COMMUNICATION

First synthesis of 25,26-bridged thiacalix[4]crowns by the use of a 25,26-*O*-disiloxanediyl-capped *p-tert*-butylthiacalix[4]arene

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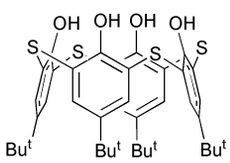
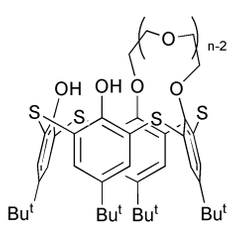
The first and facile synthesis of 25,26-bridged thiacalix[4]-crowns (2a–f) is disclosed by treatment of readily available 25,26-*O*-tetraisopropyldisiloxanediyl-capped *p-tert*-butyl-thiacalix[4]arene (3) with difunctional alkylating agents (5a–f) and subsequent desilylation.

Calix[*n*]crowns are macrocycles characterized by possessing two kinds of receptor elements composed of the subunits of a calix-[*n*]arene[1] and a crown ether[2] joined *via* the phenolic oxygens of the calix component. The interest in this class of compounds as host compounds has mainly arisen from the hope for improving the binding ability as well as selectivity to a particular guest species such as an organic molecule[3] or an alkali metal ion[4] by the synergic effects of the two receptor elements arranged in a defined three-dimensional alignment. In these endeavors, 25,27-calix[4]crowns, in which a calix[4]arene is linked at the distal phenolic oxygens with a poly(oxyethylene) chain, have usually been utilized as the molecular scaffold. In this context, thia-calix[4]crowns, in which the calix skeleton is comprised of *p*-alkylphenols connected at the *o,o′*-positions with epithio linkages, are very intriguing because of the improved metal-binding ability of the thiacalix[4]arene molecular framework[5] (*e.g.* **1**) by ligation of the lone-pair electrons on the sulfurs to metal cations.[5c,6] Quite recently, Vicens and coworkers reported the first synthesis of 25,27-26,28-doubly bridged thiacalix[4]-bis(crown-*n*)s (n = 5 and 6) for investigation of their ability to extract Na^+ and Cs^+ ions.[7] On the other hand, little is known about the chemistry of 25,26-bridged calix[4]crowns,[8] and to the best of our knowledge, no examples of 25,26-bridged *thia*-calixcrowns have been reported. These are mainly due to the scarcity of efficient methods for introducing substituents at the proximal 25,26-*O*-positions, the crucial prerequisite for the intramolecular 25,26-bridging. Considering the anticipated potential metal-binding ability of the 25,26-thiacalix[4]crown-class compounds by cooperative complexation using the ligating sites comprised of the tridentate O^-–S–O^- and the crown ether moiety arranged in an apparently suitable steric arrangement, development of a convenient method to these new hosts would be highly desirable. We experienced, however, that attempted synthesis of 25,26-bidged thiacalix[4]crown-4 (**2c**) by the method used for the synthesis of the corresponding 25,26-bridged calix[4]crown-4[8a] was quite disappointing. In our previous paper,[9] we reported an efficient method for a net proximal dialkylation of calix[4]arenes at the lower rim *via* the dialkylation of readily available 25,26-*O*-disiloxanediyl-capped calix-[4]arenes (*e.g.* **3**) and subsequent facile desilylation. Then, it occurred to us to extend the 25,26-*O*-disiloxane-capping–27,28-*O*-dialkylation–deprotection protocol to an intramolecular proximal *O*-bridging version by use of a difunctional alkylating agent, and herein we report the first and facile synthesis of 25,26-bridged thiacalix[4]crowns (**2a–f**).

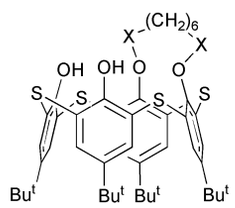
Reactions of disiloxane-capped thiacalix[4]arene **3** with



***p-tert*-butylthiacalix[4]arene (1)**

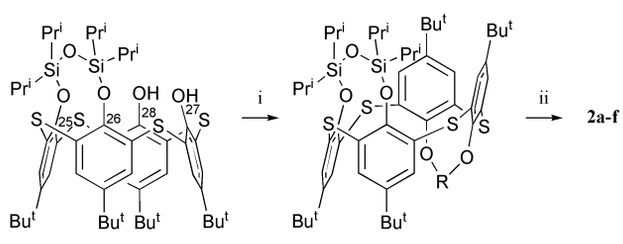


2a-d: n = 2-5



2e: X = CH_2
2f: X = CO

several oligo(ethylene glycol) bistoluene-*p*-sulfonates **5a–d** using Cs_2CO_3 as the base cleanly proceeded in THF, DMF, or their mixture to give the 25,26-*O*-disiloxanediyl-bridged thia-27,28-calix[4]crowns **4a–d** in 71–89% isolated yield, implying that the intramolecular cyclization step should be much faster than the first intermolecular *O*-alkylation (Scheme 1, Table 1).



3 **4a-f**

Scheme 1 *Reagents*: (i) X–R–X **5a–f**, Cs_2CO_3 or NEt_3, DMF–THF (1 : 1) or DMF or THF; (ii) tetrabutylammonium fluoride, THF.

It can be seen that only a slight excess of the alkylating agents (**5b–d**) is required, although bridging by ethylene required a 3 molar equiv. of the bistoluene-*p*-sulfonate **5a** because of the sluggishness of the reaction probably due to steric reasons (*vide infra*). These products were identified as the intrabridged entities by FD-MS spectra and ^{1}H NMR spectra (500 MHz, $CDCl_3$), showing two singlets for *tert*-butyl protons (each 18H) and four doublets for the aryl protons (each 2H). The NMR required their conformation to be cone or 1,2-alternate, the latter rather than the former was assigned based on the ^{1}H NMR signals of the disiloxane moiety and/or bridging methylene protons connected to the 27,28-phenoxy oxygens as follows.

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Table 1 Synthesis of thiacalix[4]crowns **2a**–**f** by use of an intermediate **3**

R–X–R **5** (mol equiv.)	Base (mol equiv.)	Solvent	Yield (%)[a] of **4**	Yield (%)[b] of **2**
$TsOCH_2CH_2OTs$[c] **5a** (3.0)	Cs_2CO_3 (3.0)	THF–DMF (1 : 1)	89 (**4a**)	91 (**2a**)
$TsOCH_2CH_2OCH_2CH_2OTs$ **5b** (1.2)	Cs_2CO_3 (3.0)	DMF	71 (**4b**)	99 (**2b**)
$TsOCH_2(CH_2OCH_2)_2CH_2OTs$ **5c** (1.2)	Cs_2CO_3 (3.0)	THF	84 (**4c**)	96 (**2c**)
$TsOCH_2(CH_2OCH_2)_3CH_2OTs$ **5d** (1.2)	Cs_2CO_3 (3.0)	THF	75 (**4d**)	96 (**2d**)
$BrCH_2(CH_2)_6CH_2Br$ **5e** (1.2)	Cs_2CO_3 (3.0)	THF–DMF (1 : 1)	57 (**4e**)	92 (**2e**)
$ClCO(CH_2)_6COCl$ **5f** (1.2)	NEt_3 (4.0)	THF	50[d] (**4f**)	96 (**2f**)

[a] Isolated yield based on **3**. [b] Isolated yield based on **4**. [c] TS = toluene-*p*-sulfonate. [d] Calculated from ^{1}H NMR of the reaction mixture.

Isopropylmethyl protons of **3** appear at 0.80, 1.15, 1.18, and 1.38 ppm as four sets of doublet (each 6H) indicating that the rotation around the bonds between the Si and Pr^i groups is restricted by steric hindrance.[9] It has been shown previously that 27,28-*O*-dialkylation products of **3** were in the 1,2-alternate conformation as evidenced by an upfield shift of the isopropylmethyl proton signals to 0.47, 0.80, 1.03, and 1.09 ppm due to the anisotropic shielding effect of the aryl rings at the 27,28-positions. Thus, the upfield shift of the isopropylmethyl protons up to *ca.* 0.4 ppm should make a good probe for judging the 1,2-alternate conformation of a disiloxane-capped thiacalix[4]crown **4**.

For **4b**–**d**, the ^{1}H NMR signals of the most shielded isopropylmethyl protons appeared at 0.33–0.45 ppm, suggesting that these compounds also should be in the 1,2-alternate conformation. It is interesting that the ^{1}H NMR spectrum of **4a** showed no isopropylmethyl protons shifted upfield to the 0.4 ppm region. However, its bridging ethylene protons connected to the 27,28-phenolic oxygens appeared at 1.60–3.95 ppm, significantly shifted upfield as compared with (4.55–4.75 ppm) of the product (**2a**) obtained after desilylation. Similarly, the methylene protons of **4b**–**d** connected to the 27,28-phenoxy oxygens appeared at *ca.* 2.5 ppm, which were shifted to *ca.* 4.5 ppm region after desilylation to **2b**–**d** (*vide infra*). These results strongly suggest that the methylene protons of **4a**–**d** connected to the 27,28-phenoxy oxygens are subjected to the shielding effect of the aryl rings at the 25,26-positions, which, in turn, substantiates that all **4a**–**d** take 1,2-alternate conformation. It may be concluded that the single ethylene bridge of **4a** pulls the 27,28-phenoxy oxygens inwardly to push the phenoxy nuclei at the 27- and 28-positions away from the calix ring, thus reducing the shielding effect on the disiloxane moiety.

The reaction of **3** with alkyl dihalide **5e** or diacid dichloride **5f** instead of oligo(ethylene glycol) bistoluene-*p*-sulfonates could also be carried out smoothly to give 25,26-27,28-doubly bridged compounds **4e**,**f** in good yields, the conformations of which were assigned also as 1,2-alternate based on the ^{1}H NMR criteria of the isopropylmethyl protons as stated above.

Deprotection of **4a**–**f** was easily carried out by simply treating with tetrabutylammonium fluoride in THF to liberate the proximal 25,26-bridged thiacalix[4]crowns and their analogues **2a**–**f** quantitatively (Scheme 1, Table 1). ^{1}H NMR signals for the $ArOCH_2$ moiety of these thiacalix[4]crowns appeared at 4.0–5.0 ppm, in sharp contrast to those of **4a**–**d** that appeared at 2.0–3.8 ppm. These results show that the $ArOCH_2$ protons of **2a**–**d** are free from the shielding effect of the 27,28-aryl rings, which, in turn, suggests that these 25,26-calix[4]crowns are in the cone conformation in $CDCl_3$ at ambient temperature.

Experimental

The synthesis of 2,8,14,20-tetrathia-25,26-calix[4]crown-4 (2c) *via* 27,28-*O*-disiloxanediyl-bridged 2,8,14,20-tetrathia-25,26-calix[4]crown-4 (4c)

To a solution of **3** (0.48 g, 0.50 mmol) in anhydrous THF (50 ml) were added caesium carbonate (0.49 g, 1.5 mmol) and tri(ethylene glycol) bistoluene-*p*-sulfonate **5c** (0.28 g, 0.60 mmol). After heating at reflux with stirring for 30 hours, the mixture was cooled to 0 °C, diluted with 2 M HCl, and extracted with chloroform. The organic layer was washed and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* to obtain a crude product, which was purified by column chromatography (silica gel, AcOEt–*n*-hexane = 1 : 10) to give **4c** in 84% yield (0.45 g).

To a solution of **4c** (0.32 g, 0.30 mmol) in THF (15 ml) was added a 1.0 M solution of tetrabutylammonium fluoride in THF (0.30 ml, 0.30 mmol) at room temperature. After stirring for 1 hour, the mixture was cooled to 0 °C, diluted with 2 M HCl, and extracted with chloroform. The organic layer was washed with water and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed *in vacuo* to obtain a crude product, which was purified by column chromatography (silica gel, AcOEt–*n*-hexane = 1 : 3) to give **2c** in 96% yield (0.24 g).

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