Rapid Syntheses of Some Indole Alkaloids of the Calabar Bean

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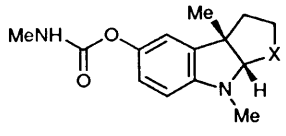
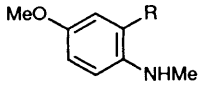
A rapid, efficient route to 3,3-disubstituted oxindoles from *o*-iodo anilines has been developed. It involves the cyclisation of the corresponding fumarate amides **4** and **15** with butyllithium at −100 °C in the presence of an excess of trimethylchlorosilane. An X-ray crystal structure of **4** suggests that the speed and efficiency of this intramolecular Michael addition is dependent on the conformation adopted by **4** which is particularly suitable for the reaction. This method has been applied to the synthesis of the alkaloids physovenine, physostigmine and esermethole in very high overall yields.

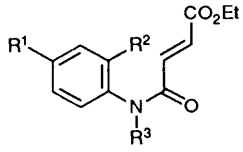
The pyrrolo[2,3-*b*]indole alkaloid physostigmine **1** isolated from the Calabar bean of West Africa is well known for its inhibition of acetylcholine esterase. Many syntheses of both **1** and its oxygen analogue physovenine **2** have been reported.[1] We now describe a novel, simple route to 3,3-disubstituted oxindoles, a structural feature of many oxindole alkaloids, and its application to the synthesis of **1** and **2** in high yield.



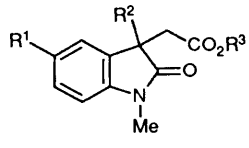
1 X = NMe
2 X = O



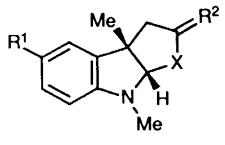
13 R = H
14 R = I



3 $R^1 = R^3 = H$, $R^2 = I$
4 $R^1 = H$, $R^2 = I$, $R^3 = Me$
7 $R^1 = H$, $R^2 = Br$, $R^3 = H$
8 $R^1 = H$, $R^2 = Br$, $R^3 = Me$
15 $R^1 = OMe$, $R^2 = I$, $R^3 = Me$



5 $R^1 = R^2 = H$, $R^3 = Et$
9 $R^1 = H$, $R^2 = Me$, $R^3 = Et$
11 $R^1 = R^3 = H$, $R^2 = Me$
16 $R^1 = OMe$, $R^2 = H$, $R^3 = Et$
17 $R^1 = OMe$, $R^2 = Me$, $R^3 = Et$
19 $R^1 = OMe$, $R^2 = Me$, $R^3 = H$



10 $R^1 = R^2 = H$, X = O
12 $R^1 = H$, $R^2 = X = O$
18 $R^1 = OMe$, $R^2 = H$, X = O
20 $R^1 = OMe$, $R^2 = X = O$
21 $R^1 = OMe$, $R^2 = H$, X = NMe

6

Our synthetic investigations were begun with commercially available *ortho*-iodoaniline which was acylated with the mono acid chloride of ethyl fumarate and the resulting amide **3** methylated with sodium hydride and methyl iodide to the *N*-methyl amide **4**. Cyclisation to the oxindole **5** by intramolecular Michael addition was triggered by lithium–iodine exchange (butyllithium at −100 °C for 30 s). Quenching the resulting mixture with aqueous ammonium chloride at this temperature revealed that much polymeric and ill-defined material was formed together with only a 43% yield of the desired product **5**. We attributed the low yield to anionic polymerisations initiated by the ester enolate that results from the cyclisation. To forestall such processes 5 equiv. of trimethylchlorosilane were added to the reaction mixture before the addition of butyllithium at −100 °C. The results confirmed our hypothesis, polymerisation was prevented by silylation of the ester enolate and the yield of the desired oxindole was doubled (85%). It is quite remarkable that no aromatic silylation could be detected under these conditions. The intramolecular cyclisation of the aryllithium intermediate produced by the exchange must take place so rapidly that silylation cannot compete even in the presence of an excess of chlorosilane. In order to clarify the nature of the structural features of compound **4** that seem to promote the cyclisation an X-ray crystal structure was completed, and the result is shown in Fig. 1. The molecule adopts a conformation where the plane of the amide substituent (N_7–C_{13}) is essentially orthogonal to the plane of the benzene ring and this conformation is probably maintained by the fact that the steric interactions between the C_8 N-methyl group and the C_2 iodine and C_6 hydrogen are at a minimum. The N_7–C_9 bond has normal amide character (1.343 Å) and we find that no change in the ^{1}H NMR spectrum of **4** occurs between 213 and 333 K. The double bond character of the N_7–C_9 amide also helps to maintain planarity in the N_7 to C_{13} segment of the molecule. The X-ray structure of **6** shows similar features.[2]

A different view of the molecule (Fig. 2) aligns the reacting centres C_2 and C_{11} and shows their relationship and proximity more clearly; C_2 and C_{11} are 3.529 Å apart and the C_2–C_{11}–C_{12} angle is 150.7° in **4**. The exchange reaction produces the C-2 lithiated intermediate and a PC Model† minimisation of this compound using the X-ray coordinates of **4** with iodine replaced by lithium showed a very similar relationship between C_2 and C_{11}–C_{12} in the minimised structure. Furthermore, the calculations indicate that a rotation of ±20° about the C_1–N_7 bond results in an increase in energy of only 1.0 kcal mol^{-1} using the rigid rotor approximation within PC Model. It therefore seems that the lithium–iodine exchange produces an intermediate well suited to the trajectory requirements of the intramolecular 5-*exo*-*trig* addition and it must occur virtually instantaneously. For this reason, intermolecular silylation of the intermediate cannot compete.

† This copy of PC Model was kindly provided by Dr. Kosta Steliou of the University of Montreal and is distributed by Serena Software, Bloomington, Indiana.

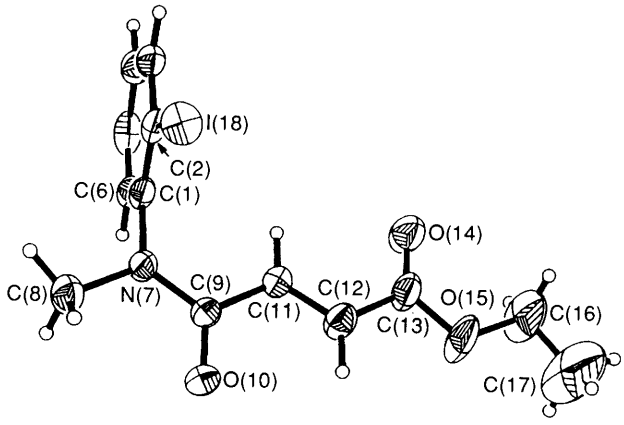


Fig. 1

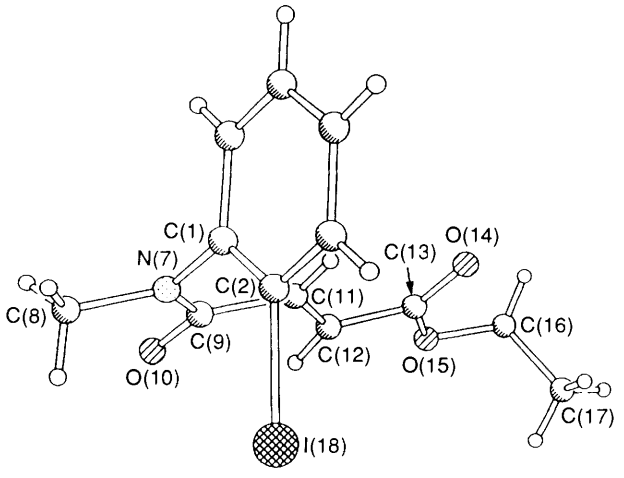


Fig. 2

The bromo analogue **8**, obtained by methylation of **7**, does not cyclise even after 1 h at −90 °C. Addition of butyllithium to the alkene double bond and extensive polymerisation is observed instead. The aromatic region of the ^{1}H NMR spectrum of the crude product mixture indicates that the bromine remains largely unexchanged in the polymeric material. Lithium–iodine exchange is much faster than lithium–bromine exchange, and the failure of the cyclisation with **8** must be attributed to this fact. Intramolecular cyclisations of aryl bromides, promoted by tributyltin hydride and proceeding by a radical mechanism have been employed however, to prepare both oxindoles[3] and pyrrolo[2,3-*b*] indoles.[4] We find that with substrates similar to **4**, the radical pathway gives a lower yield[3,4] of the cyclised product which is also more difficult to purify.

The oxindole **5** was methylated at C-3 with sodium hydride and methyl iodide at 0 °C to give **9** which was reduced with lithium aluminium hydride in THF (tetrahydrofuran) at 0 °C to the tricyclic furo-indole **10**, a model for the alkaloid physovenine. The oxindole **9** was saponified to the acid **11** which after conversion into its salt with sodium hydride, was reduced with lithium triethylborohydride at 0 °C and acidified to provide the lactone **12** which was a model for physostigmine.

The successful conclusion of these sequences in excellent overall yields allowed us to proceed with the synthesis of **1** and **2**. *N*-methyl-*p*-anisidine was *ortho*-iodinated by adaptation of the recent four-step, 'one-pot' process used for *ortho*-functionalisation of aromatic amines.[5] Thus, treatment of **13** with butyllithium at −60 °C was followed by gaseous CO_2 at 25 °C, recooling to −60 °C, *ortho* deprotonation with 1.2 mol of *tert*-butyllithium and warming to −20 °C. After 1 h at that temperature, iodination was conducted by adding 1.5 mol of 1,2-diiodoethane. The reaction mixture was allowed to reach room temperature and the iodinated product **14** isolated in 55% yield after hydrolysis of the carbamate with 5% aqueous hydrochloric acid. Many attempts at direct bromination and iodination of **13** were made without success.

The *o*-iodoanisidine **14** was now subjected to a similar sequence as the one worked out with the model series. Thus acylation to **15** was followed by cyclisation to the oxindole **16** in 92% yield with butyllithium and 5 equiv. of trimethylchlorosilane at −100 °C. Methylation as before to **17** was followed by reduction[6] to the tricyclic furoindole **18**. Conversion of the latter into physovenine **2** by demethylation with boron tribromide and treatment of the resulting phenol with methyl isocyanate had been reported[7] to proceed in 83% overall yield. Thus, our route to physovenine provides this alkaloid in 30% overall yield from the commercial material *N*-methyl-*p*-anisidine.

The oxindole **17** was converted into the tricyclic lactone **20** through the acid **19** as before. This lactone which is obtainable in 35% overall yield from **14** has been quantitatively converted[8] into esermethole **21** by ammonolysis with methylamine and reduction of the amide by lithium aluminium hydride. Physostigmine **1** is available from esermethole by the same demethylation (boron tribromide), acylation (methyl isocyanate) sequence as before. The synthesis of **20** thus concludes a formal synthesis of physostigmine. We are currently investigating the applicability of the cyclisation process to the synthesis of other oxindole alkaloids.

Experimental

All reactions involving air and/or moisture sensitive reagents were carried out in flame and/or oven dried glassware which was assembled hot, and cooled under a positive pressure of argon. Reaction temperatures refer to external cooling bath temperatures unless otherwise noted. THF and diethyl ether were distilled from sodium benzophenone ketyl. DMF (*N*,*N*-dimethylformamide), hexanes and TMSCl were distilled from CaH_2. Oxalyl chloride and iodomethane were distilled from $CaCl_2$. Pyridine was dried over anhydrous KOH. 2-Iodoaniline was purchased from Fluka Chemical Company. All other reagents were purchased from Aldrich Chemical Company and used without further purification. Flash chromatography was carried out using Merck 9385 silica gel 60 (230–400 mesh). M.p.s were determined on a Fischer Mel-Temp apparatus in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmer 983 spectrophotometer with only the strongest and/or most diagnostic bands reported relative to the 1601 cm^{-1} band of polystyrene. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 or AM-250 spectrometers in $CDCl_3$. Chemical shifts are reported relative to internal tetramethylsilane (δ 0.00) for ^{1}H spectra and to $CDCl_3$ (δ 77.00) for ^{13}C spectra, and coupling constants (J) are reported in Hz. Mass spectra were recorded on a Kratos MS 890 spectrometer using electron impact ionization (unless otherwise noted) at the Guelph Mass Spectrometry Centre, University of Guelph, Guelph, Ontario and are reported in the order *m*/*z* (relative intensity to base peak, assignment). Elemental analyses were performed by M-H-W Laboratories, Phoenix, Az., U.S.A.

2-Iodo-4-methoxy-N-methylaniline **14**.—To a cold (−60 °C, internal temperature) solution of *N*-methyl-*p*-anisidine **13** (1.87 g, 13.6 mmol) in THF (80 cm^3) was added BuLi (1.6 mol dm^{-3} solution in hexanes; 9.40 cm^3, 15.0 mmol). The solution was warmed to 25 °C for 20 min while a slow stream of dry CO_2 was passed over and then the resulting bright yellow solution concentrated under reduced pressure. The residue was taken up in dry THF (80 cm^3), cooled to −60 °C, and treated dropwise

with *tert*-BuLi (9.60 cm^3 of a 1.7 mol dm^{-3} solution in pentane, 16.3 mmol). After warming to −20 °C for 1 h, the reaction mixture was cooled to −60 °C and quenched with a THF (40 cm^3) solution of 1,2-diiodoethane (5.70 g, 20.4 mmol). After warming to 25 °C slowly overnight, the solution was treated cautiously at 0 °C with 5% HCl until the evolution of CO_2 had ceased and then basified at 0 °C with 2 mol dm^{-3} NaOH. The organic materials were extracted with $CHCl_3$ (3 × 25 cm^3) and the combined extracts washed (brine, 25 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography of the residue (silica, 50% $CHCl_3$–hexanes eluent) yielded 1.96 g (55%) of **14** (short path distillation of **14** is possible but not advisable as extensive decomposition was noted): b.p. 76–80 °C (0.05 Torr); ν_{max}(film)/cm^{-1} 3393, 1606, 1035, 848, 799 and 745; δ_H(200 MHz; $CDCl_3$) 2.84 (s, 3 H, NMe), 3.73 (s, 3 H, OMe), 3.80 (br s, 1 H, NH), 6.51 (d, *J* 8.9, 1 H, 6-H), 6.87 (dd, *J* 8.9, 2.8, 1 H, 5-H) and 7.28 (d, *J* 2.8, 1 H, 3-H); *m/z* 263 (100, M^+), 248 (80), 136 (7), 121 (17), 120 (16), 93 (16), 92 (19), 78 (15), 77 (11), 67 (13), 66 (14), 65 (11), 63 (13) and 52 (13) (Found: M^+, 262.9808. $C_8H_{10}INO$ requires M, 262.9808).

General Procedure for Preparation of Amides **3**, **7** *and* **15**.—To a solution of monoethyl fumarate (5.75 g, 40 mmol) in THF (40 cm^3) was added oxalyl chloride (7.0 cm^3, 80 mmol) and DMF (2 drops) (*Caution*: vigorous gas evolution). After 1 h, the solution was concentrated under reduced pressure and the crude acid chloride taken up in Et_2O (200 cm^3). After cooling to −78 °C, a solution of either **14**,2-iodoaniline or 2-bromoaniline (44 mmol) and pyridine (3.5 cm^3, 44 mmol) in Et_2O (60 cm^3) was added dropwise (provision for efficient stirring is absolutely necessary). The resulting pink suspension was warmed to 25 °C for 1 h and then partitioned between EtOAc (200 cm^3) and brine (200 cm^3). The separated phase was extracted with EtOAc (3 × 100 cm^3) and the combined organic phases were washed successively with 5% HCl (100 cm^3) and brine (100 cm^3). Drying (Na_2SO_4) and concentration under reduced pressure yielded crude amides which were triturated with cold Et_2O and recrystallized to afford analytical samples.

Ethyl (E)-4-[N-(2′-*iodophenyl*)*amino*]-4-*oxobut*-2-*enoate* **3**. 84%; m.p. 144.5–145 °C (EtOAc) (Found: C, 41.8; H, 3.6. $C_{12}H_{12}INO_3$ requires C, 41.76; H, 3.51%); ν_{max}($CHCl_3$)/cm^{-1} 3374, 1718, 1691 and 1584; δ_H(200 MHz) 1.34 (t, *J* 7.1, 3 H, $CO_2CH_2CH_3$), 4.29 (q, *J* 7.1, 2 H, $CO_2CH_2CH_3$), 6.89 (dt, *J* 7.7, 1.6, 1 H, 4′-H), 6.97, 7.09 (ABq, J_{AB} 15.3, 2 H, 2-H, 3-H), 7.37 (dt, *J* 7.7, 1.6, 1 H, 5′-H), 7.72 (br s, 1 H, NH), 7.81 (dd, *J* 7.7, 1.6, 1 H, 3′-H) and 8.33 (d, *J* 7.9, 1 H, 6′-H); *m/z* 345 (18, M^+), 300 (9), 219 (68), 218 (100), 145 (19), 127 (17), 99 (21) and 91 (13).

Ethyl (E)-4-[N-(2′-*bromophenyl*)*amino*]-4-*oxobut*-2-*enoate* **7**. 64%; m.p. 125.5–126.5 °C (EtOAc–hexanes) (Found: C, 48.15; H, 4.3. $C_{12}H_{12}BrNO_3$ requires C, 48.34; H, 4.06%); ν_{max}($CHCl_3$)/cm^{-1} 3393, 1720, 1692, 1302, 1202 and 1154; δ_H(200 MHz) 1.31 (t, *J* 7.1, 3 H, $CO_2CH_2CH_3$), 4.25 (q, *J* 7.1, 2 H, $CO_2CH_2CH_3$), 6.91, 7.03 (ABq, J_{AB} 15.3, 2 H, 2-H, 3-H), 6.99 (dt, *J* 1.5, 8.0, 1 H, 4′-H), 7.31 (dt, *J* 1.3, 8.0, 1 H, 5′-H), 7.52 (dd, *J* 8.0, 1.5, 1 H, 3′-H), 7.85 (br s, 1 H, NH) and 8.41 (d, *J* 8.0, 1 H, 6′-H); *m/z* 299 (8, M^+), 297 (8), 254 (7), 252 (6), 218 (100), 173 (44), 171 (41), 145 (18), 127 (26) and 99 (23).

Ethyl (E)-4-[N-(2′-*iodo*-4′-*methoxyphenyl*)-N-*methylamino*]-4-*oxobut*-2-*enoate* **15**. 90%; m.p. 70.5–71 °C (Et_2O–hexanes) (Found: C, 43.35; H, 4.35. $C_{14}H_{16}INO_4$ requires C, 43.20; H, 4.15); ν_{max}($CHCl_3$)/cm^{-1} 1718, 1657, 1592, 1031, 784, 755 and 735; δ_H(200 MHz) 1.25 (t, *J* 7.1, 3 H, $CO_2CH_2CH_3$), 3.24 (s, 3 H, NMe), 3.83 (s, 3 H, OMe), 4.16 (q, *J* 7.1, 2 H, $CO_2CH_2CH_3$), 6.66, 6.86 (ABq, J_{AB} 15.6, 2 H, 2-H, 3-H), 6.94 (dd, *J* 8.7, 2.7, 1 H, 5′-H), 7.14 (d, *J* 8.7, 1 H, 6′-H) and 7.42 (d, *J* 2.7, 1 H, 3′-H); *m/z* 389 (6, M^+), 263 (49), 262 (100), 189 (22), 188 (13), 135 (71), 134 (18), 120 (25), 119 (13), 118 (25) and 77 (20).

General Procedure for Preparation of N-*Methyl Amides* **4** *and* **8**.—To a suspension of NaH (60% wt dispersion washed free of oil with 2 × 20 cm^3 of hexanes; 1.60 g, 40 mmol) in THF (60 cm^3) at 0 °C was added dropwise a solution of amide **3** or **7** (33.3 mmol) in THF (100 cm^3). The resulting bright yellow solution was warmed to 25 °C for 30 min, recooled to 0 °C, quenched with iodomethane (4.2 cm^3, 67 mmol) and stirred for 12 h at 25 °C. Water (100 cm^3) was added and the THF removed under reduced pressure. The aqueous residue was extracted with EtOAc (3 × 100 cm^3) and the combined extracts were washed (brine, 100 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to provide the crude amides which were flash chromatographed (silica, 30% EtOAc–hexanes) and recrystallized to provide crystalline solids.

Ethyl (E)-4-[N-(2′-*iodophenyl*)-N-*methylamino*]-4-*oxobut*-2-*enoate* **4**. 79%, m.p. 93–94 °C (Et_2O–hexanes) (Found: C, 43.6; H, 4.0. $C_{13}H_{14}INO_3$ requires C, 43.47; H, 3.94%); ν_{max}($CHCl_3$)/cm^{-1} 1720, 1660, 1636, 1577 and 1302; δ_H(200 MHz) 1.24 (t, *J* 7.2, 3 H, CO_2CH_3), 3.27 (s, 3 H, NMe), 4.15 (q, *J* 7.2, 2 H, $CO_2CH_2CH_3$), 6.60, 6.88 (ABq, J_{AB} 15.2, 2 H, 2-H, 3-H), 7.12 (ddd, *J* 7.8, 7.4, 1.7, 1 H, 4′-H), 7.25 (dd, *J* 7.8, 1.6, 1 H, 6′-H), 7.44 (dt, *J* 7.7, 1.4, 1 H, 5′-H) and 7.94 (dd, *J* 7.9, 1.4, 1 H, 3′-H); δ_C(50 MHz) 14.07 ($CO_2CH_2CH_3$), 36.53 (NCH_3), 60.98 ($CO_2CH_2CH_3$), 99.32 (C-2′), 129.22 (C-6′), 130.09 (C-5′), 130.36 (C-4′), 131.65 (C-2), 133.47 (C-3), 140.38 (C-3′), 144.69 (C-1′), 163.86 (C-4) and 165.47 (C-1); *m/z* (CI) 360 (93, M^+ + 1), 235 (12), 234 (78), 161 (13) and 160 (100).

Ethyl (E)-4-[N-(2′-*bromophenyl*)-N-*methylamino*]-4-*oxobut*-2-*enoate* **8**. 85%; m.p. 79–80 °C (hexanes) (Found: C, 49.85; H, 4.5. $C_{13}H_{14}BrNO_3$ requires C, 50.02; H, 4.53%); ν_{max}($CHCl_3$)/cm^{-1} 1720, 1662 and 1639; δ_H(250 MHz) 1.24 (t, *J* 7.2, 3 H, $CO_2CH_2CH_3$), 3.30 (s, 3 H, NMe), 4.15 (q, *J* 7.2, 2 H, $CO_2CH_2CH_3$), 6.64, 6.87 (ABq, J_{AB} 15.2, 2 H, 2-H, 3-H), 7.25–7.44 (m, 3 H, 4′-H, 5′-H, 6′-H) and 7.70 (dd, *J* 6.9, 1.5, 1 H, 3′-H); *m/z* 314 (0.1, M^+), 312 (0.3), 232 (100), 204 (29), 187 (25), 185 (25), 159 (15), 127 (15) and 77 (19).

General Procedure for Preparation of Oxindoles **5** *and* **16**.—To a cold (−100 °C, internal temperature) solution of amide **4** or **15** (5.6 mmol) in THF–Et_2O–hexanes (4:1:1 by volume, 45 cm^3) containing TMSCl (3.6 cm^3, 28 mmol) in a 3-necked round bottom flask equipped with Ar inlet, low temperature thermometer and rubber septum was added BuLi (1.6 mol dm^{-3} solution in hexanes; 3.9 cm^3, 6.2 mmol) at a rate such that the reaction temperature was maintained ≤ −95 °C. Immediately following the addition, sat. aqueous NH_4Cl (10 cm^3) was added and the solution allowed to reach 25 °C. Water (10 cm^3) was added and the organic solvents were removed under reduced pressure. The aqueous residue was extracted with EtOAc (3 × 25 cm^3) and the combined extracts were washed (brine, 25 cm^3) and dried (Na_2SO_4). Concentration under reduced pressure afforded oils which were flash chromatographed (silica, 30% EtOAc–hexanes eluent) and then Kugelrohr distilled or recrystallized to afford analytical samples.

3-*Ethoxycarbonylmethyl*-1-*methylindol*-2(3H)-*one* **5**. 85%; b.p. 95–100 °C (0.04 Torr, Kugelrohr) (Found: C, 65.3; H, 6.7. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.85); ν_{max}(film)/cm^{-1} 1717, 1663 and 1611; δ_H(250 MHz) 1.20 (t, *J* 7.2, 3 H, $CO_2CH_2CH_3$), 2.78 (dd, *J* 16.8, 8.1, 1 H, $CHCO_2Et$), 3.08 (dd, *J* 16.8, 4.4, 1 H, CH, CO_2Et), 3.23 (s, 3 H, NMe), 3.78 (dd, *J* 8.1, 4.4, 1 H, 3-H), 4.09–4.18 (AB of ABX_3, 2 H, $CO_2CH_2CH_3$), 6.83 (d, *J* 7.7, 1 H, 7-H), 7.03 (m, 1 H, 5-H) and 7.23–7.32 (m, 2 H, 4-H, 6-H); *m/z* 233 (10, M^+), 188 (2), 160 (12), 159 (24), 74 (9), 73 (61), 61 (22), 60 (10), 45 (100) and 43 (46).

3-*Ethoxycarbonylmethyl*-5-*methoxy*-1-*methylindol*-2(3H)-*one* **16**. 92%; m.p. 88–89 °C (Et_2O–hexanes) (Found: C, 64.0; H, 6.6. $C_{14}H_{17}NO_4$ requires C, 63.86; H, 6.52); ν_{max}($CHCl_3$)/cm^{-1} 1727, 1601, 1248 and 1032; δ_H(200 MHz) 1.22 (t, *J* 7.1, 3 H,

$CO_2CH_2CH_3$), 2.75 (dd, *J* 16.9, 8.2, 1 H, $CHCO_2Et$), 3.07 (dd, *J* 16.9, 4.4, 1 H, $CHCO_2Et$), 3.21 (s, 3 H, NMe), 3.78 (s, 3 H, OMe), 4.15 (q, *J* 7.1, 2 H, $CO_2CH_2CH_3$), 6.73 (d, *J* 8.4, 1 H, 6-H) and 6.79–6.91 (m, 2 H, 4-H, 7-H); *m/z* 263 (43, M^+), 218 (8), 190 (50), 189 (100), 174 (34), 147 (5), 146 (5), 118 (6) and 117 (4).

General Procedure for the Preparation of Furoindoles **10** *and* **18**.—To a cold (0 °C) solution of oxindole **5** or **16** (0.433 mmol) in THF (4 cm^3) was added LAH (66 mg, 1.7 mmol) in small portions. The mixture was stirred an additional 1 h at 0 °C and then treated with brine (1 cm^3) cautiously until the evolution of H_2 had ceased. Filtration and concentration under reduced pressure produced oils which were taken up in Et_2O (10 cm^3), and washed (brine, 5 cm^3), dried (Na_2SO_4) and concentrated. Purification through a short plug of silica eluting with 10% Et_2O–hexanes yielded furoindoles **10** and **18** respectively as colourless oils.

3a,8-*Dimethyl*-3,3a,8,8a-*tetrahydro*-2H-*furo*[2,3-b]*indole* **10**. 80%. (Found: M^+, 189.1161. $C_{12}H_{15}NO$ requires *M*, 189.1154); δ_H(250 MHz) 1.46 (s, 3 H, CH_3), 1.98–2.17 (m, 2 H, 2 × 3-H), 2.92 (s, 3 H, NMe), 3.40–3.50 (m, 1 H, 2α-H), 3.91–3.98 (m, 1 H, 2β-H), 5.06 (s, 1 H, 8a-H), 6.36 (d, *J* 7.8, 1 H, 7-H), 6.67 (dt, *J* 7.4, 0.8, 5-H) and 7.02–7.13 (m, 2 H, 4-H, 6-H); δ_C(63 MHz) 24.82 (CH_3), 30.94 (NCH_3), 41.84 (C-3), 52.38 (C-3a), 67.35 (C-2), 104.96 (C-7 or C-8a), 105.16 (C-8a or C-7), 117.38 (C-6), 122.48 (C-5), 128.16 (C-4), 134.58 (C-3b) and 150.52 (C-7a); *m/z* 189 (100, M^+), 158 (39), 144 (30), 143 (11), 130 (6), 115 (5) and 77 (4).

3a,8-*Dimethyl*-5-*methoxy*-3,3a,8,8a-*tetrahydro*-2H-*furo*-[2,3-b]*indole* **18**. 90%. (Found: M^+, 219.1260. $C_{13}H_{17}NO_2$ requires *M*, 219.1260); δ_H(250 MHz) 1.44 (s, 3 H, CH_3), 1.96–2.16 (m, 2 H, 2 × 3-H), 2.87 (s, 3 H, NMe), 3.41–3.51 (m, 1 H, 2α-H), 3.74 (s, 3 H, OMe), 3.90–3.97 (m, 1 H, 2β-H), 5.02 (s, 1 H, 8a-H), 6.27 (d, *J* 8.1, 1 H, 6-H) and 6.63–6.69 (m, 2 H, 4-H, 7-H); δ_C(63 MHz) 24.59 (CH_3), 31.72 (NMe), 41.57 (C-3), 52.58 (C-3a), 56.19 (OMe), 67.44 (C-2), 105.35 (C-6 or C-8a), 105.74 (C-6 or C-8a), 110.54 (C-4 or C-7), 112.31 (C-4 or C-7), 136.10 (C-3b), 145.04 (C-7a) and 152.81 (C-5); *m/z* 219 (100, M^+), 204 (64), 188 (62), 174 (30), 160 (18), 132 (15) and 69 (14).

General Procedure for Preparation of Acids **11** *and* **19**.—A solution of either ethyl ester **5** or **16** (2.0 mmol) and NaOH (2 mol dm^{-3}; 3 cm^3) in MeOH (12 cm^3) was stirred 24 h at 25 °C and then concentrated under reduced pressure. To the residue was added water (15 cm^3) and the aqueous solution extracted once with hexanes (10 cm^3). To the aqueous phase was added CH_2Cl_2 (10 cm^3) and the two phase system acidified at 0 °C with 5% HCl to pH 2. The organic phase was separated and the aqueous residue extracted with CH_2Cl_2 (2 × 10 cm^3). Washing of the combined extracts (brine, 15 cm^3), drying over Na_2SO_4, and concentration under reduced pressure afforded the corresponding acids **11** and **19** as colourless solids. Recrystallization afforded analytical samples.

3-*Carboxymethyl*-1,3-*dimethylindol*-2(3H)-*one* **11**. 98%; m.p. 179–180.5 °C (EtOAc–hexanes) (Found: M^+, 219.0891. $C_{12}H_{13}NO_3$ requires *M*, 219.0896); ν_{max}($CHCl_3$)/cm^{-1} 3400–2400, 1708 and 1611; δ_H(250 MHz) 1.40 (s, 3 H, CH_3), 2.78, 2.98 (ABq, J_{AB} 16.4, 2 H, CH_2CO_2H), 3.23 (s, 3 H, NMe), 6.86 (d, *J* 7.8, 1 H, 7-H), 7.07 (dt, *J* 7.3, 0.7, 1 H, 5-H), 7.19 (d, *J* 6.8, 1 H, 4-H) and 7.28 (dt, *J* 7.1, 1.2, 1 H, 6-H); *m/z* 219 (54, M^+), 174 (19), 160 (100), 130 (16), 117 (9), 95 (8) and 77 (8).

3-*Carboxymethyl*-5-*methoxy*-1,3-*dimethylindol*-2(3H)-*one* **19**. 99%; m.p. 129–130 °C (EtOAc–hexanes) (Found: C, 62.55; H, 5.95. $C_{13}H_{15}NO_4$ requires C, 62.64; H, 6.08); δ_H(200 MHz) 1.39 (s, 3 H, CH_3), 2.78, 2.96 (ABq, J_{AB} 16.5, 2 H, CH_2CO_2H), 3.20 (s, 3 H, NMe), 3.78 (s, 3 H, OMe) and 6.72–6.82 (m, 3 H, 4-H, 6-H, 7-H); *m/z* 249 (64, M^+), 234 (20), 190 (66), 165 (44), 55 (53) and 40 (7).

Table 1 Atomic coordinates (× 10^4)

	x	*y*	*z*
Molecule 1			
C(1)	8 056(5)	1 145(3)	1 503(2)
C(2)	9 475(5)	1 285(4)	1 006(3)
C(3)	9 542(6)	1 651(4)	125(3)
C(4)	8 182(5)	1 837(4)	−247(3)
C(5)	6 772(6)	1 641(4)	273(3)
C(6)	6 661(5)	1 322(4)	1 093(3)
N(7)	7 930(4)	840(3)	2 417(2)
C(8)	7 395(7)	1 953(4)	2 832(3)
C(9)	8 270(4)	−379(3)	2 898(2)
O(10)	8 114(3)	−582(3)	3 680(2)
C(11)	8 838(5)	−1 470(3)	2 463(2)
C(12)	9 416(5)	−2 707(4)	2 882(2)
C(13)	9 929(5)	−3 807(4)	2 458(2)
O(14)	9 919(4)	−3 706(3)	1 715(2)
O(15)	10 340(4)	−4 951(3)	3 027(2)
C(16)	10 917(7)	−6 142(5)	2 696(3)
C(17)	12 270(7)	−6 534(6)	2 424(4)
I(18)	11 569.1(3)	882.1(3)	1 575.3(2)
Molecule 2			
C(1)	5 287(5)	2 213(3)	5 380(2)
C(2)	6 429(5)	2 804(4)	4 965(2)
C(3)	6 025(5)	3 902(4)	4 312(2)
C(4)	4 446(5)	4 411(4)	4 084(2)
C(5)	3 257(5)	3 823(4)	4 535(3)
C(6)	3 643(5)	2 781(4)	5 139(2)
N(7)	5 700(4)	1 041(3)	6 042(2)
C(8)	6 405(6)	−213(4)	5 784(3)
C(9)	5 369(4)	1 048(3)	6 871(2)
O(10)	5 634(3)	9(3)	7 412(2)
C(11)	4 696(5)	2 333(4)	7 114(2)
C(12)	4 428(5)	2 412(4)	7 914(2)
C(13)	3 708(6)	3 702(4)	8 158(3)
O(14)	3 281(5)	4 750(3)	7 665(2)
O(15)	3 530(5)	3 562(3)	8 986(2)
C(16)	2 763(11)	4 789(6)	9 307(4)
C(17)	2 523(16)	4 472(8)	10 175(5)
I(18)	8 810.7(3)	2 008.5(3)	5 349.3(2)

General Procedures for the Preparation of Lactones **12** *and* **20**.—To a cold (0 °C) suspension of NaH (21 mg of a 60% wt dispersion washed free of oil with 2 × 2 cm^3 of hexanes, 0.52 mmol) in THF (5 cm^3) was added a solution of acid **11** or **19** (0.44 mmol) in THF (2 cm^3). The resulting solution was warmed briefly to 25 °C and then recooled to 0 °C and treated with $LiBHEt_3$ (1.0 mol dm^{-3} solution in hexanes; 0.48 cm^3, 0.48 mmol). After warming to 25 °C for 15 h, brine (2 cm^3) was added at 0 °C and the organic solvents were removed under reduced pressure. The aqueous residue was adjusted to pH 6 at 0 °C with 5% HCl, saturated with NaCl, and extracted with EtOAc (4 × 5 cm^3). The combined extracts were washed with brine (10 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure to yield crude oils which were purified through a short plug of silica gel (20% EtOAc–hexanes eluent). Recrystallization afforded analytical samples.

3a,8-*Dimethyl*-3,3a,8,8a-*tetrahydrofuro*[2,3-b]*indol*-2-*one* **12**. 72%; m.p. 106.5–107.5 °C (Et_2O–hexanes) (lit.,[8] m.p. 107 °C); ν_{max}($CHCl_3$)/cm^{-1} 1763, 1609; δ_H(250 MHz) 1.45 (s, 3 H, CH_3), 2.80, 2.96 (ABq, J_{AB} 17.7, 2 H, 2 × 3-H), 3.01 (s, 3 H, NMe), 5.53 (s, 1 H, 8a-H), 6.51 (d, *J* 7.8, 1 H, 7-H), 6.80 (dt, *J* 7.4, 0.7, 1 H, 5-H), 7.07 (dd, *J* 7.2, 0.8, 1 H, 4-H) and 7.18 (dt, *J* 7.7, 1.1, 1 H, 6-H); δ_C(50 MHz) 23.75 (CH_3), 31.36 (NMe), 42.24 (C-3), 48.65 (C-3a), 105.66 (C-8a or C-7), 107.35 (C-8a or C-7), 119.53 (C-6), 122.78 (C-5), 129.18 (C-4), 133.70 (C-3b), 148.01 (C-7a) and 175.03 (C-2); *m/z* 203 (49, M^+), 159 (14), 158 (100), 144 (46), 91 (4), 68 (7) and 55 (36).

5-*Methoxy*-3a,8-*dimethyl*-3,3a,8,8a-*tetrahydrofuro*[2,3-b]-*indol*-2-*one* **20**. 87%; m.p. 98.5–100 °C (Et_2O) (lit.,[9] m.p. 95–

97 °C); $\nu_{max}(CHCl_3)/cm^{-1}$ 1766, 1600, 1285 and 1035; δ_H(200 MHz) 1.45 (s, 3 H, CH_3), 2.78, 2.94 (ABq, J_{AB} 17.6, 2 H, 2 × 3-H), 2.97 (s, 3 H, NMe), 3.75 (s, 3 H, OMe), 5.53 (s, 1 H, 8a-H), 6.42 (d, J 7.9, 1 H, 7-H) and 6.70–6.76 (d, partially overlapping dd, J 7.9, 2.5, 2 H, 4-H, 6-H); δ_C(63 MHz) 23.53 (CH_3), 31.81 (NCH_3), 42.27 (C-3), 48.91 (C-3a), 56.16 (OMe), 106.35 (C-4), 107.78 (C-6), 110.53 (C-7), 113.53 (C-8a), 135.13 (C-3b), 142.17 (C-7a), 154.15 (C-5) and 174.76 (C-2); m/z 233 (56, M^+), 189 (17), 188 (100), 174 (36) and 55 (24).

Crystal Data for **4**.—$C_{13}H_{14}INO_3$, M = 359.2. Triclinic, a = 8.848(1), b = 11.364(2), c = 16.610(2) Å, α = 73.56(1), β = 77.08(1), γ = 67.04(1)°, V = 1462.8(3) Å^3 (by least-squares refinement of 25 automatically centred reflections, 22 < 2θ < 32 , λ = 0.710 73 Å). Space group $P\bar{1}$, Z = 4, D_c = 1.631 g cm^{-3} Colourless polyhedron. Crystal dimensions 0.37{001} × 0.36{110} × 0.33{011} × 0.37{101} × 0.42{111} nm, μ(Mo-Kα) = 21.63 cm^{-1}, F(000) = 704.

Data collection and processing. Siemens R3m/V diffractometers, ω scan mode with a scan width of 1.2°, ω scan speed 2.93–29.30 deg min^{-1}, graphite monochromated Mo-Kα radiation; 5185 reflections measured (4 < 2θ ≤ 50°, +h, ±k, ±l), 5185 unique, face-indexed numerical absorption correction min/max (transmission factors 0.496–0.554), giving 4321 with $F \geq 6\sigma(F)$.

Structure solution and refinement. Patterson and Fourier solution for two independent molecules per asymmetric unit. Full-matrix least-squares refinement with all non-hydrogen atoms anisotropic and hydrogen atoms (all locatable by difference synthesis) constrained in calculated positions with refined isotropic thermal parameters. Weighting scheme $\omega^{-1} = \sigma^2(F) + aF^2$, a = 0.0014. Final R and R_w values are 0.0299 and 0.0379. Largest difference peak (hole) 0.64 (−0.39) e Å^{-3}. Siemens SHELXTL PLUS Software.

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