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Simple Preparation of 5-Hydroxy-25,26,27,28-tetraalkyloxycalix[4]arenes: Synthesis of Multiple Calixarenes

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Abstract: A simple method for the preparation of 5-hydroxy-25,26,27,28-tetrapropoxycalix[4]arene has been found. Lithiation of the initial monobromo derivative and subsequent oxidation by oxygen led directly to the proposed calix[4]arene derivative bearing a hydroxy group on the upper rim. The product has been used for the preparation of novel molecular receptors based on multiple calix[4]arenes.

Keywords: Calixarenes; Lithiation; Oxidation; Complexation

Calix[n]arenes are a well known family of macrocyclic oligophenols,[1,2] very popular due to their unique molecular structures and simple preparations. They are widely used as very important building blocks in supramolecular chemistry[3] where they found many applications in the design of more elaborated molecular structures and assemblies. The chemistry of calix[4]arene has experienced especially rapid development during the last decade. As a result, many methods for regioselective derivatization or the introduction of certain functional groups into a calix[4]arene skeleton have been described in the literature. In this contribution we report on a novel simple preparation of tetraalkylated calix[4]arene derivatives bearing one hydroxy group on the upper rim and the utilisation of this hydroxycalix[4]arene for the synthesis of multiple calixarenes.

During our attempts at the preparation of calix[4]arene monoaldehyde (via lithiation of monobromide **2** and consecutive reaction with DMF) we have found, that the required compound is accompanied by unknown byproduct in approx. 2% yield. Surprisingly, using the combination of ^{1}H NMR spectroscopy and MS, the structure of this byproduct was proven to be the monohydroxy derivative of calix[4]arene **4**. Possible explanation of its formation lies in the oxidation of organolithium compound by oxygen present in the argon used as an inert atmosphere. We have realised that such a simple oxidation of intermediate lithiated derivatives[4] could be quite a straightforward way to hydroxycalix[4]arenes.

The introduction of a hydroxy group onto the upper rim of calixarene has been already mentioned in the literature. The strategy was based on the Baeyer-Villiger reaction consisting in the oxidation of appropriate acetyl[5] or formyl[6] derivatives, and subsequent hydrolysis of ester intermediates. While the tetrahydroxy

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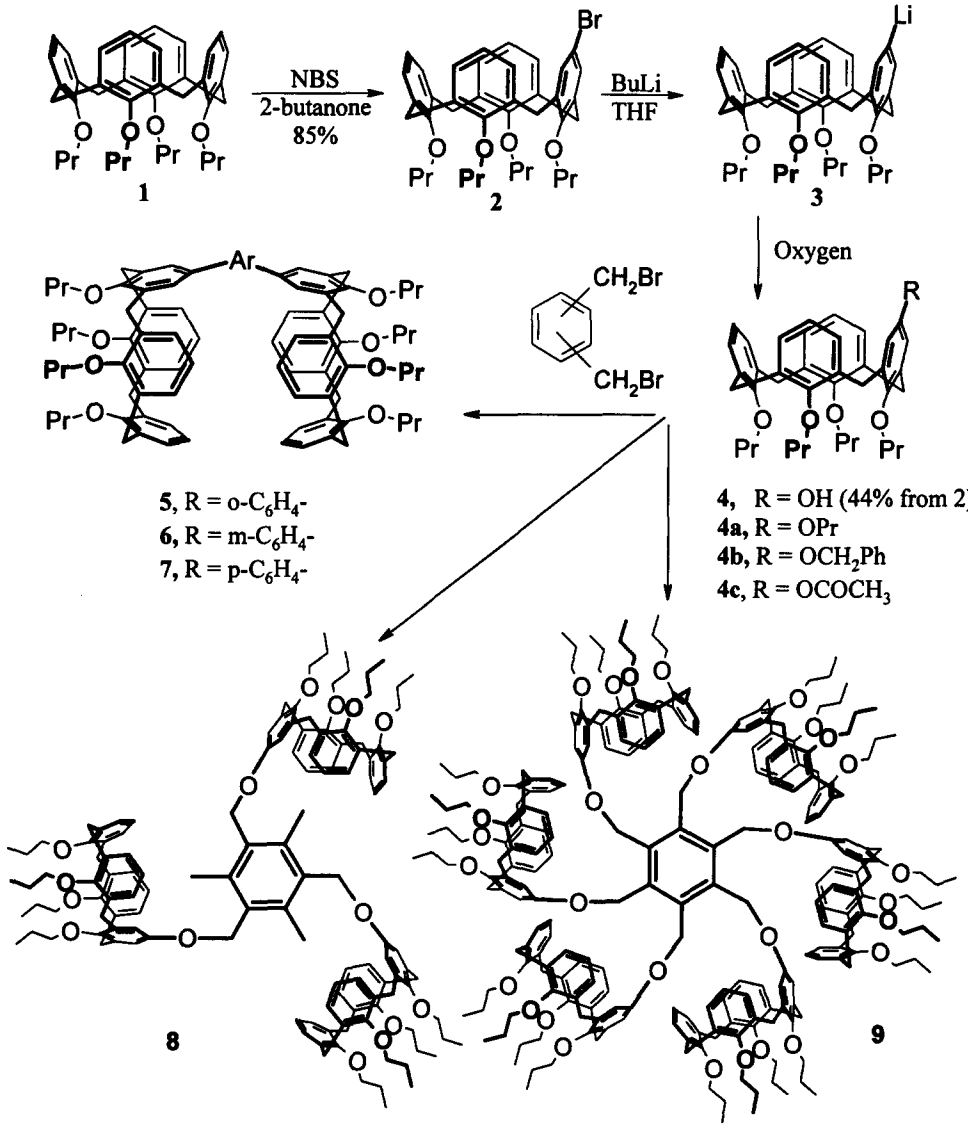
derivative has been obtained in good yield, the monohydroxy derivative has thus far been prepared only in low yield.



Scheme 1: The preparation of multiple calixarenes

We have carried out several attempts at direct oxidation of monolithiated calixarene derivative **3** prepared by the lithiation of bromo derivative **2** (Scheme 1). The air was bubbled for 1 h through the solution of lithiated derivative **3** (3 eq. of BuLi, 30 min stirring at -78 °C) in THF at -78 °C, the air used was pumped over a drying column based on solid NaOH and P_2O_5. This arrangement gave relatively low yields of **4** (~15%), on the other

hand the reduced product, tetrapropoxycalix[4]arene **1**, was isolated in approx. 50% yield. A much better result was obtained under similar conditions using drying with liquid nitrogen, where the proposed product **4** was isolated in 31% yield, again accompanied by 45% of calix[4]arene **1**. The best result was achieved using pure oxygen instead of air (dried by P_2O_5 + silica gel) where we isolated **4** in 44% yield (based on **2**) and approximately the same amount of **1** (40%). The required product **4** can be easy separated using chromatography on silica gel due to the large differences in R_f values. Surprisingly, the oxidation of lithiated calixarene was found to be solvent-dependent. The same reactions carried out in diethyl ether instead of THF did not give any detectable amount of **4**, on the other hand 1,2-dimethoxyethane showed similar results (40% yield) to THF. An attempt at the oxidation of the organozinc derivative in THF (after the transmetallation of lithiated derivative with $ZnCl_2$) has failed.

The structure of **4** was proven with the help of ^1H NMR spectrometry where one can find the splitting pattern typical of the monosubstituted cone conformation - four doublets of Ar-CH_2-Ar groups, three different propyl groups and one singlet in the aromatic region. The proposed molecular peak 608 m/z was observed in the MS FAB spectrum.

The presence of one hydroxy group in derivative **4** was further demonstrated by its chemical transformations. The alkylation of hydroxy group with propyl iodide and NaH in DMF led to the corresponding pentapropoxy calixarene **4a** in 76% yield. The same reaction with benzyl chloride gave benzyloxyderivative **4b** in 52%. Similarly, the reaction with acetic anhydride under the catalysis of p-$CH_3C_6H_4SO_3H$ gave the appropriate acetyl derivative **4c** in 70% yield (Scheme 1). The structures of all derivatives were proven by common spectroscopic methods.

Derivative **4** was further used as a suitable concave building block for the construction of novel molecular receptors based on bis-calix[4]arenes. Thus, the alkylation of **4** with 1,2-bis(bromomethyl)benzene in DMF, using NaH as a base, led to the construction of bis-calixarene **5** (67%). Similarly, m- and p-substituted

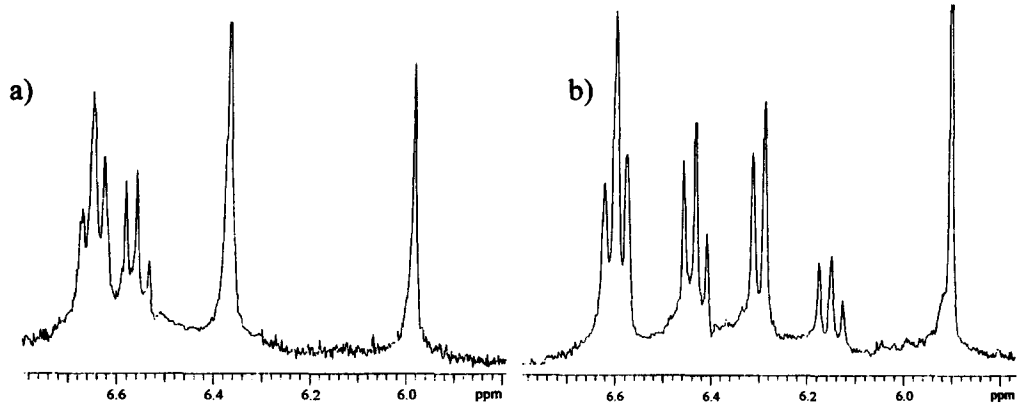


Figure 1: a) The partial ^1H NMR spectrum of **6** ($CDCl_3$:CD_3CN = 4:1, 0.5 mmol/l), b) the same after the addition of 200 equivs. of **1-MP**.

derivatives **6** and **7** were prepared in 55% and 72% yield, respectively. These compounds can serve as a receptors for quaternary ammonium salts using cation-π interactions between the positively charged guest and the π-system of the calixarene.[7] The complexation ability of **6** toward N-methylpyridinium iodide (**1-MP**) was studied by ^{1}H NMR titration in $CDCl_3$:CD_3CN (4:1, v/v) mixture at 298 K. As follows from Figure 1, the addition of **1-MP** to the solution of **6** caused a visible shift of aromatic protons in both calix[4]arene subunites (up to 75 Hz). The dependence between the complexation induced chemical shift and the concentration of guest (**1-MP**) follows the theoretical curve for the formation of a 1:1 complex (Figure 2). The appropriate complexation constant (K_C = 1.9 ± 0.3 mol^{-1}dm^3) was computed using original nonlinear regression fitting-curve program and corresponds probably to the complexation of the guest by one calixarene subunit with possible electrostatic contribution of the upper rim oxygen atom (Ar-CH_2-*O*-calix). N-Methylisoquinolinium iodide gave a similar complexation constant (1.8 ± 0.3 mol^{-1}dm^3), which implies the binding does not exhibit the expected cooperative effect. Hence, more suitable guests for the multipoint recognition process have to be used in future (probably multiple ammonium salts) for further complexation study.

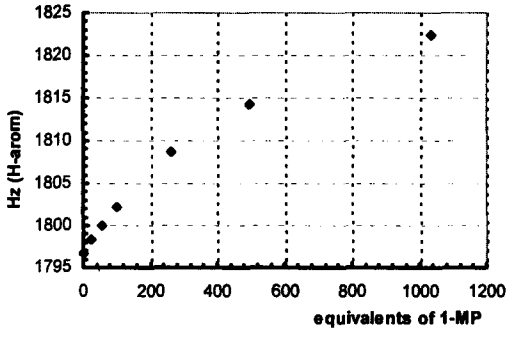


Figure 2: Titration curve of **6** with **1-MP**.

The usefulness of derivative **4** for the construction of more complex receptors can be demonstrated by the synthesis of multiple calixarenes. The alkylation of **4** with 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene[8] and NaH in DMF at room temperature gave the appropriate tris-calixarene **8** in 54% yield. Accordingly, hexakis-calix[4]arene **9** was prepared using similar reaction conditions from hexakis(bromomethyl)benzene[8] in 51% yield. The shape of this derivative resembles[9] the *„molecular bucket excavator"* (see Scheme 1) and represents a molecule with potential multi-point recognition ability. The structure of **9** was proved unequivocally with the help of the MALDI TOF MS technique where one can see two signals m/z 3822 and 3838 corresponding to $[M+Na]^+$ and $[M+K]^+$ ions together with peaks showing the elimination of one {m/z 3231 and 3246 for $[(M\text{-calix})+Na]^+$ and $[(M\text{-calix})+K]^+$} and two calix[4]arene subunits {m/z 2639 and 2655 for $[(M\text{-}2\cdot calix)+Na]^+$ and $[(M\text{-}2\cdot calix)+K]^+$}, respectively. The ^{1}H NMR spectrum of **9** reflects the high symmetry of molecule showing a typical splitting pattern of monosubstituted calixarene - two sets of doublets for equatorial and axial - CH_2- protons together with three signals for propyl groups in the 1:2:1 ratio. The temperature dependent ^{1}H NMR spectra measured in the temperature region -90 °C to 120 °C (CD_2Cl_2, $CDCl_2$-$CDCl_2$) did not show any unusual conformational behaviour of this compound.

In conclusion, we have found a simple procedure leading directly from bromosubstituted calix[4]arene to the appropriate monohydroxy derivative via the oxidation of lithiated species. The application of this oxidation reaction to di- or tetrasubstituted calixarenes as well as the further complexation study of new derivatives are currently under investigation.

EXPERIMENTAL PART:

Melting points were determined with a Boetius Block apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Gemini 300, a Bruker AMX3 400 and a Bruker Avance DRX 500 spectrometers using tetramethyl silane as an internal standard. IR spectra were measured using a Nicolet 740 spectrometer.

5-Hydroxy-25,26,27,28-tetrapropoxycalix[4]arene (4): Bromoderivative **2** (200 mg) was dissolved in 100 ml of THF, cooled to -78 °C and 1.6 M BuLi in hexane (8 eq.) was added dropwise. The mixture was then stirred for 0.5 h at the same temperature. A stream of dry oxygen (dried on the column filled with a mixture of P_2O_5 and silica gel) was then bubbled through a solution for 1 h and the reaction mixture was poured into diluted aqueous HCl. After extraction with $CHCl_3$ the organic layer was washed with 10% $Na_2S_2O_3$, water and dried over $MgSO_4$. The crude product was purified on silica gel column using CH_2Cl_2/petroleum ether (1:3) as eluent to give 81 mg (44%) of **4** (yellowish crystals, m.p.: 163-166 °C, acetone-$CHCl_3$) and 71 mg of **1** (white solid, 40%). ^{1}H NMR of **4** ($CDCl_3$, 300 MHz) δ: 0.98 (t, 6H, J = 7.7 Hz, CH_3), 1.03 (t, 3H, J = 7.2 Hz, CH_3), 1.04 (t, 3H, J = 7.2 Hz, CH_3), 1.91 (m, 8H, -CH_2-CH_3), 3.08 (d, 2H, J = 13.7 Hz, CH_2-eq.), 3.17 (d, 2H, 13.7 Hz, CH_2-eq.), 3.73 (t, 2H, J = 7.1 Hz, O-CH_2-CH_2-), 3.80 (t, 2H, J = 7.1 Hz, O-CH_2-CH_2-), 3.90 (t, 4H, J = 7.2 Hz, O-CH_2-CH_2-), 4,42 (d, 2H, J = 13.2 Hz, CH_2-ax.), 4.47 (d, 2H, J = 13.2 Hz, CH_2-ax.), 5.87 (s, 2H, H-arom), 6.42-6.52 (m, 3H, H-arom), 6.67-6.82 (m, 6H, H-arom), 7.26 (s, 1H, OH); MS FAB ($C_{40}H_{48}O_5$) calcd. 608.35, found 608.1 (M^+); EA: calcd./found, C 78.91/78.73, H 7.95/7.71; IR ($CHCl_3$) ν_{max} (cm^{-1}): 3602 (OH).

5,25,26,27,28-pentapropoxycalix[4]arene (4a): The mixture of hydroxy derivative **4** (50 mg), NaH (60% oil susp., 10 mg) and 40 ml of propyl iodide was dissolved in 10 ml of DMF and stirred overnight at room temperature. The reaction mixture was poured into water, extracted with CH_2Cl_2 and organic layer was dried over $MgSO_4$. The crude product was purified on preparative TLC (silica gel) using mixture $CHCl_3$/petroleum ether (3:1) as an eluent to give of **4a** as white solid in 76% yield, m.p.: 131-33 °C, acetone. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.92-1.03 (m, 12H, 5 x CH_3), 1.65 (m, 2H, -CH_2-CH_3), 1.91 (m, 8H, -CH_2-CH_3), 3.09 (d, 2H, J = 13.7 Hz, CH_2-eq.), 3.15 (d, 2H, 13.7 Hz, CH_2-eq.), 3.57 (t, 2H, J = 6.6 Hz, O-CH_2-CH_2-), 3.75 (t, 2H, J = 7.1 Hz, O-CH_2-CH_2-), 3.85 (m, 6H, O-CH_2-CH_2-), 4.42 (d, 2H, J = 13.2 Hz, CH_2-ax.), 4.46 (d, 2H, J = 13.2 Hz, CH_2-ax.), 6.03 (s, 2H, H-arom), 6.50 (m, 3H, H-arom), 6.60-6.72 (m, 6H, H-arom); MS FAB ($C_{43}H_{54}O_5$) calcd. 650.40, found 650.2 (M^+).

5-Benzyloxy-25,26,27,28-tetrapropoxycalix[4]arene (4b): Prepared using the same procedure as for **4a** with benzyl chloride as an alkylation agent. Yield: 52 %, white solid, m.p.: 145-147 °C (AcOEt-cyclohexane), ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.98 (t, 6H, J = 7.2 Hz, -CH_2-*CH_3*), 1.05 (t, 6H, J = 7.7 Hz, -CH_2-*CH_3*), 1.91-1.96 (m, 8H, -*CH_2*-CH_3), 3.12 (d, 2H, J = 13.2 Hz, CH_2-eq.), 3.18 (d, 2H, J = 13.2 Hz, CH_2-eq.), 3.77 (t, 2H, J = 7.2 Hz, O-*CH_2*-CH_2-), 3.83 (t, 2H, J = 7.7 Hz, O-*CH_2*-CH_2-), 3.91 (t, 6H, J = 7.7 Hz, O-*CH_2*-CH_2-), 4.46 (d, 2H, J = 13.2 Hz, CH_2-ax.), 4.49 (d, 2H, J = 13.2 Hz, CH_2-ax.), 4.68 (s, 2H, Ar-O-*CH_2*-Ar), 6.10 (s, 2H, H-arom), 6.49 (s, 3H, H-arom), 6.69-6.71 (m, 2H, H-arom), 6.75-6.79 (m, 4H, H-arom), 7.36 (brs, 5H, H-arom); MS FAB ($C_{47}H_{54}O_5$) calcd. 698.40, found 698.7 (M^+).

5-acetoxy-25,26,27,28-tetrapropoxycalix[4]arene (4c): Hydroxy derivative **4** (56 mg) was dissolved in 5 ml of acetic anhydride, then a catalytic amount of p-toluenesulphonic acid was added and the reaction mixture was refluxed for 20 h. The reaction mixture was poured into water and extracted with $CHCl_3$. The chloroform layer was dried with $MgSO_4$ and evaporated to dryness. The crude product was purified by preparative TLC on silica gel plates using petroleum ether:chloroform (10:1) as an eluent to yield 42 mg of **4b** (70%) as a yellowish oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.95 (t, 6H, J = 7.2 Hz, CH_3), 1.03 (t, 3H, J = 7.2 Hz, CH_3), 1.04 (t, 3H, J = 7.2 Hz, CH_3), 1.91 (m, 8H, -*CH_2*-CH_3), 2.14 (s, 3H, $COCH_3$), 3.15 (d, 2H, J = 13.2 Hz, CH_2-eq.), 3.19 (d, 2H, 13.7 Hz, CH_2-eq.), 3.79 (m, 4H, O-*CH_2*-CH_2-), 3.90 (t, 4H, J = 7.7 Hz, O-*CH_2*-CH_2-), 4,44 (d, 2H, J = 13.2 Hz, CH_2-ax.), 4.46 (d, 2H, J = 13.2 Hz, CH_2-ax.), 6.12 (s, 2H, H-arom), 6.40-6.52 (m, 3H, H-arom), 6.68-6.82 (m, 6H, H-arom); MS FAB ($C_{42}H_{50}O_6$) calcd. 650.36, found 650.5 (M^+); IR ($CHCl_3$) ν_{max} (cm^{-1}): 1744 (C=O).

Bis-calix[4]arene (5): Hydroxy derivative **4** (50 mg) was dissolved in 5 ml of dry DMF, NaH (6 mg, 60% oil dispersion, 2.1 equiv.) was added and the solution was stirred 30 min at room temperature. 1,2-bis(bromomethyl)benzene (10 mg, 0.95 equiv.) was then added and the reaction mixture was stirred for 2 days at room temperature. The reaction mixture was poured into dilute hydrochloric acid (1:10), extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$. The crude product was purified by preparative TLC on silica gel using petroleum ether:$CHCl_3$ (10:1) as an eluent to give proposed product **5** in 67% yield as white solid, m.p.: 88-93 °C ($CHCl_3$-methanol), ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88-0.92 (m, 6H, CH_3), 0.97-1.08 (m, 18H, CH_3), 1.91-1.96 (m, 16H, -*CH_2*-CH_3), 3.11 (d, 4H, J = 13.2 Hz, CH_2-eq.), 3.18 (d, 4H, 13.7 Hz, CH_2-eq.), 3.78 (t, 4H, J = 7.7 Hz, O-*CH_2*-CH_2-), 3.83 (t, 4H, J = 7.2 Hz, O-*CH_2*-CH_2-), 3.91 (t, 8H, J = 7.7 Hz, O-*CH_2*-CH_2-), 4.46 (d, 4H, J = 12.7 Hz, CH_2-ax.), 4.49 (d, 4H, J = 13.2 Hz, CH_2-ax.), 4.74 (s, 4H, O-CH_2-Ar), 6.10 (s, 4H, H-arom), 6.17 (brs, 6H, H-arom), 6.62-6.67 (m, 4H, H-arom), 6.71-6.75 (m, 8H, H-arom), 7.33 (m, 2H, H-arom), 7.40 (m, 2H, H-arom). EA for $C_{88}H_{102}O_{10}$: calcd./found, C 80.09/79.63, H 7.79/7.65.

Bis-calix[4]arene (6): Similar procedure as for derivative **5** using 1,3-bis(bromomethyl)benzene as an alkylation agent. Yield: 55%, white solid, m.p.: 78-82 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.97 (t, 12H, J = 7.7 Hz, CH_3), 1.03 (t, 12H, J = 7.7 Hz, CH_3), 1.92 (m, 16H, -CH_2-CH_3), 3.15 (d, 4H, J = 13.2 Hz, CH_2-eq.), 3.18 (d, 4H, 13.2 Hz, CH_2-eq.), 3.75 (t, 4H, J = 7.7 Hz, O-CH_2-CH_2-), 3.81 (t, 4H, J = 7.7 Hz, O-CH_2-CH_2-), 3.89 (t, 8H, J = 7.7 Hz, O-CH_2-CH_2-), 4.43 (d, 4H, J = 13.2 Hz, CH_2-ax.), 4.46 (d, 4H, J = 13.2 Hz, CH_2-ax.), 4.66 (s, 4H, O-CH_2-Ar), 6.08 (s, 4H, H-arom), 6.48 (brs, 6H, H-arom), 6.63-6.76 (m, 12H, H-arom), 7.27-7.35 (m, 4H, H-arom). MS FAB calcd. for $C_{88}H_{102}O_{10}$ 1318.74, found 1318.9 (M^+).

Bis-calix[4]arene (7): Similar procedure as for derivative **5** using 1,4-bis(bromomethyl)benzene as an alkylation agent. Yield: 72 %, white solid, m.p.: 98-101 °C ($CHCl_3$-methanol). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.99 (t, 12H, J = 7.5 Hz, CH_3), 1.05 (t, 12H, J = 7.5 Hz, CH_3), 1.91-1.97 (m, 16H, -CH_2-CH_3), 3.12 (d, 4H, J = 13.7 Hz, CH_2-eq.), 3.18 (d, 4H, 13.2 Hz, CH_2-eq.), 3.77 (t, 4H, J = 7.5 Hz, O-CH_2-CH_2-), 3.83 (t, 4H, J = 7.5 Hz, O-CH_2-CH_2-), 3.92 (t, 8H, J = 7.7 Hz, O-CH_2-CH_2-), 4.46 (d, 4H, J = 13.7 Hz, CH_2-ax.), 4.49 (d, 4H, J = 13.2 Hz, CH_2-ax.), 4.67 (s, 4H, O-CH_2-Ar), 6.09 (s, 4H, H-arom), 6.49 (brs, 6H, H-arom), 6.66-6.71 (m, 4H, H-arom), 6.76-6.80 (m, 8H, H-arom), 7.33 (s, 4H, H-arom). EA for $C_{88}H_{102}O_{10}$: calcd./found, C 80.09/79.59, H 7.79/7.55.

Tris-calix[4]arene (8): The mixture of hydroxy derivative **4** (135 mg) and NaH (60% oil susp., 18 mg) was dissolved in 20 ml of DMF and stirred for 30 minutes. Then 1,3,5-tris(bromomethyl)-2,4,6-trimethylbenzene (28 mg) was added and the mixture was stirred for 2 days at room temperature. The reaction mixture was poured into diluted hydrochloric acid (1:10), extracted with $CHCl_3$ and organic layer was dried over $MgSO_4$. The crude product was purified on preparative TLC (silica gel) using a mixture of $CHCl_3$/petroleum ether (1:10) as an eluent to give 75 mg (55 %) of **8** as white solid (m.p.: 248-9 °C, ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.96-1.03 (m, 36H, 12 x CH_3), 1.93 (m, 24H, -CH_2-CH_3), 2.28 (s, 9H, Ar-CH_3), 3.11 (d, 6H, J = 13.2 Hz, CH_2-eq.), 3.15 (d, 6H, J = 13.2 Hz, CH_2-eq.), 3.76-3.90 (m, 24H, O-CH_2-CH_2-), 4.44 (d, 6H, J = 13.2 Hz, CH_2-ax.), 4.46 (d, 6H, J = 13.2 Hz, CH_2-ax.), 4.71 (s, 6H, Ar-CH_2-O), 6.21 (s, 6H, H-arom), 6.52-6.71 (m, 27H, H-arom). EA for $C_{132}H_{156}O_{15}$: calcd./found, C 79.96/79.51, H 7.93/7.61.

Hexakis-calix[4]arene (9): The mixture of hydroxy derivative **4** (525 mg) and NaH (60% oil susp., 70 mg) was dissolved in 50 ml of DMF and stirred for 30 minutes. Then hexakis(bromomethyl)benzene (55 mg) was added and the mixture was stirred for 2 days at room temperature. The reaction mixture was poured into diluted hydrochloric acid (1:10), extracted with $CHCl_3$ and the organic layer was dried over $MgSO_4$. The crude product was purified by column chromatography (silica gel) using a mixture of $CHCl_3$/petroleum ether (1:1) as an eluent to give 169 mg (52 %) of **9** as white solid (m.p.: 173-5 °C, ethyl acetate). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 0.88

(t, 18H, J = 7.4 Hz, 6 x CH_3), 0.93-1.01 (m, 54H, 18 x CH_3), 1.83-1.92 (m, 48H, -CH_2-CH_3), 3.03 (d, 12H, J = 13.8 Hz, CH_2-eq.), 3.11 (d, 12H, J = 13.2 Hz, CH_2-eq.), 3.75 (t, 36H, J = 7.5 Hz, O-CH_2-CH_2-), 3.86 (t, 12H, J = 7.7 Hz, O-CH_2-CH_2-), 4.36 (d, 12H, J = 13.2 Hz, CH_2-ax.), 4.43 (d, 12H, J = 13.2 Hz, CH_2-ax.), 4.99 (brs, 12H, Ar-CH_2-O), 6.36 (s, 12H, H-arom), 6.42-6.47 (m, 36H, H-arom), 6.61-6.67 (m, 18H, H-arom). MALDI TOF MS: calcd. for $C_{252}H_{294}O_{30}$ 3800.15, found m/z 3822 and 3838 for $[M+Na]^+$ and $[M+K]^+$, m/z 3231 and 3246 for $[(M\text{-calix})+Na]^+$ and $[(M\text{-calix})+K]^+$, m/z 2639 and 2655 for $[(M\text{-}2\cdot calix)+Na]^+$ and $[(M\text{-}2\cdot calix)+K]^+$, respectively.

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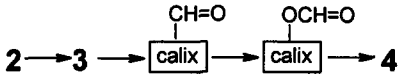
6. Derivative **4** was prepared according to the following scheme:



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9. In fact, this compound has probably up and down alternating arrangement of calixarene units as other hexa-substituted benzen derivatives of this type. See: Hardy A. D. U., MacNicol D. D., Wilson D. R. *J. Chem. Soc. Perkin. Trans. II*, **1979**, 1011-1019.

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