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Synthesis of Mono-*O*-alkylated Homooxacalix[3]arene and a Protection−Deprotection Strategy for Homooxacalix[3]arene

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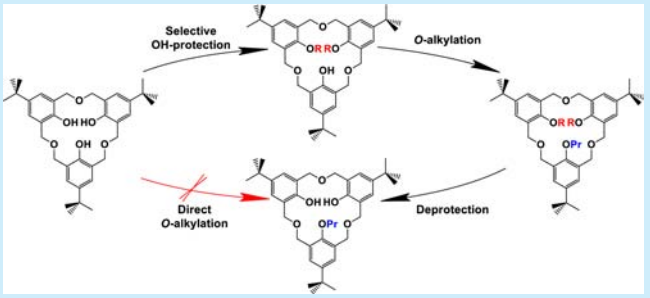
Supporting Information

ABSTRACT: The regioselective synthesis of mono-*O*-alkylated homooxacalix[3]arene is accomplished for the first time. The synthetic route relies on two key steps: (i) a facile protection of two OH groups at the lower rim of the homooxacalix[3]arene and (ii) the deprotection of 9-anthrylmethyl groups via the Pd/C-catalyzed hydrogenation under atmospheric hydrogen. An efficient protection−deprotection strategy for the functionalization of homooxacalix[3]arene is presented.



Homooxacalix[3]arene is related to calix[4]arene and to 18-crown-6 ether and possesses unique structural features, such as a cavity composed of an 18-membered ring, together with two basic conformations (cone and partial-cone) and C_3-symmetry. The macrocycles including three ethereal linkages are relatively flexible and thus can provide a suitable binding environment for species that require trigonal-planar, tetrahedral, or octahedral coordination.[1] In recent years, homooxacalix[3]arenes have been extensively investigated as host compounds that may be functionalized to induce specific recognition for metal cations,[2] ammonium ions,[3] lanthanide ions,[4] and fullerenes.[5]

In most cases, the functionalization of homooxacalix[3]arene has been achieved by *O*-alkylation of the OH groups at the lower rim. Shinkai et al. reported the influence of *O*-substituents on the conformational isomerism of homooxacalix[3]arene. It was established that the interconversion between conformers, which occurs via oxygen-through-the-annulus rotation (Figure 1), is sterically allowed for methyl and ethyl groups, but inhibited by *O*-substituents the size of propyl and beyond.[6] Previous reports have confirmed that the template effect of alkali metal cations plays an important role in the *O*-alkylation reaction of homooxacalix[3]arene and allows for the different conformers of homooxacalix[3]arene to be selectively synthesized.[6,7] Various functional groups have been introduced into the lower rim of homooxacalix[3]arene by *O*-alkylation reactions with XCH_2Y type functionalized alkyl halides (X is a leaving group, and Y is a functional group).

It is known that three different kinds of derivatives (mono-, di-, and tri-*O*-alkylation) exist in *O*-alkylated homooxacalix[3]arene. Among them, a great number of tri-*O*-alkylated homooxacalix[3]arenes have been synthesized as C_3-symmetric hosts for the complexation of organic and inorganic guest species.[8] On the other hand, the di-*O*-alkylated homooxacalix[3]arenes exhibit inherently chiral pseudo-C_2 symmetry and have been used to explore chiral recognition.[9] Given the associated synthetic difficulty, the selective mono-*O*-alkylation of an OH group at the lower rim of a homooxacalix[3]arene has not yet been reported. Lately, a very interesting protection−deprotection methodology providing general access to monofunctionalized homooxacalix[3]arene was reported, allowing the introduction of a single *para*-OH group and its subsequent transformation into the monoquinone.[10] Herein, we report the synthesis of the mono-*O*-alkylated homooxacalix-

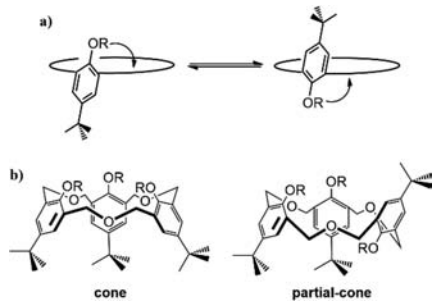


Figure 1. (a) Rotation of phenol ring and (b) two conformational isomers of homooxacalix[3]arene.

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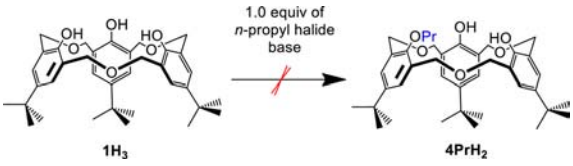
[3]arene by using a protection−deprotection method with 9-anthrylmethyl groups.

In terms of introduction of bulky substituents onto the OH groups, the *n*-propyl group (Pr) is bulky enough to suppress the oxygen-through-the-annulus rotation and results in conformational isomers.[6,11] Thus, in this study we used an *n*-propyl group to fix the conformation. In order to synthesize the mono-*O*-alkylated homooxacalix[3]arene **4PrH$_2$**, the parent homooxacalix[3]arene **1H$_3$** was *O*-alkylated with 1.0 equiv of *n*-propyl halide under various reaction conditions including using different halides, solvents, bases, and reaction times (Scheme 1). However, all attempts to synthesize **4PrH$_2$** directly from

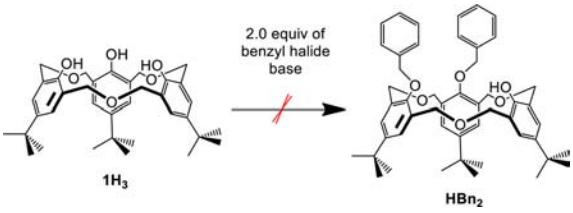
Scheme 1. Direct Mono-*O*-alkylation of Homooxacalix[3]arene 1H$_3$



homooxacalix[3]arene **1H$_3$** failed, affording the di- and tri-*O*-alkylated derivatives, as well as the recovery of the starting compound **1H$_3$**. This finding can be rationalized by the different reaction rates in the *O*-alkylation reaction processes; the trisubstituted process has the fastest reaction rate, whereas the monosubstituted process is the slowest.[7f] The regioselective synthesis of the mono-*O*-alkylated **4PrH$_2$** proved to be more difficult given that the usual methods for the direct introduction of one propyl group at the phenolic oxygen of **1H$_3$** were unsuccessful. To overcome this problem, we resorted to an indirect protection−deprotection route.

Among protecting groups, benzyl derivatives have attracted much attention due to their deprotection conditions being orthogonal to other protecting and functional groups. They have been extensively used as a protecting group for alcohols, phenols, amines, and carboxylic acids.[12] Inspired by these results, we attempted the synthesis of di-*O*-benzylated homooxacalix[3]arene **HBn$_2$** by *O*-benzylation of **1H$_3$** with 2.0 equiv of benzyl halide (Scheme 2). However, it was disappointing

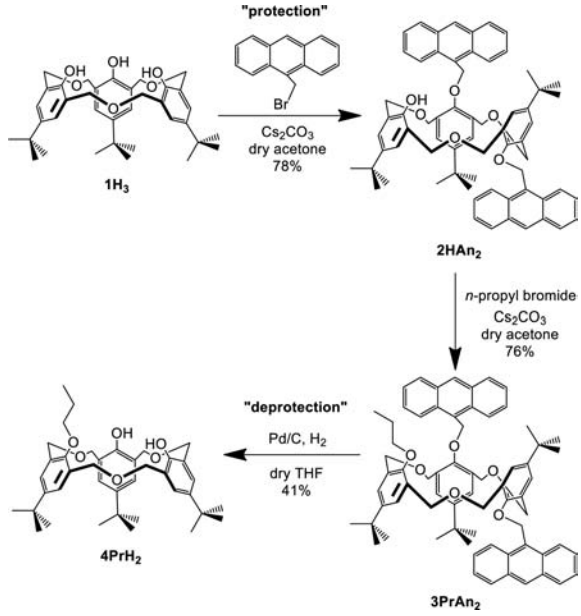
Scheme 2. Synthesis of Di-*O*-benzylated Homooxacalix[3]arene HBn$_2$



that the regioselective introduction of two benzyl groups onto the phenolic oxygens of **1H$_3$** was unsuccessful despite alterations to the reaction conditions. Only the tri-*O*-benzylated product was obtained together with the recovery of the starting compound **1H$_3$**. Thus, the synthesis of **4PrH$_2$** by using benzyl as the protecting group was not possible.

Interestingly, recent studies conducted in our laboratory have demonstrated that the di-*O*-9-anthrylmethyl-substituted homooxacalix[3]arene **2HAn$_2$** could be conveniently synthesized in good yield by the reaction of **1H$_3$** with 9-anthrylmethyl bromide.[13] This finding inspired us to further explore the possibility of utilizing the 9-anthrylmethyl group as a protecting group for homooxacalix[3]arene. Thus, we have attempted to synthesize the mono-*O*-alkylated homooxacalix[3]arene **4PrH$_2$** by using 9-anthrylmethyl as protecting groups, and the synthetic route is shown in Scheme 3. The selective *O*-

Scheme 3. Synthesis of Mono-*O*-alkylated Homooxacalix[3]arene 4PrH$_2$



alkylation reaction of homooxacalix[3]arene **1H$_3$** with 2.0 equiv of 9-anthrylmethyl bromide using acetone as solvent in the presence of either Cs_2CO_3 or K_2CO_3 as base, afforded the di-*O*-substituted **2HAn$_2$** in 78% yield. The ^{1}H NMR spectrum of **2HAn$_2$** presents two singlets for the *tert*-butyl protons at δ 1.15 and 1.21 ppm (relative intensity 2:1). Additionally, the resonances for the two anthracene groups appear as a set of peaks in the range δ 7.18 to 8.35 ppm. The rotation of the unmodified OH group is still allowed, so that the two 9-anthrylmethyl groups are regarded to be equivalent both in a cone and in a partial-cone conformation. Therefore, one cannot specify the conformation from the ^{1}H NMR spectrum. Fortunately, X-ray diffraction quality single crystals of **2HAn$_2$·1.5EtOAc** were obtained by slow evaporation of a solution of **2HAn$_2$** in ethyl acetate. The structure and conformation of **2HAn$_2$** were confirmed by a single crystal X-ray diffraction analysis. It revealed that one of the anthracene groups of **2HAn$_2$** is directed upward and the second downward (Figure 2). Thus, both the NMR spectroscopy and the X-ray crystallographic analysis revealed that **2HAn$_2$** adopts a partial-cone conformation.

Subsequently, the di-*O*-substituted homooxacalix[3]arene **2HAn$_2$** with one residual OH group was reacted with excess *n*-propyl bromide in the presence of Cs_2CO_3 in acetone to give **3PrAn$_2$** in 76% yield. The ^{1}H NMR spectrum of **3PrAn$_2$** exhibits a triplet at δ 0.74 ppm, a multiplet at δ 1.32−1.37 ppm, and a double triplet at δ 3.18 and 3.31 ppm, which indicated that the *n*-propyl group was successfully introduced. Moreover, different from the case of **2HAn$_2$**, the resonances for the *tert*-butyl protons appeared as three singlets at δ 0.85, 0.89, and 1.20 ppm (relative intensity 1:1:1). The three inequivalent *tert*-

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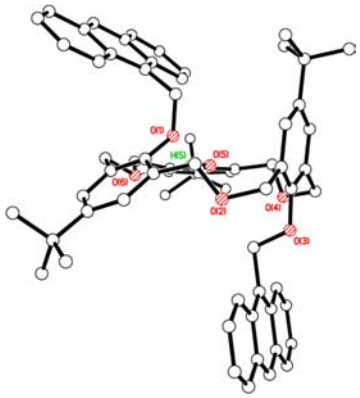

Figure 2. X-ray crystal structure of **2HAn$_2$**. Hydrogen atoms except phenolic H(5) which H-bonds to O(6) are omitted for clarity.

butyl peaks support the partial-cone conformation of **3PrAn$_2$**. Since the oxygen-through-the-annulus rotation is inhibited, the precursor **2HAn$_2$** adopts a partial-cone conformation in which the 9-anthrylmethyl groups are placed on opposite sides. Thus, the two anthracene groups of **3PrAn$_2$** are regarded to be inequivalent, which results in two sets of peaks ranging from δ 7.29 to 8.43 ppm (Figure 3).

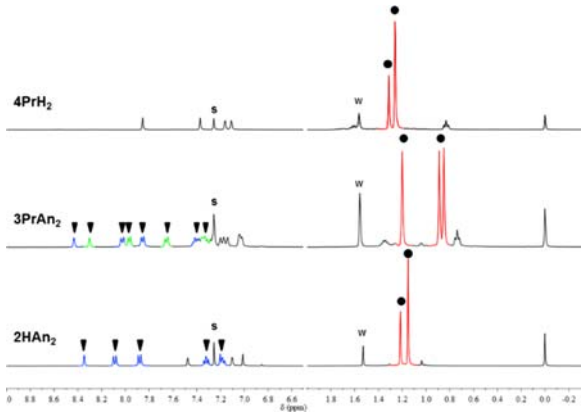

Figure 3. Comparative ^{1}H NMR spectra (300 K, 400 MHz, $CDCl_3$) of **2HAn$_2$**, **3PrAn$_2$**, and **4PrH$_2$** (from bottom to top). (●) *tert*-Butyl; (▼) anthracene; **w** = water; **s** = solvent.

In our designed synthetic strategy, the development of an effective deprotection method with tolerance toward the propyl group is very desirable. Previous reports have demonstrated that regioselective *O*-propylated calix[4]arenes and calix[6]-arenes had been synthesized via protection−deprotection with a benzyl group. The deprotection of the benzyl group could be efficiently achieved in the presence of Me_3SiBr at room temperature.[14] Motivated by these results, we attempted the deprotection of the 9-anthrylmethyl groups of **3PrAn$_2$** by Me_3SiBr. Unfortunately, such an attempt resulted in the parent homooxacalix[3]arene **1H$_3$**, indicating that not only the 9-anthrylmethyl groups but also the propyl group were removed from **3PrAn$_2$**. Thus, deprotection of 9-anthrylmethyl groups of **3PrAn$_2$** by Me_3SiBr was unsuccessful. In the course of our studies, we noticed that Pd/C-catalyzed hydrogenation under atmospheric hydrogen is also a useful deprotection method; simple benzyl ethers are preferentially hydrogenated.[15] Therefore, we expanded our experiments in order to explore the possibility of deprotecting the 9-anthrylmethyl groups of **3PrAn$_2$** by Pd/C-catalyzed hydrogenation. As expected, Pd/C is an effective catalyst for the selective deprotection of the 9-anthrylmethyl group of **3PrAn$_2$**. The deprotection reaction of **3PrAn$_2$** was performed under atmospheric hydrogen in the presence of Pd/C in THF at room temperature for 5 h to afford the desired **4PrH$_2$** in 41% yield.

The identity of **4PrH$_2$** is confirmed by its ^{1}H NMR spectrum which reveals the disappearance of the anthracene protons. This disappearance confirms the full deprotection of the 9-anthrylmethyl groups (Figure 3). Furthermore, the singlet appearing at around δ = 7.85 ppm was attributed to the protons of the newly formed OH groups (confirmed by D_2O exchange) (Figure S7). Additionally, the resonances for the *tert*-butyl protons now appeared as two singlets at δ 1.26 and 1.31 ppm (relative intensity 2:1). The structure and conformation of **4PrH$_2$** were further confirmed by a single-crystal X-ray diffraction analysis. The crystal structure of **4PrH$_2$** revealed a mono-*O*-propylated homooxacalix[3]arene unit (Figure 4).

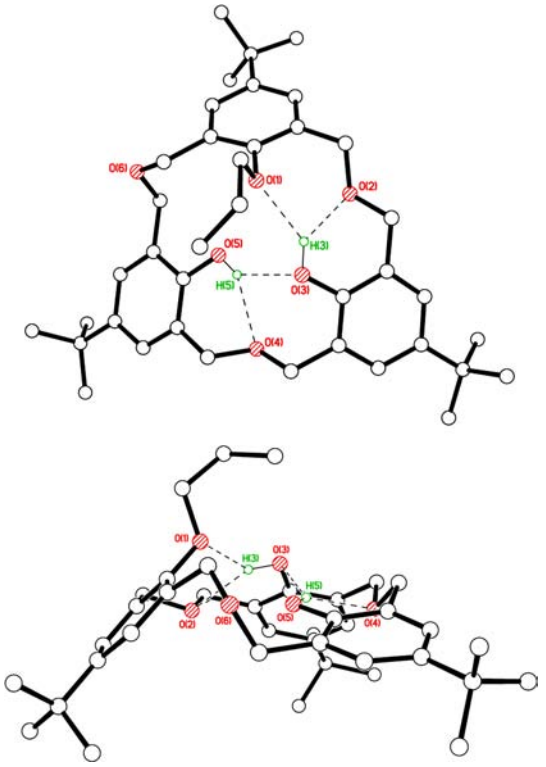

Figure 4. X-ray crystal structure of **4PrH$_2$** showing the hydrogen bond interactions. (Above) Top view. (Below) Side view showing the ^{n}Pr group above the lower rim. Hydrogen atoms except those involved in H-bonding are omitted for clarity.

One *n*-propyl group was introduced at the lower rim of the homooxacalix[3]arene and lies directly above the homooxacalix[3]arene cavity. Interestingly, intramolecular hydrogen bonding was present at the lower rim of the homooxacalix[3]-arene. These hydrogen bonds between the unsubstituted phenolic protons with the adjacent oxygen atoms exhibited donor···acceptor distances varying from 2.764(3) to 2.856(3) Å. In common with the homooxacalix[3]arene **1H$_3$**, **4PrH$_2$** is conformationally mobile; the presence of unmodified OH groups on the lower rim of **4PrH$_2$** allows for rapid interconversion between the cone and partial-cone conformations by free rotation through the annulus. However, **4PrH$_2$**

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prefer a more stable cone conformation as a result of the hydrogen-bond motifs.[16]

We have demonstrated that the regioselective synthesis of mono-*O*-alkylated homooxacalix[3]arene **4PrH$_2$** can be accomplished by a protection−deprotection method using the 9-anthrylmethyl group as a protecting group. It is noteworthy that the method is simple, efficient, and recommended as a useful strategy for the functionalization of homooxacalix[3]arene. The mono-*O*-alkylated product was useful as a basic skeleton for the design of tailor-made functionalized homooxacalix[3]arene receptors for metal cations and organic molecules which we are currently exploring.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03338.

Details of single-crystal X-ray crystallographic data; full experimental details; and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF)
Crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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