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General Strategy for the Syntheses of Corynanthe, Tacaman, and Oxindole Alkaloids

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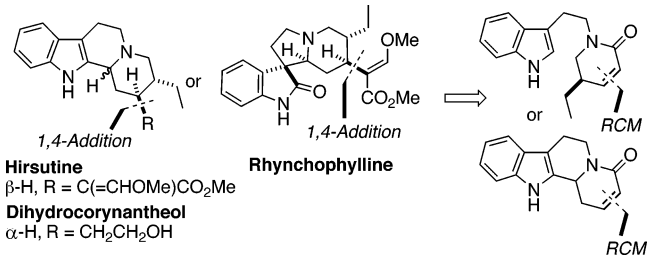

We report herein the total synthesis of the corynanthe alkaloid dihydrocorynantheol and the formal syntheses of the indole alkaloids tacamonine, rhynchophylline, and hirsutine. The strategies for assembling the corynanthe and tacaman skeletal frameworks comprised of both the classical ABD → ABCD and ABC → ABCD approaches wherein the variously substituted piperidinone D-rings were formed via ring-closing metathesis (RCM) followed by a 1,4-addition to introduce the requisite side chain at C(15). Since 1,4-additions to α,*β*-unsaturated lactams represent an underdeveloped field, we conducted a series of studies with two unsaturated lactams employing organocuprates and metal enolates as the nucleophiles. These studies revealed that organocuprates derived from Grignard reagents and either stoichiometric amounts of CuCN or catalytic amounts of CuBr·DMS complex are excellent nucleophiles for such additions; TMSCl was a crucial additive for optimizing these reactions. The anion derived from ethyl 1,3-dithiolane-2-carboxylate was also an excellent nucleophile in these 1,4-additions, although the stereochemistry of such 1,4-additions to carboline-derived, unsaturated lactams was sensitive to substitution on the indole nitrogen atom. The ABD → ABCD approach to these alkaloids featured a novel one-pot sequence of an RCM reaction and a zirconocene-catalyzed carbomagnesation followed by a second RCM to generate the D-ring.

Introduction

We have had a long-standing interest in developing unified strategies for the synthesis of structurally diverse indole alkaloids. A number of years ago we discovered that vinylogous Mannich reactions[1] could be exploited to quickly generate intermediates that might be elaborated via subsequent hetero-Diels−Alder reactions or Michael additions in designing general approaches to a number of indole alkaloids including reserpine, tetrahydroalstonine, geissoschizine, ajmalicine, rugulovasines A and B, setoclavine, akuammicine, strychnine, and *N*-methylvellosimine.[2] When Fu and Grubbs showed in 1992 that α,*ω*-dienes containing nitrogen atoms in the tethering chain between the two olefins could be cyclized via ring-closing metathesis (RCM),[3,4] we immediately recognized the tremendous potential of such cyclizations as a general approach for alkaloid synthesis, and we have completed the syntheses of a variety of alkaloids employing an RCM reaction as a key step.[5] Indeed, our use of an RCM reaction to fabricate the ABCE ring system of

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(1) For reviews, see: (a) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (b) Bur, S. K.; Martin, S. F. *Tetrahedron* **2001**, *57*, 3221.

(2) For examples, see: (a) Martin, S. F.; Rüeger, H.; Williamson, S. A.; Grzejszczak, S. *J. Am. Chem. Soc.* **1987**, *109*, 6124. (b) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161. (c) Martin, S. F.; Clark, W. C.; Corbett, J. W. *J. Org. Chem.* **1995**, *60*, 3236. (d) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (e) Liras, S.; Lynch, C. L.; Fryer, A. M.; Vu, B. T.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 5918. (f) Deiters, A.; Chen, K.; Eary, C. T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541.

(3) Fu, G. C.; Grubbs, R. H. *J. Am. Chem. Soc.* **1992**, *114*, 7324.

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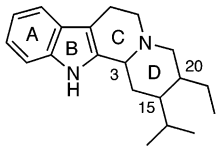
manzamine A represents one of the first applications of RCM to the synthesis of complex natural products.[5d] Herein, we report a general approach to the synthesis of the corynanthe indole alkaloids, which have the generic structure **1**, by a novel strategy in which RCM plays a pivotal role for elaborating the D-ring. The obvious biogenetic relationship between the corynanthe alkaloids and the oxindole and tacaman alkaloids, which are characterized by the corresponding structures **2** and **3**, inspired us to adapt the strategy toward their synthesis.[6]



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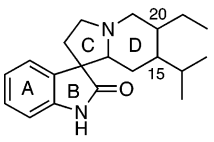

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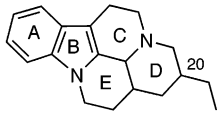
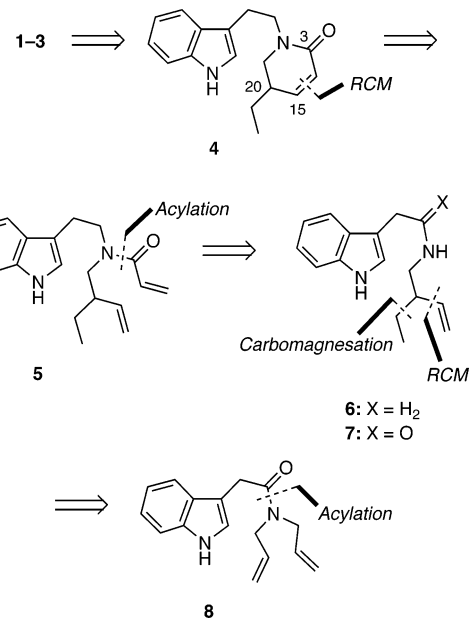


3

Results and Discussion

A. ABD → ABCD Approach. Consideration of the general structures **1**−**3** reveals that the common motif is an indole ring that is joined via either a fused or a spiro C-ring to the piperidine D-ring, which has an ethyl side chain at C(20).[7] It thus occurred to us that **4** might serve as a useful intermediate in an ABD → ABCD entry to alkaloids of the corynanthe, oxindole, and tacaman families (Scheme 1).[8] The α,β-unsaturated lactam moiety in **4** would allow for the introduction of substituents at C(15) by a diastereoselective 1,4-addition, and the tetracyclic corynanthe skeleton would then be formed via a Bischler−Napieralski reaction and stereoselective reduction. An expedient route to **4** would involve the RCM of the tryptamine derivative **5**. Although **5** would superficially appear to be an easy synthetic target, closer inspection reveals that the obvious precursor **6**

SCHEME 1



contains a branched homoallylic amino group, which represents a modest synthetic challenge.[9] Indeed, a preliminary series of experiments made it apparent that preparing **6** by classical amination protocols involving alkylations or reductive aminations was problematic. Hence, we developed a novel route to **6** by an approach that featured a one-pot procedure for transforming **8** into **7** via sequential RCM and zirconocene-catalyzed carbomagnesation reactions. Although various carbometalations have been widely used in organic synthesis,[10] zirconocene-catalyzed carbomagnesations of double bonds are less common,[11] and to our knowledge such reactions have been used only once in natural product synthesis.[12]

1. Synthesis of the Unsaturated Lactam 4. Compound **4** was a pivotal intermediate in the ABD → ABCD approach to the indole alkaloids **1**−**3**, and an efficient means for its synthesis was developed that commenced with the EDCI-mediated amide coupling between indole-3-acetic acid (**9**) and diallylamine to furnish **8** in 88% yield (Scheme 2). The diallyl amide **8** was then the substrate for a one-pot RCM−carbomagnesation sequence to prepare **7**. In the event, the RCM of **8** proceeded smoothly with only 1 mol % Grubbs' catalyst **11** in THF at room temperature, and after the starting material had been consumed, EtMgCl (4 equiv) and Cp_2ZrCl_2 (15 mol %) were simply added, leading to the formation of **7** in 71% overall yield. Hoveyda has shown that carbomagnesations of cyclic allyl amides may occur enantioselectively using the chiral catalyst

(4) For selected reviews of olefin metathesis, see: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Schrock, R. R. *Tetrahedron* **1999**, *55*, 8141. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012. (d) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18. (e) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592. (f) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900. (g) *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, Germany, 2003; Vol. 2. (h) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199.

(5) For some examples, see: (a) Martin, S. F.; Liao, Y.; Chen, H.-J.; Pätzel, M.; Ramser, M. N. *Tetrahedron Lett.* **1994**, *35*, 6005. (b) Martin, S. F.; Chen, H.-J.; Courtney, A. K.; Liao, Y.; Pätzel, M.; Ramser, M. N.; Wagman, A. S. *Tetrahedron* **1996**, *52*, 7251. (c) Fellows, I. M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781. (d) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (e) Martin, S. F.; Neipp, C. E. *J. Org. Chem.* **2003**, *68*, 8867. (f) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523. (g) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301. (h) Andrade, R. A.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733.

(6) Stöckigt, J. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic Press: London, 1980; Chapter 6, p 113.

(7) The atoms are numbered according to the "biogenetic numbering" of Le Men and Taylor: Le Men, J.; Taylor, W. I. *Experientia* **1965**, *21*, 508.

(8) For a preliminary account of some of these results, see: Deiters, A.; Martin, S. F. *Org. Lett.* **2002**, *4*, 3243.

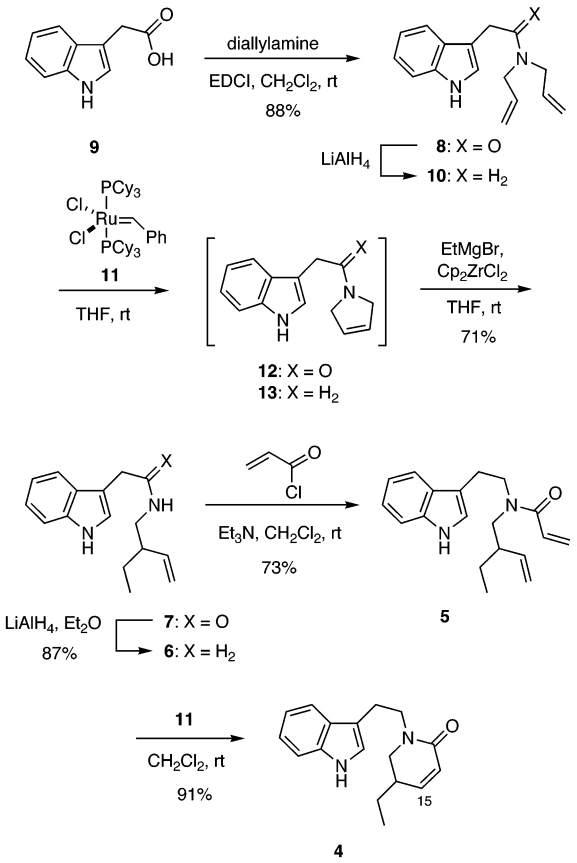
(9) For approaches to homoallylic amines, see: (a) Neipp, C. E.; Humphrey, J. M.; Martin, S. F. *J. Org. Chem.* **2001**, *66*, 531 and references therein. (b) Ramachandran, P. V.; Burghardt, T. E. *Chem.−Eur. J.* **2005**, *11*, 4387 and references therein.

(10) Reviews on carbometalations: (a) Marek, I.; Normant, J. F. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Ed.; Wiley-VCH: Weinheim, Germany, 1998; p 271. (b) Fallis, A. G.; Forgione, P. *Tetrahedron* **2001**, *57*, 5899. (c) Link, J. T. In *The Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed.; Wiley: Sons: New York, 2002; Vol. 1, p. 1523.

(11) Reviews on Zr- and Ti-catalyzed carbomagnesations: (a) Negishi, E.-I. *Pure Appl. Chem.* **2001**, *73*, 239. (b) Hoveyda, A. H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, Germany, 2002; p 180.

(12) Houri, A. F.; Xu, Z.; Cogan, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1995**, *117*, 2943.

SCHEME 2

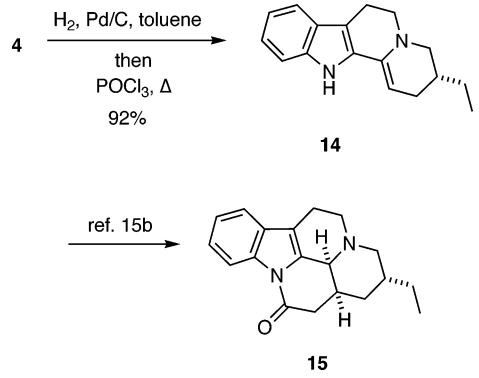


(EBTHI)Zr-binol,[13] but we did not pursue this clear opportunity to prepare enantiomerically pure **7**.

Although it was not necessary to protect the acidic indole NH in this sequence, the electron-withdrawing amide moiety was critical to the success of both the RCM and the carbomagnesation steps in this sequence. For example, we found that neither the free base **10** nor its hydrochloride salt cyclized in the presence of Grubbs' catalyst **11** in CH_2Cl_2 at room temperature or by heating under reflux. Furthermore, the amine **13**, which was independently prepared (62%) by reaction of 3-(2-bromoethyl)indole with 2,5-dihydropyrrole (2 equiv), did not undergo carbomagnesation (EtMgCl and Cp_2ZrCl_2 in THF at room temperature or 65 °C). Although this result suggests that the amide might play a significant role in facilitating the fragmentation of the intermediary organomagnesium species, carbomagnesations of tertiary amines are in fact known.[13] The amide **7** was then reduced with $LiAlH_4$ at room temperature to provide the amine **6** (87%), which was treated with acryloyl chloride in the presence of Et_3N to deliver **5** in 73% yield, thereby setting the stage for the second RCM reaction. Cyclization of **5** with 5 mol % **11** then furnished the α,β-unsaturated lactam **4** in only five distinct chemical operations and 36% overall yield from commercially available **9**.

2. Formal Synthesis of Tacamonine (15). 15 is a member of the relatively small group of tacaman indole alkaloids[14] and was first isolated in 1984 from *Tabernaemontana eglandulosa* (Apocynaceae), the root of which is used to treat snake bites in Central Africa.[14b] Although tacamonine has been prepared before,[15] it occurred to us that **4** was nicely suited as an intermediate, and we developed a facile one-pot procedure for its transformation into **14**, which had been previously converted in two simple steps into **15**.[15b] Thus, following reduction of **4** by catalytic hydrogenation [10% Pd/C, H_2 (1 atm)], $POCl_3$ was added, and the reaction was heated at 100 °C for 3 h to give **14** in 92% yield (Scheme 3). The ^{1}H NMR and ^{13}C NMR spectra of synthetic **14** were consistent with those reported in the literature.[16] This route to **14** comprises six distinct operations and proceeded in 33% overall yield, making it comparable to the best of the known syntheses of **14**.

SCHEME 3



3. Total Synthesis of Dihydrocorynantheol (21). Members of the corynanthe group of indole alkaloids have historically received considerable interest because they exhibit a variety of important biological properties, including antiparasitic, antiviral, and analgesic activities.[17] The archetypal alkaloid in this family is **21**, which was first isolated from the bark of *Aspidosperma marcgravianum* (Apocynaceae) in 1962.[18] Dihydrocorynantheol has been a popular target to showcase the development of novel synthetic methodologies, and several partial and total syntheses have been reported.[19] However, the opportunity to design a more concise approach to this important alkaloid and analogues thereof was appealing, and **4** seemed a potentially useful intermediate.

(13) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291.

(14) (a) Beek, T. A. van; Lankhorst, P. P.; Verpoorte, R.; Baerheim Svendsen, A. *Planta Med.* **1982**, *44*, 30. (b) Beek, T. A. van; Verpoorte, R.; Baerheim Svendsen, A. *Tetrahedron* **1984**, *40*, 737.

(15) (a) Massiot, G.; Oliveira, F. S.; Lévy, J. *Tetrahedron Lett.* **1982**, *23*, 177. (b) Ihara, M.; Setsu, F.; Shohda, M.; Taniguchi, N.; Tokunaga, Y.; Fukumoto, K. *J. Org. Chem.* **1994**, *59*, 5317. (c) Lounasmaa, M.; Karinen, K.; Din Belle, D.; Tolvanen, A. *Tetrahedron* **1998**, *54*, 157. (d) Lavilla, R.; Coll, O.; Bosch, J.; Orozco, M.; Luque, F. J. *Eur. J. Org. Chem.* **2001**, *19*, 3719. (e) Ho, T.-L.; Su, C.-Y. *Tetrahedron* **2001**, *57*, 507. (f) Danieli, B.; Lesma, G.; Passarella, D.; Sacchetti, A.; Silvani, A. *Tetrahedron Lett.* **2001**, *42*, 7237. (g) Ho, T.-L.; Gorobets, E. *Tetrahedron* **2002**, *58*, 4969.

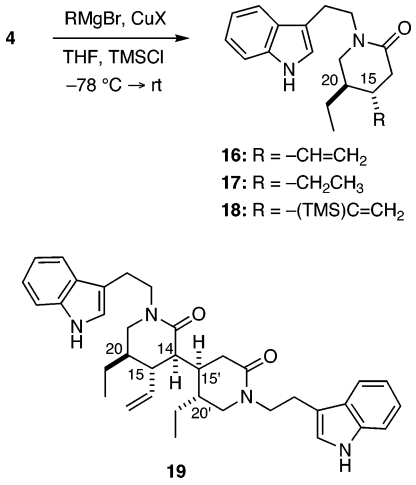
(16) (a) Wassermann, H. H.; Kuo, G.-H. *Tetrahedron* **1992**, *48*, 7071. (b) Lounasmaa, M.; Karvinen, E. *Heterocycles* **1991**, *32*, 489.

(17) (a) Yamamoto, L. T.; Horie, S.; Takayama, H.; Aimi, N.; Sakai, S.; Yano, S.; Shan, J.; Pang, P. K.; Ponglux, D.; Watanabe, K. *Gen. Pharmacol.* **1999**, *33*, 73. (b) Staerk, D.; Lemmich, E.; Christensen, J.; Kharazmi, A.; Olsen, C. E.; Jaroszewski, J. W. *Planta Med.* **2000**, *66*, 531.

(18) Lounasmaa, M.; Tolvanen, A. In *Monoterpenoid Indole Alkaloids*; Saxton, J. E., Ed.; Wiley-Interscience: New York, 1994; Supplement to Vol. 25, Part 4, Chapter 3.

(19) For example, see: (a) Ziegler, F. E.; Sweeny, J. G. *Tetrahedron Lett.* **1969**, *10*, 1097. (b) Suzuki, T.; Sato, E.; Unno, K.; Kametani, T. *Chem. Pharm. Bull.* **1986**, *34*, 1584. (c) Ihara, M.; Taniguchi, N.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 1438. (d) Beard, R. L.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2091. (e) Ohba, M.; Ohashi, T.; Fuji, T. *Heterocycles* **1991**, *32*, 319. (f) Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 321. (g) Diez, A.; Vila, C.; Sinibaldi, M.-E.; Troin, Y.; Rubiralta, M. *Tetrahedron Lett.* **1993**, *34*, 733.

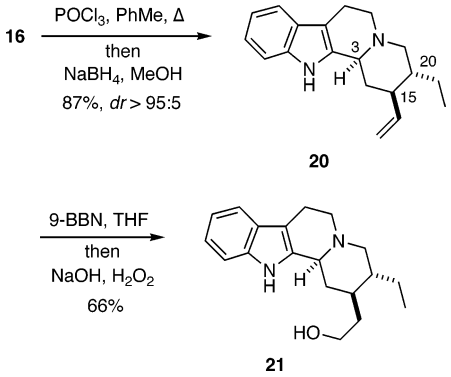
SCHEME 4



The challenge at this stage of our synthetic effort was inducing a stereoselective 1,4-addition onto **4**, as simple α,*β*-unsaturated lactams are notoriously poor Michael acceptors.[20] Indeed, only a few examples of 1,4-additions of organometallic reagents to unsaturated piperidinones have been reported.[21] In most of these cases an additional electron-withdrawing group is present on either the nitrogen or the α-carbon center to increase the electrophilicity of the unsaturated lactam. However, employing such a strategy for activation would entail additional steps involving introduction and removal of these redundant functionalities. After surveying a number of organometallic reagents and conditions,[22] we discovered that optimal conditions for effecting conjugate additions to **4** required organocuprates derived from Grignard reagents and the use of TMSCl as an additive.[23] A brief discussion of some of these experiments is informative. It should be noted in advance that protection of the acidic indole NH was unnecessary in all of these reactions.

The reactions of vinyl organometallic reagents with **4** was studied most extensively because the adduct **16** was an intermediate in the eventual synthesis of dihydrocorynantheol. When stoichiometric amounts of CuCN and vinylmagnesium bromide were used, the resultant cyano Gilman cuprate added to **4** to give **19** as the major product (57% yield); the desired adduct **16** was formed in only 21% yield, albeit with >95:5 diastereoselectivity (Scheme 4). The formation of **19** presumably ensues from the addition of the vinyl Gilman reagent to **4** to generate a copper enolate that then added in a 1,4-sense to a second molecule of **4**; both of these additions appear to proceed with complete stereoselectivity. The tentative structural assign-

SCHEME 5



ment for **19** derives from its mass and an analysis of its ^{1}H NMR spectrum. For example, the vicinal coupling constant of 9.0 Hz between the protons at C(14) and C(15) suggests a *trans* diaxial relationship for these two protons. The *cis* stereochemical relationship between protons at C(14) and C(20) is supported by a strong NOE interaction as well as the appearance of the proton at C(15) as an apparent quartet (J = 9.0 Hz), consistent with a *trans* diaxial relationship with the protons at C(20) and C(14). The *trans* relationship between the protons at C(15′) and C(20′) derives from the stereochemistry of other additions to **4** (vide infra) and the absence of an NOE between these protons. The addition of TMSCl to this reaction completely suppressed the formation of **19**, and **16** was formed in 91% yield with high diastereoselectivity (dr = 92:8). Hence, TMSCl was used as an additive in all other cuprate additions. When CuBr·DMS or CuI rather than CuCN was used to generate the Gilman reagent, **16** was obtained in no better than 35% yield.

We then explored other 1,4-additions to the α,*β*-unsaturated lactam **4**. For example, when **4** was allowed to react with ethylmagnesium chloride in the presence of either stoichiometric amounts of CuCN or catalytic amounts of CuBr·DMS complex, the expected adduct **17** was isolated in 99% yield, albeit with a diastereomeric ratio of only about 77:23.[24] The addition of the sterically more demanding [1-(trimethylsilyl)vinyl]magnesium bromide required use of stoichiometric amounts of CuCN to deliver **18** in good yield (75%) and excellent diastereoselectivity (dr > 95:5).

Returning to the task at hand, we were ready to complete the synthesis of **21**. The requisite indoloquinolizidine skeleton was then fabricated by a Bischler−Napieralski reaction of **16** ($POCl_3$, toluene, 100 °C) followed by a stereoselective hydride reduction ($NaBH_4$, CH_3OH, 0 °C) to furnish **20** in 87% yield as the only diastereomer (Scheme 5). The relative configurations at C(3), C(15), and C(20) were tentatively assigned on the basis of NOE experiments. Regioselective hydroboration of the pendant vinyl group in **20** (9-BBN, THF, room temperature) followed by an oxidative workup (NaOH, H_2O_2, 0 °C) delivered **21** in 66% yield. The analytical data (mp, ^{1}H and ^{13}C NMR spectra) of synthetic **21** were consistent with those previously reported.[19d−f] This stereoselective synthesis of **21** is exceedingly efficient, consisting of only eight distinct chemical operations, none of which involve protection or deprotection, to deliver **21** in 19% overall yield.

4. Formal Syntheses of Rhynchophylline (27) and Isorhynchophylline (28). **27** and its C(7)-epimer **28** were isolated

(20) (a) Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* **1985**, *26*, 657. (b) Hagen, T. J. *Synlett* **1990**, 63.

(21) (a) Overman, L. E.; Robichaud, A. J. *J. Am. Chem. Soc.* **1989**, *111*, 300. (b) Herdeis, C.; Kaschinski, C.; Karla, R. *Tetrahedron: Asymmetry* **1996**, *7*, 867. (c) Amat, M.; Pérez, M.; Llor, N.; Bosch, J.; Lago, E.; Molins, E. *Org. Lett.* **2001**, *3*, 611. (d) Hanessian, S.; van Otterlo, W. A. L.; Nilsson, I. Bauer, U. *Tetrahedron Lett.* **2002**, *43*, 1995. (e) Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 1486. (f) Cossy, J.; Mirguet, O.; Pardo, D. G.; Desmurs, J.-R. *New J. Chem.* **2003**, *27*, 475. (g) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681. (h) Pineshi, M.; Moro, D. D.; Gini, F.; Minnaard, A. J.; Ferringa, B. *Chem. Commun.* **2004**, *12*, 1244. See also ref 20.

(22) Reagents that were evaluated included various combinations of RLi, RMgCl, or RMgBr in the presence of catalytic and stoichiometric amounts of CuBr·DMS, CuI, or CuCN in THF or Et_2O with or without TMSCl as an additive.

(23) (a) Corey, E. J.; Boaz, N. W. *Tetrahedron Lett*. **1985**, *26*, 6019 (b) Alexis, A.; Berlan. J.; Besace, Y. *Tetrahedron Lett.* **1986**, *27*, 1047.

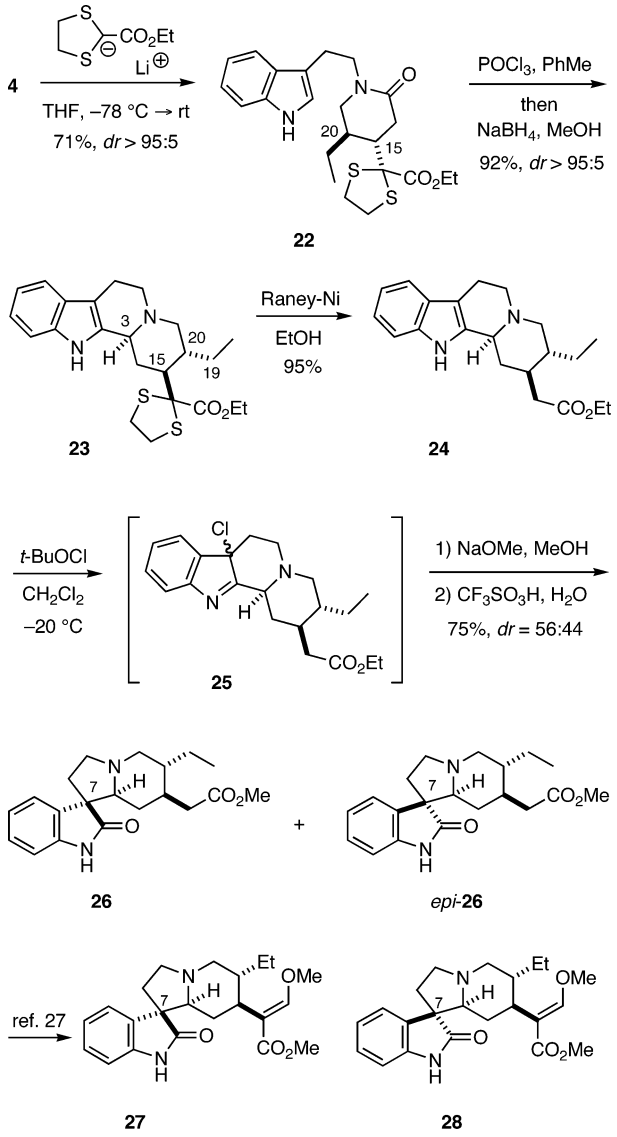
(24) (a) van Tamelen, E. E.; Aldrich, P. A.; Katz, T. J. *J. Am. Chem. Soc.* **1957**, *79*, 6426. (b) Battersby, A. R. *J. Chem. Soc. C* **1968**, 2467. (c) van Tamelen, E. E.; Hester, J. B. *J. Am. Chem. Soc.* **1969**, *91*, 7342.

from *Uncaria rhynchophylla* (Rubiaceae),[25] a species of plant that has been used in traditional medicine in Malaysia for the treatment of cardiovascular disorders such as hypertension. More recently these alkaloids have been found to protect against glutamate-induced neuronal death in cultured cerebellar granule cells.[26] The only total syntheses of rhynchophylline and isorhynchophylline reported to date involve nine steps, but four separations of diastereomers were required owing to the nonselective introduction of the stereogenic center C(15) and early formation of the configurationally labile oxindole skeleton.[27] Because the stereocenter at C(15) was correctly set in **4**, we envisioned that it might be an intermediate in an improved synthesis of these alkaloids.

Our initial efforts toward elaborating **4** into **27** and **28** involved examining the feasibility of the 1,4-addition of anions of dimethyl malonate to **4**. Although the sodium and potassium salts of dimethyl malonate added to **4** with high diastereoselectivity (dr > 95:5), the yields of the desired adduct were only 30% at best.[28] On the other hand, we discovered that the addition of the lithium enolate of ethyl 1,3-dithiolane-2-carboxylate proceeded with excellent diastereoselectivity (dr > 95:5) to afford the ethyl ester **22** in 71% yield (Scheme 6).[29] It is perhaps noteworthy that the addition of the closely related anion of ethyl 1,3-dithiane-2-carboxylate to **4** proceeded in only low yields (<25%). The natural product **27** possesses a methyl ester, not an ethyl ester as in **22**. However, all attempts to produce the methyl ester corresponding to **22** by reaction of the anion of methyl 1,3-dithiolane-2-carboxylate with **4** were low yielding as a consequence of cross-Claisen reactions that led to the preferential production of a β-keto ester derivative of the desired adduct.

Compound **22** was then cyclized via a Bischler−Napieralski reaction ($POCl_3$, toluene, 70 °C, 2 h), and the iminium ion intermediate was reduced in situ with $NaBH_4$ (MeOH, 0 °C → rt) to deliver **23** in 92% yield as a single diastereomer. The preliminary assignment of the relative configurations at C(3), C(15), and C(20) in **23** was consistent with the observed NOE interactions between the axial protons at C(3) and C(15) and between the protons at C(15) and C(19); no NOE contacts were observed between the protons at C(15) and C(20). Having served its role, the dithiolane moiety was removed by treating **23** with Raney Ni to provide the ester **24** (95% yield). The ^1H and ^{13}C NMR data of **24** were consistent with those reported in the literature.[30] The oxindole framework was then installed in a convenient three-step sequence,[31] commencing with chlorination of the indole ring in **24** to give **25**. When the crude **25** was treated with NaOMe, a 1,2-rearrangement ensued to give an intermediate imino ether that was hydrolyzed under acidic conditions to furnish a separable mixture of **26** (42% yield) and epi-**26** (33% yield), which are epimeric at C(7). The methyl ester in **26** and epi-**26** arose as planned from a transesterification

SCHEME 6



that was incidental to the rearrangement step. The spectral data of the synthetic **26** and epi-**26** and the melting point of **26** were consistent with those reported.[27] The stereochemistry at C(7) of the lower R_f spirocycle, which was assigned as **26** by Ban,[27] was unambiguously confirmed by X-ray crystallographic analysis of synthetic **26**, thus correcting a structural misassignment in a previous report claiming the synthesis of **26**.[32] Although the C(7)-epimers are separable by chromatography, they are not configurationally stable and interconvert readily under acidic or basic conditions via a retro-Mannich/Mannich reaction in a process commonly observed for alkaloids of the 2-oxindole family.[27,31] While both **26** and epi-**26** could in principle be advanced to their corresponding natural products, epi-**26** has been converted into both **27** and **28** in three and two steps, respectively.[27] Hence, the present route to epi-**26** therefore constitutes a formal synthesis of **27** and **28**.

B. ABC → ABCD Approach. Encouraged by the successful 1,4-additions of organocuprates and metal enolates to the

(25) (a) Kondo, H.; Fukuda, T.; Tomita, M. *J. Pharm. Soc. Jpn.* **1928**, *48*, 321. (b) Kondo, H.; Ikeda, T. *J. Pharm. Soc. Jpn.* **1937**, *57*, 881.

(26) Shimada, Y.; Goto, H.; Itoh, T.; Sakakibara, I.; Kubo, M.; Sasaki, H.; Terasawa, K. *J. Pharm. Pharmacol.* **1999**, *51*, 715.

(27) Ban, Y.; Seto, M.; Oishi, T. *Chem. Pharm. Bull.* **1975**, *23*, 5.

(28) A 34% yield is reported for the same tranformation: Takano, S.; Sato, M.; Ogasawara, K. *Heterocycles* **1981**, *16*, 799.

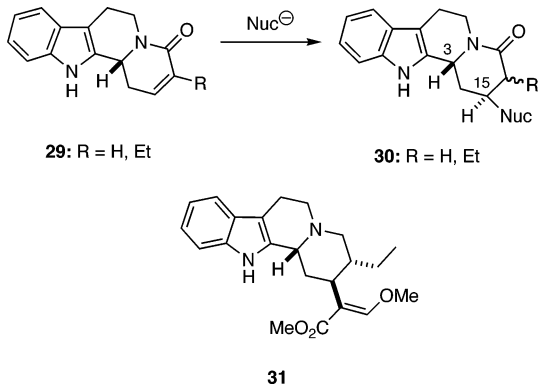
(29) For related 1,4-additions, see ref 21g and references therein.

(30) Andreae, S.; Blaskó, G.; Szántay, C. *J. Prakt. Chem.* **1987**, *329*, 374.

(31) (a) Awang, D. V. C.; Vincent, A.; Kindack, D. *Can. J. Chem.* **1984**, *62*, 2667. (b) Martin, S. F.; Mortimore, M. *Tetrahedron Lett.* **1990**, *31*, 4557. (c) Stahl, R.; Borschberg, H.-J.; Acklin, P. *Helv. Chim. Acta* **1996**, *79*, 1361.

(32) The preparation of **26** has been claimed, but the ^1H NMR data reported match our spectral data for epi-**26**. See: Rosenmund, P.; Hosseini-Merescht, M.; Bub, C. *Liebigs Ann. Chem.* **1994**, 151.

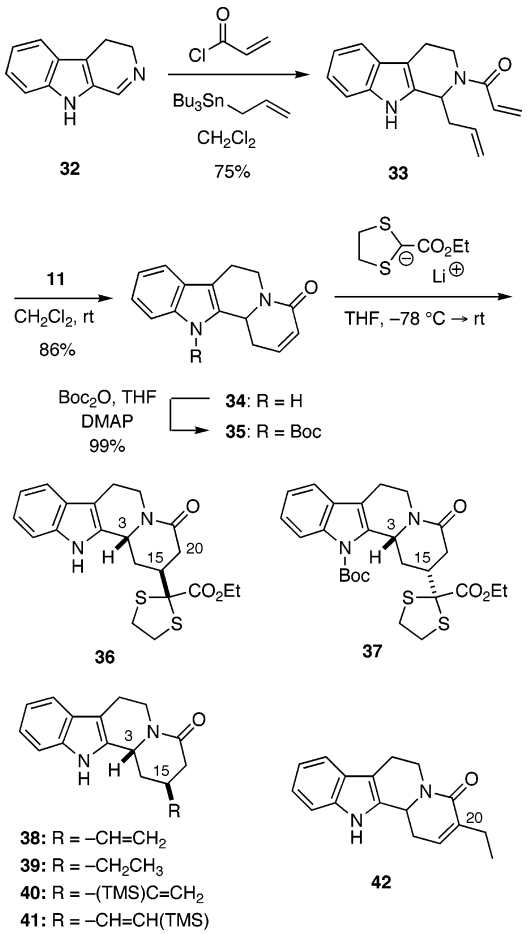
SCHEME 7



unsaturated lactam **4** that culminated in the syntheses of the indole alkaloids **15**, **21**, **27**, and **28**, we decided to expand on this strategy and to explore the potential utility of conjugate additions to tetracyclic compounds of the general structure **29**. While conjugate additions to **4** followed by Bischler−Napieralski cyclizations led to indole alkaloids in which the protons at C(3) and C(15) were positioned in a *cis* relationship, 1,4-additions of nucleophiles to **29** should give compounds such as **30** in which there is a *trans* relationship between these protons owing to the stereoelectronic preference for axial attack (Scheme 7). Such a mode of addition would thus provide access to members of the pseudo-corynanthe family such as hirsutine (**31**). **31** has long been a target for synthesis,[33] in part due to the fact that it is significantly more active against influenza A (subtype H3N3) than ribavarin, which is in clinical use.[34] Moreover, like rhynchophylline and isorhynchophylline, hirsutine also protects against glutamate-induced neuronal death in cultured cerebellar granule cells.[26] It also did not escape our attention that intermediates in the synthesis of hirsutine could also be diverted to prepare other alkaloids, including those of the oxindole family.

1. Extending the Scope of 1,4-Additions to Unsaturated Piperidinones. The requisite tetracyclic Michael acceptor **34** is a known compound, but previous reports of its synthesis required six or seven steps, proceeding with a relatively low overall yield.[35] We thus developed a significantly improved route to **34** that involved an RCM as a key step.[36] In the event, the dihydrocarboline **32**, which may be prepared in two steps from tryptamine,[37] was treated with allyltributyltin and acryloyl chloride to furnish **33** in 75% yield (Scheme 8). Cyclization of

SCHEME 8



33 in the presence of 4 mol % Grubbs' catalyst **11** then delivered **34** in 87% yield.

The reactions of **34** with a number of nucleophiles were then examined. Sodium and lithium enolates and silyl ketene acetals derived from methyl acetate and copper enolates of *N*,*N*-dimethyl acetamide and *tert*-butyl acetate failed to undergo the desired addition. The 1,4-addition of the sodium enolate of dimethyl malonate proceeded slowly (48 h) to give the expected adduct in 74% yield, but the diastereoselectivity was poor (dr = 60:40). On the other hand, as we observed in additions to **4**, 1,4-addition of the lithium enolate derived from ethyl 1,3-dithiolane-2-carboxylate to **34** proceeded in excellent diastereoselectivity (dr = 91:9) to give **36**, which could be isolated cleanly in 55−60% yield after facile separation of the diastereomers by column chromatography. To obtain reproducible results in this reaction, it was necessary to degas the solvent thoroughly by three freeze−pump−thaw cycles. Even when this was done, there was an erosion in the dr on scaleup. The relative stereochemistry of the C(3)H and C(15)H protons of **36** was tentatively assigned as being *trans* on the basis of the known stereoelectronic preference for axial attack, coupled with the prediction that the nucleophile should approach form the convex face of the alkene. This structural assignment was unequivocally confirmed at a later stage of the synthesis by single-crystal X-ray analysis of **44** (vide infra).

We also briefly explored the copper(I)-mediated conjugate additions of organometallic reagents to **34** in the presence of TMSCl. We had found that CuCN-derived cuprate reagents were best for additions to **4**, but use of catalytic amounts (10

(33) For example, see: (a) Aimi, N.; Yamanaka, E.; Endo, J.; Sakai, S.; Haginawa, J. *Tetrahedron* **1973**, *29*, 2015. (b) Brown, R. T.; Chapple, C. L.; Charalambides, A. A. *J. Chem. Soc., Chem. Commun.* **1974**, 756. (c) Wenkert, E.; Vankar, Y. D.; Yadav, J. S. *J. Am. Chem. Soc.* **1980**, *102*, 7972. (d) Brown, R. T.; Ford, M. J. *Tetrahedron Lett.* **1990**, *31*, 2033. (e) Gomez-Pardo, D.; Desmaële, D; d'Angelo, J. *Tetrahedron Lett.* **1992**, *33*, 6633. (f) Lounasmaa, M.; Jokela, R.; Laine, C.; Hanhinen, P. *Heterocycles* **1998**, *49*, 445. (g) Tietze, L. F.; Zhou, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 2045.

(34) Takayama, H.; Iimura, Y.; Kitayama, M.; Aimi, N.; Konno, K.; Inoue, H.; Fujiwara, M.; Mizuta, T.; Yokota, T.; Shigeta, S.; Tokuhisa, K.; Hanasaki, Y.; Katsuura, K. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3145.

(35) For example, see: (a) Oehl, R.; Lenzer, G.; Rosenmund, P. *Chem. Ber.* **1976**, *109*, 705. (b) Massiot, G.; Mulamba, T.; Levy, J. *Bull. Soc. Chim. Fr.* **1982**, II-241. (c) Massiot, G.; Mulamba, T *J. Chem. Soc., Chem. Commun.* **1983**, 1147.

(36) Since this work was completed, a related approach to the asymmetric synthesis of **34** was reported. See: Itoh, T.; Miyazaki, M.; Nagata, K.; Nakamura, S, Ohsawa, A. *Heterocycles* **2004**, *63*, 655.

(37) Martin, S. F.; Benage, B.; Hunter, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 5925.

mol %) of CuBr·DMS complex was better when **34** was the substrate. This observation suggests that subtle effects are at play in cuprate additions to unsaturated lactams. Although the addition of the organocopper reagent derived from vinylmagnesium bromide to **34** proceeded in 80% yield to give **38**, the diastereoselectivity was poor (dr = 60:40) (Scheme 8). On the other hand, cuprates derived from ethylmagnesium bromide and [1-(trimethylsilyl)vinyl]magnesium bromide added in excellent (84−98%) yield to give the corresponding adducts **39** and **40** with >95:5 diastereoselectivity. Whereas addition of the cuprate derived from [2-(trimethylsilyl)vinyl]magnesium bromide and CuBr·DMS to **34** was both inefficient (52%) and nonselective (dr = 65:35), the related reaction with [2-(trimethylsilyl)vinyl]lithium in the presence of CuI gave **41** in 84% yield with >95:5 diastereoselectivity. It is noteworthy that the vinylsilyl groups in **40** and **41** are masked equivalents of acetyl and acetaldehyde substituents, respectively.[38] The relative stereochemical course in these additions was not rigorously determined, but the structural assignment is consistent with NOE studies conducted on compound **39**.

Converting **36** into hirsutine requires introducing an ethyl group onto **36** or a derived intermediate by alkylation at C(20). It occurred to us that this extra step might be avoided if the ethyl group were already incorporated in the unsaturated lactam as found in **42**. Although **42** is known,[39] we developed an improved and more concise route to this compound that features the RCM of an α-ethylacrylamide derivative of **33** that required only three steps and proceeded in 60% overall yield from **32**. Consistent with the report that **42** is a poor Michael acceptor,[39] we were unable to detect any 1,4-addition products when **42** was allowed to react with either the lithium or sodium enolates of ethyl 1,3-dithiolane-2-carboxylate or various cuprate reagents. Either the addition was disfavored owing to steric or electronic factors or the 1,4-adduct was kinetically unstable under these conditions. We then considered the alternate possibility that the enolate formed upon addition of lithiated ethyl 1,3-dithiolane-2-carboxylate to **34** might be alkylated to provide a derivative of **36** bearing an ethyl group at C(20). However, this tactic was complicated by concomitant and unavoidable ethylation of the indole nitrogen atom. We therefore examined conjugate additions to the protected indole **35**, anticipating that alkylation of the intermediate enolate would proceed without difficulty.

Toward this end, we found that **35** could be obtained in 99% yield by protecting **34** under standard conditions (Scheme 8). However, an even more efficient approach involved adding Boc-anhydride and DMAP directly to the reaction mixture obtained after completion of the RCM of **33**, thus giving **35** in 93% yield in one step from **33**. Surprisingly, reaction of **35** with ethyl 2-lithio-1,3-dithiolane-2-carboxylate gave **37** in 71% yield and high diastereoselectivity (dr > 95:5) (Scheme 8), not the expected adduct in which the protons at C(3) and C(15) were positioned *trans* as in **36**.[40] It should be noted that the stereochemistry in **37** corresponds to that found in the corynanthe alkaloids and thus may serve as a useful intermediate in their synthesis.

(38) Boeckman, R. K., Jr.; Bruza, K. J. *J. Org. Chem.* **1979**, *44*, 4781.
(39) Yamanaka, E.; Narushima, M.; Inukai, K.; Sakai, S. *Chem. Pharm. Bull.* **1986**, *34*, 77.
(40) Our observation of reversal of the diastereoselectivity by introducing a *tert*-butyl carbamate was corroborated in the following paper, which was published during the preparation of this manuscript: Allin, S. M.; Khera, J. S.; Thomas, C. I.; Witherington, J.; Doyle, K.; Elsegood, M. R. J.; Edgar, M. *Tetrahedron Lett.* **2006**, *47*, 1961.

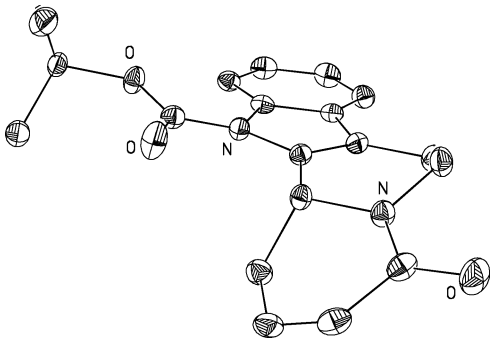


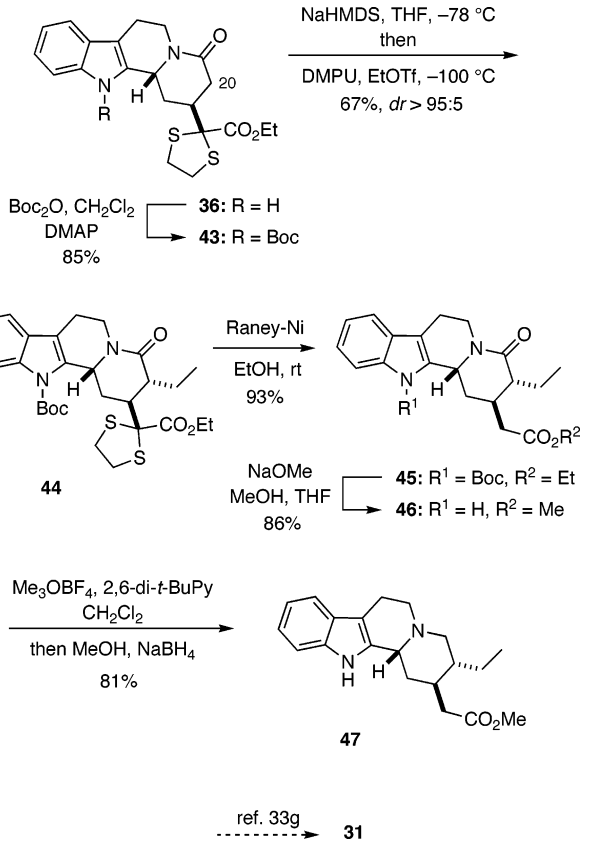
FIGURE 1. ORTEP plot of **35**. The hydrogen atoms have been removed for clarity. Displacement ellipsoids are scaled to the 50% probability level.

A clue for this unexpected reversal in diastereoselectivity in the addition to **35** may be found through analysis of its X-ray structure (Figure 1). Examination of this structure of **35** reveals that the α,β-unsaturated lactam is twisted away from the plane of the indole and the bulky Boc group. Assuming that the conformation of **35** in solution resembles that in the solid state, the top face of the α,β-unsaturated lactam moiety is partially shielded from nucleophilic attack by the Boc group, so it appears that steric factors may override the usual stereoelectronic preference for axial attack. Alternatively, axial attack might occur on the other half-chair conformer of the unsaturated lactam ring, although the approach of a nucleophile via that trajectory would also incur a 1,3-diaxial interaction.

2. Formal Synthesis of 31. The observed stereoselectivities in the conjugate additions to **34** and **35** provided crucial guidance for planning the synthesis of **31**. The next task involved introducing an ethyl group, and prior experimentation (vide supra) suggested that selective ethylation at C(20) of **36** might be problematic, owing to competing alkylation of the indole nitrogen atom. Indeed, a few preliminary experiments validated this concern, and protecting the indole as its Boc derivative was clearly indicated. Although it was possible to carry out the protection in the same pot as the 1,4-addition to afford **43** in 60−65% yield, the two diastereomers thus obtained (dr = 91:9) were not easily separable by chromatography at this stage. Instead, diastereomerically pure **36** was converted to **43** in 85% yield upon reaction with Boc_2O in the presence of catalytic amounts of DMAP (Scheme 9).

Optimizing the tactics for introducing an ethyl group at C(20) of **43** required rather extensive experimentation. The lithium enolate derived from **43** was unreactive with ethyl iodide, even in the presence of additives such as HMPA and DMPU, at −78 °C, and at higher temperatures the enolate underwent a retro-Michael reaction to give **35**. Use of KHMDS as the base in the presence of HMPA led to extensive cleavage of the dithiolane ring via elimination and *S*-alkylation of the thiolate thus formed. Although the corresponding sodium enolate of **43** did undergo alkylation at −78 °C, **44** was produced in only 40−45% yield. Gratifyingly, we eventually discovered that reaction of the sodium enolate of **43** with EtOTf in the presence of DMPU at −100 °C furnished **44** in 67% yield and as a single diastereomer. Starting material (25−30%) was invariably recovered from these reactions, despite meticulous efforts to avoid adventitious water. The structure of **44** was unequivocally established through single-crystal X-ray analysis, thereby confirming not only the stereochemistry of the alkylation but also the stereochemistry of the conjugate addition to **34** to give **36** (vide supra). A severe

SCHEME 9

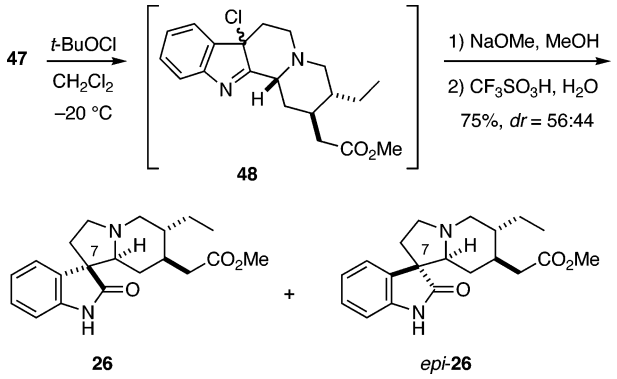


steric interaction between the Boc group and the dithiolane moiety is apparent in this structure, a factor that may account for the observed propensity for the enolate of **43** to undergo retro-Michael reaction.

Having thus served its dual role of enabling the 1,4-addition to **35** and the selective alkylation at C(20) of **43**, the dithiolane moiety was reductively removed using Raney Ni to afford **45** in 93% yield. Subsequent removal of the Boc group by the action of NaOMe proceeded as planned with concomitant transesterification of the ethyl ester to furnish **46** in 86% yield. Selective reduction of the lactam function in **46** was then achieved according to the Borch protocol,[41] delivering **47** in 81% yield. The ^{1}H and ^{13}C NMR spectral data for **47**, which had been previously converted into **31** in two steps,[33g] were consistent with those reported in the literature,[42] thereby completing a formal synthesis of **31**.

3. Second-Generation Formal Synthesis of 27 and 28. It occurred to us that the indoloquinolizidine **47** might be an intermediate in an alternative route to **27** and **28**. This hypothesis was founded upon our previous observations that the stereochemistry at C(3) of oxindoles related to **26** and epi-**26** could also be equilibrated via retro-Mannich/Mannich reactions that occur consequent to the oxidative rearrangement.[2d] A two-step sequence for inducing the oxidative rearrangement of **47** was first examined. However, when **47** was treated with *tert*-butyl hypochlorite and the resultant crude chloroindolinine **48** heated under reflux in MeOH/AcOH to effect rearrangement and hydrolysis in the same pot,[2d] **26** and epi-**26** were obtained in

SCHEME 10



only 10% and 14% yields, respectively. Hence, the same three-step sequence we previously adopted was employed to convert **47** into a mixture (55:45) of **26** and epi-**26** in 75% overall yield, thereby completing a second formal synthesis of **27** and **28** (Scheme 10).[27]

Summary

We have developed a novel and general approach to a variety of indole alkaloids possessing a corynanthe, an oxindole, or a tacaman skeleton. By employing a sequence of two RCM reactions and one zirconocene-catalyzed carbomagnesation, the construction of the α,β-unsaturated piperidinone ring in the key intermediate **4** was completed in just five chemical operations and 36% overall yield. Although we did not explore this option, it would be possible to use a known chiral zirconocene catalyst in the carbomagnesation step to assemble **4** in enantiomerically pure form. To install a variety of substituents at C(15) in **4**, we explored the feasibility of inducing conjugate additions of various carbon nucleophiles onto α,β-unsaturated lactams, a still underdeveloped area in organic synthesis. Our studies revealed that organocuprates derived from organomagnesium compounds and, depending upon the nature of the lactam, either stoichiometric amounts of CuCN or catalytic amounts of CuBr·DMS complex are superior nucleophiles for such 1,4-additions. It was crucial to use TMSCl as an additive as its presence prevents undesired side reactions. Having established the optimal parameters for effecting the requisite conjugate additions, we completed an extremely concise total synthesis of the corynanthe alkaloid **21** in just eight distinct chemical operations and 19% overall yield. Inspired by the obvious biogenetic relationship between the corynanthe alkaloids and those natural products possessing the oxindole or pseudoeburnan skeleton, we adapted our approach to **21** and developed novel formal syntheses of **15**, **27**, and **28** from **4**. It is noteworthy that these syntheses avoid the use of any protecting groups, thereby simplifying the execution. In a related series of studies, we explored the 1,4-addition of various organocuprates and enolates to the unsaturated lactam **34** as a key step in developing an alternate approach to indole and oxindole alkaloids. During the course of these studies, we discovered that the diastereoselectivity of the 1,4-addition of the lithium enolate of ethyl 1,3-dithiolane-2-carboxylate to **34** could be reversed by simply introducing a Boc protecting group on the indole nitrogen atom prior to the conjugate addition. This work led to a short formal synthesis of **31** as well as second-generation syntheses of **27** and **28**. Taken together, the two strategies reported herein represent a unified approach to indole alkaloids possessing either a H(3)/

(41) Borch, R. F. *Tetrahedron Lett.* **1968**, *9*, 61.

(42) (a) Lounasmaa, M.; Jokela, R.; Tirkkonen, B.; Miettinen, J.; Halonen, M. *Heterocycles* **1992**, *34*, 321. (b) Seguin, E.; Koch, M. *Helv. Chim. Acta* **1980**, *63*, 1335.

H(15)-*cis* or a H(3)/H(15)-*trans* stereochemical relationship, and further applications of these tactics to other problems in alkaloid synthesis are in progress.

Experimental Section

***N,N*-Diallyl-2-(1*H*-indol-3-yl)acetamide (8).** EDCI (5.47 g, 28.5 mmol) was added to a solution of indole-3-acetic acid (5.00 g, 28.5 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After 3 min, diallylamine (5.30 mL, 43.0 mmol) was added, and the resultant solution was stirred for 2 h at 0 °C and for 17 h at room temperature. Aqueous HCl (1 M, 40 mL) was added, and the phases were separated. The aqueous layer was extracted with EtOAc (3 × 50 mL), and the combined organic phases were washed with H_2O (30 mL) and saturated aqueous $NaHCO_3$ (30 mL), dried ($MgSO_4$), and filtered. The solvents were removed under reduced pressure to give 6.37 g (88%) of **8** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (br s, 1 H), 7.59−7.06 (comp, 4 H), 6.95 (m, 1 H), 5.81−5.66 (comp, 2 H), 5.21−5.04 (comp, 4 H), 4.02 (d, J = 6.0 Hz, 2 H), 3.89−3.87 (m, 2 H), 3.80 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 136.2, 133.07, 132.9, 127.1, 122.7, 121.8, 119.3, 118.5, 117.2, 116.6, 111.3, 108.8, 49.5, 47.9, 30.9; IR (neat) 3277, 1628, 1458, 1415, 1340, 1221, 924, 741 cm^{-1}; MS (CI) *m*/*z* 255.1500 [$C_{16}H_{19}N_2O$ (M + 1) requires *m*/*z* 255.1497].

***N*-(2-Ethylbut-3-enyl)-2-(1*H*-indol-3-yl)acetamide (7).** A mixture of **8** (1.29 g, 5.08 mmol) and $[(C_6H_{11})_3P]_2Cl_2RuC_2H_3Ph$ (42 mg, 0.05 mmol, 1 mol %) in THF (60 mL) was stirred for 29 h at room temperature, whereupon a 2 M solution of EtMgCl in Et_2O (10.2 mL, 20.3 mmol) and Cp_2ZrCl_2 (222 mg, 0.76 mmol) were added. The mixture was stirred for 1 h, and 2 M aqueous HCl (30 mL) was injected. The layers were separated, and the organic phase was extracted with EtOAc (3 × 30 mL). The combined organic phases were dried ($MgSO_4$), and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexanes (1:1 → 7:3 → EtOAc), to give 926 mg (71%) of **7** as a yellow viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (br s, 1 H), 7.55−7.09 (comp, 5 H), 5.77 (br s, 1 H), 5.28 (ddd, J = 9.0, 9.5, 16.8 Hz, 1 H), 4.76 (dd, J = 1.6, 10.2 Hz, 1 H), 4.59 (ddd, J = 0.6, 1.6, 16.8 Hz, 1 H), 3.73 (s, 2 H), 3.37 (ddd, J = 4.9, 8.0, 13.0, 1 H), 2.86 (ddd, J = 4.9, 8.0, 13.0 Hz, 1 H), 1.90−1.80 (m, 1 H), 1.40−1.20 (m, 1 H), 1.20−1.03 (m, 1 H), 0.78 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 139.6, 136.4, 126.9, 123.8, 122.4, 119.8, 118.7, 116.6, 111.4, 108.7, 45.9, 42.6, 33.3, 24.9, 11.3; IR (neat) 3403, 3277, 2962, 2926, 1650, 1530, 1457, 1340, 918, 741 cm^{-1}; MS (CI) *m*/*z* 257.1657 [$C_{16}H_{21}N_2O$ (M + 1) requires *m*/*z* 257.1653].

(2-Ethylbut-3-enyl)[2-(1*H*-indol-3-yl)ethyl]amine (6). $LiAlH_4$ (1.47 g, 38.6 mmol) was added to a solution of **7** (1.65 g, 6.44 mmol) in Et_2O (130 mL), and the suspension was stirred at room temperature overnight. After addition of more $LiAlH_4$ (400 mg, 10.5 mmol), stirring was continued for 4 h, and then, sequentially, H_2O (1.9 mL), 15% aqueous NaOH (1.9 mL), and H_2O (5.7 mL) were added. The suspension was stirred for 30 min, the solids were removed by vacuum filtration, and the filtrate was concentrated under reduced pressure to give 1.36 g (87%) of **6** as a yellow oil. The crude product was used without further purifications: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.20 (s, 1 H, N(1)H), 7.63−7.00 (comp, 5 H), 5.49−5.36 (m, 1 H), 4.95 (m, 2 H), 3.00−2.87 (m, 4 H), 2.67 (dd, J = 5.0, 11.4 Hz, 1 H), 2.47 (dd, J = 8.7, 11.4 Hz, 1 H), 2.21−2.04 (m, 1 H), 1.44−1.32 (m, 1 H), 1.25−1.18 (m, 1 H), 0.84 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 136.3, 127.2, 122.1, 121.6, 118.9, 188.5, 116.6, 112.8, 111.1, 53.0, 49.5, 45.6, 25.5, 25.1, 11.4; IR (neat) 3058, 2920, 1454, 1354, 1231, 1108, 917, 740 cm^{-1}; MS (CI) *m*/*z* 243.1853 [$C_{16}H_{23}N_2$ (M + 1) requires *m*/*z* 243.1861].

***N*-(2-Ethylbut-3-enyl)-*N*-[2-(1*H*-indol-3-yl)ethyl]acrylamide (5).** Acryloyl chloride (94 μL, 1.15 mmol) was added to a stirred solution of **5** (280 mg, 1.15 mmol) and Et_3N (0.32 mL, 2.31 mmol) in CH_2Cl_2 (15 mL) at 0 °C. After 13 h, the volatiles were evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexanes (1:1), to give 250 mg (73%) of **5** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 8.48 (br s, 0.5 H), 8.37 (br s, 0.5 H), 7.70 (d, J = 7.8 Hz, 0.5 H), 7.56 (d, J = 7.5 Hz, 0.5 H), 7.37−7.33 (m, 1 H), 7.22−7.09 (comp, 2 H), 7.00 (d, J = 2.1 Hz, 0.5 H), 6.35 (d, J = 2.4 Hz, 0.5 H), 6.57 (dd, J = 10.2, 16.5 Hz, 0.5 H), 6.45 (dd, J = 10.2, 16.5 Hz, 0.5 H), 6.40 (dd, J = 2.1, 16.5 Hz, 0.5 H), 6.26 (dd, J = 2.4, 16.5 Hz, 0.5 H), 5.68 (dd, J = 2.1, 10.2 Hz, 0.5 H), 5.63−5.41 (comp, 1.5 H), 5.06−4.95 (comp, 2 H), 3.71−3.58 (comp, 2 H), 3.50 (dd, J = 6.0, 13.5 Hz, 0.5 H), 3.34−3.14 (comp, 1.5 H), 3.08−2.97 (comp, 2 H), 2.42−2.30 (m, 0.5 H), 2.24−2.14 (m, 0.5 H) 1.50−1.32 (m, 1 H), 1.30−1.10 (m, 1 H), 0.88−0.82 (comp, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 166.6, 166.4, 140.2, 138.8, 136.3, 128.1, 127.6, 127.5, 127.3, 126.9, 122.2, 122.0, 121.8, 119.4, 119.2, 118.7, 118.1, 117.5, 116.3, 113.1, 111.9, 111.4, 111.2, 52.9, 50.7, 49.1, 48.5, 46.4, 45.0, 25.2, 25.1, 24.8, 23.2, 11.5; IR (neat) 3269, 2963, 2927, 1642, 1603, 1455, 1354, 1225, 916, 741 cm^{-1}; mass spectrum (CI) *m*/*z* 297.1971 [$C_{19}H_{25}N_2O$ (M + 1) requires *m*/*z* 297.1967].

5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-5,6-dihydro-1*H*-pyridin-2-one (4). A solution of **5** (250 mg, 0.84 mmol) and $((C_6H_{11})_3P)_2Cl_2RuC_2H_3Ph$ (35 mg, 0.04 mmol, 5 mol %) in CH_2Cl_2 (30 mL) was stirred for 20 h. $(HOCH_2)_3P$ (50 mg) and Et_3N (2 mL) were added, and stirring was continued for 15 min. The solvents were removed under reduced pressure, and the crude product was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 206 mg (91%) of **4** as a colorless solid: mp 88−89 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) 8.50 (br s, 1 H), 7.65 (d, J = 7.8 Hz, 1 H), 7.35 (d, J = 8.1 Hz, 1 H), 7.19−7.08 (comp, 2 H), 7.02 (d, J = 2.1 Hz, 1 H), 6.41 (dd, 1 H, J = 3.6, 9.8 Hz, 1 H), 5.90 (dd, J = 1.8, 9.8 Hz, 1 H), 3.82−3.62 (comp, 2 H), 3.30 (dd, J = 6.0 Hz, 12.3, 1 H), 3.12 (dd, J = 8.4, 12.3 Hz, 1 H), 3.04 (t, J = 7.4 Hz, 2 H), 2.21 (br s, 1 H), 1.46−1.26 (comp, 2 H), 0.84 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.2, 144.0, 136.3, 127.4, 124.5, 122.2, 121.8, 119.1, 118.6, 112.8, 111.2, 50.7, 47.6, 35.9, 24.9, 23.6, 11.2; IR (neat) 3260, 1654, 1597, 1487, 817, 741 cm^{-1}; MS (CI) *m*/*z* 269.1645 [$C_{17}H_{21}N_2O$ (M + 1) requires *m*/*z* 269.1654].

3-Ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizine (14). Palladium (10% on carbon) was added to a solution of **4** (30 mg, 0.30 mmol) in toluene (4 mL). The suspension was pressurized by a H_2 balloon and stirred for 14 h. Freshly distilled $POCl_3$ (63 μL, 0.67 mmol) was added, and the reaction mixture was heated to 100 °C for 3 h. A saturated aqueous solution of NH_4OH (2 mL) was added, and heating under reflux was continued for 30 min. The reaction mixture was allowed to cool to room temperature, the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 3 mL). The combined organic layers were dried ($MgSO_4$), and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/TEA (98:2), to furnish 26 mg (92%) of **14** as a brown viscous oil. The ^{1}H and ^{13}C NMR spectra were consistent with those reported in the literature.[16]

***trans*-5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-4-vinylpyridin-2-one (16).** A freshly prepared 0.9 M solution of vinylmagnesium bromide in THF (8.3 mL, 7.45 mmol) was added to a suspension of CuCN (333 mg, 3.73 mmol) in THF (15 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 3 min and then recooled to −78 °C. A solution of **4** (200 mg, 0.75 mmol) in THF (4 mL) was added, and after 5 min freshly distilled TMSCl (0.47 mL, 3.73 mmol) was added. The suspension was warmed to room temperature over 3.5 h, and stirring was continued for 15 min. A mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 5 mL) and H_2O (5 mL) were added, and the mixture was stirred for 20 min. A 1 M solution of TBAF in THF (0.5 mL, 0.5 mmol) was added, and stirring was continued for 15 min. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated

under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 200 mg (91%, dr = 98:2) of **16** as colorless needles: mp 159−161 °C (EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (br s, 1 H), 7.66 (d, J = 7.8 Hz), 7.36 (d, J = 8.1 Hz), 7.12−7.09 (m, 2 H), 7.04 (d, J = 2.1 Hz), 5.62−5.50 (m, 1 H), 5.05−4.99 (comp, 2 H), 3.77−3.57 (comp, 2 H), 3.19 (dd, J = 4.8, 12.1 Hz, 1 H), 3.05 (t, J = 7.5 Hz, 2 H), 2.87 (dd, J = 9.9, 12.1 Hz, 1 H), 2.49 (dd, J = 4.5, 16.5 Hz, 1 H), 2.30−2.12 (comp, 2 H), 1.59−1.28 (comp, 2 H), 1.12−1.01 (m, 1 H), 0.74 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 139.7, 136.3, 127.5, 122.0, 121.9, 119.2, 118.7, 115.6, 113.1, 111.2, 52.1, 48.2, 42.5, 39.3, 37.4, 23.9, 23.0, 10.9; IR (CH_2Cl_2) 3255, 2962, 2927, 2868, 1625, 1503, 1456, 1357, 916, 741 cm^{-1}; MS (CI) m/z 297.1969 [$C_{19}H_{25}N_2O$ (M + 1) requires m/z 297.1967].

4,5-Diethyl-1-[2-(1*H*-indol-3-yl)ethyl]pyridin-2-one (17). A 2 M solution of ethylmagnesium chloride in THF (1.86 mL, 3.73 mmol) was added to a suspension of CuBr·DMS (11 mg, 56 μmol) in THF (15 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 3 min and then recooled to −78 °C. Freshly distilled TMSCl (0.14 mL, 1.11 mmol) and a solution of **4** (100 mg, 0.37 mmol) in THF (1.5 mL) were added. The suspension was warmed to room temperature over 3.5 h, and stirring was continued for 15 min. A mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 6 mL) was added. After the resulting mixture was stirred for 10 min, a 1 M solution of TBAF in THF (0.35 mL, 0.35 mmol) was added, and stirring was continued for 15 min. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 110 mg (99%, dr = 77:23) of **17** as a mixture of inseparable diastereomers and as a colorless foam: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 8.59 (br s, 1 H), 7.64 (d, J = 7.7 Hz, 1 H), 7.34 (d, J = 7.9 Hz, 1 H), 7.18−7.06 (comp, 2 H), 6.99 (d, J = 1.8 Hz, 1 H), 3.75−3.56 (comp, 2 H), 3.19−3.10 (comp, 1 H), 3.07−3.01 (comp, 2.2 H) 2.86 (dd, J = 12.0, 8.2 Hz, 0.8 H), 2.50 (dd, J = 17.3, 5.2 Hz, 0.8 H), 2.40 (dd, J = 17.6, 5.6 Hz, 0.2 H), 2.27 (dd, J = 17.6, 6.7 Hz, 0.2 H), 2.05 (dd, J = 17.3, 8.6 Hz, 0.8 H), 1.78−1.59 (comp, 0.4 H), 1.51−1.02 (comp, 5.6 H), 091−70.72 (comp, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 170.0, 136.3, 127.4, 122.1, 121.7, 119.1, 118.6, 112.8, 111.2, 51.5, 50.6. 48.1, 48.0, 38.9, 38.2, 37.6, 37.1, 36.1, 35.8, 25.5, 23.5, 23.1, 22.9, 21.8, 19.9, 12.0, 11.8, 10.9, 10.4; IR spectrum identical to that previously reported;[24] MS (CI) m/z 299.2133 [$C_{19}H_{27}N_2O$ (M + 1) requires m/z 299.2123].

***trans*-5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-4-[1-(trimethylsilyl)-vinyl]pyridin-2-one (18).** Freshly prepared [1-(trimethylsilyl)vinyl]-magnesium bromide (1.50 mmol) in THF (1.5 mL) was added to a suspension of CuCN (67 mg, 0.75 mmol) in THF (5 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 3 min and then recooled to −78 °C. A solution of **4** (40 mg, 0.15 mmol) in THF (1 mL) was added, and after 5 min freshly distilled TMSCl (95 μL, 0.75 mmol) was added. The suspension was warmed to room temperature over 3.5 h, and stirring was continued for 15 min. A mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 2 mL) and H_2O (2 mL) were added. After 30 min TBAF (0.3 mL) was injected and stirring continued for 10 min. The layers were separated, and the aqueous phase was extracted with EtOAc (4 × 15 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 41 mg (75%, dr > 95:5) of **18** as colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (br s, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.12 (t, J = 8.0 Hz, 1 H), 7.04 (d, J = 2.0 Hz, 1 H), 5.57 (d, J = 1.8 Hz, 1 H), 5.49 (d, J = 1.8 Hz, 1 H), 3.75 (dt, J = 7.4, 13.0 Hz, 1 H), 3.60 (dt, J = 7.4, 13.0 Hz, 1 H), 3.23 (dd, J = 5.2, 12.4 Hz, 1 H), 3.06 (t, J = 7.6 Hz, 2 H), 2.84 (dd, J = 9.2, 12.0 Hz, 1 H), 2.51 (dd, J = 3.6, 16.0 Hz, 1 H), 2.35−2.22 (comp, 2 H), 1.69−1.49 (comp, 2 H), 0.98−0.88 (m, 1 H), 0.72 (t, J = 7.6 Hz, 3 H), 0.10 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 153.6, 136.5, 127.8, 125.7, 122.2, 122.1, 119.5, 119.0, 113.4, 111.5, 52.8, 48.7, 43.6, 39.8, 39.4, 24.5, 23.5, 11.8, −0.5; IR (neat) 3269, 2957, 1633, 1504, 1455, 1248, 837, 740 cm^{-1}; MS (CI) m/z 369.2368 [$C_{22}H_{33}N_2OSi$ (M + 1) requires m/z 369.2362].

5,5′-Diethyl-1,1′-bis[2-(1*H*-indol-3-yl)ethyl]-4-vinyl[3,4′]-bipiperidinyl-2,2′-dione (19). A freshly prepared 0.9 M solution of vinylmagnesium bromide in THF (1.2 mL, 1.12 mmol) was added to a suspension of CuCN (50 mg, 0.56 mmol) in THF (3 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 3 min and then recooled to −78 °C. A solution of **4** (30 mg, 0.11 mmol) in THF (0.5 mL) was added. The suspension was warmed to room temperature over 3 h, and stirring was continued for 15 min. A mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 1 mL) was added, the layers were separated, and the aqueous phase was extracted with EtOAc (3 × 1 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc → EtOAc/MeOH (9:1), to give 7 mg (21%, dr > 95:5) of **16** and 18 mg (57%, dr > 95:5) of **19** as a colorless foam: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (br s, 1 H), 8.32 (br s, 1 H), 7.65 (d, J = 7.6 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 1 H), 7.34 (d, J = 8.0 Hz, 1 H), 7.18 (t, J = 6.8 Hz, 2 H), 7.12 (t, J = 6.8 Hz, 2 H), 7.02 (d, J = 2.0 Hz, 1 H), 6.99 (d, J = 2.0 Hz, 1 H), 5.38 (ddd, J = 9.6, 10.0, 17.2 Hz, 1 H), 5.07 (d, J = 10.0 Hz, 1 H), 4.94 (d, J = 16.8 Hz, 1 H), 3.83 (dt, J = 8.0, 13.2 Hz, 1 H), 3.80−3.71 (m, 1 H), 3.60−3.50 (comp, 2 H), 3.12 (dd, J = 4.8, 11.8 Hz, 1 H), 3.09−2.94 (comp, 5 H), 2.89 (t, J = 11.6 Hz, 1 H), 2.76 (dd, J = 9.6, 11.8 Hz, 1 H), 2.57 (dd, J = 11.2, 16.4 Hz, 1 H), 2.38 (d, J = 8.8 Hz, 1 H), 2.36−2.30 (m, 1 H), 2.23 (dd, J = 5.6, 16.4 Hz, 1 H), 1.99−1.91 (m, 1 H), 1.62−1.42 (comp, 2 H), 1.28−1.21 (m, 1 H), 1.05−0.85 (m, 1 H), 0.85−0.81 (m, 1 H), 0.70 (t, J = 7.6 Hz, 3 H), 0.66 (t, J = 7.6 Hz, 3 H); ^{13}C NMR (125 MHz) δ 170.7, 170.1, 140.1, 136.5, 136.3, 127.5, 127.4, 122.2, 122.1, 122.0, 121.9, 119.3, 119.2, 118.7, 118.6, 117.7, 113.1, 112.7, 111.3, 111.2, 52.3, 51.5, 48.7, 48.1, 46.9, 46.5, 39.7, 39.2, 36.8, 35.4, 23.8, 23.4, 23.2, 23.1, 10.7, 10.6; IR (CH_2Cl_2) 3270, 2965, 2928, 1621, 1494, 1455, 1342, 1298, 1232, 909, 737 cm^{-1}; MS (CI) m/z 565.3544 [$C_{36}H_{45}N_4O_2$ (M + 1) requires m/z 565.3543].

3-Ethyl-2-vinyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (20). Freshly distilled $POCl_3$ (0.23 mL, 2.42 mmol) was added to a suspension of **16** (90 mg, 0.30 mmol) in toluene (4 mL), and the reaction mixture was heated to 100 °C for 1 h. The volatiles were evaporated under reduced pressure, and MeOH (6 mL) was added. The solution was cooled to 0 °C, and $NaBH_4$ (92 mg, 2.42 mmol) was added. The reaction mixture was allowed to warm to room temperature over 1 h. A saturated aqueous solution of $NaHCO_3$ (0.2 mL) was added, and the organic solvent was removed under reduced pressure. The residue was dissolved in EtOAc (6 mL), and the solution was dried ($MgSO_4$). The solvents were removed under reduced pressure, and the residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexane (2:1), to furnish 74 mg (87%, dr > 95:5) of **20** as a yellow solid: mp 162−163 °C (EtOAc/hexane); ^{1}H NMR (300 MHz) δ 7.76 (br s, 1 H), 7.48 (d, J = 7.2 Hz, 1 H), 7.28 (d, J = 7.2 Hz, 1 H), 7.16−7.06 (comp, 2 H), 5.69−5.62 (m, 1 H), 5.12−5.03 (comp, 2 H), 3.26 (dd, J = 2.1, 12.0 Hz, 1 H), 3.19−2.97 (m, 3 H), 2.74 (m, 1 H), 2.62 (dt, J = 4.2, 10.8 Hz, 1 H), 2.12−2.01 (comp, 2 H), 1.93 (m, 1 H), 1.70−1.51 (comp, 3 H), 1.11−1.01 (m, 1 H), 0.91 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz) δ 141.9, 136.0, 134.7, 127.4, 121.3, 119.4, 118.1, 115.0, 110.7, 108.2, 60.1, 59.5, 53.3, 46.6, 41.6, 36.7, 24.3, 21.7, 11.2; IR (CH_2Cl_2) 3189, 2943, 2804, 2750, 1450, 1321, 911, 739 cm^{-1}; MS (CI) m/z 281.2018 [$C_{19}H_{25}N_2$ (M + 1) requires m/z 281.2017].

Dihydrocorynantheol (21). 9-BBN (0.5 M solution in THF, 0.54 mL, 0.27 mmol) was added to a solution of **20** (30 mg, 0.11 mmol) in THF (3 mL), and the reaction mixture was stirred at room

temperature for 12 h. The mixture was then cooled to 0 °C, and a 3 M solution of aqueous NaOH (134 μL) and a 30% aqueous solution of H_2O_2 (134 μL) were added. Stirring was continued for 1 h, whereupon EtOAc (3 mL) and saturated aqueous $NaHCO_3$ (3 mL) were added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 4 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 21 mg (66%) of **21** as a pale yellow solid: mp 175−177 °C (lit.[19a] mp 178−180 °C). The ^{1}H and ^{13}C NMR spectra were consistent with those reported in the literature.[8,19c−f]

***trans*-2-{5-Ethyl-1-[2-(1*H*-indol-3-yl)ethyl]-2-oxopiperidin-4-yl}[1,3]dithiolane-2-carboxylic Acid Ethyl Ester (22).** A solution of *n*-BuLi in hexanes (1.95 M, 1.43 mL, 2.80 mmol) was added to a solution of *i*-Pr_2NH (0.47 mL, 3.35 mmol) in THF (10 mL) at −78 °C. The solution was warmed to 0 °C and then stirred for 30 min. The mixture was then cooled to −78 °C, and ethyl 1,3-dithiolane-2-carboxylate (0.40 mL, 2.80 mmol) was added. The solution was stirred for 1 h, and a solution of **4** (150 mg, 0.56 mmol) in THF (2 mL) was injected. The brown solution was allowed to warm to room temperature over 3 h and was stirred for an additional 17 h. EtOH (2 mL) was added, and stirring was continued for 1 h. Aqueous HCl (0.5 M, 5 mL) was added, and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexanes (1:1 → EtOAc), to give 177 mg (71%, dr > 95:5) of **22** as a yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39 (br s, 1 H), 7.63 (d, J = 7.5 Hz, 1 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.20−7.08 (m, 2 H), 7.04 (d, J = 2.1 Hz, 1 H), 4.20 (q, J = 8.5 Hz, 2 H), 3.85 (dt, J = 7.1, 7.1 Hz, 1 H), 3.78 (dt, J = 7.1, 7.1 Hz, 1 H), 3.39−3.18 (comp, 5 H), 3.05−2.99 (comp, 2 H), 2.93 (dd, J = 5.7, 13.2 Hz, 1 H), 2.77 (dd, J = 6, 15.4 Hz, 1 H), 2.71−2.64 (m, 1 H), 2.51 (dd, J = 8.7, 15.4 Hz, 1 H), 1.66−1.54 (m, 1 H), 1.49−1.36 (m, 1 H), 1.28 (t, J = 8.5 Hz, 3 H), 1.24−1.12 (m, 1 H), 0.76 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.0, 136.3, 127.4, 122.0, 121.9, 119.2, 118.6, 112.9, 111.2, 75.0, 62.4, 50.1, 48.1, 43.0, 40.1, 39.8, 39.3, 34.7, 25.7, 23.4, 13.9, 11.7; IR (neat) 2935, 2786, 1722, 1577, 1469, 1276, 1177, 996, 912, 747 cm^{-1}; MS (CI) *m*/*z* 447.1771 [$C_{23}H_{31}N_2O_3S_2$ (M + 1) requires *m*/*z* 447.1776].

2-(3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)[1,3]dithiolane-2-carboxylic Acid Ethyl Ester (23). Freshly distilled $POCl_3$ (56 μL, 0.60 mmol) was added to a solution of **22** (38 mg, 0.09 mmol) in toluene (2 mL), and the reaction mixture was heated to 70 °C for 2 h. The volatiles were evaporated over 1.5 h, whereupon MeOH (2 mL) was added, and the solution was cooled to 0 °C. $NaBH_4$ (26 mg, 0.68 mmol) was added, and the reaction mixture was stirred for 1.5 h at 0 °C and was then allowed to warm to room temperature over 30 min. Saturated aqueous $NaHCO_3$ (5 mL) and EtOAc (5 mL) were added, and the layers were separated. The aqueous phase was extracted with EtOAc (3 × 4 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc, to furnish 34 mg (92%, dr > 95:5) of **23** as a pale yellow oil: ^{1}H NMR (300 MHz, C_6D_6) δ 7.60−7.57 (m, 1 H), 7.25−7.21 (comp, 2 H), 7.05 (br s, 1 H), 7.00−6.97 (m, 1 H), 4.14−4.00 (comp, 2 H), 3.15 (d, J = 12.0 Hz, 1 H), 3.10−2.97 (comp, 3 H), 2.90−2.77 (comp, 3 H), 2.76−2.63 (comp, 2 H), 2.62−2.49 (comp, 2 H), 2.42 (dt, J = 4.2, 11.0 Hz, 1 H), 2.04−1.95 (comp, 2 H, C(20)H), 1.94−1.77 (comp, 2 H, C(14)H_a), 1.30−1.19 (m, 1 H), 1.02 (t, J = 6.9 Hz, 3 H), 0.86 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz, C_6D_6) δ 172.5, 136.7, 135.2, 128.3, 121.5, 119.7, 118.5, 111.3, 108.8, 75.9, 62.1, 60.1, 60.0, 52.8, 46.2, 44.0, 39.5, 39.4, 33.1, 23.7, 22.4, 13.8, 11.6; IR (neat) 3380, 2958, 2924, 2802, 2746, 1715, 1453, 1211, 1026, 741, 500 cm^{-1}; MS (CI) *m*/*z* 431.1832 [$C_{23}H_{31}N_2O_2S_2$ (M + 1) requires *m*/*z* 431.1827].

3-Ethyl-2-(carboethoxymethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (24). A slurry of Raney nickel in water (840 mg) was added to a solution of **23** (80 mg, 0.18 mmol) in EtOH (6 mL), and the reaction mixture was stirred at room temperature for 28 h. EtOAc (6 mL) was added, and the mixture was dried ($MgSO_4$). The solids were removed by filtration through a plug of Celite, and the filtrate was concentrated under reduced pressure to give 58 mg (95%) of **24** as a pale green foam. The analytical data (^{1}H and ^{13}C NMR spectra) were consistent with those reported.[30]

Spirooxindoles 26 and Epi-26. A solution of *t*-BuOCl in CCl_4 (0.5 M, 0.22 mL, 0.11 mmol) was added to a suspension of **24** (25 mg, 0.07 mmol) in CH_2Cl_2 (5 mL) at −20 °C. The reaction mixture was stirred for 0.5 h. After evaporation of the volatiles under reduced pressure, the remaining yellow oil was dissolved in MeOH (3 mL), and $NaOCH_3$ (80 mg) was added. The resultant solution was stirred for 6 h, whereupon saturated aqueous $NaHCO_3$ (2.5 mL) and brine (2.5 mL) were added. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic layers were dried ($MgSO_4$). The volatiles were evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 (6 mL). Water (1 mL) was added, the mixture was cooled to 0 °C, and CF_3SO_3H (62 μL, 0.70 mmol) was injected. The mixture was stirred for 1 h at 0 °C and for an additional 5 h at room temperature. Saturated aqueous $NaHCO_3$ was then added until the aqueous phase had a pH of 8. H_2O (1 mL) and CH_2Cl_2 (3 mL) were added, and the layers were separated. The aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. From the ^{1}H NMR of the crude product a dr = 60:40 (**26**/epi-**26**) was determined. The crude mixture was then separated by flash column chromatography on silica gel, eluting with EtOAc/hexane (1:1 → 100% EtOAc), to furnish 8 mg (33%) of epi-**26** (less polar) as a yellow oil and 10 mg (42%) of **26** (more polar) as a colorless solid: mp 172−174 °C (Et_2O/pentane) (lit.[27] mp 167−168 °C). Data for epi-**26**: ^{1}NMR (500 MHz, DMSO-d_6) δ 10.32 (s, 1 H), 7.21 (d, J = 7.4 Hz, 1 H), 7.14 (td, J = 7.6, 1.2 Hz, 1 H), 6.94 (td, J = 7.4, 0.8 Hz, 1 H), 6.80 (d, J = 7.6, Hz, 1 H), 3.46 (s, 3 H), 3.24−3.17 (comp, 2 H), 2.45 (dd, J = 15.5, 3.8 Hz, 1 H), 2.30 (app q, J = 8.7 Hz, 1 H) 2.22 (dd, J = 11.3, 2.3 Hz, 1 H), 2.16 (ddd, J = 12.8, 9.5, 2.4 Hz, 1 H), 1.90−1.79 (comp, 2 H), 1.69 (app t, J = 10.9 Hz, 1 H), 1.52−1.44 (m, 1 H), 1.42−1.34 (m, 1 H), 1.20−1.12 (m, 1 H), 1.08−0.98 (comp, 2 H), 0.82 (t, J = 7.4 Hz, 3 H), 0.60 (app q, J = 11.9, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.9, 172.6, 141.4, 133.5, 127.4, 124.3, 121.4, 109.1, 70.9, 56.9, 55.9, 53.2, 51.1, 40.5, 37.3, 36.6, 34.6, 31.5, 22.7, 10.7; IR (neat) 3208, 2932, 2804, 1726, 1708, 1619, 1470, 1342, 1223, 1167, 754 cm^{-1}; MS (CI) *m*/*z* 343.2032 [$C_{20}H_{26}N_2O_3$ (M + 1) requires *m*/*z* 343.2022], 197, 311, 343 (base). Data for **26**: ^{1}NMR (500 MHz, DMSO-d_6) δ 10.15 (s, 1 H, NH), 7.23 (d, J = 9.2 Hz, 1 H), 7.14 (t, J = 7.3, Hz, 1 H), 6.95 (t, J = 7.4, Hz, 1 H), 6.77 (d, J = 7.6, Hz, 1 H), 3.48 (s, 3 H), 3.16−3.12 (comp, 2 H), 2.51−2.47 (multiplicity obscured by DMSO peak, 1 H), 2.40−2.34 (m, 1 H) 2.18−2.10 (comp, 2 H), 2.00 (dd, J = 15.5, 8.6 Hz, 1 H), 1.85 (dd, J = 12.4, 7.4 Hz, 1 H), 1.64 (app t, J = 10.7 Hz, 1 H), 1.54−1.45 (m, 1 H), 1.36−1.08 (comp, 4 H), 1.04−0.96 (m, 1 H), 0.81 (t, J = 7.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 179.6, 172.7, 141.8, 133.8, 127.7, 123.1, 121.6, 108.8, 73.8, 56.4, 55.1, 54.0, 51.1, 37.4, 36.9, 34.3, 30.8, 22.8, 10.7; IR (neat) 3233, 2935, 2779, 1727, 1619, 1476, 1333, 1219, 1178, 758 cm^{-1}; MS (CI) *m*/*z* 343.2018 [$C_{20}H_{26}N_2O_3$ (M + 1) requires *m*/*z* 343.2022], 343 (base), 371.

1-(1-Allyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)propenone (33). Acryloyl chloride (485 mg, 435 μL, 5.36 mmol) was added to a mixture of 4,9-dihydro-3*H*-β-carboline (1.00 g, 5.88 mmol) and allyltributyltin (1.62 g, 1.51 mL, 4.88 mmol) in CH_2Cl_2 (60 mL) at 0 °C. The reaction mixture was stirred for 2 h at 0 °C and 12 h

at room temperature. The volatiles were evaporated under reduced pressure, and the residue was purified by flash column chromatography on silica gel, eluting with EtOAc/hexanes (1:2 → 2:3), to give 980 mg (75%) of **33** as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, rotamers) δ 8.86 (br s, 0.7 H), 8.72 (br s, 0.3 H), 7.52 (d, J = 5.7 Hz, 0.3 H), 7.48 (d, J = 5.7 Hz, 0.7 H), 7.50−7.32 (m, 1 H), 7.21−7.10 (comp, 2 H), 6.74 (dd, J = 7.8, 12.4 Hz, 0.7 H), 6.66 (dd, J = 7.5, 12.4 Hz, 0.3 H), 6.39 (dd, J = 1.2, 12.4 Hz, 0.7 H), 6.37 (d, J = 12.4 Hz, 0.3 H), 5.99−5.88 (comp, 2 H), 5.81 (dd, J = 1.2, 8.1 Hz, 0.7 H), 5.72 (d, J = 7.8 Hz, 0.3 H), 5.25−5.01 (comp, 2 H), 4.21 (d, J = 10.2 Hz, 0.7 H), 3.60−3.51 (m, 0.7 H), 3.12 (dt, J = 3.6, 9.2 Hz, 0.3 H), 2.93−2.62 (comp, 4.3 H); ^{13}C NMR (75 MHz, $CDCl_3$, rotamers) δ 135.9, 134.0, 133.5, 133.2, 128.0, 127.9, 127.8, 126.2, 121.8, 121.5, 119.3, 119.1, 118.2, 118.0, 117.7, 111.1, 111.0, 109.2, 107.3; IR (neat) 3268, 3060, 2916, 1640, 1602, 1446, 1221, 974, 910, 741 cm^{-1}; MS (CI) m/z 267.1506 [$C_{17}H_{19}N_2O$ (M + 1) requires m/z 267.1497].

6,7,12,12b-Tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (34). $[(C_6H_{11})_3P]_2Cl_2RuC_2HPh$ (462 mg, 0.561 mmol, 4 mol %) was added to a solution of **33** (3.73 g, 14.0 mmol) in CH_2Cl_2 (610 mL) at room temperature. The reaction mixture was stirred for 15 h, whereupon dimethyl sulfoxide (2.00 mL, 2.20 g, 28.1 mmol) was added, and the reaction was stirred at room temperature overnight. The solvent was removed under reduced pressure, EtOAc (10 mL) was added, and the mixture was cooled to 4 °C overnight. The crude solid was triturated with EtOAc and recrystallized from CH_2Cl_2/$CHCl_3$, and the mother liquors were purified by flash column chromatography on silica gel, eluting with EtOAc, to afford a total of 2.91 g (87%) of **34** as a pale gray solid: mp 228−229 °C (CH_2Cl_2) (lit.[36] mp 229−231 °C). The ^{1}H and ^{13}C NMR spectra are consistent with those previously reported for **34**.[36]

Reaction of the Sodium Enolate of Dimethyl Malonate with 34. 2-(4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)malonic Acid Dimethyl Ester. Dimethyl malonate (0.29 mL, 2.51 mmol) was added to a suspension of NaH (60% suspension in mineral oil, 30 mg, 1.25 mmol) in THF (15 mL) and the resulting mixture stirred for 5 min. Solid **34** (60 mg, 0.25 mmol) was added, and the solution was heated under reflux for 48 h. The reaction mixture was cooled to room temperature, and a saturated aqueous solution of $NaHCO_3$ (0.3 mL) and EtOAc (10 mL) was added. Stirring was continued for 15 min, the mixture was dried ($MgSO_4$), and the volatiles were removed under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 68 mg (74%, dr = 60:40) of the title compound as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diastereomers) δ 8.72 (br s, 0.6 H), 8.64 (br s, 0.4 H), 7.48 (d, J = 7.5 Hz, 0.6 H), 7.46 (d, J = 7.5 Hz, 0.4 H), 7.36 (d, J = 7.5 Hz, 0.4 H), 7.29 (d, J = 7.8 Hz, 0.6 H), 7.19−7.06 (comp, 2 H), 5.18−5.10 (m, 0.6 H), 5.04−4.99 (m, 0.4 H), 4.97−4.90 (m, 0.4 H), 4.81 (dd, J = 3.3, 10.8 Hz, 0.6 H), 3.77 (s, 1.2 H), 3.74 (s, 1.8 H), 3.73 (s, 1.8 H), 3.70 (s, 1.2 H), 3.40 (d, J = 8.7 Hz, 0.4 H), 3.32 (d, J = 7.8 Hz, 0.6 H), 3.02−2.94 (m, 0.6 H), 2.92−2.60 (comp, 4.4 H), 2.58−2.10 (comp, 2.4 H), 1.56 (q, J = 11.4 Hz, 0.6 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 168.3, 168.2, 168.1, 168.0, 167.6, 136.3, 136.2, 132.9, 132.6, 127.2, 126.5, 122.0, 119.7, 119.6, 118.3, 118.1, 111.2, 110.9, 110.3, 109.0, 60.4, 55.5, 54.3, 53.6, 52.9, 52.7, 52.6, 42.0, 39.9, 36.5, 36.1, 32.8, 31.2, 29.9, 29.8, 21.0, 20.9, 20.8, 14.1; IR (neat) 3256, 2954, 1731, 1621, 1435, 1305, 1234, 1157, 1020, 910, 735 cm^{-1}; MS (CI) m/z 371.1600 [$C_{20}H_{23}N_2O_5$ (M + 1) requires m/z 371.1607].

2-(4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)[1,3]dithiolane-2-carboxylic Acid Ethyl Ester (36). A solution of *n*-BuLi (0.28 mL, 0.67 mmol) in hexanes (2.44 M) was added to a solution of *i*-Pr_2NH (81 mg, 112 μL, 0.80 mmol) in degassed THF (16 mL) at −78 °C. After the resulting mixture was stirred at −78 °C for 15 min, the flask was transferred to an ice/water bath, and stirring was continued for 15 min. The mixture was then recooled to −78 °C. Neat ethyl 1,3-dithiolane-2-carboxylate (120 mg, 96 μL, 0.67 mmol) was added, and the resulting solution was stirred at −78 °C for 30 min. A solution of **34** (80 mg, 0.34 mmol) in degassed THF (16 mL) at −78 °C was added via cannula. The dry ice/acetone bath was removed, and the reaction was stirred for 2 h at room temperature, whereupon NH_4Cl (2.0 mL) was added, and 50% of the volatiles were removed under reduced pressure. The mixture was poured into a separatory funnel containing 0.5 M HCl (20 mL) and extracted with EtOAc (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The crude mixtures of diastereomers (dr = 91:9) were separated by flash column chromatography, eluting with hexanes/EtOAc (1:3 → 100% EtOAc), to afford 84 mg (60%) of the major diasteromer **36** as a pale yellow solid: mp 200−201 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 1 H), 7.20 (t, J = 7.6 Hz, 1 H), 7.13 (t, J = 7.6 Hz, 1 H), 5.03−4.94 (comp, 2 H), 4.32−4.20 (comp, 2 H), 3.49−3.28 (comp, 4 H), 3.12−2.98 (comp, 2 H), 2.79−2.69 (comp, 2 H), 2.68−2.50 (comp, 3 H), 2.18−2.03 (m, 1 H), 1.29 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.8, 169.3, 136.0, 133.0, 127.4, 122.1, 119.8, 118.1, 111.2, 110.9, 72.9, 62.7, 53.8, 42.6, 40.8, 40.2, 36.6, 35.9, 30.3, 20.9, 14.1; IR (CH_2Cl_2) 3265, 2928, 1714, 1621, 1469, 1445, 1303, 1266, 1212, 1022, 908, 732 cm^{-1}; MS (CI) m/z 417.1304 [$C_{21}H_{25}N_2O_3S_2$ (M + 1) requires m/z 417.1307].

2-Vinyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (38). Freshly prepared vinylmagnesium bromide (0.84 mmol) in THF (0.84 mL) was added to a suspension of CuBr·DMS (1.7 mg, 8 μmol) in THF (3 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 3 min and then recooled to −78 °C. Freshly distilled TMSCl (21 μL, 0.17 mmol) and a solution of **34** (20 mg, 0.08 mmol) in THF (2 mL) were added. The suspension was warmed to room temperature over 2 h, whereupon a mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 2 mL) was added, and stirring was continued for 30 min. A 1 M solution of TBAF in THF (0.2 mL, 0.20 mmol) was added, and the mixture was stirred for 15 min, the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 18 mg (80%, dr = 60:40) of **38** as a mixture of nonseparable diastereomers: yellow solid; mp 258−262 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diastereomers) δ 8.00 (br s, 1 H), 7.51−7.48 (m, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.19 (t, J = 7.2 Hz, 1 H), 7.12 (t, J = 8.0 Hz, 1 H), 5.92 (ddd, J = 6.0, 10.4, 17.2 Hz, 0.4 H), 5.79 (ddd, J = 6.4, 10.4, 16.8 Hz, 0.6 H), 5.22−5.05 (comp, 3 H), 4.88−4.80 (m, 1 H), 2.99−2.62 (comp, 3 H), 2.57−2.48 (comp, 2 H), 2.32−2.10 (comp, 2 H), 1.68−1.59 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of diastereomers) δ 168.4, 168.1, 139.8, 138.7, 136.1, 133.0, 132.8, 128.5, 126.6, 122.1, 119.8, 118.3, 118.2, 115.6, 114.6, 110.8, 110.2, 109.7, 109.5, 53.8, 56.7, 40.9, 39.9, 38.0, 36.7, 35.2, 35.1, 33.1, 21.1; IR (CH_2Cl_2) 3249, 2919, 2848, 1614, 1445, 1303, 1233, 911, 736 cm^{-1}; MS (CI) m/z 267.1506 [$C_{17}H_{19}N_2O$ (M + 1) requires m/z 267.1497].

2-Ethyl-2,3,6,7,12,12b-hexahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (39). EtMgCl (0.84 mmol) in THF (0.42 mL) was added to a suspension of CuBr·DMS (1.7 mg, 8 μmol) in THF (3 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 3 min and then recooled to −78 °C. Freshly distilled TMSCl (21 μL, 0.17 mmol) and a solution of **34** (20 mg, 0.08 mmol) in THF (2 mL) were added. The suspension was warmed to room temperature over 2 h. A mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 2 mL) was added, and stirring was continued for 30 min. A 1 M solution of TBAF in THF (0.2 mL, 0.20 mmol) was added, and the mixture was stirred for 15 min, the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 22 mg (98%, dr > 95:5) of **39** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (br s,

1 H), 7.49 (d, J = 7.2 Hz, 1 H), 7.34 (d, J = 7.5 Hz, 1 H), 7.12 (t, J = 7.5 Hz, 1 H), 5.13−5.08 (m, 1 H), 4.91 (t, J = 6.4 Hz, 1 H), 3.00−2.86 (comp, 2 H), 2.73 (d, J = 11.6 Hz, 1 H), 2.55 (dd, J = 5.2, 17.2 Hz, 1 H), 2.26 (dd, J = 7.2, 17.2 Hz, 1 H), 2.19−2.10 (comp, 2 H), 1.84−1.76 (m, 1 H), 1.52−1.40 (comp, 2 H), 0.98 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 135.9, 133.3, 126.9, 121.9, 119.6, 118.1, 110.9, 109.9, 52.2, 41.4, 38.2, 32.4, 31.4, 26.9, 21.1, 11.6; IR (neat) 3256, 2959, 2922, 1614, 1449, 1302, 1266, 908, 734 cm^{-1}; MS (CI) m/z 269.1657 [$C_{17}H_{21}N_2O$ (M + 1) requires m/z 269.1654].

2-[1-(Trimethylsilyl)vinyl]-2,3,6,7,12,12b-hexahydro-1*H*-indolo-[2,3-*a*]quinolizin-4-one (40). Freshly prepared [1-(trimethylsilyl)-vinyl]magnesium bromide (0.84 mmol) in THF (0.84 mL) was added to a suspension of CuBr·DMS (1.7 mg, 8 μmol) in THF (3 mL) at −78 °C. The reaction mixture was warmed to 0 °C for 3 min and then recooled to −78 °C. Freshly distilled TMSCl (21 μL, 0.17 mmol) and a solution of **34** (20 mg, 0.08 mmol) in THF (2 mL) were added. The suspension was warmed to room temperature over 2 h. A mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 2 mL) was added, and stirring was continued for 30 min. A 1 M solution of TBAF in THF (0.2 mL, 0.20 mmol) was added, and the mixture was stirred for 15 min, the layers were separated, and the aqueous phase was extracted with EtOAc (2 × 3 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with EtOAc, to give 24 mg (84%, dr > 95:5) of **40** as a white solid: mp 213−215 °C ($CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (br s, 1 H), 7.51 (d, J = 7.6 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.19 (t, J = 7.2 Hz, 1 H), 7.13 (t, J = 7.2 Hz, 1 H), 5.66 (s, 1 H), 5.48 (d, J = 1.6 Hz), 5.26−5.14 (m, 1 H), 4.83 (dd, J = 4.4, 11.6 Hz, 1 H), 2.94−2.73 (comp, 4 H), 2.72−2.65 (m, 1 H), 2.53−2.43 (m, 1 H), 2.88 (dd, J = 12.4, 17.2 Hz, 1 H), 1.77 (q, J = 12.4 Hz, 1 H), 0.17 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 153.7, 136.1, 132.9, 126.6, 124.0, 122.0, 119.6, 118.3, 110.9, 109.2, 68.6, 54.3, 40.0, 39.7, 35.9, 35.4, 21.2; IR (CH_2Cl_2) 3259, 2954, 1614, 1445, 1305, 1249, 837, 737 cm^{-1}; MS (CI) m/z 339.1893 [$C_{20}H_{27}N_2OSi$ (M + 1) requires m/z 339.1893].

2-[2-(Trimethylsilyl)vinyl]-2,3,6,7,12,12b-hexahydro-1*H*-indolo-[2,3-*a*]quinolizin-4-one (41). A solution of *t*-BuLi (0.80 mmol) in hexanes (0.5 mL) was added to a solution of (*E*)-2-(trimethylsilyl)-vinyl bromide (62 μL, 0.40 mmol) in Et_2O (0.8 mL) at −78 °C. The reaction mixture was warmed to −20 °C for 0.5 h, recooled to −78 °C, and then added to a suspension of CuI (38 mg, 0.20 mmol) in Et_2O (0.8 mL) at −78 °C. The reaction mixture was warmed to −20 °C for 0.5 h and recooled to −78 °C, and TMSCl (22 μL, 0.20 mmol) was added. The mixture was stirred for 1 h and then added to a solution of **34** (10 mg, 0.04 mmol) in Et_2O (3 mL). Then the mixture was allowed to warm to room temperature over 3 h, and stirring was continued for an additional 17 h. A mixture of saturated aqueous NH_4Cl/NH_4OH (9:1, 0.5 mL) and a 1 M solution of TBAF in THF (0.4 mL, 0.4 mmol) were added, and the mixture was stirred for 15 min. The layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 1 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel, eluting with EtOAc/hexanes (1:1), to give 12 mg (84%, dr > 95:5) of **41** as a colorless oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (br s, 1 H), 7.49 (d, J = 8.0 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.18 (t, J = 8.0 Hz, 1 H), 7.12 (t, J = 8.0 Hz, 1 H), 6.08 (dd, J = 5.0, 18.5 Hz, 1 H), 5.78 (dd, J = 1.5, 18.5 Hz, 1 H), 5.14−5.10 (m, 1 H), 4.82−4.78 (m, 1 H), 2.96−2.81 (comp, 2 H), 2.76−2.67 (comp, 2 H), 2.60−2.50 (comp, 2 H), 2.31−2.25 (m, 1 H), 2.11 (ddd, J = 3.5, 8.5, 12.5 Hz, 1 H) 0.07 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 146.2, 136.1, 133.1, 131.3, 127.1, 122.2, 119.9, 118.4, 110.9, 110.4, 51.6, 40.8, 36.5, 34.9, 32.9, 21.0, 1.9; IR (CH_2Cl_2) 3260, 2950, 1620, 1451, 1304, 1247, 878, 838, 739 cm^{-1}; MS (CI) m/z 339.1888 [$C_{20}H_{27}N_2OSi$ (M + 1) requires m/z 339.1892].

1-Allyl-2,3,4,9-tetrahydro-1*H*-β-carboline. BF_3·OEt_2 (1.08 mL, 8.56 mmol) was added to a solution of 4,9-dihydro-3*H*-β-carboline **32** in THF (44 mL) cooled to −30 °C. The solution was stirred for 10 min, whereupon a 1.0 M solution of allylmagnesium bromide in ether (1.0 M, 25.6 mL, 25.6 mmol) was added via addition funnel over 45 min. After the addition was complete, the stirring was continued at −30 °C for 2 h, whereupon saturated aqueous $NaHCO_3$ (10 mL) was added. The resulting slurry was poured into a separatory funnel containing saturated aqueaous $NaHCO_3$ (50 mL) and water (50 mL), and the mixture was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with Et_3N/MeOH/CH_2Cl_2 (1:3:97), to give 1.52 g (81%) of the title compound as a yellow solid. The ^{1}H NMR spectrum was identical to that previously reported in the literature.[43]

1-(1-Allyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-2-ethylpropenone. A solution of 1-allyl-2,3,4,9-tetrahydro-1*H*-β-carboline (100 mg, 0.42 mmol), 2-ethylacrylic acid (57 mg, 0.57 mmol), Et_3N (0.12 mL, 0.83 mmol), HOBT (113 mg, 0.83 mmol), and EDCI·HCl (88 mg, 0.46 mmol) in CH_2Cl_2 (4.2 mL) was stirred for 16 h at room temperature. The reaction was poured into EtOAc (20 mL), and the organic mixture was washed with 0.5 M aqueous HCl (2 × 10 mL), saturated aqueous $NaHCO_3$ (2 × 10 mL), and brine (10 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (1:3), to afford 105 mg (85%) of the title compound as a white solid: mp 113−115 °C; ^{1}H NMR (500 MHz) δ 8.33 (s, 1H), 7.45 (d, J = 7.8 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.18−7.12 (m, 1 H), 7.11−7.08 (m, 1 H), 6.01−5.91 (m, 1 H), 5.79 (t, J = 6.6 Hz, 1 H), 5.19 (s, 1 H), 5.14−5.10 (comp, 2 H), 5.07 (s, 1 H), 4.25−4.18 (m, 1 H), 3.51−3.41 (m, 1 H), 2.81−2.74 (comp, 2 H), 2.39 (q, J = 7.3 Hz, 2 H), 1.11 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (125 MHz) δ 171.8, 146.8, 136.1, 134.4, 133.6, 126.5, 121.9, 119.5, 118.4, 118.0, 112.6, 111.1, 107.7, 48.35, 41.86, 39.1, 27.3, 22.3, 11.7; IR (neat) 3258, 2962, 2906, 1601, 1470, 1442, 1300, 1180, 913, 741 cm^{-1}; MS (CI) m/z 295.1807 [$C_{19}H_{22}N_2O$ (M + 1) requires m/z 295.1810], 253, 295 (base), 323, 335, 377.

3-Ethyl-6,7,12,12b-tetrahydro-1*H*-indolo[2,3-*a*]quinolizin-4-one (42). A solution of 1-(1-allyl-1,3,4,9-tetrahydro-β-carbolin-2-yl)-2-ethylpropenone (21 mg, 0.07 mmol) and Grubbs' second-generation catalyst (9.1 mg, 0.01 mmol) in degassed CH_2Cl_2 (3.55 mL) was stirred at 45 °C under argon for 16 h. The mixture was cooled to room temperature, DMSO (40 μL, 0.564 mmol) was added, and the mixture was stirred for 16 h. The reaction was concentrated under reduced pressure, and the residue was purified by flash column chromatography, eluting with MeOH/CH_2Cl_2 (0.5:99.5), to give 16 mg (87%) of **42** as a clear colorless glass. The ^{1}H NMR spectrum was identical to that previously reported in the literature.[39]

4-Oxo-1,6,7,12b-tetrahydro-4*H*-indolo[2,3-*a*]quinolizine-12-carboxylic Acid *tert*-Butyl Ester (35). A solution of **34** (1.10 g, 4.62 mmol), Boc_2O (4.97 g, 23.1 mmol), and (dimethylamino)-pyridine (DMAP) (113 mg, 0.92 mmol) in THF (100 mL) was stirred at room temperature for 4 h, whereupon the reaction was concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (1:1 → 1:2) to give 1.54 g (99%) of **35** as a white solid: mp 181−183 °C; ^{1}NMR (500 MHz) δ 8.06 (d, J = 8.2 Hz, 1 H), 7.47−7.45 (m, 1 H), 7.32−7.28 (m, 1 H), 7.27−7.24 (m, 1 H), 6.67 (ddd, J = 9.6, 6.5, 2.1 Hz, 1 H), 6.07 (dd, J = 9.6, 2.9 Hz, 1 H) 5.26−5.21 (m, 1 H), 5.00 (ddd, J = 12.7, 4.6, 1.6 Hz, 1 H), 3.01 (ddd, J = 17.1, 6.5, 3.6 Hz, 1 H), 2.87−2.79 (comp, 3 H), 2.15 (dddd, J = 17.1, 13.1, 2.9, 2.1, Hz, 1 H), 1.67 (s, 9 H); ^{13}C NMR (125 MHz) δ 164.8, 150.0, 139.1, 136.6, 134.1, 128.5, 125.4, 124.7, 123.1,

(43) Nakamura, M.; Hirai, A,; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489.

118.4, 118.0, 115.8, 84.5, 53.3, 37.6, 31.6, 28.2, 21.5; IR ($CDCl_3$) 2982, 2919, 1727, 1659, 1607, 1423, 1366, 1308, 1146, 1052, 817, 718 cm^{-1}; MS (CI) *m*/*z* 339.1721 [$C_{20}H_{23}N_2O_3$ (M + 1) requires *m*/*z* 339.1709], 283, 311, 339 (base), 367, 422.

4-Oxo-1,6,7,12b-tetrahydro-4*H*-indolo[2,3-*a*]quinolizine-12-carboxylic Acid *tert*-Butyl Ester (35). To a degassed solution of $[(C_6H_{11})_3P]_2Cl_2C_2HPh$ (18 mg, 0.02 mmol, 4 mol %) in CH_2Cl_2 (25 mL) was added a solution of **35** (149 mg, 0.56 mmol) in degassed CH_2Cl_2 (7 mL) via cannula. The reaction mixture was stirred at room temperature for 24 h, whereupon Boc_2O (603 mg, 2.80 mmol) and DMAP (14 mg, 0.11 mmol) were added. The reaction mixture was stirred for 1.5 h, whereupon ethanol (0.2 mL) and activated carbon (180 mg) were added. After being stirred for 20 h, the reaction was filtered through a plug of Celite, and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (1:1 → 1:2) to give 175 mg (93%) of **35** as a white solid. The ^{1}H NMR spectrum was identical to that previously reported (vide supra).

(3*R,15*R**)-2-(4-Oxo-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl)[1,3]dithiolane-2-carboxylic Acid Ethyl Ester (37).** A solution of *n*-BuLi (0.28 mL, 0.67 mmol) in hexanes (2.40 M) was added to a solution of *i*-Pr_2NH (75 mg, 98 μL, 0.74 mmol) in THF (16 mL) at −78 °C. After the resulting mixture was stirred at −78 °C for 15 min, the flask was transferred to an ice/water bath, and stirring was continued for 15 min. The mixture was then recooled to −78 °C. Neat ethyl 1,3-dithiolane-2-carboxylate (180 mg, 0.14 mL, 1.01 mmol) was added, and the resulting solution was stirred at −78 °C for 30 min. A solution of **35** (114 mg, 0.34 mmol) in THF (16 mL) at −78 °C was added via a cannula. The dry ice/acetone bath was removed, and the reaction was stirred for 3 h at room temperature, whereupon NH_4Cl (1.0 mL) was added, and 50% of the volatiles were removed under reduced pressure. The mixture was poured into a separatory funnel containing 0.5 M HCl (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (1:2 → 1:3), to give 123 mg (71%, dr > 95:5) of **37** as a white solid: mp 150−151 °C; ^{1}NMR (500 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1 H), 7.42−7.40 (m, 1 H), 7.30−7.27 (m, 1 H), 7.24−7.21 (m, 1 H), 5.16−5.08 (comp, 2 H), 4.23 (app dq, J = 7.2, 1.1 Hz, 2 H), 3.38−3.31 (comp, 2 H), 3.30−3.23 (comp, 2 H), 2.97 (tdd, J = 11.9, 5.51, 2.6 Hz, 1 H), 2.87−2.81 (comp, 3 H), 2.81−2.65 (comp, 2 H), 2.50 (dd, J = 17.5, 11.6 Hz, 1 H), 1.68 (s, 9 H), 1.44−1.37 (m, 1 H), 1.31 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (125 MHz) δ 171.2, 168.7, 150.2, 136.8, 134.7, 128.6, 124.7, 123.0, 118.6, 118.3, 115.5, 84.5, 74.2, 62.5, 54.4, 40.2, 40.0, 39.0, 38.3, 35.8, 33.7, 28.1, 21.6, 13.9; IR (neat) 2974, 2923, 1727, 1640, 1457, 1431, 1411, 1365, 1314, 1222, 1141, 1023, 906, 728 cm^{-1}; MS (CI) *m*/*z* 516.1747 [$C_{26}H_{32}N_2O_5S_2$ (M^+) requires *m*/*z* 516.1753], 237, 289, 339, 362, 391, 517 (base).

(3*R,15*S**)-2-[2-(Ethoxycarbonyl)[1,3]dithiolan-2-yl]-4-oxo-1,3,4,6,7,12b-hexahydro-2*H*-indolo[2,3-*a*]quinolizine-12-carboxylic Acid *tert*-Butyl Ester (43).** A solution of **36** (550 mg, 1.32 mmol), Boc_2O (1.14 g, 5.28 mmol), and DMAP (16 mg, 0.13 mmol) in CH_2Cl_2 (40 mL) was stirred at room temperature for 4 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by flash column chromatography, eluting with hexanes/EtOAc (1:2), to give **43** (578 mg, 85%) as a white solid: mp 115−118 °C; ^{1}NMR (500 MHz) δ 7.99 (d, J = 8.1 Hz, 1 H), 7.42 (d, J = 8.1 Hz, 1 H), 7.28 (m, 1 H), 7.23 (m, 1 H), 5.30−5.26 (m, 1 H), 4.96−4.94 (m, 1H) 4.23−4.10 (m, 1 H), 3.41−3.25 (comp, 4 H), 2.88 (app td, J = 11.8, 3.6 Hz, 1 H), 2.84−2.79 (m, 1 H), 2.79−2.73 (m, 1 H), 2.71−2.65 (comp, 2 H), 2.42 (dd, J = 14.7, 11.6 Hz, 1 H), 2.99 (ddd, J = 14.1, 8.8, 6.0 Hz, 1 H), 2.21−2.15 (m, 1 H), 1.66 (s, 9 H), 1.17 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (125 MHz) δ 171.2, 171.1, 150.1, 136.7, 134.9, 128.7, 124.6, 123.0, 118.9, 118.3, 115.4, 84.4, 74.6, 62.5, 53.5, 40.5, 40.2, 39.9, 37.1, 35.8, 33.3, 28.2, 21.3, 13.9; IR (neat) 2980, 2924, 1723, 1649, 1453, 1413, 1311, 1214, 1141, 754 cm^{-1}; MS (CI) *m*/*z* 517.1830 [$C_{26}H_{32}N_2O_{5S2}$ (M + 1) requires *m*/*z* 517.1831], 417, 461, 517 (base).

(3*R,15*R**,24*S**)-2-[2-(Ethoxycarbonyl)[1,3]dithiolan-2-yl)-3-ethyl-4-oxo-1,3,4,6,7,12b-hexahydro-2*H*-indolo[2,3-*a*]quinolizine-12-carboxylic Acid *tert*-Butyl Ester (44).** A solution of sodium hexamethyldisilazide in THF (0.39 mL, 2.0 M, 0.774 mmol) was added dropwise over 12 min to a solution of **43** (200 mg, 0.387 mmol) in degassed THF (2.5 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h, whereupon it was cooled −100 °C. 1,3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidone (DMPU) (74 mg, 70 μL, 0.58 mmol) was added followed by ethyl triflate (276 mg, 0.20 mL, 1.55 mmol). The mixture was stirred at −100 °C for 2.5 h, whereupon benzylamine (249 mg, 0.25 mL, 2.32 mmol) and ethanol (0.2 mL) were added. The flask was transferred to a −78 °C bath, and stirring was continued for 45 min. A saturated aqueous solution of NH_4Cl (2 mL) was added, and the cold bath was removed. After the reaction was allowed to warm to room temperature, the mixture was poured into a separatory funnel containing 0.5 M HCl (10 mL) and EtOAc (10 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with pentane/acetone (2:1) to give 39 mg (20%) of recovered **43** and 142 mg (67%, dr > 95:5) of **44** as a colorless foam that could be recrystallized from CH_2Cl_2/heptane: mp 151−153 °C; ^{1}NMR (500 MHz) δ 7.91−7.87 (m, 1 H), 7.43−7.40 (m, 1 H), 7.27−7.20 (comp, 2 H), 5.41−5.35 (m, 1 H), 5.18−5.12 (m, 1H), 4.32 (q, J = 7.2 Hz, 2 H), 3.50−3.44 (comp, 2 H), 3.34−3.25 (comp, 3 H), 2.86−2.65 (comp, 6 H), 1.97−1.88 (m, 1 H), 1.76 (ddd, J = 14.3, 11.8, 4.8 Hz, 1 H), 1.67 (s, 9 H), 1.60−1.50 (m, 1H), 1.34 (t, J = 7.2 Hz, 3 H), 1.00 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 172.7, 171.3, 150.3, 136.5, 135.9, 128.9, 124.4, 122.9, 118.5, 118.3, 115.5, 84.2, 74.1, 62.2, 53.0, 44.6, 41.7, 39.5, 39.2, 38.7, 28.5, 28.2, 27.2, 22.0, 13.9, 12.1; IR (neat) 2975, 2923, 1723, 1635, 1453, 1417, 1370, 1303, 1219, 1136, 1022, 731 cm^{-1}; MS (CI) *m*/*z* 545.2143 [$C_{28}H_{37}N_2O_5S_2$ (M + 1) requires *m*/*z* 545.2144], 233, 339, 445, 545 (base).

(3*R,15*S**,22*S**)-2-[(Ethoxycarbonyl)methyl]-3-ethyl-4-oxo-1,3,4,6,7,12b-hexahydro-2*H*-indolo[2,3-*a*]quinolizine-12-carboxylic Acid *tert*-Butyl Ester (45).** A slurry of Raney nickel in water (2.9 g) was added to a solution of **44** (312 mg, 0.57 mmol) in EtOH (20 mL), and the reaction was stirred at room temperature for 4 h. EtOAc (20 mL) was added, and the mixture was dried (Na_2SO_4) and filtered through Celite. The solids were washed with EtOAc (20 mL), and the filtrate was concentrated under reduced pressure. Purification of the residue by flash column chromatography, eluting with hexane/EtOAc (1:1), gave 242 mg (93%) of **45** as a clear colorless oil: ^{1}NMR (125 MHz) δ 7.94−7.90 (m, 1 H), 7.44−7.39 (m, 1 H), 7.30−7.20 (comp, 2 H), 5.21−5.18 (m, 1 H), 5.06−5.03 (m, 1 H), 4.15 (q, J = 7.0 Hz, 2 H), 2.83−2.76 (m, 1 H), 2.72−2.67 (comp, 2 H), 2.61 (dd, J = 15.9, 7.4 Hz, 1 H), 2.52 (dd, J = 15.9, 7.4 Hz, 1 H), 2.48−2.37 (comp, 3 H), 2.21−2.15 (m, 1 H), 1.87−1.79 (m, 1 H), 1.75−1.64 (comp, 10 H), 1.56−1.52 (m, 1 H), 1.27 (t, J = 7.0 Hz, 3 H), 0.98 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (500 MHz) δ 172.2, 172.0, 150.3, 136.5, 135.7, 128.8, 124.4, 122.9, 118.4, 118.3, 115.5, 84.3, 60.5, 51.8, 47.6, 39.2, 38,1, 30.5, 29.7, 28.2, 25.5, 21.7, 14.2, 12.1; IR (neat) 2970, 2927, 1728, 1656, 1640, 1455, 1414, 1368, 1311, 1249, 1219, 1158, 1136, 1116, 745 cm^{-1}; MS (CI) *m*/*z* 455.2559 [$C_{26}H_{35}N_2O_5$ (M + 1) requires *m*/*z* 455.2546], 355, 399, 455 (base).

(3*R,15*S**,20*R**)-3-Ethyl-4-oxo-1,2,3,4,6,7,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl]acetic Acid Methyl Ester (46).** A solution of 4.4 M NaOMe (1.20 mL, 5.28 mmol), which was freshly prepared by the addition of sodium (404 mg, 17.6 mmol) to degassed methanol (4 mL), was added to a solution of **45** (240 mg, 0.53 mmol) in degassed THF (5 mL) at 0 °C. The ice bath was removed, and the reaction was stirred at room temperature for 1 h, whereupon the reaction was cooled to 0 °C, and a saturated

aqueous solution of NH_4Cl (3 mL) and water (15 mL) were added. The mixture was poured into a separatory funnel containing EtOAc (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure. The residue was recrystallized from CH_2Cl_2/ether, and the mother liquor was purified by flash chromatography, eluting with hexane/EtOAc (1:1), to afford a total of 155 mg (86%) of **46** as a white solid: mp 186−189 °C dec; ^{1}NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.48 (d, J = 7.6 Hz, 1 H), 7.33 (d, J = 8.0 Hz, 1 H), 7.19−7.15 (m, 1 H), 7.12−7.09 (m, 1 H), 5.14−5.08 (m, 1 H), 4.83 (dd, J = 9.4, 5.2 Hz, 1 H), 3.72 (s, 3 H), 2.89−2.81 (comp, 2 H), 2.77−2.70 (m, 1 H), 2.55−2.38 (comp, 3 H), 2.25−2.19 (comp, 2 H), 2.17−2.11 (m, 1 H), 1.82−1.74 (m, 1 H), 1.64−1.55 (m, 1 H), 0.92 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 172.5, 171.0, 136.2, 133.1, 127.0, 122.2, 119.9, 118.3, 111.0, 110.0, 51.8, 50.7, 48.2, 40.7, 37.3, 29.4, 28.6, 24.9, 21.1, 11.8; IR (neat) 3255, 2962, 2930, 1733, 1612, 1466, 1434, 1351, 1304, 1262, 1236, 1199, 1168, 739 cm^{-1}; 340.1777 [$C_{20}H_{24}N_2O_3$ S_2 (M^+) requires m/z 340.1787], 241, 273, 305, 341 (base), 369.

(3*R,15*S**,20*S**)-3-Ethyl-1,2,3,4,6,7,12b-octahydroindolo[2,3-*a*]quinolizin-2-yl]acetic Acid Methyl Ester (47).** A slurry of **46** (72 mg, 0.21 mmol), trimethyloxonium tetrafluoroborate (83 mg, 0.56 mmol), and 2,6-di-*tert*-butylpyridine (118 mg, 0.14 mL, 0.619 mmol) in CH_2Cl_2 (7 mL) was stirred at room temperature for 21 h, during which time a homogeneous yellow solution was produced. The reaction mixture was cooled to 0 °C, and anhydrous MeOH (2.5 mL) was added. After 15 min, $NaBH_4$ (83 mg, 2.18 mmol) was added, and the reaction mixture was stirred for an additional 20 min. Saturated $NaHCO_3$ (5 mL) and CH_2Cl_2 (10 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 8 mL). The combined organic fractions were dried (Na_2SO_4), and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography, eluting with 2.5−10% MeOH in CH_2Cl_2, to afford 56 mg (81%) of **47** as a foam: ^{1}NMR (500 MHz, $CDCl_3$) δ 8.00 (br s, 1H), 7.50 (d, J = 7.4 Hz, 1 H), 7.40−7.38 (m, 1 H), 7.18 (app td, J = 7.4, 1.2 Hz, 1 H), 7.12 (app td, J = 7.4, 1.2 Hz, 1 H), 4.13 (br s, 1 H), 3.75 (s, 3 H), 3.23 (dd, J = 11.9, 5.2 Hz, 1 H), 3.10 (dd, J = 11.9, 4.4 Hz, 1 H), 3.08−2.99 (m, 1 H), 2.76 (dd, J = 11.4, 3.4 Hz, 1 H), 2.69−2.64 (m, 1 H), 2.63 (dd, J = 16.3, 4.4 Hz, 1 H), 2.56 (dd, J = 11.4, 8.0 Hz, 1 H), 2.31−2.24 (comp, 2 H), 1.82−1.74 (comp, 2 H), 1.58−1.49 (m, 1 H), 1.46−1.38 (m, 1 H), 1.27−1.19 (m, 1 H), 0.87 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (125 MHz) δ 173.7, 136.0, 133.2, 127.6, 121.4, 119.4, 118.0, 111.1, 107.8, 54.3, 51.9, 51.6, 51.4, 41.2, 36.9, 32,8, 32.2, 24.1, 18.5, 11.5; IR (neat) 3397, 3245, 2941, 1731, 1452, 1168, 1004, 732 cm^{-1}; MS (CI) m/z 327.2076 [$C_{20}H_{27}N_2O_2$ (M + 1) requires m/z 327.2073], 325, 327 (base), 326, 341.[42]

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Supporting Information Available: ^{1}H NMR spectra for all new compounds and crystallographic data for compounds **26**, **35**, and **44**. This material is available free of charge via the Internet at http://pubs.acs.org.

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