Regioselective Monoalkylation of Calixarenes. Synthesis of Homodimer Calixarenes

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The selective monoalkylation at the smaller (lower) rim of the p-*tert*-butylcalix[4]- and -[6]arenes using bis(butyltin)oxide and different alkylating agents is described. The procedure is remarkable for the mild conditions used allowing an efficiently access to monoalkylated calixarene derivatives in moderate to good yields. Monoalkynylcalix[4]arene and monoalkynylcalix[6]arene have been synthetically exploited for the synthesis of bis-calix[n]arenes ($n = 4, 6$) with a diyne bridge by oxidative coupling of alkynes. In addition, intermolecular methathesis of the obtained monoalkenylcalix[4]arene allowed the preparation of bis-calix[4]arene that are single bridged at the smaller (lower) rim with a 2-butenyl moiety.

Introduction

The development of supramolecular chemistry has led to a growing interest in the design and synthesis of macrocyclic molecules containing intramolecular cavities.[1] In this regard, calixarenes[2] have been used as building blocks for the synthesis of a large host molecules with different supramolecular functions because they are readily accessible for chemical modification on both smaller (lower) and larger (upper) rims by attachment of a wide range of potential ligating groups.

General and efficient procedures for the selective alkylation of calix[4]arenes at the smaller (lower) rim have been reported allowing the synthesis of monoalkoxycalixarenes and 1,2- and 1,3-dialkoxycalixarenes. The reason of the observed selectivity is mainly due to the different acidities of the phenolic OH groups which can be selectively ionized by using an appropriate base. The regioselective reaction of a single hydroxy group in calixarenes is in particular important for the construction of larger molecules using calixarenes as building units.[3] One of the first examples described of selective functionalization from unsubstituted calix[4]arene was the synthesis of a tribenzoate derivative from which monoethers were prepared after hydrolysis of the ester groups.[4] Another indirect procedure for the preparation of monoalkoxycalix[4]arenes has been devised that uses the controlled cleavage of 1,3-dialkoxy- or tetraalkoxycalix[4]arenes with either 1 or 3 equiv of trimethylsilyl iodide.[5] Complementary to those indirect monoalkylation procedures, regioselective monoalkylation has been carried out using an excess of the alkylating agent and K_2CO_3 or CsF as a weak base,[6] NaH,[7] or $Ba(OH)_2$.[7a] Compared with calix[4]arenes, the regiochemical control of calix[6]arene funtionalization is more difficult because of the presence of a larger number of reactive centers and a higher conformational mobility. However, high selectivity has been obtained in the synthesis of monobenzyl ethers of calix[6]arene and *p-tert*-calix[6]arene, using a weak base (K_2CO_3) and stoichiometric amount of benzyl bromide in dry acetone.[8]

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The versatility of calix[4]arenes as host molecules has suggested that they can serve as potential building blocks for designing more elaborate structures consisting of double calix[4]arenes.[9] Three possibilities have been envisaged: connection via both larger (upper) rims, *head-to-head*, via both smaller (lower) rims, *tail-to-tail*, or via the larger rim of one with the smaller rim of another, *head-to-tail*. Shinkai et al.[10] have reported the synthesis of a series of bis-calix[4]arenes possessing two metal binding sites, each of which contains four ester or four ether groups. Double and triple calix[4]arenes connected via the oxygen atoms have been described[11] by reactions between calix[4]arenes 1,3-difunctionalized at the smaller (lower) rim and difunctional reagents such as diacid dichlorides or diamines.[11,12] Also, double-calixarenes linked through one bridge at the smaller (lower) rim and bearing urea groups on the larger (upper) rims have also been reported.[13] Recently, Rebek et al. have described[14] the synthesis and the encapsulation behavior of bis-calix[4]arenes linked via one bridge at the larger (upper) rims and bearing urea groups in the same rims. Bis-calix[*n*]arenes that are singly and doubly bridged at the larger (upper) rims with 2-butenyl or 2-methylenepropyl moieties have been prepared by tandem Claisen rearrangement of bis-calix[*n*]arenes that are singly and doubly bridged via ether linkages at the smaller (lower) rims with the same spanners.[15] A series of bis-calix[4]arenes derivatives linked through the phenolic oxygens with the help of single aliphatic or aromatic chain (tail-to-tail) were obtained by alkylation of 25,26,27-tripropoxy-28-hydroxycalix[4]arenes with α,ω-dibromoalkanes in the presence of NaH,[16] by condensation of *p-tert*-butylcalix[4]arene with methyl 2,6-bis(bromomethyl)benzoate,[17] 2,6-bis(bromomethyl)-4-methylanisole,[18] or 5,5′-bis(bromomethyl)-2,2′-bipyridine *N*,*N*′-dioxide.[19] Bis- and oligocalix[4]arenes have been obtained by intermolecular methathesis of dialkenylcalix[4]arene derivatives.[20]

Trialkylstannyl ethers and dialkylstannylene acetals have become widely used intermediates in synthesis mainly of carbohydrate derivatives.[21] The transformation of hydroxy groups into organotin alkoxides strongly increases the nucleophilic character of the oxygen atoms, allowing easy alkylation and providing reliable, high-yielding methods for obtaining monosubstituted derivatives of diols or polyols often with high regioselectivity. Application of these reagents in the phenol chemistry is rare, and to the best of our knowledge, only Woodward et al.[22] have applied this approach for the selective monoacylation of 2,2′-binaphthol.

We report in this paper the results of a systematic study on the selective monoalkylation of the smaller (lower) rim of the *p-tert*-butylcalix[4]- and -[6]arenes using bis(butyltin)oxide and the synthetic applications of the obtained monoalkynyl- and monoallylcalix[n]arene ($n = 4, 6$) derivatives for the synthesis of bis-calix[4]-arenes by oxidative coupling of alkynes and intermolecular methathesis, respectively.

Results and Discussion

In a project directed to the synthesis of modified calixarenes, an efficient and general methodology was needed for access to monoalkylated calixarenes. Considering the demonstrated utility of stannylene acetals for the regioselective alkylation and acylation in the sugar chemistry, it was thought that formation of these intermediates in the case of calixarenes could be also an adequate way for the synthesis of the desired targets. To find the optimal conditions for those transformations, *p-tert*-butyl calixarene (**1**) was chosen as the starting material and propargyl bromide as the electrophile reagent. The reaction was initially performed using Bu_2SnO (0.5 equiv) in refluxing toluene with azeotropic removal of water for 8 h. After this time, Bu_4NBr and propargyl bromide were added keeping the reflux for additional 2 h. Compound **3** was thus isolated in 33% yield (see Scheme 1). It was found that the use of Bu_4NI instead of Bu_4NBr increased the yield up to 43% or up to 52% when the initial treatment with Bu_2SnO was prolonged for 24 h. After several experiments, it was finally found that the use of $(Bu_3Sn)_2O$ (0.5 equiv) allowed better results by extending the treatment of **1** with this reagent for 4 days and subsequent treatment with the alkylating reagent in the presence of Bu_4NI. Thus, the monoalkylated derivative **3** was obtained in 76% (see Scheme 1), and these conditions were adopted for the present study. Also, it should be mentioned that compound **3** was prepared following the conditions described by Reinhoudt et al.[6] for the synthesis of several monoalkylated calix[4]arenes by using CsF. However, in our hands this procedure led to compound **3** in low yield (31%).

Compound **1** was then subsequently treated with $(Bu_3Sn)_2O$ (0.5 equiv) and bromoacetonitrile, allyl bromide, ethyl bromoacetate, 4-iodobenzyl iodide, benzyl bromide, and 5-iodo-1-pentyne, respectively. In all of those reactions the corresponding monoalkylated derivatives **4**−**9** were easily obtained in 34−84% yield (see Scheme 1). The study was then extended to *p-tert*-butylcalix[6]arene **2** using the same alkylating reagents. In this case, the reaction with propargyl bromide led to a complex mixture from which compound **10** could not be isolated. In the rest of the cases, the corresponding monoalkylated derivatives **11**−**16** were obtained but with yields (23−

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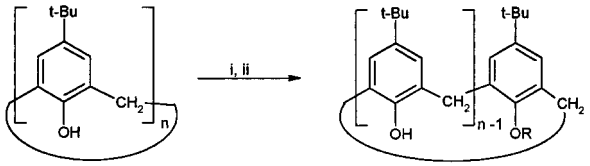
Scheme 1. Synthesis of Monoalkylated Calix[*n*]arenes (*n* = 4, 6)[a,b]



Entry	Calixarene	R-X	Compound	Yield (%)
1	**1** (n = 4)	$BrCH_2C{\equiv}CH$	**3** (n = 4)	73
2	**1** (n = 4)	$BrCH_2CN$	**4** (n = 4)	50
3	**1** (n = 4)	$BrCH_2C{=}CH_2$	**5** (n = 4)	80
4	**1** (n = 4)	$BrCH_2COOEt$	**6** (n = 4)	34
5	**1** (n = 4)	4-$IC_6H_4CH_2I$	**7** (n = 4)	56
6	**1** (n = 4)	$C_6H_5CH_2Br$	**8** (n = 4)	47
7	**1** (n = 4)	$I(CH_2)_3C{\equiv}CH$	**9** (n = 4)	66
8	**2** (n = 6)	$BrCH_2C{\equiv}CH$	**10** (n = 6)	[a]
9	**2** (n = 6)	$BrCH_2CN$	**11** (n = 6)	23
10	**2** (n = 6)	$BrCH_2C{=}CH_2$	**12** (n = 6)	51
11	**2** (n = 6)	$BrCH_2COOEt$	**13** (n = 6)	47
12	**2** (n = 6)	4-$IC_6H_4CH_2I$	**14** (n = 6)	38
13	**2** (n = 6)	$C_6H_5CH_2Br$	**15** (n = 6)	52
14	**2** (n = 6)	$I(CH_2)_3C{\equiv}CH$	**16** (n = 6)	27

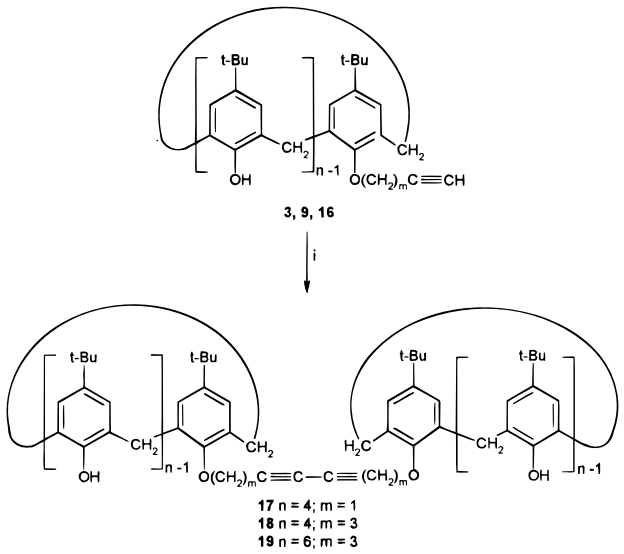
[a] A complex mixture was obtained from which compound **10** could not be isolated. [b] Reagents and conditions: (i) $(Bu_3Sn)_2O$, toluene, reflux; (ii) RX, Bu_4NI, toluene, reflux.

52%) lower than those obtained when **1** was the starting material (see Scheme 1).

Once the monoalkylated calixarenes were synthesized, we thought that the alkynyl **3**, **9**, **16** and allyl **5**, **12** derivatives could be adequate precursors for the synthesis of homodimer calixarenes using carbon−carbon bond-forming reactions such as oxidative dimerization under Glasser's conditions or olefin methathesis. Both types of reactions were successfully carried out. Thus, treatment of **3**, **9**, and **16** with cuprous iodide and a catalytic amount of bis(triphenylphosphine) palladium dichloride in DMF/Et_3N[23] gave the corresponding diynes **17**−**19** in moderate to high yields (37−95%) (see Scheme 2). On the other hand, homodimerization of compound **5** in refluxing dichlomethane in the presence of the Grubb's catalyst[24] [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] allowed the preparation of a *Z*/*E* mixture of dimers **20** + **21** in a 3:1 proportion. Pure *Z*-isomer **20** could be obtained when calix[4]arene **1** was reacted with (Z)-1,4-dichlorobutene following the procedure described by Gutsche et al.[15] in good yield (69%). Olefin hydrogenation of the *Z*/*E* mixture of isomers **20** + **21** or pure *Z*-isomer **20** was effected using Pd/C, and compound **22** was obtained (40%) (see Scheme 3).

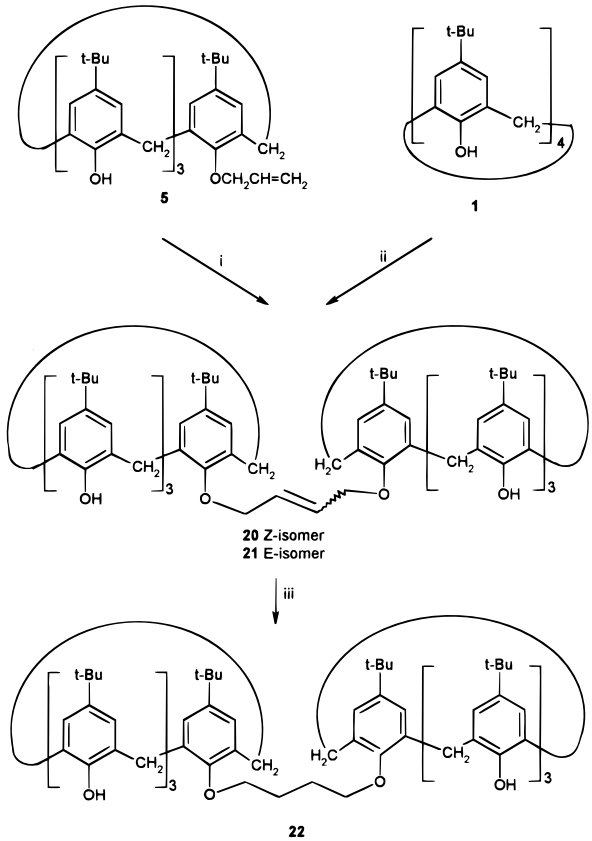
In conclusion, use of bis(butyltin) oxide is first described in the calixarene chemistry allowing the regioselective synthesis of monoalkylated calix[4]arenes and calix[6]arenes. The procedure is remarkable for its efficiency and mild conditions. This last characteristic allowed the use of alkylating agents having different functionalities (nitrile, esters, alkynes). Finally, we used the monoalkynyl and monoalkenyl calixarenes for the synthesis of homodimer calixarenes connected by the smaller (lower) rims.

Scheme 2[a]



[a] Reagents and conditions: (i) $Pd(PPh_3)_2Cl_2$, CuI, Et_3N−DMF, rt.

Scheme 3[a]



[a] Reagents and conditions: (i) Grubb's catalyst, CH_2Cl_2, reflux; (ii) NaH, (*Z*)-1,4-dichlorobutene, CH_2Cl_2, rt; (iii) H_2, Pd−C, methanol−THF.

Experimental Section

General Experimental Details. TLC was performed on Merck silica gel $60F_{245}$ aluminum sheets with detection using the Mostain reagent [ceric sulfate (1%w/v and ammonium

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molybdate (2.5% w/v) in 10% (v/v) aqueous sulfuric acid] and by UV light when applicable. Flash column chromatography on silica gel Merck or Scharlau (230−400 mesh ASTM). All the concentrations were carried out under diminished pressure at 40 °C. Melting points were determinated with a Gallenkamp apparatus and are uncorrected. NMR spectra were recorded at room temperature on a Bruker AM-300 spectrometer. ^{1}H NMR chemical shifts are given in ppm and referenced to internal $CHCl_3$ (δ = 7.26) for $CDCl_3$ solutions. ^{13}C NMR chemical shifts are given in ppm and referenced to $CDCl_3$ (δ = 77.0). FAB mass spectra were obtained on a Fissons VG Autospec-Q spectrometer using *m*-nitrobenzyl alcohol or thioglicerol as matrix. Anhydrous solvents were prepared according to standard procedures and were freshly distilled prior to use. For reasons of clarity and to reduce space the names calix[4]arene and calix[6]arene were used instead of the original IUPAC names: pentacyclo[19.3.1.1.^{3,7}1.^{9,13}1^{15,19}]-octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene and heptacyclo[31.3.1.1.^{3,7}1.^{9,13}1.^{15,19}1.^{21,25}1^{27,31}]dotetraconta-1(37),3,5,7(42),9,11,13(41),15,17,19(40),21,23,25(39),-27,29,31(38),33,35-octadecaene.

5-Iodo-1-pentyne was obtained from 4-pentyn-1-ol in two steps.[25] 4-Iodo-benzyl iodide was obtained from 4-nitrobenzyl alcohol in two steps: reduction to 4-amino-benzyl alcohol and reaction with $NaNO_2$ and NaI.[26]

General Procedure for the Monoalkylation of 1 and 2. Synthesis of 3−16. A suspension of the correponding calixarene (1 mmol) in dry toluene (25 mL) was refluxed for 4 days in the presence of bis(tributyltin)oxide (0.5 mmol) in a flask equipped with a Dean−Stark separator. The corresponding alkylating agent (1.1 mmol) and tetrabutylammonium iodide (1.1 mmol) were added, and the solution was refluxed for 1−5 h. Toluene (50 mL) was added, and the organic phase was treated with $NaHCO_3$ saturated solution (2 × 50 mL) and water (25 mL). The organic phase was dried and concentrated yielding a crude product that was purified by column chromatography.

5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-propargyloxycalix[4]arene (3). Column chromatography of the crude (dichloromethane/hexane 1.1) gave **3** (76%) as a solid: mp 177−179 °C; IR (KBr) ν 3314, 3237, 2135, 1483, 1460, 1364, 1298, 1202, 1213 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.03 (s, 1 H), 9.20 (s, 2 H), 7.09 (s, 2 H), 7.04 (d, 2 H, J = 2.3 Hz), 7.03 (s, 2 H), 6.98 (d, 2 H, J = 2.3 Hz), 4.91 (d, 2 H, J = 2.4 Hz), 4.46 (d, 2 H, J = 13.1 Hz), 4.27 (d, 2 H, J = 13.6 Hz), 3.43 (d, 4 H, J = 13.4 Hz), 2.72 (t, 1 H, J = 2.0 Hz), 1.22 (s, 9 H), 1.20 (s, 18 H), 1.19 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 148.8, 148.4, 147.8, 143.7, 143.3, 133.8, 128.2, 128.1, 127.8, 126.6, 125.9, 125.8, 125.6, 78.0, 77.4, 63.5, 34.3, 34.1, 34.0, 33.0, 32.7, 31.6, 31.3; HRMS (FAB) *m*/*z* 709.4221 for [M + Na]$^+$, calcd for $C_{47}H_{58}O_4Na$ M 709.4232.

5,11,17,23-Tetra-*tert*-butyl-25-cyanomethyloxy-26,27,-28-trihydroxycalix[4]arene (4). Column chromatography of the crude (dichloromethane/hexane 1:3) gave **4** (50.0%) as a solid: mp 252−254 °C dec; IR (KBr) ν 3416, 3167, 1483, 1362, 1202 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.78 (s, 1 H), 8.70 (s, 2 H), 7.14 (s, 2 H), 7.10 (d, 2 H, J = 2.3 Hz), 7.07 (s, 2 H), 7.04 (d, 2 H, J = 2.3 Hz), 5.02 (s, 2 H), 4.35 (d, 2 H, J = 13.2 Hz), 4.26 (d, 2 H, J = 13.8 Hz), 3.55 (d, 2 H, J = 13.3 Hz), 3.48 (d, 2 H, J = 13.8 Hz), 1.24 (s, 9 H), 1.24 (s, 18 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 148.4, 147.5, 144.0, 146.6, 133.0, 128.1, 127.5, 123.3, 126.2, 126.1, 125.8, 127.7, 115.0, 60.4, 34.4, 34.1, 32.7, 32.5; HRMS (FAB) *m*/*z* 710.4187 for [M + Na]$^+$, calcd for $C_{46}H_{57}NO_4Na$ M 710.4158.

5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-(2-propenyloxy)calix[4]arene (5). Column chromatography of the crude (dichloromethane-hexane 1:4) gave **5** (80.5%) as a solid: mp 167−168 °C (lit.[6] mp 273−275 °C); ^{1}H and ^{13}C NMR are identical as those reported;[6] HRMS FAB+ *m*/*z* calcd for $C_{47}H_{60}O_4Na$ [M + Na]$^+$ 711.4379, found 711.4389.

5,11,17,23-Tetra-*tert*-butyl-25-ethoxycarbonylmethyloxy-26,27,28-trihydroxycalix[4]arene (6). Column chromatography of the crude (dichloromethane-hexane 2:1) gave **6** (34%) as a solid: mp 269−271 °C (lit.[6] mp 264−266 °C); ^{1}H NMR identical as those reported in ref 6; HRMS (FAB) *m*/*z* 757.4444 for [M + Na]$^+$, calcd for $C_{48}H_{62}O_6Na$ M 757.4428.

5,11,17,23-Tetra-*tert*-butyl-25-(4-iodobenzyloxy)-26,27,-28-trihydroxycalix[4]arene (7). Column chromatography of the crude (dichloromethane/hexane 1:3) gave **7** (56%) as a solid: mp 122−124 °C; IR (KBr) ν 3318, 1487, 1364, 1206, 1008 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.96 (s, 1 H), 9.32 (s, 2 H), 7.66 (4 H, AB system, J = 8.2 Hz, $\Delta\nu$ = 59.0 Hz), 7.11 (s, 2 H), 7.04 (d, 2 H, J = 2.3 Hz), 7.03 (s, 2 H), 6.97 (d, 2 H, J = 2.3 Hz), 5.09 (s, 2 H), 4.29 (d, 2 H, J = 13.0 Hz), 4.22 (d, 2 H, J = 13.6 Hz), 3.41 (d, 4 H, J = 13.4 Hz), 1.21 (s, 9 H), 1.21 (s, 18 H), 1.20 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 148.6, 148.5, 147.7, 143.7, 143.2, 138.2, 135.4, 133.6, 130.9, 128.3, 127.9, 127.6, 126.7, 125.8, 125.7, 95.0, 78.4, 34.4, 34.1, 34.0, 33.0, 32.5; HRMS (FAB) *m*/*z* 887.3511 for [M + Na]$^+$, calcd for $C_{51}H_{61}IO_4Na$ M 887.3555.

25-Benzyloxy-5,11,17,23-tetra-*tert*-butyl-26,27,28-trihydroxycalix[4]arene (8). Column chromatography of the crude (dichloromethane/hexane 1:3) gave **8** (47%) as a solid: mp 198−200 °C (lit.[5] mp 202−203 °C); ^{1}H and ^{13}C NMR are identical to those described in ref 5.

5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-(4-pentyn-1-yloxy)calix[4]arene (9). Column chromatography of the crude (dichloromethane/hexane 1:2) gave **9** (66%) as a solid: mp 165−167 °C; IR (KBr) ν 3314, 1485, 1362, 1203 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.15 (s, 1 H), 9.52 (s, 2 H), 7.11 (s, 2 H), 7.08 (d, 2 H, J = 2.4 Hz), 7.05 (s, 2 H), 7.01 (d, 2 H, J = 2.4 Hz), 4.38 (d, 2 H, J = 12.9 Hz), 4.28 (d, 2 H, J = 13.7 Hz), 4.26 (t, 2 H, J = 6.4 Hz), 3.45 (d, 2 H, J = 13.7 Hz), 3.45 (d, 2 H, J = 13.0 Hz), 2.75 (dt, 2 H, J = 6.9 and 2.7 Hz), 2.35 (m, 2 H), 2.06 (t, 1 H, J = 2.6 Hz), 1.24 (s, 9 H), 1.23 (s, 18 H), 1.21 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 148.5, 148.3, 147.7, 143.7, 143.2, 133.5, 128.4, 128.1, 127.5, 126.5, 125.8, 125.7, 125.7, 125.2, 83.3, 75.4, 69.5, 34.3, 34.1, 33.9, 33.1, 32.0, 31.9, 28.6, 15.4; HRMS (FAB) *m*/*z* 737.4553 for [M + Na]$^+$, calcd for $C_{49}H_{62}O_4Na$ M 737.4546.

5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-cyanomethyloxycalix[6]arene (11). Column chromatography of the crude (dichloromethane/hexane 1:1) gave **11** (23%) as a solid: mp 274−276 °C dec; IR (KBr) ν 3295, 2361, 2343, 1485,1364,1292, 1204 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (s, 2 H), 7.72 (s, 2 H), 7.17 (s, 2 H), 7.13 (d, 6 H), 7.09 (s, 2 H), 6.96 (d, 2 H), 4.87 (s, 2 H), 4.03 (br s, 4 H), 3.89 (br s, 2 H), 3.70 (br s, 4 H), 1.29 (s, 18 H), 1.27 (s, 18 H), 1.21 (s, 9 H), 1.10 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.8, 148.0, 146.5, 143.9, 143.9, 132.2, 128.5, 127.6, 127.3, 126.8, 126.5, 126.3, 126.1, 126.0, 125.9, 115.5, 60.1, 34.4, 34.1, 33.1, 32.6, 32.3; HRMS (FAB) *m*/*z* 1034.6288 for [M + Na]$^+$, calcd for $C_{68}H_{85}NO_6Na$ M 1034.6274.

5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-(2-propen-1-yloxy)calix[6]arene (12). Column chromatography of the crude (dichloromethane/hexane 1:2) gave **12** (51%) as a solid: mp 150−152 °C; IR (KBr) ν 3231, 1487, 1362, 1206 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.84 (br s, 2 H), 9.50 (br s, 1 H), 9.00 (s, 2 H), 7.13, 7.10, 7.08, 7.02 (4 s, 12 H), 6.24 (m, 1 H), 5.92 (d, 1 H, J = 16.9 Hz), 5.56 (d, 1 H, J = 10.9 Hz), 4.66 (d, 2 H, J = 4.5 Hz), 4.00−3.50 (m, 12 H), 1.28 (s, 18 H), 1.26 (s, 18 H), 1.21 (s, 9 H), 1.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 148.3, 148.1, 146.9, 144.4, 143.7, 143.1, 132.6, 128.2, 127.8, 126.3, 126.2, 126.1, 125.9, 125.5, 132.6, 117.8, 75.8, 34.1, 33.3, 32.6, 31.7, 31.7, 31.6, 31.5; HRMS (FAB) *m*/*z* 1035.6472 for [M + Na]$^+$, calcd for $C_{69}H_{88}O_6$-Na M 1035.6503.

5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-ethoxycarbonylmethyloxycalix[6]arene (13). Column chromatography of the crude (dichloromethane/hexane 1:1) gave **13** (47%) as a solid: mp 273−275 °C; IR (KBr) ν 3302,

(25) Conventional mesylation of 4-pentyn-1-ol in dry dichloromethane at 0 °C with methanesulfonyl chloride gave the corresponding mesyl derivative that was reacted with KI in dry butanone under reflux for 24 h to give 5-iodo-1-pentyne (65% overall yield) as a yellow liquid: ^{1}H NMR (300 MHz, $CDCl_3$): 3.30 (t, 2 H, J = 6.7 Hz), 2.33 (dt, 2 H, J = 6.7, 2.6 Hz), 1.99 (q, 2 H, J = 2.73 Hz), 1.98 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 82.3, 69.5, 31.9, 19.5, 5.1.

(26) Santoyo-González, F.; Pérez-Balderas, F. M. Unpublished results.

3200, 1749, 1489, 1464, 1207, 1067 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.70 (s, 2 H), 8.70 (s, 2 H), 7.13, 7.06, 7.00 (s, 12 H), 4.71 (s, 2 H), 4.41 (q, 2 H, J = 7.2 Hz), 4.36 (d, 2 H, J = 14.0 Hz), 4.16 (d, 2 H, J = 14.4 Hz), 3.95 (d, 2 H, J = 13.5 Hz), 3.55 (d, 2 H, J = 14.4 Hz), 3.61 (d, 2 H, J = 14.0 Hz), 3.52 (d, 2 H, J = 13.9 Hz), 1.41 (t, 3 H, J = 7.2 Hz), 1.28 (s, 18 H), 1.25 (s, 18 H), 1.23 (s, 9 H), 1.14 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5, 149.4, 148.4, 147.1, 143.6, 143.0, 132.3, 127.3, 127.0, 126.9, 126.2, 126.1, 126.0, 125.5, 71.9, 61.7, 34.0, 33.1, 32.6, 32.5, 31.7, 31.6, 31.5, 31.3, 14.4; HRMS (FAB) m/z 1081.6538 for $[M + Na]^+$, calcd for $C_{70}H_{90}O_8Na$ M 1081.6557.

5,11,17,23,29,35-Hexa-*tert*-butyl-37-(4-iodobenzyloxy)-38,39,40,41,42-pentahydroxycalix[6]arene (14). Column chromatography of the crude (dichloromethane/hexane 1:4) gave **14** (38%) as a solid: mp 178−180 °C; IR (KBr) ν 3422, 3225, 1485, 1364, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.92−9.80 (br s, 3 H), 8.88 (br s, 2 H), 7.96 (d, 2 H, J = 8.2 Hz), 7.47 (d, 2 H, J = 8.2 Hz), 7.12 (m, 12 H), 5.12 (s, 2 H), 4.37 (d, 4 H, J = 13.4 Hz), 4.28 (d, 2 H, J = 14.1 Hz), 3.99 (d, 2 H, J = 13.9 Hz), 3.59 (d, 2 H, J = 14.2 Hz), 3.52 (d, 2 H, J = 13.6 Hz), 3.39 (d, 2 H, J = 13.9 Hz), 1.27 (s, 18 H), 1.26 (s, 18 H), 1.22 (s, 9 H), 1.17 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 149.3, 148.4, 148.2, 146.7, 144.5, 143.7, 143.1, 138.3, 136.1, 132.6, 129.3, 127.6, 125.9, 127.5, 127.2. 126.8, 126.3, 126.2, 126.1, 125.8, 125.6, 94.4, 77.2, 34.4, 34.1, 35.1, 32.0, 33.4, 32.8; HRMS (FAB) m/z 1211.8653 for $[M + Na]^+$, calcd for $C_{73}H_{89}IO_6Na$ M 1211.8645.

37-Benzyloxy-5,11,17,23,29,35-hexa-*tert*-butyl-38,39,40,-41,42-pentahydroxycalix[6]arene (15). Column chromatography of the crude (dichloromethane/hexane 1:3) gave **15** (52%) as a solid: mp 225−227 °C (lit.[32] mp 228−231 °C); ^1H and ^{13}C NMR spectra are identical to those reported.[8b]

5,11,17,23,29,35-Hexa-*tert*-butyl-38,39,40,41,42-pentahydroxy-37-(4-pentyn-1-yloxy)calix[6]arene (16). Column chromatography of the crude (dichloromethane-hexane 1:1) gave **16** (27%) as a solid: mp 157−159 °C; IR (KBr) ν 3310, 2360, 1485, 1362, 1292, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.77, 9.00 (2 br s, 5 H), 7.12−7.01 (m, 12 H), 4.36 (d, 2 H, J = 14.8 Hz), 4.28 (t, 2 H, J = 5.7 Hz), 4.22 (d, 2 H, J = 13.6 Hz), 4.00 (d, 2 H, J = 13.6 Hz), 3.60−3.40 (m, 6 H), 2.81 (dt, 2 H, J = 6.7 and 2.5 Hz), 2.27 (m, 2 H), 2.02 (t, 1 H, J = 2.5 Hz), 1.28 (s, 18 H), 1.26 (s, 18 H), 1.21 (s, 9 H), 1.15 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 148.3, 148.0, 146.7, 143.7, 143.1, 132.5, 127.4, 127.3, 127.1, 126.8, 126.3, 126.1, 126.0, 125.9, 125.5, 83.3, 73.9, 69.6, 36.5, 34.3, 32.6, 33.3, 32.7, 31.7, 29.1, 15.2; HRMS (FAB) m/z 1061.6653 for $[M + Na]^+$, calcd for $C_{71}H_{90}O_6Na$ M 1061.6635.

1,6-Bis(5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-oxycalix[4]arene)-2,4-hexadiyne (17). To a degassed solution of **3** (0.425 g, 0.61 mmol) in dry Et_3N/DMF (30:3 mL) were added $Pd(PPh_3)_2Cl_2$ (0.04 g) and CuI (0.230 g). The reaction mixture was stirred at room temperature for 1 h. Filtration over Celite was followed by concentration. Column chromatography (dichloromethane/hexane 1:2) of the crude gave **17** (0.156 g, 37%) as a solid: mp 85−87 °C; IR (KBr) ν 3406, 3258, 2361, 2342, 1485, 1362, 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.01 (s, 2 H), 9.12 (s, 4 H), 7.09 (s, 4H), 7.04 (d, 4 H, J = 2.3 Hz), 7.03 (s, 4 H), 6.97 (d, 4 H, J = 2.3 Hz), 5.03 (s, 4 H), 4.43 (d, 4 H, J = 13.1 Hz), 4.26 (d, 4 H, J = 13.6 Hz), 3.46 (d, 4 H, J = 13.1 Hz), 3.42 (d, 4 H, J = 13.6 Hz), 1.21, 1.20, 1.20, 1.18 (3 s, 72 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.9, 148.4, 147.8, 143.7, 143.3, 133.6, 128.2, 128.0, 127.7, 126.7, 125.9, 125.8, 125.6, 74.8, 72.8, 64.0, 34.3, 34.0, 33.0, 32.7, 31.5, 31.3; HRMS (FAB) m/z 1393.8435 for $[M + Na]^+$, calcd for $C_{94}H_{114}O_8Na$ M 1393.8411.

1,10-Bis[5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-oxycalix[4]arene]-4,6-decadiyne (18). To a degassed solution of **9** (0.250 g, 0.35 mmol) in dry Et_3N/DMF (15:1 mL) were added $Pd(PPh_3)_2Cl_2$ (0.026 g) and CuI (0.075 g). The reaction mixture was stirred at room temperature for 1 h. Filtration over Celite was followed by concentration. Column chromatography (dichloromethane/hexane 1:1) of the crude gave **18** (0.237 g, 95%) as a solid: mp 210−212 °C; IR (KBr) ν 3329, 1485, 1460, 1362, 1298 1204 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 2 H), 9.48 (s, 4 H), 7.09 (s, 4 H), 7.06 (d, 4 H, J = 2.4 Hz), 7.04 (s, 4 H), 6.98 (d, 4 H, J = 2.4 Hz), 4.34 (d, 4 H, J = 13.0 Hz), 4.26 (d, 4 H, J = 13.9 Hz), 4.21 (t, 4 H, J = 6.3 Hz), 3.44 (d, 4 H, J = 12.0 Hz), 3.43 (d, 4 H, J = 13.8 Hz), 2.83 (t, 4 H, J = 6.6 Hz), 2.33 (m, 4 H), 1.22 (s, 18 H), 1.21 (s, 36 H), 1.19 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.1, 148.6, 148.3, 147.7, 143.8, 143.2, 133.6, 128.5, 128.1, 127.6, 126.6, 125.9, 125.8, 76.5, 75.4, 66.5, 34.3, 34.1, 34.0, 33.1, 32.2, 28.6, 16.4.; HRMS (FAB) m/z 1449.9027 for $[M + Na]^+$, calcd for $C_{98}H_{122}O_8Na$ M 1449.9096.

1,10-Bis[5,11,17,23,29,35-hexa-*tert*-butyl-37,38,39,40,41-pentahydroxy-42-oxycalix[6]arene]-4,6-decadiyne (19). To a degassed solution of **16** (0.230 g, 0.22 mmol) in dry Et_3N (15 mL) were added $Pd(PPh_3)_2Cl_2$ (0.016 g) and CuI (0.043 g). The reaction mixture was stirred at room temperature for 1 h. Filtration over Celite was followed by concentration. Column chromatography (dichloromethane/hexane 1:2) of the crude gave **19** (0.086 g, 81%) as a solid: mp 216 °C dec; IR (KBr) ν 3320, 1485, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.81 (br s, 4 H), 8.98 (br s, 4 H), 7.45 (br s, 2 H), 7.19 (d, 4 H, J = 2.4 Hz), 7.18, 7.17, 7.10, 7.07 (4s, 16 H), 7.13 (d, 4 H, J = 2.4 Hz), 4.30 (d, 4 H, J = 12.6 Hz), 4.22 (d, 4 H, J = 14.4 Hz), 4.18 (t, 4 H, J = 5.6 Hz), 3.97 (d, 4 H; J = 13.9 Hz), 3.54 (d, 4 H, J = 14.6 Hz), 3.52 (d, 4 H, J = 14.3 Hz), 3.44 (d, 4 H, J = 14.1 Hz), 2.87 (t, 4 H, J = 6.5 Hz), 2.20 (m, 4 H), 1.32 (s, 36 H), 1.30 (s, 36 H), 1.26 (s, 18 H), 1.21 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 148.3, 148.0, 146.9, 144.3, 143.6, 143.1, 132.5, 127.4, 127.3, 127.1, 126.8, 126.8, 126.2, 126.1, 125.9, 125.5, 76.3, 73.8, 66.8, 34.3, 34.0, 33.3, 32.7, 29.0, 16.0; HRMS (FAB) m/z 2076.3350 for $[M + H]^+$, calcd for $C_{142}H_{179}O_{12}$ M 2076.3396; 2099.3250 for $[M + Na]^+$, calcd for $C_{142}H_{178}O_{12}Na$ M 2099.3250.

(*Z*)-1,4-Bis[5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-oxycalix[4]arene]-2-butene (20). To a solution of **1** (1 g, 1.54 mmol) in dry dichloromethane (50 mL) was added NaH (0.07 g, 3.08 mmol). The mixture was stirred for 30 min under an inert atmosphere, treated with (*Z*)-1,4-dichloro-2-butene (0.57 g, 1,54 mmol) and tetrabutylammonium iodide (0.57 g), and stirred at room temperature for 24 h. The reaction mixture was washed with 1 N HCl (25 mL) and water (25 mL) and then dried (Na_2SO_4) to yield after concentration a crude product that was purified by column chromatography (dichloromethane/hexane 1:1) giving **20** (0.714 g, 69%) as a solid: mp 115−117 °C; IR (KBr) ν 3374, 1485, 1462, 1362, 1205 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.11 (s, 2 H), 9.44 (s, 4 H), 7.09 (s, 4 H), 7.02 (s, 8 H), 6.97 (d, 4 H, J = 2.1 Hz), 6.63 (t, 2 H, J = 4.0 Hz), 4.89 (d, 4 H, J = 4.9 Hz), 4.39 (d, 4 H, J = 13.1 Hz), 4.20 (d, 4 H, J = 13.6 Hz), 3.43 (d, 4 H, J = 13.0 Hz), 3.38 (d, 4 H, J = 13.8 Hz), 1.26 (s, 18 H), 1.21 (s, 36 H), 1.18 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.5, 147.9, 143.6, 143.2, 133.7, 128.3, 128.1, 127.9, 126.6, 126.0, 125.9, 125.8, 125.7, 129.4, 71.3, 34.0, 33.0, 32.6; HRMS (FAB) m/z 1371.8562 for $[M + Na]^+$, calcd for $C_{92}H_{116}O_8Na$ M 1371.8626.

(*Z*,*E*)-1,4-Bis(5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-oxycalix[4]arene)-2-butene (20 + 21). To a solution of **5** (0.200 g, 0.029 mmol) in dry dichloromethane (2 mL) was added Grubbs' catalyst [bis(tricyclohexylphosphine)benzylidene ruthenium(IV) dichloride] (0.012 g, 0.003 mmol). The resulting solution was allowed to reflux under a nitrogen atmosphere for 7 h. Concentration yielded a crude produt that was purified by column chromatography (dichloromethane/hexane 1:1) giving **20** + **21** (0.140 g, 72%) as a solid: ^1H NMR (300 MHz, $CDCl_3$) selected signals δ 10.15 (s, 1.3 H, compound **20**), 10.11 (s, 0.7 H, compound **21**), 9.46 (s, 2.7 H compound **20**), 9.44 (s, 1.3 H, compound **21**), 7.10−6.90 (m, 16 H, compounds **20** and **21**), 6.69 (m, 1.3 H, compound **20**), 6.63 (m, 0.7 H, compound **21**), 4.89−4.80 (m, 4 H, compounds **20** and **21**), 4.44 (d, J = 13.0 Hz, compound **20**), 4.14 (d, J = 13.7 Hz, compound **20**), 3.46 (d, J = 13.0 Hz, compound **20**), 3.29 (d, J = 13.8 Hz, compound **20**), 1.26−1.1 (several s, 72 H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.5, 147.9, 143.5, 413.1, 133.7, 128.3, 128.1, 128.0, 127.8, 126.6, 125.7, 130.2, 77.5, 34.0, 33.3, 32.5, 32.2, 31.8, 31.0; HRMS (FAB) m/z 1371.8562 $[M + Na]^+$, calcd for $C_{92}H_{116}O_8Na$ M 1371.8626.

1,4-Bis(5,11,17,23-tetra-*tert*-butyl-25,26,27-trihydroxy-28-oxycalix[4]arene)butane (22). A solution of **20** + **21** (0.150 g, 0.110 mmol) in methanol/THF (1:1, 20 mL) was

hydrogenated (3 atm) in the presence of Pd−C (50 mg). The reaction was monitored by TLC (dichloromethane/hexane 1:2). Filtration over Celite was followed by concentration and purification of the resulting crude product by column chromatography (dichloromethane/hexane 1:2) giving **22** (0.090 g, 40%) as a solid: mp 258−259 °C; IR (KBr) ν 3358, 3230, 1492, 1205, 1064 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.18 (s, 2 H), 9.61 (s, 4 H), 7.10 (s, 4 H), 7.06 (d, 4 H, J = 2.4 Hz), 7.03 (s, 4 H), 6.96 (d, 4 H, J = 2.4 Hz), 4.43 (d, 4 H, J = 12.9 Hz), 4.38 (br s, 4 H), 4.21 (d, 4 H, J = 13.6 Hz), 3.46 (d, 4 H, J = 13.0 Hz), 3.38 (d, 4 H, J = 13.8 Hz), 2.62 (br s, 4 H), 1.21 (s, 18 H), 1.20 (s, 36 H), 1.19 (s, 18 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 148.6, 143.6, 148.3, 147.8, 143.6, 143.1, 133.6, 128.4, 128.2, 127.6, 126.6, 125.8, 125.9, 76.5, 34.3, 34.1, 34.0, 33.0, 32.4, 29.8, 26.6; HRMS (FAB) m/z 1373.8712 for $[M + Na]^+$, calcd for $C_{92}H_{118}O_8Na$ M 1373.8724.

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