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A Study of Vinyl Radical Cyclization Using *N*-Alkenyl-7-bromo-Substituted Hexahydroindolinones

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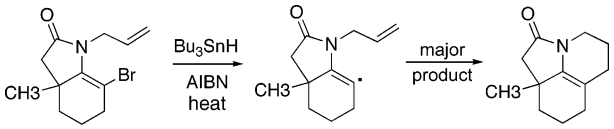
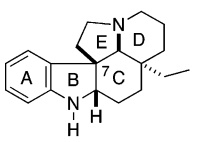
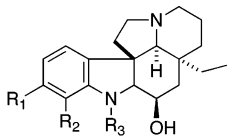


A new method for the synthesis of the octahydropyrrolo[3,2,1-*ij*]quinoline ring system that possesses the characteristic skeleton of the aspidosperma family of alkaloids has been developed. The method utilizes an intramolecular Diels−Alder reaction of an amido-substituted furan across a tethered indole π-bond. To apply this strategy to the synthesis of the indole alkaloid spegazzinidine, it was necessary to address the problem of assembling the final D-ring of the pentacyclic skeleton. Radical cyclization of a model *N*-allyl-7-bromo-3a-methylhexahydroindolinone system was found to preferentially lead to the 6-*endo-trig* cyclization product, with the best yield being obtained under high dilution conditions. The six-membered cyclized product is generated through two reaction pathways: (a) 6-*endo-trig* ring closure and (b) rearrangement of an intermediate methylene−cyclopentyl radical obtained by 5-*exo-trig* cyclization. A number of related 7-bromo-substituted hexahydroindolinones containing tethered olefinic groups were prepared and found to undergo efficient cyclization under both radical and palladium-mediated reaction conditions. Vinyl radical cyclization with several *N*-butenyl-substituted systems afforded a mixture of 6-*exo* and 7-*endo* cyclization products. A protocol to introduce an ethyl substituent into the C_{20}-position of the aspidospermidine skeleton was also developed.

The indole alkaloids feature many indoline-containing compounds with important biological activity[1] including strychnine[2] and the clinically used anticancer agents vincristine and vinblastine.[3,4] These compounds share as part of their structure, the [6,5,6,5]-ABCE ring system found in aspidospermidine (**1**) and spegazzinidine (**2**). The presence of the sterically congested C(7) quaternary carbon center represents a particular challenge toward the synthesis of this family of natural products.[5] The structures of these alkaloids have long attracted the attention of the synthetic community and a major focus of interest has been in finding efficient routes for the introduction of the B/C cyclic junction, shown in aspidospermidine **1**.[6] Our interest in this area led us to consider an approach to the ABCE tetracyclic core **4** wherein an amido-substituted furan undergoes an intramolecular Diels−Alder reaction across a tethered indole π-bond. In



Aspidospermidine (**1**)



Spegazzinidine (**2**)
$R_1 = R_2 = OH$; $R_3 = COCH_3$

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(3) (a) Kutney, J. P.; Ratcliffe, A. H.; Treasurywala, A. M.; Wunderly, S. *Heterocycles* **1975**, *3*, 639. (b) Vukovic, J.; Goodbody, A. E.; Kutney, J. P.; Misawa, M. *Tetrahedron* **1988**, *44*, 325. (c) Kutney, J. P.; Choi, L. S. L.; Nakano, J.; Tsukamoto, H.; McHugh, M.; Boulet, C. A. *Heterocycles* **1988**, *27*, 1845.

(4) Kuehne, M. E.; Matson, P. A.; Bornmann, W. G. *J. Org. Chem.* **1991**, *56*, 513.

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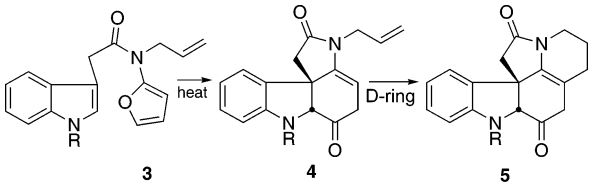

earlier reports we showed that the [4+2]-cycloaddition rearrangement sequence[7] was remarkably efficient given that two aromatic rings were compromised in the reaction (Scheme 1).[8] To apply this strategy to the synthesis of the alkaloid spegazzinidine (**2**),[9] we needed to address the problem of assembling the final D-ring of the pentacyclic skeleton and to insert the necessary ethyl group. In this paper, we report an account of our efforts dealing with the preparation of various octahydropyrrolo[3,2,1-*ij*]quinolines from readily available amines and 2-(oxocyclohexyl)acetic acid.[10]

Results and Discussion

The potential of using hexahydroindolinone derivatives such as **4** for the synthesis of various aspidosperma alkaloids prompted us to first carry out some model studies to probe the likelihood of this approach. Our synthesis of the starting bicyclic lactam substrates follows a methodology similar to that previously described in the literature.[11] Condensation of the appropriate amine with 1-methyl-2-(oxocyclohexyl)acetic acid **6** under Dean−Stark conditions in xylene at 140 °C for 1 h afforded the desired bicyclic lactam in high yield. Our initial investigation began with the synthesis of hexahydroindolinone **7**, which was readily assembled by heating a sample of ketoacid **6** with 3-(*tert*-butyldimethylsilyloxy)propylamine. We reasoned that by converting the OTBS functionality into a better leaving group (i.e., X = Br or OMs), it might be possible to induce the modestly activated enamide π-bond to undergo cyclization to give octahydropyrrolo[3,2,1-*ij*]quinoline **9**.[12] However, all of our attempts to convert the OTBS group present in **7** into the corresponding hydroxyl group resulted in the formation of 1-oxa-4a-azabenzo[*c*]inden-5-one **10** as the exclusive product in 72% isolated yield (Scheme 2). To avoid this undesired iminium ion cyclization, we first prepared 1,3,3a,4,5,6-hexahydroindol-2-one (NH parent) and treated it with NaH/DMF followed by a subsequent alkylation with 1,3-dibromobutane. This sequence of reactions afforded bromide **8** in 40% overall yield for the two steps. Unfortunately, all of our efforts to induce the cyclization

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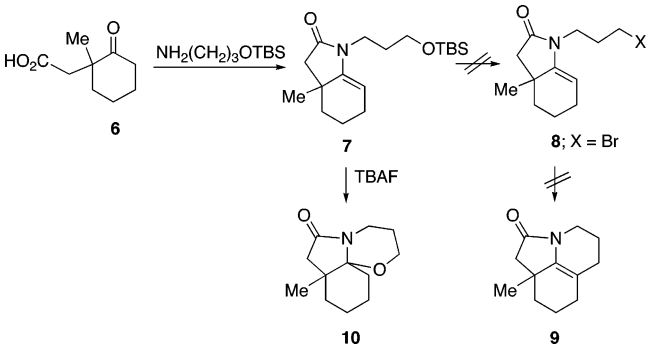

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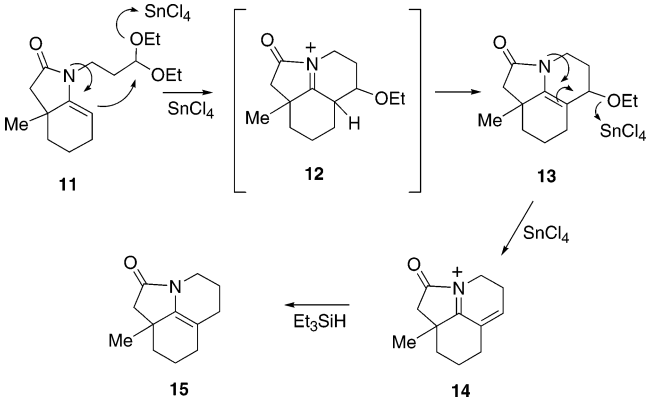

of **8** into **9** failed to produce the desired compound. We were able, however, to bring about the desired cyclization by using the more activated *N*-(3,3-diethoxypropyl)-substituted hexahydroindolinone **11**. When **11** was treated with $SnCl_4/Et_3SiH$ in toluene it reacted to furnish pyrrolo[3,2,1-*ij*]quinolinone **15** in 85% yield (Scheme 3). The conversion of **11** into **15** undoubtedly proceeds via the intermediacy of *N*-acyliminium ion **12**. The most obvious path available to **12** is proton loss thereby providing **13** as a transient and nondetectable intermediate. More than likely, under the Lewis acid conditions, **13** suffers loss of the ethoxy group and the resulting iminium ion **14** reacts further by a hydride transfer from Et_3SiH to give **15**. Bromide **8** is insufficiently activated to undergo the cyclization.

Radical-Mediated Cyclizations

Although we were able to effect the desired hexahydroindolinone cyclization (i.e., **11** → **15**), this approach had several drawbacks. The high cost of using 3,3-diethoxypropylamine and the difficulty associated with the $SnCl_4/Et_3SiH$ scale-up were most troublesome. It occurred to us that we might circumvent these troublesome issues if we could carry out a free radical-induced cyclization reaction using 3-(bromopropyl)hexahydroindolinone **8**. The development of free radical cyclization reactions in total synthesis and in new synthetic methodology has been extensively investigated in recent years.[13] Radical cyclizations of highly reactive aryl and vinyl radicals onto double and triple bonds have proven to be very useful for construction of both carbocycles and heterocycles.[14] To investigate whether bromo-substituted hexahydroindolinones could be used as precursors for

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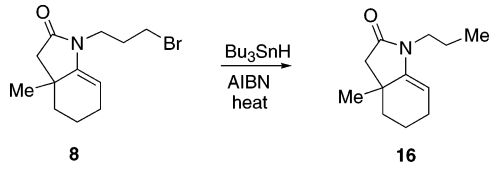
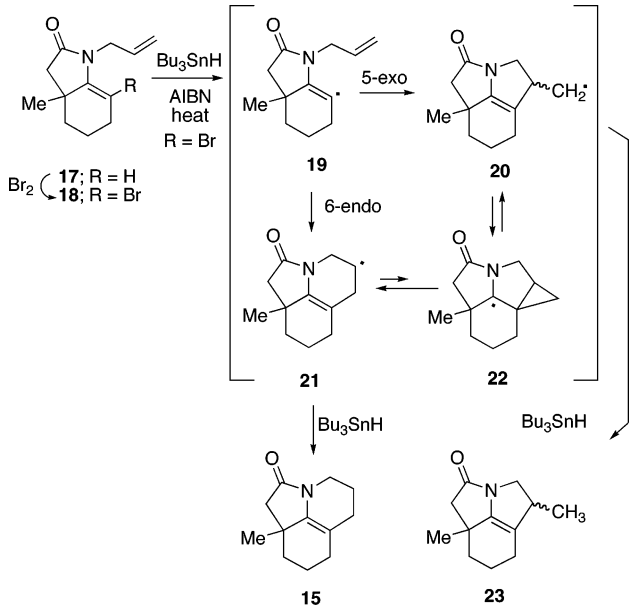


radical cyclization chemistry, we explored the reaction of **8** with *n*-Bu_3SnH under standard radical-forming conditions. We found, however, that the initially formed primary radical failed to cyclize on the enamido π-bond but instead gave the reduction product **16** in 84% yield even under very low concentrations of *n*-Bu_3SnH (Scheme 4).

We thought that radical cyclization might be enhanced by working with the more reactive vinyl radical derived from a 7-bromo-substituted hexahydroindolinone derivative. Aza heterocycles of various ring sizes have been obtained by radical addition to *N*-vinyl amides (enamides).[15] However, the use of related compounds containing the *N*-vinyl unit such as enaminones has been less frequently studied.[16] As far as we can tell, there were no examples in the literature describing an intramolecular addition of an enamido vinyl radical onto any type of π-system when we initiated our studies with hexahydroindolinone **18** (vide infra). We reasoned that the selective bromination of the enamido π-bond present in **17** (Scheme 5) should be extremely rapid and efficient since analogous examples are known.[17] We hoped that generation of a cyclohexenyl radical (i.e., **19**) from bromide **18** would initiate a 6-*endo-trig* cyclization ulti-

SCHEME 5



mately leading to **15** after abstraction of hydrogen from tributyltin hydride (Scheme 5). A model study designed to test the feasibility of this concept began by the condensation of allylamine with 1-methyl(2-oxocyclohexyl)acetic acid to give the desired bicyclic lactam **17** in 90% yield. Hexahydroindolinone **17** was subsequently treated with bromine in CH_2Cl_2 followed by reaction with NEt_3 to deliver the cyclization precursor **18** in 95% yield. Exposure of **18** to several radical cyclization conditions led to various mixtures of the 6-*endo* and 5-*exo-trig* cyclization products **15** and **23**, with the best yield and product ratio obtained by using *n*-Bu_3SnH/AIBN in refluxing benzene under slow addition conditions.

Since their introduction in 1982,[18] vinyl radical cyclizations have been widely used in organic synthesis,[13,19] although preparative sequences incorporating vinyl radicals as part of a heterocyclic array are much less common.[20] Seminal studies by the groups of Beckwith[21] and Stork[22] have shown that, under tin hydride mediated reaction conditions, vinyl radical cyclization gives a mixture of both 5-*exo* and 6-*endo* products. The kinetic work by Beckwith revealed that formation of the six-membered ring is not solely due to a 6-*endo-trig* cyclization but is the result of a rapid rearrangement of the methylene−cyclopentyl radical, via a reversible 3-*exo-trig* cyclization.[23] We thought that by keeping the hydride concentration low, rearrangement of the kinetically formed radical **20** derived from bromide **18** to the thermodynamically more stable radical **21** would occur,

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(17) (a) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459. (b) Goffin, E.; Legrand, Y.; Viehe, H. G. *J. Chem. Res., Synop.* **1977**, 105.

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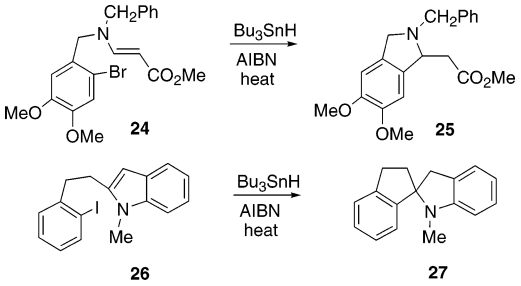
SCHEME 6

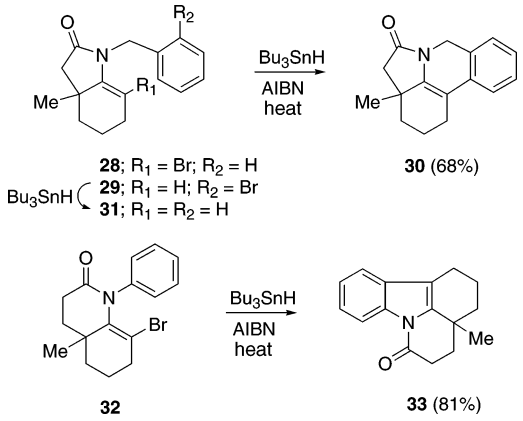


leading to product **15**. Comparison of the strain energies of **20** and **21**, as well as radical stability, supports this idea. Indeed, when **18** (0.01 M) was treated with tributyltin hydride and a catalytic amount of AIBN, six-membered-ring product **15** was the major product formed in 89% yield. In contrast, when bromide **18** was treated with *n*-Bu_3SnH at a concentration of 0.1 M, a significant quantity (20%) of the 5-*exo* cyclization product **23** (3:1 mixture of diastereomers) was obtained along with the 6-*endo* cyclization product **15** in a ratio of 1:3, together with the simple reduction product **17** (19%). These results clearly indicate that the vinyl radical rearrangement pathway is responsible, to a considerable extent, for the regiochemical outcome of the reaction.

The preferential formation of the pyrrolo[3,2,1-*ij*]-quinoline ring system from hexahydroindolinone **18** stands in marked contrast with intramolecular aryl radical cyclization studies with somewhat related *N*-vinyl amides. Radical cyclization of *N*-benzyl enamides such as **24** has been studied and found to furnish a product derived from exclusive 5-*exo-trig* closure (**25**).[24] A similar reactivity profile was noted in an aryl cyclization reaction involving indole **26** (Scheme 6). Thus, the primary product obtained from the tin-induced radical cyclization of iodide **26** was that derived from a 5-*exo-trig* spirocyclization at C_2 of the indole ring.[25,26] With these related systems, radical rearrangement is unlikely to occur as this would disrupt aromaticity and consequently only the kinetically derived product from 5-*exo-trig* cyclization is observed.

The cyclization method was next extended to the *N*-benzyl-substituted hexahydroindolinones **28** and **29**. Exposure of bromo-enamide **28** to *n*-Bu_3SnH under standard radical forming conditions furnished pyrrolo-[3,2,1-*de*]phenanthridinone **30** in 68% yield together with 27% of the reduced hexahydroindolinone **31**. In this case, selective 6-*endo* cyclization took place on the aromatic ring. Interestingly, the closely related *o*-bromobenzyl-substituted hexahydroindolinone **29** failed to cyclize but instead gave largely the reduction product **31** in 75% yield. The different behavior observed with these two

SCHEME 7



systems is presumably reflective of the slower rate of addition to the enamido π-bond.[24] The successful cyclization of **28** encouraged us to also apply the reaction to the simpler 8-bromohexahydro-1*H*-quinolinone system **32**. Gratifyingly, subjecting a sample of **32** to the standard radical conditions furnished the cyclized pyrido[3,2,1-*jk*]-carbazolonone **33** in 81% yield, thereby demonstrating the facility of the 5-*exo-trig* cyclization pathway (Scheme 7).[26,27] At this juncture, we decided to extend our studies toward the homologous *N*-butenyl-substituted hexahydroindolinone **34**. A review of the literature revealed, somewhat surprisingly, that simple 1,6-heptadienyl radicals have not been thoroughly investigated.[13] This state of affairs is most likely attributable to the poorer prospects for synthetic utility of this higher homologue of the 1,5-hexadienyl radical. On the basis of using the parent 6-heptenyl radical as a model,[28] the rate of 6-*exo-trig* cyclization is expected to be an order of magnitude slower than the 1,5-hexadienyl cyclization, its ring closure should be considerably less regioselective, and it is also possible that a [1,5]-hydrogen atom transfer could occur to produce a 1-butenylallyl-type radical. A solution of **34** in benzene was treated with *n*-Bu_3SnH/AlBN at 80 °C for 12 h.

Workup and chromatography led to a 7:2 mixture of the 6-*exo* and 7-*endo* cyclization products.[29] The regiochemical preference in cyclization of vinyl radicals is known to parallel that of the alkyl analogues.[30] Although 6-*exo-trig* and 7-*endo-trig* modes of cyclization are possible with hexahydroindolinone **34**, six-membered-ring formation predominates (Scheme 8). Interestingly, when 7-bromo-*N*-(3-bromobut-3-enyl)hexahydroindolinone **37** was reacted with *n*-Bu_3SnH/AlBN under similar conditions, the same two products were formed but in a strikingly different ratio. With this system, the preferred route now corresponds to 7-*endo-trig* cyclization leading to **36** in 72% yield together with minor quantities of the 6-*exo* cyclized product **35** (18%). The presence of a

(23) More recently, Crich's group reported preferential formation of the 5-*exo* product when the reaction was conducted in a rapid radical quenching environment (i.e., PhSeSePh/Bu_3SnH), reconfirming that the five-membered ring closure is the kinetically favored process, see: Crich, D.; Hwang, J.-T.; Liu, H. *Tetrahedron Lett.* **1996**, *37*, 3105.

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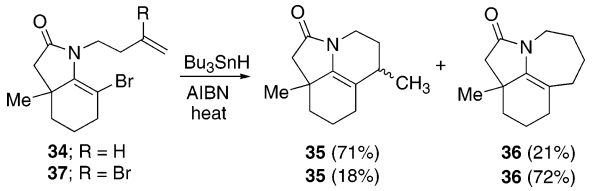
(27) The cyclization of **32** to **33** is somewhat related to systems studied by Ishibashi and co-workers. For leading references, see: Ishibashi, H.; Ishita, A.; Tamura, O. *Tetrahedron Lett.* **2002**, *43*, 473.

(28) (a) Beckwith, A. L. J.; Moad, G. *J. Chem. Soc., Chem. Commun.* **1974**, 472. (b) Chatgilialoglu, C.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1981**, *103*, 7739. (c) Newcomb, M. *Tetrahedron* **1993**, *49*, 1151.

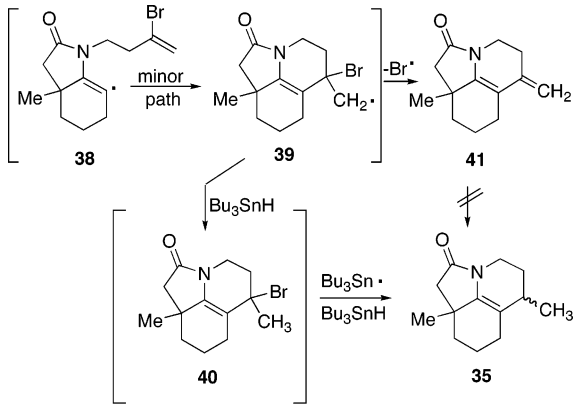
(29) Pyrrolo[3.2.1-*ij*]quinolin-2-one **35** was obtained as a 2.3:1 mixture of diastereomers.

(30) Beckwith, A. L. J.; Ingold, K. U. In *Rearrangement in Ground and Excited States*; de Mayo, P., Ed.; Academic Press: New York, 1980.

SCHEME 8



SCHEME 9

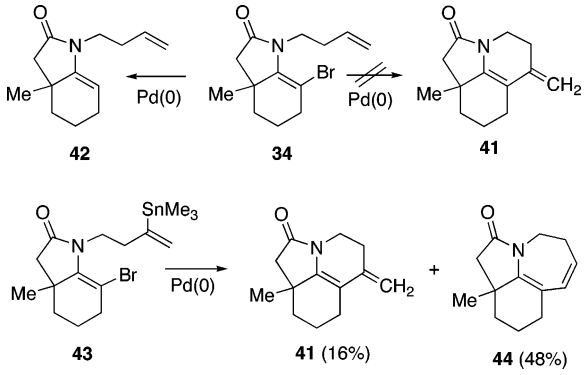


3-bromo substituent on the *N*-but-3-enyl π-bond sufficiently retards the 6-*exo-trig* cyclization, so that 7-*endo* closure now becomes the predominant path. Formation of azepine[3,2,1-*hi*]indolone **36** from the initially generated 7-*endo* cyclized radical would involve hydrogen atom abstraction from *n*-Bu_3SnH followed by further reaction of the resulting secondary bromide with tributyltin radical in the traditional manner. The isolation of **35** as the minor product from this reaction is also consistent with the suggestion that the 6-*exo* cyclized radical (i.e., **39**) is rapidly quenched by hydrogen abstraction to give tertiary bromide **40**, which is then reduced under the reaction conditions (Scheme 9). Another possible explanation is that radical **39** ejects the adjacent bromine atom to give diene **41**, which in turn is reduced to **35**.[31] Although this pathway seems less likely, we decided to prepare a sample of **41** in order to probe the likelihood of this possibility. We found (vide infra) that when diene **41** was subjected to the standard *n*-Bu_3SnH/AIBN conditions, it could be recovered unchanged, thereby eliminating this mechanistic possibility.

Palladium-Mediated Cyclizations

Our first attempt toward the synthesis of diene **41** involved an intramolecular Heck reaction.[32] Cyclization reactions mediated by palladium are often complementary to those proceeding by radical intermediates.[33] They often occur from the same starting material (i.e., aromatic or vinyl halides carrying an unsaturated chain) and lead to cyclized products with different oxidation states.[34] The palladium-mediated reaction delivers the unsaturated

SCHEME 10



product.[35] In contrast, radical cyclization mediated by tributyltin hydride leads to the reduced product.[13] Both processes are generally performed under mild conditions and tolerate many functional groups. However, our attempts to induce the cyclization of 7-bromohexahydroindolinone **34** to diene **41** under standard experimental conditions led only to the reduced *N*-butenyl system **42** (Scheme 10). The structure of **42** was unequivocally established by comparison with a sample prepared by treating 1-methyl-2-(oxocyclohexyl)acetic acid (**6**) with 3-butenyl-1-amine (Scheme 10). A successful synthesis of diene **41** was eventually carried out by an intramolecular Stille cross-coupling reaction[36] of hexahydroindolinone **43**. The intramolecular Stille reaction was performed with $PdCl_2(PPh_3)_2$ (5 mol %) as catalyst, using a microwave reactor at 100 °C. To our surprise, the palladium-catalyzed reaction of **43** gave the seven-membered cyclized diene **44** as the major product in 48% yield together with lesser quantities of the six-ring diene **41** (16%). The formation of **44** presumably results from a preferential 7-*endo-trig* cyclization, and the regiochemical outcome is similar to that encountered with the radical cyclization of dibromide **37** (see Scheme 8).

The reluctance of *N*-butenylhexahydroindolinone **34** to undergo a 6-*exo-trig* Pd(0)-catalyzed carbocyclization led us to investigate the influence of the size of the *N*-alkenyl substituent on the course of the reaction. We found that, in contrast to **34**, the palladium-mediated cyclization of *N*-allylhexahydroindolinone **18** in the presence of vinyl tributyltin under Jeffrey conditions[34] led to 1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolinone **46** in 68% yield as a 6.5:1 mixture of diastereomers. The formation of **46** can be explained in terms of a 6-*endo-trig* cyclization followed by a subsequent trapping of the initially formed palladium intermediate **45** with the vinyl tin reagent. Presumably the 6-*endo-trig* mode of cyclization is entropically favored over the more demanding 6-*exo-trig* process that is required for hexahydroindolinone **34**.

The remaining step in our planned approach toward spegazzinidine (**2**) (Scheme 1) was to introduce the

(31) Still another possibility is the occurrence of a 1,2-bromo group migration followed by quenching the tertiary radical and eventual reduction of the resulting primary bromide.

(32) Heck, R. F. Vinyl Substitution with Organopalladium Intermediates. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: Oxford, UK, 1991; Vol. 4, p 842.

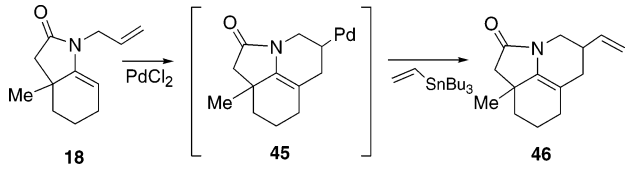
(33) Berteina, S.; De Mesmaeker, A. *Synlett* **1998**, 1227.

(34) (a) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291. (b) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S.; Worakun, T. *Tetrahedron* **1990**, *46*, 4003. (c) Grigg, R.; Sridharan, V.; Stevenson, P.; Sukirthalingam, S. *Tetrahedron* **1989**, *45*, 3557.

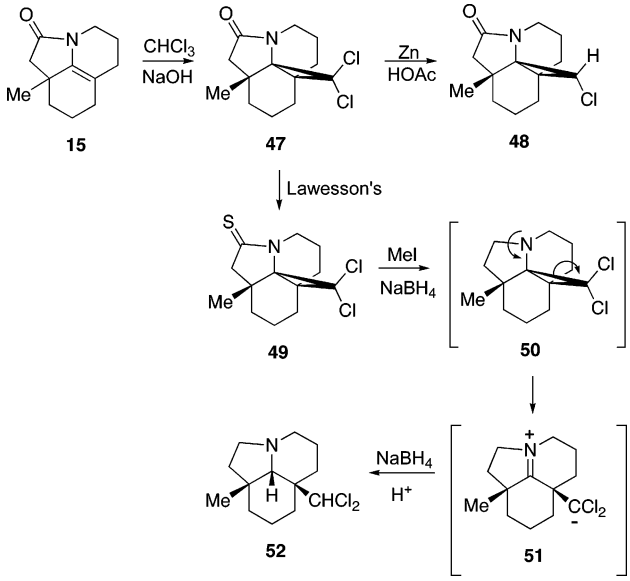
(35) (a) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695. (b) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc.* **1993**, *115*, 3030. (c) Rawal, V. H.; Iwasa, S. *J. Org. Chem.* **1994**, *59*, 2685.

(36) (a) Marsault, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 3317. (b) Brückner, S.; Abraham, E.; Klotz, P.; Suffert, J. *Org. Lett.* **2002**, *4*, 3391. (c) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.

SCHEME 11



SCHEME 12



necessary ethyl group at the C_{20}-position with the correct stereochemistry starting from enamide **5**. Since there were several concerns that we had about this approach, we decided to carry out some model studies using octahydropyrrolo[3,2,1-*ij*]quinoline **15** (Scheme 12). We found that addition of dichlorocarbene to **15** proceeded uneventfully and gave the expected amido-dichlorocyclopropane **47** as a single diastereomer.[37] The stereochemistry of the carbene addition was found to proceed from the least hindered position cis to the methyl group. This was established by the procurement of an X-ray crystal structure of monochloride **48** that was, in turn, obtained from the zinc−acetic acid induced reduction of **47**. To complete the model study, we needed to reduce the lactam carbonyl group and regioselectively open the cyclopropane ring. This was accomplished by first converting the amido group in **47** to the corresponding thioamide with use of Lawesson's reagent,[38] which provided **49** in 94% yield. Treatment of **49** with methyl iodide/$NaBH_4$ gave 6a-dichloromethyl-9a-methyldecahydropyrrolo[3,2,1−*ij*]quinoline **52** in 56% yield. The exclusive formation of **52** from this reaction can be rationalized by assuming that the initially formed tricyclic amine **50** is sufficiently nucleophilic to induce preferential cleavage of the cyclopropane bond, which leads to the most stable zwitterionic intermediate (i.e., **51**).[39] Further reduction of iminium ion **51** with $NaBH_4$ gives **52**. At this point, we decided to stop further work with the model system as we assumed that we would eventually be able to convert the dichloromethyl group into an ethyl substituent (perhaps via the corresponding aldehyde).

In summary, a new strategy for the synthesis of indole alkaloid derivatives has been developed that should be amenable to the preparation of certain aspidosperma alkaloids such as spegazzinidine. This approach involves an intramolecular Diels−Alder reaction between an *N*-allyl-substituted amidofuran moiety tethered onto an indole component to deliver a cycloadduct in which the ABCE tetracyclic core of aspidospermidine is rapidly assembled. Radical cyclization of a model *N*-allyl-7-bromo-3a-methylhexahydroindolinone preferentially led to the 6-*endo-trig* cyclization product, with the best yield being obtained under high dilution conditions. The six-membered cyclized product is generated through two reaction pathways: (a) 6-*endo-trig* ring closure and (b) rearrangement of an intermediate methylenecyclopentyl radical obtained by 5-*exo-trig* cyclization. We have also developed a protocol to introduce an ethyl substituent into the C_{20}-position of the aspidospermidine skeleton. The present methodology should be useful for the construction of other heterocyclic ring systems. Further work on these cyclizations and the synthesis of spegazzinidine and its analogues is currently underway and will be reported in due course.

Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. The microwave reactor and reaction vessels were purchased from CEM Corporation. All solids were recrystallized from ethyl acetate/hexane for analytical data.

General Procedure for the Preparation of Hexahydroindol-2-ones. In a 35 mL reaction tube were placed (1-methyl-2-oxocyclohexyl)acetic acid (**6**)[40] (2.0 mmol), the appropriate amine (2.2 mmol), and xylene (5 mL). The tube was sealed and then heated in an oil bath at 160 °C for 1 h. An alternative procedure involved heating the mixture in a microwave reactor at 160 °C for 10 min at 100 W. The reaction mixture was allowed to cool to room temperature, the solvent was removed, and the residue was purified by flash silica gel chromatography, using a 50% ether/hexane mixture as the eluent.

1-[3-(*tert*-Butyldimethylsilanyloxy)propyl]-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (7). To a solution of 1-amino-3-propanol (8.4 mL, 110 mmol) and TBDMSCl (18.2 g, 120 mmol) in CH_2Cl_2 (200 mL) was added NEt_3 (23 mL, 165 mmol). The cloudy mixture was vigorously stirred at room temperature for 12 h. The resulting clear solution was washed with water and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by distillation (bp 65−70 °C at 3.5 mm) to give 3-(*tert*-butyldimethylsilanoxy)propylamine in 97% yield.[41]

A mixture of the above amine (1.0 g, 5.3 mmol) and (1-methyl-2-oxocyclohexyl)acetic acid (**6**) (0.75 g, 4.4 mmol) in xylene (4 mL) was heated in a sealed tube at 180 °C for 2 h. After being cooled to room temperature, the mixture was concentrated under reduced pressure and the residue was subjected to silica gel column chromatography, using a 30%

(37) (a) Wentrup, C. *Adv. Heterocycl. Chem.* **1981**, *28*, 231. (b) Conia, J.; Blanco, L. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, UK, 1983; p 331. (c) Nelson, D. J. *Tetrahedron Lett.* **1999**, *40*, 5823.

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Et_2O in hexane mixture as the eluent, to give (1.3 g, 93%) of the titled compound **7** as a colorless oil; IR (neat) 1709, 1690, 1464, 1348, and 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 3H), 0.02 (s, 3H), 0.86 (s, 9H), 1.14 (s, 3H), 1.49 (ddd, 1H, J = 11.9, 11.9, and 5.7 Hz), 1.65−1.80 (m, 5H), 2.03−2.11 (m, 1H), 2.14−2.22 (m, 1H), 2.20 (s, 2H), 3.27 (ddd, 1H, J = 13.8, 8.1, and 5.7 Hz), 3.58 (t, 2H, J = 6.2 Hz), 3.64 (ddd, 1H, J = 14.3, 8.1, and 6.7 Hz), 4.81 (t, 1H, J = 3.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −5.2, 18.4, 18.5, 22.7, 26.0, 26.2, 30.3, 34.0, 36.3, 36.3, 46.6, 60.7, 97.2, 145.9, and 173.8; HRMS calcd for $C_{18}H_{33}NO_2Si$ 323.2281, found 323.2289.

1-(3-Bromopropyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (8). To a solution of keto acid **6** (1.0 g, 5.9 mmol) in benzene (15 mL) was added oxalyl chloride (1.5 mL, 17.6 mmol) and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue was dissolved in THF (15 mL) and cooled in an ice bath. A 30% aqueous solution of NH_4OH (10 mL) was slowly added. The reaction mixture was stirred at 0 °C for 2 h and was then partitioned between EtOAc and water. The organic layer was separated and the aqueous phase was extracted with EtOAc. The combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (15 mL) and *p*-TsOH (0.05 g) was added. The mixture was heated at reflux for 6 h and the solvent was subsequently removed under reduced pressure. The crude product was purified by flash silica gel chromatography to give 3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one as a white solid in 58% yield; mp 103−105 °C; IR (KBr) 1717, 1679, 1458, 1356, 1320, and 1167 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.46−1.54 (m, 1H), 1.67−1.80 (m, 3H), 2.00−2.13 (m, 2H), 2.15 (d, 1H, J = 15.7 Hz), 2.25 (d, 1H, J = 15.7 Hz), 4.80 (t, 1H, J = 3.3 Hz), and 8.28 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 22.8, 25.8, 34.0, 38.0, 46.7, 99.2, 143.5, and 177.0.

A solution containing 0.1 g (0.66 mmol) of the above compound in DMF (6.0 mL) was cooled in an ice bath and NaH (60%, 0.05 g, 1.3 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 30 min and then 1,3-dibromopropane (0.1 mL, 1.0 mmol) was added dropwise. The solution was stirred for 4 h at room temperature and was then quenched with water. The mixture was extracted with ether and the combined organic phase was washed with brine, dried over $MgSO_4$, flitered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to give 1-(3-bromopropyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (**8**) as a colorless oil in 67% yield; IR (neat) 1718, 1677, 1404, 1317, and 1241 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 3H), 1.46−1.53 (m, 1H), 1.71−1.80 (m, 3H), 2.03−2.11 (m, 3H), 2.19 (dd, 1H, J = 8.1 and 3.8 Hz), 2.22 (s, 2H), 3.31 (dd, 1H, J = 13.8 and 6.7 Hz), 3.34 (t, 2H, J = 6.7 Hz), 3.71 (dt, 1H, J = 13.8 and 7.1 Hz), and 4.82 (t, 1H, J = 3.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5, 22.8, 26.3, 30.4, 30.7, 34.0, 36.4, 38.0, 46.3, 97.5, 145.7, and 174.1; HRMS calcd for $C_{12}H_{18}BrNO$ 271.0572, found 271.0581.

1-(3,3-Diethoxypropyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (11) was prepared in 76% yield from keto acid **6** and 3,3-diethoxypropylamine; IR (neat) 1722, 1680, 1408, 1129, and 1061 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.16 (t, 3H, J = 7.0 Hz), 1.17 (t, 3H, J = 7.0 Hz), 1.21 (s, 3H), 1.43−1.55 (m, 1H), 1.66−1.90 (m, 5H), 2.06 (dtd, 1H, J = 17.8, 8.6, and 3.5 Hz), 2.12−2.20 (m, 1H), 2.19 (s, 2H), 3.21 (ddd, 1H, J = 14.0, 8.3, and 5.7 Hz), 3.38−3.50 (m, 2H), 3.55−3.72 (m, 3H), 4.45 (t, 1H, J = 5.7 Hz), and 4.77 (t, 1H, J = 3.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5, 18.5, 22.8, 26.1, 31.4, 34.0, 35.4, 36.3, 46.4, 61.6, 61.8, 97.3, 101.3, 145.7, and 173.7; HRMS calcd for $C_{16}H_{27}NO_3$ 281.1991, found 281.1986.

9a-Methyl-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (15). To a solution of the above acetal **11** (1.0 mmol) in 10 mL of anhydrous toluene cooled in an ethylene glycol−CO_2 bath was added Et_3SiH (0.16 mL, 1.0 mmol) and $SnCl_4$ (0.12 mL, 1.0 mmol). The solution was allowed to warm to room temperature, stirred for 1 h, and then quenched by the addition of 10 mL of water. The mixture was extracted with ether and the combined organic phase was dried over $MgSO_4$, flitered, and concentrated. The crude product was purified by flash chromatography on silica gel, using 50% ether/hexane as the eluent, to give **15** in 85% yield; IR (neat) 1691, 1676, 1456, 1409, and 1366 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.15 (s, 3H), 1.40−1.51 (m, 1H), 1.60−2.09 (m, 9H), 2.22 (dd, 2H, J = 20 and 15.9 Hz), 3.19 (ddd, 1H, J = 13.0, 9.5, and 3.2 Hz), and 3.77 (dt, 1H, J = 13.0 and 5.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 21.6, 25.5, 25.7, 27.0, 34.2, 35.3, 38.8, 47.2, 106.8, 138.8, and 173.1. Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.10; H, 9.00; N, 7.20.

1-Allyl-7-bromo-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (18). A solution of the above enamide **17** (0.6 g) in CH_2Cl_2 (25 mL) was cooled in an ice bath. Bromine (0.13 mL) was slowly added via a syringe and the colorless mixture was stirred for 5 min at 0 °C. Triethylamine (1.1 mL) was added in one portion and the mixture was allowed to warm to room temperature, stirred for 10 min, and washed with water. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography, using a 30% Et_2O/hexane mixture as the eluent. The titled compound **18** was obtained as a colorless oil in 96% yield; IR (neat) 1725, 1670, 1328, 1175, and 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 3H), 1.54−1.65 (m, 1H), 1.73−1.93 (m, 3H), 2.23 (d, 1H, J = 15.6 Hz), 2.33 (d, 1H, J = 15.9 Hz), 2.57 (dd, 2H, J = 8.6 and 4.4 Hz), 4.48 (dd, 1H, J = 15.6 and 6.4 Hz), 4.55 (ddt, 1H, J = 15.6, 5.4, and 1.6 Hz), 5.17 (dd, 1H, J = 10.4 and 1.3 Hz), 5.25 (dd, 1H, J = 17.2 and 1.6 Hz), and 5.74−5.85 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 25.5, 33.7, 35.9, 42.3, 43.8, 46.3, 96.9, 117.8, 133.0, 142.0, and 174.7; HRMS calcd for $C_{12}H_{16}BrNO$ 269.0416, found 269.0427.

5,8a-Dimethyl-4,5,6,7,8,8a-hexahydro-1*H*-pyrrolo[3,2,1-*hi*]indol-2-one (23). To a solution of the above bromo-enamide **18** (0.2 g, 0.7 mmol) in benzene (70 mL) was added *n*-Bu_3SnH (0.4 mL, 1.1 mmol) and AIBN (0.012 g, 0.07 mmol). The mixture was heated at reflux for 12 h and then the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography on silica gel. The major product **15** isolated from the reaction in 71% yield was identified as 9a-methyl-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (**15**). The minor product **23** was a colorless oil that was isolated in 21% yield and consisted of a 3:1 mixture of diastereomers; IR ($CHCl_3$) 1678, 1447, 1419, and 1055 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.19 (s, 3H), 1.30 (d, 3H, J = 7.2 Hz), 1.47−1.60 (m, 5H), 1.62−1.86 (m, 2H), 2.09 (d, 1H, J = 16.0 Hz), 2.74 (d, 1H, J = 16.0 Hz), 2.91 (dd, 1H, J = 12.0 and 2.0 Hz), and 3.73 (dd, 1H, J = 12.0 and 8.4 Hz); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 19.6, 20.6, 21.9, 29.8, 37.6, 41.7, 42.1, 48.9, 49.2, 99.5, 145.0, and 169.0; HRMS calcd for $C_{12}H_{17}NO$ 191.1310, found 191.1308.

1-Benzyl-7-bromo-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (28). A sample of 1-benzyl-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one **(31)** was prepared in 76% yield from (1-methyl-2-oxocyclohexyl)acetic acid (**6**) and benzylamine: ^1H NMR ($CDCl_3$, 400 MHz) δ 1.16 (s, 3H), 1.50−1.57 (m, 1H), 1.68−1.74 (m, 2H), 1.80 (dt, 1H, J = 12.4 and 3.3 Hz), 1.98−2.06 (m, 1H), 2.08−2.15 (m, 1H), 2.33 (s, 2H), 4.38 (d, 1H, J = 15.7 Hz), 4.71 (t, 1H, J = 3.8 Hz), 4.82 (d, 1H, J = 15.7 Hz), and 7.19−7.31 (m, 5H). The spectral data of this compound are identical with those reported in the literature.[42]

A solution of enamide **31** (0.5 g) in CH_2Cl_2 (20 mL) was cooled in an ice bath. Bromine (0.13 mL) was slowly added via a syringe and the colorless mixture was stirred for 5 min at 0 °C. Triethylamine (1.0 mL) was added in one portion and

(42) Cassayre, J.; Quiclet-Sire, B.; Saunier, J.-B.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 1029.

the mixture was allowed to warm to room temperature, stirred for 10 min, and washed with water. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography, using a 30% Et_2O/hexane mixture as the eluent. The titled compound **28** was obtained as a white solid in 88% yield: mp 99−100 °C; IR (KBr) 1725, 1677, 1395, 1330, and 1021 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (s, 3H), 1.56−1.63 (m, 1H), 1.17−1.83 (m, 3H), 2.26 (d, 1H, J = 15.7 Hz), 2.37 (d, 1H, J = 15.7 Hz), 2.50−2.61 (m, 2H), 5.12−5.18 (m, 2H), and 7.22−7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.5, 25.0, 33.7, 36.0, 42.3, 44.5, 46.2, 97.4, 127.4, 128.1, 128.5, 137.5, 141.7, and 175.0. Anal. Calcd for $C_{16}H_{18}BrNO$: C, 60.01; H, 5.67; N, 4.37. Found: C, 60.17; H, 5.79; N, 4.43.

3a-Methyl-2,3,3a,4-tetrahydro-1*H*,7*H*-pyrrolo[3,2,1-*de*]phenanthridin-5-one (30). To a solution of bromo-enamide **28** (0.2 g) in benzene (35 mL) was added n-Bu_3SnH (0.4 mL) and AIBN (0.012 g). The mixture was heated at reflux for 12 h and then the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash chromatography on silica gel. The major product **30** isolated from the above free radical cyclization reaction was obtained in 68% yield as a white solid; mp 104−106 °C; IR (KBr) 2930, 1714, 1677, 1360, and 1323 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 3H), 1.47 (dt, 1H, J = 12.4 Hz), 1.80−1.96 (m, 3H), 2.17−2.31 (m, 3H), 2.39−2.45 (m, 1H), 4.46 (d, 1H, J = 16.4 Hz), 5.17 (d, 1H, J = 16.4 Hz), 6.98−7.08 (m, 3H), 7.14 (t, 1H, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 21.9, 25.7, 33.6, 36.6, 42.7, 46.1, 105.8, 120.9, 126.1, 126.2, 127.6, 127.6, 132.2, 142.3, and 172.9; HRMS calcd for $C_{16}H_{17}NO$ 239.1310, found 239.1300.

4a-Methyl-1-phenyl-3,4,4a,5,6,7-hexahydro-1*H*-quinolin-2-one. A mixture of 3-(1-methyl-2-oxocyclohexyl)propionic acid methyl ester[43] (0.5 g, 2.51 mmol) and aniline (0.7 mL, 7.6 mmol) was heated in a sealed tube at 190 °C for 20 h. The reaction mixture was allowed to cool to room temperature and was subjected to silica gel chromatography, using a 50% Et_2O/hexane mixture as the eluent. The title compound was obtained as a white solid in 74% yield; mp 141−143 °C; IR (KBr) 1665, 1640, 1450, 1391, 1353, and 1209 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.29 (s, 3H), 1.46−1.53 (m, 1H), 1.60−1.66 (m, 2H), 1.68−1.74 (m, 2H), 1.79 (td, 1H, J = 12.9 and 7.1 Hz), 1.90−2.01 (m, 2H), 2.68 (ddd, 1H, J = 18.6, 7.1, and 1.9 Hz), 2.74 (ddd, 1H, J = 19.0, 12.9, and 7.1 Hz), 4.38 (dd, 1H, J = 5.2, and 3.3 Hz), 7.08 (d, 2H, J = 7.6 Hz), 7.31 (t, 1H, J = 7.6 Hz), and 7.42 (t, 2H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 22.9, 24.5, 29.5, 32.4, 34.3, 37.9, 108.4, 127.5, 128.8, 129.4, 140.2, 145.1, and 168.7. Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.74; H, 7.94; N, 5.83.

8-Bromo-4a-methyl-1-phenyl-3,4,4a,5,6,7-hexahydro-1*H*-quinolin-2-one (32). A solution of the above hexahydro-1*H*-quinolin-2-one (0.63 g, 2.6 mmol) in CH_2Cl_2 (25 mL) was cooled in an ice bath. Bromine (0.13 mL, 2.6 mmol) was slowly added via a syringe and the colorless mixture was stirred for 5 min at 0 °C. Triethylamine (1.1 mL, 7.8 mmol) was added in one portion and the mixture was allowed to warm to room temperature, stirred for 10 min, and washed with water. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography, using a 30% Et_2O/hexane mixture as the eluent. The bromo-enamide was obtained as a white solid in 90% yield; mp 118−119 °C; IR (KBr) 1696, 1679, 1632, 1491, 1453, and 1294 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.67−1.90 (m, 6H), 2.45−2.49 (m, 2H), 2.52−2.58 (m, 1H), 2.61 (ddd, 1H, J = 18.1, 9.5, and 6.2 Hz), 7.15 (t, 1H, J = 7.1 Hz), and 7.31−7.39 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.9, 26.9, 32.0, 35.1, 37.2, 37.6, 39.9, 116.5, 125.4, 128.5, 140.8, 142.0, and 171.0. Anal. Calcd for $C_{16}H_{18}BrNO$: C, 60.01; H, 5.67; N, 4.37. Found: C, 60.21; H, 5.68; N, 4.41.

3a-Methyl-1,2,3,3a,4,5-hexahydropyrido[3,2,1-*jk*]carbazol-6-one (33). To a solution of the above bromo-enamide **32** (0.5 g, 1.6 mmol) in benzene (30 mL) was added n-Bu_3SnH (0.84 mL, 3.1 mmol) and AIBN (0.05 g, 0.31 mmol). The mixture was heated at reflux for 12 h and the solvent was were removed under reduced pressure. The crude product was purified by flash silica gel chromatography, using a 30% Et_2O/hexane mixture as the eluent. The title compound **33** was obtained as a white solid in 81% yield; mp 98−100 °C; IR (KBr) 1695, 1633, 1453, 1373, and 1191 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 3H), 1.53 (td, 1H, J = 12.9 and 3.8 Hz), 1.79 (td, 1H, J = 13.3 and 4.8 Hz), 1.84 (dt, 1H, J = 12.9 and 3.3 Hz), 1.88 (ddd, 1H, J = 12.9, 5.7, and 1.4 Hz), 1.99−2.10 (m, 2H), 2.52 (ddd, 1H, J = 16.7, 10.9, and 7.1 Hz), 2.70−2.73 (m, 1H), 2.73−2.76 (m, 1H), 2.99 (ddd, 1H, J = 18.1, 13.8, and 5.7 Hz), 7.22−7.30 (m, 2H), 7.37 (d, 1H, J = 7.6 Hz), and 8.40 (d, 1H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 20.0, 23.9, 30.6, 31.3, 35.7, 37.1, 113.6, 116.3, 117.0, 123.8, 124.1, 130.1, 135.2, 140.1, and 168.8. Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.31; H, 7.19; N, 5.84.

7-Bromo-1-but-3-enyl-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (34). A solution of the above hexahydroindol-2-one (0.6 g) in CH_2Cl_2 (25 mL) was cooled in an ice bath. Bromine (0.12 mL) was slowly added via a syringe and the colorless mixture was stirred for 5 min at 0 °C. Triethylamine (1.1 mL) was added in one portion and the mixture was allowed to warm to room temperature, stirred for 10 min, and washed with water. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography, using a 30% Et_2O/hexane mixture as the eluent. The titled compound **34** was obtained as a colorless oil in 82% yield: IR (neat) 1727, 1668, 1360, 1328, and 1298 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.12 (s, 3H), 1.56 (td, 1H, J = 12.9 and 3.3 Hz), 1.72−1.89 (m, 3H), 2.18 (d, 1H, J = 15.7 Hz), 2.18−2.24 (m, 1H), 2.27 (d, 1H, J = 15.2 Hz), 2.33−2.40 (m, 1H), 2.55 (dd, 2H, J = 9.1 and 4.8 Hz), 3.89 (ddd, 1H, J = 13.8, 9.1, and 5.2 Hz), 3.96 (ddd, 1H, J = 13.8, 9.1, and 7.6 Hz), 5.00 (d, 1H, J = 10.0 Hz), 5.07 (dd, 1H, J = 17.1 and 1.9 Hz), and 5.75 (qt, 1H, J = 10.0 and 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 25.9, 32.5, 33.6, 35.9, 40.3, 42.1, 46.2, 96.5, 117.1,134.9, 141.9, and 174.6; HRMS calcd for $C_{13}H_{18}BrNO$ 283.0572, found 283.0581.

6,9a-Dimethyl-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (35). To a solution of the above bromo-enamide **34** (0.5 g) in benzene (30 mL) was added n-Bu_3SnH (0.8 mL) and AIBN (0.05 g). The mixture was heated at reflux for 12 h and the solvent was removed under reduced pressure. The crude product was purified by flash silica gel chromatography, using a 30% Et_2O/hexane mixture as the eluent. The major product (71%) obtained from the reaction was identified as 1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (**35**) and was isolated as a 2.3:1 mixture of diastereomers: IR (neat) 1728, 1690, 1404, 1365, and 1312 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.92 and 0.96 (d, 3H, J = 7.1 Hz), 1.08−1.10 (s, 3H), 1.34−1.50 (m, 2H), 1.63−1.75 (m, 3H), 1.77−2.08 (m, 3H), 2.12−2.21 (m, 3H), 3.14 (td, 1H, J = 13.8 and 3.8 Hz) and 3.25 (ddd, 1H, J = 12.4, 8.1, and 4.3 Hz), 3.60 (ddd, 1H, J = 12.4, 8.1, and 4.8 Hz) and 3.72 (dt, 1H, J = 12.9 and 4.8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.9, 18.7, 18.8, 19.9, 24.1, 24.9, 25.8, 28.8, 29.5, 29.8, 30.0, 33.9, 34.0, 35.1, 35.2, 35.4, 36.9, 46.8, 47.2, 110.8, 111.3, 137.9, 138.1, 172.7, and 172.9; HRMS calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1474.

10a-Methyl-4,5,6,7,8,9,10,10a-octahydro-1*H*-azepino[3,2,1-*hi*]indol-2-one (36). The minor fraction isolated from the chromatographic separation in 21% yield was a colorless oil and was assigned as **36** on the basis of its spectral properties; IR (neat) 1718, 1680, 1392, 1359, and 1302 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.08 (s, 3H), 1.39−1.52 (m, 3H),

(43) House, H. O.; Roelofs, W. L.; Trost, B. M. *J. Org. Chem.* **1966**, *31*, 646.

1.66−1.76 (m, 3H), 1.82−1.88 (m, 2H), 1.99−2.15 (m, 4H), 2.16 (d, 1H, J = 15.7 Hz), 2.25 (d, 1H, J = 15.7 Hz), 2.76 (t, 1H, J = 11.9 Hz), and 4.36 (m,1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 25.5, 27.1, 28.3, 31.2, 34.0, 34.3, 38.7, 43.6, 47.0, 114.3, 140.9, and 174.3; HRMS calcd for $C_{13}H_{19}NO$ 205.1467, found 205.1469.

1-(3-Bromobut-3-enyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one was prepared in 80% yield from (1-methyl-2-oxocyclohexyl)acetic acid (**6**) and 3-bromo-3-butenyl-1-amine: IR (neat) 1720, 1677, 1402, 1317, and 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (s, 3H), 1.45−1.56 (m, 1H), 1.70−1.83 (m, 3H), 2.00−2.15 (m, 1H), 2.20−2.28 (m, 1H), 2.22 (s, 2H), 2.58−2.71 (m, 2H), 3.36 (dt, 1H, J = 14.0 and 6.4 Hz), 3.86 (dt, 1H, J = 14.0 and 7.3 Hz), 4.84 (t, 1H, J = 3.2 Hz), 5.43 (s, 1H), and 5.63 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 18.5, 22.8, 26.3, 34.0, 36.4, 37.7, 38.7, 46.4, 97.5, 118.9, 130.5, 145.4, and 174.9; HRMS calcd for $C_{13}H_{18}BrNO$ 283.0572, found 283.0586.

7-Bromo-1-(3-bromobut-3-enyl)-3a-methyl-1,3,3a,4,5,6-hexahydroindol-2-one (37). A solution of the above hexahydroindol-2-one (0.5 g) in CH_2Cl_2 (20 mL) was cooled in an ice bath. Bromine (0.13 mL) was slowly added via a syringe and the colorless mixture was stirred for 5 min at 0 °C. Triethylamine (1.0 mL) was added in one portion and the mixture was allowed to warm to room temperature, stirred for 10 min, and washed with water. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash silica gel chromatography, using a 30% Et_2O/hexane mixture as the eluent. The titled compound **37** was obtained in 88% yield as a colorless oil: IR (neat) 1724, 1669, 1326, 1297, and 1173 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (s, 3H), 1.58 (ddd, 1H, J = 19.1, 14.6, and 4.8 Hz), 1.73−1.90 (m, 3H), 2.22 (d, 1H, J = 15.9 Hz), 2.30 (d, 1H, J = 15.9 Hz), 2.55−2.60 (m, 2H), 2.63 (ddd, 1H, J = 14.9, 8.3, and 6.7 Hz), 2.79 (ddd, 1H, J = 14.0, 9.2, and 4.8 Hz), 4.03 (ddd, 1H, J = 14.0, 8.9, and 4.8 Hz), 4.17 (ddd, 1H, J = 14.0, 8.9, and 6.7 Hz), 5.47 (d, 1H, J = 1.6 Hz), and 5.68 (d,1H, J = 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.6, 25.8, 33.7, 36.0, 39.7, 40.0, 42.2, 46.3, 97.0, 118.7, 130.2, 141.9, and 174.7; HRMS calcd for $C_{13}H_{17}Br_2NO$ 360.9678, found 360.9692.

The *n*-Bu_3SnH/AIBN-induced radical reaction of dibromohexahydroindolinone **37** afforded a mixture of the 6-*exo* (**35**) (18%) and 7-*endo* (**36**) (72%) cyclized products which were separated by silica gel chromatography and compared to those obtained from 7-bromohexahydroindolinone **34**.

7-Bromo-3a-methyl-1-(3-trimethylstannanylbut-3-enyl)-1,3,3a,4,5,6-hexahydroindol-2-one (43). In a microwave reaction vessel was placed dibromo-hexahydroindolinine **37** (0.1 g, 0.28 mmol), $PdCl_2(PPh_3)_2$ (0.01 g, 0.014 mmol), hexamethylditin (0.14 g, 0.41 mmol), and degassed 1,4-dioxane (1.0 mL). The vessel was sealed and the mixture was stirred at room temperature for 5 min until a homogeneous solution was obtained. The vessel was then placed in the microwave reactor and was heated at 150 W at 140 °C for 10 min. The mixture was allowed to cool to room temperature and was transferred into a round-bottom flask. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel, using a 8% Et_2O/hexane mixture as the eluent. The title compound **43** was obtained as a colorless oil in 69% yield; IR (neat) 1720, 1667, 1294, and 772 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H), 1.13 (s, 3H), 1.52−1.60 (m, 1H), 1.72−1.90 (m, 3H), 2.18 (d, 1H, J = 15.7 Hz), 2.28 (d, 1H, J = 15.7 Hz), 2.35 (ddd, 1H, J = 13.3, 10.5, and 6.2 Hz), 2.53−2.62 (m, 3H), 3.84 (ddd, 1H, J = 13.8, 9.1, and 3.3 Hz), 3.92 (ddd, 1H, J = 13.8, 11.0, and 6.2 Hz), 5.21 (s, 1H), and 5.74 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ −9.1, 20.7, 25.8, 33.7, 36.0, 38.8, 41.2, 42.2, 46.3, 96.6, 127.1, 142.2, 151.5, and 174.6; HRMS calcd for $C_{16}H_{26}BrNOSn$ 445.0220, found 445.0216.

9a-Methyl-6-methylene-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (41). In a microwave reaction vessel was placed a 0.07 g (0.16 mmol) sample of **43**, $PdCl_2(PPh_3)_2$ (5.0 mg, 7.1 μmol), Bu_3NBr (0.06 g, 0.19 mmol), and DMF (1.0 mL). The vessel was sealed and heated at 100 °C for 20 min. The mixture was allowed to cool to room temperature and was transferred into a separatory funnel. Water (5 mL) and Et_2O (25 mL) were added and the organic phase was collected, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Flash chromatography of the cruder residue on silica gel, using a 30% Et_2O/hexane mixture as the eluent, gave **41** as the minor product in 16% yield; IR (neat) 1717, 1663, 1414, 1349, and 1186 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 3H), 1.51 (td, 1H, J = 12.4 and 4.3 Hz), 1.75−1.90 (m, 3H), 2.08−2.16 (m, 1H), 2.25−2.35 (m, 1H), 2.30 (s, 2H), 2.42−2.52 (m, 2H), 3.37 (ddd, 1H, J = 13.3, 7.6, and 4.8 Hz), 3.75 (dt, 1H, J = 11.9 and 5.7 Hz), 4.67 (s, 1H), and 4.75 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 22.2, 25.9, 30.0, 33.7, 36.0, 38.9, 47.0, 106.0, 107.6, 139.2, 143.6, and 173.1; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1312.

10a-Methyl-4,5,8,9,10,10a-hexahydro-1*H*-azepino[3,2,1-*hi*]indol-2-one (44) was isolated from the column as the major product in 48% yield; IR (neat) 1716, 1662, 1615, 1363, and 1173 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 (s, 3H), 1.41−1.52 (m, 1H), 1.69−1.82 (m, 3H), 2.10−2.33 (m, 3H), 2.25 (d, 2H, J = 1.9 Hz), 2.47 (dddd, 1H, J = 16.8, 7.0, 5.4, and 1.3 Hz), 2.93 (dd, 1H, J = 13.0 and 9.5 Hz), 4.26 (ddd, 1H, J = 13.0, 5.4, and 2.9 Hz), 5.56 (dd, 1H, J = 11.4 and 1.9 Hz), and 5.71 (ddd, 1H, J = 11.4, 7.6, and, 4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 26.1, 29.3, 30.2, 33.6, 37.7, 41.0, 46.7, 108.4, 128.5, 129.3, 143.9, and 173.4; HRMS calcd for $C_{13}H_{17}NO$ 203.1310, found 203.1316.

9a-Methyl-5-vinyl-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo-[3,2,1-ij]quinolin-2-one (46). A mixture of bromo-hexahydroindolinone **18** (0.2 g, 0.74 mmol), vinyl-tributyltin (0.3 mL, 1.1 mmol), $PdCl_2(PPh_3)_2$ (0.025 g, 0.04 mmol), and Bu_4NBr (0.29 g, 0.9 mmol) in DMF (3.0 mL) was heated at 100 °C for 6 h. The mixture was diluted with Et_2O and washed with water. The organic phase was separated, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, using a 50% Et_2O/hexane mixture as the eluent. The title compound **46** was obtained as a 6.5:1 mixture of diastereomers in 68% yield; IR (neat) 1719, 1679, 1404, and 1314 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.14 and 1.16 (s, 3H), 1.36−1.52 (m, 1H), 1.56−2.00 (m, 7H), 2.04−2.28 (m, 4H), 2.44−2.56 (m, 1H), 3.02 (dd, 1H, J = 13.0 and 5.1 Hz), 3.83 (dt, 1H, J = 13.0 and 4.1 Hz), 4.87−5.08 (m, 2H), and 5.67 (ddd, 1H, J = 17.2, 10.2, and 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 17.5, 18.8, 22.0, 25.5, 25.9, 26.0, 26.6, 27.0, 34.0, 34.1, 35.0, 35.4, 39.1, 40.0, 46.7, 46.8, 49.0, 106.3, 107.1, 115.2, 135.9, 139.7, 140.0, and 172.8; HRMS calcd for $C_{14}H_{19}NO$ 217.1467, found 217.1474.

9a-Methyl-6a,9b-dichlorocyclopropyloctahydropyrrolo-[3,2,1-*ij*]quinolin-2-one (47). To a solution of 9a-methyl-5,6,7,8,9,9a-hexahydro-1*H*,4*H*-pyrrolo[3,2,1-*ij*]quinolin-2-one (**15**) (2.1 g, 11.1 mmol) and Bu_4NBr (0.5 g) in $CHCl_3$ (150 mL) was added 50 mL of a 50% aqueous solution of NaOH dropwise. The mixture was vigorously stirred for 4 h and diluted with water, the organic layer was separated and extracted with Et_2O, and the combined organic phase was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, using a 50% Et_2O−hexane mixture as the eluent. The major product formed **47** was obtained as a white solid in 70% yield; mp 136−138 °C; IR (KBr) 1709, 1690, 1464, 1348, and 1316 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18−1.36 (m, 2H), 1.46 (s, 3H), 1.44−1.48 (m, 2H), 1.49−1.54 (m, 1H), 1.55−1.64 (m, 1H), 1.85 (ddd, 1H, J = 14.8, 5.2, and 2.9 Hz), 2.05 (m, 2H), 2.33 (dd, 1H, J = 17.2 and 1.0 Hz), 2.42 (d, 1H, J = 17.2 Hz), 2.43 (ddd, 1H, J = 14.8, 14.8, and 6.2 Hz), 3.22 (ddd, 1H, J = 13.3, 13.3, and 1.9 Hz), and 4.06 (ddd, 1H, J = 13.3, 4.3, and 1.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 21.6, 25.6, 25.9, 29.8, 30.9, 32.6, 34.4, 39.8, 47.1, 53.6, 74.4, and 177.3. Anal.

Calcd for $C_{13}H_{17}Cl_2NO$: C, 56.95; H, 6.25; N, 5.11. Found: C, 57.00; H, 6.18; N, 5.05.

9a-Methyl-6a-chlorocyclopropyloctahydropyrrolo[3,2,1-*ij*]quinolin-2-one (48). A mixture of the above dichlorocyclopropyloctahydropyrrolo[3,2,1-*ij*]quinoline **47** (0.15 g, 0.55 mmol) and zinc powder (0.2 g) in acetic acid (5.0 mL) was heated at reflux for 6 h. The reaction mixture was allowed to cool to room temperature and was diluted with 20 mL of EtOAc. The organic layer was washed with 1.0 N NaOH, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash silica gel chromatography, using a 50% Et_2O in hexane mixture as the eluent. Recrystallization of the major chromatographic fraction from hexanes−EtOAc afforded 0.06 g (46%) of **48** as a crystalline solid, which was suitable for X-ray analysis; mp 114−116 °C; IR (KBr) 1706, 1689, 1464, 1345, and 1315 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18−1.36 (m, 2H), 1.45 (s, 3H), 1.45−1.82 (m, 7H), 1.90−2.00 (m, 1H), 2.12 (dd, 1H, J = 17.2 and 1.0 Hz), 2.48 (d, 1H, J = 17.2 Hz), 2.75−2.85 (m, 1H), 3.70 (s, 1H), and 3.88−3.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.5, 19.6, 22.0, 25.1, 25.7, 27.8, 33.6, 34.0, 35.8, 40.2, 45.6, 49.8, and 174.4; HRMS calcd for $C_{13}H_{18}ClNO$ 239.1077, found 239.1068.

9a-Methyl-6a,9b-dichlorocyclopropyloctahydropyrrolo-[3,2,1-*ij*]quinolin-2-thione (49). To a solution of lactam **47** (0.6 g, 2.2 mmol) in THF (20 mL) was added Lawesson's reagent (1.0 g, 2.6 mmol) and the mixture was stirred at room temperature overnight. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography on silica gel, using a 30% Et_2O−hexane mixture as the eluent. Thioamide **49** was obtained as a white solid in 94% yield; mp 155−156 °C; IR (KBr) 1465, 1445, 1312, 1178, 1137, and 1013 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.32−1.44 (m, 4H), 1.38 (s, 3H), 1.56−1.63 (m, 2H), 1.81 (ddd, 1H, J = 14.8, 5.2, and 2.9 Hz), 1.98 (ddd, 1H, J = 14.8, 12.4, and 5.2 Hz), 2.01 (dd, 1H, J = 14.8 and 6.7 Hz), 2.46 (ddd, 1H, J = 15.2, 13.3, and 6.7 Hz), 2.84 (d, 1H, J = 17.6 Hz), 2.95 (dd, 1H, J = 17.6 and 1.4 Hz), 3.59−3.68 (m, 1H), and 4.90 (ddd, 1H, J = 13.3, 5.2, and 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 21.5, 24.9, 28.6, 28.9, 32.0, 36.7, 44.8, 58.8, 59.5, 73.7, and 205.5. Anal. Calcd for $C_{13}H_{17}Cl_2NS$: C, 53.79; H, 5.90; N, 4.83. Found: C, 53.93; H, 5.96; N, 4.77.

6a-Dichloromethyl-9a-methyldecahydropyrrolo[3,2,1-*ij*]quinoline (52). A solution of the above thioamide **49** (0.2 g, 0.7 mmol) and methyl iodide (0.2 mL, 3.5 mmol) in THF (6.0 mL) was stirred at room temperature overnight. The yellow mixture was concentrated under reduced pressure and the resulting residue was dissolved in MeOH (6.0 mL) at 0 °C. To this solution was added $NaBH_4$ (0.05 g, 1.4 mmol) in one portion and the mixture was stirred for 2 h at 0 °C. The reaction mixture was quenched with water and extracted with Et_2O, and the organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel, using a 30% Et_2O/hexane mixture as the eluent. The major product **52** was obtained as a colorless oil in 56% yield; IR (neat) 2938, 2796, 1448, 1183, and 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (s, 3H), 1.20−1.25 (m, 1H), 1.38−1.73 (m, 10H), 1.85−1.90 (m, 1H), 2.00 (ddd, 1H, J = 13.3, 13.3, and 5.2 Hz), 2.11 (ddd, 1H, J = 10.5, 9.1, and 6.7 Hz), 2.90 (d, 1H, J = 10.5 Hz), 3.02 (ddd, 1H, J = 13.3, 9.1, and 4.3 Hz), and 6.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 21.6, 25.0, 26.9, 27.4, 35.4, 39.1, 40.1, 44.4, 52.0, 53.2, 70.5, and 81.1; HRMS calcd for $C_{13}H_{21}NCl_2$ 261.1051, found 261.1060.

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Supporting Information Available: Spectroscopic and experimental procedures for compounds **10**, **16**, **17**, **29**, and **42**; ^1H and ^{13}C NMR spectra for new compounds lacking elemental analyses; and an ORTEP drawing for structure **48**. This material is available free of charge via the Internet at http://pubs.acs.org. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Centre.

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