

Catalytic Enolate Arylation with 3-Bromoindoles Allows the Formation of β -Carbolines

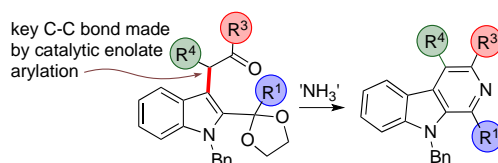
C. Henrique Alves Esteves,^a Peter D. Smith^b and Timothy J. Donohoe^{a*}

^a Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK.

^b AstraZeneca, Pharmaceutical Sciences, Silk Road Business Park, Macclesfield, SK10 2NA, UK.

timothy.donohoe@chem.ox.ac.uk

RECEIVED DATE (will be automatically inserted after manuscript is accepted).



The synthesis of substituted β -carbolines was accomplished by utilizing the catalytic enolate arylation reaction of ketones in conjunction with several 3-bromoindole derivatives. Quenching of the arylation reaction *in situ* with an electrophile allowed ready incorporation of functionality at the carboline C-4 position in an efficient one-pot protocol.

β -Carbolines are important *N*-heterocyclic aromatic compounds that have been extensively studied for their wide-ranging bioactivity.¹ These compounds are also widely found in natural products extracted from various sources, such as the dichotomides,² from the roots of *Stellaria dichotoma*; the metatacarbolines,³ from the fruiting bodies of *Mycena metata*; hirsutaside D,⁴ from the leaves of *Uncaria hirsute*; hyrtiocarboline,⁵ from the marine sponge *Hyrtios reticulatus*; and stolonines,⁶ from the marine tunicate *Cnemidocarpa stolonifera*.

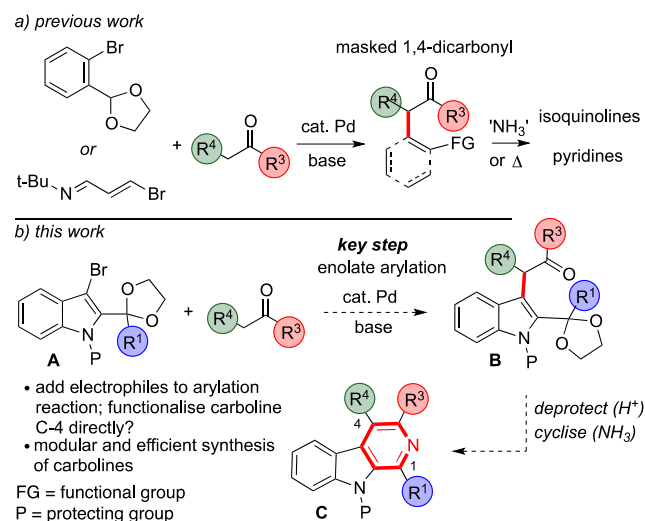
Some of the recently reported methodologies to prepare β -carbolines involve the metal-catalyzed iminoannulation of alkynes,⁷ the Rh-catalyzed cycloaddition of yne-ynamides with methylcyanoformate,⁸ cascade annulation of alkynols,⁹ photocyclization of anilinothalopyridines,¹⁰ coupling of anilines and halopyridines,¹¹ Pd-catalyzed ring-expansion of azidoalcohols¹² and cyclization of vinylindoles.¹³ While impressive, the main limitations of these methods lie in the formation of regioisomers or the limited accessibility of a variety of substitution patterns in the heterocyclic ring.

We sought a route to these heterocycles that would allow the introduction of many different groups onto the aromatic nucleus but without the complications arising from the formation of regioisomers. In this regard, our approach to the synthesis of carbolines relies on the use of catalytic enolate arylation reaction of ketones,¹⁴ a powerful catalytic reaction

still underused in the synthesis of aromatic heterocycles.¹⁵ Previous work from our group has shown that ketones can be easily arylated by reaction of substituted aryl or vinyl halides so that the products are ideally configured (masked 1,4-dicarbonyls) for an aromatization step to furnish substituted isoquinolines¹⁶ or pyridines¹⁷ (Figure 1a).

Herein, we have chosen a 3-bromoindole partner **A** for the enolate arylation (Figure 1b).¹⁸ The installation of a protected carbonyl at C-2 of the indole bromide partner would provide the functionality required to aromatize the ring after arylation was complete (see **B**→**C**). Moreover, from previous precedent,^{16,19} we anticipated that an ability to add an electrophile directly to the catalytic arylation reaction would allow extra functionalization to be added to the product (see **R**⁴ in **B**) that would ultimately allow derivatisation at the C-4 position of the carboline without the addition of extra synthetic steps.

Figure 1: Catalytic enolate arylation route to β -carbolines



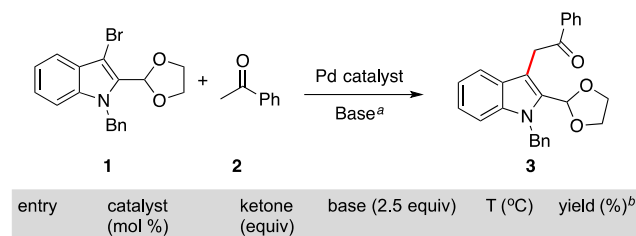
Initially, we selected 1-benzyl-3-bromo-2-(1,3-dioxolan-2-yl)-1*H*-indole (**1**) and acetophenone (**2**) for optimization studies using catalytic palladium (Table 1). Compound **1** was made in high yield from the precursor indole-2-carboxaldehyde *via* reaction with NBS, followed by *N*-benzylation with base and BnBr and then acetal formation with ethylene glycol and *p*TSA.²⁰

We began our screening by treating **1** and acetophenone (**2**) with catalytic Pd(dtbpf)Cl₂²¹ and NaOtBu in THF (Table 1), which are conditions previously used for related arylations in our laboratory,¹⁶ and they afforded product **3** in an encouraging 52 % yield (entry 1). Pleasingly, compound **3** could be isolated in 93 % yield when the NaOtBu base was replaced by LiHMDS (entry 2).

Further studies showed that the arylation was tolerant of changes to the reaction parameters. For example, lower catalyst loadings and/or ketone equivalents were examined, and these delivered the desired product in good yields (entries 3-5). Moreover, a reasonable yield of **3** (66%) was obtained

when the arylation reaction was carried out at room temperature (entry 6). Finally, a different catalyst was screened with Pd(amphos)₂Cl₂, (this was also previously very active in our hands) delivering the product in a disappointing 17 % yield (entry 7).

Table 1: Optimization Studies for the Pd-Catalyzed α -Arylation of **1**



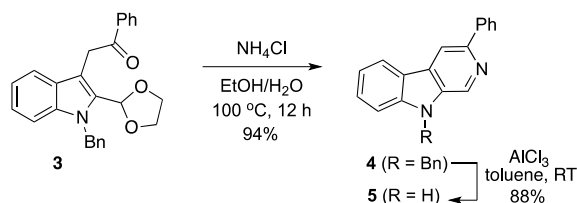
entry	catalyst (mol %)	ketone (equiv)	base (2.5 equiv)	T (°C)	yield (%) ^b
1	Pd(dtbtf)Cl ₂ (5)	2	NaOtBu	50	52
2	Pd(dtbtf)Cl ₂ (5)	2	LiHMDS	50	93
3	Pd(dtbtf)Cl ₂ (5)	1.2	LiHMDS	50	80
4	Pd(dtbtf)Cl ₂ (2.5)	2	LiHMDS	50	86
5	Pd(dtbtf)Cl ₂ (2.5)	1.2	LiHMDS	50	70
6	Pd(dtbtf)Cl ₂ (5)	2	LiHMDS	RT	66
7	Pd(amphos)Cl ₂ (5)	2	LiHMDS	50	17

^a Indole **1** (1.0 eq.), THF, 24 h

^b Isolated yields

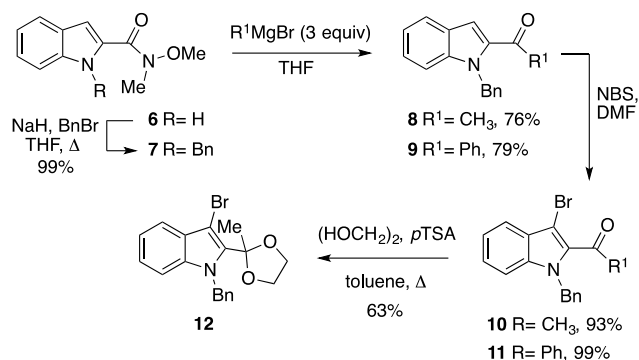
Pleasingly, the reaction of arylated product **3** with ammonium chloride in ethanol/water was sufficiently acidic to deprotect the acetal and allow cyclisation to give the corresponding carboline **4** in 94 % yield (Scheme 1), thus validating our approach to these aromatic heterocycles. Moreover, the N-benzyl group was easily removed from the carboline products using AlCl₃ (**4**→**5** in 88% yield).²²

Scheme 1: Cyclization of **3 to furnish β -carboline **4****



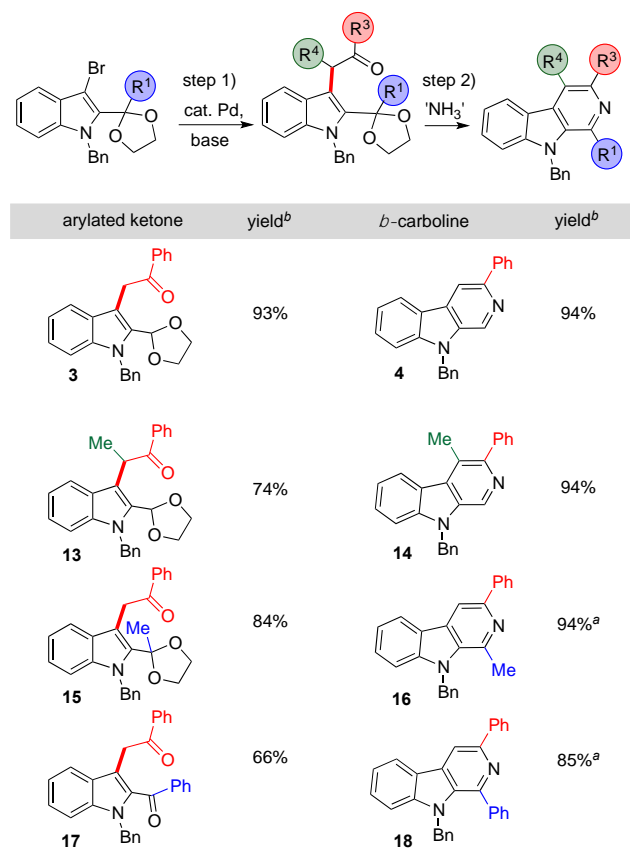
The next stage involved an exploration of the substrate scope, and in order to do this we prepared more substituted indole bromides to be coupled with a selection of commercially available ketones (Scheme 2). Our synthesis of the requisite indole bromides began from readily available compound **6**,²³ which was N-benzylated (**7**) and then derivatised into two different ketones (**8**, **9**) *via* reaction with a Grignard reagent. After bromination at C-3 (**10**, **11**), ketone **10** was protected as an acetal (**12**) under standard conditions.

Scheme 2: Synthesis of substituted indole bromides



With the key compounds in hand, we were able to explore the substrate scope, and Table 2 shows a set of carbolines (**4**, **14**, **16**, **18**) that were prepared *via* this two-step sequence of enolate arylation, using the optimized conditions from Table 1, followed by aromatization. Use of this methodology allowed substitution at the carboline C-1, C-3 and C-4 positions simply by using a substituted ketone or altering the substitution pattern of the ketal protected indole bromide in the arylation step. Note that some groups (eg Ph) could be introduced at the carboline C-1 position without the need for ketal protection (see **11**→**17**→**18**); in this case the conjugated nature of the ketone at C-2 of the indole makes it unreactive to competing aldol type side reactions.

Table 2: Synthesis of substituted β -carbolines in two steps



Reaction conditions: 1) Indole (1.0 equiv), Pd(dtbpf)Cl₂ (5.0 mol%), LiHMDS (2.5 equiv), ketone (2.0 equiv), THF, 50 °C, 24 h; 2) NH₄Cl (10 equiv); EtOH/H₂O 3:1, 100 °C, 12 h.

^a Solvent: EtOH/H₂O/DMF (3:1:2), 110 °C, 12 h.

^b Isolated yields

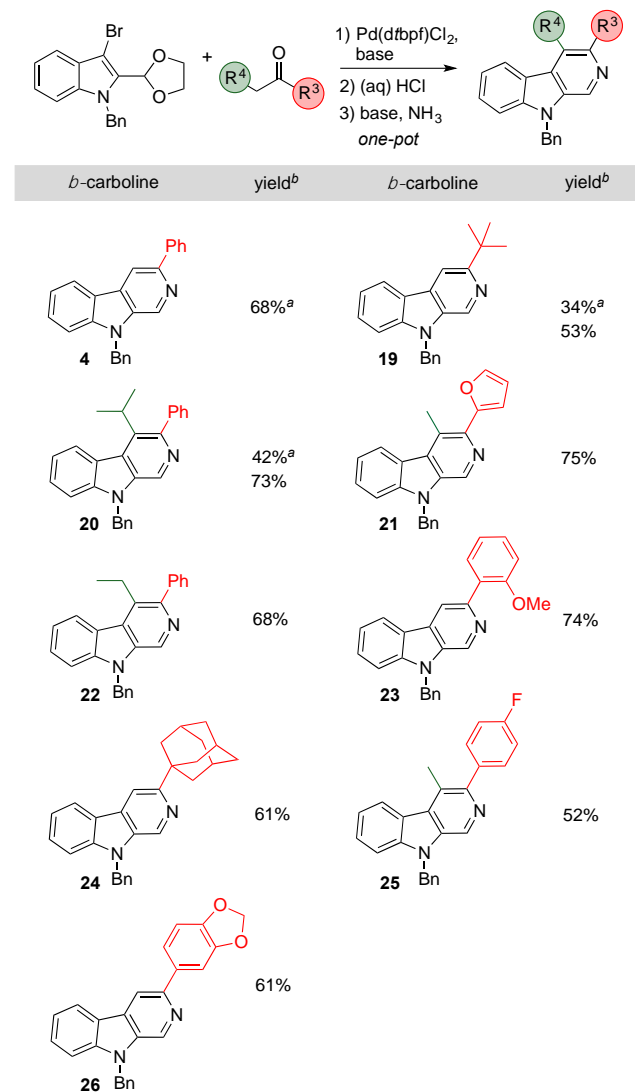
After these positive results we then sought to develop a one-pot procedure for the arylation/aromatization sequence. This worked well and starting from **1** and **2** we could quench the arylation reaction directly with acid and then ammonia to furnish carboline **4** in 68% yield for the one-pot process (Table 3). The one-pot sequence was optimal when it began with an enolate arylation, followed by the sequential addition of acid (to hydrolyse the acetal), neutralization (NaHCO₃) and then addition of ammonia (7M in MeOH) to perform the aromatization.

However, as we switched to more substituted ketone substrates in order to expand the methodology, we found the arylation conditions that had proved optimal for acetophenone in Table 1 showed poor conversion (see **19** and **20** with 34 % and 42 % yield, respectively). Therefore, we examined other conditions from Table 1 that had also delivered arylated product and found that a change of base to NaOtBu, together with an increase in the temperature, delivered an arylation reaction that was more reliable across a wider range of ketones (for example, compounds **19** and **20** were now formed in 53 % and 73% yield, respectively).

With these new arylation conditions, the one-pot synthesis of various carbolines was then possible in excellent yields. Using this approach, alkyl substituents could be incorporated with ease at either the C-3 or C-4 positions on the carboline

nucleus (Table 3). Note that attempts at the one-pot synthesis of **18** via the dicarbonyl intermediate **17** were unsuccessful.

Table 3: One-pot synthesis of substituted β -Carbolines



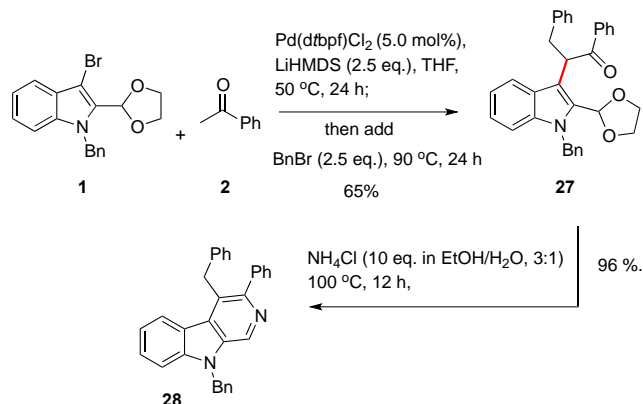
Reaction conditions: 1) Indole (1.0 equiv), Pd(dtbpf)Cl₂ (5.0 mol%), NaOtBu (2.5 equiv), ketone (2.0 equiv), THF, 75 °C, 24 h; 2) (aq.) 1 M HCl; 3) NaHCO₃ (20 equiv), NH₃ (20 equiv, 7M in MeOH), EtOH, DMF, 100 °C, 12 h.

^a LiHMDS (2.5 eq.) as base, 50 °C

^b Isolated yields

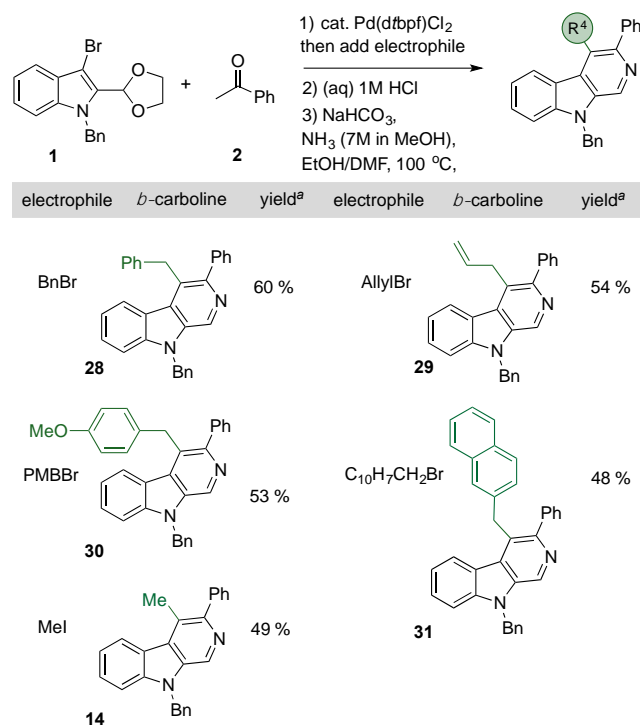
Next we examined the direct functionalization of the arylated products *in situ*, which was accomplished by quenching the arylation reaction of a methyl ketone with an electrophile (see **1**→**27** with the addition of benzyl bromide, Scheme 3). This protocol works well because the initial arylation reaction requires at least two equivalents of base to reach completion and, therefore, the initial arylation product is actually present in the reaction mixture as an enolate, which can be quenched. As expected, the benzylated compound **27** was then easily aromatized to carboline **28** under standard conditions (Scheme 3).

Scheme 3: *in situ* enolate alkylation to furnish C-4 substituted β -carbolines



This precedent then provided the basis for a one-pot arylation/enolate-quench/aromatization sequence, starting from **1** and **2**, that provided several C-4 derivatised products in good yields, (see **14**, **28–31**, Table 4). This chemistry represents a particularly convenient and short route to C-3,4-disubstituted carbolines which installs the desired functionality with complete control of regiochemistry.

Table 4: One-pot synthesis of C-4 functionalized β -carbolines



Reaction conditions: **1**) Indole (1.0 equiv), $\text{Pd}(\text{d}t\text{bpf})\text{Cl}_2$ (5.0 mol%), LiHMDS (2.5 equiv), ketone (2.0 equiv), THF, 50 °C, 24 h; then electrophile, 90 °C;

^a Isolated yields

To conclude, we have extended the enolate arylation/aromatization sequence to accomplish the synthesis of carbolines by using indole-based bromides as coupling

partners. A variety of (heterocyclic) substitution patterns were compatible with this approach, either by arylation of a functionalized ketone or by a direct enolate arylation and electrophilic quenching sequence. The ability to combine an enolate arylation with a one-pot aromatization sequence is particularly advantageous. This convenient and modular approach allows access to a wide range of carboline derivatives with many potential uses.

Experimental Section:

General Methods: All reagents were used as purchased. Solvents were dried using standard laboratory techniques. All reactions requiring dry equipment were carried out in flame-dried glassware under argon atmosphere. Flash column chromatography was performed using Geduran® silica gel 60 (40–63 μm). Thin layer chromatography was performed on Merck Kieselgel 60 F254 0.25 mm pre-coated aluminum-backed plates. Product spots were visualized under UV light ($\lambda_{\text{max}} = 254 \text{ nm}$) and/or by staining with vanillin, phosphomolybdic acid or basic potassium permanganate solutions. ¹H nuclear magnetic resonance (NMR) spectra were recorded using a Bruker AVII400, AVIII400, or AVII500 instruments at 400 MHz or 500 MHz. ¹³C NMR spectra were recorded at 100 MHz or 125 MHz. ¹⁹F NMR spectrum was recorded at 376 MHz. Chemical shifts, δ , are reported relative to residual solvent peaks and quoted in parts per million (ppm) to the nearest 0.01 for ¹H and to the nearest 0.1 ppm for ¹³C and ¹⁹F. Coupling constants, J, are quoted to the nearest 0.1 Hz. Assignments were based upon DEPT, COSY, HSQC, and HMBC experiments. High-resolution mass spectra were acquired using electrospray ionisation (ESI) as ionization source and were recorded on a Fisons Platform II with TOF detector. Infrared spectra (IR) were obtained from evaporated films using a Bruker Tensor 27 spectrometer, equipped with a PIKE Miracle Attenuated Total Reflectance (ATR) sampling accessory. Absorption maxima are quoted in wavenumbers (cm^{-1}) for the range 3500–600 cm^{-1} . Melting points (m.p.) were obtained by using a Leica VMTG heated-stage microscope and are uncorrected.

General Procedure A for α -Arylation of ketones. A fresh solution of LiHMDS was prepared in a dry vial adding sequentially dry THF (2 mL), HMDS (80 μL , 0.38 mmol, 2.5 eq.), a 2.5 M solution of *n*BuLi (0.15 mL, 0.38 mmol, 2.5 eq.) and stirring at -78 °C for 10 minutes. The ketone (0.31 mmol, 2.0 eq.) was then added at 0 °C and stirred for 15 minutes. In a second dry vial were added bromo indole (0.15 mmol) and $\text{Pd}(\text{d}t\text{bpf})\text{Cl}_2$ (5 mg, 8 μmol , 5 mol%). The flask was sealed, evacuated and backfilled with argon. The freshly formed enolate solution was then transferred *via* syringe to the flask. The mixture was stirred at 50 °C for 24 hours in an oil bath. The resulting mixture was filtered through a plug of silica and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluted with a mixture of petroleum ether/ EtOAc) to afford the ketone product.

General Procedure B for the Cyclization of α -Arylated Ketones. To a reaction flask were added the arylated ketone (4.15 mmol) and a 1M solution of NH_4Cl (4.1 mL, 10 eq.) in EtOH/H₂O 3:1. The mixture was stirred at 90 °C for 12 h.

NH₄HCO₃ (6.97 g, 83.0 mmol, 20 eq.) was then added to the flask and the solution was stirred at 90 °C for 3 hours. The crude product was concentrated *in vacuo*, re-dissolved in pure EtOAc and mixed with water. The aqueous layer was extracted twice with EtOAc; the organic extracts were combined, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (eluted with a mixture of petroleum ether/EtOAc) to afford the β-carboline product.

General Procedure C for the Synthesis of Ketones from Weinreb Amide 7. To a dry reaction flask were added indole 7 (2.00 g, 6.79 mmol) and dry THF (68 mL). A 3M solution of the appropriate Grignard reagent (6.8 mL, 20 mmol, 3 eq.) was slowly added over 30 minutes at -78 °C and then allowed to stir at 0 °C for 1 hour. The mixture was then quenched at 0 °C with NH₄Cl_(aq.) and the aqueous layer was extracted twice with EtOAc. The organic extracts were combined, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (eluted with a mixture of petroleum ether/ EtOAc) to afford the product ketone.

General Procedure D for the One-pot Synthesis of β-Carbolines. To a dry vial were added bromo indole 1 (110 mg, 307 μmol), Pd(dtbpf)Cl₂ (10 mg, 15 μmol, 5 mol%) and NaOtBu (74 mg, 0.77 mmol, 2.5 eq.). The flask was sealed, evacuated and backfilled with argon twice and then dry THF (4 mL) and the corresponding ketone (0.61 mmol, 2 eq.) were added in sequence. The mixture was stirred for 24 hours at 75 °C. After cooling to room temperature, HCl_(aq.) (1 M, 10 eq.) was added and the mixture was stirred for 12 hours at 90 °C. After cooling to room temperature, DMF (2 mL), EtOH (4 mL), NaHCO₃ (516 mg, 6.14 mmol, 20 eq.) and NH₃ (7 M solution in MeOH, 0.88 mL, 6.1 mmol, 20 eq.) were added and the mixture was stirred at 110 °C for 24 hours. The crude product was concentrated *in vacuo*, re-dissolved in pure EtOAc and mixed with water. The aqueous layer was extracted twice with EtOAc and the organic extracts were combined, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (eluted with a mixture of petroleum ether/ EtOAc) to afford the β-carboline product.

General Procedure E for the Bromination of Keto-Indoles. To a dry reaction flask were added the appropriate ketone (5.45 mmol) and DMF (3.9 mL). A solution of NBS (1.11 g, 6.27 mmol, 1.15 eq.) in DMF (3.9 mL) was added over 30 minutes at 0 °C and the resulting mixture was then stirred at room temperature for 2 hours. 70 mL of H₂O was added and the resulting slurry was extracted three times with EtOAc; the organic extracts were combined and washed five times with H₂O, dried over MgSO₄, filtered and concentrated *in vacuo*, affording the bromo indole product or, alternatively, were purified by flash column chromatography (eluted with a mixture of petroleum ether/ EtOAc) to afford the bromo indole product.

General Procedure F for the One-pot Synthesis of β-Carboline with addition of electrophiles. A fresh solution of LiHMDS was prepared in a dry vial adding sequentially dry THF (4 mL), HMDS (0.16 mL, 0.77 mmol, 2.5 eq.) and a 2.5 M solution of *n*BuLi (0.31 mL, 0.77 mmol, 2.5 eq.) and

stirring at -78 °C for 10 minutes. Acetophenone (72 μL, 0.61 mmol, 2.0 eq.) was then added at 0 °C and stirred for 15 minutes. In a second dry vial were added bromo indole 1 (110 mg, 307 μmol) and Pd(dtbpf)Cl₂ (10 mg, 15 μmol, 5 mol%). The flask was sealed, evacuated and backfilled with argon. The freshly formed enolate solution was then transferred *via* syringe to the flask. The mixture was stirred at 50 °C for 24 hours in an oil bath. After cooling to room temperature, the appropriate electrophile (0.77 mmol, 2.5 eq.) was added and the mixture was stirred at 90 °C for 24 hours. After cooling to room temperature, 1M HCl_(aq.) (3.1 mL, 10 eq.) was added and the mixture was stirred for 12 hours at 90 °C. After cooling to room temperature, DMF (2mL), EtOH (4 mL), NaHCO₃ (516 mg, 6.14 mmol, 20 eq.) and NH₃ (7 M solution in MeOH, 0.88 mL, 6.1 mmol, 20 eq.) were added and the mixture was stirred at 110 °C for 24 hours. The crude product was concentrated *in vacuo*, re-dissolved in pure EtOAc and mixed with water. The aqueous layer was extracted twice with EtOAc and the organic extracts were combined, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solids were purified by flash column chromatography (eluted with a mixture of petroleum ether/ EtOAc) to afford the β-carboline product.

Synthesis of 1-benzyl-3-bromo-2-(1,3-dioxolan-2-yl)-1H-indole (1). To a dry reaction flask connected to a Dean-Stark apparatus were added 1-benzyl-3-bromo-1H-indole-2-carbaldehyde (330 mg, 1.05 mmol), ethylene glycol (116 μL, 2.09 mmol, 2 eq.), *p*-toluenesulfonic acid monohydrate (20 mg, 105 μmol, 10 mol%) and toluene (10 mL). The resulting mixture was heated at reflux for 14 hours and then cooled to room temperature and quenched with NaHCO_{3(aq.)}. The aqueous layer was extracted twice with EtOAc, the organic extracts combined, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (eluted with 9:1 petroleum ether/EtOAc), affording 1 (350 mg, 93%) as a yellow solid. Mp: 64 – 67 °C. IR ν_{max} (thin film) 3060, 2888, 1075 cm⁻¹. HRMS: calculated for C₁₈H₁₇BrNO₂, 358.04372 [M+H]⁺, found *m/z* 358.04379, Δ = 0.20 ppm. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 7.62-7.55 (1H, m, HC_{Ar}), 7.30-7.00 (8H, m, 8 × HC_{Ar}), 6.21 (1H, s, CH(OR)₂), 5.46 (1H, s, PhCH₂R), 4.06-3.86 (4H, m, (OCH₂)₂); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 137.9, 137.4, 129.3 (3 × C_{Ar}), 128.6 (HC_{Ar}), 127.3 (HC_{Ar}), 126.7 (C_{Ar}), 126.3, 124.3, 120.7, 120.0, 110.6 (5 × HC_{Ar}), 98.7 (CH(OR)₂), 94.5 (C(3)), 65.2 ((OCH₂)₂), 48.5 (PhCH₂R).

2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1H-indol-3-yl)-1-phenylethan-1-one (3). This compound was prepared according to general procedure A, affording 3 (57 mg, 93%) as a brown solid. Mp: 100 - 102 °C. IR ν_{max} (thin film) 3368, 3060, 2925, 1613, 1082, 745 cm⁻¹. HRMS: calculated for C₂₆H₂₄O₃N, 398.17507 [M+H]⁺, found *m/z* 398.17496, Δ = - 0.30 ppm. ¹H NMR (400 MHz, CDCl₃) δ_{H} : 8.15-8.10 (2H, m, 2 × HC_{Ar}), 7.63-7.54 (2H, m, 2 × HC_{Ar}), 7.48 (2H, t, *J* = 7.4 Hz, 2 × HC_{Ar}), 7.33-7.03 (9H, m, 9 × HC_{Ar}), 6.13 (1H, s, CH(OR)₂), 5.54 (1H, s, PhCH₂R), 4.65 (2H, s, CH₂C(O)), 4.05-3.90 (4H, m, (OCH₂)₂); ¹³C NMR (100 MHz, CDCl₃) δ_{C} : 196.7 (C(O)), 137.1, 136.4, 135.9 (3 × C_{Ar}), 131.8 (HC_{Ar}), 129.8 (C_{Ar}), 127.5, 127.5, 127.4 (3 × HC_{Ar}), 126.6 (C_{Ar}), 126.0, 125.0, 121.9, 118.7, 118.2, 109.0 (6 × HC_{Ar}), 108.2

(C_{Ar}), 97.9 (CH(OR)₂), 63.9 ((OCH₂)₂), 46.7 (RCH₂Ph), 34.0 (CH₂C(O)).

9-Benzyl-3-phenyl-9H-pyrido[3,4-b]indole (4). This compound was prepared according to general procedure B on a 4.15 mmol scale, affording **4** (1.30 g, 94%) as a light brown solid. Mp: 143 - 146 °C. IR ν_{\max} (thin film) 3059, 3030, 1460, 733, 694 cm⁻¹. HRMS: calculated for C₂₄H₁₉N₂, 335.15428 [M+H]⁺, found m/z 335.15350, Δ = -2.3 ppm. ¹H NMR (400 MHz, CDCl₃) δ : 8.82 (1H, s, C(1)), 8.33 (1H, s, C(4)), 8.13 (1H, d, J = 7.8 Hz, HC_{Ar}), 8.08 (2H, d, J = 7.5 Hz, HC_{Ar}), 7.55-7.43 (3H, m, 3 \times HC_{Ar}), 7.40-7.31 (2H, m, 2 \times HC_{Ar}), 7.30-7.15 (4H, m, 4 \times HC_{Ar}), 7.14-7.05 (2H, m, 2 \times HC_{Ar}), 5.41 (2H, s, PhCH₂Ar); ¹³C NMR (100 MHz, CDCl₃) δ : 147.9, 141.9, 140.6, 136.5, 136.0 (5 \times C_{Ar}), 131.9 (HC(1)), 129.8 (C_{Ar}), 129.0, 128.8, 128.6, 127.9, 127.8, 126.9, 126.7, 122.0 (8 \times HC_{Ar}), 121.7 (C_{Ar}), 120.0, 111.4, 109.9 (3 \times HC_{Ar}), 47.0 (PhCH₂Ar). ¹H and ¹³C NMR data were consistent with those previously reported.^{7c}

Synthesis of 3-Phenyl-9H-pyrido[3,4-b]indole (5). To a dry reaction flask were added freshly sublimed AlCl₃ (287 mg, 2.15 mmol, 6 eq.) and toluene (1.8 mL). A solution of β -carboline **4** (120 mg, 359 μ mol) in toluene (1.8 mL) was added at 0 °C over 10 minutes and stirred at room temperature for 2 hours. The resulting mixture was quenched with NaHCO_{3(aq.)} and the aqueous layer extracted twice with EtOAc. The organic extracts were combined, dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solids were purified by flash column chromatography (eluted with a 19:1 mixture of CHCl₃/ MeOH) to afford the β -carboline product **5** (71 mg, 88%) as a white solid. Mp: 226 - 229 °C. IR ν_{\max} (thin film) 3125, 3018, 2923, 2755, 1137, 738, 696 cm⁻¹. HRMS: calculated for C₁₇H₁₃N₂, 245.10732 [M+H]⁺, found m/z 245.10730, Δ = -0.10 ppm. ¹H NMR (400 MHz, CDCl₃) δ : 8.99 (1H, s, HC_{Ar}), 8.57 (1H, bs, NH), 8.40 (1H, s, HC_{Ar}), 8.20 (1H, d, J = 7.8 Hz, HC_{Ar}), 8.12-8.07 (2H, m, 2 \times HC_{Ar}), 7.59-7.46 (4H, m, 4 \times HC_{Ar}), 7.43-7.36 (1H, m, HC_{Ar}), 7.32 (1H, dd, J = 8.1, 7.0 Hz, HC_{Ar}). ¹H NMR (400 MHz, DMSO-d₆) δ : 11.69 (1H, s, NH), 9.00 (1H, s, HC(1)), 8.77 (1H, s, HC(4)), 8.36 (1H, d, J = 7.9 Hz, HC_{Ar}), 8.22 (2H, ddd, J = 8.3, 1.2, 1.0 Hz, 2 \times HC_{Ar}), 7.66-7.60 (1H, m, HC_{Ar}), 7.58 (1H, dd, J = 6.9, 1.2 Hz, HC_{Ar}), 7.54-7.48 (2H, m, 2 \times HC_{Ar}), 7.41-7.35 (1H, m, HC_{Ar}), 7.28 (1H, ddd, J = 8.0, 6.9, 1.0 Hz, HC_{Ar}); ¹³C NMR (100 MHz, CDCl₃); ¹³C NMR (100 MHz, DMSO-d₆) δ : 146.0, 141.6, 140.6, 135.9 (4 \times C_{Ar}), 134.0 (HC(1)), 129.3 (C_{Ar}), 129.1, 128.7, 127.9, 126.6, 122.5, (5 \times HC_{Ar}), 121.5 (C_{Ar}), 119.8, 112.5 (2 \times HC_{Ar}), 111.6 (HC(4)). ¹H NMR data were consistent with those previously reported.²⁴

Synthesis of 1-Benzyl-N-methoxy-N-methyl-1H-indole-2-carboxamide (7). To a dry reaction flask equipped with a reflux condenser were added indole **6** (12.0 g, 58.7 mmol) and dry THF (590 mL). NaH (60% in mineral oil, 2.82 g, 70.5 mmol, 1.2 eq.) was added slowly at 0 °C over 10 minutes and the resulting mixture was heated at reflux for 30 minutes. After cooling to room temperature, benzyl bromide (8.4 mL, 70 mmol, 1.2 eq.) was added and the solution was heated at reflux for 2 hours and then cooled to 0 °C, when it was quenched using NH₄Cl_(aq.). The aqueous layer was extracted twice with EtOAc and the organic extracts were combined,

dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (eluted with 4:1 petroleum ether/EtOAc) to afford protected indole **7** (17.1 g, 99%) as a white solid. Mp: 34 - 37 °C. IR ν_{\max} (thin film) 3060, 3030, 2931, 1632, 1453, 739 cm⁻¹. HRMS: calculated for C₁₈H₁₈O₂N₂, 295.14410 [M+H]⁺, found m/z 295.14398, Δ = -0.41 ppm. ¹H NMR (400 MHz, CDCl₃) δ : 7.79-7.40 (1H, m, HC_{Ar}), 7.44 (1H, dd, J = 8.4, 0.8 Hz, HC_{Ar}), 7.33 (1H, ddd, J = 8.3, 7.0, 1.2 Hz, HC_{Ar}), 7.31-7.19 (5H, m, 6 \times HC_{Ar}), 7.13 (2H, d, J = 6.6 Hz, 2 \times HC_{Ar}), 5.77 (2H, s, PhCH₂R), 3.53 (3H, s, OCH₃), 3.34 (3H, s, NCH₃); ¹³C NMR (100 MHz, CDCl₃) δ : 162.8 (C(O)), 138.6, 138.4, 129.6 (3 \times C_{Ar}), 128.6, 127.3, 126.8 (3 \times HC_{Ar}), 126.7 (C_{Ar}), 124.4, 122.3, 120.6, 110.6, 108.1 (5 \times HC_{Ar}), 61.2 (OCH₃), 47.9 (RCH₂Ph), 33.9 (NCH₃).

1-(1-Benzyl-1H-indol-2-yl)ethan-1-one (8). This compound was prepared according to general procedure C, affording **8** (1.28 g, 76%) as a white solid. Mp: 125 - 126 °C. IR ν_{\max} (thin film) 3061, 3031, 2924, 1657, 725 cm⁻¹. HRMS: calculated for C₁₇H₁₆ON, 250.12264 [M+H]⁺, found m/z 250.12302, Δ = 1.50 ppm. ¹H NMR (400 MHz, CDCl₃) δ : 7.81-7.77 (1H, m, HC_{Ar}), 7.45-7.36 (3H, m, 3 \times HC_{Ar}), 7.32-7.20 (4H, m, 4 \times HC_{Ar}), 7.14-7.08 (2H, m, 2 \times HC_{Ar}), 5.91 (s, 2H, NCH₂Ph), 2.66 (s, 3H, C(O)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ : 191.3 (C(O)), 140.0, 138.4, 134.4 (3 \times C_{Ar}), 128.5, 127.1, 126.5, 126.3 (4 \times HC_{Ar}), 126.0 (C_{Ar}), 123.0, 121.1, 113.0, 111.0 (4 \times HC_{Ar}), 48.2 (PhCH₂N), 28.1 (C(O)CH₃). ¹H NMR data were consistent with those previously reported.²⁵

1-Benzyl-1H-indol-2-yl(phenyl)methanone (9). This compound was prepared according to general procedure C on a 10.2 mmol scale, affording **9** (2.51 g, 79%) as a white solid. Mp: 107 - 110 °C. IR ν_{\max} (thin film) 3060, 3030, 2923, 1633, 718, 694 cm⁻¹. HRMS: calculated for C₂₂H₁₇ONNa, 334.12024 [M+Na]⁺, found m/z 334.12023, Δ = -0.02 ppm. ¹H NMR (400 MHz, CDCl₃) δ : 7.95-7.90 (2H, m, 2 \times HC_{Ar}), 7.73 (1H, d, J = 8.0, HC_{Ar}), 7.65-7.58 (1H, m, HC_{Ar}), 7.54-7.48 (2H, m, 2 \times HC_{Ar}), 7.44 (1H, dd, J = 8.5, 0.7 Hz, HC_{Ar}), 7.38 (1H, ddd, J = 8.4, 6.9, 1.1 Hz, HC_{Ar}), 7.31-7.18 (4H, m, 4 \times HC_{Ar}), 7.18-7.14 (2H, m, 2 \times HC_{Ar}), 7.12 (1H, d, J = 0.6 Hz, C(3)), 5.91 (2H, s, PhCH₂R); ¹³C NMR (100 MHz, CDCl₃) δ : 188.6 (C(O)), 140.2, 139.4, 138.4, 134.7 (4 \times C_{Ar}), 132.2, 129.8, 128.6, 128.2, 127.2, 126.6, 126.2 (7 \times HC_{Ar}), 126.1 (C_{Ar}), 123.1, 121.1, 115.8, 111.1 (4 \times HC_{Ar}), 48.1 (PhCH₂R). ¹H NMR data were consistent with those previously reported.²⁶

1-(1-Benzyl-3-bromo-1H-indol-2-yl)ethan-1-one (10). This compound was prepared according to general procedure E, affording **10** (1.66 g, 93%) as a white solid. Mp: 118 - 120 °C. IR ν_{\max} (thin film) 3061, 3032, 2921, 16511, 726 cm⁻¹. HRMS: calculated for C₁₇H₁₅ONBr, 328.03315 [M+H]⁺, found m/z 328.03348, Δ = 0.99 ppm. ¹H NMR (400 MHz, CDCl₃) δ : 7.80-7.74 (1H, m, HC_{Ar}), 7.43-7.39 (2H, m, 2 \times HC_{Ar}), 7.32-7.22 (4H, m, 4 \times HC_{Ar}), 7.08-7.03 (2H, m, 2 \times HC_{Ar}), 5.80 (2H, s, PhCH₂N), 2.83 (3H, s, C(O)CH₃); ¹³C NMR (100 MHz, CDCl₃) δ : 192.0 (C(O)), 138.4, 138.0, 132.6 (3 \times C_{Ar}), 128.6, 127.3, 127.1 (3 \times HC_{Ar}), 126.8 (C_{Ar}), 126.3, 121.9, 121.8, 111.0 (4 \times HC_{Ar}), 100.0 (C_{Ar}), 48.9 (PhCH₂N), 31.9 (C(O)CH₃).

1-Benzyl-3-bromo-1H-indol-2-yl(phenyl)methanone (11). This compound was prepared according to general procedure

E on a 4.17 mmol scale, affording **11** (1.62 g, 99%) as a white solid. Mp: 87 - 89 °C. IR ν_{\max} (thin film) 3060, 3030, 1719, 722, 692 cm^{-1} . HRMS: calculated for $\text{C}_{22}\text{H}_{17}\text{ONBr}$, 390.04880 $[\text{M}+\text{H}]^+$, found m/z 390.04959, $\Delta = 2.02$ ppm. ^1H NMR (400 MHz, CDCl_3) δ : 7.82-7.78 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 7.68 (1H, d, $J = 8.0$ Hz, HC_{Ar}), 7.62-7.56 (1H, m, HC_{Ar}), 7.46-7.34 (4H, m, $4 \times \text{HC}_{\text{Ar}}$), 7.27 (1H, ddd, $J = 8.0, 6.6, 1.3$ Hz, HC_{Ar}), 7.24-7.14 (3H, m, $3 \times \text{HC}_{\text{Ar}}$), 7.08-7.03 (2H, m, HC_{Ar}), 5.60 (2H, s, PhCH_2R); ^{13}C NMR (100 MHz, CDCl_3) δ : 189.4 ($\text{C}(\text{O})$), 138.0, 138.0, 137.5, 133.5 ($4 \times \text{C}_{\text{Ar}}$), 133.3, 130.2, 128.7, 128.5, 127.6 ($5 \times \text{HC}_{\text{Ar}}$), 126.8 (C_{Ar}), 126.7, 126.2, 121.6, 121.3, 110.9 ($5 \times \text{HC}_{\text{Ar}}$), 98.1 (C_{Ar}), 48.3 (PhCH_2R).

Synthesis of 1-Benzyl-3-bromo-2-(2-methyl-1,3-dioxolan-2-yl)-1H-indole (12). To a dry reaction flask connected to a Dean-Stark apparatus were added bromo indole **10** (3.00 g, 9.14 mmol), ethylene glycol (5.1 mL, 91 mmol, 10 eq.), *p*-toluenesulfonic acid monohydrate (175 mg, 914 μmol , 10 mol%) and toluene (91 mL). The resulting mixture was heated at 120 °C for 60 hours and then cooled to room temperature and quenched with $\text{NaHCO}_3(\text{aq})$. The aqueous layer was extracted twice with EtOAc, the organic extracts combined, dried over MgSO_4 , filtered and concentrated *in vacuo*. The resulting solid was purified by flash column chromatography (eluted with 1:0.8 petroleum ether/ CHCl_3), affording **12** (2.14 g, 63%) as a white solid. Mp: 89 - 90 °C. IR ν_{\max} (thin film) 3031, 2990, 2892 cm^{-1} . HRMS: calculated for $\text{C}_{19}\text{H}_{18}\text{O}_2\text{NBr}$, 372.05937 $[\text{M}+\text{H}]^+$, found m/z 372.05930, $\Delta = -0.19$ ppm. ^1H NMR (400 MHz, CDCl_3) δ : 7.59-7.53 (1H, m, HC_{Ar}), 7.20-7.05 (6H, m, $6 \times \text{HC}_{\text{Ar}}$), 7.85-6.79 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 5.60 (2H, s, PhCH_2N), 3.95-3.83 (2H, m, $\text{CH}_a\text{H}_b\text{CH}_a\text{H}_b$), 3.65-3.53 (2H, m, $\text{CH}_a\text{H}_b\text{CH}_a\text{H}_b$); 1.60 (3H, s, CCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ : 138.4, 137.1, 135.4 ($3 \times \text{C}_{\text{Ar}}$), 128.6 (HC_{Ar}), 127.4 (C_{Ar}), 127.0, 125.7, 123.6, 120.7, 119.8, 110.3 ($6 \times \text{HC}_{\text{Ar}}$), 106.4, 89.6 ($2 \times \text{C}_{\text{Ar}}$), 64.6 (OCH_2), 48.6 (PhCH_2N), 26.4 (CCH_3).

2-(1-Benzyl-2-(1,3-dioxolan-2-yl)-1H-indol-3-yl)-1-phenylpropan-1-one (13). This compound was prepared according to general procedure A, affording **13** (47 mg, 74%) as a yellow solid. Mp: 159 - 164 °C. IR ν_{\max} (thin film) 3061, 2974, 2930, 2890, 1680, 1079, 745 cm^{-1} . HRMS: calculated for $\text{C}_{27}\text{H}_{25}\text{O}_3\text{N}$, 412.19072 $[\text{M}+\text{H}]^+$, found m/z 412.19196, $\Delta = 3.0$ ppm. ^1H NMR (400 MHz, CDCl_3) δ : 8.01 (2H, d, $J = 7.40$ Hz, $2 \times \text{HC}_{\text{Ar}}$), 7.64 (1H, d, $J = 7.6$ Hz, HC_{Ar}), 7.34 (1H, t, $J = 7.4$ Hz, HC_{Ar}), 7.24 (2H, t, $J = 7.4$ Hz, $2 \times \text{HC}_{\text{Ar}}$), 7.21-7.13 (3H, m, $3 \times \text{HC}_{\text{Ar}}$), 7.08-6.99 (3H, m, $3 \times \text{HC}_{\text{Ar}}$), 6.90-6.84 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 6.18 (1H, s, $\text{CH}(\text{OR})_2$), 5.42 (1H, s, $\text{PhCH}_a\text{H}_b\text{R}$), 5.41 (1H, s, $\text{PhCH}_a\text{H}_b\text{R}$), 5.15 (1H, q, $J = 6.8$, CHCH_3), 4.12-3.92 (4H, m, $(\text{OCH}_2)_2$), 1.66 (3H, d, CH_3CH); ^{13}C NMR (100 MHz, CDCl_3) δ : 201.1 ($\text{C}(\text{O})$), 138.1, 137.64, 137.0 ($3 \times \text{C}_{\text{Ar}}$), 132.4, 128.8 ($2 \times \text{HC}_{\text{Ar}}$), 128.7 (C_{Ar}), 128.6, 128.2, 127.1, 125.9 ($4 \times \text{HC}_{\text{Ar}}$), 125.8 (C_{Ar}), 123.1, 120.2, 119.9 ($3 \times \text{HC}_{\text{Ar}}$), 116.7 (C_{Ar}), 110.1 (HC_{Ar}), 98.6 ($\text{CH}(\text{OR})_2$), 65.2 ($\text{CHO}_2\text{C}_a\text{H}_2\text{C}_b\text{H}_2$), 65.0 ($\text{CHO}_2\text{C}_a\text{H}_2\text{C}_b\text{H}_2$), 47.7 (PhCH_2R), 39.8 (CHCH_3), 18.0 (CHCH_3).

9-Benzyl-4-methyl-3-phenyl-9H-pyrido[3,4-*b*]indole (14). This compound was prepared according to general procedure B on a 0.15 mmol scale, affording **14** (50 mg, 94%) as a yellow solid. Mp: 164 - 167 °C. IR ν_{\max} (thin film) 3055, 3030, 2924, 1454, 737, 701 cm^{-1} . HRMS: calculated for

$\text{C}_{25}\text{H}_{21}\text{N}_2$, 349.16993 $[\text{M}+\text{H}]^+$, found m/z 349.16946, $\Delta = -1.3$ ppm. ^1H NMR (400 MHz, CDCl_3) δ : 8.82 (1H, s, $\text{HC}(1)$), 8.33 (1H, d, $J = 8.0$ Hz, HC_{Ar}), 7.65-7.60 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 7.59 (1H, ddd, $J = 8.3, 7.1, 1.2$ Hz, HC_{Ar}), 7.54-7.47 (3H, m, $3 \times \text{HC}_{\text{Ar}}$), 7.45-7.39 (1H, m, HC_{Ar}), 7.34 (1H, t, $J = 8.0$ Hz, $\text{HC}(6)$), 7.32-7.25 (3H, m, $3 \times \text{HC}_{\text{Ar}}$), 7.22-7.17 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 5.58 (2H, s, PhCH_2R), 2.91 (3H, s, RCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ : 149.2, 141.7, 141.2, 136.6, 135.6 ($5 \times \text{C}_{\text{Ar}}$), 130.0, 129.3 ($2 \times \text{HC}_{\text{Ar}}$), 129.0 ($\text{C}(1)$), 128.4 (C_{Ar}), 128.1, 127.8, 127.8, 127.2, 126.6 ($5 \times \text{HC}_{\text{Ar}}$), 124.9 (C_{Ar}), 124.2 ($\text{C}(5)$), 122.4 (C_{Ar}), 119.9 ($\text{C}(6)$), 109.6 (HC_{Ar}), 46.9 (PhCH_2R), 17.6 (RCH_3).

2-(1-Benzyl-2-(2-methyl-1,3-dioxolan-2-yl)-1H-indol-3-yl)-1-phenylethan-1-one (15). This compound was prepared according to general procedure A on 0.15 mmol scale, affording **15** (50 mg, 84%) as an off-white solid. Mp: 128 - 131 °C. IR ν_{\max} (thin film) 3058, 3029, 2989, 2891, 1691, 1197, 742 cm^{-1} . HRMS: calculated for $\text{C}_{27}\text{H}_{25}\text{O}_3\text{NNa}$, 434.17266 $[\text{M}+\text{Na}]^+$, found m/z 434.17270, $\Delta = 0.08$ ppm. ^1H NMR (400 MHz, CDCl_3) δ : 8.15-8.11 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 7.63-7.56 (1H, m, HC_{Ar}), 7.55-7.46 (3H, m, $3 \times \text{HC}_{\text{Ar}}$), 7.30-7.12 (6H, m, $6 \times \text{HC}_{\text{Ar}}$), 6.98-6.93 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 5.67 (2H, s, PhCH_2N), 4.72 (2H, s, $\text{ArCH}_2\text{C}(\text{O})$), 3.88-3.80 (2H, m, $\text{CH}_a\text{H}_b\text{CH}_a\text{H}_b$), 3.68-3.62 (2H, m, $\text{CH}_a\text{H}_b\text{CH}_a\text{H}_b$), 1.65 (3H, s, CCH_3); ^{13}C NMR (100 MHz, CDCl_3) δ : 198.2 ($\text{C}(\text{O})$), 139.0, 137.5, 137.4, 136.6 ($4 \times \text{C}_{\text{Ar}}$), 132.8, 128.6, 128.5 ($3 \times \text{HC}_{\text{Ar}}$), 128.4 (C_{Ar}), 128.3, 126.7, 125.8, 122.5, 119.8, 118.6, 110.3 ($7 \times \text{HC}_{\text{Ar}}$), 107.3, 106.8 ($\text{C}_{\text{Ar}} + \text{CCH}_3$), 64.8 (OCH_2), 48.0 (PhCH_2N), 35.2 ($\text{ArCH}_2\text{C}(\text{O})$), 27.2 (CCH_3).

9-Benzyl-1-methyl-3-phenyl-9H-pyrido[3,4-*b*]indole (16). This compound was prepared according to a modification of general procedure B on a 85 μmol scale, affording **16** (28 mg, 94%) as a brown solid. A mixture of EtOH/ H_2O /DMF (3:1:2) was used as solvent and the temperature was kept at 110 °C for this cyclization. Mp: 127 - 129 °C. IR ν_{\max} (thin film) 3060, 3030, 1472, 734, 694 cm^{-1} . HRMS: calculated for $\text{C}_{25}\text{H}_{21}\text{N}_2$, 349.16993 $[\text{M}+\text{H}]^+$, found m/z 349.16943, $\Delta = -1.41$ ppm. ^1H NMR (500 MHz, CDCl_3) δ : 8.31 (1H, s, $\text{HC}(4)$), 8.22 (1H, d, $J = 7.7$ Hz, HC_{Ar}), 8.16-8.12 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 7.56-7.48 (3H, m, $3 \times \text{HC}_{\text{Ar}}$), 7.41-7.35 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 7.34-7.22 (4H, m, $5 \times \text{HC}_{\text{Ar}}$), 7.05-7.00 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 5.81 (2H, s, PhCH_2N), 2.95 (3H, s, CH_3); ^{13}C NMR (125 MHz, CDCl_3) δ : 145.9, 141.3, 140.2, 139.4, 137.0, 133.9, 129.2 ($7 \times \text{C}_{\text{Ar}}$), 127.9, 127.6, 127.3, 126.5, 126.5, 125.7, 124.4 ($7 \times \text{HC}_{\text{Ar}}$), 120.7 (C_{Ar}), 120.4, 119.0, 108.9 ($3 \times \text{HC}_{\text{Ar}}$), 108.5 ($\text{C}(4)$), 47.2 (PhCH_2N), 22.4 (CH_3).

2-(2-Benzoyl-1-benzyl-1H-indol-3-yl)-1-phenylethan-1-one (17). This compound was prepared according to general procedure A on a 6.36 mmol scale, affording **17** (1.75 g, 64%) as a yellow solid. Mp: 132 - 134 °C. IR ν_{\max} (thin film) 3059, 3030, 1689, 1637, 745, 729 cm^{-1} . HRMS: calculated for $\text{C}_{30}\text{H}_{23}\text{O}_2\text{NNa}$, 452.16210 $[\text{M}+\text{Na}]^+$, found m/z 452.16183, $\Delta = -0.59$ ppm. ^1H NMR (400 MHz, CDCl_3) δ : 7.78 (2H, ddd, $J = 8.0, 1.3, 0.9$ Hz, $2 \times \text{HC}_{\text{Ar}}$), 7.74-7.69 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 7.58 (1H, d, $J = 8.0$ Hz, HC_{Ar}), 7.54-7.48 (1H, m, HC_{Ar}), 7.43-7.13 (11H, m, $11 \times \text{HC}_{\text{Ar}}$), 7.05-7.00 (2H, m, $2 \times \text{HC}_{\text{Ar}}$), 5.59 (2H, s, PhCH_2Ar), 4.26 (2H, s, $\text{CH}_2\text{C}(\text{O})$); ^{13}C NMR (100 MHz, CDCl_3) δ : 196.4, 190.2 ($2 \times \text{C}(\text{O})$), 139.6, 138.8, 138.0, 136.6, 134.5 ($5 \times \text{C}_{\text{Ar}}$), 133.0, 132.8, 129.4, 128.6,

128.6, 128.5, 128.1 (7 × HC_{Ar}), 127.5 (C_{Ar}), 127.3, 126.5, 125.6, 121.1, 120.9 (5 × HC_{Ar}), 116.1 (C_{Ar}), 110.9 (HC_{Ar}), 48.1 (PhCH₂Ar), 36.0 (CH₂C(O)).

9-Benzyl-1,3-diphenyl-9H-pyrido[3,4-b]indole (18). This compound was prepared according to a modification of general procedure B on a 0.17 mmol scale, affording **18** (61 mg, 85%) as a yellow solid. A mixture of EtOH/H₂O/DMF (3:1:2) was used as solvent and the temperature was kept at 110 °C for this cyclization. Mp: 170 - 174 °C. IR ν_{max} (thin film) 3058, 3031, 1468, 1450, 737, 694 cm⁻¹. HRMS: calculated for C₃₀H₂₂N₂, 411.18558 [M+H]⁺, found *m/z* 411.18452, Δ = -2.57 ppm. ¹H NMR (400 MHz, CDCl₃) δ: 8.48 (1H, s, HC(4)), 8.30 (1H, ddd, *J* = 7.8, 1.2, 0.8 Hz, HC_{Ar}), 8.23-8.18 (2H, m, 2 × HC_{Ar}), 7.58-7.47 (5H, m, 5 × HC_{Ar}), 7.45-7.30 (6H, m, 6 × HC_{Ar}), 7.20-7.10 (3H, m, 3 × HC_{Ar}), 6.68-6.62 (2H, m, 2 × HC_{Ar}), 5.25 (2H, s, PhCH₂N); ¹³C NMR (100 MHz, CDCl₃) δ: 147.1, 144.0, 143.2, 140.3, 139.9, 137.1, 134.0, 131.8 (8 × C_{Ar}), 129.6, 128.7, 128.6, 128.4, 128.3, 128.0, 127.8, 127.1, 127.0, 125.8 (10 × HC_{Ar}), 122.0 (C_{Ar}), 121.6, 120.3 (2 × HC_{Ar}), 110.8 (C(3)), 110.2 (HC_{Ar}), 48.2 (PhCH₂N).

9-Benzyl-3-(tert-butyl)-9H-pyrido[3,4-b]indole (19). This compound was prepared according to general procedure D, affording **19** (51 mg, 53%) as a brown solid. Mp: 132 - 134 °C. IR ν_{max} (thin film) 3030, 2956, 2864, 1468, 740, 698 cm⁻¹. HRMS: calculated for C₂₂H₂₃N₂, 315.18558 [M+H]⁺, found *m/z* 315.18530, Δ = -0.86 ppm. ¹H NMR (400 MHz, CDCl₃) δ: 8.82 (1H, d, *J* = 0.9 Hz, HC(1)), 8.19 (1H, d, *J* = 7.8 Hz, HC_{Ar}), 8.19 (1H, d, *J* = 0.9 Hz, HC(4)), 7.55 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, HC_{Ar}), 7.43 (1H, d, *J* = 8.3 Hz, HC_{Ar}), 7.32-7.18 (6H, m, 6 × HC_{Ar}), 5.53 (2H, s, PhCH₂N), 1.51 (9H, s, (CH₃)₃C); ¹³C NMR (100 MHz, CDCl₃) δ: 159.0, 141.8, 136.7, 135.0 (4 × C_{Ar}), 130.8 (C(1)), 129.3 (C_{Ar}), 128.9, 128.2, 127.8, 126.7, 121.8 (5 × HC_{Ar}), 121.6 (C_{Ar}), 119.6, 109.6 (2 × H_{Ar}), 109.4 ((4)), 47.1 (PhCH₂N), 37.2 ((CH₃)₃C), 30.9 ((CH₃)₃C).

9-Benzyl-4-isopropyl-3-phenyl-9H-pyrido[3,4-b]indole (20). This compound was prepared according to general procedure D, affording **20** (84 mg, 73%) as a brown solid. Mp: 170 - 171 °C. IR ν_{max} (thin film) 3055, 3030, 2990, 2958, 2929, 2872, 1439, 741, 701 cm⁻¹. HRMS: calculated for C₂₇H₂₄N₂, 377.20123 [M+H]⁺, found *m/z* 377.20139, Δ = 0.42 ppm. ¹H NMR (500 MHz, CDCl₃) δ: 8.89 (1H, s, HC(1)), 7.62-7.53 (3H, m, 3 × HC_{Ar}), 7.46-7.37 (4H, m, 4 × HC_{Ar}), 7.33-7.23 (5H, m, 5 × HC_{Ar}), 6.95 (1H, dd, *J* = 8.0, 6.9 Hz, HC_{Ar}), 6.83 (1H, d, *J* = 8.0 Hz, HC_{Ar}), 5.53 (2H, s, PhCH₂N), 3.18 (1H, hept, *J* = 6.8 Hz, CH(CH₃)₂), 1.29 (6H, d, *J* = 6.8 Hz, CH(CH₃)₂); ¹³C NMR (100 MHz, CDCl₃) δ: 153.9, 141.8, 138.6, 136.7, 134.9 (5 × C_{Ar}), 130.9, 129.3, 128.9, 128.9 (4 × HC_{Ar}), 128.9, 128.8 (2 × C_{Ar}), 127.8, 127.8, 127.8, 126.8, 123.5 (5 × HC_{Ar}), 121.6 (C_{Ar}), 119.4, 109.3 (2 × HC_{Ar}), 47.0 (PhCH₂N), 30.9 (CH(CH₃)₂), 23.2 (CH(CH₃)₂).

9-benzyl-3-(furan-2-yl)-4-methyl-9H-pyrido[3,4-b]indole (21). This compound was prepared according to general procedure D, affording **21** (78 mg, 75%) as a brown solid. Mp: 156 - 159 °C. IR ν_{max} (thin film) 3141, 2918, 1488, 1301, 733, 696 cm⁻¹. HRMS: calculated for C₂₃H₁₉ON₂, 339.14919 [M+H]⁺, found *m/z* 339.14883, Δ = -1.05 ppm. ¹H NMR (500 MHz, CDCl₃) δ: 8.63 (1H, s, HC(1)), 8.19 (1H, d, *J* = 8.0

Hz, HC_{Ar}), 7.50 (1H, dd, *J* = 1.9, 0.7 Hz, OCH), 7.44 (1H, ddd, *J* = 8.2, 7.2, 1.1 Hz, HC_{Ar}), 7.33 (1H, d, *J* = 8.3 Hz, HC_{Ar}), 7.20 (1H, ddd, *J* = 8.0, 7.3, 0.6 Hz, HC_{Ar}), 7.16-7.09 (3H, m, 3 × HC_{Ar}), 7.03-6.99 (2H, m, 2 × HC_{Ar}), 6.67 (1H, dd, *J* = 3.3, 0.7 Hz, OCCCH), 6.46 (1H, dd, *J* = 3.3, 1.9 Hz, OCHCH), 5.39 (2H, s, PhCH₂N), 2.89 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 154.1 (C_{Ar}), 142.2 (OCH), 141.6, 139.1, 136.4, 135.3 (4 × C_{Ar}), 129.6 (C(1)), 128.9 (HC_{Ar}), 128.3 (C_{Ar}), 127.8, 127.8, 126.5 (3 × HC_{Ar}), 125.4 (C_{Ar}), 124.2 (HC_{Ar}), 122.4 (C_{Ar}), 120.1 (HC_{Ar}), 111.2 (OCHCH), 109.7 (HC_{Ar}), 109.6 (OCCCH), 46.8 (PhCH₂N), 16.8 (CH₃).

9-Benzyl-4-ethyl-3-phenyl-9H-pyrido[3,4-b]indole (22).

This compound was prepared according to general procedure D, affording **22** (76 mg, 68%) as a brown solid. Mp: 136 - 138 °C. IR ν_{max} (thin film) 3056, 2969, 2933, 2873, 1441, 730, 700 cm⁻¹. HRMS: calculated for C₂₆H₂₃N₂, 363.18558 [M+H]⁺, found *m/z* 363.18530, Δ = -0.75 ppm. ¹H NMR (500 MHz, CDCl₃) δ: 8.81 (1H, s, C(1)), 8.28 (1H, d, *J* = 8.0 Hz, HC_{Ar}), 7.61-7.55 (3H, m, 3 × HC_{Ar}), 7.52-7.46 (3H, m, 3 × HC_{Ar}), 7.44-7.39 (1H, m, HC_{Ar}), 7.35 (1H, ddd, *J* = 8.0, 7.1, 1.0 Hz, HC_{Ar}), 7.32-7.26 (3H, m, 3 × HC_{Ar}), 7.24-7.20 (2H, m, 2 × HC_{Ar}), 5.60 (2H, s, PhCH₂N), 3.26 (2H, q, *J* = 7.5 Hz, CH₂CH₃), 1.44 (3H, t, *J* = 7.5 Hz, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 149.1, 141.7, 141.5, 136.6, 136.2, 131.2 (6 × C_{Ar}), 129.5 (C(1)), 129.4, 129.0, 128.1, 127.8, 127.8 (5 × HC_{Ar}), 127.4 (C_{Ar}), 127.2, 126.6, 124.2 (3 × HC_{Ar}), 121.5 (C_{Ar}), 120.1, 109.7 (2 × HC_{Ar}), 46.9 (PhCH₂N), 23.4 (CH₂CH₃), 14.5 (CH₂CH₃).

9-Benzyl-3-(2-methoxyphenyl)-9H-pyrido[3,4-b]indole (23)

This compound was prepared according to general procedure D, affording **23** (83 mg, 74%) as a yellow solid. Mp: 95 - 97 °C. IR ν_{max} (thin film) 3030, 2935, 2834, 1491, 727, 700 cm⁻¹. HRMS: calculated for C₂₅H₂₀N₂O, 365.16484 [M+H]⁺, found *m/z* 365.16464, Δ = -0.54 ppm. ¹H NMR (500 MHz, CDCl₃) δ: 8.94 (1H, d, *J* = 1.0 Hz, HC(1)), 8.51 (1H, d, *J* = 1.0 Hz, HC(4)), 8.22 (1H, ddd, *J* = 7.8, 1.2, 0.7 Hz, HC_{Ar}), 7.84 (1H, dd, *J* = 7.6, 1.8 Hz, HC_{Ar}), 7.57 (1H, ddd, *J* = 8.3, 7.1, 1.2 Hz, HC_{Ar}), 7.46-7.42 (1H, m, HC_{Ar}), 7.38 (1H, ddd, *J* = 8.3, 7.4, 1.8 Hz, HC_{Ar}), 7.34-7.18 (6H, m, 6 × HC_{Ar}), 7.14-7.09 (1H, m, HC_{Ar}), 7.06 (1H, dd, *J* = 8.3, 1.0 Hz, HC_{Ar}), 5.58 (2H, s, PhCH₂N), 3.91 (3H, s, CH₃O); ¹³C NMR (125 MHz, CDCl₃) δ: 156.8, 146.0, 141.8, 136.6, 135.7 (5 × C_{Ar}), 131.6 (HC_{Ar}), 131.5 (C(1)), 130.2, 129.0 (2 × C_{Ar}), 128.9, 128.9, 128.4, 127.8, 126.7, 122.0 (6 × HC_{Ar}), 121.7 (C_{Ar}), 121.1, 119.8 (2 × HC_{Ar}), 115.9 (C(4)), 111.5, 109.7 (2 × HC_{Ar}), 55.8 (CH₃O), 47.0 (PhCH₂N).

3-((3*r*,5*r*,7*r*)-Adamantan-1-yl)-9-benzyl-9H-pyrido[3,4-b]indole (24).

This compound was prepared according to general procedure D, affording **24** (73 mg, 61%) as a brown solid. Mp: 241 - 243 °C. IR ν_{max} (thin film) 2901, 2846, 1464, 1452, 738, 698 cm⁻¹. HRMS: calculated for C₂₈H₃₀N₂, 393.23253 [M+H]⁺, found *m/z* 393.23257, Δ = 0.12 ppm. ¹H NMR (500 MHz, CDCl₃) δ: 8.82 (1H, d, *J* = 1.0 Hz, HC(1)), 8.17 (1H, d, *J* = 7.8 Hz, HC_{Ar}), 7.96 (1H, d, *J* = 1.0 Hz, HC(4)), 7.54 (1H, ddd, *J* = 8.3, 7.2, 1.1 Hz, HC_{Ar}), 7.43 (1H, d, *J* = 8.3 Hz, HC_{Ar}), 7.30-7.23 (4H, m, 4 × HC_{Ar}), 7.22-7.18 (2H, m, 2 × HC_{Ar}), 5.53 (2H, s, PhCH₂N), 2.19-2.15 (3H, m, 3 × CH), 2.14 (6H, d, *J* = 2.9 Hz, RC(CH₂)₃), 1.84 (6H, t, *J* = 3.1, 3 × CH₂); ¹³C NMR (125 MHz, CDCl₃) δ: 158.0, 140.7,

135.7, 134.0 (4 × C_{Ar}), 129.9 (C(1)), 128.3 (C_{Ar}), 127.8, 127.1, 126.7, 125.7, 120.7 (5 × HC_{Ar}), 120.6 (C_{Ar}), 118.5 (HC_{Ar}), 108.5 (C(4)), 108.2 (HC_{Ar}), 46.0 (PhCH₂N), 41.6 (RC(CH₂)₃), 37.6 (RC(CH₂)₃), 35.9 (CH₂), 28.0 (CH).

9-Benzyl-3-(4-fluorophenyl)-4-methyl-9H-pyrido[3,4-b]indole (25). This compound was prepared according to general procedure D, affording **25** (58 mg, 52%) as a brown solid. Mp: 183 - 185 °C. IR ν_{max} (thin film) 3056, 1455 1219, 731, 699 cm⁻¹. HRMS: calculated for C₂₅H₁₉FN₂, 367.16050 [M+H]⁺, found *m/z* 367.16034, Δ = -0.45 ppm. ¹H NMR (500 MHz, CDCl₃) δ: 8.78 (1H, s, HC(1)), 8.32 (1H, d, *J* = 7.8 Hz, HC_{Ar}), 7.62-7.54 (3H, m, 3 × HC_{Ar}), 7.49 (1H, d, *J* = 8.2, HC_{Ar}), 7.35 (1H, t, *J* = 7.6 Hz, HC_{Ar}), 7.37-7.24 (3H, m, 3 × HC_{Ar}), 7.21-7.14 (4H, m, 4 × HC_{Ar}), 5.59 (2H, s, PhCH₂N), 2.89 (3H, s, CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 161.2 (d, *J* = 246 Hz, CF), 147.0, 140.6 (2 × C_{Ar}), 136.1 (d, *J* = 3.3 Hz, CCHCHCF), 135.4, 134.6 (2 × C_{Ar}), 130.5 (d, *J* = 8.1 Hz, CHCF), 128.2 (HC_{Ar}), 127.9 (HC(1)), 127.4 (C_{Ar}), 126.8 (d, *J* = 6.2 Hz, CHCF), 125.5 (HC_{Ar}), 123.8 (C_{Ar}), 123.1 (HC_{Ar}), 121.2 (C_{Ar}), 118.9, 114.0, 113.8, 108.6 (4 × HC_{Ar}), 45.8 (PhCH₂N), 16.5 (CH₃); ¹⁹F NMR (376 MHz, CDCl₃) δ_F: 115.4 (tt, *J* = 8.8, 5.5 Hz).

3-(Benzo[d][1,3]dioxol-5-yl)-9-benzyl-4-methyl-9H-pyrido[3,4-b]indole (26). This compound was prepared according to general procedure D, affording **26** (71 mg, 61%) as a brown solid. Mp: 152 - 155 °C. IR ν_{max} (thin film) 2890, 1459, 725 cm⁻¹. HRMS: calculated for C₂₅H₁₉N₂, 379.14410 [M+H]⁺, found *m/z* 379.14352, Δ = -1.53 ppm. ¹H NMR (500 MHz, CDCl₃) δ: 8.84 (1H, d, *J* = 0.9 Hz, HC(1)), 8.30 (1H, d, *J* = 0.9 Hz, HC(4)), 8.20 (1H, d, *J* = 7.8 Hz, HC_{Ar}), 7.64-7.54 (3H, m, 3 × HC_{Ar}), 7.43 (1H, d, *J* = 8.3 Hz, HC_{Ar}), 7.34-7.22 (4H, m, 4 × HC_{Ar}), 7.20-7.16 (2H, m, 2 × HC_{Ar}), 6.94 (1H, d, *J* = 8.1 Hz, HC_{Ar}), 6.01 (2H, s, O₂CH₂), 5.54 (2H, s, PhCH₂N); ¹³C NMR (125 MHz, CDCl₃) δ: 148.2, 147.5, 147.5, 141.9, 136.5, 135.8, 135.1 (7 × C_{Ar}), 131.6 (HC(1)), 129.8 (C_{Ar}), 129.0, 128.6, 127.9, 126.6, 121.9 (5 × HC_{Ar}), 121.6 (C_{Ar}), 120.4, 120.0 (2 × HC_{Ar}), 110.8 (HC(4)), 109.8, 108.5, 107.4 (3 × HC_{Ar}), 101.2 (O₂CH₂), 47.0 (PhCH₂N).

Synthesis of 2-(1-benzyl-2-(1,3-dioxolan-2-yl)-1H-indol-3-yl)-1,3-diphenylpropan-1-one (27). A fresh solution of LiHMDS was prepared in a dry vial adding sequentially dry THF (7.3 mL), HMDS (290 μL, 1.39 mmol, 2.5 eq.), a 2.5 M solution of *n*BuLi (1.39 mmol, 558 μL, 2.5 eq.) and stirring at -78 °C for 10 minutes. Acetophenone (130 μL, 1.07 mmol, 2 eq.) was then added at 0 °C and stirred for 15 minutes. In a second dry vial were added bromo indole **1** (200 mg, 558 μmol) and Pd(drbpf)Cl₂ (18 mg, 27.9 μmol, 5 mol%). The flask was sealed, evacuated and backfilled with argon twice. The freshly formed enolate solution was then transferred *via* syringe to the flask. The mixture was stirred at 50 °C for 24 hours in an oil bath. After cooling to room temperature, benzyl bromide (166 μL, 1.39 mmol, 2.5 eq.) was added and the mixture was stirred at 90 °C for 24 h. The resulting mixture was filtered through a plug of silica and concentrated *in vacuo*. The crude product was purified by flash column chromatography (eluted with 9:1 petroleum ether/EtOAc) to afford product **27** (177 mg, 65%) as a brown solid. Mp: 134 - 135 °C. IR ν_{max} (thin film) 3060, 3027, 2924, 1679, 1083, 742, 697 cm⁻¹. HRMS: calculated for C₃₃H₃₀O₃N, 488.22202

[M+H]⁺, found *m/z* 488.22195, Δ = -0.14 ppm. ¹H NMR (400 MHz, C₆D₆) δ: 8.24 (2H, ddd, *J* = 8.2, 1.9, 1.5 Hz, HC_{Ar}), 8.05 (1H, d, *J* = 8.05 Hz, HC_{Ar}), 7.17-7.14 (1H, m, HC_{Ar}), 7.12-6.89 (12H, m, HC_{Ar}), 6.86 (1H, d, *J* = 8.2 Hz, HC_{Ar}), 6.72 (2H, ddd, *J* = 7.6, 1.9, 1.3 Hz, 2 × HC_{Ar}), 5.92 (1H, s, CH(OR)₂), 5.39 (1H, dd, *J* = 8.4, 6.0 Hz, CH₂CHC(O)), 5.15 (1H, d, *J* = 17.1 Hz, PhCH₂H_bAr), 5.09 (1H, d, *J* = 17.1 Hz, PhCH₂H_bAr), 3.99 (1H, dd, *J* = 13.5, 6.0 Hz, PhCH₂H_bCH), 3.59 (1H, dd, *J* = 13.5, 8.4 Hz, PhCH₂CH_bCH), 3.36-3.13 (4H, m, (OCH₂)₂); ¹³C NMR (100 MHz, C₆D₆) δ_C: 198.9 (C(O)), 140.8, 138.3, 137.6, 137.3 (4 × C_{Ar}), 132.0 (HC_{Ar}), 129.9, (C_{Ar}), 129.4, 128.8, 128.3, 128.0, 128.0, 126.7 (6 × HC_{Ar}), 126.3 (C_{Ar}), 125.9, 125.8, 123.1, 120.5, 120.3 (5 × HC_{Ar}), 113.9 (C_{Ar}), 110.3 (HC_{Ar}), 99.5 (CH(OR)₂), 64.6 (O₂C₆H₃C_bH₂), 64.3 (O₂C₆H₃C_bH₂), 48.0 (CH₂CHC(O)), 47.5 (PhCH₂Ar), 38.2 (CH₂CH).

4,9-Dibenzyl-3-phenyl-9H-pyrido[3,4-b]indole (28). This compound was prepared according to general procedure B on a 0.18 mmol scale, affording **28** (75 mg, 96%) as an off-white solid. Mp: 201 - 204 °C. IR ν_{max} (thin film) 3056, 3026, 1448, 740, 728, 699 cm⁻¹. HRMS: calculated for C₃₁H₂₅N₂, 425.20123 [M+H]⁺, found *m/z* 425.20102, Δ = -0.48 ppm. ¹H NMR (400 MHz, CDCl₃) δ: 8.95 (1H, s, HC(1)), 7.89 (1H, d, *J* = 8.0 Hz, HC_{Ar}), 7.55-7.44 (4H, m, 4 × HC_{Ar}), 7.42-7.10 (14H, m, 14 × HC_{Ar}), 5.64 (2H, s, PhCH₂N), 4.68 (2H, s, PhCH₂Ar); ¹³C NMR (100 MHz, CDCl₃) δ_C: 150.3, 141.8, 141.0, 139.7, 136.5, 136.0 (6 × C_{Ar}), 130.3 (HC(1)), 129.5, 129.0 (2 × HC_{Ar}), 128.9 (C_{Ar}), 128.7, 128.2, 128.0, 128.0, 127.9, 127.4, 126.7, 126.1 (8 × HC_{Ar}), 126.0 (C_{Ar}), 124.4 (HC_{Ar}), 121.5 (C_{Ar}), 120.1, 109.6 (2 × HC_{Ar}), 47.0 (PhCH₂N), 36.4 (PhCH₂Ar).

4-Allyl-9-benzyl-3-phenyl-9H-pyrido[3,4-b]indole (29). This compound was prepared according to general procedure F, affording **29** (62 mg, 54%) as an off-white solid. Mp: 156 - 158 °C. IR ν_{max} (thin film) 3056, 2926, 1487, 739, 700 cm⁻¹. HRMS: calculated for C₂₇H₂₃N₂, 375.18558 [M+H]⁺, found *m/z* 375.18552, Δ = -0.16 ppm. ¹H NMR (400 MHz, CDCl₃) δ: 8.75 (1H, s, HC(1)), 8.09 (1H, d, *J* = 8.0 Hz, HC_{Ar}), 7.52 (2H, d, *J* = 7.0 Hz, 2 × HC_{Ar}), 7.44 (1H, t, *J* = 7.5 Hz, HC_{Ar}), 7.39-7.25 (4H, m, 4 × HC_{Ar}), 7.23-7.05 (6H, m, 6 × HC_{Ar}), 6.23-6.10 (1H, m, ArCH₂CHCH₂), 5.48 (2H, s, PhCH₂N), 5.08 (1H, dd, *J* = 10.3, 1.3 Hz, CH_{cis}H_{trans}CHAr), 4.87 (1H, dd, *J* = 17, 1.3 Hz, CH_{cis}H_{trans}CHAr), 3.92-3.84 (2H, m, ArCH₂CHCH₂); ¹³C NMR (100 MHz, CDCl₃) δ_C: 149.8, 141.8, 141.1, 136.5, 135.9 (5 × C_{Ar}), 135.6 (ArCH₂CHCH₂), 130.0, 129.5, 129.0 (3 × HC_{Ar}), 128.4 (C_{Ar}), 128.0, 128.0, 127.9, 127.4, 126.6 (5 × HC_{Ar}), 125.9 (C_{Ar}), 124.6 (HC_{Ar}), 121.4 (C_{Ar}), 120.0 (HC_{Ar}), 116.8 (ArCH₂CHCH₂), 109.7 (HC_{Ar}), 47.0 (PhCH₂N), 34.5 (ArCH₂CHCH₂).

9-Benzyl-4-(4-methoxybenzyl)-3-phenyl-9H-pyrido[3,4-b]indole (30). This compound was prepared according to general procedure F, affording **30** (74 mg, 53%) as a yellow solid. Mp: 208 -209 °C. IR ν_{max} (thin film) 3058, 2932, 2835, 1244, 735, 699 cm⁻¹. HRMS: calculated for C₃₂H₂₆N₂O, 455.21179 [M+H]⁺, found *m/z* 455.21158, Δ = -0.46 ppm. ¹H NMR (400 MHz, CDCl₃) δ: 8.80 (1H, s, HC(1)), 7.78 (1H, d, *J* = 8.0 Hz, HC_{Ar}), 7.42-7.30 (4H, m, 4 × HC_{Ar}), 7.28-7.08 (8H, m, 8 × HC_{Ar}), 7.05-6.98 (1H, m, HC_{Ar}), 6.94 (2H, d, *J* = 8.6 Hz, 2 × HC_{Ar}), 6.70-6.65 (2H, m, 2 × HC_{Ar}), 5.49 (2H, s,

PhCH₂N), 4.47 (2H, s, PMBCH₂Ar), 3.63 (3H, s, CH₃O); ¹³C NMR (100 MHz, CDCl₃) δ_c: 157.9, 150.2, 141.8, 141.0, 136.5, 136.0, 131.7 (7 × C_{Ar}), 130.3 (C(1)), 129.5, 129.1, 129.0 (3 × HC_{Ar}), 128.9 (C_{Ar}), 128.0, 128.0, 127.9, 127.4, 126.7 (5 × HC_{Ar}), 126.4 (C_{Ar}), 124.5 (HC_{Ar}), 121.5 (C_{Ar}), 120.1, 114.1, 109.6 (3 × HC_{Ar}), 55.2 (CH₃O), 47.0 (PhCH₂N), 35.6 (PMBCH₂Ar).

9-Benzyl-4-(naphthalen-2-ylmethyl)-3-phenyl-9H-pyrido[3,4-b]indole (31). This compound was prepared according to general procedure F, affording **31** as a brown solid (70 mg, 48%). Mp: 181 - 183 °C. IR ν_{max} (thin film) 3052, 734, 699 cm⁻¹. HRMS: calculated for C₃₅H₂₇N₂, 475.21688 [M+H]⁺, found *m/z* 475.21644, Δ = -0.91 ppm. ¹H NMR (500 MHz, CDCl₃) δ_H: 9.01 (1H, s, HC(1)), 7.88 (1H, d, *J* = 8.1 Hz, HC_{Ar}), 7.85-7.81 (2H, m, 2 × HC_{Ar}), 7.61 (1H, d, *J* = 7.8 Hz, HC_{Ar}), 7.57-7.52 (2H, m, 2 × HC_{Ar}), 7.51-7.46 (3H, m, 3 × HC_{Ar}), 7.45-7.25 (11H, m, 11 × HC_{Ar}), 7.09-7.03 (1H, m, HC_{Ar}), 5.66 (2H, s, PhCH₂N), 4.84 (2H, s, C₁₀H₇CH₂Ar); ¹³C NMR (125 MHz, CDCl₃) δ_c: 150.3, 141.9, 140.9, 137.4, 136.5, 136.1, 133.8, 132.2 (8 × C_{Ar}), 130.5 (C(1)), 129.5, 129.0 (2 × HC_{Ar}), 129.0 (C_{Ar}), 128.5, 128.1, 128.0, 127.9, 127.8, 127.6, 127.5, 127.0, 126.7, 126.3, 126.0 (11 × HC_{Ar}), 125.8 (C_{Ar}), 125.4, 124.4 (2 × HC_{Ar}), 121.5 (C_{Ar}), 120.5, 109.6 (2 × HC_{Ar}), 47.1 (PhCH₂N), 36.8 (C₁₀H₇CH₂Ar).

Acknowledgment. We thank CAPES, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior, Brazil and AstraZeneca for supporting this project.

Supporting Information Available: Spectroscopic data for all new compounds are available. This material is available free of charge via the Internet at <http://pubs.acs.org>.

(1) (a) Freedland, C. S.; Mansbach, R. S. *Drug Alcohol Depend.* **1999**, *54*, 183. (b) Hassani, M.; Cal, W.; Koelsch, K. H.; Holley, D. C.; Rose, A. S.; Olang, F.; Lineswala, J. P.; Hollaway, W. G.; Gerdes, J. M.; Behforouz, M.; Beall, H. D. *J. Med. Chem.* **2008**, *51*, 3104. (c) Dai, J.-K.; Dan, W.-J.; Li, N.; Du, H.-T.; Zhang, J.-W.; Wang, J.-R. *Bioorg. Chem. Lett.* **2016**, *26*, 580. (d) Frédérick, R.; Bruyère, C.; Vancraeynest, C.; Reniers, J.; Meinguet, C.; Pochet, L.; Backlung, A.; Masereel, B.; Kiss, R.; Wouters, J. *J. Med. Chem.* **2012**, *55*, 6489.
(2) Sun, B.; Morikawa, T.; Matsuda, H.; Tewtrakul, S.; Wu, L. J.; Harima, S.; Yoshikawa, M. *J. Nat. Prod.* **2004**, *67*, 1464.
(3) Jaeger, R. J. R.; Lambshöft, M.; Gottfried, S.; Spiteller, M.; Spiteller, P. *J. Nat. Prod.* **2013**, *76*, 127.
(4) Xin, W.-B.; Chou, G.-X.; Wang, Z.-T. *Phytochem. Lett.* **2011**, *4*, 380.
(5) Inman, W. D.; Bray, W. M.; Gassner, N. C.; Lokey, R. S.; Tenney, K.; Shen, Y. Y.; TenDyke, K.; Suh, T.; Crews, P. *J. Nat. Prod.* **2010**, *73*, 255.
(6) Tran, T. D.; Pham, N. B.; Ekins, M.; Hooper, J. N. A.; Quinn, R. J. *Mar. Drugs* **2015**, *13*, 4556.
(7) (a) Too, P. C.; Chua, S. H.; Wong, S. H.; Chiba, S. *J. Org. Chem.* **2011**, *76*, 6159. (b) Ding, S.; Shi, Z.; Jiao, N. *Org. Lett.* **2010**, *12*, 1540. (c) Zhang, H.; Larock, C. *J. Org. Chem.* **2002**, *67*, 9318.
(8) Nissen, F.; Richard, V.; Alayrac, C.; Witulski, B. *Chem. Commun.* **2011**, *47*, 6656.
(9) Dhiman, S.; Mishra, U.K.; Ramasastry, S. S. V. *Angew. Chem. Int. Ed.* **2016**, *55*, 7737.
(10) Laha, J. K.; Barolo, S. M.; Rossi, R. A.; Cuny, G. D. *J. Org. Chem.* **2011**, *76*, 6421.
(11) Namjoshi, O. A.; Gryboski, A.; Cooj, J. M. *J. Org. Chem.* **2011**, *76*, 4721.

(12) Chiba, S.; Xu, Y.-J.; Wang, Y.-F. *J. Am. Chem. Soc.* **2009**, *131*, 12886.
(13) Kamlah, A.; Lirk, F.; Bracher, F. *Tetrahedron* **2016**, *72*, 837-845.
(14) (a) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1997**, *119*, 11108-11109. (b) Palucki, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 12382-12383. (c) Satoh, T.; Kawamura, Y.; Miura, M.; Nomura, M. *Angew. Chem. Int. Ed.* **1997**, *36*, 1740-1742. For reviews, see: (d) Bellina, F.; Rossi, R. *Chem. Rev.* **2010**, *110*, 1082. (e) Johansson, C. C. C.; Colacot, T. J. *Angew. Chem. Int. Ed.* **2010**, *49*, 676.
(15) Potukuchi, H. K.; Spork, A. P.; Donohoe, T. J. *Org. Biomol. Chem.* **2015**, *13*, 4367.
(16) (a) Donohoe, T. J.; Pilgrim, B. S.; Jones, C. R.; Bassuto, J. A. *Proc. Natl. Acad. Sci. US* **2012**, *109*, 11605. (b) Pilgrim, B.; Gatland, A. E.; McTernan, C.; Procopiou, P.; Donohoe, T. J. *Org. Lett.* **2013**, *15*, 6190. (c) Gatland, A. E.; Pilgrim, B. S.; Procopiou, P. A.; Donohoe, T. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 14555. (d) Pilgrim, B. S.; Esteves, C. H. A.; McTernan, C. T.; Jones, G. R.; Tatton, M. R.; Procopiou, P. A.; Donohoe, T. J. *Org. Biomol. Chem.* **2016**, *14*, 1065.
(17) Hardegger, L. A.; Habegger, J.; Donohoe, T. J. *Org. Lett.* **2015**, *17*, 3222.
(18) Solé, D.; Bannasar, M.-L.; Jiménez, I. *Org. Biomol. Chem.* **2011**, *9*, 4535-4544.
(19) (a) Beare, N. A.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 541. (b) Si, C.; Myers, A. G. *Angew. Chem. Int. Ed.* **2011**, *50*, 10409.
(20) Biswas, S.; Batra, S. *Adv. Synth. Catal.* **2011**, *353*, 2861-2867.
(21) Kawatsure, M.; Hartwig, J. F. *J. Am. Chem. Soc.* **1999**, *121*, 1473.
(22) Suzuki, H.; Iwata, C.; Sakurai, K.; Tokumoto, K.; Takahashi, H.; Hanada, M.; Yokoyama, Y.; Murakami, Y. *Tetrahedron* **1997**, *53*, 1593-1606.
(23) Kolhatkar, R. B.; Ghorai, S. K.; George, C.; Reith, M. E. A.; Dutta, A. K. *J. Med. Chem.* **2003**, *46*, 2205-2215.
(24) Benson, S. C.; Gross, J. L.; Snyder, J. K. *J. Org. Chem.* **1990**, *55*, 3257-3269.
(25) Sechi, M.; Derudas, M.; Dallochio, R.; Dessì, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 5298-5310.
(26) Miki, Y.; Hachiken, H.; Yoshikawa, I. *Heterocycles* **1997**, *45*, 1143-1150.