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Oxyfunctionalization of Calixarene Quinone Rings

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ABSTRACT

The epoxidation of quinone rings of calixquinones represents a valid route for the introduction of oxygenated functionalities into the de-*tert*-butylated calixarene walls originating *cis*-diepoxy-*p*-dione moieties. Carbonyl reduction of these systems leads to hybrid calixarenes containing dianhydroinositol moieties (*calixinositols*) belonging to the calixcyclitols family. The regio- and stereochemistry of these derivatives was determined by 2D NMR studies, in conjunction with MM3 calculations and X-ray crystallography.

Calixarenes[1] are a class of hosts ubiquitous in supramolecular chemistry. The main reason for their success is their synthetic versatility. In fact, in the past two decades a plethora of procedures for the chemical modification of calixarenes has been developed.[1] Attention has been primarily focused on functionalization at the para positions of the aromatic rings (the *upper* or *wide rim*) or at the phenolic hydroxyls (the *lower* or *small rim*), while only recently, procedures for the functionalization of the methylene groups have been reported by Biali.[2] More recently, we have become interested at the modification of the aromatic "walls" of the calix cavity.[3] In particular, our goal was the introduction of oxygenated functions into the calix walls to give rise to polar, cyclodextrin-like hosts. Thus, we obtained the first examples of diepoxy-*p*-quinol and diepoxy-diol calix[4]arene derivatives by means of base-promoted direct addition of molecular oxygen (oxygenation) to the calixarene phenol rings.[4] The reductive opening of the resulting epoxides with $LiAlH_4$ afforded calixcyclitol[5] derivatives, which represent a new class of polar hybrid hosts with interesting recognition properties toward anionic guests.

In these instances, the direct oxygenation of phenoxide anions leads to definite reaction products (generally epoxy-*p*-quinol or epoxy-*o*-quinol) only if a *tert*-butyl group is present at the para position, otherwise oxidative coupling of phenolic rings or other oxidation processes take place.[6]

Thus, in order to develop a procedure for the introduction of oxygenated functionalities into de-*tert*-butylated calixarene rings we decided to investigate the epoxidation of quinone moieties in calixquinone[1,3d−m] derivatives. Interestingly, we found that epoxidation of calixquinone derivatives[7] can be achieved by treatment with *tert*-butyl hydroperoxide in the

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(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. (e) Böhmer, V. In *The Chemistry of Phenols*; Rappoport, Z., Ed.; Wiley: Chichester, U.K., 2003; Chapter 19. (f) *Calixarenes in the Nanoworld*; Vicens J., Harrowfield, J., Eds.; Springer, Dordrecht, 2007.

(2) For a procedure for the functionalization of all methylene groups via tetrabromocalix[4]arene derivatives, see: (a) Columbus, I.; Biali, S. E. *Org. Lett.* **2007**, 32, 3201. For the functionalization of methylene bridge via ketocalixarenes, see: (b) Kuno, L.; Seri, N.; Biali, S. E. *Org. Lett.* **2007**, *9*, 1577. For the functionalization of methylene bridge via spirodienone calixarene derivatives, see: (c) Agbaria, K.; Biali, S. E. *J. Am. Chem. Soc.* **2001**, *123*, 12495. (d) Simaan, S.; Agbaria, K.; Biali, S. E. *J. Org. Chem.* **2002**, *67*, 6136. (e) Simaan, S.; Biali, S. E. *J. Org. Chem.* **2004**, *69*, 95.

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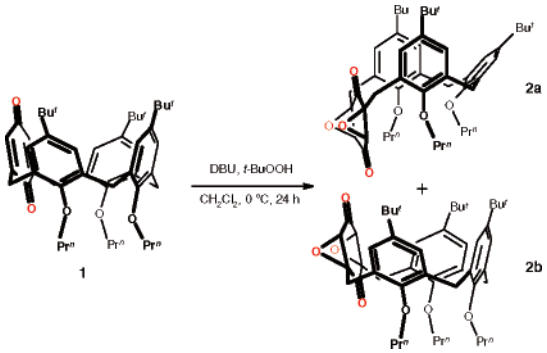
presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as base,[8] and we wish to report here the first examples of diepoxy-*p*-dione and bis(diepoxy-*p*-dione) calix[4]arene derivatives thus obtained.

As groundwork to define the regio- and stereoselectivity of the reaction, we first studied the epoxidation of tripropoxycalix[4]monoquinone **1**,[9] bearing a single quinone ring. Thus, the treatment of monoquinone **1** with 12 equiv of DBU and 24 equiv of *t*-BuOOH in dry CH_2Cl_2, at 0 °C for ca. 24 h, resulted in the formation of two stereoisomeric derivatives **2a** and **2b** isolated in 30% and 60% yield, respectively, after column chromatography on silica gel.[10] Elemental analysis and ESI(+) mass spectrometry confirmed the stereoisomeric nature of the derivatives **2a** and **2b**, while the presence of diepoxy-*p*-dione moiety was confirmed by the pertinent signals in the ^{1}H and ^{13}C NMR spectra.[10] The presence in the ^{1}H NMR spectra of **2a** and **2b** of a single 2H signal for epoxy H protons (3.81 and 3.85 ppm for **2a** and **2b**, respectively) and two 2:1 *t*-Bu singlets (0.86 and 1.22 ppm for **2a**, 0.93 and 1.35 ppm for **2b**) indicated a C_s symmetry, which was only compatible with a cis geometry of the two epoxy rings. Clearly, the stereoisomerism of **2a** and **2b** arises from the attack of the peroxide anion at the quinone ring, exo or endo with respect to calixarene cavity. By means of a detailed 2D NOESY study[10] we demonstrated that the peroxide attack was endo for **2a** and exo for **2b**. In fact, a strong cross-peak was observed at 3.85/6.57 ppm in the 2D NOESY spectrum of derivative **2b** between epoxy H and the close ArH protons, which was absent in the case of **2a**. Examination of ^{1}H and ^{13}C NMR spectra indicates

Scheme 1



that **2b** adopts a cone conformation. In fact, two AX systems relative to $ArCH_2$ groups [4.36/3.13 (J = 12.7 Hz), 4.20/1.87 ppm (J = 13.6 Hz)] were present in its ^{1}H NMR spectrum,[11] while the ^{13}C NMR spectrum displayed two $ArCH_2$ resonances at 30.2 and 31.3 ppm.[11c,d,12] *endo-cis*-Diepoxy-*p*-dione **2a** displays temperature-dependent ^{1}H NMR spectra due to the easy through-the-annulus rotation of the diepoxy-*p*-dione ring. In this way, a cone/partial-cone slow interconversion occurs at room temperature. At higher temperatures the equilibrium becomes fast giving rise to sharp signals for diastereotopical $ArCH_2$ protons.

MM3 calculations[13] were in accord with these results indicating as the lowest energy structure a cone conformation for derivative **2b** and a partial cone conformation, with inverted diepoxy-dione ring, for **2a**.

A definitive proof of the stereochemistry of **2b** was obtained by means of X-ray analysis of a single-crystal grown from $CHCl_3/CH_3OH$ (Figure 1).[10] In the solid state, **2b** was

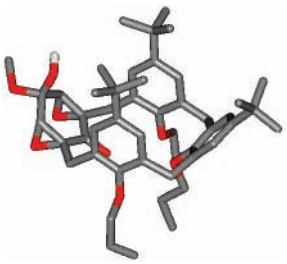


Figure 1. X-ray crystal structure of methyl monohemiketal derivative of **2b** (nonpolar H atoms omitted).

(3) 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. For examples relative to hydrogenation to cyclohexane-based calixarene derivatives, see: (b) Columbus, I.; Haj-Zaroubi, M.; Biali, S. E. *J. Am. Chem. Soc.* **1998**, *120*, 11806 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. For examples relative to oxidation of calixarene phenol rings to quinone or dienone systems, see: (d) Morita, Y.; Agawa, T.; Kai, Y.; Kanehisa, N.; Kasai, N.; Nomura, E., Taniguchi, H. *Chem. Lett.* **1989**, 1349. (e) Morita, Y.; Agawa, T.; Kai, Y.; Nomura, E. Taniguchi, H. *J. Org. Chem.* **1992**, *57*, 3658. (f) 1349 Reddy, P. A.; Kashyap, R. P.; Watson, W. H.; Gutsche, C. D. *Isr. J. Chem.* **1992**, *32*, 89. (g) Gaeta, C.; Gregoli, L.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2002**, *43*, 8875. (h) Webber, P. R. A.; Beer, P. D.; Chen, G. Z.; Felix, V.; Drew, M. G. B. *J. Am. Chem. Soc.* **2003**, *125*, 5774. (i) Gaeta, C.; Martino, M.; Neri, P. *Tetrahedron Lett.* **2003**, *44*, 9155. (j) Biali, S. E. *Synlett* **2003**, 1. (k) Consoli, G. M. L.; Geraci, C.; Cunsolo, F.; Neri, P.; *Tetrahedron Lett.* **2003**, *44*, 53. (l) Ferro, R.; Tedesco, C.; Gaeta, C.; Neri, P. *J. Inclusion Phenom. Macrocyclic Chem.* **2005**, *52*, 85. (m) Lin, Y.-L-; Yu, T.-S.; Wang, W.-Y.; Lin, L.-G. *Tetrahedron Lett.* **2006**, *62*, 6082.

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

(5) Troisi, F.; Mogavero, L.; Gaeta, C.; Gavuzzo, E.; Neri, P. *Org. Lett.* **2007**, *9*, 915.

(6) (a) Haynes, R. K.; Musso, H. *Chem. Ber.* **1974**, *107*, 3723. (b) Hewgill, F. R.; Lee, S. L. *J. Chem. Soc. C.* **1948**, 1549. (c) Nilson, A.; Ronlan, A.; Parker, V. D. *J. Chem. Soc., Perkin Trans. 1* **1973**, 2337. (d) Nishinaga, A.; Itahara, T.; Shimizu, T.; Matsuura, T. *J. Am. Chem. Soc.* **1978**, *100*, 1820.

(7) For examples of syntheses using calixquinones derivatives as starting material, see: (a) Reddy, P. A.; Gutsche, C. D. *J. Org. Chem* **1993**, *58*, 3245. (b) Lee, M.-D.; Yang, K.-M.; Tsoo, C.-Y.; Shu, C.-M.; Lin, L.-G. *Tetrahedron* **2001**, *57*, 8095. (c) Yang, K.-M.; Lee, M.-D.; Chen, R.-F.; Chen, Y.-L.; Lin, L.-G. *Tetrahedron* **2001**, *57*, 8101.

(8) (a) Yadav, V. K.; Kapoor, K. K. *Tetrahedron* **1995**, *51*, 8573. (b) Taylor, R. J. K.; Alcaraz, L.; Kapfer-Eyer, I.; Macdonald, G.; Xudong, W.; Lewis, N. *Synthesis* **1998**, 775.

(9) Tripropoxycalix[4]monoquinone **1** was synthesized according to a literature procedure: Lu, L.-G.; Li, G.-K.; Peng, X.-X.; Chen, C.-F.; Huang, Z.-T. *Tetrahedron Lett.* **2006**, *47*, 6021.

(10) See the Supporting Information for additional details.

(11) (a) Gutsche, C. D. *Calixarenes*; Royal Society of Chemistry: Cambridge, 1989; pp 110−111. (b) Kanamathareddy, S.; Gutsche, C. D. *J. Org. Chem.* **1992**, *57*, 3160. (c) Bifulco, G.; Gomez-Paloma, L.; Riccio, R.; Gaeta, C.; Troisi, F.; Neri, P. *Org. Lett.* **2005**, *7*, 5757. (d) Bifulco, G.; Riccio, R.; Gaeta, C.; Neri, P. *Chem. Eur. J.* **2007**, *13*, 7185.

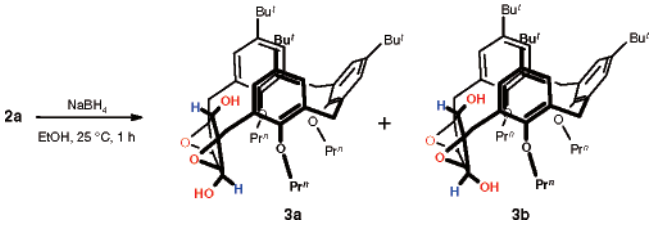
(12) Jaime, C.; de Mendoza, J.; Prados, P.; Nieto, P. M.; Sanchez, C. *J. Org. Chem.* **1991**, *56*, 3372. Magrans, J. O.; de Mendoza, J.; Pons, M.; Prados, P. *J. Org. Chem.* **1997**, *62*, 4518.

(13) Molecular modeling was performed with MacroModel-9.0/Maestro-4.1 program: Mohamadi, F.; Richards, N. G.; Guida, W. C.; Liskamp,R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

found as the corresponding methyl hemiketal derivative, which adopts a cone conformation.[14] In fact, a methanol solvent molecule attacked the carbonyl group at the upper rim, whereas the carbonyl group at the lower rim remained unreacted because of the steric hindrance at this position.[15]

The treatment of **2a** with $NaBH_4$ in EtOH resulted in the formation of two stereoisomeric diepoxy-diols **3a** and **3b**, each isolated in 34% yield, after column chromatography on silica gel (Scheme 2).[10] Clearly, their stereoisomerism

Scheme 2

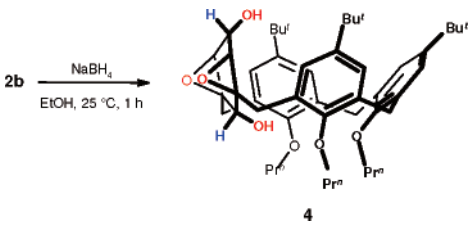


should arises from the exo or endo attack of $NaBH_4$ to the ketone groups present at both the upper and lower rim.

A detailed 1D and 2D NMR study of derivatives **3a** and **3b** indicated that they both had a partial cone conformation with the diepoxy-diol ring inverted. As concerns the stereochemistry of the reduction, 2D NOESY spectra in conjunction with MM3 calculations[10] indicated that for **3a** the hydride attack was exo to the ketone functionality at the upper rim and endo to that at the lower rim, while for **3b** the hydride attack was endo to both ketone functionalities.[10]

The analogous treatment of derivative **2b** with $NaBH_4$ in EtOH resulted in the formation of diepoxy-diol **4** in 60% yield, after column chromatography on silica gel (Scheme 3).[10] Differently from **3a** and **3b**, derivative **4** adopts a cone

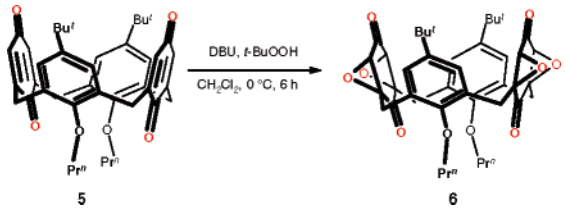
Scheme 3



conformation, as indicated by 1D and 2D NMR spectra. A detailed 2D NOESY study demonstrated that for **4** the hydride attack was exo to both ketone functionalities.[10]

The above results induced us to extend the epoxidation to 1,3-calixdiquinone derivatives **5**,[3f] which under conditions similar (0 °C, 6 h) to **2**, gave bis(diepoxy-*p*-dione) **6** in 60% yield (Scheme 4).[10]

Scheme 4

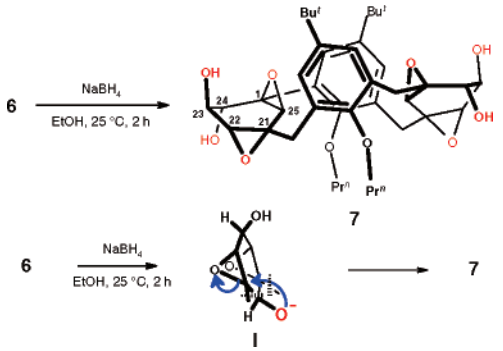


The molecular mass of **6** was confirmed by a pseudomolecular ion at *m*/*z* 713 in the ESI(+) MS spectrum, while a single 4H epoxy signal at 3.95 ppm and two carbonyl resonances at 191.3 and 196.9 ppm in its ^1H and ^{13}C NMR spectra, respectively, were indicative of two equivalent diepoxy-*p*-dione moieties with a calix[4]arene structure possessing two orthogonal binary symmetry elements (C_{2v} symmetry).[10]

These symmetry elements are only compatible with a cis geometry of the two epoxide rings on each of the two distal diepoxy-*p*-dione moieties. Instead, the exo or endo face selectivity of the epoxidation remains to be defined. The exo stereochemistry of the equivalent diepoxy-*p*-dione systems was confirmed by a NOESY cross-peak at 3.95/6.71 ppm between the epoxy H proton and the close ArH proton. This cross-peak was consistent with a calix[4]arene cone conformation for derivative **6**, which was confirmed by the presence of an AX system for $ArCH_2$ groups in its ^1H NMR spectrum (1.89/4.19 ppm, 8H, J = 13.7 Hz).[10] The high exo face selectivity observed for the epoxidation of **5** could be explained by the high kinetic or thermodynamic stability of the cone conformation of the starting material and of the relevant intermediates.

The treatment of **6** with $NaBH_4$ in EtOH resulted in the formation of **7**, isolated in 27% yield, after column chromatography on silica gel (Scheme 5).[10] The presence of two

Scheme 5



rearranged dianhydroinositol[16,17] systems in **7** was readily evidenced by 1D and 2D NMR spectra.[10] It is worth noting

(14) For another example of stable monohemiketal calix[4]arene derivative, see: Timmerman, P.; Harkema, S.; van Hummel, G. J.; Verboom, W.; Reinhoudt, D. N. *J. Inclusion Phenom. Macrocyclic Chem.* **1993**, *16*, 189.

(15) Analogously, Lin and coworkers (see ref 7b) reported that when a calix[4]monoquinone derivative was protected with ethylene glycol only the carbonyl group at the upper rim was masked with a ketal functionality whereas the carbonyl group at the lower rim was left unreacted because of steric hindrance.

(16) (a) Suami, T.; Ogawa, S.; Oki, S. *Chem. Lett.* **1973**, *52*, 901. (b) Ogawa, S.; Oki, S.; Suami, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1095.

Figure 2. X-ray crystal structure of calixinositol **7** (nonpolar H atoms omitted).

that derivatives **3**, **4**, and **7** represent hybrid calixarenes containing inositol moieties, and therefore, they can be termed as *calixinositols*, a subclass of the larger calixcyclitol family.[5,17]

The two dianhydroinositol moieties in **7** are symmetrically interchangeable via a C_2 axis giving rise to only one set of dianhydroinositol resonances in the ^{1}H NMR spectrum. In particular, a 2H epoxy singlet at 2.56 ppm relative to proton on C-25 (see Scheme 5) was present in the ^{1}H NMR spectrum, while the epoxy H-22 proton resonated at 3.27 ppm and showed a *J* coupling of 2.9 Hz with the vicinal carbinolic H-23 proton (4.32 ppm, 2H). This coupling constant indicated their trans relationship.

The carbinolic H-23 signal indeed appeared as a double−double−doublet because, in addition to H-22, it showed vicinal *J* couplings with D_2O-exchangeable 23-OH proton at 3.18 ppm ($J = 12.3$ Hz) and with vicinal carbinolic H-24 proton (4.05 ppm, $J = 2.8$ Hz). This latter signal was further coupled ($J = 12.5$ Hz) to its vicinal 24-OH proton at 3.06 ppm. The structure of dianhydroinositol system was confirmed by means of a 2D-NOESY spectrum.[10] In fact, a diagnostic cross-peak was observed between H-23 and H-24, indicating their spatial proximity. In addition, strong cross-peaks were observed between carbinolic H-23 and 24-OH protons, and between carbinolic H-24 and 23-OH protons.

A single-crystal X-ray diffraction study confirmed the structural assignment of calixinositol **7** (Figure 2).[10] In the solid state **7** adopts a very flattened cone conformation with the two inositol moieties in *out* orientation. Each hydroxyl group is engaged in an intramolecular H-bond with the proximal cis epoxy oxygen (the O···O distances are 2.77 and 2.86 Å). The two syn-distal aromatic rings are almost parallel (16.3°) and staggered by 36.7° because of a structural distortion which leads to a twisted cone conformation. It is worth noting that **7** is a chiral compound; therefore, in the centrosymmetric crystal two 1:1 mirror-image molecules are present.

The formation of calixinositol **7** from bis(diepoxy-*p*-dione) **6** is likely the result of an initial exo reduction of carbonyl groups in **6** to give **I** (Scheme 5). Then, a Payne's rearrangement,[18] gives rise to an oxirane-ring migration converting intermediate **I** to **7**.[19]

In conclusion, we have here reported a valid procedure for the introduction of oxygenated functions into de-*tert*-butylated calixarene walls to give *cis*-diepoxy-*p*-dione systems. The easy $NaBH_4$ reduction of these derivatives affords hybrid calixinositols, which belongs to the larger calixcyclitol family.[5] The reductive opening of the epoxy rings of **3**, **4**, and **7** and the extension of these procedures to larger calix[*n*]arenes ($n = 6$, 7, and 8) are currently under study with the aim to exploit larger calixarene cavities in recognition processes.

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Supporting Information Available: Synthetic details, ^{1}H/^{13}C and 2D NMR data, MM3 energy-minimized structures, and X-ray crystal data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) In accordance with the IUPAC cyclitol nomenclature, the diepoxy-cyclohexanediol moieties in **3**, **4**, and **7** can be defined as dianhydroinositol rings (*J. Biol. Chem.* **1968**, *22*, 5809). In fact, for the IUPAC rules, 1,2,3,4,5,6-cyclohexanehexols are termed generically as 'inositols', which are a class of the cyclitol (cycloalkanes containing one hydroxyl group on each of three or more ring atoms) family.

(18) Payne, G. B. *J. Org. Chem.* **1962**, *27*, 3819.

(19) A very similar epoxy interchange was already observed in the $LiAlH_4$-mediated synthesis of some calixcyclitol derivatives.[5] In that case, a subsequent reductive epoxy-opening followed by an intramolecular S_N2 attack led to an oxetane ring forming an unusual 6-oxabicyclo[3:1:1]heptane system.