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A "Classical" Tetrahydroxycalix[4]arene Adopting the 1,2-Alternate Conformation

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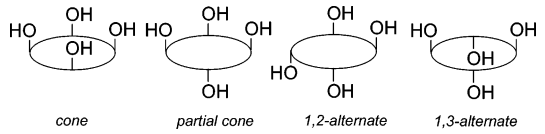
The first example of a "classical" tetrahydroxycalixarene, which adopts the 1,2-alternate conformation both in solution and in the crystal, is described. Calixarene derivatives with two distal methylene groups substituted in a trans fashion by phenyl (**5a**) or mesityl (**5b**) groups were synthesized via addition of PhMgBr/CuCN or MesMgBr/CuCN to the bis(spirodiene) derivative **3**. Whereas the phenyl-substituted calixarene derivative **5a** adopts the usual "cone" conformation, solution NMR data and X-ray crystallography indicate that the more crowded mesityl derivative **5b** adopts a 1,2-alternate conformation with the two mesityl groups located at isoclinal positions of the macrocycle.

Introduction

One of the central conformational paradigms of "classical"[1] tetrahydroxycalix[4]arenes (possessing phenol groups interconnected by methylene bridges, e.g., **1a**) is that their preferred conformation is the cone.[2] This conformation is stabilized over the other possible up−down forms (partial cone, 1,3-alternate, and 1,2-alternate, Scheme 1) by a circular array of hydrogen bonds between the OH groups. The energy gap between the cone conformation (possessing four intramolecular hydrogen bonds) and the 1,2-alternate form (possessing only two such bonds) of **1a** has been estimated by MM3 calculations as 7.5−7.7 kcal/mol.[3] A rather large number of tetrahydroxycalixarene derivatives structurally related to **1** and differing in the substituent at the aryl groups and/or at the bridges have been reported so far. Polar substituents may stabilize the noncone conformations by formation of intramolecular hydrogen bonds with the OH groups,[4,5] and in some cases, dipole−dipole interactions between substituents may destabilize the cone form.[6,7] However, in all cases where the substituents on the calix skeleton were alkyl or aryl groups, the preferred solution conformation was the cone or the pinched cone. Here we report the first example of a "classical" tetrahydroxycalix[4]arene, which as a result of the steric destabilization of the cone form adopts the 1,2-alternate conformation.

SCHEME 1



Results and Discussion

Steric Destablization of the Cone Conformation. When two distal methylene groups of the calix scaffold are substituted in a trans fashion (e.g., **1b**−**d**) the cone conformation may be sterically destabilized relative to other up−down forms. Necessarily, in the cone form, one substituent must be located in an axial position and one in an equatorial position. In the 1,2-alternate form, both substituents can be located at diaxial, diequatorial, or diisoclinal positions (Scheme 2, the hydroxyl groups are omitted for clarity). A conformational change of the macrocycle from cone to 1,2-alternate can reduce the

(1) We use the term "classical" to designate calixarenes possessing pairs of phenol units connected by a single sp^3 carbon as opposed to "thiacalixarenes" (sulfur bridges) and "silacalixarenes" (silicon atoms).

(2) (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. (e) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19.

(3) (a) Harada, T.; Ohseto, F.; Shinkai, S. *Tetrahedron* **1994**, *50*, 13377. (b) Thondorf, I.; Brenn, J. *J. Mol. Struct. (THEOCHEM)* **1997**, *398*−*399*, 307.

(4) Calixarenes structurally related to **1** but with the methylene bridges replaced by oxidized sulfur atoms (e.g., sulfoxides or sulfones) adopt the 1,3-alternate conformation in the crystal. This conformation is stabilized by intramolecular hydrogen bonds between the OH groups and the sulfonyl or sulfone groups at the bridges. See: (a) Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Tetrahedron Lett.* **1999**. *40*, 1129. (b) Mislin, G.; Graf, E.; Hosseini, M. W.; De Cian, A.; Fischer, J. *Chem. Commun.* **1998**, 1345.

(5) A tetranitrocalix[4]arene has been shown to adopt the 1,2-alternate conformation in the crystal. Desroches, C.; Parola, S.; Vocanson, F.; Perrin, M.; Lamartine, R.; Letoffe, J. M.; Bouix, J. *New J. Chem.* **2002**, *26*, 651.

(6) *p*-Hexanoylcalix[4]arene undergoes a solid-phase transition upon heating. In each phase, the calixarene adopts a different conformation (cone and partial cone). See: Shinkai, S.; Nagasaki, T.; Iwamoto, K.; Ikeda, A.; He, G.-X.; Matsuda, T.; Iwamoto, M. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 381.

(7) A calixarene derivative in which the methylene bridges have been formally replaced by carbonyl groups (a "ketocalixarene") adopts the 1,3-alternate conformation both in solution and in the crystal. Seri, N.; Simaan, S.; Botoshansky, M.; Kaftory, M.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7140.

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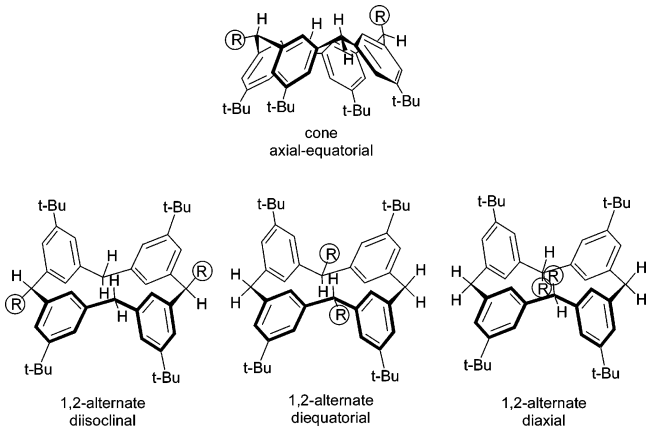
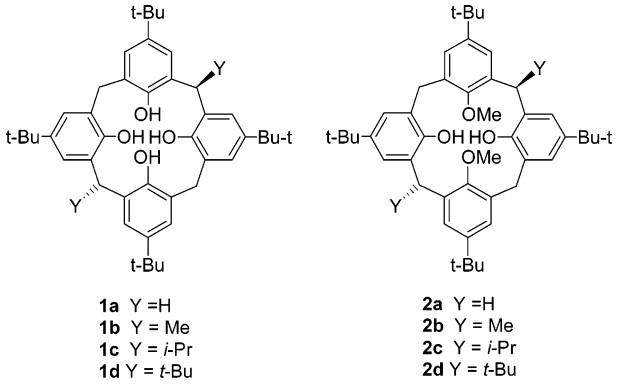
SCHEME 2



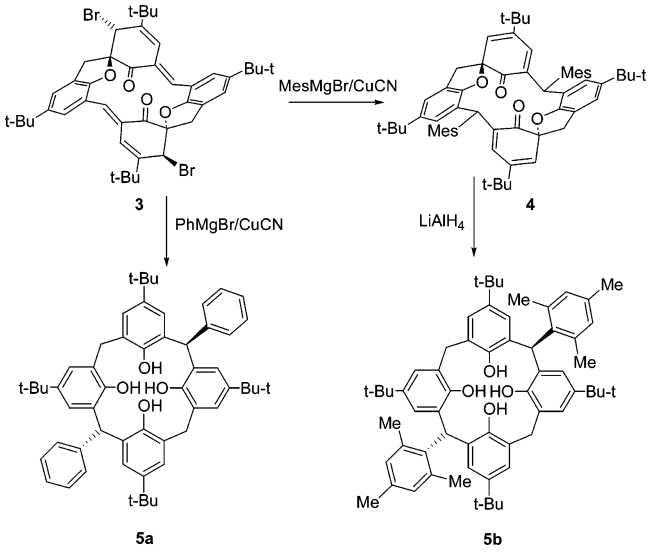
repulsive steric interactions by allowing the groups to be located at the less hindered diisoclinal or diequatorial positions.[8]



The formal introduction of a pair of trans alkyl substituents (e.g., isopropyl or *tert*-butyl) results in a change of the conformational preferences of the 1,3-dimethyl ether derivative from cone in the unsubstituted derivative **2a** to 1,2-alternate in **2c** and **2d**.[9] This is reminiscent of the conformational behavior of some alkyl-substituted cyclohexane derivatives where the preferred conformation is the twist form due to the unavoidable 1,3-diaxial interactions in the chair conformation.[10] However, in the case of the tetrahydroxy calixarenes **1b**−**d**, the repulsive steric interactions ensuing from the presence of an axial substituent are insufficient to overcome the stabilization of the circular array of hydrogen bonds, and as in the parent **1a**, the preferred conformation is the cone.[9]

Since the cone form was preferred even in the presence of the bulky *tert*-Bu groups (e.g., **1d**), we synthesized and examined the conformational preferences of the mesityl derivative **5b**. Although both mesityl and *tert*-Bu are bulky groups, they strongly differ in their shape, and therefore their steric interactions with the macrocyclic

SCHEME 3



ring can differ. For comparison purposes, the diphenyl derivative **5a** was also prepared.

Syntheses of 5a and 5b. Several tetrahydroxycalix[4]arenes possessing a pair of aryl substituents at distal methylene bridges have been prepared by the fragment condensation method (i.e., cyclocondensation of two suitable fragments), which afforded a mixture of trans and cis forms.[11,12] In all cases, the preferred conformation was the cone. For the preparation of **5a** and **5b**, the bis(spirodiene) derivative **3**[9,13] was reacted with PhMgBr/CuCN or MesMgBr/CuCN (Scheme 3). In the first case, the reaction afforded the substituted calixarene derivative **5a**, whereas in the reaction with MesMgBr/CuCN, a mixture of the substituted bis(spirodienone) derivative (**4**)[14] and bimesityl was obtained, as judged from ^{1}H NMR spectroscopy. This mixture was reacted with $LiAlH_4$, and the resulting calixarene (**5b**) was isolated and purified.

NMR Spectra of 5a and 5b. The ^{1}H NMR spectrum of **5a** (400 MHz, 240 K, $CDCl_3$) was fairly similar to those reported for other calix[4]arene derivatives with trans aryl substituents on opposite bridges.[11] Calixarene **5a** displayed two signals for the methine groups (at 6.06 and 5.40 ppm, assigned to axial and equatorial methine protons), two *tert*-butyl signals, and an OH signal at 10.3 ppm, in agreement with the presence of a "frozen" (on the NMR time scale) cone conformation of C_s symmetry

(8) The two trans substituents can be located at diequatorial positions of the 1,2-alternate form since these positions are mutually trans, whereas such an arrangement is impossible in the cone form since diequatorial positions are in a cis relationship.

(9) (a) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 3634. (b) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2003**, *68*, 7685.

(10) For a computational study of the chair/twist boat energy gap of polyalkylcyclohexanes see: Weiser, J.; Golan, O.; Fitjer, L.; Biali, S. E. *J. Org. Chem.* **1996**, *61*, 8277.

(11) See: (a) Grüttner, C.; Böhmer, V.; Vogt, W.; Thondorf, I.; Biali, S. E.; Grynszpan, F. *Tetrahedron Lett.* **1994**, *35*, 6267. (b) 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.

(12) For other examples of the use of the fragment condensation method for the preparation of calixarenes substituted at the bridges, see: (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) 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. (e) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037. (f) Tsue, H.; Enyo, K.; Hirao, K. *Org. Lett.* **2000**, *2*, 3071.

(13) (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.

(14) For a review on spirodienone calixarene derivatives, see: Biali, S. E. *Synlett* **2003**, 1.

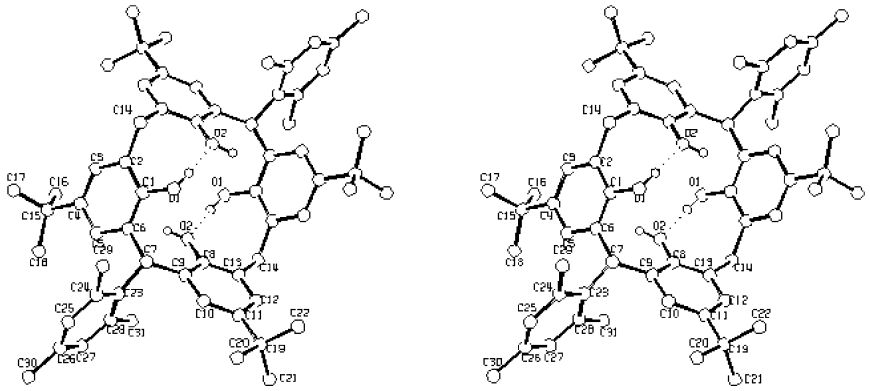


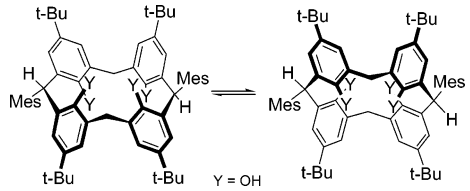
FIGURE 1. Stereoscopic view of the crystal structure of **5b** (top view). The molecule adopts the 1,2-alternate conformation with the two mesityl groups located at isoclinal positions of the macrocycle. The chloroform molecules that cocrystallized were omitted for clarity.

possessing one phenyl located in an equatorial position and one in an axial position. In contrast, the ^{1}H NMR of **5b** ($CDCl_3$, 240 K) displayed a rather different pattern of signals for the central macrocycle. A single signal at 6.06 ppm was observed for the methine protons, in agreement with a structure in which both methines are symmetry related. Notably, the OH signals of **5b** resonated at an unusually high field for a tetrahydroxycalixarene (5.75 and 7.67 ppm), suggesting that, in contrast to **5a**, no circular array of hydrogen bonds is present. On the basis of the symmetry of the NMR pattern and the lack of a cyclic array of hydrogen bonds, we ascribe to calixarene **5b** a 1,2-alternate conformation. Within the 1,2-alternate conformation, a pair of trans substituents located at distal bridges can occupy diaxial, diequatorial, or diisoclinal positions (cf. Scheme 2). The chemical shifts of the methylene protons (4.04 and 3.43 ppm in $CDCl_3$) and their separation ($\Delta\delta$: 0.61 ppm) are characteristic of a pair of protons located at axial and equatorial positions of the macrocycle. By exclusion, the mesityl rings must be located at the diisoclinal positions of the calix skeleton.[15] In the ^{1}H NMR spectrum, the mesityl groups of **5b** displayed three aliphatic and two aromatic signals, indicating a slow rotation around the CH-Mes bonds on the NMR time scale at 240 K.

Crystal Structure of 5b. A single crystal of **5b** was grown from $CHCl_3$ and submitted to X-ray crystallography. The molecule crystallized with two solvent molecules. As shown by the crystal data, the molecule adopts a 1,2-alternate conformation of crystallographic C_i symmetry (Figure 1) with the mesityl groups located at isoclinal positions. In contrast to the cyclic array of hydrogen bonds present in the cone conformation, only two intramolecular hydrogen bonds (between pairs of rings oriented syn) are present in **5b**.

Rotational Barriers of 5b. Upon raising the temperature, signals of **5b** broadened and coalesced. From the chemical shift difference under slow exchange conditions of pairs of aromatic, *t*-Bu, and methylene protons ($\Delta\delta$: 51.2, 52.0 and 254.1 Hz) and their coalescence temperatures (308.5, 309.9, and 330.7 K, respectively), a rotational barrier of 15.2 kcal/mol was determined.[16] The dynamic process is ascribed to a 1,2-alternate-to-1,2-alternate inversion process (Scheme 4), which involves rotation through the annulus of the four phenolic groups and mutually exchanges the methylene protons, the *t*-Bu groups, as well as pairs of aromatic protons ortho or para to the substituted bridge. The cone-to-cone inversion barrier of **5a** was somewhat lower (14.5 kcal/mol). In addition, coalescence phenomena were observed for the ortho methyl and aromatic protons of the mesityl groups. Notably, the barrier determined from the mutual exchange of the *o*-Me groups (15.1 kcal/mol) was identical within experimental error to the barrier determined for the ring inversion process. This suggests that either both barriers are fortuitously similar or that a single process is being followed. Addition of pyridine-d_5 to the $CDCl_3$ solution allowed both alternatives to be distinguished.[17] The barrier for ring inversion of **5b** in 4:1 (v/v) $CDCl_3$/pyridine-d_5 was 14.4 kcal/mol (0.8 kcal/mol lower than in pure $CDCl_3$) but the barrier for mesityl rotation was now also 14.4 kcal/mol. This suggests that the minimum energy pathway for rotation of the mesityl ring requires a conformational change of the calix macrocycle. In the crystal conformation of **5b**, one ortho methyl is pointing toward the center of the calix annulus and the neighboring rings can restrict the rotations of the mesityl ring. It may be possible that during the 1,2-alternate-to-1,2-alternate interconversion process, these steric restrictions are reduced, allowing the mesityl ring to rotate.

SCHEME 4



(15) One of the *o*-Me signals of the mesityl group displayed NOE cross-peaks in the ROESY spectrum with an aromatic proton of a neighboring phenol ring and the OH signal of a second phenol ring. This is in agreement with an anti arrangement of the two phenol rings vicinal to the mesityl group, i.e., with an isoclinal disposition of the substituent.

(16) Exchange rates at the coalescence temperatures (k_c) were estimated using the equations $k_c = 2.22\ \Delta\nu$ or $k_c = 2.22\ (\Delta\nu^2 + 6J^2)^{1/2}$. See: Juaristi E. *Stereochemistry and Conformational Analysis*; Wiley: New York, 1991; pp 253−254.

(17) The cone-to-cone inversion barrier of **1a** is lower in pyridine-d_5 (13.7 kcal/mol) than in $CDCl_3$ (15.7 kcal/mol) since the circular array of hydrogen bonds is disrupted by the pyridine molecules. See: Gutsche, C. D.; Bauer, L. J. *J. Am. Chem. Soc.* **1985**, *107*, 6052.

In contrast to the calixarene dimethyl ether derivatives, where in the 1,2-conformation the alkyl groups at the bridges are located at equatorial positions, in the solution and crystal conformation of **5b**, the mesityl substituents are located at the isoclinal positions of the 1,2-alternate form. This conformational preference indicates that the repulsive steric interactions are larger in the equatorial positions than in the isoclinal positions. Assuming that the steric environments of the equatorial positions at the cone and 1,2-alternate are similar, this suggests that the cone conformation is destabilized not only by the presence of the axial substituent but also by the equatorial substituent as well.

Conclusions. The first example of a "classical" tetrahydroxycalixarene that adopts a 1,2-alternate conformation in solution is described. The shift in the conformational preferences from cone to 1,2-alternate is due to the steric destabilization of the cone conformation as a result of the presence of the bulky mesityl substituents in the axial and equatorial positions of the macrocycle in that conformation.

Experimental Section

Crystal data for 5b. Data were collected in a Bruker Apex CCD. Crystal dimensions: 0.24 × 0.22 × 0.08 mm, triclinic, $P\bar{1}$, a = 9.654(2) Å, b = 12.542(2) Å, c = 13.779(3) Å, α = 102.905(3)°, β = 105.500(3)°, γ = 107.444(3)°, V = 1447.7(5) Å^3, Z = 1, ρ_{calc} = 1.289 Mg m^{-3}, $2\theta_{max}$ = 56.26°, Mo Kα radiation, 0.71073 Å, temp = 100(2) K, no. of measured and independent reflections: 16 835/6766, no. of parameters = 348, R_1 = 0.0711, wR_2 = 0.1832, residual electron density: 0.816 e/Å^3.

Preparation of 5a. A mixture of 0.46 g (5.1 mmol) CuCN and 6 mL of PhLi (1.8 M solution in 70:30 cyclohexane/ether) was stirred in 50 mL of dry THF at 0 °C under an inert atmosphere until a homogeneous solution was obtained. To the mixture was then added 1 g of **3** (1.25 mmol), and the mixture was stirred for 3 h and allowed to reach room temperature. After treatment with water, the organic phase was extracted with CH_2Cl_2 and the combined organic phases were evaporated. The residue was triturated with a mixture of $CHCl_3$/MeOH. The product was purified by chromatography (silica, eluent 2:1 hexane/CH_2Cl_2) yielding 0.24 g (24%) of **5a**, mp 212 °C: ^{1}H NMR (400 MHz, $CDCl_3$, 240 K) δ 10.34 (br s, OH), 7.39 (m, 3H, Ph), 7.28 (m, 9 H, Ph), 7.16 (br s, 2H, Ar−H), 7.07 (d, J = 1.9 Hz, 2H, Ar−H), 7.04 (d, J = 1.9 Hz, 2H, Ar−H), 6.06 (s, 1H, ax C*H*Ph), 5.40 (s, 1H, eq C*H*Ph), 4.26 (d, J = 13.9 Hz, 2H, CH_2), 3.59 (d, J = 14.0 Hz, 2H, CH_2), 1.28 (s, 18H, *t*-Bu), 1.13 (s, 18H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_3$, 260 K), δ 147.1, 147.0, 144.2, 144.1, 141.8, 138.9, 130.9, 129.4, 128.8, 128.7, 127.9, 127.8, 127.6, 127.2, 127.0, 126.9, 126.5, 125.9, 125.5, 125.2, 57.2, 41.1, 34.1, 34.0, 32.6, 31.5, 31.2 ppm; CI MS (+DCI) m/z 801.3 (MH$^+$).

Preparation of 5b. The reaction with the organocopper reagent was conducted as described above starting from 1 g of **3** (1.25 mmol), 0.46 g (5.1 mmol) of CuCN, 10.5 mL of mesitylmagnesium bromide (1.0 M solution in THF), and 50 mL of dry THF. After trituration with $CHCl_3$/MeOH, 0.8 g of a ca. 2:1 mixture of bimesityl and the substituted spirodienone derivative was obtained. To a suspension of this mixture in 50 mL of dry THF were added 0.3 g of $LiAlH_4$ under an inert atmosphere. After treatment with water, phase separation, and extraction of the aqueous phase with CH_2Cl_2, the combined organic phases were evaporated. The residue was crystallized from $CHCl_3$/MeOH yielding 0.27 g of **5b**. Recrystallization from $CHCl_3$ (100 mg requires 0.5 L of solvent) afforded 68 mg of pure material (17% yield for the **3** → **5b** conversion), mp 370 °C (dec): ^{1}H NMR (400 MHz, $CDCl_3$, 240 K) δ 7.67 (s, 2H, OH), 7.17 (d, J = 1.8 Hz, 2H, Ar−H), 7.14 (d, J = 2.0 Hz, 2H, Ar−H), 6.85 (s, 2H, Mes-H), 6.80 (s, 2H, Mes-H), 6.75 (d, J = 1.9 Hz, 2H, Ar−H), 6.62 (d, J = 1.7 Hz, 2H, Ar−H), 6.06 (s, 2H, MesC*H*), 5.75 (s, 2H, OH), 4.04 (d, J = 13.6 Hz, 2H, CH_2), 3.43 (d, J = 13.7 Hz, 2H, CH_2), 2.28 (s, 6H, *p*-Me), 2.19 (s, 6H, *o*-Me), 1.77 (s, 6H, *o*-Me), 1.18 (s, 18H, *t*-Bu), 1.05 (s, 18H, *t*-Bu); ^{13}C NMR (100.6 MHz, $CDCl_2CDCl_2$, 400 K) δ 149.3, 144.2, 138.0, 137.2, 135.5, 129.8, 128.4, 126.5, 126.0, 44.9, 33.9, 32.1, 31.3, 20.6, 20.5 ppm; CI MS (+DCI) m/z 885.1 (MH$^+$).

Acknowledgment. We thank Dr. Shmuel Cohen for the crystal structure determination of **5b**. This research was supported by the Israel Science Foundation (Grant No. 44/01-1).

Supporting Information Available: Crystallographic data for **5b** (CIF) and NMR spectra of **5a** and **5b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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