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Synthesis of Bridged Azabicyclic Structures via Ring-Closing Olefin Metathesis

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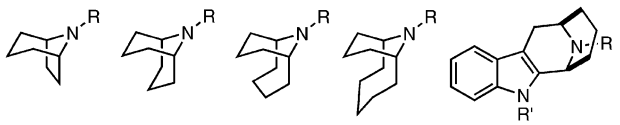
A new strategy for the facile synthesis of azabicyclo[*m*.*n*.1]alkenes ($m = 3-5$; $n = 3$, 2) has been developed that involves the ring-closing metathesis (RCM) reaction of *cis*-2,6-dialkenyl-*N*-acyl piperidine derivatives. The requisite 2,6-dialkenylpiperidines may be readily prepared in six steps starting from glutarimide (**11**) or three steps from 4-methoxypyridine (**25**). In one example that establishes the practical utility of the procedure, the functionalized 8-azabicyclo[3.2.1]octane **32**, which is a potential intermediate for the syntheses of various tropane alkaloids, was prepared. Additionally, a new route for the construction of the bridged tetrahydro-β-carboline ring system **5** has been developed that features the ring-closing metathesis of the enyne **45** to construct the bridging ring in **46**. This concise route to **46** also features a potentially general and useful procedure for the one-step preparation of a terminal alkyne from an ester function. Selective oxidation of the vinyl group in **46** afforded the unsaturated aldehyde **47**, which may serve as a useful intermediate in syntheses of several *Sarpagine* alkaloids.

Introduction

In the context of a longstanding interest in alkaloid synthesis, we became attracted to the problem of developing novel and general entries to the bridged bicyclic ring systems **1**−**4**. Each of these compounds is characterized by the presence of a nitrogen atom in the one-atom bridge of a [*n*.3.1] bicyclic core, a substructure that is commonly found in many biologically active nitrogen-containing natural and unnatural substances.[1] Such ring systems are found not only in simple substances such as the tropane alkaloids[1] but also in complex natural products such as the *Sarpagine* and *Ajmaline* alkaloids that possess the tetrahydro-β-carboline core structure **5**.[2] Owing to the importance of these ring systems, there has been considerable interest in the design of general and efficient methods for their synthesis.[3]



1 **2** **3** **4** **5**

Previous work in our laboratories established the efficacy of employing ring-closing metathesis (RCM) reactions for the construction of simple fused nitrogen heterocycles.[4,5] More recently we have applied RCM cyclizations to the synthesis of more complex targets such as dihydrocorynantheol[6] and the anticancer alkaloids manzamine A[7] and FR900482.[8] Other groups have also reported applications of RCM to preparing various fused bicyclic nitrogen heterocycles.[9] However, despite the extensive use of RCM reactions in organic synthesis, there are few applications to the synthesis of bridged azabicyclic,[10] carbobicyclic,[11] and oxabicyclic[12] frame-

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works. Indeed, when we began our studies in this area, there were no examples where RCM had been employed to prepare an azabicyclo[*n*.3.1]alkane with a nitrogen atom in the one-atom bridge, and we sought to address this significant deficiency. The details of our studies, some of which have been previously reported,[13] are presented herein. After this preliminary report, Kibayashi described the synthesis of an azabicyclo[3.3.1]-nonane via RCM.[14]

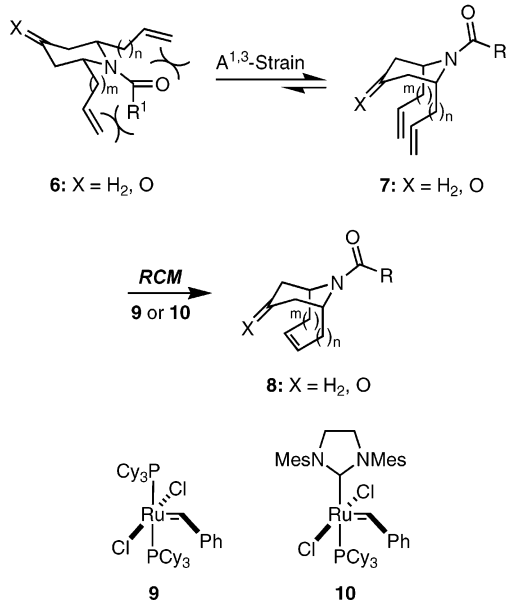
Results and Discussion

At the outset of our investigations, we reasoned that *cis*-2,6-disubstituted piperidines bearing an *N*-acyl group would be ideal candidates for cyclization via RCM. This hypothesis was based upon the well-known preference for such compounds to exist in the chair conformer **7**, wherein the substituents at the 2- and 6-positions are in axial orientations in order to avoid $A^{1,3}$-interactions with the *N*-acyl group that are present in the alternate chair conformer **6** (Scheme 1).[15] The two alkenyl groups in **7** are thus already properly disposed to undergo RCM in the presence of catalysts such as **9** and **10** to furnish the corresponding bridged azabicyclic compounds **8**.

To access a variety of bicyclic arrays of form **8**, it would be necessary to develop a general route to the intermediate *cis*-2,6-dialkenyl piperidines, and two such entries were devised. In the first of these, glutarimide (**11**) was selected as a starting material. Hydride reduction of **11** in the presence of acid followed by reaction of the resultant alkoxy lactam **12** with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ proceeded as described to provide the known lactam **14b** (Scheme 2).[16] We originally envisioned that **12** would serve as a suitable substrate for alkylations by unsaturated Grignard reagents to prepare **14a** and **14c**. Indeed, the groups of Coulton and Knaus have described related alkylations of 5-alkoxy-2-pyrrolidinones by reactions with Grignard reagents, including vinylmagnesium bromide.[17] However, no alkylation was observed upon treatment of **12** with vinylmagnesium bromide. When the reaction was conducted in the presence of $BF_3{\cdot}OEt_2$, some of the desired **14a** was isolated, but the yields of this reaction were low and irreproducible.

We were then inspired by the work of Petrini, who reported that acyclic α-sulfonyl amides reacted smoothly with vinylmagnesium bromide.[18] In this context, we queried whether a cyclic amino sulfone such as **13** might react with Grignard reagents to provide **14a** and **14c**. Toward this end, we found that **13** could be readily prepared in gram quantities by the reaction of crude **12** with sodium benzenesulfinate in the presence of formic acid. When **13** was treated with either vinylmagnesium bromide or 3-butenylmagnesium bromide, **14a** and **14c** were obtained in 74% and 63% yield, respectively. *N*-Acylation of **14a**−**c** with benzyl chloroformate (Cbz-Cl) provided the imides **15a**−**c** (74−92%). Hydride reduction of the lactam carbonyl groups of **15a**−**c** followed by stereoselective reaction of the crude *N*-acyl hemiaminals with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ then furnished inseparable mixtures (*cis*/*trans* = 16:1, 20:1, and 18:1, respectively) of the *cis*-2-allyl-6-alkenylpi-

SCHEME 1



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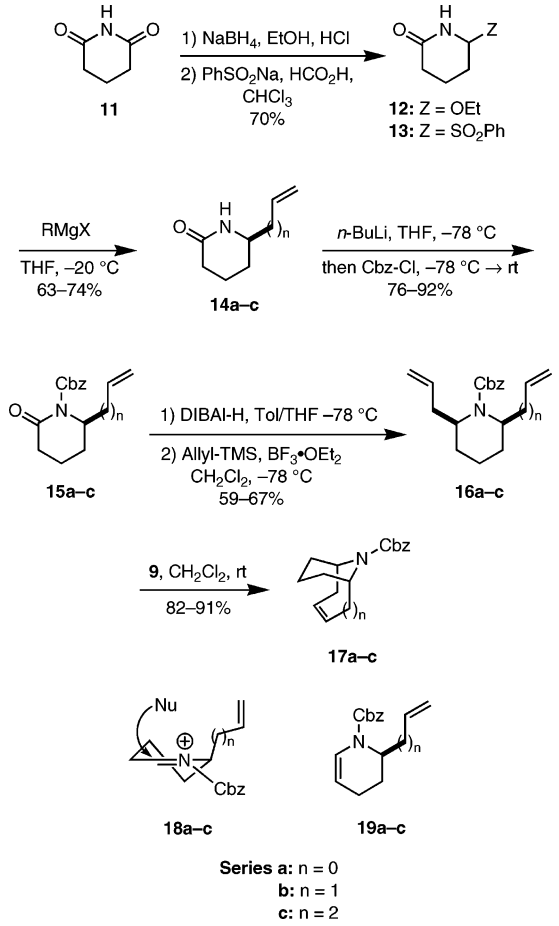
SCHEME 2



peridines **16a**−**c** and their corresponding *trans* isomers. The isomeric ratios were determined by ^{1}H NMR (500 MHz) at 100 °C. The high *cis*-stereoselectivity presumably arises from preferential axial attack of the nucleophile on the intermediates **18a**−**c** via chairlike transition states, wherein the substituent at C(6) is pseudoaxial to avoid A1,3-interactions with the *N*-acyl group.[19] A major byproduct in each of these reactions was the enamide **19a**−**c**, which was presumably generated by deprotonation of the *N*-acyliminium ion intermediate. Although it was not possible to separate **19a**−**c** from **16a**−**c** by chromatography, these enamides were selectively decomposed by simply warming the mixture to room temperature for 15 min following completion of the initial addition reaction, thus enabling isolation of pure **16a**−**c**.

The 2,6-dialkenylpiperidines **16a**−**c** underwent facile and efficient RCM at room temperature in the presence of the Grubbs catalyst **9** to give the corresponding bicyclic nitrogen heterocycles **17a**−**c** in 82−91% yield. These yields are based upon total amount of starting material, including the *trans* isomer, so the actual yields would be slightly higher. The cyclizations of 2,6-dialkenylpiperidines **16a,b** proceeded smoothly at substrate concentrations of 0.1 M, whereas the RCM of **16c** was efficient at 0.01 M.[20]

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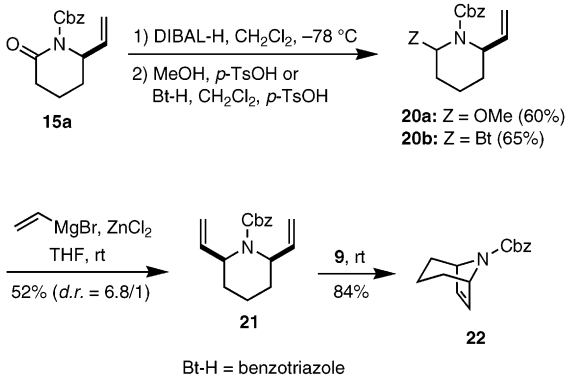
SCHEME 3



Having successfully applied RCM to the synthesis of several azabicyclo[*n*.3.1]alkanes, we turned our attention to preparing the 8-azabicyclo[3.2.1]octane or tropane ring system. Toward this end, **15a** was converted to **20a** in 60% yield by DIBAL-H reduction, followed by treatment of the crude hemiaminal with catalytic *p*-toluenesulfonic acid (*p*-TsOH) in MeOH (Scheme 3). Because organocopper reagents were known to add to piperidine-derived *N*-acyl iminium ions in the presence of BF_3•OEt_2,[21] we first examined the reaction of **20a** with the organocopper reagent derived from vinylmagnesium bromide, CuBr•SMe_2, and BF_3•OEt_2; however, the enamide **19a** was the only isolable product. Despite the precedent in related work of Comins,[22] we found that treatment of **19a** with vinylmagnesium bromide/zinc chloride in the presence of BF_3•OEt_2 led primarily to the enamide **19a**, and only small quantities of the desired **21** were obtained.

At this juncture, we decided to explore other precursors of the *N*-acyliminium ion. Our previous success with the use of **13** suggested that an α-sulfone derivative of the carbamate **20a** might be a viable intermediate. However, an initial attempt to prepare such a compound was not encouraging. This result was perhaps not surprising in retrospect in light of a report by Ley, who found that α-*N*-formyl- and α-*N*-tosylsulfones could be prepared in good yields but forming the related α-*N*-carboalkoxysulfones was less efficient.[23] We were thus attracted to the extensive work of Katritzky, who had shown that benzotriazole (Bt) was an excellent leaving group in reactions that proceeded via the intermediacy of *N*-acyliminium ions.[24] In the event, **15a** was reduced with DIBAL-H, and the intermediate hemiaminal was allowed to react directly with Bt-H in the presence of catalytic *p*-TsOH to provide **20b** in 66% yield as a complex mixture of diastereomers and benzotriazole regioisomers. This mixture was then treated with vinylmagnesium bromide/zinc chloride to give a mixture (*cis*/*trans* = 6.8:1) of adducts **21** in 52% total yield; the pure *cis* isomer was isolated in

(20) The RCM of **16c** and **21** at a substrate concentration of 0.1 M in methylene chloride and at room temperature also provided the corresponding products **17c** and **22**, albeit in lower yields of 67% and 64%, respectively.

(21) (a) Ludwig, C.; Wistrand, L. *Acta Chem. Scand.* **1990**, *44*, 707−710. (b) Ludwig, C.; Wistrand, L. *Acta Chem. Scand.* **1994**, *48*, 367−371.

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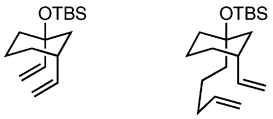
26% yield via flash chromatography. The enamide **19a** that was formed as a byproduct was simply destroyed prior to chromatography by treating the crude reaction mixture with $BF_3 \cdot OEt_2$ in methylene chloride. When **21** was exposed to the Grubbs catalyst **9** in CH_2Cl_2 at a substrate concentration of 0.01 M, the RCM proceeded smoothly at room temperature to give the tropane derivative **22**.[20]

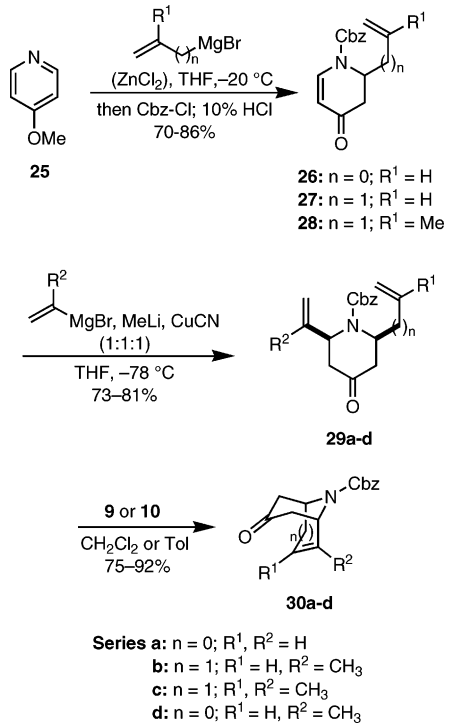
The facility with which the *cis*-2,6-dialkenyl-*N*-acyl piperidines **16a**−**c** and **21** underwent RCM is interesting as cyclizations of related carbocyclic systems are much less efficient. For example, Grubbs has recently studied cyclizations of **23** and **24**.[11d] The diene **23**, which is similar to **21**, underwent efficient cyclization via RCM catalyst **9** only at elevated temperatures and at a concentration of 0.005 M, but at higher concentrations significant quantities of polymer were formed. On the other hand, exposure of diene **24** to **9** led only to the formation of oligomeric products, irrespective of concentration. These results stand in marked contrast to the facile cyclizations of the corresponding nitrogen containing systems **16c** and **21**, which proceeded cleanly at room temperature and at substrate concentrations ranging up to 0.1 M.[20]



23 **24**

In the context of applying RCM to the synthesis of alkaloids and other biologically active nitrogen bicyclics, we were also interested in preparing more highly functionalized azabicyclo[*n*.3.1]alkanes. We were thus attracted to the reports of Comins, who has exploited the reactions of 4-methoxypyridine derivatives with organometallic reagents in the presence of chloroformates to access 2-piperidin-4-ones.[25] Thus, reaction of 4-methoxypyridine (**25**) with either vinylmagnesium bromide and Cbz-Cl or a suitable allylic Grignard reagent in the presence of zinc chloride and Cbz-Cl followed by hydrolysis of the intermediate methoxydiene gave the unsaturated 4-piperidones **26**−**28** in excellent yields (Scheme 4). When **26**−**28** were allowed to react with vinyl cuprates, inseparable mixtures of the *cis*-2,6-divinyl piperidines **29a**−**d** and their corresponding *trans* isomers were formed in good yield. The preferential transfer of the vinyl group rather than the methyl group in this reaction is noteworthy and similar to a report of Lipshutz.[26] The *cis*/*trans* ratios of **29a**−**d** were determined to be approximately 20:1, 14:1, 17:1, and 9:1, respectively, based on their ^{1}H NMR spectra (500 MHz) at 100 °C. Significantly, this route to *cis*-2,6-dialkenyl piperidin-4-ones nicely avoids the formation of enamides, a problem that had plagued our earlier work in which **19a**−**c** were formed as side products during the preparation of **16a**−**c**.

SCHEME 4



The cyclizations of the *cis*/*trans* mixtures of dienes **29a**−**d** in the presence of the RCM catalysts **9** and **10** were then examined. Although **29a** underwent RCM using **9** at room temperature, the corresponding cyclizations of **29b**−**d** with this catalyst were slow and inefficient. For example, RCM of **29d** provided **30d** in only 43% yield, even after prolonged heating at 40 °C and addition of further portions of **9**; significant quantities of starting **29d** remained even under these conditions. No cyclization of **29c** was observed when **9** was employed as the catalyst. When the more reactive RCM catalyst **10** was employed, however, cyclizations of **29b,d** proceeded readily at room temperature. To induce the cyclization of **29c**, it was necessary to conduct the reaction at 100 °C with multiple additions of catalyst **10** to give the tetrasubstituted alkene **30c** in 75% yield. It was also necessary to perform the cyclizations of **29b**−**d** at substrate concentrations of 0.01 M in order to avoid the formation of oligomeric products. Unreacted starting diene remaining after the RCM reaction was enriched in the *trans* isomer, as determined by ^{1}H NMR (500 MHz).

One of the driving forces for developing RCM as a useful device for preparing azabicyclo[*n*.3.1]alkanes lay in the possibility that such constructions could be applied to the synthesis of compounds of biological interest. In that context, the tropane alkaloids represented ideal targets, and the chemistry outlined in Scheme 4 appeared ideally suited to their synthesis. For example, we found that the copper enolate derived from conjugate addition of a vinyl cuprate to **26** could be trapped with methyl cyanoformate to give **31**, which existed predominantly as the enol tautomer according to NMR evidence (Scheme 5). Compound **31** underwent facile RCM to provide **32**, the conversion of which into cocaine (**33**), ferruginine (**34**), and other tropane derivatives may be envisioned.[27]

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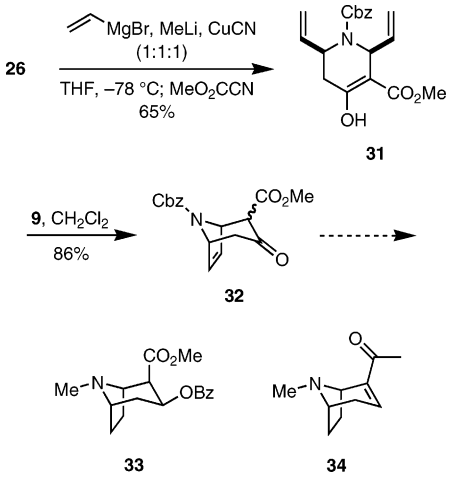
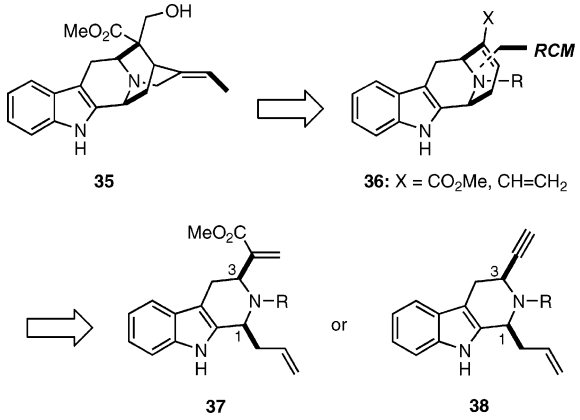
SCHEME 5



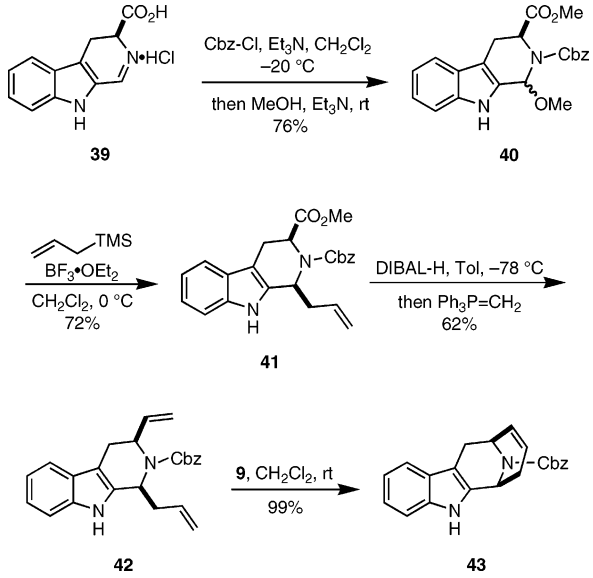
SCHEME 6



We have also been interested in developing novel approaches to more complex indole alkaloids of the *Sarpagine* family that incorporate the tetrahydro-β-carboline core structure **5**.[28] For example, one might envision tactics for the synthesis of the μ-selective opioid receptor agonist akuammidine (**35**) from **36** (Scheme 6).[29] The strategy would involve the construction of the azabicyclo[3.3.1]nonane ring system in **36** via RCM of an appropriately functionalized tetrahydro-β-carboline such as **37** or **38** that contains suitable unsaturated substituents in the 1 and 3 positions with *cis*-relative stereochemistry. While unsaturated esters were known to participate in RCM reactions, there were no reports of forming bridging six-membered rings by the RCM of alkenes bearing electron-withdrawing groups. Moreover, we were aware of only one example of an enyne RCM that produced a bridged carbobicyclic ring system.[11i]

To assess the viability of the projected RCM in a simple system, we first prepared **42** by the sequence of reactions

SCHEME 7



outlined in Scheme 7. The carboline **39**, which may be prepared in a single flask from L-tryptophan,[30] was converted into a diastereomeric mixture of aminals **40** (76% yield) via a one-pot procedure involving sequential treatment with Cbz-Cl and triethylamine and then MeOH. The subsequent reaction of **40** with allyltrimethylsilane in the presence of $BF_3 \cdot OEt_2$ provided a mixture (*cis*/*trans* $\approx$ 5.5:1) of adducts from which **41** could be isolated in 72% yield after chromatography. The methyl ester functionality of **41** was then transformed into the diene **42** in another one-pot procedure featuring a DIBAL-H reduction of the ester moiety followed by Wittig methylenation of the intermediate aldehyde. Gratifyingly, the diene **42** then underwent facile and efficient RCM in the presence of catalyst **9** to provide the desired tetrahydro-β-carboline **43** in nearly quantitative yield.

At the outset of these studies we wanted to develop a concise procedure for converting the ester group in **41** into an unsaturated ester as found in **37**. Unfortunately, we have not yet been able to invent an efficient method to accomplish this useful transformation. It was thus necessary to examine the feasibility of employing an enyne metathesis to prepare systems of the general type **36** that might be elaborated into *Sarpagine* alkaloids. Toward this objective, the methyl ester moiety of **41** was reduced with DIBAL-H, and the intermediate aldehyde was treated with the diazophosphonate reagent **44** in the presence of NaOMe to give the alkyne **45** in 55% yield (Scheme 7).[31] To our knowledge, this is the first example of combining these two reactions to provide a one-pot procedure for converting an ester into an alkyne. Subsequent exposure of **45** to the Grubbs catalyst **9** at room temperature under an atmosphere of ethene provided the enyne metathesis product **46** in 97% yield. The terminal olefin of **46** was then selectively cleaved by dihydroxylation with AD-mix-α,[32] followed by oxidation of the resultant crude diol with $NaIO_4$ to give the aldehyde **47** in 54% yield over the two steps. Compound **47** and

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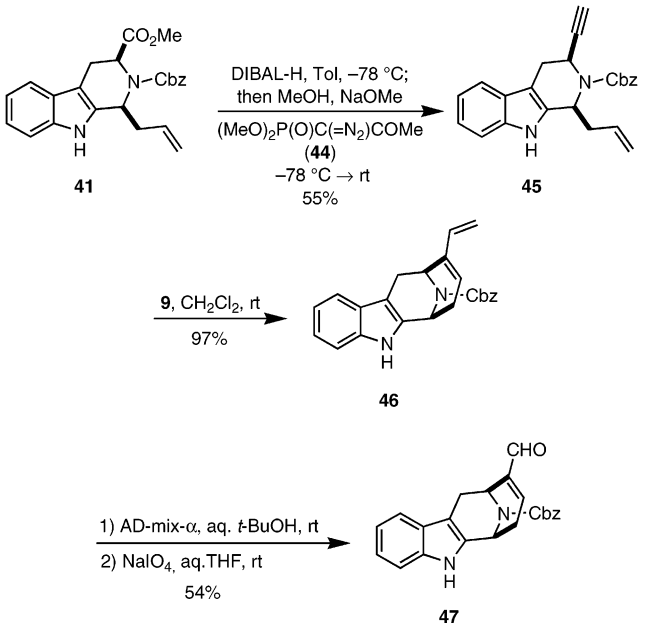
(31) (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561−564. (b) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521−522.

SCHEME 8



analogues thereof are expected to be useful intermediates for the synthesis of the complex alkaloids of the *Sarpagine* family.

Conclusions

A concise and general approach to the synthesis of azabicyclo[*m*.*n*.1]alkenes ($m = 3-5$; $n = 3$, 2) has been developed that features the RCM of 2,6-*cis*-dialkenyl piperidines, which were readily prepared from glutarimide or 4-methoxypyridine. The utility of this new entry to such bridged nitrogen heterocycles was then established by the preparation of the β-keto ester **32**, which is a potential precursor of a variety of tropane alkaloids such as cocaine and related biologically active compounds. Moreover, we developed a quick entry to the bridged tetrahydro-β-carboline structure **47**, a key structural subunit of the more complex indole alkaloids of the *Sarpagine* and *Ajmaline* families. The applications of this new methodology to the syntheses of a number of important alkaloid natural products is the subject of ongoing research in our laboratories, and the results of these investigations will be reported in due course.

Experimental Section

6-Benzenesulfonyl-2-piperidinone (13). $NaBH_4$ (832 mg, 22 mmol) was added in one portion to a stirred slurry of glutarimide (**11**) (1.0 g, 8.8 mmol) in EtOH (50 mL) at 4 °C (internal temp). A solution of 2 M HCl in EtOH (3−4 drops) was added every 15 min for 4 h. Ethanolic 2 M HCl (15 mL) was then cautiously added while maintaining the reaction temperature between 0 and 5 °C. The ice bath was removed, and stirring was continued for 12 h, whereupon the reaction was neutralized with 6 M NaOH (2 mL). The solvents were then removed under reduced pressure, and the resultant white solid was dried under high vacuum (0.1 mmHg) for 1 h. This solid was extracted with $CHCl_3$ (5 × 10 mL), and the combined organics were filtered under vacuum to give a solution of crude **12** to which was added $PhSO_2Na$ (2.89 g, 17.6 mmol) and 88% HCO_2H (0.83 mL, 18.8 mmol) with stirring. The mixture was stirred for 12 h at room temperature, whereupon saturated NaCl (10 mL) was added. The layers were separated, and the organic layer was dried (Na_2SO_4) and filtered. The solvent was removed under reduced pressure, and the crude solid was dried under high vacuum (0.1 mmHg) for 30 min, washed with Et_2O (2 × 5 mL), and then dried again under high vacuum (0.1 mm Hg) to give 1.48 g (70%) of **13** as a white solid: mp 135−137 °C; ^{1}H NMR δ 7.92−7.87 (m, 2 H), 7.75−7.69 (m, 1 H), 7.64−7.58 (m, 2 H), 6.19 (br s, 1 H), 4.49 (dt, $J = 8.5$, 6.2 Hz, 1 H), 2.36−1.60 (comp, 6 H); ^{13}C NMR δ 171.6, 134.8, 134.62, 134.56, 129.6, 72.3, 30.9, 21.4, 17.5; IR ($CHCl_3$) 3018, 1682, 1215 cm^{-1}; MS (CI) *m*/*z* 240.0701 [$C_{11}H_{13}NO_3S$ (M + 1) requires 240.0694], 240 (base), 138, 126.

Representative Procedure for Preparing 6-Alkenyl Lactams. Synthesis of 6-Ethenyl-2-piperidinone (14a). A 0.8 M solution of vinylmagnesium bromide in THF (7.84 mL, 6.3 mmol) was added dropwise over 2.5 min to a stirred solution of **13** (500 mg, 2.1 mmol) in THF (7 mL) at −78 °C (bath temp). The reaction mixture was then placed in an ice bath at −20 °C, and stirring was continued for 20 min, whereupon saturated $NaHCO_3$ (15 mL) was added. The ice bath was removed, and stirring was continued for 30 min. The solids were removed by vacuum filtration, and the filter cake was rinsed with $CHCl_3$ (3 × 10 mL). The combined filtrate and washings were transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with $CHCl_3$ (4 × 5 mL). The combined organic layers were washed with saturated NaCl (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 5% EtOH/EtOAc to give 195 mg (74%) of **14a** as a white solid. Compound **14a** has been prepared previously,[33] but no characterization was reported: mp 48−50 °C; ^{1}H NMR δ (CD_3OD) 5.83 (ddd, $J = 17.0$, 10.4, 6.0 Hz, 1 H), 5.20 (dt, $J = 14.9$, 1.3 Hz, 1 H), 5.15 (dt, $J = 7.9$, 1.3 Hz, 1 H), 3.97 (app q, $J = 6.0$ Hz, 1 H), 2.28 (app t, $J = 6.7$ Hz, 1 H), 2.27 (app t, $J = 6.7$ Hz, 1 H), 1.97−1.52 (comp, 4 H); ^{13}C NMR(CD_3OD) δ 175.1, 140.4, 116.1, 56.1, 31.9, 29.1, 19.3; IR ($CHCl_3$) 2997, 2955, 1657, 1464; MS (CI) *m*/*z* 126.0923 [$C_7H_{11}NO$ (M + 1) requires 126.0919], 156, 126 (base), 98, 89.

6-(3-Butenyl)-2-piperidinone (14c). Prepared as a white solid in 68% yield according to the procedure described above for **14a**. The ^{1}H and ^{13}C NMR spectra were consistent with those previously reported,[34] although not all spectral data was provided: mp 32−34 °C; ^{1}H NMR δ 5.97 (br s, 1 H), 5.76 (app ddt, $J = 16.9$, 10.2, 6.7 Hz, 1 H), 5.07−4.96 (m, 2 H), 3.40−3.31 (m, 1 H), 2.41−1.29 (comp, 10 H); ^{13}C NMR δ 172.5, 137.3, 115.1, 52.2, 35.6, 31.1, 29.3, 27.8, 19.4; IR ($CHCl_3$) 3397, 1654, 1215 cm^{-1}; MS (CI) *m*/*z* 154.1229 [$C_9H_{15}NO$ (M + 1) requires 154.1232], 154 (base), 182, 194.

2-Ethenyl-6-oxo-1-piperidinecarboxylic Acid Phenylmethyl Ester (15a). A 1.3 M solution of *n*-BuLi in hexanes (1.5 mL, 1.91 mmol) was added dropwise over 2.5 min to a stirred solution of **14a** (200 mg, 1.6 mmol) in THF (5.3 mL) at −78 °C (bath temp). Stirring was continued for 30 min, whereupon Cbz-Cl (0.450 mL, 3.2 mmol) was added dropwise over 30 s. The ice bath was removed, and the reaction was stirred for 1.5 h. Saturated aqueous NH_4Cl (5 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (3 × 3 mL), and the combined organic layers were washed with saturated NaCl (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 380 mg (92%) of **15a** as a clear, colorless oil: ^{1}H NMR δ 7.41−7.26 (comp, 5 H), 5.78 (ddd, $J =$ 17.2, 10.5, 4.6 Hz, 1 H), 5.24 (s, 2 H), 5.18 (dd, $J = 10.5$, 1.5

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Hz, 1 H), 5.09 (dd, J = 17.2, 1.8 Hz, 1 H), 4.90−4.86 (m, 1 H), 2.60−2.39 (m, 2 H), 2.00−1.66 (comp, 4 H); ^{13}C NMR δ (CD_3-OD) 174.0, 155.0, 139.0, 136.9, 129.5, 129.3, 129.2, 116.3, 69.5, 59.3, 35.1, 28.2, 17.9; IR ($CHCl_3$) 3016, 2957, 1768, 1716, 1378 cm^{-1}; MS (CI) m/z 260.1294 [$C_{15}H_{17}NO_3$ (M + 1) requires 260.1287], 260 (base), 216, 187, 126.

2-Oxo-6-(2-propenyl)-1-piperidinecarboxylic Acid Phenylmethyl Ester (15b). A 1.3 M solution of *n*-BuLi in hexanes (2.5 mL, 3.3 mmol) was added dropwise over 2.5 min to a stirred solution of **14b**[16] (380 mg, 2.8 mmol) in THF (9.2 mL) at −78 °C (bath temp). Stirring was continued for 1 h, whereupon Cbz-Cl (0.79 mL, 5.5 mmol) was added dropwise over 1 min. The ice bath was removed, the reaction was stirred for 3 h, and saturated aqueous NH_4Cl (5 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with saturated NaCl (5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 637 mg (85%) of **15b** as a clear, colorless oil: ^{1}H NMR δ 7.43−7.29 (comp, 5 H), 5.74−5.60 (m, 1 H), 5.26 (s, 2 H), 5.08−5.06 (m, 1 H), 5.04−5.00 (m, 1 H), 4.36−4.27 (m, 1 H), 2.54−2.44 (m, 2 H), 2.30−2.20 (m, 2 H), 1.94−1.74 (comp, 4 H); ^{13}C NMR δ 171.5, 154.2, 135.3, 133.6, 128.5, 128.2, 128.0, 118.2, 68.4, 55.4, 38.2, 34.4, 25.1, 16.7; IR ($CHCl_3$) 3070, 3018, 2956, 1765, 1712 cm^{-1}; MS (CI) m/z 274.1444 [$C_{16}H_{19}NO_3$ (M + 1) requires 274.1443], 274 (base), 177, 153.

2-(3-Butenyl)-6-oxo-1-piperidinecarboxylic Acid Phenylmethyl Ester (15c). A 1.3 M solution of *n*-BuLi in hexanes (0.600 mL, 0.78 mmol) was added dropwise over 1 min to a stirred solution of **14c** (100 mg, 0.65 mmol) in THF (2.2 mL) at −78 °C (bath temp). After stirring for 1.5 min, HMPA (0.110 mL, 0.65 mmol) was added. Cbz-Cl (0.187 mL, 1.3 mmol) was then added dropwise over 45 s, the ice bath was removed, and the reaction was stirred for 5 h. Saturated aqueous NH_4Cl (2 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 1 mL), and the combined organic layers were washed with saturated NaCl (1 × 1 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 139 mg (74%) of **15c** as a clear, colorless oil: ^{1}H NMR δ 7.42−7.27 (comp, 5 H), 5.71 (app ddt, J = 16.8, 10.4, 6.6, 1 H), 5.27 (d, J = 13.3 Hz, 1 H), 5.23 (d, J = 13.3 Hz, 1 H), 5.02−4.92 (m, 2 H), 4.32−4.24 (m, 1 H), 2.58−2.42 (m, 2 H), 2.14−1.53 (comp, 8 H); ^{13}C NMR δ 171.5, 154.1, 137.0, 135.3, 128.4, 128.1, 127.9, 115.2, 68.3, 55.4, 34.2, 32.6, 30.1, 25.1, 16.7; IR ($CHCl_3$) 3027, 2956, 1764, 1713, 1453 cm^{-1}; MS (CI) m/z 288.1593 [$C_{17}H_{21}NO_3$ (M + 1) requires 288.1600], 288, 188, 152, 138, 91 (base).

Representative Procedure for Preparing *cis*-2,6-Dialkenyl-*N*-acyl Piperidines. Synthesis of *cis*-2,6-Di-2-propenyl-1-piperidinecarboxylic Acid Phenylmethyl Ester (16b). A 1 M solution of DIBAL-H in toluene (14.0 mL, 14.0 mmol) was added dropwise over 35 min to a stirred solution of **15b** (1.2 g, 4.5 mmol) in THF (23 mL) at −78 °C (bath temp). Stirring was continued for 45 min, whereupon MeOH (0.90 mL, 23 mmol) was added dropwise over 15 min. The reaction was poured into saturated Rochelle's salt (35 mL) with vigorous stirring. Stirring was continued for 1 h, and then the layers were separated. The aqueous layer was extracted with EtOAc (4 × 10 mL), and the combined organic layers were washed with saturated NaCl (1 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residual solvent was removed under high vacuum (0.1 mmHg) for 1 h. The resulting pale yellow oil was dissolved in CH_2Cl_2 (23 mL) under argon and cooled to −78 °C (bath temp). Allyltrimethylsilane (3.6 mL, 23 mmol) was added in one portion with stirring, and then $BF_3{\cdot}OEt_2$ (2.6 mL, 23 mmol) was added dropwise over 8 min. Stirring was continued for 1 h, whereupon the ice bath was removed and the reaction stirred for an additional 15 min. The reaction was poured slowly into a stirred solution of saturated $NaHCO_3$ (25 mL) and saturated NaCl (10 mL; **caution**: *vigorous* gas evolution). The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with saturated NaCl (1 × 10 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 830 mg (61%) of **16b** as a clear, colorless oil and as an inseparable mixture (20:1) of *cis*/*trans* diastereomers (based on 500 MHz ^{1}H NMR at 100 °C): ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.37−7.28 (comp, 5 H), 5.73 (dddd, J = 17.2, 10.2, 7.1, 6.7 Hz, 2 H), 5.09 (s, 2 H), 5.03 (app ddt, J = 17.2, 2.0, 1.6 Hz, 1 H), 4.99 (app ddt, J = 10.2, 2.0, 1.1 Hz, 1 H), 4.20−4.16 (m, 2 H), 3.86−3.82 (m, 0.05 H), 2.37−2.26 (m, 4 H), 1.72−1.37 (comp, 6 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.6, 136.6, 135.6, 127.7, 127.1, 126.9, 115.9, 65.7, 49.6, 38.1, 37.5, 26.0, 23.6, 13.1; IR ($CHCl_3$) 2945, 2862, 1680 cm^{-1}; MS (CI) m/z 300.1969 [$C_{19}H_{25}NO_2$ (M + 1) requires 300.1964], 300, 177, 121 (base).

***cis*-2-Ethenyl-6-(2-propenyl)-1-piperidinecarboxylic Acid Phenylmethyl Ester (16a).** Prepared in 67% yield as a clear, colorless oil and as an inseparable mixture (16:1) of *cis*/*trans* diastereomers (based on 500 MHz ^{1}H NMR at 100 °C) according to the procedure shown above for **16b**: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38−7.28 (comp, 5 H), 5.95 (ddd, J = 17.4, 10.6, 5.4 Hz, 1 H), 5.70 (app ddt, J = 17.2, 10.2, 7.0 Hz, 1 H), 5.15−4.96 (comp, 6 H), 4.74−4.71 (m, 1 H), 4.42−4.38 (m, 0.06 H), 4.25−4.20 (m, 1 H), 3.92−3.88 (m, 0.06 H), 2.33−2.24 (m, 2 H), 1.90−1.38 (comp, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 139.6, 136.9, 136.1, 128.4, 127.82, 127.76, 116.9, 114.9, 67.0, 51.6, 50.7, 38.5, 27.5, 26.7, 14.2; IR ($CHCl_3$) 3009, 2945, 2890, 1683, 1411 cm^{-1}; MS (CI) m/z 286.1809 [$C_{18}H_{23}NO_2$ (M + 1) requires 286.1807], 286 (base), 244, 178.

***cis*-2-(3-Butenyl)-6-(2-propenyl)-1-piperidinecarboxylic Acid Phenylmethyl Ester (16c).** Prepared in 59% yield as a clear, colorless oil and as an inseparable mixture (18:1) of *cis*/*trans* diastereomers (based on 500 MHz ^{1}H NMR at 100 °C) according to the procedure shown above for **16b**: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38−7.28 (comp, 5 H), 5.78 (app ddt, J = 17.0, 13.1, 6.6 Hz, 1 H), 5.73 (app ddt, J = 17.2, 10.2, 7.0 Hz, 1 H), 5.08 (s, 2 H), 5.05−4.89 (comp, 4 H), 4.22−4.18 (m, 1 H), 4.15−4.11 (m, 1 H), 3.82−3.75 (m, 0.06 H), 2.35−2.25 (m, 2 H), 2.09−2.01 (m, 1 H), 1.99−1.91 (m, 1 H), 1.70−1.48 (comp, 7 H), 1.42−1.36 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.9, 138.2, 136.9, 136.1, 128.4, 127.8, 116.9, 114.6, 66.9, 50.2, 39.1, 33.8, 31.6, 27.3, 26.8, 14.0; IR ($CHCl_3$) 3018, 2944, 1679, 1416 cm^{-1}; MS (CI) m/z 314.2129 [$C_{20}H_{27}NO_2$ (M + 1) requires 314.2120], 314 (base), 272, 258, 206.

***cis*-2,6-Diethenyl-1-piperidinecarboxylic Acid Phenylmethyl Ester (21).** A 1 M solution of DIBAL-H in toluene (9.3 mL, 9.3 mmol) was added dropwise with stirring over 7 min to a solution of **15a** (800 mg, 3.1 mmol) in THF (16 mL) at −78 °C (bath temp). Stirring was continued for 1 h, whereupon MeOH (0.63 mL, 16 mmol) was added dropwise over 10 min. The ice bath was removed, saturated Rochelle's salt (25 mL) was added, and the mixture was stirred vigorously for 1 h. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with saturated NaCl (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was dried under high vacuum (0.1 mmHg) for 1 h. The resulting pale yellow oil was dissolved in CH_2Cl_2 (16 mL), and benzotriazole (1.8 mg, 16 mmol) was added. The mixture was stirred for 5 min at room temperature, and *p*-TsOH·H_2O (59 mg, 0.31 mmol) was added. Stirring was continued for 1.5 h, whereupon saturated $NaHCO_3$ (5 mL) was added. The layers were separated, and the organic layer was washed with saturated NaCl (1 × 3 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 722 mg (65%) of **20a,b** as a clear, colorless oil that was used in the next step without further purification: MS (CI; minor isomer) m/z 363.1831 [$C_{21}H_{22}N_4O_2$ (M + 1) requires 363.1821], 200, 244 (base), 363; MS (CI; major

isomer) *m*/*z* 363.1818 [$C_{21}H_{22}N_4O_2$ (M + 1) requires 363.1821], 200, 244 (base), 279, 363.

A slurry of $ZnCl_2$ (536 mg, 3.9 mmol) in THF (4 mL) was added dropwise over 1 min with stirring to a solution of 0.8 M vinylmagnesium bromide in THF (2.5 mL) at 0 °C (bath temp). The ice bath was removed, and the mixture was stirred for 1 h. A solution of **20a,b** (236 mg, 0.66 mmol) in THF (1.3 mL) was then added dropwise, and stirring was continued for 24 h. Saturated $NaHCO_3$ (5 mL) was added, and the solids were removed by vacuum filtration through a pad of Celite. The layers in the filtrate were separated, and the aqueous layer was extracted with EtOAc (4 × 1 mL). The combined organic layers were washed with saturated NaCl (1 × 1 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was dried under high vacuum for 5 min. The residue was dissolved in CH_2Cl_2 (7 mL), and $BF_3{\cdot}OEt_2$ (0.15 mL, 1.3 mmol) was added with stirring. Stirring was continued for 10 min, whereupon saturated $NaHCO_3$ (2 mL) was added. The layers were separated, and the organic layer was washed with saturated NaCl (1 × 1 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 5% EtOAc/hexanes to give 47 mg (26%) of pure **21** as a clear colorless oil; 47 mg (26%) of a mixture (2.9:1) of **21** and its *trans* isomer was also obtained: ^{1}H NMR (400 MHz; *cis*-isomer) δ 7.34−7.26 (comp, 5 H), 5.95 (ddd, J = 17.0, 10.5, 6.4 Hz, 2 H), 5.14 (s, 2 H), 5.10−5.04 (m, 4 H), 4.82−4.77 (m, 2 H), 1.88−1.47 (comp, 6 H); ^{13}C NMR (400 MHz; *cis*-isomer) δ 155.3, 138.7, 136.4, 128.0, 127.5, 127.4, 115.0, 67.1, 52.8, 28.7, 15.3; IR (film; *cis*-isomer) 3080, 3032, 2942, 2869, 1694, 1498, 1449, 1402, 1317 cm^{-1}; MS (CI; *cis*-isomer) *m*/*z* 272.1646 [$C_{17}H_{21}NO_2$ (M + 1) requires 272.1651], 164, 228, 272 (base), 300.

2-Ethenyl-3,4-dihydro-4-oxo-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (26). A solution of 0.8 M vinylmagnesium bromide in THF (5.91 mL, 4.7 mmol) was added dropwise over 2 min to a stirred solution of 4-methoxypyridine (0.43 g 0.40 mL, 3.9 mmol) in THF (3.9 mL) at −78 °C (bath temp). The reaction was cooled to −20 °C (bath temp), whereupon Cbz-Cl (0.84 mL, 5.9 mmol) was added dropwise. The mixture was stirred for 20 min, whereupon 10% HCl (6 mL) was added. The ice bath was removed, and stirring was continued for an additional 10 min. The layers were separated, and the aqueous layer was extracted with Et_2O (4 × 2 mL). The combined organic layers were washed with 1 M NaOH (1 × 2 mL) and saturated NaCl (1 × 2 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography eluting with 30% EtOAc/hexanes to give 865 mg (86%) of **26** as a clear, colorless oil. This compound has been prepared previously,[35] but no experimental data or spectral characterization were provided: ^{1}H NMR δ 7.79 (br d, J = 8.7 Hz, 1 H), 7.40−7.34 (comp, 5 H), 5.79 (ddd, J = 16.8, 10.4, 5.1 Hz, 1 H), 5.31 (d, J = 8.7 Hz, 1 H), 5.27 (d, J = 11.2 Hz, 1 H), 5.23 (d, J = 11.2 Hz, 1 H), 5.20 (d, J = 10.4 Hz, 1 H), 5.13 (d, J = 16.8 Hz, 1 H), 5.12 (br s, 1 H), 2.89 (dd, J = 16.5, 6.8 Hz, 1 H), 2.53 (br d, 16.5 Hz, 1 H); ^{13}C NMR δ 192.1, 152.4, 141.4, 134.8, 132.6, 128.74, 128.68, 128.4, 117.5, 107.5, 69.1, 54.6, 39.8; IR ($CHCl_3$) 3031, 3011, 1726, 1666, 1606, 1333, 1300 cm^{-1}; MS (CI) *m*/*z* 258.1127 [$C_{15}H_{15}NO_3$ (M + 1) requires 258.1807], 298, 286, 258 (base), 214.

Representative Procedure for Preparing 2-Allyl-3,4-dihydro-1(2*H*)-*N*-acyl Piperidinones. Synthesis of 2-(2-Propenyl)-4-oxo-3,4-dihydro-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (27). $ZnCl_2$ (403 mg, 3.0 mmol) was melted under high vacuum (0.4 mmHg) with flame. After 10 min, the $ZnCl_2$ was melted once again and allowed to stand for another 10 min, whereupon THF (3 mL) was added. The resulting solution was cooled to 0 °C (bath temp) with stirring, and a solution of 2 M allylmagnesium chloride in THF (0.74 mL, 1.5 mmol) was added dropwise. The ice bath was removed, and stirring was continued for 1 h. The resulting white slurry was cooled to −20 °C (bath temp), whereupon 4-methoxypyridine (0.11 g, 0.1 mL, 1 mmol) was added dropwise over 30 s. After 10 min of stirring, Cbz-Cl (0.21 mL, 1.5 mmol) was added dropwise, and the mixture was stirred for 20 min. Aqueous 10% HCl (3 mL) and EtOAc (1 mL) were then added, and the layers were separated. The organic layer was washed with saturated NaCl (1 × 1 mL), and the aqueous layers were combined and extracted with EtOAc (4 × 1 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 × 1 mL), saturated NaCl (1 × 1 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography eluting with 40% EtOAc/hexanes to give 206 mg (77%) of **27** as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.78 (dd, J = 8.3, 1.5 Hz, 1 H), 7.43−7.34 (comp, 5 H), 5.74−5.66 (m, 1 H), 5.27 (s, 2 H), 5.25 (dd, J = 8.4, 1.4 Hz, 1 H), 5.00 (app t, J = 1.1 Hz, 1 H), 4.99−4.96 (m, 1 H), 4.62 (app ddt, J = 14.3, 6.8, 1.6 Hz, 1 H), 2.84 (dd, J = 16.7, 6.8 Hz, 1 H), 2.39−2.28 (comp, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 191.0, 151.7, 140.8, 135.0, 133.0, 127.9, 127.7, 127.4, 117.5, 106.4, 67.8, 52.0, 38.8, 34.4; IR ($CHCl_3$) 3018, 1725, 1666, 1604, 1427, 1386 cm^{-1}; MS (CI) *m*/*z* 272.1281 [$C_{16}H_{17}NO_3$ (M + 1) requires 272.1287], 157, 186, 201, 228, 256, 272 (base), 362.

2-(2-Methyl-propenyl)-4-oxo-3,4-dihydro-1(2*H*)-pyridinecarboxylic Acid Phenylmethyl Ester (28). Prepared as white solid in 70% yield using 2-methylallylmagnesium chloride according to the procedure described above for **27**: mp 42−44 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.79 (dd, J = 8.3, 1.6 Hz, 1 H), 7.43−7.30 (comp, 5 H), 5.27 (d, J = 1.4 Hz, 1 H), 5.26 (s, 2 H), 4.76 (app p, J = 1.6 Hz, 1 H), 4.72−4.67 (m, 1 H), 4.60−4.59 (m, 1 H), 2.83 (dd, J = 16.6, 6.6 Hz, 1 H), 2.31 (br dd, J = 12.6, 7.2, 1 H), 2.30 (app dt, J = 16.6, 1.5 Hz, 1 H), 2.21 (ddd, J = 13.4, 8.4, 0.7, 1 H), 1.66 (t, J = 1.0 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 191.1, 151.6, 140.7, 140.4, 135.0, 127.9, 127.7 127.5, 113.4, 106.4, 67.8, 50.8, 38.6, 37.7, 21.2; IR ($CHCl_3$) 3019, 1724, 1668, 1605, 1426, 1385, 1328 cm^{-1}; MS (CI) *m*/*z* 286.1441 [$C_{17}H_{19}NO_3$ (M + 1) requires 286.1443], 242, 270, 286 (base), 314, 326.

Representative Procedure for Preparing *cis*-2,6-Dialkenyl-*N*-acyl Piperidinones. Synthesis of *cis*-2,6-Diethenyl-4-oxo-1-piperidinecarboxylic Acid Phenylmethyl Ester (29a). A solution of 1.2 M MeLi in Et_2O (1.46 mL, 1.75 mmol) was added dropwise over 2 min to a stirred slurry of CuCN (157 mg, 1.75 mmol) in THF (2.7 mL) at −78 °C (bath temp). The reaction was placed in a 0 °C bath, stirred for 1 min, and then cooled to −78 °C (bath temp). A solution of 0.8 M vinylmagnesium bromide in THF (2.19 mL, 1.75 mmol) was then added dropwise over 4 min. The mixture was stirred for 10 min, whereupon a solution of **26** (300 mg, 1.17 mmol) in THF (0.6 mL) was added dropwise. The resulting orange slurry was stirred for 6 h, whereupon the mixture was poured into a vigorously stirred mixture (9:1) of saturated NH_4Cl/NH_4OH (9 mL; **caution**: exotherm). Stirring was continued for 8 h, and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 3 mL). The combined organic layers were washed with saturated NaCl (1 × 3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 243 mg (73%) of **29a** as a clear, colorless oil and as an inseparable mixture (20:1) of *cis*/*trans* diastereomers (based on ^{1}H NMR at 300 MHz): ^{1}H NMR δ 7.36−7.30 (comp, 5 H), 5.88 (ddd, J = 17.0, 10.6, 6.2 Hz, 2 H), 5.17−5.11 (comp, 8 H), 2.90−2.80 (m, 0.13 H), 2.64 (d, J = 5.6 Hz, 4 H), 2.60−2.50 (m, 0.13 H); ^{13}C NMR δ 206.5, 155.5, 138.6, 136.1, 128.5, 128.1, 128.0, 116.4, 67.7, 53.9, 42.8; IR ($CHCl_3$) 2991, 2915, 1722, 1692, 1406; MS (CI) *m*/*z* 286.1443 [$C_{17}H_{19}NO_3$ (M + 1) requires 286.1443], 286 (base), 268, 242.

2-(1-Methylethenyl)-6-(2-propenyl)-4-oxo-1-piperidinecarboxylic Acid Benzyl Ester (29b). Prepared from **27**

(35) Comins, D. L.; Brooks, C., A.; Ingalls, C. L. *J. Org. Chem.* **2001**, *66*, 2181−2182.

using 2-propenylmagnesium bromide in 81% yield as a clear, colorless oil and as an inseparable mixture (14:1) of *cis*/*trans* diastereomers (based on ^{1}H NMR at 500 MHz) according to the procedure described above for **29a**: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.39−7.29 (m, 5 H), 5.76−5.68 (m, 1 H), 5.17 (d, J = 12.5 Hz, 1 H), 5.14 (d, J = 12.5 Hz, 1 H), 5.05−5.00 (m, 2 H), 4.96 (br t, J = 5.9 Hz, 1 H), 4.90−4.87 (m, 2 H), 4.76−4.68 (m, 0.07 H), 4.55 (dddd, J = 8.7, 7.2, 6.4, 5.2 Hz, 1 H), 4.34−4.28 (m, 0.07 H), 2.72 (ddd, J = 16.8, 5.9, 0.7 Hz, 1 H), 2.68 (dd, J = 16.8, 5.9 Hz, 1 H), 2.63 (dd, J = 16.4, 7.2 Hz, 1 H), 2.56−2.50 (m, 1 H), 2.38 (dd, J = 5.2 Hz, 16.4, 1 H), 2.27 (app dddt, J = 14.1, 7.7, 6.4, 1.3 Hz, 1 H), 1.72 (t, J = 0.6 Hz, 3 H), 1.67 (t, J = 0.6 Hz, 0.21 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.7, 154.9, 145.8, 141.3, 136.1, 127.7, 127.2, 127.1, 112.3, 111.2, 66.4, 66.1, 55.1, 50.4, 43.6, 43.1, 41.51, 41.45, 40.9, 21.1, 21.0, 19.5; IR ($CHCl_3$) 3079, 3034, 2975, 1717, 1689, 1455, 1409, 1323 cm^{-1}; MS (CI) m/z 328.1909 [$C_{19}H_{23}NO_3$ (M + 1) requires 328.1913], 182, 228, 272, 284, 328 (base).

2-(1-Methylethenyl)-6-(2-methyl-2-propenyl)-4-oxo-1-piperidinecarboxylic acid benzyl ester (29c). Prepared from **28** using 2-propenylmagnesium bromide in 77% yield as a clear, colorless oil and as an inseparable mixture (17:1) of *cis*/*trans* diastereomers (based on ^{1}H NMR at 500 MHz) according to the procedure described above for **29a**: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.39−7.30 (m, 5 H), 5.17 (d, J = 12.5 Hz, 1 H), 5.14 (d, J = 12.5 Hz, 1 H), 4.97 (br t, J = 5.9 Hz, 1 H), 4.91−4.67 (comp, 4 H), 4.67 (app ddt, J = 10.1, 7.2, 4.7 Hz, 1 H), 2.73 (ddd, J = 16.6, 5.9, 0.6 Hz, 1 H), 2.69 (ddd, J = 16.6, 5.9, 0.6 Hz, 1 H), 2.61 (dd, J = 16.3, 7.2 Hz, 1 H), 2.49 (dd, J = 13.4, 4.7 Hz, 1 H), 2.35 (ddd, J = 16.3, 4.7, 0.6 Hz, 1 H), 2.21 (ddd, J = 13.4, 10.1, 0.8 Hz, 1 H), 2.17−2.12 (m, 0.06 H), 1.72 (app dt, J = 1.4, 0.7 Hz, 3 H), 1.68−1.66 (comp, 0.36 H), 1.66 (t, J = 0.7 Hz, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.7, 154.9, 145.8, 141.3, 136.1, 127.7, 127.2, 127.1, 112.3, 111.2, 66.4, 66.1, 55.1, 50.4, 43.6, 43.1, 41.51, 41.45, 40.9, 21.1, 21.0, 19.5; IR ($CHCl_3$) 3079, 3034, 2975, 1717, 1689, 1455, 1409, 1323 cm^{-1}; MS (CI) m/z 328.1909 [$C_{20}H_{25}NO_3$ (M + 1) requires 328.1913], 182, 228, 272, 284, 328 (base).

2-Ethenyl-6-(1-methylethenyl)-4-oxo-piperidine-1-carboxylic Acid Phenylmethyl Ester (29d). Prepared from **26** using 2-propenylmagnesium bromide in 78% yield as a clear, colorless oil and as an inseparable mixture (9:1) of *cis*/*trans* diastereomers (based on ^{1}H NMR at 500 MHz) according to the procedure described above for **29a**: ^{1}H NMR (500 MHz, toluene-d_8, 100 °C) δ 7.06−6.96 (comp, 5 H), 5.80 (ddd, J = 17.1, 10.5, 6.5 Hz, 1 H), 5.63 (ddd, J = 17.3, 10.6, 4.5 Hz, 0.1 H), 5.05 (s, 2 H), 5.04 (d, J = 12.5 Hz, 0.1 H), 5.01 (d, J = 12.5 Hz, 0.1 H), 4.95 (app dt, J = 17.1, 1.3 Hz, 1 H), 4.93 (app dddt, J = 7.5, 6.5, 5.0, 1.3 Hz, 1 H), 4.90−4.87 (m, 0.2 H), 4.82 (app dt, J = 10.5, 1.3 Hz, 1 H), 4.81−4.77 (m, 1 H, C6−H), 4.79 (br d, J = 0.7 Hz, 1 H), 4.75−4.72 (m, 0.1 H), 4.70 (app q, J = 1.3 Hz, 0.1 H), 4.67 (app dq, J = 1.4, 0.7 Hz, 1 H), 4.62 (br t, J = 6.7 Hz, 0.1 H), 2.59 (dd, J = 17.4, 6.7 Hz, 0.1 H), 2.47 (ddd, J = 16.5, 5.0, 0.7 Hz, 1 H), 2.35 (dd, J = 17.4, 2.4 Hz, 0.1 H), 2.33 (ddd, J = 16.5, 5.0, 0.7 Hz, 1 H), 2.18 (ddd, J = 16.5, 7.5, 0.7 Hz, 1 H), 2.17 (ddd, J = 16.5, 6.5, 0.7 Hz, 1 H), 1.56 (app dt, J = 1.4, 0.7 Hz, 3 H), 1.46 (app dt, J = 1.4, 0.7 Hz, 0.3 H); ^{13}C NMR (125 MHz, toluene-d_8, 100 °C) δ 204.1, 156.4, 146.8, 139.4, 137.9, 129.4, 128.7, 128.5, 137.9, 116.2, 115.1, 112.7, 111.4, 68.2, 67.9, 57.0, 55.1, 53.7, 43.4, 42.9, 42.5, 20.6; IR ($CHCl_3$) 3018, 1719, 1692, 1453, 1406; MS (CI) m/z 300.1594 [$C_{18}H_{21}NO_3$ (M + 1) requires 300.1600], 300 (base), 256, 177.

4-Hydroxy-2,6-diethenyl-5,6-dihydro-1,3(2*H*)-pyridinedicarboxylic Acid 3-Methyl Ester 1-Phenylmethyl Ester (31). A solution of 1.2 M MeLi in Et_2O (1.46 mL, 1.75 mmol) was added dropwise over 2 min to a stirred slurry of CuCN (157 mg, 1.75 mmol) in THF (2.7 mL) at −78 °C (bath temp). The mixture was cooled to 0 °C (bath temp), stirred for 1 min, and then recooled to −78 °C (bath temp). A solution of 0.8 M vinylmagnesium bromide in THF (2.19 mL, 1.75 mmol) was added dropwise. The reaction was stirred for 10 min, whereupon a solution of **26** (300 mg, 1.17 mmol) in THF (0.6 mL) was added dropwise. The resulting orange slurry was stirred for 6 h, whereupon MeO_2CCN (0.46 mL, 5.8 mmol) was added dropwise. The ice bath was removed, and stirring was continued for 30 min at room temperature. The reaction was poured into a vigorously stirred mixture (9:1) of saturated NH_4Cl/NH_4OH (9 mL; **caution**: exotherm), and stirring was continued for 30 min. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 3 mL). The combined organic layers were washed with saturated NaCl (1 × 3 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 5% EtOAc/hexanes to give 261 mg (65%) of **31** as a clear, colorless oil and as an inseparable mixture (15:1) of *cis*/*trans* diastereomers (based on ^{1}H NMR at 300 MHz): ^{1}H NMR (500 MHz) δ 12.27 (br s, 1 H), 7.37−7.28 (comp, 5 H), 5.87 (ddd, J = 17.0, 10.5, 6.6 Hz, 1 H), 5.83 (ddd, J = 16.5, 10.3, 6.1 Hz, 1 H), 5.46 (br s, 1 H), 5.20−4.80 (comp, 5 H), 5.18 (d, J = 12.4 Hz, 1 H), 5.14 (d, J = 12.4 Hz, 1 H), 3.73 (s, 3 H), 2.70−2.65 (m, 1 H), 2.90 (dd, J = 16.7, 7.4 Hz, 0.07 H), 2.81 (dd, J = 15.8, 6.3 Hz, 0.05 H), 2.46 (dd, J = 17.8, 3.5 Hz, 1 H); ^{13}C NMR (125 MHz) δ 170.8, 169.7, 155.0, 138.6, 138.4, 137.4, 137.0, 136.5, 128.4, 128.1, 128.0, 127.9, 117.5, 116.7, 116.4, 115.9, 97.8, 67.9, 67.5, 57.9, 56.7, 53.5, 52.7, 51.7, 51.5, 41.6, 31.6; IR ($CHCl_3$) 2954, 1690, 1663, 1622, 1446, 1412, 1358, 1322, 1300, 1276 cm^{-1}; MS (CI) m/z 344.1492 [$C_{19}H_{21}NO_5$ (M + 1) requires 344.1498], 300, 312, 344 (base), 372, 384.

(3*S*)-4,9-Dihydro-(3*H*)-pyrido[3,4-*b*]indole-3-carboxylic Acid Monohydrochloride (39). Acetic anhydride (5.54 mL, 58.8 mmol) was added to a stirred solution of L-tryptophan (10 g, 49.0 mmol) in 98% HCO_2H (19 mL) at room temperature. Stirring was continued for 1.5 h, whereupon 88% HCO_2H (50 mL) and concentrated HCl (13 mL) were added. The reaction was heated to 55 °C (bath temp) for 2.5 h. The reaction was then stored at 0 °C for 12 h. The green precipitate was removed by vacuum filtration, washed with Et_2O (5 × 20 mL), and then dried under high vacuum for 12 h to give 7.69 g (63%) of **39**, which was used without further purification, as a yellow/green solid: mp 247−249 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.13 (d, J = 1.0 Hz, 1 H), 7.81 (dd, J = 8.1, 0.7 Hz, 1 H), 7.56 (d, J = 8.1 Hz, 1 H), 7.44 (ddd, J = 8.1, 6.8, 1.0 Hz, 1 H), 7.17 (ddd, J = 8.1, 6.8, 1.0 Hz, 1 H), 5.11 (app t, J = 7.9 Hz, 1 H), 3.68 (dd, J = 18.1, 7.9 Hz, 1 H), 3.59 (dd, J = 18.1, 7.9 Hz, 1 H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 168.7, 154.5, 140.8, 128.5, 124.4, 123.2, 122.3, 121.5, 121.1, 113.2, 54.0, 22.7.

(1*S*,3*S*)-1-(2-Propenyl)-1,3,4,9-tetrahydro-(2*H*)-pyrido-[3,4-*b*]indole-2,3-dicarboxylic Acid 3-Methyl 2-Phenylmethyl Ester (41). Et_3N (1.11 mL, 7.98 mmol) was added to a stirred slurry of **39** (2.0 g, 8.0 mmol) in CH_2Cl_2 (40 mL) at room temperature. The slurry was cooled to −20 °C (bath temp), and Cbz-Cl (3.42 mL, 23.9 mmol) was added dropwise. The mixture was stirred for 15 min, whereupon MeOH (6.0 mL) and Et_3N (3.34 mL, 23.9 mmol) were added sequentially. The ice bath was removed, and stirring was continued for 1.5 h. The reaction was poured into Et_2O (300 mL), and the resulting slurry was filtered under vacuum. The solids were rinsed with Et_2O (4 × 50 mL), and the combined filtrate and washings were concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 30%−50% EtOAc/hexanes to give 2.38 g (76%) of **40** as a white solid and as an inseparable mixture of diastereomers: mp 62−65 °C; MS (CI) m/z 395.1605 [$C_{22}H_{22}N_2O_5$ (M + 1) requires 395.1607], 363 (base), 395.

A portion of **40** (965 mg, 2.45 mmol) was dissolved in CH_2Cl_2 (12.3 mL) containing allyltrimethylsilane (1.95 mL, 12.3 mmol) at 0 °C (bath temp), and then BF_3·OEt_2 (0.56 mL, 4.9 mmol) was added dropwise with stirring. The solution was stirred for 1 h, whereupon saturated $NaHCO_3$ (20 mL) was added. The layers were separated, and the aqueous layer was extracted with EtOAc (4 × 5 mL). The combined organic layers were washed with saturated NaCl (1 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product

was purified by flash chromatography eluting with 10% EtOAc/hexanes to give 711 mg (72%) of **41** as a white solid: mp 134−136 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.39 (br s, 1 H), 7.44 (d, J = 7.5 Hz, 1 H), 7.41−7.30 (comp, 5 H), 7.33 (d, J = 7.5 Hz, 1 H), 7.07 (app td, J = 7.5, 1.0 Hz, 1 H), 6.99 (app td, J = 7.5, 0.9 Hz, 1 H), 5.94 (app ddt, J = 17.2, 10.2, 7.1 Hz, 1 H), 5.34 (br t, J = 7.1 Hz, 1 H), 5.32 (dd, J = 7.3, 3.0 Hz, 1 H), 5.22 (d, J = 12.6 Hz, 1 H), 5.18 (d, J = 12.6 Hz, 1 H), 5.09 (dd, J = 17.2, 1.6 Hz, 1 H), 5.02 (dd, J = 10.2, 1.0 Hz, 1 H), 3.61 (s, 3 H), 3.29 (dd, J = 15.7, 3.0 Hz, 1 H), 3.03 (ddd, J = 15.7, 7.3, 1.3 Hz, 1 H), 2.63 (app dtd, J = 14.4, 7.1, 1.0 Hz, 1 H), 2.55 (app dt, J = 14.4, 7.1 Hz, 1 H); ^{13}C NMR (125 MHz) δ 171.4, 154.9, 136.1, 135.9, 134.5, 132.5, 127.7, 127.3, 127.0, 125.6, 120.6, 118.1, 117.1, 116.2, 110.7, 103.9, 66.6, 51.7, 51.2, 51.0, 39.2, 21.2; IR ($CHCl_3$) 3456, 1742, 1695, 1450, 1410 cm^{-1}; MS (CI) m/z 405.1804 [$C_{24}H_{24}N_2O_4$ (M + 1) requires 405.1814], 271, 363, 405 (base), 433, 445.

(1*S*,3*S*)-3-Ethenyl-(2-propenyl)-1,3,4,9-tetrahydro-(2*H*)-pyrido[3,4-*b*]indole-2,3-dicarboxylic Acid 3-Methyl 2-Phenylmethyl Ester (42). A solution of 1 M DIBAL-H in CH_2Cl_2 (0.69 mL, 0.69 mmol) was added dropwise to a stirred solution of **41** (160 mg, 0.40 mmol) in toluene (2.0 mL) at −78 °C (bath temp). Stirring was continued for 1 h, whereupon MeOH (0.032 mL, 0.79 mmol) was added dropwise. In a separate flask, a solution of $Ph_3P{=}CH_2$ was prepared by adding a solution of 2.2 M *n*-BuLi in hexanes (0.73 mL, 1.6 mmol) to a solution of Ph_3PCH_3Br (564 mg, 1.6 mmol) in THF (7.9 mL) at 0 °C (bath temp); the resultant mixture was stirred for 15 min. This solution of $Ph_3P{=}CH_2$ was then added directly to the solution containing aldehyde, and stirring was continued at room temperature for 2 h. Saturated Rochelle's salt (3 mL) was then added, and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 1 mL), and the combined organic layers were washed with saturated NaCl (1 × 1 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 91 mg (62%) of **42** as a white solid: mp 114−115 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.4 (br s, 1 H), 7.42 (d, J = 7.8 Hz, 1 H), 7.41−7.30 (comp, 5 H), 7.32 (d, J = 8.0 Hz, 1 H), 7.06 (ddd, J = 8.0, 7.0, 1.1, Hz, 1 H), 6.98 (ddd, J = 7.8, 7.0, 0.9 Hz, 1 H), 5.96 (ddd, J = 17.3, 10.7, 6.4 Hz, 1 H), 5.93 (dddd, J = 17.2, 10.1, 7.6, 7.0 Hz, 1 H),), 5.34 (dd, J = 8.8, 5.7 Hz, 1 H), 5.33 (m, 1 H), 5.19 (d, J = 12.5 Hz, 1 H), 5.17 (app dt, J = 17.3, 1.5 Hz, 1 H), 5.16 (d, J = 12.5 Hz, 1 H), 5.06 (app ddt, J = 17.2, 1.9, 1.5 Hz, 1 H), 5.05 (ddd, J = 10.7, 1.5, 1.4 Hz, 1 H), 5.02 (app ddt, J = 10.1, 1.9, 1.2 Hz, 1 H), 2.95 (dd, J = 4.1, 1.0 Hz, 2 H), 2.74 (app dddt, J = 14.8, 7.0, 5.7, 1.5 Hz, 1 H), 2.60 (app dddt, J = 14.8, 8.8, 7.6, 1.2 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.7, 138.7, 136.4, 136.0, 134.7, 132.6, 127.7, 127.2, 127.0, 126.1, 120.4, 118.0, 117.0, 116.3, 115.3, 110.6, 103.9, 66.2, 50.9, 50.6, 39.8, 23.3; IR ($CHCl_3$) 3464, 2926, 1687, 1409, 1317 cm^{-1}; MS (CI) m/z 373.1912 [$C_{24}H_{24}N_2O_2$ (M + 1) requires 373.1916], 239, 286, 331, 373 (base), 401, 413.

(1*S*,3*S*)-3-Ethynyl-1-(2-propenyl)-1,3,4,9-tetrahydro-(2*H*)-pyrido[3,4-*b*]indole-2-carboxylic Acid Phenylmethyl Ester (45). A solution of 1 M DIBAL-H in CH_2Cl_2 (2.73 mL, 2.7 mmol) was added dropwise to a stirred solution of **41** (630 mg, 1.6 mmol) in toluene (7.8 mL) at −78 °C (bath temp). Stirring was continued for 1 h, whereupon MeOH (0.13 mL, 3.1 mmol) was added dropwise. The cooling bath was removed, and NaOMe (421 mg, 7.8 mmol) was added. A solution of **44** (600 mg, 3.1 mmol) in THF (13 mL) was then added, and stirring was continued for 45 min. Saturated Rochelle's salt (30 mL) was added, and the layers were separated. The aqueous layer was extracted with EtOAc (4 × 10 mL), and the combined organic layers were washed with saturated NaCl (1 × 1 mL). The combined organic layers were then dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 317 mg (55%) of **45** as a white solid: mp 48−50 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.5 (br s, 1 H), 7.42−7.30 (comp, 7 H), 7.07 (ddd, J = 8.2, 7.2, 1.2 Hz, 1 H), 6.99 (ddd, J = 7.9, 7.2, 1.0 Hz, 1 H), 5.97 (dddd, J = 17.0, 10.1, 7.8, 6.6 Hz, 1 H), 5.66 (app dt, J = 6.1, 3.2 Hz, 1 H), 5.34 (ddd, J = 9.1, 5.2, 1.1 Hz, 1 H), 5.17 (s, 2 H), 5.13 (app dq, J = 17.0, 1.5 Hz, 1 H), 5.04 (app ddt, J = 10.1, 2.1, 1.1 Hz, 1 H), 3.10−2.96 (comp, 3 H), 2.88 (d, J = 3.2 Hz, 1 H), 2.87−2.83 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.2, 136.0, 135.9, 134.7, 132.5, 127.7, 127.3, 127.1, 126.1, 120.6, 118.1, 117.1, 116.5, 110.6, 103.6, 84.3, 72.3, 66.5, 51.1, 40.1, 38.7, 27.0; IR ($CHCl_3$) 3462, 3306, 3063, 3009, 2932, 2852, 1693, 1410, 1320 cm^{-1}; MS (CI) m/z 371.1759 [$C_{24}H_{24}N_2O_2$ (M + 1) requires 371.1759], 258, 329, 371 (base), 399.

General Procedures for Ring-Closing Metathesis. Method A. A solution of the RCM substrate (0.1 M in CH_2Cl_2) containing the ruthenium catalyst **9** (0.1 equiv) was stirred at room temperature for 15 h. The mixture was then concentrated under reduced pressure, and the residue was purified by flash chromatography using the indicated solvent systems.

Method B. Same as Method A except the reaction was run at a substrate concentration of 0.01 M.

Method C. Same as Method B except the ruthenium catalyst **10** was used.

9-Azabicyclo[3.3.1]non-2-ene-9-carboxylic Acid Phenylmethyl Ester (17a). The RCM of **16a** was performed on a scale of 0.18 mmol according to Method A, and the crude product was purified by flash chromatography eluting with 10% EtOAc/hexanes to give **17a** in 91% yield as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.37−7.28 (comp, 5 H), 5.94 (app dddt, J = 10.0, 4.3, 2.9, 0.7 Hz, 1 H), 5.69 (dddd, J = 10.0, 5.2, 2.3, 2.1 Hz, 1 H), 5.10 (s, 2 H), 4.58 (br s, 1 H), 4.37 (br t, J = 5.3 Hz, 1 H), 2.51−2.45 (m, 1 H), 1.93 (ddd, J = 18.5, 4.3, 2.1 Hz, 1 H), 1.81 (app qt, J = 13.1, 4.7 Hz, 1 H), 1.68−1.55 (comp, 3 H), 1.52−1.44 (comp, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 153.1, 136.8, 127.7, 127.4, 127.0, 126.8, 126.7, 65.4, 47.0, 45.2, 31.0, 29.2, 26.7, 15.1; IR ($CHCl_3$) 3010, 2941, 1684, 1432, 1326; MS (CI) m/z 258.1497 [$C_{16}H_{19}NO_2$ (M + 1) requires 258.1494], 257, 170, 91 (base).

10-Azabicyclo[4.3.1]dec-3-ene-10-carboxylic Acid Phenylmethyl Ester (17b). The RCM of **16b** was performed on a scale of 0.17 mmol according to Method A, and the crude product was purified by flash chromatography eluting with 5% EtOAc/hexanes to give **17b** in 82% yield as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38−7.27 (comp, 5 H), 5.65−5.59 (m, 2 H), 5.13 (d, J = 19.4 Hz, 1 H), 5.09 (d, J = 19.4 Hz, 1 H), 4.37−4.36 (m, 2 H), 2.48 (dd, J = 14.0, 5.2 Hz, 2 H), 2.29−2.24 (m, 2 H), 2.20−2.10 (m, 1 H), 1.76−1.63 (m, 4 H), 1.41−1.35 (m, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.5, 136.8, 128.1, 127.7, 127.0, 126.8, 65.5, 46.5, 33.8, 29.4, 16.7; IR ($CHCl_3$) 1676, 1523, 1422 cm^{-1}; MS (CI) m/z 272.1654 [$C_{17}H_{21}NO_2$ (M + 1) requires 272.1651], 271, 172, 136, 91 (base).

10-Azabicyclo[5.3.1]undec-3-ene-11-carboxylic Acid Phenylmethyl Ester (17c). The RCM of **16c** was performed on a scale of 0.24 mmol according to Method B, and the crude product was purified by flash chromatography eluting with 10% EtOAc/hexanes to give **17c** in 84% yield as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 150 °C) δ 7.36−7.26 (comp, 5 H), 5.49−5.39 (comp, 2 H), 5.04 (s, 2 H), 4.45−4.40 (m, 1 H), 4.29 (app dt, J = 12.1, 6.4 Hz, 1 H), 2.73−2.62 (m, 1 H), 2.32−2.12 (comp, 3 H), 1.94 (ddd, J = 14.6, 8.3, 6.4 Hz, 1 H), 1.91−1.83 (m, 1 H), 1.75 (dddd, J = 13.5, 11.0, 6.7, 4.9 Hz, 1 H), 1.68−1.57 (comp, 3 H), 1.53−1.43 (comp, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6, 150 °C) δ 154.7, 136.7, 130.9, 127.3, 126.61, 126.57, 122.7, 65.3, 49.3, 47.1, 29.9, 28.9, 27.31, 27.27, 26.9, 13.6; IR ($CHCl_3$) 3008, 2938, 2877, 1672, 1446, 1389, 1333 cm^{-1}; MS (CI) m/z 286.1808 [$C_{18}H_{23}NO_2$ (M + 1) requires 286.1807], 150, 178, 242, 286 (base), 314, 326.

8-Azabicyclo[3.2.1]oct-6-ene-8-carboxylic Acid Phenylmethyl Ester (22). The RCM of **21** was performed on a scale of 0.17 mmol according to Method B, and the crude product was purified by flash chromatography eluting with 10% EtOAc/

hexanes to give **22** in 84% yield as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38−7.28 (comp, 5 H), 6.12 (app t, J = 1.1 Hz, 2 H), 5.11 (s, 2 H), 4.47 (br s, 2 H), 1.71 (dtt, J = 17.1, 12.5, 5.5 Hz, 1 H), 1.61 (app tdd, J = 12.5, 5.1, 3.0 Hz, 2 H), 1.44−1.39 (m, 1 H), 1.32−1.28 (comp, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 151.3, 136.7, 129.8, 127.7, 127.1, 126.8, 65.2, 57.7, 22.9, 15.3; IR ($CHCl_3$) 3019, 1731, 1694, 1521, 1425 cm^{-1}; MS (CI) m/z 244.1333 [$C_{24}H_{24}N_2O_2$ (M + 1) requires 244.1338], 136, 244 (base), 272.

3-Oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylic Acid Phenylmethyl Ester (30a). The RCM of **29a** was performed on a scale of 0.35 mmol according to Method A, and the crude product was purified by flash chromatography eluting with 15%−30% EtOAc/hexanes to give **30a** in 92% yield as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.39−7.29 (comp, 5 H), 6.30−6.27 (m, 2 H), 4.79 (app ddt, J = 4.4, 1.2, 0.8 Hz, 2 H), 2.64 (dd, J = 16.5, 4.4 Hz, 2 H), 2.28 (ddd, J = 16.5, 1.5, 1.2 Hz, 2 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 203.9, 151.7, 136.2, 133.3, 127.8, 127.3, 127.0, 65.9, 55.7, 44.7; IR ($CHCl_3$) 3026, 3011, 2960, 1701, 1422 cm^{-1}; MS (CI) m/z 258.1128 [$C_{15}H_{15}NO_3$ (M + 1) requires 258.1130], 214, 242, 258 (base).

2-Methyl-7-oxo-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic Acid Phenylmethyl Ester (30b). The RCM of **29b** was performed on a scale of 0.13 mmol according to Method C, and the crude product was purified by flash chromatography eluting with 20%−40% EtOAc/hexanes to give **30b** in 84% yield as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.42−7.29 (comp, 5 H), 5.40−5.39 (m, 1 H), 5.19 (d, J = 12.6 Hz, 1 H), 5.16 (d, J = 12.6 Hz, 1 H), 4.78 (t, J = 7.3 Hz, 1 H), 4.63 (d, J = 4.5 Hz, 1 H), 2.68 (dd, J = 15.6, 7.3 Hz, 1 H), 2.60 (dd, J = 14.7, 4.5 Hz, 1 H), 2.55−2.45 (m, 1 H), 2.33 (app dt, J = 14.7, 1.9 Hz, 1 H), 2.12 (app dt, J = 15.6, 1.5 Hz, 1 H), 1.94 (dd, J = 18.0, 4.9 Hz, 1 H), 1.63−1.62 (m, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.4, 153.2, 136.3, 133.8, 127.8, 127.2, 126.9, 118.2, 66.1, 51.4, 45.9, 45.8, 42.2, 30.0, 19.2; IR ($CHCl_3$) 2917, 1695, 1449, 1427, 1321 cm^{-1}; MS (CI) m/z 286.1445 [$C_{17}H_{19}NO_3$ (M + 1) requires 286.1443], 194, 224, 242 (base), 286, 314, 326.

2,3-Dimethyl-7-oxo-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic Acid Phenylmethyl Ester (30c). A solution of **29c** (17 mg, 0.052 mmol) and catalyst **10** (3.6 mg, 0.0043 mmol) in toluene (4.3 mL) was stirred at 100 °C in a sealed vial for 2 h. Another portion of catalyst **10** (1.8 mg, 0.0021 mmol) was added, and stirring was continued at 100 °C for 2 h. Additional catalyst **10** (1.8 mg, 0.0021 mmol) was added, and stirring was continued at 100 °C for 15 h. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography eluting with 20%−30% EtOAc/hexanes to give 11 mg (75%) of **30c** as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.42−7.29 (comp, 5 H), 5.18 (d, J = 12.6 Hz, 1 H), 5.16 (d, J = 12.6 Hz, 1 H), 4.77 (t, J = 7.1 Hz, 1 H), 4.58 (d, J = 4.5 Hz, 1 H), 2.66 (dd, J = 15.6, 7.1 Hz, 1 H), 2.56 (dd, J = 14.6, 4.5 Hz, 1 H), 2.53−2.48 (m, 1 H), 2.31 (ddd, J = 14.6, 2.0, 1.8 Hz, 1 H), 2.12 (ddd, J = 15.6, 1.8, 1.5 Hz, 1 H), 1.84 (d, J = 17.6 Hz, 1 H), 1.58 (s, 3 H), 1.55 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 205.6, 153.1, 136.3, 127.8, 127.2, 126.9, 125.8, 123.4, 66.1, 52.0, 46.7, 45.9, 42.5, 35.9, 17.2, 15.2; IR ($CHCl_3$) 2914, 1695, 1430, 1331 cm^{-1}; MS (CI) m/z 300.1609 [$C_{18}H_{21}NO_3$ (M + 1) requires 300.1600], 208, 256 (base), 300, 328, 340.

6-Methyl-3-oxo-8-azabicyclo[3.2.1]oct-6-ene-8-carboxylic Acid Phenylmethyl Ester (30d). The RCM of **29d** was performed on a scale of 0.33 mmol according to Method C, and the crude product was purified by flash chromatography eluting with 20% EtOAc/hexanes to give **30d** in 92% yield as a clear, colorless oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.38−7.29 (comp, 5 H), 5.83 (app dq, J = 3.5, 1.7 Hz, 1 H), 5.16 (s, 2 H), 4.70 (br s, 1 H), 4.52 (d, J = 4.2 Hz, 1 H), 2.62 (dd, J = 16.6, 4.2 Hz, 1 H), 2.58 (dd, J = 16.5, 4.3 Hz, 1 H), 2.38 (d, J = 16.6 Hz, 1 H), 2.22 (d, J = 16.5 Hz, 1 H), 1.78 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 204.1, 151.6, 143.1, 136.3, 127.8, 127.3, 127.0, 126.5, 65.8, 58.7, 55.9, 43.9, 43.6, 12.6; IR ($CHCl_3$) 3019, 2960, 1700, 1422 cm^{-1}; MS (CI) m/z 272.1293 [$C_{16}H_{17}NO_3$ (M + 1) requires 272.1287], 272 (base), 228, 129.

3-Oxo-8-azabicyclo[3.2.1]oct-6-ene-2,8-dicarboxylic Acid 2-Methyl Ester 8-Phenylmethyl Ester (32). The RCM of **31** was performed according to Method B, and the crude product was purified by flash chromatography eluting with 30% EtOAc/hexanes to give **32** in 86% yield as a clear, colorless oil and as an undetermined mixture of diastereomers epimeric at C(2): ^{1}H NMR (500 MHz, DMSO-d_6, 50 °C) δ 7.41−7.31 (comp, 5 H), 6.41−6.33 (comp, 2 H), 5.16−4.79 (comp, 4 H), 3.85 (d, J = 3.6 Hz, 0.5 H), 3.65 (s, 1.6 H), 3.50 (br s, 1.4 H), 3.40 (s, 0.5 H), 2.78 (dd, J = 13.6, 4.3 Hz, 0.5 H), 2.75 (dd, J = 13.6, 4.3 Hz, 0.5 H), 2.38 (d, J = 16.0 Hz, 0.5 H), 2.29 (dd, J = 16.0, 1.4 Hz, 0.5 H); ^{13}C NMR (125 MHz, DMSO-d_6, 50 °C) δ 200.9, 200.2, 168.0, 167.7, 151.6, 136.3, 135.9, 134.7, 132.6, 132.5, 128.5, 128.21, 128.18, 127.8, 127.7, 127.5, 127.3, 66.4, 66.2, 61.4, 61.3, 59.1, 58.9, 57.5, 56.5, 56.0, 52.0, 51.6, 44.0, 43.4; IR ($CHCl_3$) 3020, 2955, 1741, 1705, 1425 cm^{-1}; MS (CI) m/z 316.1192 [$C_{17}H_{17}NO_5$ (M + 1) requires 316.1185], 316, 272 (base), 240.

(6*S*,10*S*)-6,7,10,11-Tetrahydro-6,10-imino-5*H*-cyclooct-[*b*]indole-12-carboxylic Acid Phenylmethyl Ester (43). A solution of **42** (57 mg, 0.15 mmol) and **9** (12.6 mg, 0.0153 mmol) in CH_2Cl_2 (1.5 mL) was stirred at room temperature for 1 h. The reaction was concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with 30% EtOAc/hexanes to give **43** in 99% yield as a white solid: mp 66−68 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.5 (br s, 1 H), 7.30 (d, J = 4.5 Hz, 1 H), 7.29 (d, J = 8.0 Hz, 1 H), 7.35−7.28 (comp, 5 H), 7.03 (app td, J = 7.3, 1.2 Hz, 1 H), 6.95 (app td, J = 7.3, 1.0 Hz, 1 H), 5.80−5.77 (m, 1 H), 5.65 (dd, J = 10.0, 5.2 Hz, 1 H), 5.43 (d, J = 5.6 Hz, 1 H), 5.16 (d, J = 12.7 Hz, 1 H), 5.11 (d, J = 12.7 Hz, 1 H), 4.97 (br t, J = 5.3 Hz, 1 H), 2.99 (dd, J = 15.5, 5.3 Hz, 1 H), 2.65 (ddd, J = 17.6, 5.6, 2.2 Hz, 1 H), 2.63 (dd, J = 15.5, 0.9 Hz, 1 H), 2.17 (dd, J = 17.6, 5.2 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 153.2, 136.4, 135.4, 134.1, 127.9, 127.8, 127.2, 126.9, 126.4, 123.2, 120.2, 118.0, 116.9, 110.6, 104.6, 65.9, 47.1, 45.6, 29.4, 24.8; IR ($CHCl_3$) 3018, 1694, 1428 cm^{-1}; MS (CI) m/z 345.1597 [$C_{22}H_{20}N_2O_2$ (M + 1) requires 345.1603], 301, 345 (base).

(6S,10S)-6,7,10,11-Tetrahydro-9-ethenyl-6,10-imino-5*H*-cyclooct[*b*]indole-12-carboxylic Acid Phenylmethyl Ester (46). A solution of **45** (233 mg, 0. 63 mmol) and **9** (52 mg, 0.0629 mmol) in CH_2Cl_2 (6.3 mL) was stirred under an atmosphere of ethene at room temperature for 1.5 h. The reaction was concentrated under reduced pressure, and the crude product was purified by flash chromatography eluting with 20% EtOAc/hexanes to give 227 mg (97%) of **46** as a white solid: mp 73−75 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.55 (br s, 1 H), 7.35−7.28 (comp, 7 H), 7.03 (ddd, J = 8.2, 7.1, 1.2 Hz, 1 H), 6.94 (ddd, J = 7.9, 7.1, 1.0 Hz, 1 H), 6.23 (dd, J = 17.9, 11.1 Hz, 1 H), 5.72 (dd, J = 5.3, 1.9 Hz, 1 H), 5.47 (d, J = 5.7 Hz, 1 H), 5.28 (d, J = 17.9 Hz, 1 H), 5.27 (d, J = 5.8 Hz, 1 H), 5.18 (d, J = 12.7 Hz, 1 H), 5.14 (d, J = 12.7, 1 H), 5.07 (d, J = 11.1 Hz, 1 H), 3.08 (dd, J = 15.5, 5.8 Hz, 1 H), 2.78 (br dd, J = 18.5, 5.7 Hz, 1 H), 2.77 (dd, J = 15.5, 1.0 Hz, 1 H), 2.32 (dd, J = 18.5, 5.3 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 153.2, 136.4, 136.1, 136.0, 135.5, 133.6, 127.7, 127.2, 126.8, 126.2, 124.9, 120.3, 118.0, 116.9, 111.3, 110.6, 104.9, 66.0, 46.6, 45.3, 30.9, 24.6; IR (film) 3397, 3031, 2894, 1681, 1430, 1317, 1099, 1049, 742 cm^{-1}; MS (CI) m/z 371.1757 [$C_{24}H_{22}N_2O_2$ (M + 1) requires 371.1760], 279, 327, 371 (base), 399.

(6*S*,10*S*)-6,7,10,11-Tetrahydro-9-formyl-6,10-imino-5*H*-cyclooct[*b*]indole-12-carboxylic Acid Phenylmethyl Ester (47). A solution of **46** (100 mg, 0.27 mmol) in *t*-BuOH (3.5 mL) was added to a slurry of K_3FeCN_6 (267 mg, 0.81 mmol), K_2CO_3 (112 mg, 0.81 mmol), $K_2OsO_2(OH)_4$ (2 mg, 0.0054 mmol), and $(DHQ)_2PHAL$ (21 mg, 0.027 mmol) in H_2O (2.5 mL)

at room temperature, and the resulting mixture was stirred at room temperature for 20 h. Solid Na_2SO_3 (200 mg, 1.59 mmol) was then added, the mixture was stirred for 30 min, and Et_2O (5 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3 × 1 mL). The combined organic layers were washed with saturated NaCl (1 × 2 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the residue was dissolved in a mixture (1:1) of THF/H_2O (5 mL) containing $NaIO_4$ (173 mg, 0.81 mmol). The mixture was stirred for 30 min, whereupon Et_2O (5 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (4 × 1 mL). The combined organic layers were washed with saturated NaCl (1 × 2 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography eluting with 75% EtOAc/hexanes to give 54 mg (54%) of **47** as a white solid: mp 96−98 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 10.61 (br s, 1 H), 9.36 (s, 1 H), 7.38−7.28 (comp, 7 H), 7.04 (ddd, J = 8.2, 7.1, 1.2 Hz, 1 H), 6.95−6.92 (comp, 2 H), 5.53 (d, J = 5.3 Hz, 1 H), 5.32 (d, J = 5.9 Hz, 1 H), 5.17 (d, J = 12.6 Hz, 1 H), 5.13 (d, J = 12.6 Hz, 1 H), 3.08 (dd, J = 15.8, 5.9 Hz, 1 H), 3.00−2.90 (m, 1 H), 2.64 (dd, J = 15.8, 1.0 Hz, 1 H), 2.60 (dd, J = 19.7, 5.3 Hz, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 191.5, 153.2, 147.5, 140.6, 136.2, 135.6, 133.3, 127.8, 127.3, 126.9, 126.1, 120.6, 118.1, 117.1, 110.7, 104.4, 66.2, 45.4, 44.9, 31.8, 24.6; (IR (film) 3392, 3030, 2849, 1681, 1622, 1497, 1425, 1360, 1334, 1300, 1268, 1186, 1170, 1097 cm^{-1}; MS (CI) m/z 373.1548 [$C_{23}H_{20}N_2O_3$ (M + 1) requires 373.1552], 117, 129, 177, 329, 373 (base).

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Supporting Information Available: Copies of ^{1}H NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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