JOC Article
pubs.acs.org/joc

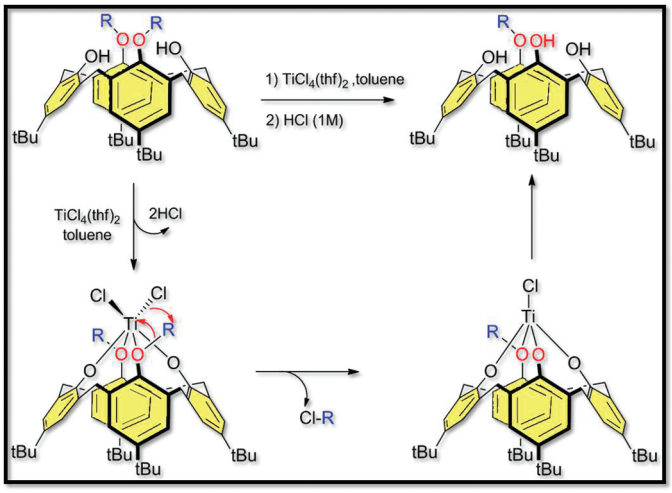
Easy and Selective Method for the Synthesis of Various Mono-*O*-functionalized Calix[4]arenes: De-*O*-functionalization Using $TiCl_4$

Joackim Bois,[†] Jeff Espinas,[†,‡] Ulrich Darbost,[†] Caroline Felix,[†] Christian Duchamp,[†] Denis Bouchu,[†] Mostafa Taoufik,*[,‡] and Isabelle Bonnamour*[,†]

[†]*Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, Equipe CSAp, CNRS, UMR 5246, Université de Lyon, Lyon, Université Lyon 1, Villeurbanne, 43 Boulevard du 11 Novembre 1918, F-69622 Villeurbanne, France, and* [‡]*UMR 5265, C2P2, CNRS-CPE Lyon, Université de Lyon, Lyon, Université Lyon 1, Villeurbanne, 43 Boulevard du11 Novembre 1918, F-69616 Villeurbanne, France*

isabelle.bonnamour@univ-lyon1.fr; taoufik@cpe.fr

Received July 5, 2010



An efficient and selective method for the monofunctionalization of *p-tert*-butylcalix[4]arene is described. A mono-de-*O*-functionalization of disubstituted *p-tert*-butylcalix[4]arenes using titanium tetrachloride was developed to synthesize a series of monosubstituted *p-tert*-butylcalix[4]arenes with the pendant functions being ethoxycarbonylmethyloxy, 3-ethoxycarbonylpropyloxy, cyanomethyloxy, 3-cyanopropyloxy, 4-bromobutyloxy, 3-hydroxypropyloxy, propyloxy, 2-methylpropyloxy, 3-butynyloxy, and 3-cyanopropyloxy groups. The reaction mechanism of the formation of 5,11,17,23-tetra-*tert*-butyl-26,27,28-trihydroxy-25-(3-ethoxycarbonylpropyloxy) calix[4]arene was studied by ^{1}H NMR and GC/mass spectroscopy monitoring. Reaction of $TiCl_4$ with the disubstituted *p-tert*-butylcalix[4]arene produced the corresponding dioxocalix[4]arene titanium dichloride complex, which undergoes elimination of ethyl 4-chlorobutyrate, leading to a trioxocalix[4]arene titanium dichloride complex and to monosubstituted calix[4]arene after hydrolysis. These two complexes were also synthesized, isolated, and fully characterized.

Introduction

The *p-tert*-butylcalix[4]arenes are a major class of organic macrocyclic compounds and have become inescapable in the field of macrocyclic and supramolecular chemistry.[1−3] With the constant increase in need for novel supramolecular hosts based on these macrocycles, chemists have developed new

(1) Mandolini, L., Ungaro, R., Eds. *Calixarenes in Action*; Imperial College Press: London, 2000.
(2) Asfari, Z., Bohmer, V., Harrowfield, J., Vicens, J., Eds. *Calixarenes 2001*; Kluwer: Dordrecht, The Netherlands, 2001.
(3) Gutsche, C. D., Ed. *Calixarenes: An Introduction*, 2nd ed.; Royal Society of Chemistry: London, 2008.
(4) Tabakci, M.; Memon, S.; Yilmaz, M. *Tetrahedron* **2007**, *63*, 6861–6865.

Published on Web 10/20/2010 DOI: 10.1021/jo101319s

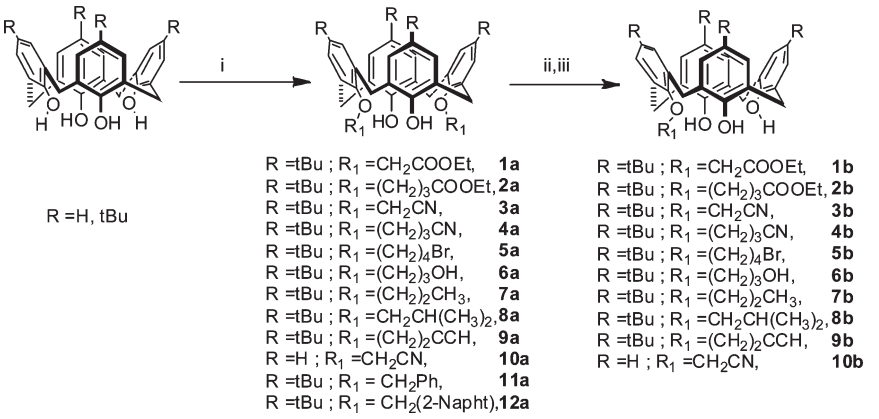
synthesis tools for their selective functionalization.[4−8] The 1,3-dialkylation of *p-tert*-butylcalix[4]arenes is well-described and reproducible, leading selectively to numerous and diverse 1,3-dialkylated *p-tert*-butylcalix[4]arenes in high yield.[9−20] However, the elaboration of heterofunctionalized calixarenes is still particularly difficult, requiring synthesis of a monoalkylated *p-tert*-butylcalix[4]arene key intermediate obtained in low to moderate yields. Direct alkylation of *p-tert*-butylcalix[4]arene with alkyl halides in presence of 1 equiv of base often yields a difficult to separate mixture of mono- and dialkylated calix[4]arenes and unreacted starting material.[21−26] Multistep routes for the preparation of monoalkylated *p-tert*-butylcalix[4]arenes have also been described involving protection and deprotection sequences of phenoxyl groups of *p-tert*-butylcalix[4]arene by using silyl compounds.[27,28] The above pathways allow the synthesis of different heterofunctionalized *p-tert*-butylcalix[4]arenes but involve laborious synthesis procedures. Another approach is to use an oxophilic metallic element as a coordinating template for the selective functionalization of *p-tert*-butylcalix[4]arenes. However, this strategy is as yet not well-studied. Recently, the synthesis of monoalkoxy *p-tert*-butylcalix[4]arenes by selective dealkylation of 1,2-dialkylated *p-tert*-butylcalix[4]arenes with aluminum chloride in benzene has been described.[29] The mono-*O*-methoxy-*p-tert*-butylcalix[4]arene was obtained by an original reaction of dealkylation of one oxygen atom of the 1,3-di-*O*-methoxy-*p-tert*-butylcalix[4]arene precursor. This σ bond destruction was inherent in the oxophilicity of a titanium tetrachloride corresponding complex and was interpreted by Floriani[30,31] as a Lewis acid assisted cleavage of one ether functionality. This elegant pathway was successfully reused by Radius[32] for the synthesis of mono-*O*-R-*tert*-butylcalix[4]arene (R = Bn and $Si(Me)_3$). Among all of these published examples, the monofunctionalization of *p-tert*-butylcalix[4]arene corresponds mainly to the incorporation of an alkyl group. Only a few papers[26,33,34] describe the synthesis of monofunctionalized calix[4]arenes with different kinds of functions as alcohol, nitrile, and ester. Moreover, reported methods do not always match with fragile functions as ester, bromide, or terminal alkyne derivatives. There is clearly a lack of a general method for the synthesis of various classes of monofunctionalized *p-tert*-butylcalix[4]arenes. On the basis of our recent work[35] on *p-tert*-butylcalix[4]arenes−Ti complexes, and the expectation that the titanium coordination chemistry could lead to a key intermediate orienting the reaction toward the selective mono-*O*-defunctionalization, we undertook the in-depth investigation of the behavior of such Ti complexes. As a result, we propose a simple and reproducible procedure allowing the preparation of a range of monofunctionalized *p-tert*-butylcalix[4]arenes. Moreover, thanks to a complete characterization of the reaction intermediates and a careful monitoring of the byproduct, we demonstrated the mechanism of this titanium-driven-force pathway.

Results and Discussion

Synthesis and Characterization. With the aim to synthesize a series of monofunctionalized *p-tert*-butylcalix[4]arenes, we have selected a panel of different functions such as alkyl, ester, alcohol, nitrile, or bromide. With this goal in mind, we first undertook the classical difunctionalization of the *p-tert*-butylcalix[4]arene in acetonitrile with an excess of the corresponding bromo derivative. Once obtained, the resulting disubstituted calix[4]arenes (**1a**−**10a**) were then totally converted into monosubstituted *p-tert*-butylcalix[4]arenes (**1b**−**10b**) by refluxing with titanium tetrachloride in toluene, followed by acidic hydrolysis (Scheme 1). This original procedure allows an efficient and selective access to monofunctionalized *p-tert*-butylcalix[4]arenes **1b**−**10b** with various substituents as ester (**1b**,[26] **2b**), nitrile (**3b**,[33] **4b**, **10b**), halogen (**5b**), alcohol (**6b**), alkyl (**7b**,[25] **8b**), and alkynyl (**9b**) groups (Table 1) and isolated with moderate to high yields (from 53 to 85% except for the monoester **1b** (15%)).

(5) Boyko, V. I.; Yakovenko, A. V.; Matvieiev, Y. I.; Kalchenko, O. I.; Shishkin, O. V.; Shishkina, S. V.; Kalchenko, V. I. *Tetrahedron* **2008**, *64*, 7567–7573.
(6) Bois, J.; Bonnamour, I.; Duchamp, C.; Parrot-Lopez, H.; Darbost, U.; Felix, C. *New J. Chem.* **2009**, *33*, 2128–2135.
(7) Boyko, V. I.; Matvieiev, Y. I.; Klyachina, M. A.; Yesypenko, O. A.; Shishkina, S. V.; Shishkin, O. V.; Kalchenko, V. I. *Tetrahedron* **2009**, *65*, 4220–4227.
(8) Da Silva, E.; Memmi, L.; Coleman, A. W.; Rather, B.; Zaworotko, M. J. *J. Supramol. Chem.* **2002**, *1*, 135–138.
(9) Collins, E. M.; McKervey, M. A.; Madigan, E.; Moran, M. B.; Owens, M.; Ferguson, G.; Harris, S. J. *J. Chem. Soc., Perkin Trans. 1* **1991**, 3137–3142.
(10) Sun, J.; Liu, D. M.; Wang, J. X.; Yan, C. G. *J. Inclusion Phenom. Macrocyclic Chem.* **2009**, *64*, 317–324.
(11) Zhang, W. C.; Huang, Z. T. *Synthesis* **1997**, 1073–1076.
(12) Chawla, H. M.; Pant, N.; Srivastava, B. *Tetrahedron Lett.* **2005**, *46*, 7259–7262.
(13) Chen, X.; Dings, R. P. M.; Nesmelova, I.; Debbert, S.; Haseman, J. R.; Maxwell, J.; Hoye, T. R.; Mayo, K. H. *J. Med. Chem.* **2006**, *49*, 7754–7765.
(14) Creaven, B. S.; Gernon, T. L.; McGinley, J.; Moore, A.-M.; Toftlund, H. *Tetrahedron* **2006**, *62*, 9066–9071.
(15) Li, Z.-T.; Ji, G.-Z.; Zhao, C.-X.; Yuan, S.-D.; Ding, H.; Huang, C.; Du, A.-L.; Wei, M. *J. Org. Chem.* **1999**, *64*, 3572–3584.
(16) Scheerder, J.; Fochi, M.; Engbersen, J. F. J.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 7815–7820.
(17) Yakovenko, A. V.; Boyko, V. I.; Kalchenko, V. I.; Baldini, L.; Casnati, A.; Sansone, F.; Ungaro, R. *J. Org. Chem.* **2007**, *72*, 3223–3231.
(18) Halouani, H.; Dumazet-Bonnamour, I.; Perrin, M.; Lamartine, R. *J. Org. Chem.* **2004**, *69*, 6521–6527.
(19) Hosseini, A.; Taylor, S.; Accorsi, G.; Armaroli, N.; Reed, C. A.; Boyd, P. D. W. *J. Am. Chem. Soc.* **2006**, *128*, 15903–15913.
(20) Kenis, P. J. A.; Noordman, O. F. J.; Schonherr, H.; Kerver, E. G.; Snellink-Ruel, B. H. M.; van Hummel, G. J.; Harkema, S.; van der Vorst, C. P. J. M.; Hare, J.; Picken, S. J.; Engbersen, J. F. J.; van Hulst, N. F.; Vancso, G. J.; Reinhoudt, D. N. *Chem.—Eur. J.* **1998**, *4*, 1225–1234.
(21) Da Silva, E.; Coleman, A. W. *Tetrahedron* **2003**, *59*, 7357–7364.
(22) Alekseeva, E. A.; Mazepa, A. V.; Gren, A. I. *Russ. J. Gen. Chem.* **2001**, *71*, 1786–1792.
(23) Shu, C.-M.; Chung, W.-S.; Wu, S.-H.; Ho, Z.-C.; Lin, L.-G. *J. Org. Chem.* **1999**, *64*, 2673–2679.
(24) Arnaud-Neu, F.; Caccamese, S.; Fuangswasdi, S.; Pappalardo, S.; Parisi, M. F.; Petringa, A.; Principato, G. *J. Org. Chem.* **1997**, *62*, 8041–8048.
(25) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325–4342.
(26) Groenen, L. C.; Ruel, B. H. M.; Casnati, A.; Verboom, W.; Pochini, A.; Ungaro, R.; Reinhoudt, D. N. *Tetrahedron* **1991**, *47*, 8379–8384.
(27) Shang, S.; Khasnis, D. V.; Burton, J. M.; Santini, C. J.; Fan, M.; Small, A. C.; Lattman, M. *Organometallics* **1994**, *13*, 5157–5159.
(28) Casnati, A.; Arduini, A.; Ghidini, E.; Pochini, A.; Ungaro, R. *Tetrahedron* **1991**, *47*, 2221–2228.
(29) Matvieiev, Y. I.; Boyko, V. I.; Podoprigorina, A. A.; Kalchenko, V. I. *J. Inclusion Phenom. Macrocyclic Chem.* **2008**, *61*, 89–92.
(30) Floriani, C.; Floriani-Moro, R. *Adv. Organomet. Chem.* **2001**, *47*, 167–233.
(31) Zanotti-Gerosa, A.; Solari, E.; Giannini, L.; Floriani, C.; Re, N.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chim. Acta* **1998**, *270*, 298–311.
(32) Friedrich, A.; Radius, U. *Eur. J. Inorg. Chem.* **2004**, 4300–4316.
(33) Santoyo-Gonzalez, F.; Torres-Pinedo, A.; Sanchez-Ortega, A. *J. Org. Chem.* **2000**, *65*, 4409–4414.
(34) Gong, S.; Wang, W.; Chen, Y.; Meng, L.; Wan, T. *New J. Chem.* **2002**, *26*, 1827–1830.
(35) Espinas, J.; Darbost, U.; Pelletier, J.; Jeanneau, E.; Duchamp, C.; Bayard, F.; Boyron, O.; Broyer, J. P.; Thivolle-Cazat, J.; Basset, J. M.; Taoufik, M.; Bonnamour, I. *Eur. J. Inorg. Chem.* **2010**, 1349–1359.

SCHEME 1[a]



[a]Reagents and conditions: (i) R^1-X, K_2CO_3, acetonitrile, reflux; (ii) $TiCl_4(THF)_2$, toluene, reflux, 48 h; (iii) 1 M HCl, room temperature.

When the difunctionalization step was taken into account, overall yields range from 37 to 64%, except for the monoester **1b** (10%). The reaction of compounds **11a** and **12a** in the same conditions as compounds **1a**−**10a** did not yield the targeted monosubstituted compounds, and a total defunctionalization occurs, leading to the formation of *p-tert*-butylcalix[4]arene.

The ^{1}H NMR spectra of all of these monosubstituted calix[4]arenes exhibit two signals for phenolic protons in the range of of 8.6−10.3 ppm, integrating, respectively, 2:1, a W plan coupling ($J \sim 2.5$ Hz) for the aromatic protons of the phenolic units close to the substituted one, two pairs of AB-type signals between 4.2 and 4.6 ppm and between 3.3 and 3.6 ppm ($J \sim 13$ Hz) corresponding to the two sets of ArCH_2Ar protons (see Supporting Information). The ^{13}C NMR spectra display signals between 32 and 35 ppm attributed to the methylene bridge (ArCH_2Ar), consistent with the calixarene being in cone conformation.[36] All of the NMR spectra are given in the Supporting Information (Figures S1−S39).

Mechanism Study. According to the results obtained in the literature with the monomethoxy calixarene,[31,32] we expected that the mechanism of the reaction involves the formation of the two successive titana−calix[4]arenes complexes (**13** and **14**) (Scheme 2). During the reaction, two distinct colors of the mixture were clearly observed: A first dark red one appears at room temperature just after the addition of the titanium tetrachloride into the disubstituted calix[4]arene solution. After refluxing the mixture, a second orange coloration of the solution is observed. We assumed that the first coloration was the result of the formation of the bis-*O*-functionalized titana−calix[4]arene complex **13**; this complex then probably undergoes the defunctionalization of one of the oxygen atoms, leading to the resulting mono-*O*-functionalized titana−calix[4]arene complex **14**. After an acidic hydrolysis, **14** would lead to the corresponding mono-*O*-functionalized calix[4]arene.

With the aim to demonstrate this postulate, we undertook the study of the reaction mechanism through the synthesis of compound **2a**. At first, we synthesized, isolated, and characterized titanium complexes **2a-Ti** and **2b-Ti** (Scheme 3). In the second time, we investigated, by ^{1}H NMR monitoring of the reaction, the formation of the different species. In order to detect the fragment of defunctionalization, GC/MS analysis was also realized.

TABLE 1. Yields and Overall Yields of Monofunctionalized *p-tert*-Butylcalix[4]arenes

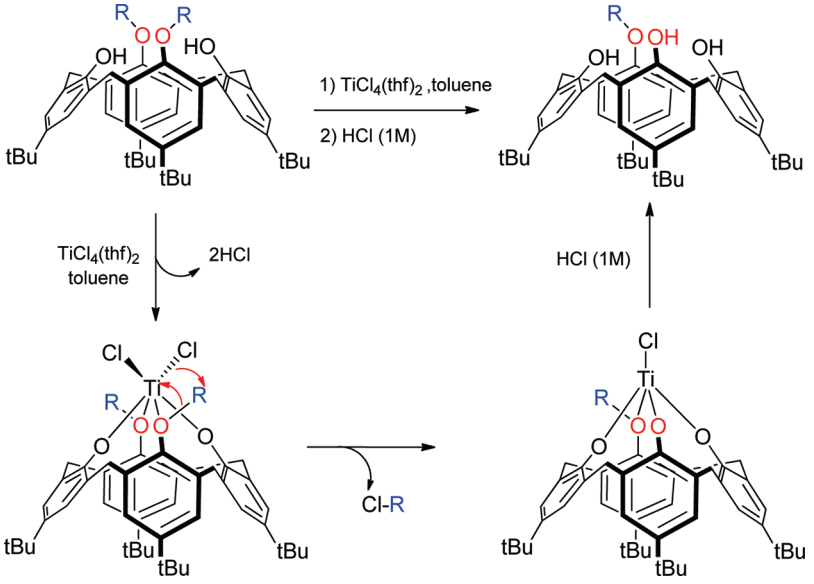
R	R^1	compounds	yield (%)	overall yield (%)
t-Bu	CH_2COOEt	**1b**	15	10
t-Bu	$(CH_2)_3COOEt$	**2b**	75	64
t-Bu	CH_2CN	**3b**	58	37
t-Bu	$(CH_2)_3CN$	**4b**	60	44
t-Bu	$(CH_2)_4Br$	**5b**	85	60
t-Bu	$(CH_2)_3OH$	**6b**	70	63
t-Bu	$(CH_2)_2CH_3$	**7b**	77	47
t-Bu	$CH_2CH(CH_3)_2$	**8b**	57	47
t-Bu	$(CH_2)_2CCH$	**9b**	78	63
H	CH_2CN	**10b**	53	40

Synthesis of Titanium Complexes. 1,3-Dioxotitanium complex **2a-Ti** was synthesized by stirring the calixarene diester derivative **2a** with titanium tetrachloride in dry toluene for more than 1 h at 40 °C and then isolating the complex (Scheme 3a). This titanium complex **2a-Ti**, by refluxing in dry toluene for more than 50 h, evolves into trioxotitanium complex **2b-Ti** (Scheme 3b).

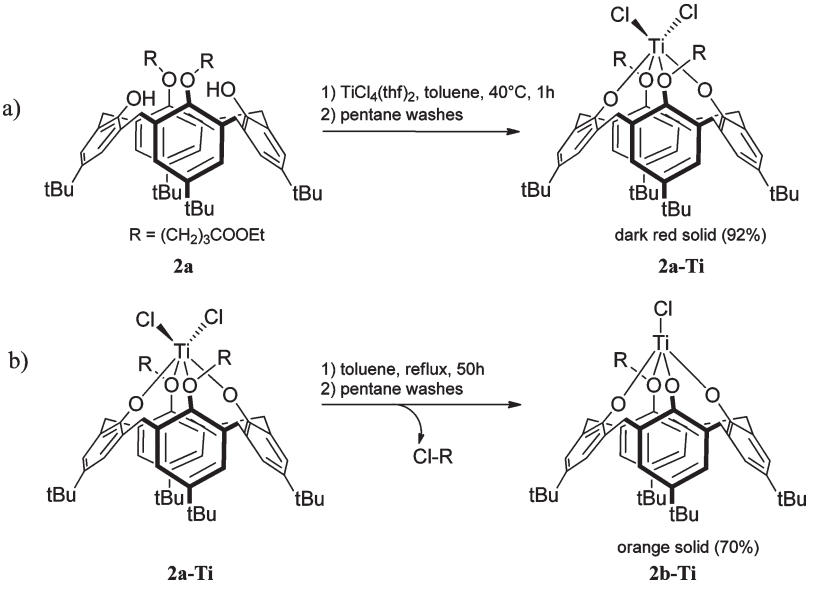
Characterization. In order to determine the conformation of the different species **2a**, **2b**, **2a-Ti**, and **2b-Ti**, an exhaustive ^{1}H NMR study was realized (spectra **a**−**d**, Figure 1). Compared to the free ligands **2a** and **2b**, the ^{1}H NMR spectra of the corresponding Ti complexes **2a-Ti** and **2b-Ti** display several relevant differences (Figure 1). ^{1}H NMR spectra of **2a** and **2a-Ti** (Figure 1c,d) show an AB system for the bridging CH_2 protons ($J_{H-H} \sim 13$ Hz) characteristic of a C_{2v} symmetry, consistent with the calixarene being in cone conformation. However, in the case of complex **2a-Ti**, compared with **2a**, it should be emphasized that axial CH_2 (4.78 ppm) is downfield shifted ($\Delta\delta = +0.41$ ppm) and equatorial CH_2 (3.25 ppm) is upfield shifted ($\Delta\delta = -0.11$ ppm). This different NMR signature is probably due to a rearrangement of the calixarene skeleton. Indeed, to coordinate the metallic Ti center, the oxygen atoms of **2a-Ti** are attracted toward the central axis of the cavity, consequently constraining the calixarene structure in a more flattened cone conformation. This phenomenon has clearly been demonstrated by the X-ray structures of parent Ti complexes in the literature.[30,32,35]

(36) Jaime, C.; De Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372–3376.

SCHEME 2. Proposed Mechanism for the Formation of Monosubstituted Calix[4]arenes



SCHEME 3. Synthesis of Titanium Complexes 2a-Ti and 2b-Ti



Moreover, compared with the ^{1}H NMR spectra of free ligand **2a**, the spectra of **2a-Ti** show a significant downfield shift ($\Delta\delta$) of the α protons (Ar-OCH_2) of the alkoxy chains ($\Delta\delta$ = +1.21 ppm), indicating that the two oxygen atoms of the alkoxy chains participate as ancillary ligands in the coordination with the titanium atom. An upfield shift of CH_2CO protons ($\Delta\delta$ = −1.22 ppm) is also observed, which can be attributed to both the electron-attracting nature of the titanium atom and the anisotropic effect due to the calixarene cavity and the chlorine atoms, as observed in a recently reported study.[35] ^{1}H NMR spectra of **2b** and **2b-Ti** (Figure 1a,b) show two AB systems for the bridging CH_2 protons ($J_{H-H} \sim 13$ Hz) typical of a C_s cone conformation. In the case of the complex **2b-Ti**, the strong flattening of the calixarene core induces a significant downfield shift ($\Delta\delta$ = +0.52 ppm) for one of the AB systems of the bridging axial CH_2 protons. Compared with the free ligand **2b**, the ^{1}H NMR spectra of **2b-Ti** show, as observed between **2a** and **2a-Ti**, a significant downfield shift ($\Delta\delta$) of the α protons (Ar-OCH_2) of the alkoxy chain ($\Delta\delta$ = +0.49 ppm) and an upfield shift of CH_2CO protons ($\Delta\delta$ = −0.57 ppm). As confirmed by the value of the shift (chemical-induced shift), the electron-attracting nature of the titanium is conducted through the carbon chain and is experienced by the terminal protons of the ester group ($\Delta\delta$ = −0.2 and −0.08 ppm for OCH_2 of **2a-Ti** and **2b-Ti**, respectively, and $\Delta\delta$ = −0.09 and −0.05 ppm for OCH$_2$CH_3 of **2a-Ti** and **2b-Ti**, respectively). These original electronic features were recently reported for Ti complexes.[35]

NMR Monitoring. To highlight the formation of the two complexes **2a-Ti** and **2b-Ti** during the reaction, ^{1}H NMR monitoring was undertaken (Figure 2) in toluene-d_8. The

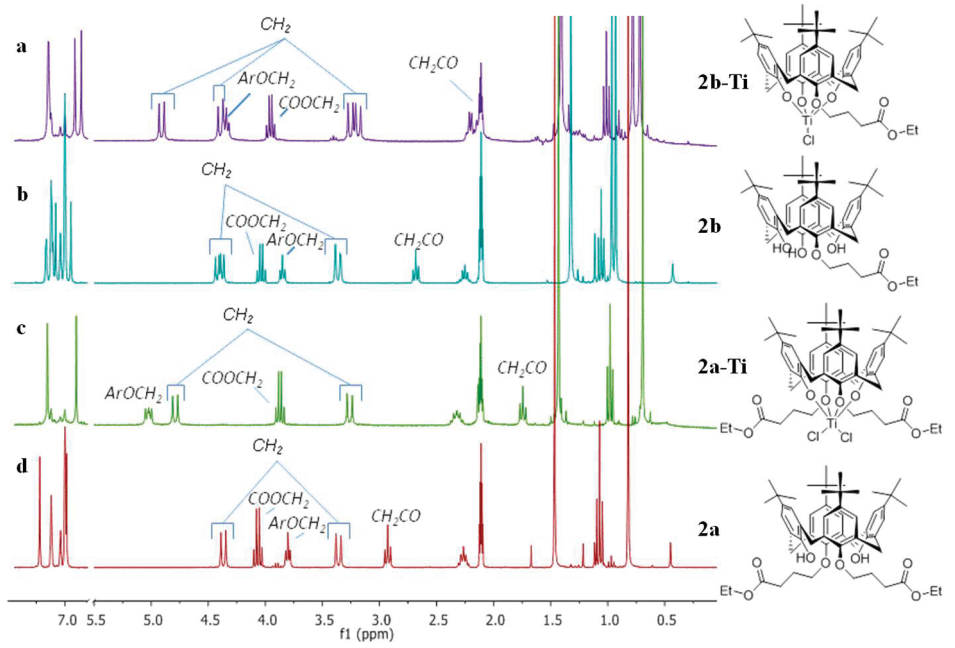


FIGURE 1. ^{1}H NMR spectra of compounds **2b-Ti** (a), **2b** (b), **2a-Ti** (c), **2a** (d): data were collected on a 300 MHz spectrometer using toluene-d_8 as a solvent.

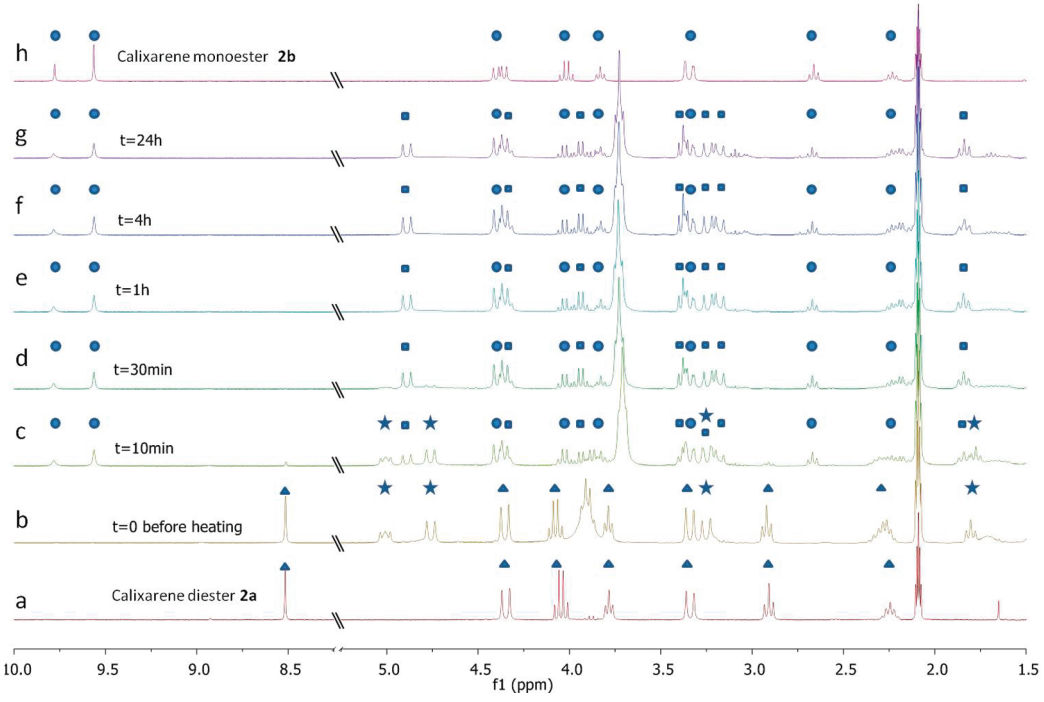


FIGURE 2. ^{1}H NMR monitoring of the reaction: data were collected on a 300 MHz spectrometer using toluene-d_8 as a solvent: proton peaks of compounds (▲) **2a**, (★) **2a-Ti**, (■) **2b-Ti**, and (●) **2b**.

previous experiments of characterization allowed us to carefully attribute all of the ^{1}H NMR signals from each species. In the first minutes of the reaction and before heating, the complex **2a-Ti** appears spontaneously (Figure 2b). After 10 min of refluxing, the ligand **2a** has disappeared and the complexes **2a-Ti** and **2b-Ti** coexist with compound **2b** (Figure 2c). After 24 h, **2a-Ti** has completely disappeared and only the mono-*O*-alkylated products **2b-Ti** and **2b** are present in solution (Figure 2g), consistent with the total conversion of the complex **2a-Ti** in the complex **2b-Ti** through defunctionalization under reflux conditions.

During the ^{1}H NMR monitoring, we also observed the appearance of ethyl 4-chlorobutyrate signals corresponding to the elimination product (Figure 3a). A GC/MS analysis of the reaction mixture after 24 h heating confirms the presence of this compound (Figure 3b). The formation of the chloroester during the reaction is consistent with the proposed mechanism of monodefunctionalization.

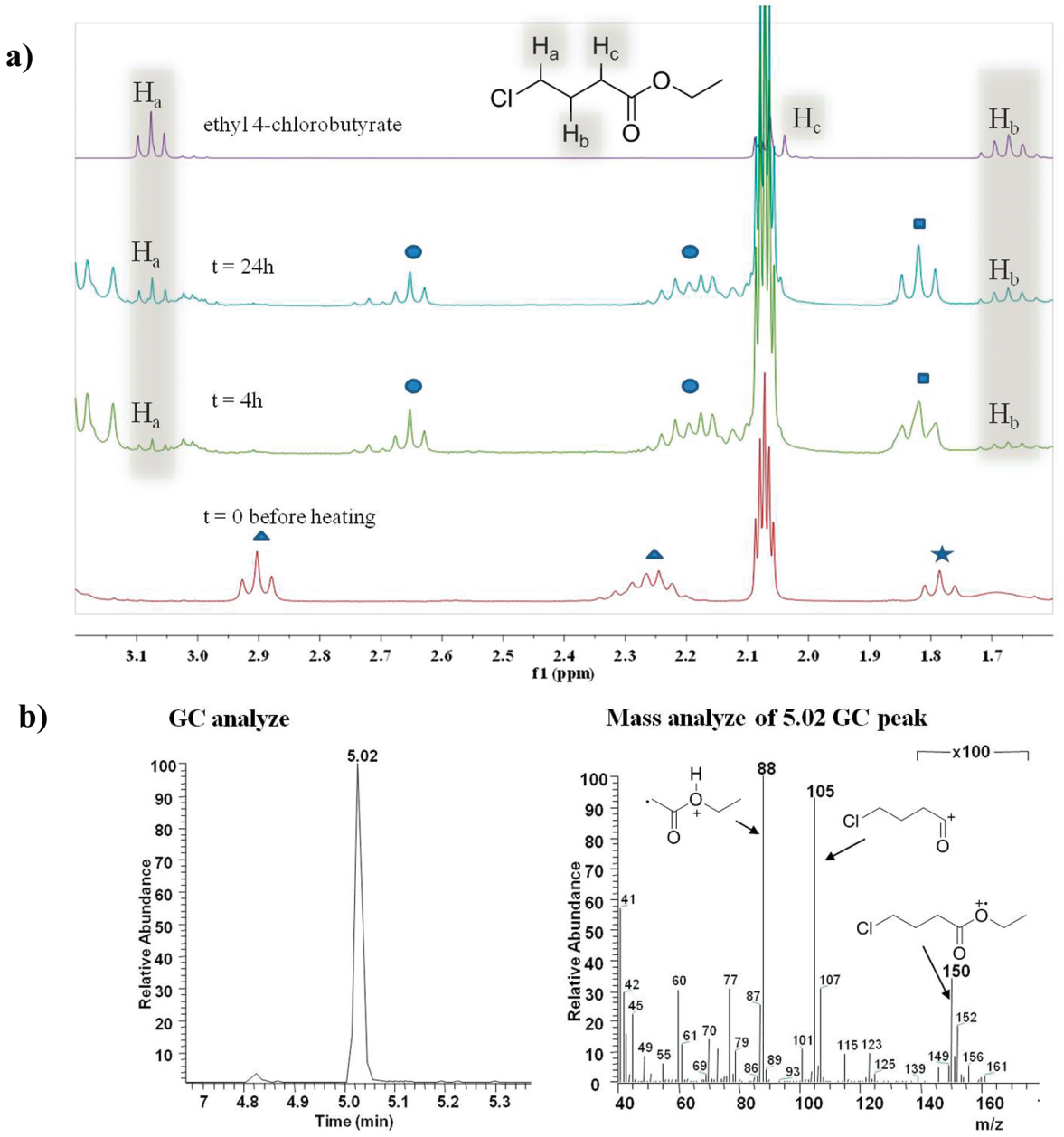


FIGURE 3. (a) ^{1}H NMR monitoring of the ethyl 4-chlorobutyrate formation. Data were collected on a 300 MHz spectrometer using toluene-d_8 as a solvent. (b) GC/MS analysis after 24 h refluxing.

Discussion. Complete characterizations of each ligand and complex allow identification with certitude of the formation and the disappearance of each species during the reaction process. In the presence of titanium tetrachloride, compound **2a** leads spontaneously to the complex **2a-Ti**. This MO_2Cl_2-$(OR)_2$-type complex displays a sterically strained structure in which the tetrahedral Ti is coordinated by four L ligands (two oxygens and two chlorine atoms) and two ancillary ligands (OR). When the mixture is heated under toluene reflux, it has clearly been demonstrated that complex **2a-Ti** undergoes a σ bond metathesis between a Ti−Cl and an O−R bond with R−Cl evolution and consequently leads to the more constrained $MO_3Cl(OR)_1$ complex **2b-Ti** due to the proximity between the pendant groups and the titanium center imposed by the calixarene core. In these conditions, the system possesses enough energy to pass the highly instable transition state and lead to a more electronically stable complex **2b-Ti**, a species less favored than **2a-Ti** in a conformational point of view. This behavior clearly emphasizes that the driving force is the coordination of the metal and particularly the oxophilic feature of titanium. This oxophilic feature of titanium can also explain the low yield of compound **1b**. It seems that the presence of oxygen atoms of ethoxycarbonylmethyloxy groups, which are very close to other phenolic oxygens, obstructs the reaction. This is probably due to the stabilization of the bis-*O*-ethoxycarbonylmethyloxy titana−calix[4]arene complex by two bonds between the titanium center and the carbonyl groups, preventing the de-*O*-alkylation. Moreover, in the case of the reaction of compounds **11a** and **12a**, bearing, respectively,

benzyl and 2-naphthylmethyloxy pendant groups, a complete defunctionalization is observed and *p-tert*-butylcalix[4]arene is quantitatively obtained. This is probably due to the higher reactivity of the OCH_2Ph and OCH_2(2-naphthyl) carbon atoms compared to the other OCH_2 carbon atoms of pendant groups used, leading to the complete de-*O*-functionalization rather than the mono-de-*O*-functionalization. It should be emphasized that $TiCl_4$ could also be used as reagents for complete de-*O*-benzylation of calixarene.

Conclusion

The synthesis of a range of monofunctionalized calix[4]arene derivatives and two titanium calixarene complexes has been achieved in honorable yields. ^{1}H NMR and GC−mass spectroscopy monitoring of the reaction has allowed us to clearly establish the reaction mechanism. The impressive force of the oxophilic nature of titanium has been used here as an efficient synthesis tool for the preparation of seven new monosubstituted calix[4]arenes. These series of monofunctionalized *p-tert*-butylcalix[4]arenes with different kinds of functions such as haloalkane, nitrile, alcohol, ester, and alkyne are key intermediates for the elaboration of heterofunctionalized calixarenes.

Experimental Section

Materials. Solvents were purified and dried by standard methods prior to use. All reactions were carried out under nitrogen. Column chromatography was performed using silica gel (0.040−0.063 nm). Reactions were monitored by TLC on silica gel plates and visualized by UV light. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz ($CDCl_3$). Mass spectra were acquired on a LCQ Advantage ion trap instrument, detecting positive ions (+) or negative ions (-) in the ESI mode. Samples (in methanol-dichloromethane-water, 45: 40: 15, v/v/v) were infused directly into the source (5 mL.min^{-1}) using a syringe pump. The following source parameters were applied: spray voltage 3.0−3.5 kV, nitrogen sheath gas flow 5−20 arbitrary units. The heated capillary was held at 200 °C. Compounds **1a**,[9] **2a**,[17] **3a**[9] **4a**,[13] **5a**,[15] **6a**,[19] **7a**,[12] **8a**,[20] **10a**,[18] **11a**,[37] **12a**[38] were prepared according to literature procedures.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-25,26-bis(but-3-ynyloxy)-27,28-dihydroxycalix[4]arene (9a). To a suspension of tetra-*tert*-butylcalix[4]arene (2.5 g, 3.85 mmol) and potassium carbonate (1.330 g, 9.62 mmol) in dry acetonitrile (70 mL) was added 4-bromobut-1-yne (2.138 g, 16.2 mmol), and the reaction mixture was refluxed for 17 h. After cooling, the solvent was removed and the colorless suspension was quenched with HCl (2 M, 30 mL) and extracted with dichloromethane (2 × 40 mL). The organic layer was washed with water (2 × 40 mL) and brine (50 mL) and then dried over anhydrous $MgSO_4$. Column chromatography of the crude (heptane/ethyl acetate 8:2) gave **9a** (49%) as a white solid: mp 228−230 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (s, 18H, ^{t}Bu), 1.31 (s, 18H, ^{t}Bu), 2.08 (t, 2H, J = 2.6 Hz, CC*H*), 2.90 (td, 4H, J_1 = 2.6 Hz, J_2 = 7.1 Hz, CH_2-CCH), 3.33 (d, 4H, J = 13.0 Hz, CH_2), 4.13 (t, 4H, J = 7.1 Hz, O-CH_2), 4.32 (d, 4H, J = 13.0 Hz, CH_2), 6.80 (s, 4H, Ar-*H*), 7.07 (s, 4H, Ar-*H*), 7.08 (s, 2H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 31.4, 32.1, 32.1, 34.2, 34.3, 70.7, 74.2, 80.9, 125.5, 126.0, 128.2, 132.9, 141.9, 147.4, 149.9, 151.0; LRMS (ES$^+$) m/z 775.4 ([M + Na]$^+$); HRMS (ES$^+$) for $C_{50}H_{66}O_6Na^+$, calcd 775.4702, found 775.4697; IR (FTIR) ν = 3411, 3320, 2955, 2869, 2123, 2050, 1485, 1194, 1032, 869 cm^{-1}.

General Procedure for the Preparation of Monofunctionalized Calix[4]arene Derivatives. Corresponding di-*O*-substituted calixarene (1 equiv) and $TiCl_4 \cdot 2THF$ (1.5 equiv) were refluxed for 2 days in dry toluene. After cooling to room temperature, the reaction mixture was quenched with 1 M HCl for 2−10 h. The organic layer was washed with water and dried with $MgSO_4$. After evaporation of the solvent, the remaining crude product was taken up in MeOH or was purified by column chromatography.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-25-ethoxycarbonylmethyloxy-26,27,28-trihydroxycalix[4]arene (1b). Column chromatography of the crude (heptane/ethyl acetate 8:2) gave **1b** (15%) as a white solid: mp 248−250 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.21 (s, 9H, ^{t}Bu), 1.22 (s, 18H, ^{t}Bu), 1.25 (s, 9H, ^{t}Bu), 1.41 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.44 (d, 4H, J = 13.6 Hz, CH_2), 4.32 (d, 2H, J = 13.6 Hz, CH_2), 4.42 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 4.50 (d, 2H, J = 13.2 Hz, CH_2), 4,90 (s, 2H, OCH_2), 7.00 (d, 2H, J = 2.3 Hz, *H*-Ar), 7.07 (m, 4H, *H*-Ar), 7.11 (s, 2H, *H*-Ar), 9.27 (s, 2H, O*H*), 10.24 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 30.9, 31.3, 31.6, 32.6, 33.0, 34.0, 34.1, 34.3, 62.0, 72.1, 125.7, 125.8, 125.9, 126.7, 127.8, 128.1, 128.1, 133.4, 143.3, 143.6, 147.8, 148.2, 148.5, 150.1, 169.7; LRMS (ES$^+$) m/z 735.3 ([M + H]$^+$); HRMS (ES$^+$) for $C_{48}H_{62}O_6Na^+$, calcd 757,4446, found 757.4446; IR (FTIR) ν = 3349, 2955, 2865, 17404, 1484, 1191, 1065, 872, 784 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-(3-ethoxycarbonylpropyloxy)calix[4]arene (2b). The crude product was triturated in methanol to give **2b** (83%) as a white solid: mp 200−202 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H, ^{t}Bu), 1.21 (s, 18H, ^{t}Bu), 1.23 (s, 9H, ^{t}Bu), 1.30 (t, 3H, J = 7.2 Hz, CH_2CH_3), 2.40−2.50 (m, 2H, CH_2-CH_2-CH_2), 2.83 (t, 2H, J = 7.2 Hz, CH_2CO), 3.42 (d, 2H, J = 13.0 Hz, CH_2), 3.44 (d, 2H, J = 13.7 Hz, CH_2), 4.17 (t, 2H, J = 6.3 Hz, OCH_2), 4.21 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 4.27 (d, 2H, J = 13.7 Hz, CH_2), 4.32 (d, 2H, J = 13.0 Hz, CH_2), 6.99 (d, 2H, J = 2.6 Hz, *H*-Ar), 7.05 (s, 2H, *H*-Ar), 7.06 (d, 2H, J = 2.6 Hz, *H*-Ar), 7.08 (s, 2H, *H*-Ar), 9.50 (s, 2H, O*H*), 10.12 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4, 25.4, 30.8, 31.4, 31.6, 31.6, 32.3, 33.1, 34.1, 34.2, 34.4, 60.7, 76.2, 125.8, 125.8, 125.9, 126.6, 127.6, 128.1, 128.5, 133.6, 143.3, 143.8, 147.8, 148.4, 148.6, 149.2, 173.3; LRMS (ES$^+$) m/z 785.4 ([M + Na]$^+$); HRMS (ES$^+$) for $C_{50}H_{66}O_6Na^+$, calcd 785.4757, found 785.4757; IR (FTIR) ν = 3331, 3174, 2961, 1740, 1482, 1179, 1006, 871 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-25-cyanomethyloxy-26,27,28-trihydroxycalix[4]arene (3b). Column chromatography of the crude (heptane/ethyl acetate 8:2) gave **3b** (58%) as a white solid: mp 252−254 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 9H, ^{t}Bu), 1.22 (s, 18H, ^{t}Bu), 1.22 (s, 9H, ^{t}Bu), 3.46 (d, 2H, J = 13.8 Hz, CH_2), 3.53 (d, 2H, J = 13.4 Hz, CH_2), 4.24 (d, 2H, J = 13.8 Hz, CH_2), 4.33 (d, 2H, J = 13.4 Hz, CH_2), 5.00 (s, 2H, CH_2CN), 7.02 (d, 2H, J = 2.4 Hz, *H*-Ar), 7.05 (s, 2H, *H*-Ar), 7.07 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.11 (s, 2H, *H*-Ar), 8.67 (s, 2H, O*H*), 9.75 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) 31.2, 31.6, 31.6, 32.5, 32.9, 34.1, 34.2, 34.5, 60.4, 114.9, 125.8, 125.9, 126.2, 127.3, 127.5, 127.5, 128.2, 133.0, 143.6, 143.9, 147.5, 148.4, 149.8; LRMS (ES$^+$) m/z 688.2 ([M + H]$^+$); HRMS (ES$^+$) for $C_{45}H_{57}NO_4Na^+$, calcd 710,4185, found 710.4185; IR (FTIR) ν = 3260, 2953, 2901, 2865, 1483, 1362, 1203, 1006, 872, 782 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-(3-cyanopropyloxy)calix[4]arene (4b). Column chromatography of the crude (heptane/ethyl acetate 9:1) gave **4b** (60%) as a white solid: mp 171−173 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 9H, ^{t}Bu), 1.21 (s, 18H, ^{t}Bu), 1.22 (s, 9H, ^{t}Bu), 2.36−2.46 (m, 2H, CH_2-CH_2-CH_2), 3.05 (t, 2H, J = 6.9 Hz, CH_2CN), 3.44 (d, 2H, J = 13.8 Hz, CH_2), 3.47 (d, 2H, J = 12.9 Hz,

(37) Gutsche, C. D.; Reddy, P. A. *J. Org. Chem.* **1991**, *56*, 4783–4791.
(38) Stoikov, I. I.; Khrustalev, A. A.; Antipin, I. S.; Konovalov, A. I. *Dokl. Akad. Nauk* **2000**, *374*, 202–205.

CH_2), 4.23 (t, 2H, J = 6.1 Hz, OCH_2), 4.25 (d, 2H, J = 14.3 Hz, CH_2), 4.26 (d, 2H, J = 13.2 Hz, CH_2), 7.00 (d, 2H, J = 2.3 Hz, *H*-Ar), 7.05 (s, 2H, *H*-Ar), 7.07 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.09 (s, 2H, *H*-Ar), 9.36 (s, 2H, O*H*), 10.02 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 26.3, 31.3, 31.6, 31.6, 32.2, 33.0, 34.0, 34.2, 34.4, 74.4, 119.4, 125.8, 125.9, 126.0, 126.8, 127.4, 127.9, 128.4, 133.4, 143.5, 143.9, 147.5, 148.5, 148.7, 148.8; LRMS (ES^+) m/z 716.2 ($[M + H]^+$); HRMS (ES^+) for $C_{48}H_{61}NO_4Na^+$, calcd 738.4498, found 738.4499; IR (FTIR) ν = 3260, 2957, 2901, 2856, 1483, 1201 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-(4-bromobutyloxy)calix[4]arene (5b). Column chromatography of the crude (heptane/ethyl acetate 9:1) gave **5b** (85%) as a white solid: mp 168−171 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H, ^{t}Bu), 1.22 (s, 18H, ^{t}Bu), 1.24 (s, 9H, ^{t}Bu), 2.27−2.38 (m, 4H, CH_2-CH_2-CH_2-CH_2), 3.44 (d, 2H, J = 13.0 Hz, CH_2), 3.46 (d, 2H, J = 13.8 Hz, CH_2), 3.65 (t, 2H, J = 6.1 Hz, CH_2Br), 4.17 (t, 2H, J = 6.1 Hz, OCH_2), 4.28 (d, 2H, J = 13.8 Hz, CH_2), 4.33 (d, 2H, J = 13.0 Hz, CH_2), 7.00 (d, 2H, J = 2.3 Hz, *H*-Ar), 7.06 (s, 2H, *H*-Ar), 7.07 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.10 (s, 2H, *H*-Ar), 9.52 (s, 2H, O*H*), 10.13 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.6, 29.2, 31.4, 31.6, 31.6, 32.4, 33.1, 33.6, 34.0, 34.2, 34.4, 76.1, 125.8, 125.9, 125.9, 126.6, 127.7, 128.1, 128.4, 133.5, 143.3, 143.8, 147.8, 148.4, 148.6, 149.3; LRMS (ES^+) m/z 783.4 ($[M + H]^+$); HRMS (ES^+) for $C_{48}H_{63}BrO_4Na^+$, calcd 805.3809, found 805.3809; IR (FTIR) ν = 3296, 2955, 2901, 2865, 1483, 1362, 1200, 872, 782 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-(3-hydroxypropyloxy)calix[4]arene (6b). Column chromatography of the crude (heptane/ethyl acetate 7:3) gave **6b** (70%) as a white solid: mp 98−100 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 9H, ^{t}Bu), 1.22 (s, 18H, ^{t}Bu), 1.23 (s, 9H, ^{t}Bu), 2.24−2.32 (m, 4H, CH_2-CH_2-CH_2), 3.46 (d, 4H, J = 13.4 Hz, CH_2), 3.54 (t, 1H, J = 5.0 Hz, -O*H*), 4.17 (m, 2H, CH_2OH), 4.27 (d, 2H, J = 13.4 Hz, CH_2), 4.28 (t, 2H, J = 6.0 Hz, O-CH_2), 4.31 (d, 2H, J = 12.8 Hz, CH_2), 7.00 (d, 2H, J = 2.3 Hz, *H*-Ar), 7.06 (s, 2H, *H*-Ar), 7.08 (d, 2H, J = 2.4 Hz, *H*-Ar), 7.09 (s, 2H, *H*-Ar), 9.77 (s, 2H, O*H*), 10.25 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.4, 31.6, 31.6, 31.9, 32.3, 33.1, 34.1, 34.2, 34.4, 58.9, 73.9, 125.9, 125.96, 126.7, 127.6, 128.1, 128.4, 133.5, 143.6, 143.9, 147.6, 148.2, 148.5, 149.0; LRMS (ES^+) m/z 729.5 ([M + Na]$^+$); HRMS (ES^+) for $C_{48}H_{64}O_5Na^+$, calcd 729.4495, found 729.4496; IR (FTIR) ν = 3188, 2953, 2869, 1483, 1362, 1203, 1047, 872, 782 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-25-propyloxy-26,27,28-trihydroxycalix[4]arene (7b). Column chromatography of the crude (heptane/ethyl acetate 95:5) gave **7b** (77%) as a white solid: mp 228−230 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H, ^{t}Bu), 1.22 (s, 18H, ^{t}Bu), 1.23 (s, 9H, ^{t}Bu), 1.26 (t, 3H, J = 4.4 Hz, CH_3), 2.13−2.26 (m, 2H, CH_2-CH_2-CH_3), 3.42 (d, 2H, J = 13.0 Hz, CH_2), 3.45 (d, 2H, J = 13.8 Hz, CH_2), 4.11 (t, 2H, J = 7.0 Hz, O-CH_2), 4.29 (d, 2H, J = 13.7 Hz, CH_2), 4.37 (d, 2H, J = 13.0 Hz, CH_2), 7.00 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.06 (s, 2H, *H*-Ar), 7.07 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.10 (s, 2H, *H*-Ar), 9.62 (s, 2H, O*H*), 10.21 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.8, 23.4, 31.4, 31.6, 31.6, 32.4, 33.2, 34.1, 34.1, 34.4, 79.0, 125.8, 125.8, 125.9, 126.5, 127.8, 128.3, 128.5, 133.7, 143.2, 143.7, 147.9, 148.2, 148.6, 149.5; LRMS (ES^+) m/z 713.5 ([M + Na]$^+$); HRMS (EI) for $C_{47}H_{62}O_4^+$, calcd 690.4648, found 690.4648; IR (FTIR) ν = 3324, 3169, 2956, 2870, 1484, 1362, 1203, 872, 782 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy25-(2-methylpropyloxy)calix[4]arene (8b). Column chromatography of the crude (heptane/ethyl acetate 95:5) gave **8b** (57%) as a white solid: mp 154−156 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.22 (s, 9H, ^{t}Bu), 1.25 (s, 18H, ^{t}Bu), 1.26 (s, 9H, ^{t}Bu), 1,30 (d, 6H, J = 6.6 Hz), 2.45−2.59 (m, 1H, C*H*-$(CH_3)_2$), 3.44 (d, 2H, J = 13.0 Hz, CH_2), 3.47 (d, 2H, J = 13.8 Hz, CH_2), 3.91 (d, 2H, J = 6.6 Hz, O-CH_2), 4.31 (d, 2H, J = 13.8 Hz, CH_2), 4.39 (d, 2H, J = 13.0 Hz, CH_2), 7.02 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.08 (s, 2H, *H*-Ar), 7.10 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.11 (s, 2H, *H*-Ar), 9.57 (s, 2H, O*H*), 10.19 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9, 29.3, 31.4, 31.6, 31.7, 32.2, 33.2, 34.0, 34.2, 34.4, 84.5, 125.8, 125.8, 125.9, 126.6, 127.5, 128.2, 128.6, 133.5, 143.2, 143.8, 147.8, 148.1, 148.8, 149.6; LRMS (ES^+) m/z 727.4 ([M + Na]$^+$); HRMS (ES^+) for $C_{48}H_{65}O_4^+$, calcd 705.4877, found 705.4864; IR (FTIR) ν = 3306, 3184, 2953,2870, 1482,1203, 1006, 906, 872, 731 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-26,27,28-trihydroxy-25-(3-butynyloxy)calix[4]arene (9b). The crude product was crystallized from methanol to give **9b** (78%) as a white solid: mp 154−156 °C (dec.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.20 (s, 9H, ^{t}Bu), 1.22 (s, 18H, ^{t}Bu), 1.23 (s, 9H, ^{t}Bu), 2.16 (t, 1H, J = 2.3 Hz, C*H*), 3.04 (m, 2H, CH_2-CCH), 3.43 (d, 4H, J = 13.4 Hz, CH_2), 4.27 (d, 2H, J = 13.5 Hz, CH_2), 4.29 (t, 2H, J = 6.1 Hz, O-CH_2) 4.32 (d, 2H, J = 12.9 Hz, CH_2), 7.00 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.05 (s, 2H, *H*-Ar), 7.06 (d, 2H, J = 2.5 Hz, *H*-Ar), 7.09 (s, 2H, *H*-Ar), 9.27 (s, 2H, O*H*), 10.07 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2, 31.4, 31.6, 31.7, 32.4, 33.2, 34.2, 34.1, 34.4_3, 71.0, 74.4, 80.4, 125.8, 125.9, 126.0, 126.7, 127.8, 128.1, 128.5, 133.6, 143.3, 143.8, 147.9, 148.5, 148.6, 149.2; LRMS (ES^+) m/z 723.4 ([M + Na]$^+$); HRMS (ES^+) for $C_{48}H_{60}O_4Na^+$, calcd 723.4389, found 723.4387; IR (FTIR) ν = 3311, 2954, 2901, 2865, 1483, 1361, 1203, 1021, 871 cm^{-1}.

Synthesis of 26,27,28-trihydroxy-25-(3-cyanopropyloxy)calix-[4]arene (10b). Column chromatography of the crude (heptane/ethyl acetate 9:1) gave **10b** (53%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.39−2.49 (m, 2H, CH_2-CH_2-CH_2), 3.08 (t, 2H, J = 6.9 Hz, CH_2CN), 3.49 (d, 2H, J = 13.8 Hz, CH_2), 3.52 (d, 2H, J = 13.2 Hz, CH_2), 4.25 (d, 2H, J = 13.4 Hz, CH_2), 4.25 (t, 2H, OCH_2, 6.2 Hz), 4.28 (d, 2H, J = 13.0 Hz, CH_2), 6.67−6.73 (m, 3H, *H*-Ar), 6.86−7.11 (m, 9H, *H*-Ar), 9.17 (s, 2H, O*H*), 9.52 (s, 1H, O*H*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 26.3, 31.5, 31.9, 74.5, 119.3, 121.2, 122.4, 126.8, 128.6, 128.9, 129.1, 129.7, 128.1, 128.3, 128.7, 133.9, 148.9, 150.7, 150.9; LRMS (ES^-) m/z 492.2 ([M + H]$^+$); HRMS (ES^+) for $C_{32}H_{29}NO_4Na^+$, calcd 514.1994, found 514.1995; IR (FTIR) ν = 3282, 2921, 2876, 1594, 1450, 1190, 1034, 752 cm^{-1}.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-25,27-dioxo-26,28-di-(3-ethoxycarbonylpropyloxy)calix[4]arene titanium(IV) dichloride (2a-Ti). A slurry of compound **2a** (0.302 g, 0.344 mmol) and $TiCl_4 \cdot 2THF$ (0.115 g, 0.344 mmol) in 10 mL of dry toluene was stirred over 1 h at 40 °C. After evaporation of the volatiles, the residue was washed with pentane (5 + 3 mL) and dried under vacuum to provide a dark red solid (0.315 g, 92%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.17 (s, 18H, ^{t}Bu), 1.20 (t, 6H, J = 7.2 Hz, OCH_2CH_3), 1.30 (s, 18H, ^{t}Bu), 2.24−2.40 (m, 8H, CH_2-CH_2-CH_2 + CH_2CO), 3.41 (d, 4H, J = 13.5 Hz, CH_2), 4.07 (q, 4H, J = 7.2 Hz, OCH_2CH_3), 4.49 (d, 4H, J = 13.4 Hz, CH_2), 4.94 (m, 4H, OCH_2), 7.10 (s, 4H, *H*-Ar), 7.11 (s, 4H, *H*-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 23.9, 30.4, 31.7, 31.9, 34.9, 35.1, 61.2, 85.2, 125.2, 128.3, 129.9, 132.6, 145.9, 150.7, 156.1, 165.7, 172.6; LRMS (ES^+) m/z 1015.1 ([M + Na]$^+$); HRMS (ES^+) for $C_{56}H_{74}O_8TiCl_2Na$, calcd 1015.4138, found 1015.4139.

Synthesis of 5,11,17,23-Tetra-*tert*-butyl-25,26,27-trioxo-28-(3-ethoxycarbonylpropyloxy)calix[4]arene titanium(IV) chloride (2b-Ti). Compound **2a-Ti** (0.150 g, 0.151 mmol) in 5 mL of toluene was refluxed for 50 h. After evaporation of the volatiles, the residue was washed with pentane (3 + 3 mL) to provide an orange solid (0.085 g, 70%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.15 (s, 9H, ^{t}Bu), 1.16 (s, 9H, ^{t}Bu), 1.22 (t, 3H, J = 7.2 Hz, CH_2CH_3), 1.26 (s, 18H, ^{t}Bu), 2.25−2.36 (m, 2H, CH_2-CH_2-CH_2), 2.63 (t, 2H, J = 7.0 Hz, CH_2CO), 3.35 (d, 4H, J = 13.8 Hz, CH_2), 4.11 (q, 2H, J = 7.2 Hz, OCH_2CH_3), 4.36 (d, 2H, J = 12.6 Hz, CH_2), 4.48 (t, 2H, J = 6.8 Hz, OCH_2), 4.70 (d, 2H, J = 13.0 Hz, CH_2), 7.05 (s, 2H, *H*-Ar), 7.07 (s, 2H, *H*-Ar), 7.11 (d, 2H, J = 2.3 Hz, *H*-Ar), 7.12 (d, 2H, J = 2.3 Hz, *H*-Ar); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 25.1, 31.5, 31.7,

31.8, 31.9, 33.8, 34.3, 34.6, 34.7, 34.8, 61.9, 79.4, 124.5, 125.6, 125.7, 126.3, 127.9, 130.8, 131.4, 132.9, 146.9, 147.1, 149.0, 152.1, 161.1, 163.3, 174.6; LRMS (EI^+) *m*/*z* 842 ($[M]^+$); HRMS (EI) for $C_{50}H_{63}O_6TiCl^+$, calcd 842.3799, found 842.3799.

GC/MS Analysis of the Ethyl 4-chlorobutyrate Formation. To a solution of **2a** (0.502 g, 0.572 mmol) in dry toluene (50 mL) was added $TiCl_4 \cdot 2THF$ (0,250 g, 0,751 mmol). The reaction mixture was refluxed for 24 h and then distillated to collect toluene and other volatile compounds. Distillate is then analyzed by GC/MS. Details of the GC/MS method are available in Supporting Information.

Acknowledgment. This work was supported by the French Government through the "MATCALCAT" ANR Project (Contract ANR 07-CP2D-21-02) and the pole of competitiveness AXELERA "Chemistry and Environment".

Supporting Information Available: NMR spectra of all new compounds and complexes (Figures S1−S39); GC/MS analysis (Figure S40). This material is available free of charge via the Internet at http://pubs.acs.org.