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Acid-catalysed reactions of activated benzofuranylmethanols: formation of calixbenzofurans

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Dedicated to Professor Lutz Tietze on the occasion of his 60th birthday

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Abstract—Regiochemistry of electrophilic substitution of the 3-substituted-4,6-dimethoxybenzofurans is largely controlled by the substituents at C3. The presence of a 3-aryl group results in the preferred formation of 2-substituted benzofuran derivatives whereas a bulky *tert*-butyl 3-substituent leads to a dominance of 7-substituted products. Acid-catalysed reactions of 2-hydroxymethylbenzofurans give mainly unsymmetrically linked calix[3]benzofurans. However, acid treatment of 7-hydroxymethylbenzofurans affords only the symmetrically linked calix[3]benzofurans in high yields. Benzofuranyl glyoxylamides, glyoxylates and ketones can be obtained in high yields and the acid-catalysed reactions of their corresponding alcohol reduction products generally give moderate to high yields of the symmetrically linked calix[3]benzofurans together with a minor amount of a calix[4]benzofuran.

1. Introduction

We have previously shown that calix[3]benzofurans could be obtained from the reactions of activated benzofurans with aldehydes.[1] In general, these trimeric macrocycles are formed predominantly with an unsymmetrical [2,2;7,2;7,7] linkage pattern. We now report that some activated benzofuranylmethanols undergo acid-catalysed cyclo-oligomerisation to give a range of calix[3]- and [4]benzofurans. Similar reactions on analogous indoles have also been reported by our research group.[2]

2. Results and discussion

A series of activated benzofuranylmethanols was thus prepared via regioselective electrophilic substitution reactions. 3-Substituted-4,6-dimethoxybenzofurans were formylated using phosphoryl chloride and *N*,*N*-dimethylformamide, as previously described on related indoles,[3–6] and this was followed by a reduction step to afford hydroxymethylbenzofuran derivatives. Benzofuran ketone derivatives were prepared by a similar method[7,8] using phosphoryl chloride and appropriate *N*,*N*-dimethylamides. 3-Substituted-4,6-dimethoxybenzofurans were also acylated with oxalyl chloride and were subsequently converted to glyoxylic amide and ester derivatives by the previously reported method utilised to prepare analogous indoles.[6] The benzofuranylmethanols were then obtained by a simple reduction process.

The Vilsmeier formylation of the 3-phenylbenzofuran **1a** with *N*,*N*-dimethylformamide and phosphoryl chloride at 0–25°C gave only the 2-carbaldehyde derivative **2a** in 90% yield, since C2 of the activated benzofurans is generally more reactive than C7. When the temperature of the reaction mixture was raised to 50°C, the 7-carbaldehyde isomer **3a** was obtained in 11% yield together with a 76% yield of the 2-carbaldehyde **2a**. However, when the 3-*tert*-butylbenzofuran **1b** was formylated under the same conditions, the major product was the 7-carbaldehyde **3b**, formed in 68% yield together with 31% of the 2-isomer **2b**, because of the steric hindrance effect of the 3-*tert*-butyl group. Reactions of the benzofuran **1a** with *N*,*N*-dimethylarylamides or *N*,*N*-dimethylacetamide in the presence of phosphoryl chloride at 90°C gave similarly only the 2-substituted derivatives **4a–c** in yields of 45–71% (Scheme 1).

We have previously reported that 3-aryl-4,6-dimethoxyindoles undergo reaction with oxalyl chloride to give a mixture of 2- and 7-glyoxyloyl chloride derivatives.[9] In contrast, the reaction of oxalyl chloride with 4,6-dimethoxy-3-phenylbenzofuran **1a** resulted in the formation of only the 2-substituted glyoxyloyl chloride, which reacted readily with amines and methanol to give the corresponding glyoxylic amides **5a–c** and ester **5d** in 82–99% yield (Scheme 2).

Reduction of activated benzofuran aldehydes and ketones to the corresponding benzofuranylmethanols **6**, **7** and **10** was

Keywords: calixarenes; benzofurans; oligomerisation; macrocycles.

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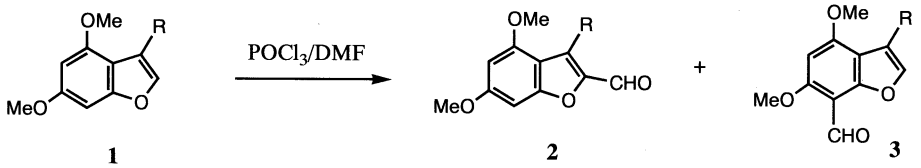
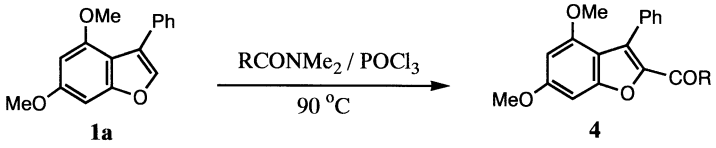
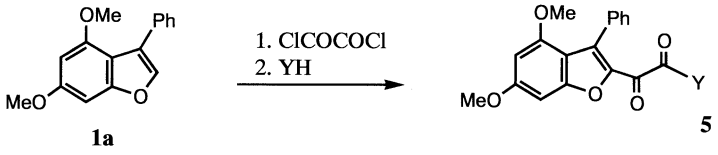


1-3	R	Temp	Yield of 2	Yield of 3
a	Ph	RT	90%	0%
		50 °C	76%	11%
b	CMe_3	RT	31%	68%



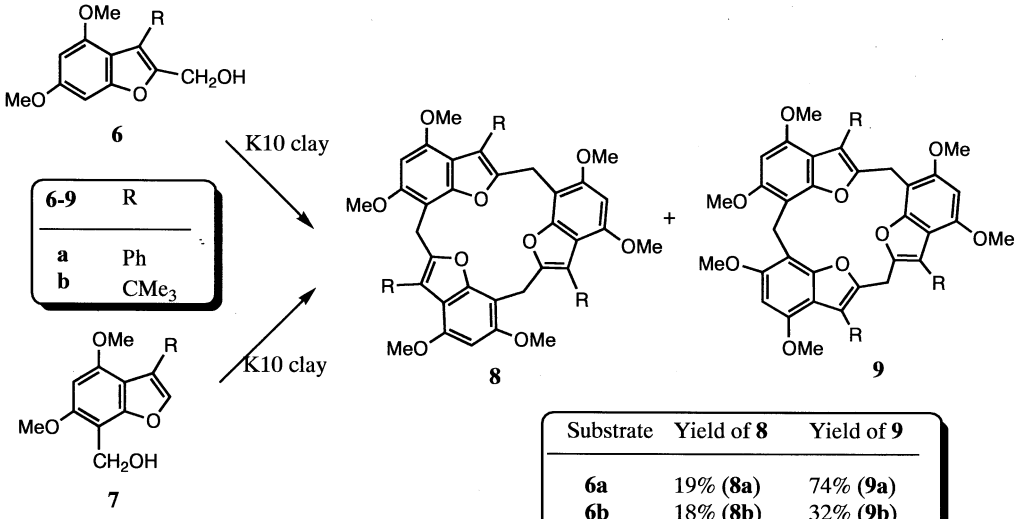
4	R	Yield
a	4-MeC_6H_4	45%
b	4-ClC_6H_4	71%
c	Me	55%

Scheme 1.



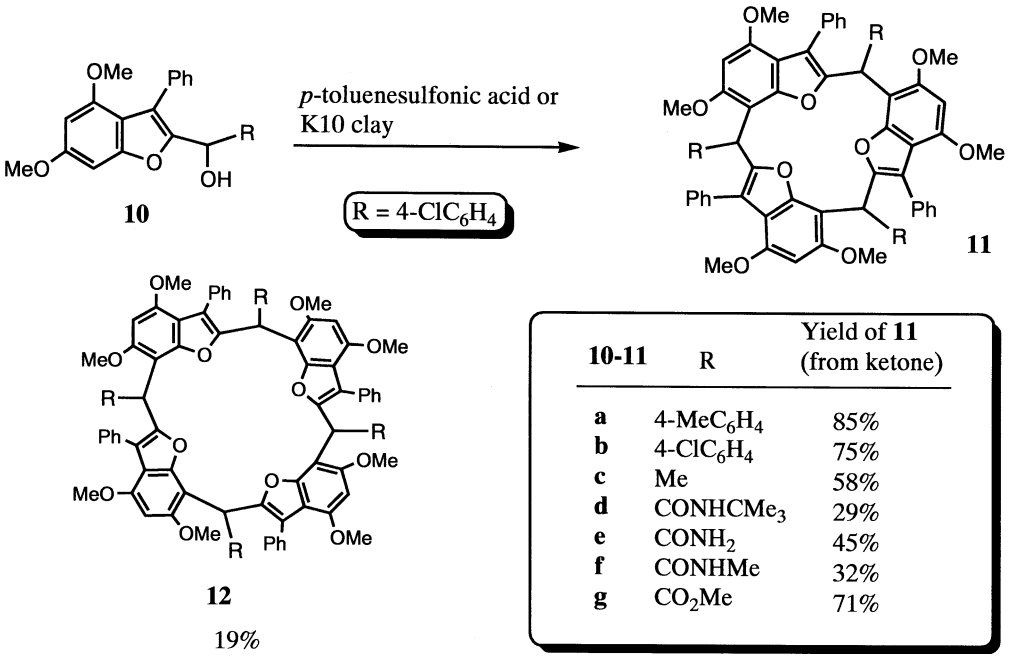
5	Y	Yield
a	$NHCMe_3$	93%
b	NH_2	90%
c	NHMe	82%
d	OMe	99%

Scheme 2.



Substrate	Yield of 8	Yield of 9
6a	19% (8a)	74% (9a)
6b	18% (8b)	32% (9b)
7a	76% (8a)	-
7b	97% (8b)	-

Scheme 3.



Scheme 4.

carried out with sodium borohydride at room temperature or diisobutylaluminium hydride at −76°C. Treatment of 2-hydroxymethylbenzofurans **6a**, **b** with Montmorillonite clay in dichloromethane gave the unsymmetrically linked calix[3]benzofurans **9a**, **b**, respectively, as major products whereas the acid-catalysed reactions of 7-hydroxymethylbenzofurans **7a**, **b** afforded only the symmetrically linked calix[3]benzofurans **8a**, **b** in high yields (Scheme 3).

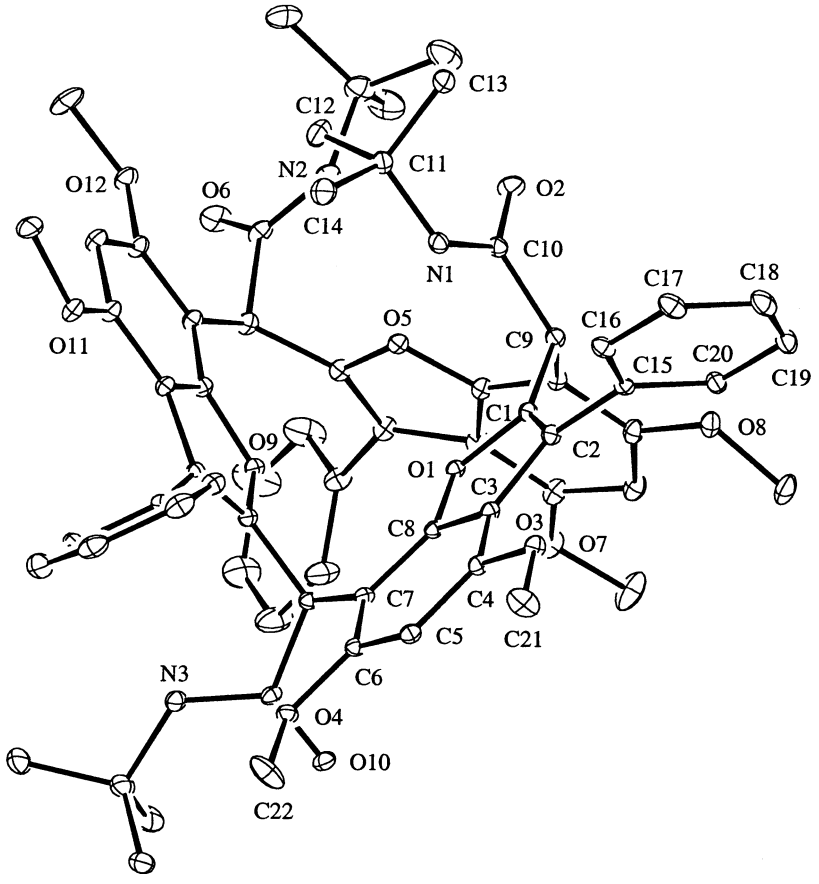


Figure 1. X-Ray crystal structure of compound **11d(i)**.

Molecular mechanics calculations indicate that the symmetrically linked calix[3]benzofuran **8** is less stable than the unsymmetrically linked isomer **9**, consistent with compound **8** being the kinetic product and compound **9** the thermodynamic product. Reactions of the 7-methanols **7** are faster than those of the 2-methanols **6**, because C2 is more nucleophilic than C7. It is interesting that the 3-*t*-butyl group does not impede reaction of the benzylic alcohol at C2.

In contrast to the 2-substituted benzofuran primary alcohols, the acid-catalysed reactions of secondary alcohol derivatives **10a–g** gave only the symmetrically oriented calixbenzofurans **11a–g** in 26–85% yields. Incorporation of the 4-chlorophenyl substituent led to the formation of the calix[4]benzofuran **12** in 19% yield as well as the major component (75%) of calix[3]benzofuran **11b** (Scheme 4). Compound **12** is the first example of a calix[4]hetarene with substitution at the linking carbon atom.

Compound **11a** has previously been prepared by the acid-catalysed reaction of benzofuran **1a** with 4-tolualdehyde, and also characterised by its X-ray crystal structure.[1] Compound **11d** was a mixture of two configurational isomers and these were separated by flash chromatography. The crystal structure of one isomer **11d(i)** (Fig. 1) shows the product to exist in a symmetrically linked flattened partial cone configuration with the three *tert*-butylcarboxamido groups oriented in one equatorial and two axial positions. From the ^{1}H NMR data, it appears that this compound is in equilibrium with a cone conformer in solution. The spectrum shows singlet resonances at δ 1.11, 5.27, 5.60, 6.17 ppm designated to *t*-butyl, alkyl CH, amide NH and benzofuran H5, respectively, and this pattern is consistent with a cone structure.[10] In the ^{1}H NMR spectrum of the flattened partial cone isomers, each of these groups give rise to three singlets and that is consistent with the data obtained for the other isomer **11d(ii)**. A crystal structure of this product could not be obtained, so the precise orientation of the substituted glyoxylic amide groups is unclear.

3. Conclusions

Both 2- and 7-hydroxymethylbenzofurans have been shown to undergo acid-catalysed trimerisation to form calix[3]-benzofurans. The 2-methanols favour formation of the unsymmetrically-oriented structural isomer, while the 7-methanols give only the symmetrically-oriented isomers. This latter isomer appears to be the kinetic product, which would be favoured by the higher nucleophilicity of C2 over C7. However, when the 2-hydroxymethyl group is substituted, so that the alcohol is secondary, the symmetrically-oriented isomer is preferred. Steric effects are probably relevant here, because a symmetrically-oriented calix[4]-benzofuran is isolated as a minor product in one case.

4. Experimental

4.1. 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. ^{1}H 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 ionising 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}. For the structure determination of compound **11d(i)**, 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.[11] Reflections with $I > 3\sigma(I)$ were considered observed. The structure was determined by direct phasing and Fourier methods. Reflection weights used were $1/\sigma^2(F_0)$, with $\sigma(F_0)$ being derived from $\sigma(I_0) = [\sigma^2(I_0) + (0.04I_0)^2]^{1/2}$. The weighted residual is defined as $R_w = (\sum w\Delta^2/\sum wF_0^2)^{1/2}$. Atomic scattering factors and anomalous dispersion parameters were from International Tables for X-ray Crystallography.[12] Structure solution was by SIR92[13] and refinement used RAELS.[14] ORTEP-II[15] running on a Power Macintosh was used for the structural diagram, and a DEC Alpha-AXP workstation was used for calculations.

4.1.1. 4,6-Dimethoxy-3-phenylbenzofuran-2-carbaldehyde (2a). (i) A solution of phosphoryl chloride (0.21 ml, 2.27 mmol) in *N*,*N*-dimethylformamide (3 ml) was allowed to stir for 1 h. 4,6-Dimethoxy-3-phenylbenzofuran[1] **1a** (0.5 g, 1.97 mmol) was then added and the resulting mixture was allowed to continue stirring overnight at room temperature. A solution of sodium hydroxide (10%) was then added and the mixture was extracted with dichloromethane (3×15 ml). The combined extracts were concentrated and the remaining crude residue was chromatographed to give *4,6-dimethoxy-3-phenylbenzofuran-2-carbaldehyde* **2a** (0.50 g, 90%) as colourless crystals, mp 177–179°C (from ethyl acetate/light petroleum). (Found: C, 72.1; H, 4.8. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%). ^{1}H NMR spectrum: δ 3.74, 3.89 (6H, 2s, OMe); 6.32 (1H, d, J=2.0 Hz, H5); 6.69 (1H, d, J=2.0 Hz, H7); 7.45–7.59 (5H, m, aryl); 9.53 (1H, s, CHO). ^{13}C NMR spectrum: δ 55.5, 55.9 (OMe); 87.9, 95.7 (C5, C7); 127.8, 128.8, 130.8 (5×aryl CH); 110.0, 129.6, 135.7, 147.3, 156.7, 158.1, 163.5 (aryl C); 178.7 (CO). Mass spectrum: *m/z* 282 (M, 90%), 267 (10). IR (KBr) ν_{max} 2847, 1669, 1618, 1319, 1239, 1153, 1111 cm^{-1}.

(ii) The above experiment was carried out at 50°C and the crude residue obtained was chromatographed (ethyl acetate/light petroleum, 15:85 and then 30:70) to give two fractions. The first fraction contained aldehyde **2a** (470 mg, 76% from 560 mg of the starting material). The second fraction contained *4,6-dimethoxy-3-phenylbenzofuran-7-carbaldehyde* **3a** (70 mg, 11%) as pale yellow crystals, mp 210–213°C (from ethyl acetate/light petroleum). (Found: C, 71.8; H, 5.0. $C_{17}H_{14}O_4$ requires C, 72.3; H, 5.0%). ^{1}H NMR spectrum: δ 3.91, 4.00 (6H, 2s, OMe); 6.33 (1H, s,

H5); 7.61 (1H, s, H2); 7.36–7.56 (5H, m, aryl); 10.48, s (CHO). ^{13}C NMR spectrum: δ 55.6, 56.6 (OMe); 89.7 (C5); 141.4 (C2); 127.3, 127.9, 129.3 (5×aryl CH); 106.2, 110.8, 122.1, 131.5, 141.4, 160.1, 163.2 (aryl C); 186.2 (CO). Mass spectrum: *m/z* 282 (M, 32%), 236 (5), 182 (40), 139 (100). IR (KBr) ν_{max} 2954, 1674, 1600, 1339, 1229, 1111, 1069 (CO) cm^{-1}.

4.1.2. 3-*t*-Butyl-4,6-dimethoxybenzofuran-2-carbaldehyde (2b) and 3-*t*-butyl-4,6-dimethoxybenzofuran-7-carbaldehyde (3b). As described for benzofuran **1a**, 4,6-dimethoxy-3-*t*-butylbenzofuran[1] **1b** (770 mg, 6.40) was treated with a mixture of phosphoryl chloride (0.6 ml, 6.45 mmol) and *N*,*N*-dimethylformamide (4 ml) to give a crude residue which was chromatographed (ethyl acetate/light petroleum, 30:70) to give two fractions. The first fraction contained *3-t-butyl-4,6-dimethoxybenzofuran-2-carbaldehyde* **2b** (270 mg, 31%) as colourless crystals, mp 111–113°C (from ethyl acetate/light petroleum). (Found: C, 68.5; H, 7.2. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%). ^{1}H NMR spectrum: δ 1.60 (9H, s, CMe_3); 3.84, 3.94 (6H, 2s, OMe); 6.32 (1H, d, *J*=2.0 Hz, H5); 6.64 (1H, d, *J*=2.0 Hz, H7); 10.22 (1H, s, CHO). ^{13}C NMR spectrum: δ 31.6 (CMe_3); 33.9 (CMe_3); 55.1, 55.4 (OMe); 87.6, 95.2 (C5, C7); 111.5, 143.1, 146.9, 155.3, 158.0, 162.2 (aryl C); 180.6 (CO). IR (KBr) ν_{max} 2956, 1651, 1622, 1578, 1205, 1153, 1121 cm^{-1}. Mass spectrum: *m/z* 262 (M, 90%), 247 (100).

The second fraction contained *3-t-butyl-4,6-dimethoxybenzofuran-7-carbaldehyde* **3b** (590 mg, 68%) as colourless crystals, mp 162–164°C (from ethyl acetate/light petroleum). (Found: C, 68.8; H, 7.1. $C_{15}H_{18}O_4$ requires C, 68.7; H, 6.9%). ^{1}H NMR spectrum: δ 1.37 (9H, s, CMe_3); 3.98, 4.05 (6H, 2s, OMe); 6.31 (1H, s, H5); 7.30 (1H, s, H2); 10.44 (1H, s, CHO). ^{13}C NMR spectrum: δ 30.0 (CMe_3); 30.4 (CMe_3); 55.3, 56.4 (OMe); 89.2 (C5); 139.0 (C2); 105.8, 111.6, 130.3, 156.9, 159.0, 162.5 (aryl C); 186.1 (CO). Mass spectrum: *m/z* 262 (M, 60%), 247 (100). IR (KBr) ν_{max} 2948, 1669, 1610, 1385, 1211, 1175, 1118 cm^{-1}.

4.1.3. 4,6-Dimethoxy-2-(4′-methylbenzoyl)-3-phenylbenzofuran (4a). A mixture of *N*,*N*-dimethyl-4-methylbenzamide (1.03 g, 6.32 mmol) and phosphoryl chloride (0.45 ml, 4.83 mmol) was heated at 60°C for 30 min. Benzofuran **1a** (1.0 g, 3.94 mmol) was then added and the resulting mixture was heated at 90°C overnight. A solution of sodium hydroxide (10%) was then added and the solution was extracted with dichloromethane (3×15 ml). The combined extracts were dried, evaporated and chromatographed to give *4,6-dimethoxy-2-(4′-methylbenzoyl)-3-phenylbenzofuran* **4a** (660 mg, 45%) as a yellow gum which solidified on standing, mp 103–105°C (from ethyl acetate/light petroleum). (Found: C, 75.3; H, 5.2. $C_{24}H_{20}O_4.0.5H_2O$ requires C, 75.6; H, 5.5%). ^{1}H NMR spectrum: δ 2.34 (3H, s, *Me*Ph); 3.70, 3.88 (6H, 2s, OMe); 6.32 (1H, d, *J*=2.0 Hz, H5); 6.71 (1H, d, *J*=2.0 Hz, H7); 7.08, 7.69 (4H, 2d, *J*=8.2 Hz; Me*Ph*); 7.07–7.42 (5H, m, aryl). ^{13}C NMR spectrum: δ 21.5 (Me); 55.4, 55.8 (OMe); 87.8, 95.3, (C5, C7); 127.1, 127.5, 128.5, 129.7, 130.7 (9×aryl CH); 111.7, 130.0, 131.7, 135.0, 142.7, 146.5, 156.3, 156.9, 162.1 (aryl C); 184.7 (CO). Mass spectrum: *m/z* 372 (M, 52%), 225 (5), 152 (12), 119 (60), 91 (100). IR (KBr) ν_{max} 2458, 1637, 1506, 1278, 1153, 1111 cm^{-1}.

4.1.4. 2-(4′-Chlorobenzoyl)-4,6-dimethoxy-3-phenylbenzofuran (4b). As described for the preparation of ketone **4a**, benzofuran **1a** (1.0 g, 3.94 mmol) was treated with a mixture of *N*,*N*-dimethyl-4-chlorobenzamide (1.20 g, 6.54 mmol) and phosphoryl chloride (0.45 ml, 4.83 mmol) to give a crude residue which was chromatographed to give two fractions. The first fraction contained the starting material (0.19 g, 19%). The second fraction contained *2-(4′-chlorobenzoyl)-4,6-dimethoxy-3-phenylbenzofuran* **4b** (1.10 g, 71, 88% based on recovered starting material) as yellow crystals, mp 74–76°C (from ethyl acetate/light petroleum). (Found: C, 70.3; H, 4.3. $C_{23}H_{17}ClO_4$ requires C, 70.3; H, 4.4%). ^{1}H NMR spectrum: δ 3.65, 3.85 (6H, 2s, OMe); 6.30 (1H, d, *J*=2.1 Hz, H5); 6.68 (1H, d, *J*=2.1 Hz, H7); 7.20–7.71 (1H, m, aryl). ^{13}C NMR spectrum: δ 55.2, 55.6 (OMe); 87.6, 95.3 (C5, C7); 126.9, 127.6, 127.9, 130.5, 130.7 (9×aryl CH); 111.4, 131.3, 135.8, 138.0, 145.8, 156.2, 156.9, 162.3 (aryl C); 183.2 (CO). Mass spectrum: *m/z* 394 (M ^{37}Cl, 33%), 392 (M ^{35}Cl, 100%), 139 (100). IR (KBr) ν_{max} 2444,1643, 1542, 1506, 1285, 1528, 1111 cm^{-1}.

4.1.5. 2-Acetyl-4,6-dimethoxy-3-phenylbenzofuran (4c). As described for the preparation of ketone **4a**, benzofuran **1a** (250 mg, 0.98 mmol) was reacted with a mixture of *N*,*N*-dimethylacetamide (0.15 ml, 1,57 mmol) and phosphoryl chloride (0.11 ml, 1.18 mmol) to give *2-acetyl-4,6-dimethoxy-3-phenylbenzofuran* **4c** (160 mg, 55%) as pale brown crystals, 198–200°C (from ethyl acetate/light petroleum). (Found: C, 72.8, H, 5.5. $C_{18}H_{16}O_4$ requires C, 73.0; H, 5.5%). ^{1}H NMR spectrum: δ 2.23 (3H, s, Me); 3.61, 3.85 (6H, 2s, OMe); 6.25 (1H, d, *J*=2.1 Hz, H5); 6.66 (1H, d, *J*=2.1 Hz, H7); 7.39–7.46 (5H, m, aryl). ^{13}C NMR spectrum: δ 28.0 (3H, s, Me); 55.3, 55.6 (OMe); 87.6, 95.2 (C5, C7); 127.4, 128.0, 130.0 (5×aryl CH); 112.2, 129.1, 132.0, 146.5, 156.4, 156.5, 162.3 (aryl C); 188.0 (CO). Mass spectrum: *m/z* 296 (M, 100%), 295 (80), 281 (58), 225 (38). IR (KBr) ν_{max} 2457, 1675, 1620, 1557, 1314, 1221, 1157, 1107 cm^{-1}.

4.1.6. *N*-*t*-Butyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)glyoxylamide (5a). To a solution of benzofuran **1a** (1.0 g, 3.94) in dichloromethane (40 ml) was added oxalyl chloride (0.4 ml, 4.53 mmol) and the resulting solution was stirred overnight at 45°C. An excess of *tert*-butylamine was then added and the solution was allowed to continue to stir for a further 1 h. The solvent was then evaporated and the remaining residue was chromatographed (ethyl acetate/light petroleum, 30:70) to give *N-t-butyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)glyoxylamide* **5a** (1.40 g, 93%) as pale yellow crystals, mp 146–147°C (from ethyl acetate/light petroleum). (Found: C, 69.5; H, 6.4; N, 3.8. $C_{22}H_{23}NO_5$ requires C, 69.3; H, 6.1; N, 3.7%). ^{1}H NMR spectrum: δ 1.30 (9H, s, CMe_3); 3.66, 3.87 (6H, 2s, OMe); 6.27 (1H, d, *J*=2.2 Hz, H5′); 6.74 (1H, d, *J*=2.2 Hz, H7′); 6.58 (1H, s, NH); 7.38–7.44 (5H, m, aryl). ^{13}C NMR spectrum: δ 28.2 (CMe_3); 51.5 (CMe_3); 55.4, 55.8 (OMe); 87.9, 95.6 (C5′, C7′); 127.3, 128.1, 130.1 (5×aryl CH); 112.0, 131.7, 134.6, 144.6, 156.6, 158.1, 161.0 (aryl C); 163.2, 179.2 (CO). Mass spectrum: *m/z* 381 (M, 5%), 281 (100), 254 (100), 225 (100). IR (Nujol) ν_{max} 3254, 1671, 1640, 1451, 1375, 1194 cm^{-1}.

4.1.7. 2-(4′,6′-Dimethoxy-3′-phenylbenzofuran-2′-yl)-glyoxylamide (5b). As described for the preparation of glyoxylamide **5a**, benzofuran **1a** (500 mg, 1.97 mmol) was reacted with oxalyl chloride and then quenched with an excess of ammonia to give *2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)glyoxylamide* **5b** (711 mg, 90%) as pale yellow crystals, mp 186–187°C (from ethyl acetate/light petroleum). (Found: C, 66.3; H, 4.8; N, 4.3. $C_{18}H_{15}NO_5$ requires C, 66.5; H, 4.7; N, 4.3%). ^{1}H NMR spectrum: δ 3.67, 3.88 (6H, 2s, OMe); 5.57 (1H, s, NH); 6.27 (1H, d, *J*=2.0 Hz, H5′) 6.71 (1H, d, *J*=2.0 Hz, H7′); 6.57 (1H, s, NH); 7.38–7.50 (5H, m, aryl). ^{13}C NMR spectrum: δ 55.4, 55.8 (OMe); 87.8, 95.7 (C5′, C7′); 127.2, 128.4, 130.2 (5×aryl CH); 112.0, 131.2, 134.9, 144.2, 156.6, 158.2, 163.5 (aryl C); 164.3, 178.1 (CO). Mass spectrum: *m/z* 325 (M, 6%), 313 (12), 281 (50), 225 (10). IR (KBr) ν_{max} 3449, 3196, 1704, 1648, 1617, 1306, 1534, 1220 cm^{-1}.

4.1.8. *N*-Methyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)glyoxylamide (5c). As described for the preparation of glyoxylamide **5a**, benzofuran **1a** (500 mg, 1.97 mmol) was treated with oxalyl chloride and then quenched with excess of methylamine (20% aqueous solution) to give *N-methyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)glyoxylamide* **5c** (550 mg, 82%) as pale yellow crystals, mp 176–178°C (from ethyl acetate/light petroleum). (Found: C, 67.2; H, 4.9; N, 4.1. $C_{19}H_{17}NO_5$ requires C, 67.3; H, 5.1; N, 4.1%). ^{1}H NMR spectrum: δ 2.76 (3H, d, *J*=5.1 Hz, NMe); 3.68, 3.88 (6H, 2s, OMe); 6.27 (1H, d, *J*=2.0 Hz, H5′); 6.72 (2d, *J*=2.0 Hz, H7′); 6.56 (1H, br s, CONH); 7.39–7.48 (5H, m, aryl). ^{13}C NMR spectrum: δ 25.8 (NMe); 55.3, 55.7 (OMe); 87.8, 95.6 (C5′, C7′); 127.1, 128.3, 130.1 (5×aryl CH); 111.9, 131.2, 134.6, 144.3, 156.6, 158.1, 163.2 (aryl C); 163.3, 179.0 (CO). Mass spectrum: *m/z* 339 (M, 40%), 281 (100), 266 (7), 225 (35). IR (Nujol) ν_{max} 3303, 1670, 1647, 1624, 1458, 1368, 1299 cm^{-1}.

4.1.9. Methyl 2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)glyoxylate (5d). As described for the preparation of glyoxylamide **5a**, benzofuran **1a** (1.0 g, 3.94 mmol) was reacted with oxalyl chloride (0.4 ml, 4.53 mmol) and then quenched with methanol to give *methyl 2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)glyoxylate* **5d** (1.32 g, 99%) as pale yellow crystals, mp 157–158°C. (Found: C, 66.7; H, 4.8. $C_{19}H_{16}O_6$ requires C, 67.1; H, 4.7%). ^{1}H NMR spectrum: δ 3.36 (3H, s, COOMe); 3.67, 3.89 (6H, 2s, ArOMe); 6.28 (1H, d, *J*=2.0 Hz, H5′); 6.68 (1H, d, *J*=2.0 Hz, H7′); 7.48 (5H, m, aryl). ^{13}C NMR spectrum: δ 52.1 (COO*Me*); 55.3, 55.7 (ArO*Me*); 87.6, 95.6 (C5′, C7′); 127.3, 128.6, 130.2 (5×aryl CH); 111.7, 134.8, 143.6, 157.0, 158.1, 163.6 (aryl C); 163.8, 175.6 (CO). Mass spectrum: *m/z* 340 (M, 20), 281 (100), 267 (15), 225 (20). IR (KBr) ν_{max} 3097, 1749, 1662, 1625, 1549, 1505, 1229 cm^{-1}.

4.1.10. 2-Hydroxymethyl-4,6-dimethoxy-3-phenylbenzofuran (6a). To a stirred solution of aldehyde **2a** (140 mg, 0.496 mmol) in methanol (10 ml) was added an excess of sodium borohydride. After 1 h water was added and the solution was concentrated in vacuo and extracted with dichloromethane (3×10 ml). The combined extracts were dried and evaporated to give *2-hydroxymethyl-4,6-dimethoxy-3-phenylbenzofuran* **6a** (139 mg, 99%) as a colourless solid, mp 135–136°C (from ethyl acetate). (Found: C, 71.5; H, 5.9. $C_{17}H_{16}O_4$ requires C, 71.8; H, 5.7%). ^{1}H NMR spectrum: δ 3.72, 3.86 (6H, 2s, OMe); 4.67, (2H, s, C*H*$_2$OH); 6.33 (1H, d, 2.6 Hz, H5′); (1H, d, *J*=2.6 Hz, H7); 7.37–7.52 (5H, m, aryl). ^{13}C NMR spectrum: δ 55.4, 55.8 (OMe); 56.2 (CH_2OH); 88.2, 94.6 (C5, C7); 127.2, 127.7, 130.4 (5×aryl CH); 111.1, 119.9, 132.2, 150.0, 154.9, 156.4, 159.4 (aryl C). Mass spectrum: *m/z* 284 (M, 100%), 267 (80). IR (KBr) ν_{max} 3379, 2956, 1621, 1501, 1211, 1146, 1114 cm^{-1}.

4.1.11. 7-Hydroxymethyl-4,6-dimethoxy-3-phenylbenzofuran (7a). As described for the preparation of alcohol **6a**, treatment of aldehyde **3a** (100 mg, 0.355 mmol) with an excess of sodium borohydride gave *7-hydroxymethyl-4,6-dimethoxy-3-phenylbenzofuran* **7a** (98%) as a colourless solid, mp 138–140°C (from dichloromethane). (Found: C, 71.2; H, 6.1. $C_{17}H_{16}O_4$ requires C 71.8; H, 5.7%). ^{1}H NMR spectrum: δ 3.84, 3.96 (6H, 2s, OMe); 4.29, s_{br}, OH); 4.98 (2H, d, *J*=5.1 Hz, C*H*$_2$OH); 6.42 (1H, s, H5); 7.52 (1H, s, H2); 7.33–7.62 (5H, m, aryl). ^{13}C NMR spectrum: δ 54.9 (CH_2OH); 55.6, 56.6 (OMe); 90.9 (C5); 127.1, 127.9, 129.2 (5×aryl CH); 140.3 (C2); 106.4, 120.0, 120.1, 122.9, 130.9, 132.2, 154.2 (aryl C). Mass spectrum: *m/z* 284 (M, 100%), 267 (90), 252 (50), 237 (60). IR (KBr) ν_{max} 3462, 2937, 1628, 1513, 1333, 1122, 1088 cm^{-1}.

4.1.12. 3-*t*-Butyl-7-hydroxymethyl-4,6-dimethoxybenzofuran (7b). As described for the preparation of alcohol **6a**, treatment of aldehyde **3b** (410 mg, 1.55 mmol) with an excess of sodium borohydride gave *3-t-butyl-7-hydroxymethyl-4,6-dimethoxybenzofuran* **7b** (405 mg, 98%) as a colourless solid, mp 110–111°C (from ethyl acetate/light petroleum). (Found: C, 68.0; H, 7.9. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%). ^{1}H NMR spectrum: δ 1.39 (9H, s, CMe_3); 3.93, 3.96 (6H, 2s, OMe); 4.91 (2H, s, C*H*$_2$OH); 6.37 (1H, s, H5); 7.19 (1H, s, H2). ^{13}C NMR spectrum: δ 30.1 (C*Me*$_3$); 30.6 (*C*Me$_3$); 54.7 (CH_2OH); 55.1, 56.6 (OMe); 90.2 (C5); 137.9 (C2); 105.9, 110.8, 131.2, 153.1, 156.0, 156.5 (aryl C). Mass spectrum: *m/z* 264 (M, 100%), 249 (80). IR (KBr) ν_{max} 3494, 2956, 1627, 1516, 1205, 1120, 1094 cm^{-1}.

4.1.13. α-(4-Chlorophenyl)-4,6-dimethoxy-3-phenylbenzofuran-2-methanol (10b). As described for the preparation of alcohol **6a**, treatment of ketone **4b** (870 mg, 2.22 mmol) with an excess of sodium borohydride gave *α-(4-chlorophenyl)-4,6-dimethoxy-3-phenylbenzofuran-2-methanol* **10b** (0.86 g, 99%) as a colourless gum which solidified on standing, mp 64–66°C (methanol). (Found: C, 69.7; H, 4.9. $C_{23}H_{19}ClO_4$ requires C, 70.0; H, 4.9%). ^{1}H NMR spectrum: δ 2.62 (1H, s, OH); 3.70, 3.82 (6H, 2s, OMe); 5.83 (1H, s, alkyl CH); 6.32 (1H, d, 2.0 Hz); 6.62 (1H, d, *J*=2.0 Hz, H7′); 7.29–7.50 (5H, m, aryl). ^{13}C NMR spectrum: δ 55.4, 55.7 (OMe); 67.4 (alkyl CH); 88.3, 94.7 (C5, C7); 127.4, 127.8, 127.9, 128.5, 130.3 (9×aryl CH); 110.9, 119.8, 132.0, 133.5, 139.6, 149.9, 154.8, 156.3, 159.5 (aryl C). Mass spectrum: *m/z* 396 (M ^{37}Cl, 31%), 394 (M ^{35}Cl, 90%), 379 (40), 377 (100), 363 (38), 139 (100). IR (KBr) ν_{max} 3417, 2960, 1616, 1505, 1217, 1153, 1111 cm^{-1}.

4.1.14. *N-t*-Butyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)-2-hydroxyethanamide (10d). As described for the preparation of alcohol **6a**, reaction of glyoxylamide

5a (1.40 g, 3.67 mmol) with an excess of sodium borohydride gave *N-t-butyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)-2-hydroxyethanamide* **10d** (1.39 g, 99%) as colourless crystals, mp 85–88°C (from ethyl acetate/light petroleum). (Found: C, 68.2; H, 6.8; N, 3.6. $C_{22}H_{25}NO_5$ requires C, 68.9; H, 6.6; N, 3.7). ^{1}H NMR spectrum: δ 1.31 (9H, s, CMe_3); 3.70, 3.84 (6H, 2s, OMe); 5.03 (1H, s, C*H*OH); 5.30 (1H, s, CHO*H*); 5.84 (1H, br, CONH); 6.32 (1H, d, J=2.0 Hz H5′); 6.65 (1H, d, J=2.0 Hz, H7′); 7.36–7.62 (5H, m, aryl). ^{13}C NMR spectrum: δ 28.3 (CMe_3); 51.1 (CMe_3); 55.1, 55.4 (OMe); 66.2 (alkyl CH); 88.1, 94.4 (C5′, C7′); 127.1, 127.4, 130.3 (5×aryl CH); 110.7, 121.1, 131.5, 147.8, 154.5, 156.0, 159.2 (aryl C); 168.8 (CO). Mass spectrum: *m/z* 383 (M, 5%), 283 (100), 267 (10). IR (KBr) ν_{max} 3371, 3215, 1737, 1656,1528, 1215, 1153, 1111 cm^{-1}.

4.1.15. 2-(4′,6′-Dimethoxy-3′-phenylbenzofuran-2′-yl)-2-hydroxyethanamide (10e). As described for the preparation of alcohol **6a**, treatment of glyoxylamide **5b** (460 mg, 1.425 mmol) with an excess of sodium borohydride gave *2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)-2-hydroxyethanamide* **10e** (457 mg, 98%) as colourless crystals, mp 88–90°C (from ethyl acetate/light petroleum). (Found: C, 66.2; H, 5.5; N, 4.1. $C_{18}H_{17}NO_5$ requires C, 66.1; H, 5.2; N, 4.3%). ^{1}H NMR spectrum: δ 2.60 (1H, s_{br}, CHO*H*); 3.71, 3.83 (6H, 2s, OMe); 5.17 (1H, s, C*H*OH); 5.74, 6.07 (2H, 2s, $CONH_2$); 6.31 (1H, d, J=2.0 Hz, H5′); 6.64 (1H, d, J=2.0 Hz, H7′); 7.37–7.60 (5H, m, aryl). ^{13}C NMR spectrum: δ 55.4, 55.8 (OMe); 66.0 (CHOH); 88.3, 94.9 (C5′, C7′); 127.6, 127.9, 130.4 (5×aryl CH); 110.7, 131.4, 133.1, 146.8, 154.9, 156.4, 159.9 (aryl C); 172.1 (CO). Mass spectrum: *m/z* 327 (M, 10%), 283 (90), 267 (15). IR (KBr) ν_{max} 3445, 3147, 1699, 1606, 1507, 1222, 1146, 1111 cm^{-1}.

4.1.16. *N*-Methyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)-2-hydroxyethanamide (10f). As described for the preparation of alcohol **6a**, treatment of glyoxylamide **5c** (475 mg, 1.401 mmol) with an excess of sodium borohydride gave *N-methyl-2-(4′,6′-dimethoxy-3′-phenylbenzofuran-2′-yl)-2-hydroxyethanamide* **10f** (473 mg, 99%) as colourless crystals, mp 100–103°C (from ethyl acetate/light petroleum). (Found: C, 66.4; H, 5.9; N, 3.8. $C_{19}H_{19}NO_5$ requires C, 66.8; H, 5.6; N, 4.1%). ^{1}H NMR spectrum: δ 1.05 (1H, s_{br}, CHO*H*); 2.84 (3H, d, J=5.1 Hz, NMe); 3.70, 3.83 (6H, 2s, OMe); 5.30 (1H, s, C*H*OH); 6.14 (1H, d, J=5.1 Hz, NH); 6.31 (1H, d, J=2.0, H5′); 6.64 (1H, d, J=2.0, H7′); 7.36–7.61 (5H, m, aryl). ^{13}C NMR spectrum: δ 26.3 (NMe); 55.4, 56.0 (OMe); 66.2 (CHOH); 88.3, 94.8 (C5′, C7′); 127.5, 127.8, 130.5 (5×aryl CH); 110.8, 122.0, 131.5, 147.2, 145.8, 156.3, 159.7 (aryl C); 170.4 (CO). Mass spectrum: *m/z* 341 (M, 1%), 327 (5), 280 (60), 249 (30), 207 (30), 180 (100), 165 (100). IR (KBr) ν_{max} 3396, 3228, 1662, 1538, 1507, 1222, 1153, 1111 (CO) cm^{-1}.

4.1.17. Reaction of alcohol 6a with K10 clay to give calixbenzofurans (8a and 9a). To a solution of alcohol **6a** (90 mg, 0.317 mmol) in dichloromethane (20 ml) was added K10 clay and the mixture was allowed to stir overnight, then filtered through Celite. The filtrate was evaporated and chromatographed (ethyl acetate/light petroleum, 25:75) 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* **8a** (16 mg, 19%) as colourless crystals, mp 278–281°C (from ethyl acetate/light petroleum) (lit.,[1] 278–281°C). The second fraction contained *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* **9a** (62 mg, 74%) as colourless crystals, mp 185–187°C (from ethyl acetate/light petroleum) (lit.[1] 185–187°C).

4.1.18. Reaction of alcohol 7a with K10 clay to give calixbenzofuran (8a). As described for alcohol **6a**, alcohol **7a** (100 mg, 0.352 mmol) was treated with K10 clay to give calix[3]benzofuran **8a**[1] (71 mg, 76%).

4.1.19. Reaction of alcohol 7b with K10 clay to give calixbenzofuran (8b). As described for alcohol **6a**, alcohol **7b** (220 mg, 0.833 mmol) was treated with K10 clay to give *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* **8b** (199 mg, 97%) as colourless crystals, mp 273–275°C (lit.[1] 273–275°C).

4.1.20. Reduction of aldehyde 2b with sodium borohydride and reaction of the resulting alcohol 6b with K10 clay to give calixbenzofurans (8b and 9b). Benzofuran **2b** (300 mg, 1.15 mmol) was reduced with sodium borohydride as described for the preparation of alcohol **6a**. The resulting alcohol **6b** was treated directly with K10 clay in dichloromethane. After stirring overnight, the solution was filtered through Celite. The filtrate was evaporated and chromatographed (ethyl acetate/light petroleum, 7:93 and then 10:90) to give two fractions. The first fraction contained calix[3]benzofuran **8b** (50 mg, 18% for two steps). 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* **9b** (90 mg, 32% for two steps) as colourless crystals, mp 174–177°C (from ethyl acetate/light petroleum) (lit.[1] 174–177°C).

4.1.21. Reduction of ketone 4a and reaction of the resulting alcohol 10a with K10 clay to give calixbenzofuran (11a). As described for the preparation of alcohol **6a**, ketone **4a** (315 mg, 0.85 mmol) was reduced with sodium borohydride to give alcohol **10a** (312 mg, 99%). This alcohol (260 mg, 0.7 mmol) was treated with K10 clay as described for the synthesis of calix[3]benzofuran **8a** to give *6,8,14,16,22,24-hexamethoxy-2,10,18-tri(4′-methylphenyl)-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* **11a** (210 mg, 85%) as colourless crystals, mp 190–192°C (from ethyl acetate/light petroleum) (lit.[1] 190–192°C).

4.1.22. Reaction of alcohol 10b with K10 clay to give calixbenzofurans (11b and 12). As described for the preparation of calix[3]benzofuran **8a**, alcohol **10b** (590 mg, 1.496 mmol) was treated with K10 clay to give a crude residue which was chromatographed (ethyl acetate/light petroleum, 15:85 and then 30:70) to afford two

fractions. The first fraction contained *2,10,18-tri(4′-chlorophenyl)-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* **11b** (420 mg, 75%) as colourless crystals, mp 204–207°C (ethyl acetate/light petroleum). (Found: C, 73.2; H, 4.6. $C_{69}H_{51}Cl_3O_9$ requires C, 73.3; H, 4.6%). ^{1}H NMR spectrum: δ 3.54, 3.64, 3.74, 3.75, 3.84, 4.00 (18H, 6s, OMe); 5.97, 6.10, 6.18 (3H, 3s, alkyl CH); 6.21, 6.34, 6.50 (3H, 3s, benzofuran H5); 6.57–7.51 (27, m, aryl). ^{13}C NMR spectrum: δ 37.1, 38.8, 38.9 (alkyl CH); 55.2, 55.4, 55.6, 56.0, 56.8, 57.1 (OMe); 90.5, 91.0, 91.4 (benzofuran C5); 126.6, 127.0, 127.1, 127.2, 127.4, 128.1, 128.7, 129.8, 129.9, 130.0, 130.4, 131.2, 133.2 (27×aryl CH); 105.9, 106.5, 109.7, 111.8, 113.0, 113.5, 115.1, 115.7, 117.9, 125.8, 126.0, 130.5, 132.1, 132.9, 138.6, 139.0, 139.7, 151.0, 151.7, 152.5, 153.0, 153.1, 153.9, 154.5 (aryl C). IR (KBr) ν_{max} 2932, 2835, 1609, 1489, 1327, 1208, 1142, 1100 cm^{-1}. Mass spectrum: *m/z* (MALDI) 1129 (M+1, ^{35}Cl, ^{35}Cl, ^{35}Cl).

The second fraction contained *2,10,18,26-tetra-(4′-chlorophenyl)-6,8,14,16,22,24,30,32-octamethoxy-4,12,20,28-tetraphenyl-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* **12** (105 mg, 19%) as colourless crystals after evaporation, mp>330°C (ethyl acetate/light petroleum). (Found: C, 73.1; H, 4.5. $C_{92}H_{68}Cl_4O_{12}$ requires C, 73.3; H, 4.6%). ^{1}H NMR spectrum: δ 3.01, 3.15, 3.31, 3.49, 3.51, 3.52, 3.62, 3.92 (24H, 8s, OMe); 5.52, 5.84, 5.89, 5.98 (4H, 4s, alkyl CH); 6.07, 6.12, 6.33 (4H, 3s, 4×H5′); 6.45–7.60 (32H, m, aryl). ^{13}C NMR spectrum: δ 36.8, 38.7, 39.8, 40.8 (alkyl CH); 54.9, 55.4, 55.6, 55.7, 55.8, 56.2, 56.5, 57.3 (OMe); 91.3, 91.6, 92.5 (4×benzofuran C5); 125.2, 126.9, 127.2, 127.4, 127.8, 128.1, 129.3, 129.6, 130.1, 130.2, 130.3, 131.1 (36×aryl CH); 105.5, 105.6, 106.6, 106.7, 110.0, 112.3, 114.2, 114.9, 117.1, 117.7, 118.7, 118.9, 124.6, 125.0, 126.4, 126.5, 128.5, 130.0, 131.3, 131.5, 132.1, 132.6, 133.3, 133.9, 134.0, 139.5, 140.1, 140.3, 140.6, 148.3, 149.0, 150.6, 151.3, 152.9, 153.0, 153.1, 153.2, 153.4, 153.5, 154.0 (aryl C). Mass spectrum: *m/z* (MALDI) 1505 (M+1, ^{35}Cl, ^{35}Cl, ^{35}Cl, ^{35}Cl). IR (KBr) ν_{max} 2932, 2835, 1610, 1489, 1211, 1141, 1093 cm^{-1}.

4.1.23. Reduction of ketone 4c and reaction of the resulting alcohol 10c with K10 clay to give calixbenzofuran (11c). Ketone **4c** (110 mg, 0.37 mmol) was reduced with sodium borohydride using the usual procedure. This resulting alcohol **10c** was treated with K10 clay as described for the preparation of calix[3]benzofuran **8a** to give *6,8,14,16,22,24-hexamethoxy-2,10,18-trimethyl-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* **11c** (60 mg, 58% for two steps) as a colourless solid, mp>300°C(from ethyl acetate/light petroleum). (Found: C, 77.3; H, 6.1. $C_{54}H_{48}O_9$ requires C, 77.1; H, 5.8%). ^{1}H NMR spectrum: δ 1.16, 1.51, 1.56 (9H, 3d, *J*=8.2 Hz, Me); 3.26, 3.59, 3.63, 3.71, 3.72, 3.89 (18H, 6s, OMe); 4.70, 4.76, 5.31 (3H, 3q, *J*=8.2 Hz, alkyl CH); 6.10, 6.24, 6.43 (3H, 3s, benzofuran H5); 7.07–7.63 (1H, m, aryl CH). ^{13}C NMR spectrum: δ 16.6, 17.8, 18.9 (Me); 26.7, 28.0, 28.5 (alkyl CH); 55.6, 55.8, 55.9, 57.0, 57.8 (6×OMe); 90.6, 91.5, 92.0 (benzofuran C5); 125.9, 126.1, 126.4, 127.0, 127.1, 127.6, 130.1, 130.3, 130.7 (15×aryl CH); 107.4, 108.1, 111.7, 113.1, 113.3, 114.0, 114.6, 115.0, 130.9, 133.6, 134.4, 134.5, 152.1, 152.2, 152.5, 153.2, 153.4, 153.5, 153.7, 153.8, 154.7, 154.9, 155.2, 155.9 (aryl C). Mass spectrum: *m/z* 841 (M+1). IR (KBr) ν_{max} 2932, 2335, 1615, 1506, 1329, 1205, 1153 cm^{-1}.

4.1.24. Reaction of alcohol 10d with *p*-toluenesulfonic acid to give calixbenzofurans (11d). To a stirred solution of alcohol **10d** (610 mg, 1.59 mmol) in dichloromethane (100 ml) was added *p*-toluenesulfonic acid and the mixture was stirred for 5 days. The solvent was evaporated and the crude residue was chromatographed (ethyl acetate/light petroleum, 50:50) to give two fractions. The first fraction contained *tri-t-butyl 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-2,10,18-tricarboxamide* **11d(i)** (65 mg, 12%) as a colourless solid, mp 201–203°C (from ethyl acetate/light petroleum). (Found: C, 71.2; H, 6.1; N, 3.6. $C_{66}H_{69}N_3O_{12}\cdot H_2O$ requires C, 71.1; H, 6.4; N, 3.8%). ^{1}H NMR spectrum: δ 1.11 (27H, s, 3×CMe$_3$); 3.58, 3.64 (18H, 2s, 6×OMe); 5.27 (3H, s, 3×CH); 5.60 (3H, s, 3×CONH); 6.17 (3H, s, 3×benzofuran H5); 7.20–7.50 (15H, m, aryl). ^{13}C NMR spectrum: δ 28.5 (3×C*Me*$_3$); 42.2 (3×alkyl CH); 51.1 (3×*C*Me$_3$); 56.3, 56.8 (6×OMe); 91.7 (3×benzofuran C5); 126.8, 127.4, 130.2 (15×aryl CH); 102.8, 110.6, 117.9, 132.5, 147.2, 152.5, 154.3, 155.6 (24×aryl C); 167.9 (3×CO). Mass spectrum: *m/z* 1096 (M+1, 100%), 731 (50). IR (KBr) ν_{max} 3420, 2958, 1687, 1612, 1513, 1222, 1111 cm^{-1}.

Crystal data for CCDC 178458.[16] $C_{69}H_{75}N_3O_{13}$, *M* 1154.4, monoclinic, space group $P2_1/c$, *a* 28.070 (13), *b* 22.912 (4), *c* 21.396 (9) Å, β 107.44 (2)°, *V* 13128 (8) Å^3, D_c 1.17 g cm^{-3}, *Z* 8, μ_{Cu} 6.19 cm^{-1}. Crystal size 0.19×0.22×0.27 mm^3, $2\theta_{max}$ 90°, min. and max.transmission factors 0.87 and 0.90. The number of reflections was 6485 considered observed out of 10,585 unique data, with R_{merge} 0.022 for 203 pairs of equivalent 0*kl* reflections. Final residuals *R*, R_w were 0.088, 0.134 for the observed data. The structure was described as a combination of four types of refineable identical groups (benzofuran, phenyl, *t*-butyl, and acetone) and single atoms. The benzofuran, phenyl and acetone groups were maintained planar, and the *t*-butyl groups had three-fold symmetry. Thermal motion was described by TLX rigid body thermal parameters, one for the macrocycle, and one for each phenyl and *t*-butyl-amide and acetone. Hydrogen atoms were included in positions calculated each cycle, and their thermal motions were assigned to the appropriate group.

The second fraction contained the isomer **11d(ii)** (100 mg, 17%) as a colourless solid, mp 277–279°C (from ethyl acetate/light petroleum). (Found: C, 72.2; H, 6.7; N, 3.6. $C_{66}H_{69}N_3O_{12}$ requires C, 72.3; H, 6.3; N, 3.8%). ^{1}H NMR spectrum: δ 0.88, 0.92, 0.95 (3s, (27H, 3s, 3×CMe$_3$); 3.43, 3.60, 3.62, 3.68, 3.83 (18H, 5s, 6×OMe); 5.11, 5.22, 5.30 (3H, 3s, alkyl CH); 5.60, 5.72, 6.04 (3H, 3s, CONH); 6.04, 6.26, 6.31 (3H, 3s, benzofuran H5); 6.70–7.53 (15H, m, aryl). ^{13}C NMR spectrum: δ 28.0, 28.2, 28.5 (C*Me*$_3$); 41.2, 41.5, 44.7, (*C*Me$_3$); 50.5, 50.7, 51.3 (alkyl CH);

55.3, 55.4, 55.8, 56.3, 56.9 (6×OMe); 90.6, 91.8, 92.2, (benzofuran C5); 126.2, 126.7, 127.1, 127.2, 127.4, 127.7, 129.9, 130.0, 130.6 (15×aryl CH); 102.5, 103.2, 104.5, 111.5, 112.2, 114.0, 117.6, 117.8, 119.4, 132.3, 133.0, 133.1, 148.6, 149.0, 150.1, 152.8, 153.6, 153.8, 153.9, 155.1, 155.5, 155.8, 156.5 (aryl C); 166.8, 167.3, 168.4 (CO). Mass spectrum: *m/z* 1096 (M+1, 100%), 731 (10). IR (KBr) ν_{max} 3431, 2972, 1681, 1612, 1513, 1333, 1208, 1090 cm^{-1}.

4.1.25. Reaction of alcohol 10e with *p*-toluenesulfonic acid to give calixbenzofuran (11e). As described for the preparation of calix[3]benzofuran **11d**, alcohol **10e** (200 mg, 0.612) was treated with *p*-toluenesulfonic acid to give *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-2,10,18-tricarboxamide* **11e** (85 mg, 45%) as a colourless solid, mp 275–278°C (from ethyl acetate/light petroleum). (Found: C, 67.2; H, 5.0, N, 4.3. $C_{54}H_{45}N_3O_{12}\cdot 2H_2O$ requires C, 67.3; H, 5.1, N, 4.4%). ^{1}H NMR spectrum: δ 3.32, 3.63, 3.67, 3.78, 3.80, 3.81 (18H, 6s, OMe); 5.33, 5.69, 5.72 (3H, 3s, CH); 5.82, 5.88, 6.50 (3H, 3 br s, CONH); 6.16, 6.35, 6.37 (3H, 3s, benzofuran H5); 7.33–7.57 (15H, m, aryl). ^{13}C NMR spectrum: δ 39.1, 40.7, 43.2 (alkyl CH); 55.6, 56.1, 56.8, 56.9 (6×OMe); 91.0, 91.1, 91.4 (benzofuran C5); 127.0, 127.1, 127.2, 127.4, 127.6, 127.8, 130.1, 130.6 (15×aryl CH); 102.1, 102.6, 103.5, 111.2, 112.3, 112.6, 119.2, 119.3, 119.7, 131.9, 132.5, 132.6, 147.7, 148.4, 148.5, 153.4, 153.8, 153.9, 154.1, 154.9, 155.3, 155.8, 155.9 (aryl C); 171.9, 172.0, 172.6 (CO). Mass spectrum: *m/z* 928 (M+1, 90%). IR (KBr) ν_{max} 3476, 3377, 1693, 1600, 1513, 1333, 1139, 1097 cm^{-1}.

4.1.26. Reaction of alcohol 10f with *p*-toluenesulfonic acid to give calixbenzofuran (11f). As described for the preparation of calix[3]benzofuran **11d**, alcohol **10f** (400 mg, 1.173 mmol) was treated with *p*-toluenesulfonic acid to give *trimethyl 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-2,10,18-tricarboxamide* **11f** (120 mg, 32%) as a colourless solid, mp 234–236°C (from ethyl acetate/light petroleum). (Found: C, 68.5; H, 5.3; N, 3.8. $C_{57}H_{51}N_3O_{12}\cdot 2H_2O$ requires C, 68.1; H, 5.5; N, 4.2%). ^{1}H NMR spectrum: δ 2.10, 2.36, 2.50 (9H, 3d, *J*=4.1 Hz, NH*Me*); 3.46, 3.60, 3.63, 3.69, 3.70, 3.92 (18H, 6s, OMe); 5.28, 5.57, 6.34 (3H, 3d, *J*=4.1 Hz, NH); 5.51, 5.59, 5.99 (3H, 3s, CH); 6.18, 6.20, 6.40 (3s, benzofuran H5); 6.97–7.56 (15H, m, aryl). ^{13}C NMR spectrum: δ 26.0, 26.3, 27.1 (NMe); 40.1, 41.8, 43.0 (alkyl CH); 55.5, 55.6, 55.8, 56.0, 56.5, 57.4 (OMe); 90.8, 91.0, 92.0 (benzofuran C5); 126.6, 127.0, 127.1, 127.2, 127.5, 129.8, 130.1, 130.3, 130.6 (15×aryl CH); 102.0, 102.5, 103.7, 111.7, 111.8, 112.8, 117.4, 118.1, 119.6, 132.0, 132.4, 133.2, 148.3, 148.7, 149.1, 153.2, 153.5, 153.6, 153.8, 154.2, 155.0, 155.4, 156.0 (aryl C); 169.1, 169.6, 170.7 (CO). Mass spectrum: *m/z* 970 (M+1, 100%), 648 (100), 486 (20). IR (KBr) ν_{max} 3433, 2930, 1681, 1612, 1513, 1333, 1153, 1097 cm^{-1}.

4.1.27. Reduction of glyoxylic ester 5d and reaction of the resulting alcohol 10g with *p*-toluenesulfonic acid to give calixbenzofuran (11g). To a solution of glyoxylic ester **5d** (770 mg, 2.24 mmol) in dichloromethane, under an atmosphere of nitrogen and cooled at −76°C with an acetone/liquid nitrogen bath, was added diisobutylaluminium hydride (2.5 ml, 2.5 mmol). The solution was stirred at −76°C for 45 min, allowed to come to room temperature and a 50:50 mixture of water/methanol was added dropwise. The two layers were separated and the aqueous phase was extracted with dichloromethane. The combined organic extracts were dried, evaporated and chromatographed (ethyl acetate/light petroleum) to give the crude alcohol **10g** (545 mg, 71%) as a pale yellow gum. ^{1}H NMR spectrum: δ 3.45 (1H, d, *J*=5.0 Hz, OH); 3.71 (3H, s, COOMe); 3.78, 3.85 (6H, 2s, ArOMe); 5.23 (1H, d, *J*=5.0 Hz, C*H*OH); 6.32 (1H, d, 1.7 Hz, H5′); 6.65 (1H, d, *J*=1.7 Hz, H7′); 7.36–7.44 (5H, m, aryl). ^{13}C NMR spectrum: δ 53.3 (COO*Me*); 55.4, 55.8 (2×ArO*Me*); 65.3 (alkyl CH); 88.2, 94.8 (C5′, C7′); 127.5, 127.7, 130.5 (5×aryl CH); 110.9, 121.6, 131.6, 146.5, 155.0, 156.3, 159.8 (aryl C); 172.2 (CO). Mass spectrum: *m/z* 342 (M, 20%), 312 (5), 283 (100), 267 (27).

As described for the preparation of calix[3]benzofuran **11d**, the crude alcohol **10g** (400 mg, 1.170 mmol) was treated with *p*-toluenesulfonic acid to give *trimethyl 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-2,10,18-tricarboxylate* **11g** (50 mg, 26%) as colourless crystals, mp 176–178°C (from ethyl acetate/light petroleum). (Found: C, 69.8; H, 5.1. $C_{57}H_{48}O_{15}$ requires C, 70.4; H, 5.0%). ^{1}H NMR spectrum: δ 3.05, 3.27, 3.59, 3.63, 3.65, 3.67, 3.75, 3.79 (27H, 8s, 9×OMe); 5.35, 5.76, 5.79 (3H, 3s, CH); 6.12, 6.32, 6.38 (3H, 3s, benzofuran H5); 7.32–7.55 (15H, m, aryl). ^{13}C NMR spectrum: δ 37.5, 39.3, 41.7 (COOMe); 51.7, 52.3, 52.4 (alkyl CH); 55.5, 55.6, 55.9, 56.8, 57.4 (6×OMe); 90.3, 91.0, 91.4 (benzofuran C5); 126.6, 127.2, 127.3, 127.6, 130.1, 130.2, 130.7 (15×aryl CH); 101.9, 103.6, 112.1, 112.6, 112.8, 117.9, 118.3, 118.9, 132.9, 133.5, 147.5, 147.7, 149.1, 153.4, 153.6, 153.8, 154.4, 155.0 (aryl C); 169.7, 170.3, 170.7 (CO). Mass spectrum: *m/z* 973 (M+1, 100%). IR (KBr) ν_{max} 2954, 2836, 1749, 1612, 1513, 1333, 1150, 1097 cm^{-1}.

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