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Synthesis of 2-Alkyl- and 2-Carboxy-*p*-*tert*-butylcalix[4]arenes via the Lithiation of Tetramethoxy-*p*-*tert*-butylcalix[4]arene

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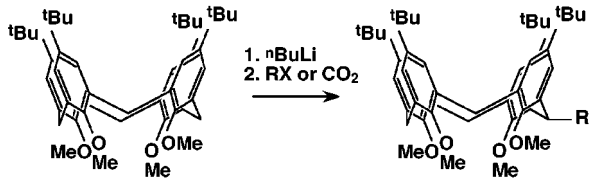
ABSTRACT



Tetramethoxy-*p*-*tert*-butylcalix[4]arene reacts readily with *n*-butyllithium to give a putative monolithiated intermediate that is substituted with alkyl halides and carbon dioxide to give in 60–75% yield conformationally mobile calix[4]arenes monosubstituted at the methylene bridge (2-position). 2-Alkyl- and 2-benzyl-substituted tetramethoxycalix[4]arenes are converted in 62–68% overall yield to the corresponding tetrahydroxy-*p*-*tert*-butylcalix[4]arenes by treatment with boron tribromide. The tetrahydroxy-*p*-*tert*-butylcalix[4]arenes exist in the *cone* conformation at room temperature in $CDCl_3$ as judged by NMR spectroscopy.

Because it takes on well-defined conformations and is easily modified at the upper (aromatic) and lower (phenolic) rim positions, the calix[4]arene[1] forms the core of many complex molecules.[2,3] Relatively unexplored are modifications at the methylene group that joins the aromatic rings of the calix[4]arene (methylene bridge). Work by others to make such derivatives either by fragment condensation[4−8] or by direct reaction[9−12] often has had the drawbacks of low yields and limited variability of the substituent group.[13] Despite these obstacles, the methylene bridge region (2,8,14,20-) remains an attractive target for modification. Among other reasons, it provides a site of reactivity complementary to the upper

(1) The IUPAC names for these molecules are long (e.g., 5,11,17,23-tetrakis(1,1-dimethylethyl)-25,26,27,28-tetramethoxypentacyclo-[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene for compound **1**). We use an abbreviated nomenclature suggested by Gutsche in ref 3.

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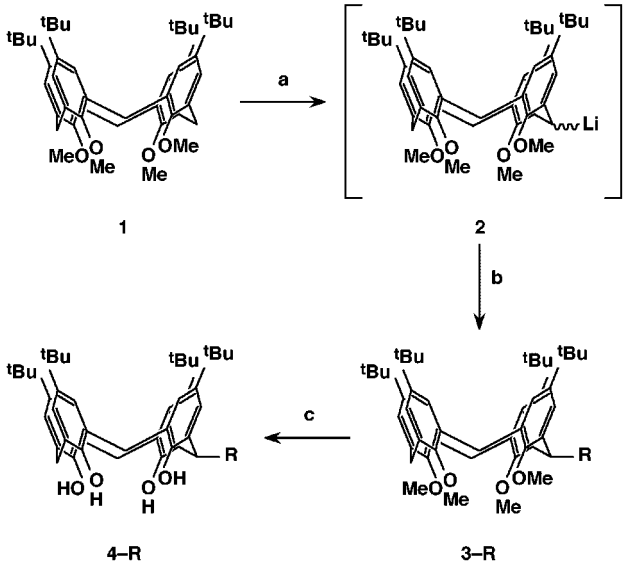
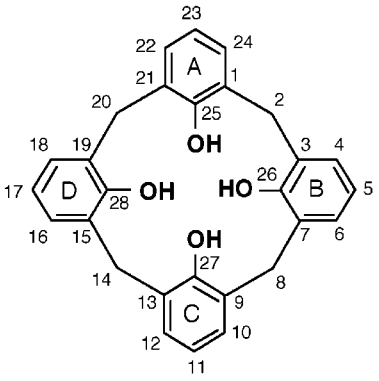
(5,11,17,23-) and lower rim (25,26,27,28-) sites in that substituents at the methylene bridge are likely to be equatorial,[8] extending in a direction nearly perpendicular to the principal axis of the calixarene rather than nearly parallel to it. Such substituents could provide diverse functions including enhanced solubility or linkage to a solid support, while leaving all upper and lower rim sites open to modification. We report here our preliminary results on a straightforward reaction for the monosubstitution of tetramethoxycalix[4]-arenes at the methylene bridge position (Scheme 1). This

Scheme 1 [a]



[a] Reagents and conditions: (a) 4.5 equiv ^{n}BuLi, THF, rt; (b) excess (typically 8.0 equiv) electrophile; (c) (for R = Me, Et, CH_2Ph) excess (>6.0 equiv) BBr_3, CH_2Cl_2, −78 → 25 °C.

reaction proceeds in good yield, incorporates alkyl and carboxy groups, and allows for further reactivity at all upper and lower rim sites and in some cases (carboxy, *p*-bromobenzyl) at the methylene bridge substituent itself.



It is well-known that benzylic positions with electron-donating ortho substituents can be deprotonated with strong base (lateral lithiation, directed ortho metalation)[14,15] and subsequently reacted with electrophiles.[16] The calixarene 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetramethoxycalix[4]-arene[17] (**1**) possesses four benzylic sites per molecule and no other acidic hydrogens.[18] The potential for multiple deprotonation and the formation of product mixtures and regioisomers exists in this system, but, as will be shown below, conditions completely favoring monosubstitution were easily achieved.

Calixarene **1** (room temperature, THF) reacted immediately with ^{n}BuLi (4.5 equiv, 1.2−1.6 M in hexanes) to produce a blood red solution, which was presumed to contain lithiated intermediate **2**. Similar results were obtained when 6.0 equiv tetramethylethylenediamine (TMEDA) was added to augment the ^{n}BuLi; reactions described below (see Table 1) were carried out by either or both methods. Methyl iodide

Table 1. Electrophiles Used and Yields Obtained in the Synthesis of Tetramethoxycalixarenes (**3**-R) and Tetrahydroxycalixarenes (**4**-R)

R	electrophile	**3**-R yield (%)	**4**-R[a] yield (%)
Me	MeI	75[b]	68
Et	EtI	64	66[b]
CH_2Ph	$PhCH_2Br$	72	62[b]
COOH	CO_2	75[b]	
CH_2Ar^{Br}	*p*-bromobenzylbromide	60	

[a] Yields of calixarene **4**-R are for the overall conversion from **1** without recrystallizing intermediate **3**-R. [b] Six equivalents of TMEDA used in deprotonation reaction.

(8.0 equiv) added to the reaction mixture quenched the color within 1 s; within 30 s a fine white precipitate of lithium iodide began to form. The product was isolated after workup as a yellow residue that was recrystallized from methanol to a colorless microcrystalline powder (**3**-Me) in 75% yield.[19]

The ^{1}H NMR spectrum of compound **3**-Me exhibited broad overlapping resonances and was distinct from that of compound **1** but was not helpful in further characterization of the substance. Tetramethoxycalix[4]arene **1** is conformationally mobile at room temperature in $CDCl_3$;[20] the spectrum of **3**-Me suggested a similar conformationally mobile tetramethoxycalix[4]arene, presumably methylated at one or more methylene bridge positions. A mixture of products (including starting material) could not be ruled out from this spectrum. High resolution quadropole time-of-flight electrospray mass spectrometry definitively established the presence of a monosubstituted product (M + Na calcd 741.4859, M + Na found 741.4852, Δ 0.9 ppm).

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To further prove the structure of **3**-Me we investigated its reactivity with BBr_3, a reagent used for the facile conversion of aryl methyl ethers to phenols.[21] A solution of calixarene **3**-Me in CH_2Cl_2 was cooled to −78 °C after which 6.0 equiv of BBr_3 in CH_2Cl_2 was added via syringe. The dark brown reaction mixture was allowed to warm to room temperature and stir for 1 h. After an aqueous workup and recrystallization from chloroform/methanol, product **4**-Me was obtained in 68% yield.

The ^1H and $^{13}C\{^1H\}$ NMR spectra of compound **4**-Me leave no doubt about its identity. Compound **4**-Me is a tetrahydroxycalix[4]arene that adopts the *cone* conformation in $CDCl_3$ solution. Its ^1H NMR spectrum is consistent with C_s symmetry, exhibiting two *tert*-butyl signals, two sets of aromatic AB spin systems, and resonances attributable to the methyl group and methylene bridge protons. A singlet for the hydroxyl protons suggests they are either accidentally equivalent or undergoing exchange. The spectrum shows distinct AX systems for the methylene bridge protons across from the methyl substituent (14-position) and for the methylene bridge protons adjacent to the methylated position (8-, 20-positions). The methine proton at the 2-position is coupled to the 2-methyl protons ($J = 7.3$ Hz). Its chemical shift (δ 4.74 ppm) suggests that it is in an axial position,[8] and thus the substituent is equatorial. More convincing evidence comes from the 2D-NOESY spectrum for **4**-Me (400 MHz, C_6D_6) where cross-peaks are observed between the hydroxyl proton and methine proton and between the 2-methyl protons and aryl protons, which are in accord with the experimental and theoretical work of others on similar calixarenes.[7,8] The $^{13}C\{^1H\}$ NMR spectrum shows 12 aromatic resonances (12 expected) and six aliphatic resonances (eight expected; *tert*-butyl resonances accidentally equivalent). In this case and all others discussed below, a single conformation of the calixarene is detected by NMR spectroscopy; the spectra are consistent with mutual interconversion of equatorial and axial conformers that is *either* fast or slow on the NMR time scale.[8] The conformational equilibria of these calixarenes will be the subject of future investigations.

Compound **4**-Me was analytically pure; the ^1H NMR spectrum showed only resonances for monoalkylated product. There was no evidence of unsubstituted tetrahydroxycalixarene 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene (**5**) nor of any multiply substituted calixarenes when either ^{n}BuLi or ^{n}BuLi/TMEDA was used. This indicates that the lithiation reaction was essentially complete and selective for monoalkylation. To obtain the highest yields of **4**-Me, demethylation was carried out on crude **3**-Me that had not been purified by recrystallization.

Reconsidering **3**-Me, it was possible to observe it in the *cone* conformation as an adduct with Na^+ in a 2:1 mixture of $CDCl_3$ and CD_3CN that was saturated with sodium iodide. The NMR spectra (^1H and $^{13}C\{^1H\}$) of the Na^+ adduct [**3**-Me-Na^+] show sharp resonances that are consistent with the *cone* conformation.[22] In the ^1H NMR spectrum, resonances similar to those for **4**-Me were observed, except that there were no resonances for phenolic hydrogens but instead two distinct singlets attributed to the methoxy hydrogens. The ^{13}C NMR spectrum showed the appropriate number of resonances. All 2-substituted tetramethoxycalixarenes described below were characterized by this method as well as by HRMS; some were also converted to tetrahydroxycalixarenes.

To check the propensity of the calixarene anion to serve as a base rather than a nucleophile, it was allowed to react under similar conditions with ethyl iodide (possible β-elimination) and benzyl bromide (possible α-elimination). If elimination occurred, calixarene **1** would be regenerated; this would be easier to ascertain after the deprotection reaction, which would generate calixarene **5**. Reactions with each electrophile proceeded smoothly to give good yields of tetramethoxycalixarenes (**3**-Et, **3**-CH_2Ph) and tetrahydroxycalixarenes (**4**-Et, **4**-CH_2Ph), none of which contained measurable amounts of **1** or **5**, showing that elimination pathways are negligible under these reaction conditions.

Lithiated intermediate **2** reacted swiftly with excess CO_2 (added as a solid) to give the 2-carboxy-tetramethoxycalixarene **3**-COOH after a modified workup and recrystallization from methanol/water. Interestingly, the solubility of this calixarene is very different from that of the parent and alkylated calixarenes, which are soluble in halogenated solvents such as CH_2Cl_2 but not very soluble in alcohols such as methanol. Carboxy calixarene **3**-COOH showed a markedly higher solubility in methanol than did the alkyl-substituted calixarenes. As the limited solubility of typical calixarenes is cited as a drawback to their use in various applications,[2] such modifications that increase solubility should lead to more uses of calixarenes.

This synthetic method provides access to calixarenes with pendant functional groups at the methylene bridge, which are of interest for more complex syntheses. For example, calixarene **3**-COOH is expected to undergo further reactions (e.g., amide bond formation) at the carboxy position via standard organic reactions. To prepare a substrate for C−X (X = C, N, O) bond-forming reactions,[23] an aryl bromide functional group was added at the 2-position of the calixarene by the reaction of *p*-bromobenzylbromide with the lithiated intermediate **2**. This reaction gave the 2-(*p*-bromobenzyl)-tetramethoxycalix[4]arene in good yield (60%).

In summary, we have developed a new method for the selective preparation of monosubstituted calix[4]arenes with a variety of methylene bridge substituents, including some suitable for further reaction to make more complex molecules. Further studies on the scope of the reaction, the application of the products, and their conformational properties are currently underway.

Acknowledgment. We thank Dr. Steve Svejda (Air Force Research Laboratory Propulsion Directorate) for assistance

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with the 2-D NMR spectra. Mass spectrometry studies were conducted at the Ohio State University Campus Chemical Instrumentation Center. We are grateful to Aru Hill and Jill Pavlicek for experimental assistance. Partial support of this research from the Camille and Henry Dreyfus Foundation is acknowledged. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. This research was partially supported by an award from Research Corporation. The support of Denison University and the Denison University Research Foundation is gratefully acknowledged.

Supporting Information Available: Detailed experimental procedures and characterization data (^{1}H NMR, ^{13}C NMR, IR, HRMS or CH combustion analysis) for all **3**-R and **4**-R species and 2-D NOESY spectrum for **4**-Me. This material is available free of charge via the Internet at http://pubs.acs.org.

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