49 (dd, J = 13.5 and 4.0 Hz, 1H), 2.24–2.10 (m, 2H), 2.02–1.96 (m, 2H), 1.72–1.61 (m, 1H), 1.49–1.27 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 0.97 (d, J = 6.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.1, 129.3, 127.4, 60.2, 39.4, 39.3, 33.0, 29.3, 24.2, 19.8, 14.2. IR (film): 3021, 2958, 2926, 2873, 1736, 1459, 1370, 1342, 1270, 1246, 1187, 1152, 1036 cm^{-1}. Exact mass calcd for $C_{11}H_{18}O_2$ $[M]^+$, 182.1307; not found. MS (CI-LRMS) m/z (relative intensity): 95 (100%), 94 (98%), 93 (92%), 79 (90%), 108 (87%), 139 (84%), 109 (76%), 137 (70%), 183 (44%), 182 (33%).

(±)-2-((1*S,6*R**)-6-Methylcyclohex-2-enyl)acetaldehyde (5).** Prepared according to a literature procedure.[63] To a flame-dried flask under an atmosphere of argon was added ester **4** (0.26 g, 1.4 mmol) in dichloromethane (0.15 M, 9.3 mL). The mixture was cooled with an ether/dry ice bath to below −78 °C. After a few minutes of stirring, diisobutyl aluminum hydride (1.0 M in toluene, 1.4 mL, 1.0 equiv) was added along the side of the flask. The reaction mixture was stirred for 1 h, and then the reaction was quenched with dry MeOH (1.4 mL) and a saturated solution of Rochelle salt (5.6 mL). The mixture was diluted with ether, removed from the ice bath, and stirred for 20 min. The solution was filtered over Celite, which was further washed with ether. The organic layer was dried with sodium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography (16% ether/hexanes) gave the aldehyde as a light-yellow oil (0.15 g, 1.1 mmol, 77% yield, 95% brsm). TLC: R_f 0.38 (8% ether/hexanes). The aldehyde was then used for the following reaction.

(±)-1-((1*S,6*R**)-6-Methylcyclohex-2-enyl)-3-nitrohexan-2-ol.** Prepared according to a modified literature procedure[28] but can also be prepared in an aqueous medium.[64] To a flame-dried flask was

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added aldehyde **5** (0.40 g, 2.9 mmol), nitrobutane (0.36 g, 3.5 mmol, 1.5 equiv) in a 1:1 mixture of THF (1.9 M, 1.5 mL), and *tert*-butanol (1.9 M, 1.5 mL). The reaction mixture was cooled to 0 °C, and potassium *tert*-butoxide (0.32 g, 2.9 mmol, 1.0 equiv) was added. The ice bath was removed after 15 min, and the mixture was stirred at room temperature for 2 h. The reaction was quenched with a saturated solution of ammonium chloride, and the mixture was extracted with ether. The combined organic layers were dried with sodium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography (16% ether/hexanes) gave the product as a light-yellow oil (0.546 g, 2.26 mmol, 78% yield; mixture of diastereoisomers). TLC: R_f 0.11 (8% ether/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.78−5.66 (m, 1H), 5.66−5.48 (m, 1H), 4.44 (ddd, J = 14.9, 7.9, and 3.6 Hz, 1H), 4.23−4.10 (m, 1H), 2.42 (dd, J = 18.4 and 4.3 Hz, 1H), 2.21−2.04 (m, 1H), 2.04−1.92 (m, 2H), 1.83−1.59 (m, 3H), 1.54 (t, J = 6.2 Hz, 1H), 1.48−1.23 (m, 4H), 1.03−0.88 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 129.7, 128.7, 128.1, 127.7, 92.6, 92.1, 71.0, 69.8, 39.4, 38.3, 37.6, 37.4, 33.0, 31.8, 30.3, 29.5, 29.4, 28.2, 24.2, 23.4, 19.8, 19.7, 19.3, 13.5, 13.5. IR (film): 3447, 2964, 2922, 2877, 1546, 1455, 1375, 1356 cm^{-1}. HRMS (EI) m/z (relative intensity): 237.9917 (11.8%), 236.9803 (62.2%), 218.9570 (23.6%), 215.0195 (35.5%), 214.9851 (34.8%), 158.9971 (28.6%), 138.1005 (21.1%), 137.0224 (93.1%), 109. 0996 (47.3%), 95.0855 (75.6%).

(±)-(3*S,4*R**)-4-Methyl-3-((*Z*)-3-nitrohex-2-enyl)cyclohex-1-ene (6).** Prepared according to a literature procedure.[28b] A solution of the nitroalcohol (0.16 g, 0.67 mmol) and acetic anhydride (0.075 g, 0.069 mL, 0.73 mmol, 1.1 equiv) in ether (0.15 M, 4.4 mL) was cooled to 0 °C and stirred for a few minutes. DMAP (0.016 g, 0.13 mmol, 0.20 equiv) was added, and the reaction mixture was allowed to stir at room temperature for 2 h. The mixture was diluted with ether, and the reaction was quenched with water. The organic layer was washed sequentially with a saturated solution of sodium bicarbonate and then ammonium chloride. The aqueous layers were back-extracted with ether. The combined organic layers were dried with sodium sulfate, filtered, and concentrated in vacuo. The crude material was used directly for the next reaction.

To the crude nitroacetate was added *t*-BuOH (0.14 M, 4.8 mL) at room temperature followed by potassium carbonate (0.11 g, 0.80 mmol, 1.2 equiv). The reaction mixture was warmed to 35 °C and stirred at that temperature overnight under an argon atmosphere. The reaction was quenched with water, and the mixture was extracted with ether. The combined organic layers were dried with sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (4% ether/hexanes) to afford **6** as a yellow oil (0.15 g, 0.67 mmol, >99% yield). TLC: R_f 0.26 (4% ether/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.12 (dd, J = 8.8 and 6.7 Hz, 1H), 5.76 (ap dq, J = 10.1 and 2.3 Hz, 1H), 5.45 (ap dq, J = 10.0 and 2.1 Hz, 1H), 2.66−2.50 (m, 2H), 2.48−2.32 (m, 1H), 2.31−2.18 (m, 1H), 2.09−1.90 (m, 3H), 1.76−1.62 (m, 1H), 1.61−1.46 (m, 2H), 1.45−1.21 (m, 2H), 1.00 (d, J = 6.3 Hz, 3H), 0.95 (t, J = 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 152.3, 135.1, 128.9, 128.6, 42.1, 32.8, 32.2, 29.7, 28.3, 24.4, 21.2, 20.0, 13.7. IR (film): 3021, 2964, 2926, 2842, 1664, 1520, 1459, 1432, 1379, 1337, 1105, 847, 729 cm^{-1}. HRMS (EI): exact mass calcd for $C_{13}H_{21}NO_2$ $[M]^+$, 223.1572; found, 223.1581.

(±)-1-((1*R,6*S**)-6-Methylcyclohex-2-enyl)hexan-3-one Oxime (7).** Prepared according to a literature procedure.[29] A round-bottom flask was charged with a stir bar, and zinc dust (1.04 g, 15.9 mmol, 9.90 equiv) was added. The flask was flame-dried under argon. 1,2-Dibromoethane (0.035 mL) was added in THF (0.5 mL), and the solution was flamed to boiling three times. Chlorotrimethylsilane (0.032 mL) was added, and the reaction mixture was stirred for approximately 5 min at room temperature. Once the zinc was successfully activated, half of the THF (0.95 M, 17 mL) was added, and the mixture was cooled to 0 °C. A 4 M solution of acetic acid (8.0 mL, 31.9 mmol, 19.8 equiv) was added, and the reaction mixture was stirred for a few more minutes. Nitroalkene **6** (0.359 g, 1.61 mmol) was diluted with the rest of the THF and then added by cannula into the reaction mixture, which was stirred for 5 min. The reaction was quenched slowly with a saturated solution of sodium bicarbonate. The mixture was filtered over Celite, and the aqueous layer was extracted with ethyl acetate. The combined organic layers were dried with sodium sulfate, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (20% ether/hexanes) to afford **7** as a clear oil (0.237 g, 1.13 mmol, 70% yield). TLC: R_f 0.37 and 0.31 (20% EtOAc/hexanes) because of the two oxime stereoisomers. Characterization was done on the mixture of stereoisomers. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.50 (br s, 1H), 5.75−5.66 (m, 1H), 5.60 (ddd, J = 10.1, 4.0, and 1.9 Hz, 0.6 H), 5.54 (ddd, J = 10.1, 4.2, and 2.1 Hz, 0.4H), 2.44−2.06 (m, 4H), 2.01−1.95 (m, 2H), 1.81−1.60 (m, 3H), 1.60−1.38 (m, 4H), 1.38−1.17 (m, 1H), 0.99−0.91 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.1, 162.1, 130.2, 130.0, 127.3, 127.2, 42.4, 41.9, 36.2, 32.2, 32.1, 30.8, 30.0, 29.8, 29.7, 29.6, 29.1, 24.5, 24.5, 24.3, 20.0, 19.6, 19.1, 14.4, 13.9. IR (film): 3231, 3100, 3019, 2959, 2924, 2872, 2842, 1652, 1455, 1435, 1376, 955 cm^{-1}. HRMS (EI): exact mass calcd for $C_{13}H_{23}NO$ $[M]^+$, 209.1780; found, 209.1793.

(±)-*N*-Hydroxy-1-((1*S,6*R**)-6-methylcyclohex-2-enyl)-hexan-3-amine (1).** Prepared according to a literature procedure[14a] and worked up using a known method.[6S] To a solution of oxime **7** (0.053 g, 0.26 mmol) in MeOH (0.078 M, 3.3 mL) was added a crystal of methyl orange (just enough to render a yellow color to the solution). Sodium cyanoborohydride (0.018 g, 0.28 mmol, 1.1 equiv) was then added under an inert atmosphere. The yellow solution was stirred at room temperature, and a HCl/MeOH (1:5) solution was added dropwise so as to keep the solution pink. After the solution had stayed pink for 30 min, the reaction was analyzed by TLC and judged to be complete. The mixture was neutralized with a 25% aqueous NaOH solution and then poured into brine. The suspension was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by flash chromatography (60% ether/hexanes) gave a colorless oil (0.051 g, 0.24 mmol, 95% yield). TLC: R_f 0.08 (20% EtOAc/hexanes). Characterization was performed on a mixture of stereoisomers. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.45 (br s, 2H), 5.66 (ddd, J = 10.0, 5.9, and 3.5 Hz, 1H), 5.56−5.52 (m, 1H), 2.81−2.77 (m, 1H), 1.98−1.97 (m, 2H), 1.74−1.58 (m, 2H), 1.57−1.45 (m, 3H), 1.45−1.21 (m, 7H), 0.95 (d, J = 6.6 Hz, 3H), 0.91 (t, J = 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz): δ 130.5, 130.5, 126.8, 126.8, 61.7, 61.7, 42.4, 42.4, 33.7, 33.4, 32.4, 32.3, 29.8, 29.8, 29.6, 29.6, 28.0, 27.9, 24.4, 24.4, 20.0, 19.1, 19.0, 14.3. IR (film): 3256, 3020, 2959, 2929, 2868, 1652, 1458, 1431, 1378, 686 cm^{-1}. HRMS (EI): exact mass calcd for $C_{13}H_{25}NO$ $[M]^+$, 211.1936; found, 211.1919.

(±)-*N*-Hydroxy-(2*R,4a*S**,5*R**,8a*R**)-decahydro-5-methyl-2-propylquinoline [(±)-*N*-Hydroxy-2-*epi*-pumiliotoxin C (8*α*)] and (±)-*N*-Hydroxy-(2*S**,4a*S**,5*R**,8a*R**)-decahydro-5-methyl-2-propylquinoline [(±)-*N*-Hydroxypumiliotoxin C (8*β*)].** *Because of facile oxidation of the hydroxylamine, great care was taken to eliminate traces of oxygen from the reaction mixture. n-PrOH and H_2O were distilled under argon prior to use.* To a pressure vessel equipped with a magnetic stir bar was added hydroxylamine **1** (0.0955 g, 0.452 mmol), which was then dissolved in a mixture of *n*-PrOH (0.15 M, 3.0 mL) and H_2O (0.081 mL, 4.5 mmol, 10 equiv) under argon. The solution was degassed at 0 °C by bubbling argon for 10 min. The pressure vessel was capped and it was heated in the microwave at 180 °C for 5 h. After the mixture was cooled to room temperature, more H_2O was added, and the mixture was extracted with EtOAc. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography (10−60% Et_2O/hexanes) gave *N*-hydroxy-2-*epi*-pumiliotoxin C (0.036 g, 0.17 mmol, 37% yield) with 20% Et_2O/hexanes as the eluent and *N*-hydroxypumiliotoxin C (0.0089 g, 0.042 mmol, 9.3% yield) with 8% Et_2O/hexanes as the eluent, both as white solids. The unreacted starting hydroxylamine was also found with 60% Et_2O/hexanes as the eluent (0.0389 g, 0.184 mmol, 41% yield) as one stereoisomer.

*Data for **8α**.* TLC: R_f 0.29 (20% EtOAc/hexanes). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.47 (d, J = 9.9 Hz, 1H), 2.75 (t, J = 9.3 Hz, 1H), 2.10−1.10 (m, 17H), 1.04 (d, J = 7.0 Hz, 3H), 0.91 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 61.5, 58.6, 42.0, 35.5, 33.4, 30.4, 27.1, 24.5, 19.9, 19.0, 18.0, 14.5, 14.3. IR (film): 3127, 2955, 2933,

2863, 1464, 1371 cm^{-1}. HRMS (EI): exact mass calcd for $C_{13}H_{25}NO$ $[M]^+$, 211.1936; found, 211.1952.

Data for 8β. TLC: R_f 0.58 (20% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.73 (br s, 1H), 2.47 (t, *J* = 10.0 Hz, 1H), 2.37 (d, *J* = 14.2 Hz, 1H), 2.05−1.58 (m, 6H), 1.57−1.17 (m, 9H), 1.08−0.94 (m, 1H), 0.92 (t, *J* = 7.2 Hz, 3H), 0.81 (d, *J* = 6.5 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 69.0, 67.3, 44.7, 35.9, 35.2, 29.0, 28.5, 26.3, 25.9, 20.8, 19.9, 18.9, 14.4. IR (film): 3412, 3356, 2963, 2952, 2928, 2872, 2859, 2823, 1454, 1443 cm^{-1}. HRMS (EI): exact mass calcd for $C_{13}H_{25}NO$ $[M]^+$, 211.1936; found, 211.1936.

(±)-(2*R,4a*S**,5*R**,8a*R**)-Decahydro-5-methyl-2-propylquinoline [(±)-2-*epi*-Pumiliotoxin C (9)].** Prepared according to a literature procedure.[37] *N*-Hydroxy-*epi*-pumiliotoxin C (0.0145 g, 0.0687 mmol) was dissolved in a 10 M AcOH aqueous solution (0.040 M, 1.7 mL). The mixture was heated to 55 °C, and then zinc dust (0.045 g, 0.69 mmol, 10 equiv) was added with vigorous stirring. After 4 h, TLC analysis revealed complete consumption of the starting material. The reaction mixture was cooled, diluted with 13 mL of H_2O, and basicified to pH 14 by addition of 6 M KOH. The solution was extracted with $CHCl_3$. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated in vacuo. Purification by column chromatography (0−100% EtOAc/$CHCl_3$) gave 2-*epi*-pumiliotoxin C as the free base as a white solid (0.013 g, 0.067 mmol, 72% yield) with 20−100% EtOAc/$CHCl_3$ as the eluent. TLC: R_f 0.06 (10% MeOH/EtOAc). ^1H NMR ($CDCl_3$, 300 MHz): δ 3.12 (dt, *J* = 10.2 and 4.1 Hz, 1H), 2.86−2.73 (m, 1H), 2.28 (br s, 1H), 1.91−1.63 (m, 4H), 1.62−1.46 (m, 4H), 1.46−1.22 (m, 6H), 1.20−1.03 (m, 2H), 0.98 (d, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 50.0, 49.5, 41.7, 38.2, 32.5, 31.2, 28.1, 25.1, 20.4, 19.3, 19.2, 14.2. The ^1H and ^{13}C NMR spectral data were found to be in good agreement with those in the literature.[66]

(±)-2-*epi*-Pumiliotoxin C Hydrochloride Salt (9·HCl). The free amine was converted into its hydrochloride salt by bubbling dry HCl gas for 25 min in a MeOH solution. ^1H NMR ($CDCl_3$, 500 MHz): δ 9.44−9.25 (br m, 1H), 9.23−9.02 (br m, 1H), 3.64−3.53 (m, 1H), 3.27−3.10 (m, 1H), 2.06−1.14 (m, 16H), 1.02 (d, *J* = 7.0 Hz, 3H), 0.93 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 51.3, 51.2, 38.3, 34.1, 31.9, 29.6, 26.9, 23.8, 23.2, 19.6, 18.9, 18.8, 13.8.

(±)-(2*S,4a*S**,5*R**,8a*R**)-Decahydro-5-methyl-2-propylquinoline [(±)-Pumiliotoxin C].** Prepared according to the same literature procedure as described previously for 2-*epi*-pumiliotoxin C.[23] Purification by column chromatography (0−50% EtOAc/$CHCl_3$) gave pumiliotoxin C as the free base as a white solid (0.0035 g, 0.018 mmol, 92% yield) with 0−20% EtOAc/$CHCl_3$ as the eluent. TLC: R_f 0.12 (10% MeOH/EtOAc). ^1H NMR ($CDCl_3$, 300 MHz): δ 2.90−2.85 (m, 1H), 2.62−2.49 (m, 1H), 2.03−1.03 (m, 17H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H). The ^1H NMR spectral data were found to be in good agreement with reported literature data.[67]

***N*-Allyl-*N*-oxyl-1-((1*S*,6*R*)-6-methylcyclohex-2-enyl)hexan-3-amine (11).** A solution of *N*-allylhydroxylamine (0.0276 g, 0.110 mmol, 1.0 equiv) in C_6D_6 (1 mL, 0.1 M) in a sealed tube was degassed by bubbling of argon for 15 min. The mixture was then heated to 150 °C for 9 h. The solvent was evaporated, and purification by column chromatography (20−100% Et_2O/hexanes) gave a colorless oil as the major product (0.011 g, 0.044 mmol, 40% yield; mixture of diastereoisomers). TLC: R_f 0.14 (20% EtOAc/hexanes). ^1H NMR ($CDCl_3$, 300 MHz): δ 5.92 (tdd, *J* = 16.3, 10.2, and 6.1 Hz, 1H), 5.67 (ddd, *J* = 9.4, 5.8, and 3.4 Hz, 1H), 5.54 (ddd, *J* = 10.0, 4.5, and 2.8 Hz, 1H), 5.18 (ddd, *J* = 17.2, 3.1, and 1.6 Hz, 1H), 5.08 (dd, *J* = 10.2 and 1.0 Hz, 1H), 3.24 (ap d, *J* = 6.2 Hz, 2H), 2.59−2.48 (m, 1H), 2.04−1.94 (m, 2H), 1.77−1.14 (m, 12H), 0.97−0.85 (m, 6H) (the ^1H NMR spectrum was contaminated with Et_2O signals since further evaporation led to the appearance of new peaks). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.5, 130.6, 130.6, 127.0, 126.9, 117.2, 56.8, 56.7, 49.1, 42.4, 42.4, 35.4, 35.2, 32.4, 32.3, 29.9, 29.2, 29.0, 24.5, 20.1, 18.9, 18.7, 14.3. IR (film): 3081, 3020, 2955, 2925, 2872, 1735, 1640, 1458, 990, 914 cm^{-1}.

***N*-Hydroxyconiine (13).** To a sealed tube equipped with a magnetic stir bar were added (*Z*)-*N*-hydroxyoct-5-en-1-amine (0.10 g, 0.72 mmol) in *n*-propanol (60 mL) and sodium cyanoborohydride (0.044 g, 0.72 mmol). Argon was bubbled in the solution for 10 min. The tube was sealed and heated at 140 °C for 16 h, after which the reaction mixture was cooled to room temperature, dissolved in EtOAc, and then washed twice with brine. The organic extract was then dried on Na_2SO_4 and concentrated in vacuo to give a residue. The crude mixture was purified by silica gel column chromatography (80% EtOAc in hexanes) to yield the desired compound as a colorless oil (0.023 g, 23%). TLC: R_f 0.26 (80% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 3.32 (ap d, *J* = 11.3 Hz, 1H), 2.49 (ap t, *J* = 13.0 Hz, 1H), 2.29−2.22 (m, 1H), 1.96−1.82 (m, 2H), 1.74−1.54 (m, 3H), 1.44−1.10 (m, 5H), 0.92 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 67.5, 59.7, 35.5, 30.9, 25.8, 23.8, 18.9, 14.4. IR (film): 3203, 2937, 2860, 1447, 1040 cm^{-1}. HRMS (EI): exact mass calcd for $C_8H_{17}NO$ $[M]^+$, 143.1310 (100%), 144.13437 (9%); found, 144.1342.

1-(Allyloxy)-2-propylpiperidine (17). In a sealed tube equipped with a magnetic stir bar, hydroxylamine **16** (0.050 g, 0.27 mmol) was dissolved in benzene (2.7 mL). Argon was bubbled in the solution for 10 min. The tube was sealed and heated at 150 °C for 16 h. The reaction mixture was cooled to room temperature and then directly purified by flash chromatography on silica gel with a gradient of 1% to 10% diethyl ether in hexanes to yield the desired compound as a yellow oil (0.021 g, 42%). TLC: R_f 0.78 (50% EtOAc/hexanes). ^1H NMR (300 MHz, $CDCl_3$): δ 5.97−5.89 (tdd, *J* = 16.5, 10.4, and 6.1 Hz, 1H), 5.27 (dd, *J* = 15.8 and 1.5 Hz, 1H), 5.16 (ap d, *J* = 10.3 Hz, 1H), 4.25−4.15 (m, 2H), 3.36 (d, *J* = 9.9 Hz, 1H), 2.41 (ap t, *J* = 10.4 Hz, 1H), 2.31 (ap t, *J* = 6.4 Hz, 1H), 1.87−1.78 (m, 2H), 1.71−1.68 (m, 1H), 1.61−1.53 (m, 2H), 1.42−1.36 (m, 1H), 1.34−1.27 (m, 2H), 1.25−1.14 (m, 2H), 0.91 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.6, 117.9, 74.4, 67.3, 57.4, 35.7, 31.2, 26.2, 24.3, 19.1, 14.9. IR (film): 3085, 2936, 2859, 2828, 1648, 1443, 1036, 995, 921 cm^{-1}. HRMS (EI): exact mass calcd for $C_{11}H_{21}NO$ $[M]^+$, 183.1623; found, 183.1621.

***N*-Hydroxy-1-(3-isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline (20).** In an oven-dried sealed tube equipped with a magnetic stir bar, the primary hydroxylamine (crude, 0.14 mmol) and $NaCNBH_3$ (0.0085 g, 0.14 mmol) were dissolved in *n*-PrOH (14 mL). The reaction mixture was purged with argon for 15 min through a septum. The septum was quickly replaced by a Teflon screw cap, and the reaction vessel was sealed. The reaction mixture was heated at 120 °C for 16 h, cooled, transferred to a separate round-bottomed flask, and rinsed three times with additional n-PrOH, and the solvent was evaporated. The crude residue was purified by silica column chromatography with an eluent of 50% EtOAc in hexanes, affording a yellow oil (0.029 g, 51%). TLC: R_f 0.72 (70% EtOAc/hexanes). ^1H NMR (400 MHz, C_6D_6): δ 6.94 (d, *J* = 2.0 Hz, 1H), 6.81 (dd, *J* = 8.1 and 1.9 Hz, 1H), 6.63 (s, 1H), 6.61 (d, *J* = 8.2 Hz, 1H), 6.38 (s, 1H), 4.37−4.31 (m, 2H), 4.27−4.20 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.34−3.28 (m, 2H), 3.15−3.06 (m, 2H), 2.78 (ddd, *J* = 12.2, 5.6, and 5.6 Hz, 1H), 2.67 (ddd, *J* = 16.4, 6.1, and 6.1 Hz, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.19 (d, *J* = 6.0 Hz, 3H), 1.17 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (100 MHz, C_6D_6): δ 150.1, 150.0, 148.0, 146.3, 132.8, 129.5, 122.81, 118.9, 116.4, 113.0, 112.6, 71.5, 71.3, 68.7, 55.7, 55.5, 51.9, 26.6, 22.4, 22.4, 22.3, 22.1. IR (film): 2979, 2934, 2842, 1607, 1512, 1445, 1261, 1235, 1109, 1033, 934, 858, 813, 771 cm^{-1}. HRMS (EI): exact mass calcd for $C_{13}H_{18}NO_3$ [M − 3-isopropoxy-4-methoxybenzyl]$^+$, 236.1287; found, 236.1268.

(*Z*)-*N*-(2-(3-Isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxyprop-2-en-1-amine (23a). To a flame-dried round-bottom flask equipped with a magnetic stir bar was added (*Z*)-2-[2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenyl]-*N*-hydroxyethanamine (0.042 g, 0.10 mmol), which was dissolved in acetonitrile (0.5 mL). Potassium carbonate (0.042 g, 0.30 mmol) and distilled allyl bromide (0.026 mL, 0.30 mmol) were subsequently added, and the solution was purged with argon. The reaction mixture was stirred overnight under argon, diluted with ethyl acetate, filtered (rinsing with ethyl acetate), and concentrated. The resulting crude oil was purified by silica gel chromatography (50% EtOAc/hexanes), which yielded a colorless oil (0.023 g, 50%). TLC: R_f

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0.51 (50% EtOAc/CH_2Cl_2). The unpurified oil was used directly in the next step due to instability.

1-(3-Isopropoxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-7-isopropoxy-6-methoxyisoquinoline-*N*-(2-allyloxide) (21a). In an oven-dried sealed tube equipped with a magnetic stir bar, (*Z*)-*N*-(2-(3-isopropoxy-4-methoxystyryl)-4-isopropoxy-5-methoxyphenethyl)-*N*-hydroxyprop-2-en-1-amine (0.014 g, 0.031 mmol) was dissolved in benzene (3.0 mL). Distilled water (0.005 mL, 0.3 mmol) was added, and the reaction mixture was purged with argon for 15 min through a septum. The septum was quickly replaced by a Teflon screw cap, and the reaction vessel was sealed. The reaction mixture was heated at 120 °C for 16 h, cooled, transferred to a separate round-bottom flask, and rinsed three times with additional benzene, and the solvent was evaporated. The crude residue was purified by silica column chromatography (10−40% EtOAc/hexanes), affording a clear, colorless oil (0.0063 g, 45%). TLC: R_f 0.80 (30% EtOAc/hexanes). ^{1}H NMR (500 MHz, C_6D_6): δ 6.97 (d, J = 1.9 Hz, 1H), 6.83 (dd, J = 8.2 and 2.0 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.59 (s, 1H), 6.40 (s, 1H), 5.97 (tdd, J = 16.3, 10.5, and 5.9 Hz, 1H), 5.20 (dd, J = 17.3 and 1.7 Hz, 1H), 5.03 (dd, J = 10.4 and 1.8 Hz, 1H), 4.50 (t, J = 6.1 Hz, 1H), 4.39−4.32 (m, 1H), 4.31−4.28 (m, 2H), 4.26−4.18 (m, 1H), 3.39 (s, 3H), 3.38 (s, 3H), 3.32−3.27 (m, 2H), 3.20 (ddd, J = 12.0, 5.3, and 5.3 Hz, 1H), 3.06 (dd, J = 14.1 and 6.6 Hz, 1H), 2.95−2.89 (m, 1H), 2.54 (ddd, J = 16.0, 5.1, and 5.1 Hz, 1H), 1.21 (d, J = 6.1 Hz, 3H), 1.20 (d, J = 6.3 Hz, 3H), 1.19 (d, J = 6.5 Hz, 3H), 1.17 (d, J = 6.1 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz): δ 150.1, 149.9, 147.9, 146.3, 135.4, 133.0, 129.6, 126.9, 122.8, 118.9, 117.0, 116.6, 112.8, 112.6, 73.6, 71.4, 71.2, 66.8, 55.6, 55.5, 48.5, 41.0, 26.2, 22.4, 22.4, 22.3, 22.3. IR (film): 2975, 2926, 2830, 1614, 1566, 1512, 1265, 1219, 1139, 1105, 1033, 991, 919, 843 cm^{-1}. Exact mass calcd for $C_{27}H_{37}NO_5$ [M + H], 455.2672; not found. LRMS (electrospray): found 455.6.

Propyl 2-(1*H*-Indol-3-yl)acetate (32a). Prepared following a procedure developed by Jackson.[50] Indole-3-acetic acid (6.00 g, 34.3 mmol) was dissolved in 170 mL of *n*-propanol (distilled over CaH_2) in a dry three-neck flask. HCl gas generated in situ with NaCl and H_2SO_4 was bubbled through the mixture for ca. 20 min until saturation, whereupon the mixture was refluxed at 110 °C for 2.5 h, at which point TLC indicated reaction completion. The solvent was evaporated in vacuo and extracted with ether and sat. $NaHCO_3$. The organic phase was washed with water and then brine, dried over Na_2SO_4, and concentrated in vacuo to afford the crude product as a red-brown oil. The crude product was purified over a short silica gel column with 3:7 EtOAc/hexanes to yield the product (7.44 g, >99%) as a beige solid. TLC: R_f 0.30 (3:7 EtOAc/hexanes). The NMR data are in accordance with literature values.[68]

***tert*-Butyl 2-Bromo-3-(2-oxo-2-propoxyethyl)-1*H*-indole-1-carboxylate (34).** Prepared following a procedure adapted from reports by Feldman.[51] In a dry round-bottom flask flushed with argon was added propyl 2-(1*H*-indol-3-yl)acetate (7.44 g, 34.3 mmol) followed by distilled CH_2Cl_2 (35 mL). The dissolved solution was cooled to 0 °C, and freshly recrystallized *N*-bromosuccinimide (6.12 g, 34.3 mmol) was added in three portions, upon which the color of the solution turned deep purple. The mixture was maintained at 0 °C and stirred for 2 h. TLC indicated reaction completion. The mixture was concentrated in vacuo to yield the crude material as a purple oil, which was filtered through silica gel and concentrated to afford a yellow oil (7.66 g, 25.9 mmol, 86%). The yellow oil was dissolved in distilled CH_2Cl_2 (225 mL). DMAP (5.00 g, 41.2 mmol) was added, followed by Boc_2O (8.95 g, 41.2 mmol). The solution was stirred at room temperature for 30 min, at which point TLC indicated reaction completion. The mixture was added to 30 mL of CH_2Cl_2, and the resulting mixture was extracted with 30 mL of water (2×). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product as a yellow solid. The crude material was purified over silica gel chromatography with 1:9 EtOAc/hexanes to yield the product (8.2 g, 61% over two steps) as a yellow oil. TLC: R_f 0.24 (1:9 EtOAc/hexanes). ^{1}H NMR (300 MHz, acetone-d_6): δ 8.10 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 7.8 Hz, 1H), 7.33−7.27 (m, 1H), 7.23 (td, J = 1.3 and 1.1 Hz, 1H), 4.04 (t, J = 6.6 Hz, 2H), 3.81 (s, 2H), 1.71 (s, 9H), 1.68−1.54 (m, 2H), 0.88 (t, J = 7.4 Hz, 3H). ^{13}C NMR (100 MHz, acetone-d_6): δ 170.4, 149.7, 137.4, 129.7, 125.6, 123.9, 119.6, 117.9, 116.0, 111.4, 86.0, 67.1, 31.9, 28.4, 22.8, 10.7. IR (film): 2974, 2937, 1738, 1449, 1353, 1318, 1155, 745 cm^{-1}. HRMS (EI): exact mass calcd for $C_{18}H_{22}N_1O_4Br$ [M]$^+$, 395.0732; found, 395.0721.

***tert*-Butyldimethyl(pent-4-ynyl-1-oxy)silane.** Prepared following procedures developed by Snider.[69] To a dry flask under an argon atmosphere was added distilled CH_2Cl_2 (5.00 mL) followed by 4-pentyn-1-ol (0.330 mL, 3.57 mmol) and distilled triethylamine (0.696 mL, 17.9 mmol). The solution was cooled to 0 °C and *tert*-butyldimethylsilyl chloride (0.645 g, 4.28 mmol) dissolved in 1.00 mL of distilled CH_2Cl_2 was added to the reaction flask slowly. The solution was warmed to room temperature. The solution gradually turned from yellow to pink over the course of 24 h. The reaction was quenched with a few drops of water, and the reaction mixture was extracted with CH_2Cl_2 (10 mL) and water (10 mL). The aqueous phase was extracted with 1:1 EtOAc/hexanes (2 × 10 mL). The combined organic phases were dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the crude product as a light-yellow oil. The crude material was purified by flash silica gel chromatography with hexanes to yield the product as a clear colorless oil (0.544 g, 78%). TLC: R_f 0.90 (1:9 EtOAc/hexanes). The NMR data were in accordance with literature values.[68]

***tert*-Butyl 2-(5-(*tert*-Butyldimethylsilyloxy)pent-1-ynyl)-3-(2-oxo-2-propoxyethyl)-1*H*-indole-1-carboxylate (35).** Prepared following a procedure adapted from Baran's original report.[52] *tert*-Butyl 2-bromo-3-(2-oxo-2-propoxyethyl)-1*H*-indole-1-carboxylate (3.00 g, 7.57 mmol) and *tert*-butyldimethyl(pent-4-ynyloxy)silane (2.25 g, 11.4 mmol) were dissolved in degassed DME (30.0 mL, distilled over CaH_2) in a dry round-bottom flask charged with argon. Tetrakis(triphenylphosphine)palladium (2.60 g, 2.27 mmol) was added to the solution, and the solution was degassed again with argon. CuI (1.00 g, 5.30 mmol) was subsequently added to the mixture, which was degassed. Degassed isopropylamine (6.45 mL, 75.7 mmol, distilled over NaOH) was added to the mixture, which was again degassed with argon. The reaction flask was equipped with a dry condenser, and the contents were heated to 70 °C for 3.5 h. TLC indicated that the reaction was complete. The brown reaction mixture was cooled to room temperature, added to saturated $NaHCO_3$ (15 mL), and extracted with EtOAc (2 × 25 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated to yield the crude product as a brown oil. Silica gel column chromatography using 0.3% acetone in toluene afforded the product with trace impurities (3.89 g, 100%) as a brown oil. TLC: R_f 0.32 (0.3% acetone in toluene). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.17 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.36−7.21 (m, 2H), 4.03 (t, J = 6.6 Hz, 2H), 3.89−3.80 (m, 4H), 2.65 (t, J = 7.1 Hz, 2H), 1.92−1.81 (m, 2H), 1.69 (s, 9H), 1.67−1.55 (m, 2H), 0.97−0.84 (m, 12H), 0.09 (s, 6H). ^{13}C NMR (100 MHz, acetone-d_6): δ 170.7, 150.1, 136.3, 129.6, 126.2, 123.8, 121.6, 120.9, 120.1, 116.2, 100.5, 84.6, 72.7, 66.8, 62.2, 32.6, 31.4, 28.3, 26.3, 22.7, 18.8, 16.9, 10.6, −5.1. IR (film): 2953, 2930, 2854, 1729, 1455, 1360, 1326, 1254, 1147, 832, 740 cm^{-1}. HRMS (EI): exact mass calcd for $C_{29}H_{43}N_1O_5Si$ [M]$^+$, 513.2911; found, 513.2899.

(*Z*)-*tert*-Butyl 2-(5-(*tert*-Butyldimethylsilyloxy)pent-1-enyl)-3-(2-oxo-2-propoxyethyl)-1*H*-indole-1-carboxylate (36). Prepared following modified versions of procedures developed by Carreira.[53] *tert*-Butyl 2-(5-(*tert*-butyldimethylsilyloxy)pent-1-ynyl)-3-(2-oxo-2-propoxyethyl)-1*H*-indole-1-carboxylate (0.329 g, 0.641 mmol) was dissolved in freshly distilled 1:1 EtOAc/1-hexene (64 mL) in a dry flask under argon. Pd/C (10% w/w) (0.110 g, 30 wt %) was added to the solution, and hydrogen was bubbled through the solvent. The mixture was stirred vigorously for 45 min, whereupon proton NMR indicated that the reaction was complete. The mixture was filtered through Celite and washed with EtOAc (2 × 10 mL). The solution was concentrated in vacuo to afford the product as a clear light-yellow oil (0.320 g, 97%) with no further purification. TLC: R_f 0.68 (1:9 EtOAc/hexanes). ^{1}H NMR (100 MHz, $CDCl_3$): δ 8.14 (d, J = 8.3 Hz, 1H), 7.47 (d, J = 7.5 Hz, 1H), 7.35−7.18 (m, 2H), 6.45 (d, J = 11.3 Hz, 1H), 5.84 (dt, J = 7.4 and 11.3 Hz, 1H), 4.03 (t, J = 6.8 Hz, 2H), 3.60 (s, 2H), 3.53 (t, J = 6.6 Hz, 2H), 2.12−1.97 (m, 2H), 1.72−1.50 (m, 13H), 0.88 (t, J = 7.4 Hz, 3H), 0.80 (s, 9H), −0.03 (s, 6H).

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^{13}C NMR (100 MHz, $CDCl_3$): δ 171.2, 150.3, 136.1, 133.9, 133.4, 129.7, 124.1, 122.5, 121.4, 118.7, 115.7, 115.6, 83.7, 62.6, 62.1, 60.4, 32.4, 28.3, 25.8, 25.7, 21.1, 18.2, 14.2, 5.3. IR (film): 2930, 2857, 1731, 1459, 1359, 1137, 1117, 837, 775, 745 cm^{-1}. HRMS (EI): exact mass calcd for $C_{29}H_{45}N_1O_3Si$ $[M]^+$, 515.3067; found, 515.3015.

(*Z*)-*tert*-Butyl 2-(5-(*tert*-Butyldimethylsilyloxy)pent-1-enyl)-3-(2-hydroxyethyl)-1*H*-indole-1-carboxylate (37). Prepared following a procedure adapted from Iwabuchi's original report.[54] (*Z*)-*tert*-Butyl 2-(5-(*tert*-butyldimethylsilyloxy)pent-1-enyl)-3-(2-oxo-2-propoxyethyl)-1*H*-indole-1-carboxylate (0.35 g, 0.68 mmol) was dissolved in distilled THF (1.5 mL). The solution was cooled to 0 °C, and $LiAlH_4$ (0.031 g, 0.81 mmol) was added. The solution was stirred at 0 °C for 15 min. TLC indicated completion of the reaction. Water was added, and the solution was stirred at room temperature for 10 min. Filtration over Celite followed by concentration afforded the crude product, which was purified by flash chromatography (25% EtOAc/Hexane) to afford the desired product as a colorless oil (0.240 g, 77%). TLC: R_f 0.30 (1:4 EtOAc/hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.15 (d, J = 8.2 Hz, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.28−7.24 (m, 2H), 6.46 (d, J = 11.3 Hz, 1H), 5.82 (d, J = 11.2 Hz, 1H), 3.84 (t, J = 6.8 Hz, 2H), 3.55 (t, J = 6.5 Hz, 2H), 2.89 (t, J = 6.8 Hz, 2H), 2.08 (d, J = 7.3 Hz, 2H), 1.70−1.53 (m, 12H), 0.80 (s, 9H), −0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 136.2, 134.0, 133.5, 129.8, 124.2, 122.6, 121.5, 118.8, 115.9, 115.7, 83.8, 62.7, 62.2, 32.5, 28.4, 28.3, 26.0, 25.8, 18.3, −5.2. IR (film): 2930, 2857, 1732, 1456, 1360, 837, 774, 744 cm^{-1}. HRMS (EI): exact mass calcd for $C_{26}H_{41}N_1O_4Si$ $[M]^+$, 459.2805; found, 459.2844.

(*Z*)-*tert*-Butyl 2-(5-(*tert*-Butyldimethylsilyloxy)pent-1-enyl)-3-(2-oxoethyl)-1*H*-indole-1-carboxylate (38). Prepared following a procedure adapted from Mukai's original report.[55b] (*Z*)-*tert*-Butyl 2-(5-(*tert*-butyldimethylsilyloxy)pent-1-enyl)-3-(2-hydroxyethyl)-1*H*-indole-1-carboxylate (0.503 g, 1.09 mmol) was dissolved in distilled CH_2Cl_2 (5.50 mL). DMSO (0.230 mL, 3.28 mmol) and Et_3N (0.420 mL, 3.28 mmol) were added, and the solution was cooled to 0 °C. Pyridine−sulfur trioxide complex (0.522 g, 3.28 mmol) was added, and the solution was stirred at 0 °C for 2 h. TLC indicated completion of the reaction. A saturated solution of NH_4Cl was added, and the layers were separated. The aqueous phase was extracted three times with CH_2Cl_2. The organic layers were combined, dried over $MgSO_4$, and concentrated to afford the crude product, which was purified by flash chromatography (5% EtOAc/Hexane) to afford the desired product (0.343 g, 69%) as a colorless oil. TLC: R_f 0.56 (1:10 EtOAc/hexanes). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.69 (t, J = 2.2 Hz, 1H), 8.18 (d, J = 8.3 Hz, 1H), 7.41−7.36 (m, 1H), 7.34−7.31 (m, 1H), 7.28−7.23 (m, 1H), 6.45 (d, J = 11.2 Hz, 1H) 5.87 (dt, J = 11.3 and 7.4 Hz, 1H), 3.64 (d, J = 2.2 Hz, 2H), 3.55 (t, J = 6.4 Hz, 2H), 2.06 (qd, J = 7.5 and 1.6 Hz, 2H), 1.67 (s, 9H), 1.64−1.55 (m, 2H), 0.80 (s, 9H), −0.02 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 199.2, 150.1, 135.9, 134.4, 134.3, 129.4, 124.5, 122.8, 120.9, 118.4, 115.7, 110.5, 84.0, 62.3, 40.0, 32.2, 28.2, 25.8, 25.7, 18.1, −5.4. IR (film): 3447, 2956, 1730, 1472, 1453 cm^{-1}. HRMS (EI): exact mass calcd for $C_{21}H_{31}NO_2Si$ [M − Boc + H]$^+$, 357.2124; found, 357.2143.

(*Z*)-*tert*-Butyl 3-(2-(Hydroxyamino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (40). Prepared following a procedure adapted from Fuchs' original report.[70] (*Z*)-*tert*-Butyl 2-(5-(*tert*-butyldimethylsilyloxy)pent-1-enyl)-3-(2-oxoethyl)-1*H*-indole-1-carboxylate (0.42 g, 0.92 mmol) was dissolved in *i*-PrOH (3.00 mL). Sodium acetate (0.226 g, 2.76 mmol) was added, followed by hydroxylamine hydrochloride salt (0.0700 g, 1.01 mmol). The solution was stirred at room temperature for 1.5 h. TLC indicated completion of the reaction. A saturated solution of $NaHCO_3$ was added, followed by water. The layers were separated, and the aqueous phase was extracted three times with EtOAc. The organic layers were combined, dried over $MgSO_4$, and concentrated to afford a crude oxime as a yellow oil (0.385 g, 88%). To a solution of this oxime (0.591 g, 1.25 mmol) in MeOH (6.5 mL) was added a pinch of methyl orange followed by HCl (20% in MeOH) until a pink color was obtained. $NaBH_3CN$ (0.0950 g, 1.50 mmol) was added, followed by the HCl solution until the pink color was persistent (pH ∼3). The solution was then stirred at room temperature for 1 h. The reaction was quenched to pH 8 with 3 M NaOH. The solution was dropped in brine and extracted three times with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography (10% MeOH/CH_2Cl_2) to afford a colorless oil (0.310 g, 69%). TLC: R_f 0.39 (10% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.11 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.31−7.22 (m, 2H), 6.47 (d, J = 11.2 Hz, 1H), 5.88−5.81 (m, 1H), 3.58 (t, J = 6.3 Hz, 2H), 3.19 (t, J = 7.1 Hz, 2H), 2.87 (t, J = 6.0 Hz, 2H), 2.19−2.10 (m, 2H), 1.68−1.63 (m, 11H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 135.9, 133.6, 132.8, 129.6, 124.2, 122.6, 121.6, 118.7, 116.9, 115.6, 83.9, 62.3, 52.9, 31.9, 28.2, 25.9, 22.3. IR (film): 3340, 2979, 2926, 2850, 1729, 1463, 1371, 1330 cm^{-1}. HRMS m/z (relative intensity): 322.2878 (31.5%), 215.0222 (25.5%), 214.0172 (24.9%), 168.0329 (27.5%), 167.0255 (20.5%), 57.0709 (100%), 41.0511 (30.6%).

(*Z*)-*tert*-Butyl 3-(2-(Allyl(hydroxy)amino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (41a). (*Z*)-*tert*-Butyl 3-(2-(hydroxyamino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (0.15 g, 0.42 mmol) was dissolved in THF (2.1 mL). K_2CO_3 (0.175 g, 1.26 mmol) was added, followed by allyl bromide (0.110 mL, 1.26 mmol). The suspension was then stirred at room temperature for 6 h. TLC analysis indicated completion of the reaction. The solution was concentrated in vacuo to afford the crude product, which was purified by flash chromatography (10% MeOH/CH_2Cl_2) to afford the title product (0.080 g, 48%) as a colorless oil. TLC: R_f 0.61 (10% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 8.51 (d, J = 8.2 Hz, 1H), 7.71 (d, J = 7.4 Hz, 1H) 7.30−7.26 (m, 1H), 7.22−7.19 (m, 1H), 6.46 (d, J = 11.2 Hz, 1H), 6.09−5.99 (m, 1H), 5.71−5.64 (m, 1H), 5.15−5.06 (m, 2H), 3.38−3.34 (m, 4H), 3.16−3.13 (m, 2H), 3.02−2.98 (m, 2H), 2.18−2.12 (m, 2H), 1.54−1.47 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 136.7, 134.3, 133.6, 132.7, 130.2, 124.4, 122.8, 121.9, 119.2, 118.3, 117.7, 116.0, 83.0, 63.8, 61.9, 58.8, 32.3, 27.8, 26.2, 23.1. IR (film) 3382, 2983, 2937, 2854, 1728, 1457, 1369 cm^{-1}. HRMS (EI): exact mass calcd for $C_{20}H_{26}NO_3$ [M − $N(C_3H_5)OH$ + H]$^+$, 328.1907; found, 328.1815.

(*Z*)-*tert*-Butyl 3-(2-(Hydroxy(2-methallyl)amino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (41b). (*Z*)-*tert*-Butyl 3-(2-(hydroxyamino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (0.15 g, 0.42 mmol) was dissolved in THF (2.1 mL) and DMF (0.040 mL). DBU was added (0.070 mL, 0.46 mmol), followed by 3-chloro-2-methylpropene (0.125 mL, 1.26 mmol). The solution was heated at reflux for 4 h, diluted with EtOAc, and extracted five times with a 1:1 solution of brine and water. The combined organic phases were dried over $MgSO_4$ and concentrated to afford the crude product, which was purified by flash chromatography (50% EtOAc/hexane) to afford the desired product (0.065 g, 38%) as a yellow oil. TLC: R_f 0.45 (60% EtOAC, hexane). ^{1}H NMR (400 MHz, C_6D_6): δ 8.50 (d, J = 8.2 Hz, 1H), 7.68 (d, J = 7.8 Hz, 1H), 7.29 (t, J = 7.4 Hz, 1H), 7.20 (t, J = 7.6 Hz, 1H), 6.45 (d, J = 11.2 Hz, 1H), 5.70−5.63 (m, 1H), 4.95 (s, 1H), 4.85 (s, 1H), 3.38−3.34 (m, 2H), 3.28 (br s, 2H), 3.15−3.12 (m, 2H), 3.00−2.97 (m, 2H), 2.16−2.10 (m, 2H), 1.76 (s, 3H), 1.54−1.47 (m, 2H), 1.40 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.4, 141.5, 136.7, 133.6, 132.7, 130.2, 124.4, 122.8, 121.9, 119.1, 117.7, 116.0, 114.5, 83.1, 67.1, 61.9, 58.5, 32.3, 27.8, 26.2, 22.8, 21.3. IR (film) 3386, 2979, 2936, 2865, 1729, 1458, 1370 cm^{-1}. HRMS (EI): exact mass calcd for $C_{20}H_{26}NO_3$ [M − $N(C_4H_7)OH$ + H]$^+$, 328.1907; found, 328.1815.

***tert*-Butyl 2-Hydroxy-1-(4-hydroxybutyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (42).** To a solution of (*Z*)-*tert*-butyl 3-(2-(hydroxyamino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (0.110 g, 0.31 mmol) in *t*-BuOH (20 mL) was added $NaBH_3CN$ (0.02 g, 0.31 mmol). Argon was bubbled through the solution until saturation (15 min). The reaction mixture was stirred for 4 or 16 h in a sealed tube at 120 °C in an oil bath or in a microwave reactor. The solution was concentrated and purified by flash chromatography (5% MeOH in CH_2Cl_2) to yield the product as a colorless oil (0.096 g, 87%). TLC: R_f 0.5 (10% MeOH in CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ 8.34 (d, J = 8.2 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.32, (ddd, J = 8.4, 7.2, and 1.3 Hz, 1H), 7.25−7.21 (m, 2H), 4.92 (dd, J = 10.3 and 2.1 Hz, 1H), 3.50 (td, J = 6.3 and 2.8 Hz,

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2H), 3.28−3.22 (m, 1H), 3.11−3.00 (m, 2H), 2.27−2.23 (m, 1H), 2.08−2.00 (m, 2H), 1.93−1.74 (m, 2H), 1.65−1.50 (m, 2H), 1.40−1.25 (br m, 10 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.2, 135.9, 135.4, 129.2, 123.9, 122.6, 118.0, 115.7, 113.3, 83.8, 64.2, 62.7, 46.1, 34.4, 32.3, 28.3, 23.0, 16.3. IR (film) 3333, 2922, 2850, 1728, 1455, 1368 cm^{-1}. HRMS (EI): exact mass calcd for $C_{20}H_{28}N_2O_4$ $[M]^+$, 360.2049; found, 360.2050.

***tert*-Butyl 2-(Allyloxy)-1-(4-hydroxybutyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (43a).** (*Z*)-*tert*-Butyl-3-(2-(allyl(hydroxy)amino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (0.073 g, 0.18 mmol) was dissolved in benzene (18 mL). Distilled water (0.034 μL) was added, and argon was bubbled through the solution for 15 min. The solution was stirred for 16 h in a sealed tube at 120 °C, concentrated, and purified by flash chromatography (5% MeOH/CH_2Cl_2) to afford the desired product (0.047 g, 64%) as a colorless oil. TLC: R_f 0.71 (10% MeOH/CH_2Cl_2). ^{1}H NMR (400 MHz, C_6D_6): δ: 8.33 (d, J = 8.3 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H), 7.34−7.30 (m, 1H), 7.25−7.21 (m, 1H), 6.03−5.93 (m, 1H), 5.18 (dq, J = 17.3 and 1.6 Hz, 1H), 5.02 (ddt, J = 10.4, 2.0, and 1.1 Hz, 1H), 4.97 (d, J = 10.5 Hz, 1H), 4.25 (dq, J = 6.0 and 1.3 Hz, 2H), 3.48 (t, J = 6.4 Hz, 2H), 3.38−3.33 (m, 1H), 3.11−2.95 (m, 2H), 2.26−2.21 (m, 1H), 2.07−1.98 (m, 1H), 1.97−1.88 (m, 1H), 1.84−1.75 (m, 1H), 1.60−1.52 (m, 2H), 1.36 (s, 9H), 1.30−1.20 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.9, 137.3, 136.8, 136.0, 130.5, 124.4, 123.3, 118.7, 117.5, 116.7, 114.7, 83.5, 73.7, 62.9, 62.6, 44.6, 35.4, 33.4, 28.3, 24.1, 17.7. IR (film) 3405, 2972, 2935, 2865, 1728, 1456, 1372 cm^{-1}. HRMS (EI): exact mass calcd for $C_{23}H_{32}N_2O_4$ $[M]^+$, 400.2362; found, 400.2382.

***tert*-Butyl 1-(4-Hydroxybutyl)-2-(2-methallyloxy)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (43b).** (*Z*)-*tert*-Butyl 3-(2-(hydroxy(2-methallyl)amino)ethyl)-2-(5-hydroxypent-1-enyl)-1*H*-indole-1-carboxylate (0.054 g, 0.13 mmol) was dissolved in benzene (13 mL). Distilled water (0.020 mL) was added, and argon was bubbled through the solution for 15 min. The solution was stirred for 16 h in a sealed tube at 120 °C, concentrated, and purified by flash chromatography (60% EtOAC/hexane) to afford the desired product (0.029 g, 53%) as a colorless oil. TLC: R_f 0.7 (60% EtOAC/hexane). ^{1}H NMR (300 MHz, C_6D_6): δ 8.29 (d, J = 8.1 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.29−7.25 (m, 1H), 7.20−7.15 (m, 1H), 4.99 (s, 1H), 4.92 (d, J = 10.5 Hz, 1H), 4.80 (s, 1H), 4.17 (s, 2H), 3.44 (t, J = 6.5 Hz, 2H), 3.35−3.29 (m, 1H), 3.08−2.88 (m, 2H), 2.22−2.16 (m, 1H), 2.02−1.83 (m, 2H), 1.78−1.70 (m, 1H), 1.64 (s, 3H), 1.54−1.47 (m, 2H), 1.32 (s, 9H), 1.21−1.10 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.0, 143.0, 137.3, 136.8, 130.5, 124.4, 123.3, 118.7, 116.7, 114.7, 113.4, 83.5, 76.8, 62.9, 62.6, 44.5, 35.4, 33.4, 28.3, 24.1, 20.4, 17.7. IR (film): 3431, 2983, 2926, 2850, 1727, 1456, 1372 cm^{-1}. HRMS (EI): exact mass calcd for $C_{24}H_{34}N_2O_4$ $[M]^+$, 414.2519; found, 414.2502.

1-(4-Hydroxybutyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole (43). To a solution of *tert*-butyl 2-hydroxy-1-(4-hydroxybutyl)-3,4-dihydro-1*H*-pyrido[3,4-*b*]indole-9(2*H*)-carboxylate (0.055 g, 0.19 mmol) in CH_2Cl_2 (1 mL) was added TFA (1 mL) dropwise. The solution was allowed to stir at room temperature for 12 h, and water (1 mL) was added, followed by zinc dust (0.124 g, 1.9 mmol). The solution was stirred overnight, and 6 M NaOH was added until pH 10 was reached. The solution was filtered through Celite with hot methanol. The resulting solution was extracted three times with CH_2Cl_2 and a saturated NaCl solution. The organic layers were combined, dried over $MgSO_4$, and condensed to afford the crude product as a yellow oil (0.035 g, 73%). The product was used without further purification for the next step.

(±)-10-Desbromoarborescidine A (45). Prepared following a procedure adapted from the original report of Hurvois.[56] To a solution of $SOCl_2$ (0.02 mL, 0.21 mmol) in CH_2Cl_2 (1 mL) was added dropwise a solution of amino alcohol **43** in CH_2Cl_2 (0.035 g, 0.14 mmol in 1 mL). The solution was stirred at 40 °C for 3 h in a sealed tube. The solution was concentrated to afford a dark-brown solid. Boiling ether was added, and the liquid was decanted to afford a light-brown solid. The solid was dissolved in NaOH (1 mL) and CH_2Cl_2 (1.5 mL), and the mixture was stirred overnight. The phases were separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were washed twice with water, dried over $MgSO_4$, and condensed to afford a brown oil. The oil was purified by column chromatography to afford the product as a white solid. TLC: R_f 0.33 (5:1:94 MeOH/NH_4OH/CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (br s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.32 (d, J = 7.3 Hz, 1H), 7.12 (dt, J = 14.5 and 7.1 Hz, 2H), 3.27 (d, J = 10.3 Hz, 1H), 3.12−3.00 (m, 3H), 2.77−2.63 (m, 2H), 2.41 (td, J = 10.7 and 3.6 Hz, 1H), 2.09 (d, J = 12.5 Hz, 1H), 1.92 (d, J = 12.4 Hz, 1H), 1.73−1.79 (m, 2H), 1.48−1.64 (m, 2H). HRMS (EI): exact mass calcd for $C_{15}H_{18}N_2$ $[M]^+$, 226.1470; found, 226.1467. The NMR data were in accordance with literature values.[57c,71]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NMR spectra of all new compounds and EPR spectrum of **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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