Extraannular Fluorinated Calixarenes: Regiospecificity of the Deoxofluorination Reactions of Bis(spirodienol) Derivatives

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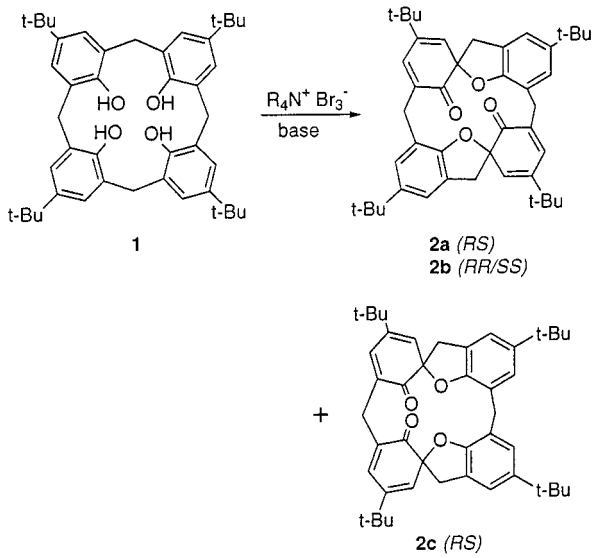
A new route for the partial displacement of OH groups of *p-tert*-butylcalixarene via spirodienol derivatives is described. $NaBH_4$ reduction of the bis(spirodienone) calixarene derivatives **2a**−**2c** afforded the corresponding bis(spirodienols) **3a**−**3c** in stereospecific fashion. ^{1}H NMR NOESY spectroscopy indicated that in the case of **2a**, the reaction proceeds by attack at the exo face of the two carbonyls (the face located anti to the spiro C−O bond). The spirodienols readily revert to *p-tert*-butylcalix[4]arene when heated. The reaction of **3a** with the deoxofluorinating agent DAST (Et_2NSF_3) afforded a mixture of extraannular substituted calixarenes possessing one or two fluoro-substituted dehydroxylated rings. The bisfluorinated calixarene **6a** adopts in the crystal a conformation (1,3-alternate) similar to that adopted in solution by the di-dehydroxylated calixarene **6b**. An experiment conducted with a selectively deuterated spirodienol derivative indicated that the deoxofluorination reaction involves regiospecific nucleophilic attack at the γ position of the pentadienol subunit.

Introduction

Calixarenes are organic macrocycles, readily synthesized by the condensation of para-substituted phenols and formaldehyde, which have emerged as one of the most useful building blocks in the preparation of molecular hosts.[1] To alter their preferred conformation, chemical properties, and binding capabilities, the calixarenes have been modified at the intraannular ("lower rim") and extraannular ("upper rim") positions.[1] These reactions have usually been based on the derivatization, rather than on the replacement, of the phenolic OH groups (a process requiring C−O cleavage). This is not surprising since, in contrast to an aliphatic OH group, its phenolic counterpart is notoriously reticent to undergo displacement reactions.[2,3] However, the calixarenes are polyphenolic compounds, thus allowing additional synthetic routes which would be extremely unlikely in simple phenols. Mild oxidation of the parent *p-tert*-butylcalix[4]arene (**1**) affords a mixture of bis(spirodienone) derivatives **2a**−**c** which can be separated by chromatography (eq 1).[4−7] In principle, it could be envisioned that the reduction of the carbonyl groups of **2a**−**c** should afford the corresponding bis(spirodienol) calixarene derivatives. The OH group of a spirodienol subunit is expected to undergo displacement reactions via treatment with a suitable reagent. In this paper, we describe the preparation of the bis(spirodienol) calixarenes **3a**−**c**, the displacement of the OH groups of **3a** by fluorine atoms, and the regioselectivity of the latter reaction.



1 **2a** *(RS)* **2b** *(RR/SS)* **2c** *(RS)* (1)

Results and Discussion

Preparation of the Bis(spirodienol) Derivatives 3a−c. The two faces of a given carbonyl group of **2a**−**c**

* To whom correspondence should be addressed.

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

(2) For a review on the OH replacement in calixarenes, see: Biali, S. E. *Isr. J. Chem.* **1997**, *37*, 131.

(3) 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. For a recent attempt to replace the OH groups of a calixarene, see: Chowdhury, S.; Bridson, J. N.; Georghiu, P. E. *J. Org. Chem.* **2000**, *65*, 3299.

(4) Litwak, A. M.; Grynszpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S. E. *J. Org. Chem.* **1993**, *58*, 393.

(5) For reviews on spirodienone calixarene derivatives, see: Aleksiuk, O.; Grynszpan, F.; Litwak, A. M.; 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, p 266.

(6) A modification of the reaction conditions enables the isolation of the major isomer **2a** without resorting to chromatography. See: Wang, W.-G.; Zhang, W.-C.; Huang, Z.-T. *J. Chem. Res., Synop.* **1998**, 462.

(7) For spirodienone derivatives of calixnaphthols, see: Georghiou, P. E.; Ashram, M.; Clase, H. J.; Bridson, J. N. *J. Org. Chem.* **1998**, *63*, 1819.

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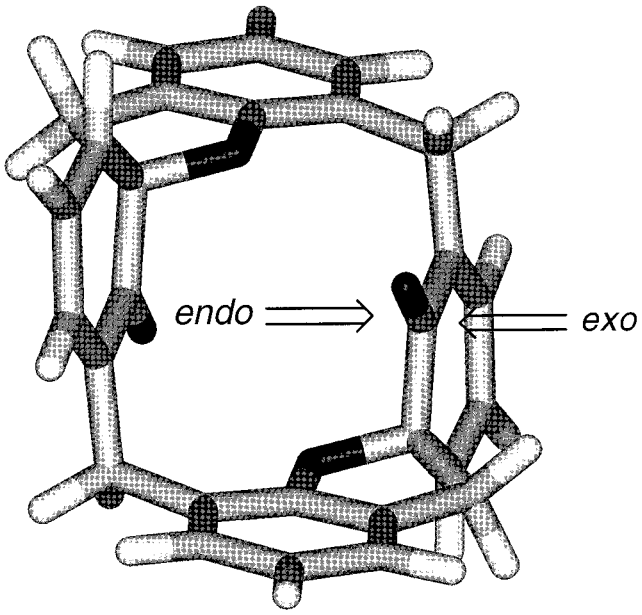


Figure 1. Exo and endo faces of the carbonyl groups of the meso bis(spirodienone) calixarene derivative **2a**. The *tert*-butyl groups have been omitted for clarity. The exo face is the one that is oriented anti to the spiro C−O bond.

are diastereotopic. These faces can be designated exo or endo on the basis of their location (on the external or internal surface of the molecule, Figure 1). The reaction of **2a**−**c** with $NaBH_4$ in a mixture of THF and EtOH proceeded in a stereospecific fashion and afforded in each case a different bis(spirodienol) derivative. The reaction of **2c** afforded a mixture of **3c** and **3a**, suggesting that some isomerization of the bis(spirodienone) derivative took place under the reaction conditions used. The reaction of **2a** with $NaBD_4$ afforded the methine-labeled derivative **4**. The signal patterns obtained in the ^1H and ^{13}C NMR spectra of **3a**−**c** are consistent with bis(spirodienol) derivatives retaining the symmetry of their corresponding bis(spirodienone) starting materials (C_i, C_2, and C_s point group symmetries for **2a**, **2b**, and **2c**, respectively). This indicates that in each case, the two carbonyl groups present in a given bis(spirodienone) derivative were attacked at the symmetry-related faces. The bis(spirodienol) derivatives possess four stereocenters, with two originating from the bis(spirodienone) starting material. The forms **3a** and **3c** are meso compounds, while **3b** is a chiral form obtained as a racemate (only one of the two enantiomers is depicted in the structural drawing of **3b**, see Chart 1).[8]

The methine proton of **3a** was readily identified in the ^1H NMR spectrum by comparison between the spectra of **3a** and its labeled derivative **4** (Figure 2). The methine protons of **3a**−**c** resonate at $\delta = 4.25-4.37$ ppm with a coupling constant to the OH proton in the range of $^3J_{HCOH} = 10.1-11.6$ Hz. Such a large coupling constant is consistent with the antiperiplanar torsional angles of the HCOH units.[9] The OH groups of **3c** resonate at a substantially lower field ($\delta = 4.75$ ppm) than those of **3a**

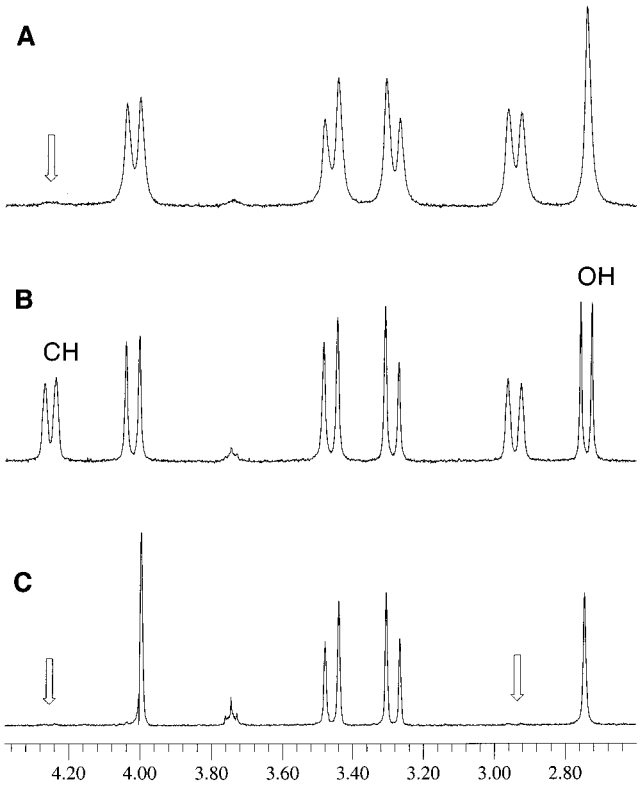
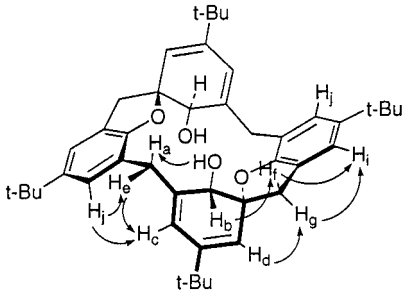


Figure 2. ^1H NMR spectra of the methylene region of **3a** (B, middle spectrum) and its dideuterio (**4**, A) and tetradeuterio (**8**, C) derivatives. The signals absent in the labeled compounds are indicated by arrows. The small signals at $\delta = 3.76$ ppm are due to residual THF.

Scheme 1



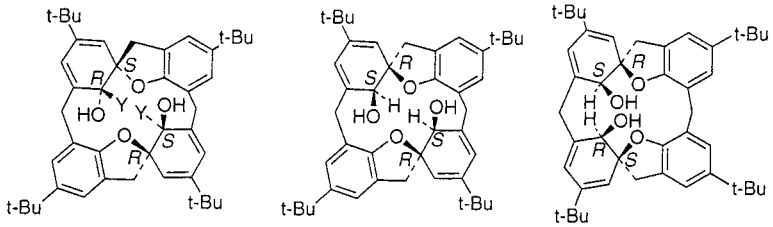
and **3b** ($\delta = 2.71$ and 2.87 ppm, respectively). The vinylic proton of **3a** that is resonating at 5.62 ppm (assigned to H_c, Scheme 1) appears as an apparent quartet. A DQF COSY spectrum indicated that this proton is coupled to the vinylic proton H_d, the equatorial methylene proton H_e, and the methine proton H_b. The latter coupling interaction (^4J ca. 2 Hz) is in agreement with a methine proton located in a pseudoaxial position of the cyclohexadiene ring. Such an arrangement, in which the methine C−H bond is nearly perpendicular to the neighboring double bond, is the ideal one for maximizing the usually small ^4J coupling interaction of the type H−C(sp^3)-C=CH.[10] To unravel the diastereoselectivity of the reduction of the carbonyl group and to assign the stereochemistry of the two new stereocenters formed, the NOESY NMR spectrum of **3a** was determined. A summary of the NOE interactions observed is depicted in Scheme 1. The doublets at 4.00 and 2.92 ppm were assigned to the axial

(8) The two enantiomers of **3b** could be rendered diastereotopic in the ^1H NMR spectrum by the addition of the chiral solvating agent (*S*)-2,2,2-trifluoro-1-(anthryl)ethanol (Pirkle, W. H.; Beare, S. D. *J. Am. Chem. Soc.* **1969**, *91*, 5150) to a $CDCl_3$ solution of **3b**.

(9) (a) Stollow, R. D.; Gallo, A. A. *Tetrahedron Lett.* **1968**, 3331. (b) Fraser, R. R.; Kaufman, M.; Morand, P.; Govil, G. *Can. J. Chem.* **1969**, *47*, 403.

(10) Günther, H. *NMR Spectroscopy*; Wiley: Chichester, 1980; p 116.

Chart 1

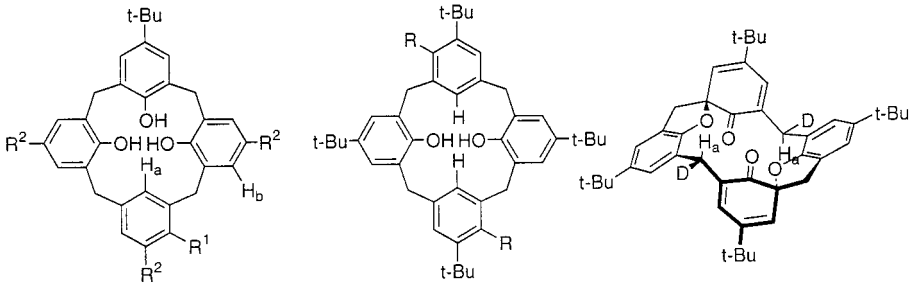


3a Y = H
4 Y = D

3b

3c

Chart 2



5a R^1 = F, R^2 = t-Bu
5b R^1 = H, R^2 = t-Bu
5c R^1 = H, R^2 = Me

6a R = F
6b R = H

7

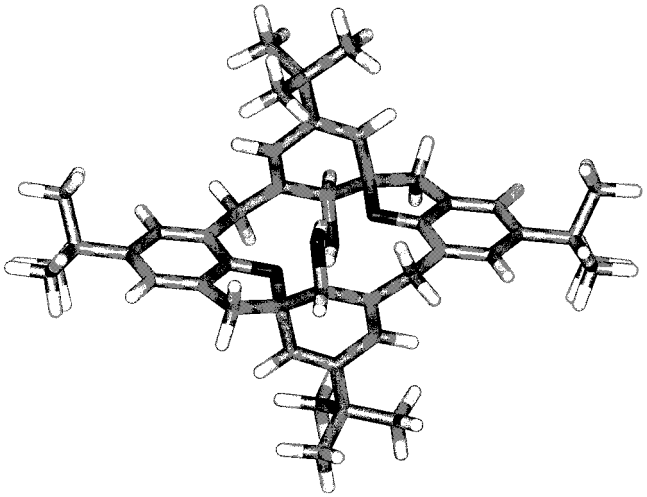


Figure 3. Calculated (MM3) structure of the bis(spirodienol) derivative **3a**.

and equatorial methylene protons H_a and H_e. NOE cross peaks were observed between the methine signal H_b resonating at 4.25 ppm and the dihydrofuran methylene proton H_f while the OH doublet displayed a NOE interaction with the axial methylene proton H_a. These NOE interactions suggest that the methine proton is located on the external surface of the molecule, while the OH is in the proximity of the axial methylene proton H_a. From the NOE interactions observed, it can be concluded that the bis(spirodienol) product obtained is derived from the delivery of the hydride to the exo face of each carbonyl group.

MM3 calculations were conducted on the bis(spirodienol) obtained from **2a**, assuming that the compound originated from the delivery of hydride in the manner described above (i.e., **3a**). The calculated conformation of **3a** (Figure 3) is very similar to the one determined by X-ray crystallography for **2a**,[4] and its interatomic nonbonded distances are in full agreement with the experimentally observed NOE interactions. The methine proton is located in a pseudoaxial position of the cyclohexadiene ring, while the OH is on a pseudoequatorial position. The two dihydrofuran oxygens are oriented toward the center of the macrocyclic ring.

By analogy with **3a**, it seems highly likely that both **3b** and **3c** are also derived from an exo face carbonyl reduction process. The downfield shift of the OH groups of **3c** (compared to those of **3a** and **3b**) is also consistent with exo attack, since it suggests an intramolecular hydrogen bond interaction, and only when directed to the central part of the macrocycle can the two OH groups be engaged in such a bond.[11] The observed selectivity of the hydride delivery for the exo face is reasonable, since this is the less hindered face, and reactions of a dioxamethylene monospirodienone derivative with $NaBH_4$[12] and of the bis(spirodienone) **2b** with MeLi[13] have been shown to proceed via attack at the exo faces of the carbonyl groups.

The spirodienols **3a**−**3c** are all structural isomers of the parent **1** and are converted to this compound by being heated or by being treated with acids. Compound **3b** (derived from the less stable bis(spirodienone) isomer **2b**)[4] was the less kinetically stable spirodienol isomer and rapidly reverted to **1** in solution, even in the absence of acids.

Nucleophilic Substitution of Allylic Systems. Allylic derivatives can undergo nucleophilic displacement of a leaving group via S_N1 or S_N2 mechanisms.[14] These routes lead to products with the nucleophile attached to

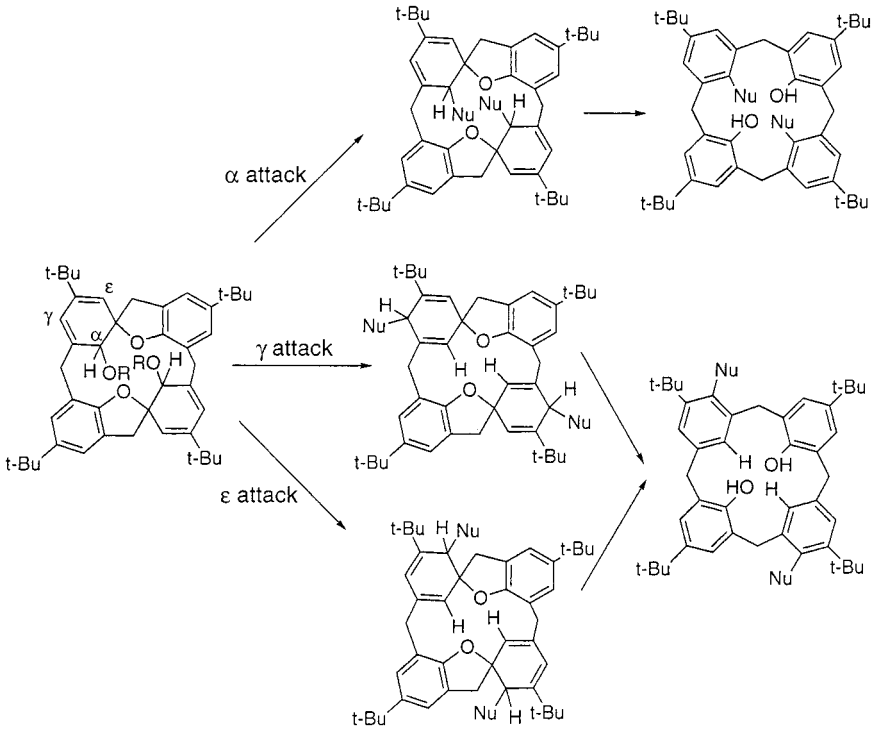
(11) The distance between the two nonvicinal cyclohexadienol rings of **3a** and **3b** is most likely too large to allow for an intramolecular hydrogen bond.

(12) Wöhnert, J.; Brenn, J.; Stoldt, M.; Aleksiuk, O.; Grynszpan, F.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1998**, *63*, 3866.

(13) Van Gelder, J. M.; Brenn, J.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **1997**, *62*, 3511.

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

Scheme 2



the carbon that was formerly connected to the leaving group. Alternatively, the replacement can proceed with a concomitant double bond shift (an allylic rearrangement or allylic shift) via S_N1' or S_N2' mechanisms. This yields products with the nucleophile attached to the former allylic (γ) position to the leaving group.[14] Substituted pentadienols possess an additional reactive position (ϵ to the OH group) that is capable of undergoing nucleophilic attack.[17]

The bis(spirodienol) **3a** was chosen as the substrate for a nucleophlic substitution reaction, since it is derived from **2a** which is the bis(spirodienone) derivative obtained with the highest yield. In principle, nucleophilic attack at the bis(spirodienol) calixarene derivatives (e.g., after increasing the nucleofugality of the OH groups via derivatization) might occur at the α, γ, or ϵ positions, with the last two pathways involving the concomitant shift of one or two double bonds. The reactions involving attack at the γ or ϵ position are expected to afford, after aromatization of the resulting products, meta-substituted systems possessing a hydrogen atom at the intraannular positions. Nucleophilic displacement at the α position followed by aromatization should afford derivatives with the nucleophile located at the intraannular position. The possible reaction routes, assuming that both spirodienol subunits react with identical regioselectivities, are summarized in Scheme 2.

Displacement of the Alcoholic OH Group by Fluorine. The OH group of aliphatic alcohols can be replaced by fluorine by treatment with the deoxofluorinating reagent DAST (Et_2NSF_3).[15] The deoxofluorination of an allylic OH group using DAST can occur with or without allylic rearrangement depending on the substrate.[16,17]

A solution of bis(spirodienol) **3a** in CH_2Cl_2 reacted rapidly with DAST at −78 °C giving a mixture of the mono- and difluorinated derivatives **5a** and **6a** (8 and 29% yields, respectively) together with **1**. The isolation of the fluorinated calixarenes indicates that the initially formed fluorine-substituted spirodienes were aromatized under the reaction conditions. The presence of a single difluoro derivative suggests that the reaction proceeds with high regioselectivity and that a single position of the dienol group (γ or ϵ to the OH group) was selectively attacked.

^{1}H NMR Spectra of 6a and 5a. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **6a** resembles that of the unsubstituted 1,3-dehydroxylated calixarene **6b**,[18] which according to low temperature ^{1}H NMR spectra adopts a 1,3-alternate conformation in solution.[18b,19] The presence of the fluorine substituent was evident in the NMR spectrum since two aromatic protons signals at $\delta = 7.12$ and 6.06 ppm showed a substantial ^{1}H, ^{19}F coupling ($^4J_{HF} = 6.4$ Hz). By analogy to **6b**, the high field signal is assigned to the intraannular aromatic protons, and its chemical shift suggests that the molecule adopts a 1,3-alternate conformation in solution.[19,20] In such an arrangement, the intraannular protons are located in the shielding regions of the adjacent rings, thus resulting in an upfield shift of these protons. This assignment of the high field aromatic signal to the intraannular protons

(15) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.
(16) See for example: Hammond, G. B.; deMendonca, D. J. *J. Fluorine Chem.* **2000**, *102*, 189.
(17) Gree, D.; Gree, R.; Boukerb, A.; Laabassi, M. *Tetrahedron Lett.* **1997**, *38*, 6209.
(18) (a) Grynszpan, F.; Goren, Z.; Biali, S. E. *J. Org. Chem.* **1991**, *56*, 532. (b) Grynszpan, F.; Biali, S. E. *Tetrahedron Lett.* **1991**, *38*, 5155. (c) Ting, Y.; Verboom W.; Groenen, L. C.; van Loon, J.-D.; Reinhoudt, D. N. *J. Chem. Soc., Chem. Commun.* **1990**, 1432. (d) Sachleben, R. A.; Urvoas, A.; Bryan, J. C.; Haverlock, T. J.; Moyer, B. A.; Hay, B. P. *Chem. Commun.* **1999**, 175.
(19) Harada, T.; Ohseto, F.; Shinkai, S. *Tetrahedron* **1994**, *50*, 13377.
(20) For MM3 calculations on the conformation and rotational barriers of **6b**, see: Thondorf. I. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1791 and ref 19. The MM3 calculations underestimate the relative stability of the 1,3-alternate form.

was corroborated by a labeling experiment (see below). A single singlet was observed for the methylene protons of **6a**, in agreement with fast rotations around the Ar−CH_2 bonds on the NMR time scale, and an accidental isochrony of the two heterotopic methylene groups ortho and para to the fluorine substituent. The accidental isochrony between the two methylene groups observed in $CDCl_3$ was removed in C_6D_6 where the groups appeared as two well-separated singlets at 4.00 and 3.92 ppm. The signal of the *t*-Bu groups on the fluorinated rings (identified by a 2D H−C correlation NMR spectrum) was broader than the *t*-Bu signal on the nonfluorinated rings due to an unresolved long-range ^1H, ^{19}F coupling.

The ^1H NMR spectrum of **5a** in C_6D_6 is more complex than that of **5b**[21a] due to its lower symmetry and the presence of the magnetically active fluorine atom. As observed for **6a**, the two aromatic protons on the dehydroxylated ring display a substantial coupling ($J_{HF} = 7.7$ Hz) to the fluorine atom. One of the signals of the phenol aromatic protons resonated at a lower field than the rest. This signal appeared as a triplet ($J = 2.2$ Hz) indicating that in addition to the ^1H,^1H meta coupling a ^1H,^{19}F coupling is also present and that the two coupling constants are accidentally of the same magnitude. The presence of a ^1H,^{19}F coupling interaction was corroborated by a fluorine decoupling experiment (Figure 4). Since the number of bonds separating the fluorine and its closest proton is too large (at least six bonds) for a conventional "through bond" coupling interaction, the observed scalar spin−spin ^1H,^{19}F coupling must be through space. This type of coupling interaction is observed when the two nuclei are in steric proximity.[22] On this basis, this signal is assigned to the unique phenol aromatic proton vicinal to the fluorine atom (H_b). In contrast to **6a**, the intraannular aromatic proton of **5a** (H_a) resonated at low field (7.45 ppm). The downfield location of H_a and H_b and the presence of a through space ^1H,^{19}F coupling are in agreement with a syn arrangement of the fluorinated ring and the phenol ring being vicinal to the fluorine substituent. The chemical shift of H_a shows a significant dependence on the concentration and temperature of the sample, changing from $\delta = 7.45$ at 298 K to $\delta = 7.18$ at 347 K. These temperature and concentration effects, previously observed by Fukazawa[21b] and Shinkai[19] for the calixarene **5c**,[21a] have been rationalized as indicating an intermolecular hydrogen bond between two mono-dehydroxylated calixarene molecules.

^{13}C NMR Spectrum. Fluorocalixarene **6a** displayed in the ^{13}C NMR a doublet for the fluorinated carbons at 158.7 ppm ($^1J_{C-F} = 247$ Hz). Two well-separated signals at 29.19 and 37.38 ppm were observed for the methylene carbons. The higher field signal appeared as a doublet with a noticeable coupling constant ($J = 6.8$ Hz). This coupling is ascribed to a $^3J_{C-F}$ interaction, and therefore, this signal is assigned to the methylene carbons ortho to a fluorine atom.[23] Corroborating evidence for this assignment was obtained by a 2D C−H correlation spectrum. The signal of the $C(CH_3)_3$ atoms on the dehydroxylated rings ($\delta = 30.09$ ppm) could be identified by its coupling to the fluorine atom ($J = 3.4$ Hz).

X-ray Crystallography. Single crystals of the fluorinated calixarene **6a** were grown from chloroform/acetonitrile and submitted to X-ray crystallography. Compound **6a** adopts in the crystal a 1,3-alternate conformation (Figure 5). The crystal structure of the parent **6b**·2MeOH[18a] has shown that it adopts a 1,2-alternate conformation, in contrast to solution data and calculations which suggest the presence of the 1,3-alternate from. The presence of the higher energy 1,2-alternate form in the crystal of **6b** is probably due to hydrogen bonds between **6b** and the MeOH molecules as well as due to packing forces.

Regioselectivity of the Deoxofluorination: γ vs ϵ Attack. The symmetry of product **6a** indicates that both the spirodienol groups in **3a** react with identical regioselectivity. Thus, both groups were attacked by the nucleophile at the same γ (allylic) or ϵ (pentadienylic) positions to the alcoholic OH group. Unfortunately, the spontaneous isomerization of the initial product "erases" the information concerning the initial regioselectivity of the nucleophile attack since the two isomeric spirodiene derivatives resulting from the attack at either the γ or ϵ carbon yield identical products after the isomerization (Scheme 2).

To determine the regioselectivity of the nucleophilic attack, the labeled spirodienol **8** was prepared by reduction of the deuterated bis(spirodienone) **7** (possessing two trans deuterium atoms at the methylene positions)[24] with $NaBD_4$. The ^1H NMR spectrum of **8** resembles that of the parent spirodienol **3a**, except that the signals ascribed to the equatorial methylene proton H_e and to the methine protons H_b are absent in the labeled derivative (Figure 2). The axial methylene proton H_a and the OH proton (which are coupled to H_e and H_b, respectively, in **3a**) appear as singlets in **8**, due to the replacement of the latter protons by deuterons.[25]

The labeled derivative **8** enabled us to distinguish between the two possible reaction pathways. If the deoxofluorination reaction involves γ attack, the meta fluorine atoms in the product should be located ortho to a labeled methylene group (**9a**), whereas if the reaction proceeds by ϵ attack, the fluorine should be located para to a labeled methylene (**9b**, Scheme 3).

Reaction of the labeled **8** with DAST largely afforded a labeled difluorinated product. A comparison of the ^1H NMR spectrum of the labeled derivative with that of **6a** indicated that the signal resonating at 6.06 ppm is missing. Hence, it must correspond to the intraannular protons of the dehydroxylated rings. The absence of such a signal in the labeled derivative indicates that the methine C−D bond in the spirodienol is not cleaved during the reaction. A comparison of the ^{13}C NMR spectra of **6a** with that of the labeled difluorinated product (Figure 6) indicated that the signals at $\delta = 124.51$ (assigned to the intraannular carbon on the fluorinated ring) and at 29.19 ppm (assigned to the carbon ortho to the fluorine substituent) almost completely disappeared

(21) (a) Grynszpan, F.; Aleksiuk, O.; Biali, S. E. *J. Org. Chem.* **1994**, *59*, 2070. (b) Fukazawa, Y.; Deyama, K.; Usui, S. *Tetrahedron Lett.* **1992**, *33*, 5803.

(22) Ernst, L.; Ibrom, K. *Magn. Reson. Chem.* **1997**, *35*, 868.

(23) Chemical shift arguments also support this assignment. For example, the calculated ^{13}C NMR chemical shifts of the methylene groups ortho and para to the fluorines (calculated by the ChemDraw 6.0 program on the basis of group increments) are $\delta = 21.5$ and 32.3 ppm.

(24) The preparation of the labeled bis(spirodienone) will be reported elsewhere: Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.*, in press.

(25) A H, D coupling is 6.5 times smaller than the corresponding H, H coupling as a result of the smaller gyromagnetic ratio of the deuteron. Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982; p 124.

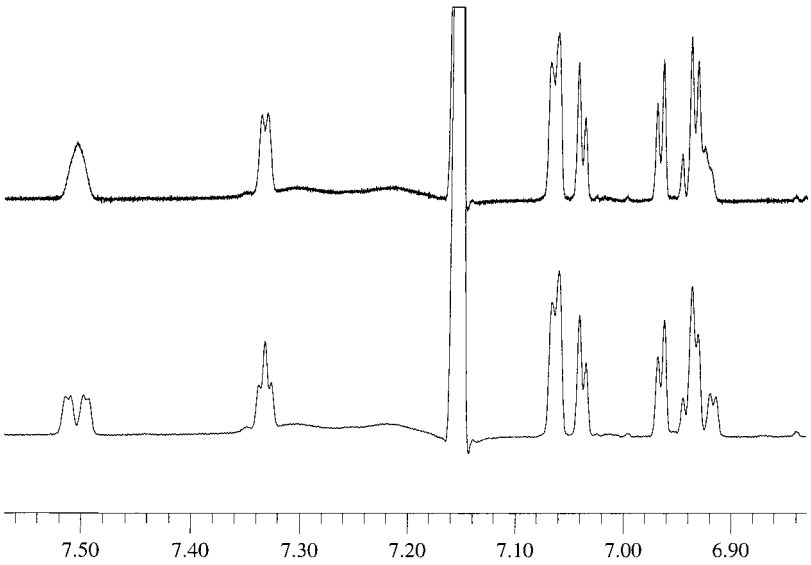


Figure 4. Resolution enhanced 400 MHz ^{1}H NMR spectrum of **5a** in C_6D_6 (aromatic region) with (top) and without (bottom) ^{19}F irradiation. In addition to the changes observed in the signals of the fluorinated ring, the phenolic aromatic triplet at 7.33 ppm becomes a doublet upon irradiation. The changes observed for the phenolic signal are consistent with the presence of a through space ^{1}H, ^{19}F coupling interaction. The small singlet at 6.94 ppm is due to the presence of a small amount of **1** in the sample.

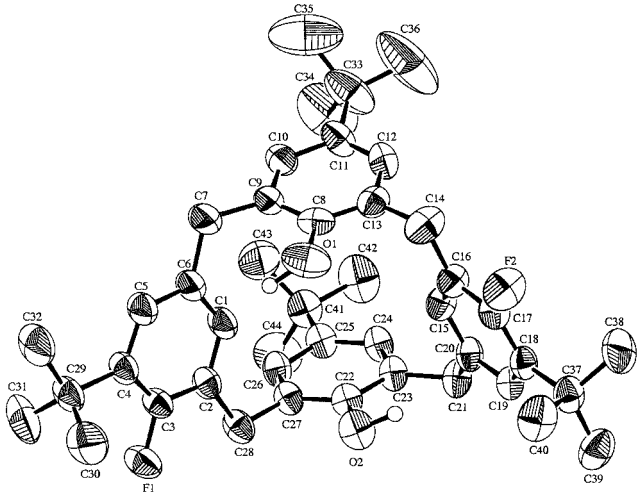
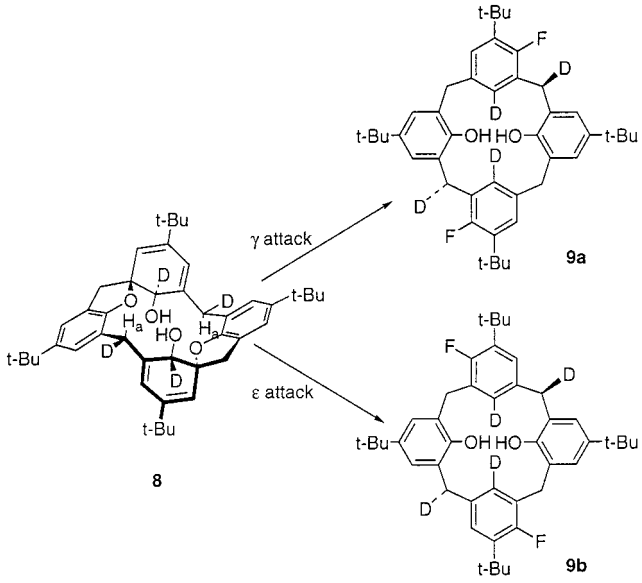


Figure 5. X-ray structure of the difluorocalixarene derivative **6a**.

Scheme 3



in the product. These signals must correspond to carbons that in the labeled difluorinated product are attached to deuterons.[26] The methylene carbon para to the fluorine group remained unchanged in the ^{13}C NMR spectrum. We conclude that the product obtained is **9a**, generated by γ attack, with the fluorine groups ortho to a labeled methylene. The preferential formation of **9a** demonstrates that the reaction of **3a** with DAST proceeds by a regiospecific attack at the γ position of the dienol.

Conclusions. $NaBH_4$ reduction of the carbonyl groups of the bis(spirodienone) derivative proceeds in an exo fashion and affords spirodienol derivatives. These spirodienols readily revert to calixarenes when heated or when treated with acid. Deoxofluorination of spirodienol **3a** is achieved by reaction with DAST. Labeling experiments indicate that the reaction proceeds by a nucleophilic attack at the γ (i.e., allylic) position to the OH group with a high regioselectivity.

Experimental Section

MM3(94) calculations were performed using the Alchemy 2000 program.[27] ^{19}F chemical shifts are relative to $FCCl_3$.

Crystallography. The X-ray diffraction data were measured with an Enraf-Nonius CAD-4 computer-controlled diffractometer. Cu Kα (λ = 1.541 78 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. Crystal data for **6a**: $C_{44}H_{54}O_2F_2$, space group $P\bar{1}$, a = 13.346(4) Å, b =16.260(7) Å, c = 9.495(6) Å, α = 96.82(4)°, β = 108.31(4)°, γ

(26) Under usual conditions for the acquisition of carbon NMR signals (i.e., broadband proton decoupling and pulse delays shorter than their relaxation time), deuterated carbons display substantially weaker ^{13}C NMR signals than protonated carbons. The weaker signals are a result of the absence of H, C NOE enhancements, the presence of C, D coupling interactions, and the longer relaxation times of the deuterated carbons. See: Wehrli, F. W.; Wirthlin, T. *Interpretation of Carbon-13 NMR Spectra*; Heyden: London, 1976; p 107.

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

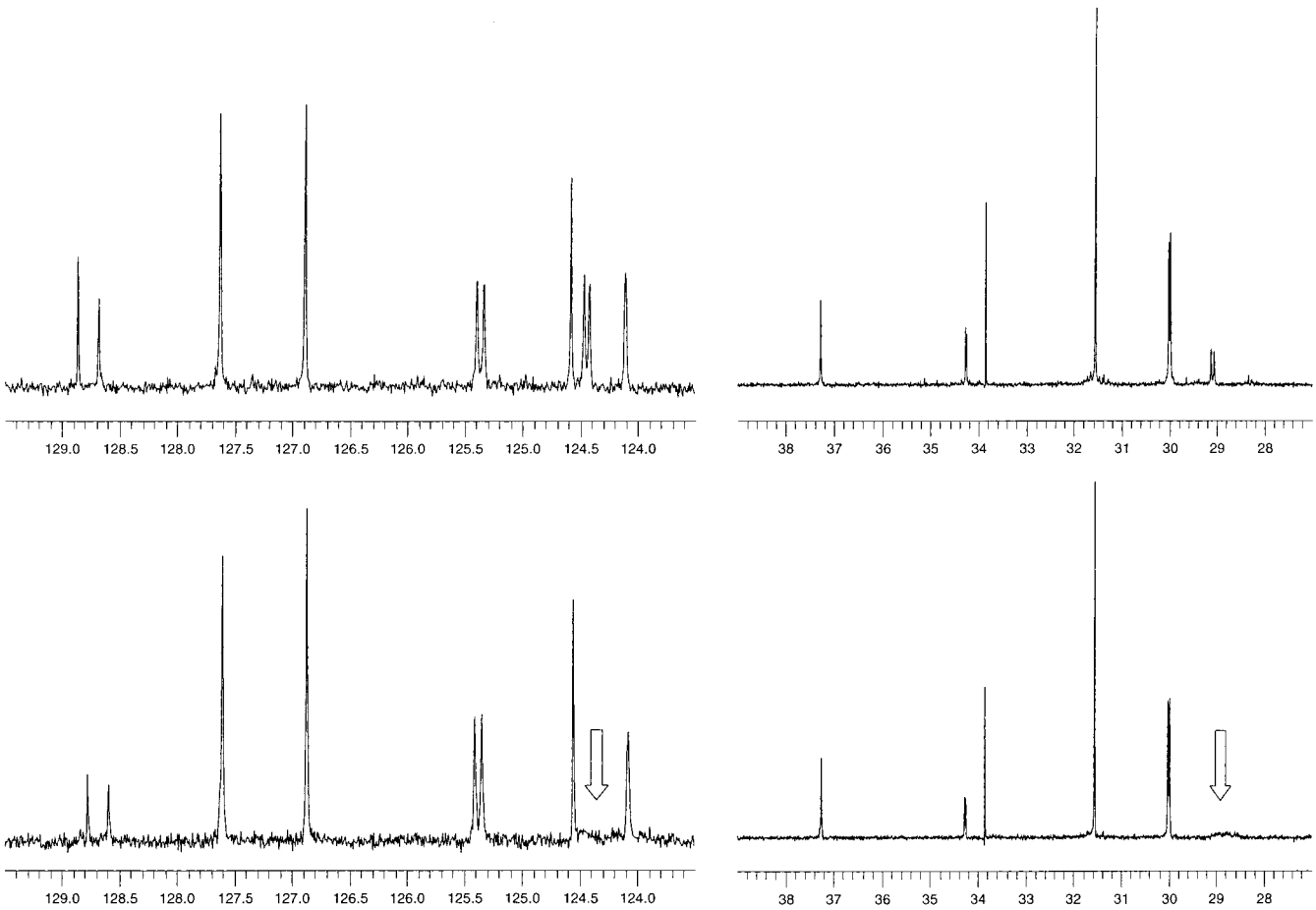


Figure 6. ^{13}C NMR spectra (left, part of the aromatic region; right, aliphatic region) of the difluorocalixarene **6a** (top) and its tetradeutero derivative **9a** (bottom). The high field doublet in the methylene region of **6a** (assigned to the methylenes ortho to the fluorine atoms) is absent in the labeled product (right arrow), while the upfield methylene signal (corresponding to the methylenes para to the fluorines) remained unchanged. This suggests that the deoxofluorination reaction proceeded via γ attack. The labeled intraannular aromatic carbon is missing in the spectrum of **9a** (left arrow).

= 98.27(3)°, V = 1906(2) Å^3, Z = 2, ρ_{calc} = 1.14 g cm^{-3}, μ (Cu Kα) = 5.88 cm^{-1}, no. of unique reflections = 7229, no. of reflections with $I \geq 3\sigma_I$ = 5871, R = 0.060, and R_w = 0.078.

Preparation of the Bis(spirodienol) Calixarene Derivative 3a. To 500 mg (0.77 mmol) of **2a** dissolved in 300 mL of a 1:1 mixture of THF and EtOH was added 1 g (26.4 mmol) of $NaBH_4$. After the mixture was stirred at room temperature for 20 min, the solvent was evaporated and the solid residue was dissolved in CH_2Cl_2. After the solution was washed twice with water, the solvent was evaporated at room temperature. Treatment of the residue with toluene/methanol afforded 241 mg (0.37 mmol, 48%) of pure **3a**, mp 178−182 °C (dec). ^1H NMR (400.133 MHz, $CDCl_3$, rt): δ 7.05 (s, 2H, ArH$_i$), 6.98 (s, 2H, Ar-H$_j$), 5.62 (q, J = 2.0 Hz, 2H, C=CH$_c$), 5.48 (s, 2H, C=CH$_d$), 4.25 (br d, ^2J = 11.1 Hz, 2H, H_b-COH), 4.00 (d, ^2J = 13.2 Hz, 2H, HCH_a), 3.44 (d, ^2J = 15.4 Hz, 2H, HCH_f), 3.27 (d, ^2J = 15.6 Hz, 2H, HCH_g), 2.92 (br d, ^2J = 15.1 Hz, 2H, HCH_e), 2.71 (d, ^2J = 12.5 Hz, 2H, OH), 1.33 (s, 18H, *t*-Bu), 0.94 (s, 18H, *t*-Bu). ^{13}C NMR (100.61 MHz, rt, $CDCl_3$): δ 154.4, 147.1, 143.0, 142.8, 125.9, 125.6, 122.5, 121.2, 119.7, 118.1, 87.3 (C spiro), 75.7 (CHOH), 42.4, 34.2, 34.0, 31.8, 29.7, 28.5 ppm. CI MS m/z 649.1 (MH$^+$).

Preparation of 3b. A 1 g portion (1.54 mmol) of bis(spirodienol) **2b** was dissolved in a mixture of 60 mL of THF and 20 mL of EtOH. The reaction mixture was cooled to 0 °C, and then 0.5 g of $NaBH_4$ was added. After the mixture was stirred for 1 h at 0 °C, 20 mL of water and 80 mL of CH_2Cl_2 were added. The organic layer was separated, dried, and evaporated at room temperature. The residue was treated with 30 mL of CH_3OH, and the undissolved solid (*p*-*tert*-butylcalix[4]arene, **1**) was filtered. Evaporation of the solvent at room temperature afforded 0.35 g (35%) of **3b**, mp (dec) 70 °C. ^1H NMR (400.133 MHz, $CDCl_3$, rt): δ 7.01 (s, 2H, ArH), 6.92 (s, 2H, Ar-H), 5.87 (br s, 2H, C=CH), 5.54 (s, 2H, C=CH), 4.32 (d, ^2J = 10.1 Hz, 2H, *H*COH), 3.73 (d, ^2J = 16.8 Hz, 2H, CH$_2$), 3.64 (d, ^2J = 16.8 Hz, 2H, CH$_2$), 3.41 (d, ^2J = 15.3 Hz, 1H, CH$_2$), 3.12 (d, ^2J = 15.8 Hz, 2H, CH$_2$), 2.87 (d, ^2J = 10.2 Hz, 2H, OH), 1.27 (s, 18H, *t*-Bu), 1.01 (s, 18H, *t*-Bu). ^{13}C NMR (100.61 MHz, rt, $CDCl_3$): δ 154.94, 146.59, 143.10, 139.37, 127.32, 125.34, 121.17, 119.86, 119.63, 118.55, 87.31, 77 (HCOH, hidden by solvent), 41.42, 38.49, 34.12, 34.01, 31.73, 28.66.

Preparation of 3c. The bis(spirodienone) calixarene derivative **2c** (753 mg, 1.15 mmol) was dissolved in a mixture of 230 mL of THF and 250 mL of ethanol. $NaBH_4$ (1.02 g) was added to the solution, and the mixture was stirred at room temperature for 20 min. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 and washed twice with water, and the organic phase was dried and evaporated. After the residue was dissolved in methanol, the precipitate that formed was filtered yielding 275 mg of a mixture of **3a** and **3c**. Trituration of the solid with hot *n*-hexane followed by filtration and evaporation of the filtrate afforded 180 mg (0.28 mmol, 25%) of **3c**, mp 164 °C (the residue consisted of 80 mg of **3a**). ^1H NMR (400.133 MHz, $CDCl_3$, rt): δ 7.11 (s, 2H, ArH), 6.96 (s, 2H, Ar-H), 6.04 (s, 2H, C=CH), 5.54 (s, 2H, C=CH), 4.75 (d, ^2J = 11.6 Hz, 2H, OH), 4.37 (d, ^2J = 11.6 Hz, 2H, *H*COH), 4.11 (d, ^2J = 13.0 Hz, 1H, CH$_2$), 3.44 (d, ^2J = 15.3 Hz, 3H, CH$_2$), 3.26 (d, ^2J = 13.5 Hz, 1H, CH$_2$), 3.12 (d, ^2J = 15.5 Hz, 2H, CH$_2$), 2.94 (d, ^2J = 13.6 Hz, 1H, CH$_2$), 1.26 (s, 18H, *t*-Bu), 1.07 (s, 18H, *t*-Bu). ^{13}C NMR (100.61 MHz, rt, $CDCl_3$): δ 154.3, 147.9, 143.8, 142.9, 126.6, 125.5, 121.9, 121.5, 119.5, 119.3,

88.2 (C spiro), 75.8 (CHOH), 40.6, 34.2, 31.7, 28.5, 22.7, 14.1 ppm. CI MS *m*/*z* 649.1 (MH^+).

Preparation of the Monofluoro- and Difluorocalixarene Derivatives 5a and 6a. To a stirred solution of 1.6 g (2.4 mmol) of bis(spirodienol) **3a** in 180 mL of dry CH_2Cl_2 at −78 °C was added, during 10 min under an inert atmosphere, 6 mL (43.5 mmol) of DAST. The temperature was raised slowly to room temperature, and the mixture was stirred for 12 h. The excess of DAST was quenched with water (100 mL). After phase separation, the organic phase was washed several times with water and evaporated. The residue was treated with 30 mL of Et_2O, and the undissolved material (a mixture of **5a** and **1** according to NMR) was filtered. The residue obtained after evaporation of the solvent was purified by chromatography (silica, $CHCl_3$/hexane, 3:1) yielding 0.45 g (29%) of **6a**, mp 268 °C. Purification of **5a** was achieved by trituration of the mixture of **5a** + **1** with hot hexane (which dissolved **5a**). The solvent was evaporated, and the residue was recrystallized from Et_2O, yielding 0.12 g (8%) of **5a**, mp 248 °C.

Spectroscopic Data of 6a. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt): δ 7.12 (br d, J = 6.4 Hz, 2H, ArH), 7.01 (d, J = 2.4 Hz, 2H, ArH), 6.96 (d, J = 2.4 Hz, 2H, ArH), 6.06 (br d, J = 6.4 Hz, 2H, ArH), 4.11 (s, 2H, OH), 3.90 (s, 8H, CH_2), 1.40 (s, 18H, *t*-Bu), 1.22 (s, 18H, *t*-Bu). ^{13}C NMR (100.61 MHz, rt, $CDCl_3$): δ 158.7 (C_{Ar}-F, d, J = 247 Hz), 150.26, 143.45, 136.69 (d, J = 13.0 Hz), 133.92 (d, J = 3.7 Hz), 128.86 (d, J = 18.3 Hz), 127.72, 126.98, 125.45, (d, J = 6.2 Hz), 124.64, 124.51 (d, J = 4.9 Hz), 124.17, 37.38, 34.37 (d, J = 2.5 Hz), 33.95, 31.65, 30.09 (d, J = 3.4 Hz), 29.19 (d, J = 6.8 Hz). ^{19}F NMR (376.4 MHz, $CDCl_3$): δ −117.56 ppm. CI MS *m*/*z* 653.1 (MH^+).

Spectroscopic Data of 5a. ^{1}H NMR (400.133 MHz, C_6D_6, rt): δ 8.78 (OH, br) 7.44 (dd, J = 6.4, 2.0 Hz, 1H, H_a), 7.32 (t, J = 2.2 Hz, 1H, H_b), 7.30 (OH, br), 7.21 (OH, br), 7.06 (overlapping dd, J = 2.1 Hz, 2H, Ar−H), 7.04 (d, J = 2.3 Hz, 1H, Ar−H), 6.95 (d, J = 2.3 Hz, 1H, Ar−H), 6.92 (d, J = 2.1 Hz, 1H, Ar−H), 6.91 (partially hidden dd, J = 2.0 Hz, 1H, Ar−H), 3.92 (s, 2H, CH_2), 3.845 (s, 2H, CH_2), 3.838 (s, 2H, CH_2), 3.78 (s, 2H, CH_2), 1.22 (s, 9H, *t*-Bu), 1.21 (s, 9H, *t*-Bu), 1.10 (s, 9H, *t*-Bu), 1.00 (s, 9H, *t*-Bu). ^{13}C NMR (100.61 MHz, rt, $CDCl_3$): δ 158.54 (C−F, d, J = 246.1 Hz), 148.28, 148.14, 147.21, 144.57, 144.31, 144.18, 136.62 (d, J = 13.0 Hz), 136.00 (d, J = 4.5 Hz), 128.96 (d, J = 17.9 Hz), 128.27, 127.82, 127.78, 127.68, 127.63, 127.54, 127.41, 126.83, 125.96, 125.83, 125.76, 125.73, 125.61, 125.54, 37.32, 34.32 (d, J = 2.0 Hz), 34.09, 34.05, 33.09, 32.89, 31.48, 30.0 (d, J = 3.4 Hz), 29.4 (d, J = 4.6 Hz). ^{19}F NMR (376.4 MHz, $CDCl_3$): δ −118.86 ppm. CI MS *m*/*z* 651.5 (MH^+).

General Procedure for the Preparation of the Labeled Bis(spirodienol) Derivatives. To a solution of 0.5 g of **2a** or **7** in 300 mL of THF/EtOH (1:1) was added 1 g (24 mmol) of $NaBD_4$. The mixture was stirred at room temperature for 1 h. The solvent was evaporated, and the solid residue was dissolved in 50 mL of CH_2Cl_2. The organic layer was washed several times with water, filtered, and dried. The solvent was evaporated, and to the residue were added 15 mL of $CHCl_3$ and 70 mL of CH_3OH. The precipitate was filtered, washed with 10 mL of CH_3OH, and dried under suction yielding 0.24 g (47%) of the corresponding labeled bis(spirodienol), mp 178−183 °C (dec) (**4**) and 178−182 (dec) °C (**8**). The products can be further purified by dissolution in cold toluene and precipitation by the addition of MeOH.

Spectroscopic Data for 8. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt): δ 7.07 (s, 2H, ArH), 7.00 (s, 2H, Ar-H), 5.64 (d, J = 1.8 Hz, 2H, C=CH), 5.48 (d, J = 1.8 Hz, 2H, C=CH), 4.00 (s, 2H, CHD), 3.46 (d, ^2J = 15.3 Hz, 2H, CH_2), 3.29 (d, ^2J = 15.3 Hz, 2H, CH_2), 2.75 (s, 2H, OH), 1.33 (s, 18H, *t*-Bu), 0.95 (s, 18H, *t*-Bu). ^{13}C NMR (100.4 MHz, rt, $CDCl_3$): δ 154.5, 147.1, 143.1, 142.8, 125.9, 125.7, 122.4, 121.3, 119.7, 118.2, 87.4 (C spiro), 42.4, 34.3, 34.1, 31.9, 28.6 ppm. CI MS *m*/*z* 652.5.

Preparation of the Labeled Difluorocalixarene 9a. The reaction was conducted using the procedure described for **6a**. Compound **8** (1 g, 1.5 mmol) dissolved in 120 mL of dry CH_2Cl_2 was reacted at −78 °C with 4 mL (29 mmol) of DAST. After chromatography and recrystallization from petroleum ether, 0.32 g (32%) of **9a** was obtained, mp 266 °C. ^{1}H NMR (400.133 MHz, $CDCl_3$, rt): δ 7.14 (br d, J = 6.4 Hz, 2H, ArH), 7.03 (d, J = 2.4 Hz, 2H, ArH), 6.98 (d, J = 2.4 Hz, 2H, ArH), 4.12 (s, 2H, OH), 3.92 (s, 4H, CH_2), 3.90 (s, 2H, CHD), 1.41 (s, 18H, *t*-Bu), 1.24 (s, 18H, *t*-Bu). ^{13}C NMR (100.4 MHz, rt, $CDCl_3$) δ 158.7 (C_{Ar}-F, d, J = 247 Hz), 150.27, 143.46, 136.74 (d, J = 13.0 Hz), 133.85 (d, J = 3.7 Hz), 128.78 (d, J = 18.3 Hz), 127.70, 126.97, 125.47 (d, J = 6.2 Hz), 124.65, 124.18, 37.36, 34.37 (d, J = 2.5 Hz), 33.96, 31.66, 30.09 (d, J = 3.4 Hz). CI MS *m*/*z* 657.5.

Acknowledgment. We thank Dr. Shmuel Cohen for the crystal structure determination and Dr. Joel M. Van Gelder and Dr. Iris Thondorf for discussions.

Supporting Information Available: Crystallographic tables for **6a** and ^{1}H NMR spectra of **3a**−**c**, **4**, **5a**, **6a**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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