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,3 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 20E-ethylidene) substituents.4 The same arrangement was also found in vallesamine5 and later in a small number of alkaloids, including 16(S)-hydroxy-16,22-dihydroapparicine6 or ervaticine,7 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 itself10 and, more

![Figure 1](image-url)

**FIGURE 1.** Apparicine and related alkaloids.

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recently, pericline (subincanadine E) \(^{11}\) have been transformed in vitro into the respective C-5 nor-alkaloids (vallesamine and apparine) by treatment of the N-oxides with trifluoroacetic anhydride (modified Polonovski reaction).\(^{12}\)

**SCHEME 1. Biosynthesis of Apparicine Alkaloids**

Their synthetically challenging structures make apparine 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 apparine (i.e., 20-deethylideneervatine) but proved unsuitable for the total synthesis of the alkaloid.\(^{13}\)

We envisaged apparine 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 ethylideneethanone 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 20ε-ethylidene and (when R² = 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,\(^ {16}\) minfensine,\(^ {17}\) apogeissoschizene,\(^ {18}\) and ervitine.\(^ {19}\) 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 and our own work on RCM of indole-containing dienes\(^ {22}\) 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-indolylacetyl radical cyclization\(^ {23}\) and manipulation of the resulting ketone was also investigated.\(^ {24}\) This Article deals with the development of the above indole annulation chemistry and its application to complete the first total synthesis of (+)-apparicine.\(^ {25}\)

**Results and Discussion**

**Initial Studies.** We set out to study the indole-templated RCM en route to apparine, directly targeting 6-methylazocino[4,3-\(\epsilon\)]indoles (A, R² = 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


\(^{(24)}\) For a preliminary approach to apparine ABC substructures, see: (a) Street, J. D.; Harris, M.; Bishop, D. I.; Hazlett, E.; Beddows, R. L.; Mills, O. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans.* 1987, 1599–1606. (b) See also ref 13b.

\(^{(25)}\) For a previous different approach to apparine ABC substructures, see: (a) Street, J. D.; Harris, M.; Bishop, D. I.; Hazlett, E.; Beddows, R. L.; Mills, O. S.; Joule, J. A. *J. Chem. Soc., Perkin Trans.* 1987, 1599–1606. (b) See also ref 13b.
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\(_2\)Cl\(_2\) 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. Azepinoindoles 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

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\[\begin{align*}
\text{(1)} & \quad \text{CHO} & \quad \text{Pd(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}} & \quad \text{SnBu\textsubscript{3}} & \quad \text{DMF, 85 °C} \\
\text{MOM} & \quad \text{El} & \quad \text{EtNBr} \\
\text{N} & \quad \text{Cl} \\
\text{CHO} & \quad \text{NaBH(OAc)\textsubscript{3}} & \quad \text{AcOH, CH\(_2\)Cl\(_2\), rt} \\
\text{MOM} & \quad \text{CHO} & \quad \text{2 (80%)} \\
\text{N} & \quad \text{R} & \quad \text{B} & \quad \text{Cl} & \quad \text{PCy\textsubscript{3}} \\
\text{MOM} & \quad \text{CHO} & \quad \text{1. H\(_2\)N\textsubscript{2} + NaBH(OAc)\textsubscript{3}} & \quad \text{AcOH, CH\(_2\)Cl\(_2\), rt} \\
\text{N} & \quad \text{R} & \quad \text{B} & \quad \text{2. (t-BuOCOC\textsubscript{2})\textsubscript{2}O} & \quad \text{MeOH, Et\(_3\)N, reflux or TsCl, CH\(_2\)Cl\(_2\), Et\(_3\)N, rt} \\
\text{MOM} & \quad \text{CHO} & \quad \text{2 (65%) (R = Boc)} & \quad \text{3b (60%) (R = Ts)} \\
\text{N} & \quad \text{R} & \quad \text{B} & \quad \text{Cl} & \quad \text{PCy\textsubscript{3}} \\
\text{MOM} & \quad \text{CHO} & \quad \text{1. H\(_2\)N\textsubscript{2} + NaBH(OAc)\textsubscript{3}} & \quad \text{AcOH, CH\(_2\)Cl\(_2\), rt} \\
\text{N} & \quad \text{R} & \quad \text{B} & \quad \text{2. (t-BuOCOC\textsubscript{2})\textsubscript{2}O} & \quad \text{MeOH, Et\(_3\)N, reflux or TsCl, CH\(_2\)Cl\(_2\), Et\(_3\)N, rt} \\
\text{MOM} & \quad \text{CHO} & \quad \text{2 (65%) (R = Boc)} & \quad \text{3b (60%) (R = Ts)} \\
\text{N} & \quad \text{R} & \quad \text{B} & \quad \text{Cl} & \quad \text{PCy\textsubscript{3}}
\end{align*}\]
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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 azocinonoindoles 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.

SCHEME 4. Studies in the 6-Demethyl Series

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\[\begin{align*}
\end{align*}\]
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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)\(_2\),...


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K₂CO₃, TBACl, HCO₂Na, DMF, 80 °C] previously used by Overman¹⁷ on a related substrate was N-dealkylation. After this unsuccessful result, a variety of palladium precatalysts [Pd(OAc)₂, Pd(PPh₃)₄, Pd₂(dba)₃], ligands (PPh₃, dppe), and cosolvents (toluene, CH₃CN, THF) were examined in the presence of Et₃N 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 ethyldiene configuration.³⁰ The yield of 10 was raised to 30% on exposure of 9 to Pd(PPh₃)₄ in 1:1 THF–Et₃N in a sealed tube at 90 °C for 24 h. On the other hand, under cationic conditions [Pd(OAc)₂, PPh₃, Ag₂CO₃, 1:1 toluene–Et₃N, 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 HCO₂Na as the reductant or KCN, K₃[Fe(CN)₆], TMSCN, or tributylvinylstannane as trapping agents.

SCHEME 5

The formation of unusual Heck cyclization products like 10 has been previously observed³¹ and rationalized³² by considering that the initial 6-exo cyclization is followed by an intramolecular carbbopalladation on the exocyclic alkene. The resulting cyclopropane intermediate would undergo rearrangement, with concomitant inversion of the alkene geometry, and final β-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 the synthesis of the Heck precursor would now require an additional isomerization step of the resulting double bond.

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

Attention was then focused on the isomerization step. Considering recent reports on alkene isomerizations mediated
by suitably modified ruthenium-metathesis catalysts, 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, a slow isomerization of the double bond took place to its N-conjugated counterpart (3,4-position), providing the ene-carbamate 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 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, 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.

**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 apparicaine 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. 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 H2SO4 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 keto (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-indolylacryl radical upon an amino tethered alkene. 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. 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 phenylenelation through the corresponding carboxylic acid. Treatment of selenoester 25 with n-Bu3SnH as the radical mediator and Et3B 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, CH3CN, 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.

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Although loss of material was still extensive. Thus, when the catalysts, and additives, resulting only in the recovery of the starting material or decomposition products. However, the frameworks with concomitant incorporation of the exocyclic secondary amine proved to be highly unstable and was secondary subjected to reaction 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.

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$_2$CO$_3$ (2 equiv) in 1:1 toluene–Et$_3$N at 80 ºC for a short reaction time (1.5 h), apparicine was obtained in a consistent, reproducible 15% isolated yield. The $^1$H and $^{13}$C NMR spectroscopic data of synthetic apparicine essentially matched those described in the literature for the natural product. The chromatographic (TLC) behavior of synthetic apparicine was identical to an authentic sample.

**Conclusion**

In summary, the first total synthesis of (+)-apparicine has been accomplished by employing a concise route involving a vinyl halide Heck cyclization to close the bridged piperidine ring in the last synthetic step. The key azocinoidole 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 keto–alkene functional group interconversion.

**Experimental Section**

2-Isopropenyl-1-(methoxymethyl)indole-3-carbaldehyde (2). Tetraethylammonium bromide (0.42 g, 2.01 mmol), Bu$_3$SnCH$_2$CH$_2$CHO (1.33 g, 4.02 mmol), and Pd(PPh$_3$)$_2$Cl$_2$ (42 mg, 0.06 mmol) were successively added to a solution of aldehyde 1 (0.45 g, 2.01 mmol) in DMF (30 mL), and the mixture was stirred at 85 ºC 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 an oil: 0.37 g (65%); IR (film) 3057, 2934, 1663 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 2.25 (s, 3H), 3.31 (s, 3H), 5.25 (s, 1H), 5.44 (s, 2H), 5.76 (s, 1H), 7.33 (m, 2H), 7.49 (d, $J = 7.5$ Hz, 1H), 8.35 (d, $J = 7.5$ Hz, 1H), 10.0 (s, 1H); $^{13}$C NMR (CDCl$_3$, 100.6 MHz) $\delta$ 50.3 (CH$_3$), 57.2 (CH$_2$), 110.4 (C), 115.2 (C), 122.1 (CH$_3$), 123.4 (CH), 123.9 (CH$_2$), 124.2 (C), 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)$_2$ (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$_2$Cl$_2$ (10 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH$_2$Cl$_2$ and 10% aqueous Na$_2$CO$_3$ and extracted with CH$_2$Cl$_2$. 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-BuO)$_2$CO (0.45 g, 2.06 mmol) and Et$_3$N (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$_2$Cl$_2$ 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$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 1.53 (br s, 9H), 2.12 (s, 3H), 2.13 (m, 2H), 3.10 (m, 2H), 3.26 (s, 3H), 4.66 (s, 1H), 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,

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7a. The organic solution was stirred at rt overnight. The reaction mixture was partitioned between CH₂Cl₂ and brine. The organic solution was dried and concentrated, and the resulting residue was chromatographed (91-hexanes – AcOEt) to give sulfonamide 7a as a pale yellow solid: 0.29 g (60%); mp 131.0-132.0 °C.

1H NMR (400 MHz)  $\delta$ 7.85 (1H, J = 7.6 Hz, 1H), 7.75 (m, 1H), 7.45 (br m, 1H); 13 C NMR (100.6 MHz)  $\delta$ 120.4 (CH), 121.5 (CH), 122.4 (CH), 122.5 (CH), 127.9 (C), 135.5 (CH), 136.3 (C), 141.3 (C), 155.7 (C); ESI-HRMS [M + H]$^+$ calculated for C₂₂H₃₀N₂O₃Na 393.2139, found 393.2136.

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 (91-hexanes – AcOEt) to give secondary amine 8a as a pale yellow solid: 0.29 g (60%); mp 131.0-132.0 °C.

1H NMR (400 MHz)  $\delta$ 1.74 (m, 2H), 2.30 (m, 2H), 2.37 (s, 3H), 3.16 (s, 3H), 3.36 (m, 2H), 4.50 (d, $J = 8$ Hz, 2H), 5.30 (s, 2H, CH₂), 6.07 (m, 1H), 6.58 (d, $J = 11$ Hz, 1H); 13 C NMR (100.6 MHz)  $\delta$ 12.5 (CH₂), 79.4 (C), 109.4 (CH), 110.8 (C), 119.6 (CH, C-10), 120.6 (CH, C-9), 122.5 (CH, C-8), 127.0 (C), 132.5 (CH, C-5), 136.2 (C), 137.4 (C), 138.0 (C), 138.4 (C), 139.5 (C), 139.7 (C), 143.2 (C). Anal. Calcd for C₂₄H₂₈N₂O₃S: C, 67.80; H, 6.63; N, 6.58; S, 7.68.

7-(Methoxymethyl)-2-tert-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 CH₂Cl₂ (30 mL), and the resulting mixture was heated at reflux overnight. The reaction mixture was concentrated, and the residue was chromatographed (82-hexanes – AcOEt) to give azocinoindole 8b as a white solid: 103 mg (65%); mp 154-155 °C (Et₂O); IR (film) 1696 cm⁻¹, 1330, 1462 cm⁻¹. 1H NMR (400 MHz)  $\delta$ 7.88 (1H, J = 7.5 Hz, 1H), 7.75 (d, $J = 18$ Hz, 1H), 7.22 (m, 1H, 5-H), 7.35 and 7.39 (2d, $J = 12$ Hz, 1H, 8-H), 7.56 and 7.70 (2, J = 8 Hz, 1H, 11-H); 13 C NMR (100.6 MHz) assignments aided by gHSQC, major rotamer)  $\delta$ 28.4 (CH₂, 28.6 (CH₂, C-4), 43.2 (CH₂, C-2), 45.8 (CH₂, C-3), 55.4 (CH₂), 73.8 (CH₂), 79.4 (C), 109.2 (CH, C-8), 112.3 (C), 116.7 (C), 118.7 (C, C-11), 119.8 (CH, C-10), 120.6 (CH, C-9), 122.5 (CH, C-8), 127.0 (C), 132.5 (CH, C-5), 136.2 (C), 137.4 (C), 156.2 (C); ESI-HRMS [M + H]$^+$ calculated for C₂₉H₂₈N₂O₃Na 434.1606, found 434.1605; [M + Na]$^+$ calculated for C₃₀H₃₀N₂O₃Na 365.1835, found 365.1837.

2-(2-Iodo-2-(Z)-butenyl)-7-(methoxymethyl)-1,2,3,4-tetrahydroazocino[4,3-b]-indole (8c). 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% NaOH solution, and the residue was partitioned between CH₂Cl₂ and H₂O and extracted with CH₂Cl₂. The organic extracts were dried and concentrated to give the crude secondary amine (0.18 g), K₂CO₃ (0.16 g, 1.15 mmol) and (Z)-2-ido-2-butenyl tosylate ¹⁵Na¹²C (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 Et₂O and washed with H₂O. The organic solution was dried and concentrated to give the crude product. After chromatography

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(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); 13C NMR (100.6 MHz) δ 21.7 (CH3), 26.9 (CH2), 47.6 (CH2), 49.5 (CH3), 55.9 (CH3), 65.4 (CH2), 74.5 (CH2), 109.4 (CH3), 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 C16H24N2O2 326.1209, found 326.1212.

2-(1-Methyl-2-(E)-butenyl)-1-(phenylsulfonyl)indole-3-carbalde

hyde (12). Indole 11 (1 g, 3.07 mmol) in CH2Cl2 (20 mL) was added to a cooled (−78 °C) solution of TiCl4 (1 M in CH2Cl2, 6.15 mL, 6.15 mmol) and Cl3CHOCH (0.55 mL, 6.15 mmol) in CH2Cl2 (10 mL), and the resulting mixture was stirred at −78 °C for 4 h. The reaction mixture was diluted with H2O, basified with a saturated aqueous Na2CO3 solution, and extracted with CH2Cl2. 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); 13C NMR (100.6 MHz) δ 17.7 (CH3), 22.5 (CH2), 33.8 (CH), 114.7 (CH), 119.3 (C), 122.1 (CH2), 125.2 (CH), 125.7 (CH), 125.9 (CH), 126.3 (C), 126.5 (C), 129.6 (2CH), 133.3 (CH), 134.4 (CH), 136.4 (C), 139.4 (C), 155.3 (C), 187.5 (CH); ESI-HRMS [M + H]+ calcd for C16H24N2O2Na 354.1158, found 354.1165.

3-[N-Allen-V-(tert-butoxycarbonyl)aminomethyl]-2-(1-methyl-2-(E)-butenyl)-1-(phenylsulfonyl)indole (13). Allylamine (0.21 mL, 2.83 mmol), NaBH(OAc)2 (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 CH2Cl2 (17 mL), and the resulting mixture was stirred at rt overnight. The reaction mixture was partitioned between CH2Cl2 and 10% aqueous Na2CO3 and extracted with CH2Cl2. 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-BuOCO)2O (0.54 g, 2.77 mmol) and Et3N (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 CH2Cl2 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 2.12 (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 = 7.4 Hz, 2H), 7.43 (m, 2H), 7.60 (dm, J = 8.4 Hz, 2H); 13C NMR (100.6 MHz) δ 18.1 (CH2), 21.7 (CH3), 28.6 (CH3), 33.5 (CH3), 40.0 (CH2), 46.8 (CH2), 80.1 (C), 115.4 (CH), 115.6 (CH2), 117.2 (C), 119.7 (CH), 122.9 (CH2), 124.7 (CH2), 125.2 (CH2), 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 C28H34N6O11Na 571.2311, found 571.2144.

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 CH2Cl2 (5.7 mL), and the resulting mixture was heated at reflux for 4.5 h. The reaction mixture was concentrated, and the crude was chromatographed (9:1 hexanes−AcOEt) to give azocinonide 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 gH COSY, mixtures of rotamers) δ 1.42 (br s, 9H, Boc), 1.47 (br s, 3H, CH2O), 2.85 (m, 1H, 3-CH), 3.81 and 4.03 (2m, 1H, 3-CH), 4.37 (br s, 1H, 1-H), 4.65 (m, 1H, 6-CH), 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), 8.26 (d, J = 7.8 Hz, 1H); 13C NMR (100.6 MHz, assignments aided by gHSQC) δ 24.3 (CH2), 28.4 (CH3), 32.5 (CH2-C), 37.0 (CH2-C), 38.0 (CH2-C), 79.90 (C), 115.6
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(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 + Na\]^+\ calculated for C_{23}H_{25}BrN_2NaO_4 453.1842, found 453.1851; [M + Na\]^+\ calculated for C_{23}H_{25}BrN_2NaO_4NaS 475.1662, found 475.1670.

**Methyl 1-(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)\_2 (7.32 g, 35.0 mmol), and AcOH (1.32 mL, 23.0 mmol) in anhydrous CH\_2\_CL (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 (crude secondary amine) was dissolved in anhydrous dioxane (100 mL) and treated with (t-BuO)OC\_3 (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 H\_2O and extracted with Et\_2O. The organic extracts were concentrated and the crude product was chromatographed.

**2-(tert-Butoxycarbonyl)-6-oxo-1,2,3,4-tetrahydroazocin-4,3-bindle (26).** A solution of ketoene 26 as an orange solid: 0.64 g (54%); \(^1H\) NMR (400 MHz, assignment aided by gHSQC, mixture of rotamers) \(\delta\) 1.30 and 1.50 (2s, 9H, Me), 1.96 and 2.04 (2m, 2H, 4-H), 2.97 (2m, 2H, 5-H), 3.48 and 3.62 (2m, 2H, 3-H), 4.88 and 5.01 (2s, 2H, 1-H), 7.16 (1s, J = 7.2 Hz, 1H, 10-H), 7.35 (dd, 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); \(^1C\) NMR (CDCl\_3, 100.6 MHz, gHSQC, mixture of rotamers) \(\delta\) 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-2), 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 126.7 (CH, C-9), 127.5 and 127.8 (C), 132.7 and 133.9 (C), 135.8 and 136.0 (C), 151.1 and 152.2 (C), 197.3 and 193.4 (C); ESI-HRMS [M + Na\]^+\ calculated for C\_24\_H\_25BrN\_2NaO\_3Se 475.1662, found 475.1672.

**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 carbino (0.45 g, p-Toluensulfonic 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\_2\_Cl\_2 and washed with a saturated aqueous Na\_2CO\_3 solution. Concentration of the organic solution gave 15: 0.36 g (70%).
and extracted with CH$_2$Cl$_2$. The organic extracts were dried and concentrated to give the secondary amine (127 mg), which was directly used in the next step. Disopropylethylamine (0.15 mL, 0.89 mmol) and (Z)-2-iodo-2-butenyl tosylate (230 mg, 0.65 mmol) were added to a solution of the above amine (127 mg, 0.59 mmol) in 1:1 CH$_2$Cl$_2$-acetonitrile (21 mL). After the reaction mixture was stirred at rt for 2 h, Me$_2$NH (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$_2$Cl$_2$ 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 (yellow oil): 70 mg (30%); IR (film) 3408, 2923, 1612, 1460, 742 cm$^{-1}$; $^1$H NMR (400 MHz) $\delta$ 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, $J$ = 6.6 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) $\delta$ 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$_{22}$N$_2$ 393.0822, found 393.0831.

(±)-Apparicine. Pd(OAc)$_2$ (7.6 mg, 0.034 mmol), PPh$_3$ (26 mg, 0.10 mmol) and Ag$_2$CO$_3$ (93 mg, 0.34 mmol) were added under Ar to a solution of amine (27 mg, 0.17 mmol) in 1:1 toluene-Et$_3$N (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$_2$Cl$_2$ and a saturated aqueous NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$. The organic extracts were dried and concentrated, and the resulting residue was chromatographed (SiO$_2$, flash, CH$_2$Cl$_2$ to 9:1 CH$_2$Cl$_2$-MeOH). An additional chromatography (SiO$_2$, 0.5% Et$_2$O-diethylamine) gave pure (±)-apparicine as an amorphous solid: 6.6 mg (15%); $^1$H NMR (CDCl$_3$, 400 MHz, assignments aided by gHSQC) $\delta$ 1.46 (dd, $J$ = 6.8 and 2.4 Hz, 1H, 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, 17-H), 4.28 (d, $J$ = 17.8 Hz, 1H, 6-H), 5.41 (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 (dddd, $J$ = 7.6, 7.2, and 1.2 Hz, 1H, 10-H), 7.18 (ddd, $J$ = 7.6, 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) $\delta$ 12.6 (CH$_3$, C-18), 29.6 (CH$_3$, 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.