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Syntheses of Strychnine, Norfluorocurarine, Dehydrodesacetylretuline, and Valparicine Enabled by Intramolecular Cycloadditions of Zincke Aldehydes

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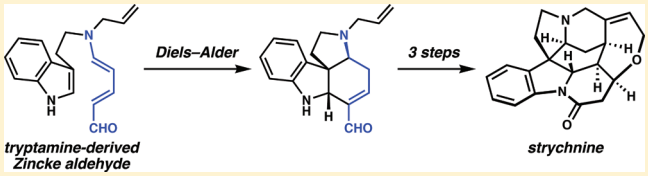
Supporting Information

ABSTRACT: A full account of the development of the base-mediated intramolecular Diels–Alder cycloadditions of tryptamine-derived Zincke aldehydes is described. This important complexity-generating transformation provides the tetracyclic core of many indole monoterpene alkaloids in only three steps from commercially available starting materials and played a key role in short syntheses of norfluorocurarine (five steps), dehydrodesacetylretuline (six steps), valparicine (seven steps), and strychnine (six steps). Reasonable mechanistic possibilities for this reaction, a surprisingly facile dimerization of the products, and an unexpected cycloreversion to regenerate Zincke aldehydes under specific conditions are also discussed.



INTRODUCTION

The current state-of-the-art of organic chemistry owes much to the study of alkaloids, and the *Strychnos* family is certainly exemplary. The *Strychnos* alkaloids (Figure 1) were the subject

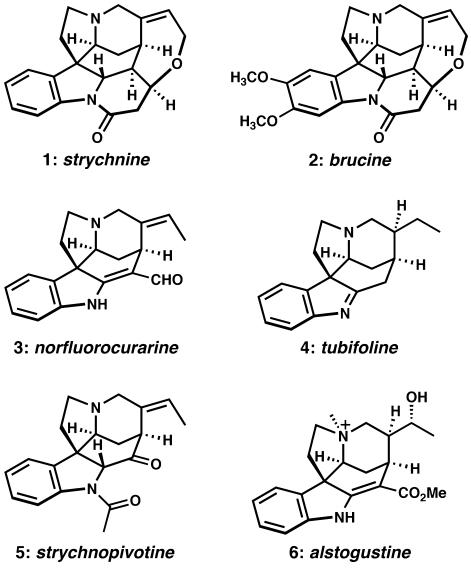


Figure 1. Representative *Strychnos* alkaloids.

of intense investigation at all stages in the development of organic chemistry, from the early 1800s to modern day. The ready availability of certain *Strychnos* alkaloids in pure form (e.g., strychnine) allowed their elemental composition to be determined by the 1830s.[1,2] The determination of their structure took a century of extensive degradation studies and led to the widespread use and popularization of many reactions in the toolbox of the classical organic chemist (e.g., Hofmann elimination, Emde degradation, von Braun reaction, Polonovski reaction).[3−5] The similarities (and differences) among members of the *Strychnos* and related alkaloid classes (*Aspidosperma*, *Iboga*, *Corynanthé*) would lead to biogenetic hypotheses that could be experimentally probed in vivo or in the chemistry laboratory.[6] Since the 1940s, the intricate architectures of these alkaloids have challenged chemists to develop new methods and tactics to achieve ever more efficient, stereocontrolled syntheses.[7,8] To this day, they remain a testing ground for strategies in alkaloid synthesis.

The most famous and recognizable member of this family, strychnine (**1**, Figure 2), is believed to be the first indole alkaloid ever isolated in pure form, as reported by Pelletier and Caventou in 1818.[1] As suggested above, its elemental composition would be determined by Regnault a mere 20 years later,[2] but the correct structure would not be proposed until 1946 and confirmed in 1948, after a "decades-long chemical degradative assault".[3,4] Various acid-, base-, and oxidation-induced fragmentations and rearrangements of the strychnine skeleton were the hallmarks of this period. The field of alkaloid synthesis took a giant leap forward with Woodward's landmark synthesis that was completed in 1954.[7a] This group took advantage of many lessons learned from degradation studies in the planning and execution of this synthesis. Woodward was equally inspired by his early thoughts on the biogenesis of the *Strychnos* alkaloids, incorporating elements of his proposal into the synthesis.[9] Beginning in the 1990s, a renaissance of interest in strychnine led to the completion of a further 17 syntheses.[7] Without exception, these syntheses have been creative and instructive, often relying on new technologies that have arisen since the time of Woodward's

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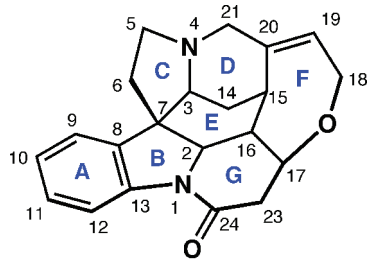


Figure 2. Biogenetic numbering system shown here is used throughout the text (C22 has been biochemically excised).[10]

achievement. In this context, strychnine continues to serve as a benchmark target against which organic chemists may measure the state-of-the-art of natural product synthesis strategy.

BACKGROUND: ZINCKE ALDEHYDES AS VERSATILE BUILDING BLOCKS

A major focus of our research group is the use of Zincke aldehydes (5-amino-2,4-pentadienals) as versatile intermediates for organic synthesis.[11] Zincke aldehydes are the products of the century-old Zincke procedure for ring-opening of pyridinium salts with secondary amines (Figure 3).[12] Building

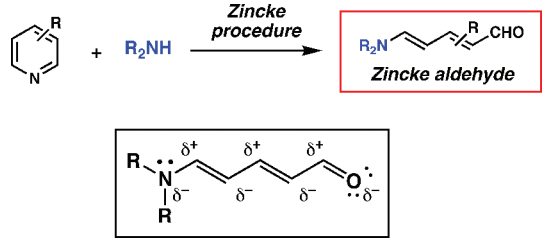


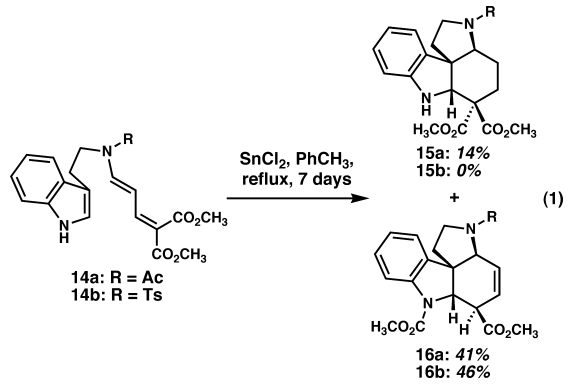
Figure 3. Zincke aldehydes: versatile intermediates readily available from pyridines.

upon a considerable body of literature related to Zincke aldehydes,[13] we have focused our attention on their application toward complex molecule synthesis via reactions that lead to a rapid buildup of molecular complexity.

Early on in our studies, we wondered whether the diene of the Zincke aldehyde could be leveraged in an intramolecular Diels–Alder reaction to give complex, polycyclic products suitable for alkaloid synthesis. In particular, we were inspired by the idea that a tryptamine-derived Zincke aldehyde might undergo an intramolecular Diels–Alder cycloaddition to furnish the tetracyclic fragment shown in Scheme 1. This motif constitutes the ABCE ring system of the curan skeleton (**13**) common to most *Corynanthé-Strychnos* alkaloids and is also found in many members of the *Aspidosperma* and *Iboga* families of alkaloids. Isomerization of the initial cycloaddition product would generate the conjugated enal, which would enable a well-precedented closure of the D ring to give the fully elaborated *Strychnos* skeleton in only a handful of steps.[7e,14] By judicious choice of the N4-substituent and manipulation of the aldehyde group, we envisioned the synthesis of many alkaloids of this class by a unified strategy.[7q,15]

INTRAMOLECULAR ZINCKE ALDEHYDE CYCLOADDITIONS

There are two major challenges in the proposed intramolecular Diels–Alder reaction: first, indoles are stable aromatic compounds whose C2–C3 π-systems are notoriously poor dienophilic partners for [4 + 2] cycloadditions. Reported intermolecular examples generally require triplet photosensitization,[16] stoichiometric generation of an indole radical cation,[17] deprotonation to give the indole anion,[18] or feature highly reactive dienes such as masked *o*-benzoquinones.[19] At least in some cases, these reactions proceed in a stepwise fashion (with radical and/or charged intermediates) rather than via concerted pathways. Intramolecular *formal* cycloadditions of indoles are also known, including an interesting Lewis acid-catalyzed reaction reported by Rosenmund and co-workers that bears a close resemblance to our desired reaction (eq 1) but makes use



of particularly harsh conditions.[20] In previous approaches to strychnine, the Bodwell and Padwa groups have demonstrated Diels–Alder reactions of *N*-alkyl and *N*-acyl indoles with a tethered pyridazine and amidofuran, respectively (Scheme 2, disconnection a).[7k,n] Both of these reactions occur only at elevated temperature (150–215 °C) and are likely driven forward by a subsequent irreversible fragmentation of the bicyclic [4 + 2] product.[21] Although not directly related to the cycloaddition that we were planning, two other cycloaddition approaches to strychnine should also be highlighted. Rawal reported the first intramolecular Diels–Alder reaction that constructed both the indoline B-ring and the E-ring (Scheme 2, disconnection b), allowing for the controlled formation of three contiguous stereocenters.[7e] Finally, the recent synthesis reported by MacMillan and co-workers established the viability of incorporating a 2-vinylindole as the 4π component in an elegant application of their enantioselective iminium catalysis (Scheme 2, disconnection c).[7r] Notably, three of the four Diels–Alder disconnections that allow direct construction of the C7 quaternary center have been successfully employed in the synthesis of strychnine.

The second challenge to our proposed reaction is that Zincke aldehydes are known to be poorly reactive dienes in cycloadditions.[22] To the best of our knowledge, there are no reported examples of successful Diels–Alder reactions with Zincke aldehydes serving as the 4π component, almost certainly owing to their high donor–acceptor stabilization.[23]

Clearly, the problems associated with both components of our prospective cycloaddition substrates caused some initial trepidation. Nonetheless, given the intramolecular setting, the ease of substrate synthesis, and the ready (albeit unattractive) possibility of electronic perturbation of the indole fragment, we

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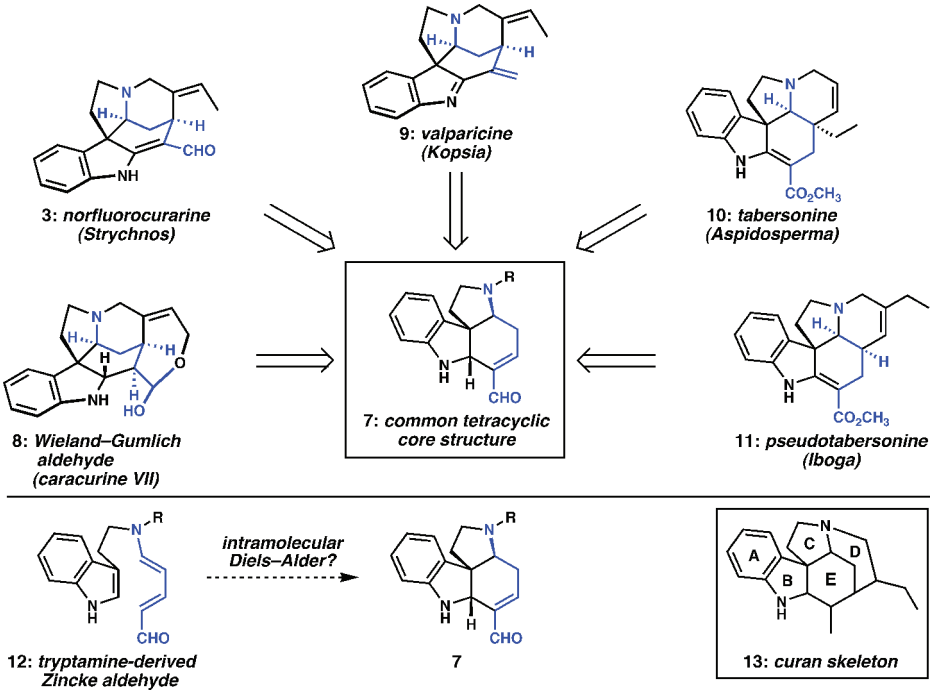
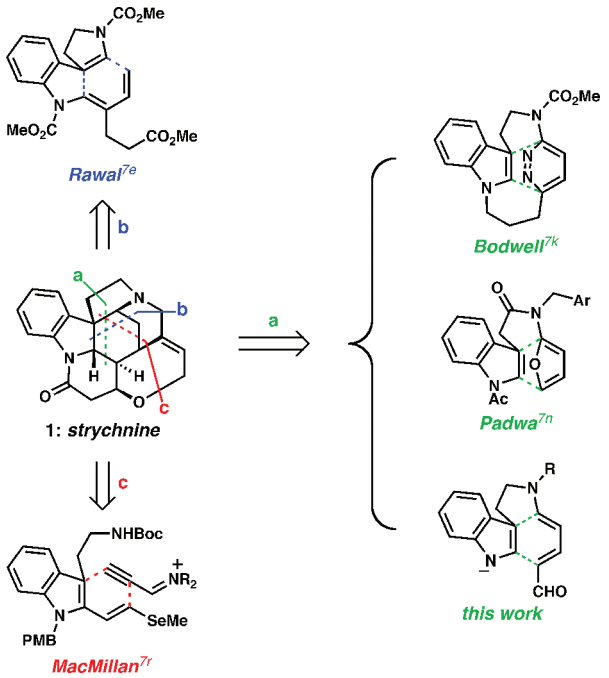
Scheme 1. Common Tetracyclic Core Structure of Many Indole Monoterpene Alkaloids in Addition to Strychnine Might Be Accessed by an Intramolecular Diels–Alder Cycloaddition of a Tryptamine-Derived Zincke Aldehyde



Scheme 2. Diels–Alder Disconnections Used in Syntheses of Strychnine



remained optimistic. In addition, we established that the overall transformation should be thermodynamically favored by comparison of the calculated ground-state energies of the starting materials and products, despite loss of aromaticity of the five-membered indole ring and loss of the extensive conjugation in the Zincke aldehyde (Figure 4).[24] Satisfied that this plan was feasible, and particularly inspired by the potential utility of the prospective cycloaddition, we set out to reduce this idea to practice.

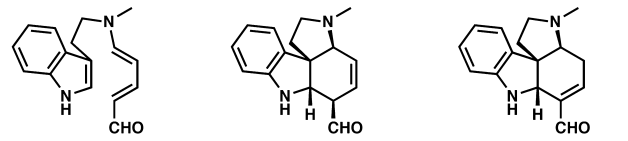


Figure 4. Relative ground-state energies of Zincke aldehyde precursor and potential cycloaddition products. (Values obtained using Turbomole v6.3, pbe0 functional, def2-TZVP basis set, and **12a** was not restricted to the conformation shown.)

RESULTS AND DISCUSSION

Reaction Discovery. Our initial investigations began with the synthesis of substrate **12b**, which is readily available in two steps from tryptamine on multigram scale in 83% overall yield. We began with attempts to perform thermal Diels–Alder reactions in a variety of solvents. At lower temperatures, we observed no reaction; however, above approximately 150 °C in aromatic solvents, we observed the formation of a new, isomeric product. By ^{1}H NMR, the indole resonances were left intact while the resonances corresponding to the Zincke aldehyde were replaced with a new set of signals in the alkene region of the spectrum. The product was *Z*-α,β,γ,δ-unsaturated amide **21** (Scheme 3). This completely unexpected reaction is quite general, and has been observed in attempts to initiate thermal Diels–Alder reactions with other Zincke aldehydes. While clearly of no use for the synthesis of *Strychnos* alkaloids, this interesting reaction has been further explored in our group in terms of scope and mechanism and is being exploited for the synthesis of other natural products.[11b,d,f]

Our investigations continued with a screen of additives. A variety of Lewis acids and protic acids did not promote the desired cycloaddition and, in many cases, resulted in indole degradation or apparent Pictet–Spengler-like reactivity. Nuhant

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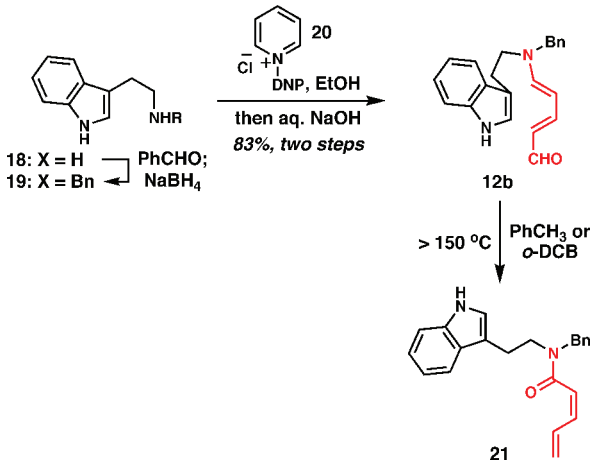
Scheme 3. Unexpected Formation of *Z*-α,β,γ,δ-Unsaturated Amide 21 under Thermal Conditions[a]

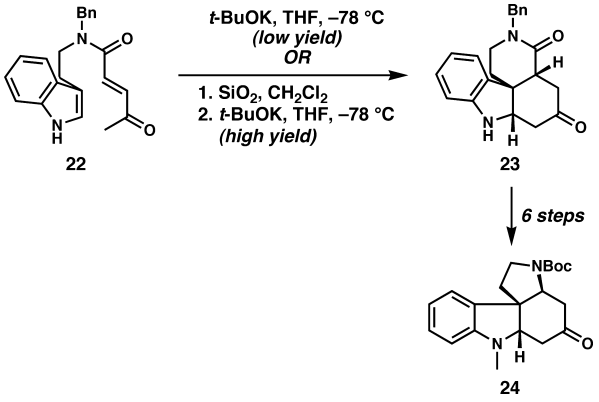


[a]DNP = 2,4-dinitrophenyl, *o*-DCB = *o*-dichlorobenzene.

and co-workers have since reported a method for performing Pictet–Spengler-type reactions of similar Zincke aldehydes using TFAA, in a reaction that provides complementary access to tetrahydro-β-carbolines and appears to be applicable to several *Corynanthé* natural products.[25] We also briefly examined the use of aminium radical catalysis through the use of the commercially available salt $N(4\text{-}BrC_6H_4)_3SbF_6$.[17,26] We anticipated that an indole radical cation would engage the Zincke aldehyde; however, productive reactivity was never observed.

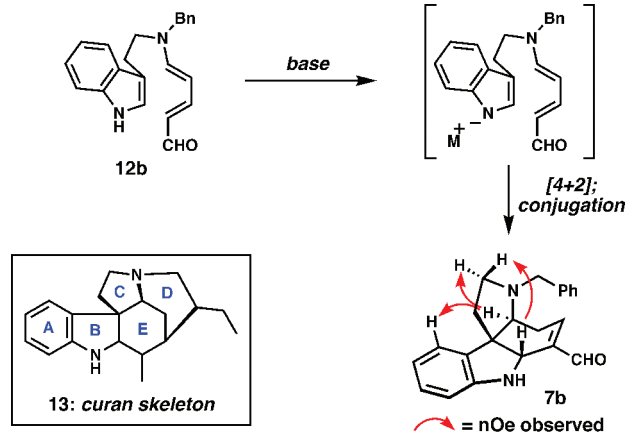
The final strategy that we explored was a base-induced cycloaddition. We were inspired by the bicyclization of Markó (**22** → **23**, Scheme 4) that proceeded in low yield by a single

Scheme 4. Related Anionic Bicyclization Reported by Markó and Co-workers



base-mediated operation or in higher yield via silica-induced spirocyclization followed by base-mediated Mannich ring closure.[27,28] In our particular case, we anticipated that deprotonation of the indole should drive the direct formation of the desired product, because equilibration of the enolate would not be required as it was in Markó's chemistry. We explored a variety of organic and inorganic bases, and obtained promising results with those featuring potassium counterions (Scheme 5). Exposure of Zincke aldehyde **12b** to a stoichiometric amount of KO-*t*-Bu in THF at 50 °C for 4 h led to 40% conversion to a new product isomeric with the starting material. We identified the product as tetracyclic aldehyde **7b**; not surprisingly, the

Scheme 5. Selected Results from the Optimization of the Base-Mediated Cycloaddition Reaction[a]



Conditions	Result
DBU, phosphazine bases, Na_2CO_3, K_2CO_3, Cs_2CO_3, variety of solvents/temperatures	NR
MeLi, NaH or EtMgBr, THF, 0 to 50 °C	NR
EtMgBr, THF, 80°C μW	NR
KO*t*-Bu, THF, 50 °C, 4 h	40% conversion
KO*t*-Bu, THF, 80 °C (sealed tube), < 2 h	**85% yield**

[a]DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, NR = no reaction, μW = microwave irradiation.

basic conditions had caused conjugation of the alkene with the aldehyde. The relative configuration of the product was assigned by nOe correlations and was found to match that of the ABCE ring systems of most indole monoterpene alkaloids. Further optimization was plagued by issues of reproducibility, which were eventually traced back to the purity of the substrates. While in most cases the Zincke aldehyde could be obtained in apparently pure form (>95% by ^{1}H NMR) after a single chromatographic separation, further purification by chromatography always led to the separation of various highly colored byproducts, eventually providing the Zincke aldehyde as a yellow solid. No byproducts could be isolated in sufficient quantity or purity to determine their structure. Based on the steady march of numerous highly colored bands from the chromatography column, there are apparently many different highly conjugated molecules formed in trace quantities during the Zincke pyridinium ring-opening reaction.[29] Eventually, an empirical solution to the reproducibility problem was found: after chromatographic purification (generally 1–2 iterations), the Zincke aldehyde was treated with activated charcoal in CH_2Cl_2 for 1 h at rt, filtered through Celite, and concentrated. The resulting yellow solid (or foam) showed much improved reliability in our bicyclization reaction, and this protocol is now used whenever highly pure Zincke aldehyde material is needed. Reaction optimization led to a simple and reliable protocol: treatment of Zincke aldehyde **12b** in THF (0.06 M) with KO-*t*-Bu (1 M solution in THF) at 80 °C in a sealed tube routinely afforded tetracycle **7b** in 85% yield.

Mechanistic Discussion. A detailed mechanistic study has not been undertaken at this time because of the particular sensitivity of the reaction toward even modest changes in

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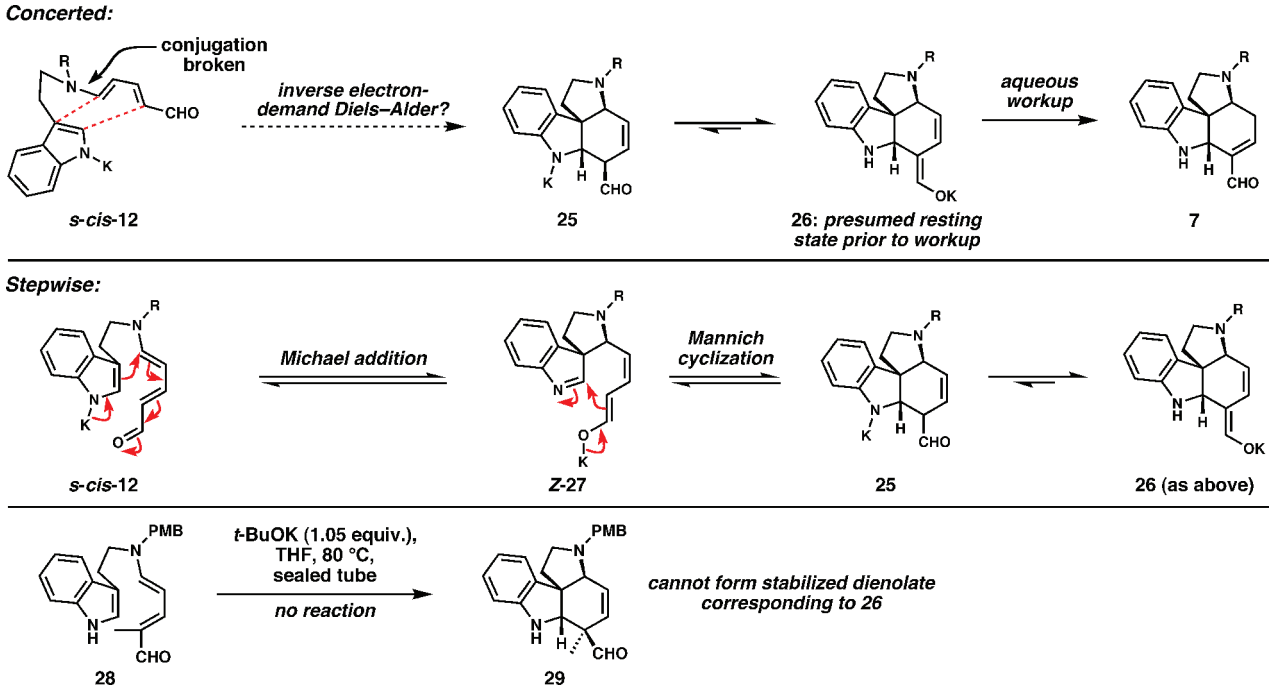
Scheme 6. Two Reasonable Mechanistic Possibilities for the Base-Mediated Cycloaddition Reaction and an Experiment Suggesting the Importance of the Stabilized Dienolate Product



reaction conditions, including solvent, base stoichiometry, temperature, and concentration. Nonetheless, we put forth two plausible mechanistic scenarios (Scheme 6): (1) a concerted Diels–Alder reaction between a deprotonated indole and the Zincke aldehyde diene or (2) a stepwise metalloenamine Michael addition to the Zincke aldehyde to form a dienolate, followed by subsequent Mannich cyclization onto the transient indolenine. In order to achieve proper orbital alignment for a concerted Diels–Alder reaction, molecular models suggest that conjugation must be broken between the N_b-lone pair and the dienal of the Zincke aldehyde (see *s-cis*-**12**), which could further favor the inverse electron demand Diels–Alder reaction (in this case, the nitrogen atom would serve only as an inductively electron-withdrawing group). From this reactive conformation, only the desired stereochemical outcome, as shown in **25**, is reasonable. It is possible that the thermal requirements of the reaction reflect the need to break conjugation in the donor–acceptor system, which then enables inverse-electron-demand cycloaddition. In the stepwise mechanism, the Zincke aldehyde must still adopt the *s-cis* conformation in order to generate the requisite dienolate geometry (see *Z*-**27**); the s-*trans* conformation would lead to an intermediate dienolate with an E-configured double bond that would be unable to undergo the terminal Mannich cyclization. Similarly, the improper relative configuration of the two new stereogenic centers in intermediate *Z*-**27** would preclude Mannich cyclization. If the stepwise mechanism were operative, then an improperly configured dienolate would presumably revert back to starting material, eventually funneling to the observed product, because no partially cyclized intermediates have been observed to date. In either case, the unconjugated enal **25** would presumably be formed first, with subsequent isomerization to the more stable dienolate **26**. Importantly, dienolate **26** is apparently stable under the reaction conditions, and self-destruction by elimination of either of the two amino groups is not significant.[20,30] A considerable component of the thermodynamic driving force for the overall cycloaddition reaction, regardless of mechanism, might be the formation of the stable dienolate. The intramolecular Diels–Alder reactions reported by Bodwell and Padwa also result in loss of aromaticity of the indole ring (as well as a pyridazine or furan, respectively) and may be driven forward by a subsequent entropically favored fragmentation.[7k,n] A single experiment to probe the importance of this equilibration was performed: when the Zincke aldehyde derived from 3-picoline (**28**) was exposed to the cycloaddition reaction conditions, no reaction to form **29** was observed, even under forcing conditions. This singular data point provides circumstantial evidence for the importance of the formation of the stable dienolate.

Substrate Scope. Most of the substrates that we have successfully employed in our bicyclization reaction are shown in Table 1 (for some substrates that did not perform well in this reaction, see below). Larger N-substituents such as benzyl, *p*-methoxybenzyl (PMB), 2,4-dimethoxybenzyl (DMB), and 2-silylbutenyl groups were associated with efficient reactions (see **12b,c,d,j**: 80–85% yield). In these cases, the ^{1}H NMR of the crude reaction mixture typically showed only the desired product, and in cases with only moderate isolated yields, the fate of the mass balance is unclear. Yields are typically lower with smaller N-substituents such as methyl and primary aliphatic groups. Consistent with this trend, the yield increases upon transitioning from allylamine-derived Zincke aldehyde to the larger methallyl and 2-(trimethylsilyl)butenyl substrates (48%, 56%, and 84%, respectively). Groups much larger than benzyl (e.g., benzhydryl) could not be investigated because of the failure of the pyridinium ring-opening reaction. Propargylic systems were poor substrates, likely owing to base-induced isomerization to the corresponding allenamines, which could react further and lead to decomposition. The siloxacycle **12k** was investigated in an early route to strychnine. Using KO-*t*-Bu as the base, we observed exclusively protodesilylation of the starting material. In an effort to circumvent this problem, we

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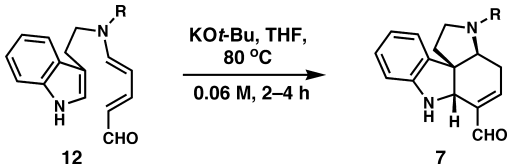
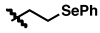
Table 1. Substrate Scope of Base-Mediated Cycloaddition[e]

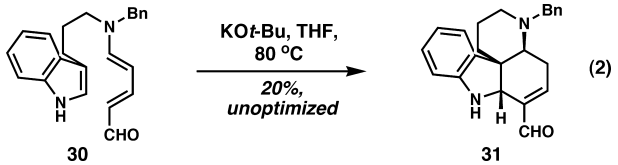


Zincke aldehyde	R	% yield[a]
12a	Me	46
12b	Bn	85
12c	PMB	80
12d	DMB	82
12e		45
12f		43
12g		48, 54[b], 64[c]
12h		56
12i		65[b]
12j		84
12k		9[d]
12l		~15

[a]Isolated yield. [b]0.04 M. [c]0.02 M. [d]KHMDS used as base. [e]Reaction conditions: 1.05 equiv KO*t*-Bu, 0.06 M in THF (unless otherwise noted), 80 °C in a sealed tube for 2–4 h. PMB = *p*-methoxybenzyl; DMB = 2,4-dimethoxybenzyl.

used KHMDS, which afforded the cyclized product in only 9% yield. The use of KHMDS with PMB-bearing substrate **12c** also gave a low yield (31% + 15% recovered SM). As a result, whenever the substrate was stable to an alkoxide base, KO-*t*-Bu was used, and KHMDS was used as a backup when problems arose.

The reaction is also applicable to homotryptamine-derived substrates, giving products with a 6-membered piperidine C-ring, although the reaction efficiency suffers substantially (**30** → **31**, eq 2). There are only two reports of these C-ring

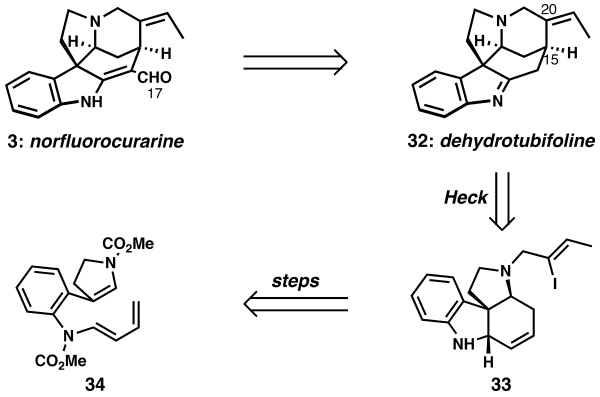


homologated structures in the literature.[31] The straightforward access to these compounds using our Zincke aldehyde methodology could prove useful for the production of fully elaborated C-ring homologues of *Strychnos* and related alkaloids.

In cases with smaller N-substituents, a large percentage of the material is recovered as the secondary amine resulting from cleavage of the Zincke aldehyde. It is known that heating Zincke aldehydes with aqueous base results in hydrolysis.[32] Significant efforts were made to exclude moisture in these reactions with only minor improvements; therefore, it appears as though some other process is causing decomposition via loss of the Zincke aldehyde. We have found empirically that this undesired product can be minimized by running the reaction at higher dilution. For example, as the reaction concentration is reduced from 0.06 to 0.04 M to 0.02 M, the *N*-allyl product **7g** is obtained in 48%, 54%, and 64% yield, respectively. These results suggest that some intermolecular process is at play, but its exact nature is still unknown.

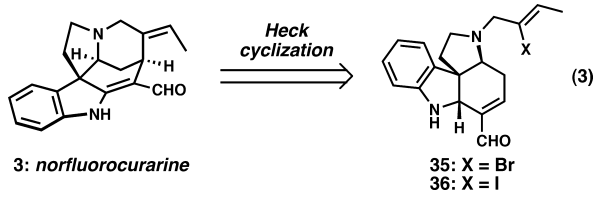
Synthesis of Norfluorocurarine: Previous Syntheses and Retrosynthesis. With the success of our new stereoselective bicyclization reaction, we turned our attention to the synthesis of the *Strychnos* alkaloid norfluorocurarine. This relatively simple *Strychnos* alkaloid was first reported in 1961 by Stauffacher and was subsequently isolated as a racemate.[33] Norfluorocurarine has been previously synthesized by the groups of Harley-Mason, Bonjoch, and Rawal.[34] The Rawal synthesis relied on the formylation of dehydrotubifoline (**32**, Scheme 7), which they had synthesized using an intramolecular

Scheme 7. Successful Approach to Norfluorocurarine via Dehydrotubifoline As Reported by Rawal and Co-workers



Heck reaction of **33**.[14b,35] This Heck reaction was the first reported example of this strategy for the synthesis of a *Strychnos* alkaloid, and this versatile method has subsequently been used for similar ring closures in the synthesis of strychnine, akuammicine and many other (indole) alkaloids.[7e,i–k,o,p,r,30,36–38] In addition to constructing the bridged D-ring via C15–C20 bond formation, this stereospecific reaction necessarily provides complete control of alkene geometry.

We envisioned that an intramolecular Heck reaction of a vinyl halide (either **35** or **36**, eq 3), inspired by the work of



Rawal, would serve as the final key step to close the D ring and directly generate the natural product. As outlined above, this strategy was expected to efficiently close the D-ring with complete control of alkene geometry. In addition, this Heck strategy would generate the vinylogous amide of

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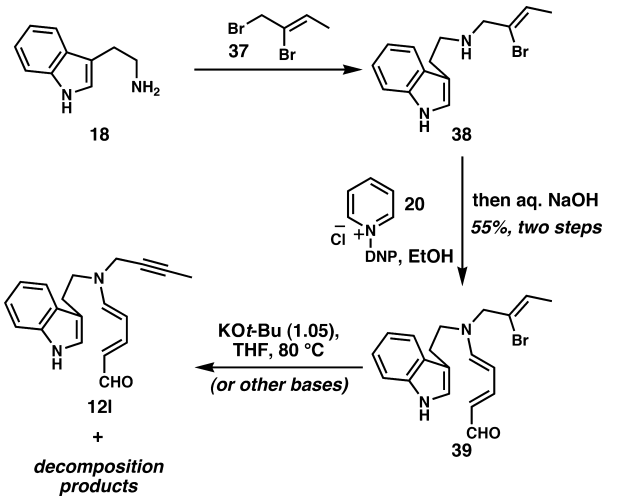
norfluorocurarine directly by transposition of the double bond, taking full advantage of the functionality in our bicyclization products.

First-Generation Synthesis of Norfluorocurarine. The synthesis of our desired Heck reaction substrate **35** was initially pursued by deprotection of the benzyl-type cycloadducts **7b–d** (Table 1) that could be prepared efficiently in three steps on large scale. All attempts at deprotection were unsuccessful (for a detailed discussion, see below). We therefore sought to prepare vinyl bromide **35** directly from the corresponding Zincke aldehyde **39** (Scheme 8). This substrate was prepared

Scheme 8. Synthesis of Vinyl Bromide Substrate 39 and Failed Anionic Bicyclization

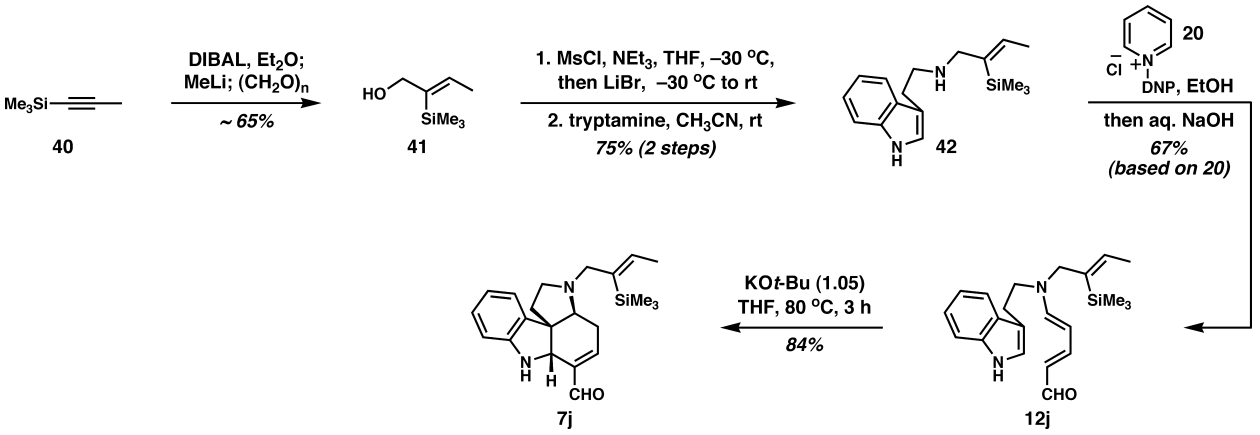


by alkylation of tryptamine with known dibromide **37**[14b,39] (readily prepared from crotonaldehyde in three steps), followed by formation of the Zincke aldehyde. Unfortunately, under the standard reaction conditions for anionic bicyclization, we were unable to isolate any of desired tetracyclic product **35**. The single identifiable product isolated was the corresponding alkyne **12l**, presumably formed via base-mediated dehydrohalogenation.[37a] Other products might derive from dehydrohalogenation to afford an unstable allenamine, which could decompose further. As a result, we were forced to find a suitable vinyl halide surrogate, which came in the form of a vinylsilane.

Zincke aldehyde **12j** was similarly prepared in a four-step sequence from commercially available 1-(trimethylsilyl)-propyne (Scheme 9).[15] Following a known procedure, hydroalumination of **40** with DIBAL-H, treatment of the resulting vinylalane with methyllithium, and reaction of the aluminate with paraformaldehyde afforded allylic alcohol **41**.[40] This compound was converted to the corresponding allylic bromide (via the mesylate) and used to alkylate tryptamine. Zincke aldehyde **12j** was produced from secondary amine **42** under standard conditions. To our delight, the rather harsh reaction conditions for anionic bicyclization produced tetracycle **7j** in 84% yield, once again as a single diastereomer.

At this stage, an iododesilylation reaction was required to provide Heck substrate **36**;[41] however, a variety of attempts using standard reaction conditions led to complex reaction mixtures in which only small quantities of desired vinyl iodide could be observed. This reaction was primarily complicated by preferential iodination of the electron-rich aromatic ring. We were hopeful that an azaphilic Lewis acid could be found that would sufficiently deactivate the indoline ring, possibly with chelation to the adjacent aldehyde group, but efforts along these lines were unfruitful. After dozens of attempts to optimize this reaction, including variation of solvent, source of I^+, additives, and temperature, we could obtain **36** in at most 19% yield after painstaking chromatographic separation (Scheme 10). To obviate these issues of chemoselectivity, a three-step protocol involving temporary N-trifluoroacetylation of the indoline was adopted. The trifluoroacetyl group was introduced and removed with high efficiency, and proved effective at deactivating the indoline ring, enabling formation of the desired iodide **36** in a more reasonable 63% overall yield. In both iododesilylation reactions, the use of HFIP (1,1,1,3,3,3-hexafluoroisopropyl alcohol) as cosolvent provided optimal reactivity and avoided issues of stereochemical infidelity.[42] Finally, we were able to explore the key Heck cyclization of iodide **36**. Using conditions reported by Rawal (Jeffery's conditions)[43] for his synthesis of dehydrotubifoline,[14b] only minute quantities of norfluorocurarine were produced. Recognizing that the electronic nature of our alkene was different from that in Rawal's substrate, we explored a variety of different conditions, and found the more classical conditions shown to be optimal. Heck cyclization provided up to a 70% yield of (±)-norfluorocurarine (**3**), whose spectral data were in agreement with those previously reported.[33c] This successful route proceeds via longest linear sequences of five steps from

Scheme 9. Synthesis and Cycloaddition of Vinylsilane Substrate



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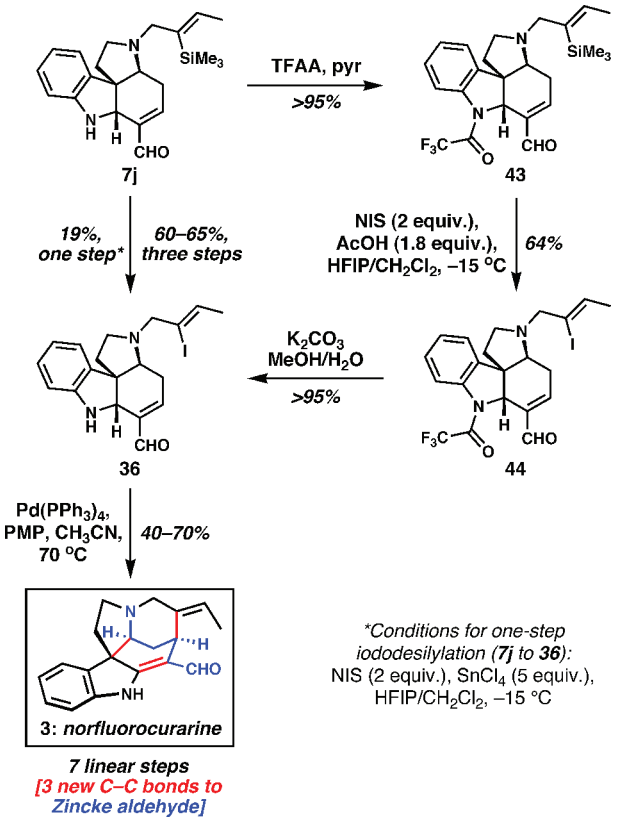
Scheme 10. First-Generation Synthesis of Norfluorocurarine[a]

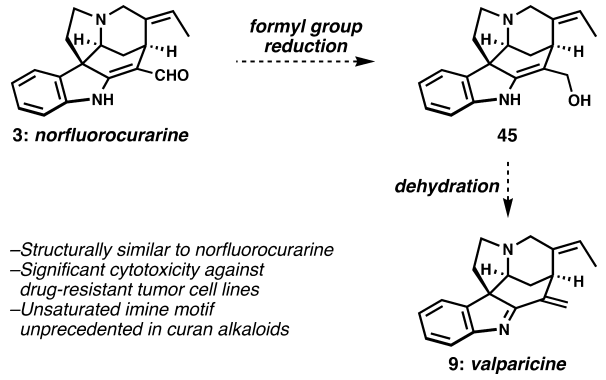


[a]NIS = *N*-iodosuccinimide, HFIP = 1,1,1,3,3,3-hexafluoroisopropyl alcohol, TFAA = trifluoroacetic anhydride, PMP = 1,2,2,6,6-pentamethylpiperidine.

tryptamine or seven steps from 1-(trimethysilyl)propyne using the poorly efficient direct iodination protocol, and seven or nine steps, respectively, using the optimal three-step iodination sequence. Our synthesis demonstrates that the cycloaddition of tryptamine-derived Zincke aldehydes not only serves to efficiently construct the tetracyclic core of many *Strychnos* alkaloids, but also directly introduces the α,β-unsaturated aldehyde at the proper position for subsequent D-ring formation and at the proper oxidation state to enable a particularly concise synthesis.

First-Generation Synthesis of Valparicine. Given the brevity of our approach to norfluorocurarine, we also aimed to synthesize the structurally similar alkaloid valparicine (**9**, Schemes 1 and 11), which was recently isolated from *Kopsia arborea* by Kam and co-workers.[44] This alkaloid exhibits pronounced cytotoxicity toward drug-sensitive and drug-resistant KB cells as well as Jurkat cells. The promising antitumor activity likely arises from the presence of the α,β-unsaturated imine motif, which might serve as a Michael acceptor toward nucleophilic motifs within its biological target.[45] Valparicine features the curan skeleton, but the isolation group has suggested that it might biogenetically derive from pericine via its *N*-oxide, both of which were also isolated from *K. arborea*. This hypothesis was strengthened by this group's conversion of pericine *N*-oxide to valparicine via a Potier–Polonovsky reaction.[44a] While that proposal seems very likely to be correct, in the absence of further supporting evidence, it cannot be ruled out that valparicine might originate by simpler biochemical functional group manipulations

Scheme 11. Strategy To Access Valparicine from Synthetic Norfluorocurarine

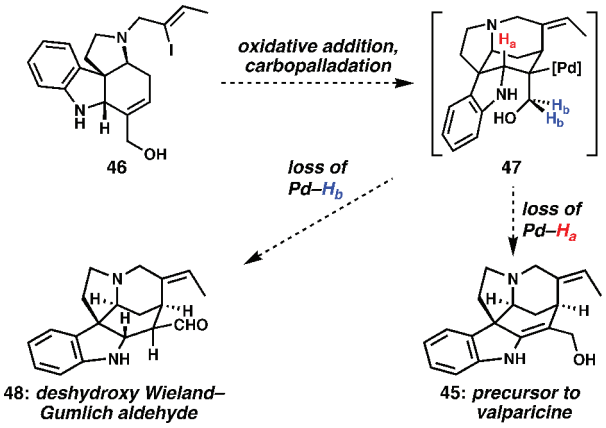


of an alkaloid with the *Strychnos* skeleton already in place. Certainly, there are many degenerate potential pathways for interconversion among indole monoterpene alkaloids, and some *Strychnos*-type alkaloids have been isolated from species of the genus *Kopsia*.[46] Regardless of the true biogenesis of valparicine, we wished to use our synthetic sample of the *Strychnos* alkaloid norfluorocurarine as a key precursor to this bioactive alkaloid.[47]

Initially, we aimed to convert norfluorocurarine to valparicine by carbonyl reduction to give vinylogous hemiaminal **45**, followed by dehydration (Scheme 11). This reduction proved difficult, and only starting material or over-reduced products could be recovered. This outcome almost certainly arises from the vinylogous amide character of this system; indeed, redox chemistry in related systems has been reported to be troublesome.[48]

We wondered if a simple change in the order of operations could be used to circumvent these problems. The aldehyde group of norfluorocurarine precursor **36** might be reduced to give allylic alcohol **46** (Scheme 12). A Heck reaction of this

Scheme 12. Possible Outcomes for Heck Reaction of Allylic Alcohol 46



substrate could have two possible outcomes: β-hydride elimination could take place toward N1 (as was the case for norfluorocurarine) to give the desired vinylogous hemiaminal **45**. Alternatively, β-hydride elimination could occur in the direction of the hydroxyl group to give, after tautomerization, aldehyde **48** (18-deshydroxy-Wieland–Gumlich aldehyde—itself a natural product).[49] The latter outcome would be welcome because incorporation of a C18 hydroxyl group in the

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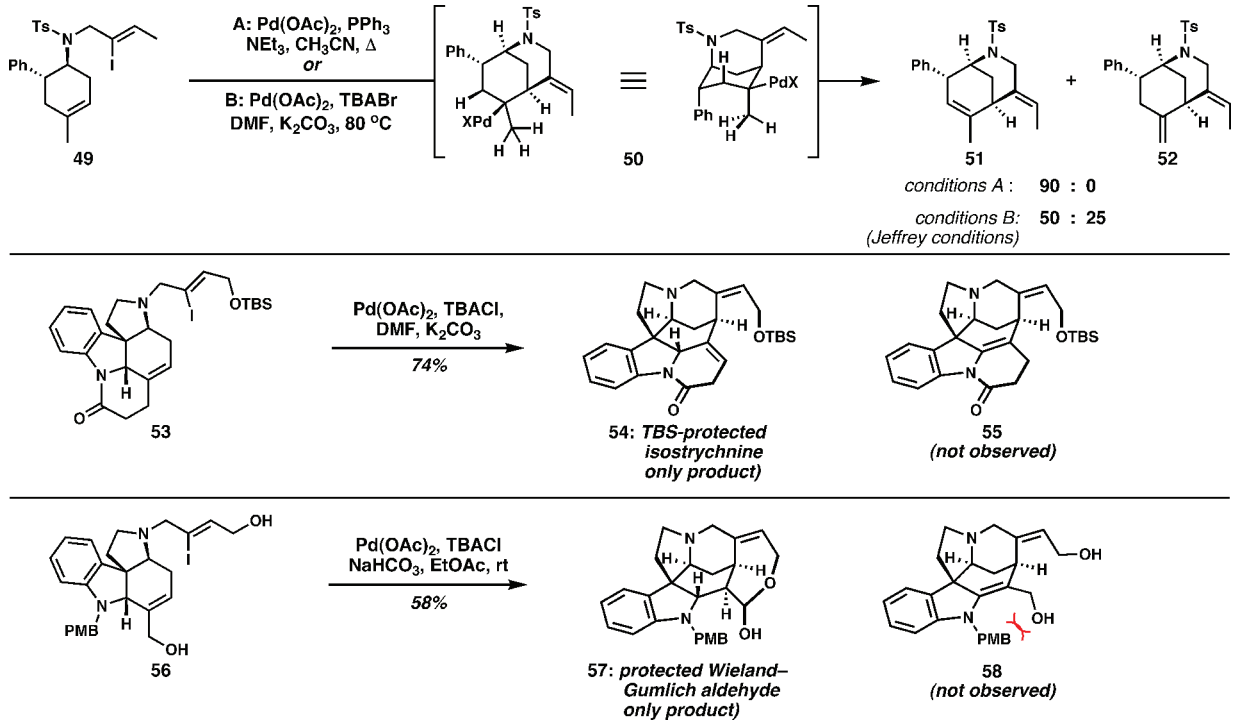
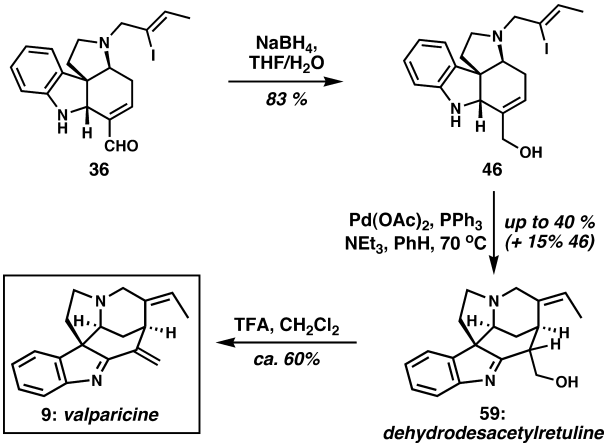
Scheme 13. Literature Examples of Relevant β-Hydride Elimination Behavior



Heck substrate would allow for the synthesis of the Wieland–Gumlich aldehyde, a known precursor to strychnine. At the time, we were aware of some similar systems that had been reported to give variable selectivity, and could in at least one case be tuned by reaction conditions (see **49** → **51**/**52**, Scheme 13).[14,50] Both the Rawal and very recent MacMillan strychnine syntheses take advantage of D-ring Heck cyclizations in which β-hydride elimination proceeds away from nitrogen (**53** → **54** and **56** → **57**).[7e,r]

To test our hypothesis, the aldehyde group of **36** was reduced to give allylic alcohol **46** (Scheme 14). Under a variety of Heck conditions, no aldehyde products were observed. The major product isolated was identified as imine **59**, a tautomer of our expected enamine product **45**, which is in fact the known *Strychnos* alkaloid dehydrodesacetylretuline.[51] We later learned that allylic alcohol **46** had been previously synthesized by Rawal and He via a different route and converted to dehydrodesacetylretuline, also using a Heck reaction.[34c] Although the efficiency is not high, the selectivity in this Heck reaction is notable, and the factors that determine the direction of β-hydride elimination in this and closely related systems are unclear, although a combination of steric effects and stereoelectronic factors (i.e., alignment of C–H and C–Pd bonds, $n_N \rightarrow \sigma^*_{C-H}$ interactions) is likely at play. In any case, treatment of imine **59** with trifluoroacetic acid induced dehydration to yield valparicine (**9**). The spectral data of synthetic valparicine were identical with those reported by Kam and co-workers.[44]

Scheme 14. Synthesis of Valparicine via Dehydrodesacetylretuline



Improved Strategy for Norfluorocurarine and Valparicine. Based on our experience with the synthesis of norfluorocurarine and valparicine, as well as some of our initial forays toward the synthesis of strychnine, we identified some limitations of our bicyclization reaction. A sampling of Zincke aldehydes that were incompatible with the reaction conditions is shown in Figure 5. Problematic functional groups include vinyl halides, free alcohols, alkynes, and some silicon groups. Given the desire to evaluate a variety of such substrates in D-ring-closure experiments, we aimed to find a more general

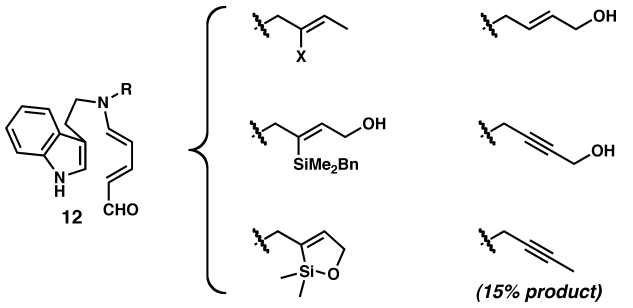


Figure 5. Substrates that were unsuccessful in the bicyclization reaction.

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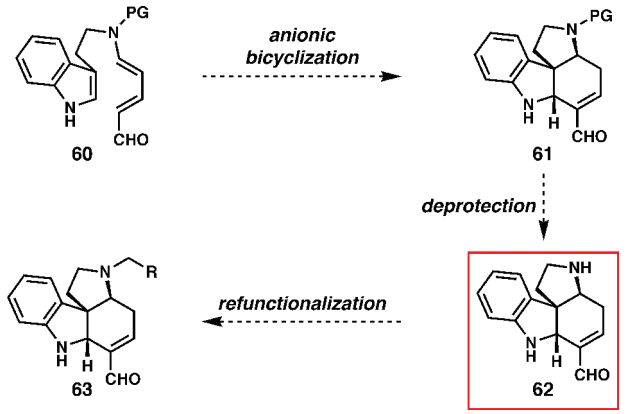
strategy to access N4-functionalized tetracycles. More specifically, we wished to identify a protecting group that could be incorporated into the Zincke aldehyde (see **60**, Scheme 15),

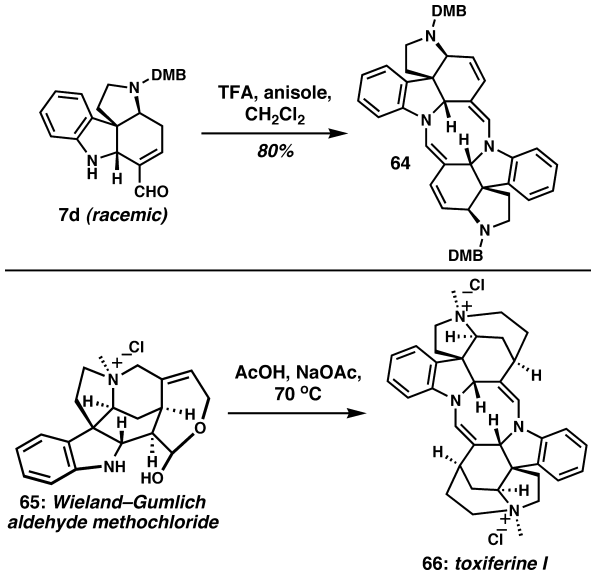
Scheme 15. Second-Generation Approach Incorporating a Protecting Group Would Enable Access to Tetracyclic Alkaloid Cores with Useful Functionality for Subsequent D Ring Closure



carried through the bicyclization reaction, and removed to reveal tetracycle **62** bearing a secondary amine. This strategy would enable the incorporation of a variety of side chains by alkylation chemistry after the cycloaddition reaction with its attendant harshly basic conditions. Tetracycle **62** could not be synthesized directly by cycloaddition, owing to the limited stability of Zincke aldehydes derived from primary amines—substrate **60** (PG = H) would be expected to readily convert to the corresponding pyridinium salts under the cycloaddition conditions. In addition, strongly electron-withdrawing groups (Boc, Ts, Ac, etc.) are precluded because formation of Zincke aldehydes is only efficient for relatively electron-rich secondary amines. We therefore began by experimenting with compounds that we already had on hand.

Our initial efforts to access the desired N-unsubstituted tetracycle from a variety of N-substituted precursors were not successful. Instead, we quickly came to appreciate the sensitive nature of the intermediates we were working with. Removal of benzyl-type protecting groups under reductive conditions was precluded by the reactive α,β-unsaturated aldehyde. Oxidative removal of PMB and the more electron rich DMB groups was similarly unsuccessful owing to complications from the electron-rich aromatic ring. Another method for the removal of the DMB group from amines is by protonolysis with a strong acid such as TFA in the presence of a sacrificial nucleophile such as anisole.[52] Under these conditions, we observed clean dimerization of our starting material **7d** to give **64** containing a central 8-membered diazocine ring (Scheme 16). This product arises from the mutual condensation of the indoline and aldehyde groups of two molecules to afford the dimer as a single diastereomer.[24] Our identification of the product was guided by the knowledge that dimers such as toxiferine I (**66**) are themselves natural products, and similar biomimetic dimerization of *Strychnos* alkaloids has been reported to occur under acidic conditions (AcOH, NaOAc, 70 °C). Natural and semisynthetic analogues of toxiferine I have been explored due to their allosteric modulation of the muscarinic acetylcholine receptor.[53] At this juncture, the structure of **64** has been tentatively assigned presuming that there is a strong bias for

Scheme 16. Dimerization of Tetracyclic Substrates and Analogous Dimerization of *Strychnos* Alkaloids[a]



[a]DMB = 2,4-dimethoxybenzyl.

homodimerization, and calculations indicate a significant thermodynamic preference for this outcome.[24,54] Other conditions that resulted in this type of dimerization process in our studies include: AcOH (solvent), 80 °C; $BF_3{\cdot}OEt_2$, $TiCl_4$ or $Sc(OTf)_3$ in CH_2Cl_2, rt; Meldrum's acid in $CDCl_3$, CH_3CN or MeOH, rt.

Another strategy that held some promise was the acylative dealkylation using reagents such as TFAA[55] or α-chloroethyl chloroformate (ACE-Cl).[56] Acylation of the indoline took place quite readily with several cycloadduct substrates (see **7a,b,c,d** → **67**, Scheme 17), but under the typical conditions required to induce acylation of the tertiary amine (and subsequent dealkylation), we observed no further reaction in any case. After we had abandoned this approach, Andrade and co-workers reported their synthesis of strychnine which relied on exactly this reaction, but with the corresponding methyl ester **69** (rather than our aldehyde).[7o] They found it necessary to heat the amine in neat ACE-Cl at 135 °C for 48 h to achieve debenzylation. Subsequent methanolysis at reflux gave the tetracyclic ester **71** bearing the liberated secondary amine in good overall yield. Given the sensitivity of our α,β-unsaturated aldehyde under a variety of conditions, as well as the propensity of our target **62** to decompose above 0 °C (see below), we chose not to revisit this strategy, especially given the success of the methods that we investigated next.

Given the failure of the methods described above, we tried some more exotic solutions to our problem that deserve brief comment. Two other protecting groups that we explored were Si- and Se-substituted ethyl groups. It was our hope that the 2-(trimethylsilyl)ethyl group could be cleaved with fluoride to reveal the desired NH product with release of ethylene. For the selenoethyl group, our hope was that the chalcogen atom could be oxidized to the selenoxide, setting up for a syn elimination that would provide an enamine that could be subsequently hydrolyzed.[57] The required substrates could be accessed from $TMSCH_2CH_2Br$ and $PhSeCH_2CHO$ in three steps each.[24] Not surprisingly, when TMS-ethylamine-derived substrate **7e** was treated with different fluoride sources under a variety of

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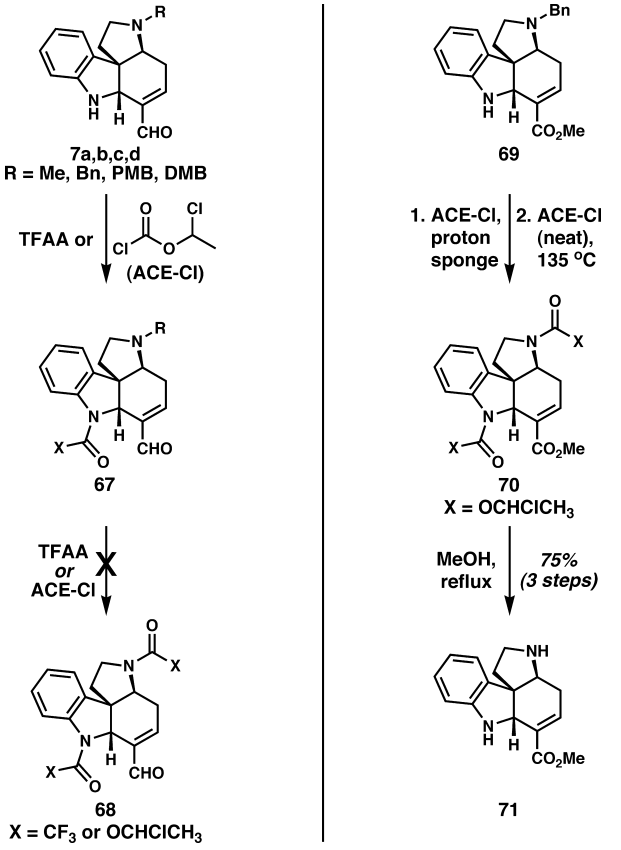
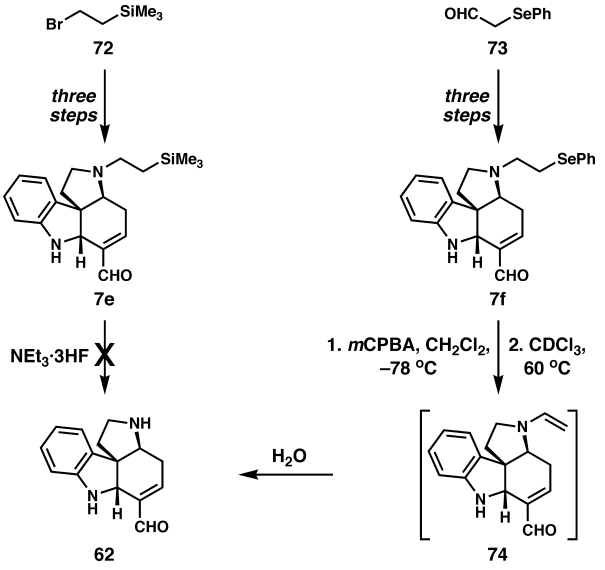
Scheme 17. Acylative Dealkylation Is Unsuccessful for Our Aldehyde-Bearing Substrates but Was Successfully Employed by Andrade and Co-workers on the Corresponding Ester 69



Scheme 18. Early Efforts in Protecting Group Strategy Proved that Deprotected Tetracycle Was Isolable



conditions, only slight decomposition of the silane was observed, and the majority of the starting material was left unchanged. Attempted alkylation (using electrophiles that would introduce useful side chains onto the nitrogen atom) to form the quaternary ammonium salt prior to dealkylation, a strategy that held more promise, also proved unworkable in the presence of the free indoline. Conversely, when the selenide **7f** was treated with 1 equiv of *m*CPBA at −78 °C, clean conversion to the selenoxide was observed. This intermediate was stable and could be observed after aqueous workup. When heated to 60 °C to initiate syn elimination, followed by aqueous workup and column chromatography, we were delighted to observe the first sample of tetracycle **62** (Scheme 18). It was a relief to observe that this compound was reasonably stable to isolation, given the presence of two nucleophilic amines and two electrophilic carbon atoms. The lengthy synthesis of the selenide substrate and associated low yields forced us to find a more readily available substrate that could be deprotected under mild conditions.

The final protecting group that we would explore was the allyl group. The allyl group has seen some use as a protecting group for nitrogen, although Alloc carbamates are much more prevalent. Deprotection of allylic amines has been accomplished by KO-*t*-Bu- or Rh/Ir-mediated isomerization to the enamine followed by hydrolysis, as well as by Pd-catalyzed deallylation.[52,58] Our synthesis began with N_b-allyltryptamine, a known compound that is most efficiently prepared by reaction of tryptophyl bromide with allylamine, which was converted to the corresponding Zincke aldehyde **12g** in 81% overall yield.[24,59]

The bicyclization of **12g** (Scheme 19) was sensitive to concentration, giving the highest yield (64%) at 0.02 M (see above). Although we observed small amounts of KO-*t*-Bu-mediated deallylation in the course of cycloadditions run above 80 °C, it was more effective to prevent this reaction and maximize the yield of the product **7g**. We were delighted to observe that Pd-catalyzed deallylation of **7g** was effective under very mild conditions (0 °C, <1 h) using *N*,*N*′-dimethylbarbituric acid (**75**) as the allyl scavenger;[58] however, this deallylation was accompanied by a Knoevenagel condensation followed by Michael addition of a second equivalent of the nucleophile, delivering **76**. This undesired process could be easily prevented by incorporation of an alkyl group on the barbituric acid derivative to prevent the dehydration step of the Knoevenagel reaction, and Bn derivative **77** or commercially available 5-methyl Meldrum's acid was used for all our subsequent investigations. Now, for the first time, we were able to isolate tetracycle **62** in appreciable yield.[60] As alluded to above, the resultant product was poorly stable. As a consequence, isolated yields of **62** were not as high as expected, and storage led to degradation; however, in situ realkylation of the liberated secondary amine provided an attractive solution to this problem, giving access to many new substrates of type **63** in good yields (see below for examples).

Having developed a short, efficient, and more convergent approach to substrates that were previously unavailable directly from the bicyclization reaction, we briefly revisited our syntheses of norfluorocurarine and valparicine. As discussed above, the required vinyl halide could not be carried through the bicyclization reaction owing to competitive dehydrohalogenation. Deallylation of **7g** in $CDCl_3$ in the presence of methyl Meldrum's acid (**78**) followed by addition of allylic bromide **79**,[39] Hünig's base and CH_3CN provided key Heck precursor **36** in 68% yield (Scheme 20). It is noteworthy that Pd^0 reacts with the protonated allylic amine efficiently at 0 °C but that oxidative addition of residual catalyst to the allylic bromide or the vinyl iodide is not a competing process at that temperature. This improved approach accesses intermediate **36** in only four steps from commercially available tryptophyl bromide and, most importantly, avoids the problematic iododesilylation step,

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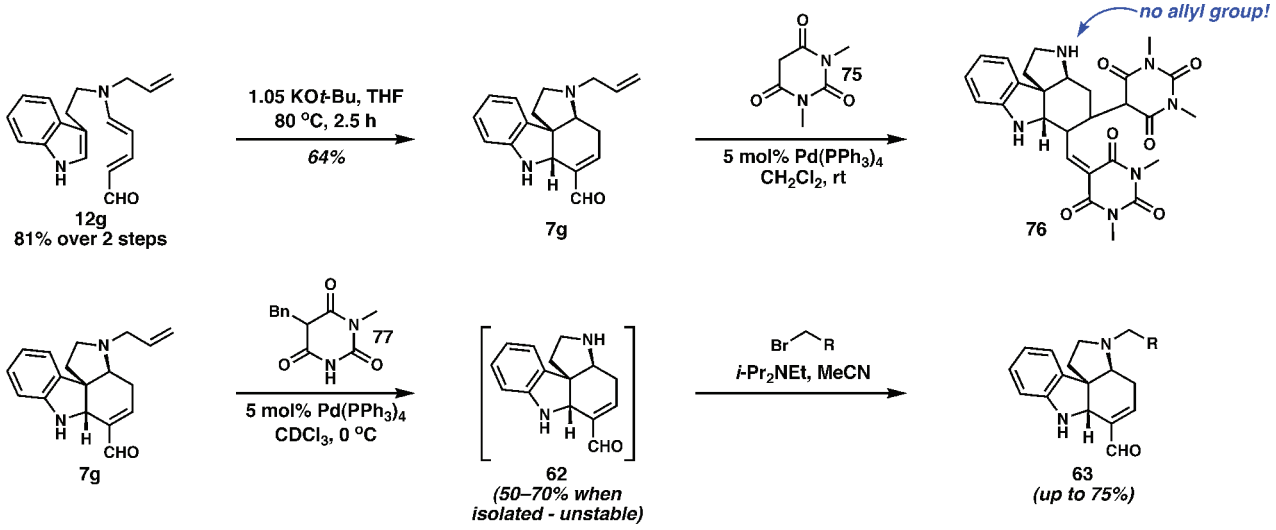
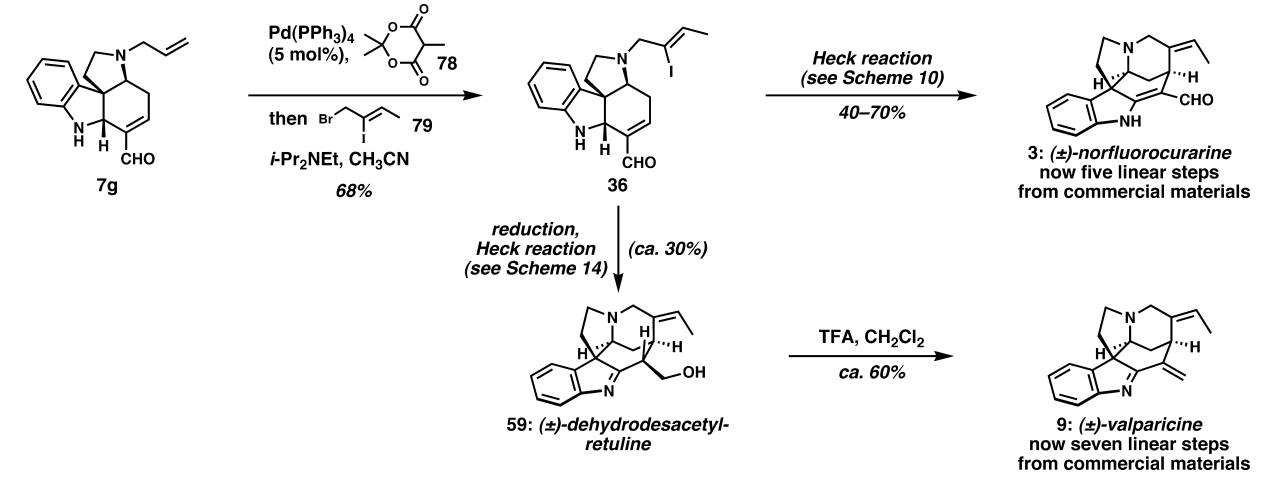
Scheme 19. Smooth Removal of the Allyl Protecting Group Allows in Situ Refunctionalization To Access Products Not Available by Direct Cycloaddition

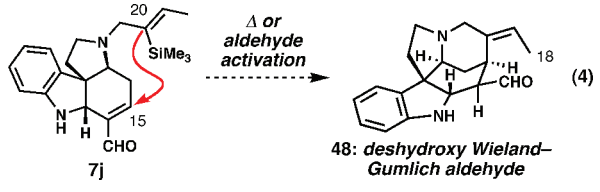


Scheme 20. Improved Syntheses of Norfluorocurarine, Dehydrodesacetylretuline and Valparicine



thereby obviating the need for indoline protection. Using the Heck cyclization that we had previously optimized, the synthesis of norfluorocurarine can now be carried out in only five linear steps (25% overall yield), and valparicine can now be synthesized in seven linear steps (6% overall yield), providing a practical route for further biological investigations of this interesting molecule.

First Attempted Synthesis of Strychnine: An Unexpected Cycloreversion. Having established an efficient route to the alkaloids norfluorocurarine and valparicine, we were excited to develop a concise synthesis of the flagship member of the *Strychnos* family. Taking inspiration from many previous syntheses, our penultimate target en route to strychnine would be the Wieland–Gumlich aldehyde, and the missing piece was a method to close the D-ring. Although a Heck reaction had been successful in our synthesis of norfluorocurarine, this reaction type precludes access to the pentacyclic core without introduction of an undesired C2–C16 double bond (see above). Conjugate addition procedures were therefore evaluated to access products of the desired oxidation state. Given the established utility of vinylsilanes as nucleophiles for cyclization reactions,[61] we were compelled to investigate the cyclization of our previously synthesized vinylsilane substrate **7j** to form 18-deshydroxy Wieland–Gumlich aldehyde (eq 4). As before, this reaction would serve as a model for an analogous approach to the Wieland–Gumlich aldehyde itself.



(4)

We began by simply heating vinylsilane **7j**, with or without microwave irradiation. In most cases no reaction was observed, although at 220 °C in *o*-DCB we observed slow decomposition of the starting material. We next treated this substrate with Lewis acids to activate the α,β-unsaturated aldehyde toward nucleophilic attack. A variety of Lewis acids ($TiCl_4$, $Sc(OTf)_3$, etc.) were ineffective in generating any cyclization products, although in some cases dimerization occurred to give diazocine products (similar to protic acids; see above). We also considered the use of a secondary amine to generate a more electrophilic α,β-unsaturated iminium species; examples of

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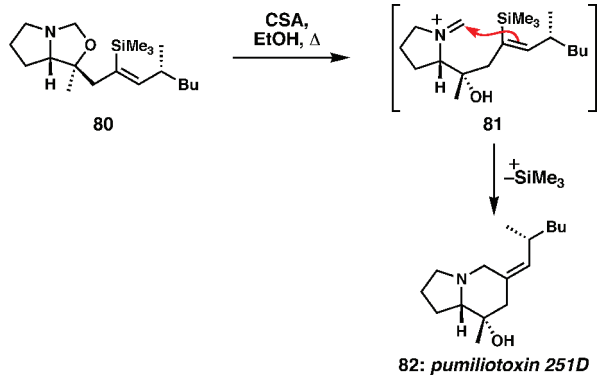
iminium-initiated vinylsilane-terminated cyclization reactions are well-known from Overman and co-workers. An example is shown in Scheme 21.[61]

Scheme 21. Vinylsilane-Terminated Iminium Cyclization in the Overman Synthesis of Pumiliotoxin 251D[a]



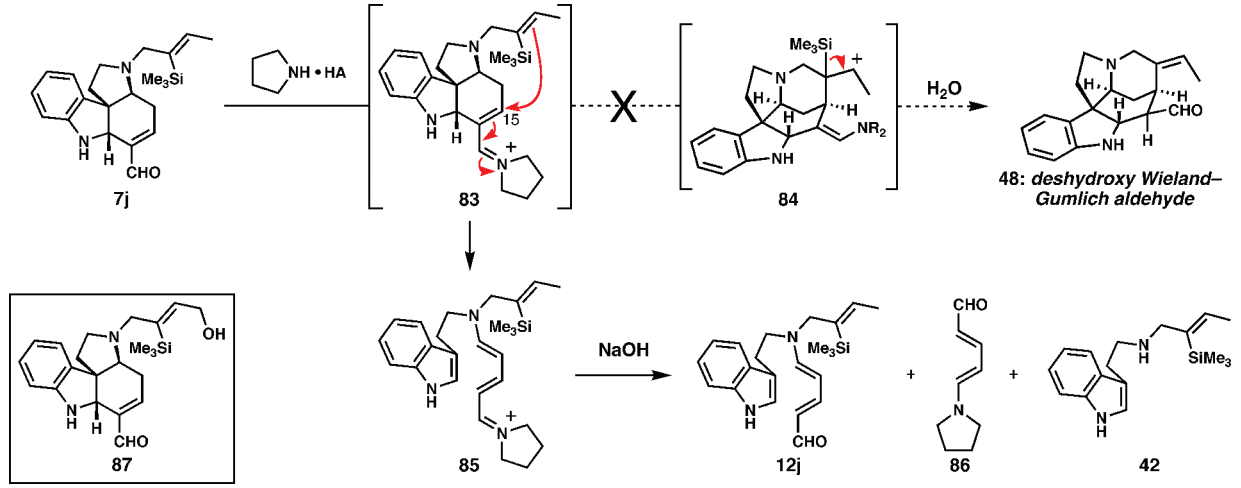
[a]CSA = camphorsulfonic acid.

In our case, the unsaturated iminium ion would be activated for intramolecular attack at C15, analogous to the iminium activation popularized by MacMillan and others.[62] Using stoichiometric pyrrolidine as a secondary amine with acid catalysis (TFA or HF), we could observe the apparent formation of an iminium intermediate **83** (Scheme 22) by mass spectrometry. Even after substantial heating, no cyclization was observed, but a new product with the same mass as the iminium species was observed. After aqueous workup, we isolated a familiar product: Zincke aldehyde **12j**. Similar results were obtained using different secondary amines (Et_2NH, morpholine) in different solvents (CD_3CN, $CDCl_3$, *i*-PrOH, HFIP) and using the C18-hydroxylated silane **87** (see below for its preparation). Seemingly, iminium species **83** undergoes cycloreversion (stepwise or concerted) to give the fully conjugated iminium species **85**, rather than piperidine **84** that should lead to deshydroxy Wieland–Gumlich aldehyde. Contrasting with the successful cycloaddition, in which the formation of the tetracyclic product—as its corresponding enolate—is clearly favored, this unexpected cycloreversion is likely favored by restoration of aromaticity of the indole and the generation of the stable, highly conjugated iminium ion. This dichotomy is remarkable and is the subject of ongoing studies.

A Successful Conjugate Addition Strategy Enables a Six Step Linear Synthesis of Strychnine. Given the failure of efforts to directly initiate a conjugate addition reaction using the C19–C20 π-bond of vinylsilane **7j**, we returned to the arena of transition metal catalysis. A conjugate addition reaction of a suitable vinylmetal species was the most attractive option to directly deliver the Wieland–Gumlich aldehyde without the need for subsequent redox manipulations. Most often, vinylmetal species are generated by lithium–halogen exchange of the vinyl halide precursors, and the resulting nucleophiles can engage in conjugate addition processes with catalytic or stoichiometric quantities of copper salts.[63,64] Given the presence of the indoline NH and sensitive aldehyde, an approach involving reactive organolithium species seemed unlikely to be successful, and a few experiments rapidly confirmed that suspicion. We therefore sought a precursor that could potentially be directly transmetalated to a transition metal such as copper. While a vinyltin or vinylboron species might be ideal for this purpose, potential routes for the stereoselective synthesis of compounds **88** or **89** (to be incorporated by alkylation of tetracycle **62**) appeared lengthy, especially given our desire to access this building block in a minimum number of steps to maximize convergency and minimize step count. In addition, β-bromostannanes related to **88** were known to be unstable with respect to allene formation and loss of R_3SnBr.[65] Based on our previous experience, we expected that the corresponding vinylsilane (**90**) would be quite stable. Although aryl- and vinyltrialkylsilanes generally transmetallate quite slowly, we recognized that the cis-disposed alcohol might participate in activation of the silicon toward transmetalation to copper, as shown by Takeda and co-workers and more recently by Smith and co-workers (Scheme 23).[66,67]

Previous routes to electrophiles of the types shown in Figure 6 were lengthy; for example, vinyl iodide **91** used by Rawal and others was made in six steps from propargyl alcohol, including three protecting group manipulations. Ultimately, these operations never served to lengthen the linear reaction sequence because the synthesis of the core always required more steps. We felt compelled to advance a new and more

Scheme 22. Attempted Use of Iminium Catalysis To Effect Vinylsilane Cyclization Results in an Unexpected Retro-Cycloaddition Reaction To Afford Zincke Aldehyde Products



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Scheme 23. Recent Examples of Copper-Mediated Brook Rearrangements with Functionalization of the Resultant Vinylcopper

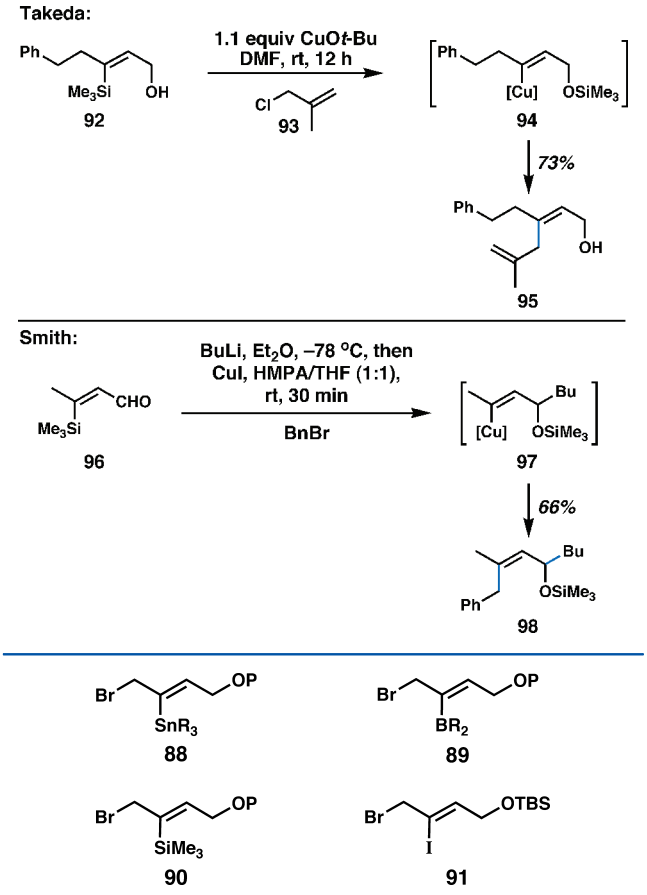
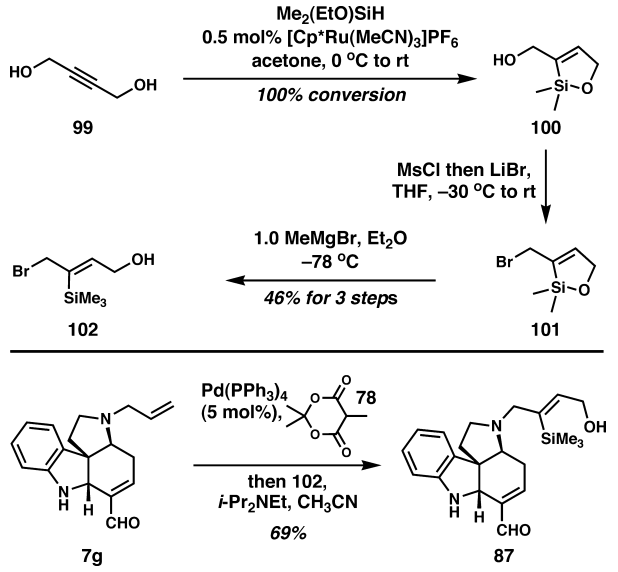


Figure 6. Potential reagents for introduction of useful vinylmetalloids and known vinyl iodide **91**.

direct solution. We began with a ruthenium-catalyzed trans-hydrosilylation of 1,4-butynediol using conditions reported by Trost and Ball,[68] which provided silane **100** with complete control of alkene geometry in high yield (Scheme 24). This reaction is scalable, proceeds with as little as 0.5 mol % catalyst, and converts inexpensive 1,4-butynediol into the required *Z*-vinylsilane, while at the same time differentiating the two hydroxyl groups. With one of the hydroxyl groups internally protected as a silyl ether, the other could be converted to the bromide (**101**) under standard conditions. Subsequent treatment with methylmagnesium bromide chemoselectively opened the siloxacycle and provided the desired vinylsilane **102** in 46% yield over three steps. This efficient sequence quickly provides access to significant quantities of this polyfunctional, stereodefined trisubstituted alkene. Importantly, the free alcohol in **102** did not readily suffer alkylation, even when it was stored neat at −20 °C. When allylic bromide **102** was added to the reaction mixture after complete deallylation of **7g** using methyl Meldrum's acid, refunctionalized core **87** was isolated in 69% yield. The alkylation was chemoselective for N_b-alkylation, and the ability to work with the free hydroxyl group eliminated the need for protecting group manipulations.

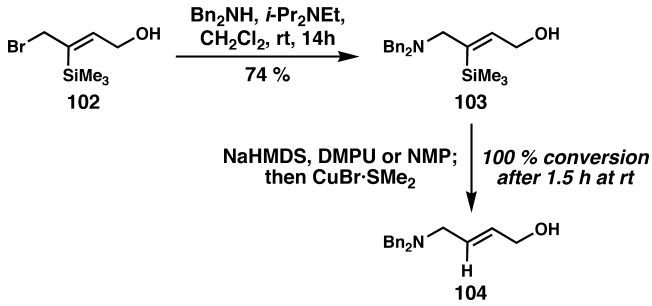
With access to vinylsilane **87**, we began investigation of the final C−C bond formation, which we hoped would take the form of a sequential Brook rearrangement[69]/conjugate addition process, related to the reactions shown in Scheme 23.

Scheme 24. Stereoselective Synthesis of Trisubstituted Alkene 102 and Alkylation of the Tetracyclic Core To Generate 87



Application of conditions reported by Takeda and co-workers (CuO-*t*-Bu, THF, or DMF)[66] resulted in recovery of starting materials at lower temperatures, and decomposition at elevated temperature. Similarly, conditions inspired by Smith and co-workers (*n*-BuLi or NaHMDS, then CuI, THF/HMPA or THF/DMPU)[67] were not successful in promoting the desired process in the desired system or model system **103** (Scheme 25), which

Scheme 25. Model System Confirmed That Allylic Amine Is Tolerated in a Brook Rearrangement[a]



[a]NaHMDS = sodium hexamethyldisilazide, NMP = *N*-methylpyrrolidinone, DMPU = 1,3-dimethylpyrimidin-2-one.

also incorporates the potentially problematic allylic tertiary amine. Smith reported that the addition of a polar cosolvent was necessary to trigger the Brook rearrangement of the alkoxide.[67] Indeed it was not until DMPU was used as the sole solvent that the Brook rearrangement/protonolysis product was observed in the model system, cleanly generating **104**.

When these optimal conditions were applied to the real system (**87**), Brook rearrangement could be triggered in the presence of excess base, but cyclization did not occur; only protodesilylation to form **105** (Scheme 26) was observed. When the reaction mixture was heated to 40 °C, partial cyclization was observed, and small quantities (<5% recovery) of the Wieland−Gumlich aldehyde (**8**) were painstakingly isolated. As we had envisioned, the free alcohol present in **87** enabled a Brook rearrangement of the corresponding alkoxide

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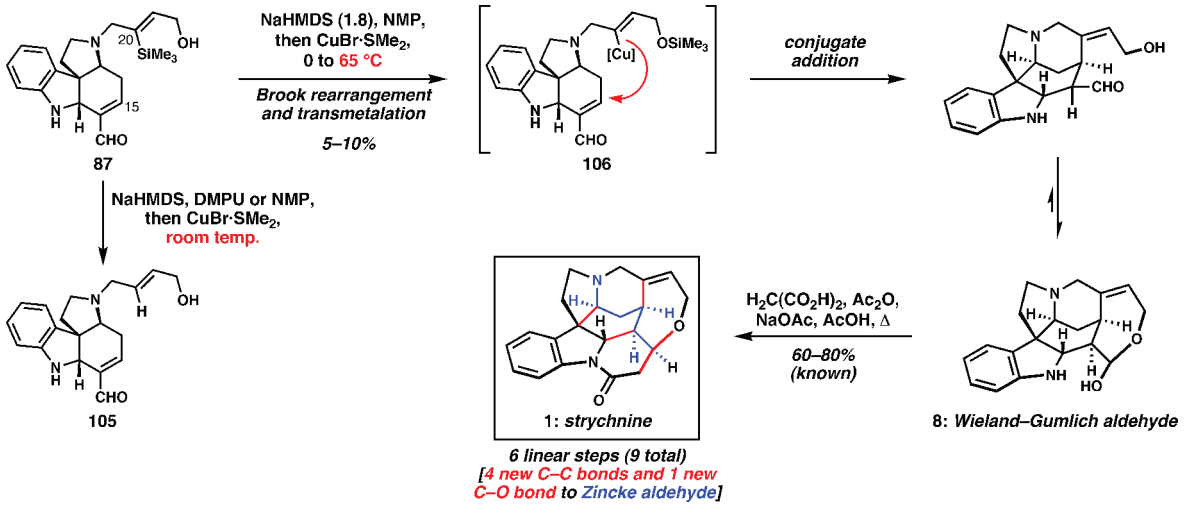
Scheme 26. Completion of the Synthesis of Strychnine Using a Brook Rearrangement/Conjugate Addition Cascade[a]

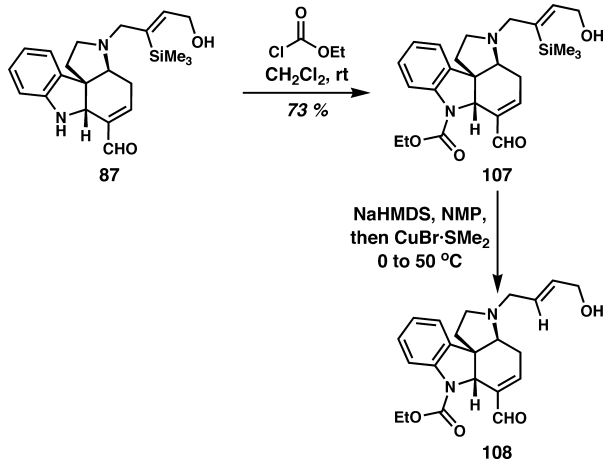


[a]NaHMDS = sodium hexamethyldisilazide, NMP = *N*-methylpyrrolidinone.

with presumed transmetalation to copper (see **106**), followed by intramolecular conjugate addition to afford the Wieland–Gumlich aldehyde, albeit in low yield. All optimization to date led to the identification of NMP as the better solvent, NaHMDS and KHMDS as preferred bases (Li prevents Brook rearrangement), and 65 °C as the temperature of choice for cyclization, yielding the Wieland–Gumlich aldehyde in up to 10% yield. Higher temperatures did not improve the cyclization yield. While the efficiency of this final bond construction is certainly lower than desired, there are several other reports that highlight the difficulty in forging the C15–C20 bond in related contexts.[7i,37c,65] With the known conversion of the Wieland–Gumlich aldehyde to strychnine, the adoption of this Brook rearrangement-based strategy enabled the completion of the synthesis in only six linear steps from commercially available starting materials because of the rapid, convergent assembly of vinylsilane **87**.

In our investigations, we explored a variety of potential ligands (phosphines, phosphites, phosphine oxides, pyridine, bipy), precatalysts (CuI, CuCN, CuTC, Cu-NHC complexes),[70,71] and additives (NaOAc, $Sc(OTf)_3$, $BF_3{\cdot}OEt_2$), but were unable to increase the yield above about 10%. In most reactions, the mass balance consists largely of the formal protodesilylation product **105** that likely arises via Brook rearrangement/hydrolysis of the resulting vinylmetal. Given the presence of acidic protons in the substrate and product, this premature quenching of the key reactive organometallic reagent is not readily avoided and results in an inefficient and irreproducible reaction. In addition, the excess base used may result in partial deprotonation of the *α,β*-unsaturated aldehyde, with the resulting dienolate no longer electrophilic at C15. We believe that these two issues conspire to render the efficiency of conversion of **87** to the Wieland–Gumlich aldehyde inherently limited. In an effort to minimize self-quenching, carbamate-protected **107** (Scheme 27) was synthesized and subjected to the Brook rearrangement/conjugate addition conditions. In this case, no cyclized product was observed and only protodesilylated material (**108**) was isolated. We surmise that the presence of the carbamate group forces the aldehyde out of conjugation with the alkene, preventing conjugate addition of the vinylcopper nucleophile. Once again, deprotonation of the *α,β*-unsaturated aldehyde may also prevent cyclization or prematurely quench the key reactive intermediate.

Scheme 27. Attempted Use of an Indoline Protecting Group to Avoid Protonation[a]



[a]NaHMDS = sodium hexamethyldisilazide, NMP = *N*-methylpyrrolidinone.

Efforts To Develop an Improved D-Ring Closure. Given the relative inefficiency of the Brook rearrangement/conjugate addition reaction in accessing the Wieland–Gumlich aldehyde, we examined slightly altered approaches to improve the key D-ring formation. We believe that the low yields in this final reaction primarily arise from premature protonation of the presumed vinylcopper intermediate, as discussed above. Given the ease with which the required vinylsilane was constructed, and the promising reactivity we observed, we wondered if a change in the order of the last two steps of our synthesis could circumvent these problems. Inspired by the mechanistic rationale for the well-established conversion of the Wieland–Gumlich aldehyde to strychnine,[3c,24] we considered the product of a similar reaction of *α,β*-unsaturated aldehyde **87** with dimethyl malonate as a potential starting point for further investigations. The *α,β,γ,δ*-unsaturated malonamate derivative **110** (Scheme 28) would have the following advantages in the requisite Brook rearrangement/conjugate addition cascade:

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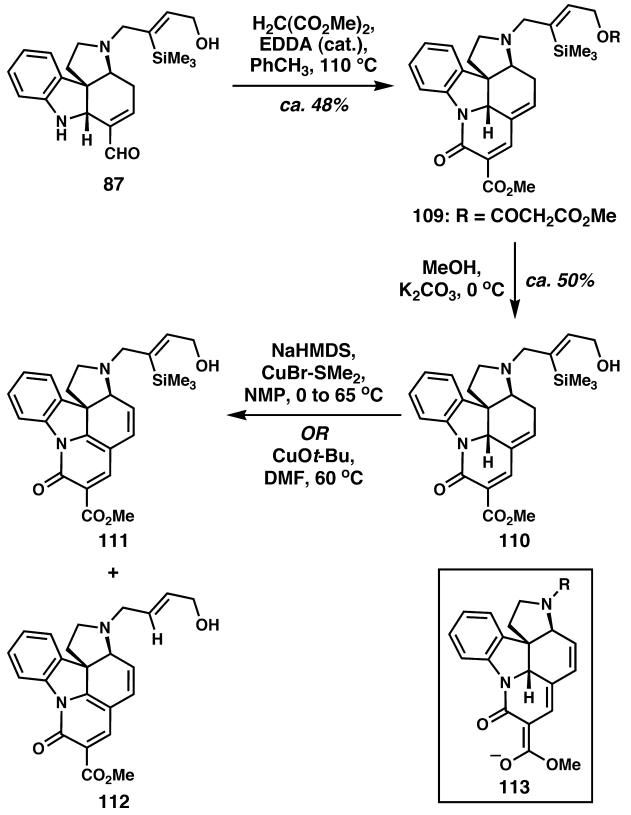
Scheme 28. Formation of Unsaturated Malonamate 110 and Attempts at Brook Rearrangement/Conjugate Addition Resulting in Pyridone Products[a]



[a]EDDA = ethylenediamine-*N*,*N*′-diacetic acid, NaHMDS = sodium hexamethyldisilazide, NMP = *N*-methylpyrrolidinone.

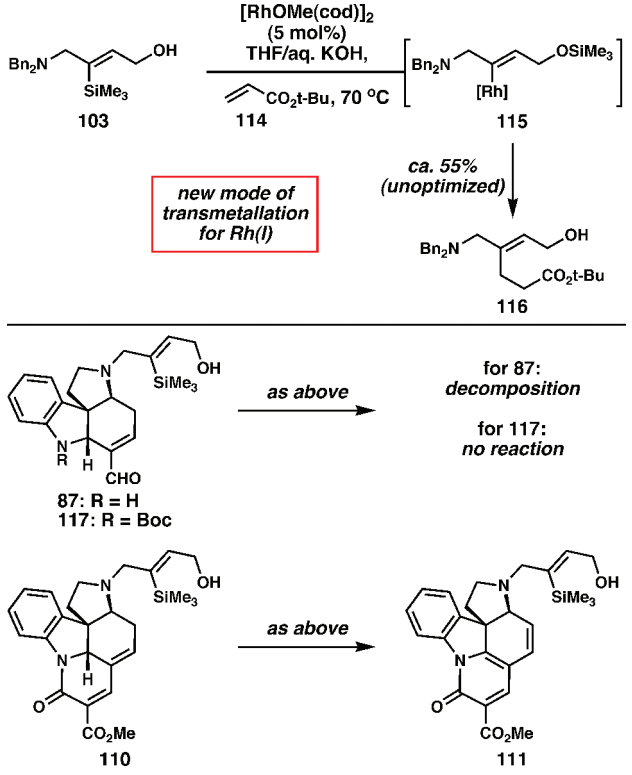
(1) it no longer has an acidic indoline NH group; (2) it no longer has a reactive aldehyde group; and (3) the olefinic C15 position is now activated by two electron-withdrawing groups (although further removed), which could potentially enhance its electrophilic character. Furthermore, a demethoxycarboxylation reaction of the product should deliver strychnine (or isostrychnine) in a single step.

Unsaturated malonamate derivative **110** was accessed by Knoevenagel condensation of tetracycle **87** under conditions that minimize acid-catalyzed dimerization of the enal as well as amine-catalyzed ring-opening (see above).[72] This condensation/cyclization was accompanied by trans-esterification of dimethyl malonate with the primary alcohol, requiring subsequent methanolysis of the undesired ester in **109**. Although the recent procedure of Andrade and co-workers[73] would likely render this transformation more efficient, we obtained enough material to explore the desired cyclization reaction using our previously developed conditions. The major products under the basic conditions used for the Brook rearrangement/conjugate addition cascade were identified as pyridones **111** and **112**. These products likely derive from undesired deprotonation at C14 to form stabilized trienolate **113**, facilitated by the second electron-withdrawing group. This product apparently suffers oxidation by molecular oxygen or copper(I) to give the observed pyridone. Similar pyridone intermediates had previously been reported by Woodward and Vollhardt in their respective syntheses of strychnine.[7a,i,65]

Unfortunately, we have thus far been unable to prevent this unwanted process.

The problems associated with premature protonation of the basic vinylcopper intermediate led us to also explore rhodium(I) as an alternative, because of its established ability to mediate conjugate addition, its tolerance of water, and the potential to render the reaction catalytic in transition metal. While there are reports of transmetalation of tetraorganosilanes to Cu(I) and to Pd(II) by assistance of a proximal alkoxide, transmetalation of these species to Rh(I) was not found in the literature.[74] We determined the feasibility of the desired process using our model system **103**. Treatment of this vinylsilane with 5 mol % of dimeric Rh(I) catalyst in THF/aq KOH in the presence of *tert*-butyl acrylate led to the desired Brook rearrangement/conjugate addition product in 55% unoptimized yield (Scheme 29). This result confirmed that the desired

Scheme 29. New Transmetalation Reaction to Rh(I) and Its Attempted Use To Access the Wieland−Gumlich Aldehyde



transmetalation reaction does occur and that the overall process proceeds well with catalytic quantities of rhodium. We were eager to apply these conditions to the key C15−C20 bond formation. Using free indoline **87** resulted in decomposition in the presence of the rhodium catalyst, while using Boc-protected indoline **117** resulted only in recovery of starting material; no Brook rearrangement was observed in this more complex system. We also subjected malonamate **110** to the rhodium catalyst, and the basic conditions once again led to facile oxidation to the pyridone **111** without Brook rearrangement. The lack of reactivity in these complex systems is not fully understood at this point, and an extensive evaluation of different catalysts and conditions has not been undertaken. Nonetheless, given the promising reactivity observed in the model system (**103** → **116**), this type of Brook rearrangement/

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transmetalation/C−C bond-forming reaction is worthy of further study.

CONCLUSION

We have developed a base-mediated anionic bicyclization reaction of tryptamine-derived Zincke aldehydes to form the ABCE tetracyclic core of a variety of monoterpene indole alkaloids in just three steps from tryptamine or tryptophyl bromide. The use of the N-allyl protected tetracycle as a readily accessible and versatile intermediate enables facile access to more complex N-functionalized tetracycles that were previously unavailable due to the harsh conditions required for the bicyclization reaction. The convergent approach that resulted enabled concise syntheses of the indole alkaloids norfluorocurarine, dehydrodesacetylretuline, valparicine, the Wieland−Gumlich aldehyde and strychnine, clearly documenting the utility of Zincke aldehydes for complex molecule synthesis. This strategy also enables four-step access to complex tetracyclic intermediates that may prove broadly useful for the synthesis of many other monoterpene indole alkaloids. Our synthesis of strychnine is particularly notable; in the course of only four steps, four new carbon−carbon bonds and one carbon−oxygen bond are forged to the five carbons of the Zincke aldehyde, exploiting much of the latent functionality present in this type of donor−acceptor diene. In the context of this strychnine synthesis, we also identified a sequence featuring Ru-catalyzed trans-hydrosilylation and Cu-mediated Brook rearrangement/transmetalation/conjugate addition that might prove generally applicable to the synthesis of other stereodefined, trisubstituted allylic alcohols.

New aspects of our work described for the first time include: (1) examination of the substrate scope of the key cycloaddition reaction; (2) preliminary mechanistic discussion; (3) a second-generation five-step synthesis of norfluorocurarine; (4) short syntheses of dehydrodesacetylretuline and the antitumor alkaloid valparicine; (5) a surprisingly facile dimerization of our tetracyclic enal intermediates; (6) a fascinating retro-cycloaddition that converts tetracyclic intermediates back to Zincke aldehydes; and (7) some new reactivity at the nexus of Brook rearrangements and Rh(I) catalysis.

The successes and unexpected detours in our efforts to define short syntheses of several *Strychnos* alkaloids, including the benchmark target strychnine, highlight the fascinating yet largely unexploited reactivity of Zincke aldehydes and their potential to serve as building blocks for the synthesis of complex natural products.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an inert atmosphere of nitrogen or argon in oven-dried or flame-dried glassware with magnetic stirring, unless otherwise noted. Solvents were dried by passage through columns of activated alumina. THF (for anionic bicyclization reactions) and acetone (for hydrosilylation reactions) were degassed by three cycles of freeze/pump/thaw. Pyridine, diisopropylethylamine, triethylamine, and *N*-methyl-2-pyrrolidinone (NMP) were distilled from calcium hydride prior to use. 5-Methyl Meldrum's acid (**78**) was recrystallized from acetone/H_2O.[75] [Cp*Ru-$(CH_3CN)_3$]PF_6 was purchased from a commercial supplier and stored in a glovebox at −20 °C. All other reagents were prepared by known literature procedures or used as obtained from commercial sources, unless otherwise indicated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm coated commercial silica gel plates (F254 precoated glass plates) using UV light as visualizing agent and $KMnO_4$ and heat as a developing agent. Flash chromatography was performed on silica gel (230−400 mesh). Melting points uncorrected. ^1H and ^{13}C NMR spectra were obtained at 500 or 600 MHz at 298 K, unless otherwise indicated. Abbreviations for multiplicity are as follows: app indicates apparent, br indicates broad, d indicates doublet, t indicates triplet, q indicates quartet, m indicates multiplet. Chemical shifts are reported in ppm referenced to the internal solvent residual of $CDCl_3$ or DMSO-d_6 at 7.27 ppm and 2.50 ppm for ^1H NMR and 77.1 ppm and 39.5 ppm for ^{13}C NMR, respectively. IR spectra were obtained on an FT-IR spectrophotometer using NaCl plates. High-resolution mass spectrometry data were obtained by LC-ESI or GC-CI.

Notes. (1) Chromatographic purification of Zincke aldehydes usually yields a brown semisolid that appears pure by ^1H and ^{13}C NMR analysis. Further purification by treatment with activated charcoal in CH_2Cl_2 yields a yellow solid. This additional purification was critical for the success of the cycloaddition reaction. (2) Compound numbering protocols, as referred to in the NMR data provided below, can be found in the Supporting Information.

Compounds Not Referred to in Text. There are numerous new compounds made as intermediates in the course of the work described in this paper that are not explicitly mentioned in the text above. Experimental details and characterization data for these compounds can be found below. The chemical structures of these compounds (labeled **S1** through **S31**) can be found in the Supporting Information.

Compounds Previously Described by Our Research Group. A graphical listing of compounds mentioned in this paper that were previously described in refs 7q and 15 can be found in the Supporting Information.

General Procedure a for Zincke Aldehyde Formation. To a solution of secondary amine (2.1 equiv) in EtOH (0.4−0.8 M in amine) was added 1-(2,4-dinitrophenyl)pyridinium chloride (**20**)[12a] (1.0 equiv). After being stirred for 30 min at rt, the red mixture was heated to 80 °C for 1−4 h and then cooled to rt. The reaction mixture was quenched with 2 M NaOH (2−4 equiv NaOH), stirred at rt for 30 min, and then diluted with EtOAc and H_2O. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed successively with 2 M NaOH and brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography to yield the desired product as a red-brown solid or oil and recovered amine. Further purification by column chromatography and treatment with activated charcoal (~1 mass equivalent) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal gave a yellow solid or foam.

(1*E*,3*E*)-5-Oxopenta-1,3-dienyl pivalate (S8).[76] To a suspension of potassium glutaconaldehyde[77] (10.2 g, 75.0 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL, 0.30 M) at 0 °C was added triethylamine (10.4 mL, 75.0 mmol, 1.0 equiv) followed by trimethylacetyl chloride (10.2 mL, 82.5 mmol, 1.1 equiv). The reaction solution was stirred at 0 °C for 3 h and then washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo to afford 13.2 g of a yellow oil. The oil was purified by flash chromatography (15:85 EtOAc/hexanes) to afford the desired product (12.4 g, 91%) as a crystalline yellow solid: mp = 59−61 °C; R_f = 0.3 (1:3 Et_2O/hexanes); ^1H NMR (500 MHz, $CDCl_3$) δ 9.56 (d, J = 8.0 Hz, 1H, C*H*O), 7.82, (d, J = 12.1 Hz, 1H, δ-C*H*), 7.13 (dd, J = 15.2, 11.7 Hz, 1H, β-C*H*), 6.30 (dd, J = 12.1, 11.7 Hz, 1H, γ-C*H*), 6.20 (dd, J = 15.2, 8.0 Hz, 1H, α-C*H*), 1.29 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 193.2, 174.7, 148.3, 146.0, 131.7, 113.2, 38.9, 26.8; IR (thin film) ν 3074, 2977, 1754, 1687, 1645, 1128 cm^{-1}; HRMS (GC-CI) m/z calcd for $C_{10}H_{15}O_3$ $(M + H)^+$ 183.1021, found 183.1013.

General Procedure B for Zincke Aldehyde Formation. To a solution of secondary amine (1.0 equiv) in MeOH or *i*-PrOH (0.10 M) was added NEt_3 (5.0 equiv). The reaction mixture was cooled to 0 °C, pivalate **S8** (1.5 equiv) was added, and stirring was continued for 1−3 h at 0 °C. The reaction mixture was quenched with 1 M NaOH (~10 equiv), allowed to warm to rt, and diluted with EtOAc and H_2O. The aqueous layer was separated and extracted with EtOAc. The combined organic extracts were washed successively with 2 M NaOH and brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography

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to yield the desired product as a red−orange solid or oil. Subsequent treatment with charcoal is required. This procedure allows for 100% theoretical yield with respect to the amine partner (rather than ~50% for the traditional Zincke reaction) and is substantially higher yielding for certain substrates.

General Procedure C for the Anionic Cycloaddition Reaction of Zincke Aldehydes. To a solution of Zincke aldehyde (1.0 equiv) in THF (0.06 M unless otherwise specified) in a sealed tube temporarily capped with a septum was added KO-*t*-Bu (1.0 M in THF, 1.05 equiv), yielding an orange to light brown, slightly cloudy solution. The tube was tightly sealed, heated to 80 °C for 1−4 h, and then cooled to rt. A saturated aqueous solution of $NaHCO_3$ was added, followed by EtOAc and H_2O. The aqueous layer was extracted with EtOAc, and the combined organics were washed with brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography to yield the desired tetracyclic product.

General Deallylation/Alkylation Procedure of Tetracycle 7g. To a solution of **7g** (1 equiv) and 5-methyl Meldrum's acid (**78**) (2.2 equiv) in $CDCl_3$ (0.2 M) at 0 °C was added $Pd(PPh_3)_4$ (5 mol %). The reaction mixture was stirred at 0 °C for 1 h, at which point ^1H NMR analysis of an aliquot generally indicated complete deallylation. To the reaction mixture were added diisopropylethylamine (3.5 equiv) and allylic/propargylic bromide (2.2 equiv, neat or as a solution in CH_3CN) rinsing with CH_3CN (equal volume as $CDCl_3$, [final] = 0.1 M). The resulting solution was stirred at 0 °C for 2.5 h, diluted with EtOAc and saturated aqueous $NaHCO_3$, and warmed to rt. The mixture was diluted with EtOAc and H_2O. The layers were separated, and the aqueous layer was extracted with EtOAc. The combined organic extracts were washed with aqueous $NaHCO_3$ and brine and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 1:4 → 1:3 EtOAc/CH_2Cl_2) to yield the desired product. The phenallyl group could also be deprotected under these conditions and gave similar product yields.[78] In previous experiments, barbituric acid derivative **77** was used in place of 5-methyl Meldrum's acid with similar results.

***α*-Methyl Zincke Aldehyde 28.** To a solution of N_b-PMB-tryptamine (**S7**)[15] (2.45 g, 8.74 mmol, 2.1 equiv) in EtOH (22 mL, 0.4 M in amine) was added 1-(2,4-dinitrophenyl)-3-methylpyridinium chloride[79] (1.23 g, 4.16 mmol, 1.0 equiv). After being stirred for 30 min at rt, the red mixture was heated to 80 °C for 2 h and then cooled to rt. The reaction mixture was quenched with 2 M NaOH (25 mL, 50 mmol, 12 equiv), stirred at rt for 45 min, and then diluted with EtOAc (100 mL) and 2 M NaOH (50 mL). The aqueous layer was separated and extracted with EtOAc (20 mL). The combined organic extracts were washed successively with 2 M NaOH (20 mL) and brine (20 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material (~8.5:1 mixture of *α*-Me:*γ*-Me) was purified by column chromatography (SiO_2, 0:100 → 1:4 EtOAc/CH_2Cl_2) to yield the desired product as a red−brown oil (1.1 g, 71%). Further elution (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2) gave recovered amine (0.94 g, 73% recovery of excess). Further purification by column chromatography (SiO_2, 4:5:1 → 5:4:1 EtOAc/hexaxes/CH_2Cl_2) and treatment with activated charcoal (~1 mass equiv) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal, gave an orange foam: R_f = 0.4 (1:4 EtOAc/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) *δ* 9.19 (s, 1H, C*H*O), 8.22 (br s, 1H, N_a-*H*), 7.52 (d, *J* = 7.7 Hz, 1H, indole C4-*H*), 7.40 (d, *J* = 7.9 Hz, 1H, indole C7-*H*), 7.23 (t, *J* = 7.7 Hz, 1H, indole C6-*H*), 7.14 (dd, *J* = 7.9, 7.7 Hz, 1H, indole C5-*H*), 7.10 (d, *J* = 8.3 Hz, 2H, PMB), 7.00 (s, 1H, indole C2-*H*), 6.82−6.91 (m, 4H, PMB + ZA *β*+*δ*-C*H*), 5.46 (app t, *J* = 12.1 Hz, 1H, ZA *γ*-C*H*), 4.27 (br s, 2H, N_b-CH_2), 3.82 (s, 3H, OCH_3), 3.51 (t, *J* = 7.2 Hz, 2H, CH_2-N_b), 3.03(t, *J* = 7.2 Hz, 2H, Ar-CH_2), 1.75 (s, 3H, ZA *α*-CH_3); ^{13}C NMR (125 MHz, DMSO, 373 K) *δ* 190.1, 158.5, 152.7, 150.6, 136.0, 128.5, 128.4, 126.7, 123.8, 122.4, 120.4, 117.8, 117.4, 113.7, 110.9, 110.6, 94.4, 54.7, 54.3, 51.1, 22.6, 8.2; IR (thin film) *ν* 3051, 2922, 1557, 1204, 1010, 741 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{24}H_{27}N_2O_2$ $(M + H)^+$ 375.2072, found 375.2078

Zincke Aldehyde 12a. Prepared according to general procedure B using N_b-methyltryptamine (**S9**)[80] (251 mg, 1.44 mmol) in *i*-PrOH (14 mL) at 0 °C for 2.5 h. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (227 mg, 62%) as a red-orange foam. Further purification by treatment with activated charcoal (~0.2 g) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal, gave a yellow foam: R_f = 0.4 (0.7:6.3:93 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) *δ* 9.26 (d, *J* = 8.3 Hz, 1H, C*H*O), 8.56 (br s, 1H, N_a-*H*), 7.57 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.40 (d, *J* = 8.1 Hz, 1H, indole C7-*H*), 7.23 (dd, *J* = 8.1, 7.3 Hz, 1H, indole C6-*H*), 7.16 (dd, *J* = 7.8, 7.3 Hz, 1H, indole C5-*H*), 7.00 (dd, *J* = 14.3, 12.1 Hz, 1H, ZA [Zincke aldehyde] *β*-C*H*), 6.98 (s, 1H, indole C2-*H*), 6.67 (d, *J* = 12.5 Hz, 1H, ZA *δ*-C*H*), 5.84 (dd, *J* = 14.3, 8.3 Hz, 1H, ZA *α*-C*H*), 5.26 (dd, *J* = 12.5, 12.1 Hz, 1H, ZA *γ*-C*H*), 3.52 (t, *J* = 7.0 Hz, 2H, CH_2-N_b), 3.04 (t, *J* = 7.0 Hz, 2H, Ar−CH_2); 2.89 (s, 3H, N_b-CH_3); ^{13}C NMR (125 MHz, DMSO, 373 K) *δ* 189.6, 155.6, 152.3, 136.0, 126.7, 122.5, 120.4, 117.82 (2C), 117.5, 110.8, 110.5, 96.0, 54.9, 36.5, 23.0; IR (thin film) *ν* 3038, 2918, 1556, 1150, 743 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{16}H_{19}N_2O$ $(M + H)^+$ 255.1497, found 255.1490.

Tetracycle 7a. Prepared according to general procedure C using Zincke aldehyde **12a** (34.4 mg, 0.135 mmol) in THF (2.25 mL, 0.06 M) at 80 °C for 1 h. The crude material was purified by column chromatography (SiO_2, 2:98 → 5:95 MeOH/CH_2Cl_2) to yield the desired product (14.0 mg, 41%) as a tan solid. A reaction performed on 86.6 mg of **12a** at 0.04 M gave 40.1 mg (46%): mp =78−80 °C; R_f = 0.3 (8:92 MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) *δ* 9.48 (s, 1H, C17-*H*), 7.01−7.07 (m, 2H, C9-*H* + C11-*H*), 6.84 (dd, *J* = 5.8, 2.3 Hz, 1H, C15-*H*), 6.72 (t, *J* = 7.2 Hz, 1H, C10-*H*), 6.56 (d, *J* = 7.8 Hz, 1H, C12-*H*), 4.49 (br s, 1H, NH), 4.34 (s, 1H, C2-*H*), 3.26−3.33 (m, 1H, C5-*H*), 2.86 (app d, *J* = 4.0 Hz, 1H, C3-*H*), 2.63 (dd, *J* = 19.9, 5.5 Hz, 1H, C14-*H*), 2.54 (td, *J* = 10.0, 5.9 Hz, 1H, C5-*H*), 2.39−2.46 (m, 1H, C14-*H*), 2.40 (s, 3H, NCH_3), 2.25 (ddd, *J* = 13.2, 8.3, 6.0 Hz, 1H, C6-*H*), 1.97 (ddd, *J* = 13.2, 10.2, 5.5 Hz, 1H, C6-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 194.8, 150.5, 150.4, 140.8, 131.9, 128.3, 122.6, 118.7, 109.3, 67.0, 60.1, 54.5, 53.7, 41.0, 38.4, 25.8; IR (thin film) *ν* 3397, 2947, 1679, 1485, 1177, 743 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{16}H_{19}N_2O$ $(M + H)^+$ 255.1497, found 255.1494.

Tryptamine S10. A solution of $BrCH_2CH_2SiMe_3$ (**72**)[81] (1.70 g, 9.38 mmol, 1.0 equiv), tryptamine (3.76 g, 23.5 mmol, 2.5 equiv), and NEt_3 (1.57 mL, 11.3 mmol, 1.2 equiv) in CH_3CN (67 mL, 0.14 M) was heated to 60 °C for 16 h and then cooled to rt. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (50 mL), followed by EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with brine (40 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.2:1.8:98 → 0.7:6.3:93 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (622 mg, 25%) as a light brown solid: R_f = 0.2 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) *δ* 8.15 (br s, 1H, N_a-*H*), 7.65 (d, *J* = 7.9 Hz, 1H, indole C4-*H*), 7.38 (d, *J* = 8.1 Hz, 1H, indole C7-*H*), 7.21 (dd, *J* = 8.1, 7.3 Hz, 1H, indole C6-*H*), 7.13 (dd, *J* = 7.9, 7.3 Hz, 1H, indole C5-*H*), 7.05 (s, 1H, indole C2-*H*), 2.99−3.03 (m, 2H, ArCH_2), 2.95−2.99 (m, 2H, C$H_2$$N_b$), 2.64−2.70 (m, 2H, N_bCH_2), 1.66 (br s, 1H, N_b-*H*), 0.74−0.79 (m, 2H, CH_2Si), −0.02 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 136.4, 127.4, 121.94, 121.91, 119.2, 118.9, 114.0, 111.1, 49.6, 45.6, 25.7, 18.1, −1.6; IR (thin film) *ν* 3415, 2951, 1456, 1248, 861, 836, 739 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{15}H_{25}N_2Si$ $(M + H)^+$ 261.1787, found 261.1780.

Zincke Aldehyde 12e. Prepared according to general procedure A using tryptamine **S10** (546 mg, 2.10 mmol) in EtOH (5.3 mL) at 80 °C for 2 h. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.3:2.7:97 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (247 mg, 72%) as a brown foam along with recovered amine (285 mg, 99% recovery of excess). Further purification by column chromatography (SiO_2, 4:5:1 → 5:4:1 EtOAc:hexanes:CH_2Cl_2) and treatment with activated charcoal (~0.2 g) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal gave a yellow foam (229 mg). General procedure B using 56.3 mg amine gave

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48 mg of product (65%), but purification was more tedious: R_f = 0.5 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, J = 8.3 Hz, 1H, C*H*O), 8.18 (br s, 1H, N_a-*H*), 7.58 (d, J = 8.0 Hz, 1H, indole C4-*H*), 7.41 (d, J = 8.1 Hz, 1H, indole C7-*H*), 7.24 (dd, J = 8.1, 7.0 Hz, 1H, indole C6-*H*), 7.17 (dd, J = 8.0, 7.0 Hz, 1H, indole C5-*H*), 7.02−7.10 (m, 1H, ZA β-C*H*), 7.02 (s, 1H, indole C2-*H*), 6.71 (br s, 1H, ZA δ-C*H*), 5.83 (dd, J = 14.2, 8.3 Hz, 1H, ZA α-C*H*), 5.26−5.37 (m, 1H, ZA γ-C*H*), 3.51 (t, J = 7.2 Hz, 2H, CH_2-N_b), 3.13−3.19 (m, 2H, N_b-CH_2), 3.05 (t, J = 7.2 Hz, 2H, Ar−CH_2), 0.84−0.90 (m, 2H, CH_2Si), 0.01 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, DMSO, 373 K) δ 189.4, 155.9, 151.1, 136.0, 126.7, 122.4, 120.4, 117.8, 117.43, 117.42, 110.8, 110.7, 95.9, 50.9, 47.1, 23.0, 15.0, −2.4; IR (thin film) ν 2951, 1568, 1557, 1149, 838, 740 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{20}H_{29}N_2OSi$ $(M + H)^+$ 341.2049, found 341.2040.

Tetracycle 7e. Prepared according to general procedure C using Zincke aldehyde **12e** (204 mg, 0.600 mmol) in THF (12 mL, 0.05 M) at 80 °C for 2.5 h. The crude material was purified by column chromatography (SiO_2, 0.1:0.9:99 → 0.7:6.3:93 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (92 mg, 45%) as a tan solid: mp =128−130 °C dec; R_f = 0.3 (0.3:2.7:97 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.47 (s, 1H, C17-*H*), 7.00−7.07 (m, 2H, C9-*H* + C11-*H*), 6.81 (dd, J = 5.4, 2.5 Hz, 1H, C15-*H*), 6.71 (t, J = 7.3 Hz, 1H, C10-*H*), 6.56 (d, J = 7.7 Hz, 1H, C12-*H*), 4.52 (br s, 1H, NH), 4.29 (s, 1H, C2-*H*), 3.18−3.24 (m, 1H, C5-*H*), 3.05 (app d, J = 3.4 Hz, 1H, C3-*H*), 2.83−2.90 (m, 1H, C21-*H*), 2.50−2.62 (m, 2H, C5-*H* + C14-*H*), 2.35−2.43 (m, 2H, C14-*H* + C21-*H*), 2.23 (ddd, J = 13.0, 8.3, 4.9 Hz, 1H, C6-*H*), 1.89 (ddd, J = 13.0, 10.1, 6.3 Hz, 1H, C6-*H*), 0.72−0.84 (m, 2H, C20-H_2), 0.01 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 150.8, 150.5, 140.7, 131.9, 128.2, 122.7, 118.6, 109.3, 63.6, 59.9, 53.5, 50.4, 49.3, 37.8, 26.1, 14.7, −1.4; IR (thin film) ν 2885, 1667, 1645, 1486, 838, 738 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{20}H_{29}N_2OSi$ $(M + H)^+$ 341.2049, found 341.2051.

Tryptamine S11. This reaction is a modification of the procedure of Pannecoucke et al.[82] A solution of α-(phenylseleno)acetaldehyde (**73**)[83] (382 mg, 1.92 mmol, 1.0 equiv) and tryptamine (338 mg, 2.11 mmol, 1.1 equiv) in MeOH (19 mL, 0.1 M) was stirred at rt for 17 h. The reaction mixture was cooled to −78 °C, and to this slushy orange reaction mixture was added solid $NaBH_3CN$ (60.3 mg, 0.96 mmol, 0.50 equiv), followed by AcOH (110 μL, 1.92 mmol, 1.0 equiv) dropwise. After 1 h of stirring at −78 °C, the heterogeneous reaction mixture was warmed to −30 °C. After 30 min of stirring at −30 °C, the homogeneous reaction mixture was quenched with H_2O (10 mL) and EtOAc (20 mL), warmed to rt, and further diluted with H_2O (50 mL) and EtOAc (30 mL). The organic layer was washed with 1 M NaOH (10 mL) and brine (40 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.2:1.8:98 → 0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (132 mg, 20%) as a light brown solid: R_f = 0.3 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (br s, 1H, N_a-*H*), 7.62 (d, J = 8.0 Hz, 1H, indole C4-*H*), 7.36−7.42 (m, 3H, SePh + indole C7-*H*), 7.17−7.25 (m, 4H, SePh + indole C6-*H*), 7.14 (dd, J = 7.7, 7.3 Hz, 1H, indole C5-*H*), 7.03 (s, 1H, indole C2-*H*), 3.03 (t, J = 6.7 Hz, 2H, ArCH_2), 2.93−3.00 (m, 4H, CH_2CH_2Se), 2.89 (t, J = 6.7 Hz, 2H, CH_2N_b), 1.76 (br s, 1H, N_b-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 133.1, 129.4, 129.1, 127.4, 127.1, 122.12, 122.09, 119.4, 118.9, 113.9, 111.2, 49.4, 48.9, 28.4, 25.8; IR (thin film) ν 3413, 3054, 2924, 1456, 1437, 738 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{18}H_{21}N_2Se$ $(M + H)^+$ 345.0871, found 345.0874.

Zincke Aldehyde 12f. Prepared according to general procedure B using amine **S11** (116 mg, 0.338 mmol) in *i*-PrOH (3 mL) and MeOH (3 mL for solubility, 0.056 M total) at 0 °C for 40 min and then rt for 20 min. The crude material was purified by column chromatography (SiO_2, 0.1:1:99 → 0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (84 mg, 59%) as a red-orange foam along with recovered amine (29 mg, 25% recovery). Further purification by treatment with activated charcoal (~60 mg) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal, gave a yellow foam. This compound lies on a failed route to strychnine, and full characterization data for this compound was not obtained prior to abandoning this route: R_f = 0.5 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.27 (d, J = 8.3 Hz, 1H, C*H*O), 8.20 (br s, 1H, N_a-*H*), 7.48−7.53 (m, 3H, SePh + indole C4-*H*), 7.40 (d, J = 8.1 Hz, 1H, indole C7-*H*), 7.28−7.35 (m, 3H, SePh), 7.24 (dd, J = 8.1, 7.3 Hz, 1H, indole C6-*H*), 7.15 (dd, J = 8.0, 7.3 Hz, 1H, indole C5-*H*), 6.93−7.02 (m, 2H, ZA β-C*H* + indole C2-*H*), 6.59 (d, J = 12.8 Hz, 1H, ZA δ-C*H*), 5.76 (dd, J = 13.9, 8.3 Hz, 1H, ZA α-C*H*), 5.11 (br s, 1H, ZA γ-C*H*), 3.46 (t, J = 7.2 Hz, 2H, CH_2-N_b), 3.36 (t, J = 7.6 Hz, 2H, N_b-CH_2), 2.99 (t, J = 7.2 Hz, 2H, Ar−CH_2), 2.93 (t, J = 7.6 Hz, 2H, CH_2Se); IR (thin film) ν 3054, 2925, 1566, 1146, 739 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{23}H_{25}N_2OSe$ $(M + H)^+$ 425.1133, found 425.1137.

Tetracycle 7f. Prepared according to general procedure C using Zincke aldehyde **12f** (6.9 mg, 16 μmol) in THF (0.8 mL, 0.02 M) at 80 °C for 2 h. The crude material was purified by column chromatography (SiO_2, 4:5:1 → 5:4:1 EtOAc/hexanes/CH_2Cl_2) to yield the desired product (3.0 mg, 43%) as a yellow foam. This compound lies on a failed route to strychnine, and it was not possible to obtain complete characterization data for this compound prior to abandoning this route: R_f = 0.7 (6:3:1 EtOAc/hexanes/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H, C17-*H*), 7.46−7.50 (m, 2H, Ph), 7.21−7.28 (m, 3H, Ph), 7.00−7.05 (m, 2H, C9-*H* + C11-*H*), 6.78 (dd, J = 5.1, 2.6 Hz, 1H, C15-*H*), 6.70 (t, J = 7.4 Hz, 1H, C10-*H*), 6.56 (d, J = 7.3 Hz, 1H, C12-*H*), 4.51 (br s, 1H, NH), 4.27 (s, 1H, C2-*H*), 3.21−3.28 (m, 1H, C5-*H*), 2.97−3.13 (m, 4H, C3-*H* + C20-H_2 + C21-*H*), 2.72−2.78 (m, 1H, C21-*H*), 2.61 (td, J = 10.1, 4.5 Hz, 1H, C5-*H*), 2.47−2.54 (m, 1H, C14-*H*), 2.33−2.40 (m, 1H, C14-*H*), 2.22 (ddd, J = 12.8, 8.3, 4.5 Hz, 1H, C6-*H*), 1.93 (ddd, J = 12.8, 10.4, 6.6 Hz, 1H, C6-*H*); LRMS (LC-ESI) m/z calcd for $C_{23}H_{25}N_2OSe$ $(M + H)^+$ 425.1/423.1, found 425.1/423.1.

Tryptamine S12. To a solution of technical grade (90%) 3-chloro-2-methylpropene (1.00 mL, ~9.14 mmol, 1.0 equiv) and tryptamine (4.40 g, 27.4 mmol, 3.0 equiv) in CH_3CN (138 mL, 0.2 M in amine) were added K_2CO_3 (1.25 g, 9.14 mmol, 1.0 equiv) and NaBr (188 mg, 1.83 mmol, 0.20 equiv). The reaction mixture was stirred at rt for 13 h and then diluted with EtOAc (100 mL), saturated aqueous $NaHCO_3$ (50 mL), and H_2O (100 mL). The organic layer was washed with H_2O (50 mL) and brine (50 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.4:3.6:96 → 0.6:5.4:94 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (969 mg, 49%) as a brown oil: R_f = 0.4 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 8.10 (br s, 1H, N_a-*H*), 7.65 (d, J = 7.9 Hz, 1H, indole C4-*H*), 7.37 (d, J = 8.1 Hz, 1H, indole C7-*H*), 7.21 (dd, J = 8.1, 7.5 Hz, 1H, indole C6-*H*), 7.13 (dd, J = 7.9, 7.5 Hz, 1H, indole C5-*H*), 7.06 (d, J = 2.0 Hz, 1H, indole C2-*H*), 4.85 (s, 1H, C=C*H*), 4.82 (s, 1H, C=C*H*), 3.21 (s, 2H, N_bCH_2), 3.00−3.04 (m, 2H, ArCH_2), 2.94−2.98 (m, 2H, CH_2N_b), 1.74 (br s, 1H, N_b-*H*), 1.71 (s, 3H, vinyl-CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8, 136.4, 127.5, 122.1, 122.0, 119.3, 119.0, 114.1, 111.2, 110.8, 55.5, 49.3, 25.7, 20.9; IR (thin film) ν 3414, 2917, 1456, 1106, 893, 740 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{14}H_{19}N_2$ $(M + H)^+$ 215.1548, found 215.1552.

Zincke Aldehyde 12h. Prepared according to general procedure A using amine **S12** (665 mg, 3.10 mmol) in EtOH (5 mL) at 80 °C for 1 h 20 min. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.8:7.2:92 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (347 mg, 80%) as a brown foam along with recovered amine (244 mg, 70% recovery of excess). Further purification by column chromatography (SiO_2, 4:5:1 → 5:4:1 EtOAc/hexanes/CH_2Cl_2) and treatment with activated charcoal (~0.3 g) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal, gave a yellow foam: R_f = 0.5 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^1H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, J = 8.3 Hz, 1H, C*H*O), 8.12 (br s, 1H, N_a-*H*), 7.58 (d, J = 7.7 Hz, 1H, indole C4-*H*), 7.41 (d, J = 7.9 Hz, 1H, indole C7-*H*), 7.24 (dd, J = 7.9, 7.3 Hz, 1H, indole C6-*H*), 7.16 (dd, J = 7.7, 7.3 Hz, 1H, indole C5-*H*), 7.03−7.11 (m, 1H, ZA β-C*H*), 7.03 (s, 1H, indole C2-*H*), 6.76 (d, J = 12.4 Hz, 1H, ZA δ-C*H*), 5.84 (dd, J = 13.8, 8.3 Hz, 1H, ZA α-C*H*), 5.34−5.44 (m, 1H, ZA γ-C*H*), 4.95 (s, 1H, C=C*H*), 4.81 (s, 1H, C=C*H*), 3.64 (s, 2H, N_b-CH_2), 3.47−3.53 (m, 2H, CH_2-N_b), 3.03−3.08 (m, 2H, Ar−CH_2), 1.69

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(s, 3H, vinyl-CH_3); ^{13}C NMR (125 MHz, DMSO, 373 K) δ 189.7, 155.7, 151.8, 139.9, 136.0, 126.7, 122.4, 120.4, 118.2, 117.8, 117.5, 112.0, 110.9, 110.6, 96.6, 56.9, 51.4, 22.7, 18.9; IR (thin film) ν 2967, 1557, 1152, 1016, 742 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{19}H_{22}N_2ONa$ (M + Na)$^+$ 317.1630, found 317.1627.

Tetracycle 7h. Prepared according to general procedure C using Zincke aldehyde **12h** (123 mg, 0.418 mmol) in THF (7.0 mL, 0.06 M) at 80 °C for 2.5 h. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.2:1.8:98 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (69 mg, 56%) as a yellow oil: R_f = 0.6 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.49 (s, 1H, C17-*H*), 7.09 (d, *J* = 7.5 Hz, 1H, C9-*H*), 7.03 (dd, *J* = 7.8, 7.6 Hz, 1H, C11-*H*), 6.81 (dd, *J* = 5.1, 3.2 Hz, 1H, C15-*H*), 6.72 (dd, *J* = 7.6, 7.5 Hz, 1H, C10-*H*), 6.57 (d, *J* = 7.8 Hz, 1H, C12-*H*), 4.89 (s, 1H, C19-*H*), 4.79 (s, 1H, C19-*H*), 4.52 (br s, 1H, NH), 4.32 (s, 1H, C2-*H*), 3.30 (d, *J* = 13.2 Hz, 1H, C21-*H*), 3.07–3.13 (m, 2H, C3-*H* + C5-*H*), 2.90 (d, *J* = 13.2 Hz, 1H, C21-*H*), 2.53–2.62 (m, 2H, C5-*H* + C14-*H*), 2.36–2.44 (m, 1H, C14-*H*), 2.18 (ddd, *J* = 12.6, 8.7, 4.9 Hz, 1H, C6-*H*), 1.95 (ddd, *J* = 12.6, 10.3, 6.6 Hz, 1H, C6-*H*), 1.69 (s, C18-H_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 150.6, 150.3, 144.0, 140.9, 132.3, 128.2, 123.0, 118.6, 111.8, 109.2, 63.9, 60.6, 59.7, 53.5, 51.1, 37.5, 26.0, 20.7; IR (thin film) ν 3390, 2917, 2810, 1682, 1485, 743 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{19}H_{23}N_2O$ (M + H)$^+$ 295.1810, found 295.1810.

α-Bromomethylstyrene (S13). According to the procedure of Suginome,[84a] a mixture of α-methylstyrene (1.90 mL, 14.7 mmol, 1.0 equiv) and *N*-bromosuccinimide (3.00 g, 16.9 mmol, 1.15 equiv) in $CHCl_3$ (3.0 mL, 5.0 M) was heated to 80 °C for 16 h, cooled to 0 °C, filtered to remove precipitated succinimide, and concentrated in vacuo. To remove the remaining succinimide, the crude mixture was taken up in Et_2O (100 mL), washed with H_2O (2 × 25 mL) and brine (25 mL), and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the crude material (3.08 g, mixture of desired allylic bromide and corresponding vinyl bromide ~4:1) was used without further purification. The spectral data for the major (desired) product **S13** were consistent with literature values:[84b] ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.50 (d, *J* = 7.5 Hz, 2H, Ar-*H*), 7.39 (t, *J* = 7.5 Hz, 2H, Ar-*H*), 7.33–7.36 (m, 1H, Ar-*H*), 5.57 (s, 1H, vinyl-*H*), 5.50 (s, 1H, vinyl-*H*), 4.40 (2, 2H, CH_2Br).

Tryptamine S14. A solution of crude bromide **S13** (2.95 g, mixture of isomers, <11.4 mmol allylic bromide) and tryptamine (6.76 g, 42.2 mmol, 3–3.5 equiv) in CH_3CN (70 mL, 0.6 M in tryptamine) was stirred at rt for 16 h. The reaction mixture was diluted with H_2O (50 mL), EtOAc (120 mL), saturated aqueous $NaHCO_3$ (50 mL), and hexanes (80 mL). The organic layer was washed with brine (50 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude material was purified by column chromatography (SiO_2, 0.2:1.8:98 → 0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (0.41 g) as a brown solid and mixed material (1.6 g). The mixed material was further purified by column chromatography (SiO_2, 0.1:0.9:99 → 0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2) to yield additional desired product (1.38 g, ~60% total yield over two steps): mp =82–83 °C; R_f = 0.25 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (br s, 1H, N_a-*H*), 7.20 (d, *J* = 7.9 Hz, 1H, indole C4-*H*), 7.34–7.39 (m, 3H, Ph + indole C7-*H*), 7.24–7.32 (m, 3H, Ph), 7.21 (dd, *J* = 8.0, 7.2 Hz, 1H, indole C6-*H*), 7.12 (dd, *J* = 7.9, 7.2 Hz, 1H, indole C5-*H*), 6.95 (d, *J* = 2.1 Hz, 1H, indole C2-*H*), 5.37 (app s, 1H, vinyl-C*H*), 5.22 (d, *J* = 1.1 Hz, 1H, vinyl-C*H*), 3.70 (s, 2H, N_bCH_2), 2.96–3.03 (m, 4H, CH_2CH_2), 1.52 (br s, 1H, N_b-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5, 140.0, 136.4, 128.5, 127.6, 127.5, 126.2, 122.1, 121.8, 119.3, 119.0, 114.1, 113.2, 111.2, 53.4, 49.2, 25.8; IR (thin film) ν 3417, 3054, 2920, 1456, 1101, 741 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{19}H_{21}N_2$ (M + H)$^+$ 277.1705, found 277.1707.

Zincke Aldehyde 12i. Prepared according to general procedure A using amine **S14** (1.37 g, 4.96 mmol) in EtOH (16.5 mL) at 80 °C for 2.5 h. The crude material was purified by column chromatography (SiO_2, 0:1 → 1:3 EtOAc/CH_2Cl_2) to yield the desired product (643 mg, 76%) as a brown foam. Further elution (→ 0.3:2.7:97 NH_4OH/MeOH/CH_2Cl_2) gave recovered amine (660 mg, 92% recovery of excess). Further purification of **12i** by treatment with activated charcoal (~0.6 g) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal, gave a yellow foam that turns brown upon storage at rt: R_f = 0.35 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, *J* = 8.3 Hz, 1H, C*H*O), 8.11 (br s, 1H, N_a-*H*), 7.57 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.41 (d, *J* = 8.2 Hz, 1H, indole C7-*H*), 7.27–7.38 (m, 5H, Ph), 7.24 (dd, *J* = 8.3, 7.3 Hz, 1H, indole C6-*H*), 7.16 (dd, *J* = 7.8, 7.3 Hz, 1H, indole C5-*H*), 7.05 (t, *J* = 14.4, 12.0 Hz, 1H, ZA β-C*H*), 7.00 (s, 1H, indole C2-*H*), 6.78 (d, *J* = 12.5 Hz, 1H, ZA δ-C*H*), 5.83 (dd, *J* = 14.4, 8.3 Hz, 1H, ZA α-C*H*), 5.49 (s, 1H, vinyl-C*H*), 5.39 (dd, *J* = 12.5, 12.0 Hz, 1H, ZA γ-C*H*), 5.10 (s, 1H, vinyl-C*H*), 4.11 (s, 2H, N_b-CH_2), 3.52 (t, *J* = 7.2 Hz, 2H, CH_2-N_b), 3.05 (t, *J* = 7.2 Hz, 2H, Ar-CH_2); ^{13}C NMR (125 MHz, DMSO, 373 K) δ 189.8, 155.6, 151.7, 142.5, 138.2, 136.0, 127.8, 127.3, 126.7, 125.6, 122.4, 120.4, 118.4, 117.8, 117.5, 114.0, 110.9, 110.6, 96.8, 54.8, 51.2, 22.6; IR (thin film) ν 2923, 1574, 1557, 1150, 742 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{24}H_{25}N_2O$ (M + H)$^+$ 357.1967, found 357.1966.

Tetracycle 7i. Prepared according to general procedure C using Zincke aldehyde **12i** (126 mg, 0.353 mmol) in THF (5.9 mL, 0.06 M) at 80 °C for 3 h. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.1:0.9:99 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (64 mg, 51%) as a yellow foam. A reaction performed on 260 mg of **12i** at 0.04 M gave 170 mg (65%): R_f = 0.6 (0.3:2.7:97 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H, C17-*H*), 7.45 (d, *J* = 7.3 Hz, 2H, Ph), 7.24–7.31 (m, 3H, Ph), 6.98–7.04 (m, 2H, C9-*H* + C11-*H*), 6.74 (dd, *J* = 4.8, 3.1 Hz, 1H, C15-*H*), 6.68 (t, *J* = 7.3 Hz, 1H, C10-*H*), 6.54 (d, *J* = 7.7 Hz, 1H, C12-*H*), 5.42 (s, 1H, C19-*H*), 5.26 (s, 1H, C19-*H*), 4.47 (br s, 1H, NH), 4.24 (s, 1H, C2-*H*), 3.83 (d, *J* = 13.6 Hz, 1H, C21-*H*), 3.36 (d, *J* = 13.6 Hz, 1H, C21-*H*), 3.16 (app t, *J* = 3.2 Hz, 1H, C3-*H*), 3.08–3.14 (m, 1H, C5-*H*), 2.59–2.69 (s, 2H, C5-*H* + C14-*H*), 2.42 (app d, *J* = 19.8 Hz, 1H, C14-*H*), 2.15 (ddd, *J* = 13.0, 8.7, 4.7 Hz, 1H, C6-*H*), 1.93 (ddd, *J* = 13.0, 10.2, 6.5 Hz, 1H, C6-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 150.31, 150.28, 145.5, 140.9, 140.1, 132.0, 128.2, 128.1, 127.6, 126.4, 123.0, 118.6, 114.4, 109.2, 63.8, 59.6, 58.2, 53.5, 50.6, 37.4, 25.8; IR (thin film) ν 2923, 2811, 1682, 1485, 1182, 908, 744 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{24}H_{25}N_2O$ (M + H)$^+$ 357.1967, found 357.1974.

4-Tosyloxy-2-butyn-1-ol (S15). This reaction is a modification of the procedure of Tanabe.[85a] To a solution of 1,4-butynediol (7.75 g, 90.0 mmol, 5 equiv), NEt_3 (4.00 mL, 28.8 mmol, 1.6 equiv) and Me_3N·HCl (172 mg, 1.8 mmol, 0.10 equiv) in CH_3CN (60 mL) at −6 °C was added TsCl (3.43 g, 18.0 mmol, 1.0 equiv) in one portion. The reaction mixture was stirred at −6 °C for 40 min, warmed to rt, and quenched with H_2O (150 mL) and EtOAc (150 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organics were washed with half-saturated aqueous NH_4Cl (80 mL) and brine (100 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material (~10:1 mono-OTs/bis-OTs) was purified by column chromatography (SiO_2, 3:7 → 1:1 EtOAc/hexanes) to yield the desired product (2.74 g, 63%) as a light yellow oil. This compound has been previously synthesized (no procedure given):[85b] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3 Hz, 2H, Ar*H*), 7.37 (d, *J* = 8.3 Hz, 2H, Ar*H*), 4.75 (t, *J* = 1.6 Hz, 2H, TsOCH_2), 4.18 (dt, *J* = 6.2, 1.6 Hz, 2H, CH_2OH), 2.47 (s, 3H, ArCH_3), 1.39 (t, *J* = 6.2 Hz, 1H).

Tryptamine S16. To a solution of tosylate **S15** (2.16 g, 8.99 mmol, 1.0 equiv) in THF (20 mL, 0.45 M) was added LiBr (1.17 g, 13.5 mmol, 1.5 equiv). The reaction mixture warmed (minor exotherm) and was stirred at rt for 45 min. To the resulting mixture were added tryptamine (4.3 g, 27 mmol, 3.0 equiv) and THF (40 mL, final concentration = 0.15 M), and stirring was continued at rt for 15 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (100 mL), followed by EtOAc (150 mL) and H_2O (50 mL). The aqueous layer was extracted with EtOAc (100 mL). The combined organics were washed with saturated aqueous $NaHCO_3$ (65 mL) and brine (40 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.5:4.5:95 → 1:9:90 NH_4OH/MeOH/

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CH_2Cl_2) to yield the desired product (1.37 g, 67%) as a light yellow oil: R_f = 0.25 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (br s, 1H, N_a-*H*), 7.62 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.34 (d, *J* = 8.1 Hz, 1H, indole C7-*H*), 7.20 (dd, *J* = 8.1, 7.2 Hz, 1H, indole C6-*H*), 7.12 (dd, *J* = 7.8, 7.2 Hz, 1H, indole C5-*H*), 6.99 (d, *J* = 2.1 Hz, 1H, indole C2-*H*), 4.20 (t, *J* = 1.7 Hz, 2H, CH_2OH), 3.39 (t, *J* = 1.7 Hz, 2H, N_bCH_2), 2.94−3.02 (m, 4H, CH_2CH_2), 2.64 (br s, 2H, N_b-*H* + O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.7, 127.5, 122.6, 122.2, 119.4, 119.0, 113.3, 111.6, 83.1, 82.7, 50.8, 48.7, 38.5, 25.5; IR (thin film) ν 3288, 2918, 1456, 1338, 1011, 744 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{14}H_{17}N_2O$ (M + H)$^+$ 229.1341, found 229.1334.

Zincke Aaldehyde S17. Prepared according to general procedure B using **S16** (535 mg, 2.34 mmol) in MeOH (16 mL, 0.15 M) at 0 °C for 2.5 h. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (341 mg, 47%) as an orange foam along with recovered amine (111 mg, 21% recovery). A similar experiment on 253 mg of amine using 1 M aqueous NaOH (1.66 mL, 1.5 equiv) as base in MeOH gave 218 mg of product (64%), but purification was more tedious. This compound lies on a failed route to strychnine, and full characterization data for this compound was not obtained prior to abandoning this route. Downstream compound **7k** is fully characterized: R_f = 0.4 (0.8:7.2:92 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.3 Hz, 1H, C*H*O), 8.16 (br s, 1H, N_a-*H*), 7.60 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.41 (d, *J* = 8.1 Hz, 1H, indole C7-*H*), 7.24 (dd, *J* = 8.1, 7.2 Hz, 1H, indole C6-*H*), 7.17 (dd, *J* = 7.8, 7.2 Hz, 1H, indole C5-*H*), 7.04 (d, *J* = 2.1 Hz, 1H, indole C2-*H*), 7.01 (dd, *J* = 14.3, 11.7 Hz, 1H, ZA β-C*H*), 6.66 (d, *J* = 12.8 Hz, 1H, ZA δ-C*H*), 5.87 (dd, *J* = 14.3, 8.3 Hz, 1H, ZA α-C*H*), 5.40 (dd, *J* = 12.8, 11.7 Hz, 1H, ZA γ-C*H*), 4.28 (s, 2H, CH_2OH), 3.93 (s, 2H, N_b-CH_2), 3.60 (t, *J* = 7.1 Hz, 2H, CH_2-N_b), 3.10 (t, *J* = 7.1 Hz, 2H, Ar−CH_2), 1.86 (br s, 1H, O*H*); HRMS (LC-ESI) *m*/*z* calcd for $C_{19}H_{20}N_2O_2Na$ (M + Na)$^+$ 331.1422, found 331.1422.

Zincke Aldehyde 12k. This reaction is a modification of the procedure of Trost.[68] To a solution of **S17** (204 mg, 0.662 mmol, 1.0 equiv) and Me_2Si(OEt)H (109 μL, 0.794 mmol, 1.2 equiv) in CH_2Cl_2/acetone (2.5 mL + 0.5 mL, 0.2 M) at −10 °C was added [Cp*Ru(CH_3CN)$_3$]PF_6 (16.7 mg, 33 μmol, 0.05 equiv). The resulting solution was stirred at −10 °C for 1 h and warmed to rt, and an additional portion of [Cp*Ru(CH_3CN)$_3$]PF_6 (16.7 mg, 33 μmol, 0.05 equiv) was added. The resulting solution was stirred at rt for 1.5 h, then concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 0.2:1.8:98 → 0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (79 mg pure +37 mg mixed with starting material, ~48%) as a light brown foam. Treatment with activated charcoal (~0.1 g) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal gave a yellow foam. This compound lies on a failed route to strychnine, and full characterization data for this compound was not obtained prior to abandoning this route. Downstream compound **7k** is fully characterized: R_f = 0.5 (0.8:7.2:92 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.30 (d, *J* = 8.3 Hz, 1H, C*H*O), 8.08 (br s, 1H, N_a-*H*), 7.56 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.41 (d, *J* = 8.1 Hz, 1H, indole C7-*H*), 7.25 (dd, *J* = 8.1, 7.3 Hz, 1H, indole C6-*H*), 7.17 (dd, *J* = 7.8, 7.3 Hz, 1H, indole C5-*H*), 7.02−7.09 (m, 1H, ZA β-C*H*), 7.02 (s, 1H, indole C2-*H*), 6.73 (d, *J* = 12.7 Hz, 1H, ZA δ-C*H*), 6.51 (s, 1H, vinyl-C*H*), 5.84 (dd, *J* = 14.3, 8.3 Hz, 1H, ZA α-C*H*), 5.30−5.39 (m, 1H, ZA γ-C*H*), 4.57 (s, 2H, CH_2O), 3.93 (s, 2H, N_b-CH_2), 3.49 (t, *J* = 7.3 Hz, 2H, CH_2-N_b), 3.06 (t, *J* = 7.3 Hz, 2H, Ar−CH_2), 0.23 (s, 6H, SiCH_3); HRMS (LC-ESI) *m*/*z* calcd for $C_{21}H_{27}N_2O_2Si$ (M + H)$^+$ 367.1842, found 367.1847.

Tetracycle 7k. General procedure C yielded only protodesilylation and decomposition. Modified procedure: To a solution of Zincke aldehyde **12k** (19.8 mg, 54.0 μmol) in THF (0.7 mL) was added a freshly prepared solution of KHMDS (142 μL, 0.4 M in THF, 56.8 μmol, 1.05 equiv), yielding an orange, slightly cloudy solution. This solution was transferred to a Schlenk tube, rinsing with THF (0.3 mL, final concentration 0.045 M). The tube was tightly sealed and heated to 80 °C for 2 h, then cooled to rt. A saturated aqueous solution of $NaHCO_3$ (2 mL) was added, followed by EtOAc (5 mL) and H_2O (2 mL). The aqueous layer was extracted with EtOAc (5 mL), and the combined organics were washed with brine (2 mL), then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2) to yield the desired tetracyclic product (2.4 mg contaminated with 20% unidentified impurities, <10% yield) as a yellow film, along with protodesilylated material and decomposition products. The identity of the product was confirmed by synthesis via a different route (see below): R_f = 0.4 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H, C17-*H*), 7.01−7.06 (m, 2H, C9-*H* + C11-*H*), 6.78−6.81 (m, 1H, C15-*H*), 6.71 (t, *J* = 7.6 Hz, 1H, C10-*H*), 6.59 (br s, 1H, C19-*H*), 6.56 (d, *J* = 7.6 Hz, 1H, C12-*H*), 4.59 (d, *J* = 15.7 Hz, 1H, C18-*H*), 4.52 (d, *J* = 15.7 Hz, 1H, C18-*H*), 4.50 (br s, 1H, NH), 4.27 (s, 1H, C2-*H*), 3.64 (dq, *J* = 13.7, 2.1 Hz, 1H, C21-*H*), 3.09−3.19 (m, 3H, C3-*H* + C5-*H* + C21-*H*), 2.59 (dd, *J* = 19.4, 4.8 Hz, 1H, C14-*H*), 2.49 (ddd, *J* = 10.3, 10.1, 4.8 Hz, 1H, C5-*H*), 2.39−2.47 (m, 1H, C14-*H*), 2.20 (ddd, *J* = 12.7, 8.5, 4.8 Hz, 1H, C6-*H*), 1.93 (ddd, *J* = 12.7, 10.4, 6.5 Hz, 1H, C6-*H*), 0.18 (s, 3H, SiCH_3), 0.15 (s, 3H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.7, 150.4, 150.2, 142.1, 141.1, 141.0, 131.5, 128.3, 122.8, 118.6, 109.3, 71.8, 63.7, 59.8, 54.7, 53.5, 51.8, 37.6, 26.2, 0.7, −0.2; IR (thin film) ν 2922, 2849, 1682, 1485, 1070, 828, 744 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{21}H_{26}N_2O_2SiNa$ (M + Na)$^+$ 389.1661, found 389.1657.

1-Bromo-2-butyn-4-ol (S18). To a solution of monotosylate **S15** (1.00 g, 4.16 mmol, 1 equiv) in acetone (6.6 mL, 0.6 M) was added LiBr (0.72 g, 8.3 mmol, 2.0 equiv) which caused the mixture to warm (minor exotherm). The mixture was stirred at rt for 1 h and then diluted with Et_2O (30 mL) and H_2O (15 mL). The organic layer was washed with brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo, and the crude material (577 mg, ~90%) was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.34 (dt, *J* = 6.2, 2.0 Hz, 2H, CH_2O), 3.96 (t, *J* = 2.0 Hz, 2H, BrCH_2), 1.68 (t, *J* = 6.2 Hz, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 84.9, 80.9, 51.2, 14.2.

Tetracycle S19. To a solution of **7g** (42.8 mg, 0.153 mmol, 1 equiv) and barbituric acid **77** (82.7 mg, 0.336 mmol, 2.2 equiv) in $CDCl_3$ (0.76 mL, 0.2 M) at 0 °C was added Pd(PPh_3)$_4$ (8.8 mg, 7.7 μmol, 5 mol %). The reaction mixture was stirred at 0 °C for 1 h. To the reaction mixture were added diisopropylethylamine (93 μL, 0.536 mmol, 3.5 equiv) and propargylic bromide **S18** (57 mg, 0.38 mmol, 2.5 equiv) via syringe. The resulting solution was stirred at 0 °C for 4 h, then placed in a fridge (~4 °C) for 15 h, removed, and stirred with warming to rt. The reaction mixture was diluted with EtOAc (10 mL), saturated aqueous $NaHCO_3$ (4 mL), and H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (3 mL) and brine (3 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.1:0.9:99 → 0:20:80 → 0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (32.7 mg, 69%) as a yellow foam: R_f = 0.4 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.46 (s, 1H, C17-*H*), 7.08 (d, 1H, *J* = 7.3 Hz C9-*H*), 7.04 (dd, *J* = 7.8, 7.3 Hz, C11-*H*), 6.78−6.82 (m, 1H, C15-*H*), 6.72 (t, *J* = 7.3 Hz, 1H, C10-*H*), 6.56 (d, *J* = 7.8 Hz, 1H, C12-*H*), 4.51 (br s, 1H, N*H*), 4.36 (s, 2H, C18-H_2), 4.31 (s, 1H, C2-*H*), 3.61 (app d, *J* = 17.6 Hz, 1H, C21-*H*), 3.53 (app d, *J* = 17.6 Hz, 1H, C21-*H*), 3.37 (app d, *J* = 4.2 Hz, 1H, C3-*H*), 3.14−3.20 (m, 1H, C5-*H*), 2.96 (td, *J* = 10.1, 4.8 Hz, 1H, C5-*H*), 2.56 (dd, *J* = 19.7, 5.6 Hz, 1H, C14-*H*), 2.38−2.45 (m, 1H, C14-*H*), 2.27 (ddd, *J* = 12.9, 8.3, 4.9 Hz, 1H, C6-*H*), 1.94 (ddd, *J* = 12.8, 10.3, 6.7 Hz, 1H, C6-*H*), 1.88 (br s, 1H, O*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9, 150.5, 150.1, 140.8, 131.2, 128.4, 122.7, 118.7, 109.4, 83.7, 80.3, 61.3, 59.7, 53.5, 51.2, 49.9, 40.8, 38.2, 25.6; IR (thin film) ν 3394, 2923, 2245, 1674, 1485, 1101, 1018 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{19}H_{21}N_2O_2$ (M + H)$^+$ 309.1603, found 309.1610.

Tetracycle 7k (Alternative Synthesis). This reaction is a modification of the procedure of Trost.[68] To a solution of propargyl alcohol **S19** (42.0 mg, 0.136 mmol, 1.0 equiv) and Me_2Si(OEt)H

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(22.5 μL, 0.163 mmol, 1.2 equiv) in acetone (0.7 mL, 0.2 M) at 0 °C was added $[Cp^*Ru(CH_3CN)_3]PF_6$ (4.3 mg, 7.0 μmol, 0.05 equiv). The resulting solution was stirred at 0 °C for 5 min, warmed to rt and stirred at rt for 70 min, then concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 0.1:0.9:99 → 0.3:2.7:97 $NH_4OH/MeOH/CH_2Cl_2$) to yield the desired product (16.8 mg, 34%) as a yellow foam. (Spectral data tabulated above for alternate synthesis.)

Tryptamine S20. A solution of 1-bromo-2-butyne (0.30 mL, 3.30 mmol, 1.0 equiv), tryptamine (1.6 g, 9.97 mmol, 3.0 equiv), and NEt_3 (0.69 mL, 5.0 mmol, 1.5 equiv) in THF (33 mL, 0.1 M) was stirred at rt for 19 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (20 mL), followed by EtOAc (100 mL) and H_2O (50 mL). The organic layer was washed with H_2O (40 mL) and brine (40 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.3:2.7:97 → 0.6:5.6:94 $NH_4OH/MeOH/CH_2Cl_2$) to yield the desired product (404 mg, 57%) as a tan solid: mp = 97−99 °C; R_f = 0.3 (1:9:90 $NH_4OH/MeOH/CH_2Cl_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (br s, 1H, N_a-*H*), 7.66 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.38 (d, *J* = 8.1 Hz, 1H, indole C7-*H*), 7.21 (dd, *J* = 8.1, 7.3 Hz, 1H, indole C6-*H*), 7.13 (dd, *J* = 7.8, 7.3 Hz, 1H, indole C5-*H*), 7.07 (d, *J* = 1.9 Hz, 1H, indole C2-*H*), 3.40 (q, *J* = 2.3 Hz, 2H, N_bCH_2), 2.98−3.06 (m, 4H, CH_2CH_2), 1.80 (t, *J* = 2.3 Hz, 3H, alkyne-CH_3), 1.46 (br s, 1H, N_b-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.5, 127.5, 122.1, 122.0, 119.3, 119.0, 114.0, 111.2, 79.0, 77.3, 48.9, 38.6, 25.7, 3.6; IR (thin film) ν 3410, 2918, 2238, 1456, 1339, 742 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{14}H_{17}N_2$ $(M + H)^+$ 213.1392, found 213.1391.

Zincke Aldehyde 12l. Prepared according to general procedure B using amine **S20** (182 mg, 0.857 mmol) in MeOH (5 mL, 0.15 M) at 0 °C for 1.5 h. The crude material was purified by column chromatography (SiO_2, 0.1:0.9:99 → 0.2:1.8:98 $NH_4OH/MeOH/CH_2Cl_2$) to yield the desired product (180 mg, 72%) as a red foam. Further purification by column chromatography (SiO_2, 0:0:100 → 0.2:1.8:98 $NH_4OH/MeOH/CH_2Cl_2$) and treatment with activated charcoal (∼150 mg) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal gave a yellow foam: R_f = 0.5 (0.5:4.5:95 $NH_4OH/MeOH/CH_2Cl_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.4 Hz, 1H, C*H*O), 8.46 (br s, 1H, N_a-*H*), 7.60 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.40 (d, *J* = 8.1 Hz, 1H, indole C7-*H*), 7.23 (dd, *J* = 8.1, 7.2 Hz, 1H, indole C6-*H*), 7.16 (dd, *J* = 7.8, 7.2 Hz, 1H, indole C5-*H*), 7.00−7.07 (m, 2H, ZA β-C*H* + indole C2-*H*), 6.70 (d, *J* = 12.4 Hz, 1H, ZA δ-C*H*), 5.87 (dd, *J* = 14.3, 8.4 Hz, 1H, ZA α-C*H*), 5.41 (dd, *J* = 12.4, 12.1 Hz, 1H, ZA γ-C*H*), 3.87 (s, 2H, N_b-CH_2), 3.58 (t, *J* = 7.1 Hz, 2H, CH_2-N_b), 3.09 (t, *J* = 7.1 Hz, 2H, Ar−CH_2), 1.85 (s, 3H, alkyne-CH_3); ^{13}C NMR (125 MHz, DMSO, 373 K) δ 190.0, 155.4, 150.6, 136.0, 126.7, 122.5, 120.4, 119.0, 117.8, 117.5, 110.9, 110.5, 97.2, 80.6, 73.4, 51.8, 40.2, 22.9, 2.3; IR (thin film) ν 2920, 2850, 2239, 1574, 1567, 1145 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{19}H_{20}N_2ONa$ $(M + Na)^+$ 315.1473, found 315.1469.

Tetracycle 7l. Prepared according to general procedure C using Zincke aldehyde **12l** (21.9 mg, 74.9 μmol) in THF (1.1 mL, 0.07 M) at 80 °C for 2 h. Analysis of the crude material indicated substantial decomposition, and only traces of the desired product (<2 mg, <10%) could be isolated as a mixture with other decomposition products. It was not possible to obtain reliable characterization data for this compound.

***N*-Benzyl-3-(3-indolyl)propionamide (S21).** This reaction is a modification of the procedure of Pedras et al.[86] To a solution of indole-3-propionic acid (800 mg, 4.23 mmol, 1.0 equiv) and triethylamine (1.76 mL, 12.7 mmol, 3.0 equiv) in THF (21 mL, 0.20 M) cooled in an ice−water bath (0 °C) was added methyl chloroformate (344 μL, 4.44 mmol, 1.05 equiv) dropwise over 5 min. After the mixture was stirred at 0 °C for 40 min, benzylamine (925 μL, 8.46 mmol, 2 equiv) was added, and the mixture was allowed to warm to rt and stirred for 1.5 h. The reaction was diluted with EtOAc (50 mL) and washed with 1 M HCl (30 mL). The aqueous layer was extracted with EtOAc (20 mL). The combined organic extracts were washed with 1 M HCl (15 mL) and brine (25 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The desired product (1.19 g, quant) was isolated as a cream solid and used without further purification. The spectral data were consistent with literature values.[87]

***N*-Benzyl-3-(3-indolyl)propylamine (S22).** This reaction is a modification of the procedure of Mewshaw et al.[88] To a solution of amide **S21** (1.19 g, ≤ 4.23 mmol, 1.0 equiv) in THF (8.5 mL, 0.50 M) cooled in an ice−water bath (0 °C) was added $LiAlH_4$ (482 mg, 12.7 mmol, 3.0 equiv) in three portions over 5 min, and then the mixture was allowed to warm to rt and stirred for 15 min. The reaction mixture was then heated to reflux (70 °C oil bath) for 2 h and then cooled to rt. To the vigorously stirring reaction mixture were added H_2O (1.3 mL), 0.4 M NaOH (1.3 mL), H_2O (3 × 1.3 mL), and a small scoop of $MgSO_4$ (∼100 mg). After being stirred at rt for 10 min, the mixture was filtered, and the white filter cake was washed with EtOAc. The filtrate was concentrated in vacuo, and the residue was dissolved in EtOAc (50 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude material (∼1.2 g) was purified by column chromatography (SiO_2, 0:5:95, then 0.5:4.5:95 − 0.7:6.3:93 $NH_4OH/MeOH/CH_2Cl_2$) to yield the desired product as a viscous, light brown oil (840 mg, 75% over two steps). The spectral data were consistent with literature values.[89]

Zincke Aldehyde 30. Prepared according to general procedure A using homotryptamine **S22** (688 mg, 2.60 mmol) in EtOH (5.2 mL, 0.5 M in amine) at 80 °C for 2 h. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.6:5.4:94 $NH_4OH/MeOH/CH_2Cl_2$) to yield the desired product (360 mg, 95% pure by ^{1}H NMR, ∼81%) and recovered amine (285 mg, 82% recovery). Further purification by column chromatography (SiO_2, 4:5:1 EtOAc/hexanes/CH_2Cl_2) followed by charcoal treatment gave the desired product (293 mg, 69%) as a yellow foam: R_f = 0.3 (0.5:4.5:95 $NH_4OH/MeOH/CH_2Cl_2$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.29 (d, *J* = 8.4 Hz, 1H, C*H*O), 8.03 (br s, 1H, N_a-*H*), 7.54 (d, *J* = 7.9 Hz, 1H, indole C4-*H*), 7.39 (d, *J* = 8.2 Hz, 1H, indole C7-*H*), 7.29−7.37 (m, 3H, Ph-*H*), 7.23 (dd, *J* = 7.9, 7.2 Hz, 1H, indole C6-*H*), 7.11−7.17 (m, 3H, Ph-*H* + indole C5-*H*), 7.07 (dd, *J* = 14.4, 11.6 Hz, 1H, ZA β-C*H*), 6.95 (d, *J* = 2.2 Hz, 1H, indole C2-*H*), 6.88 (d, *J* = 12.6 Hz, 1H, ZA δ-C*H*), 5.75 (dd, *J* = 14.4, 8.4 Hz, 1H, ZA α-C*H*), 5.29 (dd, *J* = 12.6, 11.6 Hz, 1H, ZA γ-C*H*), 4.37 (s, 2H, CH_2Ph), 3.24 (t, *J* = 7.3 Hz, 2H, CH_2N), 2.78 (t, *J* = 7.3 Hz, 2H, ArCH_2), 2.01 (quintet, *J* = 7.3 Hz, 2H, ArCH_2CH_2); ^{13}C NMR (125 MHz, DMSO, 373 K) δ 189.8, 155.8, 152.0, 136.5, 136.1, 128.0, 126.9, 126.8, 126.7, 121.7, 120.3, 118.4, 117.63, 117.62, 113.2, 110.8, 96.7, 54.8, 50.5, 27.2, 21.5; IR (thin film) ν 2924, 1574, 1557, 1392, 1149, 742 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{23}H_{24}N_2ONa$ $(M + Na)^+$ 367.1786, found 367.1777.

Tetracycle 31. Prepared according to general procedure C using Zincke aldehyde **30** (45.0 mg, 0.131 mmol) in THF (2.2 mL, 0.06 M) at 80 °C for 2 h. Analysis of the crude material by ^{1}H NMR indicated a mixture of tetracycle **31** (∼25%), Zincke aldehyde **30** (∼25%), amine **S22** (∼40%), and unknown byproducts (∼10%). The crude material was purified by column chromatography (SiO_2, 4:96 EtOAc/CH_2Cl_2) to yield the desired product (8.9 mg, 20%) as a light brown solid: R_f = 0.3 (5:95 EtOAc:CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, 323 K) δ 9.46 (s, 1H, C17-*H*), 7.31 (d, *J* = 7.6 Hz, 1H, C9-*H*), 7.18−7.28 (m, 5H, Ph*H*), 7.03 (t, *J* = 7.6 Hz, 1H, C11-*H*), 6.74 (t, *J* = 7.6 Hz, 1H, C10-*H*), 6.64 (t, *J* = 4.1 Hz, 1H, C15-*H*), 6.58 (d, *J* = 7.6 Hz, 1H, C12-*H*), 4.42 (br s, 1H, N*H*), 4.41 (s, 1H, C2-*H*), 3.81 (d, *J* = 14.0 Hz, 1H, C21-*H*), 3.44 (d, *J* = 14.0 Hz, 1H, C21-*H*), 3.06 (t, *J* = 4.8 Hz, 1H, C3-*H*), 2.80−2.86 (m, 1H, C5-*H*), 2.77 (dt, *J* = 19.4, 4.8 Hz, 1H, C14-*H*), 2.43−2.52 (m, 2H, C5-*H* + C14-*H*), 1.83−1.98 (m, 2H, C6-*H* + C6′-*H*), 1.75−1.83 (m, 1H, C6-*H*), 1.52 (ddd, *J* = 12.8, 9.3, 4.9 Hz, 1H, C6′-*H*); ^{13}C NMR (125 MHz, $CDCl_3$, 323 K) δ 194.7, 149.7, 149.6, 141.6, 139.7, 134.7, 128.5, 128.2, 128.0, 126.9, 124.3, 118.5, 110.0, 60.5, 59.4, 59.3, 51.0, 48.0, 33.2, 24.5, 22.6; IR (thin film) ν 3030, 2925, 2802, 1678, 1482, 738 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{23}H_{25}N_2O$ $(M + H)^+$ 345.1967, found 345.1966. Selected NOE correlations for **31** can be found in the Supporting Information.

***(Z)*-α-Bromocrotonaldehyde (S23).** This reaction is a modification of the procedure of Dai et al.[90] To a solution of trans-crotonaldehyde (5.92 mL, 71.4 mmol, 1.0 equiv) in dry CH_2Cl_2 (100 mL, 0.71 M) cooled in an ice−water bath (0 °C) was added

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bromine (3.7 mL, 71.8 mmol, 1.01 equiv) in CH_2Cl_2 (4 mL) dropwise over 10 min, followed by stirring at 0 °C for 1 h. Triethylamine (12 mL, 86.1 mmol, 1.21 equiv) was added, and the mixture was allowed to stir at rt for 1.5 h. The reaction was quenched with saturated aqueous $Na_2S_2O_3$ (20 mL), and the organic layer was washed with 1 M HCl (10 mL), brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The desired product (9.44 g, 89%, >95:5 *Z*:*E*) was isolated as a pale yellow liquid and used without further purification. The spectral data of the crude product were consistent with literature values.[90]

(*Z*)-2-Bromo-2-buten-1-ol (S24). This reaction has been previously performed by Loh et al. (no experimental procedures given).[91] To a solution of (*Z*)-α-bromocrotonaldehyde (**S23**) (9.44 g, 63.4 mmol, 1.0 equiv) in THF/H_2O (9:1, 160 mL, 0.4 M) cooled in an ice−water bath (0 °C) was added sodium borohydride (1.48 g total, 38.0 mmol, 0.6 equiv) in three portions over 5 min, followed by stirring at 0 °C for 30 min. The reaction was quenched with 1 M HCl (10 mL) and warmed to rt. The reaction mixture was diluted with EtOAc/hexanes (1:4, 175 mL) and H_2O (200 mL). The aqueous layer was separated and extracted with EtOAc/hexanes (1:4, 175 mL). The organic layer was separated and washed with brine (50 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The crude material (8.23 g, 86%) was purified by Kugelrohr distillation (90 °C oven temp, 15 mmHg) to give the desired product (7.48 g, 78%) as a pale yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.08 (q, *J* = 6.6 Hz, 1H, vinyl-*H*), 4.26 (s, 2H, OCH_2), 2.24 (br s, 1H, O*H*), 1.80 (d, *J* = 6.6 Hz, 3H, CH_3).

(*Z*)-1,2-Dibromo-2-butene (37).[39] To a solution of allylic alcohol **S24** (4.26 g, 28.2 mmol) and NEt_3 (4.90 mL, 35.3 mmol, 1.25 equiv) in THF (56 mL, 0.5 M) at −30 °C was added methanesulfonyl chloride (2.62 mL, 33.9 mmol, 1.2 equiv). The solution was stirred at −30 °C for 1 h, LiBr (6.10 g, 70.5 mmol, 2.5 equiv) was added, and the reaction mixture was warmed to rt and stirred for 4 h. The reaction was diluted with hexanes (100 mL) and quenched with H_2O (100 mL). The layers were separated, and the aqueous layer was extracted with hexanes (100 mL). The combined organic extracts were washed with H_2O (50 mL) and brine (50 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to give the desired product as a yellow oil (6.33 g, ∼90% pure by ^{1}H NMR) that was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.20 (q, *J* = 6.6 Hz, 1H, vinyl-*H*), 4.26 (s, *J* = 6.5 Hz, 2H, BrCH_2), 1.79 (d, *J* = 6.6 Hz, 3H, CH_3).

Tryptamine 38. To a solution of tryptamine (10.8 g, 67.2 mmol, 3.3 equiv) in CH_3CN (350 mL, 0.19 M in amine) was added crude **37** (4.79 g, ∼90% pure, ∼20.2 mmol). After being stirred for 14 h at rt, the reaction mixture was concentrated in vacuo, and the crude residue was diluted with EtOAc (200 mL), saturated aqueous $NaHCO_3$ (150 mL), and H_2O (150 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (100 mL). The combined organic extracts were washed with 1 M NaOH (50 mL) and brine (120 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material (10.7 g) was purified by column chromatography (SiO_2, 0:0.8:100−0.6:5.4:94 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product as a viscous, brown oil (4.96 g, 84% over two steps): R_f = 0.2 (0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (br s, 1H, N_a-*H*), 7.63 (d, *J* = 7.9 Hz, 1H, indole C4-*H*), 7.37 (d, *J* = 8.0 Hz, 1H, indole C7-*H*), 7.21 (dd, *J* = 8.0, 7.4 Hz, 1H, indole C6-*H*), 7.13 (dd, *J* = 7.9, 7.4 Hz, 1H, indole C5-*H*), 7.07 (d, *J* = 1.7 Hz, 1H, indole C2-*H*), 5.88 (q, *J* = 6.6 Hz, 1H, C=C*H*), 3.51 (s, 2H, N_bCH_2), 2.99 (t, *J* = 7.2 Hz, 2H, CH_2-N_b), 2.89 (t, *J* = 7.2 Hz, 2H, Ar−CH_2), 1.74 (d, *J* = 6.6 Hz, 3H, CH_3), 1.61 (br s, 1H, N_b-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.4, 128.4, 127.5, 125.1, 122.1, 121.9, 119.3, 119.0, 114.1, 111.2, 57.9, 48.0, 25.9, 16.6; IR (thin film) ν 3413, 2918, 2851, 1456, 1108, 741 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{14}H_{18}N_2Br$ $(M + H)^+$ 293.0653, found 293.0656.

Zincke Aldehyde 39. Prepared according to general procedure A using **38** (5.40 g, 18.42 mmol) in EtOH (61 mL, 0.3 M in amine) at 80 °C for 3 h 20 min. The crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product mixed with recovered amine (4.64 g) as a viscous brown oil. Further purification by column chromatography (SiO_2, 0:0:100 → 0.5:3:96.5 AcOH/MeOH/CH_2Cl_2) gave desired product (1.79 g, 55%) as a brown foam. Further purification by treatment with activated charcoal (∼2 g) in CH_2Cl_2 for 1 h, followed by filtration and solvent removal gave a yellow foam: R_f = 0.4 (0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.31 (d, *J* = 8.4 Hz, 1H, C*H*O), 8.12 (br s, 1H, N_a-*H*), 7.56 (d, *J* = 7.8 Hz, 1H, indole C4-*H*), 7.41 (d, *J* = 8.0 Hz, 1H, indole C7-*H*), 7.24 (dd, *J* = 8.0, 7.5 Hz, 1H, indole C6-*H*), 7.16 (dd, *J* = 7.8, 7.5 Hz, 1H, indole C5-*H*), 7.10 (br dd, *J* = 14.3, 12.0 Hz, 1H, ZA β-C*H*), 7.03 (d, *J* = 2.0 Hz, 1H, indole C2-*H*), 6.76 (d, *J* = 12.6 Hz, 1H, ZA δ-C*H*), 5.88 (dd, *J* = 14.3, 8.4 Hz, 1H, ZA α-C*H*), 5.79 (q, *J* = 6.6 Hz, 1H, C=C*H*), 5.43 (dd, *J* = 12.6, 12.0 Hz, 1H, ZA γ-C*H*), 3.86 (s, 2H, N_b-CH_2), 3.52 (t, *J* = 7.2 Hz, 2H, CH_2-N_b), 3.06 (t, *J* = 7.2 Hz, 2H, Ar−CH_2), 1.77 (d, *J* = 6.6 Hz, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO, 373 K) δ 190.0, 155.5, 151.3, 136.0, 126.8, 126.7, 123.0, 122.5, 120.5, 119.1, 117.9, 117.5, 110.9, 110.6, 97.1, 59.6, 50.4, 22.5, 15.7; IR (thin film) ν 2914, 1581, 1557, 1138, 1016, 742 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{19}H_{22}N_2OBr$ $(M + H)^+$ 373.0916, found 373.0911.

(*Z*)-2-Iodo-2-buten-1-ol (S25). This reaction is a modification of the procedure of Krafft.[92] To a solution of trans-crotonaldehyde (5.0 mL, 60 mmol, 1 equiv) in 1:1 THF/H_2O (300 mL) was added K_2CO_3 (10 g, 72 mmol, 1.2 equiv), followed by I_2 (23 g, 90 mmol, 1.5 equiv) and DMAP (1.47 g, 12.1 mmol, 0.2 equiv). After the mixture was stirred at rt for 2 h, $NaBH_4$ (2.5 g, 66 mmol, 1.1 equiv) was slowly added, and the mixture lightened in color from purple to red. After the mixture was stirred at rt for 45 min, saturated aqueous $Na_2S_2O_3$ (75 mL) was added. The mixture was extracted with ether (2 × 100 mL). The combined organic extracts were washed with brine (75 mL) and dried over $MgSO_4$. The solvent was evaporated in vacuo to yield the desired product (9.8 g, 82%) as an orange oil that was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (q, *J* = 6.4 Hz, 1H, vinyl-*H*), 4.25 (d, *J* = 6.5 Hz, 2H, OCH_2), 2.03 (t, *J* = 6.5 Hz, 1H, O*H*), 1.79 (d, *J* = 6.6 Hz, 3H, CH_3).

(*Z*)-1-Bromo-2-iodo-2-butene (79).[14b] To a solution of the crude allylic alcohol **S25** (9.8 g, ∼49 mmol, 1 equiv) and NEt_3 (9.6 mL, 69 mmol, 1.4 equiv) in THF (125 mL) at −30 °C was added methanesulfonyl chloride (4.6 mL, 59 mmol, 1.2 equiv). The solution was stirred at −30 °C for 1 h, LiBr (11.0 g, 124 mmol, 2.5 equiv) was added, and the reaction mixture was warmed to rt and stirred for 2 h. Saturated NH_4Cl (75 mL) was added, followed by H_2O (25 mL). The mixture was extracted with EtOAc (2 × 100 mL), and the combined organic extracts were washed with $Na_2S_2O_3$ (75 mL) and brine (75 mL) and dried over $MgSO_4$. The solvent was removed in vacuo to give the desired product as a light brown oil (10 g, 80%, ∼90% pure by ^{1}H NMR) that was used without further purification: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (q, *J* = 6.5 Hz, 1H, vinyl-*H*), 4.36 (s, 2H, BrCH_2), 1.81 (d, *J* = 6.5, 3H, CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1, 103.5, 43.5, 22.3; IR (thin film) ν 2922, 2368, 1208 cm^{-1}.

Tetracycle 36. To a solution of **7g** (268.5 mg, 0.958 mmol, 1 equiv) and 5-methyl Meldrum's acid (333.4 mg, 2.11 mmol, 2.2 equiv) in $CDCl_3$ (4.8 mL, 0.2 M) at 0 °C was added $Pd(PPh_3)_4$ (56.0 mg, 47.9 μmol, 5 mol %). The reaction mixture was stirred at 0 °C for 1 h, at which point ^{1}H NMR analysis of an aliquot indicated complete deallylation. To the reaction mixture were added diisopropylethylamine (550 μL, 3.352 mmol, 3.5 equiv) and allylic bromide **79** (570 mg, 2.107 mmol, 2.2 equiv), rinsing with CH_3CN (total volume = 4.8 mL CH_3CN). The resulting solution was stirred at 0 °C for 2.5 h, diluted with EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (10 mL), and warmed to rt. The mixture was diluted with EtOAc (10 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (10 mL) and brine (10 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.4:3.6:96 → 0.8:7.2:92 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (275.8 mg, 68%) as a yellow foam. Spectral data were identical with our previously reported data.[15,73]

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Allylic Alcohol 46. To a solution of enal **36** (19 mg, 45.2 μmol, 1.0 equiv) in THF/H_2O (9:1, 0.5 mL + 60 μL, 0.01 M) at 0 °C was added $NaBH_4$ (1.6 mg, 27.1 μmol, 0.06 equiv). The reaction mixture was stirred at 0 °C for 1 h, quenched with 0.1 M HCl (5 drops), diluted with EtOAc (8 mL) and H_2O (2 mL), and warmed to rt. The layers were separated, and the organic layer was extracted with EtOAc (4 mL). The combined organics were washed with brine (2 mL), and dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude material was purified by column chromatography (SiO_2, 0.2:1.8:98 → 0.4:3.6:96 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (16.9 mg, 88%) as a light yellow foam. A reaction performed on 220.1 mg of **36** gave 183.3 mg (83%): R_f = 0.4 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.6 Hz, 1H, C9-*H*), 7.05 (dd, *J* = 7.6, 7.4 Hz, 1H, C11-*H*), 6.76 (dd, *J* = 7.6, 7.4 Hz, 1H, C10-*H*), 6.64 (d, *J* = 7.6 Hz, 1H, C12-*H*), 5.87 (q, *J* = 6.3 Hz, 1H, C19-*H*), 5.76 (t, *J* = 4.2 Hz, 1H, C15-*H*), 4.60 (br s, 1H, NH), 4.18–4.25 (m, 2H, C17-H_2), 4.10 (s, 1H, C2-*H*), 3.58 (d, *J* = 14.2 Hz, 1H, C21-*H*), 3.29 (d, *J* = 14.2 Hz, 1H, C21-*H*), 3.02–3.10 (m, 2H, C3-*H* + C5-*H*), 2.69 (ddd, *J* = 9.4, 9.3, 6.0 Hz, 1H, C5-*H*), 2.14–2.20 (m, 2H, C14-H_2), 1.98–2.14 (m, 2H, C6-H_2), 1.79 (d, *J* = 6.3 Hz, 3H, C18-H_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.2, 136.7, 134.8, 130.9, 127.9, 124.8, 123.6, 119.2, 110.0, 109.7, 67.5, 65.2, 64.3, 64.2, 54.4, 50.7, 38.4, 24.4, 21.7; IR (thin film) ν 3351, 2919, 2803, 1606, 1484, 990, 742 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{19}H_{24}N_2OI$ $(M + H)^+$ 423.0934, found 423.0942.

Dehydrodesacetylretuline (59). A solution of $Pd(OAc)_2$ (4.0 mg, 18 μmol, 0.20 equiv), PPh_3 (9.4 mg, 35 μmol, 0.40 equiv), and NEt_3 (37.0 μL, 264 μmol, 3.0 equiv) in C_6H_6 (6.0 mL, 0.015 M in iodide) was premixed in a sealed tube temporarily capped with a septum at rt for 1 h. To this catalyst solution was added iodide **46** (37.2 mg, 88.1 μmol, 1.0 equiv). The tube was tightly sealed, heated to 85 °C for 8 h, and then cooled to rt. The reaction mixture was diluted with EtOAc, filtered through Celite, and concentrated in vacuo, and the crude material was purified by preparative TLC (SiO_2, 5:5:90 NEt_3/MeOH/Et_2O) to yield the desired product (11.5 mg, 90% purity, ~40%) along with recovered starting material (6.3 mg, 15% recovery). Spectral data were consistent with literature values: R_f = 0.5 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.6 Hz, 1H, C12-*H*), 7.38 (d, *J* = 7.3 Hz, 1H, C9-*H*), 7.34 (dd, *J* = 7.6, 7.3 Hz, 1H, C11-*H*), 7.23 (t, *J* = 7.3 Hz, 1H, C10-*H*), 5.44 (d, *J* = 6.6 Hz, 1H, C19-*H*), 4.57 (br s, 1H, O-*H*), 4.12 (dd, *J* = 8.6, 3.6 Hz, 1H, C17-*H*), 4.04 (d, *J* = 8.6 Hz, 1H, C17-*H*), 4.00 (s, 1H, C3-*H*), 3.80 (d, *J* = 15.4 Hz, 1H, C21-*H*), 3.38–3.46 (m, 1H, C14-*H*), 3.27–3.34 (m, 1H, C14-*H*), 3.21 (d, *J* = 15.5 Hz, 1H, C21-*H*), 3.01–3.06 (m, 1H, C14-*H*), 2.82 (s, 1H, C15-*H*), 2.34 (d, *J* = 7.6 Hz, 1H, C5-*H*), 2.02–2.09 (m, 1H, C5-*H*), 1.87 (d, *J* = 14.2 Hz, 1H, C6-*H*), 1.71 (d, *J* = 6.6 Hz, 3H, C18-H_3), 1.08 (d, *J* = 14.2 Hz, 1H, C6-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 192.2, 153.6, 144.0, 140.9, 128.0, 125.9, 121.4, 120.2, 119.8, 67.4, 66.0, 64.5, 56.8, 54.5, 46.7, 35.7, 34.3, 26.1, 13.3; HRMS (LC-ESI) *m*/*z* calcd for $C_{19}H_{23}N_2O$ $(M + H)^+$ 295.1810, found 295.1808.

Valparicine (9). To a solution of dehydrodesacetylretuline (**59**) (7.3 mg, 25 μmol, 1.0 equiv) in CH_2Cl_2 (1.65 mL, 0.015 M) at −10 °C was added TFA (99.2 μL, 0.25 M in CH_2Cl_2, 25 μmol, 1.0 equiv). The reaction mixture was stirred at −10 °C for 2 h, warmed to rt for 0.5 h, quenched with NEt_3 (10 μL), and diluted with EtOAc (8 mL), 1 M NaOH (2 mL) and H_2O (2 mL). The layers were separated, and the organic layer was extracted with EtOAc (4 mL). The combined organics were washed with brine (2 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by preparative TLC (SiO_2, 1:9:90 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (6.6 mg, ~65% purity, ~60%) mixed with $OPPh_3$ and unidentified byproducts. Half of the material was further purified by Agilent 1100 reversed-phase HPLC (Phenomenex Gemini-NX 5 μm C18, 250 × 21.20 mm, 13 mL/min, UV detection at 254 nm, 29.7:0.3:70 H_2O/NH_4OH/MeOH). The volatiles were evaporated in vacuo, and the water was removed by lyophilization to yield pure valparicine (1 mg, ~95% purity, ~30%). Spectral data were consistent with literature values: R_f = 0.5 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, *J* = 7.7 Hz, 1H, C12-*H*), 7.38 (d, *J* = 7.5 Hz, 1H, C9-*H*), 7.35 (t, *J* = 7.7 Hz, 1H, C11-*H*), 7.23 (t, *J* = 7.5 Hz, 1H, C10-*H*), 6.02 (s, 1H, C17-*H*), 5.51 (q, *J* = 6.8 Hz, 1H, C19-*H*), 5.39 (s, 1H, C17-*H*), 4.08 (s, 1H, C3-*H*), 3.85 (s, 1H, C15-*H*), 3.75 (d, *J* = 15.0 Hz, 1H, C21-*H*), 3.31–3.38 (m, 1H, C5-*H*), 3.28 (d, *J* = 15.0 Hz, 1H, C21-*H*), 3.20–3.25 (m, 1H, C5-*H*), 2.43 (ddd, *J* = 13.0, 9.3, 6.5 Hz, 1H, C6-*H*), 2.01 (dt, *J* = 14.1, 3.2 Hz, 1H, C14-*H*), 1.96 (ddd, *J* = 13.0, 5.9, 4.0 Hz, 1H, C6-*H*), 1.78 (d, *J* = 6.8 Hz, 3H, C18-H_3), 1.38 (dt, *J* = 14.1, 2.5 Hz, 1H, C14-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.6, 154.5, 144.8, 144.6, 139.3, 128.1, 126.0, 121.2, 120.9, 120.1, 116.6, 65.2(2), 56.6, 54.6, 37.4, 36.9, 27.1, 13.9; HRMS (LC-ESI) *m*/*z* calcd for $C_{19}H_{21}N_2$ $(M + H)^+$ 277.1705, found 277.1703.

Tetracycle 87. The synthetic procedure for the synthesis of tetracycle **87** is found in ref 7q. Incorrect spectral data was provided in the Supporting Information for ref 7q. Corrected spectral data is provided: mp = 115–117 °C; R_f = 0.3 (1:3 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H, C17-*H*), 7.06 (d, *J* = 7.5 Hz, 1H, C9-*H*), 7.03 (t, *J* = 7.5 Hz, 1H, C11-*H*), 6.81 (dd, *J* = 5.2, 2.9 Hz, 1H, C15-*H*), 6.71 (t, *J* = 7.5 Hz, 1H, C10-*H*), 6.56 (d, *J* = 7.5 Hz, 1H, C12-*H*), 6.31 (t, *J* = 6.6 Hz, 1H, C19-*H*), 4.50 (br s, 1H, N*H*), 4.26 (s, 1H, C2), 4.19–4.27 (m, 2H, C18-*H*), 3.66 (d, *J* = 11.7 Hz, 1H, C21-*H*), 2.96–3.02 (m, 2H, C3-*H* and C5-*H*), 2.76 (d, *J* = 11.7 Hz, 1H, C21-*H*), 2.60 (app dd, *J* = 19.9, 3.8 Hz, 1H, C14-*H*), 2.50 (td, *J* = 10.2, 5.1 Hz, 1H, C5-*H*), 2.42 (app d, *J* = 19.9, 1H, C14-*H*), 2.16 (ddd, *J* = 12.8, 8.8, 5.1 Hz, 1H, C6-*H*), 1.88 (ddd, *J* = 12.8, 10.3, 6.1 Hz, 1H, C6-*H*), 1.40 (br s, O*H*), 0.10 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.8 (C17), 150.8 (C15), 150.1 (C13), 142.5 (C19), 141.4 (C20), 140.6 (C16), 132.0 (C8), 128.1 (C11), 122.8 (C9), 118.5 (C10), 109.2 (C12), 63.8 (C3), 62.9 (C), 61.8 (C), 59.7 (C2), 53.3 (C7), 50.8 (C5), 36.9 (C6), 25.6 (C14), 0.1 (CH_3Si); IR (thin film) ν 3380, 2952, 2807, 1679, 1485, 1246, 840, 743 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{22}H_{31}N_2O_2Si$ $(M + H)^+$ 383.2155, found 383.2158.

Nonacyclic Dimer 64. To a solution of enal **7d** (27.2 mg, 69.7 μmol, 1.0 equiv) in CH_2Cl_2 (0.60 mL, 0.1 M) at 0 °C was added TFA (10.3 μL, 139 μmol, 2.0 equiv). The reaction mixture was slowly warmed to rt and then stirred at rt for 14 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$ (2 mL) and diluted with EtOAc (8 mL). The layers were separated, and the aquous layer was extracted with EtOAc (4 mL). The combined organics were washed with H_2O (2 mL) and brine (2 mL) and dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.2:1.8:98 → 0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (20.7 mg, 80%) as a yellow oil. No DMB-deprotection was observed under a variety of similar conditions: R_f = 0.5 (1:9:90 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.9 Hz, 1H, Ar-*H*), 7.12 (dd, *J* = 7.8, 7.6 Hz, 1H, C11-*H*), 7.07 (d, *J* = 7.6 Hz, 1H, C9-*H*), 6.83 (t, *J* = 7.6 Hz, 1H, C10-*H*), 6.62 (d, *J* = 7.8 Hz, 1H, C12-*H*), 6.53 (s, 1H, C17-*H*), 6.48–6.53 (m, 2H, Ar-*H*), 6.36 (d, *J* = 9.9 Hz, 1H, C15-*H*), 5.64 (dd, *J* = 9.9, 5.0 Hz, 1H, C14-*H*), 5.19 (s, 1H, C2-*H*), 3.97 (d, *J* = 13.7, 1H, C21-*H*), 3.83 (s, 6H, OCH_3), 3.77 (d, *J* = 13.7, 1H, C21-*H*), 3.34 (d, *J* = 5.0, 1H, C3-*H*), 3.09 (ddd, *J* = 13.5, 9.0, 4.5 Hz, 1H, C5-*H*), 2.61–2.68 (m, 1H, C5-*H*), 2.10–2.17 (m, 1H, C6-*H*), 1.88 (ddd, *J* = 13.5, 9.4, 4.5 Hz, 1H, C6-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.8, 158.7, 145.5, 137.1, 131.74, 131.71, 131.5, 128.1, 122.3, 120.7, 118.6, 116.4, 113.0, 108.9, 103.8, 98.4, 66.5, 62.8, 55.34, 55.31, 53.3, 50.2, 49.6, 40.2; IR (thin film) ν 2931, 2833, 1629, 1591, 1485, 1208, 1035 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{48}H_{49}N_4O_4$ $(M + H)^+$ 745.3754, found 745.3761.

Nonacyclic Dimer S26. A solution of enal **87** (11.1 mg, 29.0 μmol, 1 equiv), dimethyl malonate (6.7 μL, 58 μmol, 2.0 equiv), and pyrrolidine (0.5 μL, 6 μmol, 0.2 equiv) in AcOH (0.29 mL, 0.1 M) was heated to 80 °C for 70 min. The reaction mixture was cooled to rt and diluted with EtOAc (8 mL), saturated aqueous $NaHCO_3$ (2 mL), and H_2O (2 mL). The aqueous layer was extrated with EtOAc (5 mL). The combined organics were washed with brine (2 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and ^{1}H NMR analysis of the crude material showed mostly undesired dimerization product. A similar experiment without pyrrolidine gave a similar result. The two crude reaction mixtures were combined and

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purified by column chromatography (SiO_2, 0.1:0.9:99 → 0.2:1.8:98 $NH_4OH/MeOH/CH_2Cl_2$) to yield the title product (9.6 mg, 45%) as a tan solid. This product was also made in 72% yield by treatment of enal **87** with 2 equiv of TFA in THF (see procedure for **64**): mp >230 °C dec; R_f = 0.3 (0.5:4.5:95 $NH_4OH/MeOH/CH_2Cl_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.12 (dd, J = 7.8, 7.6 Hz, 1H, C11-*H*), 7.07 (d, J = 7.3 Hz, 1H, C9-*H*), 6.84 (dd, J = 7.6, 7.3 Hz, 1H, C10-*H*), 6.65 (d, J = 7.8 Hz, 1H, C12-*H*), 6.54 (s, 1H, C17-*H*), 6.32 (d, J = 9.8 Hz, 1H, C15-*H*), 6.29 (t, J = 6.4 Hz, 1H, C19-*H*), 5.43 (dd, J = 9.8, 5.4 Hz, 1H, C14-*H*), 5.22 (s, 1H, C2-*H*), 4.20−4.29 (m, 2H, C18-H_2), 3.76 (d, J = 11.5, 1H, C21-*H*), 3.18 (d, J = 5.3, 1H, C3-*H*), 2.93−3.20 (m, 1H, C5-*H*), 2.79 (d, J = 11.5, 1H, C21-*H*), 2.34−2.42 (m, 1H, C5-*H*), 1.97−2.05 (m, 1H, C6-*H*), 1.83−1.91 (m, 1H, C6-*H*), 1.62 (br s, 1H, O*H*), 0.14 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.8, 142.2, 142.1, 135.6, 133.7, 131.4, 128.3, 122.4, 121.0, 115.1, 112.8, 109.0, 66.4, 63.1, 62.9, 62.0, 53.9, 50.5, 39.4, −0.5; IR (thin film) ν 2951, 2775, 1627, 1484, 838 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{44}H_{57}N_4O_2Si_2$ $(M + H)^+$ 729.4020, found 729.4002.

Zincke Aldehyde S27 (by Cycloreversion of 87). A solution of vinylsilane **87** (4.6 mg, 12 μmol, 1 equiv) and pyrrolidine (3.9 μL, 48 μmol, 4 equiv) in HFIP (1 mL, 0.01 M) was heated in a microwave reactor at 120 °C for 4 h. The solvent was removed in vacuo, and the residue was diluted with EtOAc (1 mL) and 2 M NaOH (1 mL) and stirred vigorously for 3 h to ensure complete hydrolysis of iminium ions. The mixture was diluted with EtOAc (5 mL). The layers were separated, and the organic layer was washed with brine (2 mL) and then dried over Na_2SO_4. The solvent was removed in vacuo, and the crude material was purified by column chromatography (SiO_2, 0.2:1.8:98 → 0.8:7.2:92 $NH_4OH/MeOH/CH_2Cl_2$) to yield Zincke aldehyde **S27** (2.0 mg, 43%) along with some of the corresponding secondary amine **S28** and Zincke aldehyde **86**. It was not possible to obtain complete characterization data for this compound, and the structures of **S27** and **S28** were assigned by analogy to Zincke aldehyde **12j** and amine **42** lacking only the C18 hydroxyl group: R_f = 0.25 (1:9:90 $NH_4OH/MeOH/CH_2Cl_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (d, J = 8.4 Hz, 1H, C*H*O), 8.13 (br s, 1H, N_a-*H*), 7.56 (d, J = 7.9 Hz, 1H, indole C4-*H*), 7.41 (d, J = 8.0 Hz, 1H, indole C7-*H*), 7.24 (dd, J = 8.0, 7.4 Hz, 1H, indole C6-*H*), 7.16 (t, J = 7.9, 7.4 Hz, 1H, indole C5-*H*), 7.07 (app t, J = 12.7 Hz, 1H, ZA β-C*H*), 7.03 (d, J = 1.8 Hz, 1H, indole C2-*H*), 6.75 (d, J = 12.0 Hz, 1H, ZA δ-C*H*), 5.93 (t, J = 6.6 Hz, 1H, vinyl-*H*), 5.84 (dd, J = 14.2, 8.4 Hz, 1H, ZA α-C*H*), 5.27−5.42 (br s, 1H, ZA γ-C*H*), 4.22 (d, J = 6.6 Hz, 2H, CH_2O), 3.69 (s, 2H, N_b-CH_2), 3.49 (t, J = 6.9 Hz, 2H, CH_2-N_b), 3.04 (t, J = 6.9 Hz, 2H, Ar−CH_2), 1.40 (br s, 1H, O*H*), 0.11 (s, 9H, SiCH_3); LRMS (LC-ESI) m/z calcd for $C_{22}H_{31}N_2O_2Si$ $(M + H)^+$ 383.2, found 383.2; calcd for $C_{22}H_{30}N_2O_2SiNa$ $(M + Na)^+$ 405.2, found 405.2.

Allylic Alcohol 105. In the Brook rearrangement reactions, the major product in most cases was protodemetalated product **105**, isolated as a light yellow oil. See ref for the experimental procedure for its formation: R_f = 0.3 (0.7:6.3:93 $NH_4OH/MeOH/CH_2Cl_2$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H, C17-*H*), 7.06 (d, J = 7.7 Hz, 1H, C9-*H*), 7.03 (t, J = 7.7 Hz, 1H, C11-*H*), 6.82 (dd, J = 5.3, 2.8 Hz, 1H, C15-*H*), 6.72 (t, J = 7.7 Hz, 1H, C10-*H*), 6.56 (d, J = 7.7 Hz, 1H, C12-*H*), 5.76−5.88 (m, 2H, C19-*H* + C20-*H*), 4.51 (br s, 1H, N*H*), 4.32 (s, 1H, C2-*H*), 4.17 (app d, J = 4.7 Hz, 2H, C18-H_2), 3.47 (dd, J = 13.8, 5.0 Hz, 1H, C21-*H*), 3.15−3.21 (m, 1H, C14−H), 3.10−3.13 (m, 1H, C3-*H*), 3.02 (dd, J = 13.8, 6.7 Hz, 1H, C21-*H*), 2.66 (td, J = 19.9, 5.0 Hz, 1H, C14-*H*), 2.60 (app dd, J = 20.0, 5.1 Hz, 1H, C5-*H*), 2.37−2.44 (m, 1H, C5-*H*), 2.21 (ddd, J = 13.1, 8.3, 5.0 Hz, 1H, C6-*H*), 1.94 (ddd, J = 13.1, 10.0, 5.0 Hz, 1H, C6-*H*); ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.9 (C17), 150.44 (C15), 150.37 (C13), 140.8 (C16), 131.94 (C8), 131.87 (C19 or C20), 128.8 (C19 or C20), 128.3 (C11), 122.8 (C9), 118.6 (C10), 109.3 (C12), 63.9 (C3), 63.3 (C18), 59.7 (C2), 55.3 (C21), 53.4 (C7), 51.1 (C5), 37.9 (C6), 26.0 (C14); IR (thin film) ν 3254, 2918, 1668, 1391, 747 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{19}H_{23}N_2O_2$ $(M + H)^+$ 311.1760, found 311.1761.

Vinylsilane 107. To a solution of vinylsilane **87** (17.0 mg, 44.4 μmol, 1 equiv) in CH_2Cl_2 (0.4 mL, 0.1 M) was added ethyl chloroformate (89 uL, 0.5 M in CH_2Cl_2, 44.4 μmol, 1.0 equiv). The resulting mixture was stirred at rt for 16 h, quenched with saturated aqueous $NaHCO_3$ (10 drops), and then diluted with EtOAc (8 mL) and H_2O (5 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with brine (2 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 1:9 → 1:4 EtOAc/CH_2Cl_2) to yield the desired product (14.7 mg, 73%) as a yellow oil. This compound lies on a failed route to strychnine, and IR data for this compound was not obtained prior to abandoning this route: R_f = 0.6 (1:3 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H, C17-*H*), 7.69−7.77 (m, 1H, C12-*H*), 7.21 (t, J = 7.6 Hz, 1H, C11-*H*), 7.19 (d, J = 7.6 Hz, 1H, C9-*H*), 7.06 (t, J = 7.6 Hz, 1H, C10-*H*), 7.00 (dd, J = 7.5, 3.2 Hz, 1H, C15-*H*), 6.29 (t, J = 6.6 Hz, 1H, C19-*H*), 4.97 (s, 1H, C2-*H*), 4.17−4.29 (m, 4H, C18-H_2 + C23-H_2), 3.61 (d, J = 11.7 Hz, 1H, C21-*H*), 2.98−3.03 (m, 1H, C5-*H*), 2.62 (ddd, J = 17.0, 7.5, 1.5 Hz, 1H, C14-*H*), 2.56−2.59 (m, 1H, C3-*H*), 2.52 (d, J = 11.7 Hz, 1H, C21-*H*), 2.32 (dt, J = 17.0, 3.6 Hz, 1H, C14-*H*), 2.13−2.27 (m, 2H, C5-*H* + C6-*H*), 1.73−1.82 (m, 1H, C6-*H*), 1.24−1.31 (m, 3H, C24-H_3), 0.12 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.6, 153.7, 149.9, 143.1, 142.2, 141.1, 139.7, 136.8, 128.1, 123.7, 123.1, 115.4, 73.5, 63.3, 62.0, 61.8, 60.5, 54.1, 53.6, 37.6, 25.4, 14.5, 0.3; LRMS (LC-ESI) m/z calcd for $C_{25}H_{35}N_2O_4Si$ $(M + H)^+$ 455.2, found 455.2; calcd for $C_{25}H_{34}N_2O_4SiNa$ $(M + Na)^+$ 477.2, found 477.2.

Carbamate S29. A solution of **7g** (64.5 mg, 0.230 mmol, 1 equiv) and Boc_2O (132 uL, 0.580 mmol, 2.5 equiv) in $(CH_2Cl)_2$ (0.77 mL, 0.3 M) was heated to 80 °C in a sealed tube for 22 h. The reaction mixture was cooled to rt and concentrated in vacuo, and the crude material was purified by column chromatography (SiO_2, 1:9 → 1:3 EtOAc/CH_2Cl_2) to yield the desired product (72.1 mg, 82%) as a tan solid: R_f = 0.25 (1:3 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (s, 1H, C17-*H*), 7.66−7.71 (m, 1H, C12-*H*), 7.19 (t, J = 7.7 Hz, 1H, C11-*H*), 7.16 (d, J = 7.3 Hz, 1H, C9-*H*), 7.03 (dd, J = 7.7, 7.3 Hz, 1H, C10-*H*), 6.98 (dd, J = 7.2, 3.3 Hz 1H, C15-*H*), 5.91 (dddd, J = 17.1, 10.2, 7.5, 5.5 Hz, 1H, C20-*H*), 5.20 (d, J = 17.1 Hz, 1H, *Z*-C19-*H*), 5.13 (d, J = 10.2 Hz, 1H, *E*-C19-*H*), 4.98 (s, 1H, C2-*H*), 3.38 (dd, J = 13.7, 5.5 Hz, 1H, C21-*H*), 3.11−3.17 (m, 1H, C5-*H*), 2.87 (dd, J = 13.7, 7.5 Hz, 1H, C21-*H*), 2.76 (app d, J = 2.0 Hz, 1H, C3-*H*), 2.61 (ddd, J = 17.2, 7.2, 2.0 Hz, 1H, C14-*H*), 2.49 (app q, J = 9.0 Hz, 1H, C5-*H*), 2.32 (dt, J = 17.2, 3.6 Hz, 1H, C14-*H*), 2.17 (ddd, J = 13.2, 7.7, 2.6 Hz, 1H, C6-*H*), 1.87 (ddd, J = 13.2, 8.3, 9.2 Hz, 1H, C6-*H*), 1.51 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 152.9, 148.3, 142.6, 139.8, 136.7, 135.1, 128.0, 123.4, 122.8, 117.4, 115.8, 82.0, 71.5, 60.7, 56.7, 54.0, 53.2, 37.6, 28.6, 25.8; IR (thin film) ν 2875, 2929, 1698, 1480, 1369, 1167, 752 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{23}H_{29}N_2O_3$ $(M + H)^+$ 381.2178, found 381.2171.

Vinylsilane 117. To a solution of **S29** (71.6 mg, 0.188 mmol, 1 equiv) and 5-methyl Meldrum's acid (65.5 mg, 0.414 mmol, 2.2 equiv) in $CDCl_3$ (0.94 mL, 0.2 M) at 0 °C was added $Pd(PPh_3)_4$ (10.9 mg, 9.0 μmol, 5 mol %). The reaction mixture was stirred at 0 °C for 1 h, at which point ^{1}H NMR analysis of an aliquot indicated incomplete deallylation. An additional portion of $Pd(PPh_3)_4$ (10.9 mg, 9.0 μmol, 5 mol %) was added, and the reaction mixture was stirred at 0 °C for 2 h. To the reaction mixture were added diisopropylethylamine (115 μL, 0.658 mmol, 3.5 equiv) and allylic bromide **102** (111 mg, 0.498 mmol, 2.65 equiv) as a solution in $CDCl_3$, rinsing with $CDCl_3$ (1.0 mL total). The resulting solution was placed in a refrigerator (~4 °C) for 12 h, removed, stirred at 0 °C for 4 h, and then stirred to rt for an additional 3 h. The reaction mixture was diluted with EtOAc (10 mL), saturated aqueous $NaHCO_3$ (5 mL), and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with aqueous $NaHCO_3$ (3 mL) and brine (3 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0:1:10 → 0:20:80 → 1:20:79 NEt_3/EtOAc/CH_2Cl_2) to yield the desired product (69.0 mg, 76%) as a yellow oil:; R_f = 0.25 (15:85 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 (s, 1H, C17-*H*), 7.62−7.71 (m, 1H, C12-*H*), 7.19 (t, J = 7.5 Hz, 1H, C11-*H*), 7.15 (d, J = 7.5 Hz, 1H, C9-*H*), 7.03 (t, J = 7.5 Hz, 1H, C10-*H*), 6.94−6.98 (m, 1H, C15-*H*), 6.29 (t, J = 6.5 Hz, 1H, *E*-C19-*H*), 4.95 (s, 1H, C2-*H*), 4.19−4.28 (m, 2H, C18-H_2), 3.63

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(d, J = 11.7 Hz, 1H, C21-*H*), 3.00 (t, J = 8.4 Hz, 1H, C5-*H*), 2.57−2.64 (m, 2H, C3-*H* + C14-*H*), 2.54 (d, J = 11.7 Hz, 1H, C21-*H*), 2.20−2.37 (m, 1H, C14-*H*), 2.24 (app q, J = 9.0 Hz, 1H, C5-*H*), 2.09−2.17 (m, 1H, C6-*H*), 1.76−1.85 (m, 1H, C6-*H*), 1.51 (s, 9H, *t*-Bu), 0.12 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 191.9, 152.9, 148.6, 143.1, 142.5, 141.2, 139.7, 136.7, 128.0, 123.4, 122.9, 115.7, 82.0, 72.2, 63.4, 61.8, 60.7, 53.9, 53.3, 37.3, 28.6, 25.5, 0.3; IR (thin film) ν 2956, 2803, 1694, 1372, 1249, 1167, 839 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{27}H_{39}N_2O_4Si$ (M + H)$^+$ 483.2679, found 483.2681.

Ester 109. To a solution of enal **87** (42.0 mg, 0.110 mmol, 1 equiv) and dimethyl malonate (101 μL, 0.88 mmol, 8 equiv) in toluene (2 mL, 0.05 M) was added ethylenediaminediacetic acid (10 mg, 0.055 mmol, 0.5 equiv). The resulting mixture was heated to 100 °C for 38 h and then cooled to rt. The reaction mixture was diluted with EtOAc (8 mL), saturated aqueous $NaHCO_3$ (2 mL), and H_2O (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with brine (2 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 1:9 → 2:8 EtOAc/CH_2Cl_2) to yield the desired product (26 mg, 42%) as a yellow oil: R_f = 0.6 (1:3 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.2 Hz, 1H, C12-*H*), 7.71 (s, 1H, C17-*H*), 7.53 (d, J = 7.5 Hz, 1H, C9-*H*), 7.25 (dd, J = 8.2, 7.7 Hz, 1H, C11-*H*), 7.03 (dd, J = 7.7, 7.5 Hz, 1H, C10-*H*), 6.40 (app d, J = 7.2 Hz, 1H, C15-*H*), 6.22 (t, J = 6.9 Hz, 1H, C19-*H*), 4.68−4.78 (m, 2H, C18-H_2), 4.61 (s, 1H, C2-*H*), 3.91 (s, 3H, C25-H_3), 3.74 (s, 3H, C29-H_3), 3.45 (d, J = 12.2 Hz, 1H, C21-*H*), 3.40 (s, 2H, C27-H_2), 3.25−3.29 (m, 1H, C5-*H*), 3.22 (d, J = 12.2 Hz, 1H, C21-*H*), 2.85 (dd, J = 9.5, 5.1 Hz, 1H, C3-*H*), 2.64 (app td, J = 10.6, 4.2 Hz, 1H, C5-*H*), 2.54 (ddd, J = 18.0, 6.5, 5.1 Hz, 1H, C14-*H*), 2.20−2.31 (m, 2H, C6-*H* + C14-*H*), 2.06−2.13 (m, 1H, C6-*H*), 0.16 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.9, 166.3, 165.1, 158.3, 144.1, 144.0, 140.4, 138.9, 136.7, 134.6, 130.5, 128.5, 126.9, 125.4, 124.1, 115.5, 64.4, 63.1, 60.6, 59.0, 52.60, 52.58, 51.8, 48.1, 41.4, 37.1, 23.4, −0.1; IR (thin film) ν 2950, 1738, 1645, 1479, 838 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{30}H_{36}N_2O_7SiNa$ (M + Na)$^+$ 587.2189, found 587.2197.

Malonamate 110. To a solution of ester **109** (21.1 mg, 37.4 μmol, 1 equiv) in MeOH (1.9 mL, 0.02 M) at 0 °C was added K_2CO_3 (1.9 mg, 18.7 μmol, 0.5 equiv). The resulting mixture was stirred at 0 °C for 1 h 45 min and then diluted with EtOAc (8 mL) and H_2O (5 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with brine (2 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 1:20:79 → 1:30:69 NEt_3/EtOAc/CH_2Cl_2) to yield the desired product (**110**) (11.3 mg, ∼90% purity, ∼58%) as a yellow oil, contaminated with a byproduct that we believe has structure **S30**.[24] Further purification by preparative TLC (SiO_2, 1:3 EtOAc/CH_2Cl_2) gave the desired product **110** (9.2 mg, 53%) as a yellow foam: R_f = 0.4 (1:3 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, J = 8.1 Hz, 1H, C12-*H*), 7.70 (s, 1H, C17-*H*), 7.54 (d, J = 7.7 Hz, 1H, C9-*H*), 7.25 (dd, J = 8.1, 7.7 Hz, 1H, C11-*H*), 7.03 (t, J = 7.7 Hz, 1H, C10-*H*), 6.39 (app d, J = 7.3 Hz, 1H, C15-*H*), 6.29 (t, J = 6.8 Hz, 1H, C19-*H*), 4.60 (s, 1H, C2-*H*), 4.20−4.28 (m, 2H, C18-H_2), 3.90 (s, 3H, OCH_3), 3.44 (d, J = 12.1 Hz, 1H, C21-*H*), 3.23−3.30 (m, 1H, C5-*H*), 3.21 (d, J = 12.1 Hz, 1H, C21-*H*), 2.86 (dd, J = 9.5, 4.9 Hz, 1H, C3-*H*), 2.65 (app td, J = 10.6, 4.2 Hz, 1H, C5-*H*), 2.50−2.60 (m, 1H, C14-*H*), 2.20−2.30 (m, 2H, C6-*H* + C14-*H*), 2.05−2.14 (m, 1H, C6-*H*), 1.63 (br s, 1H, O*H*), 0.14 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 158.3, 144.0, 142.7, 140.8, 140.3, 139.0, 134.7, 130.4, 128.5, 126.9, 125.4, 124.1, 115.5, 63.1, 62.0, 60.5, 59.1, 52.6, 51.8, 48.1, 37.1, 23.4, 0.1; IR (thin film) ν 2959, 2927, 1738, 1651, 1249, 839, 732 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{26}H_{32}N_2O_4SiNa$ (M + Na)$^+$ 487.2029, found 487.2028.

Pyridones 111 and 112. To a solution of malonamate **110** (10.6 mg, 22.8 μmol, 1.0 equiv) in NMP (380 μL, 0.06 M) in a 4 mL vial at 0 °C was added NaHMDS (32 μL, 1 M in THF, 32 μmol, 1.4 equiv). The reaction mixture was stirred at 0 °C for 15 min, and then CuBr·SMe_2 (328 μL, 0.125 M in NMP, 41.0 μmol, 1.8 equiv) was added. The resulting brown solution was stirred at 0 °C for 10 min and warmed to rt for 5 min, the septum was replaced with an unpierced septum cap, and the reaction mixture was heated to 65 °C for 1 h 40 min. The reaction mixture was cooled, quenched with H_2O, then diluted with EtOAc (8 mL) and 3% aqueous NH_4OH (4 mL). The layers were separated and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed aqueous NH_4OH (2 mL), H_2O (2 × 2 mL), and brine (2 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude material was purified by column chromatography (SiO_2, 0.1:0.9:99 → 0.3:2.3:97 NH_4OH/MeOH/CH_2Cl_2) to yield the pyridone **111** (1.6 mg, ∼15%) as a highly fluorescent film along with some recovered starting material. According to the precedent of Takeda et al.,[66] reaction using CuO-*t*-Bu in DMF at 60 °C for 4 h yielded ∼20% of pyridone **111** along with a small amount of pyridone **112** (assigned by analogy to **111** by evaluation of ^{1}H NMR data, full spectral data not obtained).

111: R_f = 0.3 (0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.71 (d, J = 8.1 Hz, 1H, C12-*H*), 8.13 (s, 1H, C17-*H*), 7.70 (d, J = 7.7 Hz, 1H, C9-*H*), 7.44 (dd, J = 8.1, 7.7 Hz, 1H, C11-*H*), 7.03 (t, J = 7.7 Hz, 1H, C10-*H*), 6.46 (dd, J = 10.0, 1.3 Hz, 1H, C14-*H* or C15-*H*), 6.38 (t, J = 6.7 Hz, 1H, C19-*H*), 5.99 (dd, J = 10.0, 1.3 Hz, 1H, C14-*H* or C15-*H*), 4.26−4.30 (m, 2H, C18-H_2), 4.24 (s, 1H, C3-*H*), 3.96 (s, 3H, OCH_3), 3.72 (d, J = 12.1 Hz, 1H, C21-*H*), 3.45 (d, J = 12.1 Hz, 1H, C21-*H*), 3.27−3.32 (m, 1H, C5-*H*), 2.53−2.62 (m, 2H, C5-*H* + C6-*H*), 1.92−1.98 (m, 1H, C6-*H*), 0.28 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2, 158.2, 158.0, 143.1, 141.9, 140.9, 140.7, 139.3, 128.7, 127.1, 124.1, 123.8, 122.5, 119.1, 118.5, 108.0, 66.7, 62.0, 59.7, 52.8, 52.5, 50.2, 39.7, 0.3; IR (thin film) ν 2923, 1732, 1667, 1632, 1544, 1200, 838 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{26}H_{30}N_2O_4SiNa$ (M + Na)$^+$ 485.1873, found 485.1863.

Vinylsilane 103. To a solution of bromide **102** (360 mg, 1.61 mmol, 1.0 equiv) in CH_2Cl_2 (8.1 mL, 0.2 M) at 0 °C were added Bn_2NH (0.62 mL, 3.22 mmol, 2.0 equiv) and *i*-Pr_2NEt (0.56 mL, 3.22 mmol, 2.0 equiv). The reaction mixture was slowly warmed to rt and stirred at rt for 13 h. The reaction mixture was diluted with EtOAc (30 mL), saturated aqueous $NaHCO_3$ (50 mL), and H_2O (10 mL). The aqueous layer was extrated with EtOAc (10 mL). The combined organics were washed with brine (40 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo and the crude material was purified by column chromatography (SiO_2, 1:20 → 1:10 EtOAc:hexanes) to yield the desired product (403 mg, 74%) as a colorless oil: R_f = 0.5 (1:3 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.40 (m, 8H, Ph), 7.23−7.27 (m, 2H, Ph), 6.43 (t, J = 6.8 Hz, 1H, vinyl-C*H*), 4.25 (d, J = 6.8 Hz, 1H, C*H*2O), 3.49 (s, 4H, PhCH_2), 3.11 (s, 2H, NCH_2), 1.24 (br s, 1H, O*H*), 0.11 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.6, 141.4, 139.2, 129.3, 128.2, 126.9, 62.5, 62.1, 57.9, 0.2; IR (thin film) ν 3343, 2951, 2792, 1454, 1248, 839 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{21}H_{30}NOSi$ (M + H)$^+$ 340.2097, found 340.2097.

Ester 116. A solution of vinylsilane **103** (20.8 mg, 61.3 μmol, 1.0 equiv), *tert*-butyl acrylate (27.0 μL, 184 μmol, 3.0 equiv), [MeORh(cod)]$_2$ (1.5 mg, 3.1 μmol, 0.05 equiv), and 1 M aqueous KOH (61 μL, 61 μmol, 1 equiv) in THF (0.55 mL, 0.1 M) was heated to 70 °C for 16 h. The yellow solution was cooled to rt and concentrated in vacuo. The crude material was purified by column chromatography (SiO_2, 1:9 → 1:4 EtOAc/hexanes) to yield the desired product (12.7 mg, 53%) as a colorless oil: R_f = 0.4 (1:3 EtOAc/hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.38 (m, 8H, Ar*H*), 7.24 (t, J = 7.2 Hz, 2H, Ar*H*), 5.77 (t, J = 7.2 Hz, 1H, vinyl-*H*), 4.16 (d, J = 7.2 Hz, 2H, CH_2OH), 3.48 (s, 4H, PhCH_2), 2.94 (s, 2H, NCH_2), 2.47 (t, J = 7.3 Hz, CH_2CH$_2$CO$_2$R), 2.11 (t, J = 7.3 Hz, CH$_2$CH_2CO$_2$R), 2.10 (br s, 1H, O*H*), 1.38 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.2, 139.7, 139.6, 128.9, 128.31, 128.29, 127.0, 80.5, 59.3, 58.5, 58.2, 33.0, 28.1, 23.6; IR (thin film) ν 2973, 2795, 1729, 1149, 748 cm^{-1}; HRMS (LC-ESI) m/z calcd for $C_{25}H_{34}NO_3$ (M + H)$^+$ 396.2539, found 396.2537.

Dihydrofuran S31. If insufficient H_2O is added in the conversion of **103** to **116**, as described above, protonation of the intermediate Rh-enolate is inefficient and the major product is **S31** (54%), which presumably arises from β-hydride elimination and cyclization of the

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hydroxyl group of this Heck-type product. For similar observations in a related Rh-catalyzed conjugate addition/Heck reaction, see ref 93: R_f = 0.4 (1:3 EtOAc:hexanes); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.38 (m, 8H, Ar*H*), 7.25 (t, *J* = 7.2 Hz, 2H, Ar*H*), 5.80 (br s, 1H, C6-*H*), 5.21−5.26 (m, 1H, C3-*H*), 4.57−4.66 (m, 2H, C5-H_2), 3.78 (d, *J* = 13.5 Hz, 2H, C9-H_2), 3.27 (d, *J* = 13.5 Hz, 2H, C9-H_2), 3.13 (d, *J* = 14.4 Hz, 1H, C8-*H*), 3.02 (d, *J* = 14.4 Hz, 1H, C8-*H*), 2.37 (dd, *J* = 14.9, 2.9 Hz, 1H, C2-*H*), 2.10 (dd, *J* = 14.9, 8.2 Hz, 1H, C2-*H*), 1.47 (s, 9H, *t*-Bu); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 140.0, 139.2, 128.9, 128.3, 127.1, 124.1, 83.1, 80.4, 74.5, 58.3, 50.7, 40.4, 28.2; IR (thin film) ν 2977, 2798, 1731, 1367, 1150, 749, 699 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{25}H_{32}NO_3$ (M + H)$^+$ 394.2382, found 394.2381.

In Scheme S2 found only in the Supporting Information, we describe a different, partially successful approach to D-ring formation. The relevant experimental details follow:

Propargylsilane S3. To a solution of **7g** (235 mg, 0.838 mmol) and barbituric acid **77** (454 mg, 1.84 mmol, 2.2 equiv) in $CDCl_3$ (4.2 mL, 0.2 M) at 0 °C was added $Pd(PPh_3)_4$ (48.4 mg, 42.0 μmol, 5 mol %). The reaction mixture was stirred at 0 °C for 1 h, at which point ^{1}H NMR analysis of an aliquot indicated complete deallylation. To the reaction mixture were added diisopropylethylamine (438 μL, 2.51 mmol, 3.0 equiv) and propargylic bromide **S2**[94] (378 mg, 1.84 mmol, 2.2 equiv). The resulting solution was stirred at 0 °C for 4.5 h, diluted with EtOAc (10 mL) and saturated aqueous $NaHCO_3$ (4 mL), and warmed to rt. The mixture was diluted with EtOAc (10 mL) and H_2O (4 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (10 mL). The combined organic extracts were washed with brine (10 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo, and the crude material was purified by column chromatography (SiO_2, 0:0:100 → 0.2:1.8:98 NH_4OH/MeOH/CH_2Cl_2) to yield the desired product (138 mg, 45%) as a yellow foam: R_f = 0.3 (SiO2, 0.5:4.5:95 NH_4OH/MeOH/CH_2Cl_2), 0.6 (Al_2O_3, 1:3 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.45 (s, 1H, C17-*H*), 7.01−7.07 (m, 2H, C9-*H* + C11-*H*), 6.77−6.81 (m, 1H, C15-*H*), 6.71 (t, *J* = 7.6 Hz, 1H, C10-*H*), 6.56 (d, *J* = 7.6 Hz, 1H, C12-*H*), 4.54 (br s, 1H, NH), 4.30 (s, 1H, C2-*H*), 3.53 (app q, *J* = 2.1 Hz, 2H, C21-H_2), 3.46 (app d, *J* = 4.0 Hz, 1H, C3-*H*), 3.10−3.17 (m, 1H, C5-*H*), 3.02 (td, *J* = 10.2, 4.5 Hz, 1H, C5-*H*), 2.56 (dd, *J* = 19.8, 5.5 Hz, 1H, C14-*H*), 2.35−2.42 (m, 1H, C14-*H*), 2.31 (ddd, *J* = 12.8, 8.2, 4.4 Hz, 1H, C6-*H*), 1.90 (ddd, *J* = 12.8, 10.5, 6.9 Hz, 1H, C6-*H*), 1.56 (app t, *J* = 2.1 Hz, 2H, C18-H_2), 0.17 (s, 9H, SiCH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.0, 150.5, 150.2, 140.7, 131.2, 128.4, 122.6, 118.5, 109.3, 83.5, 72.4, 60.4, 59.9, 53.4, 49.3, 40.7, 38.1, 25.5, 7.2, −1.8; IR (thin film) ν 3368, 2951, 2226, 2186, 1666, 844, 742 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{22}H_{29}N_2OSi$ (M + H)$^+$ 365.2049, found 365.2050.

Allene S4. To a solution of silane **S3** (10.0 mg, 27.4 μmol, 1.0 equiv) in CH_2Cl_2 (1.1 mL, 0.025 M) at 0 °C was added $BF_3{\cdot}OEt_2$ (20.3 μL, 164 μmol, 6.0 equiv). The resulting solution was slowly warmed to rt and stirred at rt for 18 h. The reaction mixture was diluted with EtOAc (5 mL) and half-saturated Na_2CO_3 (2 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (5 mL). The combined organic extracts were washed with brine (2 mL) and then dried over Na_2SO_4. The solvent was evaporated in vacuo and analysis of the crude material indicated ∼1:1 mixture of starting material and allene product with small impurities. The crude material was purified by column chromatography (neutral Al_2O_3, Brockman activity I, 1:3 EtOAc/CH_2Cl_2) to yield the desired product mixed with starting material (2.3 mg, ∼ 90% purity, ∼25%) as a yellow film. Because of the inefficiency of this sequence, a complete characterization data set could not be compiled, and this avenue of exploration was not pursued: R_f = 0.15 (Al_2O_3, 1:3 EtOAc/CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$, assignments tentative) δ 9.99 (s, 1H, C17-*H*), 7.06 (dd, *J* = 7.8, 7.3 Hz, 1H, C11-*H*), 7.01 (d, *J* = 7.2 Hz, 1H, C9-*H*), 6.73 (dd, *J* = 7.3, 7.2 Hz, 1H, C10-*H*), 6.56 (d, *J* = 7.8 Hz, 1H, C12-*H*), 4.77 (dt, *J* = 10.7, 4.0 Hz, 2H, C18-*H*), 4.68 (dt, *J* = 10.7, 4.0 Hz, 2H, C18-*H*), 4.24 (s, 1H, N-*H*), 3.85−3.89 (m, 2H, C2-*H* + C3-*H*), 3.82 (dt, *J* = 15.0, 4.0 Hz, 1H, C21-*H*), 3.34 (br s, 1H, C15-*H*), 3.19 (dd, *J* = 8.4, 9.6 Hz, 1H, C5-*H*), 2.84−2.94 (m, 2H, C5-*H* + C21-*H*), 2.15−2.30 (m, 3H, C6-*H* + C14-*H* + C16-*H*), 1.57−1.68 (m, 2H, C6-*H* + C14-*H*); ^{13}C NMR (125 MHz, $CDCl_3$, assignments tentative, signals for C8 or C20 not unambiguously identified) δ 204.6 (C17), 203.0 (C19), 149.7(C13), 128.5 (C11), 122.2 (C9), 118.8 (C10), 109.6 (12), 78.5 (C18), 60.4 (C2), 59.6 (C16), 58.6 (C3), 53.7 (C7), 52.0 (C5), 50.2 (C21), 38.1 (C14), 27.6 (C15), 24.7 (C6); IR (thin film) ν 2950, 2847, 1951, 1714, 1485, 1464, 851 cm^{-1}; HRMS (LC-ESI) *m*/*z* calcd for $C_{20}H_{25}N_2O_2$ (M + MeOH + H)$^+$ 325.1916, found 325.1914.

■ ASSOCIATED CONTENT

Supporting Information

Procedures for the synthesis of all new compounds, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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