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Synthesis of Cryptophanes with Two Different Reaction Sites: Chemical Platforms for Xenon Biosensing

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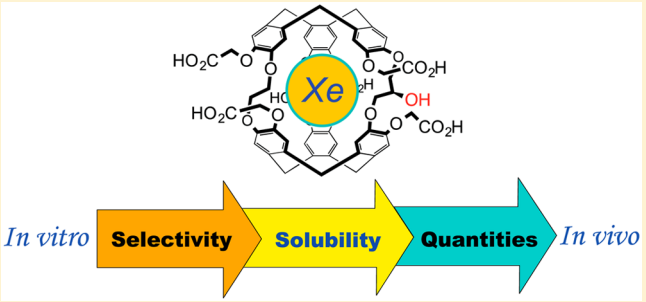
Supporting Information

ABSTRACT: We report the synthesis of new water-soluble cryptophane host molecules that can be used for the preparation of ^{129}Xe NMR-based biosensors. We show that the cryptophane-223 skeleton can be modified to introduce a unique secondary alcohol to the propylenedioxy linker. This chemical functionality can then be exploited to introduce a functional group that is different from the six chemical groups attached to the aromatic rings. In this approach, the generation of a statistical mixture when trying to selectively functionalize a symmetrical host molecule is eliminated, which enables the efficient large-scale production of new cryptophanes that can be used as chemical platforms ready to use for the preparation of xenon biosensors. To illustrate this approach, two molecular platforms have been prepared, and the ability of these new derivatives to bind xenon has been investigated.



INTRODUCTION

Cryptophane derivatives are of great interest as host molecules in molecular recognition applications.[1] They can bind a large variety of guest molecules, such as neutral molecules,[2] cationic and anionic species,[3] and even small gases (CH_4, Xe, Rd) in solution.[4] Interestingly, entrapment of these guests into the rigid structure made of six aromatic rings produces strong electronic and magnetic effects that can be easily detected and exploited by NMR spectroscopy. For instance, a specific spectral signature is encountered for xenon encapsulated in cryptophanes.[4a] Moreover, the sharp signal associated with the high responsiveness of the noble gas nucleus to its local environment makes it possible for encapsulated xenon to be exploited to discriminate between several cryptophane diastereomers present in solution or even distinguish two cryptophanes that differ only by the number of deuterium atoms.[5] This high sensitivity combined with the use of hyperpolarization techniques aimed at increasing the nuclear magnetization of xenon led to the concept of ^{129}Xe NMR-based biosensors in which cryptophanes bearing biological ligands were designed.[6] Xenon in such biosensors connected to the biological target produces a specific ^{129}Xe NMR signal that can be exploited to record a sensitive and specific magnetic resonance image.[7]

Several biosensors have been prepared for in vitro experiments,[8] and more recently for in cellulo experiments,[9] but an extension of this concept in vivo has not yet been performed. The technical difficulty of in vivo experiments as well as toxicity and biodistribution concerns need to be addressed; however, the major limiting factor to date has been one of scale. It is anticipated that for in vivo experiments the final biosensors need to be prepared on the 100−1000 mg scale. Therefore, new host molecules as well as new methods for the synthesis of these molecules that can allow for their production in the required amount are needed.

For the synthesis of new biosensors, two points have to be considered: (i) the synthesis and purification of these cryptophane biosensors need to be improved by avoiding the production of complex statistical mixtures; (ii) the cryptophane core needs to be more hydrophilic. For example, the cryptophanol-A derivative is the cryptophane molecule most widely employed for in vitro biosensing experiments.[10] This cryptophane has a single hydroxyl function and five methoxy groups on the aromatic rings. This molecule can be prepared in gram quantities, possesses C_1-symmetry, and can be used to introduce a single ligand aimed at recognizing a biological target. However, this host molecule suffers from very low solubility in biological media, which hampers its use for in vivo experiments unless water-solubilizing groups are added to the tether. Moreover, its hydrophobic character favors nonspecific interactions with cell membranes or leads to the formation of aggregates even at very low concentrations.[11] For this reason, a water-soluble cryptophane bearing six carboxylic acid moieties

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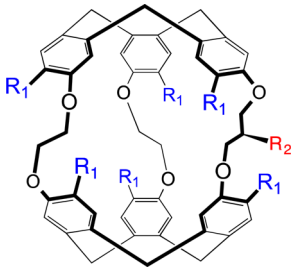
has been recently developed in racemic[12] and enantiopure[13] forms. Unfortunately, this cryptophane possesses a high D_3-symmetry that complicates the introduction of a unique tether. To date, biosensors generated from this cryptophane have been difficult to purify, and the high symmetry of this cryptophane strongly hampers the production of the large quantities required for in vivo experiments. Other synthetic strategies have been proposed for obtaining water-soluble cryptophanes,[14] but these new molecules are also difficult to prepare on a large scale and to selectively functionalize. Noteworthily, different approaches can be proposed to increase the solubility of cryptophane in biological media without modifying the cryptophane skeleton. For instance, in 2006, Pines and co-workers proposed using cryptophane derivatives embedded into PAMAM dendritic structures.[14] More recently, Schröder and co-workers have used liposomes as molecular carriers for dissolving cryptophane in biological fluids.[8f]

Aware of this problem, we thus decided to turn our attention toward the construction of new cryptophane skeletons. The cryptophane-223 backbone appears to be an interesting starting material for designing biosensors. This molecule is made of two cyclotribenzylene (CTB) units connected together by two ethylenedioxy linkers and one propylenedioxy linker. This compound possesses a slightly bigger inner cavity than cryptophane-A. Nevertheless, both cryptophane-223 (Scheme 1, R_1 = OCH_3, R_2 = H) and its water-soluble congener

Scheme 1. Generic Structure of the Cryptophanes Presented in This Article



cryptophane **3** (Scheme 1, R_1 = OCH_2COOH, R_2 = H) have large association constants for xenon.[12,15] In addition, the kinetics of the in−out xenon exchange is appropriate for ^{129}Xe NMR-based biosensing applications (still in slow exchange at the NMR time scale but higher than that with cryptophane-A).[16] Importantly, the cryptophane-223 backbone offers the possibility of introducing a new functionality on the propylenedioxy linker, which can be different from those attached on the benzene rings (Scheme 1, R_2 not hydrogen and different from R_1).

The advantages of such a strategy are 2-fold. First, the presence of this new functional group does not introduce complexity in the structure. The central carbon bearing the alcohol function is not a stereogenic center if the two CTB caps possess the same absolute configuration *M* or *P*. Second, the presence of a new function located on the propylenedioxy bridge allows for the introduction of a linker that can be different from the six other functional groups attached to the phenyl rings. This approach also allows for the introduction of an extra water-solubilizing group, as one of the phenol residues no longer has to be sacrificed for the introduction of the sensing ligand. These new host compounds are expected to facilitate the design of future ^{129}Xe-based biosensors. Herein, we describe the synthetic strategy employed to obtain these new derivatives as starting points for the construction of xenon biosensors in the future. The ability of these new derivatives to bind xenon in solution is examined.

RESULTS AND DISCUSSION

Synthesis of Water-Soluble Cryptophane-223 Congeners. The strategy to prepare these new water-soluble derivatives is similar to the route reported for the synthesis of cryptophane-223.[15] Bis-functionalized cyclotribenzylene (CTB; **4**) is efficiently produced by the reaction of 3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[*a*,*d*,*g*][9]annulene-2,7,12-triol and (4-(2-bromoethoxy)-3-methoxyphenyl)methanol used as starting materials.[16] At this stage, two different strategies have been used to synthesize these new cryptophane derivatives. Both approaches present advantages and disadvantages.

The first approach (see Scheme 2) involves an S_N2 type reaction between CTB **4** and oxirane **5** and does not require the protection of the two benzyl alcohol functions. Compound **5** was obtained in 65% yield by reacting 2-methoxy-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol with an excess of 2-(chloromethyl)-oxirane in acetonitrile (Supporting Information Figures S1 and S2). The reaction between **4** and **5** in the presence of cesium carbonate in acetone gave rise to tris-functionalized CTB **6** in good yield (73%) (Supporting Information Figures S3 and S4). Attempts to optimize the experimental conditions did not allow us to significantly increase this yield. For instance, a change in the solvent (DMF, 120 °C) provided desired compound **6** with lower yield (56%). This ring opening reaction provides a new CTB derivative with an alcohol functional group located on the central carbon of the propylenedioxy unit. With compound **6** in hand, we first investigated the possibility of performing the second ring closure reaction without protecting the secondary alcohol. Unfortunately, in the first attempt, formic acid in $CHCl_3$ (50/50 v/v) at 60 °C failed to promote the formation of the second CTB unit. ^{1}H NMR spectroscopic analysis of the crude product revealed a mixture of compounds, but the desired cryptophane could not be identified. Because formic acid is often used to prepare cryptophane derivatives, it is likely that the unprotected OH group reacts with formic acid under these conditions. We thus turned our attention toward other reagents that could promote the second ring-closure reaction. We have previously reported that scandium triflate $Sc(OTf)_3$ promotes cryptophane formation in acetonitrile or dichloromethane.[17] This approach is particularly well adapted for aromatic rings bearing strong electron-donating substituents, such as compound **6**. Reacting derivative **6** in the presence of excess $Sc(OTf)_3$ in acetonitrile at 80 °C furnished desired *anti*-cryptophane **7** in moderate yield (23%) (Supporting Information Figures S5 and S6). Changing the experimental conditions (temperature; $Sc(OTf)_3$ stoichiometry) did not allow us to improve this yield. It is noteworthy that cryptophane **7** is the first cryptophane prepared to date that possesses two distinct reactive functions, one of which is located on the linker. Interestingly, the eight diastereomers of **6** initially present in solution are transformed to two enantiomers of **7**, because the two CTB caps of **7** possess the same absolute configuration (compounds-*anti*; *MM* or *PP*). A ^{1}H NMR spectrum recorded in DMSO-d_6 allowed for the identification of the alcohol functional group (δ = 4.93 ppm). The removal of the six methyl groups was accomplished by reacting **7** with an excess of freshly prepared lithium diphenylphosphide (1 M). The reaction

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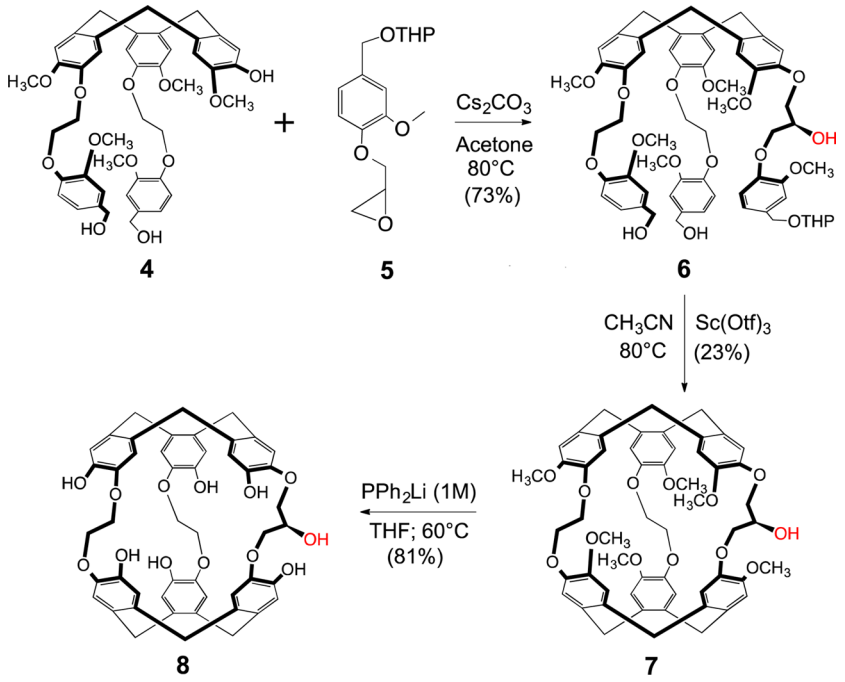
Scheme 2. Synthesis of Cryptophane 8 Using $Sc(OTf)_3$ as the Reagent



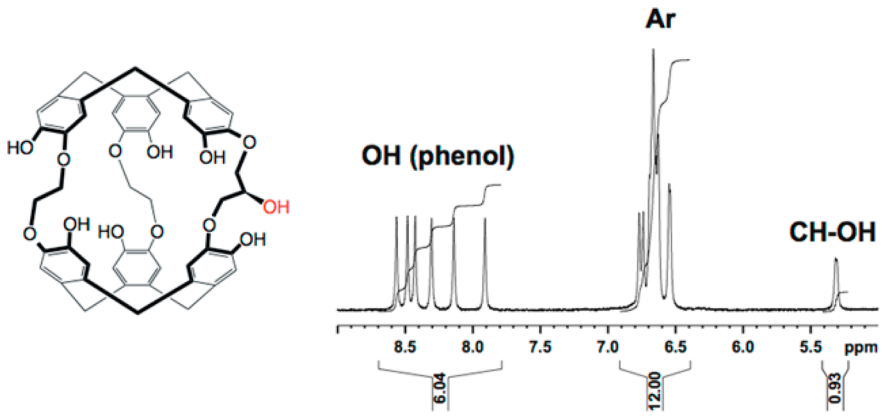


Figure 1. Structure of compound **8**. ^{1}H NMR spectrum of **8** recorded in DMSO-d_6 at 298 K (showing only the 9.0−5.0 ppm spectral region); see Supporting Information Figures S7 and S8 for the full spectrum.

provided compound **8** in good yield (81%) after purification on silica gel (Supporting Information Figures S7 and S8). A ^{1}H NMR spectrum (see Figure 1) recorded in DMSO-d_6 revealed the presence of the six phenols groups in the 8−9 ppm region. Cryptophane **8** represents a key compound for the construction of new derivatives because it possesses two distinct functionalities (one alcoholic and six phenolic functional groups). These two functionalities can react at different stages of the synthesis, thus allowing the preparation of new derivatives with two distinct chemical groups.

In a second approach, we attempted to improve the yield of the synthesis of **8** using a new synthetic route that requires initial protection of the alcohol located on the linker. We assumed that protection of the alcoholic function would be desirable and would increase the yield of the desired cryptophane upon reaction of the CTB precursor under acidic conditions. Thus, with the alcohol protected, we expected that formic acid could be used to perform the second ring closing reaction. To investigate this, we treated CTB **4** at room temperature with a slight excess of 3,4-dihydro-2*H*-pyran to give **9** in good yield (72%, see Scheme 3) (Supporting Information Figures S9 and S10). Compound **9** then reacted with oxirane **5** in DMF (80 °C) in the presence of 1,4-diazabicyclo[2.2.2]octane (DABCO) as a base. The reaction provided compound **10** in good yield (76%) (Supporting Information Figures S11 and S12). This compound is characterized by a very complicated ^{1}H NMR spectrum resulting from the formation of 32 diastereomers. Protection of the secondary alcohol was then achieved with allyl bromide in THF in the presence of excess sodium hydride to give compound **11** in 85% yield (Supporting Information Figures S13 and S14). Then, derivative **11** was reacted with formic acid in $CHCl_3$ (50/50 v/v) at 60 °C for 5 h. This gave desired cryptophane **12** as a racemic mixture in 40−44% yield (Supporting Information Figures S15 and S16). The yield obtained by this method is a significant improvement over the one achieved with $Sc(OTf)_3$. However, this new approach required two additional steps.

The reaction of compound **12** with excess lithium diphenylphosphide (1 M) in THF at 60 °C for 2 days allowed

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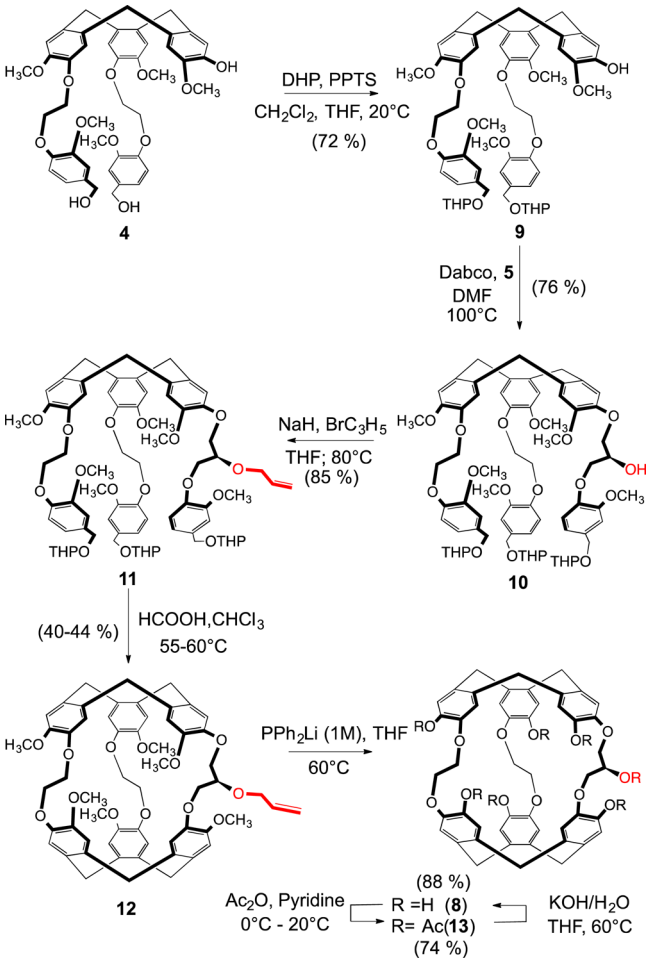
Scheme 3. Synthesis of Cryptophane 8 with Protection of the Secondary Alcohol Function



for efficient deprotection of the six methoxy groups. It is noteworthy that under these conditions the allyl group was not stable and was also removed. Thus, this reaction afforded compound **8** in excellent yield (95%; crude yield). The crude product was contaminated by trace impurities, and thus an additional purification step was necessary. This was achieved by reacting **8** with excess acetic anhydride in pyridine at room temperature to give protected derivative **13** in good yield (74%) after purification (Supporting Information Figures S17 and S18). Compound **8** was finally recovered in good yield (88%) by hydrolysis of the ester functions under basic conditions.

To produce highly water-soluble derivatives, we attached six ester functional groups to the benzene rings by reacting compound **8** with a slight excess of bromomethyl acetate in DMF at room temperature (Scheme 4). The reaction provided desired hexa-functionalized derivative **14** with moderate yield (53%) (Supporting Information Figures S19 and S20). An increase in temperature seemed detrimental to the formation of **14** because alkylation of the central OH group occurred under these conditions. The hydrolysis of compound **14** under basic conditions (KOH/H_2O-THF mixture) gave rise to desired hexa-carboxylic acid derivative **1** in 85% yield.

Compound **1** (Supporting Information Figures S21 and S22) and its protected version **14** are very interesting derivatives because these molecules can directly be used as chemical platforms for the design of ^{129}Xe NMR-based biosensors. Indeed, thanks to the presence of the unreacted alcohol functional group, it is now possible to attach a tether that can be different than the six substituents on the aromatic rings. More importantly, the presence of a unique reactive OH group is expected to facilitate the synthesis of future biosensors.

Compound **2**, possessing six polyethylene glycol groups attached on the phenyl rings, was prepared to illustrate the possibility of introducing other water-solubilizing substituents (Rousseau and Schröder recently reported the synthesis of pegylated cryptophanes from a cryptophane-222 skeleton).[18] Compound **8** was thus combined with excess of an activated PEG-3 derivative and potassium carbonate in DMF to provide compound **2** in good yield (82%) (Supporting Information Figures S23 and S24). Under these conditions, the alcohol function was left unreacted. This compound is soluble in water as well as other polar solvents, such as methanol. Finally, to demonstrate that derivatives **1**, **2**, and **14** could be used as chemical platforms for the construction of biosensors, we needed to show that the free alcoholic function was accessible for subsequent reactions. As an example, compound **14** was allowed to react with methyl sulfonyl chloride to provide compound **15** in good yield (71%) (Supporting Information Figures S25 and S26). This demonstrates that the central group is able to act as a nucleophile and react with a small electrophile efficiently.

^{129}Xe NMR Spectroscopy. The use of hyperpolarized xenon multiplies the NMR signal by several orders of magnitude and facilitates the detection of a low concentration of Xe@cryptophane complexes dissolved in water or organic solvents. Thus, not only can ligand-decorated cryptophanes be good candidates for xenon biosensing, but hyperpolarized ^{129}Xe NMR (combined with ^1H NMR) can also serve to understand the synthesis yields and the behaviors of some intermediate compounds. Derivatives **7**, **13**, and **14** are interesting compounds as xenon hosts, but in contrast to compounds **1**, **2**, and **8**, these molecules are only soluble in organic solvents. Thus, the interaction of xenon with these derivatives was investigated in 1,1,2,2-tetrachloroethane-d_2, a solvent that does not enter the cavity of cryptophanes **7**, **13**, and **14**.[19]

The Xe@**7** complex in $(CDCl_2)_2$ exhibits a sharp signal located at 64 ppm at 293 K (Supporting Information Figure S27). This chemical shift is typically in the same spectral region as that of the Xe@cryptophane-223 complex recorded previously.[20] Encapsulation of xenon in the cavity of **7** also produces strong modifications in its ^1H NMR spectrum, which are the result of the conformational changes of the three linkers occurring during the binding process (spectra not shown). Under the same experimental conditions, Xe@**14** exhibits a signal located at 58 ppm (fwhm = 385 ± 1.5 Hz, see Figure 2a and Supporting Information Figure S28). Interestingly, a different situation is observed with the Xe@**13** complex. Indeed, in contrast to what is observed with compounds **7** and **14**, the Xe@**13** complex exhibits a very large signal (8 times broader than that of Xe@**14**, fwhm = 3179 ± 9 Hz), whose maximum is located at 82 ppm (Figure 2b; Supporting Information Figure S29). This strange behavior can be more easily explained by examining the ^1H NMR spectra of compound **13** in different solvents (spectra not shown). It appears that both the intensity and chemical shift of the acetate moiety located on the bridge are strongly affected by changing the solvent. For instance, in $CHCl_3$, the ^1H NMR signal of this methyl group shows a very broad and weak peak located at δ =

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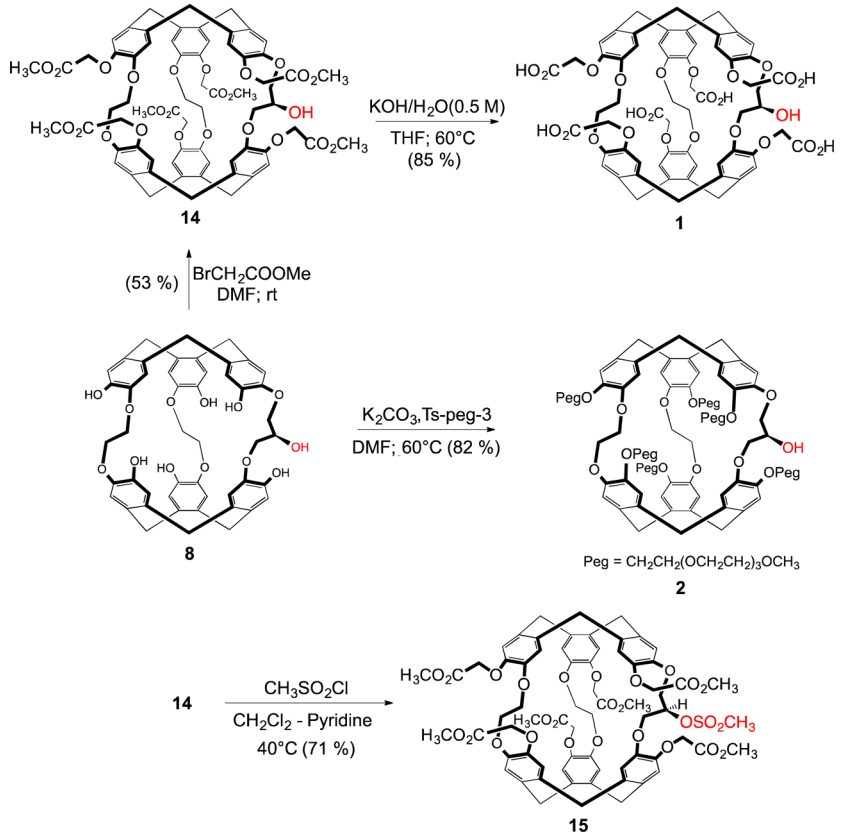
Scheme 4. Synthesis of Hexa-acid Derivative 1 and its Hexa-pegylated Congener 2, and synthesis of Mesylated Alcohol 15 from 14



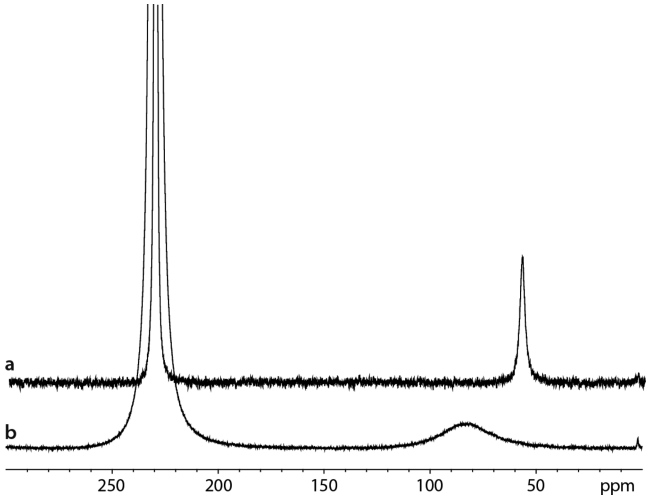


Figure 2. One-scan ^{129}Xe NMR spectra recorded at 298 K on solutions in tetrachloroethane-d_2 of cryptophane **14** (a) and cryptophane **13** (b).

1.7 ppm. Replacing $CHCl_3$ by CH_2Cl_2 makes this signal sharper and shifted toward higher frequencies (δ = 2.07 ppm). In $(CDCl_2)_2$ or in DMSO-d_6, different behaviors are still observed, and the ^{1}H NMR spectra show broad high-field shifted signals located at −0.5 and 0.17 ppm, respectively. Taken together, these observations suggest a strong conformational change of the propylenedioxy bridge depending on the nature of the solvent. Thus, in $(CDCl_2)_2$, it seems that the acetate moiety can enter (or partially enter) the cavity of **13**, which can prevent xenon from having easy access to the cavity of **13**. The presence of six electron-withdrawing acetate moieties also modifies the affinity of the xenon for the inner cavity of **13**.

Compounds **1**, **2**, and **8** represent the most interesting examples of the series because these molecules are water-soluble and they can be used directly for the construction of xenon biosensors. The ^{129}Xe NMR spectra of compounds **1** and **8** have been recorded under basic conditions to facilitate their solubilization. At room temperature, the Xe@**8** signal appears at 63 ppm (Supporting Information Figure S30), and the Xe@**1** signal appears at 50 ppm (Supporting Information Figure S31). In contrast, derivative **2** bearing six PEG-3 functional groups is soluble in D_2O even at pH 7. At room temperature, the Xe@**2** signal is located at 67 ppm (Supporting Information Figure S32). Interaction of xenon with congeners of **1** and **8** were previously investigated by ^{129}Xe NMR spectroscopy.[20] The xenon complexes of these molecules revealed a behavior that strongly depends on the nature of the solution used to dissolve these molecules. Molecules **1** and **8** are likely to behave similarly, and a more detailed study of these derivatives is required in the future.

The preliminary results obtained by ^{129}Xe NMR spectroscopy reveal that these host molecules, and especially the water-soluble hosts **1** and **2**, possess all of the characteristics needed for the construction of xenon biosensors. Indeed, slow exchange dynamics on the NMR time scale is observed for both compounds, and the ^{129}Xe NMR signals of these complexes resonate at a frequency located far away from the free xenon in solution. The in−out exchange dynamics, which are also another important parameter to take into account for the design of xenon biosensors, were fast enough to allow the

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easy detection of these complexes at micromolar concentrations. As an example, Figure 3a displays the ^{129}Xe NMR

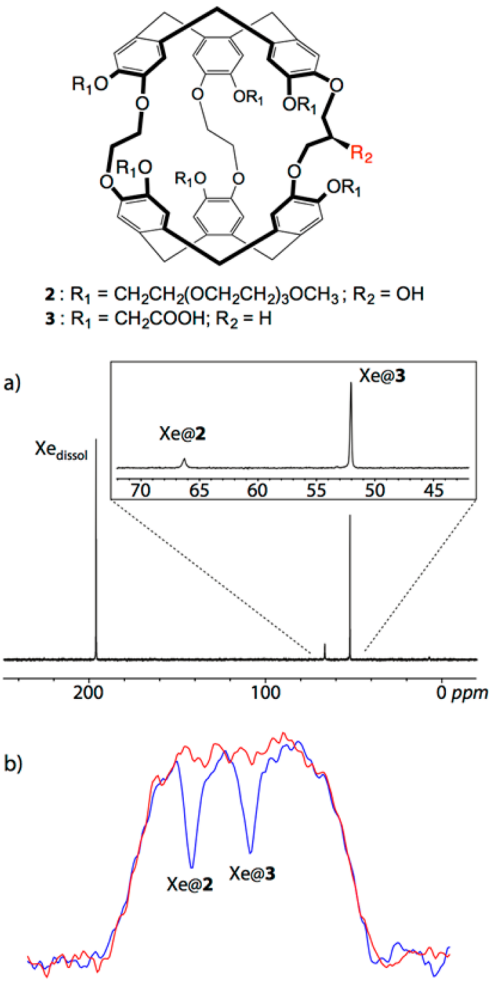

Figure 3. ^{129}Xe NMR experiments on an equimolar (93 μM) mixture of cryptophanes **2** and **3** in D_2O. (a) One-scan ^{129}Xe NMR spectrum. An expansion of the 42−72 ppm region is shown in the insert. (b) ^{129}Xe UFZ-spectrum with (blue) and without (red) saturation. For the blue subspectrum, a CW saturation of 1.7 μT was applied over 8 s. The field gradient value during saturation and detection was 4 G/cm.

spectrum of an equimolar mixture of cryptophane **2** and cryptophane **3** (Scheme 1, R_1 = OCH_2COOH, R_2 = H). The signals of xenon in cryptophanes **3** and **2** resonate at 52.7 and 67.0 ppm, respectively. However, the presence of imploded forms of compound **2** that do not encapsulate xenon impede safe estimation of the xenon binding constant in this cryptophane (as seen on the ^{1}H NMR spectrum; spectrum not shown), the ^{129}Xe UFZ-spectroscopy performed with a low quantity of hyperpolarized xenon exhibits signals of similar depths for xenon in both cryptophanes.[21] This shows that cryptophane **2** has in−out xenon exchange properties favorable for HyperCEST detection.

■ CONCLUSIONS

We have reported a new approach for the preparation of cryptophanes for ^{129}Xe NMR biosensing applications. This strategy is based on a chemical transformation of the cryptophane-223 skeleton. The originality of this approach comes from the possibility of introducing a reactive group different from the six reactive groups attached on the phenyl rings on the central carbon of the propylenedioxy linker. To exemplify this new method, we synthesized derivatives **1**, **2**, **8**, **13**, and **14**. In these molecules, the free phenol residues have been functionalized in an orthogonal fashion to the secondary alcohol present on the central carbon of the propylenedioxy bridge. The secondary alcohol can then be used as a handle for the synthesis of new reactive cryptophane derivatives. To illustrate this, we synthesized molecule **15**. In the future, the strategy developed in this article will facilitate the synthesis and purification of biosensors. More importantly, this approach is expected to provide larger quantities of biosensors, thus allowing an extension of this concept to in vivo applications. The ^{129}Xe NMR spectra of water-soluble compounds **1**, **2**, and **8** show a slow exchange on the NMR time scale. The chemical shift signals of the complexes are located far away from the free xenon in solution and the in−out exchange dynamics appear to be fast enough to easily detect these complexes at low concentrations in aqueous solutions.

Cryptophanes **1** and **2** are interesting derivatives because they can be used as chemical platforms for the synthesis of xenon biosensors. These molecules do not require additional chemical transformations because chemists can take advantage of the unreacted OH group to introduce a linker whose nature can be varied. This is expected to enable the rapid generation of a number of new xenon biosensors for different applications.

■ EXPERIMENTAL SECTION

The HRMS-ESI mass spectra were recorded in positive-ion mode (or negative) on a hybrid quadrupole time-of-flight mass spectrometer with an Electrospray Ionization (ESI) ion source. ^{1}H and ^{13}C NMR spectra were recorded at 499.83 and 125.7 MHz, respectively. Chemical shifts are in δ values from Me_4Si (^{1}H, ^{13}C). Column chromatographic separations were carried out over silica gel 60 (0.040−0.063 mm). Analytical thin layer chromatography (TLC) was performed on silica gel TLC plates F-254. The melting point of compound **5** was measured on a calorimeter. The solvents were distilled prior to use, with DMF and CH_2Cl_2 from CaH_2, THF from Na/benzophenone, and pyridine from KOH.

2-((3-Methoxy-4-(oxiran-2-ylmethoxy)benzyl)oxy)-tetrahydro-2*H*-pyran 5 (Mixture of Diastereomers). (*rac*)-2-(Chloromethyl)-oxirane (7.8 g, 6.6 mL, 84 mmol) dissolved in acetonitrile (10 mL) was added in one portion to a mixture of 2-methoxy-4-(((tetrahydro-2*H*-pyran-2-yl)oxy)methyl)phenol (4.0 g, 16.8 mmol) and cesium carbonate (5.48 g, 16.8 mmol) in dry acetonitrile (30 mL). The mixture was heated at 95 °C under an argon atmosphere for 48 h. The solvent was then removed under reduced pressure. Water was added to the residue, and the desired compound was extracted twice with diethyl ether. The organic layer was washed with brine and then dried over sodium sulfate. Filtration and evaporation of the solvent under reduced pressure gave a residue, which was purified on silica gel (Et_2O/petroleum ether: 8/2). Desired oxirane **5** was then collected as an oily product (3.2 g, 65%), which rapidly recrystallized to give a white solid. Mp = 40 °C. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.91−6.87 (m, 3 H), 4.70 (d, J = 12 Hz, 1 H), 4.66 (m, 1 H), 4.42 (d, J = 12 Hz, 1 H), 4.20 (m, 1 H), 4.05 (m, 1 H), 3.88 (m, 1 H), 3.86 (s, 3 H), 3.53 (m, 1 H), 3.37 (m, 1 H), 2.88 (m, 1 H), 2.72 (m, 1 H), 2.00−1.40 (m, 6 H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C): δ 149.5, 147.4, 131.9, 120.4, 114.0, 111.9, 97.6, 70.3, 68.7, 62.2, 55.9, 50.1, 44.9, 30.4, 25.4, 19.4. Anal. Calcd for $C_{16}H_{22}O_5$ (294.347): C, 65.29; H, 7.53. Found: C, 65.46; H, 7.78.

Compound 6 (Mixture of Diastereomers). Oxirane **5** (3 g, 7.85 mmol) was added in one portion to a solution containing compound **4** (3 g, 3.9 mmol) and cesium carbonate (6.45 g, 19.8 mmol) in acetone (15 mL). The mixture was heated under reflux conditions for 36 h. The solvent was then removed under reduced pressure to give a residue, which was poured into a mixture of $CHCl_3$ and water. The

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aqueous layer was extracted three times with $CHCl_3$, and the combined organic layers were washed once with brine and then dried over sodium sulfate. Filtration of the solution followed by evaporation of the solution under reduced pressure gave an oily residue, which was purified by chromatography on silica gel (AcOEt/EtOH: 9/1). Desired CTB **6** was finally obtained as a white solid (3.07 g; 73%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.00−6.68 (m, 15 H), 4.73−4.66 (m, 5 H), 4.58−4.56 (m, 3 H), 4.48−4.29 (m, 9 H), 4.21−4.03 (m, 5 H), 3.89 (m, 1 H), 3.82−3.46 (m, 21 H), 3.28−3.26 (m, 2 H), 1.83−1.53 (m, 6 H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 149.8, 149.7, 149.5, 148.7, 148.5, 147.9, 147.5, 147.4, 147.3, 146.7, 146.5, 146.4, 134.6, 133.2, 133.0, 132.9, 131.95, 131.9, 131.8, 131.7, 120.5, 120.4, 119.3, 117.5, 116.7, 116.0, 114.65, 114.4, 114.0, 113.9, 113.7, 113.2, 111.8, 110.9, 97.5, 73.3, 71.5, 71.1, 70.9, 70.2, 69.0, 68.65, 68.3, 68.2, 68.1, 67.8, 65.0, 62.3, 60.3, 56.2, 56.1, 55.8, 55.7, 55.6, 55.2, 36.3, 30.5, 25.4, 21.0, 19.4. HRMS (ESI) calcd for $C_{60}H_{70}O_{17}$ [M + Na^+]: 1085.4505; found, 1085.4470.

***(rac)*-Cryptophane 7.** A solution of **6** (800 mg, 0.75 mmol) in 200 mL of dry acetonitrile was added dropwise over a period of 8 h to a stirred solution of $Sc(OTf)_3$ (925 mg, 1.9 mmol) in acetonitrile (20 mL) heated at 80 °C. After the addition was complete, the solution was stirred for 10 h at 80 °C. The solvent was removed under reduced pressure to give a residue, which was then purified by column chromatography on silica gel (CH_2Cl_2/Acetone: 8/2). A glassy product was obtained after evaporation of the solvents. The addition of Et_2O and filtration on a frit gave rise to expected cryptophane **7** as a white solid (159 mg; 23%). ^{1}H NMR (500 MHz, DMSO-d_6, 25 °C): δ 6.86−6.84 (8 s, 8 H), 6.79 (s, 1 H), 6.76 (s, 1 H), 6.75 (s, 2 H), 4.93 (d, J = 3.5 Hz, 1 H), 4.51 (m, 6 H), 4.30−4.20 (m, 2 H), 4.15−3.90 (m, 7 H), 3.90−3.75 (m, 3 H), 3.74 (2 s, 6 H), 3.72 (s, 3 H), 3.71 (s, 3 H), 3.69 (s, 3 H), 3.67 (s, 3 H), 3.36 (m, 6 H). ^{13}C NMR (126.7 MHz, DMSO-d_6, 25 °C) δ 148.8 (2C), 148.7, 148.6, 147.9, 147.6, 146.6, 146.4, 145.6 (2C), 145.5 (2C), 133.8 (2C), 133.5 (2C), 132.3, 131.9, 131.7, 131.6, 131.4, 131.2, 131.0 (2C), 119.5, 119.4, 119.2, 118.9, 115.6, 114.6, 114.5, 114.1, 113.6, 113.5, 70.4, 69.3, 68.6 (3C), 68.1, 68.0, 56.1, 55.6, 55.5 (2C), 55.4, 54.9, 35.0 (2C), 34.8 (4C). HRMS (ESI) calcd for $C_{55}H_{57}O_{13}$ [M + H^+]: 925.3794; found, 925.3815.

Compound 9 (Mixture of Diastereomers). Pyridinium *p*-toluene sulfonate (0.12 g, 0.47 mmol) dissolved in CH_2Cl_2 (5 mL) was added in one portion to a stirred solution of bis-functionalized CTB **4** (1.82 g, 2.38 mmol) and 3,4-dihydropyran (0.56 g, 6.66 mmol) in THF (40 mL). The solution was stirred for 16 h at room temperature. Solvents were removed under reduced pressure to give an oily residue. Water and AcOEt were added, and the aqueous layer was extracted twice with AcOEt. The combined organic layers were washed once with brine and then dried over Na_2SO_4. Filtration and evaporation of the solvent gave an oily residue, which was then purified by column chromatography (AcOEt 70/petroleum ether 30). The second spot eluted on the column was collected, and the fractions were evaporated under reduced pressure. Compound **9** was thus collected as a white glassy product (1.6 g, 72%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.00 (s, 2H), 6.9−6.77 (m, 10H), 5.44−5.40 (2s, 1H; OH), 4.73−4.66 (m + d, J = 11.5 Hz, 7H), 4.42 (d, J = 11.5 Hz, 2H), 4.34 (m, 8H), 3.93 (m, 2H), 3.91−3.71 (m, 15 H), 3.50 (m, 5H), 1.80−1.40 (m, 12H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 149.5 (2C), 148.5 (2C), 147.5 (2C), 146.9, 146.7, 145.3, 144.1, 133.0, 132.9, 132.2, 132.0, 131.7, 131.6, 131.2, 120.5 (2C), 116.8, 116.7, 116.6, 115.6, 113.8, 113.6 (2C), 112.1, 111.9 (2C), 68.7, 68.2, 68.1, 67.7 (2C), 62.2 (2C), 56.2 (2C), 55.9, 55.8 (2C), 36.4 (2C), 36.2, 30.6 (2C), 25.4 (2C), 19.4 (2C) (mixture of diastereomers). HRMS (ESI) calcd for $C_{54}H_{64}O_{14}Na$ [M + Na^+]: 959.4194; found, 959.4191.

Compound 10 (Mixture of Diastereomers). 1,4-Diazabicyclo-[2.2.2]octane (0.12 g, 1.0 mmol) was added to a solution of **9** (2.0 g, 2.13 mmol) in dry DMF (20 mL). The solution was stirred for 15−20 min at room temperature; then, oxirane **5** (1.27 g, 4.3 mmol) was added to the solution under an argon atmosphere. The solution was then heated at 100 °C for 48 h. The dark solution was then poured into water, and the compound was extracted several times with AcOEt. The combined organic layers were washed several times with water to remove DMF and then dried over sodium sulfate. Filtration followed by evaporation of the solvent gave a residue, which was purified on silica gel (AcOEt/petroleum ether: 9/1; then, AcOEt: 100%). Complete removal of the solvent under reduced pressure afforded compound **10** as a white glassy product (2.0 g; 76%). ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.94−6.81 (m, 15 H), 4.75−4.65 (m, 9 H), 4.42 (d, J = 12 Hz, 3 H), 4.33 (m, 9 H), 4.21−4.00 (m, 4 H), 3.90 (m, 3 H), 3.84−3.69 (m, 18 H), 3.53−3.50 (m, 6 H), 1.85−1.50 (m, 18 H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 149.7, 149.5, 148.6, 147.6, 146.9, 146.7, 133.3, 133.0, 132.9, 132.2, 132.1, 131.9, 131.8, 131.7, 131.6, 120.5, 117.1, 117.0, 116.7, 114.9, 114.6, 113.8, 111.9, 111.85, 97.6, 71.5, 71.4, 71.1, 70.9, 68.7, 68.5, 68.2, 67.7, 62.3, 56.2, 56.1, 55.9, 55.8, 36.4, 30.6, 25.4, 19.5. HRMS (ESI) calcd for $C_{70}H_{86}O_{19}Na$ [M + Na^+]: 1253.5661; found, 1253.5666.

Compound 11 (Mixture of Diastereomers). CTB **10** (2.0 g, 1.6 mmol) in THF (20 mL) was added dropwise to a cooled solution (0 °C) of sodium hydride (0.130 g, 60% in oil; 3.3 mmol) in THF (5 mL). The solution was allowed to warm to room temperature and was stirred for 20 min at this temperature under an argon atmosphere. Then, allyl bromide (0.39 g, 0.28 mL, 3.3 mmol) was added with a syringe. The solution was heated at 80 °C overnight under argon. The solution was poured into cold water and extracted four times with AcOEt. The combined organic layers (V = 400 mL) were washed two times with brine and then dried over Na_2SO_4. Filtration and elimination of the solvent under reduced pressure left a residue, which was then purified on silica gel (AcOEt/petroleum ether: 75/25). Evaporation of the solvents under reduced pressure gave rise to compound **11** (1.76 g, 85%) as a white glassy product. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 7.07−6.80 (m, 15 H), 5.88 (m, 1 H), 5.26−5.10 (m, 2 H), 4.71−4.65 (m, 9 H), 4.43−4.40 (d, J = 12 Hz, 3 H), 4.33 (m, 8 H), 4.29−4.03 (m, 7 H), 3.90 (m, 3 H), 3.87−3.65 (m, 18 H), 3.58−3.45 (m, 6 H), 1.83−1.43 (m, 18 H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 149.7, 149.5, 148.5, 147.8, 147.6, 147.1, 146.9, 134.9, 133.0, 132.7, 132.5, 131.9, 131.6, 120.5, 117.2, 116.7, 116.1, 115.8, 113.8, 113.7, 113.5, 112.1, 111.9, 97.6, 75.6, 71.8, 71.7, 70.0, 69.9, 69.4, 69.1, 68.7, 68.2, 67.7, 62.3, 56.2, 56.0, 55.9, 36.4, 30.6, 25.5, 19.5. HRMS (ESI) calcd for $C_{73}H_{90}O_{19}Na$ [M + Na^+]: 1293.5974; found, 1293.5973.

***(rac)*-Cryptophane-12.** Formic acid (300 mL) was added in one portion to a solution of **11** in $CHCl_3$ (300 mL). The solution was stirred for 5 h at 60 °C. The solvents were removed under reduced pressure to leave a yellow residue. $CHCl_3$ was added several times to remove traces of formic acid (azeotropic distillation). The residue was purified by column chromatography on silica gel (CH_2Cl_2/Acetone: 9/1). The second spot was collected, and the solvents were removed under reduced pressure. The pale yellow solid was then washed with diethyl ether on a frit. Another column chromatography on silica gel (CH_2Cl_2/Acetone: 9/1) provided compound **12** as a white solid (0.23 g, 44%). It was then recrystallized in a $CHCl_3$/EtOH mixture. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ 6.77 (s, 2H), 6.72 (s, 2H), 6.66 (s, 2H), 6.65 (s, 1H), 6.64 (s, 3H), 6.58 (s, 1H), 6.55 (s, 1H), 6.00 (m, 1H), 5.4−5.2 (m, 2H), 4.61 (3d, J = 13.5 Hz, 3H), 4.58 (3d, J = 13.5 Hz, 3H), 4.30−3.82 (m, 12 H), 3.80 (2s, 6H), 3.78 (s, 3H), 3.71 (2s, 6H), 3.75 (s, 3H), 3.41 (2d, J = 13.5 Hz, 2H), 3.38 (2d, J = 13.5 Hz, 4H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C): δ 149.5 (3 C), 149.4, 148.2, 147.7, 147.1, 146.7 (3 C), 146.6 (2 C), 135.0, 134.0 (2 C), 133.9 (2 C), 133.3, 132.2, 131.9 (2 C), 131.5 (2 C), 130.8, 130.7, 120.4 (2 C), 120.2 (2 C), 117.4, 114.0 (2C), 113.8, 113.5 (3 C), 113.3, 112.5, 75.8, 70.90, 69.6 (2 C), 68.95 (2 C), 66.2, 65.9, 56.2 (2 C), 55.8 (2 C), 55.5 (2 C), 36.5 (2 C), 36.1 (2 C), 36.0 (2 C). HRMS (ESI) calcd for $C_{58}H_{60}O_{13}$ [M^+]: 964.4034; found, 964.4033.

***(rac)*-Cryptophane 8: Method A.** A freshly prepared 1 M lithium diphenylphosphide solution in THF (6.81 mL, 6.72 mmol) was added at room temperature to a stirred solution of cryptophane **7** (300 mg, 0.32 mmol) in 3 mL of dry THF. The dark red mixture was then heated at 60 °C for 48 h. The mixture was then poured into water (50 mL). The aqueous layer was washed four times with CH_2Cl_2 (15 mL each time). The aqueous layer was then collected, cooled to 0 °C, and acidified with a concd HCl solution. The solid precipitate was collected on a frit, washed several times with water and Et_2O, and finally dried on a frit. The solid was then purified by column

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chromatography (AcOEt/EtOH/H_2O: 90/8/2) to give rise to cryptophane **8** as a white solid (220 mg, 81%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.56 (s, 1 H), 8.48 (s, 1 H), 8.43 (s, 1 H), 8.30 (s, 1 H), 8.14 (s, 1 H), 7.91 (s, 1 H), 6.77 (s, 1 H), 6.38 (s, 1 H), 6.69–6.63 (m, 8 H), 6.55 (m, 2 H), 5.32 (s, 1 H), 4.50–3.70 (m, 18 H), 3.22 (m, 6 H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 146.4, 146.35, 145.7, 145.6, 145.5, 145.4, 145.3, 145.1, 144.5, 144.3 (2 C), 144.1, 133.9, 133.8, 133.6, 133.5, 133.3 (2 C), 131.1 (2 C), 130.5 (2 C), 129.5, 128.9, 120.2, 119.8, 119.0, 118.1 (2 C), 118.0, 117.6, 117.5, 117.4, 117.0, 116.9, 116.5. 71.5, 70.5, 69.2, 68.5 (3C), 68.2, 68.1, 35.1, 34.9, 34.8. HRMS $[M + H]^+$ calcd. for $C_{49}H_{45}O_{13}$: 841.2892; found, 841.2855.

Method B (Purification): Synthesis of (rac)-*anti*-Cryptophane-13. Acetic anhydride (1.4 mL) was added in one portion to a cooled solution of **8** (0.22 g, 0.26 mmol) in pyridine (5 mL). The solution was then allowed to warm to room temperature and was stirred for 4–5 h. The solution was then poured into a cooled mixture of CH_2Cl_2/H_2O. The product was extracted three times with CH_2Cl_2. The combined organic layers were then washed once with H_2O and dried over Na_2SO_4. Filtration followed by removal of the solvent under reduced pressure left an oily residue, which was purified by chromatography on silica gel. Purification on silica gel (CH_2Cl_2/Acetone: 9/1) gave rise to compound **13** (0.22 g, 74%) as a white glassy solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.13 (s, 1H), 7.09 (s, 2H), 7.04 (s, 1H), 7.02 (s, 2H), 6.99 (s, 1H), 6.97 (s, 1H), 6.96 (s, 1H), 6.935 (s, 1H), 6.93 (s, 1H), 6.87 (s, 1H), 4.89 (m, 1H), 4.65–4.55 (m, 6H), 4.30–3.95 (m, 12H), 3.45 (m, 6H), 2.39 (s, 3H), 2.34 (s, 3H), 2.29 (s, 6H), 2.28 (s, 3H), 2.24 (s, 3H), 0.18 (s, broad, 3H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 170.2, 167.0 (4 C), 168.8 (2 C), 149.2 (2 C), 149.1, 149.0, 148.7, 148.4, 140.7 (2C), 140.6, 140.5, 139.4, 139.1, 138.5, 138.3, 138.2, 138.0, 137.5, 137.2, 133.85, 133.8, 133.7, 133.4, 132.4, 132.0, 125.0, 124.9, 124.5, 124.4, 124.0, 123.4, 120.8, 120.4, 120.2, 120.1, 114.7, 114.1, 70.8, 69.5, 69.2, 65.0, 64.5, 36.6, 36.5, 36.2 (4 C), 21.0 (5 C), 20.8. HRMS (ESI) calcd for $C_{63}H_{58}O_{20}$ $[M^+]$: 1135.3594; found, 1135.3625. Compound **8** was recovered by hydrolysis under a basic solution. A solution of NaOH/H_2O (7 mL, 0.5 M) was added in one portion to a stirred solution of **13** (0.20 g, 0.17 mmol) in THF (7 mL). The mixture was stirred overnight at 60 °C under an argon atmosphere for 16 h. The organic layer was removed under reduced pressure, and 7 mL of water was added to the solution. The solution was then cooled in an ice bath and acidified with a few drops of a concd HCl solution. The white precipitate was collected on a frit, washed several times with water, and then dried on the frit. It was then washed several times with diethyl ether to give rise to compound **8** (0.13 g, 88%) as a pale yellow compound.

***(rac)*-Cryptophane 14.** Methylbromoacetate (67.5 μL, 0.71 mmol) was added to a stirred mixture of **8** (50 mg, 0.06 mmol) and potassium carbonate (99 mg, 0.71 mmol) in dry DMF (4 mL). The mixture was stirred for 20 h at room temperature under an argon atmosphere. The reaction was then quenched by the addition of water and ethyl acetate (EtOAc). The aqueous layer was extracted twice with EtOAc and then dried with sodium sulfate. Filtration followed by evaporation of the solvent under reduced pressure gave rise to a white solid. Purification by column chromatography ($CHCl_3$/Acetone: 7/3) gave desired compound **14** as a white solid (40 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (s, 1 H), 6.80 (s, 1 H), 6.78 (s, 1 H), 6.77 (s, 1 H), 6.76 (s, 1 H), 6.73 (s, 1 H), 6.69 (s, 1 H), 6.67 (s, 3 H), 6.65 (s, 2 H), 4.70–4.40 (m, 18 H), 4.40–3.90 (m, 13 H), 3.84 (s, 6 H), 3.81 (s, 12 H), 3.50–3.30 (m, 6 H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C): δ 170.0, 169.9 (2 C), 169.8, 169.7 (2 C), 147.7, 147.6 (2 C), 147.5, 147.4 (4 C), 147.3 (2 C), 147.1, 146.8, 134.5, 133.7, 133.5, 134.4 (2 C), 133.35, 133.3, 133.25, 133.2, 132.7, 132.5, 120.9, 120.8, 120.0 (2 C), 119.3 (2 C), 118.3, 118.0, 117.9, 117.5 (2 C), 115.9, 71.3, 69.4, 69.2, 68.7, 68.6, 68.3, 67.7 (3 C), 67.6, 67.2, 67.1 (2 C), 52.15, 52.1, 52.05 (2 C), 52.0 (2 C), 36.2 (2 C), 35.9 (4 C). HRMS (ESI) calcd for $C_{67}H_{69}O_{25}$ $[M + H^+]$: 1273.4122; found, 1273.4111.

***(rac)*-Cryptophane 15.** Mesyl chloride (364 μL) was added under an argon atmosphere to a stirred mixture of cryptophane **14** (0.2 g, 0.157 mmol) in a mixture CH_2Cl_2 (10 mL) and pyridine (670 μL). The solution was heated under reflux conditions for 60 h. TLC ($CHCl_3$/Acetone: 7/3) was used to monitor the reaction. Then, methanol (10 mL) was added to the solution. Evaporation of the solvents gave rise to a dark brown solid. Water and CH_2Cl_2 were added, and the product was extracted three times with CH_2Cl_2. The combined organic layers were washed with water and then with brine. Then, the organic layer was washed with Na_2SO_4. Filtration and evaporation of the solvents under reduced pressure gave a yellow solid, which was purified by column chromatography on silica gel ($CHCl_3$/Ethyl Acetate: 5/5). Evaporation of the solvents afforded a product, which was then recrystallized in a $CHCl_3$/EtOH mixture. Compound **15** (151 mg, 71%) was collected on a frit. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.94 (s, 1H), 6.85 (s, 1 H), 6.82 (s, 1H), 6.81 (s, 1H), 6.81 (s, 1 H), 6.80 (s, 1 H), 6.76 (s, 1 H), 6.72 (s, 1 H), 6.70 (s, 1 H), 6.67 (s, 1 H), 6.63 (s, 1 H), 6.58 (s, 1 H), 6.54 (s, 1H), 5.08 (m, 1 H), 4.80–4.40 (m, 29 H), 3.90 (m, 1 H), 3.85 (s, 6 H), 3.80 (s, 12 H), 3.45–3.31 (m, 6H), 3.31 (s, 3 H). ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C): δ 170.0, 169.9 (2 C), 169.8, 169.7, 169.3, 147.8 (3 C), 147.6, 147.5, 147.3, 147.2, 147.1, 147.0 (4 C), 134.7, 134.3, 133.9, 133.7, 133.6, 133.35 (2 C), 133.3, 133.2, 133.1, 133.0, 132.8, 121.4, 120.7, 120.6, 120.1, 120.05, 119.0, 118.9, 118.0, 117.3, 116.8, 116.4, 116.35, 81.4, 70.8, 69.8, 69.5, 69.05, 68.7, 68.5, 68.0, 67.6, 66.6 (3 C), 66.3, 52.15, 52.1 (2 C), 52.05, 52.0 (2 C), 38.8, 36.1 (3 C), 36.0 (2 C), 35.9. HRMS (ESI) calcd for $C_{68}H_{70}NaO_{27}S$ $[M + Na^+]$: 1373.3717; found, 1373.3760.

***(rac)*-Cryptophane 1.** A solution of KOH/H_2O (5.7 mL, 28.4 mmol; 0.5 M) was added in one portion to a stirred solution of **14** (120 mg, 0.094 mmol) in THF (5 mL). The mixture was heated at 60 °C for 18 h. The THF layer was then removed under reduced pressure. Water (5 mL) was then added, and the solution was cooled in an ice bath. The aqueous solution was then acidified with a few drops of a concd HCl solution. The resulting precipitate was then collected on a frit and washed three times with water. It was then dried on the frit and finally washed several times with diethyl ether. Desired compound **1** was obtained as a white powder (95 mg; 85%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.90 (s, 3 H), 6.88 (s, 1 H), 6.85 (s, 1 H), 6.84 (s, 1 H), 6.83 (s, 1 H), 6.82 (s, 3 H), 6.80 (s, 1 H), 6.76 (s, 1 H), 4.80–4.40 (m, 19 H), 4.40–3.70 (m, 12 H), 3.31 (m, 6 H). ^{13}C NMR (126.7 MHz, DMSO-d_6, 25 °C): δ 170.9, 170.5 (5 C), 147.2 (5 C), 146.5 (3 C), 146.2, 146.0, 145.6 (2 C), 133.7, 133.5, 133.4, 133.3, 133.1, 133.0, 132.6 (2 C), 132.5 (2 C), 132.3 (2 C), 119.7, 119.4, 118.7 (2 C), 118.2, 118.0 (2 C), 117.0, 116.8, 116.5, 116.4, 116.2, 72.6, 70.8, 68.8, 68.0 (4 C), 66.6 (2 C), 66.1 (2 C), 65.8 (2 C), 34.9 (6 C). HRMS (ESI) calcd for $C_{61}H_{57}O_{25}$ $[M + H^+]$: 1189.3183; found, 1189.3221.

***(rac)*-Cryptophane 2.** To a stirred solution of **8** (60 mg, 0.070 mmol) and K_2CO_3 (0.16 g, 0.84 mmol) in DMF (2 mL) was added tosylate derivative **17** (0.44 g, 1.4 mmol) dissolved in DMF (2 mL). This solution was heated at 60 °C for 16 h under an atmosphere of argon. The solvent was evaporated, and the residue was redissolved in 7/2/1 EtOAc/MeOH/H_2O and absorbed onto SiO_2. Purification by flash chromatography on silica gel (EtOAc/MeOH/H_2O: 7/2/1) afforded the product as a colorless oil. Precipitation of PEG impurities was achieved by dissolution in ether followed by filtration. Evaporation of the filtrate afforded the purified product as a colorless oil (0.10 g, 82%). ^{1}H NMR (500 MHz, MeOD): δ 6.96–6.79 (12 H, m, ArH), 4.67–4.57 (6 H, m), 4.49–3.57 (87 H, m), 3.44–3.31 (23 H, m). ^{13}C NMR (125 MHz, MeOD): δ 149.5, 149.4, 149.3, 149.2(8) (2 C), 149.2(1), 149.1(4), 149.1(1), 148.9, 148.4, 147.8, 147.7, 135.3(5), 133.3(3), 135.3, 135.2, 135.1, 135.0, 134.7 (2 C), 134.5(2 C), 134.3(3), 134.3(0), 121.1, 121.0, 120.9, 120.8, 120.6, 120.4, 120.2, 120.0, 119.6, 119.3, 118.2, 117.4, 73.1, 73.0, 72.9, 72.2, 71.9, 71.8(5), 71.8(0), 71.6, 71.5, 71.4, 71.3, 71.2, 70.5, 69.5, 69.4, 69.2, 59.2, 59.1, 36.8, 36.7(4), 36.7(0), 36.6, 30.7 (32 magnetically equivalent carbons overlapping or obscured). MS (ESI) m/z: 1736 ($[M + NH_4]^+$, 100%). HRMS (ESI, $[M + 2H]^+$) calcd for $C_{91}H_{130}O_{31}$, 859.4293; found, 859.4277.

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■ ASSOCIATED CONTENT

Supporting Information

^{1}H NMR (500 MHz) and ^{13}C NMR (125.7 MHz) spectra of compounds **1**−**16**; xenon NMR spectra of compounds **1**, **2**, **7**, **8**, **13**, and **14**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00653.

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Notes

The authors declare no competing financial interest.

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