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# Synthesis of tethered indoles in the search for conformationally controlled calixindoles: an indole 3-substituent tether

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**Abstract**—3-(2-Hydroxyphenyl)-4,6-dimethoxyindole **8** has been synthesised and linked to 1,3,5-tribromomethylbenzene and 1,2,4,5-tetrabromomethylbenzene to give the tri-indolyl and tetra-indolyl compounds **18** and **23**, respectively. Attempts to generate capped calix[3]-indoles and calix[4]indoles from these compounds were unsuccessful. 

## 1. Introduction

Calix[3]indoles and calix[4]indoles have been synthesised by the reaction of specifically activated indoles with aryl aldehydes, and also by the acid-catalysed cyclo-oligomerisation of indolyl methanols.[1–4] The use of alcohols derived from indolylglyoxylamides has led to the formation of minor amounts of the thermodynamically less stable cone configurational isomers together with major amounts of the thermodynamically more stable flattened partial cone isomers.[5] In an attempt to stabilise and maximise the cone conformation it was proposed to synthesise calix[3]indoles, which were capped either at the lower or upper rim through the cyclo-oligomerisation of suitably tethered indoles. Calixarenes have been capped via the upper rim using polymethylene bridges.[6–9] Calixresorcinarenes have been successfully capped via the upper rim using methylene, polymethylene, silyl and diazanaphthalene bridges.[10–11] In our case, the upper rim linkage strategy required an indole that had suitable functionality at the upper rim enabling it to be tied to a linker. This functionality was chosen to be a hydroxyphenyl group positioned at the three position of the indole ring. Molecular models indicated that a 2-hydroxyphenyl substituent would give rise to the least strained capped calix[3]indole. The target indole was therefore 3-(2-hydroxyphenyl)-4,6-dimethoxyindole **8**, the synthesis and reactions of which are described in this paper.

## 2. Results and discussion

General synthetic approaches to 3-aryl-4,6-dimethoxyindoles have been developed within our group.[12] 3-Aryl-4,6-dimethoxyindoles have been synthesised most effectively by the acid-catalysed cyclisation of N-protected anilino ketones followed by deprotection. N-protected anilino ketones are required because of their lower reactivity compared to the unprotected keto anilines,[13–16] which undergo a Bischler rearrangement in the presence of a small amount of aniline hydrobromide to give a 2-arylindole. The trifluoroacetyl protecting group is effective for the synthesis of 3-aryl-4,6-dimethoxyindoles[12,17] because of its ease of removal, although other protecting groups have also been used.[13–15]

### 2.1. Synthesis of 3-(2-hydroxyphenyl)-4,6-dimethoxyindole 8

2-Hydroxyacetophenone **1** was brominated using cupric bromide [18–20] to give the 2-hydroxyphenacyl bromide **2** in only moderate yield due to the presence of unreacted starting material and dibrominated product. The phenacylbromide **2** was then reacted with 3,5-dimethoxyaniline **3** in refluxing ethanol and potassium hydrogen carbonate to yield the anilino ketone **4** in 88% yield. This was stirred at room temperature in acetic anhydride for 3 h to yield the N-acetylanilino ketone **5** (Scheme 1). The complete hydrolysis of acetic anhydride and removal of the resulting acetic acid is crucial as the presence of acetic acid in the subsequent cyclisation step reduces the potency of trifluoroacetic acid such that cyclisation does not occur. This protection method is simpler and cheaper than the use of trifluoroacetyl protection, which also gave unreliable results and unwanted by-products, and has now become general for the synthesis of 3-aryl-4,6-dimethoxyindoles[12]. When anilino ketone **4** was added to the refluxing acetic anhydride the doubly protected anilino ketone **6** resulted. Cyclisation of the N-acetyl compound **5** was achieved with refluxing trifluoroacetic acid to yield the N-acetylindole **7** cleanly and reproducibly. The N,O-diacetyl compound **6** gave the same

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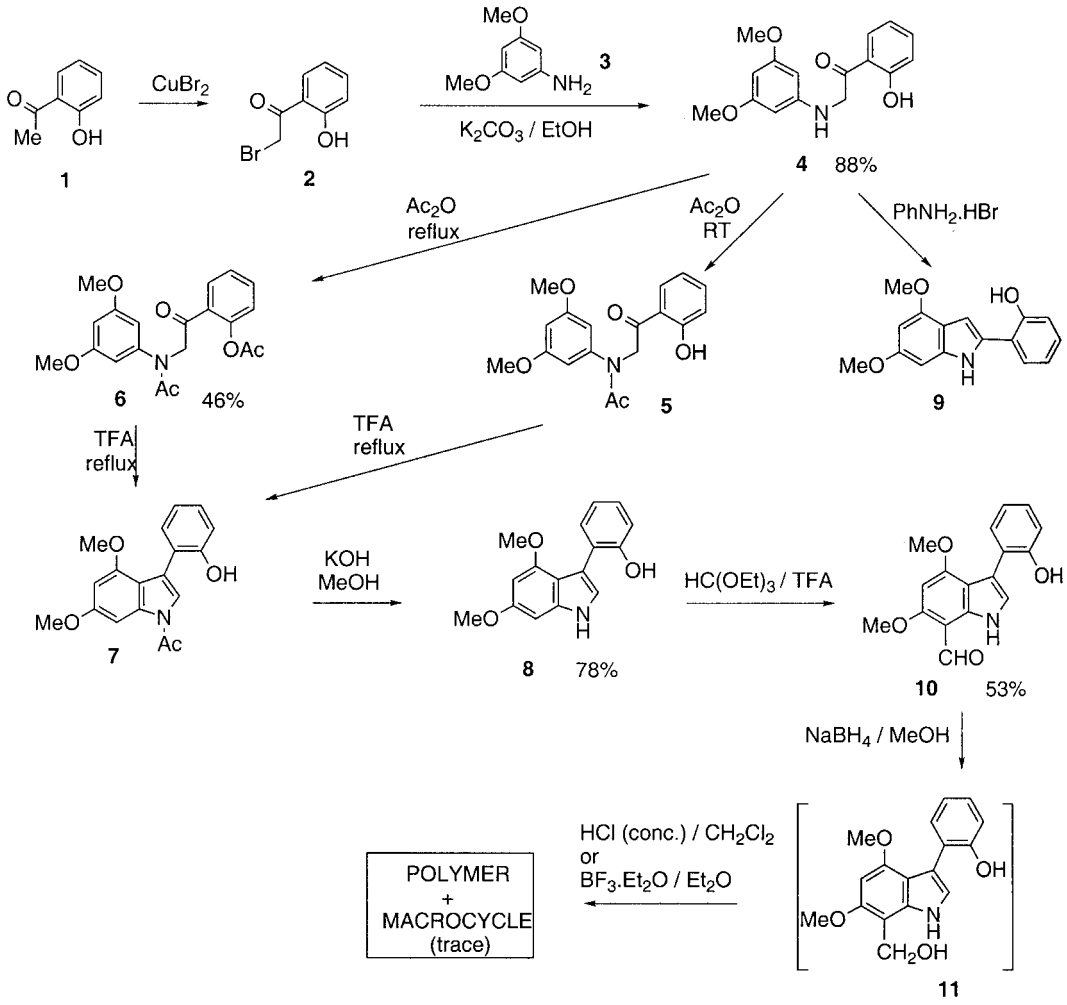



**Scheme 1.**

product on treatment with refluxing trifluoroacetic acid. The O-acetyl group was presumably cleaved by the strongly acidic cyclisation conditions. Removal of the N-acetyl protecting group was achieved by the use of potassium hydroxide in methanol to yield the desired new indole 3-(2-hydroxyphenyl)-4,6-dimethoxyindole **8** reproducibly in a yield of 78% from the anilino ketone **4** (Scheme 1). The 3-arylindole **8** was shown to be different from the corresponding 2-arylindole **9**, which was synthesized by reacting the anilino ketone **4** with aniline hydrobromide.[16]

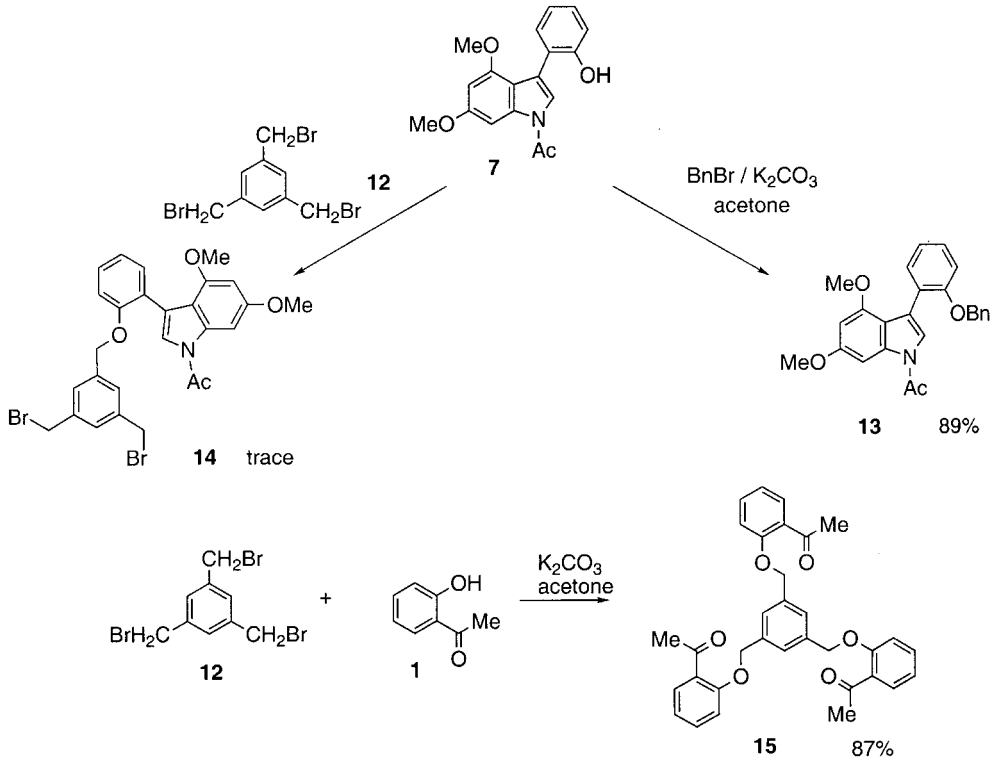
## 2.2. Reactions of 3-(2-hydroxyphenyl)-4,6-dimethoxyindole 8

To investigate the effect of a phenolic group on calixindole formation, the syntheses of methylene bridged and arylmethine bridged calixindoles were attempted. When the phenolic indole **8** was subjected to standard Vilsmeier formylation conditions numerous products were obtained. From this mixture small amounts of the 7-formyl and 2-formyl compounds were identified but these products were accompanied by a number of other unidentified products. Clearly, the phenolic hydroxyl group was involved and it also possibly activated the 3-aryl ring to substitution. Reaction of the indole **8** with triethylorthoformate in trifluoroacetic acid[21] gave the 7-formylindole **10** as the major product (Scheme 1). The success of this formylation method is attributed to protonation of the phenolic oxygen and consequently its effective protection. The 7-formylindole **10** could be reduced with sodium borohydride in methanol to give the hydroxymethyl compound **11**, although this was unstable and could not be characterised. Instead the hydroxymethyl indole **11** was formed in situ and then reacted with various acidic reagents which resulted in only trace amounts of the desired calix[3]indole accompanied by large amounts of polymeric material. The presence of the free phenolic group appears to increase the extent of polymerisation over macrocyclisation.

The phenolic indole **8** was also reacted with 4-chlorobenzaldehyde and phosphoryl chloride in an attempt to form arylmethine bridged calix[3]indoles. These attempts also resulted in only polymeric material.

To form an upper rim capped calix[3] indole, it was initially proposed to join three indole building blocks through the upper rim to a linker to obtain the capped calix[3]indole precursor. Macrocyclisation using the existing methodology could then lead to an upper rim capped calix[3]indole.

1,3,5-Tris(bromomethyl)benzene **12** was chosen as the linker because of its one-step synthesis from mesitylene




**Scheme 2.**

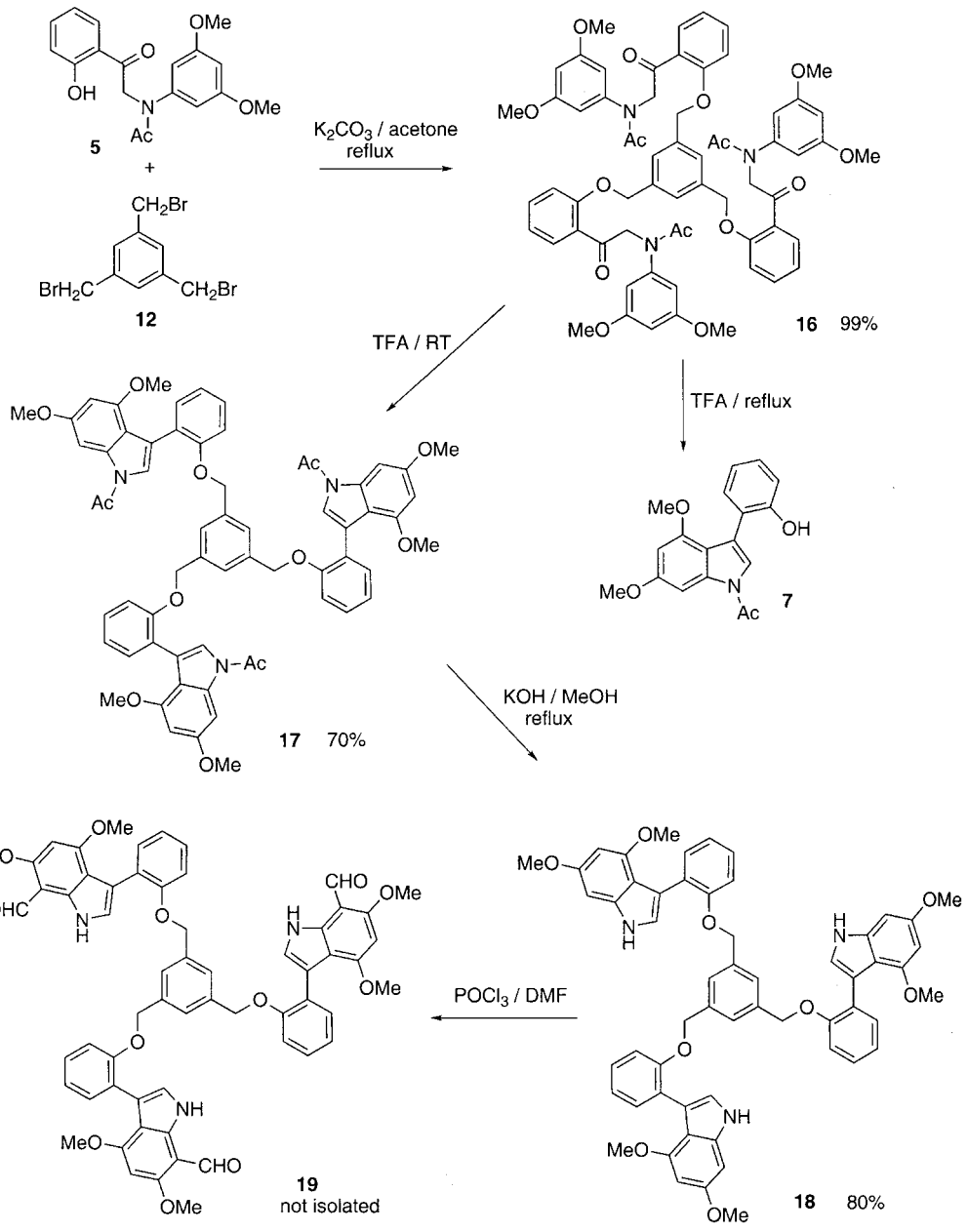
and the high reactivity of benzylic halides. Rather than using the free indole **8** as the building block and risk benzylation of the indole nitrogen, it was proposed to use its direct precursor, the N-acetyl indole **7**. The linker **12** was synthesized in low yield by reacting mesitylene with N-bromosuccinimide in carbon tetrachloride under irradiation by strong light.[22] The crude material from this reaction required repeated recrystallisations to afford the benzylbromide **12** in sufficient purity for subsequent steps.

Prior to linking 3 equiv. of the indole **7** to the tris(benzyl)bromide **12**, suitable conditions for the benzylation of indole **7** were sought. Reaction with benzyl bromide in refluxing acetone and potassium carbonate gave the desired benzylated compound **13** in 89% (Scheme 2). When indole **7** was reacted with the linker **12** in refluxing acetone and potassium carbonate, only the mono-substituted product **14** was observed and was identified only by electrospray mass spectroscopic analysis. The lack of reactivity could be explained by insolubility of the reactants or by steric hindrance. However, use of the more powerful solvent dimethyl formamide at 100°C, with the addition of a catalytic amount of potassium iodide, did not enable the reaction to proceed.

An alternative strategy involved reaction of the indole precursor 2-hydroxyacetophenone **1** with the linker **12** in order to reduce the effect of steric hindrance in the phenol: the indoles could subsequently be constructed while attached to the linker. Three moles of 2-hydroxyacetophenone **1** were reacted with tris(bromomethyl)benzene **12** in refluxing acetone and potassium carbonate to yield the desired tri-substituted benzene **15** (Scheme 2). The success of the synthesis using acetophenone **1** rather than indole **7** supported the hypothesis that 1,3,5-tris(bromomethyl)benzene **12** required a relatively small nucleophile to affect tribenzylation. Bromination of compound **15** was attempted using a wide variety of brominating conditions, but gave mixtures of under- or over-brominated products rather than the desired tribromo compound, so this approach was abandoned.

### 2.3. Synthesis of 1,3,5-tris(indolyl)benzene

It was thought that the N-protected anilino ketone **5** could undergo reaction three times with the linker **12** as it would avoid both the difficult synthetic steps and the steric hindrance about the phenol. The reaction between 3 mol of N-acetylanilino ketone **5** and 1 mol of 1,3,5-tris(bromomethyl)benzene **12** in refluxing acetone with potassium carbonate for 24 h yielded the desired tri-substituted compound **16** (Scheme 3). This reaction can be performed on a 10 g scale in 99% yield. The compound displays a three-fold axis of symmetry as shown by its $^1$H NMR spectrum and is a low melting, honeycomb-like solid that defied recrystallization. The tris-aniline **16** was then refluxed in trifluoroacetic acid in order to effect cyclisation to the tris-*N*-acetylindole **17** but instead gave the N-acetylindole **7** as the sole product. The strong acid presumably protonated the phenolic oxygen and followed by cleaving the benzyloxy bond. The reaction of compound **16** with trifluoroacetic acid at room temperature gave the tris-N-acetylindole **17**, with less than 5% of the cleaved product as observed by $^1$H NMR spectroscopy. The removal of the N-acetyl group proceeded in refluxing methanolic potassium hydroxide to give the capped calix[3]indole precursor **18** (Scheme 3). The $^1$H




**Scheme 3.**

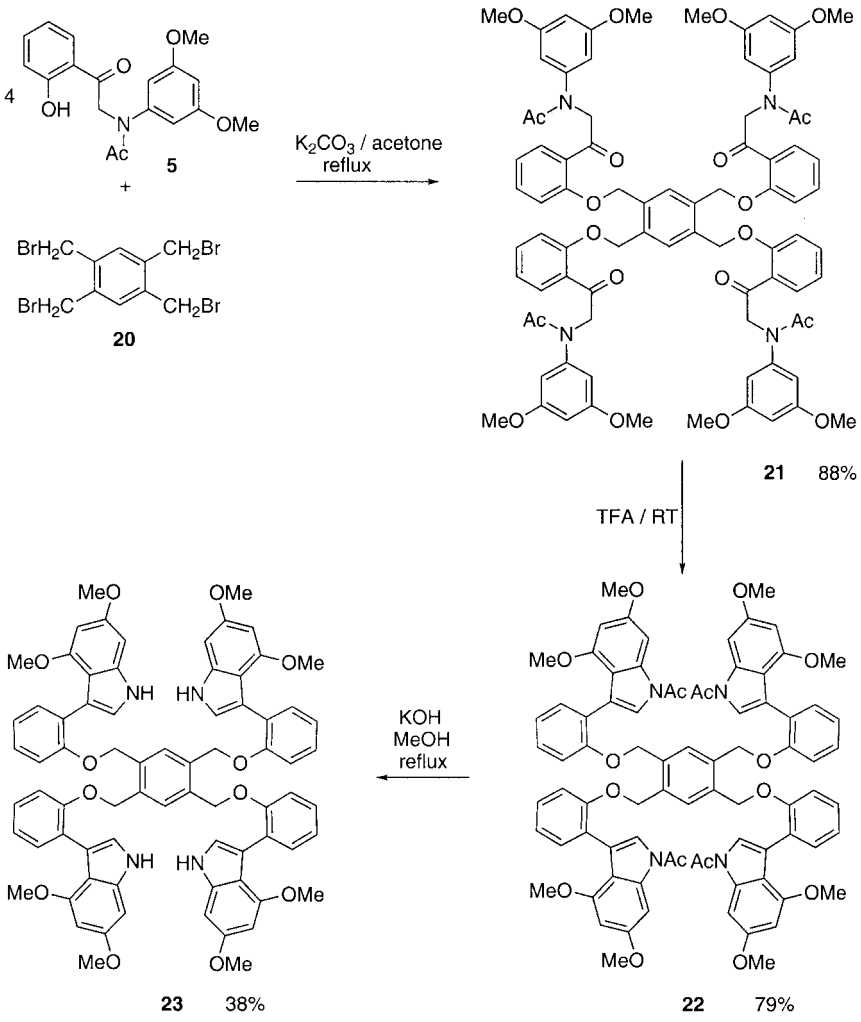
NMR spectrum of the tris-indole compound shows only one set of signals, reflecting the three-fold axis of symmetry.

## 2.4. Attempted capped calix[3]indole formation

In an attempt to form capped C-arylcalix[3]indoles, the tris-indole **18** was reacted with *p*-chlorobenzaldehyde and phosphoryl chloride in chloroform, but only polymeric material was observed by $^1$H NMR spectroscopy.

To obtain a capped methylene bridged calix[3]indole the tris-indole **18** was formylated using phosphoryl chloride and dimethyl formamide to yield the tris(formylindolyl)-benzene **19** which was not characterized (Scheme 3). Although standard Vilsmeier conditions failed to give satisfactory results with the parent indole **8**, the tris-indole **18** gave a clean and selective result due to the very bulky benzyl protecting group on the phenols. The resulting tris-(formylindolyl)benzene **19** was reduced in situ to the tris-alcohol using sodium borohydride in methanol but subsequent attempts to cyclise the alcohol with boron trifluoride etherate in tetrahydrofuran, 4-toluenesulfonic acid in dichloromethane or acetic acid failed to give anything other than the polymer. The tris-indole **18** was also reacted with formaldehyde in acetic acid in an attempt to form methylene bridged calix[3]indoles but this reaction also resulted in only polymeric material.

Tris-indole **18** was reacted with oxalyl chloride in dichloromethane and then quenched with tertiary butylamine to give a mixture of 2- and 7-substituted products. Owing to the number of isomers, this mixture was not separated but




**Scheme 4.**

reduced to the corresponding hydroxyethanoates with sodium borohydride in methanol and treated in situ with concentrated hydrochloric acid. The result of this reaction sequence was only the polymeric material.

### 2.5. Attempted capped calix[4]indole formation

The strategy described above can also be applied to the possible formation of capped a calix[4]indoles, with very little synthetic variation, simply requiring a tetrabromide instead of a tribromide. Consequently, 4 mol of the anilino ketone **5** were reacted with 1,2,4,5-tetrabromomethylbenzene **20** to give the tetra-substituted benzene **21**, which was cyclized to tetra-N-acetylindole **22** in moderate yield using trifluoroacetic acid at room temperature (Scheme 4). The tetra-substituted compound **21** required a considerably longer reaction time to effect complete cyclisation compared with the tri-substituted compound **17**. Deprotection of the tetra-N-acetylindole **22** was performed using methanolic potassium hydroxide to give a low yield of the desired tetra-indole **23**, which could not be characterised fully. When the crude tetra-indole **23** was reacted with 4-chlorobenzaldehyde and phosphoryl chloride in an attempt to form arylmethine capped calix[4]indoles only polymeric material was indicated by $^1$H NMR spectroscopy. Formaldehyde, in acetic acid was also reacted with the tetra-indole **23** and only polymer was observed rather than the desired methylene bridge capped calix[4]indole.

## 3. Conclusions

The failure of 3-phenolic indole **8** coupled to polybenzyl linkers to form capped calixindoles of either three or four indole units in size shows that this system is not suitable for the capping of cone calixindoles. The use of aryl groups as the major portion of the cap might be unsuitable due to the size of the aryl rings. Alkyl chains might be more appropriate linkers as they would allow greater flexibility in the cap portion of the molecule.

## 4. Experimental

### 4.1. General information

$^1$H and $^{13}$C NMR spectrum were recorded at 300 MHz on a Bruker AC300F spectrometer and at 500 MHz on a Bruker AM500 spectrometer. Chemical shifts were measured on the $\delta$ scale internally referenced to the solvent peaks:

$CDCl_3$ (7.30, 77.7 ppm) and $d_6$-DMSO (2.30, 39.0 ppm). EI mass spectral analyses were performed on a VG Quattro mass spectrometer at 70 eV ionisation voltage and 200°C ion source temperature. Microanalyses were performed by Dr H. P. Pham of the UNSW Microanalytical Unit. Infrared spectra were obtained on a Perkin–Elmer 298 IR spectrometer and a Mattson Sirius FTIR using KBr discs while ultraviolet spectra were carried out on a Hitachi U-3200 and Carey 5 spectrophotometers.

**4.1.1. 2-Hydroxyphenacylbromide**[19] **(2).** Cupric bromide (100.25 g, 0.449 mol) was partially dissolved in ethyl acetate (400 ml) and brought to reflux. 2-Hydroxyacetophenone **1** (27.1 ml, 0.225 mol) was dissolved in chloroform (200 ml) and added rapidly to the refluxing solution and the mixture heated overnight. The solution was allowed to cool and the cuprous bromide was filtered off and washed with ethyl acetate. The combined organic phases were washed with copious amounts of water until neutral, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield **2** as golden oil (46.3 5 g, 96%), which solidified on standing at room temperature. This material was used without further purification.

**4.1.2. 2-Hydroxy-(3,5-dimethoxyanilino)-acetophenone (4).** A mixture of 3,5-dimethoxyaniline **3** (2.65 g, 17.3 mmol), 2-hydroxyphenacylbromide **2** (5.66 g, 26.3 mmol) and sodium bicarbonate (1.55 g) in anhydrous ethanol (50 ml) was refluxed for 2.5 h. The mixture was allowed to cool to room temperature and the resulting yellow precipitate was filtered off, washed with water (250 ml) and dried to yield the anilino ketone **4** (4.37 g, 88%) as pale cream *needles*, mp 158–159°C (from ethyl acetate/light petroleum) (Found: C, 66.9; H, 6.2; N, 4.8. $C_{16}H_{17}NO_4$ requires C, 66.9; H, 6.0; N, 4.9%); $\nu_{max}$, 3407w, 1644m, 1620m, 1583m, 1199m, 1156m, 756m $cm^{-1}$; $\lambda_{max}$ 251 ($\epsilon$ 17,300), 327 nm (3,800); $\delta_H$ ($d_6$-DMSO) 3.75 (6H, s, OMe), 4.74 (2H, s, $CH_2$), 5.87 (1H, s, aryl), 5.97 (2H, d, $J$=1.1 Hz, aryl), 7.05, 7.60 (2H, 2t, $J$=7.5 Hz, aryl), 7.11, 8.04 (2H, 2d, $J$=7.4 Hz, aryl); $\delta_C$ (d6-DMSO) 54.8 ($CH_2$), 58.2 (OMe), 92.4, 94.8, 121.2, 122.5, 133.6, 139.2 (aryl CH), 123.8, 153.5, 163.7, 164.7 (aryl C), 204.5 (carbonyl C). *m/z* 287 (M, 10%), 167 (10), 166 (100).

**4.1.3. N-Acetyl-2-hydroxy-(3,5-dimethoxyanilino)-acetophenone (5), 1-acetyl-3-(2-hydroxyphenyl)-4,6-dimethoxyindole (7) and 3-(2-hydroxyphenyl)-4,6-dimethoxyindole (8).** The anilino ketone **4** (2.02 g, 7.03 mmol) was partially dissolved in acetic anhydride (10 ml) and stirred at room temperature for 3 h. Water (2 ml) was added and the solution was warmed to 50–60°C. Water was then added slowly so that the temperature did not drop below 50°C until the volume was tripled. Stirring was continued until the solution cooled to room temperature (approx. 1 h.). The solution was extracted with ethyl acetate, the organic phase washed with water until neutral, saturated sodium hydrogen carbonate solution, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield golden oil that was used directly in the next step. Crystallization of a sample from ethyl acetate/light petroleum gave the protected anilino ketone **5** as light cream *needles*, mp 111–112°C (Found: C, 65.8; H, 6.0; N, 4.2. $C_{18}H_{19}NO_5$ requires C, 65.6; H, 5.8; N, 4.3%); $\nu_{max}$ 3136w, 1662m, 1596m, 1200m, 1155m, 728m, 707m $cm^{-1}$; $\lambda_{max}$ 252 ($\epsilon$ 12,400), 278 (3,700), 325 nm (3,400); $\delta_H$ ($CDC_3$) 2.07 (3H, s, COMe), 3.82 (6H, s, OMe), 5.13 (2H, s, $CH_2$), 6.47 (1H, t, $J$=2.4 1 Hz, aryl), 6.57 (2H, d, $J$=2.1 Hz, aryl), 6.90 (1H, dt, $J$=1.1, 7.6 Hz, aryl), 7.00 (IH, dd, $J$=8.0, 0.9 Hz, aryl), 7.49 (IH, dt, $J$=1.5, 7.8 Hz, aryl), 7.72 (1H, dd, $J$=8.0, 1.5 Hz, aryl), 11.89 (1H, s, OH); $\delta_C$ ($CDCl_3$) 22.6 (COMe), 56.0, 56.2 (OMe), 100.7, 106.9, 119.2, 119.7, 129.5, 137.3 (aryl CH), 118.6, 145.6, 162.1, 162.9 (aryl C), 171.5, 199.6 (carbonyl C); *m/z* 329 (M, 22%), 311 (10), 287 (10), 208 (10), 166 (100), 121 (20).

Crude protected anilino ketone **5** was dissolved in trifluoroacetic acid (15 ml) and the solution was refluxed for 11 h. After cooling to room temperature, ice/water (100 ml) was added to the reaction mixture. The resulting solid was filtered and washed with water until washings were neutral. The solid was dried under vacuum and a sample of the crude product was purified using a pad of silica gel with dichloromethane eluant to give the N-acetylindole **7** as colourless *needles*, mp 166°C (from ethyl acetate/light petroleum) (Found: C, 69.5; H, 5.5; N, 4.5. $C_{18}H_{17}NO_4$ requires C, 69.4; H, 5.5; N, 4.5%); $\nu_{max}$ 3518m, 1707s, 1597w, 1308m, 1211m, 826w $cm^{-1}$; $\lambda_{max}$ 244 ($\epsilon$ 17,600), 275 (7,700), 316 nm (4,500); $\delta_H$ ($CDCl_3$) 2.63 (3H, s, COMe), 3.77, 3.91 (6H, 2s, OMe), 5.77 (1H, br, OH), 6.44 (1H, d, $J$=2.0 Hz, H5), 6.98–7.07 (4H, m, aryl), 7.22 (1H, s, H2), 7.31 (1H, d, $J$=8.2 Hz, aryl), 7.79 (1H, d, $J$=2.0 Hz, NH); $\delta_C$ ($CDCl_3$) 24.0 (COMe), 55.4, 55.4 (OMe), 92.7 (C5), 95.3 (C7), 114.9 (C2), 118.0, 122.7, 128.2, 131.5 (aryl CH), 113.6, 118.6, 121.5, 136.8, 154.0, 155.6, 158.7 (aryl C), 169.7 (carbonyl C); *m/z* 311 (M, 70%), 269 (100), 254 (70), 238 (15), 226 (15), 211 (20).

Excess crushed potassium hydroxide was added to a partially dissolved solution of crude N-acetylindole **7** in methanol (70 ml). The mixture was stirred at room temperature for 2 h and the resulting precipitate was filtered off. The filtrate was concentrated to give more solid, and both solid fractions were combined to yield indole **8** (1.71 g, 78% from compound **4**) as clear *rhombs*, mp 112°C (from ethyl acetate/light petroleum) (Found: C, 71.6; H, 5.8; N, 5.2. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%); $\nu_{max}$ 3310m, 1632w, 1543m, 1202m, 1144m, 1101m, 802m, 748m $cm^{-1}$; $\lambda_{max}$ 223 ($\epsilon$ 37,500), 272 nm (12,500); $\delta_H$ ($CDCl_3$) 3.80, 3.90 (6H, 2s, OMe), 5.95 (1H, s, OH), 6.30 (1H, d, $J$=1.9 Hz, H5), 6.57 (1H, d, $J$=1.9 Hz, H7), 6.97–7.07, 7.26–7.35 (4H, 2m, aryl), 8.28 (1H, br, NH); $\delta_H$ ($d_6$-DMSO) 3.72, 3.85 (6H, 2s, OMe), 6.24, 6.61 (2H, 2d, $J$=1.4 Hz, H5, H7), 6.84 (1H, t, $J$=7.4 Hz, H5′), 6.93 (1H, d, $J$=7.9 Hz, H3′), 7.10 (1H, t, $J$=7.4 Hz, H4′), 7.19 (1H, d, $J$=1.4 Hz, H2), 7.33 (1H, d, $J$=7.9 Hz, H6′), 8.97 (1H, s, OH), 11.03 (1H, br, NH); $\delta_C$ ($d_6$-DMSO) 55.3, 55.5 (OMe), 87.4 (Cs), 91.8 (C7), 115.3 (C2), 118.3, 122.7, 126.8, 132.8 (aryl CH), 111.4, 112.0, 123.7, 138.1, 154.5, 155.2, 156.7 (aryl C); *m/z* 269 (M, 100%), 254 (48), 237 (8), 226 (10), 211 (10).

**4.1.4. N-Acetyl-2-acetoxy-(3,5-dimethoxyanilino)-acetophenone (6).** The anilino ketone **4** (0.50 g, 1.74 mmol) was partially dissolved in acetic anhydride (15 ml). The mixture was heated to reflux for 1.5 h and water was added slowly at this temperature until the volume was

tripled. The solution was allowed to cool to room temperature and extracted with dichloromethane. The organic phase was washed with water until neutral, saturated sodium hydrogen carbonate brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield the diacetyl compound **6** (0.30 g, 46%) as colourless *plates*, mp 123°C (from ethyl acetate/light petroleum) (Found: C, 64.8; H, 5.9; N, 3.8. $C_{20}H_{21}NO_6$ requires C, 64.7; H, 5.7; N, 3.8%); $\nu_{max}$ 1759m, 1698s, 1659s, 1605s, 1186s, 1007w, 762m $cm^{-1}$; $\lambda_{max}$ 236 ($\epsilon$ 13,600), 277 nm (4,400); $\delta_H$ ($CDCl_3$) 2.04, 2.31 (6H, 2s, COMe), 3.81 (6H, s, OMe), 4.91 (2H, s, $CH_2$), 6.45 (1H,t, $J$=2.2 Hz, aryl), 7.16 (2H, 2dd, $J$=8.2, 0.8 Hz, aryl), 7.33 (1H, td, $J$=7.6, 0.9 Hz, aryl), 7.55 (1H, td, $J$=7.7, 1.6 Hz, aryl), 7.82 (1H, dd, $J$=7.8, 1.6 Hz, aryl); $\delta_C$ ($CDCl_3$) 21.7, 22.6 (COMe), 56.1, 58.7 (OMe), 100.8, 106.8, 124.2, 126.7, 130.2, 133.9 (aryl CH), 106.9, 145.8, 149.4, 162.0 (aryl C), 169.8, 171.2, 194.9 (carbonyl C); *m/z* 371 (M, 5%), 329 (5), 208 (10), 167 (10), 166 (100), 163 (10),121 (25).

**4.1.5. 2-(2-Hydroxyphenyl)-4,6-dimethoxyindole (9).** Indole **9** was prepared according to the method of Black et al.[16] to yield a cream *solid*, mp 120°C (Found: C, 71.2; H, 5.3; N, 5.0. $C_{16}H_{15}NO_3$ requires C, 71.4; H, 5.6; N, 5.2%); $\nu_{max}$ 3425w, 3320w, 785s, 755s $cm^{-1}$; $\delta_H$ ($CDCl_3$) 3.85, 3.94 (6H, 2s, OMe), 6.24, 6.52 (2H, 2d, $J$=2.0 Hz, H5, H7), 6.87 (1H, s, H3), 6.89 (1H, d, $J$=7.6 Hz, H3′), 6.99 (1H, t, $J$=8.1 Hz, H5′), 7.15 (1H, td, $J$=7.8, 1.7 Hz, H4′), 7.65 (1H, dd, $J$=7.8, 1.7 Hz, H6′), 9.22 (1H, br, NH); *m/z* 270 (M+1, 20%), 269 (M, 100), 255 (20), 254 (100), 226 (25), 211 (50).

**4.1.6. 3-(2-Hydroxyphenyl)-4,6-dimethoxyindole-7-carbaldehyde (10).** Triethylorthoformate (3 ml) was added dropwise to the indole **8** (1.07 g, 3.97 mmol) in trifluoroacetic acid (10 ml) and the mixture was stirred for 45 min at room temperature. Water (50 ml) was added and stirring was continued for 10 min. The solution was then extracted with ethyl acetate and the organic phase was washed with water until neutral, then brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude, product was purified by chromatography on a silica gel column with dichloromethane as the eluant to yield the formyl indole **10** (63 g, 53%) as yellow *needles*, mp 223°C (from ethyl acetate/light petroleum) (Found: C, 68.7; H, 5.3; N, 4.6. $C_{17}H_{15}NO_4$ requires C, 68.7; H, 5.1; N, 4.7%); $\nu_{max}$ 3440m, 1265w, 1210w, 1075w, 980w $cm^{-1}$; $\lambda_{max}$ 251 ($\epsilon$ 24,500), 272 (16,200), 334 (11,800), 358 nm (9,800); $\delta_H$ ($CDCl_3$) 3.91, 4.04 (6H, 2s, OMe), 6.23 (1H, s, $H_5$), 6.94 (1H, td, $J$=7.4, 1.2 Hz, H4′), 7.00 (1H, dd, $J$=7.3, 1.2 Hz, H6′), 7.21–7.29 (2H, m, aryl), 10.42 (1H, s, CHO), 10.62 (1H, br, NH); $\delta_C$ ($CDCl_3$) 56.4, 57.1 (OMe), 87.7 (C5), 115.9 (C2), 120.6, 123.5, 129.3, 132.3 (aryl CH), 105.3, 111.8, 112.1, 122.8, 138.2, 154.7, 161.7, 164.0 (aryl C), 188.8 (carbonyl C); *m/z* 298 (M+1, 20%), 297 (M, 100), 282 (40), 254 (20), 211 (25).

**4.1.7. 1,3,5-Tris(bromomethyl)benzene[22] (12).** Mesitylene (23.7 g, 0.20 mol), N-bromosuccinimide (112.47 g, 0.63 mol), and dibenzoylperoxide (approximately 50 mg) were dissolved in carbon tetrachloride (500 ml) and refluxed under irradiation by a 250 W lamp for 16 h. The solution was then cooled in an ice bath and the succinimide was filtered off and washed with carbon tetrachloride. The filtrate was washed with saturated sodium hydrogen carbonate solution, water and dried ($MgSO_4$). The volume was reduced to approximately 100 ml and then light petroleum (200 ml) was added. The solution was placed in the freezer and the resulting oily solid was filtered off. This process was repeated several times and the crops of oily solid were combined. This material was then carefully recrystallized a number of times from chloroform/light petroleum to yield 1,3,5-tris(bromomethyl)benzene **12** as colourless *needles* (30.0 g, 43%), mp 87–89°C (lit.[22] 94°C); $\delta_H$ ($CDCl_3$) 4.49 (2H, s, $CH_2$), 7.39 (3H, s, aryl).

**4.1.8. 1-Acetyl-3-(2-benzyloxyphenyl)-4,6-dimethoxyindole (13).** Acetylindole **7** (0.20 g, 0.64 mmol), benzylbromide (83 μl, 0.70 mmol) and potassium carbonate (0.27 g, 1.92 mmol) were added to acetone (30 ml). The mixture was refluxed under an atmosphere of argon overnight and then poured onto concentrated hydrochloric acid/ice (100 ml) and extracted with ethyl acetate (3×20 ml). The organic phase was washed with water, brine and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (dichloromethane/light petroleum 50:50) to yield the benzyloxyindole **13** (0.22 g, 89%) as colourless *needles*, mp 124°C (from ethyl acetate/light petroleum) (Found: C, 74.7; H, 5.9; N, 3.6. $C_{25}H_{23}NO_4$ requires C, 74.8; H, 5.8; N, 3.5%); $\nu_{max}$ 1707m, 1605w, 1310m, 1211m, 748m $cm^{-1}$; $\lambda_{max}$ 249 ($\epsilon$ 24,200), 276 (12,200), 315 nm (5,700); $\delta_H$ ($CDCl_3$) 2.60 (3H, s, COMe), 3.70, 3.99 (6H, 2s, OMe), 5.14 (2H, s, $CH_2$), 6.45 (1H, d, $J$=2.1 Hz, H5), 7.08–7.53 (9H, m, aryl), 7.31 (1H, s, H2), 7.88 (1H, d, $J$=2.1 Hz, H7); $\delta_H$ ($CDCl_3$) 24.7 (COMe), 55.8, 56.4 (OMe), 70.9 ($CH_2$), 93.6 (C5), 96.4 (C7), 112.8 (C2), 120.9, 122.3, 127.4, 128.1, 128.9, 129.2, 132.4 (aryl CH), 114.6, 120.2, 124.7, 137.9, 138.2, 154.8, 157.6, 160.1 (aryl C), 169.7 (carbonyl C); *m/z* 401 (M, 60%),359 (20), 268 (100), 257 (50), 91 (50).

**4.1.9. 1,3,5-Tris(2-acetylphenoxymethyl)benzene (15).** 2-Hydroxyacetophenone **1** (0.46 ml, 3.82 mmol), 1,3,5-tris(bromomethyl)benzene **12** (0.44 g, 1.23 mmol) and potassium carbonate (1.06 g, 7.64 mmol) were added to acetone (50 ml) and the mixture was refluxed under an atmosphere of argon overnight. The mixture was filtered through a pad of celite and washed with acetone. The solvent was removed under reduced pressure to yield the tri-substituted compound **15** (0.56 g, 87%) as a white *solid*, mp 95°C (from ethyl acetate/light petroleum) (Found: C, 76.0; H, 5.9. $C_{33}H_{30}O_6$ requires C, 75.9; H, 5.8%); $\nu_{max}$ 1665br, 1599s, 1294s, 1235s, 750m $cm^{-1}$; $\lambda_{max}$ 246 ($\epsilon$ 19,400); 303 nm (9,600); $\delta_H$ ($CDCl_3$) 2.59 (3H, s, COMe), 5.25 (2H, s, $CH_2$), 7.06 (1H, t, $J$=7.7 Hz, aryl), 7.02 (1H, d, $J$=7.7 Hz, aryl), 7.47 (1H, td, $J$=8.6, 1.8 Hz, aryl), 7.77 (1H, dd, $J$=6.0, 1.7 Hz, aryl), 7.54 (1H, s, aryl); $\delta_C$ ($CDCl_3$) 32.5 (COMe, 70.9 ($CH_2$), 113.5, 121.8, 126.9, 131.1, 134.2 (aryl CH), 129.4, 138.2, 158.2 (aryl C), 200.2 (carbonyl C); *m/z* 545 (M+Na, 90%).

**4.1.10. 1,3,5-Tris-(2-(1-acetyl-3,5-dimethoxyphenylaminoacetyl))phenoxymethylbenzene (16).** 1,3,5-Tris(bromomethyl)benzene **12** (3.18 g, 8.91 mmol), anilino ketone **6** (9.11 g, 27.62 mmol) and potassium carbonate (5.53 g, 41.43 mmol) were added to acetone (150 ml) and the

mixture was refluxed under an atmosphere of argon for 24 h. The mixture was filtered through a pad of celite and washed with acetone. The solvent was removed under reduced pressure to yield the tri-substituted compound **16** (9.73 g, 99%) as a honeycomb like *solid*, mp 77°C; (Found: C, 68.3; H, 6.0; N, 3.6. $C_{63}H_{63}N_3O_{15}$ requires C, 68.7; H, 5.8; N, 3.8%); $\nu_{max}$ 1660s, 1600s, 750m, 700m $cm^{-1}$; $\lambda_{max}$ 244 ($\epsilon$26,000), 280 (13,000), 304 nm (8,500); $\delta_H$ ($CDCl_3$) 1.99 (3H, s, COMe), 3.74 (6H, s, OMe), 5.01, 5.21 (4H, 2s, $CH_2$), 6.39 (1H, t, *J*=2.6 Hz, aryl), 6.52 (2H, d, *J*=2.6 Hz, aryl), 7.01 (1H, d, *J*=8.2 Hz, aryl), 7.06 (1H, t, *J*=7.7 Hz, aryl), 7.47 (1H, t, *J*=7.2 Hz, aryl), 7.50 (1H, s, aryl), 7.87 (1H, dd, *J*=7.7, 2.1 Hz, aryl); $\delta_C$ ($CDCl_3$) 22.5 (CO*Me*), 56.0 (OMe), 61.1, 70.7 ($CH_2$), 100.2, 106.6, 113.5, 121.8, 131.4, 134.6, 161.7 (aryl CH), 126.3, 127.0, 138.0, 146.2, 158.3 (aryl C), 171.0, 195.7 (carbonyl C); *m/z* 1139 (40%, M+K), 1124 (40, M+Na).

**4.1.11. 1,3,5-Tris-(2-(1-acetyl-4,6-dimethoxyindol-3-yl))-phenoxymethylbenzene (17).** Tri-substituted compound **16** (2.30 g, 2.09 mmol) was dissolved in trifluoroacetic acid (15 ml) and stirred at room temperature for 3 h. Ice/water (100 ml) was then added, and the resulting solid was filtered and washed with water until neutral. The solid was dried, dissolved in dichloromethane and purified using a pad of silica gel to yield the tris(N-acetylindolyl)benzene **17** (1.54 g, 70%) as colourless *needles*, mp 234–235°C (from ethyl acetate) (Found: C, 71.0; H, 5.8; N, 3.9. $C_{63}H_{57}N_3O_{12}\cdot H_2O$ requires C, 71.0; H, 5.6; N, 3.9%); $\nu_{max}$ 1700s, 1600m, 1570m, 1205s, 825m, 765m $cm^{-1}$; $\lambda_{max}$ 271 nm ($\epsilon$ 19,000); $\delta_H$($CDCl_3$) 2.56 (3H, s, COMe), 3.49, 3.91 (6H, 2s, OMe), 4.62 (2H, s, $CH_2$), 6.33, 7.82 (2H, 2d, *J*=2.1 Hz, indole H5, H7), 6.62 (1H, s, indole H2), 7.00 (1H, d, *J*=7.7 Hz, aryl), 7.01 (1H, t, *J*=7.7 Hz, aryl), 7.15 (1H, s, aryl), 7.39–7.43 (2H, m, aryl; *m/z* 1047 (M, 2%), 1005 (2), 738 (8), 696 (7), 654 (5), 268 (100).

**4.1.12. 1,3,5-Tris-(2-(4,6-dimethoxyindol-3-yl))phenoxymethylbenzene (18).** Excess crushed potassium hydroxide was added to a partially dissolved solution of the tris-(N-acetylindolyl)benzene **17** (0.54 g, 0.52 mmol) in methanol. The mixture was refluxed for 2 h and after cooling it room temperature the resulting precipitate was filtered. Water was added to the filtrate and the resulting second crop was collected. The two crops were combined to yield the tris(indolyl)benzene **18** (0.38 g, 80%) as colourless *crystals*, mp 164–166°C (from ethyl acetate) (Found: C, 74.1; H, 5.7; N, 4.3. $C_{57}H_{5I}N_3O_9$ requires C, 74.3; H, 5.6; N, 4.6%); $\nu_{max}$ 3380br, 1635m, 1590m, 1550m, 800m $cm^{-1}$; $\lambda_{max}$ 221 ($\epsilon$ 101,000), 274 nm (50,000); $O_H$ ($CDCl_3$) 3.58, 3.67 (6H, 2s, OMe), 4.63 (2H, s, $CH_2$), 6.14, 6.16 (2H, 2d, *J*=1.8 Hz, indole H5, H7), 6.62 (1H, d, *J*=2.1 Hz, indole H2), 6.74 (1H, s, aryl), 6.93(1H, d, *J*=8.1 Hz, aryl), 7.04 (1H, t, *J*=7.5 Hz, aryl), 7.27 (1H, td, *J*=6.0 Hz, aryl), 7.46 (1H, dd, *J*=6.9, 1.6 Hz, aryl), 7.63 (1H, d, *J*=1.8 Hz, NH); $\delta_C$ ($CDCl_3$) 55.7, 56.1 (OMe), 70.7 ($CH_2$), 87.4 (indole C5), 92.7 (indole C7), 113.1 (indole C2), 120.1, 122.5, 125.0, 128.0, 132.9 (aryl CH), 112.2, 113.4, 126.6, 138.2, 138.3, 155.5, 157.4, 157.9 (aryl C); *m/z* 921 (M, 5%), 654 (10), 269 (100), 237 (85).

**4.1.13. 1,2,4,5-Tetrakis-(2-(N-acetyl-3,5-dimethoxyphenylaminoacetyl))phenoxymethylbenzene (21).** N-Acetylanilino ketone **5** (1.20 g, 3.65 mmol), 1,2,4,5-tetrakis(bromomethyl)benzene **20** (0.40 g, 0.88 mmol) and potassium carbonate (0.54 g, 4.67 mmol) were added to acetone (50 ml) and refluxed for 4.5 h. The mixture was then filtered through a pad of celite and washed with acetone and the solvent removed under reduced pressure to yield the tetra-anilino ketone **21** (1.13 g, 88%) as cream *needles*, mp 185–187°C (from ethyl acetate/light petroleum) (Found: C, 68.5; H, 5.8; N, 3.7. $C_{82}H_{82}N_4O_{20}$ requires C, 68.2; H, 5.7; N, 3.9%); $\nu_{max}$ 1685s, 1670s, 1650s, 1600s, 1210s, 1150s, 700m, 760m, 770m $cm^{-1}$; $\lambda_{max}$ 274 nm ($\epsilon$ 14,800); $\delta_H$ ($CDCl_3$) 1.94 (6H, s, COMe), 3.69 (12H, s, OMe), 4.94, 5.25 (8H, 2s, $CH_2$), 6.35 (2H, t, *J*=2.2 Hz, aryl), 6.44 (4H, d, *J*=2.2 Hz, aryl), 7.00–7.07 (2H, m, aryl), 7.44 (2H, td, *J*=7.9, 1.6 Hz, aryl), 7.78 (2H, dd, *J*=9.0, 1.7 Hz, aryl), 7.77 (1H, s, aryl); $\delta_C$ ($CDCl_3$) 22.6 (CO*Me*), 56.0 (OMe), 60.6, 69.0 ($CH_2$), 100.4, 106.8, 113.7, 122.0, 131.3, 134.7, 130.4 (aryl CH), 127.3, 135.5, 146.1, 158.0, 161.8 (aryl C), 171.0, 196.1 (carbonyl C); *m/z* 1480 (M+K, 25%), 1465 (M+Na, 30%).

**4.1.14. 1,2,4,5-Tetrakis-(2-(1-acetyl-4,6-dimethoxyindol-3-yl))phenoxymethylbenzene (22).** Tetra-anilino ketone **21** (2.68 g, 1.86 mmol) was dissolved in trifluoroacetic acid (15 ml) and stirred at room temperature for 6.5 h. Ice/water (100 ml) was then added and the resulting solid was filtered and washed with water until neutral. The solid was dried, dissolved in dichloromethane and purified using a pad of silica gel to yield the tetrakis-N-acetylindole **22** (2.01 g, 79%) as a cream *solid*, mp 218–219°C (from ethyl acetate) (Found: C, 71.5; H, 5.8; N, 3.8. $C_{82}H_{74}N_4O_{16}$ requires C, 71.8; H, 5.4; N, 4.1%); $\delta_H$ ($CDCl_3$) 2.39 (6H, s, COMe), 3.39, 3.83 (12H, 2s, OMe), 4.68 (4H, s, $CH_2$) 6.25, 7.72 (4H, 2d, *J*=2.0 Hz, indole H5, H7), 6.60 (2H, d, *J*=8.1 Hz, aryl), 6.91 (1H, s, aryl), 7.00 (2H, t, *J*=7.6 Hz, aryl), 7.08 (2H, s, indole H2), 7.20 (2H, td, *J*=7.9, 1.7 Hz, aryl), 7.35 (2H, dd, *J*=7.5, 1.6 Hz, aryl); $\delta_C$ ($CDCl_3$) 24.5 (CO*Me*), 55.6, 56.3 (OMe), 68.4 ($CH_2$), 93.5 (indole C5), 96.4 (indole C7), 112.4 (indole C2), 120.9, 122.0, 128.3, 129.3, 132.2 (aryl CH), 114.6, 120.4, 124.6, 135.0, 138.1, 154.9, 157.1, 160.1 (aryl C), 169.6 (carbonyl C); *m/z* 1390 (M+Na. 10%), 1327 (20).

**4.1.15. 1,2,4,5-Tetrakis-(2-(4,6-dimethoxyindol-3-yl)-phenoxymethylbenzene (23).** Excess crushed potassium hydroxide was added to a partially dissolved solution of the tetra-N-acetylindole **22** (1.40 g, 1.02 mmol) in methanol. The mixture was brought to reflux for 6 h, and after cooling to room temperature the resulting precipitate was filtered. The solid was washed with water and dried under vacuum to yield the tetrakis-indole **23** (0.47 g, 38%) as a white solid, 233–234°C, which could not be obtained analytically pure. $\nu_{max}$ 3390br, 1620m, 1580s, 1540m, 1210s, 1140s, 805m, 755m, 740m $cm^{-1}$; $\lambda_{max}$ 221 ($\epsilon$ 19,400), 274 nm (8,900); $\delta_H$ ($CDCl_3$) 3.55, 3.71 (12H, OMe), 4.73 (4H, s, $CH_2$), 6.10, 6.13 (4H, 2s, indole H5, H7), 6.66 (2H, d, *J*=2.1 Hz, indole H2), 6.83 (2H, d, *J*=7.7 Hz, aryl), 7.03 (1H, s, aryl), 7.03 (2H, t, *J*=6.7 Hz, aryl), 7.19 (2H, t, *J*=6.7 Hz, aryl), 7.49 (2H, dd, *J*=7.7, 1.8 Hz, aryl), 7.69 (2H, br, NH); *m/z* 1200 (M+H, 55%); HRMS (ES): $(M+K)^+$, found 1241.4239. $C_{74}H_{66}N_4O_{12}+K$ requires 1241.4308.

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