JOC The Journal of Organic Chemistry

Article

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Azepinoindole Synthesis via a *N*-Bromosuccinimide-Induced Cycloisomerization of Enaminoester/Enaminone

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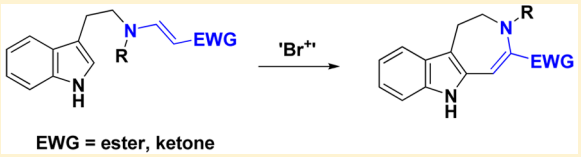
Supporting Information

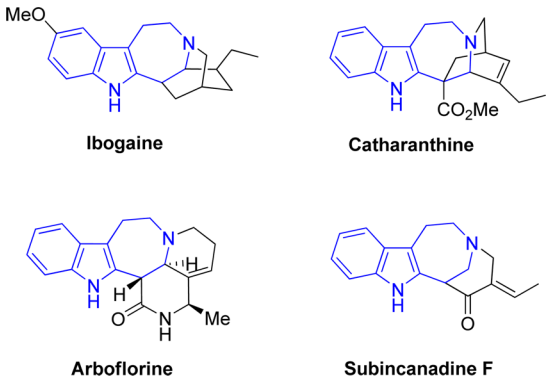
ABSTRACT: A protocol based on a newly developed *N*-bromosuccinimide (NBS)-induced cycloisomerization was described to prepare tricyclic azepino[4,5-*b*]indoles from simple *β*-enaminoesters or *β*-enaminones containing an indole unit. A mechanism involving a Pictet−Spengler cyclization, an aziridine ring formation, and a regioselective C−N bond cleavage was proposed to account for the medium-sized ring formation and the migration of electron-withdrawing group (ester, ketone).



INTRODUCTION

Azepine compounds are a kind of medium-sized nitrogen-containing heterocycles.[1] As a member of azepines, azepino[4,5-*b*]indole features an annulation of indole and azepine rings. The tricyclic seven-membered ring system has gained considerable attention for the following reasons: (1) an array of alkaloids such as ibogaine,[2] catharanthine,[3] arboflorine,[4] and subincanadine F[5] share the common azepinoindole skeleton while displaying diverse and important biological properties (Scheme 1); (2) some azepino[4,5-*b*]indoles were identified as potent 5-HT6 ligands or agonists of farnesoid X receptor.[6,7]

Scheme 1. Selected Azepino[4,5-*b*]indole-Type Alkaloids



Owing to the significant values of the azepinoindole-type alkaloids, many efforts have been devoted to their chemical synthesis, which led to the birth of a variety of methods for the construction of the tricyclic heterocycle (Scheme 2). The traditional synthesis of azepino[4,5-*b*]indoles relies on Fischer indole cyclization of phenylhydrazones generated from azepin-4-ones, which suffer from limitations such as limited substrate scope and poor regioselectivity.[8] Although modern strategies based on palladium(II)-assisted intramolecular oxidative Heck coupling or the palladium(0)-catalyzed reductive Heck-type cyclization between the C2 position of indole with the pendent alkene were advanced to construct azepino[4,5-*b*]indole rings, the unfavorable transannular interactions and entropic factors in the 7-*exo*-*trig* cyclization resulted in poor to moderate yields.[9] Distinct from the tactics by stepwise construction of either an indole ring or an azepine ring, a protocol based on ring expansion of tetrahydro-*β*-carboline was first established by Kuehne in 1985.[10] The one-carbon ring enlargement reaction was later applied by Li and Waters to their independent synthesis of alkaloid subincanadine F.[11] Recently, another ring expansion triggered by an Ir-catalyzed allylic dearomatization was developed by You, which provides an asymmetric construction of azepino[4,5-*b*]indole from tetrahydro-*γ*-carboline.[12] Following our continuing studies on indole-annulated medium-sized rings, we herein present a new NBS-induced cycloisomerization to achieve azepino[4,5-*b*]indoles from easily available *β*-enaminoesters or *β*-enaminones with a pendent indole unit. The metal-free protocol features an ester or a ketone group migration from the *β*-carbon to the *α*-carbon adjacent to the nitrogen atom of the enamine group accompanied by an azepine ring formation.

RESULTS AND DISCUSSION

At the beginning, with the aim to investigate the 6-*endo*-*dig* cycloisomerization of aza-1,5-enyne, we designed enaminoester **1a** containing an indole unit as the model substrate. Owing to the basicity of the nitrogen atom, the desired gold-catalyzed cycloisomerization of **1a** did not happen. However, in a cooperative catalysis combined by stoichiometric methanesulfonic acid and a catalytic amount of gold(I) complex, a domino Pictet−Spengler cyclization/ring expansion of tetrahydro-*β*-

Received: November 17, 2016
Published: January 13, 2017

DOI: 10.1021/acs.joc.6b02760
J. Org. Chem. 2017, 82, 1567−1574

Scheme 2. Strategies for Azepino[4,5-*b*]indole Synthesis

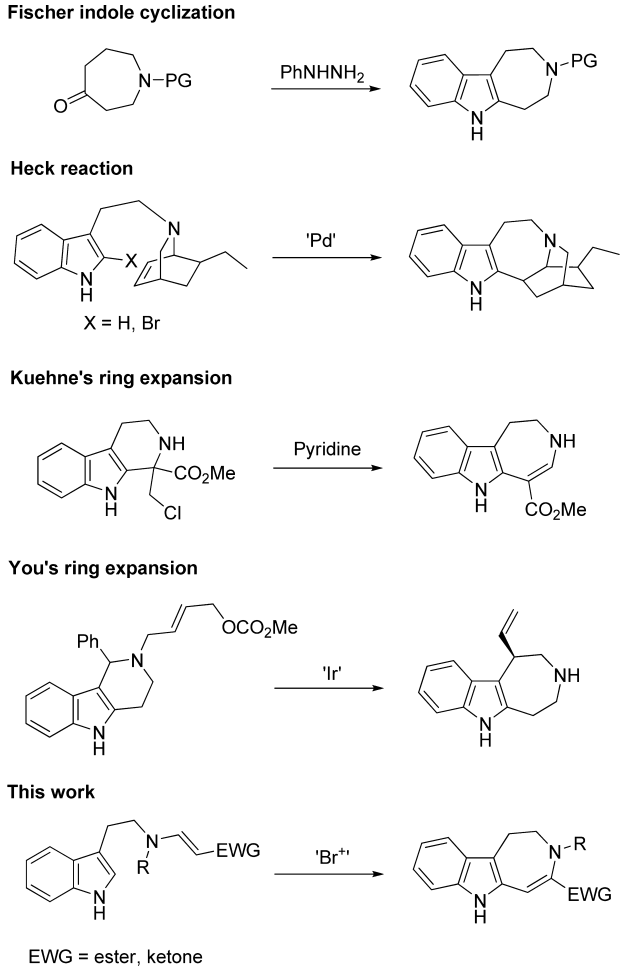
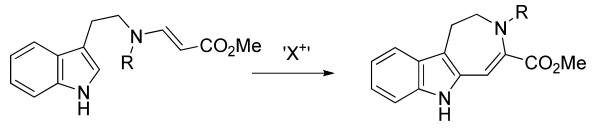


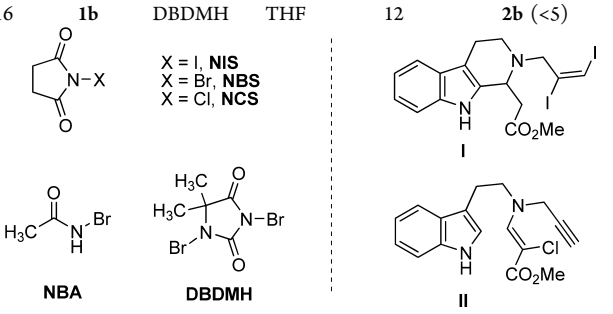
Table 1. Initial Discovery and Reaction Optimization[15a,b]



1a, R = **2a**, R =

1b, R = **2b**, R =

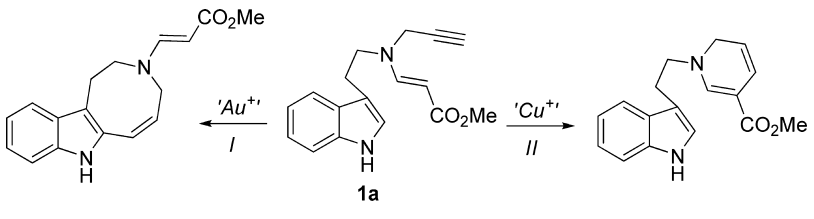
entry	substrate	'X+'[a]	solvent	time (h)	product (yield [%][b])
1	**1a**	NIS	DCE	4	**2a** (0)
2	**1a**	NIS	MeCN	4	**2a** (0)
3	**1a**	NIS	toluene	4	**2a** (0)
4[c]	**1a**	ICl	toluene	4	**2a** (0)
5[c,d]	**1a**	I_2	toluene	4	**2a** (0)
6[e]	**1a**	NCS	DCE	4	**2a** (0)
7	**1a**	NBS	THF	12	**2a** (49)
8	**1b**	NBS	THF	12	**2b** (70)
9	**1b**	NBS	DCE	12	**2b** (49)
10	**1b**	NBS	MeCN	12	**2b** (43)
11	**1b**	NBS	toluene	12	**2b** (39)
12	**1b**	NBS	$MeNO_2$	12	**2b** (<5)
13[f]	**1b**	NBS	THF	12	**2b** (45)
14	**1b**	NBA	THF	12	**2b** (65)
15	**1b**	Br_2	THF	12	**2b** (60)
16	**1b**	DBDMH	THF	12	**2b** (<5)



[a]1.0 equiv of electrophilic reagent was used. [b]Isolated yield after column chromatography. [c]2.0 equiv of $NaHCO_3$ was employed as additive. [d]Tetrahydro-*β*-carboline **I** was isolated. [e]Chlorinated enaminoester **II** was isolated. [f]The reaction was performed at 65 °C.

carboline took place by accident, delivering azocinoindole as major product (Scheme 3, route I).[13] It was confirmed that the Bronsted acid prefers to activate the enamine group rather than the terminal alkyne of **1a**, which initiated a Pictet–Spengler cyclization to yield tetrahydro-*β*-carboline intermediate. Almost concurrently, Oguri reported a copper(I) complex-catalyzed 6-*endo* cyclization of aza-1,5-enyne with the same enyne moiety as **1a** (Scheme 3, route II).[14] This finding revealed that the alkynophilic copper complex is prone to interact with the terminal alkyne instead of the enamine group. The divergent reactivity of this type of aza-1,5-enyne encouraged us to further explore possible new transformations by judiciously tuning different kinds of electrophilic reagents.[15] To our disappointment, when iodonium reagents such as NIS or ICl were employed, a messy mixture was obtained even though the starting material was consumed completely (Table 1, entries 1–4). Attempts to optimize the reaction by screening solvents proved futile. When the halonium electrophile was switched to molecular iodine, a concomitant Pictet–Spengler cyclization and 1,2-addition across the terminal alkyne was encountered (Table 1, entry 5). Further screening revealed that a chlorinated enaminoester was captured when NCS was used as an electrophile (Table 1, entry 6). To our surprise, treatment of **1a** with 1 equiv of NBS in THF afforded a less polar product in 49% yield, which was identified as 3-propargyl azepino[4,5-*b*]indole **2a** (Table 1, entry 7). The exciting results in which the terminal alkyne was kept untouched attracted us, where an ester group translocation occurred and a seven-membered nitrogen-containing ring was formed without incorporation of any

Scheme 3. Known Cycloisomerization of 1a



DOI: 10.1021/acs.joc.6b02760
J. Org. Chem. 2017, 82, 1567–1574

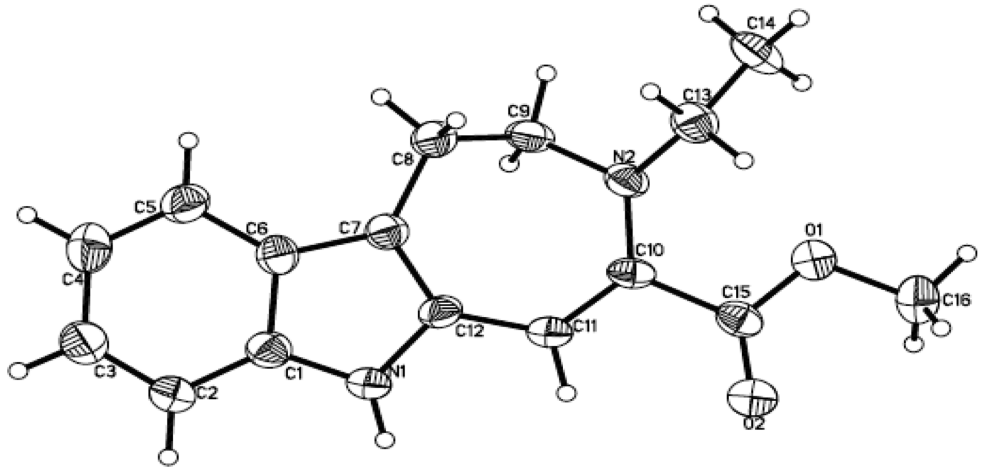


Figure 1. Thermal ellipsoid plot of **2b** (30% probability levels).

bromine atom. To further optimize the NBS-induced cycloisomerization with a consideration to exclude the possible interference of the alkyne group, we prepared β-enaminoester **1b** with an ethyl substituent instead of a propargyl group. According to the identical condition, **1b** underwent the cycloisomerization smoothly to give azepino[4,5-*b*]indole **2b** in 70% yield (Table 1, entry 8). Gratifyingly, its structure was confirmed unambiguously by X-ray crystallographic analysis (Figure 1).[16] Solvent screening revealed that THF is the best solvent. When the reaction was performed in other solvents, such as DCE, MeCN, toluene, or $MeNO_2$, the yield dropped to less than 50% (Table 1, entries 9−12). Attempts to perform the reaction at a higher temperature resulted in a decreased yield (Table 1, entry 13). When NBA or bromine was used in place of NBS, a similar scenario appeared (Table 1, entries 14 and 15). In contrast, DBDMH containing two bromine atoms proved detrimental for the transformation, and only a trace amount of azepino[4,5-*b*]indole **2b** was isolated (Table 1, entry 16).

The scope of the transformation was subsequently investigated according to the optimized condition combined by NBS and THF. As well as **1b**, enaminoesters containing a methyl and a benzyl group on the nitrogen atom of the indole ring participated in the cycloisomerization as anticipated, giving the azepinoindoles **2c,d** in comparable yields (Table 2, entries 1 and 2). On the contrary, the reaction was inhibited when an electron-withdrawing group (such as Ts) was introduced, which indicated that the electronic effect of substituents attached on the nitrogen atom is critical.[17] However, a variety of substituents with different electron properties (MeO, Me, Cl) at the C5 position of the indole ring were very compatible, and all azepinoindoles **2e−g** were isolated in an average yield greater than 86% (Table 2, entry 3). Furthermore, the presence of ester group on the side chain of enaminoester **1h** did not interfere with the conversion, furnishing the diester-substituted azepino[4,5-*b*]indole **2h** in 71% yield (Table 2, entry 4). Next, a range of enaminones **1i−k** with an aryl group attached to the carbonyl carbon were examined (Table 2, entry 5). Each enaminone substrate was transformed to the corresponding azepinoindole product, and the yield range was from 47 to 85%. It was demonstrated that an electron-donating group on the aryl ring of enaminone facilitates the cycloisomerization. When the alkylated enaminone **1l** was subjected to identical conditions, the azepinoindole **2l** was achieved in a yield similar to that of its aryl counterparts (Table 2, entry 6). In addition, as an advanced intermediate of alkaloid arboflorine, enaminone **1m**, underwent the NBS-induced cycloisomerization uneventfully to produce the multifunctionalized azepinoindole **2m** in moderate yield (Table 2, entry 7). The migration of the α-aminoketone unit was carried out successfully, which warrants further modifications such as reductive coupling of ketone with an ester group and δ-lactam formation.

Based on the above results, a plausible mechanism was proposed for the NBS-induced cycloisomerization. As shown in Scheme 4, the selective bromination of β-enaminoester or β-enaminone may yield tetrahydro-β-carboline **III**, a Pictet−Spengler product with a bromine atom located at the α position of the electron-withdrawing group. The domino sequence involves formation of a bromonium ion intermediate and an intramolecular electrophilic aromatic substitution.[18] Then, an intramolecular nucleophilic substitution takes place to give an aziridinium intermediate **IV** with a 1-azabicyclo[4.1.0]heptane scaffold. A subsequent regioselective C−N σ bond cleavage results in ring expansion of **IV** and the formation of the final azepino[4,5-*b*]indole, which is reminiscent of a retro-aza-Michael reaction. What deserves to be mentioned is that the ring opening of **IV** is independent of any nucleophile, which is complementary to the classic aziridinium reactivity patterns in which a nucleophile is essential.[19]

■ CONCLUSION

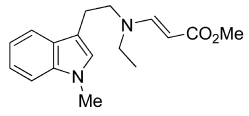
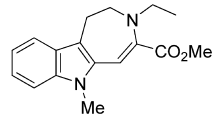
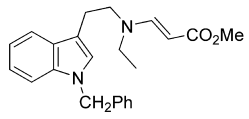
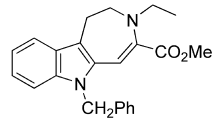
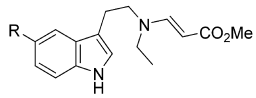
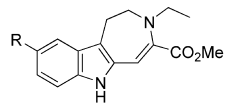
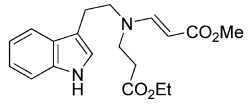
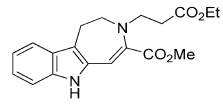
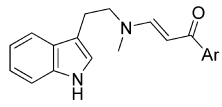
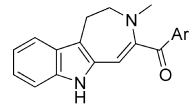
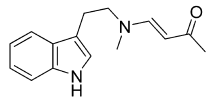
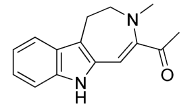
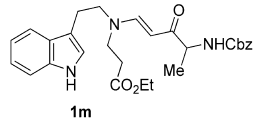
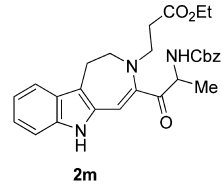
A new NBS-induced cycloisomerization of β-enaminoester or β-enaminone containing an indole unit was first developed, which provides an approach to prepare a variety of tricyclic azepino[4,5-*b*]indoles. A possible mechanism involving a Pictet−Spengler cyclization, an aziridine ring formation, and a C−N σ bond cleavage was proposed to account for the azepine ring formation as well as the translocation of an electron-withdrawing group (ester, ketone). Further detailed study of the mechanism and application of the metal-free cycloisomerization in the synthesis of polycyclic indole alkaloids is underway.

■ EXPERIMENTAL SECTION

General Information. All melting points were determined without correction. ^{1}H NMR spectra were obtained at 300, 400, and 600 MHz, and ^{13}C NMR spectra were obtained at 75, 100, and 150 MHz. Spectra were recorded in $CDCl_3$ and DMSO-d_6 solution using the residual

DOI: 10.1021/acs.joc.6b02760
J. Org. Chem. 2017, 82, 1567−1574

Table 2. Azepinoindole Synthesis by a NBS-Induced Cycloisomerization[a]

entry	enaminoester/ enaminone	azepino[4,5-*b*]indole	yield (%)[b]
1	 **1c**	 **2c**	81
2	 **1d**	 **2d**	60
3	 **1e**: R = MeO **1f**: R = Me **1g**: R = Cl	 **2e**: R = MeO **2f**: R = Me **2g**: R = Cl	89 86 88
4	 **1h**	 **2h**	71
5	 **1i:** Ar = Ph **1j:** Ar = 4-MeOPh **1k:** Ar = 4-NO_2Ph	 **2i:** Ar = Ph **2j:** Ar = 4-MeOPh **2k:** Ar = 4-NO_2Ph	47 85 60
6	 **1l**	 **2l**	66
7	 **1m**	 **2m**	45

[a]Reaction conditions: enamine substrate (0.5 mmol), NBS (0.5 mmol), THF (10.0 mL), rt, 12 h. [b]Isolated yield after column chromatography.

protonated solvent as the internal standard; *J* values were given in hertz. High-resolution mass spectrometry measurements were carried out on a Q-TOF apparatus.

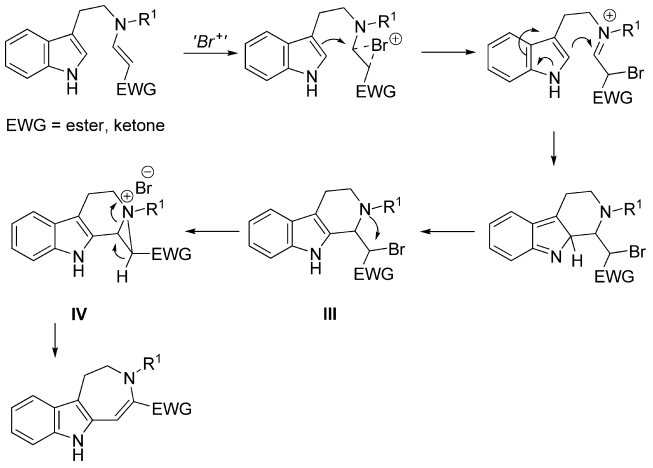
General Procedure for the Preparation of Enaminoesters or Enaminones. A solution of methyl propiolate or prop-2-yn-1-one (5.5 mmol, 1.1 equiv) and tryptamine (5.0 mmol) in dry THF (20 mL) was stirred at room temperature for 5 h in open air. The reaction mixture was concentrated under vacuum to afford the crude product, which was purified by flash silica gel column chromatography (petroleum ether/ethyl acetate, 3:1 v/v for **1a**−**1h**; 1:1 v/v for **1i**−**1m**) to give pure enaminoester or enaminone.

*(E)-Methyl 3-[(2-(1H-Indol-3-yl)ethyl)(prop-2-yn-1-yl)amino]-acrylate (**1a**):*[14] Colorless oil, 1.13 g, 80% yield; R_f (PE/EtOAc 2:1) = 0.20; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.47 (d, *J* = 13.1 Hz, 1H), 7.37 (d, *J* = 7.7 Hz, 1H), 7.22 (t, *J* = 7.0 Hz, 1H), 7.15 (t, *J* = 7.1 Hz, 1H), 6.98 (d, *J* = 1.3 Hz, 1H), 4.80 (d, *J* = 13.2, 1H), 3.81 (d, *J* = 1.9 Hz, 2H), 3.71 (s, 3H), 3.52 (t, *J* = 7.0 Hz, 2H), 3.06 (t, *J* = 7.2 Hz, 2H), 2.33 (t, *J* = 2.2 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 150.8, 136.2, 126.9, 122.3, 121.9, 119.3, 118.2, 111.7, 111.3, 85.8, 77.6, 73.4, 50.6, 23.6; IR (KBr) ν_{max} 3288, 1674, 1608, 1159, 744 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{17}H_{19}N_2O_2$ 283.1447 $[M + H]^+$, found 283.1445.

*(E)-Methyl 3-[(2-(1H-Indol-3-yl)ethyl)(ethyl)amino]acrylate (**1b**):* Colorless oil, 1.21 g, 89% yield; R_f (PE/EtOAc 3:1) = 0.26; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 13.1 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.21 (dt, J_1 = 7.1 Hz, J_2 = 1.0 Hz, 1H), 7.14 (dt, J_1 = 7.9 Hz, J_2 = 1.0 Hz, 1H), 7.00 (s, 1H), 4.66 (d, *J* = 12.6 Hz, 1H), 3.68 (s, 3H), 3.44 (t, *J* = 7.2 Hz, 2H), 3.15 (q, *J* = 7.2

DOI: 10.1021/acs.joc.6b02760
J. Org. Chem. 2017, 82, 1567−1574

Scheme 4. Proposed Mechanism



Hz, 2H), 3.02 (t, J = 7.0 Hz, 2 H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 151.3, 136.2, 127.0, 122.1, 122.0, 119.3, 118.3, 111.3, 83.2, 50.5; IR (KBr) ν_{max} 3411, 3307, 2946, 1673, 1601, 1423, 1359, 1153, 788, 743; HRMS (ESI) m/z calcd for $C_{16}H_{20}N_2NaO_2$ 295.1422 $[M + Na]^+$, found 295.1419.

*(E)-Methyl 3-[Ethyl(2-(1-methyl-1H-indol-3-yl)ethyl)amino]-acrylate (**1c**):* Colorless oil, 1.28 g, 90% yield; R_f (PE/EtOAc 3:1) = 0.21; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 7.9 Hz, 1H), 7.50 (d, J = 13.1 Hz, 1H), 7.31 (d, J = 8.2 Hz, 1H), 7.25 (dt, J_1 = 6.9 Hz, J_2 = 1.0 Hz, 1H), 7.14 (td, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 6.86 (s, 1H), 4.68 (d, J = 12.2 Hz, 1H), 3.75 (s, 3H), 3.69 (s, 3H), 3.42 (t, J = 7.3 Hz, 2H), 3.16 (q, J = 7.2 Hz, 2H), 3.00 (t, J = 7.1 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 151.1, 136.9, 127.5, 126.7, 121.7, 118.9, 118.5, 109.3, 83.3, 50.4, 32.5; IR (KBr) ν_{max} 2974, 2944, 1688, 1608, 1142, 786, 741 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{23}N_2O_2$ 287.1760 $[M + H]^+$, found 287.1755.

*(E)-Methyl 3-[(2-(1-Benzyl-1H-indol-3-yl)ethyl)(ethyl)amino]-acrylate (**1d**):* Colorless oil, 1.54 g, 85% yield; R_f (PE/EtOAc 2:1) = 0.17; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 7.8 Hz, 1H), 7.50 (d, J = 13.1 Hz, 1H), 7.34−7.27 (m, 4H), 7.22 (td, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.18−7.11 (m, 3H), 6.94 (s, 1H), 5.28 (s, 2H), 4.68 (d, J = 11.6 Hz, 1H), 3.69 (s, 3H), 3.45 (t, J = 7.1 Hz, 2H), 3.15 (q, J = 7.2 Hz, 2H), 3.03 (t, J = 7.1 Hz, 2H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 151.1, 137.4, 136.6, 128.7, 127.7, 127.5, 126.7, 126.1, 121.9, 119.2, 118.6, 109.8, 83.3, 50.4, 49.8; IR (KBr) ν_{max} 2975, 2953, 1608, 1467, 1357, 1142, 786, 740 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{26}N_2NaO_2$ 385.1892 $[M + Na]^+$, found 385.1889.

*(E)-Methyl 3-[Ethyl(2-(5-methoxy-1H-indol-3-yl)ethyl)amino]-acrylate (**1e**):* Colorless oil, 1.40 g, 93% yield; R_f (PE/EtOAc 3:1) = 0.20; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.48 (d, J = 13.0 Hz, 1H), 7.26 (d, J = 8.8 Hz, 1H), 6.99 (dd, J_1 = 12.5 Hz, J_2 = 1.5 Hz, 2H), 6.87 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 4.67 (d, J = 9.9, 1H), 3.88 (s, 3H), 3.67 (s, 3H), 3.42 (t, J = 7.2 Hz, 2H), 3.14 (q, J = 7.2 Hz, 2H), 2.98 (t, J = 7.0 Hz, 2H), 1.12 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 154.1, 151.2, 131.4, 127.5, 122.8, 112.3, 112.0, 100.3, 83.4, 55.9, 50.5; IR (KBr) ν_{max} 3310, 2945, 2831, 1673, 1601, 1146, 793, 639 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{23}N_2O_3$ 303.1709 $[M + H]^+$, found 303.1706.

*(E)-Methyl 3-[Ethyl(2-(5-methyl-1H-indol-3-yl)ethyl)amino]-acrylate (**1f**):* Colorless oil, 1.35 g, 95% yield; R_f (PE/EtOAc 3:1) = 0.28; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.49 (d, J = 13.1 Hz, 1H), 7.35 (s, 1H), 7.26 (d, J = 8.2 Hz, 1H), 7.03 (d, J = 8.2 Hz, 1H), 6.96 (s, 1H), 4.66 (d, J = 11.5 Hz, 1H), 3.68 (s, 3H), 3.43 (t, J = 7.2 Hz, 2H), 3.16 (q, J = 7.2 Hz, 2H), 2.99 (t, J = 8.1 Hz, 2H), 2.47 (s, 3H), 1.14 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 151.3, 134.6, 128.7, 127.3, 123.7, 122.2, 118.0, 111.0, 83.3, 50.5, 21.5; IR (KBr) ν_{max} 3307, 1672, 1604, 1423, 1359, 1194, 1146, 791 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{23}N_2O_2$ 287.1760 $[M + H]^+$, found 287.1758.

*(E)-Methyl 3-[(2-(5-Chloro-1H-indol-3-yl)ethyl)(ethyl)amino]-acrylate (**1g**):* Colorless oil, 1.30 g, 88% yield; R_f (PE/RtOAc 3:1) = 0.23; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H), 7.50 (d, J = 1.5 Hz, 1H), 7.44 (d, J = 12.9 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.13 (dd, J_1 = 8.6 Hz, J_2 = 1.9 Hz, 1H), 6.98 (s, 1H), 4.64 (d, J = 13.0 Hz, 1H), 3.68 (s, 3H), 3.37 (t, J = 7.2 Hz, 2H), 3.11 (q, J = 7.2 Hz, 2H), 2.92 (t, J = 7.7 Hz, 2H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 151.2, 134.6, 128.2, 125.1, 123.6, 122.3, 117.8, 112.4, 83.4, 50.5; IR (KBr) ν_{max} 3289, 2946, 1671, 1604, 1463, 1423, 1359, 1254, 1197, 1149, 1101, 794 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{19}ClN_2NaO_2$ 329.1033 $[M + Na]^+$, found 329.1031.

*(E)-Methyl 3-[(2-(1H-Indol-3-yl)ethyl)(3-ethoxy-3-oxopropyl)-amino]acrylate (**1h**):* Colorless oil, 1.55 g, 90% yield; R_f (PE/EtOAc 3:1) = 0.21; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.57 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 13.2 Hz, 1H), 7.36 (d, J = 7.9 Hz, 1H), 7.20 (dt, J_1 = 7.2 Hz, J_2 = 1.1 Hz, 1H), 7.13 (dt, J_1 = 7.9 Hz, J_2 = 1.2 Hz, 1H),, 6.97 (d, J = 2.1 Hz, 1H), 4.67 (d, J = 13.1 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.70 (s, 3H), 3.48−3.36 (m, 4H), 3.00 (t, J = 7.9 Hz, 2H), 2.51 (t, J = 6.9 Hz, 2H), 1.24 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.0, 151.2, 136.2, 126.9, 122.1, 122.0, 119.3, 118.3, 111.9, 111.3, 84.5, 77.2, 60.8, 53.4, 50.5, 14.0; IR (KBr) ν_{max} 3408, 3317, 2981, 2946, 1731, 1605, 1147, 1053, 744 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{25}N_2O_4$ 345.1814 $[M + H]^+$, found 345.1811.

*(E)-3-[(2-(1H-Indol-3-yl)ethyl)(methyl)amino]-1-phenylprop-2-en-1-one (**1i**):* Yellow solid, 1.21 g, 80% yield; mp 182−184 °C (EtOAc/PE); R_f (PE/EtOAc 1:1) = 0.22; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.82−7.78 (m, 3H), 7.57−7.55 (m, 1H), 7.44−7.35 (m, 4H), 7.24−7.15 (m, 2H), 6.98 (s, 1H), 5.70 (d, J = 12.4 Hz, 1H), 3.59 (t, J = 7.2 Hz, 2H), 3.06−2.88 (m, 5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 185.9, 153.7, 140.2, 136.2, 130.7, 128.1, 127.1, 127.0, 123.3, 121.0, 118.4, 118.2, 111.4, 110.5, 91.1, 58.0, 35.4, 24.4; IR (KBr) ν_{max} 3185, 2925, 1634, 1581, 1533, 1231, 1058, 751, 710 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{21}N_2O$ 305.1654 $[M + H]^+$, found 305.1651.

*(E)-3-[(2-(1H-Indol-3-yl)ethyl)(methyl)amino]-1-(4-methoxyphenyl)prop-2-en-1-one (**1j**):* White solid, 1.44 g, 85% yield; mp 161−163 °C (EtOAc/PE); R_f (PE/EtOAc 1:1) = 0.16; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31(s, 1H), 7.82−7.78 (m, 3H), 7.58 (s, 1H), 7.37 (d, J = 7.9 Hz, 1H), 7.22 (t, J = 7.1 Hz, 1H), 7.15 (t, J = 7.0 Hz, 1H), 6.99 (s, 1H), 6.89 (d, J = 8.7 Hz, 2H), 5.69 (d, J = 12.4 Hz, 1H), 3.85 (s, 3H), 3.58 (t, J = 7.2 Hz, 2H), 3.06−2.92 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 187.8, 161.8, 153.5, 136.3, 132.9, 129.4, 126.9, 122.4, 121.8, 119.1, 118.1, 113.2, 111.5, 111.2, 92.0, 58.6, 55.2, 35.9, 25.2; IR (KBr) ν_{max} 3162, 2928, 2841, 1598, 1511, 1370, 1240, 1164, 902, 780, 738, 600 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{23}N_2O_2$ 335.1760 $[M + H]^+$, found 335.1759.

*(E)- and (Z)-3-[(2-(1H-Indol-3-yl)ethyl)(methyl)amino]-1-(4-nitrophenyl)prop-2-en-1-one (**1k**):* Yellow solid (a mixture contains E and Z isomers), 1.40 g, 80% yield; mp 168−171 °C (EtOAc/PE); R_f (PE/EtOAc 1:1) = 0.12; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.23−8.15 (m, 4.6 H), 7.90−7.68 (m, 4H), 7.59 (t, J = 8.3 Hz, 2.2 Hz), 7.40 (d, J = 8.7 Hz, 1.6 H), 7.33−7.14 (m, 4.3 H), 7.02 (s, 1.7 H), 5.63 (d, J = 12.4 Hz, 1.1 H), 5.48 (d, J = 12.4 Hz, 0.6 H), 3.65 (q, J = 7.2 Hz, 3.1 H), 3.17−3.02 (m, 4.7 H), 2.98 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 183.9, 183.5, 154.9, 148.4, 148.37, 145.9, 145.8, 136.3, 136.2, 128.4, 127.0, 123.5, 123.4, 121.0, 118.4, 118.3, 111.6, 111.4, 110.8, 110.3, 91.3, 90.7, 58.1, 50.4, 42.9, 35.5, 24.2, 21.4; IR (KBr) ν_{max} 3181, 2925, 2842, 1596, 1513, 1370, 1240, 1164, 902, 779, 738, 600 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{20}N_3O_3$ 350.1505 $[M + H]^+$, found 350.1502.

*(E)-4-[(2-(1H-Indol-3-yl)ethyl)(methyl)amino]-but-3-en-2-one (**1l**):* Yellow oil, 1.09 g, 90% yield; R_f (PE/EtOAc 1:1) = 0.1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.53 (d, J = 7.8 Hz, 1H), 7.40 (d, J = 12.9 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.18 (td, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 7.11 (td, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H), 6.91 (s, 1H), 5.07 (d, J = 12.8 Hz, 1H), 3.46 (t, J = 7.4 Hz, 2H), 2.98 (t, J = 7.1 Hz, 2H), 2.78 (s, 3H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 192.9, 152.5, 136.2, 127.0, 123.4, 121.0, 118.4, 111.4, 110.6, 79.2, 57.4, 54.9, 34.8, 24.4; IR (KBr) ν_{max} 3407, 3245, 2924, 1622, 1558, 1361, 1264,

DOI: 10.1021/acs.joc.6b02760
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965, 743 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{19}N_2O$ 243.1497 $[M + H]^+$, found 243.1499.

*(E)-Ethyl 3-[(2-(1H-Indol-3-yl)ethyl)(4-(benzyloxycarbonylamino)-3-oxopent-1-enyl)amino]propanoate (**1m**):* Yellow oil, 1.79 g, 73% yield; R_f (PE/EtOAc 1:1) = 0.21; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.59−7.55 (m, 2H), 7.36−7.29 (m, 4H), 7.21 (td, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 7.14 (td, J_1 = 7.9 Hz, J_2 = 1.1 Hz, 1H), 6.98 (s, 1H), 5.76 (s, 1H), 5.12−5.06 (m, 3H), 4.30 (t, J = 6.0 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.54 (t, J = 7.2 Hz, 2H), 3.46 (t, J = 6.9 Hz, 2H), 3.04 (t, J = 7.2 Hz, 2H), 2.53 (t, J = 6.9 Hz, 2H), 1.32−1.23 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.7, 170.7, 155.4, 151.9, 151.5, 136.3, 136.0, 128.0, 127.5, 127.48, 122.1, 121.6, 117.7, 111.2, 92.0, 76.4, 66.1, 60.6, 56.7, 51.3, 48.8, 44.0, 33.7, 30.6, 25.2, 21.6, 19.5, 13.7; IR (KBr) ν_{max} 3319, 2979, 1724, 1561, 1455, 1370, 1285, 1044, 742 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{34}N_3O_5$ 492.2498 $[M + H]^+$, found 492.2491.

General Procedure for the *N*-Bromosuccinimide-Induced Cycloisomerization of Enaminoester/Enaminone. To a single-necked flask containing enaminoester or enaminone (0.5 mmol) and dry THF (10.0 mL) was added *N*-bromosuccinimide (90 mg, 0.5 mmol) at room temperature in open air. The mixture was stirred until completion of reaction (monitored by TLC). The reaction mixture was concentrated under reduced pressure, and then the residue was dissolved in CH_2Cl_2 (30 mL). The obtained solution was washed with brine (20 mL) and water (20 mL) successively and then dried with Na_2SO_4. After filtration, the filtrate was concentrated under vacuum. The residue was purified by flash aluminum oxide column chromatography (petroleum ether/ethyl acetate, 6:1 v/v for **2a−2h**; 3:1 v/v for **2i−2m**) to give pure azepinoindole.

*Methyl 3-(Prop-2-ynyl)-1,2,3,6-tetrahydroazepino[4,5-b]indole-4-carboxylate (**2a**):* Yellow solid, 68.6 mg, 49% yield; mp 219−220 °C (EtOAc/PE); R_f (PE/EtOAc 6:1) = 0.28; ^1H NMR (600 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.56 (d, J = 7.9 Hz, 1H), 7.32 (d, J = 8.1 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 6.94 (s, 1H), 3.94 (d, J = 2.4 Hz, 2H), 3.87 (s, 3H), 3.35 (t, J = 4.2 Hz, 2H), 3.22 (t, J = 4.7 Hz, 2H), 2.23 (t, J = 2.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.1, 136.1, 135.8, 130.9, 128.9, 123.1, 119.8, 118.7, 117.7, 111.1, 110.6, 80.8, 72.0, 52.4, 49.4, 42.6, 25.1; IR (KBr) ν_{max} 3334, 3275, 1689, 1597, 1257, 768, 742; HRMS (ESI) m/z calcd for $C_{17}H_{17}N_2O_2$ 281.1290 $[M + H]^+$, found 281.1287.

*Methyl 3-Ethyl-1,2,3,6-tetrahydroazepino[4,5-b]indole-4-carboxylate (**2b**):* Yellow solid, 94.5 mg, 70% yield; mp 181−182 °C (EtOAc/PE); R_f (PE/EtOAc 6:1) = 0.42; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 7.1 Hz, 1H), 7.11 (td, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 6.73 (s, 1H), 3.86 (s, 3H), 3.19 (t, J = 4.2 Hz, 2H), 3.08−3.03 (m, 4H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 138.1, 136.0, 131.7, 129.0, 122.6, 119.6, 118.3, 116.5, 110.5, 107.6, 52.3, 47.9, 47.4, 25.3, 14.4; IR (KBr) ν_{max} 3344, 1687, 1597, 1273, 1216, 735 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{19}N_2O_2$ 271.1447 $[M + H]^+$, found 271.1449.

*Methyl 3-Ethyl-6-methyl-1,2,3,6-tetrahydroazepino[4,5-b]indole-4-carboxylate (**2c**):* Yellow solid, 115.0 mg, 81% yield; mp 97−98 °C (EtOAc/PE); R_f (PE/EtOAc 6:1) = 0.60; ^1H NMR (600 MHz, $CDCl_3$) δ 7.55 (d, J = 7.9 Hz, 1H), 7.28 (d, J = 8.2 Hz, 1H), 7.23 (t, J = 7.3 Hz, 1H), 7.09 (t, J = 7.4 Hz, 1H), 6.88 (s, 1H), 3.88 (s, 3H), 3.78 (s, 3H), 3.17 (t, J = 4.1 Hz, 2H), 3.09 (t, J = 4.0 Hz, 2H), 3.04 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.1, 137.8, 137.5, 132.7, 127.5, 122.4, 119.1, 118.3, 116.5, 108.9, 105.2, 52.3, 48.1, 47.2, 29.4, 25.3, 14.3; IR (KBr) ν_{max} 2842, 1704, 1593, 1334, 1262, 1187, 766, 740 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_2$ 285.1603 $[M + H]^+$, found 285.1602.

*Methyl 6-Benzyl-3-ethyl-1,2,3,6-tetrahydroazepino[4,5-b]indole-4-carboxylate (**2d**):* Yellow solid, 108.0 mg, 60% yield; mp 70−71 °C (EtOAc/PE); R_f (PE/EtOAc 3:1) = 0.6; ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.7 Hz, 1H), 7.27−7.20 (m, 4H), 7.17 (td, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.12−7.08 (m, 3H), 6.78 (s, 1H), 5.41 (s, 2H), 3.78 (s, 3H), 3.15 (t, J = 3.8 Hz, 2H), 3.08 (t, J = 3.2 Hz, 2H), 3.00 (q, J = 7.0 Hz, 2H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 138.1, 137.9, 137.3, 132.5, 128.6, 127.7, 127.2, 126.3, 122.5, 119.4, 118.3, 116.8, 109.3, 104.6, 52.2, 48.1, 47.1, 46.2, 25.4, 14.2; IR (KBr) ν_{max} 2921, 1713, 1593, 1452, 1258, 1232, 1095, 735, 694 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{25}N_2O_2$ 361.1916 $[M + H]^+$, found 361.1914.

*Methyl 3-Ethyl-9-methoxy-1,2,3,6-tetrahydroazepino[4,5-b]-indole-4-carboxylate (**2e**):* Yellow solid, 133.5 mg, 89% yield; mp 178−180 °C (EtOAc/PE); R_f (PE/EtOAc 6:1) = 0.32; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.20 (d, J = 8.8 Hz, 1H), 6.97 (d, J = 2.3 Hz, 1H), 6.85 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.70 (s, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.19 (t, J = 4.1 Hz, 2H), 3.08−3.01 (m, 4H), 1.25 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0, 154.2, 137.9, 132.5, 131.2, 129.3, 116.2, 112.8, 111.3, 107.9, 100.1, 55.9, 52.2, 47.8, 47.5, 25.3, 14.3; IR (KBr) ν_{max} 3347, 2927, 1694, 1600, 1448, 1275, 1212, 764, 629 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{20}N_2NaO_3$ 323.1372 $[M + Na]^+$, found 323.1370.

*Methyl 3-Ethyl-9-methyl-1,2,3,6-tetrahydroazepino[4,5-b]indole-4-carboxylate (**2f**):* Yellow solid, 122.0 mg, 86% yield; mp 161−162 °C (EtOAc/PE); R_f (PE/EtOAc 6:1) = 0.46; ^1H NMR (400 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.33 (s, d, J = 0.5 Hz, 1H), 7.19 (d, J = 8.2 Hz, 1H), 7.01 (dd, J_1 = 8.2 Hz, J_2 = 1.1 Hz, 1H), 6.73 (s, 1H), 3.86 (s, 3H), 3.17 (t, J = 4.2 Hz,, 2H), 3.07−3.02 (m, 4H), 2.47 (s, 3H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 137.8, 134.4, 131.8, 129.2, 128.8, 124.2, 118.0, 116.1, 110.2, 108.0, 52.2, 47.8, 47.4, 25.2, 21.5, 14.3; IR (KBr) ν_{max} 3351, 1687, 1596, 1434, 1328, 1270, 1212, 789, 770, 610 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_2$ 285.1603 $[M + H]^+$, found 285.1600.

*Methyl 9-Chloro-3-ethyl-1,2,3,6-tetrahydroazepino[4,5-b]indole-4-carboxylate (**2g**):* Yellow solid, 133.8 mg, 88% yield; mp 180−181 °C (EtOAc/PE); R_f (PE/EtOAc 6:1) = 0.22; ^1H NMR (600 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.48 (d, J = 1.3 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 7.11 (dd, J_1 = 8.5 Hz, J_2 = 1.7 Hz, 1H), 6.64 (s, 1H), 3.86 (s, 3H), 3.17 (t, J = 3.7 Hz, 2H), 3.05 (q, J = 7.0 Hz, 2H), 2.99 (t, J = 4.3 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.8, 138.9, 134.3, 133.2, 130.0, 125.2, 122.5, 117.7, 115.6, 111.4, 106.4, 52.3, 47.9, 47.5, 25.3, 14.3; IR (KBr) ν_{max} 3337, 1687, 1593, 1270, 1212, 1059, 793; HRMS (ESI) m/z calcd for $C_{16}H_{18}ClN_2O_2$ 305.1057 $[M + H]^+$, found 305.1059.

*Methyl 3-(3-Ethoxy-3-oxopropyl)-1,2,3,6-tetrahydroazepino[4,5-b]indole-4-carboxylate (**2h**):* Yellow solid, 121.0 mg, 71% yield; mp 140−142 °C (EtOAc/PE); R_f (PE/EtOAc 6:1) = 0.11; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (s, 1H), 7.54 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.19 (dt, J_1 = 7.0 Hz, J_2 = 1.1 Hz, 1H), 7.11 (dt, J_1 = 8.0 Hz, J_2 = 1.1 Hz, 1H), 6.76 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.85 (s, 3H), 3.35 (t, J = 7.3 Hz, 2H), 3.18−3.07 (m, 4H), 2.75 (t, J = 7.7 Hz, 2H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 166.6, 137.3, 136.0, 131.3, 128.9, 122.9, 119.6, 118.4, 116.7, 110.5, 108.8, 60.5, 52.2, 49.2, 48.4, 34.5, 25.5, 14.1; IR (KBr) ν_{max} 3345, 2948, 1731, 1686, 1596, 1273, 1184, 744, 614 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{23}N_2O_4$ 343.1658 $[M + H]^+$, found 343.1655.

*3-Methyl-1,2,3,6-tetrahydroazepino[4,5-b]indol-4-yl)(phenyl)-methanone (**2i**):* Red solid, 80 mg, 47% yield; mp 210−212 °C (EtOAc/PE); R_f (PE/EtOAc 3:1) = 0.30; ^1H NMR (300 MHz, $CDCl_3$) δ 7.89−7.86 (m, 3H), 7.60−7.55 (m, 2H), 7.45 (t, J = 7.2 Hz, 2H), 7.29 (d, J = 7.6 Hz, 1H), 7.18 (dt, J_1 = 7.0 Hz, J_2 = 1.2 Hz, 1H), 7.12 (dt, J_1 = 7.8 Hz, J_2 = 1.3 Hz, 1H), 6.20 (s, 1H), 3.27 (t, J = 4.4 Hz, 2H), 3.15−3.12 (m, 2H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194..8, 145.9, 138.6, 136.1, 132.3, 132.0, 129.6, 128.9, 128.2, 122.5, 119.5, 118.2, 116.5, 110.5, 108.9, 51.4, 41.5, 25.0; IR (KBr) ν_{max} 3300, 2898, 1644, 1567, 1341, 1222, 732, 704, 685, 648 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{17}N_2O$ 301.1341 $[M - H]^-$, found 301.1343.

*4-Methoxyphenyl-(3-methyl-1,2,3,6-tetrahydroazepino[4,5-b]-indol-4-yl)methanone (**2j**):* Red solid, 141.0 mg, 85% yield; mp 205−207 °C (EtOAc/PE); R_f (PE/EtOAc 3:1) = 0.18; ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.92 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 7.4 Hz, 1H), 7.27 (d, J = 9.9 Hz, 1H), 7.18−7.07 (m, 2H), 6.93 (d, J = 8.6 Hz, 2H), 6.14 (s, 1H), 3.87 (s, 3H), 3.25 (s, 2H), 3.11 (s, 2H), 2.69 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.4, 163.2, 146.3, 136.0, 132.3, 132.0, 131.1, 129.0, 122.3, 119.5, 118.1, 115.8, 113.5, 110.4, 106.6, 55.4, 51.5, 41.6, 25.1; IR (KBr) ν_{max} 3306, 2839, 1638, 1589,

DOI: 10.1021/acs.joc.6b02760
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1566, 1342, 1259, 1172, 782, 734, 644 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{19}N_2O_2$ $[M - H]^-$ 331.1447, found 331.1446.

*3-Methyl-1,2,3,6-tetrahydroazepino[4,5-b]indol-4-yl)(4-nitrophenyl)methanone (**2k**):* Red solid, 104.0 mg, 60% yield; mp 208−210 °C (EtOAc/PE); R_f (PE/EtOAc 3:1) = 0.31; ^1H NMR (400 MHz, $CDCl_3$) δ 8.31−8.29 (m, 2H), 8.01−7.99 (m, 2H), 7.91 (s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.31 (d, J = 8.1 Hz, 1H), 7.22 (dt, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.14 (dt, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 6.31 (s, 1H), 3.26−3.24 (m, 2H), 3.17−3.15 (m, 2H), 2.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.6, 149.6, 145.1, 144.2, 136.4, 131.4, 130.4, 128.8, 123.4, 123.3, 119.9, 118.7, 118.2, 111.3, 110.6, 51.2, 41.6, 24.9; IR (KBr) ν_{max} 3387, 2923, 1651, 1566, 1518, 1338, 1220, 1093, 753, 717, 656, 481 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{16}N_3O_3$ $[M - H]^-$ 346.1192, found 346.1189.

*1-(3-Methyl-1,2,3,6-tetrahydroazepino[4,5-b]indol-4-yl)ethanone (**2l**):* Yellow solid, 80 mg, 66% yield; mp 142−144 °C (EtOAc/PE); R_f (PE/EtOAc 3:1) = 0.23; ^1H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.20 (dt, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.12 (dt, J_1 = 8.0 Hz, J_2 = 1.0 Hz, 1H), 6.63 (s, 1H), 3.13−3.08 (m, 4H), 2.77 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 146.7, 136.3, 131.4, 128.8, 122.9, 119.6, 118.5, 117.5, 110.6, 109.2, 51.0, 41.1, 27.0, 23.8; IR (KBr) ν_{max} 3300, 2933, 1661, 1573, 1342, 1190, 738, 639, 528 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{15}N_2O$ $[M - H]^-$ 239.1184, found 239.1180.

*Ethyl 3-(4-(2-(Benzyloxycarbonylamino)propanoyl)-1,2-dihydroazepino[4,5-b]indol-3(6H)-yl)propanoate (**2m**):* Yellow solid, 110.0 mg, 45% yield; mp 49−52 °C (EtOAc/PE); R_f (PE/EtOAc 3:1) = 0.19; ^1H NMR (400 MHz, $CDCl_3$) δ 8.33 (s, 1H), 7.56 (d, J = 7.8 Hz, 1H), 7.37−7.29 (m, 6H), 7.22 (dt, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 7.13 (dt, J_1 = 7.8 Hz, J_2 = 0.6 Hz, 1H), 6.70 (s, 1H), 5.85 (s, 1H), 5.20−5.14 (m, 3H), 4.09 (q, J = 7.1 Hz, 2H), 3.49−3.45 (m, 1H), 3.29−3.20 (m, 3H), 2.98−2.92 (m, 1H), 2.80−2.65 (m, 3H), 1.40 (d, J = 7.0 Hz, 3H), 1.19 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 172.1, 155.8, 143.0, 136.4, 136.3, 131.0, 128.7, 128.5, 128.1, 127.9, 123.3, 119.7, 118.7, 118.1, 110.9, 110.8, 66.8, 60.5, 52.0, 48.9, 48.2, 34.4, 29.6, 25.7, 20.0, 14.0; IR (KBr) ν_{max} 3234, 2979, 1715, 1634, 1541, 1445, 1237, 1203, 1024, 744, 697 cm^{-1}; HRMS (ESI) m/z calcd for $C_{28}H_{31}N_3NaO_5$ $[M + Na]^+$ 512.2161, found 512.2159.

*(E)-Methyl 2-(2-(2,3-Diiodoallyl)-2,3,4,9-tetrahydro-1H-pyrido-[3,4-b]indol-1-yl)acetate (**I**):* Oil, 60% yield; R_f (PE/EtOAc 2:1) = 0.52; ^1H NMR (400 MHz, $CDCl_3$) δ 8.46 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.18 (td, J_1 = 8.1 Hz, J_2 = 1.2 Hz, 1H), 7.11 (td, J_1 = 7.0 Hz, J_2 = 2.7 Hz, 1H), 7.07 (s, 1H), 4.15 (dd, J_1 = 9.6 Hz, J_2 = 4.4 Hz, 1H), 3.76 (s, 3H), 3.47 (d, J = 14.3 Hz, 1H), 3.37 (d, J = 14.2 Hz, 1H), 3.17−3.15 (m, 1H), 3.08−2.93 (m, 3H), 2.88 (dd, J_1 = 17.4 Hz, J_2 = 9.7 Hz, 1H), 2.68−2.62 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 135.6, 133.8, 126.9, 121.8, 119.2, 118.2, 111.0, 107.8, 105.4, 80.9, 63.7, 53.1, 52.0, 44.1, 40.6, 18.2; IR (KBr) ν_{max} 3399, 2946, 1722, 1437, 1302, 741 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{19}I_2N_2O_2$ 536.9536 $[M + H]^+$, found 536.9523.

*(Z)-Methyl 3-[(2-(1H-Indol-3-yl)ethyl)(pro-2-ynyl)amino]-2-chloroacrylate (**II**):* Oil, 80% yield; R_f (PE/EtOAc 2:1) = 0.27; ^1H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.54 (s, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.22 (td, J_1 = 7.0 Hz, J_2 = 1.1 Hz, 1H), 7.15 (td, J_1 = 7.9 Hz, J_2 = 0.9 Hz, 1H), 7.03 (d, J = 2.2 Hz, 1H), 4.16 (d, J = 2.4 Hz, 2H), 3.81 (t, J = 7.4 Hz, 2H), 3.75 (s, 3H), 3.15 (t, J = 8.0 Hz, 2H), 2.41 (t, J = 2.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 143.5, 136.2, 127.0, 122.3, 122.1, 119.4, 118.4, 111.8, 111.3, 90.3, 78.6, 73.9, 53.5, 52.2, 42.9, 25.3; IR (KBr) ν_{max} 3413, 3299, 1686, 1621, 908, 738 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{17}Cl\ N_2NaO_2$ 339.0876 $[M + Na]^+$, found 339.0875.

(E)-Methyl 3-[Ethyl(2-(1-tosyl-1H-indole-3-yl)ethyl)amino]-acrylate: Oil, R_f (PE/EtOAc 2:1) = 0.21; ^1H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.44−7.41 (m, 2H), 7.34 (s, 3H), 7.30 (td, J_1 = 8.0 Hz, J_2 = 0.8 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.17 (d, J = 8.2 Hz, 2H), 4.61 (d, J = 13.2 Hz, 2H), 3.64 (s, 3H), 3.38 (t, J = 7.2 Hz, 2H), 3.01 (q, J = 7.2 Hz, 2H), 2.89 (t, J = 7.7 Hz, 2H), 2.29 (s, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 150.7, 144.8, 134.98, 134.95, 130.3, 129.7, 126.6, 124.8, 123.2, 123.1, 118.9, 113.6, 83.8, 50.3, 21.3; IR (KBr) ν_{max} 2977, 2945, 1686, 1609, 1447, 1364, 976, 744 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{26}N_2NaO_4S$ 449.1511 $[M + Na]^+$, found 449.1513.

(E)-Methyl 3-[4-Methyl-N-(2-(1-methyl-1H-indol-3-yl)ethyl)-phenylsulfonamido]acrylate: Oil, R_f (PE/EtOAc 3:2) = 0.18; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 14.0 Hz, 1H), 7.65 (d, J = 8.2 Hz, 2H), 7.56 (d, J = 7.8 Hz, 1H), 7.23−7.17 (m, 4H), 7.10 (d, J = 7.6 Hz, 1H), 6.80 (s, 1H), 5.25 (d, J = 14.0 Hz, 1H), 3.73 (s, 3H), 3.63−3.58 (m, 5H), 3.02−2.98 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 144.5, 141.4, 136.7, 135.0, 129.8, 127.1, 126.7, 126.6, 121.5, 118.8, 118.2, 109.6, 109.1, 97.1, 51.0, 46.6, 32.2, 22.6, 21.2; IR (KBr) ν_{max} 2949, 1711, 1630, 1327, 1089, 954, 742 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{24}N_2NaO_4S$ 435.1354 $[M + Na]^+$, found 435.1350.

(Z)-Methyl 2-Bromo-3-[ethyl(2-(1-tosyl-1H-indol-3-yl)ethyl)-amino]acrylate: Oil, R_f (PE/EtOAc 2:1) = 0.28; ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.2 Hz, 1H), 7.77 (s, 1H), 7.74 (d, J = 8.3 Hz, 2H), 7.48 (d, J = 7.7 Hz, 1H), 7.38 (s, 1H), 7.33 (t, J = 7.4 Hz, 1H), 7.26 (d, J = 6.7 Hz, 1H), 7.20 (d, J = 8.1 Hz, 2H), 3.73−3.70 (m, 5H), 3.30 (q, J = 7.0 Hz, 2H), 2.98 (t, J = 7.1 Hz, 2H), 2.32 (s, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 146.0, 144.9, 135.1, 135.0, 130.4, 129.8, 126.6, 124.8, 123.5, 123.2, 119.1, 118.9, 113.7, 75.6, 52.2, 25.4, 21.4, 14.7; IR (KBr) ν_{max} 3129, 1686, 1617, 1400, 1173, 749 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{26}BrN_2O_4S$ 505.0797 $[M + H]^+$, found 505.0788.

(E)-Methyl 3-[N-(2-(2-Bromo-1-methyl-1H-indol-3-yl)ethyl)-4-methylphenylsulfonamido]acrylate: Oil, R_f (PE/EtOAc 3:2) = 0.45; ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 14.0 Hz, 1H), 7.70 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 7.7 Hz, 1H), 7.29−7.26 (m, 3H), 7.23 (td, J_1 = 6.8 Hz, J_2 = 1.1 Hz, 1H), 7.16 (td, J_1 = 8.0 Hz, J_2 = 1.4 Hz, 1H), 5.40 (d, J = 14.0 Hz, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.56−3.52 (m, 2H), 3.07−3.03 (m, 2H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 144.7, 141.7, 136.8, 135.3, 130.1, 127.2, 126.8, 122.1, 120.1, 117.8, 113.8, 110.1, 109.4, 97.5, 51.4, 45.5, 31.4, 23.0, 21.6; IR (KBr) ν_{max} 3158, 1712, 1623, 1365, 1153, 956, 741 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{23}BrN_2NaO_4S$ 513.0460 $[M + Na]^+$, found 513.0455.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02760.

Copies of ^1H and ^{13}C NMR spectra (PDF)

X-ray crystallographic data for **2b** (CIF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The work was financially supported by the National Science Foundation of China (21572098) and the Natural Science Foundation of Jiangsu Province (BK 20141313).

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(16) CCDC 928806 contains the supplementary crystallographic data for this paper.
(17) Two N-tosylated enaminoesters were subjected to the standard NBS-induced cycloisomerization condition, and only brominated products were obtained. The characterization data for N-tosylated and brominated enaminoesters are included in the Experimental Section.
(18) For the cases involving NBS-promoted bromination of enamine or enamide, see: (a) Alix, A.; Lalli, C.; Retailleau, P.; Masson, G. *J. Am. Chem. Soc.* **2012**, *134*, 10389. (b) Hong, B.; Li, H.; Wu, J.; Zhang, J.; Lei, X. *Angew. Chem., Int. Ed.* **2015**, *54*, 1011. For the haloarylation cases, see: (c) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 3416. (d) Hajra, S.; Maji, B.; Bar, S. *Org. Lett.* **2007**, *9*, 2783. (e) Hajra, S.; Maji, B.; Karmakar, A. *Tetrahedron Lett.* **2005**, *46*, 8599. (f) Lavilla, R.; Coll, O.; Bosch, J.; Orozco, M.; Luque, F. J. *Eur. J. Org. Chem.* **2001**, *2001*, 3719. (g) Lavilla, R.; Coll, O.; Nicolas, M.; Bosch, J. *Tetrahedron Lett.* **1998**, *39*, 5089.
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DOI: 10.1021/acs.joc.6b02760
J. Org. Chem. 2017, 82, 1567−1574