A Pd[0]-catalyzed Ullmann cross-coupling/reductive cyclization approach to C-3 mono-alkylated oxindoles and related compounds

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ABSTRACT

The Pd[0]-catalyzed Ullmann cross-coupling of o-nitrohaloarenes **1a–e** with the brominated heterocycles **2a–f** delivers the expected products **3a–j** in good to excellent yields. The reductive cyclization of such products, as well as N-acyl derivatives **3k**, **l**, and **m**, has been investigated and provided the C-3 mono-substituted oxindoles **5a–d**, **f**, **g**, **k**, and **m**, the direct reduction products **4i** and **j** or indole **5l**.

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1. Introduction

The oxindole or indolone motif represents a privileged structure in medicinal chemistry.[1] Thus, for example, this heterocycle is encountered in antiproliferative agents,[2] in serotonergic agents,[3] in growth hormone secretagogues,[4] in the anti-Parkinsonian drug ropinirole,[5] in P-glycoprotein-mediated MDR inhibitors,[6] in non-opioid nociceptin receptor ligands,[7] and in anti-inflammatory agents.[8] In addition, a number of prominent natural products embody oxindole substructures including welwitindolinone A isonitrile,[9,10] rhynchophylline,[10] horsfiline,[11] coerulescine,[12] elacomine,[13] gelsemine,[14] the gelsenicine-related oxindole alkaloids,[15] and the spirotryprostatins.[10,16] Most of these display intriguing biological properties. Oxindoles also serve as precursors to a range of other heterocyclic compounds including indoles proper.[17] Accordingly, numerous routes to the title heterocyclic system have been developed and various of these have been summarized in recent reviews.[10,18] Notwithstanding the impressive repertoire of methodologies available, the controlled assembly of C3-mono-alkylated oxindoles remains a challenging matter.[19] Herein, therefore, we describe a new approach to such systems that arises from our earlier studies[20] on the Pd[0]-catalyzed Ullmann cross-coupling reaction.

2. Synthetic plan

On the basis of our earlier work[20] we proposed (Scheme 1) a two-step method for preparing oxindoles. This involved an initial Pd[0]-catalyzed Ullmann cross-coupling[21] of o-nitrohaloarenes **1** with an α-brominated α,β-unsaturated cycloimide, lactam or lactone of the general form **2** to give the corresponding o-nitroarylated heterocycle **3**. In the second step of the proposed sequence, the cross-coupled compound **3** would be treated with dihydrogen in
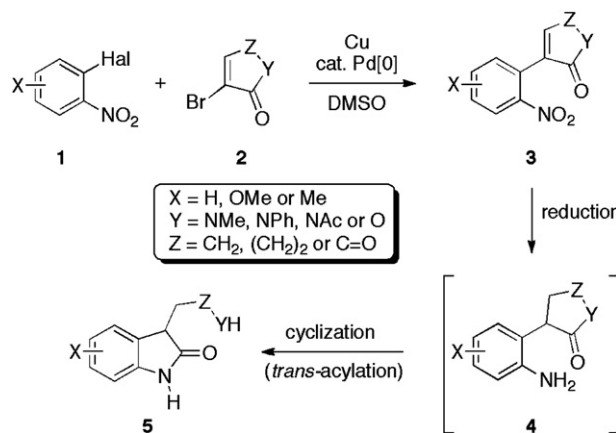
Scheme 1.

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the presence of palladium on carbon so as to effect a reductive cyclization process and thereby generate, presumably via intermediate **4**, the target C-3 mono-alkylated oxindole **5**. The successful implementation of such an approach is now described.

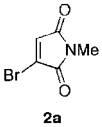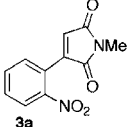## 2.1. The palladium-catalyzed Ullmann cross-coupling reaction. Formation of the o-nitroarylated heterocycles 3a–j
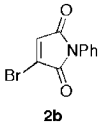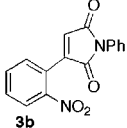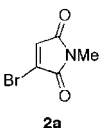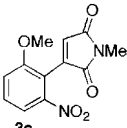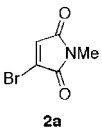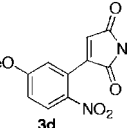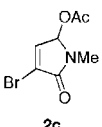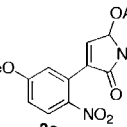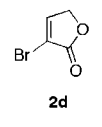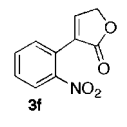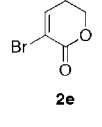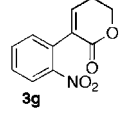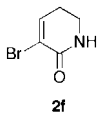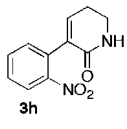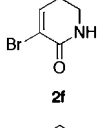
The coupling partners **1a–e** and **2a–f** required for the present study were either obtained commercially or prepared according to the procedures specified in the Experimental section. A single-crystal X-ray analysis (see Experimental section for details) of the alcohol precursor to coupling partner **2c** served to establish the regiochemical outcome of the reduction process leading to this compound.

The Pd[0]-catalyzed Ullmann cross-coupling of various combinations of the above-mentioned species was carried out using modifications of the reaction conditions employed earlier.[20] In particular, 3 micron dendritic copper was sonicated in an aqueous solution of EDTA to clean and activate the surface of the metal, which was then washed with deionized water, acetone, and methanol before being dried under vacuum then suspended in DMSO under nitrogen. A DMSO solution of the relevant *o*-nitrohaloarene **1**, two molar equivalents of the appropriate brominated heterocycle **2** and 5 mol % of Pd₂(dba)₃ contained in a separate flask was degassed then warmed, under a nitrogen atmosphere, to 40–50 °C before being treated, over 1.5 h, with five equal aliquots of the activated copper powder suspended in DMSO. The resulting mixture was heated at 40–50 °C for a further 1.5–3.5 h then cooled and subjected to conventional work-up. By such means the expected, but previously unreported, products **3a–j** were obtained in good to excellent yield (see Table 1). The spectral data obtained on each of these were fully consistent with the assigned structures. Interestingly, under the specified conditions almost no homo-coupling of the *o*-nitrohaloarenes **1** was observed.

2.2. The reductive cyclization reaction. Formation of oxindoles 5a–d, f, g, k, and m, reduction products 4i and j and indole 5l
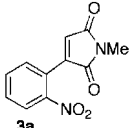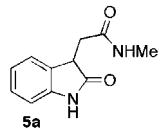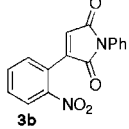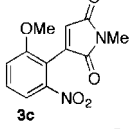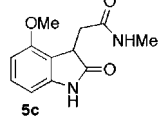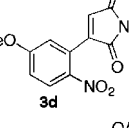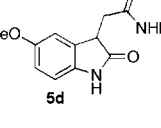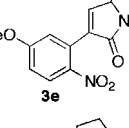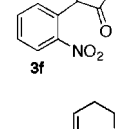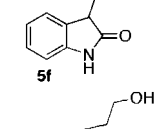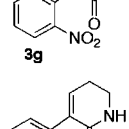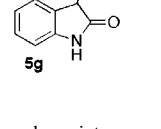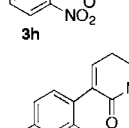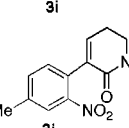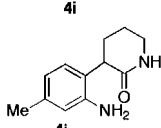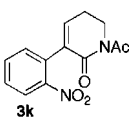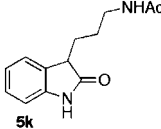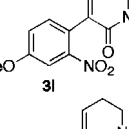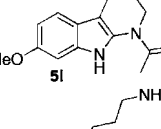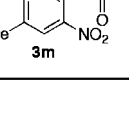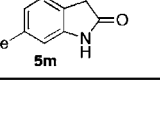
With the cross-coupling products **3a–j** in hand an investigation of their capacities to engage in the reductive cyclization processes specified in Scheme 1 could be investigated. The outcomes of the relevant studies are shown in Table 2. Thus, entries 1–4, 6, and 7 reveal that upon exposure of a methanolic solution of each of the relevant cross-coupling products to 1 atm of dihydrogen in the presence of 10% Pd on C the anticipated conversions take place and thus affording the 3-substituted oxindoles **5a–d**, **f**, and **g** in good to excellent yields. The origins of our inability to effect the reductive cyclization of compounds **3e** and **3h** remain unclear at this stage. The spectral data obtained on each of the above-mentioned oxindoles were fully consistent with the assigned structures. Compounds **5b**,[22] **5f**,[23] and **5g**[24] have been reported previously and where comparisons were possible the two sets of spectral data proved to be good matches. Furthermore, the appearance of the resonance due to the carbonyl carbon of the oxindole moiety within the range 181.5–179.0 ppm served as a useful means of establishing that the *trans*-acylation reaction **4→5** had taken place in each of the conversions mentioned thus far. Entries 9 and 10 of Table 2 reveal situations in which only the direct reduction products **4i** and **4j** are produced. In these cases, the ¹³C NMR spectra displayed lactam carbonyl resonances at δ 173.7 and 173.8, respectively, and thus strongly suggesting that the cyclization process leading to oxindole formation had not taken place. Confirmation of this followed from the single-crystal X-ray analysis of compound **4i** (see Experimental section for details). However, cyclization of such systems could be readily effected by *N*-acylation of the lactam

Table 1
Pd[0]-catalyzed Ullmann cross-coupling of *o*-nitrohaloarenes **1a–e** with brominated heterocycles **2a–f** to form *o*-nitroarylated heterocycles **3a–j**

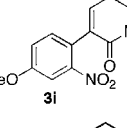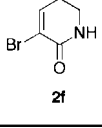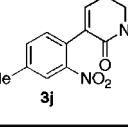| Entry	o-Nitrohaloarene 1	Brominated heterocycle 2	Cross-coupling product 3	Yield (%)
1	1a	2a	3a	85
2	1a	2b	3b	82
3	1b	2a	3c	89
4	1c	2a	3d	67
5	1c	2c	3e	58
6	1a	2d	3f	77
7	1a	2e	3g	78
8	1a	2f	3h	61
9	1d	2f	3i	73
10	1e	2f	3j	61

nitrogen in their precursors and then subjecting the resulting imides, e.g., compounds **3k**, **3l**, and **3m**, to the by now standard reductive cyclization conditions. The first and third of these substrates gave the anticipated oxindoles **5k** and **5m**, respectively, in good yield and the structure of the former product (**5k**) was established by single-crystal X-ray analysis. In contrast, reductive cyclization of compound **3l** afforded the annulated indole **5l** in 93%

Table 2
Cyclization of *o*-nitroarylated heterocycles **3a**–**d** and **3f**–**i** to form oxindoles **5a**–**d**, **f**, **g**, **k**, and **m**, reduction products **4i** and **j** and indole **5l**

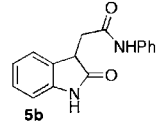| Entry	Cross-coupling product	Oxindole	Yield (%)
1	**3a**	**5a**	87
2	**3b**	**5b**	99
3	**3c**	**5c**	77
4	**3d**	**5d**	54
5	**3e**	Decomposition	—
6	**3f**	**5f**	96
7	**3g**	**5g**	74
8	**3h**	Complex mixture	—
9	**3i**	**4i**	97
10	**3j**	**4j**	84
11	**3k**	**5k**	72
12	**3l**	**5l**	93
13	**3m**	**5m**	60

yield. This rather unstable product, the structure of which was also established by single-crystal X-ray analysis (see Experimental section), presumably arises through cyclodehydration of the initially formed oxindole.

Confirmation of the likely sequence of events associated with the oxindole-forming processes **3**→**5** presented in Table 2 follow from the observation that compound **4d** could be isolated from the reduction of compound **3d** when short reaction times were used and that when the former material was allowed to stand neat for ten days it isomerized, quantitatively, to the oxindole **5d** (Scheme 2).

Scheme 2.
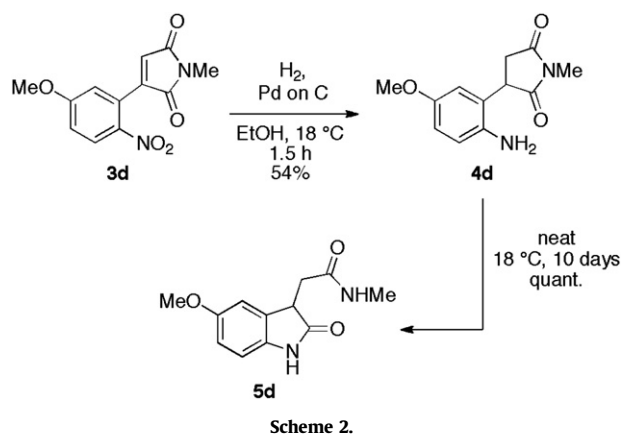
3. Conclusions

A new method for the synthesis of C-3 mono-alkylated oxindoles has been developed. This involves the Pd[0]-catalyzed Ullmann cross-coupling of *o*-nitrohaloarenes with various α-brominated α,β-unsaturated cycloimides, lactams or lactones followed by reductive cyclization of the coupling products. The cross-coupling process can be carried out effectively in the presence of a useful range of functionalities and the reductive cyclization process proceeds smoothly provided the *trans*-acylation step **4**→**5** involves a substrate possessing an imide- or lactone-containing side-chain. In keeping with expectations, when substrates incorporating a lactam-containing side-chain are involved then the conversion **4**→**5** fails to take place. The protocols described here offer various possibilities for assembling more complex oxindoles including natural products containing this motif. Efforts directed toward such ends are now underway in these laboratories and results will be reported in due course.

4. Experimental section

4.1. General experimental procedures

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on either a Varian Gemini or a Bruker AV800 machine operating at 300 and 800 MHz, respectively. Unless otherwise specified, spectra were acquired at 20 °C in deuterochloroform (CDCl$_3$) that had been filtered through basic alumina immediately prior to use. Chemical shifts are recorded as δ values in parts per million (ppm). Infrared spectra (ν_{max}) were normally recorded on a Perkin−Elmer 1800 Series FTIR Spectrometer and samples were analyzed as thin films on NaCl plates. Low-resolution ESI mass spectra were recorded on a Micromass−Waters LC-ZMD single quadrupole liquid chromatograph-mass spectrometer while low- and high-resolution EI mass spectra were recorded on a VG Fisons AUTOSPEC three-sector double-focusing instrument. Melting points were measured on Reichert hot-stage microscope and are uncorrected. Analytical thin

layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F$_{254}$ plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included mixtures of phosphomolybdic acid:ceric sulfate:sulfuric acid (concd):water (37.5 g:7.5 g:37.5 g:720 mL), potassium permanganate: potassium carbonate:5% sodium hydroxide aqueous solution:water (3 g:20 g:5 mL:300 mL) or ninhydrin:glacial acetic acid:ethanol (4.5 g:9 mL:300 mL). The retardation factor (R_f) values cited here have been rounded at the first decimal point. Flash chromatographic separations were carried out following protocols defined by Still et al.[25] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. THF, DMF, dichloromethane, benzene, and toluene were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.[26] Methanol and ethanol were used as obtained from the above-mentioned suppliers. Where necessary, reactions were performed under a nitrogen atmosphere.

Compounds **1a**, **1d**, and **1e** were obtained from commercial sources.

4.2. Specific experimental procedures

4.2.1. Part A: preparation of cross-coupling partners **1b**, **1c**, and **2a–f**.

*4.2.1.1. 2-Iodo-3-methoxy-1-nitrobenzene (**1b**). Step i*: A mixture of DMSO (40 mL) and H$_2$SO$_4$ (40 mL of a 30% v/v aqueous solution) was treated with 2-amino-3-nitrophenol (2.48 g, 16.1 mmol, ex. Aldrich Chemical Co.) and the ensuing mixture stirred at 50 °C for 1 h then cooled to 0 °C. The resulting solution was treated, over 5 min, with a solution of sodium nitrite (1.52 g, 22 mmol) in water (5 mL). The ensuing mixture was stirred at 0 °C for 1 h then treated, in one portion, with potassium iodide (7.50 g, 45 mmol) in water (15 mL). After a further 1 h the reaction mixture was warmed to 18 °C, kept at this temperature for 0.5 h then extracted with diethyl ether (1×100 mL). The separated organic phase was washed with sodium thiosulfate (2×25 mL of a saturated aqueous solution), water (2×25 mL) then brine (1×25 mL) before being dried (MgSO$_4$), then filtered, and concentrated under reduced pressure to give a crude sample of 2-iodo-3-nitrophenol[27] (3.46 g, ca. 81%) as an orange-brown solid. This material was used, as obtained, in the next step of the reaction sequence.

Step ii: A solution of 2-iodo-3-nitrophenol (2.48 g, 9.36 mmol) in DMF (15 mL) was treated with anhydrous K$_2$CO$_3$ (6.22 g, 45 mmol). The ensuing mixture was stirred vigorously at 18 °C for 0.25 h then methyl iodide (0.64 mL, 10.3 mmol) was added in one portion. The resulting mixture was stirred at 18 °C for 5 h under nitrogen then diluted with sodium hydroxide (15 mL of a 2 M aqueous solution) and diethyl ether (25 mL). The separated aqueous phase was acidified with HCl (2 M aqueous solution to pH 4) then extracted with diethyl ether (3×25 mL). The combined organic phases were washed with water (1×40 mL) and brine (1×40 mL) before being dried (MgSO$_4$) then filtered. The filtrate was treated with silica (5 g of TLC-grade material) and the ensuing mixture concentrated under reduced pressure to give a free-flowing orange powder. This material was added to the top of a flash chromatography column (silica), which was then eluted with 1:4 v/v ethyl acetate/hexane. Concentration of the relevant fractions (R_f=0.3) afforded the title compound **1b**[28] (2.02 g, 77%) as vivid-orange crystals, mp=102–103 °C (lit.[28] mp=102.5–103.5 °C) (Found: M$^{+\bullet}$, 278.9392. C, 30.40; H, 2.26; N,

4.96. C$_7$H$_6$INO$_3$ requires M$^{+\bullet}$, 278.9392. C, 30.13; H, 2.17; N, 5.02%). ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.55 (t, J=8.0 Hz, 1H), 7.39 (dd, J=8.0 and 1.2 Hz, 1H), 7.25 (dd, J=8.0 and 1.2 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 160.3, 156.6, 131.7, 117.0, 115.2, 81.3, 58.3; IR ν_{max} (KBr) 3079, 2923, 2852, 1581, 1523, 1463, 1428, 1349, 1295, 1268, 1184, 1047, 1019, 900, 792, 734 cm^{-1}; Mass spectrum (EI, 70 eV) *m/z* 279 (M$^{+\bullet}$, 100%), 218 (37), 203 (37), 76 (26), 63 (21).

*4.2.1.2. 2-Iodo-4-methoxy-1-nitrobenzene (**1c**). Step i*: A solution of 3-iodophenol (5.90 g, 27 mmol) in methanol (10 mL) was slowly added to a vigorously stirred solution of concentrated sulfuric acid (3.7 mL, 70 mmol) and sodium nitrite (6.3 g, 74 mmol) in water (10 mL) maintained at 15 °C. After 36 h the reaction mixture was diluted with ethyl acetate (20 mL) and the separated aqueous layer was extracted with ethyl acetate (3×20 mL). The combined organic phases were then washed with brine (1×50 mL) before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield a dark-brown oil (3.7 g). Subjection of this material to flash chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) afforded two fractions, A and B.

Concentration of fraction A (R_f=0.5) afforded 5-iodo-2-nitro-phenol[29,30] (1.40 g, 20%) as bright-yellow needles, mp=94 °C (lit.[29] mp=96 °C) (Found: M$^{+\bullet}$, 264.9239. C$_6$H$_4$INO$_3$ requires M$^{+\bullet}$, 264.9236). ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.55 (s, 1H), 7.78 (d, J=8.9 Hz 1H,), 7.60 (d,J=1.7 Hz, 1H), 6.90 (dd,J=8.9 and 1.7 Hz, 1H); MS (EI, 70 eV) *m/z* 265 (M$^{+\bullet}$, 100).

Concentration of fraction B (R_f=0.2) afforded 3-iodo-4-nitro-phenol[29,30] (3.80 g, 54%) as orange needles, mp=112 °C (lit.[29] mp=124 °C) (Found: M$^{+\bullet}$, 264.9239. C$_6$H$_4$INO$_3$ requires M$^{+\bullet}$, 264.9236). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.97 (d, J=9.0 Hz, 1H), 7.52 (d,J=2.7 Hz, 1H), 6.91 (dd,J=9.0 and 2.7 Hz, 1H), 5.81 (s, 1H); MS (EI, 70 eV) *m/z* 265 (M$^{+\bullet}$, 100).

Step ii: A magnetically stirred solution of 3-iodo-4-nitrophenol (2.47 g, 9.31 mmol) and potassium hydroxide (2.68 g, 47.8 mmol) in DMSO (30 mL) was treated, in one portion and at 18 °C, with methyl iodide (3.0 mL, 48 mmol). The resulting mixture was stirred at 18 °C for 4 h then diluted with water (30 mL) and ethyl acetate (30 mL). The separated aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic phases were washed with water (2×30 mL) and brine (1×50 mL) before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield compound **1c**[29,31] (2.13 g, 99%) as a yellow solid, mp=62–64 °C (lit.[29] mp=69–70 °C) (Found: M$^{+\bullet}$, 278.9383. C$_7$H$_6$INO$_3$ requires M$^{+\bullet}$, 278.9392). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.99 (d,J=9.1 Hz, 1H), 7.53 (d, J=2.7 Hz, 1H), 6.95 (dd,J=9.1 and 2.7 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.5, 127.5, 127.1, 114.1, 88.2, 56.1 (one signal obscured or overlapping); IR ν_{max} (KBr) 3097, 2941, 2840, 1588, 1517, 1478, 1336, 1283, 1233, 1183, 1126, 1021, 868, 815, 747, 686, 615 cm^{-1}; MS (EI, 70 eV) *m/z* 279 (M$^{+\bullet}$, 100), 249 (85), 218 (61), 63 (86).

*4.2.1.3. 3-Bromo-1-methyl-1H-pyrrole-2,5-dione (**2a**).* Molecular bromine (1 mL, 20 mmol) was added to a magnetically stirred slurry of 1-methyl-1*H*-pyrrole-2,5-dione (1.99 g, 18.0 mmol, ex. Aldrich Chemical Co.) in ether (25 mL). The ensuing mixture was heated at reflux for 1 h then cooled to 0 °C and triethylamine (2.8 mL, 20 mmol) added. The reaction mixture was then stirred for a further 2 h at 0 °C before being warmed to 18 °C and diluted with ethyl acetate (40 mL) and water (40 mL). The separated aqueous layer was extracted with ethyl acetate (3×20 mL) and the combined organic phases were washed with water (1×30 mL) and brine (1×30 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure to a pale-brown solid. This material was rinsed with hexane and then dried under reduced pressure to afford compound **2a**[32,33] (3.42 g, 100%) as pale-brown plates, mp=86–88 °C (lit.[32] mp=88–89 °C) (Found: M$^{+\bullet}$, 188.9428. C, 31.78; H, 2.34; N, 7.23. C$_5$H$_4$^{79}BrNO$_2$

requires: M$^{+\bullet}$, 188.9425. C, 31.61; H, 2.12; N, 7.37%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.88 (s, 1H), 3.08 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.4, 165.2, 131.8, 131.1, 24.4; IR ν_{max} (KBr) 3104, 1777, 1713, 1589, 1442, 1385, 1259, 1161, 1107, 968, 869, 826, 762, 706 cm^{-1}; MS (EI, 70 eV) m/z 189 and 191 (M$^{+\bullet}$, both 98%), 162 and 160 (20), 134 and 132 (80), 106 and 104 (70), 53 (100).

4.2.1.4. 3-Bromo-1-phenyl-1H-pyrrole-2,5-dione (*2b*). Bromination of 1-phenylmaleimide (ex. Aldrich Chemical Co.) in the same manner as described immediately above gave a brown solid on work-up. Subjection of this material to flash chromatography (silica, 1:7 v/v ethyl acetate/hexane elution) and concentration of the appropriate fractions (R_f=0.3) gave the title compound **2b**[34] (95%) as a white, crystalline solid, mp=157.5–158 °C (lit.[34] mp=150–153 °C) (Found: M$^{+\bullet}$, 250.9579. C, 47.49; H, 2.37; N, 5.45. C$_{10}$H$_6$^{79}BrNO$_2$ requires M$^{+\bullet}$, 250.9582. C, 47.65; H, 2.40, N, 5.56%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.55–7.30 (complex m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 168.0, 164.8, 132.7, 131.5, 130.9, 129.0, 128.2, 127.1; IR ν_{max} (KBr) 1719, 1591, 1504, 1398, 1193, 1149, 1048, 865, 848, 799, 751, 699 cm^{-1}; MS (EI, 70 eV) m/z 253 and 251 (M$^{+\bullet}$, 98 and 100%), 144 (25), 134 and 132 (32 and 34), 128 (46), 53 (52).

4.2.1.5. 4-Bromo-1-methyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl acetate (*2c*). Step i: A solution of compound **2a** (750 mg, 3.9 mmol) and cerium(III) chloride heptahydrate (1.50 g, 4.0 mmol) in ethanol (40 mL) was stirred at 18 °C for 0.25 h then cooled to 0 °C over 25 min. Sodium borohydride (150 mg, 4.0 mmol) was then added, in portions, and the ensuing mixture stirred for 1 h at 0 °C before being quenched by the addition of ice-water (30 mL). The resulting mixture was stirred for a further 0.25 h at 18 °C then the ethanol was removed under reduced pressure. The residue thus obtained was extracted with ethyl acetate (3×30 mL) and the combined organic phases washed with brine (1×30 mL) before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure to afford white solid comprised of a ca. 9:1 mixture of the 3-bromo-5-hydroxy-1-methyl-1H-pyrrol-2(5H)-one and 4-bromo-5-hydroxy-1-1H-pyrrol-2(5H)-one (684 mg, 91%). Fractional crystallization (from hot chloroform containing a small amount of hexane) of this material gave *3-bromo-5-hydroxy-1-methyl-1H-pyrrol-2(5H)-one* (400 mg, 53%) as white crystals, mp=118–120 °C (Found: M$^{+\bullet}$, 190.9587. C, 31.42; H, 3.50; N, 7.05. C$_5$H$_6$^{79}BrNO$_2$ requires M$^{+\bullet}$, 190.9582. C, 31.28; H, 3.15, N, 7.27%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.08 (d, J=1.7 Hz, 1H), 5.26 (dd, J=11.7 and 1.7 Hz, 1H), 3.03 (s, 3H), 2.54 (d, J=11.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.3, 129.7, 122.0, 84.3, 27.2; IR ν_{max} (KBr) 3313, 3078, 1695, 1678, 1596, 1443, 1409, 1284, 1235, 1124, 1091, 1025, 971, 898, 850, 760, 734 cm^{-1}; MS (EI, 70 eV) m/z 193 and 191 (M$^{+\bullet}$, both 20%), 176 and 174 (both 15), 112 (100), 58 (27), 53 (28), 42 (51).

Step ii: A solution of 3-bromo-5-hydroxy-1-methyl-1H-pyrrol-2(5H)-one (4.60 g, 24 mmol), prepared as described immediately above, in acetic anhydride (40 mL) was treated with sodium acetate (1.6 g, 19 mmol) and DMAP (0.02 g). The ensuing mixture was stirred at 18 °C for 1 h then diluted with water (100 mL), and extracted with dichloromethane (3×40 mL). The combined organic phases were washed with brine (1×100 mL) before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure to yield *acetate* **2c** (5.60 g, 98%) as large, glassy crystals, mp=49 °C (Found: C, 36.06; H, 3.50; N, 5.86. C$_7$H$_8$^{79}BrNO$_3$ requires C, 35.92; H, 3.45; N, 5.98%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.08 (d, J=1.9 Hz, 1H), 6.34 (d, J=1.9 Hz, 1H), 2.99 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.3, 164.9, 138.8, 123.7, 83.0, 27.9, 20.8; IR ν_{max} (KBr) 3105, 2954, 1726, 1610, 1480, 1460, 1431, 1399, 1389, 1374, 1284, 1227, 1214, 1118, 1048, 1015, 997, 971, 940, 898, 837, 754, 743 cm^{-1}.

4.2.1.6. 3-Bromofuran-2(5H)-one (*2d*). A magnetically stirred solution of 2(5H)-furanone (2.11 g, 25.1 mmol, ex. Alfa Aesar) in diethyl ether (20 mL) that had been protected from light was treated, dropwise over 0.5 h, with a solution of molecular bromine (1.5 mL, 4.81 g, 30 mmol) in diethyl ether (20 mL). The ensuing mixture was heated at reflux for 4 h then cooled to 18 °C. Excess bromine was removed by sparging the reaction mixture with nitrogen gas for 10 min. The resulting solution was cooled to 0 °C (ice bath) before being treated, dropwise over 10 min, with a solution of triethylamine (4.15 mL, 30 mmol) in diethyl ether (5.5 mL) then stirred for 1 h during which time it was allowed to warm to 18 °C. The ensuing mixture was washed with water (3×25 mL) and brine (1×25 mL) before being dried (MgSO$_4$) then filtered through a sintered-glass funnel. The filtrate was treated with flash chromatography-grade silica gel (5 g) then concentrated, under reduced pressure, to a free-flowing powder. This was added to the top of a flash chromatography column which was then eluted with 1:2 v/v ethyl acetate/hexane. Concentration of the relevant fractions (R_f=0.3) gave the title lactone **2d**[35] (2.31 g, 46%) as tan-colored crystals, mp=57–58 °C (lit.[35] mp=56–58 °C) (Found: M$^{+\bullet}$, 161.9316. C, 29.72; H, 1.99. C$_4$H$_3$^{79}BrO$_2$ requires M$^{+\bullet}$, 161.9316. C, 29.48; H, 1.86%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.62 (t, J=1.9 Hz, 1H), 4.86 (d, J=1.9 Hz, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.0, 149.7, 112.4, 71.5; IR ν_{max} (KBr) 1785, 1758, 1605, 1453, 1346, 1279, 1156, 1048, 990, 830, 753, 719 cm^{-1}; MS (EI, 70 eV) m/z 164 and 162 (M$^{+\bullet}$, 97 and 100%), 135 and 133 (36 and 37), 107 and 105 (both 22).

4.2.1.7. 3-Bromo-5,6-dihydropyran-2-one (*2e*). A magnetically solution of 5,6-dihydropyran-2-one (1.0 g, 10.2 mmol, ex. Aldrich Chemical Co.) in dichloromethane (20 mL) maintained at 18 °C was treated, dropwise over 1.5 h, with a solution of molecular bromine (0.76 mL, 2.4 g, 15 mmol) in dichloromethane (15 mL). After a further 1.5 h the reaction mixture was treated, dropwise over 5 min, with a solution of triethylamine (2.2 mL, 11 mmol) in dichloromethane (20 mL). The ensuing mixture was stirred at 18 °C for 0.75 h then washed with water (3×50 mL) and brine (1×50 mL) before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure to give an amber-colored oil (2.02 g). This material was subjected to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane) and thus affording, after concentration of the appropriate fractions (R_f=0.25), the title lactone **2e**[36] (1.66 g, 92%) as a pale-yellow solid, mp=34–36 °C (lit.[36] mp=27–30 °C) (Found: M$^{+\bullet}$, 175.9469. C, 33.97; H, 2.96. C$_5$H$_5$^{79}BrO$_2$ requires M$^{+\bullet}$, 175.9473. C, 33.93; H, 2.85%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30–7.20 (m, 1H), 4.45 (t, J=6.0 Hz, 2H), 2.55–2.45 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.4, 146.0, 113.8, 66.8, 26.7; IR ν_{max} (KBr) 2900, 1727, 1611, 1468, 1394, 1317, 1269, 1159, 1090, 1020, 965, 883, 850, 758 cm^{-1}; MS (EI, 70 eV) m/z 178 and 176 (M$^{+\bullet}$, 21 and 22%), 148 and 146 (40 and 38), 73 (65), 69 (100), 57 (76), 55 (80), 43 (95).

4.2.1.8. 3-Bromo-5,6-dihydropyridin-2(1H)-one (*2f*). A magnetically stirred solution of 3,3-dibromo-2-piperidinone[37] (500 mg, 1.95 mmol) in DMF (15 mL) maintained under a nitrogen atmosphere was treated with CaCO$_3$ (250 mg, 2.50 mmol) and the resulting mixture heated at 80 °C for 36 h. The cooled reaction mixture was diluted with water (50 mL) and extracted with dichloromethane (3×25 mL). The combined organic phases were washed with brine (3×50 mL) and water (1×50 mL) then dried (MgSO$_4$), filtered, and concentrated under reduced pressure. The resulting light-brown oil was subjected to flash chromatography (silica, 3:97 v/v methanol/diethyl ether elution) and thus affording, after concentration of the appropriate fractions (R_f=0.3), the title lactam **2f** (222 mg, 65%) as colorless needles, mp=87.5–88 °C (Found: M$^{+\bullet}$, 174.9633. C, 34.34; H, 3.44; N, 7.91. C$_5$H$_6$^{79}BrNO requires M$^{+\bullet}$, 174.9633. C, 34.12; H, 3.44; N, 7.96%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.04 (broad t, J=4.5 Hz, 1H), 6.44 (broad s, 1H), 3.56–3.44 (m, 2H), 2.50–2.36 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.3, 142.1, 118.1, 39.7, 26.4; IR ν_{max} (KBr) 3309, 3255, 3034, 2943, 2866, 1680,

1643, 1608, 1475, 1449, 1422, 1347, 1282, 1270, 1202, 1110, 1055, 1019, 994, 893, 878, 858, 845, 763, 704 cm^{-1}; MS (EI, 70 eV) m/z 177 and 175 (M$^{+\bullet}$, 97 and 99%), 148 and 146 (97 and 100), 120 and 118 (41 and 42), 96 (43), 53 (31), 39 (66).

4.2.2. Part B: the Pd[0]-catalyzed Ullmann cross-coupling reactions.

4.2.2.1. General procedure. A suspension of copper 'dust' (600 mg of 3 micron dendritic material, ex. Aldrich Chemical Co.) in EDTA (100 mL of a 0.02 M solution in distilled water) was subjected to irradiation in a 100 W Branson ultrasonication bath at 18 °C for 0.5 h. The copper dust was then allowed to settle and the supernatant decanted. The residual solid was washed with deionized and deoxygenated water (4×25 mL) then acetone (3×25 mL) and methanol (2×25 mL). The material obtained after the final wash was transferred to a round-bottom flask and the residual methanol removed by rotary evaporation and thus providing ca. 500 mg of the activated metal. This was used promptly in the cross-coupling reaction. Thus, this activated material was suspended in dry DMSO (5 mL) and held under nitrogen. In a separate flask, a solution of the appropriate *o*-nitrohaloarene **1a**−**e** (1 mmol) in DMSO (20 mL) was treated with the relevant heterocyclic cross-coupling partner **2a**−**f** (2 mmol) and Pd$_2$(dba)$_3$ (47 mg, 0.05 mmol, 5 mol %) and the resulting mixture degassed then warmed, under a nitrogen atmosphere, to 40−50 °C then treated, over 1.5 h, with five equal aliquots of the activated copper suspended in DMSO. Heating was continued for further 1.5−3.5 h then the reaction mixture was cooled to 18 °C, diluted with ethyl acetate (25 mL) and filtered through a pad of Celite™ that was rinsed with ethyl acetate (50 mL). The combined filtrates were washed with ammonia (4×25 mL of a 5% w/v aqueous solution), water (2×25 mL) and brine (1×25 mL) before being dried (MgSO$_4$) and filtered. The filtrate was treated with flash chromatographic grade silica (1 g) and then concentrated under reduced pressure to a free-flowing powder. This was applied to the top of a flash chromatography column that was eluted with the appropriate combination of ethyl acetate and hexane (see below). Concentration of the appropriate fractions then gave the relevant cross-coupling product.

4.2.2.2. 1-Methyl-3-(2-nitrophenyl)-1H-pyrrole-2,5-dione (3a). Cross-coupling of arene **1a** and heterocycle **2a** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.3) gave compound **3a** (197 mg, 85%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a white, crystalline solid, mp=148−149 °C (Found: M$^{+\bullet}$, 232.0484. C, 56.71; H, 3.44; N, 12.05. C$_{11}$H$_8$N$_2$O$_4$ requires M$^{+\bullet}$, 232.0484. C, 56.90; H, 3.47; N, 12.06%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.19 (dd, J=8.1 and 1.5 Hz, 1H), 7.78−7.64 (m, 2H), 7.47 (dd, J=7.5 and 1.5 Hz, 1H), 6.70 (s, 1H), 3.08 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.9, 168.6, 148.0, 145.5, 133.8, 131.4(0), 131.3(6), 126.4, 125.0, 124.4, 24.2; IR ν_{max} (KBr) 3109, 3072, 2962, 1768, 1705, 1602, 1571, 1521, 1441, 1387, 1345, 1265, 1247, 1117, 1096, 1059, 960, 879, 800, 726, 716, 686 cm^{-1}; MS (EI, 70 eV) m/z 232 (M$^{+\bullet}$, 16%), 186 (38), 175 (20), 147 (85), 146 (56), 130 (58), 119 (72), 103 (81), 89 (100), 76 (73), 75 (63).

4.2.2.3. 3-(2-Nitrophenyl)-1-phenyl-1H-pyrrole-2,5-dione (3b). Cross-coupling of arene **1a** and heterocycle **2b** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (silica, 1:2 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.3) gave compound **3b** (241 mg, 82%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a white,

crystalline solid, mp=163−164 °C (Found: M$^{+\bullet}$, 294.0642. C, 65.62; H, 3.79; N, 9.52. C$_{16}$H$_{10}$N$_2$O$_4$ requires M$^{+\bullet}$, 294.0641. C, 65.31; H, 3.43; N, 9.52%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.22 (dd, J=7.8 and 1.2 Hz, 1H), 7.82−7.66 (m, 2H), 7.58−7.30 (complex m, 6H), 6.83 (s, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.8, 167.6, 148.3, 145.7, 134.1, 131.8, 131.7, 131.4, 129.3, 128.2, 126.5, 126.2, 125.4, 124.5; IR ν_{max} (KBr) 3092, 1714, 1641, 1597, 1572, 1531, 1518, 1500, 1457, 1382, 1349, 1201, 1144, 1128, 1030, 873, 858, 790, 753, 712, 699, 683 cm^{-1}; MS (EI, 70 eV) m/z 295 [(M+H)$^+$, 28%], 294 (M$^{+\bullet}$, 100), 248 (16), 147 (43), 146 (32), 119 (52), 103 (48), 89 (46), 76 (35).

4.2.2.4. 3-(2-Methoxy-6-nitrophenyl)-1-methyl-1H-pyrrole-2,5-dione (3c). Cross-coupling of arene **1b** and heterocycle **2a** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.25) gave compound **3c** (233 mg, 89%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a white, crystalline solid, mp=126−127.5 °C (Found: M$^{+\bullet}$, 262.0594. C, 54.89; H, 3.94; N, 10.68. C$_{12}$H$_{10}$N$_2$O$_5$ requires M$^{+\bullet}$, 262.0590. C, 54.97; H, 3.84; N, 10.68%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.72 (dd, J=8.4 and 1.0 Hz, 1H), 7.56 (t, J=8.4 Hz, 1H), 7.26 (dd, J=8.4 and 1.0 Hz, 1H), 6.74 (s, 1H), 3.89 (s, 3H), 3.07 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.7, 169.6, 158.1, 149.6, 139.6, 131.5, 129.7, 116.8, 116.1, 112.9, 56.8, 24.3; IR ν_{max} (KBr) 3097, 3026, 2950, 1775, 1714, 1630, 1599, 1566, 1531, 1437, 1381, 1356, 1277, 1254, 1165, 1117, 1053, 956, 910, 858, 810, 795, 780, 751, 724, 685 cm^{-1}; MS (EI, 70 eV) m/z 263 [(M+H)$^+$, 13%], 262 (M$^{+\bullet}$, 76), 216 (100), 177 (76), 147 (37), 133 (41), 132 (38), 105 (42), 104 (45), 103 (51), 76 (82), 62 (45).

4.2.2.5. 3-(5-Methoxy-2-nitrophenyl)-1-methyl-1H-pyrrole-2,5-dione (3d). In a variation on the general procedure specified above, arene **1c** (270 mg, 1.1 mmol), imide **2a** (110 mg, 0.57 mmol), and Pd$_2$(dba)$_3$ (60 mg, 0.06 mmol) were added to a magnetically stirred suspension of copper powder (200 mg, 12 mmol) in DMSO (10 mL). The ensuing mixture was stirred at 50 °C for 3.5 h then cooled, diluted with diethyl ether (40 mL) and water (40 mL). The separated aqueous layer was extracted with diethyl ether (3×40 mL) then the combined organic phases were washed with water (2×20 mL) and brine (20 mL) before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure to give a viscous and orange-colored oil (1.90 g). Subjection of this material to flash chromatography (silica, 1:4 v/v ethyl acetate/hexane) and concentration of the appropriate fractions (R_f=0.3 in 2:3 v/v ethyl acetate/hexane) yielded compound **3d** (100 mg, 67%) as yellow needles, mp=179−181 °C (Found: M$^{+\bullet}$, 262.0590. C, 55.16; H, 4.18; N, 10.19. Calculated for C$_{12}$H$_{10}$N$_2$O$_5$ M$^{+\bullet}$, 262.0590. C, 54.97; H, 3.84, N, 10.68%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.24 (d, J=9.3 Hz, 1H), 7.07 (dd, J=9.3 and 2.7 Hz, 1H), 6.85 (d, J=2.7 Hz, 1H), 6.64 (s, 1H), 3.93 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.9, 168.6, 163.5, 146.2, 140.9, 127.7, 127.0, 126.1, 116.7, 115.2, 56.2, 24.2; IR ν_{max} (KBr) 3110, 2923, 1699, 1607, 1576, 1505, 1449, 1389, 1337, 1309, 1257, 1245, 1183, 1106, 1057, 1031, 977, 881, 838, 724 cm^{-1}; MS (EI, 70 eV) m/z 262 (M$^{+\bullet}$, 20%), 216 (100), 177 (33), 175 (30), 106 (65).

4.2.2.6. 4-(5-Methoxy-2-nitrophenyl)-1-methyl-5-oxo-2,5-dihydro-1H-pyrrol-2-yl acetate (3e). In a variation on the general procedure specified above, arene **1c** (1.80 g, 6.3 mmol), lactam **2c** (840 mg, 3.6 mmol), Pd$_2$(dba)$_3$ (460 mg, 0.51 mmol), and copper powder (810 mg, 13 g-atom) were added to DMSO (10 mL). The ensuing mixture was stirred at 55 °C for 2.75 h then cooled, diluted with diethyl ether (125 mL) and water (250 mL). The separated aqueous layer was extracted with diethyl ether (3×125 mL) then the combined organic phases were washed with water (1×125 mL)

and brine (1×125 mL), before being dried (MgSO$_4$), filtered, and concentrated under reduced pressure to give a viscous and orange-colored oil (1.90 g). Subjection of this material to flash chromatography (silica, 1:2→9:11 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions (R_f=0.6 in 7:3 v/v ethyl acetate/hexane elution) afforded *compound* **3e** (640 mg, 58%) as pale-yellow crystals, mp=58 °C (Found: M$^{+•}$, 306.0851. C, 54.37; H, 4.70; N, 8.96. Calculated for C$_{14}$H$_{14}$N$_2$O$_6$ M$^{+•}$, 306.0852. C, 54.90; H, 4.61, N, 9.15%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.15 (d, J=9.0 Hz, 1H), 6.99 (dd, J=9.0 and 2.7 Hz, 1H), 6.92 (d, J=1.8 Hz, 1H), 6.82 (d, J=2.7 Hz, 1H), 6.52 (d, J=1.8 Hz, 1H), 3.90 (s, 3H), 3.00 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.7, 167.3, 163.2, 141.7, 141.0, 134.7, 128.8, 127.5, 116.8, 114.5, 82.9, 56.2, 27.4, 21.1; IR ν$_{max}$ (KBr) 2943, 1714, 1609, 1578, 1518, 1435, 1398, 1344, 1214, 1113, 1017, 940, 865, 779, 760, 745, 715 cm^{-1}; MS (EI, 70 eV) m/z 306 (M$^{+•}$, 10%), 260 (15), 247 (60), 246 (50), 218 (45), 177 (52), 176 (57), 149 (51), 43 (95), 42 (100).

*4.2.2.7. 3-(2-Nitrophenyl)furan-2(5H)-one (**3f**).* Cross-coupling of arene **1a** and heterocycle **2d** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (2:3 v/v ethyl acetate/hexane) and concentration of the relevant fractions (R_f=0.3) gave *compound* **3f** (158 mg, 77%) as a white, crystalline solid, no mp (decomposition above 158 °C) (Found: M$^{+•}$, 205.0370. C, 58.73; H, 3.55; N, 6.83. Calculated for C$_{10}$H$_7$NO$_4$ M$^{+•}$, 205.0375. C, 58.54; H, 3.44; N, 6.83%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.09 (dd, J=8.1 and 1.2 Hz, 1H), 7.20–7.52 (complex m, 3H), 7.46 (dd, J=7.5 and 1.5 Hz, 1H), 5.04 (d, J=1.8 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d$_6$) δ 171.3, 150.2, 148.0, 134.0, 132.2, 130.6, 129.7, 125.0, 124.7, 71.5; IR ν$_{max}$ (KBr) 3087, 2924, 1745, 1523, 1450, 1352, 1330, 1264, 1134, 1049, 1004, 965, 856, 841, 798, 738, 683 cm^{-1}; MS (EI, 70 eV) m/z 205 (M$^{+•}$, 63%), 176 (42), 159 (85), 132 (41), 104 (51), 103 (60), 91 (50), 77 (100), 51 (66).

*4.2.2.8. 5,6-Dihydro-3-(2-nitrophenyl)pyran-2-one (**3g**).* Cross-coupling of arene **1a** and heterocycle **2e** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (silica, 2:3 v/v ethyl acetate/hexane elution) and concentration of the relevant fractions (R_f=0.25) gave *compound* **3g** (171 mg, 78%) as a pale-yellow, crystalline solid. For the purposes of full characterization, a sample of this material was subjected to further flash chromatography (silica, 1:9 v/v acetone/toluene elution) and after concentration of the appropriate fractions (R_f=0.3) an analytically pure sample of compound **3g** was obtained as a white, crystalline solid, mp=144–145 °C (Found: M$^{+•}$, 219.0532. C, 60.12; H, 4.33; N, 6.38. Calculated for C$_{11}$H$_9$NO$_4$ M$^{+•}$, 219.0532. C, 60.28; H, 4.14, N, 6.39%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.11 (dd, J=8.1 and 1.5 Hz, 1H), 7.69–7.61 (m, 1H), 7.56–7.48 (m, 1H), 7.38 (dd, J=7.8 and 1.5 Hz, 1H), 6.93 (t, J=4.5 Hz, 1H), 4.63–4.54 (m, 2H), 2.69–2.60 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 163.1, 147.7, 140.3, 133.7, 132.6, 131.5, 131.3, 129.4, 124.6, 66.6, 24.4; IR ν$_{max}$ (KBr) 3063, 2997, 2953, 2911, 1716, 1571, 1524, 1466, 1402, 1352, 1282, 1265, 1201, 1163, 1092, 1054, 1009, 980, 968, 891, 865, 846, 797, 785, 754, 722, 703 cm^{-1}; MS (EI, 70 eV) m/z 219 (M$^{+•}$, 7%), 173 (100), 145 (45), 115 (48).

*4.2.2.9. 5,6-Dihydro-3-(2-nitrophenyl)pyridin-2(1H)-one (**3h**).* Cross-coupling of arene **1a** and heterocycle **2f** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (ethyl acetate) and concentration of the relevant fractions (R_f=0.3) gave *compound* **3h** (133 mg, 61%) as a white, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give white needles, no mp (decomposition above 191 °C) [Found: (M–NO$_2^•$)$^+$, 172.0764. C, 60.64; H, 4.34; N, 12.59. Calculated for C$_{11}$H$_{10}$N$_2$O$_3$ (M–NO$_2^•$)$^+$,

172.0762. C, 60.55; H, 4.62, N, 12.84%]. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.05 (dm, J=7.5 Hz, 1H), 7.61 (tm, J=7.5 Hz, 1H), 7.49 (tm, J=7.5 Hz, 1H), 7.37 (dm, J=7.5 Hz, 1H), 6.72 (t, J=4.5 Hz, 1H), 5.84 (broad s, 1H), 3.64–3.54 (m, 2H), 2.60–2.52 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.9, 148.7, 137.2, 135.2, 133.4, 132.4, 131.8, 129.0, 124.5, 39.8, 24.6; IR ν$_{max}$ (KBr) 3435, 3193, 3060, 2890, 1681, 1671, 1617, 1524, 1487, 1356, 1288, 863, 746, 546 cm^{-1}; MS (EI, 70 eV) m/z 172 [(M–NO$_2^•$)$^+$, 100], 115 (19), 77 (19), 57 (27), 55 (34).

*4.2.2.10. 5,6-Dihydro-3-(4-methoxy-2-nitrophenyl)pyridin-2(1H)-one (**3i**).* Cross-coupling of arene **1d** and heterocycle **2f** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (9:1 v/v ethyl acetate/hexane) and concentration of the relevant fractions (R_f=0.25) gave *compound* **3i** (209 mg, 73%) as a pale-yellow, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a cream-colored, crystalline solid, no mp (decomposition above 194 °C) (Found: M$^{+•}$, 248.0796. C, 58.02; H, 4.67; N, 11.28. Calculated for C$_{12}$H$_{12}$N$_2$O$_4$ M$^{+•}$, 248.0797. C, 58.06; H, 4.87; N, 11.28%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.58 (d, J=2.7 Hz, 1H), 7.31–7.24 (m, 1H), 7.14 (dd, J=8.4 and 2.7 Hz, 1H), 6.68 (t, J=4.5 Hz, 1H), 6.17 (broad s, 1H), 3.89 (s, 3H), 3.62–3.52 (m, 2H), 2.58–2.48 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 165.2, 159.8, 149.2, 136.6, 134.9, 132.6, 124.6, 119.8, 109.4, 56.0, 39.8, 24.6; IR ν$_{max}$ (KBr) 3185, 3116, 3062, 2890, 1671, 1621, 1533, 1499, 1485, 1451, 1357, 1305, 1284, 1266, 1222, 1074, 1038, 1008, 917, 885, 869, 856, 822, 801 cm^{-1}; MS (EI, 70 eV) m/z 248 (M$^{+•}$, 4%), 203 (20), 202 [(M–NO$_2^•$)$^+$, 100].

*4.2.2.11. 3-(4-Methyl-2-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (**3j**).* Cross-coupling of arene **1e** and heterocycle **2f** under the conditions specified in the general procedure followed by subjection of the crude product to flash chromatography (ethyl acetate) and concentration of the relevant fractions (R_f=0.3) gave *compound* **3j** (141 mg, 61%) as an off-white, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give fine, white needles, mp=199–200 °C (with decomposition) [Found: (M–NO$_2^•$)$^+$, 186.0919. C, 62.18; H, 5.10; N, 12.12. Calculated for C$_{12}$H$_{12}$N$_2$O$_3$ (M–NO$_2^•$)$^+$, 186.0919. C, 62.06; H, 5.21, N, 12.06%]. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.85 (s, 1H), 7.41 (d, J=7.8 Hz, 1H), 7.28–7.20 (m, 1H), 6.69 (t, J=4.2 Hz, 1H), 6.09 (broad s, 1H), 3.60–3.52 (m, 2H), 2.58–2.48 (m, 2H), 2.43 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 164.8, 148.3, 139.4, 136.5, 135.0, 133.9, 131.4, 129.4, 124.8, 39.7, 24.5, 20.9; IR ν$_{max}$ (KBr) 3189, 3060, 2889, 1681, 1615, 1528, 1485, 1421, 1358, 1287, 1271, 1251, 1123, 1051, 1015, 888, 859, 830, 802, 760, 714, 675 cm^{-1}; MS (EI) m/z 232 (M$^{+•}$, <1%), 187 (22), 186 [(M–NO$_2^•$)$^+$, 100], 115 (15), 91 (15).

*4.2.2.12. 1-Acetyl-3-(2-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (**3k**).* Following a procedure described by Minami et al.,[38] a magnetically stirred solution of lactam **3h** (152 mg, 0.70 mmol) in acetic anhydride (10 mL) was treated with sodium acetate (160 mg, 1.95 mmol). The resulting mixture was heated at reflux for 1.5 h then cooled, diluted with ethyl acetate (50 mL), and the resulting solution poured into sodium hydrogen carbonate (200 mL of a saturated aqueous solution). The ensuing biphasic mixture was stirred vigorously for 0.3 h then the separated organic phase was washed with water (1×25 mL) and brine (1×25 mL) before being dried (MgSO$_4$) then filtered. The filtrate was treated with flash chromatography-grade silica gel (1.0 g) and the resulting mixture concentrated under reduced pressure. The free-flowing solid thus obtained was added to the top of a flash chromatography column. Elution of the column (with 2:3 v/v ethyl acetate/hexane) and concentration of the relevant fractions (R_f=0.3) under reduced pressure afforded the *title compound* **3k** (172 mg, 95%) as a colorless resin (Found: M$^{+•}$, 260.0795. Calculated for C$_{13}$H$_{12}$N$_2$O$_4$ M$^{+•}$, 260.0797). ^{1}H

NMR (300 MHz, CDCl$_3$) δ 8.12 (broadened d, J=7.8 Hz, 1H), 7.66 (broadened t, J=7.8 Hz, 1H), 7.54 (td, J=7.8 and 1.2 Hz, 1H), 7.37 (dd, J=7.8 and 1.2 Hz, 1H), 6.94 (t, J=3.9 Hz, 1H), 4.17 (broad s, 2H), 2.65–2.55 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.3, 164.8, 148.3, 140.8, 136.3, 133.8, 131.8, 129.5, 124.7, 40.9, 27.6, 24.8 (one signal obscured or overlapping); IR ν_{max} (KBr) 2940, 1691, 1524, 1469, 1389, 1368, 1349, 1302, 1265, 1241, 1188, 1136, 1031 cm^{-1}; MS (EI, 70 eV) m/z 260 (M$^{+\bullet}$, 2%), 214 (43), 172 (94), 115 (18).

4.2.2.13. 1-Acetyl-3-(4-methoxy-2-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (3l). Following the procedure described immediately above, lactam **3i** (135 mg, 0.55 mmol) was converted into the *title compound* **3l** (131 mg, 83%), which was obtained as a pale-yellow solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (ethyl acetate/hexane) to give white needles, mp=100–102 °C (Found: M$^{+\bullet}$, 290.0901. C, 57.99; H, 5.05; N, 9.66. Calculated for C$_{14}$H$_{14}$N$_2$O$_5$ M$^{+\bullet}$, 290.0903. C, 57.93; H, 4.86; N, 9.65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.64 (d, J=2.7 Hz, 1H), 7.30–7.26 (m, 1H), 7.18 (dd, J=8.7 and 2.7 Hz, 1H), 6.90 (t, J=4.5 Hz, 1H), 4.14 (broad s, 2H), 3.90 (s, 3H), 2.64–2.54 (m, 2H), 2.51 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.1, 164.8, 159.9, 148.7, 140.3, 135.7, 132.6, 123.8, 119.7, 109.5, 55.9, 40.8, 27.4, 24.6; IR ν_{max} (KBr) 2940, 2842, 1692, 1620, 1531, 1466, 1388, 1368, 1349, 1303, 1273, 1227, 1188, 1135, 1035 cm^{-1}; MS (EI, 70 eV) m/z 290 (M$^{+\bullet}$, 5%), 244 (37), 202 (100).

4.2.2.14. 1-Acetyl-3-(4-methyl-2-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (3m). Following the procedure described above for the conversion **3h→3k**, lactam **3j** (116 mg, 0.50 mmol) was converted into the *title compound* **3m** (133 mg, 97%), which was obtained as a pale-yellow solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (chloroform/hexane) to give white needles, mp=120–121 °C (Found: M$^{+\bullet}$, 274.0960. C, 61.24; H, 5.01; N, 10.03. Calculated for C$_{14}$H$_{14}$N$_2$O$_4$ M$^{+\bullet}$, 274.0954. C, 61.31; H, 5.14; N, 10.21%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.93 (broad s, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.27–7.22 (partially obscured m, 1H), 6.90 (t, J=4.8 Hz 1H), 4.16 (broad s, 2H), 2.61–2.54 (m, 2H), 2.51 (s, 3H), 2.46 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.3, 164.9, 148.1, 140.3, 140.1, 136.3, 134.5, 131.6, 129.0, 125.1, 40.9, 27.6, 24.7, 21.1; IR ν_{max} (KBr) 3364, 2900, 1693, 1681, 1528, 1499, 1463, 1425, 1385, 1357, 1296, 1272, 1244, 1194, 1132, 1028 cm^{-1}; MS (EI, 70 eV) m/z 274 (M$^{+\bullet}$, 3%), 228 (50), 186 (100).

4.2.3. Part C: the reduction and reductive cyclization reactions.

4.2.3.1. General procedure. A magnetically stirred solution of the relevant cross-coupled product **3a–d** or **3f–i** (1 mmol) in ethanol (15 mL) was treated with 10% Pd on C (20% w/w wrt substrate) and the resulting mixture sparged with dihydrogen and then maintained under an atmosphere of dihydrogen at 18 °C until TLC analysis indicated that all of the staring material had been consumed (ca. 2–4 h). The reaction mixture was filtered through a No. 3 porosity sintered-glass funnel and the solids thus retained washed with ethanol (15 mL). The combined filtrates were concentrated under reduced pressure and the residue taken up in ethyl acetate (20 mL). The solution thus obtained was filtered through a thin pad of TLC-grade silica gel that was washed with additional ethyl acetate (10 mL). The combined filtrates were concentrated under reduced pressure to give the relevant reduction product as specified under the individual headings shown below.

4.2.3.2. 3-(2-Amino-5-methoxyphenyl)-1-methylpyrrolidine-2,5-dione (4d). A magnetically stirred solution of compound **3d** (260 mg, 0.98 mmol) in methanol (10 mL) was treated with 5% Pd on C (40 mg) and the resulting mixture purged with dihydrogen then stirred, at 18 °C, under an atmosphere of dihydrogen for 1.5 h.

The reaction mixture was then filtered through a pad of Celite™ and the solids thus retained washed with methanol (10 mL). The combined filtrates were concentrated under reduced pressure to give the *title compound* **4d** (125 mg, 54%) as an amorphous white powder (Found: M$^{+\bullet}$, 234.1005. Calculated for C$_{12}$H$_{14}$N$_2$O$_3$ M$^{+\bullet}$, 234.1004). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.82–6.73 (complex m, 3H), 4.90 (s, 2H), 3.80–3.65 (m, 1H), 3.73 (s, 3H), 2.92–2.75 (m, 1H), 2.73 (s, 3H), 2.60–2.45 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 181.4, 173.3, 157.2, 136.8, 131.8, 113.8, 112.3, 111.2, 56.1, 44.5, 37.1, 26.4; IR ν_{max} (KBr) 3283, 2923, 1702, 1637, 1489, 1464, 1296, 1276, 1212, 1140, 1028, 811 cm^{-1}; MS (EI, 70 eV) m/z 237 [(C$_{12}$H$_{12}$D$_2$N$_2$O$_3$+H)$^+$, 86%], 236 [(C$_{12}$H$_{13}$DN$_2$O$_3$+H)$^+$, 80], 235 [(M+H)$^+$, 32], 234 (M$^{+\bullet}$, 8), 178 (80), 177 (98), 176 (100), 175 (75), 161 (70) (deuterium in sample arises from its prolonged storage in CDCl$_3$).

4.2.3.3. 3-(2-Amino-4-methoxyphenyl)piperidin-2-one (4i). Reduction of cross-coupling product **3i** under the conditions specified in the general procedure gave the *title compound* **4i** (214 mg, 97%) as a pale-pink oil that crystallized on standing. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a pale-pink, crystalline solid, no mp (decomposition above 148 °C) (Found: M$^{+\bullet}$, 220.1208. C, 65.42; H, 7.22; N, 12.57. Calculated for C$_{12}$H$_{16}$N$_2$O$_2$ M$^{+\bullet}$, 220.1212. C, 65.43; H, 7.32, N, 12.72%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.01 (d, J=8.4 Hz, 1H), 6.42–6.28 (complex m, 3H), 4.10 (broad s, 2H), 3.75 (s, 3H), 3.65 (dd, J=9.0 and 6.0 Hz, 1H), 3.44–3.36 (m, 2H), 2.20–1.78 (complex m, 4H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.8, 159.4, 146.7, 128.9, 119.4, 104.7, 103.2, 55.3, 43.0, 42.9, 26.9, 22.0; IR ν_{max} (KBr) 3407, 3343, 3178, 2933, 1660, 1614, 1583, 1514, 1496, 1455, 1416, 1325, 1294, 1264, 1218, 1170, 1147, 1031, 847, 799, 665 cm^{-1}; MS (EI, 70 eV) m/z 221 [(M+H$^+$), 32%], 220 (M$^{+\bullet}$, 96), 203 (47), 175 (100), 163 (53), 149 (62), 136 (66).

4.2.3.4. 3-(2-Amino-4-methylphenyl)piperidin-2-one (4j). Reduction of cross-coupling product **3j** under the conditions specified in the general procedure gave the *title compound* **4j** (172 mg, 84%) as a honey-colored solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (acetone/diethyl ether) to give a white, crystalline solid, no mp (decomposition above 138 °C) (Found: M$^{+\bullet}$, 204.1265. Calculated for C$_{12}$H$_{16}$N$_2$O M$^{+\bullet}$, 204.1263). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.99 (d, J=7.8 Hz, 1H), 6.64–6.55 (m, 2H), 6.10 (broad s, 1H), 3.92 (broad s, 2H), 3.72–3.64 (m, 1H), 3.46–3.34 (m, 2H), 2.24 (s, 3H), 2.20–1.94 (complex m, 3H), 1.92–1.80 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.7, 145.2, 137.7, 128.0, 123.9, 120.3, 118.4, 43.3, 42.8, 26.8, 22.0, 21.1; IR ν_{max} (KBr) 3342, 3233, 2944, 1655, 1510, 1490, 1447, 1355, 1319, 1110, 800, 730 cm^{-1}; MS (EI, 70 eV) m/z 204 (M$^{+\bullet}$, 58%), 187 (33), 159 (47), 99 (100), 84 (56), 55 (78), 43 (78), 42 (98).

4.2.3.5. N-Methyl-2-(2-oxoindolin-3-yl)acetamide (5a). Reductive cyclization of cross-coupling product **3a** under the conditions specified in the general procedure gave *oxindole* **5a** (178 mg, 87%) as a white, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (methanol) to give a fine white crystalline solid, mp=101–103 °C (Found: M$^{+\bullet}$, 204.0903. C, 64.93; H, 5.93; N, 13.93. Calculated for C$_{11}$H$_{12}$N$_2$O$_2$ M$^{+\bullet}$, 204.0899. C, 64.69; H, 5.92, N, 13.72%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.17–7.09 (m, 1H), 6.98 (d, J=7.8 Hz, 1H), 6.86–6.78 (m, 2H), 4.30–4.24 (m, 1H), 4.07 (broad s, 2H), 3.20–2.96 (complex m, 2H), 3.02 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 179.0, 176.6, 145.5, 128.9, 126.0, 122.7, 119.9, 118.2, 41.2, 34.6, 25.2; IR ν_{max} (KBr) 3431, 3356, 2995, 2947, 1772, 1688, 1621, 1497, 1443, 1387, 1283, 1121, 1061, 951, 809, 786, 763, 697 cm^{-1}; MS (EI, 70 eV) m/z 205 [(M+H)$^+$, 29%], 204 (M$^{+\bullet}$, 100), 146 (83), 145 (97), 128 (30), 119 (95), 118 (75), 117 (55), 91 (53).

4.2.3.6. 2-(2-Oxoindolin-3-yl)-N-phenylacetamide (5b). Reductive cyclization of cross-coupling product **3b** under the conditions specified in the general procedure gave oxindole **5b**[22] (264 mg, 99%) as a pale-pink, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (acetone) to give a white, crystalline solid, no mp (decomposition above 184 °C) (lit.[22] mp=202–203 °C) (Found: M$^{+\bullet}$, 266.1055. C, 71.98; H, 5.49; N, 10.30. Calculated for C$_{16}$H$_{14}$N$_2$O$_2$ M$^{+\bullet}$, 266.1055. C, 72.17; H, 5.30, N, 10.52%). ^{1}H NMR (300 MHz, acetone-d_6) δ 9.47 (s, 1H), 9.42 (s, 1H), 7.66 (d, J=7.5 Hz, 2H), 7.35–7.26 (m, 3H), 7.20–7.14 (m, 1H), 7.09–7.02 (m, 1H), 6.96–6.88 (m, 2H), 3.92–3.83 (m, 1H), 3.12 (dd, J=15.9 and 4.5 Hz, 1H), 2.72 (dd, J=15.9 and 8.7 Hz, 1H); ^{13}C NMR (75 MHz, acetone-d_6) δ 179.1, 179.0, 169.5, 169.4, 143.6, 143.4, 140.2, 140.1, 130.6, 129.5, 128.7, 125.1, 124.2, 122.4, 120.0, 119.9, 110.1(3), 110.0(8), 43.0, 38.3, 38.2 (additional signals due to the presence of amide rotamers); IR ν_{max} (KBr) 3315, 3213, 3092, 2875, 1702, 1679, 1623, 1600, 1551, 1498, 1472, 1446, 1346, 1317, 1184, 961, 7841, 692 cm^{-1}; MS (EI, 70 eV) m/z 266 (M$^{+\bullet}$, 43), 173 (30), 146 (45), 145 (100), 132 (24), 117 (28), 93 (58), 77 (27).

4.2.3.7. 2-(4-Methoxy-2-oxoindolin-3-yl)-N-methylacetamide (5c). Reductive cyclization of cross-coupling product **3c** under the conditions specified in the general procedure gave oxindole **5c** (181 mg, 77%) as a pale-pink, crystalline solid. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (ethanol) to give a white, crystalline solid, no mp (decomposition above 145 °C) (Found: M$^{+\bullet}$, 234.1004. C, 61.61; H, 6.11; N, 11.68. Calculated for C$_{12}$H$_{14}$N$_2$O$_3$ M$^{+\bullet}$, 234.1004. C, 61.53; H, 6.02, N, 11.96%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.05 (t, J=8.1 Hz, 1H), 6.44–6.32 (m, 2H), 4.08–3.98 (m, 1H), 3.67 (s, 3H), 3.65 (broad s, 2H), 3.06 (s, 3H), 3.06–2.96 (m, 1H), 2.73 (dd, J=18.0 and 5.1 Hz, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 179.3, 177.2, 158.0, 145.8, 129.0, 111.7, 110.8, 102.4, 55.6, 37.4, 35.5, 24.9; IR ν_{max} (KBr) 1692, 1599, 1472, 1439, 1384, 1283, 1121, 1092, 951, 776 cm^{-1}; MS (EI, 70 eV) m/z 234 (M$^{+\bullet}$, 100), 176 (48), 175 (68), 149 (18), 134 (19).

4.2.3.8. 2-(5-Methoxy-2-oxoindolin-3-yl)-N-methylacetamide (5d). Reductive cyclization of cross-coupling product **3d** under the conditions specified in the general procedure gave oxindole **5d** (127 mg, 54%) as an off-white, crystalline solid, no mp (decomposition above 145 °C) (Found: M$^{+\bullet}$, 234.1004. Calculated for C$_{12}$H$_{14}$N$_2$O$_3$ M$^{+\bullet}$, 234.1004). ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.67 (broad d, J=4.2 Hz, 1H), 7.30 (broad s, 1H), 7.21 (d, J=2.7 Hz, 1H), 7.02 (d, J=8.4 Hz, 1H), 6.85 (dd, J=8.4 and 2.7 Hz, 1H), 4.10–4.00 (m, 1H), 3.71 (s, 3/2H), 3.67 (s, 3/2H), 3.18 (dd, J=15.0 and 4.2 Hz, 1H), 2.89 (s, 3/2H), 2.87 (s, 3/2H), 2.76–2.55 (m, 1H); ^{13}C NMR (75 MHz, toluene-d_8/DMSO-d_6) δ 179.1, 170.8, 155.5, 136.9, 131.8, 112.6, 112.1, 110.0, 55.4, 43.6, 37.0, 26.0; MS (EI, 70 eV) m/z 234 (M$^{+\bullet}$, 98), 176 (88), 175 (100), 160 (61).

4.2.3.9. 3-(2-Hydroxyethyl)indolin-2-one (5f). Reductive cyclization of cross-coupling product **3f** under the conditions specified in the general procedure gave oxindole **5f**[23] (170 mg, 96%) as a pale-yellow oil that crystallized on standing. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (chloroform) to give a white, crystalline solid, mp=109.5–111 °C (lit.[23] mp=109–111 °C) (Found: M$^{+\bullet}$, 177.0786. C, 67.77; H, 6.23; N, 7.78. Calculated for C$_{10}$H$_{11}$NO$_2$ M$^{+\bullet}$, 177.0790. C, 67.78; H, 6.26, N, 7.90%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.14 (broad s, 1H), 7.28–7.18 (m, 2H), 7.07–6.99 (m, 1H), 6.93–6.87 (m, 1H), 3.94–3.84 (m, 2H), 3.66–3.58 (m, 1H), 3.47 (t, J=6.0 Hz, 1H), 2.31–2.19 (m, 1H), 2.14–2.05 (m, 1H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 181.5, 141.3, 129.4, 128.1, 123.9, 122.6, 110.0, 60.7, 44.8, 33.1; IR ν_{max} (KBr) 3353, 3157, 2953, 2884, 1688, 1618, 1472, 1348, 1298, 1213, 1183, 1108, 1037, 805, 761, 661 cm^{-1}; MS (EI, 70 eV) m/z 178 [(M+H)$^+$, 35%], 177 (M$^{+\bullet}$, 81), 159 (56), 146 (100), 144 (56), 133 (56), 130 (48), 77 (38).

4.2.3.10. 3-(2-Hydroxypropyl)indolin-2-one (5g). Reductive cyclization of cross-coupling product **3g** under the conditions specified in the general procedure gave oxindole **5g**[24] (141 mg, 74%) as a clear, colorless oil that slowly crystallized on standing. For the purposes of spectroscopic characterization, a sample of this material was recrystallized (ethyl acetate/hexane) to give colorless needles, mp=99–101 °C (lit.[24] mp=105–105.5) (Found: M$^{+\bullet}$, 191.0946. Calculated for C$_{11}$H$_{13}$NO$_2$ M$^{+\bullet}$, 199.0946). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.69 (broad s, 1H), 7.28–7.14 (m, 2H), 7.03 (t, J=7.8 Hz, 1H), 6.89 (d, J=7.8 Hz, 1H), 3.68–3.58 (m, 2H), 3.54–3.46 (m, 1H), 2.16–1.96 (m, 2H), 1.70–1.50 (m, 2H) (signal due to OH group proton not observed); ^{13}C NMR (75 MHz, CDCl$_3$) δ 180.7, 141.6, 129.6, 128.1, 124.2, 122.6, 109.9, 62.5, 45.7, 28.9, 26.7; IR ν_{max} (KBr) 3233, 1701, 1621, 1471, 1338, 1221, 1057, 751 cm^{-1}; MS (EI, 70 eV) m/z 191 (M$^{+\bullet}$, 64%), 173 (66), 146 (100), 145 (83), 133 (40), 132 (53), 117 (39), 77 (30).

4.2.3.11. N-[3-(2-Oxoindolin-3-yl)propyl]acetamide (5k). Reductive cyclization of cross-coupling product **3k** (92 mg, 0.35 mmol) under the conditions specified in the general procedure gave a colorless and unstable resin. Subjection of this material to rapid flash chromatography (silica, 8:92 v/v methanol/ethyl acetate) gave oxindole **5k** (59 mg, 72%) as a clear, colorless resin, R$_f$=0.3 (Found: M$^{+\bullet}$, 232.1218. Calculated for C$_{13}$H$_{16}$N$_2$O$_2$ M$^{+\bullet}$, 232.1212). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.58 (s, 1H), 7.25–7.17 (m, 2H), 7.00 (t, J=7.5 Hz, 1H), 6.88 (d, J=8.4 Hz, 1H), 5.83 (broad s, 1H), 3.30–3.15 (m, 2H), 2.06–1.92 (m, 3H), 1.95 (s, 3H), 1.62–1.50 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 180.5, 170.5, 141.8, 129.3, 128.2, 124.2, 122.6, 110.0, 45.6, 39.4, 27.6, 25.6, 23.4; IR ν_{max} (KBr) 3268, 2937, 2465, 1704, 1622, 1554, 1471, 1370, 1336, 1295, 1222, 1104 cm^{-1}; MS (EI, 70 eV) m/z 232 (M$^{+\bullet}$, 85%), 228 (52), 185 (36), 157 (57), 145 (78), 133 (50), 173 (100).

4.2.3.12. 1-Acetyl-7-methoxy-2,3,4,9-tetrahydro-1H-pyrido[2,3-b]indole (5l). In a variation of the general procedure for reductive cyclization specified above, a magnetically stirred solution of the cross-coupling product **3i** (65 mg, 0.22 mmol) in methanol (25 mL) was cooled to 10 °C then treated with 10% Pd on C (15 mg). The resulting mixture was deoxygenated then charged with dihydrogen (1 atm) and stirred at 10 °C for 3 h. The reaction mixture was then filtered through a pad of Celite™ and the solids thus retained washed with methanol (25 mL). The combined filtrates were concentrated under reduced pressure to give a mauve-colored solid. Recrystallization (9:1 v/v i-propanol/methanol) of this material gave the title indole **5l** (51 mg, 93%) as white needles, no mp (decomposition above 129 °C), R$_f$=0.3 (8:92 v/v methanol/ethyl acetate) (Found: M$^{+\bullet}$, 244.1212. Calculated for C$_{14}$H$_{16}$N$_2$O$_2$ M$^{+\bullet}$, 244.1212). ^{1}H NMR (300 MHz, CDCl$_3$) δ 10.39 (s, 1H), 7.30 (d, J=8.7 Hz, 1H), 6.86 (d, J=2.1 Hz, 1H), 6.76 (dd, J=8.7 and 2.1 Hz, 1H), 3.84 (s, 3H), 3.83–3.78 (m, 2H), 2.75 (t, J=6.3 Hz, 2H), 2.31 (s, 3H), 2.18–2.06 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 169.1, 155.7, 132.9, 132.7, 120.2, 117.9, 109.2, 96.5, 95.1, 55.9, 47.0, 23.3, 23.2, 19.2; IR ν_{max} (KBr) 3350, 2935, 2846, 1647, 1621, 1585, 1573, 1486, 1394, 1344, 1242, 1206, 1146, 1118, 1027 cm^{-1}; MS (EI, 70 eV) m/z 244 (M$^{+\bullet}$, 100%), 229 (14), 201 (85), 187 (67), 173 (24).

4.2.3.13. N-[3-(6-Methyl-2-oxoindolin-3-yl)propyl]acetamide (5m). Reductive cyclization of cross-coupling product **3j** (105 mg, 0.38 mmol) under the conditions specified in the general procedure gave a colorless and unstable resin. Subjection of this material to rapid flash chromatography (silica, 6:94 v/v methanol/ethyl acetate) gave oxindole **5m** (57 mg, 60%) as a clear, colorless resin, R$_f$=0.3 (Found: M$^{+\bullet}$, 246.1369. Calculated for C$_{14}$H$_{18}$N$_2$O$_2$ M$^{+\bullet}$, 246.1368). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.27 (s, 1H), 7.08 (d, J=7.5 Hz, 1H), 6.84 (d, J=7.5 Hz, 1H), 6.72 (s, 1H), 5.76 (broad s, 1H), 3.46 (t, J=5.7 Hz, 1H), 3.30–3.15 (m, 2H), 2.33 (s, 3H), 2.01–1.88 (m, 2H), 1.94 (s, 3H), 1.60–1.48 (m, 2H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 180.5, 170.3, 141.5,

138.3, 126.3, 124.0, 123.2, 110.7, 45.3, 39.4, 27.7, 25.7, 23.4, 21.7; IR ν_{max} (KBr) 3284, 2927, 2243, 1707, 1631, 1552, 1460, 1370, 1338, 1295, 1245, 1142, 1122 cm^{-1}; MS (EI, 70 eV) m/z 246 (M$^{+\bullet}$, 82%), 204 (17), 187 (100), 159 (98), 146 (33).

4.3. X-ray crystallographic studies

4.3.1. Crystal data.

4.3.1.1. 3-Bromo-5-hydroxy-1-methyl-1H-pyrrol-2(5H)-one (hydroxy-precursor to 2c). C$_5$H$_6$BrNO$_2$, M=192.01, T=200 K, monoclinic, space group $P2_1$, Z=2, a=6.1963(2), b=8.4242(3), c=6.4605(2) Å, β=101.407(2)°, V=330.570(19) Å^3, D_x=1.929 g cm^{-3}, 1418 unique data (2θ_{max}=55°); R=0.0204 [for 1317 reflections with I>3$\sigma(I)$], Rw=0.0234 [I>3$\sigma(I)$], S=1.0976, Flack parameter=−0.026(12).

4.3.1.2. Compound 3d. C$_{12}$H$_{10}$N$_2$O$_5$, M=262.22, T=200 K, monoclinic, space group $P2_1/n$, Z=4, a=5.8333(1), b=11.3778(3), c=17.2688(4) Å, β=95.8027(17)°, V=1140.26(4) Å^3, D_x=1.527 g cm^{-3}, 2611 unique data (2θ_{max}=55°); R=0.038 [for 1942 reflections with I>2$\sigma(I)$], Rw=0.106 (all data), S=0.92.

4.3.1.3. Compound 4i. C$_{12}$H$_{16}$N$_2$O$_2$, M=220.27, T=200 K, monoclinic, space group $P2_1/c$, Z=4, a=5.0020(1), b=9.6361(3), c=22.8159(5) Å, β=95.6724(15)°, V=1094.34(5) Å^3, D_x=1.337 g cm^{-3}, 2494 unique data (2θ_{max}=55°); R=0.041 [for 1942 reflections with I>2$\sigma(I)$], Rw=0.099 (all data), S=0.97.

4.3.1.4. Compound 5k. C$_{13}$H$_{16}$N$_2$O$_2$, M=232.28, T=200 K, orthorhombic $P2_12_12_1$, Z=4, a=5.4192(2), b=8.4005(3), c=26.6311(9) Å, V=1212.35(7) Å^3, D_x=1.273 g cm^{-3}, 1626 unique data (2θ_{max}=55°); R=0.042 [for 1447 reflections with I>2$\sigma(I)$], Rw=0.104 (all data), S=1.05.

4.3.1.5. Compound 5l. C$_{14}$H$_{16}$N$_2$O$_2$, M=244.29, T=200 K, monoclinic, space group $P2_1/n$, Z=4, a=6.6514(4), b=16.3906(8), c=11.2602(8) Å, β=101.439(3)°, V=1203.21(13) Å^3, D_x=1.349 g cm^{-3}, 2138 unique data (2θ_{max}=50.4°); R=0.044 [for 1539 reflections with I>2$\sigma(I)$], Rw=0.114 (all data), S=0.99.

4.3.2. Structure determinations.
Images were measured on a Nonius Kappa CCD diffractometer (Mo Kα, graphite monochromator, λ 0.71073 Å) and data extracted using the DENZO package.[39] The structure solutions were by direct methods (SIR92).[40] The structures of the compounds were refined using the CRYSTALS program package.[41] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre [CCDC numbers 728950 (hydroxy-precursor to **2c**), 728951 (**3d**), 780305 (**4i**), 780306 (**5k**), and 780307 (**5l**)]. These data can be obtained free-of-charge from www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Supplementary data

Anisotropic displacement ellipsoid plots for compounds **3d**, **4i**, **5k**, **5l** and the hydroxy-precursor to **2c** are provided as well as the ^{1}H or ^{13}C NMR spectra of compounds **2a**−**f**, **3a**−**m**, **4d**, **i**, **j**, **5a**−**d**, **f**, **g**, **k**−**m** and the hydroxy-percursor to **2c**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.09.042.

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