Alkylated Homooxacalix[3]arene and an Efficient Protection-Deprotection Strategy for Homooxacalix[3]arene

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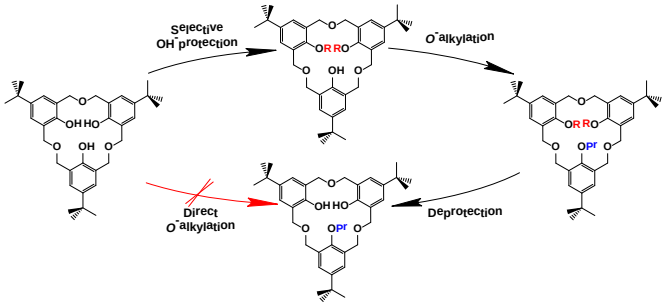
Supporting Information Placeholder



ABSTRACT: The regioselective synthesis of mono-*O*-alkylated homooxacalix[3]arene was 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, only two basic conformations (cone and partial-cone), and C_3-symmetry. This last feature can provide a suitable binding environment for species that require trigonal-planar, tetrahedral or octahedral coordination. Furthermore, the flexibility of the macrocycles can allow them to establish ideal bond distances and angles to bind such species.[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] Functionalized alkyl halides of the type XCH_2Y, where X is a leaving group and Y is a functional group, have been widely used to introduce a variety of functional groups into the lower rim of homooxacalix[3]arene.

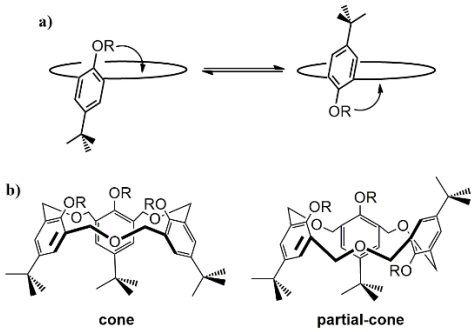
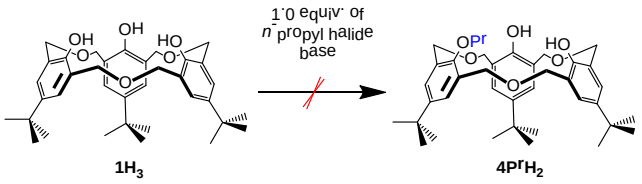


Figure 1. (a) Rotation of phenol ring and (b) two conformational isomer of homooxacalix[3]arene.

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 homo-

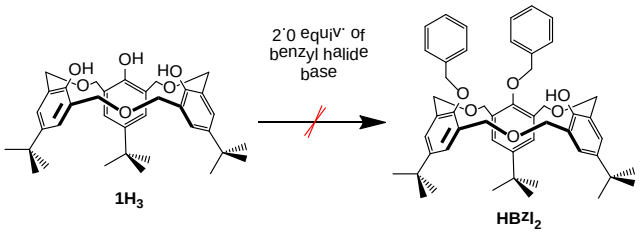
oxacalix[3]arene exhibit inherently chiral pseudo-C_2 symmetry, and had been used to explore chiral recognition.[9] Given the associated synthetic difficulty, the selective mono-*O*-alkylation of an OH group at the lower-rim of a homooxacalix[3]arene has not yet been reported. Herein, we report the first synthesis of the mono-*O*-alkylated homooxacalix[3]arene by using a protection-deprotection method with 9-anthrylmethyl groups. An efficient protection and deprotection strategy for homooxacalix[3]arene is presented in this study .

Introduction of bulky substituents into the OH groups, however, suppresses the oxygen-through-the-annulus rotation and results in conformational isomers; the *n*-propyl group (Pr) is bulky enough to achieve this.[6,10] 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 at synthesizing **4PrH$_2$** directly from homooxacalix[3]arene **1H$_3$** failed, affording the di- and tri-*O*-alkylated derivatives, as well as the recovery of the starting compound **1H$_3$**. 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$_3$** was unsuccessful. To overcome this problem, we resorted to an indirect protection-deprotection route.

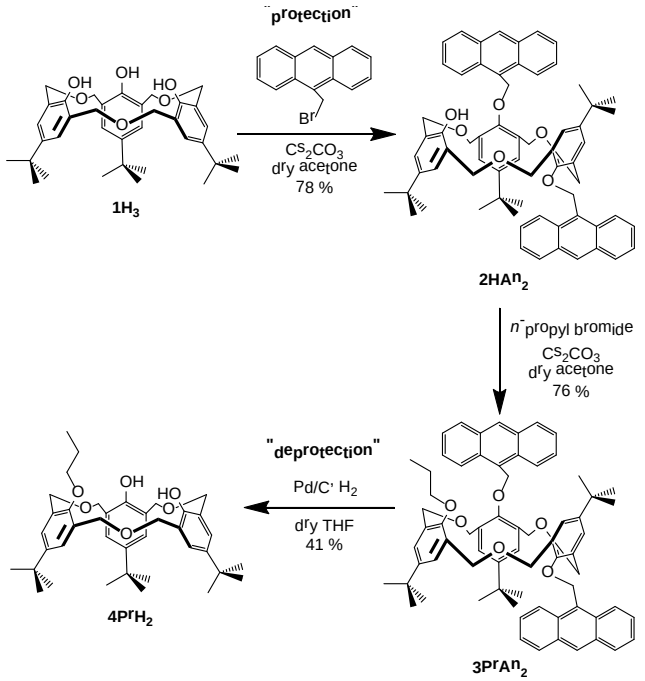


Scheme 1. Directly *O*-alkylation of homooxacalix[3]arene **1H$_3$**.

Among protecting groups, benzyl derivatives occupy a unique position due to their deprotection conditions being orthogonal to other protecting and functional groups, and due to their extensive application, including use in the protection of alcohols, phenols, amines, and carboxylic acids.[11] Inspired by these results, we attempted the synthesis of di-*O*-benzylated homooxacalix[3]arene **HBzl$_2$** by *O*-benzylation of **1H$_3$** with 2.0 equiv. of benzyl halide (Scheme 2). However, it was disappointing 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 group as protecting group was not possible.



Scheme 2. Synthesis of di-*O*-benzylated homooxacalix[3]arene **HBzl$_2$**.



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

Interestingly, recently studies conducted in our laboratory have demonstrated that the di-*O*-9-anthrylmethyl-substituted homooxacalix[3]arene **2HAn$_2$** was conveniently synthesized in good yield by the reaction of **1H$_3$** with 9-anthrylmethyl bromide.[12] This finding inspired us to further explore the possibility of utilizing 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*-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 resonance 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 a partial-cone conformation. Therefore, one cannot specify the conformation from the ^{1}H NMR

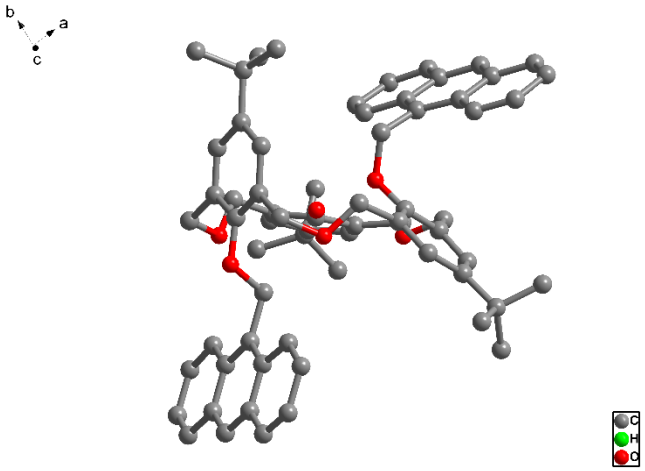


Figure 2. X-ray crystal structure of **2HAn$_2$**. Hydrogen atoms are omit-

ted for clarity.

spectrum. Fortunately, X-ray diffraction quality single crystals of **2HAn$_2$** were obtained by slow evaporation of a solution of **2HAn$_2$** in a chloroform/methanol mixture. The structure and conformation of **2HAn$_2$** was 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 for **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), respectively. The three inequivalent *tert*-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 to the opposite side. Thus, the two anthracene groups of **3PrAn$_2$** are regarded to be inequivalent, which exhibited as two set of peaks ranged from δ 7.29 to 8.43 ppm (Figure 3).

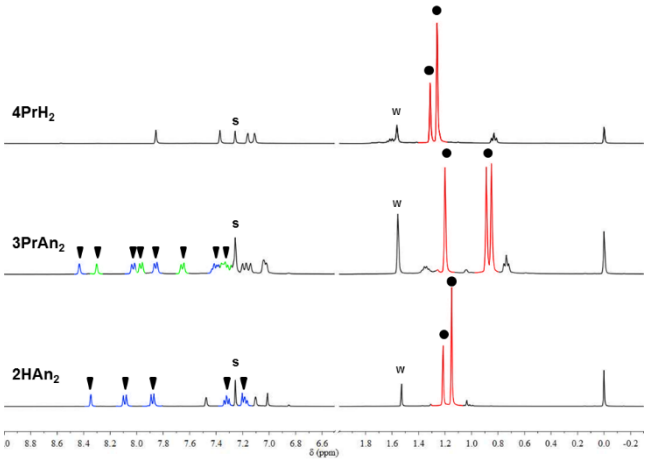


Figure 3. Comparative ^{1}H NMR spectra (300 K, 400 MHz, $CDCl_3$) of **2HAn$_2$**, **3PrAn$_2$** and **4PrH$_2$** (from bottom to top). ● *tert*-butyl; ▼ anthracene; **w** = water; **s** = solvent.

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. [13] Motivated by these results, we attempted the deprotection of 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 the Pd/C-catalyzed hydrogenation under atmospheric hydrogen is also a useful deprotection method; simple benzyl ethers are preferentially hydrogenated.[14] 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.

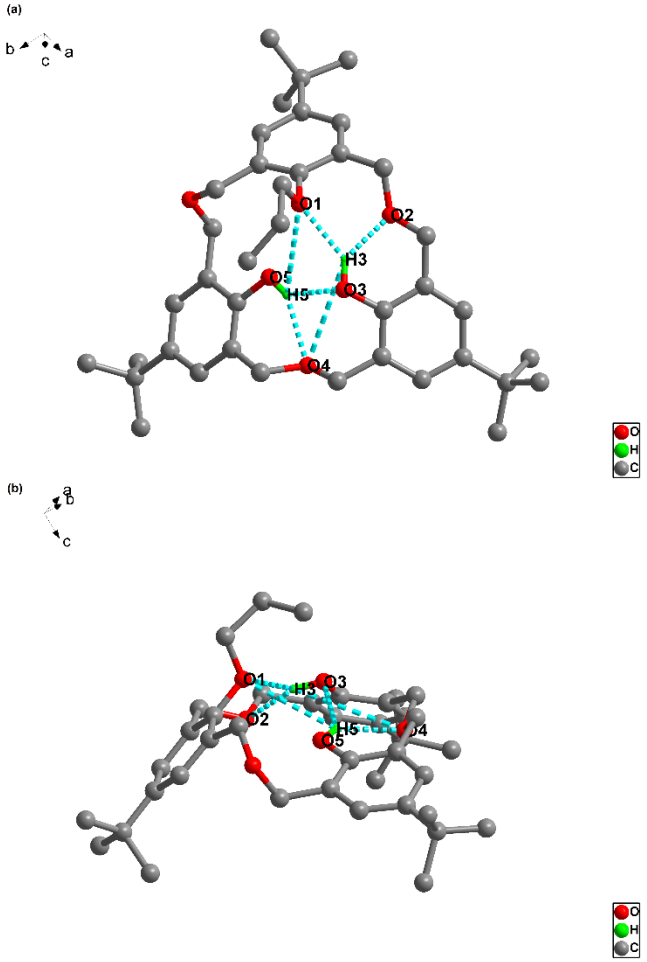


Figure 4. X-ray crystal structure of **4PrH$_2$** and the hydrogen bond interactions in **4PrH$_2$**. (a) Top view. (b) side view. Hydrogen atoms are omitted for clarity.

As expected, Pd/C is an effective catalyst for the selective deprotection of 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. These signals disappear confirming 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$_2$** was 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). One *n*-propyl group was introduced at the lower rim of the homooxacalix[3]arene, and pointed inside 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 to 2.995 Å. Due to these intramolecular hydrogen bond interactions, the free

rotation of the unmodified OH group is sterically hindered. Thus, the homooxacalix[3]arene skeleton of **4PrH$_2$** is immobilized in the cone conformation.

We have demonstrated for the first time that the regioselective synthesis of mono-*O*-alkylated homooxacalix[3]arene **4PrH$_2$** can be accomplished by a protection-deprotection method using 9-anthrylmethyl group as a protecting group. Interestingly, a novel protection-deprotection method for the OH group at the lower rim of homooxacalix[3]arene was developed. It is noteworthy that the method is simple, efficient, and is 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; such studies will be reported separately.

ASSOCIATED CONTENT

Supporting Information

Details of single-crystal X-ray crystallographic data. Full experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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