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Shorter Synthesis of Trifunctionalized Cryptophane-A Derivatives

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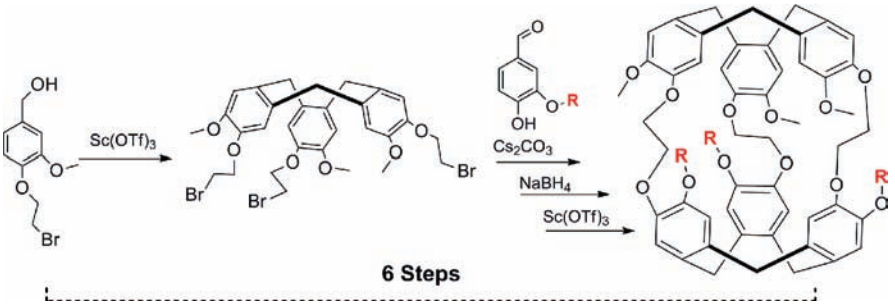
ABSTRACT



Efficient syntheses of trisubstituted cryptophane-A derivatives that are versatile host molecules for many applications are reported. Trihydroxy cryptophane was synthesized in six or seven steps with yields as high as 9.5%. By a different route, trihydroxy cryptophane modified with three propargyl, allyl, or benzyl protecting groups was synthesized with yields of 4.1−5.8% in just six steps. Hyperpolarized ^{129}Xe NMR chemical shifts of 57−65 ppm were measured for these trisubstituted cryptophanes.

Cryptophane organic host molecules, constructed from two cyclotriguaiacylene (CTG) units connected by three alkane linkers, possess a hydrophobic cavity that can encapsulate a wide variety of guests. One important application involves xenon binding to cryptophane, which can be delivered to specific cellular targets for detection and resolution by ^{129}Xe magnetic resonance spectroscopy or imaging.[1] Currently, water-soluble cryptophane-A derivatives show the highest known xenon affinity with $K_A \approx 30\,000\ M^{-1}$ in buffer at rt.[2] ^{129}Xe can be hyperpolarized to generate $\sim 10^5$ NMR signal enhancements and provides a greater than 200 ppm ^{129}Xe NMR chemical shift window, with resonance frequencies that depend sensitively on the molecular environment.[3] Thus, cryptophane hosts functionalized with different recognition moieties allow the simultaneous detection of multiple targets (i.e., multiplexing), as is desirable for biomolecular imaging.[4] The importance of *in vivo* studies has motivated the development of synthetic routes capable of producing large quantities of functionalized cryptophane.[5]

A previously described multistep template strategy allowed the synthesis of diverse mono-[6] and trifunctionalized cryptophane-A derivatives[2,7] as well as enantiopure (−)-cryptophane-A.[8] However, even improved synthetic routes typically involve nine or more steps with low yields.[5b] The preparation of separate connecting linkers and CTG units is time-consuming, and the hydroxyl functionalities must be protected to avoid side products

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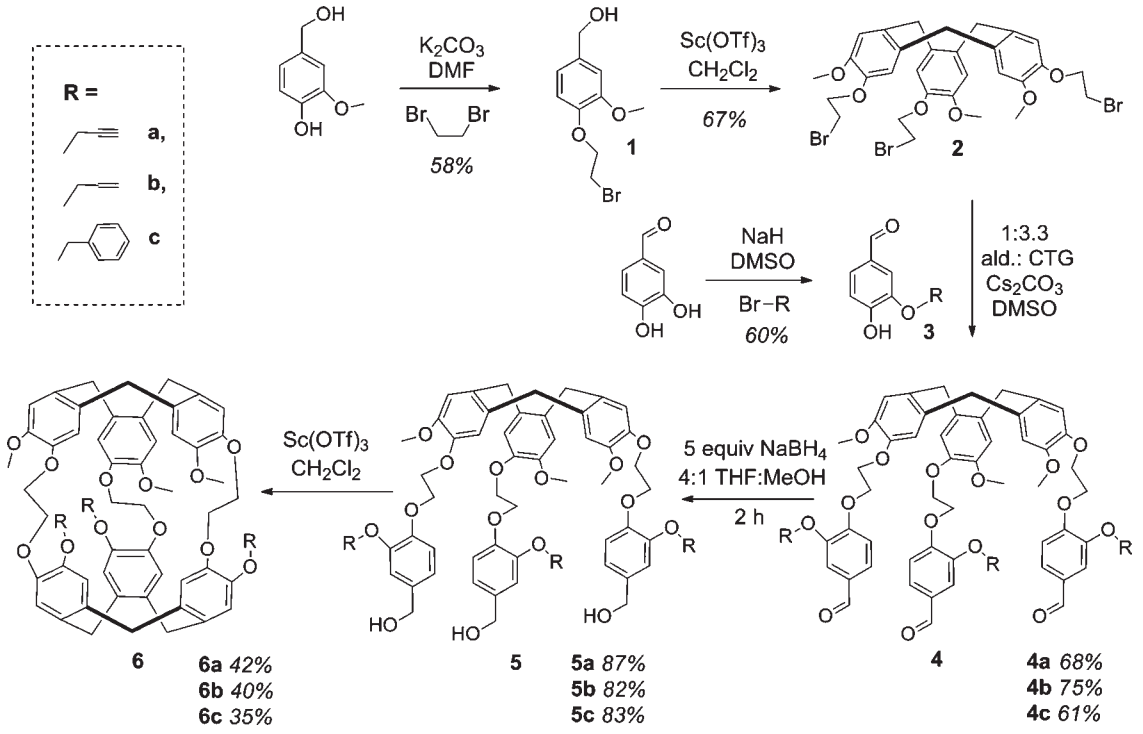
Scheme 1. Synthesis of Trisubstituted Derivatives of Cryptophane-A[a]



[a] Tripropargyl (**6a**), triallyl (**6b**), and tribenzyl (**6c**) cryptophane-A derivatives were synthesized in six steps in good yields.

during the cryptophane synthesis. Moreover, the two cyclization reactions to produce first CTG and finally cryptophane typically involve strong acid such as perchloric acid in methanol or formic acid.[9] These conditions are incompatible with the synthesis of new CTG derivatives bearing acid-sensitive moieties, and very often dilute conditions are required to avoid polymerization, as in the case with propargyl groups.[2] Recently, Brotin and co-workers reported cyclization reaction conditions using a milder reagent as a Lewis acid, $Sc(OTf)_3$.[10] Notably, in some cases even better yields were obtained, and the purification steps were made easier.

Based on these observations, we developed a shorter, six-step synthesis of trisubstituted cryptophanes (**6**, Scheme 1) from commercial starting materials vanillyl alcohol, 1,2-dibromoethane, and 3,4-dihydroxybenzaldehyde. Importantly, the trimerization of compound **1** with catalytic $Sc(OTf)_3$ yields tri-(2-bromoethyl)-cyclotriguaiacylene **2**, which eliminates the need for vanillyl alcohol protection and deprotection steps to obtain a functionalized CTG intermediate by a widely used method. Linkers **3** carrying propargyl, allyl, or benzyl groups were prepared by the reaction of 3,4-dihydroxybenzaldehyde with the desired bromo-derivatives. The alkyl-brominated CTG **2** was reacted with hydroxy linkers **3** (3.3 equiv) deprotonated with Cs_2CO_3 to produce **4**. It was easier to solubilize and purify the trialkylated intermediates by maintaining the aldehyde functionality of the linkers. For similar reasons, tetrahydropyranyl (THP) protecting groups were used previously to mask the benzyl alcohol functionalities in the synthesis of monosubstituted cryptophanes.[10,11] Finally, borohydride reduction of the CTG-trialdehyde **4** gave the CTG-trialcohol **5** without the need for column chromatography purification, followed by cyclization with $Sc(OTf)_3$ to give trifunctionalized cryptophane **6** in six total steps.

Both cyclization steps performed under mild conditions with catalytic amounts of $Sc(OTf)_3$ gave product in yields similar to or higher than those reported previously in reactions run in strong acid.[12] The overall yield of tripropargyl cryptophane-A derivative **6a** via this synthetic route was 5.8%, which improves the lab's previously published nine-step procedure.[2] We have shown previously that **6a** can undergo a copper(I)-catalyzed [3 + 2] cycloaddition with organic azides in nearly quantitative yields.[13] This approach allows the introduction of one, two, or three different moieties

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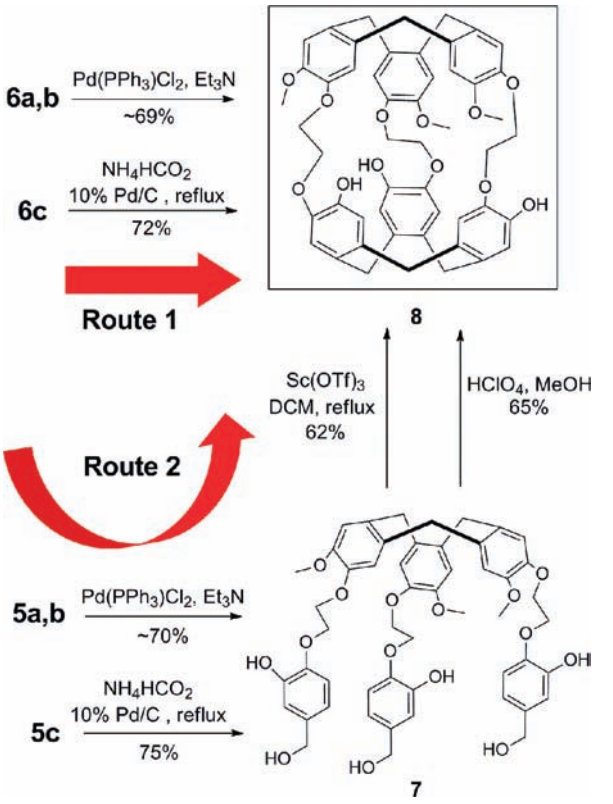
Scheme 2. Synthesis of Trihydroxy Cryptophane (**8**) via Two Different Seven-Step Routes



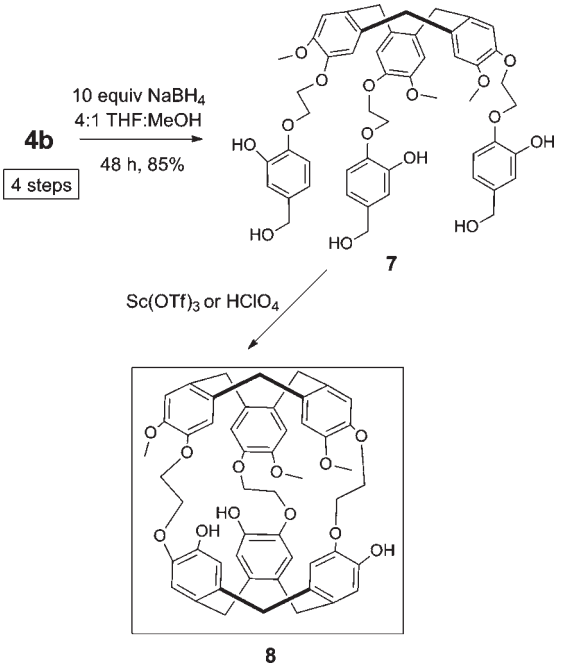
on the cryptophane periphery in order to tune the biological and spectroscopic properties of the xenon biosensor.[5a,14]

Propargyl, allyl, and benzyl moieties in synthesized trifunctionalized cryptophanes **6a**−**6c** can be removed to give trihydroxy cryptophane **8** (Scheme 2, Route 1), which is useful for preparing functionalized cryptophane derivatives.[14,16] One approach involved removal of propargyl and allyl groups of **6a,b** in the presence of a Pd(II) catalyst to afford **8** in ~70% yield (Scheme 2, Route 1). Debenzylation of **6c** using ammonium formate and 10% Pd/C gave trihydroxy cryptophane **8** in similar yields. The overall synthetic yield of **8** via Route 1 (Scheme 2) in seven total steps was 4.0%.

However, by Route 2 (Scheme 2) trihydroxy cryptophane was prepared with a higher overall yield of 6.0% where propargyl, allyl, and benzyl groups were eliminated to give **7** before cyclization into **8**. Thus, depropargylation and deallylation of **5a** and **5b** were performed using Pd(PPh$_3$)Cl$_2$ in ~70% yield to give precursor **7**. Compound **7** can be also obtained via removal of benzyl groups of **5c** in the presence of ammonium formate and 10% Pd/C at reflux in 75% yield. Notably, **7** could be cyclized using Sc(OTf)$_3$ in dry dichloromethane or perchloric acid in methanol in diluted conditions to form **8** in ~65% yield.

It is particularly useful that aldehyde groups in **4b** can be reduced to alcohols simultaneously with allyl group removal using 10 equiv NaBH$_4$ in a 48 h reaction to give **7**. By this last approach, cryptophane **8** was obtained in just six steps with an overall yield of 9.5% (Scheme 3).

Scheme 3. Six-Step Synthesis of Trihydroxy Cryptophane (**8**)



Xenon binding to the synthesized trifunctionalized cryptophane-A derivatives can be readily studied by hyperpolarized ^{129}Xe NMR spectroscopy. As ^{129}Xe NMR chemical shifts are very sensitive to host molecule structures, each of these compounds shows distinct chemical shifts for the cryptophane−Xe complex (Table 1; experimental details can be found in the Supporting Information).

Table 1. Hyperpolarized ^{129}Xe NMR Chemical Shifts for Cryptophane-A and Trisubstituted Cryptophane-A Derivatives[a]

cryptophane	^{129}Xe NMR chemical shift of cryptophane-Xe peak (ppm)
cryptophane-A (R = CH$_3$)	63.96 ± 0.03
tripropargyl cryptophane (**6a**)	65.33 ± 0.03
triallyl cryptophane (**6b**)	64.98 ± 0.05
tribenzyl cryptophane (**6c**)	63.1 ± 0.5[b]
trihydroxy cryptophane (**8**)	57.16 ± 0.03

[a] Cryptophanes were dissolved in $C_2D_2Cl_4$, and spectra were recorded at 284.5 ± 0.1 K. All spectra are calibrated by the Xe@$C_2D_2Cl_4$ peak chemical shift (227.85 ppm at 284.5 K).[17] [b] This value has temperature fluctuation ±1 K, which leads to greater uncertainty (details included in the Supporting Information).

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As shown in Table 1, the hyperpolarized ^{129}Xe NMR chemical shifts of cryptophane-A−Xe, **6a**−Xe, **6b**−Xe, and **6c**−Xe complexes appear between 63 and 65 ppm, indicating similar stereoelectronic environments of the encapsulated Xe nuclei. This is consistent with similar cryptophane conformations and Xe binding environments observed for cryptophane-A−Xe, **6a**−Xe, and **6b**−Xe by X-ray crystallography.[15] By comparison, the ^{129}Xe NMR resonance for the **8**−Xe complex is shifted significantly upfield. Lacking all three methyl groups on one CTG unit, **8** has somewhat larger portals than cryptophane-A for greater Xe accessibility. It is likely that **8** can sample more open conformations in which Xe has fewer close-range deshielding interactions, particularly with the cage benzene rings.[16] Efforts are underway to crystallize the **8**−Xe complex, in order to quantify more directly these important van der Waals interactions. The range of ^{129}Xe NMR chemical shifts observed in these experiments should allow the detection of multiple analytes in solution, e.g., in biosensing applications.

In conclusion, shorter- and higher-yielding syntheses of trisubstituted cryptophane-A derivatives were developed, which eliminate the protection and deprotection steps typically required to produce these versatile host molecules. ^{129}Xe NMR chemical shifts of 57−65 ppm were reported for trifunctionalized cryptophane−xenon complexes in $C_2D_2Cl_4$.

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Supporting Information Available. Experimental procedures and characterization data for all synthesized compounds and ^{129}Xe NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.