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NOTE

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Conformationally Restricted Calix[8]arenes Substituted at All Methylene Bridges

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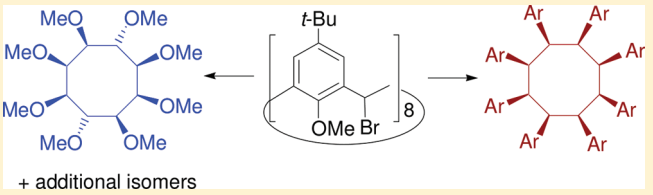
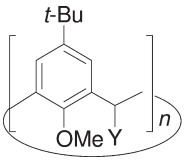
Supporting Information

ABSTRACT: Reaction under S_N1 conditions of the octabromocalix[8]arene derivative **2d** with alcohols proceeds in nonstereoselective fashion, but all-*cis* octaryl derivatives are the single major products in the reaction with arenes. The incorporation of aryl substituents at the bridges rigidifies the calix[8]arene skeleton.



The introduction of substituents at the methylene bridges of the calixarenes (**1**)[1,2] is of interest as a means to modify the properties of the calixarene scaffold, while keeping all the lower-rim binding groups intact. This structural modification can alter the intrinsic conformational preferences of the scaffold and increase the rigidity and preoganization of the calix macrocycle.[3] In this Note we report such structural modification in the notoriously conformationally flexible calix[8]arene scaffold.

Bromocalixarenes derivatives **2a**−**c**, readily available via photochemical bromination of the corresponding calixarene methyl ether derivatives **1a**−**c**,[4] are useful synthetic intermediates for the preparation of methylene-functionalized calixarenes.[5] Typically, the replacement of the bromine atoms by O-, N-, and C-nucleophiles is conducted under S_N1 conditions in an ionizing solvent such as TFE or hexafluoroisopropanol (HFIP).



a: $n = 4$, **b:** $n = 5$
c: $n = 6$, **d:** $n = 8$

1 Y = H
2 Y = Br

A calix[8]arene with eight bridges identically monofunctionalized possesses eight stereocenters, and 18 diastereomeric forms are possible arising from the possible *cis*/*trans* arrangements of the substituents. The 18 forms, their symmetry elements, and their point group symmetries are shown in Figure 1. Each form is characterized by a configurational descriptor describing in a sequential clockwise fashion the *cis* (*c*) or *trans* (*t*) relationship of the substituents relative to a reference substituent (*r*).[6]

It has been reported that photochemical bromination of octamethoxycalix[8]arene **1d** in CCl_4 with excess NBS (28 equiv) affords a single product.[4b] The simplicity of the NMR data reported is consistent with either the rc_7 (i.e, all-*cis*) or the *rtctctct* (i.e., all-*trans*) forms. However, in our hands the photochemical bromination using the experimental conditions yielded, as judged from ^{1}H NMR analysis, a mixture of products (Figure 2), none of them possessing the simple spectrum reported in the literature. Photochemical bromination using 8 equiv of NBS yielded a nearly identical mixture of products suggesting that the bromination of each bridge did not proceed beyond the monobromination stage. On this basis, the complex pattern of signals is ascribed to a mixture of stereoisomers of **2d**. Replacing the solvent in the bromination reaction by CH_2Cl_2 resulted in a nearly identical product composition.

The major component in the isomeric mixture (as judged by ^{1}H NMR) was isolated in nearly pure form by overnight trituration of the crude mixture with hot *i*-PrOH. The compound displayed in the ^{1}H NMR spectrum two *t*-Bu and two methoxy singlets, three singlets (in a 2:4:2 ratio) for the methine protons, and four doublets for the aromatic signals, a pattern consistent with C_{2v} symmetry. Assuming that the molecule is conformationally flexible on the NMR time scale at room temperature, this pattern is consistent with only one isomer out of the 18 isomeric forms, namely, the rt_3ct_3 form (in blue in Figure 1).

One of the components of the isomeric mixture (in magenta in Figure 2) displayed a relative simple signal pattern (two singlets for the aromatic protons, one singlet for the methine protons) consistent only with the $rct_2c_2t_2$ form of D_{2d} symmetry (in magenta in Figure 1). From the signal pattern of the isomer colored in green (two doublets and two singlets for the aromatic protons, two singlets for the methine protons), it could be deduced that this isomer possesses C_{2h} symmetry, but since two different isomers possess this symmetry (marked in green in Figure 1), only a partial configurational assignment could be made. The fourth isomer displayed an even complex pattern of signals (six doublets and two singlets for the aromatic protons and four singlets for the methine protons, shown in red in Figure 2). The signals pattern is consistent with a structure possessing either a C_2 axis or mirror plane bisecting a pair of opposite rings as the single symmetry element. The four isomeric forms with those symmetries are shown in red in Figure 1. The composition of the crude product consisted of about 31% of the rt_3ct_3 isomer, 9% of the $rct_2c_2t_2$ and 8% and 7% of two additional isomers of C_s (or C_2) and C_{2h} symmetry, respectively, and 45% of additional isomers. Although the spectrum of the crude product

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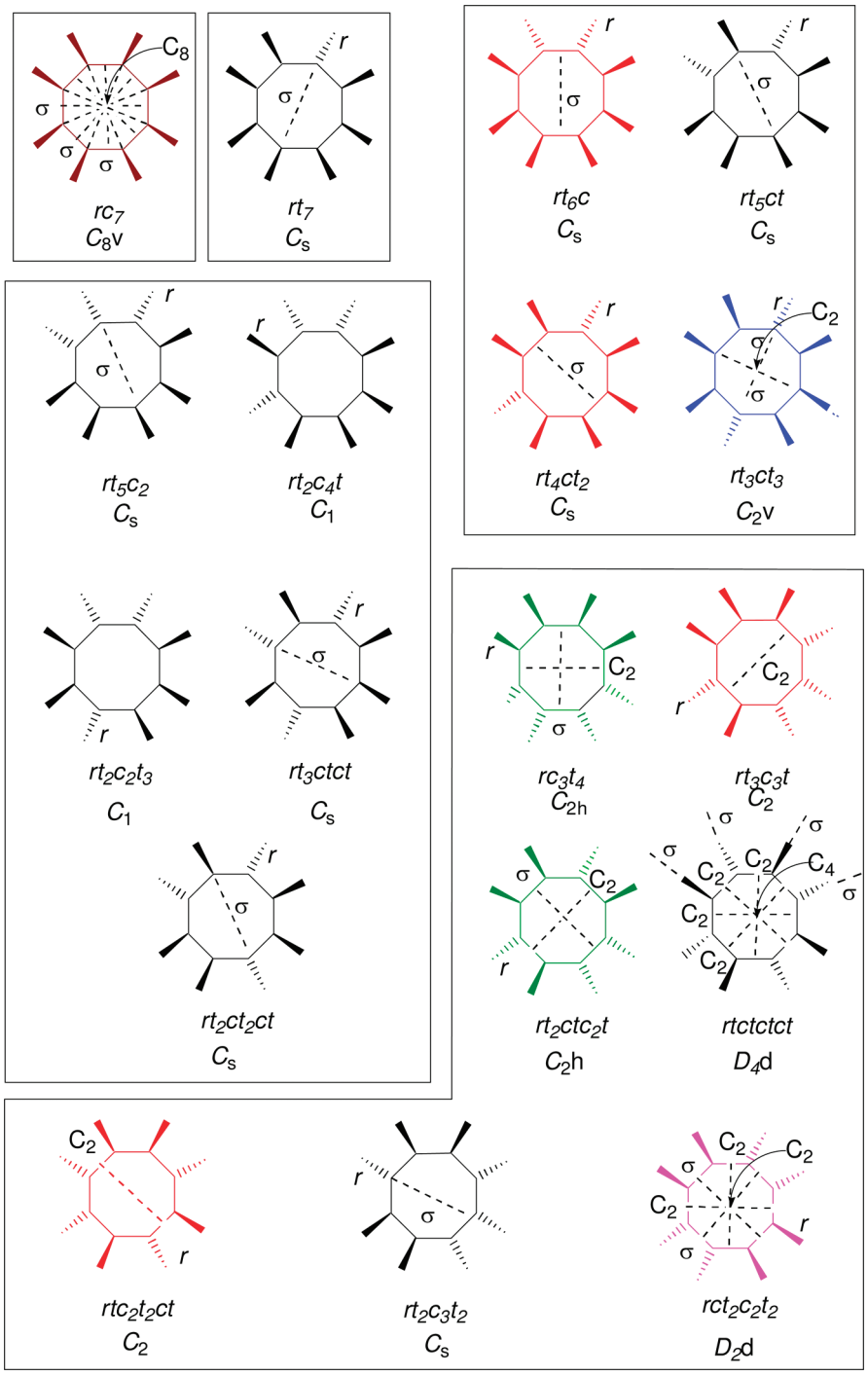

Figure 1. The 18 diastereomeric forms of a calix[8]arene possessing eight bridges identically monosubstituted. Assuming fast rotations of the rings, the macrocycle is represented by a planar regular octagon where each corner represents a monosubstituted bridge. Isomers are grouped according to the number of hashed wedged bonds (none, one, two, three, or four). For the chiral isomers only one enantiomer is shown.

(Figure 1) indicated a complex mixture, a "simpler" spectrum showing the nearly exclusive presence of the four isomers was obtained when the crude product was recrystallized from hexane (Figure S1, Supporting Information).[7]

Upon heating of a sample of **2d** (rt_3ct_3 isomer) in tetrachloroethane-d_2 to 348 K, an extensive isomerization was observed after 10 min, as judged by ^{1}H NMR spectroscopy (see Figure S2, Supporting Information). Further heating did not result in any appreciable change in the spectrum, suggesting that an equilibrium mixture has been reached. The equilibrium mixture at 348 K consisted of ca. 22% of the rt_3ct_3 form, ca. 8% of the $rct_2c_2t_2$ form, and additional isomers. Compound **2d** (rt_3ct_3 isomer) also slowly isomerizes upon standing in $CDCl_3$ solution at room temperature. Such behavior was not observed in the smaller bromocalixarenes analogues **2a**−**c**, suggesting that **2d** is substantially more reactive than its smaller analogues. The increased reactivity suggested by the relative ease by which **2d** undergoes isomerization (a process that involves heterolytic

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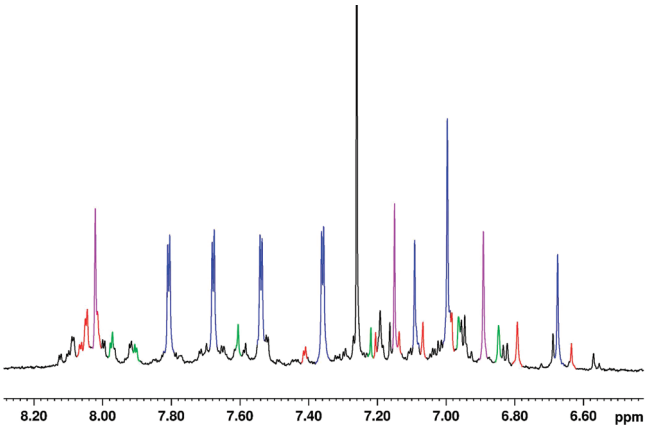
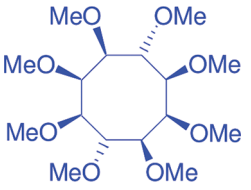


Figure 2. ^{1}H NMR spectrum (low-field region) of a mixture of octabromocalix[8]arene derivatives **2d** (crude mixture). Blue, rt_3ct_3 isomer; magenta, $rct_2c_2t_2$ isomer; green, isomer of C_{2h} symmetry, red, isomer of C_s or C_2 symmetry.

cleavage of the C−Br bonds) is probably a result of the larger conformationally flexibility of the calix[8]arene scaffold. This flexibility enables in the transition state a better orbital overlap of the two geminal aryl rings with the developing cationic orbital on the bridge, thus facilitating the C−Br bond cleavage.

3a R = Me
4 R = Et



3b

Heating overnight a heterogeneous mixture of the crude product obtained in the bromination of **2d** with MeOH in the presence of propylene oxide (a scavenger of HBr) yielded a complex mixture, but filtration of the solid that precipitated yielded a single isomer of the octamethoxy derivative.[8] This isomer displayed in the ^{1}H NMR spectrum a simple signal pattern (single singlets for the methine, methoxy group at the bridges, and pair of singlets for the *t*-Bu, aromatic protons, and lower rim methoxy groups). The isomer is ascribed to **3a** possessing the $rct_2c_2t_2$ configuration of D_{2d} symmetry. A second octamethoxy derivative was isolated after several recrystallizations of the filtrate from acetone. This isomer is ascribed to **3b** possessing the rt_3ct_3 configuration. The ^{1}H NMR spectrum of **3b** displayed two singlets each for the lower rim methoxy and *t*-Bu groups, three singlets for the methoxy groups at the bridges, three singlets for the methine protons, and four doublets for the aromatic signals. Since the configuration of **3b** is identical to the configuration of the major isomer obtained in the bromination and it is a major product (41%) in the crude mixture of octamethoxy isomers, we examined whether **3b** is formed via a stereospecific reaction of **2d** (rt_3ct_3). Due to the poor solubility in MeOH of pure **2d** (rt_3ct_3), the reaction was conducted in a mixture of $CHCl_3$/MeOH. Examination of the crude product showed a very complex mixture, essentially identical to the one obtained in the reaction of crude **2d** (i.e., a mixture of isomers) indicating that under the reaction conditions the reaction

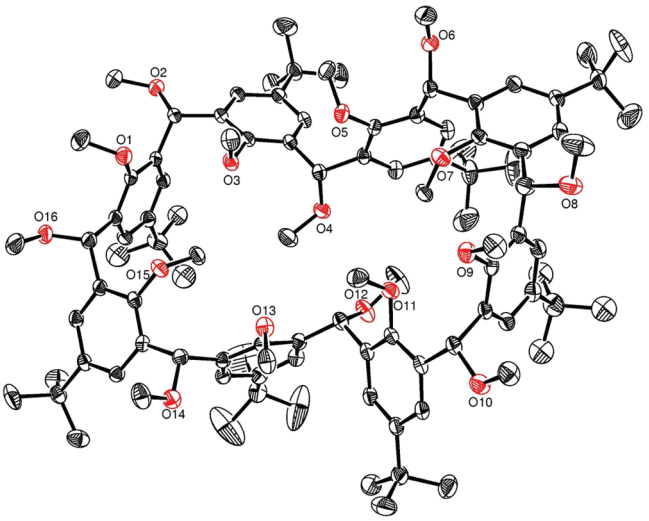
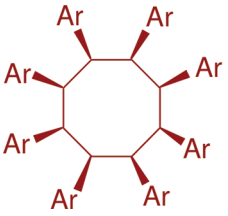


Figure 3. Crystal structure of the octamethoxycalix[8]arene **3b**.

proceeds in nonstereospecific fashion. No mutual interconversion was observed after heating to reflux a methanolic solution of **3a** or **3b** for 18 h, and therefore we conclude that the isomeric mixture was formed under kinetic control. Examination of the crude product of the reaction of **2d** (mixture of isomers) with EtOH indicated also the formation of a complex mixture of products, but small amounts of a single isomer could be obtained via slow recrystallization of the mixture. To this isomer is assigned the $rct_2c_2t_2$ configuration (**4**) on the basis of its ^{1}H NMR spectrum, which is remarkable similar to that of **3a**.

Crystallization of **3b** from acetone afforded a single crystal suitable for X-ray diffraction. The structural determination by X-ray diffraction confirmed the rt_3ct_3 configurational assignment (Figure 3). In contrast to the reported structure of the parent calix[8]arene **1d** (with unsubstituted bridges), which adopts a nearly square-shaped conformation of approximately C_{4v} symmetry,[9] **3b** adopts in the crystal a conformation of approximately C_2 symmetry with the two unique methoxy groups at the bridges (the pair of opposite groups in a *trans* relationship to the six methoxy groups in a *cis* arrangement) pointing toward the molecular cavity.

m-Xylyl groups were incorporated at the bridges of the calix scaffold by means of a solvolytic Friedel−Crafts reaction.[10] The reaction was conducted by heating to reflux the mixture of stereoisomers of **2d** and *m*-xylene in a mixture of $CHCl_3$ and HFIP. Although under analogous conditions the reaction also proceeds with *p*-xylene or mesitylene, replacement of the ionizing solvent (HFIP) by $AgClO_4$ afforded a cleaner product.[11] Starting from either pure **2d** (rt_3ct_3) or the isomeric mixture afforded in both cases in nearly stereoselective fashion a single major product, **6** or **7**, respectively.



5 Ar = 2,4-$Me_2C_6H_3$
6 Ar = 2,5-$Me_2C_6H_3$
7 Ar = 2,4,6-$Me_3C_6H_2$

Single crystals of **6** and **7** were obtained by slow evaporations of solutions in $CHCl_3$/acetonitrile and *p*-xylene, respectively. The X-ray structures of **6** and **7** indicate that the configuration of

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the stereocenters is rc_7 (i.e, all-*cis*, Figure S3, Supporting Information).[12] The crystal conformations of both molecules are very similar. Six anisole rings of the calix macrocycle are twisted relative to the mean macrocyclic plane while the two remaining rings (at 12 and 6 o'clock positions) are nearly parallel to that plane (Figure S3, Supporting Information). The pair of rings at 3 and 9 o'clock positions direct their *t*-Bu groups toward the center of the macrocycle. Ideally, this conformation possesses C_{2v} symmetry, with the two mutually perpendicular mirror planes bisecting pairs of opposite rings at 3 and 9 o'clock and at 12 and 6 o'clock positions. Pairs of geminal anisole rings are oriented *syn*, with the mesityl group located in an equatorial-like position of the bridge connected to the two rings. Notably, the three rings of a given triarylmethyl subunits are all twisted in the same sense relative to the plane defined by the three ipso carbons (a propeller conformation).[13]

Compounds **5**−**7** display in the ^{1}H NMR spectrum a signal pattern indicating that the calix macrocycle possesses three types of symmetry nonequivalent anisole rings (the aromatic protons of those rings appear as two singlets and a pair of doublets) and two types of symmetry nonequivalent aryl substituents at the bridges. In the case of **7**, pairs of *ortho* methyls appear as separate signals. The signal pattern at rt is consistent only with a single preferred conformation of C_{2v} symmetry, which is rigid at rt on the NMR time scale. Most likely, this rigid conformation corresponds to the conformation present in the crystal. Upon raising the temperature, signals coalesced and the spectrum became simpler. For example, the spectrum of **5** at 410 K (in tetrachloroethane-d_2) displayed only single average signals for the *t*-Bu, OMe, and methine protons (Figure S4, Supporting Information).

The preferred formation of all-*syn* products in the reaction of **2d** with arenes was previously observed also in the analogous reaction of the smaller bromocalixarenes **2a**−**c**. Although the possibility of transannular anchimeric assistance of the heterolytic cleavage of the C-Br groups cannot be ruled out (in particular in the large calix[8]arene macrocycle),[14] it may be possible that this stereoselectivity is connected to the conformational preferences of bulky substituents on the bridges to avoid axial or axial-like positions.

In summary, the reaction of octabromocalixarene **2d** with alcohols proceeds in nonstereoselective fashion. However, a single major product is obtained in the reaction with aromatic rings, thus providing a facile and convenient synthetic entry into conformationally restricted calix[8]arene systems.

EXPERIMENTAL SECTION

2,8,14,20,26,32,38,44-Octabromo-5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene (2d). A mixture of **1d** (2.00 g, 1.42 mmol), NBS (2.07 g, 11.41 mmol), and dichloromethane (100 mL) was stirred overnight at room temperature while being irradiated with a spotlight (100 W). Aqueous $NaHSO_3$ was added, and after phase separation the organic phase was washed with water, dried ($MgSO_4$), and evaporated. After treatment of the residue with 40 mL of hexanes, a mixture of octabromo calix[8]arene derivatives **2d** precipitated (1.97 g, 68%). Overnight trituration with 60 mL of 2-propanol and 0.5 mL of 1,2-epoxybutane yielded the rt_3ct_3 octabromo isomer in almost pure form (0.35 g, 12%). Mp 280 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, J = 2.3 Hz, 4H), 7.68 (d, J = 2.3 Hz, 4H), 7.54 (d, J = 2.3 Hz, 4H), 7.36 (d, J = 2.3 Hz, 4H), 7.09 (s, 2H), 7.00 (s, 4H), 6.67 (s, 2H), 3.91 (s, 12H), 3.38 (s, 12H), 1.25 (s, 36H), 1.19 (s, 36H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.8, 150.7, 147.2, 146.9, 134.7, 134.4, 133.7, 133.3, 128.5, 127.8, 127.6, 127.0, 61.7, 61.4, 42.9, 42.3, 42.1, 34.7, 34.6, 31.5, 31.3, 31.2 ppm. HRMS (ESI) m/z, 2042.2475 [$(M + H)^+$, calcd for $C_{96}H_{121}Br_8O_8$, 2042.2480].

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-2,8,14,20,26,32,38,44,49,50,51,52,53,54,55,56-hexadecamethoxycalix[8]arene ($rct_2c_2t_2$ Isomer 3a and rt_3ct_3 Isomer 3b). A mixture of 200 mg of **2d** (isomeric mixture), 20 mL of methanol, and 0.5 mL of 1,2-epoxybutane was heated to reflux overnight. The solid product was filtered to give 18 mg (11%) of the $rct_2c_2t_2$ isomer **3a**, mp 354−356 °C. Evaporation of the filtrate and repeated recrystallizations from acetone afforded the rt_3ct_3 isomer **3b** (53 mg, 33%), mp 340−342 °C (dec). $rct_2c_2t_2$ isomer (**3a**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 8H), 7.06 (s, 8H), 5.85 (s, 8H), 3.81 (s, 12H), 3.33 (s, 24H), 3.14 (s, 12H), 1.37 (s, 36H), 1.06 (s, 36H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 153.9, 146.4, 146.1, 133.7, 133.5, 125.5, 123.6, 74.4, 62.2, 60.7, 57.1, 34.6, 34.3, 31.6, 31.1 ppm. HRMS (ESI) m/z, 1673.0380 [$(M + Na)^+$, calcd for $C_{104}H_{144}NaO_{16}$, 1673.0386]. rt_3ct_3 isomer (**3b**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (d, J = 2.5 Hz, 4H), 7.30 (d, J = 2.6 Hz, 4H), 7.29 (d, J = 2.6 Hz, 4H), 6.92 (d, J = 2.4 Hz, 4H), 6.13 (s, 2H), 6.02 (s, 4H), 5.63 (s, 2H), 3.84 (s, 12H), 3.47 (s, 6H), 3.42 (s, 12H), 3.00 (s, 12H), 2.78 (s, 6H), 1.28 (s, 36H), 1.05 (s, 36H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ 154.5, 154.3, 146.5, 146.1, 134.0, 133.7, 133.4, 133.0, 125.1, 124.8, 124.2, 123.8, 73.9, 73.8, 73.2, 62.3, 61.1, 57.4, 56.0, 50.7, 34.6, 34.3, 31.4, 31.1. HRMS (ESI) m/z, 1673.0381 [$(M + Na)^+$, calcd for $C_{104}H_{144}NaO_{16}$, 1673.0386].

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-2,8,14,20,26,32,38,44-octaethoxy-49,50,51,52,53,54,55,56-octamethoxycalix-[8]arene (4). A mixture of 200 mg of **2d** (isomeric mixture), 20 mL of ethanol and 0.5 mL of 1,2-epoxybutane were heated to reflux overnight. After evaporation of the solvent, the residue was recrystallized from ethanol to give 23 mg (13%) of **4** ($rct_2c_2t_2$ isomer), mp 322−324 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 8H), 7.03 (s, 8H), 5.94 (s, 8H), 3.79 (s, 12H), 3.47 (m, 16H), 3.15 (s, 12H), 1.37 (s, 36H), 1.20 (t, J = 7.0 Hz, 24H), 1.04 (s, 36H) ppm.^{13}C NMR (126 MHz, $CDCl_3$) δ 154.9, 153.9, 146.1, 145.7, 134.3, 133.8, 125.7, 123.7, 72.7, 64.6, 62.1, 60.7, 34.6, 34.3, 31.6, 31.3, 31.1, 15.5 ppm. HRMS (ESI) m/z, 1785.1632 [$(M + Na)^+$, calcd for $C_{112}H_{160}NaO_{16}$, 1785.1638].

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octamethoxy-2,8,14,20,26,32,38,44-octakis-(2,4-dimethylphenyl)calix[8]arene (rc_7 isomer, 5). A mixture of **2d** (isomeric mixture, 0.10 g, 0.049 mmol), 8 mL of chloroform, 2 mL of HFIP, and 1 mL of *m*-xylene was refluxed overnight. After evaporation of the solvents, the residue was recrystallized from $CHCl_3$/MeOH to yield 25 mg (23%) of **5**, mp 300 °C (dec). ^{1}H NMR (500 MHz, $C_2D_2Cl_4$) δ 7.00 (d, J = 2.1 Hz, 4H), 6.95 (s, 4H), 6.88 (overlapping peaks, 16H), 6.81 (d, J = 8.2 Hz, 4H), 6.74 (d, J = 8.0 Hz, 4H), 6.67 (s, 4H), 6.35 (d, J = 7.9 Hz, 4H), 6.31 (s, 4H), 6.13 (s, 4H), 3.34 (s, 12H), 3.00 (s, 6H), 2.71 (s, 6H), 2.28 (s, 12H), 2.25 (s, 12H), 2.03 (s, 12H), 2.02 (s, 12H), 1.05 (s, 36H), 1.00 (s, 18H), 0.82 (s, 18H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.0, 153.8, 145.8, 145.4, 144.6, 141.10, 140.7, 137.8, 136.5, 136.3, 136.2, 135.7, 135.0, 133.8, 131.2, 131.1, 129.9, 128.1, 127.2, 127.0, 126.4, 126.0, 126.0, 125.8, 125.0, 101.5, 60.5, 60.4, 59.8, 40.9, 39.8, 34.3, 34.2, 34.1, 31.3, 31.2, 31.1, 21.0, 20.9, 19.4, 19.2 ppm. HRMS (ESI) m/z, 2265.4543 [$(M + Na)^+$, calcd for $C_{160}H_{192}NaO_8$, 2265.4548].

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octamethoxy-2,8,14,20,26,32,38,44-octakis-(2,5-dimethylphenyl)calix[8]arene (rc_7 isomer, 6). A suspension of **2d** (isomeric mixture, 0.20 g, 0.10 mmol) and $AgClO_4$ (0.17 g, 0.82 mmol) in 3 mL of *p*-xylene was stirred in the dark for 30 min at 0 °C. The reaction was quenched by adding water (20 mL) and CH_2Cl_2 (20 mL). The AgBr was filtered, and the organic phase was washed twice with water, dried ($MgSO_4$), and evaporated. The crude product was

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recrystallized from $CHCl_3$/acetonitrile, giving 56 mg of **6** (25%), mp 305 °C (dec). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.01 (s, 8H), 6.96 − 6.82 (overlapping signals, 20H), 6.74 (s, 4H), 6.63 (s, 4H), 6.34 (s, 4H), 6.29 (s, 4H), 6.16 (s, 4H), 3.33 (s, 12H), 2.76 (s, 6H), 2.73 (s, 6H), 2.18 (s, 12H), 2.14 (s, 12H), 2.04 (s, 12H), 1.96 (s, 12H), 1.07 (s, 36H), 1.01 (s, 18H), 0.87 (s, 18H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 154.1, 153.9, 153.5, 145.9, 145.6, 144.8, 143.8, 143.7, 136.5, 136.3, 134.7, 134.2, 134.0, 133.8, 133.7, 133.0, 130.1, 129.3, 129.2, 128.9, 128.0, 126.9, 126.6, 126.4, 126.1, 125.1, 60.4, 60.1, 59.7, 41.3, 40.4, 34.3, 34.2, 34.1, 31.3, 31.2, 31.0, 21.2, 21.1, 18.82, 18.78 ppm. HRMS (ESI) *m*/*z*, 2243.4724 [$(M + H)^+$, calcd for $C_{160}H_{193}O_8$, 2243.4729].

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-49,50,51,52,53,54,55,56-octamethoxy-2,8,14,20,26,32,38,44-octakis-(2,4,6-trimethylphenyl)calix[8]arene (*rc*$_7$ isomer, 7). A suspension of **2d** (isomeric mixture, 0.40 g, 0.2 mmol) and $AgClO_4$ (0.5 g, 2.41 mmol) in 7 mL of mesitylene was stirred in dark for 30 min at 0 °C. The reaction was quenched by adding water (20 mL) and CH_2Cl_2 (20 mL). The AgBr was filtered, and the organic phase was washed twice with water, dried ($MgSO_4$), filtered, and evaporated. The residue was treated with 20 mL of cold acetone to yield 170 mg (36%) of the pure octamesityl derivative **7**, mp 312 °C (dec). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, J = 2.3 Hz, 4H), 7.18 (d, J = 2.4 Hz, 4H), 7.10 (s, 4H), 6.90 (s, 4H), 6.74 (s, 8H), 6.63 (s, 4H), 6.58 (s, 4H), 6.36 (s, 4H), 6.30 (s, 4H), 3.10 (s, 12H), 2.89 (s, 6H), 2.48 (s, 6H), 2.28 (s, 6H), 2.26 (s, 6H), 2.17 (s, 12H), 2.11 (s, 6H), 2.06 (s, 6H), 1.55 (s, 6H), 1.12 (s, 36H), 1.10 (s, 18H), 0.72 (s, 18H) ppm. ^{13}C NMR (126 MHz, $CDCl_3$) δ 155.6, 154.0, 153.5, 146.7, 145.4, 143.0, 138.58, 138.55, 138.2, 138.0, 137.7, 136.7, 136.1, 135.7, 135.3, 135.0, 134.7, 133.7, 131.2, 131.1, 129.6, 129.5, 128.3, 127.1, 126.0, 61.5, 60.1, 60.0, 41.4, 40.8, 34.3, 34.2, 33.8, 31.3, 31.2, 31.0, 24.3, 22.2, 21.1, 21.0, 20.7, 20.6 ppm. HRMS (ESI) *m*/*z*, 2377.5795 [$(M + H)^+$, calcd for $C_{168}H_{209}O_8$, 2377.5800].

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C spectra for **2d**, **3**−**7** and crystallographic information file (CIF) of **3b**, **6**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ REFERENCES

(1) For reviews on calixarenes see: (a) *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000. (b) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.,; Wiley: Chichester, 2003; Chapter 19. (c) Gutsche, C. D. *Calixarenes: An Introduction*; Royal Society of Chemistry: Cambridge, 2008.

(2) Several different approaches have been developed to synthesize calixarenes with a single, several, or all methylene bridges functionalized. See for example: (a) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741. (b) Tabatabai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (c) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667. (d) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (e) Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577. (f) Gopalsamuthiram, V.; Predeus, A. V.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 18018. (g) Gruber, T.; Gruner, M.; Fischer, C.; Seichter, W.; Bombicz, P.; Weber, E. *New J. Chem.* **2010**, *34*, 250.

(3) For selected examples of conformationally restricted calix[8]arenes, see: (a) Cunsolo, F.; Piatelli, M.; Neri, P. *J. Chem. Soc., Chem. Commun.* **1994**, 1917. (b) Mascal, M.; Naven, R. T.; Warmuth, R. *Tetrahedron Lett.* **1995**, *36*, 9361. (c) Arduini, A.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1995**, 879. (d) Cunsolo, F.; Consoli, G. M. L.; Piatelli, M.; Neri, P. *Tetrahedron Lett.* **1996**, *37*, 715. (e) Mascal, M.; Warmuth, R.; Naven, R. T.; Edwards, R. A.; Hursthouse, M. B.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3435. (f) Gloede, J.; Ozegowski, S.; Matt, D.; De Cian, A. *Tetraedron Lett.* **2001**, *42*, 9139. (g) Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2002**, *4*, 2649.

(4) (a) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967. (b) Kumar, S. K.; Chawla, H. M.; Varadarajan, R. *Tetrahedron Lett.* **2002**, *43*, 7073.

(5) (a) Columbus, I.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2927. (b) Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 2598. (c) Kogan, K.; Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 7327. (d) Kogan, K.; Biali, S. E. *J. Org. Chem.* **2009**, *74*, 7172. (e) Kogan, K.; Itzhak, N.; Biali, S. E. *Supramol. Chem.* **2010**, *22*, 704. (f) Kuno, L.; Biali, S. E. *J. Org. Chem.* **2011**, *76*, 3664.

(6) Each descriptor unambiguously characterizes each isomer. Several descriptors are possible for some structures, depending on the identity of the substituent chosen as reference and whether a clockwise or counterclockwise sequencing order is used. Arbitrarily, one of the more "compact" descriptors (e.g., rt_7, instead of rc_6t) is the one chosen for each structure. See ref 5c.

(7) This mixture consisted of 58% of the rt_3ct_3 isomer, 14% of the $rct_2c_2t_2$ form, and 16% and 12% of C_s (or C_2) and C_{2h} symmetry forms, respectively.

(8) For simplicity, we refer to **3a** and **3b** as octamethoxy derivatives, disregarding the eight additional methoxy groups at the lower rim.

(9) Bolte, M.; Brusko, V.; Böhmer, V. *J. Supramol. Chem.* **2002**, *2*, 57. A less symmetric conformation was found in the crystal structure of the *p*-Br derivative of **1d**. See:Baudry, R.; Felix, C.; Bavoux, C.; Perrin, M.; Vocanson, F.; Dumazet-Bonnamour, I.; Lamartine, R. *New J. Chem.* **2003**, *9*, 1540. Bolte, M.; Brusko, V.; Böhmer, V. *Acta Crystallogr.* **2003**, *E59*, 1691.

(10) Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew Chem., Int. Ed.* **2004**, *43*, 5402.

(11) For examples of silver-mediated substitutions in bromodienone calixarene derivatives, see: (a) Troisi, F.; Pierro, T.; Gaeta, C.; Neri, P. *Org. Lett.* **2009**, *11*, 697. (b) Troisi, F.; Pierro, T.; Gaeta, C.; Carratu, M.; Neri, P. *Tetrahedron Lett.* **2009**, *50*, 4436.

(12) The all-*cis* configuration of stereocenters may not be immediately obvious by inspection of the crystal conformation, but it is clearly visible in a molecular model once the rings of the macrocycle are rotated into a cone-like conformation (a process that does not affect the configuration of the stereocenters).

(13) Gust, D.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 1535.

(14) It has been experimentally demonstrated that the calix[8]arene scaffold is sufficiently large to allow for the formation of a transannular spiro C−O spiro bond. See: Gaeta, C.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 9155.