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Synthetic approaches to activated pyrrolo[3,2,1-*hi*]indoles: synthesis of 6,8-dimethoxy pyrrolo[3,2,1-*hi*]indole

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ABSTRACT

6,8-Dimethoxypyrrolo[3,2,1-*hi*]indole **25** has been formed by the dehydrogenation of the related tetrahydro compound **23**, which in turn was formed by reduction of the related isatin **22**. Approaches to achieve the cyclisation of *N*-hydroxyethylindoles, *N*-dimethylacetamidoindoles, and *C*7-substituted chloroacetylindoles were unsuccessful.

1. Introduction

The synthesis of pyrrolo[3,2,1-*hi*]indoles can be achieved effectively by the aldol cyclisation of 7-formyl-*N*-indolylacetates, derived from the formylation of *N*-alkyl indoles.[1] The related, but less effective, cyclisation of *N*-phenacylindole-7-carbaldehydes has also been reported.[1] These cyclisation processes made the final connection between substituents at N1 and C7: functionalisation at C7 was made possible by the use of specifically activated indoles. Given such activation, it is also possible in principle to complete a cyclisation by a direct connection between the N1 substituent and C7 itself. Indeed various cyclisations of this type are worthy of investigation. Additionally, there is also the potential cyclisation of a C7 substituent directly onto N1. This paper deals with investigations of some of these strategies, which although found to be unsuccessful, helped to define the scope of pyrrolo[3,2,1-*hi*]indole synthesis. The strain factor involved in a 6,5,5-fused ring system[2] can be reduced by a strategy that involves the cyclisation on an indoline framework: subsequent dehydrogenation is then required to form the pyrrolo[3,2,1-*hi*]indole. A successful example of this approach is also described herein.

2. Results and discussion

2.1. Reactions of *N*-phenacylindoles

It has been previously reported[1] that the reaction of 3,5-dimethoxyaniline with 2 equiv of 4-bromophenacyl bromide gave a disubstituted aniline, which was cyclised directly with trifluoroacetic acid to give *N*-phenacylindole **1**. Attempts to achieve the second cyclisation through reaction with stronger acids, such as polyphosphoric acid, failed to form pyrroloindoles. However, during formylation of indole **1** with the Vilsmeier reagent, a pyrroloindole was obtained as a byproduct in poor yield.[1]

In order to aim for a less strained dihydropyrroloindole ring system, the phenacylindole was reduced with sodium borohydride to give benzylic alcohol **2**, which was then subjected to a variety of acidic conditions capable of generating a benzylic cation for intramolecular substitution at C7. Cyclisation could not be achieved and in most cases the reactions gave complex product mixtures. However, treatment of alcohol **2** with boron trifluoride etherate in boiling benzene gave the phenyl substituted product **3** in 63% yield, but no cyclisation was observed (Scheme 1). Similar treatment in other solvents gave no reaction.

2.2. Reactions of *N*-indolylacetamides

Indoles **4**–**8** were reacted with *N*,*N*-dimethylchloroacetamide and potassium hydroxide in dimethylsulfoxide at room temperature for 30 min to give the corresponding *N*-substituted indoles

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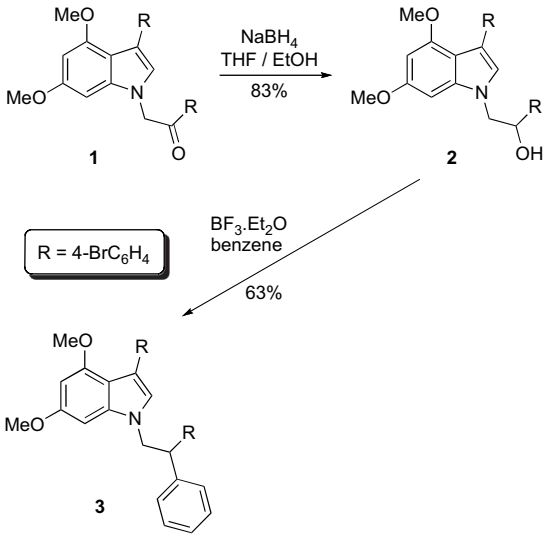
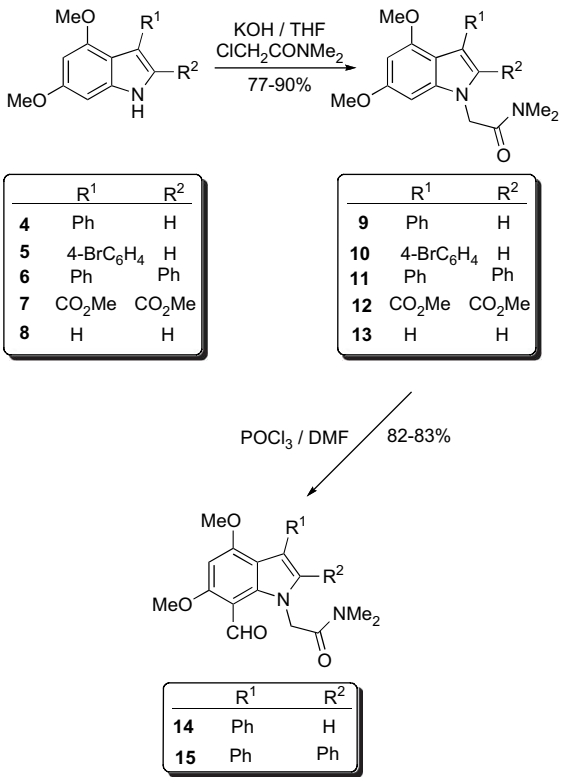


Scheme 1.



	R^1	R^2
4	Ph	H
5	4-BrC_6H_4	H
6	Ph	Ph
7	CO_2Me	CO_2Me
8	H	H

	R^1	R^2
9	Ph	H
10	4-BrC_6H_4	H
11	Ph	Ph
12	CO_2Me	CO_2Me
13	H	H

	R^1	R^2
14	Ph	H
15	Ph	Ph

Scheme 2.

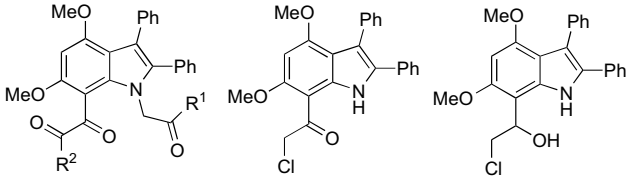
9–**13** in 77–90% yield. In the case of the less reactive indole diester **7**, the addition of potassium iodide was essential for the substitution to proceed. In general the reactions of these indoles with the α-chloroacetamide were much more effective than those with α-bromoacetates,[1] as they rapidly went to completion and usually gave pure products without the need for chromatography. Presumably the acetamide reagent and products were more stable than the related acetates under the basic conditions involved. The ^{1}H NMR spectra of the *N*-substituted indoles **9**–**13** showed singlet resonances for the acetyl methylene protons at around 4.7 ppm, pairs of singlets for the *N*-methyl protons at 2.8–3.1 ppm, and typical doublets at 6.1–6.4 ppm for H5 and H7.

All attempts to cyclise the indolyl acetamides by treatment even with excess phosphoryl chloride to generate the electrophilic iminium salts failed. No reaction could be observed at room temperature, while at higher temperatures inseparable product mixtures were obtained. None of the product mixtures were highly coloured, ruling out the formation of an indigo-like product that could arise by oxidative dimerisation of the desired cyclised pyrro-indolone product. Replacement of phosphoryl chloride by trifluoromethanesulfonic anhydride[3] yielded similar product mixtures.

Given that the 7-formyl *N*-indolyl acetates undergo ready aldol cyclisation to give pyrroloindoles,[1] the two *N*-indolyl acetamides **9** and **11** were formylated at C7 by typical Vilsmeier conditions to give aldehydes **14** and **15** in high yield (Scheme 2). The Vilsmeier reagent is known to react at the methylene position of acetamides to give dimethylaminomethylene amides,[4] but no reaction was observed in these examples, probably because of the superior reactivity at the indole C7 position.

Aldol cyclisation of compounds **14** and **15** could not be achieved, despite the investigation of numerous bases. In many cases no reaction was observed. Treatment with sodium hydride in dimethylformamide gave the related indole 7-aldehydes, resulting from the loss of the acetylacetamide group. Similar treatment in tetrahydrofuran additionally gave *N*-indolyl acetamides **9** and **11**, resulting from the loss of the formyl group. Presumably the reduced acidity of the acetamide methylene protons, compared with those of the acetates, led to the failure to effect cyclisation.

7-Glyoxylic amide **16**, readily prepared from *N*-indolyl acetamide **11**, also failed to undergo cyclisation. Similarly, 7-glyoxylic ester **17** was also subjected to the standard cyclisation conditions without success.[1] These results can be explained by the geometry of compounds **16** and **17**, which because of steric hindrance between the two adjacent substituents does not allow appropriate attack of the carbanion on the carbonyl carbon. This information is indicated by an X-ray crystal structure of compound **16** (see Fig. 1).



	R^1	R^2
16	NMe_2	NMe_2
17	OEt	OMe

2.3. Reactions of 7-chloroacetylindoles

Alternative potential precursors for the formation of pyrroloindolones are the 7-chloroacetylindoles. 2-Acylaminochloroacetophenones have been shown to undergo cyclisation on treatment with base, followed by dehydration, to give *N*-acetylindolones.[5] Reduction of such products gives *N*-acetylindoles. Treatment of indole **6** with excess of a reagent formed from phosphoryl chloride and *N*,*N*-dimethylchloroacetamide at 80 °C afforded 7-chloro acetylindole **18** in 90% yield. The reaction of indole with *N*, *N*-dimethylchloroacetamide under Vilsmeier conditions has been reported to give the 3-acetylated indole in 37% yield.[6] Treatment of indole **18** with either sodium hydride in tetrahydrofuran or potassium hydroxide in dimethylsulfoxide gave only polymeric material, and the application of milder bases such as triethylamine or

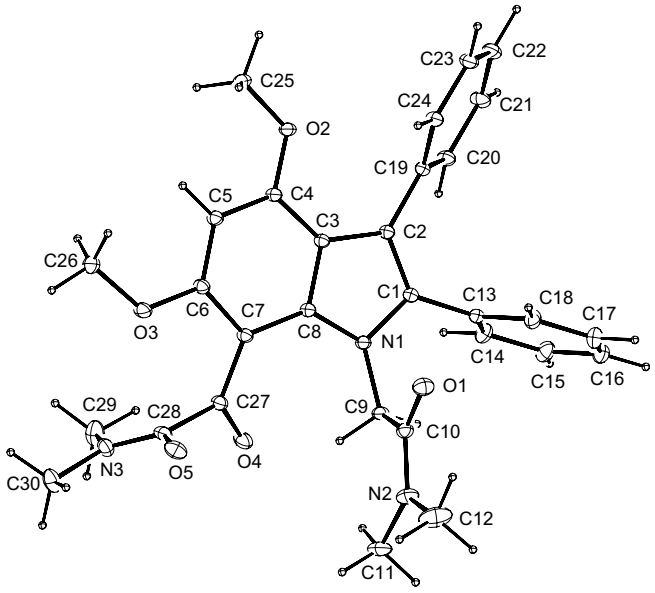
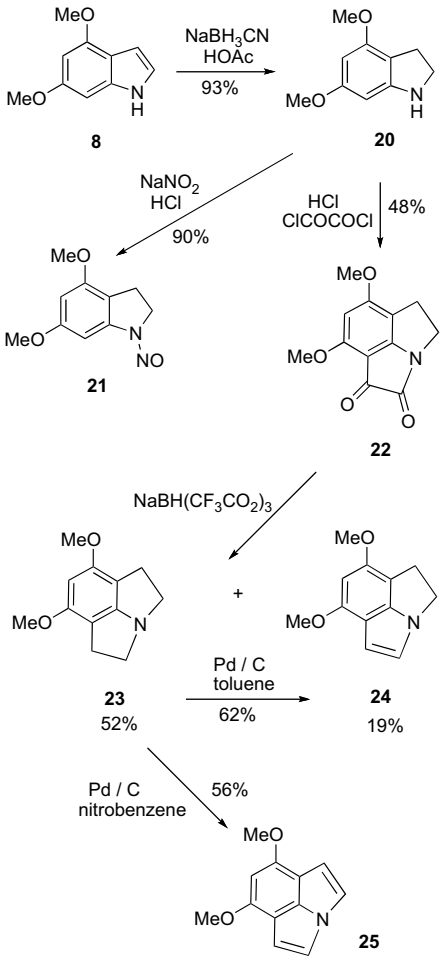


Figure 1. ORTEP diagram derived from the single-crystal X-ray analysis of compound **16**.

pyridine also failed to initiate any reaction. The alcohol reduction products of 2-acylaminochloroacetophenones have also been reported to undergo cyclisation to give *N*-acetylindoles directly.[5] Consequently, indole **18** was reduced by sodium borohydride to give alcohol **19** in 86% yield. Although this material could not be fully purified, attempts were made to effect cyclisation using a variety of bases and elevated temperatures, but no cyclic products could be identified.

2.4. Approaches from 4,6-dimethoxyindoline

In order to minimise problems involving strain in the cyclisation process, 4,6-dimethoxyindoline **20** became a desirable starting material. This can be produced from the known 4,6-dimethoxy indole **8**,[7,8] but here we describe an improved synthesis for this compound (*see* Experimental). Indoles can be effectively reduced to indolines by reaction with sodium cyanoborohydride in acetic acid.[9–13] Using these conditions, indole **8** was readily reduced to indoline **20** in 94% yield (Scheme 3). However, fairly swift purification of the product was necessary to prevent re-oxidation occurring. In an attempt to apply the Fischer synthesis to form a dihydropyrroloindole, indoline **20** was nitrosated by treatment with nitrous acid in ethanol and gave *N*-nitroso-indole **21** in 90% yield. However, attempted reduction of the nitroso compound to the related hydrazine only generated complex product mixtures, so this approach was not viable. An alternative approach via an isatin was then investigated. Indoline **20** was converted into its hydrochloride salt, which was reacted with excess oxalyl chloride at 140 °C to give the bright yellow indoline isatin **22** in 48% yield. Treatment of the isatin **22** with lithium aluminium hydride led to products of ring opening, which could not be purified satisfactorily. This reaction once again illustrates the issue of strain in the 6,5,5-fused ring system. Ring opening was also observed when sodium borohydride or sodium acetoxyborohydride was used. However, treatment of isatin **22** with a large excess of sodium trifluoroacetoxyborohydride gave tetrahydropyrrolo indole **23** in 52% yield, together with a trace of indole **24** (Scheme 3). As sodium trifluoroacetoxyborohydride is known to be a hydroborating agent,[14,15] it was found to be advantageous to add hydrogen peroxide during work-up. Although the yield of the tetrahydro compound **23** was not increased, that of the dihydrocompound **24** rose



Scheme 3.

to 19%. Treatment of tetrahydropyrroloindole **23** with palladium on charcoal in nitrobenzene at reflux under a nitrogen atmosphere for 4 h gave pyrroloindole **25** in 56% yield (Scheme 3). It was observed that the first dehydrogenation forming indole **24** occurred at approximately 120 °C and was complete in less than an hour. However, the second dehydrogenation leading to pyrroloindole **25** required heating at 210 °C and still did not reach completion after 4 h. This indicates that the activation energy involved for the conversion of tetrahydropyrroloindole **23** to indole **24** is less than that involved for the conversion of indole **24** to pyrroloindole **25**. The synthesis of indole **24** was also carried out by treatment of tetrahydropyrroloindole **23** with palladium on charcoal in toluene at reflux under a nitrogen atmosphere for 2.5 h. Indole **24** was obtained in 62% yield, but could not be obtained analytically pure. The mass spectrum of pyrroloindole **25** revealed a molecular ion at 201 (100%) and its elemental analysis was in agreement with the structure. The ^{1}H NMR spectrum established that the molecule is symmetrical (and therefore aromatic according to Paudler and Shin[16]), as H2 and H4 were identical (doublet at 6.85 ppm, *J* 3.0 Hz), as well as H1 and H5 (doublet at 7.36 ppm, *J* 3.0 Hz), and also the protons of the two methoxy groups (singlet, 4.13 ppm). Furthermore, the ^{13}C NMR spectrum showed only one methoxy peak, three CH signals, and three quaternary carbon resonances.

3. Conclusions

Although it was not possible to cyclise *N*-hydroxyethylindoles, *N*-dimethylacetamidoindoles or *C*7-substituted chloroacetylindoles to

form pyrrolo[3,2,1-*hi*]indoles, the simple 6,8-dimethoxypyrrolo[3,2,1-*hi*]indole **25** could be readily prepared via isatin **22** and indoline **23**.

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$_{254}$.

*4.1.1. 3-(4′-Bromophenyl)-1-{2-(4′-bromophenyl)-2-hydroxy ethyl}-4,6-dimethoxyindole (**2**)*

Sodium borohydride (0.086 g, 2.28 mmol) was added into a cooled solution of phenacylindole **1** (0.30 g, 0.57 mmol) in a mixture of absolute ethanol and tetrahydrofuran (1:1, 10 mL). The mixture was stirred at 0 °C for 45 min and then at room temperature for another 30 min. The solvent was removed under reduced pressure and the residue was diluted with water (40 mL). The resulting precipitate was filtered, washed with water, and dried to give hydroxyindole **2** as a white solid (0.25 g, 83%), mp 97–99 °C (from dichloromethane/light petroleum). (Found: C, 53.9; H, 4.2; N, 2.3. $C_{24}H_{21}Br_2NO_3$ requires: C, 54.3; H, 4.0; N, 2.6%.) λ_{max} 214 nm (ε 4700 cm^{-1} M^{-1}), 315 (5600). ν_{max} 3200, 1620, 1590, 1545, 1340, 1205, 1165, 1060, 1010, 800 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.06 (1H, br s, OH), 3.78 and 3.85 (6H, 2s, OMe), 4.16 (2H, d, *J* 6.2 Hz, CH_2), 4.98 (1H, d, *J* 6.2 Hz, CH), 6.26 (1H, br s, H5), 6.35 (1H, br s, H7), 6.82 (1H, s, H2), 7.17–7.51 (8H, m, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 54.0 (CH_2), 55.1 and 55.7 (OMe), 72.8 (CH), 85.6 (C5), 92.1 (C7), 110.6, 117.0, 119.6, 122.2, 134.7, 138.7, 140.0, 155.0 and 157.7 (ArC), 125.0 (C2), 127.6, 130.6, 131.0 and 131.8 (ArCH). Mass spectrum: *m*/*z* 533 (M, ^{81}Br, 21%), 531 (M, ^{79,81}Br, 42), 529 (M, ^{79}Br, 21), 347 (20), 346 (97), 344 (100), 77 (28).

*4.1.2. 3-(4′-Bromophenyl)-4,6-dimethoxy-1-(1-phenyl-4′-bromophenethyl)indole (**3**)*

Boron trifluoride etherate (four drops) was added into a cooled solution of indole **2** (0.20 g, 0.35 mmol) in dry benzene (10 mL). The mixture was heated at reflux for 2 h, allowed to cool, diluted with chloroform (80 mL), washed with water, dried over magnesium sulfate, and evaporated to leave a brown oil. Thin layer chromatography and elution with light petroleum in dichloromethane (1:4) afforded phenethylindole **3** as a yellow solid (0.13 g, 63%), mp 87–89 °C. (Found: C, 61.7; H, 4.9; N, 2.0. $C_{30}H_{25}Br_2NO_2\cdot 0.3C_5H_{12}$ requires: C, 61.7; H, 4.7; N, 2.3%.) ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 3.80 and 3.82 (6H, 2s, OMe), 4.45 (1H, t, *J* 7.4 Hz, CH), 4.60 and 4.63 (2H, 2d, *J* 7.4 Hz, CH_2), 6.25 (1H, d, *J* 1.8 Hz, H5), 6.27 (1H, d, *J* 1.8 Hz, H7), 6.40 (1H, s, H2), 6.99–7.43 (13H, m, ArH). Mass spectrum (MALDI): *m*/*z* 590 (M+1, ^{79}Br, 47%), 400 (32), 379 (46), 190 (95), 172 (95), 146 (52).

*4.1.3. N,N-Dimethyl-4,6-dimethoxy-3-phenylindol-1-ylacetamide (**9**)*

A mixture of powdered potassium hydroxide (0.47 g, 5.93 mmol) and dimethyl sulfoxide (20 mL) was stirred at room temperature for 10 min, then phenylindole **4**[17,18] (1.50 g, 5.93 mmol) was added and the mixture was stirred for another 30 min. *N*,*N*-Dimethylchloroacetamide (1.10 g, 8.90 mmol) was added dropwise and then stirring continued for another 2 h. Water (100 mL) was added and the resulting precipitate was filtered, washed with water and dried to afford indolylacetamide **9** as a yellow solid (1.54 g, 77%), mp 143–145 °C (from dichloromethane/light petroleum). (Found: C, 70.7; H, 6.7; N, 8.1. $C_{20}H_{22}N_2O_3$ requires: C, 71.0; H, 6.6; N, 8.2%.) ν_{max} 1660, 1325, 1200, 1150, 1040 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.98 and 3.00 (6H, 2s, NMe_2), 3.83 and 3.89 (6H, 2s, OMe), 4.79 (2H, s, CH_2), 6.31 (1H, d, *J* 1.8 Hz, H5), 6.40 (1H, d, *J* 1.8 Hz, H7), 6.92 (1H, s, H2), 7.29 (1H, t, *J* 7.2 Hz, H4′), 7.39 (2H, t, *J* 7.2 Hz, H3′), 7.64 (2H, d, *J* 7.2 Hz, H2′). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 35.9 and 36.5 (NMe_2), 48.4 (CH_2), 55.0 and 55.6 (OMe), 85.3 (C5), 92.0 (C7), 124.7, 125.4, 127.3 and 129.3 (ArCH), 110.6, 118.4, 135.7, 139.0, 155.0 and 157.6 (ArC), 167.0 (CONMe$_2$). Mass spectrum: *m*/*z* 339 (M+1, 23%), 338 (M, 85), 267 (30), 266 (100), 250 (49), 208 (28), 152 (22), 72 (83).

*4.1.4. N,N-Dimethyl-3-(4′-bromophenyl)-4,6-dimethoxyindol-1-ylacetamide (**10**)*

A suspension of powdered potassium hydroxide (0.030 g, 0.54 mmol) in dimethyl sulfoxide (4 mL) was reacted with bromo phenylindole **5**[17,19] (0.10 g, 0.30 mmol) and *N*,*N*-dimethylchloroacetamide (0.060 g, 0.45 mmol) according to the method of preparation of compound **9**. The resulting precipitate was filtered, washed with water, dried and recrystallised from dichloromethane/light petroleum to give indolylacetamide **10** as a white solid (0.11 g, 88%), mp 195–197 °C. (Found: C, 57.4; H, 5.3; N, 6.5. $C_{20}H_{21}BrN_2O_3$ requires: C, 57.6; H, 5.1; N, 6.7%.) λ_{max} 213 nm (ε 8600 cm^{-1} M^{-1}), 248 (9200), 287 (9400), 303 (9300). ν_{max} 1650, 1620, 1580, 1545, 1330, 1205, 1145, 1050, 795 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.97 and 2.98 (6H, 2s, NMe_2), 3.78 and 3.84 (6H, 2s, OMe), 4.77 (2H, s, CH_2), 6.25 (1H, d, *J* 2.0 Hz, H5), 6.33 (1H, d, *J* 2.0 Hz, H7), 6.86 (1H, s, H2), 7.44 (4H, s, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 36.0 and 36.6 (NMe_2), 48.3 (CH_2), 55.1 and 55.6 (OMe), 85.4 (C5), 92.2 (C7), 124.8 (C2), 130.5 and 131.0 (ArCH), 110.4, 117.3, 119.5, 134.8, 139.1, 154.9 and 157.8 (ArC), 166.9 (CO). Mass spectrum: *m*/*z* 418 (M, ^{81}Br, 64%), 416 (M, ^{79}Br, 66), 346 (78), 344 (83), 330 (22), 207 (22), 72 (100).

*4.1.5. N,N-Dimethyl-4,6-dimethoxy-2,3-diphenylindol-1-ylacetamide (**11**)*

This was prepared by reacting a suspension of potassium hydroxide (0.72 g, 12.77 mmol) in dimethyl sulfoxide (40 mL) with diphenylindole **6**[17] (3.0 g, 9.12 mmol) and *N*,*N*-dimethylchloroacetamide (1.66 g, 13.68 mmol) according to the method of preparation of compound **9**. The resulting precipitate was filtered, washed with water, dried and recrystallised from dichloromethane/light petroleum to give indolylacetamide **11** as a white solid (3.41 g, 90%), mp 168–171 °C. (Found: C, 75.2; H, 6.5; N, 6.6. $C_{26}H_{26}N_2O_3$ requires: C, 75.3; H, 6.3; N, 6.8%.) ν_{max} 1650, 1580, 1330, 1270, 1215, 1140, 1060, 805, 760, 700 cm^{-1}. ^{1}H NMR spectrum (300 MHz, $CDCl_3$): δ 2.87 and 2.99 (6H, 2s, NMe_2), 3.72 and 3.90 (6H, 2s, OMe), 4.73 (2H, s, CH_2), 6.29 (1H, d, *J* 1.3 Hz, H5), 6.37 (1H, d, *J* 1.3 Hz, H7), 7.10–7.40 (10H, m, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 36.0 and 36.3 (NMe_2), 46.3 (CH_2), 55.3 and 55.7 (OMe), 85.9 (C5), 92.5 (C7), 125.2, 126.7, 127.6, 128.2, 131.2 and 131.5 (ArCH), 111.7, 115.8, 131.9, 135.7, 135.8, 139.1, 155.1 and 157.6 (ArC), 167.5, CO. Mass spectrum: *m*/*z* 414 (M, 49%), 342 (22), 327 (24), 210 (67), 209 (44), 151 (100), 83 (48), 72 (33).

*4.1.6. Dimethyl 4,6-dimethoxy-1-(N,N-dimethylacetamido)indolyl-2,3-dicarboxylate (**12**)*

Method A. Sodium hydride (80% in paraffin oil, 29 mg, 0.96 mmol) was added into an ice-cooled solution of indole diester **7**[18] (0.20 g, 0.68 mmol) in dry tetrahydrofuran (10 mL) under nitrogen. The mixture was stirred at 0 °C for 15 min, then *N*,*N*-dimethylbromoacetamide (0.17 g, 1.02 mmol) was added dropwise

and stirring continued at room temperature overnight. Excess hydride was destroyed by the slow addition of cold water (40 mL) and the resulting precipitate was filtered, washed with water and dried. Thin layer chromatography and elution with dichloromethane in ethyl acetate (1:3) gave indolylacetamide **12** as a white solid (0.18 g, 70%), mp 227–229 °C. (Found: C, 57.5; H, 5.8; N, 7.3. $C_{18}H_{22}N_2O_7$ requires: C, 57.1; H, 5.9; N, 7.4%). λ_{max} 213 nm (ε 14,800 cm^{-1} M^{-1}), 249 (15,900), 312 (16,500). ν_{max} 1705, 1665, 1625, 1580, 1535, 1280, 1240, 1210, 1160 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.96 and 3.10 (6H, 2s, NMe_2), 3.78, 3.79, 3.83 and 3.90 (12H, 4s, OMe and CO_2Me), 5.15 (2H, s, CH_2), 6.15 (1H, s, H5), 6.18 (1H, s, H7). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 35.8 and 36.3 (NMe_2), 46.3 (CH_2), 51.8, 52.4, 55.5 and 55.7 (OMe), 84.4 (C5), 93.7 (C7), 110.0, 116.5, 121.7, 140.4, 154.7 and 160.8 (ArC), 161.4, 167.0 and 167.5 (*C*ONMe_2 and *C*O_2Me). Mass spectrum: *m*/*z* 379 (M+1, 22%), 378 (M, 100), 347 (21), 306 (90), 276 (37), 72 (39).

Method B. Sodium hydride (80% in paraffin oil, 20 mg, 0.48 mmol) was added into an ice-cooled solution of indole diester **7**[18] (0.010 g, 0.34 mmol) in dry tetrahydrofuran (6 mL) under nitrogen. The mixture was stirred at 0 °C for 15 min, then potassium iodide (0.090 g, 0.51 mmol) was added followed by *N*,*N*-dimethylchloroacetamide (80 mg, 0.68 mmol) dropwise and then stirring continued at room temperature for 4 h. Further treatment and purification according to method A afforded indolylacetamide **12** as a white solid (0.010 g, 78%), mp 227–230 °C.

4.1.7. *N,N-Dimethyl-4,6-dimethoxyindol-1-ylacetamide (**13**)*

This was prepared by reacting a suspension of powdered potassium hydroxide (0.090 g, 1.61 mmol) in dimethyl sulfoxide (4 mL) with 4,6-dimethoxyindole **8**[7,8] (0.19 g, 1.06 mmol) and *N*,*N*-dimethylchloroacetamide (0.21 g, 1.70 mmol) according to the method of preparation of compound **9**. The resulting precipitate was filtered, washed with water and dried to afford indolylacetamide **13** as a white solid (0.23 g, 82%), mp 176–178 °C (from dichloromethane/light petroleum). (Found: C, 64.0; H, 7.2; N, 10.5. $C_{14}H_{18}N_2O_3$ requires: C, 64.1; H, 6.9; N, 10.7%.) λ_{max} 212 nm (ε 7400 cm^{-1} M^{-1}), 232 (7300), 269 (7500). ν_{max} 1650, 1585, 1340, 1310, 1270, 1200, 1145, 1045, 810, 700 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.94 and 2.97 (6H, 2s, NMe_2), 3.84 and 3.90 (6H, 2s, OMe), 4.78 (2H, s, CH_2), 6.22 (1H, d, *J* 1.8 Hz, H5), 6.35 (1H, d, *J* 1.8 Hz, H7), 6.55 (1H, d, *J* 3.1 Hz, H3), 6.85 (1H, d, *J* 3.1 Hz, H2). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 36.0 and 36.6 (NMe_2), 48.7 (CH_2), 55.3 and 55.7 (OMe), 85.4, 91.6, 99.6 and 125.4 (ArCH), 113.5, 137.9, 153.8 and 157.8 (ArC), 167.3, CO. Mass spectrum: *m*/*z* 262 (M, 66%), 190 (100), 175 (32), 132 (30), 72 (38).

4.1.8. *N,N-Dimethyl-4,6-dimethoxy-7-formyl-3-phenylindol-1-ylacetamide (**14**)*

A cooled solution of phosphoryl chloride (0.31 mL, 3.33 mmol) in dry dimethylformamide (1.0 mL) was added dropwise into an ice-cooled solution of indole **9** (0.75 g, 2.22 mmol) in dry dimethylformamide (15 mL). The mixture was stirred at 0 °C for 30 min and then at room temperature for another 1 h. Cold water (10 mL) was added, followed by 2 M aqueous sodium hydroxide, until the mixture was strongly basic. The suspension was stirred at room temperature overnight, the resulting precipitate was filtered, washed with water, dried and recrystallised from dichloromethane/light petroleum to give formylindole **14** as a yellow solid (0.67 g, 83%), mp 223–225 °C. (Found: C, 69.0; H, 6.1; N, 7.5. $C_{21}H_{22}N_2O_4$ requires C, 68.8; H, 6.1; N, 7.7%). λ_{max} 212 nm (ε 15,100 cm^{-1} M^{-1}), 228 (13,600), 260 (15,900), 340 (8800). ν_{max} 1660, 1570, 1550, 1335, 1270, 1220, 1070 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.92 and 3.08 (6H, 2s, NMe_2), 3.81 and 3.90 (6H, 2s, OMe), 5.48 (2H, s, CH_2), 6.18 (1H, s, H5), 6.78 (1H, s, H2), 7.23 (1H, t, *J* 7.2 Hz, H4′), 7.31 (2H, t, *J* 7.2 Hz, H3′), 7.49 (2H, d, *J* 7.2 Hz, H2′), 10.34 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 35.6 and 36.1 (NMe_2), 53.1 (CH_2), 55.1 and 56.8 (OMe), 87.4 (C5), 125.7, 127.2, 129.5 and 129.6 (ArCH), 106.7, 112.9, 118.7, 135.4, 136.7, 160.9, 164.9 and 168.2 (ArC), 188.4 (CHO). Mass spectrum: *m*/*z* 366 (M, 49%), 294 (100), 266 (68), 236 (22), 84 (27), 72 (96).

4.1.9. *N,N-Dimethyl-4,6-dimethoxy-7-formyl-2,3-diphenylindol-1-ylacetamide (**15**)*

This was prepared by reacting a cooled solution of phosphoryl chloride (0.33 mL, 3.62 mmol) in dry dimethylformamide (1.0 mL) with an ice-cooled solution of indole **11** (1.0 g, 2.41 mmol) in dry dimethylformamide (15 mL) according to the method of preparation of compound **14**. The resulting precipitate was filtered, washed with water and dried. Flash chromatography and elution with ethyl acetate in dichloromethane (1:9) afforded formylindole **15** as a white solid (0.88 g, 82%), mp 216–218 °C. (Found: C, 73.5; H, 6.2; N, 6.3. $C_{27}H_{26}N_2O_4$ requires C, 73.3; H, 5.9; N, 6.3%.) λ_{max} 211 nm (ε 24,000 cm^{-1} M^{-1}), 259 (21,800), 329 (10,700), 355 (9100). ν_{max} 3310, 1665, 1575, 1265, 1220, 1170, 1050, 755, 700 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.84 and 2.88 (6H, 2s, NMe_2), 3.76 and 3.96 (6H, 2s, OMe), 5.41 (2H, s, CH_2), 6.23 (1H, s, H5), 7.13–7.28 (10H, m, ArH), 10.41 (1H, s, CHO). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 35.6 and 36.1 (NMe_2), 49.8 (CH_2), 55.2 and 56.9 (OMe), 87.9 (C5), 125.4, 126.6, 127.8, 128.0, 131.3 and 131.5 (ArCH), 106.8, 113.5, 116.8, 131.8, 135.6, 137.2, 139.4, 161.0, 165.0 and 168.3 (ArC), 188.5 (CHO). Mass spectrum: *m*/*z* 442 (M, 48%), 370 (52), 342 (24), 72 (100), 58 (33).

4.1.10. *N,N-Dimethyl-4,6-dimethoxy-1-(N,N-dimethylacetamido)-2,3-diphenylindol-7-yl-glyoxylamide (**16**)*

Oxalyl chloride (0.08 mL, 0.96 mmol) was added dropwise into a solution of indole **11** (0.20 g, 0.48 mmol) in dry benzene (10 mL) under nitrogen. The mixture was stirred at room temperature for 2 h, then aqueous dimethylamine (40%, 0.37 mL, 2.88 mmol) was added and the stirring continued for another 30 min. The mixture was diluted with chloroform (80 mL), then washed with water, dried over magnesium sulfate and evaporated to leave a yellow solid. Recrystallisation from dichloromethane/light petroleum afforded indolylglyoxylamide **16** as a bright yellow solid (0.22 g, 89%), mp 243–245 °C. (Found: C, 68.8; H, 6.2; N, 7.8. $C_{30}H_{31}N_3O_5 \cdot 0.5H_2O$ requires C, 69.0; H, 6.2; N, 8.0%.) λ_{max} 214 nm (ε 14,100 cm^{-1} M^{-1}), 240 (13,900), 264 (14,800), 333 (8300), 364 (6700). ν_{max} 1645, 1570, 1260, 1215, 1120, 1150, 760, 700 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.81, 2.87, 2.99 and 3.06 (12H, 4s, NMe_2), 3.73 and 3.86 (6H, 2s, OMe), 4.93 (2H, s, CH_2), 6.21 (1H, s, H5), 7.11–7.28 (10H, m, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 34.2, 35.8, 36.2 and 37.1 (NMe_2), 48.6 (CH_2), 55.3 and 57.5 (OMe), 88.6 (C5), 125.4, 126.6, 127.8, 127.9, 131.3 and 131.6 (ArCH), 105.5, 114.4, 116.7, 131.7, 135.6, 137.5, 140.0, 160.2 and 161.3 (ArC), 168.0 and 169.6 (*C*ONMe_2), 189.8 (*CO*CONMe_2). Mass spectrum: *m*/*z* 514 (M, 13%), 513 (34), 441 (60), 413 (21), 72 (78), 58 (100). Crystals for X-ray determination were obtained from isopropanol/chloroform.

4.1.11. *Methyl 1-carbethoxymethyl-2,3-diphenylindol-7-ylglyoxylate (**17**)*

Oxalyl chloride (0.10 mL, 1.08 mmol) was added dropwise into a solution of ethyl 2,3-diphenylindol-1-ylacetate[1] (0.15 g, 0.36 mmol) in dry benzene (7 mL) under nitrogen. The mixture was stirred at room temperature for 15 min and then warmed at 70 °C for 2 h. The mixture was allowed to cool, excess methanol was added and stirring continued for 30 min. The resulting precipitate was filtered, washed with dichloromethane/light petroleum (1:1) (20 mL) and dried to give indolylglyoxylate **17** as a light yellow solid (0.080 g, 44%), mp 185–187 °C. (Found: C, 69.6; H, 5.6; N, 2.7. $C_{29}H_{27}NO_7$ requires C, 69.5; H, 5.4; N, 2.8%.) λ_{max} 213 nm (ε 14,200 cm^{-1} M^{-1}), 245 (14,600), 267 (15,200), 325 (10,100), 371

(7900). ν_{max} 1740, 1660, 1580, 1305, 1245, 1210, 1160, 1055, 705 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 1.17 (3H, t, *J* 6.9 Hz, CH_2CH_3), 3.74, 3.88 and 3.90 (9H, 3s, OMe), 4.11 (2H, q, *J* 6.9 Hz, CH_2CH_3), 4.82 (2H, s, CH_2), 6.24 (1H, s, H5), 7.13–7.28 (10H, m, ArH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 14.0 (CH_2CH_3), 49.1 and 61.2 (CH_2), 52.4, 55.3 and 57.4 (OMe), 88.6 (C5), 125.6, 126.7, 128.2, 128.4, 131.2 and 131.4 (ArCH), 104.3, 114.1, 117.0, 131.1, 135.1, 136.4, 139.2, 160.3 and 161.6 (ArC), 165.3 and 169.1 (CO_2Et and $COCO_2Me$), 185.1 ($COCO_2Me$). Mass spectrum: *m*/*z* 502 (M, 26%), 501 (82), 443 (30), 442 (100), 399 (23), 355 (24), 254 (31), 59 (49).

4.1.12. 2-Chloro-(4′,6′-dimethoxy-2′,3′-diphenylindol-7′-yl)ethanone (**18**)

Phosphoryl chloride (0.70 mL, 7.60 mmol) was added dropwise into cooled *N*,*N*-dimethylchloroacetamide (1.85 g, 15.20 mmol) and then diphenylindole **6**[17] (0.50 g, 1.52 mmol) was added. The mixture was stirred at 0 °C for 15 min, then heated at 80 °C for 2 h and further treatment was according to the method of preparation of compound **15**. Flash chromatography and elution with dichloromethane yielded chloroacetylindole **18** as a yellow solid (0.56 g, 90%), mp 233–235 °C. (Found: C, 70.1; H, 5.1; N, 3.3. $C_{24}H_{20}ClNO_3 \cdot 0.2H_2O$ requires C, 70.4; H, 5.0; N, 3.4%.) λ_{max} 213 nm (ε 900 cm^{-1} M^{-1}), 269 (900), 304 (900), 330 (1000), 358 (900). ν_{max} 3410, 1635, 1590, 1215, 1160, 1140, 990, 700 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.85 and 4.08 (6H, 2s, OMe), 4.97 (2H, s, CH_2), 6.22 (1H, s, H5), 7.26–7.44 (10H, m, ArH), 11.15 (1H, s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 52.2 (CH_2), 55.4 and 56.3 (OMe), 86.8 (C5), 126.1, 127.1, 127.4, 127.6, 128.3 and 131.2 (ArCH), 102.2, 128.0, 128.7, 132.2, 133.2, 135.5, 138.0, 160.7 and 160.8 (ArC), 190.1 (CO). Mass spectrum: *m*/*z* 407 (M+1, 37%), 406 (M, 32), 405 (100), 357 (20), 356 (76), 254 (38), 178 (38), 133 (39), 49 (44).

4.1.13. 2-Chloro-(4′,6′-dimethoxy-2′,3′-diphenylindol-7′-yl) ethanol (**19**)

Sodium borohydride (60 mg, 1.59 mmol) was added into a cooled solution of indole **18** (0.15 g, 0.37 mmol) in 5% aqueous dioxane (10 mL). The mixture was stirred at 0 °C for 30 min, then at room temperature for another 2 h and further treatment was according to the method of preparation of compound **2**. Recrystallisation from dichloromethane/light petroleum gave the hydroxyethylindole as a white solid (0.13 g, 86%), but it was unstable and could not be obtained pure. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.73 and 3.96 (6H, 2s, OMe), 3.89 (1H, m, CH_2), 4.10 (1H, t, *J* 10.5 Hz, CH_2), 5.48 (1H, qt, *J* 4.9 Hz, CH), 6.04 (1H, d, *J* 4.9 Hz, OH), 7.35 (10H, br s, ArH), 10.35 (1H, s, NH). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 49.0 (CH_2), 55.3 and 56.9 (OMe), 68.1 (CH), 89.4 (C5), 104.5, 113.2, 113.4, 132.5, 132.6, 135.7, 136.2, 152.9 and 154.0 (ArC), 126.0, 127.0, 127.3, 128.2, 128.3 and 131.3 (ArCH).

4.1.14. 4,6-Dimethoxyindole (**8**)

The original procedure[7] for the preparation of this compound was as follows: to an ice cold, stirred suspension of lithium aluminium hydride (4.62 g, 122.0 mmol) in dioxane (200 mL) was slowly added 4,6-dimethoxyisatin (5.0 g, 24.0 mmol). The mixture was cautiously heated to boiling over a 5 h period and then maintained at reflux for 15 h. The mixture was cooled and treated with absolute ethanol and water followed by removal of the solvent in vacuo. The residue was thrice extracted with chloroform and the combined extracts were dried over magnesium sulfate and evaporated in vacuo to leave a purple solid residue. Chromatography on silica gel with elution by chloroform gave 1.82 g (43%) of white crystals, mp 119–120.5 °C (from benzene/cyclohexane).

Some difficulties leading to an uncontrolled reaction were found when this procedure was used for the reduction of more than 10 g of 4,6-dimethoxyisatin. The following procedure was found to be safer and gave comparable yields.

4,6-Dimethoxyisatin (12.0 g, 58.0 mmol) was added in portions over a period of 2 h into a mixture of lithium aluminium hydride (11.0 g, 289.9 mmol) in dry dioxane (300 mL) at reflux. Heating was continued for another 10 h, then the mixture was cooled and excess hydride was destroyed by cautious treatment with cold water (60 mL). The solvent was removed under reduced pressure and the residue was extracted with dichloromethane (3×90 mL). The combined organic layers were washed once with brine (40 mL), dried over magnesium sulfate and evaporated to leave a purple solid. Flash chromatography and elution with dichloromethane gave indole **8** as a white solid (4.98 g, 49%), mp 118–120 °C (lit.[7] 119–120.5 °C).

4.1.15. 4,6-Dimethoxyindoline (**20**)

Method A. Sodium cyanoborohydride (6.41 g, 101.7 mmol) was added into a solution of 4,6-dimethoxyindole **8** (6.0 g, 33.9 mmol) in glacial acetic acid (120 mL) at 15 °C under nitrogen. The mixture was stirred for 45 min, then diluted with water (250 mL), cooled in an ice bath and made strongly basic by slowly adding sodium hydroxide pellets. The resulting white suspension was extracted with ether (3×90 mL) and the combined ethereal layers were washed with water, dried over magnesium sulfate and evaporated to give an off-white solid. Recrystallisation from dichloromethane/light petroleum afforded the indoline **20** as a white solid (5.70 g, 94%), mp 60–62 °C. (Found: C, 67.0; H, 7.4; N, 7.8; $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%). λ_{max} 214 nm (ε 6100 cm^{-1} M^{-1}), 230 (5900), 285 (2000). ν_{max} 3280, 1610, 1500, 1350, 1200, 1140, 1100, 1040, 800, 780 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.92 (2H, t, *J* 8.5 Hz, H3), 3.39 (1H, s, NH), 3.56 (2H, t, *J* 8.5 Hz, H2), 3.74 and 3.80 (6H, 2s, OMe), 5.90 (1H, d, *J* 2.1 Hz, H5), 5.94 (1H, d, *J* 2.1 Hz, H7). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 26.3 (C3), 47.7 (C2), 55.3 and 55.5 (OMe), 89.1 and 89.6 (C5,7), 108.1, 153.4, 156.7 and 161.3 (ArC). Mass spectrum: *m*/*z* 179 (M, 100%), 178 (93), 163 (20), 150 (24), 148 (40), 147 (26), 136 (22).

Method B. Palladium on charcoal (10%, 1.00 g) was added into a solution of 4,6-dimethoxyindole **8** (1.89 g, 10.68 mmol) in formic acid (90%, 35 mL) under nitrogen. The mixture was heated at 70 °C for 1.5 h, then the catalyst was filtered and washed with 80% aqueous methanol (100 mL). The combined filtrate was evaporated, and the resulting reddish-oily residue of the *N*-formylindoline was heated at reflux for 2 h with a solution of potassium hydroxide (6.00 g, 106.80 mmol) in methanol (100 mL). The solvent was removed under reduced pressure and the residue diluted with water (60 mL). The resulting brown precipitate was filtered, washed with water and dried. Flash chromatography and elution with ethyl acetate in dichloromethane (3:17) afforded indoline **20** as a pale yellow solid (0.67 g, 35%, mp 58–62 °C).

4.1.16. 4,6-Dimethoxy-N-nitrosoindoline (**21**)

A solution of sodium nitrite (0.25 g, 3.63 mmol) in water (1 mL) was added dropwise into a cooled solution of indoline **20** (0.50 g, 2.79 mmol) in absolute ethanol (15 mL) containing concentrated hydrochloric acid (0.3 mL). The mixture was stirred at 0 °C for 45 min and then at room temperature for another 1 h. The mixture was poured into cold water (50 mL) and the resulting suspension was extracted with dichloromethane (3×50 mL). The combined organic layers were washed with water, dried over magnesium sulfate and evaporated to give nitrosoindoline **21** as a grey solid (0.52 g, 90%), mp 134–136 °C (from isopropanol/chloroform). (Found: C, 57.8; H, 5.6; N, 13.2. $C_{10}H_{12}N_2O_3$ requires C, 57.7; H, 5.8; N, 13.5%.) λ_{max} 213 nm (ε 4600 cm^{-1} M^{-1}), 242 (4800), 282 (5000), 325 (5900). ν_{max} 1630, 1610, 1510, 1300, 1265, 1240, 1210, 1160, 1035, 820 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 2.96 (2H, t, *J* 7.7 Hz, H3), 3.79 and 3.80 (6H, 2s, OMe), 4.06 (2H, t, *J* 7.7 Hz, H2), 6.26 (1H, d, *J* 2.0 Hz, H5), 6.90 (1H, d, *J* 2.0 Hz, H7). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 22.7 (C3), 46.9 (C2), 55.4 and 55.7 (OMe),

88.6 and 97.0 (ArCH), 112.1, 142.3, 156.9 and 161.7 (ArC). Mass spectrum (ES): *m*/*z* 209 (M+1, 92%), 179 (100).

4.1.17. 4,5-Dihydro-6,8-dimethoxy-1,2-dioxopyrrolo[3,2,1-hi] indole (**22**)

Hydrogen chloride gas was passed through a solution of indoline **20** (4.75 g, 26.50 mmol) in diethyl ether (200 mL) at room temperature for 1.5 h. The resulting white precipitate was filtered, washed with diethyl ether (80 mL) and dried. This indoline hydrochloride salt (5.42 g) was added in portions with stirring into oxalyl chloride (15.82 mL, 185.5 mmol) over a period of 30 min and then the mixture was heated directly at 135–140 °C for 2 h. The resulting green solid was washed with light petroleum (150 mL), then flash chromatographed and eluted with ethyl acetate in dichloromethane (1:9) to give dihydrodioxopyrroloindole **22** as a bright yellow solid (2.83 g, 48%), mp 212–214 °C. (Found: C, 60.7; H, 5.1; N, 5.8. $C_{12}H_{11}NO_4\cdot 0.2H_2O$ requires C, 60.9; H, 4.9; N, 5.9%.) λ_{max} 211 nm (ε 14,900 $cm^{-1}\,M^{-1}$), 228 (12,400), 249 (94,00), 300 (10,800), 350 (4300). ν_{max} 1730, 1675, 1590, 1310, 1260, 1225 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.29 (2H, t, *J* 7.4 Hz, H5), 3.89 and 4.10 (6H, 2s, OMe), 4.12 (2H, t, *J* 7.4 Hz, H4), 5.82 (1H, s, H7). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 29.4 (C5), 46.3 (C4), 56.2 and 59.0 (OMe), 94.1 (C7), 94.6, 103.6, 157.3, 157.7, 161.1 (ArC), 163.2 and 178.6 (CO). Mass spectrum: *m*/*z* 233 (M, 14%), 207 (43), 205 (100), 204 (65), 178 (30), 177 (21), 148 (25), 120 (33), 69 (32).

4.1.18. 6,8-Dimethoxy-1,2,4,5-tetrahydropyrrolo[3,2,1-hi] indole (**23**)

A solution of trifluoroacetic acid (14.81 mL, 192.30 mmol) in dioxane (30 mL) was added dropwise over a period of 45 min into a stirred suspension of sodium borohydride (7.27 g, 192.30 mmol) in dioxane (220 mL) at 10–15 °C under nitrogen. Indoline isatin **22** (2.24 g, 9.61 mmol) was added and then the mixture was heated at 70 °C for 2 h. The mixture was concentrated under reduced pressure, diluted with water (200 mL) and extracted with dichloromethane (3×80 mL). The combined organic layers were washed once with brine (70 mL), dried over magnesium sulfate and evaporated to leave an orange oil. This oil was dissolved in tetrahydrofuran (60 mL), then a solution of sodium hydroxide (2.69 g, 67.27 mmol) in water (14 mL) was added, followed by hydrogen peroxide (27.5%, 7.49 mL, 67.27 mmol). The mixture was stirred at room temperature for 3 h, then the organic layer was separated and the aqueous phase was extracted with ether (3×70 mL). The combined organic layers were washed once with brine (80 mL), dried over magnesium sulfate and evaporated to give a brown oil. Flash chromatography and elution with dichloromethane afforded dihydropyrroloindole **24** as a white solid (0.36 g, 19%), mp 127–130 °C. Further elution with ethyl acetate in dichloromethane (1:19) gave tetrahydropyrroloindole **23** as a colourless oil (1.02 g, 52%). (Found: C, 70.0; H, 7.6; N, 6.7. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%.) ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.24 (8H, m, CH_2), 3.81 (6H, s, OMe), 5.75 (1H, s, H5); ($C_6D_5CD_3$): δ 2.87 (4H, t, *J* 7.2 Hz, H1,5), 3.11 (4H, t, *J* 7.2 Hz, H2,4), 3.47 (6H, s, OMe), 5.80 (1H, s, H7). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 32.8 (C1,5), 56.2 (OMe), 58.1 (C2,4), 90.4 (C7), 101.7, 156.1 and 167.7 (ArC). Mass spectrum: *m*/*z* 205 (M, 100%), 204 (51), 190 (27), 69 (38), 43 (23).

4.1.19. 4,5-Dihydro-6,8-dimethoxypyrrolo[3,2,1-hi]indole (**24**)

Palladium on charcoal (10%, 1.74 g) was added to a suspension of tetrahydropyrroloindole **23** (0.77 g, 3.76 mmol) in toluene (35 mL) under nitrogen. The mixture was heated at reflux for 2.5 h, then the catalyst was filtered off and washed with dichloromethane (70 mL). The combined filtrate was evaporated to leave a brown solid. Flash chromatography and elution with dichloromethane gave dihydropyrroloindole **24** as a white solid (0.47 g, 62%), which could not be obtained analytically pure. Mp 126–128 °C. λ_{max} 215 nm (ε 2700 $cm^{-1}\,M^{-1}$), 241 (2800), 267 (3000), 291 (3200). ν_{max} 1645, 1610, 1525, 1500, 1430, 1325, 1270, 1210, 1200, 1170, 1105, 1070, 725 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 3.85 (2H, t, *J* 7.2 Hz, H5), 3.91 and 3.95 (6H, 2s, OMe), 4.43 (2H, t, *J* 7.2 Hz, H4), 6.04 (1H, s, H7), 6.42 (1H, d, *J* 2.8 Hz, H1), 6.92 (1H, d *J* 2.8 Hz, H2). Mass spectrum: *m*/*z* 203 (M, 100%), 188 (95), 145 (27), 117 (24).

4.1.20. 6,8-Dimethoxypyrrolo[3,2,1-hi]indole (**25**)

Palladium on charcoal (10%, 2.0 g) was added into a solution of tetrahydropyrroloindole **23** (0.87 g, 4.24 mmol) in nitrobenzene (30 mL) under nitrogen. The mixture was brought to reflux over a period of 1.5 h and then heated at that temperature for another 4 h. The mixture was allowed to cool, then the catalyst was filtered off and washed with quinoline (10 mL). The combined filtrate was distilled under reduced pressure and the residue was dissolved in dichloromethane (90 mL), washed with 5% hydrochloric acid (2×30 mL) followed by water, dried over magnesium sulfate and evaporated to leave a brown oil. Flash chromatography and elution with dichloromethane in light petroleum (2:3) afforded pyrroloindole **25** as a pale yellow solid (0.48 g, 56%) mp 64–66 °C. (Found: C, 71.3; H, 5.8; N, 7.0. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%.) λ_{max} 209 nm (ε 13,200 $cm^{-1}\,M^{-1}$), 232 (13,200), 293 (14,400). ν_{max} 1650, 1590, 1500, 1350, 1265, 1190, 1140 cm^{-1}. ^1H NMR spectrum (300 MHz, $CDCl_3$): δ 4.13 (6H, s, OMe), 6.44 (1H, s, H7), 6.85 (2H, d, *J* 3.0 Hz, H1,5), 7.36 (2H, d, *J* 3.0 Hz, H2,4). ^{13}C NMR spectrum (75 MHz, $CDCl_3$): δ 57.3 (OMe), 96.7 (C7), 108.7 (C1,5), 120.8 (C2,4), 102.6, 140.2 and 155.5 (ArC). Mass spectrum: *m*/*z* 202 (M+1, 20%), 201 (M, 100), 186 (57), 158 (49), 143 (32), 101 (24).

4.2. Crystallographic study on compound 16

4.2.1. Crystal data

$C_{30}H_{31}N_3O_5$, *M* 513.6, triclinic, space group *P*−1, *a* 10.652(3), *b* 11.222(3), *c* 12.014(4) Å, α 80.63(2)°, β 86.21(2)°, γ 71.14(2)°, *V* 1340.6(7) $Å^3$, D_c 1.27 g cm^{-3}, *Z* 2, μ_{Cu} 7.08 cm^{-1}, $2\theta_{max}$ 140°. The number of reflections was 4199 considered observed out of 5076 unique data. Final residuals *R*, R_w were 0.046, 0.082 for the observed data.

4.2.2. Structure determination

Reflection data were measured with an Enraf–Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using graphite monochromatized copper (λ 1.5418 Å) or molybdenum radiation (λ 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.[20] Structure solutions were by SIR92[21] and refinement used RAELS.[22] ORTEP-II[23] 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 694314). 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 Rd, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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