Tetrahedron Vol. 47, No. 26, pp. 4645-4664, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

A DIECKMANN/RING EXPANSION APPROACH TO TETRAHYDROPYRIDO- AND TETRAHYDROAZEPINO-[1,2-a]INDOLES

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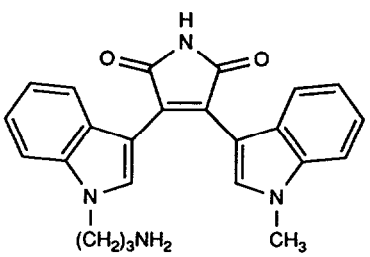
(*Received in UK* 21 *February* 1991)

A general Dieckmann/ring expansion approach to fused [1,2-a]indole systems is reported. This approach has allowed the synthesis of a large variety of substituted systems required for the preparation of a series of potent and selective inhibitors of Protein Kinase C.

Protein kinase C (PKC) is thought to be an essential element of many signal transduction pathways[1] and is implicated in a wide range of physiological processes including cellular growth and differentiation[2]. Recently, bis-indolylmaleimides (e.g. **1**[3]) have been shown to be potent and selective inhibitors of this isoenzyme family[4]. As part of our programme to develop protein kinase inhibitors as drugs we set out to design a series of compounds which, we believed, would be more potent and selective inhibitors of PKC. To this end structures **2** were designed which possessed a conformationally restricted side chain bearing a terminal cationic substituent. It was envisaged that such compounds would come from the parent unsubstituted systems **3**, which could readily be elaborated to the desired compounds by use of an intramolecular Perkin-type reaction[5].



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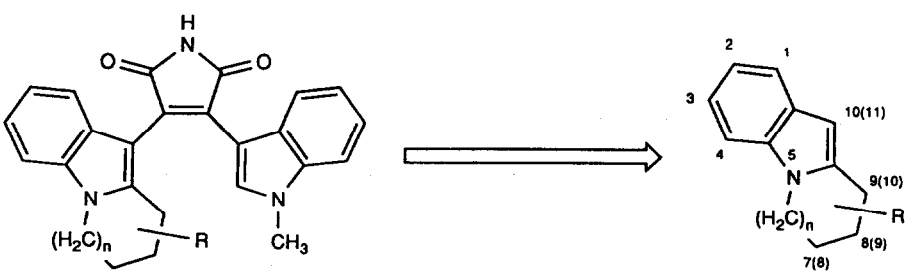
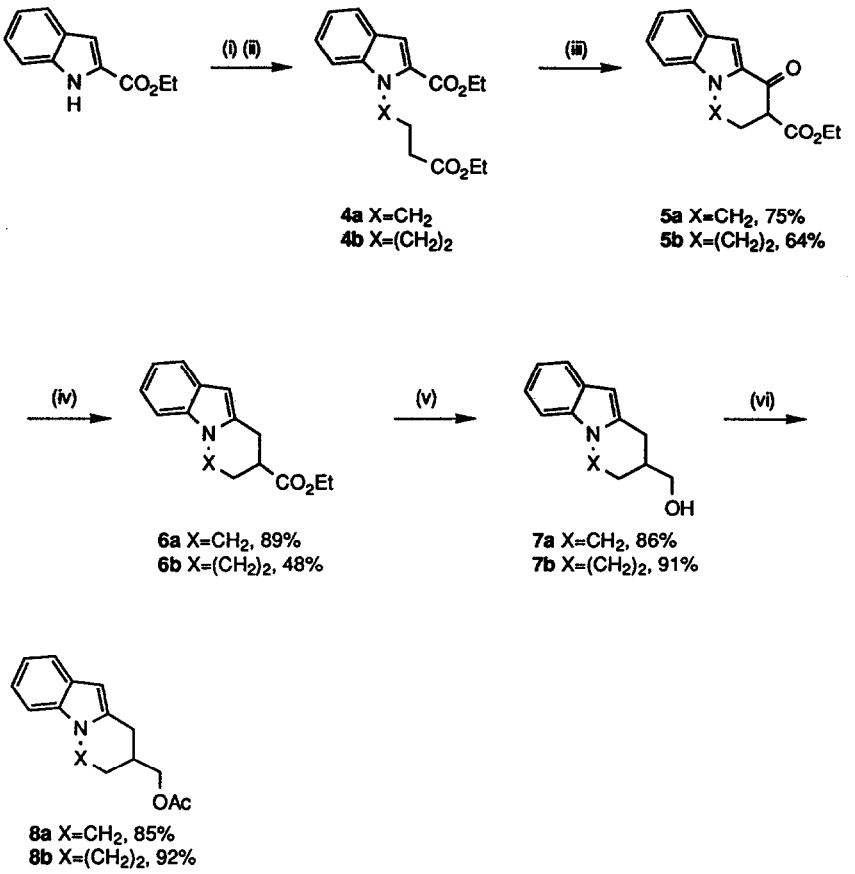


2 **3** n=1(n=2)

We were particularly interested in a series of substituted tetrahydropyrido- and tetrahydroazepino-[1,2-a]indoles. However, an examination of the literature for the required 10- and 11-unsubstituted indoles showed that relatively few examples of these systems were known[6] and that none of the reported syntheses had been demonstrated to be general with respect to substitution. Therefore, we needed to develop a general approach which would be applicable to the synthesis of a wide variety of such systems.



SCHEME 1

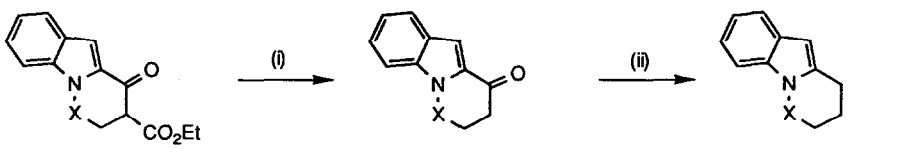
Conditions: (i) NaH, DMF; (ii) $BrX(CH_2)_2CO_2Et$; (iii) KO^tBu, THF; (iv) Raney nickel, EtOH, reflux; (v) $LiAlH_4$, Et_2O; (vi) Ac_2O, pyridine.

We required a synthesis which would fulfil three general criteria. Firstly, only basic and neutral reaction conditions could be employed since 3-unsubstituted indoles are often sensitive to acidic reaction conditions[7].

Secondly, the starting materials should be readily available and, finally, the approach should be general and flexible enough to accommodate a variety of substitution patterns. A synthetic strategy based on the Dieckmann condensation was therefore chosen.

Despite the fact that Dieckmann reactions of substrates containing indoles have met with mixed success[8] we believed that the problems encountered by others could be overcome by judicious choice of base and reaction conditions. All of the required compounds could, in principle, come from the commercially available ethyl indole-2-carboxylate and the Dieckmann products should be easily modified to give materials in a suitable form for coupling to give the desired bis-indolylmaleimides. In general we required the substituents on the alicyclic moiety to be in the form of a suitably protected amine or alcohol. In addition, the β-ketoester products offered an ideal opportunity to access larger rings by alkylation at the α-carbon followed by a base catalysed ring expansion.

For our purposes the most convenient Dieckmann reactions are those which can only undergo cyclisation in one direction consequently affording a single product and we therefore chose a substrate with an ester moiety directly attached to an aromatic ring system. The required diester precursors **4** for the Dieckmann cyclisations were readily prepared by alkylation of ethyl indole-2-carboxylate with the corresponding bromoalkylesters (scheme 1). These diesters were subjected to a variety of base catalysed reaction conditions and the highest yields were obtained with potassium tert.butoxide in anhydrous THF. The ketone was then best removed from the β-ketoesters by heating the products **5** to reflux with Raney nickel in ethanol[9]. The esters **6** were easily converted into the desired acetates **8** by reaction with lithium aluminium hydride followed by acetylation with acetic anhydride.

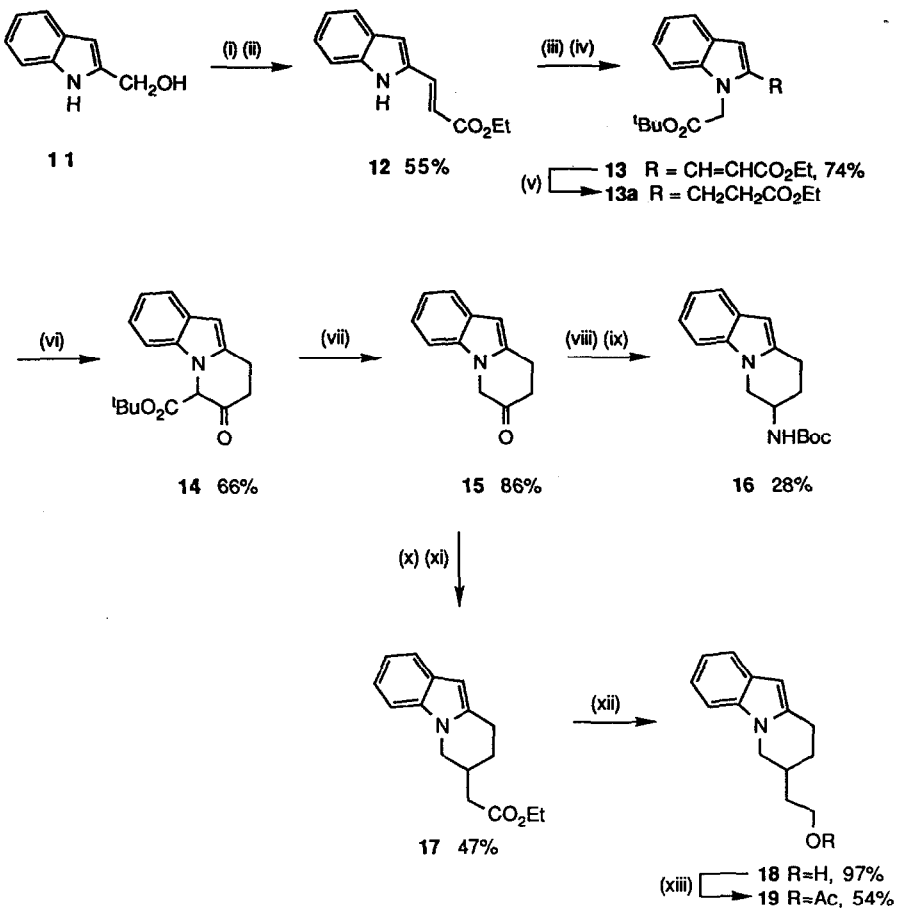


5a X=CH_2 **9a** X=CH_2, 76% **10a** X=CH_2, 80%
5b X=$(CH_2)_2$ **9b** X=$(CH_2)_2$, 93% **10b** X=$(CH_2)_2$, 54%

SCHEME 2

Conditions: (i) NaOH or HCl, EtOH, reflux; (ii) Raney nickel, EtOH, reflux.

The parent unsubstituted systems **10** were also readily prepared by decarboxylation of the β-ketoesters **5** to give the ketones **9**, followed by reductive removal of the keto group with Raney nickel (scheme 2).

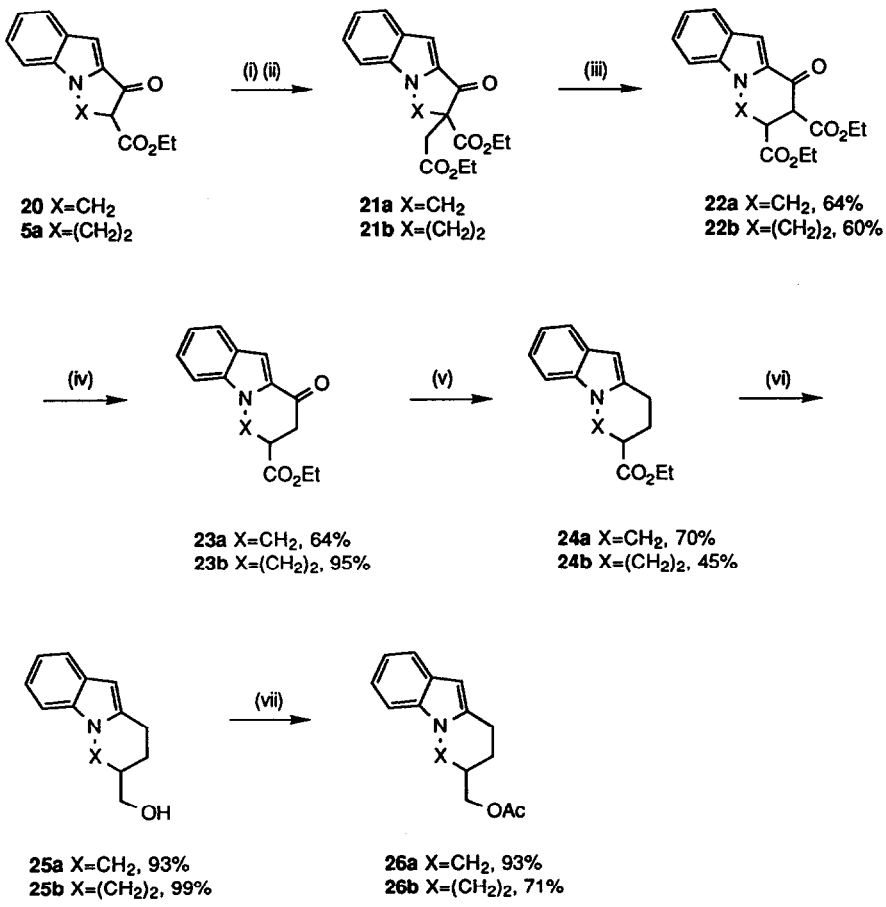


SCHEME 3

Conditions: (i) MnO_2, CH_2Cl_2, rt; (ii) $Ph_3P{=}CHCO_2Et$, CH_2Cl_2, reflux; (iii) NaH, DMF, rt; (iv) $BrCH_2CO_2{}^tBu$; (v) H_2, 10%Pd-C, EtOH, RT; (vi) $KO{}^tBu$, THF, -10°C; (vii) SiO_2, toluene, reflux; (viii) NH_4OAc, $NaCNBH_3$, THF, rt; (ix) $({}^tBuOCO)_2O$, NEt_3, 0°C; (x) $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, rt; (xi) H_2, 10%Pd-C, EtOH, rt; (xii) $LiAlH_4$, THF, rt; (xiii) Ac_2O, pyridine.

An alternative Dieckmann cyclisation has also been achieved (scheme 3), but in this case the diester precursor **13a** can cyclise to form two products. The diester was prepared from indole-2-methanol by oxidation with manganese dioxide[10], followed by a Wittig reaction with carbethoxymethylenetriphenyl phosphorane to give the *trans* ester **12**. Alkylation of this ester with tert.butyl bromoacetate and catalytic reduction of the product **13** gave the diester **13a** in good yield. The tert.butyl ester was selected because it was thought that the steric bulk of the tert.butyl group would direct the Dieckmann reaction in one direction. This was indeed found

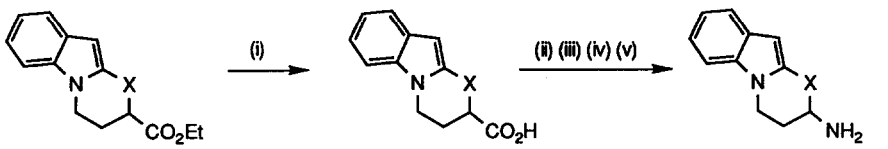
to be the case and only trace quantities of the readily removed alternative Dieckmann product were found. The decarboxylated product **15** was converted directly into an amine by reductive amination and the product was protected in a suitable form for our coupling reaction with 1-methyl-3-indolylacetic acid[5]. Additionally, the ketone **15** could be used as a precursor to a longer alkyl chain analogue and consequently was treated with a Horner-Emmons reagent. The olefin obtained was catalytically reduced to give the ester **17**, which was then converted into the desired acetate **19** by reduction and acetylation.



SCHEME 4

Conditions: (i) NaH, DMF; (ii) $BrCH_2CO_2Et$; (iii) KO^tBu, THF, -78°C; (iv) $B(OH)_3$; (v) Raney nickel, EtOH, reflux; (vi) $LiAlH_4$, Et_2O; (vii) Ac_2O, pyridine.

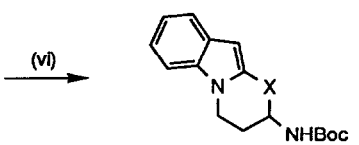
Since both β-ketoesters **20**[11] and **5a** are readily available we decided to use these as precursors for a ring expansion approach to both the 7-substituted tetrahydropyridoindole **26a** and the 8-substituted tetrahydroazepinoindole **26b**(scheme 4). The β-ketoesters were alkylated in good yield and the products **21** were treated with potassium tert.butoxide in anhydrous THF to afford the ring expanded products **22** in excellent yield. In our hands these reaction conditions were found to be far superior to those previously reported[12] and avoided the use of DMSO. The central carboxyl groups of the ketodiesters **22** were then conveniently removed by fusion with boric acid[13] and the products **23** were reduced with Raney nickel to afford the desired monofunctionalised materials **24**. Elaboration of these compounds to the desired acetates **26** proved straightforward.



6a X=CH_2
24b X=$(CH_2)_2$

27a X=CH_2, 96%
27b X=$(CH_2)_2$, 56%

28a X=CH_2, 71%
28b X=$(CH_2)_2$, 89%

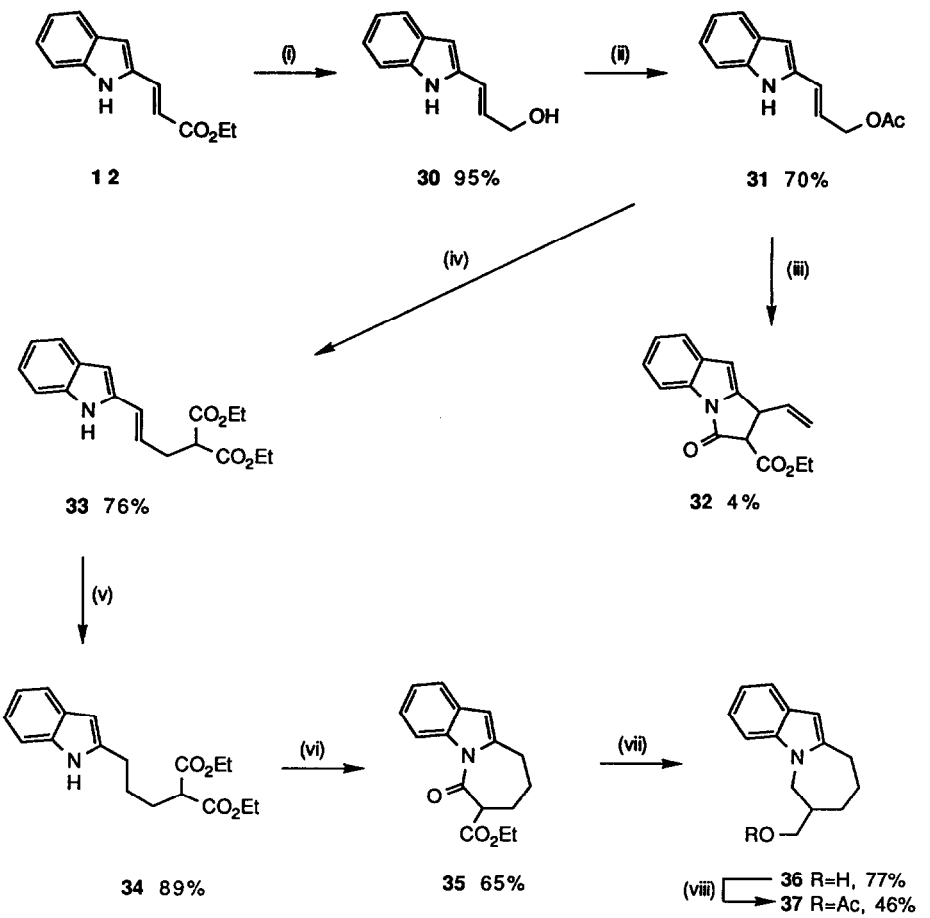


29a X=CH_2, 90%
29b X=$(CH_2)_2$, 95%

SCHEME 5

Conditions: (i) NaOH, EtOH; (ii) EtOCOCl, NEt_3, acetone/water, O°C; (iii) NaN_3; (iv) toluene, reflux; (v) NaOH; (vi) $(^tBuOCO)_2O$, NEt_3, CH_2Cl_2, rt.

This Dieckmann/ring expansion approach allows the synthesis of a variety of substituted analogues, since the ketones may be reduced, reductively aminated or modified to produce longer chain derivatives and the ester group in any position can easily be converted into the corresponding amine *via* a Curtius reaction (scheme 5). Hence esters **6a** and **24b** were hydrolysed to the corresponding acids, which were subjected to the standard Curtius conditions[14]. The amines **28** were then protected as the tert.butoxycarbonyl derivatives **29** in excellent yield.



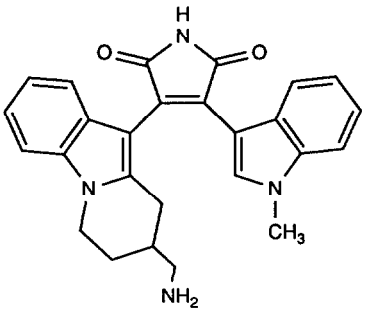
SCHEME 6

Conditions: (i) DIBAL, toluene, rt; (ii) Ac_2O, pyridine, rt; (iii) NaH, $CH_2(CO_2Et)_2$, DMF, 50°C; (iv) NaH, $CH_2(CO_2Et)_2$, DMF,$Pd(PPh_3)_4$, rt; (v) H_2, 10%Pd-C, EtOH, rt; (vi) KO^tBu, THF, reflux; (vii) BH_3.THF, reflux; (viii) Ac_2O, pyridine.

For the synthesis of the 7-substituted tetrahydroazepinoindole we chose a different approach, which again used ethyl indole-2-carboxylate as starting material. Thus, the ester **12** was reduced with diisobutylaluminium hydride to the alcohol **30** and subsequently acetylated to afford acetate **31**. Initial attempts to react this with the anion generated from diethyl malonate and sodium hydride to afford the diester **33** were unsuccessful and resulted only in minor amounts of the β-ketoester **32**. This product could well arise from a displacement of the acetate by an S_N1' process followed by ring closure to give the observed five membered ring structure **32**. It is unlikely that acylation of the indole occurred before cyclisation, since some uncyclised alkylated material was

also isolated. Nevertheless, to overcome this problem we investigated the promotion of the reaction in the desired manner by using the known steric sensitivity of reactions with π-allyl palladium species[15] which should enforce alkylation of diethyl malonate at the terminal position of the π-allyl palladium moiety to give the required malonate **33**. This proved very effective and gave good yields of the desired diester **33**, which was catalytically reduced to **34**. Cyclisation of the diester to the 7-membered ring system proceeded smoothly in the presence of potassium tert.butoxide in dry THF to give the β-ketoester **35**. Reduction of this material with borane/THF led directly to the alcohol **36**, which was protected as the acetate in excellent yield.

In conclusion, the Dieckmann/ring expansion approach is a general, versatile synthesis of these fused[1,2-a]indole systems and should allow the preparation of other larger ring analogues. The chemistry described here has culminated in the synthesis of compounds which are very potent inhibitors of PKC, e.g. imide **38** has an IC_{50} of 8nM. Full details of the design and final steps for the synthesis of such compounds and structure activity relationships will appear elsewhere.



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EXPERIMENTAL

General

Melting points were determined on a Buchi apparatus in glass capillary tubes and are uncorrected. Thin-layer chromatography was performed on silica gel aluminium backed plates (5554) and glass backed plates (5719) purchased from E. Merck & Co., and flash chromatography was performed on Sorbsil C60 40/60A (Crosfield Chemicals). Mass spectra were obtained with either a Kratos MS902 mass spectrometer in the electron impact mode or a Finnigan 8430 instrument in chemical ionisation mode. ^1H NMR spectra were recorded on either a Bruker AC-250 or a Bruker WM-300 spectrometer and chemical shifts are given in ppm from tetramethylsilane as internal standard. IR spectra were recorded on a Perkin Elmer Model 782 spectrometer.

Ethyl 6,7-Dihydro-9-hydroxypyrido[1,2-a]indole-8-carboxylate (5a)

A solution of ethyl indole-2-carboxylate (25g, 132mmol) in DMF (400ml) was added dropwise to a stirred solution of NaH (5.5g of a 60% dispersion in mineral oil, 137mmol) in DMF (40ml) under a nitrogen atmosphere. Ethyl bromobutyrate (30.9g, 159mmol) was then added dropwise to the mixture at 0°C and the resulting mixture was stirred at room temperature for 18h. The reaction was quenched by the addition of water (100ml) and 2M HCl (30ml) and the mixture was extracted with CH_2Cl_2 (2 x 200ml). The combined organic extracts were washed with water (4 x 200ml), dried (Na_2SO_4) and evaporated to give 49g of a yellow oil. The oil was dissolved in EtOAc (200ml) and the solution was washed with water (2 x 150ml), dried

(Na_2SO_4) and evaporated to dryness to give 39g of a yellow oil. This oil was added dropwise to a stirred suspension of KO^tBu (20.5g, 184 mmol) in dry THF (750ml) at room temperature under a nitrogen atmosphere. After 1h water (200ml) and then 2M HCl (92 ml) were added and the mixture was concentrated under reduced pressure. The resulting brown precipitate was filtered off and dried to give 25.3g (75%) of the title compound. A sample was crystallized from MeOH to give a white solid of melting point 101-103°C. υ_{max}(nujol mull) 1670 and 1730cm^{-1}; δ(300MHz, $CDCl_3$) 1.25-1.40(3H, 2 x t, J=8Hz, $CO_2CH_2\underline{CH_3}$), 2.50-2.63 and 2.70-2.92(2H, m, ring), 3.65-3.75 and 4.05-4.45(4H, m, ring and $CO_2\underline{CH_2}CH_3$), 7.00-7.40(4H, m, indole aromatics), 7.64-7.76(1H, 2 x d, J=7Hz, 1-H), 12.18(1H, bs, enol); m/z 257(M^+), 211; calculated for $C_{15}H_{15}NO_3$ (257.289) C:70.02; H:5.88; N:5.44%; found C:70.14; H:5.89; N:5.38%.

Ethyl 7,8-Dihydro-10-hydroxy-6H-azepino[1,2-a]indole-9-carboxylate (5b)

A solution of ethyl indole-2-carboxylate (9.45g, 50 mmol) in dry DMF (50ml) was added dropwise to a stirred suspension of NaH (1.32g, 55mmol) in dry DMF (25ml) under a nitrogen atmosphere. After 1h a solution of ethyl bromovalerate (10.5g, 50 mmol) was then added dropwise and the resulting mixture was stirred at room temperature for 48h. The reaction mixture was poured into water (250ml) and the mixture was extracted with CH_2Cl_2 (3 x 100ml). The combined organic extracts were washed with water (100ml), dried (Na_2SO_4) and evaporated to give 12.7g of a yellow oil. A solution of this oil in dry THF (50ml) was added dropwise to a stirred suspension of KO^tBu (5.5g, 49mmol) in dry THF (50ml) at room temperature under a nitrogen atmosphere. After 36h the mixture was concentrated under reduced pressure and the residue was partitioned between water (250ml) and Et_2O (250ml). The ethereal extract was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 9:1) and crystallized (EtOAc/hexane) to give 8.7g (64%) of the title compound as a pale yellow solid of melting point 79-81°C. υ_{max}(nujol mull) 1620, 1690 and 3310cm^{-1}; δ(300MHz, $CDCl_3$) 1.25(3H, d x t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 2.10-2.60(3H, m, ring), 3.95(1H, d x d, J=7Hz, ring), 4.15-4.45(4H, m, ring and $CO_2\underline{CH_2}CH_3$), 7.10-7.72(5H, m, indole aromatics), 12.90(1H, bs, enol); m/z 271(M^+), 225; calculated for $C_{16}H_{17}NO_3$ (271.316) C:70.83; H:6.32; N:5.16%; found C:70.83; H:6.29; N:5.08%.

Ethyl 6,7,8,9-Tetrahydropyrido[1,2-a]indole-8-carboxylate (6a)

A suspension of **5a** (19.4g, 75.5mmol) and W-2 Raney nickel (16 spoon spatula measures) in EtOH (480ml) and water (240ml) was heated to reflux for 3.5h. A further 4 spoon spatula measures of Raney nickel were then added and the reaction mixture was heated to reflux for a further 1.5h. The supernatent was decanted off and the catalyst was washed with EtOAc (2 x 200ml). The combined organic phases were concentrated under reduced pressure and the precipitate was filtered off and dried to give 16.3g (89%) of the title compound as a pale yellow solid. A sample was crystallized from MeOH to give a white solid of melting point 70-72°C. υ_{max}(nujol mull) 1720cm^{-1}; δ(300MHz, d6-DMSO) 1.23(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 2.00-2.19(1H, m, ring), 2.30-2.45(1H, m, ring), 2.82-3.08(2H, m, ring), 3.18-3.27(1H, m, ring), 3.83-4.00(1H, m, 6-H), 4.13(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.19-4.29(1H, m, 6-H), 6.20(1H, s, 10-H), 6.92-7.08(2H, m, indole aromatics), 7.32(1H, d, J=7Hz, 4-H), 7.43(1H, d, J=7Hz, 1-H); m/z 243(M^+); calculated for $C_{15}H_{17}NO_2$ (243.306) C:74.05; H:7.04; N:5.76%; found C:74.15; H:7.10; N:5.80%.

Ethyl 7,8,9,10-Tetrahydro-6H-azepino[1,2-a]indole-9-carboxylate (6b)

A suspension of **5b** (5.5g, 20.3mmol) and W-2 Raney nickel (11 spoon spatula measures) in EtOH (400ml) and water (200ml) was heated to reflux for 4h. The cooled mixture was filtered and the catalyst was washed with EtOAc (2 x 250ml). The filtrate was extracted with EtOAc (2 x 250ml) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil. Purification by flash chromatography (CH_2Cl_2) gave 2.5g (48%) of the title compound as a white solid of melting point 69-70°C. υ_{max}(nujol mull) 1730cm^{-1}; δ(300MHz, $CDCl_3$) 1.22(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 1.50-2.45(5H, m, ring), 2.95(1H, m, ring), 3.25(1H, d, J=12Hz, ring), 3.86(1H, m, ring), 4.09(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.38(1H, d x d, J=5 and 10Hz, ring), 6.25(1H, s, 11-H), 7.00(1H, t, J=8Hz, indole aromatic), 7.10(1H, t, J=8Hz, indole aromatic),

7.20(1H, d, J=8Hz, 4-H), 7.45(1H, d, J=8Hz, 1-H); m/z 257(M^+); calculated for $C_{16}H_{19}NO_2$ (257.333) C:74.68; H:7.44; N:5.44%; found C:74.27; H:7.48; N:5.39%.

6,7,8,9-Tetrahydro-8-(hydroxymethyl)pyrido[1,2-a]indole (7a)

A solution of **6a** (16.2g, 66.6mmol) in THF (200ml) was added slowly to a suspension of $LiAlH_4$ (2g, 53mmol) in THF (600ml) at 0°C under a nitrogen atmosphere. After 0.5h the reaction was quenched by the successive additions of EtOAc (20ml), water (250ml) and 2M HCl (100ml) and the mixture was extracted with Et_2O (2 x 300ml). The combined ethereal extracts were dried (Na_2SO_4) and evaporated to dryness and the residue obtained was crystallized from Et_2O/hexane to give 11.5g (86%) of the title compound as a white solid of melting point 110-111°C. υ_{max}(nujol mull) 3000-3500cm^{-1}; δ(300MHz, d6-DMSO) 1.60-1.78(1H, m, ring), 1.83-2.00(1H, m, ring), 2.12-2.22(1H, m, ring), 2.45-2.60(1H, m, 9-H), 3.05(1H, d x d, J=4 and 16Hz, 9-H), 3.46(2H, m, $\underline{CH_2}OH$), 3.71-3.87(1H, m, 6-H), 4.22-4.33(1H, m, 6-H), 4.71(1H, t, J=5Hz, OH), 6.14(1H, s, 10-H), 6.92-7.08(2H, m, indole aromatics), 7.32(1H, d, J=7Hz, 4-H), 7.43(1H, d, J=7Hz, 1-H); m/z 201(M^+); calculated for $C_{13}H_{15}NO$ (201.269) C:77.58; H:7.51; N:6.96%; found C:77.57; H:7.59; N:7.00%.

7,8,9,10-Tetrahydro-9-(hydroxymethyl)-6H-azepino[1,2-a]indole (7b)

A solution of **6b** (2.5g, 9.7mmol) in dry THF (50ml) was added slowly to a suspension of $LiAlH_4$ (0.45g, 12mmol) in dry THF (20ml) under a nitrogen atmosphere. After completion of the addition the mixture was stirred for 2h and the reaction was quenched by the addition of water (50ml). The resulting mixture was extracted with Et_2O (2 x 50ml) and the combined ethereal extracts were dried ($MgSO_4$) and evaporated to dryness. The residue obtained was purified by flash chromatography (CH_2Cl_2) to give 1.90g (91%) of the title compound as a colourless solid of melting point 109-111°C. υ_{max}(nujol mull) 3000-3500cm^{-1}; δ(300MHz, $CDCl_3$) 1.50-2.10(6H, m, ring and OH), 2.68(1H, d x d, J=5 and 10Hz, 10-H), 3.10(1H, d, J=15Hz, 10-H), 3.52(2H, d, J=7Hz, $\underline{CH_2}OH$), 3.92(1H, d x d, J=5 and 10Hz, 6-H), 4.35(1H, d x d, J=5 and 10Hz, 6-H), 6.28(1H, s, 11-H), 7.05(1H, t, J=7Hz, indole aromatic), 7.15(1H, t, J=7Hz, indole aromatic), 7.25(1H, d, J=7Hz, 4-H), 7.55(1H, d, J=7Hz, 1-H); m/z 215(M^+), 145; calculated for $C_{14}H_{17}NO$ (215.296) C:78.14; H:7.91; N:6.51%; found C:77.79; H:8.24; N:6.44%.

8-(Acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole (8a)

Acetic anhydride (11.4g, 110mmol) was added to a solution of **7a** (11g, 54.8mmol) in pyridine (100ml) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 18h. The solvent was removed under reduced pressure and the residue was acidified with 2M HCl and extracted with Et_2O (2 x 150ml). The combined ethereal extracts were washed with $NaHCO_3$ solution (50ml) and water (50ml), dried (Na_2SO_4) and evaporated to dryness to give 11.25g (85%) of the title compound. An analytical sample was crystallized from Et_2O/hexane to give a light brown solid of melting point 62-63°C. υ_{max}(nujol mull) 1740cm^{-1}; δ(250MHz, $CDCl_3$) 1.75-1.95(1H, m, ring), 2.14(3H, s, OAc), 2.17-2.35(2H, m, ring), 2.70(1H, d x d, J=11 and 16Hz, 9-H), 3.18(1H, d x d, J=16 and 4Hz, 9-H), 3.90(1H, d x t, J=5 and 12Hz, 6-H), 4.17(2H, d, $\underline{CH_2}OAc$), 4.27-4.39(1H, m, 6-H), 6.24(1H, s, 10-H), 7.06-7.22(2H, m, indole aromatics), 7.30(1H, d, J=7Hz, 4-H), 7.56(1H, d, J=7Hz, 1-H); m/z 243(M^+); calculated for $C_{15}H_{17}NO_2$ (243.306) C:74.05; H:7.04; N:5.76%; found C:73.97; H:6.97; N:5.79%.

9-(Acetoxymethyl)-7,8,9,10-tetrahydro-6H-azepino[1,2-a]indole (8b)

Acetic anhydride (1.7g, 16.8mmol) and pyridine (0.66g, 8.4mmol) were added to a solution of **7b** (1.8g, 8.4mmol) in Et_2O (100ml) at 0°C and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 8h. More pyridine (5g, 64mmol) was then added and the mixture was stirred for 76h. The solvents were removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2) to give 1.98g (92%) of the title compound as a white solid of melting point 65°C. υ_{max}(nujol mull) 1735cm^{-1}; δ(300MHz, $CDCl_3$) 1.50-1.70(2H, m, ring), 1.90-2.05(3H, m, ring), 2.08(3H, s, OAc), 2.72(1H, d x d, J=5 and 10Hz, 10-H), 3.05(1H, d, J=15Hz, 10-H), 3.90-4.05(3H, m, 6-H and $\underline{CH_2}OAc$), 4.37(1H, d x d, J=5 and

7Hz, 6-H), 6.30(1H, s, 11-H), 7.04(1H, t, J=7Hz, indole aromatic), 7.14(1H, t, J=7Hz, indole aromatic), 7.25(1H, d, J=7Hz, 4-H), 7.55(1H, d, J=7Hz, 1-H); m/z 257(M^+); accurate mass calculated for $C_{16}H_{19}NO_2$ 257.1416; found 257.1418.

7,8-Dihydropyrido[1,2-a]indol-9(6H)-one (9a)

A solution of **5a** (1.03g, 4mmol) in EtOH (20ml) and 50% aqueous HCl (20ml) was heated at 80°C for 1.5h. The solvents were removed by evaporation and the residue was extracted with Et_2O (100ml). The ethereal extract was washed with $NaHCO_3$ solution (50ml), dried ($MgSO_4$) and concentrated under reduced pressure to about 20ml. The precipitate was filtered off and dried to give 560mg (76%) of the title compound as a white solid of melting point 141-142°C. υ_{max}(nujol mull) 1665cm^{-1}; δ(300MHz, $CDCl_3$) 2.42(2H, quintet, J=7Hz, 7-H), 2.76(2H, t, J=7Hz, 8-H), 4.27(2H, t, J=7Hz, 6-H), 7.13-7.23(1H, m, indole aromatic), 7.33(1H, s, 10-H), 7.35-7.47(2H, m, indole aromatics), 7.74(1H, d, J=7Hz, 1-H); m/z 185(M^+); calculated for $C_{12}H_{11}NO$ (185.226) C:77.80; H:5.99; N:7.56%; found C:77.92; H:6.19; N:7.58%.

6,7,8,9-Tetrahydro-10H-azepino[1,2-a]indol-10-one (9b)

A suspension of **5b** (9.7g, 35.7mmol) in 2M NaOH (200ml) was refluxed for 1.5h. The reaction mixture was cooled, acidified with 2M HCl and extracted with EtOAc (2 x 200ml). The combined organic extracts were dried (MgSO4) and concentrated under reduced pressure to give 6.6g (93%) of the title compound as a colourless solid of melting point 86-87°C. υ_{max}(nujol mull) 1635cm^{-1}; δ(250MHz, $CDCl_3$) 2.04(2H, quintet, J=7Hz, ring), 2.16(2H, quintet, J=7Hz, ring), 2.94(2H, t, J=7Hz, 9-H), 4.46(2H, t, J=7Hz, 6-H), 7.10-7.72(5H, m, indole aromatics); m/z 199(M^+); accurate mass calculated for $C_{13}H_{13}NO$ 199.0997; found 199.1004.

6,7,8,9-Tetrahydropyrido[1,2-a]indole (10a)

A suspension of **9a** (500mg, 2.7mmol) and W-2 Raney nickel (1 spoon spatula measure) in EtOH (20ml) and water (10ml) was heated to reflux for 1.5h. The catalyst was filtered off and washed with EtOAc (20ml). The combined organic phases were concentrated under reduced pressure and the precipitate was filtered off and dried to give 370mg (80%) of the title compound as a white solid of melting point 57-58°C (lit. m.p. = 52°C[6e]). δ(300MHz, $CDCl_3$) 1.30-1.44(2H, m, ring), 2.00-2.15(2H, m, ring), 2.97(2H, t, J=7Hz, 9-H), 4.05(2H, t, J=7Hz, 6-H), 6.20(1H, s, 10-H), 7.04-7.18(2H, m, indole aromatics), 7.26(1H, d, J=7Hz, 4-H), 7.53(1H, d, J=7Hz, 1-H); m/z 171(M^+); accurate mass calculated for $C_{13}H_{13}N$ 171.1047; found 171.1044.

7,8,9,10-Tetrahydro-6H-azepino[1,2-a]indole (10b)

A suspension of **9b** (1.0g, 5mmol) and W-2 Raney nickel (1.5 spoon spatula measures) in EtOH (25ml) and water (50ml) was heated to reflux for 4h. The catalyst was filtered off and washed with EtOAc (20ml). The filtrate was extracted with EtOAc (2 x 50ml) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give 500mg (54%) of the title compound as a white solid of melting point 83-85°C (lit. m.p. = 87°C[6e]). δ(300MHz, $CDCl_3$) 1.86(6H, m, ring), 2.96(2H, m, 10-H), 4.22(2H, m, 6-H), 6.34(1H, s, 11-H), 7.08-7.54(4H, m, aromatic); m/z 185(M^+); accurate mass calculated for $C_{13}H_{15}N$ 185.1204; found 185.1208.

Ethyl (E)-2-Indolyl-2-propenoate (12)

A solution of indole-2-methanol **11** (14g, 95mmol) in CH_2Cl_2 (500ml) was stirred at room temperature with activated MnO_2 (76.4g, 870mmol). After 1h the solid was filtered off and washed with CH_2Cl_2 (2 x 100ml) and the combined filtrate and washings were concentrated to about 400ml. (Carbethoxymethylene)triphenylphosphorane (33g, 94.7mmol) was then added and the resulting solution was heated to reflux under a nitrogen atmosphere for 18h. The solvent was removed by evaporation and the residue was purified by flash chromatography (EtOAc/hexane, 1:3) and crystallized from MeOH to give 11.3g (55%) of the title compound as a white solid of melting point 120-122°C. υ_{max}(nujol mull) 1680 and 3180-3420cm^{-1}; δ(300MHz, $CDCl_3$)

1.36(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 4.30(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 6.26(1H, d, J=17Hz, $\underline{CH}CO_2Et$), 6.82(1H, d, J=2.5Hz, 3-H), 7.12(1H, t, J=7Hz, indole aromatic), 7.25(1H, t, J=7Hz, indole aromatic), 7.36(1H, d, J=7Hz, 7-H), 7.62(1H, d, J=7Hz, 4-H), 7.69(1H, d, J=17Hz, $\underline{CH}$=$CHCO_2Et$), 8.57(1H, bs, NH); m/z 215(M^+), 169; calculated for $C_{13}H_{13}NO_2$ (215.252) C:72.54; H:6.09; N:6.51%; found C:72.54; H:5.98; N:6.64%.

Ethyl (E)-3-[1-(tert.Butoxycarbonyl)methyl]-2-indolyl-2-propenoate (13)

A solution of **12** (7.2g, 33.5mmol) in dry DMF (120ml) was added to NaH (1.47g of a 60% dispersion in mineral oil, 36.8mmol) and the resulting brown solution was cooled to 0°C. tert.Butyl bromoacetate (7.17g, 36.8mmol) was then added dropwise under a nitrogen atmosphere. After stirring for 2h the mixture was poured into 2M HCl (100ml) and extracted with EtOAc (2 x 200ml). The combined organic extracts were washed with water (3 x 200ml), dried (Na_2SO_4) and evaporated to dryness to give a yellow oil. The oil was purified by flash chromatography (Et_2O/petrol) and crystallized from Et_2O/hexane to give 8.1g (74%) of the title compound as pale yellow needles of melting point 66-68°C. υ_{max}(nujol mull) 1695 and 1735cm^{-1}; δ(300MHz, $CDCl_3$) 1.35(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 1.45(9H, s, ^{t}Bu), 4.27(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.85(2H, s, $\underline{CH_2}CO_2{}^t$Bu), 6.46(1H, d, J=17Hz, $\underline{CH}CO_2Et$), 7.00(1H, s, 3-H), 7.10-7.18(1H, m, indole aromatic), 7.21-7.30(2H, m, indole aromatic), 7.62(1H, d, J=7Hz, 4-H), 7.67(1H, d, J=17Hz, $\underline{CH}$=$CHCO_2Et$); m/z 329(M^+), 273; calculated for $C_{19}H_{23}NO_4$ (329.396) C:69.28; H:7.04; N:4.25%; found C:69.05; H:7.00; N:4.28%.

tert.Butyl 6,7,8,9-tetrahydro-7-oxo-pyrido[1,2-a]indole-6-carboxylate (14)

A solution of **13** (8g, 24.3mmol) in EtOH (300ml) was shaken with 10% Pd-C (800mg) under a hydrogen atmosphere for 1h. The catalyst was filtered off and washed with EtOAc (2 x 50ml). The combined filtrate and washings were evaporated to dryness to give a pale yellow oil which was dissolved in dry THF (100ml). This solution was added dropwise to a stirred solution of KO^{t}Bu (2.8g, 25mmol) in THF (300ml) under a nitrogen atmosphere. After completion of the addition the solution obtained was stirred at room temperature for 1h and the solvent was then removed under reduced pressure. The residue was partitioned between EtOAc (200ml) and 2M HCl (50ml) and the organic extract was washed with water (50ml), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (Et_2O/hexane, 1:4) to give 4.55g (66%) of the title compound as a yellow oil. υ_{max}(CH_2Cl_2) 1730 and 1745cm^{-1}; δ(300MHz, $CDCl_3$) 1.40(9H, s, ^{t}Bu), 2.60-2.75(1H, m, ring), 2.94(1H, d x t, J=16 and 5Hz, ring), 3.22-3.42(2H, m, ring), 5.41(1H, s, $\underline{CH}CO_2{}^t$Bu), 6.38(1H, s, 3-H), 7.10-7.26(3H, m, indole aromatics), 7.53(1H, d x d, J=7 and 2Hz, 1-H); m/z 285(M^+), 185; accurate mass calculated for $C_{17}H_{19}NO_3$ 285.1360; found 285.1366.

8,9-Dihydropyrido[1,2-a]indol-7(6H)-one (15)

A solution of **14** (4.5g, 15.8mmol) in toluene (200ml) was treated with silica gel (sorbsil C60 [Crosfield Chemicals], 4 spoon spatula measures) and the mixture obtained was heated to reflux for 3h under a nitrogen atmosphere. The solid was filtered off and washed with toluene (2 x 50ml). The combined filtrate and washings were evaporated to dryness under reduced pressure to give a pale brown solid, which was crystallized from Et_2O/hexane to give 2.5g (86%) of the title compound as a white solid of melting point 126-128°C. υ_{max}(nujol mull) 1730cm^{-1}; δ(300MHz, $CDCl_3$) 2.80(2H, m, ring), 3.27(2H, t, J=7Hz, ring), 4.69(2H, s, $N\underline{CH_2}$), 6.36(1H, s, 3-H), 7.21-7.27(3H, m, indole aromatics), 7.59(1H, d, J=7Hz, 1-H); m/z 185(M^+), 156; calculated for $C_{12}H_{11}NO$ (185.226) C:77.81; H:5.99; N:7.56%; found C:77.79; H:5.98; N:7.36%.

7-tert.Butoxyformamido-6,7,8,9-tetrahydropyrido[1,2-a]indole (16)

A suspension of **15** (555mg, 3mmol) and ammonium acetate (4.62g, 60mmol) in MeOH (15ml) was treated with $NaCNBH_3$ (250mg, 4mmol). The mixture was stirred at room temperature for 6h and was then partitioned between EtOAc (150ml) and water (150ml). The organic phase was dried (Na_2SO_4) and evaporated to dryness. The residual oil was purified by flash chromatography (MeOH/CH_2Cl_2, 1:9) and the indoline obtained was dissolved in toluene (30ml) and heated to reflux with 10% Pd-C (50mg) for 4h. The catalyst was filtered off and washed with toluene (30ml) and the combined filtrate and washings

were evaporated to dryness to give 170mg of 7-amino-6,7,8,9-tetrahydropyrido[1,2-a]indole as a pale green oil.

A stirred solution of this oil in CH_2Cl_2 (20ml) was treated with triethylamine (112mg, 1.1mmol) and di-tert.butyl dicarbonate (225mg, 1.03mmol) at 0°C under a nitrogen atmosphere. After 18h the solution was washed with aqueous $NaHCO_3$ (20ml), dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil. Crystallization from Et_2O gave 240mg (28%) of the title compound as a buff solid of melting point 137-139°C. υ_{max}(nujol mull) 1675 and 3320cm^{-1}; δ(300MHz, $CDCl_3$) 1.45(9H, s, ^tBu), 1.83-2.00(1H, m, 8-H), 2.04-2.20(1H, m, 8-H), 2.98-3.18(2H, m, 9-H), 3.75-3.88(1H, m, 6-H), 4.20-4.36(2H, m, 6-H and 7-H), 4.70-4.84(1H, bs, NH), 6.25(1H, s, 10-H), 7.05-7.20(2H, m, indole aromatics), 7.22-7.30(1H, m, indole aromatic), 7.53(1H, d, J=7Hz, 1-H); m/z 286(M^+), 169; accurate mass calculated for $C_{17}H_{22}N_2O_2$ 286.1686; found 286.1682.

Ethyl 6,7,8,9-tetrahydropyrido[1,2-a]indole-7-acetate (17)

A stirred solution of triethyl phosphonoacetate (2.24g, 10mmol) in dry DME (40ml) was treated with NaH (400mg of a 60% dispersion in mineral oil, 10mmol) at room temperature under a nitrogen atmosphere. After 1h the solution obtained was cooled to 0°C and a solution of **15** (1.85g, 10mmol) in DME (10ml) was added dropwise. The mixture was stirred at room temperature for 18h and then evaporated to dryness. The residue was partitioned between CH_2Cl_2 (200ml) and water (50ml) and the organic phase was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by flash chromatography (Et_2O/petrol, 1:3) to give 1.55g of a mixture of ethyl (E)- and (Z)-(6,7,8,9-tetrahydropyrido[1,2-a]indol-7-ylidene)acetate as a colourless oil.

A stirred solution of this oil in EtOH (70ml) was shaken with 10% Pd-C (280mg) under a hydrogen atmosphere for 72h. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was crystallised from Et_2O/petrol to give 1.2g (47%) of the title compound as a beige solid of melting point 66-68°C. υ_{max}(nujol mull) 1725cm^{-1}; δ(250MHz, $CDCl_3$) 1.32(3H, t, J=8Hz, $CO_2CH_2\underline{CH_3}$), 1.50-1.72(1H, m, ring), 2.02-2.18(1H, m, ring), 2.45-2.70(3H, m, ring and $\underline{CH_2}CO_2Et$), 2.88-3.15(2H, m, ring), 3.59(1H, d x d, J=11 and 11Hz, 6-H), 4.22(2h, q, J=8Hz, $CO_2\underline{CH_2}CH_3$), 4.33(1H, d x d, J=11 and 11 Hz, 6-H), 6.22(1H, s, 10-H), 7.00-7.23(2H, m, indole aromatics), 7.24-7.33(1H, m, indole aromatic), 7.55(1H, d, J=7Hz, 1-H); m/z (CI) 258($[M+H]^+$); accurate mass calculated for $C_{16}H_{19}NO_2$ 257.1416; found 257.1407.

6,7,8,9-tetrahydro-7-(2-hydroxyethyl)pyrido[1,2-a]indole (18)

A solution of **17** (1.2g, 4.67mmol) in dry Et_2O (100ml) was treated with $LiAlH_4$ (3.5ml of a 1M solution in Et_2O, 3.5mmol) and the resulting mixture was stirred at room temperature for 1h. The reaction mixture was quenched with aqueous NH_4Cl (50ml) and extracted with Et_2O (150ml). The ethereal extract was dried (Na_2SO_4) and evaporated to dryness and the resulting foam was crystallized from Et_2O/petrol to give 980mg (97%) of the title compound as a beige solid of melting point 70-72°C. υ_{max}(nujol mull) 2600-3600cm^{-1}; δ(250MHz, $CDCl_3$) 1.40-1.90(4H, m, ring and OH), 2.05-2.42(2H, m, ring), 2.85-3.20(2H, m, ring), 3.55(1H, d x d, J=11 and 11Hz, NC$\underline{H}$), 3.87(2H, t, J=7Hz, $\underline{CH_2}OH$), 4.30(1H, d x d, J=5 and 11Hz, NC$\underline{H}$), 6.21(1H, s, 10-H), 7.05-7.22(2H, m, indole aromatics), 7.29(1H, d, J=7Hz, 4-H), 7.53(1H, d, J=7Hz, 1-H); m/z 215(M^+); accurate mass calculated for $C_{14}H_{17}NO$ 215.1310; found 215.1304.

7-(2-Acetoxyethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole (19)

A solution of **18** (1.04g, 4.83mmol) in CH_2Cl_2 (30ml) was treated with acetic anhydride (6ml) and pyridine (3ml) and the solution obtained was stirred at room temperature for 18h under a nitrogen atmosphere. The mixture was evaporated to dryness and the residue was partitioned between CH_2Cl_2 (30ml) and 2M HCl (30ml). The organic extract was washed with water (30ml), dried (Na_2SO_4) and evaporated to dryness. The residue was purified by flash chromatography (Et_2O/petrol, 1:4) to give 670mg (54%) of the title compound as a colourless oil. υ_{max}(CH_2Cl_2) 1735cm^{-1}; δ(250MHz, $CDCl_3$) 1.40-1.90(3H, m, ring), 2.05-2.42(2H, m, ring), 2.11(3H, s, OAc), 2.85-3.20(2H, m, ring), 3.55(1H, d x d, J=11 and 11Hz, 6-H), 4.20-4.40(3H, m, 6-H and $\underline{CH_2}$OAc), 6.22(1H, s, 10-H), 7.05-7.24(2H, m, indole aromatics), 7.28(1H, d, J=7Hz, 4-H), 7.55(1H, d, J=7Hz, 1-H); m/z 257(M^+); calculated for $C_{16}H_{19}NO_2$ (257.335) C:74.68; H:7.44; N:5.44%; found C:74.79; H:7.51; N:5.62%.

Ethyl 2-(Ethoxycarbonyl)-2,3-Dihydro-1-oxo-1H-pyrrolo[1,2-a]indole-2-acetate (21a)

A stirred solution of **20** (18g, 74mmol) in dry DMF (300ml) was treated with NaH (2.33g of an 80% dispersion in mineral oil, 77mmol) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 0.75h. A solution of ethyl bromoacetate (13g, 77mmol) in dry DMF (100ml) was then added at 0°C and the mixture obtained was stirred for 1.5h at room temperature. The solvent was removed under reduced pressure and the residue was partitioned between water (400ml) and with Et_2O (2 x 200ml). The combined ethereal extracts were washed with water (300ml), $NaHCO_3$ solution (40ml), dried (Na_2SO_4) and concentrated to give 25.8g of the crude title compound as a yellow oil. A sample was purified by flash chromatography (Et_2O/petrol) to give the title compound as a white solid of melting point 64-66°C. υ_{max}(nujol mull) 1710cm^{-1}; δ(300MHz, $CDCl_3$) 1.20(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 1.25(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 2.85(1H, d, J=17.5Hz, $\underline{CH}CO_2Et$), 3.50(1H, d, J=17.5Hz, $\underline{CH}CO_2Et$), 4.20(4H, m, 2 x $CO_2\underline{CH_2}CH_3$), 4.40(1H, d, J=11Hz, 3-H), 5.20(1H, d, J=11Hz, 3-H), 7.10(1H, s, 9-H), 7.25-7.45(3H, m, indole aromatics), 7.77(1H, d, J=7Hz, 8-H); m/z 329(M^+), 182; calculated for $C_{18}H_{19}NO_5$ (329.352) C:65.64; H:5.82; N:4.25%; found C:66.01; H:5.84; N:4.07%.

Ethyl 8-(Ethoxycarbonyl)-6,7,8,9-tetrahydro-9-oxopyrido[1,2-a]indole-8-acetate (21b)

A stirred solution of **5a** (5g, 19mmol) in dry DMF (200ml) was treated with NaH (550mg, 23mmol) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 0.5h. A solution of ethyl bromoacetate (3.6g, 23mmol) in dry DMF (50ml) was then added and the mixture obtained was stirred for 16h at room temperature. The mixture was poured into water (100ml) and extracted with Et_2O (2 x 100ml). The combined ethereal extracts were washed with water (100ml), dried ($MgSO_4$) and concentrated to give 4.4g (68%) of a colourless oil. υ_{max}(CH_2Cl_2) 1685 and 1740cm^{-1}; δ(250MHz, $CDCl_3$) 1.18(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 1.25(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 2.80(2H, m, 7-H), 3.06(2H, s, $\underline{CH_2}CO_2Et$), 4.12-4.44(6H, m, 2 x $CO_2\underline{CH_2}CH_3$ and 6-H), 7.12-7.75(5H, m, indole aromatics); m/z 343(M^+); accurate mass calculated for $C_{19}H_{21}NO_5$ 343.1419; found 343.1411.

Diethyl 6,7-Dihydro-9-hydroxypyrido[1,2-a]indole-7,8-dicarboxylate (22a)

A solution of **21a** (24.3g, 74mmol) in dry THF (100ml) was added dropwise over a period of 1h to a stirred solution of KO^tBu (9g, 80mmol) in dry THF (300ml) at -78°C. The mixture was stirred for 0.25h before glacial acetic acid (5ml) was added and the mixture was allowed to warm to room temperature. The solvent was removed under reduced pressure and the residue was partitioned between dilute $NaHCO_3$ (340ml) and Et_2O (400ml). The ethereal extract was washed with water (300ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residue was crystallized from Et_2O/hexane to give 15.5g (64%) of the title compound as a pale yellow solid of melting point 85-87°C. υ_{max}(nujol mull) 1630, 1720cm^{-1}; δ(300MHz, $CDCl_3$) 1.00-1.38(6H, m, $CO_2CH_2\underline{CH_3}$), 3.88-4.95(7H, m, $CO_2\underline{CH_2}CH_3$, 6-H and 7-H), 7.05-7.78(5H, m, indole aromatics), 12.35(1H, bs, enol); m/z 329(M^+), 256; calculated for $C_{18}H_{19}NO_5$ (329.352) C:65.64; H:5.82; N:4.25%; found C:65.55; H:5.91; N:4.28%.

Diethyl 7,8-Dihydro-10-hydroxy-6H-azepino[1,2-a]indole-8,9-dicarboxylate (22b)

A solution of **21b** (5g, 14.6mmol) in dry THF (200ml) was added dropwise over a period of 1h to a stirred solution of KO^tBu (2g, 18mmol) in dry THF (50ml) at room temperature. The mixture was stirred for 16h before glacial acetic acid (1ml) was added and the mixture was poured into water and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to give 3g (60%) of the title compound as a yellow oil. υ_{max}(CH_2Cl_2) 1670 and 1730cm^{-1}; δ(250MHz, $CDCl_3$) 1.10-1.45(6H, m, 2 x $CO_2CH_2\underline{CH_3}$), 1.92-3.25(4H, m, 7-H, 8-H and 9-H), 3.98-4.70(6H, m, 2 x $CO_2\underline{CH_2}CH_3$ and 6-H), 7.05-7.45(4H, m, indole aromatics), 7.58-7.76(1H, m, 1-H); m/z 343(M^+); accurate mass calculated for $C_{19}H_{21}NO_5$ 343.1419; found 343.1411.

Ethyl 6,7,8,9-Tetrahydro-9-oxopyrido[1,2-a]indole-7-carboxylate (23a)

A mixture of **22a** (1.5g, 4.56mmol) and boric acid (350mg, 4.67mmol) was heated to 150°C for 1.25h. The cooled

reaction mixture was treated with ice-water (10ml) and extracted with CH_2Cl_2 (160ml). The organic extract was washed with water (2 x 100ml), dried (Na_2SO_4) and concentrated under reduced pressure. The residual brown oil was purified by flash chromatography (Et_2O/hexane, 1:1) to give 750mg (64%) of the title compound as a beige solid of melting point 84-87°C. υ_{max}(nujol mull) 1680 and 1725cm^{-1}; δ(300MHz, $CDCl_3$) 1.25(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 2.92-3.08(2H, m, 8-H), 3.40-3.55(1H, m, 7-H), 4.20(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.40(1H, d x d, J=9 and 16Hz, 6-H), 4.60(1H, d x d, J=4.5 and 16Hz, 6-H), 7.15-7.22(1H, m, indole aromatic), 7.35(1H, s, 10-H), 7.40(2H, m, indole aromatics), 7.75(1H, d, J=7Hz, 1-H); m/z 257(M^+), 184; calculated for $C_{15}H_{15}NO_3$ (257.289) C:70.02; H:5.88; N:5.44; found C:70.07; H:5.38; N:5.38%.

Ethyl 7,8,9,10-Tetrahydro-10-oxo-6H-azepino[1,2-a]indole-8-carboxylate (23b)

A mixture of **22b** (2.8g, 8.2mmol) and boric acid (0.5g, 8.4mmol) was heated to 150°C for 1h and at 170°C for 3h. The cooled reaction mixture was treated with ice-water (50ml) and extracted with CH_2Cl_2 (2 x 50ml). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to give 2.1g (95%) of the title compound as a dark coloured oil. υ_{max}(CH_2Cl_2) 1665 and 1725cm^{-1}; δ(250MHz, $CDCl_3$) 1.00(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 2.10-3.00(5H, m, ring), 3.94(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.22(2H, m, 6-H), 3.05(1H, m, ring), 6.85-7.50(5H, m, indole aromatics); accurate mass calculated for $C_{16}H_{17}NO_3$ 271.1208; found 271.1214.

Ethyl 6,7,8,9-Tetrahydropyrido[1,2-a]indole-7-carboxylate (24a)

A suspension of **23a** (1.5g, 5.84mmol) and W-2 Raney nickel (2 spoon spatula measures) in EtOH (100ml) and water (50ml) was heated to reflux for 1h. The cooled mixture was filtered and the catalyst was washed with EtOAc (2 x 50ml). The combined organic phases were concentrated under reduced pressure and the residue was extracted with CH_2Cl_2 (100ml). The organic extract was dried (Na_2SO_4) and concentrated under reduced pressure to give a brown oil. Purification by flash chromatography (Et_2O/hexane, 1:1) gave 1.0g (70%) of the title compound as a white solid of melting point 56-58°C. υ_{max}(nujol mull) 1730cm^{-1}; δ(300MHz, $CDCl_3$) 1.32(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 2.00(1H, m, ring), 2.35(1H, m, ring), 2.90-3.20(3H, m, ring), 4.05(1H, d x d, J=11 and 11Hz, 6-H), 4.25(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.40(1H, m, 6-H), 6.20(1H, s, 10-H), 7.00(1H, m, indole aromatic), 7.30(2H, m, indole aromatics), 7.52(1H, d, J=7Hz, 1-H); m/z 243(M^+); calculated for $C_{15}H_{17}NO_2$ (243.306) C:74.05; H:7.04; N:5.76; found C:74.10; H:7.11; N:5.61%.

Ethyl 7,8,9,10-Tetrahydro-6H-azepino[1,2-a]indole-8-carboxylate (24b)

A suspension of **23b** (2.1g, 7.8mmol) and W-2 Raney nickel (4 spoon spatula measures) in EtOH (80ml) and water (50ml) was heated to reflux for 4h. The cooled mixture was filtered and the catalyst was washed with EtOAc (2 x 50ml). The filtrate was extracted with EtOAc (3 x 50ml) and the combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give a colourless oil. Purification by flash chromatography (CH_2Cl_2) gave 0.89g (45%) of the title compound as a pale yellow oil. υ_{max}(CH_2Cl_2) 1725cm^{-1}; δ(250MHz, $CDCl_3$) 1.34(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 1.75-3.22(7H, m, ring), 3.90-4.05(1H, m, 6-H), 4.25(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 4.50(1H, d x d, J=11 and 11Hz, 6-H), 6.34(1H, s, 11-H), 7.10-7.54(4H, m, indole aromatics); m/z 257(M^+); accurate mass calculated for $C_{16}H_{19}NO_2$ 257.1416; found 257.1412.

6,7,8,9-Tetrahydro-7-(hydroxymethyl)pyrido[1,2-a]indole (25a)

A solution of **24a** (1.0g, 4.12mmol) in dry Et_2O (80ml) was added slowly to a solution of $LiAlH_4$ (4ml of a 1M solution in Et_2O, 4mmol) under a nitrogen atmosphere. After completion of the addition the mixture was stirred for 0.25h and the reaction was quenched by the sequential additon of water (150μl), 2M NaOH (300μl) and water (500μl). The resulting mixture was filtered and the solid was washed with EtOAc (2 x 40ml). The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness to give 770mg (93%) of the title compound as a pale yellow solid of melting point 76-78°C. υ_{max}(nujol mull) 3250cm^{-1}; δ(300MHz, $CDCl_3$) 1.50-1.68(2H, m, ring and OH), 1.98-2.12(1H, m, ring), 2.25-2.40(1H, m, ring), 2.85-3.02(1H, m, 9-H), 3.12(1H, d x t, J=16 and 5Hz, 9-H), 3.66(1H, d x d, J=11 and 11Hz, 6-H), 3.65-3.85(2H, m, $\underline{CH_2}OH$), 4.34(1H, d x d, J=5 and

11Hz, 6-H), 6.22(1H, s, 10-H), 7.00-7.19(2H, m, indole aromatics), 7.28(1H, d, J=7Hz, 4-H), 7.53(1H, d, J=7Hz, 1-H); m/z (CI) 202($[M+H]^+$); accurate mass calculated for $C_{13}H_{15}NO$ 201.1153; found 201.1147.

7,8,9,10-Tetrahydro-8-(hydroxymethyl)-6H-azepino[1,2-a]indole (25b)

A solution of **24b** (0.85g, 3.3mmol) in dry THF (50ml) was added slowly to a suspension of $LiAlH_4$ (140mg, 3.7mmol) in dry THF (50ml) under a nitrogen atmosphere. After completion of the addition the mixture was stirred for 1h and the reaction was quenched by the additon of water (100ml). The resulting mixture was extracted with Et_2O (3 x 50ml) and the combined ethereal extracts were dried ($MgSO_4$) and evaporated to dryness. The residue obtained was purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to give 0.70g (99%) of the title compound as a white solid of melting point 90-91°C. $\upsilon_{max}(CH_2Cl_2)$ 3000-3500cm^{-1}; δ(250MHz, $CDCl_3$) 1.25-2.10(5H, m, ring), 2.74-3.15(2H, m, ring), 3.40-4.10(4H, m, ring and OH), 4.30-4.60(1H, m, ring), 6.28(1H, s, 11-H), 7.02-7.40(3H, m, indole aromatics), 7.56(1H, d, J=7Hz, 1-H); m/z 257(M^+); accurate mass calculated for $C_{14}H_{17}NO$ 215.1310; found 215.1320.

7-(Acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole (26a)

Acetic anhydride (510mg, 5mmol) and pyridine (2ml) were added to a solution of **25a** (750mg, 3.7mmol) in CH_2Cl_2 (10ml) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 16h. The solvents were removed under reduced pressure and the residue was partitioned between CH_2Cl_2 (100ml) and 2M HCl (60ml). The organic extract was washed with $NaHCO_3$ solution (30ml), water (30ml), dried (Na_2SO_4) and concentrated under reduced pressure to give 840mg (93%) of the title compound as a pale orange oil. $\upsilon_{max}(CH_2Cl_2)$ 1735cm^{-1}; δ(300MHz, $CDCl_3$) 1.57-1.73(1H, m, ring), 2.01-2.15(1H, m, ring), 2.13(3H, s, OAc), 2.38-2.54(1H, m, ring), 2.87-3.03(1H, m, 9-H), 3.13(1H, d x t, J=16 and 5Hz, 9-H), 3.65(1H, d x d, J=11 and 11Hz, 6-H), 4.13(1H, d x d, J=7 and 11Hz, CHOAc), 4.22-4.35(2H, m, CHOAc and 6-H), 6.22(1H, s, 10-H), 7.05-7.19(2H, m, indole aromatics), 7.28(1H, d, J=7Hz, 4-H), 7.53(1H, d, J=7Hz, 1-H); m/z 243(M^+); accurate mass caiculated for $C_{15}H_{17}NO_2$ 243.1260; found 243.1257.

8-(Acetoxymethyl)-7,8,9,10-tetrahydro-6H-azepino[1,2-a]indole (26b)

Acetic anhydride (0.66g, 6.5mmol) and pyridine (0.39g, 4.8mmol) were added to a solution of **25b** (0.7g, 3.3mmol) in Et_2O (50ml) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 6h. More pyridine (1g, 12.3mmol) and acetic anhydride (1g, 9.8mmol) were then added and the mixture was stirred for 16h. The solvents were removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2) to give 0.6g (71%) of the title compound as a white solid of melting point 77-79°C. $\upsilon_{max}(CH_2Cl_2)$ 1725cm^{-1}; δ(250MHz, $CDCl_3$) 1.60-2.10(5H, m, ring), 2.05(3H, s, OAc), 2.76-3.05(2H, m, ring), 3.75-4.00(1H, m, ring), 4.18-4.30(2H, m, ring), 4.42-4.62(1H, m, ring), 6.28(1H, s, 11-H), 7.00-7.30(3H, m, indole aromatics), 7.33(1H, d, J=7Hz, 1-H); m/z 257(M^+); accurate mass calculated for $C_{16}H_{19}NO_2$ 257.1416; found 257.1415.

6,7,8,9-Tetrahydropyrido[1,2-a]indole-8-carboxylic Acid (27a)

A solution of NaOH (300mg, 7.5mmol) in water (5ml) was added to a stirred solution of **6a** (1.35g, 5.55mmol) in EtOH (25ml) and the resulting mixture was heated to reflux for 0.25h. Water (10ml) and 2M HCL (2ml) were added and the precipitate obtained was filtered off and dried to give 1.14g (96%) of the title compound as a white solid of melting point 244-246°C. υ_{max}(nujol mull) 1700 and 2400-3200cm^{-1}; δ(300MHz, $CDCl_3$) 2.10-2.29(1H, m, ring), 2.40-2.54(1H, m, ring), 2.72-2.88(1H, m, ring), 3.12(1H, d x d, J=11 and 16Hz, ring), 3.31(1H, d x d, J=5 and 16Hz, ring), 3.85-4.00(1H, m, 6-H), 4.25-4.36(1H, m, 6-H), 6.23(1H, s, 10-H), 7.00-7.16(2H, m, indole aromatics), 7.26(1H, d, J=7Hz, 4-H), 7.50(1H, d, J=7Hz, 1-H); m/z 215(M^+); calculated for $C_{13}H_{13}NO_2$ (215.252) C:72.54; H:6.09; N:6.51%; found C:72.20; H:5.99; N:6.43%.

7,8,9,10-Tetrahydro-6H-azepino[1,2-a]indole-8-carboxylic Acid (27b)

A solution of **24b** (800mg, 3.1mmol) in EtOH (25ml) was treated with NaOH (187mg, 4.7mmol) and the solution obtained was stirred at room temperature for 18h. The solvent was removed under reduced pressure and the residue was partitioned between water (50ml) and CH_2Cl_2 (10ml). The aqueous phase was acidified with 2M HCl and the precipitate was filtered off and dried to give 400mg (56%) of the title compound as a light brown solid of melting point 168-170°C. υ_{max}(nujol mull) 1690 and 2400-3500cm^{-1}; δ(300MHz,d6-DMSO) 1.40-1.65(2H, m, ring), 2.06-2.25(2H, m, ring), 2.65-2.91(2H, m, ring), 2.96-3.10(1H, m, ring), 4.01(1H, d x d, J=11 and 15Hz, 6-H), 4.52(1H, d x d, J=6 and 15Hz, 6-H), 6.22(1H, s, 11-H), 6.96(1H, t, J=7Hz, indole aromatic), 7.06(1H, t, J=7Hz, indole aromatic), 7.30-7.45(2H, m, indole aromatics), 12.34(1H, bs, CO_2H); m/z 229(M^+); accurate mass calculated for $C_{14}H_{15}NO_2$ 229.1103; found 229.1117.

8-Amino-6,7,8,9-tetrahydropyrido[1,2-a]indole (28a)

A stirred suspension of **27a** (900mg, 4.18mmol) in acetone (20ml) and water (1ml) was cooled to 0°C and treated with triethylamine (490mg, 4.85mmol) followed by ethyl chloroformate (576mg, 5.3mmol). After 0.5h sodium azide (345mg, 5.3mmol) was added and the mixture was stirred at 0°C under nitrogen for a further 1h. The acetone was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (2 x 100ml). The combined extracts were evaporated to dryness and the residue was purified by flash chromatography (CH_2Cl_2) to give 760mg of a white solid, which was dissolved in toluene (10ml) and heated at 100°C under a nitrogen atmosphere for 4h. The solvent was removed under reduced pressure and the residue was dissolved in THF (50ml) and stirred at room temperature with 2M NaOH (4ml) for 18h. The solvent was removed under reduced pressure and the residue was extracted with CH_2Cl_2. The organic extract was evaporated under reduced pressure to give 550mg (71%) of the title compound as a colourless oil. υ_{max}(CH_2Cl_2) 3000-3400cm^{-1}; δ(250MHz, $CDCl_3$) 1.45-1.80(2H, bs, NH_2), 1.85-2.10(1H, m, ring), 2.15-2.40(1H, m, ring), 2.75(1H, d x d, J=9 and 16Hz, 9-H), 3.17-3.44(2H, m, ring), 3.88-4.05(1H, m, 6-H), 4.22-4.40(1H, m, 6-H), 6.25(1H, s, 10-H), 7.03-7.24(2H, m, indole aromatics), 7.30(1H, d, J=7Hz, indole aromatic), 7.52(1H, d, J=7Hz, 1-H); m/z 186(M^+), 143; accurate mass calculated for $C_{12}H_{14}N_2$ 186.1157; found 186.1172.

8-Amino-7,8,9,10-tetrahydro-6H-azepino[1,2-a]indole (28b)

A stirred suspension of **27b** (400mg, 1.75mmol) in acetone (20ml) and water (1ml) was cooled to 0°C and treated with triethylamine (205mg, 2.0mmol) followed by ethyl chloroformate (240mg, 2.2mmol). After 0.5h sodium azide (144mg, 2.2mmol) was added and the mixture was stirred at 0°C under nitrogen for a further 1h. The acetone was removed under reduced pressure and the residue was extracted with CH_2Cl_2 (100ml). The extract was evaporated to dryness and the residue was purified by flash chromatography (CH_2Cl_2) to give 760mg of a white solid, which was dissolved in toluene (10ml) and heated at 100°C under a nitrogen atmosphere for 4h. The solvent was removed under reduced pressure and the residue was dissolved in THF (20ml) and stirred at room temperature with 2M NaOH (3ml) for 18h. The solvent was removed under reduced pressure and the residue was partitioned between water (100ml) and CH_2Cl_2 (100ml). The organic extract was dried ($MgSO_4$) and evaporated to dryness to give 310mg (89%) of the title compound as a yellow solid of melting point196°C(dec.). υ_{max}(CH_2Cl_2) 3200-3400cm^{-1}; δ(250MHz, $CDCl_3$) 1.24-1.60(4H, m, ring), 2.10(2H, m, ring), 2.75(1H, m, ring), 3.10(2H, m, ring), 3.88(1H, m, 6-H), 4.46(1H, m, 6-H), 6.27(1H, s, 11-H), 7.03-7.32(3H, m, indole aromatics), 7.45(1H, d, J=7Hz, 1-H); m/z (CI) 201([M+H]$^+$); accurate mass calculated for $C_{13}H_{16}N_2$ 200.1313; found 200.1323.

8-tert.Butoxyformamido-6,7,8,9-tetrahydropyrido[1,2-a]indole (29a)

A stirred solution of **28a** (550mg, 2.96mmol) in CH_2Cl_2 (50ml) was treated with triethylamine (300mg, 3mmol) and di-tert.butyl dicarbonate (645mg, 3mmol) at 0°C. The mixture was then stirred at room temperature for 72h, washed with $NaHCO_3$ solution (30ml) and the organic phase was dried (Na_2SO_4) and evaporated to dryness. The residue was extracted with Et_2O (100ml) and the ethereal extract was concentrated under reduced pressure. The solid obtained was triturated with petrol to give 760mg (90%) of the title compound as a white solid of melting point 155-157°C. υ_{max}(CH_2Cl_2) 1695 and 3200-3450cm^{-1};

δ(250MHz, $CDCl_3$) 1.48(9H, s, ^tBu), 2.03-2.40(2H, m, 7-H), 2.88(1H, d x d, J=8 and 16Hz, 9-H), 3.31(1H, d x d, J=5 and 16Hz, 9-H), 3.98-4.26(3H, m, 6-H and 8-H), 4.61(1H, bs, NH), 6.25(1H, s, 10-H), 7.03-7.22(2H, m, indole aromatics), 7.29(1H, d, J=7Hz, 4-H), 7.45(1H, d, J=7Hz, 1-H); m/z 286(M^+), 169; accurate mass calculated for $C_{17}H_{22}N_2O_2$ 286.1681; found 286.1693.

8-tert.Butoxyformamido-7,8,9,10-tetrahydro-6H-azepino[1,2-a]indole (29b)

A solution of **28b** (700mg, 3.5mmol) in CH_2Cl_2 (50ml) was added dropwise to a stirred solution of triethylamine (350mg, 3.5mmol) and di-tert.butyl dicarbonate (840mg, 3.5mmol) at 0°C. The mixture was then stirred at room temperature for 18h, washed with 1M HCl (50ml), $NaHCO_3$ solution (50ml) and water (2 x 50ml) and the organic phase was dried (Na_2SO_4) and evaporated to dryness to give 1.0g (95%) of the title compound as a pale yellow solid of melting point 178-180°C. $\upsilon_{max}(CH_2Cl_2)$ 1695 and 3200-3450cm^{-1}; δ(250MHz, $CDCl_3$) 1.50(9H, s, ^tBu), 1.63(3H, m, ring), 2.28(2H, m, ring), 2.80(1H, m, ring), 3.08(1H, m, ring), 3.90(2H, m, 6-H and NH), 4.42(1H, m, 6-H), 6.27(1H, s, 11-H), 7.02-7.26(3H, m, indole aromatics), 7.55(1H, d, J=7Hz, 1-H); m/z 301($[M+H]^+$); accurate mass calculated for $C_{18}H_{24}N_2O_2$ 300.1858; found 300.1837.

3-(2-Indolyl)-2-Propen-1-ol (30)

A solution of DIBAL (71ml of a 1M solution in toluene, 71mmol) was added dropwise to a stirred solution of **12** (6.9g, 32mmol) in dry toluene (150ml) under a nitrogen atmosphere at 0°C. After 1h the reaction was quenched with 2M HCl (125ml) and the mixture was extracted with EtOAc (2 x 100ml). The combined organic extracts were washed with $NaHCO_3$ solution (50ml), brine (50ml), water (50ml), dried ($MgSO_4$) and evaporated to dryness to give 5.51g (95%) of a colourless oil. $\upsilon_{max}(CH_2Cl_2)$ 3100-3500cm^{-1}; δ(250MHz, $CDCl_3$) 2.25(1H, bs, OH), 4.32(2H, d, J=7Hz, $\underline{CH_2}OH$), 6.18(1H, d x t, J=20 and 7Hz, CH=$\underline{CH}CH_2$), 6.46(1H, s, 3-H), 6.61(1H, d, J=20Hz, $\underline{CH}$=$CHCH_2$), 7.06-7.62(4H, m, indole aromatics), 8.53(1H, bs, NH); m/z 173(M^+); accurate mass calculated for $C_{11}H_{11}NO$ 173.0840; found 173.0837.

2-(3-Acetoxy-1-propenyl)indole (31)

Acetic anhydride (7.1g, 70mmol) was added to a solution of **30** (5.5g, 32mmol) and pyridine (5.5g, 70mmol) in Et_2O (150ml) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 18h. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (MeOH/CH_2Cl_2, 1:19) to give 4.8g (70%) of the title compound as a white solid of melting point 53°C. $\upsilon_{max}(CH_2Cl_2)$ 1720 and 3340cm^{-1}; δ(250MHz, $CDCl_3$) 2.15(3H, s, OAc), 4.75(2H, d, J=7Hz, $\underline{CH_2}$OAc), 6.10(1H, d x t, J=20 and 7Hz, CH=$\underline{CH}CH_2$), 6.54(1H, s, 3-H), 6.80(1H, d, J=20Hz, $\underline{CH}$=$CHCH_2$), 7.05-7.37(3H, m, indole aromatics), 7.58(1H, d, J=7Hz, 1-H), 8.24(1H, bs, NH); m/z 215(M^+); accurate mass calculated for $C_{13}H_{13}NO_2$ 215.0946; found 215.0953.

Ethyl 2,3-Dihydro-3-oxo-1-vinyl-1H-pyrrolo[1,2-a]indole-2-carboxylate (32)

Diethyl malonate (4.67g, 29mmol) was added to a stirred suspension of NaH (0.7g, 29mmol) in DMF (80ml) at room temperature under a nitrogen atmosphere. After 0.25h the resulting solution was treated with a solution of **31** (5.7g, 26.5mmol) in DMF (20ml) and heated to 50°C for 48h. The cooled solution was poured into water (300ml) and extracted with CH_2Cl_2 (3 x 200ml). The combined organic extracts were washed with brine (100ml), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (CH_2Cl_2/MeOH, 49:1) to give 300mg (4%) of a pale yellow solid of melting point 76-77°C. $\upsilon_{max}(CH_2Cl_2)$ 1720 and 1745cm^{-1}; δ(300MHz, $CDCl_3$) 1.34(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 3.90(1H, d, J=5Hz, 2-H), 4.32(2H, m, $CO_2\underline{CH_2}CH_3$), 4.46(1H, m, 1-H), 5.28(1H, m, CH=$\underline{CH}$(H)), 5.40(1H, m, CH=CH($\underline{H}$)), 5.96(1H, m, $\underline{CH}$=CH_2), 6.36(1H, m, 9-H), 7.30(2H, m, 6-H and 7-H), 7.51(1H, m, 8-H), 8.03(1H, m, 5-H); m/z 269(M^+); accurate mass calculated for $C_{16}H_{15}NO_3$ 269.1051; found 269.1049.

Diethyl 2-[3-(2-Indolyl)propenyl]malonate (33)

Diethyl malonate (0.52g, 3.2mmol) was added to a stirred suspension of NaH (78mg, 3.2mmol) in dry THF (25ml) at room temperature under a nitrogen atmosphere. After 0.25h the resulting solution was treated with a mixture of **31** (0.7g, 3.2mmol) and tetrakis(triphenylphosphine)palladium (188mg, 3mol%) in THF (25ml). The mixture obtained was stirred at room temperature for 3h, poured into water (100ml) and extracted with CH_2Cl_2 (100ml). The organic phase was dried ($MgSO_4$), evaporated to dryness and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to give 780mg (76%) of the title compound as a yellow oil. $\upsilon_{max}(CH_2Cl_2)$ 1725cm^{-1}; δ(250MHz, $CDCl_3$) 1.30(6H, t, J=7Hz, 2 x $CO_2CH_2\underline{CH_3}$), 2.84(2H, m, CH=CH$\underline{CH_2}$), 3.54(1H, t, J=7Hz, $\underline{CH}(CO_2Et)_2$), 4.25(4H, q, J=7Hz, 2 x $CO_2\underline{CH_2}CH_3$), 6.03, (1H, d x t, J=20 and 7Hz, CH=$\underline{CH}CH_2$), 6.45(1H, s, 3-H), 6.50(1H, d, J=20Hz, $\underline{CH}$=CHCH$_2$), 7.04-7.34(3H, m, indole aromatics), 7.56(1H, d, J=7Hz, 1-H), 8.27(1H, bs, NH); m/z (CI) 316([M+H]$^+$); accurate mass calculated for $C_{18}H_{21}NO_4$ 315.1471; found 315.1471.

Diethyl 2-[3-(2-Indolyl)propyl]malonate (34)

A solution of **33** (800mg, 2.5mmol) in EtOH (50ml) was shaken with 10% Pd-C (80mg) under a hydrogen atmosphere for 3h. The catalyst was filtered off and washed with EtOAc (2 x 10ml). The combined filtrate and washings were evaporated to dryness and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 49:1) to give 720mg (89%) of the title compound as a pale yellow oil. $\upsilon_{max}(CH_2Cl_2)$ 1725cm^{-1}; δ(250MHz, $CDCl_3$) 1.36(6H, t, J=7Hz, 2 x $CO_2CH_2\underline{CH_3}$), 2.08(2H, m, CH_2), 2.76(2H, m, CH_2), 2.98(1H, t, J=7Hz, $\underline{CH}(CO_2Et)_2$), 4.21(2H, t, J=7Hz, arylCH_2), 4.29(4H, q, J=7Hz, 2 x $CO_2\underline{CH_2}CH_3$), 6.32(1H, s, 3-H), 7.24(2H, m, indole aromatics), 7.33(1H, m, indole aromatic), 7.63(1H, m, indole aromatic), 8.09(1H, bs, NH); m/z 318 (CI) ([M+H]$^+$); accurate mass calculated for $C_{18}H_{24}NO_4$ 318.1699; found 318.1696.

Ethyl 7,8,9,10-Tetrahydro-6-oxo-6H-azepino[1,2-a]indole-7-carboxylate (35)

A mixture of **34** (700mg, 2.2mmol) and KO^{t}Bu (247mg, 2.2mmol) in dry THF (50ml) was heated to reflux under a nitrogen atmosphere for 24h. The cooled reaction mixture was poured into water (150ml) and extracted with CH_2Cl_2 (3 x 75ml). The combined organic extracts were washed with water (100ml), dried ($MgSO_4$) and evaporated to dryness. The residue was purified by flash chromatography (CH_2Cl_2) to give 390mg (65%) of the title compound as a yellow oil. $\upsilon_{max}(CH_2Cl_2)$ 1690 and 1735cm^{-1}; δ(250MHz, $CDCl_3$) 1.34(3H, t, J=7Hz, $CO_2CH_2\underline{CH_3}$), 1.85-2.44(4H, m, $CH\underline{CH_2}\underline{CH_2}$), 2.90(2H, m, aryl$\underline{CH_2}$), 4.05(1H, d x d, J=5 and 10Hz, $\underline{CH}CO_2Et$), 4.33(2H, q, J=7Hz, $CO_2\underline{CH_2}CH_3$), 6.40(1H, s, 11-H), 7.37(2H, m, indole aromatics), 7.46(1H, m, indole aromatic), 8.45(1H, m, 4-H); m/z 272(M$^+$); accurate mass calculated for $C_{16}H_{17}NO_3$ 271.1208; found 271.1209.

7,8,9,10-Tetrahydro-7-(hydroxymethyl)-6H-azepino[1,2-a]indole (36)

Borane.THF (7ml of a 1M solution in THF, 7mmol) was added dropwise to a stirred solution of **35** (310mg, 1.14mmol) in dry THF (50ml). The solution obtained was heated to reflux under nitrogen for 2h, cooled and treated with SiO_2 (3 spoon spatula measures). The solvent was removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 19:1) to give 190mg (77%) of the title compound as a colourless oil. $\upsilon_{max}(CH_2Cl_2)$ 3290cm^{-1}; δ(250MHz, $CDCl_3$) 1.30-2.00(2H, m, ring), 2.00-2.35(2H, m, ring), 2.55-2.95(2H, m, ring), 3.10-3.30(1H, m, ring), 3.45-3.70(2H, m, $\underline{CH_2}$OH), 3.77-4.04(2H, m, 6-H and OH), 4.50-4.65(1H, m, 6-H), 6.28(1H, s, 11-H), 7.00-7.36(3H, m, indole aromatics), 7.58(1H, m, indole aromatic); m/z 215(M$^+$); accurate mass calculated for $C_{14}H_{17}NO$ 215.1310; found 215.1308.

7-(Acetoxymethyl)-7,8,9,10-tetrahydro-6H-azepino[1,2-a]indole (37)

Acetic anhydride (180mg, 1.8mmol) was added to a solution of **36** (190mg, 0.9mmol) and pyridine (139mg, 1.8mmol) in Et_2O (25ml) and the resulting solution was stirred at room temperature under a nitrogen atmosphere for 24h. More acetic anhydride (1ml) and pyridine (1ml) were added and the solution obtained was stirred for a further 3h at room temperature. The solvent was removed under reduced pressure and the residue was purified by flash chromatography (CH_2Cl_2/MeOH, 49:1) to give

105mg (46%) of the title compound as a white solid of melting point 83-85°C. υ_{max}(nujol mull) 1740cm^{-1}; δ(250MHz, $CDCl_3$) 1.20-1.32(2H, m, ring), 1.64-1.74(2H, m, ring), 1.90-2.10(1H, m, ring), 2.10(3H, s, OAc), 2.88-3.06(2H, m, ring), 3.79(1H, t, J=7Hz, ring), 4.01-4.08(2H, m, ring), 4.36(1H, d, J=7Hz, ring), 6.25(1H, s, 11-H), 7.02-7.26(3H, m, indole), 7.55(1H, m, aromatic); m/z 257(M^+); accurate mass calculated for $C_{16}H_{19}NO_2$ 257.1411; found 257.1413.

Acknowledgements: We would like to thank the Physical Methods Department for the spectral and analytical data and Dr. J. Nixon and Mrs. S. Wilkinson for the IC_{50} against protein kinase C.

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