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Synthesis of Bicyclic Pyrazinones *via* Addition of Heterocyclic Amines to a Nitro-alkene

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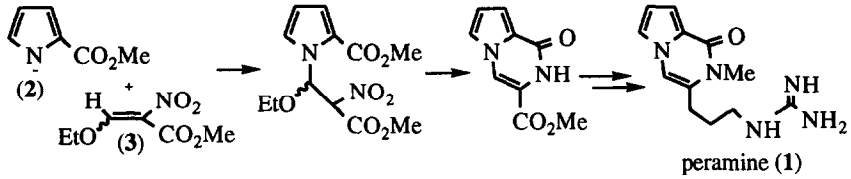
Abstract: Michael addition of heterocyclic amines (**6**), (**10**), (**13**) and (**17**) to nitro-olefin (**3**) followed by reduction/cyclization of the nitro group of the adduct provides a convenient synthesis of the bicyclic pyrazinones (**8**), (**12**), (**16**), (**19**) and (**20**) which are found in several natural products.

INTRODUCTION

The key step in our synthesis[1] of the insect feeding deterrent peramine (**1**)[2] made use of a Michael addition of a pyrrole anion (**2**) to a nitro-alkene (**3**) to effect the key *N*-alkylation step (Scheme 1). Reduction of the nitro group to the amine, followed by cyclization to the lactam and then elimination of the ethoxy group provided the pyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring system. We now wish to report the convenient *N*-alkylation of other heterocyclic amines with nitro-alkene (**3**), thereby providing an efficient entry to other bicyclic pyrazinones present in several natural products.



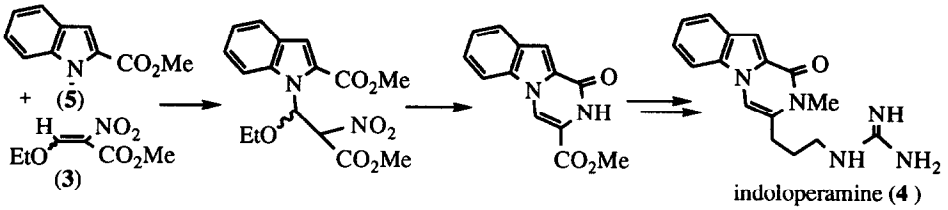
Scheme 1

DISCUSSION

Initial work focused on the synthesis of the indoloperamine (**4**) *via* the addition of the potassium anion of methyl indole-2-carboxylate (**5**) to nitro-alkene (**3**) (Scheme 2) analogous to our earlier work in the pyrrole series. Despite the use of a number of reagents and conditions the successful Michael addition of this anion to nitro-alkene (**3**) was not realized. Disappointed with this result we then focused on the addition of saturated heterocyclic amines bearing a carbomethoxy group at C-2, to nitro-olefin (**3**), thereby eliminating the need to generate a heteroanion prior to the addition.

Addition of methyl piperidine-2-carboxylate (**6**) (prepared *in situ* by treatment of the hydrochloride salt[3] with sodium acetate) to nitro-olefin (**3**), in methanol at room temperature for 0.75 h., afforded Michael adduct (**7**) in 85% yield (Table). Despite the use of an *E:Z* mixture of nitro-olefin (**3**)[4] only the *Z*-adduct (**7**) was

formed. This observed stereoconvergence is consistent with a multistep nucleophilic substitution in which the rate of rotation about the (H,EtO)C-C(NO_2,CO_2Me) bond is faster than the rate of elimination of the ethoxy group.[5] A similar observation has been observed by Seebach *et al.*[6]



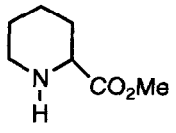
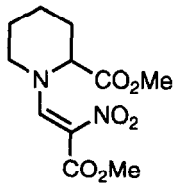
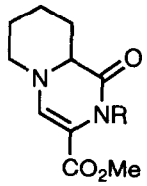
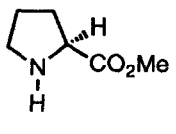
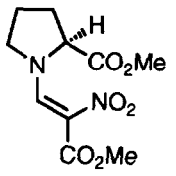
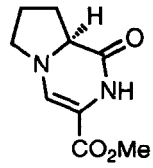
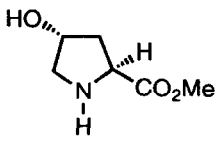
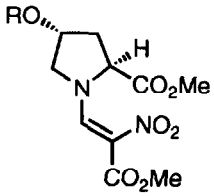
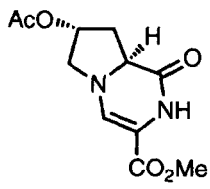
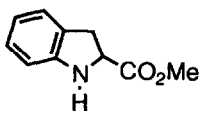
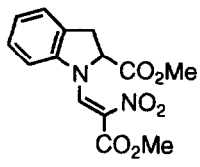
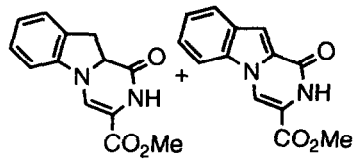
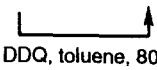
Scheme 2

Nitroadduct (**7**) analysed correctly for $C_{11}H_{16}N_2O_6$, with a molecular ion at *m/z* 272 in the mass spectrum supporting this molecular formula. The infrared spectrum exhibited two strong absorbances at 1742 and 1724 cm^{-1} (C=O), indicating the presence of the two ester carbonyl groups, and an absorbance at 1619 cm^{-1} (C=C), supporting the formation of an olefin. The ^1H n.m.r. spectrum exhibited a six proton singlet at δ_H 3.81 assigned to the two methoxy groups and a one proton singlet at δ_H 8.01 assigned to H-1', providing strong evidence for the formation of a nitro-olefin. The ^{13}C n.m.r. spectrum was assigned on the basis of chemical shift with the aid of DEPT spectra. The resonances at δ_C 119.3 (singlet) and δ_C 149.9 (doublet) assigned to C-2' and C-1' respectively once again supported the formation of a nitro-olefin. The clean high field ^1H and ^{13}C n.m.r. spectra supported the formation of only one diastereomer from this reaction.

A number of reagents were evaluated to effect the reduction of the nitro group of adduct (**7**) to the lactam (**8**). The optimum procedure used $Mg/HgCl_2/TiCl_4$[7] in THF/^{t}BuOH (1:2) affording the lactam (**8**) in modest yield. *N*-methylation of lactam (**8**) (NaH, DMSO, MeI, 0°C) afforded the more stable tertiary lactam (**9**). Lactam (**8**) has the same ring system as that present in the mycotoxin verruculotoxin[8] isolated from green peanuts infected with *Penicillium verruculosum.*

Lactam (**8**) analysed correctly for $C_{10}H_{14}N_2O_3$, with a molecular ion at *m/z* 210, confirming this as the molecular formula. The infrared spectrum showed a strong absorbance at 3271 cm^{-1} assigned to the NH group, and two strong absorbances at 1740 and 1680 cm^{-1} assigned to the ester and lactam carbonyl groups respectively. The ^1H n.m.r. spectrum exhibited an upfield shift in the resonances assigned to the olefin from δ_H 8.01 in the Michael adduct (**7**) to δ_H 6.83 in the lactam (**8**), consistent with the replacement of the strongly electron withdrawing nitro group with an amide. A broad resonance at δ_H 7.36 was assigned to the secondary amide (NH). Moreover the presence of only one methoxy group at δ_H 3.74 suggested that cyclisation to the lactam (**8**) had occurred. The ^{13}C n.m.r. spectrum was assigned on the basis of chemical shift with the aid of DEPT spectra. Resonances at δ_C 119.3 and δ_C 149.9 assigned to C-2' and C-1' in the Michael adduct (**7**) displayed an upfield shift resonating at δ_C 101.0 and δ_C 129.9 and assigned to C-3 and C-4 respectively in the lactam (**8**). The upfield shifts observed for these vinylic carbons was consistent with the replacement of the strongly electron withdrawing nitro group for a secondary amide.

Table

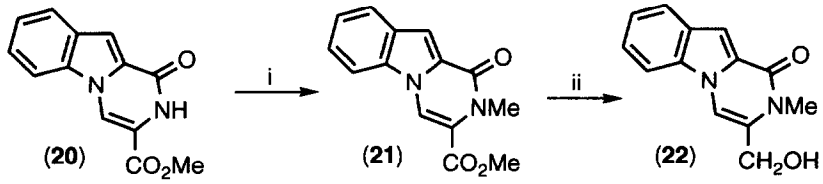
Heterocyclic amine	Adduct	Lactam
 (6)	 (7) : 85%	 (8) : R = H : 48% $Mg/HgCl_2$, $TiCl_4$, THF/^{t}BuOH (9) : R = Me : 74%
 (10)	 (11) : 98%	 (12) : 38% $Mg/HgCl_2$, $TiCl_4$, THF/^{t}BuOH
 (13)	 (14) R = H : 97% (15) R = Ac : 93%	 (16) : 71% H_2, Pd/C, 16h., room temp., MeOH
 (17)	 (18) : 58%	 (19) : 48% (20) : 10% $Mg/HgCl_2$, $TiCl_4$, THF/^{t}BuOH  DDQ, toluene, 80%

Synthesis of the tetrahydropyrrolo[1,2-*a*]pyrazin-1(2*H*)-one ring systems (**12**) and (**16**) were achieved in a similar manner to lactam (**8**). Thus addition of L-proline methyl ester (**10**) and *trans*-4-hydroxyproline methyl ester (**13**) (also prepared *in situ* from the corresponding hydrochloride salts) to nitro-olefin (**3**) afforded the *Z*-adducts (**11**) and (**14**) in 98% and 97% yield respectively. Subsequent reduction / cyclization of adduct (**14**) to a lactam proved difficult in that use of the Ti(II) reagent used above and catalytic hydrogenation resulted in hydrogenolysis to the starting material (**13**). However, conversion of adduct (**14**) to the acetate derivative (**15**) facilitated subsequent reduction (H_2, Pd/C) to the lactam (**16**) in 71% yield. Lactams (**12**) and (**16**) were unstable, readily darkening upon standing rendering elemental analysis difficult to obtain. High field ^1H and ^{13}C n.m.r. spectra and high resolution mass spectral data, however, supported the given structures.

Extension of the above methodology to the pyrazino-indolone ring system (**20**) was achieved indirectly. This involved the use of methyl indoline-2-carboxylate (**17**) as the nucleophile in the Michael addition step forming the desired adduct (**18**) in 58% yield. Reduction of adduct (**18**) using $Mg/HgCl_2/TiCl_4$ then afforded lactams (**19**) and (**20**) in 48% and 10% yield respectively, which were readily separated by flash chromatography. Lactam (**19**) readily aromatized upon standing to lactam (**20**), however, this conversion was achieved more efficiently using DDQ in toluene at room temperature, affording the aromatic lactam (**20**) in 80% yield.

The concise synthesis of indole-lactam (**20**) and dihydroindole-lactam (**19**) represent syntheses of the ring systems present in several natural products, for example gliotoxin[9] and dioxopyrazinoindole C[10] respectively. Our synthetic effort, however, was directed towards the synthesis of the indole analogue of the insect feeding deterrent peramine (**4**).

With the successful synthesis of indole-lactam (**20**) in hand, it was envisaged that the synthetic methodology developed in our synthesis of peramine (**1**) for the elaboration of the C-3 methoxycarbonyl group to the *n*-propyl guanidino group could be applied to the present work (Scheme 3). After *N*-methylation (KH, DMSO, MeI) to the tertiary lactam (**21**) the desired oxidation level was achieved by reduction of the ester to the alcohol (**22**) using sodium borohydride in 89% yield. Extension of the side chain then required conversion of the alcohol (**22**) to a suitable leaving group. This was achieved in the peramine work by generation of the mesylate at low temperature followed by addition of lithium bromide also at low temperature before adding the nucleophile, cyanomethylcuprate. Despite taking extreme care to generate the mesylate and the bromide at low temperature this approach to indoloperamine (**4**) was hindered by the capricious nature of the mesylate and the bromide. An alternative approach is now required.



Reagents : (i) KH, DMSO, MeI, 57%; (ii) $NaBH_4$, MeOH, 89%

Scheme 3

EXPERIMENTAL

General Methods.

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Infrared spectra were recorded on a BIO-RAD FTS-7 or a BIO-RAD FTS-40 spectrophotometer as Nujol mulls or thin films between sodium chloride plates. ^{1}H n.m.r. spectra were obtained at 270 MHz using a Jeol GX270 spectrometer. ^{13}C n.m.r. were obtained at 67.8 MHz using a Jeol GX270 spectrometer. Microanalyses were performed at the microanalytical laboratory, University of Otago, Dunedin. Mass spectra and accurate mass measurements were recorded on a Varian VG70-250S double focussing magnetic sector mass spectrometer with an ionization potential of 70 eV. Merck Kieselgel 60 (230-400 mesh) was used for flash chromatography. All solvents and reagents were purified and dried if necessary before use.

Methyl 2-nitro-3-ethoxyacrylate (3). Nitro-olefin (**3**) was prepared from methyl nitroacetate[11], triethylorthoformate and acetic anhydride according to the method of Kamlet[4] as a colourless liquid, b.p 119-121 °C / 1.0 mm Hg (lit.[4] b.p 119-121°C / 1.0 mm Hg).

Methyl piperidine-2-carboxylate hydrochloride (**6**). Ester (**6**) was prepared from piperidine-2-carboxylic acid (15.0 g, 105 mmol) and thionyl chloride (10 ml, 329 mmol), according to the method of Yasutake *et al.*[3] as a white crystalline solid (18.6 g, 91 %), m.p 214-216°C (lit.[12] m.p 213-215°C).

(Z)-Methyl 1-(2'-methoxycarbonyl-2'-nitroethenyl)piperidine-2-carboxylate (7). To a solution of methyl piperidine-2-carboxylate hydrochloride (**6**) (5.0 g, 28 mmol) and sodium acetate (7.6 g, 56 mmol) in methanol (150 ml), was added a solution of nitro-acrylate (**3**) (4.9 g, 56 mmol) in methanol (10 ml). The solution was stirred at room temperature for 0.75 h and the methanol removed at reduced pressure. The resultant yellow suspension was dissolved in ethyl acetate (100 ml), washed with water (3 x 25 ml), and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded a yellow solid that was triturated with diethyl ether to give the *title compound* (**7**) (6.4 g, 85%) as yellow prisms m.p. 96.5-97.5°C (Found: C, 48.3; H, 5.7; N, 10.3. $C_{11}H_{16}N_2O_6$ requires: C, 48.5; H, 5.9; N, 10.3%); υ_{max} (Nujol) / cm^{-1} 1742, 1724 (s, C=O) and 1619 (m, C=C); δ_H (270 MHz; $CDCl_3$), 1.24-2.39 (6H, m, 3 x CH_2), 3.32-3.91 (2H, m, CH_2N), 3.81 (6H, s, 2 x CO_2Me), 4.23 (1H, d, *J* 5.2 Hz, CHN), 8.01 (1H, s, HC=C), δ_C (67.8 MHz; $CDCl_3$) 19.2, 24.7, 27.4 (t, C-3, C-4, C-5), 52.5 (q, OMe), 52.5 (d, C-2), 52.6 (t, C-6), 119.3 (s, C-2'), 149.9 (d, C-1'), and 162.9, 169.5 (s, 2 x CO_2Me); *m/z* 272 (M^+, 12%), 22.6 (M-NO_2, 4), 213 (M-CO_2Me, 100), 137 (24), and 85 (43).

3-Methoxycarbonyl-5,6,7,8,9,9a-hexahydropyrido[1,2-a]pyrazin-1(2H)-one (8). To a suspension of mercuric chloride (165 mg, 0.61 mmol) in dry tetrahydrofuran (8 ml), under nitrogen, was added magnesium powder (36 mesh, 268 mg, 11.04 mmol), and the reaction mixture stirred at room temperature for 0.15 h. The turbid supernatant liquid was withdrawn by syringe and the amalgam washed with dry tetrahydrofuran (3 x 10 ml). The amalgam was then suspended in dry tetrahydrofuran (16 ml), cooled to -10°C and titanium tetrachloride (1.05 g, 5.53 mmol) added slowly in one portion. To this was added a solution of nitro-alkene (**7**) (500 mg, 1.84 mmol) in dry tetrahydrofuran / t-butanol (2:1) (12 ml) and the reaction mixture stirred for 1 h at 0 °C. The reaction mixture was quenched with water (5 ml), diluted with diethyl ether (50 ml) and dried

(Na_2SO_4). After filtration through a short pad of celite the solvent was removed at reduced pressure. The resultant black oil was purified by flash chromatography using hexane-ethyl acetate (1:2) as eluant affording the *title compound* (**8**) (179 mg, 48%) as an orange oil, which upon trituration using diethyl ether gave colourless needles, m.p. 87-88°C (Found: C, 56.9; H, 6.4; N, 13.3. $C_{10}H_{14}N_2O_3$ requires: C, 57.1; H, 6 .7; N, 13.3%); υ_{max} (thin film) /cm^{-1} 3271 (m, NH), 1740 (s, C=O, ester), and 1680 (s, C=O lactam); δ_H (270 MHz, $CDCl_3$) 1.51-2.25 (6H, m, 3 x CH_2), 3.09-3.15 (1H, m, 6-H), 3.37-3.43 (1H, m, 6-H'), 3.74 (3H, s, OMe), 3.74-3.81 (1H, m, CHN), 6.83 (1H, s, HC=C), and 7.36 (1H, br s, NH); δ_C (67.8 MHz, $CDCl_3$) 24.1, 25.0, 27.7 (t, C-7, C-8, C-9), 51.3 (q, OMe), 53.2 (t, C-6), 59.1 (d, C-9a), 101.0 (s, C-3), 129.9 (d, C-4), and 162.6, 162.9 (s, C-1, C=O ester); *m/z* 210 (M^+, 100%), 179 (M-OCH_3, 15), and 123 (4).

3-Methoxycarbonyl-2-methyl-5,6,7,8,9,9a-hexahydropyrido[1,2-a]pyrazin-1(2H)-one. (9). To a stirred solution of lactam (**8**) (104 mg, 50 mmol) in dry dimethyl sulphoxide (2 ml), under nitrogen was added sodium hydride (18 mg, 74 mmol). The resultant suspension was stirred for 0.5 h, cooled to 0°C, then methyl iodide (71 mg, 0.50 mmol) added and the suspension disappeared. The resultant solution was stirred for a further 0.5 h, then aqueous sodium dihydrogen phosphate (1 ml) added, followed by 2M HCl (1 ml). The mixture was extracted with ethyl acetate (3 x 30 ml), washed with water (2 x 10 ml), and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded a brown oil, that was purified by flash chromatography using hexane-ethyl acetate (1:2) as eluant to give the *title compound* (**9**) (58 mg, 74%) as an oil (Found M^+, 224.1158. $C_{11}H_{16}N_2O_3$ requires *M*, 224.1161); υ_{max} (thin film) / cm^{-1} 1750 (s, C=O, ester), and 1664 (s, C=O, lactam); δ_H (270 MHz, $CDCl_3$) 1.24-2.18 (6H, m, 3 x CH_2), 2.19-3.11 (1H, m, 6-H), 3.32-3.42 (1H, m, 6-H'), 3.31 (3H, s, NMe), 3.67 (3H, s, OMe), 3.62-3.88 (1H, m, CHN), and 7.02 (1H, s, HC=C); d_C (67.8 MHz; $CDCl_3$ 23.6, 24.8, 26.9 (t, C-7, C-8, C-9), 31.7 (q, NMe), 50.9 (q, OMe), 52.8 (t, C-6), 59.1 (d, C-9a) 106.5 (s, C-3), 135.0 (d, C-4), and 162.8, 164.2 (s, C-1, C=O, ester); *m/z* 224 (M^+, 100%), 195 (M-NMe, 22), and 181 (88).

(Z)-Methyl 1-(2'-methoxycarbonyl-2'-nitroethenyl)pyrrolidine-2-carboxylate (11). The *title compound* (**11**) was prepared from L-proline methyl ester hydrochloride (**10**) (1.0 g, 6 mmol), sodium acetate (1.65 g, 12.0 mmol), and nitro-acrylate (**3**) (1.06g, 6.0 mmol) using the procedure described for nitro-alkene (**7**). Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluant gave the *title compound* (**11**) (1.5 g, 98%) as yellow prisms, m.p. 75-76°C (Found: C, 46.7; H, 5.6; N, 10.5. $C_{10}H_{14}N_2O_6$ requires: C, 46.5; H, 5.5; N, 10.8%); υ_{max} (thin film) / cm^{-1} 1744,1722 (s, C=O), 1618 (m, C=C), and 1565 (w, NO_2); δ_H (270 MHz, $CDCl_3$) 2.02-2.34 (4H, m, 2 x CH_2), 3.25-3.46 (2H, m, CH_2N), 3.74-3.96 (1H, m, CHN), 3.81 (6H, s, 2 x OMe), and 8.29 (1H, br s, HC=C); δ_C (67.8 MHz, $CDCl_3$) 24.4, 28.9 (t, C-3, C-4), 48.9 (t, C-5), 52,9, 53.1 (q, 2 x OMe), 66.6 (d, C-2), 120.2 (s, C-2'), 147.3 (d, C-1'), and 162.6, 170.6 (s, 2 x CO_2Me); *m/z* 258 (M^+, 19%), 212 (M-NO_2, 3), 199 (M-CO_2Me, 100), 183 (13), 95 (19), 71 (50), and 43 (20).

3-Methoxycarbonyl-6,7,8,8a-tetrahydropyrrolo[1,2-a]pyrazin-1(2H)-one (12). The *title compound* (**12**) was prepared from nitro-alkene (**11**) (490 mg, 1.90 mmol), using the procedure described for lactam (**8**). Purification by flash cromatography using hexane-ethyl acetate (1:2) as eluant afforded the *title compound* (**12**) (141 mg, 38%) as a pale yellow oil that darkened on standing (Found: M^+, 196.0856, $C_9H_{12}N_2O_3$ requires *M*, 196.0848); υ_{max} (thin film) / cm^{-1}, 3430 (br, m, NH), 1739 (s, C=O, ester), and 1677 (s, C=O, lactam); δ_H

(270 MHz, $CDCl_3$) 1.94-2.45 (4H, m, 2 x CH_2), 3.48-3.55 (2H, m, CH_2N), 3.75 (3H, s, OMe), 3.86-3.98 (1H, m, CHN), 7.08 (1H, s, HC=C), and 7.46 (1H, br s, NH); δ_C (67.8 MHz, $CDCl_3$) 23.0, 28.2 (t, C-7, C-8), 50.3 (q, OMe), 51.4 (t, C-6), 59.5 (d, C-8a), 103.6 (s, C-3), 128.3 (d, C-4), and 162.1, 162.6 (s, C-1, C=O, ester); *m/z* 196 (M^+, 100%), 181 (M-CH_3, 6), 156 (36), 140 (44), and 108 (48).

(2S,4R)-(-)-(Z)-Methyl 4-hydroxy-1-(2'-methoxycarbonyl-2'-nitroethenyl)piperidine-2-carboxylate (**14**). The *title compound* (**14**) was prepared from (2S,4R)-(-)-methyl 4-hydroxypyrrolidine-2-carboxylate hydrochloride (**13**) (100 mg, 0.55 mmol), sodium acetate (150 mg, 1.10 mmol), and nitro-acrylate (**3**) using the procedure described for nitro-alkene (**7**). Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluant gave the *title compound* (**14**) (147 mg, 97%) as yellow prisms, m.p. 81-83°C;$[\alpha]_D$ -420.5° (c, 0.394, $CHCl_3$). (Found (acetate): C, 45.4; H, 5.3; N, 8.6. $C_{12}H_{12}N_2O_8$ requires: C, 45.6; H, 5.1; N, 8.9%); υ_{max} (Nujol) /cm^{-1} 3480 (br, m OH), 1743, 1721 (s, C=O), and 1616 (m, C=C); δ_H (270 MHz, CD_3OD) 2.22-2.46 (2H, m, CH_2), 3.37 (2H, d, *J* 10.3 Hz, CH_2N), 3.84 (3H, s, OMe), 4.50 (1H, m, CHN), 5.09-5.16 (2H, m, C*H* OH) and 8.36 (1H, br s, HC=C); δ_C (67.8 MHz, CD_3OD) 37.0 (t, C-3), 52.3, 53.1 (q, 2 x OMe), 59.1 (t, C-5), 64.6 (d, C-2), 69.4 (d, C-4), 119.5 (s, C-2'), 147.8 (s, C-1'), and 162.4, 170.7, (s, 2 x OMe); *m/z* 274 (M^+, 13%), 215 (M-CO_2Me, 100), and 192 (13).

(2S,4R)-(-)-(Z)-Methyl 4-acetoxy-1-(2'-methoxycarbonyl-2'-nitroethenyl)pyrrolidine-2-carboxylate (**15**). To a solution of nitro-alkene (**14**) (196 mg, 0.72 mmol) in dichloromethane (5 ml) was added triethylamine (148 mg, 1.46 mmol), acetic anhydride (112 mg, 1.09 mmol) and 4-dimethylaminopyridine (DMAP) (3 mg), and the reaction mixture allowed to stand at room temperature for 1 h. The reaction mixture was quenched with water (5 ml), extracted with dichloromethane (2 x 10 ml), washed with water (2 x 5 ml), and dried (Na_2SO_4). Removal of the solvent at reduced pressure afforded a yellow oil that was purified by flash chromatography using hexane-ethyl acetate as eluant to give the *title compound* (**15**) (210 mg, 93%), as a pale yellow oil;$[\alpha]_D$ -269.7° (c, 0.064, $CHCl_3$); (Found: C, 45.4; H, 5.3; N, 8.6; $C_{12}H_{16}N_2O_8$ requires: C, 45.6; H, 5.1; N, 8.9%); υ_{max} (thin film) / cm^{-1} 1735 (s, C=O, ester), and 1624 (m, C=C); δ_H (270 MHz, $CDCl_3$) 2.05 (3H, s, OAc), 2.24-2.59 (2H, m, CH_2), 3.75-3.88 (2H, m, CH_2N), 3.83 (6H, s, 2 x OMe), 4.64-4.70 (1H, m, CHN), 5.23-5.38 (1H, m, C*H*O), and 8.37 (1H, br s, HC=C); δ_C (67.8 MHz, $CDCl_3$) 20.7 (q, CH_3), 34.4 (t, C-3), 52.6, 53.2 (q, 2 x OMe), 56.0 (t, C-5), 64.2 (d, C-2), 71.7 (d, C-4), 121.2 (s, C-2'), 148.4 (d, C-1'), 162.2, 170.0 (s, 2 x C=O, ester); *m/z* 317 (MH^+, 8%), 316 (M^+, 8), 257 (M-CO_2Me, 12), 197 (46), 165 (76), 121 (100).

(8aS,7R)-(-)-7-Acetoxy-3-methoxycarbonyl-6,7,8,8a-tetrahydropyrrolo[1,2-a]pyrazin-1(2H)-one (**16**). To a solution of nitro-alkene (**15**) (990 mg, 3.13 mmol) in methanol (150 ml) was added 5% palladium on charcoal (20 mg), and the reaction flask flushed with hydrogen. The reaction mixture was stirred at room temperature under a hydrogen atmosphere for 16 h. After filtration through a short celite pad, the solvent was removed at reduced pressure to afford a brown oil, that was purified by flash chromatography using hexane-ethyl acetate as eluant to give the *title compound* (**16**) (566 mg, 71%) as a pale yellow oil that darkened on standing; $[\alpha]_D$ -27.2° (c, 0.206, MeOH); (Found: M^+, 254.0897. $C_{11}H_{14}N_2O_5$ requires *M*, 254.0903); υ_{max} (thin film) / cm^{-1} 3450 (m, NH), 1737 (s, C=O, ester), and 1683 (s, C=O, lactam); δ_H (270 MHz, $CDCl_3$) 2.06 (3H, s, OAc), 2.07-2.26 (2H, m, CH_2), 3.03-3.08 (1H, m, 6-H), 3.30 (1H, dd, $J_{6,6'}$ 12.5, $J_{6,7}$ 4.8 Hz, 6-H'),

3.75 (3H, s, OMe), 4.00 (1H, t, $J_{8a,8}$ 7.8 Hz, 8a-H), 5.22-5.32 (1H, m, C*H*OAc), and 7.09 (1H, s, HC=C); δ_C (67.8 MHz, $CDCl_3$) 20.9 (q, CH_3),36.4 (t, C-8), 52.1 (q, OMe), 52.4 (t, C-6), 58.3 (d, C-8a), 71.2 (d, C-7), 103.2 (s, C-3), 127.1 (d, C-4), and 165.1, 170.4, 174.4 (s, C-1, C=O, ester, acetate); *m/z* 254 (M^+, 34%), 223 (M-CO_2Me, 6), 194 (M-HOAc, 95), 134 (43), 82 (49), 68 (100), and 43 (82).

Methyl 1-(2'-methoxycarbonyl-2'-nitroethenyl)indoline-2-carboxylate (18). To a solution of DL-methyl indoline-2-carboxylate (**17**) (526 mg, 2.96 mmol) in methanol (10 ml) was added a solution of nitro-acrylate (**3**) (520 mg, 2.96 mmol) in methanol (1 ml). A yellow precipitate formed, and the resultant mixture was stirred for 1 h. The precipitate was filtered, washed with methanol (2 x 10 ml), and dried to give the *title compound* (**18**) (456 mg, 58%) as pale yellow needles, m.p. 131.5-132°C. (Found: C, 55.0; H, 4.7; N, 9.2%, $C_{14}H_{14}N_2O_6$ requires: C, 54.9; H, 4.6; N, 9.2%); υ_{max} (Nujol) /cm^{-1} 1588 (m, NO_2), 1627 (m, C=C), 1709, and 1755 (s, 2 x C=O); δ_H (270 MHz, $CDCl_3$) 3.34 (1H, dd, $J_{3,3'}$ 16.9, $J_{3',2}$ 3.3 Hz, 3-H'), 3.68 (1H, dd, $J_{3,3'}$ 16.9, $J_{3,2}$ 10.6 Hz, 3-H), 3.74 (3H, s, OMe), 3.87 (3H, s, OMe), 5.22 (1H, dd, $J_{2,3}$ 10.6, $J_{2,3'}$ 3.3 Hz, 2-H), 7.15-7.35 (4H, m, Ar-H), and 8.83 (1H, m, HC=C); δ_C (67.8 MHz, $CDCl_3$) 34.0 (t, C-3), 53.1, 53.2 (q, 2 x OMe), 62.1 (d, C-2), 110.8, 125.8, 126.0, 128.8 (d, C-4, C-5, C-6, C-7), 128.7 (s, C-2') 134.5 (s, C-3a), 138.4 (d, C-1'), 143.2 (s, C-7a),, and 162.6, 169.7 (s, C=O, ester); *m/z* 306 (M^+, 52%), 247 (M-CO_2Me, 28), 171 (100), 118 (51).

10,10a-Dihydro-3-methoxycarbonylpyrazino[1,2-a]indol-1(2H)-one (19) and 3-Methoxycarbonyl-pyrazino[1,2-a]indol-1(2H)-one (20). The *title compounds* (**19**) and (**20**) were prepared from nitro-alkene (**18**) (2.1 g, 6.8 mmol) using the procedure described for lactam (**8**). Purification by flash chromatography using hexane-ethyl acetate (1:1) as eluant gave the *lactam* (**19**) (807 mg, 48%), as a pale yellow solid, m.p. 259-261°C (changes form to needles 195-198°C); (Found: M^+, 244.0859, $C_{13}H_{12}N_2O_3$ requires *M*, 244.0848); υ_{max} (Nujol) / cm^{-1} 3187 (m, NH), 1718 (s, C=O ester), 1660 (s, C=O lactam); δ_H (270 MHz, CD_3OD) 3.24 (1H, d, *J* 10.5 Hz, CH_2), 3.72 (3H, s OMe), 4.57 (1H, t, *J* 10.5 Hz, CHN), 6.89 (1H, t, *J* 7.3 Hz, 8-H or 7-H), 7.17 (1H, d, *J* 7.3 Hz, 7-H or 8-H), 7.23 (1H, d, *J* 7.3 Hz, 6-H or 9-H), 7.28 (1H, d, *J* 7.3 Hz, 9-H or 6-H), 7.79 (1H, s, 4-H), and 9.48 (1H, s, NH); δ_C (67.8 MHz, CD_3OD) 30.1 (t, C-10), 51.4 (q, OMe), 59.6 (d, C-10a), 108.1 (s, C-3), 108.9, 120.0, 122.0, 125.4, 127.9 (d, C-4, C-6, C-7, C-8, C-9), 128.8 (s, C-9a), and162.1, 163.2 (s, C-1, C=O, ester); *m/z* 244 (M^+, 100%), 242 (M-2H, 24), and 156 (33) and *lactam* (**20**) (164 mg, 10%) as colourless needles, m.p 270-271°C (Found: C, 64.3; H, 4.3; N, 11.6; $C_{13}H_{10}N_2O_3$ requires: C, 64.5; H, 4.2; N, 11.6%); υ_{max} (Nujol) / cm^{-1} 3187 (w, NH), 1669 (s, C=O, ester), and 1637 (s, C=O, lactam); δ_H (270 MHz, $CDCl_3$) 3.99 (3H, s, OMe), 7.40 (1H, t, *J* 7.8 Hz, 7-H or 8-H), 7.51 (1H, t, *J* 8.1 Hz, 8-H or 7-H), 7.53 (1H, s, 10-H),7.76 (1H, d, *J* 8.1 Hz, 6-H or 9-H), 7.86 (1H, d, *J* 8.1 Hz, 9-H or 6-H), 8.21 (1H, s, 4-H), and 8.41 (1H, br s, NH); δ_C (67.8 MHz, $CDCL_3$) 53.0 (q, OMe), 106.4 (s, C-3), 106.4, 110.8, 112.5, 123.1, 123.9, 125.4 (d, C-4, C-6, C-7, C-8, C-9, C-10), 114.1, 127.5, 128.6, 133.4 (s, C-3, C-5a, C-9a, C-10a), 156.0 (s, C-1), and 162.0 (s, C=O, ester); *m/z* 242 (M^+, 100%), 182 (M-CO_2Me-H, 33), and 154 (27).

3-Methoxycarbonylpyrazino[1,2-a]indol-1(2H)-one (20). To a solution of lactam (**19**) (1.17 g, 4.8 mmol) in toluene (150 ml) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). The reaction mixture was stirred for 0.5 h, filtered, and washed with toluene (2 x 25 ml), to give a tan solid that was purified

by flash chromatography using ethyl acetate as eluant to afford the *lactam* (**20**) (928 mg, 80%) for which the spectroscopic data was in agreeement with that reported above.

3-Methoxycarbonyl-2-methylpyrazino[1,2-a]indol-1(2H)-one (21). To a solution of lactam (**20**) (300 mg, 1.22 mmol) in dry dimethylsulphoxide (10 ml) was added potassium hydride (100 mg, 2.45 mmol). The reaction mixture was stirred at room temperature for 0.5 h then methyl iodide (261 mg, 1.84 mmol) was added. After 0.5 h aqueous sodium dihydrogen phosphate (2 ml) and water (25 ml) were added and the reaction mixture extracted with ethyl acetate (3 x 50 ml). The organic extract was washed with water (2 x 20 ml), and dried (Na_2SO_4). Removal of the solvent under reduced pressure afforded a pale cream solid that was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluant to give the *title compound* (**21**) (181 mg, 57%) as colourless needles, m.p. 173-174 °C (Found: C, 65.4; H, 4.7; N, 10.9; $C_{14}H_{12}N_2O_3$ requires: C, 65.6; H,4.7; N,10.9%); υ_{max} (Nujol) / cm^{-1} 1719 (s, C=O, ester), and 1651 (s, C=O, lactam); δ_H [270 MHz, $(CD_3)_2SO$] 3.39 (3H, s, NMe), 3.88 (3H, s, OMe), 7.36 (1H, s, 10-H), 7.37 (1H, t, *J* 8.2 Hz, 7-H or 8-H), 7.47 (1H, t, 8-H, or 7-H), 7.84(1H, t, d, *J* 8.2 Hz, 6-H or 9-H), 8.26 (1H, d, 9-H or 6-H),and 8.69 (1H, s, 4-H); δ_C [67.8 MHz, $(CD_3)_2SO$] 31.7 (q, NMe), 52.4 (q, OMe), 104.3, 112.2, 114.8, 122.2, 123.4, 124.6 (d, C-4, C-6, C-7, C-8, C-9, C-10), 117.7, 126.6, 127.9, 132.8 (s, C-3, C-5a, C-9a, C-10a), 156.2 (s, C-1), and 162.2 (s, C=O, ester); *m/z* 256 (M^+, 100), 197 (M-CO_2Me, 10).

3-Hydroxymethyl-2-methylpyrazino[1,2-a]indol-1(2H)-one (22) To a solution of ester (136) (181 mg, 0.71 mmol), in methanol (10 ml), under nitrogen was added sodium borohydride (540 mg, 14.3 mmol). The reaction mixture was left to stand at room temperature for 16 h. After quenching with water (5 ml) the methanol was removed by rotary evaporation and the residue extracted with ethyl acetate (3 x 25 ml). The organic extract was washed with water (2 x 5 ml) dried (Na_2SO_4), and the solvent removed at reduced pressure to give a pale yellow solid that was purified by flash chromatography using hexane-ethyl acetate (1:1) as eluant to give the *title compound* (**22**) (143 mg, 89%) as colourless needles, m.p. 190-191°C (decomp); (Found: C, 68.2; H, 5.3; N, 12.0. $C_{13}H_{12}N_2O_2$ requires: C, 68.4; H, 5.3; N, 12.3%); υ_{max} (Nujol) / cm^{-1} 3332 (br, w, OH), and 1623 (s, C=O, lactam); δ_H [270 MHz, $(CD_3)_2SO$] 3.53 (3H, s, NMe), 4.47 (1H, d, *J* 4.1 Hz, CH_2OH), 5.51 (1H, br t, *J* 4.1 Hz, OH), 7.23 (1H, s, 10-H), 7.23 (1H, t, *J* 7.8 Hz, 7-H or 8-H), 7.41 (1H, t, *J* 7.8 Hz, 8-H or 7-H), 7.81 (1H, d, *J* 7.8 Hz, 6-H or 9-H), 7.98 (1H, s, 4-H), and 8.03 (1H, d, *J* 7.8 Hz, 9-H or 6-H); δ_C [67.8 MHz, $(CD_3)_2SO$] 28.6 (q, NMe), 58.8 (t, CH_2OH), 101.1, 105.7, 111.4, 122.0, 122.2, 123.5 (d, C-4, C-6, C-7, C-8, C-9, C-10), 126.4, 126.7, 127.0, 131.7 (s, C-3, C-4a, C-9a, C-10a), and 156.7 (s, C-1); *m/z* 228 (M^+, 100%), 231 (M-CH_3, 14), 211 (M-OH, 35), and 197 (M-CH_2OH, 8).

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