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Approaches to calix[3]indoles from activated indole carboxylic acids

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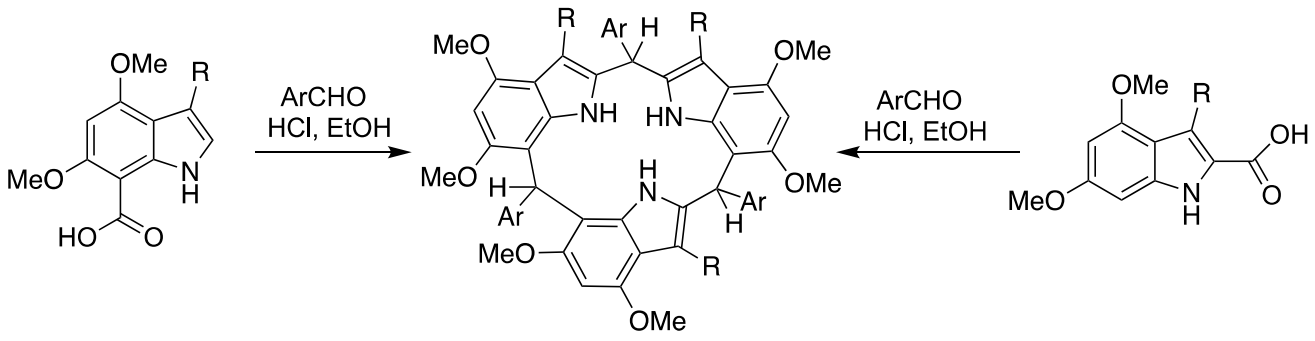
Abstract

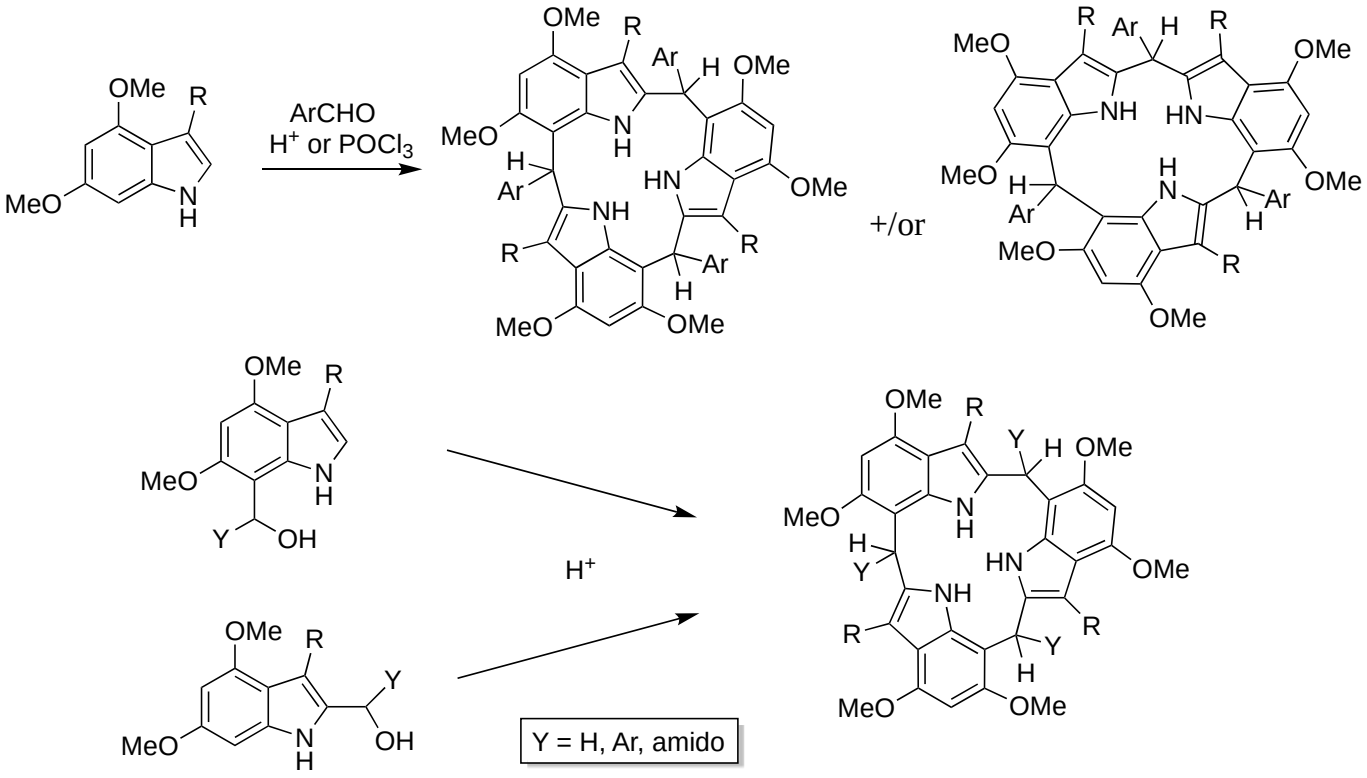
Acid-catalyzed reactions of 3-substituted 4,6-dimethoxyindole-7- and -2-carboxylic acids with aryl aldehydes generate unsymmetrically-oriented calix[3]indoles, with one 2,2'-linkage, one 2,7'-linkage and one 7,7'-linkage, in a wide range of yields. This behavior contrasts with similar reactions of the parent indoles, which more commonly yield the symmetrically-oriented calix[3]indoles, with three 2,7'-linkages. The starting material carboxylic acids were prepared via the hydrolysis of trifluoroacetyl and trichloroacetyl substituents formed by acylation of the parent 3-substituted-4,6-dimethoxyindoles.



Keywords: Indoles, carboxylic acids, calix[3]indoles, acid-catalysis, macrocycles

Introduction

We have previously reported the synthesis of calix[3]indoles from indole precursors activated by the presence of methoxy groups at C4 and C6.[1-6] Two direct methods have been used. The first involves the combination of a 3-substituted-4,6-dimethoxyindole with an aryl carbaldehyde under acidic conditions. The second requires the treatment of either 2- or 7-hydroxyalkyl-3-substituted-4,6-dimethoxyindoles with acid. Two different structural isomers of calix[3]indoles can be formed, depending on the reaction conditions. One has three 2,7'-linkages (the so-called symmetrically-oriented isomer) and the other has one 2,2'-linkage, one 2,7'-linkage and one 7,7'-linkage (the so-called unsymmetrically-oriented isomer) (Scheme 1). The symmetrically-oriented isomer generally takes up a flattened partial cone conformation, but under certain circumstances a cone conformation can be achieved by the introduction of suitable hydrogen bonding.[4,5] In addition, application of the second method can give rise to the formation of calix[4]indoles containing four 2,7'-linkages. There are four possible structural isomers of calix[4]indoles. A third method using a stepwise set of reactions can be applied to the synthesis of all possible calixindole isomers. In this paper we consider only the first two direct methods and the application of suitable indole carboxylic acids to the formation of calix[3]indoles, with concomitant decarboxylation. In general, we have found that in reactions of activated indoles with aryl aldehydes, under acidic reaction conditions involving phosphoryl chloride, the symmetrically-oriented isomer is selectively formed in rapid reactions with strongly electrophilic aldehydes, whereas the unsymmetrically-oriented isomer is preferred in slower reactions with weakly electrophilic aldehydes. We therefore decided to investigate reactions of the related less reactive indole carboxylic acids with aryl aldehydes, in the desire to achieve a simple, direct formation of unsymmetrically-oriented calix[3]indoles as a result of slower reactions.

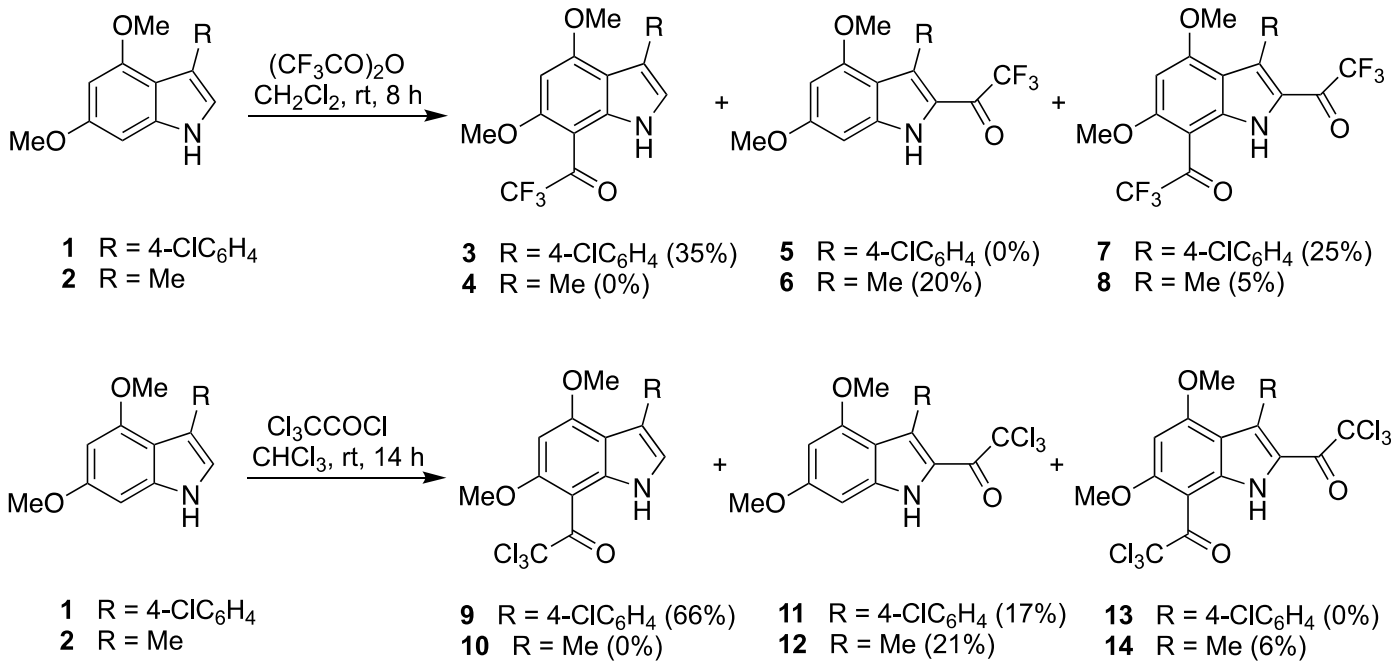


Scheme 1. Possible formation of calix[3]indoles from activated indole derivatives.

Results and Discussion

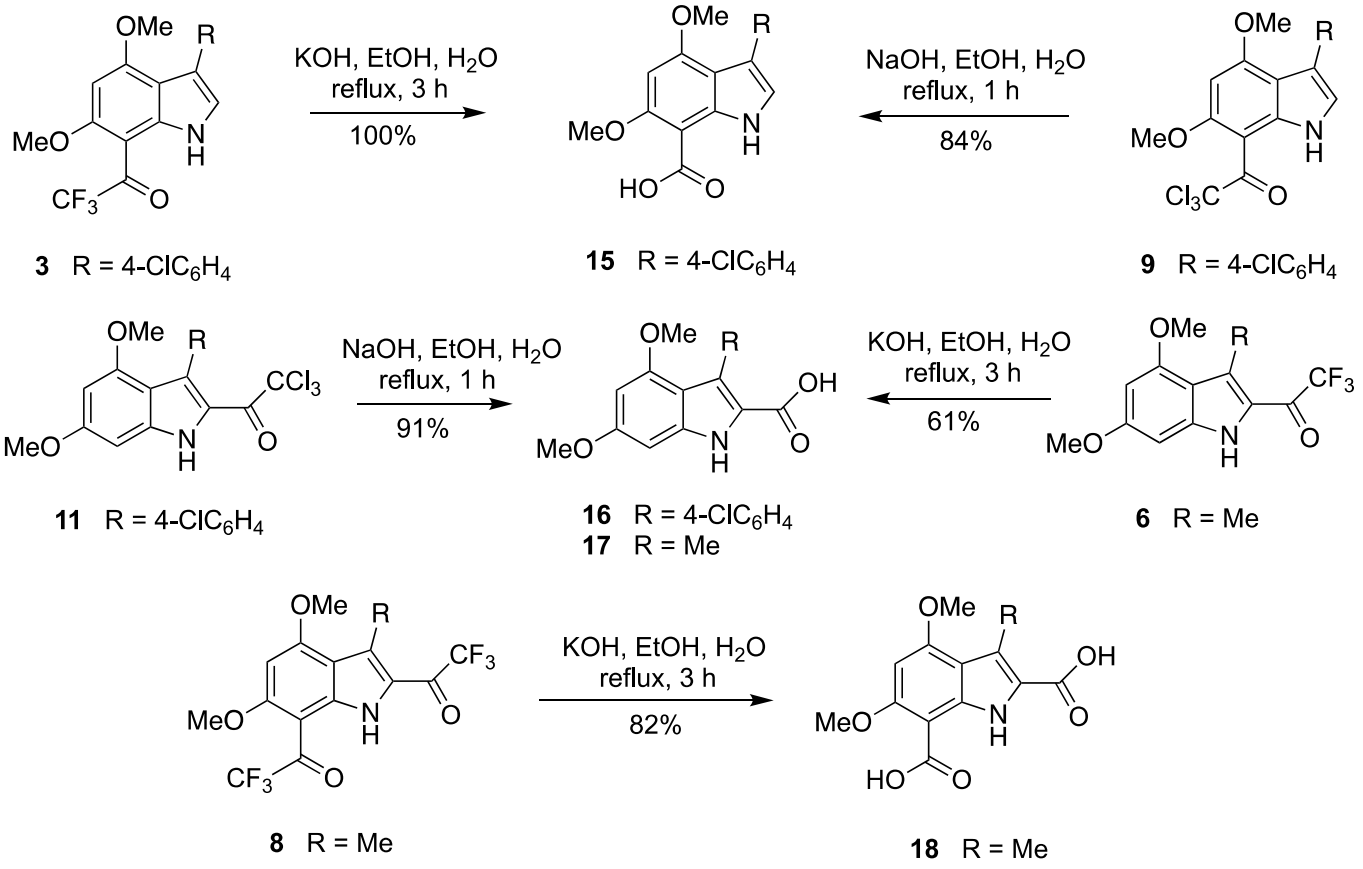
Preparation of the starting indole carboxylic acids

The chosen starting materials comprised examples of indole-7- and 2-carboxylic acids, indole-2,7-dicarboxylic acids, and 2-hydroxyalkylindole-7- and 2-carboxylic acids. These new compounds were prepared by routine reactions which made use of the activation bestowed on the indole nucleus by the methoxy groups. Treatment of the 3-arylindole **1** with trifluoroacetic anhydride gave the 7-trifluoracetyl indole **3** and the 2,7-ditrifluoroacetylindole **7**, but not the 2-trifluoroacetylindole **5** (Scheme 2). Similar reaction of the 3-methylindole **2** gave the 2-trifluoroacetylindole **6** and the 2,7-ditrifluoroacetylindole **8**, but not the 7-trifluoroacetylindole **4**. Treatment of indole **1** with trichloroacetyl chloride gave the 7-trichloroacetylindole **9** and the 2-trichloroacetylindole **11**, but not the 2,7-ditrichloroacetylindole **13**. Similar reaction of indole **2** gave the 2-trichloroacetylindole **12** and the 2,7-ditrichloroacetylindole **14**, but not the 7-trichloroacetylindole **10** (Scheme 2). Yields were generally low, but were not optimized because it was important to maintain the same conditions over the range of reactions for purposes of comparison.



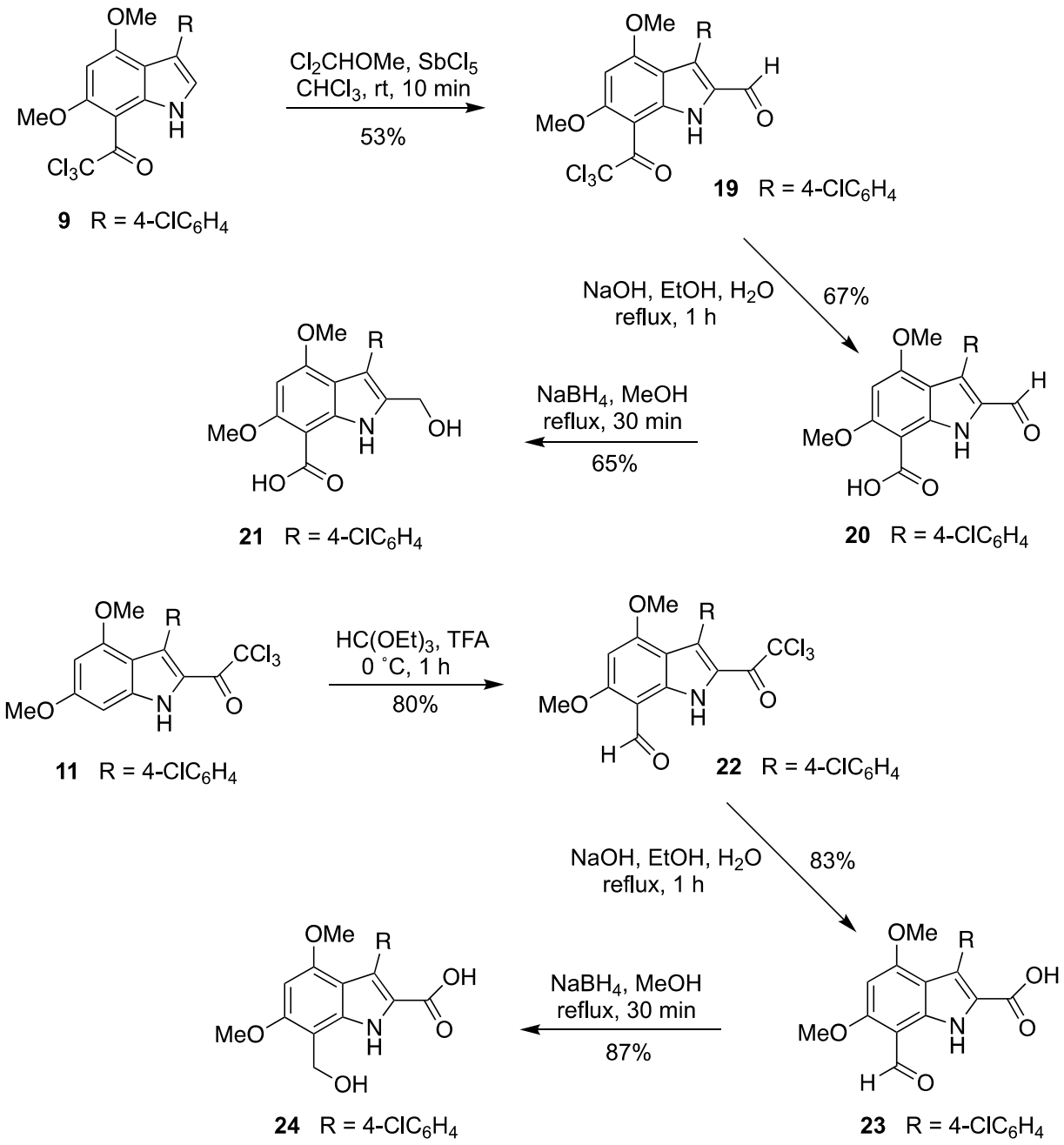
Scheme 2. Reaction of indoles **1** and **2** with trifluoroacetic anhydride and trichloroacetyl chloride.

The 3-arylindole-7-carboxylic acid **15** was obtained by base hydrolysis of either the trifluoroacetylindole **3** or the trichloroacetylindole **9** (Scheme 3). The 3-arylindole-2-carboxylic acid **16** was similarly derived from the trichloroacetylindole **11**, while the 3-methylindole-2-carboxylic acid **17** was derived from the trifluoroacetylindole **6**. Base hydrolysis of the ditrifluoroacetylindole **8** gave the 3-methylindole-2,7-dicarboxylic acid **18** (Scheme 3). Yields were generally high. The choice of sodium or potassium hydroxide relates to the solubility of the indoles. Conditions for the hydrolysis of trichloroacetyl compounds have been reported to use sodium hydroxide, so these were followed.[7]



Scheme 3. Formation of indole carboxylic and dicarboxylic acids **15**-**18**.

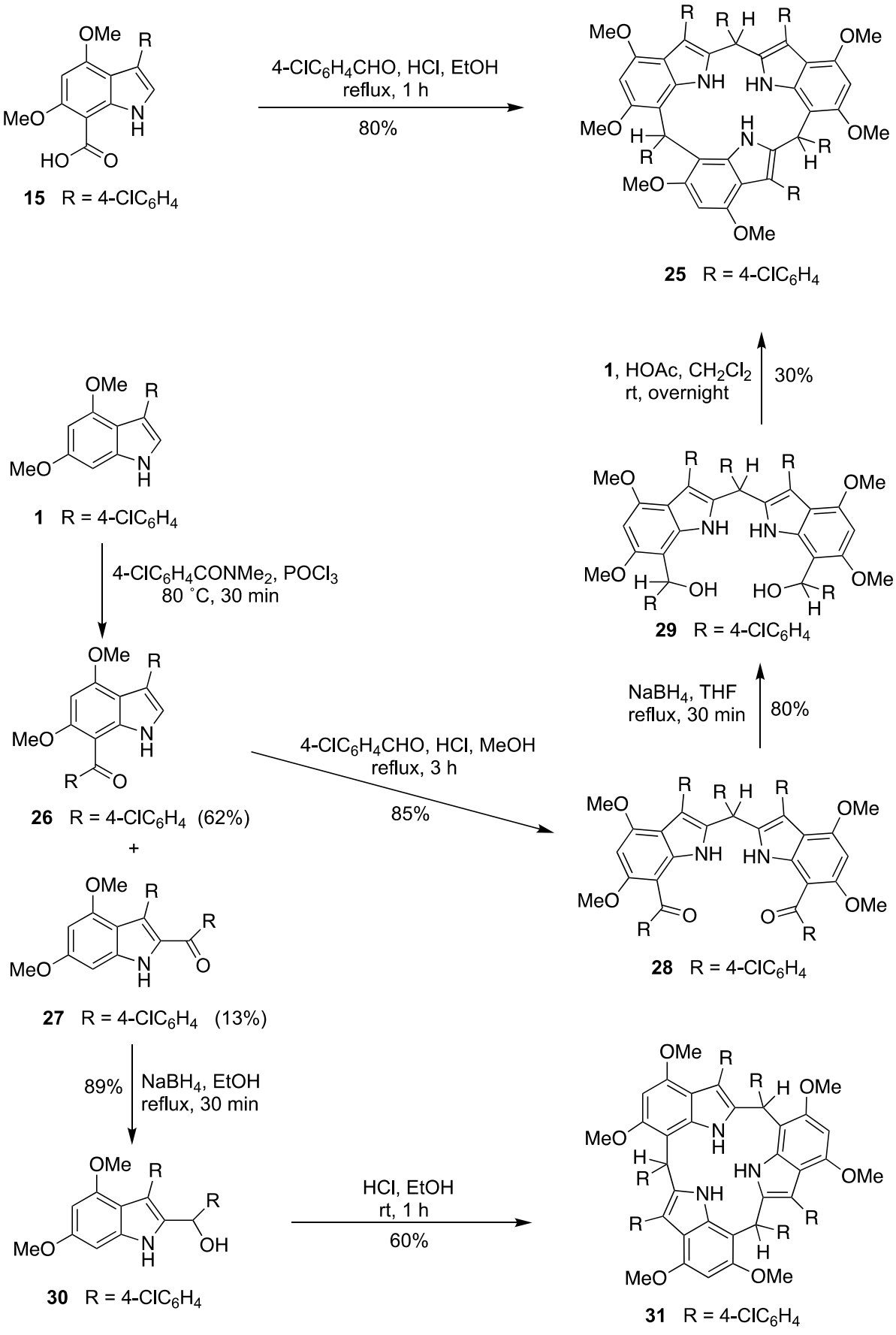
The 2-hydroxymethylindole-7-carboxylic acid **21** was prepared in a sequence of reactions from the indole **9**, involving formylation to give the 2-carbaldehyde **19**, hydrolysis of the trichloroacetyl group to give the indole acid **20**, followed by reduction of this compound with sodium borohydride to give the 2-hydroxymethylindole-7-carboxylic acid **21**. In a corresponding reaction sequence, the indole **11** was formylated at C7 to give the carbaldehyde **22**: this was hydrolysed to the indole acid **23**, which was reduced by sodium borohydride to give the 7-hydroxymethylindole-2-carboxylic acid **24** (Scheme 4). Neither hydroxy acids **21** nor **24** could be fully purified, so were submitted directly to further reactions (see later).



Scheme 4. Formation of hydroxymethylindole carboxylic acids **21** and **24**.

Reactions of indole carboxylic acid 15 with aryl aldehydes

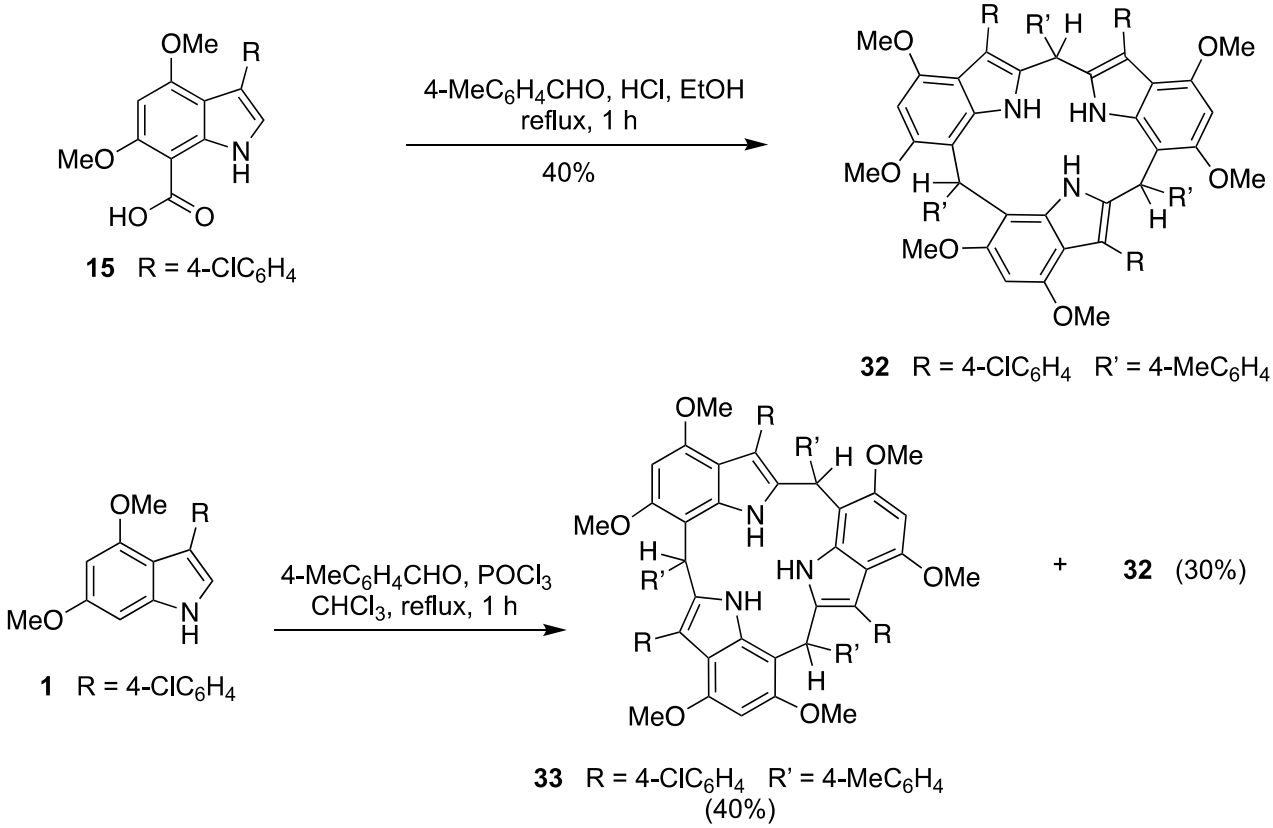
The indole-7-carboxylic acid **15** was heated under reflux with one equivalent of 4-chlorobenzaldehyde in ethanol containing concentrated hydrochloric acid and gave the unsymmetrically-oriented calix[3]indole **25** in 80% yield (Scheme 5). The structure of compound **25** was clear from NMR data, in particular with the application of ^{1}H-^{13}C and ^{1}H-^{15}N correlations, which allowed a distinction between symmetrically-oriented and unsymmetrically-oriented structures. However, in this case, the calix[3]indole **25** was also synthesized using an unambiguous stepwise route. Indole **1** was reacted with 4-chloro-*N*,*N*-dimethylbenzamide and phosphoryl chloride to give a mixture of the 7-(4-chlorobenzoyl)indole **26** and the 2-(4-chlorobenzoyl)indole **27** in 62 and 13% yields, respectively. The 7-isomer **26** was reacted with 4-chlorobenzaldehyde in methanol containing concentrated hydrochloric acid to give the diindolylmethane **28** in 85% yield. Reaction of this compound with



Scheme 5. Formation of calix[3]indoles **25** and **31**.

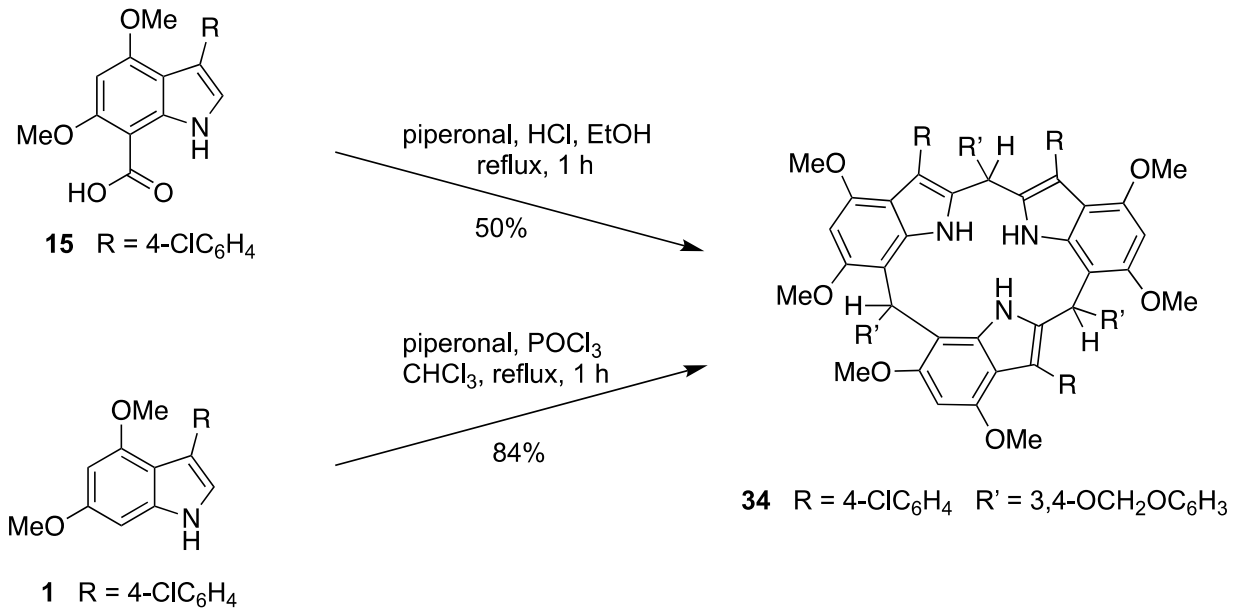
sodium borohydride gave the dialcohol **29**, which was without purification directly combined with one equivalent of indole **1** in dichloromethane containing acetic acid to give the unsymmetrically-oriented calix[3]indole **25** in 30% yield (Scheme 5). Furthermore, the 2-isomer **27** was reduced by sodium borohydride to the alcohol **30**, which without purification on treatment with ethanol containing concentrated hydrochloric acid was converted into the symmetrically-oriented calix[3]indole **31** in 60% yield (Scheme 5). Thus both calix[3]indole isomers were available for comparison and structural confirmation.

Similar treatment of the indole-7-carboxylic acid **15** with 4-tolualdehyde in ethanol containing concentrated hydrochloric acid gave the unsymmetrically-oriented calix[3]indole **32** in 40% yield. For the sake of comparison, the related symmetrically-oriented calix[3]indole **33** was obtained in 40% yield by the reaction of the indole **1** with 4-tolualdehyde in phosphoryl chloride: however in this case the unsymmetrically-oriented calix[3]indole **32** was also formed in 30% yield (Scheme 6)



Scheme 6. Formation of calix[3]indoles **32** and **33**.

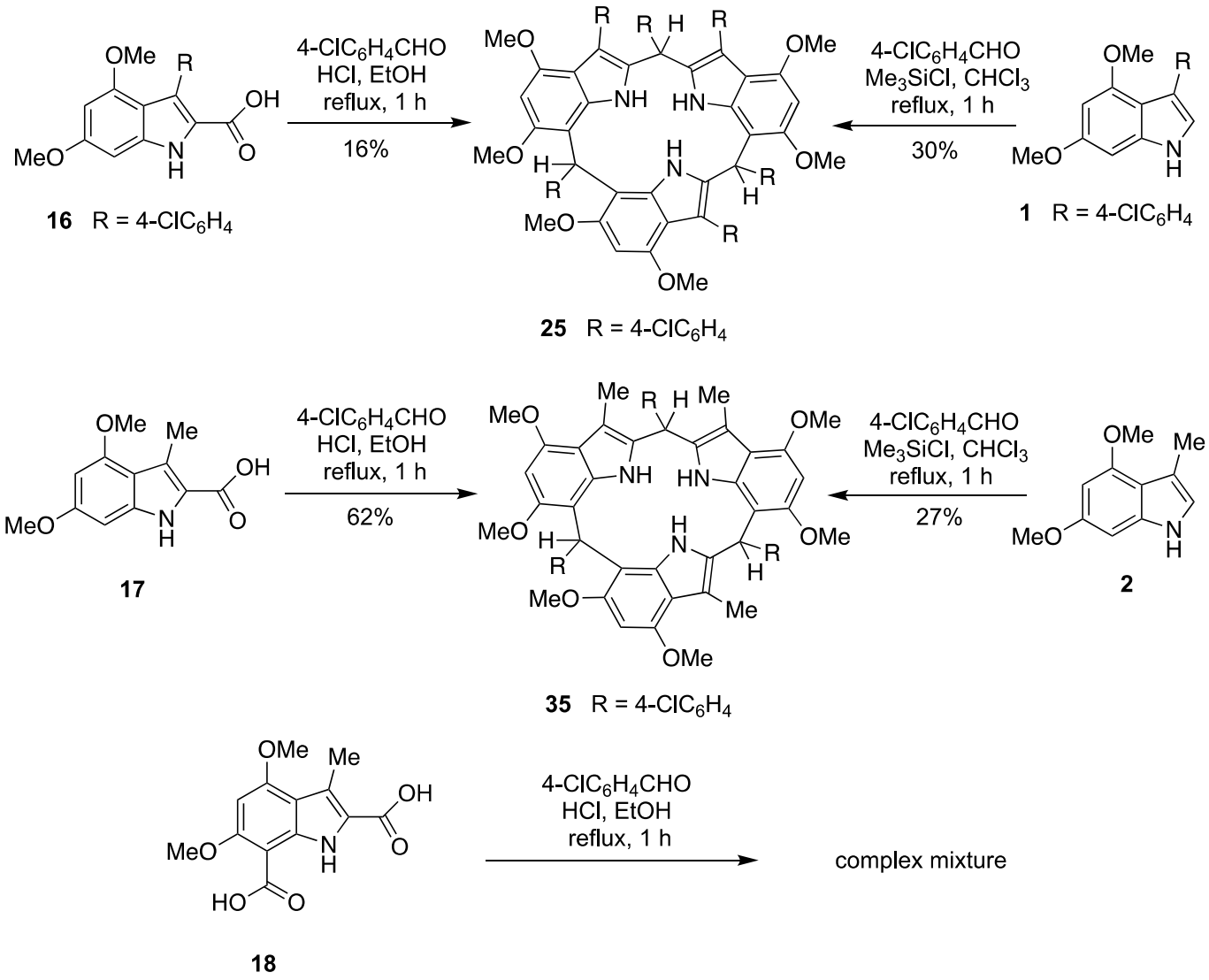
Similar treatment of the indole-7-carboxylic acid **15** with piperonal in ethanol containing concentrated hydrochloric acid gave the unsymmetrically-oriented calix[3]indole **34** in 50% yield (Scheme 7). In this case, the comparative reaction of the indole **1** with piperonal in phosphoryl chloride (conditions that usually favor formation of the symmetrically-oriented isomer) gave only the unsymmetrically-oriented calix[3]indole **34** in 84%. This result shows the effect of a relatively slower reaction because of the less electrophilic aldehyde.



Scheme 7. Formation of calix[3]indole **34**.

Reactions of indole carboxylic acids 16-18 with aryl aldehydes

To explore the situation with an indole-2-carboxylic acid, two starting materials were available, carboxylic acids **16** and **17**, with the latter being the more accessible. Both underwent reaction with 4-chloro-benzaldehyde in ethanol containing concentrated hydrochloric acid and gave the unsymmetrically-oriented calix[3]indoles **25** and **35** in 16 and 62% yield, respectively (Scheme 8). These compounds were also formed respectively in 30 and 27% yield by reaction of the indoles **1** and **2** with 4-chlorobenzaldehyde catalyzed by chlorotrimethylsilane. Reaction of the indole-2,7-dicarboxylic acid **18** with 4-chlorobenzaldehyde in ethanol containing concentrated hydrochloric acid gave only a complex mixture.



Scheme 8. Formation of calix[3]indoles **25** and **35**.

Reaction of hydroxymethylindole carboxylic acids 21 and 24 with acid

The crude hydroxymethylindole carboxylic acids **21** and **24** were submitted to a wide variety of acidic conditions but failed to generate clean reactions and isolable products. However, there was no evidence for the formation of any calix[3]indoles or calix[4]indoles, as were obtained from the related hydroxymethylindoles without carboxyl substituents.[2]

Conclusions

Acid-catalyzed reactions of 3-substituted 4,6-dimethoxyindole-7- and -2-carboxylic acids with aryl aldehydes generate unsymmetrically-oriented calix[3]indoles, with one 2,2'-linkage, one 2,7'-linkage and one 7,7'-linkage, in a wide range of yields. This behavior contrasts with similar reactions of the parent indoles, which more commonly yield the symmetrically-oriented calix[3]indoles, with three 2,7'-linkages. The starting material carboxylic acids were prepared via the hydrolysis of trifluoroacetyl and trichloroacetyl substituents formed by acylation of the parent 3-substituted-4,6-dimethoxyindoles. These results expand the scope for the

synthesis of calix[3]indoles by relatively simple one-pot acid-catalyzed reactions, and compliment other approaches involving linear sequences. The additional nucleophilic character of the 4,6-dimethoxyindoles leads to further new possibilities for synthesis of structurally diverse products.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC300F (^{1}H: 300 MHz, ^{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 UNSW Microanalytical Unit and 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.

Preparation of indole carboxylic acids

3-(4-Chlorophenyl)-4,6-dimethoxy-7-trifluoroacetylindole (3) and 3-(4-chlorophenyl)-2,7-di(trifluoroacetyl)-4,6-dimethoxyindole (7). A mixture of indole **1** (0.30 g, 1.00 mmol) and trifluoroacetic anhydride (1.00 g, 7.10 mmol) in dichloromethane (20 mL) was stirred at room temperature for 8 h. Water was added and the organic layer was extracted with dichloromethane. The organic layer was washed with water until neutral, then dried ($MgSO_4$). The solvent was evaporated and the product purified by chromatography on silica gel using ethyl acetate/light petroleum (50:50) as eluent. The first fraction yielded compound **3** (140 mg, 35%) as a yellow solid, mp 220 ˚C (from CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3350, 1635, 1580, 1320, 1220, 1150, 1090. UV/Vis (λ_{max}, nm, ε, cm^{-1}M^{-1}): 203 (44,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.94, 4.01 (each 3H, 2s, OMe), 6.21 (1H, s, H5), 7.08 (1H, d, J 2.4 Hz, H2), 7.35-7.48 (4H, m, aryl), 10.61 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.6, 56.6 (OMe), 87.7 (C5), 100.1 (CF_3), 110.6, 115.5, 118.6, 119.3 (aryl C), 121.7 (C2), 127.9 (aryl CH), 130.7 (aryl C), 131.1 (aryl CH), 132.2, 133.6, 139.4 (aryl C), 162.5 (CO). MS (+EI, *m/z*, %): 385 (M+2, $Cl^{37/37}$, 30), 383 (M+1, $Cl^{35/35}$, 90), 316 (35), 314 (100). Anal. calcd for $C_{18}H_{13}ClF_3NO_3$: C, 56.3; H, 3.4; N, 3.7. Found: C, 56.6; H, 3.7; N, 3.5%. The second fraction yielded compound **7** (100 mg, 25%) as a yellow solid, mp 200 ˚C (from EtOAc). IR (ν_{max}, cm^{-1}): 3400, 1685, 1640, 1600, 1590, 1560, 1330, 1220, 1190, 1150,1030, 990. UV/Vis (λ_{max}, nm, ε, cm^{-1}M^{-1}): 211 (34,000), 252 (20,000), 346 (18,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.80, 4.06 (each 3H, 2s, OMe), 6.16 (1H, s, H5), 7.26-7.35 (4H, m, aryl), 11.31 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 56.0, 56.8 (OMe), 88.7 (C5), 99.4 (CF_3), 113.7, 114.4, 118.2, 119.0, 124.7 (aryl C), 127.5 (aryl CH), 129.6, 131.1 (aryl C), 131.7 (aryl CH), 134.1, 140.3 (aryl C), 164.7, 166.4 (CO). MS (+EI, *m/z*, %): 481 (M+2, $Cl^{37/37}$, 25), 479 (M+1, $Cl^{35/35}$, 80), 412 (30), 410 (95), 69 (100). Anal. calcd for $C_{20}H_{12}ClF_6NO_4$: C, 50.1; H, 2.5; N, 2.9. Found: C, 50.2; H, 2.4; N, 2.8%.

4,6-Dimethoxy-3-methyl-2-trifluoroacetylindole (6) and 4,6-dimethoxy-3-methyl-2,7-di(trifluoroacetyl)-indole (8). A mixture of indole **2** (0.50 g, 2.60 mmol) and trifluoroacetic anhydride (2.60 g, 18.3 mmol) in dichloromethane (20 mL) was stirred at room temperature for 8 h. Water was added and the organic layer was

extracted with dichloromethane. The organic layer was washed with water until neutral, then dried ($MgSO_4$). The solvent was evaporated and the product purified by chromatography on silica gel using ethyl acetate/light petroleum (50:50) as eluent. The first fraction yielded compound **8** (50 mg, 5%) as an orange solid, mp 180 ˚C (from CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3420, 1650, 1590, 1510, 1340, 1240, 1200, 1160, 1100, 1020, 940. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 209 (29,000), 251 (15,000), 348 (12,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.80 (3H, s, Me), 4.05, 4.09 (each 3H, 2s, OMe), 6.16 (1H, s, H5), 11.05 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.5 (Me), 56.2, 56.7 (OMe), 88.1 (C5), 99.3 (CF_3), 114.8, 115.2, 118.6, 119.0, 124.8, 130.7, 140.7 (aryl C), 165.7, 166.4 (CO). MS (+EI, *m/z*, %): 384 (M+1, 5), 383 (M, 15), 315 (15), 314 (100). Anal. calcd for $C_{15}H_{11}F_6NO_4$: C, 47.0; H, 2.9; N, 3.7. Found: C, 47.0; H, 2.8; N, 3.5%. The second fraction yielded compound **6** (150 mg, 20%) as a yellow solid, mp 168 ˚C (from CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3360, 1710, 1600, 1570, 1410, 1320, 1260, 1250, 1150, 1070, 960. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 211 (131,000), 253 (43,000), 348 (86,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.80 (3H, s, Me), 3.85, 3.89 (each 3H, 2s, OMe), 6.10 (1H, d, *J* 1.5 Hz, H5), 6.31 (1H, d, *J* 1.5 Hz, H7), 8.58 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 12.6 (Me), 55.4, 55.6 (OMe), 85.3 (C5), 93.5 (C7), 114.7, 115.2, 119.0, 124.6, 140.7, 158.1 (aryl C), 162.9 (CO). MS (+EI, *m/z*, %): 288 (M+1, 15), 287 (M, 100), 287 (65). Anal. calcd for $C_{13}H_{12}F_3NO_3$: C, 54.4; H, 4.2; N, 4.9. Found: C, 54.3; H, 4.4; N, 4.7%.

3-(4-Chlorophenyl)-4,6-dimethoxy-7-trichloroacetylindole (9) and 3-(4-chlorophenyl)-4,6-dimethoxy-2-trichloroacetylindole (11). Trichloroacetylchloride (2.00 mL, 17.9 mmol) was added dropwise to a solution of the indole **1** (1.00 g, 3.50 mmol) in chloroform (20 mL). After completion of the addition, the solution was heated under reflux in N_2 overnight. The mixture was allowed to cool to room temperature, and water (20 mL) was added. The organic layer was extracted with dichloromethane (2 × 20 mL) and the organic layer was dried ($MgSO_4$), and the solvent evaporated. Column chromatography of the residue using dichloromethane/light petroleum (50:50) as eluent gave, as the first fraction, compound **9** as an orange solid (1.0 g, 66%), mp 178 ˚C (CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3380, 1610, 1580, 1560, 1340, 1245, 1215, 1080. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 212 (14,000), 256 (12,600), 343 (8,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.43, 3.99 (each 3H, 2s, OMe), 6.23 (1H, s, H5), 7.08 (1H, d, *J* 2.0 Hz, H2), 7.35-7.48 (4H, m, aryl), 10.29 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.5, 55.6 (OMe), 87.7 (C5), 98.7 (CCl_3), 110.8, 118.5, 121.5 (aryl C), 121.8 (C2), 127.8, 130.7, (aryl CH), 132.1, 133.8, 139.8, 160.4, 161.4 (aryl C), 182.4 (CO). MS (+EI, *m/z*, %): 435 (M+2, $Cl^{37/37}$, 7), 433 (M, $Cl^{35/35}$, 15), 316 (33), 314 (100). Anal. calcd for $C_{18}H_{13}Cl_4NO_3$: C, 49.9; H, 3.0; N 3.2. Found: C, 50.0; H, 3.0; N, 3.1%. The second fraction yielded compound **11** (300 mg, 17%) as a yellow solid, mp 214 ˚C (from CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3400, 1670, 1615, 1570, 1380, 1350, 1250, 1210, 1150. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 210 (21,200), 281 (14,300), 360 (9,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.63, 3.88 (each 3H, 2s, OMe), 6.13 (1H, d, *J* 2.0 Hz, H5), 6.45 (1H, d, *J* 2.0 Hz, H7), 7.36-7.48 (4H, m, aryl), 8.95 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.3, 55.7 (OMe), 87.6 (C5), 94.0 (C7), 96.3 (CCl_3), 113.2, 120.7 (aryl C), 127.3, 131.6 (aryl CH), 132.4, 132.9, 133.3, 139.1, 156.6, 161.5 (aryl C), 170.6 (CO). MS (+EI, *m/z*, %): 435 (M+2, $Cl^{37/37}$, 10), 433 (M^+, $Cl^{35/35}$, 25), 314 (35), 279 (90), 264 (50), 150 (100). Anal. calcd for $C_{18}H_{13}Cl_4NO_3$: C, 49.9; H, 3.0; N, 3.2. Found: C, 50.0; H, 2.9; N, 3.3%.

4,6-Dimethoxy-3-methyl-2-trichloroacetylindole (12) and 4,6-dimethoxy-3-methyl-2,7-ditrichloroacetyl-indole (14). The title compounds **12** and **14** were prepared according to the method of preparation of compound **9** using the indole **2** (0.80 g, 4.19 mmol) and trichloroacetyl chloride (2.30 mL, 21.0 mmol). The first fraction contained compound **14** as a green solid (120 mg, 6%), mp 188 ˚C (MeOH/CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3380, 1675, 1615, 1575, 1500, 1370, 1355, 1220, 1170, 1140, 980. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 208 (5,800), 232 (4,900), 344 (4,800). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.48 (3H, s, Me), 4.03, 4.08 (each 3H, 2s, OMe), 6.17 (1H, s, H5), 11.16 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.2 (Me), 55.8, 56.1 (OMe), 88.0 (C5), 96.0 (aryl C), 97.9, 98.2 (CCl_3), 113.9, 122.2, 132.5, 140.3, 164.2, 164.3 (aryl C), 172.0, 181.5 (CO). MS (+EI, *m/z*, %): 484

(M+2, $Cl^{37/37}$, 5), 483 (M+1, $Cl^{37/35}$, 10), 481 (M, $Cl^{35/35}$, 15), 377 (80), 349 (100). Anal. calcd for $C_{15}H_{11}Cl_6NO_4$: C, 37.4; H, 2.3; N, 2.9. Found: C, 37.6; H, 2.4; N, 3.1%. The second fraction contained compound **12** (300 mg, 21%) as a yellow solid, mp 178 ˚C (CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3395, 1640, 1620, 1590, 1500, 1370, 1320, 1260, 1220, 1200, 1150. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 213 (22,600), 346 (12,300), 253 (8,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.85 (3H, s, Me), 3.85, 3.90 (each 3H, 2s, OMe), 6.12 (1H, d, *J* 1.5 Hz, H5), 6.35 (1H, d, *J* 1.5 Hz, H7), 8.66 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 13.3 (Me), 55.4, 55.8 (OMe), 85.5 (C5), 93.2 (C7), 96.5 (CCl_3), 114.0, 121.3, 133.3, 139.6, 157.6, 162.4 (aryl C), 171.2 (CO). MS (+EI, *m/z*, %): 337 (M+2, $Cl^{37/37}$, 4), 335 (M, $Cl^{35/35}$, 5), 274 (55), 272 (100). Anal. calcd for $C_{13}H_{12}Cl_3NO_3$: C, 46.4; H, 3.6; N, 4.2. Found: C, 46.5; H, 3.7; N, 4.3%.

3-(4-Chlorophenyl)-4,6-dimethoxyindole-7-carboxylic acid (15). Method a: A mixture of 7-trichloroacetyl-indole **9** (50.0 mg, 0.12 mmol) and NaOH (50.0 mg, 1.25 mmol) was heated under reflux in ethanol/water (75:25; 25 mL) for 1 h. After cooling, the mixture was acidified with conc. HCl to afford compound **15** (32 mg, 84%) as a colorless solid, mp 236 ˚C (EtOAc). IR (ν_{max}, cm^{-1}): 3360, 1700, 1580, 1260, 1210. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 239 (20,000), 214 (12,000), 310 (11,000). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.87, 3.94 (each 3H, 2s, OMe), 6.46 (1H, s, H5), 7.19 (1H, s, H2) 7.37-7.51 (4H, m, aryl), 11.09 (1H, br s, NH), 12.06 (1H, br s, CO_2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.6, 57.3 (OMe), 89.2 (C5), 110.0, 115.9 (aryl C), 123.6 (C2), 123.9 (aryl C), 127.7 (aryl CH), 130.3 (aryl C), 130.9 (aryl CH), 134.8, 138.4, 158.1, 159.1 (aryl C), 167.1 (CO). MS (+EI, *m/z*, %): 335 (M+2, $Cl^{37/37}$, 5) 331(M, $Cl^{35/35}$, 20) 251 (50), 177 (55). Anal. calcd for $C_{17}H_{14}ClNO_4$: C, 61.6; H, 4.3; N, 4.2. Found: C, 61.3; H, 4.5; N, 4.1%.

Method b: A mixture of 7-trifluoroacetylindole **3** (0.14 g, 0.36 mmol) and KOH (0.50 g, 8.90 mmol) was heated under reflux in ethanol/water (75:25, 25 mL) for 3 h. After cooling, the mixture was acidified with conc. HCl to afford the title compound **15** (120 mg, 100%) as a colorless solid.

3-(4-Chlorophenyl)-4,6-dimethoxyindole-2-carboxylic acid (16). Compound **16** was prepared according to Method a for preparation of compound **15** using indole **11** (0.10 g, 0.23 mmol) and NaOH (1.00 g, 0.03 mol) as a colorless solid (70 mg, 91%), mp 232 ˚C (MeOH). IR (ν_{max}, cm^{-1}): 3400, 1650, 1630, 1580, 1520, 1270, 1200, 1140. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 201 (128,200), 249 (91,800), 308 (51,000). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.56, 3.77 (each 3H, 2s, OMe), 6.12 (1H, d, *J* 2.0 Hz, H5), 6.50 (1H, d, *J* 2.0 Hz, H7), 7.33-7.34 (4H, m, aryl), 11.61 (1H, br s, NH), 12.45 (1H, br s, CO_2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 55.1, 55.4 (OMe), 86.7 (C5), 92.7 (C7), 112.0, 121.4, 122.0 (aryl C), 126.5 (aryl CH), 131.1 (aryl C), 133.0 (aryl CH), 134.2, 138.0, 155.5, 159.2 (aryl C), 162.6 (CO). MS (+EI, *m/z*, %): 333 (M+2, $Cl^{37/37}$, 30), 331 (M, $Cl^{35/35}$, 95), 313 (90), 287 (100). Anal. calcd for $C_{17}H_{14}ClNO_4$: C, 61.6; H, 4.3; N 4.2. Found: C, 61.2; H, 4.3; N 4.6%.

4,6-Dimethoxy-3-methylindole-2-carboxylic acid (17). Compound **17** was prepared according to Method b for preparation of compound **15** using indole **6** (0.10 g, 0.34 mmol) and KOH (0.50 g, 0.87 mmol) as a colorless solid (50 mg, 61%), mp 236 ˚C. IR (ν_{max}, cm^{-1}): 3380, 1645, 1590, 1430, 1290, 1230, 1205, 1145, 1110. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 2.62 (3H, s, Me), 3.74, 3.81 (each 3H, 2s, OMe), 6.08 (1H, d, *J* 1.5 Hz, H5), 6.31 (1H, d, *J* 1.5 Hz, H7), 11.11 (1H, br s, NH), 12.50 (1H, br s, CO_2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 12.1 (Me), 55.3, 55.4 (OMe), 86.6 (C5), 91.9 (C7), 113.0, 119.3, 121.7, 156.3, 138.3, 159.2 (aryl C), 163.5 (CO). MS (+EI, *m/z*, %): 236 (M+1,15), 235 (100), 217 (75), 174 (45).

4,6-Dimethoxy-3-methylindole-2,7-dicarboxylic acid (18). Compound **18** was prepared according to the method of preparation of compound **17** using the indole **8** (0.30 g, 0.78 mmol) and KOH (1.00 g) as a colorless solid (180 mg, 82%), mp 260 ˚C. IR (ν_{max}, cm^{-1}): 3400, 3200, 1650, 1580, 1430, 1250, 1210, 1160, 970, 790, 760. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.40 (3H, s, Me), 3.98, 4.11 (each 3H, 2s, OMe), 6.20 (1H, s, H5), 6.84 (1H, br s, NH), 10.07, 10.81 (each 1H, 2br s, CO_2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 11.9 (Me), 55.5, 57.5 (OMe), 86.2 (C5), 105.0, 105.3, 112.1, 121.1, 138.7, 157.6, 159.9 (aryl C), 167.0 (CO). MS (+EI, *m/z*, %): 279 (M, 3), 235 (50), 217

(100), 159 (50). Anal. calcd for $C_{13}H_{13}NO_6 \cdot 0.2H_2O$: C, 55.2; H, 4.8; N, 4.9. Found: C, 55.2; H, 4.8; N, 4.7%.

Preparation of indole hydroxy carboxylic acids

3-(4-Chlorophenyl)-2-formyl-4,6-dimethoxy-7-trichloroacetylindole (19). A solution of the 7-trichloroacetyl-indole **9** (0.30 g, 0.70 mmol) and *α*,*α*'-dichloromethyl methyl ether (0.30 mL, 3.50 mmol) in chloroform (10 mL) was cooled at 0 ˚C. Antimony pentachloride (0.40 mL, 3.50 mmol) was added dropwise to the reaction mixture. After addition was complete, the reaction mixture was stirred at room temperature for 10 min, HCl (2M, 30 mL) was then added, followed by water (35 mL). The organic layer was separated and dried ($MgSO_4$). The solvent was evaporated off and the residue chromatographed using dichloromethane as eluent to yield the title compound **19** (200 mg, 53%) as a yellow solid, mp 233 ˚C (CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3380, 1640, 1560, 1520, 1200, 1150, 970, 810, 780, 710. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 204 (38,200), 253 (19,800), 335 (18,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.87, 4.02 (each 3H, 2s, OMe), 6.21 (1H, s, H5), 7.42 (4H, s, aryl), 9.54 (1H, s, CHO), 10.63 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.8 (OMe), 88.4 (C5), 97.9 (CCl_3), 98.6, 112.5 (aryl C), 127.9 (aryl CH), 128.7, 130.3, 131.8 (aryl C), 132.4 (aryl CH), 134.2, 140.3, 163.2, 163.3 (aryl C), 180.8, 182.2 (CO). MS (+EI, *m/z*, %): 461 (M, 10), 344 (30), 342 (100), 306 (25), 150 (80). Anal. calcd for $C_{19}H_{13}Cl_4NO_4 \cdot 0.2H_2O$: C, 49.1; H, 2.9; N, 3.0. Found: C, 49.1; H, 2.7; N, 2.7%.

3-(4-Chlorophenyl)-2-formyl-4,6-dimethoxyindole-7-carboxylic acid (20). According to the method of preparation of compound **16**, reaction of indole **19** (0.17 g, 0.37 mmol) with NaOH (1.0 g) gave the title compound **20** (89 mg, 67%) as a pale-yellow solid, mp 252 ˚C (CH_2Cl_2/MeOH). IR (ν_{max}, cm^{-1}): 3400, 3330, 1700, 1640, 1590, 1280, 1200, 980. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 256 (21,700), 331 (23,200), 288 (9,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.86, 4.17 (each 3H, 2s, OMe), 6.25 (1H, s, H5), 7.41 (4H, s, aryl), 9.57 (1H, s, CHO), 10.50 (1H, br s, NH), 10.99 (1H, br s, CO_2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.7, 57.6 (OMe), 87.7 (C5), 94.5, 112.8 (aryl C), 127.8 (aryl CH), 128.0, 130.3, 132.4 (aryl C), 132.5 (aryl CH), 134.2, 139.5, 161.0, 161.5 (aryl C), 165.8, 181.1 (CO). MS (+EI, *m/z*, %): 361 (M, 10), 359 (20), 306 (35), 177 (60), 164 (90), 150 (100), 137 (85). Anal. calcd for $C_{18}H_{14}ClNO_5 \cdot 0.5CH_2Cl_2$: C, 55.2; H, 3.8; N, 3.5. Found: C, 55.6; H, 3.7; N, 3.2%.

3-(4-Chlorophenyl)-2-hydroxymethyl-4,6-dimethoxyindole-7-carboxylic acid (21). Compound **20** (60.0 mg, 0.17 mmol) was partially dissolved in methanol (25 mL) and excess sodium borohydride (62.0 mg, 1.70 mmol) was added to the reaction mixture, which was then heated under reflux for 30 min. Water (15 mL) was added and the solution was then acidified with conc. HCl to yield a precipitate, which was filtered off and dried to yield the title compound **21** (40 mg, 65%), mp 206 ˚C. IR (ν_{max}, cm^{-1}): 3300, 1680, 1590, 1240, 1200, 1070, 900. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 238 (12,800), 224 (12,800), 208 (12,700), 312 (5,600). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.34 (1H, s, OH), 3.83, 4.14 (each 3H, 2s, OMe), 4.45 (2H, s, CH_2), 6.24 (1H, s, H5), 7.33 (4H, s, aryl), 10.58 (1H, br s, NH), 10.83 (1H, br s, CO_2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.4, 57.5 (OMe), 58.2 (CH_2), 87.1 (C5), 94.3, 112.4, 115.3 (aryl C), 127.5 (aryl CH), 131.8 (aryl C), 132.2 (aryl CH), 132.3, 133.1, 138.0, 157.7, 159.1 (aryl C), 166.7 (CO). Satisfactory microanalysis could not be obtained.

3-(4-Chlorophenyl)-7-formyl-4,6-dimethoxy-2-trichloroacetylindole (22). A solution of indole **12** (0.35 g, 0.81 mmol) in trifluoroacetic acid (2.5 mL) was cooled in ice and triethyl orthoformate (1.0 mL) was added dropwise to the solution, which was stirred in an ice-cooled bath for 1 h. Water (30 mL) was added and the mixture was extracted with dichloromethane, the extract dried ($MgSO_4$) and concentrated. The residue was chromatographed (dichloromethane as eluent) to give the title compound **22** (300 mg, 80%) as a yellow solid, mp 234 ˚C (CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3400, 1700, 1650, 1600, 1520, 1420, 1360, 1340, 1250, 1000. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 241 (20,600), 215 (14,000), 339 (14,000), 288 (8,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.78, 4.02 (each 3H, 2s, OMe), 6.13 (1H, s, H5), 7.26-7.35 (4H, m, aryl), 10.36 (1H, s, CHO), 11.56 (1 H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.8, 56.5 (OMe), 87.8 (C5), 95.9 (CCl_3), 103.7, 112.4, 122.0 (aryl C), 127.5 (aryl CH), 131.2 (aryl C), 131.6 (aryl CH), 132.2, 133.6, 137.7, 163.7, 166.6 (aryl C), 171.3, 187.9 (CO). MS

(+EI, *m/z*, %): 465 (M, $Cl^{37}/^{37}$, 3), 463 (M, $Cl^{37/35}$, 10), 461 (M, $Cl^{35}/^{35}$, 20), 459 (15), 344 (30), 342 (100), 307 (60). Anal. calcd for $C_{19}H_{13}Cl_4NO_4 \cdot 0.5CH_2Cl_2$: C, 46.5; H, 2.8; N, 2.8. Found: C, 46.1; H, 2.7; N, 2.9%.

3-(4-Chlorophenyl)-7-formyl-4,6-dimethoxyindole-2-carboxylic acid (23). According to the method of preparation of compound **20**, reaction of indole **22** (0.20 g, 0.43 mmol) with NaOH (40.0 mg, 1.00 mmol) gave compound **23** (130 mg, 83%) as a colorless solid, mp 234 ˚C (CH_2Cl_2/MeOH). IR (ν_{max}, cm^{-1}): 3450, 1680, 1650, 1540, 1280, 1240, 1160, 990. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 247 (31,000), 205 (29,500), 336 (18,000). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.79, 4.01 (each 3H, 2s, OMe), 6.44 (1H, s, H5), 7.36-7.37 (4H, m, aryl), 10.25 (1H, s, CHO), 10.70 (1H, br s, NH), 13.01 (1H, br s, CO_2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 56.3, 57.4 (OMe), 89.0 (C5), 126.8, 132.9 (aryl CH), 103.2, 111.6, 122.0, 123.1, 131.8, 132.8, 135.6, 161.9, 162.7 (aryl C), 165.1, 187.2 (CO). MS (+EI, *m/z*, %): 361 (M, $Cl^{37/37}$, 30), 359 (M, $Cl^{35/35}$, 100), 314 (7), 312 (30), 287 (20), 284 (30). Anal. calcd for $C_{18}H_{14}ClNO_5 \cdot 0.5H_2O$: C, 58.6; H, 4.1; N 3.8. Found: C, 58.3; H, 4.0; N, 3.8%.

3-(4-Chlorophenyl)-7-hydroxymethyl-4,6-dimethoxyindole-2-carboxylic acid (24). The indole **23** (0.10 g, 0.30 mmol) in methanol (15 mL) was treated with sodium borohydride (60.0 mg, 1.60 mmol) and the mixture was heated under refluxed in N_2 for 30 min, allowed to cool to room temperature then diluted with water. The mixture was acidified with HCl (1M) and the resulting precipitate was filtered and dried to give the title compound **24** (87 mg, 87%), mp 296 ˚C (CH_2Cl_2-MeOH). IR (ν_{max}, cm^{-1}): 3400, 3320, 1650, 1620, 1590, 1260, 1210, 1150, 1120, 990. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 206 (8,500), 250 (6,800), 313 (3,000). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.64, 4.16 (each 3H, 2s, OMe), 4.21 (2H, s, CH_2), 6.51 (1H, s, H5), 7.33 (4H, s, aryl), 10.47 (1H, br s, NH), 12.72 (1H, br s, CO_2H). The OH signal was not observed. ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 17.9 (CH_2), 55.5, 57.3 (OMe), 89.4 (C5), 126.6, 132.9 (aryl CH), 102.4, 112.4, 121.9, 122.7, 131.3, 133.7, 136.6, 153.6, 154.5 (aryl C), 163.3 (CO). MS (+EI, *m/z*, %): 361 (M, $Cl^{35/35}$, 5), 359 (15), 315 (70), 301 (80), 287 (100), 286 (55), 251 (100). Satisfactory microanalysis could not be obtained.

Reactions of indole carboxylic acids and related compounds

2,4,10,12,18,24-Hexa(4-chlorophenyl)-6,8,14,20,22-hexamethoxy-25,28,30-triazaheptacyclo-[17.5.2.23,9.05,29.013,27.023,26]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene (25). Method a: A mixture of indole **15** (50.0 mg, 0.15 mmol) and 4-chlorobenzaldehyde (21.0 mg, 0.15 mmol) in ethanol (25 mL) containing conc. HCl (1 mL) was heated under reflux for 1 h. The mixture was then allowed to cool to room temperature and the precipitate was filtered off and purified using chromatography with dichloromethane/light petroleum ether (50:50) as eluent to yield the title compound **25** (50 mg, 80%), mp >330 ˚C (CH_2Cl_2/light petroleum); IR (ν_{max}, cm^{-1}): 3420, 1620, 1600, 1350, 1270, 1220, 1100, 1000. ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.46, 3.65, 3.69, 3.78 (each 3H, 4s, OMe), 3.71 (6H, s, OMe), 5.34, 5.74, 6.47 (each 1H, 3s, CH), 6.09, 6.17, 6.24 (each 1H, 3s, H5), 6.37 (4H, s, aryl), 6.87-6.92 (9H, m, aryl), 7.06-7.20 (11H, m, aryl), 6.75, 7.43, 7.57 (each 1H, 3s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 37.6, 39.2, 39.7 (CH), 55.0, 55.1, 55.7, 57.0, 57.2, 57.6 (OMe), 89,4, 89.8, 90.1 (C5), 104.1, 105.8, 106.6, 113.5, 113.7, 114.6, 115.4 (aryl C), 127.1, 127.4, 127.5, 128.3, 128.7, 129.0, 131.6, 131.8, 131.9, 132.9, 133.3, 134.0 (aryl CH), 135.9, 136.3, 139.2, 139.4, 142.7, 153.3, 153.5, 154.1, 154.8, 155.0 (aryl C). MS (MALDI, *m/z*, %): 1231 (M, 60). Anal. calcd for $C_{69}H_{51}Cl_6N_3O_6 \cdot 4.6CH_2Cl_2$: C, 54.5; H, 3.7; N, 2.6. Found: C, 54.5; H, 3.7; N, 3.0%.

Method b: A mixture of indole **16** (50.0 mg, 0.15 mmol) and 4-chlorobenzaldehyde (21.0 mg, 0.15 mmol) in ethanol (25 mL) containing conc. HCl (1 mL) was heated under reflux for 1 h. The mixture was then allowed to cool to room temperature and the precipitate was filtered off and purified using chromatography with dichloromethane/light petroleum ether (50:50) as eluent to yield the title compound **25** (10 mg, 16%).

Method c: To a mixture of indole **1** (0.30 g, 1.00 mmol) and 4-chlorobenzaldehyde (0.15 g, 1.30 mmol) in chloroform (25 mL) was added trichloromethylsilane (0.20 mL, 1.70 mmol) and the mixture was heated under reflux for 1 h. Cold water was added to the mixture and the chloroform extract washed with 4M NaOH until

the washings were basic, then dried ($MgSO_4$) and concentrated. The residue was chromatographed using dichloromethane/light petroleum (50:50) as eluent to yield compound **25** (130 mg, 30%).

7-(4-Chlorobenzoyl)-3-(4-chlorophenyl)-4,6-dimethoxyindole (26) and 2-(4-chlorobenzoyl)-3-(4-chlorophenyl)-4,6-dimethoxyindole (27). Phosphoryl chloride (0.50 mL, 5.60 mmol) was added to warm (60 ˚C) 4-chloro-*N*,*N*′-dimethylbenzamide (2.00 g, 10.9 mmol) and the mixture was stirred for 5 min and indole **1** (1.50 g, 5.20 mmol) was added. The mixture was heated at 80 ˚C for 30 min. After cooling, NaOH (2M, 100 mL) was added and the mixture was extracted with dichloromethane (3 × 50 mL). The organic layer was washed with NaOH (2M, 100 mL), water, dried and concentrated. The residue was chromatographed using dichloromethane as eluent to afford as the first fraction, a yellow solid being the title compound **26** (1.40 g, 62%), mp 208 ˚C (EtOH/CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3320, 1620, 1580, 1350, 1285, 1130, 1100. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 266 (24,300), 373 (9,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.64, 3.92 (each 3H, 2s, OMe), 6.21 (1H, s, H5), 7.11 (1H, d, *J* 2.6 Hz, H2), 7.30-7.59 (8H, m, aryl), 10.29 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.3, 56.2 (OMe), 88.0 (C5), 103.8, 110.7, 117.8, 120.4 (aryl C), 121.8 (C2), 127.8, 127.9, 129.7, 130.7 (aryl CH), 131.8, 134.1, 136.7, 139.3, 140.7, 159.9 (aryl C), 194.6 (CO). MS (+EI, *m/z*, %): 428 (M+ 2, $Cl^{37/37}$, 15), 426 (M, $Cl^{35/35}$, 45), 111 (100). Anal.calcd for $C_{23}H_{17}Cl_2NO_3 \cdot 1.5H_2O$: C, 60.9; H, 4.4; N, 3.1. Found: C, 60.8; H, 4.2; N, 2.9%. The second fraction produced a yellow solid, being the title compound **27** (300 mg, 13%), mp 236 ˚C (EtOH/CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3360, 1640, 1605, 1520, 1420, 1290, 1230, 1210, 1140, 1090. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 265 (23,400), 346 (15,450). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.67, 3.88 (each 3H, 2s, OMe), 6.16 (1H, d, *J* 2.0 Hz, H5), 6.47 (1H, d, *J* 2.0 Hz, H7), 7.04-7.06 (4H, m, aryl), 7.27-7.29 (4H, m, aryl), 9.23 (1H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.1, 55.7 (OMe), 85.8 (C5), 93.5 (C7), 112.8, 125.1 (aryl C), 126.8, 127.8 (aryl CH), 130.0 (aryl C), 130.4 (aryl CH), 132.8 (aryl C), 133.0 (aryl CH), 136.3, 137.5, 138.9, 157.0, 161.4 (aryl C), 187.3 (CO). MS (+EI, *m/z*, %): 430 (M+4, $Cl^{37/37}$, 10), 428 (M+2, $Cl^{37/37}$, 55), 425 (100). Anal. calcd for $C_{23}H_{17}Cl_2NO_3 \cdot 0.5CH_2Cl_2$: C, 60.2; H, 3.8; N, 3.0. Found: C, 60.4; H, 3.4; N, 2.9%.

4-Chlorophenyl-di-{2-[7-(4-chlorobenzoyl)-3-(4-chlorophenyl)-4,6-dimethoxy]indolyl}-methane (28). The mixture of indole **26** (0.50 g, 1.20 mmol) and 4-chlorobenzaldehyde (0.10 g, 0.60 mmol) in methanol (25 mL) containing conc. HCl (1.8 mL) was heated under reflux for 3 h. The resulting precipitate was filtered off, washed with water and dried to yield the title compound **28** (800 mg, 85%) as a yellow solid, mp 268 ˚C (MeOH/CH_2Cl_2). IR (ν_{max}, cm^{-1}): 3400, 1620, 1590, 1550, 1490, 1290, 1220, 1090, 1020, 990. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 263 (50,300), 333 (21,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.60, 3.77 (each 6H, 2s, OMe), 5.63 (1H, s, CH), 6.13 (2H, s, H5), 6.99-7.52 (20H, m, aryl), 10.03 (2H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 25.4 (CH), 55.3, 56.2 (OMe), 88.2 (C5), 114.6 (aryl C), 127.4, 127.7 (aryl CH), 129.4, 129.5 (aryl C), 129.8, 131.7 (aryl CH), 132.1, 132.7, 133.1, 138.2, 140.6, 159.5 (aryl C), 194.2 (CO). MS (+EI, *m/z*, %): 974 (M, $Cl^{35/35}$, 7), 552 (30), 548 (100), 512 (40). Anal. calcd for $C_{53}H_{37}Cl_5N_2O_6 \cdot 1.5H_2O$: C, 63.5; H, 4.0; N, 2.8. Found: C, 63.5; H, 4.5; N, 2.4%.

4-Chlorophenyl-di-(2-{3-(4-chlorophenyl)-7-[(4-chlorophenyl)hydroxymethyl]-4,6-dimethoxy}indolyl)-methane (29). Excess sodium borohydride (0.50 g, 4.10 mmol) was added to a suspension of the indole **28** (0.30 g, 0.30 mmol) in tetrahydrofuran (25 mL) and the mixture was heated under reflux for 30 min. After cooling to room temperature, the solvent was evaporated to dryness, the residue was collected and washed with water to yield the title compound **29** (420 mg, 80%) as a colorless solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.61, 3.73 (each 6H, 2s, OMe), 5.49 (1H, s, CHPh), 6.13 (2H, s, CHO), 6.26 (2H, br s, OH), 6.34 (2H, s, H5), 6.68-6.97 (8H, m, aryl), 7.07-7.20 (4H, m, aryl), 7.23-7.39 (8H, m, aryl), 10.13 (2H, br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 55.5, 57.2 (OMe), 60.6, 67.5 (CH), 90.3 (C5), 108.3, 111.6, 113.4 (aryl C), 127.4, 127.6 (aryl CH), 127.8 (aryl C), 128.0, 129.0 (aryl CH), 129.6 (aryl C), 130.9 (aryl CH), 131.0 (aryl C), 132.1 (aryl CH), 132.5, 134.1, 135.9, 144.7, 152.8, 153.5, 157.4 (aryl C). Satisfactory microanalysis could not be obtained.

1-(4-Chlorophenyl)-1-[3-(4-chlorophenyl)-4,6-dimethoxyindol-2-yl]methanol (30). Sodium borohydride (0.20 g, 4.10 mmol) was added to a suspension of the indole **27** (0.20 g, 0.50 mmol) in absolute ethanol (20 mL). The mixture was heated under reflux for 30 min and after cooling to room temperature, the solvent was evaporated to dryness. The residue was collected and washed with water to yield the title compound **30** (180 mg, 89%), as a colorless solid, mp 170 ˚C (aqueous EtOH). IR (ν_{max}, cm^{-1}): 3320-3300, 1600, 1200, 1150, 1010, 820, 780, 710. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 223 (51,000), 276 (18,000). ^{1}H NMR (300 MHz, DMSO-d_6): δ_H 3.62, 3.73 (each 3H, 2s, OMe), 5.68 (1H, br s, OH), 6.10 (1H, d, *J* 3.8 Hz, H5), 6.14 (1H, s, CH), 6.48 (1H, br s, H7), 7.23 (2H, d, *J* 8.3 Hz, aryl), 7.33-7.39 (6H, m, aryl), 10.91 (1H, br s, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ_C 55.4, 55.7 (OMe), 66.5 (CH), 87.8 (C5), 92.1 (C7), 103.1, 106.4, 112.5, 114.6 (aryl C), 127.6, 128.5, 130.8 (aryl CH), 131.8 (aryl C), 132.8 (aryl CH), 135.1, 135.6, 138.0, 156.5, 157.2 (aryl C). MS (+EI, *m/z*, %): 430 (M+2, 7), 429 (20), 427 (30), 411 (40), 374 (100), 359 (20), 316 (20), 139 (55). Satisfactory microanalysis could not be obtained.

2,4,10,12,18,20-Hexa(4-chlorophenyl)-6,8,14,16,22,24-hexamethoxy-26,28,30-triazaheptacyclo-[17.5.2.23,9.211,17.05,29.013,27.021,25)triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene (31). The indole **30** (60.0 mg, 0.21 mmol) was partially dissolved in ethanol (10 mL) and conc. HCl (3 drops) was added to the mixture, which was stirred at room temperature for 1 h, then diluted with water (25 mL). The product was extracted with dichloromethane (3 × 15 mL), the organic layer was washed and dried ($MgSO_4$). The solvent was concentrated and the residue chromatographed using dichloromethane/light petroleum (50:50) as eluent to afford the title compound **31** (52 mg, 60%), mp 270 ˚C (EtOAc/light petroleum). IR (ν_{max}, cm^{-1}): 3540, 1620, 1600, 1495, 1350, 1220, 1160, 1100, 1020, 1000. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 302 (12,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.55 (6H, s, OMe), 3.72, 3.73, 3.88, 3.89 (each 3H, 4s, OMe), 5.84, 6.12, 6.46 (each 1H, 3s, CH), 6.23, 6.36, 6.39 (each 1H, 3s, H5), 6.49 (2H, d, *J* 8.2 Hz, aryl), 6.57 (2H, d, *J* 8.2 Hz, aryl), 6.74 (2H, d, *J* 8.7 Hz, aryl), 6.79-6.88 (6H, m, aryl), 7.04-7.19 (8H, m, aryl), 7.33 (4H, s, aryl), 6.75, 7.01, 7.96 (each 1H, 3s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 36.1, 37.8, 38.9 (CH), 55.1, 55.3, 55.4, 56.5, 57.2, 57.4 (OMe), 89.2, 89.8 (C5), 104.4, 105.3, 106.7, 112.1, 113.6, 113.9, 114.7, 115.1 (aryl C), 127.1, 127.2 (aryl CH), 127.5, 128.2 (aryl C), 128.5, 128.7 (aryl CH), 129.1, 129.5, 129.9, 130.9 (aryl C), 131.4, 131.6 (aryl CH), 132.1, 132.9, 133.4, 134.1, 134.3, 134.5, 134.7, 134.8, 136.4, 137.6, 138.9, 139.9, 153.1, 153.6, 153.8, 154.0 (aryl C). MS (MALDI, *m/z*, %): 1230 (M, 45). Anal. calcd for $C_{69}H_{51}Cl_6N_3O_6$: C, 67.3; H, 4.2; N, 3.4. Found: C, 67.0; H, 4.0; N, 3.1 %.

4,12,24-Tri(4-chlorophenyl)-6,8,14,20,22-hexamethoxy-2,10,18-tri-(4-tolyl)-25,28,30-triazaheptacyclo-[17.5.2.23,9.05,29.013,27.023,26]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene (32). The mixture of indole **15** (75.0 mg, 0.22 mmol) and 4-tolualdehyde (27.0 mg, 0.22 mmol) in ethanol (25 mL) containing concentrated HCl (1 mL) was heated under reflux for 1 h. After cooling, the precipitate was filtered off and chromatographed using dichloromethane/light petroleum (50:50) as eluent to yield the title compound **32** (40 mg, 40%), mp >330 ˚C (EtOAc/light petroleum). IR (ν_{max}, cm^{-1}): 3410, 1620, 1595, 1575, 1490, 1420, 1340, 1210, 1150, 1100, 1000. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 297 (7,000). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.18, 2.21, 2.35 (each 3H, 3s, Me), 3.37, 3.60, 3.64, 3.65, 3.67, 3.77 (each 3H, 6s, OMe), 5.37, 5.72, 6.49, (each 1H, 3s, CH), 6.09, 6.11, 6.77 (each 1H, 3s, H5), 6.32 (4H, d, *J* 8.2 Hz, aryl), 6.68 (2H, d, *J* 7.2 Hz, aryl), 6.78 (2H, d, *J* 8.2 Hz, aryl), 6.82-6.97 (7H, m, aryl), 7.04-7.15 (9H, m, aryl), 7.34, 7.40, 7.42 (each 1H, 3 br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 21.1, 21.2, 21.4 (Me), 36.1, 37.8, 38.9 (CH), 54.7, 55.1, 55.2, 57.4, 57.6, 57.9 (OMe), 90.1, 90.5, 90.8 (C5), 106.0, 107.8, 112.1, 112.5, 113.0, 114.0, 114.1, 114.8 (aryl C), 124.8, 127.0, 127.1, 127.3, 128.0, 128.9, 129.0, 129.2, 129.5 (aryl CH), 132.6, 133.5, 133.8, 135.4, 135.6, 136.0, 136.3, 137.7, 138.0, 138.1, 141.0, 152.9, 153.0, 153.3, 153.7, 154.6, 154.8 (aryl C). MS (MALDI, *m/z*, %): 1169 (M, 60). Anal. calcd for $C_{72}H_{60}Cl_3N_3O_6 \cdot 1.0H_2O$: C, 72.8; H, 5.3; N, 3.5. Found: C, 72.6; H, 5.5; N, 3.4%.

4,12,24-Tri-(4-chlorophenyl)-6,8,14,20,22-hexamethoxy-2,10,18-tri-(4-tolyl)-25,28,30-triazaheptacyclo-[17.5.2.23,9.05,29.013,27.023,26]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)dodecaene (32) and 2,10,18-Tri-(4-chlorophenyl)-4,12,20-tri(4-tolyl)-6,8,14,16,22,24-hexamethoxy-26,28,30-triazahepta-cyclo[17.5.2.23,9.211,17.05,29.013,27.021,25)triaconta-1(24),3,5(29),6,8, 11,13(27),14,16,19,21(25),22-dodecaene (33). Phosphoryl chloride (0.20 mL, 2.20 mmol) was added to an ice-cold solution of indole **1** (0.30 g, 1.10 mmol) and 4-tolualdehyde (0.13 g, 1.10 mmol) in dry chloroform (15 mL) and the mixture was heated under reflux for 1 h. Cold water (15 mL) was added and the chloroform extract was dried ($MgSO_4$) and concentrated to give a residue which was chromatographed using dichloromethane/light petroleum (50:50) as eluent. The first fraction gave the symmetrically linked calix[3]indole **33** (160 mg, 40%), mp 140 ˚C (EtOAc). IR (ν_{max}, cm^{-1}): 3410, 1730, 1620, 1600, 1515, 1490, 1340, 1275, 1210, 1150, 1090, 1000. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 289 (58,100). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 2.08, 2.27, 2.38 (each 3H, 3s, Me), 3.52, 3.54, 3.69, 3.70, 3.77, 3.78 (each 3H, 6s, OMe), 5.89 (1H, s, CH), 6.11 (2H, s, H5+CH), 6.22 (1H, s, H5), 6.23 (s1H, CH), 6.26 (1H, s, H5), 6.37-6.39 (4H, m, aryl), 6.59 (2H, d, *J* 7.7 Hz, aryl), 6.73 (2H, d, *J* 8.2 Hz, aryl), 6.80 (2H, d, *J* 8.2 Hz, aryl), 6.85-6.97 (6H, m, aryl), 7.00 (2H, s, NH), 7.01-7.13 (4H, m, aryl), 7.30-7.36 (4H, m, aryl), 8.08 (1H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 20.9, 21.3 (Me), 36.6, 38.8, 39.0 (CH), 55.2, 55.4, 56.9, 57.3, 57.9 (OMe), 89.4, 89.8, 90.5 (C5), 106.0, 106.7, 107.7, 112.1, 113.5, 113.8, 114.2, 114.6 (aryl C), 126.4, 126.9, 127.0, 127.1, 127.5, 128.4, 128.5, 129.3, 129.7 (aryl CH), 130.9, 131.4 (aryl C), 131.8, 132.0, 132.2 (aryl CH), 134.0, 134.3, 134.6, 134.9, 135.1, 135.4, 136.1, 136.3, 136.5, 137.3, 138.5, 152.8, 153.2, 153.7 (aryl C). MS (MALDI, *m/z*, %): 1169 (M, 60). Anal. calcd for $C_{72}H_{60}Cl_3N_3O_6 \cdot 0.5H_2O$: C, 73.4; H, 5.2; N, 3.6. Found: C, 73.5; H, 5.5; N, 3.3%. The second fraction gave compound **32** (120 mg, 30%), mp >330 ˚C (EtOAc/light petroleum).

4,12,24-Tri-(4-chlorophenyl)-6,8,14,20,22-hexamethoxy-2,10,18-tripiperonyl-25,28,30-triazaheptacyclo-[17.5.2.23,9.05,29.013,27.023,26]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene (34). Method a: The mixture of indole **15** (60.0 mg, 0.18 mmol) and piperonal (27.0 mg, 0.22 mmol) in ethanol (25 mL) containing concentrated HCl (1 mL) was heated under reflux for 1 h. After cooling, the precipitate was filtered off and chromatographed using dichloromethane as eluent to yield the title compound **34** (38.0 mg, 50%), as a pale colorless solid, mp 256 ˚C (EtOAc/light petroleum). IR (ν_{max}, cm^{-1}): 3460, 3420, 1745, 1635, 1600, 1490, 1440, 1345, 1240, 1220, 1050, 1000. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 204 (30,700), 292 (11,700). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 3.43, 3.61, 3.73, 3.75 (each 3H, 4s, OMe), 3.69 (6H, s, OMe), 5.30, 5.64, 6.42 (each 1H, 3s, CH), 5.82 (4H, s, CH_2), 5.88 (2H, s, CH_2), 6.11, 6.17, 6.37 (each 1H, 3s, H5), 6.01-6.12 (4H, m, aryl), 6.26-6.31 (4H, m, aryl), 6.43-6.57 (4H, m, aryl), 7.04-7.16 (9H, m, aryl), 6.29, 6.97, 7.38 (3H, s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 37.5, 38.7, 40.2 (CH), 54.6, 55.1, 55.2, 57.4, 57.8 (OMe), 89.8, 90.4, 90.8 (C5), 100.8, 100.9, 101.2 (CH_2O), 106.3, 107.5, 107.7, 108.2, 109.4, 111.7, 114.9, 120.1 (aryl C), 127.1, 127.3, 127.4, 131.8, 131.9 (aryl CH), 133.2, 133.5, 134.3, 135.6, 136.4, 137.6, 146.0, 147.6, 147.9, 153.5, 154.6, 155.1 (aryl C). MS (MALDI, *m/z*, %): 1258 (M, 60). Anal. calcd for $C_{72}H_{54}Cl_3N_3O_{12} \cdot 4.0H_2O$: C, 64.9; H, 4.7; N, 3.2. Found: C, 64.9; H, 4.2; N, 3.1%.

Method b: Phosphoryl chloride (0.20 mL, 2.20 mmol) was added to an ice-cold solution of indole **1** (0.30 g, 1.10 mmol) and piperonal (0.16 g, 1.00 mmol) in dry chloroform (15 mL) and the mixture was heated under reflux for 1 h. Cold water (15 mL) was added and the chloroform extract was dried ($MgSO_4$) and concentrated to give a residue which was chromatographed using dichloromethane as eluent to produce compound **34** (360 mg, 84%).

2,10,18-Tri-(4-chlorophenyl)-6,8,14,20,22-hexamethoxy-4,12,24-trimethyl-25,28,30-triazaheptacyclo-[17.5.2.23,9.05,29.013,27.023,26]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene (35). Method a: The mixture of indole **17** (30.0 mg, 0.13 mmol) and 4-chlorobenzaldehyde (17.8 mg, 0.13 mmol) in ethanol (25 mL) containing concentrated HCl (1 mL) was heated under reflux for 1 h. After cooling, the

precipitate was filtered off and chromatographed using dichloromethane-light petroleum (50:50) as eluent to yield the title compound **34** (25 mg, 62%), as a pale colorless solid, mp 214 ˚C (CH_2Cl_2/light petroleum). IR (ν_{max}, cm^{-1}): 3420, 3400, 1590, 1570, 1330, 1320, 1220, 1200, 1155, 1120, 1080, 980, 800. UV/Vis (λ_{max}, nm, ε, $cm^{-1}M^{-1}$): 232 (22,200), 285 (15,400). ^{1}H NMR (300 MHz, $CDCl_3$): δ_H 1.99, 2.34, 2.48 (each 3H, 3s, Me), 3.57, 3.60, 3.65, 3.85, 3.88, 3.93 (each 3H, 6s, OMe), 5.44, 5.87 (each 1H, 2s, CH), 5.98, 6.21, 6.31 (each 1H, 3s, H5), 6.25 (1H, d, *J* 8.6 Hz, aryl), 6.30 (1H, s, aryl), 6.34 (2H, s, CH + aryl), 6.62-6.65 (2H, m, aryl), 6.71 (2H, d, *J* 7.5 Hz, aryl), 6.95-7.01 (3H, m, aryl), 7.13 (2H, d, *J* 7.9 Hz, aryl), 6.41, 7.08, 7.52 (each 1H, 3br s, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ_C 10.3, 10.5, 10.8 (2C, Me), 37.4, 38.1, 39.2 (CH), 55.1, 55.2, 57.1, 57.5, 57.9 (OMe), 88.9, 89.1, 89.5 (C5), 104.1, 105.3, 106.3, 110.0, 125.9 (aryl C), 128.0, 128.6, 129.0, 129.5, 130.9, 132.0, 132.5 (aryl CH), 135.7, 137.8, 139.1, 140.1, 143.3, 153.1, 154.3 (aryl C). Anal. calcd for $C_{54}H_{48}Cl_3N_3O_6 \cdot 2.0H_2O$: C, 66.4; H, 5.4; N, 4.3. Found: C, 66.2; H, 5.6; N, 3.5%.

Method b: To a mixture of indole **2** (0.25 g, 1.31 mmol) and 4-chlorobenzaldehyde (0.18 g, 1.30 mmol) in chloroform (25 mL) was added trichloromethylsilane (0.2 mL, 1.7 mmol) and the mixture was heated under reflux for 1 h. Cold water was added to the mixture and the chloroform extract washed with 4M NaOH until the washings were basic, then dried ($MgSO_4$) and concentrated. The residue was chromatographed using dichloromethane/light petroleum (50:50) as eluent to yield compound **35** (110 mg, 27%).

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