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Calix[6]arenes incorporating functionalised substituents at the methylene bridges†

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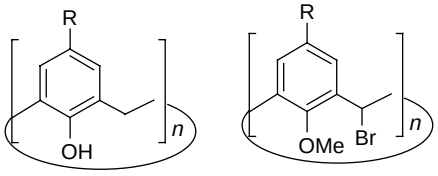
The hexabromocalix[6]arene **5** reacts with *p-tert-Bu*-phenol, thymol and propargyl alcohol to afford the corresponding hexasubstituted methylene-functionalised calixarenes. The substituents at the bridges were further functionalised via acetylation or click chemistry. Reaction of the hexahydroxy derivative **10** with DAST afforded **11**, a first example of a calixarene with all bridges monofluorinated.

Keywords: calixarenes; methylene-functionalised; synthesis

Introduction

Most supramolecular applications of the calixarenes require modification of the parent *p-tert*-butylcalix[*n*]arene scaffold (**1**) (*1*). Usually, the calixarene macrocycle can be functionalised via derivatisation or even replacement of the OH groups at the lower rim, or via substitution, oxidation or reduction of the aryl rings (*2*). In contrast to the large number of known synthetic routes allowing the chemical modification of the calix scaffold at the upper or lower rim, only a handful of methods are known allowing the incorporation of substituents at the methylene bridges. Such modifications are of interest since the substituents at the bridges may modify the physical and chemical properties of the macrocycle, and may preorganise and rigidify the calix skeleton in a desired conformation.



1

2: R = *t*-Bu, *n* = 4
3: R = H, *n* = 4
4: R = *t*-Bu, *n* = 5
5: R = *t*-Bu, *n* = 6

Two main different approaches have been used for the preparation of calixarenes substituted at the bridges. In the first approach (e.g. the fragment condensation method) (*3*), fragments possessing the proper functionalities at the bridges are synthesised and then cyclocondensed to afford the functionalised calixarenes. A disadvantage of the method is that, when applied to larger calixarenes, in some cases, the cyclocondensation step affords macrocycles of different sizes than the one targeted (*4*). Recently, optically active methylene-functionalised calixarenes have been prepared by Wulff and co-workers (*3f*) via the reaction of a biscarbene complex with a bisalkyne. In the second approach, the substituents are directly introduced on a preformed calix[*n*]arene, thus avoiding the need to find out the proper reaction conditions for conducting the macrocyclisation step with the functionalised fragments. Methylene-functionalised systems have been prepared by this approach via a homologous anionic ortho-Fries rearrangement, (*5*) via a lithiation/alkylation sequence, (*6*) via a spirodienone route (*7*) and via the addition of organolithium reagents to a ketocalixarene derivative (*8*, *9*).

We have recently reported that the bromocalixarene derivatives **2**–**5** (*10*) are useful intermediates for the preparation of a wide array of methylene-functionalised derivatives (*11*). Under S_N1 conditions, these compounds undergo nucleophilic substitution at the carbon bridges. O-, N-, S- and even some C-nucleophiles can be introduced by this route. The reaction does not require dry reagents or an inert atmosphere and is usually conducted by refluxing solutions of the bromocalixarene and the nucleophile in ionising solvents such as 2,2,2-trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP). Due to its high ionising power and low nucleophilicity, HFIP can be considered as the ideal solvent for conducting the reactions, but it is relatively expensive. Mixtures of HFIP and chloroform can be used instead of the pure fluorinated solvent to reduce the costs (and in some cases, to increase the solubility of the

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reagents), but this results in slower reactions due to the decrease in the ionising power of the medium.

In this paper, we report some additional reactions of the hexabromocalix[6]arene derivative **5**, and the derivatisation/chemical modification of the functional groups at the bridges of selected methylene-substituted calix[6]arene derivatives.

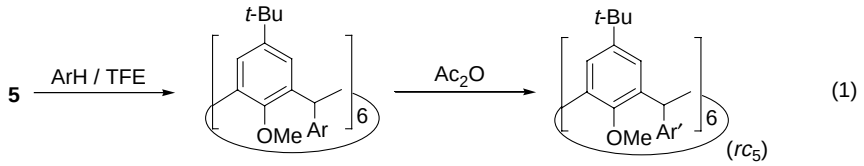
Results and discussion

Reaction of 5 with phenols

In principle, reaction of **5** with an ambident nucleophile should yield methylene-functionalised calixarenes with functionalised substituents. These functional groups may further contribute to the binding properties of the ligand and may allow a facile modification of the additional functionality. Ideally, the two nucleophilic sites at the ambident nucleophile should react at different rates, otherwise mixtures of compounds are to be expected. We have previously shown that **4** reacts with *p-tert-Bu*-phenol and thymol via C-alkylation (*11d*). Since, as observed with **4**, the ambident nucleophile reacts *para* to the OH group in the case of thymol, but *ortho* in the case of *p-tert-Bu*-phenol, the two phenols should afford derivatives differing in the relative location of the OH group at the side arms.

The reaction of **5** with *p-tert*-butylphenol was conducted by refluxing a mixture of the compounds in TFE. An extremely insoluble product precipitated from the reaction mixture. The low solubility of this product (ascribed to the hexasubstituted derivative **6a**) is most likely due to intramolecular hydrogen bonds between the OH groups at the side arms in the solid state. To determine the NMR spectra of **6a**, it was necessary to use pyridine-d_5 (a hydrogen-bond-accepting solvent) and a high temperature (381 K). Lowering the temperature by 5°C resulted in the fast precipitation of the compound. The ^{1}H NMR spectra of **6a** at 381 K displayed two *t*-Bu signals and a single methoxy signal, in agreement with a hexasubstituted derivative of rc_5 configuration (i.e. all *cis*). Precluding accidental isochrony, and assuming a preferred pinched cone conformation, the high symmetry indicated by the NMR spectra of **6a** at high temperatures (consistent with six-fold symmetry) indicates that the pinched cone/pinched cone interconversion is fast on the NMR timescale (see below).

To increase the solubility in organic solvents, the crude **6a** was acetylated, affording the hexasubstituted derivative **7a** (Equation (1)). Calixarene **7a** is sufficiently soluble in $CDCl_3$ to allow the determination of its spectra at room temperature. Compound **7a** displayed in the ^{1}H NMR spectrum pairs of singlets for the *t*-Bu, methoxy and aromatic protons of the macrocycle, but single signals for the substituents attached at the bridges. This pattern, indicating three-fold symmetry of the molecule, is consistent with a frozen 'pinched cone' conformation on the NMR timescale. In this conformation, the six bridges are symmetry equivalent, but the rings at positions 1, 3 and 5 are less twisted than the rings at positions 2, 4 and 6. We have hypothesised previously that this conformation, observed in the crystal structure of two hexasubstituted (all-*cis*) methylene-functionalised calix[6]arene derivatives, is adopted also in solution (*11c*).



(1)

6a Ar = 2-OH, 5-*t*-Bu-C_6H_3
6b Ar = 2-Me, 4-OH, 5-*i*-Pr-C_6H_2

7a Ar′ = 2-OAc, 5-*t*-Bu-C_6H_3
7b Ar′ = 2-Me, 4-OAc, 5-*i*-Pr-C_6H_2

Upon raising the temperature, pairs of signals of **7a** broadened and eventually coalesced. The dynamic process responsible for these spectral changes can be ascribed to a pinched cone/pinched cone interconversion (Figure 1) involving rotation of the aryl rings, and mutually exchanging the two types of rings on the macrocycle. From the chemical difference under slow exchange conditions for the pair of methoxy signals at 400 MHz ($\Delta\nu = 222.6$ Hz) and the coalescence temperature (362.3 K), a barrier of 16.9 kcal mol^{-1} was calculated for the dynamic process.

The reaction of **5** with thymol was conducted in a similar fashion to that with *t*-Bu phenol (Equation (1)). The crude mixture was acetylated yielding **7b**.

Notably, while both **6b** and **7b** display in the ^{1}H NMR spectrum a signal pattern indicating three-fold symmetry, the isopropyl groups display two doublets for its CH_3 groups (Figure 2). The diastereotopicity of the CH_3 groups of the isopropyls is in full agreement with a preferred pinched cone conformation. In such conformation, the six bridges are symmetry equivalent, but since there are no mirror planes bisecting each substituted bridge, the two CH_3 groups of a given isopropyl are diastereotopic, even under fast rotation around the Ar-*i*-Pr bonds.

Click chemistry on the substituent at the bridge

The Huisgen 1,3-dipolar cycloaddition of azides with acetylenes to yield 1,2,3-triazoles (click chemistry) (*12*) is

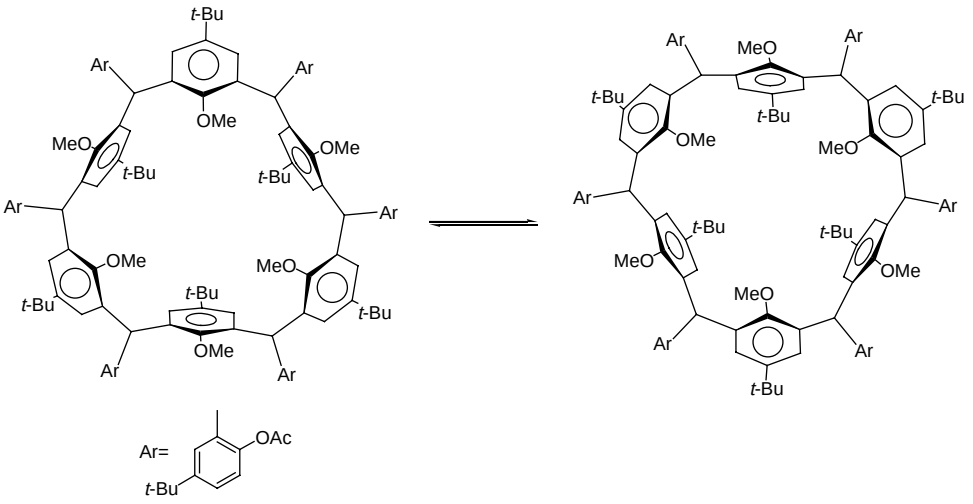
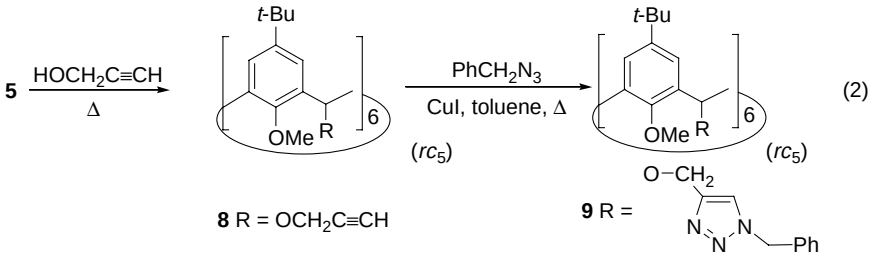


Figure 1. Pinched cone/pinched cone interconversion in **6b**. This dynamic process mutually exchanges the two types of rings of the calixarene skeleton.

a versatile reaction which has proved very useful for the modification of the calixarene scaffold (*13*). The six-fold incorporation of 1,2,3-triazol groups was conducted according to Equation (2):



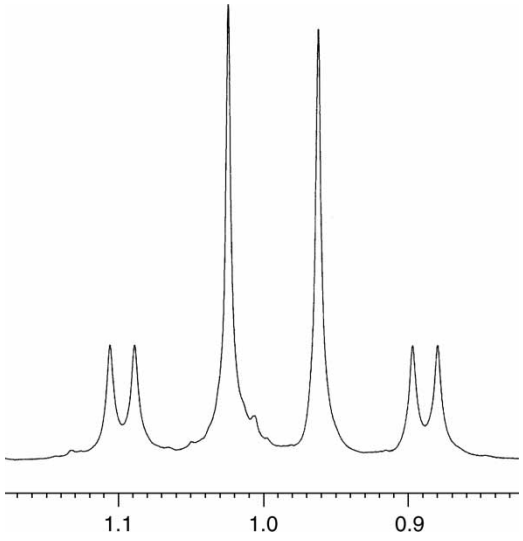


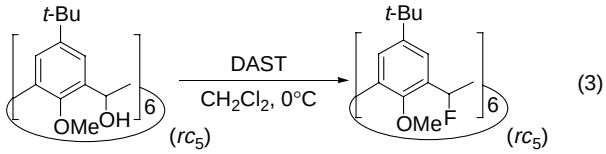
Figure 2. 500 MHz ^{1}H NMR spectrum ($CDCl_3$, r.t.) of **7b** (high-field region). The two isopropyl methyls are diastereotopic and appear as separate signals (doublets) at 1.10 and 0.89 ppm.

Bromocalix[6]arene **5** readily reacts with neat primary and secondary alcohols (no additional fluorinated alcohol is needed). The first step was conducted simply by heating at reflux a mixture of **5** and propargyl alcohol. On the basis of the ^{1}H and ^{13}C NMR patterns indicating six-fold symmetry, an rc_5 (i.e. all-*cis*) configuration is ascribed to the product. The reaction of the hexapropargyloxy derivative **8** with azidomethyl benzene proceeded readily and afforded the derivative incorporating triazole rings at all bridges (**9**).

Full monofluorination of the bridges of calix[6]arene

The hydroxyl group of a calix[6]arene possessing a single hydroxymethylene bridge can be replaced by a fluorine by means of the deoxofluorinating agent DAST (Et_2NSF_3) (*14*). To test whether this reaction can be conducted at all bridges in a stereoselective fashion, we reacted the hexahydroxycalix[6]arene **10** (previously obtained by acetolysis of **5** followed by $LiAlH_4$ reduction of the resulting hexaacetate derivative) (*11c*) with DAST (Equation (3)). As observed in most of the reactions of **5**, a single major product was obtained. Hexafluoro-calix[6]arene **11** displayed a doublet for the methylene bridges ($J = 46.6$ Hz) as a result of the geminal coupling

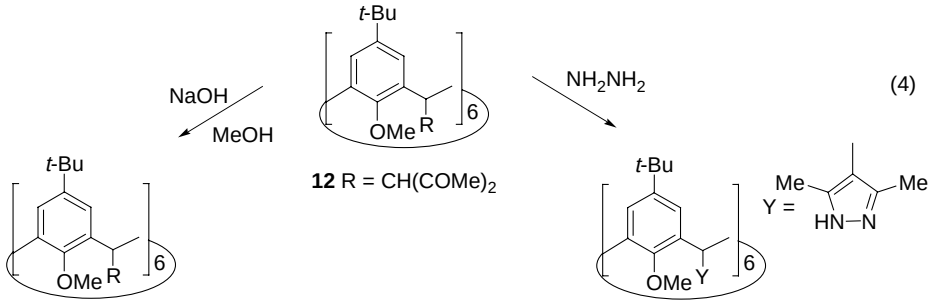
between the proton and the fluorine of each bridge. On the basis of the high symmetry of the NMR pattern, the all-*cis* configuration is ascribed to this derivative.



10 **11** (3)

Cleavage and reaction with hydrazine of acetylacetonyl groups

We also examined the chemical modification of the acetoacetonyl groups of calixarene **12**, previously obtained via reaction of **5** with the ambident nucleophile acetylacetone (*11c*). We found that, as previously observed for the calix[5]arene analogue of **12**, the acetoacetonyl groups are readily cleaved in the presence of a base, affording the corresponding hexa(2-propanonyl) derivative **13** and reaction of **12** with hydrazine affords the hexapyrazolyl derivative **14** (Equation (4)).



Conclusions

The hexabromocalix[6]arene **5** reacts with the ambident nucleophiles to afford the corresponding hexasubstituted derivatives. The functional group at the substituent (OH, triple bond, acetylacetonyl) can be derivatised or functionalised.

Experimental section

Reaction of bromocalixarene 5 with p-tert-butylphenol or thymol

A stirred mixture of **5** (0.10 g, 0.07 mmol), the corresponding phenol (12 equivalents) in TFE (6 ml) and chloroform (6 ml) was heated at reflux overnight. On cooling to room temperature, a white solid was separated. The crude product was filtered, triturated successively with chloroform and methanol, and dried.

6a. Yield: 0.070 g (54%), mp 302°C. ^{1}H NMR (pyridine-d_5, 381 K, 500 MHz): δ 7.56 (d, $J = 2.0$ Hz, 6H), 7.47 (s, 12H), 7.38 (s, 6H), 7.17 (dd, $J = 8.5$, 2.0 Hz, 6H), 6.93 (d, $J = 8.1$ Hz, 6H), 3.35 (s, 18H), 1.41 (s, 54H), 1.34 (s, 54H) ppm. ^{13}C NMR (pyridine-d_5, 381 K, 125 MHz): δ 155.6, 153.9, 145.2, 142.2, 137.6, 133.4, 128.1, 126.9, 116.8, 61.1, 38.4, 35.1, 34.8, 32.5, 32.2 ppm. HR-MS (ESI): *m/z* 1947.2649 ($M + H^+$). Calcd for $C_{132}H_{169}O_{12}$: 1947.2648.

6b. Yield: 0.055 g (43%) mp 355°C. ^{1}H NMR (acetone-d_6, 500 MHz, r.t.): δ 7.77 (s, 6H), 7.13 (s, 6H), 6.95 (s, 6H), 6.92 (s, 6H), 6.54 (s, 6H), 6.46 (s, 6H), 3.18 (h, $J = 6.8$ Hz, 6H), 2.95 (s, 9H), 2.52 (s, 9H), 2.08 (s, 18H), 1.17 (d, $J = 6.8$ Hz, 18H), 1.1 (s, 27H), 1.06 (s, 27H), 1.01 (d, $J = 6.8$ Hz, 18H) ppm. ^{13}C NMR (acetone-d_6, 125 MHz, r.t.): δ 155.07, 155.01, 153.5, 146.1, 145.9, 138.2, 136.9, 136.1, 135.2, 132.5, 127.8, 127.7, 127.0, 118.5, 61.2, 61.1, 40.5, 35.6, 35.4, 32.5, 32.3, 28.0, 24.0, 23.8, 21.0, 19.7 ppm. HR-MS (ESI): *m/z* 1969.2462 ($M + Na^+$). Calcd for $C_{132}H_{168}O_{12}Na$: 1969.2467.

Acetylation of 6a and 6b

A stirred mixture of **6a** or **6b** (0.10 g, 0.05 mmol) in acetic anhydride (4 ml) containing 0.1 ml H_2SO_4 was heated to reflux for 3 h. The hot solution was poured into crushed ice and extracted with chloroform (20 ml). The organic solution was washed successively with brine, aq. $NaHCO_3$ and brine, dried on Na_2SO_4 and evaporated. The crude residue was recrystallised from acetone yielding 0.066 g (62%) **7a**, mp 338°C (dec), and 0.062 g (60%) **7b**, 358°C (dec).

7a. ^{1}H NMR ($CDCl_3$, 400 MHz, r.t.): δ 7.13 (br, 15H), 6.88 (br, 15H), 6.42 (s, 6H), 2.17 (br s, 18H), 1.15 (s, 54H), 0.98 (br s, 54H) ppm. ^{13}C NMR ($C_2D_2Cl_4$, 410 K, 125 MHz): δ 168.1, 153.8, 147.5, 146.5, 144.7, 135.7, 135.2, 126.9, 126.1, 123.2, 121.9, 60.4, 37.7, 34.1, 33.9, 31.2, 31.0, 20.4 ppm. HR-MS (ESI): *m/z* 2199.3276 (M + H). Calcd for $C_{144}H_{181}O_{18}$: 2199.3281.

7b. ^{1}H NMR ($CDCl_3$, 400 MHz, r.t.): δ 7.04 (s, 6H), 6.96 (s, 6H), 6.74 (s, 6H), 6.67 (s, 6H), 6.41 (s, 6H), 2.87 (s, 9H), 2.83 (h, $J = 6.9$ Hz, 6H), 2.45 (s, 9H), 2.21 (s, 18H), 2.11 (s, 18H), 1.09 (d, $J = 6.8$ Hz, 18H), 1.02 (s, 27H), 0.96 (s, 27H), 0.89 (d, $J = 6.8$ Hz, 18H) ppm.

^{13}C NMR ($CDCl_3$, 125 MHz, r.t.): δ 169.4, 153.8, 153.4, 145.8, 145.1, 144.9, 141.4, 136.2, 136.1, 135.0, 134.3, 126.6, 126.2, 125.8, 123.7, 60.8, 59.9, 39.5, 34.2, 34.1, 31.2, 31.1, 30.2, 30.1, 30.0, 27.0, 23.3, 23.1, 20.9, 18.8 ppm. HR-MS (ESI): *m/z* 2199.3279 (M + H). Calcd for $C_{144}H_{181}O_{18}$: 2199.3281.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexapropargyloxy-calix[6]arene (8)

A mixture of **5** (0.50 g, 0.33 mmol) and 35 ml of propargyl alcohol was refluxed for 2 h. After evaporation, the residue was recrystallised from $CHCl_3$/MeOH affording 0.21 g (47%) of **8**, mp 265–267°C (dec); ^{1}H NMR ($CDCl_3$, 400 MHz, r.t.): δ 7.28 (s, 18H), 6.40 (s, 6H), 4.16 (d, $J = 2.31$ Hz, 12H), 3.18 (s, 18H), 2.46 (t, $J = 2.24$ Hz, 6H), 1.09 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, r.t.): δ 154.7, 146.3, 132.8, 125.5, 79.8, 74.7, 70.7, 62.0, 56.4, 34.4, 31.3 ppm. HR-MS (ESI): *m/z* 1403.7733 $(M + Na)^+$. Calcd for $C_{90}H_{108}NaO_{12}$: 1403.7738.

Click chemistry reaction of 8

A mixture of **8** (0.1 g, 0.072 mmol), azidomethyl-benzene (0.28 g, 2.10 mmol), CuI (85.4 mg, 0.45 mmol) and 20 ml of toluene was refluxed overnight. After evaporation, the residue was washed several times with acetone to afford 0.13 g (82%) of **9** as a greenish powder, mp 193–195°C dec; ^{1}H NMR ($CDCl_3$, 500 MHz, r.t.): δ 7.46 (s, 6H), 7.38–7.28 (m, 42H), 6.21 (s, 6H), 5.52 (s, 12H), 4.64 (s, 12H), 2.90 (s, 18H), 1.03 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, r.t.): δ 154.4, 146.3, 145.2, 135.3, 134.6, 133.0, 129.1, 128.9, 128.8, 128.7, 128.6, 128.2, 128.1, 127.3, 125.4, 122.8, 70.8, 62.7, 61.3, 54.8, 54.1, 34.3, 31.2, 31.8 ppm; HR-MS (ESI): *m/z* 1091.0927 $(M + 2H)^{2+}$. Calcd for $C_{132}H_{152}N_{18}O_{12}/2$, 1091.0935.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexafluoro-calix[6]arene (11)

Twenty-five drops of DAST were added to an ice-cooled suspension of **10** (0.40 g, 0.35 mmol) and dichloromethane (30 ml). The reaction was left to warm to room temperature for 4 h and quenched with water. After phase separation, drying ($MgSO_4$) and evaporation of the solvent, the residue was recrystallised from $CHCl_3$/MeOH affording 0.075 g (19%) of **11**, mp 243–245°C (dec); ^{1}H NMR ($CDCl_3$, 400 MHz, r.t.): δ 7.35 (s, 12H), 7.16 (d, $J = 46.6$ Hz, 6H), 3.20 (s, 18H), 1.12 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz, r.t.): δ 153.3, 146.8, 132.0 (d, $J = 22.52$ Hz), 125.6, 83.7 (d, $J = 167.07$ Hz), 62.4, 34.5, 31.2 ppm. ^{19}F NMR ($CDCl_3$, 376.4 MHz, r.t.): δ – 164.9 ppm. HR-MS (ESI): *m/z* 1187.6534 $(M + Na)^+$. Calcd for $C_{72}H_{90}F_6NaO_6$, 1187.6539.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexa(2-propanonyl)-calix[6]arene (13)

A solution of 1.5 M $NaOH_{aq}$ (10 ml) was added to a suspension of **12** (0.20 g, 0.12 mmol) in 20 ml of warm methanol. The mixture was refluxed for 15 min and left to cool overnight. After vacuum filtration, the white solid was recrystallised from $CHCl_3$/MeOH to afford compound **13** (82 mg, 48%), mp 215–217°C (dec); ^{1}H NMR ($CDCl_3$, 500 MHz, r.t.): δ 6.95 (s, 12H), 5.28 (t, $J = 7.84$ Hz, 6H), 3.55 (s, 18H), 2.99 (d, $J = 7.84$ Hz, 12H), 2.06 (s, 18H), 1.05 (s, 54H) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz, r.t.): δ 206.9, 152.9, 146.0, 135.7, 123.5, 60.6, 50.6, 34.31, 33.52, 31.3, 29.8 ppm; HR-MS (ESI): *m/z* 1415.8672 $(M + Na)^+$. Calcd for $C_{90}H_{120}NaO_{12}$, 1415.8677.

5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,40,41,42-hexamethoxy-2,8,14,20,26,32-hexa(dimethylpyrazolyl)-calix[6]arene (14)

A suspension of **12** (0.10 g, 0.061 mmol), 15 ml of ethanol and 1 ml of hydrazine monohydrate was refluxed for 3 h. The white solid was vacuum filtered and washed several times with water to afford **14** (54 mg, 55%), mp 420–422°C (dec); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.02–11.84 (m, 6H), 7.00 (br s, 6H), 6.91 (s, 6H), 6.04 (s, 6H), 3.15 (s, 9H), 2.24 (s, 9H), 1.86 (br s, 18H), 1.71 (s, 18H), 1.18 (s, 27H), 0.82 (s, 27H) ppm. ^{13}C NMR (DMSO-d_6, after addition of *p*-toluenesulphonic acid, 125 MHz): δ 153.3, 151.9, 145.6, 145.3, 142.5, 139.5, 135.4, 134.7, 125.6, 117.4, 59.5, 33.8, 33.7, 33.1, 30.5, 11.3, 10.1 ppm; HR-MS (ESI): *m/z* 1623.0499 $(M + H)^+$. Calcd for $C_{102}H_{133}N_{12}O_6$, 1623.0505. Anal. Calcd for $C_{102}H_{132}N_{12}O_6$: C, 75.52; H, 8.20. Found: C, 75.65; H, 8.54.

Acknowledgement

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References

(1) For recent reviews on calixarenes see: (a) Mandolini, L., Ungaro, R., Eds.; *Calixarenes in Action*; Imperial College Press: London, 2000. (b) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19. (c) Gutsche, C.D. *Calixarenes: An Introduction*; Royal Society of Chemistry: Cambridge, 2008.

(2) For recent examples see: (a) Troisi, F.; Mogavero, L.; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2007**, *9*, 915–918. (b) Troisi, F.; Citro, L.; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2008**, *10*, 1393–1396.

(3) (a) Tabatabai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295–3298. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin*

Trans. 1 **1994**, 1657–1658. (c) Biali, S.E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E.F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938–12949. (d) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M.A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037–13052. (e) For a review on the synthesis of calixarenes via the stepwise and fragment condensation methods see: Böhmer, V. *Liebigs Ann./Recueil* **1997**, 2019–2030. (f) Gopalsamuthiram, V.; Predeus, A.V.; Huang, R.H.; Wulff, W.D. *J. Am. Chem. Soc.* **2009**, *131*, 18018–18019.

(4) See for example: Biali, S.E.; Böhmer, V.; Columbus, I.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E.F.; Thondorf, I. *J. Chem. Soc. Perkin Trans. 2* **1998**, 2261–2270.

(5) Middel, O.; Greff, Z.; Taylor, N.J.; Verboom, W.; Reinhoudt, D.N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667–675.

(6) (a) Scully, P.A.; Hamilton, T.M.; Bennett, J.L. *Org. Lett.* **2001**, *3*, 2741–2744. (b) Hertel, M.P.; Behrle, A.C.; Williams, S.A.; Schmidt, J.A.R.; Fantini, J.L. *Tetrahedron* **2009**, *65*, 8657–8667. J.L. Fantini previously published as J.L. Bennett. (c) For a recent study of the conformation behavior of a calix[4]arene with a single methylene group substituted by a carboxyl functionality see: Gruber, T.; Gruner, M.; Fischer, C.; Seichter, W.; Bombicz, P.; Weber, E. *New J. Chem.* **2010**, *34*, 250–259. (d) For agostic and methylene hydride complexes of calix[4]arene see: Buccella, D.; Parkin, G. *J. Am. Chem. Soc.* **2006**, *128*, 16358–16364.

(7) Agbaria, K.; Biali, S.E. *J. Am. Chem. Soc.* **2001**, *123*, 12495–12503.

(8) Kuno, L.; Seri, N.; Biali, S.E. *Org. Lett.* **2007**, *9*, 1577–1580; Kuno, L.; Biali, S.E. *Org. Lett.* **2009**, *11*, 3662–3665.

(9) For the preparation and reactions of ketocalixarenes see: (a) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Macromol. Chem.* **1990**, *191*, 81. (b) Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 5550–5560. (c) Seri, N.; Simaan, S.; Botoshansky, M.; Kaftory, M.; Biali, S.E. *J. Org. Chem.* **2003**, *68*, 7140–7142. (d) Kogan, K.; Biali, S.E. *Org. Lett.* **2007**, *9*, 2393–2396.

(10) (a) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967–8968. (b) Kumar, S.K.; Chawla, H.M.; Varadarajan, R. *Tetrahedron Lett.* **2002**, *43*, 7073–7076.

(11) (a) Columbus, I.; Biali, S.E. *Org. Lett.* **2007**, *9*, 2927–2929. (b) Columbus, I.; Biali, S.E. *J. Org. Chem.* **2008**, *73*, 2598–2606. (c) Kogan, K.; Columbus, I.; Biali, S.E. *J. Org. Chem.* **2008**, *73*, 7327–7335. (d) Kogan, K.; Biali, S.E. *J. Org. Chem.* **2009**, *74,* 7172–7175.

(12) Kolb, H.C.; Finn, M.G.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **2001**, *40*, 2004–2021.

(13) For modifications of the calix skeleton based on click chemistry see for example: (a) Simaan, S.; Agbaria, K.; Biali, S.E. *J. Org. Chem.* **2002**, *67*, 6136–6142. (b) Ryu, E.-H.; Zhao, Y. *Org. Lett.* **2005**, *7*, 1035–1037. (c) Morales-Sanfrutos, J.; Ortega-Munoz, M.; Lopez-Jaramillo, J.; Hernandez-Mateo, F.; Santoyo-Gonzalez, F. *J. Org. Chem.* **2008**, *73*, 7768–7771. (d) Park, S.Y.; Yoon, J.H.; Hong, C.S.; Souane, R.; Kim, J.S.; Matthews, S.E.; Vicens, J. *J. Org. Chem.* **2008**, *73*, 8212–8218. (e) Bew, S.P.; Brimage, R.A.; L'Hermite, N.; Sharma, S.V. *Org. Lett.* **2007**, *9*, 3713–3716. (f) Vecchi, A.; Melai, B.; Marra, A.; Chiappe, C.; Dondoni, A. *J. Org. Chem.* **2008**, *73,* 6437–6440. (g) Tzadka, E.; Goldberg, I.; Vigalok, A. *Chem. Commun.* **2009**, 2041–2043. (h) Fiore, M.; Chambery, A.; Marra, A.; Dondoni, A. *Org. Biomol. Chem.* **2009**, *7*, 3910–3917.

(14) Itzhak, N.; Biali, S.E. *J. Org. Chem.* **2010**, *75*, 3437–3442.