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# Effective synthetic routes to activated pyrrolo[3,2,1-*hi*]indoles

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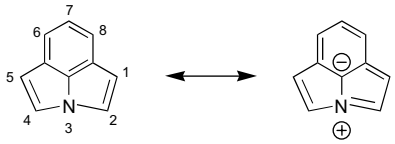
ABSTRACT

Pyrrolo[3,2,1-*hi*]indoles have been formed by the aldol cyclisation of 7-formyl-*N*-indolylacetates. The synthetic sequence incorporates three steps from suitably activated indoles: these are alkylation at nitrogen with a bromoacetic ester, formylation at C7 and an aldol condensation between these two substituents. An X-ray crystal structure of pyrrolo[3,2,1-*hi*]indole **24** is described.



## 1. Introduction

Pyrrolo[3,2,1-*hi*]indoles **1a**,**b** are indoles bearing an etheno link between the indole N1 and C7 positions. The numbering system for the pyrroloindoles is different from that of simple indoles, as shown in structure **1a**. Pyrrolo[3,2,1-*hi*]indoles can be considered to be benzo-analogues of pyrrolizidines, heterocycles found in the structures of numerous biologically active alkaloids.[1,2] The fundamental structure is also of interest in connection with the effects of aromaticity on its reactions. In addition to its aromaticity by virtue of being an 'oscillating' indole, the effect of a zwitterionic resonance structure **1b** could be to confer a 10π peripheral conjugated system on the molecule.




**1a** **1b**

Although some examples are known, these heterocyclic compounds have been rather neglected. Anet et al.[3] prepared 1,2,4,5-tetramethylpyrrolo[3,2,1-*hi*]indole by oxidation of a dihydropyrroloindole formed by a Fischer synthesis[4–6] starting with an *N*-aminoindoline. NMR spectroscopic data clearly showed that the molecule contained an axis of symmetry along N3 to C7 (see structure **1a**). Using a similar route from *N*-aminoindoline, Paudler and Shin[7] constructed the parent compound **1**. Cyclisation of *N*,*N*-disubstituted anilines, derived from aniline and phenacyl bromide or bromoacetone, with polyphosphoric acid also gave pyrroloindoles.[8,9]

It was of particular interest to investigate synthetic routes to 6,8-dimethoxypyrrolo[3,2,1-*hi*]indoles, making use of the specific reactivity of 4,6-dimethoxyindoles at C7. Although the Fischer synthetic methodology seemed attractive, it is known that arylhydrazones bearing electron-donating groups, especially *ortho*- or *para*- to the hydrazine unit, perform very poorly in the Fischer synthesis.[10,11] We therefore concentrated on cyclisation processes involving activated indoles.

## 2. Results and discussion

### 2.1. Reactions of diphenacylanilines

In principle, cyclisation of *N*,*N*-disubstituted anilines should be an attractive option, and should be facilitated by the presence of additional electron-donating groups.

Reaction of 3,5-dimethoxyaniline with 2 equiv of phenacyl bromide or 4-bromophenacyl bromide gave the disubstituted anilines, which were cyclised directly with trifluoroacetic acid to give the respective *N*-phenacylindoles **2** and **3** (Scheme 1). Attempts to achieve the second cyclisation through reaction with stronger acids, such as polyphosphoric acid, failed to form pyrroloindoles. By contrast, the spectroscopic evidence indicated the formation of poor yields of indolo-isoquinolines, as a result of migration of the C3-aryl

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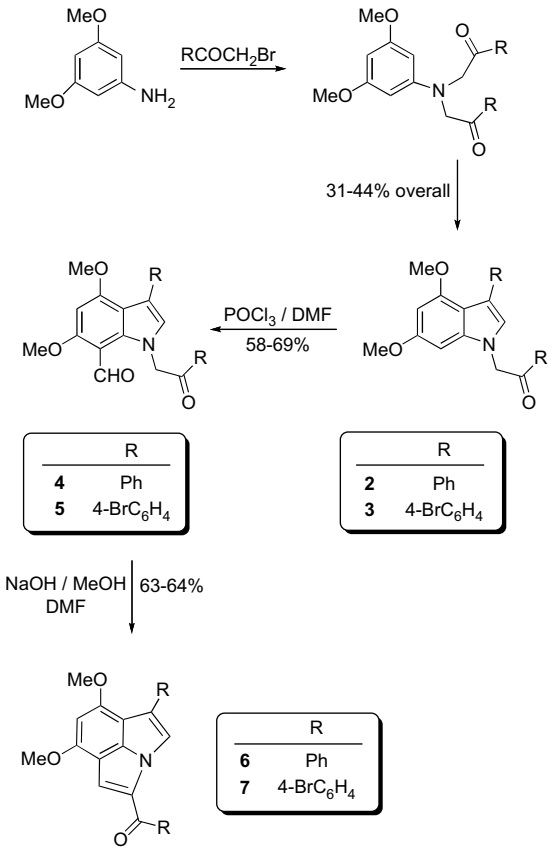
group to C2, followed by cyclisation to form a six-membered ring. Consequently this approach was not investigated further.




**Scheme 1.**

## 2.2. Cyclisation of 1,7-disubstituted indoles

The most accessible cyclisation route would involve the aldol condensation of an active methylene group on the indole nitrogen atom with a carbonyl substituent at the indole C7 position. Electrophilic substitution of 3-aryl-4,6-dimethoxyindoles occurs predominantly at C7, with Vilsmeier formylation readily affording the 7-carbaldehydes. Formylation at C7 should be preceded by the alkylation with an α-halocarbonyl compound at the indole nitrogen. Not only would the *N*-alkylated indole be more reactive towards the Vilsmeier reagent, but a 7-carbaldehyde would be less reactive towards alkylation: indeed it has been found that N-alkylation of 4,6-dimethoxy-2,3-diphenylindole-7-carbaldehyde could not be effected.[12]

### 2.2.1. Formylation of *N*-phenacylindoles

Formylation of *N*-phenacylindoles **2** and **3** with 1.5 equiv of the Vilsmeier reagent afforded 7-carbaldehydes **4** and **5** in 58 and 69% yield, respectively. Only moderate yields were obtained as the formyl compounds underwent further cyclisation to the ultimately desired pyrroloindoles **6** (10%) and **7** (18%) (Scheme 1). While formylation of 4,6-dimethoxyindoles has been reported to occur at 0 °C or room temperature,[12–14] heating at 80 °C was required for the formylation of indoles **2** and **3**. This lower reactivity is presumably caused by the steric effect of the relatively bulky phenacyl substituent at N1. The $^1$H NMR spectra of compounds **4** and **5** displayed singlets for H5 (6.25–6.28 ppm), singlets for H2 (6.79–6.84 ppm) and downfield singlets for CHO (10.24–10.30 ppm). The fact that pyrroloindoles **6** and **7** were already found in the formylation stage of the sequence indicated that the α-$CH_2$ protons of indoles **4** and **5** were sufficiently acidic to undergo deprotonation with aqueous sodium hydroxide, used for the hydrolysis of the iminium salt intermediate in the Vilsmeier reaction.

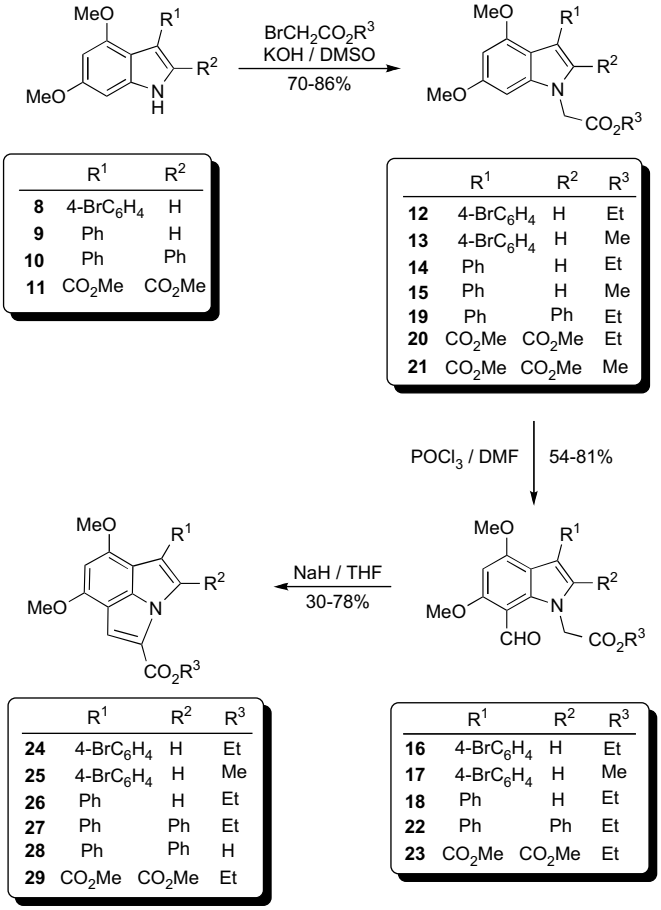
### 2.2.2. Aldol cyclisation of *N*-phenacylindole-7-carbaldehydes

As sodium hydroxide seemed to be a useful base for the intramolecular aldol condensation of formylindoles **4** and **5**, the actual condensation was carried out by treating the formylindoles in dimethylformamide with excess saturated sodium hydroxide in methanol to afford pyrroloindoles **6** and **7** in 63–64% yield. Although the reactions were fast and simple, and the majority of the pyrroloindoles crystallised out after stirring for 15 min, the *N*-unsubstituted indole-7-carbaldehydes were also produced as minor products. The use of alternative bases still gave rise to product mixtures. A one-pot technique, combining the formylation and aldol cyclisation reaction, also gave mixtures of the same types of products.

Compounds **6** and **7** were fully characterised by analytical and spectroscopic data. For example, the $^1$H NMR spectrum of compound **6** showed the presence of three singlets at 6.65, 7.66 and 8.22 ppm corresponding to H7, H5 and H2, respectively.

## 2.3. Preparation and formylation of *N*-indolylacetates

Given the product mixtures obtained from the phenacylindole carbaldehydes, it was decided to investigate the slightly less reactive ester systems derived from α-haloacetates. The *N*-indolylacetates **12**–**15** were obtained in 70–78% yield by the treatment of the respective 3-aryl-4,6-dimethoxyindoles **8**and **9** with potassium hydroxide in dimethylsulfoxide followed by ethyl or methyl 2-bromoacetate (Scheme 2). Formylation of indoles **12**–**14** using the




**Scheme 2.**

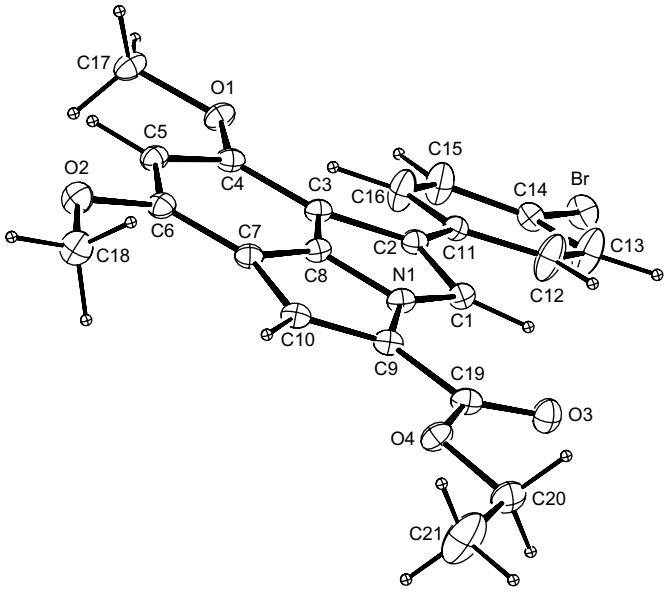



**Figure 1.** ORTEP diagram derived from the single-crystal X-ray analysis of compound **24**.

Vilsmeier reagent at 0 °C was regioselective and gave the related indole-7-carbaldehydes **16–18** in 54–81% yield, without formation of the 2-isomers. The $^1$H NMR spectroscopic data showed the replacement of the H5 and H7 doublets of the starting materials with an H5 singlet and a formyl proton. 2,3-Diphenyl-4,6-dimethoxyindole **10** and dimethyl 4,6-dimethoxyindole-2,3-dicarboxylate **11** were also converted to the related indolylacetates **19–21** in 80–86% yield, and compounds **19** and **20** were formylated to give the 7-aldehydes **22** and **23** in 78–79% yield (Scheme 2).

Treatment of the 7-formyl-*N*-indolylacetates **16**–**18**, **22** and **23** with sodium hydride in boiling tetrahydrofuran gave only moderate yields of the pyrroloindoles **24**–**27** and **29** (Scheme 2). The starting aldehydes were relatively insoluble and some ester hydrolysis also occurred. The use of weaker bases (triethylamine, or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)) was ineffective, while stronger bases (potassium hydride or *n*-butyllithium) resulted in removal of the carboxymethyl group and formation of the respective indole-7-aldehyde.

Compounds **24**–**26** and **29** were fully characterised and the $^1$H NMR spectroscopic data for compounds **24**–**26** showed the presence of three singlets at 6.4–6.5, 7.3–7.6 and 7.4–7.9 ppm corresponding to H7, H5 and H2, respectively. The infrared carbonyl stretching frequency of the aldehyde at 1750 cm$^{-1}$ in the starting material was no longer observed.

An X-ray crystal structure of compound **24** (Fig. 1) showed that the pyrroloindole ring is essentially planar and that the bond lengths and bond angles of the two pyrrolic rings are similar. The C6 methoxy group is unusually angled away from C7, while the C8 methoxy group is angled towards C7. Crystallographic data for 4,6-dimethoxyindoles invariably show both methoxy groups angled towards C5. Compound **27** could not be obtained analytically pure, but was hydrolysed to the related carboxylic acid **28**, which was fully characterised.

## 3. Conclusions

A series of pyrrolo[3,2,1-*hi*]indoles has been formed by the aldol cyclisation of 7-formyl-*N*-indolylacetates, which have in turn been obtained by the N-alkylation of indole-7-carbaldehydes. This sequence is more general and effective than a related one involving the cyclisation of *N*-phenacyl-indole-7-carbaldehydes.

## 4. Experimental

### 4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed by Dr H. P. Pham at UNSW. $^1$H and $^{13}$C NMR spectra were obtained on a Bruker AC300F (300 MHz) or a Bruker AM500 (500 MHz) spectrometer. Mass spectra were recorded on either a VG Quattro MS (EI) or a Finnegan MAT (MALDI). Infrared spectra were recorded with a Perkin Elmer 298 IR spectrometer. Ultraviolet-visible spectra were recorded using a Hitachi U-3200 spectrometer. Column chromatography was carried out using Merck 230–400 mesh ASTM silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 60GF$_{254}$.

### 4.2. 4,6-Dimethoxy-1-phenacyl-3-phenylindole (2)

A mixture of 3,5-dimethoxyaniline (3.0 g, 19.6 mmol), α-bromoacetophenone (7.80 g, 39.2 mmol) and sodium carbonate (8.30 g, 78.4 mmol) in 95% ethanol (50 mL) was heated at reflux for 4 h. The mixture was allowed to cool, the resulting precipitate was filtered, washed with water and recrystallised from chloroform/light petroleum to give the diphenacylaniline as a brown solid (2.74 g, 36%), mp 130–133 °C. $^1$H NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.67 (6H, s, OMe), 4.9 (4H, s, $CH_2$), 5.72 (2H, d, *J* 2.5 Hz, H2,6), 5.92 (1H, t, *J* 2.5 Hz, H4), 7.51, 7.61 and 8.01 (10H, m, ArH). $^{13}$C NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 55.0 (OMe), 58.0 ($CH_2$), 89.6 (C4), 92.4 (C2,6), 127.8, 128.8 and 133.6 (ArCH), 135.1, 150.4 and 161.6 (ArC), 196.4 (CO). Mass spectrum: *m*/*z* 389 (M, 8%), 284 (62), 166 (22), 105 (84), 91 (100), 84 (30), 77 (74).

The diphenacylaniline (0.20 g, 0.51 mmol) was added into ice-cooled trifluoroacetic acid (4.0 mL), then the mixture was heated at 70 °C for 1 h. The mixture was allowed to cool, diluted with ice-water (15 mL) and the resulting precipitate was filtered, washed with water and dried. Thin layer chromatography and elution with chloroform afforded the phenacylindole **2** as a brown solid (0.17 g, 87%), mp 96–98 °C. (Found: C, 77.5; H, 6.0; N, 3.6. $C_{24}H_{21}NO_3$ requires C, 77.6; H, 5.7; N, 3.8%.) $\lambda_{max}$ 210 nm ($\varepsilon$ 63,900 cm$^{-1}$ M$^{-1}$), 241 (70,600), 282 (39,000). $\nu_{max}$ 1700, 1620, 1600, 1220, 1200, 1140 cm$^{-1}$. $^1$H NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.80 and 3.81 (6H, 2s, OMe), 5.39 (2H, s, $CH_2$), 6.25 (1H, d, *J* 2.3 Hz, H5), 6.28 (1H, d, *J* 2.3 Hz, H7), 6.89 (1H, s, H2), 7.36 and 7.51 (6H, 2 t, *J* 7.3 Hz, *meta*, *para*-ArH), 7.63 and 8.00 (4H, 2d, *J* 7.3 Hz, *ortho*-ArH). $^{13}$C NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 52.5 ($CH_2$), 55.1 and 55.7 (OMe), 85.3 (C5), 92.3 (C7), 111.0, 118.8, 134.8, 135.9, 139.2, 155.2 and 157.8 (ArC), 125.1, 125.6, 127.5, 128.1, 129.0 and 129.6 (ArCH), 134.0 (C2), 192.9 (CO). Mass spectrum: *m*/*z* 372(M+1, 13%), 371 (M, 53), 266 (100), 250 (21), 105 (27), 77 (28), 69 (30).

### 4.3. 1-(4′-Bromophenacyl)-3-(4′-bromophenyl)-4,6-dimethoxyindole (3)

A mixture of 3,5-dimethoxyaniline (5.0 g, 32.6 mmol), α-bromo-4′-bromoacetophenone (18.2 g, 65.3 mmol) and sodium carbonate (13.8 g, 130.4 mmol) in 95% ethanol (80 mL) was heated at reflux for 4 h. The mixture was allowed to cool, and the resulting precipitate was filtered, washed with water and recrystallised from chloroform/light petroleum to give a yellow solid. This diphenacylaniline was reacted with cooled trifluoroacetic acid (15 mL) according to the method of preparation of compound **2**. The resulting solid was flash chromatographed with light petroleum/dichloromethane (1:2) as eluent afforded the bromophenacylindole **3** as a pale-yellow solid (7.60 g, 44%), mp 185–188 °C. (Found: C, 54.8; H, 3.8; N, 2.5. $C_{24}H_{19}Br_2NO_3$ requires C, 54.5; H, 3.6; N, 2.7%.) $\lambda_{max}$ 206 nm ($\varepsilon$ 38,700 cm$^{-1}$ M$^{-1}$), 215 (33,200), 247 (29,400), 276 (20,100), 296

(13,900). $\nu_{max}$ 1710, 1630, 1600, 1560, 1230, 1210, 1150, 1000 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.79 (6H, s, OMe), 5.35 (2H, s, $CH_2$), 6.19 (1H, d, *J* 1.8 Hz, H5), 6.27 (1H, d, *J* 1.8 Hz, H7), 6.85 (1H, s, H2), 7.46 (4H, s, ArH), 7.65 and 7.84 (4H, 2d, *J* 8.2 Hz, ArH). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 52.3 ($CH_2$), 55.1 and 55.6 (OMe), 85.3 (C5), 92.4 (C7), 117.7, 119.7, 125.0, 133.3, 134.7, 139.2, 155.0, 158.0 and 192.0 (ArC), 125.0 (C2), 129.5, 130.6, 131.1 and 132.3 (ArCH), 209.6 (CO). Mass spectrum: *m*/*z* 531(M, $^{81}Br$, 19%), 530 (M+1, $^{79,81}Br$, 18), 529 (M, $^{79,81}Br$, 58), 528 (M+1, $^{79}Br$, 11), 527 (M, $^{79}Br$, 23), 346 (87), 345 (42), 344 (100), 207 (32), 185 (37), 185 (39), 156 (62), 155 (65), 76 (68), 75 (58), 69 (53), 43 (47).

### 4.4. 4,6-Dimethoxy-1-phenacyl-3-phenylindole-7-carbaldehyde (4)

A cooled solution of phosphoryl chloride (0.19 mL, 2.03 mmol) in dry dimethylformamide (1.0 mL) was added dropwise to a cooled solution of the phenacylindole **2** (0.5 g, 1.35 mmol) in dry dimethylformamide (4 mL). The mixture was stirred at 0 °C for 15 min, then warmed at 80 °C for another 30 min. Cold water (10 mL) was added, followed by excess 2 M sodium hydroxide solution until the mixture was strongly basic. The suspension was stirred at room temperature overnight, the resulting precipitate was filtered, washed with water and dried. The resulting solid was flash chromatographed with dichloromethane elution and yielded the formylindole **4** as a white solid (0.37 g, 69%), mp 208–211 °C. (Found: C, 75.4; H, 5.3; N, 3.5. $C_{25}H_{21}NO_4$ requires C, 75.2; H, 5.3; N, 3.5%.) $\lambda_{max}$ 214 nm ($\varepsilon$ 5000 $cm^{-1}\,M^{-1}$), 252 (6500), 268 (6800), 340 (5400), 353 (5500). $\nu_{max}$ 1700, 1650, 1590, 1550, 1270, 1220, 1060, 1030, 610 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.90 and 3.98 (6H, 2s, OMe), 6.18 (2H, s, $CH_2$), 6.28 (1H, s, H5), 6.84 (1H, s, H2), 7.31, 7.55 and 8.05 (10H, m, ArH), 10.30 (1H, s, CHO). $^{13}C$ NMR spectrum (75 MHz, DMSO-$d_6$): $\delta$ 55.3 and 56.8 (OMe), 58.0 ($CH_2$), 87.8, 125.5, 127.2, 127.6, 128.5, 129.1, 129.8 and 133.0 (ArCH), 106.0, 112.0, 117.7, 134.7, 135.1, 136.2, 160.5 and 164. 4 (ArC), 186.8 (CHO), 193.2 (CO). Mass spectrum: *m*/*z* 400 (M+1, 12%), 399 (M, 51), 295 (16), 294 (100), 279 (32), 264 (17), 236 (23), 208 (13), 105 (21), 77 (31).

### 4.5. 1-(4′-Bromophenacyl)-3-(4′-bromophenyl)-4,6-dimethoxyindole-7-carbaldehyde (5) and 4-(4′-bromobenzoyl)-1-(4′-bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-*hi*]indole (7)

Indole **3** (1.61 g, 3.05 mmol) was dissolved in dry dimethylformamide (15 mL), then reacted with a solution of phosphoryl chloride (0.42 mL, 4.58 mmol) in dry dimethylformamide (1 mL) according to the method of preparation of compound **4**. The resulting brown precipitate was filtered, washed with water and dried. Flash chromatography and elution with dichloromethane gave two products. The first product was the formylindole **5** as a pale-yellow solid (0.98 g, 58%), mp 210–212 °C. (Found: C, 54.2; H, 3.6; N, 2.2. $C_{25}H_{19}Br_2NO_4$ requires C, 53.9; H, 3.4; N, 2.5%.) $\lambda_{max}$ 213 nm ($\varepsilon$ 14,300 $cm^{-1}\,M^{-1}$), 260 (19,000), 336 (6200), 351 (6200). $\nu_{max}$ 1720, 1670, 1590, 1570, 1270, 1230, 1170 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.88 and 3.95 (6H, 2s, OMe), 6.07 (2H, s, $CH_2$), 6.25 (1H, s, H5), 6.79 (1H, s, H2), 7.42 and 7.77 (8H, m, ArH), 10.24 (1H, s, CHO). $^{13}C$ NMR spectrum (75 MHz, DMSO-$d_6$): $\delta$ 55.8 and 57.3 (OMe), 58.1 ($CH_2$), 88.7, 129.9, 130.3, 130.5, 131.3 and 131.9 (ArCH), 106.0, 111.8, 116.2, 119.2, 127.6, 133.8, 134.5, 136.2, 160.6 and 164.6 (ArC), 187.0 (CHO), 192.9 (CO). Mass spectrum: *m*/*z* 559 (M, $^{81}Br$, 16%), 558 (M+1, $^{79,81}Br$, 18), 557 (M, $^{79,81}Br$, 32), 556 (M+1, $^{79}Br$, 15), 555 (M, $^{79}Br$, 22), 375 (20), 374 (100), 373 (14), 372 (84), 359 (22), 357 (21), 314 (18), 220 (29), 207 (34), 185 (43), 182 (42), 157 (89), 155 (88), 76 (72), 75 (58), 50 (36).

The second product was the pyrroloindole **7** as a bright yellow solid (0.31 g, 20%), mp 250–253 °C. (Found: C, 55.8; H, 3.3; N, 2.4. $C_{25}H_{17}Br_2NO_3$ requires C, 55.7; H, 3.2; N, 2.6%.) $\lambda_{max}$ 210 nm ($\varepsilon$ 20,200 $cm^{-1}\,M^{-1}$), 221 (15,700), 267 (10,500), 281 (9200), 365 (10,100). $\nu_{max}$ 1630, 1590, 1520, 1350, 1230, 1180, 1160, 980 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, DMSO-$d_6$): $\delta$ 4.04 and 4.19 (6H, 2s, OMe), 6.65 (1H, s, H7), 7.61, 7.81 and 7.91 (8H, m, ArH), 7.66 (1H, s, H5), 8.22 (1H, s, H2). The compound was not sufficiently soluble to obtain a $^{13}C$ NMR spectrum. Mass spectrum: *m*/*z* 542 (M+1, $^{81}Br$, 13%), 541 (M, $^{81}Br$, 51), 540 (M+1, $^{79,81}Br$, 33), 539 (M, $^{79,81}Br$, 73), 537 (M, $^{79}Br$, 30), 188 (22), 185 (94), 183 (54), 182 (80), 158 (98), 155 (100), 76 (58), 75 (78), 69 (34), 55 (22), 43 (40).

When the formylindole **5** (0.11 g, 0.20 mmol) was dissolved in dimethylformamide (4 mL), then reacted with a saturated solution of sodium hydroxide in methanol according to the method of preparation of compound **6**, the pyrroloindole **7** was obtained as a bright yellow solid (69 mg, 64%), mp 251–253 °C.

### 4.6. 4-Benzoyl-6,8-dimethoxy-1-phenylpyrrolo[3,2,1-*hi*]-indole (6)

Excess saturated solution of sodium hydroxide in methanol was added dropwise to a solution of formylindole **4** (0.1 g, 0.25 mmol) in dimethylformamide (4 mL) until the mixture was strongly basic. The mixture was stirred at room temperature for 30 min, the resulting yellow precipitate was filtered, washed with water and dried. Thin layer chromatography and elution with dichloromethane gave the pyrroloindole **6** as a yellow solid (60 mg, 63%), mp 160–163 °C. (Found: C, 78.5; H, 5.3; N, 3.7. $C_{25}H_{19}NO_3$ requires C, 78.7; H, 5.0; N, 3.7%.) $\lambda_{max}$ 207 nm ($\varepsilon$ 43,600 $cm^{-1}\,M^{-1}$), 220 (25,000), 255 (18,700), 277 (10,800), 362 (22,200). $\nu_{max}$ 1720, 1650, 1620, 1590, 1340, 1230, 1200 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 4.03 and 4.17 (6H, 2s, OMe), 6.48 (1H, s, H7), 7.32, 7.43, 7.53, 7.60 and 7.97 (10H, m, ArH), 7.39 (1H, s, H5), 8.15 (1H, s, H2). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 56.2 and 57.5 (OMe), 94.9 (C7), 119.1 (C5), 120.3 (C2), 126.5, 127.8, 128.3, 128.4, 128.8 and 131.9 (ArCH), 102.4, 102.9, 127.0, 132.8, 134.7, 138.6, 141.5, 158.6 and 158.9 (ArC), 186.7 (CO). Mass spectrum: *m*/*z* 382 (M+1, 27%), 381 (M, 100), 105 (81), 77 (53).

### 4.7. Ethyl 3(4′-bromophenyl)-4,6-dimethoxyindol-1-ylacetate (12)

A mixture of powdered potassium hydroxide (0.12 g, 2.1 mmol) and dimethylsulfoxide (10 mL) was stirred at room temperature for 10 min, indole **8** (0.50 g, 2.0 mmol) was added, and the mixture was stirred for another 30 min. Ethyl α-bromoacetate (0.4 mL, 3.6 mmol) was added dropwise, and the mixture was stirred overnight. The resulting brown-yellow mixture was diluted with water (70 mL), extracted with dichloromethane (3×60 mL) and the combined organic layers were washed with water, dried over magnesium sulfate and evaporated to give a brown oil. Flash chromatography and elution with dichloromethane afforded the ethyl indolylacetate **12** as an off-white solid (0.63 g, 78%), mp 104–105 °C. (Found: C, 57.1; H, 4.6; N, 3.1. $C_{20}H_{20}BrNO_4$ requires C, 57.4; H, 4.8; N, 3.4%.) $\lambda_{max}$ 208 nm ($\varepsilon$ 29,800 $cm^{-1}\,M^{-1}$), 223 (31,000), 231 (25,400), 284 (13,500), 299 (12,100). $\nu_{max}$ 1740, 1620, 1280, 1220, 1200, 1160, 790 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.28 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.80 and 3.86 (6H, 2s, OMe), 4.24 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 4.76 (2H, s, $CH_2$), 6.28 (1H, d, *J* 2.0 Hz, H5), 6.31 (1H, d, *J* 2.0 Hz, H7), 6.91 (1H, s, H2), 7.47 (4H, s, ArH). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 14.2 ($CH_2CH_3$), 48.1 ($CH_2$), 55.2 and 55.7 (OMe), 61.8 ($CH_2CH_3$), 85.2 (C5), 92.5 (C7), 124.9 (C2), 110.7, 117.7, 119.7, 134.8, 139.0, 155.0 and 158.0 (ArC), 130.6 and 131.1 (ArCH), 168.3 (CO). Mass spectrum: *m*/*z* 419 (M, $^{81}Br$, 13%), 417 (M, $^{79}Br$, 15), 185 (93), 183 (100), 157 (29), 155 (31), 76 (37), 75 (32), 69 (39), 57 (41), 55 (36).

### 4.8. Methyl 3(4′-bromophenyl)-4,6-dimethoxyindol-1-ylacetate (13)

This was prepared by reacting a suspension of potassium hydroxide (0.35 g, 6.33 mmol) in dimethylsulfoxide (25 mL) with indole **8**[15,16] (1.50 g, 4.52 mmol) and methyl α-bromoacetate (1.1 mL, 11.30 mmol) according to the method of preparation of compound **12**. The resulting brown solid was flash chromatographed, and elution with light petroleum in dichloromethane (3:7) gave the methyl indolylacetate **13** as an orange solid (1.28 g, 70%), mp 123–125 °C. (Found: C, 56.5; H, 4.5; N, 3.4. $C_{19}H_{18}BrNO_4$ requires C, 56.5; H, 4.5; N, 3.5%.) $\lambda_{max}$ 210 nm ($\varepsilon$ 19,300 $cm^{-1}$ $M^{-1}$), 230 (19,500), 280 (10,600), 298 (9300). $\nu_{max}$ 1740, 1620, 1590, 1330, 1280, 1210, 1170, 1140, 1010 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.77, 3.80 and 3.87 (9H, 3s, OMe), 4.77 (2H, s, $CH_2$), 6.30 (1H, br s, H5), 6.32 (1H, br s, H7), 6.89 (1H, s, H2), 7.47 (4H, s, ArH). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 47.9 ($CH_2$), 52.6, 55.1 and 55.7 (OMe), 85.1 (C5), 92.4 (C7), 124.8 (C2), 110.6, 117.7, 119.7, 134.7, 139.0, 155.0 and 158.0 (ArC), 130.6 and 131.1 (ArCH), 168.8 (CO). Mass spectrum: *m*/*z* 406 (M+1, $^{81}Br$, 20%), 405 (M, $^{81}Br$, 97), 404 (M+1, $^{79}Br$, 20), 403 (M, $^{79}Br$, 100), 346 (33), 344 (31), 309 (45), 207 (30), 174 (30), 152 (28), 69 (40), 59 (29), 43 (35).

### 4.9. Methyl 4,6-dimethoxy-3-phenylindol-1-ylacetate (15)

A suspension of powdered potassium hydroxide (0.16 g, 2.8 mmol) in dimethylsulfoxide (10 mL) was reacted with indole **9**[16,17] (0.50 g, 2.0 mmol) followed by methyl α-bromoacetate (0.4 mL, 4.3 mmol) according to the method of preparation of compound **12**. The resulting brown oil was flash chromatographed, and elution with dichloromethane gave the methyl indolylacetate **15** as a white solid (0.47 g, 72%), mp 103–105 °C. (Found: C, 70.5; H, 6.2; N, 4.4. $C_{19}H_{19}NO_4$ requires C, 70.1; H, 5.9; N, 4.3%.) $\lambda_{max}$ 208 nm ($\varepsilon$ 23,200 $cm^{-1}$ $M^{-1}$), 224 (27,640), 269 (10,800), 279 (11,280). $\nu_{max}$ 1750, 1580, 1270, 1210, 1200, 1160, 1040, 770, 700 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.64, 3.69, 3.76 (9H, 3s, OMe), 4.64 (2H, s, $CH_2$), 6.19 (1H, d, *J* 2.0 Hz, H5), 6.22 (1H, d, *J* 2.0 Hz, H7), 6.79 (1H, s, H2), 7.16 (1H, t, *J* 7.1 Hz, H4′), 7.26 (2H, t, *J* 7.1 Hz, H3′), 7.53 (2H, d, *J* 7.1 Hz, H2′). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 47.9 ($CH_2$), 52.6, 55.2 and 55.7 (OMe), 85.1 (C5), 92.3 (C7), 124.8 (C2), 110.9, 118.9, 135.7, 139.0, 155.2 and 157.9 (ArC), 125.7, 127.5 and 129.5 (ArCH), 168.9 (CO). Mass spectrum: *m*/*z* 326 (M+1, 20%), 325 (M, 100), 310 (20), 266 (48), 250 (29), 208 (21), 152 (25), 134 (36), 105 (56), 83 (20), 77 (34), 69 (46), 57 (47).

### 4.10. Ethyl 3-(4′-bromophenyl)-7-formyl-4,6-dimethoxyindol-1-ylacetate (16)

Indole **12** (0.60 g, 1.50 mmol) was dissolved in dry dimethylformamide (4 mL), the solution cooled in ice, then a cooled solution of phosphoryl chloride (0.2 mL, 2.25 mmol) in dry dimethylformamide (1.0 mL) was added dropwise. The mixture was stirred at 0 °C for 1 h, then at room temperature for another 30 min. Cold water (10 mL) was added, followed by excess 2 M sodium hydroxide solution until the mixture was strongly basic. The suspension was stirred at room temperature overnight, the resulting precipitate was filtered, washed with water and dried. Flash chromatography and elution with dichloromethane afforded the formylindole **16** as a white solid (0.54 g, 81%), mp 209–211 °C. (Found: C, 56.5; H, 4.5; N, 3.0. $C_{21}H_{20}BrNO_5$ requires C, 56.5; H, 4.5; N, 3.1%.) $\lambda_{max}$ 208 nm ($\varepsilon$ 10,700 $cm^{-1}$ $M^{-1}$), 234 (8700), 259 (11,200), 333 (4100). $\nu_{max}$ 1750, 1650, 1580, 1550, 1270, 1210, 810, 780 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.28 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.86 and 3.96 (6H, 2s, OMe), 4.22 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 5.33 (2H, s, $CH_2$), 6.24 (1H, s, H5), 6.79 (1H, s, H2), 7.35 and 7.46 (4H, 2d, *J* 8.5 Hz, ArH), 10.71 (1H, s, CHO). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 14.2 ($CH_2CH_3$), 53.2 ($CH_2$), 55.3 and 57.0 (OMe), 61.3 ($CH_2CH_3$), 87.9 (C5), 129.1 (C2), 106.9, 113.0, 118.0, 120.2, 134.2, 136.7, 160.8, 165.1 (ArC), 130.5 and 131.4 (ArCH), 169.5 (CO), 188.2 (CHO). Mass spectrum: *m*/*z* 448 (M+1, $^{81}Br$, 10%), 447 (M, $^{81}Br$, 62), 446 (M+1, $^{79}Br$, 10), 445 (M, $^{79}Br$, 67), 374 (45), 372 (49), 344 (27), 220 (28), 207 (33), 192 (33), 178 (32), 163 (36), 151 (39), 69 (69), 55 (100), 54 (100).

### 4.11. Methyl 3-(4′-bromophenyl)-7-formyl-4,6-dimethoxyindol-1-ylacetate (17)

Indole **13** (0.65 g, 1.61 mmol) in dry dimethylformamide (3.5 mL) was reacted with phosphoryl chloride (0.25 mL, 2.41 mmol) in dry dimethylformamide (1.0 mL) according to the method of preparation of compound **16**. The resulting solid was flash chromatographed, and elution with dichloromethane/chloroform (1:1) yielded the formylindole **17** as a brown solid (0.51 g, 73%), mp 243–245 °C. (Found: C, 55.3; H, 4.3; N, 3.1. $C_{20}H_{18}BrNO_5$ requires C, 55.6; H, 4.2; N, 3.2%.) $\lambda_{max}$ 212 nm ($\varepsilon$ 18,400 $cm^{-1}$ $M^{-1}$), 227 (17,200), 257 (10,300), 281 (5800). $\nu_{max}$ 1770, 1600, 1590, 1570, 1280, 1225 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, DMSO-$d_6$): $\delta$ 3.63, 3.90 and 3.98 (9H, 3s, OMe), 5.33 (2H, s, $CH_2$), 6.54 (1H, s, H5), 7.24 (1H, s, H2), 7.38 and 7.53 (4H, 2d, *J* 7.8 Hz, ArH), 10.23 (1H, s, CHO). $^{13}C$ NMR spectrum (75 MHz, DMSO-$d_6$): $\delta$ 52.0, 55.8 and 57.3 (OMe), 52.4 ($CH_2$), 88.9 (C5), 130.3 (C2), 130.5 and 131.3 (ArCH), 106.0, 111.8, 116.4, 119.3, 134.4, 135.9, 160.5 and 164.5 (ArC), 169.8 (CO), 187.1 (CHO). Mass spectrum: *m*/*z* 433 (M, $^{81}Br$, 14%), 432 (M+1, $^{79}Br$, 12), 431 (M, $^{79}Br$, 28), 361 (100), 359 (95), 265 (53), 194 (23), 178 (27), 150 (36), 139 (38), 83 (48), 69 (28), 59 (22).

### 4.12. Ethyl 4,6-dimethoxy-7-formyl-3-phenylindol-1-ylacetate (18)

Indole **9**[16,17] (0.66 g, 2.61 mmol) was reacted with a suspension of powdered potassium hydroxide (0.21 g, 3.65 mmol) in dimethylsulfoxide (12 mL) followed by ethyl α-bromoacetate (0.7 mL, 6.53 mmol) according to the method of preparation of compound **12**. The resulting brown oil (0.67 g), presumably compound **14**, was dissolved in dry dimethylformamide (4 mL), cooled in ice, then a cooled solution of phosphoryl chloride (0.3 mL, 2.94 mmol) in dry dimethylformamide (1.0 mL) was added dropwise. Work-up according to the method of preparation of compound **16** afforded the formylindole **18** as a brown solid (0.52 g, 54%), mp 135–137 °C. (Found: C, 68.5; H, 5.8; N, 3.6. $C_{21}H_{21}NO_5$ requires C, 68.7; H, 5.8; N, 3.8%.) $\lambda_{max}$ 216 nm ($\varepsilon$ 9900 $cm^{-1}$ $M^{-1}$), 233 (9900), 262 (11,000), 337 (7200). $\nu_{max}$ 1755, 1650, 1590, 1570, 1555, 1280, 1225, 1210 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.29 (3H, t, *J* 8.2 Hz, $CH_2CH_3$), 3.82 and 3.93 (6H, 2s, OMe), 4.22 (2H, q, *J* 8.2 Hz, $CH_2CH_3$), 5.33 (2H, s, $CH_2$), 6.21 (1H, s, H5), 6.80 (1H, s, H2), 7.31 (4H, m, H2′,3′), 7.51 (1H, d, *J* 9.1 Hz, H4′), 10.39 (1H, s, CHO). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 14.1 ($CH_2CH_3$), 53.1 ($CH_2$), 55.1 and 56.8 (OMe), 61.1 ($CH_2CH_3$), 87.7 (C5), 126.0 (C2), 106.6, 112.9, 119.1, 135.1, 136.5, 160.9 and 164.9 (ArC), 127.4, 129.1 and 129.7 (ArCH), 169.5 (CO), 188.1 (CHO). Mass spectrum: *m*/*z* 368 (M+1, 18%), 367 (M, 100), 310 (22), 294 (57), 236 (27), 69 (22).

### 4.13. Ethyl 4,6-dimethoxy-2,3-diphenylindol-1-ylacetate (19)

A suspension of powdered potassium hydroxide (0.24 g, 4.2 mmol) in dimethylsulfoxide (2 mL) was reacted with indole **10**[16] (1.0 g, 3.0 mmol) followed by ethyl α-bromoacetate (1.35 mL, 12.2 mmol). After 4 h, water (100 mL) was added to the stirred mixture and the resulting solid was collected to give ethyl indolylacetate **19** as a white solid (1.09 g, 86%), mp 190–192 °C (from ethanol). (Found: C, 75.3; H, 6.0; N, 3.4. $C_{26}H_{25}NO_4$ requires C, 75.2; H, 6.1; N, 3.4%.) $\nu_{max}$ 1752, 1622, 1609, 1595, 1579, 1507, 1467, 1457,

1342, 1271, 1203, 1154, 1052, 706 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.25 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.72 and 3.88 (6H, 2s, OMe), 4.22 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 4.65 (2H, s, $CH_2$), 6.29 (1H, d, *J* 1.6 Hz, H5), 6.34 (1H, d, *J* 2.0 Hz, H7), 7.20 (10H, m, ArH). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 14.2 ($CH_2CH_3$), 46.3 ($CH_2$), 55.3 and 55.7 (OMe), 61.5 ($CH_2CH_3$), 85.4 (C5), 92.7 (C7), 111.7, 116.1, 131.6, 135.8, 138.6, 155.2, 157.2, 157.8 (ArC), 125.4, 126.8, 127.8, 128.3, 131.3 and 131.5 (ArCH), 167.0 (CO). Mass spectrum: *m*/*z* 415 (M, 100%), 400 (18), 342 (14).

### 4.14. Dimethyl 4,6-dimethoxy-1-ethoxycarbonylmethylindol-2,3-dicarboxylate (20)

This was prepared from the indole diester **11**[17] (1.0 g, 3.4 mmol), 50% sodium hydride (0.2 g, 4.0 mmol) and ethyl α-bromoacetate (0.4 mL, 3.6 mmol) in dry tetrahydrofuran (80 mL). After 4 h, ice-water (10 mL) was added and the solvent was evaporated to give a residue, which was recrystallised from dichloromethane/light petroleum to give the ethyl indolylacetate **20** as a white solid (1.05 g, 81%), mp 160–162 °C. (Found: C, 56.7; H, 5.5; N, 3.8. $C_{18}H_{21}NO_8$ requires C, 57.0; H, 5.6; N, 3.7%.) $\nu_{max}$ 1763, 1744, 1717, 1631, 1541, 1279, 1243, 1210, 1169, 1157 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.25 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.84, 3.86 and 3.94 (12H, 3s, OMe), 4.22 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 5.17 (2H, s, $CH_2$), 6.21 (2H, br s, H5, H7). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 15.3 ($CH_2CH_3$), 47.1 ($CH_2$), 52.4 and 53.0 ($CO_2Me$), 56.0 and 56.2 (OMe), 61.8 ($CH_2CH_3$), 84.0 (C5), 93.5 (C7), 109.4, 116.1, 120.9, 138.8, 159.5, 159.6 (ArC), 153.4, 165.5, 166.6 (CO). Mass spectrum: *m*/*z* 379 (M, 100%), 306 (21).

### 4.15. Dimethyl 4,6-dimethoxy-1-methoxycarbonylmethylindol-2,3-dicarboxylate (21)

This was prepared as described for compound **20** from the indole diester **11**[17] (1.0 g, 3.4 mmol), 50% sodium hydride (0.2 g, 4.0 mmol) and methyl α-bromoacetate (0.4 mL, 4.2 mmol) in dry tetrahydrofuran (80 mL) to give the methyl indolylacetate **21** as a white solid (1.0 g, 80%), mp 156–158 °C. (Found: C, 55.8; H, 5.1; N, 3.9. $C_{17}H_{19}NO_8$ requires C, 55.9; H, 5.2; N, 3.9%.) $\nu_{max}$ 1751, 1735, 1713, 1627, 1546, 1514, 1269, 1238, 1209, 1171, 1154, 1016 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.74, 3.84, 3.86 and 3.94 (15H, 4s, OMe), 5.19 (2H, s, $CH_2$), 6.21 (1H, br s, H5), 6.22 (1H, br s, H7). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 47.0 ($CH_2$), 52.5, 52.9 and 53.0 ($CO_2Me$), 56.0 and 56.2 (OMe), 83.9 (C5), 93.6 (C7), 109.3, 116.1, 120.8, 138.8, 159.5, 159.6 (ArC), 153.4, 165.5, 167.2 (CO). Mass spectrum: *m*/*z* 365 (M, 100%), 332 (31), 331 (29), 306 (31), 276 (24), 274 (31).

### 4.16. Ethyl 4,6-dimethoxy-7-formyl-2,3-diphenylindol-1-ylacetate (22)

Indole **19** (0.35 g, 0.34 mmol) was dissolved in dry dimethylformamide (1.0 mL), cooled in ice, then a cooled solution of phosphoryl chloride (0.1 mL, 1.0 mmol) in dry dimethylformamide (1.0 mL) was added dropwise. Work-up according to the method of preparation of compound **15** afforded the formylindole **22** as white crystals (0.30 g, 80%), mp 218–219 °C (from dichloromethane/light petroleum). (Found: C, 72.9; H, 5.6; N, 3.2. $C_{27}H_{25}NO_5$ requires C, 73.1; H, 5.7; N, 3.3%.) $\lambda_{max}$ 258 nm ($\varepsilon$ 21,700 $cm^{-1}$ $M^{-1}$), 325 (9200), 360 (7200). $\nu_{max}$ 1758, 1649, 1587, 1576, 1560, 1271, 1220, 1210, 1170, 1120, 820, 725, 701 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.19 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.78 and 3.98 (6H, 2s, OMe), 4.11 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 5.19 (2H, s, $CH_2$), 6.26 (1H, s, H5), 7.21 (10H, m, ArH), 10.44 (1H, s, CHO). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 14.1 ($CH_2CH_3$), 50.3 ($CH_2$), 55.3 and 57.0 (OMe), 60.9 ($CH_2CH_3$), 88.2 (C5), 106.8, 113.5, 117.1, 135.4, 137.0, 139.3, 161.0, 165.0 and 170.1 (ArC), 125.6, 126.8, 128.1, 128.2, 131.3 and 131.5 (ArCH), 169.5 (CO), 188.1 (CHO). Mass spectrum: *m*/*z* 443 (M, 100%), 370 (32), 354 (14).

### 4.17. Ethyl 1-(4′-bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-*hi*]indole-4-carboxylate (24)

Sodium hydride (80% in paraffin oil, 0.16 g, 5.38 mmol) was added into an ice-cooled solution of formylindole **16** (1.50 g, 4.20 mmol) in dry tetrahydrofuran (100 mL). The mixture was heated at reflux for 2 h, then allowed to cool and excess sodium hydride was destroyed by cautious treatment with ice-water (120 mL). The resulting suspension was extracted with dichloromethane (3×90 mL), and the combined organic layers were washed with water, dried over magnesium sulfate and evaporated to give a brown solid. Flash chromatography and elution with light petroleum in dichloromethane (1:3) afforded the pyrroloindole **24** as a light yellow solid (0.55 g, 48%), mp 164–166 °C. (Found: C, 58.8; H, 4.1; N, 3.2. $C_{21}H_{18}BrNO_4$ requires C, 58.9; H, 4.2; N, 3.3%.) $\lambda_{max}$ 205 nm ($\varepsilon$ 5000 $cm^{-1}$ $M^{-1}$), 245 (2600), 263 (2000), 334 (2800). $\nu_{max}$ 1710, 1580, 1350, 1300, 1260, 1230, 1210 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.50 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 4.03 and 4.26 (6H, 2s, OMe), 4.49 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 6.52 (1H, s, H7), 7.57 and 7.81 (4H, 2d, *J* 6.7 Hz, ArH), 7.63 (1H, s, H5), 7.92 (1H, s, H2). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 14.5 ($CH_2CH_3$), 56.3 and 58.0 (OMe), 61.0 ($CH_2CH_3$), 74.3, 102.3, 120.5, 125.7, 133.8, 139.4, 153.1, 154.4 and 155.6 (ArC), 95.7 (C7), 115.9 (C5), 119.2 (C2), 129.8 and 131.5 (ArCH), 158.3 (CO). Mass spectrum: *m*/*z* 430 (M+1, $^{81}Br$, 19%), 429 (M, $^{81}Br$, 92), 428 (M+1, $^{79}Br$, 20), 427 (M, $^{79}Br$, 100), 401 (25), 399 (26), 305 (30), 69 (41).

### 4.18. Methyl 1-(4′-bromophenyl)-6,8-dimethoxypyrrolo[3,2,1-*hi*]indole-4-carboxylate (25)

This was prepared by reacting sodium hydride (80% in paraffin oil, 14 mg, 0.47 mmol) with a solution of the formylindole **17** (0.10 g, 0.23 mmol) in dry tetrahydrofuran (15 mL) according to the method of preparation of compound **24**. Thin layer chromatography and elution with dichloromethane afforded the pyrroloindole **25** as a yellow-greenish solid (30 mg, 30%), mp 132–134 °C. (Found: C, 58.1; H, 4.3; N, 3.2. $C_{20}H_{16}BrNO_4$ requires C, 58.0; H, 3.9; N, 3.4%.) $\lambda_{max}$ 211 nm ($\varepsilon$ 78,700 $cm^{-1}$ $M^{-1}$), 329 (21,800). $\nu_{max}$ 1720, 1600, 1350, 1270, 1240, 1220, 1180 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 3.98, 3.99 and 4.20 (9H, 3s, OMe), 6.47 (1H, s, H7), 7.53 (2H, d, *J* 8.7 Hz, H2′), 7.58 (1H, s, H5), 7.77 (2H, d, *J* 8.7 Hz, H3'), 7.87 (1H, s, H2). $^{13}C$ NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 51.9, 56.2 and 57.8 (OMe), 95.4 (C7), 115.9 (C5), 119.0 (C2), 129.3 and 131.3 (ArCH), 102.2, 102.4, 120.4, 125.2, 125.8, 133.7, 141.1 and 158.2 (ArC), 161.8 (CO). Mass spectrum: *m*/*z* 416 (M+1, $^{81}Br$, 20%), 415 (M, $^{81}Br$, 99), 414 (M+1, $^{79}Br$, 18), 413 (M, $^{79}Br$, 100), 319 (22), 201 (23), 188 (29), 183 (22), 149 (21), 59 (28).

### 4.19. Ethyl 6,8-dimethoxy-1-phenylpyrrolo[3,2,1-*hi*]indole-4-carboxylate (26)

This was prepared by reacting sodium hydride (80% in paraffin oil, 0.25 g, 8.33 mmol) with a solution of the formylindole **18** (1.50 g, 4.20 mmol) in dry tetrahydrofuran (100 mL) according to the method of preparation of compound **24**. Thin layer chromatography and elution with light petroleum in dichloromethane (1:9) gave the pyrroloindole **26** as a yellow solid (0.88 g, 60%), mp 148–151 °C. (Found: C, 71.9; H, 5.6; N, 3.9. $C_{21}H_{19}NO_4$ requires C, 72.2; H, 5.5; N, 4.0%.) $\lambda_{max}$ 212 nm ($\varepsilon$ 58,000 $cm^{-1}$ $M^{-1}$), 236 (45,500), 265 (24,000), 333 (52,500). $\nu_{max}$ 1700, 1595, 1230, 1200, 1180 $cm^{-1}$. $^1H$ NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.41 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.93 and 4.16 (6H, 2s, OMe), 4.41 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 6.41 (1H, s, H7), 7.25 (1H, t, *J* 7.7 Hz, H4′), 7.38 (2H, t, *J* 7.7 Hz, H3′), 7.52 (1H, s,

H5), 7.83 (1H, s, 2), 7.84 (2H, t, *J* 7.7 Hz, H2′). $^{13}$C NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 14.5 ($CH_2CH_3$), 56.3 and 57.9 (OMe), 61.0 ($CH_2CH_3$), 93.50, 103.62, 104.04, 122.44, 126.82, 127.40, 134.25 and 158.05 (ArC), 95.6 (C7), 115.9 (C5), 119.2 (C2), 126.7, 128.0 and 128.4 (ArCH). Mass spectrum: *m*/*z* 350 (M+1, 22%), 349 (M, 100), 321 (27), 190 (29), 163 (29), 69 (28).

### 4.20. Ethyl 4,6-dimethoxy-1,2-diphenylpyrrolo[3,2,1-*hi*]-indole-4-carboxylate (27)

Sodium hydride (80% in paraffin oil, 1.0 g, 33.3 mmol) was added into an ice-cooled solution of formylindole **22** (2.95 g, 6.66 mmol) in dry tetrahydrofuran (170 mL) containing dry dimethylformamide (6.8 mL). The mixture was heated at reflux for 4 h, and further treatment was according to the method of preparation of compound **24**. Flash chromatography and elution with light petroleum in dichloromethane (1:3) gave the pyrroloindole **27** as a yellow solid (2.20 g, 78%), mp 164–166 °C. $\lambda_{max}$ 244 nm ($\varepsilon$ 23,900 $cm^{-1}$ $M^{-1}$), 329 (26,000). $^1$H NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 0.95 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.88 and 4.23 (6H, 2s, OMe), 3.94 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 6.49 (1H, s, H7), 7.26 (10H, m, ArH), 7.68 (1H, s, H5). $^{13}$C NMR spectrum (75 MHz, $CDCl_3$): $\delta$ 13.8 ($CH_2CH_3$), 56.3 and 57.9 (OMe), 60.6 ($CH_2CH_3$), 95.5 (C7), 101.6, 103.9, 123.6, 127.6, 132.9, 133.4, 134.6, 140.7, 157.3 and 158.0 (ArC), 117.7 (C5), 126.2, 127.4, 127.5, 127.8, 130.8 and 131.3 (ArCH), 161.0 (CO). Mass spectrum: *m*/*z* 425 (M, 31%), 424 (100), 396 (19). This material could not be obtained analytically pure and was hydrolysed directly to the carboxylic acid (**29**).

### 4.21. 6,8-Dimethoxy-1,2-diphenylpyrrolo[3,2,1-*hi*]indole-4-carboxylic acid (28)

A mixture of pyrroloindole **27** (0.50 g, 1.18 mmol) in 0.5 M ethanolic potassium hydroxide (23.5 mL, 11.76 mmol) was heated at reflux for 1 h. The mixture was allowed to cool and the solvent removed under reduced pressure. The residue was diluted with water (30 mL) and acidified with 5% hydrochloric acid. The resulting precipitate was collected, washed with water and dried to afford the pyrroloindole carboxylic acid **28** as a yellow solid (0.43 g, 92%), mp 217–219 °C (from chloroform/light petroleum). (Found: C, 73.6; H, 5.1; N, 3.2. $C_{25}H_{19}NO_4.0.6H_2O$ requires C, 73.6; H, 5.0; N, 3.4%.) $\lambda_{max}$ 212 nm ($\varepsilon$ 13,900 $cm^{-1}$ $M^{-1}$), 247 (14,300), 327 (17,600). $\nu_{max}$ 3370, 1680, 1660, 1330, 1260, 1215, 1000, 720 $cm^{-1}$. $^1$H NMR spectrum (300 MHz, DMSO-$d_6$): $\delta$ 3.95 and 4.27 (6H, 2s, OMe), 6.68 (1H, s, H7), 7.23–7.39 (10H, m, ArH), 7.45 (1H, s, H5), 12.65 (1H, br s, COOH). $^{13}$C NMR spectrum (75 MHz, DMSO-$d_6$): $\delta$ 56.6 and 58.2 (OMe), 95.7 (C7), 117.3 (C5), 101.6, 103.3, 123.0, 128.3, 132.4, 133.4, 134.6, 140.0, 157.5 and 157.8 (ArC), 126.6, 127.6, 127.7, 128.0, 130.7 and 131.5 (ArCH), 161.4 (CO). Mass spectrum: *m*/*z* 398 (M+1, 24%), 397 (M, 100), 353 (33), 105 (24), 69 (25).

### 4.22. Dimethyl, ethyl 6,8-dimethoxypyrrolo[3,2,1-*hi*]indole-1,2,4-tricarboxylate (29)

Indole **20** (0.20 g, 0.54 mmol) was dissolved in dry dimethylformamide (1.0 mL), cooled in ice, then a cooled solution of phosphoryl chloride (0.1 mL, 1.0 mmol) in dry dimethylformamide (1.0 mL) was added dropwise. Work-up according to the method of preparation of compound **16** afforded the formylindole **23** as white crystals (0.18 g, 78%), mp 146–147 °C. $\nu_{max}$ 1755, 1714, 1663, 1583, 1547, 1285, 1267, 1232, 1220, 1208, 1195, 1143 $cm^{-1}$. $^1$H NMR spectrum (300 MHz, $CDCl_3$): $\delta$ 1.28 (3H, t, *J* 7.1 Hz, $CH_2CH_3$), 3.83, 3.92, 3.97 and 3.98 (12H, 4s, OMe), 4.23 (2H, q, *J* 7.1 Hz, $CH_2CH_3$), 5.66 (2H, s, $CH_2$), 6.24 (1H, s, H5), 10.35 (1H, s, CHO). Mass spectrum: *m*/*z* 407 (M, 91%), 346 (100).

A mixture of formylindole **23** (0.15 g, 0.37 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (0.28 mL, 1.85 mmol) in dry acetonitrile (10 mL) was heated at reflux for 16 h. The mixture was allowed to cool, then diluted with dichloromethane (80 mL), washed with 5% hydrochloric acid (2×20 mL) followed by water, dried over magnesium sulfate and evaporated to leave an off-white solid. Preparative thin layer chromatography and elution with ethyl acetate in dichloromethane (1:12) gave the pyrroloindole **29** as a white solid (0.050 g, 35%), mp 143–145 °C. (Found C, 58.6; H, 5.2; N, 3.4. $C_{19}H_{19}NO_8$ requires C, 58.6; H, 4.9; N, 3.6%.) $\lambda_{max}$ 208 nm ($\varepsilon$ 41,500 $cm^{-1}$ $M^{-1}$), 239 (31,700), 310 (24,100), 349 (33,100). $\nu_{max}$ 1750, 1715, 1660, 1590, 1345, 1220 $cm^{-1}$. $^1$H NMR spectrum ($CDCl_3$): $\delta$ 1.38 (3H, t, *J* 7.2 Hz, $CH_2CH_3$), 3.90, 4.01, 4.05 and 4.16 (12H, s, OMe), 4.37 (2H, q, *J* 7.2 Hz, $CH_2CH_3$), 6.44 (1H, s, H7), 7.63 (1H, s, H5). $^{13}$C NMR spectrum ($CDCl_3$): $\delta$ 14.4 ($CH_2CH_3$), 52.0, 53.1, 56.7 and 58.0 (OMe), 61.2 ($CH_2CH_3$), 96.9 (C7), 119.4 (C5), 100.9, 101.1, 114.8, 126.5, 130.9, 139.8, 159.2 and 159.4 (ArC), 160.3, 163.0 and 163.7 (CO). Mass spectrum: *m*/*z* 389 (M, 66%), 358 (24), 328 (30), 286 (43), 254 (100), 242 (36), 225 (53), 184 (57), 155 (69), 127 (78), 115 (60), 59 (98).

### 4.23. Crystallographic study on compound 24

#### *4.23.1. Crystal data*

$C_{21}H_{18}BrNO_4$, *M* 428.3, monoclinic, space group $P2_1/c$, *a* 23.543(9), *b* 4.545(2), *c* 17.226(9) Å, $\beta$ 96.50(3)°, *V* 1831(2) $Å^3$, $D_c$ 1.55 g $cm^{-3}$, *Z* 4, $\mu_{Cu}$ 33.34 $cm^{-1}$, $2\theta_{max}$ 140°. The number of reflections was 2690 considered observed out of 3485 unique data. Final residuals *R*, $R_w$ were 0.055, 0.074 for the observed data.

#### *4.23.2. Structure determination*

Reflection data were measured with an Enraf-Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using graphite monochromatized copper ($\lambda$ 1.5418 Å) or molybdenum radiation ($\lambda$ 0.7107) Å. Reflections with $I>2\sigma(I)$ were considered observed. The structures were determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full matrix least squares.

Reflection weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o)=[\sigma^2(I_o)+(0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w=(\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography.[18] Structure solutions were by SIR92[19] and refinement used RAELS.[20] ORTEP-II[21] running on an eMac was used for the structural diagrams, and the eMac was also used for calculations.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 694313). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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