Approaches to polymetallated calixarene derivatives

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Abstract

Tetrabrominated calix[4]arene analogue **4** was subjected to lithium-halogen exchange with *tert*-butyl lithium to give a tetra-lithium salt which could be silylated with chlorotrimethylsilane to give tetrasilylated derivative **5** and the trisilylated analogue **6**. However, attempts to use boron electrophiles resulted in only partial boronation. Attempts to brominate calix[6]arene **12** proved surprisingly difficult, which prevented the isolation of **13** and hence generation of the corresponding hexa-lithium salt. Bromination of calix[8]arene **14b** was possible and the octa-lithium salt was generated by lithium-halogen exchange of **15** with *tert*-butyl lithium. Subsequent reaction with chlorotrimethylsilane though, only resulted in partial silylation to give **16**.

**Keywords:** Calixarene, metallation, silylation, boronation

Introduction

Calixarenes[1], the cyclic products of the condensation of molecules such as *para*-substituted phenol and formaldehyde, represent a class of receptor which is readily available in varying ring sizes, particularly **1a-c**. These receptors have been widely used for ligating cations and neutral organic molecules in solution, due to: (i) their ease of access *via* simple one-pot processes; (ii) their formation of well defined stable cyclic derivatives possessing varying cavity sizes suitable for binding different guests; (iii) their ease of chemical modification, and functionalisation. However, the synthesis of anion binding derivatives of benzenoid calixarenes has been much less studied[2], with no reported examples of calixarenes containing Lewis-acid metals directly attached to the benzene rings. The only examples of the construction of calixarene-based Lewis-acidic receptors have relied upon attaching the metals to the oxygen moieties of calixarenes such as **1a**[3], for example bis-tetraalkoxy silanes[3a] which can act as anion or Lewis-base acceptors.

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Poly-Lewis-acidic receptors[4] have been applied as selective binding agents for various Lewis-basic systems, such as carbonyl groups[5] and anions[6] and have even been recently used as Diels-Alder catalysts[7]. However, systems containing four[5c] or more Lewis-acidic groups are extremely rare, despite the fact that it has been shown that the four mercury atoms of a [12]mercuracarborand can behave cooperatively to bind chloride ion[6m].

1

a; n = 1
b; n = 3
c; n = 5

2

**a**; n = 1
b; n = 3
c; n = 5
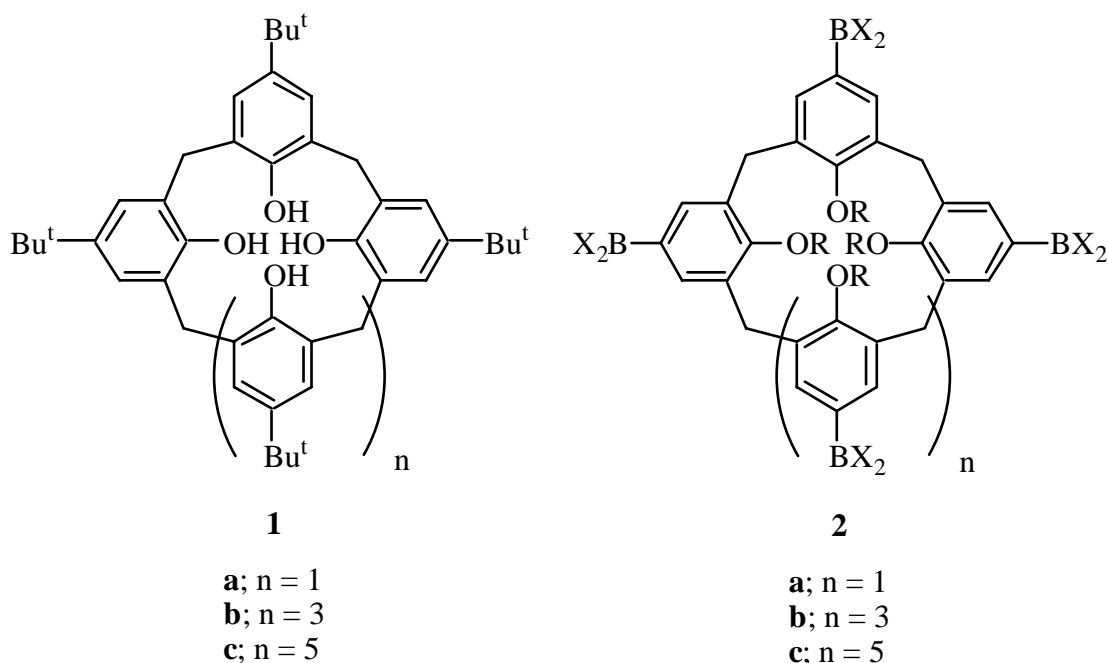
We became interested in developing new poly-Lewis-acid based receptors containing four, six and eight Lewis-acid functions and viewed calixarenes as suitable relatively rigid frameworks for the attachment of multiple metals, for example structures **2**, with the expectation that such systems would behave cooperatively to bind anions as shown schematically by **Figure 1**. In this paper we report our approaches to the synthesis of polymetal-substituted calixarenes, using silicon to demonstrate the methods for poly-metal attachment.
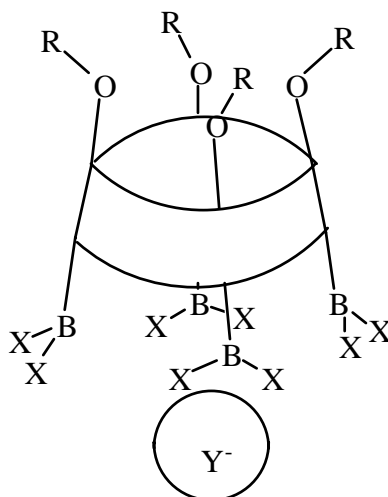
Figure 1. Schematic diagram of the binding of an anion to calixarene derivative **2a**.

Results and Discussion

The possibility of incorporating silicon, with a view to attaching Lewis-acidic atoms such as boron, onto the benzene rings of calixarenes was initially explored using the calix[4]arene ring system **1a** since it possesses both minimal functionality and conformational flexibility[1,8]. Calixarene **1a**[9] was therefore subjected to removal of the *tert*-butyl groups, followed by O-methylation[9] and bromination[10] using similar methods to those reported in the literature. Thus, calixarene **1a** was converted into compound **4** as shown in **Scheme 1**.
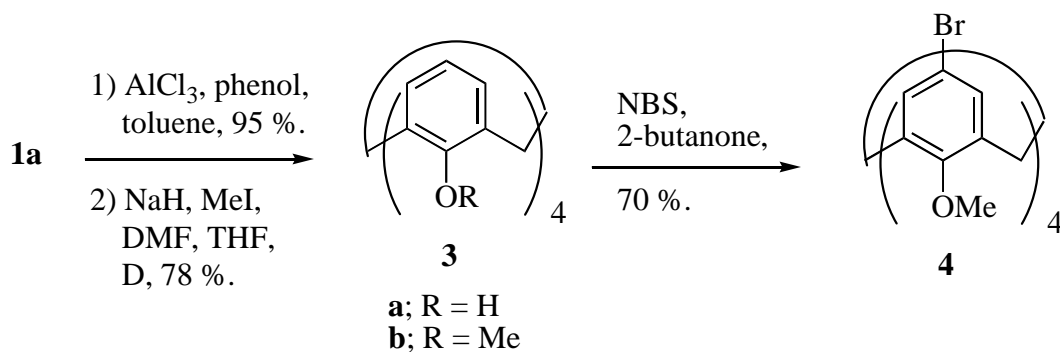
Scheme 1. De-*tert*-butylation bromination on the calix[4[arene.

After obtaining **4**, it was possible to examine different methods for obtaining the tetra(trimethylsilylated)calix[4]arenes **5**. After much experimentation, it was found that the lithiation of **4** was possible, but only by using an excess of *tert*-butyllithium (3 equivalents per bromine), followed by silylation with excess chlorotrimethylsilane (**Equation 1**). Silica gel

chromatography gave two compounds with similar mobility, which could be separated by fractional recrystallisation to give compound **5** (21%) and **6** (32%).
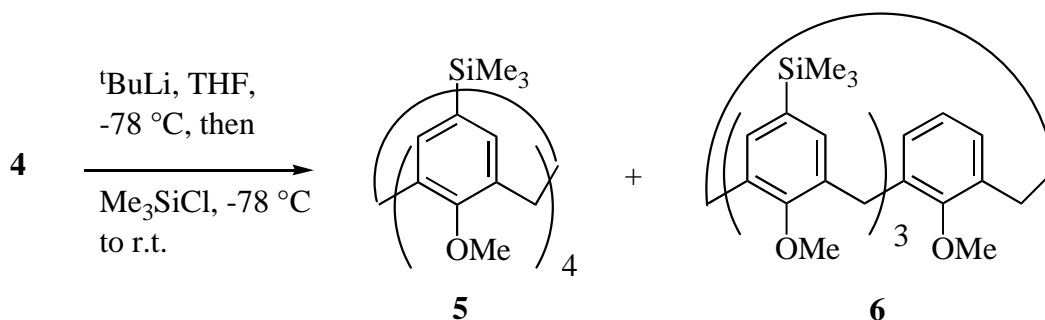
**Equation 1.** Lithiation-silylation of the calix[4]arene.

The successful synthesis of the silylated calixarenes **5** and **6** was then extended to boronation using standard methods consisting of lithiation of **4** followed by reaction with various boron electrophiles, such as trialkylborates and trihaloboranes. For example, **4** was reacted with excess *tert*-butyllithium, followed by addition of excess trimethylborate. In separate reactions, both pinacol and ethylene gylcol were added to the reactions in order to isolate stable boronate esters of type **7** and **8** respectively. After the reaction, white solids were obtained, however, these solids (reactions A and B) were insoluble in organic solvents. The +ve ion f.a.b. mass spectrum of the solid from reaction B did show peaks at m/z 621, 620, 619, 618 (corresponding to M + H$^+$ and M$^+$ of **10** rather than **8**), but when the experiments were repeated *via* the boronic acid intermediate[11] followed by addition of pinacol or ethylene glycol (reaction C and E, **Scheme 2**), no tractable material could be isolated. The main problem with reactions C and E (**Scheme 2**) seemed to be the high solubility of the reaction product in water.

In order to obtain more direct evidence for the attachment of boron to the benzene rings of the calix[4]arenes ring system, **4** was lithiated, quenched with trimethylborate, and the crude product subjected to oxidation with H_2O_2/NaOH[12]. The crude products were then acylated to obtain **9** (reaction D, **Scheme 2**). A white solid was obtained, whose mass spectrum showed peaks at m/z 538 and 481 corresponding to (M + H$^+$) of **11** and **3b** respectively. This result suggests that intramolecular lithioaryl aggregation may be responsible for the formation of unreactive intermediates, which fail to react cleanly with the boron electrophiles.
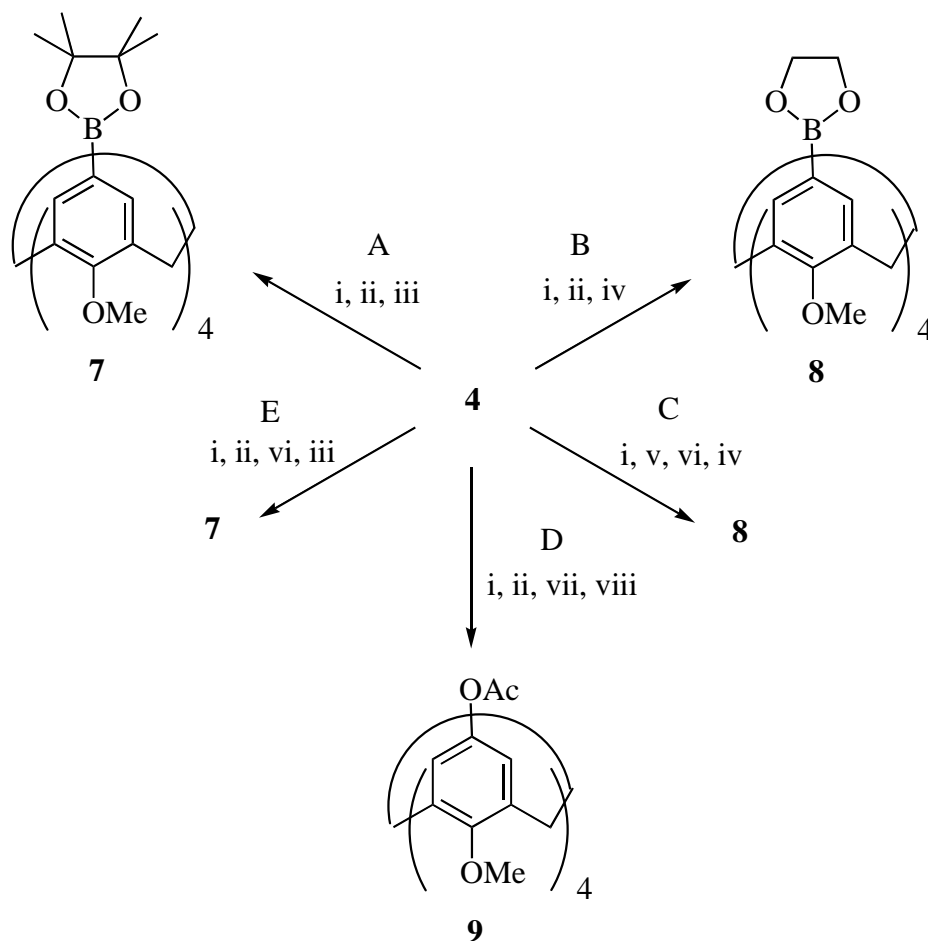
Reagents: i. ^{t}-BuLi, -78 °C; ii. B(OMe)$_3$, -78 °C-r.t.; iii. pinacol, r.t.; iv. ethylene glycol, r.t.; v. B(OMe)$_3$, -78 °C - reflux; vi. 10% HCl, r.t.; vii. 2M NaOH, 30% H$_2$O$_2$, viii. Ac$_2$O, pyridine

Scheme 2. Conversion of the boronate system **4** to boronate and acetate derivatives.
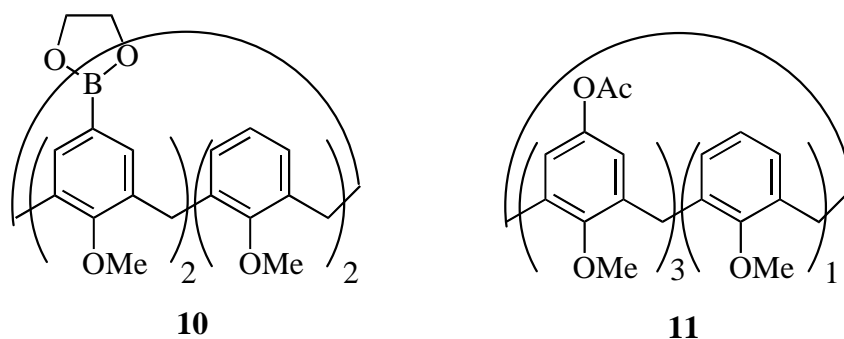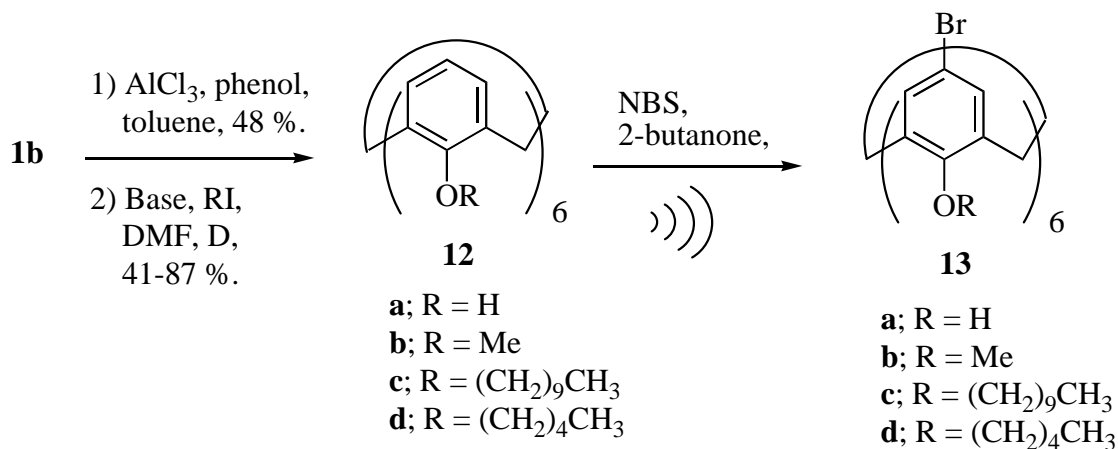

The use of alternative boron electrophiles after lithiation of **4**, i.e. boron trifluoride, boron trichloride and boron tribromide (to lead to **2a**, X = F, Cl, and Br respectively), under a variety of reaction conditions, also led to the formation of complex product mixtures from which pure

materials could not be isolated. However, having produced the tetra(trimethylsilyl) derivative **5**, an alternative route to boron Lewis-acid receptors **2a** (X = Cl or Br) might involve a desilylation-boronation reaction of **5**, with either boron trichloride or boron tribromide. Unfortunately, quantitative and rapid demethylation and desilyation occurred to give **3a** in each case after hydrolysis.

Having been successful in incorporating trimethylsilyl groups onto the calix[4]arene ring system, attention was focused to the next larger member of the benzenoid calixarene family, *i.e.* the calix[6]arene ring system. The cavities of the calix[6]arenes are larger than those of the calix[4]arenes, and therefore should have better properties for the formation of inclusion complexes[13]. However, the calix[6]arenes have received little attention, mainly because of their higher degree of functionality and flexibility (which normally makes their chemistry more complex[14,15] than that of the calix[4]arenes. To combat this problem, functionalization (e.g. hexa-O-alkylation) could be envisaged as a means of controlling the ring flexibility, and therefore modulating the properties of the calix[6]ene derivatives.

In order to prepare the trimethylsilyl derivatives of the calix[6]arenes, the bromo-derivative had to be prepared first for metalation and reaction with chlorotrimethylsilane. The starting material **1b**[9] was converted to **12b** as shown in **Scheme 3**. However, compound **12b** could not be brominated cleanly under a variety of conditions, such as N-bromosuccinimide in 2-butanone with sonnication and bromine/ iron(III) bromide. Failure to brominate **12b** was thought to be largely due to the insolubility of this material, thus the more soluble calix[6]arene derivatives **12c** and **12d** were employed (**Scheme 3**) and subjected to bromination over extended periods in order to access **13c** and **13d** respectively.

1b →
1) AlCl₃, phenol, toluene, 48 %.
2) Base, RI, DMF, D, 41-87 %.

12
a; R = H
b; R = Me
c; R = (CH₂)₉CH₃
d; R = (CH₂)₄CH₃

NBS, 2-butanone,

13
a; R = H
b; R = Me
c; R = (CH₂)₉CH₃
d; R = (CH₂)₄CH₃

Scheme 3. De-*tert*-butylation, bromination of the calix[6]arene.

Since it was not possible to brominate the calix[6]arene ring system, the calix[8]arene ring system was then examined to find out it would prove more convenient to brominate and hence

access the trimethylsilylated derivative. Thus removal of the *tert*-butyl groups of **1c** gave **14a**, which was methylated to give **14b** (**Scheme 4**).
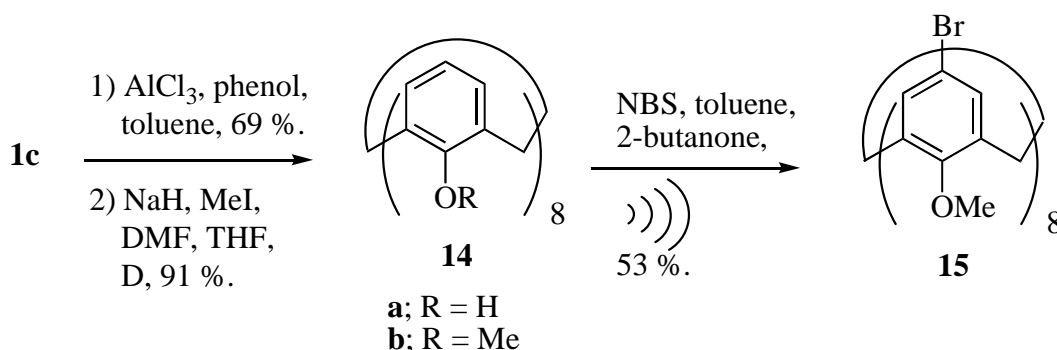
Scheme 4. De-*tert*-butylation, bromination of the calix[8]arene.

Bromination of **14b** was possible using N-bromosuccinimide in a 3:5 mixture of toluene and 2-butanone under sonnication to give **15** in 53% yield. Lithiation of **15** with excess *tert*-butyllithium followed by reaction with chlorotrimethylsilane (**Equation 2**) gave a major product **16**, i.e. with only two trimethylsilyl groups attached. Considerable manipulation of the reaction conditions failed to improve the efficiency of this process, which again suggests that relatively stable, hindered intramolecular poly-lithium complexes are formed as intermediates, which are unreactive towards electrophiles larger than a proton.
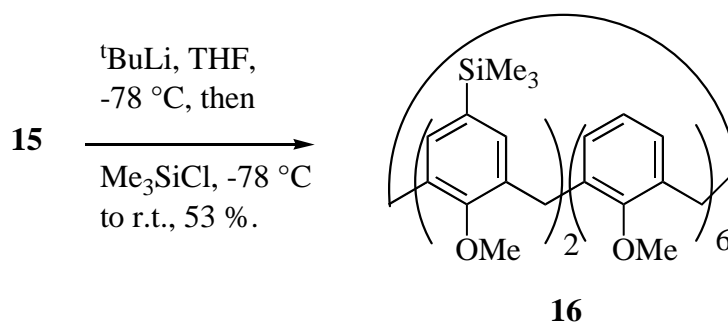
Equation 2. Lithiation-silylation of the calix[8]arene.

Summary

Although calix[4]arene **3b** was converted into the corresponding tetrasilylated derivative **5** using a bromination, lithiation, and silylation sequence, attempts to use boron electrophiles in place of silicon resulted in only partial boronation. Attempts to brominate calix[6]arenes **12** proved surprisingly difficult, which prevented the isolation of **13** and hence generation of the

corresponding hexa-lithium salt. However, bromination of calix[8]arene **14b** was possible and the octa-lithium salt was generated by lithium-halogen exchange of **15**. Subsequent reaction with chlorotrimethylsilane though, only resulted in partial silylation to give **16**. Alternative strategies for the construction poly-Lewis-acid receptors are under investigation.

Experimental Section

General Procedures. Dichloromethane was distilled over calcium hydride. Light petroleum refers to the fraction boiling in the range 40-60 °C. Anhydrous tetrahydrofuran was distilled prior to use over benzophenone-ketyl. All other compounds were purchased from Aldrich and were used without further purification. T.l.c. was performed on Merck plastic or aluminium sheets coated with silica gel 60 F_{254} (Art. 5735); the chromatograms were initially examined under u.v. light and then developed either with iodine vapour or an ethanolic anisaldehyde (1.0 %) solution containing sulfuric acid (9%) used as a spray and visualised by heating with a heat gun. Column chromatography was achieved under medium pressure or under gravity, using Merck Kieselgel H (Type 60) or Prolabo neutral alumina (50-160 mm). All anhydrous, low temperature reactions were carried out in glassware which was dried prior to use by storage in a glass oven maintained at 140 °C and cooled under a stream of argon. All organic extractions were dried with anhydrous magnesium sulfate or anhydrous sodium sulfate. Evaporations were carried out using a Büchi rotary evaporator or Büchi cold-finger rotary evaporator, followed by evaporation under high vacuum (typically at approximately 2 mmHg). Kugelruhr distillations were carried out using a Büchi GKR-51 Kugelrohr apparatus. Melting points were determined using an Electrothermal melting point apparatus and were uncorrected. ^{1}H spectra were recorded at 200 or 300 MHz on a Bruker AC200 or AC300 n.m.r. spectrometer. ^{13}C spectra were recorded at 75 MHz on a Bruker AC300. Both ^{1}H and ^{13}C spectra were recorded using $CDCl_3$ and $CHCl_3$ as internal standards respectively. I.r. spectra were recorded on a Perkin-Elmer 783 equipped with a PE600 data station or Perkin-Elmer 598 and u.v. spectra were recorded on a Perkin-Elmer l15 spectrometer. Electron impact (e.i.) (70 e.v.) and chemical ionisation (c.i.) spectra were recorded with a Kratos MS25. Fast atom bombardment (f.a.b.) spectra were recorded on a Kratos MS50, using a *meta*-nitrobenzyl alcohol matrix and accurate mass determinations were carried out on a Kratos Concept IS spectrometer. Microanalyses were performed using a Carlo-Erba 1106 elemental analyser.

Preparation of 5,11,17,23-tetra(trimethylsilyl)-25,26,27,28-tetramethoxycalix[4]arene (5a) and 5,11,17-tris(trimethylsilyl)-25,26,27,28-tetramethoxycalix[4]arene (6). To a stirred solution of **4** (0.500g, 0.63mmol) in tetrahydrofuran (30 ml) was added *tert*-butyllithium (4.50 ml, 7.65 mmol) dropwise at -78 °C under argon. The reaction mixture was stirred at -78 °C for 0.5 h and a further 0.5 h at room temperature. Chlorotrimethylsilane (4.00ml, 31.70mmol) was added dropwise to the resulting yellow solution at -78 °C. After stirring for 0.5h at room temperature, the reaction mixture was heated under reflux for 45 min, washed with a saturated

aqueous solution of ammonium chloride (2 x 50 ml), dried, filtered and concentrated to yield a light yellow oil (0.510g). Purification by silica gel column chromatography (toluene as eluant) gave the first fraction as a white crystalline solid (0.290 g) which showed 2 spots by t.l.c. (toluene). Fractional recrystallisation from dichloromethane/methanol yielded compound **5a** as white crystals (0.100g 21%): M.p. 238-240 ^{o}C; υ_{max} (KBr disc) inter alia 3020 (Ar-H), 2960, 2820 (C-H), 1585 (C=C); δ (^{1}H, 300 MHz CDCl$_3$) 0.00-0.20 (36H, m, 12 x CH$_3$Si); 2.71, 3.01, 3.16, 3.33, 3.51, 3.56, 3.76, 4.15 (20H, all br s, 4 x CH$_2$ and 4 x CH$_3$O), 6.86, 7.06, 7.13, 7.21, 7.88 (8H, all br s, aromatic); δ (^{13}C, CDCl$_3$) -1.2 (12 x CH$_3$Si), 29.1, 30.3, 36.7 (4 x CH$_2$), 60.0 (4 x CH$_3$O), 132.7, 133.1, 133.5, 133.7, 134.4, 135.0, 135.5, 158.1 (aromatic); m/z (+ve e.i.) 768 (M$^+$, base peak); Accurate mass, C$_{44}$H$_{64}$O$_4$Si$_4$; requires: m/z 768.3882, found: 768.3886. The filtrate was concentrated to yield **6** as a white solid (0.140 g, 32%): M.p. 228-230 ^{o}C; υ_{max}(KBr disc) inter alia 3020 (Ar-H), 2960, 2820 (C-H), 1585 (C=C); δ (^{1}H, 300 MHz, CDCl$_3$) 0.00-0.20 (27H, m, 9 x CH$_3$Si); 2.75, 3.01, 3.61, 3.68, 3.71, 3.83, 3.91, 4.16, 4.33 (20H, all br, s, 4 x CH$_2$ and 4 x CH$_3$O), 6.88, 7.06, 7.16, 7.21, 7.41 (9H, all br s, 9 x aromatic); δ (^{13}C, CDCl$_3$) -1.0 (9 x CH$_3$Si),29.7, 30.5, 36.9 (4 x CH$_2$), 58.5, 60.2 (4 x CH$_3$O), 131,6, 132.5, 132.9, 133.3, 133.7, 133.9, 134.6, 134.9, 135.2, 135.6, 157.7, 158.3 (aromatic); m/z ($^+$ e.i.) 697 (M$^+$), 73 (Me$_3$Si$^+$, base peak); Accurate mass, C$_{41}$H$_{56}$O$_4$Si$_3$; requires: m/z 697.3564, found: 697.3558.

Preparation of 37,38,39,40,41,42-hexapentyloxycalix[6]arene (12d). A mixture of **12a** (0.100g, 0.16mmol), barium hydroxide octahydrate (1.500g, 4.76mmol), 1-iodopentane (1.60ml, 12.57mmol) in dimethylformamide (30ml) was stirred at room temperature for 4 d. Water (20ml) added, the mixture was extracted with chloroform (2 x 50ml), dried, filtered and concentrated to yield a light yellow liquid. Trituration with methanol (10ml) yielded a light yellow solid (0.120g). Recrystallization from chloroform/methanol gave compound **12d** as light yellow crystals (0.090g, 51%): M.p. 181-183 ^{o}C; υ_{max}(KBr disc) *inter alia* 3060, 3020 (Ar-H), 2920, 2860 (C-H), 1585 (C=C) cm^{-1}; δ (^{1}H, 300 MHz, CDCl$_3$) 0.95 (18H, t, *J* 7.5 Hz, 6 x CH$_3$), 1.32 {36H, m, 6 x (CH$_2$)$_3$}, 3.22 (12H, br s, 6 x OCH$_2$), 3.92 (12H ,br s, 6 x ArCH$_2$Ar), 6.80 (6H, t, *J* 7.5 Hz, 6 x CCHC<u>H</u>), 7.02 (12H, br s, 12 x CC<u>H</u>CH); δ (^{13}C, CDCl$_3$) 14.2 (6 x CH$_3$), 22.8, 28.5, 30.1 {6 x (CH$_2$)$_3$}, 30.4 (6 x ArCH$_2$Ar), 72.8 (6 x OCH$_2$), 123.4 (6 x CCHC<u>H</u>), 129.9 (12 x C<u>C</u>HCH), 134.7 (12 x <u>C</u>CHCH), 152.4 (6 x <u>C</u>OCH$_2$); Analysis, C$_{72}$H$_{96}$ O$_6$.1/8CHCl$_3$, requires: C, 80.7; H, 9.0; Cl, 1.2; found: C, 80.7; H, 9.2; Cl, 1.4%.

Preparation of 37,38,39,40,41,42-hexadecyloxycalix[6]arene (12c). A mixture of **12a** (0.110g, 0.10mmol), barium hydroxide octahydrate (1.500g, 4.76mmol) and 1-iododecane (2.00ml, 9.36mmol), in dimethylformamide (30ml) was heated at 100 ^{o}C for 24h. Water (50ml) added and extracted with chloroform (3 x 50ml), dried, filtered and concentrated to yield a light yellow liquid.   Trituration with methanol gave a white solid (0.194 g). Recrystallization from chloroform/methanol gave **12c** as white crystals (0.160g, 64%): M.p. 66-68 ^{o}C; υ_{max} (KBr disc) *inter alia* 3060, 3020 (Ar-H), 2920, 2860 (C-H), 1585 (C=C) cm^{-1}; δ (^{1}H, 300 MHz, CDCl$_3$) 0.90 (18H, m, 6 x CH$_3$), 1.30 {96H, s, 6 x (CH$_2$)$_8$}, 3.25 (12H, br s, 6 x COCH$_2$), 3.92 (12H, br s, 6 x ArCH$_2$Ar), 6.77 (6H, br m, 6 x CCHC<u>H</u>), 7.00 (12H, br s, 12 x CC<u>H</u>CH); δ (^{13}C, CDCl$_3$) 14.3 (6 x CH$_3$), 22.9, 26.5, 30.0, 30.5 {(6 x CH$_2$)$_8$}, 32.1 (6 x ArCH$_2$Ar), 73.0 (6 x OCH$_2$), 123.4

(6 x CCH<u>CH</u>), 129.1 (12 x C<u>C</u>HCH), 134.8 (12 x <u>C</u>CHCH), 155.3 (6 x <u>C</u>OCH$_2$); Analysis, C$_{102}$H$_{15}$O$_6$, requires: C, 82.9; H, 10.6; found: C, 82.6; H, 10.9%.

Preparation of 5,11,17,23,29,35,41,47-octabromo-49,50,52,53,54,55,56-octamethoxycalix[8]arene (15). A mixture of **14b** (0.800g, 0.88mmol) and N-bromosuccinimide (2.070g, 11.63mmol) in 2-butanone (50ml) and toluene (30ml) was sonnicated for 45min and stirred at room temperature for 3 d. The reaction mixture was washed with a 10 % aqueous solution of sodium bisulfite (70ml) and extracted with toluene (3 x 50ml), dried, filtered and concentrated to yield a white solid. Recystallization from chloroform/methanol afforded **15** as white crystals (0.69 g, 53%): M.p. 295-297 ^{o}C; υ_{max} (KBr disc) *inter alia* 3020, 3000 (Ar-H), 2940, 2820 (C-H), 1510 (C=C) cm^{-1}; δ (^{1}H, 300 MHz,CDCl$_3$) 3.54 (24H, s, 8 x CH$_3$O), 3.94 (16H, s, 8 x ArC<u>H</u>$_2$Ar), 7.01 (16H, s, 16 x CCHC); δ (^{13}C, CDCl$_3$) 30.0 (8 x Ar<u>C</u>H$_2$Ar), 61.1 (8 x CH$_3$O), 117.2 (8 x CBr), 132.0 (16 x <u>C</u>HCBr), 135.9 (16 x C<u>C</u>CH), 155.7 (8 x <u>C</u>OCH$_3$); m/z (e.i) inter alia 1586, 1587, 1588, 1589, 1590, 1591, 1592, 1593 (base peaks), 1594, 1595, 1596, 1597, 1598, 1599 (all M + H$^+$); Analysis, C$_{64}$H$_{56}$O$_8$.2CHCl$_3$.MeOH, requires: C, 42.9; H, 3.3; Br, 34.1; Cl, 11.9; found: C, 42.8; H, 3.3; Br, 33.9 Cl, 12.2%.

Preparation of calix[8]arene (16). To a stirred solution of **15** (0.20 g, 0.13mmol) in tetrahydrofuran (20ml) was added *tert*-butyllithium (1.80 ml, 3.01 mmol) dropwise at -78 ^{o}C under argon. The reaction mixture was stirred at -78 ^{o}C for 1 h. Chlorotrimethylsilane (1.50 ml, 11.89 mmol) was added dropwise to the resulting yellow solution at -78 ^{o}C. After stirring for 0.5h at room temperature, the reaction mixture was heated under reflux for 3h, washed with a saturated aqueous solution of ammonium chloride (2 x 50ml), dried, filtered and concentrated to yield a light yellow oil (0.291g) which crystallized upon standing. Methanol (5ml) was added and filtered to yield the title compound as a cream solid (0.073g, 53%): δ (^{1}H, 300 MHz,CDCl$_3$) 0.13 (18H, m, 6 x CH$_3$Si), 3.53 (24H, m, 8 x CH$_3$O), 4.05 (16H, s, 8 x ArC<u>H</u>$_2$Ar), 6.80 and 7.10 (22H, m, aromatic); δ (^{13}C, CDCl$_3$) -0.9 (6 x CH$_3$Si), 29.9, 30.2, (8 x Ar<u>C</u>H$_2$Ar), 60.8 (8 x CH$_3$O), 124.0, 129.0, 129.1, 133.2, 134.3, 134.4, 156.7, 157.7 (aromatic C's).

Acknowledgements

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