Calixhydroquinones: a novel access to conformationally restricted, *meta*-substituted calixarenes †

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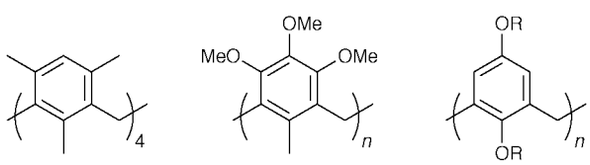
An efficient and versatile synthetic route to calixhydroquinones is described. These macrocycles are activated towards *meta* substitution, and reaction with bromine gives the first examples of persubstituted, phenol-derived calixarenes. The effect of *meta* substitution on calixarene mobility is demonstrated by the fixation of an otherwise mobile calix[4] system in the partial cone conformer, and the slowing of the ring inversion rate in calix[8]arenes.

Introduction

The fast developing field of nanotechnology[1] has created a demand for molecules which are at the same time spatially well defined and chemically interconnectable to serve as components for the 'molecular construction kit.' There are, in effect, two conceptual approaches to meeting this demand: (i) the custom synthesis of appropriately functionalised species with intrinsically rigid frameworks,[2] and (ii) the conformational freezing of otherwise flexible molecules by introducing insurmountable steric barriers. Related to this are efforts to restrict the mobility of macrocycles in order to 'preorganise' them for the accommodation of a guest.[3] In calixarenes, which are not intrinsically rigid, this is accomplished either through transannular tethers or by introducing sterically demanding substituents at the lower rim which suppress rotation through the aryl axis.[4] While this serves to block conformational isomerism in calix[4]arenes, interconversion in the calix[6]- and [8]arenes can still occur, especially at elevated temperatures. We thus became interested in the prospect of further reducing the overall flexibility of these species by introducing substituents at the free positions α to the methylene bridges, hereafter referred to as the '*meta*' positions due to their relationship to the phenolic oxygen in the parent compound. The close proximity of the *meta* carbons in neighbouring rings, especially in cone or partial-cone conformers, suggested that substitution here could profoundly influence both shape and molecular dynamics in the calixarene ring systems.

Since calixarenes are usually already substituted in the *para* position, substitution at the *meta* positions results in a *persubstituted* system. Although attempts to make persubstituted calixarenes can be traced back to the 1960s,[5,6] few examples of such materials are found in the modern literature. Unconventional calix[4]arenes **1** lacking oxygen functionality at the lower rim were first produced by self-condensation of chloromethylmesitylene,[6] and substitution of the *para* positions and modifications of the method led to a range of persubstituted derivatives.[7] The reaction of 3,4,5-trimethoxytoluene with formaldehyde also gives persubstituted calixarenes **2**, most notably systems possessing up to 13 aromatic rings, most however in yields between 1.0 and 2.6%, and even the calix[4] product in <10% yield.[8] Resorcinarenes, which are by definition already *meta* substituted, can also be functionalised to give a persubstituted system,[9] but again lacking oxygen at the lower rim.

We however reasoned that calix[*n*]*hydroquinones* **3**–**5** would



1 **2** **3** $n = 4$ **4** $n = 6$ **5** $n = 8$

be sufficiently activated towards electrophilic attack to make possible the preparation of multiply *meta*-substituted derivatives, with both lower and upper rim oxygen functionality. We have described in brief the first examples of persubstituted, phenol-derived calixarenes,[10] and now report in full on the synthesis and properties of these novel, conformationally restricted macrocycles.

Results and discussion

The effect of *meta* substitution on calix[4]arenes is to favour two conformational isomers, *i.e.* a pinched partial cone and the 1,3-alternate, with the cone and the 1,2-alternate precluded. Whether the higher calixarenes could be immobilised in this way and what conformations would be frozen out was however no matter of certainty.

A preliminary modelling study (CPK) suggested that replacement of the *meta* protons in the calix[6]- and [8]arene systems with anything larger than a methyl group introduced such serious steric congestion that persubstitution appeared unlikely in either case. However it seemed feasible that in the course of substitution, these macrocycles could become locked into $(up–down)_n$ 'pleated loop' conformations which might lead to alternately substituted rings. This was of potential interest since molecular mechanics simulations[11] show that these compounds have low energy conformations with defined cavities (Fig. 1).

Calixhydroquinones

The first calix[4]hydroquinone synthesis was reported in 1977

† Supplementary data available: Fig. 1(*a*) and 1(*b*) as .pdb files. For direct electronic access see http://www.rsc.org/suppdata/p1/1999/3435.

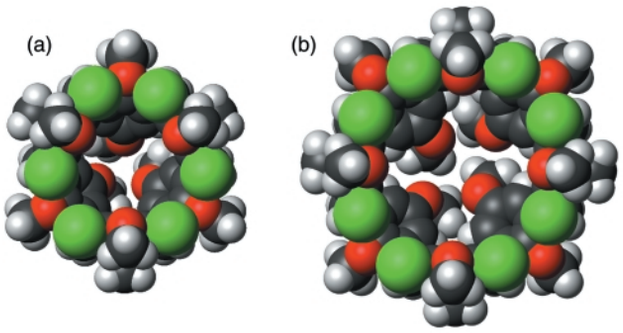
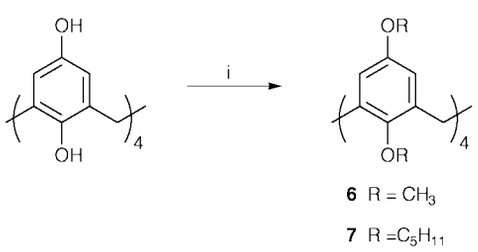


Fig. 1 Energy minimised conformations of calixhydroquinones with *meta* bromine substituents on alternate rings: (a) $Br_6(OMe)_{12}$calix[6]-arene and (b) $Br_8(OMe)_{16}$calix[8] arene.

by standard base-catalysed condensation of hydroquinone monomethyl ether with formaldehyde,[12] a method re-employed 20 years later to produce calix[8]hydroquinones.[13] Another synthetic approach to calix[4]hydroquinone which featured a Baeyer–Villiger oxidation of a tetraacetylcalix[4]arene[14] was adapted by us to the synthesis of the corresponding calix[8]-hydroquinone in good yield,[10] which at that point had only been accessed *via* the quinone itself,[15] or in patented procedures.[16] Since then, the only other example of higher calixhydroquinones to appear in the literature is the above mentioned hydroquinone monoether–formaldehye condensation,[13] which gives reasonable yields for the calix[8]-, but not calix[6]hydroquinone.

Calix[4]hydroquinone was thus prepared as described[14] and simple methylation gave its octamethyl ether **6** (Scheme 1).



Scheme 1 *Reagents and conditions*: (i) NaH, RX, THF, reflux.

Parallel synthesis in the calix[6] and calix[8] series first involved literature acetylmethoxycalixarene preparations[17] followed by Baeyer–Villiger reaction under carefully controlled conditions to give acetoxymethoxycalixarenes **10** and **11**, which could be hydrolysed to **12** and **13** (Scheme 2). Methylation then provided the hydroquinone ethers **14** and **15**. Octamethoxycalix[4]arene **6** crystallised in the form of platelets suitable for X-ray crystal structure determination. Interestingly, **6** occurs as an acutely pinched cone in the solid state (Fig. 2), while in chloroform solution a mixture of the cone and partial cone (1 : 2.7 by NMR in $CDCl_3$, respectively) is present.

Bromination of calixhydroquinones

It was to our surprise when, on exposure to acetyl chloride under Friedel–Crafts conditions, these electron rich macrocycles gave no evidence of reaction. However, electrophilic bromination gave not only octabromocalix[4]arene **17** from **6**, but also hexadecabromocalix[8]arene **18** from **15** (Scheme 3). The reaction of calix[6]arene **14** with bromine also resulted in persubstitution at the aromatic positions (by NMR), but a complex mixture of products was obtained which could not be separated. Interestingly, although the calix[8]hydroquinone **15** was successfully brominated using standard conditions (Br_2–CH_2Cl_2, reflux), similar treatment of the calix[4] analogue **6** resulted in extensive dealkylation and gave mainly oxidised products. It was for this reason that milder conditions were

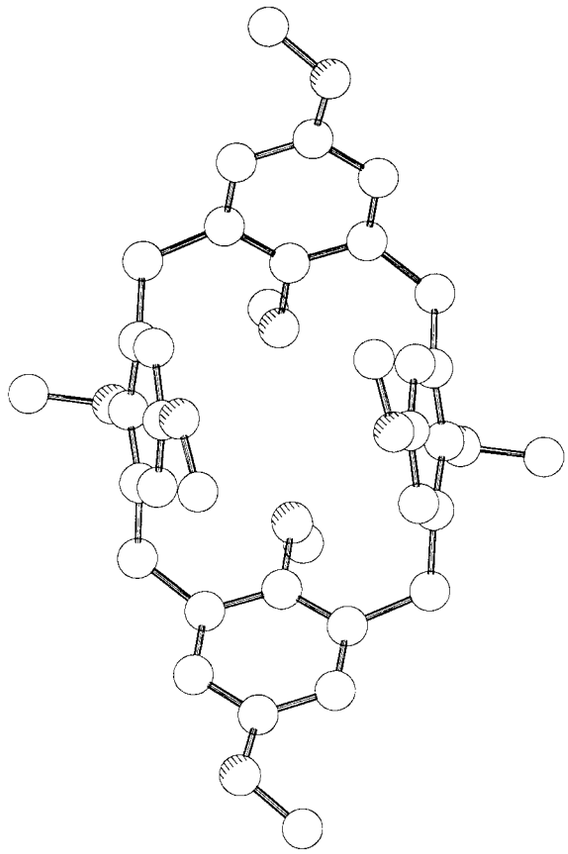
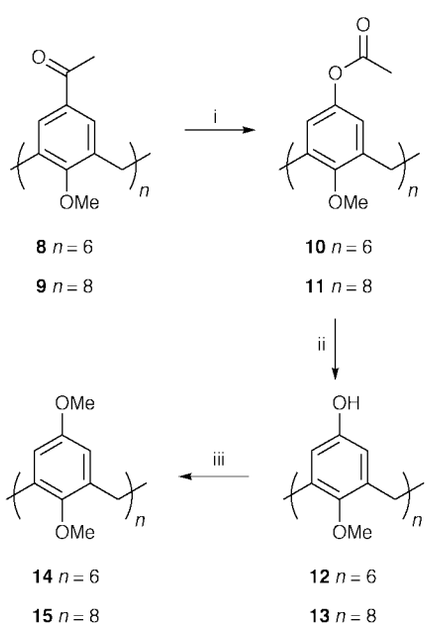


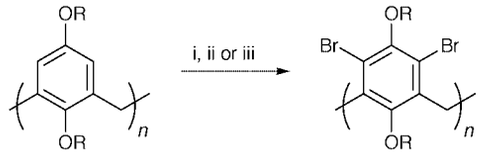
Fig. 2 X-Ray crystal structure of calix[4]hydroquinone octamethyl ether **6**.



Scheme 2 *Reagents and conditions*: (i) *m*-CPBA, $CHCl_3$, 4 °C; (ii) NaOH–MeOH; (iii) NaH, MeI, THF, reflux.

devised for the bromination of **6**, but even then this provided **17** in modest yield alongside a mixture of brominated calixquinones.

Octabromooctamethoxycalix[4]arene **17** was found by NMR to exist as the partial cone conformer in chloroform solution. Molecular modelling[11] suggests a pinched partial cone is favoured energetically over the 1,3-alternate, but only by a margin of 10–15 kJ mol^{-1}. Attempted equilibration of the conformers by heating at reflux in diphenyl ether solution (260 °C) for several hours was unsuccessful, demonstrating that the



6 $n = 4$, R = Me — **17** $n = 4$, R = Me

15 $n = 8$, R = Me — **18** $n = 8$, R = Me

7 $n = 4$, R = C_5H_{11} — **19** $n = 4$, R = C_5H_{11}

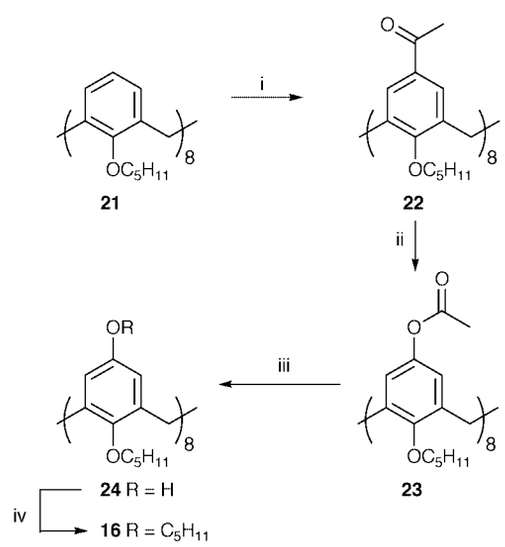
16 $n = 8$, R = C_5H_{11} — **20** $n = 8$, R = C_5H_{11}

Scheme 3 *Reagents and conditions*: (i) Br_2, CH_2Cl_2, reflux; (ii) NBS, CH_2Cl_2–EtOH–HCl; (iii) Br_2, $AgNO_3$, $CHCl_3$–HNO_3.

mobility in **17** could be effectively suppressed by *meta* substitution. The observation of the partial cone structure in a persubstituted calix[4]arene contrasts with published reports on the conformational preferences of such systems, where the 1,3-alternate is the only conformer described.[7,18]

The hexadecabromocalix[8]arene **18** showed three broad resonances in the ^{1}H NMR ($CDCl_3$) at room temperature representing the methylene protons and the two methoxy groups. These coalesced to sharp singlets at 60 °C. Cooling the sample led to a complex spectrum which was incompletely resolved, even at −90 °C (CD_2Cl_2). Although total immobilisation has clearly not been effected in the larger calixarene, the conformer interconversion rate was reduced considerably by substitution at the *meta* positions with bromine.

It remained then to attempt the concurrent use of *meta* substitution *and* steric bulk at the peripheral oxygen sites to determine to what extent conformer interconversion could be slowed by a combination of these strategies. Groups larger than ethyl at the lower rim are sufficient to restrict through-annulus rotation in calix[4]arenes.[19] To this end, octapentoxycalix[4]arene **7** and hexadecapentoxycalix[8]arene **16** were prepared, the former again by simple alkylation of the parent calix[4]-hydroquinone, and the latter as described in Scheme 4. It was



Scheme 4 *Reagents and conditions*: (i) MeCOCl, $AlCl_3$, CH_2Cl_2, −78 ⟶ −8 °C; (ii) *m*-CPBA, $CHCl_3$, 4 °C; (iii) NaOH–MeOH; (iv) NaH, $C_5H_{11}Br$, THF, reflux.

decided to abandon the calix[6] series at this point due to the ambiguous results in the bromination of **14**.

Bromination of calix[4]arene **7** proceeded smoothly to give the octabromide **19** in good yield (Scheme 3). Like its precursor **7**, bromocalix **19** was seen to exist in the unusual 1,3-alternate conformation (by NMR in $CDCl_3$). Immobilised molecules **7** and **19** constitute, in effect, ideal bidirectional

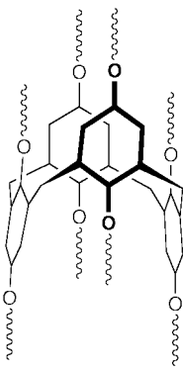


Fig. 3 A skeletal representation of 1,3-alt-**19**.

building blocks for the calix 'nano-tube' concept recently put forward by Shinkai.[20] The unusual arrangement of eight C–O bonds in parallel (Fig. 3) makes available four metal binding sites composed of two hard, phenolic oxygens as well as two other sites composed of two soft, π-basic aryl rings. Although the pentyl chains used in this instance are a functional dead-end, synthesis of an analogue of **7** with ω-functionalised chains should not be problematic.

The spectral characteristics of hexadecabromocalix[8] species **20** revealed a reduced degree of conformational mobility than was present in methyl analogue **18**, and yet it was clear that complete fixation of the molecule had not been effected. The room temperature ^{1}H NMR spectrum ($Cl_2DCCDCl_2$) was broad but interpretable, and sharpened sufficiently at 120 °C to give a spectrum comparable to that of the compound before bromination, but lacking of course the aromatic protons. As was the case for **18**, cooling the sample (RT to −60 °C in $CDCl_3$) did not produce an interpretable spectrum.

Conclusion

Analysis of the molecular dynamics of calix[8]hydroquinones **18** and **20** by NMR supports the argument that *meta* substitution reduces mobility in these large ring macrocycles, without however giving any direct indication of structure. Monte-Carlo simulations[11] of such large molecules are nontrivial and produce clusters of saddle-points within a close range of energies rather any definitive minimum energy structure. Although crystallography remains yet an option to ascertain what conformations of **18** and **20** preside in the solid state, perhaps the most intriguing application of *meta* substitution of the higher calixarenes would be the stabilisation of the previously mentioned 'pleated loop' conformers shown in Fig. 1. These species may be accessible *via* partial bromination of **14** or **15**, or by stepwise synthesis. Recent work on fullerene–hydroquinone complexes[21] and the inclusion of C_{60} in calix[6]- and [8]arenes[22] suggests that higher calixhydroquinones with fixed cavities may be of particular interest in this area. We have however demonstrated that an otherwise mobile calix[4]arene can through per-substitution be fixed in a single conformation, while at the same time retaining both upper and lower rim phenolic oxygen functionality. Since fixation is not covalent but steric, involving only the *meta* bromine substituents, these peripheral oxygen sites may be freely manipulated. This conceptual approach to limiting calixarene mobility whilst retaining the full functional capacity of the molecule may prove useful in the development of new nanosynthons.

Experimental

5,11,17,23,25,26,27,28-Octamethoxycalix[4]arene 6

To sodium hydride (2.0 g, 60% in paraffin, 50 mmol), washed with hexane (3 × 20 cm^3) under nitrogen, was added a solution

of octahydroxycalix[4]arene[14] (250 mg, 0.51 mmol) in tetrahydrofuran (THF) (60 cm^3) and the mixture was stirred for 30 min. Excess methyl iodide (12.5 cm^3) was then added and the reaction heated at reflux for 20 h. On cooling, 1 M HCl (80 cm^3) was added and the aqueous phase was extracted with chloroform (2 × 50 cm^3). The combined organic layer was concentrated and the residue preabsorbed onto silica gel and chromatographed (1–7% ethyl acetate in hexane). Recrystallisation of the resulting off-white solid from *n*-butanol gave **6** as white crystals (184 mg, 60%), mp 184–185 °C (Found C, 71.91; H, 6.98. $C_{36}H_{40}O_8$ requires C, 71.98; H, 6.71%); ν_{max}/cm^{-1} 2997, 2936, 2818, 1602, 1479, 1303, 1221, 1142, 1059, 1021 and 851; δ_H (400 MHz; DMSO-d_6; 100 °C) 6.42 (8 H, br s, ArH), 3.59 (24 H, br s, OMe) and 3.49 (8 H, br s, CH_2); δ_C (100 MHz; $CDCl_3$) 154.2, 153.9, 151.6, 136.9, 135.4, 133.9, 132.2, 115.3, 114.5, 113.7, 112.9, 61.4, 60.7, 59.6, 59.1, 55.0, 35.7 and 30.7; *m*/*z* (FAB) 600 (100%, M^+).

5,11,17,23,29,35-Hexaacetyl-37,38,39,40,41,42-hexamethoxycalix[6]arene 8

A higher yielding modification of the method of Gutsche *et al.*[17] was used: a mixture of aluminium chloride (6.25 g, 46.9 mmol) and acetyl chloride (13.0 cm^3, 14.4 g, 190 mmol) in dry dichloromethane (20 cm^3) was added dropwise over 1 h to a solution of 37,38,39,40,41,42-hexamethoxycalix[6]arene·$2H_2O$[17] (2.20 g, 2.91 mmol) in dry dichloromethane (50 cm^3) at −6 °C under nitrogen. After stirring for 6.5 h at this temperature water (100 cm^3) was cautiously added. The mixture was allowed to come to room temperature and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 100 cm^3) and the combined organic layer dried over $MgSO_4$. The solvent was evaporated and the residue dissolved in the minimum quantity of hot dichloromethane. Product **8** was precipitated by the addition of methanol and collected on a filter as a white solid (2.72 g, 96%), mp 312–315 °C (lit.,[17] 320–322 °C).

5,11,17,23,29,35-Hexaacetoxy-37,38,39,40,41,42-hexamethoxycalix[6]arene 10

A mixture of **8** (2.35 g, 2.41 mmol) and *m*-chloroperbenzoic acid (*m*-CPBA) (50–60%, 30 g, 87–104 mmol) in chloroform (350 cm^3) was prepared and kept at 4 °C for 10 d. Chloroform (300 cm^3) was added and the solution was washed with a 1:1 mixture of 2 M aq. sodium sulfite and 0.33 M pH 7 phosphate buffer (2 × 100 cm^3). After drying over $MgSO_4$ most of the solvent was removed and the residue was preabsorbed onto silica gel. Chromatography (1:2 to 3:2 ethyl acetate in hexane) gave **10** (2.45 g, 95%) as a white solid, mp 312–314 °C (Found C, 67.15; H, 5.75. $C_{60}H_{60}O_{18}$ requires C, 67.41; H, 5.66%); ν_{max}/cm^{-1} 2939, 1764, 1595, 1469, 1429, 1369, 1203, 1023 and 905; δ_H (250 MHz; $CDCl_3$) 6.72 (12 H, s, ArH), 3.92 (12 H, s, CH_2), 3.22 (18 H, s, OMe) and 2.23 (18 H, s, $COCH_3$); δ_C (68 MHz; $CDCl_3$) 169.6, 153.7, 146.1, 135.2, 122.0, 60.4, 30.2 and 21.1; *m*/*z* (FAB) 1069 (58%, M + 1), 1026 (100, M − CH_2CO), 984 (36) and 942 (15).

5,11,17,23,29,35-Hexahydroxy-37,38,39,40,41,42-hexamethoxycalix[6]arene 12

A solution of **10** (2.30 g, 2.15 mmol) in 0.5 M methanolic sodium hydroxide (200 cm^3) was stirred at room temperature for 3 h. The resulting brown solution was acidified with conc. HCl and concentrated under vacuum. Water (30 cm^3) was added and the resulting white precipitate filtered and washed with water. The crude product was dissolved in methanol–chloroform and preabsorbed onto silica gel. Chromatography (12–30% methanol in chloroform) gave **12** (1.34 g, 76%) as a white solid; ν_{max}/cm^{-1} 3397, 2949, 2828, 1597, 1546, 1464, 1431, 1317, 1295, 1216, 1175, 1031, 863 and 770; δ_H (250 MHz; DMSO-d_6) 8.93 (6 H, br s, OH), 6.36 (12 H, s, ArH), 3.71 (12 H, s, CH_2) and 3.03 (18 H, s, OMe); δ_C (68 MHz; DMSO-d_6) 152.5, 148.1, 134.7, 115.1, 59.8 and 29.1.

5,11,17,23,29,35,37,38,39,40,41,42-Dodecamethoxycalix[6]arene 14

Sodium hydride (500 mg, 60% in paraffin, 12.5 mmol), washed with hexane under nitrogen, was suspended in THF (15 cm^3) and a solution of **12** (150 mg, 0.18 mmol) in dimethylformamide (DMF) (5 cm^3) was added. The mixture was stirred for 10 min and excess methyl iodide (5.0 cm^3) was added. The reaction was heated to reflux under nitrogen and additional methyl iodide (2.5 cm^3) was added at 12 h intervals over 5 d. The volatiles were removed under vacuum and the solid residue was washed with water and collected on a filter. The crude product was chromatographed on silica (35% ethyl acetate in hexane) to give **14** (50 mg, 30%) as an off-white powder, mp 286–288 °C (Found C, 71.87; H, 6.95. $C_{54}H_{60}O_{12}$ requires C, 71.98; H, 6.71%); ν_{max}/cm^{-1} 2938, 2834, 1602, 1590, 1476, 1428, 1306, 1231, 1214, 1169, 1146, 1056, 1013 and 861; δ_H (400 MHz; $CDCl_3$) 6.49 (12 H, s, ArH), 3.92 (12 H, s, CH_2), 3.62 (18 H, s, OMe) and 3.20 (18 H, s, OMe); δ_C (68 MHz; $CDCl_3$) 155.2, 150.0, 135.1, 113.9, 60.3, 55.3 and 30.6; *m*/*z* (FAB) 900 (100%, M^+).

5,11,17,23,29,35,41,47-Octaacetyl-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene 9

A higher yielding modification of the method of Gutsche *et al.*[17] was used: a mixture of aluminium chloride (2.30 g, 17.2 mmol) and acetyl chloride (8.5 cm^3, 9.4 g, 0.12 mol) in dry dichloromethane (25 cm^3) was added dropwise over 1 h to a solution of 49,50,51,52,53,54,55,56-octamethoxycalix[8]arene·$CHCl_3$[17] (1.64 g, 1.52 mmol) in dry dichloromethane (35 cm^3) at 0 °C under nitrogen. After stirring for 3 h at this temperature water (50 cm^3) was cautiously added. The mixture was allowed to come to room temperature and the layers were separated. The aqueous layer was extracted with dichloromethane (2 × 50 cm^3) and the combined organic layer dried over $MgSO_4$. The solvent was evaporated and the residue dissolved in the minimum quantity of hot chloroform. The crude product was precipitated by the addition of methanol and recrystallised from chloroform–methanol to give **9**·$CHCl_3$ as colourless crystals (1.80 g, 84%), mp 306–310 °C (lit.,[17] 316–318 °C).

5,11,17,23,29,35,41,47-Octaacetoxy-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene 11

A mixture of **9** (1.80 g, 1.27 mmol) and *m*-chloroperbenzoic acid (50–60%, 29 g, 84–101 mmol) in chloroform (250 cm^3) was prepared and kept at 4 °C for 11 d. Chloroform (250 cm^3) was added and the solution was washed with a 1:1 mixture of 1 M aq. sodium sulfite–0.33 M pH 7 phosphate buffer (3 × 500 cm^3). After drying over $MgSO_4$ the solvent was evaporated and the residue dissolved in chloroform (20 cm^3). Hexane (250 cm^3) was added and the precipitate was filtered and washed with hexane (2 × 20 cm^3). Drying gave the pure *title compound* **11** (1.54 g, 85%) as a white solid, mp 170–174 °C (Found C, 67.20; H, 5.87. $C_{80}H_{80}O_{24}$ requires C, 67.41; H, 5.66%); ν_{max}/cm^{-1} 2940, 1765, 1597, 1472, 1430, 1370, 1205, 1169, 1024 and 905; δ_H (250 MHz; $CDCl_3$) 6.65 (16 H, s, ArH), 3.97 (16 H, s, CH_2), 3.47 (24 H, s, OMe) and 2.16 (24 H, s, $COCH_3$); δ_C (68 MHz; $CDCl_3$) 169.4, 153.8, 146.1, 134.6, 121.6, 60.8, 29.9 and 20.8; *m*/*z* (FAB) 1425 (100%, M + H) and 1383 (82).

5,11,17,23,29,35,41,47-Octahydroxy-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene 13

A solution of **11** (2.00 g, 1.40 mmol) and sodium hydroxide (0.90 g, 23 mmol) in methanol (50 cm^3) was stirred at room temperature for 2 h. The reaction mixture was concentrated and

water (30 cm^3) was added followed by conc. HCl (2 cm^3). The resulting precipitate was filtered and washed with water (2 × 15 cm^3). The crude product was preabsorbed onto silica gel and chromatographed (16% methanol in chloroform) to give **13**·$2H_2O$ (1.30 g, 82%) as a white solid, mp 156–159 °C (Found C, 68.47; H, 6.13. $C_{64}H_{64}O_{16}$·$2H_2O$ requires C, 68.32; H, 6.09%); ν_{max}/cm^{-1} 3382, 2944, 2380, 1599, 1463, 1431, 1315, 1294, 1220, 1173, 1005 and 860; δ_H (DMSO-d_6) 8.90 (8 H, br s, OH), 6.29 (16 H, s, ArH), 3.76 (16 H, s, CH_2) and 3.38 (24 H, s, OMe); δ_C (68 MHz; DMSO-d_6) 152.9, 148.5, 134.3, 115.0, 60.4 and 29.4; *m*/*z* (FAB) 1088 (21%, M^+).

5,11,17,23,29,35,41,47,49,50,51,52,53,54,55,56-Hexadecamethoxycalix[8]arene 15

Sodium hydride (2.0 g, 60% in paraffin, 50 mmol), washed with hexane under nitrogen, was suspended in THF (120 cm^3) and a solution of **13**·$2H_2O$ (1.25 g, 1.11 mmol) in DMF (4 cm^3) was added. The mixture was stirred for 30 min, excess methyl iodide (12.5 cm^3) was added, and the reaction heated at reflux for 20 h under nitrogen. The reaction mixture was concentrated and 1 M HCl (80 cm^3) was added. This mixture was extracted with chloroform (3 × 100 cm^3) and the combined organic layer dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on silica (35% ethyl acetate in hexane) to give **15** (900 mg, 67%) as a white crystalline solid, mp 184–185 °C (Found C, 71.91; H, 6.85. $C_{72}H_{80}O_{16}$ requires C, 71.98; H, 6.71%); ν_{max}/cm^{-1} 2991, 2938, 2833, 1604, 1476, 1428, 1311, 1219, 1170, 1144, 1058, 1010 and 861; δ_H (250 MHz; $CDCl_3$) 6.42 (16 H, s, ArH), 3.98 (16 H, s, CH_2) and 3.53 (48 H, s, OMe); δ_C (68 MHz; $CDCl_3$) 155.5, 150.2, 134.7, 113.9, 60.9, 55.1 and 30.3; *m*/*z* (FAB) 1200 (100%, M^+).

4,6,10,12,16,18,22,24-Octabromo-5,11,17,23,25,26,27,28-octamethoxy calix[4]arene 17

A solution of **6** (20 mg, 0.033 mmol) and *N*-bromosuccinimide (59 mg, 0.33 mmol) was prepared in dichloromethane (8 cm^3) containing ethanol (30 μl). A stream of HCl gas was passed through this solution for 5 min, and after standing a further 30 min, additional *N*-bromosuccinimide (30 mg, 0.17 mmol) was added. After 3 h, saturated aq. sodium carbonate (10 cm^3) was added, followed by water (10 cm^3), and the mixture was stirred vigorously for 10 min. This mixture was then extracted with chloroform (2 × 50 cm^3) and the combined organic extract dried over Na_2SO_4. Evaporation of the solvent gave an off-white solid which was chromatographed on silica (4% ethyl acetate in petroleum ether) to give **17** (13 mg, 32%) as a white solid, mp 364 °C (dec.) (Found C, 35.12; H, 2.59. $C_{36}H_{32}Br_8O_8$ requires C, 35.10; H, 2.62%); ν_{max}/cm^{-1} 2936, 2850, 1553, 1451, 1385, 1291, 1207, 1062, 1010 and 962; δ_H (400 MHz; $CDCl_3$) 4.32 (2 H, d, *J* 14 Hz, CH_2), 4.21 (2 H, d, *J* 14 Hz, CH_2), 4.03 (2 H, d, *J* 15 Hz, CH_2), 3.98 (2 H, d, *J* 15 Hz, CH_2), 3.92 (6 H, s, OMe), 3.90 (3 H, s, OMe), 3.78 (6 H, s, OMe), 3.61 (6 H, s, OMe) and 2.75 (3 H, s, OMe); δ_C (100 MHz; $CDCl_3$) 157.2, 155.8, 155.3, 150.1, 149.9, 149.6, 134.2, 133.6, 133.4, 131.7, 121.7, 121.0, 119.9, 117.7, 65.7, 63.5, 62.1, 60.4, 60.3, 60.1, 33.7 and 31.6.

4,6,10,12,16,18,22,24,28,30,34,36,40,42,46,48-Hexadecabromo-5,11,17,23,29,35,41,47,49,50,51, 52,53,54,55,56-hexadecamethoxycalix[8]arene 18

To a solution of **15** (200 mg, 0.166 mmol) in dichloromethane (3 cm^3) was added bromine (0.50 cm^3, 1.55 g, 9.7 mmol) and the reaction was heated at reflux under nitrogen for 20 h. Dichloromethane (30 cm^3) was added and the mixture was washed with 1 M aq. sodium thiosulfate and dried over $MgSO_4$. The solvent was evaporated and the residue preabsorbed onto silica gel and chromatographed (20% ethyl acetate in hexane) to give **18** (150 mg, 37%) as a white solid, mp 237–240 °C (dec.) (Found C, 35.41; H, 2.61. $C_{72}H_{64}Br_{16}O_{16}$ requires C, 35.10; H, 2.62%); ν_{max}/cm^{-1} 2933, 2850, 1453, 1386, 1305, 1067, 1014 and 944; δ_H (250 MHz; $CDCl_3$) 4.27 (2 H, br s, CH_2), 3.73 (3 H, br s, OMe) and 3.18 (3 H, br s, OMe); δ_C (68 MHz; $CDCl_3$) 154.8, 150.9, 133.4, 119.4, 61.3, 60.3 and 32.9.

5,11,17,23,25,26,27,28-Octapentoxycalix[4]arene 7

To sodium hydride (2.0 g, 60% in paraffin, 50 mmol), washed with hexane (3 × 20 cm^3) under nitrogen, was added a solution of octahydroxycalix[4]arene[14] (488 mg, 1.00 mmol) in THF (60 cm^3) and the mixture was stirred for 30 min. Excess 1-bromopentane (12.5 cm^3) was then added and the reaction heated at reflux for 20 h. On cooling, 1 M HCl (100 cm^3) was added and the aqueous phase was extracted with chloroform (2 × 50 cm^3). The combined organic layer was concentrated and the residue preabsorbed onto silica gel and chromatographed (1% ethyl acetate in petroleum ether). Recrystallisation of the resulting light yellow solid from isopropanol gave **7** as white crystals (100 mg, 10%), mp 141–142 °C (Found C, 77.74; H, 10.25. $C_{68}H_{104}O_8$ requires C, 77.82; H, 9.99%); ν_{max}/cm^{-1} 2955, 2932, 2859, 1600, 1466, 1388, 1218, 1155, 1060, 1021, 858 and 835; δ_H (400 MHz; $CDCl_3$) 6.57 (8 H, s, ArH), 3.85 (8 H, t, *J* 6.5 Hz, OCH_2), 3.64 (8 H, s, $ArCH_2$), 3.38 (8 H, t, *J* 7.4 Hz, OCH_2), 1.76 (8 H, m, CH_2), 1.40 (24 H, m, CH_2), 1.32 (8 H, m, CH_2), 1.21 (8 H, m, CH_2), 0.94 (24 H, m, CH_3); δ_C (68 MHz; $CDCl_3$) 153.4, 150.5, 134.3, 115.1, 71.4, 67.9, 37.8, 29.7, 29.4, 28.4, 28.2, 22.8, 22.6, 14.1 and 14.0; *m*/*z* (FAB) 1049 (84%, M + H).

49,50,51,52,53,54,55,56-Octapentoxycalix[8]arene 21

Sodium hydride (2.0 g, 60% in paraffin, 50 mmol), washed with hexane under nitrogen, was suspended in THF (50 cm^3) and a solution of 49,50,51,52,53,54,55,56-octahydroxycalix[8]arene[17] (3.00 g, 3.53 mmol) in DMF (5 cm^3) was added. The mixture was stirred for 30 min, excess 1-bromopentane (23.0 cm^3) was added, and the reaction heated at reflux for 2 d under nitrogen. The reaction mixture was concentrated and 2 M HCl (100 cm^3) was added. This mixture was extracted with chloroform (3 × 100 cm^3) and the combined organic layer dried over $MgSO_4$. Evaporation of the solvent gave a residue which was chromatographed on silica (1 : 1 dichloromethane in hexane) to give **21** (2.45 g, 49%) as a colourless oil (Found C, 82.00; H, 9.29. $C_{96}H_{128}O_8$ requires C, 81.77; H, 9.15%); ν_{max}/cm^{-1} 2956, 2932, 2869, 1590, 1454, 1381, 1246, 1203, 1084, 1048, 1006 and 765; δ_H (250 MHz; $CDCl_3$) 6.85 (24 H, m, ArH), 4.06 (16 H, s, $ArCH_2$), 3.66 (16 H, t, *J* 6.5 Hz, OCH_2), 1.69 (16 H, m, CH_2), 1.44–1.20 (32 H, m, CH_2) and 0.83 (24 H, t, *J* 7.1 Hz, CH_3); δ_C (68 MHz; $CDCl_3$) 155.4, 134.2, 128.8, 123.7, 73.4, 30.0, 29.7, 28.3, 22.6 and 14.0.

5,11,17,23,29,35,41,47-Octaacetyl-49,50,51,52,53,54,55,56-octapentoxycalix[8]arene 22

A mixture of aluminium chloride (480 mg, 3.60 mmol) and acetyl chloride (4.0 cm^3, 4.42 g, 58.5 mmol) in dry dichloromethane (7 cm^3) was added dropwise over 1 h to a solution of **21** (300 mg, 0.213 mmol) in dry dichloromethane (15 cm^3) at −78 °C under nitrogen. The reaction mixture was then brought up to −8 °C and stirred for 24 h. Chloroform (20 cm^3) was added, followed by the cautious addition of water (50 cm^3). The layers were separated and the aqueous extracted with dichloromethane (2 × 50 cm^3). The combined organic layer was dried over $MgSO_4$ and the solvent evaporated. The residue was chromatographed on silica (1 : 1 ethyl acetate in hexane) to give **22** (320 mg, 86%) as a white solid, mp 255–257 °C (Found C, 76.83; H, 8.45. $C_{112}H_{144}O_{16}$ requires C, 77.03; H, 8.31%); ν_{max}/cm^{-1} 2956, 2932, 2871, 1682, 1597, 1463, 1421, 1357, 1298, 1177, 1092, 980 and 757; δ_H (250 MHz; $CDCl_3$) 7.51 (16 H, s, ArH), 4.06 (16 H, s, $ArCH_2$), 3.71 (16 H, t, *J* 6.5 Hz, OCH_2), 2.25 (24 H, s, $COCH_3$), 1.75–1.55 (16 H, m, CH_2), 1.35–1.15 (32

H, m, CH_2) and 0.77 (24 H, t, *J* 7.0 Hz, CH_3); δ_C ($CDCl_3$) 196.7, 159.7, 133.9, 133.0, 129.6, 73.7, 30.4, 29.8, 28.1, 26.2, 22.4 and 13.9.

5,11,17,23,29,35,41,47-Octaacetoxy-49,50,51,52,53,54,55,56-octapentoxycalix[8]arene 23

A solution of **22** (300 mg, 0.172 mmol) and *m*-chloroperbenzoic acid (50–60%, 3.0 g, 8.7–10.4 mmol) in chloroform (30 cm^3) was left standing at 4 °C for 21 d. The reaction mixture was diluted with chloroform (70 cm^3), washed with a 1 : 1 mixture of 1 M aq. sodium sulfite and 0.33 M N pH 7 phosphate buffer (3 × 100 cm^3). After drying over $MgSO_4$ the solvent was evaporated and the residue was chromatographed on silica (0–2% methanol in chloroform) to give **23** (260 mg, 81%) as a white solid, mp 163–165 °C (Found C, 71.76; H, 7.95. $C_{112}H_{144}O_{24}$ requires C, 71.77; H, 7.74%); ν_{max}/cm^{-1} 2956, 2933, 2870, 1767, 1596, 1460, 1369, 1195, 1023, 906 and 757; δ_H (270 MHz; $CDCl_3$) 6.59 (16 H, m, ArH), 3.97 (16 H, s, $ArCH_2$), 3.64 (16 H, t, *J* 6.4 Hz, OCH_2), 2.08 (24 H, s, $COCH_3$), 1.65 (16 H, m, CH_2), 1.28 (32 H, m, CH_2) and 0.82 (24 H, t, *J* 7.2 Hz, CH_3); δ_C (68 MHz; $CDCl_3$) 169.5, 153.0, 146.2, 134.8, 121.7, 73.7, 29.8, 28.1, 22.5, 20.9 and 13.9.

5,11,17,23,29,35,41,47-Octahydroxy-49,50,51,52,53,54,55,56-octapentoxycalix[8]arene 24

A solution of **23** (1.15 g, 0.614 mmol) and sodium hydroxide (2.6 g, 65 mmol) in methanol (130 cm^3) was stirred at room temperature for 2 h. The reaction mixture was concentrated and 2 M HCl (50 cm^3) was added. The resulting precipitate was filtered and washed with water. The crude product was chromatographed (2 : 3 hexane in ethyl acetate) to give **24** (820 mg, 87%) as a white solid, the data for which (δ_H, δ_C) were in agreement with published values.[13]

5,11,17,23,29,35,41,47,49,50,51,52,53,54,55,56-Hexadecapentoxycalix[8]arene 16

To sodium hydride (300 mg, 60% in paraffin, 7.50 mmol), washed with hexane (3 × 20 cm^3) under nitrogen, was added a solution of **24** (200 mg, 0.13 mmol) in THF (15 cm^3) and the mixture was stirred for 30 min. Excess 1-bromopentane (1.6 cm^3) was then added and the reaction heated at reflux for 40 h. On cooling, 1 M HCl (20 cm^3) was added and the aqueous phase was extracted with chloroform (2 × 50 cm^3). The combined organic layer was concentrated and the residue preabsorbed onto silica gel and chromatographed (0.5% ethyl acetate in petroleum ether). Crystallisation from isopropanol gave **16** as a white solid (100 mg, 37%), mp 112–114 °C; ν_{max} /cm^{-1} 2957, 2932, 2871, 1603, 1589, 1463, 1381, 1328, 1204, 1147 and 1055; δ_H (400 MHz; $CDCl_3$) 6.47 (16 H, s, ArH), 3.95 (16 H, s, $ArCH_2$), 3.67 (16 H, t, *J* 6.4 Hz, OCH_2), 3.58 (16 H, t, *J* 6.2 Hz, OCH_2), 1.60 (32 H, m, CH_2), 1.4–1.2 (64 H, m, CH_2) and 0.85 (48 H, m, CH_3); δ_C (100 MHz, $CDCl_3$) 154.8, 149.1, 134.8, 114.5, 73.5, 67.8, 30.2, 30.0, 29.0, 28.3, 28.2, 22.6, 22.5 and 13.9.

4,6,10,12,16,18,22,24-Octabromo-5,11,17,23,25,26,27,28-octapentoxycalix[4]arene 19

A solution of **7** (25 mg, 0.024 mmol) in chloroform (0.5 cm^3) was added to 2 M HNO_3 (1 cm^3). The two-phase mixture was vigorously stirred while bromine (66.7 μl, 207 mg, 1.29 mmol) was added, followed by the addition of 22% $AgNO_3$ in 2 M HNO_3 (100 μl, 0.13 mmol). After 60 h the aqueous phase was extracted with chloroform (2 × 50 cm^3) and the combined organic layer concentrated. The residue was preabsorbed onto silica gel and chromatographed (0.5% ethyl acetate in petroleum ether). Recrystallisation of the resulting yellow solid from isopropanol gave **19** (27 mg, 67%) as an off-white solid, mp 164–165 °C (Found C, 48.32; H, 5.92. $C_{68}H_{96}Br_8O_8$ requires C, 48.59; H, 5.76%); ν_{max}/cm^{-1} 2955, 2870, 1552, 1466, 1423, 1377, 1295, 1205, 1075 and 1008; δ_H (400 MHz; $CDCl_3$) 4.42 (8 H, s, $ArCH_2$), 3.93 (8 H, t, OCH_2), 3.43 (8 H, t, OCH_2), 1.88 (8 H, m, CH_2), 1.44 (16 H, m, CH_2), 1.11 (16 H, m, CH_2), 0.94 (12 H, t, CH_3), 0.85 (12 H, t, CH_3) and 0.80 (8 H, m, CH_2); δ_C (68 MHz; $CDCl_3$) 152.8, 149.1, 132.7, 118.0, 72.3, 70.7, 36.3, 29.6, 29.0, 28.0, 27.6, 22.9, 22.6, 14.3 and 14.0.

4,6,10,12,16,18,22,24,28,30,34,36,40,42,46,48-Hexadecabromo-5,11,17,23,29,35,41,47,49,50,51,52,53,54,55,56-hexadecapentoxycalix[8]arene 20

To a solution of **16** (39 mg, 0.019 mmol) in dichloromethane (0.5 cm^3) was added bromine (31 μl, 96 mg, 0.60 mmol) and the reaction was heated at reflux under nitrogen for 20 h. The solvent and excess bromine were evaporated and the residue preabsorbed onto silica gel chromatographed (0.5% ethyl acetate in petroleum ether) to give **20** as a light yellow resin (32 mg, 51%) (Found C, 48.45; H, 5.69. $C_{136}H_{192}Br_{16}O_{16}$ requires C, 48.59; H, 5.76%); ν_{max}/cm^{-1} 2956, 2931, 2871, 1586, 1449, 1419, 1373, 1229, 1078 and 1002; δ_H (400 MHz; $Cl_2DCCDCl_2$, 120 °C) 4.40 (16 H, s, $ArCH_2$), 3.95 (16 H, m, OCH_2), 3.80 (16 H, m, OCH_2), 1.86 (16 H, m, CH_2), 1.64 (16 H, br, CH_2), 1.50 (32 H, m, CH_2), 1.44 (32 H, m, CH_2), 0.96 (24 H, t, CH_3) and 0.87 (24 H, br m, CH_3).

Crystal data for 6‡

Single crystals by slow evaporation from 5% ethyl acetate in light petroleum; $C_{36}H_{40}O_8$, $M = 600.71$, orthorhombic, $a = 11.8738(5)$, $b = 14.3436(6)$, $c = 17.840(4)$ Å, $V = 3038.3(7)$ $Å^3$, $T = 120$ K, space group *Pbcn* (no. 60), $Z = 4$, μ(Mo-Kα) = 0.092 mm^{-1}. 11635 data were collected on a FAST TV area detector diffractometer and merged to give 2448 unique ($R_{int} = 0.0548$). The structure was solved using direct methods and refined on F_o^2 by full matrix least squares using all unique data corrected for Lorentz and polarisation factors. Final R_1 (on *F*) and wR_2 (on F_o^2) values were 0.0775 and 0.0707 for all 2448 data and 279 parameters. The corresponding *R*-values were 0.0329 and 0.0663 for 1474 data with $I > 2\sigma(I)$.

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References

1 K. E. Drexler, *Nanosystems*, *Molecular Machinery*, *Manufacturing and Computation*, Wiley, Chichester, 1992.
2 For example: *p*-carboranes (X. Yang, W. Jiang, C. B. Knobler and M. F. Hawthorne, *J. Am. Chem. Soc.*, 1992, **114**, 9719; J. Müller, K. Base, T. F. Magnera and J. Michl, *J. Am. Chem. Soc.*, 1992, **114**, 9721); cubanes (P. E. Eaton, E. Galoppini and R. Gilardi, *J. Am. Chem. Soc.*, 1994, **116**, 7588); and bicyclo[1.1.1]pentanes (P. Kaszynsky, A. C. Friedli and J. Michl, *J. Am. Chem. Soc.*, 1992, **114**, 601).
3 D. J. Cram, *Science*, 1983, **219**, 1177; *Host–Guest Complex Chemistry/Macrocycles*, eds. F. Vögtle and E. Weber, Springer-Verlag, Berlin, 1985; L. F. Lindoy, *The Chemistry of Macrocyclic Ligands*, Cambridge University Press, Cambridge, 1989; D. J. Cram and J. M. Cram, *Container Molecules and Their Guests*, Royal Society of Chemistry, Cambridge, 1994.
4 For a review, see: A. Ikeda and S. Shinkai, *Chem. Rev.*, 1997, **97**, 1713.
5 J. L. Ballard, W. B. Kay and E. L. Kropa, *J. Paint Technol.*, 1966, **38**, 251.
6 F. Bottino, G. Montaudo and P. Maravigna, *Ann. Chim.* (*Rome*), 1967, **57**, 972.
7 S. Pappalardo, G. Ferguson and J. F. Gallagher, *J. Org. Chem.*, 1992, **57**, 7102.
8 R. Schätz, C. Weber, G. Schilling, T. Oeser, U. Huber-Patz, H. Irngartinger, C.-W. von der Lieth and R. Pipkorn, *Liebigs Ann.*, 1995, 1401.
9 P. Timmerman, K. G. A. Nierop, E. A. Brinks, W. Verboom, F. C. J. M. Vanveggel, W. P. Vanhoorn and D. N. Reinhoudt, *Chem. Eur. J.*, 1995, **1**, 132.
10 M. Mascal, R. T. Naven and R. Warmuth, *Tetrahedron Lett.*, 1995, **51**, 9361.

11 MM2* force field in *MACROMODEL v 5.5*: F. Mohamadi, N. G. J. Richards, W. C. Guida, R. Liskamp, M. Lipton, C. Caufield, G. Chang, T. Hendrickson and W. C. Still, *J. Comp. Chem.*, 1990, **11**, 440.
12 T. B. Patrick and P. A. Egan, *J. Org. Chem.*, 1977, **42**, 382.
13 A. Casnati, R. Ferdani, A. Pochini and R. Ungaro, *J. Org. Chem.*, 1997, **62**, 6236.
14 Y. Morita, T. Agawa, Y. Kai, N. Kanehisa, N. Kasai, E. Nomura and H. Taniguchi, *Chem. Lett.*, 1989, 1349; Y. Morita and T. Agawa, *J. Org. Chem.*, 1992, **57**, 3658.
15 P. A. Reddy, R. P. Kashyap, W. H. Watson and C. D. Gutsche, *Israel J. Chem.*, 1992, **32**, 89.
16 U. Morita, Jap P 02 15,040/1990 (*Chem. Abstr.*, 1990, **113**, 114845); Y. Morita, Jap P 03 120,236/1991 (*Chem. Abstr.*, 1992, **116**, 58956).
17 C. D. Gutsche and L.-G. Lin, *Tetrahedron*, 1986, **42**, 1633.
18 X. Delaigue and M. W. Hosseini, *Tetrahedron Lett.*, 1993, **34**, 8111.
19 K. Iwamoto, K. Araki and S. Shinkai, *J. Org. Chem.*, 1991, **56**, 4955.
20 A. Ikeda and S. Shinkai, *J. Chem. Soc.*, *Chem. Commun.*, 1994, 2375.
21 O. Ermer, *Helv. Chim. Acta*, 1991, **74**, 1330; O. Ermer and C. Röbke, *J. Am. Chem. Soc.*, 1993, **115**, 10077.
22 R. Williams and J. W. Verhoeven, *Recl. Trav. Chim. Pays-Bas*, 1992, **111**, 531; T. Suzuki, K. Nakashima and S. Shinkai, *Chem. Lett.*, 1994, 699; J. L. Atwood, G. A. Koutsantonis and C. A. Raston, *Nature*, 1994, **368**, 229.

Paper 9/06442G