

## Calixarene-bound dendritic macromolecules

George Ferguson,<sup>a</sup> John F. Gallagher,<sup>a</sup> M. Anthony McKervey<sup>b</sup> and Evelyn Madigan<sup>b</sup>

<sup>a</sup> Department of Chemistry and Biochemistry, University of Guelph, Guelph, Ontario, Canada N1G 2W1

<sup>b</sup> School of Chemistry, The Queen's University, Belfast BT9 5AG, UK

Calixarenes have been used as polyfunctional core molecules to construct several dendritic polyether macromolecules based on 3,5-dihydroxybenzyl building blocks.

The convergent growth approach to macromolecules with dendritic architecture<sup>1</sup> has been elegantly exploited by Frechet and co-workers<sup>2</sup> to produce collections of hyperbranched speciality compounds with properties that can differ significantly from those of linear polymers. Frechet's approach employs 3,5-dihydroxybenzyl alcohol as the building block to construct large dendritic groups or wedges, the final step being the attachment of several of these wedges to a polyfunctional core whose shape and symmetry can influence the overall molecular architecture. By variation on this general theme, both the number and location of branch ends (functional groups) at the periphery of the macrocycle can be controlled to produce a variety of functionalised dendrimers. Some of the compounds, e.g. those with carboxylate branch ends, function as unimolecular micelles with an ability to solvate hydrophobic guest molecules comparable to that of conventional multimolecular micelles.<sup>3</sup> Calixarenes<sup>4</sup> are attractive candidates for polyfunctional cores in dendritic molecules. Not only do these macrocyclic phenols have numerous sites for attaching dendritic wedges, but they possess conformations that can be fixed in distinctly different architectures through appropriate substitution.<sup>4</sup> A calix[4]arene, for example, acting as a dendritic core, is capable of producing four dendritic macromolecules depending on whether the core is fixed in the cone, partial cone, 1,2-alternate or 1,3-alternate conformation. The only previous example of a dendritic calixarene is that of Newkome *et al.*<sup>5</sup> who attached nine primary hydroxy functions *via* three amide bonds to a calix[4]arene to form a water soluble derivative. We now report preliminary attempts to use the lower rim of calix[4]- and -[5]-arenes as polyfunctional cores of a new series of dendrimers.

Polyether wedges **1**, **2** and **3** were prepared according to Frechet's procedures.<sup>2b</sup> Exposure of *p*-*tert*-butylcalix[4]arene **4** to bromide **1** in THF–DMF with sodium hydride as base afforded the fully substituted derivative **5**, mp 52–54 °C in 28% yield. The <sup>1</sup>H NMR spectrum of **5** revealed that the molecule possesses the cone conformation in solution, *i.e.* it does have tree-like architecture. This was confirmed by X-ray diffraction which revealed a distorted cone conformation (Fig. 1) with two opposite core aromatic rings A and C almost normal to each other [interplanar angle 93.5(1)°] with their two counterparts (B and D) almost parallel to each other [interplanar angle 2.3(1)°]. The conformation of the core of **5** is defined by the angles which the core aromatic rings make with the plane of the four adjoining methylene groups, *viz.* 135.1(1)° (A), 92.1(1)° (B), 138.4° (C) and 90.0° (D). The three aromatic rings of each of the four pendant dendryl groups adopt 'random' orientations, presumably due to crystal packing forces. Three of these dendryls are positioned above the calixarene core with the fourth overhanging the core. To extend this first generation dendrimer synthesis to larger calixarenes *p*-*tert*-butylcalix-

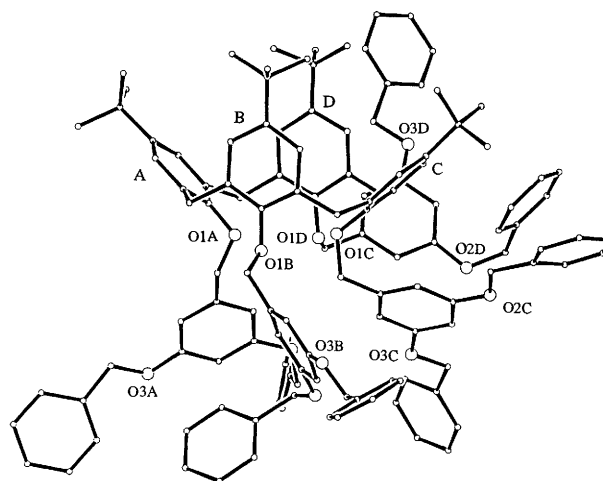
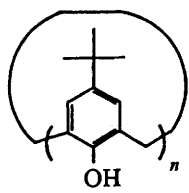


Fig. 1 A view of **5** showing the solid-state conformation; where there is *tert*-butyl or phenyl disorder, only one of the components is shown. H atoms are omitted.

[5]arene **6** was exposed to bromide **1** (NaH in THF–DMF) to afford pentamer derivative **7**, mp 55.5–57.5 °C in 30% yield; again, the cone conformation was easily confirmed by the <sup>1</sup>H NMR data.

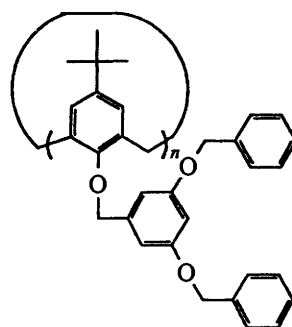
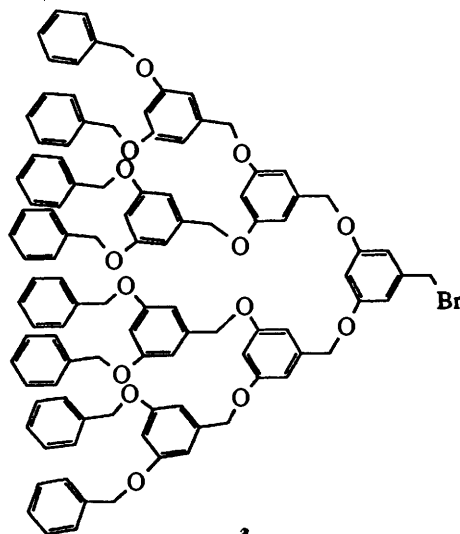
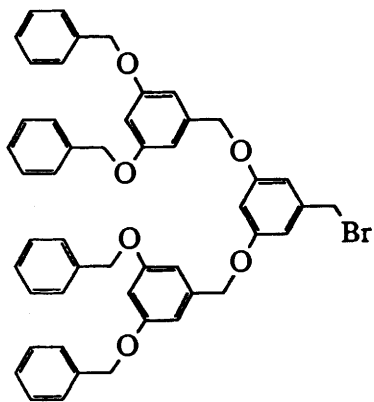
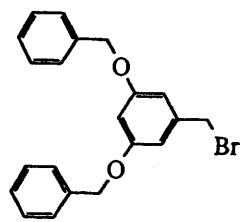
The availability of dendritic wedges **2** and **3** enabled us to extend the synthesis to second and third generation dendrimers. Bromide **2** with NaH in THF–DMF was used to produce second generation derivatives **8** (19%) and **9** (40%) from **4** and **6**, respectively. Both **8** and **9** were isolated as low melting solids and their spectra features were fully consistent with cone conformations. To complete the fully substituted series third generation derivatives **10** (21%) and **11** (22%) were similarly produced from bromide **3**.

It is also possible to prepare incompletely substituted dendritic calixarenes through varying the reaction conditions. Thus, when the reaction of bromide **1** with tetramer **4** was conducted in acetone with potassium carbonate as base, the major product (68%) was the 1,3-disubstituted (distal) derivative **12**, mp 83.5–84.5 °C, in the cone conformation. Similarly, bromide **2** and tetramer **4** produced 1,3-disubstituted product **13** (22%). Preliminary work in the tetramer series on the formation of 1,3-disubstituted dendrimers with functionalised branch ends has shown that bromides **14**<sup>3</sup> and **15**<sup>3</sup> produced **16** (63%), mp 109–110 °C, and **17** (40%), mp 103–104 °C, respectively, when treated with tetramer **4** in acetone containing potassium carbonate. Hydrolysis of **16** and **17** with sodium hydroxide in a mixture of THF, water and methanol furnished water-soluble sodium salts of carboxylic acids **18** and **19**. Not only do these 1,3-distal derivatives allow access to mixed dendritic derivatives through substitution, but functionalised derivatives such as **16** and **17** can be used as precursors for fully substituted dendrimers with different kinds of branch ends.



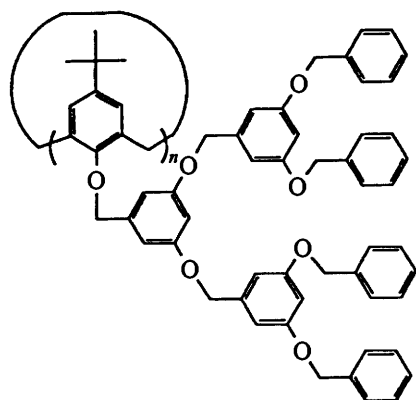
4  $n=4$

6  $n=5$



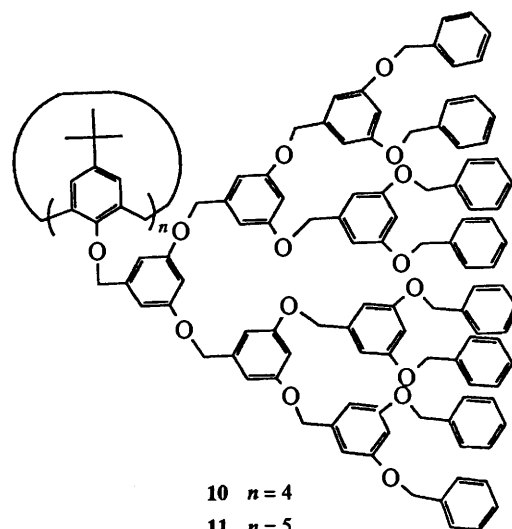
5  $n=4$

7  $n=5$



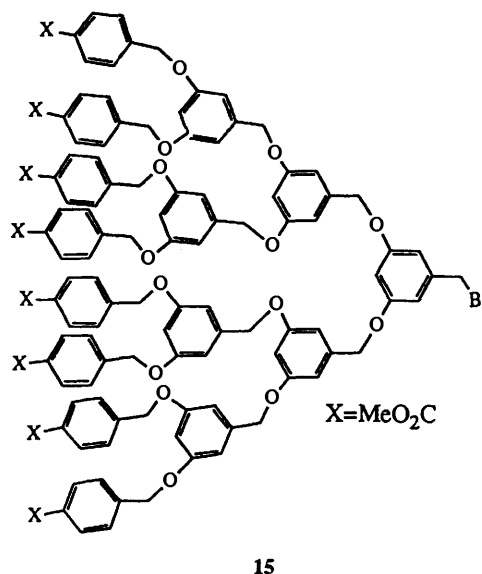
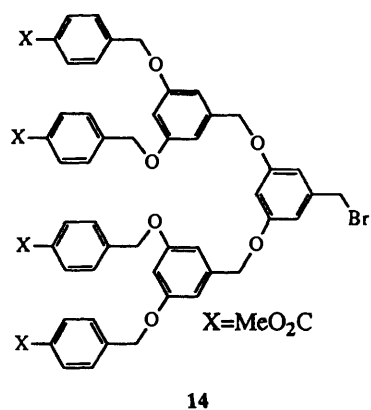
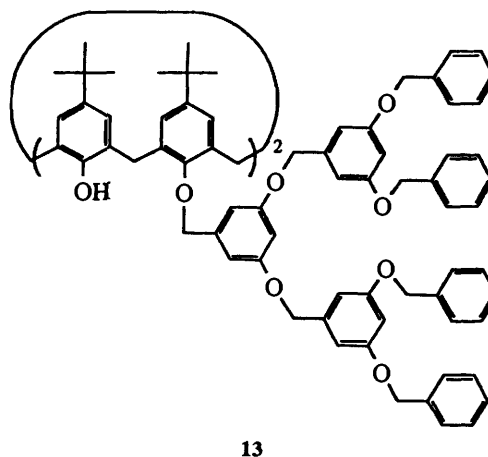
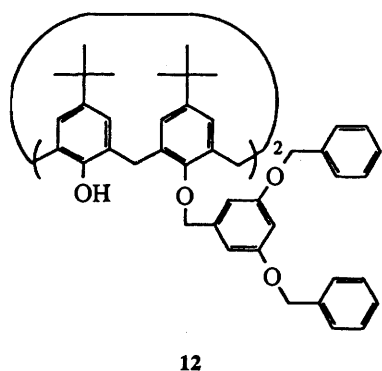
8  $n=4$

9  $n=5$



10  $n=4$

11  $n=5$



## Experimental

### Crystal data for 5

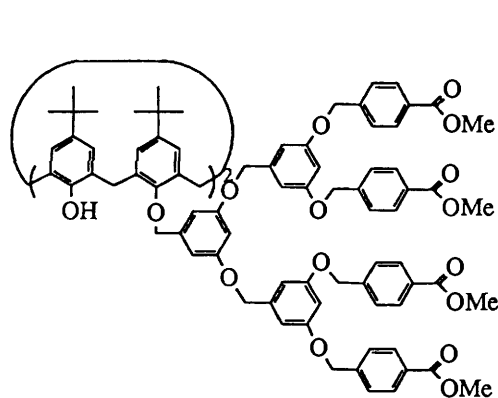
$C_{128}H_{128}O_{12}$ ,  $M_r = 1858.4$ , a block-shaped colourless crystal was used ( $0.35 \times 0.30 \times 0.15$  mm), triclinic, space group  $P\bar{1}$ , with  $a = 16.464(1)$ ,  $b = 17.850(2)$ ,  $c = 19.178(2)$  Å,  $\alpha = 96.447(9)$ ,  $\beta = 94.725(8)$ ,  $\gamma = 96.343(9)^\circ$ ,  $V = 5540(1)$  Å<sup>3</sup>,  $Z = 2$ ,  $D_c = 1.11$  g cm<sup>-3</sup>; CAD4 diffractometer using the  $\omega$ - $2\theta$  mode, 10 287 unique reflections, only 2751 with  $I > 2.0\sigma(I)$ ,  $2\theta_{max} = 40^\circ$ , Mo-K $\alpha$  ( $\lambda = 0.7093$  Å) radiation,  $T = 21$  °C. Data corrected for Lorentz and polarisation effects. The structure was solved by direct methods (SHELXS86)<sup>6</sup> and refined initially with NRCVAX<sup>7</sup> and finally with SHELXL-93<sup>8</sup> using all data (as  $F^2$ ) to an  $R$  value of 0.090,  $R_w(F^2)$  0.21. All aromatic rings were constrained to be planar hexagons (C-C 1.39 Å). Condensed explanation of disorder: The analysis was complicated by disorder of various parts of the molecule. The *tert*-butyl methyl carbons on C8A and C8C are disordered over two distinct orientations [occupancies 0.50 (atoms C9A-C11A) and 0.50 (atoms C9Z-C11Z) for the atoms bonded to C8A, and 0.67 (atoms C9C-C11C) and 0.33 (atoms C9Y-C11Y) for those bonded to C8C). One of the terminal phenyl rings (atoms C31D-C36D) was also disordered over two orientations [with 0.57 (atoms C31D-C36D) and 0.43 (atoms C32X-C36X) occupancies]. During the refinement, all aromatic rings were constrained to be regular hexagons (with C-C 1.39 Å) and the *tert*-butyl groups were required to have regular tetrahedral geometry by use of appropriate DFIX instructions in the SHELXL-93 refinement runs. Despite these difficulties, the analysis clearly established the connectivity and gross stereochemical features of 1. Fig. 1 was prepared with

PLUTON-95.<sup>9</sup> Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/1. Copies of the structure factor listing the complete crystallographic material in CIF format are available from the authors.

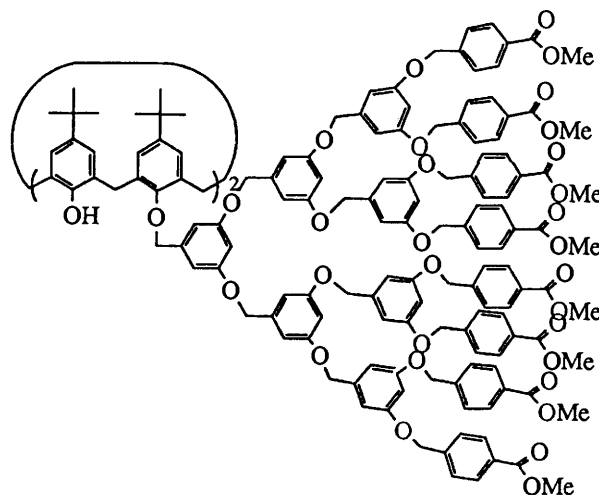
**Selected spectroscopic and analytical data for 5.**  $\delta_H$ (CDCl<sub>3</sub>, 500 MHz) 1.05 [36 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 2.78 (4 H, d,  $J$  12.8, ArCH<sub>2</sub>Ar), † 4.12 (4 H, d,  $J$  12.8, ArCH<sub>2</sub>Ar), 4.73 (16 H, s, CH<sub>2</sub>O), 4.99 (8 H, s, CH<sub>2</sub>O), 6.47 (4 H, t,  $J$  2.0, ArH), 6.57 (8 H, d,  $J$  2.0, ArH), 6.69 (8 H, s, ArH) and 7.22 (40 H, s, PhH);  $\delta_C$ (CDCl<sub>3</sub>, 125 MHz) 31.4 [C(CH<sub>3</sub>)<sub>3</sub>], 31.9 (ArCH<sub>2</sub>Ar), 33.8 [C(CH<sub>3</sub>)<sub>3</sub>], 69.8 (CH<sub>2</sub>O), 76.2 (CH<sub>2</sub>O), 101.5, 108.7, 124.8, 127.5, 127.7, 138.3, 134.0, 136.9, 140.5, 144.4, 152.5 and 159.4 (Ar) (Found: C, 81.0; H, 6.8.  $C_{128}H_{128}O_{12} \cdot EtOAc$  requires C, 81.5; H, 7.0%).

**Selected spectroscopic and analytical data for 10.**  $\delta_H$ (CDCl<sub>3</sub>, 500 MHz) 0.99 [36 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 2.90 (4 H, d,  $J$  13.2, ArCH<sub>2</sub>Ar), 4.31 (4 H, d,  $J$  13.2, ArCH<sub>2</sub>Ar), 4.61 (16 H, s, CH<sub>2</sub>O), 4.65 (32 H, s, CH<sub>2</sub>O), 4.81 (72 H, s, CH<sub>2</sub>O), 6.32 (8 H, m, ArH), 6.38 (16 H, m, ArH), 6.48 (52 H, m, ArH), 6.56 (8 H, s, ArH), 6.80 (8 H, s, ArH), 7.16-7.30 (160 H, m, PhH);  $\delta_C$ (CDCl<sub>3</sub>, 125 MHz) 29.7 [C(CH<sub>3</sub>)<sub>3</sub>], 31.5 [C(CH<sub>3</sub>)<sub>3</sub>], 33.8 (ArCH<sub>2</sub>Ar), 69.7 (CH<sub>2</sub>O), 69.9 (CH<sub>2</sub>O), 69.9 (CH<sub>2</sub>O), 70.1 (CH<sub>2</sub>O), 101.5, 101.8, 106.4, 108.6, 124.9, 127.5, 127.8, 128.0,

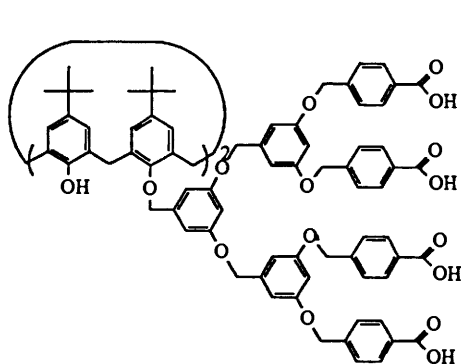
†  $J$  Values in Hz.



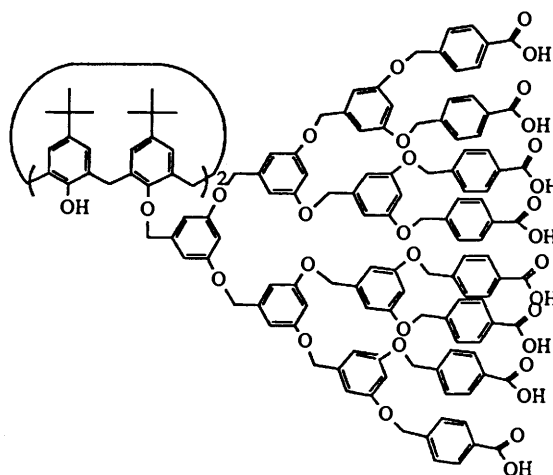
16



17



18



19

128.0, 128.5, 134.0, 136.8, 139.2, 139.3, 140.7, 144.5, 152.6, 159.5, 159.9 and 160.0 (ArC) (Found: C, 78.2; H, 6.2.  $C_{464}H_{416}O_{60} \cdot 2CH_2Cl_2$  requires C, 78.6; H, 5.9%).

**Selected spectroscopic and analytical data for 17.**  $\nu_{max}$  (KBr/ $cm^{-1}$ ) 3424 and 1721;  $\delta_H$  (CDCl<sub>3</sub>, 500 MHz) 0.94 [18 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 1.27 [18 H, s, C(CH<sub>3</sub>)<sub>3</sub>], 3.32 (4 H, d, *J* 12.7, ArCH<sub>2</sub>Ar), 3.86 (48 H, s, OCH<sub>3</sub>), 4.35 (4 H, d, *J* 12.7, ArCH<sub>2</sub>Ar), 4.63 (8 H, s, CH<sub>2</sub>O), 4.74 (16 H, s, CH<sub>2</sub>O), 4.87 (32 H, s, CH<sub>2</sub>O), 4.92 (4 H, s, CH<sub>2</sub>O), 6.38 (4 H, t, *J* 2.0, ArH), 6.42 (8 H, t, *J* 2.0, ArH), 6.51 (2 H, t, *J* 2.0, ArH), 6.53 (8 H, d, *J* 2.0, ArH), 6.56 (16 H, d, *J* 2.0, ArH), 6.82 (4 H, s, ArH), 6.96 (4 H, d, *J* 2.0, ArH), 7.07 (4 H, s, ArH), 7.34 (8 H, d, *J* 8.3, ArH), 7.50 (2 H, s, OH) and 7.94 (8 H, d, *J* 8.3, ArH);  $\delta_C$  (CDCl<sub>3</sub>, 125 MHz) 30.9 [C(CH<sub>3</sub>)<sub>3</sub>], 31.2 [C(CH<sub>3</sub>)<sub>3</sub>], 31.4 [C(CH<sub>3</sub>)<sub>3</sub>], 31.6 (ArCH<sub>2</sub>Ar), 31.6 [C(CH<sub>3</sub>)<sub>3</sub>], 52.1 (OCH<sub>3</sub>), 69.1 (OCH<sub>3</sub>), 69.3 (OCH<sub>3</sub>), 69.5 (OCH<sub>3</sub>), 77.8 (OCH<sub>3</sub>), 101.3, 101.4, 104.7, 106.1, 106.3, 106.4, 125.1, 125.6, 126.8, 126.9, 127.7, 129.5, 129.6, 129.7, 132.4, 139.4, 139.6, 141.8, 147.3, 149.6, 153.0, 159.6, 159.7, 160.0 (ArC) and 166.7 (CO) (Found: C, 72.4; H, 5.6.  $C_{286}H_{268}O_{64}$  requires C, 72.6; H, 5.7%).

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### References

1 For useful background references see D. A. Tomalia, A. M. Naylor and W. A. Goddard, III, *Angew. Chem. Int., Ed. Engl.*, 1990, **29**, 118;

D. A. Tomalia, H. Baker, J. Dewald, M. Hall, G. Kalbos, S. Martin, J. Roeck, J. Ryder and P. Smith, *Polymer J.*, 1985, **17**, 117; G. R. Newkome, Z. Yao, G. R. Baker and V. K. Gupta, *J. Org. Chem.*, 1985, **50**, 2003; E. M. M. de Brabander-van Den Berg and E. W. Meijer, *Angew. Chem., Int. Ed. Engl.*, 1993, **32**, 1308.

- (a) C. J. Hawker and J. M. J. Frechet, *J. Chem. Soc., Chem. Commun.*, 1990, 1010; (b) K. L. Wooley, C. J. Hawker and J. M. J. Frechet, *J. Chem. Soc., Perkin Trans. 1*, 1991, 1059; (c) R. Spindler and J. M. J. Frechet, *J. Chem. Soc., Perkin Trans. 1*, 1993, 913.
- C. J. Hawker, K. L. Wooley and J. M. J. Frechet, *J. Chem. Soc., Perkin Trans. 1*, 1993, 1287.
- C. D. Gutsche, *Calixarenes*, in *Monographs in Supramolecular Chemistry*, ed. J. F. Stoddart, Royal Society of Chemistry, 1989, vol. 1; V. Böhmer and J. Vicens, eds., *Topics in Inclusion Phenomena, Calixarenes a Versatile Class of Macrocyclic Compounds*, Kluwer Academic Publishers, 1990.
- G. R. Newkome, Y. Hu, M. J. Saunders and F. R. Fronczek, *Tetrahedron Lett.*, 1991, **32**, 1133.
- G. M. Sheldrick, SHELXS86. Crystallographic computing 3, G. M. Sheldrick, C. Kruger and R. Goddard, Oxford University Press, London, 1986, pp. 175–179.
- E. J. Gabe, Y. LePage, J. P. Charland, F. L. Lee and P. S. White, *J. Appl. Cryst.*, 1989, **22**, 384.
- G. M. Sheldrick, SHELXL-93, Program for the refinement of crystal structures, University of Göttingen, Germany.
- A. L. Spek, PLUTON-95, Molecular graphics program, University of Utrecht, The Netherlands.

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