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PAPER

Medium-sized and strained heterocycles from non-catalysed and gold-catalysed conversions of β-carbolines†

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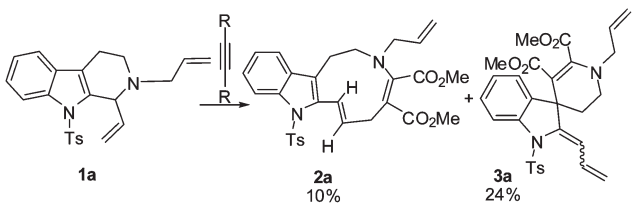
2-Allyl-1-vinyl-β-carbolines and dihydropyrrolo-β-carbolines react with activated internal alkynes through novel rearrangement reactions leading to complex polycyclic structures. Favored reaction pathways depend on reaction conditions and on the presence of gold catalysts. In particular, upon reaction with 2 equiv. of the alkyne, new hexacyclic structures **10** are formed with total stereocontrol.

Introduction

The β-carboline structure is present in numerous natural products like the harman family and more complex systems like eburnamine, vincamine, and alkaloids from *Schizozygia* species, which often exhibit biological activity.[1] In addition, some β-carbolines have gained use as synthetic intermediates and chiral ligands for certain catalytic processes. Alkaloids with a β-carboline nucleus possess widespread and potent biological activities and this has prompted many groups to design new derivatives as potential drugs for the treatment of various diseases. Some natural β-carboline alkaloids display antineoplastic activity,[2] anticonvulsant/anxiolytic activity,[3] or antimalarial activity.[4] Certain β-carbolines have been designed successfully as anti-thrombosis agents[5] or neurotoxic agents.[6] The importance of these compounds is the cause of the great efforts devoted to their synthesis and further transformations.[7]

Tandem reactions and molecular rearrangements are a powerful building tool to rapidly increase the complexity of a substrate starting from relatively simple precursors. Nitrogen containing heterocycles are known to give Michael reactions with activated alkynes that lead to further molecular rearrangements giving complex polycycles.[8] Thus, we[9] and others[10] have described reactions of tetrahydro-β-carbolines and other tetrahydropyridine containing substrates with alkynes to give novel tandem transformations into complex products. In particular, we have shown the transformation of pyrrolo-β-carbolines and vinyl-β-carbolines, upon reaction with acetylenedicarboxylates or propyolates through a Michael type addition followed by nucleophilic attack



Scheme 1 Preliminary reaction of vinyl-β-carboline **1a**.

to one unsaturated carbon which leads to new polycycles with a substantial increase in skeletal complexity (Scheme 1).[9]

We were intrigued by the possibility of catalyzing these processes with metal salts hopefully providing a way to control the different reaction pathways and improving conversions. We show herein the influence of gold salts in the results of these kinds of reactions. Novel divergent reaction pathways are shown.

Results and discussion

The behavior of compounds **1a–c** in their reaction with alkynes was studied first. Synthesis of **1b** was carried out following similar procedures to those for **1a**, already published.[9] The reaction of these three substrates with dimethyl acetylenedicarboxylate (DMAD) was studied under different conditions and the results are summarized in Table 1, Scheme 2.

The preliminary result,[9] in which **1a** gave a mixture of **2a** and **3a** in low yields (entry 1), was improved in terms of selectivity and efficiency by selecting suitable reaction conditions. Thus, increasing the amount of DMAD from 2 to 5 equiv. and prolonging the reaction time to 48 h provided **2a** in good yield (68%), with no presence of **3a** in the crude mixture. When separating the mixture through column chromatography in silica, an additional new product was isolated and assigned to structure **4a** (entry 2). A higher excess of DMAD gave, upon chromatography, higher yields of **4a**, a compound that could be formed upon evolution of **2a** (entry 3) in the presence of water. For the

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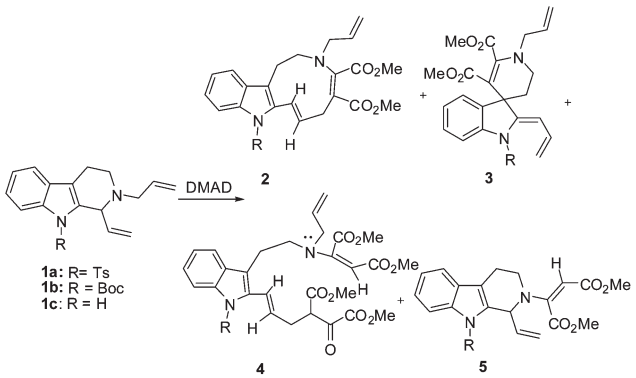
† Electronic supplementary information (ESI) available: Spectra for new products. A cif file with details on the X-ray analysis of compound **10a** is also included. CCDC XXXXXX. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25755f

Table 1 Reaction of 2-allyl-1-vinyl-β-carbolines with DMAD



No.	Subs.	$AuCl_3$	DMAD[b]	Temp.	Time (h)	Ratio crude (**2** : **3** : **5**)	Yield[a] (%) **2**	**3**	**4**	**5**
1	**1a**	No	2	Rt	16	1 : 3 : 0	10	24		
2	**1a**	No	5	rt	48	1 : 0 : 0	68	—	16	—
3	**1a**	No	10	rt	48	1 : 0 : 0	50	—	42	—
4	**1a**	No	10	*Δ* (DCM)	2.5	1 : 0 : 0[c]	41	—	—	—
5	**1a**	0.05	5	rt	0.5	1 : 0 : 3	20	—	—	55
6	**1a**	0.05	5	0° (2 h)–rt	3	4 : 0 : 1	55		5	10
7	**1b**	No	5	rt	20	4 : 1 : 0	55	15	5	—
8	**1b**	No	10	rt	48	4 : 1 : 0	25	20	40	
9	**1b**	0.05	5	rt	2	2 : 1 : 1	30	14	—	15[d]
10	**1b**	0.05	5	0°–rt		3 : 0 : 1	20		20	
11	**1c**	No	10	rt	18	1 : 0 : 0	11			
12	**1c**	No	5	Rt	18	1 : 0 : 0	35		—	

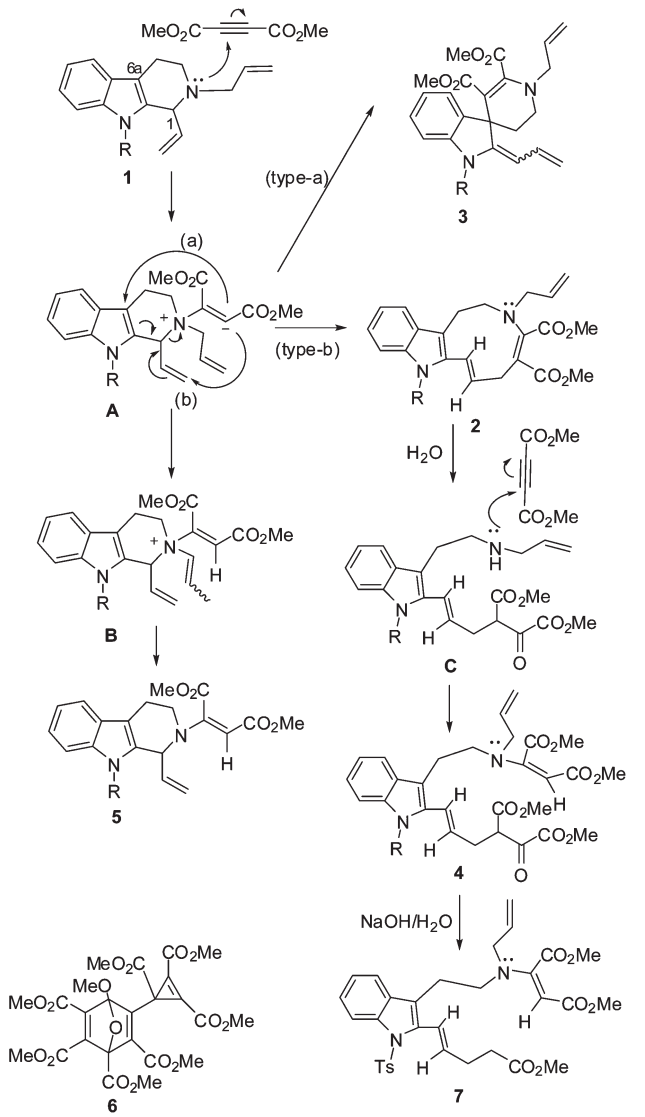
[a] In pure product. [b] Equivalents. [c] 21% of the starting material was recovered. [d] Not characterized.

rest of the reactions, short pads of silica were used for separation which reduced or avoided the formation of this compound. Change of the solvent to DCM at reflux precluded total conversion with recovery of the starting material (21%) and formation of **2a** as the only reaction product (41%, entry 4). Gold salts are well known alkynophilic catalysts that favour many interesting synthetic processes including cyclizations and intramolecular rearrangements.[11] We studied the possible effect of a 5% of gold trichloride in the reaction.[12] These new conditions (entry 5) provided a mixture of **2a** and a new structure, **5a** which is a result of a deallylation process.[13] These deallylation reactions have been observed with various metals, and can be minimized if adding the catalysts at 0 °C (entry 6).[14] In entries 7–10, results of the parent reactions of substrate **1b** are recorded. The behavior of this substrate is similar to **1a**, observing products **2b**, **3b** and **4b**. The use of gold catalysis produced small amounts of **5b** along with moderate yields of **2b**. Entries 11–12 show the results of the reaction of **1c** which is prone to decomposition and only gave poor yields of **2c** under the conditions tested.

In Scheme 2 we show the possible reaction pathways leading from compounds **1a–c** to the different products. The processes would start with a Michael type attack onto common intermediate **A**. The anionic centre in **A** may attack two possible positions, namely the vinyl group attached to C1 or to C6a. These attacks would lead respectively to products **2** and **3**. Alternatively if the anion traps a proton the reaction may follow a deallylation pathway which gives product **5** through the enamine intermediate **B**. This route is only observed in the presence of gold salts and is apparently favored by higher temperatures (entry 5).[15] The formation of **4** was presumed to start from product **2**. This was checked by reacting **2b** with 3 equiv. of DMAD in the presence of silica gel. This reaction gave **4b** in 95% yield after 6 h. The same mixture in the absence of silica gel did not produce any observable transformation. We propose in Scheme 2 a possible pathway for the transformation of **2** into **4**. The reaction would start with a hydrolysis of the enamine catalysed by the silica gel and Michael attack of the resulting secondary amine **C** to a molecule of DMAD and subsequent protonation to give **4**.

The structure of this product was established by 2D-NMR experiments. Isolation of DMAD tetramer **6** in these reactions may be related with the formation of **4**. This DMAD derivative has been previously described to be formed under harsh reaction conditions like high pressures or temperatures.[16] In addition we treated **4a** with a 1 N solution of sodium hydroxide which gave **7** upon a retro Claisen process.

Our next target was to study the behavior of pyrrolotetrahydro-β-carboline **8** in the reaction with triple bonded dienophiles. These reactions gave unexpected products due to the Michael type attack of the β-carboline nitrogen to the dienophile and skeletal rearrangement (Table 2, Scheme 3). The reaction of **7** with DMAD at rt (entry 1) gave us a mixture of two reaction products, the minor product, **9a**, being the result of a Michael-type attack and further skeletal rearrangement upon reaction with C7a

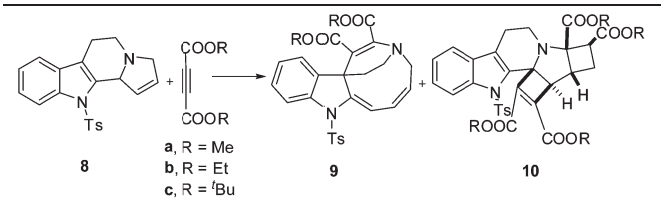


Scheme 2 Possible reaction pathways for the formation of products **3**–**7** from **1**.

of the pyrrolo-β-carboline system. This compound was expected as it implies a similar reactivity to that for substrate **1a**. Interestingly another compound which incorporated two molecules of DMAD was the major product albeit isolated in low yield. The structure of this new product was assigned as **10a** using several NMR techniques and finally established by an X-ray diffraction analysis (Fig. 1). The strained structure of this compound is really unusual as it bears two small rings including a cyclobutene being a compound with high connectivity. In the next reaction we increased the amount of DMAD which gave **10a** as the only reaction product in 65% yield. The effect of a gold salt was studied next. In the presence of 5% of $AuCl_3$ the reaction only gave compound **9a** in 58% yield. Temperature was lowered to avoid decomposition of **9** in the presence of the gold salt. Therefore the reaction pathway is easily controlled by just switching the reaction conditions (Table 2).

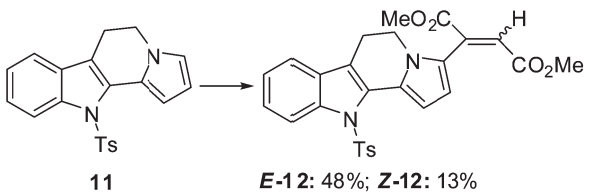
Reactions with the parent diethoxycarbonylacetylene and di-*tert*-butoxycarbonyl acetylene were next studied and followed

Table 2 Reaction of pyrrolo-β-carbolines with acetylenedicarboxylates



No.	$AuCl_3$	R (equiv.)	Temp.	Time	Yield[a] (%) 9	10
1	No	Me (3)	rt	48 h	6	30
2	No	Me (5)	rt	48 h	<5	65
3	0.05	Me (5)	0 °C	20 min	58	—
4	0.05	Me (5)	0 °C	80 min	11	—
5	No	Et (5)	rt	48 h	<5	60
6	0.05	Et (5)	0 °C	2 h	49	—
7	No	tBu (5)	rt	48 h	10	42
8	0.05	tBu (5)	0 °C	2 h	39	—

[a] In pure product.



Scheme 3 Electrophilic aromatic substitution of **11** with DMAD.

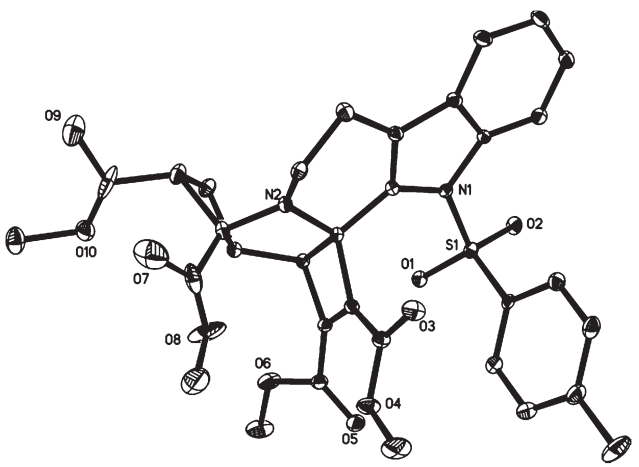


Fig. 1 ORTEP drawing for **10a**.

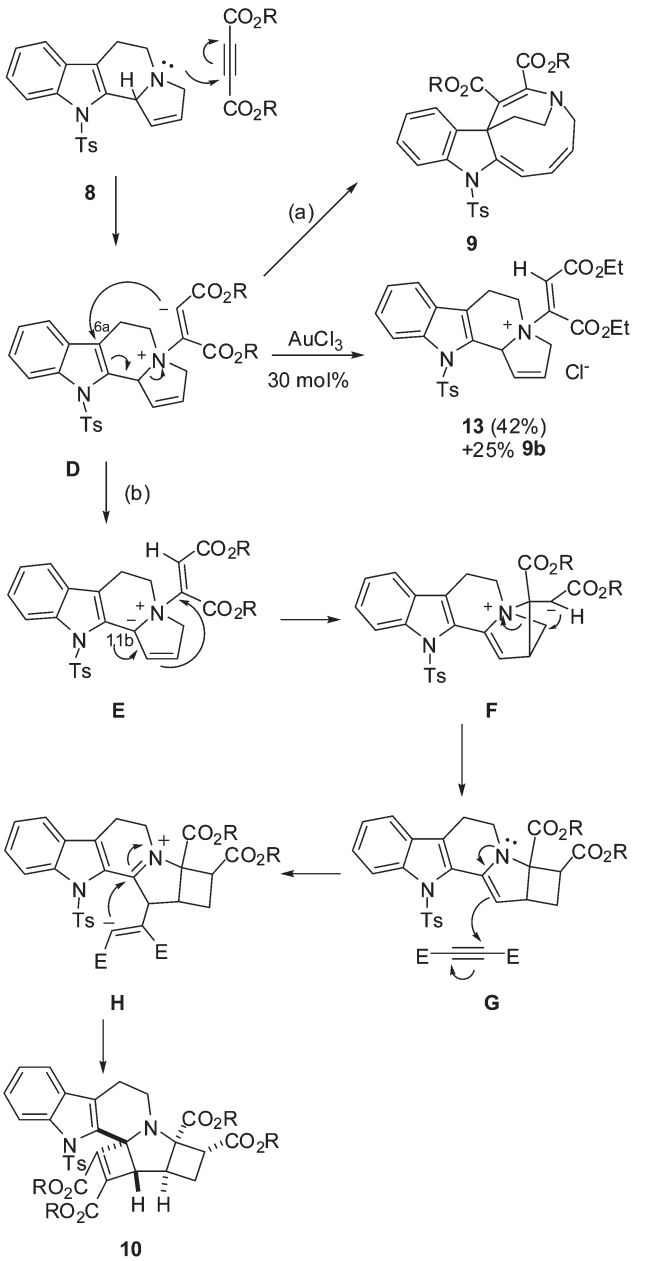
similar behaviour. Thus, in the absence of gold catalysts these reactions produced products **10b** and **10c** in 60% and 42% yields as the major products along with small amounts of compounds **9b** and **9c** (entries 5 and 7), whereas in the presence of $AuCl_3$ the only reaction products were **9b** and **9c** in moderate yields (entries 6 and 8). The hexacyclic compounds **10** are formed in a totally stereoselective manner in the five new stereogenic centers created. On the other hand non-activated alkynes

such as 3-hexyne did not react with **8** and the starting material was recovered after 48 h. The reactivity of this substrate with terminal alkynes like ethylpropyolate resulted in different reorganization processes and will be published elsewhere.

One interesting observation with these substrates was that if performing the reaction under air we observed the formation of small amounts of a mixture of two isomeric products, **12**. We assumed that a partial oxidation to the pyrrole in the starting material **8** had occurred and that a further electrophilic aromatic substitution reaction with DMAD had produced these products. To check this we oxidised **7** by stirring a solution in acetonitrile under air, and when t.l.c. analysis showed total conversion into indole **11** (12 h) we added 5 equiv. of DMAD. After 3 h we isolated a 48% yield of ***E*-12** and 13% of ***Z*-12**. The two isomers were separated and characterized. Stereochemistry was assigned according to chemical shift of the olefinic proton (Scheme 3).[12]

The plausible reaction pathway that explains the formation of **9** and **10** is depicted in Scheme 4. After Michael type attack to the acetylenedicarboxylate reagent and formation of **D**, reaction of the anionic carbon with position C6a of the heterocycle gives product **9**. Alternatively, a proton exchange with C11b produces **E**, an ylide-type intermediate that appears in the Stevens rearrangement reaction. This species rearranges onto **F** and a nucleophilic attack gives cyclobutane derivative **G**. The reaction of this intermediate with a second molecule of acetylenedicarboxylate has to be very favorable as we have not detected this compound. The new Michael attack of **G** gives **H** which cyclizes finally into **10**.

The role of gold catalysis is not very clear. As it favours pathway (a) leading to **9**, it may be assumed that gold salts preclude proton abstraction from C11b possibly by coordination with **E**. This disfavors the formation of **F** and the pathway to **10**. To have some more information on this we performed a reaction using 30 mol% of $AuCl_3$ and 5 equiv. of diethyl acetylene dicarboxylate. These conditions allowed the formation of **9b** (25%) and the isolation of a new compound which was identified as **13** (42%), a salt that arises from intermediate **D** which is possibly formed during the isolation procedure.[14]



Scheme 4 Possible reaction pathways for the formation of products **9–10** from **8**.

Conclusions

In conclusion, new cascade reactions from β-carboline substrates have produced novel polycyclic structures upon Michael attack to activated alkynes and rearrangements. Several reaction pathways arise and may be controlled by simple selection of conditions including the use of gold catalysis. Synthetic applications to natural or biologically active compounds as well as more mechanistic studies are underway.

Experimental section

General procedures

^{1}H NMR and ^{13}C NMR spectra were taken on a 300 MHz spectrometer. Chemical shifts™ are in parts per million relative to tetramethylsilane at 0.00 ppm. IR spectra were determined by an FT-IR spectrometer. TLC analyses were performed on commercial aluminium sheets bearing a 0.25 mm layer of silica gel. Silica gel 0.035–0.070 mm, 60 Å was used for column chromatography. Medium pressure liquid chromatography (MPLC) was performed using Si 25+M 2593-2 compact columns. Elemental analyses were carried out using CHN equipment. All solvents were distilled just before their use. THF and benzene were refluxed over Na–benzophenone; DCM was refluxed over calcium hydride. All reactions were conducted under an argon atmosphere and in flame-dried flasks. Compounds **1a**, **2a**, **3a**, **8** were previously described.[9]

Starting materials

Preparation of 2-allyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-2-ium-bromide. To a solution of 4,9-dihydro-3*H*-pyrido[3,4-*b*]indole

(1.0 g, 5.86 mmol) in anhydrous THF (8.5 mL $mmol^{-1}$) was added allyl bromide (1.3 mL, 14.69 mmol) under an argon atmosphere. After 16 h of stirring at room temperature, the precipitate was collected obtaining 1.5 g (88%) of salt, as an orange solid (mp = 181–183 °C). ^{1}H-NMR (DMSO) δ 3.36 (t, 2H, J = 9.4 Hz, CH_2CH_2N), 4.06 (t, 2H, J = 8.9 Hz, CH_2CH_2N), 4.66 (d, 2H, J = 6.2 Hz, $CH_2CH{=}CH_2$), 5.49 (dd, 1H, J_1 = 10.1 Hz, J_2 = 1.2 Hz, CH=CH_2), 5.60 (dd, 1H, J_1 = 1.7 Hz, J_2 = 1.2 Hz, CH=CH_2), 6.03–6.17 (m, 1H, CH=CH_2), 7.20–7.25 (m, 1H, Ar), 7.46–7.51 (m, 1H, Ar), 7.61 (d, 1H, J = 8.5 Hz, Ar), 7.80 (d, 1H, J = 8.4 Hz, Ar), 9.16 (s, 1H, H1), 12.33 (bs, 1H, H9). ^{13}C-NMR ($CDCl_3$) δ 20.1, 49.4, 61.7, 114.5, 122.5, 122.8, 123.1, 124.1, 124.5, 126.4, 129.7, 131.4, 142.4, 156.4. IR (KBr) 3036, 1646, 1538 cm^{-1}. Anal. Calcd for $C_{14}H_{15}BrN_2$: C, 57.75; H, 5.19; N, 9.62. Found: C, 57.80; H, 5.23; N, 9.70.

Preparation of *tert*-butyl 2-allyl-1-vinyl-3,4-dihydro-1*H*-pyrido-[3,4-*b*]indole-9(2*H*)-carboxylate, 1b. To a solution of 2-allyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole, **1c** (1.0 g, 4.20 mmol) in anhydrous THF (21 mL) at −40 °C was added *via* a syringe LiHDMS (12.6 mL, 12.6 mmol). The reaction mixture was stirred for 1 h. Then, di-*tert*-butyl dicarbonate (1.8 g, 8.4 mmol) was added, stirring for 30 min. The reaction was extracted with 1 N HCl (20 mL), washed with $NaHCO_3$ (15 mL), and dried over $MgSO_4$. After filtration, the solvent was eliminated under reduced pressure, and the resulting mixture was purified by flash chromatography on silica gel (Hex–EtOAc 9 : 1), obtaining 911 mg (75%) of **1b** as an orange oil. ^{1}H-NMR ($CDCl_3$) δ 1.61 (s, 9H, C(CH_3)$_3$), 2.52 (dd, 1H, J_1 = 16.2 Hz, J_2 = 4.4 Hz, CH_2), 2.78–2.99 (m, 2H, CH_2), 3.09–3.39 (m, 3H, CH_2), 4.76 (dt, 1H, J_1 = 17.3 Hz, J_2 = 1.5 Hz, CH=CH_2), 4.99–5.00 (d, 1H, J = 4.4 Hz, H1), 5.15–5.23 (m, 3H, CH=CH_2), 6.91–6.14 (m, 2H, 2 × CH=CH_2), 7.20–7.31 (m, 2H, Ar), 7.44 (d, 1H, J = 7.0 Hz, Ar), 8.20 (d, 1H, J = 7.5 Hz, Ar). ^{13}C-NMR ($CDCl_3$) δ 18.0, 28.1, 42.2, 56.2, 58.3, 83.6, 115.6, 115.7, 117.4, 117.6, 117.9, 122.5, 124.0, 129.2, 133.2, 136.3, 136.4, 137.9, 150.1. IR (NaCl) 1722, 1650, 1600 cm^{-1}. Anal. Calcd for $C_{21}H_{26}N_2O_2$: C, 74.52; H, 7.74; N, 8.28. Found: C, 74.60; H, 7.79; N, 8.35. ESI-MS: m/z = 339 $[M + H]^+$.

Preparation of 2-allyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-pyrido-[3,4-*b*]indole, 1c. To a suspension of 2-allyl-4,9-dihydro-3*H*-pyrido[3,4-*b*]indol-2-ium bromide (1.2 g, 3.82 mmol) in anhydrous THF (36 mL) at 0 °C, vinyl magnesium bromide was added slowly. The reaction mixture was then allowed to come to room temperature. After 2.5 h the reaction mixture was again cooled at 0 °C and quenched by the addition of NH_4Cl (50 mL) and extracted with AcOEt (3×). The organic layer was washed with water (25 mL), brine and dried over $MgSO_4$. Solvent was eliminated under reduced pressure and after flash chromatography in Hex–AcOEt 9 : 1 we obtained 833.7 mg (97%) of **1c** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.79–2.87 (m, 1H, CH_2), 2.98 (bs, 1H, CH_2), 3.26 (dd, 1H, J_1 = 13.7 Hz J_2 = 7.4 Hz, CH_2), 3.38–3.45 (m, 1H, CH_2), 3.66 (dd, 1H, J_1 = 13.7 Hz, J_2 = 4.9 Hz, CH_2), 4.21 (d, 1H, J = 7.8 Hz, CH_2), 5.40–5.51 (m, 5H, 2 × CH=CH_2 and H1), 6.01–6.24 (m, 2H, 2 × CH=CH_2), 7.29–7.39 (m, 3H, Ar), 7.71 (d, 1H, J = 6.3 Hz, Ar), 7.97 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ 20.4, 46.8, 56.7, 62.0, 108.1, 110.6, 117.6, 117.9, 118.7, 118.9, 121.1, 127.1, 132.5, 135.2, 135.8, 137.8. IR (NaCl) 1650, 1600 cm^{-1}. Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.75. Found: C, 81.90; H, 7.73; N, 11.35. ESI-MS: m/z = 239 $[M + H]^+$.

Preparation of 11-tosyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]-indole, 11. To a solution of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **7** (100.0 mg, 0.27 mmol) in AcOEt (5 mL), Pd/C was added (10% weight) and the resulting mixture was stirred for 30 min at room temperature. After that, the crude mixture was filtered through Celite and the solvent was eliminated under reduced pressure. Compound **10** was obtained analytically pure, 99 mg (100%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 2.28 (s, 3H, CH_3), 2.92 (t, 2H, J = 6.9 Hz, CH_2CH_2N), 4.06 (t, 2H, J = 6.9 Hz, CH_2CH_2N), 6.25 (dd, 1H, J_1 = 3.8 Hz, J_2 = 2.8 Hz, H2), 6.77 (bs, 1H, H1), 7.05–7.08 (m, 3H, Ar), 7.25–7.34 (m, 3H, Ar and H3), 7.48 (dd, 2H, J_1 = 6.6 Hz, J_2 = 1.6 Hz, Ar), 8.27 (dd, 1H, J_1 = 6.6 Hz, J_2 = 1.6 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.5, 21.7, 44.3, 108.0, 110.4, 115.7, 116.5, 117.7, 122.5, 122.6, 124.2, 124.3, 126.7, 129.5, 129.9, 130.9, 134.4, 137.7, 144.4. IR (NaCl) ν 1620 cm^{-1}. Anal. Calcd for $C_{21}H_{18}N_2O_2S$: C, 69.59; H, 5.01; N, 7.73. Found: C, 69.67; H, 5.12; N, 7.81. ESI-MS: m/z = 363 $[M + H]^+$.

General procedure A for the reaction of 2-allyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carbolines 1a–c with internal alkynes

To a solution of **1a–c** (1.0 mmol) in anhydrous DCM (16 mL $mmol^{-1}$) was added the alkyne (5.0 mmol) *via* a syringe at room temperature. The reaction was stirred for 48 h. The solvent was eliminated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel.

General procedure B for the reaction of 2-allyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carbolines 1a–c and internal alkynes

To a solution of the alkyne (5 mmol) and gold trichloride (0.05 mmol) in anhydrous DCM (8 mL) at 0 °C was added *via* a syringe **1a–c** in 8 mL of DCM. The reaction was controlled by t.l.c., and upon disappearance of the starting materials it was filtered through Celite and extracted with water (15 mL), brine (15 mL) and dried over $MgSO_4$. The solvent was eliminated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel.

Preparation of dimethyl (4*E*,7*E*)-3-allyl-9-tosyl-2,3,6,9-tetrahydro-1*H*-azecino[5,4-*b*]indole-4,5-dicarboxylate, 2a. Following general procedure A the reaction of 2-allyl-9-tosyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline, **1a** (100.0 mg, 0.26 mmol) and DMAD (184.7 mg, 1.13 mmol) in DCM (4.2 mL) at 0 °C afforded after flash chromatography (Hex–AcOEt 20 : 1 to 9 : 1) 98.6 mg (68%) of **2a** as a yellow oil and 29.4 mg (16%) of **4a** as a yellow oil.

Preparation of dimethyl (4*E*,7*E*)-3-allyl-9-(4-(*tert*-butoxycarbonyl)-2,3,6,9-tetrahydro-1*H*-azecino[5,4-*b*]indole-4,5-dicarboxylate, 2b. Following general procedure A the reaction of 2-allyl-9-(*tert*-butoxycarbonyl)-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline, **1b** (123.6 mg, 0.37 mmol) and DMAD (259.5 mg, 1.83 mmol)

in DCM (6.0 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 20 : 1 to 9 : 1) 100.0 mg (55%) of **2b** as a light yellow oil, 22.8 mg (15%) of **3b** as a yellow oil and 4.9 mg (5%) of **4b** as an orange oil. ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 9H, C(CH_3)$_3$), 2.67–3.08 (m, 4H, CH_2), 3.22–3.59 (m, 3H, CH_2), 3.73 (s, 3H, OCH_3), 3.80–3.97 (m, 1H, CH_2), 3.84 (s, 3H, OCH_3), 5.06 (dd, 1H, J_1 = 10.1 Hz, J_2 = 1.2 Hz, CH=CH_2), 5.16 (dd, 1H, J_1 = 17.1 Hz, J_2 = 1.3 Hz, CH=CH_2), 5.31–5.41 (m, 1H, *H*7), 5.70–5.83 (m, 1H, *CH*=CH_2), 6.62 (d, 1H, J = 16.3 Hz, *H*8), 7.20–7.31 (m, 2H, Ar), 7.41 (d, 1H, J = 7.9 Hz, Ar), 8.09 (d, 1H, J = 7.6 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 24.7, 28.7, 33.0, 51.9, 52.5, 52.9, 60.7, 84.5, 116.0, 116.5, 117.7, 118.5, 121.5, 123.0, 124.8, 124.9, 126.1, 130.9, 135.1, 135.3, 135.6, 150.9, 150.9, 167.4, 169.4. IR (NaCl): 1723, 1558 cm^{-1}. Anal. Calcd for $C_{27}H_{32}N_2O_6$: C, 67.48; H, 6.71; N, 5.83. Found: C, 67.56; H, 6.79; N, 5.88. ESI-MS: m/z = 481 [M + H]$^+$.

Preparation of dimethyl (4*E*,7*E*)-3-allyl-2,3,6,9-tetrahydro-1*H*-azecino[5,4-*b*]indole-4,5-dicarboxylate, 2c. Following general procedure A the reaction of 5,6,11,11b-tetrahydro-3*H*-indolizino-[8,7-*b*]indole, **1c** (200.0 mg, 0.84 mmol) and DMAD (596.5 mg, 4.2 mmol) in DCM (13.4 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 9 : 1 to 4 : 1) 116.5 mg (35%) of **2c** as a light yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.85–2.94 (m, 4H, CH_2), 3.28–3.32 (m, 3H, CH_2), 3.72–3.88 (m, 1H, CH_2), 3.73 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 5.07 (d, 1H, J = 10.1 Hz, CH=CH_2), 5.14 (d, 1H, J = 17.1 Hz, CH=CH_2), 5.53–5.63 (m, 1H, *H*7), 5.66–5.80 (m, 1H, *CH*=CH_2), 6.26 (d, 1H, J = 15.0 Hz, *H*8), 6.29 (s, 1H, *H*9), 7.11–7.24 (m, 2H, Ar), 7.37 (d, 1H, J = 7.4 Hz, Ar), 7.45 (d, 1H, J = 7.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 24.9, 32.9, 52.2, 52.9, 53.5, 60.5, 115.5, 117.9, 118.2, 119.1, 119.7, 121.4, 122.1, 124.1, 130.1, 131.3, 134.7, 136.0, 136.2, 151.2, 167.3, 169.2. IR (NaCl): 1735, 1694, 1576 cm^{-1}. Anal. Calcd for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.58; H, 6.47; N, 7.42. ESI-MS: m/z = 381 [M + H]$^+$.

Preparation of dimethyl 1-tosyl-1′-allyl-2-(prop-2-en-1-ylidene)-1,2,5′,6′-tetrahydro-1′*H*-spiro[indole-3,4′-pyridine]-2′,3′-dicarboxylate, 3a. Following general procedure A the reaction of 2-allyl-9-tosyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline, **1a** (250.0 mg, 0.64 mmol) and DMAD (0.16 mL, 1.28 mmol) in DCM (10 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 9 : 1 to 4 : 1) 33 mg (10%) of **2a** as a yellow oil and 83 mg (24%) of **3a** as a yellow oil.[9]

Preparation of (*Z*)-dimethyl 1′-allyl-2-allylidene-1-(4-*tert*-butoxycarbonyl)-2′,3′-dihydro-1′*H*-spiro[indoline-3,4′-pyridine]-5′,6′-dicarboxylate, 3b. Following general procedure A the reaction of 2-allyl-9-(*tert*-butoxycarbonyl)-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline, **1b** (110.0 mg, 0.30 mmol) and DMAD (426.3 mg, 3.00 mmol) in DCM (4.6 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 9 : 1 to 4 : 1) 39.5 mg (25%) of **2b** as a yellow oil, 33.8 mg (20%) of **3b** as a yellow oil and 82.5 mg (40%) of **4b** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 9H, C(CH_3)$_3$), 1.80 (dt, 1H, J_1 = 13.7 Hz, J_2 = 3.5 Hz, CH_2CH_2N), 2.22–2.32 (m, 1H, CH_2CH_2N), 3.14–3.22 (m, 1H, CH_2CH_2N), 3.34 (s, 3H, OCH_3), 3.43 (td, 1H, J_1 = 13.0 Hz, J_2 = 3.5 Hz, CH_2CH_2N), 3.80 (t, 2H, J = 4.5 Hz, CH_2CH=CH_2), 3.91 (s, 3H, OCH_3), 4.99 (dd, 1H, J_1 = 9.7 Hz, J_2 = 2.1 Hz, CH_2CH=CH_2), 5.10 (dd, 1H, J_1 = 16.2 Hz, J_2 = 1.9 Hz, CH_2CH=CH_2), 5.26–5.32 (m, 2H,=CH–CH=CH_2), 5.82–5.95 (m, 1H, CH_2C*H*=CH_2), 6.73–6.85 (m, 1H,=CH–C*H*=CH_2), 6.97–7.01 (m, 3H, Ar), 7.16–7.22 (m, 1H,=*CH*–CH=CH_2), 7.74 (d, 1H, J = 8.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 28.4, 35.5, 43.1, 46.3, 50.9, 52.8, 55.7, 82.7, 98.1, 111.6, 115.7, 116.0, 119.1, 122.6, 122.9, 127.5, 131.4, 132.7, 138.7, 140.7, 147.1, 148.9, 151.8, 166.0, 166.1. IR (NaCl): 1731, 1702 cm^{-1}. Anal. Calcd for $C_{27}H_{32}N_2O_6$: C, 67.48; H, 6.71; N, 5.83. Found: C, 67.29; H, 6.90; N, 5.77. ESI-MS: m/z = 481 [M + H]$^+$.

Preparation of dimethyl 2-(allyl(2-(2-((*E*)-6-methoxy-4-(methoxycarbonyl)-5,6-dioxohex-1-enyl)-1-tosyl-1*H*-indol-3-yl)ethyl)amino)-maleate, 4a. Following general procedure A the reaction of 2-allyl-9-tosyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline, **1a** (100.0 mg, 0.26 mmol) and DMAD (177.6 mg, 2.5 mmol) in DCM (4.2 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 9 : 1 to 4 : 1) 70.3 mg (50%) of **2a** as a yellow oil and 75.6 mg (42%) of **4a** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.29 (s, 3H, Ts–CH_3), 2.91–3.03 (m, 4H, 2 × CH_2), 3.22–3.32 (m, 4H, 2 × CH_2), 3.64 (s, 3H, OCH_3), 3.78, (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 3.92 (s, 3H, OCH_3), 4.39 (t, 1H, J = 6.9 Hz, CO–C*H*–COOMe), 4.68 (s, 1H, *H*3), 4.91 (d, 1H, J = 17.1 Hz, CH_2CH=CH_2), 5.10 (d, 1H, J = 10.7 Hz, CH_2CH=CH_2), 5.51–5.65 (m, 1H, CH_2C*H*=CH_2), 5.84 (dt, 1H, J_1 = 16.2 Hz, J_2 = 6.7 Hz, Indole–CH=C*H*–CH_2), 6.79 (d, 1H, J = 16.2 Hz, Indole–C*H*=CH–CH_2), 7.14 (d, 2H, J = 8.2 Hz, Ar), 7.23–7.36 (m, 2H, Ar), 7.40 (d, 1H, J = 8.0 Hz, Ar), 7.55 (d, 2H, J = 8.3 Hz, Ar), 8.19 (d, 1H, J = 8.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.5 (Ts–CH_3), 23.2 (br, Indole–CH_2), 30.8 (CH_2–CH–CO_2Me), 49.9 (br, CH_2–CH_2–N), 50.8 (OCH_3), 52.9 (OCH_3), 53.0 (OCH_3), 53.4 (OCH_3), 53.5 (CH_2–*CH*–CO_2Me), 53.7 (br, N–CH_2–CH=), 84.8 (*HC*(3)), 115.5 (Indole *CH*), 118.2 (=CH_2), 118.9 (Indole *CH*), 119.0 (Indole *C*), 123.0 (Indole-*CH*=CH), 124.0 (Indole *CH*), 125.3 (Indole *CH*), 126.8 (Ts 2 × *CH*), 129.6 (Ts 2 × *CH*), 130.5 (Indole *C*), 131.5 (Indole–CH=*CH*), 131.6 (*CH*=CH_2), 135.1 (Indole *C*), 135.3 (Ts *C*), 136.2 (Indole *C*), 144.7 (Ts *C*), 153.7 (*C*2), 160.6 (*CO*OMe), 165.9 (*CO*OMe), 168.0 (*CO*OMe), 168.8 (*CO*OMe), 188.2 (*C*=*O*). IR (NaCl): 1735, 1576 cm^{-1}. Anal. Calcd for $C_{35}H_{38}N_2O_{11}S$: C, 60.51; H, 5.51; N, 4.03. Found: C, 60.95; H, 5.70; N, 4.19. ESI-MS: m/z = 695 [M + H]$^+$.

Preparation of dimethyl 2-(allyl(2-(1-(*tert*-butoxycarbonyl)-2-((*E*)-6-methoxy-4-(methoxycarbonyl)-5,6-dioxohex-1-enyl)-1*H*-indol-3-yl)ethyl)amino)maleate, 4b. A solution of dimethyl (4*E*,7*E*)-3-allyl-9-(4-(*tert*-butoxycarbonyl)-2,3,6,9-tetrahydro-1*H*-azecino[5,4-*b*]indole-4,5-dicarboxylate, **2b** (31.0 mg, 0.064 mmol) in anhydrous DCM (16 mL mmol^{-1}), DMAD (45.8 mg, 0.323 mmol) and silica gel (35 mg) were added at room temperature. After 6 h stirring the reaction mixture was filtered and the solvent was eliminated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel (Hex–AcOEt 2 : 1), obtaining 39.1 mg (95%) of **4b** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 9H, C(CH_3)$_3$), 2.91–2.98 (m, 2H, CH_2), 2.99–3.06 (m, 2H, CH_2), 3.34–3.38 (m, 2H, CH_2), 3.67 (s, 3H, OCH_3), 3.71 (bs, 2H, CH_2), 3.78 (s, 3H, OCH_3), 3.93 (s, 3H, OCH_3), 3.94 (s, 3H, OCH_3), 4.36 (t, 1H, J = 4.3 Hz, CO–C*H*–COOMe), 4.76 (s, 1H, *H*1), 5.16 (d,

1H, J = 10.3 Hz, $CH_2CH{=}CH_2$), 5.22 (d, 1H, J = 5.6 Hz, $CH_2CH{=}CH_2$), 5.71–5.84 (m, 2H, $CH_2CH{=}CH_2$ and Indole–$CH{=}CH{-}CH_2$), 6.72 (d, 1H, J = 9.6 Hz, Indole-$CH{=}CH{-}CH_2$), 7.26–7.33 (m, 2H, Ar), 7.52 (d, 1H, J = 4.4 Hz, Ar), 8.09 (d, 1H, J = 4.8 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.0, 28.3, 30.9, 50.8, 52.7, 52.8, 52.9, 53.3, 53.4, 53.8, 84.0, 84.9, 115.6, 116.1, 117.8, 118.0, 118.6, 122.8, 124.7, 124.9, 128.9, 129.6, 134.8, 135.5, 150.3, 153.9, 160.7, 166.0, 168.1, 168.9, 188.1. IR (NaCl): 1735, 1694, 1576 cm^{-1}. Anal. Calcd for $C_{33}H_{40}N_2O_{11}$: C, 61.86; H, 6.29; N, 4.37. Found: C, 61.97; H, 6.41; N, 4.49. ESI-MS: m/z = 641 $[M + H]^+$.

Preparation of dimethyl (*E*)-2-(9-tosyl-1-vinyl-1,3,4,9-tetrahydro-2*H*-β-carbolin-2-yl)but-2-enedioate, 5a. Following general procedure B the reaction of 2-allyl-9-tosyl-1-vinyl-2,3,4,9-tetrahydro-1*H*-β-carboline, **1a** (100.0 mg, 0.26 mmol), DMAD (753.2 mg, 1.27 mmol) and $AuCl_3$ (3.9 mg, 0.013 mmol) in DCM (4.2 mL mmol^{-1}) at 0 °C afforded after flash chromatography (Hex–AcOEt 9 : 1 to 4 : 1) 28.1 mg (20%) of **2a** as a yellow oil and 70.6 mg (55%) of **5a** as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.17 (s, 3H, CH_3), 2.65 (dd, 1H, J_1 = 16.2 Hz, J_2 = 3.6 Hz, CH_2CH_2N), 2.87–2.98 (m, 1H, CH_2CH_2N), 3.42–3.67 (m, 2H, CH_2CH_2N), 3.68 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 5.03 (s, 1H, $HC{=}C$), 5.05 (dd, 1H, J_1 = 17.8 Hz, J_2 = 1.1 Hz, $CH{=}CH_2$), 5.36 (dd, 1H, J_1 = 10.4 Hz, J_2 = 0.8 Hz, $CH{=}CH_2$), 5.78 (bs, 1H, *H*4), 6.10–6.21 (m, 1H, $CH{=}CH_2$), 7.17–7.35 (m, 5H, Ar), 7.62 (d, 2H, J = 8.5 Hz, Ar), 8.06 (d, 1H, J = 8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.9, 30.7, 31.3, 51.4, 53.6, 86.4, 115.5, 119.0, 119.3, 124.3, 125.6, 125.9, 127.1, 127.9, 129.7, 130.0, 130.3, 132.5, 135.1, 137.0, 145.4, 154.4, 166.5, 168.6. IR (NaCl): 1731, 1690, 1572 cm^{-1}. Anal. Calcd for $C_{26}H_{26}N_2O_6S$: C, 63.14; H, 5.30; N, 5.66. Found: C, 63.09; H, 5.75; N, 6.39. ESI-MS: m/z = 495 $[M + H]^+$.

Preparation of dimethyl 2-(allyl(2-(2-((*E*)-5-methoxy-5-oxopent-1-enyl)-1-tosyl-1*H*-indol-3-yl)ethyl)amino)maleate, 7. To a solution of dimethyl 2-(allyl(2-(2-((*E*)-6-methoxy-4-(methoxycarbonyl)-5,6-dioxohex-1-enyl)-1-tosyl-1*H*-indol-3-yl)ethyl)amino)-maleate, **4a** (70.0 mg, 0.10 mmol) in DCM (5 mL) at room temperature, 5 mL of 1 N NaOH were added and the mixture was extracted after 5 min stirring. The solvent was dried over $MgSO_4$ and eliminated under reduced pressure to give 48.3 mg of **7** (80%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, CH_3), 2.53–2.61 (m, 4H, 2 × CH_2), 2.84–2.88 (m, 2H, CH_2), 3.16–3.25 (m, 4H, 2 × CH_2), 3.57 (s, 3H, OCH_3), 3.65, (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.59 (s, 1H, *H*1), 4.84 (d, 1H, J = 17.1 Hz, $CH_2CH{=}CH_2$), 5.03 (d, 1H, J = 10.2 Hz, $CH_2CH{=}CH_2$), 5.43–5.65 (m, 1H, $CH_2CH{=}CH_2$), 5.70–5.80 (dt, 1H, J_1 = 16.2 Hz, J_2 = 6.0 Hz, Indole–$CH{=}CH{-}CH_2$), 6.67 (d, 1H, J = 16.2 Hz, Indole-$CH{=}CH{-}CH_2$), 7.05 (d, 2H, J = 8.1 Hz, Ar), 7.16–7.33 (m, 3H, Ar), 7.50 (d, 2H, J = 8.1 Hz, Ar), 8.15 (d, 1H, J = 8.1 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.5 (Ts–CH_3), 22.7 (br, Indole-CH_2), 28.3 ($MeO_2C{-}CH_2{-}CH_2$), 33.2 ($CH_2{-}CH_2{-}CO_2Me$), 49.7 (br, $CH_2{-}CH_2{-}N$), 50.8 (OCH_3), 51.8 (OCH_3), 52.9 (OCH_3), 53.6 (br, $N{-}CH_2{-}CH{=}$), 84.7 (*HC*-(3)), 115.4 (Indole *CH*), 118.2 (Indole *C*), 118.3 ($=CH_2$), 118.8 (Indole *CH*), 121.0 (Indole-$CH{=}CH$), 131.5 ($CH{=}CH_2$), 123.9 (Indole *CH*), 125.2 (Indole *CH*), 126.8 (Ts 2 × *CH*), 129.5 (Ts 2 × *CH*), 130.5 (Indole *C*), 135.4 (Indole-$CH{=}CH$), 135.6 (Indole *C*), 135.7 (Ts *C*), 136.3 (Indole *C*), 144.7 (Ts *C*), 153.8 (*C*2), 165.9 (*CO*OMe), 168.1 (*CO*OMe), 173.3 (*CO*OMe). IR (NaCl): 1738, 1696, 1642 cm^{-1}. Anal. Calcd for $C_{32}H_{36}N_2O_8S$: C, 63.14; H, 5.96; N, 4.60. Found: C, 63.05; H, 5.91; N, 4.52. ESI-MS: m/z = 631 $[M + Na]^+$.

General procedure C for the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole 8 with internal alkynes

To a solution of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino-[8,7-*b*]indole **7** (1.0 mmol) in anhydrous DCM (16 mL mmol^{-1}) was added *via* a syringe the alkyne (5.0 mmol) at room temperature. The reaction mixture was stirred for 48 h, and the solvent was eliminated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel.

General procedure D for the reaction 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole 8 with internal alkynes

To a solution of the alkyne (5 mmol) and gold trichloride (0.05 mmol) in 8 mL of anhydrous DCM at 0 °C was added *via* a syringe the 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]-indole in 8 mL of DCM. The reaction was controlled by t.l.c., and upon disappearance of the starting materials it was filtered through Celite and extracted with water (15 mL), brine (15 mL) and dried over $MgSO_4$. The solvent was eliminated under reduced pressure. The resulting mixture was purified by flash chromatography on silica gel.

Preparation of dimethyl (9*E*,11*Z*)-8-tosyl-8,14-diazatetracyclo-[12,2,2,0^{1,9},0^{2,7}]octadeca-2,4,6,9,11,15-hexaen-15,16-dicarboxylate, 9a. Following general procedure D the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **8** (100.0 mg, 0.27 mmol), gold trichloride (4.1 mg, 0.013 mmol) and DMAD (191.8 mg, 1.35 mmol) in DCM (4.3 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 9 : 1) 61.0 mg (58%) of **9a** as a brown oil. ^{1}H NMR ($CDCl_3$) δ 0.04–0.10 (m, 1H, CH_2CH_2N), 1.51–1.62 (m, 1H, CH_2CH_2N), 2.35 (s, 3H, CH_3), 3.03–3.09 (m, 2H, CH_2CH_2N), 3.24 (s, 3H, OCH_3), 3.53–3.70 (m, 2H,$=CCH_2N$), 3.77 (s, 3H, OCH_3), 5.45 (dd, 1H, J_1 = 14.6 Hz, J_2 = 2.9 Hz, *H*12), 5.98 (t, 1H, J = 12.5 Hz, *H*11), 6.76 (d, 1H, J = 7.3 Hz, Ar), 6.88 (d, 1H, J = 9.7 Hz, *H*10), 7.07 (t, 1H, J = 7.8 Hz, Ar), 7.16 (d, 2H, J = 7.8 Hz, Ar), 7.27 (t, 1H, J = 8.8 Hz, Ar), 7.51 (d, 2H, J = 8.3 Hz, Ar), 7.88 (d, 1H, J = 7.8 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.6, 35.0, 46.5, 47.4, 51.3, 52.7, 53.0, 116.8, 118.3, 121.2, 121.7, 122.1, 125.3, 127.3, 128.0, 128.4, 129.3, 134.7, 136.5, 139.5, 141.4, 144.8, 147.8, 166.8, 167.2. IR (NaCl) 1730, 1620 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_6S$: C, 64.02; H, 5.17; N, 5.53. Found: C, 63.92; H, 5.02; N, 5.74. ESI-MS: m/z = 529 $[M + Na]^+$.

Preparation of diethyl (9*E*,11*Z*)-8-tosyl-8,14-diazatetracyclo-[12,2,2,0^{1,9},0^{2,7}]octadeca-2,4,6,9,11,15-hexaen-15,16-dicarboxylate, 9b. Following general procedure D the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **8** (100.0 mg, 0.27 mmol), gold trichloride (4.1 mg, 0.013 mmol) and diethyl but-2-ynedioate (233.4 mg, 1.35 mmol) in DCM (4.3 mL) at room temperature afforded after flash chromatography (Hex–

AcOEt 9 : 1) 70.5 mg (49%) of **9b** as a brown oil. ^{1}H NMR ($CDCl_3$) δ −0.04–0.01 (m, 1H, CH_2CH_2N), 0.60 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.15–1.22 (m, 3H, OCH_2CH_3), 1.45–1.56 (m, 1H, CH_2CH_2N), 2.27 (s, 3H, CH_3), 2.95–3.01 (m, 2H, CH_2CH_2N), 3.44–3.54 (m, 1H,=CCH_2N), 3.58–3.66 (m, 1H,=CCH_2N), 4.10–4.25 (m, 3H, OCH_2CH_3), 4.59–4.73 (m, 1H, OCH_2CH_3), 5.37 (dd, 1H, J_1 = 14.6 Hz, J_2 = 3.8 Hz, *H*12), 5.90 (t, 1H, J = 12.3 Hz, *H*11), 6.72 (dd, 1H, J_1 = 7.5 Hz, J_2 = 0.7 Hz, Ar), 6.79 (d, 1H, J = 10.2 Hz, *H*10), 6.98 (t, 1H, J = 7.5 Hz, Ar), 7.08 (d, 2H, J = 8.0 Hz, Ar), 7.16–7.22 (m, 1H, Ar), 7.43 (d, 2H, J = 8.2 Hz, Ar), 7.79 (d, 1H, J = 8.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 13.4, 13.9, 21.6, 35.1, 46.6, 47.5, 52.7, 60.2, 62.0, 116.8, 118.2, 121.6, 121.8, 125.3, 127.4, 127.9, 128.5, 129.3, 129.9, 134.8, 136.9, 139.8, 141.7, 144.8, 148.1, 165.3, 165.5. IR (NaCl): 1732, 1597 cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_6S$: C, 65.15; H, 5.66; N, 5.24. Found: C, 65.31; H, 5.43; N, 5.54. ESI-MS: m/z = 557 $[M + Na]^+$.

Preparation of di-*tert*-butyl (9*E*,11*Z*)-8-tosyl-8,14-diazatetracyclo-[12,2,2,0^{1,9},0^{2,7}]octadeca-2,4,6,9,11,15-hexaen-15,16-dicarboxylate, 9c. Following general procedure D the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **8** (82.5 mg, 0.23 mmol), gold trichloride (3.8 mg, 0.011 mmol) and di-*tert*-butyl but-2-ynedioate (256.1 mg, 1.13 mmol) in DCM (3.7 mL) at 0 °C afforded after flash chromatography (Hex–AcOEt 9 : 1 to 4 : 1) 53.3 mg (39%) of **9c** as a yellow solid (mp: 157–160 °C). ^{1}H NMR ($CDCl_3$) δ −0.06–0.00 (m, 1H, CH_2CH_2N), 0.98 (s, 9H, C(CH_3)$_3$), 1.47 (s, 9H, C(CH_3)$_3$), 1.47–1.52 (m, 1H, CH_2CH_2N), 2.34 (s, 3H, CH_3), 2.98–3.03 (m, 2H, CH_2CH_2N), 3.52 (dd, 1H, J_1 = 19.6 Hz, J_2 = 1.5 Hz,=CCH_2N), 3.72 (dd, 1H, J_1 = 19.9 Hz, J_2 = 5.2 Hz,=CCH_2N), 5.41 (dd, 1H, J_1 = 14.6 Hz, J_2 = 3.8 Hz, *H*12), 5.95 (t, 1H, J = 14.5 Hz, *H*11), 6.84 (d, 1H, J = 11.2 Hz, *H*10), 6.85 (d, 1H, J = 7.3 Hz, Ar), 7.07 (td, 1H, J_1 = 7.4 Hz, J_2 = 0.9 Hz, Ar), 7.14 (d, 2H, J = 8.0 Hz, Ar), 7.27 (td, 1H, J_1 = 7.9 Hz, J_2 = 1.3 Hz, Ar), 7.50 (d, 2H, J = 8.3 Hz, Ar), 7.87 (d, 1H, J = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.6, 27.5, 27.5, 34.8, 46.5, 47.4, 52.6, 80.1, 82.4, 113.8, 116.4, 118.2, 121.5, 122.1, 125.4, 127.4, 127.6, 128.6, 129.3, 134.8, 137.8, 139.9, 142.3, 144.7, 149.3, 164.7, 164.9. IR (KBr): 1732, 1597 cm^{-1}. Anal. Calcd for $C_{33}H_{38}N_2O_6S$: C, 67.10; H, 6.48; N, 4.74. Found: C, 67.21; H, 6.32; N, 4.54. ESI-MS: m/z = 613 $[M + Na]^+$.

Preparation of tetramethyl (2*S,2b*S**,9b*S**,11a*S**,11b*R**)-9-tosyl-1,2,2a,3,4,9,11a,11b-octahydro-2b,9-diazadicyclobuta[*a*,*c*]-indeno[2,3-*e*]indene-2,2a,10,11-tetracarboxylate, 10a.** Following general procedure C the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **8** (100 mg, 0.27 mmol) and DMAD (194.7 mg, 1.37 mmol) in DCM (4.3 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 4 : 1 to 2 : 1) 110.4 mg (65%) of **10a** as a brown oil. ^{1}H NMR ($CDCl_3$) δ (ppm): 1.92–2.01 (m, 1H, *H*1), 2.32 (s, 3H, CH_3), 2.39–2.48 (m, 1H, *H*1), 2.79 (dd, 1H, J_1 = 16.1 Hz, J_2 = 4.4 Hz, *H*4), 2.87–2.99 (m, 2H, *H*4 and *H*11b), 3.37–3.42 (m, 3H, 2 × *H*3 and *H*2), 3.44 (s, 3H, CH_3), 3.63 (s, 3H, CH_3), 3.69 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.25 (s, 1H, *H*11a), 7.11 (d, 2H, J = 8.5 Hz, Ar), 7.30–7.38 (m, 2H, Ar), 7.42–7.49 (m, 3H, Ar), 8.26 (d, 1H, J = 7.9 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ (ppm): 21.4, 22.8, 25.3, 37.9, 40.1, 44.8, 51.4, 51.8, 51.9, 52.0, 58.7, 71.6, 75.3, 115.5, 118.7, 123.1, 123.6, 125.5, 126.2, 129.3, 129.6, 132.3, 136.1, 137.9, 144.3, 145.1, 146.6, 161.1, 161.6, 171.5, 172.8. IR (NaCl) ν 1740, 1650, 1590 cm^{-1}. Anal. Calcd for $C_{33}H_{32}N_2O_{10}S$ (648.68): C, 61.10; H, 4.97; N, 4.32. Found: C, 60.87; H, 5.16; N, 4.08. ESI-MS: m/z = 649 $[M + H]^+$.

Preparation of tetraethyl (2*S,2b*S**,9b*S**,11a*S**,11b*R**)-9-tosyl-1,2,2a,3,4,9,11a,11b-octahydro-2b,9-diazadicyclobuta[*a*,*c*]-indeno[2,3-*e*]indene-2,2a,10,11-tetracarboxylate, 10b.** Following general procedure C the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **8** (52 mg, 0.15 mmol) and diethyl but-2-ynedioate (173.8 mg, 0.77 mmol) in DCM (2.4 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 4 : 1 to 2 : 1) 63.4 mg (60%) of **10b** as a brown oil. ^{1}H NMR ($CDCl_3$) δ 1.01 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.17–1.28 (m, 6H, 2 × OCH_2CH_3), 1.38 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.90–2.00 (m, 1H, *H*1), 2.29 (s, 3H, CH_3), 2.29–2.43 (m, 1H, *H*1), 2.77 (dt, 1H, J_1 = 15.8 Hz, J_2 = 2.5 Hz, *H*4), 2.85–2.97 (m, 2H, *H*4 and *H*11b), 3.43–3.53 (m, 3H, 2 × *H*3 and *H*2), 3.68–3.88 (m, 2H, OCH_2CH_3), 4.00–4.17 (m, 4H, 2 × OCH_2CH_3), 4.27 (s, 1H, *H*11a), 4.32 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 7.09 (d, 2H, J = 8.2 Hz, Ar), 7.28–7.37 (m, 3H, Ar), 7.46 (d, 2H, J = 8.5 Hz, Ar), 8.26 (d, 1H, J = 7.7 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 13.8, 13.9, 14.2, 14.3, 21.5, 23.1, 25.4, 37.8, 39.9, 45.1, 58.7, 60.3, 60.7, 60.8, 61.0, 71.8, 74.7, 115.7, 118.7, 123.2, 123.7, 125.5, 126.3, 129.3, 129.6, 132.8, 136.4, 138.0, 144.3, 145.1, 147.0, 160.8, 161.5, 171.0, 172.6. IR (NaCl): 1726, 1645, 1555 cm^{-1}. Anal. Calcd for $C_{37}H_{40}N_2O_{10}S$: C, 63.05; H, 5.72; N, 3.97. Found: C, 63.19; H, 5.84; N, 4.01. ESI-MS: m/z = 703 $[M + H]^+$.

Preparation of tetra-*tert*-butyl (2*S,2b*S**,9b*S**,11a*S**,11b*R**)-9-tosyl-1,2,2a,3,4,9,11a,11b-octahydro-2b,9-diazadicyclobuta[*a*,*c*]-indeno[2,3-*e*]indene-2,2a,10,11-tetracarboxylate, 10c.** Following general procedure C the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **8** (80 mg, 0.22 mmol) and di-*tert*-butyl but-2-ynedioate (182.0 mg, 1.08 mmol) in DCM (3.6 mL) at room temperature afforded after flash chromatography (Hex–AcOEt 20 : 1 to 9 : 1) 75.5 mg (42%) of **10c** as a brown oil. ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 9H, C(CH_3)$_3$), 1.44 (s, 9H, C(CH_3)$_3$), 1.46 (s, 9H, C(CH_3)$_3$), 1.55 (s, 9H, C(CH_3)$_3$), 1.76–1.85 (m, 1H, *H*1), 2.18–2.27 (m, 1H, *H*1), 2.27 (s, 3H, CH_3), 2.72 (dd, 1H, J_1 = 15.5 Hz, J_2 = 5.1 Hz, *H*4), 2.81–2.92 (m, 2H, *H*4 and *H*11b), 3.27–3.49 (m, 3H, 2 × *H*3 and *H*2), 4.23 (s, 1H, *H*11a), 7.12 (d, 2H, J = 8.0 Hz, Ar), 7.22–7.33 (m, 2H, Ar), 7.38–7.41 (m, 1H, Ar), 7.57 (d, 2H, J = 8.3 Hz, Ar), 8.20 (d, 1H, J = 7.9 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.9, 23.1, 28.1, 28.4, 28.5, 28.6, 30.1, 32.0, 37.7, 46.6, 58.8, 72.4, 75.5, 80.9, 81.2, 81.8, 81.9, 116.2, 118.9, 123.3, 123.9, 125.5, 126.9, 130.1, 130.4, 134.1, 136.7, 138.2, 144.7, 147.3, 149.0, 160.3, 161.0, 171.2, 173.1. IR (NaCl): 1731, 1696 cm^{-1}. Anal. Calcd for $C_{45}H_{56}N_2O_{10}S$: C, 66.15; H, 6.91; N, 3.43. Found: C, 66.21; H, 6.82; N, 3.54. ESI-MS: m/z = 817 $[M + H]^+$.

Preparation of methyl (2*Z* and 2*E*)-2-[11-(tosyl)-6,11-dihydro-5*H*-indolizino[8,7-*b*]indol-3-yl]-but-2-enedioate, *Z*-11 and *E*-12. To a solution of 11-tosyl-6,11-dihydro-5*H*-indolizino[8,7-*b*]-indole, **11** (64.1 mg, 0.18 mmol) in anhydrous DCM (3.0 mL) DMAD (125.7 mg, 0.88 mmol) was added *via* a syringe at room

temperature. The reaction mixture was stirred for 3 h. The solvent was eliminated under reduced pressure and the resulting mixture was purified by flash chromatography on silica gel (Hex–AcOEt 9 : 1 to 4 : 1) to yield 43.7 mg (48%) of ***E*-12** as a red oil and 12 mg (13%) of ***Z*-12** as an orange oil. Data for ***E*-12**: ^{1}H NMR ($CDCl_3$) δ 2.27 (s, 3H, CH_3), 2.82 (t, 2H, J = 6.7 Hz, CH_2CH_2N), 3.68 (s, 3H, OCH_3), 3.72 (t, 2H, J = 6.7 Hz, CH_2CH_2N), 3.85 (s, 3H, OCH_3), 6.33 (d, 1H, J = 4.1 Hz, *H*1), 7.05 (s, 1H, *H*C═), 7.06 (d, 2H, J = 8.2 Hz, Ar), 7.08 (d, 1H, J = 4.1 Hz, *H*2), 7.23–7.32 (m, 3H, Ar), 7.45 (d, 2H, J = 8.3 Hz, Ar), 8.26 (d, 1H, J = 9.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.6, 29.7, 42.2, 52.0, 53.1, 110.8, 112.6, 116.9, 117.5, 118.0, 124.5, 124.7, 125.3, 126.3, 126.9, 128.4, 129.3, 129.7, 129.9, 134.2, 134.6, 138.3, 144.4, 165.4, 166.4. IR (NaCl): 1722, 1595 cm^{-1}. Anal. Calcd for $C_{27}H_{24}N_2O_6S$: C, 64.27; H, 4.79. Found: C, 64.32; H, 4.62; N, 6.61. ESI-MS: m/z = 527 $[M + Na]^+$ Data for ***Z*-12**: ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 3H, CH_3), 2.90 (t, 2H, J = 6.9 Hz, CH_2CH_2N), 3.79 (s, 3H, OCH_3), 3.96 (s, 3H, OCH_3), 4.13 (t, 2H, J = 6.8 Hz, CH_2CH_2N), 5.86 (s, 1H, *H*C═), 6.54 (d, 1H, J = 4.4 Hz, *H*1), 7.05 (d, 2H, J = 8.0 Hz, Ar), 7.10 (d, 1H, J = 4.2 Hz, *H*2), 7.26–7.34 (m, 3H, Ar), 7.40 (d, 2H, J = 8.3 Hz, Ar), 7.27 (d, 1H, J = 9.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 21.6, 29.7, 41.7, 52.0, 53.0, 112.1, 113.9, 115.8, 116.9, 118.4, 119.1, 124.7, 125.4, 126.7, 127.8, 128.4, 128.8, 129.3, 129.4, 134.1, 138.6, 139.9, 144.7, 165.5, 167.8. IR (NaCl): 1743, 1791, 1597 cm^{-1}. Anal. Calcd for $C_{27}H_{24}N_2O_6S$: C, 64.27; H, 4.79; N, 5.55. Found: C, 64.21; H, 4.83; N, 6.73. ESI-MS: m/z = 527 $[M + Na]^+$.

4-(1,2-Bis-ethoxycarbonyl-vinyl)-11-(toluene-4-sulfonyl)-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indol-4-ium chloride, 13. Following general procedure D the reaction of 11-tosyl-5,6,11,11b-tetrahydro-3*H*-indolizino[8,7-*b*]indole, **7** (50.0 mg, 0.14 mmol), gold trichloride (12.3 mg, 0.039 mmol) and diethyl but-2-ynedioate (117.7 mg, 0.67 mmol) in DCM (2.3 mL) at 0 °C afforded after flash chromatography (Hex–AcOEt 9 : 1 to 4 : 1) 17.5 mg (25%) of **9b** as a brown oil and 31 mg (42%) of **13** as a yellow solid (mp: 76 °C, dec). ^{1}H NMR ($CDCl_3$) δ 1.27–1.29 (m, 3H, OCH_2CH_3), 1.44 (t, 3H, J = 4.3 Hz, OCH_2CH_3), 2.35 (s, 3H, CH_3), 2.68 (dd, 1H, J_1 = 16.0 Hz, J_2 = 4.1 Hz, *H*6), 3.03–3.09 (m, 1H, *H*6), 3.53–3.59 (m, 1H, *H*5), 3.66 (dd, 1H, J_1 = 14.2 Hz, J_2 = 5.7 Hz, *H*5), 4.13–4.18 (m, 2H, OCH_2CH_3), 4.21–4.36 (m, 2H, 2 × *H*3), 4.44–4.56 (m, 2H, OCH_2CH_3), 5.03 (s, 1H,═C*H*CO_2Et), 5.76–5.88 (m, 2H, *H*1 and *H*2), 5.90 (d, 1H, J = 5.3 Hz, *H*11b), 7.23–7.25 (m, 2H, Ar), 7.26–7.29 (m, 1H, Ar), 7.32–7.39 (m, 2H, Ar), 7.71 (d, 2H, J = 8.5 Hz, Ar), 8.05 (d, 1H, J = 8.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ 14.4, 14.9, 22.0, 30.1, 39.9, 60.1, 63.1, 68.6, 88.6, 115.3, 118.8, 119.2, 119.7, 124.4, 125.8, 127.2, 129.6, 130.0, 130.4, 130.6, 134.0, 135.2, 136.8, 145.6, 153.8, 165.9, 167.7. IR (KBr): 2982, 2927, 2871, 1375, 1699, 1575 cm^{-1}. Anal. Calcd for $C_{29}H_{31}ClN_2O_6S$: C, 60.99; H, 5.47; Cl, 6.21; N, 4.91. Found C, 61.15; H, 5.60; Cl, 6.31; N, 5.02. ESI-MS: m/z = 593 $[M + Na]^+$.

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