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Communications

Oxidative Cyclization of Calix[4]arene

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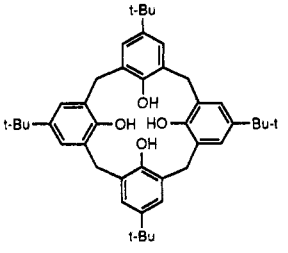
Summary: *p-tert*-Butylcalix[4]arene was converted in a single step into a system containing carbonyl and ether binding groups.

Introduction

Calix[*n*]arenes are synthetic macrocycles composed of *n* phenolic and methylenic units.[1] Considerable synthetic efforts have been invested in the last years in the modification of the binding OH groups of the calixarenes.[1,2] In this paper we report that the parent 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene[3] (**1**) can be converted in a single step into a system (**2**) with carbonyl and five-membered cyclic ether functionalities. The procedure permits one to convert calixarenes into molecules containing carbonyl and ether binding sites like those of a variety of natural ionophores.



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For the desired transformation of **1** two OH groups must be converted into cyclic five-membered ether functionalities while the remaining two groups must be transformed into keto binding groups. Reaction of **1** with tetrabutylammonium tribromide in a two-phase basic system (CH_2Cl_2, aqueous NaOH) resulted in a smooth conversion to system **2**.[4] In this oxidative cyclization reaction[5] two phenolic rings are converted to cyclohexadienone rings, while the remaining phenolic aryl groups retain their aromaticity, and their hydroxylic groups form a cyclic ether by reaction with the 2-position of the cyclohexadienone rings.[6] No ring bromination is observed (i.e., electrophilic aromatic substitution) since the para and ortho positions to the OH groups are blocked by the *tert*-butyl and methylene groups, respectively. In the absence of base no reaction was observed and only starting material was isolated. The formation of **2** can be rationalized by assuming that under the reaction conditions the calixarene is deprotonated and the resulting phenolate is brominated yielding, in the first step, a *o*-bromocyclohexadienone derivative, which in a second step undergoes an intramolecular nucleophilic substitution reaction in which the

(1) For comprehensive reviews on calixarenes see: Gutsche, C. D. *Calixarenes*, Royal Society of Chemistry: Cambridge, 1989; Gutsche, C. D. In *Synthesis of Macrocycles: Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; p 93.

(2) For a recent example see: Nakasaki, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 1063.

(3) Gutsche, C. D.; Iqbal, M. *Org. Synth.* **1989**, *68*, 234.

(4) Preparation of **2**: To a solution of 1 g of **1** (1.54 mmol) and 1.48 g tetrabutylammonium tribromide (3.07 mmol) in 75 mL of CH_2Cl_2 were added 50 g of a 28% aqueous NaOH solution. The solution was refluxed under stirring for 5 h. The solution was cooled to rt and 50 mL of CH_2Cl_2 and 50 mL water were added, and after phase separation the organic phase was washed with brine and water and then dried ($MgSO_4$). After evaporating the organic solvent the residue was chromatographed (medium pressure, silica, eluent: petroleum ether/methylene chloride (2:3)). 300 mg of **2A** (0.466 mmol, 30%) and 170 mg of **2B** (0.264 mmol, 17%) were obtained. Both compounds have mp 270 °C, dec.

(5) Oxidation reactions of calixarenes to calixquinones have been previously reported. Morita, Y.; Agawa, T.; Kasai, N.; Nomura, E.; Taniguchi, H. *Chem. Lett.* **1989**, 1349. van Loon, J.-D.; Arduini, A.; Coppi, L.; Verboom, W.; Pochini, A.; Ungaro, R.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1990**, *55*, 5639. Grynszpan, F.; Dinoor, N.; Biali, S. E. *Tetrahedron Lett.* **1991**, *32*, 1909.

(6) For a review on spirodienones see: Ward, R. S. *Chem. Brit.* **1973**, *9*, 444. See also: Kasturi, T. R.; Rajasekhar, B.; Raju, G. J.; Reddy, G. M.; Sivaramakrishnan, R.; Ramasubbu, N.; Vankatesan, K. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2375.

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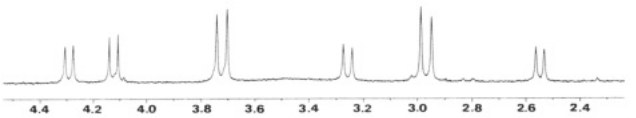
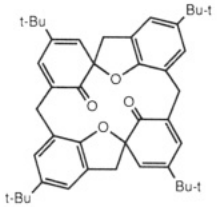


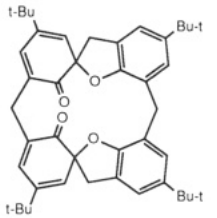
Figure 1. 400-MHz ^{1}H NMR spectrum of the methylene region of **2B**.

bromine is replaced by the phenoxy group of a neighboring ring resulting in a cyclic five-membered ether. The tetrabutylammonium tribromide serves a double role: as a normal phase-transfer catalyst in facilitating the base-induced deprotonation and as a carrier of bromine.

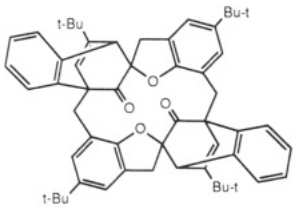
The products of the reaction described above were two yellow species **2A** and **2B** which were separated by medium pressure liquid chromatography (SiO_2, eluent: petroleum ether/CH_2Cl_2). **2A** and **2B** slowly isomerize to



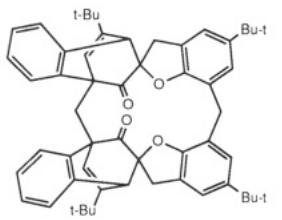
2A



2B



3A



3B

one another in solution. Their yellow colors are in agreement with a dienone structure. Microanalysis indicated that no bromine atoms were incorporated in the products. Both species contain carbonyl groups and no OH groups as judged by the IR (ν C=O stretching (Nujol) **2A**: 1670 (s), 1650 (w); **2B**: 1690 (s), 1645 (w) cm^{-1}) and ^{13}C NMR data (δ C=O ($CDCl_3$) **2A**: 195.7; **2B**: 195.1 ppm). A peak at m/z 644 which appears in the EI mass spectra of each compound corresponds to the molecular peak as suggested by the CI and FAB mass spectra. In addition to the carbonyl signal, **2A** displays 10 signals in the ^{13}C NMR in the δ 152–119 ppm region, corresponding to carbons of sp^2 hybridization. A signal is present at δ 81.7 which can be ascribed to C-2, i.e., the sp^3 carbon attached to the ether oxygen. Six aliphatic signals were observed in the δ 38.1–27.9 ppm region. **2A** displays in the ^{1}H NMR spectrum (400 MHz, $CDCl_3$) two *t*-Bu signals (δ 1.31 and 0.99 ppm), two aromatic signals at δ 7.08 and 7.00 ppm, two cyclohexadienone signals at δ 6.58 and 5.81 ppm, and four doublets at δ 4.10–2.91 ppm for the methylene protons. The observed spectrum is consistent only with a structure of either C_2 or C_i symmetry, i.e., with a structure with alternating *o*-cyclohexadienone and aromatic rings. Heating a sample of **2A** in nitrobenzene-d_5 did not result in any broadening of the NMR signals, but resulted only in **2A** $\rightleftharpoons$ **2B** equilibration. Compound **2B** displays in the ^{13}C NMR a single C=O signal, eight signals corresponding to sp^3 carbons (including C-2), and 10 signals corresponding to C(sp^2). Compound **2B** displays in the ^{1}H NMR two *t*-Bu signals (δ 1.24, 1.13 ppm), four signals at low field (two aromatic signals at δ 7.14 and 6.95 and two cyclohexadienone signals at δ 6.80 and 5.91 ppm) and *six* doublets in a 1:1:2:1:2:1 ratio (δ 4.29 (J = 12.4 Hz), 4.12 (J = 13.1 Hz), 3.72 (d, J = 15.5 Hz), 3.26 (J = 13.2 Hz), 2.96 (J = 15.5 Hz), 2.54 ppm (J = 12.4 Hz)) for the methylene protons (Figure 1). The NMR spectrum is compatible only with a structure with C_s symmetry in which the mirror plane is bisecting two non vicinal methylene carbons. In order to accommodate this symmetry, the two cyclohexadienone rings must therefore be located at proximal (1,2) positions. On the basis of these data, we assign the structures shown to compounds **2A** and **2B**. Compound **2A** has a cyclic disposition of the binding groups and is therefore analogous to the rotolactones[7] while **2B** with a mirror symmetry disposition of the binding groups is analogous to the reflactones.[7] The calculated structures of both compounds using the MM2 program as implemented in MACROMODEL V3.0[8] are shown in Figure 2.[9]

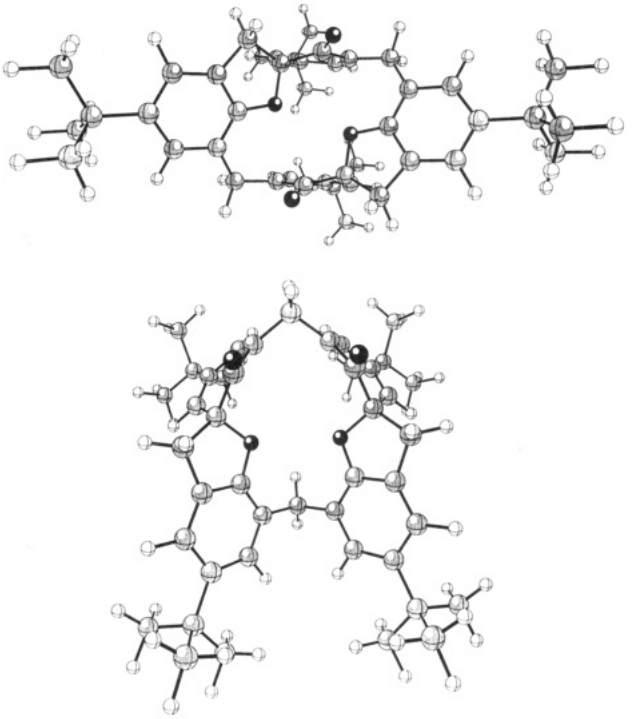


Figure 2. Calculated conformations of compounds **2A** (top) and **2B** (bottom).

The carbonyl groups of **2A** do not react with hydrazine or hydroxylamine. Treatment of **2A** with $LiAlH_4$ or with $H_2/Rh/Al_2O_3$ regenerates **1**. Treatment of **2A** and **2B** with benzyne (generated from benzenediazonium 2-carboxylate)[10] results in the formation of the bis-Diels–Alder adducts **3A** and **3B**, respectively. In contrast with **2A** and **2B**, **3A** and **3B** do not isomerize in solution. According to the NMR spectra **3A** and **3B** have C_2 or C_i and C_s symmetry, respectively, which indicates that the symmetry of the starting material was retained, and therefore that for each compound both Diels–Alder additions occurs with similar face selectivity.

Compounds **2** and **3** represent the first example in which the hydroxylic oxygens groups of a calixarene have been

(7) For a review on the synthesis of synthetic ionophores see: Lifson, S.; Felder, C. E.; Shanzer, A.; Libman, J. In *Synthesis of Macrocycles: Design of Selective Complexing Agents*; Izatt, R. M., Christensen, J. J., Eds.; Wiley: New York, 1987; p 241.

(8) For a description of the MACROMODEL program see: Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, E.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *11*, 440.

(9) According to the calculations, the C_2 stereoisomer of **2A** is of lower energy than the meso (C_i) form.

(10) Adams, R.; Johnson, J. R.; Wilcox, C. F., Jr. *Laboratory Experiments in Organic Chemistry*; Macmillan: New York, 1970; p 452.

converted into nonquinonic carbonyl oxygens. The properties of **2** and related systems are currently under study and will be reported in due course.

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Registry No. 1, 60705-62-6; **2A**, 138899-86-2; **2B**, 138899-87-3; **3A**, 138899-88-4; **3B**, 138899-89-5; benzyne, 462-80-6.

Strain-Directed Bridge Cleavage of (Phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane Derivatives: Application to the Total Synthesis of Carba-α-DL-glucopyranose[1]

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Summary: New methodology to prepare highly oxygenated cyclohexenylsulfones by regioselective β-elimination of (phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane derivatives has been developed, and its application to the total synthesis of carba-α-DL-glucopyranose is described.

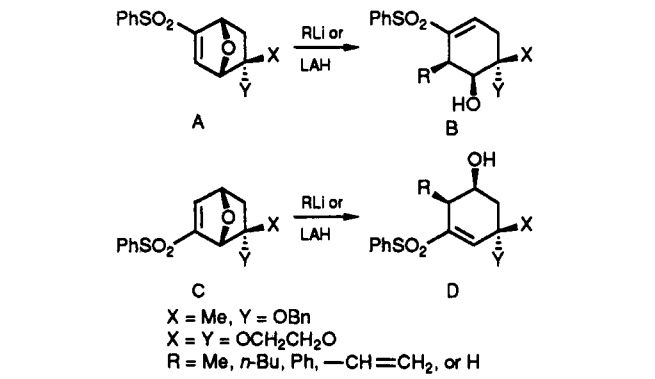
7-Oxanorbornenic derivatives are useful intermediates in syntheses of molecules of biological interest.[2] The key step in many of the efforts in this area is the cleavage of the oxygen bridge under basic,[3] reductive,[4] or acidic[5] conditions. However, most of these methods fail in some cases,[6] and thus this bridge opening step remains a current problem.

A few years ago we reported a regiospecific synthesis of substituted cyclohexenediols from 7-oxanorbornen-2-ols and organolithium reagents.[7] Subsequently, we developed fully regiocontrolled methodology toward either regioisomer via vinyl sulfones A and C (Scheme I) to produce hydroxycyclohexenyl sulfones B and D.[8] While some R groups (—CH=CH_2) may be readily transformed into oxygenated functionalities, we sought a more direct route to introduce an oxygen-centered nucleophile in order to increase the scope of the methodology (synthesis of cyclitols, pseudosugars, etc.). Unfortunately, a number of attempts to carry out the direct S_N2' bridge cleavage using oxygen and nitrogen nucleophiles were unsuccessful.

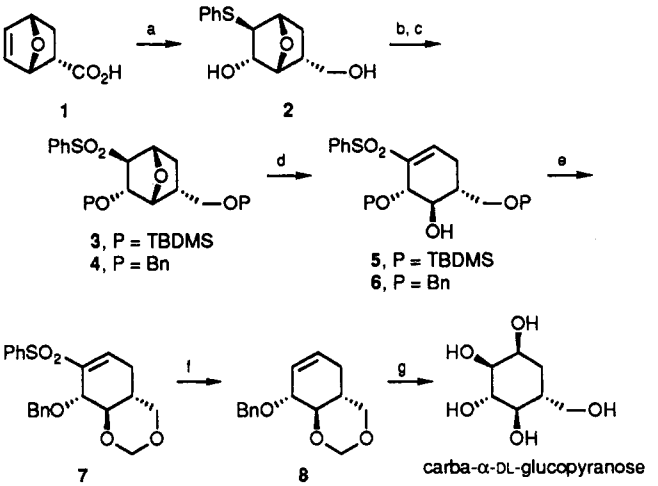
At this stage we envisioned that deprotonation and subsequent β-elimination of a readily available[9] bicyclic sulfone such as E, in which the sulfone functionality is flanked by two ethereal oxygens at the β and β′ positions, could proceed selectively toward F due to the strained character of the oxygen bridge.[10] In this report we disclose our preliminary results in this field and the application of this strain-directed process to the total synthesis of carba-α-DL-glucopyranose.[11]

Regio- and stereospecific sulfenolactonization of 7-oxabicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid 1[9,12] followed by reduction with LAH afforded diol **2** in excellent yield[13] (Scheme II). Protection as a bis-(*tert*-butyldimethylsilyl) ether followed by oxidation with magnesium monoperoxyphthalate (MMPP) yielded the desired model bicyclic sulfone **3**. Strain-directed β-elimination was then achieved by deprotonation with 1.5 equiv of *n*-BuLi in toluene, using freshly distilled TMEDA (20%) as a cosolvent, at −78 °C to give **5**. It should be pointed out that the use of the toluene–TMEDA system is crucial for the success of the reaction.[14] The challenging desulfonylation[15] of highly oxygenated vinyl sulfone **5** was then addressed, and a number of procedures were examined; however, the analysis of the reaction mixtures was com-

Scheme I



Scheme II[a]



[a] Key: (a) (1) PhSCl, $CHCl_3$, 0 °C to rt, 48 h, 82%; (2) LAH, THF, 0 °C, 1 h, 90%; (b) TBDMSCl, imidazole, DMF, rt, 48 h, 95% (for **3**) or BnCl, KOH, dioxane, Δ, 3 h, 90% (for **4**); (c) MMPP, MeOH, 0 °C, overnight, (95% for **3**, 97% for **4**); (d) 1.5 equiv *n*-BuLi, Tol/TMEDA, −78 °C, 2 h, 80% (for **5**) or 3 equiv of *n*-BuLi, Tol/TMEDA/CH_2Cl_2, −78 °C, 15 min, 90% (for **6**); (e) $(MeO)_2CH_2$, *p*-TsOH, CH_2Cl_2, 3A MS, Δ, 36 h, 88%; (f) Na(Hg), MeOH, Na_2HPO_4, −20 °C to rt, 4 h, 75%; (g) (1) OsO_4, Me_3NO, acetone/H_2O, rt, overnight, 95%; (2) BF_3·OEt_2, EtSH, rt, overnight, 90%.

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