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# The *p*-Bromodienone Route to Nucleophilic Functionalization of Calixarene *Exo* Rim

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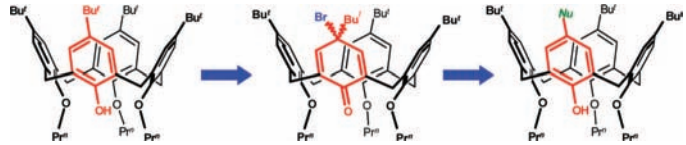
## ABSTRACT



**Easily accessible calixarene *p*-bromodienone derivatives undergo a silver-mediated nucleophilic substitution and a subsequent rearomatization with a range of different *O*-nucleophiles (alcohols and carboxylates) to give *p*-alkoxy- or *p*-acyloxycalixarenes in workable yields. This approach can be considered a general "*p*-bromodienone route" to functionalize calixarene *exo* rim with nucleophiles.**

Over the past two decades, the chemical modification of calixarenes has been largely investigated to change the chemical and supramolecular properties of the parent macrocycles.[1] Among the possible approaches,[2] their functionalization at the *para* position of the aromatic rings (the *upper* or *wide* or *exo rim*)[3] has received considerable attention because it was considered the best way to exploit the preformed calix cavity in recognition processes. The more common paths to introduce new functionalities at the calixarene *exo* rim include a range of electrophilic aromatic substitutions,[4] and the classical "Claisen rearrangement route",[5] "*p*-quinone-methide route",[6] and "*p*-chloromethylation route"[7] devised by Gutsche and Ungaro. Obviously, in all these instances no direct attachment of a nucleophile to the *para* aromatic carbon can be obtained, which, on the other hand, would give access to a range of novel interesting derivatives.

In a previous paper, we anticipated that a possible way to achieve this result is the nucleophilic substitution and the subsequent rearomatization on easily accessible calixarene

(1) For comprehensive reviews on calixarenes, see: (a) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713. (b) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713. (c) Gutsche, C. D. *Calixarenes Revisited*; Royal Society of Chemistry: Cambridge, 1998. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001. (e) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, UK, 2003; Chapter 19. (f) *Calixarenes in the Nanoworld*; Vicens, J., Harrowfield, J., Eds.; Springer: Dordrecht, 2007.

(2) Besides to functionalization at the para positions, these approaches include modification at the lower rim,[2a,b] bridging methylenes,[2c,d] aromatic walls,[2e,f] and meta positions.[2h] For general accounts see ref 1, while for representative or recent examples, see: (a) Gutsche, C. D. *Tetrahedron* **1986**, *42*, 1633. (b) Iwamoto, K.; Araki, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325. (c) Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 2598. (d) Kogan, K.; Columbus, I.; Biali, S. E. *J. Org. Chem.* **2008**, *73*, 7327, and references therein. (e) Troisi, F.; Mogavero, L.; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2007**, *9*, 915. (f) Troisi, F.; Citro, L.; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2008**, *10*, 1393, and references therein. (h) Mascal, M.; Warmuth, R.; Naven, R. T.; Edwards, R. A.; Hursthouse, M. B.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3435.

(3) Gutsche, C. D. *Calixarenes, An Introduction*; Royal Society of Chemistry: Cambridge, UK, 2008, pp 25−26, and following chapters.

(4) The most common electrophilic aromatic substitutions include sulfonation,[4a] acylation,[4b] nitration,[4c] halogenation,[4d] formylation,[4e] and chlorosulfonation.[4f] For general reviews see ref 1, while for representative or recent examples, see: (a) Shinkai, S.; Koreishi, H.; Ueda, K.; Arimura, T.; Manabe, O. *J. Am. Chem. Soc.* **1987**, *109*, 6371. (b) Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633. (c) Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313. (d) Gutsche, C. D.; Pagoria, P. F. *J. Org. Chem.* **1985**, *50*, 5795. (e) Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A. R.; Ugozzoli, F. *J. Org. Chem.* **1995**, *60*, 1448. (f) Casnati, A.; Ting, Y.; Berti, D.; Fabbi, M.; Pochini, A.; Ungaro, R.; Sciotto, D.; Lombardo, G. G. *Tetrahedron* **1993**, *49*, 9815.

(5) Gutsche, C. D.; Levine, J. *J. Am. Chem. Soc.* **1982**, *104*, 2652.

(6) Gutsche, C. D.; Nam, K. C. *J. Am. Chem. Soc.* **1998**, *110*, 6153.

(7) Almi, M.; Arduini, A.; Casnati, A.; Pochini, A.; Ungaro, R. *Tetrahedron* **1989**, *45*, 2177.

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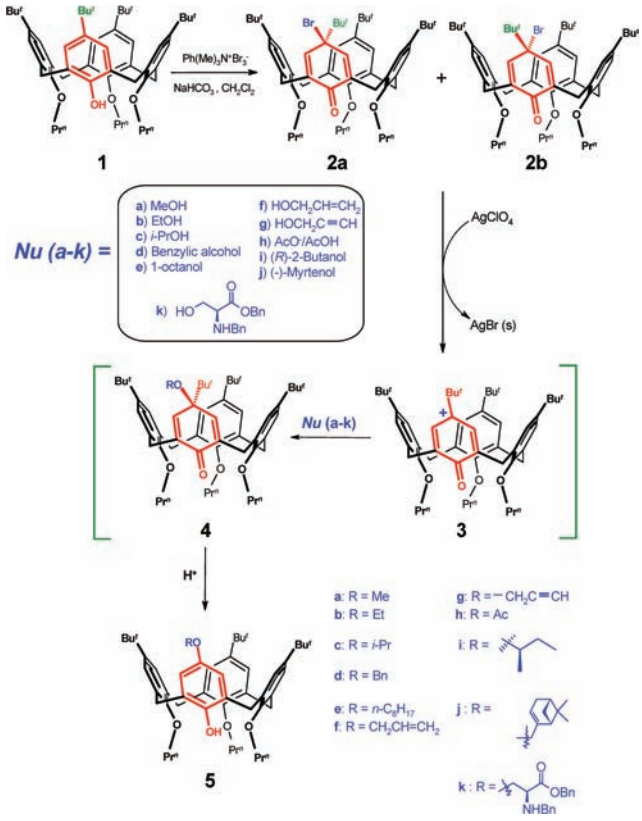
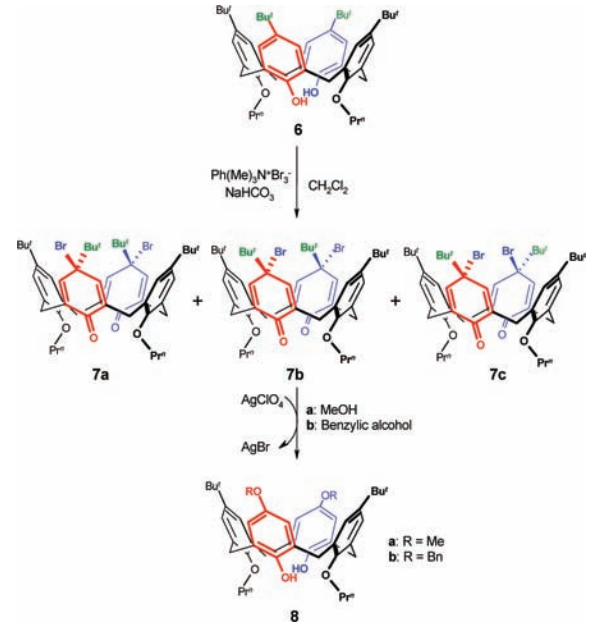
**Scheme 1**




**Scheme 2**




*p*-bromodienone derivatives (exemplified by **2a**,**b** in Scheme 1) recently reported by us.[8] Here, we wish to report on a study on these reactions, which can be considered as a general "*p*-bromodienone route" to functionalize the calixarene *exo* rim with nucleophiles.[9]

The first examples of calixarene *p*-bromodienones were unexpectedly obtained,[8] in good yields, under conditions usually used for the preparation of monospirodienones,[10] by treatment of the appropriate substrate with trimethylphenylammonium tribromide and a saturated solution of $NaHCO_3$ (Scheme 1). Alternatively, they can also be prepared by using $Br_2$/AcOH as brominating agent.[11] The results of our studies[8] showed that calixarene *p*-bromodienones are of general accessibility when isolated, *nonproximal*, phenol rings are present in the starting macrocycle.[8]

To verify the feasibility of nucleophilic substitution of bromine on calixarene *p*-bromodienones we tested the silver ion mediated displacement with alcohols reported by Omura for 4-bromo-2,6-di-*tert*-butylcyclohexa-2,5-dienone.[12] Thus, the *exo* stereoisomer of *p*-bromodienone-tripropoxycalix[4]arene **2a**, selectively obtainable in 81% yield from tripropoxy-*p*-*tert*-butylcalix[4]arene **1** (Scheme 1),[8] was treated with a methanolic solution of $AgClO_4$ for 2 h at 0 °C. Soon after the addition, a yellow precipitate of AgBr was formed.[13] Column chromatography on silica gel of the reaction mixture unexpectedly afforded *p*-methoxycalix[4]arene derivative **5a** in 60% yield with respect to **2a** (Table 1, entry 1).[13,14]

The structure of **5a** was easily assigned by means of spectral analysis. In particular, the presence of a pseudomolecular ion peak at *m*/*z* 749 in the ESI(+) mass spectrum confirmed the molecular formula. The $C_s$ symmetry was confirmed by pertinent signals in the $^1$H and $^{13}$C NMR spectra. In particular, two 2:1 *tert*-butyl singlets at 0.86 and 0.94 ppm, respectively, and one OMe signal at 3.79 ppm were a clear evidence of the displacement of a *t*-Bu group by a methoxyl one, while bromine was precipitated as AgBr.[13] The absence of dienone resonances both in $^1$H and $^{13}$C NMR spectra and the presence of the pertinent aromatic ones were a clear proof of the rearomatization of dienone system. Obviously, this was also confirmed by the disappearance of the typical dienone yellow color and by UV measurements. Clearly, the complication of *exo/endo* stereoisomerism of the starting *p*-bromodienone derivative **2a** was overcome in the rearomatization step.

On the basis of this result, we decided to test the reaction directly on the mixture of *exo/endo* isomers of **2** to avoid an useless isolation step. Thus, the mixture of stereoisomers **2a** and **2b**, obtained by oxidation of **1** with trimethylphenylammonium tribromide (Scheme 1), was directly treated with a methanolic solution of $AgClO_4$ for 2 h at 0 °C. Column

(8) Gaeta, C.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 9155.
(9) After the submission of this paper, a related alkoxy/de-*tert*-butylation transformation based on a calixarene spirodienone derivative was reported by Varma and co-workers (Thulasi, S.; Bhagavathy, G. V.; Eliyan, J.; Varma, L. R. *Tetrahedron Lett.* **2009**, *50*, doi: 10.1016/j.tetlet.2008.11.118).
(10) Agbaria, K.; Aleksiuk, O.; Biali, S. E.; Böhmer, V.; Frings, M.; Thondorf, I. *J. Org. Chem.* **2001**, *66*, 2891.
(11) Paquette, L. A.; Hefferon, G. J.; Samodral, R.; Hanzawa, Y. *J. Org. Chem.* **1983**, *48*, 1262.
(12) Omura, K. *J. Org. Chem.* **1996**, *61*, 7156.
(13) See the Supporting Information for additional details.
(14) In addition to **5a**, tripropoxy-*p*-*tert*-butylcalix[4]arene **1** and the corresponding tripropoxycalix[4]monoquinone were also isolated in 28% and 9% yield, respectively.

**Table 1.** *p*-Alkoxy- or *p*-Acyloxycalix[4]Arenes Obtained in the Silver-Mediated Nucleophilic Substitution on *p*-Bromodienones **2a**,**b** (Compounds **5a**−**k**) and Bis(*p*-bromodienones) **7a**−**c** (Compounds **8a**,**b**).

| entry | substrate | nucleophile | solvent | isolated compd (yield, %) |
|---|---|---|---|---|
| 1 | **2a** | MeOH | MeOH | **5a** (60[a]) |
| 2 | **2a**,**b** | MeOH | MeOH | **5a** (42[b]) |
| 3 | **2a**,**b** | EtOH | EtOH | **5b** (42[b]) |
| 4 | **2a**,**b** | *i*-PrOH | *i*-PrOH | **5c** (42[b]) |
| 5 | **2a**,**b** | $PhCH_2OH$ | $PhCH_2OH$ | **5d** (42[b]) |
| 6 | **2a**,**b** | 1-octanol | 1-octanol | **5e** (42[b]) |
| 7 | **2a**,**b** | allylic alcohol | allylic alcohol | **5f** (51[b]) |
| 8 | **2a**,**b** | propargylic alcohol | propargylic alcohol | **5g** (45[b]) |
| 9[f] | **2a**,**b** | $AcO^-$ | AcOH | **5h** (44[b]) |
| 10 | **2a**,**b** | (*R*)-2-butanol | (*R*)-2-butanol | **5i** (46[b]) |
| 11 | **2a**,**b** | (−)-myrtenol | DME | **5j** (33[b]) |
| 12 | **2a**,**b** | *N*-benzyl-L-serine benzyl ester | DME | **5k** (46[b]) |
| 13 | **7a** | MeOH | MeOH | **8a** (67[c]) |
| 14 | **7b** | MeOH | MeOH | **8a** (40[d]) |
| 15 | **7a**−**c** | MeOH | MeOH | **8a** (46[e]) |
| 16 | **7a**−**c** | $PhCH_2OH$ | $PhCH_2OH$ | **8b** (35[e]) |

[a] Yield is given with respect to **2a** as starting material. [b] Yield is given with respect to tripropoxycalix[4]arene **1** as starting material. [c] Yield is given with respect to **7a** as starting material. [d] Yield is given with respect to **7b** as starting material. [e] Yield is given with respect to dipropoxycalix[4]arene **6** as starting material. [f] This reaction was conducted in the absence of $AgClO_4$.

chromatography on silica gel of the reaction mixture afforded *p*-methoxycalix[4]arene derivative **5a** in 42% yield with respect to **1** (Table 1, entry 2).[13] Clearly, in this way the entire procedure is made more expeditious.

The formation of **5a** can be explained by the silver-mediated initial formation of carbocation **3** (aryloxenium cation),[15,16] which reacts with methanol to give intermediate *p*-methoxydienone derivative **4a**. This latter then undergoes acidic de-*tert*-butylation to give rearomatized *p*-methoxycalix[4]arene **5a**.

To verify the influence of the alcoholic moiety on the reaction outcome, methanol was substituted by other alcohols and, for convenience, the reaction was performed directly on the mixture of **2a** and **2b**. Thus, it was evidenced that primary (ethanol) and secondary (isopropyl alcohol) alcohols behave in the same way giving *p*-ethoxy- and *p*-isopropoxycalix[4]arene, **5b** and **5c**, both in 42% yield with respect to **1** (Table 1, entries 3 and 4).[13] On the other hand, by using *tert*-butyl alcohol under various conditions no *tert*-butoxy derivative could be traced. This difficulty could be explained either by the steric crowding of the intermediate *p*-*tert*-butoxydienone as well as by the lability of the final *tert*-butyl ether linkage.

Interestingly, the reaction with an heavier primary alcohol, namely benzylic alcohol, was successful giving *p*-benzyloxycalix[4]arene **5d** also in 42% yield (Table 1, entry 5).[13] Long-chain alcohols such as 1-octanol gave very similar results (**5e** in 42% yield, Table 1, entry 6). Analogously, unsaturated allylic and propargylic alcohols gave the corresponding derivatives **5f** and **5g** in 51% and 45% yield, respectively (Table 1, entries 7 and 8).[13]

To expand the potentiality of the *p*-bromodienone route we decided to test acetate anion as an additional oxygen nucleophile. Therefore, an *exo/endo* mixture of *p*-bromodienones **2a**,**b** was reacted with $CH_3COOK$ using acetic acid as a solvent. Also in this instance, usual workup of reaction mixture afforded *p*-acetoxycalix[4]arene **5h** in 44% yield (Table 1, entry 9).[13]

To verify the *p*-bromodienone route on substrates bearing two *p*-bromodienone systems, we decided to prepare a distal bis(*p*-bromodienone) calix[4]arene derivative. Therefore, distal dipropoxycalix[4]arene **6**[17] was treated with trimethylphenylammonium tribromide, under conditions similar to those used for the preparation of **2a**,**b**, to give a mixture of products **7a**−**c**, which clearly originated from the *exo* or *endo* *ipso*-attack of bromine to the *para* positions (Scheme 2). Interestingly, repeated treatment with diethyl ether of this reaction mixture allowed the selective precipitation of each stereoisomer, namely *exo,exo*-**7a** (38%), *exo,endo*-**7b** (56%),

(15) Aryloxenium cations, also named as phenoxonium[15a,b] and aryloxylium,[15c] have been frequently invoked as key intermediates in synthetically useful oxidations of phenols.[15a,b] Evidence for the existence of these cations has been often based on proposed mechanistic pathways,[15d] trapping experiments,[15e] or the detection of UV−vis spectra of transients from laser flash photolysis experiments,[15f] but examples of stable, isolatable, highly delocalized specie are known.[15g−i] (a) Taylor, W. I.; Battersby, A. R. *Oxidative Coupling of Phenols*; Marcel Dekker: New York, 1967. (b) Swenton, J. S.; Callinan, A.; Chen, Y.; Rohde, J. L.; Kerns, M. L.; Morrow, G. L. *J. Org. Chem.* **1996**, *61*, 1267. (c) Hegarty, A. F.; Keogh, J. P. *J. Chem. Soc., Perkin Trans. 2* **2001**, 758. (d) Eickhoff, H.; Jung, G.; Rieker, A. *Tetrahedron* **2001**, *57*, 353. (e) Glover, S. A.; Novak, M. *Can. J. Chem.* **2005**, *83*, 1372. (f) Wang, Y.-T.; Wang, J.; Platz, M. S.; Novak, M. *J. Am. Chem. Soc.* **2007**, *129*, 14566. (g) Williams, L. L.; Webster, R. D. *J. Am. Chem. Soc.* **2004**, *126*, 12441. (h) Lee, S. B.; Lin, C. Y.; Gill, P. M.; Webster, R. D. *J. Org. Chem.* **2005**, *70*, 10466. (i) Peng, H. M.; Webster, R. D. *J. Org. Chem.* **2008**, *73*, 2169.

(16) Intermediate calixarene carbocations have been recently proposed by Biali for the functionalization of methylene bridges under $S_N1$ conditions performed on the corresponding bromocalixarene derivatives.[2c,d]

(17) Iwamoto, K.; Shinkai, S. *Tetrahedron* **1991**, *47*, 4325.

and *endo,endo*-**7c** (2%), which were fully characterized.[13,18]

At this point, *exo,exo*-bis(*p*-bromodienone) **7a** was treated with a methanolic solution of $AgClO_4$, as described above for **2a** to give distal *p*-dimethoxycalix[4]arene derivative **8a** in 67% yield (Table 1, entry 13).[13] As expected, the analogous treatment of *exo,endo*-**7b** afforded **8a** in a 40% yield (Table 1, entry 14). This clearly demonstrated that *p*-bromodienone route can be also applied to calixarenes bearing two *p*-bromodienone systems. In addition, the absence of *exo/endo* stereoisomerism in the final product **8a** induced us to test the nucleophilic substitution reaction directly on the stereoisomeric mixture **7a**−**c**. As expected, good yields of **8a** (46%, Table 1, entry 15) were obtained also in this instance, making faster the entire procedure.

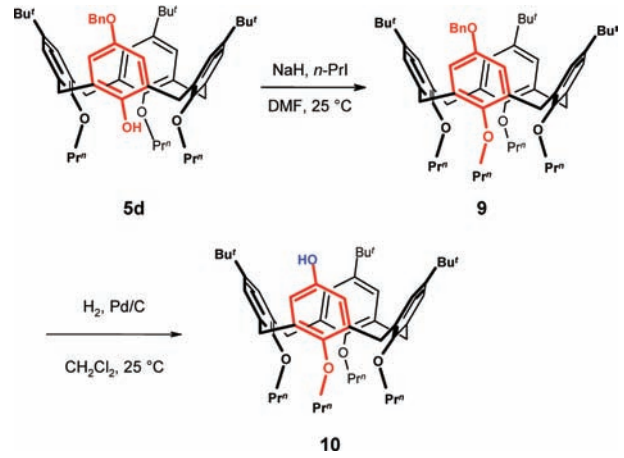
Substitution reaction on stereoisomeric mixture **7a**−**c** was also extended to the larger benzylic alcohol, which also gave the corresponding *p*-dibenzyloxycalix[4]arene **8b** in 35% yield (Table 1, entry 16).

The usefulness of *p*-bromodienone route can be increased by a subsequent chemical modification of the introduced nucleophile. Thus, *p*-benzyloxycalix[4]arene **5d** can be fully propylated (Scheme 3) to give **9** (54% yield) and then subjected to hydrogenolysis ($H_2$, Pd/C, Scheme 3) to give *p*-hydroxycalix[4]arene **10** in 95% yield,[13] which would be more difficult to prepare by different routes.[19]

*p*-Bromodienone route can also be conveniently exploited for introducing chirality into the calixarene structure by appending appropriate chiral substituents. Therefore, an *exo/endo* mixture of calix[4]arene *p*-bromodienones **2a**,**b** was treated with (*R*)-2-butanol in the presence of $AgClO_4$ to give the corresponding *p*-*sec*-butoxycalix[4]arene **5i** in 46% yield (Table 1, entry 10).[13] In a similar way, calix[4]arene **5j**, bearing a chiral myrtenyl group, was obtained in 33% yield by treatment with myrtenol using dimethoxyethane (DME) as solvent (Table 1, entry 11).[13]

Under similar conditions the reaction with a serine protected both at the amino and carboxy group, namely *N*-benzyl-L-serine-benzyl ester, gave the very interesting chiral derivative **5k** (Table 1, entry 12), which can be considered a novel type of "calixarene-amino acid". Differently from other known examples of calixarene amino acid derivatives,[20] in this instance, peptide chains can be equally grown either from the C- or the N-side.[21]

**Scheme 3**




In conclusion, we have reported a convenient procedure for the functionalization of calixarene *exo* rim by direct attachment of a nucleophile to the para aromatic carbon. This result was achieved through the nucleophilic substitution and the subsequent rearomatization on easily accessible calixarene *p*-bromodienone derivatives. This approach can be considered as a novel "*p*-bromodienone route" to functionalize the calixarene *exo* rim with nucleophiles. In order to expand the potentiality of this route, future work will be directed to the use of other nucleophiles including N-, S-, and C-nucleophiles and aromatic rings.

**Supporting Information Available:** Synthetic details, 1D and 2D $^1H$ and $^{13}C$ NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) The stereoisomeric nature of derivatives **7a-c** was readily evidenced by MS and elemental analysis data. $^1H$ and $^{13}C$ NMR spectra of more abundant stereoisomer **7b**, reported in Figure S31 and S32, evidenced the presence of a single plane of symmetry ($C_s$-symmetry) and, therefore, are only compatible with the *exo,endo* stereochemistry of structure **7b**. The second more abundant stereoisomer **7a**, showed more symmetrical $^1H$ and $^{13}C$ NMR spectra (Figures S27−S30) indicative of the presence of two orthogonal symmetry planes ($C_{2v}$-symmetry) compatible with both *exo,exo* or *endo,endo* stereochemistry. In addition to favorable thermodynamic and kinetic considerations, the *exo,exo* stereochemistry was assigned to **7a** on the basis of a ROESY experiment (Figure S38). Consequently, the *endo,endo* stereochemistry was assigned by exclusion to the far less abundant stereoisomer **7c**.

(19) For other examples of *p*-hydroxycalixarenes, see ref 2h and: (a) Morita, Y.; Agawa, T.; Nomura, E.; Taniguchi, H. *J. Org. Chem.* **1992**, *57*, 3658. (b) Gaeta, C.; Procida, G.; Gavuzzo, E.; Neri, P. *J. Incl. Phenom. Macrocycl. Chem.* **2008**, *60*, 115.

(20) Several examples of calixarenes bearing *N*-, or *C*-linked amino acid or peptides are known: (a) Sansone, F.; Barboso, S.; Casnati, A.; Fabbi, M.; Pochini, A.; Ugozzoli, F.; Ungaro, R. *Eur. J. Org. Chem.* **1998**, 897. (b) Lazzarotto, M.; Sansone, F.; Baldini, L.; Casnati, A.; Cozzini, P.; Ungaro, R. *Eur. J. Org. Chem.* **2001**, 595. (c) Francese, S.; Cozzolino, A.; Caputo, I.; Esposito, C.; Martino, M.; Gaeta, C.; Troisi, F.; Neri, P. *Tetrahedron Lett.* **2005**, *46*, 1611. In addition, a peculiar example of calixarene bearing both an amino and a carboxy group directly bound to two distal aromatic rings has been also reported. (d) Sansone, F.; Baldini, L.; Casnati, A.; Chierici, E.; Faimani, G.; Ugozzoli, F.; Ungaro, R. *J. Am. Chem. Soc.* **2004**, *126*, 6204.

(21) Conceptually related calix[4]arenes constructed with L-tyrosine units have been mentioned in a very preliminary communication: Bew, S. P.; Sharma, S. V.; Brimage, R. A. In *Abstracts of 9th International Conference on Calixarene Chemistry (Calix 2007)*; College Park, MD, Aug 6−9, 2007, SL-5.