JOC Article

Synthesis of *p-tert*-Butylcalix[4]arene Derivatives with *trans*-Alkyl Substituents on Opposite Methylene Bridges

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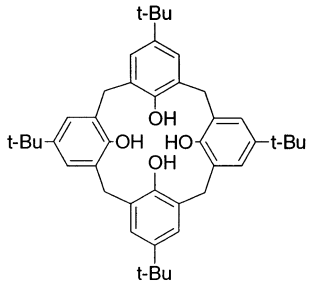
Reaction of the bis(spirodiene) calixarene derivative **9** possessing exocyclic double bonds with tetraethylammonium fluoride or chloride afforded bis(spirodienone) calixarene derivatives substituted by the corresponding halogen atoms (**11** and **12**). Reaction of **9** with alkyl cuprates yielded in one step *p-tert*-butylcalix[4]arene derivatives with opposite methylene groups substituted in a trans fashion by identical alkyl substituents (methyl, ethyl, or isopropyl). The isopropyl derivative **16** displayed the largest cone-to-cone inversion barrier of the series.

Introduction

The calix[*n*]arenes are synthetic macrocycles consisting of a cyclic array of phenol groups connected by methylene bridges.[1] The aromatic rings of the calixarenes are readily amenable to chemical modifications, usually via derivatization of the OH groups or via electrophilic substitution after de-*tert*-butylation of the aromatic rings.[1] The replacement of the methylene protons of the parent *p-tert*-butylcalix[4]arene (**1**) by a different group has been achieved in few instances. This functionalization has been accomplished using radical bromination,[2] homologous anionic ortho Fries rearrangement,[3] CrO_3 oxidation of the tetraacetate derivative of **1** followed by hydride reduction of the resulting carbonyl groups,[4] and deprotonation of the methylene protons (after protection of the phenolic OH groups) followed by reaction with a suitable electrophile.[5]

In a different approach, mono- and bis-1,1-alkanediylcalix[4]arenes have been prepared independently by the groups of Böhmer and Sartori via cyclocondensation of two suitable precursors.[6,7] Condensation of two fragments possessing aryl substituents at the bridges resulted in a mixture of cis and trans isomers. However, when both bridges were substituted by alkyl groups, the reaction afforded almost exclusively the cis products **3**−**6** and only in the case of the small methyl substituent could be obtained traces (0.3%) of the trans isomer **2** (Scheme 1).[7e] The diastereoselectivity of the reactions follows the relative stabilities of the products predicted by molecular mechanics calculations.



1

We have reported a novel method for the trans difunctionalization of two distal methylene groups of the calix[4]arene scaffold (Scheme 2).[8] Initially, the brominated calixarene **9** with two exocyclic double bonds was obtained from **1** by mild oxidation to give the bis(spirodienone) derivative **7**[9,10] followed by a bromination/dehydrobromination reaction sequence.[8a] Reaction of **9**

(1) (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. Gutsche, C. D. *Aldrichim. Acta* **1995**, *28*, 1. (b) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (c) For very recent reviews on calixarenes, see: *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001.

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

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

(7) (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. See also: (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. (g) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 3037. (h) Tsue, H.; Enyo, K.; Hirao, K. *Org. Lett.* **2000**, *2*, 3071.

(8) (a) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (b) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136.

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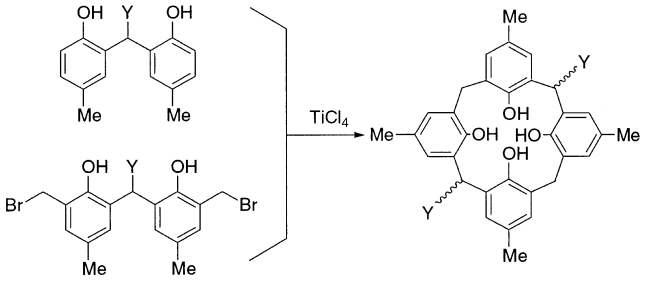
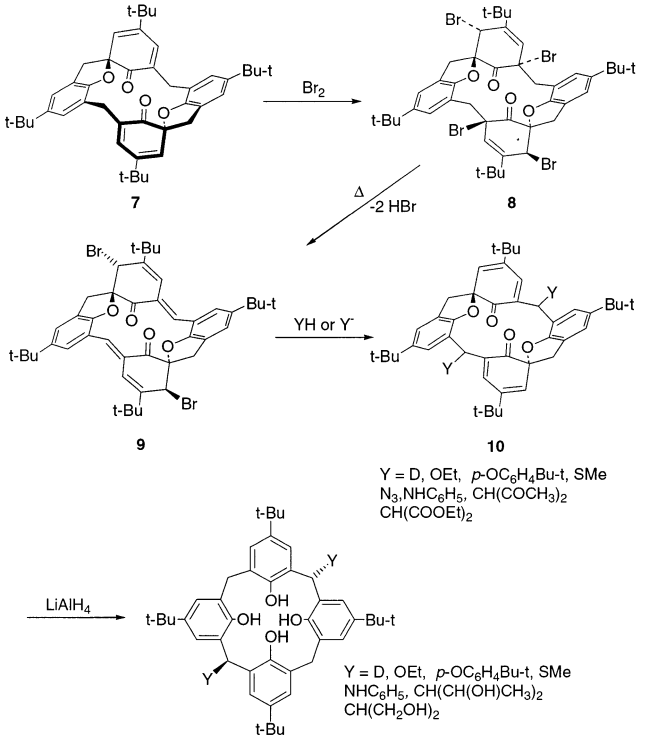
SCHEME 1



SCHEME 2



with nucleophiles proceeded in a regio- and stereoselective fashion, yielding meso bis(spirodienone) derivatives with a pair of opposite methylene bridges substituted in a trans fashion. Finally, $LiAlH_4$ reduction of the spirodienone derivative yielded the corresponding trans-disubstituted calixarenes. The bis(spirodiene) **9** reacts with deuteride and O-, N-, and S-containing nucleophiles at the exocyclic double bond.[8] The reaction failed when alkyllithium reagents were used but was successful with "soft" carbon nucleophiles (such as the sodium enolates derived from acetylacetone or diethylmalonate).[8b] In this paper, we report the reaction of the bis(spirodiene) **9** with fluoride and chloride anions and with alkyl cuprate nucleophiles, the latter reaction affording *p-tert*-butylcalix-

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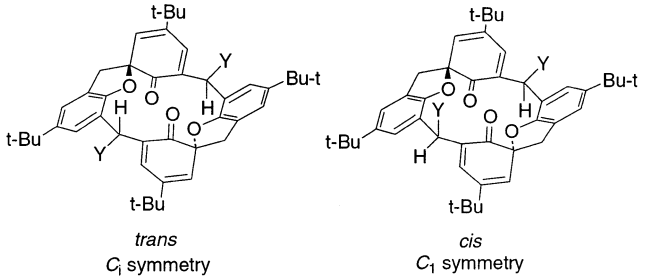
SCHEME 3

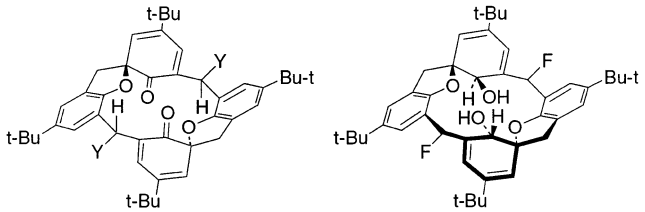


[4]arene derivatives with *trans*-alkyl substituents on opposite methylene bridges.

Results and Discussion

Stereoselectivity and NMR Pattern. Since the two spiro stereocenters of **7** are not affected by the reaction, the cis/trans disposition of the two methylene substituents in the product can be readily determined by examination of the ^1H NMR pattern. Only if the two substituents are in a trans relationship can the C_i symmetry of the starting material be retained in the product, whereas if the groups are cis the symmetry is lowered to C_1 (Scheme 3). Pairs of groups related by the inversion center in the trans isomer are symmetry nonequivalent in the cis form. In such cases, for example, separate signals are expected for the two methine protons on the bridges (one located in a pseudoaxial and one in a pseudoequatorial position). In principle, two different trans products are possible with both methylene substituents located at either pseudoequatorial or pseudoaxial positions. In all cases examined so far,[8] the reaction proceeded with high stereoselectivity yielding exclusively the trans-disubstituted product. X-ray crystallography of an alkoxy derivative indicated that both substituents are located at pseudoequatorial positions.[8a]

Reaction with Fluoride and Chloride. To determine the reactivity of spirodiene **9** with halide nucleophiles, we examined its reaction with an excess of tetrabutylammonium fluoride and chloride. In the case of fluoride, the reaction proceeded rapidly under reflux of CH_2Cl_2. NMR of the crude product indicated the almost exclusive presence of the product **11**. For the chloride nucleophile, the reaction was more sluggish requiring a larger excess of the halide reagent and longer reaction times and under the reaction conditions utilized it proceeded up to 80% conversion, as judged by NMR spectroscopy. However, the chloro derivative **12** could be separated from the starting material **9** via chromatography.



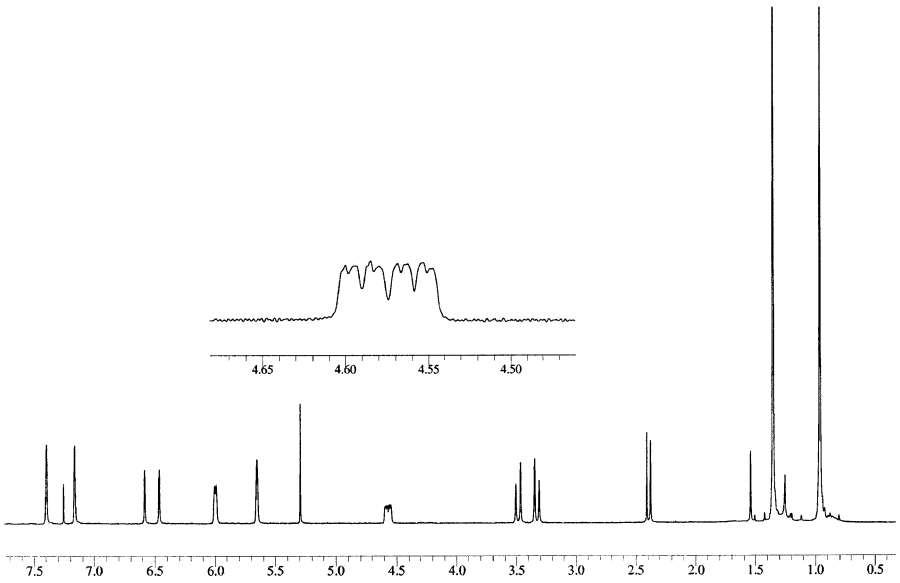


FIGURE 1. Bottom: ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the fluoro bis(spirodienol) derivative **13.** Top: expansion of the C*H*(OH) signal displaying a ddd pattern.

The ^{1}H NMR signal pattern of the product obtained in the reaction with fluoride was consistent with a bis(spirodienone) derivative trans disubstituted on the methylene bridges. The signal showing the largest coupling to the fluorine (δ 6.60 ppm, $^2J_{HF} = 46.2$ Hz) was assigned to the proton of the substituted bridge. This $^2J_{HF}$ value is similar to the one reported for fluorocyclohexane ($^2J_{HF} = 49$ Hz).[11] The diene proton proximal to the substituted methylene (resonating at 6.90 ppm) appears at 400 MHz as a triplet. This is due to the fortuitous similar values of its long range ^4J coupling constants with the second dienone proton and the fluorine atom. The signals of the compound were assigned by a combination of COSY and ROESY spectra and were in full agreement with the proposed structure. The NMR spectrum of the chlorine-containing spirodienone **12** was similar to that of **11** but with the two expected main differences: (i) No coupling of the protons to the halogen was present. (ii) The substituted bridges resonated at 6.20 ppm, their relative upfield shift (compared to **11**) the result of the lower electronegativity of the chlorine than the fluorine substituent. In both **11** and **12**, one of the aromatic proton signals was shifted downfield as compared to the parent **7**. This is in agreement with a pseudoequatorial disposition of the halogen groups since in that arrangement they are in steric proximity to the aromatic proton located ortho to a substituted methylene, resulting in its van der Waals deshielding.

Reaction of either **11** or **12** with $LiAlH_4$ did not generate a calixarene with two bridges substituted by halides but yielded the parent unsubstituted calixarene **1**. Apparently, in addition to reductively cleaving the spiro bonds, the strong reducing reagent $LiAlH_4$ reduces also the halide-containing methylene bridges. In an attempt to avoid the use of $LiAlH_4$, the reduction was conducted using the milder $NaBH_4$, which reduces bis(spirodienone)calixarenes to their corresponding bis(spirodienol) derivatives which readily isomerize to calixarene by heating.[8,12] The reaction of **11** with $NaBH_4$ proceeded readily yielding the fluorinated bis(spirodienol) derivative **13**. This product displayed in the ^{1}H NMR a ddd signal pattern (eight lines)[14] for the C*H*(OH) proton as a result of its ^3J coupling to the OH proton and the different ^4J couplings to the diene protons and the fluorine atom (Figure 1).[15] Attempts to isomerize **13** to the corresponding fluorinated calixarene either thermally in the solid state or in solution in the absence and presence of acids failed, and in each case, only decomposition products were obtained.

Reaction of 9 with Alkyl Cuprates. Our initial attempts to incorporate alkyl substituents into the methylene scaffold by reaction of **9** with alkyllithium (CH_3-Li, BuLi) or Grignard (MeMgBr) reagents failed. NMR analysis of the reaction product indicated that in all cases an identical product was obtained in which no alkyl group has been incorporated in the macrocycle. This product proved to be unstable and its $CDCl_3$ solutions rapidly decomposed.

Since the reaction of **9** proceeded well with "soft" nucleophiles, we examined its reaction with alkyl cuprates that are softer nucleophiles than the corresponding alkyllithium or Grignard reagents. Initial experiments were conducted utilizing an excess of RMgX/CuCl in THF, but the yields of the products obtained with this heterogeneous mixture were irreproducible. However, reaction with an excess of RMgX/CuCN[13] (X = Br for R = Me, Et; X = Cl for R = *i*-Pr) yielded a homogeneous solution and proceeded in reproducible fashion. Notably, in all cases the reaction afforded directly the disubsti-

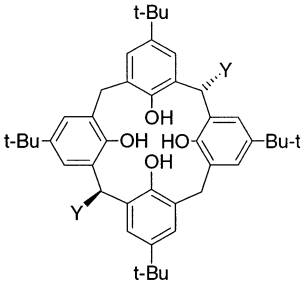
(11) Günther, H. *NMR Spectroscopy—An Introduction*; Wiley: Chichester, 1980; p 351.

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

(13) Underiner, T. L.; Goering, H. L. *J. Org. Chem.* **1990**, *55*, 2757.

(14) For the analysis of this pattern, see: Hoye, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014.

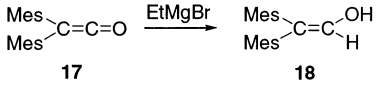
(15) The signal pattern changes into a doublet of doublets upon treatment of the NMR sample with a drop of D_2O.



14 Y = Me
15 Y= Et
16 Y = i-Pr

tuted calixarene (i.e., **14**−**16**) rather than the corresponding disubstituted bis(spirodienone) derivative.

A β-hydride transfer can successfully compete with the addition of Grignard reagents to crowded carbonyl groups. For example, reaction of dimesitylketene **17** with EtMgBr affords the enol **18** resulting from reduction of the ketene and not the addition product (eq 1).[16] In our case, in all three cases the major product was the calixarene rather than the substituted bis(spirodienone), indicating that a reduction step took place under the reaction conditions. Interestingly, even for the methyl reagent (lacking β hydrogens) the substituted calixarene derivative was obtained. At least in the case of the methyl reagent an alternative reduction pathway to the β-hydride transfer must be operating.[17]



17 **18** (1)

NMR Spectra of the Calixarenes. The expected ^{1}H NMR spectrum of a calixarene substituted in a cis or trans fashion by alkyl groups at opposite methylene bridges has been analyzed.[7e] For compounds **2**−**6**, it was found that in all cases the macrocycle adopts a cone (or slightly distorted cone conformation).[7e] The ^{1}H NMR spectra of calixarenes **14** and **15** (400 MHz) displayed at room temperature broad signals for the methylene and methine signals, suggesting that the rate of the cone-to-cone inversion (a process that exchanges the axial and equatorial methine and methylene protons as well as the axial and equatorial substituents, Scheme 4) is comparable to the NMR time scale. In contrast, the ^{1}H NMR signals of **16** were sharp at room temperature, and separate signals were observed (inter alia) for the axial and equatorial methine protons suggesting a larger cone-to-cone inversion barrier for this derivative (see below). The large coupling constant (11.1 Hz) observed for the methine protons on the bridges is indicative of an anti disposition of the HCCH subunits in the $CHCHMe_2$ moieties. Calculations conducted on a calixarene with one bridge substituted by an isopropyl group had indicated

SCHEME 4

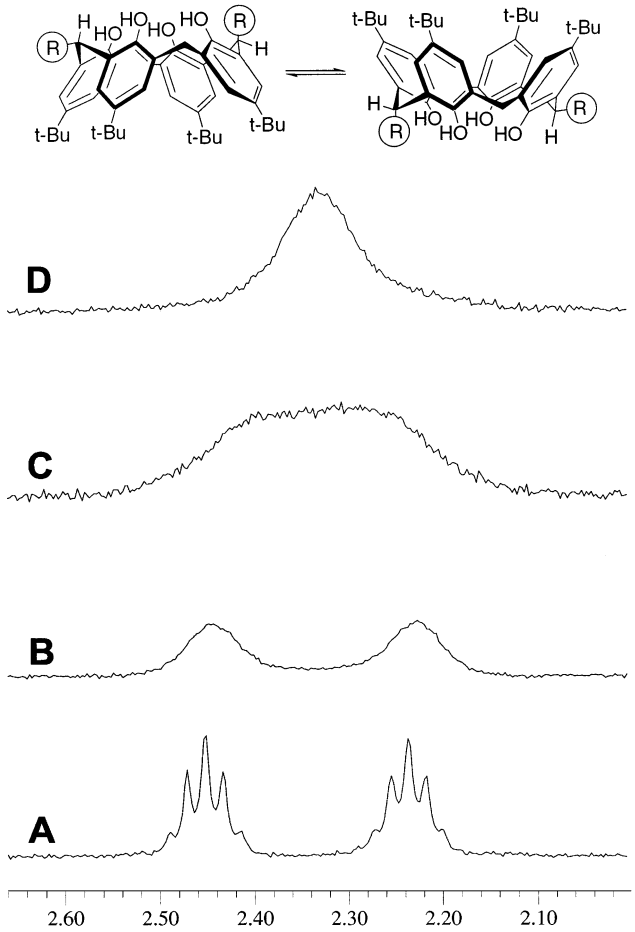


FIGURE 2. ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of the CH_2 groups of the ethyls of **15** at different temperatures: (A) 240 K, (B) 290 K, (C) 309.8 K (coalescence), (D) 320 K.

that this arrangement of the alkyl group is the lowest in energy.[7e]

Cone-to-Cone Inversion Barriers of the *trans*-Alkyl-Substituted Derivatives. The influence of an alkyl substituent on the axial/equatorial conformational equilibrium and the rotational barriers of **2**−**6** have been reported.[7e] It was found that the rotational barriers increase with the bulk of the substituent reaching its maximum value for the isopropyl group and then decrease for the *t*-Bu substituent, probably as a result of the destabilization of the ground state. For the trans-substituted derivative **2**, the barrier was 14.6 kcal mol^{-1}, a value 3.4 kcal mol^{-1} lower than the one estimated for the derivative with a single methylene bridge substituted by a methyl substituent.[7e]

The slow exchange ^{1}H NMR spectra of **14**−**16** (230 K for **14**, rt for **16**) displayed separate signals for the axial and equatorial substituents on the bridges. In the case of **15**, the rotational barrier was determined from the coalescence temperature of the pair of CH_2 signals of the two ethyls in the ^{1}H NMR spectrum (Figure 2) while for **14** and **16** the coalescence of the CH_3 signals was followed. From the chemical shift difference of these groups under slow exchange conditions in $CDCl_3$ at 400 MHz (92.8 (**14**), 86.3 (**15**), and 43.5 (**16**) Hz) and their coalescence temperatures (291.4, 309.8, and 354.2 K,

(16) Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 3669.
(17) It seems likely that the reduction proceeds via a electron-transfer pathway. See, for example: Berz, S. H.; Dabbagh, G.; Mujsce, A. M. *J. Am. Chem. Soc.* **1991**, *113*, 631. For a review on the structure and reaction mechanisms of organocopper reagents, see: Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3751.

respectively), barriers of 13.9, 14.9, and 17.6 kcal mol^{-1} were calculated by means of the Gutowsky−Holm[18] and Eyring equations. The barrier of **14** is lower than the one of **1** (15.7 kcal mol^{-1} in $CDCl_3$),[19] but increasing the bulk of the substituent raises the barrier significantly.

Conclusions

Reaction of the spirodiene calixarene derivative **9** with alkyl cuprates affords in stereoselective fashion *p-tert*-butylcalix[4]arene derivatives with *trans*-alkyl substituents on opposite methylene bridges. These derivatives are not available by the fragment condensation method, and the spirodiene route provides a facile synthetic entry into this family of systems.

Experimental Section

Preparation of 1. *p-tert*-Butylcalix[4]arene (**1**) was prepared by a minor modification of the procedure of Gutsche and Iqbal.[20] A 50 g portion of *p-tert*-butylphenol was mixed with 0.7 g of NaOH and 35 mL of a 32% formaldehyde solution. The mixture was rapidly heated with a heating mantle with stirring under nitrogen until a solid yellow-green mass was obtained. At this point, the heating was *immediately* discontinued, 800 mL diphenyl ether was added, and the reaction continued according to the procedure of Gutsche and Iqbal. Using this slightly modified procedure, we repeatedly obtained yields of 40−42 g (74−77%) of **1** (prior to recrystallization), which are somewhat higher than the 61% yield reported in ref 20 for the crude product.

Reaction of Spirodiene 9 with Tetrabutylammonium Fluoride. Spirodiene **9**[8a] (0.3 g, 0.37 mmol) was dissolved in 50 mL of CH_2Cl_2, and to the solution was added 1 g of tetrabutylammonium fluoride hydrate. After 3 h reflux, the solution was washed with water several times, and the organic phase was dried ($MgSO_4$) and evaporated. The residue was recrystallized from $CHCl_3$/MeOH yielding 0.15 g (59%) **11**: mp 278−280 °C dec; ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.41 (br s, 2H, Ar−H), 7.19 (br s, 2H, Ar-H), 6.90 (t, J = 2.6 Hz, 2H, C═C-H), 6.60 (d, $^2J_{HF}$ = 46.2 Hz, 2H, CHF), 5.96 (t, J = 1.7 Hz, 2H, C═C-H), 3.79 (d, J = 15.5 Hz, 2H, CH_2), 3.07 (d, J = 15.5 Hz, 2H, CH_2), 1.36 (s, 18H, *t*-Bu), 1.03 (s, 18H, *t*-Bu); ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 193.4, 150.4 (d, J = 6.6 Hz), 144.8 (d, J = 2.8 Hz), 144.0, 140.6 (d, J = 4.7 Hz), 134.1 (d, J = 16.4 Hz), 129.2 (d, J = 2.6 Hz), 126.2 (d, J = 2.4 Hz), 122.1 (d, J = 26.0 Hz), 121.0, 118.8 (d, J = 10.0 Hz), 82.6 (d, J = 174.1 Hz), 82.4, 37.4, 34.6, 34.3, 31.8, 28.3; CI MS (−DCI) m/z 680.3 ($M^{\bullet-}$).

Reaction of Spirodiene 9 with Tetrabutylammonium Chloride. Spirodiene **9** (0.2 g, 0.37 mmol) was dissolved in 50 mL of CH_2Cl_2, and to the solution was added 4 g of tetrabutylammonium chloride hydrate. After reflux overnight, the solution was washed with water several times, and the organic phase was dried ($MgSO_4$) and evaporated. The product **12** was separated from the starting material **9** by chromatography (silica, eluent: 2:1 CH_2Cl_2/hexane) and further recrystallized from $CHCl_3$/MeOH yielding 50 mg (28%) **12**: mp 252 °C dec; ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ 7.64 (br s, 2H), 7.20 (br s, 2H), 6.87 (d, J = 2.4 Hz), 6.20 (s, 2H), 5.91 (d, J = 2.3 Hz), 3.84 (d, J = 15.5 Hz, 2H), 3.08 (d, J = 15.5 Hz, 2H), 1.38 (s, 18H), 1.03 (s, 18H); ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 192.9, 150.9, 145.9, 144.2, 141.4, 136.9, 128.4, 126.2, 121.9, 121.6, 121.1, 82.7, 50.0, 37.2, 34.7, 34.4, 31.8, 28.3; CI MS (+DCI) m/z 713.3 (MH^+).

Reaction of 11 with $NaBH_4$. A 0.4 g (0.6 mmol) portion of **11** was dissolved in 50 mL of dry THF, and to the mixture were added 0.4 g (10.5 mmol) of $NaBH_4$. The mixture was stirred at rt under an inert atmosphere for 3 h. After the mixture was quenched with water and extracted with $CHCl_3$, the organic phase was evaporated and the residue precipitated from a mixture of $CHCl_3$/MeOH yielding 70 mg of crude **13**. The product was further purified by chromatography (silica, eluent 3:1 $CHCl_3$/hexane) yielding 45 mg of **13** (11%): mp 238 °C dec; ^{1}H NMR (400.133 MHz, $CDCl_3$) δ 7.40 (d, 2H), 7.17 (d, 2H), 6.53 (d, $^2J_{HF}$ = 48.3 Hz, 2H), 6.00 (ddd, J_1 = 1.9 Hz, J_2 = 2.6 Hz, J_3 = 5.6 Hz, 2H), 5.66 (m, 2H), 4.58 (ddd, J_1 = 2.0 Hz, J_2 = 5.9 Hz, J_3 = 12.6 Hz, 2H), 3.49 (d, J = 15.7 Hz, 2H), 3.33 (d, J = 15.6 Hz, 2H), 2.39 (d, J = 12.6 Hz, 2H), 1.36 (s, 18H), 0.97 (s, 18H); ^{13}C NMR (100.133 MHz, $CDCl_3$, rt) δ 151.5 (J = 6.3 Hz), 147.0 (J = 5.6 Hz), 143.7, 141.2 (J = 11.6 Hz), 125.4, 125.1 (J = 8.8 Hz), 121.4 (J = 25.4 Hz), 120.7, 119.5 (J = 9.9 Hz), 87.8, 84.5 (J = 172.4 Hz), 74.5, 41.6, 34.6, 34.2, 31.8, 28.3; CI MS (-DCI) m/z 684.2 ($M^{\bullet-}$).

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,-14-dimethylcalix[4]arene (Trans Isomer, 14). Into 50 mL of dry THF at 0 °C were added under an inert atmosphere 3.5 mL of a 3 M MeMgBr solution in diethyl ether (10.5 mmol) and 0.34 g of CuCN (3.8 mmol). The mixture was stirred until a clear solution was obtained. After addition of 1 g of **9** (1.25 mmol), the mixture was stirred for 2 h, and during this time it was allowed to reach rt. After quenching with water and extraction of the aqueous phase with CH_2Cl_2, the combined organic phases were evaporated and the residue was recrystallized from $CHCl_3$/EtOH yielding 0.5 g (59%) **14**. Alternatively, the compound could be purified by recrystallization from pyridine: mp 252 °C (from pyridine); ^{1}H NMR (400.133 MHz, $CDCl_3$, 240 K) δ 10.56 (br s, 4H), 7.15 (br s, 2H), 7.13 (br s, 2H), 7.00 (br s, 2H), 6.99 (br s, 2H), 4.73 (q, J = 6.9 Hz, 1H), 4.22 (d, J = 13.8 Hz, 2H), 4.10 (q, J = 7.7 Hz, 1H), 3.53 (d, J = 13.9 Hz, 2H), 1.94 (d, J = 7.6 Hz, 3H), 1.71 (d, J = 6.8 Hz, 3H), 1.20 (s, 18H), 1.18 (s, 18H) ppm; ^{13}C NMR (100.133 MHz, $CDCl_3$, 230 K), δ 147.4, 145.8, 144.2, 143.7, 131.9, 130.4, 128.6, 127.2, 127.0, 126.2, 125.1, 121.4, 48.1, 34.1, 33.9, 32.2, 31.3, 31.2, 29.4, 18.3, 16.6; CI MS (−DCI) m/z 676.4 ($M^{\bullet-}$).

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,-14-diethylcalix[4]arene (Trans Isomer, 15). EtMgBr was prepared by reacting 3 mL of EtBr (0.04 mol) and Mg (0.95 g, 0.04 mmol) in 20 mL of dry THF. A 5 mL portion of the resulting solution of the Grignard reagent (10 mmol) was added to 50 mL of dry THF at 0 °C under an inert atmosphere followed by 0.34 g of CuCN (3.8 mmol). After a homogeneous solution was obtained, **9** (1 g, 1.25 mmol) was added, and the stirring was continued for 3 h until the mixture reached rt. After quenching with water, extraction with CH_2Cl_2, and evaporation of the organic phase, the residue was recrystallized from $CHCl_3$/MeOH yielding 0.2 g (23%) **15**: mp 250 °C; ^{1}H NMR (400.133 MHz, $CDCl_3$, 240 K) δ 7.11 (d, J = 2.1 Hz, 2H), 7.08 (d, J = 2.0 Hz, 2H), 6.98 (d, J = 2.0 Hz, 2H), 6.95 (d, J = 2.1 Hz, 2H), 4.37 (t, J = 7.8 Hz, 1H), 4.20 (d, J = 13.9 Hz, 2H), 3.74 (t, J = 8.5 Hz, 1H), 3.50 (d, J = 14.0 Hz, 2H), 2.42 (q, J = 7.6 Hz, 2H), 2.20 (q, J = 7.4 Hz, 2H), 1.19 (s, 18H), 1.16 (s, 18H), 0.92 (overlapping t, 6H); ^{13}C NMR (100.133 MHz, $CDCl_3$, 230 K) δ 147.1, 146.3, 144.2, 143.6, 130.9, 129.2, 128.3, 127.9, 126.9, 126.1, 124.9, 121.6, 56.6, 37.2, 34.0, 33.9, 32.3, 31.3, 31.2, 24.9, 23.2, 13.8, 12.7; CI MS (−DCI) m/z 704.5 ($M^{\bullet-}$).

5,11,17,23-Tetra-*tert*-butyl-25,26,27,28-tetrahydroxy-2,-14-di(2-propyl)calix[4]arene (Trans Isomer, 16). To 50 mL of dry THF were added under an inert atmosphere at 0 °C 10.5 mL of a 2 M solution of *i*-PrMgCl in ether (21 mmol) and 0.34 g of CuCN (3.8 mmol). The mixture was stirred until a homogeneous solution was obtained, and then **9** (1 g, 1.25 mmol) was added. The mixture was stirred for 4 h, and during this period it was allowed to reach rt. After quenching with water, the aqueous phase was extracted with chloroform and the organic phase was dried ($MgSO_4$) and evaporated. The residue was recrystallized from $CHCl_3$/MeOH yielding 0.2 g (22%) **16**: mp 286 °C; ^{1}H NMR (400.133 MHz, $CDCl_3$, rt) δ

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10.52 (br s, 4H), 7.10 (d, $J = 2.0$ Hz, 2H), 7.07 (d, $J = 1.9$ Hz, 2H), 6.90 (d, $J = 1.9$ Hz, 4H), 4.19 (d, $J = 13.9$ Hz, 2H), 3.98 (d, $J = 11.1$ Hz, 1H), 3.47 (d, $J = 14.0$ Hz, 2H), 3.29 (d, $J = 11.8$ Hz, 1H), 3.12 (m, 1H), 2.77 (m, 1H), 1.21 (s, 18H), 1.15 (s, 18H), 0.94 (d, $J = 6.3$ Hz, 6H), 0.83 (d, $J = 6.3$ Hz, 6H); ^{13}C NMR (100.133 MHz, $CDCl_3$, 298 K) δ 147.1, 146.9, 144.3, 143.9, 131.0, 129.6, 128.5, 128.3, 127.2, 126.1, 124.8, 122.4, 34.1, 33.9, 32.8, 31.44, 31.36, 29.2, 27.3, 22.6, 21.6; CI MS (+DCI) 733.4 *m*/*z* (MH^+).

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **11**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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