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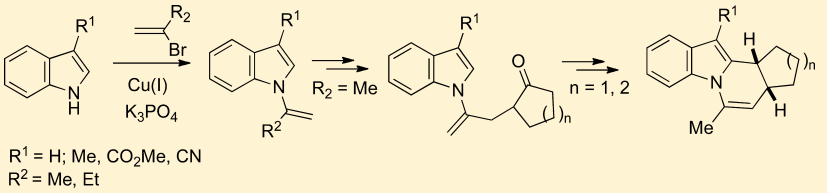
N-Alkenyl Indoles as Useful Intermediates for Alkaloid Synthesis

Hao Li, Nawong Boonnak, and Albert Padwa*

Department of Chemistry, Emory University, Atlanta, Georgia 30322, United States

Supporting Information



ABSTRACT: A mild cross-coupling reaction to access several *N*-alkenyl-substituted indoles has been developed. The coupling procedure involves treating a *NH*-indole with various alkenyl bromides using a combination of 10 mol % of copper(I) iodide and 20 mol % of ethylenediamine as the catalyst in dioxane at 110 °C in the presence of K_3PO_4 as the base. When treated with acid, these unique enamines produce a dimeric product derived from a preferred protonation reaction at the enamine π-bond. A cationic cyclization reaction of the readily available 2-(2-(1*H*-indol-1-yl)allyl)cyclopentanol was utilized to construct tetracyclic indole derivatives with a quaternary stereocenter attached to the C_2-position of the indole ring. An alternative strategy for selective functionalization at the C_2-position of a *N*-alkenyl-substituted indole derivative that was also studied involves a radical cyclization of a xanthate derivative. The work described provides an attractive route to the tetracyclic core of some vinca alkaloids, including the tetrahydroisoquinocarbazole RS-2135.

INTRODUCTION

The vinca family of indole alkaloids occupies a central place in natural product chemistry because of the wide range of complex structural variation in its molecular framework.[1,2] Members of the vinca family exhibit strong vasodilation activity which brings about an enhancement of the overall cerebral blood flow.[3] The development of synthetic methods for constructing this family of alkaloids has attracted much attention for several decades due to the important pharmacological properties and diverse structures of this class of natural products.[4−11] Although several strategies for the synthesis of vinca alkaloids have been reported,[12] the search for more efficient and general methods which provide flexible entries to structural analogues of the pentacyclic core still remains a challenging goal. In particular, RS-2135 (**1**), a pentacyclic tetrahydroisoquinocarbazole analogue of the vinca alkaloid eburnamonine (**2**), attracted our attention due to its potent antiarrhythmic activity.[13] We envisaged that the tetracyclic core (i.e., **3**) of RS-2135 could be quickly assembled by cyclization of an appropriately substituted *N*-alkenyl indole with a suitable tethered functional group at the C_2-position of the ring (vide infra) (Figure 1).

In recent years, the utilization of transition-metal-catalyzed reactions for the synthesis of 2,3-disubstituted alkenyl indoles, starting from *o*-alkynylanilines or derivatives thereof[14] as well as *o*-haloanilines,[15] has been intensively studied. Another effective strategy for the introduction of an alkenyl side chain into the indole skeleton is the palladium-catalyzed oxidative reaction of alkenes via C−H bond cleavage.[16] The alkenylation generally occurs at the electron-rich C_3-position of the indole ring due to the electrophilic nature of the reaction.[17] In an effort to further expand the diversity of substituents that can be positioned on the indole scaffold, we became interested in accessing indole derivatives substituted at the N-position with various alkenyl groups. Such derivatives, in addition to incorporating structural elements that expand the potential for natural product synthesis, also provide an opportunity for manipulating the electronic characteristics of the indole ring itself. Surprisingly, *N*-alkenyl indoles are not well represented in the chemical literature,[18] and their application as an enamine equivalent in electrophilic reactions has not been investigated in any detail. In this paper, we report a synthetically useful procedure that allows generation of a variety of *N*-alkenyl indoles and a study of their acid-promoted electrophilic addition reactions as well as their radical cyclizations. Our intention was to carry out some model studies with these systems which we hoped could eventually be used in a total synthesis of the vinca alkaloid RS-2135 (**1**).

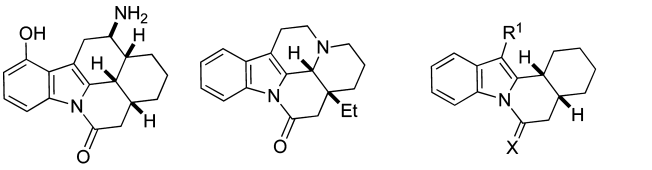


Figure 1. Skeleta of some vinca alkaloids.

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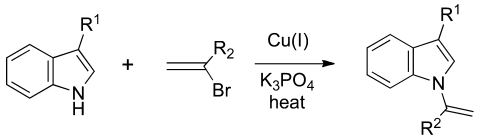
RESULTS AND DISCUSSION

N-Alkenylation has previously been carried out employing a variety of methods including mercuric acetate/sulfuric-acid-catalyzed alkenylation of NH-heteroaromatics with vinyl acetate,[19a] alkylation with dibromoethane followed by elimination,[19b] palladium(II)-catalyzed alkenylation of amides with electron-deficient acrylates,[19c] palladium(0)-catalyzed alkenylation with alkenyl bromides[19d] and triflates,[19e] and cesium-hydroxide-catalyzed addition of alcohols and amine derivatives to alkynes and styrenes.[19f] The drawbacks of these methods are the need to use elevated temperatures and a lack of generality and/or substrate scope. We found that, by using a N-alkenylation protocol originally developed by Lam and co-workers[18a] and more recently employed by Xi,[20a,b] we were able to prepare a series of *N*-alkenyl indoles in good yield.[20c] The coupling procedure involved treating a *NH*-indole with various alkenyl bromides using a combination of 10 mol % of copper(I) iodide and 20 mol % of ethylenediamine as the catalyst in dioxane at 110 °C in the presence of K_3PO_4 as the base (Scheme 1). Thus, the parent N−H and 3-substituted N−H

Scheme 1



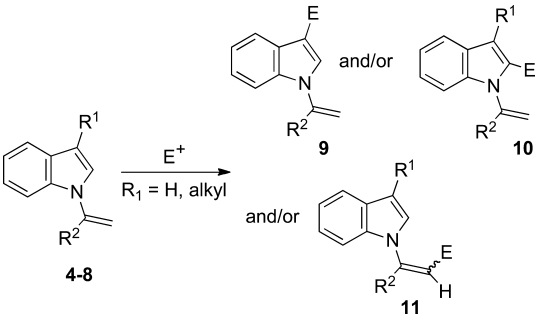
4; R^1 = H, R^2 = Me, 79%
5; R^1 = COOMe, R^2 = Me, 85%
6; R^1 = Me, R^2 = Me, 86%
7; R^1 = CN, R^2 = Me, 98%
8; R^1 = COOMe, R^2 = Et, 90%

indole system underwent ready coupling with 2-bromoprop-1-ene as well as 2-bromobut-1-ene to give the corresponding *N*-alkenyl-substituted indoles **4**−**8** in good to excellent yields. This effective coupling reaction tolerates both electron-rich (e.g., **6**) and electron-deficient substituents (e.g., **5**, **7**, and **8**).

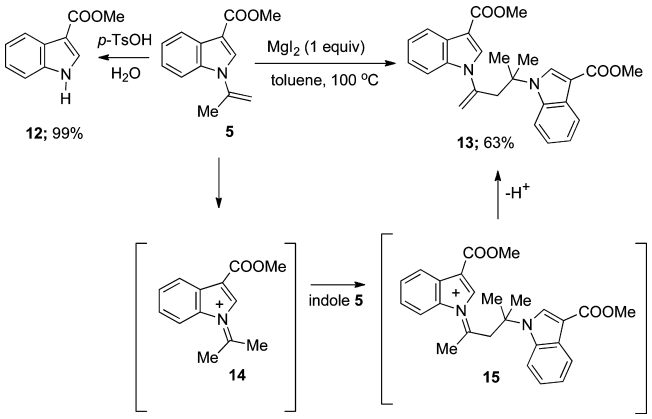
Enamines are among the most widely used building blocks in organic synthesis.[21] A conventional enamine acts as a nucleophile in a chemical transformation by enlisting its nitrogen lone pair toward nucleophilic attack. We became interested in examining the extent of interaction between the indole nitrogen lone pair of electrons and the enamine double bond present in systems such as **4**−**8**. In particular, we recognized that *N*-alkenyl-substituted indoles represent a unique class of enamines that bear a multitude of nucleophilic sites and which could lead to various products (i.e., **9**−**11**) when allowed to react with an electrophile (Scheme 2).

We first examined the behavior of *N*-alkenyl indole **5** toward Brønsted or Lewis-acid-promoted electrophilic additions. Exposure of **5** to 1.0 equiv of *p*-toluene sulfonic acid monohydrate (*p*-TsOH·H_2O) in CH_2Cl_2 at 25 °C for 1 h afforded methyl 1*H*-indole-3-carboxylate (**12**) in 99% yield by a standard hydrolysis reaction. However, when **5** was allowed to react with a milder Lewis acid such as MgI_2, the dimeric indole **13** was formed in 63% yield (Scheme 3). We assume that the formation of **13** proceeds by protonation of the enamine π-bond of **5** to give iminium ion **14**. Further reaction of **14** with another equivalent of *N*-alkenyl indole **5** leads to a second iminium ion **15**, which rapidly undergoes deprotonation to give dimer **13**.

Scheme 2

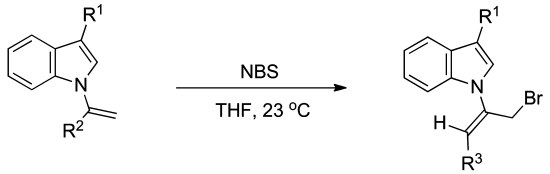


Scheme 3



In a subsequent study, we opted to examine the bromination reactions of these *N*-alkenyl-substituted indoles as a potential method for further elaboration of their scaffold. This electrophilic reaction was initially explored by exposing *N*-alkenyl indole **5** to bromine/Et_3N at −78 °C, which resulted in the formation of allyl bromide **16**, but only in 13% yield. However, when *N*-bromosuccinimide (NBS) was used as the brominating reagent,[22] the yield of **16** improved to 65% (Scheme 4). In a related manner, *N*-indolyl bromide **17** was

Scheme 4



5; R^1 = COOMe, R^2 = Me
7; R^1 = CN, R^2 = Me
8; R^1 = COOMe, R^2 = Et

16; R^1 = COOMe, R^3 = H, 65%
17; R^1 = CN, R^3 = H, 54%
18; R^1 = COOMe, R^3 = Me, 38%

also prepared in 54% yield from indole **7**. (*E*)-Methyl 1-(1-bromobut-2-en-2-yl)-1*H*-indole-3-carboxylate (**18**) was also obtained as the major product when *N*-alkenyl indole **8** was subjected to the bromination conditions, and its *E*-sterochemistry was confirmed by NOE experiments.

Allylic halides are known to be active reaction partners with cyclic enamines generally producing α-alkylated ketones in high yield.[21] With the *N*-indolyl allylic bromides **16** and **17** in hand, alkylation of these substrates with cyclic enamines **19** and **20** was next investigated (Scheme 5). We found that these *N*-indolyl allylic bromides reacted smoothly with enamines **19** and

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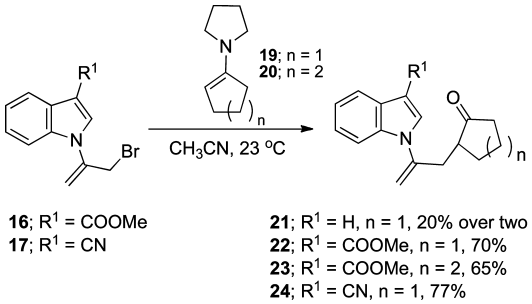
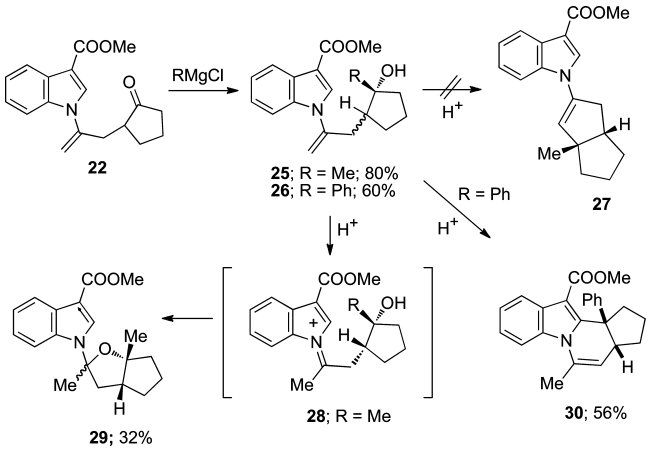
Scheme 5



20 to afford the α-allyl-substituted ketones **22**–**24** in good yield after an aqueous workup. The simpler cyclopentanone **21** was also prepared but by a two-step sequence starting from *N*-alkenyl indole **4** because the corresponding allylic bromide intermediate derived from indole **4** is not stable when exposed to air.

The Grignard addition of MeMgCl to ketone **22** afforded the expected tertiary alcohol **25** as a 3:1 mixture of diastereomers in 80% yield. However, all of our attempts to induce an acid-catalyzed cyclization of **25** to **27** failed. Instead, the only product that was obtained in 32% yield corresponded to tetrahydrofuran **29** (Scheme 6). This compound is formed by

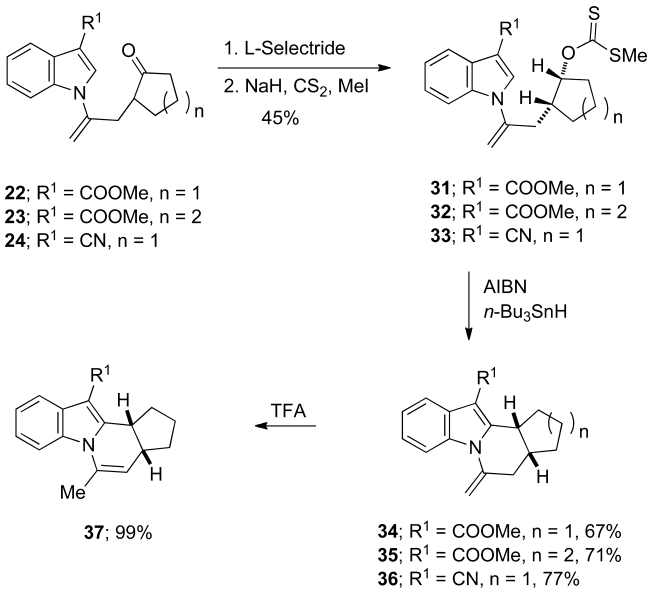
Scheme 6



an initial protonation of the enamine double bond to give iminium ion **28**, which is subsequently trapped by the neighboring hydroxyl group. In contrast to this result, when the related phenyl-substitued tertiary alcohol **26** was treated with acid, the tetracyclic indole derivative **30** was the only product isolated in 56% yield. The reactivity difference between alcohols **25** and **26** can be attributed to the formation of a more stable benzylic cationic intermediate from **26**, which allows for cylization onto the indole nucleus followed by proton loss and double bond isomerization.[23] This overall reaction constitutes a rapid approach to a tetracyclic indole derivative with a quaternary stereocenter attached to the C_2-position of the indole ring.

An alternative strategy for selective functionalization at the C_2-position of a *N*-alkenyl-substituted indole derivative is via a radical cyclization.[24] In a preliminary study, xanthates **31**–**33** were easily prepared in reasonable yield by an initial reduction of ketones **22**–**24** with L-selectride[25] followed by reaction of the resulting secondary alcohols with NaH, CS_2, and methyl iodide.[26] Previous work in this field suggests that cyclization should occur regioselectively at the 2-position of the indole ring.[27] Indeed, the radical derived from xanthate **31** (AIBN, *n*-Bu_3SnH)[28] undergoes a smooth 6-*exo*-*trig*-cyclization onto the indole ring to give the 1*H*-cyclopenta[3,4]-pyrido[1,2-*a*]indole derivative **34** in 67% yield. The same sequence was applied to the xanthates **32** and **33**, which afforded tetracyclic indole derivatives **35** and **36** in comparable overall yield (Scheme 7).

Scheme 7



Compound **35** represents the core structure of the vinca alkaloid RS-2135.[29] Formation of the *cis*-fused ring can be attributed to the steric constraints imposed by the ring system as well as stereoelectronic effects in the transition state for the radical cyclization.[30] Presumably, an important factor for the efficiency of the radical cyclization is the presence of an electron-withdrawing substituent on the 3-position of the indole ring that stabilizes the radical intermediate, thereby facilitating the overall reaction. When treated with TFA, indole **34** underwent smooth double bond isomerization to give **37** in quantitative yield. The exocyclic double bond present in **34** can also serve as a handle to access structurally diverse tetracyclic indole derivatives due to its enamine characteristics. For example, reaction of **34** with Eschenmoser's salt afforded the tetracyclic indole derivative **38** in 89% yield. Oxidative cleavage of the exocyclic double bond of **34** using a protocol developed by Rapoport[31] led to lactam **39** (78%) (Scheme 8).[31]

To further expand the scope of the radical cyclization reaction, we have also examined the $NaBH_3CN$ reduction of tosylhydrazone **40** as an alternative method for assembling the tetracyclic core of several indole alkaloid derivatives. Earlier reports by Kim[32] and Taber[33] have shown that alkyl radicals can be prepared efficiently from ketones by $NaBH_3CN$ reduction of the derived tosylhydrazones. The alkyl radicals generated in this manner underwent efficient cyclization to give the thermodyamically less stable *cis*-1,2-dialkylcyclopentane derivatives. With this in mind, we carried out the reaction of hydrazone **40** with $NaBH_3CN$. This resulted in the formation of the same tetracyclic indole derivative **34** as was obtained from the xanthate-induced cyclization but in somewhat lower yield (i.e., 46%). The high degree of diastereoselectivity for the

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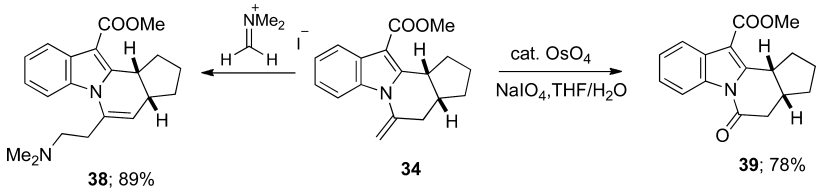
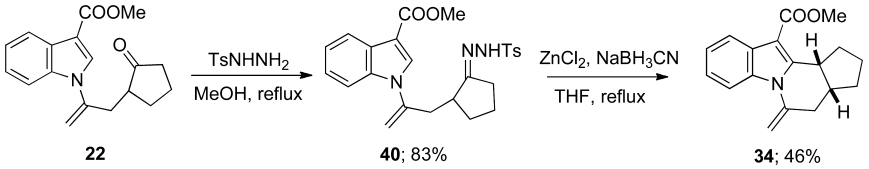
Scheme 8



Scheme 9



formation of **34** may be explained by the assumption of a highly ordered cyclic transition state during radical addition to the aromatic system (Scheme 9).

In summary, we have investigated a mild cross-coupling reaction to access several *N*-alkenyl-substituted indoles. When treated with acid, these unique enamines produce a dimeric product derived from a preferred protonation reaction at the enamine π-bond. A cationic cyclization reaction was utilized to construct tetracyclic indole derivatives with a quaternary stereocenter attached to the C_2-position of the indole ring. This work also highlights the synthetic utility of the radical cyclization of several *N*-alkenyl-substituted indoles and provides an attractive route to the tetracyclic core of some vinca alkaloids, including the tetrahydroisoquinocarbazole RS-2135. Further studies concerning the total synthesis of various vinca alkaloids using these versatile *N*-alkenyl indoles will be reported in due course.

EXPERIMENTAL SECTION

3-Methyl-1-(prop-1-en-2-yl)-1*H*-indole (6). To a 48 mL pressure tube charged with 3-methyl-1*H*-indole (1.57 g, 12 mmol) were sequentially added K_3PO_4 (4.24 g, 20 mmol), CuI (190 mg, 1 mmol), 10 mL of degassed dioxane, and ethane-1,2-diamine (0.13 mL, 2 mmol). This was followed by the addition of 0.9 mL (10 mmol) of 2-bromoprop-1-ene in one portion. The pressure tube was sealed with a PTFE plug, and the mixture was heated at 110 °C for 24 h. The mixture was cooled to room temperature, and ethyl acetate (20 mL) was added followed by filtration through a short plug of Celite. The organic phase was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 1.47 g (86%) of the titled compound **6** as a pale yellow oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.27 (s, 3H), 2.34 (s, 3H), 5.00 (s, 1H), 5.13 (s, 1H), 7.02 (s, 1H), 7.14 (t, 1H, J = 7.5 Hz), 7.21 (t, 1H, J = 7.2 Hz), 7.57 (d, 1H, J = 7.5 Hz), and 7.63 (d, 1H, J = 8.1 Hz).

Methyl 1-(but-1-en-2-yl)-1*H*-indole-3-carboxylate (8). To a 48 mL pressure tube charged with methyl 1*H*-indole-3-carboxylate (2.10 g, 12 mmol) were sequentially added K_3PO_4 (4.24 g, 20 mmol), CuI (190 mg, 1 mmol), 10 mL of degassed dioxane, and ethane-1,2-diamine (0.13 mL, 2 mmol). This was followed by the addition of 1.02 mL (10 mmol) of 2-bromobut-1-ene in one portion. The pressure tube was sealed with a PTFE plug, and the mixture was heated at 110 °C for 24 h. The mixture was cooled to room temperature, and ethyl acetate (20 mL) was added followed by filtration through a short plug of Celite. The organic phase was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 2.06 g (90%) of the titled compound **8** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, 3H, J = 7.6 Hz), 2.60 (q, 2H, J = 7.6 Hz), 3.92 (s, 3H), 5.26 (s, 1H), 5.30 (s, 1H), 7.26–7.29 (m, 2H), 7.50–7.52 (m, 1H), 7.87 (s, 1H), and 8.18–8.20 (m, 1H).

Dimethyl 1,1′-(4-methylpent-1-ene-2,4-diyl)bis(1*H*-indole-3-carboxylate) (13). To a 48 mL pressure tube charged with methyl 1*H*-indole-3-carboxylate (2.1 g, 12 mmol) were sequentially added K_3PO_4 (4.24 g, 20 mmol), CuI (190 mg, 1 mmol), 10 mL of degassed dioxane, and ethane-1,2-diamine (0.13 mL, 2 mmol). This was followed by the addition of 0.9 mL (10 mmol) of 2-bromoprop-1-ene in one portion. The pressure tube was sealed with a PTFE plug, and the mixture was heated at 110 °C for 24 h. The mixture was cooled to room temperature, and ethyl acetate (20 mL) was added followed by filtration through a short plug of Celite. The organic phase was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 1.83 g (85%) of methyl 1-(prop-1-en-2-yl)-1*H*-indole-3-carboxylate (**5**) as a pale yellow oil: IR (thin film) 2945, 1704, 1654, and 1537 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.28 (s, 3H), 3.92 (s, 3H), 5.23 (s, 1H), 5.26 (s, 1H), 7.27–7.29 (m, 2H), 7.57–7.59 (m, 1H), 7.90 (s, 1H), and 8.19–8.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 51.2, 108.5, 109.3, 112.1, 121.9, 122.4, 123.4, 127.1, 132.7, 136.2, 140.2, and 165.5; HRMS calcd for $[C_{13}H_{13}NO_2 + H^+]$ 216.1019, found 216.1018.

To a flame-dried glass microwave tube charged with the above *N*-alkenyl indole **5** (43 mg, 0.2 mmol) in toluene (2 mL) was added MgI_2 (1.0 equiv, 56 mg, 0.2 mmol) at room temperature under an argon atmosphere. The microwave reaction vial was sealed with a septum cap and was heated to 100 °C for 19 h under microwave irradiation. The reaction mixture was cooled to room temperature and filtered through a short plug of Celite. The filtrate was concentrated under reduced pressure and was purified by silica gel column chromatography to give 27 mg (63%) of **13** as a colorless oil: IR (thin film) 2947, 1700, 1558, and 1535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.66 (s, 6H), 3.41 (s, 2H), 3.87 (s, 6H), 4.86 (s, 1H), 5.16 (s, 1H), 7.15 (t, J = 7.2 Hz, 1H), 7.19 (d, J = 7.2 Hz, 1H), 7.21–7.24 (m, 2H), 7.26–7.29 (m, 1H), 7.48 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.65 (s, 1H), 8.03–8.05 (m, 1H), and 8.10 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.3, 44.6, 51.0, 51.2, 59.5, 106.3, 108.6, 111.4, 113.4, 114.8, 121.8, 121.9, 122.3, 122.5, 123.5, 126.8, 128.4, 132.2, 132.8, 135.3, 135.9, 139.6, 165.1, and 165.4; HRMS calcd for $[C_{26}H_{26}N_2O_4 + Na^+]$ 453.1784, found 453.1781.

Methyl 1-(1-bromobut-2-en-2-yl)-1*H*-indole-3-carboxylate (18). To a 10 mL round-bottom flask charged with alkenyl indole **8** (46 mg, 0.2 mmol) were sequentially added 2 mL of dry THF and NBS (36 mg, 0.2 mmol). The reaction mixture was stirred at 25 °C for 120 h and was then quenched with 100 mL of a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ether, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 23 mg (38%) of the titled compound **18** as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (d, 3H, J = 7.6 Hz), 3.92 (s, 3H), 4.33 (s, 2H), 6.01 (q, 1H, J = 7.2 Hz), 7.26–7.32

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(m, 3H), 7.89 (s, 1H), and 8.19−8.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 27.4, 51.3, 108.4, 110.8, 122.0, 122.5, 123.4, 126.6, 130.1, 134.0, 134.4, 137.0, and 165.5.

2-(2-(1*H*-Indol-1-yl)allyl)cyclopentanone (21). To a 48 mL pressure tube charged with 1*H*-indole (1.40 g, 12 mmol) were sequentially added K_3PO_4 (4.24 g, 20 mmol), CuI (190 mg, 1 mmol), 10 mL of degassed dioxane, and ethane-1,2-diamine (0.13 mL, 2 mmol). This was followed by the addition of 0.9 mL (10 mmol) of 2-bromoprop-1-ene in one portion. The pressure tube was sealed with a PTFE plug, and the reaction mixture was heated at reflux at 110 °C for 24 h. The mixture was cooled to room temperature, and ethyl acetate (20 mL) was added followed by filtration through a short plug of Celite. The organic phase was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 1.24 g (79%) of 1-(prop-1-en-2-yl)-1*H*-indole (**4**) as a pale yellow oil which was used in the next step without any further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 3H), 5.07 (s, 1H), 5.17 (s, 1H), 6.57 (d, 1H, J = 3.2 Hz), 7.12 (t, 1H, J = 7.6 Hz), 7.22 (t, 2H, J = 7.6 Hz), and 7.63 (d, 2H, J = 7.2 Hz).

To a 10 mL round-bottom flask charged with the above alkenyl indole (32 mg, 0.2 mmol) were sequentially added 2 mL of dry THF and NBS (36 mg, 0.2 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and was then quenched with 2 mL of a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ether, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was taken up in CH_3CN (2 mL) in a 10 mL round-bottom flask and 1-(cyclopent-1-en-1-yl)pyrrolidine (**19**) (58 μL, 0.4 mmol) was subsequently added at 25 °C. After stirring for 2 h, the reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 10 mg (20% over two steps) of the titled compound **21** as a colorless oil: ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.45−1.52 (m, 1H), 1.57−1.64 (m, 1H), 1.89−1.93 (m, 1H), 1.95−2.07 (m, 3H), 2.25 (dd, 1H, J = 19.2 and 7.8 Hz), 2.37 (dd, 1H, J = 15.6 and 10.2 Hz), 3.26 (dd, 1H, J = 15.6 and 3.0 Hz), 5.20 (s, 1H), 5.23 (s, 1H), 6.57 (d, 1H, J = 3.0 Hz), 7.13 (t, 1H, J = 7.8 Hz), 7.19 (d, 1H, J = 5.4 Hz), 7.22 (t, 1H, J = 7.8 Hz), 7.57 (d, 1H, J = 8.4 Hz), and 7.62 (d, 1H, J = 7.8 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.5, 29.5, 36.1, 37.9, 47.2, 103.4, 108.4, 111.4, 120.4, 121.2, 122.5, 126.4, 129.4, 136.0, 143.0, and 219.9.

Methyl 1-(3-(2-oxocyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (22). To a 250 mL round-bottom flask charged with *N*-alkenyl indole **5** (3.30 g, 15.4 mmol) were sequentially added 150 mL of dry THF and NBS (2.73 g, 15.4 mmol). The reaction mixture was stirred at 25 °C for 48 h and was then quenched with 100 mL of a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ether, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 2.93 g (65%) of methyl 1-(3-bromoprop-1-en-2-yl)-1*H*-indole-3-carboxylate (**16**) as a white solid: mp 72−73 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 4.34 (s, 2H), 5.50 (s, 1H), 5.71 (s, 1H), 7.29−7.33 (m, 2H), 7.43−7.45 (m, 1H), 7.93 (s, 1H), and 8.20−8.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.5, 51.4, 109.3, 111.2, 105.2, 122.0, 122.7, 123.8, 126.8, 133.0, 136.8, 140.6, and 165.3.

To a 250 mL round-bottom flask charged with the above bromide **16** (1.18 g, 4.0 mmol) were sequentially added 40 mL of CH_3CN and 1-(cyclopent-1-en-1-yl)pyrrolidine (**19**) (1.16 mL, 8.0 mmol). After stirring at 25 °C for 4 h, the mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 0.82 g (70%) of the titled compound **22** as a pale yellow solid: mp 64−66 °C; IR (thin film) 2949, 1735, 1702, and 1535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41−1.51 (m, 1H), 1.58−1.66 (m, 1H), 1.89−2.10 (m, 4H), 2.27 (dd, 1H, J = 20.0 and 8.8 Hz), 2.41 (dd, 1H, J = 15.6 and 10.0 Hz), 3.24 (dd, 1H, J = 15.6 and 3.2 Hz), 3.92 (s, 3H), 5.31 (s, 1H), 5.35 (s, 1H), 7.27−7.31 (m, 2H), 7.52−7.55 (m, 1H), 7.88 (s, 1H), and 8.19−8.21 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 29.5, 35.8, 37.7, 46.9, 51.3, 108.8, 111.6, 111.7, 121.9, 122.6, 123.6, 127.0, 132.8, 136.6, 142.5, 165.4 and 219.2; HRMS calcd for $C_{18}H_{19}NO_3$ 297.1359, found 297.1358.

Methyl 1-(3-(2-oxocyclohexyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (23). To a 250 mL round-bottom flask charged with methyl 1-(3-bromoprop-1-en-2-yl)-1*H*-indole-3-carboxylate (**16**) (1.0 g, 3.4 mmol) were sequentially added 34 mL of CH_3CN and 1-(cyclohex-1-en-1-yl)pyrrolidine (**20**) (1.1 mL, 6.8 mmol). After stirring at 25 °C for 3 h, the reaction mixture was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 0.73 g (65%) of the titled compound **23** as a pale yellow solid: mp 60−62 °C; IR (thin film) 2943, 1706, 1651, and 1535 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.30−1.37 (m, 1H), 1.45−1.52 (m, 1H), 1.56−1.64 (m, 1H), 1.78−1.81 (m, 1H), 2.00−2.04 (m, 1H), 2.10−2.21 (m, 3H), 2.35−2.41 (m, 2H), 3.29 (dd, 1H, J = 15.6 and 4.8 Hz), 3.92 (s, 3H), 5.31 (s, 1H), 5.32 (s, 1H), 7.27−7.30 (m, 2H), 7.51−7.53 (m, 1H), 7.85 (s, 1H), and 8.19−8.20 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.1, 27.9, 33.8, 35.4, 42.2, 47.6, 51.3, 108.7, 111.7, 111.9, 121.9, 122.5, 123.6, 127.0, 132.8, 136.6, 142.4, 165.5 and 211.4; HRMS calcd for $C_{19}H_{21}NO_3$ 311.1516, found 311.1516.

Methyl 1-(3-(2-hydroxy-2-methylcyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (25). To a 10 mL round-bottom flask charged with methyl 1-(3-(2-oxo-cyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (**22**) (89 mg, 0.3 mmol) were sequentially added 3 mL of dry THF and MeMgCl (3.0 M in THF, 0.3 mL, 0.9 mmol) at −78 °C. The reaction mixture was slowly allowed to warm to −35 °C, and after stirring at this temperature for 4 h, the mixture was quenched by the addition of 4 mL of a saturated aqueous $NaHCO_3$ solution and then warmed to room temperature. The mixture was extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 75 mg (80%) of the titled compound **25** as a colorless oil as a 3:1 mixture of diastereomers: IR (thin film) 3461, 2955, 1702, 1652, and 1535 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 1.22 (s, 3H), 1.35−1.50 (m, 3H), 1.53−1.73 (m, 4H), 2.51 (dd, 1H, J = 14.8 and 10.4 Hz), 2.92 (dd, 1H, J = 14.8 and 3.6 Hz), 3.92 (s, 3H), 5.26 (s, 1H), 5.32 (s, 1H), 7.27−7.30 (m, 2H), 7.52−7.55 (m, 1H), 7.88 (s, 1H), and 8.18−8.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 20.8, 26.1, 29.9, 35.0, 41.8, 46.6, 51.3, 80.0, 108.5, 110.6, 111.9, 121.8, 122.4, 123.4, 126.9, 132.9, 136.6, 144.2, and 165.6; HRMS calcd for $C_{19}H_{23}NO_3$ 313.1672, found 313.1670.

Methyl 1-(2,6*a*-dimethylhexahydro-2*H*-cyclopenta[*b*]furan-2-yl)-1*H*-indole-3-carboxylate (29). To a 10 mL round-bottom flask charged with alcohol **25** (31 mg, 0.1 mmol) were sequentially added 2 mL of dry CH_2Cl_2 and $BF_3{\cdot}OEt_2$ (25 μL, 0.2 mmol) at 25 °C. After stirring for 10 min, the reaction mixture was quenched with 2 mL of a saturated aqueous $NaHCO_3$ solution. The reaction mixture was then extracted with ether, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 10 mg (32%) of a colorless oil which consisted of a 4:1 mixture of diastereomers of the titled compound **29**: IR (thin film) 2949, 1701, and 1531 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) major isomer δ 1.22−1.27 (m, 1H), 1.35−1.42 (m, 2H), 1.49 (s, 3H), 1.53−1.61 (m, 1H), 1.68−1.76 (m, 4H), 1.96−2.04 (m, 1H), 2.46−2.52 (m, 1H), 2.69 (dd, 1H, J = 14.0 and 9.2 Hz), 2.77 (dd, 1H, J = 14.0 and 4.0 Hz), 3.91 (s, 3H), 7.22−7.25 (m, 2H), 7.63−7.66 (m, 1H), and 8.17−8.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) major isomer δ 24.8, 27.8, 30.3, 32.7, 40.5, 45.0, 49.2, 51.1, 96.2, 97.9, 106.4, 113.6, 121.8, 121.9, 122.4, 128.2, 132.0, 135.1, and 166.0; HRMS calcd for $C_{19}H_{23}NO_3$: 313.1672, found 313.1671.

Methyl 1-(3-(2-hydroxy-2-phenylcyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (26). To a 10 mL round-bottom flask charged with methyl 1-(3-(2-oxocyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (**22**) (89 mg, 0.3 mmol) were sequentially added 3 mL of dry THF and PhMgCl (3.0 M in ether, 0.3 mL, 0.9 mmol) at −78 °C. The reaction was slowly warmed to −10 °C, and

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after stirring at this temperature for 20 h, the mixture was quenched with 4 mL of a saturated aqueous $NaHCO_3$ solution and was then allowed to warm to room temperature. The reaction mixture was extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 67 mg (60%) of the titled compound **26** as a colorless oil: IR (thin film) 3480, 2949, 1686, 1652, and 1535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59−1.70 (m, 2H), 1.78−1.93 (m, 4H), 1.98−2.04 (m, 1H), 2.51 (dd, 1H, J = 14.8 and 10.4 Hz), 2.68 (dd, 1H, J = 15.2 and 3.2 Hz), 3.91 (s, 3H), 5.16 (s, 1H), 5.21 (s, 1H), 7.20 (t, 1H, J = 8.0 Hz), 7.24−7.30 (m, 6H), 7.36 (d, 1H, J = 8.0 Hz), 7.55 (s, 1H), and 8.18 (d, 1H, J = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 29.4, 34.3, 43.7, 48.5, 51.2, 84.0, 108.3, 111.0, 111.9, 121.7, 122.4, 123.4, 125.0, 126.9, 128.5, 128.7, 133.0, 136.5, 143.8, 144.9, and 165.4; HRMS calcd for $C_{24}H_{25}NO_3$ 375.1829, found 375.1826.

Methyl 5-methyl-11*b*-phenyl-2,3,3*a*,11*b*-tetrahydro-1*H*-cyclopenta[3,4]pyrido-[1,2-*a*]indole-11-carboxylate (30). To a 10 mL round-bottom flask charged with alcohol **26** (38 mg, 0.1 mmol) were sequentially added 2 mL of dry CH_2Cl_2 and $BF_3{\cdot}OEt_2$ (25 μL, 0.2 mmol) at 25 °C. After stirring for 10 min, the reaction mixture was quenched with 2 mL of saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with ether, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 20 mg (56%) of the titled compound **30** as a colorless oil: IR (thin film) 2947, 1708, 1528, and 1447 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41−1.51 (m, 1H), 1.76−1.90 (m, 2H), 1.97−2.04 (m, 1H), 2.51−2.65 (m, 5H), 3.03 (ddd, 1H, J = 13.6 Hz, 8.4 Hz, and 4.0 Hz), 3.56 (s, 3H), 5.25 (d, 1H, J = 5.2 Hz), 7.05−7.08 (m, 2H), 7.12−7.15 (m, 1H), 7.19−7.25 (m, 4H), 7.78−7.80 (m, 1H), and 8.12−8.14 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.0, 24.7, 33.9, 42.1, 49.5, 50.9, 52.5, 106.4, 113.3, 113.8, 121.6, 122.0, 122.9, 125.8, 125.9, 128.1, 131.9, 134.2, 148.0, 150.5 and 165.3; HRMS calcd for $[C_{24}H_{23}NO_2 + H^+]$ 358.1801, found 358.1798.

Methyl 1-(3-(2-(((methylthio)carbonothioyl)oxy)-cyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (31). To a 250 mL round-bottom flask charged with methyl 1-(3-(2-oxocyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (**22**) (0.93 g, 3.13 mmol) were sequentially added 31 mL of dry THF and L-selectride (1.0 M in THF, 6.26 mL, 6.26 mmol) at −78 °C. After stirring at −78 °C for 3 h, the mixture was quenched with 30 mL of a saturated aqueous NH_4Cl solution and warmed to room temperature. The solution was extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel, and concentrated under reduced pressure. The resulting residue was taken up in 30 mL of dry THF at 0 °C and imidazole (11 mg, 0.16 mmol) and NaH (60% dispersion in mineral oil, 626 mg, 15.65 mmol) were sequentially added. The mixture was warmed to 25 °C and stirred at this temperature for 0.5 h. This was followed by the dropwise addition of CS_2 (0.94 mL, 15.65 mmol), and the mixture was kept at 25 °C for 1 h. To this solution was slowly added MeI (0.98 mL, 15.65 mmol), and after stirring for 1 h, the mixture was quenched with 30 mL of a saturated aqueous NH_4Cl solution and was warmed to room temperature. The mixture was then extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.55 g (45% over the two steps) of the titled xanthate **31** as a colorless oil: IR (thin film) 2948, 1704, 1651, 1536, and 1198 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.50−1.61 (m, 2H), 1.73−1.82 (m, 2H), 1.85−1.92 (m, 3H), 2.57 (s, 3H), 2.71 (dd, 1H, J = 15.2 and 7.6 Hz), 2.87 (dd, 1H, J = 15.2 and 8.0 Hz), 3.93 (s, 3H), 5.26 (s, 1H), 5.30 (s, 1H), 5.77−5.79 (m, 1H), 7.26−7.31 (m, 2H), 7.51−7.55 (m, 1H), 7.86 (s, 1H), and 8.17−8.22 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 19.2, 22.2, 30.0, 32.3, 35.3, 42.4, 51.3, 87.4, 108.7, 111.3, 111.8, 121.8, 122.5, 123.5, 126.9, 132.7, 136.6, 142.9, 165.5 and 215.3; HRMS calcd for $C_{20}H_{23}NO_3S_2$ 389.1113, found 389.1112.

Methyl 1-(3-(2-(((methylthio)carbonothioyl)oxy)cyclohexyl)-prop-1-en-2-yl)-1*H*-indole-3-carboxylate (32). To a 100 mL round-bottom flask charged with methyl 1-(3-(2-oxocyclohexyl)-prop-1-en-2-yl)-1*H*-indole-3-carboxylate (**23**) (0.42 g, 1.35 mmol) were sequentially added 14 mL of dry THF and L-selectride (1.0 M in THF, 2.70 mL, 2.70 mmol) at −78 °C. After stirring at −78 °C for 4 h, the mixture was quenched by the addition of 14 mL of a saturated aqueous NH_4Cl solution and then warmed to room temperature. The resulting mixture was extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel, and concentrated under reduced pressure. The resulting residue was taken up in 14 mL of dry THF at 0 °C, and a sample of imidazole (5 mg, 0.07 mmol) and NaH (60% dispersion in mineral oil, 270 mg, 6.75 mmol) was sequentially added. The mixture was then warmed to 25 °C and was stirred for 0.5 h. This was followed by the dropwise addition of CS_2 (0.41 mL, 6.75 mmol), and the solution was kept at 25 °C for 1 h. To this mixture was slowly added MeI (0.42 mL, 6.75 mmol). After stirring at 25 °C for 1 h, the solution was quenched with 14 mL of a saturated aqueous NH_4Cl solution and was then warmed to room temperature. The mixture was extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.24 g (45% over the two steps) of the titled xanthate **32** as a pale yellow oil: IR (thin film) 2925, 2854, 1709, 1537, and 1201 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 1.13−1.20 (m, 1H), 1.24−1.30 (m, 1H), 1.35−1.58 (m, 5H), 1.69 (d, 1H, J = 13.8 Hz), 2.12 (dd, 1H, J = 13.8 and 2.4 Hz), 2.55−2.59 (m, 4H), 2.67 (dd, 1H, J = 14.4 and 6.6 Hz), 3.92 (s, 3H), 5.22 (s, 1H), 5.28 (s, 1H), 5.72 (s, 1H), 7.24−7.29 (m, 2H), 7.55−7.58 (m, 1H), 7.86 (s, 1H), and 8.17−8.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 20.6, 24.8, 27.6, 28.9, 38.0, 38.3, 51.2, 81.2, 108.7, 111.8, 112.0, 121.7, 122.4, 123.5, 126.9, 132.4, 136.5, 141.5, 165.3 and 215.2; HRMS calcd for $C_{21}H_{25}NO_3S_2$ 403.1270, found 403.1268.

***O*-2-(2-(3-Cyano-1*H*-indol-1-yl)allyl)cyclopentyl (*S*)-methyl carbonodithioate (33).** To a 48 mL pressure tube charged with methyl 1*H*-indole-3-carbonitrile (1.70 g, 12 mmol) were sequentially added K_3PO_4 (4.24 g, 20 mmol), CuI (190 mg, 1 mmol), 10 mL of degassed dioxane, and ethane-1,2-diamine (0.13 mL, 2 mmol). This was followed by the addition of 0.9 mL (10 mmol) of 2-bromoprop-1-ene in one portion. The pressure tube was sealed with a PTFE plug, and the mixture was heated at 110 °C for 24 h. The mixture was cooled to room temperature, and ethyl acetate (20 mL) was added followed by filtration through a short plug of Celite. The organic phase was concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 1.78 g (98%) of 1-(prop-1-en-2-yl)-1*H*-indole-3-carbonitrile (**7**) as an off white solid: mp 48−50 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 5.29 (s, 1H), 5.30 (s, 1H), 7.31 (t, 1H, J = 7.2 Hz), 7.36 (t, 1H, J = 7.2 Hz), 7.60 (d, 1H, J = 8.0 Hz), 7.69 (s, 1H), and 7.77 (d, 1H, J = 8.4 Hz).

To a 250 mL round-bottom flask charged with the above *N*-alkenyl indole **7** (1.13 g, 6.21 mmol) were sequentially added 62 mL of dry THF and NBS (1.32 g, 7.45 mmol). The reaction mixture was stirred at 25 °C for 96 h and was then quenched with 100 mL of a saturated aqueous $NaHCO_3$ solution. The mixture was extracted with ether, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 0.87 g (54%) of 1-(3-bromoprop-1-en-2-yl)-1*H*-indole-3-carbonitrile (**17**) as a white solid: mp 85−86 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 4.33 (s, 2H), 5.54 (s, 1H), 5.79 (s, 1H), 7.32−7.40 (m, 2H), 7.47−7.49 (m, 1H), 7.76 (s, 1H), and 7.78−7.80 (m, 1H).

To a 100 mL round-bottom flask charged with the above bromide **17** (0.4 g, 1.53 mmol) were sequentially added 15 mL of CH_3CN and 1-(cyclopent-1-en-1-yl)pyrrolidine (**19**) (0.46 mL, 3.06 mmol). After stirring at 25 °C for 4 h, the reaction mixture was concentrated under

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reduced pressure and the resulting residue was purified by silica gel chromatography to furnish 0.31 g (77%) of 1-(3-(2-oxocyclopentyl)-prop-1-en-2-yl)-1*H*-indole-3-carbonitrile (**24**) as a pale yellow solid: mp 74−75 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.44−1.52 (m, 1H), 1.64−1.71 (m, 1H), 1.92−2.22 (m, 4H), 2.29 (dd, 1H, J = 19.2 and 8.4 Hz), 2.43 (dd, 1H, J = 15.2 and 9.6 Hz), 3.19 (dd, 1H, J = 15.2 and 3.2 Hz), 5.34 (s, 1H), 5.40 (s, 1H), 7.32 (td, 1H, J = 8.0 and 1.2 Hz), 7.36 (td, 1H, J = 7.2 and 1.2 Hz), 7.56 (d, 1H, J = 7.6 Hz), 7.68 (s, 1H), and 7.77 (d, 1H, J = 7.2 Hz).

To a 50 mL round-bottom flask charged with the above compound **24** (216 mg, 0.82 mmol) were sequentially added 8 mL of dry THF and L-selectride (1.0 M in THF, 1.64 mL, 1.64 mmol) at −78 °C. After stirring at −78 °C for 3 h, the reaction mixture was quenched with 8 mL of a saturated aqueous NH_4Cl solution and was then warmed to room temperature. The mixture was then extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of silica gel, and concentrated under reduced pressure. The resulting residue was taken up in 8 mL of dry THF at 0 °C and imidazole (3 mg, 0.04 mmol) and NaH (60% dispersion in mineral oil, 164 mg, 4.10 mmol) were sequentially added. The solution was warmed to 25 °C and was stirred at this temperature for 0.5 h. This was followed by the dropwise addition of CS_2 (0.25 mL, 4.10 mmol), and the solution was kept at 25 °C for 1 h. To this mixture was slowly added MeI (0.26 mL, 4.10 mmol). After stirring for 1 h, the mixture was quenched with 8 mL of a saturated aqueous NH_4Cl solution and was warmed to room temperature. The solution was then extracted with ether, and the combined organic phase was washed with water and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromato-graphy to furnish 132 mg (45% over the two steps) of the titled xanthate **33** as a white solid: mp 92−93 °C; IR (thin film) 2945, 2223, 1657, and 1221 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ1.54−1.59 (m, 2H), 1.75−1.81 (m, 2H), 1.85−1.92 (m, 3H), 2.57 (s, 3H), 2.70 (dd, 1H, J = 15.0 and 7.2 Hz), 2.85 (dd, 1H, J = 15.0 and 7.8 Hz), 5.28 (s, 1H), 5.35 (s, 1H), 5.75 (td, 1H, J = 5.4 and 2.4 Hz), 7.30 (t, 1H, J = 7.2 Hz), 7.34 (td, 1H, J = 7.8 and 1.2 Hz), 7.55 (d, 1H, J = 8.4 Hz), 7.66 (s, 1H), and 7.75 (d, 1H, J = 7.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.2, 22.1, 30.0, 32.3, 35.2, 42.4, 87.0, 87.7, 112.0, 112.2, 115.5, 120.0, 122.7, 124.6, 127.9, 133.3, 135.3, 142.5 and 215.2; HRMS calcd for $C_{19}H_{20}N_2OS_2$ 356.1011, found 356.1010.

Methyl 5-methylene-2,3,3*a*,4,5,11*b*-hexahydro-1*H*-cyclopenta[3,4]pyrido[1,2-*a*]indole-11-carboxylate (34). To a 50 mL round-bottom flask connected to a condenser charged with xanthate **31** (39 mg, 0.1 mmol) was added 10 mL of dry benzene. A solution of AIBN (8 mg, 0.05 mmol) and *n*-Bu_3SnH (0.13 mL, 0.5 mmol) in 10 mL of dry benzene was added via syringe pump over a 4 h period at 80 °C. The reaction mixture was heated at reflux for 17 h under argon, cooled to room temperature, and stirred for another 2 h. The mixture was then concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 19 mg (67%) of the titled compound **34** as a colorless oil: IR (thin film) 2949, 1699, 1653, and 1540 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.42−1.49 (m, 1H), 1.57−1.69 (m, 2H), 1.71−1.79 (m, 1H), 1.96−2.02 (m, 1H), 2.39−2.46 (m, 2H), 2.52−2.64 (m, 2H), 3.93 (s, 3H), 4.07 (q, 1H, J = 9.0 Hz), 5.03 (s, 1H), 5.34 (s, 1H), 7.22−7.26 (m, 2H), 7.72−7.74 (m, 1H), and 8.15−8.16 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.8, 32.4, 34.2, 36.5, 36.7, 38.1, 50.9, 101.8, 112.1, 121.7, 122.6, 122.7, 128.1, 130.9, 131.1, 134.3, 140.3, and 166.1; HRMS calcd for $[C_{18}H_{19}NO_2 + H^+]$ 282.1488, found 282.1485.

Methyl 6-methylene-1,2,3,4,4*a*,5,6,12*b*-octahydroindolo-[2,1-*a*]isoquinoline-12-carboxylate (35). To a 250 mL round-bottom flask connected to a condenser charged with xanthate **32** (190 mg, 0.47 mmol) was added 47 mL of dry benzene. A solution of AIBN (39 mg, 0.24 mmol) and *n*-Bu_3SnH (0.62 mL, 2.35 mmol) in 47 mL of dry benzene was added via syringe pump over a period of 4 h at 80 °C. The reaction mixture was heated at reflux for 17 h under argon, cooled to room temperature, and stirred for another 2 h. The mixture was then concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 98 mg (71%) of the titled compound **35** as a colorless oil: IR (thin film) 2921, 2850, 1697, 1647, and 1543 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41−1.60 (m, 4H), 1.75−1.77 (m, 3H), 2.01−2.04 (m, 1H), 2.33−2.39 (m, 2H), 3.01 (t, 1H, J = 14.4 Hz), 3.87−3.93 (m, 4H), 4.89 (s, 1H), 5.35 (s, 1H), 7.20−7.27 (m, 2H), 7.79−7.82 (m, 1H), and 8.14−8.17 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 26.3, 28.2, 30.7, 32.7, 32.8, 36.0, 51.1, 99.0, 103.6, 113.3, 121.8, 122.7, 128.4, 134.5, 142.0, 151.7 and 166.1; HRMS calcd for $[C_{19}H_{21}NO_2 + H^+]$ 296.1645, found 296.1643.

5-Methylene-2,3,3*a*,4,5,11*b*-hexahydro-1*H*-cyclopenta[3,4]-pyrido[1,2-*a*]indole-11-carbonitrile (36). To a 100 mL round-bottom flask connected to a condenser charged with xanthate **33** (53 mg, 0.15 mmol) was added 15 mL of dry benzene. A solution of AIBN (12 mg, 0.075 mmol) and *n*-Bu_3SnH (0.20 mL, 0.75 mmol) in 15 mL of dry benzene was added via syringe pump over a period of 4 h at 80 °C. The reaction mixture was heated at reflux for 17 h under argon, cooled to room temperature, and stirred for another 2 h. The mixture was then concentrated under reduced pressure, and the resulting residue was purified by silica gel chromatography to furnish 29 mg (77%) of the titled compound **36** as a colorless oil: IR (thin film) 2958, 2212, 1658, and 1545 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.50−1.58 (m, 1H), 1.65−1.81 (m, 3H), 1.99−2.07 (m, 1H), 2.38 (dd, 1H, J = 13.2 and 8.0 Hz), 2.50−2.57 (m, 2H), 2.62−2.69 (m, 1H), 3.64 (q, 1H, J = 8.4 Hz), 5.06 (d, 1H, J = 0.8 Hz), 5.37 (s, 1H), 7.27−7.31 (m, 2H), 7.67−7.69 (m, 1H), and 7.73−7.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 25.3, 31.7, 34.1, 36.6, 36.8, 37.6, 101.9, 112.7, 116.3, 119.3, 122.9, 123.7, 128.7, 133.6, 139.7, and 150.8; HRMS calcd for $[C_{17}H_{16}N_2 + H^+]$ 249.1386, found 249.1384.

Methyl 5-methyl-2,3,3*a*,11*b*-tetrahydro-1*H*-cyclopenta[3,4]-pyrido[1,2-*a*]indole-11-carboxylate (37). To a 5 mL round-bottom flask charged with tetracyclic indole derivative **34** (14 mg, 0.05 mmol) were sequentially added 2 mL of $CDCl_3$ and trifluoroacetic acid (2 μL, 0.025 mmol) at 25 °C. After stirring for 10 min, the mixture was quenched by the addition of 2 mL of a saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with ether, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, and filtered through a short plug of silica gel to furnish 14 mg (99%) of the titled compound **37** as a colorless oil: IR (thin film) 2917, 1698, and 1558 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.54−1.64 (m, 1H), 1.70−1.77 (m, 2H), 1.79−1.84 (m, 1H), 2.00−2.05 (m, 1H), 2.22−2.25 (m, 1H), 2.54 (s, 3H), 2.92 (bs, 1H), 3.93 (s, 3H), 4.08 (q, 1H, J = 9.0 Hz), 4.85 (s, 1H), 7.17 (t, 1H, J = 7.2 Hz), 7.21 (t, 1H, J = 7.2 Hz), 7.72 (d, 1H, J = 8.4 Hz), and 8.16 (d, 1H, J = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 23.7, 31.4, 33.8, 35.8, 37.2, 51.0, 104.3, 113.0, 115.9, 121.7, 121.9, 122.7, 127.6, 132.1, 134.9, 148.6, and 166.2; HRMS calcd for $[C_{18}H_{19}NO_2 + H^+]$ 282.1488, found 282.1487.

Methyl 5-(2-(dimethylamino)ethyl)-2,3,3*a*,11*b*-tetrahydro-1*H*-cyclopenta[3,4]-pyrido[1,2-*a*]indole-11-carboxylate (38). To a 5 mL round-bottom flask charged with tetracyclic indole derivative **34** (14 mg, 0.05 mmol) were sequentially added 2 mL of CH_2Cl_2 and Eschenmoser's salt (11 mg, 0.055 mmol) at 25 °C. After stirring for 48 h, the mixture was quenched with 2 mL of a saturated aqueous $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 15 mg (89%) of the titled compound **38** as a colorless oil: IR (thin film) 2947, 2869, 1698, 1558, and 1391 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60−1.84 (m, 4H), 1.98−2.08 (m, 1H), 2.17−2.23 (m, 1H), 2.28 (s, 6H), 2.44−2.57 (m, 2H), 2.85−2.91 (m, 2H), 3.16−3.24 (m, 1H), 3.94 (s, 3H), 4.08 (q, 1H, J = 9.2 Hz), 4.95 (s, 1H), 7.20−7.23 (m, 2H), 7.65−7.68 (m, 1H), and 8.15−8.18 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.8, 30.9, 32.6, 33.6, 36.0, 37.2, 45.6, 51.1, 58.2, 104.5, 112.7, 117.1, 121.7, 122.0, 123.1, 127.6, 134.4, 148.8, and 166.1; HRMS calcd for $[C_{21}H_{26}N_2O_2 + H^+]$ 339.2067, found 339.2065.

Methyl 5-oxo-2,3,3*a*,4,5,11*b*-hexahydro-1*H*-cyclopenta[3,4]-pyrido[1,2-*a*]indole-11-carboxylate (39). To a 50 mL round-bottom flask charged with tetracyclic indole derivative **34** (14 mg, 0.05

mmol) were sequentially added 4 mL of THF, $NaIO_4$ aqueous solution (0.067 M, 2.2 mL, 0.15 mmol), and OsO_4 (6 mg, 0.023 mmol) at 25 °C. After stirring for 24 h, the reaction mixture was quenched with 4 mL of a saturated aqueous $NaHCO_3$ solution. The mixture was then extracted with benzene, and the combined organic phase was washed with a saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 11 mg (78%) of the titled compound **39** as a colorless oil: IR (thin film) 2950, 2873, 1704, and 1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.57−1.76 (m, 2H), 1.88 −2.03 (m, 3H), 2.51−2.59 (m, 1H), 2.65 (dd, 1H, J = 16.8 and 12.4 Hz), 2.73 (dd, 1H, J = 16.8 and 5.6 Hz), 2.77−2.83 (m, 1H), 3.96 (s, 3H), 3.99−4.03 (m, 1H), 7.33−7.35 (m, 2H), 8.06−8.09 (m, 1H), and 8.47−8.49 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.6, 29.8, 31.3, 36.3, 37.7, 38.1, 51.5, 109.2, 116.4, 121.4, 125.0, 125.2, 127.6, 134.6, 149.3, 165.4, and 169.7; HRMS calcd for $[C_{17}H_{17}NO_3 + H^+]$ 284.1281, found 284.1280.

Methyl 1-(3-(2-(2-tosylhydrazono)cyclopentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (40). To a 15 mL pressure tube charged with methyl 1-(3-(2-oxocyclo-pentyl)prop-1-en-2-yl)-1*H*-indole-3-carboxylate (**22**) (125 mg, 0.4 mmol) were sequentially added 4 mL of MeOH and *p*-toluenesulfonyl hydrazide (82 mg, 0.44 mmol). The pressure tube was sealed with a PTFE plug, and the reaction mixture was heated at reflux at 80 °C for 20 h. After cooling down to room temperature, the mixture was concentrated under reduced pressure and the resulting residue was purified by silica gel chromatography to furnish 155 mg (83%) of the titled compound **40** as a pale yellow solid: mp 63−64 °C; IR (thin film) 3206, 2949, 1700, 1652, and 1534 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.19−1.25 (m, 1H), 1.47−1.52 (m, 1H), 1.75−1.81 (m, 2H), 2.07−2.19 (m, 2H), 2.30−2.40 (m, 2H), 2.42 (s, 3H), 3.17 (dd, 1H, J = 14.0 and 3.2 Hz), 3.93 (s, 3H), 5.24 (s, 1H), 5.26 (s, 1H), 7.26−7.31 (m, 4H), 7.38 (s, 1H), 7.47−7.50 (m, 1H), 7.83−7.86 (m, 3H), and 8.18−8.20 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 22.4, 27.9, 31.2, 37.7, 42.5, 51.3, 108.5, 111.6, 111.7, 121.8, 122.5, 123.5, 126.9, 128.2, 129.7, 133.0, 135.3, 136.5, 142.6, 144.3, 165.5 and 167.4; HRMS calcd for $[C_{25}H_{27}N_3O_4S + H^+]$ 466.1795, found 466.1792.

To a 15 mL pressure tube charged with the above hydrazone **40** (48 mg, 0.1 mmol) were sequentially added 2 mL of THF, $ZnCl_2$ (0.5 M in THF, 0.28 mL, 0.14 mmol), and $NaCNBH_3$ (1.0 M in THF, 0.14 mL, 0.14 mmol). The pressure tube was sealed with a PTFE plug, and the reaction mixture was heated at reflux at 75 °C for 22 h. After cooling to room temperature, the mixture was quenched with 6 mL of a saturated aqueous $NaHCO_3$ solution. The reaction mixture was then extracted with ethyl acetate, and the combined organic phase was washed with brine, dried over anhydrous $MgSO_4$, filtered through a short plug of Celite, and concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography to furnish 13 mg (46%) of methyl 5-methylene-2,3,3*a*,4,5,11*b*-hexahydro-1*H*-cyclopenta-[3,4]pyrido[1,2-*a*]indole-11-carboxylate (**34**).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR data of various key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: chemap@emory.edu.

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