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Intramolecular Heck reaction of 2- and 3-iodoindole derivatives for the synthesis of β- and γ-carbolinones

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Abstract—A new synthesis of β- and γ-carbolinone derivatives was achieved by an intramolecular Heck cyclisation from the corresponding 3-iodo-1*H*-indole-2-carboxylic acid allyl-amides **8** and 2-iodo-1*H*-indole-3-carboxylic acid allyl-amides **9**.

As a part of our ongoing interest in developing new synthetic strategies for the construction of carbolines,[1] we focused our attention on the intramolecular Heck reaction of 2-iodo-1*H*-indole-3-carboxylic acid allyl-amide and 3-iodo-1*H*-indole-2-carboxylic acid allyl-amide derivatives to obtain β- and γ-carbolinone derivatives. The Heck reaction, a palladium catalysed coupling reaction of an aryl or a vinyl halide with an alkene, is a highly efficient and mild procedure for C–C bond formation as well as for the synthesis of heterocyclic compounds.[2] The synthetic strategy was thus to introduce a suitable allyl group on the nitrogen atom of the indole carboxamide and hence achieve palladium-catalysed ring closure to form β- and γ-carbolinones.

The synthesis of β-[3] and γ-carbolinones[4] has indeed attracted some interest in the recent years and the development of new synthetic methods is an interesting research area.

The 1,2-dihydro-pyrido[3,4-*b*]indol-1-one (β-carbolinone) nucleus occurs in some natural alkaloids. For example, bauerine C **I**, has been isolated from the terrestrial blue–green alga *Dichothrix baueriana* GO-25-2.[5] Sponges of the genus *Fascaplysinopsis* are a rich source of alkaloids with promising biological activities.[6,7] One of these metabolites, isolated from *F. reticulata*, is secofascaplysin **II**, the first naturally occurring β-carbolinone[7] (Fig. 1). β-Carbolinones are also of interest in medicine and in recent years many of these derivatives have been patented[8] and described as useful central nervous system depressant and antitumor agents. A novel series of human leukocyte elastase (HLE) inhibitors containing the β-carbolinone ring system have also been reported.[9]

The isomeric 2,5-dihydro-pyrido[4,3-*b*]indol-1-ones (γ-carbolinones) are less widespread. The γ-carbolinone ring system is present in indolonaphtyridone **III**, which acts as a conformationally restricted 5-HT_3 receptor antagonist[10] and in the potential antitumoral scaffold indolo[3,2-*c*]quinoline **IV**.[11] Many of these compounds have been patented and described as cannabinoid receptor modulators for treating respiratory and non-respiratory diseases.[12]

In this paper we describe the synthesis of β- and γ-carbolinones, respectively, starting from 3-iodo-1-methoxymethyl-1*H*-indole-2-carboxylic acid **3** and 2-iodo-1-methoxymethyl-1*H*-indole-3-carboxylic acid **7**, prepared following Schemes 1 and 2. The 3-iodo-1*H*-indole-2-carboxylic acid ethyl ester **1**[13] was protected at the indolic nitrogen and the obtained 3-iodo-1-methoxymethyl-1*H*-

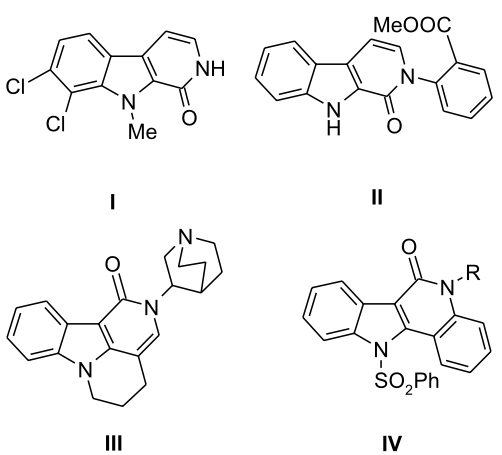

Figure 1.

Keywords: Heck reaction; Pd catalyst; intramolecular cyclization; indoles; carbolines.

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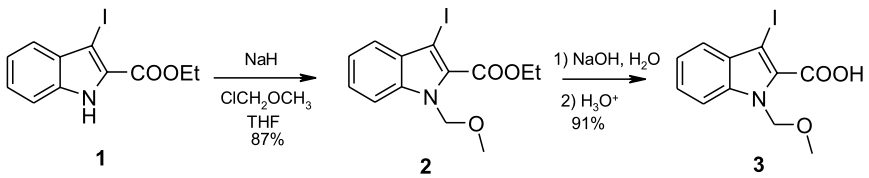
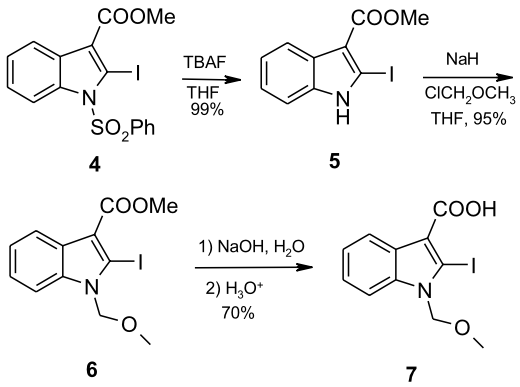


Scheme 1.

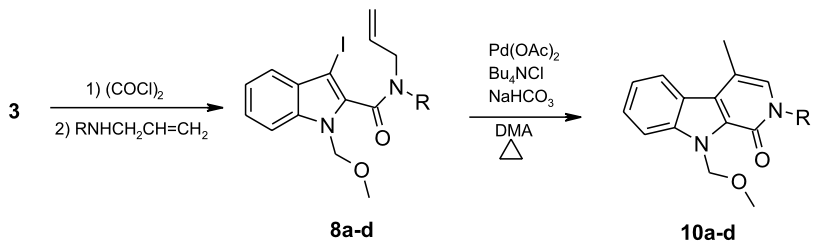


Scheme 2.

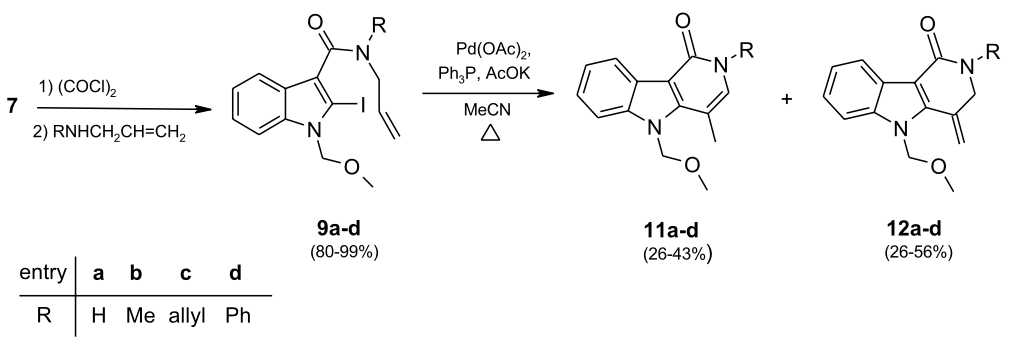
indole-2-carboxylic acid ethyl ester **2** hydrolysed to the corresponding acid **3** (Scheme 1). The 2-iodo-1-benzenesulfonyl-1*H*-indole-3-carboxylic acid methyl ester **4** was obtained in better yield than described[14] (85 vs. 45% yield) via lithiation with LDA of 1-benzenesulfonyl-1*H*-indole-3-carboxylic acid methyl ester[15] followed by electrophilic substitution with iodine (see Section 1). Desulfonylation to give compound **5** was achieved with tetrabutylammonium fluoride (TBAF) in tetrahydrofuran.[16] Compound **6** was obtained from **5** via nitrogen protection; subsequent alkaline hydrolysis of **6** gave the acid **7** (Scheme 2).

From the acids **3** and **7**, the corresponding allylamides **8a–d** and **9a–d** were prepared via intermediate unisolated acyl chlorides, and reaction with the suitable allylamines (Schemes 3 and 4). The ^{1}H and ^{13}C NMR spectral data of the tertiary amides **8b–d** and **9b–d** evidentiated the presence of a mixture of rotamers in solution at room temperature. As reported by literature data[17] the rotameric mixture is sensitive to the substitution pattern of the amide. In fact for the secondary amide **8a** and **9a** the NMR data exhibited a single set of resonance. Dreiding models suggested that a bulky substituent in both C-2 and C-3 positions of the indole nucleus, significantly inhibits rotation about the C-2 carbon–carboxamide bond. Further evidence for the existence of rotamers was secured from a variable temperature NMR spectra in DMSO-d_6. Increasing the temperature in intervals of approximately 20°C resulted in the coalescence of the signals until the spectra at 100°C showed a first-order pattern for each group.

The cyclization reaction to give compounds **10a–d** was performed with a catalyst system containing 10 mol% of palladium(II)acetate, 1.0 equiv. of tetrabutylammonium



Scheme 3.



Scheme 4.

chloride (TBAC) and 2.5 equiv. of sodium hydrogen carbonate in dimethylacetamide at 90°C for the reported time (Scheme 3). In the case of compounds **9b–d**, better results were obtained using 10 mol% of palladium(II)-acetate, 20 mol% of triphenylphosphine, 3.0 equiv. of potassium acetate in acetonitrile at reflux for the reported time. In these conditions, besides the γ-carbolinones **11b–d**, the isomeric γ-carbolinones with exocyclic double bond, **12b–d** were also obtained (Scheme 4). These compounds isomerise in solution in a short time to more stable isomers **11b–d**. Only in the case of compound **9a** different conditions were necessary to obtain the cyclised product: $Pd(OAc)_2$ 5 mol%, Ph_3P 15 mol%, tetrapropylammonium bromide (TPAB) 1.0 equiv., AcOK 4.0 equiv. in DMF at 80°C for 1.5 h.

These results demonstrate once again the usefulness of the intramolecular Heck reaction and establish an efficient approach for the synthesis of β- and γ-carbolinones.

1. Experimental

1.1. General

Melting points were determined on a Buchi 510 or an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded on a Jasco IR Report 100 spectrophotometer, in nujol mull for solids and as a liquid film for oils. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200, Bruker AC 200 and Bruker Avance 300 spectrometer in $CDCl_3$ solution unless otherwise stated. Column chromatography was performed on Merck Kieselgel 60, 0.063–0.2 mm. Evaporation was carried out under vacuum in a rotary evaporator.

1.1.1. 3-Iodo-1-methoxymethyl-1*H*-indole-2-carboxylic acid ethyl ester 2. 3-Iodo-1*H*-indole-2-carboxylic acid ethyl ester **1** (1.58 g, 5 mmol) was dissolved in anhydrous THF (20 ml) and NaH (300 mg, 7.5 mmol) was added portionwise under N_2 at 0°C. After 15 min chloromethylmethylether (HAZARD: carcinogen) (0.76 ml, 10 mmol) was added. The reaction was run for 1.5 h at 35–40°C, the solvent was then evaporated and the residue diluted with 1 M HCl, extracted with CH_2Cl_2 (2×20 ml) and dried over Na_2SO_4. The organic layer was evaporated and the residue purified by silica gel column chromatography, eluent hexane–Et_2O 4:1, to give 1.55 g of **2**, 87% yield, mp 42–44°C (cream crystals from CH_2Cl_2–hexane). IR: 1685br, 1590 cm^{-1}; ^{1}H NMR: 1.52 (3H, t, *J*=7.3 Hz), 3.28 (3H, s), 4.50 (2H, q, *J*=7.3 Hz), 5.96 (2H, s), 7.29 (1H, dt, *J*=1.5, 8.1 Hz), 7.44 (1H, dt, *J*=1.1, 8.4 Hz), 7.53 (1H, d, *J*=8.4 Hz), 7.61 (1H, d, *J*=8.1 Hz); ^{13}C NMR: 14.2, 56.2 (CH_3), 62.8, 75.4 (CH_2), 111.2, 121.9, 124.1, 127.3 (CHAr), 73.5, 127.5, 130.2, 138.9, 166.2 (C). Anal. calcd for $C_{13}H_{14}INO_3$: C, 43.47; H, 3.93; N, 3.90. Found: C, 43.64; H, 3.89; N, 3.88.

1.1.2. 3-Iodo-1-methoxymethyl-1*H*-indole-2-carboxylic acid 3. Compound **2** (1.44 g, 4 mmol) was dissolved in CH_3OH (30 ml) and KOH (1.12 g, 20 mmol) in H_2O (5 ml) was added. The mixture was heated to reflux for 30 min, then the solvent evaporated and the residue diluted with 1 M HCl and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue crystallized to give 1.20 g of **3**, yield 91%, mp 160–162°C (white crystals from hexane–Et_2O). IR: 2930br, 1689, 1596 cm^{-1}; ^{1}H NMR: 3.32 (3H, s), 4.50 (1H, br s, D_2O exch.), 6.02 (2H, s), 7.32 (1H, dt, *J*=1.1, 8.1 Hz), 7.49 (1H, dt, *J*=1.1, 8.1 Hz), 7.57 (1H, d, *J*=8.1 Hz), 7.66 (1H, d, *J*=8.1 Hz); ^{13}C NMR: 56.3 (CH_3), 75.8 (CH_2), 111.4, 122.6, 124.6, 127.6 (CHAr), 73.4, 127.4, 130.9, 139.7, 165.6 (C). Anal. calcd for $C_{11}H_{10}INO_3$: C, 39.90; H, 3.04; N, 4.23. Found: C, 39.78; H, 3.00; N, 4.30.

1.1.3. 2-Iodo-1-sulfonyl-1*H*-indole-3-carboxylic acid methyl ester 4.[13] 1-Sulfonyl-1*H*-indole-3-carboxylic acid methyl ester (1.26 g, 4 mmol) was dissolved in anhydrous THF (15 ml) and under N_2, at −70°C LDA 2 M (2.5 ml, 5 mmol) was added. When the temperature was raised to −50°C, I_2 (1.27 g, 5 mmol) in anhydrous THF (5 ml) was added. The mixture was then allowed to warm to room temperature, the solvent evaporated and the residue diluted with brine and extracted with Et_2O (2×20 ml). The organic layer was washed with a solution of $Na_2S_2O_4$ (1 g), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by silica gel column chromatography, eluent hexane–Et_2O 2:1, to give compound **4**, 1.55 g, 88% yield, mp 142°C (white crystals from Et_2O–hexane). IR: 1680, 1496 cm^{-1}; ^{1}H NMR: 3.98 (3H, s), 7.35 (2H, m), 7.41–7.66 (3H, m), 7.95 (2H, m), 8.07 (1H, m), 8.43 (1H, m). Anal. calcd for $C_{16}H_{12}INO_4S$: C, 43.55; H, 2.74; N, 3.17. Found: C, 43.71; H, 2.68; N, 3.09.

1.1.4. 2-Iodo-1*H*-indole-3-carboxylic acid methyl ester 5. Compound **4** (442 mg, 1 mmol) was dissolved in anhydrous THF (20 ml) and 1 M solution of tetrabutylammonium fluoride (1 ml, 1 mmol) in THF was added. The mixture was heated to reflux for 1.5 h then the solvent was evaporated and the residue diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue purified by silica gel column chromatography, eluent CH_2Cl_2, to give compound **5**, 297 mg, yield 99%, mp 161°C (white needles from CH_2Cl_2–hexane). IR: 3250, 1667, 1460 cm^{-1}; ^{1}H NMR: 4.00 (3H, s), 7.20 (2H, m), 7.38 (1H, m), 8.16 (1H, m), 8.98 (1H, br s, D_2O exch.); ^{13}C NMR: 50.6 (CH_3), 110.8, 122.2, 122.8, 123.6 (CHAr), 94.2, 113.8, 127.5, 138.2, 164.5 (C). Anal. calcd for $C_{10}H_8INO_2$: C, 39.89; H, 2.68; N, 4.65. Found: C, 40.12; H, 2.80; N, 4.58.

1.1.5. 2-Iodo-1-methoxymethyl-1*H*-indole-3-carboxylic acid methyl ester 6. To a solution of compound **5** (1.2 g, 4 mmol) in anhyd. THF (15 ml), 60% NaH (320 mg, 8 mmol) was added portionwise under nitrogen. After 15 min at room temperature, chloromethylmethylether (1 ml, 12 mmol) was added. The reaction was stirred at 35–40°C for 1 h, then the solvent was evaporated and the residue diluted with 1 M HCl and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue crystallized to give 1.31 g of **6**, 95% yield, mp 81–82°C (white crystals from CH_2Cl_2–hexane). IR: 1699, 1461 cm^{-1}; ^{1}H NMR: 3.36 (3H, s), 4.01 (3H, s), 5.70 (2H, s), 7.30 (2H, m), 7.56 (1H, m), 8.18 (1H, m); ^{13}C NMR: 51.3, 56.3 (CH_3), 78.0 (CH_2), 110.6, 121.8, 122.6, 123.6 (CHAr), 93.8, 113.3, 127.7, 138.8, 164.8 (C).

Anal. calcd for $C_{12}H_{12}INO_3$: C, 41.76; H, 3.50; N, 4.06. Found: C, 41.89; H, 3.41; N, 3.98.

1.1.6. 2-Iodo-1-methoxymethyl-1*H*-indole-3-carboxylic acid 7. To a solution of compound **6** (1.38 g, 4 mmol) in CH_3OH (30 ml) a solution of KOH (0.896 g, 16 mmol) in H_2O (5 ml) was added and the mixture was heated to reflux for 1.5 h. The solvent was then evaporated and the residue diluted with 1 M HCl and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue purified by silica gel column chromatography, eluent CH_2Cl_2–Et_2O 2:1, to give compound **7**, 920 mg, 70% yield, mp 185°C (white crystals from CH_2Cl_2–hexane). IR: 3250br, 1655, 1495 cm^{-1}; ^1H NMR: 3.39 (3H, s), 5.74 (2H, s), 7.30 (2H, m), 7.59 (1H, dd, *J*=2.6, 6.2 Hz), 8.29 (1H, dd, *J*=2.6, 6.2 Hz); ^{13}C NMR: 56.7 (CH_3), 78.5 (CH_2), 110.9, 122.4, 123.2, 124.1 (CHAr), 95.5, 115.5, 128.5, 139.2, 169.5 (C). Anal. calcd for $C_{11}H_{10}INO_3$: C, 39.90; H, 3.04; N, 4.23. Found: C, 39.81; H, 2.99; N, 4.28.

1.2. Synthesis of 3-iodo-1-methoxymethyl-1*H*-indole-2-carboxamides 8a–d and 2-iodo-1-methoxymethyl-1*H*-indole-3-carboxamides 9a–d: general procedure

To a mixture of compound **3** or **7** (1 mmol), CH_2Cl_2 (20 ml) and DMF (0.05 ml), and oxalyl chloride (0.3 ml, 3 mmol) were added. The reaction was run for 1 h at room temperature and for 1 h at reflux. The solvent was evaporated to dryness in vacuo, the residue taken up with CH_2Cl_2 (20 ml) and the suitable allylamine (3 mmol) was added at 0°C. After 1 h at room temperature, the mixture was washed with 1 M HCl. The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue purified by silica gel column chromatography (eluent see below).

1.2.1. 3-Iodo-1*H*-indole-2-carboxylic acid allyl-amide 8a. Allylamine, eluent CH_2Cl_2–Et_2O 20:1, 339 mg, yield 92%, mp 120°C (white crystals from CH_2Cl_2–hexane); IR: 3278, 1638, 1556 cm^{-1}; ^1H NMR: 3.33 (3H, s), 4.19 (2H, dddd, *J*=1.5, 1.8, 5.5, 5.9 Hz), 5.28 (1H, ddd, *J*=1.1, 1.5, 10.2 Hz), 5.41 (1H, ddd, *J*=1.1, 1.8, 17.2 Hz), 5.84 (2H, s), 6.02 (1H, ddt, *J*=10.2, 17.2, 5.5 Hz), 6.70 (1H, br s, exch. D_2O), 7.29 (1H, dt, *J*=1.5, 7.0 Hz), 7.41 (1H, dt, *J*=1.5, 7.0 Hz), 7.53 (2H, m); ^{13}C NMR: 56.3 (CH_3), 42.4, 75.4 (CH_2), 117.2 (CH_2=), 111.0, 122.2, 123.1, 125.8 (CHAr), 133.5 (CH=), 63.3, 130.0, 133.6, 138.1, 161.6 (C). Anal. calcd for $C_{14}H_{15}IN_2O_2$: C, 45.42; H, 4.08; N, 7.57. Found: C, 45.99; H, 4.14; N, 7.35.

1.2.2. 3-Iodo-1*H*-indole-2-carboxylic acid allyl-methyl-amide 8b. *N*-Methylallylamine, eluent hexane–Et_2O 1:1, 340 mg, yield 88%, mp 116–118°C (cream crystals from CH_2Cl_2–hexane); IR: 1632, 1531 cm^{-1}; ^1H NMR (DMSO at 100°C): 2.97 (3H, s), 3.25 (3H, s), 4.01 (2H, br s), 5.23–5.36 (2H,m), 5.48 (2H, s), 5.90 (1H, m), 7.25–7.41 (3H, m), 7.62 (1H, d, *J*=8.1 Hz); ^{13}C NMR (DMSO at 80°C): 35.6, 55.7 (CH_3), 53.1, 74.7 (CH_2), 117.3 (CH_2=), 110.9, 120.9, 121.5, 124.0 (CHAr), 132.2 (CH=), 60.3, 129.0, 135.5, 136.6, 162.3 (C). Anal. calcd for $C_{15}H_{17}IN_2O_2$: C, 46.89; H, 4.46; N, 7.29. Found: C, 47.95; H, 4.53; N, 7.19.

1.2.3. 3-Iodo-1*H*-indole-2-carboxylic acid diallyl-amide 8c. Diallylamine, eluent hexane–Et_2O 2:1, 370 mg, yield 90%, colourless oil; IR: 1630, 1530 cm^{-1}; ^1H NMR (DMSO at 100°C): 3.24 (3H, s); 3.97–4.28 (4H, br s), 5.21 (4H, br s), 5.47 (2H, s), 5.86 (2H, br s), 7.26 (1H, dt, *J*=1.0, 8.0 Hz), 7.37 (2H, m), 7.63 (1H, d, *J*=8.2 Hz); ^{13}C NMR (DMSO at 100°C): 56.7 (CH_3), 51.8 ($2CH_2$), 76.2 (CH_2), 119.1 ($2CH_2$=), 112.0, 121.9, 122.5, 125.0 (CHAr), 133.8 (2CH=), 60.6, 130.2, 136.6, 137.6, 163.6 (C). Anal. calcd for $C_{17}H_{19}IN_2O_2$: C, 49.77; H, 4.67; N, 6.83. Found: C, 49.99; H, 4.72; N, 6.79.

1.2.4. 3-Iodo-1*H*-indole-2-carboxylic acid allyl-phenyl-amide 8d. *N*-Allylaniline, eluent CH_2Cl_2–Et_2O 20:1, 422 mg, yield 95%, pale yellow oil; IR: 1635, 1580 cm^{-1}; ^1H NMR (DMSO at 100°C): 3.29 (3H, s), 4.53 (2H, d, *J*=5.8 Hz), 5.17 (1H, dd, *J*=1.5, 10.2 Hz), 5.25 (1H, dd, *J*=1.5, 17.2 Hz), 5.60 (2H, br s), 5.95 (1H, ddt, *J*=5.8, 10.2, 17.2 Hz), 7.13–7.37 (8H, m), 7.57 (1H, d, *J*=8.1 Hz); ^{13}C NMR (DMSO): 55.8 (CH_3), 51.8, 74.6 (CH_2), 117.7 (CH_2=), 110.8, 121.0, 121.3, 124.2, 126.8, 128.2, 128.4 (CHAr), 126.6 (2CHAr), 132.7 (CH=), 62.1, 128.8, 135.7, 136.5, 140.9, 161.9 (C). Anal. calcd for $C_{20}H_{19}IN_2O_2$: C, 53.83; H, 4.29; N, 6.28. Found: C, 53.90; H, 4.33; N, 6.19.

1.2.5. 2-Iodo-1*H*-indole-3-carboxylic acid allyl-amide 9a. Allylamine, eluent CH_2Cl_2–Et_2O 1:1, 333 mg, yield 90%, mp 122°C (white plates from CH_2Cl_2–hexane); IR: 3275, 1620, 1530 cm^{-1}; ^1H NMR: 3.35 (3H, s), 4.20 (2H, dd, *J*=5.5, 5.9 Hz), 5.24 (1H, dd, *J*=1.5, 10.2 Hz), 5.36 (1H, dd, *J*=1.5, 17.2 Hz), 5.65 (2H, s), 6.03 (1H, ddt, *J*=10.2, 17.2, 5.5 Hz), 6.22 (1H, br s, D_2O exch.), 7.24 (2H, m), 7.54 (1H, m), 7.96 (1H, m); ^{13}C NMR: 55.5 (CH_3), 51.6, 76.7 (CH_2), 115.1 (CH_2=), 110.6, 119.2, 120.9, 122.6 (CHAr), 135.4 (CH=), 90.2, 121.5, 126.7, 137.9, 163.7 (C). Anal. calcd for $C_{14}H_{15}IN_2O_2$: C, 45.42; H, 4.08; N, 7.57. Found: C, 45.20; H, 4.20; N, 7.69.

1.2.6. 2-Iodo-1*H*-indole-3-carboxylic acid allyl-methyl-amide 9b. *N*-Methylallylamine, purified by crystallization, 380 mg, quantitative yield, mp 89–90°C (white crystals from Et_2O); IR: 1617, 1530 cm^{-1}; ^1H NMR (DMSO at 80°C): 2.93 (3H, s), 3.27 (3H, s), 4.02 (2H, br s), 5.20 (2H, dd, *J*=9.6, 16.0 Hz), 5.57 (2H, s), 5.82 (1H, m), 7.13 (1H, dt, *J*=1.0, 7.8 Hz), 7.21 (1H, dt, *J*=1.1, 8.2 Hz), 7.38 (1H, d, *J*=7.8 Hz), 7.64 (1H, d, *J*=8.2 Hz); ^{13}C NMR (DMSO at 80°C): 34.9, 56.4 (CH_3), 51.4, 77.8 (CH_2), 118.0 (CH_2=), 111.6, 119.2, 121.9, 123.6 (CHAr), 134.4 (CH=), 88.0, 121.1, 127.7, 138.6, 166.7 (C). Anal. calcd for $C_{15}H_{17}IN_2O_2$: C, 46.89; H, 4.46; N, 7.29. Found: C, 46.70; H, 4.40; N, 7.35.

1.2.7. 2-Iodo-1*H*-indole-3-carboxylic acid diallyl-amide 9c. Diallylamine, eluent CH_2Cl_2–Et_2O 6:1, 405 mg, quantitative yield, colourless oil; IR: 1630. 1520 cm^{-1}; ^1H NMR (DMSO at 80°C): 3.26 (3H, s), 3.99 (4H, br s), 5.17 (4H, dd, *J*=9.4, 13.4 Hz), 5.57 (2H, s), 5.82 (2H, m), 7.13 (1H, dt, *J*=1.0, 7.9 Hz), 7.21 (1H, dt, *J*=1.0, 8.1 Hz), 7.38 (1H, d, *J*=7.9 Hz), 7.64 (1H, d, *J*=8.1 Hz); ^{13}C NMR (DMSO at 80°C): 56.4 (CH_3), 49.2 ($2CH_2$), 77.8 (CH_2), 118.2 ($2CH_2$=), 111.7, 119.0, 121.9, 123.6 (CHAr), 134.6 (2CH=), 88.1, 120.9, 127.7, 138.6, 166.8 (C). Anal. calcd for $C_{17}H_{19}IN_2O_2$: C, 49.77; H, 4.67; N, 6.83. Found: C, 49.62; H, 4.56; N, 6.90.

1.2.8. 2-Iodo-1*H*-indole-3-carboxylic acid allyl-phenyl-amide 9d. *N*-Allylaniline, eluent CH_2Cl_2–Et_2O 10:1, 357 mg, yield 80%, mp 74–75°C (white crystals from hexane–Et_2O); IR: 1620, 1580 cm^{-1}; ^1H NMR: 3.07 (3H, s), 4.62 (2H, d, *J*=5.9 Hz), 5.22 (1H, dd, *J*=1.1, 10.0 Hz), 5.30 (1H, dd, *J*=1.5, 17.2 Hz), 5.46 (2H, s), 6.10 (1H, m), 7.01–7.18 (7H, m), 7.36 (1H, dd, *J*=1.8, 7.0 Hz), 7.52 (1H, dd, *J*=1.8, 6.6 Hz); ^{13}C NMR: 56.0 (CH_3), 53.2, 77.6 (CH_2), 118.2 (CH_2=), 110.4, 119.7, 121.6, 123.4, 126.8 (CHAr), 127.3, 128.7 (2CHAr), 133.8 (CH=), 86.5, 121.7, 127.8, 138.1, 143.0, 166.6 (C). Anal. calcd for $C_{20}H_{19}IN_2O_2$: C, 53.83; H, 4.29; N, 6.28. Found: C, 53.95; H, 4.35; N, 6.24.

1.3. Synthesis of β-carbolinones 10a–d: general procedure

To a solution of indole **8a–d** (1 mmol) in DMA (3 ml) was added $NaHCO_3$ (210 mg, 2.5 mmol), $Pd(OAc)_2$ (22 mg, 10 mol%), TBAC (276 mg, 1 mmol) and the mixture was heated at 90°C with stirring for the reported time. After completion of the reaction (tlc), the mixture was washed with brine and extracted with Et_2O (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue chromatographed by silica gel (eluent see below).

1.3.1. 2,9-Dihydro-9-methoxymethyl-4-methyl-1*H*-pirido[3,4-*b*] indol-1-one 10a. Heated for 6 h, eluent hexane–Et_2O 2:1, 186 mg, yield 77%, mp 195–196°C (cream crystals from CH_2Cl_2–hexane); IR: 3270, 1652, 1535 cm^{-1}; ^1H NMR: 2.68 (3H, s), 3.38 (3H, s), 6.31 (2H, s), 7.06 (1H, s), 7.37 (1H, dt, *J*=1.1, 8.1 Hz), 7.60 (1H, dt, *J*=1.1, 8.4 Hz), 7.74 (1H, d, *J*=8.4 Hz), 8.19 (1H, d, *J*=8.1 Hz), 11.40 (1H, br s, exch. D_2O); ^{13}C NMR: 17.3, 56.1 (CH_3), 75.1 (CH_2), 111.7, 121.4, 123.1, 123.6, 127.5 (CHAr), 113.4, 126.7, 127.9, 141.1, 157.3 (C). Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.20; H, 5.91; N, 11.32.

1.3.2. 2,9-Dihydro-9-methoxymethyl-2,4-dimethyl-1*H*-pirido[3,4-*b*]indol-1-one 10b. Heated for 3 h, eluent hexane–Et_2O 1:1, 180 mg, yield 70%, mp 122–125°C (pale yellow powder from Et_2O); IR: 1642, 1587, 1520 cm^{-1}; ^1H NMR: 2.61 (3H, d, *J*=1.1 Hz), 3.37 (3H, s), 3.70 (3H, s), 6.33 (2H, s), 6.91 (1H, d, *J*=1.1 Hz), 7.31 (1H, m), 7.44–7.70 (2H, m), 8.12 (1H, dd, *J*=0.7, 8.1 Hz); ^{13}C NMR: 16.9, 36.7, 55.8 (CH_3), 74.7 (CH_2), 111.5, 121.1, 122.8, 126.8, 127.8 (CHAr), 112.1, 123.0, 126.1, 126.9, 140.8, 155.8 (C). Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.08; H, 6.19; N, 10.75.

1.3.3. 2-Allyl-2,9-dihydro-9-methoxymethyl-4-methyl-1*H*-pirido[3,4-*b*]indol-1-one 10c. Heated for 1.5 h, eluent hexane–Et_2O 2:1, 214 mg, yield 76%, mp 113–115°C (cream crystals from hexane–Et_2O); IR: 1650, 1589, 1568 cm^{-1}; ^1H NMR: 2.62 (3H, s), 3.73 (3H, s), 4.75 (2H, d, *J*=5.5 Hz), 5.25 (2H, m), 6.05 (1H, m), 6.35 (2H, s), 6.88 (1H, s), 7.32 (1H, t, *J*=8.1 Hz), 7.55 (1H, t, *J*=8.1 Hz), 7.71 (1H, d, *J*=8.1 Hz), 8.14 (1H, d, *J*=8.1 Hz); ^{13}C NMR: 17.4, 56.1 (CH_3), 50.9, 75.2 (CH_2), 118.1 (CH_2=), 121.4, 123.2, 111.8, 126.5, 127.2 (CHAr), 133.7 (CH=), 112.7, 118.4, 126.3, 126.9, 141.1, 155.5 (C). Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.51; H, 6.31; N, 9.75.

1.3.4. 2,9-Dihydro-9-methoxymethyl-4-methyl-2-phenyl-1*H*-pirido[3,4-*b*]indol-1-one 10d. Heated for 1.5 h, eluent CH_2Cl_2–Et_2O 20:1, 258 mg, yield 81%, mp 132–134°C (cream crystals from hexane–Et_2O); IR: 1656, 1605, 1567 cm^{-1}; ^1H NMR: 2.65 (3H, s), 3.39 (3H, s), 6.43 (2H, s), 7.01 (1H, s), 7.35 (1H, m), 7.42–7.58 (6H, m), 7.74 (1H, d, *J*=8.4 Hz), 8.17 (1H, d, *J*=8.1 Hz); ^{13}C NMR: 17.3, 56.2 (CH_3), 75.1 (CH_2), 112.0, 121.6, 123.2, 127.3, 127.5, 127.6, 127.7, 128.5, 129.6, 129.8 (CHAr), 112.5, 123.3, 126.6, 126.9, 141.3, 141.6, 155.8 (C). Anal. calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.33; H, 5.82; N, 8.68.

1.3.5. Synthesis of 2,5-dihydro-5-methoxymethyl-4-methyl-1*H*-pirido[4,3-*b*]indol-1-one 11a and 2,3,4,5-tetrahydro-5-methoxymethyl-4-methylene-1*H*-pirido[4,3-*b*]indol-1-one 12a. To a solution of indole **9a** (185 mg, 0.5 mmol) in DMF (5 ml) was added $Pd(OAc)_2$ (6 mg, 5 mol%), triphenylphosphine (19 mg, 15 mol%), potassium acetate (196 mg, 2 mmol) and tetrapropylammonium bromide (TPAB) (133 mg, 0.5 mmol). The mixture was stirred at 80°C for 1.5 h, then after cooling washed with brine and extracted with Et_2O (2×20 ml). The organic layer was dried (Na_2SO_4), filtered and evaporated and the residue chromatographed by silica gel eluent CH_2Cl_2–CH_3OH 50:1 to afford **11a**, 32 mg, 26%, mp 216–218°C (white crystals from CH_2Cl_2–hexane); IR: 3380, 1643, 1543, 1462 cm^{-1}; ^1H NMR: 2.58 (3H, s), 3.34 (3H, s), 5.79 (2H, s), 7.18 (1H, s), 7.35–7.59 (3H, m), 8.53 (1H, d, *J*=7.2 Hz), 11.47 (1H, br s, exch. D_2O); ^{13}C NMR: 16.8, 56.9 (CH_3), 75.0 (CH_2), 111.2, 122.9 125.5, 125.7, 135.2 (CHAr), 104.8, 109.5, 122.7, 140.4, 144.6, 160.5 (C). Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.58; H, 5.90; N, 11.40 and **12a**, 70 mg, 56%, pale yellow oil; IR: 3290, 1639, 1465 cm^{-1}; ^1H NMR: 3.46 (3H, s), 4.29 (2H, d, *J*=1.8 Hz), 5.50 (1H, d, *J*=1.8 Hz), 5.59 (2H, s), 5.77 (1H, br s, exch. D_2O), 5.90 (1H, d, *J*=1.8 Hz), 7.35 (1H, dt, *J*=1.5, 7.3 Hz), 7.41–7.71 (2H, m), 8.33 (1H, dd, *J*=1.8, 7.0 Hz). Anal. calcd for $C_{14}H_{14}N_2O_2$: C, 69.41; H, 5.82; N, 11.56. Found: C, 69.50; H, 5.89; N, 11.49.

1.4. Synthesis of γ-carbolinones 11b–d and 12b–d: general procedure

To a solution of indole **9a–d** (1 mmol) in dry acetonitrile (15 ml), $Pd(OAc)_2$ (22 mg, 10 mol%), triphenylphosphine (52 mg, 20 mol%), TBAC (276 mg, 1 mmol), and anhydrous potassium carbonate (414 mg, 3 mmol) were added. The mixture was heated to reflux for the reported time, the inorganic salts were filtered off and the solvent removed in vacuo. The residue was diluted with water (20 ml) and extracted with CH_2Cl_2 (2×20 ml). The organic layer was dried, filtered and evaporated and the residue chromatographed on silica gel (eluent see later) affording compounds **11** and **12**.[18]

1.4.1. 2,5-Dihydro-5-methoxymethyl-2,4-dimethyl-1*H*-pirido[4,3-*b*]indol-1-one 11b and 2,3,4,5-tetrahydro-5-methoxymethyl-2-methyl-4-methylene-1*H*-pirido[4,3-*b*]indol-1-one 12b. Reflux for 12 h, eluent from hexane–Et_2O 1:1 to Et_2O to give: **9b** (unreacted material), 107 mg, 28%, **11b** 99 mg, yield 39%, mp 119–121°C (cream crystals from Et_2O); IR: 1654, 1591 cm^{-1}; ^1H NMR: 2.55 (3H, s),

3.31 (3H, s), 3.71 (3H, s), 5.75 (2H, s), 7.08 (1H, s), 7.41 (2H, m), 7.54 (1H, d, J=7.3 Hz), 8.53 (1H, dd, J=1.5, 6.2 Hz); ^{13}C NMR: 16.4, 36.5, 56.5 (CH_3), 74.6 (CH_2), 109.9, 122.4, 122.5, 124.9, 135.0 (CHAr), 104.6, 109.2, 124.8, 140.0, 144.5, 160.1 (C). Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.42; H, 6.36; N, 10.76 and **12b** 66 mg, yield 26%, colourless oil; IR: 1615 cm^{-1}; ^{1}H NMR: 3.14 (3H, s), 3.43 (3H, s), 4.27 (2H, d, J=1.8 Hz), 5.45 (1H, d, J=1.8 Hz), 5.57 (2H, s), 5.86 (1H, d, J=1.8 Hz), 7.32–7.57 (3H, m), 8.36 (1H, dd, J=1.8, 8.4 Hz). Anal. calcd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93. Found: C, 70.39; H, 6.33; N, 10.78.

1.4.2. 2-Allyl-2,5-dihydro-5-methoxymethyl-4-methyl-1*H*-pirido[4,3-*b*]indol-1-one 11c and 2-allyl-2,3,4,5-tetrahydro-5-methoxymethyl-4-methylene-1*H*-pirido[4,3-*b*]indol-1-one 12c. Reflux for 3 h, eluent hexane–Et_2O 1:1 to give: **9c** (unreacted material), 98 mg, 24%, **11c** 98 mg, yield 35%, pale yellow oil; IR: 1659, 1592 cm^{-1}; ^{1}H NMR: 2.56 (3H, s), 3.31 (3H, s), 4.74 (2H, d, J=5.5 Hz), 5.20 (1H, dd, J=1.5, 16.9 Hz), 5.27 (1H, dd, J=1.5, 10.2 Hz), 5.75 (2H, s), 6.03 (1H, m), 7.05 (1H, s), 7.40 (2H, m), 7.54 (1H, d, J=7.0 Hz), 8.53 (1H, d, J=7.0 Hz); ^{13}C NMR: 16.5, 56.5 (CH_3), 50.1, 74.7 (CH_2), 118.2 (CH_2=), 109.1, 122.4, 122.6, 125.0, 133.8 (CHAr), 133.9 (CH=), 105.0, 109.8, 120.1, 140.0, 144.4, 159.4 (C). Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: 72.43; H, 6.55; N, 9.78 and **12c**, 107 mg, yield 38%, pale yellow oil; IR: 1620 cm^{-1}; ^{1}H NMR: 3.44 (3H, s), 4.22 (4H, m), 5.20–5.33 (2H, m), 5.46 (1H, d, J=1.8 Hz), 5.58 (2H, s), 5.86 (1H, d, J=1.8 Hz), 6.0 (1H, m), 7.30–7.42 (2H, m); 7.49 (1H, dd, J=1.5, 8.4 Hz), 8.38 (1H, dd, J=1.5, 8.4 Hz). Anal. calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.40; H, 6.51; N, 9.85.

1.4.3. 2,5-Dihydro-5-methoxymethyl-4-methyl-2-phenyl-1*H*-pirido[4,3-*b*]indol-1-one 11d and 2,3,4,5-tetrahydro-5-methoxymethyl-4-methylene-2-phenyl-1*H*-pirido[4,3-*b*]indol-1-one 12d. Reflux for 2 h, eluent CH_2Cl_2–Et_2O 20:1. **11d** 136 mg, yield 43%, mp 148–150°C (white crystals from hexane–Et_2O); IR: 1654, 1590 cm^{-1}; ^{1}H NMR: 2.59 (3H, s), 3.35 (3H, s), 5.79 (2H, s), 7.19 (1H, s), 7.34–7.59 (8H, m), 8.51 (1H, d, J=8.4 Hz); ^{13}C NMR: 16.2, 56.3, 74.5, 108.9 (CHAr), 122.4 (2CHAr), 124.7 (CHAr), 127.3 (2CHAr), 128.1, 129.2 (2CHAr), 134.4 (CH=), 104.7, 109.6, 124.9, 139.8, 141.0, 144.2, 159.2 (C). Anal. calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.29; H, 5.86; N, 8.70 and **12d**, 174 mg, yield 55%, mp 160–162°C (crystals from Et_2O); IR: 1613, 1460 cm^{-1}; ^{1}H NMR: 3.47 (3H, s), 4.70 (2H, s), 5.53 (1H, d, J=1.8 Hz), 5.63 (2H, s), 5.94 (1H, d, J=1.8 Hz), 7.32–7.45 (7H, m), 7.54 (1H, d, J=7.7 Hz), 8.37 (1H, d, J=8.4 Hz). Anal. calcd for $C_{20}H_{18}N_2O_2$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.26; H, 5.85; N, 8.72.

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