



## Easily accessible symmetrically and unsymmetrically bridge disubstituted tetrahydroxycalix[4]arenes in advantageous *trans-cone* conformation

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### ABSTRACT

A new approach to symmetrically and unsymmetrically bridge disubstituted tetrahydroxycalix[4]arenes is reported involving high yields and facile workup of the products. Strong hydrogen bonds at the lower rim force the compounds to adopt the *cone* conformation with a *trans* arrangement of the bridge substituents.

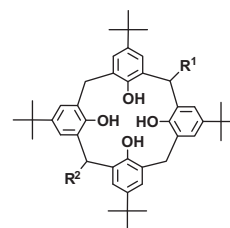
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For decades, calixarenes reflect one of the most powerful and fascinating compounds of the chemist supramolecular tool box, allowing to explore their potential more and more with regard to biological and nanophysical applications.<sup>1</sup> Commonly, this is connected with chemical modification of the upper and lower rim of the calixarene.<sup>2</sup> However, the bridge positions were left disregarded for a long time,<sup>3</sup> though this substitution mode creates essential advantages, including: (i) easy introduction of chirality by a bridge substituent,<sup>4</sup> (ii) additional reactive centre for the attachment of functional or chemosensing units,<sup>5</sup> (iii) anchoring point for the peripheral connection of the chalice and (iv) appropriate spacer for an optimized packing architecture of the chalices.<sup>6</sup> Especially points (iii) and (iv) attracted great recent importance, emerging interest in new synthetic approaches for basic bridge disubstituted calix[4]arenes<sup>6b,c</sup> such as specified in Scheme 1. Moreover, due to the free OH groups at the lower rim site, these compounds are expected to act as key intermediates available for further synthetic modifications. Whereas fragment condensation of bisphenols has been shown to exclusively yield calixarenes with *cis*-arranged bridge substituents,<sup>7</sup> the spirodienone approach is a favourable way to introduce two bridge substituents in a *trans* fashion.<sup>8</sup> Unfortunately, however, both routes are limited to symmetric bridge substituted calixarenes (since both lateral substituents are introduced simultaneously) and are connected with low yields. This has stimulated development of a new synthetic route for bridge disubstituted tetrahydroxycalix[4]arenes of which **1–4**

are typical examples allowing also for unsymmetric bridge disubstitution (Scheme 1).

Incident there to, three basic questions arise: (i) How to overcome the low yields? (ii) How to introduce two different bridge substituents? (iii) What is the conformational effect of hydroxy versus methoxy lower rim groups of a bridge disubstituted calix[4]arene, considering that for methoxy groups an *1,2-alternate* conformation was found?<sup>6c</sup> Will hydrogen bonding in the case of hydroxyls counterbalance or over-compensate this particular conformation leading to the common *cone* conformation with *trans* arranged bridge substituents?

In answer to (i) and (ii), the new approach, giving rise to respectable product yields, involves bridge monosubstitution of tetra-*tert*-butyl-tetramethoxycalix[4]arene via lithiation and substitution,

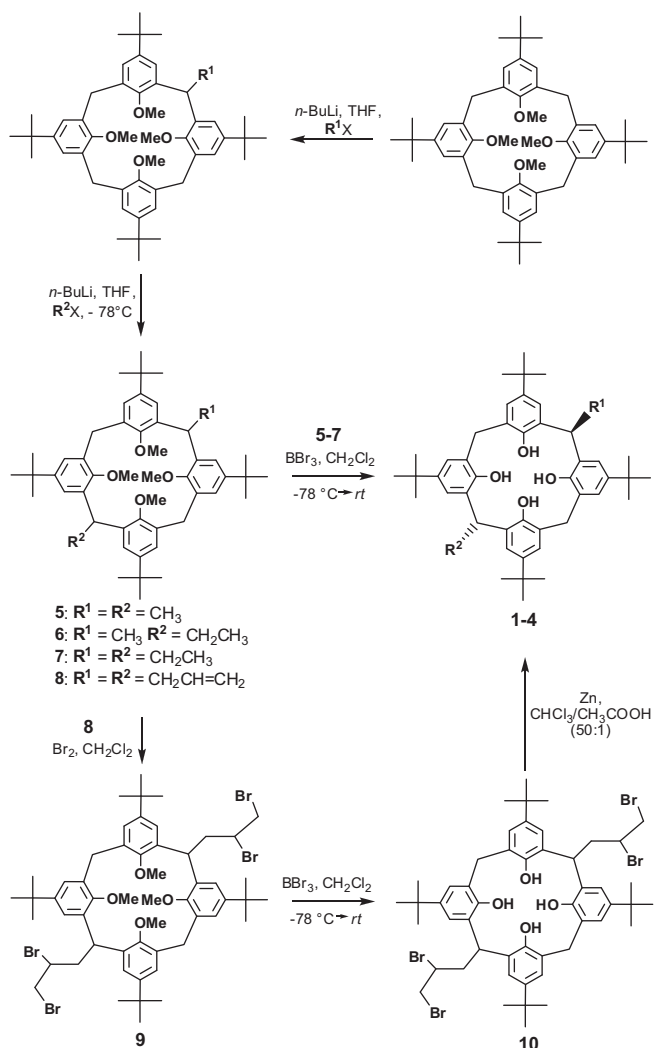


- 1:  $R^1 = R^2 = \text{CH}_3$
- 2:  $R^1 = \text{CH}_3$ ,  $R^2 = \text{CH}_2\text{CH}_3$
- 3:  $R^1 = R^2 = \text{CH}_2\text{CH}_3$
- 4:  $R^1 = R^2 = \text{CH}_2\text{CH}=\text{CH}_2$

Scheme 1. Compounds studied in this letter.

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Scheme 2. Synthesis of title compounds 1–4.

followed by additional substitution of the monosubstituted intermediate applying an analogous lithiation/substitution process and deprotection of the phenolic hydroxyls (Scheme 2). For carrying

out the deprotection of the methoxy intermediates 5–7, except 8,  $\text{BBr}_3$  in dichloromethane is directly used.<sup>9,10</sup> In the case of 8, reaction with  $\text{BBr}_3$  involves the risk of polymerization. Thus, for the synthesis of 4, a modified procedure including preliminary conversion into the tetrabrominated addition product 9, followed by  $\text{BBr}_3$  cleavage of the methoxy groups (10) and elimination of the bromine by treatment with zinc in  $\text{CHCl}_3/\text{CH}_3\text{COOH}$  has been conducted. Worthy to note, the overall yields of the calixarenes 1–4 amount to 23% ( $\pm 5\%$ ) on average, which is about 5–7 times higher compared to the yields obtained using the rather complex spirodienone route.<sup>8</sup>

Relating to (iii), the finding is as follows. While crystal structures as well as the results of the NMR measurements in  $\text{CDCl}_3$  have proven the intermediate tetramethoxy compounds 5–8 to preferably adopt the 1,2-alternate conformation,<sup>6</sup> solution  $^1\text{H}$  NMR spectra of 1–4 in  $\text{CDCl}_3$  reveal this calixarenes to exclusively adopt the cone conformation which is in accordance with previous reports.<sup>7,8</sup> Due to the possible inversion of the chalice (cone-to-cone inversion), signals occur broad at room temperature. Cooling down the samples to 265 K affords doubling of signals for both bridge substituents indicative of a *trans* arrangement (Fig. 1). In the case of compound 2, four resonances for each bridge atom of equal ratio point to the coexistence of two rotamers differing in the orientation of each lateral substituent. Upon raising the temperature, the signals of 1–4 broadened and coalesced. The respective rotational barriers for the cone-to-cone-inversion of the rotamers were estimated in the range around 15 kcal/mol (Table 1).<sup>11</sup> As outlined in the literature,<sup>8</sup> with increasing bulkiness of the substituents this barrier becomes higher.

Unfortunately, attempts to crystallize the title compounds 1–4 yielded only in microcrystalline material. However, we succeeded in obtaining a crystal suitable for X-ray diffraction<sup>12</sup> of a byproduct 3a (3% yield) of the synthesis of 3. This compound possesses one remaining MeO group at the lower rim showing the chalice in the cone conformation with a *trans* arrangement of the substituents in accordance with the results in solution (Fig. 2). Obviously, the presence of three strong hydrogen bonds between the OH-groups of the lower rim (instead of possible two in case of the corresponding 1,2-alternate conformer) accounts for the cone conformation and forces one substituent in an axial position, which is normally strictly avoided for energetical/sterical reasons.<sup>7</sup>

The cavity of 3a is occupied by an included acetonitrile molecule forming  $\text{C}-\text{H} \cdots \pi$  interactions<sup>14</sup> to neighbouring arene units (Supplementary Table S13). The increased dissymmetry due to

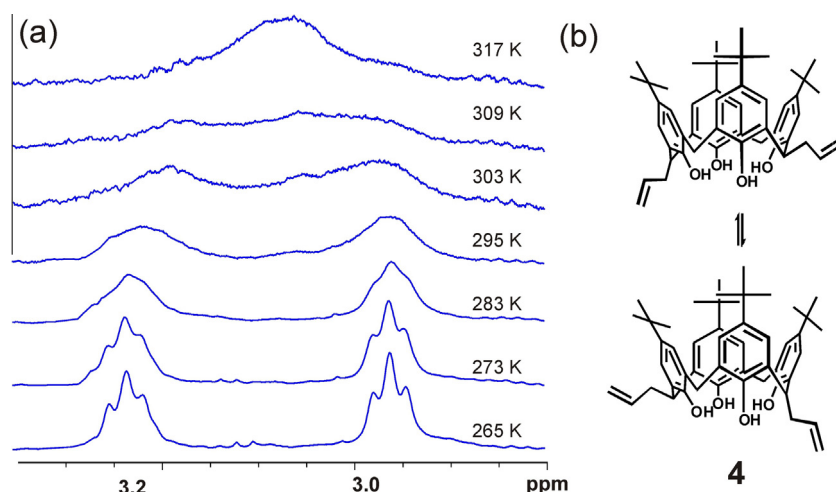


Figure 1. (a) Plot of the temperature-dependent  $^1\text{H}$  NMR spectra of compound 4 with coalescence of the bridge substituent signals. (b) Cone-to-cone inversion exemplarily for compound 4.

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