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New approaches to the synthesis of canthin-4-one alkaloids and synthetic analogues

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Dedicated to Professor Rolf Huisgen on the occasion of his 95th birthday

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ABSTRACT

Two novel approaches to the canthin-4-one ring system have been worked out. Claisen-type condensation of 1-acetyl-β-carboline with *N*-acyl benzotriazoles gives, via intermediate 1,3-diketones, 6-alkylcanthin-4-ones in one single operation, but this protocol is restricted to small alkyl substituents. An alternative approach, via 1-ethynyl-β-carboline and 1-isoxazolyl-β-carbolines, followed by reductive isoxazole cleavage and cyclization, is more versatile. 5,6-disubstituted canthin-4-ones are accessible via iodination at C-5 and subsequent Pd-catalyzed cross-coupling.

1. Introduction

The canthin-4-one alkaloids represent a very small chemotype of natural products.[1] Until now only three representatives, tuboflavine (5-ethylcanthin-4-one), norisotuboflavine (**1a**, R=methyl), and isotuboflavine (**1b**, R=ethyl) have been found in nature.[2,3] Another one was claimed, but its structure was revised later to be a canthin-6-one.[4] Significant antimicrobial activities have been shown for the parent canthin-4-one and some of its derivatives.[5] Synthetic canthin-4-ones exhibit phosphodiesterase-inhibitory activity.[6] Further, canthin-4-ones were used as intermediates for the synthesis of antimicrobial polycyclic compounds.[5,7] Ring transformation reactions of canthin-4-ones with guanidinium salts give 1-(2-aminopyrimidin-4-yl)-β-carbolines, e.g. the anxiolytic alkaloid annomontine,[8,9] and its antimalarial analogue C-117.[10]

Multistep total syntheses with very poor overall yields have been worked out decades ago for confirmation of the structures of the three alkaloids.[11–13] Another multistep approach to the canthin-4-one backbone was published in a patent.[6] Later, our group developed a versatile approach to the canthin-4-one ring system (**1**) via a condensation of 1-acyl-β-carbolines (**A**) with amide acetals or Bredereck's reagent (*tert*-butoxy-bis(dimethylamino)methane) to give enaminoketones (**B**), which undergo cyclization under the reaction conditions[4,8] (Fig. 1).

The interesting biological activities of the canthin-4-ones prompted us to explore alternative approaches to this tetracyclic ring system, with the prospect of being able to perform diverse functionalizations on the ring system.

In a first approach we aimed at a modification of our reported protocol by substitution of the orthocarboxylic acid derivatives (amide acetals and others) for easier accessible activated carboxylic acid derivatives. With these building blocks we intended to prepare 1,3-diketones (**C**) from 1-acyl-β-carbolines in a Claisen-type condensation. Cyclization of the diketones was expected to give the canthin-4-one scaffold (**1**). In a second approach we intended to find alternatives to the 1-acyl-β-carboline intermediates, since these are accessible only by using laborious methods (radical reactions,[8,14,15] organometallic chemistry[16]) or expensive organostannane building blocks.[17] 1-Isoxazolyl-β-carbolines (**D**) were considered as versatile intermediates, which should give primary enaminoketones (**E**) upon reductive ring cleavage,[18] and the latter were expected to cyclize to the canthin-4-one ring system in a similar manner as known for tertiary enaminoketone intermediates (**B**) (Fig. 1).

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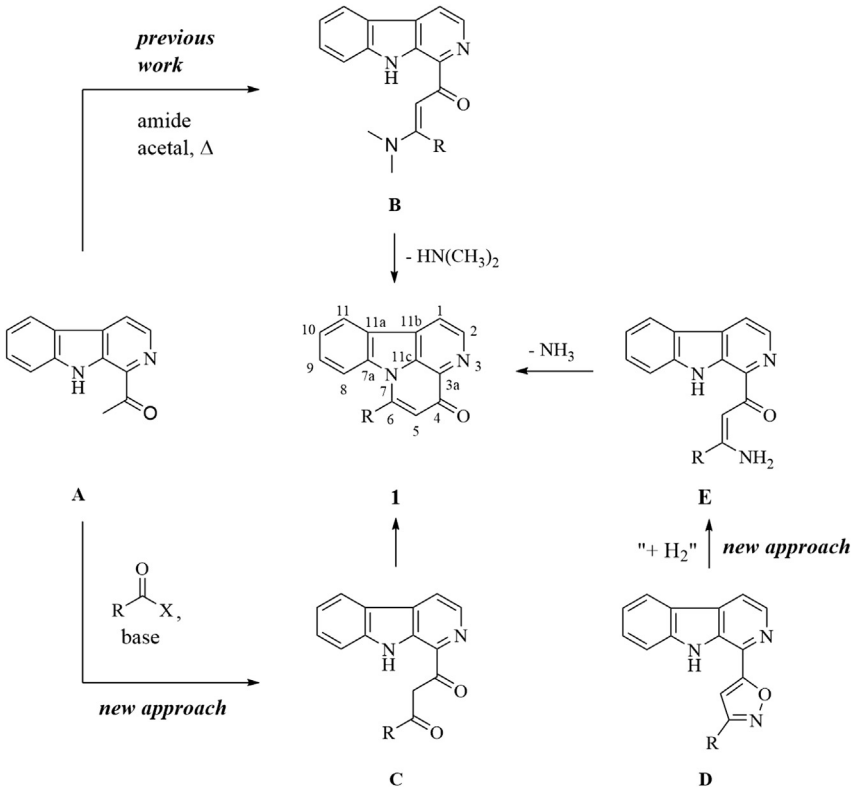
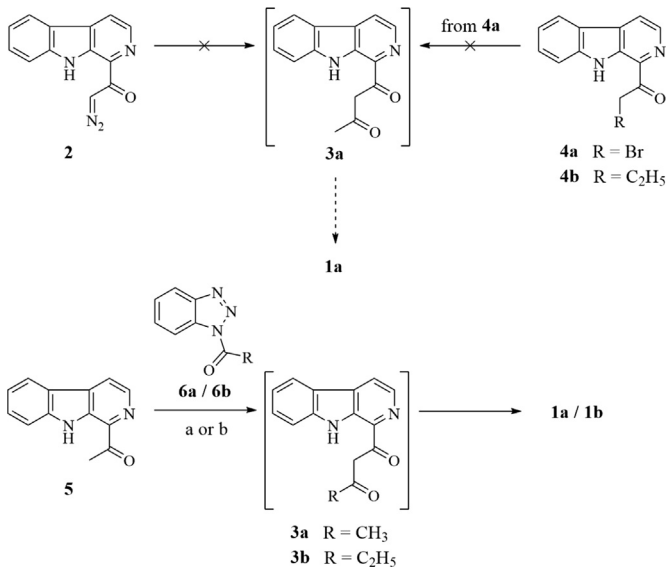


Fig. 1. Previous approach to canthin-4-ones (**A**→**B**→**1**), and two new approaches (**A**→**C**→**1**, **D**→**E**→**1**).

2. Results

2.1. 1,3-Diketone route

From previous investigations we had various 1-substituted β-carbolines in hand, which were considered as precursors for the desired 1,3-diketones. Due to anticipated troubles caused by the NH-acidic proton of the pyrrole partial structure of β-carboline precursors, we first investigated 1,3-diketone syntheses, which do not require the use of strong bases. Known diazoketone **2**[15] was reacted with acetaldehyde and $SnCl_2$ following a procedure of Padwa,[19] but complete decomposition was observed. Next, a 1,3-diketone synthesis starting from known α-bromoketone **4a**[15] and acetyl chloride, catalyzed by GaI_3[20] was explored. Under mild conditions no conversion was seen, upon heating the bromoketone decomposed, without giving any identifiable product (Scheme 1). Finally, we succeeded in preparation of norisotuboflavine (**1a**) in 34% yield by reacting 1-acetyl-β-carboline (**5**)[14,17] with *N*-acetylbenzotriazole (**6a**)[21,22] and 2 equiv of LDA in THF at 0–20 °C, obviously via the 1,3-diketone **3a**. In the same manner, alkaloid isotuboflavine (**1b**) was obtained from methyl ketone **5** and *N*-propanoylbenzotriazole (**6b**)[21] in 16% yield (Scheme 1). Significantly lower yields were obtained with the base *tert*-butyllithium. As an alternative we explored the 'soft enolization' protocol of Lim et al.[23] Thus, 1-acetyl-β-carboline (**5**) was reacted with the *N*-acylbenzotriazoles **6a**/**6b**, $MgBr_2 \cdot OEt_2$, and *i*-Pr_2NEt in CH_2Cl_2. No conversion was obtained under standard reflux conditions. However, a significant conversion was achieved under microwave irradiation at 70 °C, giving the alkaloids **1a** and **1b** in 34 and 16% yields. At higher temperatures and in other solvents (1,4-dioxane, diglyme) significant decomposition was observed. Unfortunately, this reaction was very sensitive to steric hindrance, and could not be extended to the synthesis of the corresponding 6-phenyl and 6-cyclopropyl analogues of the alkaloids.



Scheme 1. Approaches to 1,3-diketone intermediates and synthesis of alkaloids **1a**/**1b**. a) $MgBr_2 \cdot OEt_2$, *i*-Pr_2NEt, methylene chloride, microwave 100 W, 70 °C, 34%/16%; b) LDA, THF, 0 °C—rt, 34%/16%.

We also investigated, whether 5,6-disubstituted canthin-4-ones are accessible with this protocol. For this purpose condensation of 1-butanoyl-β-carboline (**4b**)[7] with *N*-acetylbenzotriazole (**6a**) was attempted. This experiment was unsuccessful, demonstrating another limitation of the 1,3-diketone route.

So the 1,3-diketone route provided a novel access to the alkaloids norisotuboflavine (**1a**) and isotuboflavine (**1b**), but was not generally applicable to the synthesis of variably substituted canthin-4-ones. Thus, we worked out an alternative approach to the desired scaffold.

2.2. Isoxazole route

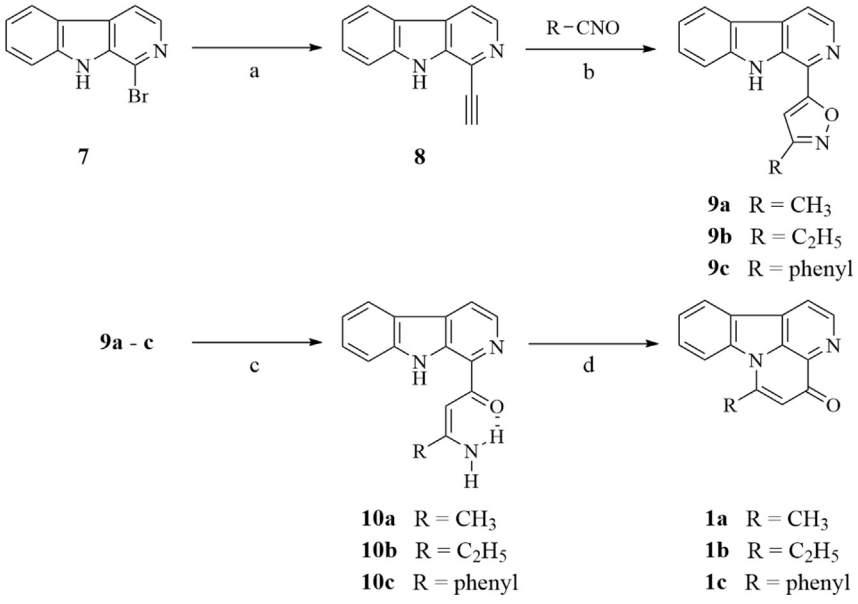
The above-mentioned examples indicated that 1,3-diketones are not versatile intermediates for the construction of the canthin-4-one ring system. So we turned back to enamine-type intermediates. Isoxazoles are readily available heterocyclic ring systems, which can be converted to primary enaminoketones by reductive cleavage.[18] Retrosynthetic analysis revealed that for our purpose (synthesis of 6-substituted canthin-4-ones) 3′-substituted 1-(isoxazol-5-yl)-β-carbolines **D** (Fig. 1) should be appropriate intermediates.

In a first attempt we intended to obtain isoxazol-5-yl-β-carbolines of type **D** by Pd-catalyzed coupling of 1-bromo-β-carboline (**7**)[16] and 3-substituted isoxazoles under CH-activation at C-5 of the isoxazole ring. Few examples of biaryl synthesis under CH-activation of C-4 of isoxazoles have been described in literature.[25] We first investigated this type of coupling in model reactions of 3-phenyl- and 3-ethylisoxazole[24] with bromobenzene. Unfortunately, we could not achieve any conversion with a broad panel of palladium catalysts and ligands, so this approach was abandoned.

Finally, the desired intermediates were conveniently obtained in a classical manner by 1,3-dipolar alkyne-nitrile oxide cycloaddition (Scheme 2).[18] The required 1-ethynyl-β-carboline (**8**) was obtained in excellent yield by Sonogashira coupling[26] of 1-bromo-β-carboline (**7**) with (trimethylsilyl)acetylene, followed by K_2CO_3-mediated desilylation.[27] Alkyne **8** was converted to the isoxazoles **9a**–**c** by cycloaddition with nitrile oxides, which in turn were prepared in situ by treatment of the oximes of acetaldehyde, propionaldehyde, and benzaldehyde with *N*-chlorosuccinimide (NCS).[18] Reductive cleavage of the isoxazoles **9a**–**c** to give the primary enaminoketones **10a**–**c** was accomplished in very high yield by Pd-catalyzed hydrogenation of the isoxazoles in ethanolic KOH solution.[28] Other reduction protocols (iron powder in acetic acid or aqueous HCl[29]) also worked well, but the catalytic hydrogenation procedure allowed the most convenient work-up procedure. In contrast to the tertiary enaminoketone intermediates **B** (Fig. 1) in our previous canthin-4-one synthesis[4,8] (Fig. 1) the obtained primary enaminoketones **10a**–**c** did not undergo spontaneous cyclization to the desired canthin-4-ones (**1a**–**c**). This is in contrast to the easy formation of quinolin-4(1*H*)-ones from primary enaminoketones attached to aminophenyl residues.[29,30] Probably, the *Z*-stereochemistry of the enaminoketones, arising from the pre-organization of the residues in the isoxazole ring, and stabilized by an intramolecular hydrogen bond, prevented nucleophilic attack of the pyrrole nitrogen at the enamine group. We investigated numerous reaction conditions and reagents for promoting the desired cyclization. Reaction with catalytic amounts of DBU in refluxing acetonitrile, a reagent used recently for a related cyclization,[31] was completely ineffective, even stoichiometric amounts of this base did not trigger the cyclization. So we intended to convert the *Z*-configured primary enaminoketone **10a** to an *E*-configured tertiary enaminoketone, related to the reactive intermediate **B** of the previous canthin-4-one synthesis (Fig. 1). Indeed, heating enaminoketone **10a** in piperidine at 125 °C for 40 h resulted in an almost quantitative cyclization to norisotuboflavine (**1a**). An analogous incubation with the tertiary amine *N*-methylpiperidine did not result in any conversion of the enaminoketone **10a**, clearly indicating that piperidine did not simply act as a base in the above-mentioned cyclization, but took part in the conversion in the sense of organocatalysis.[32] Similar yields (>90%) could also be obtained by heating enaminoketone **10a** in refluxing anhydrous DMF (bp 153 °C) or DMSO at 170 °C, but the significantly higher temperatures were indispensable for these non-catalyzed cyclizations. Obviously, these polar solvents are able to break up the intramolecular hydrogen bond of the enaminoketone moiety at very high temperature, and initiate cyclization under release of ammonia. Finally, we selected the procedure using refluxing DMF, since it allowed the most convenient work-up procedure.

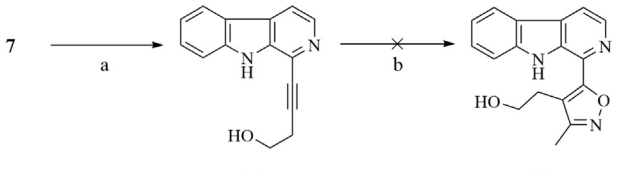
This new protocol gives 6-substituted canthin-4-ones **1a**–**c** in high yields starting from readily available 1-ethynyl-β-carboline (**8**) (Scheme 2). In contrast to the 1,3-diketone route this approach is suitable for introduction of the bulky phenyl residue at C-6. Further, this approach allowed the first high-yield total synthesis of alkaloid isotuboflavine (**1b**).

We further investigated whether this new protocol can also provide 5,6-disubstituted canthin-4-ones. For this purpose the internal alkyne 1-(4-hydroxybut-1-ynyl)-β-carboline (**11**) was prepared by Sonogashira coupling of 1-bromo-β-carboline (**7**) with 1-butyn-4-ol. Unfortunately, all attempts to convert this alkyne and acetonitrile oxide to a 3′,4′-disubstituted isoxazolyl-β-carboline **12**



Scheme 2. Synthesis of canthin-4-ones **1a**–**c** via isoxazoles. a) 1. (trimethylsilyl)acetylene, $Pd(dppf)_2Cl_2$, CuI, NEt_3, THF, rt; 2. K_2CO_3, methanol, rt, 88%; b) nitrile oxide generated in situ from oxime and NCS, pyridine, NEt_3, 1,1,2-trichloroethane, reflux, 40–63%; c) H_2, Pd/C, KOH, ethanol, rt, 75–99%; d) DMF, reflux, 90–96%.

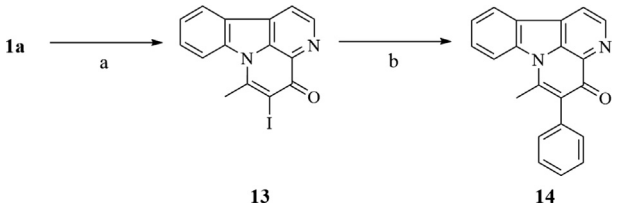
were unsuccessful (Scheme 3). Even the recently published *N*-heterocyclic carbene catalysis,[33] which has been reported to work well with 4-aryl-3-butyn-1-ols, was found to be ineffective. This lead us to the conclusion that the isoxazole route does not open a direct access to 5,6-disubstituted canthin-4-ones.



Scheme 3. Attempted synthesis of a 5,6-disubstituted canthin-4-one via an isoxazole. a) 3-butyn-1-ol, $Pd(dppf)_2Cl_2$, CuI, NEt_3, THF, reflux, 71%; b) acetaldehyde oxime, NCS, pyridine, NEt_3, 1,1,2-trichloroethane, reflux or acetaldehyde oxime, 1,3-di-*tert*-butylimidazolium tetrafluoroborate, NCS, NEt_3, methylene chloride, 0 °C to reflux.

2.3. Functionalization of a 6-substituted canthin-4-one at C-5

In order to find an approach to 5,6-disubstituted canthin-4-ones anyway, we worked out exemplarily a stepwise protocol. Norisotuboflavine (**1a**) was readily iodinated at C-5 with *N*-iodosaccharine in DMF.[34] Suzuki cross-coupling of the resulting iodocanthin-4-one **13** with phenylboronic acid gave the 5-phenyl derivative **14** in high yield (Scheme 4). This protocol opens the opportunity for preparing variably substituted canthin-4-ones in a modular synthesis.



Scheme 4. Synthesis of a 5,6-disubstituted canthin-4-one. a) *N*-iodosaccharine, DMF, 50 °C, 46%; b) phenylboronic acid, $Pd(Ph_3P)_4$, Cs_2CO_3, 1,2-dimethoxyethane-ethanol-H_2O, reflux, 93%.

3. Discussion

We have worked out two novel approaches to the canthin-4-one ring system. The '1,3-diketone route' starting from 1-acetyl-β-carboline (**5**) and utilizing *N*-acylbenzotriazoles (**6a**/**6b**) as acyl donors is limited to the synthesis of canthin-4-ones bearing small alkyl substituents at C-6, namely the alkaloids norisotuboflavine (**1a**) and isotuboflavine (**1b**). The 'isoxazole route', starting with a 1,3-dipolar cycloaddition of readily available 1-ethynyl-β-carboline (**8**) with nitrile oxides, followed by reductive opening of the isoxazole ring and thermal cyclization, gave the desired 6-substituted canthin-4-ones **1a**–**c** in high overall yields. An approach to 5,6-disubstituted canthin-4-ones is disclosed via iodination of a 6-substituted canthin-4-one at C-5, followed by Suzuki cross-coupling. This modular synthesis of variably substituted canthin-4-ones will be applied to the synthesis of a compound library for further evaluation of the biological activity of substituted canthin-4-ones.

4. Experimental section

4.1. General information

All solvents used were of HPLC grade or p.a. grade and/or purified according to standard procedures. Chemical reagents were purchased from Sigma Aldrich (Schnelldorf, Germany), ABCR (Karlsruhe, Germany) and Acros (Geel, Belgium). IR measurements were performed with a Perkin Elmer FTIR Paragon 1000 spectrometer. All melting points were determined by open tube capillary method on a Büchi melting point B-450 apparatus and are uncorrected. NMR spectra were recorded on Jeol JNMR-GX 400 (400 MHz), Jeol JNMR-GX 500 (500 MHz), Avance III HD Bruker BioSpin (400 MHz) and Avance III HD Bruker BioSpin (500 MHz) spectrometers. NMR spectra were recorded in deuterated solvents and chemical shifts are reported in parts per million (ppm). *J* values are given in hertz. Multiplicities are abbreviated as follows: s=singlet, d=doublet, t=triplet, m=multiplet. Signal assignments were carried out based on ^1H, ^{13}C, DEPT, HSQC or HMQC, HMBC and COSY spectra. Mass spectra (MS) were run by chemical impact (CI) or electron impact (EI) at 70 eV using a Hewlett Packard 5989A mass spectrometer with 59980B Particle Beam LC/MS. High-resolution mass spectra were performed by electron impact (EI) at 70 eV on a Jeol GCmate II or on a Finnigan MAT 95 spectrometer. Microwave-accelerated reactions were carried out with a Discovery single-mode microwave reactor. All reactions were monitored by thin-layer chromatography (TLC) using precoated plastic sheets POLYGRAM® SIL G/UV254 from Macherey–Nagel (Düren, Germany). Compounds on TLC plates were detected under UV light at 254 and 366 nm. Chromatographic purification of products was performed by using flash column chromatography (FCC) on Merck silica gel 60 as stationary phase. Solutions were concentrated in vacuo on a Heidolph rotary evaporator.

4.2. Norisotuboflavine (1a) from 1-acetyl-β-carboline (5) ('soft enolization protocol')

1-Acetyl-β-carboline (**5**) (200 mg, 0.95 mmol) was added to a mixture of 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)ethan-1-one (**6a**) (306 mg, 1.90 mmol) and $MgBr_2 \cdot OEt_2$ (614 mg, 2.38 mmol) in methylene chloride (3 mL), followed by *i*-Pr_2NEt (0.46 mL, 2.85 mmol). The reaction mixture was heated in a sealed vial under microwave irradiation (100 W, 70 °C, 20 min). After cooling to rt water (30 mL) was added and the mixture was extracted with methylene chloride (3×15 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using 19:1 methylene chloride–methanol to give 76 mg of **1a** (0.32 mmol, 34% yield) as a pale yellow solid. Mp 298 °C (lit.[8] 294 °C), ^1H NMR (500 MHz, CD_2Cl_2): δ=8.96 (d, *J*=4.8 Hz, 1H, 2-H), 8.20 (ddd, *J*=7.7 Hz, 1.3 Hz, 0.7 Hz, 1H, 11-H), 8.12 (d, *J*=4.7 Hz, 1H, 1-H), 7.94 (dd, *J*=8.4 Hz, 0.8 Hz, 1H, 8-H), 7.69 (ddd, *J*=8.6 Hz, 7.4 Hz, 1.3 Hz, 1H, 9-H), 7.50 (dd, *J*=7.6 Hz, 0.8 Hz, 1H, 10-H), 6.35 (d, *J*=1.0 Hz, 1H, 5-H), 2.93 (d, *J*=1.0 Hz, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ=179.1 (C-4), 147.9 (C-6), 147.0 (C-2), 140.7 (C-7a), 139.2 (C-3a), 136.3 (C-11c), 134.0 (C-11b), 131.4 (C-9), 125.9 (C-11a), 125.0 (C-10), 124.2 (C-11), 118.6 (C-5), 118.2 (C-1), 115.0 (C-8), 21.6 (CH_3) ppm. IR: $\tilde{\nu}$=3429, 3063, 1634, 1610, 1561, 1496, 1468, 1438, 1429, 1289, 1220, 828, 759, 547 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=235 (16), 234 [$M^{+\bullet}$] (100), 205 (14), 168 (38), 103 (12), 67 (14). HRMS (EI): calcd for $C_{15}H_{10}N_2O$: 234.0793 [$M^{+\bullet}$]; found 234.0771.

4.3. Norisotuboflavine (1a) from 1-acetyl-β-carboline (5) ('hard enolization protocol')

To a suspension of 1-acetyl-β-carboline (**5**) (200 mg, 0.95 mmol) in THF (1 mL) at 0 °C was added 2.0 M LDA solution (1.04 mL, 2.08 mmol) and the resulting solution was stirred for 10 min. Subsequently a solution of 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl) ethan-1-one **6a** (179 mg, 1.11 mmol) in THF (0.5 mL) was added dropwise, and the mixture was stirred at 0 °C for 2 h and at rt for additional 15 h. Water (30 mL) was added and the mixture was

extracted with methylene chloride (3×15 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using 19:1 methylene chloride–methanol to give 76 mg of **1a** (0.32 mmol, 16% yield).

4.4. Norisotuboflavine (1a) from enaminoketone 10a in DMF

Under a nitrogen atmosphere **10a** (100 mg, 0.40 mmol) was dissolved in anhydrous DMF (5 mL) and the solution was refluxed for 15 h. After cooling to rt saturated NaCl solution (20 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using 19:1 methylene chloride–methanol to give 86 mg of **1a** (0.37 mmol, 92% yield).

4.5. Norisotuboflavine (1a) from enaminoketone 10a in piperidine

Under a nitrogen atmosphere **10a** (80 mg, 0.32 mmol) was dissolved in anhydrous piperidine (4 mL) and the solution was refluxed for 15 h. After cooling to rt saturated NaCl solution (20 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using 19:1 methylene chloride–methanol to give 67 mg of **1a** (0.29 mmol, 90% yield).

4.6. Isotuboflavine (1b) from 1-acetyl-β-carboline (5) ('soft enolization protocol')

Prepared from 1-acetyl-β-carboline **5** (200 mg, 0.95 mmol), 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)propan-1-one **6b** (333 mg, 1.90 mmol), $MgBr_2 \cdot OEt_2$ (614 mg, 2.38 mmol), and *i*-Pr_2NEt (0.46 mL, 2.85 mmol) in the same manner as described for **1a** in chapter 4.2 to give 38 mg of **1b** (0.15 mmol, 16% yield) as a pale yellow solid. Mp 268 °C (decomposition) (lit.[2] 263–265 °C), ^1H NMR (400 MHz, CD_2Cl_2): δ=8.95 (d, *J*=4.8 Hz, 1H, 2-H), 8.19 (ddd, *J*=7.7 Hz, 1.4 Hz, 0.7 Hz, 1H, 11-H), 8.11 (d, *J*=4.7 Hz, 1H, 1-H), 7.89 (d, *J*=8.5 Hz, 1H, 8-H), 7.69 (ddd, *J*=8.6 Hz, 7.4 Hz, 1.3 Hz, 1H, 9-H), 7.55–7.44 (m, 1H, 10-H), 6.39 (s, 1H, 5-H), 3.27 (q, *J*=7.3 Hz, 2H, CH_2), 1.51 (t, *J*=7.4 Hz, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ=179.1 (C-4), 153.2 (C-6), 146.8 (C-2), 140.2 (C-7a), 138.9 (C-3a), 136.3 (C-11c), 133.8 (C-11b), 131.3 (C-9), 125.8 (C-11a), 124.8 (C-10), 124.0 (C-11), 118.0 (C-1), 116.2 (C-5), 115.4 (C-8), 27.0 (CH_2), 12.4 (CH_3) ppm. IR: $\tilde{\nu}$=3431, 2967, 2365, 2345, 1645, 1612, 1496, 1469, 1429, 1284, 1217, 772 cm^{-1}. MS (CI): *m*/*z* (%)=249 [M^++H] (100), 169 (12). HRMS (EI): calcd for $C_{16}H_{12}N_2O$: 248.0950 [$M^{+\bullet}$]; found 248.0958.

4.7. Isotuboflavine (1b) from 1-acetyl-β-carboline (5) ('hard enolization protocol')

Prepared from 1-acetyl-β-carboline **5** (200 mg, 0.95 mmol), 2.0 M LDA solution (1.04 mL, 2.08 mmol), and 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)propan-1-one **6b** (194 mg, 1.11 mmol) in the same manner as described for **1a** in chapter 4.3 to give 38 mg of **1b** (0.15 mmol, 16% yield).

4.8. Isotuboflavine (1b) from enaminoketone (10b)

Prepared from **10b** (120 mg, 0.45 mmol) in anhydrous DMF (5 mL) in the same manner as described for **1a** in chapter 4.4 to give 107 mg of **1b** (0.43 mmol, 96% yield).

4.9. 6-Phenyl-4*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-one (1c) from enaminoketone (10c)

Prepared from **10c** (65 mg, 0.21 mmol) in anhydrous DMF (5 mL) in the same manner as described for **1a** in chapter 4.4 to give 56 mg of **1c** (0.19 mmol, 90% yield) as a pale yellow solid. Mp 216 °C, ^1H NMR (400 MHz, CD_2Cl_2): δ=9.02 (d, *J*=4.8 Hz, 1H, 2-H), 8.16–8.13 (m, 2H, 1-H, 11-H), 7.71–7.65 (m, 1H, 4′-H), 7.64–7.61 (m, 4H, 2′-H, 3′-H, 5′-H, 6′-H), 7.38 (td, *J*=7.5 Hz, 1.0 Hz, 1H, 10-H), 7.30 (ddd, *J*=8.6 Hz, 7.4 Hz, 1.4 Hz, 1H, 9-H), 6.46 (d, *J*=8.4 Hz, 1H, 8-H), 6.43 (s, 1H, 5-H) ppm. ^{13}C NMR (100 MHz, CD_2Cl_2): δ=178.7 (C-4), 149.0 (C-6), 147.2 (C-2), 140.2 (C-7a), 139.2 (C-3a), 136.2 (C-11c), 134.2 (C-11b), 133.4 (C-1′), 131.0 (C-4′), 130.7 (C-9), 129.5 (C-3′, C-5′), 129.3 (C-2′, C-6′), 125.7 (C-11a), 124.8 (C-10), 123.6 (C-11), 119.4 (C-5), 118.3 (C-1), 115.1 (C-8) ppm. IR: $\tilde{\nu}$=3441, 3059, 2362, 2345, 1643, 1616, 1557, 1490, 1469, 1449, 1426, 1333, 1290, 1263, 1210, 1166, 1130, 1033, 752, 702, 533 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=296 (100) [$M^{+\bullet}$], 166 (25). HRMS (EI): calcd for $C_{20}H_{12}N_2O$: 296.0950 [$M^{+\bullet}$]; found 296.0944.

4.10. 1-Ethynyl-9*H*-pyrido[3,4-*b*]indole (8)

To a mixture of **7** (600 mg, 2.43 mmol), $Pd(dppf)_2Cl_2$ (91 mg, 0.12 mmol) and CuI (93 mg, 0.49 mmol) in deoxygenated THF (5.5 mL) and triethylamine (7.5 mL) was added a solution of (trimethylsilyl)acetylene (0.38 mL, 2.69 mmol) in deoxygenated THF (2 mL) under a nitrogen atmosphere. The reaction mixture was stirred at rt for 30 min, then water (100 mL) was added and the mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification was accomplished by FCC using 1:4 hexanes–methylene chloride to give a white solid, which was subsequently dissolved in methanol (20 mL), K_2CO_3 (1.00 g, 7.28 mmol) was added, and the reaction mixture was stirred at rt for 1 h. After the addition of saturated NaCl solution (100 mL) the mixture was extracted with ethyl acetate (3×50 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure to give 411 mg of **8** (2.14 mmol, 88% yield) as slightly yellow solid. Mp 174 °C, ^1H NMR (400 MHz, CD_2Cl_2): δ=8.97 (s, 1H, NH), 8.44 (d, *J*=5.2 Hz, 1H, 3-H), 8.15 (d, *J*=7.9 Hz, 1H, 5-H), 7.98 (d, *J*=5.2 Hz, 1H, 4-H), 7.63–7.56 (m, 2H, 7-H, 8-H), 7.39–7.26 (m, 1H, 6-H), 3.60 (s, 1H, 2′-H) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ=140.8 (C-8a), 140.2 (C-3), 138.6 (C-9a), 129.5 (C-7), 129.3 (C-4a), 126.0 (C-1), 122.5 (C-5), 122.1 (C-4b), 121.0 (C-6), 115.7 (C-4), 112.3 (C-8), 82.5 (C-1′), 80.1 (C-2′) ppm. IR: $\tilde{\nu}$=3438, 3298, 3136, 3054, 1626, 1563, 1501, 1458, 1427, 1390, 1324, 1280, 1253, 1230, 1067, 1013, 914, 879, 845, 825, 733, 668, 627, 596, 568, 513 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=192 (100) [$M^{+\bullet}$]. HRMS (EI): calcd for $C_{13}H_8N_2$: 192.0688 [$M^{+\bullet}$]; found 192.0683.

4.11. 3-Methyl-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole (9a)

To a solution of *N*-chlorosuccinimide (69 mg, 0.52 mmol) and pyridine (6 μL, 0.08 mmol) in 1,1,2-trichloroethane (5 mL) was added acetaldehyde oxime (34 mg, 0.52 mmol) and the solution was stirred at 50 °C for 30 min. A solution of **8** (100 mg, 0.52 mmol) and triethylamine (0.08 mL, 0.57 mmol) in 1,1,2-trichloroethane (5 mL) was added dropwise. The mixture was stirred at 50 °C for 20 min and then heated to reflux for additional 3 h. After cooling to rt, water (30 mL) was added and the mixture was extracted with methylene chloride (3×15 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using 1:1 hexanes–ethyl acetate to give 80 mg of **9a** (0.32 mmol, 62% yield) as a pale yellow solid. Mp 184 °C, ^1H NMR (400 MHz, $CDCl_3$): δ=9.55 (s, 1H, NH), 8.53 (dd, *J*=5.1 Hz, 0.6 Hz, 1H, 3-H), 8.15 (dt, *J*=7.8 Hz,

0.7 Hz, 1H, 5-H), 8.01 (dd, *J*=5.1 Hz, 0.7 Hz, 1H, 4-H), 7.64–7.58 (m, 2H, 7-H, 8-H), 7.38–7.30 (m, 1H, 6-H), 6.94 (s, 1H, 4′-H), 2.46 (s, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.0 (C-5′), 160.7 (C-3′), 140.6 (C-8a), 139.2 (C-3), 132.8 (C-9a), 130.9 (C-4a), 130.0 (C-1), 129.2 (C-7), 121.8 (C-5), 120.9 (C-4b), 120.6 (C-6), 115.9 (C-4), 111.8 (C-8), 102.8 (C-4′), 11.6 (CH_3) ppm. IR: $\tilde{\nu}$=3316, 3100, 3057, 2927, 2361, 2342, 1717, 1629, 1612, 1560, 1496, 1448, 1426, 1374, 1319, 1300, 1285, 1260, 1226, 1126, 1067, 972, 881, 803, 797, 743, 624, 595, 561, 477 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=249 (100) [M$^{+\bullet}$], 180 (20). HRMS (EI): calcd for $C_{15}H_{11}N_3O$: 249.0902 [M$^{+\bullet}$]; found 249.0906.

4.12. 3-Ethyl-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole (9b)

Prepared from *N*-chlorosuccinimide (139 mg, 1.04 mmol), pyridine (12 μL, 0.16 mmol), propionaldehyde oxime (80 μL, 1.04 mmol), **8** (200 mg, 1.04 mmol), and triethylamine (0.16 mL, 1.15 mmol) in the same manner as described in chapter 4.11 to give 172 mg of **9b** (0.65 mmol, 63% yield) as a pale yellow solid. Mp 153 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.53 (s, 1H, NH), 8.52 (d, *J*=5.1 Hz, 1H, 3-H), 8.15 (d, *J*=7.9 Hz, 1H, 5-H), 8.00 (d, *J*=5.1 Hz, 1H, 4-H), 7.64–7.54 (m, 2H, 7-H, 8-H), 7.33 (ddd, *J*=8.0 Hz, 6.3 Hz, 1.7 Hz, 1H, 6-H), 6.99 (s, 1H, 4′-H), 2.84 (q, *J*=7.6 Hz, 2H, CH_2), 1.38 (t, *J*=7.6 Hz, 3H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=170.0 (C-5′), 166.2 (C-3′), 140.8 (C-8a), 139.3 (C-3), 132.9 (C-9a), 131.1 (C-4a), 130.2 (C-1), 129.3 (C-7), 121.9 (C-5), 121.1 (C-4b), 120.7 (C-6), 116.0 (C-4), 112.0 (C-8), 101.6 (C-4′), 19.7 (CH_2), 12.9 (CH_3) ppm. IR: $\tilde{\nu}$=3422, 3321, 3060, 2969, 2937, 1891, 1629, 1609, 1558, 1492, 1426, 1411, 1321, 1299, 1285, 1261, 1229, 1125, 1068, 975, 963, 833, 813, 742, 625, 598, 561 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=263 (100) [M$^{+\bullet}$], 248 (55). HRMS (EI): calcd for $C_{16}H_{13}N_3O$: 263.1059 [M$^{+\bullet}$]; found 263.1063.

4.13. 3-Phenyl-5-(9*H*-pyrido[3,4-*b*]indol-1-yl)isoxazole (9c)

Prepared from *N*-chlorosuccinimide (139 mg, 1.04 mmol), pyridine (12 μL, 0.16 mmol), (*E*)-benzaldehyde oxime (126 mg, 1.04 mmol), **8** (200 mg, 1.04 mmol), and triethylamine (0.16 mL, 1.15 mmol) in the same manner as described in chapter 4.11 to give 131 mg of **9c** (0.42 mmol, 40% yield) as a pale yellow solid. Mp 166 °C, ^{1}H NMR (500 MHz, CD_2Cl_2): δ=9.64 (s, 1H, NH), 8.54 (d, *J*=5.1 Hz, 1H, 3-H), 8.19 (d, *J*=7.9 Hz, 1H, 5-H), 8.06 (d, *J*=5.0 Hz, 1H, 4-H), 7.99–7.91 (m, 2H, 2″-H, 6″-H), 7.68–7.59 (m, 2H, 7-H, 8-H), 7.56–7.48 (m, 3H, 3″-H, 4″-H, 5″-H), 7.44 (s, 1H, 4′-H), 7.34 (ddd, *J*=8.0 Hz, 6.4 Hz, 1.7 Hz, 1H, 6-H) ppm. ^{13}C NMR (125 MHz, CD_2Cl_2): δ=171.3 (C-5′), 163.4 (C-3′), 141.2 (C-8a), 139.7 (C-3), 133.2 (C-9a), 131.3 (C-4a), 130.7 (C-4″), 130.3 (C-1), 129.6 (C-7), 129.4 (C-3″, C-5″), 129.2 (C-1″), 127.3 (C-2″, C-6″), 122.2 (C-5), 121.3 (C-4b), 121.0 (C-6), 116.4 (C-4), 112.3 (C-8), 100.3 (C-4′) ppm. IR: $\tilde{\nu}$=3424, 3230, 3058, 1653, 1630, 1611, 1557, 1493, 1441, 1399, 1323, 1286, 1229, 757, 739, 684, 566 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=311 (100) [M$^{+\bullet}$], 283 (15). HRMS (EI): calcd for $C_{20}H_{13}N_3O$: 311.1059 [M$^{+\bullet}$]; found 311.1063.

4.14. (*Z*)-3-Amino-1-(9*H*-pyrido[3,4-*b*]indol-1-yl)but-2-en-1-one (10a)

The isoxazole **9a** (150 mg, 0.60 mmol) was dissolved in ethanol (12 mL), and KOH (452 mg, 8.05 mmol) and palladium (10 wt. %) on activated carbon catalyst (25 mg) were added. The resulting mixture was hydrogenated at atmospheric pressure and rt for 3 h. The catalyst and salts were removed by washing the mixture through silica gel with 19:1 methylene chloride–methanol, evaporation of the eluate gave 151 mg of **10a** (0.60 mmol, 99% yield) as a yellow solid. Mp 195 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ=10.69 (s, 1H, NH), 10.24 (s, 1H, NH_2), 8.49 (d, *J*=5.0 Hz, 1H, 3-H), 8.14 (dd, *J*=7.9 Hz, 0.9 Hz, 1H, 5-H), 8.05 (dd, *J*=5.1 Hz, 0.7 Hz, 1H, 4-H), 7.60–7.53 (m, 2H, 7-H, 8-H), 7.29 (ddd, *J*=8.0 Hz, 5.5 Hz, 2.6 Hz, 1H, 6-H), 6.71 (d, *J*=1.5 Hz, 1H, 2′-H), 5.31 (s, 1H, NH_2), 2.16 (s, 3H, 4′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.4 (C-1′), 163.9 (C-3′), 141.1 (C-8a), 138.4 (C-1), 137.9 (C-3), 136.0 (C-9a), 131.2 (C-4a), 128.9 (C-7), 121.9 (C-5), 121.0 (C-4b), 120.2 (C-6), 117.4 (C-4), 111.9 (C-8), 92.2 (C-2′), 23.2 (C-4′) ppm. IR: $\tilde{\nu}$=3422, 3302, 3129, 2361, 2344, 1633, 1610, 1587, 1530, 1488, 1428, 1318, 1281, 1256, 1217, 1145, 1067, 806, 746, 638, 569, 537 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=251 (100) [M$^{+\bullet}$], 222 (60), 182 (75). HRMS (EI): calcd for $C_{15}H_{13}N_3O$: 251.1059 [M]$^+$; found 251.1060.

4.15. (*Z*)-3-Amino-1-(9*H*-pyrido[3,4-*b*]indol-1-yl)pent-2-en-1-one (10b)

Prepared from the isoxazole **9b** (145 mg, 0.55 mmol) in the same manner as described in chapter 4.14 to give 130 mg of **10b** (0.49 mmol, 89% yield) as a yellow solid. Mp 139 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.73 (s, 1H, NH), 10.33 (s, 1H, NH_2), 8.49 (d, *J*=5.0 Hz, 1H, 3-H), 8.13 (d, *J*=7.8 Hz, 1H, 5-H), 8.04 (d, *J*=5.0 Hz, 1H, 4-H), 7.58–7.51 (m, 2H, 7-H, 8-H), 7.28 (ddd, *J*=8.0 Hz, 5.6 Hz, 2.5 Hz, 1H, 6-H), 6.74 (s, 1H, 2′-H), 5.39 (s, 1H, NH_2), 2.41 (q, *J*=7.6 Hz, 2H, 4′-H), 1.29 (t, *J*=7.7 Hz, 3H, 5′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=190.5 (C-1′), 169.2 (C-3′), 140.9 (C-8a), 138.3 (C-1), 137.7 (C-3), 135.8 (C-9a), 131.0 (C-4a), 128.7 (C-7), 121.7 (C-5), 120.8 (C-4b), 120.0 (C-6), 117.2 (C-4), 111.8 (C-8), 90.7 (C-2′), 30.1 (C-4′), 12.3 (C-5′) ppm. IR: $\tilde{\nu}$=3423, 3057, 2973, 1718, 1609, 1528, 1491, 1454, 1426, 1341, 1317, 1282, 1250, 1216, 1142, 1065, 811, 754, 636 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=265 (100) [M$^{+\bullet}$], 250 (70), 236 (80), 222 (28), 168 (44). HRMS (EI): calcd for $C_{16}H_{15}N_3O$: 265.1215 [M$^{+\bullet}$]; found 265.1223.

4.16. (*Z*)-3-Amino-3-phenyl-1-(9*H*-pyrido[3,4-*b*]indol-1-yl) prop-2-en-1-one (10c)

Prepared from the isoxazole **9c** (111 mg, 0.36 mmol) in the same manner as described in chapter 4.14 to give 84 mg of **10c** (0.27 mmol, 75% yield) as a yellow solid. Mp 221 °C, ^{1}H NMR (500 MHz, $CDCl_3$): δ=10.74 (s, 1H, NH), 10.48 (s, 1H, NH_2), 8.51 (d, *J*=5.0 Hz, 1H, 3-H), 8.15 (d, *J*=7.8 Hz, 1H, 5-H), 8.07 (d, *J*=5.0 Hz, 1H, 4-H), 7.75 (dd, *J*=7.8 Hz, 1.8 Hz, 2H, 2″-H, 6″-H), 7.60–7.53 (m, 2H, 7-H, 8-H), 7.53–7.42 (m, 3H, 3″-H, 4″-H, 5″-H), 7.32–7.28 (m, 1H, 6-H), 7.20 (s, 1H, 2′-H), 5.60 (s, 1H, NH_2) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ=191.0 (C-1′), 163.2 (C-3′), 140.9 (C-8a), 138.3 (C-1), 137.8 (C-3), 137.3 (C-1″), 135.9 (C-9a), 131.1 (C-4a), 130.80 (C-4″), 129.0 (C-3″, C-5″), 128.7 (C-7), 126.5 (C-2″, C-6″), 121.7 (C-5), 120.8 (C-4b), 120.1 (C-6), 117.4 (C-4), 111.8 (C-8), 91.6 (C-2′) ppm. IR: $\tilde{\nu}$=3448, 3406, 3055, 2924, 1602, 1590, 1561, 1527, 1486, 1423, 1337, 1313, 1283, 1264, 1235, 1214, 1136, 1061, 812, 740 cm^{-1}. MS (EI, 70 eV): *m*/*z* (%)=313 (100) [M$^{+\bullet}$], 284 (95), 146 (39). HRMS (EI): calcd for $C_{20}H_{15}N_3O$: 313.1215 [M$^{+\bullet}$]; found 313.1225.

4.17. 4-(9*H*-Pyrido[3,4-*b*]indol-1-yl)but-3-yn-1-ol (11)

To a mixture of **7** (400 mg, 1.62 mmol), $Pd(dppf)_2Cl_2$ (59 mg, 0.08 mmol) and CuI (62 mg, 0.32 mmol) in deoxygenated THF (4.5 mL) and triethylamine (5 mL) was added a solution of 3-butyn-1-ol (0.15 mL, 1.94 mmol) in deoxygenated THF (0.5 mL) under a nitrogen atmosphere. The mixture was heated to reflux for 30 min. Then saturated NaCl solution (50 mL) was added and the mixture was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using ethyl acetate to give 272 mg of **11** (1.15 mmol, 71% yield) as a pale yellow solid. Mp 189 °C, ^{1}H NMR (500 MHz, DMSO-d_6): δ=11.59 (s, 1H, NH), 8.45–8.26 (m, 1H, 3-H), 8.23 (d, *J*=7.8 Hz, 1H, 5-H), 8.09 (d, *J*=4.6 Hz, 1H, 4-H), 7.64 (d, *J*=8.2 Hz, 1H, 8-H), 7.57 (ddd, *J*=8.1 Hz, 7.0 Hz, 0.9 Hz, 1H, 7-H), 7.26 (ddd, *J*=8.2 Hz, 7.1 Hz, 1.0 Hz, 1H, 6-H), 5.01 (t, *J*=5.7 Hz, 1H, OH), 3.74 (dt,

J=6.9 Hz, 5.7 Hz, 2H, 4′-H), 2.75 (t, J=6.9 Hz, 2H, 3′-H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ=140.6 (C-8a), 138.5 (C-3), 137.3 (C-9a), 128.5 (C-7), 127.7 (C-4a), 126.9 (C-1), 122.0 (C-5), 120.9 (C-4b), 119.7 (C-6), 114.6 (C-4), 112.2 (C-8), 93.2 (C-2′), 78.2 (C-1′), 59.6 (C-4′), 23.7 (C-3′) ppm. IR: $\tilde{\nu}$=3440, 2955, 2872, 2363, 2345, 2226, 1627, 1565, 1498, 1469, 1454, 1428, 1320, 1279, 1238, 1053, 743, 570 cm^{-1}. MS (EI, 70 eV): m/z (%)=236 (85) [M$^{+\bullet}$], 206 (100), 205 (95). HRMS (EI): calcd for $C_{15}H_{12}N_2O$: 236.0950 [M$^{+\bullet}$]; found 236.0952.

4.18. 5-Iodo-6-methyl-4*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-one (13)

To a solution of **1a** (240 mg, 1.03 mmol) in DMF (30 mL) was added *N*-iodosaccharine (634 mg, 2.05 mmol) and the resulting solution was stirred at 50 °C for 2 h. After cooling to rt water (50 mL) was added and the mixture was extracted with ethyl acetate (3×20 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using 3:1 methylene chloride–acetone to give 168 mg of **13** (0.47 mmol, 46% yield) as a yellow solid. Mp 216 °C, ^{1}H NMR (400 MHz, CD_2Cl_4): δ=9.02 (d, J=4.7 Hz, 1H, 2-H), 8.17 (dd, J=7.8 Hz, 1.3 Hz, 1H, 11-H), 8.11 (d, J=4.7 Hz, 1H, 1-H), 7.89 (d, J=8.5 Hz, 1H, 8-H), 7.74–7.67 (m, 1H, 9-H), 7.53 (t, J=7.5 Hz, 1H, 10-H), 3.37 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, CD_2Cl_4): δ=174.1 (C-4), 148.6 (C-6), 147.3 (C-2), 140.2 (C-7a), 134.5 (C-11c), 133.3 (C-3a, C-11b), 131.2 (C-9), 125.3 (C-10), 125.0 (C-11a), 123.8 (C-11), 117.9 (C-1), 115.2 (C-8), 99.4 (C-5), 27.9 (CH_3) ppm. IR: $\tilde{\nu}$=3428, 3065, 2923, 2361, 2345, 1620, 1602, 1526, 1486, 1465, 1436, 1415, 1328, 1287, 1257, 1198, 1164, 1137, 1044, 1010, 800, 745, 717, 595 cm^{-1}. MS (EI, 70 eV): m/z (%)=360 (100) [M$^{+\bullet}$], 233 (35). HRMS (EI): calcd for $C_{15}H_9IN_2O$: 359.9760 [M$^{+\bullet}$]; found 359.9765.

4.19. 6-Methyl-5-phenyl-4*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-one (14)

Under a nitrogen atmosphere **13** (110 mg, 0.31 mmol), tetrakis(triphenylphosphine)palladium(0) (36 mg, 0.31 mmol) and phenylboronic acid (45 mg, 0.367 mmol) were suspended in a deoxygenated 3:2 mixture of 1,2-dimethoxyethane and ethanol (4 mL). The reaction mixture was stirred at rt for 10 min, then deoxygenated 2.0 M aq Cs_2CO_3 solution (0.5 mL) was added and the mixture was heated to reflux for 15 h. After cooling to rt, water (20 mL) was added and the mixture was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried over Na_2SO_4 and the solvents were concentrated under reduced pressure. Purification was accomplished by FCC using 3:1 methylene chloride–acetone to give 88 mg of **14** (0.28 mmol, 93% yield) as a yellow solid. Mp 280 °C, ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.05 (d, J=4.8 Hz, 1H, 2-H), 8.20 (d, J=7.6 Hz, 1H, 11-H), 8.11 (d, J=4.8 Hz, 1H, 1-H), 7.98 (d, J=8.4 Hz, 1H, 8-H), 7.67 (ddd, J=8.6 Hz, 7.3 Hz, 1.4 Hz, 1H, 9-H), 7.54–7.45 (m, 3H, 10-H, 3′-H, 5′-H), 7.43–7.37 (m, 1H, 4′-H), 7.36–7.31 (m, 2H, 2′-H, 6′-H), 2.82 (s, 3H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ=177.4 (C-4), 146.8 (C-2), 144.7 (C-6), 140.9 (C-7a), 138.3 (C-3a), 135.2 (C-1′), 134.9 (C-11c), 133.4 (C-11b), 131.0 (C-9, C-2′, C-6′), 130.6 (C-5), 128.8 (C-3′, C-5′), 127.9 (C-4′), 125.5 (C-11a), 124.6 (C-10), 123.9 (C-11), 117.6 (C-1), 115.2 (C-8), 19.9 (CH_3) ppm. IR: $\tilde{\nu}$=3432, 3024, 2924, 1635, 1619, 1545, 1499, 1467, 1427, 1371, 1331, 1308, 1262, 1124, 1047, 1006, 812, 742, 724, 703, 574 cm^{-1}. MS (EI, 70 eV): m/z (%)=310 (100), 309 (55) [M$^{+\bullet}$]. HRMS (EI): calcd for $C_{21}H_{14}N_2O$: 310.1106 [M$^{+\bullet}$]; found 310.1102.

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References and notes

1. Review article on canthine alkaloids: Showalter, H. D. H. *J. Nat. Prod.* **2013**, *76*, 455–467.
2. Achenbach, H.; Biemann, K. *J. Am. Chem. Soc.* **1965**, *87*, 4177–4181.
3. Kump, C.; Seibl, J.; Schmid, H. *Helv. Chim. Acta* **1963**, *46*, 498–505.
4. Wetzel, I.; Allmendinger, L.; Bracher, F. *J. Nat. Prod.* **2009**, *72*, 1908–1910.
5. Puzik, A.; Bracher, F. *Lett. Org. Chem.* **2013**, *10*, 568–572.
6. Ohashi, M.; Nishida, H.; Shudo T. US 6,467,021 B1, 2002.
7. Puzik, A.; Bracher, F. *J. Heterocycl. Chem.* **2010**, *47*, 449–453.
8. Puzik, A.; Bracher, F. *J. Heterocycl. Chem.* **2009**, *46*, 770–773.
9. Rejón-Orantes, J. C.; González-Esquinca, A. R.; Mora, M. P. *Planta Med.* **2011**, *77*, 322–327.
10. Kern, S.; Agarwal, S.; Huber, K.; Gehring, A. P.; Ströddke, B.; Wirth, C. C.; Brügl, T.; Abodo, L. O.; Dandekar, T.; Doerig, C.; Fischer, R.; Tobin, A. B.; Alam, M. M.; Bracher, F.; Pradel, G. *PLoS One* **2014**, *9*, e105732.
11. Rosenkranz, H. J.; Botyos, G.; Schmid, H. *Liebigs Ann. Chem.* **1966**, *691*, 159–164.
12. Rosenkranz, H. J.; Schmid, H. *Helv. Chim. Acta* **1968**, *51*, 565–568.
13. McEvoy, F. J.; Allen, G. R. *J. Org. Chem.* **1969**, *34*, 4199–4201.
14. Bracher, F.; Daab, J. *Synth. Commun.* **1995**, *25*, 1557–1562.
15. Bracher, F.; Puzik, A. *J. Heterocycl. Chem.* **2004**, *41*, 173–176.
16. Bracher, F.; Hildebrand, D. *Tetrahedron* **1994**, *50*, 12329–12336.
17. Bracher, F.; Hildebrand, D. *Liebigs Ann. Chem.* **1993**, 837–839.
18. Review article: Pinho e Melo, T. M. V. D. *Curr. Org. Chem.* **2005**, *9*, 925–958.
19. Padwa, A.; Hornbuckle, S. F.; Zhang, Z.; Zhi, L. *J. Org. Chem.* **1990**, *55*, 5297–5299.
20. Chen, R.; Wu, H.; Zhang, Y. *J. Chem. Res., Synop.* **1999**, 666–667.
21. Katritzky, A. R.; Zhang, Y.; Singh, S. K. *Synthesis* **2003**, 2795–2798.
22. For an overview on benzotriazole-mediated synthesis of heterocycles, see: Katritzky, A. R.; Rachwal, S. *Chem. Rev.* **2011**, *111*, 7063–7120.
23. Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139–4142.
24. Rosa, F. A.; Machado, P.; Bonacorso, H. G.; Zanatta, N.; Martins, M. A. P. *J. Heterocycl. Chem.* **2008**, *45*, 879–885.
25. For an overview, see: Roger, J.; Gottumukkala, A. L.; Doucet, H. *ChemCatChem* **2010**, *2*, 20–40.
26. Crosignani, S.; Prêtre, A.; Jorand-Lebrun, C.; Fraboulet, G.; Seenisamy, J.; Augustine, J. K.; Missotten, M.; Humbert, Y.; Cleva, C.; Abla, N.; Daff, H.; Schott, O.; Schneider, M.; Burgat-Charvillon, F.; Rivron, D.; Hamernig, I.; Arrighi, J.-F.; Gaudet, M.; Zimmerli, S. C.; Juillard, P.; Johnson, Z. *J. Med. Chem.* **2011**, *54*, 7299–7317.
27. Caddick, S.; Delisser, V. M.; Doyle, V. E.; Khan, S.; Avent, A. G.; Vile, S. *Tetrahedron* **1999**, *55*, 2737–2754.
28. Scott, J. W.; Saucy, G. *J. Org. Chem.* **1972**, *37*, 1652–1658.
29. Coffman, K. C.; Palazzo, T. A.; Hartley, T. P.; Fettinger, J. C.; Tantillo, D. J.; Kurth, M. J. *Org. Lett.* **2013**, *15*, 2062–2065.
30. Sakamoto, T.; Kondo, Y.; Uchiyama, D.; Yamanaka, H. *Tetrahedron* **1991**, *47*, 5111–5118.
31. Casuscelli, F.; Ardini, E.; Avanzi, N.; Casale, E.; Cervi, G.; D'Anello, M.; Donati, D.; Faiardi, D.; Ferguson, R. D.; Fogliatto, G.; Galvani, A.; Marsiglio, A.; Mirizzi, D. G.; Montemartini, M.; Orrenius, C.; Piutti, G. P. C.; Salom, B.; Felder, E. R. *Bioorg. Med. Chem.* **2013**, *21*, 7364–7380.
32. For an example of organocatalysis by a cyclic secondary amine, see: Morales, S.; Guijarro, F. G.; Ruano, J. L. G.; Cid, M. B. *J. Am. Chem. Soc.* **2014**, *136*, 1082–1089.
33. Kankala, S.; Vadde, R.; Vasam, C. S. *Org. Biomol. Chem.* **2011**, *9*, 7869–7876.
34. Dolenc, D. *Synlett* **2000**, 544–546.