Syntheses of Functionalised Pyrido[2,3-*b*]indoles

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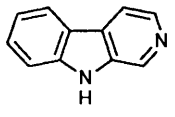
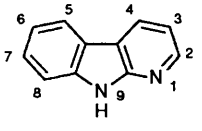
Two complementary routes for the synthesis of highly functionalised pyrido[2,3-*b*]indoles are described, starting from the readily available 2-amino-3-cyano-1-(4-methoxybenzyl)tetrahydroindole and methyl 2-aminoindole-3-carboxylate, respectively. The use of methyl 3-methoxycrotonate for pyridine-ring annelation, and the application of the 4-methoxybenzyl moiety as a protecting group for the indole nitrogen, are key features in these high yielding routes. Further transformations of the derived pyrido-[2,3-*b*]indoles are presented.

In recent years there has been a wealth of interest in the synthesis of functionalised pyrido[3,4-*b*]indoles (β-carbolines)[1] due largely to the potent affinity of these compounds for the benzodiazepine receptor and their associated pharmacological properties.[2] In contrast, the isomeric series of pyrido[2,3-*b*]-indoles (α-carbolines) has been much less well represented in the literature. We became interested in the synthesis and evaluation of a series of functionalised α-carbolines as potential anxiolytic agents. Existing synthetic routes to α-carbolines[3] suffer from several disadvantages: the starting materials can be difficult to obtain, the overall yields are generally low, and the scope for introduction of different substituents is limited. We now report two related syntheses of functionalised α-carbolines which are both high yielding and capable of modification to allow the introduction of a wide range of substituents.[4]



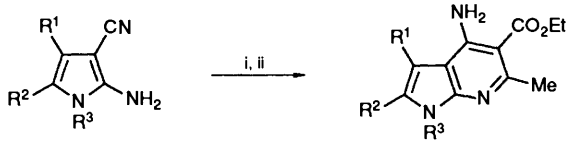
β-carboline



α-carboline

Results and Discussion

Zimmermann *et al.* have previously reported the synthesis of pyrrolo[2,3-*b*]pyridines from the corresponding 2-amino-3-cyanopyrroles (Scheme 1).[5] In particular, the preparation of the

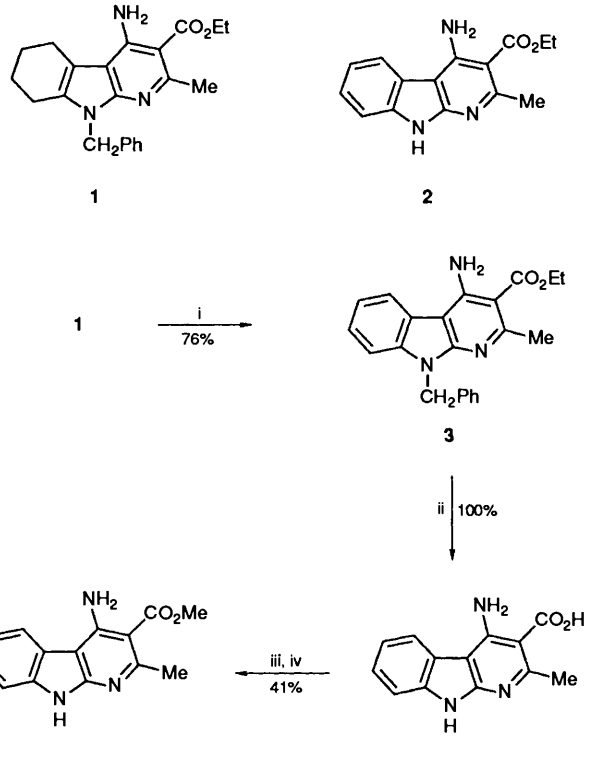


R^1, R^2, R^3 = alkyl

Scheme 1 *Reagents:* i, $MeCOCH_2CO_2Et$; ii, NaOEt

9-benzyltetrahydro-α-carboline **1** in 21% yield was described. We decided to extend this work to the synthesis of substituted α-carbolines with the initial goal of converting compound **1** into the deprotected, fully aromatic system **2**.

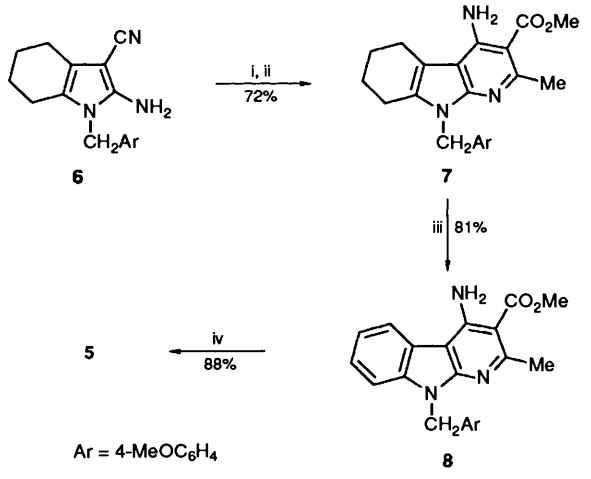
Treatment of compound **1** with palladium on charcoal, or sulfur in xylene, at reflux failed to give complete conversion into the fully aromatised product **3**. However, by use of 2 mol equiv. of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in hot benzene, a clean conversion into the target compound **3** *was* achieved. A variety of standard methods was then investigated in order to accomplish debenzylation of



Scheme 2 *Reagents and conditions:* i, DDQ, benzene, reflux; ii, $AlCl_3$, benzene, reflux; iii, $SOCl_2$, reflux; iv, NaOMe, MeOH, room temp.

compound **3**, but without success (hydrogenation, sodium in liquid ammonia, and *N*-bromosuccinimide). Fortuitously, at that time Murakami reported the use of aluminium trichloride in benzene as an effective reagent for indole *N*-debenzylation.[6] Under these conditions, a clean debenzylation of compound **3** was achieved, but with concomitant ester hydrolysis, to afford the acid **4**. Re-esterification of this extremely insoluble acid, by treatment with thionyl chloride followed by sodium methoxide, gave the desired product as the methyl ester **5** (Scheme 2).

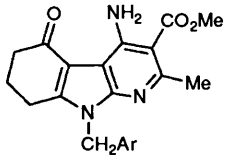
At this stage, we had achieved the initial target of synthesizing the functionalised α-carboline **5**. The overall process, however, was neither very efficient nor suitable for scale-up. In order fully to investigate functionalised α-carbolines as potential anti-anxiety agents, we required the preparation of a wide range of analogues of **5**, in multi-gram quantities. With these aims in mind, the synthetic route was significantly modified to provide a highly efficient, three-step procedure for the synthesis of compound **5** (Scheme 3).



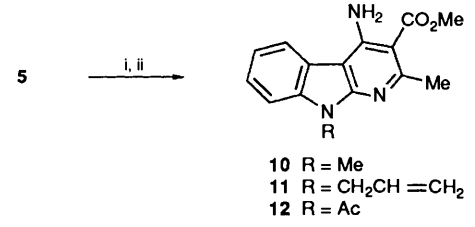
Scheme 3 *Reagents and conditions:* i, $MeOC(Me)=CHCO_2Me$, PTSA, toluene, reflux; ii, NaOMe, MeOH, reflux; iii, DDQ, toluene, 120 °C; iv, TFA, H_2SO_4, anisole, room temp.

The starting 4-methoxybenzyl-protected amino nitrile **6** was easily synthesized in large quantities by using the methodology of Roth.[7] Rather than using methyl acetoacetate as the reagent for pyridine-ring formation, we used the more reactive methyl 3-methoxycrotonate,[8] which consistently gave higher yields and cleaner reaction products. Thus, acid-catalysed addition of the nitrile **6** to methyl 3-methoxycrotonate, followed by sodium methoxide-induced cyclisation afforded, in good yield, the desired tricyclic skeleton **7**. Aromatisation to compound **8** was achieved as described above by using DDQ in benzene or toluene. Interestingly, the 4-methoxybenzyl protecting group is completely stable under these conditions. Deprotection of compound **8** was accomplished cleanly, in high yield, and without ester hydrolysis by treatment with trifluoroacetic acid (TFA), in the presence of conc. sulfuric acid and anisole. In our experience with indole chemistry, the 4-methoxybenzyl group is an excellent nitrogen-protecting group. The sequence of reactions from substrate **6** to final product **5** proceeded in 51% overall yield, and was readily scaled up to provide 100 g quantities.

On some occasions during the purification of the above DDQ reaction mixture a small amount of a more polar by-product was isolated (< 5%), which was assigned the structure **9**.* The yield of this 5-keto derivative was increased substantially by changing the reaction conditions from hot toluene to aq. tetrahydrofuran (THF) at low temperature.[9]

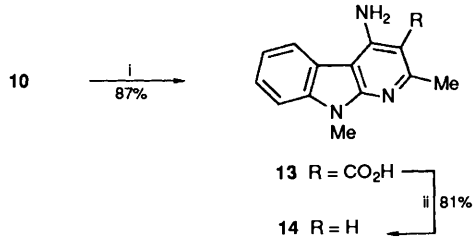


Compound **5** was found to be extremely insoluble in most common organic solvents, which made further synthetic transformations difficult. This problem was overcome by alkylation at N-9, which was accomplished regioselectively by successive treatment of compound **5** with sodium hydride in dimethylformamide (DMF) and an alkylating agent, *e.g.* methyl iodide or allyl bromide, leading to the formation in good yield of compounds **10** and **11**, respectively. In addition, reaction of the anion derived from the amine **5** with acetic anhydride furnished the *N*-acetyl derivative **12** (Scheme 4).



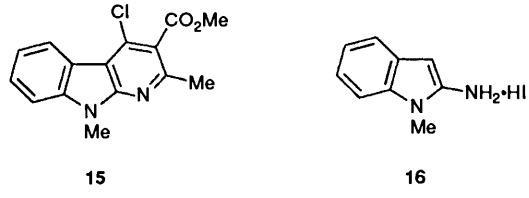
Scheme 4 *Reagents and conditions:* i, NaH, DMF, 0 °C; ii, MeI, $CH_2=CHCH_2Br$, or Ac_2O, room temp.

Compounds related to the ester **10** but without a carboxy function at C-3 could be prepared easily by hydrolysis and decarboxylation. Thus, treatment of compound **10** with aq. sodium hydroxide in ethanol provided the acid **13** which, unusually for a pyridine-3-carboxylic acid, decarboxylated smoothly in hot diphenyl ether to form compound **14** (Scheme 5). Further chemistry of the amino ester **10** will be reported at a later date.



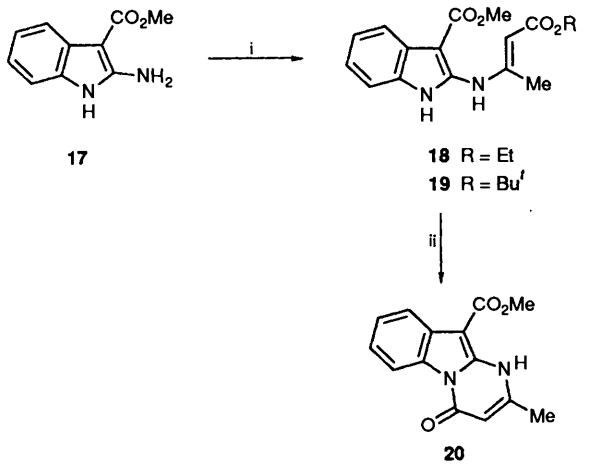
Scheme 5 *Reagents and conditions:* i, NaOH, aq. EtOH, reflux; ii, Ph_2O, reflux.

We were also interested in the synthesis of α-carbolines related to compound **10** but having different substituents at C-4. For this purpose, the 4-chloro-α-carboline **15** was regarded as the key intermediate. Not unexpectedly, attempted diazotisation of the very unreactive 4-amino group in compound **10** was completely unsuccessful.[10] An alternative route to compound **15** was therefore required.



Our initial work focused on the use of 2-amino-1-methylindole **16**.[11] All attempts, however, to build on a functionalised pyridine ring in compound **16**, using standard methodology, were singularly unsuccessful[10] due largely to the instability of the free base of the salt **16**. Our attention then turned to the use of the more stable amino ester **17**, prepared by a modified literature route.[12] Reaction of compound **17** with the acetoacetate synthon, ethyl 3-ethoxycrotonate,[8] afforded the desired enamino ester **18**, which on treatment with base gave exclusively the unwanted cyclisation product **20** (Scheme 6). A similar result has been reported by Wamhoff.[13] Surprisingly, the use of the *t*-butyl ester **19**, prepared from compound **17** and *t*-butyl 3-ethoxycrotonate,[14] did not suppress the formation of the tricyclic compound **20**.

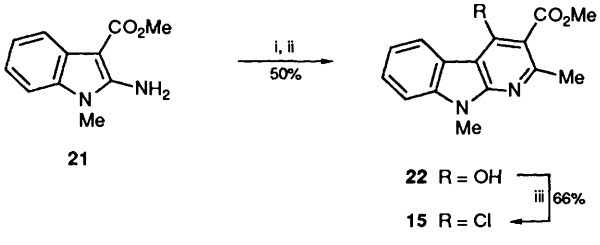
* Support for this structure rather than the isomeric 8-keto derivative came from the observation of a strong nuclear Overhauser effect between -NCH_2Ar and an adjacent methylene group.



17 18 R = Et 19 R = Bu^t 20

Scheme 6 *Reagents and conditions:* i, EtOC(Me)=CHCO$_2$R, xylene, reflux; ii, KOBu^t, DMF or NaOEt, EtOH, room temp.

To avoid this undesired cyclisation, it was found necessary to alkylate the indole nitrogen. Therefore, treatment of compound **17** with base followed by methyl iodide afforded the 1-methyl derivative **21** in reasonable yield. Despite the increased steric hindrance in compound **21**, addition to methyl 3-methoxycrotonate under carefully determined conditions proceeded smoothly, and subsequent treatment with sodium methoxide *in situ* induced cyclisation to the desired 4-hydroxy-α-carboline **22**. Reaction of compound **22** with phosphorus trichloride oxide gave the key 4-chloro derivative **15** (Scheme 7).



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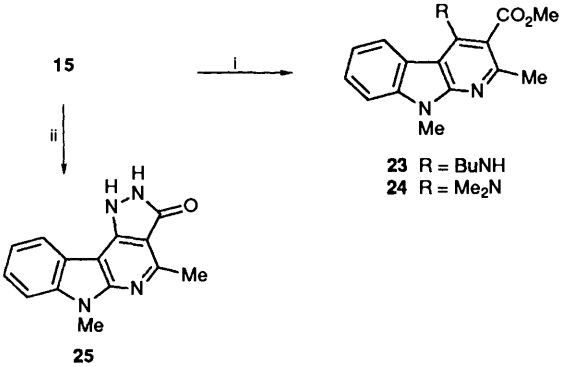
Scheme 7 *Reagents and conditions:* i, MeOC(Me)=CHCO$_2$Me, PTSA, toluene, reflux; ii, NaOMe, MeOH, reflux; iii, $POCl_3$, reflux.

As anticipated, the 4-chloro substituent proved to be extremely versatile for further transformation. Reaction of compound **15** with primary or secondary amines, *e.g.* butylamine and dimethylamine, gave the corresponding 4-amino derivatives **23** and **24**, arising *via* aromatic nucleophilic substitution. Reaction of compound **15** with hydrazine, however, resulted in displacement and concomitant ring closure to give the pyrazolone **25** (Scheme 8).



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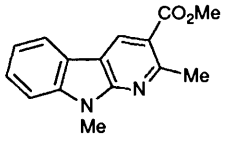
Scheme 8 *Reagents and conditions:* i, $BuNH_2$, reflux or Me_2NH, MeOH, 90 °C; ii, NH_2NH_2, MeOH, reflux.

Reductive dehalogenation of compound **15** could be achieved by treatment with zinc powder in acetic acid, which furnished the 4-unsubstituted α-carboline **26**.

In summary, two complementary routes for the synthesis of functionalised α-carbolines have been described. These routes



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use readily available starting materials, proceed in good overall yield, and allow flexibility in the introduction of a wide range of substituents. Further chemistry of functionalised α-carbolines, along with details of biological activity, will be the subjects of a future publication.

Experimental

M.p.s were determined using a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR spectra were obtained with a Varian CFT 20, JEOL GX 270, or BRUKER AC 250 spectrometer using tetramethylsilane as internal standard. *J* Values are given in Hz. Mass spectra were recorded on a JEOL JMS DX 303/DA 5000 system operating at 70 eV. DMF was dried by pre-treatment with activated 4 Å molecular sieves. Benzene and toluene were dried by treatment with sodium wire. Organic solvent extracts were dried over anhydrous sodium sulphate, and evaporations of solvents were carried out under reduced pressure. For column chromatography Merck Kieselgel 60 or neutral alumina (Brockmann Grade 1) was used.

Ethyl 4-*Amino*-9-*benzyl*-2-*methyl*-9H-*pyrido*[2,3-b]*indole*-3-*carboxylate* **3**.—A solution of ethyl 4-amino-9-benzyl-2-methyl-5,6,7,8-tetrahydro-9*H*-pyrido[2,3-*b*]indole-3-carboxylate **1**[5] (0.91 g, 2.5 mmol) in benzene (20 cm^3) was added dropwise to a solution of DDQ (1.15 g, 5 mmol) in benzene (20 cm^3) at room temperature. The vigorously stirred solution was then heated under reflux for 15 min, allowed to cool, filtered, and evaporated to dryness. Chromatography on silica gel with methylene dichloride as eluent gave the *title compound* **3** (0.69 g, 76%), m.p. 139–140 °C (from ethanol) (Found: C, 73.7; H, 6.0; N, 11.5. $C_{22}H_{21}N_3O_2$ requires C, 73.5; H, 5.9; N, 11.7%); δ_H(80 MHz; $CDCl_3$) 1.42 (3 H, t, *J* 7, OCH$_2$*Me*), 2.84 (3 H, s, 2-Me), 4.40 (2 H, q, *J* 7, OC*H*$_2$Me), 5.63 (2 H, s, NC*H*$_2$Ph), 6.70 (2 H, br s, NH_2), 7.20–7.35 (8 H, m) and 7.82 (1 H, m); *m/z* 359 (M$^+$, 87%), 313 (28) and 91 (100).

4-*Amino*-2-*methyl*-9H-*pyrido*[2,3-b]*indole*-3-*carboxylic Acid* **4**.—A solution of the *N*-benzyl compound **3** (5.0 g, 13.9 mmol) in dry benzene (174 cm^3) was added dropwise to a vigorously stirred suspension of aluminium chloride (10.4 g, 78.5 mmol) in dry benzene (90 cm^3). The mixture was then heated in an oil-bath at 65 °C for 1.5 h. After cooling, the solvent was decanted off, and the residue was washed twice with benzene. The brown residue was then digested with water (253 cm^3) and 5 mol dm^{-3} hydrochloric acid (7 cm^3). The resultant pink solid was filtered off, washed thoroughly with water, then dried at 60 °C to afford the *title compound* **4** (3.9 g, 100%), m.p. 230–232 °C (decomp.) (Found: M$^+$, 241.0840. $C_{13}H_{11}N_3O_2$ requires M, 241.0851); δ_H[80 MHz; $(CD_3)_2SO$] 2.85 (3 H, s, 2-Me), 7.25 (1 H, br s, NH), 7.27–7.83 (3 H, m), 8.39 (2 H, br s, NH_2), 8.51 (1 H, m) and 12.65 (1 H, br s, CO_2H); *m/z* 241 (M$^+$, 80%), 223 (100) and 197 (42).

Methyl 4-Amino-2-methyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **5**.—A mixture of the carboxylic acid **4** (3.0 g, 10.8 mmol) and thionyl chloride (60 cm^3) was heated under reflux for 6 h. The solution was cooled, then evaporated to dryness. The residue was cooled, and a solution of sodium methoxide in methanol (1 mol dm^{-3}; 70 cm^3) was added. The resulting suspension was vigorously stirred at room temperature for 16 h, then poured on to water (300 cm^3), and the pH was adjusted to 7 with hydrochloric acid (5 mol dm^{-3}). The brown solid was filtered off, and washed thoroughly with water. Crystallisation from methanol afforded the *title compound* **5** as brown needles (1.3 g, 41%). Recrystallisation from methanol, with charcoal treatment, gave white needles, m.p. 256–266 °C (decomp.) (Found: C, 65.7; H, 5.2; N, 16.3. $C_{14}H_{13}N_3O_2$ requires C, 65.9; H, 5.1; N, 16.5%); δ_H[80 MHz; $(CD_3)_2SO$] 2.66 (3 H, s, 2-Me), 3.90 (3 H, s, OMe), 7.20 (2 H, br s, NH_2), 7.10–7.55 (3 H, m), 8.35 (1 H, m) and 11.71 (1 H, br s, NH); *m/z* 255 (M^+, 68%) and 223 (100).

2-Amino-1-(4-methoxybenzyl)-4,5,6,7-tetrahydroindole-3-carbonitrile **6**.—A solution of 2-hydroxycyclohexanone (33.2 g, 291 mmol) and 4-methoxybenzylamine (39.8 g, 291 mmol) in dry toluene (300 cm^3) was heated under reflux for 1.5 h, with azeotropic removal of water. The resultant yellow solution was cooled, then added dropwise to a solution of malononitrile (19.1 g, 289 mmol) in dry toluene (200 cm^3) at 100 °C. The mixture was then heated under reflux for 45 min, cooled, and evaporated to dryness. Recrystallisation from ethanol afforded the *title compound* **6** (63.4 g, 77%), m.p. 122–126 °C (Found: C, 72.4; H, 6.9; N, 14.9. $C_{17}H_{19}N_3O$ requires C, 72.6; H, 6.8; N, 14.9%); δ_H(80 MHz; $CDCl_3$) 1.70–1.85 (4 H, m), 2.36 (2 H, m), 2.47 (2 H, m), 3.62 (2 H, br s, NH_2), 3.80 (3 H, s, OMe), 4.80 (2 H, s, NCH_2Ar), 6.87 (2 H, d, *J* 9) and 6.96 (2 H, d, *J* 9); *m/z* 281 (M^+, 12%), and 121 (100).

Methyl 4-Amino-9-(4-methoxybenzyl)-2-methyl-5,6,7,8-tetrahydro-9H-pyrido[2,3-b]*indole-3-carboxylate* **7**.—A solution of the amino nitrile **6** (10.0 g, 36 mmol), methyl 3-methoxycrotonate[8,14] (4.8 g, 38 mmol), and toluene-4-sulfonic acid (PTSA) (0.26 g, 1.4 mmol) in toluene (160 cm^3) was rapidly heated to boiling. The mixture was heated for 1 h with removal of solvent (15 cm^3) *via* a Dean–Stark apparatus. The reaction mixture was cooled, and a solution of sodium methoxide in methanol (1 mol dm^{-3}; 44 cm^3) was added dropwise. The solution was then heated to boiling for 2 h, with removal of solvent (60 cm^3). The reaction mixture was then cooled and poured on to brine (160 cm^3), and the pH of the aq. layer was adjusted to 8 by using dil. hydrochloric acid. The toluene layer was separated, and the aq. layer was extracted with toluene. The combined toluene extracts were washed with brine, dried, and evaporated to dryness. Crystallisation from methanol afforded the *title compound* **7** (9.8 g, 72%), m.p. 130–131 °C (Found: C, 69.5; H, 6.6; N, 11.1. $C_{22}H_{25}N_3O_3$ requires C, 69.6; H, 6.6; N, 11.1%); δ_H(270 MHz; $CDCl_3$) 1.80 (4 H, m), 2.45 (2 H, m), 2.71 (3 H, s, 2-Me), 2.87 (2 H, m), 3.75 (3 H, s, ArO*Me*), 3.88 (3 H, s, CO_2Me), 5.27 (2 H, s, NCH_2Ar), 6.33 (2 H, br s, NH_2), 6.77 (2 H, d, *J* 10) and 7.04 (2 H, d, *J* 10); *m/z* 379 (M^+, 60%) and 121 (100).

Methyl 4-Amino-9-(4-methoxybenzyl)-2-methyl-9H-pyrido-[2,3-b]*indole-3-carboxylate* **8**.—A solution of the tetrahydro compound **7** (23.3 g, 61.4 mmol) in toluene (190 cm^3) was added dropwise to a solution of DDQ (27.9 g, 123 mmol) in toluene (190 cm^3) at room temperature. The vigorously stirred solution was then heated in an oil-bath at 120 °C for 30 min. The hot solution was filtered, then evaporated to dryness. Chromatography on silica gel with methylene dichloride as eluent gave the *title compound* **8** (18.7 g, 81%), m.p. 142–145 °C (from methanol) (Found: C, 70.4; H, 5.7; N, 11.3. $C_{22}H_{21}N_3O_3$ requires C, 70.4; H, 5.6; N, 11.2%); δ_H(270 MHz; $CDCl_3$) 2.83 (3 H, s, 2-Me), 3.73 (3 H, s, ArO*Me*), 3.95 (3 H, s, CO_2Me), 5.57 (2 H, s, NCH_2Ar), 6.72 (2 H, br s, NH_2), 6.77 (2 H, m), 7.15–7.35 (5 H, m) and 7.82 (1 H, m); *m/z* 375 (M^+, 36%) and 121 (100).

Deprotection of the Pyridoindole **8**.—A mixture of the 4-methoxybenzyl derivative **8** (11.34 g, 30 mmol), anisole (9.5 cm^3, 87.5 mmol), TFA (96 cm^3), and conc. sulfuric acid (4.8 cm^3) was stirred at room temperature for 1.5 h. The solution was then added dropwise to ice-cooled, vigorously stirred, saturated, aq. sodium hydrogen carbonate (2 dm^3). The resulting suspension was kept at 5 °C for 16 h, then filtered. The solid was washed successively and thoroughly with water, cold methanol, and diethyl ether, then was dried to afford compound **5** (7.3 g, 88%), identical with that previously prepared.

Methyl 4-Amino-9-(4-methoxybenzyl)-2-methyl-5-oxo-5,6,7,-8-tetrahydro-9H-pyrido[2,3-b]*indole-3-carboxylate* **9**.—A solution of DDQ (1.2 g, 5.2 mmol) in THF (14 cm^3) was added dropwise to a stirred solution of the tetrahydro compound **7** (1.0 g, 2.6 mmol) in 90% aq. THF (28 cm^3) at 0 °C under nitrogen. After being stirred for 2.5 h, the reaction mixture was evaporated to dryness. Chromatography on alumina with methylene dichloride, followed by 1% methanol–methylene dichloride as eluent, afforded the *title compound* **9** (0.52 g, 51%) contaminated with a trace amount of starting material **7**. Repeated chromatography furnished the analytically pure product, m.p. 161–162 °C (from methanol) (Found: C, 67.2; H, 5.9; N, 10.8. $C_{22}H_{23}N_3O_4$ requires C, 67.2; H, 5.9; N, 10.7%); δ_H(270 MHz; $CDCl_3$) 2.10 (2 H, m, $CH_2CH_2CH_2$), 2.47 (2 H, t, *J* 8, $COCH_2CH_2$), 2.58 (3 H, s, 2-Me), 2.70 (2 H, t, *J* 8, CH_2CH_2Ar), 3.70 (3 H, s, ArO*Me*), 3.85 (3 H, s, CO_2Me), 5.30 (2 H, s, NCH_2Ar), 6.75 (2 H, d, *J* 9) and 7.04 (2 H, d, *J* 9); *m/z* 393 (M^+, 35%) and 121 (100).

Methyl 4-Amino-2,9-dimethyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **10**.—A suspension of the ester **5** (3.0 g, 11.7 mmol) in dry DMF (34 cm^3) was added dropwise to a stirred suspension of 80% sodium hydride (0.38 g, 12.6 mmol) in DMF (14 cm^3) at 0 °C under nitrogen. After 30 min, a solution of methyl iodide (1.84 g, 13.0 mmol) in DMF (5 cm^3) was added, and the mixture was stirred at room temperature for 16 h, poured onto water, and extracted twice with methylene dichloride. The combined extracts were washed thoroughly with water, dried, and evaporated to give a yellow oil. Crystallisation from methanol afforded the *title compound* **10** (1.94 g, 61%), m.p. 98–100 °C (Found: C, 66.9; H, 5.5; N, 15.5. $C_{15}H_{15}N_3O_2$ requires C, 66.9; H, 5.6; N, 15.6%); δ_H(80 MHz; $CDCl_3$) 2.85 (3 H, s, 2-Me), 3.91 (3 H, s), 3.98 (3 H, s), 6.70 (2 H, br s, NH_2), 7.20–7.50 (3 H, m) and 7.80 (1 H, m); *m/z* 269 (M^+, 85%) and 237 (100).

Methyl 9-Allyl-4-amino-2-methyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **11**.—A suspension of the ester **5** (2.5 g, 9.8 mmol) in dry DMF (20 cm^3) was added dropwise to a stirred suspension of 80% sodium hydride (0.32 g, 9.8 mmol) in DMF (10 cm^3) at 0 °C under nitrogen. After 30 min, allyl bromide (0.85 cm^3, 9.8 mmol) was added, and the mixture was stirred at room temperature for 16 h, then evaporated to dryness, and the residue was partitioned between methylene dichloride and water. The organic phase was washed with brine, dried, and evaporated to dryness. Chromatography on silica gel with methylene dichloride as eluent afforded a crude product, which was recrystallised from diethyl ether to afford the *title compound* **11** (1.42 g, 51%), m.p. 78–85 °C (Found: C, 69.2; H, 6.0; N, 14.1. $C_{17}H_{17}N_3O_2$ requires C, 69.1; H, 5.8; N, 14.2%); δ_H[270 MHz; $(CD_3)_2SO$] 2.65 (3 H, s, 2-Me), 3.86 (3 H, s, CO_2Me), 4.92 (1 H, dd, *J* 16 and 2, $CH_2CH{=}CH_{cis}H_{trans}$), 5.03 (2 H, d, *J* 4,

$CH_2CH{=}CH_2$), 5.08 (1 H, dd, *J* 10 and 2, $CH_2CH{=}CH_{cis}H_{trans}$), 5.98 (1 H, m, $CH_2CH{=}CH_2$), 7.20 (2 H, br s, NH_2), 7.20–7.55 (3 H, m) and 8.34 (1 H, d, *J* 9); *m/z* 295 (M^+, 100%), 280 (20) and 262 (30).

Methyl 9-Acetyl-4-amino-2-methyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **12**.—A suspension of the ester **5** (1.04 g, 4.1 mmol) in dry DMF (10 cm^3) was added dropwise to a stirred suspension of 80% sodium hydride (0.12 g, 4.1 mmol) in DMF (15 cm^3) at 0 °C under nitrogen. After 1 h, acetic anhydride (0.42 g, 4.1 mmol) was added and the mixture was stirred at room temperature for 16 h before being evaporated to dryness, and the residue was partitioned between water and methylene dichloride. The organic phase was washed with brine, dried, and evaporated to dryness. Chromatography of the residue on silica gel with ethyl acetate–pentane (1:1) as eluent afforded a crude product, which was recrystallised from diethyl ether to afford the *title compound* **12** (0.64 g, 53%), m.p. 187–188 °C (Found: C, 64.7; H, 4.8; N, 13.9. $C_{16}H_{15}N_3O_3$ requires C, 64.6; H, 5.1; N, 14.1%); δ_H[80 MHz; $(CD_3)_2SO$] 2.48 (3 H, s, COMe), 2.89 (3 H, s, 2-Me), 3.78 (3 H, s, CO_2Me), 7.02 (2 H, br s, NH_2), 7.33 (2 H, m), 8.18 (1 H, m) and 8.44 (1 H, m); *m/z* 297 (M^+, 45%), 255 (100) and 223 (90).

4-Amino-2,9-dimethyl-9H-pyrido[2,3-b]*indole-3-carboxylic Acid* **13**.—A mixture of the ester **10** (3.17 g, 11.0 mmol), ethanol (22 cm^3), and 10% aq. sodium hydroxide (22 cm^3) was heated under reflux for 2 h. The solution was allowed to cool, and the pH was adjusted to 5 with dil. hydrochloric acid. The resulting precipitate was filtered off, washed with water, and dried to afford the *title compound* **13** (2.5 g, 87%), m.p. 230–232 °C (Found: C, 57.3; H, 5.1; N, 14.1; Cl, 9.0; water, 4.2. $C_{14}H_{13}N_3O_2{\cdot}0.75\ HCl{\cdot}0.67H_2O$ requires C, 57.1; H, 5.2; N, 14.3; Cl, 9.0; water, 4.2%); δ_H[80 MHz; $(CD_3)_2SO$] 2.67 (3 H, s, 2-Me), 3.80 (3 H, s, NMe), 7.05–7.60 (5 H, m) and 8.20 (1 H, d, *J* 8); *m/z* 255 (M^+, 70%) and 237 (100).

4-Amino-2,9-dimethyl-9H-pyrido[2,3-b]*indole* **14**.—A suspension of the acid **13** (2.5 g, 9.8 mmol) in diphenyl ether (10 g) was heated under reflux for 3 h. After cooling, the reaction mixture was diluted with hexane, and the mixture was stirred for 0.5 h. The precipitate was filtered off and dried to afford the *title compound* **14** (1.67 g, 81%), m.p. 162–164 °C (from ethanol) (Found: M^+, 211.1107. $C_{13}H_{13}N_3$ requires M, 211.1109); δ_H[250 MHz; $(CD_3)_2SO$] 2.40 (3 H, s, 2-Me), 3.76 (3 H, s, NMe), 6.28 (1 H, s, 3-H), 6.42 (2 H, br s, NH_2), 7.13 (1 H, m), 7.32 (1 H, m), 7.46 (1 H, m) and 8.20 (1 H, m); *m/z* 211 (M^+, 100%) and 210 (50).

Methyl Cyano(2-nitrophenyl)acetate.—A solution of methyl cyanoacetate (24.7 g, 250 mmol) in dry DMF (50 cm^3) was added dropwise to a stirred suspension of 80% sodium hydride (8.3 g, 275 mmol) in DMF (250 cm^3) at 0 °C under nitrogen. After 30 min, a solution of 2-fluoronitrobenzene (17.6 g, 125 mmol) in DMF (20 cm^3) was added, and the mixture was stirred at room temperature for 16 h. The dark red solution was then quenched with dil. hydrochloric acid, and the solution was concentrated under reduced pressure. The residue was poured onto water and extracted with diethyl ether. The organic extracts were then re-extracted with aq. sodium hydroxide (10%). The basic aq. extracts were then washed with diethyl ether and acidified to pH 5 with dil. hydrochloric acid (5 mol dm^{-3}). Extraction with diethyl ether gave a solution, which was washed with brine, dried, and evaporated to afford the *title compound* as a solid (24.5 g, 89%), m.p. 58–59 °C (Found: C, 54.5; H, 3.7; N, 12.7. $C_{10}H_8N_2O_4$ requires C, 54.6; H, 3.7; N, 12.7%); δ_H(80 MHz; $CDCl_3$) 3.87 (3 H, s, CO_2Me), 5.70 (1 H, s, ArC*H*), 7.50–7.85 (3 H, m) and 8.20 (1 H, m); *m/z* (CI, NH_3) 238 (M^+ + 18).

Methyl 2-Aminoindole-3-carboxylate **17**.—A solution of methyl cyano(2-nitrophenyl)acetate (24.5 g, 111 mmol) in a mixture of acetic acid (61 cm^3) and toluene (184 cm^3) was heated until an internal temperature of 80 °C was reached. Zinc powder (53 g, 810 mmol) was added slowly, portionwise, to the vigorously stirred mixture at such a rate as to maintain the internal temperature within the range 80–85 °C. External heating was removed after the first addition of zinc; cooling was required on several occasions to maintain the desired temperature. After the addition of zinc was complete, the reaction mixture was cooled, filtered, and evaporated to dryness. The residue was dissolved in ethyl acetate, washed with aq. sodium hydrogen carbonate, dried, and evaporated to yield a brown solid (17 g). Chromatography on silica gel with ethyl acetate–pentane (2:3) as eluent gave the *title compound* **17** (13.3 g, 63%), m.p. 135–137 °C (Found: M^+, 190.0739. $C_{10}H_{10}N_2O_2$ requires M, 190.0742); δ_H[80 MHz; $(CD_3)_2SO$] 3.80 (3 H, s, OMe), 6.67 (2 H, br s, NH_2), 6.80–7.20 (3 H, m), 7.65 (1 H, m) and 10.65 (1 H, br s, NH); *m/z* 190 (M^+, 60%) and 158 (100).

Methyl 2-(2-Ethoxycarbonyl-1-methylvinylamino)indole-3-carboxylate **18**.—A mixture of amino ester **17** (0.48 g, 2.5 mmol) and ethyl 3-ethoxycrotonate[8] 0.79, g, 5.0 mmol) in xylenes (8 cm^3) was heated under reflux for 3 h. The reaction mixture was cooled slightly, and hexane (6 cm^3) was added slowly. The mixture was then cooled in ice and filtered to afford the *title compound* **18** (0.51 g, 67%), m.p. 150–155 °C (decomp.) (Found: M^+, 302.1265. $C_{16}H_{18}N_2O_4$ requires M, 302.1266); δ_H(80 MHz; $CDCl_3$) 1.28 (3 H, t, *J* 8, CO_2CH_2Me), 2.40 (3 H, d, *J* 1, CH=C*Me*), 3.97 (3 H, s, CO_2Me), 4.25 (2 H, q, *J* 8, CO_2CH_2Me), 4.95 (1 H, q, *J* 1, C*H*=CMe), 7.1–7.4 (3 H, m), 7.95 (1 H, m), 8.40 (1 H, br s, NH) and 12.15 (1 H, br s, NH); *m/z* 302 (M^+, 40%), 256 (55) and 224 (100).

Cyclisation of Compound **18** *with Base*.—A solution of compound **18** (0.30 g, 1.0 mmol) in dry DMF (2 cm^3) was added to a solution of potassium *t*-butoxide (0.12 g, 1.1 mmol) in DMF (2 cm^3) at 0 °C under nitrogen. The reaction mixture was stirred for 2 h, then poured on to water. After acidification to pH 4 with dil. hydrochloric acid (5 mol dm^{-3}), the precipitate was filtered off and dried to afford the *pyrimido*[1,2-a]*indole* **20** (0.20 g, 78%), m.p. 181–182 °C (Found: M^+, 256.0858. $C_{14}H_{12}N_2O_3$ requires M, 256.0848); δ_H[80 MHz; $(CD_3)_2SO$] 2.45 (3 H, d, *J* 1, CH=C*Me*), 3.95 (3 H, s, CO_2Me), 5.80 (1 H, q, *J* 1, C*H*=CMe), 7.20–7.60 (2 H, m), 8.00 (1 H, m), 8.65 (1 H, m) and 11.10 (1 H, br s, NH); *m/z* 256 (M^+, 55%) and 224 (100).

Methyl 2-(2-t-Butoxycarbonyl-1-methylvinylamino)indole-3-carboxylate **19**.—A mixture of amino ester **17** (0.19 g, 1.0 mmol), and *t*-butyl 3-ethoxycrotonate[14] (0.37 g, 2.0 mmol) in xylenes (4 cm^3) was heated under reflux for 2.5 h, then evaporated to dryness. Chromatography on silica gel with ethyl acetate–pentane (1% ⟶ 30%) as eluent gave the *title compound* **19** (0.14 g, 42%) (Found: M^+, 330.1562. $C_{18}H_{22}N_2O_4$ requires M, 330.1579); δ_H(80 MHz; $CDCl_3$) 1.50 (9 H, s, CO_2Bu^t), 2.32 (3 H, d, *J* 1, CH=C*Me*), 3.95 (3 H, s, CO_2Me), 4.86 (1 H, q, *J* 1, C*H*=CMe), 7.05–7.30 (3 H, m), 8.00 (1 H, m), 8.50 (1 H, br s, NH) and 11.90 (1 H, br s, NH); *m/z* 330 (M^+, 40%), 274 (65), 224 (75) and 198 (100).

Cyclisation of Compound **19** *with Base*.—A solution of compound **19** (0.16 g, 0.5 mmol) in toluene (2 cm^3) containing a solution of sodium ethoxide in ethanol (0.5 mol dm^{-3}; 1 cm^3) was stirred at room temperature for 0.5 h. Evaporation to

dryness and acidification afforded only the pyrimido[1,2-*a*]-indole **20**, identical with that isolated in the above experiment.

Methyl 2-Amino-1-methylindole-3-carboxylate **21**.—A solution of methyl 2-aminoindole-3-carboxylate **17** (9.5 g, 50 mmol) in dry DMF (44 cm^3) was added dropwise to a stirred suspension of 80% sodium hydride (1.97 g, 65 mmol) in DMF (37 cm^3) at 0 °C under nitrogen. After the mixture had been stirred for 30 min, a solution of methyl iodide (8.9 g, 63 mmol) in DMF (8 cm^3) was added. The mixture was stirred for 3 h and was then poured on to ice–water. The resultant brown precipitate was filtered off, washed well with water, and dried. Recrystallisation from methanol afforded the *title compound* **21** (4.5 g, 44%), m.p. 192–196 °C (Found: M^+, 204.0902. $C_{11}H_{12}N_2O_2$ requires M, 204.0899); δ_H(80 MHz; $CDCl_3$) 3.25 (3 H, s, NMe), 3.85 (3 H, s, CO_2Me), 6.80 (2 H, br s, NH_2), 6.9–7.2 (3 H, m) and 7.70 (1 H, m); *m/z* 204 (M^+, 87%) and 172 (100).

Methyl 4-Hydroxy-2,9-dimethyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **22**.—A solution of the amino ester **21** (5.4 g, 26.5 mmol), methyl 3-methoxycrotonate (6.9 g, 53 mmol), and PTSA (0.25 g, 1.3 mmol) in toluene (125 cm^3) was heated vigorously for 2 h, during which time a distillate (60 cm^3) was collected. The residual brown solution was cooled, and a solution of sodium methoxide in methanol (1 mol dm^{-3}; 31 cm^3) was added. The solution was then heated to boiling for a further 3 h, with the removal of further distillate (30 cm^3). The mixture was then cooled, and the resulting brown precipitate was collected by filtration. The solid obtained (5.0 g) was dissolved in methanol (30 cm^3), and a solution of acetic acid (1.2 g) in methanol (5 cm^3) was added, followed by water (500 cm^3). The precipitate was filtered off, and washed thoroughly with water to afford the *title compound* **22** (3.6 g, 50%), m.p. 174–176 °C (from methanol) (Found: C, 66.6; H, 4.9; N, 10.0. $C_{15}H_{14}N_2O_3$ requires C, 66.7; H, 5.2; N, 10.4%); δ_H[270 MHz; $(CD_3)_2SO$] 2.72 (3 H, s, 2-Me), 3.86 (3 H, s), 3.92 (3 H, s), 7.25–7.65 (3 H, m), 8.10 (1 H, m) and 12.25 (1 H, br s, OH); *m/z* 270 (M^+, 25%) and 238 (100).

Methyl 4-Chloro-2,9-dimethyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **15**.—A solution of the 4-hydroxy compound **22** (3.0 g, 11.1 mmol) in phosphorus trichloride oxide (45 cm^3) was heated under reflux for 3 h. The solution was then cooled, and evaporated to dryness. The dark residue was partitioned between methylene dichloride and aq. sodium hydrogen carbonate, with cooling. The organic layer was washed with brine, dried, and evaporated to afford a brown solid (3.3 g). Chromatography on silica gel with methylene dichloride as eluent gave the *title compound* **15** (2.1 g, 66%), m.p. 110–111 °C (from methanol) (Found: C, 62.6; H, 4.7; N, 9.8. $C_{15}H_{13}ClN_2O_2$ requires C, 62.4; H, 4.5; N, 9.7%); δ_H(270 MHz; $CDCl_3$) 2.75 (3 H, s, 2-Me), 3.98 (3 H, s), 4.06 (3 H, s), 7.25–7.75 (3 H, m) and 8.47 (1 H, m); *m/z* 290 (M^+, 35%), 288 (M^+, 100), 259 (27) and 257 (85).

Methyl 4-Butylamino-2,9-dimethyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **23**.—A solution of the chloro ester **15** (1.0 g, 3.5 mmol) in butylamine (20 cm^3) was heated under reflux for 3 h. The solution was allowed to cool, then was evaporated to dryness. The residue was partitioned between water and methylene dichloride. The organic layer was washed with brine, dried, and evaporated to afford a yellow oil (1.0 g). Crystallisation from methanol afforded the *title compound* **23** (0.6 g, 53%), m.p. 68–69 °C (Found: C, 70.3; H, 7.2; N, 13.1. $C_{19}H_{23}N_3O_2$ requires C, 70.1; H, 7.1; N, 12.9%); δ_H(80 MHz; $CDCl_3$) 0.90 (3 H, t, *J* 10, $[CH_2]_3Me$), 1.10–1.75 (4 H, m, $NCH_2CH_2CH_2Me$), 2.70 (3 H, s, 2-Me), 3.35–3.65 (2 H, m, $NHCH_2Pr$), 3.90 (3 H, s), 3.94 (3 H, s), 6.50 (1 H, br s, NH), 7.15–7.50 (3 H, m) and 7.90 (1 H, m); *m/z* 325 (M^+, 45%) and 250 (100).

Methyl 4-Dimethylamino-2,9-dimethyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **24**.—A mixture of the chloro ester **15** (2.0 g, 6.9 mmol) and a solution of dimethylamine in methanol (30%; 15 cm^3) was heated in a sealed vessel for 18 h at 90 °C. The cooled solution was evaporated to dryness, and the residue was partitioned between methylene dichloride and brine. The organic phase was washed with brine, dried, and evaporated to give a yellow oil (1.4 g). Chromatography on silica gel with ethyl acetate–pentane (1:3) as eluent afforded the *title compound* **24** (0.9 g, 44%), m.p. 106–108 °C (from methanol) (Found: C, 68.4; H, 6.8; N, 14.0. $C_{17}H_{19}N_3O_2$ requires C, 68.7; H, 6.5; N, 14.1%); δ_H(80 MHz; $CDCl_3$) 2.65 (3 H, s, 2-Me), 3.08 (6 H, s, NMe_2), 3.93 (3 H, s), 3.98 (3 H, s), 7.2–7.55 (3 H, m) and 8.10 (1 H, m); *m/z* 297 (M^+, 57%) and 266 (100).

4,6-*Dimethyl-1,2-dihydropyrazolo*[3′,4′:4,5]*pyrido*[2,3-b]*indol-3*(6H)-*one* **25**.—A solution of the chloro ester **15** (1.0 g, 3.5 mmol) in methanol (20 cm^3) containing hydrazine hydrate (7 cm^3) was heated under reflux for 18 h. The reaction mixture was then cooled, poured on to water, and acidified with dil. hydrochloric acid. The yellow precipitate was filtered off, and dried to give a crude product (1.1 g). Recrystallisation from DMF afforded the *title compound* **25** (0.7 g, 79%), m.p. > 320 °C (Found: C, 66.2; H, 5.0; N, 22.4. $C_{14}H_{12}N_4O$ requires C, 66.6; H, 4.8; N, 22.2%); δ_H[80 MHz; $(CD_3)_2SO$] 2.82 (3 H, s, 2-Me), 3.94 (3 H, s, NMe), 7.10–7.70 (3 H, m) and 8.30 (1 H, m); *m/z* 252 (M^+, 100%).

Methyl 2,9-Dimethyl-9H-pyrido[2,3-b]*indole-3-carboxylate* **26**.—A solution of the chloro ester **15** (1.06 g, 3.67 mmol) in acetic acid (31 cm^3) containing zinc powder (2.1 g, 32 mmol) was heated to 100 °C for 15 min. The hot mixture was filtered, and the filtrate was diluted with water. The solution was neutralised (to pH 7) with aq. sodium hydroxide (40%), and was extracted with methylene dichloride. The organic layer was washed successively with aq. sodium hydrogen carbonate and brine, then was dried and evaporated to afford a solid (0.92 g). Recrystallisation from methanol afforded the *title compound* **26** (0.84 g, 90%), m.p. 139–140 °C (Found: C, 71.3; H, 5.6; N, 11.0. $C_{15}H_{14}N_2O_2$ requires C, 70.9; H, 5.6; N, 11.0%); δ_H(80 MHz; $CDCl_3$) 3.03 (3 H, s, 2-Me), 3.98 (3 H, s), 4.01 (3 H, s), 7.20–7.60 (3 H, m), 8.10 (1 H, m) and 8.93 (1 H, s, 4-H); *m/z* 254 (M^+, 100%), 223 (65) and 195 (25).

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