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Selective Functionalization of a Single Methylene Bridge of a Calix[6]arene

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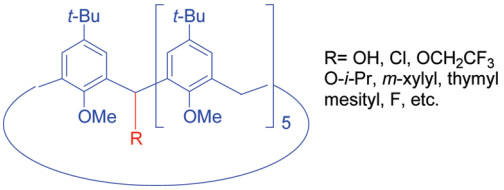
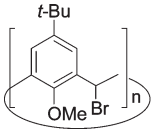


The monohydroxycalix[6]arene derivative **4a** was prepared via photochemical bromination of hexamethoxycalix[6]arene **3a** in aq THF. Monohydroxycalix[6]arene **4a** and its chloro derivative **5** are useful synthetic intermediates for the preparation of structurally diverse calix[6]arenes functionalized at a single methylene bridge.

Introduction

The functionalization of the scaffold of the calixarenes is of interest since the introduction of substituents may affect the conformational preferences of the macrocycle, its rigidity, and the physical and chemical properties of the molecule.[1] Most synthetic modifications have been conducted on the aryl rings (the walls surrounding the cavity)[1,2] and, to a much lesser extent, at the methylene bridges.

Monosubstitution of a single methylene bridge is of interest in the case where a minimal or gradual modification of the properties of the macrocycle is desirable. Monofunctionalized calixarenes have been prepared either by cyclocondensation of suitable fragments (the fragment condensation method)[3] or in straightforward fashion by direct modification of the macrocycle. So far, the latter transformation has been achieved only for the calix[4]arene scaffold and, notably, both synthetic methods reported involved metalation of a methylene bridge. The first method reported involved a homologous anionic ortho Fries rearrangement.[4] In this approach, a carbamate group originally attached to the lower rim of the calixarene is transferred to a lithiated methylene bridge via a five-membered intermediate. The second approach, developed by Fantini and co-workers, involved the monolithiation of a tetramethoxycalix[4]arene followed by reaction of the lithiated macrocycle with an alkylation agent such as primary alkyl halides or carbon dioxide.[5,6]



1a n = 4
1b n = 5
1c n = 6

We have recently reported[7,8] that the calixarenes incorporating bromine atoms at all bridges **1a**−**c** are useful starting materials for the preparation of a wide array of

(1) For recent reviews on calixarenes, see: (a) *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College Press: London, 2000. (b) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, 2003; Chapter 19. (c) Gutsche, C. D. *Calixarenes: an Introduction*; Royal Society of Chemistry: Cambridge, 2008.

(2) For recent examples, see: (a) Troisi, F.; Mogavero, L.; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2007**, *9*, 915. (b) Troisi, F.; Citro, L; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2008**, *10*, 1393.

(3) (a) Tabatabai, 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) 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*, 2261. (d) Bergamaschi, M.; Bigi, F.; Lanfranchi, M.; Maggi, R.; Pastorio, A.; Pellinghelli, M. A.; Peri, F.; Porta, C.; Sartori, G. *Tetrahedron* **1997**, *53*, 13037. (e) For a review on the synthesis of calixarenes via the stepwise and fragment condensation methods, see: Böhmer, V. *Liebigs Ann./Recueil* **1997**, 2019.

(4) Middel, O.; Greff, Z.; Taylor, N. J.; Verboom, W.; Reinhoudt, D. N.; Snieckus, V. *J. Org. Chem.* **2000**, *65*, 667.

(5) (a) Scully, P. A.; Hamilton, T. M.; Bennett, J. L. *Org. Lett.* **2001**, *3*, 2741. (b) Hertel, M. P.; Behrle, A. C.; Williams, S. A.; Schmidt, J. A. R.; Fantini, J. L. *Tetrahedron* **2009**, *65*, 8657. J. L. Fantini previously published as J. L. Bennett. (c) For a recent study of the conformation behavior of a calix[4]arene with a single methylene group substituted by a carboxyl functionality, see: Gruber, T.; Gruner, M.; Fischer, C.; Seichter, W.; Bombicz, P.; Weber, E. *New J. Chem.* **2010**, *34*, 250. (d) For agostic and methylene hydride complexes of calix[4]arene, see: Buccella, D.; Parkin, G. *J. Am. Chem. Soc.* **2006**, *128*, 16358.

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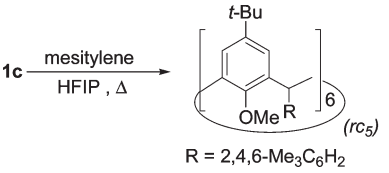
calixarenes with all the methylene bridges monofunctionalized. Replacement of the bromine atoms was conducted under S_N1 conditions, simply by refluxing a solution of the bromocalixarene and the nucleophile in an ionizing solvent such as 2,2,2-trifluoroethanol (TFE) or hexafluoro-2-propanol (HFIP) (e.g., eq 1).[9]

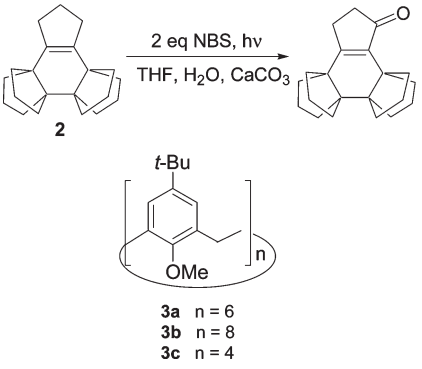


(1)

Attractive features of this route are the simplicity of the reaction conditions (no Lewis acids, inert atmosphere, or dry solvents are required) and its versatility (O-, N- S-, and C-nucleophiles can be attached to the bridges by this route). In this paper, we describe a simple route for the selective monofunctionalization of the calix[6]arene skeleton.[10]

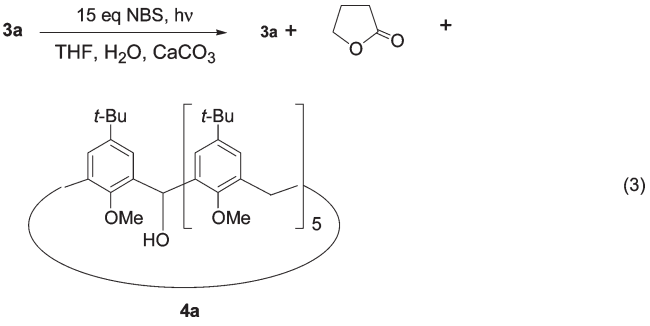
Results and Discussion

Methylene-Functionalized Monohydroxy Calix[6]arene Derivative. Recently, Fitjer and co-workers reported the oxidation of a single methylene group of the bispropellane **2** using NBS in a THF/water/$CaCO_3$ mixture (eq 2).[11]



(2)

Because of our continued interest in ketocalixarenes,[12] we decided to attempt the analogous reaction on the hexamethoxy calix[6]arene **3a** (eq 3). In an attempt to oxidize all the methylene bridges of **3a**, we conducted the photochemical reaction using 15 equiv of NBS. Unexpectedly, examination of the ^{1}H NMR spectrum of the crude product indicated the presence of a ca. 1:1 mixture of starting material and a new compound, as well as γ-butyrolactone. The new compound displayed six doublets for the methylene protons in 2:2:2:2:1:1 ratio, a pattern indicating mirror symmetry and consistent with a calix[6]arene derivative with a single bridge monofunctionalized. On the basis of the presence of a pair of doublets (J = 5.1 Hz) at 6.39 and 2.30 ppm (assigned to the methine and OH protons of the CHOH unit, respectively) the product was assigned to the monohydroxy calix[6]arene derivative **4a**. The formation of **4a** probably involves monobromination of the calixarene at a single methylene bridge followed by hydrolysis of the formed benzhydrylic-type bromine under the reaction conditions. It seems likely that the abstraction of a hydrogen atom by a bromine radical is slower in calixarene **3a** than in the bispropellane **2** due to steric hindrance, and therefore, reaction with the THF solvent molecules successfully competes with the bromination of **3a**.



(3)

Additional attempts to improve the yield of the monohydroxy derivative proved unsuccessful. For example, as shown by ^{1}H NMR spectroscopy, increasing the number of equivalents of NBS decreased the amount of unreacted starting material but resulted in the concomitant formation of additional products. In retrospect, the ratio of reagents chosen for our initial attempted "oxidation" reaction proved to be the best for the preparation of the monosubstituted product. Although the reaction yields a mixture of **4a** and unreacted **3a**, a 5 g mixture of the two compounds can be easily separated by flash chromatography due to their significantly different R_f values, and if necessary **3a** can be recycled for an additional reaction. We also attempted to achieve selective functionalization of two bridges by decreasing the amount of THF by half or by conducting the reaction on the monohydroxy derivative **4a**. However, in both cases, a complex mixture of products was obtained as shown by ^{1}H NMR spectroscopy. Apparently, the functionalization of the second bridge does not proceed in regioselective fashion.

We examined also the reaction of **3b** and **3c** to test whether the reaction conditions found for **3a** are applicable also for the selective functionalization of a single methylene bridge of larger and smaller ring calixarenes. The attempted reactions were conducted using amounts of reagents (1.05 g of calixarene, 2.67 g of NBS, 1.2 g of $CaCO_3$, and 20 mL of THF containing 5% water) identical to those used for **3a**. Although samples of identical weight of the calixarenes **3a**−**c**

(6) For examples of calixarenes modified at two or all bridges, see, for example: (a) Görmar, G.; Seiffarth, K.; Schultz, M.; Zimmerman, J.; Flämig, G. *Makromol. Chem.* **1990**, *191*, 81. (b) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (c) Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577. (d) For a recent example of an optically active methylene-substituted calix[4]arene, see: Gopalsamuthiram, V.; Predeus, A. V.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 18018.

(7) (a) Klenke, B.; Näther, C.; Friedrichsen, W. *Tetrahedron Lett.* **1998**, *39*, 8967. (b) Kumar, S. K.; Chawla, H. M.; Varadarajan, R. *Tetrahedron Lett.* **2002**, *43*, 7073.

(8) (a) Columbus, I.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2927. (b) Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 2598. (c) Kogan, K.; Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 7327. (d) Kogan, K.; Biali, S. E. *J. Org. Chem.* **2009**, *74*, 7172.

(9) For examples of silver-mediated substitutions in bromodienone calixarene derivatives, see: Troisi, F.; Pierro, T.; Gaeta, C.; Neri, P. *Org. Lett.* **2009**, *11*, 697.

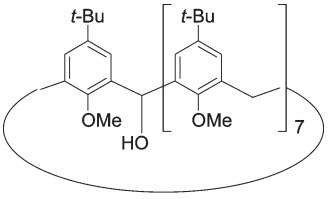
(10) Several calix[5]arenes monosubstituted at a single bridge have been prepared by the fragment condensation method. See: Biali, S. E.; Böhmer, V.; Columbus, I; Ferguson, G.; Grüttner, C.; Grynszpan, F.; Paulus, E. F.; Thondorf, I. *J. Chem. Soc., Perkin Trans. 2* **1998**, 2261.

(11) Justus, K.; Beck, T.; Noltemeyer, M.; Fitjer, L. *Tetrahedron* **2009**, *65*, 5192.

(12) (a) Seri, N.; Thondorf, I.; Biali, S. E. *J. Org. Chem.* **2004**, *69*, 4774. (b) Kogan, K.; Biali, S. E. *Org. Lett.* **2007**, *9*, 2393.

obviously differ in the total number of molecules, they possess an identical total number of methylene groups. If the reactivities of the methylene groups of the different calixarenes are similar, it could be expected that monofunctionalized calixarenes (in addition to unreacted starting material and γ-butyrolactone) should be obtained in all cases.

Reaction of **3c** afforded, as judged from ^{1}H NMR of the crude product, almost exclusively starting material and γ-butyrolactone. The lower reactivity of **3c** under the reaction conditions (as compared to **3a**) indicates that a methylene group of **3c** is significantly less reactive toward the bromine radical than the corresponding group in **3a**. The difference in reactivity may be due to the decreased conformational flexibility of the smaller calixarene. Ideally, in the transition state of the hydrogen abstraction step by the bromine radical, the π clouds of two rings geminal to the reacting methylene bridge should overlap with the orbital of the developing carbon radical. This arrangement can be more easily attainable for the larger calix[6]arene, thus the lower reactivity of **3c**. For the larger calix[8]arene **3b**, the reactivity under the reaction conditions was essentially identical to that of **3a** and afforded a ca. 1:1 mixture of starting material and its monohydroxy derivative **4b**.[13] This compound displayed in the ^{1}H NMR spectrum four *t*-Bu signals, eight doublets for the methylene protons in 2:2:2:2:2:2:1:1 ratio, and a pair of doublets (J = 4 Hz) at 6.45 and 2.71 ppm for the CHOH moiety.



4b

Crystal Structure of 4a and Conformation in Solution. A single crystal of **4a** was grown from chloroform and submitted to X-ray crystallography (Figure 1). The molecule adopts a 1,2,3-alternate conformation with four methoxy groups oriented "out" and a pair of methoxy groups oriented "in". In the crystal conformation the substituent is located between a pair of rings oriented *syn*. The OH group is intermolecularly hydrogen bonded to the oxygen of one of the methoxy groups oriented "in" (O3) of a neighboring molecule.

Ideally, in the absence of the substituent at the bridge, the 1,2,3-alternate conformation should possess C_i symmetry. However, its presence lowers the symmetry to C_1, rendering the conformation chiral. The pattern of signals observed in the ^{1}H NMR spectrum at room temperature indicates a structure of C_s symmetry, but if indeed the solution conformation is similar to the conformation found in the crystal, the pattern observed may be the result of fast exchange between two enantiomeric conformations of C_1 symmetry (an enantiomerization process, Figure 2).[14]

(13) The use of **4b** as a starting material for the preparation of methylene-functionalized calix[8]arenes is currently under investigation and will be reported in due course.

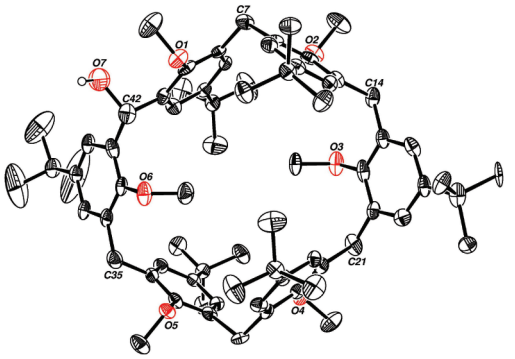
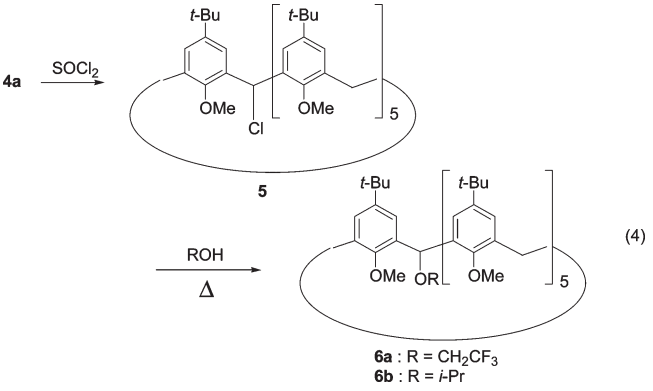


FIGURE 1. Crystal structure of the monohydroxycalix[6]arene **4a**.

Preparation and Reactions of the Chloro Derivative 5. Calixarene **4a** can provide a synthetic entry into a wide array of calix[6]arenes monofuntionalized at a single group by means of the S_N1 route utilized for the bromocalixarenes. To be on more familiar grounds, monohydroxycalix[6]arene was treated with $SOCl_2$ to afford the monochloro derivative **5**. To test whether this compound is reactive toward O-nucleophiles under solvolytic conditions, **5** was heated in solution at reflux temperature with either TFE or 2-propanol. In both cases, the corresponding ethers (**6a** and **6b**, respectively) were obtained in practically quantitative yield[15] (eq 4). As in the case of **1a**−**c**,[8] most likely the substitution reaction proceeds via a S_N1 mechanism involving a carbocation.



(4)

The solvolytic Friedel−Crafts reaction[8,16] of **5** was also examined. Reactions with the electron-rich thymol and *p*-*tert*-butylphenol were conducted in a mixture of TFE/$CHCl_3$ containing a drop of concd HBr.[17] For the less nucleophilic mesitylene, HFIP was used as the ionizing solvent yielding **7e**. Since HFIP is relatively expensive, we also examined "classical" Friedel−Crafts reaction conditions using a Lewis acid instead

(14) Lowering the temperature of a sample of **4a** in CD_2Cl_2 to 188 K resulted in extensive broadening of all signals, but no decoalescence was observed.

(15) In contrast to **1c**, the reaction of **5** with aniline (in HFIP) proceeds in nonregioselective fashion and affords a mixture of two products, derived from N-alkylation and C-alkylation of aniline.

(16) Hofmann, M.; Hampel, N.; Kanzian, T.; Mayr, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 5402.

(17) In principle, reaction of the carbocation with TFE could results in the formation of **6a**. However, if the trifluoroethoxy group of **6a** is reversibly cleaved under the acidic reaction conditions, but the electrophilic substitution reaction on the aromatic ring is irreversible, only the Friedel−Crafts product should be obtained.

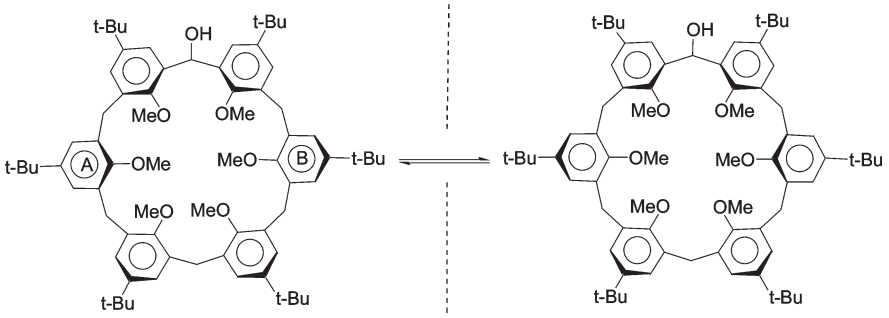
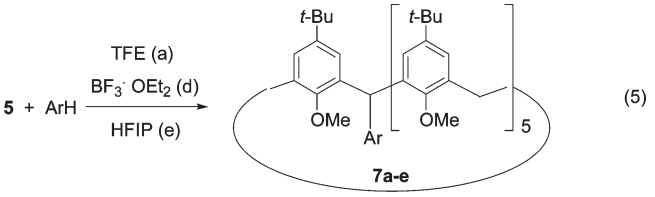


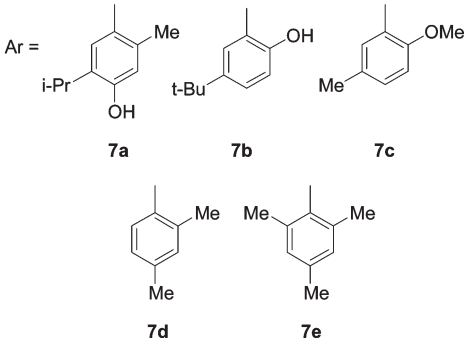
FIGURE 2. Up−down rotation of the rings A and B in the left structure results in enantiomerization. When these rotations are fast (on the NMR time scale) a signals pattern consistent with an average C_s symmetry should be observed.

of the ionizing solvent. The reaction of **5** with *m*-xylene catalyzed by boron trifluoride etherate proceeded readily and yielded the derivative **7d** (eq 5).

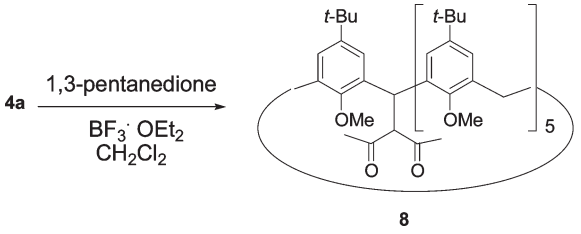
In contrast to **3**, the *t*-Bu, methylene, and methoxy signals of the **7a**−**d** displayed some broadening in the NMR spectrum at room temperature. This broadening was particularly marked for the mesityl derivative **7e**. It seems likely that this broadening is due to restricted rotation. At 373 K, sharp signals were observed for **7e** with a signal pattern indicating an average (dynamic) C_s symmetry, as observed for **4a** at rt.



(5)

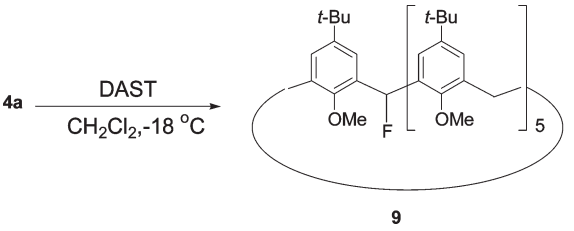


Direct Replacement of the OH Group of 4a. The possibility of conducting the reaction directly on the hydroxy derivative, rather than on the chloro derivative (whose preparation requires an additional synthetic step), was also examined. No reaction was observed when a solution of **4a** and *m*-xylene in HFIP was heated at reflux, indicating that, although the ionizing solvent is relatively acidic, its presence alone in not sufficient to generate the calixarene carbocation. However, in the presence of a Lewis acid the OH group at the bridge can be cleaved heterolytically. Treatment of a solution of **4a** and 1,3-pentadienone in CH_2Cl_2 with boron trifluoride etherate yielded the monoacetylacetonyl derivative **8** (eq 6).[18]



(6)

The OH group can be utilized for the incorporation of other groups at the bridge. The OH group of aliphatic alcohols can be replaced by fluorine by treatment with the deoxofluorinating reagent DAST (Et_2NSF_3).[19] Reaction of **4a** with DAST proceeded readily and afforded **9** (eq 7), the first calixarene derivative in which a fluorine atom has been incorporated into a bridge. The incorporation of a fluorine atom was readily evident in the ^{1}H NMR and ^{13}C NMR spectra of **9**, since in both spectra doublets indicating couplings with the fluorine atom were observed for the proton (^2J = 47 Hz) and carbon (^1J = 166 Hz) of the functionalized methylene group. In addition, a fluorine signal was observed in the ^{19}F NMR (δ −165.6 ppm).



(7)

Conclusions

In summary, we have shown that the monohydroxy and monochloro derivatives **4a** and **5** are readily synthetically available and are useful precursors for the preparation of a wide array of monofunctionalized calix[6]arenes. Interestingly, the present approach and the method developed by Fantini and co-workers involve the introduction of opposite charges (positive and negative) at a single methylene bridge. Electron-rich substituents, which can be incorporated by the S_N1 route, are not accessible via the lithiation/alkylation

(18) For recent reports of the Lewis acid-catalyzed alkylation of benzhydryl cations with compounds possessing active methylenes, see: (a) Bisaro, F.; Prestat, G.; Vitale, M.; Poli, G. *Synlett* **2002**, 1823. (b) Jana, U.; Biswas, S.; Maiti, S. *Tetrahedron Lett.* **2007**, *48*, 4066. (c) Sanz, R.; Miguel, D.; Martinez, A.; Alvarez-Gutierrez, J. M.; Rodriguez, F. *Org. Lett.* **2007**, *9*, 2027.

(19) Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

route and vice versa (primary alkyl groups, readily available by the lithiation route cannot be incorporated by the present approach), and therefore, the two synthetic methodologies are complementary.

Experimental Section

5,11,17,23,29,35-Hexa-*tert*-butyl-2-hydroxy-37,38,39,40,41,42-hexamethoxycalix[6]arene (4a). A mixture of **3a**[20] (1.05 g, 1.0 mmol), NBS (2.67 g, 15 mmol), $CaCO_3$ (1.2 g, 12 mmol), and THF containing 5% water (20 mL) was heated at reflux overnight while being irradiated with a spotlight (150 W). After evaporation of the solvent, the residue was dissolved in chloroform (30 mL) and washed with brine, diluted aq HCl, and brine. The organic phase was dried (Na_2SO_4) and evaporated. The crude product was recrystallized from methanol to give 0.6 g (60%) of a ca. 1:1 mixture of **3** and **4a**, as judged by ^{1}H NMR. The mixture was separated by flash chromatography (eluent, 100:6 CH_2Cl_2/ethyl acetate) to afford 250 mg (23%) of pure **4a**: mp 315 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (d, J = 2.4 Hz, 2H), 7.08 (d, J = 2.4 Hz, 2H), 7.03 (d, J = 2.4 Hz, 2H), 7.01 (d, J = 2.4 Hz, 2H), 6.99 (d, J = 2.4 Hz, 2H), 6.97 (d, J = 2.4 Hz, 2H), 6.39 (d, J = 5.1 Hz, 1H), 4.30 (d, J = 15.2 Hz, 2H), 4.16 (d, J = 14.8 Hz, 2H), 4.10 (d, J = 14.8 Hz, 1H), 3.84 (d, J = 14.8 Hz, 1H), 3.76 (d, J = 15.2 Hz, 2H), 3.63 (d, J = 15.2 Hz, 2H), 3.00 (s, 6H), 2.97 (s, 6H), 2.93 (s, 6H), 2.30 (d, J = 5.1 Hz, 1H, exchanges with D_2O), 1.16 (s, 18H), 1.14 (s, 18H), 1.13 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.8, 153.3, 146.1, 145.8, 145.7, 136.2, 133.6, 133.48, 133.45, 133.39, 133.29, 133.0, 127.5, 126.0, 125.5, 123.0, 60.5, 60.4, 60.0, 59.9, 34.3, 34.1, 34.0, 31.4, 31.3, 31.0, 30.5, 30.3, 30.2; HRMS (ESI) m/z 1095.7048 (M + Na^+), calcd for $C_{72}H_{96}O_7Na$ 1095.7054.

5,11,17,23,29,35,41,47-Octa-*tert*-butyl-2-hydroxy-49,50,51,52,53,54,55,56-octamethoxycalix[8]arene (4b). A mixture of **3b** (2.81 g, 2.0 mmol), NBS (5.34 g, 30 mmol), $CaCO_3$ (2.4 g, 24 mmol), and 45 mL of THF (containing 5% water) was stirred and heated under reflux overnight while being irradiated with a spotlight (150 W). After vacuum evaporation of the solvent, the residue was dissolved in chloroform (50 mL) and washed successively with brine, diluted aq HCl, and brine. The organic phase was dried (Na_2SO_4) and evaporated. The crude product was recrystallized from $CHCl_3$/MeOH to give 1.8 g (63%) of a ca. 40:60 mixture of **4b** and **3b**, as judged by NMR. The mixture was separated by flash chromatography (eluent: 100:6 methylene chloride/ethyl acetate) to afford 620 mg (22%) of pure **4b**: mp 288 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (d, J = 2.4 Hz, 2H), 7.00 (d, J = 2.4 Hz, 2H), 6.96−6.92 (overlapping d, 6H), 6.90−6.89 (overlapping d, 4H), 6.85 (d, J = 2.4 Hz, 2H), 6.45 (d, J = 4.4 Hz, 1H), 4.25 (d, J = 16.0 Hz, 2H), 4.19 (d, J = 15.6 Hz, 2H), 4.14 (d, J = 14.4 Hz, 2H), 4.05 (d, J = 16.0 Hz, 1H), 3.93 (d, J = 16.0 Hz, 1H), 3.91 (d, J = 14.4 Hz, 2H), 3.87 (d, J = 16.4 Hz, 2H), 3.81 (d, J = 16.0 Hz, 2H), 3.44 (s, 6H), 3.43 (s, 6H), 3.40 (br s, 12H), 2.71 (d, J = 4.0 Hz, 1H), 1.12 (s, 18H), 1.08 (s, 18H), 1.07 (s, 18H), 1.03 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 153.9, 146.3, 146.0, 145.97, 145.93, 135.7, 133.1, 133.0, 132.7, 127.5, 125.9, 123.2, 61.1, 60.5, 60.4, 34.3, 34.1, 31.6, 31.3; HRMS (ESI) m/z 1448.9482 (M + Na^+), calcd for $C_{96}H_{128}O_9Na$ 1448.9490.

5,11,17,23,29,35-Hexa-*tert*-butyl-2-chloro-37,38,39,40,41,42-hexamethoxycalix[6]arene (5). A mixture of **4a** (0.5 g, 0.47 mmol) in thionyl chloride (5 mL) was heated at reflux for 1 h. The solution was evaporated to dryness to afford quantitatively almost pure **5**. Recrystallization from ether gave 0.38 g (74%) pure **5**: mp 295 °C dec; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 2.4 Hz, 2H), 7.11 (d, J = 2.4 Hz, 2H), 6.98 (overlapping signals, 6H), 6.95 (br s, 3H), 4.40 (d, J = 15.6 Hz, 2H), 4.24 (d, J = 15.2 Hz, 2H), 4.16 (d, J = 14.8 Hz, 1H), 3.79 (d, J = 14.4 Hz, 1H), 3.68 (d, J = 15.2 Hz, 2H), 3.55 (d, J = 14.8 Hz, 2H), 3.09 (s, 6H), 3.05 (s, 6H), 2.98 (s, 6H), 1.16 (s, 18H), 1.12 (s, 18H), 1.10 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 152.7, 146.1, 145.8, 133.9, 133.7, 133.4, 133.3, 132.8, 128.0, 126.0, 125.9, 125.8, 125.7, 124.5, 65.1, 60.5, 60.0, 53.4, 34.3, 34.1, 31.4, 31.3, 30.3, 30.0, 15.3; HRMS (ESI) m/z 1055.7123 (M − Cl), calcd for $C_{72}H_{95}O_6$ (M − Cl) 1055.7129. Anal. Calcd for $C_{72}H_{95}ClO_6$: C, 79.19; H, 8.77. Found: C, 79.07; H, 8.71.

General Procedure for the Preparation of Monoalkoxy Calix[6]arene Derivatives. A solution of **5** (0.10 g, 0.09 mmol) in 4 mL of chloroform and 10 mL of the appropriate alcohol was heated to reflux overnight. The solvents were evaporated under vacuum to afford the corresponding derivatives in quantitative yield. A small amount was recrystallized from $CHCl_3$/MeOH for analytical purposes.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2-(2,2,2-trifluoroethoxy)calix[6]arene (6a): mp 210 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.20 (d, J = 2.4 Hz, 2H), 7.13 (d, J = 2.4 Hz, 2H), 7.00 (br m, 2H), 6.97 (br m, 6H), 6.22 (s, 1H), 4.42 (d, J = 15.2 Hz, 2H), 4.22 (d, J = 14.8 Hz, 2H), 4.15 (d, J = 15.6 Hz, 1H), 3.79 (m, 3H), 3.67 (d, J = 15.2 Hz, 2H), 3.53 (d, J = 15.6 Hz, 2H), 3.04 (s, 6H), 3.00 (s, 6H), 2.97 (s, 6H), 1.13 (s, 18H), 1.12 (s, 18H), 1.11 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 133.7, 133.6, 133.5, 133.4, 133.0, 132.0, 128.0, 126.0, 125.9, 125.8, 123.8, 73.5, 66.6, 66.3, 60.0, 59.97, 34.3, 34.1, 31.39, 31.38, 31.3, 30.4, 30.2, 30.0; HRMS (ESI) m/z 1177.7079 (M + Na^+), calcd for $C_{74}H_{97}F_3O_7Na$ 1177.7084. Anal. Calcd for $C_{74}H_{97}F_3O_7$: C, 76.91; H, 8.46. Found: C, 77.20; H, 8.45.

5,11,17,23,29,35-Hexa-*tert*-butyl-2-isopropoxy-37,38,39,40,41,42-hexamethoxycalix[6]arene (6b): mp 178 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.24 (br s, 2H), 7.07 (d, J = 2.4 Hz, 2H), 7.00 (d, J = 2.4 Hz, 2H), 6.97 (br s, 6H), 6.23 (s, 1H), 4.44 (d, J = 15.2 Hz, 2H), 4.28 (d, J = 14.8 Hz, 2H), 4.20 (d, J = 15.6 Hz, 1H), 3.75 (d, J = 15.6 Hz, 1H), 3.63 (d, J = 15.2 Hz, 2H), 3.58 (h, J = 6.0 Hz, 1H), 3.52 (d, J = 15.2 Hz, 2H), 3.02 (br s, 6H), 3.01 (br s, 6H), 2.96 (s, 6H), 1.23 (d, J = 6.0 Hz, 6H), 1.12 (s, 36H), 1.11 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.1, 153.9, 153.8, 145.7, 145.68, 134.1, 133.5, 133.45, 133.38, 133.34, 133.2, 127.3, 126.0, 125.9, 125.8, 124.4, 69.7, 69.1, 60.7, 60.01, 59.99, 41.3, 34.2, 34.1, 31.4, 31.38, 30.9, 30.5, 30.3, 30.2, 30.0, 29.0, 22.6, 22.4; HRMS (ESI) m/z 1137.7518 (M + Na^+), calcd for $C_{75}H_{102}O_7Na$ 1137.7523.

Reaction of 5 with Thymol and *p*-*tert*-Butylphenol. To a solution of **5** (0.10 g, 0.009 mmol) in 7.5 mL of TFE and 2.5 mL of $CHCl_3$ was added one drop of concentrated HBr and 0.03 mmol of the appropriate arene derivative. The mixture was heated to reflux overnight. The solvents were evaporated under vacuum. The residue was dissolved in chloroform (10 mL) and washed with brine and the organic phase dried on Na_2SO_4 and evaporated. Recrystallization from $CHCl_3$/MeOH afforded the pure compound.

7a: yield 35 mg (32%); mp 182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00 (br s, 10H), 6.85 (s, 2H), 6.78 (s, 1H), 6.50 (s, 1H), 6.29 (s, 1H), 4.58 (s, 1H), 4.44 (d, J = 15.2 Hz, 2H), 4.32 (d, J = 15.6 Hz, 2H), 4.25 (d, J = 14.8 Hz, 1H), 3.72 (d, J = 14.8 Hz, 1H), 3.64 (d, J = 15.2 Hz, 2H), 3.48 (d, J = 15.2 Hz, 2H), 3.20−2.87 (13H), 2.77 (br s, 6H), 1.23−1.08 (60 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9, 153.8, 153.6, 150.3, 145.7, 145.6, 145.2, 136.3, 135.5, 134.9, 133.5, 133.45, 133.38, 133.0, 130.9, 130.5, 128.8, 127.0, 126.1, 126.0, 125.9, 125.7, 123.4, 117.2, 60.6, 60.1, 60.0, 59.96, 59.90, 39.3, 34.3, 34.13, 34.12, 34.0, 31.4, 31.3, 30.5, 30.3, 30.2, 29.9, 29.7, 26.5, 22.8, 19.1; HRMS (ESI) m/z 1227.7987 (M + Na^+), calcd for $C_{82}H_{108}O_7Na$ 1227.7993.

7b: yield 40 mg (38%); mp 182 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.08 (dd, J = 8.0, 2.4 Hz, 1H), 7.06 (d, J = 2.4 Hz, 2H), 7.01 (br s, 4H), 6.99 (br s, 2H), 6.97 (br s, 2H), 6.94 (d, J = 2.8 Hz,

(20) Janssen, R. G.; Verboom, W.; Reinhoudt, D. N.; Casnati, A.; Freriks, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R.; Nieto, P. M. Carramolino, M.; Cuevas, F.; Prados, P.; de Mendoza, J. *Synthesis* **1993**, 380.

1H), 6.93 (d, J = 2.4 Hz, 2H), 6.71 (d, J = 8 Hz, 1H), 6.38 (s, 1H), 4.79 (s, 1H), 4.43 (d, J = 14.8 Hz, 2H), 4.27 (J = 15.2 Hz, 2H), 4.19 (d, J = 15.2 Hz, 1H), 3.76 (d, J = 15.6 Hz, 1H), 3.67 (d, J = 15.6 Hz, 2H), 3.50 (d, J = 15.2 Hz, 2H), 3.06 (br s, 6H), 2.99 (br s, 6H), 2.84 (s, 6H), 1.17 (s, 9H), 1.13 (s, 18H), 1.12 (s, 18H), 1.08 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 153.6, 151.1, 145.71, 145.69, 145.58, 142.6, 134.9, 133.6, 133.47, 133.42, 133.25. 129.9, 127.0, 126.3, 126.1, 125.9, 125.8, 125.6, 123.9, 115.3, 60.17, 60.02, 59.99, 37.13, 34.17, 34.12, 34.0, 31.47, 31.41, 31.30, 30.4, 30.3, 30.0; HRMS (ESI) m/z 1205.8169 (M + H^+), calcd for $C_{82}H_{109}O_7$ (M + H^+) 1205.8173.

Reaction of 5 with 4-Methylanisole. To a solution of **5** (0.1 g, 0.009 mmol) in TFE (8 mL) and $CHCl_3$ (1.5 mL) was added 1 drop of concd HBr and 4-methylanisole (0.1 mL). The mixture was heated to reflux overnight. After evaporation of the solvents, the residue was dissolved in $CHCl_3$ (15 mL) and washed with brine. The organic phase was dried on Na_2SO_4, and the solvent was evaporated. The crude product was recrystallized from MeOH to afford pure **7c**: yield 35 mg (33%); mp 202 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.13−6.92 (overlapping peaks, 11H), 6.84 (s, 2H), 6.80−6.72 (overlapping peaks, 2H), 6.56 (s, 1H), 4.45 (d, J = 15.0 Hz, 2H), 4.31 (d, J = 15.0 Hz, 2H), 4.23 (d, J = 15.0 Hz, 1H), 3.76 (d, J = 14.5 Hz, 1H), 3.68 (d, J = 15.0 Hz, 2H), 3.65 (s, 3H), 3.51 (d, J = 15.0 Hz, 2H), 3.06 (s, 6H), 3.03 (s, 6H), 2.93 (s, 6H), 2.22 (s, 3H), 1.16 (s, 36H), 1.08 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.2, 153.8, 145.7, 145.6, 145.0, 136.6, 133.5, 133.4, 133.3, 133.1, 132.9, 130.7, 128.9, 127.4, 125.8, 125.7, 111.2, 60.04, 59.96, 56.07, 37.1, 34.1, 31.4, 31.3, 30.4, 30.2, 30.0, 20.8; HRMS (ESI) m/z 1199.7674 (M + Na^+), calcd for $C_{80}H_{104}O_7Na$ 1199.7680.

5,11,17,23,29,35-Hexa-*tert*-butyl-2-(2,4-dimethylphenyl)-37,38,39,40,41,42-hexamethoxycalix[6]arene (7d). A mixture of **5** (0.05 g, 0.045 mmol), dry m-xylene (2 mL), and $BF_3\cdot OEt_2$ (20 μL) was heated for 2 h to 80 °C. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (15 mL). The solution was dried (Na_2SO_4) and evaporated to afford **7d**. The crude product was recrystallized form methanol: yield 20 mg (38%); mp 160 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.07−6.98 (overlapping peaks, 10H), 6.92 (s, 1H), 6.86 (d, J = 8.0 Hz, 1H), 6.84 (br s, 2H), 6.78 (d, J = 8.0 Hz, 1H), 6.32 (s, 1H), 4.42 (d, J = 15.0 Hz, 2H), 4.27 (d, J = 15.0 Hz, 2H), 4.19 (d, J = 15.0 Hz, 1H), 3.78 (d, J = 15.0 Hz, 1H), 3.69 (d, J = 15.0 Hz, 2H), 3.51 (d, J = 15.0 Hz, 2H), 3.31 (s, 6H), 3.04 (s, 6H), 2.81 (s, 6H), 2.27 (s, 3H), 2.13 (s, 3H), 1.16 (s, 18H), 1.14 (s, 18H), 1.09 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 153.7, 145.71, 145.68, 145.3, 140.1, 136.4, 136.3, 135.2, 133.6, 133.5, 133.4, 133.2, 133.0, 131.1, 128.7, 125.92, 125.88, 60.06, 60.03, 59.9, 39.8, 34.15, 34.12, 31.42, 31.41, 31.36, 30.3, 30.2, 29.8, 29.5, 20.9, 19.6; HRMS (ESI) m/z 1183.7725 (M + Na^+), calcd for $C_{80}H_{104}O_6Na$ 1183.7731.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2-mesitylcalix[6]arene (7e). To a solution of **5** (0.1 g, 0.009 mmol) in 8 mL of $CHCl_3$ and 2 mL of HFIP was added 0.2 mL of mesitylene and the mixture heated to reflux for 3 h. After the solvents were evaporated, the residue was dissolved in chloroform (15 mL) and the solution was washed with brine. The organic phase was dried (Na_2SO_4) and evaporated. Recrystallization from $CHCl_3$/MeOH afforded the pure product: yield 45 mg (41%); mp 218 °C; ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 400 K) δ 7.18−7.04 (overlapping peaks, 10H), 6.94 (s, 2H), 6.80 (s, 2H), 6.40 (s, 1H), 4.35 (d, J = 15.0 Hz, 2H), 4.26 (d, J = 14.5 Hz, 2H), 4.19 (d, J = 15.0 Hz, 1H), 3.86 (d, J = 15.0 Hz, 1H), 3.81 (d, J = 15.0 Hz, 2H), 3.63 (d, J = 15.0 Hz, 2H), 3.23 (s, 6H), 3.20 (s, 6H), 2.78 (s, 6H), 2.23 (s, 3H), 2.15 (s, 6H), 1.25 (s, 18H), 1.24 (s, 18H), 1.14 (s, 18H); ^{13}C NMR (125 MHz, $C_2D_2Cl_4$, 400 K) δ 154.2, 153.8, 145.54, 145.51, 144.8, 137.9, 137.2, 134.8, 133.4, 133.2, 133.14, 133.13, 132.9, 129.9, 126.5, 125.7, 60.4, 59.9, 59.8, 59.6, 41.1, 34.0, 33.85, 33.84, 33.80, 31.24, 31.12, 30.68, 30.41, 29.8, 21.9, 20.4; HRMS (ESI) m/z 1197.7882 (M + Na^+), calcd for $C_{81}H_{106}O_6Na$ 1197.7887.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38,39,40,41,42-hexamethoxy-2-(2,4-pentanedion-3-yl)calix[6]arene (8). To a solution of **4a** (0.1 g, 0.093 mmol) in dry CH_2Cl_2 (10 mL) were added 1,3-pentanedione (0.5 mL) and $BF_3\cdot OEt_2$ (50 μL). The mixture was stirred overnight at room temperature, the solvents were evaporated and the residue dissolved in CH_2Cl_2 (15 mL) and washed with a saturated solution of $NaHCO_3$ (5 mL) and brine. The organic layer was dried (Na_2SO_4) and evaporated. The crude product was recrystallized from methanol to afford pure **8**: yield 45 mg (43%); mp 262 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 318 K) δ 7.13 (d, J = 2.0 Hz, 2H), 7.12 (br s, 2H), 7.04 (d, J = 2.0 Hz, 2H), 6.97 (br s, 2H), 6.93 (d, J = 2.0 Hz, 2H), 6.92 (br s, 2H), 5.29 (d, J = 11.5 Hz, 1H), 4.77 (d, J = 11.7 Hz, 1H), 4.12 (d, J = 14.5 Hz, 2H), 3.99 (overlapping d, J = 14.0 Hz, 3H), 3.88 (d, J = 14.5 Hz, 1H), 3.81 (d, J = 14.5 Hz, 2H), 3.69 (d, J = 14.5 Hz, 2H), 3.16 (s, 6H), 3.13 (s, 6H), 2.74 (s, 6H), 1.98 (s, 6H), 1.17 (s, 18H), 1.15 (s, 36H); ^{13}C NMR (125 MHz, $CDCl_3$, 318 K) δ 204.2, 154.1, 154.07, 154.00, 153.9, 145.8, 145.7, 145.6, 133.8, 133.7, 133.5, 133.4, 132.6, 126.7, 126.4, 126.2, 126.1, 125.5, 124.7, 60.1, 59.9, 59.8, 34.2, 34.14, 34.08, 31.4, 31.3, 30.4, 30.2, 29.9; HRMS (ESI) m/z 1177.7467 (M + Na^+), calcd for $C_{77}H_{108}O_8Na$ 1177.7472. Anal. Calcd for $C_{77}H_{108}O_8$: C, 80.03; H, 8.90. Found: C, 79.87; H, 8.79.

5,11,17,23,29,35-Hexa-*tert*-butyl-2-fluoro-37,38,39,40,41,42-hexamethoxycalix[6]arene (9). To a cold solution (−18 °C) of **4a** (0.1 g, 0.093 mmol) in dry CH_2Cl_2 (10 mL) was added, during 10 min under an inert atmosphere, 0.1 mL (0.73 mmol) of diethylaminosulfur trifluoride (DAST). The temperature of the solution was raised slowly to room temperature, and the mixture was stirred overnight. The excess DAST was quenched with 5 mL of water, and the organic phase was separated, washed several times with brine, dried (Na_2SO_4), and evaporated. The residue was recrystallized from $CHCl_3$/MeOH: yield 20 mg (19%); mp 260 °C dec; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, J = 2 Hz, 2H), 7.16 (d, J = 2 Hz, 2H), 7.10 (d, J = 47 Hz, 1H), 6.99 (overlapping d, J = 2 Hz, 6H), 6.97 (d, J = 2 Hz, 2H), 4.34 (d, J = 15.1 Hz, 2H), 4.18 (d, J = 14.7 Hz, 2H), 4.08 (d, J = 14.7 Hz, 1H), 3.81 (d, J = 14.7 Hz, 1H), 3.72 (d, J = 14.7 Hz, 2H), 3.57 (d, J = 15.3 Hz, 2H), 3.08 (s, 6H), 3.01 (s, 6H), 2.97 (s, 6H), 1.16 (s, 18H), 1.13 (s, 18H), 1.11 (s, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.86, 153.80, 153.55, 153.52, 146.1, 145.76, 145.68, 133.6, 133.5, 133.4, 133.0, 132.3, 132.1, 128.4, 126.0, 125.9, 125.7, 123.04, 122.99, 86.05, 84.7, 60.9, 60.0, 59.9, 34.3, 34.1, 31.4, 31.37, 31.34, 30.4, 30.2, 30.1; HRMS (ESI) m/z 1097.7007 (M + Na^+), calcd for $C_{72}H_{95}FO_6Na$ 1097.7010.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C spectra of compounds **4**−**8**. This material is available free of charge via the Internet at http://pubs.acs.org.