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Nucleophilic Functionalization of the Calix[6]arene Para- and Meta-Position via *p*-Bromodienone Route

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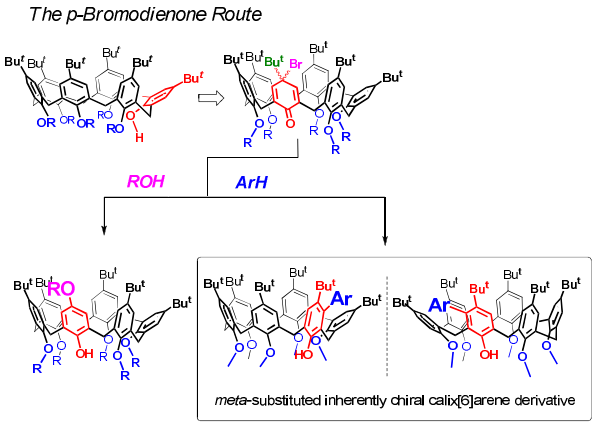

ABSTRACT. It is here demonstrated that the *p*-bromodienone route, previously reported for calix[4]arenes, is also effective for the functionalization of the calix[6]arene macrocycle. Thus,

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alcoholic *O*-nucleophiles can be introduced at the calix[6]arene *exo* rim. In addition, the reaction of a calix[6]arene *p*-bromodienone derivative with an actived aromatic substrate, such as resorcinol, led to the first example of a *meta*-functionalized, inherently chiral calix[6]arene derivative.

Today, many strategies are known for introducing functionalities at the calixarene *exo* rim,[1] which include several electrophilic aromatic substitutions[2] and three classical paths, namely the "Claisen rearrangement",[3] "*p*-quinone-methide",[4] and "*p*-chloromethylation"[5] routes. However, in the last years, significant efforts from calixarene chemists have been directed to the search for alternative ways[6] to functionalize the calixarene skeleton with the aim to obtain novel calixarene-based supramolecular hosts.

Thus, recently, our group has reported the "*p*-bromodienone route"[7] as a new synthetic strategy to introduce nucleophiles at the calix[4]arene upper rim, starting from calixarene *p*-bromodienone derivatives[8] (**2** in Scheme 1). These latter, undergo a silver-mediated nucleophilic substitution of the bromine atom with several alcoholic or carboxylic *O*-nucleophiles,[7a] then a spontaneous re-aromatization leads to *p*-alkoxy- or *p*-acyloxy-calix[4]arene derivatives. Subsequently, we demonstrated[7b] that the "*p*-bromodienone route" can be also extended to appropriate aromatic substrates, thus allowing the *para* or *meta* functionalization with aryl groups. The meta-substitution is likely obtained by rearrangement of the *p*-aryldienone intermediate. Concomitantly, a related procedure was reported by Varma[9] and co-workers in which calixarene spirodienone derivatives are used to introduce alkoxy groups into the calix[4]arene *exo* rim.[10]

Regarding the larger calix[6]arene hosts, recent reports[11] have evidenced interesting and peculiar supramolecular properties ranging from molecular recognition[11c–e] to the synthesis of interpentrated architectures.[11a,b,f] Consequently, an increased interest has been aroused for developing novel and alternative functionalization procedures of the calix[6]arene macrocycle. Thus, Reinaud[6e] and coworkers reported the *ipso*-chlorosulfonylation of calix[6]arene derivatives in which -SO_2Cl groups were

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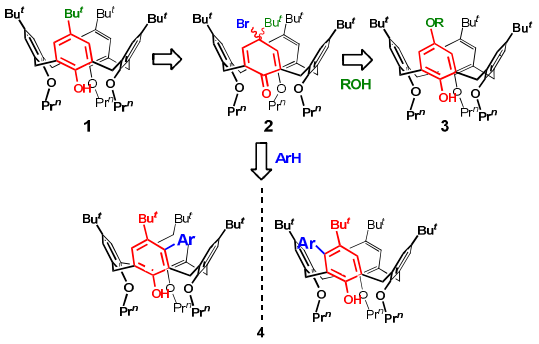
introduced selectively at their exo rim, while Jabin and coworkers[6a,b] showed interesting and novel routes for the functionalization of the calix[6]arene *endo* rim.

In order to broaden the synthetic versatility and to define new procedures for the functionalization of the calix[6]arene macrocycle, we decided to verify the feasibility of the *p*-bromodienone route on partially *O*-alkylated calix[6]arene derivatives and we report here the results of our studies.



Scheme 1. The *p*-bromodienone route.[7a,b]

We first studied the feasibility of the *p*-bromodienone route on pentamethoxy-*p*-*tert*-buylcalix[6]arene-mono-ol derivatives **8**[12] bearing a single oxidable phenol ring. The synthesis of derivative **8** is presented in Scheme 2 and is based on a protection-deprotection procedure already reported by De Mendoza and coworkers.[12] Thus, *p*-*tert*-butylcalix[6]arene **5** was monoalkylated with benzylbromide, in presence of K_2CO_3 as the base, to give **6** in 45% yield, which was exhaustively methylated with MeI in the presence of Cs_2CO_3 to give **7** in 80% yield. Finally, **7** was subjected to hydrogenolysis with Pd/C to give pentamethoxycalix[6]arene-mono-ol **8** in quantitative yield.

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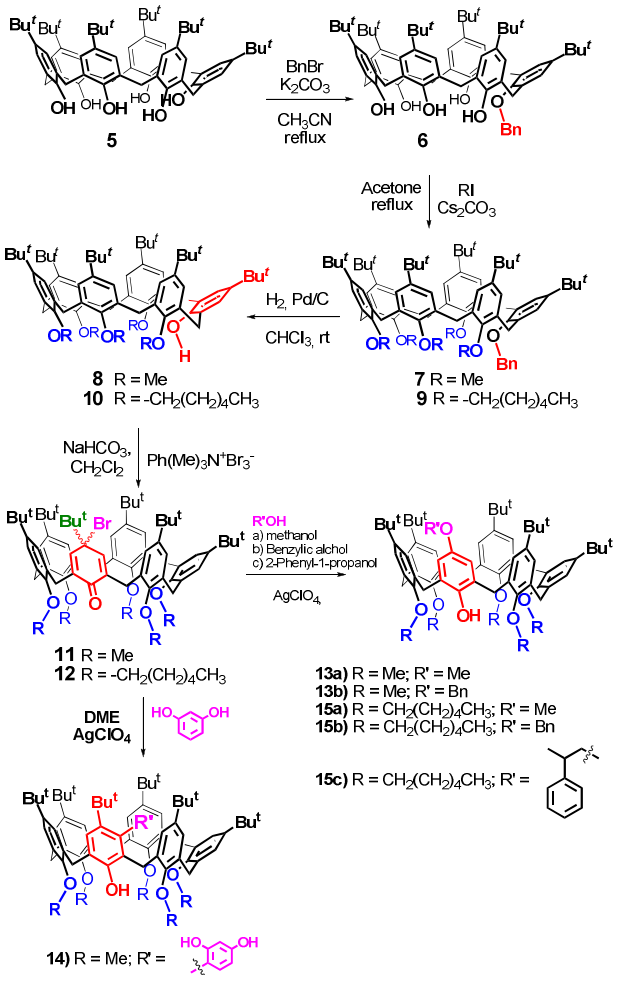

Scheme 2.

The ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 298 K) of **8**[12] shows three sharp singlets due to $ArCH_2Ar$ groups indicating a fast conformational interconversion, which is due to the small dimension of the methoxy groups at the lower rim of the macrocycle.

In the next step, we decided to perform the oxidation of the phenol ring of mono-ol **8** to the corresponding *p*-bromodienone system, under conditions usually adopted for the synthesis of the corresponding calix[4]arene derivatives.[7a] Thus, the treatment of **8** (in CH_2Cl_2 at 25°C) with trimethylphenylammonium tribromide and a saturated solution of $NaHCO_3$ resulted in the quantitative formation of the first example of calix[6]arene *p*-bromodienone derivative **11**. The structure of **11** was

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assigned by means of spectral analysis. In particular, its ESI(+) mass spectrum revealed the presence of a ion peak at 1143 *m*/*z* $(MNa)^+$ with a typical bromine isotopic pattern, in accord with the molecular formula of **11**. The ^{1}H NMR spectrum of *p*-bromodiene derivative **11** in $CDCl_3$ at 298 K (600 MHz) (Figure S5) revealed the presence of 3 singlets in a 2:2:1 ratio at 1.23, 1.16, and 1.11 ppm, respectively, due to *t*-butyl groups on anisole rings, while a broad singlet was present at 0.86 ppm due to *t*-butyl group on the oxidized *p*-bromodienone ring. In addition, three broad singlets were present at 2.90, 3.11, and 3.25 ppm due to OMe groups, while the $ArCH_2Ar$ region showed the presence of two AX systems at 4.20/3.74 ppm (J = 14.6 Hz) and 4.09/3.71 ppm (J = 14.8 Hz) and one AB system at 3.51/3.60 ppm (J = 15.0 Hz) due to $ArCH_2Ar$ groups. Regarding the 4-*tert*-butyl-4-bromo-2,5-cyclohexadienone moiety of **11**, a broad singlet at 6.60 ppm due to the dienone H-atoms was observed in the ^{1}H NMR spectrum, while in the ^{13}C NMR spectrum the C=O and C-Br resonances were present at 183.7 and 71.3 ppm, respectively.

As previously reported, the synthesis of calix[4]arene *p*-bromodienone **2** (Scheme 1), gives rise to two stereoisomers, namely the *exo* and *endo* ones (referring to the relative orientation of the Br-atom with respect to the calix[4]arene cavity), which were purified by selective precipitation from diethyl ether. Naturally, an analogous stereoisomerism should be expected for calix[6]arene *p*-bromodienone **11**, but its rapid *cone-to-cone*[1] inversion (even with respect to the NMR time scale) led to the mutual interconversion between *exo*- and *endo*-**11** stereoisomers (Figure 1). Interestingly, **11** displays temperature-dependent ^{1}H NMR spectra due to the easy *through-the-annulus* rotation of the anisole and *p*-bromodienone rings. In fact, the lowering of the temperature caused a broadening of the $ArCH_2Ar$ signals followed by decoalescence and resharpening to give at 233 K a very complicated ^{1}H NMR spectrum corresponding to the presence of the two *exo*-/*endo*-**11** stereoisomers in different conformations.

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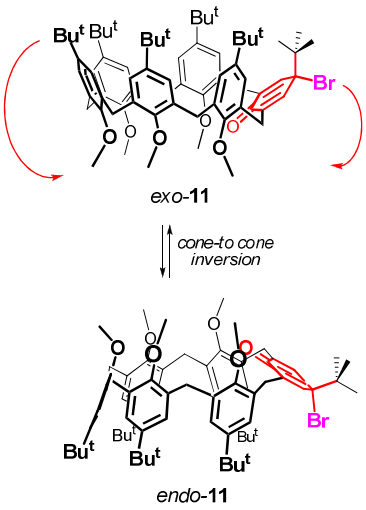

Figure 1. The *cone-to-cone* inversion interconverts the two *exo*- and *endo*-**11** stereoisomers.

At this point, we tested the feasibility of the nucleophilic substitution of bromine atom on the *p*-bromodienone derivative **11** using *O*-nucleophiles such as methanol and benzylic alcohol. Thus, a sample of **11** was treated with a cold methanolic solution of $AgClO_4$ (Scheme 2) to give *p*-methoxycalix[6]arene **13a** in 20% yield, after usual work-up. The structure of **13a** was confirmed by means of spectral analysis. In particular, ESI(+) mass spectrum confirmed the molecular formula while the C_s molecular symmetry was assigned by pertinent signals in the ^1H and ^{13}C NMR spectra. In particular, the presence in the ^1H NMR spectrum of **13a** (400 MHz, $CDCl_3$, 298 K) of only three 1:2:2 *tert*-butyl signals at 0.98, 1.13, and 1.17 ppm were a clear evidence of the displacement of a *t*-Bu group by a methoxyl one, which was corroborated by the presence of four singlets due to OMe groups at 3.02, 3.15, 3.49, and 3.57 ppm in a 2:2:1:1 ratio. Finally, due to the rapid *through-the-annulus* passage of both *exo* and *endo* rim of **13a,** the $ArCH_2Ar$ ^1H resonances were present as two singlets at 3.81 (4H) and 3.93 (8H) ppm.

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The influence of the alcoholic portion on the reaction outcome was tested by using the bulkier benzylic alcohol. Thus, the treatment of *p*-bromodienone derivative **11** with BnOH in the presence of $AgClO_4$ in DME as solvent (Scheme 2) afforded the expected *p*-benzyloxycalix[6]arene derivative **13b** in 30% yield, after usual work up. The ^{1}H NMR spectrum of **13b** (400 MHz, $CDCl_3$, 298 K) showed three 1:2:2 *tert*-butyl singlets at 0.93, 1.08, and 1.10 ppm, respectively, and one singlet at 4.73 ppm due to OCH_2Ph group, which was indicative of the displacement of the *t*-Bu group by the benzyloxy one. The ^{13}C NMR spectrum (100 MHz, $CDCl_3$, 298 K) of **13b** confirmed its C_s molecular symmetry by the presence of three signals due to $ArCH_2Ar$ groups at 29.7, 30.3, and 31.2 ppm, three signals due to -$C(CH_3)_3$ C-atoms at 31.3, 31.4, and 31.6 ppm, and one resonance at 70.2 ppm due to OCH_2Ph group.

In a previous study,[7b,e] we have shown that the *p*-bromodienone route with actived aromatic substrates (e.g.: resorcinol in Scheme 1) is a valid synthetic method to obtain *meta*-substitued inherently chiral calix[4]arene derivatives[13] (e.g.: **4** in Scheme 1). Such chiral calixarene derivatives are interesting hosts which may find applications in enantiodiscrimination processess[14] and asymmetrical catalysis.[15] A survey of the calixarene literature strangely reveals that no synthetic procedures have been so far reported for the *meta*-functionalization of calix[6]arene macrocycle. Prompted by this observation, we decided to study the reaction of calix[6]arene *p*-bromodienone derivative **11** with resorcinol under condition previously reported[7b] for the synthesis of *meta*-substituted calix[4]arene **4** (Scheme 1). Thus, the treatment of **11** with resorcinol and a cold solution of $AgClO_4$ afforded *meta*-substituted calix[6]arene **14** in 30% yield (Scheme 2). 1D and 2D NMR spectra were in agreement with the asymmetrical structure of **14**, in which the resorcinol and *t*-Bu groups were, respectively, *meta*- and *para*-linked to the calixarene phenol ring. In fact, five of the expected six *t*-Bu singlets (two accidentally isochronous) were present in the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz, 298 K) of **14** at 1.12, 1.15 (18H), 1.19, 1.21, and 1.33 ppm, while five singlets due to $ArCH_2Ar$ groups were present at 3.83, 3.97, 4.07, 4.10 (4H), and 4.12 ppm, which correlates in the HSQC spectrum with carbon resonances at 31.8 , 32.6, 30.2 (2C), 30.3, and 29.9 ppm. In addition, the ^{13}C NMR spectrum evidenced five signals due to -$C(CH_3)_3$ atoms at 31.50, 31.51 (2C), 31.54, 31.56, and 31.77 ppm, and four signals due to OMe groups

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at 60.93, 60.98 (2C), 62.27, and 62.34 ppm, which correlates in the HSQC spectrum with singlets at 3.60 (9H), 3.87 and 3.88 ppm. The asymmetric structure of **14** coupled to its three-dimensional nature makes it inherently chiral and, consequently, it should be formed as a racemic mixture. In contrast to the conformationally blocked calix[4]arene derivative **4** (Scheme 1), a rapid *cone-to-cone* inversion (Figure 2) of the calix[6]arene skeleton of **14** leads to the interconversion between the two enantiomers.

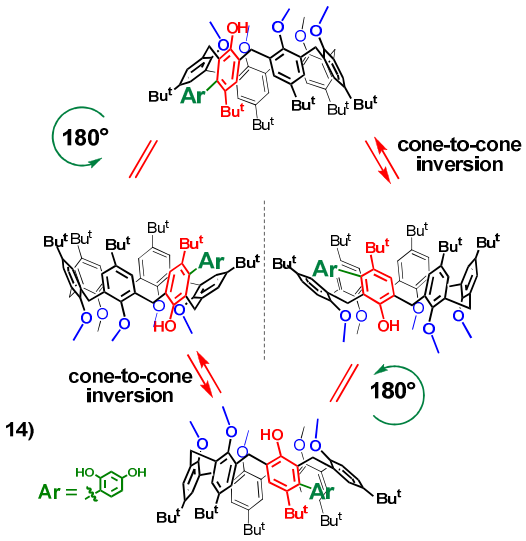

Figure 2. The *cone-to-cone* inversion interconverts the two enantiomers of **14.**

In order to extend the generality of the *p*-bromodienone route on calix[6]arene macrocycle, we synthesized calix[6]arene *p*-bromodienone **12** bearing hexyloxy chains at the *endo* rim. The synthesis of **12** was very similar to that of its methoxy analogue **11**, as outlined in Scheme 2. The mono-benzylated calix[6]arene **6** was exhaustively alkylated by treatment with Cs_2CO_3 and 1-iodohexane in acetone as solvent, to give derivative **9** in 80% yield. Successively, the benzyl group at the *endo* rim of **9** was removed by hydrogenolysis (H_2 and Pd/C) to give pentahexyloxy-mono-ol **10** in 91% yield. In contrast to pentamethoxy-mono-ol **8** bearing smaller groups at the *endo* rim, the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) of **10** displays broad signals for the methylene protons, which sharpened at 383 K into 3 singlets at 3.71, 3.73, and 3.75 ppm.

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Treatment of pentahexyloxycalix[6]arene-mono-ol **10** under conditions analogous to the synthesis of **11**, led to the formation of derivative **12** in 96% yield. Its ESI(+) mass spectrum confirmed the molecular formula of **12** by the presence of a ion peak at 1494 (MNa^+) with a typical bromine isotopic pattern, while the presence of bromine was further corroborated by the ready precipitation of AgBr upon treatment with alcoholic $AgNO_3$. The ^1H NMR spectrum of **12** in TCDE at 298 K showed 4 broad singlets due to to *t*-butyl groups at 0.71 (9H), 0.99 (18H), 1.13 (9H), and 1.31 (18H) ppm, while broad signals were presents in the methylene region indicating a slow conformational interconversion on the NMR time scale. Analogously to *p*-bromodienone **11**, lowering the temperature caused a decoalescence and resharpening to give at 243 K a very complicated ^1H NMR spectrum corresponding to the presence of the two *exo*/*end*o-**12** stereoisomers in different conformations. Upon increasing the temperature, the TCDE solution of **12** darkens progressively and the resulting ^1H NMR spectra showed a number of signals not in agreement with its molecular symmetry. The successive temperature lowering back at 298 K did not return to the original ^1H NMR spectrum, indicating that calix[6]arene *p*-bromodienone **12** irreversibly decomposes at high temperatures, in accordance with previously observed data.[7]

Analogously to *p*-bromodienone derivative **11**, the treatment of **12** with a methanolic solution of $AgClO_4$ (Scheme 2) afforded *p*-methoxycalix[6]arene **15a** in 15% yield, while its treatment benzylic alcohol (Scheme 2) afforded derivative **15b** in 17% yield.

As previously demonstrated,[7a,c] the *p*-bromodienone route can also be exploited for introducing chirality into the calixarene framework by appending appropriate chiral substituents. With this aim in mind, calix[6]arene *p*-bromodienone **12** was treated with a racemic mixture of (±)-2-phenyl-1-propanol in the presence of $AgClO_4$ (Scheme 2) to give the corresponding derivative **15c** in 15% yield.

In conclusion, we have here demonstrated that the *p*-bromodienone route is also effective for the functionalization of the calix[6]arene macrocycle. Therefore, through this route it is possible to introduce alcoholic *O*-nucleophiles at the calix[6]arene *exo* rim. In addition, the *p*-bromodienone route

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with activated aromatic substrates allowed the first example of *meta*-functionalization of a calix[6]arene macrocycle giving rise to an unprecedented meta-substituted inherently chiral calix[6]arene derivative.

Experimental Section

General: ESI(+)−MS measurements were performed on a quadrupole mass spectrometer equipped with electrospray ion source, using a mixture of H_2O/CH_3CN (1:1) and 5% HCOOH as solvent. Flash chromatography was performed on silica gel (40-63 μm). All chemicals were reagent grade and were used without further purification. When necessary compounds were dried in vacuo over $CaCl_2$. Reaction temperatures were measured externally. Reactions were monitored by TLC on silica gel plates (0.25 mm) and visualized by UV light or by spraying with H_2SO_4-$Ce(SO_4)_2$. ^1H NMR spectra were recorded at 300, 400, or 600 MHz, and ^{13}C NMR spectra were recorded at 75, 100, or 150 MHz. Chemical shifts are reported due to to the residual solvent peak. One-dimensional ^1H and ^{13}C spectra, and two-dimensional COSY-45, and heteronuclear single quantum correlation (HSQC) were used for NMR peak assignment. COSY-45 spectra were taken using a relaxation delay of 2 seconds with 30 scans and 170 increments of 2048 points each. HSQC spectra were performed with gradient selection, sensitivity enhancement, and phase-sensitive mode using Echo/Antiecho-TPPI procedure. A typical experiment comprised 20 scans with 113 increments of 2048 points each. Derivatives **8** was synthesized according to a literature procedure.[12]

Synthesis of Derivative 9. Cs_2CO_3 (9.8 g, 30 mmol) was added, under stirring, to a solution of compound **6**[12] (1.18 g, 1.11 mmol) in dry acetone (60 mL) and the mixture was heated at reflux. After 30 min, 1-iodohexane (14.8 g, 10.3 mL, 69.8 mmol) was added and the resulting mixture was kept at reflux under stirring for 48 h. The reaction was allowed to cool at room temperature and the solvent removed under reduced pressure. The crude product was solubilized in CH_2Cl_2, washed with aqueous 1N HCl, brine, and then dried over Na_2SO_4. The solvent was evaporated to dryness and the product was

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crystallized from MeOH/CH_2Cl_2 to give **9** as a pale yellow solid (1.32 g, 80% yield). Mp: 245-248 °C. ESI(+) MS: m/z = 1485 (MH^+), 1507 (MNa^+), 1522 (MK^+). ^{1}H NMR (300 MHz, TCDE, 383 K): δ 0.77 [broad, $O(CH_2)_5CH_3$, 15H], 0.94 [s, -$C(CH_3)$, 9H], 0.95 [s, -$C(CH_3)$, 18H], 1.04 [s, -$C(CH_3)$, 27H], 1.10−1.25 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 30H), 1.35−1.60 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 10H), 3.28 (broad, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 4H), 3.39 (broad, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 4H), 3.48 (t, $OCH_2CH_2CH_2CH_2CH_2CH_3$, J = 6.5 Hz, 2H), 3.79 (broad s, $ArCH_2Ar$, 12H), 4.67 (s, OCH_2Ph, 2H), 6.77 (s, ArH, 2H), 6.83 (s, ArH, 4H), 6.90 (s, ArH, 4H), 6.94 (s, ArH, 2H), 7.16−7.21 (overlapped, $OCH_2C_6H_5$, 3H), 7.30- 7.35 (m, $OCH_2C_6H_5$, 2H). ^{13}C NMR (75 MHz, TCDE, 383 K): δ 12.2, 20.8, 24.2, 28.1, 28.3, 28.4, 28.9, 29.7, 30.0, 32.1, 71.7, 73.0, 123.7, 123.9, 124.3, 124.6, 124.8, 125.6, 126.4, 131.1, 131.2, 136.5, 143.1, 143.6, 150.9, 151.6, 152.0. Anal. Calcd. for $C_{103}H_{150}O_6$: C, 83.35: H, 10.19. Found: C, 83.25; H, 10.27.

Synthesis of Derivative 10. A solution of **9** (1.32 g, 0.89 mmol) in $CHCl_3$ (80 mL) was added of Pd/C and stirred for 12 h under H_2 at 25 °C. The catalyst was filtered on a celite pad and the filtrate was evaporated under vacuum. Precipitation of the residue from methanol gave pure **10** as a yellow solid (1.13 g, 91% yield). Mp: 200-203 °C. ESI(+) MS: m/z = 1417 (MNa^+), 1434 (MK^+). ^{1}H NMR (300 MHz, TCDE, 383 K): δ 0.70 [s, -$C(CH_3)$, 9H], 0.77 [broad, $O(CH_2)_5CH_3$, 15H], 0.94 [s, -$C(CH_3)$, 9H], 1.12 [s, -$C(CH_3)$, 18H], 1.15 [s, -$C(CH_3)$, 18H], 1.06-1.40 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 30H), 1.59−1.70 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 10H), 3.09 (broad t, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 4H), 3.60 (t, $OCH_2CH_2CH_2CH_2CH_2CH_3$, J = 7.2 Hz, 2H), 3.71−3.76 (overlapped, $ArCH_2Ar$ + $OCH_2CH_2CH_2CH_2CH_2CH_3$, 16H), 6.41, (br s, ArH, 2H), 6.54 (br s, ArH, 2H), 6.57 (br s, OH, 1H), 6.77 (s, ArH, 2H), 6.91 (s, ArH, 2H), 6.96 (br s, ArH, 2H), 7.00 (br s, ArH, 2H). ^{13}C NMR (75 MHz, TCDE, 383 K): δ 11.9, 12.0, 20.6, 20.9, 24.0, 27.9, 28.4, 28.6, 29.5, 29.6, 29.8, 30.0, 32.0, 32.1, 71.7, 122.7, 123.0, 124.4, 124.5, 125.3, 130.2, 131.2, 131.8, 140.1, 142.6, 143.0, 143.1, 144.0, 149.3, 149.9, 151.7, 152.4. Anal. Calcd. for $C_{96}H_{144}O_6$: C, 82.70; H, 10.41. Found: C, 82.61; H, 10.40.

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General Procedure for the Synthesis of *p*-Bromodienone Derivatives 11 and 12. A solution of phenyltrimethylammonium tribromide (0.13 g, 0.36 mmol) in CH_2Cl_2 (5 mL) was added dropwise over 15 min to a stirred solution at 0 °C of the appropriate pentaalkoxy-calix[6]arene-mono-ol **8** or **10** (0.24 mmol) in CH_2Cl_2 (24 mL). Then, 25 mL of a saturated aqueous solution of $NaHCO_3$ was added and the resulting mixture was stirred for 15 min at room temperature. The organic phase was separated and washed with an aqueos solution of Na_2SO_3 (10% w.t.) and H_2O. The organic phase was dried over Na_2SO_4, filtered and the solvent removed under reduced pressure, to give the corresponding calix[6]arene *p*-bromodienone derivative **11** or **12** in quantitative yield.

Derivative **11** (0.26 g, 99%). Mp: > 175 °C dec. ESI(+) MS: *m*/*z* = 1143 (MNa^+), 1159 (MK^+). ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ 0.86 [s, -C(CH_3)$_3$, 9H], 1.11 [s, C(CH_3)$_3$, 9H], 1.16 [s, -C(CH_3)$_3$, 18H], 1.23 [s, C(CH_3)$_3$, 18H], 2.90 (br s, OCH_3, 6H), 3.11 (br s, OCH_3, 6H), 3.25 (br s, OCH_3, 3H), 3.51 and 3.60 (AB, $ArCH_2Ar$, *J* = 15.0 Hz, 4H), 3.71 and 4.09 (AB, $ArCH_2Ar$, *J* = 14.8 Hz, 4H), 3.74 and 4.20 (AX, $ArCH_2Ar$, *J* = 14.6 Hz, 4H), 6.60 (s, C=CH, 2H), 6.91 (br s, ArH, 2H), 7.03 (br s, ArH, 2H), 7.07 (br s, ArH, 4H), 7.11 (br s, ArH, 2H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 26.3, 30.0, 30.2, 30.8, 31.59, 31.6, 31,7, 34.3, 34.4, 39.5, 60.1, 60.4, 60.6, 71.3, 125.5, 125.9, 126.4, 126.8, 127.0, 130.0, 131.3, 133.4, 133.7, 133.8, 134.0, 137.0, 143.5, 145.8, 145.9, 146.2, 146.2, 154.0, 154.3, 183.7. Anal. Calcd. for $C_{71}H_{93}BrO_6$: C, 75.98; H, 8.35; Br, 7.12. Found: C, 76.07; H, 8.27; Br, 7.21.

Derivative **12** (0.34 g, 96%). Mp: > 168 °C dec. ESI(+) MS: *m*/*z* = 1494 (MNa^+). ^{1}H NMR (300 MHz, TCDE, 298 K): δ 0.71 [broad, -C(CH_3)$_3$, 9H], 0.89 [br s, O(CH_2)$_5$CH_3, 15H], 0.99 [s, -C(CH_3)$_3$, 18H], 1.13 [s, -C(CH_3)$_3$, 9H], 1.16−1.19 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 30H), 1.31 [s, -C($CH_3$)$_3$, 18H], 1.52−1.98 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 10H), 2.92−2.95 (broad, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 2H), 2.98−3.46 (overlapped, $ArCH_2Ar$ + $OCH_2CH_2CH_2CH_2CH_2CH_3$, 14H), 4.28−4.34 (overlapped, $ArCH_2Ar$, 6H), 6.61−7.07 (overlapped, ArH+ C=CH, 12H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 14.4, 14.5, 22.8, 22.9, 26.0, 26.2, 29.7, 29.9, 30.5, 30.7, 31.7, 31.8, 32.1, 32.3, 34.3, 38.9, 83.9, 74.2, 126.7, 126.2, 126.5, 127.0, 127.6, 131.1, 132.8, 133.2, 134.1, 136.6, 144.3,

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145.1, 145.5, 153.5, 154.1, 183.7. Anal. Calcd. for $C_{96}H_{143}BrO_6$: C, 78.27; H, 9.78; Br, 5.42. Found: C, 78.36; H, 9.69; Br, 5.31.

General Procedure for the Synthesis of Derivatives 13a-b. A solution of $AgClO_4$ (0.048 g, 0.23 mmol) in the appropriate alcohol (1.6 mL of methanol or benzylic alchol) was cooled at 0 °C and added to solid **11** (0.13 g, 0.12 mmol). The reaction mixture was allowed to warm at room temperature and stirred in the dark overnight. The solvent was removed under reduced pressure and the residue was solubilized in CH_2Cl_2 (10 mL). The organic phase was washed 3 times with water, dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure.

Derivative 13a. The crude product was purified by preparative thin-layer chromatography, eluent *n*-hexane/diethyl ether/methanol 80/20/1, *v*/*v*, to give **13a** as a white solid, 0.025 g, yield 20%. Mp: 188-191 °C. ESI(+) MS: *m*/*z* = 1017 (MH^+). ^{1}H NMR (400 MHz, $CDCl_3$, 298 K): δ 0.98 [s, -C(CH_3)$_3$, 9H], 1.13 [s, -C(CH_3)$_3$, 18H], 1.17 [s, -C(CH_3)$_3$, 18H], 3.02 (s, OCH_3, 6H), 3.15 (s, OCH_3, 6H), 3.49 (s, OCH_3, 3H), 3.57 (s, OCH_3, 3H), 3.81 (s, $ArCH_2Ar$, 4H), 3.93 (br s, $ArCH_2Ar$, 8H), 6.44 (s, ArH, 2H), 6.87 (s, ArH, 2H), 6.92 (s, ArH, 2H), 7.00 (s, ArH, 2H), 7.06 (s, ArH, 4H), 7.27 (s, OH, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz, 298 K): δ 30.5, 31.4, 31.5, 31.7, 34.2, 34.3, 55.3, 60.6, 60.9, 113.2, 125.6, 126.3, 126.5, 129.0, 132.5, 133.2, 133.4, 133.6, 133.8, 145.4, 145.8, 145.9, 146.7, 152.6, 153.2, 154.1, 154.4. Anal. Calcd. for $C_{68}H_{88}O_7$: C, 80.27; H, 8.72. Found: C, 80.36; H, 8.81.

Derivative 13b. The crude product was purified by column chromatography on silica gel using $CHCl_3$/ *n*-hexane (96/4, *v*/*v*) as eluent to give **13b** as a colourless solid, 0.040 g, 30% yield. Mp: 188-191 °C. ESI(+) MS: m/z = 1093 (MH^+). ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ 0.93 [s, -C(CH_3)$_3$, 9H], 1.08 [s, -C(CH_3)$_3$, 18H], 1.10 [s, C(CH_3)$_3$, 18H], 2.95 (s, OCH_3, 6H), 3.09 (s, OCH_3, 6H), 3.41 (s, OCH_3, 3H), 3.73 (s, $ArCH_2Ar$, 4H), 3.85 (bs, $ArCH_2Ar$, 8H), 4.73 (s, O*C*H_2Ph, 2H), 6.47 (s, ArH, 2H), 6.81 (s, ArH, 2H), 6.87 and 7.01 (AB, ArH, *J* =2.04 Hz, 4H), 6.93 and 6.96 (AB, ArH, *J* =2.04 Hz, 4H), 7.18-7.21 (overlapped, $OCH_2C_6H_5$ + OH, 6H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 29.7, 30.3, 31.2, 31.3, 31.4, 31.6, 31.9, 34.05, 34.1, 60.3, 60.7, 70.2, 114.2, 125.4, 125.7, 125.9, 126.1, 126.4, 127.5, 127.7,

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128.4, 128.6, 128.7, 132.2, 133.0, 133.2, 133.4, 133.6, 133.7, 137.4, 145.2, 145.6, 146,0, 146.5, 151.8, 153.0, 154.0, 154.3. Anal. Calcd. for $C_{74}H_{92}O_7$: C, 81.28; H, 8.48. Found: C, 81.37; H, 8.56.

Synthesis of derivative 14. To a solution of *p*-bromodienone **11** (0.52 g, 0.47 mmol) in DME (3 mL) at 0 °C was added a solution of $AgClO_4$ (0.19 g, 0.93 mmol) and resorcinol (0.52 g, 4.7 mmol) in DME (4 mL). The reaction mixture was allowed to warm at room temperature and stirred in the dark overnight. The solvent was removed under reduced pressure and the residue was solubilized in CH_2Cl_2 (15 mL) and washed with aqueous 1 N HCl and successively with water, dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2) to give derivative **14** (0.16 g, 30% yield) as a white solid. Mp: > 190 °C dec. ESI(+) MS: m/z = 1152 (MH^+). ^{1}H NMR (600 MHz, $CDCl_3$, 298 K): δ 1.12 [s, -C(CH_3)$_3$, 9H], 1.15 [bs, -C(CH_3)$_3$, 18H], 1.19 [s, -C(CH_3)$_3$, 9H], 1.21 [s, -C(CH_3)$_3$, 9H], 1.33 [s, -C(CH_3)$_3$, 9H], 3.60 (s, OCH_3, 9H), 3.83 (s, $ArCH_2Ar$, 2H), 3.88 (bs, OCH_3, 6H), 3.97 (s, $ArCH_2Ar$, 2H), 4.07 (s, $ArCH_2Ar$, 2H), 4.10 (bs, $ArCH_2Ar$, 4H), 4.12 (s, $ArCH_2Ar$, 2H), 4.76 (s, OH, 1H), 5.03 (s, OH, 1H), 6.34 (m, ArH, 1H), 6.36 (bs, ArH, 1H), 6.52 (m, ArH, 1H), 6.55 (m, ArH, 1H), 6.88−6.97 (overlapped, ArH, 3H), 7.10−7.14 (overlapped, ArH, 3H), 7.24−7.32 (overlapped, ArH, 3H), 7.81 (s, ArH, 1H), 8.55 (s, OH, 1H). ^{13}C NMR (150 MHz, $CDCl_3$, 298 K): δ 29.9, 30.2, 30.3, 31.50, 31.51, 31.54, 31.56, 31.8, 32.6, 34.37, 34.41, 34.51, 34.54, 60.93, 60.98, 62.27, 62.34, 104.1, 104.8, 107.5, 108.6, 119.9, 120.1, 125.3, 125.6, 125.7, 125.9, 126.0, 126.1, 126.4, 126.5, 127.1, 127.2, 127.3, 127.7, 131.0, 132.0, 132.3, 132.4, 132.5, 133.2, 133.3, 133.4, 133.5, 133.6, 144.2, 146.3, 146.6, 148.1, 148.3, 152.0, 152.1, 154.6, 154.7, 155.2, 155.7, 155.8, 156.8. Anal. Calcd. for $C_{77}H_{98}O_8$: C, 80.31; H, 8.58. Found: C, 80.24; H, 8.66.

General Procedure for the Synthesis of Derivatives 15a-c. A solution of $AgClO_4$ (0.048 g, 0.23 mmol) in the appropriate alcohol **a-c** in Scheme 2 (1.6 mL) at 0 °C was added to the solid *p*-bromodienone derivative **12** (0.18 g, 0.12 mmol). The reaction mixture was allowed to warm at room temperature and stirred in the dark overnight. The solvent was removed under reduced pressure and the

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residue was solubilized in CH_2Cl_2 (10 mL). The organic phase was washed 3 times with water, dried on Na_2SO_4, filtered and the solvent was removed under reduced pressure.

Derivative 15a. The crude product was purified by column chromatography on silica gel using $CHCl_3$/ *n*-hexane 96/4 as eluent to give **15a** as a white solid, 0.025 g, 15% yield. Mp: 176-179 °C. ESI(+) MS: *m/z* = 1369 (MH^+), 1391 (MNa^+). ^{1}H NMR (300 MHz, TCDE, 393 K): δ 0.79 [broad, $O(CH_2)_5CH_3$, 15H], 0.87 [s, $-C(CH_3)_3$, 18H], 0.99 [s, $-C(CH_3)_3$, 9H], 1.14 [s, $-C(CH_3)_3$, 18H], 1.14−1.73 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 40H), 3.17 (br t, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 2H), 3.60−3.80 (overlapped, $ArCH_2Ar$ + $OCH_2CH_2CH_2CH_2CH_2CH_3$, 20H), 3.70 (bs, OCH_3, 3H), 6.63 (bs, ArH, 2H), 6.70 (bs, ArH, 2H), 6.82 (s, ArH, 2H), 6.94 (bs, ArH, 2H), 7.03 (bs, ArH, 4H). ^{13}C NMR (75 MHz, TCDE, 393 K): δ 11.9, 20.5, 20.8, 21.4, 23.9, 24.1, 27.8, 27.9, 29.0, 29.5, 29.7, 32.1, 71.4, 109.4, 127.7, 123.1, 123.3, 123.8, 125.1, 125.2, 127.9, 129.6, 130.2, 131.2, 131.6, 143.0, 143.2, 144.0, 144.4, 150.2, 150.7, 151.6, 152.3. Anal. Calcd. for $C_{93}H_{138}O_7$: C, 81.65; H, 10.17. Found: C, 81.73; H, 10.25.

Derivative 15b. The crude product was purified by column chromatography on silica gel using $CHCl_3$/ *n*-hexane 40/60 as eluent to give **15b** as a pale yellow solid, 0.031 g, 17% yield. Mp: 183-186 °C. ESI(+) MS: *m/z* = 1466 (MNa^+), 1483 (MK^+). ^{1}H NMR (300 MHz, TCDE, 393 K): δ 0.77-0.80 [overlapped, $O(CH_2)_5CH_3$ + $C(CH_3)_3$, 33H], 0.98 [s, $-C(CH_3)_3$, 9H], 1.12 [s, $-C(CH_3)_3$, 18H], 1.08−1.62 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 40H), 3.16 (br t, $OCH_2CH_2CH_2CH_2CH_2CH_3$, 2H), 3.49- 3.79 (overlapped, $ArCH_2Ar$ + $OCH_2CH_2CH_2CH_2CH_2CH_3$, 20H), 4.53 (bs, OH, 1H), 4.82 (s, OCH_2Ph, 2H), 6.50−6.64 (overlapped, ArH, 6H), 6.80 (bs, ArH, 2H), 6.93 (s, ArH, 2H), 6.99 (s, ArH, 2H), 7.16−7.23 (overlapped, $OCH_2C_6H_5$, 5H). ^{13}C NMR (75 MHz, TCDE, 393 K): δ 17.0, 25.8, 29.1, 33.0, 33.3, 33.7, 34.0, 34.6, 35.0, 37.1, 74.5, 119.6, 127.9, 128.4, 130.1, 130.5, 131.5, 132.8, 134.0, 134.9, 135.4, 136.7, 148.2, 149.1, 155.9, 156.8, 157.4. Anal. Calcd. for $C_{99}H_{142}O_7$: C, 82.33; H, 9.91. Found: C, 82.26; H, 9.99.

Derivative 15c. The crude product was purified by column chromatography on silica gel using CH_2Cl_2/ petroleum ether, 60/40 as eluent to give **15c** as a pale yellow solid, 0.026 g, 15% yield. Mp: > 185 °C

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dec. ESI(+) MS: m/z = 1472 (MH^+). ^{1}H NMR (300 MHz, TCDE, 393 K): δ 0.77−0.87 [overlapped, $O(CH_2)_5CH_3$, 15H], 0.87 [overlapped, $-C(CH_3)_3$, 18H], 0.99 [s, $-C(CH_3)_3$, 9H], 1.13 [overlapped, $-C(CH_3)_3$, 18H], 1.18−1.31 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$+*Calix*-$OCH_2CH(CH_3)Ph$, 33H), 1.57−1.70 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$ + *Calix*-$OCH_2CH(CH_3)Ph$, 11H), 3.21 (t, $OCH_2CH_2CH_2CH_2CH_2CH_3$, J = 6.9 Hz, 2H), 3.53−3.81 (overlapped, $OCH_2CH_2CH_2CH_2CH_2CH_3$ + $ArCH_2Ar$ + *Calix*-$OCH_2CH(CH_3)Ph$, 22H), 6.34 (br s, ArH, 5H), 6.63 and 6.70 (AB, ArH, J = 1.7 Hz, 4H), 6.83 (s, ArH, 4H), 6.93 and 7.00 (AB, ArH, J = 2.3 Hz, 4H). ^{13}C NMR (75 MHz, TCDE, 393 K): δ 11.9, 12.0, 20.5, 20.6, 20.8, 23.9, 24.0, 24.1, 28.0, 28.2, 28.6, 29.1, 29.6, 29.7, 29.9, 32.1, 113.9, 117.4, 123.1, 123.4, 123.6, 124.9, 126.5, 129.7, 130.5, 131.2, 131.4, 131.6, 143.2, 144.1, 145.3, 146.5, 150.4, 151.7, 152.2; Anal. Calcd. for $C_{101}H_{146}O_7$: C, 82.40; H, 10.01. Found: C, 82.47; H, 9.91.

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Supporting Information: 1D and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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