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Bridge-disubstituted calix[4]arenes obtained via a new preparative route. Synthesis and structural study

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ABSTRACT

A series of calix[4]arenes bearing various substituents including alkyl, *p*-bromobenzyl, carboxy and allyl at opposite methylene bridges has been synthesized via successive metallation followed by nucleophilic substitution. In a first step, mono-lithiated calix[4]arenes react with terminal bromoalkanes to give 2-alkylated calix[4]arenes or with CO_2 the respective calixarene-2-carboxylic acid in good yields. A second lithiation step of the monosubstituted products with subsequent attachment of both polar and non-polar substituents yields several new diametrally bridge-disubstituted calix[4]arenes. 2D-NMR measurements establish the disubstituted calixarenes to predominantly adopt the 1,2-*alternate* conformation in solution. First examples of X-ray crystal structures of the new type of disubstituted calix[4]arenes are described featuring the calix[4]arene also in the rare 1,2-*alternate* conformation.

1. Introduction

Calix[*n*]arenes are well known macrocyclic molecules of defined size promising for versatile supramolecular and biological applications due to their multiple availability for chemical modification within a concentrated space.[1–3] In the special case of a calix[4]arene, there are 12 possible sites for substitution, eight of them located on the upper rim and lower rim sites of the calixarene and further four located at the connecting methylene bridges (Fig. 1). Dependent on the orientation of the arene units with regard to the central plane including the four sp^3-methylene carbons, there are four basic conformational isomers designated as 'cone', 'partial cone', '1,3-alternate' and '1,2-alternate'. They are found in a transformational equilibrium if the lower rim of the calix[4]arene is substituted with residues smaller than ethyl.[4]

The chemistry of the vertical substitution of the calix[4]arene is already intensively studied and the resulting products are characterized with reference to their conformational behaviour or inclusion properties.[1–3] By way of contrast, only a small number of publications are engaged in the impact of a lateral modification of one of the methylene bridges.[5,6] We recently demonstrated that the lateral attachment of neither a single polar carboxy group[7] nor non-polar alkyl chains of different length[8] significantly hamper the conformational equilibrium of the tetramethoxycalix[4]arene, being beneficial for the preservation of the inclusion behaviour of the chalice. Exceeding a potential use of the bridge-monosubstitution of a calixarene for the lateral attachment to a solid support, laterally disubstituted calixarenes will open further new structural possibilities for a calixarene to act as bifunctional building block for the design of more complex coordination type or covalently linked supramolecular constructions. However, till now the chemistry of bridge-disubstituted calixarenes is rather poorly developed and often associated with low yields regarding their synthesis, attributable to multi-step reaction sequences that have been used to introduce two bridge substituents to opposite methylene bridges. They include the famous spirodienone route,[9–11] a procedure via anionic *ortho*-Fries-rearrangement[12] and fragment condensation methods.[13] In the present paper, we describe a convenient two-step synthesis for bridge diametrally disubstituted calix[4]arenes and report on the promising structural properties of this type of calixarenes.

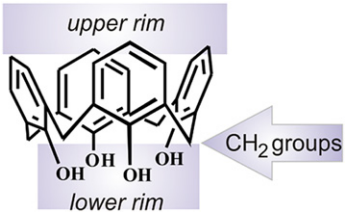

Fig. 1. Reactive centers of the basic calix[4]arene.

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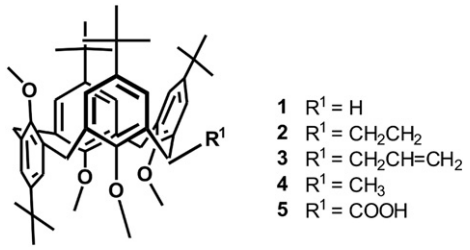
2. Results and discussion

Earlier attempts to succeed with a simultaneous twofold or multiple bridge-disubstitution of the tetramethoxycalix[4]arene **1** (Scheme 1) following an alkylation reaction under the condition of excess *n*-BuLi failed, yielding only monoalkylation product. This can be deduced from the literature data[5] and has similarly been experienced by us. Although, until now, there is no entirely plausible explanation for this unusual behaviour, hampered multisite lithiation or steric hindrance caused by particular lithium complexation might be seen potential reasons. However, this drawback has now been overcome by using a sequential lithiation–alkylation process as described below. Following this new preparative route, in a first sequence the bridge-monosubstituted calixarenes **2**–**5** (Scheme 1) were obtained via lithiation of a single methylene bridge of **1** and subsequent addition of corresponding electrophiles according to a previous description.[6] All isolated products exhibit a clear predominance of the *partial cone* conformation with an equatorial arrangement of the bridge-substituent[14] between *syn* orientated arene units in $CDCl_3$ solution, being already described in the literature.[7,8] This particular conformation is also preferred of the new allyl-compound **3**. Nevertheless, addition of small amounts NaI and acetonitrile-d_3 (1/10 v/v) fixes the bridge-monosubstituted calix[4]arenes **2**–**5** in the *cone* conformation, caused by the complexation of the sodium ion with the methoxy groups.



Scheme 1. Formula structures of the parent calixarene **1** and bridge-monosubstituted compounds **2**–**5**.

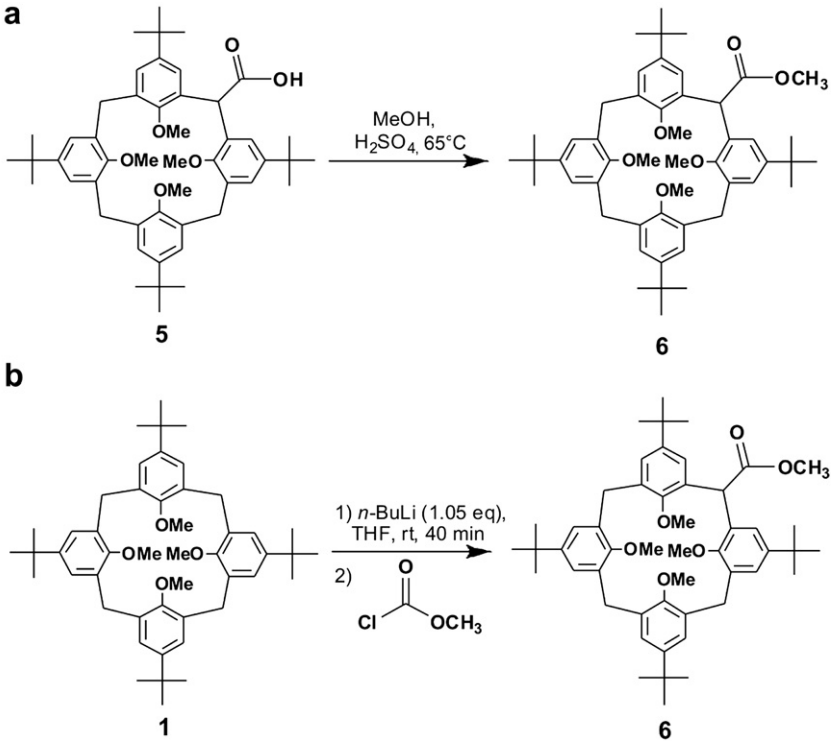
In this connection, it seemed also interesting to us to convert the carboxylic acid **5** to the corresponding methyl ester **6**. Usual acidic esterification with methanol and catalytic amounts of sulfuric acid (Scheme 2(a)) gave the respective ester **6** in moderate yield (59%). The conformational composition of **6** coincides with the other bridge-monosubstituted compounds **2**–**5**, preferably exhibiting a *partial cone* conformation in $CDCl_3$ solution.

In another attempt, we tested a possibility to directly introduce the ester function into a single bridge position by reaction with methyl chloroformate (Scheme 2(b)). Using this reagent together with 1.05 equiv *n*-BuLi under ambient conditions easily yielded 76% of the methyl ester **6** in high purity. Hence, we found a smart one-step reaction offering also an appreciated alternative for the synthesis of higher ester homologues known for their potential to switch the calixarene conformationally from the *partial cone* to the *cone* form.[15]

Fortunately, we succeeded in growing crystals of the bridge monoallyl substituted calixarene **3**, enabling us to validate the conformational influence of the substituent also in the solid state. In accordance with known structures of bridge-monosubstituted tetramethoxycalix[4]arenes,[7,8,16–18] compound **3** also adopts the *partial cone* conformation, bearing the allyl substituent equatorial between *syn* orientated arene units (Fig. 2).

Obviously, only long and sufficiently rigidified lateral residues fix the calixarene core in the prominent *cone* conformation, as shown for a bridge-monosubstituted *n*-propoxycarbonyl[15] as well as an aminoalkyl tethered calix[4]arene.[6] Due to the absence of hydrogen donor substituents, no intramolecular interactions are observed. The packing is only stabilized by weak van der Waals contacts, e.g., involving the allyl substituent (C51–H51B···H19), 2.290 (2) Å, 171°, Table S1].

Returning to the preparative route, i.e., conversion from the bridge-monosubstituted to bridge-disubstituted calix[4]arenes, a subsequent lithiation and substitution step is applied (Scheme 3). To avoid side-reactions with the first bridge substituent, the syntheses of the compounds **7**–**14** were performed under kinetically driven conditions (−78 °C) with a high excess of *n*-BuLi (6 equiv).



Scheme 2. Different pathways for the synthesis of the bridge-monoester calixarene **6**.

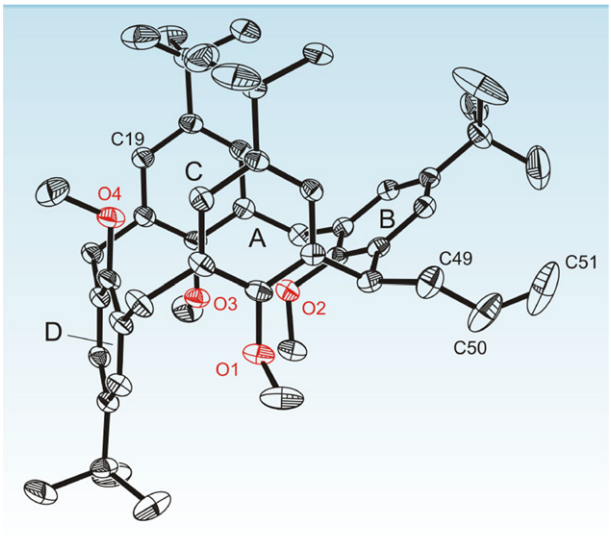
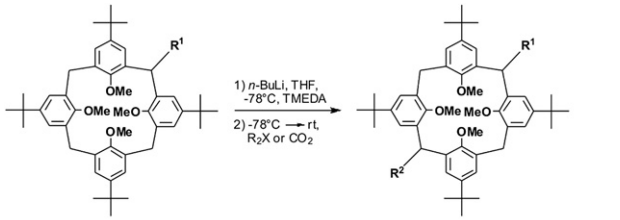


Fig. 2. Molecular structure of the monoallyl calixarene **3** in the *partial cone* conformation. Thermal ellipsoids are drawn at the 50% probability level. H atoms as well as a disordered position of one *tert*-butyl group are omitted for clarity.



2 R^1= CH_2CH_3
2 R^1= CH_2CH_3
2 R^1= CH_2CH_3

2 R^1= CH_2CH_3
3 R^1= $CH_2CH{=}CH_2$
3 R^1= $CH_2CH{=}CH_2$
4 R^1= CH_3
4 R^1= CH_3
6 R^1= $COOCH_3$

7 R^1= CH_2CH_3, R^2= CH_3
8 R^1= CH_2CH_3, R^2= $CH_2CH{=}CH_2$
9 R^1= CH_2CH_3, R^2= H_2C-Br

10 R^1= CH_2CH_3, R^2= COOH
11 R^1= $CH_2CH{=}CH_2$, R^2= $CH_2CH{=}CH_2$
12 R^1= $CH_2CH{=}CH_2$, R^2= COOH
13 R^1= CH_3, R^2= CH_3
14 R^1= CH_3, R^2= COOH
15 R^1= $C(n\text{-}Bu)_2OH$, R^2=COOH

Scheme 3. Formula structures of the laterally disubstituted calixarenes **7**–**15** obtained from subsequent substitution of the monosubstituted calix[4]arenes **2**–**4** and **6**.

Noteworthy, in spite of the excess of *n*-BuLi, there is only one substitution in the diametral bridge position showing similar behaviour as for the monosubstitution of **1**. As before, the existence of only one distinct lithiated intermediate can be assumed.

Moreover, the allylic protons in **3** obviously show a lower kinetic acidity compared to the methylene H-atoms located on the opposite site of the calixarene core, resulting in the formation of the diallyl derivative **11** as well as the allyl substituted carboxylic acid **12** on the reaction with allyl bromide or CO_2, respectively. However, the reaction of the calixarene monoester **6** with *n*-BuLi remarkably failed to yield the desired bridge-disubstituted carboxylic acid ester derivative. From NMR analysis, a signal at 77.1 ppm indicates that a reduction of the ester function to a tertiary alcohol has occurred. In connection with the C=O signal at 179.0 ppm and the result of the mass spectra, this new compound was identified as **15**.

The presence of two substituents on opposite methylene bridges can be concluded from different signals of the remaining methine protons in the ^{1}H NMR-spectra. Some of the synthesized products (**11** and **15**) exhibit a clear ^{1}H NMR spectrum with a highly limited number of signals, whereas for all the other compounds additional signals can be found, e.g., in the methoxy as well as the *tert*-butyl group region. This suggests the predominance of a single conformer at 294 K in $CDCl_3$ solution for **11** and **15**, while the other compounds should exist in at least two conformations. Following the symmetry of the compounds (C_{2h} for **11** and C_s for **15**), a singlet of the remaining methylene protons in **11** and two closely arranged doublets in a 1:1 ratio for **15** indicates their isoclinal arrangement between *anti* orientated arene units. Considering the results of the ROESY spectra for **11** and **15**, showing crosspeaks for the methine protons exclusively with the neighbouring methoxy groups as well as a ^4J coupling of the H_a and H_i protons (Fig. 3) in the COSY spectra for this single conformer, the 1,2-*alternate* conformation can be assigned, which is a very uncommon conformation in solution state calix[4]arene chemistry.[19]

Due to the high conformational flexibility at room temperature, a conformational assignment for all the other compounds is not possible under ambient conditions. Therefore we performed detailed 2D NMR measurements at 265 K. Following the specific correlations in the HSQC, HMBC, COSY and ROESY spectra (see ESD part), the aforementioned resonances indicate also the presence of the 1,2-*alternate* conformer in the other compounds in a greater amount than normally observed for calix[4]arenes, increasing with the length and bulkiness of the two bridge substituents (Table 1). The respective fractions of the 1,2-*alternate* conformer have been calculated by comparison of the methoxy signals of this specific conformer (located in all compounds between 2.78 and 3.11 ppm) to all occurring methoxy signals (see ESD Fig. S9–S26).

This behaviour may explain the high 1,2-*alternate* fraction in compounds **11** and **15**, both possessing voluminous bridge substituents. Interestingly, addition of NaI and the more polar acetonitrile-d_3 did not cause a conformational interconversion to a pure *cone* conformation, as observed for the bridge-monosubstituted calix[4]arenes. This seems reasonable because a successive rotation of two arene units would lead to an axial arrangement of at least one bridge substituent, which is avoided for steric reasons.[14]

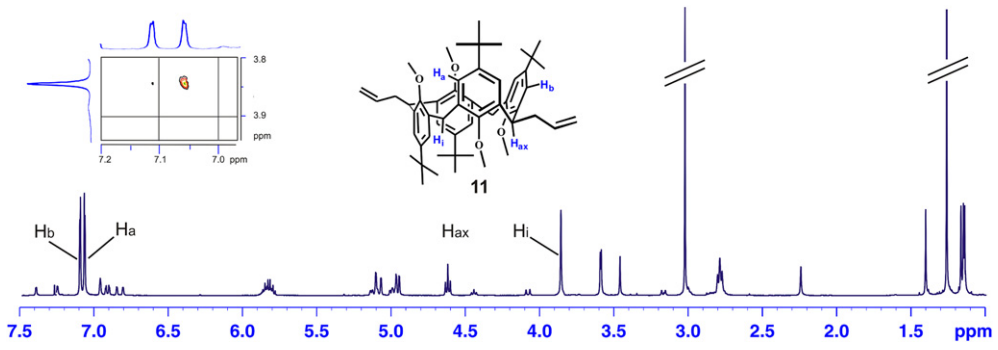


Fig. 3. ^{1}H NMR spectrum of compound **11** at 265 K indicating a high fraction of the 1,2-*alternate* conformer. Inset: Cut-out of the COSY spectrum of **11** showing the ^{4}J coupling of H_a and H_i protons.

Table 1
Fractions of the 1,2-*alternate* conformer and position of the methoxy proton signal(s) from NMR measurements in $CDCl_3$ at 265 K

Compound	1,2-*Alternate* fraction (%)	^{1}H CH_3O-signal(s) (1,2-*alternate* fraction, ppm)	
4	7	3.07	2.96
7	33	3.08	2.97
8	39	3.04	3.01
9	31	3.03	2.77
10	38	3.05	3.04
11	75	3.02	—
12	42	2.96	2.94
13	18	3.02	—
14	36	3.09	2.97
15	88	3.04	2.95

Since there are no reports on crystal structures of bridge-disubstituted tetramethoxycalix[4]arenes yet, the question arises, whether this conformational switch from a preferred *partial cone* conformation to 1,2-*alternate* by the addition of a second bridge substituent can also be found in the solid state. For related bridge-disubstituted tetrahydroxycalix[4]arenes, the *cone* conformation was determined as the preferred one in the solid state,[14,20] and only in one special case the calixarene is shown in the 1,2-*alternate* form attributed to two extremely bulky mesityl groups, located *isoclinally* at opposite methylene bridges.[21] X-ray analysis of three single crystals of the present bridge-disubstituted tetramethoxycalixarenes (**11**, **12** and **15**), reveal the calixarene core in the 1,2-*alternate* conformation proving our before mentioned assumption. The difference in the conformational behaviour between the crystallized monoallyl calixarene **3** and its diallyl pendant **11** is obvious (Fig. 4(a)) and can be easily comprehended by comparison of the metrical data (Table 2).

Beside the conformational difference, one of the methoxy groups (C19) in **11** points inside the cavity, leading to a compact molecular structure stabilized by an intramolecular C–H···π-contact[22] (Table S1). The high symmetry of the molecule enables a linear arrangement along the crystallographic *c*-direction with trans orientation of the lateral residues (Fig. S28). The compact structure of the crystal is reflected by a high KPI index,[23] indicating a closed packed structure and thus in combination with the narrowed host-cavity that any solvent incorporation is avoided.

Increasing the polarity and donor-acceptor behaviour of the molecule by exchange of the bridge allyl residue for a carboxylic function preserves again the 1,2-*alternate* conformation, but additionally enables the inclusion of solvent molecules as found in the crystals of compound **12** (Fig. 4(b)). An interesting hydrogen bonded architecture is observed involving two opposite methoxy oxygen atoms coordinated via further two solvent molecules with the next calixarene molecule along the crystallographic *a*-direction (Fig. S29). Remarkably, different C–O bond lengths in the two guest molecules are observed leading one to assume the coexistence of corresponding acid/base pairs, i.e., CH_3COOH/H_2O and CH_3COO^-/H_3O^+ in this network (Table S1). Compared to a related structure of the bridge-monofunctionalized carboxylic acid **5** including EtOH and water, the presence of a second bridge-substituent in **12** not only changes the basic conformation of the chalice from *cone* to 1,2-*alternate*, but due to the *exo* orientation of all methoxy groups expands the calixarene cavity. This special geometry allows the incorporation of a water and a hydroxonium ion moderating the channel-like arrangement of solvent molecules. The carboxylic function itself maintains a hydrogen bond to the acid molecule resulting in a crosslink of the channels along the crystallographic *c*-direction (Fig. S29).

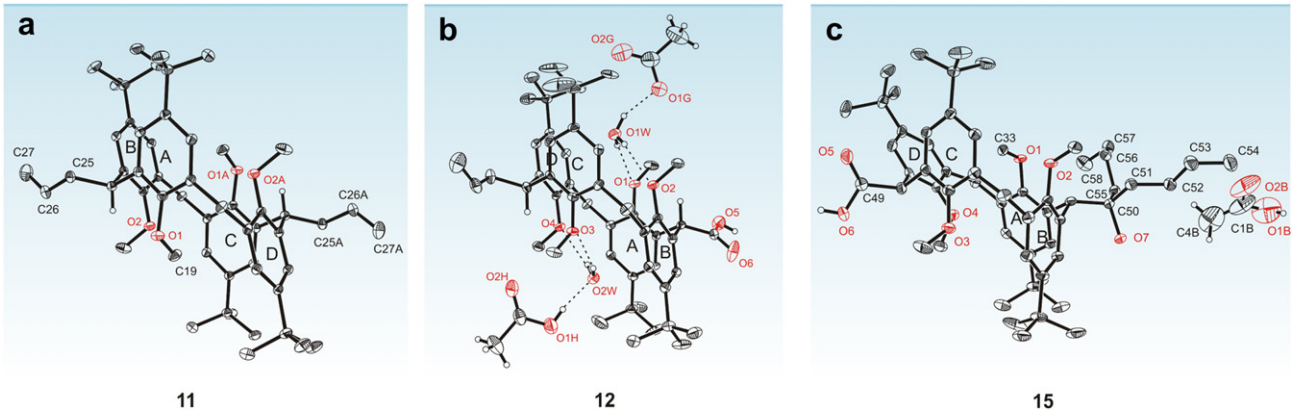


Fig. 4. X-ray crystal structures of the bridge-disubstituted calix[4]arenes **11** (a), **12** (b)and **15** (c). Non-relevant H-atoms have been omitted for clarity. O1W and O2W denote two water molecules inside the calixarene cavity of molecule **12** moderating the hydrogen-bond network.

Table 2
Selected conformational parameters of compounds **3**, **11**, **12** and **15** and their calculated packing indices (KPIs). Compounds **15** and **15a** denote two crystallographically independent molecules in this structure

	3	**11**	**12**	**15/15a**
Interplanar angle (°)				
A/mpla	88.0 (1)	78.2 (1)	68.3 (1)	67.8/62.4 (1)
B/mpla	36.0 (1)	64.9 (1)	67.9 (1)	86.2/89.5 (1)
C/mpla	88.0 (1)	78.2 (1)	68.7 (1)	88.1/87.9 (1)
D/mpla	86.6 (1)	64.9 (1)	67.0 (1)	48.3/48.2 (1)
A/C	3.6 (1)	0	0.6 (1)	20.3/25.5 (1)
B/D	50.6 (1)	0	1.0 (1)	38.1/42.8 (1)
KPI	64.1	67.9	65.7	65.5

Although crystals of **15** also feature the calixarene core in the 1,2-*alternate* conformation (Fig. 4(c)), the presence of the bulky lateral tertiary alcohol residue obtained by nucleophilic attack of an ester function results in a certain deviation of the metrical parameters of the calixarene core (Table 2). Moreover, the bulky alcoholic substituent forces a neighbouring methoxy group (C33) to point inside the cavity locking the cavity for any solvent inclusion. The packing is characterized by molecular strands along the crystallographic *c*-axis, linking the calixarene molecules alternately by a hydrogen bond involving the carboxylic function of one molecule and the OH-function of the next one (Fig. S30). Interestingly, the conformational behaviour in the solid state is only slightly affected by the donor-acceptor interactions between the bridge substituents and guest molecules, thus indicating the intrinsic conformational influence of the two bridge substituents.

3. Conclusions

A novel direct and short route for the synthesis of bridge-disubstituted calix[4]arenes, including the application of a successive lithiation and substitution sequence is demonstrated, yielding diametrally bridge-substituted calixarenes in high quantity and purity. Compared to related bridge-monosubstituted calixarenes, the twofold substituted pendants exhibit an increased fraction of the 1,2-*alternate* conformer in solution. X-ray analysis of compounds bearing the diametral substitution pattern prove this rare conformation to be the preferable one also in the solid state, independent of further host–guest-interactions. Therefore, for the first time a conformationally conducting influence of the bridge residues on the calixarene core is demonstrated. The obtained compounds feature significantly different polarities at their opposite lateral arms, being beneficial for further synthetic steps, including lateral attachment, polymerization or surface active applications. Whereas the diametral substitution pattern seems to be useful for the lateral aggregation of the calixarene core, the observed conformational adaptation upon successive lateral substitution may be of interest for the design of novel supramolecular receptors.[24,25]

4. Experimental

4.1. General

Melting points were determined on a microscope heating stage PHMK Rapido (VEB Dresden Analytik) and are uncorrected. IR spectra were measured on a Nicolet FT-IR 510 as KBr pellets. NMR spectra were recorded on a Bruker Avance DRX 500 spectrometer at 500.1 MHz (^{1}H-NMR) and 125.7 MHz (^{13}C-NMR), respectively, in $CDCl_3$ solution. Chemical shifts δ are reported in parts per million relative to the internal reference TMS. For the bridge monosubstituted allyl-compound **3** the addition of small amounts of NaI and acetonitrile-d_3 fixes the calixarene in the *cone* conformation (Fig. S7 and S8). Mass spectra were measured on a Varian 320 MS. Elemental analyses were performed on a Heraeus CHN-Rapid Analyzer. Reagents and chemicals for the synthesis were used as purchased from chemical suppliers. The solvents used were purified or dried according to common literature procedures. The 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene (**1**) was prepared from commercially available 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene according to the published procedure.[26]

4.2. Synthesis of bridge-monosubstituted calixarenes 2–5

The synthesis followed the procedure described by Scully[5] and Hertel,[6] using a solution of **1** in 50 mL dry THF and 4 equiv *n*-BuLi (1.6 M in hexanes). The analytical data of compounds **2**, **4** and **5** are in accordance with the literature.[5]

*4.2.1. 2-Allyl-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene (**3**).* Reagents: **1** (2.13 g, 3.0 mmol); *n*-BuLi (1.6 M in hexane, 7.5 mL, 12.0 mmol); allyl bromide (1.45 g, 1.05 mL, 12.0 mmol). Yield: 1.8 g (80%). ^{1}H NMR: δ=7.24 (d, 2H, H–Ar, $^4J_{HH}$=2.1 Hz), 7.17 (s, 4H, H–Ar), 7.15 (d, 2H, H–Ar, $^4J_{HH}$=2.1 Hz), 5.75 (m, 1H, $CH_2CH{=}CH_2$), 5.11 (d, 1H, $CH_2CH{=}CH_2$, $^3J_{HH}$=17.0 Hz), 5.00 (d, 1H, $CH_2CH{=}CH_2$, $^3J_{HH}$=10.0 Hz), 4.73 (t, 1H, $CHCH_2CH{=}CH_2$, $^3J_{HH}$=8.4 Hz), 4.30 (d, 3H, CH_2, $^2J_{HH}$=12.4 Hz), 4.19 (s, 6H, OCH_3), 4.15 (s, 6H, OCH_3), 3.41 (d, 3H, CH_2, $^2J_{HH}$=12.4 Hz), 2.89 (t, 2H, $CH_2CH{=}CH_2$, $^3J_{HH}$=8.4 Hz); 1.21 (s, 36H, $C(CH_3)_3$); ^{13}C NMR: δ=150.7 (2C), 148.7, 137.4, 136.0, 134.5 (2C), 134.4, 125.9, 125.6, 122.5, 117.6, 65.2, 65.0, 38.4, 35.7, 34.4, 34.2, 31.3, 31.1 (2C), 30.0. IR (cm^{-1}): 2960, 2929, 2869, 2818, 1640, 1600, 1479, 1461, 1431, 1391, 1360, 1313, 1283, 1227, 1203, 1175, 1128, 1116, 1025, 983, 951, 911, 897, 869, 810, 795, 716, 637, 598, 560. *m*/*z* (CI) 744.9 (MH^+). Elemental analysis calculated for $C_{51}H_{68}O_4$: C, 82.21; H, 9.20. Found: C, 82.06; H, 9.17.

4.3. Esterification of the calixarenecarboxylic acid 5

Usual acidic esterification with dry methanol and catalytic amounts of sulfuric acid was carried out following the described protocol (method A).[15] Alternatively, direct lithiation of the tetramethoxycalix[4]arene **1** and subsequent reaction with methyl chloroformate also yielded the desired methyl ester **6** (method B).

*4.3.1. Methyl-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene-2-carboxylate (**6**).* A: reagents: **5** (1.15 g, 1.5 mmol); methanol (20 mL); concd H_2SO_4 (3 mL). Yield 0.7 g (59%). B: reagents: **1** (0.71 g, 1.0 mmol); *n*-BuLi (1.6 M in hexane, 1.1 mL, 1.05 mmol); methyl chloroformate (81 μL, 0.1 g, 1.05 mmol). Yield 0.6 g (76%).

4.4. General procedure for the synthesis of the bridge-disubstituted calixarenes 7–15

For the preparation of compounds **7**–**15**, a solution of *n*-BuLi (6 equiv, 1.6 M in hexane) and TMEDA (7 equiv) in 30 mL dry THF is cooled to −78 °C. After 30 min, the respective bridge-monosubstituted calixarene is added via syringe and the resulting blood-red solution is allowed to warm up to room temperature. After 40 min the electrophile (alkyl halide or CO_2) is added, turning the colour of the solution immediately to yellow. After another hour, the volatiles are removed under reduced pressure and the crude products are dissolved in CH_2Cl_2. This solution is washed with brine (3×) [the carboxylated compounds **10**, **12**, **14** and **15** were additionally pre-washed with 2 M aqueous hydrochloric acid (2×)], dried over $MgSO_4$ and evaporated to obtain white powders, which were recrystallized from MeOH/$CHCl_3$ (2:1). While compounds **11** and **15** exhibit interpretable NMR spectra, the conformationally more flexible calixarenes **7**–**10** and **12**–**14** show only a few interpretable peaks (as indicated in Table 1). Most of the peaks in these compounds are broad and indistinguishable and are not assigned in the analysis part. Respective NMR spectra of these compounds, with an assignment of the MeO group signals of the different coexisting conformers can be found in the ESD part (Fig. S9–S26). For the compounds **11** and **15** only the resonances of the predominately existing 1,2-*alternate* fraction are assigned.

*4.4.1. 5,11,17,23-Tetra-tert-butyl-2-ethyl-25,26,27,28-tetra-methoxy-14-methylcalix[4]arene (**7**).* Reagents: **2** (0.44 g, 0.6 mmol); *n*-BuLi (2.2 mL, 3.6 mmol); TMEDA (0.6 mL, 0.5 g, 4.2 mmol); methyl iodide (0.3 mL, 0.68 g, 4.8 mmol). Yield: 0.35 g (78%). IR (cm^{-1}): 2958, 2928, 2869, 2819, 1601, 1478, 1460, 1391, 1287, 1245, 1203, 1128, 1023, 941, 869, 793, 745, 728, 646, 543. *m*/*z* (CI) 747.4 (MH^+). Elemental analysis calculated for $C_{51}H_{70}O_4$: C, 81.99; H, 9.44. Found: C, 81.46; H, 9.38.

*4.4.2. 2-Allyl-5,11,17,23-tetra-tert-butyl-14-ethyl-25,26,27,28-tetramethoxycalix[4]arene (**8**).* Reagents: **2** (0.37 g, 0.5 mmol); *n*-BuLi (1.9 mL, 3.0 mmol); TMEDA (0.55 mL, 0.41 g, 3.5 mmol); allyl bromide (0.35 mL, 0.48 g, 4.0 mmol). Yield: 0.30 g (77%). IR (cm^{-1}): 2957, 2932, 2870, 2820, 1640, 1601, 1478, 1461, 1429, 1391, 1360, 1284, 1243, 1202, 1128, 1021, 998, 948, 908, 868, 797, 749, 714, 645, 569, 549, 510. *m*/*z* (CI) 773.5 (MH^+). Elemental analysis calculated for $C_{53}H_{72}O_4$: C, 82.34; H, 9.39. Found: C, 81.95; H, 9.30.

*4.4.3. 2-(p-Bromobenzyl)-5,11,17,23-tetra-tert-butyl-14-ethyl-25,26,27,28-tetramethoxycalix[4]arene (**9**).* Reagents: **2** (0.37 g, 0.5 mmol); *n*-BuLi (1.9 mL, 3.0 mmol); TMEDA (0.55 mL, 0.41 g, 3.5 mmol); *p*-bromobenzyl bromide (1.0 g, 4.0 mmol). Yield: 0.2 g

(40%). IR (cm^{-1}): 2953, 2929, 2868, 2821, 1601, 1587, 1479, 1462, 1429, 1391, 1361, 1286, 1245, 1200, 1176, 1127, 1071, 1020, 1012, 949, 870, 850, 802, 757, 627, 547, 512. *m*/*z* (CI) 903.2 (MH^+). Elemental analysis calculated for $C_{57}H_{73}O_4Br$: C, 75.89; H, 8.16. Found: C, 75.60; H, 8.05.

*4.4.4. 5,11,17,23-Tetra-tert-butyl-14-ethyl-25,26,27,28-tetramethoxycalix[4]arene-2-carboxylic acid (**10**).* Reagents: **2** (0.6 g, 0.8 mmol); *n*-BuLi (3 mL, 4.8 mmol); TMEDA (0.85 mL, 0.65 g, 5.6 mmol); CO_2 (excess). Yield: 0.45 g (74%). IR (cm^{-1}): 2954, 2930, 2868, 2821, 1710, 1598, 1478, 1460, 1431, 1392, 1361, 1286, 1255, 1242, 1201, 1130, 1111, 1017, 997, 952, 932, 891, 870, 816, 806, 781, 737, 708, 663, 628, 592, 558, 509. *m*/*z* (CI) 777.4 (MH^+). Elemental analysis calculated for $C_{51}H_{68}O_6$: C, 78.83; H, 8.82. Found: C, 79.11; H, 8.73.

*4.4.5. 2,14-Diallyl-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene (**11**).* Reagents: **3** (0.54 g, 0.7 mmol); *n*-BuLi (2.6 mL, 4.2 mmol); TMEDA (0.74 mL, 0.57 g, 4.9 mmol); allyl bromide (0.5 mL, 0.7 g, 5.8 mmol). Yield: 0.45 g (82%). ^{1}H NMR: δ=7.11 (d, 4H, $^4J_{HH}$=2.1 Hz), 7.05 (d, 4H, $^4J_{HH}$=2.1 Hz), 5.82 (m, 2H, $CHCH_2CH{=}CH_2$), 5.06 (d, 2H, $CHCH_2CH{=}CH_2$, $^3J_{HH}$=17.1 Hz), 4.93 (d, 2H, $CHCH_2CH{=}CH_2$, $^3J_{HH}$=10.3 Hz), 4.60 (t, 2H, $^3J_{HH}$=8.0 Hz), 3.85 (s, 4H, CH_2), 3.04 (s, 12H, OCH_3), 2.78 (t, 4H, $CH_2CH{=}CH_2$, $^3J_{HH}$=8.0 Hz), 1.26 (s, 36H, $C(CH_3)_3$); ^{13}C NMR: δ=155.1, 154.2, 144.3, 138.3, 137.3, 137.7, 137.5, 132.7, 132.4, 126.0, 125.6, 122.6, 115.9, 115.6, 60.3, 45.6, 39.2, 37.6, 37.5, 35.3, 34.1, 34.0, 31.7, 31.5, 31.4. IR (cm^{-1}): 2954, 2929, 2867, 2821, 1640, 1600, 1477, 1444, 1430, 1392, 1360, 1314, 1290, 1277, 1241, 1224, 1199, 1172, 1131, 1112, 1091, 996, 958, 908, 891, 874, 863, 810, 798, 781, 754, 721, 670, 643, 608, 593, 547, 526, 509. *m*/*z* (CI) 785.4 (MH^+). Elemental analysis calculated for $C_{54}H_{72}O_4$: C, 82.61; H, 9.24. Found: C, 82.35; H, 9.23.

*4.4.6. 14-Allyl-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene-2-carboxylic acid (**12**).* Reagents: **3** (0.42 g, 0.56 mmol); *n*-BuLi (2.2 mL, 3.5 mmol); TMEDA (0.6 mL, 0.46 g, 4 mmol); CO_2 (excess). Yield: 0.34 g (77%). IR (cm^{-1}): 2951, 2928, 2867, 2822, 1709, 1641, 1599, 1478, 1460, 1431, 1392, 1361, 1286, 1242, 1199, 1123, 1016, 997, 957, 909, 892, 872, 814, 781, 743, 708, 640, 624, 591, 556. *m*/*z* (CI) 789.3 (MH^+). Elemental analysis calculated for $C_{52}H_{68}O_6$: C, 79.15; H, 8.69. Found: C, 78.65; H, 8.60.

*4.4.7. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-2,14-dimethylcalix[4]arene (**13**).* Reagents: **4** (0.8 g, 1.1 mmol); *n*-BuLi (4.1 mL, 6.6 mmol); TMEDA (1.2 mL, 0.9 g, 7.7 mmol); methyl iodide (0.55 mL, 1.25 g, 8.8 mmol). Yield: 0.5 g (60%). IR (cm^{-1}): 2957, 2931, 2870, 2821, 1601, 1479, 1460, 1428, 1392, 1361, 1271, 1245, 1230, 1199, 1173, 1121, 1021, 1000, 937, 873, 810, 791, 783, 746, 700, 651, 638, 598, 509. *m*/*z* (CI) 733.4 (MH^+). Elemental analysis calculated for $C_{50}H_{68}O_4$: C, 81.92; H, 9.35. Found: C, 81.91; H, 9.30.

*4.4.8. 5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-14-methylcalix[4]arene-2-carboxylic acid (**14**).* Reagents: **4** (1.08 g, 1.5 mmol); *n*-BuLi (5.6 mL, 9 mmol); TMEDA (1.6 mL, 1.23 g, 10.6 mmol); CO_2 (excess). Yield: 0.8 g (70%). IR (cm^{-1}): 2951, 2929, 2868, 2822, 1706, 1600, 1479, 1461, 1430, 1409, 1392, 1361, 1287, 1243, 1202, 1173, 1123, 1018, 998, 956, 940, 892, 874, 810, 782, 742, 698, 643, 626, 591, 539. *m*/*z* (CI) 763.5 (MH^+). Elemental analysis calculated for $C_{50}H_{66}O_6$: C, 78.70; H, 8.72. Found: C, 78.80; H, 8.73.

*4.4.9. 14-(5-Hydroxynonan-5-yl)-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxycalix[4]arene-2-carboxylic acid (**15**).* Reagents: **6** (0.40 g, 0.52 mmol); *n*-BuLi (2.0 mL, 3.2 mmol); TMEDA (0.55 mL, 0.42 g, 3.6 mmol); CO_2 (excess). Yield: 0.28 g (60%). ^{1}H NMR: δ=7.81 (s, 2H, H–Ar), 7.11 (s, 6H, H–Ar), 5.40 (s, 1H, $CHCOOH$), 4.78 (s, 1H, $CHC(C_4H_9)_2OH$), 3.97 (d, 2H, CH_2, $^2J_{HH}$=15.9 Hz), 3.80 (d, 2H, CH_2, $^2J_{HH}$=15.9 Hz), 3.04 (s, 6H, OCH_3), 2.95 (2s, 6H, OCH_3), 1.61 (m, 4H, $CHC(CH_2CH_2CH_2CH_3)_2OH$), 1.40 (m, 4H, $CHC(CH_2CH_2CH_2CH_3)_2OH$), 1.29 (s, 18H, $C(CH_3)_3$), 1.23 (s, 18H, $C(CH_3)_3$), 0.85 (m, 4H, $CHC(CH_2CH_2CH_2CH_3)_2OH$), 0.76 (t, 6H, $CHC(CH_2CH_2CH_2CH_3)_2OH$, $^3J_{HH}$=7.1 Hz); ^{13}C NMR: δ=179.0, 154.9, 154.4, 144.9, 143.8, 134.6, 132.7, 132.1, 126.8, 126.7, 126.4, 124.5, 77.1, 60.4, 60.0, 53.4, 42.0, 41.4, 38.1, 37.6, 34.1, 34.0, 31.5, 31.4, 25.4, 23.1, 13.9. IR (cm^{-1}): 2953, 2868, 2821, 1713, 1601, 1480, 1464, 1431, 1393, 1362, 1286, 1245, 1201, 1178, 1120, 1069, 1019, 998, 949, 874, 809, 775, 733, 664, 629, 542. *m*/*z* (CI) 891.2

Table 3
Crystallographic and structure refinement data of the compounds studied

Compound	**3**	**11**	**12**	**15**
Empirical formula	$C_{51}H_{68}O_4$	$C_{54}H_{72}O_4$	$C_{56}H_{80}O_{12}$	$C_{60}H_{86}O_9$
Formula weight (g/mol)	745.05	785.12	945.20	951.29
Crystal system	Monoclinic	Triclinic	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P\bar{1}$	Pc	$P2_1/c$
a (Å)	14.1884 (4)	9.2499 (3)	15.3738 (4)	18.4188 (5)
b (Å)	14.2039 (4)	9.7830 (3)	15.9383 (4)	23.1823 (6)
c (Å)	22.5528 (6)	13.6256 (5)	11.7944 (3)	26.0905 (6)
α (°)	90.00	84.574 (2)	90.00	90.00
β (°)	91.9070 (10)	82.2730 (10)	111.2710 (10)	91.2990 (10)
γ (°)	90.00	68.4730 (10)	90.00	90.00
V (Å^3)	4542.6 (2)	1135.21 (7)	2693.13 (12)	11137.5 (5)
Z	4	1	2	8
F (000)	1624	428	1024	4144
Dc (mgm^{-3})	1.089	1.148	1.166	1.135
μ (mm^{-1})	0.067	0.070	0.080	0.074
Temperature (K)	153 (2)	100 (2)	100 (2)	100 (2)
No. of collected reflections	42,902	28,956	45,823	188,516
Within the θ limit (°)	1.67–28.10	1.5–29.1	1.28–27.10	1.11–26.10
Index ranges $\pm h$, $\pm k$, $\pm l$	−18/10, −18/18, −29/29	−12/12, −13/13, −18/18	−19/19, −20/20, −15/15	−22/22, −28/28, −32/32
No. of unique reflections	11,040	6093	5956	22,120
No. of refined parameters	547	270	634	1284
No. of F values used [$I>2\sigma(I)$]	8379	5407	5198	17,336
$R(=\Sigma\|\Delta F\|/\Sigma\|F_0\|)$	0.0516	0.0402	0.0604	0.0625
wR on F^2	0.1490	0.1286	0.1719	0.1848
S (=Goodness of fit on F^2)	1.060	1.10	1.080	1.173
Final $\Delta\rho_{max}/\Delta\rho_{min}$ (e Å^{-3})	−0.445/0.47	−0.28/0.32	−0.46/0.87	−0.50/0.43

(MH^+). Elemental analysis calculated for $C_{58}H_{82}O_7$: C, 78.16; H, 9.27. Found: C, 77.81; H, 9.18.

4.5. Crystallography

Table 3 summarizes the crystal and structure refinement data of the obtained crystal structures **3**, **11**, **12** and **15**. Single crystals of the compounds suitable for X-ray diffraction study, were obtained by slow crystallization from acetone (**3**,**11**) and mixed chloroform/acetic acid (1:1; **12**,**15**). The intensity data were collected on a Kappa APEX II diffractometer (Bruker-AXS) with graphite-monochromated Cu Kα radiation (λ=0.71073 Å) using ω- and φ-scans. Reflections were corrected for background, Lorentz and polarization effects. Preliminary structure models were derived by application of direct methods[27] and were refined by full-matrix least-squares calculation based on F^2 for all reflections. An empirical absorption correction based on multiple scans was applied by using the SADABS program.[28] With exception of the disordered solvent molecules all non-hydrogen atoms were refined anisotropically. All hydrogen atoms were refined as being constrained to bonding atoms. Crystallographic data for the respective structures have been deposited at the Cambridge Crystallographic Data Centre under CCDC-819560 (**3**), CCDC-819559 (**11**), CCDC-819557 (**12**) and CCDC-819558 (**15**) and can be obtained free of charge at www.ccdc.cam.ac.uk/data_request/cif [or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 (0) 1223 336033, e-mail: deposit@ccdc.cam.ac.uk].

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Supplementary data

Supplementary data including 2D NMR spectra of compound **14** (S1-S6), NMR spectra of compounds **3** (S7, S8) and **7**–**15** (S9, S26) as well as crystallographic data of the herein described X-ray crystal structures **3**, **11**, **12** and **15** (Table S1 and S11–S14) can be found in the online version of this paper at, doi:10.1016/j.tet.2011.05.087.

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