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Qiao Yan, Emma Gin, Martin G Banwell, Anthony C Willis, and Paul D Carr

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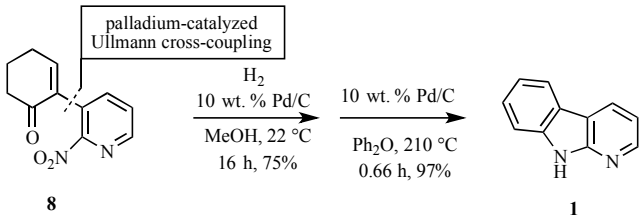
A Unified Approach to the Isomeric α-,β-,γ- and δ-Carbolines via their 6,7,8,9-Tetrahydro-counterparts

Qiao Yan, Emma Gin, Martin G. Banwell,* Anthony C. Willis and Paul D. Carr

Research School of Chemistry, Institute of Advanced Studies,

The Australian National University, Canberra, ACT 2601, Australia

Email: Martin.Banwell@anu.edu.au



A cross-coupling/reductive cyclisation protocol has been employed in a unified approach to all four carbolines. So, for example, the 2-nitropyridine **8**, which is readily prepared through an efficient palladium-catalyzed Ullmann cross-coupling reaction, is reductively cyclized under conventional conditions to give 6,7,8,9-tetrahydro-α-carboline that is itself readily aromatized to give α-carboline (**1**).

INTRODUCTION

The isomeric α-,β-,γ- and δ-carbolines (**1**-**4**, respectively in Figure 1) are important heterocyclic rings systems.[1] All are encountered, albeit to varying extents, as key structural motifs in natural products. They also feature in a wide range of medicinally relevant compounds. The utility of various of their derivatives in materials science is a further focus of current studies.[2] The α-carboline framework (**1**) is encountered in a limited number of naturally occurring anti-cancer agents and in the neuro-protective alkaloid mescengricin.[3] On the other hand, synthetically derived α-carbolines have shown anxiolytic, anti-inflammatory, CNS-stimulating and kinase inhibitory properties.[4]

β-Carboline (**2**), itself a natural product isolated from both plants and micro-organisms, is the most well known of the four systems and represents a key substructure associated with, for example, the eudistomine and manzamine classes of biologically active marine alkaloid.[5] Many medicinal agents embodying this heterocyclic framework have been identified.[5,6] Derivatives of γ-carboline (**3**) have been explored extensively as anti-cancer and anti-Alzheimer agents[7] while those associated with δ-carboline (**4**) have been studied, inter alia, for their anti-bacterial and anti-tumor properties.[1b,8] δ-Carboline-containing alkaloids have been isolated from, for example, various West and Central African plants that are prized as sources of traditional medicines for treating malaria and certain infectious diseases.[1b]

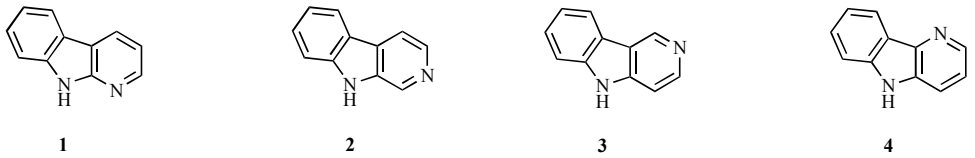


Figure 1: The Isomeric α-,β-,γ- and δ-Carbolines (**1**-**4**)

A multitude of methods has been established for the synthesis of the carbolines, including classical ones involving Graebe-Ullmann, Fischer indolization, Bischler-Napieralski and Pictet-Spengler reactions.[9,10] Variations on the Cadogan syntheses of carbazoles are also known,[11] as are routes involving the annulation of pyridines onto indoles,[9,10,12] including through Diels-Alder and electrocyclization processes. Generally speaking, though, "customized" approaches are required for the assembly of each of the α-,β-,γ- and δ-carboline frameworks and thus prompting the search for more general routes to them.[13] There has been modest success in this regard with the most effective route involving the cyclization of anilino-pyridines.[13g-j] Recently, Driver[13i] and Ray[13j] have each reported variations on such methods that allow access to three of the four frameworks. It is against this background that we now detail a distinct, operationally simple and likely flexible route to all four of the isomeric carbolines and highlight the utility of this through the synthesis of the simple natural product harman (**5**, Figure 2), a compound that displays anti-HIV and anti-bacterial properties.[14]

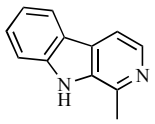


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Figure 2: The β-Carboline Alkaloid Harman (**5**)

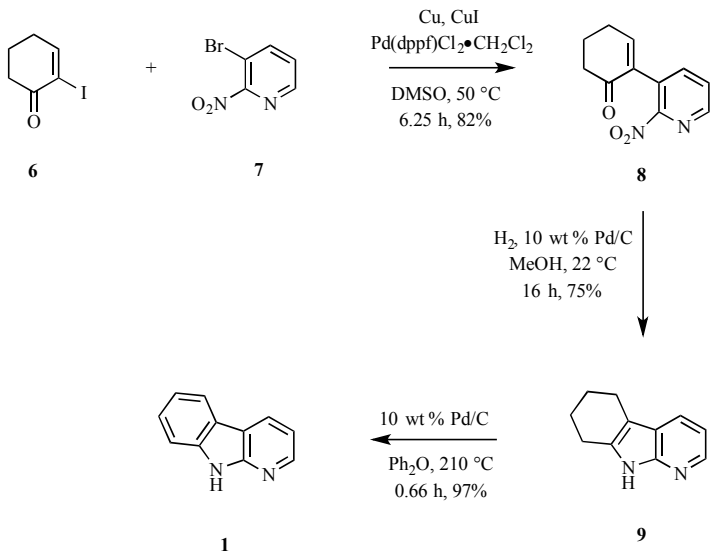
RESULTS AND DISCUSSION

The pivotal steps associated with the unified approach to the carbolines reported here are the palladium-catalyzed Ullmann cross-coupling[15] of 2-iodocyclohex-2-en-1-one[16] with the relevant halogenated nitropyridine and the reductive cyclization of the ensuing 2-pyridyl-cyclohex-2-en-1-one to give the corresponding 6,7,8,9-tetrahydrocarboline. Oxidation of these tetrahydro-compounds to their fully aromatic counterparts (viz. the carbolines) was readily accomplished using 10 wt % palladium on carbon. This sequence mirrors that used in in our recently reported syntheses of various carbazole-based natural products including glycoborine, glycozoline, clausazoline K, mukonine and karapinchamine A.[17]

The synthesis of α-carboline (**1**), as shown in Scheme 1, is illustrative and starts with the palladium-catalyzed Ullmann cross-coupling of the readily prepared[17] 2-iodocyclohex-2-en-1-one (**6**) with commercially available 3-bromo-2-nitropyridine (**7**) and thus affording the 2-pyridyl-cyclohex-2-en-1-one **8** in 82% yield. In order to reduce the extent of homo-coupling of the pyridine in this reaction, the iodo-enone **6** was treated with a combination of copper metal, copper(I) iodide and $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ in DMSO at 50 °C for 0.75 h prior the addition of compound **7**. Presumably this allows cupration of compound **6** to take place prior to a palladium-catalyzed cross-coupling reaction with halide **7** and so increasing the yields of product **8**. The reductive cyclization of compound **8** was effected using hydrogen in the presence of catalytic amounts of 10 wt. % palladium on carbon (Pd/C) in methanol at room temperature for 16 h and this produced the 6,7,8,9-tetrahydrocarboline **9**[18] in 75% yield. In our hands, the oxidation[19] of compound **9** to α-

carboline (**1**)[4a] was best carried out by exposing the former system to an equivalent mass of 10 wt % palladium on carbon in diphenyl ether at 210 °C for 0.66 h. By such means target **1** was obtained in 97% yield and all of the spectral data acquired on this material were in complete accord with the assigned structure and matched those reported in the literature. A single-crystal X-ray analysis was carried out on compound **1** and details are provided in the Experimental Section and the Supporting Information (SI).

Scheme 1: The Synthesis of α-Carboline (**1**)



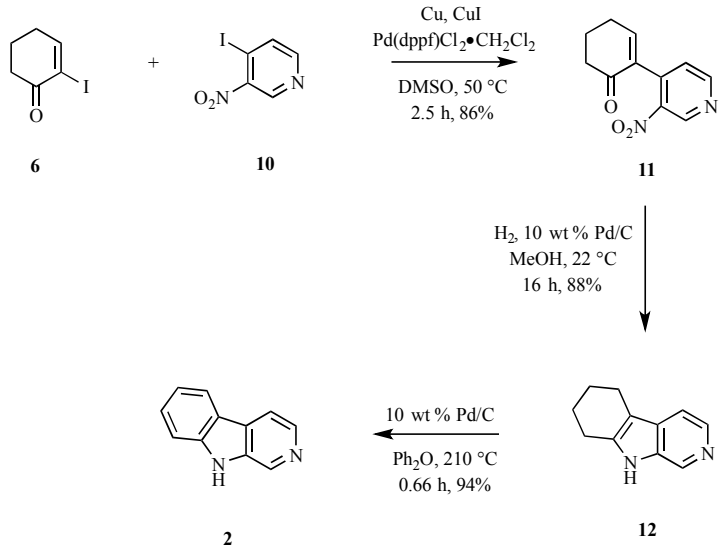
6 **7** **8** **9** **1**

Given the use of 10 wt % palladium on carbon in both the second and third steps of the reaction sequence these could, in principle, be "telescoped" so establish a one-pot process. To date, however, we have not been able to identify conditions that allow for this to be conducted in both an operationally superior way and with better outcomes.

The synthesis of β-carboline (**2**) (Scheme 2) required 4-iodo-3-nitropyridine (**10**)[20] as a coupling partner and this was readily obtained by reacting the commercially available chloro-analogue with sodium iodide in acetonitrile (see Experimental Section for details). Cross-coupling of compounds **6** and **10** proceeded smoothly under essentially the same conditions as employed for the conversion **6** + **7** → **8** and provided the anticipated

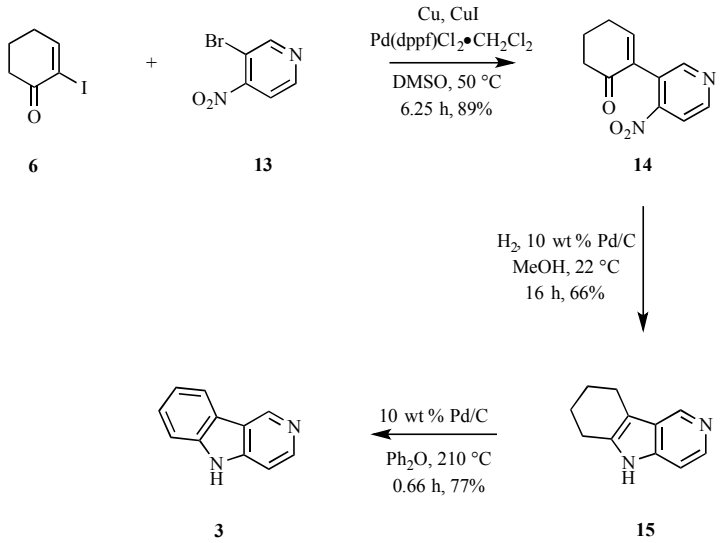
coupling product **11** in 86% yield. Reductive cyclization of compound **11** proceeded uneventfully under the previously established conditions and product **12**[21] (88%) was readily oxidized to target **2** (94%) on brief exposure to an equal mass of 10 wt % palladium on carbon in hot diphenyl ether. Once again, all the spectral data acquired on β-carboline (**2**) matched those reported[22] previously. The structure of compound **2** was also confirmed by single crystal X-ray analysis.

Scheme 2: The Synthesis of β-Carboline (**2**)



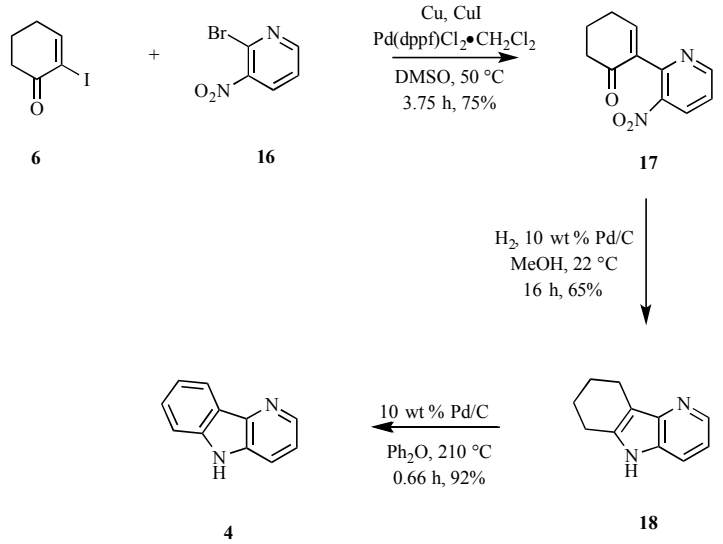
The analogous synthesis of γ-carboline (**3**) is shown in Scheme 3 and in this instance the required pyridine, **13**, was a commercially available material. Reductive cyclization of the cross-coupling product **14** (89%) produced from compound **6** and **13** proceeded as anticipated to give the tetrahydrocarboline **15**,[23] albeit in just 66% yield. Similarly, the oxidation of this last compound under the previously employed conditions was less efficient than observed in the two previous cases with compound **3**[24] being obtained in 77% yield. Once again, full characterization of this product was undertaken including through a single-crystal X-ray analysis.

Scheme 3: The Synthesis of γ-Carboline (**3**)



The establishment of a unified approach to all the carbolines followed from the successful synthesis of δ-carboline (**4**) by the pathway shown in Scheme 4.

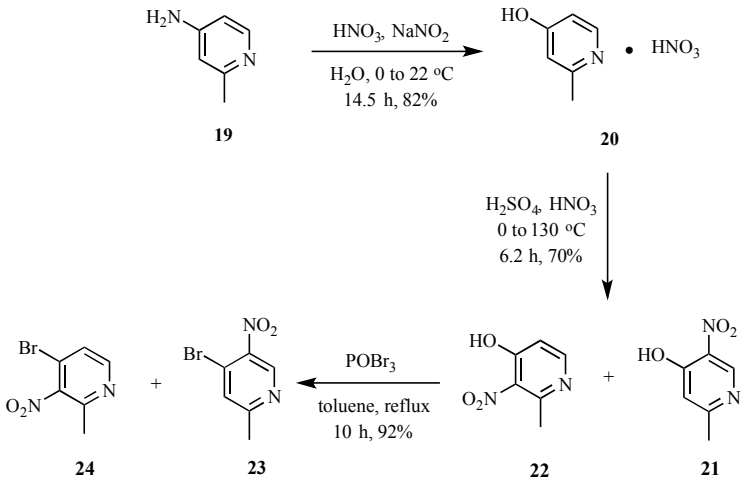
Scheme 4: The Synthesis of δ-Carboline (**4**)



So, as before, the palladium-catalyzed Ullmann cross-coupling of iodo-enone **6** with the required and commercially available pyridine **16** proceeded uneventfully to give product **17** (75%) that was reductively cyclized in the usual manner to afford the tetrahydrocarboline **18**[25] (65%). Oxidation of this last compound using an equal mass of 10 wt % palladium on carbon in hot diphenyl ether then gave δ-carboline (**4**)[26] (92%) that was subject to the usual range of spectroscopic analyses, including a single-crystal X-ray study.

In order to test the capacities of the abovementioned protocols to deliver substituted carbolines, the β-carboline-based natural product harman (**5**, Figure 2) was targeted for synthesis. The required pyridine was prepared by the route shown in Scheme 5. Thus, commercially available 2-methylpyridin-4-amine (**19**) was subjected to a Sandmeyer reaction using water as the nucleophile and so providing the previously reported nitric acid salt[27] **20** of 2-methylpyridin-4-ol.

Scheme 5: Route to the Tri-substituted Pyridine **24** Required for the S□□□□□□□□□□□□the β-Carboline Alkaloid □□□□□□ (**5**)

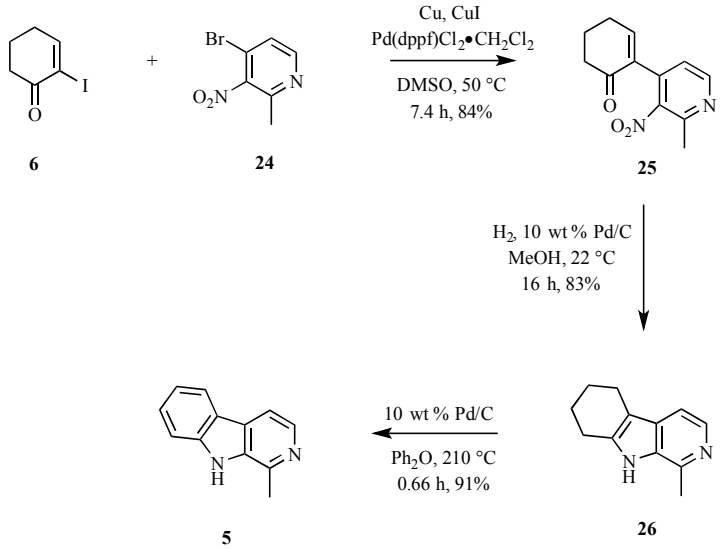


Aromatic nitration of this last compound could only be achieved under rather forcing conditions and so providing a 1:3 and inseparable mixture of pyridines **21** and **22** (70% combined yield). Accordingly, this mixture was treated with $POBr_3$ in refluxing toluene and thereby affording what is presumed to be the corresponding mixture of bromides **23**

and **24** (92% combined yield). These regioisomers could only be separated by HPLC techniques but sufficient quantities of the pure form of the latter could be accumulated by such means. The former product (presumed to be compound **23**) was not purified or subject to any spectroscopic characterization.

With compound **24** in hand, the synthesis of harman (**5**) was completed by the now standard pathway shown in Scheme 6. Thus, palladium-catalyzed Ullmann cross-coupling of iodo-enone **6** with pyridine **24** delivered the required product **25** in 84% yield. Reductive cyclization of the last compound under the usual conditions gave the tetrahydroharman **26**[28] (83%) that could be oxidized to the natural product **5**[14,29] (91%) on treatment with an equal mass of 10 wt % palladium on carbon in hot diphenyl ether. Once again, all the spectral data, including a single-crystal X-ray analysis, acquired on compound **5** confirmed the assigned structure and appropriate comparisons with those reported[14] for the natural product were entirely favorable.

Scheme 6: Completion of the Synthesis of H□□man (**5**)



CONCLUSIONS

The reaction sequences reported here should allow for the rational/logical design of pathways to a wide range of α-,β-,γ- and δ-carbolines. This is all the more so given the increasingly ready availability of a wide range of poly-substituted pyridines[30] and 2-iodocyclohex-2-en-1-ones. For similar reasons, the protocols defined here should allow for ready access to a wide range of azaindoles, compounds of considerable interest from a medicinal chemistry perspective.[31] Studies exploiting such possibilities will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures

Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at 18 °C in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{1}H NMR data are recorded as follows: chemical shift (δ) [multiplicity, coupling constant(s) *J* (Hz), relative integral] where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet or combinations of the above. In relevant cases, the signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. Samples were analyzed by infrared spectroscopy (ν_{max}) as thin films on KBr plates. Low- and high-resolution electron impact (EI) mass spectra were recorded on a double focusing, triple sector machine. Low- and high-resolution ESI mass spectra were recorded on a triple-quadrupole mass spectrometer operating in positive ion mode. Melting points are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.)/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), and *p*-anisaldehyde or vanillin/sulfuric acid (conc.)/ethanol (15 g :

2.5 mL : 250 mL). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[32] with silica gel 60 (40-63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. The melting points of solids purified by such means were recorded directly (ie after they had crystallized from the concentrated chromatographic fractions). Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and were used as supplied. The copper powder used in the palladium-catalyzed Ullmann cross-coupling reactions had a particle size of <75 μm. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al*.[33] Where necessary, reactions were performed under a nitrogen atmosphere by subjecting the relevant solution to reduced pressure for several minutes and then admitting nitrogen. This process was repeated three times.

Specific Chemical Transformations

2-(2-Nitropyridin-3-yl)cyclohex-2-en-1-one (8). A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**)[16] (2.63 g, 11.82 mmol), copper powder (1.50 g, 23.65 mmol), CuI (1.69 g, 8.87 mmol) and $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (483 mg, 0.59 mmol) in degassed DMSO (118 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time a solution of commercially available 3-bromo-2-nitropyridine (**7**) (1.20 g, 5.91 mmol) in degassed DMSO (30 mL) was added to the reaction mixture over 1.5 h. After a further 4 h the reaction mixture was cooled, quenched with water (30 mL) then diluted with ethyl acetate (50 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 50 mL) and the separated organic phase associated with the combined filtrates washed with water (2 × 100 mL) then brine (2 × 100 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:3:11 v/v/v acetone/dichloromethane/40-60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/40-60 petroleum ether), compound **8** (1.06 g, 82%) as a light-brown solid, mp = 115-116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (dd, J = 4.7 and 1.7 Hz, 1H), 7.74 (dd, J = 7.6 and 1.7 Hz, 1H), 7.60 (dd, J = 7.6 and 4.7 Hz, 1H), 7.08 (t, J = 4.2 Hz, 1H), 2.60 (m, 4H), 2.15 (m, 2H); ^{13}C NMR

(100 MHz, $CDCl_3$) δ 196.0, 157.0, 148.5, 147.8, 141.7, 137.2, 128.1, 126.7, 38.2, 26.5, 22.6; IR ν_{max} 2950, 1679, 1540, 1405, 1366, 975, 864, 810, 707 cm^{-1}; MS (ESI, +ve) *m/z* 241 [$(M+Na)^+$, 100%]; HRMS *m/z* $(M+Na)^+$ calcd for $C_{11}H_{10}N_2NaO_3$ 241.0589, found 241.0591.

6,7,8,9-Tetrahydro-5*H*-pyrido[2,3-*b*]indole (9). A magnetically stirred mixture of compound **8** (30 mg, 0.14 mmol) and 10 wt % Pd/C (12 mg) in degassed methanol (7 mL) was maintained under an atmosphere of hydrogen for 16 h at 22 °C then filtered and the solids thus retained washed with methanol (20 mL). The combined filtrates were concentrated under reduced pressure and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution). Concentration of the appropriate fractions (R_f = 0.7 in ethyl acetate) then gave compound **9**[18] (18 mg, 75%) as a white, crystalline solid, mp = 155-156 °C (lit.[18] mp = 155-156 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.65 (m, 1H), 8.19 (d, *J* = 4.3 Hz, 1H), 7.75 (dd, *J* = 7.7 and 1.3 Hz, 1H), 7.01 (dd, *J* = 7.7 and 4.3 Hz, 1H), 2.84 (t, *J* = 6.0 Hz, 2H), 2.70 (m, 2H), 1.98-1.86 (complex m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 140.8, 135.4, 125.7, 120.8, 115.1, 108.4, 23.3(4), 23.2(8), 23.1, 20.8; IR ν_{max} 3149, 3075, 2921, 2846, 1587, 1418, 1289, 786, 765, 677 cm^{-1}; MS (ESI, +ve) *m/z* 173 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1078.

9*H*-Pyrido[2,3-*b*]indole (α-carboline, 1). A magnetically stirred mixture of compound **9** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature, filtered (through filter paper) and the solids so retained washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 0:1 → 1:4 v/v ethyl acetate/40-60 petroleum ether gradient elution). Concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/40-60 petroleum ether) gave compound **1**[4a] (19 mg, 97%) as a white, crystalline solid, mp = 200-202 °C (lit.[4a] mp = 215-217 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (dd, *J* = 7.7 and 1.5 Hz, 1H), 8.34 (dd, *J* = 4.9 and 1.2 Hz, 1H), 8.09 (d, *J* = 7.9 Hz, 1H), 7.52 (d, *J* = 8.1 Hz, 1H), 7.48-7.44 (complex m, 1H), 7.26-7.19 (complex m, 2H) (signal due to N-H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 152.9, 146.1, 140.6, 129.9,

128.0, 122.0, 121.9, 121.0, 118.0, 116.1, 112.3; IR ν_{max} 3048, 2984, 2906, 1600, 1587, 1572, 1455, 1411, 1274, 998, 767, 736 cm^{-1}; MS (ESI, +ve) *m/z* 169 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_9N_2$ 169.0766, found 169.0768.

4-Iodo-3-nitropyridine (10). A magnetically stirred solution of commercially available 4-chloro-3-nitropyridine (1.00 g, 6.31 mmol) in acetonitrile (126 mL) maintained at ambient temperatures was treated with sodium iodide (17.02 g, 113.55 mmol). The ensuing mixture was heated under reflux for 2 h then cooled to 22 °C and diluted with ethyl acetate (200 mL). The resulting solution was washed with Na_2CO_3 (1 × 100 mL of a saturated aqueous solution), Na_2SO_3 (1 × 50 mL of a saturated solution), water (1 × 200 mL) and brine (1 × 100 mL) before being dried (Na_2SO_4,), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.5 twice in 1:5 v/v ethyl acetate/40-60 petroleum ether), 4-iodo-3-nitropyridine **10**[20] (1.46 g, 92%) as a light-yellow solid, mp = 80-82 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (broad s, 1H), 8.35 (d, *J* = 5.1 Hz, 1H), 8.03 (d, *J* = 5.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.5, 149.6, 145.9, 136.5, 98.5; IR ν_{max} 1572, 1540, 1521, 1357, 1223, 1058, 835, 657 cm^{-1}; MS (EI, 70 ev) *m/z* 250 ($M^{+\bullet}$, 100%), 204 (70), 177 (60); HRMS *m/z* $M^{+\bullet}$ calcd for $C_5H_3{}^{127}IN_2O_2$ 249.9239, found 249.9236.

2-(3-Nitropyridin-4-yl)cyclohex-2-en-1-one (11). A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (888 mg, 4.00 mmol), copper powder (508 mg, 8.00 mmol), CuI (571 mg, 3.00 mmol) and $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (163 mg, 0.20 mmol) in degassed DMSO (40 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time a solution of compound **10** (500 mg, 2.00 mmol) in degassed DMSO (10 mL) was added to the reaction mixture over 1 h. After a further 0.75 h the reaction mixture was cooled, quenched with water (10 mL) then diluted with ethyl acetate (15 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 15 mL) and the separated organic phase associated with the combined filtrates washed with water (2 × 30 mL) then brine (2 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a brown oil. This was subjected to flash column chromatography

(silica, 1:3:10 v/v/v acetone/dichloromethane/40-60 petroleum ether elution) and gave, after concentration of the appropriate fractions [R_f = 0.1(5) in 1:1 v/v ethyl acetate/40-60 petroleum ether], compound **11** (374 mg, 86%) as a light-yellow solid, mp = 105-107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (s, 1H), 8.78 (d, *J* = 4.9 Hz, 1H), 7.22 (d, *J* = 4.9 Hz, 1H), 7.13 (t, *J* = 4.2 Hz, 1H), 2.63-2.57 (complex m, 4H), 2.19-2.13 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.5, 153.9, 148.7, 145.3, 145.0, 140.0, 137.5, 125.6, 38.2, 26.5, 22.5; IR ν_{max} 2948, 1679, 1600, 1542, 1523, 1357, 1217, 1159, 1121, 851, 716 cm^{-1}; MS (ESI, +ve) *m/z* 219 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_{11}N_2O_3$ 219.0770, found 219.0768.

6,7,8,9-Tetrahydro-5*H*-pyrido[3,4-*b*]indole (12). A magnetically stirred mixture of compound **11** (190 mg, 0.87 mmol) and 10 wt % Pd/C (76 mg) in degassed methanol (44 mL) was maintained under an atmosphere of hydrogen for 16 h at 22 °C then filtered and the solids thus retained washed with methanol (100 mL). The combined filtrates were concentrated under reduced pressure and the white solid thus obtained subjected to flash column chromatography (silica, 1:4 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions [R_f = 0.3(5) in 1:1 v/v methanol/dichloromethane], compound **12**[21] (132 mg, 88%) as a white, crystalline solid, mp = 163-164 °C (lit.[21] mp = 199-200 °C). ^{1}H NMR (700 MHz, CD_3OD) δ 8.49 (broad s, 1H), 7.97 (broad s, 1H), 7.36 (d, *J* = 4.9 Hz, 1H), 2.77 (t, *J* = 6.0 Hz, 2H), 2.65 (t, *J* = 6.0 Hz, 2H), 1.92-1.83 (complex m, 4H) (signal due to N-H group proton not observed); ^{13}C NMR (175 MHz, CD_3OD) δ 142.2, 136.9, 134.5, 134.2, 132.6, 113.7, 110.4, 24.2(2), 24.2(0), 24.0, 21.6; IR ν_{max} 3143, 3040, 2926, 2850, 2839, 1569, 1471, 1442, 1359, 1142, 1030, 808 cm^{-1}; MS (ESI, +ve) *m/z* 173 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1078.

9*H*-Pyrido[3,4-*b*]indole (β-carboline, 2). A magnetically stirred mixture of compound **12** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature, filtered (through filter paper) and the solids so retained washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 0:1 → 1:1 v/v ethyl acetate/40-60 petroleum ether gradient elution) to give, after

concentration of the appropriate fractions (R_f = 0.5 in 1:2 v/v methanol/dichloromethane), compound **2**[22] (18 mg, 94%) as a white, crystalline solid, mp = 210-211 °C (lit.[22] mp = 199-201 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 8.79 (s, 1H), 8.27 (d, *J* = 5.3 Hz, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 8.08 (d, *J* = 5.3 Hz, 1H), 7.56 (m, 2H), 7.29-7.23 (complex m, 1H) (signal due to N-H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 142.7, 138.4, 137.8, 134.1, 130.4, 129.7, 122.7, 122.2, 120.8, 116.1, 112.8; IR ν_{max} 3134, 3052, 2963, 2754, 1628, 1449, 1331, 1245, 746, 732 cm^{-1}; MS (ESI, +ve) *m/z* 191 [$(M+Na)^+$, 70%], 169 [$(M+H)^+$, 100]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_9N_2$: 169.0766, found: 169.0766.

2-(4-Nitropyridin-3-yl)cyclohex-2-en-1-one (14). A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (2.19 g, 9.85 mmol), copper powder (1.26 g, 19.70 mmol), CuI (1.41 g, 7.39 mmol) and $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (400 mg, 0.49 mmol) in degassed DMSO (98 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time a solution of compound **13** (1.00 g, 4.93 mmol) in degassed DMSO (25 mL) was added to the reaction mixture over 1.5 h. After a further 4 h the reaction mixture was cooled, quenched with water (20 mL) then diluted with ethyl acetate (1 × 30 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 30 mL) and the separated organic phase associated with the combined filtrates washed with water (2 × 60 mL) then brine (2 × 60 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:3:11 v/v/v acetone/dichloromethane/40-60 petroleum ether elution) gave, after concentration of the appropriate fractions (R_f = 0.2 in 1:3:6 v/v/v acetone/dichloromethane/40-60 petroleum ether), compound **14** (956 mg, 89%) as a light-brown solid, mp = 94-95 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.82 (d, *J* = 5.3 Hz, 1H), 8.61 (s, 1H), 7.81 (d, *J* = 5.3 Hz, 1H), 7.17 (t, *J* = 4.2 Hz, 1H), 2.66-2.58 (complex m, 4H), 2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 154.1, 152.8, 151.4, 148.6, 136.0, 125.4, 116.6, 38.2, 26.5, 22.6; IR ν_{max} 2945, 1677, 1557, 1529, 1401, 1358, 1222, 1159, 839, 705, 675 cm^{-1}; MS (ESI, +ve) *m/z* 241 [$(M+Na)^+$, 100%], 219 [$(M+H)^+$, 15]; HRMS *m/z* $(M+Na)^+$ calcd for $C_{11}H_{10}N_2NaO_3$ 241.0589, found 241.0589.

6,7,8,9-Tetrahydro-5*H*-pyrido[4,3-*b*]indole (15). A magnetically stirred mixture of compound **14** (50 mg, 0.23 mmol) and 10 wt % Pd/C (20 mg) in degassed methanol (12 mL) was maintained under an atmosphere of hydrogen at 22 °C for 16 h then filtered and the solids so retained washed with methanol (25 mL). The combined filtrates were concentrated under reduced pressure and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions [R_f = 0.3(5) in 1:1 v/v methanol/dichloromethane], compound **15**[23] (26 mg, 66%) as a white, crystalline solid, mp = 223-224 °C (lit.[23] mp = 269-271 °C). ^{1}H NMR (700 MHz, CD_3OD) δ 8.58 (broad s, 1H), 8.05 (broad s, 1H), 7.28 (d, J = 5.3 Hz, 1H), 2.74 (m, 4H), 1.95-1.87 (complex m, 4H) (signal due to N-H group proton not observed); ^{13}C NMR (175 MHz, CD_3OD) δ 141.6, 139.9, 139.1, 138.1, 126.2, 110.3, 107.5, 24.2, 24.1, 23.9, 21.6; IR ν_{max} 2926, 2839, 2693, 1625, 1466, 1294, 1169, 1142, 989, 802, 684 cm^{-1}; MS (ESI, +ve) *m/z* 173 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1078.

5*H*-Pyrido[4,3-*b*]indole (γ-carboline, 3). A magnetically stirred mixture of compound **15** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature, filtered (through filter paper) and the solids thus retained washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 40-60 petroleum ether elution → 1:3 v/v methanol/dichloromethane gradient elution) to give, after concentration of the appropriate fractions [R_f = 0.2(5) in 1:3 v/v methanol/dichloromethane], compound **3**[24] (15 mg, 77%) as a white, crystalline solid, mp = 223-225 °C (lit.[24] mp = 225-227 °C). ^{1}H NMR [700 MHz, $(CD_3)_2SO$] δ 11.69 (s, 1H), 9.33 (s, 1H), 8.43 (s, 1H), 8.22 (d, J = 7.8 Hz, 1H), 7.56 (m, 1H), 7.47 (m, 2H), 7.26 (t, J = 7.4 Hz, 1H); ^{13}C NMR [175 MHz, $(CD_3)_2SO$] δ 144.5, 143.5, 142.7, 139.5, 126.5, 120.7, 120.6, 119.9, 119.4, 111.4, 106.4; ^{1}H NMR (700 MHz, CD_3OD) δ 9.20 (s, 1H), 8.36 (s, 1H), 8.16 (d, J = 7.8 Hz, 1H), 7.53 (d, J = 8.1 Hz, 1H), 7.49-7.46 (m, 2H), 7.28 (t, J = 7.4 Hz, 1H) (signal due to N-H group proton not observed); ^{13}C NMR (175 MHz, CD_3OD) δ 145.8, 144.4, 142.7, 141.5, 128.2, 122.4, 121.6(4), 121.6(0), 121.5, 112.4, 107.6; IR ν_{max} 3062, 2956, 2806, 2679, 1607, 1582,

1467, 1239, 999, 744 cm^{-1}; MS (ESI, +ve) *m/z* 169 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_9N_2$ 169.0766, found 169.0766.

2-(3-Nitropyridin-2-yl)cyclohex-2-en-1-one (17). A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (1.09 g, 4.93 mmol), copper powder (630 mg, 9.85 mmol), CuI (704 mg, 3.69 mmol) and $Pd(dppf)Cl_2 \bullet CH_2Cl_2$ (200 mg, 0.25 mmol) in degassed DMSO (50 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time a solution of compound **16** (500 mg, 4.93 mmol) in degassed DMSO (12 mL) was added to the reaction mixture over 1 h. After a further 2 h the reaction mixture was cooled, quenched with water (10 mL), diluted with ethyl acetate (15 mL) then filtered through a pad comprised of a mixture of diatomaceous earth and silica gel. The solids thus retained were rinsed with ethyl acetate (2 × 15 mL) and the separated organic phase associated with the combined filtrates washed with water (2 × 30 mL) then brine (2 × 30 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 1:3:12 v/v/v acetone/dichloromethane/40-60 petroleum ether elution) gave, after concentration of the appropriate fractions [R_f = 0.1(5) in 1:3:6 v/v/v acetone/dichloromethane/40-60 petroleum ether], compound **17** (403 mg, 75%) as a light-brown solid, mp = 104-106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.7 and 1.3 Hz, 1H), 8.29 (dd, *J* = 8.2 and 1.3 Hz, 1H), 7.49-7.43 (complex m, 2H), 2.65 (m, 2H), 2.58 (m, 2H), 2.20-2.13 (complex m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 152.9, 151.0, 149.4, 146.1, 139.2, 132.2, 123.4, 38.3, 26.6, 22.5; IR ν_{max} 2947, 1677, 1593, 1561, 1526, 1451, 1357, 765 cm^{-1}; MS (ESI, +ve) *m/z* 241 [$(M+Na)^+$, 100%], 219 [$(M+H)^+$, 15]; HRMS *m/z* $(M+Na)^+$ calcd for $C_{11}H_{10}N_2NaO_3$ 241.0589, found 241.0589.

6,7,8,9-Tetrahydro-5*H*-pyrido[3,2-*b*]indole (18). A magnetically stirred mixture of compound **17** (213 mg, 0.98 mmol) and 10 wt % Pd/C (86 mg) in degassed methanol (49 mL) was maintained under an atmosphere of hydrogen for 16 h at 22 °C then filtered and the solids so retained washed with methanol (100 mL). The combined filtrates were concentrated under reduced pressure and the white solid thus obtained subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/40-60 petroleum ether), compound **18**[25] (109 mg, 65%) as a white, crystalline solid, mp =

183-185 °C (lit.[25] mp = 200-202 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.86 (broad s, 1H), 8.38 (d, J = 4.3 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.00 (m, 1H), 2.84 (m, 2H), 2.76 (m, 2H), 1.95-1.84 (complex m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.6, 141.9, 139.2, 129.1, 117.4, 115.8, 110.8, 23.8, 23.2, 23.1, 20.1; IR ν_{max} 3136, 3083, 3053, 2929, 2847, 1483, 1414, 1362, 1286, 1144, 904, 767, 729 cm^{-1}; MS (ESI, +ve) *m/z* 173 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_{13}N_2$ 173.1079, found 173.1080.

5*H*-Pyrido[3,2-*b*]indole (δ-carboline, 4). A magnetically stirred mixture of compound **18** (20 mg, 0.12 mmol) and 10 wt % Pd/C (20 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature, filtered (through filter paper) and the solids thus retained washed with ethyl acetate (2 × 15 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 0:1 → 1:4 v/v ethyl acetate/40-60 petroleum ether gradient elution) to give, after concentration of the appropriate fractions [R_f = 0.2(5) in 1:1 v/v ethyl acetate/40-60 petroleum ether], compound **4**[26] (18 mg, 92%) as a white, crystalline solid, mp = 211-212 °C (lit.[26] mp = 206-207 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 8.39 (dd, J = 4.8 and 1.4 Hz, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.88 (d, J = 8.2 Hz, 1H), 7.52 (m, 2H), 7.40 (m, 1H), 7.26 (m, 1H) (signal due to N-H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 142.4, 142.3, 141.5, 135.1, 129.0, 122.4, 121.4, 121.3, 120.8, 119.9, 112.6; IR ν_{max} 3057, 2979, 2919, 2848, 2760, 1629, 1460, 1396, 1320, 1223, 741, 724 cm^{-1}; MS (ESI, +ve) *m/z* 169 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{11}H_9N_2$ 169.0766, found 169.0766.

2-Methylpyridin-4-ol Nitrate (20). Commercially available 2-methylpyridin-4-amine (8.00 g, 73.98 mmol) was dissolved in a mixture of concentrated HNO_3 (44.1 mL) and H_2O (59.4 mL) and the resulting solution was cooled, with vigorous magnetic stirring, to 0 °C. A chilled solution of $NaNO_2$ (7.40 g, 107.25 mmol) in water (21.7 mL) was then added dropwise over 0.5 h and the mixture thus formed stirred at 0 °C for 4 h before being allowed to warm to 22 °C and then stirred at this temperature for another 10 h then re-cooled to 0 °C. The resulting solid was removed by filtration, the filtrate concentrated to about one-third of its original volume then cooled to 0 °C and a second crop of solid removed by filtration. The combined solids were then air-dried to give the nitric acid

salt[27] of compound **20** (10.49 g, 82%) as a white, crystalline solid, mp = 162-164 °C (lit.[27] mp = 164-165 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 8.34 (d, J = 6.5 Hz, 1H), 7.11-7.09 (complex m, 2H), 2.62 (s, 3H) (signals due to O-H and N-H group protons not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 173.4, 156.0, 143.2, 114.7, 113.0, 19.3; IR ν_{max} 3098, 2919, 2617, 1627, 1501, 1305, 1216, 830 cm^{-1}; MS (ESI, +ve) *m/z* 110 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for C_6H_8NO 110.0606, found 110.0608.

2-Methyl-4-nitropyridin-3-ol (21) and 2-Methyl-3-nitropyridin-4-ol (22). A magnetically stirred solution of salt **20** (3.00 g, 17.43 mmol) in concentrated H_2SO_4 (6.9 mL) was cooled to 0 °C then treated, dropwise, with fuming HNO_3 (6.9 mL). The ensuing mixture reaction was stirred at 0 °C for 0.17 h, heated at 130 °C for 20 h then cooled to 0 °C and carefully neutralized with NaOH (25 mL of a 10 M aqueous solution). FC-grade silica gel (20 g) was added to the ensuing mixture and this was then concentrated under reduced pressure. The free-flowing solid thus obtained was subjected to flash column chromatography (silica, 1:19 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.6 in 1:1 v/v methanol/dichloromethane), a 1:3 mixture of 2-methyl-5-nitropyridin-4-ol (**21**) and 2-methyl-3-nitropyridin-4-ol (**22**) (1.88 g, 70% combined yield) as a white crystalline solid, mp = 148-150 °C. ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ (major product) 12.17 (broad s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 6.33 (d, J = 7.5 Hz, 1H), 2.29 (s, 3H); ^{13}C NMR [100 MHz, $(CD_3)_2SO$] δ (for mixture) 168.2, 151.2, 148.1, 143.5, 142.2, 139.4, 137.8, 137.3, 120.7, 118.0, 18.2, 15.3; IR ν_{max} 3037, 2796, 1612, 1557, 1502, 1356, 1222, 836, 768 cm^{-1}; MS (ESI, +ve) *m/z* 331 (42%), 177 [$(M+Na)^+$, 100], 155 [$(M+H)^+$, 10]; HRMS (ESI) *m/z* $(M+Na)^+$ calcd for $C_6H_6N_2NaO_3$ 177.0276, found 177.0278.

4-Bromo-2-methyl-3-nitropyridine (24). A magnetically stirred 1:3 mixture of 2-methyl-5-nitropyridin-4-ol (**21**) and 2-methyl-3-nitropyridin-4-ol (**22**) (1.12 g, 7.27 mmol), obtained as described immediately above, in toluene (8.0 mL) and maintained under a nitrogen atmosphere was treated with $POBr_3$ (2.19 g, 7.63 mmol). The ensuing mixture was heated under reflux for 10 h then cooled to 0 °C before being quenched with NaOH (30 mL of a 1 M aqueous solution). The ensuing mixture was extracted with ethyl acetate (1 × 150 mL) and washed with H_2O (2 × 150 mL). The separated organic phase was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The solid so

obtained was subjected to flash column chromatography (silica, 1:3:20 v/v/v acetone/dichloromethane/40-60 petroleum ether elution) to give, after concentration of the appropriate fractions (R_f = 0.4 in 1:3:6 v/v/v acetone/dichloromethane/40-60 petroleum ether), a 1:3 mixture of what is presumed to be 4-bromo-2-methyl-5-nitropyridine (**23**) and 4-bromo-2-methyl-3-nitropyridine (**24**) (1.46 g, 92% combined) as a white solid. A ca. 800 mg portion of this material was subjected to semi-preparative HPLC (silica, normal phase, 17:83 v/v ethyl acetate/*n*-hexane elution, 600 mL/h) to afford, after concentration of the relevant fractions (R_t = 0.45 h), a pure sample of 4-bromo-2-methyl-3-nitropyridine (**24**) (ca. 350 mg) as a white, crystalline solid, mp = 78-79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.40 (d, J = 5.3 Hz, 1H), 7.50 (d, J = 5.3 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.8, 150.5, 148.5, 126.3, 123.7, 20.9; IR ν_{max} 3072, 1575, 1534, 1365, 1266, 846, 837, 714 cm^{-1}; MS (EI, 70 eV) *m/z* 218 and 216 ($M^{+\bullet}$, both 90%), 201 and 199 (both 70), 172 and 170 (both 95), 93 and 91 (both 83), 62 (100%); HRMS *m/z* $M^{+\bullet}$ calcd for $C_6H_5{}^{79}BrN_2O_2$ 215.9534, found. 215.9533.

2-(2-Methyl-3-nitropyridin-4-yl)cyclohex-2-en-1-one (25). A magnetically stirred mixture of 2-iodocyclohex-2-en-1-one (**6**) (205 mg, 0.92 mmol), copper powder (117 mg, 1.84 mmol), CuI (132 mg, 0.69 mmol) and Pd(dppf)Cl_2•CH_2Cl_2 (38 mg, 0.05 mmol) in degassed DMSO (9 mL) was heated at 50 °C under a nitrogen atmosphere for 0.75 h. After this time a solution of compound **24** (100 mg, 0.46 mmol) in degassed DMSO (3 mL) was added to the reaction mixture over 0.66 h. After a further 6 h the reaction mixture was cooled, quenched with water (3 mL) then diluted with ethyl acetate (5 mL). The ensuing mixture was filtered through a pad comprised of a mixture of diatomaceous earth and silica gel and the solids so retained were rinsed with ethyl acetate (2 × 5 mL). The separated organic phase associated with the combined filtrates was washed with water (2 × 10 mL) then brine (2 × 10 mL) before being dried (Na_2SO_4), filtered and concentrated under reduced pressure to give a brown oil. Subjection of this material to flash column chromatography (silica, 3:9:40 v/v/v acetone/dichloromethane/40-60 petroleum ether elution) gave, after concentration of the appropriate fractions [R_f = 0.1(5) in 1:3:6 v/v/v acetone/dichloromethane/40-60 petroleum ether], compound **25** (90 mg, 84%) as a light-brown, crystalline solid, mp = 80-81 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, J = 5.0 Hz, 1H), 7.09-7.05 (complex m, 2H), 2.66 (s, 3H), 2.58-2.54 (complex m,

4H), 2.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.6, 151.4, 150.8, 150.1, 146.6, 139.0, 136.3, 123.4, 38.2, 26.5, 22.5, 22.0; IR ν_{max} 2939, 1681, 1594, 1528, 1359, 1229, 860 cm^{-1}; MS (ESI, +ve) *m/z* 255 [$(M+Na)^+$, 100%], 233 [$(M+H)^+$, 10]; HRMS *m/z* $(M+Na)^+$ calcd for $C_{12}H_{12}N_2NaO_3$ 255.0746, found 255.0734.

1-Methyl-6,7,8,9-tetrahydro-5*H*-pyrido[3,4-*b*]indole (26). A magnetically stirred mixture of compound **25** (103 mg, 0.44 mmol) and 10 wt % Pd/C (42 mg) in degassed methanol (22 mL) was maintained under an atmosphere of hydrogen at 22 °C for 16 h then filtered and the solids thus retained washed with methanol (50 mL). The combined filtrates were concentrated under reduced pressure and the white solid thus obtained was subjected to flash column chromatography (silica, 1:4 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v methanol/dichloromethane), compound **26**[28] (69 mg, 83%) as a white, crystalline solid, mp = 187-189 °C (lit.[28] mp = 184-188 °C). ^{1}H NMR (400 MHz, CD_3OD) δ 7.84 (d, *J* = 5.4 Hz, 1H), 7.19 (d, *J* = 5.4 Hz, 1H), 2.78 (broad s, 2H), 2.63 (broad s, 5H), 1.91-1.84 (complex m, 4H) (signal due to N-H group proton not observed); ^{13}C NMR (100 MHz, CD_3OD) δ 141.6, 141.2, 136.7, 133.7, 132.9, 111.9, 110.6, 24.3, 24.2, 24.1, 21.7, 19.1; IR ν_{max} 3045, 2930, 2846, 1563, 1498, 1308, 1226, 809 cm^{-1}; MS (ESI, +ve) *m/z* 187 [$(M+H)^+$, 100%]; HRMS *m/z* $(M+H)^+$ calcd for $C_{12}H_{15}N_2$ 187.1235, found 187.1232.

1-Methyl-9*H*-pyrido[3,4-*b*]indole (harman, 5). A magnetically stirred mixture of compound **26** (36 mg, 0.19 mmol) and 10 wt % Pd/C (36 mg) in diphenyl ether (15 mL) maintained under a nitrogen atmosphere was heated at 210 °C for 0.66 h. The reaction mixture was then cooled to room temperature, filtered (through filter paper) and the solids so retained washed with ethyl acetate (2 × 7 mL). The combined filtrates were concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 40-60 petroleum ether elution →1:9 v/v methanol/dichloromethane elution) to give, after concentration of the appropriate fractions (R_f = 0.5 in 1:3 v/v methanol/dichloromethane), compound **5**[29] (32 mg, 91%) as a white, crystalline solid, mp = 233-235 °C (lit.[29] mp = 235-238 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (broad s, 1H), 8.38 (d, *J* = 5.4 Hz, 1H), 8.12 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 5.4 Hz, 1H), 7.56-7.51 (complex m, 2H), 7.29 (m, 1H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.9, 140.3, 138.7, 134.8, 128.5, 128.4, 122.2, 122.0, 120.2, 113.1,

111.7, 20.5; IR ν_{max} 3135, 3068, 2925, 1626, 1568, 1504, 1450, 1323, 1251, 1237, 742 cm^{-1}; MS (ESI, +ve) *m/z* 183 [$(M+H)^+$, 100%]; HRMS (ESI) *m/z* $(M+H)^+$ calcd for $C_{12}H_{11}N_2$ 183.0922, found 183.0922.

X-ray Crystallographic Studies

Crystallographic Data

Compound **1**. $C_{11}H_8N_2$, M = 168.20, T = 150 K, monoclinic, space group $P2_1/n$, Z = 4, a = 11.1814(2) Å, b = 5.53776(8) Å, c = 13.4546(2) Å; β = 96.2939(15) °; V = 828.09(2) $Å^3$, D_x = 1.349 g cm^{-3}, 1673 unique data ($2\theta_{max}$ = 147.6°), R = 0.035 [for 1520 reflections with $I > 2.0\sigma(I)$]; Rw = 0.089 (all data), S = 1.00.

Compound **2**. $C_{11}H_8N_2$, M = 168.20, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 5.8440(1) Å, b = 9.8140(1) Å, c = 14.4195(1) Å; V = 827.00(2) $Å^3$, D_x = 1.351 g cm^{-3}, 1004 unique data ($2\theta_{max}$ = 147.8°), R = 0.027 [for 998 reflections with $I > 2.0\sigma(I)$]; Rw = 0.073 (all data), S = 1.00.

Compound **3**. $C_{11}H_8N_2$, M = 168.20, T = 150 K, orthorhombic, space group $Pna2_1$, Z = 4, a = 17.1576(6) Å, b = 12.2955(6) Å, c = 3.8213(2) Å; V = 806.15(6) $Å^3$, D_x = 1.386 g cm^{-3}, 944 unique data ($2\theta_{max}$ = 147.8°), R = 0.032 [for 906 reflections with $I > 2.0\sigma(I)$]; Rw = 0.062 (all data), S = 1.00.

Compound **4**. $C_{11}H_8N_2$, M = 168.20, T = 150 K, monoclinic, space group Ia, Z = 4, a = 12.1155(7) Å, b = 3.9036(2) Å, c = 18.1199(13) Å; β = 107.250(7) °; V = 818.42(9) $Å^3$, D_x = 1.365 g cm^{-3}, 820 unique data ($2\theta_{max}$ = 146.6°), R = 0.042 [for 807 reflections with $I > 2.0\sigma(I)$]; Rw = 0.107 (all data), S = 1.05.

Compound **5**. $C_{12}H_{10}N_2$, M = 182.23, T = 150 K, orthorhombic, space group $P2_12_12_1$, Z = 8, a = 9.5865(2) Å, b = 13.2423(4) Å, c = 15.1680(4) Å; V = 1925.54(9) $Å^3$, D_x = 1.257 g cm^{-3}, 1994 unique data ($2\theta_{max}$ = 52.0°), R = 0.032 [for 1805 reflections with $I > 2.0\sigma(I)$]; Rw = 0.073 (all data), S = 1.00.

Structure Determination

The image for compound **5** was measured on a diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å) fitted with an area detector and the data extracted using CrysAlis PRO.[34] Images for compounds **1**, **2**, **3** and **4** were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data

extracted using the CrysAlis.[34] The structure solutions for all eleven compounds were solved by direct methods (SIR92)[35] then refined using the CRYSTALS program package.[36]Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1530002, 1530003, 1530004, 1530005, 1530006). These data can be obtained free-of-charge via 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.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data (CIFs); ORTEPs derived from the single-crystal X-ray analyses of compounds **1-5**; and ^{1}H and ^{13}C NMR spectra of compounds **1-5**, **8**, **9**, **10**, **11**, **12**, **14**, **15**, **17**, **18**, **20**, **21/22** and **24-26** This material is available free of charge via the internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*Email: Martin.Banwell@anu.edu.au

Notes

The authors declare no competing financial interest

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