ORGANIC LETTERS

2007
Vol. 9, No. 5
915−918

Calixcyclitols: A New Class of Polar Hybrid Hosts Obtained by Oxygenation of Calixarene Phenol Rings

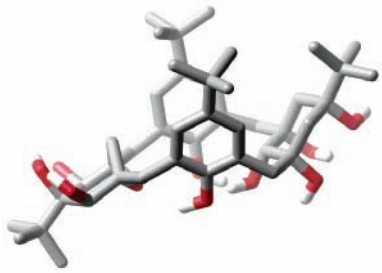
Francesco Troisi,[†] Luca Mogavero,[†] Carmine Gaeta,[†] Enrico Gavuzzo,[‡] and Placido Neri*,[†]

Dipartimento di Chimica, Università di Salerno, Via Ponte don Melillo, I-84084 Fisciano (Salerno), Italy, and Istituto di Cristallografia, Sezione di Monterotondo, CNR, Area della Ricerca Roma 1, C.P. 10, I-00016 Monterotondo Stazione (RM), Italy

neri@unisa.it

Received January 16, 2007

ABSTRACT



The first examples of hybrid calixarene hosts containing cyclitol moieties (*calixcyclitols*) have been obtained by treatment with $LiAlH_4$ of diepoxydiol and tetraepoxytetrol calix[4]arene derivatives. A 6-oxabicyclo[3:1:1]heptanetriol or a cyclohexanetetrol ring was obtained depending on the stereochemical features of the diepoxydiol moiety. Preliminary binding studies toward anionic guests showed a discrete selectivity of calixcyclitol 9 vs $H_2PO_4^-$.

Over the past two decades, calixarenes[1] have become one of the leading host systems and are currently most studied in the context of supramolecular chemistry, with a large number of applications ranging from recognition[2] to self-assembly[3] and from topological chemistry[4] to nanotechnology.[5] The main reason for this success, besides their ready availability, is their easy chemical modification, which allows the generation of new related systems with improved or profoundly different supramolecular properties. The more common transformations are usually performed by functionalization at the so-called *upper* and *lower rims* (the para positions of the aromatic rings and the phenolic hydroxyls, respectively).[1c] However, more recently, increasing attention has also been devoted to making more fundamental changes, such as the incorporation of nonclassical building units. Thus, for example, the use of heterocyclic units such as pyrrole,

[†] Dipartimento di Chimica, Università di Salerno.
[‡] Istituto di Cristallografia, Sezione di Monterotondo.

(1) For general 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.

(2) (a) Arduini, A.; Pochini, A.; Secchi, A.; Ugozzoli, F. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer: Dordrecht, 2001; Chapter 25, pp 457−475. (b) Consoli, G. M. L.; Cunsolo, F.; Geraci, C.; Mecca, T.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 7467. (c) Garozzo, D.; Gattuso, G.; Notti, A.; Pappalardo, A.; Pappalardo, S.; Parisi, F. M.; Perez, M.; Pisagatti, I. *Angew. Chem., Int. Ed.* **2005**, *44*, 4892.

(3) (a) Rudkevich, D. M. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001; Chapter 15, pp 155−180. (b) Sansone, F.; Baldini, L.; Casnati, A.; Chierici, E.; Faimani, G.; Ugozzoli, F.; Ungaro, R. *J. Am. Chem. Soc.* **2004**, *126*, 6204.

(4) (a) Vysotsky, M. O.; Bolte, M.; Thondorf, I.; Böhmer, V. *Chem.−Eur. J.* **2003**, *9*, 3375. (b) Wang, L.; Vysotsky, M. O.; Bogdan, A.; Bolte, M.; Böhmer, V. *Science* **2004**, *304*, 1312. (c) Bogdan, A.; Vysotsky, M. O.; Ikai, T.; Okamoto, Y.; Böhmer, V. *Chem.−Eur. J.* **2004**, *10*, 3324. (d) Gaeta, C.; Vysotsky, M. O.; Bogdan, A.; Böhmer, V. *J. Am. Chem Soc.* **2005**, *127*, 13136.

(5) Hong, B. H.; Bae, S. C.; Lee, C.-W.; Jeong, S.; Kim, K. S. *Science* **2001**, *294*, 348.

10.1021/ol0701161 CCC: $37.00
Published on Web 01/30/2007

thiophene, furan, indole, pyridine, and benzoxazine has led to homogeneous or hybrid heterocalixarenes, which often display remarkable host properties.[6]

One approach to introduce nonclassical units into the calixarene framework, besides the direct macrocyclization of suitable precursors, is the direct modification of the aromatic "walls" of the calix cavity.[7]

In this regard, we have recently proposed that the introduction of oxygenated functions (e.g., OH groups) into the calix walls would give rise to polar derivatives,[8,9] resembling cyclodextrin, with novel and interesting supramolecular properties.[10] This result can be achieved by exploiting the direct addition of molecular oxygen (oxygenation) to the phenoxide anion of a 2,4,6-trisubstituted phenol ring which gives rise to epoxy-*ortho*-quinol or epoxy-*para*-quinol derivatives,[11] amenable to further synthetic elaboration. Thus, recently we have reported the first examples of diepoxy-*p*-quinol and diepoxydiol calix[4]arene derivatives **1**−**4** (Figure 1), obtained by base-promoted direct oxygenation of the calixarene phenol rings.[10] The opening of the epoxy rings should allow the introduction of new polar groups into the calixarene cavity and thus the synthesis of new polar cyclodextrin-like hosts. Here, we wish to report on the reductive opening of these epoxy rings and on the first examples of hybrid calixarene hosts containing cyclitol moieties.

With the purpose of introducing additional polar OH groups on the calixarene aromatic walls, we decided to attempt a classical reductive opening of the epoxy rings of derivative **2**[10] by treatment with $LiAlH_4$.

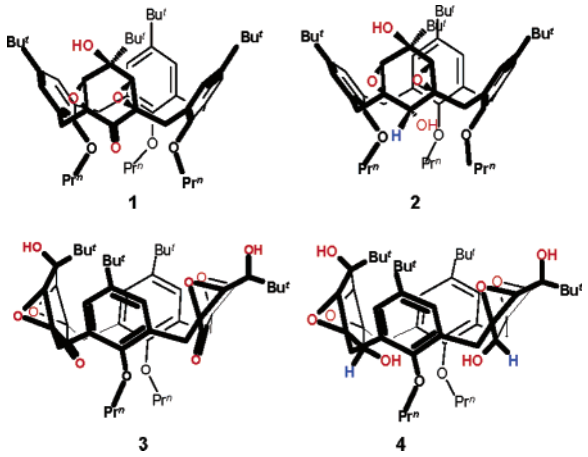
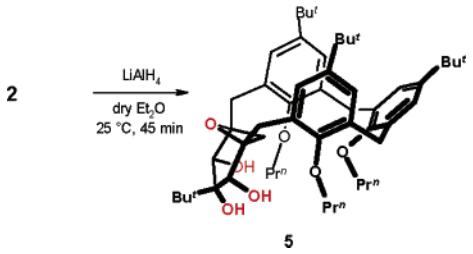


Figure 1. Diepoxy-*p*-quinol and diepoxy-diol calix[4]arene derivatives **1**−**4**.

Thus, reaction of **2**[10] with $LiAlH_4$, in dry diethyl ether at 25 °C, resulted in the formation of **5**, isolated as a colorless solid, in 61% yield, after column chromatography on silica gel (Scheme 1). The presence of a rearranged 6-oxabicyclo-

Scheme 1



[3:1:1]heptanetriol system in **5** was readily evidenced by 1D and 2D NMR experiments.[12] Support for the presence of the oxetane ring in **5** was obtained by means of X-ray analysis of a single-crystal grown from $CHCl_3/CH_3OH$.[12−14]

It is worth noting that, to the best of our knowledge, **5** represents the first example of a calixarene containing cyclitol

(6) (a) Gale, P. A.; Sessler, J. L.; Král, V. *Chem. Commun.* **1998**, 1. (b) Ito, K.; Ohba, Y.; Tamura, T.; Ogata, T.; Watanabe, H.; Suzuki, Y.; Hara, T.; Morisawa, Y.; Sone, T. *Heterocycles* **1999**, *51*, 2807. (c) Cafeo, G.; Kohnke, F. H.; La Torre, G. L.; White, A. J . P.; Williams, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 1496. (d) Vysotsky, M.; Saadioui, M.; Böhmer, V. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, 2001; Chapter 13, pp 250−265. (e) Kobayashi, N.; Inagaki, S.; Nemykin, V. N.; Nonomura, T. *Angew. Chem., Int. Ed.* **2001**, *40*, 2710. (f) Sessler, J. L.; Cho, W.-S.; Lynch, V.; Král, V. *Chem.−Eur. J.* **2002**, *8*, 1134. (g) Sessler, J. L.; An, D.; Cho, W.-S.; Lynch, V.; Yoon, D.-W.; Hong, S.-J.; Lee, C.-H. *J. Org. Chem.* **2005**, *70*, 1511.

(7) For a review on the oxidation and reduction of calixarene aromatic rings, see: (a) Biali, S. E. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens J., Eds.; Kluwer: Dordrecht, 2001; Chapter 14, pp 266−279. (b) Gaeta, C.; Gregoli, L.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2002**, *43*, 8875. (c) Webber, P. R. A.; Beer, P. D.; Chen, G. Z.; Felix, V.; Drew, M. G. *B. J. Am. Chem. Soc.* **2003**, *125*, 5774. (d) Gaeta, C.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 9155. (e) Biali, S. E. *Synlett* **2003**, 1. (f) Consoli, G. M. L.; Geraci, C.; Cunsolo, F.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 53.

(8) For examples of calixcyclohexanol derivatives, see ref 7a and: (a) Columbus, I.; Haj-Zaroubi, M.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 11806 and references therein. (b) Columbus, I.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 3060 and references therein. (c) Bilyk, A.; Harrowfield, J. M.; Skelton, B. W.; White, A. H. *J. Chem. Soc., Dalton Trans.* **1997**, 4251 and references therein.

(9) Polar, nonionic, calixarene derivatives have also been obtained by appending hydrophilic groups: (a) Grote Gansey, M. H. B.; Steemers, F. J.; Verboom, W.; Reinhoudt, D. N. *Synthesis* **1997**, 643. (b) Segura, M.; Sansone, F.; Casnati, A.; Ungaro, R. *Synthesis* **2001**, 2105 and references therein.

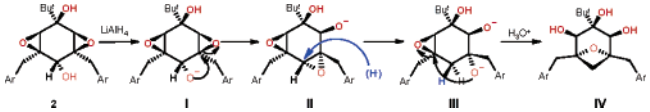
(10) Gaeta, C.; Troisi, F.; Martino, M.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2004**, *6*, 3027.

(11) (a) Nishinaga, A.; Itahara, T.; Shimizu, T.; Matsuura, T. *J. Am. Chem. Soc.* **1978**, *100*, 1820. (b) Nishinaga, A.; Itahara, T.; Matsuura, T.; Rieker, A.; Koch, D.; Albert, K.; Hitchcock, P. B. *J. Am. Chem. Soc.* **1978**, *100*, 1826. (c) Nishinaga, A.; Shimizu, T.; Matsuura, T. *J. Org. Chem.* **1979**, *44*, 2983.

(12) See the Supporting Information for additional details.

(13) The X-ray analysis supports the gross structure, although the *R* factor was 13%.

(14) This unexpected reaction outcome is likely the result of an initial epoxy interchange to give **II** (Payne's rearrangement: Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819), which is possible because of the trans disposition of the epoxy and secondary hydroxyl groups.

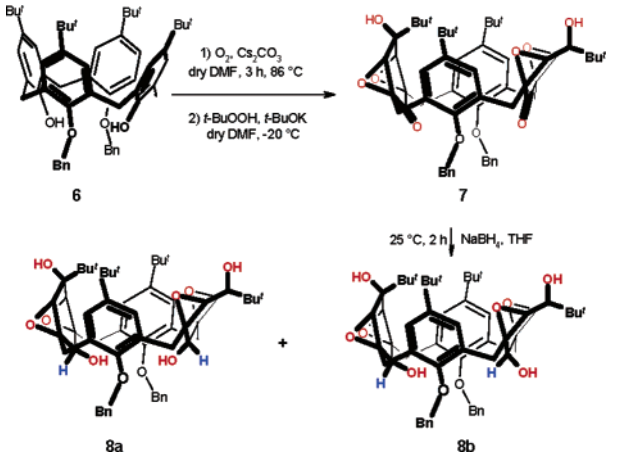


Reductive opening of the new epoxy group by S_N2 attack of the hydride ion would then give **III**, in which an intramolecular S_N2 attack of the alkoxide group to the second epoxide would give rise to the oxetane ring in **IV**.

moieties, and therefore we have termed it *calixcyclitol*.[15] Calixcyclitol **5** can be considered an interesting compound because it is known that cyclitol derivatives can mimic specific carbohydrates, associated with important signaling and recognition events, with improved efficacy, stability, and specificity.[16]

The above results induced us to extend our studies to tetraepoxytetrol derivatives, with the aim of increasing the number of polar OH groups in the calixarene cavity. Therefore, we decided to synthesize a tetraepoxytetrol derivative with removable benzyl groups at the lower rim. Thus, O_2 was bubbled into a solution of *syn*-distal dibenzyloxycalix[4]arene **6**[17] in dry DMF, in the presence of Cs_2CO_3, at 86 °C for ca. 4 h (Scheme 2). After usual workup, the crude

Scheme 2

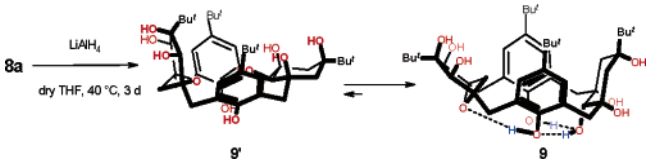


product was treated directly with *t*-BuOOH/*t*-BuOK in dry DMF to give **7** in 35% yield.[12,18] In analogy to previously reported bis(diepoxy-*p*-quinol) **3**,[10] derivative **7** was fully characterized by means of 1D and 2D NMR spectra.[12] Treatment of **7** with $NaBH_4$ in a mixture of THF/dioxane at 25 °C for 2 h afforded the two stereoisomeric tetraepoxytetrols **8a** (*X-exo,N-exo*) and **8b** (*X-exo,N-endo*) isolated in 88% and 7% yields, respectively.[19] The stereochemistry of both **8a** and **8b** was assigned by means of 2D NOESY spectra, as previously reported for analogous derivatives.[10,12]

The stereochemical features of the two diepoxydiol moieties in **8a** make it a very interesting substrate for reductive epoxide ring opening with $LiAlH_4$. In fact, the *X* ring shows an anti stereochemistry between the secondary OH and diepoxy groups, and therefore, it should allow a Payne's rearrangement to form an oxetane ring.[14] Instead, the syn stereochemistry between the same groups in the *N* ring should give rise to classical reductive opening of the epoxy groups, to form a cyclohexanetetrol system.

To verify these arguments, **8a** was treated with $LiAlH_4$ in dry THF, at 40 °C for 3 days, to afford calixcyclitol **9** in 34% yield, after column chromatography of the crude reaction mixture (Scheme 3).

Scheme 3



As reported in Scheme 3, the benzyl groups were readily removed under these conditions. The structure of calixcyclitol **9** was readily assigned by spectral analysis.[12] In particular, the presence of a pseudomolecular ion peak at *m*/*z* 755 (MH^+) in the ESI(+) mass spectrum confirmed the molecular formula. The C_s molecular symmetry was confirmed by the pertinent signals in the ^1H and ^{13}C NMR spectra. In fact, three 1:1:2 *t*-Bu singlets at 0.98, 1.10, and 1.11 ppm were present in the ^1H NMR spectrum. Concerning the cyclohexanetetrol moiety, the diastereotopic CH_2 protons form an AB system at 1.91/2.01 ppm (COSY-45, 2H each), and the carbinolic proton at 2.77 ppm (1H) shows a *J*-coupling with the vicinal OH proton at 4.92 ppm (COSY-45, D_2O exchangeable). A second AB system was present in the ^1H NMR spectrum at 2.13/2.36 ppm (COSY-45, 1H each) relative to the CH_2 oxetane protons, and the carbinolic protons at 3.97 ppm (J = 7.1 Hz, 2H) show a *J*-coupling with the vicinal OH protons at 3.41 ppm (2H, D_2O exchangeable). Interestingly, the ^{13}C NMR spectrum displayed a characteristic oxetane resonance at 85.0 ppm relative to the oxygenated tertiary carbon atoms. The 2D HMBC NMR spectrum shows crucial ^2J correlations at 2.13/85.0 and 2.36/85.0 ppm between the H-signals of the diastereotopic CH_2 oxetane protons and the C-singlet of the tertiary oxygenated carbon of the oxetane ring.[12]

The downfield position of the resonance at 7.76 ppm, relative to the phenol OH groups, suggests their involvement in hydrogen bonds. This, in conjunction with diagnostic cross-peaks in the 2D NOESY spectrum between the axial CH_2 proton of the cyclohexanetetrol moiety and the proximal aromatic proton,[12] is indicative of a cone−cone inversion of the initially formed structure **9′** to give **9**, as indicated in Scheme 3. MM3[20] calculations corroborated this hypothesis giving a difference in energy of 3 kcal/mol, favoring the inverted cone **9**, stabilized by H-bonds at the lower rim (Figure 2).[21]

(15) In fact, cyclitols are cycloalkanes containing one hydroxyl group on each of three or more ring atoms (Angyal, S. J.; Andersen, C.; Cahn, R. S.; Dowson, R. M. C.; Hoffmann-Ostenhof, O.; Klyne, W.; Posternack, T. *Pure Appl. Chem.* **1974**, *37*, 283).

(16) (a) Chapleur, Y. *Carbohydrate Mimics: Concepts and Methods*; Wiley-VCH: Weinheim, 1997. (b) Huang, C.-Y.; Cabell, L. A.; Anslyn, E. V. *J. Am. Chem. Soc.* **1994**, *116*, 2778. (c) Seras, P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **1999**, *38*, 2300. (d) Diaz, S. G.; Lynch, V.; Anslyn, E. V. *Supramol. Chem.* **2002**, *2*, 201.

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

(18) Analogous oxygenation of **6** with *t*-BuOK in dry DMF for 17 h, at 80 °C, followed by treatment with *t*-BuOOH/*t*-BuOK, resulted in the formation of **7** in 17% yield.

(19) In accordance with a previously used notation,[10] we indicate with *X* (or *N*) the ring bearing *exo*-epoxides (or *endo*-epoxides).

(20) *MacroModel*, version 9.0; Schrödinger, LLC: New York, 2005.

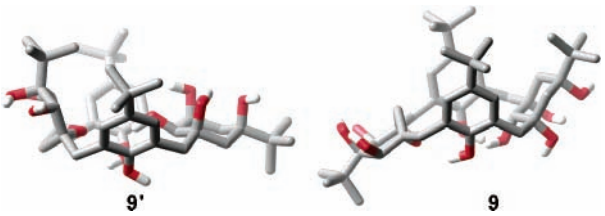


Figure 2. Lowest MM3 energy structures of cone conformers **9** and **9′**.

The presence of several OH groups should make calixcyclitol **9** a polar host likely able to bind anions by means of H-bonds. Therefore, we undertook preliminary complexation studies by means of ^{1}H NMR titrations with anions such as F^-, Cl^-, Br^-, I^-, NO_3^-, and $H_2PO_4^-$ (as tetrabutylammonium salts) in $CDCl_3$.

In all instances, significant shifts were observed in the ^{1}H NMR spectrum of calixcyclitol **9** for both diastereotopic CH_2 oxetane protons, upon titration with the anions. Additional shifts of the three adjacent OH protons converging toward the calix cavity indicate the interactions of these OH groups with anions by means of H-bonds. No appreciable shifts, and consequently no binding, were observed for the OH groups of the cyclohexanetetrol ring.[12]

A 1:1 stoichiometry for each calixcyclitol−anion complex was established by means of a Job plot.[22] The titration data (Figure 3) were analyzed by nonlinear regression analysis using the WinEQNMR program.[23] As reported in Figure 3, the values of association constants indicate a discrete selectivity vs the tetrahedral dihydrogen phosphate anion, with respect to spherical (F^-, Cl^-, Br^-, and I^-) and planar trigonal (NO_3^-) anions. This result is in line with those previously reported by Hamilton in which two adjacent OH groups (e.g., 1,2-diols) can form two chelating H-bonds with a phosphate group thanks to the complementarity between the two parts.[24]

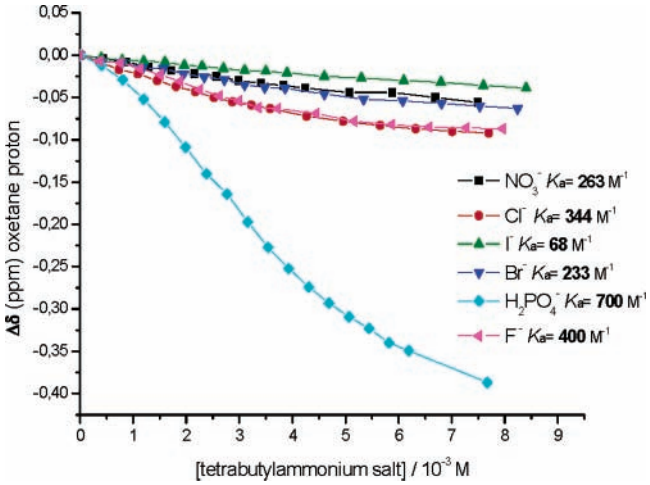


Figure 3. Plots of $\Delta\delta$ for an oxetane proton (at 2.36 ppm) of calixcyclitol **9** as a function of the concentration of tetrabutylammonium salt ($CDCl_3$, 25 °C, 400 MHz) and related association constants (K_a, error <15%).

The first examples of calixcyclitols described herein represent a new class of polar hybrid hosts with structural features approaching those of cyclodextrins. The preliminary complexation experiments reported herein clearly prove their ability to bind polar species such as anions.

Further complexation studies toward alkyl and aryl phosphonates and other anions are in progress with the aim to exploit the calix cavity in these recognition processes. It is likely that other polar, nonionic derivatives can also be complexed.

Acknowledgment. Thanks are due to Dr. P. Iannece (Dip. di Chimica, Università di Salerno) for ESI MS measurements and to Dr. P. Oliva (Dip. di Chimica, Università di Salerno) for NMR spectra acquisitions.

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

OL0701161

(21) In accordance with this high difference of energy, only signals related to cone conformer **9** are present in its ^{1}H NMR spectrum. Dynamic NMR studies (400 MHz) showed that calixcyclitol **9** is fixed in this cone conformation at room temperature and indicated a coalescence of both the $ArCH_2$ signals at temperatures higher than 393 K in TCDE. Therefore, an energy barrier higher than 17.2 kcal/mol can be estimated for its conformational inversion. Similar higher-energy barriers for the through-the-annulus rotation of cyclohexanol rings with respect to phenol rings were previously evidenced by Biali for calixcyclohexanol derivatives.[8a,b]

(22) Connors, K. A. *Binding Constants*; John Wiley & Sons: Chichester, 1987.
(23) Hynes, M. J. *J. Chem. Soc., Dalton Trans.* **1993**, 311.
(24) Das, G.; Hamilton, A. *J. Am. Chem. Soc.* **1994**, *116*, 11139.