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Novel dendritic cores based on thiacalix[4]arene derivatives

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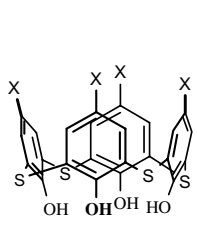
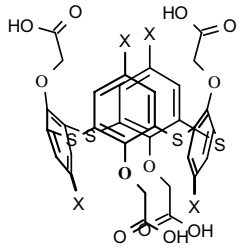
Abstract—Thiacalix[4]arenes possessing carboxylic groups were used for the design of potential dendritic cores with amino surface groups. The known tetraacetic acid in the *1,3-alternate* conformation gave the desired product in very low yield because of steric hindrance on thiacalix[4]arene moiety. Therefore, synthetic strategy based on withdrawing of the carboxyl groups via benzylic spacer from the thiacalix[4]arene moiety was successfully applied for the realization of novel thiacalix[4]arenes bearing two or four protected lysine units.

Since their discovery, thiacalixarenes[1] have been attracting considerable attention, as the presence of hetero atoms results in many novel features compared with 'classical calixarenes'.[2] Hence, thiacalix[4]arenes exhibit a broad range of interesting and potentially useful properties, such as excellent complexation ability toward transition metals, chemical modification (oxidation) of bridges or different conformational preferences.[3] Calixarenes are commonly used in supramolecular chemistry as building blocks and/or molecular scaffolds due to the easily tunable calixarene scaffold. Among others, dendritic-modified calixarenes were realized as supramolecular construction units.[4] Until now the application of the thiacalix[4]arenes in this role is still rather restricted by the lack of generally applicable derivatization methods to easily modify the outer spheres of thiacalix[4]arene derivatives. In this letter we report on the design and synthesis of novel thiacalix[4]arene-based systems with Boc-protected amino surface groups potentially usable as building block in the construction of dendritic derivatives and other supramolecular assemblies.

For the entry of general derivatization methods of the thiacalix[4]arene **1a** and **1b**, the well established thiacalix[4]arene tetraacids **2a**[5] and **2b**,[6] prepared by the hydrolysis of the thiacalix[4]arene tetraacetates[7] in *1,3-alternate* conformation, were converted into the carbonyl chloride intermediates using the oxalyl chloride method. These reactive intermediates were directly reacted (one pot procedure) with the mono-Boc-protected 1,2-diaminoethane and mono-Boc-protected 1,4-phenylenediamine in the presence of triethylamine in DCM.



1a, X = H
1b, X = Bu^t



2a, X = H
2b, X = Bu^t

To our surprise, with the exception of **3** (isolated in low yield after repeated column chromatography in Scheme 1) we were unable to obtain the desired compounds with four Boc-protected amino groups in the exterior. The ^{1}H NMR spectra of the crude reaction products after trials of the conversion of **2a** and **2b** indicated in all cases the presence of partly unreacted carboxylic groups. Indeed, compound **4** with two Boc-protected amino groups (Scheme 1) was isolated from the reaction mixture as the only product of the condensation with mono-Boc-protected 1,4-phenylenediamine. The structure of **4**

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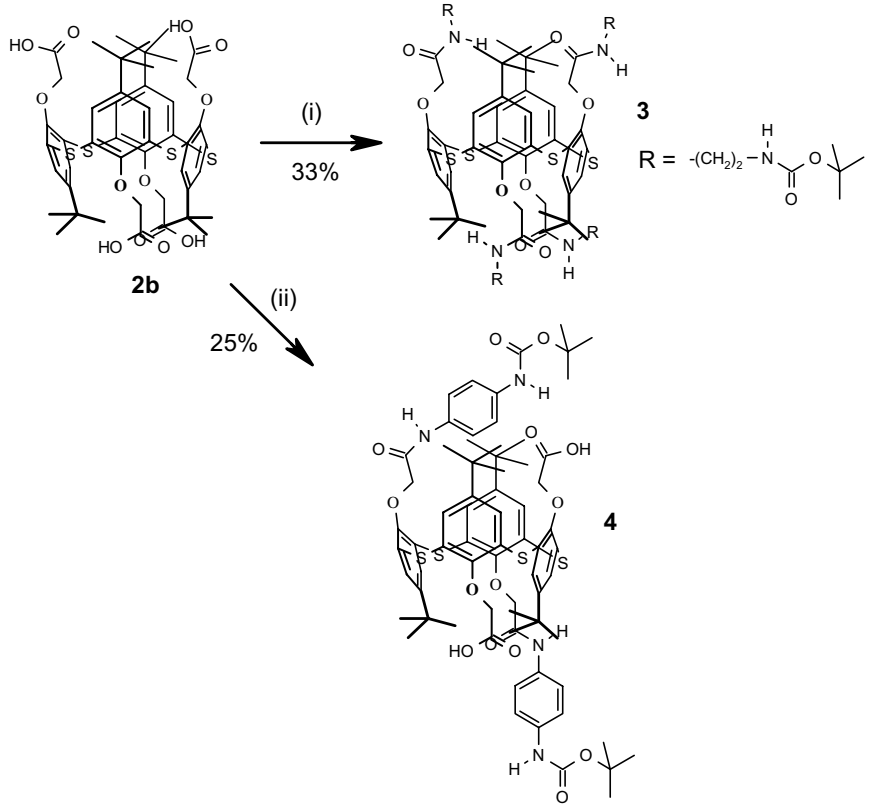


Scheme 1. Synthesis of thiacalix[4]arenes **3** and **4**. Reagents and conditions: excess $(COCl)_2/CCl_4$, 3 h under reflux; then (i) H_2N–$(CH_2)_2$–NH–Boc/Et_3N, CH_2Cl_2, rt, 1 d; (ii) *p*-H_2N–Ph–NH–Boc/Et_3N, CH_2Cl_2, rt, 1 d.

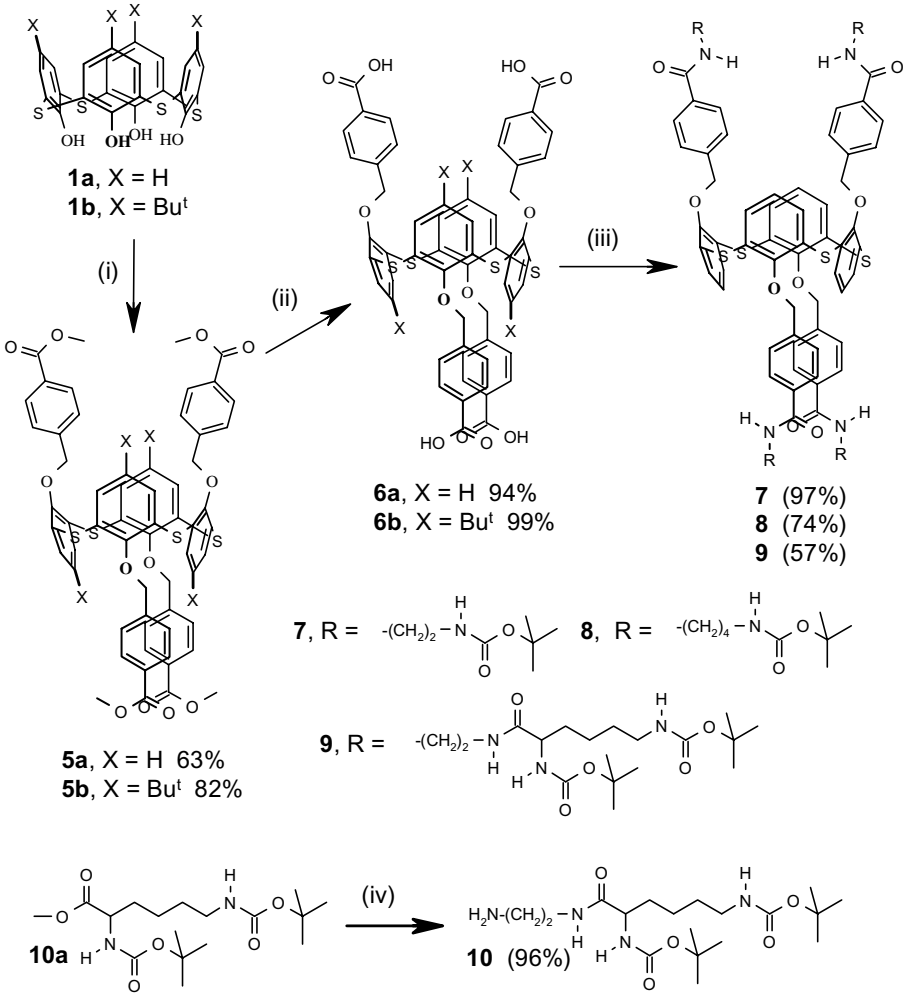
was proved by 2D-NOESY experiments (Figs. 1 and 2 in supplementary material). Its formation could be ascribed to close arrangement between NH-amide and carbonyl chloride groups resulting in H-bonding interactions during the reaction. Thus, complete conversion of the carboxylic groups in **2b** was prevented. In general, steric hindrance may be imposed to the used structures of **2a** and **2b** during the conversion with functionalized amino compounds caused by the possibility of H-bonding interaction of adjacent functional groups on the thiacalixarene moiety. Therefore, the free accessibility of nucleophiles for attacking the carbonyl chloride groups on the thiacalixarene moiety is reduced.

The results of the above reactions for **2a** and **2b** forced us to change the synthetic strategy in such a way that the reacting carboxylic groups have to be spaced more apart from the thiacalix[4]arene moiety. Hence, the commercially available methyl *p*-bromomethylbenzoate was chosen as an alkylating agent, as this compound possesses the carboxylic for subsequent derivatization, and represents highly reactive benzyl halogenide. Moreover the application of the metal template effect[6b,7–11] during the alkylation of the parent thiacalixarenes **1a** and **1b** should allow us to tune the conformational outcome of the reaction.

In order to establish *1,3-alternate* conformers (Scheme 2), thiacalix[4]arenes **1a** and **1b** were alkylated with methyl *p*-bromomethylbenzoate in refluxing acetone for 5 d in the presence of Cs_2CO_3 as a base. The desired products **5a** and **5b** bearing four ester groups were obtained after simple precipitation without additional purification steps in 63% and 82% yield, respectively (Scheme 2). Complete hydrolysis of the methyl esters in **5a** and **5b** required 5 d (Scheme 2) to isolate the corresponding tetraacid derivatives **6a** and **6b** after precipitation in high yields. The compounds **5a**, **5b**, **6a**, and **6b** were identified by 1D and 2D NMR, elemental analysis, IR, and MALDI-TOF-MS. The proposed *1,3-alternate* conformation of the thiacalix[4]arene derivatives **5** and **6** was unambiguously confirmed by 2D-NOESY experiments (Fig. 3 in supplementary material) that revealed the interactions between the benzylic CH_2 groups and aromatic protons. Very simple ^1H NMR signal patterns in the ^1H NMR spectra of these compounds reflect the high symmetry in the *1,3-alternate* conformation (Fig. 4 in supplementary material).

In order to prepare thiacalix[4]arene derivatives suitable as a dendritic core, we tested the general applicability of well-known synthetic methods in the thiacalixarene series (Scheme 2). In contrast with compound **2**, the activation of carboxyl groups in **6a** with CDI and subsequent reaction with mono-Boc-protected 1,2-diaminoethane in DCM led smoothly to the corresponding thiacalix[4]arene derivative **7** in very high yield (97%).

Similarly, the reaction of **6a** with mono-Boc-protected 1,4-diaminobutane under the identical reaction condi-



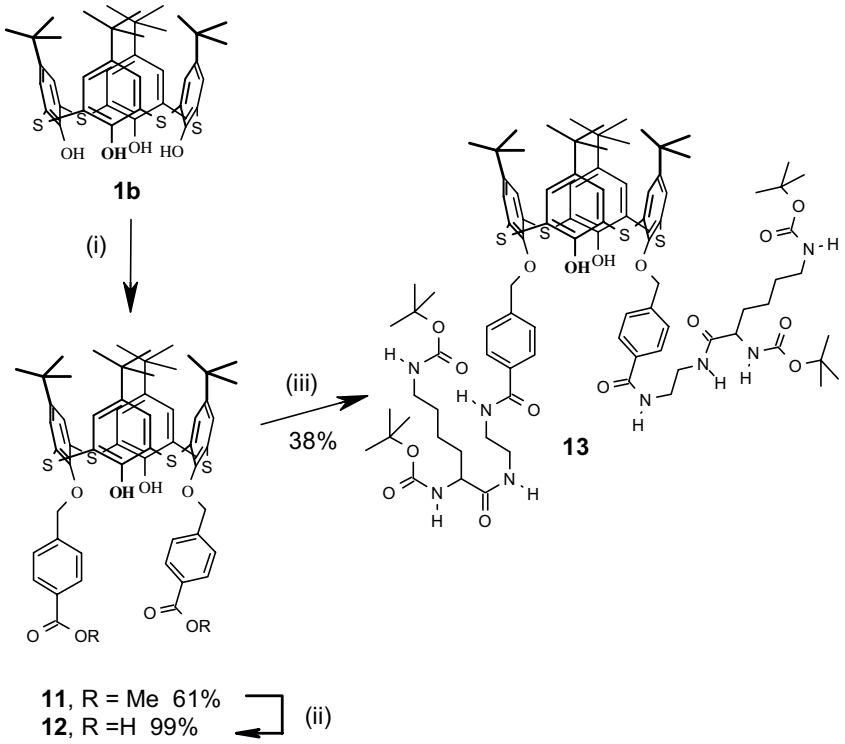
Scheme 2. Synthesis of thiacalix[4]arenes **7**–**9**. Reagents and conditions: (i) *p*-$BrCH_2$–Ph–CO_2Me/Cs_2CO_3, acetone, 60 °C, 5 d; (ii) NaOH, H_2O/EtOH, 80 °C, 5 d, then 1 N HCl; (iii) only for **6a**: CDI, CH_2Cl_2, rt, 2 h, then H_2N–$(CH_2)_x$–NH–Boc (x = 2 or 4) or H_2N–$(CH_2)_2$–NH–$Lys(Boc)_2$ **10**, rt, 1 d; (iv) excess H_2N–$(CH_2)_2$–NH_2, MeOH, rt, 4 d in the dark.

tions gave the desired thiacalix[4]arene derivative **8** in 74% yield (after column chromatography on silica gel). The use of DMF as solvent for the activation of the carboxyl groups in **6a** and their amidation with primary amines is not advantageous due to the problematic separation of DMF from the crude product.

Amides **7** and **8** represent potential thiacalixarene-based dendritic cores possessing the Boc-protected amino groups on their exterior, suitable for the subsequent transformations. To multiply the number of branching units in the core unit, we have attempted the introduction of bis-Boc-protected L-lysine derivative **10**, obtained from aminolysis of bis-Boc-lysine methyl ester **10a**[12] using excess 1,2-diaminoethane (Scheme 2). The reaction of CDI-activated carboxylic groups in **6a** with **10** yielded the desired first generation thiacalix[4]arene dendrimer **9** after column chromatography in 57% yield. Thiacalix[4]arenes **7**–**9** were fully characterized by 1D and 2D NMR, IR, and MALDI-TOF-MS. The ^1H NMR spectra of **8** and **9** are shown in Figure 5 (Supplementary material) to outline the signal assignment of each part structure in **8** and **9**.

The use of Na_2CO_3 as a base[7b] instead of Cs_2CO_3 led to the *cone* conformer possessing two benzyl spacers bearing carboxyl groups (Scheme 3). Thus, the thiacalix[4]arene **1b** was alkylated with an excess of methyl *p*-bromomethylbenzoate in refluxing acetone in the presence of 1 equiv of Na_2CO_3 to give the disubstituted methyl ester derivative **11** in 61% yield as pure compound after precipitation. Interestingly, even the use of more than 1 equiv of the base gave only the disubstituted product without any trace of tetraalkylated compound. The *cone* conformation of the thiacalix[4]arene skeleton in **11** was confirmed by 2D-NOESY experiments. The observed interactions between the phenolic OH groups and benzylic CH_2 groups clearly supported the proposed *cone* structure (see Fig. 6 in supplementary material). A comparison of the ^1H NMR spectra of the *1,3-alternate* conformers **5a** and **5b** and *cone* conformer **11** is given in Figure 4 (Supplementary material) to depict the influence of the conformation on the chemical shifts of the ether part structure in both conformers.

The hydrolysis of the methyl ester groups in **11** were accomplished by the two days reflux with NaOH in



Scheme 3. Synthesis of thiacalix[4]arene **13**. Reagents and conditions: (i) *p*-$BrCH_2$–Ph–CO_2Me/Na_2CO_3, acetone, 60 °C, 4 d; (ii) NaOH, H_2O/EtOH, 80 °C, 2 d, then 1 N HCl; (iii) CDI, CH_2Cl_2, rt, 2 h, then H_2N–$(CH_2)_2$–NH–Lys(Boc)$_2$ **10**, rt, 1 d.

aqueous ethanol (Scheme 3). The resulting carboxylic acid **12** was isolated in quantitative yield after acidification of the reaction mixture with 1 N HCl. Finally, the application of the CDI activation procedure under the identical conditions as mentioned above and subsequent reaction with amino-functionalized bis-Boc-lysine derivative **10** led to the desired product. The thiacalix[4]arene derivative **13**, as the first generation dendrimer, was obtained in 38% yield after column chromatography (Scheme 3). The ^{1}H NMR spectrum exhibits the characteristic features of the *cone* conformation (Fig. 7 in supplementary material). The thiacalix[4]arenes **11**–**13** were characterized by 1D and 2D NMR, elemental analysis, IR, and MALDI-TOF-MS.

In conclusion, we have described a synthetic strategy for the preparation of novel thiacalix[4]arene-based derivatives potentially applicable as dendritic cores. To overcome the problems with the steric hindrance on the thiacalix[4]arene moiety, the aromatic spacer bearing carboxyl groups can be used instead of common bromoacetate derivatives. The resulting carboxylic acid derivatives preorganized in the *1,3-alternate* or in the *cone* conformations serve as a starting point for the synthesis of novel amidic derivatives bearing amino groups on the surface. These compounds represent the first examples of thiacalix[4]arene derivatives potentially useful as dendritic cores for the subsequent branching derivatization.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.07.085. Spectroscopic and analytical data, experimental details for the compounds **3**, **4**, **5a**, **5b**, **6a**, **6b**, **7**, **8**, **9**, **10**, **11**, **12**, and **13**, and Figures 1–7. This material is available via the editorial office.

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