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Synthesis of substituted β-carbolines via gold(III)-catalyzed cycloisomerization of *N*-propargylamides

Guido Verniest [a,†], Dylan England [b], Norbert De Kimpe [a], Albert Padwa [b,*]

[a] Department of Organic Chemistry, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium
[b] Department of Organic Chemistry, Emory University, Atlanta, GA 30322, USA

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ABSTRACT

Indole-substituted *N*-propargylamides undergo a gold(III)-catalyzed cyclization to give oxazoles or β-carbolinones, depending on the substitution pattern at the amide nitrogen. Secondary amides furnished oxazoles via a 5-*exo*-*dig* cyclization, while tertiary indole-2-carboxamides cycloisomerized to give 2,9-dihydro-β-carbolin-1-ones upon treatment with catalytic amounts of gold(III) chloride. An optimized procedure was developed to prepare several new *N*-benzyl-β-carbolinones as well as the corresponding β-carbolines, which are of interest as core structures found in various natural products such as the harman, ervolanine, and lavendamycin class of alkaloids.

1. Introduction

Gold complexes have been extensively employed over the past several years as homogeneous catalysts for the synthesis of a wide range of heterocyclic compounds.[1] The gold-catalyzed activation of C–C multiple bonds and the subsequent attack by a nucleophilic reagent on the complex has proven to be an exceptionally powerful method to construct new C–C and C–X bonds. The π-Lewis acidic properties of gold complexes result in a chemoselective affinity of these catalysts for alkynes, allenes, and alkenes.[2] As a consequence, the gold-catalyzed activation of allenes,[3] alkenes, and especially alkynes[1] often enables mild and efficient hydroamination, hydroarylation, hydroalkoxylation, and interesting rearrangement reactions to occur. This rapidly evolving area of research has already provided many new opportunities in the atom-economic synthesis of heterocyclic compounds[4] and has recently been reviewed in some detail by a collection of authors.[1] The synthesis of azapolycyclic heterocycles based on gold-catalyzed cycloisomerization reactions involving an indole nucleus is of particular interest because significant molecular complexity can be obtained in one step starting from easily accessible systems.[5] Because of our continuing interest in the synthesis of azaheterocyclic compounds and related natural products containing an indole moiety in the molecular framework, a reactivity study of the cycloisomerization of a series of alkynyl tethered indoles was carried out. Herein, we describe the results obtained from an investigation of the $AuCl_3$-catalyzed intramolecular cyclization of indole-substituted *N*-propargylamides. In particular, the synthesis of a variety of substituted β-carbolines became of interest because the β-carboline core is found in many natural compounds, which show a broad spectrum of high bioactivity (e.g., carbolines **1**–**4**) (Fig. 1).[6]

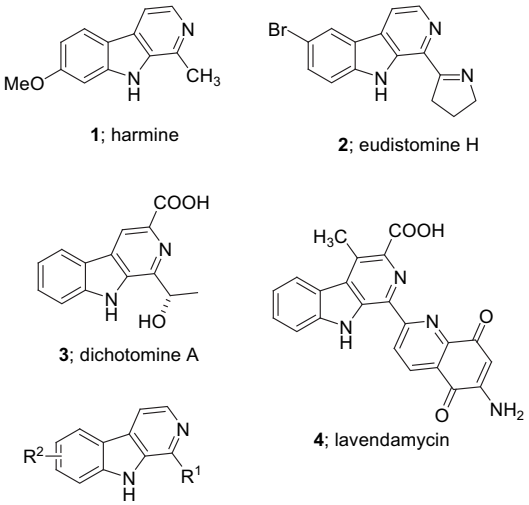

Figure 1. Selected bioactive β-carbolines.

* Corresponding author. Tel.: +1 404 727 0283.
E-mail address: chemap@emory.edu (A. Padwa).
† Postdoctoral Fellow of the Research Foundation Flanders (FWO-Vlaanderen, Belgium) at Emory University.

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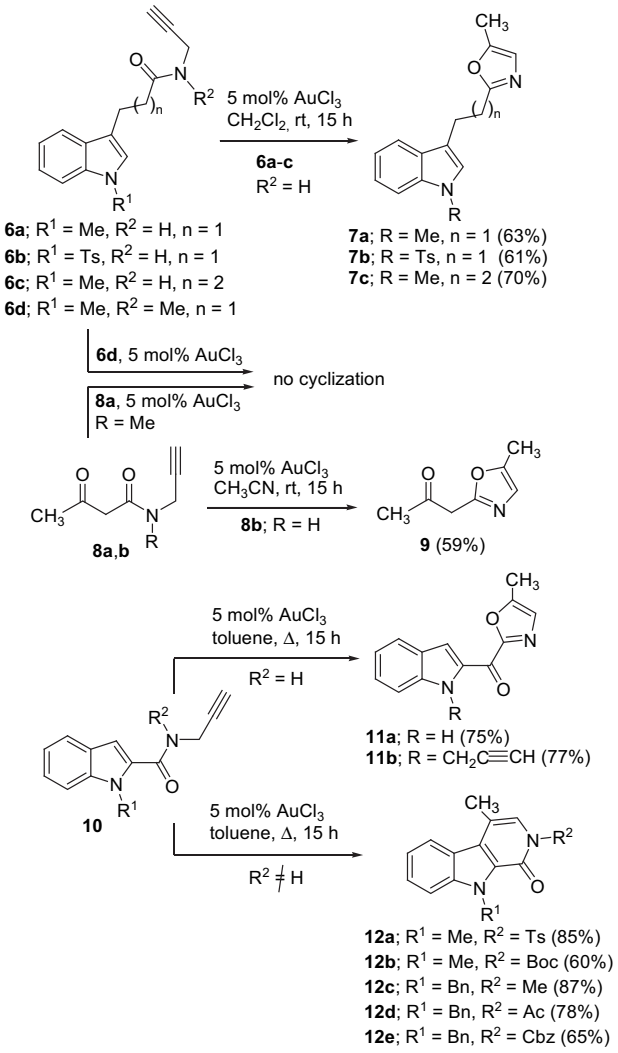
Harmine (**1**) is an antitumor agent isolated from the plants *Peganum harmala* and *Eurycoma longifolia*.[6a] The alkaloid eudistomine H (**2**) was obtained from the Caribbean Tunicate *Eudistoma olivaceum* and exhibits antiviral properties.[7] Dichotomine A (**3**) was isolated from *Stellaria dichotoma* and possesses anti-allergic properties.[8] Lavendamycin (**4**) is an antitumor and antibiotic compound isolated from *Streptomyces lavendulae*.[9] Aside from these naturally occurring β-carbolines, numerous synthetic derivatives show a wide variety of biological activities. For example, halogenated and alkoxylated β-carbolines of type **5** exhibit herbicidal and antifungal properties.[10] Despite the fact that the pharmacological importance of β-carbolines has already produced a considerable array of synthetic methods, the synthesis of specifically substituted β-carbolines still remains an attractive area of research.[11]

2. Results and discussion

Recently, the 5-*exo*-*dig* cyclization of several *N*-propargylamides and related derivatives by making use of catalytic gold(III) chemistry was reported.[12–14] We found that indolyl tethered propargylamides of type **6** smoothly cyclize to give the corresponding oxazoles **7** by reaction of the amide carbonyl group onto the gold activated triple bond (Scheme 1). In order to evaluate the reactivity of the corresponding tertiary *N*-propargylamide system, amide **6a** was methylated with NaH and MeI in DMF to give indole **6d** (R^1, R^2=Me; n=1) in 73% yield. However, the reaction of **6d** with gold(III) chloride gave no cyclized product, thereby indicating that reaction of the amido carbonyl with the activated triple bond does not occur when the *N*-atom contains an alkyl group. Even on refluxing **6d** with gold(III) chloride in dichloroethane, only starting material was recovered. We also found that the reaction of β-ketoamide **8b** (R=H) with gold(III) chloride produced the cyclized oxazole **9**. However, the *N*-methyl derivative **8a** (R=Me) did not undergo cyclization using the same catalytic system (Scheme 1). These results clearly demonstrate that the intramolecular cyclization of propargylamides to give oxazoles proceeds smoothly with secondary propargylamides, while the corresponding tertiary amide system only gave back recovered starting material when treated with a gold(III) catalyst. In a search for an indole-substituted propargylamide that can cyclize by reaction of the indole moiety with the activated triple bond, several differently substituted indoles **10** were prepared. We thought that with these systems, the NH-substituted propargylamides **10a**,**b** would cyclize to give oxazoles. On the other hand, we expected that the corresponding *N*-methylated amides **10c**–**g** would cyclize in a different manner, by reaction of the indole ring with the activated triple bond to afford β-carbolinones. Indeed, the reaction of indoles **10a**,**b** with 5 mol % $AuCl_3$ in toluene yielded the expected oxazoles **11a** and **11b** in 75 and 77% yield, respectively. However, when the amido nitrogen of the indole-2-carboxamide **10** bears a substituent other than hydrogen, 6-*exo*-*dig* cyclization occurred giving rise to β-carbolinones **12** by attack of the indole ring (C-3) onto the triple bond. This synthetic pathway leads to differently substituted β-carbolinones (i.e., **12a**–**e**) in good yield (Scheme 1). In the case of *N*-Boc-1,5-dimethylcarbolin-2-one (**12b**), this compound was further transformed into a β-carboline by N-deprotection and subsequent aromatization using $POCl_3$.[14] The reaction of indole **10d** (R^2=Boc) with $AuCl_3$, however, did not proceed as smoothly as was the case with the corresponding *N*-tosyl or *N*-methylamides **10c**,**e** and gave rise to a number of unidentified side-products. It had been reported very recently that *N*-Boc-propargylamines undergo cyclization via reaction of the Boc-group with the C–C triple bond to furnish substituted oxazolinones.[15] This could possibly be the reason for the lower yield of β-carbolinone **12b** starting from *N*-Boc-amide **10d**.

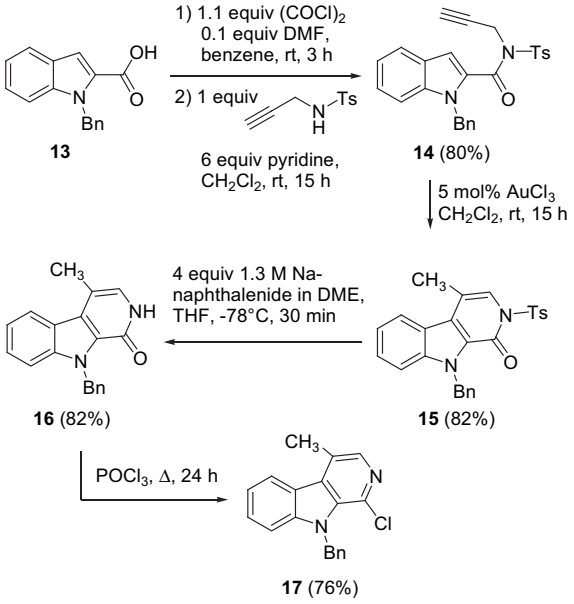


Scheme 1.

In this paper we report on an optimization of the procedure for the synthesis of different β-carbolines starting from indole-substituted *N*-propargylamides. This conversion was undertaken considering the range of bioactivities of β-carbolines and also their frequent occurrence as the core structure in various natural products, such as eudistomine H (**2**), dichotomine A (**3**), and lavendamycin (**4**). *N*-Tosylated propargylamines were chosen as the preferred starting materials for the synthesis of these new β-carbolines because of their easy availability in multigram quantities and also the high conversion previously encountered with the cyclization of indole-2-carboxamide **10c** to carbolinone **12a**.

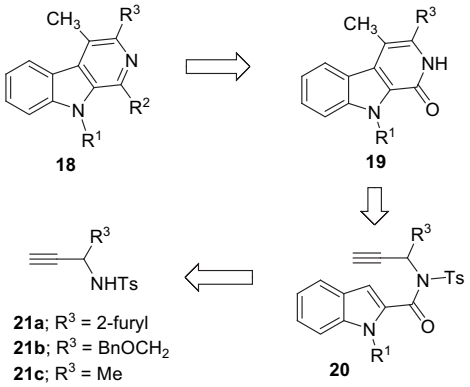
The synthesis of 9-benzyl-1-chloro-4-methyl-β-carboline (**17**) started with the preparation of 1-benzylindole-2-carboxamide (**14**), which was readily obtained from the reaction of *N*-benzyl-2-indoloyl chloride with *N*-Tos-propargylamine (Scheme 2). Treatment of the resulting amide **14** with a catalytic amount of $AuCl_3$ in dichloromethane produced *N*-tosyl-β-carbolinone **15** in 82% yield after purification by silica gel chromatography. Detosylation of **15** was easily accomplished using sodium naphthalenide in 1,2-dimethoxyethane (DME)/THF, which afforded β-carbolinone **16** in 82% yield. Compound **16** was subsequently treated with neat $POCl_3$ under reflux to give the desired 9-benzyl-1-chloro-4-methyl-carboline **17** in 76% yield, which we intend to make use of for an eventual synthesis of lavendamycin (**4**).[14]

Because of the ease and efficiency of this synthetic pathway, the scope of the method was further evaluated in order to maximize

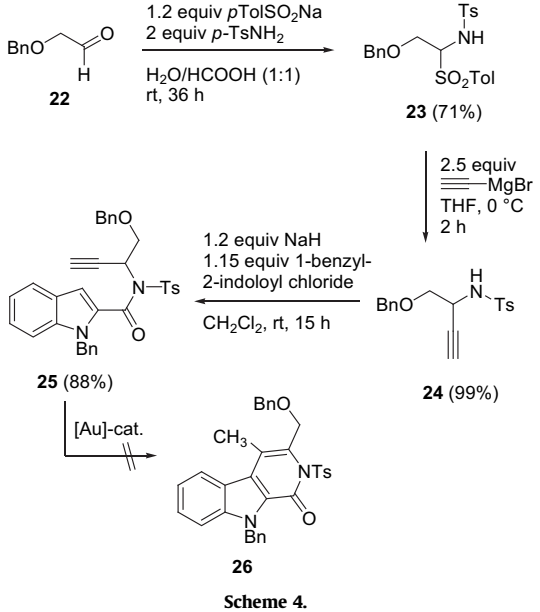


Scheme 2.

the yield of variously substituted β-carbolines. It was envisioned that polysubstituted β-carbolines of type **18** could be generated from the corresponding β-carbolinones **19**. Starting from tosyl amine **21**, we intended to prepare the requisite indole-2-carboxamide **20** by making use of its reaction with 2-indoloyl chloride and this would be followed by a subsequent cycloisomerization using $AuCl_3$ (Scheme 3). To test this possibility, the synthesis of 2-furylpropargylamine **21a** was first carried out according to literature procedures.[16] However, the desired coupling of **21a** with *N*-benzyl-2-indoloyl chloride did not give the corresponding amide **20a** (R^1=Bn, R^3=2-furyl). Other standard coupling procedures using DCC or isobutyl chloroformate only resulted in the recovery of the starting propargylamine. The less sterically hindered amine **21b** was next studied and this compound was prepared by reaction of 2-benzyloxyacetaldehyde (**22**) with *p*-tosyl amine and sodium *p*-toluenesulfinate.[17] The resulting imine precursor **23** was then treated with 2.5 equiv of ethynylmagnesium bromide to give 2-benzyloxymethylpropargylamine **24**, which was subsequently coupled with 1-benzyl-2-indoloyl chloride to produce amide **25** in 88% yield. Unfortunately, treatment of the *N*-propargylamide **25** with $AuCl_3$ did not give any of the desired β-carbolinone **26**. Other gold and platinum catalysts (i.e., Au(I)Cl, Au(I)PPh_3Cl, $PtCl_2$) were examined to promote this reaction, but no cycloisomerized product could be obtained (Scheme 4). However, we did find that the reaction of amine **21c**[18] with indoloyl chloride afforded amide **27** in 64% yield and further treatment of **27** with catalytic $AuCl_3$ produced the cyclized compound **28** (Scheme 5). For the synthesis of 9-benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline (**29**), β-carbolinone **28** was first subjected to detosylation using sodium naphthalenide and the resulting NH-pyridone was then treated with $POCl_3$ (Scheme 5). This reaction sequence afforded β-carboline **29** in 22% yield, which is clearly unsatisfactory for the development of a new synthetic method to prepare polysubstituted β-carbolines. Therefore, various reaction conditions were evaluated in order to enhance the yield of the cyclized β-carboline **29**. While the yield of the detosylation reaction of **28** to **29** using 2.5 or 5 equiv of sodium naphthalenide, sodium azide[19] in DMF or THF was not enhanced, the reaction of **28** in neat $POCl_3$ at 150 °C in a pressure vessel gave 1-chloro-β-carboline **29** in 69% yield after purification via silica gel chromatography. Use of higher temperatures only resulted in a significant increase in the amount of tarry by-products. Having now established a straightforward synthesis of β-carboline **29**, further efforts were carried out in order to further functionalize the β-carboline skeleton. For example, an oxidation of **29** to produce β-carbolinoxide **30** could easily open up an entry to the interesting 3-hydroxymethyl-β-carboline **31** via a Boekelheide rearrangement.[20] However, in complete contrast to what had been observed with related 2-chloropyridines,[21] β-carboline **29** proved to be quite resistant toward oxidation. While the reaction of **29** with $KMnO_4$, (urea)–H_2O_2, SeO_2, oxone or dimethyldioxirane only gave recovered starting material, the use of mCPBA (6 equiv) in $CHCl_3$ at 70 °C did give carbolinoxide **30** (80% conversion) after 48 h, but only if the mCPBA was added in small portions every 12 h. Although carbolinoxide **30** could be isolated in 57% yield after silica gel chromatography, the desired Boekelheide rearrangement to β-carboline **31** did not occur upon treatment with acetic anhydride or trifluoroacetic anhydride.

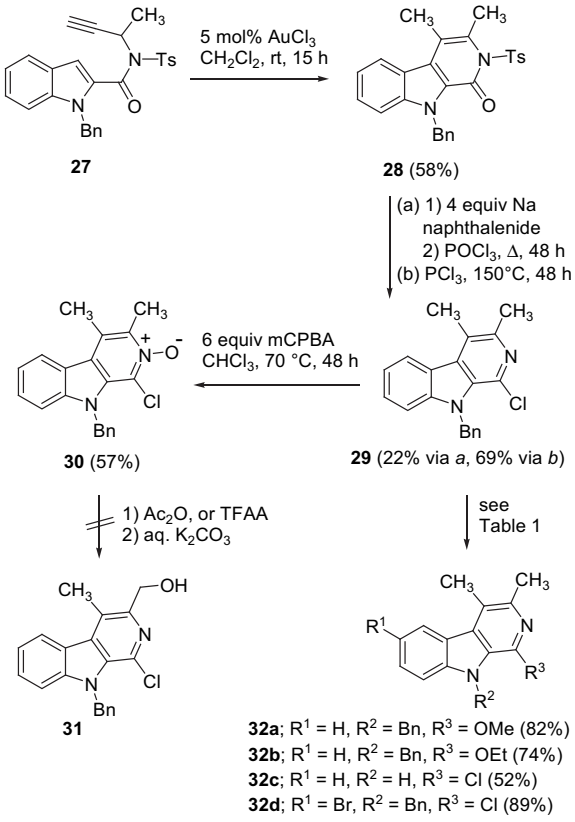


Scheme 3.



Scheme 4.

We next evaluated the reaction of 1-chloro-β-carboline **29** with several nucleophiles and electrophiles. It was found that the nucleophilic displacement of the chlorine atom at C-1 occurred easily by treating **29** with a 1 M solution of sodium methoxide (or ethoxide) in methanol (or ethanol) and DMSO (ratio methanol/DMSO=1:1), which gave the 1-alkoxy-β-carbolines **32a** or **32b** in good yield. The analogous reaction of **29** with amines (isopropylamine or morpholine) only led to a complex mixture of products,



Scheme 5.

while the use of a poor nucleophile, such as sodium azide, TBAF or KCN in DMSO or MeOH, gave recovered starting material. In order to evaluate the reactivity of β-carboline **29** toward electrophiles, this compound was treated with bromine in $CHCl_3$ at room temperature. Under these conditions a clean reaction occurred producing 6-bromocarboline **32d** as the exclusive product in 89% yield. Finally, in an attempt to carry out a Friedel–Crafts arylation, 1-chloro-β-carboline **29** was allowed to react with 1,4-dimethoxybenzene in the presence of $AlCl_3$, which led to the formation of the debenzylated β-carboline **32c** in 47% yield. A control experiment demonstrated that β-carboline **29** could also be easily debenzylated into **32c** in 52% yield by heating it in dichloroethane in the presence of AlCl3 (Table 1). This debenzylation is similar to some related cases reported in the literature using substituted indoles.[22]

In conclusion, an optimized procedure was developed to synthesize substituted 9-benzyl-1-chloro-β-carbolines, which are of some interest as core structures of various natural products. The key step consists of a gold(III) catalyzed 6-*exo-dig* cyclization of indole-substituted *N*-propargylamides, which afforded the corresponding β-carbolinones. The resulting β-carbolin-1-ones were further transformed into several substituted β-carbolines by treatment with $POCl_3$ or PCl_3. The reaction of 1-chloro-β-carbolines with alkoxides, bromine or $AlCl_3$ furnished new 1-alkoxycarbolines **32a**,**b**, 6-bromocarboline **32d**, and the debenzylated 1-chloro-carboline **32c**, respectively.

Table 1
Functionalization of 9-benzyl-1-chloro-3,4-dimethyl-β-carboline **29** to give β-carbolines **32**

Entry	Conditions	Product
1	10 equiv 1 M NaOMe in MeOH/DMSO (1:1), Δ, 15 h	**32a**
2	10 equiv 1 M NaOEt in EtOH/DMSO (1:1), Δ, 15 h	**32b**
3	2 equiv $AlCl_3$, dichloroethane, Δ, 15 h	**32c**
4	1.2 equiv Br_2, 1.2 equiv NaOAc, $CHCl_3$, rt, 5 h	**32d**

3. Experimental

3.1. General

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Solvents (THF, benzene, toluene) were dried over sodium benzophenone ketyl or calcium hydride (CH_2Cl_2) and distilled prior to use. Unless otherwise noted, all reactions were performed in flame-dried glassware under dry atmosphere ($CaCl_2$ tube). All solids were recrystallized form ethyl acetate/hexane for analytical data.

3.2. Synthesis of 9-benzyl-1-chloro-4-methyl-9H-β-carboline (17)

*3.2.1. N-(1-Benzyl-1H-indole-2-carbonyl)-4-methyl-N-prop-2-ynyl-benzenesulfonamide (**14**).* To a stirred solution of 0.5 g (2.0 mmol) of 1-benzyl-1*H*-indole-2-carboxylic acid (**13**) in 8 mL of benzene containing two drops of *N*,*N*-dimethylformamide was added 0.26 mL (2.0 mmol) of oxalyl chloride. The resulting solution was stirred at rt for 3 h, the solvent was removed under reduced pressure, and the residue was taken up in 10 mL of CH_2Cl_2. To this solution was added 1 mL of pyridine and 0.41 g (2 mmol) of 4-methyl-*N*-prop-2-ynyl-benzenesulfonamide, dissolved in 3 mL of CH_2Cl_2. The solution was allowed to stir at rt overnight. The solution was then quenched with water and extracted with CH_2Cl_2. The combined organic layer was washed with 10% HCl and brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.72 g (80%) of **14** as a pale yellow oil; IR (neat) 3290, 3060, 2924, 2127, 1673, 1596, 1514, 936, and 815 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (t, 1H, J=2.4 Hz), 2.45 (s, 3H), 4.55 (d, 2H, J=2.8 Hz), 5.49 (s, 2H), 7.01 (m, 2H), 7.22 (m, 4H), 7.34 (m, 5H), 7.74 (d, 1H, J=8.0 Hz), and 7.90 (d, 2H, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.9, 38.5, 47.9, 73.9, 78.9, 110.7, 111.0, 121.4, 123.2, 125.9, 126.2, 127.2, 127.8, 128.9, 129.1, 129.7, 129.9, 135.7, 137.9, 139.5, 145.3, and 163.9; HRMS Calcd for $[C_{26}H_{22}N_2O_3S+H^+]$: 443.1424. Found: 443.1425.

*3.2.2. 9-Benzyl-4-methyl-2-(toluene-4-sulfonyl)-2,9-dihydro-β-carbolin-1-one (**15**).* A 0.44 g (1 mmol) sample of indole **14** was stirred with 15 mg of Au(III) chloride in 10 mL of CH_2Cl_2 at rt overnight. At the end of this time, the mixture was filtered through a plug of silica gel, washed with triethylamine, rinsed with ethyl acetate, and the filtrate was concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.36 g (82%) of carbolinone **15** as a white solid; mp 181–182 °C; IR (neat) 3107, 3063, 2925, 1668, 1598, 1366, 1174, 1089, and 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.60 (d, 3H, J=0.8 Hz), 5.93 (s, 2H), 7.01 (m, 2H), 7.12 (m, 3H), 7.22 (m, 1H), 7.34 (m, 4H), 7.72 (d, 1H, J=1.2 Hz), 8.00 (d, 2H, J=8.4 Hz), and 8.06 (d, 1H, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 21.9, 48.1, 111.5, 113.4, 120.1, 121.3, 122.3, 123.2, 125.8, 126.0, 127.2, 127.4, 127.5, 128.7, 129.6 129.7, 134.9, 137.9, 141.1, 145.6, and 154.7; Anal. Calcd for $C_{26}H_{22}N_2O_3S$: C, 70.59; H, 4.98; N, 6.33. Found: C, 70.43; H,4.82; N,6.45.

*3.2.3. 9-Benzyl-4-methyl-2,9-dihydro-β-carbolin-1-one (**16**).* To a solution of 25 mg (0.06 mmol) of 9-benzyl-4-methyl-2-(toluene-4-sulfonyl)-2,9-dihydrocarbolin-1-one (**15**) in 2 mL of dry THF was added a 1.3 M solution of sodium naphthalenide (freshly prepared from sodium metal and naphthalene) in 1,2-dimethoxyethane at −78 °C until the green color persisted for more than 2 min. The solution was stirred for 30 min at −78 °C and then quenched with a saturated aqueous solution of NH_4Cl. After the addition of 5 mL of water, the mixture was extracted with CH_2Cl_2 and the extracts were dried over $MgSO_4$. After filtration and evaporation of the solvent, the crude product was subjected to flash silica gel chromatography

to give 13 mg (82%) of 9-benzyl-4-methyl-2,9-dihydro-β-carbolin-1-one (**16**) as a white solid; mp 256–258 °C; IR (neat) 2965, 2939, 1644, 1622, 1456, 1435, 744, and 700 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 2.53 (s, 3H), 6.12 (s, 2H), 6.91 (s, 1H), 7.23 (m, 6H), 7.43 (t, 1H, J=7.2 Hz), 7.62 (d, 1H, J=8.8 Hz), 8.11 (d, 1H, J=8.4 Hz), and 11.38 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.2, 48.1, 111.2, 113.1, 120.5, 121.9, 122.9, 123.2, 126.4, 126.6, 126.8, 127.2, 127.4, 128.8, 138.6, 140.5, and 157.0; Anal. Calcd for $C_{19}H_{16}N_2O$: C, 79.17; H, 5.56; N, 9.72. Found: C, 79.28; H, 5.46; N, 9.78.

*3.2.4. 9-Benzyl-1-chloro-4-methyl-9H-β-carboline (**17**).* A 0.29 g (1 mmol) sample of 9-benzyl-4-methyl-2,9-dihydro-β-carbolin-1-one (**16**) in 5 mL of $POCl_3$ was heated at reflux for 24 h. The solution was slowly quenched with a saturated aqueous solution of $NaHCO_3$, and then extracted with EtOAc. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The crude residue was subjected to flash silica gel chromatography to give 0.23 g (76%) of carboline **17** as an off-white solid; mp 157–159 °C; IR (neat) 3033, 1616, 1562, 1496, 1444, 1060, 954, and 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.79 (s, 3H), 5.96 (s, 2H), 7.04 (m, 2H), 7.22 (m, 3H), 7.32 (t, 1H, J=8.0 Hz), 7.42 (d, 1H, J=8.4 Hz), 7.56 (t, 1H, J=8.4 Hz), 7.99 (s, 1H), and 8.20 (d, 1H, J=8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 47.9, 110.6, 120.9, 121.9, 123.7, 126.2, 127.2, 127.6, 128.7, 129.0, 130.7, 131.2, 132.1, 137.9, 139.0, and 142.3; Anal. Calcd for $C_{19}H_{15}N_2Cl$: C, 74.39; H, 4.89; N, 9.14. Found: C, 74.45; H, 4.78; N, 8.99.

3.3. Synthesis of *N*-(1-benzyl-1*H*-indole-2-carbonyl)-*N*-(1-benzyloxymethylprop-2-ynyl)-4-methylbenzenesulfonamide (25)

*3.3.1. N-[2-Benzyloxy-1-(toluene-4-sulfonyl)ethyl]-4-methylbenzenesulfonamide (**23**).* A solution of 2.12 g (12 mmol) of sodium *p*-toluenesulfinate hydrate, 3.41 g (20 mmol) of *p*-toluenesulfonamide, and 1.50 g (10 mmol) of 2-benzyloxyacetaldehyde **22** in 30 mL of formic acid and 30 mL of water was stirred for 36 h at room temperature. The white solids formed were filtered, washed with water (2×20 mL) and hexane (20 mL), and subsequently dissolved in 100 mL of CH_2Cl_2 and dried over $MgSO_4$. After filtration and evaporation of 90% of the solvent, 150 mL of Et_2O was added resulting in the precipitation of (2-benzyloxy-1-toluenesulfonylethyl)-4-toluenesulfonamide **23** as a white solid, which was further purified by recrystallization from EtOAc to give 3.2 g (71%) of pure **23**; mp 115–116 °C; IR 3263, 1597, 1453, 1321, 1162, 1129, and 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 2.41 (s, 3H), 3.60 (dd, 1H, J=4.1 Hz, J=10.8 Hz), 4.07 (dd, 1H, J=3.2 Hz, J=10.8 Hz), 4.37 (d, 1H, J=11.9 Hz), 4.42 (d, 1H, J=11.9 Hz), 4.63 (ddd, 1H, J=3.2 Hz, J=4.1 Hz, J=10.1 Hz), 5.60 (d, 1H, J=10.1 Hz), 7.13–7.16 (m, 3H), 7.17 (d, 2H, J=7.9 Hz), 7.23 (d, 2H, J=7.9 Hz), 7.28–7.32 (m, 2H), 7.57 (d, 2H, J=8.3 Hz), and 7.64 (d, 2H, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.8, 21.9, 66.0, 72.9, 73.7, 127.1 (2×), 128.0 (2×), 128.1, 128.6 (2×), 129.7 (2×), 129.8 (2×), 129.9 (2×), 133.4, 136.8, 137.5, 144.0, and 145.5.

*3.3.2. N-(1-Benzyloxymethylprop-2-ynyl)-4-methylbenzenesulfonamide (**24**).* To a solution of 1.00 g (2.18 mmol) of hemiaminal **23** in 5 mL of dry THF was added 11.0 mL (5.5 mmol) of a 0.5 M solution of ethynylmagnesium bromide in THF at −78 °C under N_2 atmosphere. The solution was stirred for 1 h at −78 °C, followed by 1 h at 0 °C. After quenching with brine, the mixture was acidified to pH 4 using 1 M aqueous HCl. The aqueous mixture was then extracted with EtOAc and the extracts were dried over $MgSO_4$, filtered, and the solvents evaporated under reduced pressure to give 0.72 g (99%) of 2-benzyloxymethyl-*N*-tosylprop-2-ynamine **24** as a white solid; mp 48–49 °C; IR 3281, 2119, 1598, 1454, 1409, 1333, 1162, and 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.11 (d, 1H, J=2.5 Hz), 2.40 (s, 3H), 3.57 (d, 2H, J=4.7 Hz), 4.26 (ddt, 1H, J=2.5 Hz, J=4.7 Hz, J=8.4 Hz), 4.52 (s, 2H), 5.09 (d, 1H, J=8.4 Hz), 7.25–7.36 (m, 7H), and 7.76 (d, 2H, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 45.4, 71.8, 73.1, 73.3, 79.9, 127.5 (2×), 127.8 (2×), 127.9, 128.5 (2×), 129.5 (2×), 137.2, 137.3, and 143.6.

*3.3.3. N-(1-Benzyl-1H-indole-2-carbonyl)-N-(1-benzyloxymethylprop-2-ynyl)-4-methylbenzenesulfonamide (**25**).* To a suspension of 0.29 g (1.15 mmol) of *N*-benzylindole-2-carboxylic acid in 8 mL of dry benzene was added one drop of DMF, followed by 0.15 mL (1.52 mmol) of oxalyl chloride at rt. The solution was stirred at rt for 3 h, the solids were filtered and the filtrate was evaporated under reduced pressure to give the crude 2-indoloyl chloride, which was used as such without purification. To a suspension of 48 mg (1.2 mmol) of a 60 wt % suspension of NaH in mineral oil in 2.5 mL of dry CH_2Cl_2 was added a solution of 0.33 g (1.0 mmol) of 2-benzyloxymethyl-*N*-tosylprop-2-ynamine **24** in 2.5 mL CH_2Cl_2 at 0 °C. After stirring for 30 min at 0 °C a solution of the previously prepared *N*-benzyl-2-indoloyl chloride in 5 mL of CH_2Cl_2 was added to the reaction mixture and stirring was continued overnight allowing the temperature to reach rt. After quenching with brine and addition of 5 mL of 1 M aqueous HCl, the mixture was extracted with CH_2Cl_2. After drying and evaporation of the solvents, the crude residue was subjected to flash silica gel chromatography to yield 0.5 g (0.88 mmol, 88%) of pure *N*-(1-benzylindole-2-carbonyl)-*N*-(1-benzyloxymethylprop-2-ynyl)-4-methyl-benzenesulfonamide **25** as a sticky oil; IR 2120, 1676, 1515, 1454, 1356, 1246, 1169, and 1090 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.44 (d, 1H, J=2.2 Hz), 3.88 (dd, 1H, J=6.0 Hz, J=10.0 Hz), 4.01 (dd, 1H, J=8.3 Hz, J=10.0 Hz), 4.48 (d, 1H, J=11.8 Hz), 4.50 (d, 1H, J=11.8 Hz), 5.36–5.40 (m, 1H), 5.38 (s, 2H), 7.02–7.05 (m, 2H), 7.06 (s, 1H), 7.11–7.33 (m, 13H), 7.59 (d, 1H, J=7.9 Hz), and 7.76 (d, 2H, J=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 47.9, 51.8, 70.9, 73.3, 74.1, 79.1, 111.0, 111.3, 121.1, 122.9, 125.7, 125.9, 126.9 (2×), 127.4, 127.9 (2×), 128.5 (2×), 128.6 (2×), 128.8 (2×), 129.4 (2×), 131.0, 136.3, 137.5, 139.4, 144.8, and 164.0.

3.4. Synthesis of 3,4-dimethyl-β-carbolines 29 and 32

*3.4.1. N-(1-Benzyl-1H-indole-2-carbonyl)-4-methyl-N-(1-methylprop-2-ynyl)benzenesulfonamide (**27**).* *N*-(1-Benzyl-1*H*-indole-2-carbonyl)-4-methyl-*N*-(1-methylprop-2-ynyl)benzenesulfonamide (**27**) was prepared analogously to the synthesis of indole **14**. Purification of the crude mixture was performed via flash silica gel chromatography (EtOAc/hexanes 1:4) yielding 64% of compound **27** as an off-white solid; mp 58–59 °C; IR 1672, 1515, 1454, 1351, and 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.58 (d, 3H, J=7.1 Hz), 2.35 (d, 1H, J=2.4 Hz), 2.42 (s, 3H), 5.05 (dq, 1H, J=7.1 Hz, J=2.4 Hz), 5.48 (s, 2H), 7.01–7.04 (m, 2H), 7.13–7.34 (m, 9H), 7.67 (d, 1H, J=8.3 Hz), and 7.74 (d, 1H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6, 21.7, 47.6 (2×), 72.6, 82.1, 110.7, 111.6, 121.1, 123.0, 125.8, 125.9, 126.9 (2×), 127.5, 128.6 (2×), 128.7 (2×), 129.4 (2×), 131.2, 136.2, 137.7, 139.6, 144.7, and 163.9; MS (ES^+) m/z (%) 457 ($M+H^+$, 100). Anal. Calcd for $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14. Found: C, 70.83; H, 5.18; N,6.01.

*3.4.2. 9-Benzyl-3,4-dimethyl-2-(toluene-4-sulfonyl)-2,9-dihydro-β-carbolin-1-one (**28**).* 9-Benzyl-3,4-dimethyl-2-(toluene-4-sulfonyl)-2,9-dihydro-β-carbolin-1-one (**28**) was prepared analogous to the synthesis of carbolinone **15**. Purification of the crude mixture was performed via recrystallization from EtOAc/hexanes (1:1) yielding 58% of compound **28** as a white solid; mp 142–143 °C; IR 1661, 1586, 1456, 1348, 1163, and 818 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.40 (s, 3H), 2.60 (s, 3H), 2.71 (s, 3H), 5.79 (s, 2H), 6.84–6.87 (m, 2H), 7.05–7.40 (m, 8H), 7.89 (d, 1H, J=8.3 Hz), and 8.13 (d, 1H, J=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.4, 19.1, 21.7, 47.4, 111.0,

114.1, 120.9, 121.9, 123.4, 124.5, 125.2, 126.9 (4×), 128.3 (2×), 128.6 (2×), 129.1 (2×), 130.5, 137.3, 137.6, 140.7, 144.5, and 157.1; MS (ES^+) *m*/*z* (%) 457 ($M+H^+$, 100). Anal. Calcd for $C_{27}H_{24}N_2O_3S$: C, 71.03; H, 5.30; N, 6.14. Found: C, 70.91; H, 5.13; N, 5.95.

*3.4.3. 9-Benzyl-1-chloro-3,4-dimethyl-9H-β-carboline (**29**).* A solution of 0.55 g (1.20 mmol) of 9-benzyl-3,4-dimethyl-2-(toluene-4-sulfonyl)-2,9-dihydro-β-carbolin-1-one (**28**) and 25 mL of PCl_3 was placed in a 50 mL-pressure vessel and sealed. The solution was heated to 150 °C for 48 h. After cooling, the excess PCl_3 was evaporated in vacuo and the resulting brown oil was redissolved in CH_2Cl_2, washed with brine and aqueous $NaHCO_3$. After drying ($MgSO_4$) and evaporation of the solvent, the obtained oil was subjected to gradient flash silica gel chromatography (EtOAc/hexanes 1:5–1:1) to yield 0.26 g (0.82 mmol, 69%) of 9-benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline (**29**) as a light brown solid; mp 156–157 °C; IR 1616, 1547, 1495, 1485, 1453, 1356, 1276, 1106, and 976 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 3H), 2.82 (s, 3H), 5.99 (s, 2H), 7.05–7.08 (m, 2H), 7.19–7.29 (m, 2H), 7.32 (t, 1H, *J*=7.8 Hz), 7.42 (d, 1H, *J*=7.8 Hz), 7.54 (t, 1H, *J*=7.8 Hz), and 8.29 (d, 1H, *J*=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.7, 21.5, 47.5, 110.2, 120.4, 121.6, 123.7, 124.8, 126.0 (2×), 127.3, 128.2, 128.7 (2×), 130.9, 131.2, 137.9 (2×), 142.4, and 145.4; MS (ES^+) *m*/*z* (%) 321/323 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{17}ClN_2$: C, 74.88; H, 5.34; N, 8.73. Found: C, 74.42; H, 5.30; N, 8.56.

*3.4.4. 9-Benzyl-1-methoxy-3,4-dimethyl-9H-β-carboline (**32a**).* To a solution of 0.05 g (0.16 mmol) of 9-benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline (**29**) in 0.8 mL of DMSO was added 0.8 mL (1.6 mmol) of 2 M NaOMe in MeOH and the mixture was heated to reflux temperature for 15 h. After cooling, the reaction mixture was poured in brine (2 mL) and extracted with ethyl acetate (5×2 mL). The combined organic fractions were washed with brine (3×10 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated and the crude residue was subjected to flash silica gel chromatography (EtOAc/hexanes/Et_3N 2:3:0.1) to yield 0.04 g (1.28 mmol, 82%) of 9-benzyl-1-methoxy-3,4-dimethyl-9*H*-β-carboline (**32a**) as a white solid; mp 140–141 °C; IR 1619, 1567, 1488, 1450, 1427, 1300, and 1192 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3H), 2.70 (s, 3H), 4.03 (s, 3H), 5.79 (s, 2H), 7.08–7.10 (m, 2H), 7.12–7.23 (m, 4H), 7.34 (d, 1H, *J*=8.3 Hz), 7.40–7.45 (m, 1H), and 8.21 (d, 1H, *J*=8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.6, 21.3, 48.5, 53.0, 110.2, 118.3, 119.4, 122.8, 123.2, 123.4, 126.6 (2×), 126.7, 127.2, 128.6 (2×), 129.7, 138.9, 141.0, 141.3, and 148.5; MS (ES^+) *m*/*z* (%) 316 ($M+H^+$, 100). Anal. Calcd for $C_{21}H_{20}N_2O$: C, 79.72; H, 6.37; N, 8.85. Found: C, 79.26; H, 6.74; N, 8.37.

*3.4.5. 9-Benzyl-1-ethoxy-3,4-dimethyl-9H-β-carboline (**32b**).* 9-Benzyl-1-ethoxy-3,4-dimethyl-9*H*-β-carboline (**32b**) was prepared analogous to the synthesis of carboline **32a**. Purification was performed by flash silica gel chromatography (EtOAc/hexanes/Et_3N 2:3:0.1) to yield 74% of 9-benzyl-1-ethoxy-3,4-dimethyl-9*H*-β-carboline (**32b**) as a white solid; mp 139–140 °C; IR 1619, 1564, 1489, 1458, 1449, 1379, 1349, 1297, 1180, and 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.31 (t, 3H, *J*=7.2 Hz), 2.56 (s, 3H), 2.72 (s, 3H), 4.49 (q, 2H, *J*=7.2 Hz), 5.84 (s, 2H), 7.08–7.11 (m, 2H), 7.13–7.24 (m, 4H), 7.37–7.47 (m, 2H), and 8.23 (d, 1H, *J*=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 15.6, 21.4, 48.5, 61.4, 110.1, 118.1, 119.4, 122.8, 123.2, 123.4, 126.6 (2×), 126.7, 127.1, 128.6 (2×), 129.8, 139.0, 141.2, 141.6, and 148.4; MS (ES^+) *m*/*z* (%) 330 ($M+H^+$, 100). Anal. Calcd for $C_{22}H_{22}N_2O$: C, 79.97; H, 6.71; N, 8.48. Found: C, 80.31; H, 7.08; N, 8.61.

*3.4.6. 1-Chloro-3,4-dimethyl-9H-β-carboline (**32c**).* To a solution of 0.20 g (0.62 mmol) of 9-benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline (**29**) in 3 mL of 1,2-dichloroethane was added 0.17 g (1.25 mmol) of $AlCl_3$ at 0 °C. The ice bath was removed and the solution was heated to reflux for 15 h under N_2 atmosphere. After cooling, brine (5 mL) was added carefully and the mixture was extracted with CH_2Cl_2 (3×5 mL). After washing with $NaHCO_3$ and brine, the mixture was dried over $MgSO_4$. After filtration, the solvents were evaporated and the oily residue was subjected to flash silica gel chromatography (EtOAc/hexanes 1:5) to yield 0.07 g (0.33 mmol, 52%) of 1-chloro-3,4-dimethyl-9*H*-β-carboline (**32c**) as an orange oil; IR 1623, 1555, 1494, 1459, 1372, 1327, 1280, 1110, 1080, and 731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.68 (s, 3H), 2.79 (s, 3H), 7.32 (ddd, 1H, *J*=8.2 Hz, *J*=5.1 Hz, *J*=3.2 Hz), 7.56–7.58 (m, 2H), 8.24 (d, 1H, *J*=8.2 Hz), and 8.36 (s(br), 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 21.6, 111.9, 120.7, 122.8, 123.9, 124.9, 128.4, 129.6, 130.6, 131.3, 140.6, and 145.8; MS (ES^+) *m*/*z* (%) 231/233 ($M+H^+$, 100).

*3.4.7. 9-Benzyl-6-bromo-1-chloro-3,4-dimethyl-9H-β-carboline (**32d**).* To a solution of 0.10 g (0.31 mmol) of 9-benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline (**29**) in 2 mL of $CHCl_3$ was added 31 mg (0.37 mmol) of NaOAc and 60 mg of Br_2 at rt. The mixture was stirred for 15 h at rt, poured in aq satd $NaHCO_3$, and extracted with CH_2Cl_2. After drying ($MgSO_4$) and evaporation of the solvents, the crude mixture was subjected to flash silica gel chromatography (EtOAc/hexanes 2:3) to yield 0.11 g (0.28 mmol, 89%) of 9-benzyl-6-bromo-1-chloro-3,4-dimethyl-9*H*-β-carboline (**32d**) as a light yellow solid; mp 157–158 °C; IR 1601, 1547, 1496, 1461, 1449, 1422, 1346, 1293, 1275, and 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.65 (s, 3H), 2.70 (s, 3H), 5.88 (s, 2H), 6.98–7.00 (m, 2H), 7.17–7.26 (m, 4H), 7.58 (dd, 1H, *J*=8.8 Hz, *J*=2.2 Hz), and 8.30 (d, 1H, *J*=2.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.8, 21.5, 47.5, 111.8, 113.3, 123.3, 124.9, 126.0 (2×), 126.3, 127.6, 128.9 (2×), 129.1, 130.4, 131.1, 131.3, 137.4, 141.1, and 145.9; MS (ES^+) *m*/*z* (%) 398/400/402 ($M+H^+$, 100). Anal. Calcd for $C_{20}H_{16}BrN_2$: C, 60.10; H, 4.03; N, 7.01. Found: C, 59.65; H, 3.85; N, 6.69.

3.5. 9-Benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline-2-oxide (30)

To a solution of 0.50 g (1.56 mmol) of 9-benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline (**29**) in 20 mL of $CHCl_3$ was added 0.54 g (3.12 mmol) of mCPBA, which was purified prior to use by washing with a phosphate buffer solution (pH 7.5) and dried over $MgSO_4$. After heating the solution to 70 °C for 12 h, another portion of mCPBA (0.54 g, 3.12 mmol) was added and heating was continued. After 24 h, 0.54 g (3.12 mmol) of mCPBA was added again and the reaction mixture was further stirred for 24 h at 70 °C. After cooling, the mixture was poured in 50 mL of aq satd $NaHCO_3$ and extraction was performed with CH_2Cl_2 (3×30 mL). After drying ($MgSO_4$) and evaporation of the solvents, the crude mixture was subjected to gradient flash column chromatography (0–10% MeOH in CH_2Cl_2) to yield 0.30 g (0.89 mmol, 57%) of 9-benzyl-1-chloro-3,4-dimethyl-9*H*-β-carboline-2-oxide (**30**) as a white solid; mp 188 °C (decomp.); IR 1597, 1504, 1496, 1465, 1451, 1278, 1259, 1248, and 1183 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (s, 3H), 2.82 (s, 3H), 5.87 (s, 2H), 6.99–7.02 (m, 2H), 7.18–7.27 (m, 2H), 7.32 (t, 1H, *J*=7.8 Hz), 7.38 (d, 1H, *J*=7.8 Hz), 7.50 (t, 1H, *J*=7.8 Hz), and 8.19 (d, 1H, *J*=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.7, 16.9, 47.8, 110.2, 121.1, 121.3, 121.8, 123.0, 124.0, 124.6, 125.3, 125.9 (2×), 127.6, 127.7, 128.9 (2×), 132.1, 137.3, 140.9, and 143.1; MS (ES^+) *m*/*z* (%) 337/339 ($M+H^+$, 100).

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