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Ring Expansion

Azocinoindole Synthesis by a Gold(I)-Catalyzed Ring Expansion of 2-Propargyl-β-Tetrahydrocarboline

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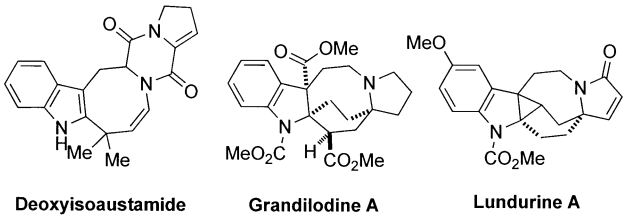
Abstract: A new methodology taking advantage of gold(I)-catalyzed ring expansion has been developed to assemble tricyclic 1*H*-azocino[5,4-*b*]indoles from 2-propargyl-β-tetrahydrocarbolines. The azocinoindoles were obtained in moderate to excellent yields; the structure of which was established by X-ray crystallographic analysis. A mechanism involving regioselective intramolecular hydroarylation, [1,2]-alkenyl migration and carbon–carbon bond-fragmentation was proposed.

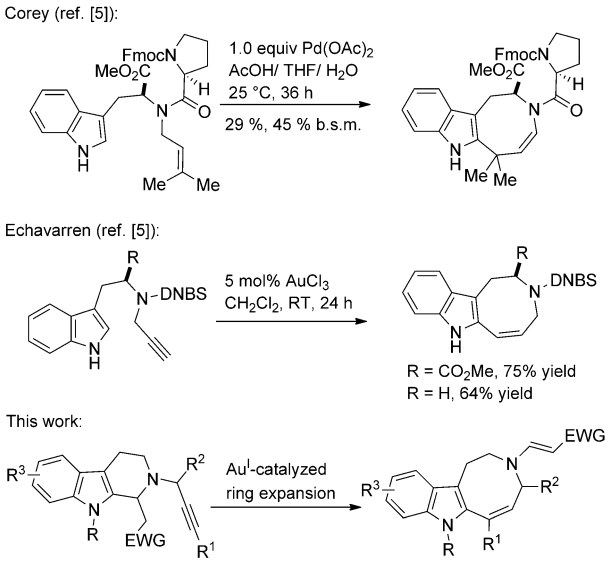
Introduction

Heteroannulated azocine derivatives belong to a kind of compounds containing an eight-membered ring.[1] As a member of heteroannulated azocine, azocinoindole features a fusion of indole and azocine rings. The tricyclic heterocycle has attracted much attention from the chemical community because a number of naturally occurring alkaloids possess the fragment in their structures. For instance, as the skeleton core of penta- and hexacyclic alkaloids okaramine,[2] grandilodine,[3] and lundurine,[4] 1*H*-azocino[5,4-*b*]indole became a common target for different research groups (Scheme 1).

Hence, diverse methodologies have been developed for the assembly of 1*H*-azocino[5,4-*b*]indole scaffold, which was designed as a key intermediate to polycyclic indole alkaloids (Scheme 2). An elegant example, taking advantage of transition-metal catalysis, was initially reported by Corey in 2002, in which an amide-protected *N*-prenyl-(*S*)-tryptophan methyl ester was employed as substrate and stoichiometric amount of palladium acetate was utilized as the catalyst.[5] A mechanistic study demonstrated that the cyclization is triggered by C–H activation at C2 position of the indole ring and the presence of methyl ester proved to be essential for the transformation. In 2006, based on the alkynophilic property of gold catalysts, Echavarren advanced a 8-*endo-dig* cycloisomerization to obtain 1*H*-azocino[5,4-*b*]indoles from *N*-propargyl-substituted tryptamine and tryptophan ester.[6] However, in the case of substrates tethered with internal alkynes, the transformation was contaminated by a competitive 7-*exo-dig* cycloisomerization as a side reaction. Furthermore, when one-valent cationic gold complex was employed in place of [$AuCl_3$], 7-*exo-dig* cyclo-



Scheme 1. 1*H*-Azocino[5,4-*b*]indole alkaloids.



Scheme 2. Transition-metal catalysis in 1*H*-azocino[5,4-*b*]indole assembly.

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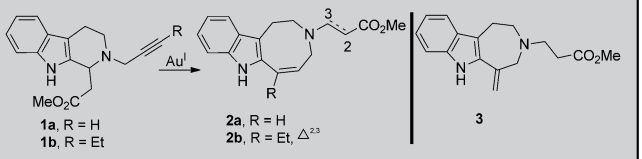
isomerization became a major reaction. Although Van der Eycken partially improved the 8-*endo-dig* cycloisomerization by switching the substrate to propiolamide, limitations in terms of substrate scope and generality of the transformation still exist.[7] Aiming at addressing the problem, we present a conceptually new strategy for the construction of 1*H*-azocino[5,4-*b*]indole by a gold(I)-catalyzed ring expansion of 2-propargyl-β-tetrahydrocarboline, which features a carbon–carbon bond fragmentation.[8,9]

Results and Discussion

We started the investigation by designing compounds **1a**,**b** as model substrates, which were prepared by selective propargylation of the same β-tetrahydrocarboline, a Pictet–Spengler reaction product of tryptamine and methyl propiolate.[10,11] When 10 mol% [$AuNTf_2(PPh_3)$] (NTf_2 = bis-{(trifluoromethyl)sulfonyl}-imide) was used as catalyst, complete conversion of 2-propargyl-β-tetrahydrocarboline **1a** was observed in CH_2Cl_2 after 12 h at room temperature. To our disappointment, we could not obtain any pure product at the beginning because partial decomposition of products always occurred during the work-up. After a thorough analysis of the crude spectra, we deduced that new functional groups such as alkene and enamino ester should be generated during the process. Therefore, to access a stable product, we envisioned a two-step protocol consisting of gold catalysis and subsequent chemoselective reduction of the enamine motif. When the gold(I)-catalyzed reaction was finished, the boron reductant $NaBH(OAc)_3$ and excess acetic acid were added in a one-pot manner (Table 1). Eventually, two products were isolated nearly at a 2:1 ratio, which were identified as 1*H*-azocino[5,4-*b*]indole **2a** and azepino[4,5-*b*]indole **3**, respectively (Table 1, entry 1). In the presence of acidic additives such as trifluoroacetic acid (TFA) and acetic acid, the gold(I)-catalyzed process can be accelerated and the product yields were improved, however, the ratio of **2a** and **3** was almost 1:1 (Table 1, entries 2 and 3). When toluene was used as solvent, similar acceleration and product distribution were observed in the absence of acids (Table 1, entry 4). Switching the catalyst from [$AuNTf_2(PPh_3)$] to [$AuCl_3$] led to the formation of a messy mixture, even though the starting material disappeared in 2 h (Table 1, entry 5). To our delight, when substrate **1b** bearing an ethyl substituent at the alkyne terminus was tested, the gold-catalyzed ring expansion proceeded cleanly, delivering 1*H*-azocino[5,4-*b*]indole **2b** in excellent yield either in dichloromethane or in toluene (Table 1, entries 6 and 7). Of note is that none of the alternative regioisomer of **2b** was detected. The attached ethyl group makes the 1*H*-azocino[5,4-*b*]indole substantially stable, thus making further reduction unnecessary, and also enhances the regioselectivity of the transformation. Further optimization revealed that even when the amount of gold catalyst was reduced as low as 1 mol%, the ring expansion reaction can still be carried out efficiently, albeit at elevated temperature (Table 1, entry 8).

Under the optimized conditions, the generality of the transformation was next evaluated. As well as β-tetrahydrocarboline **1b**, substrates **1c**–**g** containing alkyl (silyloxymethyl, *n*-pentyl) and aryl groups (Ph, 4-MeOPh, 4-NO_2Ph) appended on the alkyne tethers participated in the gold-catalyzed ring expansion smoothly, affording the expected 1*H*-azocino[5,4-*b*]indoles in good to excellent yields (Table 2, entries 1–5). The structure of 1*H*-azocino[5,4-*b*]indole **2e** was unambiguously confirmed by using X-ray crystallographic analysis (Figure 1, top).[12] It appears that the attached phenyl groups favor the conversion and the electronic effect of the substituents on the benzene moiety is not significant. However, the electronic nature of the substituents on the nitrogen atom of the indole core is critical as both electron-donating groups (Bn, Me) gave the products in an average yield up to 90%, whereas electron-withdrawing group (Ts) inhibited the reaction (Table 2, entries 6 and 7). A variety of substituents (Cl, Me, MeO) at position C6 of β-tetrahydrocarboline skeleton were well-tolerated, and the 10-methoxy-1*H*-azocino[5,4-*b*]indole **2l** was isolated in a nearly quantitative yield (Table 2, entry 8). Furthermore, the presence of methoxycarbonyl group at position C3 of β-tetrahydrocarboline **1m** derived from L-tryptophan did not interfere with the process, giving access to **2m** perfectly (Table 2, entry 9). The structure of **2m** was further confirmed by X-ray crystallographic analysis (Figure 1, bottom). To ascertain whether the methoxycarbonyl group at position C1 of β-tetrahydrocarboline is essential or not, β-tetrahydrocarboline **1n** containing a phenone unit in lieu of the ester was subjected to identical conditions, 1*H*-azocino[5,4-*b*]indole **2n** was achieved in relatively lower yield after exhaustive reduction (Table 2, entry 10). On the contrary, the ring expansion did not take place when the

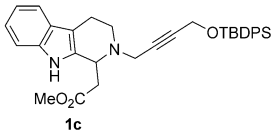
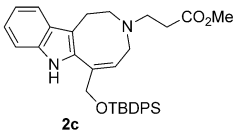
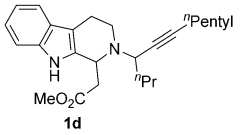
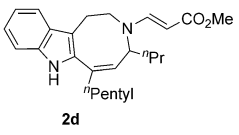
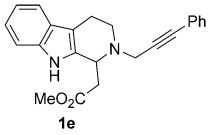
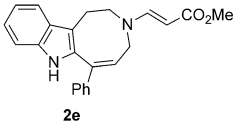
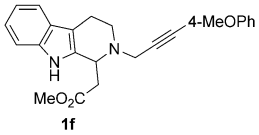
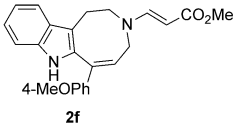
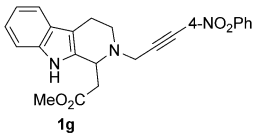
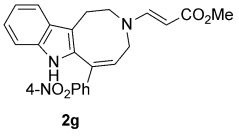
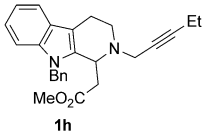
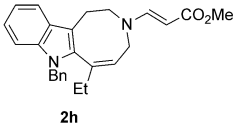
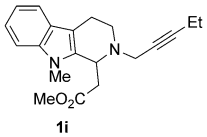
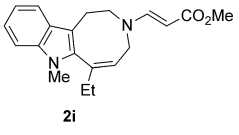
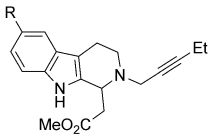
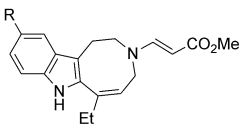
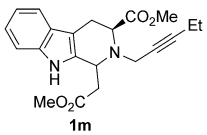
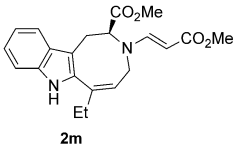
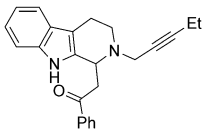
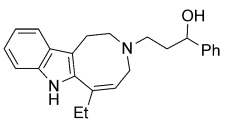
Table 1. Screened conditions for the Au^I-catalyzed ring expansion of 2-propargyl-β-tetrahydrocarboline.[a]



Entry	Substrate	Conditions	Product (yield [%])[c]
1[b]	**1a**	10 mol% [$AuNTf_2(PPh_3)$], CH_2Cl_2, RT, 12 h; then boron reduction	**2a** (24); **3** (11)
2[b]	**1a**	10 mol% [$AuNTf_2(PPh_3)$], 1.0 equiv TFA, CH_2Cl_2, RT, 2 h; then boron reduction	**2a** (46); **3** (38)
3[b]	**1a**	10 mol% [$AuNTf_2(PPh_3)$], 1.0 equiv HOAc, CH_2Cl_2, RT, 2 h; then boron reduction	**2a** (46); **3** (45)
4[b]	**1a**	10 mol% [$AuNTf_2(PPh_3)$], PhMe, RT, 2 h; then boron reduction	**2a** (38); **3** (34)
5	**1a**	10 mol% [$AuCl_3$], CH_2Cl_2, RT, 2 h	–[d]
6	**1b**	10 mol% [$AuNTf_2(PPh_3)$], CH_2Cl_2, RT, 12 h	**2b** (83)
7	**1b**	10 mol% [$AuNTf_2(PPh_3)$], PhMe, RT, 2 h	**2b** (81)
8	**1b**	1 mol% [$AuNTf_2(PPh_3)$], PhMe, 110 °C, 2 h	**2b** (92)

[a] The concentration is 0.1 M. [b] Reduction conditions: 2.0 equiv $NaBH(OAc)_3$, 20 equiv HOAc, RT, 1 h. [c] Yield of the isolated product after column chromatography. [d] Could not be determined due to the formation of a messy mixture.

Table 2. Au^{I}-catalyzed ring expansion of 2-propargyl-β-tetrahydrocarboline.[a]

Entry	2-propargyl-β-tetrahydrocarboline	1*H*-azocino[5,4-*b*]indole	Yield [%][c]
1[b]	 **1c**	 **2c**	71
2	 **1d**	 **2d**	80
3	 **1e**	 **2e**	92
4	 **1f**	 **2f**	88
5	 **1g**	 **2g**	87
6	 **1h**	 **2h**	90
7	 **1i**	 **2i**	91
8	 **1j**: R = Cl **1k**: R = Me **1l**: R = OMe	 **2j**: R = Cl **2k**: R = Me **2l**: R = OMe	87 92 98
9	 **1m**	 **2m**	95
10[b]	 **1n**	 **2n**	45

[a] Reaction conditions: 1 mol% [AuNTf$_2$(PPh$_3$)], toluene, 110 °C, 2 h. [b] Reduction conditions used as shown in Table 1. [c] Yield of the isolated product after column chromatography.

acetate moiety was replaced by either an alkyl or a phenyl group.

To account for this phenomenon, a plausible mechanism was proposed as outlined in Scheme 3. The selective coordination between the carbon–carbon triple bond and carbophilic gold(I) catalyst results in an intramolecular nucleophilic attack by β-tetrahydrocarboline. Then, a dearomatized spiro intermediate **I** is generated, which can be transformed to carbocation **II** through a preferable [1,2]-alkenyl migration. The benign electron donation of a nitrogen atom at the γ position of carbocation induces the rupture of C_α–C_β sigma bond, which is reminiscent of a cationic Grob fragmentation.[13] Subsequently, the obtained iminium **III** isomerizes to enamino ester **IV** by losing a proton. The presence of acetate group at C1 position of β-tetrahydrocarboline might promote the isomerization from iminium to enamine, which, in combination with a subsequent protodeauration, facilitates an irreversible ring expansion. After the protonolysis of the C–Au bond, the 1*H*-azocino[5,4-*b*]indole is formed.

Conclusion

A conceptually new approach has been developed to assemble tricyclic 1*H*-azocino[5,4-*b*]indoles from 2-propargyl-β-tetrahydrocarbolines by means of a gold-catalyzed ring expansion. The protocol features mild conditions and benign group tolerance, as well as high catalytic efficiency, which is complementary to the current methodologies. Further extensions of the ring expansion will be disclosed in due course.

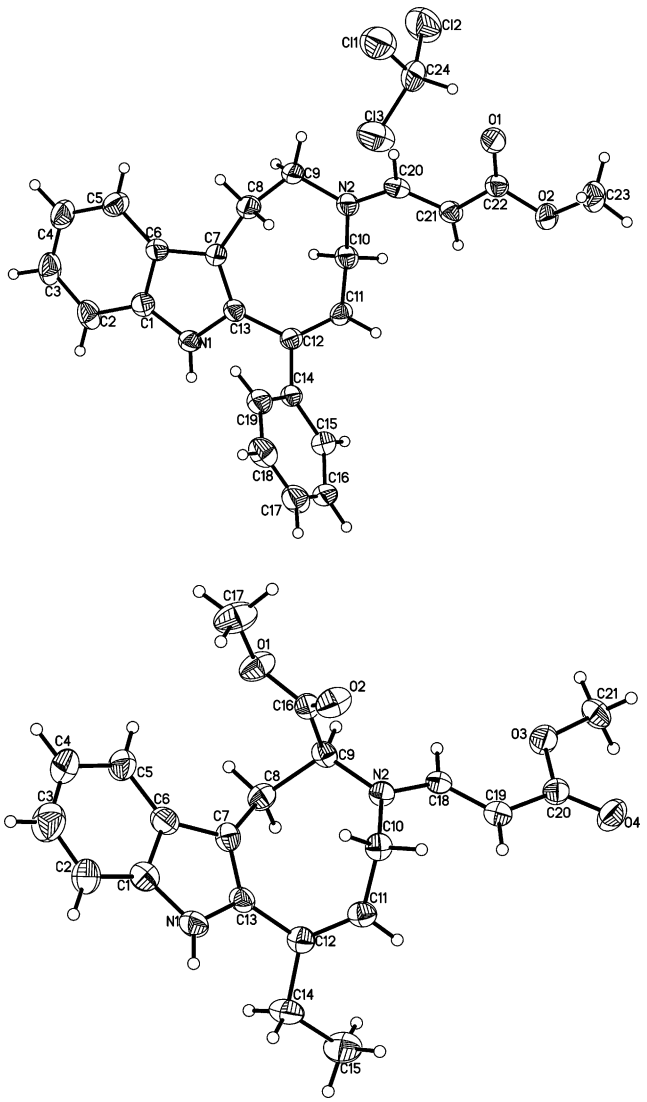
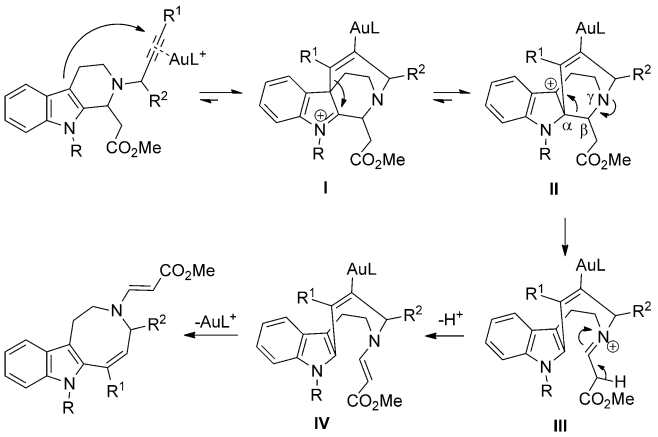


Figure 1. X-ray structure of azocinoindole **2e**·$CHCl_3$ (top) and **2m** (bottom).



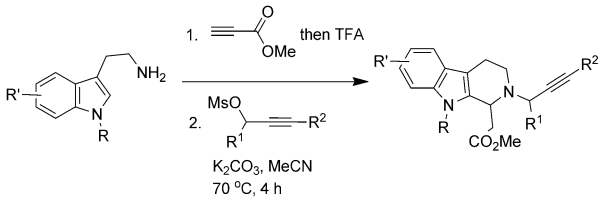
Scheme 3. Proposed mechanism of the ring expansion.

Experimental Section

All melting points were determined without correction. ^{1}H NMR spectra were obtained at 300 or 400 MHz, and ^{13}C NMR spectra were obtained at 75 or 100 MHz. Spectra were recorded in $CDCl_3$ or [D_6]DMSO solution using the residual protonated solvent as the internal standards, *J* values are given in Hz.

General procedure for the preparation of 2-propargyl-β-tetrahydrocarboline 1a–n

A solution of methyl propiolate (25.0 mmol) and tryptamine (25.0 mmol) in THF (50 mL) was stirred at room temperature for 6 h. The reaction mixture was concentrated under reduced pressure. Then, the obtained solid was dissolved in anhydrous dichloromethane (50 mL), and the formed solution was cooled to 0 °C. Trifluoroacetic acid (50.0 mmol) was added dropwise in 15 min. After the addition, the mixture was stirred at 0 °C for another 1 h. The reaction mixture was washed with saturated Na_2CO_3 solution (50 mL) and water (50 mL) successively. The organic layer was dried with anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH as eluent) to give 2-unsubstituted β-tetrahydrocarboline.



An oven-dried flask was charged with 2-unsubstituted β-tetrahydrocarboline (2.0 mmol), propargyl mesylate (2.0 mmol) and anhydrous K_2CO_3 (8.0 mmol). Dry acetonitrile (10 mL) was added and the resultant mixture was allowed to heat and stirred at 70 °C for 4 h. The reaction mixture was cooled to room temperature and excess K_2CO_3 was filtered off. After the removal of solvent under reduced pressure, the crude product was purified by flash chromatography (petroleum ether/ethyl acetate (PE/EA) as eluent) to provide 2-propargyl-β-tetrahydrocarboline.

Methyl 2-(2-(prop-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (1a): Oil. R_f (PE/EtOAc, 2:1) = 0.70; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.56 (br s, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.33 (d, J = 7.9 Hz, 1H), 7.16 (td, J_1 = 7.7, J_2 = 1.2 Hz, 1H), 7.09 (td, J_1 = 7.8, J_2 = 1.2 Hz, 1H), 4.42 (dd, J_1 = 9.9, J_2 = 3.3 Hz, 1H), 3.76 (s, 3H), 3.60–3.47 (m, 2H), 3.26–3.08 (m, 2H), 3.02 (dd, J_1 = 17.1, J_2 = 3.6 Hz, 1H), 2.94–2.76 (m, 2H), 2.67 (dt, J_1 = 15.8, J_2 = 4.4 Hz, 1H), 2.27 ppm (t, J = 2.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 135.9, 133.6, 126.9, 121.9, 119.4, 118.3, 111.1, 107.6, 80.2, 73.0, 52.7, 52.1, 45.6, 42.7, 39.8, 18.2 ppm; IR (KBr) $\tilde{\nu}$ = 3401, 3287, 2950, 1728, 1437, 1171, 745 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{19}N_2O_2$: 283.1447 $[M+H]^+$; found: 283.1444.

Methyl 2-(2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (1b): Yellow solid. M.p. 92–94 °C; R_f (PE/EtOAc, 2:1) = 0.64; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (brs, 1H), 7.49 (d, J = 7.5 Hz, 1H), 7.32 (d, J = 7.9 Hz, 1H), 7.15 (t, J = 7.3 Hz, 1H), 7.08 (t, J = 7.2 Hz, 1H), 4.40 (d, J = 7.5 Hz, 1H), 3.76 (s, 3H), 3.56–3.44 (m, 2H), 3.30–2.95 (m, 3H), 2.95–2.73 (m, 2H), 2.73–2.59 (m, 1H), 2.21 (qt, J_1 = 7.5 Hz, J_2 = 2.1 Hz, 2H), 1.13 ppm (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 135.6, 133.8, 126.7, 121.6, 119.1, 118.0, 110.9, 107.5, 86.5, 74.9, 52.4, 51.9, 45.5, 43.0, 39.5, 18.2,

13.9, 12.4 ppm; IR (KBr): $\tilde{\nu}$ = 3342, 1728, 1434, 1350, 734 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{23}N_2O_2$: 311.1760 $[M+H]^+$; found: 311.1757.

Methyl 2-(2-(4-(*tert*-butyldiphenylsilyloxy)but-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl) acetate (1 c): Oil. R_f (PE/EtOAc, 5:1) = 0.68; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.65 (br s, 1 H), 7.78 (d, J = 6.4 Hz, 4 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.52–7.33 (m, 7 H), 7.25–7.10 (m, 2 H), 4.53–4.31 (m, 3 H), 3.78 (s, 3 H), 3.64–3.51 (m, 2 H), 3.24–3.02 (m, 3 H), 2.93–2.66 (m, 3 H), 1.14 ppm (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 173.8, 135.7, 135.5, 133.6, 133.0, 129.7, 127.6, 126.7, 121.6, 119.1, 118.1, 110.9, 107.4, 83.1, 81.0, 52.7, 52.6, 51.9, 45.5, 42.9, 39.5, 26.6, 19.1, 18.2 ppm; IR (KBr): $\tilde{\nu}$ = 3413, 2929, 1726, 1429, 1111, 741, 704 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{34}H_{39}N_2O_3Si$: 551.2730 $[M+H]^+$; found: 551.2729.

Methyl 2-(2-(undec-5-yn-4-yl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (1 d): Mixed diastereomers were obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (br s, 1 H), 8.46 (br s, 1 H), 7.51 (t, J = 6.3 Hz, 2 H), 7.33 (t, J = 7.0 Hz, 2 H), 7.19–7.06 (m, 4 H), 4.62 (dd, J_1 = 9.6, J_2 = 4.1 Hz, 1 H), 4.48 (dd, J_1 = 9.9, J_2 = 4.1 Hz, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.64 (t, J = 6.9 Hz, 1 H), 3.49 (t, J = 7.1 Hz, 1 H), 3.19–2.61 (m, 12 H), 2.18–2.15 (m, 2 H), 2.04–1.99 (m, 2 H), 1.77–1.23 (m, 19 H), 1.01–0.87 ppm (m, 13 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.3, 135.7, 135.4, 135.3, 135.0, 126.9, 121.3, 121.27, 119.0, 118.0, 117.99, 117.94, 110.8, 110.7, 108.7, 108.5, 85.4, 84.9, 80.2, 78.5, 54.1, 52.9, 52.0, 51.9, 51.7, 43.2, 39.5, 37.3, 36.6, 31.0, 30.9, 28.5, 22.1, 22.0, 20.4, 20.0, 19.7, 19.5, 18.6, 18.5, 13.9, 13.8 ppm; IR (KBr): $\tilde{\nu}$ = 3404, 2956, 2931, 1725, 1464, 1437, 1349, 741 cm^{-1};HRMS (ESI) *m/z* calcd for $C_{25}H_{35}N_2O_2$ 395.2699 $[M+H]^+$; found: 395.2697.

Methyl 2-(2-(3-phenylprop-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-1-yl)acetate (1 e): Oil. R_f (PE/EtOAc 3:1) = 0.55; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.61 (br s, 1 H), 7.54 (d, J = 7.6 Hz, 1 H), 7.49–7.40 (m, 2 H), 7.40–7.28 (m, 4 H), 7.20 (t, J = 7.3 Hz, 1 H), 7.13 (t, J = 7.3 Hz, 1 H), 4.53 (dd, J_1 = 9.4, J_2 = 3.4 Hz, 1 H), 3.85–3.73 (m, 5 H), 3.39–3.15 (m, 2 H), 3.10 (dd, J_1 = 17.0, J_2 = 3.7 Hz, 1 H), 3.03–2.79 (m, 2 H), 2.73 ppm (dt, J_1 = 15.7, J_2 = 4.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.8, 135.7, 133.6, 131.7, 128.2, 128.1, 126.7, 123.0, 121.7, 119.2, 118.1, 110.9, 107.6, 85.3, 84.9, 52.6, 52.0, 45.7, 43.5, 39.6, 18.3 ppm; IR (KBr): $\tilde{\nu}$ = 3399, 2949, 1728, 1489, 1441, 757, 745 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{23}N_2O_2$: 359.1760 $[M+H]^+$; found: 359.1759.

Methyl 2-(2-(3-(4-methoxyphenyl)prop-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (1 f): Oil. R_f (PE/EtOAc 2:1) = 0.77; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (br s, 1 H), 7.52 (d, J = 7.6 Hz, 1 H), 7.41–7.31 (m, 3 H), 7.19 (t, J = 6.9 Hz, 1 H), 7.12 (t, J = 7.4 Hz, 1 H), 6.82 (d, J = 8.8 Hz, 2 H), 4.51 (dd, J_1 = 9.6, J_2 = 3.5 Hz, 1 H), 3.80–3.76 (m, 8 H), 3.35–3.14 (m, 2 H), 3.08 (dd, J_1 = 17.0, J_2 = 3.9 Hz, 1 H), 3.01–2.78 (m, 2 H), 2.71 ppm (dt, J_1 = 15.7, J_2 = 4.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.9, 159.4, 135.7, 133.6, 133.1, 126.7, 121.7, 119.2, 118.1, 115.1, 113.8, 110.9, 107.5, 84.7, 83.7, 55.2, 52.6, 52.0, 45.7, 43.5, 39.6, 18.3 ppm; IR (KBr): $\tilde{\nu}$ = 3399, 2950, 1727, 1606, 1509, 1247, 1172, 1030, 834, 745 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{24}H_{25}N_2O_3$: 389.1865 $[M+H]^+$; found: 389.1866.

Methyl 2-(2-(3-(4-nitrophenyl)prop-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (1 g): Oil. R_f (PE/EtOAc 2:1) = 0.75; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (br s, 1 H), 8.11 (d, J = 8.7 Hz, 2 H), 7.51 (d, J = 8.1 Hz, 1 H), 7.47 (d, J = 8.7 Hz, 2 H), 7.34 (d, J = 7.9 Hz, 1 H), 7.19 (t, J = 7.3 Hz, 1 H), 7.11 (t, J = 7.3 Hz, 1 H), 4.49 (dd, J_1 = 9.0, J_2 = 4.0 Hz, 1 H), 3.80–3.74 (m, 5 H), 3.34–3.15 (m, 2 H), 3.15–2.80 (m, 3 H), 2.71 ppm (dt, J_1 = 15.9, J_2 = 3.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.7, 146.9, 135.7, 133.2, 132.3, 129.8, 126.6, 123.4, 121.9, 119.3, 118.1, 111.0, 107.6, 91.4, 83.1, 52.8, 52.1, 45.6, 43.6, 39.8, 18.1 ppm; IR (KBr): $\tilde{\nu}$ = 3404, 2950, 2232, 1727, 1593, 1518, 1342, 854, 748 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{22}N_3O_4$ 404.1610 $[M+H]^+$; found: 404.1608.

Methyl 2-(9-benzyl-2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-1-yl)acetate (1 h): White solids. M.p. 113–116 °C; R_f (PE/EtOAc, 3:1) = 0.76; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.61–7.51 (m, 1 H), 7.35–7.06 (m, 6 H), 7.02–6.99 (m, 2 H), 5.39–5.26 (m, 2 H), 4.58 (dd, J_1 = 9.9, J_2 = 2.9 Hz, 1 H), 3.70 (s, 3 H), 3.49–3.33 (m, 2 H), 3.33–3.22 (m, 2 H), 3.08–2.87 (m, 1 H), 2.80 (dd, J_1 = 15.8 Hz, J_2 = 9.9 Hz, 1 H), 2.67–2.59 (m, 1 H), 2.50 (dd, J_1 = 15.8 Hz, J_2 = 3.1 Hz, 1 H), 2.16 (qt, J_1 = 7.5, J_2 = 2.1 Hz, 2 H), 1.09 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.6, 137.5, 137.0, 134.2, 128.7, 127.3, 127.0, 126.0, 121.7, 119.3, 118.2, 109.6, 107.8, 85.9, 75.6, 52.1, 51.7, 46.6, 42.64, 42.57, 39.8, 17.1, 13.8, 12.4 ppm; IR (KBr): $\tilde{\nu}$ = 2915, 1739, 1467, 1431, 1285, 1172, 1030, 744 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{26}H_{29}N_2O_2$ 401.2229 $[M+H]^+$; found: 401.2226.

Methyl 2-(9-methyl-2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-1-yl)acetate (1 i): White solids. M.p. 89–91 °C; R_f (PE/EtOAc, 3:1) = 0.69; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.49 (d, J = 7.7 Hz, 1 H), 7.29 (d, J = 8.1 Hz, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.10 (t, J = 7.3 Hz, 1 H), 4.59 (dd, J_1 = 9.8, J_2 = 2.6 Hz, 1 H), 3.77 (s, 3 H), 3.66 (s, 3 H), 3.52–3.34 (m, 2 H), 3.40–3.07 (m, 2 H), 2.95–2.79 (m, 2 H), 2.72–2.48 (m, 2 H), 2.20 (q, J = 7.4 Hz, 2 H), 1.12 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.7, 137.2, 134.2, 126.6, 121.4, 119.0, 118.2, 108.8, 107.1, 85.9, 75.7, 52.2, 51.8, 42.8, 39.6, 29.6, 17.0, 13.9, 12.5 ppm; IR (KBr): $\tilde{\nu}$ = 2945, 2797, 1738, 1472, 1438, 1364, 1330, 1167, 737 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{25}N_2O_2$ 325.1916 $[M+H]^+$; found: 325.1915.

Methyl 2-(6-chloro-2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-1-yl)acetate (1 j): Yellow solids. M.p. 122–124 °C; R_f (PE/EtOAc 3:1) = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.69 (br s, 1 H), 7.44 (s, 1 H), 7.22 (d, J = 8.6 Hz, 1 H), 7.09 (d, J = 8.6 Hz, 1 H), 4.38 (dd, J_1 = 9.9, J_2 = 2.0 Hz, 1 H), 3.76 (s, 3 H), 3.57–3.41 (m, 2 H), 3.29–2.92 (m, 3 H), 2.92–2.71 (m, 2 H), 2.61 (dt, J_1 = 15.7, J_2 = 4.5 Hz, 1 H), 2.20 (q, J = 7.4 Hz, 2 H), 1.12 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.1, 135.5, 134.0, 127.8, 124.8, 121.7, 117.6, 111.8, 107.4, 86.7, 74.7, 52.2, 52.0, 45.6, 43.0, 39.2, 18.3, 13.9, 12.4 ppm; IR (KBr): $\tilde{\nu}$ = 3338, 2951, 2231, 1725, 1439, 1349, 1317, 1270, 1163, 801 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{19}H_{22}ClN_2O_2$: 345.1370 $[M+H]^+$; found 345.1371.

Methyl 2-(6-methyl-2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indol-1-yl)acetate (1 k): White solids. M.p. 123–125 °C; R_f (PE/EtOAc 3:1) = 0.56; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.44 (br s, 1 H), 7.27 (s, 1 H), 7.21 (d, J = 8.2 Hz, 1 H), 6.98 (d, J = 8.1 Hz, 1 H), 4.38 (dd, J_1 = 9.7, J_2 = 2.6 Hz, 1 H), 3.75 (s, 3 H), 3.58–3.40 (m, 2 H), 3.25–2.92 (m, 3 H), 2.92–2.76 (m, 2 H), 2.76–2.50 (m, 1 H), 2.44 (s, 3 H), 2.21 (q, J = 7.3 Hz, 2 H), 1.13 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 134.0, 128.4, 126.9, 123.1, 117.8, 110.5, 107.0, 86.5, 75.0, 52.4, 51.9, 45.6, 43.0, 39.6, 21.4, 18.2, 13.9, 12.4 ppm; IR (KBr): $\tilde{\nu}$ = 3324, 2981, 2231, 1721, 1487, 1325, 1218, 818 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{20}H_{25}N_2O_2$ $[M+H]^+$ 325.1916, found 325.1917.

Methyl 2-(6-methoxy-2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)acetate (1 l): White solid. M.p. 145–147 °C; R_f (PE/EtOAc, 3:1) = 0.58; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.45 (br s, 1 H), 7.21 (d, J = 8.7 Hz, 1 H), 6.94 (s, 1 H), 6.81 (d, J = 8.6 Hz, 1 H), 4.51–4.28 (m, 1 H), 3.85 (s, 3 H), 3.75 (s, 3 H), 3.43–3.55 (m, 2 H), 3.41–2.95 (m, 3 H), 2.95–2.69 (m, 2 H), 2.61 (dt, J_1 = 8.5, J_2 = 3.9 Hz, 1 H), 2.21 (q, J = 7.2 Hz, 2 H), 1.13 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.0, 153.8, 134.7, 130.8, 127.1, 111.5, 111.4, 107.3, 100.3, 86.6, 74.9, 55.9, 52.4, 51.9, 45.5, 43.0, 39.5, 18.3, 13.9, 12.4 ppm; IR (KBr): $\tilde{\nu}$ = 3363, 2944, 2233, 1728, 1440, 1350, 1319, 1166, 799 cm^{-1}; HRMS (ESI) *m/z* calculated for $C_{20}H_{25}N_2O_3$ 341.1865 $[M+H]^+$; found: 341.1865.

(*S*)-Methyl 1-(2-methoxy-2-oxoethyl)-2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylate (1 m): Mixed diastereomers were obtained. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.84 (s, 0.5 H), 8.65 (s, 1 H), 7.49 (d, J = 7.7 Hz, 1.5 H), 7.32 (d, J = 7.9 Hz, 1.5 H), 7.19–7.08 (m, 3 H), 4.73 (dd, J = 10.6, 2.8 Hz, 1 H), 4.64–4.41 (m, 0.5 H), 4.17–3.96 (m, 1.5 H), 3.76 (dd, J_1 = 6.1, J_2 = 4.8 Hz, 9 H), 3.72–3.33 (m, 3 H), 3.21–2.91 (m, 4.5 H), 2.91–2.57 (m, 1.5 H), 2.30–2.10 (m, 3 H), 1.14–1.08 ppm (m, 4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.5, 173.8, 173.7, 172.5, 135.8, 133.6, 133.5, 126.4, 126.2, 121.7, 121.6, 119.2, 118.0, 110.9, 106.0, 105.7, 87.7, 86.4, 75.2, 73.6, 59.1, 57.1, 52.4, 52.0, 51.96, 42.4, 40.2, 39.6, 39.2, 23.3, 21.0, 13.8, 13.7, 12.4, 12.3 ppm; IR (KBr): $\tilde{\nu}$ = 3402, 2951, 2235, 1732, 1437, 744 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{25}N_2O_4$: 369.1814 $[M+H]^+$; found: 369.1808.

2-(2-(pent-2-ynyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indol-1-yl)-1-phenylethanone (1 n): Yellow solids. M.p. 123–125 °C; R_f (PE/EtOAc, 3:1) = 0.51; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.68 (br s, 1 H), 8.01 (d, J = 7.4 Hz, 2 H), 7.60 (t, J = 7.3 Hz, 1 H), 7.55–7.44 (m, 3 H), 7.33 (d, J = 7.8 Hz, 1 H), 7.16 (t, J = 7.4 Hz, 1 H), 7.10 (t, J = 7.4 Hz, 1 H), 4.67 (dd, J_1 = 8.9 Hz, J_2 = 3.3 Hz, 1 H), 3.82 (dd, J_1 = 18.4, J_2 = 2.3 Hz, 1 H), 3.71–3.44 (m, 3 H), 3.44–3.06 (m, 2 H), 3.06–2.82 (m, 1 H), 2.69 (dt, J_1 = 15.8, J_2 = 4.0 Hz, 1 H), 2.22 (q, J = 7.4 Hz, 2 H), 1.14 ppm (t, J = 7.5 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 200.8, 136.5, 135.5, 134.4, 133.6, 128.6, 128.0, 126.7, 121.5, 119.0, 117.9, 110.9, 107.0, 86.5, 75.2, 52.0, 45.5, 43.1, 18.0, 13.9, 12.4 ppm; IR (KBr) $\tilde{\nu}$ = 2937, 2848, 2228, 1684, 1444, 1362, 738 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{25}N_2O$: 357.1967 $[M+H]^+$; found: 357.1964.

General procedure for the preparation of 1*H*-azocino[5,4-*b*]indole from 2-propargyl-β-tetrahydrocarboline through a gold(I)-catalyzed ring expansion

Triphenylphosphine gold(I) bis(trifluoromethanesulfonyl)imidate (3.0 mg, 0.004 mmol) was added in one portion to a stirred solution of 2-propargyl-β-tetrahydrocarboline (0.4 mmol) in toluene (4.0 mL). The reaction was heated at 110 °C for 2 h. After cooling, the solution was concentrated under vacuum pressure and the residue was purified by column chromatography with EtOAc/PE (1:2) as eluent to give pure 1*H*-azocino[5,4-*b*]indole.

(*Z*)-Methyl 3-(1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)propanoate (2 a): Oil. R_f (CH_2Cl_2/MeOH 20:1) = 0.24; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.94 (br s, 1 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.27 (d, J = 7.7 Hz, 1 H), 7.18 (td, J_1 = 6.9, J_2 = 1.2 Hz, 1 H), 7.11 (td, J_1 = 6.9, J_2 = 1.2 Hz, 1 H), 6.66 (d, J = 11.0 Hz, 1 H), 5.86 (dt, J_1 = 10.9, J_2 = 7.8 Hz, 1 H), 3.67 (s, 3 H), 3.48 (d, J = 7.8 Hz, 2 H), 3.06–3.14 (m, 4 H), 2.93 (t, J = 7.3 Hz, 2 H), 2.59 ppm (t, J = 7.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.0, 135.9, 130.5, 128.8, 126.6, 125.4, 122.6, 119.5, 118.6, 113.8, 110.5, 51.7, 51.0, 50.0, 49.8, 33.2, 22.6 ppm; IR (KBr) $\tilde{\nu}$ = 3375, 2948, 1741, 1591, 1461, 1336, 1178, 769, 742 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{21}N_2O_2$: 285.1603 $[M+H]^+$; found: 285.1602.

(*E*)-Methyl 3-((*Z*)-6-ethyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)-acrylate (2 b): White solids. M.p. 100–102 °C; R_f (PE/EtOAc 2:1) = 0.59; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.59 (br s, 1 H), 7.55 (d, J = 7.8 Hz, 1 H), 7.42 (d, J = 12.1 Hz, 1 H), 7.36 (d, J = 7.8 Hz, 1 H), 7.22 (t, J = 7.2 Hz, 1 H), 7.16 (t, J = 7.4 Hz, 1 H), 5.92 (s, 1 H), 4.77 (d, J = 12.9 Hz, 1 H), 3.69 (s, 3 H), 3.65–3.54 (m, 2 H), 3.41–3.24 (m, 2 H), 3.00–2.83 (m, 2 H), 2.48 (q, J = 7.4 Hz, 2 H), 0.99 ppm (t, J = 7.4 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 152.0, 138.0, 136.1, 133.9, 127.5, 122.3, 121.0, 119.4, 118.0, 112.7, 110.9, 83.0, 54.4, 50.5, 46.7, 29.6, 25.9, 13.0 ppm; IR (KBr): $\tilde{\nu}$ = 3289, 2930, 1671, 1597, 1421, 1355, 1155, 746 cm^{-1}; HRMS (ESI): m/z calcd for $C_{19}H_{23}N_2O_2$: 311.1760 $[M+H]^+$; found: 311.1757.

(*E*)-Methyl 3-(6-((*tert*-butyldiphenylsilyloxy)methyl)-1*H*-azocino-[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)propanoate (2 c): Oil. R_f (PE/EtOAc 5:1) = 0.62; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.16 (br s, 1 H), 7.74 (dd, J_1 = 7.7, J_2 = 1.4 Hz, 4 H), 7.55 (d, J = 7.7 Hz, 1 H), 7.51–7.37 (m, 6 H), 7.30 (d, J = 7.9 Hz, 1 H), 7.22 (td, J_1 = 7.7, J_2 = 1.3 Hz, 1 H), 7.13 (td, J_1 = 7.8, J_2 = 1.3 Hz, 1 H), 5.70 (t, J = 7.9 Hz, 1 H), 4.52 (s, 2 H), 3.69 (s, 3 H), 3.37 (d, J = 7.1 Hz, 2 H), 3.09–2.96 (m, 4 H), 2.88 (t, J = 7.3 Hz, 2 H), 2.56 (t, J = 7.3 Hz, 2 H), 1.16 ppm (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.9, 135.6, 135.5, 134.9, 132.7, 131.6, 130.0, 127.8, 125.9, 122.4, 119.2, 118.5, 113.8, 110.6, 69.1, 51.6, 50.8, 50.2, 49.6, 33.2, 26.9, 22.8, 19.2 ppm; IR (KBr): $\tilde{\nu}$ = 3422, 2930, 2856, 1739, 1428, 1112, 741, 702 cm^{-1}; HRMS (ESI): m/z calcd for $C_{34}H_{41}N_2O_3Si$: 553.2886 $[M+H]^+$; found: 553.2885.

(*E*)-Methyl 3-((*Z*)-6-pentyl-4-propyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2 d): White solid. M.p. 136–139 °C; R_f (PE/EtOAc, 3:1) = 0.64; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (br s, 1 H), 7.59 (d, J = 7.7 Hz, 2 H), 7.37 (d, J = 7.9 Hz, 1 H), 7.25–7.09 (m, 2 H), 5.69 (d, J = 8.0 Hz, 1 H), 4.78 (d, J = 13.1 Hz, 1 H), 3.86–3.72 (m, 1 H), 3.69 (s, 3 H), 3.22 (dd, J_1 = 14.9, J_2 = 5.2 Hz, 2 H), 2.84–2.21 (m, 4 H), 1.91–1.50 (m, 2 H), 1.39–1.18 (m, 8 H), 0.87–0.78 ppm (m, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 147.7, 135.9, 134.5, 133.9, 130.9, 128.0, 122.5, 119.5, 118.2, 114.5, 110.8, 85.4, 60.3, 50.6, 36.8, 36.1, 31.3, 29.7, 28.1, 23.2, 22.4, 19.3, 14.0, 13.8 ppm; IR (KBr): $\tilde{\nu}$ = 3303, 2929, 1673, 1596, 1159, 792, 737 cm^{-1}; HRMS (ESI) m/z calcd for $C_{25}H_{35}N_2O_2$: 395.2699 $[M+H]^+$; found: 395.2697.

(*E*)-Methyl 3-((*Z*)-6-phenyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2 e): White solid. M.p. 259–261 °C; R_f (PE/EtOAc, 3:1) = 0.50; ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 10.81 (br s, 1 H), 7.60 (d, J = 7.7 Hz, 1 H), 7.43–7.18 (m, 7 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.03 (t, J = 7.3 Hz, 1 H), 6.44 (t, J = 6.4 Hz, 1 H), 4.81 (d, J = 12.4 Hz, 1 H), 3.84–3.68 (m, 2 H), 3.48 (s, 3 H), 3.45–3.36 (m, 2 H), 3.06–2.77 ppm (m, 2 H); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 168.8, 151.9, 140.2, 136.5, 136.0, 132.7, 128.4, 128.0, 127.6, 126.8, 124.2, 121.8, 118.6, 118.2, 113.5, 111.3, 82.7, 79.2, 53.9, 49.7, 46.9, 25.6 ppm; IR (KBr): $\tilde{\nu}$ = 3289, 1674, 1599, 1422, 1148, 771 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{23}N_2O_2$: 359.1760 $[M+H]^+$; found: 359.1756.

(*E*)-Methyl 3-((*Z*)-6-(4-methoxyphenyl)-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2 f): White solid. M.p. 221–224 °C; R_f (PE/EtOAc, 2:1) = 0.73; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 (br s, 1 H), 7.62 (d, J = 7.5 Hz, 1 H), 7.41 (d, J = 12.1 Hz, 1 H), 7.33–7.12 (m, 6 H), 6.85 (d, J = 8.8 Hz, 2 H), 6.29 (s, 1 H), 4.80 (d, J = 12.5 Hz, 1 H), 3.81 (s, 3 H), 3.77 (d, J = 6.3 Hz, 2 H), 3.62 (s, 3 H), 3.45–3.32 (m, 2 H), 3.10–2.97 ppm (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 159.9, 151.9, 136.6, 136.1, 132.1, 129.3, 127.3, 122.8, 122.1, 119.6, 118.3, 113.9, 110.9, 83.6, 55.3, 54.2, 50.5, 47.2, 26.1 ppm; IR (KBr): $\tilde{\nu}$ = 3290, 2912, 1671, 1595, 1509, 1360, 1250, 1157, 837 cm^{-1}; HRMS (ESI): m/z calcd for $C_{24}H_{25}N_2O_3$: 389.1865 $[M+H]^+$; found: 389.1863.

(*E*)-Methyl 3-((*Z*)-6-(4-nitrophenyl)-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2 g): White solid. M.p. 261–263 °C; R_f (PE/EtOAc 2:1) = 0.71; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, J = 8.7 Hz, 2 H), 7.98 (br s, 1 H), 7.63 (d, J = 7.6 Hz, 1 H), 7.40 (d, J = 8.7 Hz, 2 H), 7.35–7.15 (m, 4 H), 6.43 (t, J = 6.6 Hz, 1 H), 4.75 (d, J = 13.0 Hz, 1 H), 3.87 (d, J = 6.1 Hz, 2 H), 3.60 (s, 3 H), 3.48–3.35 (m, 2 H), 3.14–2.98 ppm (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.9, 151.7, 147.4, 146.3, 136.5, 135.2, 131.2, 128.8, 127.0, 126.8, 123.6, 123.4, 120.0, 118.4, 115.5, 111.2, 84.0, 54.5, 50.5, 47.3, 29.6, 25.7 ppm; IR (KBr): $\tilde{\nu}$ = 3267, 2948, 1673, 1592, 1517, 1443, 1342, 1164, 853 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{22}N_3O_4$: 404.1610 $[M+H]^+$; found: 404.1609.

(*E*)-Methyl 3-((*Z*)-7-benzyl-6-ethyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2 h): White solid. M.p. 94–96 °C; R_f (PE/EtOAc 3:1) = 0.70; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.55 (m, 1 H), 7.52 (d, J = 13.0 Hz, 1 H), 7.35–7.23 (m, 3 H), 7.23–7.13 (m, 3 H),

7.08–6.95 (m, 2H), 6.19 (s, 1H), 5.37–5.21 (m, 2H), 4.83 (d, J= 13.0 Hz, 1H), 3.87–3.75 (m, 1H), 3.71 (s, 3H), 3.67–3.48 (m, 1H), 3.34 (dd, J_1 = 14.8, J_2 = 5.4 Hz, 1H), 3.19–3.01 (m, 2H), 2.53–2.42 (m, 1H), 2.36 (q, J = 7.6 Hz, 2H), 0.90 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 152.1, 138.2, 137.8, 137.6, 136.5, 128.5, 127.2, 125.8, 124.6, 122.4, 119.6, 118.2, 114.2, 110.1, 83.2, 54.5, 50.4, 48.3, 46.0, 29.5, 26.3, 13.0 ppm; IR (KBr): $\tilde{\nu}$ = 2929, 1689, 1605, 1352, 1145, 744 cm^{-1}; HRMS (ESI): m/z calcd for $C_{26}H_{29}N_2O_2$: 401.2229 $[M+H]^+$; found: 401.2224.

(*E*)-Methyl 3-((*Z*)-6-ethyl-7-methyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2i): White solid. M.p. 123–125 °C; R_f (PE/EtOAc, 3:1) = 0.63; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.55 (d, J = 7.8 Hz, 1H), 7.48 (d, J = 12.6 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 7.3 Hz, 1H), 7.16 (t, J = 7.3 Hz, 1H), 6.24 (s, 1H), 4.82 (d, J = 12.7 Hz, 1H), 3.85 (dd, J_1 = 14.2, J_2 = 5.8 Hz, 1H), 3.70 (s, 3H), 3.67 (s, 3H), 3.51–3.60 (m, 1H), 3.15–3.32 (m, 2H), 3.11–2.85 (m, 1H), 2.65–2.31 (m, 3H), 0.93 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 152.1, 138.1, 137.8, 126.8, 124.3, 122.1, 119.2, 118.1, 113.3, 109.1, 83.1, 54.5, 50.5, 46.2, 31.3, 29.4, 26.3, 13.0 ppm; IR (KBr): $\tilde{\nu}$ = 2931, 1692, 1606, 1467, 1354, 1145, 743 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{25}N_2O_2$: 325.1916 $[M+H]^+$; found: 325.1914.

(*E*)-Methyl 3-((*Z*)-10-chloro-6-ethyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2j): White solid. M.p. 177–179 °C. R_f (PE/EtOAc, 3:1) = 0.46; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.32 (s, 1H), 7.48 (s, 1H), 7.30 (d, J = 12.8 Hz, 1H), 7.24 (d, J = 8.1 Hz, 1H), 7.14 (d, J = 8.6 Hz, 1H), 5.88 (t, J = 5.2 Hz, 1H), 4.69 (d, J = 12.8 Hz, 1H), 3.69–3.51 (m, 5H), 3.38–3.22 (m, 2H), 2.92–2.78 (m, 2H), 2.44 (q, J = 7.4 Hz, 2H), 0.98 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 151.9, 137.2, 135.5, 134.5, 132.2, 128.6, 125.2, 122.6, 121.5, 117.5, 111.9, 83.2, 54.6, 50.5, 46.9, 29.7, 25.7, 13.0 ppm; IR (KBr) $\tilde{\nu}$ = 3283, 2966, 1671, 1600, 1443, 1359, 1156, 1050, 795 cm^{-1}; HRMS (ESI) m/z calcd for $C_{19}H_{22}ClN_2O_2$: 345.1370 $[M+H]^+$; found: 345.1369.

(*E*)-Methyl 3-((*Z*)-6-ethyl-10-methyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2k): White solid. M.p. 183–185 °C. R_f (PE/EtOAc, 3:1) = 0.50; ^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.44 (br s, 1H), 7.42 (d, J = 12.9 Hz, 1H), 7.33 (d, J = 8.2 Hz, 1H), 7.24 (s, 1H), 7.05 (d, J = 8.2 Hz, 1H), 5.91 (s, 1H), 4.76 (d, J = 12.9 Hz, 1H), 3.69 (s, 3H), 3.62–3.52 (m, 2H), 3.38–3.22 (m, 2H), 2.96–2.79 (m, 2H), 2.55–2.24 (m, 5H), 0.98 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 170.4, 152.0, 138.1, 134.4, 134.1, 128.7, 127.7, 123.9, 120.8, 117.7, 112.4, 110.6, 82.9, 54.4, 50.5, 46.7, 29.6, 25.8, 21.4, 13.0 ppm; IR (KBr): $\tilde{\nu}$ = 3311, 2963, 1673, 1601, 1421, 1358, 1151, 795 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{25}N_2O_2$: 325.1916 $[M+H]^+$; found: 325.1914.

(*E*)-Methyl 3-((*Z*)-6-ethyl-10-methoxy-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)acrylate (2l): White solid. M.p. 210–212 °C; R_f (PE/EtOAc, 3:1) = 0.51; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (br s, 1H), 7.38 (d, J = 13.0 Hz, 1H), 7.24 (d, J = 8.7 Hz, 1H), 6.96 (s, 1H), 6.88 (d, J = 8.7 Hz, 1H), 5.91 (s, 1H), 4.73 (d, J = 13.0 Hz, 1H), 3.88 (s, 3H), 3.72–3.57 (m, 5H), 3.40–3.28 (m, 2H), 2.96–2.81 (m, 2H), 2.44 (q, J = 7.3 Hz, 2H), 0.98 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 154.0, 152.0, 137.9, 134.8, 131.3, 127.9, 120.8, 112.5, 111.7, 99.9, 83.0, 55.9, 54.5, 50.5, 46.7, 29.7, 25.9, 13.0 ppm; IR (KBr): $\tilde{\nu}$ = 3298, 2929, 1672, 1599, 1359, 1155, 788 cm^{-1}; HRMS (ESI): m/z calcd for $C_{20}H_{25}N_2O_3$: 341.1865 $[M+H]^+$; found: 341.1863.

(*S*, *Z*)-Methyl 6-ethyl-3-((*E*)-3-methoxy-3-oxoprop-1-enyl)-2,3,4,7-tetrahydro-1*H*-azocino[5,4-*b*]indole-2-carboxylate (2m): White solids. M.p. 198–200 °C; R_f (PE/EtOAc 3:1) = 0.64; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (s, 1H), 7.58 (d, J = 7.6 Hz, 2H), 7.31 (d, J = 7.8 Hz, 1H), 7.17–7.11 (m, 2H), 6.25–5.77 (m, 1H), 5.09–4.53 (m, 1H), 4.37–4.03 (m, 1H), 3.90 (dd, J = 15.6, 5.2 Hz, 2H), 3.78–3.35 (m, 7H), 2.89–2.55 (m, 1H), 2.44 (q, J = 7.3 Hz, 2H), 0.97 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.7, 170.1, 152.3, 136.1, 122.4, 119.6, 118.5, 110.9, 109.4, 84.8, 52.1, 50.6, 29.6, 13.0 ppm; IR (KBr): $\tilde{\nu}$ = 3249, 1741, 1654, 1623, 1429, 1249, 1147, 727 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{25}N_2O_4$: 369.1814 $[M+H]^+$; found: 369.1810.

(*Z*)-3-(6-Ethyl-1*H*-azocino[5,4-*b*]indol-3(2*H*,4*H*,7*H*)-yl)-1-phenylpropan-1-ol (2n): Oil. R_f (CH_2Cl_2/MeOH 20:1) = 0.48; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (br s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.45–7.29 (m, 5H), 7.28–7.09 (m, 3H), 5.80 (s, 1H), 5.00 (dd, J_1 = 7.1 Hz, J_2 = 3.7 Hz, 1H), 4.54–3.56 (m, 2H), 3.62–2.64 (m, 7H), 2.48 (q, J = 7.4 Hz, 2H), 2.18–1.72 (m, 2H), 1.06 ppm (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.0, 138.5, 136.0, 128.2, 126.8, 125.5, 122.3, 119.4, 118.3, 114.1, 110.7, 75.4, 54.7, 51.1, 34.1, 29.7, 29.5, 22.7, 13.5 ppm; IR (KBr): $\tilde{\nu}$ = 3207, 2922, 2807, 1465, 1448, 1055, 1026, 727 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{29}N_2O$: 361.2280 $[M+H]^+$; found: 361.2277.

Methyl 3-(5-methylene-1,2,4,5-tetrahydroazepino[4,5-*b*]indol-3(6*H*)-yl)propanoate (3): Oil. R_f (CH_2Cl_2/MeOH 20:1) = 0.33; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.97 (br s, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.19 (td, J_1 = 7.8, J_2 = 1.2 Hz, 1H), 7.10 (td, J_1 = 7.8, J_2 = 1.2 Hz, 1H), 5.30 (s, 1H), 5.13 (s, 1H), 3.77 (s, 2H), 3.71 (s, 3H), 3.32–3.23 (m, 2H), 2.96–3.02 (m, 4H), 2.59 ppm (t, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.1, 139.6, 135.8, 134.2, 128.9, 122.9, 119.4, 118.7, 114.6, 111.9, 110.5, 59.9, 54.1, 51.6, 46.5, 32.9, 22.7 ppm; IR (KBr): $\tilde{\nu}$ = 3390, 2922, 2843, 1732, 1436, 1333, 1195, 740 cm^{-1}; HRMS (ESI): m/z calcd for $C_{17}H_{21}N_2O_2$: 285.1603 $[M+H]^+$; found: 285.1601.

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