Full Paper

Methanal Extrusion in *ipso*-Substitution Reactions of Hydroxymethylindoles*

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A range of 3-hydroxymethylindoles undergo acid-catalysed reactions involving *ipso*-electrophilic substitution with the extrusion of methanal and the formation of diindolylmethane moieties. Both inter- and intramolecular processes lead to macrocyclic compounds **10** and **14**.

Introduction

Hydroxymethylindoles undergo a variety of acid-catalysed reactions leading to cyclic indolylmethylene oligomers. For instance, 2- and 7-hydroxymethyl-4,6-dimethoxyindoles are converted into calix-3- and calix-4-indoles.[1,2] However, when the indole nitrogen atom is substituted, the products of similar reactions are indolocyclotriveratrylenes. Reaction of 3-hydroxymethyl-1-methylindole[3–5] with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane gives a simple indolocyclotriveratrylene.[6] Similar but more complex cyclotriveratrylenes can also be generated from other *N*-substituted hydroxymethylindoles and also those derived from activated indoles.[7] Given the formation of indolocyclotriveratrylenes **2** from *N*-substituted hydroxymethylindoles **1**, it was considered that the reactions of bis-hydroxymethylindole systems **3** containing two indole rings joined by linkers through their nitrogen atoms might lead to the formation of cylindrical structures **4** capable of selectively attracting small molecules (Scheme 1). The construction and mechanistic investigation for synthesis of these precursor systems are now described.

Results and Discussion

Synthesis of 3,3′-Bishydroxymethylindoles

In principle, these compounds can be prepared using two simple routes (Scheme 2).

The indoles **5** can first be linked by an alkylation reaction with a dibromo-substituted linker, and then the resulting compounds **7** can be formylated at the 3- and 3′-positions (usually using the Vilsmeier reagent), resulting in biscarbaldehydes **8**, which can be reduced to give the bishydroxymethyl compounds **9**. Alternatively, the biscarbaldehydes **8** can be formed by linkage of two indole-3-carbaldehydes **6**. A combination of these two processes was employed for the synthesis of the dialdehydes **8**. The chosen linkers were *o*-, *m*-, and *p*-di(bromomethyl)benzenes and diiodomethane, providing compounds **7**–**9** (Fig. 1). In this way, compounds **7a**–**e** were prepared, compounds **7a**–**d** being already known,[8–10] and compound **7e** being new. The dialdehydes **8a**–**f** were usually but not always prepared from the indole-3-carbaldehydes **6** (see Experimental). Compounds **8a**–**c** have previously been reported,[11,12] whereas compounds **8d**–**f** are new. Compound **7e** was prepared from 5-benzyloxyindole[13] and *p*-di(bromomethyl)benzene, and formylation gave the dialdehyde **8e**. The biscarbaldehyde **8d** was prepared from indole-3-carbaldehyde **6a** and diiodomethane, whereas the related compound **8f** was obtained by reaction of 5-bromoindole-3-carbaldehyde **6f**[14] with *p*-di(bromomethyl)benzene. The bishydroxymethylindoles **9a**–**f** were formed by reduction of the dicarbaldehydes **8a**–**f** with sodium borohydride.

Acid-Catalysed Reactions of 3,3′-Bishydroxymethylindoles

The plan outlined in the introduction, namely to generate two cyclotriveratrylene rings joined by the linkers, was unsuccessful. No indication of such products was observed. However, clean reactions occurred in the case of compounds **9a**, **9c**, **9e**, and **9f**, whereas reactions of compounds **9b** and **9d** gave complex mixtures. None of the isolated reaction products were the result of oligomerisation of indolylmethylene moieties; instead, simple dimerisations occurred to give interesting macrocyclic compounds, as the result of *ipso*-electrophilic aromatic substitution with the loss of methanal. Bis-hydroxymethylindole **9a** gave the 22-membered macrocyclic ring compound **10a** in 62 % yield, and the bis-hydroxymethylindoles **9c**, **9e**, and **9f** gave the 26-membered macrocyclic ring compounds **10c**, **10e**, and **10f** in yields of 60, 60 and 50 % respectively (Scheme 3).

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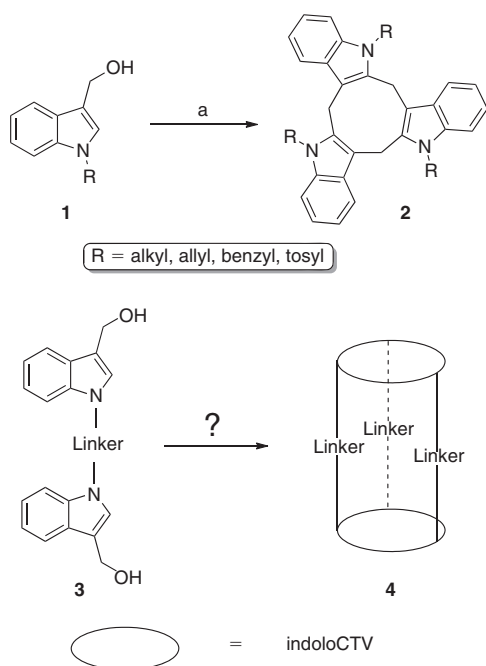
Scheme 1. Reagents and conditions: (a) *p*-TsOH, 11–47 %.
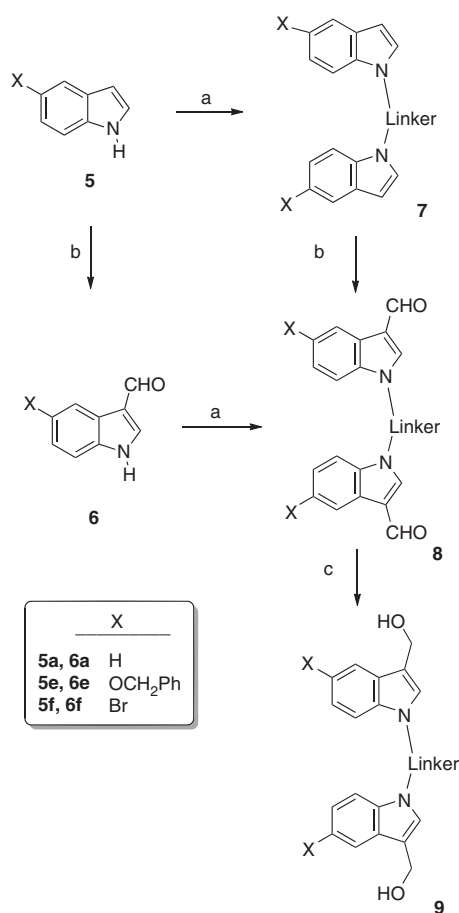
Scheme 2. Reagents and conditions: (a) linker dibromide, KOH, DMSO, 53–100 %; (b) POCl₃, DMF, 56–70 %; (c) NaBH₄, EtOH, THF, 83–99 %.
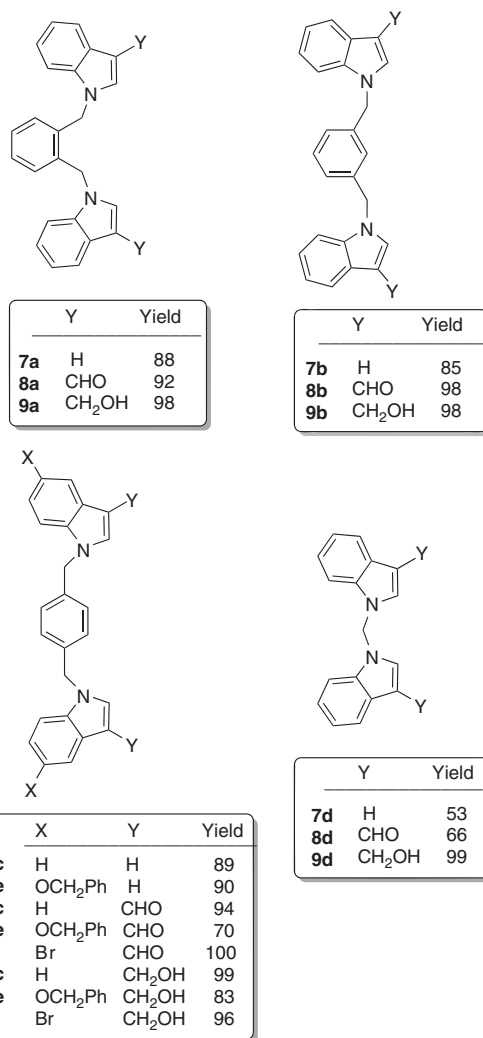

	Y	Yield
7a	H	88
8a	CHO	92
9a	CH₂OH	98

	Y	Yield
7b	H	85
8b	CHO	98
9b	CH₂OH	98

	X	Y	Yield
7c	H	H	89
7e	OCH₂Ph	H	90
8c	H	CHO	94
8e	OCH₂Ph	CHO	70
8f	Br	CHO	100
9c	H	CH₂OH	99
9e	OCH₂Ph	CH₂OH	83
9f	Br	CH₂OH	96

	Y	Yield
7d	H	53
8d	CHO	66
9d	CH₂OH	99

Fig. 1. Compounds **7**–**9** (% yield).

The macrocycle **10a** was too insoluble for NMR data to be measured, but its molecular weight determination by matrix-assisted laser desorption–ionization (MALDI) mass spectrometry gave a molecular ion at *m/z* 696.80, consistent with the macrocyclic structure. Macrocycles **10c**, **10e**, and **10f** gave NMR spectra that indicated their structural simplicity. For example, the ¹³C NMR spectrum of compound **10c** showed two methylene carbon signals at 29.8 and 49.3 ppm, six tertiary carbon signals at 109.3, 119.0, 119.4, 121.7, 126.3, and 127.1 ppm, and four quaternary carbon signals at 115.1, 128.2, 136.7, and 137.2 ppm. A proposed mechanism for the formation of compound **10a** (as a typical case) is shown in Scheme 4.

Given the outcome in which the linked 3,3′-bishydroxymethyl-lindoles underwent dimerisation, an example with a longer linker was investigated. The dialdehyde **12** was prepared from indole-3-carbaldehyde and 1,2-bis(2-bromomethylphenoxy)ethane[15] **11** in 85 % yield. Reduction with sodium borohydride gave the bis-hydroxymethyl analogue **13** in 87 % yield. Treatment of this compound **13** with a catalytic amount of *p*-toluenesulfonic acid in dichloromethane for 1 h at room temperature yielded the macrocyclic compound **14** in 68 % yield (Scheme 5).

In this case, the *ipso*-substitution reaction is intramolecular and leads to a 17-membered ring, as opposed to the formation of a 34-membered ring from an intermolecular dimerisation. The
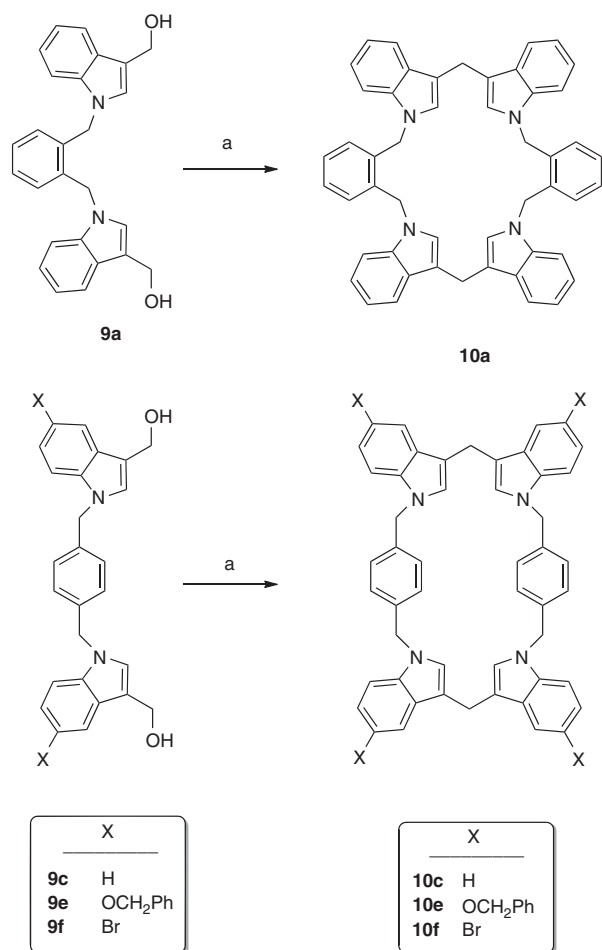
Scheme 3. Reaction conditions: (a) *p*-TsOH, anhydrous acetone, 50–62 %.

structure of compound **14** was confirmed by NMR spectroscopy. The ^{1}H NMR spectrum showed three singlet resonances at 4.14, 4.26 and 5.21 ppm, in the ratio of 1 : 2 : 2, corresponding to the three methylene groups in the molecule, namely the 3-indole-methylene, the 1-indole-methylene, and the *O*-methylene respectively.

The extrusion of methanal in *ipso*-substitution reactions involving indoles was initially observed by Leete and Marion,[16] and authenticated by Thesing[17] who obtained 3,3′-diindolyl-methane in a 74 % yield after shaking an aqueous solution of 3-hydroxymethylindole at 25°C for 20 h. Crucially, methanal in the aqueous filtrate was identified by formation of the dimedone condensation product. This methodology was later extended to other related 3-hydroxymethylindole derivatives by Leete.[18] Some more recent conversions of 3-hydroxymethylindole to 3,3′-diindolylmethane have been reported but involve more complex reaction conditions.[19,20] The reaction methodology involving methanal extrusion has also been reported for activated 3-, 4-, 6-, and 7-hydroxymethylindoles. 3-Hydroxymethyl-4,6-dimethoxy-1-methylindole was converted into the related diindolylmethane in 90 % yield by heating in water.[21] Various 4- and 6-hydroxymethyl-dimethoxyindoles can also be converted into the related diindolylmethanes by treatment with ethanoic acid at room temperature.[21] However, the most common general reactions of this kind involve the treatment of 2,3-disubstituted-7-hydroxymethyl-4,6-dimethoxyindoles with a range of acidic conditions such as ethanoic acid, trifluoroacetic acid, and K-10

clay.[22–25] The essential imperative for these methanal extrusion reactions is that the carbon atom bearing the hydroxymethyl group must be the most nucleophilic site.

Acid-Catalysed Reactions of Indole-Linked Hydroxymethylarenes

A different stepwise approach to the original aim of constructing structures in which a cyclotriveratrylene and an indolocyclo-triveratrylene are linked was briefly investigated. The new compounds **16a** and **16e** were synthesised in good yield from the known[26] iodo compound **15** by reaction with indole and 5-benzyloxyindole respectively (Scheme 6). The aim was to form a cyclotriveratrylene from the hydroxymethylarene and subsequently formylate the indole in the 3-position and reduce it to the 3-hydroxymethylindole before subjecting that to acidic conditions. The iodo compound **15** had been used as a starting material in the synthesis of cryptophanes, in which two cyclo-triveratrylenes were linked together.[26] However, on treatment of compounds **16a** and **16e** with a range of acidic reagents, the desired cyclotriveratrylenes could not be isolated from the complex reaction mixtures.

Conclusion

A new range of 3-hydroxymethylindoles undergo acid-catalysed reactions involving *ipso*-electrophilic substitution with the extrusion of methanal and the formation of diindolylmethane moieties. Both inter- and intramolecular reactions have been observed, but no cyclotriveratrylenes were formed. Bis-(3-hydroxymethyl) indoles linked by *ortho*- and *para*-xylyl moieties undergo inter-molecular dimerisation processes to give 22- and 26-membered macrocyclic compounds respectively, whereas the related *meta*-xylyl linked compounds gave only polymeric mixtures. A compound in which two 3-hydroxymethylindole units are linked by a di-(*ortho*-xylyl)ethyleneglycol moiety undergoes an intramolecular process to give a 17-membered macrocyclic compound, in preference to an intermolecular dimerisation that would lead to a 34-membered macrocylic compound.

Experimental

General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalysis was performed on a Carlo Erba Elemental Analyser EA 1108 at the Campbell Microanalytical Laboratory, University of Otago, New Zealand. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker DPX300 (300 MHz) spectrometer. Mass spectra were recorded on either a Bruker Fourier transform ion cyclotron resonance mass spec-trometry (electron ionisation) (FT-ICR MS (EI)) or a Micromass ZQ2000 (electrospray ionisation (ESI)) at UNSW, or a Shimadzu LCMS QP 8000 (ESI) at the University of Otago, New Zealand. Infrared spectra were recorded with a Thermo Nicolet 370 FT-IR spectrometer using KBr discs. Ultraviolet–visible spectra were recorded using a Varian Cary 100 Scan spectrometer. Column chromatography was carried out using Merck 230–400-mesh ASTM silica gel, whereas preparative thin-layer chromatography was performed using Merck silica gel 7730 60GF254.
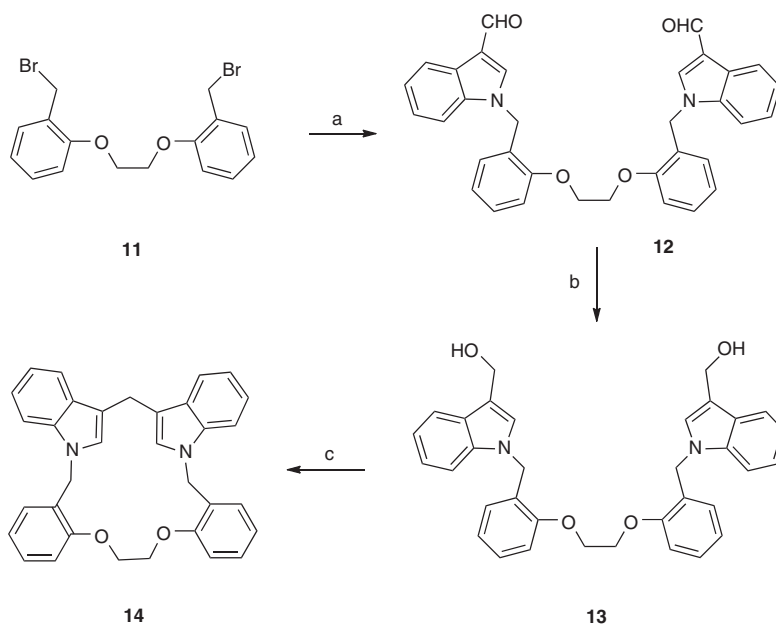
Synthesis of Novel Bis-Indole

1,4-Di-(5-benzyloxyindol-1-ylmethyl)benzene (7e)

5-Benzyloxyindole **5e** (0.22 g, 1 mmol), freshly crushed potas-sium hydroxide (0.06 g, 1 mmol), and dry dimethyl sulfoxide
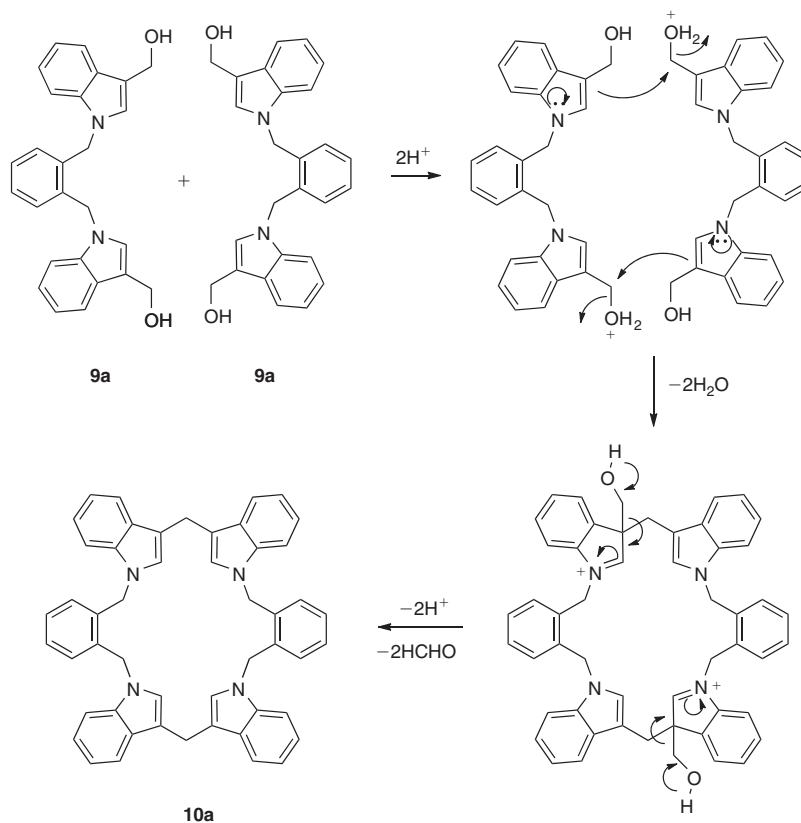
Scheme 4. Possible mechanism for the conversion of **9a** to **10a**.

Scheme 5. Reaction conditions: (a) **6a**, KOH, DMSO, 85 %; (b) NaBH$_4$, EtOH, 87 %; (c) p-TsOH, CH$_2$Cl$_2$, 68 %.

(20 mL) were stirred together at room temperature for 1 h, then α, α′-dibromo-p-xylene (0.13 g, 0.50 mmol) was added and stirring continued for a further 1 h. Water was added and the resulting precipitate was filtered off, washed with water, and dried. After flash chromatography, the diindolylxylene **7e** was obtained as a white solid (0.25 g, 90 %). Mp 179°C. Found: C 82.5, H 6.0, N 5.2; C$_{38}$H$_{32}$N$_2$O$_2$.0.25 H$_2$O requires C 82.5, H 5.9, N 5.1 %. v_{max} (KBr)/cm^{-1} 1618, 1569, 1552, 1483, 1450, 1234, 1148, 1123, 1013, 833, 792, 759, 751, 743, 702, 670. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 230 (55900), 276 (22300). δ_H (300 MHz, [D6] DMSO) 5.04 (4H, s, CH$_2$N), 5.27 (4H, s, OCH$_2$Ph), 6.34 (2H, d, J 2.6, ArH), 6.78 (2H, dd, J 2.3 and 2.6, ArH), 7.06 (4H, s, ArH),
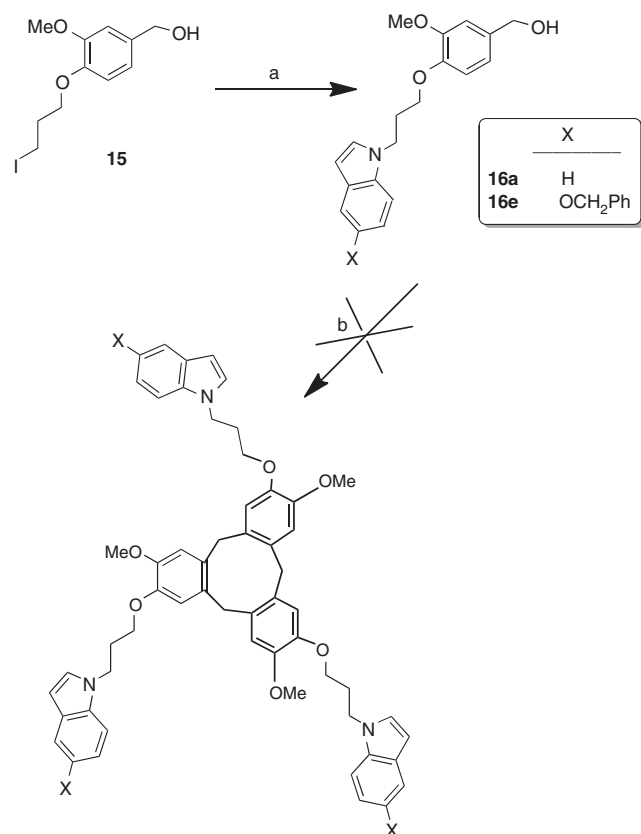
Scheme 6. Reaction conditions: (a) **6a** or **6e**, KOH, DMSO, 84%; (b) various acidic conditions.

7.11 (2H, d, J 2.3, ArH), 7.24–7.35 (14H, m, ArH). δ_C (75 MHz, CDCl$_3$) 49.8 (CH$_2$N), 70.8 (OCH$_2$Ph), 101.0, 104.2, 111.2, 112.3, 127.5, 127.9, 128.7, 129.9 (ArCH), 128.0, 129.1, 131.5, 137.8, 138.1, 152.9 (ArC). m/z (ESI$^+$) 571 ([M + Na]$^+$, 100%).

Synthesis of Diindolylxylene-3,3′-dicarbaldehydes
General Method A

To an ice-cold solution of phosphoryl chloride in dry DMF, a cold solution of the diindolylbenzene in dry DMF was added slowly. The reaction mixture was stirred with ice-cooling for 0.5 h, followed by addition of water, and basifying with 10% sodium hydroxide solution. The resulting precipitate was filtered off, washed with water until the filtrate was neutral, and dried to yield the diindolylbenzene-3,3′-dicarbaldehyde.

General Method B

A mixture of indole aldehyde, freshly crushed potassium hydroxide, and dry DMSO was stirred at room temperature. After 1 h, the dibromomethylxylene was added and the mixture stirred for a further 1 h. Water was added and the resulting precipitate was filtered off, washed with water, and dried to yield the diindolylbenzene-3,3′-dicarbaldehyde.

Di-(indol-1-yl)methane-3′,3′-dicarbaldehyde (**8d**)

A mixture of indole-3-carbaldehyde (**6a**) (0.25 g, 2.00 mmol), freshly crushed potassium hydroxide (0.11 g, 2.00 mmol), and dry DMSO (20 mL) was stirred at room temperature. After 1 h, diiodomethane (0.27 g, 1.00 mmol) was added and the mixture was stirred for a further 1 h. Water was

added and the resulting precipitate was filtered off, washed with water, and dried to yield the dialdehyde **8d** as a white solid (0.20 g, 66%). Mp 228–230°C. Found: C 74.4, H 4.7, N 9.2; C$_{19}$H$_{14}$N$_2$O$_2$.0.25 H$_2$O requires: C 74.4, H 4.8, N 9.1%. ν_{max} (KBr)/cm^{-1} 1654, 1612, 1526, 1483, 1454, 1401, 1383, 1371, 1356, 1333, 1319, 1256, 1170, 1128, 784, 746. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 240 (34400), 294 (32900). δ_H (300 MHz, [D6]DMSO) 6.88 (2H, s, CH$_2$), 7.23 (4H, m, H5, H6), 7.87 and 8.07 (4H, 2d, J 8.3, 7.5, H4, H7), 8.67 (2H, s, H2), 9.94 (2H, s, CHO). δ_C (75 MHz, CDCl$_3$) 57.1 (CH$_2$), 109.3, 120.0, 122.7, 123.8, 125.2, 125.5, 136.2, 136.5 (ArCH and ArC), 184.6 (CHO). m/z (ESI$^+$) 303 ([M + 1]$^+$ (100%), 287 (10), 275 (10), 174 (10), 158 (95), 146 (10), 130 (10), 118 (10).

1,4-Di-(benzyloxyindol-1-ylmethyl)benzene-3′,3′-dicarbaldehyde (**8e**)

According to Method A, phosphoryl chloride (0.10 mL, 1.07 mmol), diindolylbenzene **7e** (0.26 g, 0.41 mmol), and DMF (7 mL) gave compound **8e** as a white solid (0.17 g, 70%). Mp 210–212°C. Found: C 79.2, H 5.3, N 4.3; C$_{40}$H$_{32}$N$_2$O$_4$ requires: C 79.4, H 5.3, N 4.6%. ν_{max} (KBr)/cm^{-1} 1649, 1619, 1530, 1479, 1467, 1392, 1261, 1228, 1160, 1043, 756. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 228 (42100), 256 (54600), 298 (29600). δ_H (300 MHz, [D6]DMSO) 5.09 (4H, s, CH$_2$N), 5.43 (4H, s, OCH$_2$Ph), 6.93 (2H, dd, J 2.6, 2.3, ArH), 7.23 (4H, s, ArH), 7.29–7.45 (14H, m, ArH), 7.67 (2H, d, J 2.6, ArH), 8.32 (2H, s, ArH), 9.85 (2H, s, CHO). δ_C (75 MHz, CDCl$_3$) 50.0 (CH$_2$N), 70.1 (OCH$_2$Ph), 104.9, 112.6, 114.2, 127.9, 128.1, 128.7, 141.3 (ArCH), 117.5, 126.0, 132.3, 136.8, 137.7, 155.4 (ArC), 184.9 (CHO). m/z (ESI$^+$) 605 ([M + 1]$^+$ 25%), 577 (20), 337 (25), 220 (100).

1,4-Di-(bromoindol-1-ylmethyl)benzene-3′,3′-dicarbaldehyde (**8f**)

According to Method B, the aldehyde **6f** (1.12 g, 5.00 mmol), potassium hydroxide (0.28 g, 5.00 mmol), α,α′-dibromo-*m*-xylene (0.66 g, 2.50 mmol), and DMSO (20 mL) gave the dialdehyde **8f** as a yellow solid (1.38 g, 100%). Mp 282°C (dec.). Found: C 56.3, H 3.5, N 5.0; C$_{26}$H$_{18}$Br$_2$N$_2$O$_2$.0.25 H$_2$O requires: C 56.3, H 3.4, N 5.1%. ν_{max} (KBr)/cm^{-1} 1661, 1532, 1465, 1369, 1368, 1164, 1031. λ_{max} (MeOH)/nm (ε/M^{-1} cm^{-1}) 246 (23300), 301 (26200). δ_H (300 MHz, [D6]DMSO) 5.46 (4H, s, CH$_2$), 7.22 (4H, s, ArH xylene), 7.34 (2H, dd, J 2.3, 7.5, H6), 7.48 (2H, d, J 9.0, H7), 8.20 (2H, d, J 1.9, H4), 8.40 (2H, s, H2), 9.87 (2H, s, CHO). m/z (ESI$^+$) 552 ([M + 1]$^+$ ^{81,81}Br, 15%), 550 ([M + 1]$^+$ ^{79,81}Br, 40%), 548 ([M + 1]$^+$ ^{79,79}Br, 100%).

Synthesis of 3,3′-Bishydroxymethylindoles
General Method

Sodium borohydride was added to the dialdehyde in a mixture of THF and absolute EtOH and the reaction mixture was stirred at room temperature overnight. The solvent was removed and the residue suspended in 5% aqueous sodium hydroxide. The resulting precipitate was filtered off, washed with water, and dried to yield the dialcohol.

1,2-Di-(3-hydroxymethylindol-1-ylmethyl)benzene (**9a**)

The dialdehyde **8a** (0.34 g, 0.88 mmol), sodium borohydride (0.33 g, 8.80 mmol), THF (40 mL), and absolute ethanol (20 mL) yielded dialcohol **9a** as a yellow solid (0.30 g, 87%). Product not obtained analytically pure but used directly. Mp 181–182°C. ν_{max} (KBr)/cm^{-1} 3350, 1610, 1465, 1380, 1360, 1320,

1280, 1040, 1010, 980, 750. λ_{max} (MeOH)/nm (ε/M^{-1} cm^{-1}) 221 (82300), 276 (9900), 283 (10600), 293 (9100). δ_H (300 MHz, [D6] DMSO) 4.86 (4H, s, CH_2OH), 5.00 (2H, s, CH$_2$OH), 5.69 (4H, s, CH$_2$N), 6.75 (2H, s, ArH), 7.22–7.49 (6H, m, ArH), 7.52–7.83 (4H, m, ArH), 7.85 (2H, d, J 1.1, ArH). δ_C (75 MHz, [D6]DMSO) 46.6 (CH$_2$OH), 55.7 (CH$_2$N), 110.4, 119.2, 119.7, 121.8, 126.8, 127.3, 127.4 (ArCH), 116.7, 127.8, 136.0, 136.9 (ArC). m/z (EI) 397 ([M + 1]$^+$ (2 %), 396 M (10), 232 (35), 218 (100), 204 (10), 130 (15), 117 (10), 104 (25), 91 (15), 78 (20).

1,3-Di-(3-hydroxymethylindol-1-ylmethyl)benzene (9b)

The dialdehyde **8b** (0.50 g, 1.28 mmol), sodium borohydride (0.48 g, 12.8 mmol), THF (40 mL), and absolute ethanol (20 mL) yielded dialcohol **9b** as a yellow solid (0.49 g, 98 %). Product not obtained analytically pure but used directly. Mp 132–133°C. ν_{max} (KBr)/cm^{-1} 3350, 1610, 1540, 1440, 1370, 1340, 1260, 1170, 1120, 1030, 995, 960, 870, 740, 730, 710. λ_{max} (MeOH)/nm (ε/M^{-1} cm^{-1}) 221 (98300), 275 (15500), 283 (15900), 294 (13900). δ_H (300 MHz, [D6]DMSO) 4.61 (4H, d, J 5.3, CH_2OH), 4.76 (2H, t, J 5.3, CH$_2$OH), 5.30 (4H, s, CH$_2$N), 6.96–7.09 (6H, m, ArH), 7.15–7.20 (1H, m, ArH), 7.27–7.36 (6H, m, ArH), 7.57–7.60 (2H, m, ArH). δ_C (75 MHz, [D6] DMSO) 49.3 (CH$_2$OH), 55.7 (CH$_2$N), 110.4, 119.0, 119.6, 121.7, 126.5, 126.7, 127.5, 129.2 (ArCH), 116.3, 127.2, 136.6, 138.9 (ArC). m/z (EI) 397 ([M + 1]$^+$ (5 %), 396 M (10), 378 (45), 249 (15), 233 (15), 220 (25), 204 (20), 189 (10), 130 (30), 117 (25), 104 (100), 91 (25), 78 (50).

1,4-Di-(3-hydroxymethylindol-1-ylmethyl)benzene (9c)

The dialdehyde **8c** (0.24 g, 0.61 mmol), sodium borohydride (0.26 g, 7.0 mmol), THF (40 mL), and absolute ethanol (20 mL) yielded the dialcohol **9c** as a pale yellow solid (0.24 g, 99 %). Mp 181–182°C. Found: C 75.1, H 6.3, N 6.6; C$_{26}$H$_{24}$N$_2$O$_2$.H$_2$O requires: C 75.3, H 6.3, N 6.8 %. ν_{max} (KBr)/cm^{-1} 3330, 1610, 1545, 1460, 1370, 1330, 1250, 1220, 1160, 1130, 1100, 1050, 1035, 990, 960, 920, 890, 800, 785, 745, 730, 695. λ_{max} (MeOH)/nm (ε/M^{-1} cm^{-1}) 222 (72400), 274 (10400), 284 (10900), 293 (9900). δ_H (300 MHz, [D6]DMSO) 4.59 (4H, d, J 4.9, CH_2OH), 4.76 (2H, t, J 5.3, CH$_2$OH), 5.28 (4H, s, CH$_2$N), 6.96 (2H, t, J 7.2, ArH), 7.04 (2H, t, J 7.3, ArH), 7.11 (4H, s, ArH), 7.30 (2H, s, ArH), 7.36 (2H, d, J 8.3, ArH), 7.56 (2H, d, J 7.9, ArH). δ_C (75 MHz, [D6]DMSO) 49.7 (CH$_2$N), 57.3 (CH$_2$OH), 109.8, 119.3, 119.8, 122.3, 126.9, 127.4 (ArCH), 115.6, 127.3, 136.8, 136.9 (ArC). m/z (EI) 397 ([M + 1]$^+$ (5 %), 396 M (15), 378 (10), 249 (10), 220 (10), 204 (5), 189 (5), 146 (10), 130 (25), 117 (20), 104 (100), 91 (25).

Di-(3-hydroxymethylindol-1-yl)methane (9d)

The dialdehyde **8d** (0.05 g, 0.16 mmol), sodium borohydride (0.06 g, 1.65 mmol), THF (10 mL), and absolute ethanol (10 mL) yielded the dialcohol **9d** as a white solid (0.05 g, 99 %). Mp 185–186°C. Found: C 74.0, H 6.0, N 9.1; C$_{19}$H$_{18}$N$_2$O$_2$.0.125H$_2$O requires: C 74.0, H 6.0, N 9.1 %. ν_{max} (KBr)/cm^{-1} 3353, 3274, 1617, 1561, 1481, 1467, 1455, 1327, 1315, 1166, 1128, 1100, 999, 979, 743, 734. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 230 (50400), 273 (19800). δ_H (300 MHz, [D6] DMSO) 4.57 (4H, d, J 5.0, CH_2OH), 4.80 (2H, t, J 5.0, CH$_2$OH), 6.55 (2H, s, CH$_2$ bridging), 7.02 and 7.16 (4H, 2t, J 8.0, H5, H6), 7.50 (2H, s, H2), 7.54 and 7.78 (4H, 2d, J 8.0, H4, H7). δ_C (75 MHz, [D6]DMSO) 55.3 (CH$_2$OH), 55.6 (CH$_2$ bridging), 110.6, 117.3, 119.6, 119.7, 122.2, 126.7, 127.6 (ArCH and ArC). m/z (ESI) 303 ([M − 3]$^+$ (10 %), 287 (20), 273 (15), 174 (65), 160 (45), 144 (15), 130 (100).

1,4-Di-(5-benzyloxy-3-hydroxymethylindol-1-ylmethyl) benzene (9e)

The dialdehyde **8e** (1.10 g, 1.82 mmol), sodium borohydride (0.69 g, 18.2 mmol), THF (40 mL), and absolute ethanol (20 mL) yielded the dialcohol **9e** as a white solid (0.92 g, 83 %). Product not obtained analytically pure but used directly. Mp 135–137°C. ν_{max} (KBr)/cm^{-1} 3409, 2923, 2866, 1645, 1620, 1587, 1529, 1484, 1454, 1395, 1263, 1223, 1200, 1028. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 227 (58000), 273 (22000). δ_H (300 MHz, [D6]DMSO) 4.55 (4H, s, CH_2OH), 4.69 (2H, bs, CH$_2$OH), 5.04 (4H, s, CH$_2$N), 5.23 (4H, s, OCH_2Ph), 6.77 (2H, dd, J 2.6, 2.3, ArH), 7.09 (2H, s, ArH), 7.17 (2H, d, J 2.3 Hz ArH), 7.24–7.45 (14H, m, ArH). δ_C (75 MHz, [D6]DMSO) 49.1 (CH$_2$N), 55.6 (CH$_2$OH), 70.3 (OCH$_2$Ph), 103.2, 111.1, 112.2, 115.9, 127.6, 127.9, 128.0, 128.7, 132.0, 137.9, 138.1, 152.7 (ArCH and ArC). m/z (ESI) [M + Na]$^+$ 631.2574. C$_{40}$H$_{36}$N$_2$NaO$_4$ requires 631.2568.

1,4-Di-(5-bromo-3-hydroxymethylindol-1-ylmethyl) benzene (9f)

The dialdehyde **8f** (1.26 g, 2.30 mmol), sodium borohydride (0.86 g, 23.0 mmol), THF (40 mL), and absolute ethanol (20 mL) yielded the dialcohol **9f** as a yellow solid (1.22 g, 96 %). Mp 214–215°C. Found: C 56.6, H 4.2, N 4.9; C$_{26}$H$_{22}$Br$_2$N$_2$O$_2$ requires: C 56.3, H 4.0, N 5.1 %. ν_{max} (KBr)/cm^{-1} 3424, 2923, 2877, 1469, 1241, 1910, 1038. δ_H (300 MHz, [D6]DMSO) 4.56 (4H, s, CH_2OH), 4.83 (2H, bs, CH$_2$OH), 5.28 (4H, s, CH$_2$N), 7.10 (4H, s, ArH), 7.16 (2H, dd, J 1.7, H6), 7.34–7.37 (4H, m, H2, H7), 7.75 (2H, d, J 1.9, H4), 7.36 (2H, d, J 8.3, ArH), 7.56 (2H, d, J 7.9, ArH). δ_C (75 MHz, [D6]DMSO) 49.1 (CH$_2$N), 55.4 (CH$_2$OH), 111.8, 112.5, 116.1, 122.0, 124.1, 127.7, 128.7, 129.3, 135.3, 137.6 (ArCH and ArC). m/z (ESI) 553 ([M − 3]$^+$ ^{81,81}Br, 70 %), 551 ([M − 3]$^+$ ^{79,81}Br, 100 %), 548 ([M − 3]$^+$ ^{79,79}Br, 50 %).

10,19,35,44-Tetraazaundecacyclo[42,6,1,1^{3,10}, 1^{19,26},1^{28,35},0^{4,9},0^{12,17},0^{20,25},0^{29,34},0^{37,42},0^{45,50}] tetrapentaconta-1(51),3(52),4,6,8,12,14,16, 20,22,24,26(53),28(54),29,31,33,37,39,41,45, 47,49-docosaene (10a)

The dialcohol **9a** (0.26 g, 0.66 mmol) in anhydrous acetone (100 mL) was treated with a catalytic amount of p-toluenesulfonic acid monohydrate, and the mixture stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified using 'dry-column' flash chromatography with dichloromethane eluant, followed by trituration of the product with dichloromethane to yield the macrocycle **10a** as a white solid (0.054 g, 62 %). Mp 296°C. Found: C 84.8, H 5.8, N 7.8; C$_{50}$H$_{40}$N$_4$.0.5H$_2$O requires: C 85.1, H 5.9 N 7.9 %. ν_{max} (KBr)/cm^{-1} 3060, 1460, 1350, 1250, 1205, 1170, 1020, 910, 740. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 230 (124000), 291 (33500). Sample insoluble – unable to obtain ^{1}H and ^{13}C NMR measurement. m/z (MALDI) 696 (M$^+$).

10,17,33,40-Tetraazaundecacyclo[38,6,1,2^{12,15},2^{35,38} ,1^{3,10},1^{17,24},1^{26,33},0^{4,9},0^{18,23},0^{27,32},0^{41,46}] tetrapentaconta-1(47),3(48), 4,6,8,12,14,18,20,22,24(51),26 (52),27,29,31,35,37,41,43,45,49,53-docosaene (10c)

To a stirred solution of the dialcohol **9c** (0.20 g, 0.50 mmol) in anhydrous acetone (100 mL), a catalytic amount of p-toluenesulfonic acid monohydrate was added, and the mixture stirred for 1 h at room temperature. The solvent was removed

under reduced pressure and the crude product was chromatographed with dichloromethane eluant to afford the macrocycle **10c** as a white solid (0.12 g, 60 %). Mp 297–299°C. Found: C 84.5, H 5.7, N 7.7; $C_{50}H_{40}N_4.0.75H_2O$ requires: C 84.5, H 5.9, N 7.9 %. ν_{max} (KBr)/cm^{-1} 1455, 1450, 1370, 1350, 1330, 1160, 1010, 915, 730. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 231 (112000), 292 (25900). δ_H (300 MHz, CDCl$_3$) 4.20 (4H, s, CH$_2$), 5.16 (8H, s, CH$_2$N), 6.71 (4H, s, H2 indolyl), 6.93 (8H, s, ArH xylyl), 7.08 (4H, t, J 7.4, ArH), 7.18 (4H, t, J 7.5, ArH), 7.27 (4H, d, J 8.7, ArH), 7.62 (4H, d, J 7.5, ArH). δ_C (75 MHz, CDCl$_3$) 29.8 (CH$_2$), 49.3 (CH$_2$N), 109.3, 119.0, 119.4, 121.7, 126.3, 127.1 (ArCH), 115.1, 128.2, 136.7, 137.2 (ArC). *m/z* (MALDI) 696 (M$^+$).

6,21,29,44-Tetrabenzyloxy-10,17,33,40-tetraazaundecacyclo[38,6,1,2^{12,15}, 2^{35,38},1^{3,10},1^{17,24},1^{26,33},0^{4,9},0^{18,23},0^{27,32},0^{41,46}] tetrapentaconta-1(47),3(48),4,6,8,12,14,18,20,22,24 (51),26(52),27,29,31,35,37,41,43, 45,49,53-docosaene (*10e*)

To a stirred solution of the dialcohol **9e** (0.18 g, 0.30 mmol) in anhydrous acetone (200 mL), a catalytic amount of *p*-toluenesulfonic acid monohydrate was added, and the mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude product was chromatographed with dichloromethane eluant to afford the macrocycle **10e** as a white solid (0.10 g, 60 %). Mp 237–239°C. Found: C 82.6, H 6.0, N 4.9; $C_{78}H_{64}N_4O_4.0.75H_2O$ requires: C 82.6, H 6.0, N 4.9 %. ν_{max} (KBr)/cm^{-1} 2921, 2850, 1620, 1579, 1484, 1451, 1420, 1380, 1275, 1227, 1199, 1028. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 232 (135900), 285 (43700), 308 (33000). δ_H (300 MHz, CDCl$_3$) 4.10 (4H, s, CH$_2$), 5.05 (8H, s, CH$_2$N), 5.11 (8H, s, OCH$_2$Ph), 6.69 (4H, s, ArH), 6.92 (8H, s, ArH), 7.15–7.18 (8H, m, ArH), 7.29–7.39 (16H, m, ArH), 7.43–7.45 (8H, m, ArH). δ_C (75 MHz, CDCl$_3$) 22.6 (CH$_2$), 49.4 (CH$_2$N), 70.8 (OCH$_2$Ph), 77.1, 102.6, 110.0, 112.4, 116.5, 126.8, 126.9, 127.5, 127.6, 128.3, 128.4 (ArCH), 114.3, 132.0, 137.2, 137.6, 152.9, 172.6 (ArC). *m/z* (MALDI) 1119 ([M − 2]$^+$, 2 %).

6,21,29,44-Tetrabromo-10,17,33,40-tetraazaundecacyclo[38,6,1,2^{12,15},2^{35,38},1^{3,10}, 1^{17,24},1^{26,33},0^{4,9},0^{18,23},0^{27,32},0^{41,46}]tetrapentaconta-1 (47),3(48),4,6,8,12,14,18,20,22,24(51),26(52), 27,29,31,35,37,41,43,45,49,53-docosaene (*10f*)

To a stirred solution of the dialcohol **9f** (0.28 g, 0.50 mmol) in anhydrous acetone (120 mL), a catalytic amount of *p*-toluenesulfonic acid monohydrate was added, and the mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude product was chromatographed with dichloromethane eluant to afford the macrocycle **10f** as a white solid (0.13 g, 50 %). Mp >300°C. Found: C 59.4, H 3.7, N 5.3; $C_{50}H_{36}Br_4N_4$ requires: C 59.3, H 3.6, N 5.5 %. ν_{max} (KBr)/cm^{-1} 1511, 1466, 1436, 1420, 1373, 1350, 1295, 1198, 1164, 1052, 865, 820, 790. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 235 (126300), 297 (22300). δ_H (300 MHz, CDCl$_3$) 4.08 (4H, s, CH$_2$), 5.14 (8H, s, CH$_2$N), 6.67 (4H, s, H2 indolyl), 6.89 and 6.91 (12H, 2s, H7 and ArH), 7.13 (4H, d, J 8.7, H6 indolyl), 7.71 (4H, d, J 1.5, H4 indolyl). δ_C (75 MHz, [D6]DMSO) 21.7 (CH$_2$), 49.0 (CH$_2$N), 112.4, 124.0, 127.3, 127.6, 128.9 (ArCH), 111.6, 113.5, 129.7, 135.3, 137.6 (ArC). *m/z* (MALDI) 1015 ([M + 1]$^+$ ^{79,81,81,81}Br, 2 %), 1013 [M + 1]$^+$ ^{79,79,81,81}Br, 5 %), 1011 ([M + 1]$^+$ ^{79,79,79,81}Br, 4 %), 1009 ([M + 1]$^+$ ^{79,79,79,79}Br, 3 %).

Ethyleneglycol-O,O′-Bis(2-(3-formylindol-1-ylmethylbenzene)) (*12*)

A mixture of indole-3-carbaldehyde **6a** (0.15 g, 1.03 mmol) and freshly crushed potassium hydroxide (0.49 g, 8.73 mmol) in dry dimethyl sulfoxide (20 mL) was stirred for 1 h. 1,2-Bis (2-bromomethylphenoxy) ethane **11** (0.21 g, 0.52 mmol) was added and the mixture was stirred for an additional 2 h. Water was added and the yellowish product was filtered off, washed with water, and dried. The crude product was purified using gravity column chromatography with ethyl acetate/light petroleum (1 : 1) eluant to yield the dialdehyde **12** as a yellow solid (0.23 g, 85 %). Mp 177–178°C. Found: C 77.1, H 5.4, N 5.5; $C_{34}H_{28}N_2O_4$ requires: C 77.3, H 5.3, N 5.3 %. ν_{max} (KBr)/cm^{-1} 1640, 1450, 1370, 1240, 1150, 1115, 1030, 940, 920, 735. λ_{max} (MeOH)/nm (ε/M^{-1} cm^{-1}) 247 (30800), 303 (36100). δ_H (300 MHz, CDCl$_3$) 4.11 (4H, s, CH$_2$), 5.10 (4H, s, CH$_2$O), 6.81 (2H, d, J 8.2, ArH), 6.97 (2H, t, ArH), 7.07 (2H, t, ArH), 7.13–7.22 (6H, m, ArH), 7.32 (2H, t, ArH), 7.53 (2H, s, H2), 8.24 (2H, d, J 7.7, ArH), 9.77 (2H, s, CHO). δ_C (75 MHz, CDCl$_3$) 46.5 (CH$_2$), 66.4 (CH$_2$O), 110.3, 111.5, 121.4, 121.9, 122.8, 123.8, 130.0, 130.1, 138.8 (ArCH), 118.1, 123.7, 125.2, 137.6, 156.4 (ArC), 184.4 (CHO). *m/z* (EI) 529 ([M + 1]$^+$, 2 %), 528 (M, 4), 500 (6), 499 (3), 234 (5), 158 (7), 144 (20), 133 (40), 107 (65), 91 (100), 78 (60), 77 (55).

Ethyleneglycol-O,O′-Bis(2-(3-hydroxymethylindol-1-ylmethylbenzene)) (*13*)

A mixture of dialdehyde **12** (0.10 g, 0.19 mmol) and sodium borohydride (0.10 g, 2.64 mmol) in absolute ethanol was stirred for 2 h. The solvent was then evaporated almost to dryness, and the white residue was suspended in 5 % aqueous sodium hydroxide and the mixture cooled in ice. The product was filtered off, washed with water, and dried to give the dialcohol **13** as a white solid (0.09 g, 87 %). Mp 97–98°C. ν_{max} (KBr)/cm^{-1} 3320, 1610, 1450, 1390, 1240, 1180, 1130, 1040, 960, 750. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 222 (63900), 281 (9100). δ_H (300 MHz, CDCl$_3$) 4.29, 4.74, 5.16 (6H, 3s, CH$_2$), 6.86–7.30 (16H, m, H2 and ArH), 7.68 (2H, d, J 6.7, ArH). δ_C (75 MHz, CDCl$_3$) 45.1, 57.2, 66.7 (CH$_2$), 109.9, 111.5, 119.1, 119.5, 121.3, 122.0, 127.1, 129.0, 129.1 (ArCH), 115.1, 126.0, 127.0, 137.0, 156.1 (ArC). *m/z* (MALDI) 555.75, [M + Na]$^+$. *m/z* (HRMS ESI) [M + Na]$^+$ 555.2253. $C_{34}H_{32}N_2NaO_4$ requires 555.2254.

10,29-Diazaheptacyclo[27,6,1,1^{3,10},0^{4,9},0^{12,17}, 0^{30,35}]heptatriaconta-1(36),3(37),4,6,8,12,14,16, 22,24,26,30,32,34-tetradecaene (*14*)

The dialcohol **13** (0.09 g, 0.16 mmol) in dichloromethane was treated with a catalytic amount of *p*-toluenesulfonic acid and stirred for 1 h. The pink solution was evaporated and the crude product was purified using gravity column chromatography with dichloromethane/light petroleum (1 : 1) eluant to afford the macrocycle **14** as a white solid (0.05 g, 68 %). Mp 228–229°C. ν_{max} (KBr)/cm^{-1} 1590, 1455, 1380, 1330, 1250, 1160, 1120, 1070, 1050, 960, 745. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 229 (103200), 281 (27000), 293 (23500). δ_H (300 MHz, CDCl$_3$) 4.14 (2H, s, CH$_2$), 4.26 (4H, s, CH$_2$), 5.21 (4H, s, CH$_2$), 6.87–7.59 (18H, m, ArH). δ_C (75 MHz, CDCl$_3$) 20.1, 45.7, 67.9 (CH$_2$), 109.4, 112.6, 118.6, 118.9, 121.2, 121.3, 126.9, 129.7, 131.8 (ArCH), 113.7, 125.9, 128.4, 136.4, 157.4 (ArC). *m/z* (MALDI) 484.60, M$^+$. *m/z* (HRMS ESI) [M + H]$^+$ 485.2224. $C_{33}H_{29}N_2O_2$ requires 485.2229.

4-(3-(Indol-1-ylpropoxy)-3-methoxybenzene)methanol (16a)

Indole **5a** (0.21 g, 1.79 mmol) and freshly crushed potassium hydroxide (0.42 g, 7.49 mmol) were stirred for 1 h in dry dimethyl sulfoxide. 4-(3-Iodopropoxy)-3-methoxybenzene-methanol[26] **15** (1.20 g, 3.72 mmol) was added and the mixture was stirred for 1 h at room temperature. The mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated. The crude product was purified using gravity column chromatography with ethyl acetate/light petroleum (1 : 1) eluant to afford the alcohol **16a** as a colourless oil (0.47 g, 84 %). ν_{max} (KBr)/cm^{-1} 3400, 1600, 1450, 1410, 1370, 1260, 1180, 1150, 1130, 1030, 850, 800, 740. λ_{max} (CH$_2$Cl$_2$)/nm (ε/M^{-1} cm^{-1}) 231 (41600), 283 (14800), 326. δ_H (300 MHz, CDCl$_3$) 2.33 (2H, quin, CH$_2$), 3.89–3.93 (5H, m, CH$_2$ and OCH$_3$), 4.42 (2H, t, CH$_2$), 4.61 (2H, s, CH$_2$OH), 6.52 (1H, d, J 2.6, ArH), 6.76 (d, J 8.2, ArH), 6.84 (1H, d, J 8.2, ArH), 6.98 (1H, s, ArH), 7.13–7.26 (3H, m, ArH), 7.43 (1H, d, J 8.2, ArH), 7.68 (1H, d, J 7.7, ArH). δ_C (75 MHz, CDCl$_3$) 29.7, 42.5, 64.9, 65.6 (CH$_2$), 55.8 (OCH$_3$), 101.0, 109.3, 110.9, 113.5, 119.2, 119.3, 120.8, 121.3, 128.1 (ArCH), 128.5, 134.2, 135.8, 147.5, 149.6 (ArC). m/z (EI) 312 ([M + 1]$^+$, 25 %), 311 (M, 90), 174 (5), 158 (90), 130 (100), 117 (25), 77 (30).

4-(3-(5′-Benzyloxy-1′-indolylpropoxy)-3-methoxybenzene)methanol (16e)

5-Benzyloxyindole **5e** (0.65 g, 2.91 mmol) and freshly crushed potassium hydroxide (0.66 g, 11.8 mmol) were stirred in dry dimethyl sulfoxide (40 mL) for 1 h at room temperature. 4-(3-Iodopropoxy)-3-methoxybenzenemethanol[26] **15** (1.88 g, 5.84 mmol) was added and the mixture was stirred overnight. The mixture was diluted with water and extracted with dichloromethane and again with ethyl acetate. The combined extracts were washed several times with brine, dried over magnesium sulfate, and concentrated under reduced pressure. The crude product was purified using gravity column chromatography with ethyl acetate/light petroleum (1 : 1) eluant to afford the alcohol **16e** as a colourless oil, which solidified after storing in the refrigerator to become a white solid (1.02 g, 84 %). Mp 92–93°C. Found: C 74.3, H 6.6, N 3.2; C$_{26}$H$_{27}$NO$_4$ requires: C 74.8, 6.5, 3.4 %. ν_{max} (KBr)/cm^{-1} 3450, 1590, 1480, 1450, 1370, 1260, 1230, 1200, 1180, 1150, 1040, 1000, 840, 820, 790, 750, 700. λ_{max} (MeOH)/nm (ε/M^{-1} cm^{-1}) 225 (40000), 277 (10100). δ_H (300 MHz, CDCl$_3$) 2.30 (2H, quin, CH$_2$), 3.89–3.93 (5H, m, CH$_2$ and OCH$_3$), 4.37 (2H, t, CH$_2$), 4.63 (2H, d, CH$_2$OH), 5.10 (2H, s, CH$_2$Ph), 6.38 (1H, d, J 2.6, ArH), 6.74–6.97 (4H, m, ArH), 7.08 (1H, d, J 3.1, ArH), 7.17 (1H, d, J 2.0, ArH), 7.26–7.49 (6H, m, ArH). δ_C (75 MHz, CDCl$_3$) 29.9, 42.9, 65.3, 65.7, 71.0 (CH$_2$), 55.9 (OCH$_3$), 100.8, 104.3, 110.1, 111.0, 112.6, 113.7, 119.5, 127.5, 127.7, 128.5, 128.7 (ArCH), 128.9, 131.5, 134.3, 137.8, 147.7, 149.8, 153.2 (ArC). m/z (EI) 418 ([M + 1]$^+$, 10 %), 417 (30), 400 (17), 326 (30), 236 (10), 174 (50), 146 (100), 117 (35), 91 (95), 77 (15).

Supplementary Material

^{1}H NMR and ^{13}C NMR spectra verifying the identity of new compounds are available on the Journal's website.

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