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Comparative reactivity of 5,7-dimethoxyindoles with aldehydes and ketones

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Dedicated to Professor Jan Bergman on the occasion of his 80th birthday

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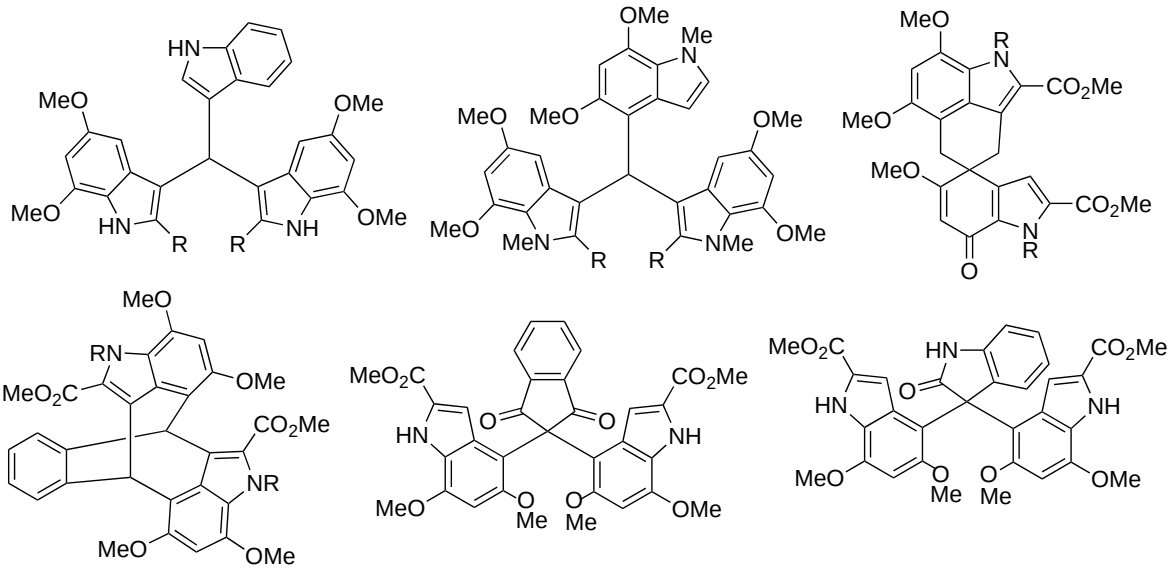
Abstract

This paper describes acid-catalysed reactions of 5,7-dimethoxy-1-methylindole and methyl 5,7-dimethoxy-indole-2-carboxylate with a range of aldehydes and ketones. The former indole reacts selectively at C3, whereas the latter reacts preferentially at C4 but also at C3 depending on the reaction conditions. Reactions of indoles with 2,2-dimethoxypropane and triethyl orthoformate are also reported. A range of di- and tri-indolylmethanes are described, together with an indolo-triptycene of novel structure.

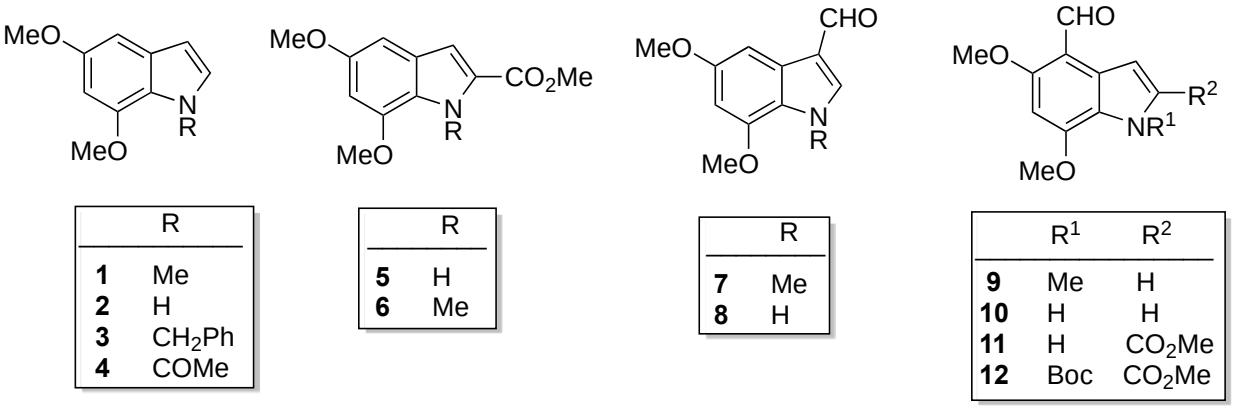


Keywords: Tri-indolylmethanes, di-indolylmethanes, indoles, benzindoles, triptycenes

Introduction

In an attempt to modify the reactivity of indoles to provide diverse substitution in the benzene ring, we have carried out extensive investigations on 4,6-dimethoxyindoles,[1-9] where the C7 position is strongly nucleophilic, and to a lesser extent on 5,7-dimethoxyindoles,[10] where the C4 position is strongly nucleophilic. The reactivity patterns also depend on the presence of other substituents, and also the fact that the methoxy groups increase the general reactivity of the whole indole framework to the extent that favoured reactivity sites can also be positions C2 and C3.[11] We have previously reported a range of electrophilic substitution reactions on 5,7-dimethoxyindoles:[10] these include formylation, acylation, bromination and nitration. Depending on the structure of the starting indole, reactions can take place at C4 or C3.

We now report a range of acid-catalysed reactions of several 5,7-dimethoxyindoles with aldehydes and ketones, with an emphasis on the comparative behaviour resulting from the structure of the starting material.[10] The two main starting indoles chosen were 5,7-dimethoxy-1-methylindole **1** and methyl 5,7-dimethoxyindole-2-carboxylate **5**: the former in general tends to favour reactions at C3 and the latter at C4. The *N*-methylindole **1** was chosen ahead of the simpler parent structure **2** because the electron-donating effect of the methyl group confers a more powerful nucleophilic reactivity at C3 (in the same way that *N*-methylindole is a more effective C3 nucleophile than indole). The presence of the electron-withdrawing carboxylic ester at C2 in indole **5** has the effect of reducing nucleophilic reactivity at C3 and therefore leading to preferential reaction at C4. Some related indoles **2**-**4, 6** and indole carbaldehydes **7**-**12** participate in some individual reactions (Figure 1). The syntheses of indoles **1** and **5** use different methodology, and all the indoles **1**-**11** have already been described.[10] The indole **12** was prepared by the reaction of indole **11** with di-*t*-butyl) carbonate. Several aspects of the following work have been mentioned in the report of a conference lecture.[12]



	R
1	Me
2	H
3	CH_2Ph
4	COMe

	R
5	H
6	Me

	R
7	Me
8	H

	R^1	R^2
9	Me	H
10	H	H
11	H	CO_2Me
12	Boc	CO_2Me

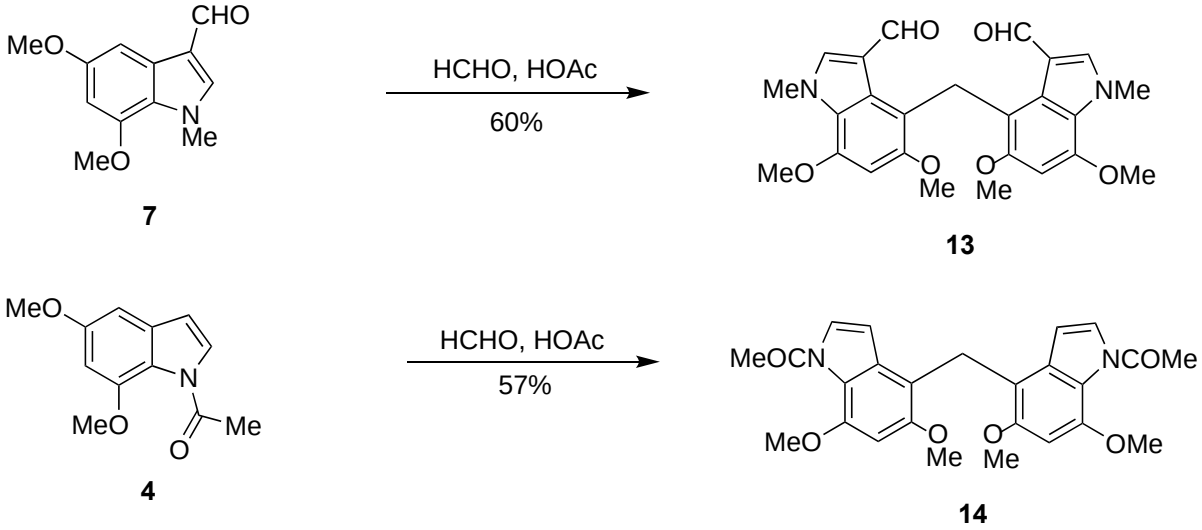
Figure 1. Selected 5,7-dimethoxyindole starting materials

Results and Discussion

Reactions with formaldehyde

The *N*-methylindole **1** failed to react with formaldehyde at room temperature but a complex mixture of products formed when the reaction mixture was heated. However, the less reactive 5,7-dimethoxy-1-methylindole-3-carbaldehyde **7** reacted smoothly with formaldehyde in glacial acetic acid at room temperature to give the 4,4'-diindolylmethane **13** in 66% yield. The *N*-acetylindole **4** also combined with formaldehyde in glacial acetic acid to give the 4,4'-diindolylmethane **14** in 57% yield (Scheme 1). Presumably the C3 position is deactivated by the electron-withdrawing acetyl group. On the other hand, 5,7-

dimethoxyindole-4-carbaldehyde **10** and also its *N*-methyl derivative **9** gave complex mixtures under the same reaction conditions.

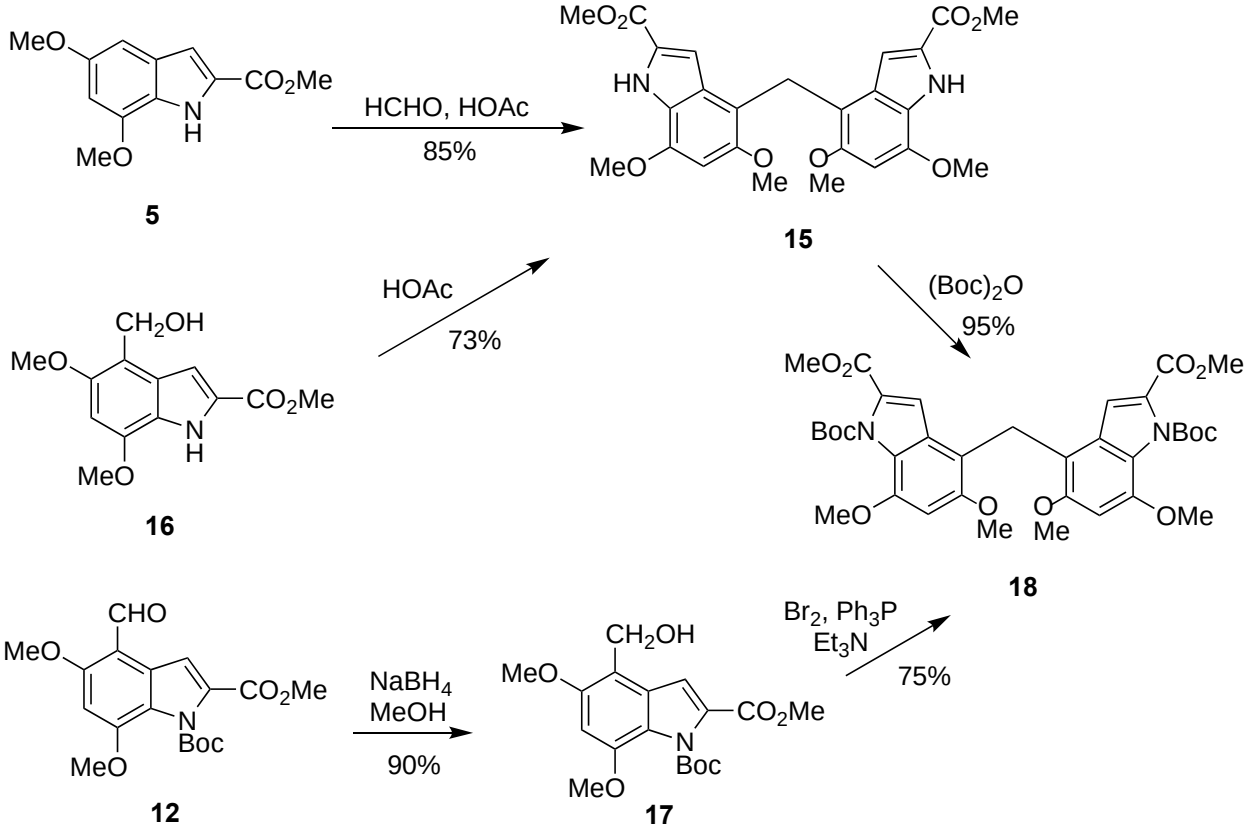


7 **13**

4 **14**

Scheme 1. Formation of 4,4'-diindolylmethanes **13** and **14**

The indole-2-carboxylate **5** reacted slowly with formaldehyde in acetic acid over several days to give the 4,4'-diindolylmethane **15** in 85% yield (Scheme 2). An attempt to achieve a faster reaction using methanolic hydrochloric acid gave a yield of only 27%. The structures of the new 4,4'-diindolylmethanes **13**, **14** and **15** were clear from their NMR spectra, and the linking methylene protons resonated at 4.99, 4.30 and 4.40 ppm respectively, and the linking carbon atoms resonated at 29.0, 22.4 and 22.6 respectively.



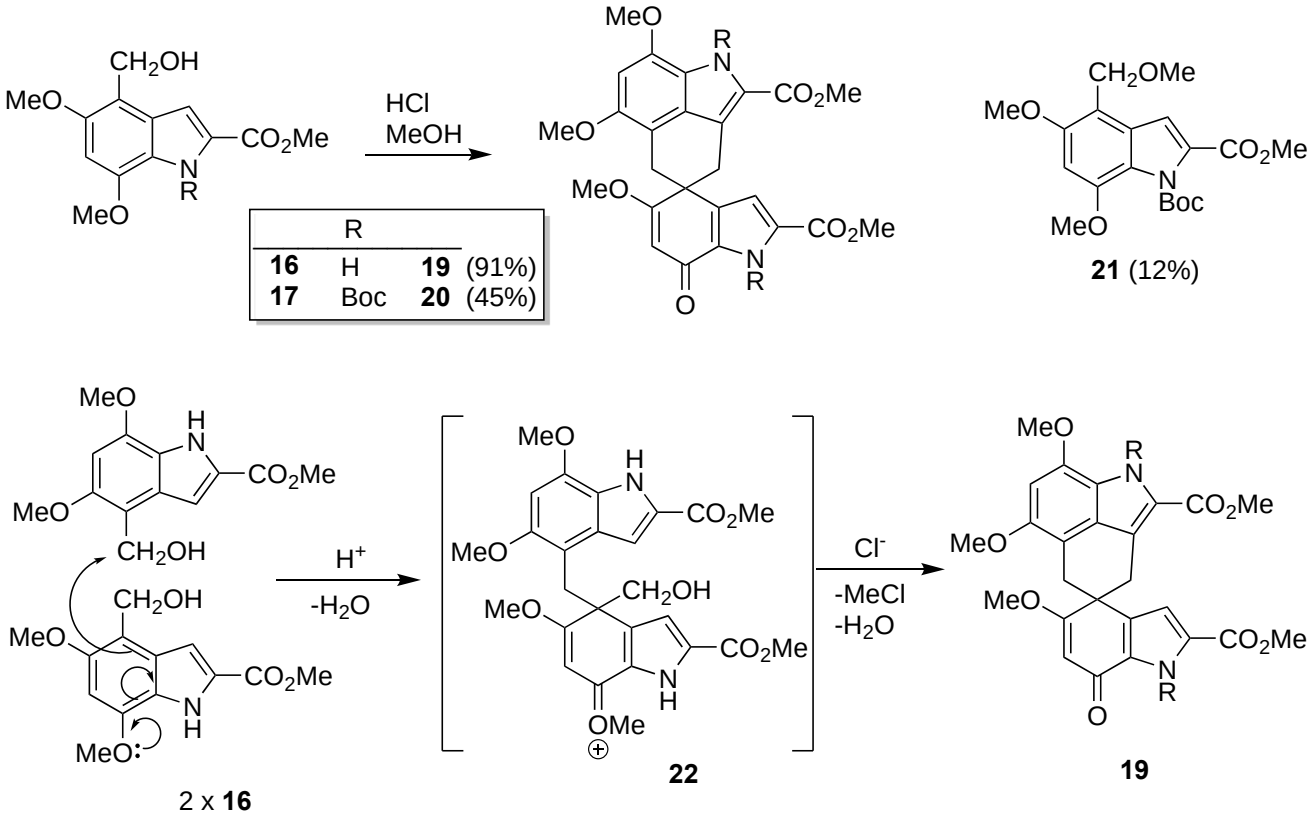
5 **15**

16 **18**

12 **17**

Scheme 2. Formation of 4,4'-diindolylmethanes **15** and **18**

In any acid-catalysed addition of an indole to formaldehyde the initial intermediate would be a hydroxymethyl derivative. Therefore the indole-4-carbaldehyde **10** was reduced by sodium borohydride to give the 4-hydroxymethylindole **16** in 77% yield: treatment of this compound with acetic acid overnight gave a 73% yield of the 4,4'-diindolylmethane **15**. The related 1-butyloxycarbonyl-4-hydroxymethylindole **17** was prepared by sodium borohydride reduction of the 1-butyloxycarbonylindole-4-carbaldehyde **12**, and in an attempt to convert this by a standard procedure[13-14] into the related 4-bromomethyl derivative, instead it gave the 1-butyloxycarbonyl-4,4'-diindolylmethane **18** in 75% yield (Scheme 2). The structure was confirmed by almost quantitative conversion of the diindolylmethane **15** into compound **18** by reaction with di-*t*-butyl carbonate in acetonitrile. The precise mechanism for the formation of the diindolylmethane **18** is not clear. Presumably the intermediate bromomethyl compound undergoes further combination with the indole **17**. However, many cases have been reported where 7-hydroxymethyl-4,6-dimethoxyindoles undergo acid-catalysed *ipso*-substitution reactions with elimination of formaldehyde to give 7,7'-diindolylmethanes,[8,9,15] (e.g. the conversion of indole **16** to diindolylmethane **15**) so the two 4-hydroxymethylindoles **16** and **17** were further investigated. When 4-hydroxymethylindole **16** was stirred in methanol with concentrated hydrochloric acid at room temperature, the spiro-dienone **19** precipitated out as a highly pure white solid in 91% yield (Scheme 3).



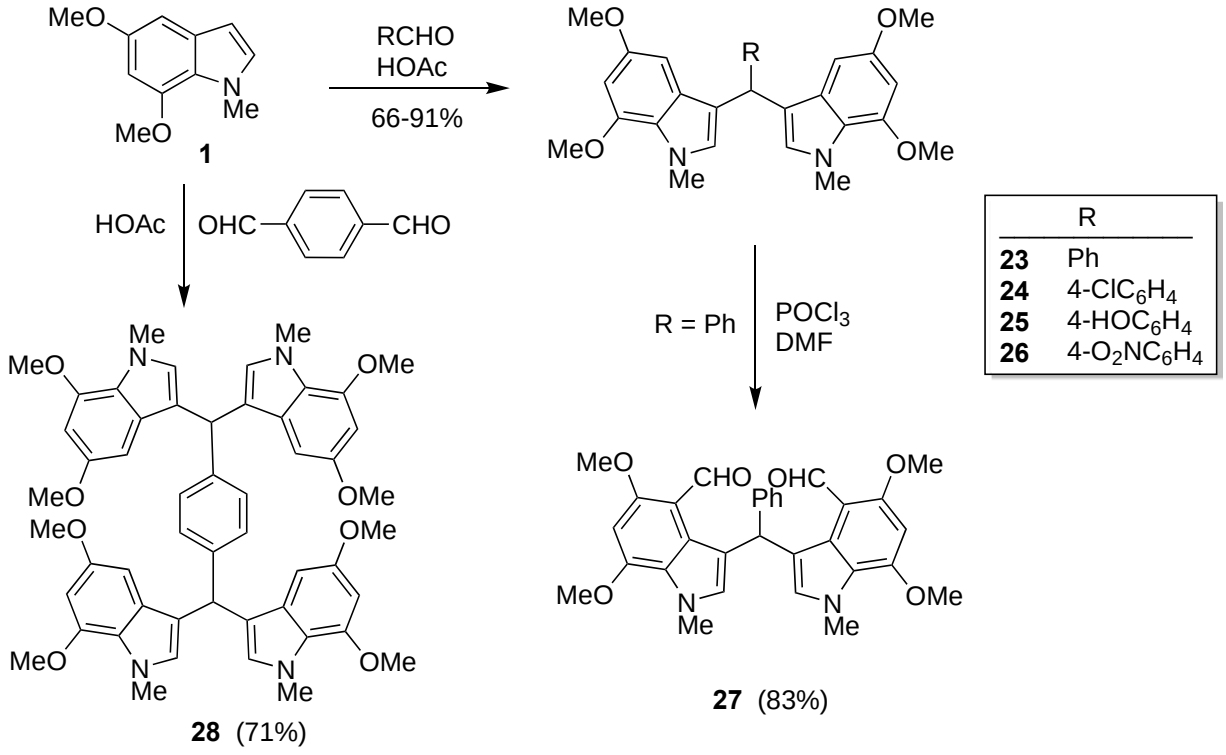
Scheme 3. Formation of indolo-spiro-dienones **19** and **20**

A similar reaction with indole **17** gave a mixture of the spiro-dienone **20** (45%), the 4,4'-diindolylmethane **18** (30%), and the 4-methoxymethylindole **21** (12%). The structure of the dienone **19** was established by extensive 1D and 2D NMR spectroscopy: a suitable crystal for X-ray structure determination could not be obtained. The ^{1}H NMR spectrum showed the presence of two NH resonances and only five methoxy proton resonances, suggesting that the compound contains two indole moieties but that one methoxy group has been lost. The ^{13}C NMR spectrum showed methoxy carbon resonances between 52 and 58 ppm representing the methoxy and ester groups. A resonance for a quaternary carbon at 44.2 ppm indicated the spiro-structure

and a resonance for the quinone-type carbonyl carbon appeared at 181.0 ppm. The proposed mechanism for the formation of the dienone **19** initially involves the electrophilic addition of a hydroxymethylene group of one molecule of indole **16** to the substituted C4 position of another molecule of indole **16** to give the C4 disubstituted indole **22**. While this intermediate might be expected to lose formaldehyde to give the diindolylmethane **15**, under these conditions electrophilic substitution occurs at the indole C3 to form the six-membered ring of the product **19.** (Scheme 3)

Reactions with aryl- and heteroaryl-aldehydes

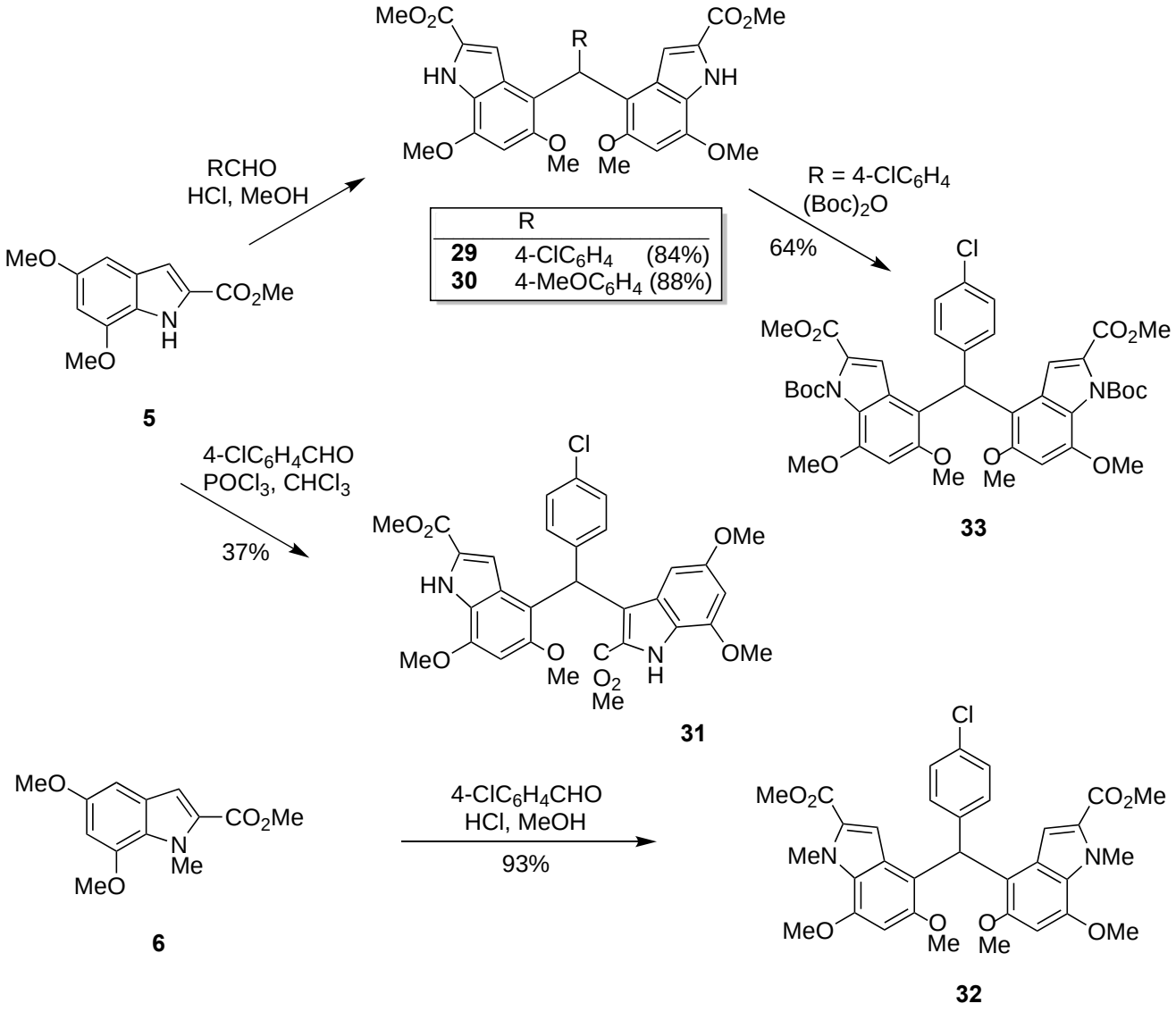
The 5,7-dimethoxyindoles **1** and **5** react readily with aryl aldehydes under acidic conditions to form diindolylmethanes. The most successful conditions involve the use of glacial acetic acid or methanolic hydrochloric acid. Indole **1** combined with a range of benzaldehydes in glacial acetic acid at room temperature to give the aryl-3,3'-diindolylmethanes **23**-**26** in 66-91% yields (Scheme 4).



Scheme 4. Formation of aryl-3,3'-diindolylmethanes **23**-**28**

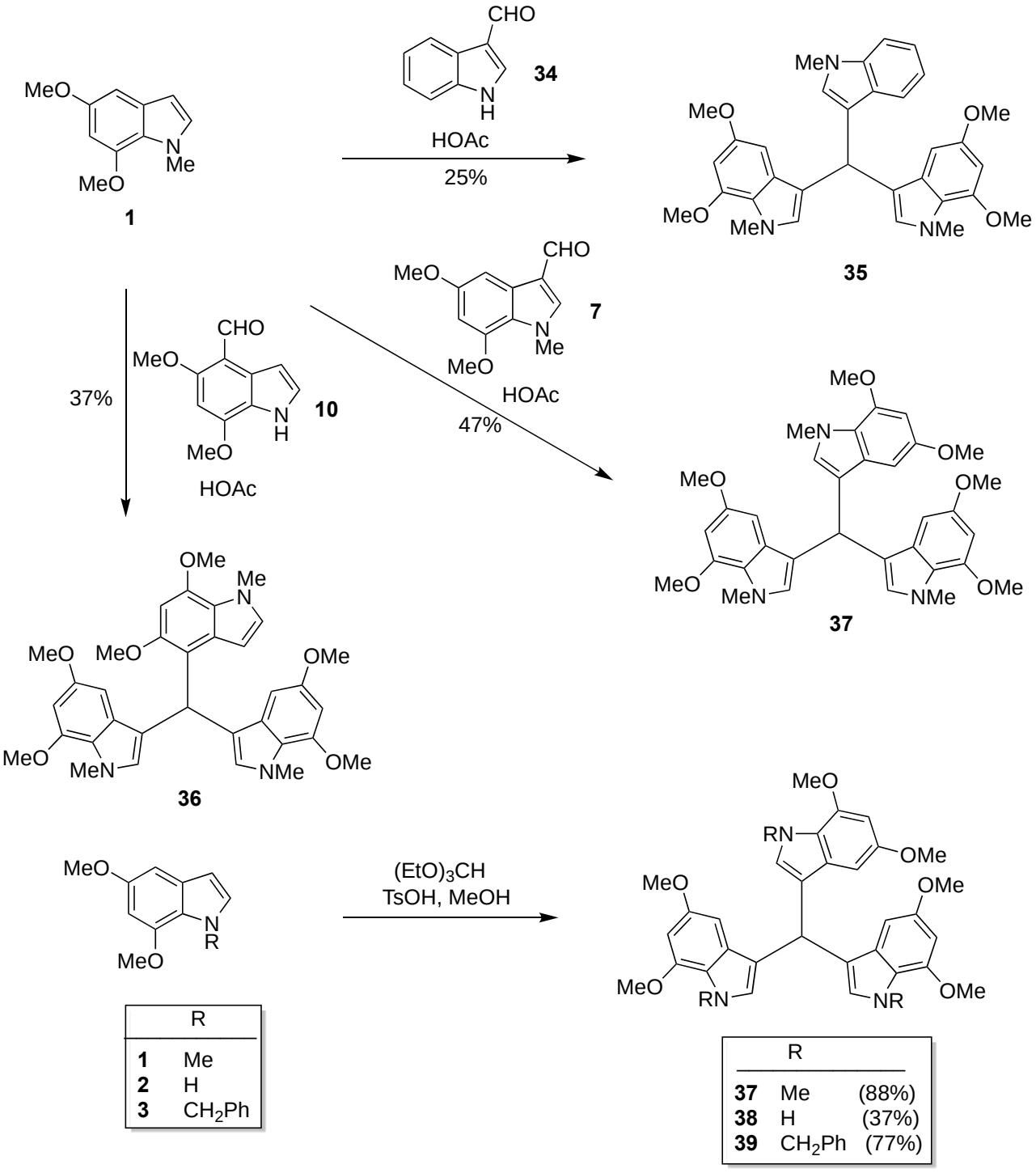
The presence of methoxy groups at C5 and C7 did not change the normal regiochemistry for the formation of diindolylmethanes.[16,17] The bond formation at C3 was established by ^{1}H NMR data showing the *meta*-coupling between H4 and H6. The diindolylmethane **23** was also converted to the 4,4'-dicarbaldehyde **27** under Vilsmeier reaction conditions. Indole **1** also reacted with terephthaldialdehyde to yield the tetraindolyl-dimethane **28** in 71% yield. In contrast, the indole **5** combined with *p*-chloro- and *p*-methoxy-benzaldehydes under the improved conditions of concentrated hydrochloric acid in methanol to give the aryl-4,4'-diindolylmethanes **29**-**30**, which precipitated out of solution in high yields (Scheme 5). Trace amounts of the more soluble 3,4'-diindolylmethane isomers were detected but not isolated and characterized. When indole **5** was reacted with *p*-chlorobenzaldehyde under the more powerful conditions of phosphoryl chloride in chloroform, a complex mixture of products was formed: after extensive chromatography only the 3,4'-diindolylmethane **31** could be isolated in 37% yield and characterized. The *N*-methyl analog **6** of the indole **5**

underwent the same reaction to give the 4,4'-diindolylmethane **32** in 93% yield. The diindolylmethane **29** was also converted to the *N*-Boc derivative **33** by reaction with di-(*t*-butyl) carbonate (Scheme 5).



Scheme 5. Formation of aryl-4,4'-diindolylmethanes **29**, **30**, **32**, **33** and aryl-3,4'-diindolylmethane **31**

In an attempt to synthesise tri-indolylmethanes, the indoles **1** and **5** were reacted with several indole aldehydes. Indole **1** reacted in glacial acetic acid with indole-3-carbaldehyde **34** to give the 3,3',3"-triindolylmethane **35** in only 25% yield. Slightly better yields of 37% and 47% were obtained in reactions with the 5,7-dimethoxyindole-4-carbaldehyde **10** and the *N*-methyl-3-carbaldehyde **7** to give the 3,3',4"-triindolylmethane **36** and the 3,3',3"-triindolylmethane **37** respectively. However, since compound **37** is completely symmetrical, its yield was dramatically increased to 88% by the reaction of indole **1** with triethyl orthoformate in methanol in the presence of a catalytic amount of *p*-toluenesufonic acid.[18-24] This reaction was more generally applied to the NH-indole **2** and the *N*-benzylindole **3** which yielded the respective 3,3'.3"-triindolylmethanes **38** and **39** in 37% and 77% yields (Scheme 6).



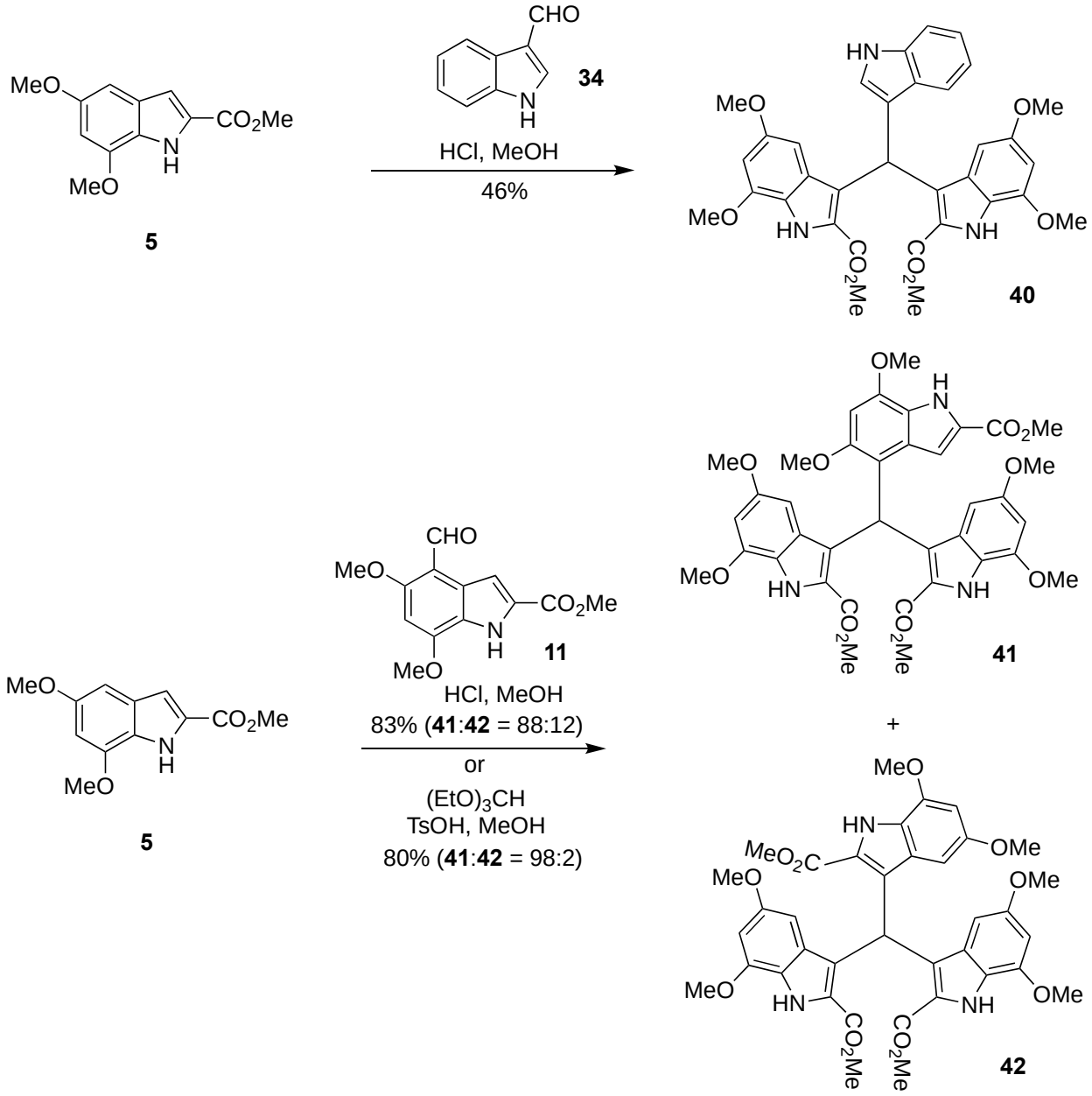
	R
1	Me
2	H
3	CH_2Ph

	R	
37	Me	(88%)
38	H	(37%)
39	CH_2Ph	(77%)

Scheme 6. Formation of 3,3’,3”-triindolylmethanes **35**, **37**-**39** and 3,3’,4”-triindolylmethane **36**

Condensation of indole **5** with indole-3-carbaldehyde **34** in methanolic hydrochloric acid gave the 3,3’,3”-triindolylmethane **40** in 46% yield, and the corresponding reaction with the methyl 5,7-dimethoxyindole-4-carbaldehyde **11** gave an 83% yield of a mixture of the 3,3’,4”-triindolylmethane **41** and the 3,3’,3”-triindolylmethane **42** in a ratio of 88:12. This result contrasts with the reaction of indole **5** with 4-chlorobenzaldehyde under the same conditions, which showed selective reaction at C4 (see Scheme 5). Presumably the greater steric bulk of the indole aldehydes **34** and **11** could be a factor in directing the reaction away from C4 to the more accessible C3. In comparison, the condensation of indole **5** with triethyl orthoformate gave an 80% yield of a mixture of the 3,3’,4”-triindolylmethane **41** and the 3,3’,3”-

triindolylmethane **42** in a ratio of 98:2 (Scheme 7). The minor product **42** presumably arises as a result of reversible steps involved in the formation of the triindolylmethanes. Several triindolylmethanes have been reported as natural products from a marine bacterium[25] and also as products from reactions of indole with *N*-methylindol-2-one or 1,3-dimethylimidazolidin-2-one and phosphoryl chloride.[26]

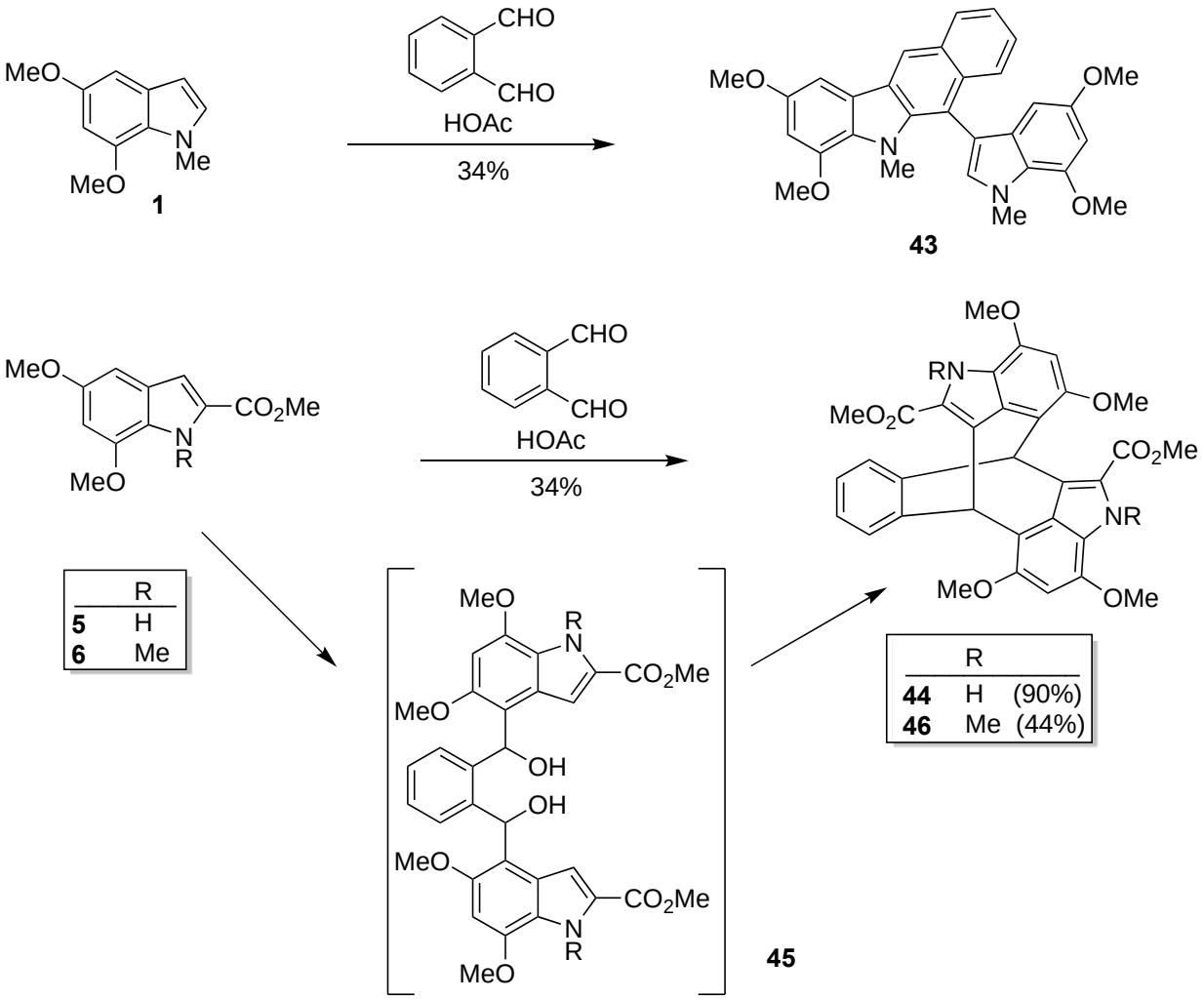


Scheme 7. Formation of 3,3',4"-triindolylmethane **41** and 3,3',3"-triindolylmethanes **40** and **42**

Reactions with *o*-phthaldialdehyde

o-Phthaldialdehyde represents a special case in reactions of aldehydes with indoles. While terephthaldialdehyde behaves normally, *o*-phthaldialdehyde has the possibility to react at two adjacent positions of an indole if they are available. We have previously shown that 1-methyl-4,6-dimethoxyindole reacts regioselectively at C2 and C3 with *o*-phthaldialdehyde to give isomeric indolylbenzocarbazoles depending on the conditions.[27] The indole **1** has positions C2, C3 and C4 available, so it was reacted with *o*-phthaldialdehyde in glacial acetic acid and found to give the 6-(3-indolyl)benzocarbazole **43** in 34% yield (Scheme 8). This is consistent with a slow reaction to give the thermodynamically more stable product, as previously described.[27]

On the other hand, indole **5** only has availability for reaction at C3 and C4: it combined with *o*-phthaldialdehyde in methanolic hydrochloric acid to give a very pure white precipitate of the hetero-triptycene **44** in 90% yield (Scheme 8). Similarly high yields were obtained when the reaction was carried out in either phosphoryl chloride or *p*-toluenesulfonic acid.



Scheme 8. Formation of indolobenzocarbazole **43** and indolotriptycenes **44** and **46**

The structure of compound **44** was established by extensive NMR spectroscopy and also by an X-ray crystal structure (Figure 2). The ^{1}H NMR spectrum showed only one NH, one H6 and three methoxy proton resonances, indicating that the two indole rings were in the same environment. A singlet at 6.90 ppm was assigned to the two bridging methines, thus establishing the presence of two 3,7'-diindolylmethane links, rather than the alternative possibility of one 3,3'-link and one 7,7'-link. The suggested mechanism proceeds via the intermediate **45** as a result of indole C7 attack on each formyl group (Scheme 8). The *N*-methylindole **6** also reacted with *o*-phthaldialdehyde to give the *N*-methylated triptycene **46** in 44% yield. The lower yield is thought to be a function of the greater solubility of the product, and no attempt was made to obtain a second crop from the filtrate after collecting the product. The characteristic triptycene structure has been put to use in a variety of applications, including materials chemistry, host-guest chemistry, and molecular motors.[28]

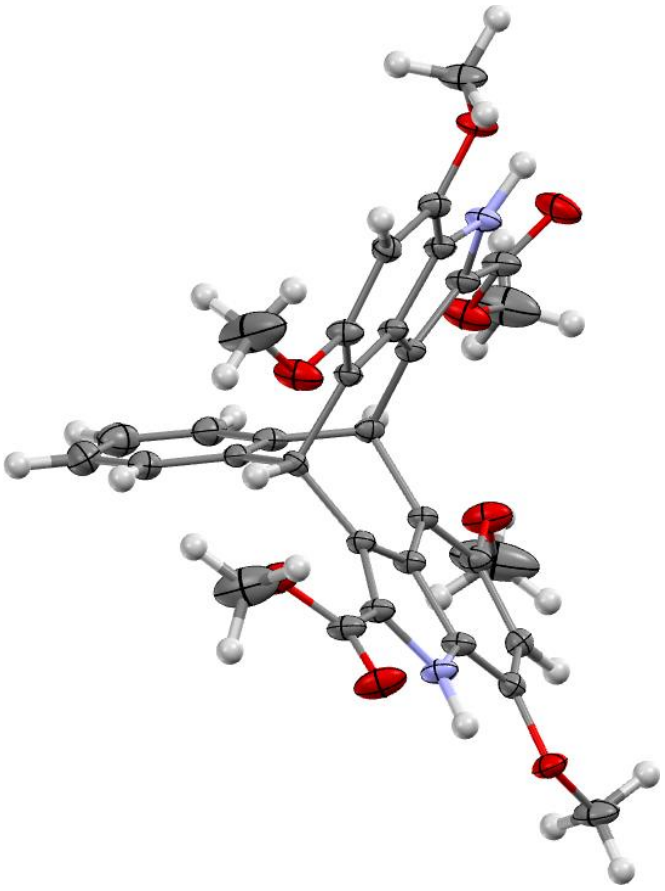
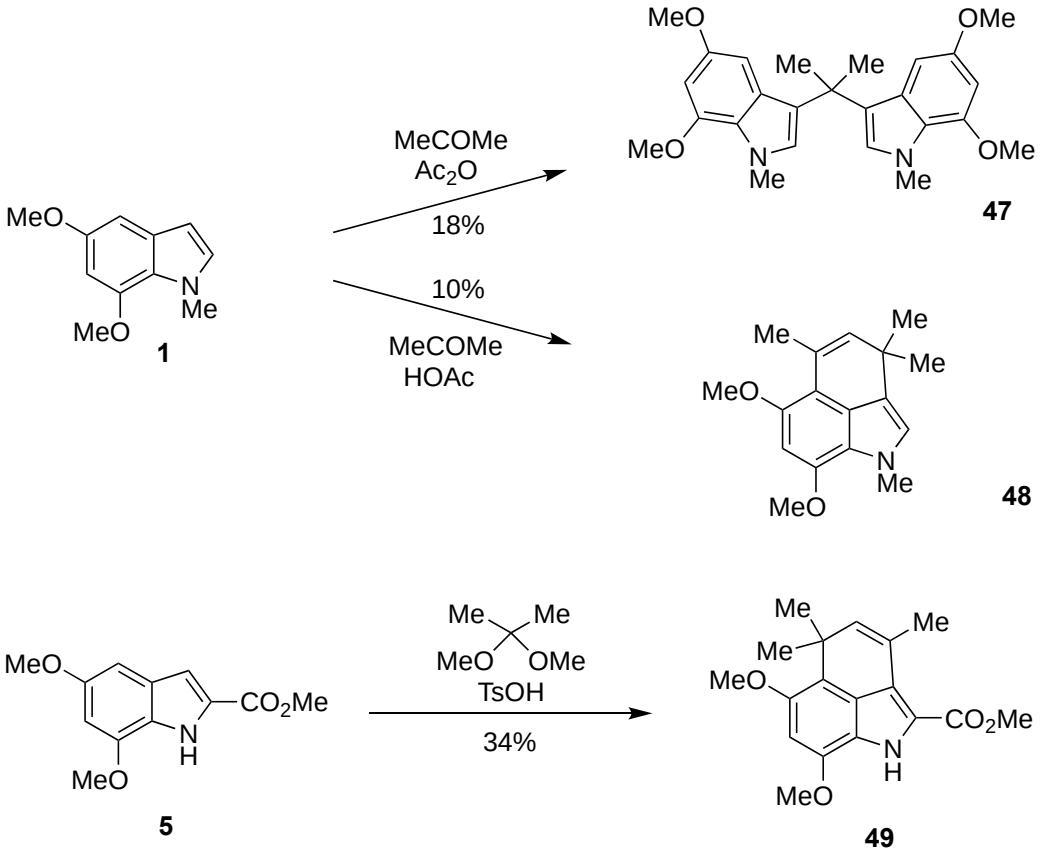


Figure 2. ORTEP diagram of compound **44**

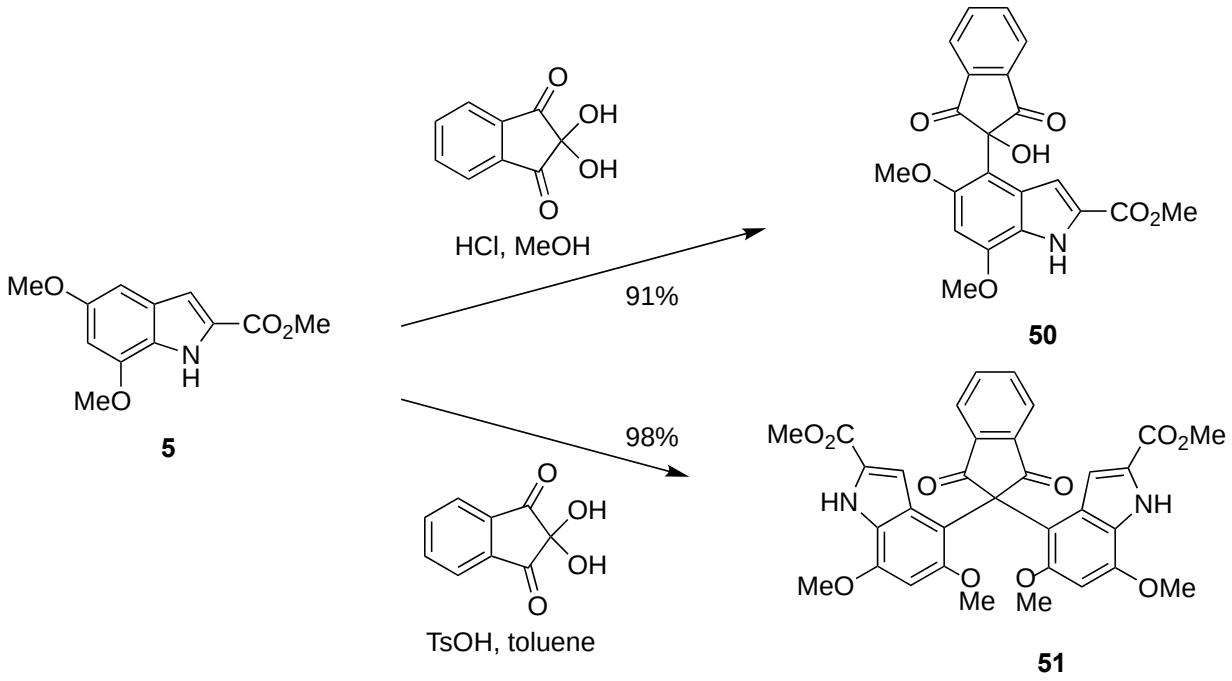
Reactions with ketones

Neither indole **1** nor **5** underwent any reaction with a range of acetophenones. The *N*-methylindole **1** underwent reaction with acetone and acetic anhydride to give the 3,3'-diindolylmethane **47** in a yield of 18%. When glacial acetic acid was used as the solvent an even lower yield (10%) of the benzo[*cd*]indole **48** was obtained from a complex mixture. The acid-catalysed condensation of indole and acetone is known to give rise to multiple products.[17,29] Indole **5** failed to react with acetone, but it did react when heated in 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid to give the benzo[*cd*]indole **49** in 34% yield (Scheme 9). The two benzoindoles **48** and **49** show different methyl substitution patterns, indicating that the initial attack for indole **1** takes place from C3, while that for indole **5** takes place from C4. The mechanism appears to be a stepwise intramolecular aldol-type, because neither indole **1** nor **5** showed any reaction with mesityl oxide. The structures of benzindoles **48** and **49** were established by extensive 1D and 2D NMR experiments. Other benz[*cd*]indole structures have been reported in similar reactions.[30]



Scheme 9. Formation of benz[*cd*]indoles **48** and **49**

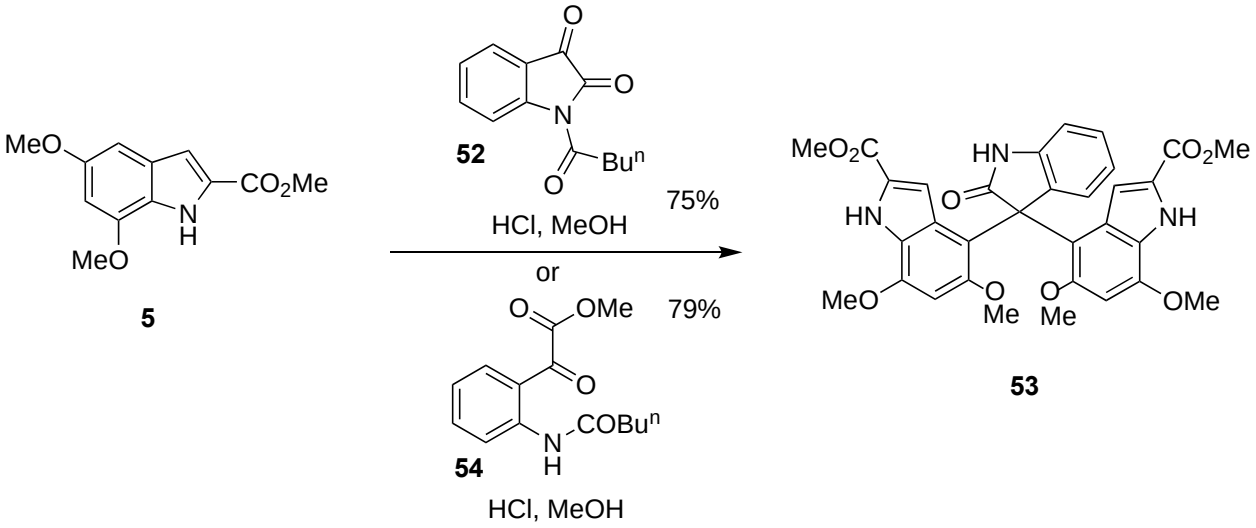
The indole **5** underwent reaction with two reactive ketones, ninhydrin and 1-pentanoylisatin. When indole **5** and ninhydrin were heated together in methanol with concentrated hydrochloric acid a yellow precipitate of the 1:1 adduct **50** was obtained in 91% yield, regardless of the stoichiometry. However, when



Scheme 10. Formation of 2-(4-indolyl)indane-1,3-dione **50** and 2,2-di(4-indolyl)indane-1,3-dione **51**

two equivalents of indole **5** and one of ninhydrin were heated together in toluene with a catalytic amount of *p*-toluenesulfonic acid, initial formation of the adduct **50** was observed, but continued heating for two days showed that this was converted into the 4,4'-diindolylmethane **51** in 98% yield (Scheme 10).

Indole **5** failed to undergo any reaction with isatin but it reacted with the more reactive 1-pentanoylisatin **52** when heated in methanol with concentrated hydrochloric acid to give the 4,4'-diindolylmethane **53** in 75% yield (Scheme 11). Under these conditions it is known[31,32] that the 1-pentanoylisatin could undergo ring-opening following attack at C2 by methanol to give the related methyl glyoxylate **54**, which could then react with the indole **5**. Subsequent hydrolysis of the amide and cyclisation, for which there is precedent,[33] would then generate the observed product **53**. This possibility was checked and it was found that compound **53** was obtained in 79% yield when indole **5** and the methyl glyoxylate **54** were reacted together under the same conditions (Scheme 11). Some 3,3-diindolylindolin-2-ones are known where the indoles are linked through C3 and also C2: these compounds show interesting biological activity.[34]



Scheme 11. Formation of 3,3-di(4-indolyl)oxindole **53**

Conclusions

A wide range of acid-catalysed reactions of 5,7-dimethoxyindoles with aldehydes and ketones has established many high yielding syntheses of diindolyl- and triindolyl-methanes, with linkages from C3 and C4. The reactions are most successful with formaldehyde, aryl aldehydes and highly reactive ketones. Aryl aldehydes give rise to aryldiindolylmethanes, while reactions with indole aldehydes yield triindolylmethanes. Reactions with *o*-phthalaldehyde generate triptycene analogs of novel structure. Unusual spiro-dienones can also be formed by double reaction at C4, and reactions with acetone give benzo[*cd*]indoles, although only in modest yield.

In summary: the positioning of methoxy groups at C5 and C7 on the indole framework greatly expands the synthetic potential of indole reactivity.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300F (^{1}H: 300MHz, ^{13}C: 75.5 MHz) or a Bruker AM500 spectrometer. The chemical shifts (δ) and coupling constants (*J*) are expressed in ppm and hertz

respectively. Carbon attribution C, CH, CH_2 and CH_3 were determined by ^{13}C, DEPT and HMQC experiments. Infrared (IR) spectra were recorded on a Mattson Genesis Series FTIR spectrometer using potassium bromide disks, except where specified. Ultraviolet and visible (UV/Vis) spectra were recorded in tetrahydrofuran or methanol using a Carey 100 spectrometer. Mass spectra were recorded on a VG Quattro MS (EI) or a Finnigan MAT (MALDI). High resolution mass spectrometry (HRMS) was carried out at the Research School of Chemistry, Australian National University. Melting points were measured using a Mel-Temp melting point apparatus. Microanalyses were performed at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. Column chromatography was carried out using Merck 230-400 mesh silica gel or Merck 70-230 mesh silica gel, whilst preparative TLC was performed using Merck 60GF_{254} silica gel. X-ray crystallography was conducted with a suitable single crystal and crystallographic data excluding structure factors have been deposited with the Cambridge Crystallographic Data Centre: Compound **44** – Deposition Number 2004528

Methyl 1-(*tert*-butyloxycarbonyl)-4-formyl-5,7-dimethoxyindole-2-carboxylate (**12**)**.** A suspension of methyl 4-formyl-5,7-dimethoxyindole-2-carboxylate (**11**) (0.49 g, 1.85 mmol), di-*tert*-butyl dicarbonate (0.79 g, 3.62 mmol) and *N,N*-dimethylaminopyridine (48 mg) in anhydrous acetonitrile (12.0 mL) was stirred at room temperature, under nitrogen, for 70 min. The solvent was then evaporated *in vacuo* and the remaining residue purified *via* suction column chromatography (dichloromethane) to give the title compound (0.66 g, 98%) as a colourless syrup that solidified upon standing, mp 164-166 ˚C. IR (ν_{max}, cm^{-1}): 1755, 1714, 1661, 1585, 1399, 1367, 1233, 1156, 1108. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 242 (21,600), 267 (12,000), 321 (18,500), 354 (11,700), 369 (8,300); ^1H NMR (300 MHz, $CDCl_3$): δ_H 1.64 (9H, s, CMe_3), 3.90, 3.94, 3.99 (each 3H, s, OMe), 6.42 (1H, s, H6), 7.98 (1H, s, H3), 10.49 (1H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.8 (CMe_3), 52.5, 57.4, 56.2 (OMe), 85.6 ($\underline{C}Me_3$), 93.2 (C6), 112.0 (C3), 111.1, 123.3, 126.4, 130.5, 150.6, 153.2 (aryl C), 162.8 and 161.4 (CO and $\underline{C}O_2Me$), 188.8 (CHO). MS (+EI, *m/z*, %): 363 (M, 5), 290 (14), 264 (12), 263 (100), 232 (20), 231 (97), 230 (32), 214 (13), 204 (17), 203 (11), 202 (63), 188 (13), 174 (22), 160 (17), 144 (11). Anal. calcd for $C_{18}H_{21}NO_7$: C, 59.5; H, 5.8; N, 3.8. Found: C, 59.5; H, 5.8; N, 3.6 %.

4,4'-Bis(5,7-dimethoxy-1-methylindolyl)methane-3,3'-dicarbaldehyde (**13**)**.** 5,7-Dimethoxy-1-methylindole-3-carbaldehyde (**7**) (0.15 g, 0.69 mmol) was dissolved in glacial acetic acid (3 mL) and the reaction mixture was put under an inert gas atmosphere. Aqueous formaldehyde solution (37%, 0.04 mL, 0.54 mmol) was added, and the reaction mixture was stirred at room temperature for 6 h. The resulting precipitate was filtered, washed with water and dried, affording 4,4'-di(5,7-dimethoxy-1-methylindolyl)methane-3,3'-dicarbaldehyde **13** (0.10 g, 66%) as a white solid, mp 294-295 ˚C. IR (vmax, cm^{-1}): 1643, 1584, 1528, 1496, 1453, 1415, 1315, 1245, 1210, 1119, 1062. UV/Vis (λmax, nm, ε, $cm^{-1}M^{-1}$): 257 (24,000), 270 (19,000), 314 (13,000), 333 (14,000). ^1H NMR (300 MHz, $CDCl_3$): δ_H 3.43, 3.84 and 4.04 (18H, s, OMe and NMe), 4.99 (2H, s, CH_2), 6.34 (2H, s, H6), 7.72 (2H, s, H2), 10.36 (2H, s, CHO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 29.0 (CH_2), 37.9 (C x 2, NMe), 55.6 and 57.1 (C x 4, OMe), 93.7 (C x 2, aryl CH), 115.9, 119.5, 123.1, 128.8, (C x 8, aryl C), 139.2 (C x 2, aryl CH), 146.2 and 154.6 (C x 4, aryl C), 185.8 (C x 2, CHO). MS (+EI, *m/z*, %): 450 (M, 13), 419 (11), 232 (33), 231 (49), 216 (45), 203 (100). Anal. calcd for $C_{25}H_{26}N_2O_6$: C, 66.7; H, 5.8; N, 6.2. Found: C, 66.7; H, 5.5; N, 6.0 %.

4,4'-Bis(1-acetyl-5,7-dimethoxyindolyl)methane (**14**)**.** 1-Acetyl-5,7-dimethoxyindole **4** (0.10 g, 0.46 mmol), 37% aqueous formaldehyde solution (0.03 mL, 0.40 mmol) and glacial acetic acid (2 mL) were combined and stirred at room temperature for 2 d under an inert gas atmosphere. The solution was diluted with water and the resulting turbid mixture was allowed to stand overnight before being filtered. The filtered material was washed with water and dried, affording 4,4'-di(1-acetyl-5,7-dimethoxyindolyl)methane **14** (23 mg, 22%) as a grey powder. Radial chromatography using 1:39 methanol : dichloromethane gave a colourless oil which solidified to yield a white solid, mp 157-159 ˚C. IR (ν_{max}, cm^{-1}): 1692, 1599, 1371, 1328, 1268, 1246, 1221,

1199, 1110, 1101. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 325 (17,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.58 (6H, s, COMe), 3.88 and 3.92 (12H, s, OMe), 4.30 (2H, s, CH_2), 6.53 (2H, s, H6), 6.66 (2H, d, *J* 3.8 Hz, H3), 7.47 (2H, d, *J* 3.8 Hz, H2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.4 (CH_2), 25.7 (C x 2, CO<u>Me</u>), 56.0 and 57.0 (C x 4, OMe), 94.7 and 107.5 (C x 4, aryl CH), 114.1 and 119.7 (C x 4, aryl C), 127.8 (C x 2, aryl CH), 134.7, 146.5 and 153.9 (C x 6, aryl C), 169.4 (C x 2, <u>C</u>OMe). MS (+EI, *m/z*, %): 451 (M+1, 24), 450 (M, 100), 408 (45), 335 (38), 190 (47), 189 (52), 160 (86). HRMS (*m/z*): Calcd for $C_{25}H_{26}N_2NaO_6$ $[M+Na]^+$, 473.1683. Found: 473.1656.

The filtrate was extracted with dichloromethane, and the organic phase was washed with water and saturated $NaHCO_3$ solution, dried (Na_2SO_4), and the solvent removed under reduced pressure affording 4,4'-di(1-acetyl-5,7-dimethoxyindolyl)methane **14** (36 mg, 35%) as an off-white powder. This product was confirmed by comparison with the other product obtained from this reaction using thin layer chromatography and ^{1}H NMR spectroscopy.

Dimethyl 4,4'-methylenebis[5,7-dimethoxy-1*H*-indole]-2,2'-dicarboxylate (**15**)**. Method A.** A solution of methyl 4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate **16** (50 mg, 0.19 mmol) in glacial acetic acid (2.0 mL) was stirred at room temperature for 5 d. The resulting precipitate was filtered through a frit, washed twice with acetic acid (1 mL), then with water, and dried to give the title compound (33 mg, 73%) as a white powder, mp 292-294 ˚C. IR (ν_{max}, cm^{-1}): 3321, 1690, 1590, 1536, 1437, 1351, 1330, 1253, 1211, 1094. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 241 (54,700), 276 (16,800, sh), 297 (53,200), 337 (8,620). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.87, 3.88, 3.94 and (each 6H, s, OMe), 4.40 (2H, s, bridging CH_2), 6.55 (2H, s, H6), 7.26 (2H, d, *J* 2.3 Hz, H3), 8.79 (2H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.6 (bridging CH_2), 51.6, 55.4, 58.2 (OMe), 62.2 (<u>C</u>O_2Me), 95.5 (C6), 108.7 (C3), 114.7, 124.2, 126.6, 128.8, 144.8, 151.2 (aryl C). MS (MALDI, *m/z*, %): 482 (M, 36), 481 (M-1, 100). Anal. calcd for $C_{25}H_{26}N_2O_8$: C, 62.2; H, 5.4; N, 5.81. Found: C, 62.0; H, 5.5; N, 5.8 %.

Method B. A solution of methyl 5,7-dimethoxyindole-2-carboxylate **5** (50 mg, 0.21 mmol) and 4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate **16** (56 mg, 0.21 mmol) in glacial acetic acid (2.0 mL) was stirred at room temperature for 75 min. The resulting precipitate was filtered through a frit, washed successively with a little acetic acid, water, saturated $NaHCO_3$ solution, water, and then dried to give the title compound (71 mg, 70%) as a white powder.

Method C. A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.25 g, 1.06 mmol) and formaldehyde (0.2 mL) in anhydrous methanol (7 mL) was stirred at room temperature with concentrated HCl (1 drop) for 19 h. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (70 mg, 27%) as a white powder.

Method D. A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.25 g, 1.06 mmol) and 40% aqueous formaldehyde (10 drops) in glacial acetic acid (4.0 mL) was stirred at room temperature for 3 d. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (0.22 g, 85%) as a white powder.

Methyl 4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate (**16**)**.** Sodium borohydride (1.44 g, 38 mmol) was added portionwise to a stirred suspension of methyl 4-formyl-5,7-dimethoxyindole-2-carboxylate **11** (1.00 g, 3.80 mmol) in methanol (100 mL) and stirring was continued at room temperature for 5.5 h. The mixture was then diluted with water and extracted with ethyl acetate. The organic extract was dried ($MgSO_4$) and the solvent evaporated *in vacuo* to give the title compound (0.78 g, 77%) as a white powder, mp 148-151 ˚C. IR (ν_{max}, cm^{-1}): 3477, 3177, 1717, 1698, 1594, 1538, 1455, 1432, 1327, 1260, 1217, 1199, 1175, 1148, 1122, 1094, 990. UV/Vis (λmax, nm, ε, $cm^{-1}M^{-1}$): 242 (29,300), 295 (19,000), 327 (4,640); δ_H (300 MHz, $CDCl_3$) 2.16 (1H, bs, CH_2O<u>H</u>), 3.97, 3.93, 3.91 (each 3H, s, OMe), 4.91 (2H, d, *J* 3.0 Hz, C<u>H</u>$_2$OH), 6.52 (1H, s, H6), 7.25 (1H, d, *J* 2.3 Hz, H3), 9.01 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 51.9, 55.5, 57.8 and (OMe); 57.8 (<u>C</u>H_2OH), 94.0 (C6), 106.8

(C3), 112.7, 123.7, 127.6, 128.0, 146.4, 152.5 (aryl C), 162.0 ($\underline{C}O_2Me$). MS (+EI, *m/z*, %): 266 (10), 265 (M, 100), 248 (23), 234 (17), 233 (80), 232 (37), 216 (76), 204 (25). Anal. calcd for $C_{13}H_{15}NO_5.0.33\ H_2O$: C, 57.6; H, 5.8; N, 5.2. Found: C, 57.4; H, 5.7; N, 5.0 %.

Methyl 1-(*tert*-butyloxycarbonyl)-4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate (**17**)**.** Sodium borohydride (0.12 g, 3.2 mmol) was added portionwise, over 15 min, to a stirred suspension of methyl 1-(*tert*-butyloxycarbonyl)-4-formyl-5,7-dimethoxyindole-2-carboxylate **12** (0.30 g, 0.83 mmol) in methanol (20 mL). After stirring for 15 min further at room temperature, the solvent was evaporated *in vacuo* and the remaining residue suspended in 1M NaOH and extracted with ethyl acetate. The organic extract was washed twice with 1M NaOH, then twice with brine, dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give the title compound (0.273 g, 90%) as a colourless crystalline solid, mp 138-141 ˚C. IR (ν_{max}, cm^{-1}): 3559, 1765, 1704, 1592, 1542, 1437, 1253, 1222, 1158, 1144, 1089, 999. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 241 (27,800), 294 (17,600), 334 (4,580). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.64 (9H, s, CMe_3), 2.05 (1H, bs, $CH_2O\underline{H}$), 3.93, 3.90, 3.89 (each 3H, s, OMe), 4.87 (2H, s, $C\underline{H_2}OH$), 6.55 (1H, s, H6), 7.28 (1H, s, H3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.3 (CMe_3), 51.9, 55.6, 57.5 (OMe), 57.5 ($\underline{C}H_2OH$), 84.6 ($\underline{C}Me_3$), 95.3 (C6), 109.1 (C3), 161.0 ($\underline{C}O_2Me$), 112.8, 123.2, 127.6, 128.3, 146.9, 150.5, 153.0 (aryl C). MS (+EI, *m/z*, %): 365 (M, 6), 292 (10), 265 (77), 248 (20), 234 (13), 233 (100), 216 (36), 204 (22), 149 (22). Anal. calcd for $C_{18}H_{23}NO_7$: C, 59.2; H, 6.3; N, 3.8. Found: C, 59.0; H, 6.4; N, 3.8 %.

Dimethyl 4,4'-methylenebis[1-(tert-butyloxycarbonyl)-5,7-dimethoxy-1*H*-indole]-2,2'-dicarboxylate (**18**)**.**
Method A. A solution of bromine (27 mg, 0.17 mmol) in carbon tetrachloride (1.5 mL) was added dropwise to a stirred suspension of triphenylphosphine (40 mg, 0.15 mmol) in carbon tetrachloride (1.0 mL). The resulting yellow suspension was stirred further for 25 min, under nitrogen, at room temperature before triethylamine (17 mg, 0.17 mmol) in carbon tetrachloride (1.0 mL) was added and stirring continued for 20 min. A solution of methyl 1-(*tert*-butyloxycarbonyl)-4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate **17** (0.56 mg, 0.15 mmol) in carbon tetrachloride (4 mL) was then added dropwise and stirring continued for 2 d. The solvent was then evaporated *in vacuo* and the remaining residue purified *via* gravity column chromatography (2% $MeOH/CH_2Cl_2$) to give the title compound (39 mg, 75%) as a colourless crystalline solid, mp 179-180 ˚C. IR (ν_{max}, cm^{-1}): 1771, 1720, 1590, 1396, 1371, 1258, 1234, 1157, 1083. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 241 (54,000), 294 (33,800), 344 (10,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.60 (18H, s, CMe_3), 3.86 (12H, s, OMe), 3.89 (6H, s, OMe), 4.32 (2H, s, bridging CH_2), 6.56 (2H, s, H6), 7.37 (2H, s, H3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.3 (bridging CH2), 27.3 ($C\underline{Me}_3$), 51.7, 55.5, 57.5, (OMe), 84.2 ($\underline{C}Me_3$), 96.2 (C6), 111.1 (C3), 114.2, 123.5, 127.3, 128.3, 145.4, 150.8, 151.7 (CO and aryl C), 161.2 ($\underline{C}O_2Me$). MS (MALDI, *m/z*, %): 682 (M, 42), 582 (18), 482 (100), 248 (69). Anal. calcd for $C_{35}H_{42}N_2O_{12}$: C, 61.6; H, 6.2; N, 4.1. Found: C, 61.5; H, 6.3; N, 4.0 %.
Method B. A suspension of dimethyl 4,4'-methylenebis[5,7-dimethoxy-1H-indole]-2,2'-dicarboxylate **15** (50 mg, 0.10 mmol) and di-(*t*-butyl)carbonate (125 mg, 0.57 mmol) in acetonitrile (3.0 mL) was stirred at room temperature, under nitrogen, with a catalytic quantity of 4-dimethylaminopyridine for 23 h. The solvent was then evaporated *in vacuo* and the remaining residue purified *via* suction column chromatography (1% $MeOH/CH_2Cl_2$) to give compound **18** (67 mg, 95%) as a white solid.

Dimethyl [1,3,4,5-tetrahydro-6,8-dimethoxybenz[*c,d*]indole]-4-spiro-4'-[1,4,7-trihydro-5'-methoxyindol-7-one]-2,2'-dicarboxylate (**19**)**.** Methyl 4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate 1**6** (77 mg, 0.30 mmol) in methanol (15 mL) was stirred at room temperature with concentrated HCl (1 drop) for 3 h. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (66 mg, 91%) as a pale yellow powder, mp 291-292 ˚C. IR (ν_{max}, cm^{-1}): 3324, 1727, 1696, 1641, 1464, 1334, 1278, 1254, 1229. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 244 (41,000), 287 (24,000), 299 (34,500), 312 (21,700), 347 (7,300).

^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.88 (1H, d, *J* 15.8 Hz, CH_2), 3.08 (1H, d, *J* 16.6 Hz, CH_2), 3.44 (1H, d, *J* 15.8 Hz, CH_2), 3.61 (1H, d, *J* 16.6 Hz, CH_2), 3.71, 3.78, 3.85, 3.89, 4.01 (each 3H, s, OMe), 5.37 (1H, d, *J* 2.3 Hz, H3'), 5.81 (1H, s, H6'), 6.55 (1H, s, H6), 8.74, 9.58 (2H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 32.5, 33.3 (CH_2), 44.2 (alkyl C), 52.1, 56.1, 57.0, 58.4 (OMe), 97.1 (C6), 102.8 (C6'), 112.9 (C3'), 108.2, 118.9, 121.3, 123.6, 126.0, 128.2, 128.3, 136.3, 145.6, 151.1 (aryl C), 161.4, 162.9 ($\underline{C}O_2Me$), 178.3 and 181.0 (C5 and quinone CO). MS (MALDI, *m/z*, %): 503 (M+Na, 10), 480 (M, 52), 479 (100); MS (+EI, *m/z*, %): 481 (23), 480 (M, 100), 449 (27), 448 (37), 421 (41), 417 (16), 416 (13), 389 (43), 345 (13), 167 (22), 149 (50). HRMS (*m/z*): Calcd for $C_{25}H_{24}N_2O_8$ $[M]^+$, 480.1533. Found: 480.1528. Anal. calcd for $C_{25}H_{24}N_2O_8.0.5\ H_2O$: C, 61.3; H, 5.1; N, 5.7. Found: C, 61.2; H, 4.9; N, 5.8 %.

Acid catalyzed reaction of methyl 1-(*tert*-butyloxycarbonyl)-4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate (**17**)**.** Methyl 1-(*tert*-butyloxycarbonyl)-4-hydroxymethyl-5,7-dimethoxyindole-2-carboxylate **17** (50 mg, 0.14 mmol) in methanol (1.5 mL) was stirred at room temperature with concentrated HCl (1 drop) for 40 min. The resulting precipitate was filtered through a frit, washed sequentially with a little methanol and water, and dried to give the diindolylmethane **18** (8 mg, 17%) as a white powder. The reaction filtrate and methanolic washings were combined and stirred for a further 4 d. The solvent was then evaporated *in vacuo* and the remaining residue purified *via* gravity column chromatography (1% $MeOH/CH_2Cl_2$) to give the three following products:

Dimethyl 4,4'-methylenebis[1-(*tert*-butyloxycarbonyl)-5,7-dimethoxy-1*H*-indole]-2,2'-dicarboxylate (**18**) (6 mg, 13%) was obtained as a white powder.

Dimethyl [1-(tert-butyloxycarbonyl)-1,3,4,5-tetrahydro-6,8-dimethoxybenz[*c,d*]indole]-4-spiro-4'-[1-(*tert*-butyloxycarbonyl)-1,4,7-trihydro-5'-methoxyindol-7-one]-2,2'-dicarboxylate (**20**)**.** (21 mg, 45%) was obtained as a white powder, mp 153-157 ˚C. IR (ν_{max}, cm^{-1}): 1779, 1720, 1594, 1456, 1371, 1257, 1220, 1157. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 246 (27,000), 297 (17,000), 340 (13,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.61 and 1.64 (each 9H, s, CMe_3), 2.93 (1H, d, *J* 15.8 Hz, CH_2), 3.07 (1H, d, *J* 17.0 Hz, CH_2), 3.16 (1H, d, *J* 16.6 Hz, CH_2), 3.42 (1H, d, *J* 17.0 Hz, CH_2), 3.68, 3.78, 3.82, 3.90, 3.96 (each 3H, s, OMe), 5.52 (1H, s, H3'), 5.64 (1H, s, H6'), 6.58 (1H, s, H6). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.7 and 27.9 (CMe_3), 33.3 and 33.6 (CH_2), 43.4 (alkyl C), 52.1, 52.2, 56.3, 56.5, 57.9 (OMe), 84.6 and 86.4 ($\underline{C}Me_3$), 98.5 and 99.6 (C6' and C6), 114.5 (C3'), 109.1, 122.6, 125.5, 128.0, 133.3, 146.4, 149.8, 151.3, 152.3, 160.6 (aryl C), 162.0 and 163.1 ($\underline{C}O_2Me$), 177.2 and 179.6 (C5' and quinone CO). MS (MALDI, *m/z*, %): 482 (76), 450 (100), 422 (97).

Methyl 1-(*tert*-butyloxycarbonyl)-5,7-dimethoxy-4-methoxymethylindole-2-carboxylate (**21**)**.** (6 mg, 12%) was obtained as a pale yellow powder. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.64 (9H, s, CMe_3), 3.35 (3H, s, $CH_2O\underline{Me}$), 3.88, 3.90, 3.93 (9H, s, OMe), 4.70 (2H, s, $C\underline{H_2}OMe$), 6.55 (1H, s, H6), 7.30 (1H, s, H3). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 27.3 (CMe_3), 51.9, 55.6, 57.6, 58.0 (OMe), 65.7 ($\underline{C}H_2OMe$), 84.5 ($\underline{C}Me_3$), 95.8 (C6), 109.9 (C3), 161.1 ($\underline{C}O_2Me$), 110.4, 123.4, 128.1, 128.5, 147.1, 150.6, 153.5 (CO and aryl C).

3,3'-Bis(5,7-dimethoxy-1-methylindolyl)phenylmethane (**23**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.10 g, 0.53 mmol), benzaldehyde (0.05 mL, 0.53 mmol) and glacial acetic acid (2 mL) were combined and stirred at room temperature for 3 h. The resulting precipitate was filtered, washed with water and dried to give 3,3'-bis-(5,7-dimethoxy-1-methylindolyl)phenylmethane **23** (94 mg, 76%) as a white powder, mp 195 ˚C. IR (ν_{max}, cm^{-1}): 1582, 1497, 1458, 1414, 1279, 1205, 1147, 1117, 1047, 809. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 213 (49,000), 229 (54,000), 266 (12,000), 273 (11,000), 299 (11,000), 307 (10,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.66 (6H, s, NMe), 3.88 (12H,s, OMe), 5.64 (1H, br s, CH), 6.28 (2H, d, *J* 2.0 Hz, H6), 6.33 (2H, d, *J* 2.0 Hz, H4), 6.37 (2H, s, H2), 7.23 (5H, m, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.1 (2C, NMe), 40.1 (CH), 55.3 and 55.7 (4C, OMe),

93.3 and 94.2 (4C, aryl CH), 117.8 and 122.5 (4C, aryl C), 125.8 (phenyl CH), 128.1 and 128.7 (4C, phenyl CH), 129.1 (2C, aryl CH), 129.6 (2C, aryl CH), 144.5 (phenyl C), 147.9 and 153.9 (4C, aryl C). MS (+EI, *m/z*, %): 471 (M, 28), 470 (100), 455 (32), 394 (17), 393 (72), 235 (28), 177 (40). HRMS (*m/z*): Calcd for $C_{29}H_{30}N_2NaO_4$ $[M+Na]^+$, 493.2098. Found: 493.2108. Anal. calcd for $C_{29}H_{30}N_2O_4$: C, 74.0; H, 6.4; N, 6.0. Found: C, 73.7; H, 6.4; N, 5.6 %.

3,3'-Bis(5,7-dimethoxy-1-methylindolyl)-4-chlorophenylmethane (**24**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), 4-chlorobenzaldehyde (0.15 g, 1.05 mmol) and glacial acetic acid (4 mL) were combined and stirred at room temperature for 3 h. The resulting precipitate was filtered, washed with water and dried to give 3,3'-di(5,7-dimethoxy-1-methylindolyl)-4-chlorophenylmethane **24** (0.22 g, 83%) as an off-white powder. Recrystallisation from dichloromethane and petroleum ether afforded a white powder, mp 194 ˚C. IR (ν_{max}, cm^{-1}): 1582, 1500, 1454, 1413, 1280, 1203, 1148, 1118, 1049, 804. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 262 (12,000), 299 (9,300), 308 (8,300). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.68, 3.88 and 3.88 (18H, s, OMe and NMe), 5.61 (1H, br s, CH), 6.29 (4H, m, aryl H), 6.34 (2H, d, *J* 0.85 Hz, H6), 7.23 (2H, d, *J* 0.85 Hz, H4), 7.23 (2H, s, H2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.1 (2C, NMe), 39.5 (CH), 55.3 and 55.8 (4C, OMe), 93.1 and 94.3 (4C, aryl CH), 117.3 and 122.5 (4C, aryl C), 128.2 (2C, phenyl CH), 128.9 (2C, aryl C), 129.6 (2C, aryl CH), 130.0 (2C, phenyl CH), 131.5 and 143.1 (aryl C), 148.0 and 154.0 (4C, aryl C). MS (+EI, *m/z*, %): 507 (M, ^{37}Cl isotope, 11), 506 (^{37}Cl isotope, 36), 505 (M, ^{35}Cl isotope, 35), 504 (^{35}Cl isotope, 100), 503 (15), 489 (32), 393 (68). HRMS (*m/z*): Calcd for $C_{29}H_{29}ClN_2NaO_4$ $[M+Na]^+$, 527.1708. Found: 527.1734. Anal. calcd for $C_{29}H_{29}ClN_2O_4$: C, 69.0; H, 5.8; N, 5.5. Found: C, 68.7; H, 5.7; N, 5.1 5 %.

3,3'-Bis(5,7-dimethoxy-1-methylindolyl)-4-hydroxyphenylmethane (**25**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.25 g, 1.31 mmol), 4-hydroxybenzaldehyde (0.12 g, 0.99 mmol) and glacial acetic acid (5 mL) were combined and stirred at room temperature for 5 h. The resulting precipitate was filtered, washed with water and dried to give 3,3'-di(5,7-dimethoxy-1-methylindolyl)-4-hydroxyphenylmethane **25** (0.29 g, 91%) as a white powder, mp 227 ˚C. IR (ν_{max}, cm^{-1}): 3396, 1582, 1511, 1498, 1455, 1280, 1205, 1148, 1117, 1044 cm. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 217 (43,000), 230 (48,000), 267 (12,000), 272 (12,000), 299 (11,000), 307 (9,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.67, 3.87 and 3.88 (18H, s, OMe and NMe), 5.58 (1H, br s, CH), 6.28 (2H, d, *J* 2.0 Hz, H4), 6.33 (2H, d, *J* 2.0 Hz, H6), 6.35 (2H, s, H2), 6.72 and 7.17 (4H, m, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.1 (2C, NMe), 39.2 (CH), 55.3 and 55.8 (4C, OMe), 93.4, 94.2 and 114.9 (6C, aryl CH), 118.1, 122.5 and 129.1 (6C, aryl C), 129.6 and 129.7 (4C, aryl CH), 136.9 (aryl C), 147.9 (2C, aryl C), 153.6 (aryl C), 153.9 (2C, aryl C). MS (+EI, *m/z*, %): 487 (M, 29), 486 (100), 485 (23), 471 (44), 393 (49), 295 (16), 243 (19), 191 (28). HRMS (*m/z*): Calcd for $C_{29}H_{30}N_2NaO_5$ $[M+Na]^+$, 509.2047. Found: 509.2020.

3,3'-Bis(5,7-dimethoxy-1-methylindolyl)-4-nitrophenylmethane (**26**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), 4-nitrobenzaldehyde (0.16 g, 1.05 mmol) and glacial acetic acid (4 mL) were combined and stirred at room temperature for 5 h. The resulting precipitate was filtered, washed with water and dried to give 3,3'-di(5,7-dimethoxy-1-methylindolyl)-4-nitrophenylmethane **26** (0.18 g, 66%) as a yellow powder. Recrystallisation from dichloromethane and petroleum ether afforded a fibrous yellow solid, mp 221-222 ˚C. IR (ν_{max}, cm^{-1}): 1583, 1514, 1491, 1455, 1341, 1280, 1208, 1148, 1118, 991. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 216 (49,000), 228 (54,000), 272 (22,000), 295 (17,000), 306 (14,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.67 (6H, s, NMe), 3.89 (12H, s, OMe), 5.74 (1H, br s, CH), 6.26 and 6.30 (4H, d, *J* 2.0 Hz, H6 and H4), 6.35 (2H, s, H2), 7.46 and 8.13 (4H, m, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.2 (2C, NMe), 40.0 (CH), 55.4 and 55.7 (4C, OMe), 92.7 and 94.4 (4C, aryl CH), 116.1 and 122.5 (4C, aryl C), 123.5 (2C, aryl CH), 128.6 (2C, aryl C), 129.4 and 129.6 (4C, aryl CH), 146.3 (aryl C), 148.1 (2C, aryl C), 152.5 (aryl C), 154.2 (2C, aryl C). MS (+EI, *m/z*, %): 516 (M, 31),

515 (100), 500 (22), 394 (18), 393 (65), 258 (15), 204 (17). Anal. calcd for $C_{29}H_{29}N_3O_6$: C, 67.6; H, 5.7; N, 8.2. Found: C, 67.8; H, 5.7; N, 7.9 %.

3,3'-Bis(5,7-dimethoxy-1-methylindolyl)phenylmethane-4,4'-dicarbaldehyde (**27**)**.** Phosphoryl chloride (0.10 mL, 1.07 mmol) was added to an ice-cold solution of 3,3'-di(5,7-dimethoxy-1-methylindolyl)phenylmethane **23** (0.10 g, 0.21 mmol) in dry *N,N*-dimethylformamide (3 mL) with stirring and cooling in ice, and the reaction mixture was heated with stirring at 70 ˚C for 15 min. After cooling, the reaction mixture was poured over ice and basified using 10% aqueous sodium hydroxide solution. After standing overnight, the precipitate was filtered, washed with water and dried to give 3,3'-di(5,7-dimethoxy-1-methylindolyl)phenylmethane-4,4'-dicarbaldehyde **27** (93 mg, 83%) as a brown powder. Recrystallisation from dichloromethane and petroleum ether afforded dark cream needles, mp 158-159 ˚C. IR (ν_{max}, cm^{-1}): 1656, 1650, 1597, 1567, 1402, 1332, 1216, 1119, 1052. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 259 (25,000), 362 (23,000). ^{1}H NMR (300 MHz, d_6-DMSO): δ_H 3.81, 3.84 and 3.99 (18H, 3s, OMe and NMe), 6.32 (2H, s, H6), 6.53 (2H, s, H2), 6.72 (1H, br s, CH), 6.96 (2H, m, aryl H), 7.15 (3H, m, aryl H), 10.26 (2H, s, CHO). ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 36.3 (2C, NMe), 43.0 (CH), 56.0 and 57.0 (4C, OMe); 90.8 (2C, aryl CH), 111.6, 118.9 and 122.4 (aryl C), 125.6 (aryl CH), 126.9 (aryl C), 127.8 and 128.8 (4C, phenyl CH), 133.7 (2C, aryl CH), 145.2, 152.7 and 159.3 (aryl C), 187.8 (2C, CHO). MS (+EI, *m/z*, %): 527 (M, 11), 526 (31), 498 (13), 497 (29), 493 (21), 292 (88), 278 (96), 249 (47), 219 (54), 105 (63). HRMS (*m/z*): Calcd for $C_{31}H_{30}N_2NaO_6$ $[M+Na]^+$, 549.1996. Found: 549.1985.

1,4-Bis[di(5',7'-dimethoxy-1'-methylindol-3'-yl)methyl]benzene (**28**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), terephthalaldehyde (50 mg, 0.37 mmol) and glacial acetic acid (4 mL) were combined and stirred at room temperature for 5.5 h. The resulting precipitate was filtered, washed with water and dried affording 1,4-bis[di(5',7'-dimethoxy-1'-methylindol-3'-yl)methyl]benzene **28** (0.16 g, 71%) as an off-white solid. Recrystallisation from acetone and petroleum ether yielded colourless crystals, mp 271-273 ˚C. IR (ν_{max}, cm^{-1}): 1584, 1497, 1455, 1412, 1281, 1207, 1148, 1117, 1050. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 265 (31,000), 302 (22,000), 306 (21,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.61, 3.86 and 3.87 (36H, s, OMe and NMe), 5.60 (2H, br s, CH), 6.27 and 6.33 (8H, d, *J* 2.1 Hz, H6 and H4), 6.35 (4H, s, H2), 7.23 (4H, s, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.1 (4C, NMe), 39.9 (2C, CH), 55.3 and 55.6 (8C, OMe), 93.2 and 94.1 (8C, aryl CH), 118.1 and 122.4 (8C, aryl C), 128.5 (4C, phenyl CH), 129.1 (4C, aryl C), 129.6 (4C, aryl CH), 141.9 (2C, phenyl C), 147.9 and 153.9 (8C, aryl C). MS (+EI, *m/z*, %): 863 (M, 0.01), 217 (16), 161 (37), 121 (90). HRMS (*m/z*): Calcd for $C_{52}H_{54}N_4NaO_8$ $[M+Na]^+$, 885.3834. Found: 885.3790.

Dimethyl 4,4'-[[4-chlorophenyl]methylene]bis[5,7-dimethoxyindole]-2,2'-dicarboxylate (**29**)**.** A solution of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.15 g, 0.64 mmol) and *p*-chlorobenzaldehyde (90 mg, 0.64 mmol) in anhydrous methanol (10.0 mL) was stirred at room temperature with concentrated HCl (3 drops) for 5 h. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (0.16 g, 84%) as a white powder, mp 265-268 ˚C. IR (ν_{max}, cm^{-1}): 3441, 3278, 1721, 1702, 1590, 1550, 1440, 1319, 1244, 1222, 1155, 986, 749. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 242 (53,700), 278 (20,200), 297 (34,900), 336 (9,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.48, 3.83 and 3.94 (each 6 H, s, OMe), 6.51 (2H, s, H6), 6.56 (1H, s, bridging CH), 6.68 (2H, d, *J* 2.3 Hz, H3), 7.07 and 7.18 (each 2H, d, *J* 8.3 Hz, *p*-chlorophenyl), 8.84 (2H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 41.6 (bridging CH), 51.7, 55.4 and 58.1 (OMe), 95.8 (C6), 109.2 (C3), 127.8 and 130.2 (*p*-chlorophenyl CH), 116.9, 124.4, 126.6, 128.6, 131.1, 142.3, 145.4 and 152.2 (aryl C), 162.1 ($\underline{C}O_2Me$). MS (+EI, *m/z*, %): 595 (M+1, ^{37}Cl, 11), 594 (M, ^{37}Cl, 37), 593 (M+1, ^{35}Cl, 33), 592 (M, ^{35}Cl, 100), 563 (24), 562 (20), 561 (61), 327 (26), 326 (30), 325 (60). Anal. calcd for $C_{31}H_{29}ClN_2O_8$: C, 62.8; H, 4.9; N, 4.7. Found: C, 62.9; H, 4.7; N, 4.8 %.

Dimethyl 4,4'-[[4-methoxyphenyl]methylene]bis[5,7-dimethoxyindole]-2,2'-dicarboxylate (**30**)**.** A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.34 g, 1.45 mmol) and *p*-methoxybenzaldehyde (99 mg, 0.73 mmol) in anhydrous methanol (5.0 mL) was stirred at room temperature with concentrated HCl (1 drop) for 2 h. The resulting precipitate was filtered through a frit, washed with a little methanol, then water, and dried to give the title compound (0.39 g, 88%) as a white powder, m.p. 256-259 ˚C (methanol). IR (ν_{max}, cm^{-1}): 3443, 1710, 1588, 1538, 1509, 1438, 1319, 1246, 1206, 1088, 984. UV/Vis (λ_{max}, nm, ε, cm^{-1} M^{-1}): 242 (55,500), 298 (35,100), 338 (9,930). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.44 (6H, s, OMe), 3.78 (3H, s, OMe), 3.81 and 3.94 (each 6H, s, OMe), 6.51 (2H, s, H6), 6.55 (1H, s, bridging CH), 6.61 (2H, d, *J* 2.3 Hz, H3), 6.78 and 7.06 (each 2H, d, *J* 8.3 Hz, *p*-methoxyphenyl), 8.81 (2H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 41.9 (bridging CH), 52.1 (OMe), 55.8 (*p*-methoxyphenyl OMe), 55.9 and 58.9 (OMe), 96.7 (C6), 110.0 (C3), 113.9 and 130.4 (*p*-methoxyphenyl CH), 118.8, 125.0, 126.9, 129.2, 136.2, 145.6, 152.7 and 158.2 (aryl C), 162.7 ($\underline{C}O_2Me$). MS (MALDI, *m/z*, %): 588 (M, 54), 587 (100). Anal. calcd for $C_{32}H_{32}N_2O_9$: C, 65.3; H, 5.5; N, 4.8. Found: C, 65.3; H, 5.6; N, 4.8 %.

Dimethyl 3,4'-[[4-chlorophenyl]methylene]bis[5,7-dimethoxyindole]-2,2'-dicarboxylate (**31**). A solution of methyl 5,7-dimethoxyindole-2-carboxylate **1** (0.15 g, 0.64 mmol) and *p*-chlorobenzaldehyde (46 mg, 0.33 mmol) in anhydrous chloroform (15 mL) was heated at reflux with phosphoryl chloride (0.1 mL, 1 mmol) for 2 h. The resulting solution was washed sequentially with iced water and dilute NaOH, and dried ($MgSO_4$). The solvent was then evaporated *in vacuo* and the remaining residue was purified *via* gravity column chromatography (CH_2Cl_2) to give the title compound (70 mg, 37%) as a white powder, mp 221-224 ˚C. IR (ν_{max}, cm^{-1}): 3418, 3347, 1698, 1584, 1536, 1440, 1436, 1323, 1251, 1201, 1155. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 241 (48,000), 273 (18,000), 298 (34,000), 339 (10,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.31, 3.45, 3.79, 3.82, 3.89 and 3.95 (each 3H, s, OMe), 6.29 and 5.83 (each 1H, d, *J* 1.9 Hz H6 and H4 respectively), 6.52 (1H, s, H6'), 6.56 (1H, d, *J* 2.3 Hz, H3'), 6.99 (1H, s, bridging CH), 7.16 (4H, m, *p*-chlorophenyl), 8.88 and 8.90 (each 1H, bs, NH and NH'). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.9 (bridging CH), 52.0, 52.2, 55.4, 55.8, 55.9 and 58.6 (OMe), 95.2, 96.4 and 97.5 (C4, C6, and C6'), 109.2 (C3'), 128.5 and 130.9 (*p*-chlorophenyl CH), 162.5 and 162.45 ($\underline{C}O_2Me$), 117.1, 123.4, 123.9, 124.9, 125.4, 127.3, 128.6, 128.9, 132.0, 142.8, 146.0, 147.0, 153.1 and 154.9 (aryl C). MS (+EI, *m/z*, %): 595 (^{37}Cl, 9), 594 (M, ^{37}Cl, 29), 593 (28), 592 (M, ^{35}Cl, 67), 591 (12), 561 (14), 560 (9), 536 (12), 535 (40), 534 (37), 533 (100), 532 (20), 531 (17), 530 (17). Anal. calcd for $C_{31}H_{29}ClN_2O_8$: C, 62.8; H, 4.9; N, 4.7. Found: C, 62.8; H, 4.9; N, 4.9 %.

Dimethyl 4,4'-[[4-chlorophenyl]methylene]bis[5,7-dimethoxy-*N*-methylindole]-2,2'-dicarboxylate (**32**). A mixture of methyl 5,7-dimethoxy-*N*-methyl-indole-2-carboxylate **6** (0.26 g, 1.05 mmol) and *p*-chloro-benzaldehyde (148 mg, 1.05 mmol) in anhydrous methanol (3 mL) was stirred at room temperature with concentrated HCl (1 drop) for 1.5 h. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (0.304 g, 93%) as a white powder, mp 178-183 ˚C. IR (ν_{max}, cm^{-1}): 1711, 1583, 1458, 1325, 1240, 1204, 1175, 1089, 991. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 244 (57,700), 280 (21,600), 300 (33,800), 347 (11,200). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.48, 3.78 and 3.91 (each 6H, s, OMe), 4.28 (6H, s, NMe), 6.48 (2H, s, H6), 6.53 (1H, s, bridging CH), 6.88 (2H, s, H3), 7.05 and 7.17 (each 2H, d, *J* 8.3 Hz, *p*-chlorophenyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 34.9 (NMe), 41.9 (bridging CH), 51.8, 56.0 and 58.4 (OMe), 97.0 (C6), 111.5 (C3), 128.2 and 130.6 (*p*-chlorophenyl CH), 116.8, 127.0, 128.4, 128.6, 131.4, 143.0, 147.8 and 152.1 (aryl C), 163.0 ($\underline{C}O_2Me$). MS (+EI, *m/z*, %): 621 (M, 4), 464 (13), 453 (14), 440 (68), 426 (100), 371 (22), 332 (13), 321 (18), 266 (29), 252 (42), 228 (79). Anal. calcd for $C_{33}H_{33}ClN_2O_8$: C, 63.8; H, 5.4; N, 4.5. Found: C, 63.6; H, 5.2; N, 4.6 %.

Dimethyl 4,4'-[(4-chlorophenyl)methylene]bis[1-tert-butyloxycarbonyl-5,7-dimethoxyindole]-2,2'-dicarbox-ylate (**33**)**.** A mixture of dimethyl *p*-chlorophenyl-4,4'-di(5,7-dimethoxyindolyl)methane-2,2'-dicarboxylate **29** (0.76 mg, 0.13 mmol), di-(*t*-butyl)carbonate (121 mg, 0.55 mmol) in anhydrous acetonitrile (5 mL) was stirred

at room temperature with a catalytic quantity of *N*,*N*-dimethylaminopyridine for 2.5 h. The solvent was then evaporated *in vacuo* and the remaining yellow syrup purified *via* suction column chromatography (CH_2Cl_2) to give the title compound (65 mg, 64%) as a white powder, mp >133 ˚C (decomp.). IR (ν_{max}, cm^{-1}): 1770, 1721, 1589, 1546, 1488, 1437, 1394, 1371, 1336, 1257, 1231v, 1157, 1081. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 243 (50,900), 296 (31,200), 343 (11,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.64 (18H, s, CMe_3, 3.50, 3.81, and 3.90 (each 6H, s, OMe), 6.51 (1H, s, bridging CH), 6.54 (2H, s, H6), 6.78 (2H, s, H3), 7.02 (2H, d, *J* 8.3 Hz, *p*-chlorophenyl), 7.19 (2H, d, *J* 8.7 Hz, *p*-chlorophenyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 41.9 (bridging CH), 27.8 (CMe_3), 52.3, 56.0 and 58.0 (OMe), 84.9 ($\underline{C}Me_3$), 97.1 (C6), 112.0 (C3), 128.4 and 130.6 (*p*-chlorophenyl CH), 116.7, 124.3, 127.7, 128.7, 131.7, 142.2, 146.4 and 153.3 (aryl C), 151.4 (CO), 161.6 ($\underline{C}O_2Me$). MS (MALDI, *m/z*, %): 790 (26), 691 (M-Boc, 14), 592 (M-2 x Boc, 100). Anal. calcd for $C_{41}H_{45}ClN_2O_{12}$: C, 62.1; H, 5.7; N, 3.5. Found: C, 61.8; H, 5.9; N, 3.56 %.

(Indol-3-yl)-bis(5',7'-dimethoxy-1'-methylindol-3'-yl)methane (**35**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), indole-3-carbaldehyde **34** (0.11 g, 0.79 mmol) and glacial acetic acid (4 mL) were combined and stirred at room temperature for 4 h under an inert gas atmosphere. The resulting precipitate was filtered, washed with water and dried, yielding (indol-3-yl)-di(5',7'-dimethoxy-1'-methylindol-3'-yl)methane **35** (67 mg, 25%) as an off-white solid. Recrystallisation from dichloromethane and petroleum ether afforded a white solid which turned pink on exposure to air, mp 224-225 ˚C. IR (ν_{max}, cm^{-1}): 3411, 3343, 1584, 1495, 1456, 1413, 1281, 1204, 1147, 1117, 1044. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 274 (21,000), 293 (19,000), 303 (17,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.68, 3.85 and 3.88 (18H, 3 x s, OMe and NMe), 5.92 (1H, br s, CH), 6.29 (2H, d, *J* 2.0 Hz, H6'), 6.46 (2H, s, H2'), 6.48 (2H, d, *J* 2.0 Hz, H4'), 6.76 (1H, d, *J* 2.0 Hz, H2), 6.99 (1H, m, H5), 7.16 (1H, m, H6), 7.35 (1H, d, *J* 8.2 Hz, H4), 7.47 (1H, d, *J* 7.7 Hz, H7), 7.87 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.9 (CH), 36.1 (2C, NMe), 55.3 and 55.8 (4C, OMe), 93.3 and 94.0 (4C, aryl CH), 110.8 (aryl CH), 117.6 (2C, aryl C), 118.8 (aryl CH), 119.7 (aryl C), 120.2 and 121.5 (aryl CH), 122.4 (2C, aryl C), 123.3 (aryl CH), 127.2 (aryl C), 129.1 (2C, aryl C), 129.4 (2C, aryl CH), 136.7 (aryl C), 147.9 and 153.7 (4C, aryl C). MS (+EI, *m/z*, %): 510 (M, 19), 509 (100), 494 (46), 391 (17), 317 (38), 191 (90), 176 (73). HRMS (*m/z*): Calcd for $C_{31}H_{31}N_3NaO_4$ $[M+Na]^+$, 532.2207. Found: 532.2206.

(5,7-Dimethoxyindol-4-yl)-bis(5',7'-dimethoxy-1'-methylindol-3'-yl)methane (**36**). 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), 5,7-dimethoxyindole-4-carbaldehyde **10** (0.16 g, 0.79 mmol) and glacial acetic acid (4 mL) were combined and stirred at room temperature overnight. The resulting precipitate was filtered, washed with water and dried, yielding an off-white powder (0.19 g). ^{1}H NMR spectroscopy showed that the powder contained (5,7-dimethoxyindol-4-yl)-di(5',7'-dimethoxy-1'-methylindol-3'-yl)methane **36** in 53% yield and unreacted 5,7-dimethoxyindole-4-carbaldehyde **10** (18% of the original amount). Radial chromatography using dichloromethane afforded (5,7-dimethoxyindol-4-yl)-di(5',7'-dimethoxy-1'-methylindol-3'-yl)methane (**36**) (0.11 g, 37%) as a purple glass. Recrystallisation from dichloromethane and petroleum ether gave purple crystals, mp 270-271 ˚C. IR (ν_{max}, cm^{-1}): 3406, 1583, 1493, 1457, 1412, 1314, 1282, 1205, 1145, 1114, 1047. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 269 (13,000), 299 (12,000), 304 (11,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.65 (6H, s, OMe or NMe), 3.77 (3H, s, OMe), 3.85 (12H, s, NMe and/or OMe), 3.95 (3H, s, OMe), 6.23 (2H, d, *J* 2.1 Hz, H6'), 6.34 (1H, dd, *J* 2.3, 3.0 Hz, H3), 6.37 (1H, t, *J* 1.1 Hz, CH), 6.44 (2H, d, *J* 2.1 Hz, H4'), 6.51 (1H, s, H6), 6.54 (2H, d, *J* 1.1 Hz, H2'), 6.90 (1H, m, H2), 8.07 (1H, m, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.2 (CH), 36.1 (2C, NMe), 55.3 (2C, OMe), 55.3 (OMe), 55.6 (2C, OMe), 59.5 (OMe), 93.3 (aryl CH), 93.5 and 93.8 (4C, aryl CH), 103.8 (aryl CH), 117.5 (2C, aryl C), 117.5 (aryl C), 122.2 (2C, aryl C), 123.0 (aryl C), 123.2 (aryl CH), 128.7 (aryl C), 129.5 (2C, aryl CH), 129.7 (2C, aryl C), 144.5 (aryl C), 147.7 (2C, aryl C), 150.7 (aryl C), 153.5

(2C, aryl C). MS (+EI, *m/z*, %): 570 (M, 15), 569 (51), 554 (34), 391 (63), 191 (80), 176 (94), 148 (74). HRMS (*m/z*): Calcd for $C_{33}H_{35}N_3NaO_6$ $[M+Na]^+$, 592.2418. Found: 592.2453.

3,3',3"-Tris(5,7-dimethoxy-1-methylindolyl)methane (**37**)**. Method 1**. 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), 5,7-dimethoxy-1-methylindole-3-carbaldehyde **7** (0.17 g, 0.79 mmol) and glacial acetic acid (4 mL) were combined and stirred at room temperature overnight. The resulting precipitate was filtered, washed with water and dried, yielding 3,3',3"-tri(5,7-dimethoxy-1-methylindolyl)methane **37** (0.14 g, 47%) as a pale pink solid. Recrystallisation from dichloromethane and petroleum ether afforded a white powder, mp 245-246 ˚C. IR (ν_{max}, cm^{-1}): 1584, 1488, 1456, 1412, 1281, 1205, 1147, 1116, 1048, 810. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 266 (16,000), 273 (15,000), 300 (17,000), 307 (16,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.68, 3.86 and 3.88 (27H, 3s, OMe and NMe), 5.78 (1H, br s, CH), 6.28 (3H, d, *J* 2.0 Hz, H6), 6.46 (3H, s, H2), 6.46 (3H, d, *J* 2.0 Hz, H4. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 30.9 (CH), 36.1 (3C, NMe), 55.3 and 55.8 (6C, OMe, 93.6 and 93.9 (6C, aryl CH), 117.8, 122.5 and 129.3 (9C, aryl C), 129.5 (3C, aryl CH), 147.9 and 153.7 (6C, aryl C). MS (+EI, *m/z*, %): 584 (M, 27), 583 (79), 568 (68), 392 (55), 391 (100), 192 (80), 191 (84), 176 (71). Anal. calcd for $C_{34}H_{37}N_3O_6$: C, 70.0; H, 6.4; N, 7.2. Found: C, 69.7; H, 6.5; N, 7.0.

Method 2. 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol) was dissolved in AR grade methanol (7 mL). Triethyl orthoformate (0.58 mL, 3.49 mmol) was added, followed by a trace amount of 4-toluenesulfonic acid, and the reaction mixture was heated at reflux for 30 min. After cooling, the resulting precipitate was filtered, washed with 10% aqueous ammonia solution followed by water and dried, affording 3,3',3"-tri(5,7-dimethoxy-1-methylindolyl)methane **37** (0.18 g, 88%) as a white solid.

3,3',3"-Tris(5,7-dimethoxyindolyl)methane (**38**)**.** 5,7-Dimethoxyindole **2** (0.20 g, 1.13 mmol) was dissolved in AR grade methanol (5 mL). Triethyl orthoformate (1.24 mL, excess) was added, followed by a trace amount of 4-toluenesulfonic acid, and the reaction mixture was heated at reflux for 1 h. After cooling, the resulting precipitate was filtered, washed with 10% aqueous ammonia solution followed by water and dried, affording 3,3',3"-tri(5,7-dimethoxyindolyl)methane **38** (75 mg, 37%) as a pale orange solid, mp 205-206 ˚C. IR (ν_{max}, cm^{-1}): 3323, 1571, 1494, 1455, 1317, 1201, 1145, 1130, 1049, 937, 814. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 267 (17,000), 293 (14,000), 302 (12,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.68 and 3.91 (18H, 2s, OMe), 5.91 (1H, m, CH), 6.32 (3H, d, *J* 2.1 Hz, H6), 6.50 (1H, m, H4), 6.71 (3H, m, H2), 7.97 (3H, br m, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.5 (CH), 55.3 and 55.9 (6C, OMe), 93.6 and 93.8 (6C, aryl CH), 119.6 and 122.5 (6C, aryl C), 123.3 (3C, aryl CH), 127.8, 146.3 and 154.3 (9C, aryl C). MS (+EI, *m/z*, %): 542 (M, 2), 363 (11), 177 (45), 162 (49), 134 (100), 119 (95). HRMS (*m/z*): Calcd for $C_{31}H_{31}N_3NaO_6$ $[M+Na]^+$, 564.2105. Found: 564.2074.

3,3',3"-Tris(1-benzyl-5,7-dimethoxyindolyl)methane (**39**)**.** 1-Benzyl-5,7-dimethoxyindole **3** (0.20 g, 0.75 mmol) was dissolved in AR grade methanol (17 mL). Triethyl orthoformate (0.88 mL, excess) was added, followed by a trace amount of 4-toluenesulfonic acid, and the reaction mixture was heated at reflux for 1.5 h. After cooling, the resulting precipitate was filtered, washed with 10% aqueous ammonia solution followed by water and dried, affording 3,3',3"-tri(1-benzyl-5,7-dimethoxy-indolyl)methane **39** (0.16 g, 77%) as a white solid. Recrystallisation from dichloromethane and petroleum ether yielded a white powder, mp 262-263 ˚C. IR (ν_{max}, cm^{-1}): 1615, 1585, 1493, 1453, 1426, 1282, 1204, 1165, 1149, 1049, 812, 700. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 266 (19,000), 274 (17,000), 301 (18,000), 307 (18,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.56 and 3.76 (18H, 2s, OMe), 5.40 (6H, s, CH_2), 5.86 (1H, br s, CH), 6.25 (3H, d, *J* 2.0 Hz, H6), 6.47 (d, *J* 2.0 Hz, H4), 6.62 (3H, s, H2), 6.98 (6H, m, aryl H), 7.18 (9H, m, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.5 (CH), 52.1 (3C, CH_2), 55.2 and 55.6 (6C, OMe), 93.5 and 94.5 (6C, aryl CH), 118.2 and 122.0 (6C, aryl C), 126.3 (6C, aryl CH), 126.7 (3C, aryl CH), 128.2 (6C, aryl CH), 129.0 (3C, aryl CH), 129.5, 140.1, 147.7 and 153.9 (12C, aryl C). MS (+EI, *m/z*, %): 812 (M, 13), 811 (24), 796 (10). HRMS (*m/z*): Calcd for $C_{52}H_{49}N_3NaO_6$ $[M+Na]^+$, 834.3513. Found: 834.3458.

Dimethyl 3,3'-[indol-3-ylmethylene]bis[5,7-dimethoxyindole]-2,2'-dicarboxylate (**40**)**.** A solution of methyl 5,7-dimethoxyindole-2-carboxylate **2** (0.10 g, 0.43 mmol) and indole-3-carbaldehyde **34** (62 mg, 0.43 mmol) in anhydrous methanol (3 mL) was stirred at room temperature with concentrated HCl (1 drop) for 24 h. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (58 mg, 46%) as a white powder, mp 220-223 ˚C. IR (ν_{max}, cm^{-1}): 3454, 3434, 3379, 3316, 1702, 1590, 1543, 1456, 1438, 1323, 1312, 1245, 1197, 1156. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 239 (49,400), 273 (21,300), 293 (31,600), 336 (10,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.87, 3.82, and 3.11 (each 6H, s, OMe), 5.94 (2H, bs, H4 and H4'), 6.23 (2H, d, *J* 1.9 Hz, H6 and H6'), 6.67 (1H, d, *J* 1.1 Hz, H2"), 7.10 and 6.90 (each 1H, dt, *J* 1.1, 7.9 Hz, H5" and H6"), 7.33 (2H, dt, *J* 1.1, 7.9 Hz, H4" and H7"), 7.49 (1H, d, *J* 1.5 Hz, bridging CH), 7.90 (1H, bs, NH"), 8.90 (2H, bs, NH and NH'). The signals at 8.90 and 7.90 ppm exchanged with D_2O. ^{1}H NMR (300 MHz, d_6, DMSO): δ_H 3.81, 3.71, and 3.05 (each 6H, s, OMe), 5.85 (2H, bs, H4 and H4'), 6.25 (2H, s, H6 and H6'), 6.54 (1H, s, H2"), 7.00 and 6.75 (each 1H, d, *J* 8.3 Hz, H5" and H6"), 7.36 and 7.08 (each 1H, d, *J* 8.3 Hz, H4" and H7"), 7.38 (1H, s, bridging CH), 10.71 (1H, bs, NH"), 11.19 (2H, bs, NH and NH'). The signals at 11.19 and 10.71 ppm exchanged with D_2O. ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 31.5 (bridging CH), 51.5, 54.5 and 55.8 (OMe), 94.5 (C4 and C4'), 96.7 (C6 and C6'), 111.6, 118.6, 119.3, 121.3 and 123.6 (indolyl CH), 117.9, 123.2, 124.0, 125.3, 127.9, 128.3, 137.0, 147.3 and 154.0 (aryl C), 162.0 ($\underline{C}O_2Me$). MS (+EI, *m/z*, %): 598 (25), 597 (M, 71), 539 (33), 538 (100), 507 (16), 506 (49), 502 (21), 235 (45), 203 (48), 174 (27), 144 (23), 117 (21). Anal. calcd for $C_{33}H_{31}N_3O_8$: C, 66.3; H, 5.2; N, 7.0. Found: C, 66.3; H, 5.1; N, 7.0 %.

Reaction of methyl 5,7-dimethoxyindole-2-carboxylate (**5**) **with methyl 4-formyl-5,7-dimethoxyindole-2-carboxylate** (**11**)**.** A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.180 g, 0.765 mmol) and methyl 4-formyl-5,7-dimethoxyindole-2-carboxylate **11** (0.106 g, 0.403 mmol) in anhydrous methanol (4 mL) was heated at reflux with concentrated HCl (2 drops) for 3.5 h. The resulting precipitate was filtered through a frit, washed with a little methanol, then water, and dried to give an isomeric mixture (0.227 g, 83%) of the 3,3',4",-triindolylmethane **41** and the 3,3',3"-triindolylmethane **42** in a 88:12 ratio, as a white powder, mp 244-247 ˚C. IR (ν_{max}, cm^{-1}): 3468, 3335, 1716, 1589, 1539, 1451, 1437, 1329, 1310, 1247, 1199, 1156. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 241 (66,800), 279 (27,600), 297 (46,400), 338 (14,400). MS (MALDI, *m/z*, %): 715 (M, 47), 714 (100). Anal. calcd for $C_{37}H_{37}N_3O_{12}.0.5H_2O$: C, 61.3; H, 5.3; N, 5.8. Found: C, 61.1; H, 5.0; N, 5.7 %.

Purification of the isomeric mixture *via* preparative thin layer chromatography led to the isolation and characterisation of compound **41**, and recovery of a trace amount of compound **42**.

Trimethyl 3'4"-methylidynetris[5,7-dimethoxyindole]-2,2',2"-tricarboxylate (**41**)**.** ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.02 (3H, s, OMe), 3.16 and 3.39 (each 3H, bs, OMe), 3.71 (3H, s, OMe), 3.75 (6H, s, OMe), 3.85, 3.87, 3.92 (each 3H, s, OMe), 5.78 and 5.95 (each 1H, bs, H4 and H4'), 6.23 and 6.27 (each 1H, d, *J* 1.9 Hz, H3" and H6"), 6.52 (2H, s, H6 and H6'), 7.73 (1H, s, bridging CH), 8.87 (2H, bs, NH and NH'), 8.94 (1H, bs, NH"). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 34.6 (bridging CH), 51.8, 51.9, 52.0, 52.1, 55.0, 55.2, 55.8, 55.9 and 59.1 (OMe), 94.9 and 95.3 (C4), 97.1, 97.3, and 97.4 (C6), 109.4 (C3), 118.8, 123.1, 123.3, 123.8, 124.1, 125.0, 126.2, 127.2, 127.3, 129.2, 129.5, 145.7, 146.9, 147.0, 153.1, 154.7, 155.1 (aryl C), 162.4, 162.5 and 162.9 ($\underline{C}O_2Me$).

Trimethyl 3',3"-methylidynetris[5,7-dimethoxyindole]-2,2',2"-tricarboxylate (**42**)**.** IR (ν_{max}, cm^{-1}): 3468, 1714, 1652, 1634, 1455, 1248, 1199, 1158; ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.87, 3.78, and 2.98 (each 6H, s, OMe), 5.95 (3H, d, *J* 1.9 Hz, H4), 6.24 (3H, d, *J* 1.9 Hz, H6), 8.15 (1H, s, bridging CH), 8.94 (3H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 32.4 (bridging CH), 51.4, 54.5, and 55.4 (OMe), 94.2 (C4), 96.7 (C6), 122.5, 123.8, 125.3, 128.7, 146.6 and 154.7 (aryl C), 162.1 ($\underline{C}O_2Me$).

Reaction of methyl 5,7-dimethoxyindole-2-carboxylate (**5**) **with triethyl orthoformate: formation of compounds 41 and 42.** mixture of methyl 5,7-dimethoxyindole-2-carboxylate (**5**) (0.250 g, 1.06 mmol) and

triethyl orthoformate (0.10 mL, 0.60 mmol) in anhydrous methanol (3 mL) was heated at reflux, with a catalytic quantity of *p*-toluenesulfonic acid, for 24 h. The resulting precipitate was filtered through a frit, washed with a little methanol, then water, and dried to give a 98:2 isomeric mixture (0.202 g, 80%) of the 3,3',4"-triindolylmethane **41** and 3,3',3"-triindolylmethane **42** as a white powder.

2,4-Dimethoxy-5-methyl-6-(5',7'-dimethoxy-1'-methylindol-3'-yl)benzo[1,2-*b*]carbazole (**43**). 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), phthalaldehyde (70 mg, 0.52 mmol) and glacial acetic acid (4 mL) were combined and stirred at room temperature for 4.5 h. The resulting precipitate was filtered, washed with water and dried, yielding 2,4-dimethoxy-5-methyl-6-(5',7'-dimethoxy-1'-methylindol-3'-yl)benzo[1,2-*b*]carbazole **43** as a bright yellow powder (87 mg, 34%). Recrystallisation from ethyl acetate and petroleum ether afforded bright yellow crystals, mp 191-192 ˚C. IR (ν_{max}, cm^{-1}): 1589, 1498, 1457, 1302, 1278, 1207, 1151, 1116, 1057. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 278 (47,000), 287 (59,000), 307 (14,000), 322 (7,500), 337 (4,000), 407 (5,600), 419 (5,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.53 (3H, br s, 5-NMe), 3.58 (3H, s, 5'-OMe), 3.90 (3H, s, 4-OMe), 3.98 (6H, s, 2-OMe and 7'-OMe), 4.16 (3H, s, 1'-NMe), 6.20 (1H, d, *J* 2.1 Hz, H4'), 6.38 (1H, d, *J* 2.1 Hz, H6'), 6.66 (1H, d, *J* 2.1 Hz, H3), 7.02 (1H, s, H2'), 7.30 (1H, m, H8), 7.35 (1H, d, *J* 2.1 Hz, H1), 7.36 (1H, m, H9), 7.82 (1H, d, *J* 8.4 Hz, H7), 8.05 (1H, dd, *J* 1.4, 8.2 Hz, H10), 8.54 (1H, s, H11). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 34.6 and 36.5 (NMe), 55.4, 55.7, 55.8 and 56.0 (OMe), 93.3, 94.9, 95.0 and 100.0 (aryl CH), 111.1 and 112.0 (aryl C), 117.7 (aryl CH), 121.8 (aryl C), 122.4 (aryl CH), 124.5 (aryl C), 124.6 and 125.8 (aryl CH), 126.4 and 128.0 (aryl C), 128.2 (aryl CH), 129.4 (aryl C), 130.8 (aryl CH), 132.1, 133.7, 141.9, 147.5, 148.1, 154.4 and 154.9 (aryl C). MS (+EI, *m/z*, %): 481 (M, 28), 480 (85), 465 (15). Anal. calcd for $C_{30}H_{28}N_2O_4$: C, 75.0; H, 5.9; N, 5.8. Found: C, 74.8; H, 5.9; N, 5.6 %.

Dimethyl 2,6,8,12-tetrahydro-3,5,9,11-tetramethoxy-6,12-o-benzeno-diindolo[4,4a,3-*bc*:4',4a',3'-*fg*]cyclo-octene-1,7-dicarboxylate (**44**). **Method A.** A stirred solution of methyl 5,7-dimethoxyindole-2-carboxylate **5** (1.75 g, 7.46 mmol) and phthaldialdehyde (0.50 g, 3.73 mmol) in anhydrous methanol (15 mL) was heated at reflux with concentrated HCl (2 drops) for 3 h. After cooling to room temperature the resulting precipitate was filtered through a frit, washed with a little methanol, then water, and dried to give the title compound (1.92 g, 90%) as a white powder, mp 316-319 ˚C. IR (ν_{max}, cm^{-1}): 3468, 3334, 1687, 1590, 1538, 1456, 1436, 1392, 1354, 1298, 1254, 1204, 1111, 1000. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 245 (49,000), 279 (18,000), 301 (21,000), 345 (11,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.85, 3.94 and 4.08 (each 6H, s, OMe), 6.46 (2H, s, H6), 6.90 (2H, s, bridging CH), 7.12 (2H, m, aryl CH), 7.48 (2H, m, aryl CH), 8.66 (2H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 40.0 (bridging CH), 52.1, 56.0 and 60.0 (OMe), 97.3 (C6), 127.5 and 130.3 (aryl CH), 117.9, 121.6, 124.2, 125.9, 127.1, 142.5, 145.6 and 150.0 (aryl C), 163.2 ($\underline{C}O_2Me$). MS (MALDI, *m/z*, %): 568 (M, 100). Anal. calcd for $C_{32}H_{28}N_2O_8$: C, 67.6; H, 5.0; N, 4.9. Found: C, 67.9; H, 5.0; N, 4.9 %.

Method B. A stirred solution of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.11 g, 0.48 mmol) and phthaldialdehyde (32 mg, 0.24 mmol) in chloroform (4 mL) was treated with phosphoryl chloride (0.02 mL, 0.2 mmol). The darkened solution was stirred at room temperature for 3 days before it was basified with 2M NaOH and extracted with dichloromethane. The organic extract was washed with water, dried ($MgSO_4$), and the solvent evaporated *in vacuo* to give the title compound (0.13 g, 93%) as a white powder.

Method C. A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.19 g, 0.79 mmol) and phthaldialdehyde (53 mg, 0.24 mmol) in anhydrous methanol (7 mL), was stirred with *p*-toluenesulfonic acid (10 mg), under nitrogen, for 4 d. The resulting precipitate was filtered through a frit, washed with a little methanol, then water, and dried to give the title compound (150 mg, 100%) as a white powder.

Dimethyl 2,6,8,12-tetrahydro-3,5,9,11-tetramethoxy-2,8-dimethyl-6,12-*o*-benzenodiindolo[4,4a,3-*b,c*:-4',4a',3'-*f,g*]cyclooctene-1,7-dicarboxylate (**46**). A stirred solution of methyl 5,7-dimethoxy-*N*-methylindole-2-

carboxylate (**6**) (0.230 g, 0.923 mmol) and phthaldialdehyde (80 mg, 0.60 mmol) in anhydrous methanol (5 mL) was stirred at ambient temperature with concentrated HCl (1 drops) for 4 h. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (0.12 g, 44%) as a white powder, mp 356-358 ˚C. IR (ν_{max}, cm^{-1}): 1713, 1586, 1457, 1394, 1320, 1288, 1227, 1202, 1116. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 247 (46,500), 277 (15,500), 300 (17,000), 356 (11,500). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.80, 3.89 and 4.05 (each 6H, bs, OMe), 4.14 (6H, s, NMe), 6.40 (2H, s, H6), 6.73 (2H, bs, bridging CH), 7.13 (2H, dd, *J* 3.4, 5.6 Hz, aryl H), 7.45 (2H, dd, *J* 3.4, 5.7 Hz, aryl H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 34.7 (NMe), 39.7 (bridging CH), 52.0, 56.2, and 59.2 (OMe), 97.0 (C6), 127.5 and 130.0 (aryl CH), 163.8 ($\underline{C}O_2Me$), 117.4, 125.0, 125.2, 126.2, 126.6, 142.4, 147.1 and 149.3 (aryl C). MS (+EI, *m/z*, %): 596 (M, 25), 581 (26), 553 (23), 538 (31), 537 (100), 536 (19), 522 (21), 521 (39), 507 (32), 506 (26), 505 (17), 493 (18), 491 (24), 477 (22), 475 (22), 463 (32), 462 (21), 461 (22), 448 (29), 447 (49). Anal. calcd for $C_{34}H_{32}N_2O_8.H_2O$: C, 66.4; H, 5.6; N, 4.6. Found: C, 66.1; H, 5.3; N, 4.6 %.

2,2-Bis(5',7'-dimethoxy-1'-methylindol-3'-yl)propane (**47**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.10 g, 0.53 mmol), AR grade acetone (1 mL, excess) and acetic anhydride (4 mL) were combined and heated at reflux in an inert gas atmosphere for 6 h. No precipitate was formed so the reaction mixture was diluted with water and allowed to stand overnight. The resulting precipitate was filtered, washed with water and dried, affording a white solid. Radial chromatography using 50:50 dichloromethane: petroleum ether yielded 2,2-bis(5',7'-dimethoxy-1'-methylindol-3'-yl)propane **47** (20 mg, 18%) as pale tan crystals, mp 168-169 ˚C. IR (ν_{max}, cm^{-1}): 1580, 1495, 1456, 1413, 1305, 1258, 1212, 1149, 1116, 1045. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 221 (42,000), 229 (43,000), 266 (10,000), 272 (10,000), 300 (11,000), 307 (10,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.83 (6H, s, Me), 3.65, 3.85 and 3.93 (18H, 3s, OMe and NMe), 6.22 (2H, d, *J* 2.3 Hz, H6), 6.44 (2H, d, *J* 2.3 Hz, H4), 6.71 (2h, s, H2). ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 29.8 (2C, Me), 34.1 (C), 36.1 (2C, NMe), 55.3 and 55.8 (4C, OMe), 93.5 and 95.0 (4C, aryl CH), 122.6 and 122.9 (4C, aryl C), 127.2 (2C, aryl CH), 128.4, 147.8 and 152.9 (6C, aryl C). MS (+EI, *m/z*, %): 423 (M, 4), 422 (14), 407 (39), 216 (13). HRMS (*m/z*): Calcd for $C_{25}H_{30}N_2NaO_4$ $[M+Na]^+$, 445.2098. Found: 445.2091.

6,8-Dimethoxy-1,3,3,5-tetramethyl-1,3-dihydrobenz[*c,d*]indole (**48**)**.** 5,7-Dimethoxy-1-methylindole **1** (0.20 g, 1.05 mmol), AR grade acetone (2 mL, excess) and glacial acetic acid (4 mL) were combined and refluxed under an inert gas atmosphere for 7 h. No precipitate was formed so the reaction mixture was diluted with water and allowed to stand overnight. The resulting colloidal solution was extracted with dichloromethane, and the organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure yielding a brown oil. Radial chromatography using 50:50 dichloromethane: petroleum ether afforded 6,8-dimethoxy-1,3,3,5-tetramethyl-1,3-dihydrobenz[*cd*]indole **48** (28 mg, 10%) as a cream solid, mp 123-125 ˚C. IR (ν_{max}, cm^{-1}): 1605, 1513, 1464, 1409, 1283, 1234, 1214, 1116, 1089, 1053, 1023. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 234 (19,000), 249 (22,000), 300 (4,800), 314 (6,800), 328 (9,300), 342 (9,500), 355 (4,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.28 (6H, s, Me), 2.28 (3H, d, *J* 1.1 Hz, Me), 3.83 (3H, s, 6-OMe), 3.90 (3H, s, 8-OMe), 3.94 (3H, s, NMe), 5.24 (1H, br d, *J* 1.1 Hz, H4), 6.26 (1H, s, H7), 6.68 (1H, s, H2). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.5 (5-Me), 33.6 (2C, 3-Me), 33.9 (C3), 35.5 (NMe), 55.5 (8-OMe), 59.4 (6-OMe), 94.8 (C7), 109.5 (C5a), 119.8 (C8a), 121.9 (C2a), 123.8 (CH_2), 127.3 (C5), 127.3 C8b), 134.6 (C4), 147.3 (C8), 149.4 (C6). MS (+EI, *m/z*, %): 271 (M, 22), 256 (100), 241 (20). HRMS (*m/z*): Calcd for $C_{17}H_{21}NNaO_2$ $[M+Na]^+$, 294.1464. Found: 294.1457. Anal. calcd for $C_{17}H_{21}NO_2$: C, 75.2; H, 7.8; N, 5.2. Found: C, 74.7; H, 8.0; N, 4.7 %.

Methyl 1,5-dihydro-6,8-dimethoxy-3,5,5-trimethylbenz[cd]indole-2-carboxylate (**49**)**.** A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.15 g, 0.64 mmol) in 2,2-dimethoxypropane (2 mL) was heated at reflux with a catalytic quantity of *p*-toluenesulfonic acid for 16 h. Water was then added and the resulting gum

decanted from the solute, dissolved in ethyl acetate, washed sequentially with water and brine, dried ($MgSO_4$), and then the solvent evaporated *in vacuo*. The remaining red residue was purified *via* gravity column chromatography (2% MeOH/CH_2Cl_2) to give the title compound (55 mg, 34%) as a yellow powder, mp (softens at 174 ˚C) 183-187 ˚C. IR (ν_{max}, cm^{-1}): 3349, 1686, 1536, 1456, 1391, 1336, 1272, 1253, 1207, 1172, 997. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 245 (15,000), 273 (11,000), 301 (13,000), 312 (12,000), 366 (6,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.46 (6H, s, Me), 2.30 (3H, d, *J* 1.1 Hz, Me), 3.86, 3.89, and 3.94 (each 3H, s, OMe), 5.45 (1H, d, *J* 1.5 Hz, H4), 6.54 (1H, s, H7), 8.46 (1H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 22.3 and 28.5 (Me), 38.0 (C5), 51.4, 55.5, and 57.6 (OMe), 97.0 (C7), 141.0 (C4), 118.6, 120.1, 120.3, 120.5, 123.7, 127.7, 143.9 and 151.5 (aryl C), 161.9 ($\underline{C}O_2Me$). MS (+EI, *m/z*, %): 315 (M, 16), 300 (67), 269 (17), 268 (100), 182 (20), 134 (15), 112 (15). HRMS (*m/z*): Calcd for $C_{18}H_{21}NO_4$ $[M]^+$, 315.1471. Found: 315.1473. Anal. calcd for $C_{18}H_{21}NO_4.0.25H_2O$: C, 66.7; H, 6.8; N, 4.3. Found: C, 66.9; H, 6.7; N, 4.0 %.

Methyl 4-(2'-hydroxy-2'-indane-1',3'-dionyl)-5,7-dimethoxyindole-2-carboxylate (**50**)**.** A stirred suspension of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.25 g, 1.1 mmol) and ninhydrin (0.19 g, 1.1 mmol) in anhydrous methanol (4 mL) was heated at reflux with concentrated HCl (3 drops) for 1.5 h. After cooling to room temperature, the resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (0.38 g, 91%) as a yellow powder, mp 238-241 ˚C. IR (ν_{max}, cm^{-1}): 3412, 3323, 1744, 1698, 1584, 1536, 1438, 1326, 1246, 1216, 1145, 973. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 241 (42,500), 282 (14,300), 297 (17,300), 329 (5,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.45, 3.90, and 3.95 (each 3H, s, OMe), 6.28 (1H, s, H6), 7.86 (2H, m, ninhydrinyl), 7.90 (1H, d, *J* 2.3 Hz, H3), 8.03 (2H, m, ninhydrinyl), 9.01 (1H, bs, NH). ^{1}H NMR (300 MHz, d_6-DMSO): δ_H 3.25, 3.84, and 3.87 (each 3H, s, OMe), 6.52 (1H, s, H6), 6.89 (1H, s, OH), 7.74 (1H, s, H3), 7.98 (4H, s, ninhydrinyl), 11.68 (1H, bs, NH). The signals at 6.89 and 11.68 ppm exchanged with D_2O. ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 51.9, 56.1 and 57.5 (OMe), 78.3 (COH), 95.4 (C6), 111.6 (C3), 123.6 and 136.5 (ninhydrinyl CH), 111.2, 125.9, 127.2, 127.7, 140.4, 147.7, 150.0 (aryl C), 161.9 ($\underline{C}O_2Me$), 199.3 (CO). MS (+EI, *m/z*, %): 395 (M, 96), 363 (19), 320 (20), 304 (18), 265 (13), 262 (14), 235 (54), 230 (52), 204 (16), 203 (100), 144 (23), 105 (13), 104 (54). Anal. calcd for $C_{21}H_{17}NO_7$: C, 63.8; H, 4.3; N, 3.5. Found: C, 63.9; H, 4.4; N, 3.6 %.

Dimethyl 2,2-bis(5,7-dimethoxyindol-4-yl)indane-1,3-dione-2',2"-dicarboxylate (**51**)**.** Methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.25 g, 1.1 mmol) and ninhydrin (95 mg, 0.53 mmol) in anhydrous toluene (50 mL) was heated at reflux with a catalytic quantity of *p*-toluenesulfonic acid for 2 d using a Dean-Stark apparatus. After cooling to room temperature, the resulting precipitate was filtered through a frit, washed with a little toluene, then light petroleum (the combined filtrate was kept aside, see below), and dried to give the title compound (0.32 g, 98%) as a yellow powder, mp 238-240 ˚C (chloroform/light petroleum). IR (ν_{max}, cm^{-1}): 3457, 3343, 1704, 1322, 1253, 1210, UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 243 (60,600), 277 (19,300), 298 (29,700), 334 (8,850). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.51, 3.74 and 3.95 (each 6H, s, OMe), 6.34 (2H, d, *J* 2.3 Hz, H3' and H3"), 6.44 (2H, s, H6' and H6"), 7.76 and 7.98 (each 2H, m, ninhydrinyl), 8.75 (2H, bs, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 52.0, 58.6, 56.0 (OMe), 63.2 (bridging C), 96.6 (C6' and C6"), 111.3 (C3' and C3"), 123.5 and 134.6 (ninhydrinyl CH), 113.4, 125.7, 127.0, 129.1, 142.3, 147.4, 152.1 (aryl C), 162.4 ($\underline{C}O_2Me$), 197.7 (CO). MS (+EI, *m/z*, %): 612 (M, 18), 577 (17), 551 (20), 369 (17), 368 (40), 367 (22), 353 (16), 339 (37), 313 (66), 299 (25), 285 (22), 265 (27), 264 (68), 262 (58), 239 (82), 238 (37), 236 (100). HRMS (*m/z*): Calcd for $C_{33}H_{28}N_2O_{10}$ $[M]^+$, 612.1744. Found: 612.1748.

1-Pentanoyl-2,3-dihydroindole-2,3-dione (**52**)**.** Valeryl chloride (10.30 g, 85.4 mmol) was added dropwise over 10 min to a stirred suspension of isatin (12.0 g, 81.6 mmol) and pyridine (8 mL) in dichloromethane (140 mL) at room temperature. The mixture was heated at reflux for 1 h and then allowed to cool before the resulting red solution was washed briefly with dilute hydrochloric acid and dried ($MgSO_4$). The solvent was then reduced *in*

vacuo to approximately 50 mL before light petroleum was added to effect the precipitation of the product, which was then filtered and washed with light petroleum. Recrystallization from cyclohexane gave the title compound (15.8 g, 84%) as a bright yellow powder, mp 96-99 ˚C. IR (ν_{max}, cm^{-1}): 1783, 1757, 1708, 1609, 1466, 1331, 1169. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 239 (18,600), 295 (4,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.97 (3H, t, *J* 7.2 Hz, Me), 1.44 and 1.74 (each 2H, m, CH_2), 3.10 (2H, t, *J* 7.5 Hz, CH_2), 7.32 and 7.71 (each 1H, t, *J* 7.5 Hz, phenyl), 7.78 and 8.43 (each 1H, d, *J* 7.5 Hz, phenyl). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.7 (Me), 22.1, 26.1 and 37.9 (CH_2), 118.2, 125.2, 125.9 and 138.8 (aryl CH), 119.2 and 148.8 (aryl C), 157.7 and 173.0 (CONHCO), 180.2 (CO). MS (+EI, *m/z*, %): 231 (M, 4), 146 (100), 90 (28), 85 (44), 57 (52). Anal. calcd for $C_{13}H_{13}NO_3$: C, 67.5; H, 5.7; N, 6.1. Found: C, 67.5; H, 5.8; N, 6.2 %.

Dimethyl 5,5",7,7"-tetramethoxy-2'-oxo-[3,3':3'(2'*H*),3"-ter-1*H*-indole]-2,2"-dicarboxylate (**53**). **Method A.** A solution of methyl 5,7-dimethoxyindole-2-carboxylate **5** (0.25 g, 1.1 mmol) and *N*-pentanoylisatin **52** (0.25 g, 1.1 mmol) in anhydrous methanol (25 mL) was heated at reflux with concentrated HCl (10 drops) for 7 h. The resulting precipitate was filtered through a frit, washed with water, and dried to give the title compound (0.24 g, 75%) as a white powder, mp 299-301 ˚C. IR (ν_{max}, cm^{-1}): 3629, 3449, 3386, 1715, 1692, 1587, 1540, 1316, 1249, 1236, 1216. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 242 (57,200), 298 (37,400), 338 (10,200). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.44, 3.46, 3.76 and 3.77 (each 3H, s, OMe), 3.94 (6H, s, OMe), 5.79 (1H, bs, H3"), 6.46 (1H, s, H3), 6.50 (2H, s, H6 and H6"), 6.81 (1H, t, *J* 7.5 Hz, indolonyl), 6.87 and 7.12 (each 1H, d, *J* 7.5 Hz, indolonyl H4' and H7'), 7.16 (1H, t, *J* 7.5 Hz, indolonyl), 7.40 (1H, bs, NH'), 8.77 and 8.79 (each 1H, bs, NH and NH"). ^{1}H NMR (300 MHz, d_6-DMSO): δ_H 3.24 and 3.41 (each 3H, s, OMe), 3.65 and 3.89 (each 6H, s, OMe), 5.87 and 6.43 (each 1H, s, H3 and H3"), 6.56 and 6.61 (each 1H, s, H6 and H6"), 6.67 (1H, t, *J* 7.5 Hz, indolonyl), 6.77 and 6.92 (each 1H, d, *J* 7.5 Hz, indolonyl), 7.04 (1H, t, *J* 7.5 Hz, indolonyl), 10.14 (1H, bs, NH'), 11.35 and 11.48 (each 1H, bs, NH and NH"). ^{13}C NMR (75 MHz, d_6-DMSO): δ_C 56.9 (bridging C, C3'), 51.7, 51.8, 55.9, 56.0, 58.4 and 58.8 (OMe), 97.8 and 98.1 (C6 and C6"), 108.7 and 109.4 (C3 and C3"), 120.7, 124.6, 126.8 (indolonyl CH), 111.7, 116.4, 125.7, 125.8, 126.2, 127.1, 128.1, 136.6, 141.5, 146.2, 151.4 (aryl C), 161.6 and 161.7 ($\underline{C}O_2Me$), 178.6 (CONH). MS (MALDI, *m/z*, %): 599 (M, 48), 598 (100). Anal. calcd for $C_{32}H_{29}N_3O_9.H_2O$: C, 62.2; H, 5.1; N, 6.8. Found: C, 62.5; H, 4.8; N, 6.8 %.

Method B. A mixture of methyl 5,7-dimethoxyindole-2-carboxylate **2** (0.16 g, 0.70 mmol) and methyl *N*-butyl-2'-acetamidophenylglyoxylic ester **54** (0.10 g, 0.39 mmol) in anhydrous methanol (2 mL) was heated at reflux with concentrated HCl (1 drop) for 3 h. The resulting precipitate was filtered through a frit, washed with a little methanol, then water, and dried to give the title compound (0.17 g, 79%) as a white powder.

Methyl 2'-(*n*-butylamido)phenylglyoxylate (**54**)**.** A mixture of *N*-pentanoylisatin **52** (1.00 g, 4.32 mmol) in anhydrous methanol (2 mL) was heated at reflux with concentrated HCl (1 drop) for 2 h. The solvent was then evaporated and the remaining residue was purified *via* suction column chromatography (dichloromethane) to give the title compound (0.64 g, 56%) as a bright yellow syrup. IR (ν_{max}, cm^{-1}): 3323, 1742, 1704, 1655, 1608, 1584, 1530, 1450, 1204, 1161, 1000, 753. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 240 (19,000), 266 (8,000), 349 (4,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 0.95 (3H, t, *J* 7.2 Hz, Me), 1.42 and 1.74 (each 2H, m, CH_2), 2.46 (2H, t, *J* 7.2 Hz, CH_2), 3.99 (3H, s, OMe), 7.13 (1H, dt, *J* 1.1, 7.5 Hz, phenyl), 7.65 (2H, m, phenyl), 8.82 (1H, dd, *J* 1.1, 8.6 Hz, phenyl), 11.07 (1H, bs, NHCO). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.6 (Me), 22.2, 27.4 and 38.3 (CH_2), 52.9 ($CO_2\underline{Me}$), 120.8, 122.5, 133.5 and 137.1 (aryl CH), 117.0 and 142.6 (aryl C), 163.8 ($\underline{C}O_2Me$), 173.0 (CONH), 190.2 (CO). MS (+EI, *m/z*, %): 263 (M, 2), 204 (64), 146 (24), 120 (100), 92 (31), 90 (22), 85 (23), 57 (63). HRMS (*m/z*): Calcd for $C_{14}H_{17}NO_4$ $[M]^+$, 263.1158. Found: 263.1159.

Supplementary data

A checkcif file (compound **44**) is available as Supplementary Data. Graphical NMR spectroscopic data are also presented for compounds **5**, **15**, **19**, **44**, **49**, and **53**.

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