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Homothiacalix[4]arenes: Synthetic Exploration and Solid-State Structures

Joice Thomas,[a] Kristof Van Hecke,[b] Koen Robeyns,[b, d] Wim Van Rossom,[a] Mahendra P. Sonawane,[a] Luc Van Meervelt,[b] Mario Smet,[a] Wouter Maes,*[a, c] and Wim Dehaen*[a]

Abstract: Homothiacalix[*n*]arenes have been largely underexposed compared with related (homo)heteracalixarenes, although their inherent structural features are particularly attractive for supramolecular host–guest chemistry. In this contribution, the synthetic macrocyclization protocols that afford homothiacalix[*n*]arenes have been revestigated and optimized, providing straightforward access to the parent homothiacalix[4]arene skeleton. Moreover, inner-rim (bis and tetrakis) ester functionalization and dimethylenethia bridge oxidation were successfully performed as well. Solution-phase (variable-temperature) NMR spectroscopy studies and solid-state X-ray structures provided complementary information on the conformational features of the novel macrocycles.

Keywords: calixarenes · conformation analysis · macrocyclic ligands · solid-state structures · supramolecular chemistry

Introduction

In recent decades, calixarenes have attracted wide interest as potential (scaffolds for) supramolecular receptors because of their capability to form complementary three-dimensional cavities. Moreover, easy functionalization at the upper and lower rim enables smooth access to a variety of site-specific functional host molecules.[1] Homoheteracalixarenes constitute a specific subclass of the various types of known "calixarenoid" cyclophanes. They are expanded analogues of calixarenes in which CH_2XCH_2 bridges (X = O, NR, S, Se) partly or completely replace the methylene bridges between the aromatic units of the classical carbon-bridged calix[*n*]arenes or the heteroatoms of regular heteracalixarenes.[2–9] The dimethylenehetera linkages impose an increased cavity size, as well as conformational mobility, and provide additional (potentially cooperative) binding sites through the heteroatoms. These features are beneficial for supramolecular binding of a suitable guest in an induced-fit fashion.

Homooxacalix[*n*]arenes[2,5] and their derivatives have been thoroughly studied as crown-like receptor molecules for the binding of alkali, alkali earth, transition metal, heavy metal, and lanthanide cations. The coordination complexes of these homoheteracalixarenes with Ti and V have been explored as catalytically active substances.[5i,j] They were also very efficient host molecules for the inclusion of both charged (tetramethylammonium) and neutral (fullerene) organic molecules. The cation- and anion-sensing receptor properties of homoazacalix[*n*]arene analogues have also scarcely been reported during the last decade.[6] On the other hand, although thiacalixarenes[4a–d] are among the most widely accepted and powerful (calixarene) host molecules for the recognition of organic molecules, as well as metal ions, homothiacalixarenes have received very little attention. There are only a few examples of homothiacalix[*n*]arenes[8] and related cyclophanes,[10] and their host–guest properties have only been explored to a minor extent. Homothiacalixarenes were initially reported to be formed in trace amounts during the synthesis of dithia[3.3]metacyclophanes.[8a,b] More recently, the synthesis of hexahomotrithiacalix[3]arenes[8d,e] and homothiaisocalixnaphthalenes,[8f] starting directly from monomeric precursors, has been reported and the complexation abilities of the latter have been investigated.

[a] J. Thomas, Dr. W. Van Rossom, M. P. Sonawane, Prof. Dr. M. Smet, Prof. Dr. W. Maes, Prof. Dr. W. Dehaen
Molecular Design and Synthesis, Department of Chemistry
Katholieke Universiteit Leuven (KUL)
Celestijnenlaan 200F, 3001 Leuven (Belgium)
Fax: (+32) 16327990
E-mail: wim.dehaen@chem.kuleuven.be

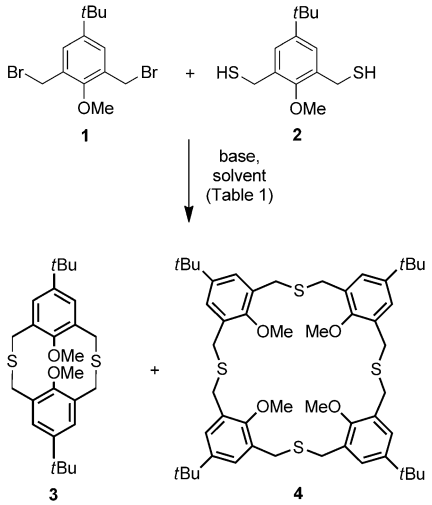
[b] Dr. K. Van Hecke, Dr. K. Robeyns, Prof. Dr. L. Van Meervelt
Biomolecular Architecture, Department of Chemistry
Katholieke Universiteit Leuven (KUL)
Celestijnenlaan 200F, 3001 Leuven (Belgium)

[c] Prof. Dr. W. Maes
Design & Synthesis of Organic Semiconductors (DSOS)
Institute for Materials Research (IMO), Hasselt University
Agoralaan - Building D, 3590 Diepenbeek (Belgium)
Fax: (+32) 11268299
E-mail: wouter.maes@uhasselt.be

[d] Dr. K. Robeyns
Present address: Institute of Condensed Matter and Nanosciences (IMCN)
Université Catholique de Louvain (UCL), Bâtiment Lavoisier
Place Louis Pasteur 1 (Bte 3), 1348 Louvain-la-Neuve (Belgium)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201101690. It includes additional experimental and characterization data, ^1H (VT) and ^{13}C NMR spectra for all novel macrocycles and precursors, HRMS (ESI^+) isotopic patterns for the homothiacalix[*n*]arenes, and extra figures for the X-ray crystallographic structures.

In general, in spite of their potential richness and versatility as ligands, combining the specific features of cyclophanes and thiacrown ethers, the synthetic and supramolecular knowledge on homothiacalixarenes is very limited relative to thiacalixarenes or other structurally related homoheteracalixarenes (notably oxa). Moreover, solid-state structural studies of homothiacalixarenes are unknown in any context to date. Therefore, herein we report a systematic investigation of the (selective) synthesis of ("all-homo"[1b]) parent homothiacalix[4]arene **4** (Scheme 1) and analogous macrocycles by a straightforward one-pot macrocyclization approach that involves substitution reactions of 1,3-bis(mercaptomethyl)benzene nucleophiles on 1,3-bis(bromomethyl)benzene derivatives under basic conditions. Our interest in (homohetera)calixarenes previously led us to discover a new class of homocalixarene macrocycles, containing CH_2SeCH_2 bridging units, with a ring size varying from three to eight monomeric building blocks.[9] A precursor enabling high solubility for all homoselenacalix[*n*]arenes ($n=3$–8) was chosen in this previous study. Therefore, we envisaged to use the same building block, 1,3-bis(bromomethyl)-5-*tert*-butyl-2-methoxybenzene (**1**), as an electrophile and its corresponding dithiol derivative **2** as the nucleophilic component (see Scheme 1). This substitution pattern also allows direct comparison with the related homooxa- and homoselenacalixarenes.[5,9]



Scheme 1. Synthetic pathway towards homothiacalix[4]arene **4**.

Results and Discussion

Synthesis and characterization: In 1981, Tashiro and Yamato described the occurrence of a cyclic tetramer,[8b] which can be regarded as an octahomotetrathiacalix[4]arene (*p*-*tert*-butyloctahomotetrathiacalix[4]arene tetramethyl ether **4**),[11] as a side product (7%) during the synthesis of dithiacyclophane **3** (56%) by a cyclocondensation reaction of 1,3-bis(-chloromethyl)-5-*tert*-butyl-2-methoxybenzene and its corresponding dithiol derivative **2** with KOH base in EtOH/benzene (see Scheme 1). Gheorghiou and co-workers only obtained metacyclophane **3** (38%), starting from precursors **1** and **2** under similar conditions.[12] The first goal of our study was to direct the synthetic protocol towards an optimum yield of cyclic tetramer **4** rather than [1+1] adduct **3**. A thorough search for the optimum macrocyclization conditions was conducted by different combinations of solvent, base, temperature, and high-dilution conditions to find a particular combination of these variants to optimize the formation of target macrocycle **4**.

As summarized in Table 1, the reaction between precursors **1** and **2** (1:1 molar ratio; Scheme 1) was strongly influenced by the base and solvent used and all of the reactions were carried out under high-dilution conditions (employing a syringe pump) at 70°C. The addition of both substrates at once increased the degree of polymer formation. The combination of K_2CO_3 with a rather polar solvent, such as ethanol or DMF, afforded 50 and 54% of [1+1] coupling product **3**, respectively, along with 22 and 15% of [2+2] coupling product **4**, respectively (Table 1, entries 1 and 2). The macrocycles were efficiently separated and purified by column chromatography (on silica gel). The same reaction in acetonitrile afforded a slightly higher amount of homothiacalix[4]arene **4** (27%), with a concurrent decrease in thiacyclophane formation (17%; Table 1, entry 3). The reaction outcome could hence be reversed, in the sense that the [2+2] macrocyclization product was favored under these conditions. When the reaction was carried out in more apolar solvents, such as toluene or 1,4-dioxane, in the presence of K_2CO_3 as a base, a mixture of inseparable oligomers was obtained (Table 1, entries 4 and 5). On the other hand, the yield of **4** improved drastically to 62% when the reaction was performed in THF (Table 1, entry 6). The dithiacyclophane adduct **3** was only obtained as a minor side product

Table 1. Effect of solvent and base on the macrocyclization outcome.[a]

Entry	Base	Solvent	Yield of **3** [%]	Yield of **4** [%]
1	K_2CO_3	EtOH	50	22
2	K_2CO_3	DMF	54	15
3	K_2CO_3	CH_3CN	17	27
4	K_2CO_3	toluene	–[b]	–[b]
5	K_2CO_3	1,4-dioxane	–[b]	–[b]
6	K_2CO_3	THF	5	62[c]
7	Cs_2CO_3	THF	2	41
8	Na_2CO_3	THF	–[b]	–[b]
9	DIPEA	THF	–[b]	–[b]
10	NaH	THF	12	29
11	K_2CO_3+[18]crown-6	THF	32	27
12	K_2CO_3+$NaBH_4$	THF	12	52

[a] The reaction was conducted at 70°C under high-dilution conditions (employing a syringe pump). Product **3** is the [1+1] product and product **4** is the [2+2] product. DIPEA = diisopropylethylamine. [b] An unidentified mixture of inseparable oligomers was obtained. [c] The rest of the reaction mixture probably consisted of polymeric material.

(5%) under these conditions. Upon changing to other bases (Cs_2CO_3, Na_2CO_3, DIPEA or NaH; Table 1, entries 7–10), yields of cyclotetramer **4** were systematically lower, although the preference for the homothiacalix[4]arene was retained for Cs_2CO_3 and NaH. A possible template effect of the K^+ counterions was analyzed by comparison with a reaction in which [18]crown-6 was added (Table 1, entry 11). The yield of [1+1] coupling product **3** increased to 32% along with a concurrent decrease in the yield of [2+2] cyclooligomer **4** to 27%, suggesting a templating effect of K^+ towards the formation of the cyclic tetramer.[5a] To suppress the possible in situ formation of the disulfide of precursor **2** during the course of the reaction, an equimolar amount of $NaBH_4$ was added to the reaction, resulting in a small decrease in the yield of **4** (to 52%; Table 1, entry 12), possibly due to competition between the Na^+ and K^+ ions.

These experimental observations indicated convincingly that both the base and the solvent played an important role in facilitating and directing macrocyclization outcome. By careful optimization of the reaction parameters, the ratio of the macrocyclic products formed could be completely reversed and the desired homothiacalix[4]arene **4** could be prepared in good yield (62%).[13] When the reaction was repeated with larger reagent quantities (3.9 mmol) and a higher concentration (10 mM), analytically pure macrocycle **4** was obtained in 53% yield. None of the larger cyclooligomers were observed in the crude mixture by ESI-MS.

Homothiacalix[4]arene **4** was completely characterized by NMR spectroscopy (^1H, ^{13}C) and high-resolution (HR) MS and showed good solubility in a variety of (medium polarity) organic solvents, such as CH_2Cl_2, ethyl acetate, and THF. The ^1H NMR spectrum of **4** was very straightforward and showed sharp singlet signals for each of the protons. The absence of coupling for the geminal protons of the benzylic methylene groups (due to diastereotopicity, as observed for thiacyclophane **3**) suggested fast conformational interconversion in solution (on the ^1H NMR spectroscopy timescale). As for classical methylene-bridged calix[4]arenes, four fundamental conformations—cone, partial cone, 1,2-alternate and 1,3-alternate—should be taken into account, as determined by the relative orientation (parallel or antiparallel) of the aromatic subunits. For similar octahomotetraoxacalix[4]arenes, it was reported that non-cone conformations (1,2- or 1,3-alternate) were probably preferred.[5a,f,k] This interpretation was based on the upfield shift of the intraannular methoxy substituents with respect to the acyclic precursors. A similar but more extensive upfield shift was observed for the methoxy protons of homothiacalix[4]arene **4**. The protons of the OCH_3 signal appeared at $\delta = 3.15$ ppm at RT (Figure 1), about 0.65 ppm upfield with respect to the standard value ($\delta = 3.80$ ppm). This indicated that the conformations in which the methoxy protons faced the rings of neighboring aromatic units were more likely to be populated in this case, and hence, reduced the chance of having a fixed cone conformation with deep cavities and facing aromatic rings. This assignment is in agreement with a 1,2- or 1,3-alternate conformation for **4**, such as that for homooxacalix[4]arenes in solution, and corresponds to the observed 1,2-alternate solid-state structure (see Figure 2). The same observations were previously made for the homoselenacalix[4]arene homologue.[9] To gain further insight into the conformational behavior of homothiacalix[4]arene **4** in solution, variable-temperature (VT) ^1H NMR spectra were recorded. No signal splitting was observed for temperatures down to 230 K, while further shielding of the methoxy pro-

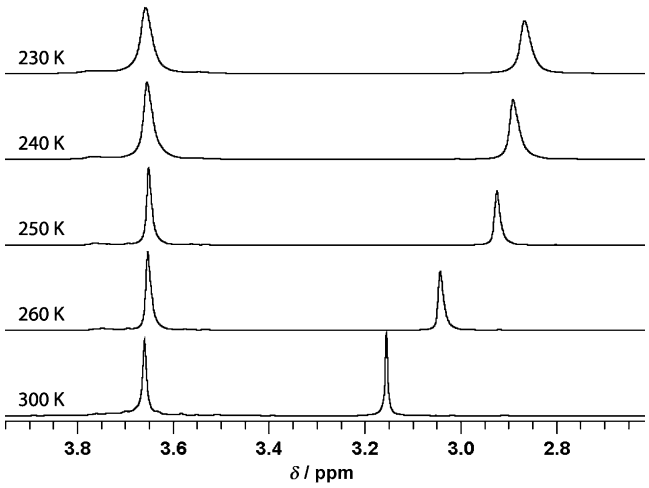


Figure 1. Upfield shift for the OCH_3 protons of homothiacalix[4]arene **4** (upon decreasing *T*).

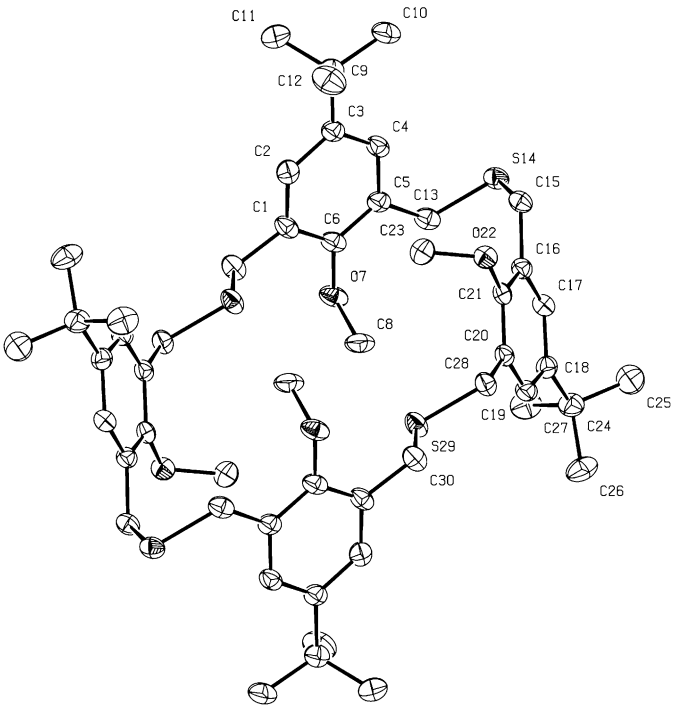
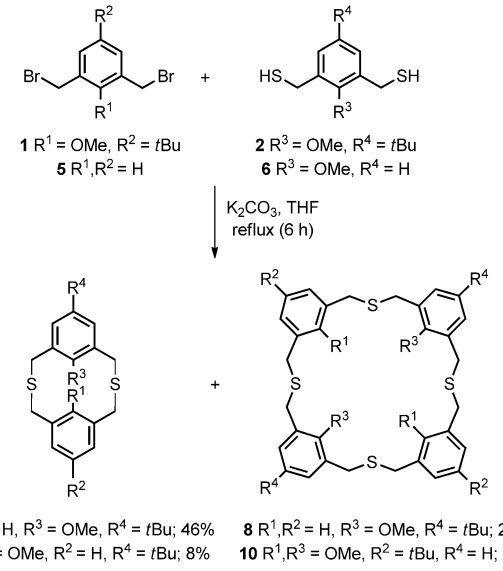


Figure 2. Molecular structure (with the atom labeling scheme of the asymmetric unit) of homothiacalix[4]arene **4**, with thermal displacement ellipsoids drawn at the 50% probability level. For clarity, hydrogen atoms are not shown.

tons was noted, ranging from $\delta = 3.15$ ppm at RT to $\delta = 2.87$ ppm at 220 K (Figure 1).

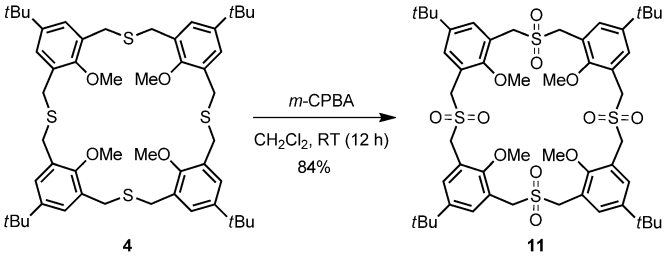
Studies on the effect of intra- and extraannular aryl substituents on the macrocyclization outcome for homoselenacalix[4]arenes indicated that the methoxy groups on the inner rim played a crucial role for the selective formation of the cyclic tetramer.[9] Hence, we decided to carry out similar studies for homothiacalix[4]arenes. Reaction of 1,3-bis(mercaptomethyl)-5-*tert*-butyl-2-methoxybenzene (**2**) and 1,3-bis(bromomethyl)benzene (**5**) under the previously optimized conditions (K_2CO_3, THF, 6 h reflux, high dilution) afforded dimeric dithia[3.3]metacyclophane **7** (46%) as the major compound, together with 22% of homothiacalix[4]arene **8** (Scheme 2). This indicates that the absence of the methoxy group *ortho* to the benzylic positions favors [1+1] cyclocondensation. On the other hand, the reaction of 2-methoxy-1,3-bis(mercaptomethyl)benzene (**6**), which is a nucleophile lacking the *tert*-butyl moiety, and 1,3-bis(bromomethyl)-5-*tert*-butyl-2-methoxybenzene (**1**) under similar conditions as those described above gave [2+2] cyclocondensation product **10** (44%) as the main macrocycle along with 8% of [1+1] cyclocondensed product **9**. The above observations indicate that, as in homoselenacalixarenes, the inner-rim methoxy groups also play a crucial role for the higher selectivity of the [2+2] coupling product in the homothiacalixarene series.



Scheme 2. Exploration of the thiacyclophane size.

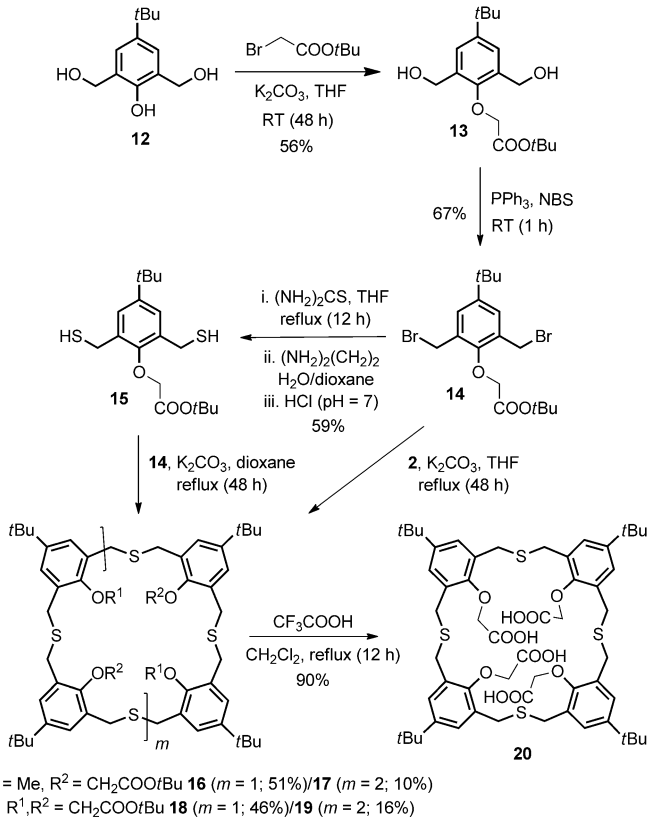
The ^{1}H NMR spectra of A_2B_2-type octahomotetrathiacalix[4]arenes **8** and **10** likewise showed shielded signals for the methoxy protons (at $\delta = 3.46$ and 3.26/3.23 ppm, respectively, at RT), indicating once more a preference for non-cone conformations in solution (see the Supporting Information).

The introduction of specific functional groups onto the lower rim, or further derivatization of the bridging sulfur atoms of homothiacalix[*n*]arenes, which may impose specific host–guest properties, has not yet been reported. The presence of sulfur atoms in the linkers enables a novel derivatization pathway for these molecules, which is not applicable to the homooxa- or homoazacalixarene subclasses, that is, oxidation to sulfinyl and sulfonyl moieties. These compounds may be of interest for the design of new receptors, according to well-established thiacalixarene chemistry.[4a–d,14] The synthetic strategy for the preparation of the tetrasulfonyl analogue was based upon complete oxidation of homothiacalix[4]arene **4** by treatment with a 12-fold excess of *m*-chloroperbenzoic acid (*m*-CPBA), affording the desired tetrasulfonylcalix[4]arene **11** in 84% yield (Scheme 3).[8d,14a] The ^{1}H NMR spectrum of **11** exhibited only one set of signals for the benzylic protons. Both the methoxy and methylene protons appeared slightly downfield (at $\delta = 3.49$ and 4.17 ppm, respectively, at RT) compared with the parent homothiacalix[4]arene **4** (see the Supporting Information). Attempts to produce the tetrasulfinyl derivative were carried out with a smaller amount of oxidant, based on previous conversions of thiacalixarenes, and the best result was obtained with hydrogen peroxide in glacial acetic acid.[14c] However, purification of the tetrasulfinylcalix[4]arene was not successful due to the presence of overoxidized products.



Scheme 3. Oxidation of the bridging sulfur atoms.

Towards further functionalization of octahomothiacalix[4]arene **4** on the lower rim, deprotection of the methoxy groups was initially pursued by using BBr_3 or trimethylsilyl iodide (TMSI) under different conditions. However, this approach was not successful because it was difficult to selectively deprotect the methoxy groups without affecting the macrocycle. Therefore, the introduction of the intraannular substituents should be preferentially performed prior to macrocyclization. We opted for the introduction of (*tert*-butyl) ester functions, since this enabled further modification on the inner rim at a later stage. The synthesis of functionalized precursors **14** and **15** was carried out in a relatively straightforward approach, as outlined in Scheme 4. (5-*tert*-Butyl-2-hydroxy-1,3-phenylene)dimethanol (**12**) was treated with *tert*-butyl 2-bromoacetate in the presence of K_2CO_3 to afford *tert*-butyl ester **13**, which was then brominated with NBS/PPh_3, yielding the corresponding bis(benzyl bromide) **14**. Treatment of **14** with thiourea followed by hydrolysis in the presence of ethylenediamine gave bis(mercapto) compound **15**. The optimized procedure for the synthesis of **4**



R^1 = Me, R^2 = $CH_2COOtBu$ **16** (m = 1; 51%)/**17** (m = 2; 10%)
R^1,R^2 = $CH_2COOtBu$ **18** (m = 1; 46%)/**19** (m = 2; 16%)

Scheme 4. Synthesis of inner-rim functionalized homothiacalix[n]arenes **16**–**20**. NBS = *N*-bromosuccinimide.

was then used for the synthesis of macrocycles with ester groups on the lower rim. The [2+2] coupling reaction of **14** and **2** gave the corresponding unsymmetrical homothiacalix[4]arene **16** in 28% yield, with concomitant formation of homothiacalix[6]arene **17** in 6% yield. The presence of acyclic oligomers in the reaction mixture indicated the need for a longer reaction time. An optimized yield of **16** (51%) and **17** (10%) was obtained by refluxing the reaction mixture for two days in THF. Changing the concentration of the reagents and avoiding high-dilution conditions resulted in a significant drop in the yield and the calixarenes could only be obtained in negligible amounts. However, none of the above optimized procedures worked well for the coupling of **14** and **15** towards the analogous tetrasubstituted ester derivative. Fortunately, the replacement of THF by the higher boiling solvent 1,4-dioxane resulted in the formation of the desired [2+2] coupling product **18** in 46% yield, along with [3+3] coupling product **19** in 16% yield. It is worth noting that all macrocycles obtained in the two reactions mentioned above were easily separated and efficiently purified by column chromatography (on silica gel). As anticipated, none of the [1+1] cyclophane products were obtained in any of these reactions because of the sterically demanding *tert*-butyl ester groups. The same steric features might also explain the formation of the enlarged homothiacalix[6]arene homologues in this case,[15] whereas they were not observed (in reasonable amounts) when starting from the inner-rim methoxy-functionalized precursors. Tetracarboxyl derivative **20** was obtained in 90% yield by treating the corresponding tetraester **18** with trifluoroacetic acid (TFA), and was soluble in water. This compound can be used for further chemical transformations by coupling various functional groups to the carboxyl moieties towards preparation of modified receptors. Similar inner-rim functionalized homotrioxacalix[3]arenes were previously explored as receptors for alkali, alkaline earth, transition, and heavy metal ions, and lanthanide cations.[5k]

Temperature-dependent ^{1}H NMR spectroscopy was applied to analyze the conformational preferences of the functionalized homothiacalix[n]arenes **16**–**20** in the liquid state (see the Supporting Information). The ^{1}H NMR spectrum of homothiacalix[4]arene **16** at room temperature in $CDCl_3$ displayed eight AB-type pairs of doublets for the bridging methylene protons and individual signals for each of the *tert*-butyl, methoxy, and side-chain methylene groups. In addition, four singlets were observed in the aromatic region. These observations indicated restricted rotation imposed by the bulky inner-rim *tert*-butyl acetate moieties, hindering rotation of the aryl groups around their C2–C6 axis (O-alkyl through-the-annulus rotation). On the other hand, a simplified set of two (broad) signals for the aromatic region and three signals for the (two distinct sets of) *tert*-butyl groups were observed at 328 K, which could be explained by the fastened conformational dynamics at higher temperature (on the ^{1}H NMR spectroscopy timescale). The ^{1}H NMR spectrum recorded in [D_6]DMSO at 353 K showed very sharp signals for most of the protons; the only exception was one of the bridging methylene moieties. The two inner-rim methoxy groups showed upfield-shifted resonances (at δ = 3.16 and 3.11 ppm at 300 K), which seemed to preclude a large contribution of cone conformations. In the solid state, a 1,2-alternate molecular structure was identified (see Figure 3). The singlet signals observed for the bridging methylene groups of enlarged homothiacalix[6]arene homologue **17** indicated enhanced flexibility and a faster conformational interconversion at room temperature. For tetrasubstituted ester derivative **18**, extensive broadening of the ^{1}H NMR signals was observed for each of the protons at 300 K, which could be ascribed to a slower interconversion of the conformers due to the presence of four substituents at the lower rim. Extensive signal splitting for all of the protons was observed while going from room temperature to 230 K; this was indicative of the presence of multiple conformers. The signals were noticeably sharper at 328 K and very sharp singlets were again observed at 353 K (in [D_6]DMSO). In this case, a 1,3-alternate molecular structure was observed by X-ray diffraction (see Figure 4). Enhanced flexibility was once more observed for the cyclic hexamer **19**. The analogous tetracarboxyl derivative **20** seemed to be somewhat more conformationally flexible. However, some broadening was still observed for the dimethylenesulfide bridges and the methylene groups at the intraannular positions at 300 K. At 328 K all signals were sharper and well defined.

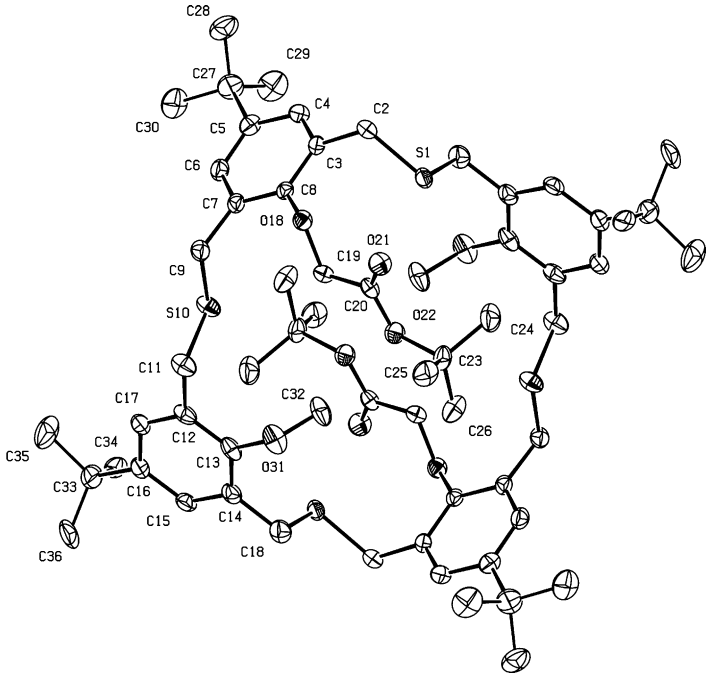


Figure 3. Molecular structure (with the atom labeling scheme of the asymmetric unit) of inner-rim difunctionalized homothiacalix[4]arene **16**, with thermal displacement ellipsoids drawn at the 50% probability level. For clarity, hydrogen atoms and disorder of the *tert*-butyl groups are not shown.

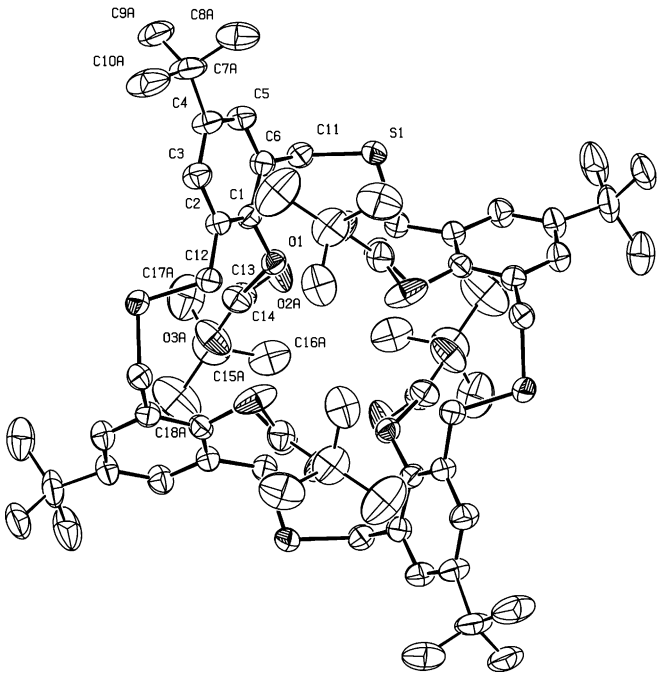
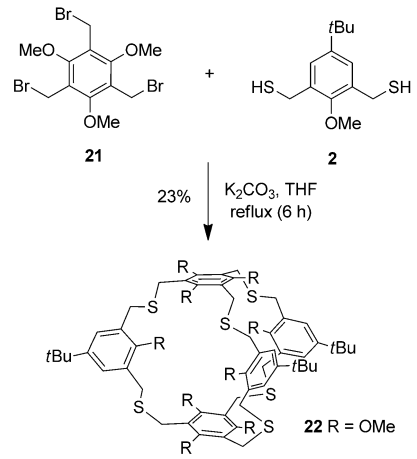


Figure 4. Molecular structure (with the atom labeling scheme of the asymmetric unit) of inner-rim tetrafunctionalized homothiacalix[4]arene **18**, with thermal displacement ellipsoids drawn at the 50% probability level. For clarity, hydrogen atoms and disorder of the *tert*-butyl groups are not shown.

In a manner similar to that used to prepare the monocyclic homothiacalix[4]arene compounds, bicyclic analogue **22** was synthesized in 23% yield through a single-step reaction of a trifunctional electrophile, 1,3,5-tris(bromomethyl)-2,4,6-trimethoxybenzene (**21**), with bisnucleophile **2** (Scheme 5)



Scheme 5. Synthetic pathway towards bicyclohomothiacalix[4]arene **22**.

in a 2:3 molar ratio. Higher polycyclic or cyclic oligomers might be formed, but we did not detect (ESI-MS) or isolate any of these species. High-dilution conditions were essential to prevent extensive polymer formation. Application of a solvent and base other than THF and K_2CO_3 did not result in the desired product. The very simple ^{1}H NMR spectrum of macrobicycle **22** indicated a symmetrical structure in solution. The upfield shift observed for the intraannular methoxy protons ($\delta = 3.07$ ppm) of the dithiol precursor part in the bicyclic structure, in comparison with the other methoxy protons ($\delta = 3.76$ ppm), indicated a diamagnetic shielding effect of the neighboring aromatic rings. This observation suggested that the methoxy groups of the nucleophilic component pointed (on average) more directly into the formed cavity, whereas the methoxy groups of the electrophilic component pointed more outwards (in solution). From the solid-state structure, it can be seen that (only) one of the methoxy groups of the nucleophilic precursor is self-included (see Figure 5). Cage compound **22**, which can be seen as a homothiacalix[4]arene with an additional phenyl cap, can possibly be applied to bind specific guest molecules. Three-dimensionally preorganized bicyclic ligands often provide a better steric fit for guests. An analogous bicyclic hexaazahomocalixarene has recently been synthesized and showed dual recognition (both cavity and cleft binding) of guest molecules (e.g., acetone).[6f]

Solid-state structural elucidation: To confirm the structures and analyze the conformations of the synthesized macrocycles in the solid state, high-quality single crystals of compounds **4**, **16**, **18**, and **22** were obtained by vapor diffusion of methanol (**4**, **18** and **22**) or pentane (**16**) in solutions of the calixarenes in chloroform. X-ray diffraction analysis thus al-

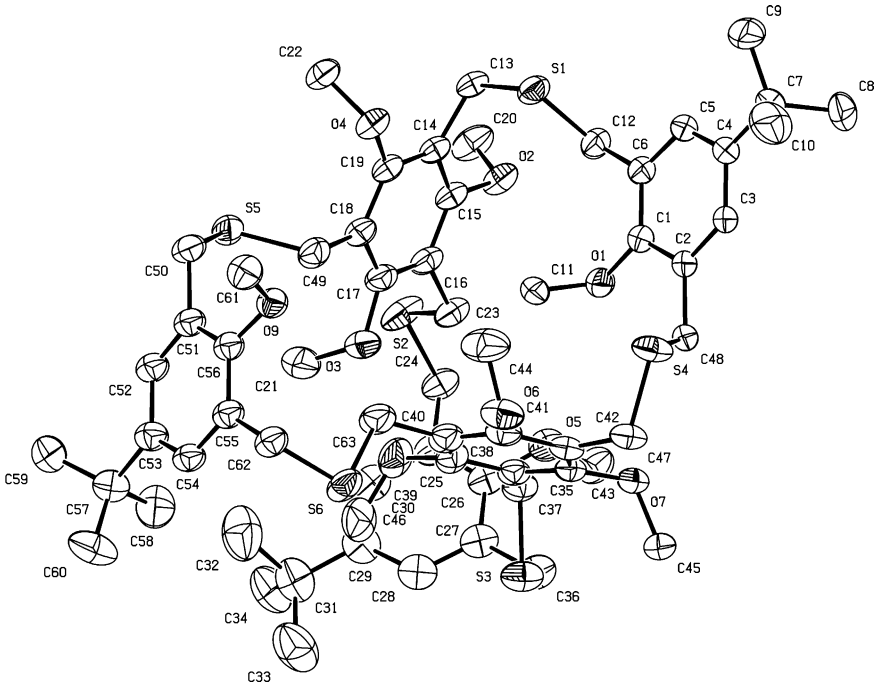


Figure 5. Molecular structure (with the atom labeling scheme) of bicyclohomothiacalix[4]arene **22**, with thermal displacement ellipsoids drawn at the 50% probability level. Only one out of three molecules in the asymmetric unit is shown. For clarity, hydrogen atoms are not shown.

lowed us to examine the structures in the solid state. An evident but important feature of the solid-state molecular structures is the rigidity of the macrorings, which simplifies conformational analysis, in contrast to the liquid state.

Homothiacalix[4]arene **4** adopted a 1,2-alternate conformation in the solid state (Figure 2), which resembled analogous homooxacalix[4]arene structures,[5b,c] but was notably different from the (highly distorted) 1,3-alternate structure obtained for the corresponding homoselenacalix[4]arene.[9] The cyclic structure of **4** was positioned on an inversion center, with two opposing sulfur atoms pointing inwards, whereas the remaining two atoms pointed outwards. The torsion angles C-C-S-C and C-S-C-C were in the *anti*/*anti* conformation (173.3 and −177.8°) for the former and in the *gauche*/*gauche* conformation (−64.6 and −52.4°) for the latter. The C–S distances (1.80–1.82 Å) and the C-S-C angles (96.6 and 100.2°) were within the expected range. The bond configuration around the S atoms was V shaped. The rectangular enclosed cavity, defined by the distances between the aryl centroids, was 5.39×7.92 Å (see the Supporting Information). These centroids were situated on the same plane, with deviations of 0.16 Å. In the packing, a 3.45 Å contact was observed between two neighboring S atoms. Another close (2.60/2.74 Å) contact was observed between a hydrogen atom of a bridging methylene group and the centroid of a neighboring aryl ring. All methoxy groups were directed inwards (self-inclusion), which may have correlated to the observed shielding effect in the ^{1}H NMR spectrum of **4**. Intramolecular CH···π interactions were observed between the protons of the self-included methoxy moieties and neighboring aryl units (CH···phenyl centroid distances of 2.61 and 2.84 Å).

Homothiacalix[4]arene **16** likewise adopted a 1,2-alternate solid-state conformation and was also situated on an inversion centre (Figure 3). A least-squares plane could be calculated through the centroids of the aryl rings (deviation 0.06/0.09 Å). The enclosed cavity, defined by the distances between the aryl centroids, was almost a square (7.16×7.66 Å; see the Supporting Information). As in macrocycle **4**, the bond configuration around the S atoms was V shaped, with bond lengths of 1.82 Å and an angle of 101.6 or 101.7°, which was close to expected values. The torsion angles around the bridging S atoms were alternating in the *anti*/*gauche* conformation (179.5/84.9°) or in the *anti*/*anti* conformation (161.0/176.8°). All of the *tert*-butyl substituents were directed outwards and they all showed twofold disorder. The inner-rim substituents were all directed inwards and further enclosed the cavity. An intermolecular close CH···π contact (2.72 Å) was observed between the *tert*-butyl protons of a methoxyphenyl moiety and the centroid of a phenyl ring with a self-included ester moiety.

For inner-rim tetrafunctionalized homothiacalix[4]arene **18**, the asymmetric unit consisted of one quarter of the total cyclic structure, which was constructed around a fourfold rotoinversion axis, and the macrocycle adopted a 1,3-alternate conformation (Figure 4). As in the crystal structures of **4** and **16**, the bond configuration around the S atoms was V shaped, with all sulfur atoms pointing outwards. The torsion angles C-C-S-C and C-S-C-C were all (because of symmetry reasons) in the *anti*/*anti* (−/+167.2 and −/+97.4°) conformations. The S−C bond lengths and C-S-C angles all equaled 1.83 Å and 102.4°, respectively. A square was formed by the aryl centroids, with a side of 6.99 Å (see the Supporting Information). These centroids were situated on the same plane (deviations of 0.56 Å). Two of the inner-rim *tert*-butyl acetate moieties were directed outwards on one side of the aryl plane, whereas the remaining two opposing moieties were also pointing outwards, but in the opposite direction on the other side of the plane. All *tert*-butyl groups, as well those of the acetate groups as those directly on the phenyl rings, were disordered. In the packing, a potential hydrogen bond was observed between the C5(H) atom of one calixarene molecule and the S1 atom of symmetry-equivalent molecules (C(H)···S distance of 3.77 Å), linking

the calixarene molecules together in the [100] and [010] directions.

Bicyclohomothiacalix[4]arene **22** crystallized in the centrosymmetric space group $P\bar{1}$, with an asymmetric unit consisting of three complete calixarene molecules. One calixarene molecule contained five aryl moieties: three *tert*-butyl acetate substituted (precursor **2**) and two trimethoxy-substituted (precursor **21**) building blocks (Figure 5). All three calixarene molecules exhibited the same bicyclic configuration, that is, a first macrocycle was formed by two *tert*-butyl acetate and two trimethoxy building blocks, whereas a second macrocycle was formed by an additional *tert*-butyl acetate precursor positioned on top of the first macrocycle. As in the crystal structures of **4**, **16**, and **18**, the bond configuration around the sulfur atoms was V shaped, with all S atoms pointing outwards. For the first macrocycle, the torsion angles C-C-S-C and C-S-C-C alternated between *gauche*/*anti* (range of 53.6 to 72.0° and −164.2 to 177.6°) and *anti*/*gauche* (range of −166.6 to 179.5 and −59.7 to −66.8°) conformations, respectively. For the second macrocycle, the torsion angles C-C-S-C and C-S-C-C were in the *gauche*/*anti* (range of 71.0 to −83.9° and 158.5 to −164.4°) conformation. The S−C bond lengths and C-S-C angles ranged from 1.77 to 1.84 Å and from 93.7 to 100.5°, respectively. Intermolecular close contacts (2.59/2.86/2.99 Å) were observed between the hydrogen atoms of the methylene bridges and neighboring phenyl rings. The protons of a self-included methoxy group (on the nucleophilic component) showed an intramolecular CH···π interaction with the neighboring aryl unit (CH···phenyl centroid distance of 2.96 Å). One $CHCl_3$ solvent molecule could be unambiguously observed, contacting two S atoms within one calixarene molecule (Cl···S distances of 3.44 and 3.35 Å).

Conclusion

An optimized one-pot procedure for the synthesis of homothiacalix[4]arenes was presented. Careful screening of the macrocyclization conditions enabled a spectacular increase in yield from 7 (previous literature) to 62%, with a concomitant decrease in dithiacyclophane formation. The presence of intraannular methoxy groups was crucial to direct the macrocyclization outcome to the cyclic tetramer rather than the cyclic dimer. The procedure could easily be extended to lower-rim *tert*-butyl ester functionalized homothiacalix[4]arenes and smooth conversion to the tetracarboxyl derivative was achieved as well. Moreover, oxidation of the bridging sulfur atoms afforded the tetrasulfonylcalix[4]arene analogue. We also demonstrated that a simple extension of this approach resulted in the synthesis of a conformationally more-rigid macrobicyclic homothiacalix[4]arene cage compound. All homothiacalixarene macrocycles were completely characterized, including single-crystal X-ray analysis of homothiacalix[*n*]arenes **4**, **16**, **18**, and **22**. Among the monocyclic homothiacalix[4]calixarenes, compounds **4** and **16** showed a 1,2-alternate solid-state conformation, whereas the tetrasubstituted derivative **18** showed a distorted 1,3-alternate conformation in the crystalline state. The solid-state structures were complemented with a view on the conformational mobility in solution, as established by (VT) ^{1}H NMR spectroscopy conformational analysis. Cone conformations appeared to be generally disfavored. The synthetic results obtained in this work enable homothiacalixarenes to (re)-claim their justified position among related powerful receptor molecules in host–guest chemistry. Our current research efforts are addressed towards this issue.

Experimental Section

General experimental methods: (Temperature-dependent) NMR spectra were acquired on commercial instruments (Bruker Avance 300 MHz, Bruker AMX 400 MHz, or Bruker Avance II$^+$ 600 MHz) and chemical shifts (δ) are reported in parts per million (ppm) referenced to tetramethylsilane (^{1}H) or the internal (NMR) solvent signals (^{13}C). Mass spectra were run by using an HP5989A apparatus (CI and EI, 70 eV ionization energy) with an Apollo 300 data system or a Thermo Finnigan LCQ Advantage apparatus (ESI). Exact mass measurements were acquired on a Kratos MS50TC instrument (performed in the EI mode at a resolution of 10000) or a Bruker Daltonics Apex2 FT-ICR instrument (performed in the ESI mode at a resolution of 60000). IR spectra were recorded on a Bruker-Alpha T FTIR spectrometer with universal sampling module. Melting points were determined by using a Reichert Thermovar apparatus. For column chromatography, 70–230 mesh silica gel 60 (Merck) was used as the stationary phase. Chemicals received from commercial sources were used without further purification. Reaction solvents (THF, ethanol) were used as received from commercial sources. Additions in (high-dilution) macrocyclization reactions were performed at a constant rate with the aid of an infusion pump.

General procedure for [2+2]/[1+1] cyclooligomerization reactions: The procedure outlined is applicable for the synthesis of homothiacalix[4]arenes **4**, **8**, and **10** and the dimeric dithia[3.3]metacyclophanes **3**, **7**, and **9**. Separate degassed solutions of the respective bis(bromomethyl)benzene (1 equiv, 0.78 mmol) and bis(mercaptomethyl)benzene (1 equiv, 0.78 mmol) precursors in THF (12 mL) were collected in syringes and added dropwise (with the aid of a syringe pump) to a stirred degassed mixture of K_2CO_3 (5 equiv, 3.9 mmol) in THF (150 mL) at reflux temperature over a period of 5 h. After complete addition, the mixture was stirred at reflux for an additional 10 h period after which time the mixture was cooled to RT and evaporated to dryness. The crude residue was redissolved in a mixture of CH_2Cl_2 and water. The organic fraction was separated, washed with water, dried over $MgSO_4$, filtered, and evaporated to dryness. Purification by column chromatography (silica gel, eluent CH_2Cl_2/hexane/diethyl ether mixtures) afforded the corresponding macrocycles as off-white solids.

Compounds 3 and 4: A mixture of K_2CO_3 (0.539 g, 3.9 mmol, 5 equiv), **1** (0.273 g, 0.78 mmol, 1 equiv), and **2** (0.200 g, 0.78 mmol, 1 equiv) was used. Purification by column chromatography (silica gel, eluent CH_2Cl_2/hexane/diethyl ether 57.5:40:2.5) afforded **3** (0.017 g, 5%) and **4** (0.215 g, 62%) as off-white solids.

Compound ***4***:[8b] M.p. 245.5–246.5°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.20 (s, 8H; ArH), 3.66 (s, 16H; CH_2), 3.16 (s, 12H; OCH_3), 1.30 ppm (s, 36H; *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25°C, TMS): δ = 154.2, 146.6, 130.7, 127.0 (CH), 61.3 (OCH_3), 34.4, 31.5 (CH_3), 30.6 ppm (CH_2); IR (ATR): $\tilde{\nu}_{max}$ = 2952, 2865, 2828, 1480, 1462, 1361, 1248, 1200, 1098, 1000, 885, 813, 635 cm^{-1}; MS (ESI$^+$): *m*/*z*: 911.6 [*M*+Na]$^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{52}H_{72}O_4S_4Na$ [*M*+Na]$^+$: 911.4206; found: 911.4214.

Compound ***3***: M.p. 225.5–226.5°C; ^{1}H NMR (300 MHz, $CDCl_3$, 25°C, TMS): δ = 7.29 (s, 4H; ArH), 3.78 (d, ^2J(H,H) = 13.3 Hz, 4H; CH_2), 3.39 (d, ^2J(H,H) = 13.4 Hz, 4H; CH_2) 3.21 (s, 6H; OCH_3), 1.36 ppm (s, 18H;

*t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.5, 146.0, 127.9, 127.7 (CH), 60.8 (OCH_3), 34.4, 31.5 (CH_3), 27.1 ppm (CH_2); IR (ATR): $\tilde{\nu}_{max}$ = 2952, 2865, 2828, 1482, 1431, 1248, 1200, 1098, 1000, 885, 813, 650 cm^{-1}; MS (EI): *m*/*z*: 444 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{26}H_{36}O_2S_2$ $[M]^+$: 444.2157; found: 444.2121.

Compounds 7 and 8: A mixture of K_2CO_3 (0.539 g, 3.9 mmol, 5 equiv), **5** (0.205 g, 0.78 mmol, 1 equiv) and **2** (0.200 g, 0.78 mmol, 1 equiv) was used. Purification by column chromatography (silica gel, eluent CH_2Cl_2/hexane/diethyl ether 47:47:6) afforded **7** (0.128 g, 46 %) and **8** (0.062 g, 22 %) as off-white solids.

Compound **7**: M.p. 183.5–184.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.04 (s, 1H; ArH), 6.94 (s, 2H; ArH), 6.88 (s, 3H; ArH), 4.26 (d, ^2J(H,H) = 14.3 Hz, 2H; CH_2), 3.78 (d, ^2J(H,H) = 14.7 Hz, 2H; CH_2), 3.69 (s, 3H; OCH_3), 3.68 (d, ^2J(H,H) = 14.7 Hz, 2H; CH_2), 3.48 (d, ^2J(H,H) = 14.3 Hz, 2H; CH_2), 1.12 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 154.2, 146.5, 137.9, 130.2, 129.4 (CH), 128.7 (CH), 126.7 (CH), 126.5 (CH), 62.2 (OCH_3), 38.0 (CH_2), 34.2, 31.4 (CH_2), 31.2 ppm (CH_3); IR (ATR): $\tilde{\nu}_{max}$ = 2947, 2854, 2826, 1604, 1478, 1435, 1255, 1203, 1100, 1004, 885, 822, 635 cm^{-1}; MS (EI): *m*/*z*: 358 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{21}H_{26}OS_2$ $[M]^+$: 358.1425; found: 358.1443.

Compound ***8***: M.p. 171–173 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.27–7.07 (m, 12H; ArH), 3.65 (s, 8H; CH_2), 3.62 (s, 8H; CH_2), 3.46 (s, 6H; OCH_3), 1.27 ppm (s, 18H; *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 154.3, 147.0, 138.6, 130.5, 129.6 (CH), 128.8 (CH), 127.6 (CH), 127.0 (CH), 62.0 (OCH_3), 36.6 (CH_2), 34.5, 31.5 (CH_3), 30.5 ppm (CH_2); IR (ATR): $\tilde{\nu}_{max}$ = 2957, 2922, 1610, 1481, 1433, 1249, 1206, 1099, 1000, 885, 649 cm^{-1}; MS (EI): *m*/*z*: 716 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{42}H_{52}O_2S_4$ $[M]^+$: 716.2850; found: 716.2835.

Compounds 9 and 10: A mixture of K_2CO_3 (0.688 g, 5.0 mmol, 5 equiv), **1** (0.349 g, 0.99 mmol, 1 equiv) and **6** (0.200 g, 0.99 mmol, 1 equiv) was used. Purification by column chromatography (silica gel, eluent CH_2Cl_2/hexane/diethyl ether 48:48:4) afforded **9** (0.031 g, 8 %) and **10** (0.170 g, 44 %) as off-white solids.

Compound ***9***: M.p. 105–107 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 6.98–6.91 (m, 4H; ArH), 6.63 (t, ^3J(H,H) = 7.3 Hz, 1H; ArH), 4.41 (d, ^2J(H,H) = 14.5 Hz, 4H; CH_2), 3.51 (s, 6H; OCH_3), 3.35 (d, ^2J(H,H) = 14.3 Hz, 4H; CH_2), 1.19 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 157.1, 155.1, 145.7, 130.9, 129.7, 129.3 (CH), 126.6 (CH), 124.6 (CH), 62.31/62.27 (OCH_3), 34.3, 31.4 (CH_3), 30.6 (CH_2), 30.2 ppm (CH_2); IR (ATR): $\tilde{\nu}_{max}$ = 2954, 2855, 2823, 1479, 1430, 1260, 1207, 1101, 1006, 874, 811, 636 cm^{-1}; MS (EI): *m*/*z*: 388 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{22}H_{28}O_2S_2$ $[M]^+$: 388.1531; found: 388.1538.

Compound ***10***: M.p. 70–72 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.22–7.15 (m, 8H; ArH), 7.01 (t, ^3J(H,H) = 7.5 Hz, 2H; ArH), 3.67 (s, 8H; CH_2), 3.66 (s, 8H; CH_2), 3.26 (s, 6H; OCH_3), 3.23 (s, 6H; OCH_3), 1.29 ppm (s, 18H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 156.5, 154.2, 146.7, 131.6, 130.6, 130.1 (CH), 127.0 (CH), 124.0 (CH), 61.54/61.48 (OCH_3), 34.4, 31.5 (CH_3), 30.7 (CH_2), 30.3 ppm (CH_2); IR (ATR): $\tilde{\nu}_{max}$ = 2958, 2863, 2821, 1485, 1431, 1264, 1208, 1101, 1000, 871, 812, 640 cm^{-1}; MS (EI): *m*/*z*: 776 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{44}H_{56}O_4S_4$ $[M]^+$: 776.3061; found: 776.3117.

Compound 11: *m*-CPBA (0.667 g, 3.87 mmol, 12 equiv) and $MgSO_4$ (0.906 g, 7.74 mmol) were mixed together in CH_2Cl_2 (10 mL) and stirred for 1 h at RT. Subsequently, homothiacalix[4]arene **4** (0.28 g, 0.31 mmol, 1 equiv) was added and the mixture was stirred at RT for 12 h (under Ar). The resulting solution was filtered, diluted with MeOH (20 mL), and CH_2Cl_2 was carefully evaporated in vacuo, resulting in the formation of a white crystalline solid, which was filtered off and washed carefully with MeOH to afford **11** as an off-white solid (0.270 g, 84 %). M.p. >335 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.56 (s, 8H; ArH), 4.17 (s, 16H; CH_2), 3.49 (s, 12H; OCH_3), 1.30 ppm (s, 36H; *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 155.7, 148.3, 131.0 (CH), 121.2, 63.2 (OCH_3), 52.6 (CH_2), 34.7, 31.4 ppm (CH_3); IR (ATR): $\tilde{\nu}_{max}$ = 2946, 2860, 2820, 1487, 1439, 1319, 1248, 1203, 1154, 1121, 1000, 893, 814, 550 cm^{-1}; MS (ESI$^+$): *m*/*z*: 1039 $[M+Na]^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{52}H_{72}O_{12}S_4Na$ $[M+Na]^+$: 1039.3804; found: 1039.3818.

Compound 13: *tert*-Butyl 2-bromoacetate (3.63 g, 18.6 mmol, 1.1 equiv) was added to a mixture of **12** (3.56 g, 17.0 mmol) and K_2CO_3 (6.13 g, 84.8 mmol, 5 equiv) in dry CH_3CN (50 mL). The mixture was stirred at RT for 3 d and then concentrated under reduced pressure. The crude residue was redissolved in a mixture of CH_2Cl_2 and water. The organic fraction was separated, washed with water, dried over $MgSO_4$, filtered, and evaporated to dryness. Pure compound **13** was obtained by precipitation from heptane, filtering, and drying in vacuo (3.07 g, 56 %). M.p. 147–148 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.29 (s, 2H; ArH), 4.70 (d, ^3J(H,H) = 6.0 Hz, 4H; CH_2-OH), 4.56 (s, 2H; OCH_2), 2.93 (t, ^3J(H,H) = 6.2 Hz, 2H; OH), 1.51 (s, 9H; O-*t*Bu), 1.30 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 169.7 (CO), 153.9, 147.7, 132.9, 126.8 (CH), 83.0 (O-*t*Bu), 71.7 (OCH_2), 61.9 (CH_2OH), 34.4 (*t*Bu), 31.4 (CH_3), 28.1 ppm (CH_3); IR (ATR): $\tilde{\nu}_{max}$ = 3442, 3388, 2952, 2820, 1736, 1484, 1432, 1363, 1242, 1202, 1120, 1057, 1033, 1008, 963, 886, 831, 792, 546 cm^{-1}; MS (ESI$^+$): *m*/*z*: 347 $[M+Na]^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{18}H_{28}O_5Na$ $[M+Na]^+$: 347.1834; found: 347.1825.

Compound 14: A degassed solution of **13** (0.865 g, 2.66 mmol) and *N*-bromosuccinimide (1.14 g, 6.41 mmol, 2.4 equiv) in CH_2Cl_2 (40 mL) was prepared in a 100 mL flask and cooled to 0 °C. The solution became slightly green after 5 min. A solution of PPh_3 (1.67 g, 6.41 mmol, 2.4 equiv) in CH_2Cl_2 (10 mL) was added dropwise by using a syringe pump over 1 h with vigorous stirring. Upon addition of the phosphine, the solution turned colorless and was stirred for an additional 1 h at 0 °C. The reaction mixture was quenched with ice water (50 mL) and extracted with CH_2Cl_2 (50 mL), dried over $MgSO_4$, filtered, and evaporated to dryness to afford the crude product. Purification by column chromatography (silica gel, eluent CH_2Cl_2/hexane 7:2) afforded **14** as an off-white solid (0.81 g, 67 %). M.p. 143–144 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.35 (s, 2H; ArH), 4.68 (s, 2H; OCH_2), 4.63 (s, 4H; CH_2Br), 1.55 (s, 9H; O-*t*Bu), 1.31 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.2 (CO), 153.4, 148.6, 131.4, 129.4 (CH), 82.5 (O-*t*Bu), 71.3 (OCH_2), 34.5, 31.3 (CH_3), 28.5 (CH_2), 28.3 ppm (CH_3); IR (ATR): $\tilde{\nu}_{max}$ = 2965, 2867, 2825, 1753, 1482, 1436, 1365, 1264, 1243, 1214, 1199, 1153, 1098, 1047, 943, 885, 852, 747, 564 cm^{-1}; MS (EI): *m*/*z*: 450 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{18}H_{26}Br_2O_3$ $[M]^+$: 450.0228; found: 450.0240.

Compound 15: A solution of **14** (0.425 g, 0.944 mmol) and thiourea (0.179 g, 2.36 mmol, 2.5 equiv) in THF (20 mL) was stirred for 20 h at 50 °C under an argon atmosphere. After the reaction mixture was cooled to RT, THF was removed under reduced pressure. The resulting bis(isothiouronium) salt was hydrolyzed by treating a suspension of the salt in dioxane/water (4:1 v/v; 35 mL) with ethylenediamine (0.180 g, 2.99 mmol) for 20 h at RT, followed by neutralization with 6 N HCl (1.2 mL) at 0 °C. The reaction mixture was extracted with CH_2Cl_2 (50 mL), dried over $MgSO_4$, filtered, and evaporated to dryness to afford the crude product. Purification by column chromatography (silica gel, eluent CH_2Cl_2/hexane 65:35) afforded **15** as an off-white solid (0.201 g, 59 %). M.p. 95–97 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.20 (s, 2H; ArH), 4.55 (s, 2H; OCH_2), 3.81 (d, ^3J(H,H) = 7.4 Hz, 4H; CH_2SH), 1.91 (t, ^3J(H,H) = 7.3 Hz, 2H; SH), 1.54 (s, 9H; O-*t*Bu), 1.30 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.4 (CO), 152.2, 148.3, 134.2, 126.4 (CH), 82.4 (O-*t*Bu), 72.1 (OCH_2), 34.6 (*t*Bu), 31.5 (CH_3), 28.3 (CH_3), 23.9 ppm (CH_2); IR (ATR): $\tilde{\nu}_{max}$ = 2965, 2867, 2820, 2562, 1753, 1484, 1432, 1369, 1250, 1199, 1120, 1050, 1025, 1002, 967, 880, 830, 780, 540 cm^{-1}; MS (EI): *m*/*z*: 356 $[M]^+$; HRMS (EI): *m*/*z* calcd for $C_{18}H_{28}O_3S_2$ $[M]^+$: 356.1480; found: 356.1465.

Compounds 16 and 17: A suspension of K_2CO_3 (0.770 g, 5.55 mmol, 5 equiv) in dry THF (70 mL) was degassed with argon for 10 min. A solution of precursors **2** (0.284 g, 1.11 mmol, 1 equiv) and **14** (0.500 g, 1.11 mmol, 1 equiv) in dry THF (10 mL) was added and the mixture was stirred at reflux temperature for 2 d, after which time the mixture was cooled to RT and evaporated to dryness. The crude residue was redissolved in a mixture of CH_2Cl_2 and water. The organic fraction was separated, washed with water, dried over $MgSO_4$, filtered, and evaporated to dryness. Separation of the homothiacalixarenes by column chromatography (silica gel, eluent CH_2Cl_2/hexane/diethyl ether 48.5:48.5:3) afforded **16** (0.310 g, 51 %) and **17** (0.060 g, 10 %) as off-white solids.

Compound ***16***: M.p. 180–182 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.32 (s, 2H; ArH), 7.31 (s, 2H; ArH), 7.19 (s, 2H; ArH), 7.17 (s, 2H; ArH), 4.46 (s, 2H; OCH_2), 4.38 (s, 2H; OCH_2), 4.15–4.07 (m, 4H; CH_2), 3.80 (d, ^2J(H,H) = 11.3 Hz, 2H; CH_2), 3.73–3.58 (m, 8H; CH_2), 3.54 (d, ^2J(H,H) = 13.6 Hz, 2H; CH_2), 3.18 (s, 3H; OCH_3), 3.13 (s, 3H; OCH_3), 1.48 (s, 9H; O-*t*Bu), 1.47 (s, 9H; O-*t*Bu), 1.33 (s, 9H; *t*Bu), 1.31 (s, 9H; *t*Bu), 1.28 (s, 9H; *t*Bu), 1.27 ppm (s, 9H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.6 (CO), 168.4 (CO), 154.5, 154.3, 153.3, 153.1, 147.1, 147.0, 131.7, 131.3, 129.9, 127.4 (CH), 127.3 (CH), 127.0 (CH), 126.9 (CH), 82.0 (O-*t*Bu), 72.0 (OCH_2), 71.9 (OCH_2), 61.8 (OCH_3), 61.6 (OCH_3), 34.5, 34.4, 32.1 (CH_2), 31.8 (CH_2), 31.6 (CH_2), 31.5 (CH_3), 30.7 (CH_2), 30.2 (CH_2), 28.3 ppm (CH_3); IR (ATR) $\tilde{\nu}_{max}$ = 2951, 2905, 2868, 2825, 1756, 1478, 1437, 1364, 1223, 1191, 1152, 1102, 1051, 1004, 887, 837, 789, 647 cm^{-1}; MS (ESI$^+$): *m*/*z*: 1112.1 [*M*+Na]$^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{62}H_{88}O_8S_4Na$ [*M*+Na]$^+$: 1111.5260; found: 1111.5274.

Compound ***17***: M.p. 87–88 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.26 (s, 6H; ArH), 7.14 (s, 6H; ArH), 4.48 (s, 6H; OCH_2), 3.80 (s, 12H; CH_2), 3.70 (s, 12H; CH_2), 3.49 (s, 9H; OCH_3), 1.48 (s, 27H; O-*t*Bu), 1.26 (s, 27H; *t*Bu), 1.21 ppm (s, 27H; *t*Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.5 (CO), 154.3, 153.4, 147.1, 147.0, 131.2, 130.5, 127.0 (CH), 126.9 (CH), 81.9 (O-*t*Bu), 72.1 (OCH_2), 61.8 (OCH_3), 35.5, 34.5, 31.5 (CH_3), 30.8 (CH_2), 28.3 ppm (CH_3); IR (ATR): $\tilde{\nu}_{max}$ = 2957, 2864, 2820, 1749, 1479, 1434, 1363, 1226, 1197, 1152, 1104, 1053, 1005, 884, 846, 791, 644 cm^{-1}; MS (ESI$^+$): *m*/*z*: 1657.2 [*M*+Na]$^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{93}H_{132}O_{12}S_6Na$ [*M*+Na]$^+$: 1656.7973; found: 1656.8061.

Compounds 18 and 19: A suspension of K_2CO_3 (0.326 g, 2.36 mmol) in dry 1,4-dioxane (170 mL) was degassed with argon for 10 min. A solution of precursors **15** (0.168 g, 0.47 mmol) and **14** (0.212 g, 0.47 mmol) in dry 1,4-dioxane (10 mL) was added and the mixture was stirred at reflux for 3 d, after which time the mixture was cooled to RT and evaporated to dryness. The crude residue was redissolved in a mixture of CH_2Cl_2 and water. The organic fraction was separated, washed with water, dried over $MgSO_4$, filtered, and evaporated to dryness. Separation of the homothiacalixarenes by column chromatography (silica gel, eluent heptane/diethyl ether 80:20) afforded **18** (0.140 g, 46%) and **19** (0.050 g, 16%) as off-white solids.

Compound ***18***: M.p. 182–184 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.20 (brs, 8H; ArH), 4.09 (brs, 16H; CH_2), 3.50 (brs, 12H; OCH_2), 1.44 (brs, 36H; *t*Bu), 1.25 ppm (brs, 36H; *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.5 (CO), 153.8, 147.0, 130.4, 127.1 (CH), 81.6 (O-*t*Bu), 71.8 (OCH_2), 34.4, 31.5 (CH_3), 30.7 (CH_2), 28.2 ppm (CH_3); IR (ATR) $\tilde{\nu}_{max}$ = 2964, 2870, 1751, 1478, 1430, 1392, 1304, 1225, 1193, 1151, 1105, 1053, 1009, 944, 846, 795, 637 cm^{-1}; MS (ESI$^+$): *m*/*z*: 1312 [*M*+Na]$^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{72}H_{104}O_{12}S_4Na$ [*M*+Na]$^+$: 1311.6308; found: 1311.6321.

Compound ***19***: M.p. 73–75 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.14 (s, 12H; ArH), 4.41 (s, 12H; CH_2), 3.79 (s, 24H; OCH_2), 1.46 (s, 54H; *t*Bu), 1.20 ppm (s, 54H; *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 168.4 (CO), 153.5, 147.2, 130.9, 127.0 (CH), 81.8 (O-*t*Bu), 72.1 (OCH_2), 34.4, 31.5 (CH_3), 31.4 (CH_2), 28.3 ppm (CH_3); IR (ATR): $\tilde{\nu}_{max}$ = 2959, 2867, 2810, 1751, 1479, 1458, 1390, 1306, 1224, 1194, 1151, 1101, 1054, 1003, 944, 845, 788, 640 cm^{-1}; MS (ESI$^+$): *m*/*z*: 1957 [*M*+Na]$^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{108}H_{156}O_{18}S_6Na$ [*M*+Na]$^+$: 1956.9541; found: 1956.9676.

Compound 20: A solution of **18** (0.100 g, 0.077 mmol) in CH_2Cl_2 (4 mL) was added to a round-bottomed flask containing a mixture of CH_2Cl_2 and TFA (3:1 ratio; 8 mL) and the resulting mixture was heated at reflux for 12 h, after which time the mixture was cooled to RT and evaporated to dryness. Pure macrocycle **20** was obtained by precipitation from heptane, filtering, and drying in vacuo (0.074 g, 90%). M.p. 154–156 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.16 (s, 8H; ArH), 4.45 (brs, 8H; OCH_2), 3.74 (brs, 16H; CH_2), 1.25 ppm (s, 36H; *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 172.6 (CO), 151.7, 148.5, 130.4, 127.5 (CH), 71.1 (OCH_2), 34.5, 32.0 (CH_2), 31.5 ppm (CH_3); IR (ATR): $\tilde{\nu}_{max}$ = 2954, 2871, 2815, 1748, 1715, 1480, 1430, 1395, 1363, 1228, 1191, 1142, 1105, 1051, 1005, 942, 820, 796, 648 cm^{-1}; MS (ESI$^+$): *m*/*z*: 1088 [*M*+Na]$^+$.

Compound 22: Separate degassed solutions of **2** (0.171 g, 0.667 mmol, 1.5 equiv) and **21** (0.200 g, 0.447 mmol, 1 equiv) in THF (12 mL) were collected in syringes and added dropwise (with the aid of a syringe pump) to a stirred degassed mixture of K_2CO_3 (0.460 g, 3.33 mmol, 5 equiv) in THF (200 mL) at reflux over a period of 5 h. After complete addition, the mixture was stirred at reflux for an additional 10 h, after which time the mixture was cooled to RT and evaporated to dryness. The crude residue was redissolved in a mixture of CH_2Cl_2 and water. The organic fraction was separated, washed with water, dried over $MgSO_4$, filtered, and evaporated to dryness. Purification by column chromatography (silica gel, eluent CH_2Cl_2/hexane/diethyl ether 55:36:9) afforded **22** as an off-white solid (0.061 g, 23%). M.p. 248–249 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 7.23 (s, 8H; ArH), 3.76 (s, 18H; OCH_3), 3.70 (s, 12H; CH_2), 3.62 (s, 12H; CH_2), 3.07 (brs, 9H; OCH_3), 1.27 ppm (s, 27H; *t*Bu); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ = 158.5, 154.4, 147.1, 130.9, 126.9 (CH), 121.9, 63.5 (OCH_3), 61.2 (OCH_3), 34.4, 31.6 (CH_3), 30.8 (CH_2), 25.1 ppm (CH_2); IR (ATR): $\tilde{\nu}_{max}$ = 2951, 2865, 2821, 1578, 1480, 1459, 1410, 1249, 1198, 1159, 1091, 1002, 895, 816, 640 cm^{-1}; MS (ESI$^+$): *m*/*z*: 1200 [*M*+Na]$^+$; HRMS (ESI$^+$): *m*/*z* calcd for $C_{63}H_{84}O_9S_6Na$ [*M*+Na]$^+$: 1199.4337; found: 1199.4355.

Crystallographic data: Data collection was performed by using $Cu_{K\alpha}$ radiation (λ = 1.54178 Å, crossed Goebel mirrors) and phi and omega scans on a Bruker diffractometer equipped with a SMART 6000 CCD detector. Prior to the diffraction experiment, the crystals were flash-cooled at 100 K. Cell refinement and data reduction were carried out by the program SAINT.[17] The structures were solved by direct methods and refined by full-matrix least squares on $|F^2|$ using the SHELXTL program package.[18] Non-hydrogen atoms were anisotropically refined and the hydrogen atoms were placed on calculated positions with temperature factors fixed at 1.2 times U_{eq} of the parent atoms and 1.5 times U_{eq} for methyl groups.

CCDC-822950 (**4**), 822951 (**16**), 822952 (**18**), and 822953 (**22**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Compound ***4***: Crystallization from methanol/$CHCl_3$; $C_{52}H_{72}O_4S_4$; M_r = 889.34; triclinic; space group $P\bar{1}$; a = 11.276(9), b = 11.1465(8), c = 12.0862(9) Å; α = 73.305(4), β = 89.965(4), γ = 63.103(3)°; V = 1265.81(17) Å^3; T = 100(2) K; Z = 1; ρ_{calcd} = 1.167 g cm^{-3}; $\mu(Cu_{K\alpha})$ = 2.040 mm^{-1}; $2\theta_{max}$ = 70.39°; $F(000)$ = 480; crystal dimensions 0.28 × 0.18 × 0.12 mm; 4720 independent reflections (R_{int} = 0.0586); final R = 0.0608 for 3906 reflections with $I > 2\sigma(I)$ and wR_2 = 0.1826 for all data.

Compound ***16***: Crystallization from pentane/$CHCl_3$; $C_{62}H_{88}O_8S_4$; M_r = 1089.56; orthorhombic; space group *Pbca*; a = 12.1055(7), b = 19.5739(11), c = 26.1194(15) Å; V = 6189.0(6) Å^3; T = 100(2) K; Z = 4; ρ_{calcd} = 1.169 g cm^{-3}; $\mu(Cu_{K\alpha})$ = 1.806 mm^{-1}; $2\theta_{max}$ = 69.20°; $F(000)$ = 2352; crystal dimensions 0.1 × 0.1 × 0.1 mm; 5757 independent reflections (R_{int} = 0.0921); final R = 0.0700 for 4517 reflections with $I > 2\sigma(I)$ and wR_2 = 0.1700 for all data.

Compound ***18***: Crystallization from methanol/$CHCl_3$; $C_{72}H_{104}O_{12}S_4$; M_r = 1289.83; tetragonal; space group $I\bar{4}2d$ (no. 122); a = b = 13.435(3), c = 41.067(9) Å; V = 7413(3) Å^3; T = 100(2) K; Z = 4; ρ_{calcd} = 1.156 g cm^{-3}; $\mu(Cu_{K\alpha})$ = 1.622 mm^{-1}; $2\theta_{max}$ = 141.68°; $F(000)$ = 2784; crystal dimensions 0.4 × 0.3 × 0.2 mm; 3543 independent reflections (R_{int} = 0.0627); final R = 0.0516 for 3267 reflections with $I > 2\sigma(I)$ and wR_2 = 0.1356 for all data.

Compound ***22***: Crystallization from methanol/$CHCl_3$; $C_{190}H_{253}Cl_3O_{27}S_{18}$; M_r = 3652.55; triclinic; space group $P\bar{1}$ (no. 2); a = 16.829(6), b = 20.088(8), c = 31.970(13) Å; α = 97.794(12), β = 97.718(12), γ = 97.520(9)°; V = 10488(7) Å^3; T = 100(2) K; Z = 2; ρ_{calcd} = 1.157 g cm^{-3}; $\mu(Cu_{K\alpha})$ = 2.548 mm^{-1}; $2\theta_{max}$ = 133.18°; $F(000)$ = 3896; crystal dimensions 0.4 × 0.2 × 0.1 mm; 35409 independent reflections (R_{int} = 0.0966); final R = 0.1086 for 22718 reflections with $I > 2\sigma(I)$ and wR_2 = 0.2204 for all data. Disordered solvent molecules (total electron count of 404) in solvent accessible voids (total of 1326 Å^3) were squeezed out.[19]

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