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Calix[4]arene Derivatives Monosubstituted at All Four Methylene Bridges

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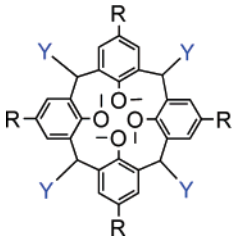

R= *t*-Bu, Y = OMe, OEt, O-*n*-Pr, OCH_2CH_2OH, O-*i*-Pr, OAc, OH, N_3, SCN, 2-methylfuranyl, 4-methylnaphthyl

R = H, Y = 2-methylfuranyl, 2,4-*m*-xylyl

The scope of the reaction of the tetrabromocalixarene derivative **2b** with alcohols under solvolytic conditions in trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP) was explored. The reaction proceeded readily with MeOH, EtOH, *n*-PrOH, ethylene glycol and *i*-PrOH affording preferentially the *rccc* isomer of the tetrasubstituted product. The methoxy derivative **6a** undergoes isomerization upon attempted recrystallization from $CHCl_3$/MeOH and its *rcct* and *rctt* forms were characterized by X-ray crystallography. Incorporation of hydroxy groups on the bridges was accomplished via solvolysis in AcOH, followed by $LiAlH_4$ reduction of the acetoxy groups. Reaction of the tetra-(2-methylfuranyl)calixarene derivative **11** with benzyne followed by deoxygenation with Me_3SiCl/NaI afforded in low yield the tetra-(4-methylnaphthyl)calix[4]arene derivative **12**. Reaction of *de-tert*-butylated tetrabromo derivative **2a** with *m*-xylene in HFIP followed by methylation of the crude product afforded the tetraxylyl derivative **14**.

Introduction

Calix[*n*]arenes are macrocyclic compounds easily prepared in multigram scale by basic condensation of *p-tert*-butylphenol and formaldehyde.[1] Although numerous modifications of the calix scaffold have been achieved, the functionalization of the methylene groups has remained relatively unexplored. Calix[4]arene derivatives substituted at one or two methylene bridges have been prepared by the fragment condensation method,[2] by a spirodienone route,[3] by an homologous anionic ortho-Fries rearrangement[4] and via alkylation of a monolithiated tetramethoxy *p-tert*-butylcalix[4]arene.[5] There are only a few "classical"[6] calix[4]arenes derivatives having all four methylene bridges monofunctionalized which have been reported in the literature.[7] These include the tetrabromo derivatives **2a**[8] and **2b**,[9]

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(1) For reviews on calixarenes see: (a) Vicens, J., Böhmer, V., Eds. *Calixarenes, a Versatile Class of Macrocyclic Compounds*; Kluwer: Dordrecht, 1991. (b) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (c) Gutsche, C. D. *Aldrichimica Acta* **1995**, *28*, 1. (d) Pochini, A.; Ungaro, R. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Vol. Ed.; Pergamon Press: Oxford, UK, 1996; Vol. 2, p 103. (e) Gutsche, C. D. *Calixarenes Revisited* Royal Society of Chemistry, Cambridge, 1998. (f) Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds. *Calixarenes 2001*; Kluwer: Dordrecht, 2001. (g) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19.

(2) (a) Tabatai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657. (c) Sartori, G.; Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, *36*, 2311. (d) Biali, S. E.; Böhmer, V.; Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I.; Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 2261. (e) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037. (f) Tsue, H.; Enyo, K.; Hirao, K. *Org. Lett.* **2000**, *2*, 3071. (g) For a review on the synthesis of calixarenes via the stepwise and fragment condensation methods see: Böhmer, V. *Liebigs Ann./Recl.* **1997**, 2019.

(3) (a) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (b) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136. (c) Simaan, S.; Biali, S. E. *J. Org. Chem.*, **2003**, *68*, 3634. (d) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7685. (e) For a review on spirodienone calixarene derivatives see: Biali, S. E. *Synlett* **2003**, 1.

(4) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667.

(5) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741.

(6) The term "classical" designates calixarenes possessing bridging methylene groups connecting the phenol rings as opposed to "thiacalixarenes" (which possess sulfur bridges) "azacalixarenes" (nitrogen atoms), "ketocalixarenes" (carbonyl groups), etc.

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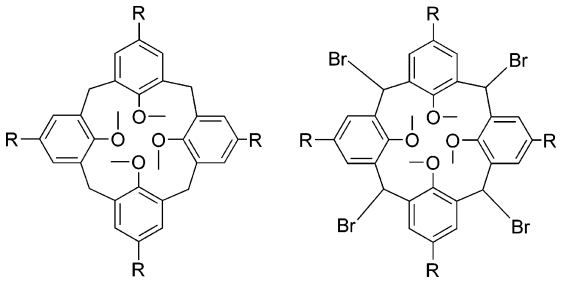
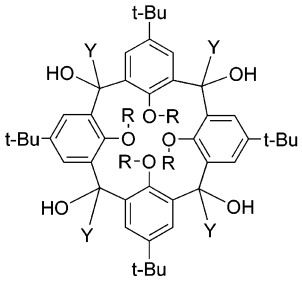
and calixarenes **3a** and **3b**, obtained by reduction or reaction of ketocalix[4]arenes derivatives with $LiAlH_4$ or PhLi, respectively.[10,11]



1a R = H
1b R = t-Bu

2a R = H
2b R = t-Bu



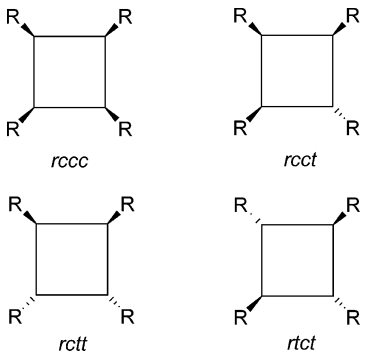
3a R = Y = H
3b R = Me, Y = Ph

We have recently reported that the tetrabromo calixarene derivatives **2a** and **2b** can be utilized as synthetic intermediates for the preparation of calix[4]arenes with all four bridges monofunctionalized.[12] Reaction of these derivatives under solvolytic (S_N1) conditions allows the fourfold replacement of the bromine atoms by trifluoroethoxy, ethoxy, azido and even 2-methylfuranyl groups. In this article we describe a reinvestigation of the bromination reaction of **1a** and **1b**, and a study of the scope and limitations of the nucleophilic substitution route in **2b**.

Results and Discussion

Stereochemistry of Fourfold Functionalized Calixarenes. Four isomers (*rccc*, *rcct*, *rctt* and *rtct*) (Figure 1) are possible for a calixarene derivative which is fourfold monosubstituted with identical substituents. These forms are configurational isomers that, necessarily, require bond cleavage for their mutual interconversion. If the four bridges are monosubstituted by two types of substituents, the number of isomers increases.

The possible arrangements of substituents (equatorial, axial or isoclinal)[13] for the four basic conformations of the calix[4]arene scaffold (cone, partial cone, 1,2-alternate and 1,3-alternate) of the four configurational isomers of a tetrasubstituted system



rccc *rcct* *rctt* *rtct*

FIGURE 1. The four possible isomers of a calix[4]arene possessing four identically functionalized methylene bridges.

are summarized in Table 1.[14] When the macrocycle adopts a cone conformation, the *rccc* form is the only one in which the four substituents at the bridges are located at the sterically unencumbered equatorial positions. In all the other forms, necessarily at least one substituent must be located in axial or isoclinal positions. The parent compounds **1a** and **1b** exist in nonpolar solvents as a conformational mixture in which the partial cone form predominates.[15]

Radical Bromination of Tetramethoxycalix[4]arene. The radical brominations of **1a** and **1b** using different reaction conditions have been described in the literature. Friedrichsen and co-workers reported the bromination of the de-*tert*-butylated calixarene **1a** using NBS and AIBN.[8] A major product was obtained (**2a**) that was characterized by X-ray crystallography as the *rccc* isomer. X-ray diffraction of single crystal of **2a** indicated that in the crystal the molecule adopts a cone conformation with all the bromine groups located at equatorial positions. Two sets of signals in a 83:17 ratio were observed in the ^1H NMR spectrum in $CDCl_3$ at rt. These signals were ascribed to the cone and partial cone conformers of the molecule. The population ratio between the two species remained unchanged upon raising the temperature to 80 °C.

We conducted the bromination of **1a** with NBS in the absence of AIBN but using irradiation. The ^1H NMR of the crude product obtained after one recrystallization was identical to that reported in the literature and displayed two sets of signals in a ca. 83:17 ratio as reported. However, upon repeated recrystallizations from $CHCl_3$/MeOH, the major form was obtained in pure form. This separation by crystallization indicates that the mutual interconversion between the two forms is slow on the human time scale. Thus, either the interconversion barrier between the cone and partial cone forms of the *rccc* form is larger than 25 kcal mol^{-1}, or more likely, the minor form observed does not correspond to a different conformer of the *rccc* form, but rather to a second configurational isomer (e.g., the *rcct* form) which adopts a partial cone conformation.

(7) Azacalix[4]arenes substituted at several nitrogen bridges have been reported. See: (a) Tsue, H.; Ishibashi, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2005**, *7*, 2165. (b) Ishibashi, K.; Tsue, H.; Tokita, S.; Matsui, K.; Takahashi, H.; Tamura, R. *Org. Lett.* **2006**, *8*, 5991.

(8) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967.

(9) Kumar, S. K.; Chawla, H. M.; Varadarajan, R. *Tetrahedron Lett.* **2002**, *43*, 7073.

(10) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Makromol. Chem.* **1990**, *191*, 81.

(11) Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577.

(12) Columbus, I.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2927.

(13) If a methylene is connected to two rings oriented anti, the positions of its protons can be designated as "isoclinal" by analogy to the term utilized for the pairs of geminal protons that are exchanged by a C_2 axis in the twist form of cyclohexane.

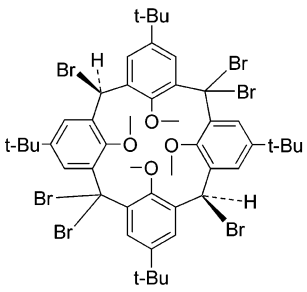
(14) For a review on calix[4]arene systems functionalized at one or two bridges see: Simaan, S.; Biali, S. E. *J. Phys. Org. Chem.* **2004**, *17*, 752.

(15) (a) Iwamoto, K.; Ikeda, A.; Araki, K.; Harada, T.; Shinkai, S. *Tetrahedron* **1993**, *49*, 9937. (b) See also: van Hoorn, W. P.; Briels, W. J.; van Duynhoven, J. P. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1998**, *63*, 1299.

TABLE 1. Possible Arrangements of the Substituents in Calix[4]arenes Derivatives Possessing Four Monosubstituted Bridges

isomer	cone	partial cone[a]	1,3-alternate	1,2-alternate
rccc	tetraequatorial tetraaxial	diequatorial−diisoclinal (I) diaxial−diisoclinal (II)	tetraisoclinal	axial−equatorial−diisoclinal
rcct	triequatorial−axial triaxial−equatorial	diequatorial−isoclinal(I)−isoclinal (II) equatorial− axial−diisoclinal(II)	tetraisoclinal	diequatorial−diisoclinal axial−equatorial−diisoclinal diaxial−diisoclinal
rctt	diequatorial−diaxial	diequatorial−diisoclinal(II) diaxial−diisoclinal(I) equatorial−axial−isoclinal(I)−isoclinal(II)	tetraisoclinal	diequatorial−diisoclinal diaxial−diisoclinal (I)
rctc	diequatorial−diaxial	equatorial− axial−isoclinal(I)−isoclinal(II)	tetraisoclinal	equatorial−axial−diisoclinal

[a] The terms "isoclinal (I)" and "isoclinal (II)" denote arbitrarily the isoclinal positions pointing away or toward the unique ring oriented *anti* to the rest, respectively (see ref 14).



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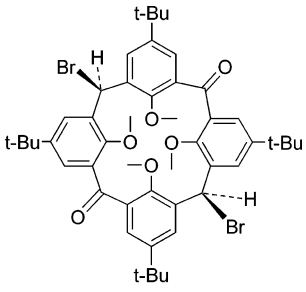

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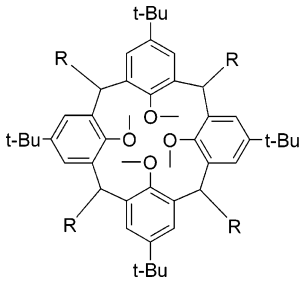
Bromination of Tetramethoxy-*p*-*tert*-butylcalix[4]arene. The bromination of **1b** was described recently by Varadarajan and co-workers.[9] Initially we conducted the photochemical bromination of **1b** as reported in the literature procedure, using a large excess of NBS (14 equiv) and refluxing the mixture for 24 h. Examination of the crude product by NMR indicated the formation of a complex mixture. Recrystallization of the crude product from hexane afforded a product that, on the basis of its ^{1}H NMR spectrum (which displayed a 8:2 integration ratio between the aromatic and methine protons) and ^{13}C NMR spectrum (which displayed signals at 41.2 and 66.9 ppm characteristic of C−Br and CBr_2 units, respectively), was characterized as the hexabromo derivative **4**. This compound proved to be quite labile, and upon attempted crystallization from $CHCl_3$/MeOH, yielded the dibromo dioxo derivative **5**, resulting from hydrolysis of the *gem*-dibromomethyl groups.[16]

Since the bromination utilizing the literature reaction conditions proceeded beyond the tetrabromo stage, we examined next the photochemical bromination of **1b** using nearly stoichiometric (4−4.2 equiv) amounts of NBS. The product displayed single signals (sharp singlets) for the *tert*-butyl, methoxy, methine and aromatic protons in the ^{1}H NMR spectrum. This spectrum is consistent with an *rccc* configuration pattern of the stereocenters. The conformation in the crystal is similar to the one reported for **2a**: the calix macrocycle adopts a cone conformation with the four bromines located at equatorial positions.[12] The NMR spectrum of the isolated **2b** is markedly different from the one reported in the literature.[9] It was reported that multiplets were observed for the aromatic, methine and methoxy signals. Surprisingly, no carbon signal in the 44 ppm region (characteristic of a C_{sp^3}−Br unit) was reported in the ^{13}C NMR spectrum. It may be possible that the compound reported in the literature corresponds to a mixture of tetrabromo isomers or products possessing different numbers of bromine atoms.

Initial Attempts To Replace the Bromine Atoms of 2b. In principle, the bromine atoms of **2b** could be replaced by other atoms or groups via lithiation followed by reaction with electrophiles (a route analogous to the one developed by Bennett and co-workers for the monoalkylation of **1b**)[5] or via reaction with strong nucleophiles under S_N2 conditions. However, since preliminary experiments conducted with BuLi/MeI or EtONa/EtOH indicated that the compound underwent decomposition, we decided to concentrate on the solvolysis reactions of **2b** under S_N1 conditions. The reaction was initially attempted in alcohols (MeOH, EtOH *i*-PrOH) using a silver salt ($AgClO_4$) as an electrophilic catalyst.[17] Examination of the NMR spectrum of the crude product indicated the formation of a complex mixture.[18] In the case of isopropanol it was possible to isolate and purify by crystallization a tetraether product that was characterized as the *rccc* form of **6d**. When the solvolysis reactions were conducted by refluxing a solution of **2b** in EtOH in the absence of a silver salt, no reaction took place. Presumably, the ionizing power of the EtOH is not sufficient to result in an appreciable reaction rate at the normal reflux temperature. Increasing the reaction temperature to 130 °C (Parr pressure reactor) afforded the tetraether **6b**, but as a mixture of the *rccc*, *rcct* and *rctt* isomers, as indicated by ^{1}H NMR spectroscopy.



6a R = OMe
6b R = OEt
6c R = O-*n*-Pr
6d R = *O-i*-Pr
6e R = OCH_2CF_3
6f R = OCH_2CH_2OH
6g R = N_3

Reaction in TFE or HFIP Media. Before attempting the reaction in the absence of an electrophilic catalyst, using instead a mixture of a nucleophile (e.g., an aliphatic alcohol) and a solvent of high ionizing power such as trifluoroethanol (TFE) or hexafluoroisopropanol (HFIP), some control experiments were conducted. The reaction involves a competition between the nucleophile and the ionizing solvent with the putative carbocation intermediate generated by dissociation of a C−Br bond. If the reaction proceeds under kinetic control, a low nucleophilicity of the ionizing solvent (which is present in a larger concentration than the nucleophile in the medium) is desirable to ensure the formation of the product with the four bridges substituted by the nucleophile. A control experiment

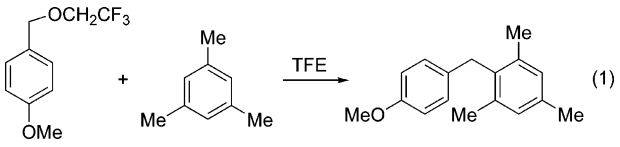
(16) A preliminary X-ray structure analysis of the molecule corroborated this structural assignment.

(17) (a) Zavada, J.; Pankova, M.; Arnold, Z. *Collect. Czech. Chem. Commun.* **1976**, *41*, 1777. (b) See also: Simaan, S.; Siegel, J. S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3699.

(18) Apparently, a mixture of isomers is obtained.

was conducted by refluxing a solution of **2b** in TFE for 2 h. The reaction afforded the tetrakis(trifluoroethoxy) derivative **6e**, previously characterized on the basis of its NMR spectrum (which resembled that of **2b**) as the *rccc* isomer.[12,19] HFIP was therefore used for reactions with weak nucleophiles such as *m*-xylene (see below), but for nucleophiles stronger than TFE the latter was chosen due to its significantly lower cost.

Cleavage of the C−OCH$_2$CF$_3$ Bond. We next addressed the question whether the C−OCH$_2$CF$_3$ bonds formed after reaction of the carbocations with TFE can be cleaved in TFE under the reaction conditions (reflux for ca. 2 h). It has been shown by Mayr and co-workers that dissolution of *p*-methoxybenzyl trifluroethyl ether and mesitylene in TFE at 20 °C affords quantitatively after 1 h the substituted diphenylmethane (eq 1).[20]



(1)

To test whether **6e** can dissociate appreciably in TFE, a solution of the compound was refluxed for 1 h in TFE in the presence of NaN_3. Only unreacted **6e** was obtained, although under such reaction conditions **2b** is transformed into the corresponding tetraazido derivative **6g**.[12] Since the cleavage of the C−OCH$_2$CF$_3$ bond might be catalyzed by the HBr released in the medium in the solvolysis reactions of **2b,** the reaction of **6e** with azide was attempted also after adding two drops of 48% aq HBr. Again, no reaction was observed, indicating that the C−OCH$_2$CF$_3$ bond is not cleaved in TFE. From a practical point of view, the experiments described above indicate that reactions of **2b** can be conducted in TFE only with nucleophiles more nucleophilic than the fluorinated solvent (e.g., with π nucleophiles possessing a *N* nucleophilic parameter larger than the N_1 parameter of TFE).[20]

Reaction of 2b with Alcohols. The reactions were conducted by refluxing a mixture of **2b**, TFE and the appropriate alcohol. Initial experiments were conducted by refluxing a 1:10 mixture of EtOH and TFE containing **2b**. The ^{1}H NMR spectrum of the crude product displayed two signals in the methine region assigned to C*H*OCH$_2$CF$_3$ and C*H*OEt groups, indicating that the bromine atoms on the bridges were replaced by both ethoxy and trifluoroethoxy groups.[12] TFE is less nucleophilic than the common aliphatic alcohols such as MeOH, EtOH and *i*-PrOH, but it is present in the reaction mixture in large quantities and therefore successfully competes with the EtOH molecules. However, when the solution consisted of a ca. 1:1 v/v TFE/EtOH mixture, the major product was the tetraethoxy derivative.[12] The reaction was also conducted in the presence of 1-propanol, 2-propanol and *t*-BuOH. With the exception of *t*-BuOH, substitution of the bromine atoms at the bridges was observed and the product obtained was the tetraalkoxy derivative. Examination of the NMR spectrum of the crude products indicated that a major product was formed, ascribed to the *rccc* form (as indicated by the single signal observed for the methine signal at ca. 6 ppm). The molecular structure of the tetraisopropoxy derivative **6d** (grown from acetonitrile) was determined by X-ray crystallography (Figure 2). The molecule adopts a cone conformation with the substituents on the bridges arranged in the *rccc*, all-equatorial disposition. The H−C(bridge)−O−C atoms are all oriented in an identical gauche conformation.

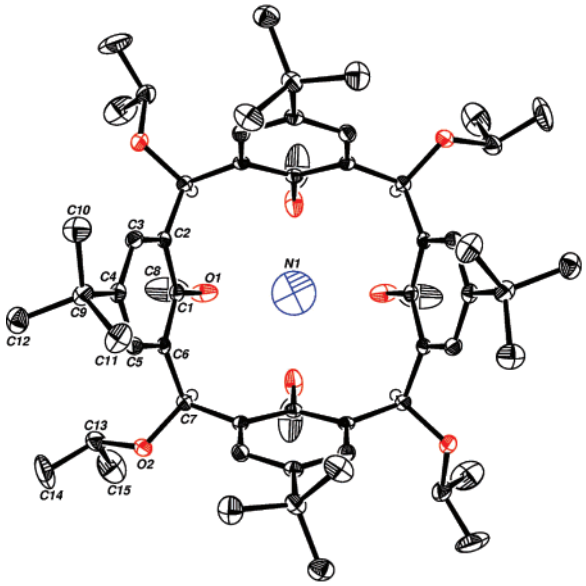


FIGURE 2. Crystal structure of one enantiomer of the tetraisopropoxy derivative **6d** viewed along the N−C axis of the acetonitrile molecule included in the cavity.

The preparation of the tetrasubstituted derivative **6f** by reaction of **2b** with ethylene glycol is of interest, since the presence of the hydroxy groups at the end of the side chains may allow further modification of the substituents at the bridges. To avoid oligomeric products (resulting from ethylene glycol molecules reacting with two calixarene systems), a large excess of the diol was used. Heating **2b** to reflux in a 1:1 mixture of ethylene glycol and TFE yielded a mixture of products substituted by both OCH$_2$CH$_2$OH and OCH$_2$CF$_3$ groups at the bridges, as shown by ^{1}H NMR spectroscopy.[21] The reaction of **2b** with ethylene glycol was therefore conducted in HFIP to avoid reaction with the ionizing solvent. As observed for the reaction with other alcohols, the *rccc* form of **6f** was obtained as the main product (22% yield after recrystallization).

Isomerization of 6a. Reaction of **2b** with ca. 2:1 TFE/MeOH yielded mainly, as indicated by ^{1}H and ^{13}C NMR spectroscopy of the crude product, the *rccc* isomer of **6a** as the major product. Surprisingly, attempts to obtain this product in pure form proved unsuccessful. Recrystallization of the crude product from CHCl$_3$/MeOH afforded, as shown by NMR analysis, a mixture of the *rccc*, *rcct* and *rctt* forms, indicating that isomerization took place. The isomerization of the *rccc* form is apparently solvent

(19) A single crystal of **6e** was grown from acetonitrile and submitted to X-ray crystallography. Although the structure could be refined only to a relatively high *R* factor (18 %), the structure corroborated the assigned *rccc* configuration of the macrocycle. The molecule adopts a cone conformation with the substituents located at equatorial positions and an acetonitrile molecule included in the cavity.

(20) (a) Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 5402. See also: (b) Mayr, H.; Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66. (c) Minegishi, S.; Kobayashi, S.; Mayr, H. *J. Am. Chem. Soc.* **2004**, *126*, 5174.

(21) It is interesting to note that, although reflux of **2b** in a 1:1 TFE/EtOH mixture yields exclusively **6b**, heating in a 1:1 TFE/ethylene glycol mixture affords products containing both trifluoroethoxy and 2-hydroxyethoxy groups at the bridges. The lower relative nucleophilicity of the ethylene glycol molecules (as compared to that of EtOH) may be connected to the presence of inter- and intramolecular hydrogen bonds, as well as to the larger viscosity of the mixture.

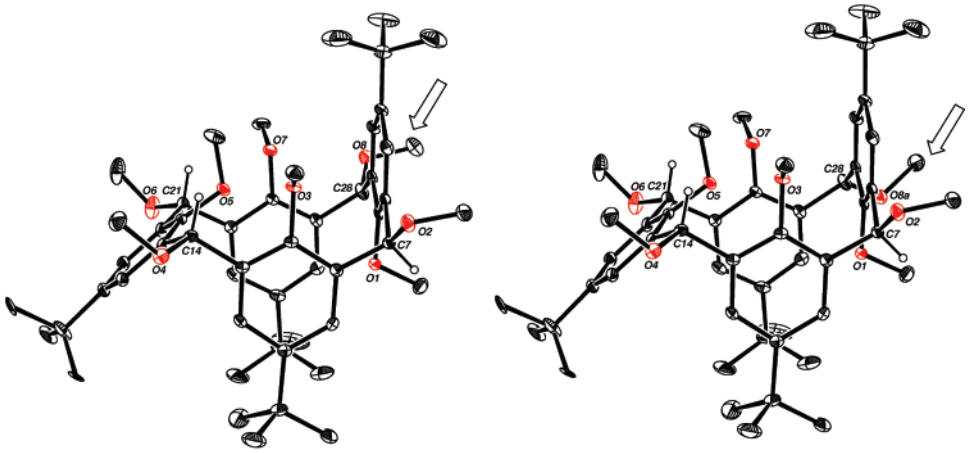
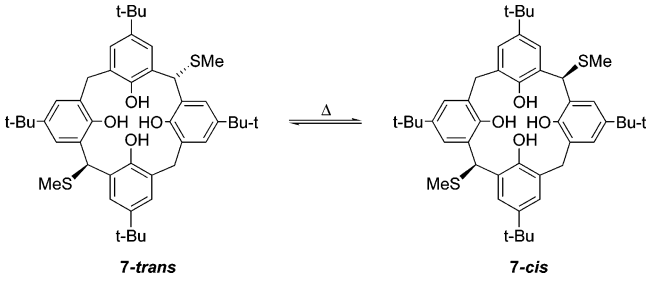


FIGURE 3. X-ray structure of a mixture of the *rcct* and *rctt* isomers of **6a.** Only an average structure was found. One methoxy group is disordered betwen two positions (O8-Me and O8a-Me, see arrows) situated *cis* and *trans* relative to the reference substituent.

SCHEME 1



dependent, and it is relatively fast in $CHCl_3$/MeOH and slow in $CHCl_3/CH_3CN$. We have observed previously the thermal isomerization of the *trans* -thiomethoxy methylene-functionalized calixarene (**7-*trans***). Upon heating in solution the compound isomerized to its most stable cis-form (**7-*cis***) (Scheme 1).[22] The methoxy-substituted derivative appears to be the more labile of all the alkoxy methylene-functionalized calixarenes studied.

Slow evaporation of the mixture of isomers in a $CHCl_3/CH_3CN$ solution afforded two types of crystals of different morphology (prisms and plates). X-ray analysis of the prisms indicated cocrystallization of a mixture of the *rcct* and *rctt* isomers of **6a**. The macrocyclic ring of the *rcct* and *rctt* forms adopts the partial cone conformation with one methoxy group disordered between two positions (O8 and O8a) (Figure 3). According to the crystal structure, in the *rcct* and *rctt* forms the substituents are located in diequatorial and diisoclinal positions. As observed in all structures so far, the substituents avoid the axial positions of the macrocycle.

Solvolysis of 2b in Acetic Acid. Incorporation of OH Groups at the Bridges. Initial attempts to prepare the tetrahydroxy derivative by solvolysis of **2b** in TFE in the presence of NaOH indicated that only decomposition products were formed. To introduce hydroxyl groups into the bridges we therefore resorted to the acetoxy group that can be viewed as a "masked" hydroxyl group.

Initial experiments were conducted by refluxing a mixture of **2b**, TFE and NaOAc, but only decomposition products were obtained. We therefore attempted the direct acetolysis of **2b**. After reflux of a solution of **2b** in AcOH, ^{1}H NMR analysis indicated the presence of a major product (23% yield after recrystallization), ascribed to the *rccc* isomer of the tetraacetoxy derivative (**8**). $LiAlH_4$ reduction of **8** proceeded readily and afforded the *rccc* isomer of the tetraalcohol **9** (Scheme 2). The ^{1}H NMR spectrum of **9** in acetone-d_6 displays a pair of mutually coupled doublets (J = 4.3 Hz) at δ 6.33 and 4.32 for the methine and OH protons, indicating a gauche conformation of the HCOH units at the bridges.

Reaction with Thiocyanate. We have shown that the cationic intermediate formed in the solvolysis of **2b** can be trapped by the azide nucleophile, yielding the tetraazido derivative **6g**.[12] To test whether also sulfur-containing nucleophiles can be attached to the calix scaffold, we conducted the reaction of **2b** with KSCN in HFIP. Judging from the ^{1}H NMR spectrum, a mixture of stereoisomers products was formed, with the *rccc* isomer **10** being the major form (Scheme 3).[23] In principle, thiocyanate ion (an ambident nucleophile) can attack the carbocation via its N or S atoms. The presence of HC−SCN bonds in the product can be concluded from the ^{13}C NMR spectrum, which displays a signal at 111.4 ppm, characteristic of the thiocyanate group.[24] It is interesting to note that the only two cases observed in which the reaction with a nucleophile in fluorinated alcohols proceeded with poor stereoselectivity and did not yield nearly exclusively the *rccc* form were in the reaction with azide and thiocyanate. In both cases, the reaction involved small and highly reactive charged nucleophiles.

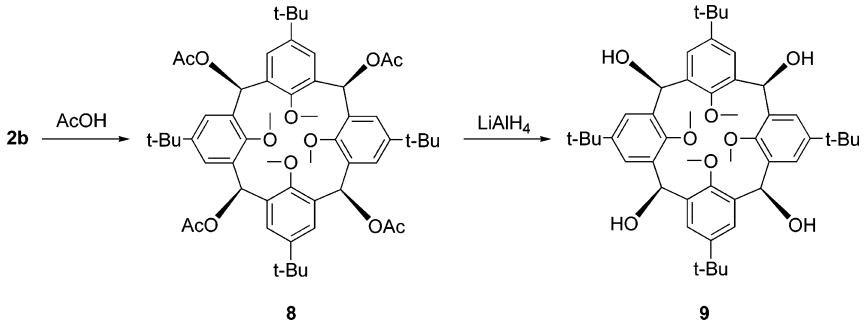
Aryl Substituents at the Bridges. (a) Modification of the 2-Methylfuranyl Functionalities. In principle, reaction of the tetrabromo derivatives with aromatic compounds under solvolytic Friedel Crafts conditions may afford calixarenes substituted at all bridges by aromatic groups. We have previously reported the preparation of a tetrakis(2-methylfuranyl)calix[4]arene derivative of **2a** by this route.[12] The furan ring is an attractive substituent since it can provide an entry into other aromatic substituents via Diels−Alder reaction with benzyne followed by deoxygenation of the resulting 1,4-endoxide (Scheme 4).[25]

(22) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136.

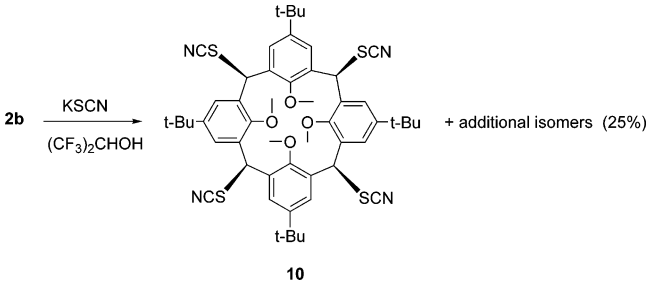
(23) When the reaction was conducted in TFE, a different isomeric mixture was obtained, the major form corresponding to the *rctt* isomer.

(24) The SCN carbon of ethyl thiocyanate resonates at 112 ppm, while in isothiocyanates the carbon resonance is about ca. 20 ppm shifted downfield. See: Ben-Efraim, D. A. In *The Chemistry of Cyanates and their Thio Derivatives*, Part 1; Patai, S., Ed., Wiley: Chichester, 1977; Chapter 5, p 227.

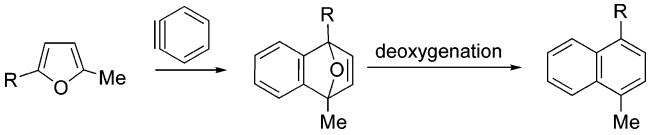
SCHEME 2



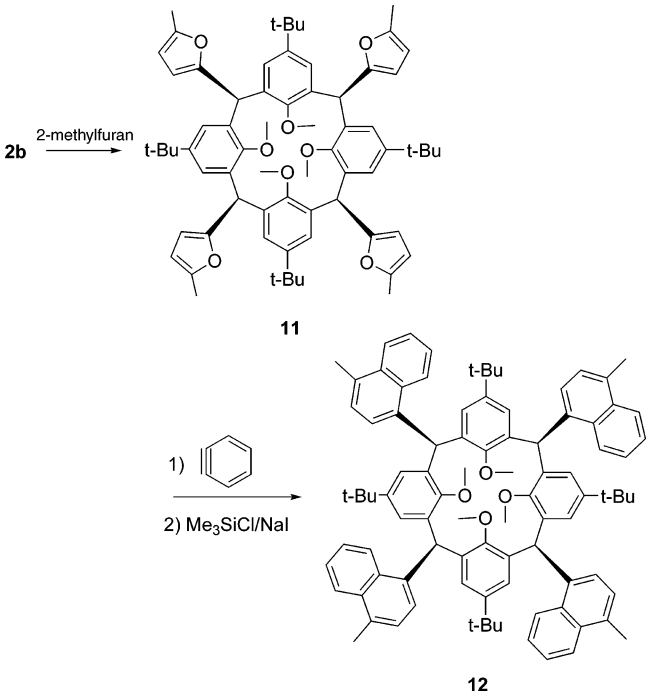
SCHEME 3



SCHEME 4



SCHEME 5



Reaction of **2b** with 2-methylfuran/TFE/1,2-butylene oxide[26] afforded a tetra-(2-methylfuranyl) calix[4]arene derivative.[27] The ^{1}H NMR spectrum of this product displayed a signal pattern similar that of its *de-tert*-butylated derivative (previously characterized by X-ray crystallography as the *rccc* isomer).[12] On the basis of this similarity, we ascribe also a *rccc* configuration to the tetrafuranyl calix[4]arene derivative **11**. Reaction of **11** with excess benzyne (generated from benzenediazonium 2-carboxylate hydrochloride) afforded a product which displayed a complex NMR spectrum.[28] The mixture was deoxygenated by reaction with trimethylsilyl iodide (generated in situ from Me_3SiCl/NaI)[29] to yield the tetranaphthyl derivative **12** in low yield (Scheme 5). Although cleavage of the O−Me bonds in *p-tert*-butylcalix[4]arenes tetramethyl ether can be achieved by treatment with Me_3SiI in $CHCl_3$,[30] no Me−O cleavage was observed in the deoxygenation step. An *rccc* configuration of the stereocenters at the bridges is assigned to this product, since the *rccc* configuration of the starting material **11** should not be affected by the Diels−Alder reaction/deoxygenation reaction sequence. The molecule displays in the ^{1}H NMR a signal pattern indicating that all the groups at the bridges are symmetry equivalent, but two types of methoxy, *t*-Bu and phenyl groups are present in the macrocycle. This is consistent with a pinched cone conformation which is "frozen" on the NMR time scale.

(b) Reaction with *m*-Xylene. Preliminary experiments conducted with anisole/HFIP indicated that, although fourfold Friedel−Crafts reaction takes place with the aromatic compound as indicated by NMR and MS analysis, a complex product mixture is obtained, apparently resulting from the different combinations of ortho/para substitution of the aromatic rings attached to the bridges. We therefore decided to study the reaction of *m*-xylene since it undergoes electrophilic substitution preferentially at a single unique position. The studies of Mayr and co-workers were not encouraging, since although they showed that a reaction proceeds readily between 4-methoxybenzyl cation (cf. eq 1) and mesitylene, no reaction occurs between diphenylmethyl cation (a better model for the cation(s) generated by ionization of **2a**/**2b**) and *m*-xylene in TFE.[20]

Initial attempts conducted by reflux of a mixture of **2b** and a 10:1 TFE/*m*-xylene under reaction conditions similar to those used for the preparation of **11** did not afford an arylated product. Probably since *m*-xylene is less nucleophilic than 2-methylfuran, it cannot compete with the TFE. We therefore conducted the reaction of **2a** in HFIP. Inspection of the ^{1}H NMR spectrum of

(25) For selected examples of this transformation in macrocyclic rings see: (a) Hart, H.; Takehira, Y. *J. Org. Chem.* **1982**, *47*, 4370. (b) Kohnke, F. H.; Parisi, M. F.; Raymo, F. M.; O'Neil, P. A.; Williams, D. J. *Tetrahedron* **1984**, *50*, 9113.

(26) For uses of propylene oxide as an HBr scavenger see: de la Vega, F.; Sasson, Y. *J. Chem. Soc., Chem. Commun.* **1989**, 653.

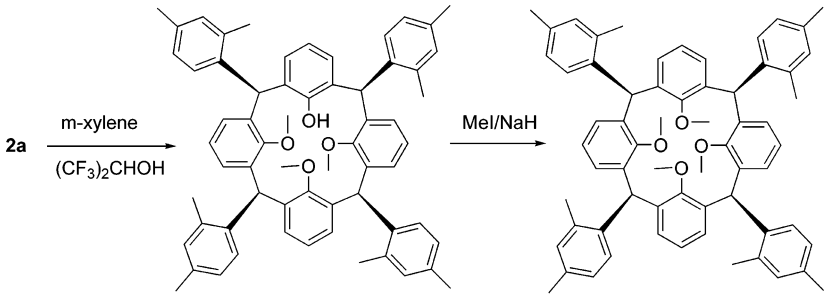
(27) Without 1,2-butylene oxide an intractable mixture of products was obtained.

(28) The complexity of the spectrum may be due to the presence of configurational isomers of the tetraaduct that adopt different conformations.

(29) Jung, K.; Koreeda, M. *J. Org. Chem.* **1989**, *64*, 5667.

(30) Casnati, A.; Arduini, A.; Ghidini, E. W.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, *47*, 2221.

SCHEME 6



13 **14**

the crude product obtained indicated that indeed four *m*-xylyl moieties were incorporated into the bridges, but unexpectedly, the reaction product was the trimethoxy derivative **13** (Scheme 6).[31] Apparently, the HBr released by the Friedel−Crafts reaction cleaves one of the methoxy groups of the calix skeleton.[32] The crude **13** was methylated (MeI/NaH) to afford **14**. The NMR of the tetraxylyl derivative **14** displayed a signal pattern indicating that all rings at the bridges are equivalent, while two types of rings are present in the calix macrocycle. By analogy to **11** and **12**, and on the basis of the symmetry indicated by the NMR pattern, we ascribed to **14** the *rccc* configuration with the macrocyclic ring adopting a frozen (on the NMR time scale) pinched cone conformation.

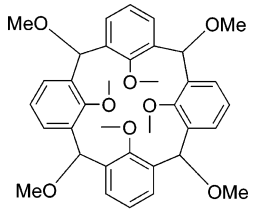
Cone/Partial Cone Energy Gap. In all the calixarenes monofunctionalized at four bridges in *rccc* fashion studied so far by X-ray crystallography (with bromine, isopropoxy and 2-methylfuranyl substituents at the bridges), the calix macrocycle adopted in the crystal a cone or pinched cone conformation. In contrast, a partial cone conformation was present in the crystal structures of the *rcct* and *rctt* forms of **6a** and the *rcct* form of **6g**. To assess whether indeed for a given substituent a change in the configuration of the bridges can modify the conformational preferences of the calix macrocycle we resorted to molecular mechanics (MM3) calculations.[33,34] MM3 calculations conducted by Shinkai and co-workers indicated that the lowest energy conformation of the parent **1a** and **1b** is the partial cone form, with the cone conformation lying 1.3−1.5 kcal mol^{-1} (for **1b**) or 0.3 kcal mol^{-1} (for **1a**) above it.[35] The cone/partial cone conformational equilibrium of the tetramethoxycalix[4]arene **1a** is strongly influenced by the solvent polarity. In general, the population of the more polar cone form increases with the solvent polarity.[36,37]

TABLE 2. Calculated (MM3) Steric Energies (in kcal mol^{-1}) of the Cone and Partial Cone Conformations of the Stereoisomers of 15[a]

	conformation	
isomer	cone	partial cone
rccc	34.4 [0.0] (tetraequatorial)	38.8 [4.4](diequatorial−diisoclinal (I))
rcct	38.3 [0.5] (triequatorial−axial)	37.8 [0.0] (diequatorial−isoclinal (I)−isoclinal(II))[b]
rctt	42.3 [4.9] (diequatorial−diaxial)	37.4 [0.0] (diequatorial−diisoclinal (II)) 38.0 [0.6] (diequatorial−diisoclinal (II))[c]

[a] Numbers in brackets are energy differences between a conformation and the lowest calculated conformer of a given isomer. [b] Conformation analogous to the one found in the crystal structure of *rcct* **6a**. [c] Conformation analogous to the one found in the crystal structure of *rctt* **6a**. The two calculated partial cone conformations of the *rctt* form differ in the orientation of the methoxy groups on the bridges.

MM3 calculations were conducted on the *de-tert*-butylated model compound **15**. Calculations on the *rccc* form indicate that, as expected in the cone form, the tetraequatorial conformation is of lower energy than the tetraaxial form (Table 2). For the partial cone form, the diequatorial−diisoclinal(I) conformer is of lower energy than the diaxial−diisoclinal(II) form, but is 4.4 kcal mol^{-1} higher than the tetraequatorial cone form.



15

For the *rcct* form, calculations indicate that the triequatorial−axial form is of lower energy than the triaxial−equatorial, but this form is about 0.5 kcal mol^{-1} higher in energy than the partial cone form with diequatorial−isoclinal(I)−isoclinal(II) disposition of substituents. For the *rctt* isomer, the energy gap between the cone form (diequatorial−diaxial) and the preferred partial cone form (diequatorial−diisoclinal(II)) is larger (4.9 kcal mol^{-1}). To summarize, the calculations suggest that, whereas the *rccc* form prefers the tetraequatorial cone form, the *rcct* and *rctt* forms prefer the partial cone conformers with diequatorial−

(31) When the reaction was conducted with **2b**, a mixture of trimethoxy and dimethoxy tetraxylyl derivatives was obtained. Since we were unable to fully methylate this mixture, we performed the reaction with the *de-tert*-butylated derivative **2a**.

(32) Preliminary experiments indicate that reaction of **1b** with excess HBr (50%) in HFIP (2 h reflux) affords the monodemethylated derivative (i.e., the trimethyl ether of *p-tert*-butylcalix[4]arene), while in TFE the demethylation proceeds further, and a mixture of the monomethyl ether and tetrahydroxycalixarene is obtained.

(33) *Alchemy 2000*; Tripos Inc.: St. Louis, MO 63144, 2000.

(34) Molecular mechanics calculations of **2a** have been reported by Friedrichsen and coworkers (ref 8). These calculations were conducted assuming that each of the four forms (*rccc, rcct, rctt, rctc*) adopts a cone conformation. However, it was not examined whether in some substitution patterns the preferred conformation is different from cone.

(35) (a) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955. (b) Harada, T.; Rudzinski, J. M.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1992**, 2109. (c) For a review on the conformation and stereodynamics of calixarenes see: Thondorf, I. in ref 1f, Chapter 15.

(36) Iwamoto, K.; Ikeda, A.; Araki, K.; Harada, T.; Shinkai, S. *Tetrahedron* **1993**, *49*, 9937.

(37) (a) van Hoorn, W. P.; Briels, W. J.; van Duynhoven, J. P. M.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *J. Org. Chem.* **1998**, *63*, 1299. (b) See also ref 3d.

TABLE 3. Summary of the Reactions Involving the Fourfold Replacement of the Bromine Atoms

calixarene	nucleophilic reagent	solvent	product
2b	TFE	TFE	**6e**
2b	MeOH	TFE	**6a**
2b	EtOH	TFE	**6b**
2b	*n*-PrOH	TFE	**6c**
2b	*i*-PrOH	TFE	**6d**
2b	2-methylfuran	TFE	**11** (**12**)[a]
2b	NaN_3	TFE or HFIP	**6g**
2b	KSCN	TFE or HFIP	**10**
2b	ethylene glycol	HFIP	**6f**
2b	acetic acid	acetic acid	**8** (**9**)[b]
2a	*m*-xylene	HFIP	**13** (**14**)[c]
2a	2-methylfuran	TFE	**6** (in ref 12)

[a] Diels−Alder reaction of the product **11** with benzyne followed by deoxygenation with Me_3SiCl/NaI yielded **12**. [b] $LiAlH_4$ reduction of the product **8** afforded the tetraalcohol **9**. [c] Methylation of the product **13** afforded **14**.

isoclinal(I)−isoclinal(II) and diequatorial−diisoclinal(II) dispositions of substituents, respectively. Apparently, conformations avoiding axial dispositions of substituents are favored.

Conclusions

The tetrabromo derivatives readily react with alcohol nucleophiles, azide, thiocyanate, acetoxy and aromatic compounds under solvolytic conditions, to afford calixarenes which are functionalized fourfold at the bridges (Table 3). In most cases examined, the reaction proceeds with high stereoselectivity, yielding the *rccc* product. The tetramethoxy derivative **6a** is configurationally labile in $CHCl_3$/MeOH solutions. The 2-methylfuranyl substituents at the bridges can be further functionalized.

Experimental Section

2,8,14,20-Tetrabromo-25,26,27,28-tetramethoxycalix[4]arene (*rccc* form) (2a). A mixture of **1a**[38] (8.0 g, 16.7 mmol), NBS (13.3 g, 74.7 mmol) and CCl_4 (300 mL) was refluxed while irradiated with a spotlight (100 W). After 4 h, a second portion of NBS (7.2 g, 40.5 mmol) was added. Reflux was continued for an additional 18 h. After cooling, the solvent was washed once with aq Na_2SO_3 and twice with water. The organic phase was dried ($MgSO_4$) and evaporated to yield 5.0 g (38%) of **2a**. The crude material is usually pure enough to be used in subsequent reactions. If needed, recrystallization can be conducted from acetone or $CHCl_3$/MeOH, mp 260−265 °C (lit[8] 265−270 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (d, J = 7.8 Hz, 8H), 6.78 (t, J = 7.8 Hz, 4H), 6.70 (s, 4H), 3.99 (s, 12H).

2,8,14,20-Tetrabromo-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix-[4]arene (*rccc* form) (2b). A mixture of **1b**[38] (15.3 g, 21.7 mmol), NBS (15.6 g, 87.6 mmol) and CCl_4 (600 mL) was refluxed for 22 h while irradiated with a spotlight (100 W). The solvent was washed once with aq Na_2SO_3 and twice with water. The organic phase was dried ($MgSO_4$) and evaporated. The crude product was recrystallized from $CHCl_3$/MeOH to yield 6.0 g (27%) of **2b**, mp 290 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 8H), 6.71 (s, 4H), 3.99 (s, 12H), 1.11 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3, 146.6, 134.0, 125.7, 61.3, 44.1 (CBr), 34.4, 31.2. MALDI MS, *m*/*z* 1042.99 $(M + Na)^+$, *m*/*z* 1058.96 $(M + K)^+$.

2,2,8,14,14,20-Hexabromo-5,11,17,23-tetra-*tert*-butyl-25,26,-27,28-tetramethoxycalix[4]arene (*cis* form) (4). The reaction was conducted as described for **2b** using 0.31 g of **1b** (0.43 mmol), 1.1 g of NBS (6.2 mmol) and 30 mL of CCl_4. Recrystallization from hexane afforded 0.11 g (22%) of **4**, mp 245 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, J = 2.2 Hz, 4H), 7.87 (d, J = 2.2 Hz, 4H), 6.29 (s, 2H), 3.33 (s, 12H), 1.38 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 145.7, 137.6, 134.3, 128.4, 127.6, 66.9, 60.3, 41.2, 34.8, 31.4. MALDI MS, *m*/*z* 1098.9 (M − Br).

General Procedure for the Reaction of 2b with Alcohols. A solution of **2b** (0.10 g, 0.10 mmol) in a mixture of 10 mL of TFE and 10 mL of of the appropriate alcohol (5 mL in the case of MeOH) was refluxed for 1−2 h (until the solution is clear). The solvent was evaporated and the residue recrystallized from $CHCl_3$/MeOH or $CHCl_3$/acetonitrile.

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20,25,26,27,28-octamethoxycalix[4]arene (6a). The *rccc*, *rcct* and *rctt* forms were not separated. The signals in the ^{1}H NMR spectrum were assigned to the different isomers on the basis of their symmetry pattern.

***rccc* form:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 8H), 5.78 (s, 4H), 3.92 (s, 12H), 3.49 (s, 12H), 1.08 (s, 36H). ***rcct* form:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 2.4 Hz, 1H), 7.44 (d, J = 2.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 2.4 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.92 (d, J = 2.4 Hz, 1H), 6.75 (d, J = 2.4 Hz, 1H), 5.53 (s, 1H), 5.49 (s, 1H), 5.13 (s, 1H), 5.01 (s, 1H), 3.75 (s, 3H), 3.67 (s, 3H), 3.63 (s, 3H), 3.55 (s, 3H), 3.45 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 2.91 (s, 3H), 1.31 (s, 9H), 1.16 (s, 9H), 1.09 (s, 9H), 1.07 (s, 9H). ***rctt* form:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 2H), 7.17 (d, J = 2.4 Hz, 2H), 7.15 (s, 2H), 7.12 (d, J = 2.4 Hz, 2H), 5.61 (s, 2H), 5.09 (s, 2H), 3.62 (s, 3H), 3.45 (s, 6H), 3.44 (s, 3H), 3.43 (s, 6H), 3.42 (s, 3H), 3.41 (s, 3H), 1.44 (s, 18H), 1.17 (s, 18H). MALDI MS, *m*/*z* 863.36 $(M + K)^+$.

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetramethoxy-2,8,14,-20-tetrapropoxycalix[4]arene (*rccc* form) (6c): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 8H), 5.87 (s, 4H), 3.90 (s, 12H), 3.53 (t, J = 6.8 Hz, 8H), 1.71 (m, 8H), 1.08 (s, 36H), 1.00 (t, J = 7.4 Hz, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 145.4, 134.4, 122.1, 72.5, 70.9, 61.4, 34.2, 31.3, 23.3, 11.0. Mp 220−225 °C. MALDI MS, *m*/*z* 959.54 $(M + Na)^+$.

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetraisopropoxy-25,26,-27,28-tetramethoxycalix[4]arene (*rccc* form) (6d): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 8H), 6.09 (s, 4H), 3.92 (s, 12H), 3.79 (h, J = 6.1 Hz, 4H), 1.28 (d, J = 6.1 Hz, 24H), 1.08 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 145.3, 134.6, 122.4, 69.3, 68.5, 61.5, 34.2, 31.3, 22.3. Mp 220−225 °C. MALDI MS, *m*/*z* 959.56 $(M + Na)^+$.

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrakis(2′-hydroxyethoxy)-25,26,27,28-tetramethoxycalix[4]arene (*rccc* form) (6f). A mixture of 0.1 g of **2b**, 10 mL of HFIP and 5 mL of ethylene glycol was refluxed for 2 h. The solvent was evaporated, and the residue was dissolved in chloroform. The organic phase was washed twice with water and then dried and evaporated. After recrystallization of the residue from $CHCl_3$/MeOH 20 mg (22%) of **6f** was obtained, mp 285−288 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 (s, 8H), 5.94 (s, 4H), 3.92 (s, 12H), 3.84 (m, 8H), 3.73 (m, 8H), 2.10 (*t*, J = 5.5 Hz, 4H, O*H*), 1.09 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2, 145.9, 134.0, 122.2, 73.3, 70.8, 62.1, 61.7, 34.2, 31.3. MALDI MS, *m*/*z* 967.7 $(M + Na)^+$.

2,8,14,20-Tetraacetoxy-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]arene (8). A solution of 1.0 g of **2b** in 150 mL of acetic acid was refluxed for 18 h. After cooling, the solvent was evaporated and the residue recrystallized from $CHCl_3$/MeOH to yield 215 mg of tetraacetoxy **8** (23%), mp 345−348 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 4H), 7.02 (s, 8H), 3.99 (s, 12H), 2.18 (s, 12H), 1.09 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 152.6, 145.6, 133.1, 122.3, 67.3, 61.9, 34.2, 31.3, 21.3. MALDI MS, *m*/*z* 959.4 $(M + Na^+)$.

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrahydroxy-25,26,27,-28-tetramethoxycalix[4]arene (**9**). To an ice-cold solution of **8**

(38) Gutsche, C. D.; Dhawan, B.; Levine, J. A.; No, K. H.; Bauer, L. J. *Tetrahedron* **1983**, *39*, 409.

(290 mg, 0.31 mmol) in 15 mL of dry THF was added $LiAlH_4$ (100 mg, 2.63 mmol) under an inert atmosphere, and the mixture was stirred for 10 min. Ethyl acetate was added to quench the excess $LiAlH_4$, and the solution was washed with water, and then with 1 M aq HCl. After drying ($MgSO_4$) the organic phase was filtered and evaporated. Recrystallization from acetone gave 50 mg of **9** (21%), mp 322−325 °C (dec).

^{1}H NMR (400 MHz, acetone-d_6) δ 7.20 (s, 8H), 6.33 (d, J = 4.3 Hz, 4H), 4.32 (d, J = 4.3 Hz, 4H), 3.92 (s, 12 H), 1.09 (s, 36 H). ^{13}C NMR (100 MHz, acetone-d_6) δ 152.6, 144.4, 137.1, 121.4, 64.5, 61.6, 33.9, 30.9. MALDI MS, m/z 791.4 (M + Na^+).

2,8,14,20-Tetrathiocyanato-5,11,17,23-tetra-*tert*-butyl-25,26,-27,28-tetramethoxycalix[4]arene (10). A mixture of **2b** (200 mg), KSCN (90 mg) and 12 mL of HFIP was refluxed for 1 h. The solvent was evaporated, chloroform was added to the residue, and the insoluble material was filtered. The residue obtained after evaporation of the filtrate was recrystallized from $CHCl_3$/MeOH to yield 45 mg of the crude product. ^{1}H NMR analysis indicated that the product consisted of 75% of the *rccc* form and 25% of a mixture of the other forms. A second recrystallization afforded the pure *rccc* form, mp 280−282 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (s, 8H), 6.35 (s, 4H), 4.05 (s, 12H), 1.12 (s, 36H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9, 147.6, 131.2, 124.4, 111.4, 62.6, 45.1, 34.5, 31.1. MALDI MS, m/z 955.2 (M + Na^+).

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetra(2-methylfuranyl)-25,26,27,28-tetramethoxycalix[4]arene (11). A mixture of 1.0 g of **2b** (1.0 mmol), 8 mL of 1,2-butylene oxide, 1.65 g (2.01 mmol) of 2-methylfuran in 100 mL of TFE was refluxed for 2 h to afford a clear, bluish solution. After cooling, the solvent was partially evaporated, and the solid that precipitated was filtered. After two crystallizations from $CHCl_3$/MeOH pure **11** (145 mg, 14%) was obtained, mp 285−288 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 6.71 (s, 8H), 5.99 (s, 4H), 5.94 (d, J = 2.5 Hz, 4H), 5.88 (d, J = 2.5 Hz, 4H), 3.87 (s, 12H), 2.27 (s, 12H), 1.01 (s, 36H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 154.3, 151.1, 144.6, 134.4, 123.7, 109.1, 105.5, 61.9, 37.8, 34.0, 31.3, 13.6. MALDI MS, m/z 1047.4 (M + Na^+)

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetra(4-methylnaphthyl)-25,26,27,28-tetramethoxycalix[4]arene (12). A mixture of 150 mg of **11** (0.15 mmol), 0.5 mL of butylene oxide, 115 mg of benzenediazonium-2-carboxylate hydrochloride[39] (0.62 mmol) and 10 mL of dichloroethane was refluxed for 90 min. After cooling, the clear-orange solution was evaporated to dryness. The crude residue was recrystallized from $CHCl_3$/MeOH to yield 110 mg (0.08 mmol) of a mixture of Diels−Alder adducts according to the ^{1}H NMR spectrum. The mixture was dissolved in 9 mL of dry CH_3-CN, and Me_3SiCl (110 mg, 1 mmol) and NaI (150 mg, 1 mmol) were added. The mixture was refluxed under nitrogen for 1 h. A 10-mL sample of 5% aq Na_2SO_3 was added, and the mixture was extracted with ether. The insoluble solid from the ether extraction was filtered and recrystallized from $CHCl_3$/MeOH to yield 10 mg of **12** (>90% purity), mp 320 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 8.27 (d, J = 7.9 Hz, 4H), 8.03 (d, J = 7.9 Hz, 4H), 7.57−7.45 (m, 16H), 6.89 (s, 4H), 6.68 (s, 4H), 6.46 (s, 4H), 4.74 (s, 6H), 3.13 (s, 6H), 2.70 (s, 12H), 0.95 (s, 18H), 0.72 (s, 18H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 153.9, 145.2, 143.5, 139.4, 137.1, 133.4, 132.8, 132.6 (double intensity), 127.1, 126.7, 126.3, 126.0, 124.8, 124.7, 124.6, 122.6, 62.4, 59.8, 40.6, 34.0, 33.9, 31.4, 31.3. MALDI MS, m/z 1288.7 (M + Na^+).

2,8,14,20-tetra(*m*-xylyl)-25,26,27,28-tetramethoxycalix[4]-arene (14). A mixture of 280 mg of **2a** and *m*-xylene (6 mL) in 80 mL of HFIP was refluxed for 24 h to give a clear-red solution. After cooling, the solvent was evaporated, and the residue recrystallized from $CHCl_3$/MeOH to get 180 mg of material, which according to the ^{1}H NMR spectrum consisted mainly (>90%) of the trimethoxy tetraxylyl derivative **13**. This product (165 mg) was dissolved in dry THF, and to the solution were added 100 mg of NaH (60% in oil) and 0.4 g of MeI. After reflux for 30 min under an inert atmosphere the mixture was cooled, MeOH was added to quench the excess NaH, and the solvent was evaporated. To the residue was added $CHCl_3$ and brine, and the organic phase was evaporated to yield 110 mg of crude product. After two crystallizations, 47 mg of the tetraxylyl tetramethoxy derivative **14** was obtained, ca. 95% purity, mp 270−275 °C (dec).

^{1}H NMR (400 MHz, $CDCl_3$, rt) δ 7.15 (d, J = 7.8 Hz, 4H), 7.02 (s, 4H), 6.31 (d, J = 7.3 Hz, 4H), 6.70 (t, J = 7.6 Hz, 2H), 6.48 (d, J = 7.7 Hz, 4H), 6.45 (t, J = 7.7 Hz, 2H), 6.17 (s, 4H), 6.12 (d, J = 7.6 Hz, 4H), 4.17 (s, 6H), 3.03 (s, 6H), 2.34 (s, 12H), 2.29 (s, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 157.1, 139.9, 137.1, 136.5, 135.6, 135.4, 131.2, 129.4, 129.0, 126.2, 125.8, 123.2, 122.2, 61.7, 60.3, 40.4, 20.9, 20.4. MALDI MS, m/z 919.9 (M + Na^+).

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Supporting Information Available: Crystallographic data for **6a** and **6d** (CIF), NMR spectra of **2a**, **4**, **6a**, **6c, 6d**, **6f, 8**−**12** and **14** and minimized coordinates (MM3) of the cone and partial cone conformers of **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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