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Calix[4]arenes with Two Different Chemical Modifications at the Bridges

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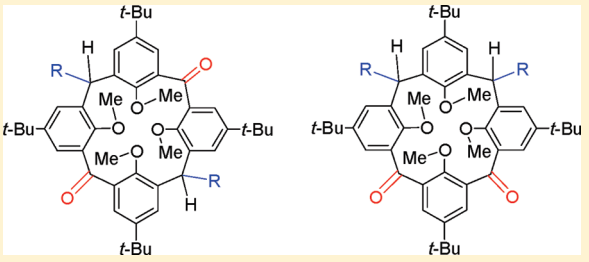
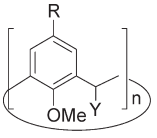
Supporting Information

ABSTRACT: Hexabromocalix[4]arene derivatives (**3a** and **3b**) possessing pairs of dibromomethylene and bromomethylene groups located at distal or proximal positions of the calix scaffold were prepared via photochemical bromination of tetramethoxycalix[4]arene. The dibromomethylene groups undergo hydrolysis to afford calix[4]arenes possessing pairs of carbonyl groups and bromomethylene groups located at distal or proximal bridges (**4a** and **4b**, respectively). The bromomethylene groups of **4** undergo reactions with nucleophiles under S_N1 conditions to afford a wide array of derivatives possessing two different chemical modifications at the bridges.



INTRODUCTION

The bromocalixarenes derivatives **1a**−**d** are useful starting materials for the preparation of a wide array of calixarenes with all the methylene bridges monosubstituted.[1,2] The carbons at the bridges readily undergo nucleophilic substitution reactions under S_N1 conditions.[3] By this route O-, N-, and even some C-nucleophiles (e.g., electron-rich aromatic rings, 2,4-pentanedione) have been incorporated at the bridges. In most cases, the *all-cis* isomer is the major product obtained.[2]



1a Y = Br, R= *t*-Bu, n = 4
1b Y = Br, R= H, n = 4
1c Y = Br, R= *t*-Bu, n = 5
1d Y = Br, R= *t*-Bu, n = 6
2 Y = H, R= *t*-Bu, n = 4

Calixarenes with a single bridge monofunctionalized have been prepared by cyclocondensation of suitable fragments (the fragment condensation method)[4] and by direct modification of the macrocycle (e.g., lithiation followed by reaction with an electrophile[5−7] or by a homologous anionic ortho Fries rearrangement).[8] Recently, we described the preparation of calix[6]arene derivatives possessing a single bridge substituted by a hydroxy group or a chlorine atom and their use as synthetic intermediates for the preparation of a wide array of calix[6]arenes monofunctionalized at a single bridge.[9]

Calix[4]arenes with two bridges functionalized have been prepared by the fragment condensation method,[4] by a homologous anionic ortho Fries rearrangement,[8] via rearrangement of a metacyclophane derivative possessing two pinacol subunits,[10] by a spirodienone route,[11] or by annulation of a biscarbene complex.[12] Calix[4]arenes with the bridges functionalized in two different fashions have been obtained by the fragment condensation method[4c] or via addition of PhLi or *t*-BuLi to a ketocalix[4]arene derivative.[13,14] Compared to the other approaches for the introduction of substituents at the bridges, the experimental conditions used for the route involving S_N1 substitution of the bromocalixarenes are remarkably simple. Typically, the reactions are conducted by heating to reflux solutions of the bromocalixarene and the nucleophile in an ionizing solvent such as 2,2,2-trifluoroethanol (TFE) or hexafluoro-2-propanol (HFIP), in the absence of a Lewis acid and without the need of dry solvents or an inert atmosphere.

We have previously reported that, in an initial attempt to obtain **1a** via photochemical bromination of calixarene tetramethoxy ether **2** with 14 equiv of NBS, a mixture of products was obtained. From this mixture, a hexabromo derivative (with distal dibromomethylene groups) was separated by recrystallization from hexane.[2b] The two dibromomethylene groups of the hexabromo derivative were found to be labile, and upon attempted recrystallization from $CHCl_3$/MeOH, they underwent hydrolysis affording a derivative possessing two carbonyl and two bromomethylene bridges.[2b] If indeed the hexabromo derivative (and/or its hydrolysis product) undergoes S_N1 reactions at the monosubstituted bridges, it could be envisioned that the compound could provide a general synthetic entry to calixarene derivatives with two types of chemically modified bridges. The present study was conducted to explore this possibility.

RESULTS AND DISCUSSION

Preparation of the Systems. The preparation of the hexabromo derivative via photochemical bromination of **2** was attempted using only 6.3 equiv of NBS (instead of 14 equiv). Examination of the crude product by ^{1}H NMR spectroscopy indicated the

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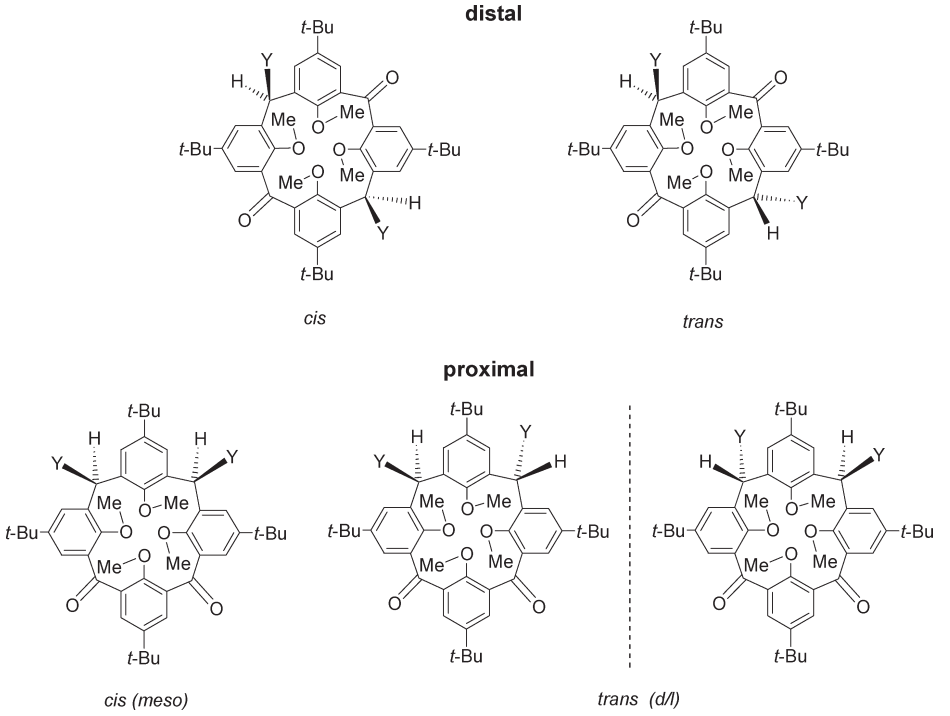
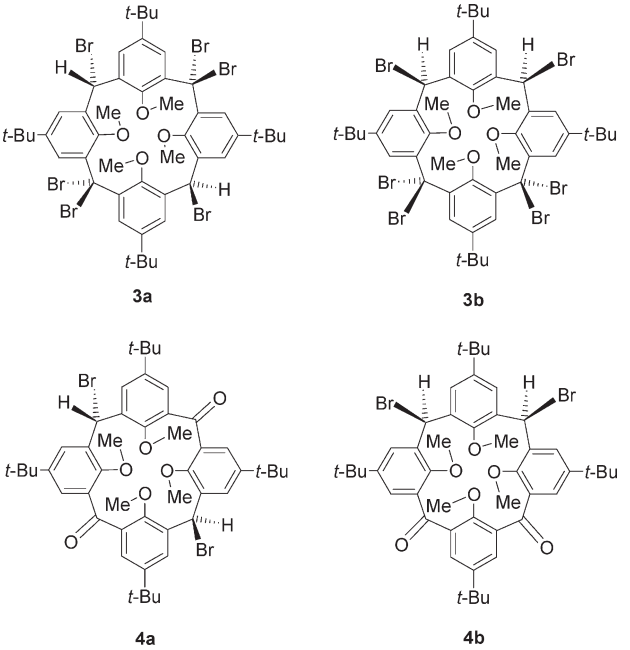


Figure 1. Isomeric forms of a dioxocalixarene possessing two identical monosubstituted bridges.

formation of *two* hexabromo derivatives (in a 7:3 ratio) as the major products together with tetrabromocalix[4]arene **1a**. The major product (identical to the hexabromo derivative previously isolated)[2b,15] displayed in the ^{1}H NMR spectrum single signals for the methine (integrating for two protons), methoxy, and *t*-Bu groups and a pair of doublets for the aromatic protons. This signal pattern is consistent with an hexabromo derivative with pairs of dibromomethylene and bromomethylene groups located on distal bridges and possessing either C_{2h} or C_{2v} symmetry. The minor product displayed three signals each for the methoxy and *t*-Bu signals, a pattern consistent with a structure with the dibromomethylene groups located on proximal bridges and possessing C_s symmetry.

The major isomer could be separated from the crude product mixture by fractional crystallization but we were unable to purify the minor isomer either via fractional crystallization or via chromatography (in the latter case, the hydrolysis product **4b** was obtained in pure form). Hexabromocalixarene **3a** readily underwent hydrolysis (for example, via reflux in aq THF) to afford the corresponding dioxo bis(bromomethylene) derivative **4a** (identical to the dioxo dibromo derivative previously isolated).[2b,15] The isomeric **4b** was obtained in nearly pure form via hydrolysis of a mixture of both hexabromo derivatives (enriched in **3b**), followed by recrystallization from chloroform/acetonitrile.

We also attempted to obtain the hexabromo derivatives via bromination of the tetrabromo derivative **1a** using the same reaction conditions used for the bromination of **2**. However, the starting material was recovered virtually unchanged after workup. Clearly, *all-cis* tetrabromocalixarene **2** is not an intermediate in the formation of the two hexabromo derivatives under the reaction conditions.



Configurational and Conformational considerations. Most of the calixarene derivatives that will be discussed in this paper possess a pair of carbonyls and a pair of identical monosubstituted bridges on either distal or proximal positions (Figure 1). Since the derivatives possess two stereocenters, both *cis* and *trans* isomers are possible. In the *cis* and *trans* isomers of the proximal form, the two stereocenters possess opposite and identical configurations, respectively. Since the configurations of the two stereocenters are identical in the *trans* form, the derivative is chiral while the *cis* isomer can be viewed as its *meso* form. The *cis* and *trans* forms of the distal isomer are achiral on a time scale of fast rotation through the annulus

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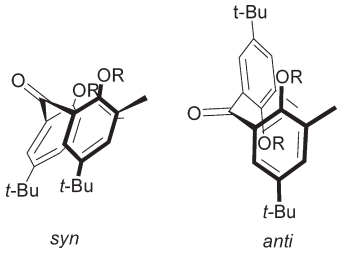


Figure 2. *Syn* and *anti* arrangements of the Ar_2CO subunit.

Scheme 1

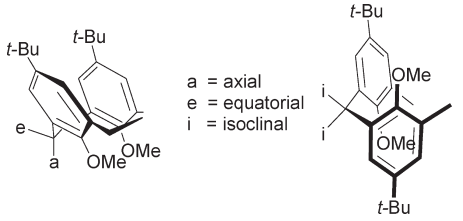


Table 1. Possible Arrangements of Substituents in Calixarenes Possessing a Pair of Carbonyl Bridges and Two Identical Monosubstituted Methylene Groups in Selected Conformations of the Macrocycle

	conformation of the macrocycle		
substitution pattern	1,2-alternate	1,3-alternate	partial cone
distal (*cis*)	axial−equatorial	diisoclinal	
distal (*trans*)	diequatorial diaxial	diisoclinal	
proximal (*cis*)		diisoclinal	diequatorial diaxial
proximal (*trans*)		diisoclinal	axial−equatorial

of all rings (Figure 1). However, these systems may be rendered chiral in some frozen conformations of the macrocycle. For example, both the *cis* and *trans* forms of the distal isomer are chiral in a frozen 1,3-alternate conformation of the macrocycle.

In ketocalixarene derivatives, pairs of geminal rings attached to a carbonyl group favor *anti* over *syn* arrangements (Figure 2).[16] On these grounds, the 1,2- and 1,3-alternate forms should be the lower energy conformations of the macrocycle of the distal derivative, whereas a partial cone[17] and the 1,3-alternate forms should be the lower energy conformations of the proximal isomer.

Depending on the conformation of the macrocycle and the *cis* or *trans* substitution pattern, the substituents at the bridges may be located at axial, equatorial, or isoclinal positions (Scheme 1). The different possible dispositions of substituents on the aforementioned selected conformations of the macrocycle are collected in Table 1.

From steric considerations, it could be expected that equatorial or isoclinal dispositions of the substituents at the substituted bridges will be favored over the more sterically crowded axial ones. In some substitution patterns, this in turn may influence the preferred conformation of the macrocycle resulting from the different "up" or "down" orientations of the rings. On this basis, it could be expected that for bulky substituents the distal (*cis*) isomer should prefer the diisoclinal 1,3-alternate conformation, while the distal (*trans*) form should prefer the diequatorial 1,2-alternate conformation. By similar considerations, it could be expected that the proximal (*cis*) isomer should prefer the diequatorial partial cone conformation, while the proximal (*trans*) form should prefer the diisoclinal 1,3-alternate conformation (cf. Table 1).

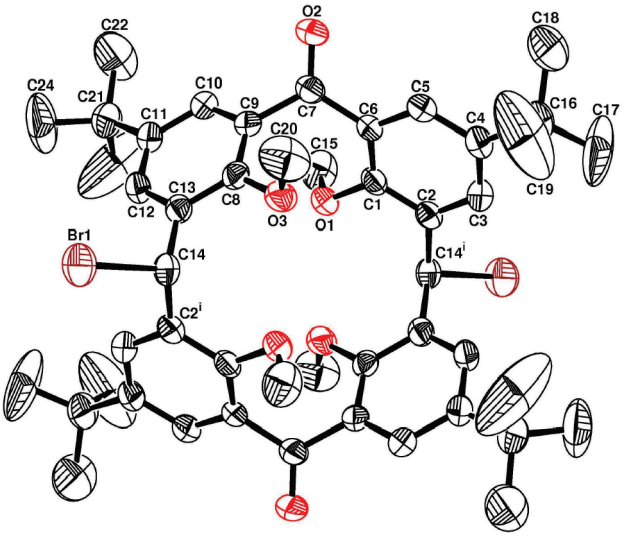
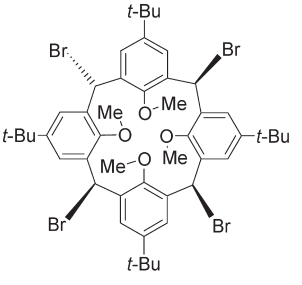


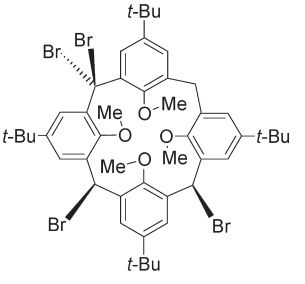
Figure 3. Crystal structure of the distal dibromo dioxocalix[4]arene **4a**.

Crystal conformation of 4a. Assuming that in **3a** the rotation of the aryl rings through the annulus is slow on the NMR time scale, and on the basis of the *anti* conformational preference of the Ar−CO−Ar subunits and the pattern of the NMR spectrum which is consistent with C_{2h} symmetry, we ascribe to the compound the distal (*trans*) structure with a diequatorial 1,2-alternate conformation of the macrocycle.[15] On similar grounds, taking into account the C_s symmetry indicated by the NMR pattern and the presence of a unique methoxy signal upfield shifted (2.10 ppm), we ascribe to the proximal isomer **3b** a (*cis*) diequatorial partial cone conformation. Since the hydrolysis reaction of the dibromomethylene groups is not expected to affect the configuration of the bromomethylene groups, compounds **4a** and **4b** are ascribed to the distal (*trans*) and proximal (*cis*) isomers.

The structural assignment of **4a** was corroborated by X-ray crystallography (Figure 3). The molecule adopts a 1,2-alternate conformation. On the basis of preliminary structural data, the structure of **4a** was incorrectly characterized by us as *cis*.[2b] Probably the source of the error was the failure to recognize that in a 1,2-alternate conformation a diequatorial disposition of substituents corresponds to a *trans* arrangement.



5 *(rcct)*



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Conformational Effects in the Bromination Reaction. As shown above, the *all-cis* derivative **1a** essentially does not undergo

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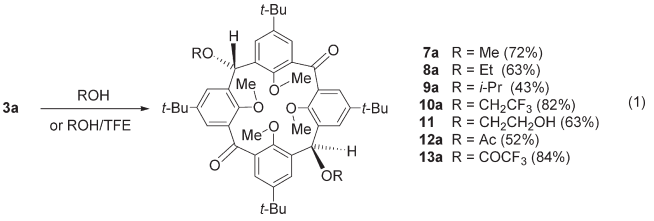
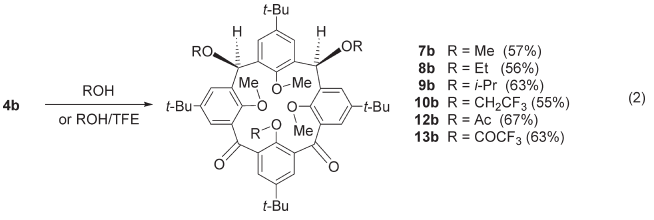
bromination under the reaction conditions, indicating that it is not an intermediate in the formation of **3a** and **3b**. It seems reasonable to assume retention of the configuration of the bromomethylene groups that do not react (i.e., those that are not converted into dibromomethylene groups) under the reaction conditions. On these grounds, **1a** can be ruled out as a precursor in the formation of **3a**, since whereas in **1a** all the bromines are in an *all-cis* disposition, the two bromines of **3a** are *trans*. However, in **3b**, the bromines at the two proximal bromomethylene bridges are *cis*, and therefore, it could be naively expected that **3b** originates from dibromination of **1a** at two proximal bridges. However, not only is tetrabromocalix[4]arene **1a** not a precursor for the formation of **3b**, but also it does not undergo further brominations under the reaction conditions. A possible explanation for these unexpected observations may be connected to conformational effects. In the preferred cone conformation of **1a**, all protons of the bromomethylene groups are located at axial positions, in between pairs of rings oriented *syn*.[2a] These protons may be less reactive that protons located between rings oriented *anti* (i.e., protons located in isoclinal positions). We have previously observed in the CrO_3 oxidation of atropisomeric calixarene tetraacetates that methylene groups located between geminal aryl rings oriented *anti* are oxidized faster than those located between aryl groups oriented *syn*.[16] It may be possible that other stereoisomeric forms of **1a** (e.g., the *rcct* form **5**) and/or that tetrabromocalixarenes possessing dibromomethylene bridges (e.g., **6**) are the precursors of the hexabromo derivatives.

Reaction with Alcohols. Reaction of **3a** with selected alcohols (eq 1) was conducted by heating to reflux a mixture of the calixarene and the appropriate alcohol (in the case of MeOH and TFE) or a mixture of the alcohol and TFE as the ionizing solvent (in the case of EtOH, *i*-PrOH and ethylene glycol). In all cases, a major product precipitated from a $CHCl_3$/MeOH mixture. NMR analysis indicated that a single isomer was isolated.[18]



7a R = Me (72%)
8a R = Et (63%)
9a R = *i*-Pr (43%)
10a R = CH_2CF_3 (82%)
11 R = CH_2CH_2OH (63%)
12a R = Ac (52%)
13a R = $COCF_3$ (84%)

(1)



7b R = Me (57%)
8b R = Et (56%)
9b R = *i*-Pr (63%)
10b R = CH_2CF_3 (55%)
12b R = Ac (67%)
13b R = $COCF_3$ (63%)

(2)

All products displayed a signal in the ^{13}C NMR spectrum at δ 200−190 ppm (characteristic of a carbonyl functionality), indicating that under the reaction conditions the dibromomethylene groups underwent hydrolysis to carbonyl groups. The signal patterns of the compounds in the ^1H NMR spectrum (single signals for the methine, methoxy, and *t*-Bu groups, two pairs of doublets for the aromatic protons) are consistent with a 1,2-alternate conformation with a *trans* configuration of the alkoxy groups. For compounds **7a** and **10a**, this structural assignment was corroborated by X-ray crystallography. Both **7a** and **10a** adopt a 1,2-alternate conformation of crystallographic C_i symmetry with the alkoxy substituents located at equatorial positions and the two carbonyl groups connected to rings oriented *anti* (Figure 4).

Since the hexabromo derivative **3b** could not be isolated in pure form, calixarenes with a pair of alkoxy groups at proximal positions of the macrocycle were prepared using the dioxo dibromo derivative **4b** as starting material (eq 2). Reactions were conducted in a mixture of TFE and the appropriate alcohol (in the case of MeOH and TFE the reaction could be conducted also in neat alcohol). In each case, the crude reaction product was recrystallized from $CHCl_3$/MeCN to afford the major isolated product in pure form. The compounds display in the ^1H NMR spectrum a pattern of signals indicating C_s symmetry (e.g., three signals each for the OMe and *t*-Bu groups). In all cases, one of the three methoxy signals was significantly upfield shifted (δ = 2.01−1.84 ppm). This is consistent with a partial cone arrangement of the rings in which a single methoxy group (attached to the ring pointing in the opposite direction to the rest) is located in the shielding region of the three remaining rings. On this basis, and the C_s symmetry indicated by the signal pattern, we assign to these molecules a *cis* configuration of the stereocenters and a partial cone conformation of the macrocycle. Because of the diastereotopicity of the protons of a given OCH_2 group in **8b** and **10b** (no symmetry plane bisects the groups), these protons appear in the ^1H NMR spectrum as the AB part of an ABX_3 coupling system. Similarly, the two methyl groups of a given *i*-Pr group of **9b** are diastereotopic and gave separate signals, although one of these signals partially overlapped one of the signals of the *t*-Bu groups. The *cis* configurational assignment of **9b** was corroborated by X-ray diffraction (Figure 5). The molecule adopts in the crystal a partial cone conformation with pairs of aryl rings connected to a given carbonyl group oriented anti and with both isopropoxy groups located at equatorial positions.

Reaction with Carboxylic Acids. Reactions of **3a** and **4b** with acetic acid or trifluoroacetic acid (TFA) were conducted by heating to reflux a mixture of each of the compounds and the corresponding acid (which served both as the ionizing solvent and the nucleophile). As observed in the reaction with alcohols, crystallization of the crude products afforded single isomeric products, which on the basis of their NMR patterns is assigned to the *trans* forms **12a** and **13a** (for the products obtained from the distal derivative **3a**) and the *cis* forms **12b** and **13b** (for the products obtained from **4b**).

Reactions of 4a with Azide Ion. Reaction of **4a** with azide ion was conducted by heating a mixture of the compound and NaN_3 in TFE. From a methanolic solution of the crude product a ca. 1:1 mixture of *cis* and *trans* isomers of the diazido derivative precipitated, suggesting that in contrast to the reaction with O-nucleophiles, the reaction proceeds with poor stereoselectivity. A similar poor stereoselectivity was observed previously in the reaction of **1a** with the small charged nucleophiles N_3^- and SCN^-.[2b] In those reactions and in contrast with the reaction with other nucleophiles, the *rccc* (*all-cis*) products were not formed preferentially.[2b] The *trans* form of the diazido derivative (**14**) was isolated via recrystallization of the isomeric mixture

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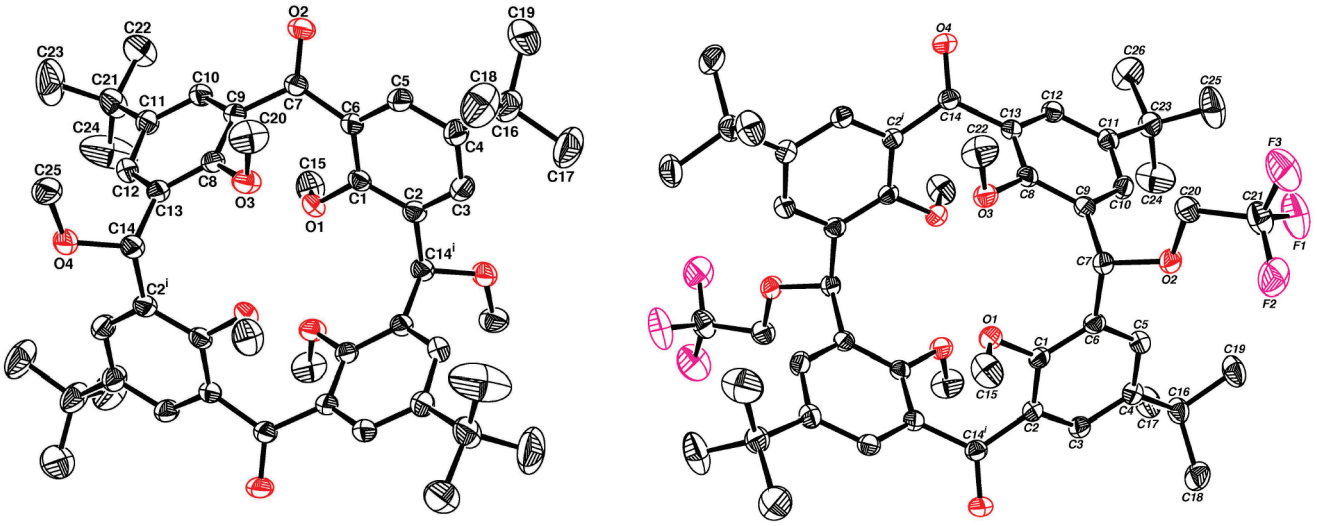


Figure 4. Crystal structures of the distal *trans*-dialkoxycalix[4]arenes **7a** (left) and **10a** (right).

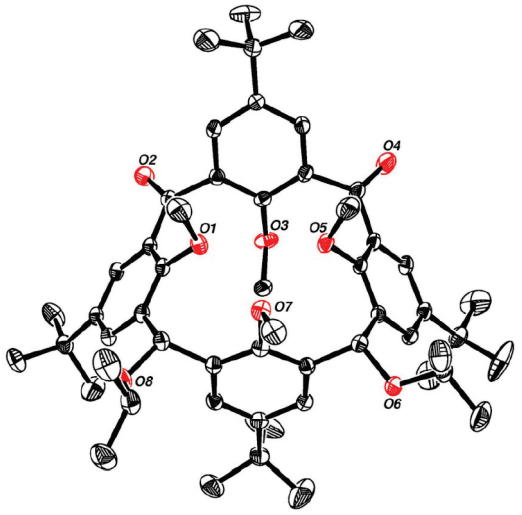
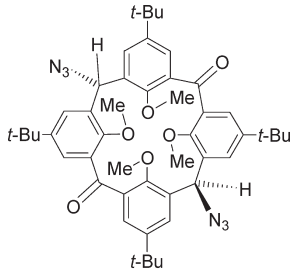


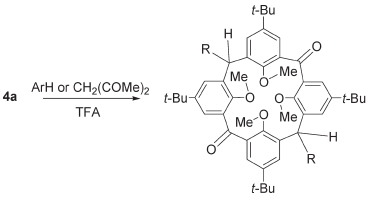
Figure 5. Crystal structure of the proximal *cis*-diisopropoxycalix-[4]arene **9b**.

from $CHCl_3$/MeOH, the first crop of crystals consisting of nearly pure **14**.



14 (28%)

Friedel–Crafts Reactions Using 4a as the Alkylating Agent. Initial experiments indicated that solvolytic Friedel–Crafts[19] alkylation reactions of activated aromatic rings with the dioxodibromocalix[4]arene **4a** proceed in a cleaner fashion than those conducted with the hexabromocalixarene **3a**. We therefore utilized the former compound as the alkylating agent in the Friedel–Crafts reactions (eq 3). Whenever possible, the reactions were conducted using TFA as the ionizing solvent instead of the relatively expensive HFIP used previously.[2]



(3)

In previous Friedel–Crafts arylation reactions of **1a–c**, we found that, although the reaction proceeds with *m*-xylene, no arylation occurs with benzene derivatives less activated toward electrophilic substitution (such as toluene).[2] Since the electron-withdrawing effect of the carbonyl groups present in **4a** was expected to increase the electrophilicity (and reactivity) of the carbocations derived from heterolytic cleavage of C–Br bonds, we attempted the reaction of **4a** with *tert*-butylbenzene. Although the aryl ring possesses a single *ortho-para* activating substituent, the bulky *t*-Bu group sterically shields the *ortho* positions, and therefore a preferential attack at the *para* positions was expected. NMR analysis of the product obtained after addition of MeOH indicated the presence of a major form (consisting of ca. 90% of the product mixture) displaying an NMR pattern consistent with the *trans*-diarylated derivative **15**. The *t*-Bu phenyl rings displayed an AB pattern, indicating that the electrophilic attack took place at the *para* position. Calixarene **4a** also reacts with toluene, and from the product mixture, the *trans* isomer derived from *para* attack to the toluene rings (**16**) was isolated in low yield. Attempted reaction with benzene in TFA afforded only the product derived from reaction with the ionizing solvent, i.e., the *trans* bis(trifluoroacetate) derivative **13a**.

Reaction of **4a** with *m*-xylene/TFA afforded after crystallization the *trans* derivative **17**, albeit in a low yield. The compound was structurally characterized by X-ray crystallography (Figure 6). As observed with the rest of the *trans* derivatives of the distal form, the

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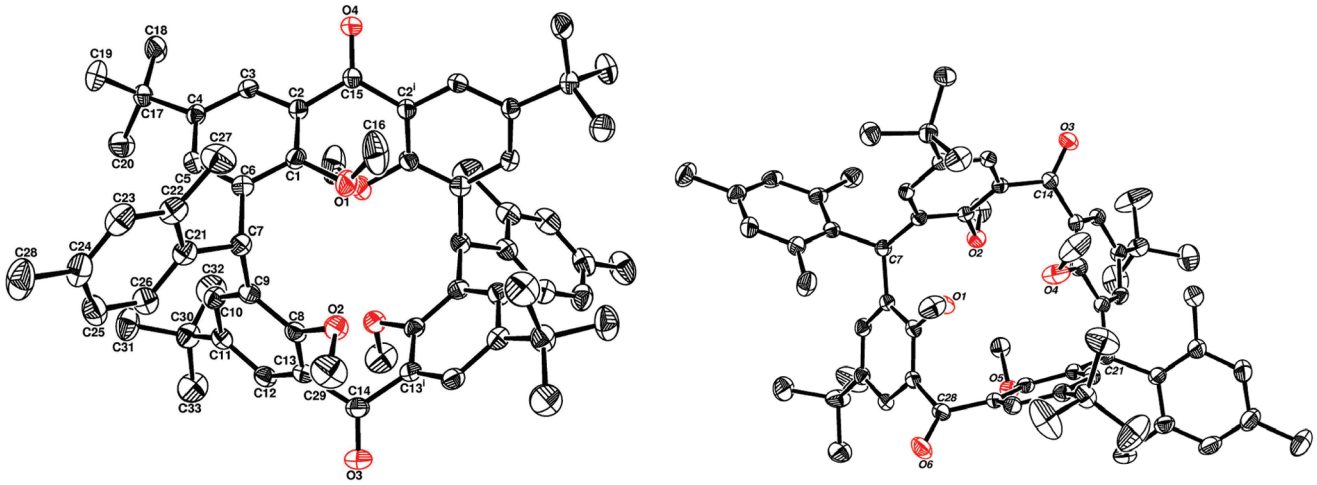

Figure 6. Crystal structures of the dixylyl calix[4]arene (*trans* form) **17** and the dimesityl derivative **18** (*cis* form).

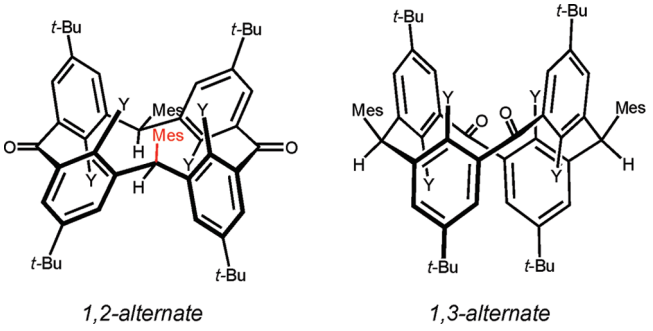

Figure 7. Two possible conformations of the *cis*-dimesityl derivative **18**. In the 1,2-alternate conformation (left), one of the mesityl substituents (marked in red) is located in a hindered axial position. In the 1,3-alternate conformation (right), both mesityls are located in isoclinal positions.

calixarene adopts in the crystal a 1,2-alternate conformation with the *m*-xylyl substituents at the bridges located at the equatorial positions.

A solvolytic Friedel–Crafts reaction was also performed with **4a** and the crowded mesitylene. The reaction proceeded in high yield and afforded a product with an NMR pattern (e.g., two signals each for the methoxy and *t*-Bu groups, four doublets for the aromatic protons of the calix macrocycle) completely different from the ones observed for the other Friedel–Crafts products. Two signals each were observed for the ortho methyls and aromatic protons of the mesityl rings, indicating slow rotation (on the NMR time scale) around the C–Mes bonds. X-ray diffraction indicated that the product obtained is the *cis* isomer with the macrocycle adopting the 1,3-alternate conformation (cf. Table 1 and Figure 7). The molecule crystallizes with a chloroform and a MeOH molecule, with the latter molecule hydrogen bonded to one of the carbonyl oxygens.[20] It seems likely that the 1,3-alternate conformation is preferred over the 1,2-alternate form (the only two conformations possessing anti arrangements of the Ar_2CO subunits) since in the former the two bulky mesityl rings are located in diisoclinal positions, whereas in the latter, necessarily, one mesityl group must be located in a crowded axial position (Figure 7).[21]

We also attempted the solvolytic Friedel–Crafts reaction with mesitylene in TFA using the bis(trifluoroacetate) calixarene **13a** as the starting material. The reaction afforded **18** in a very clean fashion, which indicates that the C–O bonds of the carbon bridges with the trifluoroacetate groups can be cleaved in TFA. The use of the trifluoroacetate derivative instead of the bromo derivative can be advantageous in cases where the HBr released can further react with the calixarene or the nucleophile. Since the trifluoroacetate groups of **13a** are cleaved in TFA, it seems likely that during the trifluoroacetolysis reaction of **3a** in TFA, the C–O bonds formed undergo a reversible heterolytic cleavage, and therefore, it can be concluded that the major isomer formed in the trifluoroacetolysis of **3a** (i.e., calixarene **13a**, with a *trans* configuration) is indeed the thermodynamic product.

The reaction of **4a** with 2-methylfuran was conducted in TFE/Et_3N. NMR analysis of the compound which precipitated upon recrystallization from $CHCl_3$/MeOH indicated the presence of a ca. 1:1 mixture of the *cis* and *trans* isomers. An additional recrystallization from $CHCl_3$/MeOH enabled the isolation of the *cis* isomer of **19** in pure form.

We have previously shown that both **1c** and **1d** react under S_N1 conditions with 1,3-pentanedione (a highly enolic compound). This reaction is of interest as an entry into systems possessing methylene bridges substituted by an sp^3 carbon. The reaction of **4a** with 1,3-pentanedione was conducted in TFA and afforded the bis(acetylacetonate) derivative **20** of *trans* configuration.

Rotational Barriers of the Dimesityl Calixarene 18. Under a time scale of fast ring inversion and C–Mes bond rotations, **18** should display single signals for the OMe and *o*-Me groups. The NMR pattern observed for **18** at rt (two signals each for the methoxy and *t*-Bu groups, four doublets for the aromatic protons of the calix macrocycle) indicates that both the 1,3-alternate-to-1,3-alternate ring inversion process of the macrocycle (a process involving passage of all rings through the annulus and resulting in enantiomerization, Figure 8) and the rotation around the C–Mes bonds are slow on the NMR time scale. No coalescence of the two closely spaced aromatic mesityl signals was observed when the temperature of an NMR sample of **18** (500 MHz, in tetrachloroethane-d_2) was raised up to 408 K. From the chemical shift difference at that temperature (0.0131 ppm) a higher limit of 14.5 s^{-1} was estimated for the exchange rate at 408 K,[22] yielding a lower limit of 22.0 kcal mol^{-1} for the barrier of rotation around the C–Mes bonds. The two *t*-Bu signals remained unchanged at high temperature, and from their separation (0.08 ppm, 38.5 Hz) a lower limit of 20.4 kcal mol^{-1} was estimated for the 1,3-alternate-to-1,3-alternate ring inversion process

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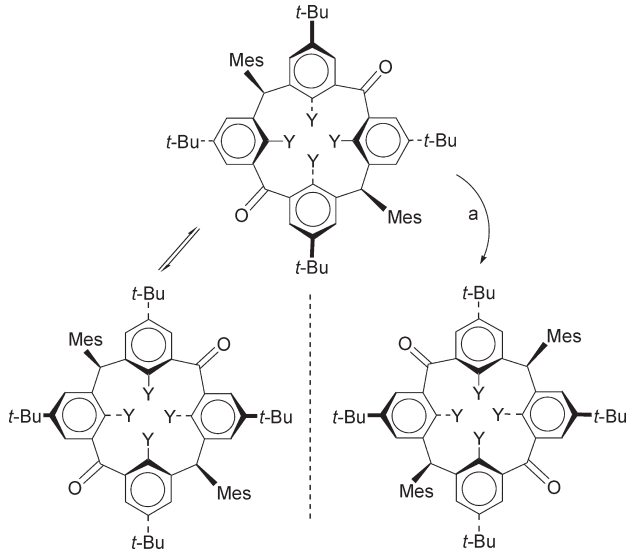
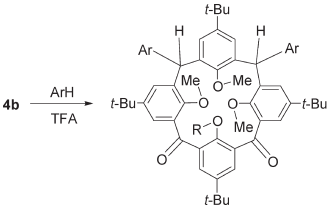


Figure 8. 1,3-Alternate-to-1,3-alternate ring inversion process of **18**. The process involves rotation through the annulus of the rings and results in enantiomerization of the molecule. This can be visualized by reorienting the molecule by a rigid 90° rotation ("a") after the ring inversion process. As readily seen at the bottom of the Figure, the two structures are enantiomeric.

of the macrocycle. The lower limits estimated for the barriers of the inversion and mesityl rotation processes are different, since at the highest temperature examined the separation between the pairs of signals of the aromatic mesityl protons and *t*-Bu groups is different. Nevertheless, it may be possible that both processes possess identical barriers and that the minimum energy pathway for rotation of the mesityl ring requires a ring inversion of the macrocycle, as previously observed for a tetrahydroxy dimesitylcalix[4]arene derivative.[21] In such a case, it seems likely that the enantiomerization barrier of compound **18** is of sufficient height to enable the resolution of its enantiomers at room temperature.[23]



21 R = Me, Ar = 4-*t*-BuC_6H_4 *(cis)* (24%)
22 R = Me, Ar = 2,4-$Me_2C_6H_3$ *(cis)* (68%)
23a R = H, Ar = Mes (*cis*) (23%)
23b R = H, Ar = Mes (*trans*) (44%) (4)

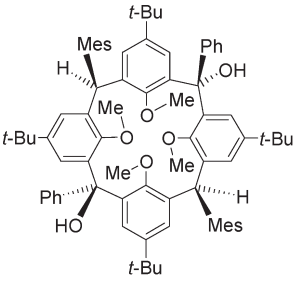
Solvolytic Friedel–Crafts Reactions of 4b. Friedel–Crafts reactions of *tert*-butylbenzene, *m*-xylene, and mesitylene using the proximal isomer **4b** as the alkylating agent and TFA as the ionizing solvent were also conducted (eq 4). In general, the reactions proceeded with a lower yield than those with the distal isomer. After recrystallization from $CHCl_3$/acetonitrile, we obtained the *cis* isomer of the derivatives **21** and **22** (identified on the basis of their ^{1}H NMR patterns indicating C_s symmetry). The structure of the *cis* isomer **22** was corroborated by X-ray crystallography (Figure 9). The molecule (which cocrystallized with acetonitrile) adopts a partial cone conformation with the two *m*-xylyl groups located at equatorial positions. This conformation is similar to that observed for the diisopropoxy derivative **9b.**

The reaction with mesitylene afforded a mixture of *cis* and *trans* isomers in a 1:3 ratio (determined by integration of the crude product mixture). NMR analysis indicated that in both compounds only three methoxy groups are present, suggesting that both isomers underwent cleavage of a methoxy group under the reaction conditions. The major product displayed in the ^{1}H NMR spectrum a pattern of signals indicating C_1 symmetry (e.g., separate signals for each *t*-Bu group) in agreement with a *trans* derivative adopting the 1,3-alternate conformation.

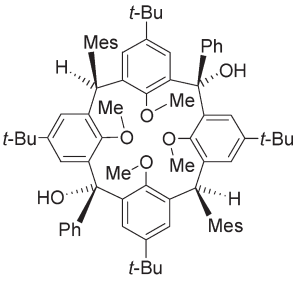
X-ray diffraction corroborated that the major product corresponds to the *trans* isomer **23b**, with the macrocycle adopting the 1,3-alternate conformation (Figure 9). The crystal structure enabled us to identify the methoxy group that underwent cleavage as the one located on the ring attached to both mesityl-substituted bridges. It is interesting to note that in both **18** and **23b** the macrocycle adopts a 1,3-alternate arrangement with the mesityl groups located at isoclinal positions. The adoption of the 1,3-alternate conformation by **23b** instead of the partial cone one can be rationalized since in the partial cone form of the *trans* isomer, one of mesityl groups must be located in a crowded axial position.

The *cis* isomer of **23b** displayed in the ^{1}H NMR spectrum a signal pattern indicating a structure of mirror symmetry. By analogy with the dixylyl derivative **22**, we assume that **23a** adopts a partial cone conformation with both mesityl groups located at equatorial positions. Notably, in the ^{1}H NMR spectrum at rt, broad signals were observed for the *o*-Me group of the mesityl rings. Upon raising the temperature, these signals coalesced, and from the chemical shift difference ($\Delta\nu$ = 107.4 Hz) and coalescence temperature (T_c = 338.2 K) a barrier of 16.2 kcal mol^{-1} was calculated for the rotation of the mesityl group. Clearly, the rotations of the mesityl groups at the equatorial position of the partial cone form are less hindered than in the isoclinal positions of the 1,3-alternate form of **18**.

We also examined the reaction of **4b** and mesitylene using HFIP as ionizing solvent. In this solvent, the **23a**:**23b** ratio was 1.5:1 (i.e., the *cis* isomer is the major product). It may be possible that the difference in polarity between TFE and HFIP is at least partially responsible for the change in stereoselectivity of the reaction.



24



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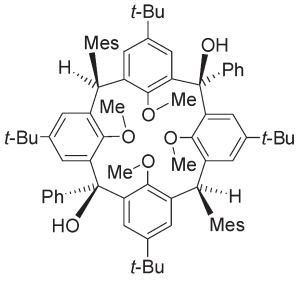

26

Regioselective Demethylation in the Formation of 23. We have observed in the past a demethylation process during a

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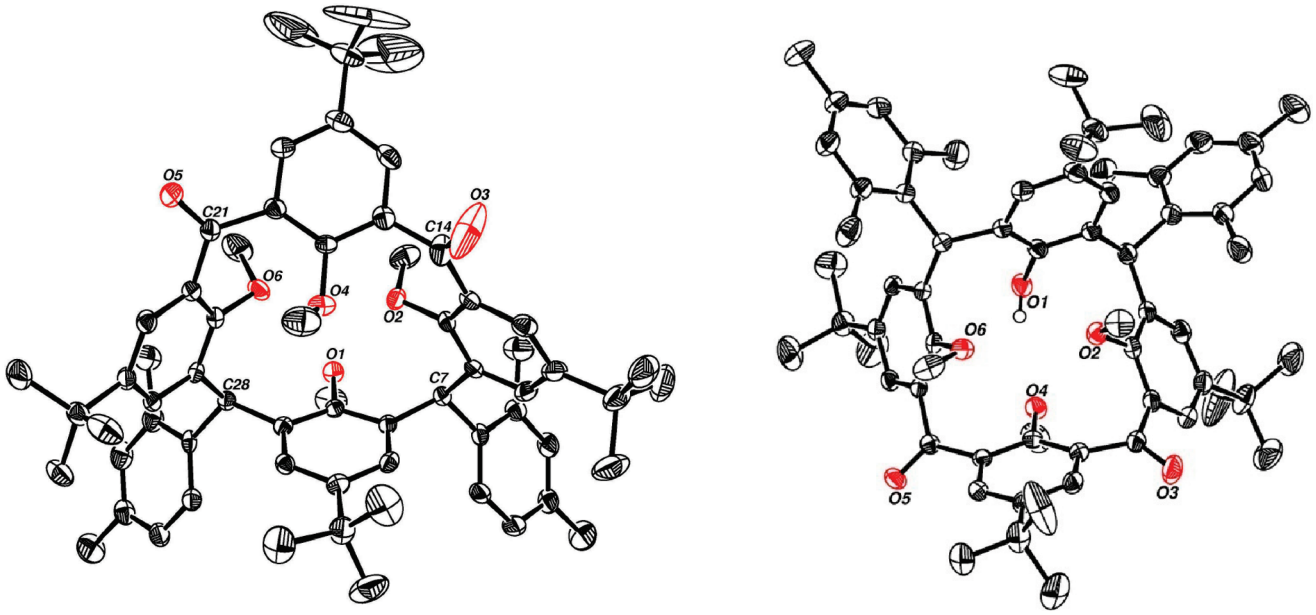


Figure 9. X-ray structure of the proximal *cis*-dixylyl derivative **22** (left) and the proximal *trans*-dimesityl derivative **23b** (right).

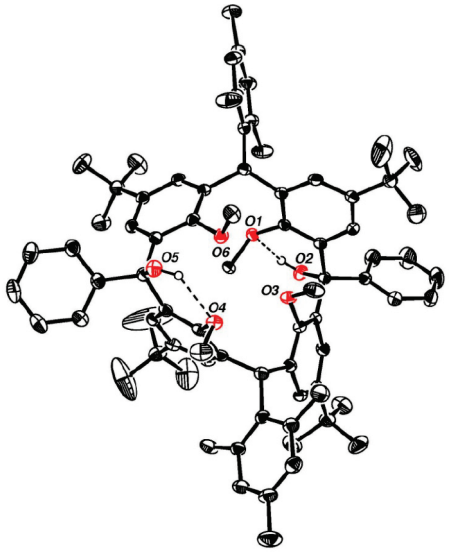
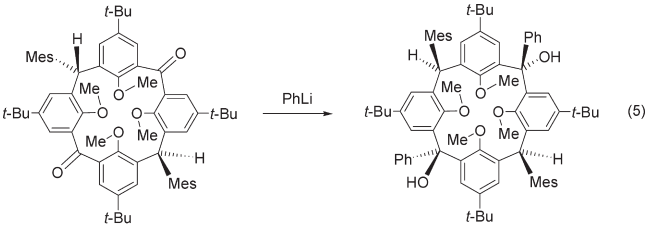


Figure 10. X-ray structure of the proximal dimesityl/diphenyl derivative **24**.

solvolytic Friedel—Crafts reaction. Reaction of the de-*tert*-butylated derivative **1b** with xylene in HFIP afforded the trimethoxy tetraxylyl product.[2a] In the reaction of **4b**, monodemethylation was observed only in the reaction with the crowded mesitylene. Notably, the methyl cleaved was the one located on the aryl ring flanked by the two mesityl rings. A possible explanation for the formation of **23a** and **23b** is that, since the reaction of the calixarene carbocation with the crowded mesitylene is slow, a demethylation reaction can successfully compete with the Fridel—Crafts alkylation. It may be possible also that the demethylation reaction occurs at a carbocation intermediate[24] and that the O-Me cleavage is facilitated on a ring involved in delocalization of the positive charge, which may rationalize why the ring selectively demethylated in the product is the one located between the two substituted bridges.

Reaction of the Carbonyl Bridges. In principle, any of the systems described could be used as starting materials for further modifications at the bridges, for example, via reaction of the carbonyl groups. As a proof of the concept, we examined the reaction of the *cis*-dimesityl derivative **18** with PhLi. The choice of **18** as starting material was based on the expectation that the presence of the bulky mesityls will increase the stereoselectivity of the addition to the carbonyls. The *trans* configuration of the two mesityl-substituted bridges is unaffected by the addition reaction, but two new stereocenters are created by the addition to the carbonyl groups. Thus, three isomers of the addition products (**24**—**26**) are to be expected if the reaction proceeds without any stereoselectivity. In compounds **25** and **26** both phenyl groups are in a mutual *cis* relationship, while in **24** they are *trans*. On the basis of statistical considerations it could be expected that **24** (of C_1 symmetry) should be favored over **25** or **26** by a factor of 2.



(5)

Examination of the crude reaction product of the reaction of **18** with PhLi (eq 5) indicated the formation of a single product displaying in the ^{1}H NMR spectrum a signal pattern indicating C_1 symmetry and consistent only with compund **24**. This structural assignment was corroborated by X-ray crystallography (Figure 10). The calix macrocycle adopts a severely distorted partial cone conformation in which the four aryl substituents are located in equatorial or isoclinal positions of the macrocycle. The

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O(2)-H group is located in an isoclinal position and is hydrogen bonded to the O(1)-Me group oriented "in" (toward the cavity center), while the O(6)-H group is located in an axial position and is hydrogen bonded to the O(4)-Me group oriented "out".

The two phenyl rings are located in different steric environments. This is clearly manifested in the ^{1}H NMR spectrum in CD_2Cl_2 at 303 K. Whereas one of the phenyl rings undergoes slow rotation on the NMR time scale at that temperature (i.e., separate signals for the two *ortho* protons at δ 7.73 and 6.75 ppm), the second phenyl displays a single average signal for those protons, indicating (precluding accidental isochrony) fast rotation on the NMR time scale. As observed for the other mesityl derivatives in the present study, the rotation of both mesityl groups of **24** is frozen on the NMR time scale at 303 K, and separate signals were observed for pairs of the *o*-Me and aromatic mesityl protons on a given ring.

CONCLUSIONS

In summary, we have developed a very simple synthetic route for the preparation of calix[4]arenes with two different chemical modifications at the bridges. Key intermediates are the hexabromo and/or the dioxo dibromo derivatives. Under S_N1 conditions, the systems react with a variety of nucleophiles and even with mildly activated aromatic rings such as toluene. Both proximal and distal systems are available by this route.

EXPERIMENTAL SECTION

Preparation of the Hexabromocalix[4]arene Derivatives. A mixture of **2** (5 g, 7.1 mmol), NBS (7.93 g, 44.6 mmol), and CCl_4 (350 mL) was refluxed for 18 h while being irradiated with a spotlight (60 W). The solvent was washed with aq $NaHSO_3$, and the organic phase was evaporated. The crude product was treated with 100 mL of *n*-hexane to give 6.4 g of a 7:3 mixture of the 1,3 (**3a**)[2b,15] and 1,2 (**3b**) hexabrominated products. The filtrate was dried and treated with a small amount of ethanol to give 686 mg of **1a** (10%). Chloroform (75 mL) was added to the mixture of the two hexabromo derivatives followed by 100 mL of *n*-hexane. The suspension was filtered to give 3.6 g (3.06 mmol, 43%) of pure **3a**.The filtrate was evaporated, and the residue was heated to reflux for 18 h with a mixture of 250 mL of THF and 12.5 mL of water. The solvent was evaporated and the residue treated with 20 mL of chloroform and 20 mL of acetonitrile to give 0.3 g of pure **4a**[2b,15] (5%) in the first fraction. The second fraction contained 1.07 g of **4b** (yield 17%). If necessary, further purification can be achieved by recrystallization from $CHCl_3$/MeCN.

*2,14-Dibromo-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxocalix[4]arene (**4a**).* A mixture of **3a** (0.1 g, 0.085 mmol), 9 mL of THF, 1 mL of water, and 3 drops of Et_3N was heated to reflux for 4 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/acetonitrile to give 56 mg of **4a** (77%): mp 325−330 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, J = 2.5 Hz, 4H), 7.56 (d, J = 2.5 Hz, 4H), 6.60 (s, 2H), 3.22 (s, 12H), 1.37 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.2, 153.1, 146.6, 134.4, 134.0, 130.0, 125.8, 62.3, 40.5, 34.7, 31.3; HRMS (ESI) m/z 891.2645 [(M + H)$^+$, calcd for $C_{48}H_{59}Br_2O_6$ 891.2658].

*8,14-Dibromo-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxy-1,20-dioxocalix[4]arene (**4b**):* mp 315−320 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 2.5 Hz, 2H), 7.76 (d, J = 2.5 Hz, 2H), 7.49 (s, 2H), 6.83 (s, 2H), 6.80 (s, 2H), 4.05 (s, 3H), 3.36 (s, 6H), 2.10 (s, 3H), 1.41 (s, 18H), 1.34 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.5, 154.6, 152.9, 151.2, 147.3, 146.9, 144.8, 135.3, 134.1, 132.1, 130.7, 127.5, 127.1, 126.5, 62.4, 62.2, 59.9, 43.4, 34.9, 34.4, 34.1, 31.4, 31.3, 30.8; HRMS (ESI) m/z 913.2476 [(M + Na)$^+$ calcd for $C_{48}H_{58}Br_2O_6Na$, 913.2477].

General Procedure for the Reaction of 3a with Alcohols. A mixture of **3a** (0.1 g, 0.085 mmol), 10 mL of TFE, and 10 mL of the appropriate alcohol was heated to reflux for 2 h (until the solution is clear). The solvent was evaporated and the residue recrystallized from $CHCl_3$/ MeOH.

*5,11,17,23-Tetra-tert-butyl-2,14,25,26,27,28-hexamethoxy-8,20-dioxocalix[4]arene (**7a**):* yield 48.5 mg (72%); mp 325−330 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, J = 2.6 Hz, 4H), 7.56 (d, J = 2.6 Hz, 4H), 5.62 (s, 2H), 3.27 (s, 6H), 3.18 (s, 12H), 1.36 (s, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.5, 155.1, 146.3, 134.5, 134.0, 126.8, 125.1, 72.7, 62.2, 56.9, 34.6, 31.4; HRMS (ESI) m/z 815.4494 [(M + Na)$^+$ calcd for $C_{50}H_{64}O_8Na$, 815.4499].

*5,11,17,23-Tetra-tert-butyl-2,14-diethoxy-25,26,27,28-tetramethoxy-8,20-dioxocalix[4]arene (**8a**):* yield 44 mg (63%); mp 345−350 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (d, J = 2.6 Hz, 4H), 7.54 (d, J = 2.6 Hz, 4H), 5.74 (s, 2H), 3.40 (q, J = 7 Hz, 4H), 3.17 (s, 12H), 1.36 (s, 36H), 1.21 (t, J = 7 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.6, 155.0, 146.1, 135.0, 134.0, 127.0, 125.0, 70.3, 64.2, 62.2, 34.5, 31.4, 31.3, 15.3; HRMS (ESI) m/z 843.4807 [(M + Na)$^+$ calcd for $C_{52}H_{68}O_8Na$, 843.4812].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxo-2,14-diisopropoxycalix[4]arene (**9a**):* yield 30.7 mg (43%); mp 355−360 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 2.6 Hz, 4H), 7.53 (d, J = 2.6 Hz, 4H), 5.93 (s, 2H), 3.49 (h, J = 6.1 Hz, 2H), 3.18 (s, 12H), 1.35 (s, 36H), 1.16 (d, J = 6.1 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.7, 154.9, 146.0, 135.3, 134.0, 127.4, 124.9, 68.4, 67.1, 62.2, 34.5, 31.4, 22.0; HRMS (ESI) m/z 871.5119 [(M + Na)$^+$ calcd for $C_{54}H_{72}O_8Na$, 871.5125].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxo-2,14-bis(trifluoroethoxy)calix[4]arene (**10a**).* To a solution of **3a** (0.1 g, 0.11 mmol) in 10 mL of TFE was added 43 mg (0.3 mmol) of L-glutamic acid, and the mixture was refluxed for 18 h. The solid L-glutamic acid was removed by filtration, the filtrate was evaporated, and the residue was recrystallized from $CHCl_3$/MeOH to afford 68 mg (82%) of **10a**: mp 318−323 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 2.5 Hz, 4H), 7.60 (d, J = 2.5 Hz, 4H), 5.95 (s, 2H), 3.73 (q, J = 8.7 Hz, 4H), 3.16 (s, 12H), 1.36 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.8, 155.1, 146.6, 133.9, 133.1, 126.8, 125.7, 124.0 (q, J = 279.3 Hz), 71.8, 65.7 (q, J = 34.2 Hz), 62.3, 34.6, 31.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ −73.6 (t, J = 8.7 Hz); HRMS (ESI) m/z 929.4422 [(M + H)$^+$ calcd for $C_{52}H_{63}F_6O_8$, 929.4427].

*5,11,17,23-Tetra-tert-butyl-2,14-bis-(2-hydroxyethoxy)-25,26,27,28-tetramethoxy-8,20-dioxocalix[4]arene (**11**).* A mixture of **4a** (0.1 g, 0.085 mmol), 10 mL of TFE, and 5 mL of ethylene glycol was heated to reflux for 18 h. The volume of the solvent was reduced to a minimum by evaporation and washed with water. The organic phase was dried with Na_2SO_4 and evaporated. The residue was recrystallized from $CHCl_3$/MeOH to give 44 mg (63%) of **11**: mp 318−323 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 2.5 Hz, 4H), 7.57 (d, J = 2.5 Hz, 4H), 5.78 (s, 2H), 3.77−3.74 (m, 4H), 3.49 − 3.46 (m, 4H), 3.17 (s, 12H), 1.95 (t, J = 5.9 Hz, 2H), 1.35 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.2, 154.9, 146.3, 134.4, 134.1, 126.9, 125.3, 71.3, 70.3, 62.3, 61.9, 34.6, 31.4; HRMS (ESI) m/z 875.4688 [(M + Na)$^+$ calcd for $C_{52}H_{68}O_{10}Na$, 875.4710].

*2, 14-Diacetoxy-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxocalix[4]arene (**12a**).* A mixture of **3a** (0.1 g, 0.085 mmol) and 10 mL of acetic acid was heated to reflux for 18 h. The solvent was evaporated, and the residue recrystallized from $CHCl_3$/MeOH: yield 37.5 mg (52%); mp 362−364 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 2.5 Hz, 4H), 7.59 (d, J = 2.5 Hz, 4H), 7.22 (s, 2H), 3.23 (s, 12H), 2.12 (s, 6H), 1.37 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$)

δ 197.8, 169.7, 154.7, 146.2, 134.2, 133.3, 126.6, 125.6, 65.5, 62.3, 34.6, 31.4, 21.3; HRMS (ESI) *m/z* 871.4392 [(M + Na)$^+$ calcd for $C_{52}H_{64}O_{10}Na$, 871.4397].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxo-2,14-bis(trifluoroacetoxy)calix[4]arene (**13a**).* A mixture of **3a** (0.1 g, 0.085 mmol) and 3 mL of trifluoroacetic acid was heated to reflux for 2 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/MeOH: yield 68.6 mg (84%); mp 357−363 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 2.5 Hz, 4H), 7.67 (d, *J* = 2.5 Hz, 4H), 7.33 (s, 2H), 3.24 (s, 12H), 1.37 (36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 156.30 (q, *J* = 42.5 Hz), 154.7, 146.9, 133.9, 131.1, 126.6, 126.2, 114.5 (q, *J* = 286.0 Hz), 69.8, 62.5, 34.6, 31.3; ^{19}F NMR (471 MHz, $CDCl_3$) δ −75.4 (s); HRMS (ESI) *m/z* 979.3826 [(M + Na)$^+$ calcd for $C_{52}H_{58}F_6O_{10}Na$, 979.3832].

General Procedure for the Reaction of 4b with Alcohols. A solution of **4b** (0.05 g, 0.043 mmol) in a mixture of 5 mL of TFE and 5 mL of the appropriate alcohol was refluxed for 18 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/acetonitrile.

*5,11,17,23-Tetra-tert-butyl-8,14,25,26,27,28-hexamethoxy-2,20-dioxocalix[4]arene (**7b**):* yield 25.2 mg (57%); mp 280−285 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 2.4 Hz, 2H), 7.71 (d, *J* = 2.6 Hz, 2H), 7.47 (s, 2H), 6.79 (s, 2H), 5.86 (s, 2H), 3.94 (s, 3H), 3.54 (s, 6H), 3.39 (s, 6H), 1.88 (s, 3H), 1.38 (s, 18H), 1.35 (s, 9H), 0.92 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 155.7, 154.6, 152.6, 147.2, 146.2, 144.4, 137.1, 135.8, 132.4, 132.3, 126.9, 126.7, 125.3, 125.0, 74.3, 63.2, 61.8, 59.0, 57.4, 34.8, 34.4, 34.1, 31.4, 31.3, 31.0; HRMS (ESI) *m/z* 793.4674 [(M + H)$^+$ calcd for $C_{50}H_{65}O_8$, 793.4679].

*5,11,17,23-Tetra-tert-butyl-8,14-diethoxy-25,26,27,28-tetramethoxy-2,20-dioxocalix[4]arene (**8b**):* yield 26 mg (56%); mp 240−245 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, *J* = 2.6 Hz, 2H), 7.70 (d, *J* = 2.6 Hz, 2H), 7.46 (s, 2H), 6.79 (s, 2H), 5.98 (s, 2H), 3.92 (s, 3H), 3.73−3.62 (m, 4H), 3.38 (s, 6H), 1.87 (s, 3H), 1.38 (s, 18H), 1.37−1.34 (m, 6H), 1.35 (s, 9H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.3, 155.7, 154.3, 152.5, 147.1, 146.1, 144.4, 137.7, 135.9, 132.7, 132.4, 126.9, 126.8, 125.20, 125.18, 72.1, 64.9, 63.2, 61.8, 59.0, 34.7, 34.4, 34.0, 31.4, 31.3, 31.0, 15.5; HRMS (ESI) *m/z* 821.4987 [(M + H)$^+$ calcd for $C_{52}H_{69}O_8$, 821.4992].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-2,20-dioxo-8,14-diisopropoxycalix[4]arene (**9b**):* yield 30 mg (63%); mp 230−235 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 2.6 Hz, 2H), 7.69 (d, *J* = 2.5 Hz, 2H), 7.47 (s, 2H), 6.81 (s, 2H), 6.17 (s, 2H), 3.92 (s, 3H), 3.80 (h, *J* = 6.1 Hz, 2H), 3.40 (s, 6H), 1.84 (s, 3H), 1.38 (s, 18H), 1.35 (d, *J* = 5.9 Hz, 6H), 1.35 (s, 9H), 1.30 (d, *J* = 6.0 Hz, 6H), 0.91 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.44, 155.70, 153.90, 152.44, 147.06, 145.93, 144.42, 138.05, 135.96, 132.80, 132.45, 127.23, 126.74, 125.51, 125.13, 69.19, 69.07, 63.40, 61.78, 58.99, 34.72, 34.40, 34.02, 31.43, 31.28, 30.96, 22.79, 21.83; HRMS (ESI) *m/z* 849.5300 [(M + H)$^+$ calcd for $C_{54}H_{73}O_8$, 849.5305].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-2,20-dioxo-8,14-bis-trifluoroethoxycalix[4]arene (**10b**):* yield 28 mg (55%); mp 255−260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 2.5 Hz, 2H), 7.72 (d, *J* = 2.5 Hz, 2H), 7.53 (s, 2H), 6.89 (s, 2H), 6.20 (s, 2H), 4.13−3.91 (m, 4H), 3.91 (s, 3H), 3.37 (s, 6H), 2.01 (s, 3H), 1.37 (s, 18H), 1.35 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.9, 155.5, 154.4, 153.1, 147.5, 146.6, 144.9, 135.6, 135.4, 132.6, 131.2, 127.7, 126.2, 125.9, 125.7, 124.1 (q, *J* = 279.2 Hz), 73.6, 66.3 (q, *J* = 34.2 Hz), 63.6, 62.0, 60.0, 34.7, 34.4, 34.1, 31.4, 31.3, 30.9; ^{19}F NMR (471 MHz, $CDCl_3$) δ −73.4 (t, *J* = 8.6 Hz); HRMS (ESI) *m/z* 929.4422 [(M + H)$^+$ calcd for $C_{52}H_{63}F_6O_8$, 929.4427].

*8,14-Diacetoxy-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxy-2,20-dioxocalix[4]arene (**12b**):* yield 32 mg (67%); mp 290−295 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (dd, *J* = 2.5, 0.5 Hz, 2H), 7.72 (d, *J* = 2.5 Hz, 2H), 7.49 (s, 2H), 7.46 (s, 2H), 6.89 (s, 2H), 3.91 (s, 3H), 3.48 (s, 6H), 2.25 (s, 6H), 1.99 (s, 3H), 1.37 (s, 18H), 1.35 (s, 9H), 0.96 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.0, 170.0, 155.1, 154.1, 152.6, 147.1, 146.0, 144.8, 136.2, 135.6, 132.6, 131.1, 127.1, 126.3, 125.7, 125.5, 67.0, 63.8, 62.0, 59.3, 34.7, 34.4, 34.1, 31.4, 31.3, 31.0, 21.3; HRMS (ESI) *m/z* 871.4392 [(M + Na)$^+$ calcd for $C_{52}H_{64}O_{10}Na$, 871.4397].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-2,20-dioxo-8,14-bis-trifluoroacetoxycalix[4]arene (**13b**):* yield 33 mg (63%); mp 275−280 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, *J* = 2.5 Hz, 2H), 7.75 (d, *J* = 2.5 Hz, 2H), 7.58 (s, 2H), 7.55 (s, 2H), 7.01 (s, 2H), 3.96 (s, 3H), 3.47 (s, 6H), 2.19 (s, 3H), 1.36 (s, 9H), 1.35 (s, 18H), 0.99 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 195.4, 156.6 (q, *J* = 42.7 Hz), 154.8, 154.0, 153.6, 147.6, 147.1, 145.4, 135.1, 133.8, 132.7, 129.5, 128.4, 126.6, 126.5, 124.8, 114.7 (q, *J* = 285.7 Hz), 71.0, 64.0, 62.2, 60.4, 34.7, 34.5, 34.2, 31.2, 30.8; ^{19}F NMR (471 MHz, $CDCl_3$) δ −75.1 (s); HRMS (ESI) *m/z* 957.4007 [(M + H)$^+$ calcd for $C_{52}H_{59}F_6O_{10}$, 957.4012].

*2,14-Diazido-5,11,17,23-tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxocalix[4]arene (**14**).* A mixture of **4a** (0.10 g, 0.11 mmol), sodium azide (0.153 g, 2.35 mmol), and 10 mL of TFE was heated at reflux for 18 h. After evaporation of the solvent, the residue was treated with 25 mL of $CHCl_3$ and the unreacted NaN_3 was removed by filtration. The filtrate was evaporated, and the residue was recrystallized from $CHCl_3$/MeOH to give 38 mg (28%) of **14**: mp 278−283 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 2.5 Hz, 4H), 7.60 (d, *J* = 2.5 Hz, 4H), 6.12 (s, 2H), 3.19 (s, 12H), 1.36 (s, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 154.6, 146.6, 134.0, 132.5, 127.4, 125.8, 62.8, 55.7, 34.6, 31.3; HRMS (ESI) *m/z* 837.4310 [(M + Na)$^+$ calcd for $C_{48}H_{58}N_6O_6$Na, 837.4316].

General Procedure for the Reaction of 4a with Arenes. A solution of **4a** (0.1 g, 0.11 mmol) in a mixture of 1 mL of TFA and 0.1 mL of the appropriate arene was refluxed for 18 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/MeOH or $CHCl_3$/acetonitrile.

*5,11,17,23-Tetra-tert-butyl-2,14-bis(p-tert-butylphenyl)-25,26,27,28-tetramethoxy-8,20-dioxocalix[4]arene (**15**):* yield 82.7 mg (74%); mp 370−375 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.5 Hz, 4H), 7.37 (d, *J* = 2.5 Hz, 4H), 7.25 (d, *J* = 8.2 Hz, 4H), 7.00 (d, *J* = 8.2 Hz, 4H), 6.00 (s, 2H), 3.18 (s, 12H), 1.30 (s, 18H), 1.28 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.8, 155.7, 148.6, 145.5, 140.7, 136.5, 134.5, 130.5, 128.5, 124.9, 123.9, 62.5, 39.6, 34.4, 34.3, 31.3; HRMS (ESI) *m/z* 1019.6160 [(M + Na)$^+$ calcd for $C_{68}H_{84}O_6Na$, 1019.6166].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxo-2,14-di(p-tolyl)calix[4]arene (**16**):* yield 60 mg (59%); mp 360−365 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.5 Hz, 4H), 7.34 (d, *J* = 2.5 Hz, 4H), 7.06 (d, *J* = 8.1 Hz, 4H), 6.98 (d, *J* = 8.0 Hz, 4H), 5.99 (s, 2H), 3.17 (s, 12H), 2.32 (s, 6H), 1.27 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 199.7, 155.7, 145.6, 140.8, 136.5, 135.3, 134.5, 130.4, 128.8, 123.9, 62.4, 39.7, 34.4, 31.3, 20.9; HRMS (ESI) *m/z* 913.5402 [(M + H)$^+$ calcd for $C_{62}H_{73}O_6$, 913.5407].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxo-2,14-bis(m-xylyl)calix[4]arene (**17**):* yield 44.3 mg (42%); mp 330−335 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J* = 2.5 Hz, 4H), 7.15 (d, *J* = 2.5 Hz, 4H), 7.09 (d, *J* = 8.4 Hz, 2H), 6.94 (d, *J* = 5.4 Hz, 4H), 5.99 (s, 2H), 3.14 (s, 12H), 2.29 (s, 6H), 1.96 (s, 6H), 1.24 (s, 36H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.7, 154.8, 144.9, 137.4, 136.4, 135.72, 135.65, 134.2, 131.7, 130.2, 128.5, 126.2, 124.2, 62.2, 38.5, 34.3, 31.3, 20.8, 20.7; HRMS (ESI) *m/z* 963.5534 [(M + Na)$^+$ calcd for $C_{64}H_{76}O_6Na$, 963.5540].

*5,11,17,23-Tetra-tert-butyl-2,14-dimesityl-25,26,27,28-tetramethoxy-8,20-dioxocalix[4]arene (**18**):* yield 77 mg (71%); mp 305−310 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 2.5 Hz, 2H), 7.49 (d, *J* = 2.6 Hz, 2H), 7.06 (m, 4H), 6.80 (s, 2H), 6.79 (s, 2H), 5.98 (s, 2H), 3.22 (s, 6H), 2.86 (s, 6H), 2.26 (s, 6H), 2.14 (s, 6H), 1.79 (s, 6H), 1.19 (s, 18H), 1.12 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.9, 156.9, 156.4, 145.4, 144.4, 139.4, 136.7, 136.5, 136.4, 135.6, 135.0, 134.5,

132.2, 131.3, 130.8, 130.0, 129.3, 125.8, 125.0, 62.4, 61.7, 44.2, 34.22, 34.15, 31.3, 31.2, 22.4, 21.7, 20.8; HRMS (ESI) m/z 991.5847 [$(M + Na)^+$ calcd for $C_{66}H_{80}O_6Na$, 991.5853].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-2,14-bis-(2-methylfuranyl)-8,20-dioxocalix[4]arene (**19**).* A solution of **4a** (0.1 g, 0.11 mmol) in a mixture of 10 mL of TFE and 1 mL of 2-methylfuran was refluxed for 18 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/MeOH: yield 37 mg (37%); mp 260−265 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (d, J = 2.6 Hz, 2H), 7.36 (d, J = 2.5 Hz, 2H), 7.35 (d, J = 2.6 Hz, 2H), 6.83 (d, J = 2.5 Hz, 2H), 5.87 (dd, J = 2.9, 1.0 Hz, 2H), 5.62 (d, J = 2.6 Hz, 2H), 5.38 (s, 2H), 2.98 (s, 6H), 2.92 (s, 6H), 2.24 (s, 6H), 1.30 (s, 18H), 1.17 (s, 18H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 200.2, 156.2, 155.2, 154.4, 151.3, 146.2, 144.4, 136.3, 134.6, 134.5, 133.2, 132.4, 129.1, 125.6, 123.9, 109.9, 106.0, 62.8, 61.6, 44.9, 34.4, 34.2, 31.4, 31.1, 13.5; HRMS (ESI) m/z 915.4806 [$(M + Na)^+$ calcd for $C_{58}H_{68}O_8Na$, 915.4812].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-8,20-dioxo-2,14-bis-(2,4-pentanedione-3-yl)calix-[4]arene (**20**).* A solution of **4a** (0.1 g, 0.12 mmol) in a mixture of 1 mL of TFA and 0.1 mL of 2,4-pentanedione was refluxed for 18 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/ MeOH yielding 41.7 mg of **20** (40%): mp 360−365 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 2.4 Hz, 4H), 7.50 (d, J = 2.5 Hz, 4H), 5.39 (d, J = 12.8 Hz, 2H), 4.91 (d, J = 12.7 Hz, 2H), 3.22 (s, 12H), 1.98 (s, 12H), 1.35 (s, 36H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 202.4, 198.8, 155.7, 145.8, 134.1, 133.5, 127.2, 124.9, 73.9, 62.2, 35.4, 34.5, 31.3, 30.4; HRMS (ESI) m/z 951.5018 [$(M + Na)^+$ calcd for $C_{58}H_{72}O_{10}Na$, 951.5023].

General Procedure for the Reaction of 4b with Arenes. A solution of **4b** (0.1 g, 0.11 mmol) in a mixture of 1 mL of TFA and 0.1 mL of the appropriate aryl was refluxed for 18 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/acetonitrile.

*5,11,17,23-Tetra-tert-butyl-8,14-bis-tert-butylphenyl-25,26,27,28-tetramethoxy-2,20-dioxocalix[4]arene (**21**):* yield 27.2 mg (24%); mp 350−355 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.68 (d, J = 2.6 Hz, 2H), 7.48 (s, 2H), 7.37 (d, J = 8.5 Hz, 4H), 7.30 (d, J = 8.1 Hz, 4H), 7.28 (d, J = 2.5 Hz, 2H), 6.65 (s, 2H), 6.24 (s, 2H), 3.51 (s, 6H), 3.41 (s, 3H), 1.97 (s, 3H), 1.37 (s, 9H), 1.35 (s, 18H), 1.23 (s, 18H), 0.93 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.8, 157.2, 156.0, 152.4, 149.0, 146.6, 144.7, 144.3, 141.1, 139.0, 136.1, 133.0, 132.3, 130.9, 128.9, 126.49, 125.46, 125.1, 124.5, 63.1, 62.2, 59.4, 42.3, 34.6, 34.4, 34.0, 31.4, 31.32, 31.28, 31.1; HRMS (ESI) m/z 997.6341 [$(M + H)^+$ calcd for $C_{68}H_{85}O_6$, 997.6346].

*5,11,17,23-Tetra-tert-butyl-25,26,27,28-tetramethoxy-2,20-dioxo-8,14-di-m-xylylcalix[4]arene (**22**):* yield 71.8 mg (68%); mp 280−285 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, J = 2.6 Hz, 2H), 7.48 (s, 2H), 7.36 (d, J = 7.9 Hz, 2H), 7.06 (d, J = 2.6 Hz, 2H), 7.05 (s, 2H), 7.02 (d, J = 7.6 Hz, 2H), 6.56 (s, 2H), 6.23 (s, 2H), 3.53 (s, 6H), 3.22 (s, 3H), 2.34 (s, 6H), 2.24 (s, 3H), 2.21 (s, 6H), 1.36 (s, 9H), 1.21 (s, 18H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 196.7, 157.2, 155.7, 152.8, 146.5, 144.1, 144.0, 140.4, 136.6, 136.5, 135.87, 135.86, 133.0, 132.0, 131.7, 129.5, 129.1, 127.7, 126.5, 126.4, 124.4, 62.5, 61.6, 60.2, 40.6, 34.5, 34.4, 33.9, 31.30, 31.25, 31.1, 20.90, 20.87; HRMS (ESI) m/z 963.5534 [$(M + Na)^+$ calcd for $C_{64}H_{76}O_6Na$, 963.5540].

*5,11,17,23-Tetra-tert-butyl-8,14-dimesityl-25,26,27,28-trimethoxy-2,20-dioxocalix[4]arene (cis) (**23a**).* A solution of **4b** (0.1 g, 0.11 mmol) in a mixture of 1 mL of HIFP and 0.5 mL of mesitylene was refluxed for 18 h. The solvent was evaporated and the residue recrystallized from $CHCl_3$/acetonitrile yielding 35.3 mg of **23a** (30%): mp 300−305 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (s, 2H), 7.27 (d, J = 2.5 Hz, 2H), 6.94 (d, J = 2.3 Hz, 2H), 6.81 (s, 4H), 6.65 (s, 2H), 5.93 (s, 2H), 3.90 (s, 1H), 3.44 (s, 6H), 2.81 (s, 3H), 2.27 (s, 6H), 2.15 (broad s, 6H), 1.91 (broad s, 6H), 1.42 (s, 9H), 1.08 (s, 18H), 0.98 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.6, 156.8, 155.1, 149.9, 147.8, 145.8, 143.0, 139.4, 138.0, 135.4, 135.3, 134.2, 134.1, 134.0, 131.6, 131.4, 130.5, 130.3, 128.9, 125.7, 123.4, 64.1, 61.9, 44.5, 34.8, 34.2, 33.5, 31.31, 31.25, 31.1, 21.3, 21.2, 20.8; HRMS (ESI) m/z 955.5885 [$(M + H)^+$ calcd for $C_{65}H_{79}O_6$, 955.5877].

*5,11,17,23-Tetra-tert-butyl-8,14-dimesityl-25,26,27,28-trimethoxy-2,20-dioxocalix[4]arene (trans) (**23b**):* yield 24.5; mg (23%); mp 250−255 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 2.7 Hz, 1H), 7.77 (d, J = 2.7 Hz, 1H), 7.72 (d, J = 2.5 Hz, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.08 (d, J = 2.4 Hz, 1H), 7.04 (d, J = 2.3 Hz, 1H), 6.86 (s, 1H), 6.82 (s, 1H), 6.79 (s, 1H), 6.78 (s, 1H), 6.66 (d, J = 2.3 Hz, 1H), 6.54 (d, J = 2.3 Hz, 1H), 6.03 (s, 1H), 5.96 (s, 1H), 4.05 (s, 1H), 3.30 (s, 3H), 3.01 (s, 3H), 2.75 (s, 3H), 2.27 (s, 9H), 2.08 (s, 3H), 1.92 (s, 3H), 1.78 (s, 3H), 1.39 (s, 9H), 1.16 (s, 9H), 1.12 (s, 9H), 0.94 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 197.0, 194.7, 157.1, 156.3, 155.1, 151.6, 146.8, 146.7, 145.9, 143.7, 139.2, 138.8, 138.1, 137.0, 136.8, 136.7, 136.3, 135.7, 135.5, 135.4, 135.3, 134.0, 133.5, 132.5, 132.0, 131.9, 131.2, 130.9, 130.8, 130.7, 130.6, 130.4, 129.1, 129.0, 125.1, 125.0, 124.3, 123.2, 63.6, 61.3, 61.0, 45.2, 44.6, 34.6, 34.5, 34.1, 33.8, 31.25, 31.22, 31.19, 31.1, 22.3, 21.5, 20.8, 20.7, 20.4; HRMS (ESI) m/z 955.5871 [$(M + H)^+$ calcd for $C_{65}H_{79}O_6$, 955.5877].

*5,11,17,23-Tetra-tert-butyl-2,20-dihydroxy-8,14-dimesityl-25,26,27,28-tetramethoxy-2,20-diphenylcalix[4]arene (**24**).* To a solution of 0.1 g (0.1 mmol) **18** in 10 mL of dry benzene at rt was added PhLi (1.5 mL 2.0 M in dibutyl ether, 3 mmol), and the mixture was stirred under an inert atmosphere for 2 h at rt. After quenching with dilute aq HCl and extraction with methylene chloride, the organic phase was evaporated. The residue was treated with a small amount of acetone, and the solid that crystallized was separated by filtration to afford 50.7 mg (44%) of **24** which was essentially pure according to ^{1}H NMR analysis. The compound was recrystallized from chloroform/acetone: mp 320−325 °C dec; ^{1}H NMR (500 MHz, CD_2Cl_2, 303 K) δ 7.73 (d, J = 7.9 Hz, 1H), 7.57 (d, J = 7.5 Hz, 2H), 7.42 (s, 1H), 7.41−7.32 (m, 4H), 7.25−7.18 (m, 2H), 7.08 (d, J = 2.2 Hz, 1H), 6.96 (s, 2H), 6.88 (s, 2H), 6.83 (d, J = 3.9 Hz, 2H), 6.81 (d, J = 2.0 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 6.65 (d, J = 2.0 Hz, 2H), 6.62 (s, 1H), 6.51 (s, 1H), 6.33 (s, 1H), 6.25 (d, J = 2.2 Hz, 1H), 6.05 (s, 1H), 4.04 (s, 3H), 3.57 (s, 3H), 3.20 (s, 3H), 2.43 (s, 3H), 2.31 (s, 3H), 2.29 (s, 3H), 2.26 (s, 3H), 2.11 (s, 3H), 2.11 (s, 3H), 1.49 (s, 3H), 1.09 (s, 9H), 0.97 (s, 9H), 0.95 (s, 9H), 0.90 (s, 9H); ^{13}C NMR (126 MHz, CD_2Cl_2, 303 K) δ 157.1, 156.2, 154.4, 153.5, 151.6, 148.5, 145.9, 145.3, 143.6, 142.3, 141.49, 141.56, 141.2, 139.9, 139.6, 138.9, 138.6, 137.7, 136.8, 136.7, 136.2, 135.9, 135.8, 135.7, 135.6, 133.0, 132.7, 131.3, 131.0, 130.8, 130.4, 129.8, 129.6, 129.3, 129.0, 128.6, 128.4, 128.2, 128.0, 127.9, 127.4, 126.8, 126.4, 126.3, 125.0, 123.9, 87.1, 82.6, 63.3, 60.3, 60.2, 57.8, 48.1, 42.5, 34.5, 34.4, 34.2, 34.0, 31.5, 31.4, 31.1, 31.0, 26.2, 24.4, 22.3, 20.9, 20.8, 20.7; HRMS (ESI) m/z 1147.6774 [$(M + Na)^+$ calcd for $C_{78}H_{92}O_6Na$, 1147.6792].

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C spectra of compounds **3**−**24** and crystallographic data (CIF) for compounds **4a**, **7a**, **10a**, **9b**, **17**, **18**, **22**, **23b**, and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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