Spirodienone Route for the Stereoselective Methylene Functionalization of *p-tert*-Butylcalix[4]arene

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Abstract: A new method for the regio- and stereoselective functionalization of two distal methylene groups of *p-tert*-butylcalixarene (**1a**) is described. Reaction of the meso bis(spirodienone) calixarene derivative **2a** with bromine afforded the tetrabrominated product **3a** derived from exo 1,4-additions of bromine to the diene subunits. A phase-transfer-catalyzed reaction of **3a** with aqueous NaOH/CH_2Cl_2 yielded the exo bis(epoxide) calixarene derivative **4**. Heating **3a** in a vacuum eliminated two molecules of HBr and afforded a product (**5b**) that retained the C_i symmetry of the starting material. X-ray analysis indicated that the calixarene derivative **5b** possesses two exocyclic double bonds of *E* configuration. Calixarene **5b** undergoes reaction with nucleophiles at the exocyclic double bonds, with concomitant bond shifts and expulsion of the bromine atoms. Selective trans monodeuteration of two methylene groups of **1** was achieved by reaction of **5b** with $NaBD_4$ followed by aromatization of the labeled spirodienol derivative. Reaction of **5b** with RONa/ROH (R = Me, Et) afforded the methylene-substituted bis(spirodienone) derivatives **9a** and **9b** possessing two trans alkoxy groups. X-ray crystallography of **9b** indicated that the two trans substituents are located at pseudoequatorial positions of the methylene groups. $LiAlH_4$ reduction of the substituted bis(spirodienone) derivatives afforded calix[4]arenes incorporating trans alkoxy groups at two distal methylene positions.

Introduction

The calix[*n*]arenes have emerged as one of the most extensively studied synthetic hosts.[1,2] These synthetic organic macrocycles, readily available by base-catalyzed condensation of *p-tert*-butylphenol and formaldehyde,[3] are capable of including a smaller molecule or ion in their molecular cavity. Most of the synthetic work to date has been conducted on *p-tert*-butylcalix[4]arene (**1**), which is the smallest member of the series that is synthetically available. The parent **1** adopts in solution and in the solid state a cone conformation with a well-defined cavity.[1]

To alter the properties of the macrocycle, the calixarene scaffold usually has been modified by introduction of substituents at the intraannular ("lower rim") and/or extraannular ("upper rim") positions.[4] Two different approaches have been utilized for the modification of the calix skeleton.[1,2] The first approach (the "fragment condensation method") consists of the preparation of suitable linear oligomers or precursors with the desired functionalities, which in a second step are cyclized into a macrocyclic ring.[5,6] A second approach for calixarene functionalization uses a *p*-alkylcalix[*n*]arene as its starting material, thus avoiding the crucial cyclization step. Although this method is somewhat more limited than the fragment condensation method (since necessarily it rests on the chemistry of the phenol group), it has the great advantage that once a synthetic methodology is developed it can be in principle applied to the whole family of calix[*n*]arenes.

Direct functionalization of the methylene groups of a calixarene has been achieved only in a few cases.[6] CrO_3 oxidation of the methylene of the tetraacetate derivative of **1a** has been reported to afford a tetraketone derivative.[7] The methylene groups of derivatives of **1a** have been functionalized by radical bromination,[8] by the use of a homologous anionic ortho Fries rearrangement[9a] and very recently via lithiation.[9b] Here we describe a new approach for the distal methylene functionalization of **1a** based on a nucleophilic substitution reaction of a calixarene derivative containing two exocyclic double bonds.

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(1) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. Gutsche, C. D. *Aldrichim. Acta* **1995**, *28*, 1. Gutsche, C. D. *Calixarenes Revisited;* Royal Society of Chemistry: Cambridge, 1998.

(2) For very recent reviews on calixarenes, see: *Calixarenes 2001;* Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.

(3) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989,** *68*, 234. Gutsche, C. D.; Dhawan, B.; Leonis, M.; Stewart, D. *Org. Synth.* **1989**, *68*, 238, Munch, J. H.; Gutsche, C. D. *Org. Synth.* **1989**, *68*, 243.

(4) Very recently, the OH groups of a thiacalixarene have been replaced by amino groups. See: Katagiri, H.; Iki, N.; Hattori, T.; Kabuto, C.; Miyano, S. *J. Am. Chem. Soc.* **2001**, *123*, 779.

(5) For a review on the synthesis of calixarenes via the stepwise and fragment condensation methods, see: Böhmer, V. *Liebigs Ann./Recueil* **1997**, 2019.

(6) The fragment condensation method has been utilized for the preparation of calixarene derivatives carrying an alkyl or aryl group at one or two methylene bridges. See, for example: (a) Tabatai, M.; Vogt, W.; Böhmer, V. *Tetrahedron Lett.* **1990**, *31*, 3295. (b) Sartori, G.; Maggi, R.; Bigi, F.; Arduini, A.; Pastorio, A.; Porta, C. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1657. (c) Sartori, G., Bigi, F.; Porta, C.; Maggi, R.; Mora, R. *Tetrahedron Lett.* **1995**, *36*, 2311, (d) Grüttner, C.; Böhmer, V., Vogt, W.; Thondorf, I., Biali, S. E.; Grynszpan, F. *Tetrahedron Lett.* **1994**, *35*, 6267. (e) Biali, S. E.; Böhmer, V., Cohen, S.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I., Vogt, W. *J. Am. Chem. Soc.* **1996**, *118*, 12938. (f) Biali, S. E.; Böhmer, V., Columbus, I.; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2261.

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

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

(9) (a) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667. (b) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741.

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Results and Discussion

Spirodienone Calixarene Derivatives. Mild oxidation of **1a** with excess tetraalkylammonium tribromide salt in the presence of base affords a mixture of isomeric bis(spirodienone) calixarene derivatives.[10−13] The major isomer obtained in the oxidation step is the meso bis(spirodienone) derivative **2a**. X-ray diffraction indicated that **2a** possesses a heterochiral (*RS*) arrangement of the spiro stereocenters and an alternant disposition of the ether and carbonyl groups.[10a] Upon heating, the spirodienone derivatives mutually isomerize and equilibration studies have indicated that **2a** is the thermodynamically most stable isomer.[10a]

Several structural features make the spirodienone calixarene derivatives attractive intermediates for the preparation of selective functionalized calixarenes. The spirodienone calixarene derivatives possess two functional groups (the carbonyl and diene moieties) that potentially can undergo reactions with a large variety of reagents. Since the systems can be readily transformed back to calixarenes by reduction, their chemical modification provides a synthetic entry to modified calixarene derivatives.[11]

In principle nucleophilic or electrophilic addition to the diene subunits can occur via attack at one of their two diastereotopic faces. The faces located anti and syn to the spiro C−O bond can be denoted exo and endo, respectively. The endo face of the diene (located in the internal surface of the molecule) is the most sterically hindered. Diels−Alder reaction of benzyne with bis(spirodienone) calixarene derivatives has been shown to proceed via exo attack.[10a] The configuration of the new stereocenters formed by attack at the diene carbons can be unambiguously described by using the *R*/*S* stereochemical descriptors. However, to pictorially describe the location of the new substituents, they will be referred to as exo or endo if derived from the attack at the exo or endo faces of the diene functionalities, respectively.

Preparation of 2a. In our original report, bis(spirodienone) **2a** was separated from the mixture by column chromatography,[10a] but Huang and co-workers have shown that if a mixture of I_2/PEG 200/25% aqueous KOH is used as the oxidation reagent, this bis(spirodienone) derivative can be isolated from the mixture by crystallization.[10b] We have found a very convenient method for the isolation of **2a** based on the observation that upon heating, the spirodienone derivatives mutually isomerize and that **2a** is the derivative most stable thermodynamically.[10,14] When a mixture of **2a** and **2b** is heated *in the solid state* at 170 °C (below the melting point of **2a** and **2b**) for several hours mutual equilibration occurs, and a mixture consisting essentially (>95%) of **2a** is obtained.[15]

Bromination of the Bis(spirodienone) Derivative. For the preparation of a calixarene with exocyclic double bonds it was first necessary to obtain a brominated derivative of **2a**. A priori, it was not clear if bromination of **2a** can be carried out in regio- and stereoselective fashion and if a bromine atom can be introduced at a position α to the carbonyl group (necessary for the introduction of an exocyclic double bond in the following step). Reaction of **2a** with 2 equiv of bromine could afford, assuming that each diene subunit reacts with a single molecule of bromine, tetrabrominated derivatives derived from 1,2- and/or 1,4-additions to the diene functionalities.

Bromination of **2a** proceeds rapidly in CH_2Cl_2 solution at 0 °C and affords essentially a single product in high yield. The ^{1}H NMR spectrum of this product displayed a signal pattern similar to that of the starting material, with two signals for the *t*-Bu groups, four signals for the methylene, and two signals each for the aromatic and vinylic protons. As observed for the parent **2a**, pairs of protons within a given methylene group were anisochronous (diastereotopic) due to the presence of the spiro stereocenters. Notably, one aromatic proton signal in the product resonated in the ^{1}H NMR spectrum at δ 7.83 ppm. This downfield shift suggests that this proton is in steric proximity to a bromine atom. The number of signals observed in the ^{1}H and ^{13}C NMR spectra (see Experimental Section) indicates, assuming that the configuration of the spiro stereocenters were not affected by the bromination, that the C_i symmetry of the starting material was retained in the product. Since according to the NMR pattern no apparent reduction of symmetry had occurred, it can be concluded that both spirodienone subunits reacted with identical regio- and stereospecificity.

As previously observed with other spirodienone calixarene derivatives, a pair of protons on the same methylene group (identified by a DQF COSY spectrum) displayed in the NOESY spectrum NOE cross-peaks of similar intensities with a single aromatic proton. These signals are assigned to the methylene protons of a dihydrobenzofuran subunit and to the aromatic proton located ortho to them, respectively. These methylene groups are bisected by the aromatic ring of the dihydrobenzofuran, and due to the similar distances between each of the two methylene protons and the ortho aromatic proton, NOE cross-peaks of similar strengths are observed.[14] The methylene protons signals of the dihydrobenzofuran ring displayed an additional NOE cross-peak with the doublet resonating at δ 4.50 ppm (assigned to the proton of the CHBr group), while the vinylic proton displayed a NOE cross-peak with a bridging methylene signal. On the basis of the NOE interactions (summarized in Scheme 1), we assign to the product a tetrabrominated structure **3** resulting from a 1,4-addition to each of the diene subunits. Since the bromination creates four new stereocenters in the macrocycle, several stereoisomeric forms are possible for each regioisomer. The four stereoisomeric forms of C_i symmetry derived from a 1,4-addition to the diene groups are depicted in Figure 1.

Inspection of molecular models indicates that only the stereoisomers with the α-bromine atoms (cf. Scheme 1) derived from exo attack can rationalize the observed downfield shift of the aromatic protons, since only in this arrangement the bromine atom and an aromatic proton are in spatial proximity. The configuration of the stereocenter at the δ-position (i.e., with the bromine in an exo or endo position) could not be unambiguously deduced from the NOESY spectrum. However, X-ray diffraction

(10) (a) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993,** *58*, 8, 393. (b) Wang, W.-G.; Zhang, W.-C.; Huang, Z.-T. *J. Chem. Res. (S)* **1998**, 462.

(11) For reviews on spirodienone calixarene derivatives, see: Aleksiuk, O.; Grynszpan, F.; Litwak, M. A.; Biali, S. E. *New J. Chem.* **1996**, *20*, 473. For a review on the oxidation and reduction of calixarenes, see: Biali, S. E. In ref 1d, pp 266−279.

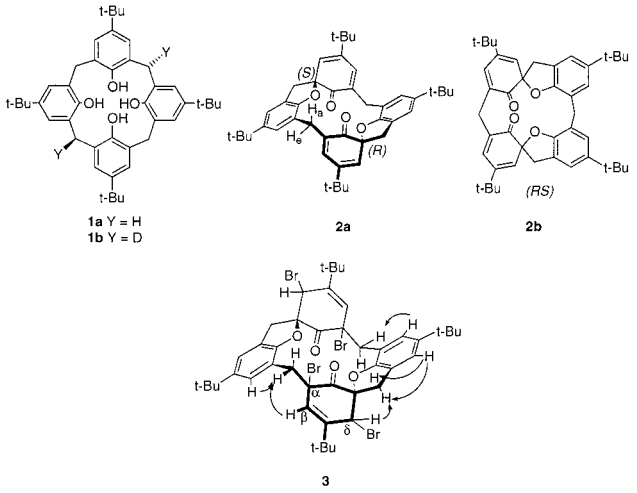
(12) For spirodienone derivatives of calixnaphthols, see: Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819. For an example of a spirodienone derivative of a dihydroxymetacyclophane, see: Yamato, T.; Matsumoto, T.; Sato, J. M.; Fujita, K.; Nagano, Y. *J. Chem. Res. (S)* **1997**, 74; *J. Chem. Res. (M)* **1997**, 518.

(13) Bicalix[*n*]arenes derivatives (n = 4, 6, 8) connected by a biphenyl-like bond at the para position of one ring are obtained by oxidation of calixarene derivatives with $FeCl_3 \cdot 6H_2O$ in refluxing acetonitrile. Neri, P.; Bottino, A.; Cunsolo, F.; Piatelli, M.; Gavuzzo, E. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 166. Bottino, A.; Cunsolo, F.; Piatelli, M.; Garozzo, D.; Neri, P. *J. Org. Chem.* **1999**, *64*, 8018.

(14) For another example of the solid-state isomerization of spirodienone derivatives, see: Agbaria, K.; Aleksiuk, O.; Biali, S. E.; Böhmer, V.; Frings, M.; Thondorf, I. *J. Org. Chem.* **2001**, *66*, 2891.

(15) Interestingly, in contrast to solution equilibration studies, even traces of the chiral stereoisomer of **2a** (i.e., the *RR*/*SS* form[10a]) could not be detected in the mixture obtained after the isomerization.

Scheme 1



analysis of the product of the bis(dehydrobromination) reaction of this compound (see below) indicates that the bromines at the δ-positions are located exo. On this basis, we assign to the isolated product a *SSR*−*RRS* disposition of stereocenters (i.e., isomer **3a** in Figure 1). This tetrabrominated product obtained is the one derived from a 1,4-all-exo-addition to the two diene subunits.

Bis(epoxide) Calixarene Derivative. To attempt the bis(dehydrobromination) reaction, **3a** was treated with aqueous $NaOH/CH_2Cl_2$ in the presence of a phase-transfer catalyst. However, under these reaction conditions the isolated product was the bis(epoxide) calixarene derivative **4** (Scheme 2). A single crystal of **4** was grown from $CH_3CN/CHCl_3$ and submitted to X-ray crystallography. The molecule retained the C_i symmetry of the original bis(spirodienone) derivative, with both epoxide groups located exo (Figure 2). The transformation **3a** → **4** can involve in its first step either a S_N1' or S_N2' type nucleophilic substitution comprising a double bond shift (an "allylic shift").[16] Arbitrarily, the formation of **4** in Scheme 2 is depicted via an S_N2'-type mechanism. It is highly likely that the OH attacks at the exo face of the double bond, since this is the face more sterically accessible. Formation of the epoxide is probably completed via an S_N1-type mechanism, involving

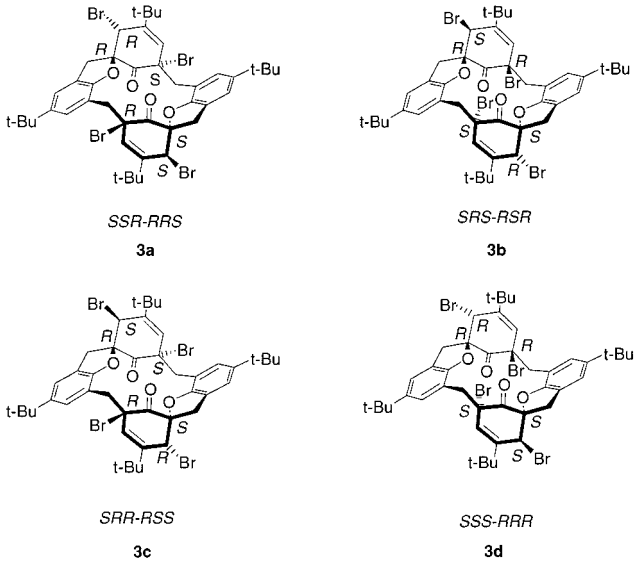


Figure 1. Four possible stereoisomers of C_i symmetry of a derivative resulting from a bis-1,4-addition of bromine to the meso bis(spirodienone) derivative **2a**.

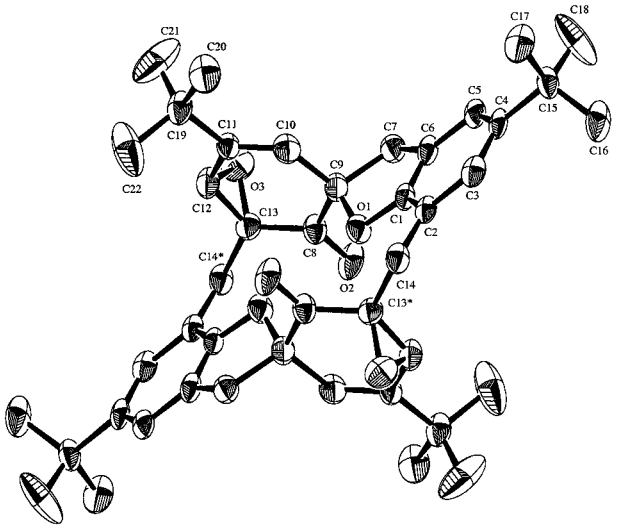
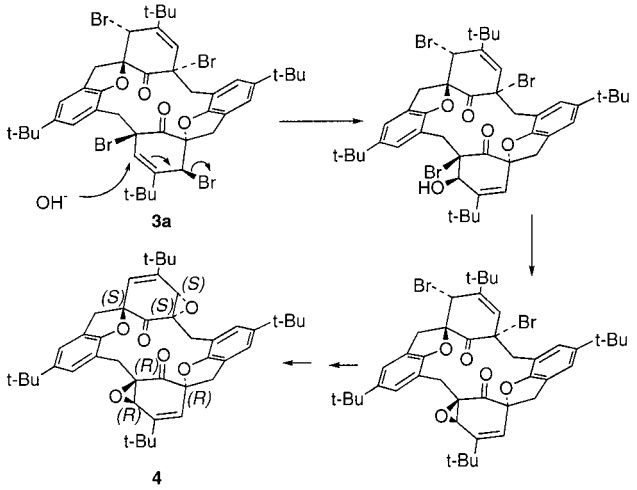


Figure 2. X-ray structure of the bis(epoxide) derivative **4**. The two epoxy groups are located exo.

Scheme 2



departure of the α-bromide of the bromohydrin,[17] followed by formation of the second C−O bond (Scheme 2).

Bisepoxide **4** could be a useful intermediate for the preparation of meta-substituted calixarenes, via reaction of the epoxide groups with strong nucleophiles.

Calixarene Derivative with Exocyclic Double Bonds. Since treatment of **3a** with aqueous NaOH failed to give the elimination product, we attempted next the thermal bis-dehydrobromination of **3a** in the absence of a base. Heating a sample of **3a** at 170 °C (below its melting point) under N_2 resulted in a major product with two exocyclic double bonds. This product displayed a ^1H and ^{13}C NMR pattern consistent with a compound retaining the original C_i symmetry of the starting material. A single crystal of the product was submitted to X-ray crystallography. Naively, we expected *Z* configurations of the double bonds (i.e., **5a**) since these seem the more natural ones when depicting the molecule in a planar representation (Scheme 3). However, the crystallographic analysis indicated that the double bonds possess *E* configurations (**5b**, Figure 3). The crystal data also indicated that **5b** possesses C_i symmetry and

(16) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley: Chichester; p 287.

(17) Carbocations can be generated at positions α to a carbonyl. See: Creary, X. *Chem. Rev.* **1991**, *91*, 1625. Creary, X.; Wang, Y.-X.; Jiang, Z. *J. Am. Chem. Soc.* **1995**, *117*, 3044.

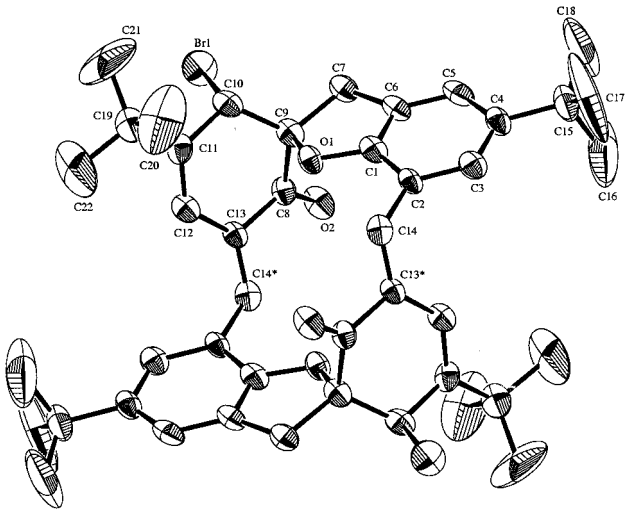
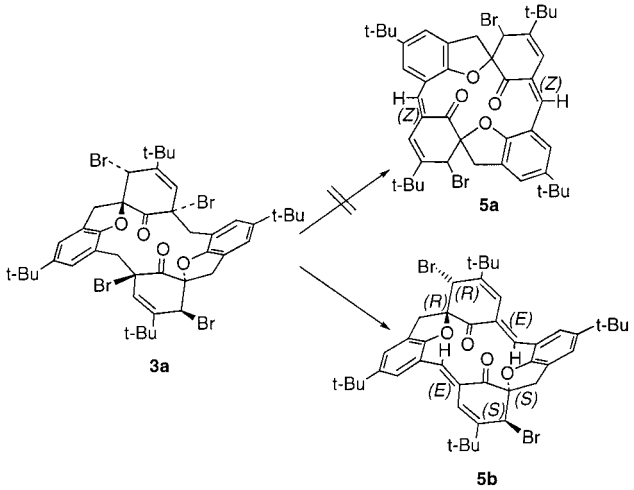


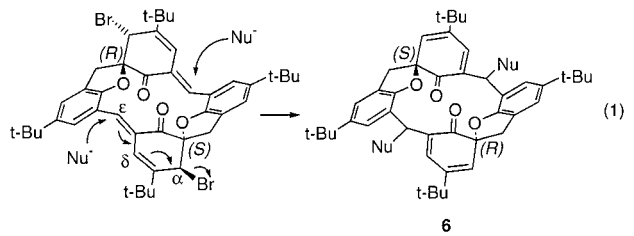
Figure 3. X-ray structure of **5b**. The two exocyclic double bonds possess an *E* configuration

Scheme 3



that the two symmetry-related δ-bromines are located exo (Figure 3). On this basis, and assuming that no epimerization took place in the elimination reaction, the configuration of the δ-carbons in the tetrabromo starting material is assigned as exo (i.e., **3a**).

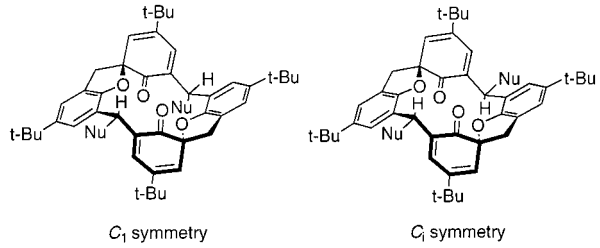
Relative Configuration of the Methylene Bridges. In principle, a nucleophilic substitution reaction of **5b** could proceed via attack at the bromine-containing carbons (α) or at the allylic (γ) or pentadienylic (ϵ) positions to the bromine. Since the bulky *tert*-butyl group sterically shields the α- and γ-positions, it could be possible that the attack at the ϵ-position (i.e., attack at the exocyclic double bonds) will be preferred. This process, when accompanied with a shift in double bonds and expulsion of the bromine leaving group, should yield methylene-substituted spirodienone derivatives (eq 1).[18]



(1)

The bonds to the spiro carbons are not cleaved during the reaction, and consequently the configurations of the two stereocenters must be retained in the product. Since these two stereocenters possess opposite configurations, the relative configuration of the substituted methylene bridges (i.e., the cis or trans disposition of the substituents) can be readily determined by examination of the NMR spectra of the substituted bis(spirodienone) derivative. If the two methylene substituents are located cis (i.e., with one substituent located in a pseudoaxial and one in pseudoequatorial position), the resulting systems should have C_1 symmetry (Scheme 4), rendering all rings and the two methylene groups symmetry nonequivalent. On the other hand, if the disposition of the methylene substituents is trans (with both substituents located in pseudoequatorial positions as shown in Scheme 4 or both located in pseudoaxial ones) the product retains the C_i symmetry of **5b**. In such a case pairs of symmetry related distal rings, methylene, and methine groups should be isochronous in the NMR spectrum in an achiral media. Thus, the assignment of the relative configuration (cis or trans) of the substituted methines can be made just by examination of the number of signals in the NMR spectra.

Scheme 4



Reduction of the carbonyl groups followed by aromatization of the spirodienol groups should yield calixarenes substituted at two distal methylene groups. The cis or trans disposition of the substituents in the methylene bridges of the substituted calixarenes should be identical to those of the disubstituted bis(spirodienone) calixarene starting material, since the bonds to the methine carbons are not involved in the reactions.[19]

Reaction of 5b with Metal Hydrides. To test the feasibility of the proposed synthetic scheme, we examined first the reaction of the spiroalkene **5b** with metallic hydrides. Reaction of **5b** with $NaBH_4$ afforded the bis(spirodienol) derivative **7a** previously obtained by $NaBH_4$ reduction of the bis(spirodienone) derivative **2a** and fully characterized spectroscopically.[20] The formation of **7a** indicates that an attack at the exocyclic double bond, double bond shifts, and displacement of the bromine had occurred. However, in addition, the carbonyl groups were reduced by the metal hydride. A less reactive reagent could attack selectively the exocyclic double bonds of **5b** without reducing the carbonyl groups. Indeed, reaction of **5b** with a less nucleophilic reagent of **5b** ($NaBH_3CN$) yielded the bis(spirodienone) derivative **2a**.

To unravel the stereochemistry of the displacement, the reactions were repeated with the labeled reagents $NaBD_4$ and $NaBD_3CN$. The ^1H NMR spectra of the methylene region of the labeled spirodienone derivative **8** obtained in the reaction with $NaBD_3CN$ and of the unlabeled **2a** are shown in Figure 4. A comparison of both spectra indicates that the higher field

(18) In the process depicted in eq 1 there is retention of the configuration of the spiro stereocenters. However, their configurational descriptors change from *R* to *S* (and vice versa). In the starting material the α-carbon has priority over the carbonyl due to the presence of the bromine substituent, whereas in the product the carbonyl has priority over the unsubstituted α-carbon.

(19) A dynamic process (such as the cone-to-cone ring inversion) cannot modify the trans arrangement of two substituents on the methylene bridges. For a detailed discussion, see ref 6f.

(20) Agbaria, K.; Wöhnert, J.; Biali, S. E. *J. Org. Chem.* **2001**, *66*, 7059.

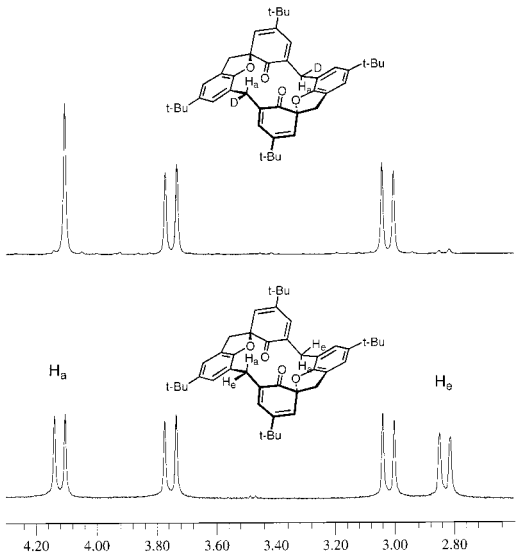


Figure 4. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the methylene region of the bis(spirodienone)derivative **2a** and its dideuterated isotopomer **8**.

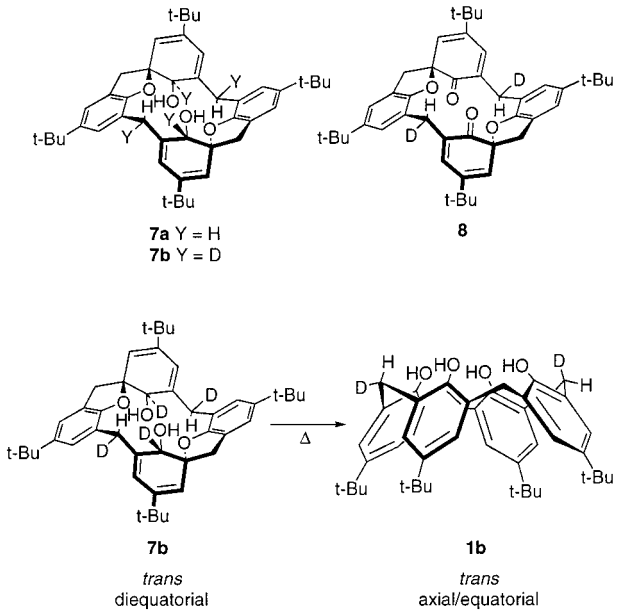
methylene doublet of **2a** (assigned to the pseudoequatorial proton H_e on the basis of its chemical shift) is absent in the labeled derivative and that the deuterium is almost exclusively (>90%) incorporated in that position. This indicates that in the reaction with the metal deuteride the two exocyclic double bonds react with an identical high stereoselectivity. The pseudoequatorial incorporation of the deuterium atoms can be rationalized by assuming that the reaction proceeded by attack at the more sterically accessible exo face of the two exocyclic double bonds. The vinylic protons of the exocyclic double bonds become the pseudoaxial protons in the bis(spirodienone) product.

Reaction of the labeled bis(spirodienone) **8** with $NaBD_4$ afforded the same bis(spirodienol) derivative (i.e., **7b**) obtained by reaction of the spiroalkene **5b** with $NaBD_4$. NOESY analysis of this compound indicated that in **8** the label is present in the pseudoequatorial positions of the bridging methylene groups, i.e., both deuterium atoms are located in a mutual trans relationship.

Selectively Labeled *p-tert*-Butylcalixarene. Spirodienol calixarenes derivatives are constitutional isomers of calixarenes and they readily isomerize to calixarenes by treatment with acids or even by simple heating.[20] Heating a toluene solution of **7b** readily afforded the dideuterated calixarene derivative **1b**. Since the transformation **7b** → **1b** does not involve cleavage of the bonds of the labeled methylene groups, the initial trans relationship between the two deuterium atoms must be retained in the labeled calixarene. Calix[4]arene **1a** adopts in solution and in the solid state a cone conformation, and the same conformation is expected for the labeled **1b**. As a result of the different conformations adopted by the bis(spirodienone) and the calixarene scaffolds, the two trans deuterium atoms, located in equatorial positions in **8**, are located in an axial and equatorial position of the methylene bridges of **1b** (Scheme 5).

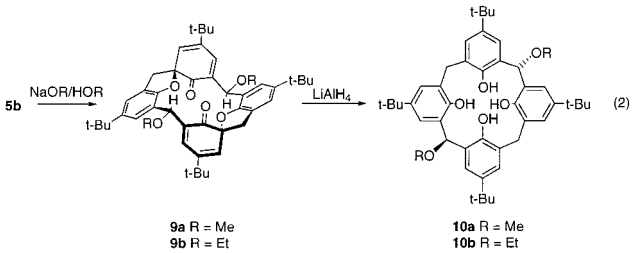
Low-temperature ^{1}H NMR data were consistent with a calixarene structure adopting a cone conformation and possessing one axial and one equatorial deuterium at distal methylene groups. The spectrum (400 MHz, $CDCl_3$, 220 K) displayed in the methylene region two apparent doublets but with the higher field transition of each doublet possessing twice the intensity (and integration) of the lower field one (Figure 5). Assuming, as observed for **8,** that the geminal HD coupling is not detectable,[20,21] this NMR pattern can be rationalized as the

Scheme 5



superposition of two doublets (corresponding to the unlabeled methylene groups) and one singlet each for the axial and equatorial CHD protons. Since a deuterium atom is weakly electron donating (as compared to a proton), the two singlets do not appear at the middle of each doublet but they are shifted upfield by a few hertz. At 400 MHz the shielding effect of the deuterium (in hertz) is equal to half the geminal coupling constant of the CH_2 groups, and the higher field transitions of each doublet accidentally coincide with one of the singlets, resulting in the experimentally observed pattern of signals.

Reaction of 5b with Oxygen Nucleophiles. The reaction of **5b** with oxygen nucleophiles was also examined to test the feasibility of the proposed synthetic scheme for the incorporation of alkoxy functionalities into the methylene bridges. The reaction of **5b** with NaOMe/HOMe or NaOEt/HOEt proceeded readily and afforded in each case a single major product (**9a** and **9b,** respectively, eq 2) that retained the symmetry of the starting material. On the basis of their NMR patterns, to these products



are assigned bis(spirodienone) structures with a pair of trans alkoxy groups located at distal methylenes groups. The ^{1}H NMR spectrum displayed an aromatic signal at a relative low field (δ 7.4 ppm) and this is assigned to the aromatic protons located ortho to the substituted methylenes. A single-crystal X-ray diffraction study of **9b** corroborated the structural assignment and indicated that the two trans ethoxy groups are located at pseudoequatorial positions of the macrocycle (Figure 6).

(21) H,D couplings are 6.5 times smaller than their corresponding H,H couplings due to the smaller gyromagnetic ratio of the deuteron (Sandström, J. *Dynamic NMR Spectroscopy;* Academic Press: London, 1982; p 124). Additionally, rapid quadrupolar relaxation of a deuteron may substantially reduce the H,D coupling. See: Dougherty, D. A.; Mislow, K.; Blount, J. F.; Wooten, J. B.; Jacobus, J. *J. Am. Chem. Soc.* **1977**, *99*, 6149.

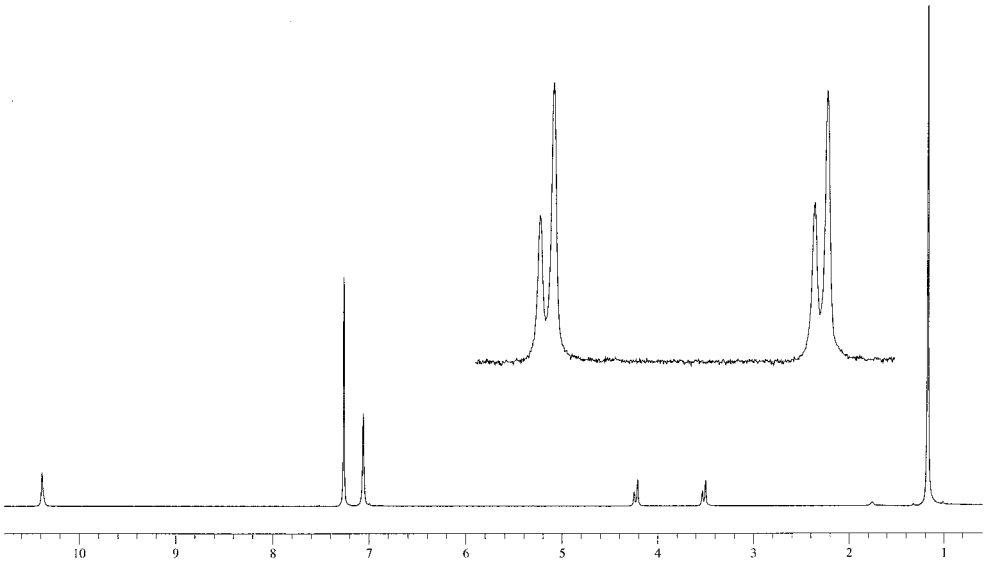


Figure 5. ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 220 K) of the dideuterated calixarene **1b**. The high-field transitions of each doublet possess twice the intensity and integration of the lower field ones.

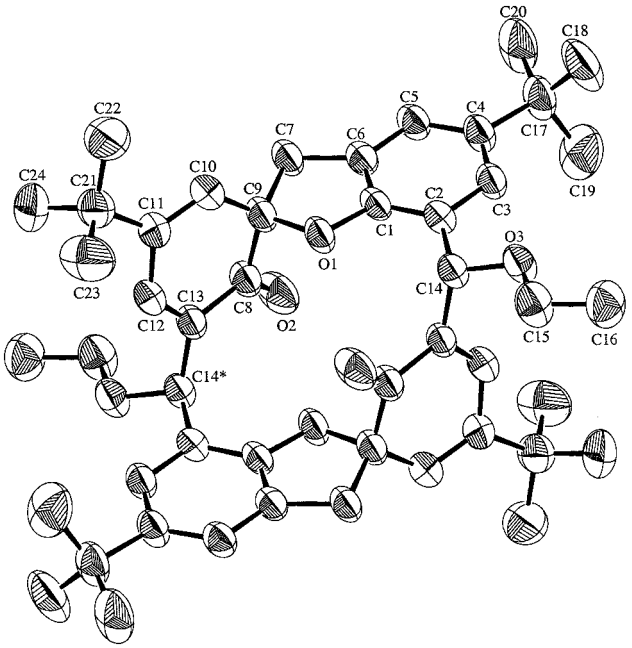
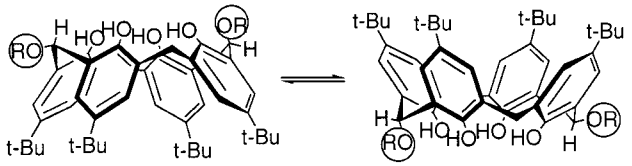


Figure 6. Crystal structure of the methylene-substituted bis(spirodienone) **9b**. The ethoxy groups are located at equatorial positions.

The methylene-substituted bis(spirodienone) derivatives **9a** and **9b** were transformed in one step to the corresponding calixarenes **10a** and **10b** by $LiAlH_4$ reduction (eq 2). As in the case of the labeled **7b**, the transformation of the bis(spirodienone) to the corresponding calixarene should retain the trans disposition of the alkoxy substituents, since the RO−C bonds are not affected by the reaction. If **10a** and **10b** adopt cone conformations, the substituents must be located one in an equatorial and one in an axial position. Cone-to-cone inversion of the calix scaffold relocates a substituent located in an axial position into an equatorial one and vice versa (Scheme 6). Under slow exchange conditions two pairs of doublets and two singlets should be expected for the bridging methylene and methine protons, whereas when the cone-to-cone process is fast on the NMR time scale, one singlet each should be observed for those methylene and methine protons.[6e]

The ^{1}H NMR spectrum of the *trans*-diethoxycalixarene displayed broad signals for the methylene groups, in agreement

Scheme 6



with the presence of a rotational process of the calix macrocycle (a cone-to-cone inversion process, see below). This process becomes slow (on the NMR time scale) at low temperatures. The ^{1}H NMR spectrum of **10b** displayed at 220 K (in $CDCl_3$) two OH signals at 10.19 and 10.11 ppm, a pair of doublets for the methylene signals at 4.23 and 3.47 ppm, two singlets for the methine protons, and two pairs of quartets and triplets for the ethoxy groups (Figure 7). The strong similarity of the NMR spectrum to that of the parent **1a** suggests, as previously observed for several calix[4]arene derivatives with one or two methylene bridges carrying an alkyl or aryl substituent,[6] that the compound adopts a cone conformation. A single aromatic signal was shifted downfield (7.33 ppm) and is ascribed to the aromatic protons located ortho to the methylene possessing the equatorial alkoxy group. The compound displays in the ^{13}C NMR (220 K), two separate signals for the methine carbon at 87.78 and 71.20 ppm. This spectrum is in agreement with a frozen cone conformation, in which one ethoxy group is located in an axial and one in an equatorial position.

Upon raising the temperature, the two methine proton signals of **10a** and **10b** broadened and coalesced. From the chemical shift difference under slow exchange conditions ($\Delta\delta$ = 205.7 and 198.0 Hz for **10a** and **10b**, respectively) and the respective coalescence temperatures (305 and 307 K), the rotational barriers for the cone-to-cone inversion process of both molecules ($\Delta G_c^{\ddagger}$ = 14.1 kcal mol^{-1} (**10a**) and 14.3 kcal mol^{-1} (**10b**)) were determined by using the Gutowsky−Holm equation.[22]

Temperature-dependent NMR studies have shown that the substitution of a methylene proton by an alkyl group in a calix[4]arene increases the cone-to-cone inversion barrier.[6d] However, the barrier (14.6 kcal mol^{-1}) for **11** was substantially lower than the one of the corresponding monosubstituted derivative **12** (18.0 kcal mol^{-1}).[6d] The rotational barriers measured for **10a** and **10b**

(22) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1956**, *25*, 1228.

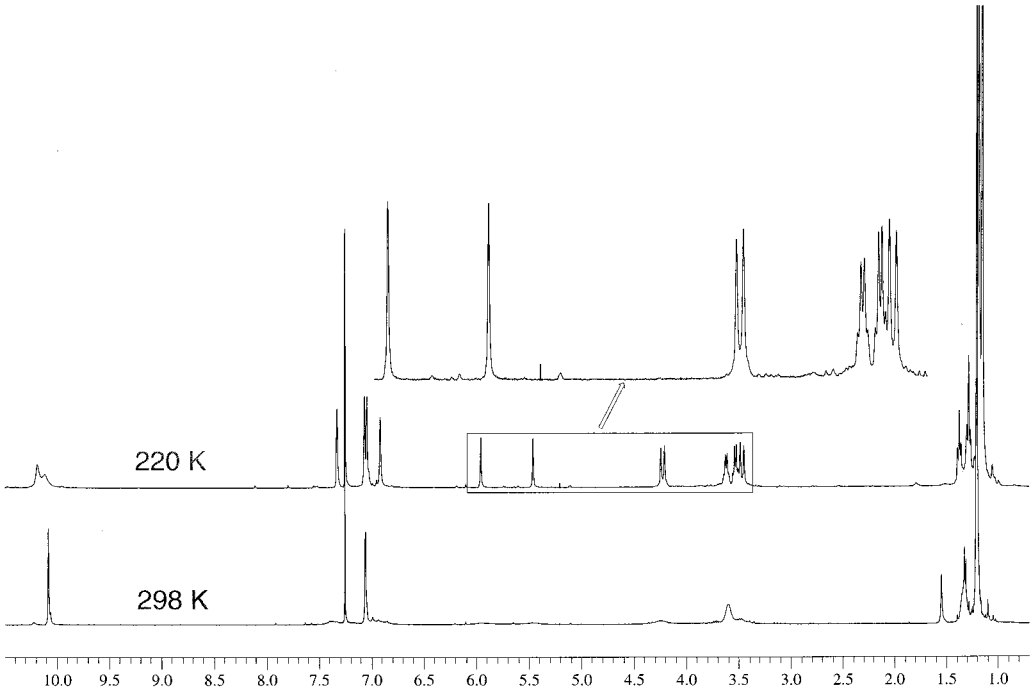
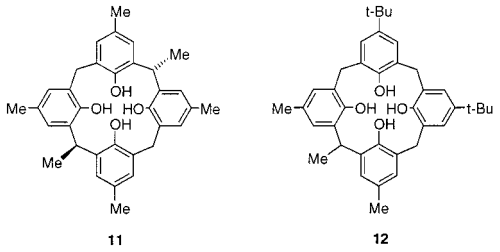


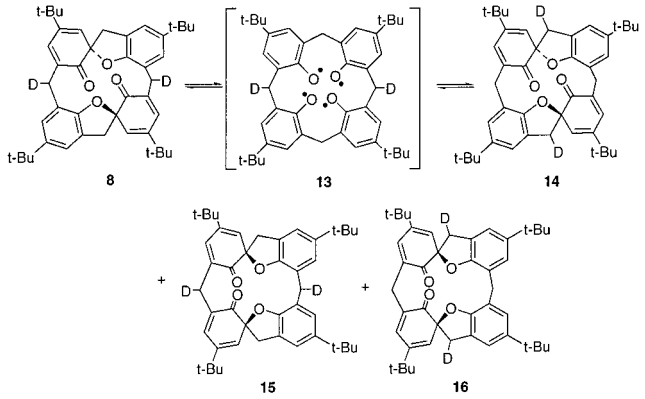
Figure 7. ^{1}H NMR spectra of **10b** at 298 and 220 K.



are also lower than the barrier of the parent **1a** (15.7 kcal mol^{-1} in $CDCl_3$),[23] suggesting than trans disubstitution lowers the rotational barrier, probably due to steric destabilization of the ground-state conformation.

Isomerization of a Labeled Bis(spirodienone) Derivative. Bis(spirodienone) calixarene derivatives mutually isomerize by heating in solution or in the solid state. In principle, two mechanisms are feasible for accounting for this isomerization. The first mechanism involves an initial homolytic cleavage of the spiro C−O bonds (yielding phenoxy radical intermediates), followed by a C−O bond formation regenerating the spirodienone subunit. A second possible mechanism involves a single-step [3.3] sigmatropic process. The sigmatropic route is the preferred mechanism for the isomerization of the spirodienone derivative of a cyclophane.[24] The synthetic availability of the selectively deuterated bis(spirodienone) derivative **8** allowed us to test whether a tetraradical intermediate (cf. **13**, Scheme 7) is involved in the isomerization. When a single spirodienone group is cleaved (yielding two phenoxy radicals), the two rings forming the spirodienone subunit in the starting material are necessarily those that will be connected after formation of the spiro C−O bond. In such a case the label should be located in the isomerization products at the bridging methylene groups. If a tetraphenoxy radical intermediate (**13**) is involved in the isomerization it should lead to labeled derivatives of **2a** and **2b** with the pair of trans deuterium atoms located at the bridging

Scheme 7



methylenes (as in the starting material **8**) and to derivatives *with the label located at the dihydrofuran subunits* (Scheme 7).

On standing at room temperature, a $CDCl_3$ solution of **8** isomerized, according to ^{1}H NMR spectroscopy (in C_6D_6), into a ca. 5:1 mixture of **8** and **15,** i.e., spirodienones labeled exclusively at the bridging methylenes. Heating the isomeric mixture in the solid state isomerized it back into mostly (>95%) **8,** again with the labels located exclusively at the bridging methylenes. The absence of **14** and **16** in these experiments indicates that **13** is not an intermediate in the reaction. The preferred isomerization pathway for the interconversion between **2a** and **2b** either involves the homolytic cleavage of a single spiro C−O bond or a [3.3] sigmatropic mechanism.

Conclusions. A bromination/dehydrobromination reaction sequence, when applied to the *meso* bis(spirodienone) calixarene **2a,** affords a *meso* derivative (**5b**) with two exocyclic double bonds. Nucleophilic substitution of **5b** using hydride or alkoxides as nucleophiles proceeds with high diastereoselectivity and affords trans methylene-functionalized spirodienone derivatives. This stereochemical outcome is the result of the molecular symmetry of the starting material. The two double bonds of **5b** are related by an inversion center and are oriented in an antiparallel fashion, and therefore addition to their exo faces

(23) Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.
(24) Yamato, T.; Matsumoto, J.; Fujita, K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 123.

results in a trans disposition of the substituents on the methylene bridges. Reaction of the methylene-functionalized spirodienone derivatives with $LiAlH_4$ affords calixarenes functionalized in trans fashion at two distal methylene groups. The sequence of reactions described provides a novel route for the selective functionalization of two distal methylene groups of *p-tert*-butylcalix[4]arene.

Experimental Section

Crystallography. The X-ray diffraction data were measured with an ENRAF−NONIUS CAD-4 computer controlled diffractometer. Cu Kα(λ = 1.54178 Å) radiation with a graphite crystal monochromator in the incident beam was used. All crystallographic computing was done on a VAX 9000 computer using the TEXSAN structure analysis software. The data of **9b** were collected on a sealed capillary tube containing acetonitrile. Crystal data for **4**: $C_{44}H_{52}O_6$, triclinic crystal system, space group $P\bar{1}$, a = 10.131(2) Å, b = 10.519(5) Å, c = 9.965(3) Å, α = 96.36(3)°, β = 112.57(2)° , γ = 103.36(2)°, V = 930.2(6) Å^3, Z = 1, ρ_{calcd} = 1.21 g cm^{-3}, range of transmission factor 0.59−1.00, μ(Cu Kα) = 6.26 cm^{-1}, 2755 unique reflections, 1581 reflections with $I \geq 2\sigma_I$, R = 0.095, R_w = 0.120, 226 parameters refined, goodness of fit 2.47. Crystal data for **5b**: $C_{44}H_{50}O_4Br_2$, monoclinic crystal system, space group $P2_1/c$, a = 14.578(8) Å, b = 11.454(9) Å, c = 12.414(5) Å, β = 101.61(4)°, V = 2030(2) Å^3, Z = 2, ρ_{calcd} = 1.31 g cm^{-3}, range of transmission factor 0.29−1.00, μ(Cu Kα) = 28.40 cm^{-1}, 3184 unique reflections, 1848 reflections with $I \geq 2\sigma_I$, R = 0.066, R_w = 0.078, 226 parameters refined, goodness of fit 1.85. Crystal data for **9b**: $C_{48}H_{60}O_6 \cdot 4CH_3CN$, triclinic crystal system, space group $P\bar{1}$, a = 10.626(4) Å, b = 14.590(8) Å, c = 10.072(4) Å, α = 96.86(4)°, β = 106.47(3)°, γ = 110.35(4)°, V = 1362(1) Å^3, Z = 1, ρ_{calcd} = 1.09 g cm^{-3}, range of transmission factor 0.71−1.00, μ(Cu Kα) = 5.59 cm^{-1}, 5153 unique reflections, 4103 reflections with $I \geq 3\sigma_I$, R = 0.064, R_w = 0.107, 317 parameters refined, goodness of fit 2.04.

Tetrabromo Derivative 3a. To a stirred solution of **2a** (4 g, 6.2 mmol) in 250 mL CH_2Cl_2 at 0 °C was added slowly during 1h a solution of 2.3 g (14.4 mmol) of Br_2 dissolved in 150 mL of CH_2Cl_2 and the mixture was stirred for an additional 2 h. The solvent was evaporated at room temperature (to avoid decomposition) and the residue was dissolved in 20 mL of $CHCl_3$, and then 150 mL CH_3OH was added and the mixture was stirred for 30 min. The precipitate that formed was filtrated, washed with 15 mL of CH_3OH, and dried. Purification was achieved by dissolving the compound in $CHCl_3$ or toluene and adding MeOH to induce crystallization, yielding 3.8 g (63.5%) of **3a**, mp 165−170 °C (dec). ^{1}H NMR (400.133 MHz, $CDCl_3$, room temperature) δ 7.83 (s, 2 H, Ar H), 7.23 (s, 2 H, Ar H), 5.80 (d, J = 1.7 Hz, 2 H, C═CH), 4.50 (d, J = 1.7 Hz, 2 H, CHBr), 4.27 (d, J = 16.9 Hz, 2 H, CH_2), 3.71 (d, J = 16.2 Hz, 2H, CH_2), 3.31 (d, J = 16.2 Hz, CH_2), 3.25 (d, J = 17.0 Hz, CH_2), 1.34 (s, 18 H, *t*-Bu), 0.90 (s, 18 H, *t*-Bu). ^{13}C NMR (100.4 MHz, room temperature, $CDCl_3$) δ 196.69 (C═O), 153.11, 145.83, 144.54, 127.24, 124.74, 124.09, 121.56, 115.57, 91.56 (CO), 62.27 (CBr), 48.50 (CBr), 39.58, 35.56, 34.63, 33.68, 31.69, 28.95 ppm. CI MS 802.9 (M − 2HBr). Anal. Calcd for $C_{44}H_{52}Br_4O_4$: C, 54.79; H, 5.43. Found: C, 54.64; H, 5.60.

Alkene 5b. Compound **3a** (2 g, 2.1 mmol) was heated at 170 °C in the solid state under N_2 with occasional stirring with a glass rod. After 4 h the reaction was complete according to ^{1}H NMR spectroscopy. The product was dissolved in 10 mL of $CHCl_3$ or toluene and crystallized by addition of 60 mL of CH_3OH, yielding 1.4 g (84%) of **5b**, mp 310−315 °C (dec). ^{1}H NMR (400.133 MHz, $CDCl_3$, room temperature) δ 7.21 (br s, 2 H, Ar H), 7.07 (br s, 2 H, Ar H), 6.98 (s, 2 H, C═CH), 6.50 (br s, 2 H, C═CH), 4.86 (d, J = 1.7 Hz, 2 H, CHBr), 4.09 (d, J = 16.2 Hz, 2 H, CH_2), 3.07 (d, J = 16.0 Hz, 2 H, CH_2), 1.31 (s, 18 H, *t*-Bu), 1.14 (s, 18 H, *t*-Bu). ^{13}C NMR (100.4 MHz, room temperature, $CDCl_3$) δ 193.06(C═O), 154.16, 147.04, 145.03, 135.32, 130.65, 126.43, 124.05, 122.37, 122.19, 118.08, 92.29, 50.38, 36.10, 34.69, 33.85, 31.80, 29.66. CI MS *m*/*z* 803.3 (MH$^+$). Anal. Calcd for $C_{44}H_{50}Br_2O_4$: C, 65.84; H, 6.28. Found: C, 65.49; H, 6.26.

Bis(epoxide) Derivative 4. To a stirred solution of 2 g (2 mmol) of **3a** and 2 g of tetrabutylammonium bromide in 200 mL of CH_2Cl_2 was slowly added during 30 min 100 mL of 30% NaOH and the mixture was stirred overnight. The organic phase was separated and washed several times with water. After evaporation of the solvent, the residue was treated with a mixture of 20 mL of $CHCl_3$ and 100 mL of MeOH. The undissolved white solid was filtered and washed with 10 mL of MeOH, yielding 0.63 g (46%) of **4**, mp 280−285 °C (dec). ^{1}H NMR (400.133 MHz, $CDCl_3$, room temperature) δ 7.05 (s, 2 H, Ar H), 6.89 (s, 2 H, Ar H), 5.58 (d, J = 2.2 Hz, 2 H, C═CH), 4.18 (d, J = 15.5 Hz, 2 H, CH_2), 3.64 (d, J = 15.4 Hz, 2 H, CH_2), 3.52 (d, J = 2.2 Hz, 2 H, C(O)H), 2.83 (d, J = 15.5 Hz, 2 H, CH_2), 2.34 (d, J = 15.6 Hz, 2 H, CH_2), 1.27 (s, 18 H, *t*-Bu), 1.07 (s, 18 H, *t*-Bu). ^{13}C NMR (100.4 MHz, room temperature, $CDCl_3$) δ 197.63 (C═O), 153.46, 145.48, 144.29, 126.12, 125.63, 123.92, 120.58, 117.27, 83.61, 59.49, 56.59, 39.78, 35.10, 34.31, 31.75, 31.06, 28.47. CI MS *m*/*z* 676.3 (M$^+$).

Reaction of 5b with $NaBD_4$. 5b (1.5 g) was dissolved in 350 mL of THF and 150 mL of EtOH. $NaBD_4$, 1.2 g (28.7 mmol), was added and the mixture was stirred at room temperature for 4 h. The solvent was evaporated and the solid residue was dissolved in 150 mL of CH_2Cl_2. The organic layer was washed several times with water and filtered, and the solvent was evaporated. Recrystallization from $CHCl_3$/hexane or toluene/CH_3OH afforded 0.65 g (54%) of labeled **7b,** mp 178−182 °C (dec). The spectroscopic data of **7b** are described in ref 20.

Labeled Bis(spirodienone) Derivative 8. 5b, 0.3 g (0.37 mmol), was dissolved in 25 mL of dry THF. $NaBD_3CN$, 0.2 g (3 mmol), was added and the reaction mixture was stirred at room temperature for 12 h. The solvent was evaporated and the solid residue dissolved in 20 mL of CH_2Cl_2. The organic layer was washed several times with water and filtered and the solvent evaporated. Recrystallization from CH_3OH afforded 0.18 g (74%) of **8**, mp 265−270 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, room temperature) δ 7.10 (s, 2 H, Ar H), 7.03 (s, 2 H, Ar H), 6.61 (d, J = 1.9 Hz, 2 H, C═CH), 5.84 (d, J = 1.9 Hz, 2 H, C═CH), 4.11 (s, 2 H, CHD), 3.75 (d, J = 15.4 Hz, 2 H, CH_2), 3.02 (d, J = 15.4 Hz, 2 H, CH_2), 1.33 (s, 18 H, *t*-Bu), 1.02 (s, 18 H, *t*-Bu). CI MS *m*/*z* 647.5 (MH$^+$), 651.5 (calix-d_2H$^+$).

5,11,17,23-Tetra-*tert-butyl*-25,26,27,28-tetrahydroxy-2,14-dideuteriocalix[4]arene (Trans Isomer, 1b). *Method A.* **7b,** 0.2 g, was heated in the solid state for 1.5 h at 160 °C under vacuum affording pure **1b** quantitatively. *Method B.* **7b,** 0.2 g was dissolved in 15 mL of toluene. The reaction mixture was refluxed for 6 h. Evaporation of the solvent followed by recrystallization of the residue from $CH_3OH/CHCl_3$ afforded 0.18 g (90%) of **1b**, mp 335−340 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, 220 K) δ 10.37 (s, 4 H, OH), 7.04 (s, 8 H, Ar H), 4.21 (d, J = 14.4 Hz, 2 H, CH_2), 4.19 (s, 1 H, CHD), 3.50 (d, J = 14.4 Hz, 2 H, CH_2), 3.48 (s, 1 H, CHD), 1.16 (s, 36 H, *t*-Bu). CI MS *m*/*z* 651.5 (MH$^+$).

Preparation of 9a. 5b, 3 g (3.7 mmol), was dissolved in 500 mL of THF and 100 mL of MeOH, and 8 g of NaOMe (37 mmol) were added. The reaction mixture was stirred at room temperature for 6 h. The solvent was evaporated and the yellow solid residue was dissolved in 150 mL of CH_2Cl_2. The organic layer was washed several times with water. After the solvent was evaporated, 10 mL of $CHCl_3$ and 80 mL of MeOH were added. The yellow precipitate was filtered and washed with 10 mL of CH_3OH and dried under suction, yielding 2.3 g (88%) of **9a**, mp 270−275 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, room temperature) δ 7.42 (s, 2 H, Ar H), 7.13 (s, 2 H, Ar H), 6.79 (d, J = 2.3 Hz, C═CH), 5.90 (d, J = 2.3 Hz, C═CH), 5.48 (s, 2 H, HCO), 3.71 (d, J = 15.3 Hz, 2 H, CH_2), 3.35 (s, 6 H, OMe), 3.06 (d, J = 15.3 Hz, 2 H, CH_2), 1.35 (s, 18 H, *t*-Bu), 1.03 (s, 18 H, *t*-Bu). ^{13}C NMR (100.4 MHz, room temperature, $CDCl_3$) δ 194.82 (C═O), 151.77, 145.33, 143.83, 139.69, 136.01, 128.32, 126.59, 123.70, 119.97, 119.75, 82.35 (C_{spiro}), 70.96 (*C*OMe), 57.05 (OMe), 38.01, 34.62, 34.38, 31.97, 28.41 ppm. CI MS (−DCI) *m*/*z* 704.3 (M$^-$).

Preparation of 9b. 5b, 3 g (3.7 mmol), was dissolved in 500 mL of THF and 100 mL of EtOH. Ten grams of NaOEt (147 mmol) were added. The reaction mixture was stirred for 6 h at room temperature. The solvent was evaporated and the yellow solid residue was dissolved in 150 mL of CH_2Cl_2. The organic layer was washed several times with water. After evaporation of the solvent, 40 mL of MeOH were added. The yellow precipitate was filtrated and washed with 5 mL of MeOH under suction, yielding 2 g (74%) of **9b**, mp 255−260 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, room temperature) δ 7.44 (s, 2 H, Ar H), 7.12 (s, 2 H, Ar H), 6.80 (d, J = 2.1 Hz, C═CH), 5.88 (d, J = 2.1 Hz, C═CH), 5.58 (s, 2 H, HCO), 3.70 (d, J = 15.2 Hz, 2 H, CH_2),

3.51 (m, 4 H, OCH_2CH_3), 3.04 (d, $J = 15.2$ Hz, 2 H, CH_2), 1.35 (s, 18 H, *t*-Bu), 1.23 (t, $J = 6.9$ Hz, 6 H, OCH_2CH_3), 1.03 (s, 18 H, *t*-Bu). ^{13}C NMR (100.4 MHz, room temperature, $CDCl_3$) δ 194.82 (C═O), 151.86, 145.24, 143.66, 139.73, 136.46, 128.26, 126.51, 124.20, 119.94, 119.88, 82.32 (C_{spiro}), 68.94, 64.61, 38.07, 34.59, 34.38, 31.97, 28.42, 15.50 ppm. CI MS *m*/*z* 733.3 (MH^+).

5,11,17,23-Tetra-*tert*-*butyl*-25,26,27,28-tetrahydroxy-2,14-dimethoxycalix[4]arene (Trans Isomer, 10a) and 5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,14-diethoxycalix[4]arene (Trans Isomer, 10b). One gram (1.36 mmol) of **9b** was dissolved in 50 mL of dry THF. One gram of $LiAlH_4$ (64.2 mmol) was added and the reaction mixture was stirred at room temperature for 10 h. The excess of $LiAlH_4$ was quenched with cold water, and 100 mL of CH_2Cl_2 was added. After phase separation the organic phase was washed with 20 mL of 1 N HCl and several times with water. The residue obtained after evaporation of the solvent was purified by chromatography (silica; eluent, CH_2Cl_2/hexane 4:1 followed by CH_2Cl_2/MeOH 40:1) yielding 0.38 (38%) of **10a**, mp 235−237 °C. Reaction of 1 g of **9b** with 1 g of $LiAlH_4$ afforded, after chromatography (silica; eluent, CH_2Cl_2/hexane 4:1) 0.45 g (45%) of **10b**, mp 198−203 °C. Spectroscopic data for **10a**. ^{1}H NMR (400.133 MHz, $CDCl_3$, 220 K) δ 10.15 (br s, 4 H, OH), 7.32 (s, 2 H, Ar H), 7.10 (s, 2 H, Ar H), 7.07 (s, 2 H, Ar H), 6.93 (s, 2 H, Ar H), 5.87 (s, 1 H, $CH_{ax}OR$), 5.36 (s, 1 H, $CH_{eq}OR$), 4.25 (d, $J = 13.8$ Hz, 2 H, CH_2), 3.54 (s, 3 H, OMe), 3.49 (d, $J = 13.8$ Hz, 2 H, CH_2), 3.42 (s, 3 H, OMe), 1.21 (s, 18 H, *t*-Bu), 1.18 (s, 18 H, *t*-Bu). ^{13}C NMR (100.133 MHz, $CDCl_3$, 260 K) δ 147.26, 145.84, 144.63, 143.30, 129.16, 128.12, 127.59, 127.10, 126.09, 125.73, 125.08, 120.79, 90.00, 73.60, 57.48, 57.29, 34.26, 33.94, 31.94, 31.38 ppm. −DCI MS *m*/*z* 707 ($M - H^+$), +DCI MS *m*/*z* 677 ($MH^+ -$ MeOH). Anal. Calcd for $C_{46}H_{60}O_6$: C, 77.93; H, 8.53. Found: C, 77.69; H, 8.37.

Spectroscopic Data for 10b. ^{1}H NMR (400.133 MHz, $CDCl_3$, 220 K) δ 10.19 (br s, 2 H, OH), 10.11 (br s, 2 H, OH), 7.33 (s, 2 H, Ar H), 7.07 (s, 2 H, Ar H), 7.05 (s, 2 H, Ar H), 6.92 (s, 2 H, Ar H), 5.96 (s, 1 H, $CH_{ax}OR$), 5.47 (s, 1 H, $CH_{eq}OR$), 4.23 (d, $J = 13.6$ Hz, 2 H, CH_2), 3.62 (q, $J = 6.8$, 2 H, OCH_2), 3.54 (q, $J = 6.8$ Hz, 2 H, OCH_2), 3.47 (d, $J = 13.6$ Hz, 2 H, CH_2), 1.38 (t, $J = 6.8$ Hz, 3 H, CH_3), 1.29 (t, $J = 6.8$ Hz, 6 H, CH_3), 1.19 (s, 18 H, *t*-Bu), 1.16 (s, 18 H, *t*-Bu). ^{13}C NMR (100.133 MHz, $CDCl_3$, 220 K) δ 147.13, 145.61, 144.35, 143.01, 129.31, 127.87, 127.40, 126.87, 125.94, 125.74, 124.88, 120.67, 87.78, 71.20, 65.09, 64.55, 34.17, 33.87, 31.71, 31.28, 31.22, 15.47 ppm. CI MS *m*/*z* 737.2 (MH^+). Anal. Calcd for $C_{48}H_{64}O_6$: C, 78.22; H, 8.68. Found: C, 77.98; H, 8.56.

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Supporting Information Available: Crystallographic tables for **4**, **5b**, and **9b** and ^{1}H NMR spectra of **4**, **8**, **9a**, and **9b** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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