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Heterocycle Synthesis

A Novel Approach to Highly Substituted β-Carbolines via Reductive Ring Transformation of 2-Acyl-3-isoxazolylindoles

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In memory of Rolf Huisgen.

Abstract: We have worked out a new approach to 1,3,4-trisubstituted β-carbolines of pharmaceutical interest. As central building blocks we used 2-acylindoles, which are readily available from indole-2-Weinreb amides. Bromination at C-3, followed by Suzuki–Miyaura cross-coupling with isoxazole-4-boronates gives 2-acyl-3-isoxazolylindoles. Ring closure to the β-carbolines was accomplished by reductive ring transformation upon catalytic hydrogenation in the presence of Cs_2CO_3.

Introduction

The β-carbolines represent a large and structurally diverse class of secondary metabolites from plants, marine invertebrates, and microorganisms. A broad spectrum of biological activities has been demonstrated for β-carbolines, e.g. antimicrobial, antiparasitic, antiviral, neuropharmacological,[1a] antitumor,[1b] and antiprotozoal[1c,1d] activities.

Previous research was mainly focused on the synthesis of β-carbolines bearing various residues at C-1, eventually in combination with substituents on ring C, e.g. a methoxy group at C-7 in harmine, a well-documented inhibitor of monoamine oxidase A (MAO-A) and protein kinases like DYRK1A.[2] The most common approaches to β-carbolines bearing residues at C-1 (reviewed in ref.[3]) start from tryptamine or tryptophan (**A**), and pyridine ring A is built up using either an aldehyde (Pictet–Spengler reaction)[4] or a carboxylic acid (Bischler-Napieralski reaction).[5] Fully aromatic compounds are obtained in a final dehydrogenation step of the intermediate di- or tetrahydro-β-carbolines. Alternatively, 1-substituted β-carbolines are available via Pd-catalyzed cross-coupling of 1-halogenated β-carbolines (**C**),[6] reaction of 1,9-dimetalated β-carboline with electrophiles,[7] and regioselective homolytic substitution reactions.[8] The precursors for these reactions are prepared from tryptamine as well. All of these approaches are primarily suitable for the construction of β-carbolines bearing various residues at C-1, and, depending on the utilization of tryptamine precursors bearing substituents on the benzene ring, β-carbolines having additional functional groups on ring C (Figure 1).

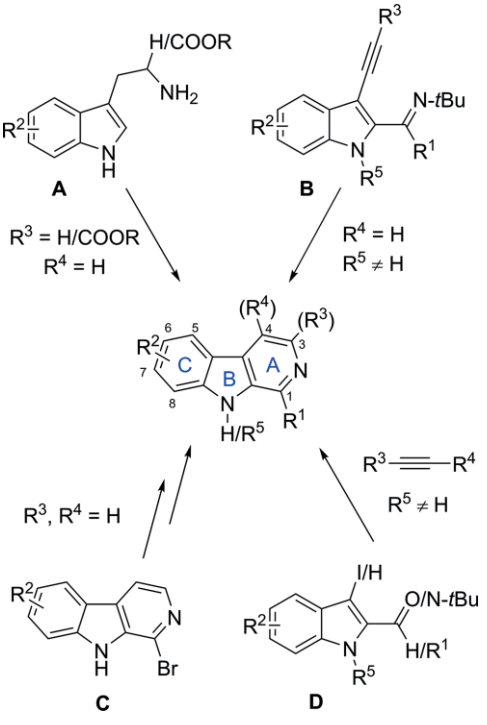

Figure 1. Published approaches to variously substituted β-carbolines with special focus on substituents on ring A.

The utilization of tryptamine building blocks in most of the common approaches towards β-carbolines means that introduction of additional residues at C-3 and C-4 of the target β-carbolines is typically not possible. Tryptamines bearing additional residues in the side chain are available via electrophilic substitution of indoles at C-3 with appropriately substituted nitroalkenes in several steps.[3] For an application in the synthesis of the alkaloid (*S*)-brevicolline, see ref.[9] Tryptamine deriva-

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tives obtained by functionalization of gramine with α-(alkylideneamino)nitriles furnished 1,3-disubstituted β-carbolines.[10] A convenient alternative approach was introduced by Larock[11] with the Pd-catalyzed cyclization of 3-alkynyl-2-formylindoles via the corresponding *tert*-butylimines (**B**, R^1 = H) to give 3-substituted β-carbolines. Rossi[12] published a variation starting from 2-acylindoles that provides 1,3-disubstituted β-carbolines in a similar manner. Larock's methodology was extended to the synthesis of 3,4-disubstituted β-carbolines by reacting internal alkynes with *tert*-butylimines of 3-iodoindole-2-carbaldehydes (**D**), but typically mixtures of regioisomers were obtained.[13] Jiao demonstrated that this iminoannulation can be accomplished even without the 3-iodo substituent on the indole-2-carbaldimine, if oxygen was used as an oxidant.[14] However, all of these methods for construction of ring A starting from alkynes require protection of the indole nitrogen, and only few examples for readily removable protective groups (sulfonyl, MOM) have been presented by the authors. For some additional approaches to ring A-substituted β-carbolines see ref.[15–18] In the past, we developed a number of β-carbolines as inhibitors of protein kinases (CLK1,[19] DYRK1A,[2,19a] PIM1[19a,20]), and detected pronounced effects of the substitution patterns at both ring C, the indole nitrogen, and C-1 on the biological activities. However, in the group of fully aromatic β-carbolines we worked on until now, substituents at C-3 and C-4 of ring A could not be investigated, since typically our building blocks were prepared from precursors that do not allow functionalization at C-3/C-4. In our attempt to establish broader structure-activity relationship (SAR) analysis of bioactive β-carbolines, we saw a need for working out novel methodologies for the synthesis of β-carbolines, which still can be modified freely at ring C (by selecting commercially available starting materials with manifold substitution patterns) and at C-1, but in addition the new protocol should enable us to introduce residues at C-3 and C-4 in a predictable manner and without formation of isomeric products.

As the chemistry of 1,3,4-trisubstituted β-carbolines is rather underexplored, we worked out an unprecedented approach to this chemotype. For the central step in the construction of the pyridine ring (ring A) we selected a formal cyclocondensation of an 1,5-diketone (or an equivalent **E** thereof) under incorporation of ammonia (Figure 2). Comparable cyclocondensations have been published before by others[21] and by us (using an enol ether as carbonyl equivalent).[22a] As building block for rings B+C as well as C-1 of ring A and the substituent R^1 located there, we selected 2-acylindoles (**G**/**H**). These are readily available from indole-2-Weinreb amides,[22] which in turn can, with a broad variety of substituents at the benzene ring, be prepared in a few steps from aromatic aldehydes via the corresponding esters obtained by Hemetsberger–Knittel synthesis and other established methods of indole chemistry.[23] A novel approach to indole-2-Weinreb amides starting from cinnamic acid Weinreb amides has been reported by us recently.[24] The remaining part of ring A (the nitrogen atom, C-3, C-4, as well as the substituents located there) was to be introduced by means of one single building block. An appropriately substituted isoxazole (**I**/**J**) appeared most promising for this purpose. On the one hand it should be feasible to introduce isoxazoles at C-3 of the indole building block by means of Pd-catalyzed cross-coupling reactions, and on the other hand, reductive ring cleavage of isoxazoles is known to give *Z*-enamino ketones.[25] The primary enamino group obtained by reduction should undergo cyclocondensation with the acyl residue at C-2 of the indole directly (or after treatment with an ammonia source) to provide carbon atoms C-3 and C-4 of the envisaged β-carboline. The other parts of the isoxazole building block would provide the substituents at C-3 and C-4 (Figure 2). The inevitable acyl group at C-4 of the resulting β-carbolines should offer the opportunity for a broad spectrum of consecutive modifications (reduction, oxidation, addition of nucleophiles) for the construction of novel, even more complex residues at this position.

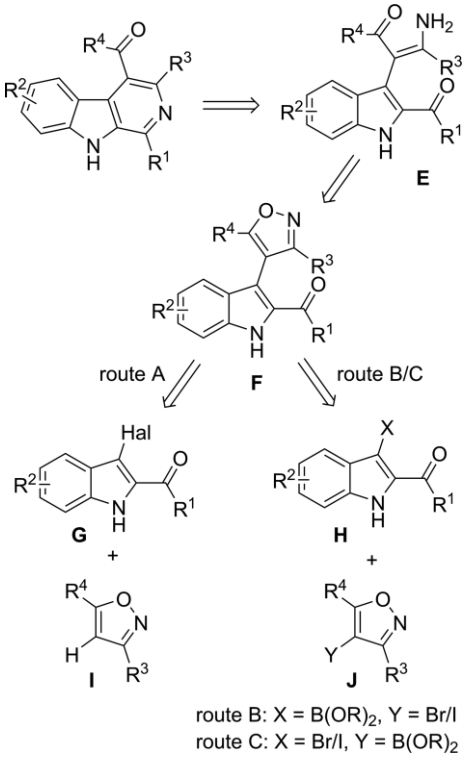
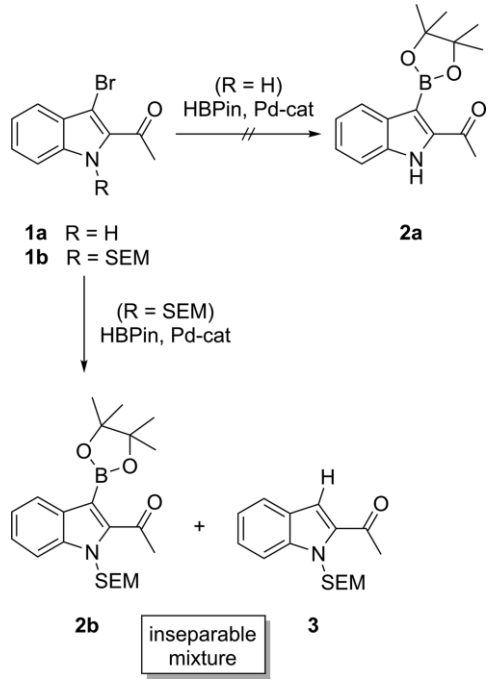


Figure 2. Attempted approach to highly substituted β-carbolines via 2-acyl-3-(isoxazol-4-yl)indoles (**F**) and envisaged routes for Pd-catalyzed cross-coupling reactions of 2-acylindoles (**G**/**H**) and isoxazole (**I**/**J**) building blocks.

The first challenge in this project was to work out an effective protocol for the connection of the 2-acylindole and isoxazole building blocks. To the best of our knowledge the synthesis of 3-(isoxazol-4-yl)indoles (**F**) has been the subject of only very few investigations, and only indole-*N*-protected compounds were obtained in low yields by 1,3-dipolar cycloaddition reactions.[26] So we intended to work out an alternative access via palladium-catalyzed biaryl synthesis. Three options appeared promising for this purpose: route A) direct arylation of 4-unsubstituted isoxazoles (**I**)[27] with 3-halogenated indoles (**G**) under C–H activation, or routes B) and C) by Suzuki–Miyaura cross-coupling of building blocks **H** and **J**, being either a 3-borylated 2-acylindole and a 4-haloisoxazole, or a 3-halogenated 2-acylindole and an isoxazole-4-boronic acid (or an ester thereof)[28] (Figure 2).

Results and Discussion

Route A appeared most attractive, since we already had 3-bromo-2-acylindoles in hands from our previous investigations,[22a] and 3,5-disubstituted isoxazoles are readily available following established methodologies, based on fundamental work of Huisgen on 1,3-diplar cycloadditions.[25a,29,30] Unfortunately, attempted couplings of 3,5-dimethylisoxazole with 2-acetyl-3-bromoindole (**1a**) and 3-bromoindole-2-Weinreb amide[22a] using published[27a] conditions resulted in negligible conversions. Consequently, we focused on Suzuki–Miyaura cross-coupling reactions. As mentioned above (Figure 2), two different combinations of aromatic building blocks (3-borylated 2-acylindole + 4-haloisoxazole (route B) or 3-halogenated 2-acylindole + 4-borylated isoxazole (route C)) were conceivable. Following route B first, we intended to introduce a pinacol boronate residue at C-3 of 2-acetylindole using a Masuda borylation.[31] Borylation of 2-acetyl-3-bromoindole (**1a**) with pinacolborane (HBpin) under Pd(0) catalysis[32] failed completely, whereas the N-SEM protected analogue **1b** gave an inseparable mixture of desired pinacol boronate **2b** and debrominated product **3**. Nevertheless, we submitted the obtained mixture to a Suzuki–Miyaura coupling with 4-bromo-3,5-dimethylisoxazole. Since we could not detect the desired biaryl in the reaction mixture, route B was abandoned (Scheme 1).



Scheme 1. Attempted borylations of 2-acetyl-3-bromoindoles **1a**/**1b**.

Finally, route C was successful. The 4-borylated isoxazoles required for this protocol can be built up de novo by regioselective 1,3-dipolar cycloaddition of nitrile oxides with alkynylboronates,[32] by Blum's oxyboration of ynone oximes,[33] or are obtained from 4-bromoisoxazoles via bromine-lithium exchange/trapping with trialkylborates[28] or by Pd-catalyzed Miyaura borylation.[34] Initial experiments were performed with commercially available isoxazole pinacolboronate **4a** and 2-acetyl-3-bromoindole (**1a**).[22a] Only poor yields (<15 %) were obtained in a first series of cross-coupling experiments using Pd(0) and Pd(II) catalysts in combination with different phosphine ligands (PPh_3, dppf, SPhos) and bases (DIPEA, K_2CO_3). These frustrating experiments gave rise to the question whether the free NH group of the indole prevented cross-coupling. So we introduced the SEM protective group, which we had identified as a very useful indole protective group in previous work.[35] But even SEM derivative **1b** gave only slightly improved yields (up to 20 %) under the cross-coupling conditions examined with **1a** before. Finally, further modifications of the catalyst system led to the $Pd(PPh_3)_4/Cs_2CO_3$ system, which gave a 61 % yield of the desired biaryl **5**. With this intermediate in hands the ring transformation reaction was examined. Reductive opening of the isoxazole ring was first attempted under conditions (catalytic hydrogenation with Pd/C catalyst in ethanolic KOH) which had given best results in our previously published approach to canthin-4-ones involving a related ring transformation.[36] But only a complex mixture of products was obtained. Fortunately, hydrogenation in ethanol without added base resulted in clean conversion (79 % yield) to the expected *Z*-enamino ketone **6**. The *Z*-configuration of the enamino ketone, which is stabilized by an intramolecular hydrogen bond, obviously prevents direct cyclization to the desired β-carboline **7** due to steric reasons. This prompted us to perform the hydrogenation in presence of ammonium acetate, hoping that nucleophilic addition/elimination of ammonia to the vinylogous ketone moiety should in situ give an *E*-enamino ketone that can undergo cyclocondensation with the acetyl group at C-2 of the indole to give the β-carboline **7**. Cyclization did not occur under these conditions, and once again the *Z*-enamino ketone **6** was isolated. Ring closure to the β-carboline **7** was achieved by heating the crude enamino ketone with ammonium acetate in ethanol/acetic acid at 60 °C (87 % overall yield from **5**). Finally, we found that hydrogenation in presence of cesium carbonate directly leads to the desired β-carboline **7**. Deprotection of the SEM group was achieved in 55 % yield (not optimized) under standard conditions (TBAF, THF) to give the 1,3,4-trisubstituted β-carboline **8** (Scheme 2).

Having proven the feasibility of the new approach we intended to reduce the number of steps of synthesis. To our delight the optimized Suzuki–Miyaura cross-coupling conditions ($Pd(PPh_3)_4/Cs_2CO_3$ catalyst system) also worked with *N*-unprotected 2-acyl-3-bromoindoles. Comparable results were obtained with sodium carbonate here, but in contrast to cesium carbonate, this base did not dissolve completely in the reaction mixture. With alkyl, phenyl and heteroaryl (2-thienyl) ketones (**1a**, **9a–g**) the cross-coupling with 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) worked in acceptable yields (50–69 %) to give biaryls **10**, **11a–g**. In contrast to the above mentioned *N*-SEM derivative **5**, the N-unsubstituted intermediate **10** did not undergo reductive ring cleavage of the isoxazole moiety under neutral conditions and with added ammonium acetate, however in presence of Cs_2CO_3 once again smooth reductive ring cleavage occurred, and fortunately, the formed *Z*-enamino ketones underwent direct ring closure to the target β-carbolines **8**, **12a–g** under the reaction conditions in yields ranging

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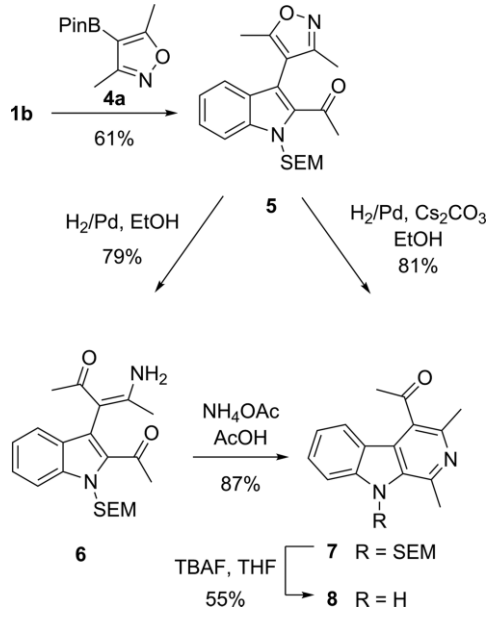
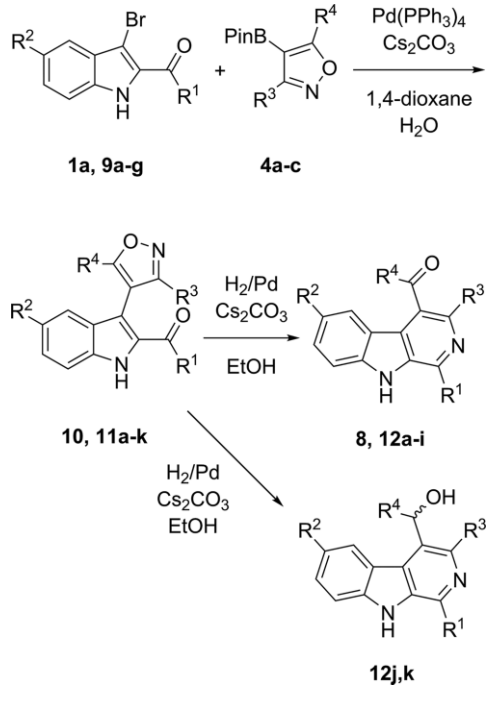


Scheme 2. Synthesis of 1,3,4-trisubstituted β-carboline **8** utilizing SEM-protection of the indole intermediates.

from 47–89 % (Scheme 3). In control experiments ammonium acetate was added as an additional source of ammonia (compare conversion of **6** into **7**), but yields of the β-carbolines were not improved.



Scheme 3. Optimized, protective group-free synthesis of 1,3,4-trisubstituted β-carbolines.

Finally, we investigated other isoxazole-4-boronates bearing different aliphatic, aromatic and heteroaromatic residues at C-3 and C-5. The boronates **4b**/**4c** were obtained from the corresponding 3,5-disubstituted isoxazoles by bromination at C-4,[37] followed by bromine-lithium exchange with *n*-butyllithium, and trapping with B-isopropoxy-pinacolborane.[38] Subjecting these boronates to cross-coupling with bromoindoles **1a**/**9d**, followed by reductive ring transformation (yields 68–88 %) gave the highly substituted β-carbolines **12h–k**. To our surprise, the pyridyl ketones arising from 5-pyridylisoxazole building block **4c** were further reduced to give the corresponding pyridyl carbinols **12j** and **12k** (Scheme 3).

The results are summarized in detail in Table 1 and Table 2.

Table 1. 3-(Isoxazol-4-yl)indoles **10,11a–k** obtained via Suzuki–Miyaura cross-coupling of indoles **1a**,**9a–g** and isoxazole-4-boronates **4a–c**.

Entry	**1a**, **9a–g**	**4a–c**	**10**, **11a–k**	
1	**1a** $R^1 = CH_3$ $R^2 = H$	**4a** $R^3 = R^4 = CH_3$	**10** $R^1 = R^2 = R^3 = CH_3$ $R^2 = H$	55 %
2	**9a** $R^1 = n\text{-}C_4H_9$ $R^2 = H$	**4a**	**11a** $R^1 = n\text{-}C_4H_9$ $R^2 = H$ $R^3 = R^4 = CH_3$	69 %
3	**9b** R^1 = phenyl $R^2 = H$	**4a**	**11b** R^1 = phenyl $R^2 = H$ $R^3 = R^4 = CH_3$	65 %
4	**9c** R^1 = thiophen-2-yl $R^2 = H$	**4a**	**11c** R^1 = thiophen-2-yl $R^2 = H$ $R^3 = R^4 = CH_3$	58 %
5	**9d** $R^1 = CH_3$ $R^2 = OCH_3$	**4a**	**11d** $R^1 = R^2 = R^3 = CH_3$ $R^2 = OCH_3$	57 %
6	**9e** $R^1 = n\text{-}C_4H_9$ $R^2 = OCH_3$	**4a**	**11e** $R^1 = n\text{-}C_4H_9$ $R^2 = OCH_3$ $R^3 = R^4 = CH_3$	57 %
7	**9f** R^1 = phenyl $R^2 = OCH_3$	**4a**	**11f** R^1 = phenyl $R^2 = OCH_3$ $R^3 = R^4 = CH_3$	58 %
8	**9g** R^1 = thiophen-2-yl $R^2 = OCH_3$	**4a**	**11g** R^1 = thiophen-2-yl $R^2 = OCH_3$ $R^3 = R^4 = CH_3$	50 %
9	**1a**	**4b** $R^3 = CH_3$ R^4 = phenyl	**11h** $R^1 = R^3 = CH_3$ $R^2 = H$ R^4 = phenyl	60 %
10	**9d**	**4b**	**11i** $R^1 = R^3 = CH_3$ $R^2 = OCH_3$ R^4 = phenyl	61 %
11	**1a**	**4c** $R^3 = n\text{-}C_3H_7$ R^4 = 2-pyridyl	**11j** $R^1 = CH_3$ $R^2 = H$ $R^3 = n\text{-}C_3H_7$ R^4 = 2-pyridyl	35 %
12	**9d**	**4c**	**11k** $R^1 = CH_3$ $R^2 = OCH_3$ $R^3 = n\text{-}C_3H_7$ R^4 = 2-pyridyl	47 %

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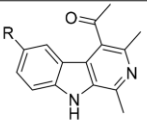
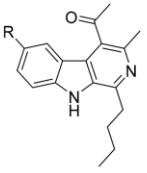
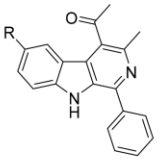
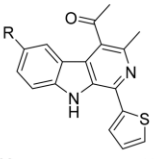
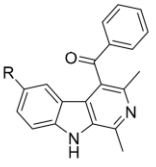
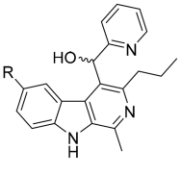
Table 2. Reductive ring transformation of 2-acyl-3-isoxazolylindoles **10**, **11a–k** into β-carbolines **8**, **12a–k**.

Entry	10,11a–k	β-carbolines 8,12a–k
1	**10**	
2	**11d**	**8** R = H 93% **12d** R = OCH_3 78%
3	**11a**	
4	**11e**	**12a** R = H 87% **12e** R = OCH_3 89%
5	**11b**	
6	**11f**	**12b** R = H 61% **12f** R = OCH_3 47%
7	**11c**	
8	**11g**	**12c** R = H 53% **12g** R = OCH_3 67%
9	**11h**	
10	**11i**	**12h** R = H 69% **12i** R = OCH_3 88%
11	**11j**	
12	**11k**	**12j** R = H 84% **12k** R = OCH_3 68%

Conclusion

In conclusion, we have worked out a new and general protocol for the synthesis of 1,3,4-trisubstituted β-carbolines (with the option for including additional substituents in the carbocyclic ring C, if substituted indole precursors are utilized). Readily available 2-acylindoles (aliphatic, aromatic, heteroaromatic acyl residues are equally suitable) are easily brominated at C-3. Suzuki–Miyaura cross-coupling with variously substituted and readily available isoxazole-4-pinacol boronates gives biaryls, which can be directly converted into the desired β-carbolines upon Pd-catalyzed hydrogenation in presence of Cs_2CO_3 in the sense of a reductive isoxazole-pyridine ring transformation. This new method favorably compares with previously developed methods for the synthesis of highly substituted β-carbolines, since it utilizes readily available building blocks, proceeds in a small number of steps, and gives complex compounds with predictable substitution patterns. In contrast to previously published protocols for the synthesis of 3,4-disubstituted β-carbolines via reaction of internal alkynes and *tert*-butylimines of (3-iodo)indole-2-carbaldehydes[13,14] via masked 1,5-dicarbonyl compounds[21b] our method is advantageous since it needs neither protection of the keto group at C-2 of the indole nor of the indole nitrogen. This new protocol should be of high interest for the total synthesis of complex β-carboline alkaloids and synthetic β-carbolines as drug candidates, hence opening new opportunities for systematic investigations of structure-activity relationships also including broad variation of substitution patterns at ring A.

Experimental Section

Solvents used were of HPLC grade or p.a. grade and/or purified according to standard procedures. All chemicals used were of analytical grade. Tetrahydrofuran was dried with sodium and distilled before usage. Chloroform was dried with molecular sieves 3 Å. Melting points were determined by open tube capillary method on a Büchi melting point B-450 apparatus and are uncorrected. IR measurements were carried out with a Perkin-Elmer FTIR Paragon 1000 spectrometer or with a Jasco FT/IR-4100 as KBr pellets or as films. NMR spectra were recorded on Avance III HD 400 MHz Bruker BioSpin and Avance III HD 500 MHz Bruker BioSpin spectrometers. 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, q = quartet, m = multiplet. Signal assignments were carried out based on ^1H, ^{13}C, DEPT, HMQC, HMBC and COSY spectra. NMR spectra were analyzed with the NMR software MestReNova, Version 5.1.1–3092. Mass spectra were performed by electron impact (EI) at 70 eV on a Thermo Finnigan MAT 95 or Jeol GCmate II spectrometer or by electrospray ionization (ESI) using a Thermo Finnigan LTQ FT Ultra Fourier Transform Ion Cyclotron resonance mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) using pre-coated plastic sheets POLYGRAM® SIL G/UV254 from Macherey-Nagel. Chromatographic purification of products was performed by flash column chromatography (FCC) on Merck silica gel 60 (0.015–0.040 mm). HPLC purities were determined using a HP Agilent 1100 HPLC with a diode array detector and an InfinityLab Poroshell column (120 EC-CN, 4.6 × 150 mm, 4.6 Micron). The column flow was 1.0 mL/min and the temperature 50 °C. Either acetonitrile/water, 70:30 (method a), 50:50 (method b) or 50:49.9 and 0.1 part 1.0 M formic acid (method c) was used as eluent.

General Procedure 1: Suzuki–Miyaura cross-coupling of 2-acyl-3-bromoindoles **1a,9a–g** with 4-borylated isoxazoles **4a–c**.

The 2-acyl-3-bromoindole **1a**,**9a–g** (0.45–1.0 mmol), tetrakis(triphenylphosphine)palladium(0) (10 mol-%) and the respective 4-borylated isoxazole **4a–c** (2.0 equivalents) were dissolved in 1,4-dioxane (6 mL/mmol indole) under nitrogen atmosphere. Cesium carbonate (5 equivalents) was dissolved in water (2 mL/mmol) under a nitrogen atmosphere and was added dropwise to the reaction mix-

ture. The reaction mixture was heated at 75 °C for 19 h. After cooling to room temperature the mixture was treated with saturated. aqueous ammonium chloride solution (15 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and the solvents were evaporated under reduced pressure. Purification was accomplished by FCC.

General Procedure 2: Reductive ring cleavage and subsequent cyclization to β-carbolines **8**,**12a–k**.

The 2-acyl-3-isoxazolylindole **10**,**11a–k** (0.15–0.30 mmol), palladium on carbon (10 %) (100 mg/mmol starting material) and an excess of cesium carbonate (1.5–3.0 equivalents) were disperged in anhydrous ethanol (2 mL). The reaction mixture was hydrogenated at 35 bar and 40 °C for 19 h. After cooling to room temperature, the catalyst was filtered off through a pad of celite, washed with ethyl acetate and the filtrate was evaporated under reduced pressure. Purification was accomplished by FCC.

Synthesis and characterization of the compounds

1-{3-Bromo-1-[(2-(trimethylsilyl)ethoxy)methyl]1*H*-indol-2-yl}ethan-1-one (1b): Under a nitrogen atmosphere 2-acetyl-3-bromoindole (**1a**) (470 mg, 1.97 mmol) was dissolved in anhydrous tetrahydrofuran (6 mL). The solution was cooled to 0 °C and sodium bis(trimethylsilyl)amide (1.0 M in tetrahydrofuran, 2.59 mL, 2.59 mmol) was added. The mixture was stirred for 15 min, then warmed up to room temperature and (trimethylsilyl)ethoxymethyl chloride (SEM-chloride; 0.52 mL, 2.9 mmol) was added. The mixture was stirred for another 2 h, then water (15 mL) was added and the mixture extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and the solvents were evaporated under reduced pressure. Purification was accomplished by FCC using 12:1 hexanes/ethyl acetate to give 663 mg (1.80 mmol, 91 %) of **1b** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70–7.67 (m, 1H, 4′-H), 7.56–7.53 (m, 1H, 7′-H), 7.43 (ddd, J = 8.4 Hz, 7.0 Hz, 1.2 Hz, 1H, 6′-H), 7.30–7.25 (m, 1H, 5′-H), 5.92 (s, 2H, NCH_2O), 3.53–3.48 (m, 2H, OCH_2CH_2), 2.86 (s, 3H, 2-H), 0.88–0.83 (m, 2H, OCH_2CH_2), –0.07 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 192.3 (C-1), 138.6 (C-7a′), 132.9 (C-2′), 127.4 (C-6′), 127.1 (C-3a′), 122.3 (C-5′), 121.9 (C-4′), 111.6 (C-7′), 101.6 (C-3′), 73.9 (NCH_2O), 66.0 (OCH_2CH_2), 32.1 (C-2), 18.0 (OCH_2CH_2), –1.3 ($Si(CH_3)_3$) ppm. IR (film): $\tilde{\nu}$ = 3056, 2952, 2895, 1665, 1497, 1473, 1376, 1337, 1248, 1202, 1084, 860, 836, 744 cm^{-1}. HRMS (EI): m/z = 367.0600 $[M^{\cdot}]^+$ (calcd for $C_{16}H_{22}BrNO_2Si^{\cdot+}$: 367.0598). HPLC purity (method b): 95 % (λ = 210 nm), > 99 % (λ = 254 nm).

3-Methyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (4b): A solution of 3-methyl-5-phenylisoxazole (557 mg, 3.50 mmol) and *N*-bromosuccinimide (664 mg, 3.75 mmol) in glacial acetic acid (5 mL) was heated at 100 °C for 3 h. After cooling to room temperature 2 N sodium hydroxide solution (15 mL) was added and the mixture extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and the solvents were evaporated under reduced pressure. Purification was accomplished by FCC using 6:1 hexanes/ethyl acetate to give 710 mg (2.98 mmol, 85 %) of 4-bromo-3-methyl-5-phenylisoxazole as a white solid, which was directly converted into the boronic acid pinacol ester as follows: A solution of 4-bromo-3-methyl-5-phenylisoxazole (360 mg, 1.51 mmol) in anhydrous tetrahydrofuran (4 mL) was cooled to –78 °C and *n*-butyllithium solution (2.5 M in hexanes, 0.91 mL, 2.3 mmol) was added. After stirring at –78 °C for 1 h the mixture was warmed up to room temperature, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (1.54 mL, 7.56 mmol) was added, and the mixture was stirred at room temperature for further 1.5 h. Then water (15 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and the solvents evaporated under reduced pressure. Purification was accomplished by FCC using 6:1 hexanes/ethyl acetate to give 319 mg (1.12 mmol, 74 %) of **4b** as a white solid. Mp 71 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.05–8.01 (m, 2H, 2′-H, 6′-H), 7.46–7.41 (m, 3H, 3′-H, 4′-H, 5′-H), 2.43 (s, 3H, 3-CH_3), 1.34 (s, 12H, 4″-$(CH_3)_2$, 5″-$(CH_3)_2$ ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 175.8 (C-5), 165.1 (C-3), 130.4 (C-4′), 128.6 (C-1′), 128.4 (C-2′, C-3′, C-5′, C-6′), 102.3 (br, C-4), 83.9 (C-4″, C-5″), 25.0 (4″-$(CH_3)_2$, 5″-$(CH_3)_2$), 12.4 (3-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3074, 2976, 2935, 1611, 1574, 1486, 1412, 1338, 1143, 1061, 962, 855, 779, 723, 691 cm^{-1}. HRMS (ESI): m/z = 286.1608 $[M + H]^+$ (calcd for $C_{16}H_{21}BNO_3^+$: 286.1609). HPLC purity (method b): 99 % (λ = 210 nm), 99 % (λ = 254 nm).

3-Propyl-5-(pyridin-2-yl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoxazole (4c): Under a nitrogen atmosphere *N*-chlorosuccinimide (1.58 g, 11.8 mmol) was dissolved in anhydrous chloroform (10 mL), then *n*-butyraldoxime (1.11 mL, 11.6 mmol) and pyridine (78 μL, 0.97 mmol) was added dropwise. The reaction mixture was heated at 50 °C for 1 h. Then 2-ethynylpyridine (0.98 mL, 9.7 mmol) and triethylamine (2.00 mL, 14.3 mmol) was added dropwise. The mixture was stirred for further 1.5 h at 50 °C. After cooling to room temperature water (20 mL) was added and the mixture extracted with dichloromethane (3 × 25 mL). The combined organic layers were dried with magnesium sulfate and the solvents were evaporated under reduced pressure. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 1.36 g (7.23 mmol, 75 %) 3-propyl-5-(pyridin-2-yl)isoxazole as a yellow oil. This isoxazole (599 mg, 3.18 mmol) and *N*-bromosuccinimide (566 mg, 3.18 mmol) were dissolved in glacial acetic acid (5 mL) and the mixture was heated at 80 °C for 18 h. After cooling to room temperature 2 N sodium hydroxide solution (20 mL) was added and extracted with ethyl acetate (3 × 25 mL). The combined organic layers were dried with magnesium sulfate and the solvents were evaporated under reduced pressure. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 507 mg (1.90 mmol, 60 %) of 4-bromo-3-propyl-5-(pyridin-2-yl)isoxazole as a pale yellow oil. A solution of this isoxazole (213 mg, 0.797 mmol) in anhydrous tetrahydrofuran (3 mL) was cooled to –78 °C and *n*-butyllithium solution (2.5 M in hexanes, 0.42 mL, 1.1 mmol) was added. After stirring at –78 °C for 1 h the mixture was warmed up to room temperature, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.50 mL, 2.4 mmol) was added, and the mixture was stirred at room temperature for further 1.5 h. Then water (15 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and the solvents evaporated under reduced pressure. Purification was accomplished by FCC using 3:1 hexanes/ethyl acetate to give 236 mg (0.751 mmol, 94 %) of **4c** as a pale yellow solid. Mp 126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.60 (ddd, J = 4.8 Hz, 1.7 Hz, 1.0 Hz, 1H, 3′-H), 7.95–7.91 (m, 1H, 6′-H), 7.79–7.74 (m, 1H, 5′-H), 7.29 (ddd, J = 7.6 Hz, 4.8 Hz, 1.2 Hz, 1H, 4′-H), 2.76–2.71 (m, 2H, 1″-H), 1.81–1.70 (m, 2H, 2″-H), 1.40 (s, 12H, 4‴-$(CH_3)_2$, 5‴-$(CH_3)_2$), 1.00 (t, J = 7.4 Hz, 3H, 3″-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 172.8 (C-5), 167.4 (C-3), 149.5 (C-3′), 147.3 (C-1′), 136.8 (C-5′), 124.3 (C-4′), 121.6 (C-6′), 104.7 (br, C-4), 84.2 (C-4‴, C-5‴), 28.7 (C-1″), 24.9 (4‴-$(CH_3)_2$, 5‴-$(CH_3)_2$), 22.3 (C-2″), 14.0 (C-3″) ppm. IR (KBr): $\tilde{\nu}$ = 3330, 3065, 2961, 2870, 1579, 1564, 1415, 1310, 1143, 1069, 856, 796, 744 cm^{-1}. HRMS (EI): m/z = 314.1784 $[M^{\cdot}]^+$ (calcd for $C_{17}H_{23}BN_2O_3^{\cdot+}$: 314.1796). HPLC purity (method c): 97 % (λ = 210 nm), 97 % (λ = 254 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-1-{[2-(trimethylsilyl)ethoxy]-methyl}-1*H*-indol-2-yl]ethan-1-one (5): Prepared from **1b** (366 mg, 0.994 mmol), tetrakis(triphenylphosphine)palladium(0)

(116 mg, 0.100 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (445 mg, 1.99 mmol) and cesium carbonate (1.80 g, 5.52 mmol) following General Procedure 1. Purification was accomplished by FCC using 9:1 hexanes/ethyl acetate to give 233 mg (0.606 mmol, 61 %) of **5** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.5 Hz, 1H, 7′-H), 7.44 (ddd, J = 8.4 Hz, 6.9 Hz, 1.2 Hz, 1H, 6′-H), 7.31–7.28 (m, 1H, 4′-H), 7.20 (ddd, J = 7.9 Hz, 7.0 Hz, 0.8 Hz, 1H, 5′-H), 5.97 (s, 2H, NCH_2O), 3.58–3.53 (m, 2H, OCH_2CH_2), 2.28 (s, 3H, 5′′-CH_3), 2.24 (s, 3H, 2-H), 2.11 (s, 3H, 3′′-CH_3), 0.89–0.85 (m, 2H, OCH_2CH_2), –0.09 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 192.8 (C-1), 167.1 (5′′-CH_3), 160.0 (3′′-CH_3), 139.1 (C-7a′), 134.2 (C-2′), 127.4 (C-3a′), 126.9 (C-6′), 122.1 (C-5′), 121.3 (C-4′), 113.1 (C-3′), 111.7 (C-7′), 109.7 (C-4′′), 73.7 (NCH_2O), 66.1 (OCH_2CH_2), 30.3 (C-2), 18.0 (OCH_2CH_2), 11.6 (5′′-CH_3), 10.7 (3′′-CH_3), –1.4 ($Si(CH_3)_3$) ppm. IR (film): $\tilde{\nu}$ = 3057, 2952, 2856, 1665, 1456, 1335, 1248, 1169, 1151, 1081, 859, 837, 747 cm^{-1}. HRMS (EI): m/z = 384.1860 [M] (calcd for $C_{21}H_{28}N_2O_3Si$: 384.1869). HPLC purity (method 2c): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

(*Z*)-3-{2-Acetyl-1-[(2-(trimethylsilyl)ethoxy)methyl]-1*H*-indol-3-yl}4-aminopent-3-en-2-one (6): Intermediate **5** (53 mg, 0.14 mmol) and palladium on carbon (17 mg, 0.016 mmol) were dispersed in anhydrous ethanol (2 mL) and hydrogenated at 30 bar and room temperature for 19 h. Then the catalyst was filtered off through a pad of celite, washed with ethyl acetate and the filtrate was evaporated under reduced pressure. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate and 5 % triethylamine to give 42 mg (0.11 mmol, 79 %) of **6** as a yellow oil. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 10.76 (s, 1H, NH_2), 7.56 (d, J = 8.0 Hz, 1.0 Hz, 1H, 7′-H), 7.53–7.49 (m, 1H, 4′-H), 7.40 (ddd, J = 8.3 Hz, 7.0 Hz, 1.2 Hz, 1H, 6′-H), 7.19 (ddd, J = 7.9 Hz, 7.0 Hz, 0.9 Hz, 1H, 5′-H), 5.97 (d, J = 2.8 Hz, 2H, NCH_2O), 5.50 (s, 1H, NH_2), 3.48–3.42 (m, 2H,OCH_2CH_2), 2.43 (s, 3H, 2′′-H), 1.76 (s, 3H, 1-H), 1.66 (s, 3H, 5-H), 0.84–0.79 (m, 2H, OCH_2CH_2), –0.12 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 196.8 (C-2), 193.4 (C-1′′), 161.4 (C-4), 139.8 (C-7a′), 134.7 (C-2′), 128.8 (C-3a′), 126.9 (C-6′), 125.2 (C-3′), 122.2 (C-4′), 121.9 (C-5′), 111.8 (C-7′), 99.9 (C-3), 74.1 (NCH_2O), 66.1 (OCH_2CH_2), 30.8 (C-2′′), 28.8 (C-1), 22.0 (C-5), 18.4 (OCH_2CH_2), –1.3 ($Si(CH_3)_3$) ppm. IR (film): $\tilde{\nu}$ = 3382, 3057, 2953, 2923, 2859, 1701, 1615, 1568, 1362, 1249, 1073, 859, 737 cm^{-1}. HRMS (EI): m/z = 386.2032 [M] (calcd for $C_{21}H_{30}N_2O_3Si$: 386.2026). HPLC purity not determined due to limited stability of the compound.

1-{1,3-Dimethyl-9-[(2-(trimethylsilyl)ethoxy)methyl]-9*H*-pyrido-[3,4-*b*]indol-4-yl}ethan-1-one (7): Method A: Isoxazolylindole **5** (56 mg, 0.15 mmol), palladium on carbon (16 mg, 0.015 mmol) and ammonium acetate (146 mg, 1.89 mmol) in anhydrous ethanol (2 mL) was hydrogenated at 30 bar and room temperature for 6.5 h. Then glacial acetic acid (1 mL) was added and the mixture was heated at 60 °C for further 2 h. After cooling to room temperature the catalyst was filtered off through a pad of celite, washed with ethyl acetate and the filtrate was evaporated under reduced pressure to give 48 mg (0.13 mmol, 87 %) of **7** as a yellow oil.

Method B: Prepared from **5** (18 mg, 0.047 mmol), palladium on carbon (6 mg, 0.006 mmol) and cesium carbonate (53 mg, 0.16 mmol) following General Procedure 2. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate and 5 % triethylamine to give 14 mg (0.038 mmol, 81 %) of **7** as a pale yellow oil. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 7.80 (d, J = 8.0 Hz, 1H, 5′-H), 7.62–7.55 (m, 2H, 7′-H, 8′-H), 7.24 (ddd, J = 8.0 Hz, 6.6 Hz, 1.5 Hz, 1H, 6′-H), 5.82 (s, 2H, NCH_2O), 3.59–3.52 (m, 2H, OCH_2CH_2), 3.02 (s, 3H, 1′-CH_3), 2.70 (s, 3H, 2-H), 2.56 (s, 3H, 3′-CH_3), 0.91–0.87 (m, 2H, OCH_2CH_2), –0.08 (s, 9H, $Si(CH_3)_3$) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 206.6 (C-1), 143.1 (C-1′, C-8a′), 141.7 (C-3′), 133.9 (C-9a′), 129.0 (C-7′), 128.4 (C-4′), 126.0 (C-4a′), 123.2 (C-5′), 121.1 (C-6′), 120.3 (C-4b′), 110.6 (C-8′), 73.8 (NCH_2O), 66.5 (OCH_2CH_2), 32.7 (C-2), 23.4 (1′-CH_3), 21.8 (3′-CH_3), 18.4 (OCH_2CH_2), –1.3 ($Si(CH_3)_3$) ppm. IR (film): $\tilde{\nu}$ = 3057, 2953, 2898, 1700, 1615, 1567, 1447, 1362, 1249, 1216, 1073, 860, 837, 738 cm^{-1}. HRMS (EI): m/z = 368.1927 [M] (calcd for $C_{21}H_{28}N_2O_2Si$: 368.1920). HPLC purity (method c): > 99 % (λ = 210 nm), > 99 % (λ = 245 nm).

1-(1,3-Dimethyl-9*H*-pyrido[3,4-*b*]indol-4-yl)ethan-1-one (8): Method A: Under a nitrogen atmosphere 121 mg (0.328 mmol) N-SEM derivative **7** was dissolved in anhydrous tetrahydrofuran (3 mL) and tetrabutylammonium fluoride solution (1.0 M in tetrahydrofuran, 0.99 mL, 0.99 mmol) was added. The mixture was heated at 70 °C for 19 h. After cooling to room temperature water (15 mL) was added and the mixture was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with magnesium sulfate and the solvents were evaporated under reduced pressure. Purification was accomplished by FCC using 1:1 hexanes/acetone to give 42 mg of **8** (0.18 mmol, 55 %) as a yellow solid.

Method B: Prepared from **10** (68 mg, 0.27 mmol), palladium on carbon (29 mg, 0.027 mmol) and cesium carbonate (261 mg, 0.801 mmol) following General Procedure 2. Purification was accomplished by FCC using 1:3 hexanes/ethyl acetate to give 59 mg (0.25 mmol, 93 %) of **8** as a yellow solid. Mp 145 °C. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.66 (s, 1H, NH), 7.86–7.82 (m, 1H, 5′-H), 7.54–7.51 (m, 2H, 7′-H, 8′-H), 7.22 (ddd, J = 8.1 Hz, 5.6 Hz, 2.5 Hz, 1H, 6′-H), 2.76 (s, 3H, 1′-CH_3), 2.72 (s, 3H, 2-H), 2.59 (s, 3H, 3′-CH_3) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 206.4 (C-1), 142.5 (C-1′), 141.6 (C-3′), 141.2 (C-8a′), 133.3 (C-9a′), 128.9 (C-7′), 128.3 (C-4′), 124.6 (C-4a′), 123.3 (C-5′), 120.8 (C-4b′, C-6′), 112.3 (C-8′), 32.6 (C-2), 22.0 (3′-CH_3), 20.6 (1′-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3367, 3134, 3061, 2922, 1696, 1621, 1498, 1404, 1289, 1232, 1184, 961, 741 cm^{-1}. HRMS (EI): m/z = 238.1105 [M] (calcd for $C_{15}H_{14}N_2O$: 238.1106). HPLC purity (method c): 97 % (λ = 210 nm), 95 % (λ = 254 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-1*H*-indol-2-yl]ethan-1-one (10): Prepared from 2-acetyl-3-bromoindole (**1a**) (104 mg, 0.437 mmol), tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (202 mg, 0.906 mmol) and cesium carbonate (708 mg, 2.17 mmol) following General Procedure 1. Purification was accomplished by FCC using 3:1 hexanes/ethyl acetate to give 61 mg (0.24 mmol, 55 %) of **10** as a yellow solid. Mp 186 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.43 (s, 1H, NH), 7.50–7.47 (m, 1H, 7′-H), 7.41 (ddd, J = 8.3 Hz, 6.9 Hz, 1.1 Hz, 1H, 6′-H), 7.33 (dd, J = 8.1 Hz, 0.9 Hz, 1H, 4′-H), 7.17 (ddd, J = 8.0 Hz, 6.9 Hz, 1.0 Hz, 1H, 5′-H), 2.30 (s, 3H, 5′′-CH_3), 2.26 (s, 3H, 2-H), 2.13 (s, 3H, 3′′-CH_3) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 190.5 (C-1), 167.3 (C-5′′), 160.1 (C-3′′), 136.1 (C-7a′), 133.7 (C-2′), 128.8 (C-3a′), 127.1 (C-6′), 121.7 (C-4′), 121.5 (C-5′), 112.4 (C-7′), 110.6 (C-3′), 109.2 (C-4′′), 27.4 (C-2), 11.7 (5′′-CH_3), 10.7 (3′′-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3381, 3060, 2918, 2849, 1706, 1650, 1534, 1405, 1330, 1233, 957, 736 cm^{-1}. HRMS (ESI): m/z = 255.1128 [M + H]$^+$ (calcd for $C_{15}H_{15}N_2O_2^+$: 255.1128). HPLC purity (method a): 98 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-1*H*-indol-2-yl]pentan-1-one (11a): Prepared from 2-pentanoyl-3-bromoindole (**9a**) (154 mg, 0.550 mmol), tetrakis(triphenylphosphine)palladium(0) (65 mg, 0.056 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (251 mg, 1.13 mmol) and cesium carbonate (895 mg, 2.75 mmol) following General Procedure 1. Purification was accomplished by FCC using 6:1 hexanes/ethyl acetate to give 112 mg (0.378 mmol, 69 %) of **11a** as a yellow solid. Mp 142 °C. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 9.60 (s, 1H, NH), 7.51 (d, J = 8.3 Hz, 1H, 7′-H), 7.39 (ddd, J = 8.2 Hz, 6.9 Hz, 1.1 Hz, 1H, 6′-H), 7.35–7.32 (m, 1H, 4′-H), 7.15

(ddd, J = 8.0 Hz, 7.0 Hz, 0.8 Hz, 1H, 5′-H), 2.57–2.52 (m, 2H, 2-H), 2.28 (s, 3H, 5″-CH_3), 2.10 (s, 3H, 3″-CH_3), 1.62–1.55 (m, 2H, 3-H), 1.30–1.20 (m, 2H, 4-H), 0.84 (t, J = 7.4 Hz, 3H, 5-H) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 193.9 (C-1), 167.6 (C-5″), 160.4 (C-3″), 136.5 (C-7a′), 134.0 (C-2′), 129.3 (C-3a′), 127.1 (C-6′), 122.0 (C-4′), 121.7 (C-5′), 112.7 (C-7′), 110.1 (C-3′), 109.7 (C-4″), 39.6 (C-2), 27.0 (C-3), 22.9 (C-4), 14.1 (C-5), 11.9 (5″-CH3), 10.8 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3284, 3060, 2954, 2930, 2870, 1657, 1538, 1403, 1340, 1197, 1067, 956, 890, 739 cm^{-1}. HRMS (ESI): m/z = 295.1455 [M – H]$^-$ (calcd for $C_{18}H_{19}N_2O_2^-$: 295.1452). HPLC purity (method a): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-1*H*-indol-2-yl](phenyl)-methanone (11b): Prepared from 2-benzoyl-3-bromoindole (**9b**) (133 mg, 0.443 mmol), tetrakis(triphenylphosphine)palladium(0) (50 mg, 0.043 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (193 mg, 0.865 mmol) and cesium carbonate (706 mg, 2.17 mmol) following General Procedure 1. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 91 mg (0.29 mmol, 65 %) of **11b** as a yellow solid. Mp 191 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.67 (s, 1H, NH), 7.59–7.55 (m, 3H, 7-H, 2′-H, 6′-H), 7.51–7.46 (m, 1H, 4′-H), 7.45–7.40 (m, 2H, 4-H, 6-H), 7.34–7.29 (m, 2H, 3′-H, 5′-H), 7.20 (ddd, J = 7.9 Hz, 7.0 Hz, 1.0 Hz, 1H, 5-H), 2.04 (s, 3H, 5″-CH_3), 2.01 (s, 3H, 3″-CH_3) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 189.2 (C=O), 167.0 (C-5″), 159.8 (C-3″), 138.1 (C-1′), 137.2 (C-7a), 132.9 (C-2, C-4′), 129.4 (C-2′, C-6′), 128.6 (C-3a), 128.3 (C-3′, C-5′), 127.3 (C-6), 122.2 (C-4), 121.9 (C-5), 112.9 (C-7), 111.9 (C-3), 110.0 (C-4″), 11.7 (5″-CH_3), 10.9 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3320, 3065, 2923, 1608, 1573, 1427, 1406, 1335, 1262, 1147, 1021, 737, 697 cm^{-1}. HRMS (ESI): m/z = 317.1283 [M + H]$^+$ (calcd for $C_{20}H_{17}N_2O_2^+$: 317.1285). HPLC purity (method c): 99 % (λ = 210 nm), 99 % (λ = 254 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-1*H*-indol-2-yl](thiophen-2-yl)-methanone (11c): Prepared from 2-acyl-3-bromoindole **9c** (200 mg, 0.653 mmol), tetrakis(triphenylphosphine)palladium(0) (76 mg, 0.066 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (291 mg, 1.30 mmol) and cesium carbonate (1.06 g, 3.25 mmol) following General Procedure 1. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 122 mg (0.378 mmol, 58 %) of **11c** as a yellow solid. Mp 205 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.41 (s, 1H, NH), 7.67 (dd, J = 4.9 Hz, 1.1 Hz, 1H, 3′-H), 7.56–7.53 (m, 1H, 7-H), 7.46–7.40 (m, 2H, 4-H, 6-H), 7.38 (dd, J = 3.8 Hz, 1.1 Hz, 1H, 5′-H), 7.21 (ddd, J = 8.1 Hz, 7.1 Hz, 1.0 Hz, 1H, 5-H), 7.01 (dd, J = 4.9 Hz, 3.8 Hz, 1H, 4′-H), 2.20 (s, 3H, 5″-CH_3), 2.07 (s, 3H, 3″-CH_3) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 180.1 (C=O), 167.3 (C-5″), 160.2 (C-3″), 142.7 (C-1′), 136.9 (C-7a), 134.4 (C-3′, C-5′), 132.9 (C-2), 128.5 (C-3a), 128.2 (C-4′), 127.0 (C-6), 122.1 (C-4), 121.9 (C-5), 112.8 (C-7), 110.6 (C-3), 110.1 (C-4″), 12.0 (5″-CH_3), 11.0 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3302, 3061, 2922, 1594, 1515, 1410, 1334, 1266, 1179, 1049, 855, 740 cm^{-1}. HRMS (EI): m/z = 322.0761 [M] (calcd for $C_{18}H_{14}N_2O_2S$: 322.0776). HPLC purity (method b): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-5-methoxy-1*H*-indol-2-yl]-ethan-1-one (11d): Prepared from 2-acyl-3-bromoindole **9d** (131 mg, 0.489 mmol), tetrakis(triphenylphosphine)palladium(0) (58 mg, 0.050 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (219 mg, 0.982 mmol) and cesium carbonate (801 mg, 2.46 mmol) following General Procedure 1. Purification was accomplished by FCC using 3:1 hexanes/ethyl acetate to give 79 mg (0.28 mmol, 57 %) of **11d** as a yellow solid. Mp 187 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.36 (s, 1H, NH), 7.41–7.37 (m, 1H, 7′-H), 7.05 (dd, J = 9.0 Hz, 2.5 Hz, 1H, 6′-H), 6.67 (d, J = 2.4 Hz, 1H, 4′-H), 3.76 (s, 3H, OCH_3), 2.29 (s, 3H, 5″-CH_3), 2.21 (s, 3H, 2-H), 2.11 (s, 3H, 3″-CH_3) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 190.4 (C-1), 167.7 (C-5″), 160.6 (C-3″), 155.8 (C-5′), 134.7 (C-2′), 131.8 (C-7a′), 129.7 (C-3a′), 119.2 (C-6′), 113.8 (C-7′), 110.3 (C-3′), 109.7 (C-4″), 101.4 (C-4′), 56.2 (OCH_3), 27.6 (C-2), 11.9 (5″-CH_3), 10.9 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3308, 3060, 2928, 1645, 1529, 1500, 1468, 1406, 1270, 1223, 1166, 1029, 806 cm^{-1}. HRMS (ESI): m/z = 283.1086 [M – H]$^-$ (calcd for $C_{16}H_{15}N_2O_3^-$: 283.1088). HPLC purity (method c): > 99 % (λ = 210 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-5-methoxy-1*H*-indol-2-yl]pentan-1-one (11e): Prepared from 2-acyl-3-bromoindole **9e** (138 mg, 0.445 mmol), tetrakis(triphenylphosphine)palladium(0) (57 mg, 0.049 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (204 mg, 0.914 mmol) and cesium carbonate (802 mg, 2.46 mmol) following General Procedure 1. Purification was accomplished by FCC using 6:1 hexanes/ethyl acetate to give 83 mg (0.25 mmol, 56 %) of **11e** as a yellow solid. Mp 188 °C. ^{1}H NMR (500 MHz, $(CD_3)_2SO$): δ = 11.90 (s, 1H, NH), 7.43 (d, J = 8.9 Hz, 1H, 7′-H), 6.99 (dd, J = 8.9 Hz, 2.4 Hz, 1H, 6′-H), 6.62 (d, J = 2.4 Hz, 1H, 4′-H), 3.71 (s, 3H, OCH_3), 2.71–2.60 (m, 2H, 2-H), 2.22 (s, 3H, 5″-CH_3), 2.00 (s, 3H, 3″-CH_3), 1.55–1.48 (m, 2H, 3-H), 1.27–1.19 (m, 2H, 4-H), 0.81 (t, J = 7.4 Hz, 3H, 5-H) ppm. ^{13}C NMR (126 MHz, $(CD_3)_2SO$): δ = 192.6 (C-1), 166.2 (C-5″), 159.6 (C-3″), 154.5 (C-5′), 133.3 (C-2′), 131.6 (C-7a′), 127.8 (C-3a′), 117.6 (C-6′), 114.1 (C-7′), 109.3 (C-4″), 107.6 (C-3′), 100.0 (C-4′), 55.3 (OCH_3), 38.7 (C-2), 26.0 (C-3), 21.8 (C-4), 13.6 (C-5), 11.4 (5″-CH_3), 10.3 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3311, 3064, 2964, 2926, 1630, 1499, 1461, 1406, 1227, 1161, 1025, 813 cm^{-1}. HRMS (ESI): m/z = 325.1556 [M – H]$^-$ (calcd for $C_{19}H_{21}N_2O_3^-$: 325.1558). HPLC-purity (method c): 96 % (λ = 210 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-5-methoxy-1*H*-indol-2-yl]-(phenyl)methanone (11f): Prepared from 2-acyl-3-bromoindole **9f** (149 mg, 0.451 mmol), tetrakis(triphenylphosphine)palladium(0) (52 mg, 0.045 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (218 mg, 0.977 mmol) and cesium carbonate (735 mg, 2.26 mmol) following General Procedure 1. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 89 mg (0.26 mmol, 58 %) of **11f** as a yellow solid. Mp 201 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.39 (s, 1H, NH), 7.56–7.53 (m, 2H, 2′-H, 6′-H), 7.50–7.43 (m, 2H, 7-H, 4′-H), 7.33–7.28 (m, 2H, 3′-H, 5′-H), 7.08 (dd, J = 9.0 Hz, 2.4 Hz, 1H, 6-H), 6.73 (d, J = 2.4 Hz, 1H, 4-H), 3.78 (s, 3H, OCH_3), 2.04 (s, 3H, 5″-CH_3), 2.01 (s, 3H, 3″-CH_3) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 188.8 (C=O), 167.0 (C-5″), 159.9 (C-3″), 155.9 (C-5), 138.2 (C-1′), 133.4 (C-2), 132.8 (C-4′), 132.4 (C-7a), 129.3 (C-2′, C-6′), 129.1 (C-3a), 128.3 (C-3′, C-5′), 119.2 (C-6), 113.9 (C-7), 111.4 (C-3), 110.1 (C-4″), 101.6 (C-4), 56.2 (OCH_3), 11.8 (5″-CH_3), 10.9 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3359, 3297, 3057, 2964, 1614, 1574, 1498, 1462, 1407, 1262, 1226, 1153, 1018, 809, 734 cm^{-1}. HRMS (EI): m/z = 346.1315 [M] (calcd for $C_{21}H_{18}N_2O_3$: 346.1317). HPLC purity (method b): 96 % (λ = 210 nm).

1-[3-(3,5-Dimethylisoxazol-4-yl)-5-methoxy-1*H*-indol-2-yl](thiophen-2-yl)methanone (11g): Prepared from 2-acyl-3-bromoindole **9g** (214 mg, 0.636 mmol), tetrakis(triphenylphosphine)palladium(0) (92 mg, 0.080 mmol), 3,5-dimethylisoxazole-4-pinacolboronate (**4a**) (296 mg, 1.32 mmol) and cesium carbonate (1.04 g, 3.18 mmol) following General Procedure 1. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 112 mg (0.318 mmol, 50 %) of **11g** as a yellow solid. Mp 186 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.91 (s, 1H, NH), 7.61 (dd, J = 4.9 Hz, 1.0 Hz, 1H, 3′-H), 7.46 (d, J = 9.0 Hz, 1H, 7-H), 7.36 (dd, J = 3.8 Hz, 1.0 Hz, 1H, 5′-H), 7.09 (dd, J = 9.0 Hz, 2.4 Hz, 1H, 6-H), 6.97 (dd, J = 4.8 Hz, 3.9 Hz, 1H, 4′-H), 6.73 (d, J = 2.3 Hz, 1H, 4-H), 3.81 (s, 3H, OCH_3), 2.21 (s, 3H, 5″-CH_3), 2.12 (s, 3H, 3″-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 179.8 (C=O), 166.8 (C-5″), 160.0 (C-3″), 155.4 (C-5), 142.2 (C-1′), 134.0 (C-3′), 133.9 (C-5′), 132.9 (C-2), 132.1 (C-7a), 128.4 (C-3a), 127.8 (C-4′),

118.7 (C-6), 113.7 (C-7), 109.9 (C-4″), 109.7 (C-3), 101.1 (C-4), 55.8 (OCH_3), 11.7 (5″-CH_3), 10.8 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3295, 2932, 1587, 1497, 1409, 1261, 1223, 1149, 1051, 856, 747 cm^{-1}. HRMS (ESI): m/z = 353.0952 $[M + H]^+$ (calcd for $C_{19}H_{17}N_2O_3S^+$: 353.0954). HPLC purity (method b): > 99 % (λ = 210 nm), > 99 % (254 nm).

1-[3-(3-Methyl-5-phenylisoxazol-4-yl)-1*H*-indol-2-yl]ethan-1-one (11h): Prepared from 2-acyl-3-bromoindole **1a** (174 mg, 0.73 mmol), tetrakis(triphenylphosphine)palladium(0) (85 mg, 0.074 mmol), **4b** (417 mg, 1.46 mmol) and cesium carbonate (1.19 g, 3.65 mmol) following General Procedure 1. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 140 mg (0.441 mmol, 60 %) of **11h** as a yellow solid. Mp 174 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 9.55 (s, 1H, NH), 7.56–7.52 (m, 3H, 7′-H, 2‴-H, 6‴-H), 7.42 (ddd, J = 8.3 Hz, 6.9 Hz, 1.1 Hz, 1H, 6′-H), 7.39–7.35 (m, 1H, 4′-H), 7.35–7.31 (m, 1H, 4‴-H), 7.30–7.25 (m, 2H, 3‴-H, 5‴-H), 7.14 (ddd, J = 8.1 Hz, 6.9 Hz, 1.0 Hz, 1H, 5′-H), 2.16 (s, 3H, 2-H), 2.12 (s, 3H, 3″-CH_3) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 190.6 (C-1), 166.1 (C-5″), 161.7 (C-3″), 136.9 (C-7a′), 133.8 (C-2′), 130.6 (C-4‴), 129.5 (C-3‴, C-5‴), 128.8 (C-3a′), 128.2 (C-1‴), 127.5 (C-6′), 126.5 (C-2‴, C-6‴), 122.1 (C-5′), 122.0 (C-4′), 112.9 (C-7′), 111.1 (C-3′), 108.4 (C-4″), 27.9 (C-2), 10.7 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3314, 3059, 2926, 1645, 1532, 1482, 1405, 1333, 1251, 1131, 944, 773, 693 cm^{-1}. HRMS (ESI): m/z = 317.1584 $[M + H]^+$ (calcd for $C_{20}H_{17}N_2O_2^+$: 317.1285). HPLC purity (method c): 97 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-[5-Methoxy-3-(3-methyl-5-phenylisoxazol-4-yl)-1*H*-indol-2-yl]ethan-1-one (11i): Prepared from 2-acyl-3-bromoindole **9d** (152 mg, 0.567 mmol), tetrakis(triphenylphosphine)palladium(0) (71 mg, 0.061 mmol), **4b** (323 mg, 1.13 mmol) and cesium carbonate (924 g, 2.83 mmol) following General Procedure 1. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 120 mg (0.346 mmol, 61 %) of **11i** as a pale yellow solid. Mp 164 °C. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 9.45 (s, 1H, NH), 7.57–7.54 (m, 2H, 2‴-H, 6‴-H), 7.43 (dd, J = 9.0 Hz, 0.5 Hz, 1H, 7′-H), 7.36–7.32 (m, 1H, 4‴-H), 7.31–7.26 (m, 2H, 3‴-H, 5‴-H), 7.07 (dd, J = 9.0 Hz, 2.4 Hz, 1H, 6′-H), 6.69 (d, J = 2.4 Hz, 1H, 4′-H), 3.69 (s, 3H, OCH_3), 2.14 (s, 3H, 3″-CH_3), 2.13 (s, 3H, 2-H) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 190.3 (C-1), 166.1 (C-5″), 161.8 (C-3″), 156.0 (C-5′), 134.2 (C-2′), 132.2 (C-7a′), 130.6 (C-4‴), 129.5 (C-3‴, C-5‴), 129.3 (C-3a′), 128.3 (C-1‴), 126.5 (C-2‴, C-6‴), 119.4 (C-6′), 114.0 (C-7′), 110.6 (C-3′), 108.6 (C-4″), 101.3 (C-4′), 56.1 (OCH_3), 27.8 (C-2), 10.8 (3″-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3311, 3062, 2928, 1643, 1496, 1459, 1275, 1250, 1218. 1162, 1033, 770, 689 cm^{-1}. HRMS (ESI): m/z = 347.1390 $[M + H]^+$ (calcd for $C_{21}H_{19}N_2O_3^+$: 347.1390). HPLC purity (method b): 99 % (λ = 210 nm), 99 % (λ = 254 nm).

1-[3-(3-Propyl-5-(pyridin-2-yl)isoxazol-4-yl)-1*H*-indol-2-yl]-ethan-1-one (11j): Prepared from 2-acyl-3-bromoindole **1a** (224 mg, 0.941 mmol), tetrakis(triphenylphosphine)palladium(0) (108 mg, 0.0935 mmol), **4c** (589 mg, 1.87 mmol) and cesium carbonate (1.56 g, 4.79 mmol) following General Procedure 1. Purification was accomplished by FCC using 2:1 hexanes/ethyl acetate to give 115 mg (0.333 mmol, 35 %) of **11j** as a yellow solid. Mp 163 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.40 (s, 1H, NH), 8.51 (ddd, J = 4.8 Hz, 1.7 Hz, 0.9 Hz, 1H, 3‴-H), 7.62–7.58 (m, 1H, 5‴-H), 7.53–7.47 (m, 2H, 7′-H, 6‴-H), 7.39 (ddd, J = 8.3 Hz, 6.9 Hz, 1.1 Hz, 1H, 6′-H), 7.35–7.32 (m, 1H, 4′-H), 7.20 (ddd, J = 7.5 Hz, 4.8 Hz, 1.2 Hz, 1H, 4‴-H), 7.12 (ddd, J = 8.0 Hz, 6.9 Hz, 0.9 Hz, 1H, 5′-H), 2.57–2.50 (m, 2H, 1‴′-H), 2.23 (s, 3H, 2-H), 1.60–1.52 (m, 2H, 2‴′-H), 0.86 (t, J = 7.4 Hz, 3H, 3‴′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 190.9 (C-1), 164.8 (C-3″, C-5″), 150.3 (C-3‴), 147.0 (C-1‴), 136.8 (C-5‴), 136.1 (C-7a′), 133.7 (C-2′), 128.5 (C-3a′), 126.9 (C-6′), 124.3 (C-4‴), 121.9 (C-6‴), 121.8 (C-4′), 121.5 (C-5′), 112.4 (C-7′), 110.9 (C-3′), 110.1 (C-4″), 27.8 (C-2), 27.5 (C-1‴′), 21.1 (C-2‴′), 13.9 (C-3‴′) ppm. IR (KBr): $\tilde{\nu}$ = 3313, 3055, 2960, 2870, 1645, 1534, 1473, 1418, 1331, 1250, 1092, 948, 743 cm^{-1}. HRMS (ESI): m/z = 344.1409 $[M – H]^-$ (calcd for $C_{21}H_{18}N_3O_2^-$: 344.1405). HPLC purity (method c): 99 % (λ = 210 nm), 99 % (λ = 254 nm).

1-[5-Methoxy-3-(3-propyl-5-(pyridin-2-yl)isoxazol-4-yl)-1*H*-indol-2-yl]ethan-1-one (11k): Prepared from 2-acyl-3-bromoindole **9d** (131 mg, 0.489 mmol), tetrakis(triphenylphosphine)palladium(0) (59 mg, 0.051 mmol), **4c** (325 mg, 1.03 mmol) and cesium carbonate (810 mg, 2.49 mmol) following General Procedure 1. Purification was accomplished by FCC using 3:1 hexanes/ethyl acetate to give 88 mg (0.23 mmol, 47 %) of **11k** as a yellow solid. Mp 144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.53 (s, 1H, NH), 8.55 (ddd, J = 4.8 Hz, 1.7 Hz, 0.9 Hz, 1H, 3‴-H), 7.61–7.57 (m, 1H, 5‴-H), 7.49–7.47 (m, 1H, 6‴-H), 7.38 (d, J = 9.0 Hz, 1H, 7′-H), 7.21 (ddd, J = 7.6 Hz, 4.8 Hz, 1.1 Hz, 1H, 4‴-H), 7.05 (dd, J = 9.0 Hz, 2.4 Hz, 1H, 6′-H), 6.63 (d, J = 2.4 Hz, 1H, 4′-H), 3.71 (s, 3H, OCH_3), 2.57–2.52 (m, 2H, 1‴′-H), 2.20 (s, 3H, 2-H), 1.60–1.52 (m, 2H, 2‴′-H), 0.87 (t, J = 7.4 Hz, 3H, 3‴′-H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$): δ = 190.7 (C-1), 164.9 (C-3″), 164.7 (C-5″), 155.4 (C-5′), 150.4 (C-3‴), 146.9 (C-1‴), 136.9 (C-5‴), 134.0 (C-2′), 131.6 (C-7a′), 128.8 (C-3a′), 124.3 (C-4‴), 121.9 (C-6‴), 119.0 (C-6′), 113.6 (C-7′), 110.3 (C-3′, C-4″), 100.9 (C-4′), 55.8 (OCH_3), 27.7 (C-2), 27.5 (C-1‴′), 21.1 (C-2‴′), 13.9 (C-3‴′) ppm. IR (KBr): $\tilde{\nu}$ = 3314, 3049, 2958, 2929, 1639, 1529, 1473, 1417, 1251, 1218, 1163, 1034, 970, 784 cm^{-1}. HRMS (ESI): m/z = 376.1656 $[M + H]^+$ (calcd for $C_{22}H_{22}N_3O_3^+$: 376.1656). HPLC purity (method c): 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-(1-Butyl-3-methyl-9*H*-pyrido[3,4-*b*]indol-4-yl)ethan-1-one (12a): Prepared from **11a** (45 mg, 0.15 mmol), palladium on carbon (17 mg, 0.016 mmol) and cesium carbonate (147 mg, 0.451 mmol) following General Procedure 2. Purification was accomplished by FCC using 2:1 hexanes/ethyl acetate to give 37 mg (0.13 mmol, 87 %) of **12a** as a pale yellow solid. Mp 159 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.62 (s, 1H, NH), 7.85 (d, J = 8.0 Hz, 1H, 5′-H), 7.53–7.45 (m, 2H, 7′-H, 8′-H), 7.21 (ddd, J = 8.1 Hz, 6.6 Hz, 1.6 Hz, 1H, 6′-H), 3.09–3.03 (m, 2H, 1″), 2.76 (s, 3H, 2-H), 2.65 (s, 3H, 3′-CH_3), 1.87–1.77 (m, 2H, 2″-H), 1.49 –1.37 (m, 2H, 3″-H), 0.92 (t, J = 7.4 Hz, 3H, 4″-H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.5 (C-1), 146.2 (C-1′), 141.3 (C-3′), 140.7 (C-8a′), 132.5 (C-9a′), 128.5 (C-7′), 127.9 (C-4′), 124.8 (C-4a′), 122.9 (C-5′), 120.5 (C-6′), 120.4 (C-4b′), 111.8 (C-8′), 34.5 (C-1″), 32.4 (C-2), 31.3 (C-2″), 23.1 (C-3″), 21.9 (3′-CH_3), 14.1 (C-4″) ppm. IR (KBr): $\tilde{\nu}$ = 3383, 3192, 3064, 2954, 2858, 1700, 1620, 1502, 1456, 1402, 1327, 1179, 748 cm^{-1}. HRMS (EI): m/z = 280.1575 [M] (calcd for $C_{18}H_{20}N_2O$: 280.1576). HPLC purity (method c): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-(3-Methyl-1-phenyl-9*H*-pyrido[3,4-*b*]indol-4-yl)ethan-1-one (12b): Prepared from **11b** (58 mg, 0.18 mmol), palladium on carbon (28 mg, 0.026 mmol) and cesium carbonate (271 mg, 0.831 mmol) following General Procedure 2. Purification was accomplished by FCC using 3:1 hexanes/ethyl acetate to give 33 mg (0.11 mmol, 61 %) of **12b** as a pale yellow solid. Mp 200 °C. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.80 (s, 1H, NH), 7.95–7.91 (m, 2H, 2″-H, 6″-H), 7.87 (dd, J = 8.1 Hz, 0.9 Hz, 1H, 5′-H), 7.59–7.51 (m, 4H, 7′-H, 8′-H, 3″-H, 5″-H), 7.25 (ddd, J = 8.1 Hz, 6.5 Hz, 1.7 Hz, 1H, 6′-H), 2.78 (s, 3H, 2-H), 2.69 (s, 3H, 3′-CH_3) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 206.3 (C-1), 143.0 (C-1′), 142.4 (C-3′), 141.5 (C-8a′), 138.7 (C-1″), 132.4 (C-9a′), 129.6 (C-3″, C-5″), 129.5 (C-4″), 129.1 (C-4′, C-7′), 128.7 (C-2″, C-6″), 126.2 (C-4a′), 123.2 (C-5′), 120.9 (C-6′), 120.6 (C-4b′), 112.3 (C-8′), 32.5 (C-2), 22.2 (3′-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3299, 3060, 2923, 1687, 1620, 1561, 1495, 1396, 1320, 1232, 1087, 742, 702 cm^{-1}. HRMS (EI): m/z = 300.1265 [M] (calcd for $C_{20}H_{16}N_2O$: 300.1263). HPLC purity (method c): 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-(3-Methyl-1-phenyl-9*H*-pyrido[3,4-*b*]indol-4-yl)ethan-1-one (12c): Prepared from **11c** (62 mg, 0.19 mmol), palladium on carbon (21 mg, 0.020 mmol) and cesium carbonate (283 mg, 0.869 mmol) following General Procedure 2. Purification was accomplished by FCC using 4:1 hexanes/acetone to give 31 mg (0.10 mmol, 53 %) of **12b** as a yellow solid. Mp 174 °C. ^{1}H NMR (400 MHz, $(CD_3)_2SO$): δ = 11.59 (s, 1H, NH), 8.11 (dd, *J* = 3.7 Hz, 1.0 Hz, 1H, 5''-H), 7.78–7.72 (m; 3H, 5'-H, 8'-H, 3''-H), 7.59 (ddd, *J* = 8.2 Hz, 7.1 Hz, 1.1 Hz, 1H, 7'-H), 7.35 (dd, *J* = 5.1 Hz, 3.7 Hz, 1H, 4''-H), 7.25 (ddd, *J* = 8.1 Hz, 7.1 Hz, 1.0 Hz, 1H, 6'-H), 2.76 (s, 3H, 2-H), 2.57 (s, 3H, 3'-CH_3) ppm. ^{13}C NMR (101 MHz, $(CD_3)_2SO$): δ = 205.6 (C-1), 142.7 (C-1'), 141.8 (C-8a'), 140.0 (C-3'), 136.0 (C-1''), 129.3 (C-9a'), 128.6 (C-7', C-3''), 128.5 (C-4''), 128.2 (C-4'), 126.3 (C-5''), 125.5 (C-4a'), 122.0 (C-5'), 120.2 (C-6'), 118.7 (C-4b'), 112.9 (C-8'), 32.0 (C-2), 21.4 (3'-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3330, 3067, 2920, 1685, 1559, 1433, 1400, 1352, 1234, 1146, 741, 702 cm^{-1}. HRMS (ESI): *m/z* = 305.0753 [M – H]$^-$ (calcd for $C_{18}H_{13}N_2OS^-$: 305.0754). HPLC purity (method b): 95 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-(6-Methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indol-4-yl)ethan-1-one (12d): Prepared from **11d** (52 mg, 0.18 mmol), palladium on carbon (20 mg, 0.019 mmol) and cesium carbonate (207 mg, 0.635 mmol) following General Procedure 2. Purification was accomplished by FCC using 1:3 hexanes/ethyl acetate to give 38 mg (0.14 mmol, 78 %) of **12d** as a yellow solid. Mp 125 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.58 (s, 1H, NH), 7.43 (dd, *J* = 8.9 Hz, 0.5 Hz, 1H, 8'-H), 7.25 (d, *J* = 2.5 Hz, 1H, 5'-H), 7.17 (dd, *J* = 8.9 Hz, 2.5 Hz, 1H, 7'-H), 3.85 (s, 3H, OCH_3), 2.74 (s, 3H, 1'-CH_3), 2.72 (s, 3H, 2-H), 2.59 (s, 3H, 3'-CH_3) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 206.4 (C-1), 154.7 (C-6'), 142.7 (C-1'), 141.2 (C-3'), 136.2 (C-8a'), 134.1 (C-9a'), 128.2 (C-4'), 124.4 (C-4a'), 121.1 (C-4b'), 118.8 (C-7'), 113.1 (C-8'), 105.2 (C-5'), 56.4 (OCH_3), 32.6 (C-2), 22.1 (3'-CH_3), 20.6 (1'-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3440, 3155, 2955, 1700, 1686, 1582, 1496, 1309, 1221, 1034, 815, 778 cm^{-1}. HRMS (EI): *m/z* = 268.1214 [M] (calcd for $C_{16}H_{16}N_2O_2$: 268.1212). HPLC purity (method c): 99 % (λ = 210 nm), 99 % (λ = 254 nm).

1-(1-Butyl-6-methoxy-3-methyl-9*H*-pyrido[3,4-*b*]indol-4-yl)-ethan-1-one (12e): Prepared from **11e** (59 mg, 0.18 mmol), palladium on carbon (20 mg, 0.019 mmol) and cesium carbonate (144 mg, 0.442 mmol) following General Procedure 2. Purification was accomplished by FCC using 2:1 hexanes/ethyl acetate to give 51 mg (0.16 mmol, 89 %) of **12e** as a yellow solid. Mp 102 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.87 (s, 1H, NH), 7.41 (d, *J* = 8.9 Hz, 1H, 8'-H), 7.26 (d, *J* = 2.5 Hz, 1H, 5'-H), 7.16 (dd, *J* = 8.9 Hz, 2.5 Hz, 1H, 7'-H), 3.85 (s, 3H, OCH_3), 3.05–2.98 (m, 2H, 1''-H), 2.74 (s, 3H, 2-H), 2.60 (s, 3H, 3'-CH_3), 1.85–1.75 (m, 2H, 2''-H), 1.45–1.33 (m, 2H, 3''-H), 0.90 (t, *J* = 7.4 Hz, 3H, 4''-H) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 206.6 (C-1), 154.6 (C-6'), 146.9 (C-1'), 141.1 (C-3'), 136.2 (C-8a'), 133.7 (C-9a'), 128.1 (C-4'), 124.7 (C-4a'), 121.1 (C-4b'), 118.7 (C-7'), 113.1 (C-8'), 105.1 (C-5'), 56.4 (OCH_3), 34.6 (C-1''), 32.7 (C-2), 31.4 (C-2''), 23.4 (C-3''), 22.1 (3'-CH_3), 14.3 (C-4'') ppm. IR (KBr): $\tilde{\nu}$ = 3635, 3194, 2956, 2856, 1701, 1580, 1496, 1438, 1354, 1311, 1223, 1033, 778 cm^{-1}. HRMS (EI): *m/z* = 310.1678 [M] (calcd for $C_{19}H_{22}N_2O_2$: 310.1681). HPLC purity (method c): 96 % (λ = 210 nm), 96 % (λ = 254 nm).

1-(6-Methoxy-3-methyl-1-phenyl-9*H*-pyrido[3,4-*b*]indol-4-yl)-ethan-1-one (12f): Prepared from **11f** (63 mg, 0.18 mmol), palladium on carbon (20 mg, 0.019 mmol) and cesium carbonate (213 mg, 0.654 mmol) following General Procedure 2. Purification was accomplished by FCC using 4:1 hexanes/ethyl acetate to give 28 mg (0.085 mmol, 47 %) of **12f** as a yellow solid. Mp 115 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.40 (s, 1H, NH), 7.94–7.90 (m, 2H, 2''-H, 6''-H), 7.60–7.55 (m, 2H, 3''-H, 5''-H), 7.51–7.46 (m, 1H, 4''-H), 7.39 (d, *J* = 8.9 Hz, 1H, 8'-H), 7.31 (d, *J* = 2.4 Hz, 1H, 5'-H), 7.19 (dd, *J* = 8.9 Hz, 2.5 Hz, 1H, 7'-H), 3.88 (s, 3H, OCH_3), 2.80 (s, 3H, 2-H), 2.73 (s, 3H, 3'-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 206.2 (C-1), 154.4 (C-6'), 143.1 (C-1'), 141.8 (C-3'), 138.2 (C-1''), 136.0 (C-8a'), 132.7 (C-9a'), 129.4 (C-3'', C-5''), 129.2 (C-4''), 128.6 (C-4'), 128.3 (C-2'', C-6''), 125.7 (C-4a'), 120.6 (C-4b'), 118.8 (C-7'), 112.6 (C-8'), 104.9 (C-5'), 56.2 (OCH_3), 32.4 (C-2), 22.1 (3'-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3372, 3057, 2925, 2831, 1695, 1571, 1490, 1280, 1220, 1143, 1031, 766, 694 cm^{-1}. HRMS (EI): *m/z* = 330.1340 [M] (calcd for $C_{21}H_{18}N_2O_2$: 330.1368). HPLC purity (method c): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

1-(6-Methoxy-3-methyl-1-(thiophen-2-yl)-9*H*-pyrido[3,4-*b*]indol-4-yl)ethan-1-one (12g): Prepared from **11g** (64 mg, 0.18 mmol), palladium on carbon (19 mg, 0.018 mmol) and cesium carbonate (207 mg, 0.635 mmol) following General Procedure 2. Purification was accomplished by FCC using 4:1 hexanes/acetone to give 41 mg (0.12 mmol, 67 %) of **12g** as a yellow solid. Mp 170 °C. ^{1}H NMR (400 MHz, CD_2Cl_2): δ = 8.66 (s, 1H, NH), 7.74 (dd, *J* = 3.7 Hz, 1.1 Hz, 1H, 3''-H), 7.51 (dd, *J* = 5.1 Hz, 1.0 Hz, 1H, 5''-H), 7.46 (dd, *J* = 8.8 Hz, 0.5 Hz, 1H, 8'-H), 7.24–7.21 (m, 2H, 5'-H, 4''-H), 7.17 (dd, *J* = 8.9 Hz, 2.5 Hz, 1H, 7'-H), 3.84 (s, 3H, OCH_3), 2.75 (s, 3H, 2-H), 2.62 (s, 3H, 3'-CH_3) ppm. ^{13}C NMR (101 MHz, CD_2Cl_2): δ = 206.2 (C-1), 155.0 (C-6'), 143.3 (C-1'), 142.0 (C-3'), 137.1 (C-1''), 136.6 (C-8a'), 131.7 (C-9a'), 129.0 (C-4'), 128.6 (C-4''), 128.1 (C-5''), 126.7 (C-4a'), 125.8 (C-3''), 120.9 (C-4b'), 119.0 (C-7'), 113.3 (C-8'), 105.1 (C-5'), 56.3 (OCH_3), 32.6 (C-2), 22.1 (3'-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3413, 3303, 3091, 2958, 2831, 1686, 1559, 1487, 1353, 1279, 1145, 1033, 847, 721 cm^{-1}. HRMS (ESI): *m/z* = 335.0859 [M – H]$^-$ (calcd for $C_{19}H_{15}N_2O_2S^-$: 335.0860). HPLC purity: 98 % (λ = 210 nm), > 99 % (λ = 254 nm).

(1,3-Dimethyl-9*H*-pyrido[3,4-*b*]indol-4-yl)(phenyl)methan-1-one (12h): Prepared from **11h** (82 mg, 0.26 mmol), palladium on carbon (28 mg, 0.026 mmol) and cesium carbonate (284 mg, 0.872 mmol) following General Procedure 2. Purification was accomplished by FCC using 1:3 hexanes/ethyl acetate to give 55 mg (0.18 mmol, 69 %) of **12h** as a yellow solid. Mp 215 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.75 (s, 1H, NH), 7.97–7.92 (m, 1H, 2'-H, 6'-H), 7.63–7.57 (m, 1H, 4'-H), 7.50–7.39 (m, 5H, 5-H, 7-H, 8-H, 3'-H, 5'-H), 7.00 (ddd, *J* = 8.1 Hz, 5.9 Hz, 2.3 Hz, 1H, 6-H), 2.82 (s, 3H, 1-CH_3), 2.51 (s, 3H, 3-CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 198.6 (C=O), 143.0 (C-3), 142.0 (C-1), 140.8 (C-8a), 137.1 (C-1'), 134.3 (C-4'), 132.8 (C-9a), 130.0 (C-2', C-6'), 129.2 (C-3', C-5'), 128.5 (C-7), 126.3 (C-4a), 125.4 (C-4), 123.4 (C-5), 120.6 (C-4b), 120.4 (C-6), 111.7 (C-8), 22.2 (3-CH_3), 20.5 (1-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3138, 3086, 2918, 1667, 1593, 1401, 1239, 1144 957, 866, 745 cm^{-1}. HRMS (ESI): *m/z* = 299.1190 [M – H]$^-$ (calcd for $C_{20}H_{15}N_2O^-$: 299.1190). HPLC purity (method c): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

(6-Methoxy-1,3-dimethyl-9*H*-pyrido[3,4-*b*]indol-4-yl)(phenyl)-methan-1-one (12i): Prepared from **11i** (60 mg, 0.17 mmol), palladium on carbon (20 mg, 0.019 mmol) and cesium carbonate (202 mg, 0.620 mmol) following General Procedure 2. Purification was accomplished by FCC using 1:3 hexanes/ethyl acetate to give 49 mg (0.15 mmol, 88 %) of **12i** as a yellow solid. Mp 207 °C. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 8.53 (s, 1H, NH), 7.95–7.90 (m, 1H, 2'-H, 6'-H), 7.64–7.59 (m, 1H, 4'-H), 7.50–7.44 (m, 2H, 3'-H, 5'-H), 7.39 (d, *J* = 8.9 Hz, 1H, 8-H), 7.06 (dd, *J* = 8.9 Hz, 2.5 Hz, 1H, 7-H), 6.78 (d, *J* = 2.5 Hz, 1H, 5-H), 3.53 (OCH_3), 2.80 (s, 3H, 1-CH_3), 2.48 (s, 3H, 3-CH_3) ppm. ^{13}C NMR (126 MHz, CD_2Cl_2): δ = 198.7 (C=O), 154.4 (C-6), 143.2 (C-3), 142.9 (C-1), 137.9 (C-1'), 136.1 (C-8a), 134.5 (C-4'), 133.9 (C-9a), 130.2 (C-2', C-6'), 129.6 (C-3', C-5'), 126.1 (C-4a), 125.5 (C-4), 121.2 (C-4b), 118.8 (C-7), 112.9 (C-8), 105.3 (C-5), 56.0 (OCH_3), 22.3 (3-CH_3), 20.7 (1-CH_3) ppm. IR (KBr): $\tilde{\nu}$ = 3448, 3114, 3034, 2924, 2853, 1664, 1578, 1491, 1305, 1220, 1026, 880, 684 cm^{-1}. HRMS

(ESI): m/z = 329.1295 [M – H]$^-$ (calcd for $C_{21}H_{17}N_2O_2^-$: 329.1296). HPLC purity (method c): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

***R,S*-(1-Methyl-3-propyl-9*H*-pyrido[3,4-*b*]indol-4-yl)(pyridin-2-yl)methanol (12j):** Prepared from **11j** (67 mg, 0.19 mmol), palladium on carbon (21 mg, 0.020 mmol) and cesium carbonate (195 mg, 0.598 mmol) following General Procedure 2. Purification was accomplished by FCC using 1:9 hexanes/ethyl acetate and 5 % triethylamine to give 55 mg (0.16 mmol, 84 %) of **12j** as a yellow solid. Mp 210 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.49 (s, 1H, NH), 8.58–8.54 (m, 1H, 3′′-H), 8.13 (d, J = 8.2 Hz, 1H, 5′-H), 7.70–7.64 (m, 1H, 5′′-H), 7.50 (d, J = 7.4 Hz, 1H, 8′-H), 7.36 (ddd, J = 8.2 Hz, 7.1 Hz, 1.1 Hz, 1H, 7′-H), 7.29 (d, J = 7.9 Hz, 1H, 6′′-H), 7.26–7.21 (m, 1H, 4′′-H), 7.00–6.95 (m, 1H, 6′-H), 6.78 (s, 1H, 1-H), 5.54 (s, 1H, OH), 2.99–2.92 (m, 2H, 1′′′-H), 2.76 (s, 3H, 1′-CH_3), 1.80–1.55 (m, 2H, 2′′′-H), 0.91 (t, J = 7.4 Hz, 3H, 3′′′-H) ppm. ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 163.0 (C-1′′), 150.2 (C-3′), 149.0 (C-3′′), 142.0 (C-8a′), 141.5 (C-1′), 137.5 (C-5′′), 134.7 (C-9a′), 128.0 (C-4a′), 127.7 (C-7′), 127.6 (C-4′), 126.8 (C-5′), 122.9 (C-4′′), 122.5 (C-4b′), 121.6 (C-6′′), 119.5 (C-6′), 112.2 (C-8′), 71.9 (C-1), 38.6 (C-1′′′), 24.9 (C-2′′′), 20.6 (1′-CH_3), 14.6 (C-3′′′) ppm. IR (KBr): $\tilde{\nu}$ = 3444, 3145, 3091, 2957, 2871, 1619, 1470, 1332, 1125, 1057, 748 cm^{-1}. HRMS (ESI): m/z = 330.1609 [M – H]$^-$ (calcd for $C_{21}H_{20}N_3O^-$: 330.1612). HPLC purity (method c): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

***R,S*-(6-Methoxy-1-methyl-3-propyl-9*H*-pyrido[3,4-*b*]indol-4-yl)-(pyridin-2-yl)methanol (12k):** Prepared from **11k** (73 mg, 0.19 mmol), palladium on carbon (24 mg, 0.023 mmol) and cesium carbonate (219 mg, 0.672 mmol) following General Procedure 2. Purification was accomplished by FCC using 1:9 hexanes/ethyl acetate and 5 % triethylamine to give 46 mg (0.13 mmol, 68 %) of **12k** as a yellow solid. Mp 182 °C. ^{1}H NMR (400 MHz, $(CD_3)_2CO$): δ = 10.30 (s, 1H, NH), 8.62–8.57 (m, 1H, 3′′-H), 7.69–7.64 (m, 1H, 5′′-H), 7.56 (d, J = 2.4 Hz, 5′-H), 7.36 (d, J = 8.8 Hz, 1H, 8′-H), 7.29–7.23 (m, 2H, 4′′-H, 6′′-H), 6.98 (dd, J = 8.8 Hz, 2.5 Hz, 1H, 7′-H), 6.66 (s, 1H, 1-H), 5.57 (d, J = 1.8 Hz, 1H, OH), 3.66 (s, 3H, OCH_3), 3.07–2.98 (m, 2H, 1′′′-H), 2.74 (s, 3H, 1′-CH_3), 1.83–1.68 (m, 2H, 2′′′-H), 0.97 (t, J = 7.4 Hz, 3H, 3′′′-H) ppm. ^{13}C NMR (101 MHz, $(CD_3)_2CO$): δ = 163.1 (C-1′′), 154.0 (C-6′), 149.6 (C-3′), 149.1 (C-3′′), 141.9 (C-1′), 137.6 (C-5′′), 136.8 (C-8a′), 135.6 (C-9a′), 127.6 (C-4a′), 127.0 (C-4′), 123.0 (C-4′′), 122.5 (C-4b′), 121.6 (C-6′′), 118.1 (C-7′), 112.7 (C-8′), 108.8 (C-5′), 72.0 (C-1), 56.0 (OCH_3), 38.7 (C-1′′′), 25.2 (C-2′′′), 20.6 (1′-CH_3), 14.6 (C-3′′′) ppm. IR (KBr): $\tilde{\nu}$ = 3432, 3128, 3082, 2953, 2827, 1594, 1579, 1495, 1434, 1302, 1222, 1038, 1001, 803 cm^{-1}. HRMS (EI): m/z = 361.1784 [M$^{\cdot}$]$^+$ (calcd for $C_{22}H_{23}N_3O_2^{\cdot+}$: 361.1785). HPLC purity (method c): > 99 % (λ = 210 nm), > 99 % (λ = 254 nm).

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