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Preparation of Activated Benzofurans and their Reactions with Aldehydes

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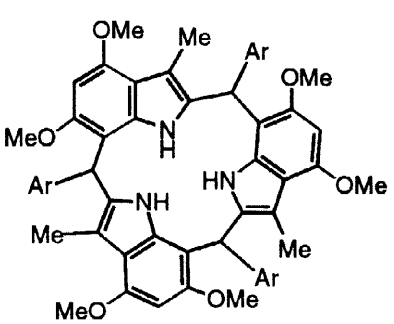
Abstract:

Reactions of 3-substituted 4,6-dimethoxybenzofurans with formaldehyde and aryl aldeydes in the presence of acetic acid and phosphoryl chloride respectively give new macrocyclic calix[3]benzofurans, predominantly with an unsymmetrical linkage pattern. Incorporation of a *t*-butyl substituent at the 3-position, however, leads to the formation of only a trimer with a symmetrical linkage pattern.

Keywords: benzofurans, calixarenes, macrocycles, aldehydes

Calixarenes are an important class of compounds which can act as hosts for guest inclusion and therefore have application as catalysts.[1] Furan has been reported to react with aldehydes or ketones under acidic conditions to give cyclic tetramers.[2,3] Thiophen[4,5] and pyrrole[6] can similarly undergo an acid-catalysed reaction with acetone. We have previously shown that 3-substituted 4,6-dimethoxyindoles, which possess two reactive sites for electrophilic substitution, can react with aryl aldehydes in the presence of phosphoryl chloride to give calix[3]indoles exemplified by structure **1**.[7]



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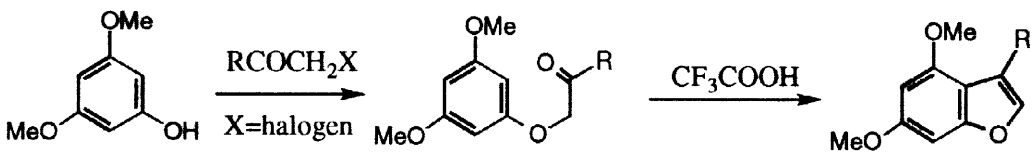
As part of a programme aimed at expanding the range of calixarenes from other activated heterocycles which behave as ambident nucleophiles, we describe the preparation of new benzofurans and their reactions with aldehydes.

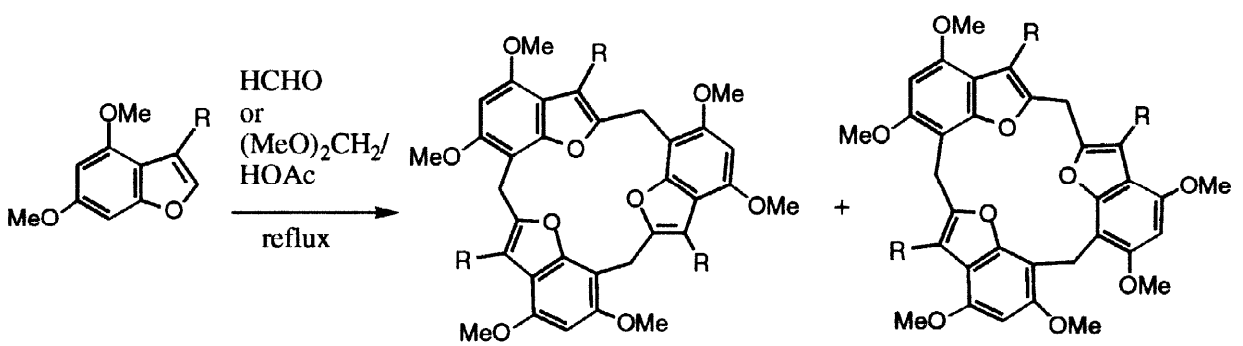
A classical route to prepare 4,6-dimethoxy-3-phenylbenzofuran was reported in 1959.[8] Recently, Chen and coworkers have reported the synthesis of 6-methoxy-3-phenylbenzofurans and analogues from the reaction of α-aryloxyketones with zeolite in xylene under refluxing conditions for 16 h.[9]

We wish to report a variation of the latter method of synthesis for activated benzofurans. 3-Substituted 4,6-dimethoxybenzofurans **3a-c** were prepared in two steps by reactions of 3,5-dimethoxyphenol with appropriate alkylating agents followed by intramolecular cyclisation of the resulting α-aryl(alkyl)oxyketones **2a-c** in the presence of trifluoroacetic acid for 1 h at room temperature.



2a) R=Ph	88%	**3a**) R=Ph	80%
2b) R=4-BrC_6H_4	55%	**3b**) R=4-BrC_6H_4	84%
2c) R=CMe_3	96%	**3c**) R=CMe_3	90%

Previously, we have shown that the treatment of activated 3,5-dimethoxyindoles with formaldehyde does not result in the selective formation of macrocycles but gives uncontrolled reactions.[7] In contrast to the activated indoles, benzofurans **3a** and **3b** react with formaldehyde in refluxing acetic acid to afford both symmetrically linked 2,7:2,7:2,7- and unsymmetrically linked 2,2:7,7:2,7-macrocyclic trimers **4a-5b** in moderate yields.

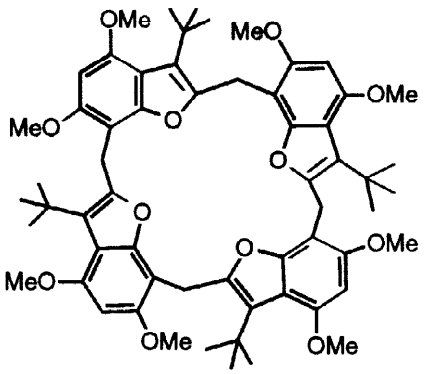


4a) R=Ph	15%	**5a**) R= Ph	21%
4b) R=4-BrC_6H_4	18%	**5b**) R=4-BrC_6H_4	26%
4c) R=CMe_3	33%	**5c**) R=CMe_3	24%

When benzofuran **3c** was treated with a large excess of formaldehyde under the same conditions the only isolated product was the macrocyclic tetramer **6** in 9% yield.

Nevertheless, macrocyclic trimers **4c** and **5c** were obtained when formaldehyde was replaced by dimethoxymethane.

The symmetrically linked isomers show a symmetrical pattern in their ^{1}H NMR spectra whereas the spectra of isomers with the unsymmetrical linkages generally exhibit six signals corresponding to the methoxy groups, three signals designated to the alkyl CH groups and three signals for the aromatic protons at the benzofuran 5-positions.



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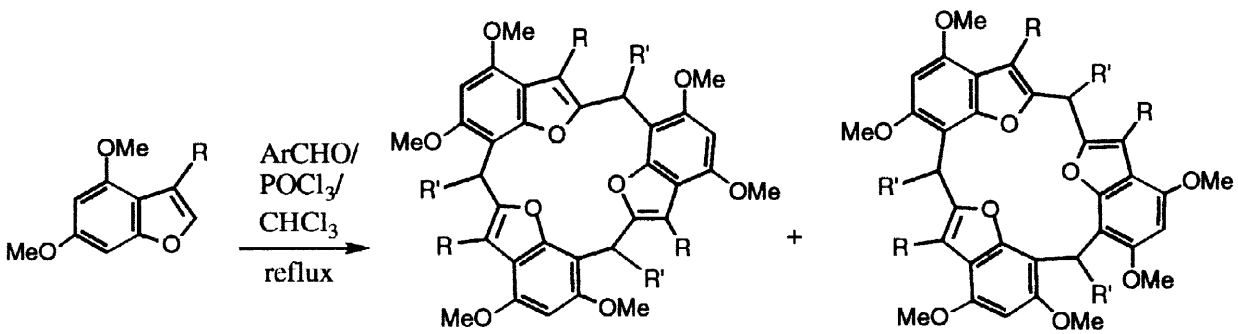
Reactions of the two activated benzofurans **3a, b** with aryl aldehydes in the presence of phosphoryl chloride gave the macrocyclic trimers **7a-8c**. The unsymmetrically linked isomers were the major products.



7a) R=Ph, R'=Ph	0%	**8a**) R=Ph, R'=Ph	62%
7b) R=Ph, R'=4-MeC$_6$H$_4$	7%	**8b**) R=Ph, R'=4-MeC$_6$H$_4$	82%
7c) R=4-BrC$_6$H$_4$, R'=Ph	13%	**8c**) R=4-BrC$_6$H$_4$, R'=Ph	67%
7d) R=CMe$_3$, R'=Ph	47%	**8d**) R=CMe$_3$, R'=Ph	0%

The reason for such product distributions is probably due to the higher reactivity of the 2 position over 7 in the activated benzofurans. However, when 3-*t*-butyl-4,6-dimethoxybenzofuran **3c** was treated with benzaldehyde under the same conditions only a symmetrically linked trimer **7d** was obtained since in this case the position 7 is more reactive because of the steric hindrance at position 2.

The ^{1}H NMR spectra of the symmetrically and unsymmetrically orientated macrocycles were distinctively different. The unsymmetrically linked isomers generally show a signal

designated to one methoxy group well apart (about 0.4 ppm) from the other signals arising from the rest of the methoxy group protons. Furthermore, the signals corresponding to two of the three alkyl CH groups are shifted upfield by about 1 ppm with respect to those in the symmetrically linked isomers. For example, in the ^{1}H NMR spectrum of **8b** one methoxy signal appears at δ 3.25 ppm and the other methoxy signals appear within a region of δ 3.66-3.75 ppm. The alkyl CH groups resonate at δ 5.39, 5.42 and 6.21 ppm in this spectrum. By comparison, the methoxy groups in the spectrum of **7b** give rise to signals from δ 3.46 - δ 3.81 ppm. The signals at δ 5.84, 6.01 and 6.04 are designated to alkyl CH groups. The structure of **7b** was confirmed by X-ray crystallography (Figure 1). The crystal structure showed the product **7b** to exist in a symmetrically linked flattened partial cone conformation.

Compounds **8b** and **8c** were mixtures of two undetermined conformational isomers in a ratio of almost 1:1 and the latter could be separated by flash chromatography. These conformers relate to the axial or equatorial nature of methine aryl groups, which cannot be interchanged by simple rotation processes.

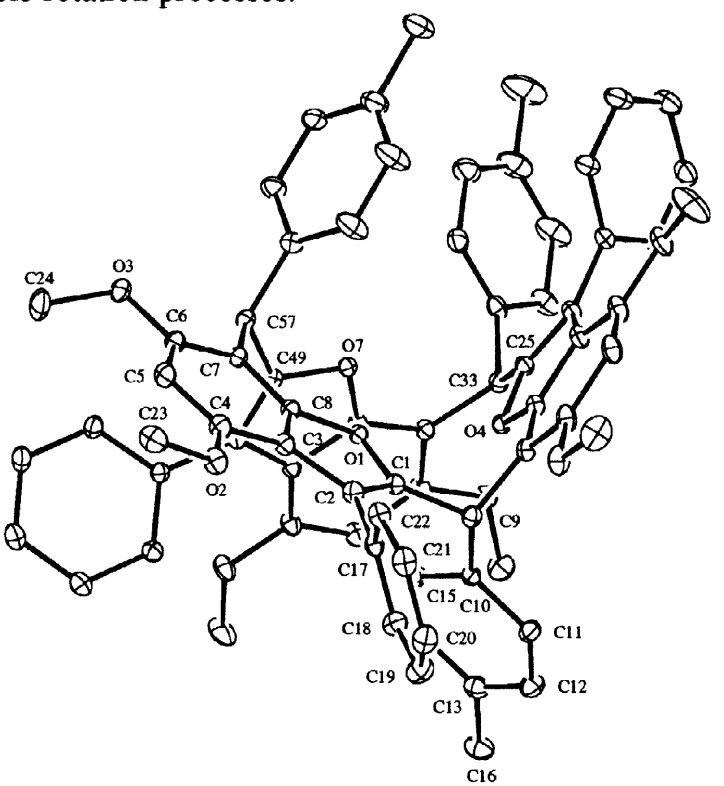


Figure 1. X-ray crystal structure of compound **7b**.

Crystallography.

Crystal data of ***7b***. $C_{72}H_{60}O_9$, M 1069.3, triclinic, space group PI, a 14.986(5), b 15.249(5), c 16.145(5)Å, α 109.54(2), β 97.53(2), γ 119.29(1)°, V 2831(2)Å^3, D_c 1.25 g cm^{-3}, Z 2, μ_{Cu} 6.17 cm^{-1}. Crystal size 0.12 by 0.13 by 0.14 mm, $2\theta_{max}$ 100°, min. and max.transmission factors 0.92 and 0.94. The number of reflexions was 3997 considered observed out of 5798 unique data. Final residuals R, R_w were 0.072, 0.099 for the observed data.

Structure Determination. Reflexion data were measured with an Enraf-Nonius CAD-4 diffractometer in θ/2θ scan mode using graphite monochromatized copper radiation (λ 1.54184Å). Data were corrected for absorption using the analytical method of de Meulenaer and Tompa[10]. Reflexions with $I > 3\sigma(I)$ were considered observed. The structure was determined by direct phasing and Fourier methods.

For refinement, the structure was paramaterized as nine planar groups of three types, benzfuran, phenyl and toluene, and the remaining atoms were included as independent entities. For each group the orientation and position were varied, and within each type planarity was maintained by keeping one coordinate at zero while allowing the other two to refine, with mm2 symmetry being maintained for the phenyl and toluene groups. Thermal motion was described using TLX rigid body temperature parameters, one for the macrocycle nucleus and one for each ring. Hydrogen atoms were included in calculated positions each cycle, and their thermal motions were included in the appropriate group.

Reflexion 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.[11] Structure solution was by SIR92[12] and refinement used RAELS.[13] ORTEP-II[14] running on a Power Macintosh was used for the structural diagram, and a DEC Alpha-AXP workstation was used for calculations.

Experimental

General: Melting points are uncorrected. Microanalyses were performed by Ms Reet Bergman of the Australian National University and Mrs Berta Litvak at the University of New South Wales. ^1H and ^{13}C NMR spectra were obtained in deuterated chloroform on a Bruker CXP 300 (300 MH) spectrometer. Infrared spectra were recorded on an ATI Mattson Genesis Series FTIR spectrometer using KBr discs. The e.i. mass spectra were recorded on a VG Quatro mass spectrometer at 70 eV ionizing potential with an ion source temperature of 210°C. MALDI spectra were obtained on a DESTR VOYAGER. Flash chromatography was carried out using Merck silica gel 230-400 mesh Kieselgel 60, whilst analytical thin-layer chromatography was performed on 0.2 mm plates precoated with silica gel 60 F_{254}.

2-(3',5'-Dimethoxyphenoxy)acetophenone (2a)

A mixture of 3,5-dimethoxyphenol (2.5 g, 16.22 mmol), 2-bromoacetophenone (3.23 g, 16.22 mmol) and potassium bicarbonate (1.62 g, 16.23 mmol) in acetone (40 ml) was refluxed overnight. The solvent was evaporated and the crude residue extracted with dichloromethane (40 ml). The extract was washed with water (2 x 10 ml) and evaporated to give a pale yellow oil which was chromatographed (ethyl acetate:light petroleum, 20:80 and then 25:75) to give *2-(3',5'-dimethoxyphenoxy)acetophenone* (**2a**) (3.9 g, 88%) as colourless crystals, m.p. 91-93°C (from ethyl acetate/light petroleum). (Found: C, 70.5; H, 6.0. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%). ^1H NMR spectrum: δ 3.76 (6H, s, 2 x OMe); 5.23

(2H, s, OCH_2); 6.11-8.00 (8H, m, aryl). ^{13}C NMR spectrum: δ 55.3 (2 x OMe); 70.7 (CH_2); 93.8, 128.1, 128.8 (aryl CH); 133.8, 134.6, 159.9, 161.6 (aryl C); 194.1 (CO). Mass spectrum m/z 272 (M, 10%), 167 (8), 152 (5), 137 (6), 122 (9), 105 (100), 77 (100). IR (KBr) υ_{max} 1714, 1650, 1120 cm^{-1}.

2-(3',5'-Dimethoxyphenoxy)-4'-bromoacetophenone (2b)

A mixture of 3,5-dimethoxyphenol (2.0 g, 12.98 mmol), 2,4'-dibromoacetophenone (3.61, 12.98 mmol) and potassium bicarbonate (1.30 g, 12.98 mmol) in acetone (40 ml) was refluxed overnight. The solvent was evaporated and the crude residue extracted with dichloromethane (40 ml). The extract was washed with water (2 x 10 ml) and evaporated to give a pale yellow oil which was chromatographed (ethyl acetate:light petroleum, 20:80) to give *2-(3',5'-dimethoxyphenoxy)-4'-bromoacetophenone* (**2b**) (2.5 g, 55%) as colourless crystals, m.p. 106-108°C (from ethyl acetate/light petroleum). (Found: C, 54.8; H, 4.3. $C_{16}H_{15}BrO_4$ requires C, 54.9; H, 4.3%). ^1H NMR spectrum: δ 3.75 (6H, s, 2 x OMe); 5.14 (2H, s, OCH_2); 6.11 (3H, s, aryl); 7.63 (2H, d, J 7.6 Hz, aryl); 7.85 (2H, d, J 7.6 Hz, aryl). ^{13}C NMR spectrum: δ 55.4 (2 x OMe), 70.8 (OCH_2); 93.8, 93.9, 129.7, 132.1 (aryl CH); 129.1, 133.3, 159.7, 161.6 (aryl C); 193.6 (CO). Mass spectrum m/z 352 (M ^{81}Br, 35%), 350 (M ^{79}Br, 35%), 185 (100). IR (KBr) υ_{max} 2945, 2875, 1704, 1600, 1475, 1400, 1150 cm^{-1}.

1-(3',5'-Dimethoxyphenoxy)pinacolone (2c)

To a stirred solution of 3,5-dimethoxyphenyl (2.0g, 12.99 mmol) in dry methyl ethyl ketone (30 ml) was added 1-chloropinacolone (2.15 ml, 95%, 16.40 mmol), potassium hydrogen carbonate (1.30 g, 12.99 mmol) and sodium iodide (5.0 g, 33.33 mmol). The mixture was refluxed overnight. The solvent was evaporated, water was then added and the solution extracted with dichloromethane. The extract was dried, evaporated and chromatographed (ethyl acetate/light petroleum, 5:95 and then 15:85) to give *1-(3',5' dimethoxyphenoxy)pinaclone* (**2c**) (3.14g, 96%) as colourless crystals, m.p. 66-68°C (from ethyl acetate/light petroleum). (Found: C, 66.5; H, 8.3. $C_{14}H_{20}O_4$ requires C, 66.7, H, 8.0%). ^1H NMR spectrum: δ 1.24 (9H, s, CMe_3); 3.75 (6H, s, 2 x OMe); 4.81 (2H, s, CH_2); 6.06-6.11 (3H, m, aryl). ^{13}C NMR spectrum: δ 26.2 ($C\underline{Me}_3$); 43.1 ($\underline{C}Me_3$); 55.2 (2 x OMe); 68.7 (OCH_2); 93.6 (aryl CH); 159.8, 161.4 (aryl C); 209.0 (CO). Mass spectrum m/z 252 (M, 40%). IR (KBr) υ_{max} 2948, 1712, 1606, 1460, 1200, 1140 cm^{-1}.

4,6-Dimethoxy-3-phenylbenzofuran (3a)

A solution of ketone **2a** (2.99 g, 10.99 mmol) in trifluoroacetic acid was stirred for 1 h and then added to an ice-ethanol cooled solution of sodium hydroxide (0.5 g) in water (70 ml). The resulting solution was extracted with dichloromethane (3 x 30 ml). The combined extracts were washed, evaporated and the remaining residue chromatographed (ethyl acetate:light petroleum, 20:80) to give *4,6-dimethoxy-3-phenylbenzofuran* (**3a**) (2.24 g, 80%) as colourless crystals, m.p. 89-91°C (from ethanol) (lit.[8] 89-90°C). ^1H NMR spectrum: δ 3.81, 3.87 (6H, 2s, OMe); 6.37 (1H, d, J 2.0 Hz, H5); 6.69 (1H, d, J 2.0 Hz, H7);

7.33-7.64 (6H, m, aryl). ^{13}C NMR spectrum: δ 55.0, 55.3 (OMe); 88.1, 94.4 (C5, C7); 126.8, 127.7, 129.1 (aryl CH); 139.7 (C2); 109.6, 122.6, 132.2, 154.5, 157.7, 159.0 (aryl C). Mass spectrum m/z 254 (M, 100%), 239 (70), 211 (10), 139 (15). IR (KBr) υ_{max} 3001, 2938, 1611, 1500, 1125 cm^{-1}.

3-(4'-Bromophenyl)-4,6-dimethoxybenzofuran (3b)

Similarly as described for **3a**, ketone **2b** (1.0 g, 2.85 mmol) was treated with trifluoroacetic acid to give *3-(4'-bromophenyl)-4,6-dimethoxybenzofuran* (**3b**) (0.8 g, 84%) as colourless crystals, m.p. 117-118°C (from ethyl acetate/light petroleum). (Found: C, 57.6; H, 3.8. $C_{16}H_{13}BrO_3$ requires C, 57.8; H, 3.9%). ^1H NMR spectrum: δ 3.81, 3.87 (6H, 2s, OMe), 6.36 (1H, d, J 2.0 Hz, H7), 6.68 (1H, d, J 2.0 Hz, H5); 7.47-7.54, (5H, m, aryl). ^{13}C NMR spectrum: δ 55.4, 55.7 (OMe); 88.4, 94.7 (C5, C7); 103.8, 131.0, 139.8 (aryl CH); 109.5, 121.1, 121.8, 131.2, 154.5, 157.9, 159.3 (arylC). Mass spectrum m/z 334 (M ^{81}Br, 100%), 332 (M ^{79}Br, 100%). IR (KBr) υ_{max} 2949, 1632, 1600, 1210, 1160 cm^{-1}.

3-*t*-Butyl-4,6-dimethoxybenzofuran (3c)

Similarly as described for **3a**, ketone **2c** (2.0 g, 7.94 mmol) was treated with trifluoroacetic acid to give *3-t-butyl-4,6-dimethoxybenzofuran* (**3c**) (1.67 g, 90%) as colourless crystals, m.p. 87-89°C (from ethyl acetate/light petroleum). (Found: C, 71.7; H, 7.8. $C_{14}H_{18}O_3$ requires C, 71.8; H, 7.7%). ^1H NMR spectrum: δ 1.41 (9H, s, CMe_3); 3.84, 3.92 (6H, 2s, OMe); 6.34 (1H, d, J 2.0 Hz, H7); 6.61 (1H, d, J 2.0 Hz, H5); 7.17 (1H, s, H2). ^{13}C NMR spectrum: 30.2 ($C\underline{Me}_3$); 30.6 ($\underline{C}Me_3$); 54.9, 55.5 (OMe); 88.3, 94.0 (C5, C7); 137.4 (C2); 110.7, 131.1, 153.7, 158.4, 158.7 (aryl C). Mass spectrum m/z 234 (M, 70%), 219 (100). IR (KBr) υ_{max} 2960, 1625, 1500, 1360, 1160, 1105 cm^{-1}.

Reaction of 4,6-dimethoxy-3-phenylbenzofuran (3a) with formaldehyde

A stirred solution of **3a** (200 mg, 0.788 mmol) and an excess of formaldehyde (38% in aqueous solution) in acetic acid (5 ml) was refluxed for 4 h. The resulting mixture was then cooled at room temperature and then filtered. The precipitate was chromatographed (ethyl acetate:light petroleum, 10:90) to give two fractions. The first fraction contained *6,8,14,16,22,24-hexamethoxy-4,12,20-triphenyl-26,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene* (**4a**) (30 mg, 15%) as colourless crystals, m.p. 278-281°C (from ethyl acetate/light petroleum). (Found: C, 74.4; H, 5.5. $C_{51}H_{42}O_9.H_2O$ requires C, 75.0; H, 5.4). ^1H NMR spectrum: δ 3.64, 3.68 (18H, 2s, 6 x OMe); 4.15 (6H, s, 3 x CH_2); 6.25 (3H, s, 3 x benzofuran H5); 7.28-7.45 (15H, m, aryl). ^{13}C NMR spectrum: δ 21.4 (CH_2); 55.7, 56.5 (OMe); 91.1 (benzofuran C5); 94.2, 94.4, 99.6, 103.1, 112.3, 151.6, 152.3, 154.3 (aryl C). m/z 799 (M+1). IR (KBr) υ_{max} 2934, 1621, 1520, 1350, 1170, 1120. The second fraction was *6,8,14,16,20,22-hexamethoxy-4,12,24-triphenyl-25,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{23,26}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene* (**5a**) (45 mg, 21%) as colourless crystals, m.p. 185-187°C (from ethyl

acetate/light petroleum). (Found: C, 74.8; H, 5.2. $C_{51}H_{42}O_9.H_2O$ requires C, 75.0; H, 5.4). ^1H NMR spectrum: δ 3.69, 3.72, 3.77, 3.78 (18H, 4s, 6 x OMe); 3.97, 4.19, 4.32 (6H, 3s, CH_2); 6.32, 6.36, 6.37 (3H, 3s, benzofuran H5); 7.20-7.52 (15H, m, aryl). ^{13}C NMR spectrum: δ 17.5, 22.5, 24.4 (CH_2); 55.5, 55.6, 55.7, 56.2, 57.4, 57.9 (OMe); 91.0, 92.1, 92.8 (benzofuran C5); 126.2, 126.5, 127.3, 127.6, 130.3, 130.4, 130.6 (aryl CH); 103.1, 106.7, 107.4, 111.6, 111.7, 117.1, 117.2, 132.8, 133.0, 134.3, 148.0, 148.2, 151.2, 151.8, 151.9, 152.4, 154.4, 155.0, 155.1, 155.4, 155.5 (aryl C). Mass spectrum m/z 799 (M+1). IR (KBr) υ_{max} 2930, 1625, 1500, 1330, 1210, 1100 cm^{-1}.

Reaction of 3-(4'-bromophenyl)-4,6-dimethoxybenzofuran (3b) with formaldehyde

A stirred solution of **3b** (300 mg, 0.90 mmol) and an excess of formaldehyde (38% aqueous solution) in acetic acid (8 ml) was refluxed for 4 h. The mixture was then cooled to room temperature and the resulting precipitate was filtered and chromatographed to give two fractions. The first fraction was *4,12,20-tri(4'-bromophenyl)-6,8,14,16,22,24-hexamethoxy-26,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene* (**4b**) (55 mg, 18%) as colourless crystals after evaporation, m.p. 392-394°C (from ethyl acetate/light petroleum). (Found: C, 56.2; H, 3.9. $C_{51}H_{39}Br_3O_9.3H_2O$ requires C, 56.3; H, 4.2%). ^1H NMR spectrum: δ 3.67, 3.70 (18H, 2s, 6 x OMe); 4.10 (6H, s, 3 x CH_2); 6.24 (3H, s, 3 x benzofuran H5); 7.30 (6H, d, J 8.2 Hz, aryl); 7.47 (6H, d, J 8.2 Hz, aryl). ^{13}C NMR spectrum: δ 21.3 (CH_2); 55.5, 56.4 (OMe); 90.6 (benzofuran C5); 130.4, 132.7 (aryl CH); 102.6, 111.7, 115.0, 120.3, 132.7, 151.7, 152.3, 154.4, 154.5 (aryl C). Mass spectrum m/z (MALDI) 1033 (M+1). IR (KBr) υ_{max} 2930, 1619, 1505, 1490, 1150, 1095 cm^{-1}. The second fraction was *4,12,24-tri(4'-bromophenyl)-6,8,14,16,20,22-hexamethoxy-25,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{23,26}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene* (**5b**) (82 mg, 26%) as colourless crystals, m.p. 213-215°C (from ethyl acetate/light petroleum). (Found: C, 58.8; H, 3.9. $C_{51}H_{39}Br_3O_9$ requires C, 59.1; H, 3.8%). ^1H NMR spectrum: δ 3.69, 3.71, 3.73, 3.75, 3.87, (18H, 5s, 6 x OMe); 3.84, 4.13, 4.28 (6H, 3s, alkyl CH_2); 6.31, 6.33, 6.35 (3H, 3s, bezofuran H5); 7.03-7.49 (12H, m, aryl). ^{13}C NMR spectrum: δ 17.4, 22.4, 24.1 (alkyl CH_2); 55.4, 55.5, 56.2, 57.3, 57.8 (OMe); 90.7, 91.8, 92.5 (benzofuran C5); 130.5, 130.7, 131.8, 132.1, (aryl CH); 102.7, 106.4, 107.2, 111.1, 116.1, 116.3, 120.3, 120.8, 120.9, 131.6, 133.2, 147.7, 148.1, 151.2, 151.6, 151.8, 152.3, 154.8, 155.2, 155.4, 155.5, 155.7 (aryl C). Mass spectrum m/z (MALDI) 1033 (M+1). IR (KBr) υ_{max} 2949, 1621, 1520, 1200, 1110 cm^{-1}.

Reaction of 3-*t*-butyl-4,6-dimethoxybenzofuran (3c) with dimethoxymethane

A stirred solution of **3c** (200 mg, 0.855 mmol) and an excess of dimethoxymethane in acetic acid (8 ml) was refluxed for 4 h. The resulting solution was evaporated and the remaining crude residue was chromatographed (ethyl acetate:light petroleum, 15:85) to give two fractions. The first fraction contained *4,12,20-tri-t-butyl-6,8,14,16,22,24-hexamethoxy-26,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,*

11,13(27),14,16,19,21(25),22-dodecaene (**4c**) (70 mg, 33%) as colourless crystals, m.p. 273-275°C (from ethyl acetate/light petroleum). (Found: C, 72.9; H, 8.1. $C_{45}H_{54}O_9$ requires C, 73.2; H, 7.4%). ^{1}H NMR spectrum: δ 1.42 (27H, s, 3 x CMe_3) 3.83, 3.90 (18H, 2s, 6 x OMe); 4.20 (6H, s, 3 x CH_2); 6.29 (3H, s, 3 x benzofuran H5). ^{13}C NMR spectrum: δ 23.5 (CH_2); 31.3 ($C\underline{Me}_3$); 31.7 ($\underline{C}Me_3$); 54.9, 56.5 (OMe); 90.2 (benzofuran C5); 103.7, 113.2, 122.0, 148.1, 151.2, 153.8, 154.9 (aryl C). Mass spectrum m/z (MALDI) 738 (M, 20%). IR (KBr) υ_{max} 2950, 1621, 1505, 1210, 1150, 1120 cm^{-1}. The second fraction was *4,12,24-tri-t-butyl-6,8,14,16,20,22-hexamethoxy-25,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{23,26}]triaconta-1(24),3,5(29),6,8, 11,13(27),14,16,19,21,23(26)-dodecaene* (**5c**) (50 mg, 24%) as colourless crystals, m.p. 174-177°C (from ethyl acetate/light petroleum). (Found: C, 71.2, H, 7.4. $C_{45}H_{54}O_9.H_2O$ requires C 71.4; H, 7.5%). ^{1}H NMR spectrum: δ 1.54 (27H, s, 3 x CMe_3); 3.58, 3.82, 3.88 (18H, 3s, 6 x OMe); 3.99, 4.21, 4.66 (6H, 3s, CH_2); 6.26, 6.27, 6.30 (3H, 3s, benzofuran H5). ^{13}C NMR spectrum: δ 16.8, 22.8, 29.7 (CH_2); 31.5, 31.9, 32.0 ($C\underline{Me}_3$); 54.8, 54.9, 55.0, 55.4, 57.4, 57.6 (OMe); 89.8, 90.9, 92.4 (benzofuran C5); 103.0, 106.2, 106.9, 109.4, 109.8, 110.2, 112.1, 112.2, 113.1, 116.6, 120.1, 122.3, 123.5, 123.6, 145.2, 148.2, 150.6, 150.7, 151.3, 154.7, 155.0 (aryl C). Mass spectrum m/z (MALDI) 761 (M+23, 40%). IR (KBr) υ_{max} 2931, 1609, 1510, 1220, 1110 cm^{-1}.

Reaction of 3-*t*-butyl-4,6-dimethoxybenzofuran (3c) with formaldehyde

A stirred solution of **3c** (200 mg, 0.85 mmol) and an excess of formaldehyde (38% aqueous solution) in acetic acid (6 ml) was refluxed for 4h. The mixture was then cooled to room temperature and the resulting precipitate was filtered and chromatographed to give *4,12,20,28-tetra-t-butyl-6,8,14,16,22,24,30,32-octamethoxy-33,35,37,39-tetraoxanonacyclo[25.5.2.2^{3,9}.2^{11,17}.2^{19,25}.0^{5,34}.0^{13,36}.0^{21,38}.0^{29,40}]tetraconta-1(40),3,5,7,9(34),11,13,15,17(36),19,21,23,25(38),27,29,31-hexadecaene* (**6**) as a colourless solid (19 mg, 9%), m.p. 201-203°C (from ethyl acetate/light petroleum). (Found: C, 72.9; H, 7.6. $C_{60}H_{72}O_{12}$ requires C, 73.2; H, 7.4%). ^{1}H NMR spectrum: δ 1.30, 1.47, 1.53, 1.55 (36H, 4s, CMe_3); 3.59-4.10 (8H, m, CH_2); 3.60, 3.69, 3.78, 3.85, 3.89, 3.90, 3.99 (24H, 7s, 8 x OMe); 6.16, 6.19, 6.22, 6.38 (4H, 4s, benzofuran H5). ^{13}C NMR spectrum: δ 16.9, 22.6, 22.9, 29.9 (CH_2); 31.5, 31.6, 31.8, 32.0 ($C\underline{Me}_3$); 54.8, 55.9, 56.2, 57.5 (OMe); 90.0, 90.1, 91.0, 91.7 (aryl CH); 103.6, 104.4, 105.9, 106.6, 106.8, 112.2, 112.3, 112.9, 121.5, 121.9, 123.2, 145.7, 146.6, 148.3, 148.6, 150.5, 150.8, 151.2, 153.9, 154.2, 154.7, 154.9, 155.0, 155.4 (aryl C). Mass spectrum m/z (MALDI) 984 (M+1). IR (KBr) υ_{max} 2950, 1622, 1505, 1210, 1160, 1130 cm^{-1}.

Reaction of 4,6-dimethoxy-3-phenylbenzofuran (3a) with benzaldehyde

To a stirred solution of **3a** (120 mg, 0.472 mmol) and benzaldehyde (0.05 ml, 0.492 mmol) in chloroform (5 ml) was added phosphoryl chloride (0.1 ml, 1.073 mmol). The solution was refluxed for 4 h, cooled to room temperature, washed with sodium hydroxide solution (2%), dried and evaporated. The crude residue was chromatographed (ethyl acetate:light petroleum, 15:85) to give *6,8,14,16,20,22-hexamethoxy-2,4,10,12,18,24-*

hexaphenyl-25,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{23,26}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene (**8a**) (100 mg, 62%) as a colourless solid, m.p. 310-312°C. (Found: C, 80.3; H, 5.8. $C_{69}H_{54}O_9$ requires C, 80.7; H, 5.3%). ^{1}H NMR spectrum: δ 3.33, 3.70, 3.73, 3.74, 3.75 (18H, 5s, 6 x OMe); 5.50, 5.58, 6.24, 6.28, 6.41, 6.46 (6H, 6s, 3 x benzofuran H5, 3 x alkyl CH); 6.62-7.35 (30H, m, aryl). ^{13}C NMR spectrum: δ 38.1, 40.0, 41.0 (alkyl CH); 54.9, 55.4, 55.5, 56.7, 57.6, 58.0 (OMe); 91.9, 92.6, 92.7 (benzofuran C5); 125.2, 125.9, 126.0, 126.5, 126.7, 126.9, 127.1, 127.2, 127.4, 127.6, 127.8, 127.9, 128.3, 128.8, 129.0, 130.1, 130.2, 130.5 (aryl CH); 108.4, 110.0, 110.7, 111.7, 111.9, 113.4, 116.1, 117.1, 117.3, 131.1, 132.5, 132.7, 134.2, 139.2, 142.3, 143.5, 150.1, 150.2, 152.1, 152.4, 152.7, 154.4, 154.8, 155.1, 155.2, 155.3, 155.6 (aryl C). Mass spectrum m/z (MALDI) 1027 (M+1). IR (KBr) υ_{max} 2948, 1603, 1505, 1330, 1200, 1140, 1100 cm^{-1}.

Reaction of 4,6-dimethoxy-3-phenylbenzofuran (3a) with *m*-tolualdehyde

A stirred solution of **3a** (200 mg, 0.787 mmol), *m*-tolualdehyde (0.09 ml, 0.787 mmol) and phosphoryl chloride (0.09 ml, 0.966 mmol) was refluxed in chloroform (5 ml) for 4h. The resulting solution was cooled to room temperature, washed with sodium hydroxide solution (2%) and evaporated. The crude residue was chromatographed (ethyl acetate:light petroleum, 25:75) to give two fractions. The first fraction was *2,10,18-tri(4'-methylphenyl)-6,8,14,16,22,24-hexamethoxy-4,12,20-triphenyl-26,28,30-trioxaheptacyclo [17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene* (**7b**) (20 mg, 7%) as colourless crystals, m.p. 190-192°C (from ethyl acetate/light petroleum). (Found: C, 80.5; H, 6.0. $C_{72}H_{60}O_9$ requires C, 80.9; H, 5.7%). ^{1}H NMR spectrum: δ 1.97, 2.25, 2.37 (9H, 3s, Me); 3.46, 3.57, 3.66, 3.68, 3.71, 3.81 (18H, 6s, OMe); 5.84, 6.01, 6.04 (3H, 3s, alkyl CH); 6.15-7.44 (27H, m, aryl). ^{13}C NMR spectrum: δ 20.8, 21.1, 21.3 (Me); 37.3, 39.2, 39.6 (alkyl CH); 55.6, 55.7, 55.8, 56.4, 57.1, 57.8 (OMe); 91.1, 91.4, 92.4 (benzofuran C5); 125.2, 125.8, 126.0, 126.2, 126.4, 127.2, 127.5, 127.8, 128.1, 128.8, 128.9, 129.7, 130.1, 130.3, 130.5 (aryl CH); 107.1, 107.3, 108.4, 110.9, 113.9, 114.2, 114.8, 117.3, 127.1, 128.2, 133.5, 133.6, 133.7, 133.8, 133.9, 134.2, 135.3, 137.2, 137.8, 138.2, 152.1, 152.4, 152.7, 152.9, 153.0, 153.2, 153.4, 153.8, 154.2, 154.3 (aryl C). Mass spectrum m/z (MALDI) 1070 (M+1). IR (KBr) υ_{max} 2932, 1612, 1505, 1320, 1205, 1130 cm^{-1}. The second fraction was a mixture of two conformational isomers of *2,10,18-tri(4'-methylphenyl)-6,8,14,16,20,22-hexamethoxy-4,12,24-triphenyl-25,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{23,26}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23(26)-dodecaene* (**8b**) (230 mg, 82%) as colourless crystals, m.p. 190-193°C (from ethyl acetate/light petroleum). (Found: C, 80.6; H, 6.0. $C_{72}H_{60}O_9$ requires C, 80.9; H, 5.7%). ^{1}H NMR spectrum: δ 1.98, 2.07, 2.13, 2.18, 2.22, 2.27 (36H, 6s, 12 x Me); 3.25, 3.59, 3.61, 3.63, 3.66, 3.68, 3.69, 3.70, 3.72, 3.74, 3.90 (36H, 11s, 12 x OMe); 5.38, 5.41, 5.60, 6.20, 6.24 (12H, 5s, 6 x alkyl CH, 6 x benzofuran H5); 6.26-7.31 (54H, m, aryl). ^{13}C NMR: δ 14.2, 20.8, 20.9, 21.0, 21.1, 21.2 (Me); 37.2, 38.0, 38.4, 39.1, 39.9, 40.9 (alkyl CH); 54.9, 55.4, 55.5, 55.6, 56.9, 57.7, 58.0, 60.4 (OMe); 91.4, 91.9, 92.0, 92.3, 92.6, 93.2 (benzofuran C5); 126.4, 126.8, 127.3, 127.4, 127.7, 127.9, 128.0, 128.1, 128.8, 129.3,

130.1, 130.2, 130.7 (aryl CH); 109.1, 110.4, 110.6, 111.6, 111.9, 113.7, 116.4, 116.7, 117.0, 125.6, 125.8, 126.0, 126.2, 126.5, 126.9, 127.0, 127.6, 128.2, 128.4, 128.9, 129.0, 129.1, 129.6, 130.0, 130.5, 131.1, 132.5, 132.7, 133.9, 134.1, 134.2, 134.5, 135.5, 136.0, 136.2, 139.9, 140.6, 150.4, 150.6, 150.8, 151.0, 151.6, 152.1, 152.3, 152.4, 152.5, 152.6, 154.4, 154.7, 154.9, 155.2, 155.3, 155.5 (aryl C). Mass spectrum m/z (MALDI) 1070 (M+1). IR (KBr) υ_{max} 2932, 1608, 1505, 1320, 1200, 1120, 1090 cm^{-1}.

Reaction of 3-(4'-bromophenyl)-4,6-dimethoxybenzofuran (3b) with benzaldehyde

To a stirred solution of **3b** (110 mg, 0.33 mmol) and benzaldehyde (0.05 ml, 0.492 mmol) in chloroform (5 ml) was added phosphoryl chloride (0.1 ml, 1.073 mmol). The solution was refluxed for 4h, cooled to room temperature, washed with sodium hydroxide solution (2%), dried and evaporated. The crude residue was chromatographed (ethyl acetate:light petroleum, 15:85) to give three fractions. The first fraction was *4,12,20-tri(4'-bromophenyl)-6,8,14,16,22,24-hexamethoxy-2,10,18-triphenyl-26,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene* (**7c**) (18 mg, 13%) as a colourless solid, m.p. 195-198°C (from ethyl acetate/light petroleum). (Found: C, 65.9; H, 4.3. $C_{69}H_{51}Br_3O_9$ requires C, 65.6; H, 4.1%). ^1H NMR spectrum: δ 3.92, 4.02, 4.08, 4.11, 4.12, 4.21 (18H, 6s, OMe); 6.26, 6.25, 6.39, 6.55, 6.67, 6.70 (6H, 6s, 3 x benzofuran H5, 3 x alkyl CH); 6.94-7.87 (27H, m, aryl). Mass spectrum m/z (MALDI) 1261 (M+1). IR (KBr) υ_{max} 2932, 1609, 1508, 1320, 1200, 1135, 1095 cm^{-1}. The second fraction contained *4,12,24-tri(4'-bromophenyl)-6,8,14,16,20,22-hexamethoxy-2,10,18-triphenyl-25,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{23,26}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21,23 (26)-dodecaene* (**8c**) (50 mg, 37%) as a colourless solid, m.p. 235-237°C (from ethyl acetate/light petroleum). (Found: C, 65.2; H, 4.2. $C_{69}H_{51}Br_3O_9$ requires C, 65.6; H, 4.1%). ^1H NMR: δ 3.31, 3.67, 3.69, 3.72, 3.74 (18H, 5s, 6 x OMe); 5.31, 5.43, 6.22, 6.25, 6.34, 6.42 (6H, 6s, 3 x benzofuran H5, 3 x alkyl CH); 6.52-7.37 (27H, m, aryl H). ^{13}C NMR specttrum: δ 38.0, 39.8, 41.1 (alkyl CH); 54.9, 55.4, 56.7, 57.6, 60.4 (OMe); 91.7, 92.4, 92.5 (benzofuran C5); 127.1, 127.7, 128.1, 128.2, 128.7, 130.1, 131.7, 131.8, 132.2 (aryl CH); 110.0, 110.6, 111.1, 111.2, 112.9, 116.2, 116.4, 120.2, 121.0, 125.3, 125.4, 126.4, 130.1, 131.4, 133.2, 138.5, 142.0, 143.1, 149.8, 150.1, 152.0, 152.7, 154.4, 155.1, 155.2, 155.6, 155.8 (aryl C). Mass spectrum m/z (MALDI) 1261 (M+1). IR (KBr) υ_{max} 2956, 1600, 1050, 1398, 1345, 1200, 1100 cm^{-1}. The third fraction was a conformational isomer of **8c** (40 mg, 30%) as a colourless solid, m.p. 235-237°C (from ethyl acetate/light petroleum). (Found: C, 64.0; H, 4.3. $C_{69}H_{51}Br_3O_9.2H_2O$ requires C, 63.9; H, 4.3%). ^1H NMR spectrum: δ 3.62, 3.66, 3.69, 3.72, 3.73, 3.90 (18H, 6s, OMe); 5.34, 5.54, 6.29, 6.31, 6.42 (6H, 5s, 3 x benzofuran H5, 3 x alkyl CH); 6.44-7.39 (27H, m, aryl). ^{13}C NMR spectrum: δ 37.7, 40.9, 41.3 (alkyl CH); 55.3, 55.6, 57.0, 57.4, 57.7 (OMe); 91.7, 91.9, 92.0 (benzofuran C5); 126.8, 127.3, 128.4, 128.6, 128.8, 129.0, 129.2, 130.5, 130.7, 131.4, 132.6 (aryl CH); 108.5, 110.1, 110.4, 111.6, 111.8, 114.0, 115.4, 115.9, 119.2, 120.8, 120.9, 125.1, 125.4, 131.6, 132.9, 138.0, 139.9, 140.9, 141.4, 150.2, 150.3, 151.4, 152.2, 152.4, 152.6, 153.7, 154.8, 155.0, 155.1, 155.5

(aryl C). **Mass spectrum** m/z (MALDI) 1261 (M+1). IR (KBr) υ_{max} 2932, 1590, 1500, 1220, 1130, 1100 cm^{-1}.

Reaction of 3-*t*-butyl-4,6-dimethoxybenzofuran (3c) with benzaldehyde

To a stirred solution of **3c** (125 mg, 0.534 mmol) and benzaldehyde (0.05 ml, 0.492 mmol) in chloroform (5 ml) was added phosphoryl chloride (0.08 ml). The solution was refluxed for 4h, cooled at room temperature, washed with sodium hydroxide solution (2%), dried and evaporated. The crude residue was chromatographed (ethyl acetate:light petroleum, 15:85) to give *4,12,20-tri-t-butyl-6,8,14,16,22,24-hexamethoxy-2,10,18-triphenyl-26,28,30-trioxaheptacyclo[17.5.2.2^{3,9}.2^{11,17}.0^{5,29}.0^{13,27}.0^{21,25}]triaconta-1(24),3,5(29),6,8,11,13(27),14,16,19,21(25),22-dodecaene* (**7d**) (80 mg, 47%) as a colourless solid, m.p. 287-290°C (from ethyl acetate/light petroleum). (Found: C, 78.1; H, 6.8. $C_{63}H_{66}O_9$ requires C, 78.2; H, 6.9%). ^{1}H NMR spectrum: δ 1.16, 1.18, 1.52 (27H, 3s, CMe_3), 3.74, 3.80, 3.90, 3.92, 3.95, 4.00 (18H, 6s, OMe); 5.91, 6.03, 6.14, 6.24, 6.38, 6.52 (6H, 6s, benzofuran H5, alkyl CH); 6.55-7.12 (15H, m, aryl). ^{13}C NMR spectrum: δ 30.7, 30.9, 31.4 ($C\underline{Me}_3$); 31.6, 32.2, 32.5 ($\underline{C}Me_3$); 39.4, 40.4, 41.6 (alkyl CH); 54.4, 54.8, 55.0, 55.7, 57.2, 57.6 (OMe); 89.4, 90.6, 91.7, (benzofuran C5); 124.4, 125.8, 126.8, 126.9, 127.1, 128.1, 128.2, 128.4, 130.4 (aryl CH); 106.1, 108.3, 112.4, 113.6, 114.4, 115.0, 121.4, 122.1, 127.7, 140.6, 141.7, 145.9, 148.4, 148.6, 148.7, 151.0, 151.2, 151.5, 151.8, 152.9, 153.7, 153.9, 154.2, 154.7 (aryl C). Mass spectrum m/z (MALDI) 967 (M+1). IR (KBr) υ_{max} 2949, 1616, 1340, 1210, 1150, 1105 cm^{-1}.

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