The Wurtz−Fittig Reaction in the Preparation of C-Silylated Calixarenes

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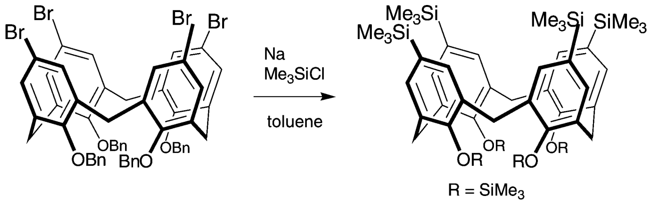

The Wurtz−Fittig reaction of tetraiodo calixarene **3** with Na/Me$_3$SiCl in DME gave a mixture of tetrakis- and tris-silylated calixarenes (**6** and **7**). Tris(silyl) calixarene **7** was assigned the flattened cone conformation. A model study using *p*-bromoanisole and *p*-iodoanisole with Na/Me$_3$SiCl gave the best results with *p*-bromoanisole in toluene. Attempts to extend this reaction to the tetrabromo calixarene **4** resulted in slow reactions giving mixtures of products. However, the Wurtz−Fittig reaction of the bromo benzyloxycalixarene **5** was faster, giving the debenzylated silyl ether **12**.

Calixarenes have been widely used as building blocks in the design and synthesis of new materials for molecular recognition and supramolecular chemistry.[1] Calixarenes substituted with silyl groups have potential for the recognition of anionic and nucleophilic substances,[2−4] as many silicon compounds can interact with nucleophiles to form hypervalent silicon adducts.[5] Although many functional groups can be easily introduced onto the upper (wide) rim of the calixarene skeleton by electrophilic substitution reactions, such reactions do not appear to be useful for the introduction of silyl groups onto aromatic rings,[6] and few C-silylated calixarenes have been reported.[4,7] We have recently developed a convenient procedure for the preparation of C-silylated calixarenes from bromocalixarenes by halogen−metal exchange (using *tert*-BuLi) followed by treatment with the clear supernatant from a mixture of chlorosilane and Et$_3$N.[3] We report here the use of the Wurtz−Fittig reaction for the preparation of silylated calixarenes.

The Wurtz−Fittig silylation reaction[8] has been known for many years as a method for preparing organosilicon compounds,[6b,9−11] and we have found it to be a useful method for the stereospecific preparation of vinylsilanes.[11] Its virtues include ease of scale up and relatively low cost (compared to reactions, for example, using *tert*-BuLi).

As an initial substrate for the Wurtz−Fittig reaction, the iodo propyloxycalixarene **3**[12] was prepared by treatment of propyl ether **1**[13] with I$_2$ and CF$_3$COOAg in CHCl$_3$[13] (70−84% yields). In some cases, a mixture of triiodo- and tetraiodocalixarenes was obtained (based on MALDI and ^{1}H NMR), and the mixture was treated with additional iodine reagent to get pure **3**. Other substrates used subsequently were the bromo propyloxycalixarene **4**,[14] prepared by treatment of **1** with NBS/MEK (86−93% yields),[15a] and the bromo benzyloxycalixarene **5**,[15b] similarly prepared by treatment of benzyl ether **2**[16] with NBS/MEK (78−88% yields) (Scheme 1).

In the Wurtz−Fittig silylation reaction, a silyl halide (usually Me$_3$SiCl) and Na are typically stirred together for several minutes, and then an aryl or vinyl halide is introduced. In our reactions, freshly pressed Na ribbon was used. The most consistent results were obtained when the reaction flask was flushed with nitrogen or argon before and immediately after pressing the Na into it and then placed on an inert gas line. The solvent and Me$_3$SiCl (each recently distilled from a drying agent) were added; the mixture was stirred for about 15 min

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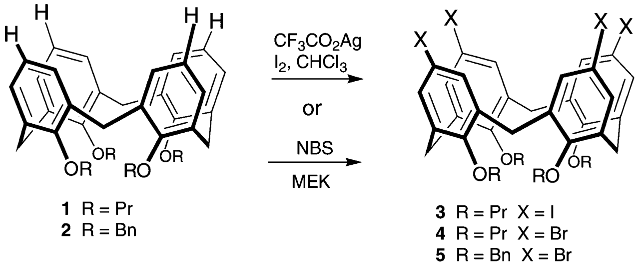
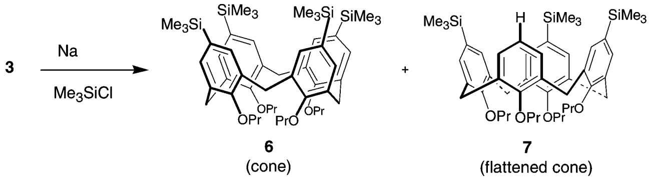
10.1021/jo070660n CCC: $37.00

SCHEME 1



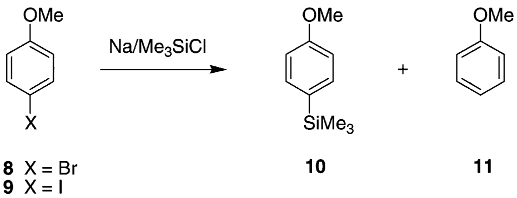
SCHEME 2



(to remove traces of water or HCl); and then the aryl halide was introduced.

Iodocalixarene **3** was subjected to the Wurtz–Fittig reaction in DME. (We initially used DME because calixarene **3** was not rapidly soluble in ether, the solvent in which we had run Wurtz–Fittig reactions to prepare vinylsilanes.[11]) The reaction, which turned a dark purple color, appeared to be complete (by NMR analysis of an aliquot) after 16 h and was worked up after 21 h. The ^{1}H NMR spectrum of the crude product suggested a mixture of compounds. Column chromatography produced two crystalline products assigned as the tetrakis(trimethylsilyl)calixarene **6**[3b] (41% yield) and the tris(trimethylsilyl)calixarene **7** (21% yield) (Scheme 2) as well as a middle fraction which was a mixture.

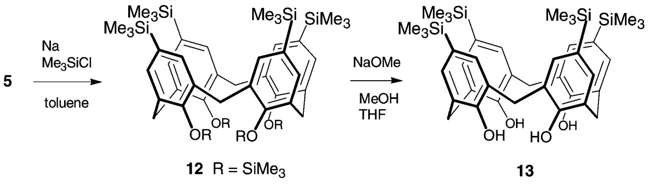
To develop a procedure for preparing **6** without competition from apparent protonation to give **7**, we tried to optimize the Wurtz–Fittig reaction conditions using 4-bromoanisole (**8**) and 4-iodoanisole (**9**) as model compounds. These reactions were carried out in the presence of *n*-undecane (internal standard) in various solvents. Aliquots were taken and analyzed by GC and sometimes also by GC/MS. GC ratios were not corrected for detector response, as this work was intended only to be a survey to compare solvents and identify those most promising to pursue with the calixarenes. In most cases, the major product was 4-trimethylsilylanisole (**10**) with smaller amounts of anisole (**11**).



The highest ratios of **10**/**11** were found using bromoanisole **8** with toluene or benzene. These reactions appeared to start very quickly (the reaction mixture turned blue) and were completed within 1–2 h, faster than any of the other reactions. The ratios of **10**/**11** under the most favorable conditions ranged from about 30:1 to 70:1 for the reactions in toluene and (in two runs) 44:1 for those in benzene.

The other solvents we tried appeared to be inferior. Typical ratios (**10**/**11**) at a time when the reactions were substantially complete were as follows: using bromoanisole **8**, dioxane, 27 (27 h); THF, 22 (24 h); ether, 19 (7 h); DME, 10 (21 h); using iodoanisole **9**, ether, 25 (24 h); toluene, 19 (23 h); THF, 8 (4 h); DME, 5 (7.5 h).

SCHEME 3



The proton source for the formation of anisole (**11**) may be residual HCl in the chlorosilane. We tried the more basic solvent, Et$_3$N, and other silylating agents, Me$_3$SiOEt and (Me$_3$Si)$_2$O. All gave inferior results. From bromoanisole **8**, with Me$_3$SiCl in Et$_3$N, the **10**/**11** ratio was 14 after 20 h; with Me$_3$SiOEt as the silylating agent and solvent, the **10**/**11** ratio was 2.9 (5 h); and with Me$_3$SiOEt in Et$_2$O, or with (Me$_3$Si)$_2$O as both the silylating agent and solvent, the product was almost exclusively **11**.

Because the best results in the model study were obtained using bromoanisole **8** in toluene, we studied the Wurtz–Fittig reaction of bromo propyloxycalixarene **4** using Na and Me$_3$SiCl in toluene. This reaction was attempted many times and appeared to start much more slowly than the corresponding reaction of bromoanisole in toluene, eventually resulting in mixtures of products by MALDI and NMR; MALDI indicated silylation was not complete. The reaction of bromocalixarene **4** in ether gave similar results.

When the benzyloxycalixarene **5** was treated with Na and Me$_3$SiCl in toluene (Scheme 3), the reaction appeared to be considerably faster than that of the propyloxy calixarene **4**. However, it was not nearly as facile as that of bromoanisole **8**, and very vigorous stirring was needed. The reaction was normally worked up in 48 h. The ^{1}H NMR spectrum of the crude product suggested the benzyl groups had been cleaved and replaced by silyl groups. The product was assigned as calixarene **12**, which was both C-silylated and O-silylated, from the NMR and MALDI-TOF of the purified product. Frequently, the ^{1}H NMR spectrum of the crude product looked remarkably clean, but small extra peaks in the region of the bridge methylene protons suggested the presence of another calixarene. The integration suggested the other calixarene had one fewer silyl group, with a ratio of **12** to the other calixarene of about 2:1. Despite the fact that the product was a mixture, it was easily purified by simple recrystallization from MeOH/CHCl$_3$ (9:1) to give calixarene **12** in 43% yield. In cases where the crude product looked less clean, the silyl ethers were directly hydrolyzed to the hydroxy compound **13** as described below, and pure **13** was obtained by recrystallization, but with lower yields.

In our work on the preparation of silylated calixarenes using halogen–metal exchange, we found that the supernatant from mixtures of chlorosilanes with Et$_3$N gave purer products and less protonation than the use of chlorosilanes alone.[3] When we used Me$_3$SiCl/Et$_3$N prepared in this manner in the above reaction (**5**, Na, Me$_3$SiCl/Et$_3$N, toluene), calixarene **12** was isolated in 51% yield after recrystallization.

The silyl ethers in **12** were hydrolyzed using NaOMe/MeOH and THF (rt, 5 min) to give tetrahydroxytetrakis(trimethylsilyl)calixarene **13** in 78% yield. As expected, silicon–carbon bond cleavage was not a problem. The NMR spectra of calixarene

12 indicated that it was in the cone conformation.[17,18] As expected, calixarenes **1**−**6** and **13** were in the cone conformation, **1**−**6** because of the method of preparation[17] and **13** because of the stability from hydrogen bonding.

The tris(silyl)calixarene **7** was assigned as a flattened (or pinched) cone conformation,[19] in which two of the aryl groups are closer together (pinched) and (almost) parallel and the other two are splayed outward. The structure of **7** was assigned from the ^{1}H and ^{13}C NMR, DEPT, and IR spectra and MALDI-TOF mass spectra. The diagnostic signals in the ^{1}H NMR for the flattened cone were two separate groups of aromatic signals, one at rather high field (δ 6.1−6.2, assigned to protons on the parallel rings), and two equally sized sets of signals for the propyloxy groups, in particular, signals of ca. δ 4.0 and δ 3.7 for OCH$_2$ groups. Tetra-O-alkylated calix[4]arenes in the cone conformation usually show ^{1}H NMR spectra expected[18] for a symmetrical cone but are believed to undergo interconversion in solution between flattened cone conformations, which is usually fast on the ^{1}H NMR time scale. Flattened cone conformations have previously been observed in the ^{1}H NMR using low temperatures or with calixarenes which favor a particular flattened conformation. This has included calixarenes with substituents on opposite rings (5,17 positions) which are large or which can participate in hydrogen bonding.[19b−d,i]

Calixarene **7** is of special interest because, in contrast to other calix[4]arenes with flattened cone conformations which we have seen, it has only one plane of symmetry. Consequently, the CH$_2$ groups of two of the propyloxy groups (on the splayed rings) have diastereotopic hydrogens. For the OCH$_2$ protons in **7**, the lower-field signal is a multiplet having the same appearance in **7** as in other flattened cone calixarenes pictured in the literature[20] and prepared in our laboratory,[21] but the upper-field signal, normally a conventional triplet, appears as two overlapping triplets in **7**.

The CH$_3$'s of the propyl groups in flattened cone calixarenes normally appear as two conventional triplets, but in **7**, they appear as one triplet at higher field and two overlapping triplets at lower field. A DQF-COSY experiment on **7** established that the higher-field OCH$_2$ signal correlated to the higher-field OCH$_2$*CH$_2$* signal which correlated with the lower-field OCH$_2$CH$_2$*CH$_3$* signal.[22] Therefore, the more atypical CH$_3$ (lower field) is from the same propyl group as the more atypical OCH$_2$ (higher field).

The separation of the multiplets for the OCH$_2$ protons (δ 4.0 and 3.7) suggests predominantly one conformer is favored. Jørgenson and co-workers have stated that the separation of the signals from the OCH$_2$ groups can be used as an estimate of the equilibrium between the two flattened cone conformations if they are in rapid exchange in the NMR time scale (ignoring effects of substituents at positions 5 and 17). Identical chemical shifts would indicate an equal mixture, whereas a difference of ca. 0.4 ppm would indicate one conformer is clearly favored.[19g,h]

Calixarene **7** most certainly has the favored flattened cone conformation with the parallel aromatic rings being those with H and SiMe$_3$ as *p*-substituents as shown in Scheme 2. The higher-field OCH$_2$ groups which are split into overlapping triplets are assigned to the diastereotopic OCH$_2$ groups on the splayed rings. (However, a small effect of the *p*-SiMe$_3$ vs H on the chemical shift of the OCH$_2$ of the propyls on the parallel rings cannot be ruled out.) This assignment reinforces an earlier assignment in a tetrapropoxythiacalix[4]arene, in which two sets of alkoxy residues were observed, with the more highly shielded OCH$_2$'s assigned to those on the declined (splayed) rings by virtue of their spatial relationship to the aromatic rings.[23]

p-C-Silylated calix[4]arenes have been previously prepared by halogen−metal exchange on bromocalixarenes with *tert*-BuLi in THF followed by treatment with silyl chlorides.[3−4,7] A tetrakis(trimethylsilyl) hexyloxy calixarene[7] and tetrakis- and tris(trimethylsilyl) methoxy calixarenes[4] have been reported; both were purified by chromatography. In the latter case, fractional crystallization was also employed to separate the tetrakis from the tris. A number of silylated calixarenes have been prepared in our laboratory by halogen−metal exchange of several *p*-bromocalix[4]arene ethers with *tert*-BuLi in THF followed by treatment with the supernatant from mixtures of several silyl chlorides and triethylamine.[3] For example, from a *p*-bromo tetrapropoxy calixarene (calixarene **4**) using Me$_3$SiCl/Et$_3$N, the tetrakis(trimethylsilyl)calixarene (calixarene **6**) was isolated in 79% yield. A similar reaction on a tetrabenzyloxycalixarene gave the tetrasilylated product in 92% yield, and hydrogenolysis to remove the benzyl ethers gave the tetrahydroxy compound (calixarene **13**) in 88% yield. The crude silylation products were crystalline, and the silylated calixarenes were purified only by a simple recrystallization.

By comparison, the Wurtz−Fittig silylation reactions using the benzyloxycalixarene (**5**) gave lower yields, but the silyl calixarenes could also be purified by simple recrystallization. The Wurtz−Fittig procedure has the potential advantage of being easier to scale up than the halogen−metal procedure.

In summary, the Wurtz−Fittig silylation reaction using Na and Me$_3$SiCl on a tetraiodo propyloxycalixarene (**3**) in DME gave a mixture of tetrakis- and tris-silylated calixarenes (**6** and **7**). Tris(silyl) calixarene **7** was assigned the flattened cone

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(17) The shapes of calix[4]arenes are usually discussed in terms of four basic conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate. For a discussion, see ref 1c, pp 41−46, and ref 1d, pp 1−10. Introduction of sufficiently large substituents onto the phenolic oxygens restricts conformational interconversion. Calixarenes **6** and **7** (as well as **3**−**5**) are frozen in the cone conformation because of the method of preparation of starting materials **1** and **2** (see refs 13 and: (a) Groenen, L. C.; Ruël, B. H. M.; Casnati, A.; Timmerman, P.; Verboom, W.; Harkema, S.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron Lett.* **1991**, *32*, 2675−2678. (b) Gutsche, C. D.; Reddy, P. A. *J. Org. Chem.* **1991**, *56*, 4783−4791) and because of the size of the substituents on the oxygens (see: Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955−4962).

(18) For a discussion of the NMR spectra of calix[4]arenes, see ref 16 and Ungaro, R. In ref 1d; pp 1−10.

(19) For references to pinched cone calix[4]arenes, see: (a) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165−4176. (b) Conner, M.; Janout, V.; Regen, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 9670−9671. (c) Arduini, A.; Fabbi, M.; Mantovani, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *60*, 1454−1457. (d) Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476−3481. (e) Jørgensen, M.; Larsen, M.; Sommer-Larsen, P.; Petersen, W. B.; Eggert, H. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2851−2855. (f) Soi, A.; Bauer, W.; Mauser, H.; Moll, C.; Hampel, F.; Hirsch, A. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1471−1478. (g) Larsen, M.; Krebs, F. C.; Harrit, N.; Jørgensen, M. *J. Chem. Soc., Perkin Trans. 2* **1999**, 1749−1757. (h) Jørgensen, M.; Krebs, F. C. *J. Chem. Soc., Perkin Trans. 2* **2000**, 1929−1934. (i) Dondoni, A.; Kleban, M.; Hu, X.; Marra, A.; Banks, H. D. *J. Org. Chem.* **2002**, *67*, 4722−4733.

(20) Supporting Information to ref 19c.

(21) Hudrlik, P. F.; Hudrlik, A. M.; Zhang, L.; Arasho, W. D.; Cho, J. *J. Org. Chem.* **2007**, *72*, 7858−7862.

(22) This assignment agrees with a previous COSY spectrum of a flattened cone calixarene in which a higher-field CH$_3$ was assigned to the same propyl as a lower-field OCH$_2$ (ref 19e).

(23) Čajan, M.; Lhoták, P.; Lang, J.; Dvořáková, H.; Stibor, I.; Koča, J. *J. Chem. Soc., Perkin Trans. 2* **2002**, 1922−1929. See also ref 19h.

conformation from the ^{1}H NMR spectrum. The effect of conditions on the Wurtz−Fittig reaction was studied using bromo- and iodoanisole (**8** and **9**) as model compounds, and the reaction with bromoanisole proceeded efficiently in toluene to give the silylated product **10**, with little or none of the protonated product **11**. Numerous attempts to extend the reaction to the tetrabromo calixarene **4** resulted in sluggish reactions and mixtures of products. However, the Wurtz−Fittig reaction using the bromo benzyloxycalixarene (**5**) resulted in a more rapid reaction and a product mixture which could be purified by recrystallization. The product (**12**) was that of debenzylation as well as of silylation on both upper and lower rims; hydrolysis produced calixarene **13**. The use of benzyloxyhalo aromatic rings as substrates in other Wurtz reactions is worthy of further study because large-scale reactions using sodium are cheaper, safer, and easier to run than those involving the more commonly employed *tert*-BuLi.

Experimental Section

5,11,17,23-Tetrakis(trimethylsilyl)-25,26,27,28-tetrakis(trimethylsilyloxy)calix[4]arene (12). Na (0.59 g, 26 mmol) was pressed as ribbon into an argon-flushed 2-neck 25 mL flask. The flask was placed on an argon line, and 15 mL of toluene was added followed by 1.0 mL (0.85 g, 7.8 mmol) of Me_3SiCl. The mixture was stirred for 15 min at rt, and then 0.274 g (0.249 mmol) of benzyloxycalixarene **5** was added. The mixture was stirred for 48 h at rt (turned blue within 12 h), and then the liquid was removed by pipet and washed with 15 mL of saturated $NaHCO_3$ followed by 15 mL of brine. (The residual Na was more finely divided in this reaction than in the previous reactions, and in subsequent runs, the reaction mixture was filtered to remove the Na before transferring to the separatory funnel.) The organic layer was then dried ($MgSO_4$), concentrated, and placed under an oil pump vacuum (2 h, 0.05 mm, rt) to give 0.246 g of the crude product as a mixture of white solid and yellowish oil. The ^{1}H NMR spectrum of the crude product indicated the disappearance of the methylene peaks of the benzyl group of the calixarene. Two large peaks were observed near 0.00 ppm assigned to the Me_3Si protons. In addition to the doublets at δ 4.39 and 3.04 (**12**), there were minor peaks at δ 4.30 (d) and 3.0 (m). (If these were due to another calixarene such as a compound having one fewer Me_3Si group, the ratio of **12** to the other calixarene is estimated at about 2:1 based on the integration at δ 4.39 and 4.30.) Recrystallization of the crude product from MeOH/$CHCl_3$ (9:1) gave a white powder which was filtered and placed under an oil pump vacuum (2 h, 0.1 mm, rt) to give 0.107 g (43% yield) of **12** as a white powder: mp 303−306 °C; ^{1}H NMR (400 MHz, $CHCl_3$ standard) δ 6.87 (s, 8 H, ArH), 4.39 (d, J = 12.7 Hz, 4 H, $ArCH_2Ar$), 3.04 (d, J = 12.7 Hz, 4 H, $ArCH_2$-Ar), 0.27 (s, 36 H, OSiMe), 0.06 (s, 36 H, ArSiMe); ^{13}C NMR (100 MHz, assignments by DEPT) δ 150.9 (C), 133.1 (CH), 132.1 (C), 130.4 (C), 30.6 (CH_2), 1.1 (CH_3), −0.7 (CH_3); IR ($CHCl_3$) 2986, 2950, 1578, 1460, 1419, 1265, 1127, 927, 843, 733, 697 cm^{-1}; MALDI-TOF MS (peaks of comparable size) 1024.6 (**12**, $[M + Na]^+$, calcd for $C_{52}H_{88}O_4Si_8Na$: 1023.5), 1000.2 (**12**, M^+, calcd for $C_{52}H_{88}O_4Si_8$: 1000.5), 952.5 (**12** − Me_3Si, $[M + Na]^+$), 928.7 (**12** − Me_3Si, M^+).

Procedure using Et_3N. Na (0.85 g, 37 mmol) was pressed as ribbon into an argon-flushed 2-neck 25 mL flask. The flask was placed on an argon line, and 15 mL of toluene was added followed by a 2.0 mL portion of the supernatant liquid from a mixture of Me_3SiCl/Et_3N (1:1 v/v, approximately 8 mmol of chlorosilane). The mixture was stirred for 30 min at rt, and then 0.231 g (0.210 mmol) of benzyloxycalixarene **5** was added. The mixture was stirred for 48 h at rt (turned blue within 12 h). The reaction mixture was filtered to remove residual Na and then washed with 15 mL of saturated $NaHCO_3$ followed by 15 mL of brine. The organic layer was dried ($MgSO_4$), concentrated, and placed under an oil pump vacuum (2 h, 0.05 mm, rt). Addition of 10 mL of MeOH/CH_2Cl_2 (9:1) resulted in the formation of white solid which was filtered and placed under an oil pump vacuum (2 h, 0.05 mm, rt) to give 0.126 g of a white powder. ^{1}H NMR indicated a mixture of products as above (as did MALDI-TOF). Recrystallization from MeOH/CH_2Cl_2 (9:1) gave 0.108 g (51% yield) of **12** as a white powder: mp 304−306 °C. The ^{1}H NMR and ^{13}C NMR spectra were essentially the same as those reported above.

5,11,17,23-Tetrakis(trimethylsilyl)-25,26,27,28-tetrahydroxycalix[4]arene (13). This procedure is based on that of Cooper.[24] Into a nitrogen-flushed 2-neck 25 mL flask was added 0.051 g (0.051 mmol) of the trimethylsilyloxycalixarene (**12**) followed by 3.0 mL of THF. The mixture was stirred for about 2 min to dissolve **12**, and then 2.5 mL of 2.0 M NaOMe in MeOH (5.0 mmol) was added. The mixture was stirred for 5 min at rt, and then 5.0 mL of distilled water was added. The mixture was transferred to a separatory funnel, and 10 mL of CH_2Cl_2 was added. The organic layer was separated, dried (Na_2SO_4), and concentrated. The product was recrystallized from MeOH/CH_2Cl_2 (9:1) and placed under an oil pump vacuum (2 h, 0.05 mm, rt) to give 0.028 g (78% yield) of **13** as white crystals: mp 263−266 °C (lit.[3b] mp 263.6−264.6 °C). The ^{1}H NMR, ^{13}C NMR, and MALDI were equivalent to those reported.[3b]

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Supporting Information Available: Experimental for the Wurtz−Fittig reaction of **3**, and ^{1}H and ^{13}C NMR spectra of **6**, **7**, **12**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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