Selective Halogen−Lithium Exchange Reaction of Bromine-Substituted 25,26,27,28-Tetrapropoxycalix[4]arene

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Received May 21, 1996[⊗]

Methods are described for the selective bromine−lithium exchange reaction of bromine-substituted calix[4]arenes with either *n*-BuLi or *t*-BuLi in THF. Quenching of the lithiated calix[4]arenes with MeOH, D_2O, CH_3SSCH_3, $B(OCH_3)_3$, DMF, or CO_2 as electrophiles resulted in 5-monosubstituted, 5,17-disubstituted, or 5,11,17,23-tetrasubstituted calix[4]arenes with H, D, SCH_3, $B(OH)_2$, CHO, or COOH functionalities.

Introduction

Calix[4]arenes are easily synthesized[1] and have been widely used in the study of supramolecular host−guest systems in the solid state[2] as well in solution.[3] The parent p-*tert*-butylcalix[4]arene contains two interesting substructures. At the *lower rim*, four hydroxyl groups are present in very close proximity and can with proper derivatization be used for cation binding[4] and transport.[5] The *upper rim* contains a hydrophobic cavity that can potentially be used for complexation of small neutral molecules. Most work has been done on the complexation of cations in the derivatized *lower rim*,[6] probably because functionalization there is easier.

In order to obtain calix[4]arenes suitable for selective supramolecular interactions with, for example, small molecules, it is desirable to be able to substitute the *upper rim* regioselectively with different functional groups. Böhmer *et al.*[7] explored the stepwise buildup of differently substituted phenolic moities. Alternatively, several groups have selectively substituted the simple calix[4]arene core. One possible route is to selectively alkylate the phenolic functions of the *lower rim* and then utilize the different reactivity *para* to the free phenolic groups *versus* ethers to introduce functionalities.[8] Another possibility is to first fix the conformation of the calix[4]arene by tetraalkylation and then introduce substituents in the *upper rim* positions. This strategy is economical and appealing in the number of steps, but requires regioselective functionalization if other than symmetrically tetrasubstituted derivatives are to be obtained. Selective Gross-formylation has been achieved by Arduini *et al.*[9] While Reinhoudt *et al.*[10] have explored selective nitration.

In this paper we have extended this strategy with selective bromine to lithium exchange. These lithiated intermediates can then be used to introduce a variety of substituents: carbon in different oxidation steps, deuterium, hydrogen, boron, sulfur. The selective bromine to lithium exchange reaction thus offers a simple route to substituted calix[4]arene with a variety of functionalities and regiocontrol.

Only few reports on halogen-to-metal exchange reactions on calix[4]arene are given in the litterature. Gutsche *et al.*[11] made the 5,11,17,23-tetralithiotetramethoxycalix[4]arene from 5,11,17,23-tetrabromotetramethoxycalix[4]arene with *n*-BuLi in THF at −78 °C. Quenching with D_2O gave the d_4-tetramethoxycalix[4]arene in 90% yield. When they treated tetrabromotetrabenzyloxycalix[4]arene with *n*-BuLi in THF, a mixture of products was obtained. Shinkai *et al.*[12] synthesized a calix[4]arene substituted with boronic acids from a dilithiocalix[4]arene. Paek *et al.*[13] synthesized 5,17-dibromo-11,23-dihydroxycalix[4]arene hexyl ether from tetrabromocalix[4]arene hexyl ether with *n*-BuLi in THF at −78 °C and reaction with $B(OMe)_3$ followed by H_2O_2/NaOH, but no experimental details are given.

Results and Discussion

We have found that 5,11,17,23-tetrabromotetrapropoxycalix[4]arene (**1**) (cone) can selectively be converted into the monolithiated, 5,17-dilithiated or tetralithiated stage by reaction with *n*-BuLi in THF and for the latter with *t*-BuLi in THF in a Br−Li exchange reaction (Scheme 1), maintaining the calix[4]arene in the cone conformation. Compound **1** was converted to 5,11,17-tribromo-23-carboxy-25,26,27,28-tetrapropoxycalix[4]arene (**2**) in a Br−Li exchange with 1 equiv of *n*-BuLi in

⊗ Abstract published in *Advance ACS Abstracts,* September 1, 1996.

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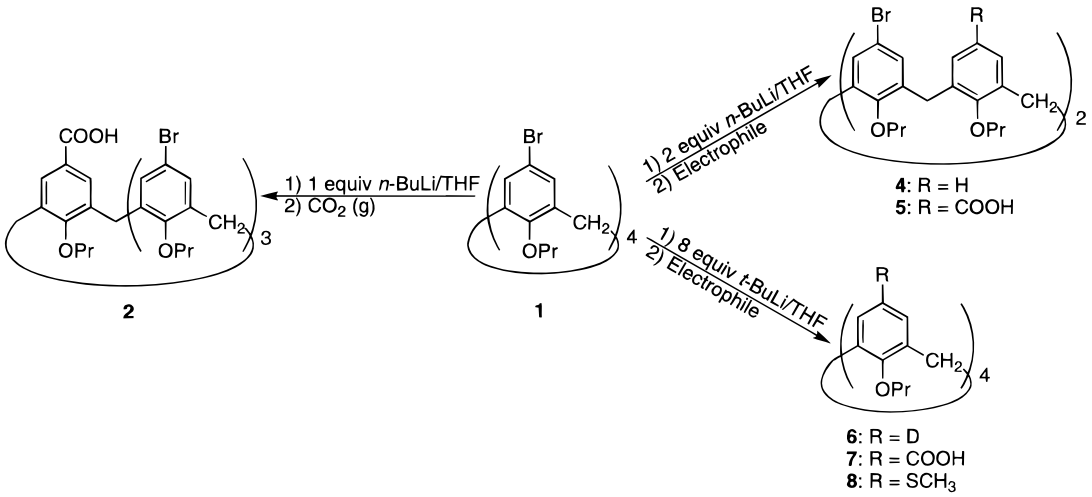
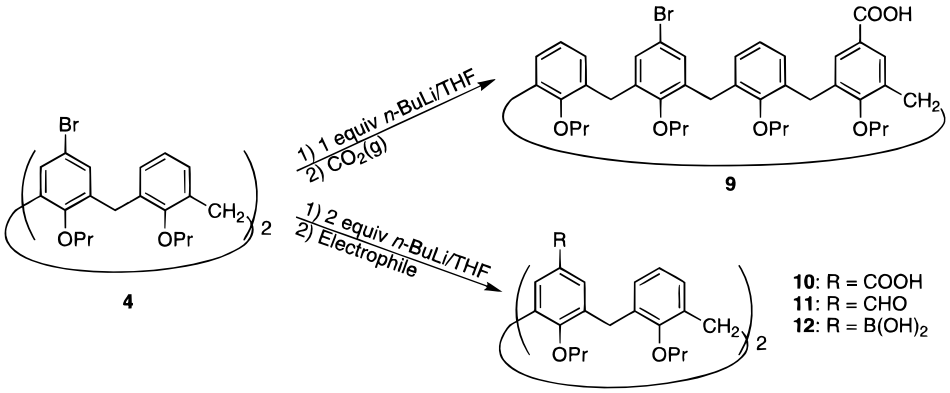
S0022-3263(96)00944-9 CCC: $12.00

Scheme 1



Scheme 2



THF at −78 °C and quenched after 15 min with CO_2 to give **2** in 72% yield.

When an excess of *n*-BuLi was used in THF at −78 °C, **1** could be selectively converted into 5,17-dibromo-11,23-dilithio-25,26,27,28-tetrapropoxycalix[4]arene **3**. Quenching **3** after 15 min with MeOH or dry CO_2 gave 5,17-dibromo-25,26,27,28-tetrapropoxycalix[4]arene (**4**) in 92% yield or 5,17-dibromo-11,23-dicarboxy-25,26,27,28-tetrapropoxycalix[4]arene (**5**) in 83% yield, respectively. Even with a large excess of *n*-BuLi the reaction proceeds only to the dilithiated stage in THF. Longer reaction times should be avoided because a nucleophilic substitution of *n*-BuBr with ArLi is taking place. This is seen in the ^{1}H NMR spectra where a triplet is present at 2.3 ppm indicating Ar$CH_2$$CH_2$R.

Shinkai *et al.*[14] have prepared **4** in an alternative way, first making the 25,27-dihydroxy-26,28-dipropoxycalix[4]arene. Bromination with 2 equiv of bromine in $CHCl_3$ at 0 °C for 1 h gave 11,23-dibromo-25,27-dihydroxy-26,28-dipropoxycalix[4]arene in 87% yield. Alkylation with *n*-PrBr in DMF/NaH at 25 °C for 12 h gave **4** in 76% yield. We failed to reproduce the procedure, obtaining several impurities which could not be separated be recrystallization or column chromatography.

When **1** is treated with 8 equiv of *t*-BuLi in THF at −78 °C for 30 min, then it can be converted into the tetralithiated stage. Quenching with D_2O, dry CO_2, or CH_3SSCH_3 gave 5,11,17,23-tetradeuterio-25,26,27,28-tetrapropoxycalix[4]arene (**6**) (88% yield), 5,11,17,23-tetracarboxy-25,26,27,28-tetrapropoxycalix[4]arene (**7**) (70.6% yield), or 5,11,17,23-tetrakis(methylthio)-25,26,27,28-tetrapropoxycalix[4]arene (**8**) (85% yield), respectively. If the reaction is performed in Et_2O, the tetralithiated stage is formed after 2 h at −78 °C. Reaction times of less than 2 h will give rise to incomplete Br−Li exchange. Quenching with dry CO_2 after 1 h results in a mixture of products according to ^{1}H NMR and ^{13}C NMR. Further characterizations of these products were not performed.

Addition of 1 equiv of *n*-BuLi in THF at −78 °C to **4** gave the monolithio compound which after being quenched with dry CO_2 gave 5-bromo-17-carboxy-25,26,27,28-tetrapropoxycalix[4]arene (**9**) in 49% yield. In the synthesis of the monoacids **2** and **9**, a small amount of starting material and diacid was present in the crude product, but the monoacids were easily purified by column chromatography. It is very important that the *n*-BuLi is titrated before use so that only 1 equiv is used in the mono-Br−Li exchange reaction to minimize the formation of the dilithio compounds.

Compound **4** can be converted into the dilithio stage with an excess of *n*-BuLi or *t*-BuLi in THF at −78 °C for 15 min (Scheme 2). Quenching with dry CO_2, DMF, or $B(OCH_3)_3$ gave 5,17-dicarboxy-25,26,27,28-tetrapropoxycalix[4]arene (**10**) (76% yield), 5,17-diformyl-25,26,27,28-tetrapropoxycalix[4]arene (**11**) (75% yield), or 25,26,27,28-tetrapropoxycalix[4]arene-5,17-diboronic acid (**12**) (42% yield), respectively. In the synthesis of **11**, the crude boronic acid is first converted into the bis-1,3-propandiol ester **11** and then hydrolyzed to the diboronic acid again.

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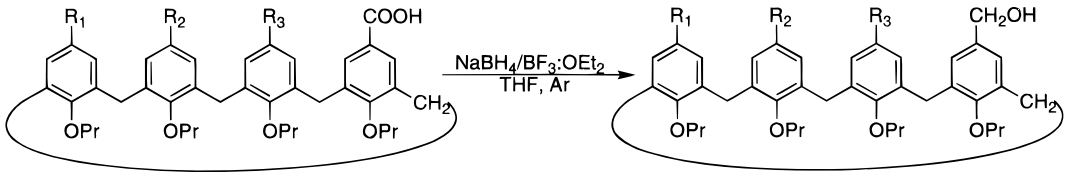
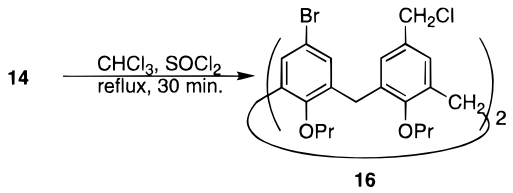
Scheme 3



2: R_1, R_2, R_3 = Br
5: R_1, R_3 = Br and R_2 = COOH
9: R_1, R_3 = H and R_2 = Br

13: R_1, R_2, R_3 = Br
14: R_1, R_3 = Br and R_2 = CH_2OH
15: R_1, R_3 = H and R_2 = Br

Scheme 4



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The reason is that the 1,3-propandiol ester is easily purified while we had difficulties in purifying **11** directly from the reaction mixture and the yield was lower.

If the monolithio stage of **1** and **4** is quenched with MeOH or MeI, it is not possible to isolate the 5,11,17-tribromo-, 5,11,17-tribromo-23-methyl-, 5-bromo-, or 5-bromo-17-methyltetrapropoxycalix[4]arene from starting material and disubstituted product.

Reduction of the acids **2**, **5**, and **9** with diborane (generated in situ from $NaBH_4$ and BF_3 etherate) in THF gave the corresponding alkohols **13**, **14**, and **15** in 81%, 83%, and 56% yields, respectively (Scheme 3). Refluxing **14** in $CHCl_3$ with $SOCl_2$ for 30 min gave the corresponding chloromethyl derivative **16** in 80% yield (Scheme 4).

Experimental Section

Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra are recorded on a Bruker DPX-250 with TMS as internal reference and at 300 K. All the NMR spectra were recorded in $CDCl_3$ unless otherwise stated. All chemicals were purchased from Aldrich and used without further purification. Solvents are all reagent grade and used without further purification, except for THF and Et_2O which were freshly distilled from sodium/benzophenone ketyl. Tetrapropoxycalix[4]arene (cone) was synthesized by the method described previously.[15] All reactions were carried out in a flame-dried glass apparatus and in an argon atmosphere. The temperatures are internal temperatures. Chromatographic separation were performed on silica gel 60 (SiO_2, E. Merck, particle size 0.040−0.063 mm, 230−240 mesh). In the ^{13}C NMR spectra of compounds **2**, **4**, **9**, and **16** there are less lines than expected for the propoxy groups, due to accidental isochrony. In compound **12** and its ester, the aromatic carbon attached to boron is not seen due to line broadening.

5,11,17,23-Tetrabromo-25,26,27,28-tetrapropoxycalix[4]arene (1). Tetrapropoxycalix[4]arene was NBS brominated by the method described previously[11] for the tetramethoxycalix[4]arene. Recrystallization from 96% EtOH gave **1** in 91% yield as white crystals: mp 280−282 °C; ^{1}H NMR δ 6.84 (s, 8H), 4.19 (d, 4H, J = 13.5 Hz), 3.86 (t, 8H, J = 7.4 Hz), 3.10 (d, 4H, J = 13.5 Hz), 1.90 (m, 8H, J = 7.5 Hz), 1.00 (t, 12H, J = 7.5 Hz); ^{13}C NMR δ 156.0, 136.8, 131.4, 115.6, 77.4, 31.2, 23.5, 10.6. Anal. Calcd for $C_{40}H_{44}Br_4O_4$: C, 52.89; H, 4.88; Br, 35.18. Found: C, 52.80; H, 4.95; Br, 35.38.

General Procedure for the Synthesis of Monolithiotetrapropoxycalix[4]arenes and Their Reactions with CO_2 (2 and 9). To a stirred solution of **1** or **4** (3.20 mmol) in dry THF (50 mL) at −78 °C was added *n*-BuLi/hexane (2.05 mL, 1.55 M, 3.20 mmol). The yellow solution was stirred at −78 °C for 15 min. Dry CO_2 was admitted at −78 °C for 30 min. Hydrochloric acid (50 mL, 6 M) was added, and the light yellow THF phase was separated. The water phase was extracted with $CHCl_3$ (2 × 100 mL), the combined organic phases were washed with water (2 × 100 mL) and dried (Na_2SO_4), and the solvent was removed on a rotary evapoator. TLC (silica, petroleum ether (60−80 °C)/EtOAc (2/1), (v/v)) shows three spots: $R_f \approx 0.95$ (**1** or **4**), $R_f \approx 0.40$ (**2** or **9**), and $R_f \approx 0.00$ (**5** or **10**). The monoacids **2** and **9** were purified by column chromatography on silica using (petroleum ether (60−80 °C)/EtOAc (2/1), (v/v)) as eluent.

5,11,17-Tribromo-23-carboxy-25,26,27,28-tetrapropoxycalix[4]arene (2) from 1. Recrystallization from 96% EtOH gave **2** in 72% yield as white crystals: mp > 300 °C dec; ^{1}H NMR δ 7.54 (s, 2H), 6.82 (s, 2H), 6.81 (d, 2H, J = 2.2 Hz), 6.78 (d, 2H, J = 2.2 Hz), 4.45 (d, 2H, J = 13.6 Hz), 4.38 (d, 2H, J = 13.6 Hz), 3.96 (t, 2H, J = 7.5 Hz), 3.90−3.75 (m, 6H), 3.24 (d, 2H, J = 13.6 Hz), 3.10 (d, 2H, J = 13.6 Hz), 2.0−1.8 (m, 8H), 1.05−0.95 (m, 12H); ^{13}C NMR δ 171.96, 161.89, 156.06, 155.86, 137.08, 136.77, 136.68, 135.29, 131.54, 131.42, 131.40, 131.18, 123.86, 115.67, 115.53, 77.46, 77.30, 31.27, 31.15, 23.62, 23.53, 23.45, 10.66, 10.58. Anal. Calcd for $C_{41}H_{45}Br_3O_6$: C, 56.37; H, 5.19; Br, 27.45. Found: C, 56.53; H, 5.30; Br, 27.23.

5-Bromo-17-carboxy-25,26,27,28-tetrapropoxycalix[4]arene (9) from 4. Recrystallization from 96% EtOH gave **9** in 49% yield as white crystals: mp 296−299 °C dec; ^{1}H NMR δ 7.38 (s, 4H), 6.72−6.62 (m, 8H), 4.46 (d, 2H, J = 13.5 Hz), 4.39 (d, 2H, J = 13.5 Hz), 3.95−3.75 (m, 8H), 3.22 (d, 2H, J = 13.5 Hz), 3.10 (d, 2H, J = 13.5 Hz), 2.0−1.8 (m, 8H), 1.10−0.80 (t, 12H); ^{13}C NMR δ 172.10, 161.86, 156.84, 156.00, 137.56, 135.68, 134.99, 134.88, 131.09, 130.89, 129.04, 128.89, 123.31, 122.94, 115.12, 77.30, 77.22, 77.18, 31.63, 31.54, 24.02, 23.88, 11.01, 10.92. Anal. Calcd for $C_{41}H_{47}BrO_6$: C, 68.80; H, 6.62. Found: C, 69.11; H, 6.77.

General Procedure for the Synthesis of Dilithiotetrapropoxycalix[4]arenes and Their Reactions with Electrophiles 4, 5, and 10−12. To a stirred solution of **1** or **4** (5.33 mmol) in dry THF (200 mL) at −78 °C was added *n*-BuLi/hexane (9.3 mL, 1.51 M, 14 mmol). The yellow solution was stirred at −78 °C for 15 min, quenched with MeOH (10 equiv), CO_2(g) (large excess), DMF (20 equiv), or $B(OCH_3)_3$ (4 equiv), and stirred for 10 min, 30 min, 10 min, or 2 h, respectively. The reaction mixture was poured into ice cold 2 M hydrochloric acid (200 mL) and extracted with $CHCl_3$ (2 × 100 mL). The organic phase was washed with water (100 mL) and dried (Na_2SO_4), and the solvent was removed *in vacuo* to yield a solid.

5,17-Dibromo-25,26,27,28-tetrapropoxycalix[4]arene (4) from 1. The raw product was recrystallized from 96% EtOH and gave **4** in 92% yield as white microcrystals: mp 243−245 °C; ^{1}H NMR δ 6.74 (s, 4H), 6.61 (s, 6H), 4.40 (d, 4H, J = 13.4 Hz), 3.83 (t, 4H, J = 7.5 Hz), 3.81 (t, 4H, J = 7.5 Hz), 3.10 (d, 4H, J = 13.4 Hz), 2.0−1.8 (m, 8H), 0.99 (t, 6H, J = 7.4 Hz), 0.97 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 156.47, 155.80, 137.31, 134.46, 130.86, 128.51, 122.57, 114.80, 77.00, 76.89, 30.96, 23.27, 10.38, 10.34. Anal. Calcd for $C_{40}H_{46}Br_2O_4$: C, 64.00; H, 6.18. Found: C, 64.32; H, 6.28.

5,17-Dibromo-11,23-dicarboxy-25,26,27,28-tetrapropoxycalix[4]arene (5) from 1. The raw product was purified by being dissolved in a minimum of hot THF, addition of MeOH

(15) Ikeda, A.; Nagasaki, T.; Araki, K.; Shinkai, S. *Tetrahedron* **1992**, *48*, 1059.

(180 mL), and evaporation *in vacuo* to half the volumn. **5** crystallizes as a white microcrystalline compound in 83% yield: mp > 300 °C dec; ^{1}H NMR δ 7.31 (s, 4H), 6.83 (s, 4H), 4.37 (d, 4H, J = 13.8 Hz), 3.96 (t, 4H, J = 8.0 Hz), 3.64 (t, 4H, J = 6.7 Hz), 3.12 (d, 4H, J = 13.8 Hz), 2.0−1.85 (m, 8H), 1.08 (t, 6H, J = 7.4 Hz), 0.84 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 171.66, 159.81, 156.84, 138.47, 133.12, 131.88, 129.80, 123.71, 115.03, 77.46, 76.96, 31.23, 23.84, 23.12, 11.14, 10.06. Anal. Calcd for $C_{42}H_{46}Br_2O_8$: C, 60.15; H, 5.53; Br, 19.06. Found: C, 60.32; H, 5.57; Br, 18.91.

5,17-Dicarboxy-25,26,27,28-tetrapropoxycalix[4]-arene (10) from 4. The crude product was titruated with hot 96% EtOH (50 mL) and cooled to −10 °C before filtration to give **10** in 76% yield as a white powder. Recrystallization from 1,4-dioxane gave an analytical sample: mp > 280 °C dec; ^{1}H NMR δ 12.87 (s, 2H), 7.17 (d, 4H, J = 7 Hz), 7.03 (t, 2H, J = 7 Hz), 6.77 (s, 4H), 4.42 (d, 4H, J = 14.0 Hz), 4.00 (t, 4H, J = 9.0 Hz), 3.66 (t, 4H, J = 6.0 Hz), 3.14 (d, 4H, J = 14.0 Hz), 1.90 (m, 8H), 1.10 (t, 6H, J = 7.0 Hz), 0.86 (t, 6H, J = 7.0 Hz); ^{13}C NMR δ 172.42, 160.13, 157.98, 136.95, 134.06, 130.11, 129.79, 123.58, 123.20, 77.29, 76.92, 31.31, 23.88, 23.33, 11.16, 10.15. Anal. Calcd for $C_{44}H_{52}O_9$ (**10** + 1/2dioxane): C, 72.90; H, 7.23. Found: C, 72.89; H, 7.40.

5,17-Diformyl-25,26,27,28-tetrapropoxycalix[4]arene (11) from 4. Recrystallization from MeOH gave **11** in 75% yield as white flakes: mp 216−218 °C; ^{1}H NMR δ 9.50 (s, 2H), 7.03 (s, 4H), 6.81−6.67 (A_2B system, 6H), 4.50 (d, 4H, J = 13.6 Hz), 3.92 (t, 4H, J = 7.2 Hz), 3.91 (t, 4H, J = 7.4 Hz), 3.26 (d, 4H, J = 13.6 Hz), 2.0−1.75 (m, 8H), 1.06 (t, 6H, J = 7.4 Hz), 1.00 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 192.34, 162.62, 157.25, 136.62, 135.46, 131.72, 130.52, 129.46, 123.34, 77.40, 77.19, 31.62, 24.06, 23.83, 11.05, 10.84. Anal. Calcd for $C_{42}H_{48}O_6$: C, 77.75; H, 7.46. Found: C, 77.64; H, 7.60.

25,26,27,28-Tetrapropoxycalix[4]arene-5,17-diboronic acid (12) from 4. The crude boronic acid was suspended in benzene (130 mL), and 1,3-propanediol (1.5 mL, 20 mmol) was added. The mixture was refluxed until all the water had been azeotropically removed. The slightly yellow solution was diluted with $CHCl_3$ (100 mL), washed with water (2 × 100 mL), dried (Na_2SO_4), evaporated to dryness on a rotary evaporator, and recrystallized from *n*-heptane. The white crystalline ester was dried in vacuum at 50 °C for 3 h and gave 60% yield: mp 248−250 °C dec; ^{1}H NMR δ 7.55 (s, 4H), 6.2−6.0 (AB_2 system, 6H), 4.42 (d, 4H, J = 13.4 Hz), 4.19 (t, 8H, J = 5.40 Hz), 4.05 (t, 4H, J = 8.0 Hz), 3.65 (t, 4H, J = 6.8 Hz), 3.18 (d, 4H, J = 13.4 Hz), 2.08 (m, 4H, J = 5.4 Hz), 2.0−1.7 (m, 8H), 1.09 (t, 6H, J = 7.4 Hz), 0.86 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 161.10, 155.40, 136.78, 135.05, 133.52, 127.87, 122.40, 77.01, 76.52, 62.40, 31.34, 27.94, 23.96, 23.42, 11.24, 10.26. Anal. Calcd for $C_{46}H_{58}B_2O_8$: C, 72.64; H, 7.69. Found: C, 72.75; H, 7.79.

The ester (1.80 g, 2.37 mmol) was hydrolyzed in THF/H_2O (110 mL, 80/30, 0.1 M hydrochloric acid was added until the pH was 4) at reflux for 1 h. The mixture was cooled on ice, and the crude boronic acid was isolated by filtration. Recrystallization from acetone yielded **12** in 71% yield as white flakes: mp 249−251 °C dec; ^{1}H NMR δ (DMSO-d_6) 7.83 (s, 4H), 7.56 (s, 4H), 6.3−6.1 (AB_2 system, 6H), 4.36 (d, 4H, J = 13.1 Hz), 4.01 (t, 4H, J = 7.7 Hz), 3.63 (t, 4H, J = 6.5 Hz), 3.13 (d, 4H, J = 13.1 Hz), 2.1−1.7 (m, 8H), 1.09 (t, 6H, J = 7.4 Hz), 0.89 (t, 6H, J = 7.4 Hz); ^{13}C NMR (DMSO-d_6) δ 159.14, 154.65, 135.07, 135.02, 132.72, 127.11, 121.52, 76.64, 75.77, 30.30, 23.01, 22.54, 10.62, 9.70. Anal. Calcd for $C_{40}H_{50}B_2O_8$: C, 70.60; H, 7.41. Found: C, 70.42; H, 7.50.

General Procedure for the Synthesis of Tetralithiotetrapropoxycalix[4]arene and Its Reactions with Electrophiles 6−8. To a stirred solution of **1** (1.00 g, 1.10 mmol) in dry THF (50 mL) at −78 °C was added *t*-BuLi/pentane (7.0 mL 1.47 M, 10 mmol). The yellow solution was stirred at −78 °C for 30 min and quenched with D_2O (10 equiv), CO_2(g) (large excess), or CH_3SSCH_3 (10 equiv). The reaction mixture was stirred for 30 min. The workup procedure is given below.

5,11,17,23-Tetradeuterio-25,26,27,28-tetrapropoxycalix-[4]arene (6). The reaction mixture was poured into water (200 mL), extracted with ether (2 × 50 mL), washed with water (50 mL), and dried (Na_2SO_4), and the solvent was removed on a rotary evaporator. Recrystallization from 96% EtOH gave **6** in 88% yield as white needles: mp 196−197 °C; ^{1}H NMR δ 6.60 (s, 8 H), 4.45 (d, 4H, J = 13.3 Hz), 3.84 (t, 8H, J = 7.4 Hz), 3.14 (d, 4H, J = 13.3 Hz), 1.90 (m, 8H), 0.99 (t, 12H, J = 7.4 Hz); ^{13}C NMR δ 157.29, 135.82, 128.69, 122.26 (t), 77.36, 31.70, 23.94, 11.02. Anal. Calcd for $C_{40}H_{44}D_4O_4$: C, 80.50; H, 7.43. Found: C, 80.51; H, 6.28.

5,11,17,23-Tetracarboxy-25,26,27,28-tetrapropoxycalix-[4]arene (7). Hydrochloric acid (10 mL, 6 M) was added to the reaction mixture. The white suspension was evaporated to dryness *in vacuo*. The crude product was boiled with 96% EtOH (230 mL) and filtered from insoluble material. Water (80 mL) was added, and the solution was evaporated to half the volumn. Cooling on ice and filtration gave **7** as a very fine white crystalline product. Drying *in vacuo* at 70 °C for 5 h afforded a 70.6% yield: mp > 300 °C dec; ^{1}H NMR (DMSO-d_6) δ 7.32 (s, 8H), 4.37 (d, 4H, J = 13.3 Hz), 3.90 (t, 8H, J = 7.2 Hz), 3.39 (d, 4H, J = 13.3 Hz), 1.90 (m, 8H), 0.99 (t, 12H, J = 7.3 Hz); ^{13}C NMR (DMSO-d_6) δ 166.74, 159.77, 134.19, 129.58, 124.69, 76.51, 30.04, 22.72, 10.04. Anal. Calcd for C_{44}-$H_{48}O_{12}$: C, 68.73; H, 6.29. Found: C, 68.49; H, 6.45.

5,11,17,23-Tetrakis(methylthio)-25,26,27,28-tetrapropoxycalix[4]arene (8). Excess CH_3SSCH_3 was destroyed by adding $NaBH_4$ (1 g, 27 mmol) and stirring at 20 °C for 30 min. The mixture was poured into NaOH(aq) (100 mL, 1 M). The organic phase was separated, and the water phase was extracted with Et_2O (2 × 100 mL). The combined organic phases were washed with NaOH (100 mL 1 M), dried (Na_2-SO_4), and evaporated to a yellow oil *in vacuo*. The oil was titruated with MeOH (20 mL), and the crude product was filtrated and washed with MeOH (50 mL). Recrystallization from MeCN gave **8** in 85% yield as white crystals: mp 178−179 °C; ^{1}H NMR δ 6.67 (s, 8H, ArH), 4.41 (d, 4H, J = 13.2 Hz), 3.84 (t, 8H, J = 7.5 Hz), 3.11 (d, 4H, J = 13.2 Hz,), 2.30 (s, 12H), 1.93 (m, 8H, J = 7.5 Hz), 1.00 (t, 12H, J = 7.5 Hz); ^{13}C NMR δ 155.52, 135.95, 131.16, 128.67, 77.60, 31.61, 23.84, 18.29, 10.96. Anal. Calcd for $C_{44}H_{56}O_4S_4$: C, 68.00; H, 7.26. Found: C, 68.01; H, 7.32.

General Procedure for the Borane Reduction of the Carboxylic Acids (13−15). The carboxylic acid (**2**, **5**, **9**) (3.78 mmol) was dissolved in dry THF (50 mL). $NaBH_4$ (1 g, 26 mmol) was added, and the suspension was stirred at 10 °C for 10 min. BF_3·OEt_2 (5 mL, 36 mmol) was added over 5 min, and the mixture was stirred at 10 °C for 2 h. MeOH (15 mL) was then carefully added to destroy excess diborane. The reaction mixture was poured into $NaHCO_3$ (100 mL, 5%) and extracted with $CHCl_3$ (2 × 50 mL). The organic phase was washed with water (50 mL) and dried (Na_2SO_4) and the solvent removed on a rotary evaporator.

5,11,17-Tribromo-23-(hydroxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene (13). Recrystallization from 96% EtOH gave **13** in 93% yield as white microcrystals: mp 224−226 °C; ^{1}H NMR δ 6.99 (d, 2H, J = 2.3 Hz), 6.95 (d, 2H, J = 2.3 Hz), 6.56 (s, 2H), 6.49 (s, 2H), 4.39 (d, 2H, J = 13.6 Hz), 4.37 (s, 2H), 4.34 (d, 2H, J = 13.6 Hz), 3.95−3.80 (m, 4H), 3.80−3.65 (m, 4H), 3.12 (d, 2H, J = 13.6 Hz), 3.06 (d, 2H, J = 13.6 Hz), 2.0−1.8 (m, 8H), 0.95 (t, 6H, J = 7.4Hz), 0.93 (t, 6H, J = 7.4Hz); ^{13}C NMR δ 156.80, 156.20, 155.97, 138.56, 137.69, 136.76, 135.97, 134.30, 132.11, 131.57, 131.30, 127.39, 115.51, 115.29, 77.51, 77.43, 77.23, 65.72, 31.59, 31.41, 23.96, 23.86, 23.65, 11.12, 11.05, 10.69. Anal. Calcd for $C_{41}H_{47}Br_3O_5$: C, 57.29; H, 5.51. Found: C, 57.41; H, 5.67.

5,17-Dibromo-11,23-bis(hydroxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene (14). Recrystallization from 96% EtOH gave **14** in 83% yield as white crystals: mp 235−237 °C; ^{1}H NMR δ 6.98 (s, 4H), 6.47 (s, 4H), 4.40 (d, 4H, J = 13.4 Hz), 4.28 (s, 4H), 3.92 (t, 4H, J = 7.3 Hz), 3.73 (t, 4H, J = 7.3 Hz), 3.11 (d, 4H, J = 13.4 Hz), 2.0−1.7 (m, 8H), 1.03 (t, 6H, J = 7.4 Hz), 0.94 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 156.55, 156.10, 138.15, 135.24, 134.11, 131.49, 127.06, 115.06, 77.52, 77.19, 65.18, 31.33, 23.70, 23.39, 10.87, 10.45. Anal. Calcd for $C_{42}H_{50}Br_2O_6$: C, 62.23; H, 6.22; Br, 19.71. Found: C, 62.11; H, 6.45; Br, 19.93.

5-Bromo-17-(hydroxymethyl)-25,26,27,28-tetrapropoxycalix[4]arene (15). Recrystallization from *n*-hexane gave **15** in 56% yield as white crystals: mp 205−207 °C; ^{1}H NMR δ

6.92−6.65 (m, 6H), 6.47 (s, 2H), 6.40 (s, 2H), 4.44 (d, 2H, J = 13.5 Hz), 4.40 (d, 2H, J = 13.5 Hz), 4.28 (s, 2H), 4.00−3.85 (m, 4H), 3.65−3.78 (m, 4H), 3.16 (d, 2H, J = 13.5 Hz), 3.09 (d, 2H, J = 13.5 Hz), 2.00−1.80 (m, 8H), 1.04 (t, 3H, J = 7.4 Hz), 1.03 (t, 3H, J = 7.4 Hz), 0.93 (t, 6H, J = 7.4 Hz); ^{13}C NMR δ 157.76, 156.20, 155.94, 137.36, 136.70, 135.84, 135.49, 134.83, 131.02, 129.69, 129.14, 127.06, 122.98, 114.88, 77.44, 77.35, 77.04, 65.90, 31.72, 31.58, 24.08, 23.99, 23.74, 11.26, 11.21, 10.71. Anal. Calcd for $C_{41}H_{49}BrO_5$: C, 70.17; H, 7.04; Br, 11.39. Found: C, 70.37; H, 7.06; Br, 11.48.

5,17-Dibromo-11,23-bis(chloromethyl)-25,26,27,28-tetrapropoxycalix[4]arene (16). To a solution of **14** (7.10 g, 8.76 mmol) in dry $CHCl_3$ (80 mL) at 25 °C was added $SOCl_2$ (1.90 mL, 25 mmol) over 1 min, and then the solution stirred at 25 °C for 45 min. Excess $SOCl_2$ was removed on a rotary evaporator. Recrystallization from *n*-hexane gave **16** in 80% yield (5.94 g) as white crystals: mp 224−226 °C; ^{1}H NMR δ 6.80 (s, 4H), 6.64 (s, 4H), 4.37 (d, 4H, J = 13.4 Hz), 4.32 (s, 4H), 3.82 (t, 8H, J = 7.5 Hz), 3.11 (d, 4H, J = 13.4 Hz), 2.0−1.8 (m, 8H), 0.97 (t, 12H, J = 7.4 Hz); ^{13}C NMR δ 156.69, 155.64, 136.91, 134.72, 131.21, 130.87, 128.67, 114.90, 77.40, 77.36, 46.93, 31.23, 23.58, 23.50, 10.63. Anal. Calcd for $C_{42}H_{48}Cl_2Br_2O_4$: C, 59.52; H, 5.71; Br, 18.86; Cl, 8.37. Found: C, 59.75; H, 5.58; Br, 17.95; Cl, 8.45.

Acknowledgment. The authors are grateful to the Danish Materials Technology Development Programme for support of this work which was performed within the framework of the Danish Polymer Centre.

JO9609440