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Novel chemistry of β-carbolines. Expedient synthesis of polycyclic scaffolds

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ABSTRACT

Functionalization of β-carbolines is a challenge as numerous natural alkaloids with different biological activities present this heterocycle. The RCM is used herein with allyl-, vinyl-, ethynyl-, and propargyl-β-carbolines to generate additionally fused hetero- and carbocycles, and it is combined with other cyclization processes to achieve great molecular complexity in one synthetic step. Thus, an RCM–Diels–Alder sequence gives pentacyclic compounds related with certain alkaloids. On the other hand, vinyl-pyrrolo[2,1-*a*]-β-carbolines and vinyl-β-carbolines give different products upon reaction with activated dienophiles. Thus, a novel domino processes affords complex polycycles like **35**–**38**. Other alkynes like 3-butyn-2-one give a Stevens rearrangement.

1. Introduction

The β-carboline structure is found abundantly in naturally occurring compounds as part of numerous alkaloids, which often exhibit biological activity. The interest in these compounds demands efficient synthetic methodologies, for the construction of the heterocyclic system and for its functionalization.[1] Natural β-carboline containing compounds can be classified into two groups: first those of low molecular weight, like the harman family, including eudistomines and manzamines, or canthines, with an additional fused cycle (Fig. 1). Initially known for their potent psychoactive and hallucinogen abilities, harmane, harmine, and harmaline β-carboline alkaloids like (+)-harmicine, exert a wide range of pharmacological properties including antimicrobial and anti-HIV activities. The second group includes those more complex systems like eburnamine, vincamine, and alkaloids from *Schizozygia* species, which have varied pharmacological activities on the cell multiplication, and cardiovascular system. This group comprises the heteroyohimban family, which includes corynantheidine, ajmalicine, prescribed widely in the treatment of cardiovascular diseases, pleiocarpamine, vobasine, and spargine alkaloids like (+)-vellosimine, which is used for the treatment of neuralgia, migraine, and hypertension. More complex β-carboline alkaloids are yohimbine, which has been used to treat erectile dysfunction, and reserpine, an antipsychotic and antihypertensive drug. In addition to these important natural products, many groups have designed new β-carboline derivatives as potential drugs for the treatment of various diseases. Some synthetic β-carbolines present antineoplasic activity,[2] others show antimalarial and antiparasite activities[3] while certain β-carbolines inhibited TNF-α[4] or MK2.[5] A new class of mGluR$_1$ antagonists was designed bearing a tricyclic β-carboline template.[6] Bromo substituted tetrahydro-β-carbolines were also described as neurotoxic agents.[7]

The metathesis reaction is a powerful method to generate different sized hetero- and carbocycles.[8] This reaction can serve to construct β-carbolines with additional heterocycles. The first examples of ring-closing metathesis (RCM) involving β-carboline containing substrates were performed on β-carbolines bearing enamines.[9] Recently, this reaction was used for the synthesis of azabicyclo[*m.n.*1]alkenes (*m*=3–5; *n*=2–3) including some β-carbolines,[10] but RCM has not been used for the total synthesis of β-carboline alkaloids such as those depicted in Figure 1. In a preliminary communication of this work[11] we established the efficacy of employing RCM reactions for the construction of fused nitrogen heterocycles, from suitable substituted 1-vinyl-β-carbolines. When we expanded this methodology combining RCM with the Diels–Alder cycloaddition[12] we reached polycyclic complex structures bearing natural alkaloid skeletons. In addition, with certain alkynes a new reactivity was observed leading to products with high connectivity.[13] Herein we present the complete study on the behavior of β-carbolines bearing unsaturated substituents in metathesis reactions and with activated dienophiles.

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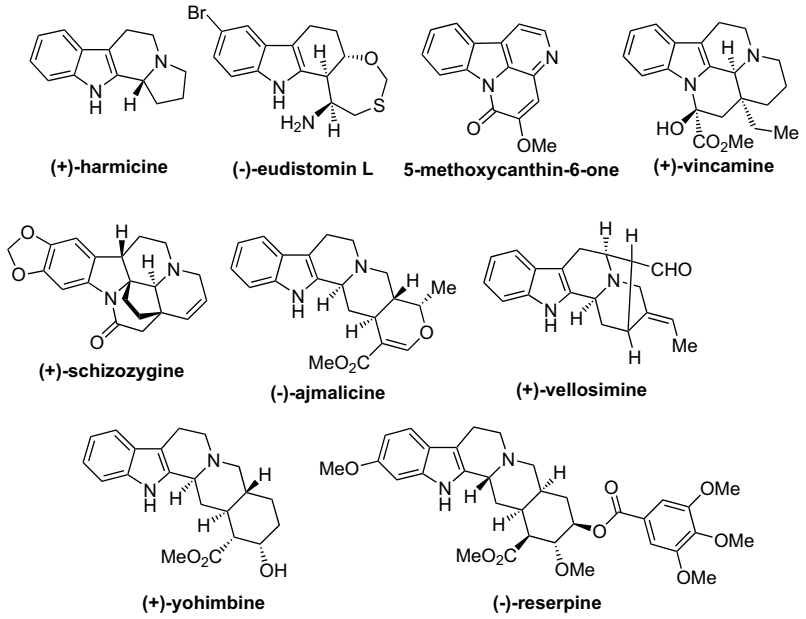


Figure 1. Some of the most representative and bioactive β-carboline alkaloids.

2. Results and discussion

The synthesis of the starting enynes was accomplished from derivatives **1**–**5**, bearing allyl and propargyl substituents. These substrates were easily prepared from tryptamine.[14] Compounds **1**–**5** were cyclized using the Bischler–Napieralski reaction, giving the corresponding dihydro-β-carbolines or dihydro-β-carbolinium salts, which were reacted with an appropriate Grignard reagent. In the case of substrates **1** and **2** the resulting β-carboline was protected as tosyl, Boc or acetyl derivatives.[15] These procedures allowed us to have a group of β-carboline-enynes, -dienynes, and -endiynes, in order to study the metathesis reaction including the possibility of cascade metathesis (Schemes 1 and 2).

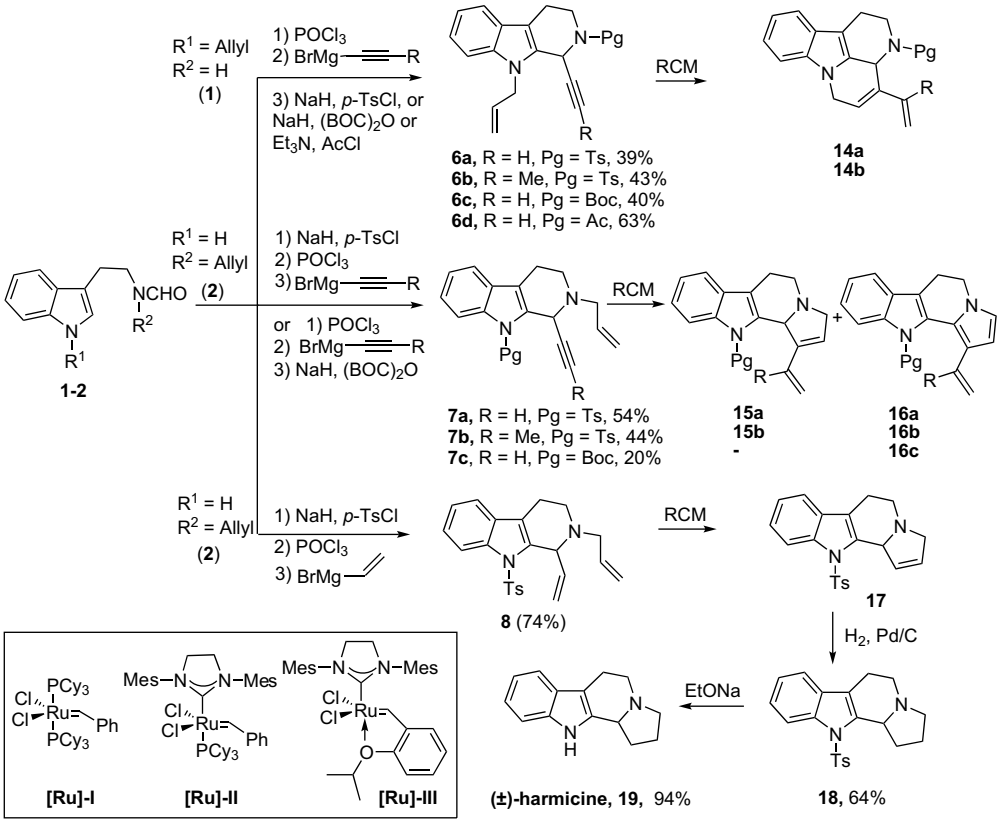
The tuning up of the metathesis reaction conditions, showed that with **[Ru]-I** none of the substrates reacted. The difficulties in performing metathesis reactions with nitrogen containing products are well known. The problem is their ability to coordinate to metal–alkylidene complexes and to interfere unproductively with catalytic activity. It is thought that efficient metathesis reactions are only possible by conversion of the amines to the corresponding carbamates or ammonium salts.[16] However, in the case of our substrates, **[Ru]-II**, and the Hoveyda–Grubbs complex **Ru-[III]**, were able to give the desired products, although there is a critical dependence of the results with the substitution pattern of the substrates. Best results were achieved in toluene, at room temperature and with 5–10 mol % of catalyst (see Table 1). With substrates **6a** and **6b**, the reactions were slow, needing at least 3 days to complete (entries 1, 2, 4). This problem was circumvented by performing the reaction under an ethylene atmosphere (entries 3 and 5). Ethylene is known to have a beneficial effect in metathesis reactions.[17] These conditions allowed the synthesis of **14a** and **14b** in 95% and 85% yield, respectively, in only 3 h, using 5% of catalysts. In contrast, compounds **6c** and **6d** did not react when using complex **[Ru]-III** or led to extensive decomposition if **[Ru]-II** was used (Scheme 1, entries 6 and 7). Metathesis reactions of **7a** and **7b** using **[Ru]-II** catalyst gave the corresponding dienes **15a** and **15b** in good yield along with small amounts of the pyrroles **16a** and **16b** (entries 8 and 9). The reaction of **7a** with **[Ru]-III** was slow and after 3 days the only product that could be isolated in moderate yield (35%, entry 10) was **16a**. On the other hand the Boc protected compound **7c** reacted after 6 days with **[Ru]-III** giving a low yield of **16c** (16%) with traces of the expected enyne metathesis product **15c** (entry 11). The formation of **16** is the result of an oxidation of **15** in the reaction media, possibly mediated by the ruthenium catalyst. This ability to oxidize the reaction product is a known non-metathetic behavior of ruthenium catalysts and it is particularly observed with complexes of type **[Ru]-III**.[18]

The RCM reaction of substrate **8**, allowed us to perform a straightforward racemic synthesis of the natural product (±)-harmicine. This compound has received some synthetic attention although it has never been obtained through a metathesis reaction.[19] Thus, after obtaining **17** in good yield, we hydrogenated the double bond to give **18**, and the final deprotection of the tosyl gave the (±)-harmicine, **19**.

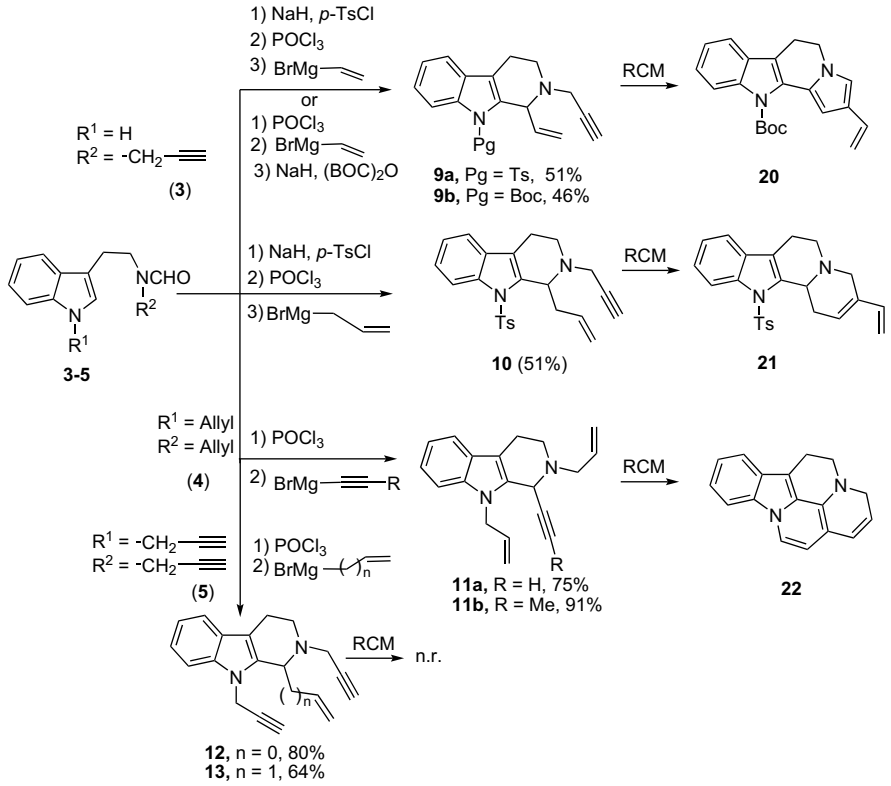
Next we addressed the reactions of substrates **9a** and **9b**. Although these compounds are structurally similar to the previous ones, only the Boc protected compound **9b** gave a 32% yield of the oxidized product **20**, which was unstable and could not be characterized (entries 13 and 14). Compound **10** was precursor of a six-membered ring and gave a moderated yield of the desired metathesis product **21** (entry 15).

Our final aim in this study on the metathesis reactions of β-carboline based substrates was to perform some cascade processes. Thus, when reacting compound **11a** under conditions similar to those used above, we isolated in low yield the new pentacyclic structure **22** (entry 16). The cascade metathesis of compound **11a** starts by the coordination of the ruthenium first with the allyl group in position 9 of the starting material[20] to give the corresponding cascade metathesis product, which is oxidized under the reaction medium to **22**.[21] This product was obtained in better yields by raising the reaction temperature to 80 °C (entry 17) and with complex **[Ru]-III**, a more stable catalyst toward heat, which was added to the reaction in 2 mol % portions every 24 h during 3 days (entry 18). Substrate **11b** did not react under any of these reaction conditions.

In contrast to the previous substrates, compounds **12** and **13** were unreactive in the presence of these ruthenium catalysts. We decided to transform them into less coordinating compounds, to avoid the interaction with the catalyst (Scheme 3). First we obtained the ammonium salts **23** and **24**, by reaction of **12** and **13**



Scheme 1. Synthesis of β-carboline substrates **6**–**8** and their behavior in metathesis reactions.



Scheme 2. Synthesis of β-carboline substrates **9**–**13** and their behavior in metathesis reactions.

Table 1
Reaction conditions and results for the metathesis reactions of β-carbolines **6–11**

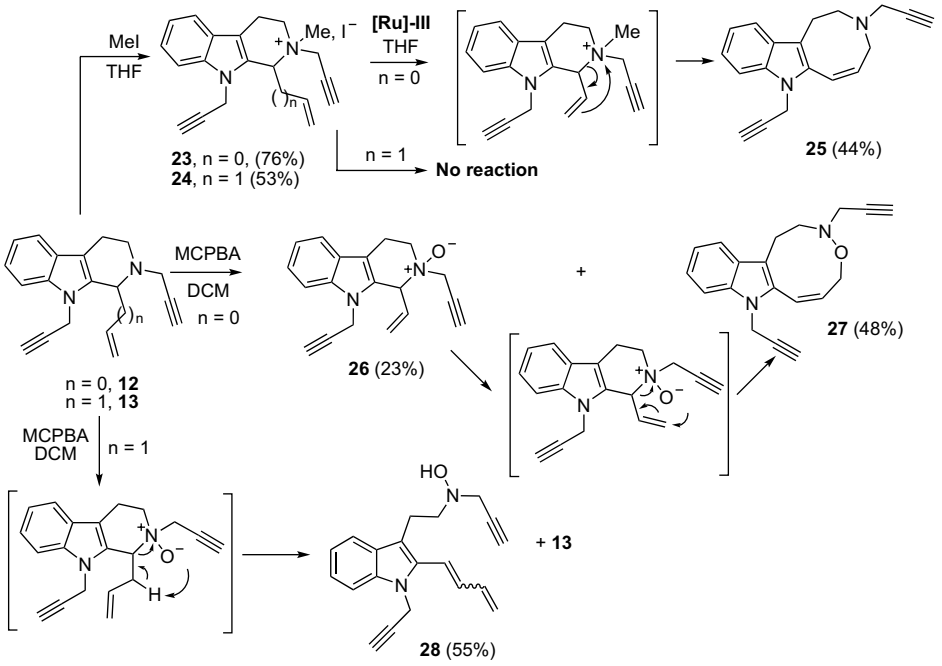
No.	Substrate	Catalyst[a]	Time	Temp	Product	Yield (%)
1	**6a**	**[Ru]-II**, 5%	3 days	rt	**14a**	52
2	**6a**	**[Ru]-III**, 10%	6 days	rt	**14a**	55
3	**6a**	**[Ru]-II**, 5%	3 h[b]	rt	**14a**	95
4	**6b**	**[Ru]-II**, 10%	3 days	rt	**14b**	72
5	**6b**	**[Ru]-II**, 5%	3 h[b]	rt	**14b**	85
6	**6c**	**[Ru]-II**, 5%	3 h[b]	rt	n.r./dec	—
7	**6d**	**[Ru]-II**, 5%	3 h[b]	rt	n.r./dec	—
8	**7a**	**[Ru]-II**, 10%	3 h	rt	**15a/16a**	62/9
9	**7b**	**[Ru]-II**, 10%	3 h	rt	**15b/16b**	51/<5
10	**7a**	**[Ru]-III**, 10%	3 days	rt	**16a**	35
11	**7c**	**[Ru]-III**, 10%	6 days[c]	80 °C	**16c**	16
12	**8**	**[Ru]-II**, 5%	3 days	rt	**17**[d]	76
13	**9a**	**[Ru]-III**, 10%	14 days	rt	dec	—
14	**9b**	**[Ru]-III**, 10%	14 days	80 °C	**20**	32
15	**10**	**[Ru]-II**, 10%	3 days	rt	**21**	44
16	**11a**	**[Ru]-II**, 10%	5 days	rt	**22**	15
17	**11a**	**[Ru]-II**, 6%[e]	3 days	80 °C	**22**	45
18	**11a**	**[Ru]-III**, 6%[e]	3 days	80 °C	**22**	67
19	**11b**	**[Ru]-II**, 6%[e]	3 days	80 °C	n.r.	—

[a] All the reactions in toluene. No substrates reacted with complex **[Ru]-I**.
[b] Performed under a 1 atm of ethylene.
[c] No reaction was observed under same conditions with **[Ru]-II** after 10 days.
[d] A small amount of the corresponding pyrrolo-β-carboline (4%) was detected and characterized.
[e] 2 mol % added every 24 h.

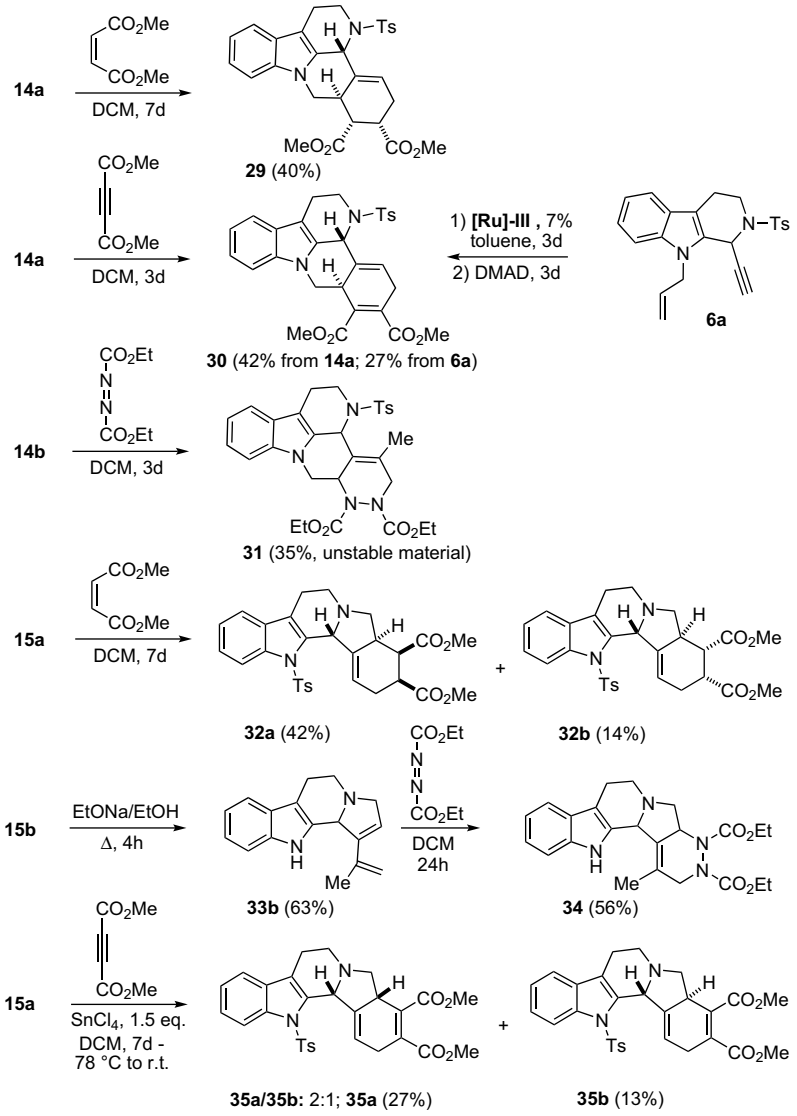
with excess of iodomethane.[22] The reaction of **23** with **[Ru]-III** complex was carried out in refluxing THF to allow complete solution of the salt. In these conditions, an allylic rearrangement took place giving azocine **25** in moderate yield. This reaction was not observed in the absence of the ruthenium catalyst. In these conditions, **24** did not react. On the other hand both **12** and **13** were reacted with *m*-chloroperbenzoic acid (MCPBA) in DCM in an attempt to form the corresponding *N*-oxides and to submit them to metathesis. Compound **12** gave only 23% of the desired oxide **26**, the major product being **27** as a result of an allylic rearrangement. In a similar way, compound **13**, gave, upon reaction with MCPBA, product **28** as a mixture of *Z*/*E* isomers.

Our next aim after the construction of vinyl-pyrrolo-[2,1-*a*]-β-carbolines and vinyl-indolo-[3,2,1-*de*]-naphthyridine via enyne metathesis reactions was to study the [4+2] cycloadditions of these compounds with several dienophiles (Scheme 4).

The reaction of **14a** with two dienophiles, dimethyl acetylenedicarboxylate (DMAD), and dimethyl maleate gave the corresponding cycloadducts, **29** and **30** in moderate yields. These reactions were totally stereoselective in view of the NMR spectra of the crude mixtures where no other cycloadducts could be detected. The relative stereochemistry of the adducts was assigned by NOE experiments (see Supplementary data). The synthesis of **30** was also carried out from **6a** in a *one pot* fashion, without isolation of



Scheme 3.



Scheme 4. Diels–Alder reactions of β-carbolines.

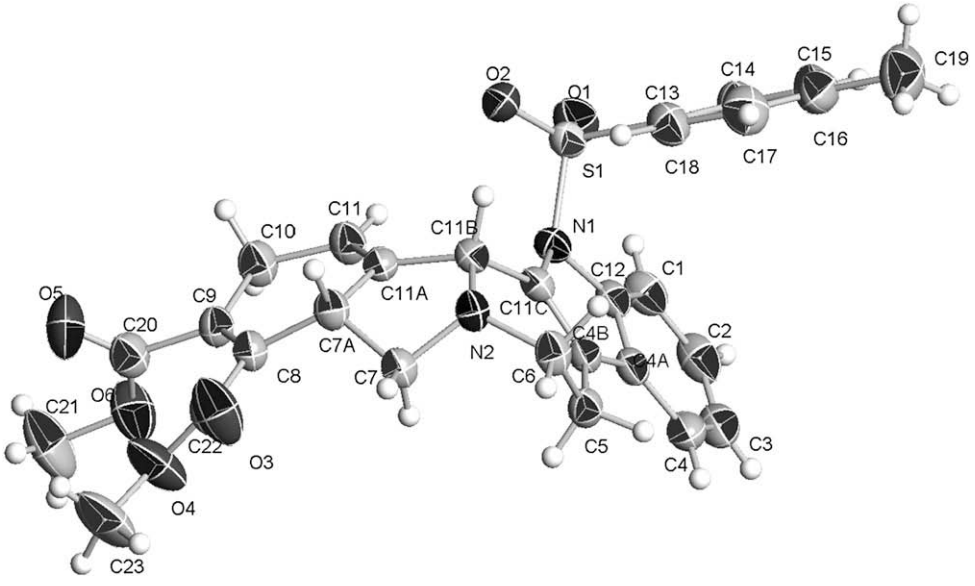
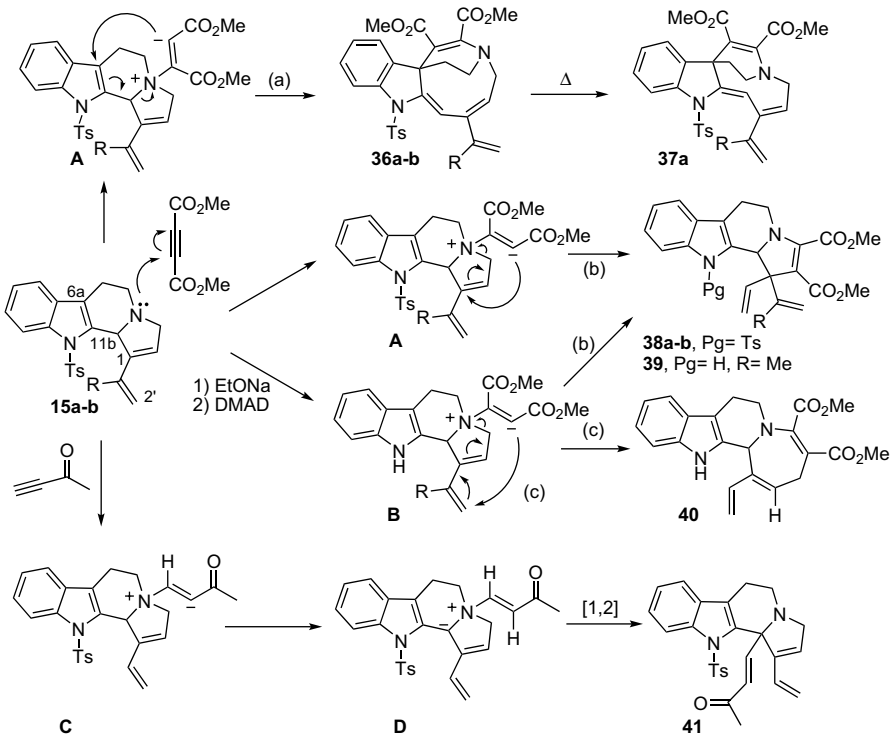


Figure 2. ORTEP drawing for **35a**.



Scheme 5. Cascade reactions of β-carbolines **15** with alkynes.

the metathesis product and by just adding the dienophile once the starting material of the metathesis step had disappeared (TLC). For the metathesis, a 7 mol % of **Ru-[III]** catalyst was used. The yield of the combined procedure was lower (27%) than the stepwise reaction (40% from **6a**). On the other hand, the reaction with diethyl azodicarboxylate, was rather sluggish and gave compound **31** with low yield as an single stereoisomer. In addition, the product rapidly decomposed after its isolation so we could not assign the stereochemistry. When **15a** was reacted in the same conditions as **14a**, with dimethyl maleate, a mixture of the four possible Diels–Alder adducts was formed. The two major isomers, **32a** and **32b**, were isolated with 42% and 14% yields, respectively and their stereochemical assignment made by NOE experiments. Contrary to **15a**, compound **15b** did not react with any of the dienophiles used. As the steric hindrance was supposed to be the cause of this behavior we eliminated the tosyl protecting group in **15b** using sodium ethoxide. Thus, with compound **33b** in hand, we performed the reaction with diethyl azodicarboxylate, which gave **34** as an only isomer. This reaction gave a moderate yield of the cycloadduct, which was unstable and decomposed before being completely characterized. The Diels–Alder reaction of **15a** with DMAD required the presence of a Lewis acid to avoid the nucleophilic attack of the β-carboline nitrogen to the triple bond of DMAD and subsequent rearrangement (vide infra). Thus, we carried out the reactions in the presence of BF_3 or $SnCl_4$. Best results were achieved with the latter acid, which gave a crude reaction mixture that showed a 2:1 ratio of Diels–Alder adducts **35a** and **35b**. Adduct **35a** was isolated in 27% yield while a 13% of **35b** was obtained unpurified with **35a**. The stereochemical assignment of these two adducts was made with NOE experiments and further supported by an X-ray analysis of **35a** (Fig. 2).

As indicated above, the reaction of compounds **15a** and **15b** with triple bonded dienophiles, in the absence of a Lewis acid, gave unexpected products due to the Michael type attack of the β-carboline nitrogen to the dienophile (Scheme 5, Table 2). The reaction begins with the formation of species **A**. Then, an intramolecular attack of this intermediate either to carbon 6a (path a), to carbon 1 (path b) or to carbon 2′ (path c) would give compounds **36**, **38**, **39**, and **40**. Our aim was to find adequate reaction conditions to favor one of the three possible paths, avoiding the formation of complex mixtures. With **15a**, the best yield in **36a** was achieved in DCM at rt, reaching 56% of this compound with isolation of a 17% of **38a** and 5% of **16a** (entry 1). Compound **15b** gave, under these conditions a mixture of **36b** (52%) and divinyl compound **38b** (8%, entry 2). Product **36b** was submitted to X-ray diffraction analysis (Fig. 3).

When the reaction of **15a** was performed in THF, no divinyl compound **38a** was detected, and the isolated yield of **36a** was 42%. Additionally, we obtained an 11% yield of pyrrole **16a**, and we detected Diels–Alder product **35a** in the crude mixture, which could not be completely purified (entry 3). Elevation of the reaction temperature to refluxing THF gave a new product, **37a**, in 46% yield, jointly with a small amount of **16a** and traces of **35a** (entry 4). Compound **37a** is the *Z* isomer of **36a**. As the formation of

Table 2
Reaction conditions and results of the cascade cyclization process

Entry	Substrate	Alkyne	Temp	Solvent	Time	Other	Result (in pure product)
1	**15a**	DMAD	rt	DCM	1 days	—	**36a**, 56%; **38a**, 17%; **16a**, 5%
2	**15b**	DMAD	rt	DCM	2 days	—	**36b**, 52%; **38b**, 8%
3	**15a**	DMAD	rt	THF	3 days	—	**36a**, 42%; **16a**, 11%
4	**15a**	DMAD	Δ	THF	2 days	—	**37a**, 46%; **16a**, 16%
5	**33a**	DMAD	rt	DCM	4 days	—	**40**, 58%
6	**33b**	DMAD	rt	DCM	2 days	—	**39**, 51%
7	**7a**	DMAD	60 °C	Toluene	4 days +5 h	**[Ru]-II** 5%	**36a**, 41%; **15a**, 8%
8	**15a**	3-Butyn-2-one	rt	DCM	24 h	—	**41**, 53%
9	**8**	DMAD	rt	DCM	16 h	—	**42**, 10%; **43**, 24%

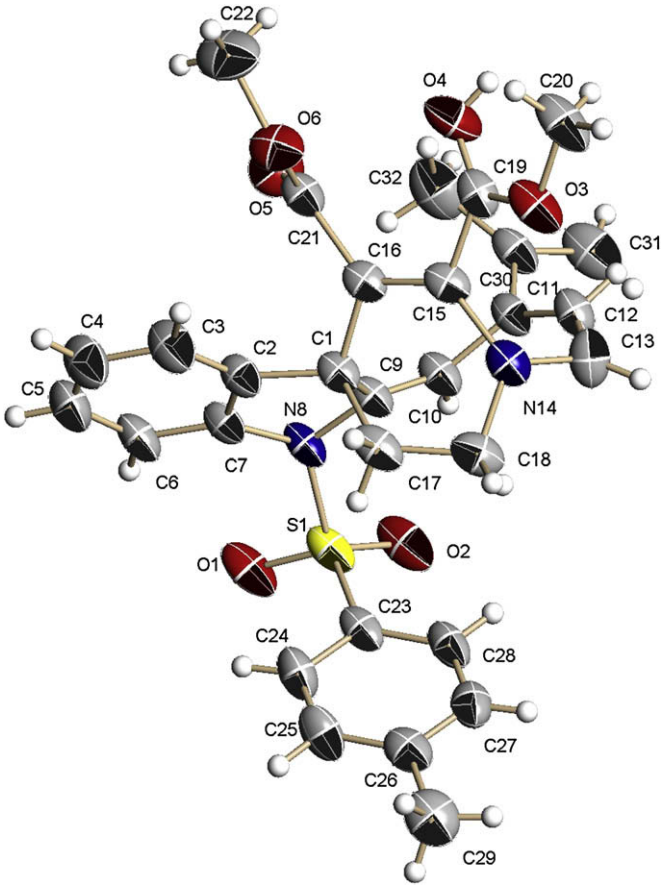


Figure 3. ORTEP drawing for **36b**.

compound **37a** only occurs under refluxing conditions,[23] we assume that it comes from the thermal isomerization of **36a**, which is primarily formed in the reaction. The cascade process through path c is not observed with these substrates although it involves the attack to carbon 2′, which is sterically unhindered. As can be seen from these results summarized in Table 2, these reactions are slow, and only after many hours reach completion. During that time, part of the starting material is spontaneously oxidized to the pyrrole **16**.

Our next step was the deprotection of compounds **15** to study the behavior of the corresponding unprotected β-carbolines **33a** and **33b** against DMAD. To our delight, compound **33a** gave the cyclohepta-β-carboline **40** in moderate yield, which implies the attack of the negative carbon in intermediate **B** to carbon 2′ and thus the feasibility of path c (entry 5). In contrast, the parent compound **33b** gave in the same conditions, compound **39**, which means the attack has occurred at carbon 1 following path b (entry 6). All these novel cascade reactions are related to the rearrangement of β- and γ-carbolines described recently by Voskressenky and co-workers. The β-carbolines used by this group give, however, completely different products.[24]

The enyne RCM reaction used for the synthesis of **15a** could be combined with the rearrangement process in a *one pot* fashion. Thus, reaction of **7a** with 5% of **Ru-[II]** catalyst and addition of DMAD after completion of the metathesis gave a 41% yield of compound **36a** along with a small amount (<5%) of **16a**. In addition, 8% of the metathesis product **15a** was recovered (entry 7).

The rearrangement reaction was next effected with another dienophile. Thus, compound **15a** was reacted with 3-butyn-2-one under the same reaction conditions. The only reaction product was assigned to structure **41** (53%, entry 8). This product is the result of the quenching of the intermediate **C**, due to the presence of acidic protons in the media and subsequent Stevens rearrangement.[25]

To gain more information on the process we reacted vinyl-β-carboline **8** with DMAD under the same conditions (Scheme 6). This substrate gave a mixture of products **42** and **43** in 1:3 ratio, with **43** being an unstable product (entry 9). These products come from the attack of the negative carbon in intermediate **E** either with carbon 6a (path of type-a) to give **43** or with carbon 2′ at the vinyl moiety (path of type c) to give **42**. This confirms that the latter process takes place only when there are less conformational restraints on the starting compounds.

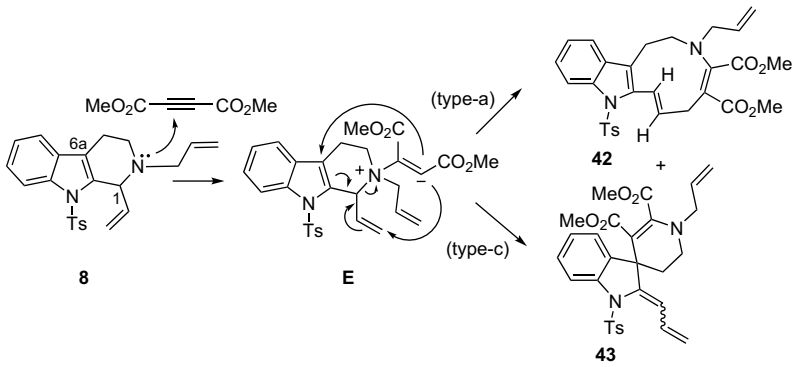
3. Conclusions

In conclusion, the functionalization of the β-carboline system, and its use as synthetic intermediate for the synthesis of more complex heterocycles is a challenge as the β-carboline system has been found in a widespread of natural products, with intriguing and useful biological activities. The RCM and its combination with Diels–Alder reactions and other novel cyclization processes have been shown. These reactions give complex structures, some of them related with natural alkaloids. In particular, vinyl-β-carbolines give, upon convenient choice of reaction conditions and reactants, a Michael type addition followed by nucleophilic attack to one unsaturated carbon, which leads to new polycycles with a substantial increase in skeletal complexity.

4. Experimental

4.1. 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. TLC analyses were performed on



Scheme 6. Cascade reactions of β-carboline **8** with alkynes.

commercial aluminum sheets bearing 0.25-mm layer of Silica gel $60F_{254}$. Silica gel 60 of 230–400 mesh ASTM 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 at the Elemental Analysis Center of the Complutense University of Madrid, using a CHN instrument. The solvents for the reactions carried under argon atmosphere were distilled just before their use. THF was refluxed over Na/benzophenone, and DCM and toluene over CaH. X-ray diffraction analysis was carried out in the CAI DRX of the Complutense University of Madrid.

4.2. Metathesis reactions

4.2.1. Synthesis of 3-tosyl-4-vinyl-2,3,3a,6-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine, ***14a***

To a 0.01 M solution of **6a** (0.20 g, 0.51 mmol) in anhydrous toluene, **[Ru]-II** catalysts (22 mg, 0.026 mmol) was added and the resulting mixture was stirred at rt under ethylene atmosphere for 3 h. The reaction mixture was filtered off through a Celite pad and washed with toluene. The solvent was removed under reduced pressure and purified by column chromatography (hexane/EtOAc 9:1) giving pure **14a** (0.19 g, 95%) as yellow oil. ^{1}H NMR (C_6D_6, 60 °C, 300 MHz) δ (ppm): 1.76 (s, 3H), 2.17–2.21 (m, 2H), 3.90–4.09 (m, 4H), 5.11 (d, 1H, J=12.1 Hz), 5.48 (d, 1H, J=17.0 Hz), 5.68 (br s, 1H), 6.30 (s, 1H), 6.59 (d, 2H, J=8.2 Hz), 6.97 (d, 1H, J=7.7 Hz), 7.01–7.13 (m, 3H), 7.24 (d, 1H, J=7.7 Hz), 7.62 (d, 2H, J=8.2 Hz). ^{13}C NMR (C_6D_6, 60 °C, 75 MHz) δ (ppm): 20.3, 21.0, 42.9, 46.8, 53.1, 106.1, 109.5, 115.4, 118.8, 119.9, 120.2, 121.6, 127.3, 128.4, 129.5, 129.9, 131.5, 134.5, 137.7, 139.1, 143.1. IR (film) ν 1600, 1340, 1160 cm^{-1}. MS (ESI) m/z 391 (M+H). Anal. Calcd for $C_{23}H_{22}N_2O_2S$ (390.50): C, 70.74; H, 5.68; N, 7.17. Found: C, 70.99, H, 5.89, N, 7.08.

4.2.2. Synthesis of 4-isopropenyl-3-tosyl-2,3,3a,6-tetrahydro-1H-indolo[3,2,1-de][1,5]naphthyridine, ***14b***

Following the same procedure than for the synthesis of **14a**, from **6b** (0.50 g 1.24 mmol) and **[Ru]-II** catalysts (52 mg, 0.062 mmol) under ethylene atmosphere, and upon purification by column chromatography (hexane/EtOAc 4:1 and 2:1), giving **14b** (0.42 g, 85%) as white solid, mp 162–164 °C. ^{1}H NMR (DMSO-d_6, 120 °C, 300 MHz) δ (ppm): 2.03 (s, 3H), 2.05 (s, 3H), 2.45–2.50 (m, 1H), 2.69–2.80 (m, 1H), 3.91 (t, 2H, J=6.1 Hz), 4.72 (t, 2H, J=3.7 Hz), 5.03 (s, 1H), 5.21 (s, 1H), 5.70 (br s, 1H), 6.19–6.24 (m, 1H), 6.89 (d, 2H, J=7.9 Hz), 6.98 (t, 1H, J=7.3 Hz), 7.09 (t, 1H, J=7.3 Hz), 7.19 (d, 1H, J=8.5 Hz), 7.31–7.35 (m, 3H). ^{13}C NMR (DMSO-d_6, 120 °C, 75 MHz) δ (ppm): 19.0, 21.0, 41.6, 45.7, 52.0, 52.2, 103.9, 108.9, 112.6, 117.2, 118.7, 120.0, 125.7, 126.8, 127.8, 128.1, 130.4, 135.4, 137.2, 140.1, 141.8, 148.4. IR (KBr) ν 1610, 1590, 1340, 1150 cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_2O_2S$ (404.53): C, 71.26; H, 5.98; N, 6.93. Found: C, 71.44; H, 6.09; N, 6.95.

4.2.3. Metathesis reaction of 2-allyl-1-ethynyl-9-tosyl-2,3,4,9-tetrahydro-1H-β-carboline, ***7a****: synthesis of* ***15a*** *and* ***16a***

Following the same procedure than for the synthesis of **14a**, from **7a** (0.50 g, 1.28 mmol) and **[Ru]-II** catalysts (0.11 g, 0.13 mmol) under argon atmosphere, and upon purification by column chromatography (hexane/EtOAc 4:1 to EtOAc), 0.310 g (62%) of **15a** were obtained as a white solid (mp 65 °C, dec), and 0.045 g (9%) of **16a** as yellow solid (mp 85 °C, dec).

4.2.3.1. 11-Tosyl-1-vinyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***15a****.* ^{1}H NMR (CD_3OD, 300 MHz) δ (ppm): 2.25 (s, 3H), 2.45–2.54 (m, 1H), 2.76–2.82 (m, 2H), 2.87–3.15 (m, 1H), 3.61 (d, 1H, J=15.8 Hz), 3.92 (d, 1H, J=15.2 Hz), 5.13 (d, 1H, J=11.0 Hz), 5.48 (d, 1H, J=17.1 Hz), 5.65 (br s, 1H), 6.01 (br s, 1H), 6.84 (dd, 1H, J_1=17.7 Hz, J_2=11.0 Hz), 7.05 (d, 2H, J=7.9 Hz), 7.18–7.31 (m, 3H), 7.47 (d, 2H, J=8.5 Hz), 8.15 (d, 1H, J=7.9 Hz). ^{13}C NMR (CD_3OD, 75 MHz) δ (ppm): 18.9, 21.4, 45.9, 57.6, 64.7, 115.5, 116.5, 118.4, 122.4, 123.3, 124.2, 124.6, 126.5, 129.2, 131.2, 133.3, 136.0, 137.7, 139.1, 142.5, 144.5. IR (KBr) ν 1600, 1370, 1170 cm^{-1}. MS (ESI) m/z 391 (M+H). Anal. Calcd for $C_{23}H_{22}N_2O_2S$ (390.50): C, 70.74; H, 5.68; N, 7.17. Found: C, 70.50; H, 5.59; N, 7.25.

4.2.3.2. 11-Tosyl-1-vinyl-6,11-dihydro-5H-indolizino[8,7-b]indole, ***16a****.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.24 (s, 3H), 2.76 (t, 2H, J=6.3 Hz), 3.98 (br s, 2H), 5.13 (dd, 1H, J_1=11.0 Hz, J_2=1.6 Hz), 5.55 (dd, 1H, J_1=17.6 Hz, J_2=1.6 Hz), 6.52 (d, 1H, J=2.8 Hz), 6.73 (d, 1H, J=2.8 Hz), 6.94 (d, 2H, J=7.7 Hz), 7.16–7.38 (m, 6H), 8.20 (d, 1H, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.5, 22.4, 44.7, 104.9, 109.2, 118.0, 118.6, 121.5, 121.7, 121.8, 122.7, 124.4, 125.3, 127.3, 128.4, 131.2, 131.3., 131.5, 133.2, 139.5, 144.3. IR (KBr) ν 1620, 1590, 1370 cm^{-1}. MS (ESI) m/z 389 (M+H). Anal. Calcd for $C_{23}H_{20}N_2O_2S$ (388.48): C, 71.11; H, 5.19; N, 7.21. Found: C, 70.92; H, 5.03; N, 7.09.

4.2.4. Synthesis of 1-isopropenyl-11-tosyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***15b***

Following the same procedure than for the synthesis of **14a**, from **7b** (0.50 g, 1.24 mmol) and **[Ru]-II** catalysts (0.10 g, 0.12 mmol) under argon atmosphere, and upon purification by column chromatography (hexane/EtOAc 4:1), giving **15b** (0.26 g, 51%) as a yellow oil. Compound **16b** was detected in crude but not isolated. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.98 (s, 3H), 2.25 (s, 3H), 2.56–2.65 (m, 1H), 2.78–2.97 (m, 2H), 3.09–3.17 (m, 1H), 3.53 (dt, 1H, J_1=14.8 Hz, J=2.2 Hz), 3.89 (d, 1H, J=14.8 Hz), 4.78 (br s, 1H), 5.01 (br s, 1H), 5.66 (br s, 1H), 5.78 (br s, 1H), 7.06 (d, 2H, J=8.2 Hz), 7.19–7.32 (m, 3H), 7.48 (d, 2H, J=8.2 Hz), 8.05 (d, 1H, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 19.7, 21.4, 23.6, 46.0, 57.8, 64.8, 114.4, 115.9, 118.3, 121.0, 123.8, 124.4, 124.9, 126.4, 129.3, 130.6, 134.0, 135.6, 137.2, 140.0, 144.3, 146.6. IR (film) ν 3050, 1630, 1590, 1370 cm^{-1}. MS (ESI) m/z 405 (M+H). Anal. Calcd for $C_{24}H_{24}N_2O_2S$ (404.53): C, 71.26; H, 5.98; N, 6.93. Found: C, 71.00; H, 5.63; N, 7.27.

4.2.5. Synthesis of tert-butyl 1-vinyl-5,6-dihydroindolizino[8,7-b]indole-11-carboxylate, ***16c***

Following the same procedure than for the synthesis of **14a**, from **7c** (0.05 g, 0.15 mmol) and **[Ru]-III** catalysts (9 mg, 0.015 mmol) under argon atmosphere was stirred at 80 °C for 6 days, and upon purification by column chromatography (hexane/EtOAc 4:1 to EtOAc), giving **16c** (8 mg, 16%) as yellow wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.64 (s, 9H), 2.97 (t, 2H, J=6.6 Hz), 4.16 (t, 2H, J=6.6 Hz), 4.99 (dd, 1H, J_1=11.0 Hz, J_2=1.6 Hz), 5.48 (dd, 1H, J_1=17.6 Hz, J_2=1.6 Hz), 6.39 (d, 1H, J=2.7 Hz), 6.62–6.71 (m, 1H), 6.69 (d, 1H, J=2.7 Hz), 7.23–7.31 (m, 2H), 7.41–7.47 (m, 1H), 8.03–8.06 (m, 1H). IR (film) ν 1620, 1580 cm^{-1}.

4.2.6. Synthesis of 11-tosyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***17***

To a solution of **8** (0.10 g, 0.25 mmol) in toluene (25 mL), **[Ru]-II** catalyst was added and the mixture was stirred at rt for 3 days. The reaction mixture was filtered off through a Celite pad and washed with toluene. The solvent was removed under reduced pressure and purified by column chromatography (hexane/EtOAc 1:1 to EtOAc) giving pure **17** (69 mg, 76%) as yellow oil and recovering 12 mg of starting material. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.31 (s, 3H), 2.45 (d, 1H, J=16.5 Hz), 2.86–2.96 (m, 1H), 3.08 (td, 1H, J_1=11.0 Hz, J_2=3.9 Hz), 3.30 (dd, 1H, J_1=13.2 Hz, J_2=3.3 Hz), 3.69 (dd, 1H, J_1=13.7 Hz, J_2=2.2 Hz), 3.80 (d, 1H, J=13.2 Hz), 5.45 (br s, 1H), 5.88 (d, 1H, J=4.4 Hz), 6.43 (dd, 1H, J_1=6.0 Hz, J_2=1.6 Hz), 7.14 (d, 2H, J=8.2 Hz), 7.20–7.31 (m, 2H), 7.35 (dd, 1H, J_1=8.2 Hz, J_2=1.6 Hz), 7.59 (d, 2H, J=8.2 Hz), 8.10 (d, 1H, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 17.2, 21.5, 44.2, 56.0, 63.9, 115.2, 118.4, 118.7, 123.7, 124.5, 126.4, 128.5, 129.6, 130.6, 131.8, 135.0, 136.7, 137.1, 144.6. IR (film) ν 1600 cm^{-1}. Anal. Calcd for $C_{21}H_{20}N_2O_2S$ (364.46): C, 69.20; H, 5.53; N, 7.69. Found: C, 69.37; H, 5.29; N, 7.83.

4.2.7. Synthesis of 11-tosyl-2,3,5,6,11,11b-hexahydro-1H-indolizino[8,7-b]indole, **18**

To a solution of **17** (0.15 g, 0.38 mmol) in EtOAc (5 mL) under H_2 atmosphere was added Pd(C) (10% weight) and the mixture was stirred at rt for 3 h. The reaction mixture was filtered off through a Celite pad and washed with EtOAc. The solvent was removed under reduced pressure and purified by column chromatography (EtOAc to EtOAc/MeOH 3%) giving pure **18** (89 mg, 64%) as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.89–1.97 (m, 2H), 2.30 (s, 3H), 2.55–3.16 (m, 8H), 4.68 (br s, 1H), 7.12 (d, 2H, J=8.2 Hz), 7.20–7.28 (m, 2H), 7.32 (t, 1H, J=7.6 Hz), 7.58 (d, 2H, J=8.2 Hz), 8.10 (d, 1H, J=7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.2, 18.7, 21.5, 23.4, 32.0, 44.9, 58.3, 115.3, 117.9, 118.4, 123.8, 124.5, 126.5, 129.6, 130.2, 134.8, 136.9, 144.6. IR (film) ν 1600 cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_2O_2S$ (366.48): C, 68.82; H, 6.05; N, 7.64. Found: C, 68.57; H, 6.28; N, 7.91.

4.2.8. Synthesis of (±)-harmicine, **19**

To a solution of EtONa (0.55 g, 8.10 mmol) in absolute EtOH (3 mL), generated in situ, was added **18** (0.10 g, 0.27 mmol) in absolute EtOH (3 mL) and the mixture was refluxed for 4 h. The mixture was quenched with water and the mixture was extracted with EtOAc (×3). The organic layer was washed with water and brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc/MeOH 2%), giving **19** (54 mg, 94%).[18]

4.2.9. Synthesis of tert-butyl 2-vinyl-5,6-dihydroindolizino[8,7-b]-indole-11-carboxylate, **20**

To a solution of **9b** (0.10 g, 0.30 mmol) in toluene (30 mL), **[Ru]-III** catalyst was added and the mixture was stirred at 80 °C for 14 days. The reaction mixture was filtered off through a Celite pad and washed with toluene. The solvent was removed under reduced pressure and purified by column chromatography (hexane/EtOAc 4:1) giving a mixture of compounds **20** with traces of **9b** (32 mg, 32%), which decomposed after a few hours. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.74 (s, 9H), 3.03 (t, 2H, J=7.1 Hz), 4.16 (t, 2H, J=7.1 Hz), 4.98 (dd, 1H, J_1=10.4 Hz, J_2=1.6 Hz), 5.45 (dd, 1H, J_1=17.6 Hz, J_2=1.6 Hz), 6.57–6.66 (m, 1H), 6.77 (d, 1H, J=1.6 Hz), 6.91 (d, 1H, J=1.6 Hz), 7.23–7.29 (m, 2H), 7.42–7.45 (m, 1H), 8.04–8.07 (m, 1H). IR (film) ν 1620, 1580 cm^{-1}.

4.2.10. Synthesis of 12-tosyl-3-vinyl-1,4,6,7,12,12b-hexahydro-indolo[2,3-a]quinolizine, **21**

To a solution of **10** (0.15 g, 0.37 mmol) in toluene (37 mL), **[Ru]-II** catalyst (31 mg, 0.037 mmol) was added and the mixture was stirred at rt for 3 days. The reaction mixture was filtered off through a Celite pad and washed with toluene. The solvent was removed under reduced pressure and purified by column chromatography (hexane/EtOAc 4:1), giving pure **21** (67 mg, 44%) as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.28 (s, 3H), 2.64–2.87 (m, 3H), 3.13–3.31 (m, 2H), 3.64 (br s, 2H), 4.15–4.19 (m, 1H), 5.00 (d, 1H, J=11.0 Hz), 5.07 (d, 1H, J=17.6 Hz), 5.90 (d, 1H, J=4.4 Hz), 6.34–6.45 (m, 1H), 7.09 (d, 2H, J=8.2 Hz), 7.19–7.37 (m, 4H), 7.51 (d, 2H, J=8.2 Hz), 8.11 (d, 1H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.5, 22.4, 32.0, 48.2, 53.6, 55.9, 110.4, 116.0, 118.4, 124.1, 124.5, 126.2, 126.5, 127.2, 128.6, 129.2, 129.3, 130.8, 133.8, 137.4, 137.9, 144.5. IR (film) ν 1600, 1370, 1170 cm^{-1}. Anal. Calcd for $C_{24}H_{24}N_2O_2S$ (404.53): C, 71.26; H, 5.98; N, 6.93. Found: C, 71.45; H, 6.18; N, 6.76.

4.2.11. Synthesis of 1,10-dihydro-11H-5a,11a-diazabenzo[cd]fluoranthene, **22**

To a solution of **11a** (0.15 g, 0.54 mmol) in anhydrous toluene (30 mL), **[Ru]-III** catalyst (7 mg, 0.011 mmol) was added every 24 h during 3 days while stirring at 80 °C. The reaction mixture was filtered off through a Celite pad and washed with dry toluene. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hexane/EtOAc 49:1) giving **22** (0.10 g, 67%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.16 (t, 2H, J=6.8 Hz), 4.22 (t, 2H, J=6.8 Hz), 4.82 (d, 2H, J=5.5 Hz), 5.61–5.69 (m, 1H), 6.14 (d, 1H, J=2.7 Hz), 6.65 (d, 1H, J=11.0 Hz), 6.70 (d, 1H, J=2.7 Hz), 7.11 (td, 1H, J_1=7.7 Hz, J_2=1.1 Hz), 7.18 (td, 1H, J_1=8.2 Hz, J_2=1.1 Hz), 7.34 (d, 1H, J=8.2 Hz), 7.51 (d, 1H, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.4, 44.0, 45.2, 103.0, 107.4, 109.3, 116.1, 116.5, 117.8, 119.6, 121.0, 121.7, 127.5, 127.6, 128.3, 130.0, 137.2. IR (film) ν 1620, 1600 cm^{-1}. MS (APCI), m/z: 247 $[M+H]^+$. Anal. Calcd for $C_{17}H_{14}N_2$ (246.31): C, 82.90; H, 5.73; N, 11.37. Found: C, 82.72; H, 5.67; N, 11.48.

4.2.12. Synthesis of 2-methyl-2,9-dipropargyl-1-vinyl-2,3,4,9-tetrahydro-1H-β-carbolin-2-ium iodide, **23**

To a solution of **12** (0.15 g, 0.55 mmol) in THF (8 mL) was added MeI (0.10 mL, 1.64 mmol) and the mixture was stirred at rt for 3 days. The reaction mixture was filtered off and the solid was washed with cooled THF, giving **23** (0.16 g, 76%) as white solid (mixture of isomers). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.22 (s, 1H), 3.31 (s, 1H), 3.39 (s, 3H), 3.85 (br s, 2H), 4.17 (d, 1H, J=7.3 Hz), 4.41–4.66 (m, 3H), 4.79–4.91 (m, 1H), 5.02–5.11 (m, 1H), 5.74–5.87 (m, 3H), 6.10–6.32 (m, 1H), 7.16 (t, 1H, J=7.3 Hz), 7.29 (t, 1H, J=7.6 Hz), 7.59 (t, 2H, J=7.9 Hz). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 17.0, 17.1, 32.7, 32.8, 45.9, 48.8, 50.4, 53.1, 54.1, 54.2, 66.6, 67.4, 71.7, 71.8, 75.4, 75.6, 78.3, 78.6, 83.7, 84.1, 105.2, 105.5, 110.3, 110.4, 118.9, 119.0, 120.1, 122.9, 123.0, 125.1, 125.2, 126.3, 126.7, 128.2, 128.3, 128.8, 136.9, 137.0. IR (KBr) ν 3200, 2100, 1590 cm^{-1}. Anal. Calcd for $C_{20}H_{21}IN_2$ (416.30): C, 57.70; H, 5.08; N, 6.73. Found: C, 57.98; H, 5.27; N, 6.46.

4.2.13. Synthesis of 1-allyl-2-methyl-2,9-dipropargyl-2,3,4,9-tetrahydro-1H-β-carbolin-2-ium iodide, **24**

To a solution of **13** (0.15 g, 0.52 mmol) in THF (8 mL) was added MeI (0.10 mL, 1.56 mmol) and the mixture was stirred at rt for 5 days. The reaction mixture was concentrated until precipitation of the salt. The solid was filtered off and washed with cooled THF, giving **24** (0.12 g, 53%) as white solid (mixture of isomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.28 (s, 3H), 2.36 (s, 1H), 3.00 (s, 1H), 3.12–3.26 (m, 4H), 3.51 (d, 1H, J=17.6 Hz), 3.69–3.75 (m, 3H), 3.99 (br s, 1H), 4.33 (d, 1H, J=16.5 Hz), 5.03 (s, 1H), 5.15–5.28 (m, 2H), 5.76–5.94 (m, 1H), 7.21–7.27 (m, 1H), 7.37 (t, 1H, J=7.7 Hz), 7.46–7.57 (m, 2H). IR (KBr) ν 3200, 2100, 1600 cm^{-1}.

4.2.14. Synthesis of (5Z)-3,7-dipropargyl-2,3,4,7-tetrahydro-1H-azocino[5,4-b]indole, **25**

To a solution of **23** (0.10 g, 0.24 mmol) in THF (50 mL), **[Ru]-III** catalyst (11 mg, 0.017 mmol) was added and the mixture was refluxed for 5 days. The reaction mixture was filtered off through a Celite pad and washed with THF. The solvent was removed under reduced pressure and purified by column chromatography (hexane/EtOAc 9:1 to 2:1) giving pure **25** (29 mg, 44%) as yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.25 (t, 1H, J=2.5 Hz), 2.28 (t, 1H, J=2.5 Hz), 3.02 (s, 4H), 3.39 (d, 2H, J=7.7 Hz), 3.47 (d, 2H, J=2.2 Hz), 4.82 (d, 2H, J=2.2 Hz), 6.09–6.17 (m, 1H), 6.78 (d, 1H, J=11.0 Hz), 7.15 (td, 1H, J_1=7.7 Hz, J_2=1.1 Hz), 7.27 (td, 1H, J_1=7.1 Hz, J_2=1.1 Hz), 7.38 (d, 1H, J=7.7 Hz), 7.56 (d, 1H, J=8.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 23.3, 32.9, 46.0, 50.3, 51.0, 72.3, 72.6, 78.4, 80.1, 109.0, 114.3, 118.6, 119.6, 121.8, 122.4, 128.0, 130.2, 132.5, 136.3. IR (film) ν 3280, 2100, 1650 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_2$ (274.36): C, 83.18; H, 6.61; N, 10.21. Found: C, 83.45; H, 6.48; N, 9.93.

4.2.15. Synthesis of **26** and **27**

To a solution of **12** (0.10 g, 0.36 mmol) in DCM (10 mL) at 0 °C was added MCPBA (63 mg, 0.36 mmol) and the mixture was stirred at this temperature for 5 h and one more hour at rt. The reaction

mixture was quenched with water and the mixture was extracted with DCM (×3). The organic layer was washed with HCl (1 N), NaOH (10%), water and brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Hexane/EtOAc 9:1), giving **27** (50 mg, 48%) as colorless oil and **26** (24 mg, 23%) as pale wax (mixture of isomers).

4.2.15.1. 2,9-Dipropargyl-1-vinyl-2,3,4,9-tetrahydro-1H-β-carboline 2-oxide, ***26****.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.27 (t, 1H, J=1.9 Hz), 2.31 (t, 1H, J=2.1 Hz), 3.08–3.19 (m, 2H), 3.23–3.32 (m, 2H), 3.73 (d, 2H, J=2.2 Hz), 4.66–4.81 (m, 3H), 5.40 (d, 1H, J=10.5 Hz), 5.74 (d, 1H, J=6.1 Hz), 6.23–6.31 (m, 1H), 7.17 (t, 1H, J=7.4 Hz), 7.25 (t, 1H, J=7.4 Hz), 7.38 (d, 1H, J=8.2 Hz), 7.57 (d, 1H, J=7.1 Hz). IR (film) ν 2100, 1650, 1590 cm^{-1}.

4.2.15.2. (6Z)-3,8-Dipropargyl-2,3,5,8-tetrahydro-1H-[1,2]oxazonino-[6,5-b]indole, ***27****.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.25 (t, 1H, J=2.7 Hz), 2.26 (t, 1H, J=2.2 Hz), 3.07 (br s, 2H), 3.14–3.18 (m, 2H), 3.54 (br s, 2H), 4.46 (br s, 2H), 4.78 (d, 2H, J=2.7 Hz), 6.24–6.32 (m, 1H), 6.71 (d, 1H, J=11.5 Hz), 7.15 (td, 1H, J_1=7.7 Hz, J_2=1.1 Hz), 7.26 (td, 1H, J_1=7.7 Hz, J_2=1.1 Hz), 7.40 (d, 1H, J=8.2 Hz), 7.56 (d, 1H, J=7.7 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 23.9, 33.1, 48.2, 57.7, 72.2, 72.6, 72.9, 78.4, 79.0, 109.3, 114.6, 118.8, 119.4, 122.0, 123.6, 127.9, 133.5, 134.9, 136.2. IR (film) ν 2100, 1650, 1590 cm^{-1}. Anal. Calcd for $C_{19}H_{18}N_2O$ (290.36): C, 78.59; H, 6.25; N, 9.65. Found: C, 78.73; H, 6.21; N, 9.40.

4.2.16. Synthesis of N-(2-{2-[(1E)-buta-1,3-dien-1-yl]-1-propargyl-1H-indol-3-yl}ethyl)-N-hydroxyprop-2-yn-1-amine, ***28***

To a solution of **13** (0.25 g, 0.87 mmol) in DCM (15 mL) at 0 °C was added MCPBA (0.15 g, 0.87 mmol) and the mixture was stirred at this temperature for 5 h and two more hour at rt. The reaction mixture was quenched with water and the mixture was extracted with DCM (×3). The organic layer was washed with brine, dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (Hexane/EtOAc 9:1 to 4:1), giving **28** (145 mg, 55%) as red oil (mixture of isomers). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.25 (s, 1H), 2.34 (s, 1H), 3.05–3.19 (m, 4H), 3.68 (dd, 2H, J_1=13.7 Hz, J_2=2.2 Hz), 4.75 (d, 1H, J=2.2 Hz), 4.87 (d, 1H, J=2.2 Hz), 5.27 (d, 1H, J=9.9 Hz), 5.43 (d, 1H, J=17.6 Hz), 6.37–6.84 (m, 3H), 7.13–7.18 (m, 1H), 7.24–7.29 (m, 1H), 7.36–7.44 (m, 1H), 7.60–7.66 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 22.5, 22.6, 33.3, 33.6, 49.3, 49.4, 58.2, 58.5, 72.3, 72.6, 73.8, 74.0, 77.4, 77.5, 78.3, 78.6, 109.2, 109.6, 112.0, 112.7, 118.7, 118.8, 118.9, 119.0, 119.8, 120.0, 120.5, 121.0, 122.2, 122.8, 128.0, 128.1, 132.9, 133.5, 133.6, 133.7, 136.4, 136.6, 137.1, 137.3. IR (film) ν 3290, 2110, 1600 cm^{-1}. Anal. Calcd for $C_{20}H_{20}N_2O$ (304.39): C, 78.92; H, 6.62; N, 9.20. Found: C, 79.13; H, 6.39; N, 9.33.

4.3. Diels–Alder reactions

4.3.1. Synthesis of dimethyl (8aR,9R*,10S*,12bR*)-1-tosyl-1,2,3,8a,9,10,11,12b-octahydro-8H-1,7b-diazabenzo[e]-acephenanthrylene-9,10-dicarboxylate,* ***29***

Treatment of **14a** (0.25 g, 0.64 mmol) in DCM (10 mL), with dimethyl maleate (0.12 mL, 0.96 mmol) at rt, gave after 7 days, upon removal of the solvent and after flash chromatography (hexane/EtOAc, 4:1), pure **29** (140 mg, 40%) as brown solid (mp 214–216 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.16–2.31 (m, 1H), 2.39 (s, 3H), 2.45–2.50 (m, 3H), 2.76 (s, 3H), 2.98–3.05 (m, 1H), 3.08–3.14 (m, 1H), 3.40 (s, 2H), 3.67 (s, 3H), 4.18 (dd, 1H, J_1=13.7 Hz, J_2=3.4 Hz), 4.35–4.49 (m, 2H), 5.61 (br s, 1H), 6.03 (br s, 1H), 7.03 (td, 1H, J_1=7.3 Hz, J_2=1.0 Hz), 7.15 (td, 1H, J_1=7.3 Hz, J_2=1.0 Hz), 7.26 (d, 2H, J=8.3 Hz), 7.29 (d, 1H, J=8.3 Hz), 7.34 (d, 1H, J=7.8 Hz), 7.77 (d, 2H, J=8.3 Hz). NOE ($H_{5.61}\rightarrow H_{4.35-4.49}$, 0.0%; $H_{2.98-3.05}\rightarrow H_{4.35-4.49}$, 0.0%; $\rightarrow H_{3.40}$, 14.0%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 20.1, 21.5, 25.0, 37.2, 41.3, 42.2, 42.7, 44.1, 51.5, 52.0, 54.4, 104.7, 109.1, 118.2, 119.1, 119.8, 121.0, 126.5, 126.8, 129.1, 129.9, 131.8, 135.8, 138.0, 143.5, 170.9, 173.4. IR (KBr) ν 1720, 1590 cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_6S$ (534.62): C, 65.15; H, 5.66; N, 5.24. Found: C, 64.88; H, 5.79; N, 5.42.

4.3.2. Synthesis of dimethyl 1-tosyl-1,2,3,8a,11,12b-hexahydro-8H-1,7b-diazabenzo[e]acephenanthrylene-9,10-dicarboxylate, ***30***

4.3.2.1. Procedure A. Treatment of **14a** (0.15 g, 0.38 mmol) in DCM (10 mL), and DMAD (0.09 mL, 0.76 mmol) at rt, gave after 3 days, and upon removal of the solvent and after flash chromatography (hexane/EtOAc, 4:1), pure **30** (86 mg, 42%) as brown solid (mp 118 °C, des.).

4.3.2.2. Procedure B. To a solution of **6a** (0.12 g, 0.32 mmol) in toluene (32 mL) was added **[Ru]-III** catalysts (14 mg, 0.022 mmol) and the mixture was stirred at rt for 3 days. DMAD (0.08 mL, 0.64 mmol) was added stirring was continued for 3 days. The reaction mixture was filtered off through a Celite pad and washed with dry toluene. The solvent was removed under reduced pressure and the residue purified by column chromatography (Hexane/EtOAc 4:1) giving **30** (45 mg, 27%) as brown solid (mp 118 °C, des.). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.11–2.23 (m, 1H), 2.49 (s, 3H), 2.49–2.54 (m, 1H), 3.07–3.18 (m, 3H), 3.39 (t, 1H, J=11.0 Hz), 3.83 (s, 3H), 3.91 (s, 3H), 4.03–4.11 (m, 1H), 4.25 (dd, 1H, J_1=14.0 Hz, J_2=3.0 Hz), 4.64 (dd, 1H, J_1=10.4 Hz, J_2=6.0 Hz), 5.37 (br s, 1H), 6.04 (br s, 1H), 7.10 (t, 1H, J=7.4 Hz), 7.18 (t, 1H, J=7.4 Hz), 7.25–7.32 (m, 3H), 7.37 (d, 1H, J=7.4 Hz), 7.80 (d, 2H, J=8.2 Hz). NOE ($H_{3.39}\rightarrow H_{5.37}$, 0%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 20.8, 21.5, 28.4, 35.6, 43.7, 49.1, 52.5, 52.6, 55.1, 108.1, 110.1, 114.9, 118.2, 120.3, 121.9, 127.1, 127.7, 130.0, 131.2, 131.2, 133.0, 136.0, 137.5, 138.3, 143.8, 167.2, 168.0. IR (KBr) ν 1730, 1650, 1600 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_6S$ (532.61): C, 65.40; H, 5.30; N, 5.26. Found: C, 65.72; H, 5.13; N, 5.41.

4.3.3. Synthesis of dimethyl 12-methyl-1-tosyl-2,3,8,8a,11,12b-hexahydro-1H-1,7b,9,10-tetraazabenzo[e]acephenanthrylene-9,10-dicarboxylate, ***31***

Treatment of **14b** (0.20 g, 0.49 mmol) and diethyl azodicarboxylate (0.18 mL, 0.99 mmol) at rt, gave after 3 days, upon removal of the solvent and after flash chromatography (petroleum ether/diethyl ether, 1:1) pure **31** (105 mg, 35%) as yellow oil. This product begins to decomposed into other products in minutes. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.17–1.40 (m, 6H), 2.02–2.07 (m, 2H), 2.24 (s, 3H), 2.26 (s, 3H), 2.28–2.36 (m, 1H), 2.45 (s, 1H), 2.51–2.65 (m, 1H), 3.48–3.67 (m, 2H), 4.12–4.37 (m, 4H), 4.49 (dd, 1H, J_1=14.9 Hz, J_2=5.2 Hz), 4.57–4.70 (m, 1H), 5.17 (dd, 1H, J_1=9.8 Hz, J_2=6.1 Hz), 6.77 (d, 1H, J=7.9 Hz), 7.01 (d, 1H, J=7.3 Hz), 7.06 (d, 2H, J=7.9 Hz), 7.19 (d, 2H, J=7.9 Hz), 7.33–7.40 (m, 1H), 7.78 (d, 1H, J=8.5 Hz). IR (film) ν 1690, 1600 cm^{-1}.

4.3.4. Reaction of 11-tosyl-1-vinyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***15a*** *with dimethyl maleate: synthesis of* ***32a*** *and* ***32b***

Treatment of **15a** (0.20 g, 0.51 mmol) and dimethyl maleate (0.13 mL, 1.03 mmol) at rt, gave after 7 days, and upon removal of the solvent a mixture of 4 isomers. After flash chromatography (hexane/EtOAc, 1:2 to EtOAc), pure **32a** (0.11 g, 42%) as yellow oil and **32b** (38 mg, 14%) as yellow oil were isolated.

4.3.4.1. Dimethyl (7aS,8R*,9S*,11bR*)-12-tosyl-5,7,7a,8,9,10,11b,12-octahydro-6H-6a,12-diazaindeno[1,2-a]fluorene-8,9-dicarboxylate,* ***32a****.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.25 (s, 3H), 2.38–2.53 (m, 2H), 2.59–2.66 (m, 1H), 2.72–2.88 (m, 3H), 2.95–3.18 (m, 4H), 3.31 (dd, 1H, J_1=6.1 Hz, J_2=3.7 Hz), 3.68 (s, 6H), 5.28 (br s, 1H), 6.41 (br s, 1H), 7.06 (d, 2H, J=7.9 Hz), 7.18–7.31 (m, 3H), 7.48 (d, 2H, J=7.9 Hz),

8.06 (d, 1H, J=7.9 Hz). NOE ($H_{3.31} \rightarrow H_{2.59-2.66}$, 6.8%; $\rightarrow H_{2.87}$, 7.5%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 18.5, 21.4, 25.5, 38.6, 41.1, 41.3, 45.6, 51.4, 51.9, 53.0, 61.2, 116.1, 118.3, 121.2, 122.0, 124.0, 124.6, 126.2, 129.2, 130.7, 134.1, 135.7, 136.9, 137.7, 144.3, 171.6, 173.9. IR (film) 1730, 1590 cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_6S$ (534.62): C, 65.15; H, 5.66; N, 5.24. Found: C, 65.28; H, 5.50; N, 5.09.

4.3.4.2. Dimethyl (7aS,8S*,9R*,11bR*)-12-tosyl-5,7,7a,8,9,10,11b,12-octahydro-6H-6a,12-diazaindeno[1,2-a]fluorene-8,9-dicarboxylate,* ***32b***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.29 (s, 3H), 2.44 (dd, 1H, J_1=9.7 Hz, J_2=3.4 Hz), 2.47–2.57 (m, 2H), 2.72–2.83 (m, 1H), 2.85–3.09 (m, 4H), 3.13–3.22 (m, 1H), 3.39 (dd, 1H, J_1=5.9 Hz, J_2=3.9 Hz), 3.46–3.58 (m, 1H), 3.54 (s, 3H), 3.71 (s, 3H), 5.36 (br s, 1H), 6.38 (br s, 1H), 7.10 (d, 2H, J=8.3 Hz), 7.17–7.32 (m, 3H), 7.52 (d, 2H, J=8.3 Hz), 7.93 (dd, 1H, J_1=7.8 Hz, J_2=1.0 Hz). NOE ($H_{3.39} \rightarrow H_{2.44}$, 14.8%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 18.0, 21.5, 27.6, 34.6, 40.0, 45.7, 46.2, 51.9, 52.0, 56.8, 61.4, 115.9, 118.5, 121.2, 121.9, 124.0, 124.7, 126.7, 129.4, 130.8, 134.0, 135.5, 137.7, 138.8, 144.4, 173.4, 173.6. IR (film) 1730, 1590 cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_6S$ (534.62): C, 65.15; H, 5.66; N, 5.24. Found: C, 64.90; H, 5.44; N, 4.99.

4.3.5. Synthesis of 1-vinyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***33a***

To a solution of EtONa (1.57 g, 23.10 mmol) in absolute EtOH (8 mL), generated in situ, was added **15a** (0.30 g, 0.77 mmol) in absolute EtOH (8 mL) and the mixture was refluxed for 4 h. The mixture was quenched with water and the mixture was extracted with EtOAc (×3). The organic layer was washed with water and brine, dried ($MgSO_4$), and the solvent removed under reduced pressure. The crude residue was purified by flash chromatography on silica gel (EtOAc to EtOAc/MeOH, 5%), giving **33a** (0.15 mg, 81%) as brown wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.66 (dd, 1H, J_1=15.4 Hz, J_2=4.6 Hz), 3.04–3.16 (m, 1H), 3.31–3.50 (m, 2H), 3.73 (dd, 1H, J_1=14.8 Hz, J_2=2.7 Hz), 3.83 (d, 1H, J=16.5 Hz), 5.39 (s, 1H), 5.45 (d, 1H, J=10.7 Hz), 5.57 (d, 1H, J=17.6 Hz), 5.91 (s, 1H), 6.76 (dd, 1H, J_1=17.6 Hz, J_2=10.7 Hz), 7.14–7.25 (m, 2H), 7.36 (d, 1H, J=7.2 Hz), 7.58 (d, 1H, J=6.9 Hz), 7.90 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 15.8, 44.0, 53.8, 59.9, 107.5, 110.8, 114.9, 118.0, 119.3, 121.6, 127.0, 129.5, 133.5, 134.0, 135.6, 141.4. IR (film) ν 3450, 1620 cm^{-1}. Anal. Calcd for $C_{16}H_{16}N_2$ (236.31): C, 81.32; H, 6.82; N, 11.85. Found: C, 81.47; H, 6.70; N, 11.99.

4.3.6. Synthesis of 1-isopropenyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***33b***

Following the same procedure than for the synthesis of **33a**, from **15b** (0.27 g, 0.67 mmol) and EtONa (1.37 g, 20.10 mmol), and upon purification by chromatography on silica gel (EtOAc), giving **33b** (106 mg, 63%) as a brown wax. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.06 (s, 3H), 2.67 (dd, 1H, J_1=16.0 Hz, J_2=4.4 Hz), 3.06–3.18 (m, 1H), 3.33–3.51 (m, 2H), 3.77 (dd, 1H, J_1=14.3 Hz, J_2=2.8 Hz), 3.87 (d, 1H, J=16.5 Hz), 5.33–5.43 (m, 3H), 5.93 (s, 1H), 7.14–7.24 (m, 2H), 7.36 (dd, 1H, J_1=7.1 Hz, J_2=1.1 Hz), 7.58 (dd, 1H, J_1=7.2 Hz, J_2=1.1 Hz), 7.99 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 15.8, 20.6, 44.0, 54.2, 60.8, 107.3, 110.8, 113.2, 117.9, 119.2, 121.5, 126.6, 127.0, 134.2, 135.4, 140.6, 143.0. IR (film) ν 3450, 1620, 1600 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2$ (250.34): C, 81.56; H, 7.25; N, 11.19. Found: C, 81.44; H, 7.00; N, 11.32.

4.3.7. Synthesis of diethyl 11-methyl-5,7,7a,10,11b,12-hexahydro-6H-6a,8,9,12-tetraaza-indeno[1,2-a]fluorene-8,9-dicarboxylate, ***34***

Treatment of **33** (61 mg, 0.25 mmol) and diethyl azodicarboxylate (0.05 mL, 0.29 mmol) at rt, gave after 24 h, upon removal of the solvent and after flash chromatography (hexane/EtOAc, 9:1 to 4:1), pure **34** (58 mg, 56%) as a yellow oil, which begun its transformation into other products in minutes. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.25–1.30 (m, 6H), 2.15 (s, 3H), 3.09–3.18 (m, 3H), 4.10–4.31 (m, 7H), 5.21 (s, 1H), 5.33 (s, 1H), 6.15 (br s, 1H), 7.00 (br s, 1H), 7.09–7.18 (m, 2H), 7.33 (dd, 1H, J_1=6.6 Hz, J_2=1.6 Hz), 7.50 (dd, 1H, J_1=7.7 Hz, J_2=1.6 Hz), 8.70 (br s, 1H). IR (KBr) ν 1690, 1590 cm^{-1}.

4.3.8. Reaction of 11-tosyl-1-vinyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***15a*** *with DMAD*

4.3.8.1. Procedure A. To a solution of **15a** (0.10 g, 0.26 mmol), $SnCl_4$ (0.05 mL, 0.38 mmol) in DCM at −78 °C, DMAD (0.08 mL, 0.51 mmol) was added. The mixture was allowed to reach rt and was stirred for 7 days. To the reaction was added 40 mL of ice/H_2O and the mixture was extracted with EtOAc (×3). The organic layers were dried over $MgSO_4$, and the solvent was removed under vacuum giving a 2:1 mixture of **35a** and **35b**. Purification by silica gel flash chromatography (hexane/EtOAc, 1:2 to EtOAc), afforded **35a** (37 mg, 27%) and a 13% of **35b** unpurified with **35a**.

4.3.8.2. Procedure B. A solution of **15a** (0.20 g, 0.51 mmol) and $BF_3 \cdot OEt_2$ (0.10 mL, 0.77 mmol) in toluene at −20 °C was stirred for 1 h. DMAD (0.19 mL, 1.54 mmol) was then added and the mixture was allowed to reach rt and was stirred for 16 h. The solvent was removed under vacuum giving a crude mixture containing **15a**, **37a**, **35a**, and **35b**, in the following ratios as calculated from integration of well resolved ^{1}H NMR signals (2:3:2:1). Separation by silica gel flash chromatography (hexane/EtOAc, 4:1 to EtOAc) afforded **15a** (20 mg, 10%), **37a** (73 mg, 27%) as yellow oil, and **35a** (36 mg, 13%) as yellow solid (mp 177–179 °C).

4.3.8.3. Dimethyl (7aR,11bS*)-12-tosyl-5,7,7a,10,11b,12-hexahydro-6H-6a,12-diazaindeno [1,2-a]fluorene-8,9-dicarboxylate,* ***35a***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.29 (s, 3H), 2.48–2.58 (m, 1H), 2.63–2.69 (m, 1H), 2.77 (t, 1H, J=9.1 Hz), 2.79–2.87 (m, 1H), 2.99–3.11 (m, 3H), 3.44 (t, 1H, J=9.1 Hz), 3.61–3.72 (m, 1H), 3.75 (s, 3H), 3.82 (s, 3H), 5.38 (s, 1H), 6.03 (br s, 1H), 7.11 (d, 2H, J=8.5 Hz), 7.22–7.34 (m, 3H), 7.54 (d, 2H, J=8.0 Hz), 8.16 (d, 1H, J=8.5 Hz). NOE ($H_{5.38} \rightarrow H_{3.61-3.72}$, 4.3%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 18.8, 21.5, 28.9, 39.1, 46.1, 52.2, 52.3, 54.2, 59.2, 115.8, 118.1, 118.5, 120.3, 124.1, 124.7, 126.5, 127.7, 129.5, 130.6, 132.5, 133.9, 135.8, 137.1, 138.2, 144.7, 167.7, 168.1. IR (KBr) 1720, 1630 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_6S$ (532.61): C, 65.40; H, 5.30; N, 5.26. Found: C, 65.73; H, 5.15; N, 5.48.

4.3.8.4. Dimethyl (7aR,11bR*)-12-tosyl-5,7,7a,10,11b,12-hexahydro-6H-6a,12-diazaindeno[1,2-a]fluorene-8,9-dicarboxylate,* ***35b***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.29 (s, 3H), 2.48–2.58 (m, 1H), 2.63–2.69 (m, 1H), 2.79–2.87 (m, 1H), 2.99–3.11 (m, 3H), 3.15–3.28 (m, 2H), 3.61–3.72 (m, 1H), 3.75 (s, 3H), 3.78 (s, 3H), 5.38 (s, 1H), 6.40 (br s, 1H), 7.10 (d, 2H, J=8.2 Hz), 7.22–7.34 (m, 3H), 7.48 (d, 2H, J=8.2 Hz), 8.05 (d, 1H, J=7.7 Hz).

4.4. Rearrangement reaction using an activated alkyne

4.4.1. Reaction of 11-tosyl-1-vinyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***15a***

4.4.1.1. Procedure A. Treatment of **15a** (0.10 g, 0.26 mmol) with DMAD (0.06 mL, 0.51 mmol) in 10 mL of DCM (24 h) gave, upon elimination of the solvent, a crude mixture containing **16a**, **36a**, **38a**, and **35b** in the following ratio as calculated from integration of well resolved ^{1}H NMR signals (2:11:5:1). Separation of this mixture by flash chromatography (hexane/EtOAc, 4:1), afforded pure **16a** (5 mg, 5%) as yellow solid (mp 85 °C, dec), **36a** (77 mg, 56%) as brown wax, and **38a** (23 mg, 17%) as yellow oil, which decomposed after few hours.

4.4.1.2. Procedure B. To a solution of **15a** (0.10 g, 0.26 mmol) in THF (6 mL) was added DMAD (0.06 mL, 0.51 mmol) and the mixture was stirred for 3 days at rt. The solvent was removed under vacuum giving a crude mixture containing **16a**, **36a**, and **35b**, in the following ratios as calculated from integration of well resolved ^{1}H NMR signals (1:3:1). Separation by silica gel flash chromatography (hexane/EtOAc, 4:1 to 1:1), afforded pure **16a** (11 mg, 11%) and **36a** (58 mg, 42%).

4.4.1.3. Procedure C. To a solution of **15a** (0.10 g, 0.26 mmol) in THF (6 mL) was added DMAD (0.06 mL, 0.51 mmol) and the mixture was stirred for 2 days at refluxing temperature. The solvent was removed under vacuum giving a crude mixture containing **16a**, **37a**, and **35b**, in the following ratios as calculated from integration of well resolved ^{1}H NMR signals (3:5:1). Separation by silica gel flash chromatography (hexane/EtOAc, 4:1 to 1:1), afforded pure **16a** (16 mg, 16%) and **37a** (63 mg, 46%).

4.4.1.4. Procedure D. To a solution of **7a** (0.39 g, 1.0 mmol) in toluene (100 mL) was added **[Ru]-II** (0.04 g, 0.05 mmol) and the mixture was stirred for 4 days. Then, DMAD (0.24 mL, 2.0 mmol) was added and the mixture was heated at 60 °C for 5 h. The crude was filtered off through a Celite pad and washed with EtOAc (30 mL). The solvent was removed under reduced pressure giving a crude mixture containing **15a**, **16a**, and **36a**, in the following ratios as calculated from integration of well resolved ^{1}H NMR signals (4:1:12). Separation by silica gel flash chromatography (hexane/EtOAc, 4:1 to EtOAc) afforded pure **15a** (32 mg, 8%) as yellow solid (mp 85 °C, dec) and **36a** (0.21 g, 41%).

4.4.1.5. Dimethyl (9E,11Z)-8-tosyl-11-vinyl-8,14-diazatetracyclo[12,2,2,2,0^{1,9},0^{2,7}]octadeca-2,4,6,9,11,15-hexaene-15,16-dicarboxylate, ***36a***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.60–0.67 (m, 1H), 1.42–1.52 (m, 1H), 2.38 (s, 3H), 2.94–3.15 (m, 2H), 3.35 (s, 3H), 3.61–3.70 (m, 1H), 3.76 (s, 3H), 3.80–3.86 (m, 1H), 5.05 (d, 1H, J=10.4 Hz), 5.20 (d, 1H, J=17.0 Hz), 5.55 (t, 1H, J=5.8 Hz), 6.29 (dd, 1H, J_1=17.0 Hz, J_2=10.4 Hz), 6.83 (d, 1H, J=7.1 Hz), 6.86 (s, 1H), 7.07 (t, 1H, J=7.4 Hz), 7.21 (d, 2H, J=8.2 Hz), 7.28 (t, 1H, 7.1 Hz), 7.65 (d, 2H, J=8.2 Hz), 7.88 (d, 1H, J=7.7 Hz). NOE ($H_{6.86} \rightarrow H_{5.20}$, 6.4%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.6, 37.9, 48.4, 48.5, 51.4, 52.4, 52.7, 115.1, 116.7, 117.2, 121.2, 121.6, 125.0, 127.2, 127.5, 128.1, 129.5, 135.3, 135.4, 135.7, 139.4, 141.3, 142.1, 144.7, 146.9, 164.8, 166.2. IR (film): 1730, 1610, 1590 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_6S$ (532.61): C, 65.40; H, 5.30; N, 5.26. Found: C, 65.81; H, 5.05; N, 5.55.

4.4.1.6. Dimethyl (9Z,11Z)-8-tosyl-11-vinyl-8,14-diazatetracyclo[12,2,2,2,0^{1,9},0^{2,7}]octadeca-2,4,6,9,11,15-hexaene-15,16-dicarboxylate, ***37a***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.90 (dd, 1H, J_1=14.3 Hz, J_2=3.8 Hz), 2.19–2.32 (m, 1H), 2.39 (s, 3H), 2.79 (s, 3H), 3.03 (dd, 1H, J_1=13.7 Hz, J_2=7.1 Hz), 3.50 (dd, 1H, J_1=13.7 Hz, J_2=8.2 Hz), 3.80–4.06 (m, 2H), 3.86 (s, 3H), 5.15 (d, 1H, J=10.4 Hz), 5.31 (d, 1H, J=17.6 Hz), 5.88 (t, 1H, J=7.7 Hz), 6.39 (dd, 1H, J_1=17.6 Hz, J_2=10.4 Hz), 6.76 (d, 1H, J=7.1 Hz), 6.98 (td, 1H, J_1=7.7 Hz, J_2=1.1 Hz), 7.05 (s, 1H), 7.24–7.30 (m, 3H), 7.73 (d, 2H, J=8.2 Hz), 7.99 (d, 1H, J=7.7 Hz). NOE ($H_{6.39} \rightarrow H_{5.88}$, 14.8%; $\rightarrow H_{5.15}$, 6.8%), ($H_{7.05} \rightarrow H_{5.31}$, 8.3%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.6, 28.0, 34.8, 45.9, 51.5, 53.0, 71.0, 107.5, 107.6, 114.6, 115.4, 123.5, 124.8, 127.2, 127.6, 128.8, 129.5, 133.2, 134.5, 137.3, 140.4, 140.9, 144.9, 151.3, 158.8, 164.8, 170.5. IR (film): 1730, 1610, 1590 cm^{-1}. Anal. Calcd for $C_{29}H_{28}N_2O_6S$ (532.61): C, 65.40; H, 5.30; N, 5.26. Found: C, 65.55; H, 5.43; N, 5.14.

4.4.1.7. Dimethyl 11-tosyl-1,1-divinyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indole-2,3-dicarboxylate, ***38a***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.22 (s, 3H), 2.73 (dd, 1H, J_1=17.0 Hz, J_2=4.9 Hz), 3.08–3.19 (m, 1H), 3.56–3.76 (m, 1H), 3.64 (s, 3H), 3.81–3.94 (m, 1H), 4.04 (s, 3H), 5.34 (dd, 1H, J_1=17.6 Hz, J_2=1.6 Hz), 5.44 (dd, 1H, J_1=11.0 Hz, J_2=1.6 Hz), 5.47 (s, 1H), 5.57 (dd, 1H, J_1=11.5 Hz, J_2=1.6 Hz), 5.59 (dd, 1H, J_1=17.6 Hz, J_2=1.6 Hz), 6.67 (dd, 1H, J_1=17.6 Hz, J_2=11.0 Hz), 6.95–7.03 (m, 3H), 7.11–7.28 (m, 3H), 7.50 (d, 2H, J=8.2 Hz), 7.93 (d, 1H, J=7.7 Hz). DEPT 135-NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.5 (CH_3), 29.7 (CH_2), 49.0 (CH_2), 51.0 (CH_3), 52.0 (CH), 53.2 (CH_3), 119.2 (CH), 120.7 (CH_2), 121.3 (CH_2), 124.6 (CH), 125.8 (CH), 127.2 (CH), 127.4 (CH), 128.9 (CH), 132.0 (CH), 132.7 (CH). IR (film) 1730, 1615 cm^{-1}.

4.4.2. Reaction of 1-isopropenyl-11-tosyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***15b***

Treatment of **15b** (0.13 g, 0.33 mmol) with DMAD (0.08 mL, 0.66 mmol) in 10 mL of DCM at rt (2 days) gave, upon elimination of the solvent, a crude mixture containing **16b**, **36b**, and **38b**, in the following ratios as calculated from integration of well resolved ^{1}H NMR signals (1:16:3). Separation by flash chromatography (hexane/EtOAc, 4:1 to 2:1) gave pure **36b** (94 mg, 52%) as yellow solid (mp 160–162 °C) and **38b** (14 mg, 8%) as yellow oil, which decomposed in a few hour.

4.4.2.1. Dimethyl (9E,11Z)-8-tosyl-11-isopropenyl-8,14-diazatetracyclo[12,2,2,2,0^{1,9},0^{2,7}]octadeca-2,4,6,9,11,15-hexaene-15,16-dicarboxylate, ***36b***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.83–0.92 (m, 1H), 1.36–1.46 (m, 1H), 1.83 (s, 3H), 2.38 (s, 3H), 2.93–3.12 (m, 2H), 3.35 (s, 3H), 3.57–3.64 (m, 1H), 3.70–3.86 (m, 1H), 3.74 (s, 3H), 4.90 (s, 1H), 4.94 (s, 1H), 5.57 (t, 1H, J=6.6 Hz), 6.69 (s, 1H), 6.85 (d, 1H, J=7.7 Hz), 7.06 (t, 1H, J=7.7 Hz), 7.20–7.28 (m, 3H), 7.66 (d, 2H, J=8.2 Hz), 7.84 (d, 1H, J=8.2 Hz). NOE ($H_{6.69} \rightarrow H_{4.94}$, 7.0%; $H_{5.57} \rightarrow H_{1.83}$, 9.3%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.5 (2C), 38.7, 48.5, 49.2, 51.4, 51.7, 52.6, 114.8, 117.1, 119.0, 121.7, 122.2, 124.2, 125.1, 127.2, 128.0, 129.4, 135.3, 135.9, 139.4, 140.2, 141.0, 144.7, 146.3, 146.8, 164.5, 166.4. IR (KBr) 1720, 1610 cm^{-1}. Anal. Calcd for $C_{30}H_{30}N_2O_6S$ (546.64): C, 65.92; H, 5.53; N, 5.12. Found: C, 65.82; H, 5.69; N, 5.01.

4.4.2.2. Dimethyl 1-isopropenyl-11-tosyl-1-vinyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indole-2,3-dicarboxylate, ***38b***. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.99 (s, 3H), 2.22 (s, 3H), 2.72 (dd, 1H, J_1=17.0 Hz, J_2=4.9 Hz), 3.13–3.17 (m, 1H), 3.53–3.66 (m, 1H), 3.64 (s, 3H), 3.73–3.94 (m, 1H), 4.04 (s, 3H), 5.40 (dd, 1H, J_1=11.0 Hz, J_2=1.6 Hz), 5.43 (d, 1H, J=1.6 Hz), 5.44 (d, 1H, J=1.6 Hz), 5.50 (dd, 1H, J_1=17.0 Hz, J_2=1.6 Hz), 5.57 (s, 1H), 6.67 (dd, 1H, J_1=17.0 Hz, J_2=11.0 Hz), 6.96 (d, 2H, J=8.2 Hz), 7.13–7.27 (m, 3H), 7.48 (d, 2H, J=8.2 Hz), 7.84 (d, 1H, J=7.7 Hz). IR (film) 1720, 1610 cm^{-1}.

4.4.3. Synthesis of dimethyl 1-isopropenyl-1-vinyl-5,6,11,11b-tetrahydro-1H-indolizino[8,7-b]indole-2,3-dicarboxylate, ***39***

Treatment of **33b** (90 mg, 0.36 mmol) with DMAD (0.07 mL, 0.54 mmol) in 10 mL of DCM at rt (2 days) gave, upon elimination of the solvent and after flash chromatography (hexane/EtOAc, 4:1) compound **39** (65 mg, 51%) as yellow oil, which decomposed in a few hours. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.05 (br s, 3H), 2.80 (dd, 1H, J_1=16.5 Hz, J_2=3.3 Hz), 3.15–3.28 (m, 1H), 3.54 (dd, 1H, J_1=13.7 Hz, J_2=3.3 Hz), 3.60 (s, 3H), 3.80–3.87 (m, 1H), 4.00 (s, 3H), 5.30–5.41 (m, 4H), 5.66 (s, 1H), 6.67 (dd, 1H, J_1=17.6 Hz, J_2=10.4 Hz), 7.10 (td, 1H, J_1=7.1 Hz, J_2=1.1 Hz), 7.22 (td, 1H, J_1=7.1 Hz, J_2=1.1 Hz), 7.32 (d, 1H, J=8.2 Hz), 7.47 (d, 1H, J=7.7 Hz), 8.88 (br s, 1H). DEPT 135-NMR ($CDCl_3$, 75 MHz) δ (ppm): 22.7 (CH_3), 29.7 (CH_2), 46.7 (CH_2), 50.7 (CH), 51.0 (CH_3), 53.0 (CH_3), 111.1 (CH), 118.9 (CH_2), 120.1 (CH), 123.8 (CH_2), 126.2 (CH), 136.3 (CH), 141.9 (CH). IR (film) ν 1720, 1610 cm^{-1}.

4.4.4. Synthesis of dimethyl 1-vinyl-6,7,12,12b-tetrahydro-3H-5a,12-diazabenzo[b]cyclohepta[g]indene-4,5-dicarboxylate, ***40***

Treatment of **33a** (0.10 g, 0.45 mmol) with DMAD (0.11 mL, 0.92 mmol) in 10 mL of DCM at rt (4 days) gave, upon elimination of

the solvent and after flash chromatography (hexane/EtOAc, 4:1) pure **40** (127 mg, 58%) as red solid (mp 198–200 °C). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 3.07–3.11 (m, 2H), 3.37–3.41 (m, 2H), 3.64 (s, 3H), 3.66–3.72 (m, 2H), 3.79 (s, 3H), 4.64 (br s, 1H), 5.22 (d, 1H, J=11.0 Hz), 5.51 (s, 1H), 5.52 (d, 1H, J=17.6 Hz), 6.46 (dd, 1H, J_1=17.6 Hz, J_2=11.0 Hz), 7.08–7.18 (m, 2H), 7.28 (dd, 1H, J_1=7.4 Hz, J_2=1.6 Hz), 7.46 (d, 1H, J=7.1 Hz), 7.68 (br s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 22.5, 29.7, 50.9, 51.4, 52.9, 54.1, 110.5, 112.6, 117.6, 119.3, 121.6, 127.0, 127.1, 127.7, 129.0, 132.4, 135.7, 139.1, 140.7, 153.6, 166.1, 168.0. IR (KBr) ν 3380, 1740, 1570 cm^{-1}. Anal. Calcd for $C_{22}H_{22}N_2O_4$ (378.42): C, 69.83; H, 5.86; N, 7.40. Found: C, 70.02; H, 5.63; N, 7.66.

4.4.5. Reaction of 11-tosyl-1-vinyl-5,6,11,11b-tetrahydro-3H-indolizino[8,7-b]indole, ***15a*** *with 3-butyn-2-one*

Treatment of **15a** (0.20 g, 0.51 mmol) and 3-butyn-2-one (0.08 mL, 1.03 mmol) in 10 mL of DCM at rt (24 h) gave, upon elimination of the solvent and after flash chromatography (hexane/EtOAc, 4:1), pure **41** (126 mg, 53%) as yellow oil.

4.4.5.1. 4-[11-Tosyl-1-vinyl-6,11-dihydro-3H,5H-indolizino[8,7-b]indol-11b-yl]-but-3-en-2-one, ***41****.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.26 (s, 3H), 2.38 (s, 3H), 2.46 (dd, 1H, J_1=17.1 Hz, J_2=4.9 Hz), 3.07–3.42 (m, 3H), 3.48 (d, 1H, J=13.4 Hz), 3.61 (d, 1H, J=13.4 Hz), 5.20 (dd, 1H, J_1=11.0 Hz, J_2=1.2 Hz), 5.44 (dd, 1H, J_1=17.1 Hz, J_2=1.2 Hz), 6.02 (br s, 1H), 6.37 (d, 1H, J=15.8 Hz), 6.95 (dd, 1H, J_1=17.1 Hz, J_2=11.0 Hz), 7.06 (d, 2H, J=7.9 Hz), 7.17–7.32 (m, 3H), 7.36 (d, 2H, J=8.5 Hz), 7.65 (d, 1H, J=15.9 Hz), 7.98 (d, 1H, J=7.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 18.2, 21.4, 27.2, 39.7, 52.9, 71.8, 115.8, 116.8, 118.7, 124.1, 124.5, 125.3, 125.9, 126.7, 129.2, 130.4, 130.6, 131.8, 134.4, 137.2, 138.7, 144.3, 144.4, 148.1, 199.4. IR (film) 1670, 1620, 1590 cm^{-1}. Anal. Calcd for $C_{27}H_{26}N_2O_3S$ (458.57): C, 70.72; H, 5.71; N, 6.11. Found: C, 70.59; H, 5.53; N, 6.36.

4.4.6. Reaction of 2-allyl-9-tosyl-1-vinyl-2,3,4,9-tetrahydro-1H-β-carboline, ***8*** *with DMAD*

Treatment of **8** (0.25 g, 0.64 mmol) and DMAD (0.16 mL, 1.28 mmol) in 10 mL of DCM at rt (16 h) gave, upon elimination of the solvent a crude mixture containing **42** and **43**, in the following ratios as calculated from integration of well resolved ^{1}H NMR signals (1:3). Separation by flash chromatography (hexane/EtOAc, 2:1) afforded pure **42** (33 mg, 10%) as yellow oil and **43** (83 mg, 24%) as yellow oil, which decomposed after few hours.

4.4.6.1. Dimethyl (4E,7E)-3-allyl-9-tosyl-2,3,6,9-tetrahydro-1H-azecino[5,4-b]indole-4,5-dicarboxylate, ***42****.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.32 (s, 3H), 2.64–2.79 (m, 2H), 2.80–3.06 (m, 2H), 3.21–3.37 (m, 1H), 3.38–3.55 (m, 2H), 3.75 (s, 3H), 3.83 (s, 3H), 3.92–4.09 (m, 1H), 5.08 (d, 1H, J=10.4 Hz), 5.16 (d, 1H, J=17.1 Hz), 5.27–5.37 (m, 1H), 5.69–5.82 (m, 1H), 6.79 (d, 1H, J=16.5 Hz), 7.16 (d, 2H, J=8.5 Hz), 7.21–7.35 (m, 3H), 7.69 (d, 2H, J=8.5 Hz), 8.20 (d, 1H, J=7.9 Hz). NOE ($H_{6.79} \rightarrow H_{5.27-5.37}$, 0.0%). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 21.5, 24.3, 32.6, 51.2, 52.1, 52.5, 60.4, 114.8, 115.5, 117.5, 118.4, 123.1, 123.4, 123.6, 125.0, 126.7, 127.9, 129.6, 131.1, 134.4, 135.1, 135.3, 135.6, 144.7, 150.5, 166.8, 168.9. IR (film) 1730, 1620 cm^{-1}. Anal. Calcd for $C_{29}H_{30}N_2O_6S$ (534.62): C, 65.15; H, 5.66; N, 5.24. Found: C, 65.34; H, 5.47; N, 5.32.

4.4.6.2. 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, ***43****.* ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.60 (dt, 1H, J_1=14.0 Hz, J_2=3.6 Hz), 1.50 (dd, 1H, J_1=13.4 Hz, J_2=4.3 Hz), 2.35 (s, 3H), 2.86 (dt, 1H, J_1=12.8 Hz, J_2=4.3 Hz), 3.12 (td, 1H, J_1=12.8 Hz, J_2=3.6 Hz), 3.23 (s, 3H), 3.63–3.87 (m, 2H), 3.89 (s, 3H), 5.09 (dd, 1H, J_1=9.8 Hz, J_2=1.8 Hz), 5.20–5.29 (m, 3H), 5.76–5.87 (m, 1H), 6.58–6.71 (m, 1H), 6.82 (d, 1H, J=11.6 Hz), 6.91 (d, 1H, J=6.7 Hz), 7.06 (t, 1H, J=7.3 Hz), 7.18 (d, 2H, J=7.9 Hz), 7.26 (td, 1H, J_1=7.6 Hz, J_2=1.2 Hz), 7.59 (d, 2H, J=8.5 Hz), 7.90 (d, 1H, J=7.9 Hz). IR (film) 1720, 1640 cm^{-1}.

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Supplementary data

Experimental procedures and spectroscopic data for compounds **1**–**13** and spectra for new compounds. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.02.051.

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15. Alternatively to the synthesis of **6a** and **6b** from **1**, as this starting material is obtained in low yield, dihydro-β-carboline was protected as the tosyl derivative, and reacted with an alkynylmagnesium bromide. The resulting 1-ethynyl or 1-(1-propynyl)-9-tosyltetrahydro-β-carboline was allylated giving **6a** and **6b** in a global yield of 42 and 49%, respectively.
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