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Total Synthesis of the Bridged Indole Alkaloid Apparicine

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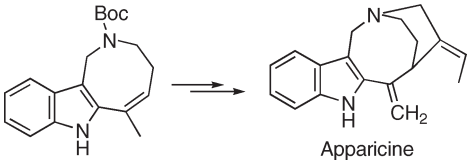

An indole-templated ring-closing metathesis or a 2-indolylacyl radical cyclization constitute the central steps of two alternative approaches developed to assemble the tricyclic ABC substructure of the indole alkaloid apparicine. From this key intermediate, an intramolecular vinyl halide Heck reaction accomplished the closure of the strained 1-azabicyclo[4.2.2]decane framework of the alkaloid with concomitant incorporation of the exocyclic alkylidene substituents.

Introduction

Apparicine (Figure 1) is a fairly widespread monoterpenoid indole alkaloid, first isolated from *Aspidosperma dasycarpon* more than 40 years ago.[1,2] Its structural elucidation,[2] carried out by chemical degradation and early spectroscopic techniques, revealed a particular skeleton with a bridged 1-azabicyclo[4.2.2]decane framework fused to the indole ring and two exocyclic alkylidene (16-methylene and 20*E*-ethylidene) substituents.[3] The same arrangement was also found in vallesamine[4] and later in a small number of alkaloids, including 16(*S*)-hydroxy-16,22-dihydroapparicine[5] or ervaticine,[6] which differ from apparicine in the substitution at C-16.[7]

The apparicine alkaloids are biogenetically defined by the presence of only one carbon (C-6) connecting the indole 3-position and the aliphatic nitrogen, which is the result of the C-5 excision from the original two-carbon tryptamine bridge of the alkaloid stemmadenine.[8] The fragmentation−iminium hydrolysis−recyclization route depicted in Scheme 1, which involves the operation of a stemmadenine *N*-oxide equivalent,[9] has been proposed to rationalize this biogenetic relationship. Such a route appears to be likely since stemmadenine itself[10] and, more

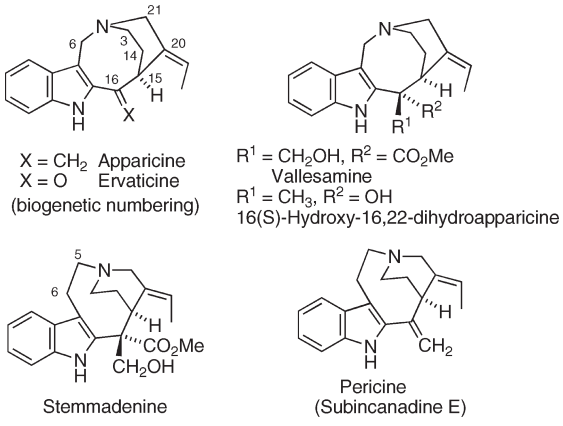

FIGURE 1. Apparicine and related alkaloids.

(1) Gilbert, B.; Duarte, A. P.; Nakagawa, Y.; Joule, J. A.; Flores, S. E.; Brissolese, J. A.; Campello, J.; Carrazzoni, E. P.; Owellen, R. J.; Blossey, E. C.; Brown, K. S., Jr.; Djerassi, C. *Tetrahedron* **1965**, *21*, 1141–1166.

(2) Joule, J. A.; Monteiro, H.; Durham, L. J.; Gilbert, B.; Djerassi, C. *J. Chem. Soc.* **1965**, 4773–4780.

(3) The *E* configuration of the ethylidene group was established some years later: Akhter, L.; Brown, R. T.; Moorcroft, D. *Tetrahedron Lett.* **1978**, *19*, 4137–4140.

(4) (a) Walser, A.; Djerassi, C. *Helv. Chim. Acta* **1965**, *48*, 391–404. (b) Atta-ur-Rahman; Alvi, A. A.; Voelter, W. *Heterocycles* **1987**, *26*, 413–419.

(5) Perera, P.; van Beek, T. A.; Verpoorte, R. *J. Nat. Prod.* **1984**, *47*, 835–838.

(6) (a) Atta-ur-Rahman; Muzaffar, A. *Heterocycles* **1985**, *23*, 2975–2978. (b) Kam, T.-S.; Pang, H.-S.; Choo, Y.-M.; Komiyama, K. *Chem. Biodiversity* **2004**, *1*, 646–656.

(7) For a review, see: Alvarez, M.; Joule, J. A. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 2001; Vol. 57, Chapter 4.

(8) Kutney, J.-P. *Heterocycles* **1976**, *4*, 429–451.

(9) Ahond, A.; Cavé, A.; Kan-Fan, C.; Langlois, Y.; Potier, P. *J. Chem. Soc., Chem. Commun.* **1970**, 517.

(10) Scott, A. I.; Yeh, C.-L.; Greenslade, D. *J. Chem. Soc., Chem. Commun.* **1978**, 947–948.

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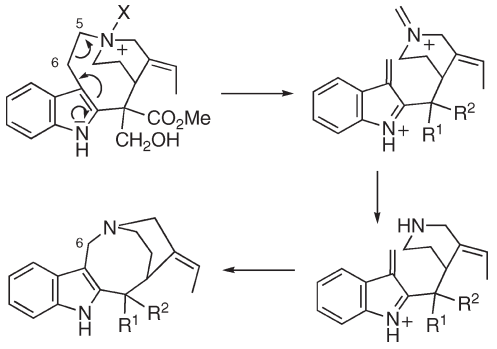
recently, pericine (subincanadine E)[11] have been transformed *in vitro* into the respective C-5 nor-alkaloids (vallesamine and appariciné) by treatment of the *N*-oxides with trifluoroacetic anhydride (modified Polonovski reaction).[12]

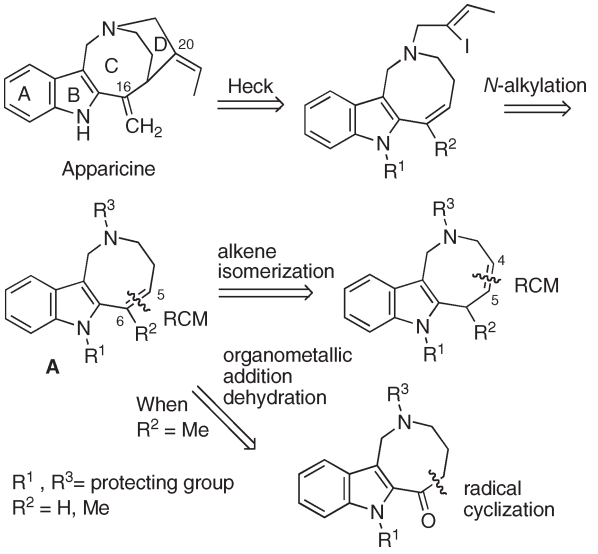
SCHEME 1. Biosynthesis of Appariciné Alkaloids



Their synthetically challenging structures make appariciné alkaloids attractive targets for synthesis. However, progress in this area has been limited to the approach developed by Joule's group in the late 1970s, which allowed the construction of the ring skeleton of appariciné (i.e., 20-deethylideneervaticine) but proved unsuitable for the total synthesis of the alkaloid.[13]

We envisaged appariciné to be accessible via tricyclic ABC substructures containing the central eight-membered ring (e.g., azocinoindoles **A**, Scheme 2), from which the carbon skeleton would be completed by inserting an ethylideneethano unit between the aliphatic nitrogen and C-5. In particular, it was planned that after *N*-alkylation with the appropriate haloalkenyl halide, an intramolecular Heck reaction[14] upon a 2-vinylindole moiety would serve to close the piperidine ring and at the same time install the requisite 20*E*-ethylidene and (when R^2 = Me) 16-methylene appendages. It should be noted that similar Heck couplings of vinyl halides and elaborated cycloalkenes have proved to be useful for the assembly of the bridged core of several indole alkaloids, including pentacyclic *Strychnos* alkaloids,[15] strychnine,[15c,16] minfiensine,[17] apogeissoschizine,[18] and ervitsine.[19] However, to the best of our knowledge, there are no reported vinyl halide Heck reactions involving (aza)cyclooctene rings to produce strained bridged systems.[20]

SCHEME 2. Synthetic Strategy



The power of ring-closing metathesis (RCM)[21] to synthesize medium-sized rings[22] and our own work on RCM of indole-containing dienes[23] made it our method of choice to assemble the indolo fused eight-membered ring of the key intermediates **A** and also to install the double bond required for the Heck reaction, either directly or after an isomerization step. In the course of our work, an alternative approach to **A** based on 2-indolylacyl radical cyclization[24] and manipulation of the resulting ketone was also investigated.[25] This Article deals with the development of the above indole annulation chemistry and its application to complete the first total synthesis of (±)-appariciné.[26]

Resuts and Discussion

Initial Studies. We set out to study the indole-templated RCM en route to appariciné, directly targeting 6-methylazocino[4,3-*b*]indoles (**A**, R^2 = Me, Scheme 2) with the trisubstituted 5,6-double bond functionality required for the Heck coupling. To this end, 2-isopropenylindoles **3**, which are equipped with Boc or Ts groups at the aliphatic nitrogen

(11) Lim, K.-H.; Low, Y.-Y.; Kam, T.-S. *Tetrahedron Lett*. **2006**, *47*, 5037–5039.

(12) Potier, P. In *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds; Academic Press: London, 1980; Chapter 8.

(13) (a) Scopes, D. I. C.; Allen, M. S.; Hignett, G. J.; Wilson, N. D. V.; Harris, M.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2376–2385. (b) Joule, J. A.; Allen, M. S.; Bishop, D. I.; Harris, M.; Hignett, G. J.; Scopes, D. I. C.; Wilson, N. D. V. *Indole and Biogenetically Related Alkaloids*; Phillipson, J. D., Zenk, M. H., Eds.; Academic: London, 1980; pp 229−247.

(14) General reviews: (a) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A.; Diederich, F., Eds; Wiley-WCH: New York, 2004; pp 217−316. (b) Zeni, G.; Larock, R. C. *Chem. Rev*. **2006**, *106*, 4644–4680.

(15) (a) Rawal, V. H.; Michoud, C. *Tetrahedron Lett*. **1991**, *32*, 1695–1698. (b) Rawal, V. H.; Michoud, C.; Monestel, R. F. *J. Am. Chem. Soc*. **1993**, *115*, 3030–3031. (c) Mori, M.; Nakanishi, M.; Kahishima, D.; Sato, Y. *J. Am. Chem. Soc*. **2003**, *125*, 9801–9807. (d) Martin, D. B. C.; Vanderwal, C. D. *J. Am. Chem. Soc*. **2009**, *131*, 3472–3473.

(16) (a) Rawal, V. H.; Iwasa, S. *J. Org. Chem*. **1994**, *59*, 2685–2686. (b) Solé, D.; Bonjoch, J.; García-Rubio, S.; Peidró, E.; Bosch, J. *Chem.—Eur. J*. **2000**, *6*, 655–665. (c) Eichberg, M. J.; Dorta, R. L.; Grotjahn, D. B.; Lamottke, K.; Schmidt, M.; Vollhardt, K. P. C. *J. Am. Chem. Soc*. **2001**, *123*, 9324–9337.

(17) (a) Dounay, A. B.; Humphreys, P. G.; Overman, L. E.; Wrobleski, A. D. *J. Am. Chem. Soc*. **2008**, *130*, 5368–5377. (b) For a related approach, see: Shen, L.; Zhang, M.; Wu, Y.; Qin, Y. *Angew. Chem., Int. Ed*. **2008**, *47*, 3618–3621.

(18) Birman, V. B.; Rawal, V. H. *J. Org. Chem*. **1998**, *63*, 9146–9147.

(19) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Synlett* **2008**, 667–670.

(20) For related Heck processes involving more robust aryl halides, see: (a) Grigg, R.; Sridharan, V.; York, M. *Tetrahedron Lett*. **1998**, *39*, 4139–4142. (b) Enders, D.; Lenzen, A.; Backes, M.; Janeck, C.; Catlin, K.; Lannou, M.-I.; Runsink, J.; Raabe, G. *J. Org. Chem*. **2005**, *70*, 10538–10551. Ribelin, T. P.; Judd, A. S.; Akritopoulou-Zanze, I.; Henry, R. F.; Cross, J. L.; Whittern, D. N.; Djuric, S. W. *Org. Lett*. **2007**, *9*, 5119–5122.

(21) General reviews: (a) Grubbs, R. H. Ed.; *Handbook of Metathesis*; Wiley-VCH: Weinheim, 2003; Vol. 2. (b) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199–2238.

(22) For reviews, see: (a) Maier, M. E. *Angew. Chem., Int. Ed*. **2000**, *39*, 2073–2077. (b) Yet, L. *Chem. Rev*. **2000**, *100*, 2963–3007. (c) Michaut, A.; Rodriguez, J. *Angew. Chem., Int. Ed*. **2006**, *45*, 5740–5750.

(23) (a) Bennasar, M.-L.; Zulaica, E.; Tummers, S. *Tetrahedron Lett*. **2004**, *45*, 6283–6285. (b) Bennasar, M.-L.; Zulaica, E.; Alonso, S. *Tetrahedron Lett*. **2005**, *46*, 7881–7884. (c) Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Tetrahedron* **2007**, *63*, 861–866.

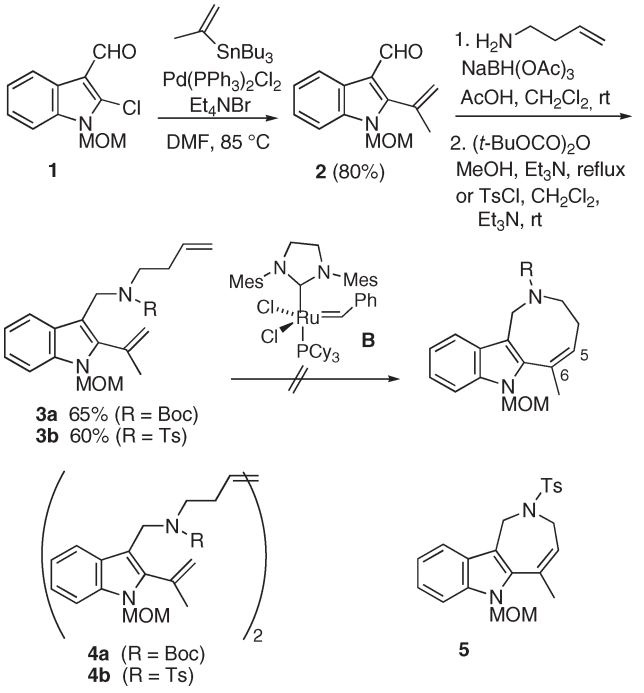
(24) Bennasar, M.-L.; Roca, T. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds; Elsevier: Amsterdam, 2009; Chapter 1, pp 1−19.

(25) For a previous different approach to appariciné ABC substructures, see: (a) Street, J. D.; Harris, M.; Bishop, D. I.; Heatley, F.; Beddoes, R. L.; Mills, O. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1599–1606. (b) See also ref 13b.

(26) For a preliminary communication, see: Bennasar, M.-L.; Zulaica, E.; Solé, D.; Alonso, S. *Chem. Commun*. **2009**, 3372–3374.

and a robust MOM group at the indole nitrogen, were selected as the starting dienes (Scheme 3). These compounds were efficiently prepared from the known 2-chloroindole-3-carbaldehyde **1**[27] by a Stille coupling with (isopropenyl)tributylstannane, followed by reductive amination of aldehyde **2** with 3-butenylamine and subsequent acylation or sulfonylation of the resulting secondary amine with di-*tert*-butyl dicarbonate or tosyl chloride, respectively. Unfortunately, exposure of dienes **3** to the second-generation Grubbs catalyst **B** in CH_2Cl_2 or toluene did not deliver the expected eight-membered ring. Instead, carbamate **3a** mainly underwent an intermolecular metathesis reaction leading to dimer **4a**, even when working under high dilution conditions (0.007 M). Sulfonamide **3b**, in turn, led to the respective dimer **4b** along with variable amounts of the ring-contracted product **5**, coming from the competitive isomerization of the terminal double bond followed by RCM with liberation of propene. Azepinoindole **5** was the only isolated product (75%) when cyclization of **3b** was performed in refluxing toluene. In both cases, the use of other metathesis catalysts, either based on ruthenium (first-generation Grubbs or second-generation Hoveyda-Grubbs catalysts) or molybdenum (Schrock's catalyst) did not lead to any improvement.

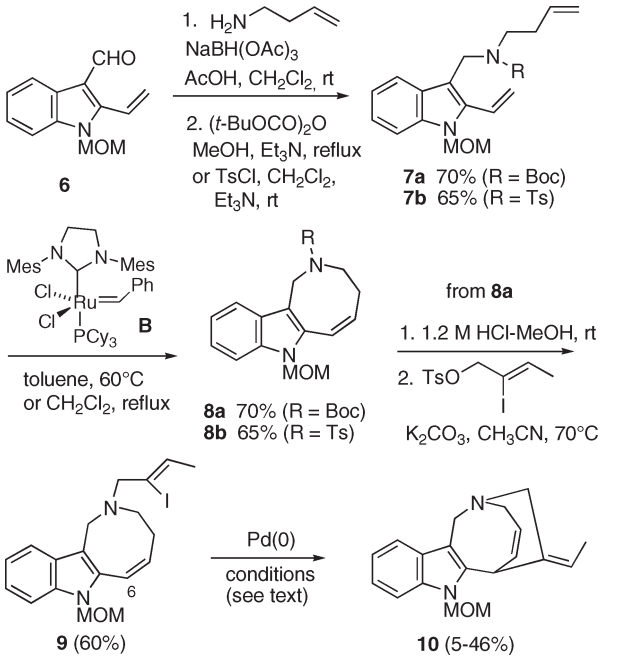
SCHEME 3. Attempted Direct RCM Synthesis of 6-Methyl-1,2,3,4-tetrahydroazocino[4,3-*b*]indoles



Because this unsuccessful result was probably due to the presence of a geminal disubstituted terminal alkene moiety in dienes **3**, we turned our attention to more easily available 6-demethyl tricyclic substructures (**A**, $R^2 = H$, Scheme 2). These model azocinoindoles would also serve as precursors for closing the piperidine ring of apparicine by a reductive Heck cyclization or a tandem Heck cyclization-capture, which could also allow the introduction of the remaining carbon atom at C-16. The implementation of this new synthetic plan is depicted in Scheme 4.

Thus, the required RCM substrates **7a** and **7b** were uneventfully prepared from 2-vinylindole-3-carbaldehyde **6**[27] by reductive amination with 3-butenylamine followed by *N*-acylation or sulfonylation, as in the above isopropenyl series. As anticipated, RCM of dienes **7a** or **7b**, involving two terminal monosubstituted alkene units, took place with the use of ruthenium complex **B** under standard conditions (0.01 M, toluene, 60 °C or CH_2Cl_2, reflux) to give azocinoindoles **8a** or **8b** in acceptable yields. At this point, access to the more advanced synthetic intermediate **9** required the manipulation of the aliphatic nitrogen of **8a** or **8b** to install the iodoalkenyl chain for eventual cyclization. As our first attempts to induce *N*-desulfonylation of **8b** under reductive conditions (Mg, NH_4Cl, MeOH or Na/naphthalenide, THF) proved problematic, affording the unchanged starting product or complex reaction mixtures, we focused on the more labile carbamate function of **8a**. Removal of the Boc group under standard acidic conditions (TFA, Me_3SiI, $ZnBr_2$) was also troublesome, leading to partial decomposition, but the deprotection took place cleanly upon exposure of **8a** to a mild acidic protocol (1.2 M HCl in MeOH at rt). The resulting secondary amine was directly subjected to alkylation with (*Z*)-2-iodo-2-butenyl tosylate in hot acetonitrile in the presence of K_2CO_3 to give **9** in 60% isolated yield over the two steps.

SCHEME 4. Studies in the 6-Demethyl Series



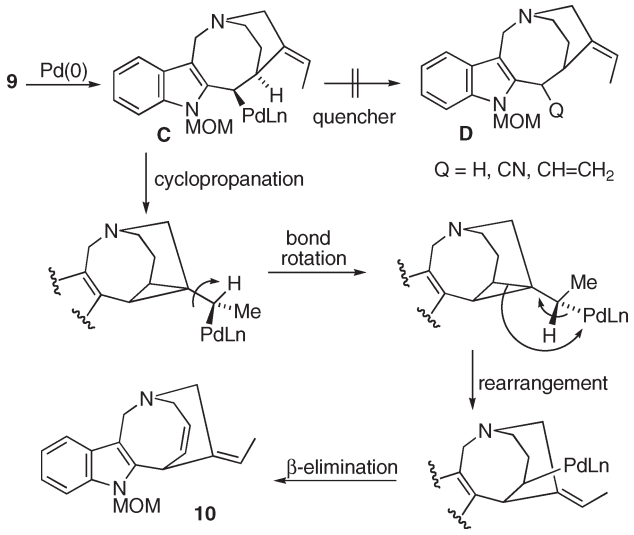
We next studied the key formation of the piperidine ring by Pd-catalyzed cyclization of the vinyl iodide upon the 2-vinylindole moiety. Our expectation was that the initially formed alkylpalladium intermediate **C** (Scheme 5), in which no β-hydrogen is available for elimination, would be stable enough to be reduced or trapped with a suitable quencher. However, when **9** was subjected to a number of standard conditions for reductive Heck reactions, the desired tetracyclic system **D** (Q = H) was never detected. The only observed process under the phosphine-free conditions[28] [$Pd(OAc)_2$,

(27) Hagiwara, H.; Choshi, T.; Nobuhiro, J.; Fujimoto, H.; Hibino, S. *Chem. Pharm. Bull.* **2001**, *49*, 881–886.

(28) (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667–2670. (b) Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.

K_2CO_3, TBACl, HCO_2Na, DMF, 80 °C] previously used by Overman[17a] on a related substrate was *N*-dealkylation. After this unsuccessful result, a variety of palladium precatalysts [$Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$], ligands (PPh_3, dppe), and cosolvents (toluene, CH_3CN, THF) were examined in the presence of Et_3N or diisopropylethylamine as the potential reductants.[16b,29] Whereas short reaction times left the starting product unchanged, prolonged heating gave low yields (5−10%) of the unexpected tetracycle **10**, coming from an apparent 7-*endo* cyclization with inversion of the ethylidene configuration.[30] The yield of **10** was raised to 30% on exposure of **9** to $Pd(PPh_3)_4$ in 1:1 THF−Et_3N in a sealed tube at 90 °C for 24 h. On the other hand, under cationic conditions [$Pd(OAc)_2$, PPh_3, Ag_2CO_3, 1:1 toluene−Et_3N, 90 °C] the cyclization proceeded readily to give tetracycle **10** in 46% isolated yield. Significantly, this result was not substantially altered when the reaction was carried out in the presence of HCO_2Na as the reductant or KCN, $K_4[Fe(CN)_6]$, TMSCN, or tributylvinylstannane as trapping agents.

SCHEME 5



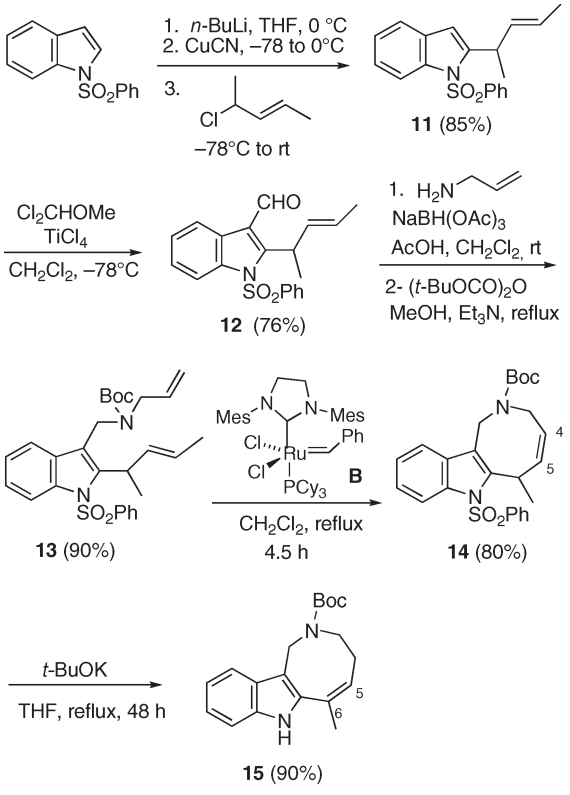
The formation of unusual Heck cyclization products like **10** has been previously observed[31] and rationalized[32] by considering that the initial 6-*exo* cyclization is followed by an intramolecular carbopalladation on the exocyclic alkene. The resulting cyclopropane intermediate would undergo rearrangement, with concomitant inversion of the alkene geometry, and final β-hydride elimination. In our case, the cyclopropanation−rearrangement route depicted in Scheme 5 would be fast enough to prevent the quenchers from intercepting the initially formed alkylpalladium intermediate **C**.

It now became apparent that the presence of a 6-methyl group in the Heck cyclization substrate was crucial to assemble the bridged framework of apparicine, as it would guarantee the β-elimination of the alkylpalladium intermediate arising from cyclization, thus hampering the above undesired route. Hence, we renewed our efforts to synthesize 6-methylazocino[4,3-*b*]indoles (**A**, R^2 = Me, Scheme 2), once again tackling the problem of RCM and ready to explore new routes.

RCM−Isomerization Route to Azocinoindole 15. Given that we were unable to directly form the trisubstituted double bond included in the azocine ring by RCM, we decided to change the cyclization site from the 5,6-position to the less crowded 4,5-position by using a 3-(allylaminomethyl)-2-allylindole such as **13** (Scheme 6) as the diene. Consequently, the synthesis of the Heck precursor would now require an additional isomerization step of the resulting double bond.

It was planned to install the α-methyl-substituted allyl-type chain at the indole 2-position taking advantage of an allylic nucleophilic substitution reaction using a suitable organometallic derivative of indole. Thus, 1-(phenylsulfonyl)indole was allowed to react with *n*-BuLi and CuCN, and the intermediate organocopper derivative was treated with (*E*)-4-chloro-2-pentene. The resulting indole **11** was then converted into the RCM precursor **13** by Friedel−Crafts formylation, reductive amination of aldehyde **12** with allylamine, and the subsequent protection of the aliphatic nitrogen with a Boc group. The overall yield of the four steps was 58%. Satisfactorily, ring closure of diene **13** took place with the second-generation Grubbs catalyst **B** under standard conditions (0.07 M, CH_2Cl_2, reflux) to give the desired 6-methylazocinoindole **14** in 80% yield.

SCHEME 6. RCM−Isomerization Route to 6-Methylazocinoindole 15

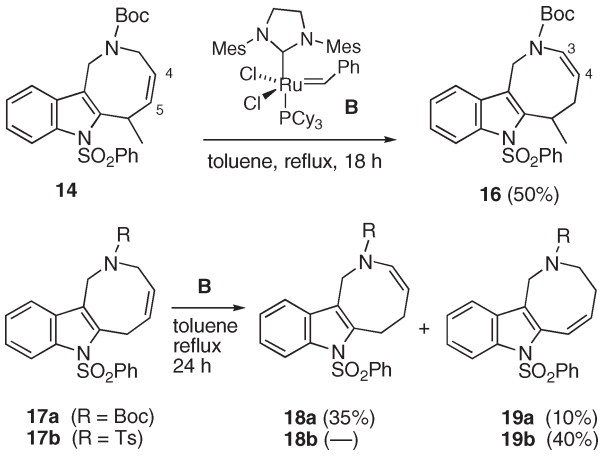


Attention was then focused on the isomerization step. Considering recent reports on alkene isomerizations mediated

(29) Minatti, A.; Zheng, X.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 9253–9258.
(30) The configuration of the ethylidene substituent was established by NOESY experiments.
(31) (a) Rawal, V. H.; Michoud, C. *J. Org. Chem.* **1993**, *58*, 5583–5584. (b) Feutren, S.; McAlonan, H.; Montgomery, D.; Stevenson, P. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1129–1137.
(32) Owczarczyk, Z.; Lamaty, F.; Vawter, E. J.; Negishi, E. *J. Am. Chem. Soc.* **1992**, *114*, 10091–10092.

by suitably modified ruthenium-metathesis catalysts,[33−36] we sought to examine if such a protocol could be synthetically useful for our purpose (Scheme 7). Unfortunately, when azocinoindole **14** was treated with catalyst **B** in refluxing toluene,[35] a slow isomerization of the double bond took place to its *N*-conjugated counterpart (3,4-position), providing the enecarbamate **16** in 50% yield (not optimized). The directing effect of the carbamate nitrogen was also decisive, although to a lesser extent, in the ruthenium-catalyzed isomerization of the 6-demethyl analogue **17a**,[23c] which led to the enamide **18a** as the major product along with minor amounts of vinylindole **19a**. Significantly, the influence of the heteroatom was suppressed in the *N*-tosyl analogue **17b**,[23c] which underwent isomerization to afford vinylindole **19b** as the only product. Finally, no isomerization was observed upon exposure of azocinoindoles **14** or **17** to catalyst **B** in hot methanol.[36]

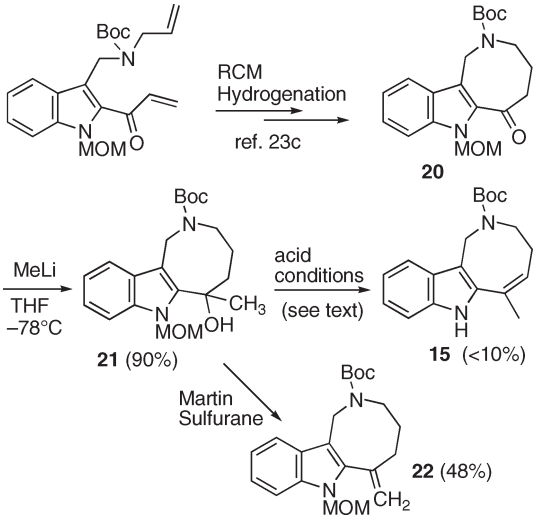
SCHEME 7. Isomerization Studies



Satisfactorily, we fortuitously discovered that the double bond of azocinoindole **14** moved into conjugation with the aromatic ring under the basic conditions used to remove the phenylsulfonyl group. Thus, long exposure of **14** to *t*-BuOK in refluxing THF brought about the anticipated indole deprotection along with alkene isomerization, affording **15** in 90% yield (Scheme 6). By using shorter reaction times and using NMR spectroscopy, we found that the migration of the double bond took place after the initial indole *N*-deprotection step, which suggests that the base-induced isomerization is only compatible with the presence of a free indole NH group.

Alternative Synthesis of 15. Although the RCM−isomerization route depicted in Scheme 6 allowed an efficient synthesis of the key apparicine intermediate **15** [41% overall yield from 2-(phenylsulfonyl)indole by way of four isolated intermediates], we explored the possibility of installing the trisubstituted double bond required for the Heck reaction from a ketone carbonyl group. To this end, the first substrate examined was the *N*-MOM tricyclic ketone **20** (Scheme 8), since it had already been prepared by RCM followed by removal of the resulting double bond by hydrogenation.[23c] Reaction of **20** with MeLi smoothly provided tertiary alcohol **21**, which was subjected to several dehydration protocols without success. Thus, the acid-catalyzed dehydration using 3 M H_2SO_4 in acetone or TsOH in benzene was complicated by the competitive indole deprotection, affording low yields of the endocyclic alkene (**15**). On the other hand, the use of Martin sulfurane resulted in a cleaner dehydration to the exocyclic alkene **22**, in which the *N*-MOM group remained unaffected.

SCHEME 8



In search of a more efficient approach, we decided to extend the above organometallic addition−dehydration sequence to an analogous indole unprotected ketone (i.e., **26**, Scheme 9). After unsuccessful attempts to remove the *N*-MOM group of **20**, the substrate was efficiently prepared by a more direct route free of indole protecting groups, based on an 8-*endo* cyclization of a 2-indolylacyl radical upon an amino tethered alkene.[24,37] The synthesis began with the preparation of selenoester **25** as the radical precursor, equipped with a bromovinyl chain to increase both the efficiency and the *endo* regioselectivity of the ring closure.[37] Thus, reductive amination of aldehyde **23** with 2-bromo-2-propenylamine followed by standard protection of the resulting secondary amine with a Boc group led to ester **24**, which was converted into **25** by phenylselenation through the corresponding carboxylic acid.[38] Treatment of selenoester **25** with *n*-Bu_3SnH as the radical mediator and Et_3B as the initiator achieved the desired ring closure affording ketone **26** in moderate yield (54%). Finally, to our satisfaction, reaction of **26** with methyllithium followed by dehydration of the resulting tertiary alcohol under mild acid conditions (TsOH, CH_3CN, rt) smoothly provided the target alkene **15**. Using this alternative route, the synthesis of **15** was accomplished from aldehyde **23** in 26% overall yield by way of only three isolated intermediates.

(33) For intentional post-RCM isomerizations, see: (a) Sutton, A. E.; Seigal, B. A.; Finnegan, D. F.; Snapper, M. L. *J. Am. Chem. Soc.* **2002**, *124*, 13390–13391. (b) Schmidt, B. *J. Org. Chem.* **2004**, *69*, 7672–7687. For a recent example, see: (c) Schmidt, B.; Biernat, A. *Chem.—Eur. J.* **2008**, *14*, 6135–6141.

(34) For reviews on the nonmetathetic behavior of Grubbs ruthenium catalysts, see: (a) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865–1880. (b) Alcaide, A.; Almendros, P.; Luna, A. *Chem. Rev.* **2009**, *109*, 3817–3858.

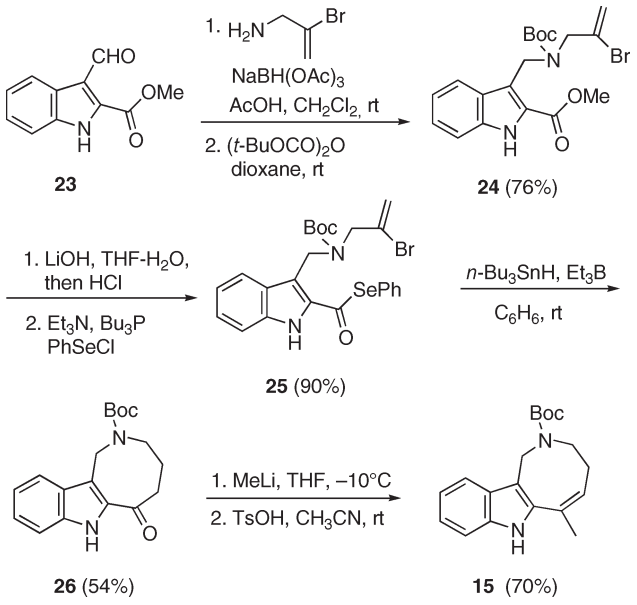
(35) Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Aceña, J. L. *J. Org. Chem.* **2006**, *71*, 2706–2714.

(36) Hanessian, S.; Giroux, S.; Larsson, A. *Org. Lett.* **2006**, *8*, 5481–5484.

(37) Bennasar, M.-L.; Roca, T.; García-Díaz, D. *J. Org. Chem.* **2007**, *72*, 4562–4565.

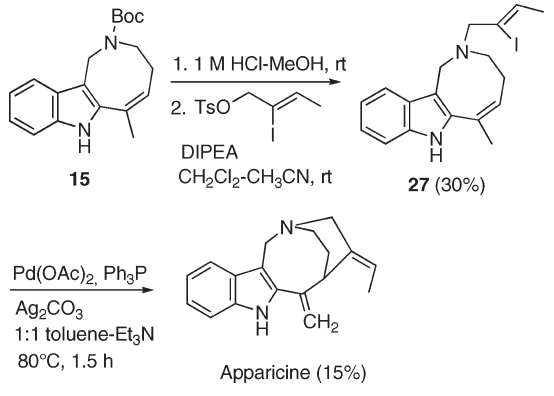
(38) Batty, D.; Crich, D. *Synthesis* **1990**, 273–275.

SCHEME 9. Radical Route to 6-Methylazocinoindole 15



Completion of the Synthesis of Appariicine. With azocinoindole **15** in hand, we next sought to manipulate the aliphatic nitrogen to install the haloalkenyl chain for the subsequent Heck reaction. As occurred with the C-6 demethyl analogue **8a** (Scheme 4), removal of the *N*-Boc group of **15** required a mild acid protocol to avoid decomposition. The resulting secondary amine proved to be highly unstable and was directly subjected to alkylation with (*Z*)-2-iodo-2-butenyl tosylate to give **27** in 30% isolated yield over the two steps (Scheme 10). Attempts to place a phenylsulfonyl group at the indole nitrogen of **15** in order to improve the yield were unsuccessful.

SCHEME 10. Completion of the Synthesis of Appariicine



The stage was now set for the completion of the synthesis by intramolecular coupling of the vinyl iodide and the trisubstituted alkene. A variety of experimental conditions were screened, including different solvents, palladium precatalysts, and additives, resulting only in the recovery of the starting material or decomposition products. However, the critical closure of the strained 1-azabicyclo[4.2.2]decane framework with concomitant incorporation of the exocyclic alkylidene substituents took place under cationic conditions, although loss of material was still extensive. Thus, when vinyl iodide **27** was subjected to a specific protocol, using $Pd(OAc)_2/PPh_3$ (0.2:0.6 equiv) and Ag_2CO_3 (2 equiv) in 1:1 toluene−Et_3N at 80 °C for a short reaction time (1.5 h), appariicine was obtained in a consistent, reproducible 15% isolated yield. The ^1H and ^{13}C NMR spectroscopic data of synthetic appariicine essentially matched those described in the literature for the natural product.[2,7,39] Additionally, the chromatographic (TLC) behavior of synthetic appariicine was identical to an authentic sample.

Conclusion

In summary, the first total synthesis of (±)-appariicine has been accomplished by a concise route employing a vinyl halide Heck cyclization to close the bridged piperidine ring in the last synthetic step. The key azocinoindole intermediate **15** has been successfully assembled by developing two alternative procedures, namely, an indole-templated RCM followed by base-induced isomerization and an acyl radical cyclization followed by ketone−alkene functional group interconversion.

Experimental Section

2-Isopropenyl-1-(methoxymethyl)indole-3-carbaldehyde (2). Tetraethylammonium bromide (0.42 g, 2.01 mmol), $Bu_3Sn(CH_3)C{=}CH_2$ (1.33 g, 4.02 mmol), and $Pd(PPh_3)_2Cl_2$ (42 mg, 0.06 mmol) were successively added to a solution of aldehyde **1**[27] (0.45 g, 2.01 mmol) in DMF (30 mL), and the mixture was stirred at 85 °C overnight. The reaction mixture was diluted with AcOEt and washed with brine. The organic solution was dried and concentrated, and the resulting residue was chromatographed (9:1 hexanes−AcOEt) to give **2** as an oil: 0.37 g (80%); IR (film) 3057, 2934, 1663 cm^{-1}; ^1H NMR (400 MHz) δ 2.25 (s, 3H), 3.31 (s, 3H), 5.35 (s, 1H), 5.44 (s, 2H), 5.76 (s, 1H), 7.33 (m, 2H), 7.49 (dm, $J = 7.5$ Hz, 1H), 8.35 (dm, $J = 7.5$ Hz, 1H), 10.0 (s, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 25.0 (CH_3), 56.3 (CH_3), 75.2 (CH_2), 110.4 (CH), 115.2 (C), 122.1 (CH), 123.4 (CH), 123.9 (CH_2), 124.3 (CH), 125.2 (C), 133.4 (C), 136.8 (C), 153.3 (C), 186.8 (CH); ESI-HRMS $[M + H]^+$ calcd for $C_{14}H_{16}NO_2$ 230.1175, found 230.1183.

3-[*N*-(3-Butenyl)-*N*-(*tert*-butoxycarbonyl)aminomethyl]-2-isopropenyl-1-(methoxymethyl)indole (3a). 3-Butenylamine (0.24 mL, 2.60 mmol), $NaBH(OAc)_3$ (0.82 g, 3.90 mmol), and AcOH (0.08 mL, 1.36 mmol) were successively added to aldehyde **2** (0.30 g, 1.30 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (0.30 g). This compound was dissolved in MeOH (10 mL) and treated with $(t\text{-BuOCO})_2O$ (0.45 g, 2.06 mmol) and Et_3N (0.58 mL, 4.12 mmol). After the mixture was heated at reflux for 4 h, the solvent was removed, and the residue was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the residue was chromatographed (8:2 hexanes−AcOEt) to give carbamate **3a** as a pale yellow oil: 0.33 g (65%); IR (film) 1689, 1462, 1415 cm^{-1}; ^1H NMR (400 MHz) δ 1.53 (br s, 9H), 2.12 (s, 3H), 2.13 (m, 2H), 3.10 (m, 2H) 3.26 (s, 3H), 4.66 (s, 2H), 4.96 (m, 2H), 5.15 (s, 1H), 5.38 (s, 2H), 5.60 (s, 1H), 5.65 (m, 1H), 7.15 (t, $J = 7.5$ Hz, 1H), 7.24 (t, $J = 7.5$ Hz, 1H), 7.40 (d,

(39) (a) Massiot, G.; Zèches, M.; Thépenier, P.; Jacquier, M.-J.; Le Men-Olivier, L.; Delaude, C. *J. Chem. Soc., Chem. Commun.* **1982**, 768–769. (b) van Beek, T. A.; Verpoorte, R.; Kinh, Q. *Planta Med.* **1985**, *51*, 277–279. (c) Atta-ur-Rahman; Fatima, T.; Mehrum-Nisa; Ijaz, S.; Crank, G.; Wasti *Planta Med.* **1987**, *53*, 57–59.

J = 7.8 Hz, 1H), 7.75 (m, 1H); ^{13}C NMR (100.6 MHz) δ 24.5 (CH_3), 28.5 ($3CH_3$), 32.6 (CH_2), 39.7 (CH_2), 44.2 (CH_2), 55.7 (CH_3), 74.7 (CH_2), 79.2 (C), 109.8 (CH), 116.1 (CH_2), 120.1 (C), 120.4 (CH), 121.5 (CH_2), 122.4 (CH), 122.5 (CH), 127.9 (C), 135.5 (CH), 135.6 (C), 136.9 (C), 141.3 (C), 155.7 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{23}H_{33}N_2O_3$ 385.2485, found 385.2477.

3-[*N*-(3-Butenyl)-*N*-(tosyl)aminomethyl]-2-isopropenyl-1-(methoxymethyl)indole (3b). Aldehyde **2** (0.25 g, 1.09 mmol) was allowed to react as above with 3-butenylamine and $NaBH(OAc)_3$. The resulting secondary amine (0.25 g) was dissolved in CH_2Cl_2 (12 mL) and treated with TsCl (0.20 g, 1.05 mmol) and Et_3N (0.15 mL, 1.05 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the resulting residue was chromatographed (9:1 hexanes−AcOEt) to give sulfonamide **3b** as a pale yellow solid: 0.29 g (60%); mp 88 °C (Et_2O); IR (KBr) 1463, 1332, 1158 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.92 (m, 2H), 2.06 (s, 3H), 2.44 (s, 3H), 3.04 (m, 2H), 3.28 (s, 3H), 4.48 (s, 2H), 4.70 (dm, J = 17 Hz, 1H), 4.78 (dm, J = 10 Hz, 1H), 5.09 (s, 1H), 5.36 (s, 2H), 5.40 (m, 1H), 5.53 (br s, 1H), 7.14 (t, J = 7.6 Hz, 1H), 7.24 (t, J = 7.6 Hz, 1H), 7.33 (m, 2H), 7.43 (d, J = 8 Hz, 1H), 7.78 (m, 3H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 24.5 (CH_3), 32.9 (CH_2), 43.4 (CH_2), 46.7 (CH_2), 55.7 (CH_3), 74.7 (CH_2), 107.1 (C), 109.8 (CH), 116.3 (CH_2), 120.1 (CH), 120.7 (CH), 121.9 (CH_2), 122.7 (CH), 127.3 (2 CH), 127.7 (C), 129.2 (2 CH), 134.8 (CH), 135.2 (C), 136.9 (2C), 141.4 (C), 143.0 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{25}H_{31}N_2O_3S$ 439.2049, found 439.2039; $[M + Na]^+$ calcd for $C_{25}H_{30}NaN_2O_3S$ 461.1869, found 461.1866. Anal. Calcd for $C_{25}H_{30}N_2O_3S$: C, 68.46; H, 6.88; N, 6.38. Found: C, 68.22; H, 6.43; N, 6.25.

3-[*N*-(3-Butenyl)-*N*-(*tert*-butoxycarbonyl)aminomethyl]-1-(methoxymethyl)-2-vinylindole (7a). 3-Butenylamine (0.39 mL, 4.20 mmol), $NaBH(OAc)_3$ (1.33 g, 6.30 mmol), and AcOH (0.12 mL, 2.10 mmol) were successively added to aldehyde **6**[1] (0.45 g, 2.10 mmol) in CH_2Cl_2 (13 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (0.50 g). This compound was dissolved in MeOH (20 mL) and treated with $(t\text{-BuOCO})_2O$ (0.52 g, 2.40 mmol) and Et_3N (0.68 mL, 4.85 mmol). After the mixture was heated at reflux for 4 h, the solvent was removed, and the residue was dissolved in CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the residue was chromatographed (9:1 hexanes−AcOEt) to give carbamate **7a** as a pale yellow oil: 0.55 g (70%); IR (film) 1687 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.54 (br s, 9H), 2.19 (br s, 2H), 3.10 (m, 2H), 3.11 (s, 3H), 4.79 (br s, 2H), 4.94 (s, 1H), 4.96 (dd, J = 8.4 and 1.6 Hz, 1H), 5.46 (s, 2H), 5.64 (d, J = 12 Hz, 1H), 5.65 (masked, 1H), 5.70 (d, J = 17 Hz, 1H), 6.90 (dd, J = 17 and 12 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.26 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 8 Hz, 1H), 7.45 (br m, 1H); ^{13}C NMR (100.6 MHz) δ 28.5 (3 CH_3), 32.7 (CH_2), 39.4 (CH_2), 44.3 (CH_2), 55.7 (CH_3), 74.4 (CH_2), 79.4 (C), 109.4 (CH), 111.9 (C), 116.2 (CH_2), 119.9 (CH), 120.6 (CH), 120.7 (CH_2), 123.0 (CH), 125.2 (CH), 127,9 (C), 135.7 (CH), 136.6 (C), 137.7 (C), 155.6 (C); ESI-HRMS $[M + Na]^+$ calcd for $C_{22}H_{30}N_2O_3Na$ 393.2148, found 393.2139.

3-[*N*-(3-Butenyl)-*N*-(tosyl)aminomethyl]-1-(methoxymethyl)-2-vinylindole (7b). Aldehyde **6** (0.45 g, 2.10 mmol) was allowed to react as above with 3-butenylamine (0.39 mL, 4.20 mmol) and $NaBH(OAc)_3$ (1.33 g, 6.30 mmol). The resulting secondary amine was dissolved in CH_2Cl_2 (30 mL) and treated with TsCl (0.48 g, 2.52 mmol) and Et_3N (0.36 mL, 2.52 mmol) at rt overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with 1 N HCl and brine. The organic solution was dried and concentrated, and the resulting residue was chromatographed (8:2 hexanes−AcOEt) to give sulfonamide **7b** as a white solid: 0.58 g (65%); mp 105 °C (Et_2O); IR (KBr) 1335, 1462, 1598 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.90 (m, 2H), 2.45 (s, 3H), 3.01 (m, 2H), 3.30 (s, 3H), 4.57 (s, 2H, CH_2), 4.68 (d, J = 17 Hz, 1H), 4.76 (d, J = 12 Hz, 1H), 5.38 (m, 1H), 5.45 (s, 2H), 5.60 (d, J = 12 Hz, 1H), 5.73 (d, J = 18 Hz, 1H), 6.80 (dd, J = 18 and 12 Hz, 1H), 7,12 (t, J = 7.5 Hz, 1H), 7.25 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 8 Hz, 2H), 7.43 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H), 7.78 (d, J = 8 Hz, 2H); ^{13}C NMR (100.6 MHz) δ 21.5 (CH_3), 33.1 (CH_2), 42.9 (CH_2), 46.9 (CH_2), 55.7 (CH_3), 74.4 (CH_2), 109.0 (C), 109.4 (CH), 116.4 (CH_2), 119.8 (CH), 120.8 (CH), 121.7 (CH_2), 123.3 (CH), 124.7 (CH), 127.3 (2CH), 129.7 (2CH), 127.8 (C), 134.8 (CH), 136.5 (C), 137.1 (C), 137.6 (C), 143.2 (C). Anal. Calcd for $C_{24}H_{28}N_2O_3S$: C, 67.80; H, 6.63; N, 6.58; S; 7.68. Found: C, 67.62; H, 6.65; N, 6.52; S, 7.70.

2-(*tert*-Butoxycarbonyl)-7-(methoxymethyl)-1,2,3,4-tetrahydroazocino[4,3-*b*]indole (8a). The second-generation Grubbs catalyst (33 mg, 10 mol %) was added under Ar to a solution of diene **7a** (150 mg, 0.40 mmol) in toluene (40 mL), and the resulting mixture was heated at 60 °C for 2.5 h. The reaction mixture was concentrated, and the residue was chromatographed (9:1 hexanes−AcOEt) to give azocinoindole **8a** as a colorless oil: 97 mg (70%); IR (film) 1689 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz, assignment aided by gHSQC, mixture of rotamers) δ 1.30 and 1.44 (2 s, 9H, Boc), 2.48 (m, 2H, 4-H), 3.19 and 3.21 (2s, 3H, OCH_3), 3.59 and 3.68 (2 apparent t, J = 5.6 Hz, 2H, 3-H), 4.62 and 4.64 (2s, 2H, 1-H), 5.37 and 5.40 (2s, 2H, OCH_2), 6.09 (m, 1H, 5-H), 6.63 (m, 1H, 6-H), 7.13 (t, J = 7.6 Hz, 1H, 10-H), 7.22 (m, 1H, 9-H), 7.35 and 7.39 (2d, J = 8 Hz, 1H, 8-H), 7.56 and 7.70 (2 d, J = 8 Hz, 1H, 11-H); ^{13}C NMR (100.6 MHz, assignments aided by gHSQC, major rotamer) δ 28.4 ($3CH_3$), 28.6 (CH_2, C-4), 43.2 (CH_2, C-1), 45.8 (CH_2, C-3), 55.4 (CH_3), 73.8 (CH_2), 79.4 (C), 109.2 (CH, C-8), 112.3 (C), 118.7 (CH, C-11), 119.8 (CH, C-10), 120.6 (CH, C-6), 122.5 (CH, C-9), 127.0 (C), 132.5 (CH, C-5), 132.6 (C), 137.4 (C), 156.2 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{27}N_2O_3$ 343.2016, found 343.2005; $[M + Na]^+$ calcd for $C_{20}H_{26}N_2O_3Na$ 365.1835, found 365.1837.

7-(Methoxymethyl)-2-tosyl-1,2,3,4-tetrahydroazocino[4,3-*b*]-indole (8b). The second-generation Grubbs catalyst (24 mg, 7 mol %) was added under Ar to a solution of diene **7b** (170 mg, 0.40 mmol) in CH_2Cl_2 (30 mL), and the resulting mixture was heated at reflux overnight. The reaction mixture was concentrated, and the residue was chromatographed (8:2 hexanes−AcOEt) to give azocinoindole **8b** as a white solid: 103 mg (65%); mp 154 °C (Et_2O); IR (KBr) 1157, 1330, 1462 cm^{-1}; ^{1}H NMR (400 MHz) δ 2.30 (m, 2H), 2.37 (s, 3H), 3.16 (s, 3H), 3.36 (m, 2H), 4.47 (s, 2H), 5.30 (s, 2H, CH_2), 6.07 (m, 1H), 6.58 (d, J = 11 Hz, 1H), 7.19 (d, J = 8 Hz, 2H), 7.22 (m, 1H), 7.26 (m, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.65 (d, J = 8 Hz, 2H), 7.84 (d, J = 8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.4 (CH_3), 28.8 (CH_2), 43.4 (CH_2), 45.5 (CH_2), 55.6 (CH_3), 74.3 (CH_2), 109.4 (CH), 110.8 (C), 119.6 (CH), 120.2 (CH), 120.6 (CH), 122.9 (CH), 127.2 (2CH), 129.5 (2CH), 127.4 (C), 133.5 (CH), 135.3 (C), 137.0 (C), 137.3 (C), 142.9 (C). Anal. Calcd for $C_{22}H_{24}N_2O_3S$. 2/3H_2O: C, 64.67; H, 6.25; N, 6.86. Found: C, 64.19; H, 6.47; N, 6.49.

2-(2-Iodo-2-(*Z*)-butenyl)-7-(methoxymethyl)-1,2,3,4-tetrahidroazocino[4,3-*b*]indole (9). A solution of carbamate **8a** (0.31 g, 0.90 mmol) in 1.2 M HCl in MeOH (3.7 mL) was stirred at rt for 18 h. The reaction mixture was basified with 20% NH_4OH and concentrated. The residue was partitioned between CH_2Cl_2 and H_2O and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (0.18 g). K_2CO_3 (0.16 g, 1.15 mmol) and (*Z*)-2-iodo-2-butenyl tosylate[15a,16c] (0.26 g, 0.74 mmol) were added to a solution of the above material (0.18 g, 0.74 mmol) in acetonitrile (20 mL), and the resulting mixture was stirred at 70 °C for 1.5 h. The solvent was removed, and the residue was dissolved in Et_2O and washed with H_2O. The organic solution was dried and concentrated to give the crude product. After chromatography

(9:1 hexanes−AcOEt) the pure tertiary amine **9** was obtained as a yellow oil: 0.23 g (60%); IR (film) 1323, 1461, 1659 cm^{-1}; ^1H NMR (400 MHz) δ 1.81 (d, J = 6.4 Hz, 3H), 2.30 (m, 2H), 2.79 (m, 2H), 3.23 (s, 3H), 3.32 (br s, 2H), 4.04 (br s, 2H), 5.44 (s, 2H), 5.80 (q, J = 6.4 Hz, 1H), 6.12 (m, 1H), 6.56 (d, J = 11.2 Hz, 1H), 7.15 (t, J = 7.6 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.41 (d, J = 8 Hz, 1H), 7.57 (d, J = 8 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 21.7 (CH_3), 26.9 (CH_2), 47.6 (CH_2), 49.3 (CH_2), 55.9 (CH_3), 65.4 (CH_2), 74.5 (CH_2), 109.4 (CH), 110.5 (C), 110.6 (C), 117.9 (CH), 118.8 (CH), 120.3 (CH), 122.5 (CH), 129.0 (C), 131.8 (CH), 135.6 (CH), 136.0 (C), 137.3 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{24}N_2OI$ 423.0927, found 423.0941.

12-(*Z*)-Ethylidene-7-(methoxymethyl)-1,2,3,6-tetrahydro-2,66-ethanoazocino[4,3-*b*]indole (10). Method A. $Pd(PPh_3)_4$ (12 mg, 0.010 mmol) was added under Ar to a solution of amine **9** (45 mg, 0.107 mmol) in 1:1 THF−Et_3N (5 mL), and the mixture was heated at 90 °C in a sealed tube for 24 h. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was chromatographed (hexanes and 8:2 hexanes−AcOEt) to give **10** as a yellow oil: 10 mg (30%); ^1H NMR (400 MHz, assignment aided by gCOSY and gHSQC) δ 1.53 (d, J = 7.2 Hz, 3H, =CHC$\underline{H}_3$), 3.23 (s, 3H, OCH_3), 3.67 (d, J = 19.2 Hz, 1H, 3-H), 3.86 (dt, J = 19.2, 3, and 2.2 Hz, 1H, 3-H), 3.89 (d, J = 17.6 Hz, 1H, 13-H), 3.95 (d, J = 17.6 Hz, 1H, 13-H), 4.24 (d, J = 9.2 Hz, 1H, 6-H), 4.28 (d, J = 17.2 Hz, 1H, 1-H), 4.41 (d, J = 17.2 Hz, 1H, 1-H), 5.34 (qt, J = 7.2 and 2.2 Hz, 1H, =C$\underline{H}$CH$_3$), 5.45 (d, J = 11.6 Hz, 1H, OCH_2), 5.50 (d, J = 11.6 Hz, $\underline{1}$H, OCH_2), 5.59 (dt, J = 10.4 and 3 Hz, 1H, 4-H), 6.07 (ddt, J = 10.4, 9.2, and 3 Hz, 1H, 5-H), 7.08 (t, J = 7.6 Hz, 1H, 10-H), 7.16 (t, J = 7.6 Hz, 1H, 9-H), 7.36 (d, J = 8.4 Hz, 1H, 8-H), 7.39 (d, J = 8 Hz, 1H, 11-H); ^{13}C NMR (100.6 MHz, assignment aided by gHSQC) δ 13.0 (=CH$\underline{C}$H$_3$), 44.0 (CH, C-6), 52.5 (CH_2, C-1), 53.0 (CH_2, C-13), 56.0 ($O\underline{C}H_3$), 57.0 (CH_2, C-3), 73.5 (OCH_2), 109.0 (CH, C-8), 112.4 (C), 118.0 (CH, C-11), 118.5 (CH, =$\underline{C}$HCH$_3$), 120.0 (CH, C-10), 121.5 (CH, C-9), 127.0 (C), 129.0 ($\underline{C}$H, C-5), 132.0 (CH, C-4), 136.9 (C), 139.0 (C), 143.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{23}N_2O$ 295.1804, found 295.1803.

Method B. $Pd(OAc)_2$ (2 mg, 0.009 mmol), PPh_3 (7 mg, 0.027 mmol), and Ag_2CO_3 (50 mg, 0.18 mmol) were added under Ar to a solution of amine **9** (40 mg, 0.095 mmol) in 1:1 toluene−Et_3N (5 mL), and the resulting mixture was heated at 90 °C for 1 h 45 min. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was chromatographed (hexanes and 8:2 hexanes−EtOAc) to give **10**: 13 mg (46%).

2-(1-Methyl-2-(*E*)-butenyl)-1-(phenylsulfonyl)indole (11). *n*-BuLi (1.6 M in hexane, 5.83 mL, 9.33 mmol) was slowly added to a cooled (0 °C) solution of 1-(phenylsulfonyl)indole (2 g, 7.78 mmol) in THF (20 mL), and the solution was stirred at 0 °C for 2 h and then cooled to −78 °C. CuCN (0.84 g, 9.38 mmol) was added and the reaction mixture was allowed to warm to rt (2−3 h) and then cooled again to −78 °C. (*E*)-4-Chloro-2-pentene (0.98 g, 9.38 mmol) was added, and the stirring was continued at rt for 12 h. The reaction mixture was diluted with 20% NH_4OH and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (hexanes and 95:5 hexanes−AcOEt) to give indole **11** as an oil: 2.15 g (85%); IR (neat) 1448, 1367, 1173 cm^{-1}; ^1H NMR (400 MHz, signals due to a minor isomer are omitted) δ 1.45 (d, J = 6.8 Hz, 3H), 1.67 (d, J = 6.0 Hz, 3H), 4.34 (m, 1H), 5.52 (m, 1H), 5.66 (m, 1H), 6.49 (s, 1H), 7.24−7.50 (m, 6H), 7.72 (m, 2H), 8.23 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 17.9 (CH_3), 21.7 (CH_3), 35.0 (CH), 108.6 (CH), 115.3 (CH), 120.3 (CH), 123.7 (CH), 124.0 (CH), 124.9 (CH), 126.2 (2CH), 129.0 (2CH), 129.9 (C), 133.5 (CH), 134.0 (CH), 137.5 (C), 139.0 (C), 147.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{19}H_{20}NO_2S$ 326.1209, found 326.1212.

2-(1-Methyl-2-(*E*)-butenyl)-1-(phenylsulfonyl)indole-3-carbaldehyde (12). Indole **11** (1 g, 3.07 mmol) in CH_2Cl_2 (20 mL) was added to a cooled (− 78 °C) solution of $TiCl_4$ (1 M in CH_2Cl_2, 6.15 mL, 6.15 mmol) and Cl_2CHOCH_3 (0.55 mL, 6.15 mmol) in CH_2Cl_2 (10 mL), and the resulting mixture was stirred at −78 °C for 4 h. The reaction mixture was diluted with H_2O, basified with a saturated aqueous Na_2CO_3 solution, and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the residue was chromatographed (hexanes and 95:5 hexanes−AcOEt) to give aldehyde **12** as an amorphous solid: 0.83 g (76%); IR (film) 1666, 1449, 1382, 1174 cm^{-1}; ^1H NMR (400 MHz) δ 1.47 (d, J = 6.8 Hz, 3H), 1.61 (dm, J = 6.4 Hz, 3H), 4.76 (m, 1H), 5.40 (m, 1H), 5.61 (dm, J = 15 Hz, 1H), 7.37 (m, 2H), 7.49 (m, 2H), 7.62 (m, 1H), 7.82 (d, J = 7.8 Hz, 2H), 8.32 (m, 2H), 10.45 (s, 1H); ^{13}C NMR (100.6 MHz) δ 17.7 (CH_3), 22.5 (CH_3), 33.8 (CH), 114.7 (CH), 119.3 (C), 122.1 (CH), 125.2 (CH), 125.7 (CH), 125.9 (CH), 126.3 (C), 126.5 (2CH), 129.6 (2CH), 133.1 (CH), 134.4 (CH), 136.4 (C), 139.4 (C), 155.3 (C), 187.5 (CH); ESI-HRMS $[M + H]^+$ calcd for $C_{20}H_{20}NO_3S$ 354.1158, found 354.1165.

3-[*N*-Allyl-*N*-(*tert*-butoxycarbonyl)aminomethyl]-2-(1-methyl-2-(*E*)-butenyl)-1-(phenylsulfonyl)indole (13). Allylamine (0.21 mL, 2.83 mmol), $NaBH(OAc)_3$ (0.90 g, 4.25 mmol), and AcOH (0.08 mL, 1.41 mmol) were successively added to aldehyde **12** (0.50 g, 1.41 mmol) in CH_2Cl_2 (17 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH_2Cl_2 and 10% aqueous Na_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the crude secondary amine (540 mg). This compound was dissolved in MeOH (5 mL) and treated with $(t\text{-BuOCO})_2O$ (0.54 g, 2.47 mmol) and Et_3N (0.70 mL, 4.94 mmol). After the mixture was heated at reflux for 5 h, the solvent was removed, and the residue was diluted with CH_2Cl_2 and washed with 2 N HCl and brine. The organic extracts were dried and concentrated to give the crude product. After chromatography (hexanes and 95:5 hexanes−AcOEt) diene **13** was obtained as a pale yellow oil: 0.63 g (90%); IR (film) 1690, 1450, 1368, 1173 cm^{-1}; ^1H NMR (400 MHz) δ 1.21 (d, J = 7.2 Hz, 3H), 1.42 (s, 9H), 1.52 (d, J = 6.4 Hz, 3H), 3.38 (br s, 2H), 4.44 (m, 1H), 4.57 (m, 2H), 4.83 (dd, J = 17.2 and 1.5 Hz, 1H), 4.92 (dd, J = 10.4 and 1.5 Hz, 1H), 5.28 (m, 1H), 5.44 (dm, J = 15.2 Hz, 1H), 5.50 (m, 1H), 7.20 (m, 2H), 7.32 (m, J = 2H), 7.43 (m, 2H), 7.60 (dm, J = 8.4 Hz, 2H), 8.18 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100.6 MHz) δ 18.1 (CH_3), 20.1 (CH_3), 28.6 ($3CH_3$), 33.5 (CH), 40.0 (CH_2), 46.8 (CH_2), 80.1 (C), 115.4 (CH_2), 115.6 (CH), 117.2 (C), 119.7 (CH), 123.9 (CH), 124.7 (CH), 125.2 (CH), 126.5 (2CH), 129.2 (C), 129.3 (2CH), 132.8 (CH), 133.8 (CH), 133.9 (CH), 137.1 (C), 139.7 (C), 142.9 (C), 156.1 (CO); ESI-HRMS $[M + Na]^+$ calcd for $C_{28}H_{34}N_2O_4NaS$ 517.2131, found 517.2144.

2-(*tert*-Butoxycarbonyl)-6-methyl-7-(phenylsulfonyl)-1,2,3,6-tetrahydroazocino[4,3-*b*]indole (14). The second-generation Grubbs catalyst (24 mg, 7 mol %) was added under Ar to a solution of diene **13** (200 mg, 0.40 mmol) in CH_2Cl_2 (5.7 mL), and the resulting mixture was heated at reflux for 4.5 h. The reaction mixture was concentrated, and the residue was chromatographed (9:1 hexanes−AcOEt) to give azocinoindole **14** as a white foam: 146 mg (80%); IR (KBr) 1689, 1450, 1370, 1172 cm^{-1} ^1H NMR (400 MHz, assignments aided by gHSQC and ^1H gCOSY, mixture of rotamers) δ 1.42 (br s, 9H, Boc), 1.47 (br s, 3H, CH_3), 2.85 (m, 1H, 3-H), 3.81 and 4.03 (2m, 1H, 3-H), 4.37 (br s, 1H, 1-H), 4.65 (m, 1H, 6-H), 4.89 and 5.01 (2m, 1H, 1-H), 5.44 (br s, 1H, 4-H), 5.80 (br d, J = 11 Hz, 1H, 5-H), 7.29 (m, 3H), 7.38 (t, J = 7.6 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.67 (d, J = 7.6 Hz, 2H), 8.28 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100.6 MHz, assignments aided by gHSQC) δ 24.3 (CH_3), 28.4 ($3CH_3$), 32.5 (CH, C-6), 37.0 (CH_2, C-1), 38.0 (CH_2, C-3), 79.90 (C), 115.6

(CH, C-8), 118.7 (CH, C-11), 118.9 (C), 121.0 (CH, C-4), 123.8 (CH, C-10), 124.8 (CH, C-9), 126.0 (2CH, Ph), 129.2 (2CH, Ph), 130.8 (C), 133.8 (CH, Ph), 136.9 (C), 137.6 (CH, C-5), 138.8 (C), 142.2 (C), 155.0 (CO); ESI-HRMS $[M + H]^+$ calcd for $C_{25}H_{29}N_2O_4S$ 453.1842, found 453.1851; $[M + Na]^+$ calcd for $C_{25}H_{28}N_2O_4NaS$ 475.1662, found 475.1670.

Methyl 3-[*N*-(2-Bromo-2-propenyl)-*N*-(*tert*-butoxycarbonyl)-aminomethyl]indole-2-carboxylate (24). A solution of methyl 3-formylindole-2-carboxylate (**23**, 2.34 g, 11.52 mmol), 2-bromo-2-propenylamine (1.88 g, 13.82 mmol), $NaBH(OAc)_3$ (7.32 g, 35.0 mmol), and AcOH (1.32 mL, 23.0 mmol) in anhydrous CH_2Cl_2 (100 mL) was stirred at rt overnight. The reaction mixture was washed with a saturated aqueous Na_2CO_3 solution. The solvent was removed, and the resulting residue (3.72 g, crude secondary amine) was dissolved in anhydrous dioxane (100 mL) and treated with $(t\text{-BuOCO})_2O$ (3.92 g, 17.96 mmol) at rt overnight. The reaction mixture was diluted with H_2O and concentrated. The residue was partitioned between Et_2O and brine and extracted with Et_2O. The organic extracts were dried and concentrated and the crude product was chromatographed (85:15 hexanes−AcOEt) to give **24** as a white solid: 3.71 g (76%); ^{1}H NMR (300 MHz, major rotamer) δ 1.49 (s, 9H), 3.89 (s, 2H), 3.96 (s, 3H), 5.11 (s, 2H), 5.49 (s, 1H), 5.57 (s, 1H), 7.16 (ddd, J = 1.5, 6.6, 8.1 Hz, 1H), 7.35 (t, J = 8.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (100.6 MHz, major rotamer) δ 28.2 (CH_3), 39.1 (CH_2), 52.0 (CH_3), 52.6 (CH_2), 80.2 (C), 111.7 (CH), 115.1 (CH_2), 118.8 (C), 120.8 (CH), 122.0 (CH), 124.8 (C), 125.9 (CH), 127.6 (C), 129.6 (C), 136.0 (C), 155.2 (C), 162.6 (C); ESI-HRMS $[M + Na]^+$ calcd for $C_{19}H_{23}BrN_2NaO_4$ 445.0733, found 445.0738. Anal. Calcd for $C_{19}H_{23}BrN_2O_4$: C, 53.91; H, 5.48; N, 6.62. Found: C, 53.85; H, 5.46; N, 6.56.

***Se*-Phenyl 3-[*N*-(2-Bromo-2-propenyl)-*N*-(*tert*-butoxycarbonyl)aminomethyl]-indole-2-carboselenoate (25).** A solution of carboxylic ester **24** (2.30 g, 5.44 mmol) and $LiOH \cdot H_2O$ (0.27 g, 6.43 mmol) in a 3:1 mixture of THF−H_2O (45 mL) was stirred at 65 °C overnight. The reaction mixture was concentrated, acidified with 1 N HCl, and extracted with CH_2Cl_2. The combined organic extracts were dried and concentrated to give the crude carboxylic acid (2.20 g). A suspension of this material in anhydrous CH_2Cl_2 (40 mL) was treated with Et_3N (1.50 mL, 10.88 mmol). After 15 min at rt, the mixture was concentrated to give the corresponding triethylammonium salt. In another flask, tributylphosphine (6.70 mL, 27.16 mmol) was added under Ar to a solution of PhSeCl (5.20 g, 27.16 mmol) in anhydrous THF (40 mL) and the mixture was stirred at rt for 10 min (yellow solution). The above triethylammonium salt in THF (40 mL) was added to this solution, and the resulting mixture was stirred overnight. The reaction mixture was partitioned between Et_2O and H_2O and extracted with Et_2O. The organic extracts were dried and concentrated and the crude product was chromatographed (hexanes and 9:1 hexanes−AcOEt) to give **25** as a yellow solid: 2.68 g (90%); ^{1}H NMR (300 MHz, major rotamer) δ 1.51 (s, 9H), 3.93 (s, 2H), 5.13 (s, 2H), 5.44 (s, 1H), 5.54 (s, 1H), 7.18 (m, 1H), 7.39 (m, 2H), 7.46 (m, 3H), 7.62 (m, 2H), 7.94 (d, J = 7.8 Hz, 1H), 8.83 (s, 1H); ^{13}C NMR (75.4 MHz, major rotamer) δ 28.3 (CH_3), 39.8 (CH_2), 53.0 (CH_2), 80.5 (C), 112.1 (CH), 115.8 (CH_2), 118.4 (C), 121.3 (CH), 122.4 (CH), 125.0 (C), 126.8 (CH), 127.8 (C), 129.4 (CH), 129.5 (CH), 132.8 (C), 136.3 (CH), 136.4 (C), 155.2 (C), 184.1 (C), (one missing quaternary carbon); HRMS $[M + Na]^+$ calcd for $C_{24}H_{25}BrN_2NaO_3Se$ 571.0105, found 571.0102. Anal. Calcd for $C_{24}H_{25}BrN_2O_3Se$: C, 52.57; H, 4.60; N, 5.11. Found: C, 52.57; H, 4.52; N, 5.11.

2-(*tert*-Butoxycarbonyl)-6-oxo-1,2,3,4,5,6-hexahydroazocino-[4,3-*b*]indole (26). *n*-Bu_3SnH (2.50 mL, 9.42 mmol) and Et_3B (1 M in hexanes, 9.50 mmol) were added to a solution of phenyl selenoester **25** (2.07 g, 3.78 mmol, previously dried azeotropically with anhydrous C_6H_6) in anhydrous C_6H_6 (135 mL). The reaction mixture was stirred at rt for 2 h with dry air constantly supplied by passing compressed air through a short tube of Drierite. Then, additional *n*-Bu_3SnH (0.50 mL, 1.89 mmol) and Et_3B (1 M in hexanes, 1.90 mmol) were added, and the reaction mixture was stirred under dry air at rt for 2 h. The reaction mixture was concentrated, and the resulting residue was partitioned between hexanes and acetonitrile. The polar layer was washed with hexanes and concentrated to give the crude product. Flash chromatography (8:2 hexanes−AcOEt) gave ketone **26** as an orange solid: 0.64 g (54%); ^{1}H NMR (400 MHz, assignment aided by gHSQC, mixture of rotamers) δ 1.30 and 1.50 (2s, 9H, Me), 1.96 and 2.04 (2m, 2H, 4-H), 2.97 (m, 2H, 5-H), 3.48 and 3.62 (2m, 2H, 3-H), 4.88 and 5.01 (2s, 2H, 1-H), 7.16 (t, J = 7.2 Hz, 1H, 10-H), 7.35 (ddd, J = 8.4, 7.2, 0.9 Hz, 1H, 9-H), 7.41 (d, J = 8.4 Hz, 1H, 8-H), [7.72 (d, J = 8.4 Hz), and 7.77 (d, J = 8 Hz), 1H, 11-H], 9.42 and 9.47 (2s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, gHSQC, mixture of rotamers) δ 23.9 and 25.1 (CH_2, C-4), 28.3 (CH_3), 38.7 and 39.5 (CH_2, C-5), 42.5 and 42.6 (CH_2, C-1), 43.0 and 46.1 (CH_2, C-3), 80.3 (C), 112.1 (CH, C-8), 117.3 and 119.3 (C), 120.3 and 120.7 (CH, C-10), 120.9 (CH, C-11), 126.4 and 126.6 (CH, C-9), 127.5 and 127.8 (C), 132.7 and 133.9 (C), 135.8 and 136.0 (C), 155.1 and 155.2 (C), 192.7 and 193.4 (C); ESI-HRMS $[M + Na]^+$ calcd for $C_{18}H_{22}N_2NaO_3$ 337.1522, found 337.1524. Anal. Calcd for $C_{18}H_{22}N_2O_3.1/2\ H_2O$ C, 66.85; H, 7,17; N, 8.66. Found: C, 67.24; H, 7.00; N, 8.33.

2-(*tert*-Butoxycarbonyl)-6-methyl-1,2,3,4-tetrahydroazocino-[4,3-*b*]indole (15). From Azocinoindole 14. *t*-BuOK (0.55 g, 4.90 mmol) was added to a solution of **14** (0.22 g, 0.49 mmol) in THF (14 mL), and the resulting solution was heated at reflux for 48 h. The reaction mixture was partitioned between a saturated aqueous NH_4Cl solution and Et_2O and extracted with Et_2O. The organic extracts were dried and concentrated to give azocinoindole **15** as a yellow foam: 138 mg (90%). An analytical sample was obtained by chromatography (hexanes and 8:2 hexanes−AcOEt); IR (film) 3321, 1670 cm^{-1}; ^{1}H NMR (400 MHz, assignments aided by gHSQC, mixture of rotamers) δ 1.35 and 1.45 (2s, 9H, Boc), 2.13 (s, 3H, CH_3), 2.37 (m, 2H, 4-H), 3.60 (m, 2H, 3-H), 4.64 (br s, 2H, 1-H), 5.69 and 5.75 (2t, J = 8 Hz, 1H, 5-H), 7.15 (m, 2H, 9-H, 10-H), 7.28 and 7.31 (2 d, J = 8 Hz, 1H, 8-H), 7.56 and 7.62 (2d, J = 8 Hz, 1H, 11-H), 7.85 and 7.89 (2 br s, 1H, NH); ^{13}C NMR (100.6 MHz, assignments aided by gHSQC,) δ 22.7 and 22.8 (CH_3), 28.4 and 28.5 ($3CH_3$, Boc), 28.7 (CH_2, C-4), 43.4 and 43.5 (CH_2, C-1), 46.0 and 46.7 (CH_2, C-3), 79.1 and 79.3 (C), 110.3 and 110.4 (CH, C-8), 110.8 and 111.0 (C), 118.5 and 119.0 (CH, C-11), 119.3 and 119.4 (CH, C-10), 122.1 and 122.2 (CH, C-9), 126.5 and 127.1 (CH, C-5), 127.2 and 127.3 (C), 128.9 and 129.5 (C), 132.8 and 133.4 (C), 135.7 and 135.9 (C), 156.1 and 156.5 (C); ESI-HRMS calcd for $C_{19}H_{24}N_2O_2$ 312.1837, found 312.1837.

From Ketone 26. Ketone **26** (0.52 g, 1.66 mmol) in anhydrous THF (35 mL) was added under Ar to a cooled (−10 °C) solution of MeLi (1.6 M in Et_2O, 10.40 mL, 16.60 mmol) in anhydrous THF (35 mL). After stirring at rt for 2 h, the reaction mixture was quenched with ice−water and extracted with AcOEt. Concentration of the organic extracts gave the crude carbinol (0.45 g). *p*-Toluenesulfonic acid monohydrate (25 mg, 0.13 mmol) was added to a suspension of the above material in acetonitrile (25 mL), and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated, and the resulting residue was dissolved in CH_2Cl_2 and washed with a saturated aqueous Na_2CO_3 solution. Concentration of the organic solution gave **15**: 0.36 g (70%).

2-(2-Iodo-2-(*Z*)-butenyl)-6-methyl-1,2,3,4-tetrahydroazocino-[4,3-*b*]indole (27). A solution of carbamate **15** (224 mg, 0.72 mmol) in 1.2 M HCl in MeOH (3.2 mL) was stirred at rt for 4.5 h. 20% NH_4OH was added and the organic solvent was removed. The residue was partitioned between CH_2Cl_2 and H_2O

and extracted with CH_2Cl_2. The organic extracts were dried and concentrated to give the secondary amine (127 mg), which was directly used in the next step. Diisopropylethylamine (0.15 mL, 0.89 mmol) and (*Z*)-2-iodo-2-butenyl tosylate[15a,16c] (230 mg, 0.65 mmol) were added to a solution of the above amine (127 mg, 0.59 mmol) in 1:1 CH_2Cl_2−acetonitrile (21 mL). After the reaction mixture was stirred at rt for 2 h, $MeNH_2$ (2 M in MeOH, 1.5 mL, 3 mmol) was added and the stirring was continued for 1 h. The reaction mixture was diluted with CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$ solution. The organic solution was dried and concentrated, and the residue was chromatographed (hexanes and 9:1 hexanes−EtOAc) to give pure tertiary amine **27** (yellow oil): 70 mg (30%); IR (film) 3408, 2923, 1612, 1460, 742 cm^{-1}; ^1H NMR (400 MHz) δ 1.79 (dd, J = 6.2 and 1.2 Hz, 3H), 2.11 (s, 3H), 2.14 (br s, 2H), 2.77 (br s, 2H), 3.35 (br s, 2H), 3.99 (br s, 2H), 5.81 (q, J = 6.2 Hz, 1H), 5.85 (t, J = 7.8 Hz, 1H), 7.15 (m, 2H), 7.33 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.95 (br s, 1H); ^{13}C NMR (100.6 MHz) δ 21.7 (CH_3), 22.5 (CH_3), 26.0 (CH_2), 48.0 (CH_2), 50.6 (CH_2), 65.3 (CH_2), 110.1 (C), 110.5 (CH), 110.6 (C), 118.9 (CH), 119.5 (CH), 121.9 (CH), 126.9 (C), 128.8 (C), 130.0 (CH), 131.3 (CH), 135.8 (C), 136.1 (C); ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{22}IN_2$ 393.0822, found 393.0831.

(±)-Apparicine. $Pd(OAc)_2$ (7.6 mg, 0.034 mmol), PPh_3 (26 mg, 0.10 mmol) and Ag_2CO_3 (93 mg, 0.34 mmol) were added under Ar to a solution of amine **27** (65 mg, 0.17 mmol) in 1:1 toluene−Et_3N (17 mL) and the mixture was heated at 80 °C for 1.5 h. The solvent was removed, and the residue was partitioned between CH_2Cl_2 and a saturated aqueous $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (SiO_2, flash, CH_2Cl_2 to 9:1 CH_2Cl_2−MeOH). An additional chromatography (SiO_2, 0.5% Et_2O−diethylamine) gave pure (±)-apparicine as an amorphous solid: 6.6 mg (15%); ^1H NMR ($CDCl_3$, 400 MHz, assignments aided by gHSQC) δ 1.46 (dd, J = 6.8 and 2.4 Hz, 3H, 18-H), 1.89 (ddt, J = 13.6, 6.8, and 2.4 Hz, 1H, 14-H), 2.16 (dddd, J = 13.6, 11.2, 8, and 5.6 Hz, 1H, 14-H), 3.07 (dddd, J = 13.2, 11.2, 6.8, and 1.2 Hz, 1H, 3-H), 3.20 (d, J = 16 Hz, 1H, 21-H), 3.42 (ddd, J = 13.2, 8, and 2 Hz, 1H, 3-H), 3.82 (dt, J = 16 and 2 Hz, 1H, 21-H), 3.92 (broad s, 1H, 15-H), 4.28 (d, J = 17.8 Hz, 1H, 6-H), 4.51 (d, J = 17.8 Hz, 1H, 6-H), 5.25 (q, J = 6.8 Hz, 1H, 19-H), 5.26 (s, 1H, 17-H), 5.39 (s, 1H, 17-H), 7.06 (ddd, J = 7.6, 7.2, and 1.2 Hz, 1H, 10-H), 7.18 (ddd, J = 8, 7.2, and 1.2 Hz, 1H, 11-H), 7.28 (d, J = 8 Hz, 1H, 12-H), 7.42 (d, J = 7.6 Hz, 1H, 9-H), 7.84 (broad s, 1H, NH); ^{13}C NMR ($CDCl_3$, 100.6 MHz, assignment aided by gHSQC) δ 12.6 (CH_3, C-18), 29.6 (CH_2, C-14), 41.2 (CH, C-15), 45.3 (CH_2, C-3), 54.2 (CH_2, C-6), 54.3 (CH_2, C-21), 110.2 (CH, C-12), 111.5 (C, C-7), 112.2 (CH_2, C-17), 118.6 (CH, C-9), 119.3 (CH, C-10), 120.1 (CH, C-19), 123.0 (CH, C-11), 129.0 (C, C-8), 131.3 (C, C-20), 135.6 (C, C-16), 137.4 (C, C-13), 145.2 (C, C-2); ESI-HRMS $[M + H]^+$ calcd for $C_{18}H_{21}N_2$ 265.1699, found 265.1705.

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Supporting Information Available: General protocols, additional experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.