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Alkylidene Dihydropyridines As Synthetic Intermediates: Model Studies toward the Synthesis of the Bis(piperidine) Alkaloid Xestoproxamine C

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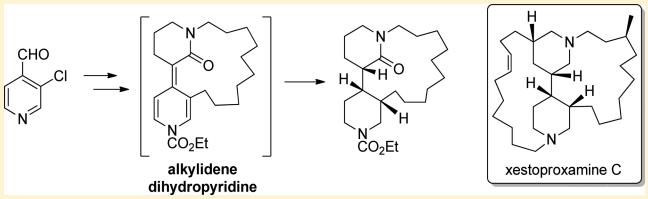
Supporting Information

ABSTRACT: Results of model studies demonstrating a stereoselective synthetic route to tricyclic analogues of the bis(piperidine) alkaloid xestoproxamine C are presented. Dearomatization of a tricyclic pyridine derivative to afford an alkylidene dihydropyridine (anhydrobase) intermediate followed by catalytic heterogeneous hydrogenation was used to install the correct relative stereochemistry about the bis(piperidine) ring system. Other key features of these model studies include development of an efficient ring-closing metathesis procedure to prepare macrocyclic derivatives of 3,4-disusbstituted pyridines, intramolecular cyclizations of alkylidene dihydropyridines to establish pyridine-substituted pyrrolidines and piperidines, successful homologation of pyridine-4-carboxaldehydes using formaldehyde dimethyl thioacetal monoxide (FAMSO), and application of B-alkyl Suzuki coupling to assemble substituted pyridines.



INTRODUCTION

The bis(piperidine) alkaloids comprise a family of marine sponge metabolites isolated from different species of the order Haplosclerida, and include haliclonacyclamines A–F,[1−3] halicyclamines A and B,[4−6] arenosclerins A–E,[7,8] halichondramine,[9] neopetrosiamine A,[10] acanthocyclamine A,[11] and xestoproxamines A–C.[12] Several of these natural products (primarily the haliclonacyclamines and the halicyclamines) have been found to display promising cytotoxicity toward various cancer cell lines, along with antibacterial (particularly antitubercular) activity.[13] The biological activity of many of these natural products, however, has not yet been evaluated. Representative examples of these alkaloids are illustrated in Figure 1 and highlight several distinguishing structural features. All possess tetracyclic ring systems with covalently linked 3,4′-bis(piperidine) rings at the core. The piperidine rings are further linked through two macrocycles that vary in terms of size, unsaturation, and substitution, according to the identity of the metabolite. The relative (and absolute) stereochemistry of the methine carbons distributed within the piperidine rings also differentiates individual members. For example, both haliclonacyclamine A (**1**) and xestoproxamine C (**5**) exhibit an all-*cis* relative configuration of the four piperidine methine hydrogens (although these two compounds possess opposite absolute stereochemistry—all (R) in **1** and all (S) in **5**). In contrast, arenosclerin B (**3**) exhibits a "*cis*-anti-*cis*" array of stereogenic centers, while other bis(piperidine) alkaloids feature *trans*-substituted piperidine rings (e.g., halicyclamine A).

The bis(piperidine) alkaloids are postulated to be biogenetically related to other important 3-alkylpyridine/piperidine alkaloids also isolated from Haplosclerids, such as manzamines, sarains, and madangamines.[14] All of these compounds are envisioned to arise from biosynthetic pathways involving intramolecular cycloaddition of macrocyclic bis(dihydropyridines), and several biogenetically inspired approaches to truncated models of the halicyclamine ring system have been reported.[15] The total synthesis of these bis(piperidine) alkaloids, however, has not received a great deal of attention, despite their interesting structures and bioactivity profiles. To date, the racemic synthesis of only one member of the family,

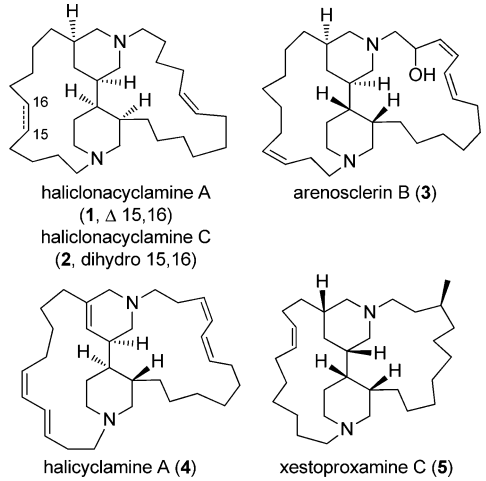


Figure 1. Representative examples of bis(piperidine) alkaloids.

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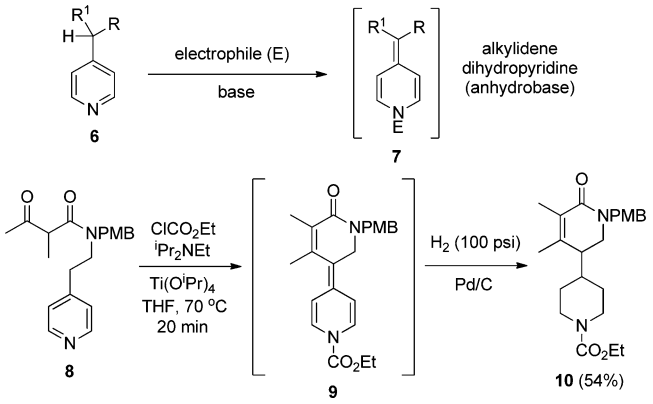
haliclonacyclamine C (**2**), has been successfully completed as reported by Sulikowski in 2010.[16] The synthetic route developed in this effort was also subsequently applied to the construction of fully saturated racemic tetrahydrohaliclonacyclamine A.[17] Apart from these studies, only two additional reports describing approaches to functionalized bis(piperidine) ring systems have appeared. Molander described a diastereoselective approach to the bis(piperidine) core of halicyclamine A which envisioned using a Diels–Alder cycloaddition to establish the correct relative stereochemistry within the piperidine rings,[18] and Banwell et al. examined the feasibility of crossed-aldol condensations between substituted 4-pyridinones as a means to construct 3,4′ bis(piperidine) derivatives.[19]

As part of general efforts aimed at developing new synthetic methods for construction and manipulation of aza-heterocyclic ring systems, we have been examining the reactivity of pyridine and related aza-arene anhydrobases (i.e., **7**, Scheme 1). We have found that activation of 4-alkylpyridines with an electrophile under mildly basic conditions can afford alkylidene dihydropyridines (anhydrobases) that are capable of participating in a variety of intramolecular C–C bond forming transformations, including aldol-like condensations,[20] Au-catalyzed cyclizations,[21] and Pd-catalyzed Heck reactions.[22] Similar electrophilic activation of 2-alkylimidazoles has also been demonstrated.[23] Aldol-like condensations of 2- and 4-alkylpyridines can be effected using Brønsted acid catalysts via transient generation of related enamine-like intermediates as well.[24] Notably, we have performed anhydrobase-mediated pyridine benzylic cyclization in tandem with catalytic hydrogenation for direct conversion of pyridine substrates to functionalized piperidines (e.g., **8** to **10** via aldol-like condensation intermediate **9**, Scheme 1).[20] Thus, when applied to an aminoethylpyridine such as **8**, this sequence delivers products (**10**) that may serve as precursors to 3,4′-linked bis(piperidine) derivatives. Moreover, stereoselectivity inherent in heterogeneous catalytic hydrogenation may provide a convenient means to control relative stereochemistry in substituted bis(piperidines) prepared through this sequence. Consequently, we have initiated efforts to apply this chemistry in the stereoselective asymmetric total synthesis of bis(piperidine) alkaloids, and have selected xestoproxamine C as our initial target. Described herein are the results of model studies that demonstrate the feasibility of our approach.

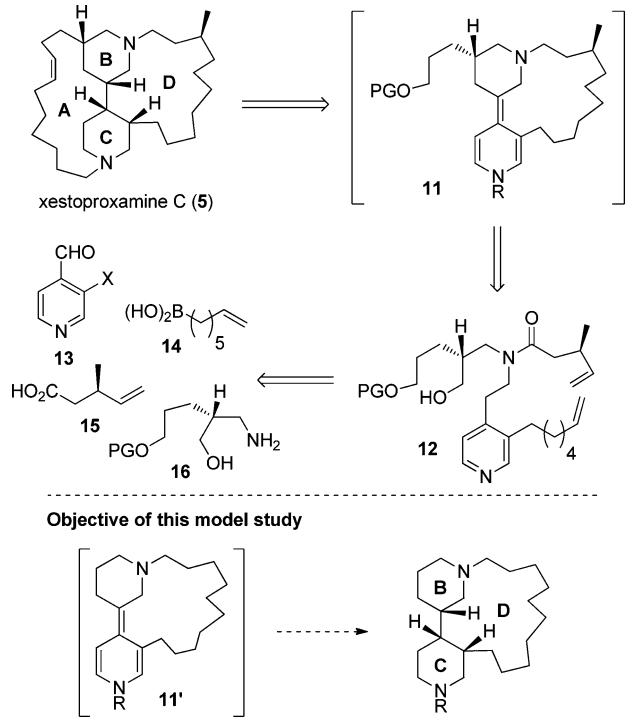
Scheme 1. Generation and Manipulation of Alkylidene Dihydropyridines



RESULTS AND DISCUSSION

A retrosynthetic analysis of xestoproxamine C is shown in Scheme 2. We envision diastereoselective hydrogenation of alkylidene dihydropyridine **11** (equipped with two of the five stereogenic centers present in the target) as the key transformation leading to the desired relative and absolute stereochemistry found in **5**. The final macrocyclic ring (**A** ring) can then be constructed using ring-closing metathesis (RCM).[25] Macrocycle ring **D** should also be accessible via RCM on pyridine derivative **12**, either before or after pyridine benzylic cyclization to assemble ring **B** of the bis(piperidine) ring system. In turn, construction of **12** is expected to be achieved from readily available starting fragments **13**–**16**. Significantly, the modular synthetic design implemented in this study should facilitate construction of other bis(piperidine) alkaloids, as well as numerous unnatural analogues in which the size, unsaturation, and substitution of the macrocyclic rings can be varied, along with the identity of the central **B**–**C** ring system (e.g., pyrrolidine-piperidine analogues).

Scheme 2. Retrosynthetic Analysis of Xestoproxamine C and General Objective of This Model Study



We approached our model studies with the objective of demonstrating the general advantages of our modular design and, more specifically, the feasibility of preparing a truncated tricyclic alkylidene dihydropyridine resembling **11′** and its successful conversion to a saturated bis(piperidine) derivative possessing an all-*cis* relative stereochemistry about the BCD ring system (bottom of Scheme 2). To address the first objective, we sought to prepare pyridine macrocycles via RCM of 3,4-disubstituted pyridines. Initial attempts to construct metathesis substrates from 3-bromo-4-pyridine carboxaldehyde via Pd-catalyzed cross-coupling proved problematic. Use of reaction conditions reported by Molander to be effective for B-alkyl Suzuki couplings of aryl chlorides, however, worked well when applied to 3-chloropyridine-4-carboxaldehyde in combi-

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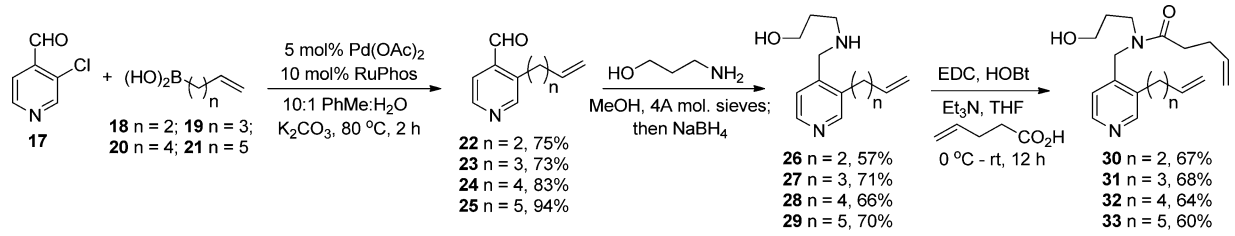
Scheme 3. Synthesis of 3,4-Disubstituted (Aminomethyl)pyridine Macrocyclization Precursors

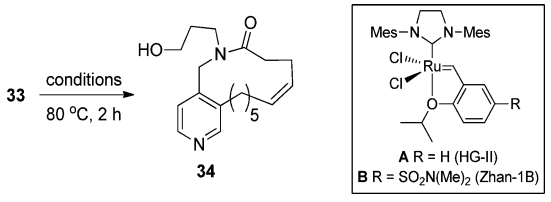


nation with alkyl boronic acids **18**–**21**.[26] The 3-alkylpyridines **22**–**25** were isolated in good to excellent yield (Scheme 3). Direct reductive amination of the aldehyde group in **22**–**25** with 3-aminopropanol followed by acylation with 4-pentenoic acid gave a homologous series of RCM substrates from which various unnatural analogues of bis(piperidine) alkaloids might be constructed.

3-Alkylpyridine **33** was selected for initial screening of RCM reaction conditions (Table 1). Preliminary experiments were performed using both Grubbs-II and Hoveyda–Grubbs-II catalysts, but the Zhan-1B catalyst was ultimately selected for optimization owing to its greater air-stability and lower cost. Not surprisingly, high dilution reaction conditions proved to be critical for successful macrocyclization (entries 3–6). Catalyst quenching with a vinyl ether additive prior to concentration of reaction mixtures was also important to obtain the desired macrocycle in high isolated yield.[27] The best reaction conditions uncovered in this screen are indicated in entry 6 and feature continuous slow syringe-pump addition of catalyst to a 0.0005 M solution of **33** in toluene at 80 °C. Macrocyclization was complete in 2 h under these conditions and, after catalyst quenching, **34** was isolated in excellent 92% yield as a mixture of *E* and *Z* isomers.[28] Notably, neither the pyridine nitrogen nor the Lewis basic amide functional group appear to interfere with metathesis.

The remaining macrocyclization substrates **30**–**32** were also subjected to the RCM reaction conditions highlighted in Table 1, entry 6. As indicted in Scheme 4, 3-butenylpyridine derivative **30** was not converted to the corresponding 11-membered macrocycle, and only formation of intractable materials (presumably oligomers) was observed. The pentenyl- and hexenyl-substituted pyridines, however, underwent smooth cyclization to afford **36**–**37** in high yield. Pyridine macrocycles **34** and **36** were further transformed via alcohol oxidation in the presence of the Dess–Martin periodinane (DMP) to the somewhat unstable aldehydes **38**–**39**. Exposure of these aldehydes to reaction conditions previously developed in our laboratory for intramolecular benzylic cyclization of 4-alkylpyridines via generation of alkylidene dihydropyridine intermediates (see Scheme 1)[20] followed by acidic workup conditions to rearomatize the pyridine ring afforded **40** and **41** in comparable, albeit modest, isolated yields. Nonetheless, the concise (six step) synthesis of tricyclic pyridines **40**–**41** offers rapid access to structural mimics of the BCD ring systems found in bis(piperidine) alkaloids, and should facilitate future construction of additional and more advanced analogues.

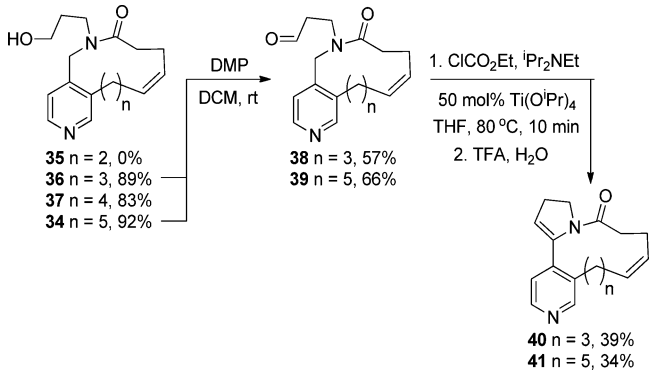
Table 1. Screening of RCM Macrocyclization Conditions



entry	catalyst[a]	solvent	[33] (mM)	% yield
1	**A**	DCE[b]	1.5	42
2	**B**	DCE	1.5	51[c]
3	**B**	DCE	0.5	59
4	**B**	DCE	0.5	72[d,e]
5	**B**	PhMe	0.5	66[d,f]
6	***B***[g]	*PhMe*	0.5	92[d]

[a]Catalyst loading: 3 mol %. [b]1,2-Dichloroethane. [c]Based on 22% recovered **33**. [d]Catalyst quenched by addition of diethylene glycol vinyl ether prior to concentration. [e]Based on 26% recovered **33**. [f]Based on 20% recovered **33**. [g]Continuous slow addition of catalyst (syringe pump).

Scheme 4. Synthesis of Macrocyclic Pyridine-Dehydropyrrolidine Derivatives



We next sought to apply RCM macrocyclization to substituted pyridines that would ultimately afford polycyclic products more closely resembling the ring systems encountered in **5** and related alkaloids. This required access to 4-(aminoethyl)pyridines, which were envisioned to be obtained by homologation and amination of 3-alkylpyridine-4-carboxaldehydes. Indeed, a straightforward method to achieve this goal starting from **24** or **25** entailed Wittig reaction to give the corresponding 4-vinylpyridines followed by hydroamination with aminopropanol under acidic conditions (Scheme 5).[29] Amines **42** and **43** were each obtained in good isolated yield over the two steps, however, efficient hydroamination required the use of a large excess of aminopropanol and extended reaction times. Acylation with 4-pentenoic acid and RCM using the reaction conditions developed in the (aminomethyl)-pyridine series (Table 1, entry 6) proceeded smoothly (yields for the RCM step >90% in each case), affording macrocycles **44** and **45**. It is noteworthy that the 15-membered macrocycle in **45** matches the size of the D ring macrocycle in xestoproxamine C and related bis(piperidine) alkaloids. Dess–Martin oxidation

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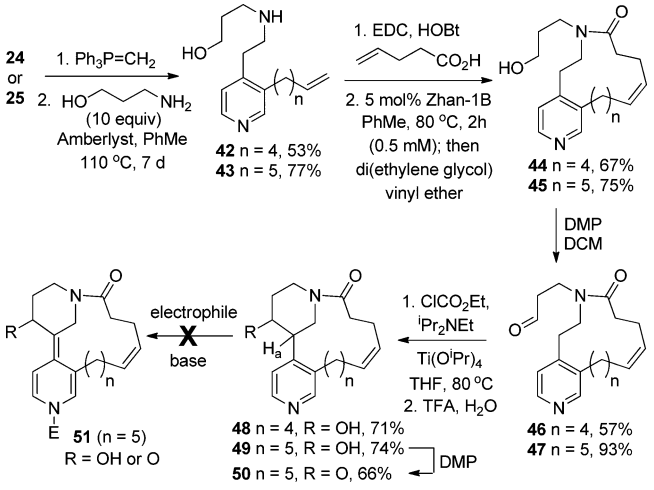
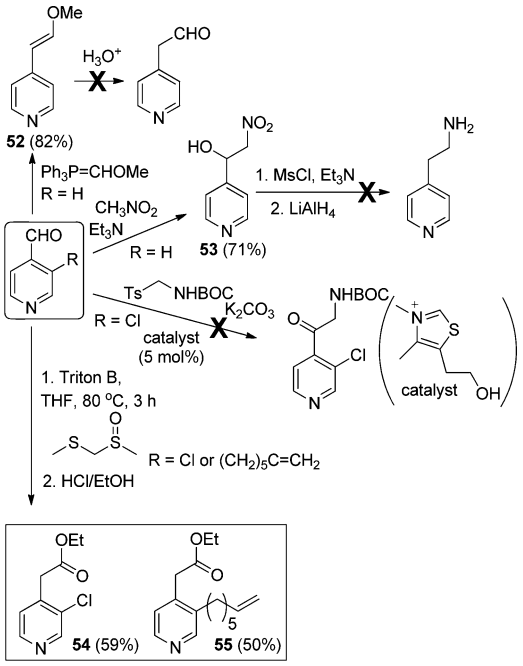
Scheme 5. Initial Approach to Bis(piperidine) Alkaloid BCD Ring Systems



of **44**/**45** afforded the corresponding aldehydes (of limited stability) which were then directly exposed to electrophile activation/anhydrobase formation/intramolecular cyclization to give the linked piperidine−pyridine derivatives **48** and **49** in good yields. Unlike similar cyclizations that generate 5-membered unsaturated aza-heterocycles, elimination of water did not occur in these reactions, and **48**/**49** were obtained as diastereomeric mixtures of secondary alcohols. Unfortunately, attempted conversion of **49** to an observable alkylidene dihydropyridine (i.e., **51**) that might then be subjected to hydrogenation was unsuccessful. These efforts involved treating **49** first with an acyl ($ClCO_2Et$) or alkyl (MeI) electrophile to form putative pyridinium salts, followed by treatment with various bases (Et_3N, $^iPr_2NEt$, NaH). Monitoring reactions by TLC and NMR, however, presented no evidence for the formation of **51**. Likewise, conversion of **49** to ketone **50**, followed by attempted generation of anhydrobase **51** also failed, despite the presumably more activated benzylic hydrogen in **50**. We speculate that the inability to obtain **51** from either **49** or **50** stems from conformational constraints in the tricyclic ring system that impede alignment of the benzylic hydrogen (H_a) with the pyridine π-system in an orientation conducive to deprotonation. Molecular modeling studies (Spartan) performed on a simpler analogue of **49** were consistent with this notion as the ground state conformation of the molecule featured an approximately 90° angle between the piperidine and pyridine rings. This conformation places H_a roughly in the plane of the pyridine and thus mandates that the molecule undergo significant conformational changes to achieve the pyridine/piperidine coplanar alignment leading to anhydrobase **51**. Further evidence in support of this notion is found in the crystal structure of a closely related compound (**59**), as discussed below. Notably, a similar ∼90° angle between piperidine rings has been observed in the actual bis(piperidine) alkaloid natural products.[1−12]

Failure to generate alkylidene dihydropyridine **51** coupled with the unattractive hydroamination transformation utilized in the preparation of **48**/**49** (which required large excess of aminopropanol) prompted re-examination of our synthetic route to macrocyclic bis(piperidine) scaffolds. We first turned to alternative methods for homologation of pyridine-4-carboxaldehyde derivatives that would deliver products amenable to eventual elaboration into 4-(aminoethyl)pyridines, as summarized in Scheme 6. Wittig reaction between pyridine-4-carboxaldehyde and (methoxymethylene)phosphorane gave

Scheme 6. Homologation of Pyridine-4-carboxaldehyde Derivatives



vinyl ether **52** in good yield, but all attempts to hydrolyze this material to the corresponding aldehyde returned intractable reaction mixtures. Similarly, pyridine carboxaldehyde underwent smooth nitro-aldol reaction to give the known nitro alcohol **53**,[30,31] but we were unsuccessful in converting this compound to 4-(aminoethyl)pyridine via reduction of an intermediate nitroethylene. Attempted thiazolium catalyzed aza-benzoin condensation between 3-chloropyridine-4-carboxaldehyde and a BOC-protected imine (generated in situ) also failed.[32] Encouragingly, however, homologation of both 3-chloropyridine-4-carboxaldehyde and 3-heptenylpyridine-4-carboxaldehyde with formaldehyde dimethyl thioacetal monoxide (FAMSO) followed by immediate hydrolysis of the resulting dithio ketene acetal with anhydrous HCl in ethanol gave the pyridine acetic acid esters **54** and **55** in serviceable yield.[33]

We envisioned that the ester moiety in **54** or **55** would serve as a convenient handle for introduction of a substituted nitrogen appropriately positioned for eventual construction of 3,4′-bis(aza-heterocycles) as required in xestoproxamine C. Thus, we continued our model studies with 3-chloropyridine **54**. B-Alkyl Suzuki coupling under conditions outlined above (see Scheme 3) gave **55** in excellent yield, although longer reaction time was required for completion compared to Suzuki coupling of **17** (Scheme 7). Ester **55** was then treated with secondary amine **56** in the presence of $AlMe_3$ to give bifunctional amide **57** equipped with functional groups to enable both piperidine ring construction and macrocyclization. Since the pyridine benzylic position is additionally activated by the amide carbonyl, we opted to attempt 6-membered ring closure first via simple intramolecular alkylation of an alkyl electrophile generated in situ. In the event, **57** was treated with $MsCl/Et_3N$ to convert the alcohol to the corresponding mesylate. Monitoring the reaction by TLC and NMR, however, indicated the initially formed mesylate was slowly converted to

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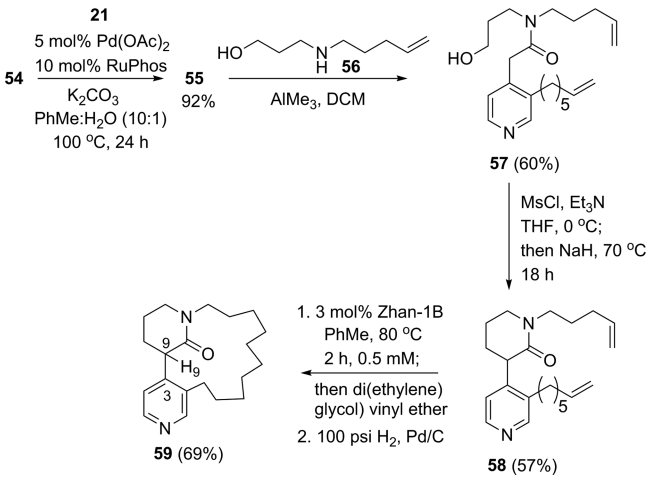
Scheme 7. Second-Generation Approach to Bis(piperidine) BCD Ring System



the alkyl chloride under the reaction conditions. Addition of NaH with heating facilitated intramolecular alkylation to give **58**. Ring-closing metathesis proceeded as expected to afford a macrocyclic alkene (presumably as a mixture of *E*/*Z* diastereomers), and was followed by reduction of the olefin to provide **59** in good yield for the two steps. Notably, the ^{1}H NMR of **59** exhibited somewhat broadened signals (especially in the aliphatic region) that we attribute to hindered rotation about the C3−C9 bond (i.e., atropisomerism). The structure of **59** was definitively established through X-ray diffractometry performed on a crystal of **59**·HCl, obtained from slow evaporation of a $CHCl_3$/EtOAc solution (Figure 2).[34] The

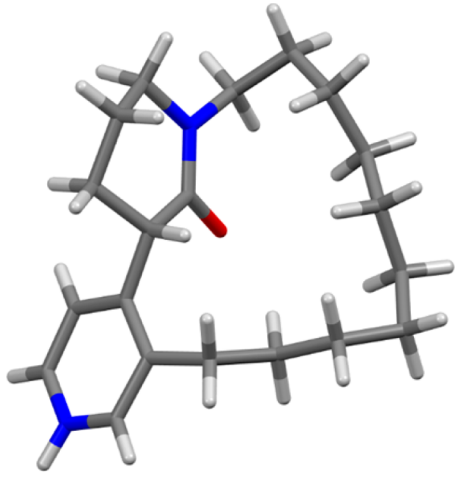
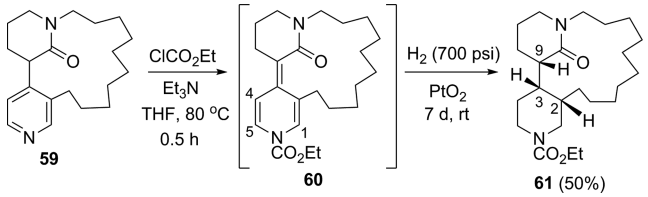


Figure 2. Molecular structure of **59**·HCl determined from X-ray crystallography. Chloride anion omitted.

molecular structure of the cation clearly reveals the ∼90° angle between the pyridine and piperidone rings that places the H9 hydrogen parallel to the plane of the pyridine ring. Consideration of the structure also highlights the likelihood of atropisomerism in the molecule as free rotation about the pyridine-piperidinone bond would clearly engender severe strain, thus only limited rotation that involves passing the lactam carbonyl through the mean plane of the macrocyclic ring is possible.

Amide **59** presents an alternative substrate on which to attempt conversion to a bis(piperidine) system via reduction of the corresponding alkylidene dihydropyridine. Unlike substrates **49**/**50** (Scheme 5), **59** features a completely saturated 10-carbon macrocyclic linker between the pyridine and piperidinone rings that is expected to impart greater conformational flexibility to the tricyclic ring system. Additionally, an amide carbonyl is positioned to assist in benzylic deprotonation and provide extended conjugation in any putative anhydrobase intermediate. Gratifyingly, exposure of **59** to $ClCO_2Et$ and Et_3N in refluxing THF gave rise to a new nonpolar species with a TLC profile in line with other pyridine anhydrobases generated in our laboratory (Scheme 8). Moreover, the ^{1}H

Scheme 8. Formation and Hydrogenation of Alkylidene Dihydropyridine 60



NMR spectrum of the crude reaction mixture revealed the clear presence of dihydropyridine resonances at 7.22 and 7.09 ppm, corresponding to the hydrogens at C1 and C5, along with a signal at 6.06 ppm corresponding to the hydrogen at C4. Each of these signals was observed as a broad singlet due to the presence of amide rotamers arising from the NCO_2Et moiety. Without further characterization, **60** was subjected to heterogeneous hydrogenation over PtO_2. The course of reduction over time was monitored by NMR and it was observed that hydrogenation of the dihydropyridine olefins occurred first, followed by much slower reduction of the tetrasubstituted alkene. After 7 days the reaction appeared to be complete, and bis(piperidine) analogue **61** was isolated after filtration of the catalyst and purification by flash column chromatography.

Assignment of the relative stereochemistry in **61**, however, is nontrivial due to overlapping signals in the ^{1}H NMR spectrum, the presence of amide rotamers about the N-CO_2Et linkage, and the hindered rotation about the piperidine-piperidinone C−C bond (C3−C9) leading to the possibility of atropisomerism on the NMR time scale. Indeed, difficulties in spectroscopic analysis of **61** somewhat mirror those encountered in characterization of the target bis(piperidine) alkaloids[12] and in the characterization of intermediates in Smith and Sulikowski's synthesis of haliclonacyclamine C.[16] In considering conversion of **60** to **61**, it seems reasonable to postulate *syn* addition of H_2 across the C3−C9 alkene, giving rise to the relative stereochemistry at these positions shown in **61**. Monitoring of the hydrogenation reaction indicated that the C1−C2 and C4−C5 alkenes undergo reaction faster than the C3−C9 olefin, thus a product possessing the epimeric relative configuration at C2 is possible if reduction of the C3−C9 alkene is not diastereoselective. Nonetheless, results of extensive variable temperature 1D- and 2D-NMR experiments are consistent with isolation of **61** as a single diastereomer possessing the *syn-cis* stereochemistry as depicted in Scheme 8.

Figure 3 shows the ^{1}H NMR spectrum of **61** and selected representative homonuclear and heteronuclear correlations.

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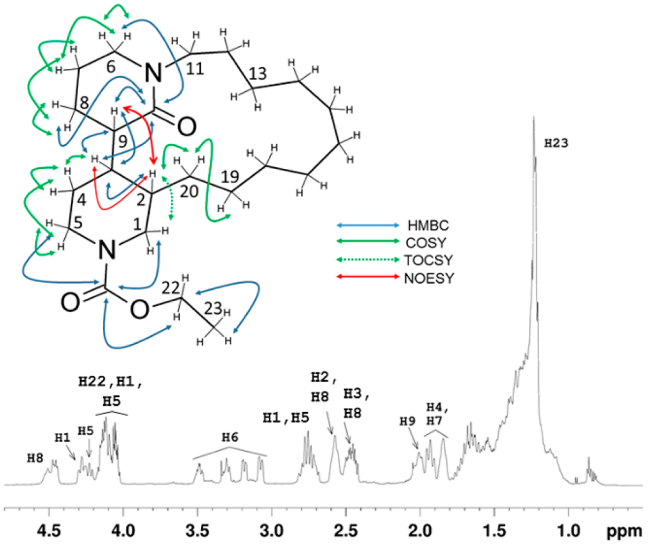

Figure 3. ^{1}H NMR spectrum (600 MHz) of **61** ($CDCl_3$, 278 K) with selected 2D NMR correlations.

The location of the carbonyl groups and the presence of extensive scalar coupling network among protons allowed the assignment of ^{1}H and ^{13}C resonances of piperidine and piperidinone rings. The bridging carbon atoms are also unique so that the HSQC-editing experiments differentiated them from other protons; note that H2, H3 and H9 are the only methine CH hydrogens in the molecule. In addition, the NMR data (1D and 2D) revealed more than one rotamer/atropisomer, as indicated by the resonance doubling in the ^{1}H and ^{13}C NMR spectra. For example, the ^{1}H resonances centered at 3.49 and 3.18 ppm correspond to the H6′ and H6″ hydrogens of one rotamer/atropisomer, while resonances at 3.30 and 3.07 ppm correspond to H6′ and H6″ of a different rotamer/atropisomer. The absence of exchange correlated cross peaks in NOESY between the resonances at 3.49 and 3.30 ppm, as well as the 3.18 and 3.07 ppm resonances, indicate that the structures are not interconverting under current experimental conditions ($CDCl_3$, 278 K). However, the stereochemistry of C9H−C3H−C2H is the same in both atropisomers as established by the J-coupling correlated peaks and NOE's observed in COSY and NOESY experiments, respectively. COSY cross peaks were observed between H3−H2 and H9−H2, but not between H9−H3, consistent with a dihedral angle close to 90° for the latter pair of hydrogens. The TOCSY experimental data also did not show any cross peaks between H3 and H9, confirming $^{3}J_{H9-H3} \approx 0$. Absence of H3−H9 coupling is also observed in the NMR spectra of bis(piperidine) natural products.[1−12] Our attempts to measure individual coupling constants were marred due to extensive resonance overlap and presence of rotamers/atropisomers. However, a medium-intensity NOE was observed between H2−H3. The semiquantitative analysis of the mixing time dependent NOEs of H2−H3 using the correlation between H6′−H6″ as a reference gives a distance of 2.52 Å between H2 and H3. Significantly, this distance is indicative of a *cis* relationship between these two hydrogens (one equatorial and the other axial). The alternative diastereomer would feature a *trans*-diaxial arrangement of the H2−H3 hydrogens that would place them >2.8 Å apart, well beyond the distance calculated from NOE analysis. The lowest energy conformation of **61** was calculated using DFT (B3LYP/6-31G(d), Gaussian09[35]) and the result is shown in Figure 4. The

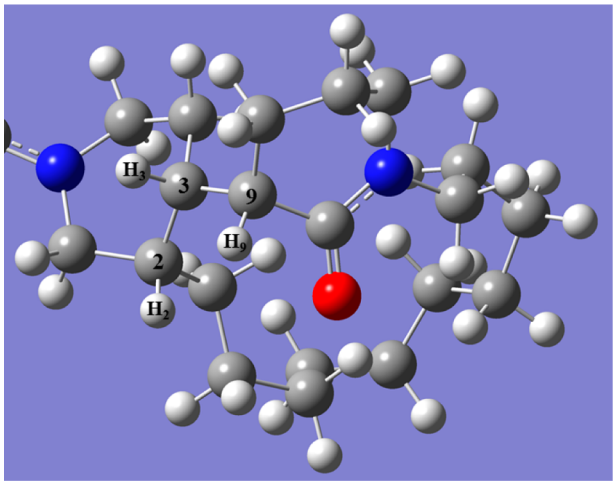

Figure 4. DFT calculated lowest energy conformation of **61** (CO_2Et group not shown).

model nicely correlates with information obtained from NMR analysis. Specifically, the H2−H3 distance in the calculated structure is 2.50 Å, consistent with the results of semi-quantitative NOE analysis described above. The calculated structure also accounts for an NOE correlation empirically observed between H2 and H9 in the NOESY spectrum.

CONCLUSIONS

We have successfully prepared a model of the bis(piperidine) macrocyclic BCD tricyclic ring system found in xestoproxamine C and structurally related marine alkaloids. Heterogeneous catalytic hydrogenation of a macrocyclic alkylidene dihydropyridine intermediate was used to convert a pyridine precursor to the desired linked piperidine-piperidinone product with apparent control of relative stereochemistry at three contiguous stereocenters. We are now seeking to adopt the key features of the synthetic route used to assemble this model structure in the total synthesis of the target natural product through incorporation of chiral nonracemic building blocks **15** and **16**. In a more general sense, this work also demonstrates the utility of alkylidene dihydropyridine intermediates in constructing more elaborate polycyclic heterocyclic ring systems. Future efforts will continue to explore the reactivity of pyridine and related azine/azole anhydrobases in a variety of bond forming transformations.

EXPERIMENTAL SECTION

All commercially available starting materials and reagents were used as received unless otherwise noted. All reactions were performed under an argon atmosphere. Solvents were dried and purified by passage through activated alumina columns. Flash column chromatography was performed using silica gel 60, 230−400 mesh. Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 300 MHz/400 MHz/500 MHz and 75 MHz/101 MHz/126 MHz, respectively. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane for ^{1}H NMR in $CDCl_3$ and residual undeuterated solvent for all other spectra. The NMR spectra for many of the compounds reported in this study reveal the presence of amide rotamers. High resolution mass spectra were obtained using positive ion electrospray ionization (ESI) and electron ionization (EI), and analyzed using a time-of-flight (TOF) analyzer. Melting points were recorded using a capillary melting point apparatus and are uncorrected. Details of 2D NMR experiments and X-ray crystallography can be found in the Supporting Information.

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3-Butenylboronic acid (18). 4-Bromobut-1-ene (2.00 mL, 19.7 mmol, 1.00 equiv) was dissolved in THF (~200 mL) and Mg turnings (0.575 g, 23.6 mmol, 1.20 equiv) were added to the reaction mixture. The mixture was heated to reflux for 12 h, and then cooled to −78 °C. Trimethylborate (6.70 mL, 59.1 mmol, 3.00 equiv) was added dropwise and the temperature maintained at −78 °C for additional 2 h. Thereafter, reaction mixture was warmed to room temperature overnight. It was then quenched with 1 M HCl (100 mL) and concentrated to remove THF. Crude mixture was extracted with ethyl acetate (100 mL × 5). The organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. Crude product was dissolved in hot hexane (100 mL) and filtered to remove insoluble inorganics. Finally, hexane was removed in vacuum to isolate **18** (1.30 g, 66%) as a yellow liquid. This was taken on to the next reaction without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.05−4.86 (m, 2H), 2.22 (m, 2H), 1.05 (t, J = 7.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.8, 113.5, 27.5, 14.2. IR (film) 3230, 1650 cm^{-1}.

4-Pentenylboronic acid (19). Using the procedure described for the preparation of **18**, 5-bromopent-1-ene (3.00 mL, 25.5 mmol, 1.00 equiv), Mg (0.735 g, 30.3 mmol, 1.20 equiv) and trimethylborate (8.70 mL, 76.5 mmol, 3.00 equiv) were reacted to give **19** (2.35 g, 81%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1H), 5.17−4.70 (m, 2H), 2.07 (m, 2H), 1.56 (m, 2H), 0.93 (t, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1, 114.9, 36.4, 22.9, 15.1. IR (film) 3245, 1637 cm^{-1}.

5-Hexenylboronic acid (20). Using the procedure described for the preparation of **18**, 6-bromohex-1-ene (5.00 g, 30.6 mmol, 1.00 equiv), Mg (0.894 g, 36.7 mmol, 1.20 equiv) and trimethylborate (10.4 mL, 91.8 mmol, 3.00 equiv) were reacted to give **20** (3.48 g, 89%) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.00−5.57 (m, 1H), 5.20−4.75 (m, 2H), 2.20−1.93 (m, 2H), 1.57−1.32 (m, 4H), 0.93 (t, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 114.4, 33.9, 31.7, 25.3, 23.1. IR (film) 3255, 1639 cm^{-1}.

6-Heptenylboronic acid (21). Using the procedure described for the preparation of **18**, 6-bromohex-1-ene (5.00 g, 28.2 mmol, 1.00 equiv), Mg (0.823 g, 33.8 mmol, 1.20 equiv) and trimethylborate (9.60 mL, 84.6 mmol, 3.00 equiv) were reacted to give **21** (3.65 g, 90%) as a yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91−5.61 (m, 1H), 5.11−4.81 (m, 2H), 2.17−1.90 (m, 2H), 1.57−1.14 (m, 6H), 0.92 (t, J = 7.7 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.3, 114.3, 33.9, 31.9, 28.9, 23.4, 15.8. IR (film) 3280, 1637 cm^{-1}.

3-(But-3-en-1-yl)isonicotinaldehyde (22). 3-Chloroisonicotanaldehyde (**17**, 0.200 g, 1.41 mmol, 1.00 equiv), 3-butenylboronic acid (**18**) (0.176 g, 1.76 mmol, 1.25 equiv), and K_2CO_3 (0.580 g, 4.23 mmol, 3.00 equiv) were dissolved in toluene:water (6 mL, 10:1, 0.25 M) and deoxygenated via bubbling Ar through the mixture for 30 min. Then $Pd(OAc)_2$ (0.016 g, 0.710 mmol, 0.05 equiv) and RuPhos (0.066 g, 1.41 mmol, 0.100 equiv) were added and mixture was heated at 80 °C for 3 h. After 3 h TLC indicated complete reaction, and 1 M aqueous NaOH (10 mL) was added. After cooling to room temperature, the reaction mixture was extracted with EtOAc (20 mL × 3). Organic extracts were combined, dried over Na_2SO_4, filtered, and concentrated. Crude product was purified via flash column chromatography using 0−20% EtOAc in hexanes. Compound **22** was isolated as a yellow liquid (0.227 g, 75%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.32 (s, 1H), 8.72 (d, J = 4.9 Hz, 1H), 8.64 (s, 1H), 7.72−7.54 (d, J = 4.9 Hz, 1H), 6.06−5.55 (m, 1H), 5.25−4.82 (m, 2H), 3.35−2.79 (m, 2H), 2.51−2.17 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.8, 153.2, 149.0, 138.9, 136.9, 136.6, 123.1, 116.5, 35.9, 29.2. IR (film) 2986, 1708, 1657 cm^{-1}. HRMS (ESI) $C_{10}H_{12}NO$ $[M + H]^+$, calculated 162.0919, found 162.0933.

3-(Pent-4-en-1-yl)isonicotinaldehyde (23). Using the procedure described for the preparation of **22**, **17** (0.200 g, 1.41 mmol, 1.00 equiv), 4-pentenylboronic acid (**19**) (0.200 g, 1.76 mmol, 1.25 equiv), and K_2CO_3 (0.580 g, 4.23 mmol, 3.00 equiv), $Pd(OAc)_2$ (0.016 g, 0.710 mmol, 0.05 equiv) and RuPhos (0.066 g, 1.41 mmol, 0.100 equiv) were reacted to give **23** as a yellow liquid (0.165 g, 73%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.71 (d, J = 4.9 Hz, 1H), 8.65 (s, 1H), 7.78−7.51 (d, J = 4.9 Hz, 1H), 6.15−5.60 (m, 1H), 5.23−4.75 (m, 2H), 3.33−2.84 (m, 2H), 2.39−1.96 (m, 2H), 1.85−1.58 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.7, 152.9, 148.8, 138.8, 137.7, 137.6, 122.9, 115.6, 33.4, 31.3, 28.9. IR (film) 3078, 1711, 1637 cm^{-1}. HRMS (ESI) $C_{11}H_{14}NO$ $[M + H]^+$, calculated 176.1075, found 176.1087.

3-(Hex-5-en-1-yl)isonicotinaldehyde (24). Using the procedure described for the preparation of **22**, **17** (0.100 g, 0.71 mmol, 1.00 equiv), 5-hexenylboronic acid (**20**) (0.113 g, 0.89 mmol, 1.25 equiv), and K_2CO_3 (0.290 g, 2.13 mmol, 3.00 equiv), $Pd(OAc)_2$ (0.008 g, 0.03 mmol, 0.05 equiv) and RuPhos (0.033 g, 0.071 mmol, 0.100 equiv) were reacted to give **24** as a yellow liquid (0.111 g, 83%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.70 (d, J = 4.9 Hz, 1H), 8.64 (s, 1H), 7.71−7.50 (d, J = 4.9 Hz, 1H), 5.95−5.66 (m, 1H), 5.14−4.87 (m, 2H), 3.09−2.89 (m, 2H), 2.26−2.00 (m, 2H), 1.80−1.57 (m, 2H), 1.57−1.36 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.7, 153.1, 148.9, 138.9, 138.4, 137.9, 122.9, 115.00, 33.5, 31.8, 29.6, 28.7. IR (film) 3073, 1708, 1650 cm^{-1}. HRMS (ESI) $C_{12}H_{16}NO$ $[M + H]^+$, calculated 190.1232, found 190.1244.

3-(Hept-6-en-1-yl)isonicotinaldehyde (25). Using the procedure described for the preparation of **22**, **17** (2.19 g, 15.5 mmol, 1.00 equiv), 6-heptenylboronic acid (**21**) (2.75 g, 19.3 mmol, 1.25 equiv), and K_2CO_3 (6.43 g, 46.5 mmol, 3.00 equiv), $Pd(OAc)_2$ (0.174 g, 0.78 mmol, 0.05 equiv) and RuPhos (0.720 g, 1.55 mmol, 0.100 equiv) were reacted to give **25** as a yellow liquid (2.96 g, 94%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.71 (d, J = 4.9 Hz, 1H), 8.64 (s, 1H), 7.63 (d, J = 4.9 Hz, 1H), 5.89−5.63 (m, 1H), 5.12−4.80 (m, 2H), 3.09−2.91 (m, 2H), 2.23−1.90 (m, 2H), 1.76−1.51 (m, 2H), 1.55−1.28 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 191.6, 152.9, 148.7, 138.7, 138.7, 137.9, 122.7, 114.5, 33.6, 32.1, 29.6, 28.9, 28.6. IR (film) 2924, 1708, 1640 cm^{-1}. HRMS (ESI) $C_{13}H_{18}NO$ $[M + H]^+$, calculated 204.1388, found 204.1394.

3-(((3-(But-3-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (26). Pyridine carboxaldehyde **22** (0.62 g, 3.85 mmol, 1.00 equiv), 3-aminopropanol (0.350 mL, 4.6 mmol, 1.20 equiv), and 4 Å molecular sieves were combined in anhydrous MeOH (40 mL) and the mixture stirred at room temperature for 30 min until complete formation of the imine was observed by NMR. After cooling to 0 °C, $NaBH_4$ (0.439 g, 11.6 mmol, 3.00 equiv) was added in portions. After 15 min the cooling bath was removed and reaction was stirred at room temperature for additional 4 h. Then it was quenched with water (30 mL) and mixture was filtered through Celite to remove molecular sieves. Filtrate was concentrated in vacuum to remove methanol. Thereafter mixture was extracted with EtOAc (30 mL × 3). Organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Crude mixture was purified via flash column chromatography using 0−30% MeOH in EtOAc to afford **26** as a colorless oil (0.488 g, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 5.0 Hz, 1H), 8.38 (s, 1H), 7.26 (d, J = 5.0 Hz, 1H), 5.90−5.75 (m, 1H), 5.16−4.83 (m, 2H), 3.88−3.65 (m, 4H), 3.12 (s, 2H), 2.91 (t, J = 5.9 Hz, 2H), 2.78−2.68 (m, 2H), 2.45−2.26 (m, 2H), 1.84−1.67 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.9, 146.3, 137.2, 135.1, 122.7, 115.9, 63.6, 49.9, 49.5, 34.8, 31.5, 29.3. IR (film) 3287, 2920, 1635 cm^{-1}. HRMS (ESI) $C_{13}H_{21}N_2O$ $[M + H]^+$, calculated 221.1654, found 221.1660.

3-(((3-(Pent-4-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (27). Using the procedure described for the preparation of **26**, 3-(pent-4-en-1-yl)isonicotinaldehyde (**23**) (0.500 g, 2.85 mmol, 1 equiv), 3-aminopropanol (0.22 mL, 2.85 mmol, 1.00 equiv), and $NaBH_4$ (0.323 g, 8.55 mmol, 3.00 equiv) were reacted to give **27** as a colorless oil (0.474 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (d, J = 5.1 Hz, 1H), 8.38 (s, 1H), 7.25 (d, J = 5.1, Hz, 1H), 5.93−5.60 (m, 1H), 5.23−4.89 (m, 2H), 3.88−3.74 (m, 4H), 2.92 (t, J = 6.0 Hz 2H), 2.79−2.51 (m, 2H), 2.25−1.97 (m, 2H), 1.87−1.47 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 147.9, 146.2, 138.1, 135.7, 122.7, 115.53, 63.9, 49.9, 49.7, 33.6, 31.4, 30.1, 29.3. IR (film) 3272, 3076, 1638 cm^{-1}. HRMS (ESI) $C_{14}H_{23}N_2O$ $[M + H]^+$, calculated 235.1810, found 235.1827.

3-(((3-(Hex-5-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (28). Using the procedure described for the preparation of **26**, 3-(hex-5-en-1-yl)isonicotinaldehyde **24** (0.900 g, 4.76 mmol, 1.00 equiv), 3-aminopropanol (0.36 mL, 4.75 mmol, 1.00 equiv), and $NaBH_4$ (0.900 g, 14.3 mmol, 3.00 equiv) were reacted to give **28** as a colorless oil

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(1.18 g, 66%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (d, J = 5.0 Hz, 1H), 8.37 (s, 1H), 7.25 (d, J = 5.0 Hz, 1H), 5.96−5.73 (m, 1H), 5.06−4.91 (m, 2H), 3.84−3.79 (m, 4H), 2.92 (t, J = 5.9 Hz, 2H), 2.84−2.69 (m, 2H), 2.69−2.59 (m, 2H), 2.18−2.05 (m, 2H), 1.83−1.73 (m, 2H), 1.65−1.54 (m, 2H), 1.54−1.38 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.9, 146.1, 138.6, 135.9, 122.6, 114.9, 63.9, 49.9, 49.6, 33.6, 31.4, 30.4, 29.9, 28.9. IR (film) 3288, 1639 cm^{-1}. HRMS (ESI) $C_{15}H_{25}N_2O$ [M + H]$^+$, calculated 249.1967, found 249.1962.

3-(((3-(Hept-6-en-1-yl)pyridin-4-yl)methyl)amino)propan-1-ol (29). Using the procedure described for the preparation of **26**, 3-(hept-6-en-1-yl)isonicotinaldehyde **25** (0.740 g, 3.60 mmol, 1.00 equiv), 3-aminopropanol (0.28 mL, 3.60 mmol, 1.00 equiv), and $NaBH_4$ (0.410 g, 10.8 mmol, 3.00 equiv) were reacted to give **29** as a colorless oil (0.658 g, 70%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.38 (d, J = 5.1 Hz, 1H), 8.36 (s, 1H), 7.26 (d, J = 5.1 Hz, 1H), 5.89−5.66 (m, 1H), 5.07−4.76 (m, 2H), 3.89−3.73 (m, 4H), 3.20 (s, 2H), 2.91 (t, J = 5.9 Hz, 2H), 2.73−2.50 (m, 2H), 2.13−1.96 (m, 2H), 1.84−1.69 (m, 2H), 1.62−1.53 (m, 2H), 1.49−1.31 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.4, 147.6, 145.6, 138.8, 135.8, 122.5, 114.5, 63.3, 49.5, 49.2, 33.6, 31.2, 30.6, 29.8, 28.9, 28.7. IR (film) 3309, 1657 cm^{-1}. HRMS (ESI) $C_{16}H_{27}N_2O$ [M + H]$^+$, calculated 263.2123, found 263.2109.

***N*-((3-(But-3-en-1-yl)pyridin-4-yl)methyl)-*N*-(3-hydroxypropyl)pent-4-enamide (30).** (Aminomethyl)pyridine **26** (0.480 g, 2.18 mmol, 1.00 equiv), 4-pentenoic acid (0.25 mL, 2.40 mmol, 1.10 equiv), triethylamine (0.91 mL, 6.54 mmol, 3.00 equiv), and HOBt (0.324 g, 2.40 mmol, 1.10 equiv) were dissolved in THF (20 mL) and cooled to 0 °C using an ice bath. After 10 min EDC·HCl (0.460 g, 2.40 mmol, 1.10 equiv) was added and the mixture was allowed to warm to room temperature. After 18 h TLC showed completion of the reaction, which was then quenched with saturated aqueous sodium bicarbonate (20 mL). Reaction mixture was concentrated to remove THF and then was extracted with EtOAc (20 mL × 3). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude mixture was purified via flash column chromatography using 0−10% MeOH in EtOAc to afford **30** as a yellow oil (0.441 g, 67%, mixture of rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 5.1 Hz, 0.65H), 8.43 (s, 0.65H), 8.36−8.32 (m, 0.7H), 6.98 (d, J = 5.1 Hz, 0.63H), 6.96 (d, J = 5.1 Hz, 0.37H), 6.00−5.66 (m, 2H), 5.16−4.94 (m, 4H), 4.65 (s, 0.7H), 4.53 (s, 1.3H), 3.67 (t, J = 5.8 Hz, 0.7H), 3.60−3.52 (m, 2.6H), 3.46−3.41 (m, 0.7H), 2.77−2.68 (m, 2H), 2.66−2.57 (m, 0.7H), 2.55−2.27 (m, 5.3H), 1.87−1.77 (m, 0.7H), 1.76−1.69 (m, 1.3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 172.9, 150.7, 150.4, 148.5, 147.7, 144.7, 143.5, 137.5, 137.1, 136.9, 136.6, 135.0, 134.3, 121.4, 119.6, 116.5, 115.97, 115.92, 115.6, 59.1, 58.5, 47.9, 45.3, 44.9, 42.9, 34.4, 34.2, 32.5, 32.3, 31.6, 30.2, 29.5, 29.4, 29.3, 29.1. IR (film) 3400, 1632 cm^{-1}. HRMS (ESI) $C_{18}H_{27}N_2O_2$ [M + H]$^+$, calculated 303.2073, found 303.2074.

***N*-(3-Hydroxypropyl)-*N*-((3-(pent-4-en-1-yl)pyridin-4-yl)methyl)pent-4-enamide (31).** Using the procedure described for the preparation of **30**, pyridine substrate **27** (0.98 g, 4.18 mmol, 1.00 equiv), 4-pentenoic acid (0.47 mL, 4.60 mmol, 1.10 equiv), triethylamine (1.80 mL, 12.5 mmol, 3.00 equiv), HOBt (0.62 g, 4.60 mmol, 1.10 equiv), and EDC·HCl (0.882 g, 4.60 mmol, 1.10 equiv) were reacted to give **31** as a yellow oil (0.899 g, 68%, mixture of rotamers). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49−8.32 (m, 2H), 7.01−6.93 (m, 1H), 5.98−5.69 (m, 2H), 5.19−4.88 (m, 4H), 4.65 (s, 0.8H), 4.51 (s, 1.2H), 3.67 (t, J = 5.8 Hz, 0.8H), 3.61−3.52 (m, 2.4H), 3.47−3.37 (m, 0.8H), 2.69−2.56 (m, 2H), 2.54−2.25 (m, 4.5H), 2.22−2.09 (m, 1.5H), 1.89−1.50 (m, 2H), 1.42−1.32 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 172.9, 150.7, 148.5, 148.4, 143.28, 143.20, 137.7, 136.9, 135.3, 134.9, 121.46, 121.40, 119.74, 119.70, 115.98, 115.92, 115.69, 115.66, 59.4, 58.5, 47.7, 45.2, 44.8, 42.9, 32.5, 32.4, 31.9, 31.6, 30.2, 29.99, 29.93, 29.36, 29.30, 29.2, 22.7, 14.18, 14.15. IR (film) 3402, 1641, 1631 cm^{-1}. HRMS (ESI) $C_{19}H_{29}N_2O_2$ [M + H]$^+$, calculated 317.2229, found 317.2232.

***N*-((3-(Hex-5-en-1-yl)pyridin-4-yl)methyl)-*N*-(3-hydroxypropyl)pent-4-enamide (32).** Using the procedure described for the preparation of **30**, pyridine substrate **28** (0.580 g, 2.33 mmol, 1.00 equiv), 4-pentenoic acid (0.260 mL, 2.56 mmol, 1.10 equiv), triethylamine (0.980 mL, 7.00 mmol, 3.00 equiv), HOBt (0.350 g, 2.56 mmol, 1.10 equiv), and EDC·HCl (0.490 g, 2.56 mmol, 1.10 equiv) were reacted to give **32** as a yellow oil (0.489 g, 64%, mixture of rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 5.1 Hz, 0.7H), 8.42 (s, 0.7H), 8.36−8.33 (m, 0.6H), 6.98 (d, J = 5.1 Hz, 0.7H), 6.95 (d, J = 5.1 Hz, 0.3H), 5.96−5.85 (m, 0.3H), 5.84−5.73 (m, 1.7H), 5.15−4.92 (m, 4H), 4.65 (s, 0.6H), 4.51 (s, 1.4H), 3.67 (t, J = 5.8 Hz, 0.7H), 3.60−3.54 (m, 2.6H), 3.46−3.36 (m, 0.7H), 2.66−2.59 (m, 2.3H), 2.52−2.45 (m, 0.7H), 2.43−2.37 (m, 1.4H), 2.37−2.28 (m, 1.4H), 2.17−2.04 (m, 2.2H), 1.85−1.78 (m, 0.6H), 1.77−1.69 (m, 1.4H), 1.65−1.55 (m, 2H), 1.55−1.45 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 172.9, 150.7, 150.5, 148.5, 147.8, 144.4, 143.2, 138.6, 138.3, 137.6, 136.9, 135.8, 135.0, 121.4, 119.7, 115.9, 115.6, 115.2, 114.9, 59.3, 58.5, 47.7, 45.1, 44.8, 42.9, 33.6, 33.5, 32.5, 32.3, 31.6, 30.2, 30.0, 29.9, 29.8, 29.6, 29.3, 28.9, 28.8. IR (film) 3404, 1632 cm^{-1}. HRMS (ESI) $C_{20}H_{31}N_2O_2$ [M + H]$^+$, calculated 331.2386, found 331.2392.

***N*-((3-(Hept-6-en-1-yl)pyridin-4-yl)methyl)-*N*-(3-hydroxypropyl)pent-4-enamide (33).** Using the procedure described for the preparation of **30**, pyridine substrate **29** (0.658 g, 2.50 mmol, 1.00 equiv), 4-pentenoic acid (0.280 mL, 2.75 mmol, 1.10 equiv), triethylamine (1.00 mL, 7.50 mmol, 3.00 equiv), HOBt (0.372 g, 2.75 mmol, 1.10 equiv), and EDC·HCl (0.527 g, 2.75 mmol, 1.10 equiv) were reacted to give **33** as a yellow oil (0.517 g, 60%, mixture of rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45 (d, J = 5.1 Hz, 0.7H), 8.42 (s, 0.7H), 8.37−8.32 (m, 0.6H), 6.98 (d, J = 5.1 Hz, 0.7H), 6.95 (d, J = 5.1 Hz, 0.3H), 5.96−5.85 (m, 0.5H), 5.85−5.73 (m, 1.5H), 5.15−4.90 (m, 4H), 4.65 (s, 0.6H), 4.51 (s, 1.4H), 3.67 (t, J = 5.8 Hz, 0.6H), 3.62−3.50 (m, 2.8H), 3.50−3.37 (m, 0.6H), 2.66−2.55 (m, 2.6H), 2.52−2.44 (m, 0.6H), 2.44−2.35 (m, 1.4H), 2.36−2.27 (m, 1.4H), 2.11−2.01 (m, 2H), 1.85−1.77 (m, 0.6H), 1.77−1.68 (m, 1.4H), 1.68−1.51 (m, 3H), 1.51−1.34 (m, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.5, 172.9, 150.7, 150.5, 148.4, 147.7, 144.4, 143.2, 138.9, 138.7, 137.6, 136.9, 135.9, 135.1, 121.4, 119.7, 115.9, 115.6, 114.8, 114.6, 59.3, 58.5, 47.7, 45.2, 44.8, 42.9, 33.81, 33.75, 32.5, 32.3, 30.4, 30.2, 30.13, 30.10, 29.9, 29.7, 29.6, 29.4, 29.3, 29.2, 29.1, 28.84, 28.80. IR (film) 3400, 3073, 1635 cm^{-1}. HRMS (ESI) $C_{21}H_{33}N_2O_2$ [M + H]$^+$, calculated 345.2542, found 345.2544.

6-(3-Hydroxypropyl)-5,8,9,12,13,14-hexahydropyrido[4,3-*c*][1]azacyclododecin-7(6*H*)-one (36). Pyridine substrate **31** (0.240 g, 0.760 mmol, 1.00 equiv) was dissolved in toluene (1.50 L, 0.500 mM), placed in an 80 °C oil bath, and purged with Ar for 1 h. In a separate flask, toluene (20 mL) was purged with Ar for 30 min, and then Zhan 1B catalyst (0.0167 g, 0.023 mmol, 0.030 equiv) was added and the mixture stirred at room temperature until the catalyst completely dissolved (~30 min). The catalyst solution was loaded into a syringe and added dropwise via syringe pump to the solution of **31** over the period of 2 h. After 2 h the reaction was complete (TLC) and di(ethylene glycol)vinyl ether (0.400 mL, 3.04 mmol, 4.00 equiv) was added to quench the catalyst. Reaction mixture was then cooled to room temperature and concentrated in vacuo. Crude product was purified directly via flash column chromatography using 0−10% MeOH in EtOAc to afford **36** as a yellow brown oil (0.195 g, 89%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54−8.07 (m, 2H), 7.17−6.77 (m, 1H), 6.00−5.09 (m, 3H), 5.13−4.76 (m, 0.3H), 4.76−4.30 (m, 0.7H), 3.94−3.06 (m, 4H), 2.96−1.09 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 172.6, 151.4, 151.2, 151.0, 150.7, 147.8, 147.2, 146.9, 146.8, 143.7, 143.1, 141.0, 138.3, 133.6, 132.3, 131.3, 130.9, 130.4, 129.54 128.7, 126.7, 126.4, 126.2, 59.0, 58.8, 58.6, 58.4, 58.3, 50.9, 45.9, 44.8, 42.7, 42.4, 39.8, 34.1, 33.7, 33.3, 32.3, 31.7, 31.2, 30.8, 30.7, 30.4, 30.1, 29.9, 29.7, 29.5, 29.3, 29.2, 28.3, 27.3, 25.9, 25.8, 24.4, 22.5. IR (film) 3381, 1634 cm^{-1}. HRMS (ESI) $C_{17}H_{25}N_2O_2$ [M + H]$^+$, calculated 289.1916, found 289.1929.

6-(3-Hydroxypropyl)-5,6,8,9,12,13,14,15-octahydro-7*H*-pyrido[4,3-*c*][1]azacyclotridecin-7-one (37). Using the procedure described for the preparation of **36**, pyridine substrate **32** (0.100 g, 0.300 mmol, 1.00 equiv), Zhan 1B catalyst (0.007 g, 0.009 mmol, 0.030 equiv), and di(ethylene glycol) vinyl ether (0.160 mL, 1.20 mmol, 4.00 equiv) were reacted to give **37** as a yellow brown oil

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(0.0750 g, 83%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54−8.24 (m, 2H), 7.21−6.98 (m, 1H), 5.95−5.77 (m, 0.7H), 5.70−5.10 (m, 2H), 4.74−4.54 (m, 1.3H), 3.78−3.35 (m, 4H), 3.07−2.86 (m, 0.7H), 2.82−1.89 (m, 7.3H), 1.89−1.17 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 174.9, 173.4, 172.7, 151.34, 151.25, 150.9, 150.1, 148.0, 147.9, 147.2, 147.0, 143.8, 143.4, 142.9, 141.2, 137.9, 134.8, 134.2, 132.5, 132.1, 131.8, 130.4, 128.7, 128.6, 128.2, 127.6, 126.4, 126.3, 124.9, 119.7, 59.3, 58.22, 58.16, 49.9, 48.4, 46.44, 46.37, 43.2, 42.89, 42.84, 40.0, 36.4, 33.8, 32.2, 32.1, 31.9, 31.5, 31.2, 31.0, 30.5, 30.3, 30.2, 30.0, 29.6, 29.5, 29.4, 29.3, 28.5, 28.2, 27.8, 27.7, 27.5, 27.2, 26.9, 26.5, 26.3, 26.2, 24.6, 24.3. IR (film) 3377, 1631 cm^{-1}. HRMS (ESI) $C_{18}H_{27}N_2O_2$ $[M + H]^+$, calculated 303.2072, found 303.2069.

6-(3-Hydroxypropyl)-5,8,9,12,13,14,15,16-octahydropyrido-[4,3-*c*][1]azacyclotetradecin-7(6*H*)-one (34). Using the procedure described for the preparation of **36**, pyridine substrate **33** (0.050 g, 0.150 mmol, 1.00 equiv), Zhan 1B catalyst (0.0033 g, 0.0050 mmol, 0.030 equiv), and di(ethylene glycol) vinyl ether (0.0820 mL, 0.600 mmol, 4.00 equiv) were reacted to give **34** as a yellow brown oil (0.0440 g, 92%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50−8.31 (m, 2H), 7.20−6.98 (m, 1H), 5.84 (d, J = 14.3 Hz, 0.3H), 5.71−5.12 (m, 2H), 4.79−4.46 (m, 1.7H), 3.88−3.40 (m, 4.4H), 3.39−3.19 (m, 0.6H), 2.82−1.93 (m, 8H), 1.91−1.11 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 175.8, 174.9, 172.7, 171.9, 151.4, 151.3, 150.9, 150.8, 150.6, 150.0, 148.4, 148.3, 147.9, 147.2, 146.6, 144.4, 143.8, 143.7, 143.5, 143.4, 135.2, 134.9, 134.6, 134.2, 132.5, 132.1, 131.7, 131.5, 131.3, 130.4, 129.7, 128.7, 128.2, 127.7, 127.55, 126.60, 126.5, 124.9, 119.8, 119.3, 119.2, 59.4, 59.3, 58.3, 58.2, 49.9, 48.4, 48.1, 46.4, 45.5, 44.1, 43.2, 43.0, 42.84, 42.78, 40.0, 36.4, 35.6, 34.8, 33.8, 32.5, 32.3, 32.1, 31.9, 31.5, 31.1, 31.0, 30.5, 30.33, 30.28, 30.2, 30.14, 30.08, 29.99, 29.97, 29.7, 29.52, 29.45, 29.3, 28.9, 28.6, 28.5, 28.2, 27.5, 27.2, 27.1, 27.0, 26.9, 26.5, 26.3, 26.2, 26.1, 25.4, 24.4, 24.3. IR (film) 3377, 1631 cm^{-1}. HRMS (ESI) $C_{19}H_{29}N_2O_2$ $[M + H]^+$, calculated 317.2229, found 317.2234.

3-(7-Oxo-7,8,9,12,13,14-hexahydropyrido[4,3-*c*][1]-azacyclododecin-6(5*H*)-yl)propanal (38). Pyridine substrate **36** (0.220 g, 0.760 mmol, 1.00 equiv) was dissolved in DCM (8 mL) and K_2CO_3 (0.315 g, 2.28 mmol, 3.00 equiv) was added. Dess−Martin periodinane (0.490 g, 1.14 mmol, 1.50 equiv) was added and the reaction stirred at room temperature for 2 h. The reaction was quenched by addition of 1 M NaOH and stirred for 15 min. Crude mixture was extracted with DCM (10 mL × 3) and all the organic layers were combined, dried over Na_2SO_4, filtered, and concentrated. Crude product was purified via flash column chromatography using 0−10% MeOH in EtOAc to afford **38** as a yellow oil (0.124 g, 57%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.85−9.51 (m, 1H), 8.53−8.09 (m, 2H), 7.21−6.81 (m, 1H), 5.88−5.11 (m, 3H), 5.09−4.77 (m, 0.1H), 4.67−4.25 (m, 0.4H), 3.86−2.93 (m, 2.5H), 2.93−0.99 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.6, 200.5, 199.1, 199.0, 174.0, 172.9, 172.2, 151.6, 151.3, 151.2, 151.1, 147.9, 147.7, 147.2, 147.0, 143.2, 142.6, 141.5, 138.2, 133.9, 132.1, 131.5, 131.2, 130.8, 129.3, 128.5, 126.7, 126.5, 126.3, 51.1, 46.2, 46.0, 45.2, 43.2, 43.0, 42.8, 42.3, 42.2, 42.0, 38.9, 38.7, 37.8, 37.0, 34.2, 33.6, 33.4, 31.9, 31.7, 31.3, 31.0, 30.8, 30.7, 30.4, 29.9, 29.7, 29.6, 29.5, 29.4, 28.2, 27.4, 26.0, 25.8, 24.4, 22.5. IR (film) 1723, 1632 cm^{-1}. HRMS (ESI) $C_{17}H_{23}N_2O_2$ $[M + H]^+$, calculated 287.1760, found 287.1760.

3-(7-Oxo-7,8,9,12,13,14,15,16-octahydropyrido[4,3-*c*][1]-azacyclotetradecin-6(5*H*)-yl)propanal (39). Using the procedure described for the preparation of **38**, pyridine substrate **34** (0.200 g, 0.630 mmol, 1.00 equiv), Dess−Martin periodinane (0.400 g, 0.950 mmol, 1.50 equiv), and K_2CO_3 (0.261 g, 1.89 mmol, 3.00 equiv) were reacted to give **39** as a yellow oil (0.130 g, 66%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.86−9.58 (m, 1H), 8.54−8.21 (m, 2H), 7.20−6.88 (m, 1H), 5.87−5.77 (m, 0.2H), 5.63−5.14 (m, 2H), 4.82−4.45 (m, 1.8H), 3.89−3.20 (m, 2H), 2.96−2.77 (m, 1H), 2.77−1.87 (m, 8H), 1.87−1.07 (m, 7H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.7, 200.6, 199.1, 198.9, 175.8, 174.5, 172.4, 171.5, 151.6, 150.8, 150.6, 150.1, 148.2, 148.1, 147.4, 146.9, 145.2, 144.56, 143.2, 137.9, 135.0, 134.8, 134.7, 134.6, 131.60, 131.56, 131.3, 129.6, 129.1, 128.0, 127.8, 126.4, 119.5, 50.4, 50.1, 50.0, 49.9, 46.7, 45.9, 43.3, 43.2, 42.9, 42.7, 41.8, 39.0, 35.6, 34.9, 33.9, 32.2, 32.22, 32.16, 31.2, 30.4, 30.2, 30.1, 30.0, 29.74, 29.66, 29.5, 29.3, 29.2, 28.8, 28.5, 28.1, 27.6, 27.6, 27.3, 27.2, 26.9, 26.1, 25.5, 24.3. IR (film) 1720, 1642 cm^{-1}. HRMS (ESI) $C_{19}H_{27}N_2O_2$ $[M + H]^+$, calculated 315.2073, found 315.2071.

6,7,10,11,14,15-Hexahydropyrido[4,3-*c*]pyrrolo[1,2-*a*][1]-azacyclododecin-12(5*H*)-one (40). Pyridine substrate **38** (0.128 g, 0.45 mmol, 1.00 equiv) was dissolved in THF (5 mL). Then $Ti(O^iPr)_4$ (0.067 mL, 0.220 mmol, 0.500 equiv) and DIPEA (0.110 mL, 0.68 mmol, 1.50 equiv) were added. Reaction mixture was then heated in an 80 °C oil bath for 2 min, followed by addition of $ClCO_2Et$ (0.0470 mL, 0.500 mmol, 1.10 equiv). After an additional 10 min, a drop of TFA and H_2O (5 mL) were added and heating continued for additional 10 min. Thereafter reaction mixture was made basic with saturated aqueous Na_2CO_3 and extracted with EtOAc (3 × 10 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude product was purified via flash column chromatography using 0−10% MeOH in EtOAc to afford **40** as a yellow oil (0.0466 g, 39%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.76−8.22 (m, 2H), 7.40−7.29 (m, 0.1H), 7.22−6.89 (m, 0.9H), 5.97−4.74 (m, 3H), 4.44−3.72 (m, 2H), 2.99−0.68 (m, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 169.5, 154.6, 152.2, 151.5, 151.2, 148.7, 147.5, 146.3, 146.2, 142.8, 136.4, 133.9, 133.8, 132.8, 131.4, 131.1, 129.4 129.2, 123.9, 123.3, 118.9, 116.4, 83.8, 82.5 64.8, 64.4, 49.7, 49.6, 49.1, 46.1, 35.7, 35.1, 34.8, 33.7, 31.8, 31.1, 29.9, 29.7, 29.5, 29.4, 29.0, 28.9, 28.1, 27.1, 26.0, 25.4, 22.9, 22.8, 14.4, 14.3, 11.6. IR (film) 1737, 1658 cm^{-1}. HRMS (ESI) $C_{17}H_{21}N_2O$ $[M + H]^+$, calculated 269.1654, found 269.1653.

6,7,8,9,12,13,16,17-Octahydropyrido[4,3-*c*]pyrrolo[1,2-*a*][1]-azacyclotetradecin-14(5*H*)-one (41). Using the procedure described for the preparation of **40**, pyridine substrate **39** (0. 0637 g, 0.200 mmol, 1.00 equiv), $Ti(O^iPr)_4$ (0.030 mL, 0.100 mmol, 0.500 equiv), DIPEA (0.050 mL, 0.300 mmol, 1.50 equiv), and $ClCO_2Et$ (0.0210 mL, 0.220 mmol, 1.10 equiv) were reacted to give **41** as a yellow oil (0.0201 g, 34%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.66−8.24 (m, 2H), 7.26−7.13 (m, 0.3H), 7.06−6.91 (m, 0.7H), 5.66−4.86 (m, 3H), 4.41−3.65 (m, 4H), 3.16−0.95 (m, 14H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 172.8, 154.6, 154.5, 151.7, 151.4, 148.6, 135.6, 135.5, 131.4, 128.1, 128.0, 120.5, 120.4, 82.6, 82.6, 64.9, 64.8, 64.7, 64.6, 60.6, 45.3, 36.0, 35.9, 33.7, 30.9, 30.5, 30.1, 30.0, 29.2, 28.2, 27.7, 27.6, 27.2, 26.9, 26.5, 26.3, 25.2, 24.2, 21.2, 14.50, 14.46, 14.4. IR (film) 1728, 1643 cm^{-1}. HRMS (ESI) $C_{19}H_{25}N_2O$ $[M + H]^+$, calculated 297.1966, found 297.1971.

3-((2-(3-(Hex-5-en-1-yl)pyridin-4-yl)ethyl)amino)propan-1-ol (42). Methyltriphenylphosphonium bromide (3.98 g, 11.1 mmol, 1.05 equiv) was dissolved in THF (80 mL) and cooled to 0 °C using an ice bath. Then *n*-BuLi (2.5 M, 4.40 mL, 11.1 mmol, 1.05 equiv) was added and the reaction maintained at 0 °C for 1 h, followed by cooling to −78 °C. Thereafter 3-(hex-5-en-1-yl)isonicotinaldehyde (**24**) (2.00 g, 10.6 mmol, 1.00 equiv) dissolved in THF (10 mL) was added and the reaction mixture was stirred at −78 °C for 2 h. Reaction mixture was then allowed to warm to room temperature overnight, and quenched with saturated aqueous NH_4Cl (40 mL). Reaction mixture was concentrated to remove THF and extracted with EtOAc (40 mL × 3). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude mixture was purified with flash column chromatography using 0−30% EtOAc in hexanes to afford 3-(hex-5-en-1-yl)-4-vinylpyridine (**i**) as a colorless liquid (1.47 g, 74%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (d, J = 5.1 Hz, 1H), 8.35 (s, 1H), 7.29 (d, J = 5.1 Hz, 1H), 6.88 (dd, J = 17.4, 11.0 Hz, 1H), 5.82 (dd, J = 17.4, 1.0 Hz, 1H), 5.79−5.71 (m, 1H), 5.46 (dd, J = 11.0, 1.0 Hz, 1H), 5.03−4.86 (m, 2H), 2.72−2.55 (m, 2H), 2.05 (dt, J = 8.5, 7.0 Hz, 2H), 1.55 (dtd, J = 9.2, 7.5, 5.9 Hz, 2H), 1.48−1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 147.8, 143.5, 138.7, 134.9, 132.6, 119.6, 119.3, 114.8, 33.7, 30.5, 30.4, 28.8. IR (film) 3077, 1639 cm^{-1}. HRMS (ESI) $C_{13}H_{18}N$ $[M + H]^+$, calculated 188.1439, found 188.1450. This

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vinylpyridine (1.47 g, 7.85 mmol, 1.00 equiv) and 3-aminopropanol (6.00 mL, 78.5 mmol, 10.0 equiv) were dissolved in toluene (40 mL) and Amberlyst-15 (1.47 g, 100% w.r.t pyridine substrate) was added. Reaction mixture was then heated in a 120 °C oil bath until complete consumption of starting material was observed by TLC (~7 days). After cooling to room temperature, the mixture was filtered through Celite and the Celite was further rinsed with MeOH to maximize product yield. The filtrate was concentrated to remove solvent. Crude product was purified via flash column chromatography using 0−30% MeOH in EtOAc to afford **42** as a yellow oil (1.47 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 8.28 (d, J = 5.0 Hz, 1H), 7.01 (d, J = 5.0 Hz, 1H), 5.83−5.61 (m, 1H), 5.05−4.84 (m, 2H), 3.78−3.72 (m, 2H), 2.87−2.79 (m, 4H), 2.78−2.73 (m, 2H), 2.61−2.55 (m, 2H), 2.10−2.00 (m, 2H), 1.71−1.62 (m, 2H), 1.59−1.50 (m, 2H), 1.48−1.37 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.7, 147.5, 146.4, 138.6, 136.4, 124.1, 114.9, 64.0, 49.9, 49.8, 33.6, 32.4, 31.1, 30.6, 30.0, 28.8. IR (film) 3270, 1632 cm^{-1}. HRMS (ESI) $C_{16}H_{27}N_2O$ [M + H]$^+$, calculated 263.2123, found 263.2130.

3-((2-(3-(Hept-6-en-1-yl)pyridin-4-yl)ethyl)amino)propan-1-ol (43). Using the procedure described for the preparation of **42**, 3-(hept-6-en-1-yl)isonicotinaldehyde (**25**) (0.950 g, 4.67 mmol, 1.00 equiv), methyltriphenylphosphonium bromide (1.75 g, 4.90 mmol, 1.05 equiv), and *n*-BuLi (2.5 M) (1.90 mL, 4.90 mmol, 1.05 equiv) were reacted to give 3-(hept-6-en-1-yl)-4-vinylpyridine (**ii**) as a colorless liquid (0.790 g, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.36 (d, J = 5.2 Hz, 1H), 8.34 (s, 1H), 7.29 (d, J = 5.2 Hz, 1H), 6.87 (dd, J = 17.4, 11.0 Hz, 1H), 5.85−5.71 (m, 2H), 5.45 (dd, J = 11.0, 1.1 Hz, 1H), 4.99−4.87 (m, 2H), 2.69−2.52 (m, 2H), 2.08−1.94 (m, 2H), 1.57−1.46 (m, 2H), 1.43−1.26 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 151.2, 147.8, 143.6, 139.0, 134.9, 132.6, 119.6, 119.3, 114.6, 33.8, 30.9, 30.6, 29.0, 28.8. IR (film) 2932, 1636 cm^{-1}. HRMS (ESI) $C_{14}H_{20}N$ [M + H]$^+$, calculated 202.1596, found 202.1611. Vinylpyridine **ii** (0.080 g, 0.400 mmol, 1.00 equiv), 3-aminopropanol (0.300 mL, 78.5 mmol, 10.0 equiv), and Amberlyst-15 (0.080 g, 100% w.r.t pyridine substrate) were reacted to give **43** as a yellow oil (0.102 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.26 (d, J = 5.0 Hz, 1H), 6.99 (d, J = 5.0 Hz, 1H), 5.83−5.65 (m, 1H), 4.98−4.81 (m, 2H), 3.79−3.67 (m, 2H), 2.99 (s, 2H), 2.84−2.77 (m, 4H), 2.77−2.67 (m, 2H), 2.59−2.50 (m, 2H), 2.04−1.88 (m, 2H), 1.70−1.60 (m, 2H), 1.55−1.45 (m, 2H), 1.40−1.27 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.6, 147.4, 146.4, 138.9, 136.4, 124.0, 114.5, 63.6, 49.8, 49.6, 33.7, 32.3, 31.2, 30.9, 30.1, 29.1, 28.8. IR (film) 3284, 1636 cm^{-1}. HRMS (ESI) $C_{17}H_{29}N_2O$ [M + H]$^+$, calculated 277.2280, found 277.2282.

6-(3-Hydroxypropyl)-5,6,8,9,12,13,14,15-octahydro-7*H*-pyrido[4,3-*c*][1]azacyclotridecin-7-one (44). Using the procedure described for the preparation of **30**, pyridine substrate **42** (1.40 g, 5.34 mmol, 1.00 equiv), 4-pentenoic acid (0.60 mL, 5.87 mmol, 1.10 equiv), triethylamine (2.30 mL, 16.0 mmol, 3.00 equiv), HOBt (0.794 g, 5.87 mmol, 1.10 equiv), and EDC·HCl (1.13 g, 5.87 mmol, 1.10 equiv) were reacted to give *N*-(2-(3-(hex-5-en-1-yl)pyridin-4-yl)-ethyl)-*N*-(3-hydroxypropyl)pent-4-enamide (**iii**) as a yellow oil (1.30 g, 71%, mixture of rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 0.6H), 8.30 (d, J = 5.0 Hz, 0.6H), 8.27 (s, 0.4H), 8.23 (d, J = 5.0 Hz, 0.4H), 7.02 (d, J = 5.0 Hz, 0.4H), 6.95 (d, J = 5.0 Hz, 0.6H), 5.89−5.61 (m, 2H), 5.07−4.79 (m, 4H), 3.63−3.57 (m, 0.4H), 3.52−3.37 (m, 5.2H), 3.36−3.28 (m, 0.4H), 2.88−2.76 (m, 2H), 2.68−2.51 (m, 2H), 2.46−2.21 (m, 4H), 2.07−1.99 (m, 2H), 1.76−1.50 (m, 4H), 1.47−1.40 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 172.5, 150.9, 150.5, 147.7, 147.2, 146.2, 144.5, 138.6, 138.3, 137.6, 137.0, 136.6, 136.1, 124.5, 124.26, 115.8, 115.3, 115.0, 114.8, 58.9, 58.3, 48.1, 47.0, 45.3, 41.9, 33.6, 33.5, 32.4, 32.3, 31.9, 31.3, 30.7, 30.6, 30.3, 30.2, 30.0, 29.8, 29.45, 29.43, 28.8, 28.4. IR (film) 3397, 3069 1643 cm^{-1}. HRMS (ESI) $C_{21}H_{33}N_2O_2$ [M + H]$^+$, calculated 345.2542, found 345.2543. Using the procedure described for the preparation of **36**, ring closing metathesis of **iii** (0.650 g, 1.89 mmol, 1.00 equiv), with Zhan 1B catalyst (0.041 g, 0.057 mmol, 0.030 equiv), followed by quenching with di(ethylene glycol) vinyl ether (1.00 mL, 7.60 mmol, 4.00 equiv) gave **44** as a yellow brown oil (0.558 g, 94%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44−8.28 (m, 2H), 7.23 (d, J = 5.2 Hz, 0.1H), 7.11−6.95 (m, 0.9H), 5.68−5.34 (m, 2H), 3.87 (s, 1H), 3.71−3.20 (m, 6H), 3.02−2.82 (m, 2H), 2.68−2.36 (m, 6H), 2.37−2.09 (m, 2H), 1.89−1.33 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.4, 174.3, 151.5, 147.9, 147.8, 147.4, 145.1, 143.9, 137.4, 136.6, 133.2, 132.6, 132.1, 129.6, 128.6, 124.2, 122.5, 58.3, 58.3, 49.7, 48.2, 46.8, 43.1, 42.8, 32.7, 32.5, 32.2, 31.2, 30.9, 30.5, 30.5, 30.0, 29.9, 29.5, 29.1, 28.5, 28.4, 27.5, 27.3, 24.3, 24.1. IR (film) 3379, 1628 cm^{-1}. HRMS (ESI) $C_{19}H_{29}N_2O_2$ [M + H]$^+$, calculated 317.2229, found 317.2239.

7-(3-Hydroxypropyl)-5,6,7,9,10,13,14,15,16,17-decahydro-8*H*-pyrido[4,3-*d*][1]azacyclopentadecin-8-one (45). Using the procedure described for the preparation of **30**, pyridine substrate **43** (0.060 g, 0.220 mmol, 1.00 equiv), 4-pentenoic acid (25.0 μL, 0.240 mmol, 1.10 equiv), triethylamine (0.10 mL, 0.660 mmol, 3.0 equiv), HOBt (0.032 g, 0.240 mmol, 1.10 equiv), and EDC·HCl (0.046 g, 0.240 mmol, 1.10 equiv) were reacted to give *N*-(2-(3-(hept-6-en-1-yl)pyridin-4-yl)ethyl)-*N*-(3-hydroxypropyl)pent-4-enamide (**iv**) as a yellow oil (0.064 g, 81%, mixture of rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.33 (s, 0.6H), 8.29 (d, J = 5.0 Hz, 0.6H), 8.26 (s, 0.4H), 8.23 (d, J = 5.0 Hz, 0.4H), 7.02 (d, J = 5.0 Hz, 0.4H), 6.95 (d, J = 5.1 Hz, 0.6H), 5.87−5.64 (m, 2H), 5.04−4.81 (m, 4H), 3.64−3.53 (m, 1H), 3.52−3.35 (m, 4.4H), 3.35−3.24 (m, 0.6H), 2.88−2.74 (m, 2H), 2.66−2.51 (m, 2H), 2.46−2.16 (m, 4H), 2.05−1.89 (m, 2H), 1.77−1.60 (m, 2H), 1.60−1.44 (m, 2H), 1.43−1.26 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.47, 172.48, 150.9, 150.4, 147.7, 147.2, 146.2, 144.5, 138.9, 138.7, 137.6, 137.0, 136.7, 136.2, 124.5, 124.3, 115.8, 115.3, 114.7, 114.5, 58.9, 58.3, 48.1, 47.0, 45.3, 41.9, 33.8, 33.7, 32.4, 32.3, 31.9, 31.3, 31.2, 31.1, 30.4, 30.2, 29.9, 29.46, 29.45, 29.2, 29.1, 28.82, 28.77. IR (film) 3399, 3077, 1642 cm^{-1}. HRMS (EI) $C_{22}H_{34}N_2O_2$ [M$^{\cdot+}$], calculated 358.2620, found 358.2613. Using the procedure described for the preparation of **36**, ring closing metathesis of **iv** (0.064 g, 0.18 mmol, 1.0 equiv) with Zhan 1B catalyst (0.004 g, 0.005 mmol, 0.030 equiv), followed by quenching with di(ethylene glycol) vinyl ether (0.097 mL, 0.72 mmol, 4.00 equiv) gave **45** as a yellow brown oil (0.547 g, 92%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47−8.27 (m, 2H), 7.27−7.20 (m, 0.1H), 7.20−7.10 (m, 0.2H), 7.10−6.97 (m, 0.7H), 5.64−5.30 (m, 2H), 3.82−3.23 (m, 7H), 3.04−2.86 (m, 2H), 2.68−2.24 (m, 6H), 2.24−2.17 (m, 0.3H), 2.15−2.05 (m, 1.7H), 1.84−1.35 (m, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.3, 174.2, 151.7, 151.4, 151.3, 147.8, 144.7, 144.2, 136.7, 136.6, 133.1, 132.4, 131.4, 129.8, 129.6, 129.2, 128.5, 128.4, 124.5, 123.1, 58.3, 58.3, 58.2, 49.3, 48.1, 43.1, 42.6, 42.1, 34.7, 34.1, 32.5, 32.4, 32.3, 32.2, 32.1, 31.8, 31.5, 31.24, 31.19, 30.9, 30.7, 30.5, 29.9, 29.5, 29.3, 28.3, 27.5, 27.4, 27.3, 26.7, 25.1, 24.8. IR (film) 3390, 1636 cm^{-1}. HRMS (ESI) $C_{20}H_{31}N_2O_2$ [M + H]$^+$, calculated 331.2386, found 331.2386.

3-(8-Oxo-5,8,9,10,13,14,15,16-octahydropyrido[4,3-*d*][1]-azacyclotetradecin-7(6*H*)-yl)propanal (46). Using the procedure described for the preparation of **38**, pyridine substrate **44** (0.200 g, 0.630 mmol, 1.00 equiv), Dess−Martin periodinane (0.400 g, 0.950 mmol, 1.50 equiv), and K_2CO_3 (0.261 g, 1.89 mmol, 3.00 equiv) were reacted to give **46** as a yellow oil (0.113 g, 57%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.82 (s, 0.3H), 9.73 (s, 0.4H), 9.59 (s, 0.3H), 8.47−8.31 (m, 2H), 7.18−7.00 (m, 1H), 5.63−5.33 (m, 2H), 3.85−3.67 (m, 2H), 3.54−3.43 (m, 1H), 3.37 (t, J = 6.1 Hz, 1H), 2.97−2.76 (m, 2H), 2.76−2.11 (m, 10H), 1.77−1.36 (m, 5H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 173.2, 173.1, 151.6, 151.5, 147.9, 147.7, 145.1, 136.6, 133.1, 131.9, 129.7, 128.8, 124.3, 122.9, 50.7, 49.5, 43.5, 43.3, 41.8, 41.1, 32.8, 32.7, 32.6, 32.5, 31.4, 30.6, 29.9, 29.6, 29.3, 29.2, 27.6, 27.4, 24.4, 23.9. IR (film) 1690, 1672 cm^{-1}. HRMS (ESI) $C_{19}H_{27}N_2O_2$ [M + H]$^+$, calculated 315.2073, found 315.2063.

3-(8-Oxo-5,6,8,9,10,13,14,15,16,17-decahydro-7*H*-pyrido-[4,3-*d*][1]azacyclopentadecin-7-yl)propanal (47). Using the procedure described for the preparation of **38**, pyridine substrate **45** (0.491 g, 1.49 mmol, 1.00 equiv), Dess−Martin periodinane (0.950 g, 2.23 mmol, 1.50 equiv), and K_2CO_3 (0.618 g, 4.47 mmol, 3.00 equiv) were reacted to give **47** as a yellow oil (0.455 g, 93%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.92−9.69 (m, 1H), 8.50−8.29 (m, 2H), 7.20−6.96 (m, 1H), 5.66−5.25 (m,

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2H), 3.83−3.29 (m, 4H), 2.99−2.76 (m, 4H), 2.75−2.01 (m, 8H), 1.76−1.33 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.9, 174.8, 174.5, 173.1, 151.7, 151.3, 147.9, 144.8, 144.3, 136.6, 132.2, 131.4, 129.9, 128.7, 124.6, 123.3, 50.7, 50.5, 49.5, 49.2, 43.4, 43.3, 43.2, 41.2, 40.8, 34.8, 34.2, 32.7, 32.4, 32.1, 31.7, 31.4, 30.9, 29.0, 28.3, 27.5, 26.7, 25.2, 24.5. IR (film) 1719, 1632 cm^{-1}. HRMS (ESI) $C_{20}H_{29}N_2O_2$ [M + H]$^+$, calculated 329.2229, found 329.2225.

24-Hydroxy-1(4,3)-pyridina-2(3,1)-piperidinacycloundecaphan-6-en-3-one (48). Using the procedure described for the preparation of **40**, pyridine substrate **46** (0.100 g, 0.320 mmol, 1.00 equiv), Ti(O^{i}Pr)$_4$ (0.048 mL, 0.160 mmol, 0.500 equiv), DIPEA (0.079 mL, 0.480 mmol, 1.50 equiv), and $ClCO_2Et$ (0.033 mL, 0.350 mmol, 1.10 equiv) reacted to give **48** as a yellow oil (0.0714 g, 71%, mixture of *E*/*Z* diastereomers and rotamers). This material proved to be unstable and only partial characterization (^{1}H NMR, HRMS) was possible. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63−8.25 (m, 2H), 7.25−6.92 (m, 1H), 5.73−5.33 (m, 2H), 4.76−4.46 (m, 2H), 3.79−3.26 (m, 4H), 2.83−1.92 (m, 7H), 1.94−1.19 (m, 8H). IR (film) 3342, 1621 cm^{-1}. HRMS (ESI) $C_{19}H_{27}N_2O_2$ [M + H]$^+$, calculated 315.2073, found 315.2070.

24-Hydroxy-1(4,3)-pyridina-2(3,1)-piperidinacyclododecaphan-6-en-3-one (49). Using the procedure described for the preparation of **40**, pyridine substrate **47** (0.050 g, 0.150 mmol, 1.00 equiv), Ti(O^{i}Pr)$_4$ (0.023 mL, 0.075 mmol, 0.500 equiv), DIPEA (0.038 mL, 0.23 mmol, 1.50 equiv), and $ClCO_2Et$ (0.017 mL, 0.170 mmol, 1.10 equiv) reacted to give **49** as a yellow oil (0.0344 g, 74%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.45−8.03 (m, 2H), 7.41 (d, *J* = 5.2 Hz, 0.1H), 7.22−6.95 (m, 0.9H), 5.80−5.17 (m, 2H), 4.81−4.39 (m, 1H), 4.29−1.09 (m, 22H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.1, 171.4, 170.5, 151.2, 150.9, 147.5, 147.3, 147.1, 136.6, 136.4, 134.48, 132.2, 131.5, 130.0, 129.9, 128.8, 122.6, 122.2, 66.6, 66.5, 44.5, 44.5, 44.4, 44.1, 37.0, 33.8, 33.4, 33.3, 33.2, 32.4, 32.2, 31.6, 30.6, 30.2, 30.0, 29.6, 28.3, 28.0, 27.8, 25.9, 22.4. IR (film) 3371, 1631 cm^{-1}. HRMS (ESI) $C_{20}H_{29}N_2O_2$ [M + H]$^+$, calculated 329.2229, found 329.2236.

1(4,3)-Pyridina-2(3,1)-piperidinacyclododecaphan-6-ene-24,3-dione (50). Using the procedure described for the preparation of **38**, pyridine substrate **49** (0.058 g, 0.18 mmol, 1.00 equiv), Dess−Martin periodinane (0.112 g, 0.26 mmol, 1.50 equiv), and K_2CO_3 (0.075 g, 0.54 mmol, 3.00 equiv) were reacted to give **50** as a yellow oil (0.0388 g, 66%, mixture of *E*/*Z* diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62−8.32 (m, 2H), 7.22−6.77 (m, 1H), 5.88−5.26 (m, 2H), 5.20−4.74 (m, 1H), 4.48−3.22 (m, 4H), 3.22−1.85 (m, 10H), 1.84−1.05 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.6, 204.4, 172.5, 170.8, 151.5, 147.5, 147.4, 147.3, 141.7, 141.3, 136.7, 132.9, 132.6, 131.7, 129.1, 128.4, 123.8, 123.1, 122.5, 53.0, 52.6, 51.5, 50.5, 42.0, 41.9, 41.6, 41.2, 41.1, 40.9, 33.7, 32.7, 32.2, 31.4, 30.5, 30.3, 29.7, 29.0, 28.0, 27.8, 27.7, 27.3, 26.8, 25.4, 22.5. IR (film) 1720, 1632 cm^{-1}. HRMS (ESI) $C_{20}H_{27}N_2O_2$ [M + H]$^+$, calculated 327.2073, found 327.2079.

(*E*)-4-(2-Methoxyvinyl)pyridine (52). Using the procedure described for the preparation of intermediate of **42**, 4-pyridinecarboxaldehyde (1.00 mL, 10.6 mmol, 1.00 equiv), methoxymethyltriphenylphosphonium chloride (3.82 g, 11.1 mmol, 1.05 equiv), and *n*-BuLi (2.5 M) (4.40 mL, 11.1 mmol, 1.05 equiv) were reacted to give **52** as a colorless liquid (1.17 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54−8.38 (m, 2H), 7.34−7.21 (m, 2H), 7.11 (d, *J* = 5.0 Hz, 2H), 5.71 (d, *J* = 13.0 Hz, 1H), 3.75 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 152.2, 149.9, 144.4, 119.7, 102.9, 56.8. HRMS (ESI) $C_8H_{10}NO$ [M + H]$^+$, calculated 136.0762, found 136.0751.

Ethyl 2-(3-chloropyridin-4-yl)acetate (54). 3-Chloro-4-pyridinecarboxaldehyde (**17**) (1.00 g, 7.10 mmol, 1.00 equiv) was dissolved in THF (70 mL). Triton B (40% weight in MeOH) (3.30 mL, 7.10 mmol, 1.00 equiv) and formaldehyde dimethyl thioacetal monoxide (FAMSO) (0.72 mL, 7.10 mmol, 1.00 equiv) were added and the reaction was heated to reflux for 3h, after which time ^{1}H NMR indicated complete consumption of the aldehyde. Water (70 mL) was added and mixture was concentrated to remove THF. The remaining aqueous solution was extracted with EtOAc (70 mL × 2). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude intermediate was dissolved in EtOH (70 mL) and saturated HCl in EtOH (10 mL) was added. Solution was refluxed for 48 h. The EtOH was then evaporated and the residue was combined with saturated aqueous $NaHCO_3$. Crude mixture was then extracted with EtOAc (70 mL × 3). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude product was purified via flash column chromatography using 0−50% EtOAc in hexanes to afford **54** as a yellow liquid (0.836 g, 59%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (s, 1H), 8.45 (d, *J* = 4.9 Hz, 1H), 7.26 (d, *J* = 4.9 Hz, 1H), 4.20 (q, *J* = 7.2 Hz, 2H), 3.77 (s, 2H), 1.27 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 149.7, 148.0, 141.2, 132.7, 125.9, 61.7, 38.6, 14.3. HRMS (ESI) $C_9H_{11}NO_2Cl$ [M + H]$^+$, calculated 200.0478, found 200.0466.

Ethyl 2-(3-(hept-6-en-1-yl)pyridin-4-yl)acetate (55). Using the procedure described for the preparation of **54**, aldehyde **25** (1.80 g, 8.87 mmol, 1.00 equiv), Triton B (40% weight in MeOH) (4.00 mL, 8.87 mmol, 1.00 equiv), formaldehyde dimethyl thioacetal monoxide (FAMSO) (0.90 mL, 8.87 mmol, 1.00 equiv), and saturated HCl in EtOH (13 mL) were reacted to give **55** as a yellow liquid (1.16 g, 50%). This material was also prepared from **54** via B-alkyl Suzuki reaction with 6-heptenylboronic acid using the experimental procedure described for the preparation of **22**. Thus, **54** (1.16 g, 5.80 mmol, 1.00 equiv), 6-heptenylboronic acid (0.991 g, 6.97 mmol, 1.20 equiv), and K_2CO_3 (2.40 g, 17.4 mmol, 3 equiv), $Pd(OAc)_2$ (0.065 g, 0.29 mmol, 0.05 equiv) and RuPhos (0.270 g, 0.580 mmol, 0.1 equiv) were reacted at 100 °C for 24 h to give **55** as a yellow liquid (1.39 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.40 (d, *J* = 5.1 Hz, 1H), 7.15 (d, *J* = 5.1 Hz, 1H), 5.89−5.72 (m, 1H), 5.12−4.74 (m, 2H), 4.18 (q, *J* = 7.2 Hz, 2H), 3.64 (s, 2H), 2.74−2.56 (m, 2H), 2.16−1.96 (m, 2H), 1.70−1.51 (m, 2H), 1.51−1.33 (m, 4H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.2, 150.7, 147.5, 140.9, 138.8, 136.5, 124.9, 114.4, 61.2, 37.9, 33.6, 30.4, 30.2, 28.9, 28.7, 14.1. HRMS (ESI) $C_{16}H_{24}NO_2$ [M + H]$^+$, calculated 262.1807, found 262.1808.

3-(Pent-4-en-1-ylamino)propan-1-ol (56). Using the procedure described for the preparation of **30**, 3-aminopropanol (3.00 mL, 39.2 mmol, 1.00 equiv), 4-pentenoic acid (4.40 mL, 43.1 mmol, 1.10 equiv), triethylamine (17.0 mL, 117 mmol, 3.00 equiv), HOBt (5.82 g, 43.1 mmol, 1.10 equiv), and EDC·HCl (8.26 g, 43.1 mmol, 1.10 equiv) were reacted to give *N*-(3-hydroxypropyl)pent-4-enamide (**v**) as a colorless liquid (4.93 g, 80%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.29 (s, 1H), 5.93−5.70 (m, 1H), 5.16−4.92 (m, 2H), 3.76−3.51 (m, 3H), 3.48−3.31 (m, 2H), 2.47−2.33 (m, 2H), 2.35−2.23 (m, 2H), 1.80−1.55 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 137.0, 115.9, 59.4, 36.4, 35.9, 32.4, 29.8. IR (film) 3302, 3085, 1657 cm^{-1}. HRMS (ESI) $C_8H_{16}NO_2$ [M + H]$^+$, calculated 158.1181, found 158.1169. Lithium aluminum hydride (1.70 g, 44.5 mmol, 3.00 equiv) was combined with THF (225 mL) and cooled to 0 °C using an ice bath. *N*-(3-Hydroxypropyl)pent-4-enamide **v** (3.50 g, 22.2 mmol, 1.00 equiv) dissolved in THF (10 mL) was added dropwise and the resulting mixture was allowed to warm to room temperature and stirred overnight. The mixture was then cooled to 0 °C and carefully quenched by addition of saturated aqueous solution of Rochelle's salt (100 mL). Insoluble material was filtered off and THF was removed from the filtrate under vacuum. The residue was extracted with EtOAc (100 mL × 3) and combined organic layers were dried over Na_2SO_4, filtered, and concentrated to yield **56** as colorless oil (3.08 g, 97%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.99−5.64 (m, 1H), 5.13−4.85 (m, 2H), 3.84−3.76 (m, 2H), 2.90−2.83 (m, 2H), 2.61 (t, *J* = 7.2 Hz, 2H), 2.17−2.01 (m, 2H), 1.76−1.62 (m, 2H), 1.63−1.50 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 114.8, 64.4, 50.0, 49.2, 31.4, 30.7, 29.0. HRMS (ESI) $C_8H_{18}NO$ [M + H]$^+$, calculated 144.1388, found 144.1384.

2-(3-(Hept-6-en-1-yl)pyridin-4-yl)-*N*-(3-hydroxypropyl)-*N*-(pent-4-en-1-yl)acetamide (57). Compound **56** (0.815 g, 5.7 mmol, 1.10 equiv) was dissolved in DCM (50 mL) and trimethylaluminum (2.0 M) (6.8 mL, 13.4 mmol, 2.60 equiv) was added dropwise. After 30 min, ethyl 2-(3-(hept-6-en-1-yl)pyridin-4-yl)acetate (**55**) (1.35 g, 5.17 mmol, 1.00 equiv) dissolved in DCM (5 mL) was added and the reaction mixture was heated to reflux for 48 h. After cooling, the reaction was quenched with 1 M HCl solution (30

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mL) and stirred for 30 min. The reaction was then made basic by addition of saturated aqueous Na_2CO_3 solution, and then extracted with DCM (50 mL × 3). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude product was purified via flash column chromatography using 10% MeOH in EtOAc to afford **57** as yellow oil (1.11 g, 60%, mixture of rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49−8.31 (m, 2H), 7.13−7.01 (m, 1H), 5.92−5.66 (m, 2H), 5.15−4.87 (m, 4H), 3.76 (s, 0.4H), 3.72 (s, 1.6H), 3.63−3.47 (m, 4H), 3.46−3.32 (m, 1H), 3.31−3.18 (m, 1H), 2.72−2.52 (m, 2H), 2.17−1.95 (m, 4H), 1.88−1.48 (m, 6H), 1.50−1.31 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7, 169.5, 150.6, 150.4, 147.6, 147.5, 141.9, 138.7, 137.7, 136.6, 136.2, 124.2, 124.1, 116.2, 115.1, 114.5, 114.4, 59.1, 58.4, 47.8, 45.6, 44.9, 42.2, 36.9, 36.7, 33.6, 31.5, 31.2, 30.8, 30.5, 30.4, 30.4, 30.2, 30.1, 29.4, 29.0, 28.7, 27.9, 26.7. HRMS (ESI) $C_{22}H_{35}N_2O_2$ $[M + H]^+$, calculated 359.2699, found 359.2698.

3-(3-(Hept-6-en-1-yl)pyridin-4-yl)-1-(pent-4-en-1-yl)-piperidin-2-one (58). Pyridine **57** (0.744 g, 2.1 mmol, 1.00 equiv) was dissolved in THF (20 mL) and triethylamine (0.74 mL, 5.25 mmol, 2.50 equiv) was added. Reaction mixture was cooled to 0 °C using an ice bath and then MsCl (0.177 mL, 2.30 mmol, 1.10 equiv) was added. The reaction was maintained at 0 °C for 20 min, after which time TLC indicated complete consumption of **57**. At this time NaH (50% dispersion, 0.30 g, 6.3 mmol, 3.00 equiv) and NaI (0.032 g, 0.21 mmol, 0.10 equiv) were added and the reaction was allowed to warm to room temperature over 1 h and then maintained at room temperature for an additional 3 h. The reaction was then heated to reflux for 18 h, after which time TLC and crude proton NMR confirmed product formation. The reaction was quenched with water (20 mL) and then extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Crude product was purified via flash column chromatography using 10% MeOH in EtOAc to afford **58** as a yellow oil (0.406 g, 57%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.36 (d, J = 5.1 Hz, 1H), 6.94 (d, J = 5.1 Hz, 1H), 5.92−5.73 (m, 2H), 5.16−4.88 (m, 4H), 3.82 (dd, J = 8.7, 6.3 Hz, 1H), 3.61−3.46 (m, 2H), 3.46−3.28 (m, 2H), 2.72−2.56 (m, 2H), 2.22−1.56 (m, 12H), 1.54−1.33 (m, 4H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.5, 151.0, 149.0, 147.7, 139.1, 137.9, 136.1, 122.9, 115.3, 114.6, 48.5, 47.6, 44.9, 33.9, 31.3, 31.2, 30.4, 30.2, 29.4, 28.9, 26.5, 22.0. HRMS (ESI) $C_{22}H_{33}N_2O$ $[M + H]^+$, calculated 341.2593, found 341.2611.

1(4,3)-Pyridina-2(3,1)-piperidinacyclododecaphan-2^2-one (59). Using the procedure described for the preparation of **36**, pyridine **58** (0.739 g, 2.17 mmol, 1.00 equiv), was subjected to RCM using the Zhan 1B catalyst (0.048 g, 0.065 mmol, 0.030 equiv), followed by quenching with di(ethylene glycol) vinyl ether (1.20 mL, 8.68 mmol, 4.00 equiv). The desired product (**vi**) was obtained as a yellow brown oil (0.630 g, 93%, mixture of E/Z diastereomers and rotamers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77−8.17 (m, 2H), 7.18−6.89 (m, 1H), 5.77−5.18 (m, 2H), 4.24−3.00 (m, 5H), 2.90−1.10 (m, 18H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.9, 169.7, 151.7, 147.9, 147.7, 147.6, 147.6, 147.5, 147.4, 147.3, 137.1, 136.6, 136.3, 131.0, 131.0, 130.7, 130.5, 130.2, 129.7, 125.2, 47.9, 47.2, 46.9, 45.3, 31.5, 31.3, 30.7, 30.2, 29.9, 29.8, 29.6, 28.7, 28.3, 27.8, 27.5, 27.5, 27.4, 26.8, 26.4, 26.2, 25.4, 25.2, 23.7, 23.5, 23.4. HRMS (ESI) $C_{20}H_{29}N_2O$ $[M + H]^+$, calculated 313.2280, found 313.2276. Compound **vi** was subjected to catalytic hydrogenation to reduce the macrocyclic alkene. The product from above was dissolved in EtOH (20 mL) and 10% Pd/C (0.060 g) was added and the solution placed under a H_2 atmosphere (100 psi) for 12h. The solution was filtered through Celite and the filtrate concentrated and purified via flash column chromatography using 20% MeOH in EtOAc to afford **59** as a yellow oil (0.472 g, 69% over 2 steps, mixture of atropisomers). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.50−8.41 (m, 1H), 8.37 (d, J = 5.1 Hz, 1H), 7.05 (d, J = 5.1 Hz, 1H), 3.70 (t, J = 8.6 Hz, 1H), 3.64−3.25 (m, 4H), 2.73−2.33 (m, 2H), 2.17−1.88 (m, 4H), 1.84−1.10 (m, 16H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 150.7, 150.6, 147.3, 147.3, 136.4 124.1, 47.5, 46.3, 30.1, 30.1, 28.7, 28.5, 27.6, 27.4, 26.9, 26.5, 26.4, 26.3, 25.7, 25.0, 23.4. HRMS (ESI) $C_{20}H_{31}N_2O$ $[M + H]^+$, calculated 315.2436, found 315.2433.

Bis(piperidine) Model Substrate (61). Pyridine **59** (0.200 g, 0.640 mmol, 1.00 equiv) was dissolved in THF (7 mL) and triethylamine (0.450 mL, 3.20 mmol, 5.00 equiv). Ethyl chloroformate (0.092 mL, 0.96 mmol, 1.50 equiv) was added and the mixture was heated to reflux for 30 min. After cooling, the Et_3NHCl formed as a byproduct of alkylidene dihydropyridine generation was filtered off and rinsed with EtOAc (this filtration was crucial to prevent rearomatization of the anhydrobase back to the starting pyridine during hydrogenation). The filtrate containing crude **60** was concentrated to remove most of the solvent and excess triethylamine. The ^{1}H NMR of the remaining residue confirmed the presence of **60** (500 MHz, $CDCl_3$, mixture of rotamers) δ 7.22 (br. s, 1H), 7.09 (br. s, 1H), 6.06 (br. s, 1H), 4.44−4.25 (m, 2H), 3.66−2.84 (m, 4H), 2.71−2.30 (m, 4H), 1.76−0.97 (m, 21H). LRMS (ESI) $C_{23}H_{35}N_2O_3$ $[M + H]^+$, calculated 387.3, found 387.3. Crude anhydrobase was redissolved in anhydrous THF (7 mL) and combined with 5% PtO_2 (0.010 g). The mixture was subjected to room temperature hydrogenation at 700 psi H_2 for 7 days. Then reaction was filtered to remove the catalyst and the concentrated filtrate was purified via flash column chromatography using 0−75% EtOAc in hexanes to afford **61** as a colorless oil. (0.105 g, 50%, mixture of rotamers/atropisomers). ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.58−4.43 (m, 1H), 4.40−4.01 (m, 4H), 3.58−3.44 (m, 0.5H), 3.38−3.30 (m, 0.5H), 3.26−3.16 (m, 0.5H), 3.16−3.07 (m, 0.5H), 2.88−2.66 (m, 2H), 2.66−2.53 (m, 1.5H), 2.55−2.40 (m, 1.5H), 2.11−2.01 (m, 1H), 2.01−1.91 (m, 1H), 1.91−1.82 (m, 1H), 1.82−1.01 (m, 25H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.9, 170.8, 156.1, 61.3, 61.2, 53.6, 50.5, 49.3, 48.9, 47.7, 47.6, 47.2, 47.0, 46.7, 46.4, 45.1, 44.9, 40.9, 40.2, 39.7, 35.7, 34.4, 29.9, 29.3, 27.6, 27.5, 27.0, 26.8, 26.7, 26.5, 26.4, 25.9, 25.7, 25.5, 25.3, 24.8, 24.7, 24.6, 24.4, 24.2, 24.2, 24.1, 23.96, 23.93, 23.6, 23.5, 22.9, 22.8, 22.0, 14.9, 14.9, 14.3. HRMS (ESI) $C_{23}H_{41}N_2O_3$ $[M + H]^+$, calculated 393.3117, found 393.3116.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b01269.

Details of X-ray crystallographic and 2D NMR experiments, 2D NMR analysis of **61**, copies of ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)

Crystal data (CIF)

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Notes

The authors declare no competing financial interest.

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