Tetrahedron 65 (2009) 5977–5983

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Synthesis of indolocyclotriveratrylenes

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ARTICLE INFO

Article history:
Received 4 March 2009
Received in revised form 12 May 2009
Accepted 28 May 2009
Available online 6 June 2009

Keywords:
Indoles
Acid-catalysts
Cyclotriveratrylenes
Benzylic alcohols

ABSTRACT

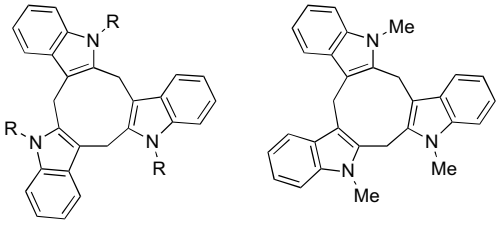
Indolocyclotriveratrylenes linked through C2 and C3 can be prepared by acid-catalysed reactions of indole-2- or -3-methanols. The initial example, compound **1** has been confirmed, and an X-ray crystal structure is reported. Seven new examples of indolocyclotriveratrylenes, namely **7**, **9**, **11**, **13**, **17**, **28** and **29** are described.

1. Introduction

Cyclotriveratrylenes,[1–6] cyclic oligomers based on the tribenzocyclononatriene core, and their derivatives have been synthesised by three methods: (i) the reaction of 1,2-disubstituted benzenes with formaldehyde under acidic conditions,[3,5] (ii) the treatment of 3,4-disubstituted benzyl alcohols with acids,[7,8] and (iii) the acid-catalysed condensation of 1,2-disubstituted benzenes with 3,3′,4,4′-tetra-alkoxy-6,6′-bis(chloromethyldiphenyl)methanes.[4,5] They have been shown to have a rigid crown conformation.

Indolocyclotriveratrylenes are cyclotriveratrylene derivatives in which the benzene rings have been replaced by indole rings. Therefore, the synthetic routes to cyclotriveratrylenes can also be applied to indolocyclotriveratrylenes. The first preparation of indolocyclotriveratrylenes was published in 1970 by Bergman and co-workers,[9] who reported that the reaction of 1-methylindole with 38% formaldehyde solution in the presence of sulfuric acid afforded a trimeric compound with either a symmetrically linked structure **1** or an unsymmetrically linked structure **2** in 24% yield. Hiremath and co-workers[10] contemplated the preparation of a pyrano[3,4-*b*]indole from the condensation of 2-hydroxymethyl-1-methylindole and α-bromoacetone, but the liberated hydrobromic acid combined with an intermediate to give the unexpected trimeric compound **1**.

More recently it has been reported that the parent indolocyclotriveratrylene **3** produced under acidic conditions from the digestion of indole-3-carbinol, which normally occurs in *Brassica* vegetables such as cabbage, kale, cauliflower, Brussels sprouts and broccoli, is a strong agonist of the oestrogen receptor.[11,12] Further, in vitro treatment of 3-hydroxymethylindole with aqueous hydrochloric acid gave rise to the cyclic trimer **3** and its oligomers. However, this method gave the indolocyclotriveratrylene only in low yields and required HPLC purification.[13] A trace (2%) of the cyclic trimer **3** was obtained from the pyrolysis of 3-(diethylaminomethyl)-indole hydrochloride.[14]



1 R=Me
3 R=H

2

More recently, Bjeldanes and Staub[15] showed that the reaction of 3-(dimethylaminomethyl)-indole and dimethylsulfate in the presence of sodium ethoxide afforded the trimer **3** in approximately 75% yield. However, the conformation of the indolocyclotriveratrylene was not reported.

2. Results and discussion

2.1. Preparation of cyclic trimer 1

It was of interest to carry out a systematic study on the synthesis of indolocyclotriveratrylenes based on the acid-catalysed

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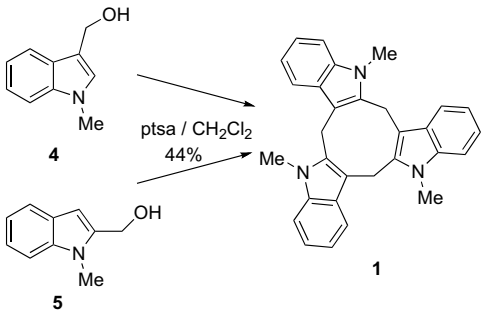
0040-4020/$ – see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2009.05.092

reactions of indole-3-methanols and indole-2-methanols. This was particularly relevant in view of earlier studies that revealed the formation of calix-3- and calix-4-indoles by the acid-catalysed reactions of 2- and 7-hydroxymethyl-4,6-dimethoxyindoles.[16,17] Initially, the known[18–20] 3-hydroxymethyl-1-methylindole **4** was treated with a catalytic amount of *p*-toluenesulfonic acid (ptsa) in dichloromethane, and after 1 h at room temperature gave the cyclic trimer **1** in 44% yield (Scheme 1). Formation of compound **1** could also be effected using other acid-catalysts such as trifluoroacetic acid in chloroform, boron trifluoride diethyl etherate in dichloromethane, K10 clay in dichloromethane, concentrated hydrochloric acid in tetrahydrofuran and concentrated sulfuric acid in glacial acetic acid. The spectroscopic properties of compound **1** were consistent with those available in the literature.[9] A suitable crystal enabled an X-ray crystal structure determination to be made, and this showed that the compound was in the saddle or propeller conformation (Fig. 1). A major steric factor is presumably the close proximity of the *N*-methyl groups to the nine-membered ring. The nine bond lengths involved in the nine-membered ring are all slightly shorter than the corresponding bond lengths in cyclotriveratrylene itself,[21] and the nine bond angles are considerably larger.



Scheme 1.

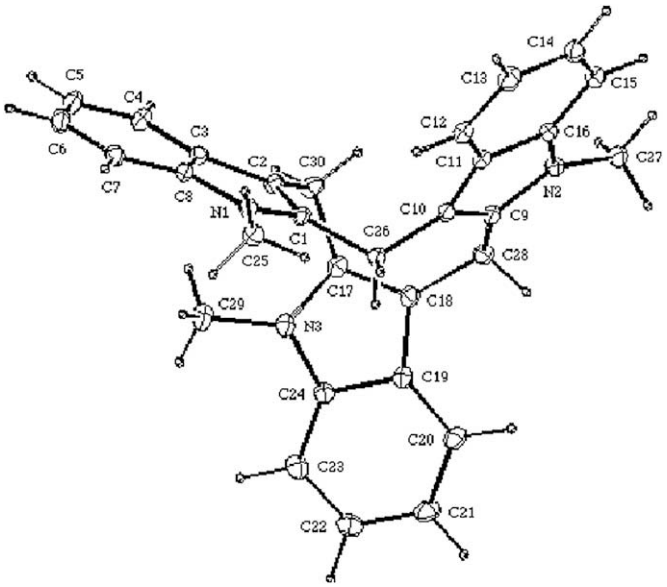
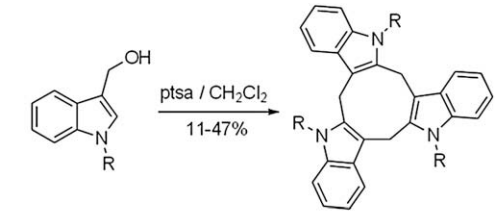


Figure 1. ORTEP diagram derived from the single-crystal X-ray analysis of compound **1**.

The cyclic trimer **1** could also be synthesised in the same yield by reaction of the 2-methanol **5** with ptsa in dichloromethane (Scheme 1). The alcohol **5** was prepared by the lithium aluminium hydride reduction of methyl 1-methylindole-2-carboxylate[22] in 87% yield, and was treated with acid directly.

2.2. Preparation of related cyclic trimers with other substituents on nitrogen

Some related indolocyclotriveratrylenes were then prepared in order to establish the generality of the reaction. Thus, the 1-allyl-3-hydroxymethylindole **6** was prepared by reduction of the related 3-aldehyde[23] with sodium borohydride and was treated directly with ptsa in dichloromethane to give the cyclic trimer **7** in 44% yield (Scheme 2).



	R
6	CH_2=$CHCH_2$
8	$PhCH_2$
10	$MeOCH_2$
12	$MeC_6H_4SO_2$

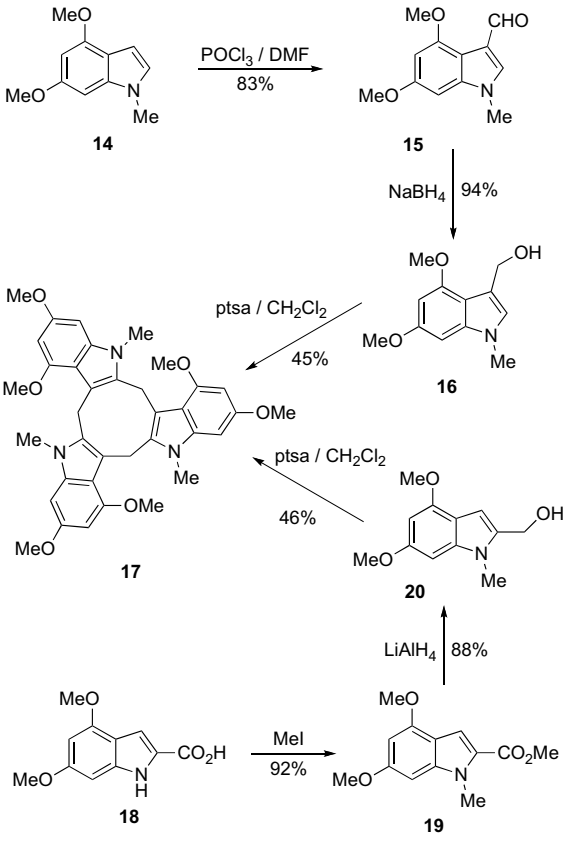
	R
7	CH_2=$CHCH_2$
9	$PhCH_2$
11	$MeOCH_2$
13	$MeC_6H_4SO_2$

Scheme 2.

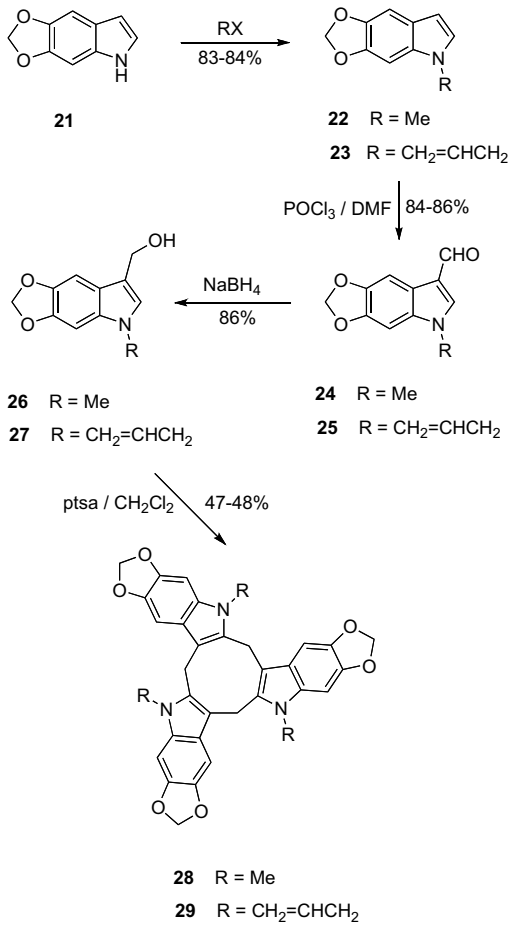
1-Benzyl-3-hydroxymethylindole[24,25] **8** similarly gave the cyclic trimer **9** in 45% yield. Reduction of 1-methoxymethylindole-3-carbaldehyde[26] with sodium borohydride gave the corresponding indole-3-methanol **10**, which was directly converted by treatment with ptsa in dichloromethane into the cyclic trimer **11** in 47% yield. Treatment of the 1-tosylindole-3-methanol[27,28] **12** with either ptsa or hydrochloric acid was ineffective, but the use of boron trifluoride diethyl etherate gave the cyclic trimer **13** in 11% yield (Scheme 2). All the indolocyclotriveratrylenes **1**, **7**, **9** and **11** show singlet resonances in the range 4.00–4.16 ppm for the bridging methylene protons in their ^{1}H NMR spectra, results which are consistent with saddle conformations.

2.3. Preparation of related cyclic trimers from activated indoles

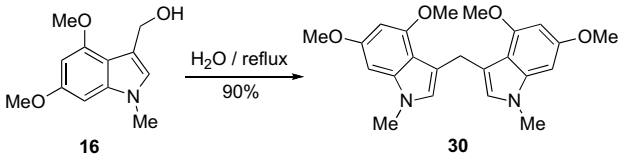
Indoles incorporating methoxy or methylenedioxy substituents frequently show greater nucleophilic reactivity, so it was of interest to investigate the application of such compounds to the formation of indolocyclotriveratrylenes, especially because of the rather moderate yields shown by the simple indole derivatives **4**, **6**, **8**, **10** and **12**. 4,6-Dimethoxyindole[29] was initially *N*-methylated to give compound **14**, and the resulting product[30,31] formylated at C3 to give the 3-carbaldehyde[32] **15**, which was reduced to the 3-hydroxymethyl compound **16** (Scheme 3). Treatment of this benzylic alcohol with ptsa in dichloromethane, as described for the earlier examples, similarly gave the cyclic trimer **17** in 45% yield. The same indolocyclotriveratrylene could also be formed in 46% yield by similar acid treatment of 2-hydroxymethyl-4,6-dimethoxy-1-methylindole **20**, derived from the lithium aluminium hydride reduction of the corresponding 2-methylester **19**. This latter compound was obtained by the methylation of 4,6-dimethoxyindole-2-carboxylic acid[33] **18** and used directly (Scheme 3).



Scheme 3.



Scheme 4.



Scheme 5.

5,6-Methylenedioxyindole[34] **21** was *N*-methylated and *N*-allylated to give indoles[35,36] **22** and **23**, respectively (Scheme 4). These in turn were formylated at C3 to give the two aldehydes **24** and **25**, which were each reduced with sodium borohydride to give the 3-hydroxymethyl compounds **26** and **27**, respectively. Treatment of these benzylic alcohols with ptsa in dichloromethane, as described above, generated a 48% yield of the cyclic trimer **28** and a 47% yield of the cyclic trimer **29**, respectively (Scheme 4).

The indolocyclotriveratrylenes **17**, **28** and **29** showed singlet resonances in their ^{1}H NMR spectra at 4.20, 3.87 and 3.83 ppm, respectively, all consistent with saddle conformations. Interestingly, there was effectively no increase in yields of indolocyclotriveratrylenes from the activated indole precursors.

2.4. A note on reaction conditions

It should be noted that whilst the cyclotrimerisation reactions reported above take place usually in dichloromethane with *p*-toluenesulfonic acid as catalyst, it has long been known that *N*-substituted-3-hydroxymethylindoles such as compound **4** are smoothly converted by heating in water at reflux to the corresponding 3,3′-diindolylmethanes.[19] Consequently, the 4,6-dimethoxy-1-methyl-3-hydroxymethylindole **16** was shown to undergo a similar conversion to the 3.3′-diindolylmethane **30**, when heated under reflux in water (Scheme 5).

3. Conclusions

The formation of the nine-membered ring containing indolocyclotriveratrylenes by the acid-catalysed reactions of 2-unsubstituted-3-hydroxymethyl indoles appears to be quite general. Several examples have also indicated that the similar reactions of 3-unsubstituted-2-hydroxymethylindoles are also probably general.

4. Experimental

4.1. General

Melting points were measured using a Mel-Temp melting point apparatus, and are uncorrected. Microanalyses were performed by the Microanalytical Unit, Research School of Chemistry, The Australian National University. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AC300F (300 MHz) spectrometer. Mass spectra were recorded on either an AEI MS 12 (EI) or a Finnegan MAT (MALDI) spectrometer. Infrared spectra were recorded with a Perkin Elmer 298 IR spectrometer. Ultraviolet–visible spectra were recorded using a Hitachi U-3200 spectrometer. Column chromatography was carried out using Merck 70–230 mesh silica gel, whilst preparative thin layer chromatography was performed using Merck silica gel 7730 60GF$_{254}$. Flash chromatography[35,36] was carried out using Merck 60H silica gel.

*4.1.1. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b]tri-1-methylindole (**1**)*

Method A: 3-Hydroxymethyl-1-methylindole[20] **4** (0.30 g, 1.86 mmol) in dichloromethane (70 mL) was treated with a catalytic

amount of *p*-toluenesulfonic acid monohydrate, and the mixture was stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified using column chromatography with dichloromethane/light petroleum (1/1) eluant to afford the cyclic trimer **1** as a white solid (0.12 g, 44%), mp 278–281 °C (lit.[9] 275 °C). ν_{max} (Nujol) 3050, 1605, 1460, 1365, 1330, 1300, 1250, 1175, 1140, 1010, 880, 845, 790, 770, 730 cm^{-1}. λ_{max} (CH_2Cl_2) 234 nm (ε 135,300 $cm^{-1}\,M^{-1}$), 290 (38,700), 296 (37,900). δ_H (300 MHz, $CDCl_3$): 3.74 (9H, s, Me), 4.05 (6H, s, CH_2), 7.09 (3H, t, H5), 7.16 (3H, t, H6), 7.27 (3H, d, H7), 7.53 (3H, d, H4). δ_C (75 MHz, $CDCl_3$): 20.4 (CH_2), 29.7 (Me), 108.9, 117.2, 118.9 and 120.7 (ArCH), 107.0, 127.5, 136.0 and 136.3 (ArC). Mass spectrum (EI): *m*/*z* 429 (M, 20), 286 (90), 285 (100), 270 (55), 255 (25), 144 (50), 129 (20). Crystals for a single-crystal X-ray determination were obtained by recrystallisation from dichloromethane/light petroleum.

Method B: Methyl 1-methylindole-2-carboxylate[22] (0.16 g, 0.85 mmol) in dry ether (45 mL) was added dropwise to lithium aluminium hydride (0.12 g, 3.16 mmol) in boiling dry ether (75 mL). When the addition was complete, the solution was heated at reflux for an additional 30 min. After cooling, ethyl acetate, cold water and a small amount of dilute sodium hydroxide were added to decompose the excess of the reducing agent. The solvent was dried over sodium sulfate and evaporated to give the hydroxymethylindole **5** (0.12 g, 86%) as a white solid. δ_H (300 MHz, $CDCl_3$): 3.73 (3H, s, Me), 4.03 (2H, s, CH_2), 7.03–7.17 (3H, m, ArH), 7.26 (1H, d, ArH), 7.51 (1H, d, ArH). δ_C (75 MHz, $CDCl_3$): 29.6 (Me), 57.1 (CH_2OH), 101.1, 109.1, 119.4, 120.7 and 121.8 (ArCH), 127.1, 138.0 and 138.6 (ArC). 2-Hydroxymethyl-1-methylindole (0.12 g, 0.75 mmol) was then treated without further purification as 3-hydroxymethyl-1-methylindole in Method A to give the trimer **1** as a white solid (0.05 g, 44%).

*4.1.2. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b]tri-1-allylindole (**7**)*

A mixture of 1-allylindole-3-carbaldehyde (0.62 g, 3.35 mmol) and sodium borohydride (0.50 g, 0.013 mol) in absolute ethanol (30 mL) was heated at reflux for 30 min. After cooling, the solution was evaporated almost to dryness and the white residue was suspended in 5% aqueous sodium hydroxide. The precipitate was filtered off, washed with water and dried to give 1-(prop-2′-enyl)-3-hydroxymethylindole **6** as a white solid (0.58 g, 95%). The crude alcohol **6** (0.58 g, 3.10 mmol) in dichloromethane (70 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate, and stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was purified by column chromatography with dichloromethane/light petroleum (1/3) eluant to afford the trimer **7** as a white solid (0.23 g, 44%), mp 297–299 °C. Found: C, 82.8; H, 6.6; N, 7.6. $C_{36}H_{33}N_3\cdot 0.75H_2O$ requires C, 82.9; H, 6.6; N, 8.1%. ν_{max} (Nujol) 3050, 1620, 1450, 1370, 1300, 1260, 1170, 920, 740 cm^{-1}. λ_{max} (MeOH) 231 nm (ε 125,700 $cm^{-1}\,M^{-1}$), 288 (31,700), 295 sh (30,500), 338 (3700). δ_H (300 MHz, $CDCl_3$): 4.12 (6H, s, CH_2), 4.86 (6H, d, *J* 3.6 Hz, H1′), 4.94 (3H, d, *J* 17.4 Hz, H3′), 5.18 (3H, d, *J* 10.2 Hz, H3′), 5.92–6.04 (3H, m, H2′), 7.15–7.34 (9H, m, ArH), 7.61 (3H, d, *J* 7.2 Hz, ArH). δ_C (75 MHz, $CDCl_3$): 20.34 (CH_2), 45.2 (C1′), 116.2 (C3′), 133.6 (C2′), 109.3, 117.34, 119.1 and 120.9 (ArCH), 107.6, 127.7, 135.6 and 135.8 (ArC). Mass spectrum (EI): *m*/*z* 508 (M+1, 25%), 507 (M, 65), 338 (100), 297 (45), 295 (90), 256 (35), 255 (70), 170 (30), 156 (20).

*4.1.3. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b:]tri-1-benzylindole (**9**)*

1-Benzyl-3-hydroxymethylindole[24] **8** (0.79 g, 3.33 mmol) in dichloromethane (70 mL) was treated with a small amount of *p*-toluenesulfonic acid monohydrate, and stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was purified using column chromatography with dichloromethane/light petroleum (1/1) eluant to afford the trimer **9** as a white solid (0.33 g, 45%), mp 232–236 °C. Found: C, 87.3; H, 6.1; N, 6.3. $C_{48}H_{39}N_3$ requires C, 87.6; H, 6.0; N, 6.4%. ν_{max} (Nujol) 3020, 1610, 1450, 1360, 1300, 1260, 1170, 1070, 1030, 920, 800, 725, 700 cm^{-1}. λ_{max} (CH_2Cl_2) 232 nm (ε 64,100 $cm^{-1}\,M^{-1}$), 289 (19,700), 296 (19,200). δ_H (300 MHz, $CDCl_3$): δ 4.00 (6H, s, CH_2 bridging), 5.39 (6H, s, CH_2), 6.96–7.26 (27H, m, ArH). δ_C (75 MHz, $CDCl_3$): 20.6 (CH_2 bridging), 46.6 (CH_2), 109.4, 117.5, 119.3, 121.2, 126.1, 127.3 and 128.8 (ArCH), 107.9, 127.7, 135.7, 136.4 and 138.0 (ArC). Mass spectrum (EI): *m*/*z* 657 (M, 10%), 438 (20), 255 (30), 91(100).

*4.1.4. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b:]tri-1-methoxymethylindole (**11**)*

A mixture of 1-methoxymethylindole-3-carbaldehyde[26] (0.34 g, 1.79 mmol) and sodium borohydride (0.34 g, 8.99 mmol) in absolute ethanol (30 mL) was stirred for 1 h. The colourless solution was evaporated almost to dryness and the white residue was suspended in 10% aqueous sodium hydroxide and extracted several times with dichloromethane. The combined extract was dried over sodium sulfate and the solvent was removed under reduced pressure to give the hydroxymethylindole **10** as a colourless oil (0.30 g, 88%). δ_H (300 MHz, $CDCl_3$): 3.20 (3H, s, OMe), 4.83 (2H, s, C*H*$_2$OH), 5.34 (2H, s, CH_2), 7.08 (1H, s, H2), 7.21 (1H, t, H5), 7.30 (1H, t, H6), 7.48 (1H, d, H7), 7.73 (1H, d, H4). δ_C (75 MHz, $CDCl_3$): 55.7 (OMe), 56.7 (CH_2OH), 77.0 (CH_2), 109.9, 119.2, 120.2, 122.4 and 126.5 (ArCH), 116.1, 127.5 and 136.7 (ArC).

The hydroxymethylindole **10** (0.30 g, 1.57 mmol) in dichloromethane (70 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid and stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was purified using column chromatography with dichloromethane/light petroleum (3/1) eluant to afford the trimer **11** as a white solid (0.13 g, 47%), mp 234–235 °C. Found: C, 75.0; H, 6.4; N, 7.6. $C_{33}H_{33}N_3O_3\cdot 0.5H_2O$ requires C, 75.0; H, 6.4; N, 7.9%. ν_{max} (Nujol) 3060, 1610, 1455, 1365, 1340, 1180, 1140, 1100, 905, 795, 740 cm^{-1}. λ_{max} (CH_2Cl_2) 231 nm (ε 201,300 $cm^{-1}\,M^{-1}$), 286 (62,400), 294 (55,900). δ_H (300 MHz, $CDCl_3$): 3.29 (9H, s, OMe), 4.16 (6H, s, CH_2 bridging), 5.51 (6H, s, CH_2), 7.12 (3H, t, H5), 7.20 (3H, t, H6), 7.41 (3H, d, H7), 7.59 (3H, d, H4). δ_C (75 MHz, $CDCl_3$): 29.7 (CH_2 bridging), 55.8 (OMe), 77.2 (CH_2), 109.8, 119.4, 119.7, 122.2 and 126.2 (ArCH), 115.4, 128.8 and 136.9 (ArC). Mass spectrum (EI): *m*/*z* 519 (M, 20%), 334 (100), 189 (40), 174 (70).

*4.1.5. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b:]tri-1-(4-toluenesulfonyl)indole (**13**)*

1-(*p*-Toluenesulfonyl)-3-hydroxymethylindole[27] **12** (0.25 g, 0.83 mmol) in ethyl acetate (50 mL) was treated with a catalytic amount of boron trifluoride diethyl etherate, and stirred for 2 h at room temperature. The solvent was evaporated and the crude product was submitted to preparative thin layer chromatography with dichloromethane/light petroleum (2/1) eluant to afford the trimer (0.026 g, 11%) as a white solid, mp 274–275 °C. Found: C, 67.2; H, 4.8; N, 4.3. $C_{48}H_{39}N_3O_6S_3\cdot 0.5H_2O$ requires C, 67.1; H, 4.7; N, 4.9%. ν_{max} (Nujol) 3050, 1670, 1590, 1450, 1370, 1260, 1160, 805, 740 cm^{-1}. λ_{max} (CH_2Cl_2) 228 nm (ε 98,600 $cm^{-1}\,M^{-1}$), 254 (41,500). δ_H (300 MHz, $CDCl_3$): 2.36 (9H, s, Me), 4.11 (6H, s, CH_2), 7.13 (6H, d, *J* 8.2 Hz, ArH), 7.22–7.33 (6H, m, H5 and H6), 7.42 (6H, d, *J* 8.2 Hz, ArH), 7.52 (3H, d, *J* 6.7 Hz, H7), 8.15 (3H, d, *J* 7.7 Hz, H4). δ_C (75 MHz, $CDCl_3$): 21.6 (Me), 21.9 (CH_2), 115.5, 118.92, 124.0, 124.9, 125.9 and 129.8 (ArCH), 120.0, 130.6, 133.6, 135.3, 136.8 and 144.9 (ArC). Mass spectrum (ES): *m*/*z* 850 (M, 25%), 288 (100), 284 (45).

*4.1.6. 4,6-Dimethoxy-1-methylindole-3-carbaldehyde (**15**)*

4,6-Dimethoxy-1-methylindole **14** (2.30 g, 12.03 mmol) in dry dimethylformamide (10 mL) was stirred in ice, and a cooled mixture of phosphoryl chloride (1.20 mL, 12.87 mmol) in dry

dimethylformamide (2 mL) was added dropwise with ice cooling. After stirring for 1 h with ice cooling, the mixture was allowed to come to room temperature and poured into ice/water. It was basified with 10% aqueous sodium hydroxide and the precipitate was filtered off, washed with water, dried and purified by flash chromatography to afford the aldehyde **15** as a white solid (2.18 g, 83%), mp 129–130 °C. Found: C, 65.5; H, 6.1; N, 6.2. $C_{12}H_{13}NO_3$ requires C, 65.7; H, 6.0; N, 6.4%. ν_{max} (Nujol) 1655, 1615, 1580, 1500, 1450, 1375, 1355, 1305, 1260, 1210, 1170, 1150, 1100, 1070, 1025, 930, 815, 770, 745, 720, 685, 670 cm^{-1}. λ_{max} (MeOH) 249 nm (ε 46,000 cm^{-1} M^{-1}), 332 (15,300). δ_H (300 MHz, $CDCl_3$): 3.77 (3H, s, Me), 3.88 and 3.95 (6H, 2s, OMe), 6.39 (1H, d, *J* 1.9 Hz, H5), 6.40 (1H, d, *J* 1.9 Hz, H7), 7.66 (1H, s, H2), 10.35 (1H, s, CHO). δ_C (75 MHz, $CDCl_3$): 34.5 (Me), 56.0 and 56.4 (OMe), 86.5 (C5), 94.7 (C7), 111.7, 118.6 and 139.5 (ArC), 155.6 and 158.8 (*C*–OMe), 188.2 (CHO). Mass spectrum (EI): *m*/*z* 219 (M, 100%), 204 (30), 173 (55), 133 (55), 105 (35).

4.1.7. 3-Hydroxymethyl-4,6-dimethoxy-1-methylindole (*16*)

A mixture of 4,6-dimethoxy-1-methylindole-3-carbaldehyde **15** (2.18 g, 9.94 mmol) and sodium borohydride (4.78 g, 0.13 mol) in absolute ethanol (30 mL) was heated at reflux for 30 min. After cooling, the solution was evaporated almost to dryness and the white residue was suspended in 5% aqueous sodium hydroxide. The precipitate was filtered off, washed with water and dried to give the alcohol **16** as a yellowish solid (2.07 g, 94%), mp 115–116 °C. Found: C, 64.7; H, 7.0; N, 6.1. $C_{12}H_{15}NO_3$ requires C, 65.1; H, 6.8; N, 6.3%. ν_{max} (Nujol) 3300, 1620, 1580, 1550, 1495, 1455, 1375, 1320, 1290, 1260, 1205, 1140, 1100, 1065, 1030, 975, 930, 790, 750, 700 cm^{-1}. λ_{max} (MeOH) 226 nm (ε 50,300 cm^{-1} M^{-1}), 273 (8400). δ_H (300 MHz, $CDCl_3$): 3.64 (3H, s, Me), 3.86 and 3.94 (6H, 2s, OMe), 4.73 (2H, d, *J* 6.7 Hz, C*H*$_2$OH), 6.24 (1H, d, *J* 1.8 Hz, H5), 6.36 (1H, d, *J* 1.8 Hz, H7), 6.75 (1H, s, H2). δ_C (75 MHz, $CDCl_3$): 32.8 (Me), 55.7 and 58.0 (OMe), 58.0 (CH_2OH), 85.7 (C5), 91.4 (C7), 124.3 (C2), 111.6, 115.2 and 139.1 (ArC), 153.6 and 157.7 (*C*–OMe). Mass spectrum (EI): *m*/*z* 221 (M, 100%), 204 (65), 146 (45), 134 (20), 118 (20).

4.1.8. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b:]tri-4,6-dimethoxy-1-methylindole (*17*)

Method A: 3-Hydroxymethyl-4,6-dimethoxy-1-methylindole **16** (0.34 g, 1.54 mmol) in dichloromethane (70 mL) was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate, and stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was purified using gravity column chromatography with dichloromethane eluant to afford the trimer **17** (0.14 g, 45%) as a white solid, mp 241–243 °C. Found: C, 69.2; H, 6.4; N, 6.7. $C_{36}H_{39}N_3O_6.H_2O$ requires C, 68.9; H, 6.6; N, 6.7%. ν_{max} (Nujol) 1620, 1580, 1450, 1370, 1350, 1330, 1285, 1250, 1205, 1140, 1080, 1050, 1030, 935, 790, 775, 740 cm^{-1}. λ_{max} (CH_2Cl_2) 234 nm (ε 193,100 cm^{-1} M^{-1}), 282 (52,800). δ_H (300 MHz, $CDCl_3$): 3.62 (9H, s, Me), 3.81 and 3.84 (18H, 2s, OMe), 4.20 (6H, s, CH_2), 6.13 (3H, d, *J* 1.9 Hz, H5), 6.32 (3H, d, *J* 1.9 Hz, H7). δ_C (75 MHz, $CDCl_3$): 21.6 (CH_2), 29.7 (Me), 55.1 and 55.7 (OMe), 85.4 (C5), 90.9 (C7), 107.0, 111.6, 137.7 and 134.4 (ArC), 154.4 and 156.1 (*C*–OMe). Mass spectrum (EI): *m*/*z* 610 (M+1, 30%), 609 (M, 80), 594 (20), 406 (30), 405 (100), 390 (30), 375 (25), 374 (20), 204 (30).

Method B: 4,6-Dimethoxyindole-2-carboxylic acid[32] **18** (1.21 g, 5.47 mmol) and freshly crushed potassium hydroxide (1.85 g, 0.033 mol) in dry dimethyl sulfoxide (20 mL) was stirred for 1 h at room temperature. Iodomethane (1.40 mL, 0.022 mol) was added and after stirring at room temperature overnight, water was added to the mixture. The resulting precipitate was filtered off, washed with water, dried and purified using flash chromatography to afford the ester **19** (1.25 g, 92%), mp >340 °C. ν_{max} (Nujol) 1700, 1630, 1605, 1580, 1500, 1460, 1380, 1350, 1305, 1240, 1210, 1180, 1160, 1100, 990, 960, 940, 810, 760, 730, 680 cm^{-1}. λ_{max} (MeOH) 228 nm (ε 114,700 cm^{-1} M^{-1}), 247 (136,300), 311 (129,600). δ_H (300 MHz, $CDCl_3$): 3.86, 3.88, 3.90 and 4.00 (12H, 4s, Me and OMe), 6.19 (1H, d, *J* 1.8 Hz, H5), 6.34 (1H, d, *J* 1.8 Hz, H7), 7.33 (1H, s, H3). δ_C (75 MHz, $CDCl_3$): 31.7 (Me), 51.2 (CO_2*Me*), 55.2 and 55.5 (OMe), 84.5 (C5), 92.4 (C7), 108.3 (C3), 112.0, 141.4, 154.9, 160.0, 162.4 and 196.8 (ArC). Mass spectrum (EI): *m*/*z* 249 (M, 100%), 234 (50), 191 (30).

Methyl 4,6-dimethoxy-1-methyl-2-carboxylate **19** (0.27 g, 1.08 mmol) in dry ether (50 mL) was added dropwise to a boiling solution of lithium aluminium hydride (0.16 g, 4.22 mmol) in dry ether (100 mL). When the addition was complete, the solution was heated at reflux for an additional 30 min. After cooling, ethyl acetate, cold water and a small amount of dilute sodium hydroxide were added and the solution was dried over sodium sulfate, and evaporated to yield the hydroxymethylindole **20** as a white solid (0.21 g, 88%). δ_H (300 MHz, $CDCl_3$): 3.67 (3H, s, Me), 3.86 and 3.89 (6H, 2s, OMe), 4.67 (2H, s, C*H*$_2$OH), 6.20 (1H, d, *J* 1.8 Hz, H5), 6.35 (1H, d, *J* 1.8 Hz, H7), 6.42 (1H, s, C3). δ_C (75 MHz, $CDCl_3$): 30.0 (Me), 55.3 and 55.6 (OMe), 57.2 (CH_2OH), 85.2 (C5), 91.4 (C7), 98.6 (C3), 112.0, 136.0 and 139.4 (ArC), 153.7 and 157.6 (*C*–OMe). The hydroxymethylindole **20** (0.21 g, 2.95 mmol) was dissolved in dichloromethane (50 mL) and treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate and stirred for 1 h. The solvent was evaporated and the crude product was purified using gravity column chromatography with dichloromethane eluant to yield the trimer **17** as a white solid (0.09 g, 46%).

4.1.9. 1-Methyl-5,6-methylenedioxyindole (*22*)

5,6-Methylenedioxyindole **21** (0.77 g, 4.78 mmol) and potassium hydroxide (1.07 g, 19.07 mmol) in dry dimethyl sulfoxide (10 mL) was stirred for 1 h at room temperature. Iodomethane (0.60 mL, 9.64 mmol) was added and after stirring at room temperature for 1 h, water was added to the mixture. The resulting precipitate was filtered off, washed with water, dried and purified using flash chromatography with chloroform/light petroleum (1/1) eluant to afford the product **22** as a white solid (0.70 g, 83%), mp 65 °C. Found: C, 68.5; H, 5.4; N, 7.6. $C_{10}H_9NO_2$ requires C, 68.6; H, 5.2; N, 8.0%. ν_{max} (Nujol) 1450, 1375, 1330, 1280, 1240, 1170, 1120, 1075, 1035, 945, 850, 830, 805, 750, 720 cm^{-1}. λ_{max} (MeOH) 222 nm (ε 18,600 cm^{-1} M^{-1}), 280 (5300), 306 (8300), 310 (8400). δ_H (300 MHz, $CDCl_3$): 3.72 (3H, s, Me), 5.93 (2H, s, CH_2), 6.35 (1H, d, *J* 3.1 Hz, H3), 6.92 (1H, d, *J* 3.1 Hz, H2), 6.79 and 7.00 (2H, 2s, H7 and H4). δ_C (75 MHz, $CDCl_3$): 33.0 (Me), 100.5 (CH_2), 90.2, 99.3, 101.0 and 127.3 (ArCH), 122.2, 132.0, 142.7 and 144.8 (ArC). Mass spectrum (EI): *m*/*z* 175 (M, 100%), 174 (30).

4.1.10. 5,6-Methylenedioxy-1-methylindole-3-carbaldehyde (*24*)

1-Methyl-5,6-methylenedioxyindole **22** (0.97 g, 5.54 mmol) in dry dimethylformamide (5 mL) was stirred in ice, and a cooled mixture of phosphoryl chloride (1.0 mL, 10.73 mmol) in dry dimethylformamide (2 mL) was added dropwise with ice cooling. After stirring for 1 h, the mixture was allowed to come to room temperature and poured into ice/water. It was basified with 10% aqueous sodium hydroxide and the crude product was filtered off, washed with water, dried and recrystallised from dichloromethane/light petroleum to afford the aldehyde **24** as a white solid (0.98 g, 86%), mp 133–134 °C. Found: C, 64.8; H, 4.2; N, 7.0. $C_{11}H_9NO_3$ requires C, 65.0; H, 4.5; N, 6.9%. ν_{max} (Nujol) 1650, 1450, 1410, 1360, 1335, 1310, 1235, 1175, 1100, 1060, 1020, 955, 805, 770, 735, 715 cm^{-1}. λ_{max} (MeOH) 254 nm (ε 14,800 cm^{-1} M^{-1}), 386 (22,900). δ_H (300 MHz, $CDCl_3$): 3.75 (3H, s, Me), 6.00 (2H, s, CH_2), 6.74, 7.47 and 7.67 (3H, 3s, H2 and ArH), 9.84 (1H, s, CHO). δ_C (75 MHz, $CDCl_3$): 33.9 (Me), 101.2 (CH_2), 90.8, 100.8 and 137.6 (ArCH), 118.3, 119.4, 133.1, 145.3 and 146.2 (ArC), 184.2 (CHO). Mass spectrum (EI): *m*/*z* 203 (M, 100%), 202 (95).

*4.1.11. 1-Allyl-5,6-methylenedioxyindole-3-carbaldehyde (**25**)*

5,6-Methylenedioxyindole **21** (1.80 g, 11.17 mmol) and freshly crushed potassium hydroxide (2.51 g, 44.73 mmol) in dry dimethyl sulfoxide (30 mL) was stirred for 1 h at room temperature. Allyl chloride (1.80 mL, 22.11 mmol) and sodium iodide (3.30 g, 22.02 mmol) were added and after stirring for an additional 1 h, water was added to the mixture. The product was extracted several times with dichloromethane. The organic layer was washed with brine, dried over magnesium sulfate and evaporated under reduced pressure. The crude product was purified using flash chromatography with dichloromethane eluant to afford the title compound **23** as an oil (1.90 g, 84%), which could not be obtained analytically pure. δ_H (300 MHz, $CDCl_3$): 4.61 (2H, s, H1′), 5.06 (1H, d, *J* 17.1 Hz, H3′), 5.18 (1H, d, *J* 10.5 Hz, H3′), 5.89–6.01 (1H, m, H2′), 5.91 (2H, s, CH_2), 6.37 (1H, d, *J* 3.2 Hz, H3), 6.94 (1H, d, *J* 3.2 Hz, H2), 6.76 and 6.99 (2H, 2s, H7 and H4). δ_C (75 MHz, $CDCl_3$): 49.2 (C1′), 117.2 (C3′), 133.4 (C2′), 100.5 (CH_2), 90.7, 99.4, 101.5 and 126.4 (ArCH), 122.4, 131.3, 142.8 and 144.7 (ArC).

The crude 1-allyl-5,6-methylenedioxyindole **23** (1.90 g, 9.44 mmol) in dry dimethylformamide (10 mL) was stirred in ice, and a cooled mixture of phosphoryl chloride (0.90 mL, 9.66 mmol) in dimethylformamide (1 mL) was added dropwise with ice cooling. After stirring for 1 h, the mixture was allowed to come to room temperature and poured into ice/water. It was basified with 10% aqueous sodium hydroxide, the precipitate was filtered off, washed with water, and dried. The crude product was purified by flash chromatography with dichloromethane eluant, followed by recrystallisation from dichloromethane/light petroleum to afford the aldehyde **25** as light brown needles (1.82 g, 84%), mp 81–82 °C. Found: C, 68.0; H, 4.9; N, 6.2. $C_{13}H_{11}NO_3$ requires C, 68.1; H, 4.8; N, 6.1%. ν_{max} (Nujol) 1640, 1520, 1450, 1375, 1335, 1260, 1175, 1120, 1080, 1030, 995, 930, 855, 820, 695 cm^{-1}. λ_{max} (MeOH) 254 nm (ε 10,300 $cm^{-1}\,M^{-1}$), 286 (17,600). δ_H (300 MHz, $CDCl_3$): 4.62 (2H, d, *J* 5.6 Hz, H1′), 5.11 (1H, d, *J* 16.9 Hz, H3′), 5.26 (1H, d, *J* 10.2 Hz, H3′), 5.87–5.99 (1H, m, H2′), 5.91 (2H, s, CH_2), 6.72, 7.51 and 7.65 (3H, 3s, ArH), 9.82 (1H, s, CHO). δ_C (75 MHz, $CDCl_3$): 49.6 (C1′), 118.7 (C3′), 136.7 (C2′), 100.0 (OCH_2O), 91.2, 100.6 and 131.5 (ArCH), 118.3, 119.2, 132.2, 145.1 and 146.0 (ArC), 184.3 (CHO). Mass spectrum (EI): *m*/*z* 230 (M+1, 25%), 229 (100), 228 (40), 200 (35), 187 (25), 160 (55).

*4.1.12. 3-Hydroxymethyl-1-methyl-5,6-methylenedioxyindole (**26**)*

A mixture of 1-methyl-5,6-methylenedioxyindole-3-carbaldehyde **24** (0.39 g, 1.70 mmol) and sodium borohydride (0.73 g, 0.019 mol) in absolute ethanol (30 mL) was heated at reflux for 30 min. After cooling, the solution was evaporated almost to dryness and the white residue was suspended in 5% aqueous sodium hydroxide. The product was extracted several times with dichloromethane, and the combined extracts were dried over sodium sulfate, concentrated under reduced pressure and recrystallised from dichloromethane/light petroleum to afford the alcohol **26** (0.30 g, 86%), mp 120 °C. Found: C, 65.0; H, 5.2; N, 7.0. $C_{11}H_{11}NO_3$ requires C, 64.4; H, 5.4; N, 6.8%. ν_{max} (Nujol) 3280, 1550, 1460, 1400, 1370, 1330, 1230, 1185, 1100, 1050, 1030, 1000, 930, 850, 835, 805, 775 cm^{-1}. λ_{max} (MeOH) 287 nm (ε 5400 $cm^{-1}\,M^{-1}$), 312 (8800). δ_H (300 MHz, $CDCl_3$): 3.67 (3H, s, Me), 4.76 (2H, s, C*H*$_2$OH), 5.93 (2H, s, OC*H*$_2$O), 6.76, 6.92 and 7.09 (3H, 3s, H7, H4, H2). δ_C (75 MHz, $CDCl_3$): 33.0 (Me), 57.2 (CH_2OH), 100.7 (OCH_2O), 90.4, 97.8 and 126.2 (ArCH), 115.0, 120.9, 132.5, 143.0 and 145.2 (ArC). Mass spectrum (EI): *m*/*z* 205 (M, 85%), 188 (100).

*4.1.13. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b:]tri-1-methyl-5,6-methylenedioxyindole (**28**)*

3-Hydroxymethyl-1-methyl-5,6-methylenedioxyindole **26** (0.11 g, 0.54 mmol) in dichloromethane was treated with a catalytic amount of *p*-toluenesulfonic acid monohydrate, and stirred for 1 h at room temperature. The solvent was removed under reduced pressure and the crude product was purified using column chromatography with dichloromethane/light petroleum (2/1) eluant, followed by recrystallisation from dichloromethane/light petroleum to afford the trimer **28** (0.048 g, 48%) as white needles, mp>310 °C. Found: C, 70.3; H, 4.9; N, 7.5. $C_{33}H_{27}N_3O_6$ requires C, 70.6; H, 4.8; N, 7.5%. ν_{max} (Nujol) 1460, 1380, 1340, 1310, 1230, 1130, 1040, 940, 885, 860, 830, 810, 735 cm^{-1}. λ_{max} (CH_2Cl_2) 232 nm (ε 78,600 $cm^{-1}\,M^{-1}$), 320 (43,100). δ_H (300 MHz, $CDCl_3$): 3.63 (9H, s, Me), 3.87 (6H, s, CH_2), 5.89 (6H, s, OCH_2O), 6.73 and 6.89 (6H, 2s, H7 and H4). δ_C (75 MHz, $CDCl_3$): 20.7 (CH_2), 30.0 (Me), 100.4 (OCH_2O), 90.4 and 96.4 (C7 and C4), 107.5, 121.4, 131.4, 134.4, 142.4 and 144.1 (ArC). Mass spectrum (MALDI): *m*/*z* 560.56 (M−1).

*4.1.14. 1,4,7-Trihydrocyclononano[2,3-b:5,6-b:8,9-b:]tri-1-allyl-5,6-methylenedioxyindole (**29**)*

A mixture of 1-allyl-5,6-methylenedioxyindole-3-carbaldehyde **25** (0.20 g, 0.87 mmol) and sodium borohydride (0.42 g, 0.011 mol) in absolute ethanol (30 mL) was heated under reflux for 30 min. After cooling, the solution was evaporated almost to dryness and the white residue was suspended in 5% aqueous sodium hydroxide. The precipitate was filtered off, washed with water and dried to give 1-allyl-3-hydroxymethyl-5,6-methylenenedioxyindole **27** as a white solid (0.18 g, 90%). The crude alcohol **27** (0.18 g, 0.78 mmol) in dichloromethane (40 mL) was treated with a small amount of *p*-toluenesulfonic acid, and stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the crude product was purified using column chromatography with chloroform eluant to afford the trimer **29** as a white solid (0.08 g, 47%), mp>350 °C. Found: C, 72.4; H, 5.2; N, 6.4. $C_{39}H_{33}N_3O_6\cdot 0.5H_2O$ requires C, 72.2; H, 5.3; N, 6.5%. ν_{max} (Nujol) 1460, 1350, 1280, 1240, 1170, 1140, 990, 940, 860, 830, 830, 800, 735 cm^{-1}. λ_{max} (CH_2Cl_2) 231 nm (ε 97,600 $cm^{-1}\,M^{-1}$), 320 (56,000). δ_H (300 MHz, $CDCl_3$): 3.83 (6H, s, CH_2 bridging), 4.64 (6H, s, H1′), 4.82 (3H, d, *J* 17.2 Hz, H3′), 5.08 (3H, d, *J* 10.2 Hz, H3′), 5.78–5.87 (3H, m, H2′), 5.87 (6H, s, CH_2), 6.69 and 6.86 (6H, 2s, H7 and H4). δ_C (75 MHz, $CDCl_3$): 20.5 (CH_2 bridging), 45.5 (C1′), 116.3 (C3′), 133.4 (C2′), 100.4 (CH_2), 90.8 and 96.5 (C7 and C4), 108.0, 121.5, 130.8, 142.5, 144.1and 134.0 (ArC). Mass spectrum (EI): *m*/*z* 640 (M+1, 40%), 639 (M, 100), 598 (25), 426 (20), 425 (50), 383 (50), 343 (30), 214 (70), 173 (40).

*4.1.15. 3,3′-Di-(4,6-dimethoxy-1-methylindolyl)methane (**30**)*

3-Hydroxymethyl-4,6-dimethoxy-1-methylindole **16** (0.44 g, 1.99 mmol) was heated under reflux overnight in water (50 mL). After cooling, the crude product was filtered off, washed with water, dried and purified using flash chromatography with dichloromethane/light petroleum eluant to yield the product **30** (0.35 g, 90%) as a white solid, mp 177 °C. Found: C, 69.7; H, 6.6; N, 7.0. $C_{23}H_{26}N_2O_4$ requires C, 70.0; H, 6.6; N, 7.1%. ν_{max} (Nujol) 1620, 1580, 1500, 1450, 1370, 1320, 1260, 1210, 1170, 1145, 1090, 1045, 930, 805, 760, 735, 710 cm^{-1}. λ_{max} (CH_2Cl_2) 232 nm (ε 102,600 $cm^{-1}\,M^{-1}$), 279 (25,000). δ_H (300 MHz, $CDCl_3$): 3.55 (6H, s, Me), 3.83 and 3.84 (12H, 2s, OMe), 4.43 (2H, s, CH_2), 6.17 (2H, d, *J* 1.9 Hz, H5), 6.30 (2H, d, *J* 1.9 Hz, H7), 6.49 (2H, s, H2). δ_C (75 MHz, $CDCl_3$): 23.3 (CH_2), 32.7 (Me), 55.2 and 55.6 (OMe), 85.0 (C5), 90.8 (C7), 124.5 (C2), 112.4, 116.5 and 138.5 (ArC), 155.5 and 157.0 (*C*–OMe). Mass spectrum (EI): *m*/*z* 395 (M+1, 35%), 394 (M, 100), 393 (45), 221 (80), 204 (100), 190 (40), 174 (25).

4.2. Crystallographic study on compound 1

4.2.1. Crystal data

$C_{30}H_{27}N_3$, *M* 429.6, monoclinic, space group $P2_1$, *a* 5.5045(8), *b* 14.473(2), *c* 14.299(3) Å, β 99.699(6)°, *V* 1122.9(3) $Å^3$, D_c 1.27 g cm^{-3}, *Z* 2, μ_{Cu} 5.41 cm^{-1}. Crystal size 0.06 by 0.07 by 0.27 mm, $2\theta_{max}$ 120°, minimum and maximum transmission factors 0.93 and 0.97. The number of reflections was 1487 considered observed out

of 1781 unique data, with R_{merge} 0.026 for equivalent reflections. Final residuals R, R_w were 0.037, 0.048 for the observed data.

4.2.2. Structure determination

Reflection data were measured with an Enraf-Nonius CAD-4 diffractometer in $\theta/2\theta$ scan mode using graphite monochromatized copper radiation (λ 1.54184 Å). Data were corrected for absorption using the analytical method of de Meulenaer and Tompa.[37] Reflections with $I>3\sigma(I)$ were considered observed. The structure was determined by direct phasing and Fourier methods. Hydrogen atoms were included in calculated positions and were assigned thermal parameters equal to those of the atom to which they were bonded. Positional and anisotropic thermal parameters for the non-hydrogen atoms were refined using full matrix least squares.

Reflection weights used were $1/\sigma^2(F_o)$, with $\sigma(F_o)$ being derived from $\sigma(I_o)=[\sigma^2(I_o)+(0.04I_o)^2]^{1/2}$. The weighted residual is defined as $R_w=(\Sigma w\Delta^2/\Sigma wF_o^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography.[38] Structure solutions were by SIR92[39] and refinement used RAELS.[40] ORTEP-II[41] running on Power MacIntosh was used for the structural diagrams, and a DEC Alpha-AXP Workstation was used for calculations.

Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC 719323). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Rd, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

Acknowledgements

Financial support from the Australian Research Council is gratefully acknowledged. M.S. acknowledges receipt of a post-graduate scholarship from the Australian Government.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.05.092.

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