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Baylis–Hillman Reaction of 1-Formyl-β-carboline: One-Step Synthesis of the Canthin-6-one Framework by an Unprecedented Cascade Cyclization Reaction

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Dedicated to Dr. A. P. Bhaduri

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A one-step access to the canthin-6-one architecture by the Baylis–Hillman reaction of methyl 1-formyl-9*H*-β-carboline-3-carboxylate or 1-formyl-9*H*-β-carboline involving an unprecedented cascade cyclization reaction is reported.

Introduction

The Baylis–Hillman (BH) reaction is one of the most efficient and atom economic C–C bond-forming reactions that has a propensity to afford adducts with high functional diversity. These adducts or their derivatives have been demonstrated to be viable precursors for a myriad of applications leading to the synthesis of heterocycles, drug intermediates and natural products.[1] Heterocyclic electrophiles, which may undergo fast BH reactions, are a fruitful addition to the substrate base as their derivatives offer opportunities for intramolecular reactions leading to annulated frameworks.[2] The β-carboline core is a key structural motif of a variety of natural products and pharmaceutical agents.[3] As a continuation of our interest in exploring the use of new heterocyclic aldehydes for the BH reaction, we disclose herein the interesting BH reactions of methyl 1-formyl-9*H*-β-carboline-3-carboxylate and 1-formyl-9*H*-β-carboline, which directly lead to the formation of the canthin-6-one skeleton in one step by an unprecedented cascade cyclization reaction.

Canthin-6-ones are a subclass of β-carboline-based natural alkaloids in which an additional D ring is present (Figure 1). First isolated from *Pentacerase australis* in 1952 by Nelson and co-workers,[4] more than 40 such alkaloids have now been reported in the literature.[5] These alkaloids are reported to have several pharmacological activities, including anti-fungal, anti-HIV, anti-bacterial, anti-tumour and anti-malarial activity.[6] As a result, several elegant strategies involving Diels–Alder, Pictet–Spengler, intramolecular Wittig or other reactions have been developed for their synthesis.[7] We envisaged that the BH adduct of 1-formyl-9*H*-β-carboline would be an obvious substrate for constructing the canthine framework. The retrosynthetic analysis outlined in Figure 2 provides the basis for this work. Cleavage of the D ring of the canthin-6-one skeleton **I** or the canthine skeleton **II** leads to the BH adduct **III**, which can be generated from methyl 1-formyl-9*H*-β-carboline-3-carboxylate or 1-formyl-9*H*-β-carboline (**IV**).

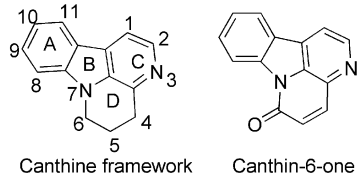

Figure 1. Canthine and canthin-6-one frameworks.

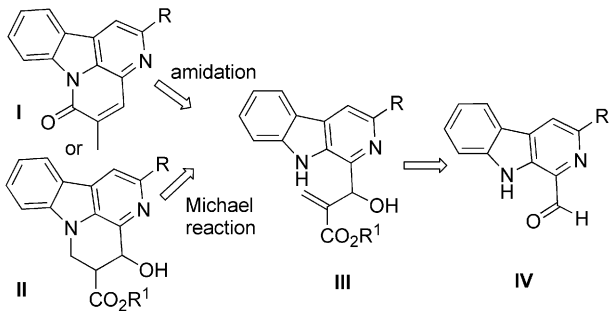

Figure 2. Retrosynthetic analysis of the canthine and canthin-6-one frameworks.

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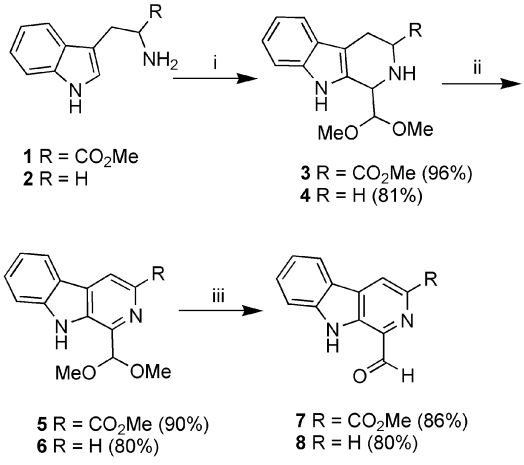
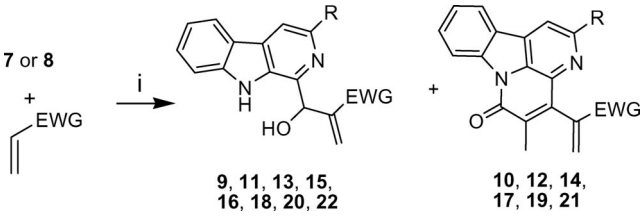
Results and Discussion

The first objective of this study was to access methyl 1-formyl-9*H*-β-carboline-3-carboxylate and 1-formyl-9*H*-β-carboline. A search through the literature revealed that these aldehydes have been synthesized by diverse strategies.[8] In response to our requirement, however, we engineered a modified protocol for obtaining this aldehyde on a large scale. Our method commenced with the Pictet–Spengler reaction of tryptophan methyl ester with dimethoxyglyoxal (60% solution in water) to afford the tetrahydro-β-carboline derivative **3** in a yield of 96% and in good purity (Scheme 1). Oxidation of **3** with $KMnO_4$ at room temperature overnight resulted in acetal **5** (90%).[9] Deprotection of the formyl group with aqueous AcOH gave the required methyl 1-formyl-9*H*-β-carboline-3-carboxylate in 86% yield. More importantly, in this three-step synthesis at no stage was any purification required and reactions could be scaled-up to obtain 10 g of the aldehyde. Subsequently, a similar series of reactions employing tryptamine as the starting material yielded the required aldehyde **8**. Compared with the reaction of tryptophan methyl ester, with tryptamine, each step in the reaction sequence was sluggish and gave slightly lower yields.



Scheme 1. Synthesis of the 1-formyl-9*H*-β-carbolines **7** and **8**. Reagents and conditions: i. $OHCCH(OMe)_2$, 5% TFA in CH_2Cl_2, room temp., 15 h for **1**, 3 d for **2**; ii. $KMnO_4$, dry THF, room temp., 15 h for **3**, 5 d for **4**; iii. $AcOH/H_2O$ (2:3), 120 °C, 45 min.

With aldehydes **7** and **8** in hand, we started to investigate their BH reactions. The optimization studies were performed with **7** as the test compound and methyl acrylate as the alkene in the presence of DABCO. A mixture of aldehyde **7** (1.0 equiv.), methyl acrylate (20 equiv.) and DABCO (1.5 equiv.) was stirred at room temperature. The reaction was complete in 8 h, but the TLC analysis indicated the presence of two products. Chromatographic purification afforded a polar compound as the major product in 55% yield and a non-polar compound, which was isolated in 10% yield (Table 1). Spectroscopic analysis of the major product indicated it to be the required adduct **9**. However the ^1H NMR spectrum of the minor product displayed a singlet signal arising from methyl protons along with signals from the methoxycarbonyl and the methylene groups, but the signal from the hydroxy group was missing. The IR spectrum indicated the presence of an amide group as well as the ester moiety. Therefore, to establish the structure of this product detailed 2D NMR experiments were conducted. Based on HMBC and HSQC experiments coupled with HRMS data, we assigned the structure of the minor product to **10** (Scheme 2). The formation of **10**, a canthin-6-one derivative, indicated that during the BH reaction, a side-reaction may occur leading to a cascade cyclization. Following this observation **7** was subjected to the BH reaction with ethyl acrylate Although this reaction was slow, being completed in 13 h, here too derivative **12** was isolated in 8% yield as a minor product in addition to the adduct **11** (54%).



Scheme 2. Baylis–Hillman reaction of **7** and **8** with acrylates. Reagents and conditions: i. DABCO, room temp. (see Table 1).

Table 1. Effect of the amount of DABCO on the BH reaction and isolated yields of the corresponding products.

Aldehyde	EWG	DABCO [equiv.]	Time [h]	Product	
				BH adduct (yield [%])	Canthin-6-one (yield [%])
7	CO_2Me	1.5	8	**9** (55)	**10** (10)
7	CO_2Et	1.5	13	**11** (54)	**12** (13)
7	CO_2Me	5	20	–	**10** (59)
7	CO_2Et	5	60	–	**12** (60)
7	CO_2nBu	5	48	**13** (38)	**14** (30)
7	CO_2nBu	5	72	–	**14** (67)
7	CO_2tBu	5	80	**15** (72)	–
8	CO_2Me	1.5	27	**16** (60)	**17** (10)
8	CO_2Et	1.5	72	**18** (55)	**19** (13)
8	CO_2Me	5	120	**16** (8)	**17** (57)
8	CO_2Et	5	120	**18** (10)	**19** (59)
8	CO_2nBu	5	120	**20** (10)	**21** (64)
8	CO_2tBu	5	120	**22** (88)	–

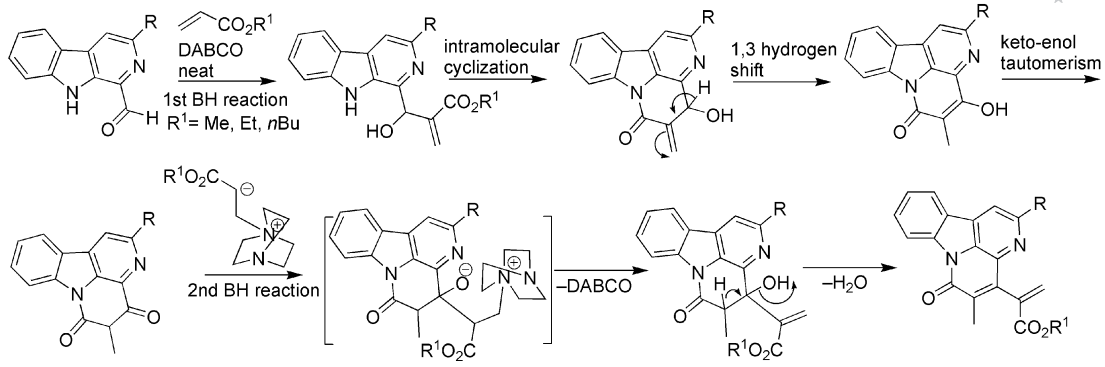


Figure 3. Possible mechanism for the formation of canthin-6-one.

Encouraged by these results we investigated the BH reactions of aldehyde **8** (Scheme 2) with methyl and ethyl acrylate in the presence of 1.5 equiv. of DABCO. Compared with the reaction of **7**, the reactions of **8** proceeded slowly, although it was pleasing to note that here too, besides the BH adducts **16** and **18**, canthin-6-one derivatives **17** and **19** were isolated in 10 and 13% yields, respectively.

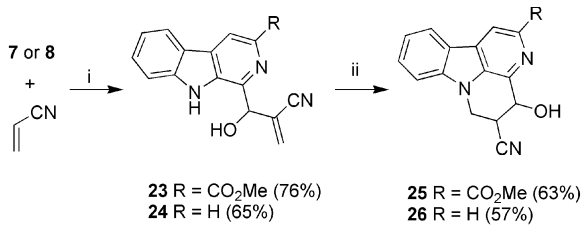
These results encouraged us to seek experimental conditions in which the canthin-6-one derivative was formed exclusively. Consequently, in a representative study, several combinations of **7**, methyl acrylate and DABCO were screened over different timescales. In the presence of 5.0 equiv. of DABCO the reaction between **7** and methyl acrylate in neat conditions was complete in 20 h, yielding **10** (59%) as the sole product.

To assess the general application of this protocol, aldehydes **7** and **8** were treated with methyl, ethyl, *n*-butyl and *tert*-butyl acrylates. We observed that, with the exception of *tert*-butyl acrylate, the corresponding canthin-6-one derivatives were isolated in good yields (Table 1). In the reactions with *tert*-butyl acrylate only the corresponding BH adducts (**15** and **22**) were obtained. Furthermore, the reactions of **8** were observed to be sluggish and were therefore allowed to proceed for 5 d.

Based on these observations we have proposed a possible mechanism for the formation of the canthin-6-one skeleton (Figure 3). It is assumed that the formation of the amide bond takes place ahead of the elimination of DABCO during the first BH reaction. This is followed by a 1,3-hydrogen shift and keto-enol rearrangement leading to an intermediate that undergoes a second BH reaction to produce the isolated product. Furthermore, we believe this cyclization to be highly concerted because once the adduct is isolated it fails to react further with the alkene to form the canthin-6-one framework.

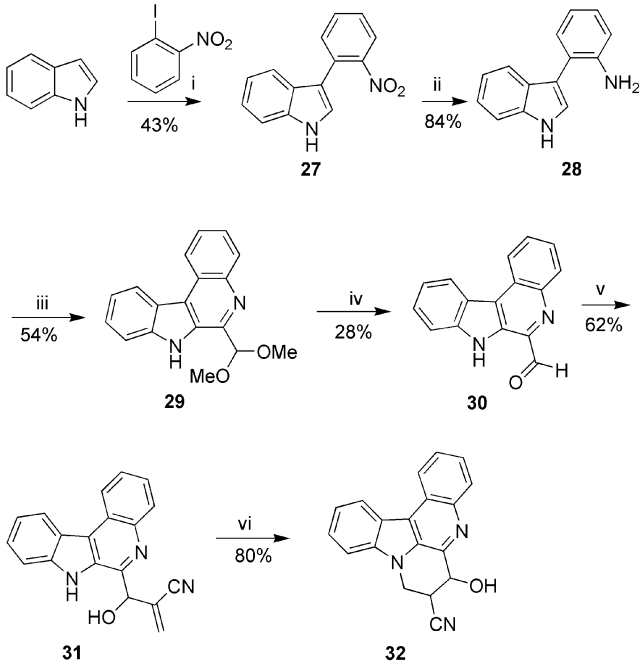
Next we examined the BH reaction of **7** and **8** with acrylonitrile. This reaction was observed to be complete in 3–5 h in the presence of 1.0 equiv. of DABCO, giving the desired adducts **23** and **24** (Scheme 3). Extending the reaction time led to polymerization. Treatment of **23** and **24** with K_2CO_3 in DMF at room temperature smoothly gave the canthine products **25** and **26** by an intramolecular Michael reaction.

To produce more diverse products by this chemistry we generated a new aldehyde (**30**) by sequential Heck



Scheme 3. Formation of canthine derivatives. Reagents and conditions: i. DABCO, room temp., 3 h for **23**, 5 h for **24**; ii. K_2CO_3, DMF, room temp., 30 min for **25**, 3 h for **26**.

reaction,[10a] reduction and Pictet–Spengler reaction (Scheme 4). The BH reaction of **30** with acrylonitrile followed by intramolecular reaction of the adduct **31** furnished the new canthine analogue **32**.[10b]



Scheme 4. Reagents and conditions: i. $Pd(OAc)_2$, K_2CO_3, 1,4-dioxane, N_2, 110 °C, 24 h; ii. Fe/AcOH, N_2, 80 °C, 1.5 h; iii. $OHCCH(OMe)_2$, 2% TFA in CH_2Cl_2, room temp., 24 h; iv. TFA/H_2O (1:1), MeCN, 80 °C, 5 h; v. CH_2=CHCN, DABCO, neat, room temp., 2 h; vi. K_2CO_3, DMF, room temp., 1 h.

Conclusions

In this report we have disclosed a new application of the BH reaction for the facile synthesis of canthin-6-one and canthine frameworks bearing functional groups for further derivatization.

Experimental Section

Melting points were determined in capillary tubes with a Precision melting point apparatus containing silicon oil and are uncorrected. IR spectra were recorded using a Perkin–Elmer RX I FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded with either a Bruker DPX-200 FT or an Avance DRX-300 spectrometer using TMS as the internal standard (chemical shifts in δ). ESMS were recorded with a MICROMASS Quadro-II LCMS system. HRMS were recorded as EI-HRMS with a JEOL spectrometer or as DART-HRMS (recorded as ES$^+$) with a JEOL-AccuTOF JMS-T100LC spectrometer equipped with a DART (Direct Analysis in Real Time) source. Elemental analyses were performed with a Carlo Erba 108 or an Elementar Vario EL III microanalyser. Room temperature varied between 21 and 35 °C.

General Procedure for the Synthesis of Compounds 10, 12, 14, 17, 19 and 21, as Exemplified for Compound 10: Methyl acrylate (2.66 mL, 29.5 mmol) was added to a mixture of **7** (0.40 g, 1.57 mmol) and DABCO (0.88 g, 7.87 mmol), and the mixture was stirred at room temperature for 20 h. After completion of the reaction, as monitored by TLC, the mixture was poured into water (35 mL) and EtOAc (50 mL) was added and the organic layer was partitioned. The aqueous layer was further extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (70 mL), dried with anhydrous Na_2SO_4 and evaporated to yield a solid residue which was further purified by silica gel (60–120 mesh) column chromatography using hexane/EtOAc as eluent [80:20, R_f = 0.38 (hexane/ethyl acetate, 70:30, v/v)] to afford **10** (0.35 g from 0.40 g, 59%) as a light-yellow solid.

Methyl 4-(3-Methoxy-3-oxoprop-1-en-2-yl)-5-methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (10): Yield: 59% (0.35 g from 0.40 g), m.p. 203–205 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1679 (CON), 1714 (CO_2CH_3) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.39 (s, 3 H, CH_3), 3.80 (s, 3 H, CO_2CH_3), 4.03 (s, 3 H, CO_2CH_3), 6.01 (d, J = 0.8 Hz, 1 H, =C*H*H), 6.95 (d, J = 0.8 Hz, 1 H, =CH*H*), 7.53–7.61 (m, 1 H, ArH), 7.70–7.79 (m, 1 H, ArH), 8.16 (d, J = 7.8 Hz, 1 H, ArH), 8.70 (d, J = 8.2 Hz, 1 H, ArH), 8.79 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 15.5, 29.8, 52.6, 53.1, 73.0, 117.5, 117.7, 123.1, 126.1, 131.2, 132.0, 136.8, 139.9, 144.0, 160.2, 166.1, 166.3 ppm. MS (ES): *m*/*z* (%) = 377.2 (100) [M + 1]$^+$. DART-HRMS (ES$^+$): calcd. for $C_{21}H_{17}N_2O_5$ 377.11028; found 377.11375.

Methyl 4-(3-Ethoxy-3-oxoprop-1-en-2-yl)-5-methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (12): The title compound was prepared following the above-described general procedure and after purification by silica gel (60–120 mesh) column chromatography [hexane/EtOAc, 80:20, R_f = 0.60 (hexane/EtOAc, 70:30, v/v)] **12** was obtained as a light-yellow solid (0.37 g from 0.40 g, 60%), m.p. 176–178 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1671 (CON), 1716 (CO_2Et) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.39 (s, 3 H, CH_3), 4.02 (s, 3 H, CO_2CH_3), 4.28 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.00 (d, J = 0.8 Hz, 1 H, =C*H*H), 6.95 (d, J = 0.8 Hz, 1 H, =CH*H*), 7.52–7.60 (m, 1 H, ArH), 7.70–7.78 (m, 1 H, ArH), 8.16 (d, J = 7.6 Hz, 1 H, ArH), 8.70 (d, J = 8.2 Hz, 1 H, ArH), 8.78 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3, 15.5, 53.0, 61.5, 117.5, 117.7, 123.0, 124.8, 126.0, 130.6, 131.2, 131.6, 131.8, 135.2, 135.9, 136.7, 139.9, 143.6, 143.9, 160.3, 165.7, 166.1 ppm. MS (ES): *m*/*z* (%) = 391.2 (100) [M + 1]$^+$. DART-HRMS (ES$^+$): calcd. for $C_{24}H_{19}N_2O_5$ 391.12607; found 391.12940.

Methyl 4-(3-Butoxy-3-oxoprop-1-en-2-yl)-5-methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridine-2-carboxylate (14): The title compound was prepared following the above-described general procedure and after purification by silica gel (60–120 mesh) column chromatography [hexane/EtOAc, 80:20, R_f = 0.70 (hexane/EtOAc, 70:30, v/v)] **14** was obtained as a white solid (0.33 g from 0.30 g, 67%), m.p. 159–161 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1674 (CON), 1716 (CO_2Me) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, J = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.19–1.26 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.53–1.60 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 2.37 (s, 3 H, CH_3), 4.01 (s, 3 H, CO_2CH_3), 4.20 (t, J = 6.5 Hz, 2 H, $OCH_2CH_2CH_2CH_3$), 6.00 (s, 1 H, =C*H*H), 6.94 (s, 1 H, =CH*H*), 7.54 (t, J = 7.5 Hz, 1 H, ArH), 7.54 (t, J = 8.0 Hz, 1 H, ArH), 8.10 (d, J = 7.6 Hz, 1 H, ArH), 8.64 (d, J = 8.1 Hz, 1 H, ArH), 8.73 (s, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.7, 15.4, 19.1, 30.6, 53.0, 65.4, 117.5, 117.7, 123.0, 124.7, 126.0, 130.5, 131.2, 131.7, 135.2, 135.9, 136.6, 139.9, 143.6, 143.9, 160.3, 165.7, 166.1 ppm. MS (ES): *m*/*z* (%) = 419.2 (100) [M + 1]$^+$. DART-HRMS (ES$^+$): calcd. for $C_{24}H_{23}N_2O_5$ 419.16023; found 419.16070.

Methyl 2-(5-Methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-yl)acrylate (17): The title compound was prepared following the above-described general procedure (5 equiv. DABCO, 120 h) and after purification by silica gel (60–120 mesh) column chromatography [hexane/EtOAc, 80:20, R_f = 0.50 (hexane/EtOAc, 70:30, v/v)] **17** was obtained as a light-yellow solid (0.19 g from 0.20 g, 57%) followed by **16** (0.023 g from 0.20 g, 8%). Data for **17**: m.p. 193–195 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1664 (CON), 1720 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.35 (s, 3 H, CH_3), 3.78 (s, 3 H, CO_2CH_3), 5.95 (s, 1 H, =C*H*H), 6.94 (s, 1 H, =CH*H*), 7.51 (d, J = 7.31 Hz, 1 H, ArH), 7.69 (d, J = 7.7 Hz, 1 H, ArH), 7.88 (d, J = 5.0 Hz, 1 H, ArH), 8.08 (d, J = 7.7 Hz, 1 H, ArH), 8.68 (d, J = 8.2 Hz, 1 H, ArH), 8.76 (d, J = 5.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.2, 52.6, 115.7, 117.4, 122.8, 124.9, 125.7, 130.1, 130.5, 130.8, 131.4, 135.3, 135.7, 136.5, 139.5, 143.4, 145.6, 160.2, 165.9 ppm. MS (ES): *m*/*z* (%) = 319.2 (100) [M + 1]$^+$. DART-HRMS (ES$^+$): calcd. for $C_{19}H_{15}N_2O_3$ 319.10600; found 319.10827.

Ethyl 2-(5-Methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-yl)-acrylate (19): The title compound was prepared following the above-described general procedure and after purification by silica gel (60–120 mesh) column chromatography [hexane/EtOAc, 80:20, R_f = 0.54 (hexane/EtOAc, 70:30, v/v)] **19** was obtained as a light-yellow solid (0.31 g from 0.31 g, 59%) followed by **18** (0.05 g from 0.31 g, 10%). Data for **19**: m.p. 122–123 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1660 (CON), 1723 (CO_2CH_3) cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.23 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.36 (s, 3 H, CH_3), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 5.94 (d, J = 0.8 Hz, 1 H, =C*H*H), 6.94 (s, 1 H, =CH*H*), 7.53 (d, J = 7.6 Hz, 1 H, ArH), 7.68–7.74 (m, 1 H, ArH), 7.90 (d, J = 5.0 Hz, 1 H, ArH), 8.11 (d, J = 7.7 Hz, 1 H, ArH), 8.71 (d, J = 8.2 Hz, 1 H, ArH), 8.78 (d, J = 5.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 15.1, 61.5, 115.6, 117.3, 122.7, 124.8, 125.6, 130.0, 130.4, 130.7, 131.1, 135.6, 136.4, 139.4, 143.5, 145.5, 160.1, 165.4 ppm. MS (ES): *m*/*z* (%) = 333.2 (100) [M + 1]$^+$. DART-HRMS (ES$^+$): calcd. for $C_{20}H_{17}N_2O_3$ 333.12097; found 333.12392.

Butyl 2-(5-Methyl-6-oxo-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-4-yl)-acrylate (21): The title compound was prepared following the

above-described general procedure and after purification by silica gel (100–200 mesh) column chromatography [hexane/EtOAc, 80:20, R_f = 0.57 (hexane/EtOAc, 70:30, v/v)] compound **21** was obtained (0.24 g from 0.20 g, 64%) as a white solid followed by **20** (0.04 g from 0.20 g, 10%). Data for **21**: m.p. 107–109 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1670 (CON), 1711 (CO_2Me) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, J = 7.3 Hz, 3 H, $OCH_2CH_2CH_2CH_3$), 1.20–1.28 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 1.52–1.60 (m, 2 H, $OCH_2CH_2CH_2CH_3$), 2.36 (s, 3 H, CH_3), 4.19 (t, J = 6.6 Hz, 2 H, $OCH_2CH_2CH_2CH_3$), 5.94 (s, 1 H, =CHH), 6.94 (s, 1 H, =CHH), 7.53 (t, J = 7.5 Hz, 1 H, ArH), 7.72 (t, J = 7.7 Hz, 1 H, ArH), 7.90 (d, J = 4.9 Hz, 1 H, ArH), 8.11 (d, J = 7.8 Hz, 1 H, ArH), 8.72 (d, J = 8.2 Hz, 1 H, ArH), 8.78 (d, J = 4.9 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 15.1, 19.1, 30.6, 65.4, 115.6, 117.4, 122.7, 124.9, 125.6, 130.0, 130.4, 130.7, 131.0, 135.5, 135.7, 139.5, 143.6, 145.5, 160.2, 165.5 ppm. MS (ES): m/z (%) = 361.2 (100) $[M + 1]^+$. EI-HRMS: calcd. for $C_{22}H_{20}N_2O_3$ 360.1474; found 360.1487.

General Procedure for the Synthesis of Compounds 25, 26 and 32, as Exemplified for Compound 25: K_2CO_3 (1.23 g, 11.79 mmol) was added to a solution of **23** (1.00 g, 3.93 mmol) in dry DMF (6 mL), and the reaction was stirred at room temperature for 30 min. After completion, water (50 mL) was added followed by EtOAc (60 mL) and the mixture was taken up in a separating funnel. The organic layer was separated and the aqueous layer was further extracted with EtOAc (4 × 25 mL). The organic layers were combined and washed with brine (50 mL), dried with anhydrous Na_2SO_4 and concentrated to yield a crude product which was further purified by crystallization using EtOAC [R_f = 0.48 ($CHCl_3$/MeOH, 95:05, v/v)] to afford **25** as a yellow solid (0.63 g from 1.00 g, 63%).

Methyl 5-Cyano-4-hydroxy-5,6-dihydro-4*H*-indolo[3,2,1-*de*][1,5]-naphthyridine-2-carboxylate (25; Mixture of Diastereomers, 10:1): Yield: 63%, m.p. 233–235 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1715 (CO_2CH_3), 2239 (CN), 3188 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.93 (s, 6 H, 2 CO_2CH_3), 4.01–4.06 (m, 2 H, 2 CHO*H*), 4.40–4.57 (m, 2 H, 2 C*H*H), 4.87–4.96 (m, 2 H, 2 CH*H*), 5.28 (t, J = 4.8 Hz, 2 H, 2 CHCN), 6.72 (d, J = 6.0 Hz, 1 H, C*H*OH), 6.81 (d, J = 6.0 Hz, 1 H, C*H*OH), 7.37–7.44 (m, 2 H, ArH), 7.68–7.75 (m, 2 H, ArH), 7.84 (t, J = 6.5 Hz, 2 H, ArH), 8.46 (t, J = 7.4 Hz, 2 H, ArH), 8.93 (d, J = 10.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 33.0, 33.3, 52.1, 65.2, 66.4, 111.0, 118.2, 118.4, 119.1, 120.9, 121.0, 121.1, 123.2, 126.0, 129.0, 129.1, 133.3, 137.2, 140.5, 140.7, 140.9, 141.6, 166.1 ppm. MS (ES): m/z (%) = 308.1 (100) $[M + 1]^+$. $C_{17}H_{13}N_3O_3$ (307.0957): calcd. C 66.44, H 4.26, N 13.67; found C 66.57, H 4.35, N 13.76.

4-Hydroxy-5,6-dihydro-4*H*-indolo[3,2,1-*de*][1,5]naphthyridine-5-carbonitrile (26; Mixture of Diastereomers, 1:1): The title compound was prepared following the above-described general procedure and after purification by column chromatography [$CHCl_3$/MeOH, 98:02, R_f = 0.51 ($CHCl_3$/MeOH, 95:05, v/v)] **26** was obtained as a grey solid (0.114 g from 0.20 g). Yield: 57%, m.p. 155–157 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2230 (CN), 3178 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 3.94–4.02 (m, 2 H, 2 CHO*H*), 4.36–4.50 (m, 2 H, CH_2), 4.80–4.89 (m, 2 H, CH_2), 5.21 (q, J = 5.3 Hz, 2 H, 2 CHCN), 6.50 (d, J = 5.8 Hz, 1 H, C*H*OH), 6.58 (d, J = 5.8 Hz, 1 H, C*H*OH), 7.33 (q, J = 7.4 Hz, 2 H, ArH), 7.62–7.69 (m, 2 H, ArH), 7.76–7.80 (m, 2 H, ArH), 8.08 (q, J = 5.3 Hz, 2 H, ArH), 8.29 (t, J = 5.8 Hz, 2 H, ArH), 8.38 (q, J = 5.3 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 33.1, 33.4, 65.5, 66.7, 110.5, 115.1, 119.4, 120.0, 120.1, 120.8, 120.9, 122.6, 122.7, 125.7, 126.0, 128.5, 128.6, 131.6, 131.8, 138.6, 138.8, 140.0, 140.2, 141.0, 141.7 ppm. MS (ES): m/z (%) = 250.2 (100) $[M + 1]^+$. $C_{15}H_{11}N_3O$ (249.0902): calcd. C 72.28, H 4.45, N 16.86; found C 72.33, H 4.17, N 16.73.

6-Hydroxy-7,8-dihydro-6*H*-benzo[*b*]indolo[3,2,1-*de*][1,5]naphthyridine-7-carbonitrile (32; Mixture of Diastereomers, 1:1): The title compound was prepared following the above-described general procedure and after purification by crystallization using EtOAc [R_f = 0.48 (hexane/EtOAc, 60:40, v/v)] **32** was obtained as a brown solid (0.04 g from 0.05 g). Yield: 80%, m.p. >240 °C. IR (KBr): $\tilde{\nu}_{max}$ = 2242 (CN), 3426 (OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]-DMSO): δ = 4.10 (d, J = 4.2 Hz, 2 H, 2 C*H*H), 4.71 (dd, J_1 = 3.5, J_2 = 11.5 Hz, 2 H, 2 CH*H*), 4.94 (dd, J_1 = 4.7, J_2 = 12.5 Hz, 2 H, 2 CHCN), 5.37 (br. s, 2 H, 2 CHO*H*), 6.78 (d, J = 5.0 Hz, 2 H, 2 C*H*OH), 7.48 (t, J = 7.7 Hz, 2 H, ArH), 7.71–7.82 (m, 7 H, ArH), 7.93 (d, J = 8.0 Hz, 2 H, ArH), 8.25 (d, J = 8.0 Hz, 1 H, ArH), 8.72 (d, J = 8.1 Hz, 2 H, ArH), 8.79 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (50 MHz, [D_6]DMSO): δ = 33.4, 66.1, 67.1, 111.1, 118.4, 119.2, 121.1, 121.4, 123.4, 124.4, 125.8, 127.1, 127.3, 128.8, 130.1, 139.0, 142.6, 145.4, 146.0 ppm. MS (ES): m/z (%) = 300.2 (100) $[M + 1]^+$. $C_{19}H_{13}N_3O$ (299.1059): calcd. C 76.24, H 4.38, N 14.04; found C 76.40, H 4.27, N 14.25.

Supporting Information (see footnote on the first page of this article): Experimental details, spectroscopic data for remaining compounds and ^1H and ^{13}C NMR spectra for all new compounds are provided.

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