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General Access to the *Vinca* and *Tacaman* Alkaloids Using a Rh(II)-Catalyzed Cyclization/Cycloaddition Cascade

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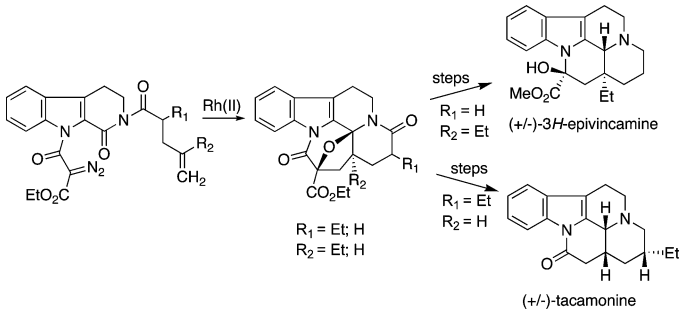

The total synthesis of several members of the *vinca* and *tacaman* classes of indole alkaloids has been accomplished. The central step in the synthesis consists of an intramolecular [3+2]-cycloaddition reaction of an α-diazo indoloamide which delivers the pentacyclic skeleton of the natural product in excellent yield. The acid lability of the oxabicyclic structure was exploited to establish the *trans*-D/E ring fusion of (±)-3*H*-epivincamine (**3**). Finally, a base induced keto-amide ring contraction was utilized to generate the E-ring of the natural product. A variation of the cascade sequence of reactions used to synthesize (±)-3*H*-epivincamine was also employed for the synthesis of the *tacaman* alkaloids (±)-tacamonine and (±)-apotacamine.

Introduction

The development of synthetic methods for constructing indole alkaloids has attracted much attention for several decades due to the important pharmacological properties and diverse structures of this class of natural products.[1−8] In particular, both the *vinca* and *tacaman* families of indole alkaloids occupy a central place in natural product chemistry because of their wide range of complex structural variation.[9,10] These two families are characterized by the presence of a common pentacyclic framework **1**, containing either a *cis*- or *trans*-fused D/E ring system (Figure 1).[11] Prototypical examples of the *vinca* alkaloids include (+)-vincamine (**2**), as well as its epimer, (±)-3*H*-epivincamine (**3**) which have been isolated from several plants of the *vinca* genus.[12] Members of the *vinca* family all exhibit strong vasodilation activity which brings about an enhancement of the overall cerebral blood flow.[13] Thus, these compounds along with their semi-synthetic derivatives have recently been the subject of intense pharmacological and synthetic studies.[14] The structurally related *tacaman* alkaloids represented by tacamine (**4**), tacamonine (**5**), and apotacamine (**6**) were isolated from the Central African plant *Tabernaemontana eglandulosa Stapf*.[15]

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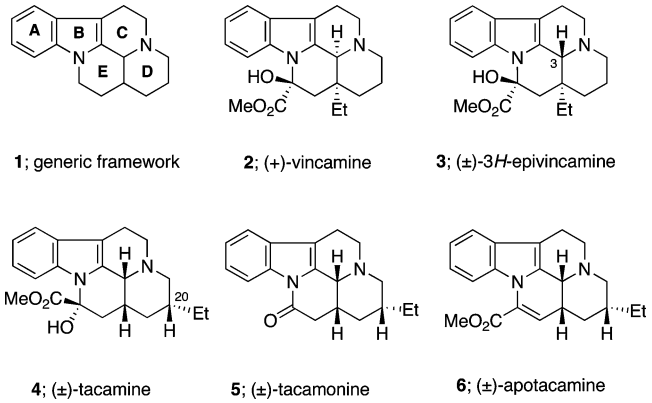

FIGURE 1. Common pentacyclic indole framework of the *vinca* and *tacaman* families.

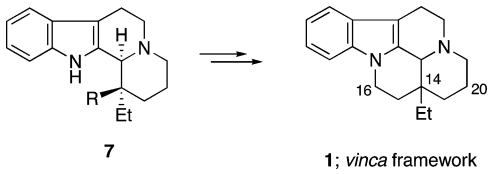

FIGURE 2. Common synthetic strategies toward the *vinca* framework.

The close chemical similarity of these alkaloids with vincamine (**2**) has also made them potential hypotensive and cerebral vasodilator candidates.[16] Attachment of an ethyl substituent at C_{20} and away from the D/E ring junction of the pentacyclic framework adds an additional stereocenter, setting all three methine hydrogens *cis* to each other (i.e., **4**−**6**), providing a further degree of complexity to these natural products.

Several strategies for the synthesis of vincamine and its structural analogues have been reported.[17] The most common route toward this particular family is to first establish the [ABCD]-type octahydroindolo[2,3-*a*]-quinolizine ring system (**7**) starting from an indole subunit and then complete the synthesis of the specific target by appending the final E-ring (Figure 2).[18] Methods for building up the requisite gem-disubstituted tetracyclic framework **7** usually involves a Pictet-Spengler cyclization,[19] a Michael-type alkylation of the so-called "Wenkert enamine"[20] or an annulation reaction of a dihydro-β-carboline derivative.[21] The strategies for assembling the *tacaman* skeleton are also quite varied and involve such protocols as a Bischler-Napieralski cyclization,[22] a double aza-Michael reaction,[23] radical cyclization chemistry,[24] ring closing metathesis to form a piperidinone ring followed by 1,4-addition to introduce the requisite side chain,[25] as well as other more classical methods.[26] Nevertheless, the search for efficient and general methods which provide flexible entries to structural analogues of the pentacyclic core of both the *vinca* and *tacaman* alkaloids still remains a challenging goal.

Our synthetic approach toward the pentacyclic framework found in the *vinca* and *tacaman* alkaloids was guided by a long standing interest in developing new applications of the intramolecular [3+2]-cycloaddition of carbonyl ylide dipoles toward the synthesis of complex natural products.[27] The generation of onium ylides through the use of transition-metal-promoted cyclizations has emerged in recent years as an important and efficient method for the construction of ring systems that are difficult to prepare by other means.[28,29] In earlier work from our laboratory, we described the formation of push−pull dipoles from the Rh(II)-catalyzed process involving cyclization of an electrophilic metallo carbenoid onto an adjacent carbonyl group.[30] Our recent total synthesis of (±)-aspidophytine[31] nicely demonstrates the utility of this cascade methodology for the construction of complex natural products. On the basis of this

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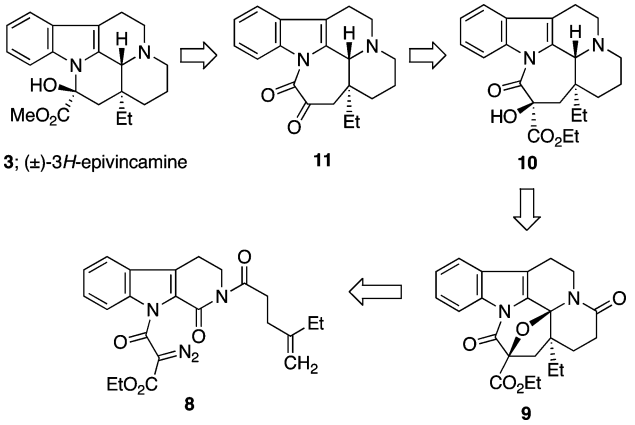
SCHEME 1. Key Disconnections for the Synthesis of (±)-3*H*-Epivincamine

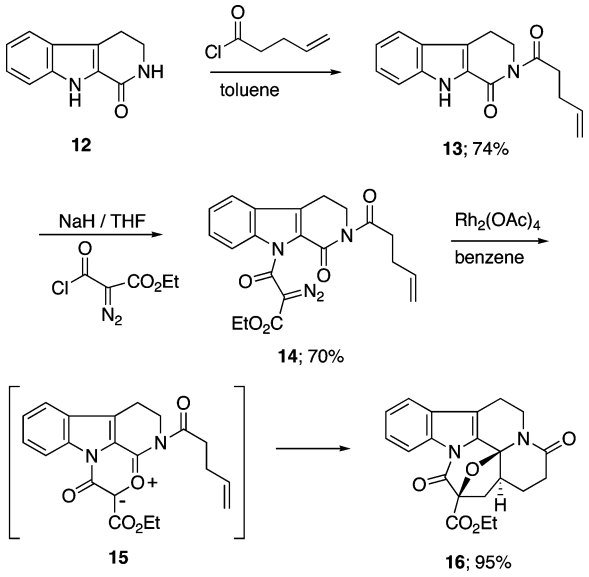


earlier work, we felt that the Rh(II)-catalyzed reaction of the α-diazo indoloamide precursor (i.e., **8**) might allow for a facile entry to the pentacyclic core skeleton of the *vinca* alkaloid 3*H*-epivincamine (**3**) as illustrated in Scheme 1. Reductive ring opening of the expected [3+2]-cycloadduct **9** would generate compound **10** which could be considered as a precursor to the required D/E ring fusion found in the natural product. Functional group manipulation of **10** would lead to **11**, and a base-induced keto-amide ring contraction reaction[32] would complete the synthesis of 3*H*-epivincamine (**3**). A similar strategy was also contemplated for the synthesis of tacamonine (**5**) (*vide infra*). In this report, we document the full results of our studies making use of this methodology.[33]

Results and Discussion

Model Studies. To test the feasibility of the retrosynthetic strategy outlined in Scheme 1, our initial efforts were focused on a model substrate. The primary goal was to prepare the core pentacyclic skeleton of the *vinca* and *tacaman* alkaloids by omitting the ethyl substituent found at the C_{14} and C_{20} positions to test the feasibility of the tandem cascade process as well as to investigate specific reactions to be used in a total synthesis effort. With this in mind, we chose to examine the Rh(II)-catalyzed cascade reaction of α-diazo indoloamide **14** as a test substrate. Compound **14** was readily prepared by treating carboline **12** with pent-4-enoyl chloride under refluxing conditions in toluene followed by reaction of the resulting *N*-acyl carboline **13** with sodium hydride and ethyl 2-diazomalonyl chloride[34] (Scheme 2). Heating α-diazo indoloamide **14** with a catalytic amount of $Rh_2(OAc)_4$ was expected to generate a rhodium carbenoid intermediate that should undergo cyclization with the neighboring amido carbonyl group to form a transient carbonyl ylide dipole **15**. Indeed, our studies showed that a subsequent intramolecular [3+2]-cycloaddition of **15** occurred across the tethered π-bond and furnished cycloadduct **16** in 95% yield and with complete diastereoselectivity as evidence by its

SCHEME 2. Rh(II)-Catalyzed Intramolecular [3+2]-Cycloaddition to Generate the Core Pentacyclic Skeleton



^{1}H NMR spectrum, thus providing support for the formation of this dipole. The intramolecular [3+2]-cycloaddition reaction produced the *endo* cycloadduct solely with regard to the dipole, and this result is in full accord with earlier observations where it was noted that the cycloaddition proceeds from the lowest-energy transition state.[35]

At this point in our planned approach toward (±)-3*H*-epivincamine (**3**), we needed to demonstrate that the [3+2]-cycloadduct could be converted into a pentacyclic keto-amide that would be required for a subsequent base-induced ring contraction reaction.[32] The first step in this contemplated sequence would require reductive ring opening of the oxabicyclic bridge followed by subsequent functional group manipulation. The game plan that we had in mind was easily tested using the readily available cycloadduct **16**. Compound **16** was treated with $BF_3{\cdot}OEt_2$ to affect ring opening, and we were pleased to note that this reaction delivered enamine **17** in 82% yield (Scheme 3). The next step envisaged the selective removal of the carboethoxy group, and this decarboxylation was initially attempted by making use of typical Krapcho conditions (i.e., NaCl, LiI, etc.).[36] Unfortunately, only a low yield of the desired product (i.e., **18**) was obtained. However, we eventually found that the carboethoxy group could be easily removed by treating **17** with MgI_2 in refluxing acetonitrile that contained a trace amount of water.[37] This resulted in the formation of α-hydroxy lactam **18** in 70% yield. Attempts to oxidize the secondary alcohol present in **18** to the desired keto-amide functionality failed to give tractable material under a variety of oxidizing conditions. We suspect this problem may be related to the susceptibility of the molecule to undergo dehydration. Instead, reduction of the enamino double bond present in **18** was investigated. The reduction could be accomplished under catalytic hydrogenation conditions using PtO_2 as the catalyst

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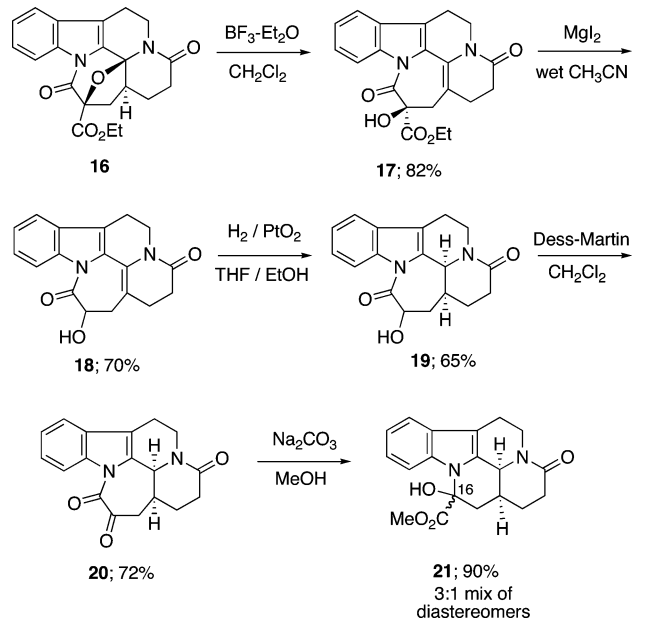
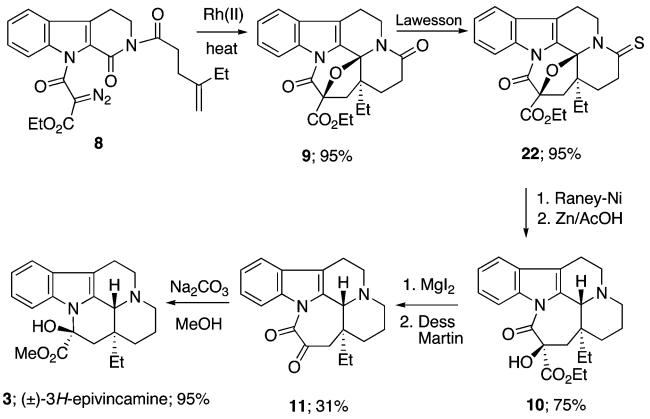
SCHEME 3. Completion of the Model Study



SCHEME 4. Total Synthesis of (±)-3*H*-Epivincamine



to give the *cis*-fused ring system **19** in 65% yield as a single diastereomer. Oxidation of **19** with Dess-Martin periodinane was now straightforward and furnished keto-amide **20** in 72% yield. With keto-amide **20** in hand, the desired conversion to the ring contracted vincamine derivative was found to occur in methanol using sodium carbonate as the base,[32] furnishing **21** in 90% yield as 3:1 mixture of diastereomers at the C_{16}-position.

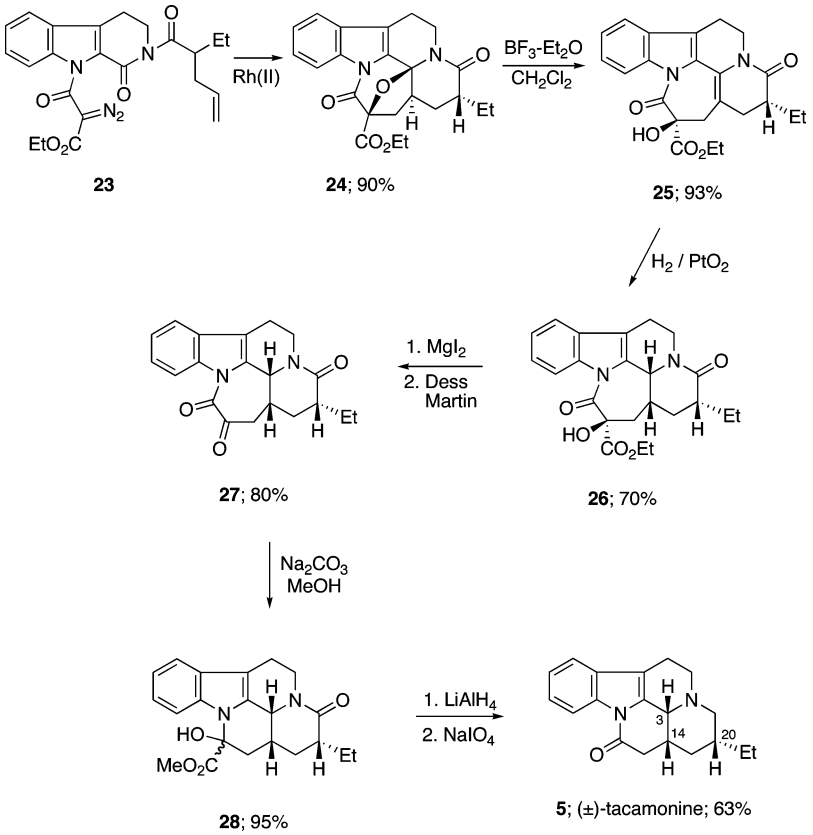
Synthesis of (±)-3*H*-Epivincamine (3). Having been encouraged by the model studies with α-diazo indoloamide **14**, we turned our attention to the preparation of α-diazo indoloamide **8** which would be used to provide the necessary quaternary ethyl substituent required for the synthesis of (±)-3*H*-epivincamine (**3**). Accordingly, compound **8** was synthesized in 60% yield by treating the readily available carboline **12** with the mixed anhydride of 4-methylenehexanoic acid followed by deprotonation of the indole N−H with sodium hydride and reaction with ethyl 2-diazomalonyl chloride. Formation of the desired carbonyl ylide dipole was achieved by treating **8** with a catalytic amount of $Rh_2(OAc)_4$ in refluxing benzene. Subsequent intramolecular [3+2]-cycloaddition furnished the key cycloadduct **9** containing the desired quaternary ethyl substituent in 95% yield as a single diastereomer (Scheme 4). The uniquely functionalized oxapolycyclic adduct **9** contains a "masked" *N*-acyliminium ion which can be released by treatment with a Lewis acid.[38] However, our initial attempts to reduce the resulting iminium ion with Et_3SiH and other hydride reagents afforded only recovered starting material. We suspected that removal of the lactam carbonyl group would help promote the reduction by enhancing the nucleophilicity of the nitrogen atom thereby facilitating oxabicyclic ring opening. Accordingly, cycloadduct **9** was converted into the corresponding thiolactam **22** with Lawesson's reagent in 95% yield. Reductive removal of the thiocarbonyl group with Raney-Ni was followed by treatment of the resulting piperidine with Zn/AcOH to give the ring opened amide **10** containing the eventually required *trans*-D/E ring fusion of 3*H*-epivincamine in 75% yield over the two steps. Reduction of the transient iminium ion with zinc occurred from the least hindered face thereby generating the required *trans*-ring junction. We were also interested in determining whether the *cis*-isomer could be formed. However, screening a variety of reducing agents (i.e., H_2/PtO_2; $NaBH_4$; $LiAl(Ot\text{-}Bu)_4$) resulted only in the formation of the *trans*-ring stereoisomer. Next, the carboethoxy group in **10** was selectively removed by treatment with MgI_2 as found with the earlier model studies. Oxidation of the resulting α-hydroxy lactam to the corresponding keto-amide **11** was carried out using Dess-Martin periodinane in 31% overall yield for the two steps. The conversion of related oxolactams to vincamine derivatives has been reported in the literature.[32] In our hands, methanolysis of **11** with sodium carbonate as base gave, after 1 h of stirring at room temperature, a 95% yield of (±)-3*H*-epivincamine (**3**) as the only diastereomer.

Synthesis of (±)-Tacamonine (5). The main challenge in designing any synthetic approach toward the *tacaman* alkaloids lies in controlling the relative configurational relationship of all three stereocenters at C_3, C_{14}, and C_{20} (all *cis*-hydrogens). Considering the success we had synthesizing (±)-3*H*-epivincamine (**3**), we decided to use a similar cyclization cascade strategy for (±)-tacamonine (**5**). However, two major variants of the approach are necessary for this particular target and which need to be taken into consideration: (1) the different placement of the ethyl substituent on the skeleton and (2) the need to control the stereochemistry of the reductive ring opening of the oxabicycle to generate the required *cis*-D/E ring fusion. Our synthesis of (±)-tacamonine (**5**) began with the preparation of α-diazo indoloamide **23** containing the ethyl substituent in the required position. Compound **23** was prepared in 65% yield by treating carboline **12** with the mixed anhydride of 2-ethyl-pent-4-enoic acid followed by deprotonation of the indole N−H and reaction with ethyl 2-diazomalonyl chloride. Subjecting α-diazo indoloamide **23** to a catalytic amount of $Rh_2(OAc)_4$ in refluxing benzene gave the desired intramolecular [3+2]-cycloadduct **24** in 90% yield as a single diastereomer (Scheme 5). Once again, the facileness of the cycloaddition shows how effective the Rh-(II)-catalyzed cascade sequence is for generating the core pentacyclic skeleton.

Carrying on with the synthesis, cycloadduct **24** was treated with $BF_3{\cdot}OEt_2$, as was done previously, to induce oxabicyclic ring opening and produce the expected enamine **25** in 93% yield. At this point, we envisioned a catalytic hydrogenation of the enamine double bond to deliver the required *cis*-ring fusion of the target molecule. We also anticipated that hydrogen would be delivered from the least hindered face opposite the ethyl substituent thereby setting the required all *cis*-stereochemistry. Gratifyingly, when enamine **25** was subjected to hydrogenation

(38) Padwa, A.; Zhang, H. *J. Org. Chem.* **2007**, *72*, 2570.

SCHEME 5. Total Synthesis of (±)-Tacamonine (5)



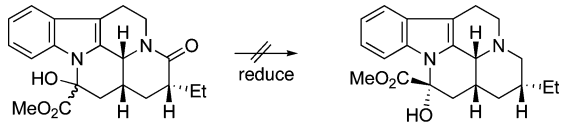
conditions using catalytic PtO_2, we were able to isolate lactam **26** in 70% yield which possesses the correct stereochemistry (i.e., all hydrogens *cis* to each other). Single-crystal X-ray analysis of **26** unequivocally confirmed this assignment.[39] Next, the carboethoxy group was removed with MgI_2 and the secondary alcohol was easily oxidized to the desired keto-amide **27** in 80% yield over the two steps.

At this point, we subjected keto-amide **27** to the base-induced ring contraction conditions and obtained the expected hydroxy ester **28** in 95% yield as a 3:2-mixture of diastereomers. The mixture of stereoisomers obtained was inconsequential since the newly formed stereocenter at C_{16} would ultimately become a carbonyl group in the final product. To complete the synthesis, hydroxy ester **28** was treated with an excess amount of lithium aluminum hydride so as to reduce both the lactam carbonyl and ester functionalities. Finally, the resulting 3:2-mixture of diols was subjected to sodium periodate oxidative cleavage to give (±)-tacamonine (**5**) as a single diastereomer in 63% yield for the last two steps.

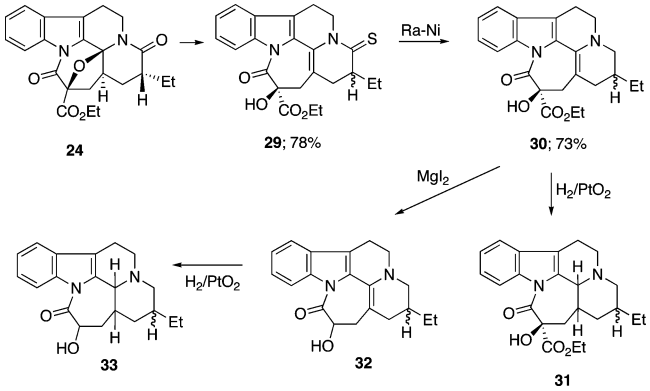
Attempted Synthesis of (±)-Tacamine (4). We considered the possibility of using the ring contracted hydroxy ester **28** as a precursor for the synthesis of (±)-tacamine (**4**). What would be required would be to selectively reduce the lactam carbonyl group in the presence of the ester functionality and then separate the resulting diastereomers (Scheme 6). Unfortunately, all of our attempts to convert **28** into (±)-tacamine (**4**) by selective reduction of the lactam carbonyl group failed to give any of the desired product under a variety of reducing conditions (BH_3·SMe_2, BH_3·THF, $NaBH_4$ + BF_3·OEt_2, etc.).

(39) We will deposit coordinates for structure **26** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

SCHEME 6. Attempts to Directly Reduce Hydroxy Ester 28 into (±)-Tacamine (4)

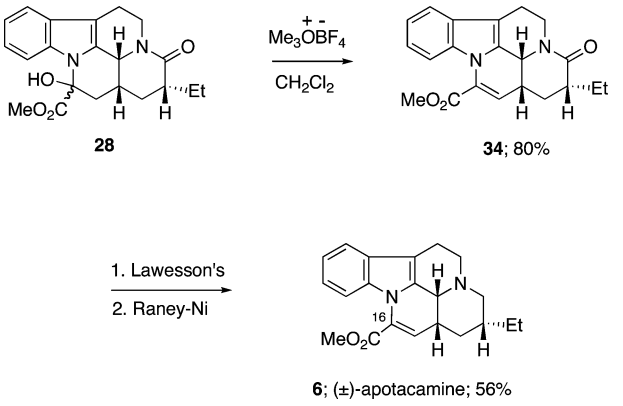


SCHEME 7. Attempted Conversion of [3+2]-Cycloadduct 24 into (±)-Tacamine (4)



Since we were not able to carry out the selective lactam reduction, we turned our attention to an alternate approach, which involves removing the lactam carbonyl group earlier on in the synthesis. Thus, starting from cycloadduct **24**, treatment with Lawesson's reagent afforded thiolactam **29** in 78% yield, but unfortunately as a 1:1-mixture of epimers (Scheme 7). It appears that under the reaction conditions used to convert lactam

SCHEME 8. Conversion of α-Hydroxy Ester 28 into (±)-Apotacamine (6)



24 into thiolactam **29**, epimerization at the C_{20} position has occurred. Reductive removal of the thiocarbonyl group with Raney-Ni does deliver enamine **30** in 73% yield but as a 1:1-mixture of inseparable epimers. At this point, we envisioned hydrogenation of the enamino double bond with the hope of obtaining some facial selectivity for the reduction. However, examination of the crude reaction mixture obtained from the hydrogenation reaction showed very little facial selectivity and, in fact, a mixture of four stereoisomers of **31** were produced. Although we were somewhat discouraged by this result, we nevertheless treated **30** with MgI_2 in wet acetonitrile to effect the decarboethoxylation. The resulting alcohol **32** was then subjected to hydrogenation but, unfortunately, this resulted in a complex mixture of all four diastereomers of **33**. Since we were unable to effect separation of the various stereoisomers of **33** by column chromatography, we subsequently abandoned further work with this synthesis.

Synthesis of (±)-apotacamine (6). Even though we had little success in converting hydroxy ester **28** into (±)-tacamine (**4**), we thought that we might be able to use this same compound for the synthesis of the natural product (±)-apotacamine (**6**) which is devoid of any stereochemistry at the C_{16} position of the E-ring. Consequently, the 3:2-mixture of epimers present in **28** was treated with Meerwein's reagent at room temperature and this resulted in a smooth dehydration and formation of the unsaturated ester **34** in 80% yield (Scheme 8). Conversion of **34** to the natural product involved converting the lactam carbonyl group to the corresponding thiolactam using Lawesson's reagent followed by reductive removal of the thio group with Raney-Ni to give (±)-apotacamine (**6**) in 56% yield for the two steps.

In conclusion, we have developed a concise total synthesis of several members of the *vinca* and *tacaman* class of indole alkaloids. The central step in the synthesis consists of an intramolecular [3+2]-cycloaddition reaction of an α-diazo indoloamide which delivers the pentacyclic skeleton of the natural product in excellent yield. The acid lability of the oxabicyclic structure was exploited to establish the *trans*-D/E ring fusion of (±)-3*H*-epivincamine (**3**). Finally, a base induced keto-amide ring contraction was utilized to generate the E-ring of the natural product. A variation of the cascade sequence of reactions used to synthesize (±)-3*H*-epivincamine (**3**) was also employed for the synthesis of the *tacaman* alkaloids (±)-tacamonine (**5**) and (±)-apotacamine (**6**). We plan to use this cascade methodology toward the synthesis of other natural products, the results of which will be disclosed in due course.

Experimental Section

2-Pent-4-enoyl-2,3,4,9-tetrahydro-β-carbolin-1-one (13). To a stirred solution containing 2.0 g (10.7 mmol) of carboline **12**[40] in 30 mL of refluxing toluene was added a solution of pent-4-enoyl chloride (43 mmol) in 10 mL of toluene via cannula. The resulting mixture was heated at reflux for 8 h and then the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 2.1 g (74%) of carboline **13** as a white solid: mp 146−147 °C; IR (neat) 3301, 3064, 2925, 1691, and 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.48−2.54 (m, 2H), 3.07 (t, 2H, J = 6.4 Hz), 3.20 (t, 2H, J = 7.3 Hz), 4.35 (t, 2H, J = 6.4 Hz), 5.02 (dd, 1H, J = 10.2 and 1.6 Hz), 5.11 (dd, 1H, J = 17.2 and 1.6 Hz), 5.87−5.97 (m, 1H), 7.19 (t, 1H, J = 7.9 Hz), 7.38 (t, 1H, J = 8.3 Hz), 7.46 (d, 1H, J = 8.3 Hz), 7.64 (d, 1H, J = 8.6 Hz), and 9.36 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 29.1, 38.5, 44.1, 112.6, 115.4, 120.8, 121.1, 123.9, 124.8, 126.5, 126.6, 137.3, 138.6, 161.8, and 175.6.

2-Diazo-3-oxo-3-(1-oxo-2-pent-4-enoyl-1,2,3,4-tetrahydro-β-carbolin-9-yl)-propionic Acid Ethyl Ester (14). To a suspension of 0.19 g (4.7 mmol) of NaH in 20 mL of THF cooled to 0 °C was added 1.1 g (3.9 mmol) of carboline **13** dissolved in 20 mL of THF via cannula. The solution was allowed to stir at 0 °C for 30 min, after which time 1.0 g (5.9 mmol) of ethyl 2-diazomalonyl chloride[34] dissolved in 10 mL of THF was added via cannula. The resulting mixture was allowed to warm to rt overnight. The solution was then quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 1.1 g (70%) of α-diazo indole **14** as a yellow oil: IR (neat) 2137, 1712, 1679, 1646, and 1307 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, 3H, J = 7.3 Hz), 2.41−2.46 (m, 2H), 3.00 (t, 2H, J = 6.4 Hz), 3.08 (t, 2H, J = 7.3 Hz), 4.16 (q, 2H, J = 7.3 Hz), 4.28−4.35 (m, 2H), 5.00 (d, 1H, J = 10.2 Hz), 5.07 (dd, 1H, J = 17.2 and 1.6 Hz), 5.82−5.92 (m, 1H), 7.30 (t, 1H, J = 7.6 Hz), 7.46 (t, 1H, J = 8.3 Hz), 7.60 (d, 1H, J = 7.9 Hz), and 7.87 (d, 1H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.2, 29.0, 38.7, 42.3, 61.7, 114.2, 115.3, 121.0, 123.6, 125.4, 128.5, 128.8, 129.2, 137.3, 139.2, 159.9, 160.3, 161.7, and 175.4.

Rh(II)-Catalyzed Formation of Dipolar Cycloadduct 16. A 1.0 g (2.4 mmol) sample of α-diazo indole **14** was stirred with rhodium(II) acetate (2 mg) in 20 mL of benzene and the mixture was heated at reflux for 1 h. At the end of this time, the mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.87 g (95%) of cycloadduct **16** as a white solid: mp 169−170 °C; IR (neat) 3422, 2936, 1750, 1719, and 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.35 (t, 3H, J = 7.3 Hz), 1.82−1.88 (m, 1H), 2.04−2.14 (m, 1H), 2.46−2.53 (m, 2H), 2.61−2.85 (m, 4H), 2.96 (dd, 1H, J = 13.8 and 9.1 Hz), 3.08 (dt, 1H, J = 12.4 and 3.8 Hz), 4.29−4.45 (m, 2H), 4.87 (dd, 1H, J = 13.0 and 4.8 Hz), 7.34−7.42 (m, 2H), 7.53 (d, 1H, J = 7.0 Hz), and 8.21 (d, 1H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.4, 26.5, 29.1, 37.8, 38.9, 39.0, 62.8, 84.1, 88.3, 114.4, 116.1, 119.5, 125.0, 125.9, 128.2, 133.3, 134.7, 165.6, and 173.3; HRMS Calcd. for $[C_{21}H_{20}N_2O_5 + H^+]$: 381.1445. Found 381.1455.

Formation of Ring-Opened Product 17. A 0.7 g (1.8 mmol) sample of cycloadduct **16** was dissolved in 25 mL of CH_2Cl_2 and cooled to 0 °C. To this mixture was added 1.6 mL (12.9 mmol) of boron trifluoride etherate in CH_2Cl_2 (10 mL) via cannula. The mixture was allowed to warm to rt overnight. The solution was then added to a saturated aqueous solution of $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was

(40) Bracher, F.; Hildebrand, D. *Liebigs Ann. Chem*. **1992**, 1315.

subjected to flash silica gel chromatography to give 0.57 g (82%) of enamine **17** as a white solid: mp 182−184 °C; IR (neat) 3411, 2927, 1731, 1671, and 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, 3H, J = 7.3 Hz), 2.31−2.36 (m, 1H), 2.47−3.10 (m, 7H), 3.17 (dt, 1H, J = 12.2 and 3.8 Hz), 4.09−4.18 (m, 2H), 4.93−4.95 (m, 1H), 4.97 (s, 1H), 7.35−7.46 (m, 2H), 7.49 (d, 1H, J = 7.6 Hz), and 8.58 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.5, 27.6, 30.9, 37.7, 37.9, 62.1, 77.6, 113.4, 117.9, 118.9, 122.4, 125.2, 126.4, 127.1, 127.6, 128.4, 138.3, 168.3, 168.9, and 170.1; HRMS Calcd. for [$C_{21}H_{20}N_2O_5$ + H^+]: 381.1445. Found 381.1444.

11-Hydroxy-1,2,4,5,11,12-hexahydro-3*a*,9*b*-diaza-benzo[*a*]-naphtho[2,1,8-*cd*] azulene-3,10-dione (18). To a 0.5 g (1.3 mmol) sample of enamine **17** in 25 mL of acetonitrile was added 1.1 g (3.9 mmol) of magnesium iodide and the mixture was heated at reflux for 24 h. The solution was then allowed to cool to rt, added to CH_2Cl_2 and extracted with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.28 g (70%) of alcohol **18** as a pale orange solid: mp 48−50 °C; IR (neat) 3451, 3051, 2924, 1692, and 1667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.24−2.29 (m, 1H), 2.44−2.54 (m, 1H), 2.60−2.84 (m, 4H), 2.91−3.00 (m, 2H), 3.12 (dt, 1H, J = 12.1 and 3.8 Hz), 4.10 (d, 1H, J = 3.5 Hz), 4.61 (dt, 1H, J = 12.1 and 3.5 Hz), 5.16 (ddd, 1H, J = 12.7, 5.1 and 2.2 Hz), 7.35 (t, 1H, J = 8.3 Hz), 7.43 (t, 1H, J = 8.3 Hz), 7.48 (d, 1H, J = 7.6 Hz), and 8.55 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 27.0, 30.9, 36.8, 37.7, 69.6, 115.2, 117.3, 118.9, 122.4, 125.0, 126.5, 127.0, 127.3, 128.3, 137.7, 169.0, and 173.3.

11-Hydroxy-1,2,4,5,11,12,12*a*,12*b*-octahydro-3*a*,9*b*-diaza-benzo[*a*]naphtho [2,1,8-*cd*]azulene-3,10-dione (19). To a stirred solution of 0.21 g (0.68 mmol) of alcohol **18** in 3 mL of THF and 3 mL of EtOH was added a catalytic amount of PtO_2 (10 mol %). The resulting mixture was hydrogenated at 5 atm for 24 h, filtered through a pad of Celite, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.14 g (65%) of alcohol **19** as a white solid: mp 204−206 °C; IR (neat) 3389, 2924, 1697, 1624, and 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41−1.52 (m, 1H), 1.71−1.85 (m, 2H), 2.41−2.81 (m, 6H), 2.94−3.03 (m, 1H), 4.03 (d, 1H, J = 3.2 Hz), 4.57 (d, 1H, J = 12.1 Hz), 5.04 (dd, 1H, J = 12.4 and 4.1 Hz), 5.10−5.12 (m, 1H), 7.34−7.43 (m, 2H), 7.47 (d, 1H, J = 7.9 Hz), and 8.55 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 26.3, 32.8, 33.4, 36.1, 42.8, 58.1, 67.4, 117.4, 118.2, 122.7, 124.7, 126.0, 129.6, 130.7, 136.3, 170.2, and 173.8; HRMS Calcd. for [$C_{18}H_{18}N_2O_3$ + H^+]: 311.1390. Found 311.1386.

1,2,5,12,12*a*,12*b*-Hexahydro-4*H*-3*a*,9*b*-diaza-benzo[*a*]naphtho-[2,1,8-*cd*] azulene-3,10,11-trione (20). To a 0.22 g (0.52 mmol) slurry of Dess-Martin periodinane in 5 mL of CH_2Cl_2 was added 2 drops of *tert*-butyl alcohol and the mixture was stirred at rt for 15 min. A solution of 0.08 g (0.26 mmol) of alcohol **19** in 3 mL of CH_2Cl_2 was then added dropwise and the solution was stirred at rt for 2 h. At the end of this time, the mixture was diluted with CH_2Cl_2 and poured into a saturated aqueous $NaHCO_3$ solution containing an excess of $Na_2S_2O_3$. The mixture was stirred for 10 min, the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.06 g (72%) as a 4:1 mixture of tautomers of keto-amide **20** as an oily foam: IR (neat) 3383, 2929, 1733, 1696, 1643, and 1457 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.69 (dq, 1H, J = 13.0 and 4.4 Hz), 1.88−1.93(m, 1H), 2.45−2.73 (m, 4H), 2.79−3.01 (m, 2H), 3.02 (dd, 1H, J = 11.4 and 8.9 Hz), 3.09−3.13 (m, 1H), 4.89 (dd, 1H, J = 12.7 and 5.7 Hz, enol), 5.01−5.12 (m, 2H), 6.17 (d, 1H, J = 9.2 Hz, enol), 7.32−7.45 (m, 2H), 7.49 (d, 1H, J = 7.9 Hz), and 8.44, 8.53 (d, 1H, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 21.7, 24.9, 26.0, 32.7, 33.4, 35.2, 35.6, 42.8, 43.4, 57.7, 111.2, 117.4, 118.4, 118.7, 124.6, 125.0, 125.4, 126.2, 126.5, 129.9, 130.0, 135.9, 142.4, 162.1, 169.7, 195.2.

5-Hydroxy-1-oxo-1,2,3,3*a*,4,5,10,11*b*-octahydro-11*H*-5*a*,11*a*-diaza-benzo[*cd*] fluoranthene-5-carboxylic Acid Methyl Ester (21). To a 0.03 g (0.1 mmol) sample of keto-amide **20** in 5 mL of methanol was added 0.10 g (1.0 mmol) of anhydrous sodium carbonate. After stirring at rt for 1 h, the solvent was removed under reduced pressure, water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.03 g (90%) as a 3:1 mixture of diastereomers of **21** as an oily foam: IR (neat) 3243, 2952, 2849, 1748, 1621, and 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.52−1.55, 1.73−1.79 (m, 1H), 1.72, 1.93 (dq, 1H, J = 13.3 and 5.1 Hz), 2.26−2.41 (m, 3H), 2.48−2.74 (m, 3H), 2.91−3.10 (m, 2H), 3.65, 3.89 (s, 3H), 4.75, 4.79 (brd, 1H, J = 6.4 Hz), 4.92−5.00 (m, 1H), 7.05−7.08 (m, 1H), 7.11−7.17 (m, 2H), and 7.33−7.35, 7.43−7.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 20.8, 22.6, 23.3, 30.9, 32.5, 33.1, 38.2, 40.3, 41.9, 42.0, 53.5, 54.0, 54.4, 54.6, 81.5, 82.1, 109.5, 109.6, 110.6, 111.7, 118.3, 118.7, 120.6, 120.9, 122.2, 122.5, 128.1, 128.8, 131.3, 131.7, 134.8, 136.1, 169.3, 169.7, 172.3, 173.8; HRMS Calcd. for [$C_{19}H_{20}N_2O_4$ + H^+]: 341.1496. Found 341.1499.

2-Diazo-3-[2-(4-methylene-hexanoyl)-1-oxo-1,2,3,4,-tetrahydro-β-carbolin-9-yl]-3-oxo-propionic Acid Ethyl Ester (8). To a stirred solution of 0.75 g (5.9 mmol) of 4-methylene-hexanoic acid[41] in 25 mL of THF cooled to 0 °C was added 0.6 mL (5.9 mmol) of 4-methylmorpholine, followed by 0.8 mL (5.9 mmol) of isobutyl chloroformate dropwise. After stirring at 0 °C for 30 min, the white precipitate that formed was removed by filtration and was washed with 5 mL of THF. The filtrate was concentrated under reduced pressure and redissolved in 10 mL of toluene. In a separate flask, was placed 2.2 g (11.8 mmol) of carboline **12** in 50 mL of toluene. To this mixture was added the preformed mixed anhydride via cannula and the resulting solution was stirred at reflux for 12 h. At the end of this time, the mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.73 g (42%) of 2-(4-methylene-hexanoyl)-2,3,4,9-tetrahydro-β-carbolin-1-one as a white solid: mp 123−124 °C; IR (neat) 3308, 3058, 2966, 1692, and 1666 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.05 (t, 3H, J = 7.3 Hz), 2.09 (q, 2H, J = 7.3 Hz), 2.46 (t, 2H, J = 7.6 Hz), 3.07 (t, 2H, J = 6.4 Hz), 3.20 (t, 2H, J = 7.6 Hz), 4.34 (t, 2H, J = 6.4 Hz), 4.77 (brs, 2H), 7.19 (t, 1H, J = 7.0 Hz), 7.38 (t, 1H, J = 7.3 Hz), 7.45 (d, 1H, J = 8.3 Hz), 7.64 (d, 1H, J = 8.3 Hz), and 8.98 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.3, 20.9, 29.0, 31.3, 37.7, 44.2, 108.1, 112.6, 120.8, 121.0, 123.9, 124.8, 126.5, 126.6, 138.5, 150.2, 161.8, and 176.0.

To a suspension of 86 mg (2.2 mmol) of NaH in 15 mL of THF cooled to 0 °C was added 0.53 g (1.8 mmol) of the above carboline dissolved in 10 mL of THF via cannula. The solution was allowed to stir at 0 °C for 30 min, after which time 0.47 g (2.7 mmol) of ethyl 2-diazomalonyl chloride dissolved in 8 mL of THF was added via cannula. The resulting mixture was allowed to warm to rt overnight, the solution was then quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.47 g (60%) of α-diazo indole **8** as a yellow oil: IR (neat) 2967, 2937, 2140, 1718, and 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.04 (t, 3H, J = 7.6 Hz), 1.22 (t, 3H, J = 7.3 Hz), 2.07 (q, 2H, J = 7.6 Hz), 2.41 (t, 2H, J = 7.6 Hz), 3.00 (t, 2H, J = 6.4 Hz), 3.12 (t, 2H, J

(41) Yokoshima, S.; Ueda, T.; Kobayashi, S.; Sato, A.; Kuboyama, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2002**, *124*, 2137.

= 7.6 Hz), 4.16 (q, 2H, *J* = 7.3 Hz), 4.28−4.34 (m, 2H), 4.73 (s, 1H), 4.75 (s, 1H), 7.30 (t, 1H, *J* = 7.9 Hz), 7.46 (t, 1H, *J* = 8.6 Hz), 7.60 (d, 1H, *J* = 7.9 Hz), and 7.87 (d, 1H, *J* = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 12.3, 14.2, 21.2, 28.9, 31.2, 37.8, 42.4, 61.7, 108.1, 114.2, 121.0, 123.6, 125.4, 128.5, 128.8, 129.2, 139.2, 150.1, 159.9, 160.3, 161.8, and 175.8.

Rh(II)-Catalyzed Formation of Dipolar Cycloadduct 9. A 0.40 g (0.9 mmol) sample of α-diazo indole **8** was stirred with rhodium(II) acetate (2 mg) in 10 mL of benzene and the mixture was heated at reflux for 1 h. At the end of this time, the mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.35 g (95%) of cycloadduct **9** as a white solid: mp 153−154 °C; IR (neat) 2970, 1752, 1722, 1690, and 1376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.87 (t, 3H, *J* = 7.3 Hz), 1.00 (dt, 1H, *J* = 13.7 and 7.3 Hz), 1.22 (dt, 1H, *J* = 13.7 and 7.3 Hz), 1.34 (t, 3H, *J* = 7.3 Hz), 1.73−1.81 (m, 1H), 1.99−2.05 (m, 1H), 2.45−2.85 (m, 6H), 3.03 (dt, 1H, *J* = 12.4 and 3.5 Hz), 4.28−4.44 (m, 2H), 4.83 (dd, 1H, *J* = 13.0 and 4.8 Hz), 7.34−7.42 (m, 2H), 7.52 (d, 1H, *J* = 8.3 Hz), and 8.22 (d, 1H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 9.0, 14.0, 20.5, 29.3, 29.8, 31.4, 39.6, 42.4, 46.3, 62.8, 82.9, 92.5, 116.2, 117.6, 119.4, 125.0, 125.9, 128.2, 131.1, 134.4, 165.9, and 173.0; Anal. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.81; H, 6.15; N, 6.61.

Formation of Thiolactam 22. To a stirred solution of 0.40 g (1.0 mmol) of cycloadduct **9** in 30 mL of toluene under N_2 was added 0.50 g (1.2 mmol) of Lawesson's reagent at rt. The mixture was heated at reflux for 1 h, cooled to rt, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.41 g (95%) of thiolactam **22** as a white solid: mp 174−175 °C; IR (neat) 2971, 2936, 1751, 1723, 1663, 1390, and 1376 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.87 (t, 3H, *J* = 7.0 Hz), 0.91−0.97 (m, 1H), 1.15 (dt, 1H, *J* = 13.0 and 7.3 Hz), 1.35 (t, 3H, *J* = 7.3 Hz), 1.66 (dt, 1H, *J* = 13.7 and 3.5 Hz), 1.90−1.95 (m, 1H), 2.61−2.82 (m, 3H), 2.95−3.00 (m, 1H), 3.18 (dt, 1H, *J* = 14.6 and 4.1 Hz), 3.30−3.39 (m, 2H), 4.32−4.42 (m, 2H), 5.71 (dd, 1H, *J* = 13.3 and 4.8 Hz), 7.38−7.46 (m, 2H), 7.57 (d, 1H, *J* = 7.6 Hz), and 8.26 (d, 1H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 9.1, 14.0, 20.0, 31.8, 33.9, 40.1, 42.4, 47.2, 47.8, 62.9, 83.0, 91.3, 116.2, 116.4, 119.5, 125.2, 126.1, 127.7, 130.5, 134.4, 165.3, 165.5, and 209.9; HRMS Calcd. for [$C_{23}H_{24}N_2O_4S$ + H^+]: 425.1530. Found 425.1527.

12*a*-Ethyl-11-hydroxy-10-oxo-2,3,5,10,11,12,12*a*,12*b*-octahydro-1*H*,4*H*-3*a*,9*b*-diaza-benzo[*a*]naphtho[2,1,8-*cd*]azulene-11-carboxylic Acid Ethyl Ester (10). An excess amount of Raney nickel (ca 1.5 g) in a 50 mL round-bottom flask under N_2 was washed three times with water, twice with dry methanol, and finally three times with dry THF. A 0.15 g (0.35 mmol) sample of thiolactam **22** in 3 mL of THF was then added dropwise to the Raney nickel suspension in 5 mL of THF. The mixture was stirred vigorously for 24 h under 1 atm of hydrogen gas, then filtered through a pad of Celite, and concentrated under reduced pressure. The crude residue was not purified but was immediately carried onto the next reaction.

To a 0.14 g (0.35 mmol) sample of the above adduct in 4 mL of AcOH and 8 mL of H_2O was added 0.4 g of Zn dust. The resulting mixture was stirred vigorously at rt for 24 h and filtered through a pad of Celite. The filtrate was added to CH_2Cl_2 and extracted with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.10 g (75% over 2 steps) of amide **10** as a white solid: mp 54−56 °C; IR (neat) 3459, 2938, 2805, 2775, 1736, 1687, and 1457 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.75 (t, 3H, *J* = 7.6 Hz), 1.07 (dt, 1H, *J* = 14.6 and 7.6 Hz), 1.41 (t, 3H, *J* = 7.3 Hz), 1.45−1.75 (m, 4H), 1.85−1.89 (m, 1H), 2.04 (dt, 1H, *J* = 14.6 and 7.6 Hz), 2.46 (dt, 1H, *J* = 12.1 and 2.5 Hz), 2.60−2.70 (m, 3H), 2.84−3.02 (m, 3H), 4.17 (s, 1H), 4.31 (s, 1H), 4.38−4.47 (m, 2H), 7.27−7.30 (m, 2H), 7.39−7.41 (m, 1H), and 8.33−8.35 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 7.1, 14.0, 22.0, 22.4, 24.7, 36.9, 38.3, 41.3, 52.5, 56.2, 63.4, 65.7, 80.8, 117.0, 117.7, 119.2, 124.1, 124.7, 129.7, 133.7, 136.6, 169.5, and 172.6; Anal. Calcd. for $C_{23}H_{28}N_2O_4$: C, 69.67; H, 7.12; N, 7.07. Found: C, 69.67; H, 7.22; N, 6.82.

12*a*-Ethyl-2,3,5,12,12*a*,12*b*-hexahydro-1*H*,4*H*-3*a*,9*b*-diaza-benzo[*a*]naphtho [2,1,8-*cd*]azulene-10,11-dione (11). To a 0.05 g (0.13 mmol) sample of amide **10** in 2 mL of acetonitrile containing 3 drops *of tert*-butyl alcohol was added 0.07 g (0.26 mmol) of magnesium iodide. The mixture was heated at reflux for 24 h and then 0.5 mL of DMF was added. The resulting solution was refluxed for a further 48 h, allowed to cool to rt, added to CH_2Cl_2 and extracted with a saturated aqueous solution of $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.026 g (62%) of 12*a*-ethyl-11-hydroxy-2,3,4,5,-11,12,12*a*,12*b*-octahydro-1*H*-3*a*,9*b*-diaza-benzo[*a*]naphtho[2,1,8-*cd*] azulen-10-one as a white solid: mp 121−123 °C; IR (neat) 3460, 2937, 2804, 2756, 1686, and 1458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.69 (t, 3H, *J* = 7.6 Hz), 0.84 (dt, 1H, *J* = 14.6 and 7.6 Hz), 1.47−1.57 (m, 2H), 1.71−1.96 (m, 4H), 2.06 (dt, 1H, *J* = 14.6 and 7.6 Hz), 2.45 (dt, 1H, *J* = 11.4 and 3.2 Hz), 2.56−2.62 (m, 2H), 2.83−2.92 (m, 1H), 2.98−3.04 (m, 2H), 3.46 (s, 1H), 3.98 (d, 1H, *J* = 3.8 Hz), 4.71−4.76 (m, 1H), 7.30−7.37 (m, 2H), 7.43 (d, 1H, *J* = 7.6 Hz), and 8.55 (d, 1H, *J* = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 6.7, 21.9, 22.2, 25.7, 36.2, 37.0, 43.1, 52.1, 56.4, 67.0, 67.5, 117.2, 117.8, 120.1, 124.3, 125.0, 129.7, 132.8, 136.1, and 174.2.

To a 0.13 g (0.30 mmol) slurry of Dess-Martin periodinane in 5 mL of CH_2Cl_2 was added 0.5 mL of pyridine and the mixture was stirred at rt for 5 min. A solution of 0.05 g (0.15 mmol) of the above alcohol in 3 mL of CH_2Cl_2 was added dropwise and the solution was stirred at rt for 1 h. At the end of this time, the mixture was diluted with CH_2Cl_2 and poured into a saturated aqueous $NaHCO_3$ solution containing an excess of $Na_2S_2O_3$. The mixture was stirred for 10 min, the organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.025 g (50%) as a 1.6:1 mixture of tautomers of keto-amide **11** as an oily foam: IR (neat) 3411, 2932, 2805, 2753, 1727, 1696, and 1458 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.77, 0.79 (t, 3H), 1.21−1.30 (m, 2H), 1.40−1.63 (m, 2H), 1.80−2.05 (m, 2H), 2.29−2.66 (m, 4H), 2.80−3.02 (m, 3H), 3.41, 3.50 (brs, 1H), 5.76 (s, 1H, enol), 6.76 (s, 1H, enol), 7.30−7.46 (m, 3H), and 8.42, 8.48 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 7.0, 8.3, 21.8, 21.9, 22.2, 24.5, 25.8, 34.5, 35.1, 39.3, 41.6, 50.8, 51.6, 52.7, 55.7, 56.2, 66.6, 68.2, 117.1, 117.8, 118.0, 118.3, 119.8, 120.8, 122.5, 124.4, 125.0, 125.2, 125.3, 129.9, 130.2, 132.2, 135.6, 137.0, 140.0, 162.6, 163.4, and 197.4.

(±)-3*H*-Epivincamine (3). To a 0.02 g (0.06 mmol) sample of keto-amide **11** in 5 mL of methanol was added 0.06 g (0.60 mmol) of anhydrous sodium carbonate. After stirring at rt for 1 h, the solvent was removed under reduced pressure, water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.02 g (95%) of (±)-3*H*-epivincamine (**3**) as white crystals: mp 155−156 °C (lit.[20a] mp 163−163.5 °C); IR (neat) 3499, 2933, 2851, 2794, 2744, 1733, 1459, and 1444 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 0.84 (t, 3H, *J* = 7.3 Hz), 1.06 (dt, 1H, *J* = 13.3 and 2.9 Hz), 1.27−1.33 (m, 1H), 1.57−1.61 (m, 1H), 1.82−2.03 (m, 4H), 2.24−2.31 (m, 2H), 2.53 (dt, 1H, *J* = 11.4 and 4.4 Hz), 2.68−2.73 (m, 1H),

2.90−2.98 (m, 2H), 3.07−3.13 (m, 2H), 3.82 (s, 3H), 4.59 (s, 1H), 7.08−7.14 (m, 3H), and 7.44−7.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.3, 19.6, 21.1, 21.2, 32.1, 36.0, 43.8, 53.0, 54.2, 55.9, 67.1, 82.3, 106.3, 110.7, 118.4, 120.1, 121.3, 128.7, 132.5, 134.7, and 174.3.

2-(2-Ethyl-pent-4-enoyl)-2,3,4,9-tetrahydro-β-carbolin-1-one. To a stirred solution of 1.2 g (9.3 mmol) of 2-ethyl-pent-4-enoic acid[42] in 50 mL of THF cooled to 0 °C was added 1 mL (9.3 mmol) of 4-methylmorpholine, followed by 1.2 mL (9.3 mmol) of isobutyl chloroformate dropwise. After stirring at 0 °C for 30 min, the white precipitate that formed was removed by filtration and was washed with 10 mL of THF. The filtrate was concentrated under reduced pressure and redissolved in 20 mL of toluene. In a separate flask was placed 2.6 g (14.0 mmol) of carboline **12** in 100 mL of toluene. To this mixture was added the preformed mixed anhydride via cannula and the resulting solution was stirred at reflux for 12 h. At the end of this time, the mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 1.1 g (40%) of 2-(2-ethyl-pent-4-enoyl)-2,3,4,9-tetrahydro-β-carbolin-1-one as a white solid: mp 86−87 °C; IR (neat) 3311, 2964, 2932, 1681, 1661, and 1479 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, 3H, J = 7.3 Hz), 1.59−1.67 (m, 1H), 1.78−1.87 (m, 1H), 2.28−2.35 (m, 1H), 2.50−2.57 (m, 1H), 3.05 (t, 2H, J = 6.4 Hz), 3.83 (tt, 1H, J = 7.3 and 6.0 Hz), 4.33 (t, 2H, J = 6.4 Hz), 4.99 (dd, 1H, J = 10.2 and 1.9 Hz), 5.07 (dd, 1H, J = 17.2 and 1.9 Hz), 5.77−5.87 (m, 1H), 7.19 (t, 1H, J = 7.0 Hz), 7.38 (t, 1H, J = 7.3 Hz), 7.45 (d, 1H, J = 8.3 Hz), 7.64 (d, 1H, J = 8.3 Hz), and 9.20 (brs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.9, 21.5, 25.5, 36.8, 45.0, 47.4, 112.8, 116.8, 121.1, 121.3, 124.3, 125.1, 126.9, 136.3, 138.8, 162.3, and 179.8.

2-Diazo-3-[2-(2-ethyl-pent-4-enoyl)-1-oxo-1,2,3,4,-tetrahydro-β-carbolin-9-yl]-3-oxo-propionic Acid Ethyl Ester (23). To a suspension of 0.10 g (2.7 mmol) of NaH in 15 mL of THF cooled to 0 °C was added 0.67 g (2.3 mmol) of the above carboline dissolved in 10 mL of THF via cannula. The solution was allowed to stir at 0 °C for 30 min, after which time 0.60 g (3.4 mmol) of ethyl 2-diazomalonyl chloride[34] dissolved in 5 mL of THF was added via cannula. The resulting mixture was allowed to warm to rt overnight. The solution was then quenched with water, and extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. The organic extracts were filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.64 g (65%) of α-diazo indole **23** as a yellow oil: IR (neat) 2966, 2935, 2140, 1719, and 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, 3H, J = 7.3 Hz), 1.21 (t, 3H, J = 7.3 Hz), 1.53−1.60 (m, 1H), 1.72−1.79 (m, 1H), 2.22−2.28 (m, 1H), 2.42−2.49 (m, 1H), 2.97 (t, 2H, J = 6.4 Hz), 3.83 (tt, 1H, J = 7.3 and 6.0 Hz), 4.15 (q, 2H, J = 7.3 Hz), 4.28−4.35 (m, 2H), 4.97 (dd, 1H, J = 10.2 and 1.6 Hz), 5.04 (dd, 1H, J = 17.2 and 1.6 Hz), 5.72−5.82 (m, 1H), 7.30 (t, 1H, J = 7.3 Hz), 7.46 (t, 1H, J = 7.3 Hz), 7.59 (d, 1H, J = 7.9 Hz), and 7.89 (d, 1H, J = 8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 14.2, 21.4, 24.9, 36.3, 42.8, 47.2, 61.6, 114.2, 116.4, 120.9, 123.6, 125.4, 128.5, 129.0, 129.2, 136.0, 139.2, 159.9, 160.4, 161.8, and 179.1.

Rh(II)-Catalyzed Formation of Dipolar Cycloadduct 24. A 0.50 g (1.15 mmol) sample of α-diazo indoloamide **23** was stirred with rhodium(II) acetate (2 mg) in 25 mL of benzene and the mixture was heated at reflux for 1 h. At the end of this time, the mixture was allowed to cool to rt and the solvent was removed under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.42 g (90%) of cycloadduct **24** as a white solid: mp 151−152 °C; IR (neat) 2937, 1751, 1720, 1686, 1662, and 1377 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.01 (t, 3H, J = 7.6 Hz), 1.35 (t, 3H, J = 7.0 Hz), 1.41−1.48 (m, 1H), 1.82−1.85 (m, 2H), 1.99−2.05 (m, 1H), 2.44−2.52 (m, 2H), 2.66−2.74 (m, 1H), 2.80−2.86 (m, 2H), 2.97 (dd, 1H, J = 13.7 and 9.2 Hz), 3.09 (dt, 1H, J = 12.1 and 3.8 Hz), 4.29−4.46 (m, 2H), 4.91 (dd, 1H, J = 13.0 and 3.2 Hz), 7.34−7.42 (m, 2H), 7.53 (d, 1H, J = 7.6 Hz), and 8.22 (d, 1H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6, 14.0, 20.4, 22.2, 32.0, 38.0, 38.1, 38.9, 62.8, 84.1, 87.9, 113.9, 116.1, 119.5, 125.0, 125.8, 128.2, 133.5, 134.7, 165.6, 165.8, and 175.4; Anal. Calcd. for $C_{23}H_{24}N_2O_5$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.52; H, 5.96; N, 6.83.

Formation of Ring-Opened Cycloadduct 25. A 0.46 g (1.12 mmol) sample of cycloadduct **24** was dissolved in 25 mL of CH_2Cl_2 and cooled to 0 °C. To this mixture was added 1 mL (7.8 mmol) of boron trifluoride etherate in CH_2Cl_2 (10 mL) via cannula. The mixture was allowed to warm to rt overnight. The solution was then added to a saturated aqueous solution of $NaHCO_3$, the organic layer was separated, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.43 g (93%) of **25** as a white solid: mp 142−143 °C; IR (neat) 3416, 2966, 2934, 1732, 1669, and 1455 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.83−0.90 (m, 1H), 1.02 (t, 3H, J = 7.3 Hz), 1.10 (t, 3H, J = 7.0 Hz), 1.46−1.55 (m, 1H), 1.99−2.08 (m, 1H), 2.24−2.35 (m, 2H), 2.42−2.49 (m, 1H), 2.72−2.81 (m, 1H), 2.88−2.92 (m, 1H), 3.00−3.12 (m, 2H), 4.12 (dq, 2H, J = 7.3 and 1.6 Hz), 4.98 (s, 1H), 5.07−5.12 (m, 1H), 7.37 (t, 1H, J = 7.3 Hz), 7.44 (dt, 1H, J = 7.6 and 1.3 Hz), 7.48 (d, 1H, J = 7.9 Hz), and 8.58 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.5, 14.0, 21.6, 22.4, 32.5, 37.7, 38.1, 40.7, 62.1, 77.5, 113.0, 117.8, 118.9, 122.3, 125.2, 126.0, 127.0, 127.7, 128.4, 138.3, 168.2, 170.1, and 171.1; HRMS Calcd. for [$C_{23}H_{24}N_2O_5$ + H^+]: 409.1758. Found 409.1755.

2-Ethyl-11-hydroxy-3,10-dioxo-2,3,5,10,11,12,12*a*,12*b*-octahydro-1*H*,4*H*-3*a*,9*b*-diaza-benzo[*a*]naphtho[2,1,8-*cd*]azulene-11-carboxylic Acid Ethyl Ester (26). To a stirred solution of 0.20 g (0.49 mmol) of enamine **25** in 5 mL of THF and 5 mL of EtOH was added a catalytic amount of PtO_2 (10 mol %). The resulting mixture was hydrogenated at 5 atm for 2 h, filtered through a pad of Celite, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.14 g (70%) of lactam **26** as a white solid: mp 161−162 °C; IR (neat) 3290, 2934, 1748, 1691, and 1628 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 7.6 Hz), 1.38 (t, 3H, J = 7.1 Hz), 1.34−1.41 (m, 1H), 1.48−1.54 (m, 1H), 1.75−1.78 (m, 1H), 1.95−2.02 (m, 1H), 2.27−2.33 (m, 2H), 2.39 (dd, 1H, J = 15.2 and 7.1 Hz), 2.63−2.89 (m, 4H), 4.32 (s, 1H), 4.36−4.48 (m, 2H), 5.05 (dd, 1H, J = 12.4 and 4.8 Hz), 5.58 (brd, 1H, J = 7.1 Hz), 7.30−7.35 (m, 2H), 7.45 (d, 1H, J = 7.6 Hz), and 8.32 (d, 1H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.1, 14.0, 22.1, 23.6, 31.0, 31.9, 35.5, 42.6, 42.9, 57.6, 63.5, 78.3, 117.3, 118.2, 121.9, 124.5, 125.5, 130.0, 131.2, 136.9, 169.5, 172.2, and 172.4; Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 66.81; H, 6.39; N, 6.70.

2-Ethyl-1,2,5,12,12*a*,12*b*-hexahydro-4*H*-3*a*,9*b*-diaza-benzo[*a*]-naphtho[2,1,8-*cd*]azulene-3,10,11-trione (27). To a 0.14 g (0.34 mmol) sample of lactam **26** in 5 mL of acetonitrile was added 0.19 g (0.68 mmol) of magnesium iodide and the mixture was heated at reflux for 24 h. The solution was then allowed to cool to rt, added to a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was immediately used in the next reaction.

To a 0.12 g (0.34 mmol) sample of the above alcohol dissolved in 10 mL of CH_2Cl_2 was added 0.29 g (0.7 mmol) of Dess-Martin periodinane and the reaction was stirred at rt for 2 h. At the end of this time, the mixture was diluted with CH_2Cl_2 and poured into a saturated aqueous $NaHCO_3$ solution containing an excess of

(42) Kuehne, M.; Okuniewicz, F. J.; Kirkemo. C. L.; Bohnert, J. C. *J. Org. Chem.* **1982**, *47*, 1335.

$Na_2S_2O_3$. The mixture was stirred for 10 min, the organic layerwas separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.09 g (80%) as an 8:1 mixture of tautomers of keto-amide **27** as an orange oily foam: IR (neat) 3277, 2965, 2934, 2876, 1730, 1693, 1621, and 1456 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.78, 0.89 (t, 3H, J = 7.3 Hz), 1.48 (q, 1H, J = 13.0 Hz), 1.51−1.60 (m, 1H), 1.89−2.03 (m, 2H), 2.32−2.40 (m, 1H), 2.63−2.71 (m, 2H), 2.85−2.95 (m, 2H), 3.02 (dd, 1H, J = 11.4 and 9.2 Hz), 3.08−3.13 (m, 1H), 5.00−5.10 (m, 2H), 6.17 (d, 1H, J = 9.2 Hz, enol), 7.33−7.45 (m, 2H), 7.48 (d, 1H, J = 7.9 Hz), and 8.43, 8.54 (d, 1H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 21.9, 23.6, 30.7, 34.8, 42.9, 43.1, 43.6, 58.0, 117.4, 118.7, 124.6, 125.4, 126.5, 129.3, 130.1, 135.9, 162.2, 172.2, and 195.3.

(±)-Tacamonine (5). To a 0.02 g (0.06 mmol) sample of keto-amide **27** in 3 mL of methanol was added 0.064 g (0.6 mmol) of anhydrous sodium carbonate. After stirring at rt for 1 h, the solvent was removed under reduced pressure, water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue containing **28** was immediately used in the next reaction.

To a stirred solution of 0.02 g (0.06 mmol) of the above mixture in 4 mL of THF cooled to 0 °C was added 0.3 mL (0.3 mmol) of lithium aluminum hydride. Once the addition was complete, the reaction was heated at reflux for 1 h, slowly quenched with water, followed by the addition of Rochelle salt and stirred for 30 min. The mixture was then partitioned between ethyl acetate and water. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. The combined organic layers were washed with water, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was immediately used in the next reaction.

To a 0.02 g (0.06 mmol) sample of the above mixture dissolved in 3 mL of THF and 1 mL of H_2O was added 0.064 g (0.3 mmol) of sodium periodate and the reaction mixture was stirred vigorously at rt for 4 h. At the end of this time, the mixture was extracted with ethyl acetate. The combined organic layers were washed with a saturated aqueous solution of Na_2SO_3, water, brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.01 g (60% over 3 steps) of (±)-tacamonine (**5**) as white needles: mp 140−141 °C, (lit.[22] mp 143 °C); IR (neat) 2917, 1700, 1635, 1453, and 1383 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.57 (q, 1H, J = 13.0 Hz), 0.85 (t, 3H, J = 7.3 Hz), 1.07−1.15 (m, 2H), 1.49−1.57 (m, 1H), 1.67 (brd, 1H, J = 13.0 Hz), 2.04 (t, 1H, J = 11.1 Hz), 2.43−2.53 (m, 2H), 2.63−2.67 (m, 1H), 2.67 (dd, 1H, J = 17.2 and 2.5 Hz), 2.86−2.95 (m, 1H), 3.01 (dd, 1H, J = 17.2 and 5.1 Hz), 3.34−3.38 (m, 2H), 4.35−4.37 (m, 1H), 7.27−7.35 (m, 2H), 7.45 (dd, 1H, J = 7.0 and 1.9 Hz), and 8.38 (dd, 1H, J = 7.3 and 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 16.3, 26.8, 31.9, 34.4, 37.6, 39.7, 50.3, 50.5, 53.3, 112.8, 116.3, 118.1, 123.8, 124.3, 129.9, 131.5, 134.4, and 167.4.

2-Ethyl-11-hydroxy-2,3,4,5,11,12-hexahydro-1*H*-3*a*,9*b*-diazabenzo[*a*] naphtho[2,1,8-*cd*]azulen-10-one (32). To a stirred solution of 0.2 g (0.49 mmol) of cycloadduct **24** in 15 mL of toluene under N_2 was added 0.2 g (0.49 mmol) of Lawesson's reagent at rt. The mixture was heated at reflux for 30 min, cooled to rt, and concentrated under reduced pressure. The crude thiolactam was subjected to flash silica gel chromatography to give 0.16 g (78%) as a 1:1 mixture of diastereomers of **29** and was immediately used in the next reaction.

An excess amount of Raney nickel (ca. 2.0 g) in a 50 mL round-bottom flask under N_2 was washed three times with water, twice with dry methanol, and finally three times with dry THF. A 0.16 g (0.38 mmol) sample of the above thiolactam in 10 mL of THF was then added dropwise to the Raney nickel suspension in 15 mL of THF. The mixture was stirred vigorously for 24 h under 1 atm of hydrogen gas, filtered through a pad of Celite, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.11 g (73%) as a 1:1 mixture of diastereomers of **30** and was immediately used in the next reaction.

To a 0.11 g (0.28 mmol) sample of **30** in 5 mL of acetonitrile was added 0.16 g (0.56 mmol) of magnesium iodide and the mixture was heated at reflux for 24 h. The solution was then allowed to cool to rt, added to a saturated aqueous solution of $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.07 g (77%) as a 1:1 mixture of diastereomers of the amido alcohol **32** as a clear oil: IR (neat) 3468, 2958, 2921, 2825, 1686, and 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.96, 0.98 (t, 3H, J = 7.6 Hz), 1.31−1.49 (m, 2H), 1.83−2.06 (m, 2H), 2.20−2.54 (m, 2H), 2.62−3.22 (m, 7H), 4.07 (brs, 1H), 4.50−4.57 (m, 1H), 7.29−7.38 (m, 2H), 7.43 (d, 1H, J = 7.9 Hz), 8.52, 8.54 (d, 1H, J = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 11.7, 21.9, 22.3, 26.0, 27.1, 33.8, 34.4, 37.1, 37.3, 37.4, 37.6, 50.0, 50.5, 55.8, 57.0, 69.9, 70.1, 108.2, 108.8, 117.2, 117.5, 118.27, 118.3, 120.8, 121.3, 124.5, 126.0, 129.0, 129.7, 132.2, 132.4, 137.7, 174.1, 174.3; HRMS Calcd. for [$C_{20}H_{20}N_2O_2$ + H^+]: 323.1754. Found 323.1754.

2-Ethyl-1-oxo-1,2,3,3*a*,10,11*b*-hexahydro-11*H*-5*a*,11*a*-diazabenzo[*cd*] fluoranthene-5-carboxylic Acid Methyl Ester (34). To a stirred solution of 0.02 g (0.054 mmol) of hydroxy ester **28** in 4 mL of CH_2Cl_2 was added 0.02 g (0.14 mmol) of trimethyloxonium tetrafluoroborate and the mixture was stirred at rt overnight. At the end of this time, the solution was diluted with H_2O and extracted with CH_2Cl_2. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.015 g (80%) of lactam **34** as a white solid: mp 175−176 °C; IR (neat) 2929, 1731, 1644, 1455, and 1427 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, 3H, J = 7.3 Hz), 1.14 (q, 1H, J = 13.0 Hz), 1.35−1.42 (m, 1H), 1.86−2.01 (m, 2H), 2.23−2.29 (m, 1H), 2.66−2.69 (m, 1H), 2.93−3.06 (m, 3H), 3.99 (s, 3H), 4.91 (brd, 1H, J = 7.6 Hz), 4.96−5.04 (m, 1H), 6.29 (d, 1H, J = 7.0 Hz), 7.14−7.27 (m, 3H), and 7.47 (d, 1H, J = 7.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 20.6, 23.0, 28.6, 32.2, 42.8, 43.5, 52.7, 53.3, 112.5, 112.8, 118.5, 119.8, 120.9, 122.9, 128.9, 130.0, 130.4, 134.7, 163.5, and 171.6; HRMS Calcd. for [$C_{21}H_{22}N_2O_3$ + H^+]: 351.1703. Found 351.1700.

(±)-Apotacamine (6). To a stirred solution of 0.02 g (0.057 mmol) of lactam **34** in 3 mL of toluene under N_2 was added 0.02 g (0.057 mmol) of Lawesson's reagent at rt. The mixture was heated at reflux for 1 h, cooled to rt, and concentrated under reduced pressure. The crude thiolactam was subjected to flash silica gel chromatography and immediately used in the next reaction.

An excess amount of Raney nickel (ca. 0.25 g) in a 25 mL round-bottom flask under N_2 was washed three times with water, twice with dry methanol, and finally three times with dry THF. A 0.02 g (0.057 mmol) sample of the above thiolactam in 2 mL of THF was then added dropwise to the Raney nickel suspension in 3 mL of THF. The mixture was stirred vigorously for 24 h under 1 atm of hydrogen gas, filtered through a pad of Celite, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.01 g (56% over 2 steps) of (±)-apotacamine (**6**)[15] as a light-yellow oil: IR (neat) 2922, 2851, 1731, 1635, and 1455 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.48 (q, 1H, J = 12.7 Hz), 0.85 (t, 3H, J = 7.3 Hz), 1.04−1.18 (m, 2H), 1.48−1.57 (m, 1H), 1.73 (brd, 1H, J = 12.7 Hz), 2.23 (t, 1H, J = 11.1 Hz), 2.56−2.61 (m, 1H), 2.70−2.72 (m, 1H), 2.77−2.85 (m, 1H), 2.97−3.06 (m, 1H), 3.35−3.38 (m, 2H), 3.95 (s, 3H), 4.48−4.50 (m, 1H), 6.40 (d, 1H, J = 7.3 Hz), 7.12−7.25 (m, 3H), and 7.48 (d, 1H, J = 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ

11.2, 16.2, 26.8, 31.3, 33.1, 36.7, 50.6, 50.7, 51.8, 52.5, 108.6, 112.5, 118.3, 120.3, 122.1, 123.4, 128.8, 129.1, 129.9, 134.3, and 163.6.

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Supporting Information Available: ^{1}H and ^{13}C NMR data of various key compounds lacking CHN analyses together with an ORTEP drawing for compound **26** as well as the corresponding CIF files. We will deposit atomic coordinates for compound **26** with the Cambridge Crystallographic Data Centre. This material is available free of charge via the Internet at http://pubs.acs.org.

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