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1-Azatriene Cyclisation as a Route to Annelated Pyrido[4,3-*b*]indoles[1]

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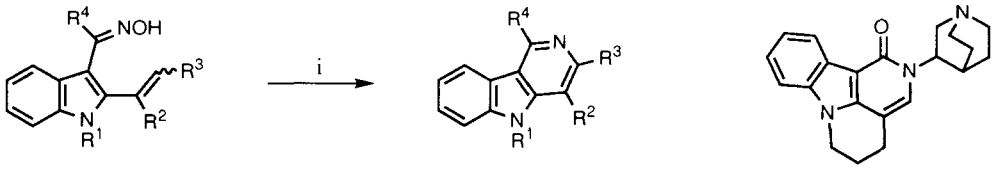
Abstract: Derivatives of indole-3-carbaldehyde oxime have been prepared that bear a carbon–carbon double bond at C-2 and a five- or six-membered ring linking the α-carbon atom of the vinyl group and the indole nitrogen atom. Compound **9**, with a five-membered ring linking the two atoms, failed to undergo a cyclisation reaction on heating. However the oximes **16** and **22**, with a six-membered ring linking the two atoms, cyclised in boiling toluene. The cyclisation led to the formation of the pyridoindoles **17** and **18**, respectively. © 1997 Elsevier Science Ltd.

We have previously described examples of the thermal electrocyclic ring closure of 1-azatrienes, a process that leads to the formation of a variety of fused pyridines.[2] Azatriene cyclisations have also been used by Hibino and his co-workers to prepare carbolines from indoles.[3] In particular, they have shown that pyrido[4,3-*b*]indoles can be prepared by cyclisation and dehydration of oximes **1** in boiling toluene (Scheme 1).[4] The aim of the present work was to investigate routes to analogues of the oximes **1** but with a tether linking the indole nitrogen to the pyridine ring. The subsequent electrocyclic ring closure should then provide a route to annelated pyrido[4,3-*b*]indoles. One of the few examples of this type of ring system in the literature is the indolonaphthyridone **2**, which acts as a conformationally restricted 5-HT_3 receptor antagonist.[5]



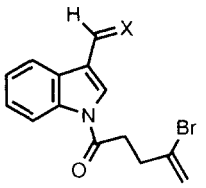
1 **2**

Scheme 1. i, toluene, 110 °C.

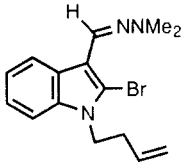
The first attempts to construct suitable precursors were based on the *N*-acylation of indole-3-carbaldehyde. 4-Bromo-4-pentenoic acid[6] was converted into its acid chloride and this reacted with indole-3-carbaldehyde in pyridine to give the 1,3-disubstituted indole **3** in moderate yield. The indole was designed to undergo an intramolecular Heck reaction. Similar reactions have previously been described for 1-acylindoles, particularly by Grigg and co-workers.[7] However,the only product that could be isolated from the attempted cyclisation of **3** was indole-3-carbaldehyde. In order to determine whether the 3-formyl group was promoting deacylation,

the less electrophilic *N,N*-dimethylhydrazone **4** was prepared. This compound also failed to cyclise under the conditions of the Heck reaction.

Heck reactions of *N*-alkenylindoles were then investigated We first prepared the dimethylhydrazone **5** from 2-bromoindole-3-carbaldehyde. The intramolecular Heck reaction gave a product in low yield which, from its NMR spectrum, was consistent with the structure **6**. The reaction was not pursued because of the inefficiency of the cyclisation. Since iodoarenes are often better starting materials for the Heck reaction than bromoarenes, we investigated the cyclisation of 1-(but-1-en-4-yl)-2-iodoindole **7**. This gave the pyrrolo[1,2-*a*]indole **8** in moderate yield with palladium(II) acetate, triphenylphosphine and potassium carbonate in DMF. In common with many other reported cylisations of this type, the 5-*exo-trig* cyclisation occurs in preference to the alternative 6-*endo-trig* process. The oxime **9** was then prepared by formylation of the indole **8** followed by reaction of the aldehyde with hydroxylamine. The oxime proved to be remarkably stable: it was recovered from boiling decalin. Apparently the fused five-membered ring prevents the expected electrocyclic ring closure from taking place, perhaps because the carbon and nitrogen termini of the azatriene are held too far apart.



3; X = O
4; X = $NNMe_2$



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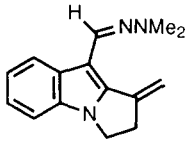

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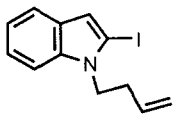

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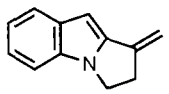

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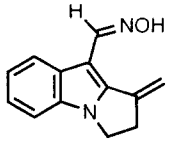

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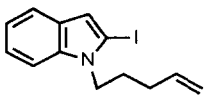
The intramolecular Heck reaction of the iodoindole **10**, bearing a longer alkenyl chain, proceeded smoothly and gave the required pyrido[1,2-*a*]indole **11**. The major product was, however, the isomeric alkene **12**. The cyclisation was carried out in acetonitrile at 80 °C. After 85 min the ratio of **11** to **12** was 1:9 but when the reaction time was reduced to 45 min the ratio was 1:1. Evidently the kinetic product **11** isomerises in the presence of palladium acetate. Grigg and co-workers have shown that double bond isomerisation is suppressed when thallium(I) salts are present.[8] In this reaction the addition of thallium(I) acetate reduced, but did not eliminate, the formation of **12**; the isomers **11** and **12** were obtained in good yield and in a ratio of 3:1.



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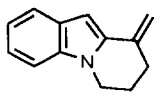

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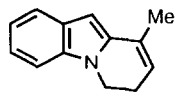
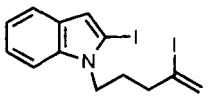


12

In order to avoid the problem of double bond isomerisation, other routes to the alkenylindole **11** were investigated. The iodopentenylindole **13** was prepared from 2-iodoindole and 2,5-diiodopent-1-ene[9] and was

subjected to palladium catalysed cross coupling. The coupled product **11** was isolated free from isomeric impurities but in low yield.



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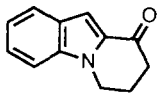

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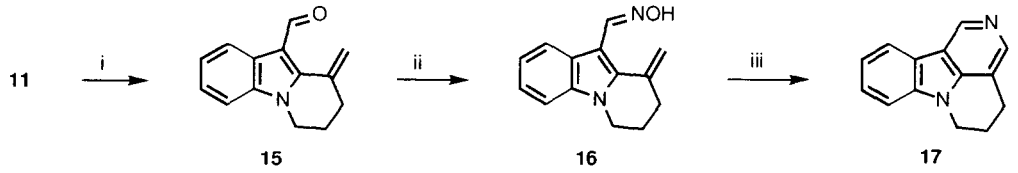
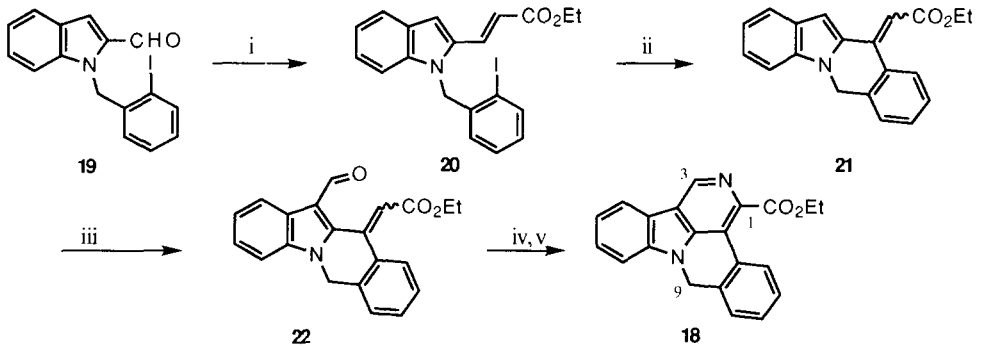
A bettter approach proved to be a Wittig reaction with the known[10] ketone **14.** This reacted with triphenylphosphonium methylide to give the alkene **11** cleanly and in good yield. A standard series of reactions, as outlined in Scheme 2, gave 5,6-dihydro-4*H*-indolo[3,2,1-*ij*][1,6]naphthyridine **17** by way of the aldehyde **15** and the oxime **16**. As with the examples reported by Hibino and co-workers, the cyclisation took place in boiling toluene. The product was assigned structure **17** on the basis of its ^{1}H NMR an mass spectra.



Scheme 2. i, $POCl_3$, DMF (72%); ii, $HONH_3^+ Cl^-$, KOAc (31%); iii, toluene, 110 °C (65%)

Another example of this ring system but containing an additional fused benzene ring, compound **18**, was prepared by way of an intramolecular Heck reaction. The series of reactions used to prepare compound **18** is outlined in Scheme 3.



Scheme 3. i, $(EtO)_2POCH_2CO_2Et$, KOH (74%); ii, $Pd(OAc)_2$, PPh_3, TlOAc, MeCN, 80 °C (90%); iii, $POCl_3$, DMF (57%); iv, $HONH_3^+ Cl^-$, KOAc, MeOH, heat; v, toluene, 110 °C (60%).

The aldehyde **19** was converted into the αβ-unsaturated ester **20** in good yield using the Wadsworth-Emmons reaction. The intramolecular Heck reaction then gave the tetracyclic ester **21** in high yield but as a mixture of stereoisomers that was carried through the subsequent steps. Vilsmeier–Haack formylation of the mixture gave the aldehydes **22**. An attempt to prepare the corresponding oximes in boiling methanol led to the formation of a mixture that contained the isomeric oximes together with a third component. This was tentatively identified as the required product of cyclisation **18**. Methanol was then removed and the mixture was heated in boiling toluene for 8 h to complete the cyclisation. The ester **18** was then isolated in 60% yield,

based on the aldehydes **22**, by column chromatography. The pentacyclic ester **18** was obtained as an orange crystalline solid. The ^{1}H NMR spectrum showed a signal for H-3 as a singlet (δ 8.93) and the two hydrogen atoms at H-9 appeared as a singlet at δ 5.33.

These two examples indicate that the electrocyclisation of oximes is a useful method for the preparation of indolo[3,2,1-*ij*][1,6]naphthyridines.

EXPERIMENTAL

General ^{1}H NMR spectra were recorded on a Bruker ACE200 spectrometer operating at 200MHz and (where indicated) on a Bruker AMX400 instrument operating at 400 MHz. The solvent is deuteriochloroform except where indicated otherwise. Mass spectra were recorded under electron impact at 70 eV on a VG Micromass 7070E instrument. M.p.'s were recorded on a Reichert hot stage and are uncorrected. Flash chromatography was performed with Merck 9385 silica as the stationary phase.

Ethyl 4-bromopent-4-enoate.[6] Lithium diisopropylamide (10 mmol) [freshly prepared *in situ* from diisopropylamine (1.39 ml, 10 mmol) and butyllithium (4.7 ml, 2.3 M, 11 mmol) in THF (1 ml) at 0 °C)] in dry THF (13 ml) was added dropwise to a well stirred solution of copper(I) iodide (3.8 g, 20 mmol) in THF (38 ml) and dry ethyl acetate (0.98 ml, 10 mmol) at –110 °C. The suspension was allowed to warm to –30 °C, 2,3-dibromopropene (1.0 g, 5 mmol) in THF (13 ml) was added dropwise and the solution was stirred for 1.5 h. The reaction mixture was quenched with saturated ammonium chloride, extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to leave the crude product. Flash chromatography and elution with ether–cyclohexane (2:3) gave ethyl 4-bromo-4-pentenoate (0.54 g, 52%) as a yellow oil; δ (200 MHz) 1.27 (3 H, t, *J* 7.0 Hz), 2.57 (2 H, t, *J* 7.0 Hz), 2.73 (2 H, t, *J* 7.0 Hz), 4.11 (2 H, q, *J* 7.0 Hz), 5.44 (1 H, d, *J* 4.0 Hz) and 5.61 (1 H, d, *J* 2.0 Hz); ν_{max} (film)/cm^{-1} 1738 and 1631.

4-Bromopent-4-enoic acid.[6] Ethyl 4-bromopent-4-enoate (0.54 g,2.62 mmol) was hydrolysed by reaction with potassium hydroxide in aqueous ethanol at room temperature to give 4-bromopent-4-enoic acid (0.27 g, 58%) as a yellow oil; δ (400 MHz) 2.55 (2 H, t, *J* 7.3 Hz), 2.66 (2 H, t, *J* 7.3 Hz), 5.37 (1 H, s), 5.58 (1 H, s) and 11.03–11.29 (1 H, br, OH); ν_{max} (film)/cm^{-1} 2926, 2675, 1712 and 1632.

4-Bromopent-4-enoyl chloride. 4-Bromopent-4-enoic acid (200) (0.80 g, 4.48 mmol) was dissolved in thionyl chloride (10 ml) and the solution was heated under reflux for 1 h. The excess thionyl chloride was removed *in vacuo* to leave 4-bromopent-4-enoyl chloride (0.76 g, 90%) as a brown oil, ν_{max} (film)/cm^{-1} 1796 and 1642, which was used without further purification.

1-(2-Bromopent-1-en-5-oyl)indole-3-carbaldehyde **3**. To a stirred solution of indole-3-carbaldehyde (0.69 g, 4.77 mmol) in pyridine (5 ml) was added 4-bromopent-4-enoyl chloride (0.94 g, 4.77 mmol) followed by a catalytic amount of 4-dimethylaminopyridine. The reaction mixture was stirred at room temperature for 17 h, washed with water and the organic product extracted into ethyl acetate. The extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography and elution with ethyl acetate–cyclohexane (4:1) gave *1-(2-bromopent-1-en-5-oyl)indole-3-carbaldehyde* **3** (0.58 g, 40%) as a yellow solid, m.p. 75–77 °C (Found: C, 54.9; H, 3.9; N, 4.5. $C_{14}H_{12}BrNO_2$ requires C, 54.9; H, 3.9; N, 4.5%); δ (200 MHz) 2.95 (2 H, t, *J* 7.8 Hz), 3.22 (2 H, t, *J* 7.8 Hz), 5.52 (1 H, d, *J* 2.1 Hz), 5.78 (1 H, d, *J* 2.1 Hz), 7.34–7.48 (2 H, m,), 8.08 (1 H, s, H-2), 8.21–8.26 (1 H, m), 8.34–8.39 (1 H, m) and 10.08 (1 H, s, CHO); ν_{max} (film)/cm^{-1} 1731, 1673 and 1552; *m/z* 307.002 (M^+, 4%. $C_{14}H_{12}BrNO_2$ requires 307.003), 226 (26) and 145 (100).

1-(2-Bromopent-1-en-5-oyl)indole-3-carbaldehyde N,N-*dimethylhydrazone* **4**. To a solution of 1-(2-bromopent-1-en-5-oyl)indole-3-carbaldehyde **3** (0.30 g, 0.982 mmol) in dry dichloromethane (15 ml) was added 1,1-dimethylhydrazine (0.07 ml, 0.982 mmol) followed by a catalytic amount of 4-toluenesulfonic acid. The reaction mixture was heated under reflux for 3 h and the solvent was distilled off. Purification of the residue by flash chromatography and elution with ether–cyclohexane (9:1) gave *1-(2-bromopent-1-en-5-oyl)indole-3-carbaldehyde* N,N-*dimethylhydrazone* **4** (0.30 g, 88%) as a yellow solid, m.p. 138–40 °C (Found:

C, 55.0; H, 5.2; N, 11.9. $C_{16}H_{18}BrN_3O$ requires C, 55.2; H, 5.2; N, 12.1%); δ (400 MHz) 2.94 (2 H, t, *J* 7.4 Hz), 2.99 (6 H, s, NMe2), 3.15 (2 H, t, *J* 7.4 Hz), 5.49 (1 H, s), 5.75 (1 H, s), 7.30–7.39 (2 H, m), 7.43 (1 H, s, H-2), 7.49 (1 H, s, CH=N), 8.27 (1 H, d, *J* 8 Hz) and 8.42 (1 H, d, *J* 8.0 Hz); ν_{max} (KBr)/cm^{-1} 2854, 2782, 1709 and 1631; *m/z* 347.064 (M^+, 12%. $C_{16}H_{18}BrN_3O$ requires 347.063) and 187 (100).

2-Bromoindole-3-carbaldehyde.[11] Phosphorus tribromide (8.92 ml, 93.9 mmol) was added dropwise to a solution of dry DMF (8.73 ml, 112.7 mmol) in dry dichloromethane (30 ml) at 0 °C. The mixture was stirred at 0 °C for 1 h and a pale yellow suspension was formed. A solution of oxindole (5.0 g, 37.6 mmol) in dry dichloromethane (50 ml) was then added and the mixture was heated under reflux for 5 h. The solvent was removed *in vacuo*, the oily residue poured onto ice water (*ca* 100 g) and the solution was neutralised with solid sodium hydrogen carbonate. The organic product was extracted into ether, the solution was washed with saturated sodium hydrogen carbonate, dried ($MgSO_4$) and the solvent removed *in vacuo*. The residue was subjected to flash chromatography; ether–cyclohexane (4:1) gave *2-bromoindole-3-carbaldehyde* (2.42 g, 28%) as an orange solid, m.p. 196–198 °C (from methanol) (Found: C, 48.3; H, 2.7; N, 6.2. C_9H_6BrNO requires C, 48.3; H, 2.7; N, 6.2 %); δ (400 MHz; CD_3COCD_3) 7.24–7.31 (2 H, m), 7.46 (1 H, dd, *J* 2.0 and 8.0 Hz), 8.19 (1 H, d, *J* 8.0 Hz) and 10.02 (1 H, s, CHO); ν_{max} (nujol)/cm^{-1} 2923, 2854 and 1642; *m/z* 222.963 (M^+, 100%. C_9H_6BrNO requires 222.963) and 194 (11).

2-Bromo-1-(but-1-en-4-yl)indole-3-carbaldehyde. To a solution of 2-bromoindole-3-carbaldehyde(1.02 g, 4.59 mmol) in dry THF (15 ml) at 0 °C was added sodium hydride (0.23 g, 9.58 mmol, 60% mineral oil dispersion) in portions over 5 min and the reaction mixture allowed to stir for 15 min at room temperature. 4-Bromobut-1-ene (0.46 ml, 4.53 mmol) was added and the reaction mixture was heated under reflux for 1.5 h. A further portion of sodium hydride (0.11 g, 4.58 mmol) was added at 0 °C followed by 4-bromobut-1-ene (0.21 ml, 2.07 mmol) and the reaction mixture heated under reflux for a further 2 h. The mixture was poured onto ice water, the solvent removed *in vacuo* and the suspension taken up into ethyl acetate. The organic extracts were combined, dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography and elution with cyclohexane–ethyl acetate (7:3) gave *2-bromo-1-(but-1-en-4yl)indole-3-carbaldehyde* (217) (0.49 g, 39%) as a yellow solid, m.p. 48–50 °C; d (200MHz) 2.50–2.61 (2 H, m), 3.95 (2 H, t, *J* 7.3 Hz), 4.71–4.81 (2 H, dd, *J* 10.4 and 17.0 Hz), 5.50 (1 H, ddt, *J* 10.4, 17.0 and 6.8 Hz), 7.13–7.16 (3 H, m), 8.14–8.18 (1 H, m) and 10.01 (1 H, s, CHO); ν_{max} (CH_2Cl_2)/cm^{-1} 2926, 2816 and 1652; *m/z* 277.010 (M^+, 25%. $C_{13}H_{12}BrNO$ requires 277.010), 236 (100) and 198 (83).

2-Bromo-1-(but-1-en-4-yl)indole-3-carbaldehyde N,N-*dimethylhydrazone* **5**. A solution of 2-bromo-1-(but-1-en-4-yl)indole-3-carbaldehyde (0.49 g, 1.77 mmol) in dichloromethane (20 ml) containing 1,1-dimethylhydrazine (0.2 ml, 2.66 mmol) and a catalytic amount of 4-toluenesulfonic acid was heated under reflux for 3.5 h. The solvent was removed *in vacuo* and the residue subjected to flash chromatography. Elution with cyclohexane–ethyl acetate (1:1) gave *2-bromo-1-(but-1-en-4yl)indole-3-carbaldehyde* N,N-*dimethylhydrazone* **5** (0.44 g, 78%) as a yellow oil (Found: C, 56.2; H, 5.6; N, 13.1. $C_{15}H_{18}BrN_3$ requires C, 56.4; H, 5.6; N, 13.1%); δ (400 MHz) 2.44–2.49 (2 H, m), 2.94 (6 H, s, NMe_2), 4.18 (2 H, t, *J* 7.4 Hz), 5.01–5.07 (2 H, dd, *J* 17.3 and 10.2 Hz), 5.77 (1 H, ddt, *J* 17.3, 10.2 and 6.8 Hz), 7.13–7.27 (3 H, m), 7.54 (1 H, s, C<u>H</u>=N) and 8.36 (1 H, d, *J* 7.7 Hz); ν_{max} (CH_2Cl_2)/cm^{-1} 3938, 2826 and 1514; *m/z* 319.069 (M^+, 100%. $C_{15}H_{18}BrN_3$ requires 319.068), 321 (99), 278 (33), 240 (86) and 197 (95).

2,3-Dihydro-1-(methylidene)pyrrolo[1,2-a]indole-9-carbaldehyde N,N-*dimethylhydrazone* **6**. To a solution of 1-(but-1-en-4-yl)-2-bromoindole-3-carbaldehyde *N,N*-dimethylhydrazone **5** (0.44 g, 1.38 mmol) in dry acetonitrile (55 ml) was added palladium(II) acetate (0.03 g, 10 mol%), triphenylphosphine (0.07 g, 20 mol%), tetraethylammonium chloride (0.25 g, 1.38 mmol) and anhydrous potassium carbonate (0.38 g, 2.76 mmol). The reaction mixture was heated under reflux for 40 min, the inorganic salts were filtered off and the solvent removed *in vacuo* to leave a deep blue solid. Repeated flash chromatography and elution with ethyl acetate-cyclohexane (1:1) gave *2,3-dihydro-1-(methylidene)pyrrolo[1,2-a]indole-9-carbaldehyde* N,N-*dimethylhydrazone* **6** (0.04 g, 12%), δ (400 MHz) 2.97 (6 H, s, NMe_2), 3.31–3.35 (2 H, m), 4.15 (2 H, t, *J* 7.0 Hz), 5.31 (1 H, s), 6.03 (1 H, s), 7.15–7.26 (4 H, m) and 8.16 (1 H, d, *J* 8.1 Hz); *m/z* 239 (M^+, 100%) and 195 (76).

1-(But-1-en-4-yl)-2-iodoindole **7**. To a solution of 2-iodoindole[12] (1.0 g, 4.12 mmol) in dry THF (10 ml) at 0 °C was added sodium hydride (60% mineral oil dispersion, 0.21 g, 8.75 mmol) in portions over 5 min and the mixture was stirred at room temperature for 15 min. 4-Bromobut-1-ene (0.42 ml, 4.14 mmol) was added dropwise and the reaction mixture was heated under reflux for 2 h. Further portions of sodium hydride (0.1 g, 4.17 mmol) and 4-bromobut-1-ene (0.21 ml, 2.07 mmol) were added and the reaction mixture heated under reflux for a further 7 h. The mixture was quenched with water and the organic product was was extracted into ethyl acetate. The organic extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification of the residue by chromatography and elution with cyclohexane-ether (4:1) gave *1-(but-1-en-4-yl)-2-iodoindole* **7** (0.65 g, 53%) as a pale yellow oil; δ (200 MHz) 2.40–2.50 (2 H, m), 4.12 (2 H, t, *J* 6.2 Hz), 5.01–5.10 (2H, dd, J_{cis} 9.9 and J_{trans} 15.2 Hz), 5.78 (1 H, ddt, J_{cis} 9.9, J_{trans} 15.2 and *J* 6.0 Hz), 6.73 (1H, s, H-3), 6.99–7.16 (2 H, m), 7.24 (1 H, d, *J* 8.4 Hz) and 7.47 (1 H, d, *J* 7.6 Hz); ν_{max} (film)/cm^{-1} 3062, 2924, 2853 and 1614; *m/z* 297.001 (M^+, 31%. $C_{11}H_{12}IN$ requires 297.001), 256 (91), 170 (100) and 129 (63).

2,3-Dihydro-1-(methylidene)pyrrolo[1,2-a]indole **8**. To a solution of 1-(but-1-en-4-yl)-2-iodoindole **7** (0.50 g, 1.68 mmol) in dry DMF (60 ml) was added palladium(II) acetate (0.04 g, 10 mol%), triphenylphosphine (0.08 g, 20 mol%) tetraethylammonium chloride (0,31 g, 1.68 mmol) and anhydrous potassium carbonate (0.46 g, 3.36 mmol). The reaction mixture was heated under reflux for 6 h, the inorganic salts were filtered off and the solvent removed *in vacuo*. Flash chromatography and elution with cyclohexane-ether (9:1) gave *2,3-dihydro-1-(methylidene)pyrrolo[1,2-a]indole* **8** (0.10 g, 35%) as a yellow solid, δ (400 MHz) 3.19–3.23 (2 H, m), 4.07 (2 H, t, *J* 6.9 Hz), 5.06 (1 H, s), 5.48 (1 H, s), 6.42 (1 H, s, H-9), 6.99 (1 H, td *J* 7.5 and 1.8 Hz) 7.05 (1 H, td, *J* 7.5 and 1.8 Hz), 7.17–7.20 (1 H, m) and 7.51 (1 H, dd, *J* 7.9 and 0.8 Hz); ν_{max} (CH_2Cl_2)/cm^{-1} 2928 and 1614; *m/z* 169.089 (M^+, 100%. $C_{12}H_{11}N$ requires 169.089). The compound was used for the next reaction without further purification.

2,3-Dihydro-1-(methylidene)pyrrolo[1,2-a]indole-9-carbaldehyde. Phosphorus oxychloride (0.1 ml, 0.976 mmol) was added to a cooled (0 °C) solution of DMF (0.3 ml, 3.91 mmol) and 2,3-dihydro-1-(methylidene)pyrrolo[1,2-*a*]indole **8** (0.15 g, 0.89 mmol) in DMF (1 ml) was added over 10 min. The reaction mixture was stirred at 0 °C for 1 h, poured onto ice water and neutralised with saturated sodium hydrogen carbonate. The mixture was boiled for 1 min, the organic product extracted into ethyl acetate and dried ($MgSO_4$). Removal of the solvent removed *in vacuo* followed by purification of the residue by flash chromatography and elution with ethyl acetate-cyclohexane gave *2,3-dihydro-1-(methylidene)pyrrolo[1,2-a]indole-9-carbaldehyde* (0.10 g, 57%) as a red-brown solid, m.p. 90–92 °C, δ (200 MHz) 3.17–3.23 (2 H, m), 3.98 (2 H, t, *J* 6.0 Hz), 5.39 (1 H, s), 6.26 (1 H, s), 7.09–7.24 (3 H, m), 8.07–8.13 (1 H, m) and 10.23 (1 H, s, CHO); ν_{max} (CH_2Cl_2)/cm^{-1} 2927, 1650 and 1527; *m/z* 197.0837 (M^+, 100%. $C_{13}H_{11}NO$ requires 197.0840) and 169 (55).

2,3-Dihydro-1-(methylidene)pyrrolo[1,2-a]indole-9-carbaldoxime **9**. A solution of 2,3-dihydro-1-(methylidene)pyrrolo[1,2-*a*]indole-9-carbaldehyde (0.10 g, 0.51 mmol) in methanol (15 ml) containing hydroxylamine hydrochloride (0.07 g, 1.0 mmol) and potassium acetate (0.1 g, 1.0 mmol) was heated under reflux for 17 h. The solvent was removed *in vacuo* to leave crude oxime. Purification by flash chromatography and elution with ethyl acetate-cyclohexane (1:1) gave *2,3-dihydro-1-(methylidene)pyrrolo[1,2-a]indole-9-carbaldoxime* **9** (0.07 g, 65%) as a red solid, δ (200MHz; CD_3COCD_3) 3.27–3.36 (2 H, m), 4.16 (2 H, t, *J* 6.0 Hz), 5.35 (1 H, s), 5.97 (1 H, s), 7.07–7.23 (2 H, m), 7.30 (1 H, d, *J* 7.3 Hz), 8.03 (1 H, d, *J* 8 Hz), 8.60 (1 H, s, CH=N) and 9.93 (1 H, s); ν_{max} (CH_2Cl_2)/cm^{-1} 3571, 2928, 2898, 1646 and 1614; *m/z* 212.095 (M^+, 28%. $C_{13}H_{12}N_2O$ requires 212.095) and 195 (100).

The oxime **9** was recovered after being heated in decalin (b.p. 187 °C) for 1 h.

2-Iodo-1-(pent-1-en-5-yl)indole **10**. To a solution of sodium hydride (60% mineral oil dispersion, pentane washed (0.42 g, 17.5 mmol) cooled to 0 °C was added 2-iodoindole[12] (2.0 g, 8.24 mmol) in dry THF (20 ml) dropwise and the reaction mixture allowed to stir at room temperature for 20 min. 5-Bromopent-1-ene (1.27 ml, 8.24 mmol) was added dropwise and the reaction mixture was heated under reflux for 5 h. The reaction mixture was quenched with water and the organic product extracted into ethyl acetate. The extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography and elution with

cyclohexane-ether (4:1) gave *2-iodo-1-(pent-1-en-5-yl)indole* **10** (2.43 g, 95%) as a yellow oil (Found: C, 50.9; H, 4.7; N, 4.5. $C_{13}H_{14}IN$ requires C, 50.2; H, 4.5; N, 4.5%); δ (400MHz) 1.82–1.89 (2 H, m), 2.11–2.14 (2 H, m), 4.13 (2 H, t, *J* 7.6 Hz), 5.03 (1 H, dd, J_{cis} 10.2 and J_{gem} 1.8 Hz), 5.07 (1 H, dd, J_{trans} 17.1 and *J* 1.8 Hz), 5.83 (1 H ddt, J_{trans} 17.1, J_{cis} 10.2 and *J* 6.3 Hz), 6.77 (1 H, s, H-3), 7.03–7.07 (1 H, m), 7.11–7.15 (1 H, m), 7.29 (1 H, d, *J* 8.2 Hz) and 7.50 (1 H, d, *J* 8.2 Hz); ν_{max} (CH_2Cl_2)/cm^{-1} 3062, 2929, 2853, 1614 and 1438; *m/z* 311.017 (M^+, 42%. $C_{13}H_{14}IN$ requires 311.017), 256 (32), 184 (100) and 130 (77).

*7,8-Dihydro-6(9H)-(methylidene)pyrido[1,2-a]indole (***11** *and 6,7-Dihydro-9-methylpyrido[1,2-a]indole* **12** To a solution of 2-iodo-1-(pent-1-en-5-yl)indole **10** (0.78 g, 2.51 mmol) in dry acetonitrile (100 ml) was added palladium(II) acetate (0.03 g, 10 mol%), triphenylphosphine (0.07 g, 20 mol%) and thallium(I) acetate (0.66 g, 2.51 mmol). The reaction mixture was heated to reflux for 15 min (TLC monitoring), the inorganic salts were removed by filtration and the solvent distilled off. Flash chromatography and elution with cyclohexane-ether (4:1) gave a 3:1 mixture (by NMR) of *7,8-dihydro-6(9H)-(methylidene)pyrido[1,2-a]indole* **11** and *6,7-dihydro-9-methylpyrido[1,2-a]indole* **12** (0.40 g, 87%) as a yellow solid, m.p. 82–84 °C (Found: C, 84.8; H, 7.2; N, 7.6. $C_{13}H_{13}N$ requires C, 85.2; H, 7.2; N, 7.6%). The following signals in the NMR spectrum were assigned to the minor isomer **12** (the spectrum of **11** is given below): δ (400 MHz) 2.06 (s, Me), 2.53–2.58 (m, CH_2), 3.95–4.05 (m, CH_2), 5.69–5.71 (m, C=CH), 6.40 (s, H-10), 7.03–7.22 (m) and 7.54 (d, *J* 7.6 Hz); *m/z* 183.105 (M^+, 100%. $C_{13}H_{13}N$ requires 183.105) and 168 (50).

2,5-Diiodopent-1-ene. To a solution of sodium iodide (4.63 g, 30.9 mmol) in acetonitrile (50 ml) was added chlorotrimethylsilane (3.92 ml, 30.9 mmol) followed by water (0.28 g, 15.5 mmol). The mixture was stirred at room temperature for 10 min then 5-iodopent-1-yne (5.0 g, 25.8 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. Water (50 ml) was added and the organic components were extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography and elution with cyclohexane–ether (4:1) gave *2,5-diiodopent-1-ene* (5.24 g, 63%) as a pale yellow oil (Found: C, 18.5; H, 2.5. $C_5H_8I_2$ requires C, 18.5; H, 2.5%); δ (200 MHz) 1.94–2.08 (2 H, m), 2.48 (2 H, t, *J* 6.6 Hz), 3.14 (2 H, t, *J* 6.6 Hz), 5.77 (1 H, s) and 6.15 (1 H, s); ν_{max} (film)/cm^{-1} 2925, 2849 and 1614; *m/z* 321.871 (*M*$^+$, 3%. $C_5H_8I_2$ requires 321.871), 195 (100) and 68 (80).

2-Iodo-1-(2-iodopent-1-en-5-yl)indole **13**. To a solution of sodium hydride (60% mineral oil dispersion, pentane washed; 0.62 g, 25.8 mmol) in dry THF (10 ml) at 0 °C was added 2-iodoindole (3.0 g, 12.3 mmol) in THF (20 ml) dropwise and the resulting green reaction mixture was stirred at 0 °C for 15 min. 2,5-Diiodopent-1-ene (3.97 g, 12.3 mmol) was added dropwise and the reaction mixture was heated under reflux for 4 h. It was then cooled, quenched with water and extracted with ethyl acetate The extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography and elution with cyclohexane–ether (4:1) gave *2-iodo-1-(2-iodopent-1-en-5-yl)indole* **13** (2.33 g, 43%) as a yellow oil (Found: C, 36.6; H, 3.1; N, 3.1. $C_{13}H_{13}I_2N$ requires C, 35.7; H, 3.0; N, 3.2%); δ (400 MHz) 1.88–1.95 (2 H, m), 2.39 (2 H, t, *J* 7.2 Hz), 4.03 (2 H, t, *J* 7.6 Hz), 5.70 (1 H, s), 6.00 (1 H, s), 6.74 (1 H, s, H-3), 7.02 (1 H, td *J* 7.4 and 0.8 Hz), 7.09 (1 H, t, *J* 8.0 Hz), 7.29 (1 H, d, *J* 7.4 Hz) and 7.48 (1 H, dd, *J* 8.0 and 0.8 Hz); ν_{max} (film)/cm^{-1} 3058, 2097, 2853 and 1614; *m/z* 436.914 (M^+, 10%. $C_{13}H_{13}I_2N$ requires 436.914), 256 (31), 183 (100) and 129 (87).

7,8-Dihydro-6(9H)-(methylidine)pyrido[1,2-a]indole **11** *from the indole* **13**. To a solution of 2-iodo-1-(2-iodopent-1-en-5-yl)indole **13** (2.33 g, 5.3 mmol) in dry acetonitile (90 ml) was added palladium(II) acetate (0.12 g, 10 mol%), triphenylphosphine (0.7 g added over 2 h, 0.2 g at t = 0, 1 h, and 0.3 g at t = 2 h, 50 mol%) and potassium carbonate (1.84 g, 13.3 mmol). After 8 h at reflux fresh catayltic mixture was added [palladium acetate (0.12 g, 10 mol%), triphenylphosphine (0.7 g 50 mol%) and potassium carbonate (1.84 g, 13.3 mmol)] and the reaction mixture was heated for a further 14 h. The inorganic salts were removed by filtration and the solvent removed *in vacuo* to leave the crude product. Purification by flash chromatography and elution with cyclohexane–ether (4:1) gave *the indole* **11** (0.21 g, 25%).

7,8-Dihydro-6(9H)-(methylidene)pyrido[1,2-a]indole **11** *from the ketone* **14**. To a stirred suspension of methyltriphenylphosphonium bromide (3.57 g, 10.0 mmol) in dry THF (25 ml) at 0 °C was added butyllithium (2.5 M, 4.0 ml, 10.0 mmol). After 30 min. a solution of 7,8-dihydropyrido[1,2-*a*]indol-9(6*H*)-one **14**[10] (1.54 g, 8.3 mmol) in dry THF (20 ml) was added dropwise and the mixture stirred at 0 °C for 1.5 h. The reaction

mixture was washed with brine, extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo* to leave the crude product. Flash chromatography and elution with ether–cyclohexane (7:3) gave *7,8-dihydro-6(9H)-(methylidene)pyrido[1,2-a]indole* **11** (1.04 g, 68%) as a yellow solid, m.p. 82–84 °C (from cyclohexane) (Found: C, 84.7; H, 7.2; N, 7.6. $C_{13}H_{13}N$ requires C, 85.2; H, 7.2; N, 7.6%); δ (400 MHz) 2.02–2.08 (2 H, m), 2.54–2.57 (2 H, m), 3.99 (2 H, t, *J* 6.0 Hz), 4.96 (1 H, s), 5.59 (1 H, s), 6.72 (1 H, s, H-10), 7.05 (1 H, t, *J* 7.4 Hz), 7.11 (1 H, t, *J* 7.4 Hz) 7.15 (1 H, d, *J* 8.0 Hz) and 7.54 (1 H, d, *J* 7.8 Hz); ν_{max} (CH_2Cl_2)/cm^{-1} 2929, 2869, 1627, 1524 and 875; *m/z* 183.105 (M^+, 100%. $C_{13}H_{13}N$ requires 183.105) and 182 (62).

7,8-Dihydro-6(9H)-(methylidene)pyrido[1,2-a]indole-10-carbaldehyde **15**. Phosphorus oxychloride (0.48 ml, 4.81 mmol) was added dropwise to a cooled (0 °C) solution of DMF (1.5 ml, 19.2 mmol) and a solution of 7,8-dihydro-6(9*H*)-(methylidene)pyrido[1,2-*a*]indole **11** (0.80 g, 4.37 mmol) in dry DMF (3 ml) was added dropwise over 5 min. The reaction mixture was stirred at 0 °C for 1 h, poured onto ice water and made neutral with saturated sodium hydrogen carbonate. The organic product was extracted into ethyl acetate, dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography and elution with ethyl acetate–cyclohexane (1:1) gave *7,8-dihydro-6(9H)-(methylidene)pyrido[1,2-a]indole-10-carbaldehyde* **15** (0.66 g, 72%) as a yellow solid, m.p. 84–86 °C (Found: C, 79.2; H, 6.2, H, 6.6. $C_{14}H_{13}NO$ requires C, 79.5; H, 6.2; N, 6.6%); δ (400 MHz) 2.18–2.24 (2 H, m), 2.61 (2 H, t, *J* 6.1 Hz), 4.04 (2 H, t, *J* 6.5 Hz), 5.46 (1 H, s), 5.72 (1 H, s), 7.22–7.29 (3 H, m), 8.37–8.39 (1 H, m) and 10.24 (1 H, s, CHO); ν_{max} (KBr)/cm^{-1} 2943, 2868 and 1632; *m/z* 211.100 (M^+, 100%. $C_{14}H_{13}NO$ requires 211.100), 210 (40) and 183 (93).

7,8-Dihydro-6(9H)-(methylidine)pyrido[1,2-a]indole-10-carbaldoxime **16**. To a solution of 7,8-dihydro-6(9*H*)-(methylidine)pyrido[1,2-*a*]indole-10-carbaldehyde **15** (0.66 g, 2.84 mmol) in methanol (10 ml) was added hydroxylamine hydrochloride (0.43g, 5.68 mmol) and potassium acetate (0.61 g, 5.68 mmol). The reaction mixture was heated under reflux for 4 h and the solvent removed *in vacuo*. Flash chromatography and elution with ethyl acetate–cyclohexane (1:1) gave *7,8-dihydro-6(9H)-(methylidine)pyrido[1,2-a]indole-10-carbaldoxime* **16** (0.2 g, 31%) as a yellow solid, m.p. 88–90 °C (Found: C, 74.3; H, 6.2; N, 12.3. $C_{14}H_{14}N_2O$ requires C, 74.3; H, 6.2; N, 12.4%); δ (200 MHz) 2.15–2.22 (2 H, m), 2.56–2.62 (2 H, m), 4.06 (2 H, t, *J* 6.1 Hz), 5.31 (1 H, s), 5.43 (1 H, s), 7.19–7.26 (3 H, m), 8.13–8.17 (1 H, m) and 8.62 (1 H, s, CH=N); ν_{max} (CH_2Cl_2)/cm^{-1} 3570, 2055 and 1605; *m/z* 226.111 (M^+, 10%. $C_{14}H_{14}N_2O$ requires 226.111), 209 (100) and 207 (60).

5,6-Dihydro-4H-indolo[3,2,1-ij][1,6]naphthyridine **17**. A solution of 7,8-dihydro-6(9*H*)-(methylidine)pyrido[1,2-*a*]indole-10-carbaldoxime **16** (0.15 g, 0.664 mmol) in toluene (10 ml) was heated under reflux for 8 h. Removal of the solvent followed by flash and preparative layer chromatography and elution with ethyl acetate–cyclohexane (1:1) gave *5,6-dihydro-4H-indolo[3,2,1-ij][1,6]naphthyridine* **17** (0.09 g, 65%) as a white solid solid,m.p.270 °C (decomp) δ (400 MHz) 2.29–2.35 (2 H, m), 3.03 (2 H, t, *J* 6.2 Hz), 4.19 (2 H, t, *J* 5.8 Hz), 7.28 (1 H, t, *J* 7.4 Hz), 7.40 (1 H, d, *J* 8.0 Hz), 7.49 (1 H, t, *J* 7.6 Hz), 8.11 (1 H, d, *J* 5.8 Hz), 8.29 (1 H, br, s) and 9.12 (1 H, br, s); *m/z* 208.100 (M^+, 100%. $C_{14}H_{12}N_2$ requires 208.100) and 207 (92).

1-(2-Iodobenzyl)indole-2-carbaldehyde **19**. To a solution of indole-2-carbaldehyde (1.0 g, 6.9 mmol) in dry DMF (15 ml) at 0 °C was added sodium hydride (60% mineral oil dispersion, 0.34 g, 14.5 mmol) in portions over 5 min. The solution was stirred at 0 °C for 15–20 min. and a solution of 2–iodobenzyl chloride (1.73 g, 6.9 mmol) in dry DMF (5 ml) was added dropwise. The reaction mixture was stirred at 0 °C for 4 h, diluted with ether and washed with brine. The organic extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. Flash chromatography and elution with chloroform (100%) gave *1-(2-iodobenzyl)indole-2-carbaldehyde* **19** (1.97 g, 77%) as an orange solid, m.p. 112–114 °C (Found: C, 54.2; H, 3.7; N, 3.5. $C_{16}H_{12}INO$ requires C, 53.2; H, 3.4; N, 3.9%); δ (400 MHz) 5.72 (2 H, s, CH_2Ph), 6.13 (1 H, d, *J* 8.0 Hz), 6.81–7.29 (5 H, m), 7.31 (1 H, s, H-3), 7.74 (1 H, d, *J* 8.0 Hz), 7.79 (1 H, d, *J* 8.0 Hz) and 9.84 (1 H, s, CHO); ν_{max} (CH_2Cl_2)/cm^{-1} 1655; *m/z* 360.996 (M^+, 28%. $C_{16}H_{12}INO$ requires 360.996), 234 (68), 217 (99) and 89 (100).

Ethyl 1-(2-iodobenzyl)indole-2-propenoate **20**. A solution of 1-(2-iodobenzyl)indole-2-carbaldehyde **19** (1.35 g, 3.74 mmol) and triethyl phosphonoacetate (0.84 g, 3.74 mmol) in THF (4 ml) was added to a suspenson of powdered potassium hydroxide (0.42 g, 7.48 mmol) in THF (10 ml). The reaction mixture was stirred at room temperature for 2 h. The solvent was removed and the residue was taken up into dichloromethane. The solution was washed with water. The organic extract was dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash chromatography and elution with chloroform gave *ethyl 1-(2-iodobenzyl)indole-2-propenoate* **20** (1.20 g, 74%) as an orange solid, m.p. 158–160 °C (Found: C, 55.2; H, 4.2; N, 3.0. $C_{20}H_{18}INO_2$ requires C, 55.7; H, 4.2; N, 3.2%); δ (400 MHz) 1.29 (3 H, t, *J* 7.0 Hz), 4.19 (2 H, q, *J* 7.0 Hz), 5.36 (2 H, s, CH_2Ph), 6.22 (1 H, d, *J* 7.6 Hz), 6.43 (1 H, d, J_{AB} 15.8 Hz), 6.91–7.24 (1 H, t, *J* 6.8 Hz), 7.01–7.24 (5 H, m) 7.59 (1 H, d, J_{AB} 15.8 Hz), 7.65 (1 H, d, *J* 8.0 Hz) and 7.87 (1 H, d, *J* 7.6 Hz); ν_{max} (KBr)/cm^{-1} 1728; *m/z* 431.039 (M^+, 36%. $C_{20}H_{18}INO_2$ requires 431.038), 358 (53) and 215 (100).

11-(Ethoxycarbonylmethylidene)-6H-indolo[1,2-b]isoquinoline **21**. To a solution of ethyl 1-(2-iodobenzyl)indole-2-propenoate **20** (0.54 g, 1.25 mmol) in dry acetonitrile (150 ml) was added palladium(II) acetate (0.03 g, 10 mol%), triphenylphosphine (0.07 g, 20 mol%) and thallium(I) acetate (0.33 g, 1.25 mmol). The reaction mixture was heated under reflux for 10 min. The inorganic salts were filtered off and the solvent was removed *in vacuo*. Flash chromatography and elution with chloroform (100%) gave *11-(ethoxycarbonylmethylidene)-6H-indolo[1,2-b]isoquinoline* **21** (0.34 g, 90%) m.p. 120 °C as a mixture of stereoisomers in a 1:3 ratio (*E* to *Z*) (Found: C, 79.0; H, 5.6; N, 4.4. $C_{20}H_{17}NO_2$ requires C, 79.2; H, 5.6; N, 4.6%); δ (400 MHz) 1.24 (2 x t, *J* 7.4 Hz, CH_3CH_2 of both isomers), 4.18–4.23 (m, CH_3CH_2 of both isomers) 5.13 (s, NCH_2Ar of minor isomer), 5.17 (s, NCH_2Ar of major isomer), 6.39 (s, C=$CHCO_2Et$ of minor isomer), 6.48 (s, C=$CHCO_2Et$ of major isomer), 6.81 (s, H-12 of minor isomer), 7.05–7.08 (m), 7.16 (s, H-12 of major isomer), 7.18–7.23 (m), 7.29–7.32 (4 H, m), 7.56–7.64 (1 H, m), 7.70 (d, *J* 7.6 Hz, major isomer) and 7.94, d, *J* 7.6 Hz, minor isomer) ν_{max} (CH_2Cl_2)/cm^{-1} 1710 and 1615; *m/z* 303.126 (M^+, 67%. $C_{20}H_{17}NO_2$ requires 303.126), 231 (100) and 230 (92).

11-(Ethoxycarbonylmethylidene)-6H-indolo[1,2-b]isoquinoline-12-carbaldehyde **22**. Phophorus oxychloride (0.11 ml, 1.22 mmol) was added dropwise to a solution of dry DMF (0.38 ml, 4.38 mmol) at 0 °C and 11-(ethoxycarbonylmethylidene)-6*H*-indolo[1,2-*b*]isoquinoline **21** (0.34 g, 1.12 mmol) in dry DMF (3 ml) was immediately added over 5 min. The reaction mixture was stirred at 0 °C for 2 h, poured onto ice water and neutralised with saturated sodium hydrogen carbonate. The mixture was boiled for 1 min, the organic product extracted into ethyl acetate and dried ($MgSO_4$). Removal of the solvent *in vacuo* followed by purification of the residue by flash chromatography and elution with ethyl acetate–cyclohexane (1:1) gave *11-(ethoxycarbonylmethylidene)-6H-indolo[1,2-b]isoquinoline-12-carbaldehyde* **22** (0.21 g, 57%) as a red oil and as a mixture of stereoisomers, δ (200 MHz) 1.22–1.35 (2 x t)), 4.17–4.29 (2 x q), 5.23 (s), 5.26 (s), 6.59 (s), 6.60 (s), 7.25–7.46 (6 H, m), 7.72–7.76 (m,), 7.91–7.95 m), 8.37–8.44 (m), 10.08 (s) and 10.37 (s); ν_{max} (CH_2Cl_2)/cm^{-1} 2982, 1713 and 1656; *m/z* 331.121 (M^+, 6%. $C_{21}H_{17}NO_3$ requires 331.121) and 258 (100).

Ethyl 9H-Benz[c]indolo[3,2,1-ij][1,6]naphthyridine-12-carboxylate **18**. To a solution of 11-(ethoxycarbonylmethylidene)-6*H*-indolo[1,2-*b*]isoquinoline-12-carbaldehyde **22** (0.17 g, 0.55 mmol) in methanol (15 ml) was added hydroxylamine hydrochloride (0.04 g, 1.09 mmol) and potassium acetate (0.05 g, 1.09 mmol). The reaction mixture was heated under reflux for 6 h then the solvent was removed *in vacuo* to leave a mixture. The mixture was dissolved in toluene (10 ml) and heated under reflux for 8 h. The solvent was removed *in vacuo* and the residue was subjected to flash chromatography and elution with ethyl acetate-cyclohexane (1:1). *Ethyl 9H-benz[c]indolo[3,2,1-ij][1,6]naphthyridine-1-carboxylate* **18** (0.11 g, 60%) was isolated as an orange solid, m.p. 178–80 °C, δ (400 MHz) 1.38 (3 H, t, *J* 7.2 Hz), 4.47 (2 H, q, *J* 7.3 Hz), 5.33 (2 H, s, CH_2Ar), 7.13–7.67 (7 H, m), 7.99 (1 H, d, *J* 7.8 Hz) and 8.93 (1 H, s, H-3); ν_{max} (CH_2Cl_2)/cm^{-1} 1732 and 1689; *m/z* 328.121 (M^+, 23%. $C_{21}H_{16}N_2O_2$ requires 328.121), 256 (100) and (56).

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