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Synthesis and application of cryptophanol hosts: ^{129}Xe NMR spectroscopy of a deuterium-labeled $(Xe)_2$@bis-cryptophane complex

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The new bis-cryptophanes **7**–**9** were prepared from cryptophanols **1**–**3** and illustrate the synthetic possibilities offered by the latter for the design of new host systems featuring the preparation of large supramolecular receptors and new polycryptophane bio-sensors for NMR imaging. Hosts **1**–**3** were obtained from the monoprotected cryptophanes **4**–**6** following a multi-step strategy. The complexation of xenon by the dissymmetrical bis-cryptophane **8** was studied by ^{129}Xe NMR spectroscopy. At low temperature, a strong discrimination ($\Delta\delta = 1.16$ ppm) of the encapsulated xenon guests inside the two cryptophane cavities was observed. The kinetic parameters for the complexation process were determined from 1D-EXSY ^{129}Xe NMR experiments. The activation energy $E_a = 39.0 \pm 3$ kJ mol^{-1} and associated parameters $\Delta H^{\neq} = 37.0 \pm 3$ kJ mol^{-1} and $\Delta S^{\neq} = -46.0 \pm 10$ kJ mol^{-1} K^{-1} are in agreement with the values determined for cryptophane-A and [D_{27}]-cryptophane-A.

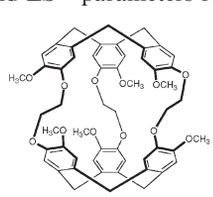
Introduction

The reversible encapsulation of various substrates in molecular capsules, cavitands or carcerands led to the formation of novel supramolecular assemblies, which anticipated the design of new materials.[1–4] For instance, giant capsules have been proven to bind two or more molecules that can be identical or different.[5–7] Another approach to multiple guest encapsulation comes from the formation of container molecules with two or more separate chambers, where the guests are isolated from the bulk solution and without a direct mutual contact.[8,9] One of the advantages of such systems is the possibility to create new systems where the response to the complexation process is multiplied according to the number of equivalent encapsulated species.

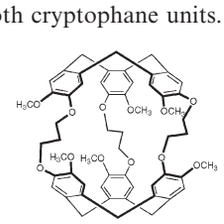
In this field of investigation, cryptophanes represent an interesting class of host molecules for the design of new materials with specific and highly selective complexation properties. For instance, cryptophanes-A and -E possess a lipophilic spherical cavity very well-suited to encapsulate small molecules with a preference for tetrahedral guests such as methane, chloroform and ammonium salts.[10–13] Cryptophane-A and related compounds with C_2 symmetry also exhibit a strong affinity for xenon in organic solution.[14,15] So far, Cryptophane-A shows the highest affinity for xenon ($K_a = 3900$ M^{-1} at 278 K) and is an excellent candidate for the design of new biological sensors.[16]

The functionalization of cryptophanes is a prerequisite to prepare new sophisticated hosts with specific binding properties and to produce optically pure cryptophanes.[17] However, a modification of the synthetic route usually used to prepare compounds with D_3 or C_3 symmetry is required to attach the desired functional groups on the cryptophane platform. Previously, we briefly described the synthesis of cryptophanols **1**–**3** from their precursors **4**–**6**, which were obtained in moderate yields.[18] Meanwhile, Pines *et al.* have reported the synthesis of a mono-functionalized cryptophane using a slightly different synthetic route, to design new cryptophane based bio-sensors.[19]

We report herein the synthesis of symmetrical and dissymmetrical bis-cryptophanes **7**–**9** from their precursors **1**–**3**, exemplifying the possibility to design supramolecular receptors incorporating several cryptophane units in oligomeric or dendritic structures. The formation of the $(Xe)_2$@**8** complex was investigated by ^{129}Xe NMR spectroscopy. The resonances of the encapsulated xenon guests showed a strong discrimination ($\Delta\delta = 1.16$ ppm) of the two cryptophane moieties, proving the extreme sensitivity of xenon to its environment. Kinetic parameters were determined from low temperature ^{129}Xe 1D-EXSY NMR experiments and allowed the determination of the activation energy for decomplexation and the related $\Delta H^{\neq}$ and $\Delta S^{\neq}$ parameters for both cryptophane units.



Cryptophane-A



Cryptophane-E

Results and discussion

Synthesis

A multi-step strategy is required to introduce a single functional group on the cryptophane structure. The *template method* offers the possibility to attach different linkers to the same cyclotriveratrylene (CTV) unit, and this approach has been successfully applied to prepare cryptophanes bearing a single deuterated methoxy group or to synthesize new

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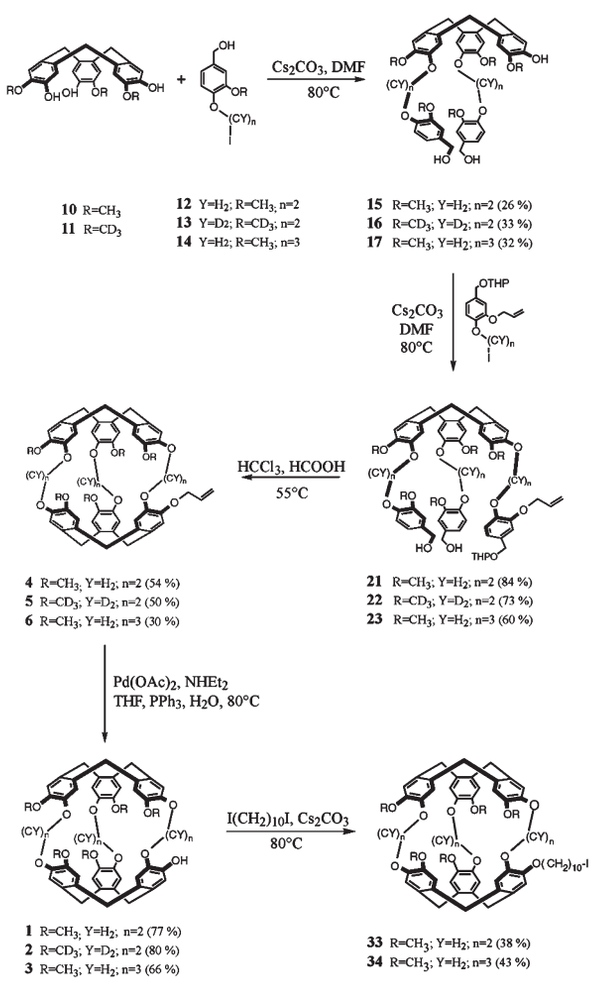
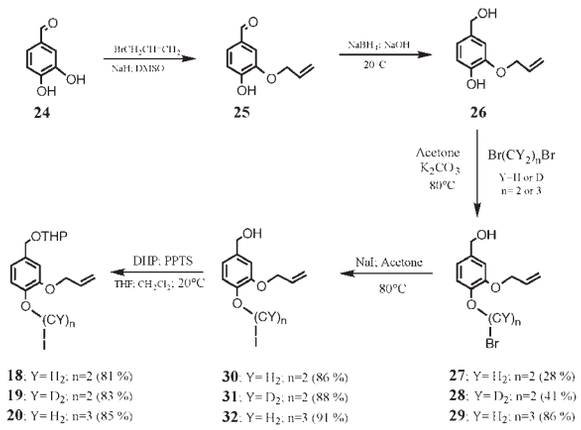
cryptophane molecules with C_2 symmetry.[15,20] It is thus necessary to use a protected hydroxyl function to avoid the formation of side-products during the cyclization step leading to the formation of the cryptophane. The protecting group must be stable under acidic conditions and then easily cleaved. This point was crucial to achieve the synthesis of compounds **1**–**6** and this choice becomes even more restricted due to additional requirements. For instance, the use of bulky substituents on the CTV units, such as long alkyl chains, should be avoided as they prevent the formation of cryptophanes. The search for a suitable protecting group was facilitated by the recent results obtained from mass spectroscopy studies on the formation of cryptophanes from their precursors. LSIMS (liquid secondary ion mass spectrometry) of cryptophane precursors showed that cryptophanes were formed in the spectrometer probe in a way similar to that in solution and it was clearly shown that both the allyl and benzyl moieties could be used as efficient protecting groups.[21]

The cyclotriveratrylene **10** and its deuterated congener **11** were prepared according to a known procedure.[20] These compounds were then allowed to react with two equivalents of the benzyl alcohol derivatives **12**, **13** or **14** in the presence of cesium carbonate to give the bis-substituted cyclotriveratrylenes **15** (26%), **16** (33%) and **17** (32%), respectively. This procedure allows easy purification by column chromatography of the desired compounds from the crude material containing mainly the mono- and tri-substituted derivatives (Scheme 1).

The reaction of **15**–**17** with the allyl-protected compounds **18**, **19** or **20**, under the same experimental conditions, afforded the cryptophane precursors **21** (81%), **22** (73%) and **23** (60%). Compounds **18**–**20** were synthesized in five steps from 3,4-dihydroxybenzaldehyde (**24**; Scheme 2). The selective



Scheme 1



Scheme 2

protection of **24** in the *meta* position with allyl bromide in presence of sodium hydride in DMSO gave compound **25** in 50% yield.[22] Reduction of **25** with $NaBH_4$ yielded almost quantitatively the allyl-protected benzyl alcohol **26**, which was then allowed to react with 1,2-dibromoethane, 1,2-[D_2]dibromoethane or 1,3-dibromopropane to give the brominated derivatives **27** (28%), **28** (41%) and **29** (86%), respectively. Reaction with sodium iodide in acetone led to the corresponding iodo compounds **30** (86%), **31** (88%) and **32** (91%). The benzyl alcohol function in **30**–**32** was protected with dihydropyran (DHP) in the presence of pyridinium *para*-toluenesulfonate (PPTS) to give the corresponding tetrahydropyranyl (THP) derivatives **18**–**20**, respectively. The introduction of the THP protecting group strongly facilitates the purification of the cryptophane precursors **21**–**23** by column chromatography on silica gel. A slightly different procedure involving the introduction of the benzyl alcohol molecule bearing the O-allyl function on the CTV unit, prior to the two other linkers, was also successfully applied and gave similar results.[18] The key step in the present synthesis is the formation of the second CTV unit under acidic conditions to give the monoallyl-protected cryptophanes **4**–**6**, without loss of the allyl group. The use of perchloric acid in methanol or pure formic acid led to a significant degradation of the starting compounds. However, the use of a 1:1 mixture of $CHCl_3$ and formic acid strongly reduced the degradation of the precursors and afforded the expected cryptophanes **4**–**6** in 30%–49% yields.

The desired products were obtained in lower yields than for cryptophane-A, suggesting that the allyl group is probably not totally stable under the present experimental conditions. The use of scandium triflate, which has been used as a catalyst to promote calixarene cyclization,[23] could be a promising reagent for the formation of the cyclotriveratrylene platform. In a first attempt, the reaction of scandium triflate with **21** in acetonitrile gave compound **4** in poor yield (10%, unoptimized). However, the mild conditions of the reaction make this catalyst very attractive for the preparation of new cryptophanes bearing sensitive functional groups, after optimization of the experimental procedure. Cryptophanes **4** and **5** were isolated as the *anti* isomers and their stereochemistry was previously determined from the synthesis of the optically active molecules.[17] Up to now, **6** has not been resolved and we have not succeeded in getting suitable crystals for X-ray structure analysis. However, the experimental procedure used herein is known to favor the formation of the *anti* isomer of cryptophane-E, which suggests that **6** was also obtained as the *anti* isomer.

The removal of the protecting group was then achieved by using a palladium catalyst to give the expected cryptophanols **1** (77%), **2** (80%) and **3** (66%). These new cryptophanes, bearing one hydroxyl function, offer new possibilities of preparing more sophisticated hosts with specific physical and chemical

properties. For instance, novel oligomeric or dendritic structures containing cryptophane moieties could be synthesized from cryptophanols **1**–**3**. The new molecules **7**–**9** consisting of two cryptophanes connected together with an alkyl chain were then prepared from **1**–**3** (Scheme 3). Compound **7** was prepared by reacting two equivalents of **1** with 1,10-diiododecane in DMF and was isolated in moderate yield (26%), suggesting a hindered hydroxyl function in **1**. The synthesis of the dissymmetrical bis-cryptophanes **8** and **9** requires a two-step synthesis involving first the preparation of cryptophanes **33** and **34**. Reaction of cryptophanols **1** and **3** with an excess of 1,10-diiododecane gave rise to molecules **33** (38%) and **34** (43%), respectively.

These two compounds were prepared in different solvents. Cryptophanol **1** is soluble in DMF and sparingly soluble in $CHCl_3$, whereas cryptophanol **3** is almost insoluble in both solvents. This difference of solubility is still unexplained but can be attributed to the free hydroxyl group, which probably influences the physical properties of hosts **1** and **3**. DMF was used in the preparation of **33**, whereas cryptophane **34** was prepared in a CH_2Cl_2–acetone mixture. Compounds **33** and **34** were then allowed to react with cryptophanols **2** and **1** in DMF to produce the unsymmetrical bis-cryptophanes **8** (77%) and **9** (61%), respectively. Bis-cryptophanes **7**, **8** and **9** were isolated as mixtures of diastereomers and were readily soluble in various organic solvents, with respect to the parent cryptophane-A and -E, allowing further investigations on their binding properties in different solvents.

The new compounds were characterized by ^1H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS) using the liquid secondary ion mass spectrometry technique (LSIMS). The low symmetry of cryptophane precursors **21**–**23** and cryptophanes **1**–**6** significantly complicated the ^1H and ^{13}C NMR spectra, and this was even more obvious with bis-cryptophanes **7**–**9** (Fig. 1). Cyclotriveratrylene derivatives **15**–**17** and **21**–**23**, bis-cryptophanes **7**–**9**, and cryptophanes **33**–**34** were isolated as glassy products, as confirmed by the absence of melting point, and decomposed over a large range of temperature. In addition, they still contain variable amounts of solvent molecules and elemental analyses are thus unable to properly characterize the new compounds. Attempts to crystallize cryptophanes **33**, **34** and **7**–**9** in appropriate mixture of solvents were also unsuccessful. Cryptophanes **1**–**6** decomposed above 200 °C.

^{129}Xe NMR investigation of the $(Xe)_2$@8 complex

Cryptophane-A is a remarkable receptor for xenon gas dissolved in organic solution. Owing to the spherical shape and the size of the internal cavity of the host (95 Å^3), xenon was readily encapsulated to form a highly stable Xe@cryptophane-A complex (K_a = 3900 M^{-1} at 278 K).[14] Recently, new cryptophanes with C_2 symmetry were prepared and exhibited interesting binding properties towards xenon with a somewhat lower binding constant.[15] ^{129}Xe NMR studies of Xe@cryptophane complexes showed an important discrimination between cryptophane-A and its deuterated congeners at low temperature.[24] This effect illustrates the exceptional sensitivity of the ^{129}Xe chemical shift with regard to a very small change in its environment. The magnitude of this effect definitely depends on the number of deuterium atoms and their location on the host structure. We took advantage of this property to investigate the exchange dynamics of xenon guests between two identical hosts differing only by their number of deuterium atoms.[24] The dissymmetrical bis-cryptophane **8** is made of one cryptophane-A (**H** site) unit and one [D_{27}]-cryptophane-A (**D** site) unit connected together by a linear $(CH_2)_{10}$ alkyl chain, the length of which was chosen arbitrary. Similar complexation properties for **8** were therefore expected compared with those of cryptophane-A and its deuterated congener when these two hosts are not linked together, but the kinetics may change since in the present case the collisions between the two units are not diffusion-controlled. A solution containing bis-cryptophane **8** in 1,1,2,2-tetrachloroethane was prepared and ^{129}Xe NMR spectra were recorded at different temperatures.

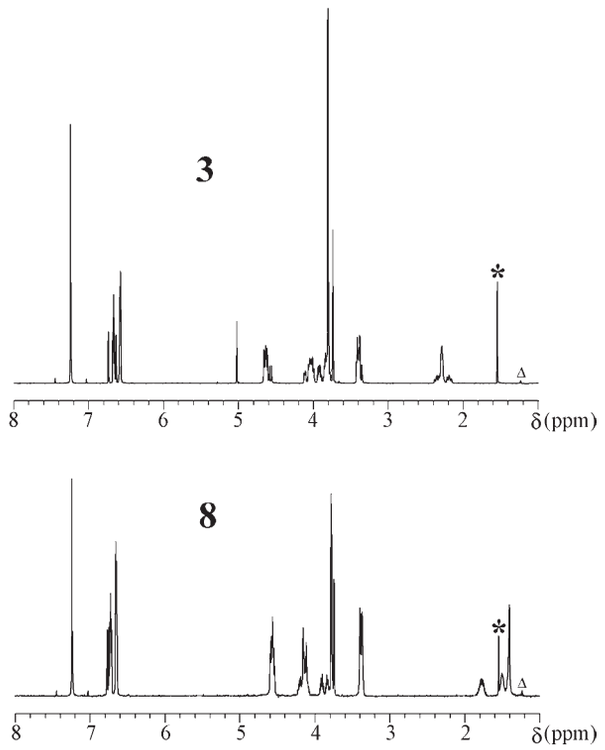
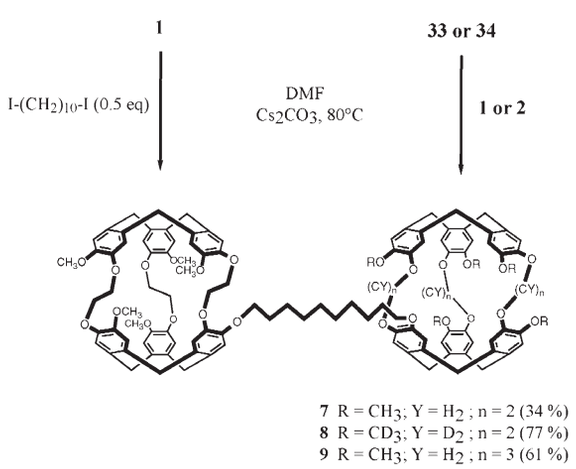


Fig. 1 ^{1}H NMR (499.83 MHz) spectra of cryptophanol-E **3** and deuterated bis-cryptophane **8** recorded at 20 °C in chloroform-*d* (stars and triangles denote respectively water and impurity from chloroform).



Scheme 3

As for cryptophane-A, two distinct effects were observed when decreasing the temperature. Firstly, we observed a high-field shift of the resonances of the encapsulated xenon guests, due to a change of the dynamics of the cryptophanes;[14] the reverse effect was observed for the unbound xenon resonance. Secondly, we noted a significant decrease of the line width of the xenon resonances due to a slowing down of the exchange dynamics, which allowed the xenons localized in both cavities to be distinguished at low temperature. At 228 K, the two signals were well-resolved with a chemical shift difference δ(Xe@**H**) − δ(Xe@**D**) = 1.16 ppm (Fig. 2). This result

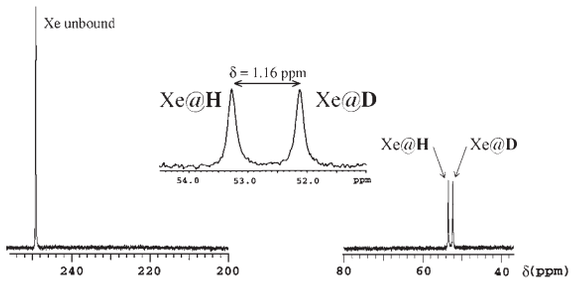


Fig. 2 ^{129}Xe 1D-NMR spectrum of bis-cryptophane **8** recorded at 228 K in 1,1,2,2-tetrachloroethane-d_2 (insert: enlarged spectrum of the two bound states).

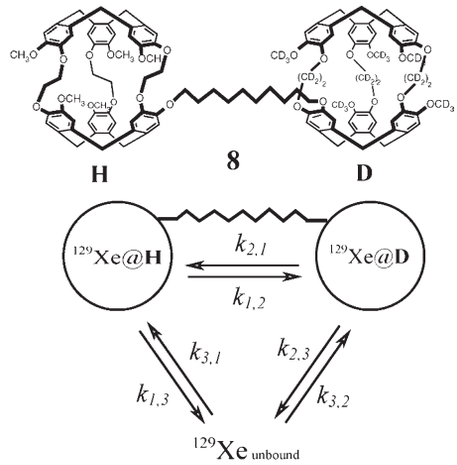
is very close to the value $\Delta\delta = 1.09$ ppm calculated from eqn. (1) by considering only the effect of the deuterium atoms attached to cryptophane-**A**.[24] N_b and N_m stand for the number of deuterium atoms located on the bridges and the methyl groups, respectively, and ***i*** is a deuterated congener of cryptophane-**A**.

$$\Delta\delta = \delta(\text{Xe@}\mathbf{A}) - \delta(\text{Xe@}\boldsymbol{i}) = 0.048\ N_b + 0.034\ N_m \quad (1)$$

The small $\Delta\delta = 0.07$ ppm (± 0.02) difference between experimental and calculated values may be attributed to the effect of the alkyl linker and the dissymmetry of the cryptophane host. This effect is, however, very small and suggests that both cryptophane moieties do not interact strongly. The absence of additional resonance lines due to the presence of several diastereomers in solution seems to support this assumption. This was recently supported by theoretical calculations of the ^{129}Xe chemical shifts in different Xe@cage complexes.[25]

The exchange dynamics of xenon in the $(Xe)_2$@**8** complex was studied by NMR at 228 K using selective excitation of the resonances of the two bound xenon or the free xenon in solution. The experimental procedure and the difficulties in carrying out these experiments have already been reported; they required a well-calibrated pulse and a very good stabilization of the temperature.[20] When these requirements are reached, the whole set of rate constants can be measured according to a given kinetic model. Previously, we demonstrated that the direct exchange of xenon between cryptophane complexes is negligible when the two hosts are not bound together. In the present case, for **8** in the presence of an excess of xenon, the kinetics are probably also dominated by the exchange of xenon guest between the host and the solution. However, the introduction of the linker between the cavities in **8** may introduce a different behavior (direct exchange through intramolecular collisions between units **H** and **D**) and its influence should be investigated. In addition, under the present experimental conditions, that is an excess of guest combined with the high binding constant of the Xe@cryptophane-A complexes, all the host cavities are occupied by xenon atoms. Thus, the kinetic model given in Scheme 4 can be proposed to describe the exchange process.

Fig. 3 shows the ^{129}Xe 1D-EXSY NMR spectra recorded at 223 K as a function of the mixing time τ_m when the resonance lines of the Xe@**H** and Xe@**D** complexes were selectively irradiated. The ^{129}Xe NMR spectrum for $\tau_m = 0$ showed that the selective irradiation slightly affects the second peak. The pulse length used for these experiments, combined with small temperature fluctuations during the experiments, probably reaches the limits to selectively irradiate each bound resonance line. However, in the present case, the determination of the rate constants is not significantly affected since initial magnetizations are used as variables. A sharper pulse (in the frequency domain) has not been utilized since it would have decreased the signal-to-noise ratio of the observed signals. Fig. 3 also reveals that the equilibrium was reached with relatively short mixing times ($\tau_m < 5$ s) since the exchange dynamics occur



Scheme 4 Pseudo-first-order kinetic model describing the ^{129}Xe 1D-EXSY NMR experiments.

much faster than the mean longitudinal relaxation time, $\langle T_1 \rangle$, which was measured to be several orders of magnitude longer.[20]

The rate constants were then determined by fitting the experimental data (intensities of each signal as a function of the mixing time) to the kinetic model given above.[26] The ***L*** matrix, which contains all the information about the exchange dynamics, is identical to the one previously used for cryptophane-A and its deuterated congener.[20] The calculated rate constants are reported in Table 1 and show that under our experimental conditions the process involving a direct exchange between the two **H** and **D** cryptophane units did not occur. As expected similar rate constants $k_{1,3}$ and $k_{2,3}$ have been obtained, within the limits of experimental error, since both cryptophane units **H** and **D** exhibit similar complexation properties toward xenon.

Variable temperature experiments allowed us to determine the activation energy for decomplexation, E_a, and the $\Delta H^{\neq}$ and $\Delta S^{\neq}$ parameters. The absence of direct intramolecular exchange ($k_{1,2} = k_{2,1} = 0$) leads to a simplification of the experimental procedure since the whole set of rate constants can be obtained by irradiating simultaneously the two

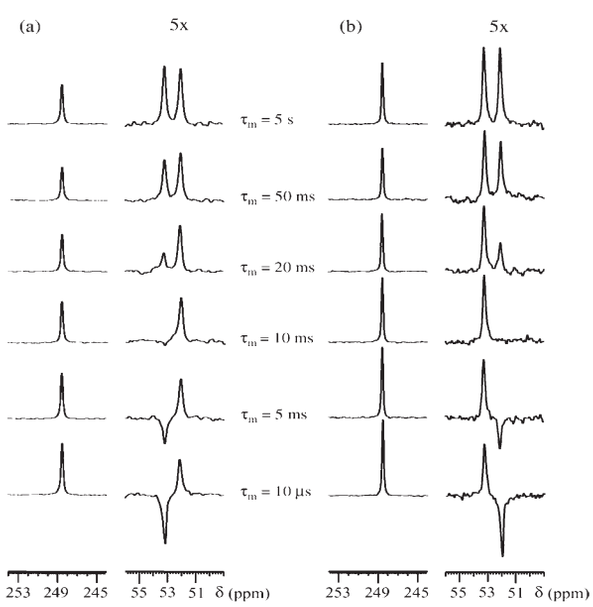


Fig. 3 1D-EXSY NMR spectra of Xe_2@**8** (228 K): evolution of the magnetization of the three sites as a function of the mixing time: (a) after selective excitation of the [^{129}Xe@**H**] signal and (b) after selective excitation of the [^{129}Xe@**D**] signal.

Table 1 Rate constants k_{ij} (in s^{-1}) obtained from ^{129}Xe 1D-EXSY experiments in 1,1,2,2-tetrachloroethane at 223 K ([unbound Xe]/[Xe@**H** or Xe@**D**] = 3.3)

$k_{1,2}$	$k_{2,1}$	$k_{1,3}$	$k_{2,3}$	$k_{3,1}$	$k_{3,2}$
0	0	37 ± 6	40 ± 6	11 ± 2	12 ± 2

resonance lines of the bound xenon. The measurements were carried out at five different temperatures and rate constants were determined by fitting the experimental data to the model reported above, assuming that direct exchange is negligible. The rate constants for decomplexation $k_{1,3}$ and $k_{2,3}$ are reported in Table 2. The Arrhenius plot affords the activation energy for decomplexation, $E_a = 39.0 \pm 3$ kJ mol^{-1}, and the associated pre-exponential factor $A = 5.3 \times 10^{10}$ s^{-1} (Fig. 4). The E_a value for **8** is in good agreement with the values reported for cryptophane-A and its deuterated derivative ($E_a = 37.5$ kJ mol^{-1}).[20] The enthalpy and entropy factors for decomplexation are determined from the Eyring plot ($\Delta H^{\neq} = 37.0 \pm 3$ kJ mol^{-1}; $\Delta S^{\neq} = -46 \pm 10$ kJ mol^{-1} K^{-1}). The large negative $\Delta S^{\neq}$ value suggests a significant reorganization of the portals of the cryptophanes to expulse xenon into the solution.

The introduction of the linker connecting the two hosts seems to have only a small effect on the exchange dynamics of xenon between the three sites, and thus the two hosts behave as independent entities. Thus bis-cryptophanes **7**, **8** and **9**, which were prepared as model compounds, can be useful to investigate the complexation of xenon or other guests in a large range of solvents due to their higher solubility, without changing significantly the binding properties or the exchange kinetics of the separated hosts.

Conclusion

A novel synthetic route for the synthesis of new cryptophanes **4**–**6** bearing a single protective group is described. This novel approach allows the preparation of cryptophanes with D_3 symmetry or more sophisticated dissymmetrical molecules. The removal of the allyl group by using a palladium catalyst was achieved in good yields to give cryptophanols **1**–**3**. These cryptophanols are key compounds to build up large supramolecular systems and bis-cryptophanes **7**–**9** were prepared as model compounds. One notes the increased solubility of these new derivatives that allow complexation experiments in different solvent conditions to be conducted. In a second part of this work we evidenced the discrimination of the two cryptophane units in the $(Xe)_2$@bis-cryptophane-**8** complex by using ^{129}Xe NMR spectroscopy. ^{129}Xe 1D-EXSY NMR experiments showed that the xenon complexes of bis-cryptophane **8**, cryptophane-A and its deuterated congener, behave similarly in solution, thus demonstrating that the alkyl linker connecting the two cryptophanes units has almost no influence on the binding properties and the exchange dynamics. The recent application of cryptophane-A as a bio-sensor showed that cryptophanes are still of wide interest in the field of supramolecular chemistry. Therefore, polycryptophane derivatives are interesting hosts for the design of poly-xenon complexes,

Table 2 Rate constants of decomplexation $k_{1,3}$ and $k_{2,3}$ obtained from ^{129}Xe 1D-EXSY NMR spectroscopy in 1,1,2,2-tetrachloroethane at different temperatures

T/K	238	233	228	223	220.5
$k_{1,3}/s^{-1}$	150 ± 8	79 ± 6	59 ± 4	36 ± 2	29 ± 2
$k_{2,3}/s^{-1}$	155 ± 8	79 ± 6	59 ± 4	37 ± 2	29 ± 2

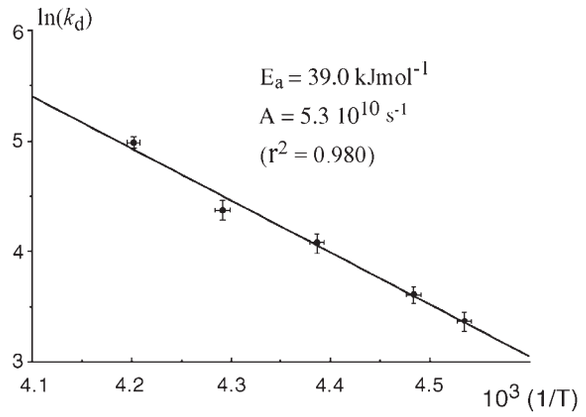


Fig. 4 Arrhenius plot of $\ln(k_d)$ *vs.* $1/T$ ($r^2 = 0.98$) where k_d is the mean value of the two rate constants for decomplexation, $k_{1,3}$ and $k_{2,3}$, obtained from ^{129}Xe 1D-EXSY NMR experiments (in 1,1,2,2-tetrachloroethane-d_2; temperature range 238–220.5 K).

exhibiting a better sensitivity for NMR imaging applications. Additionally, cryptophanols allow the introduction of bulky substituents, such as long alkyl chains, in the cryptophane structure. This cannot be reached by the usual route described for the synthesis of C_3- or D_3-symmetrical cryptophanes.

Experimental

General

3,4-Dihydroxybenzaldehyde was purchased from Aldrich. 1,2-Dibromoethane, allyl bromide and pyridinium *para*-toluenesulfonate (PPTS) were purchased from Acros Organics. Cesium carbonate and potassium carbonate were dried under vacuum before use. All the solvents were distilled before use (DMF from calcium hydride under reduced pressure, acetone and CH_2Cl_2 from calcium chloride, THF from benzophenone ketyl). Column chromatographic separations were carried out over Merck silica gel 60 (0.040–0.063 mm). Analytical thin layer chromatography (TLC) was performed on Merck silica gel TLC plates F_{254}. Melting points were measured on a Perkin–Elmer DSC7 microcalorimeter. Mass spectra were recorded in LSIMS mode on a ThermoFinnigan MAT95XL spectrometer. Exact mass measurements were obtained by "peak matching".

NMR measurements

^1H and ^{13}C NMR spectra were recorded on Varian Unity 500 or Bruker DXP 200 spectrometers (^1H 499.83 or 200.13 MHz; ^{13}C 125.66 MHz). The NMR sample used for ^{129}Xe NMR experiments was prepared by dissolving 200 mg of **8** in 1,1,2,2-tetrachloroethane. The solvent was removed under reduced pressure and the same operation was repeated twice to remove any bound substrate (mostly $CHCl_3$). 1,1,2,2-Tetrachloroethane (4 mL) was added and the solution was poured into a 10 mm NMR tube. Xenon gas (^{129}Xe, natural abundance 26.4%) was bubbled through the solution. The NMR tube was then frozen in liquid nitrogen and sealed under vacuum. Cryptophane concentration was $[C] \approx 0.026$ M. ^{129}Xe NMR experiments were carried out at 138.4 MHz on a Varian Unity 500 spectrometer using a 10 mm double resonance probe. ^{129}Xe NMR spectra were recorded at 223 K, with the sample being kept at this temperature for about 3 h before starting the experiments. The mixing times were varied in the range 0.01 ms to 5 s (14 values of τ_m were used). A Gaussian pulse was used for the 180° selective pulse (pulse width 4.45 ms). A relaxation delay of 35 s was used for each increment. Each spectrum was recorded with 64 scans for a given mixing

time value. The length of the 90° pulse was 24 μs. Each selective irradiation required about 9 h to complete an experiment. Prior to the Fourier transform a Gaussian apodization (gb = 5) was applied. The intensity of each peak was then measured with a given vertical scale value, which was kept the same for all the experiments.

Complexation dynamics

The NMR sample used for variable-temperature experiments is the same as that described above. ^{129}Xe 1D-EXSY experiments were performed at 238, 233, 228, 223 and 220.5 K, using 12 mixing times for each temperature, requiring about 7.5 h to complete an experiment. The sample was kept 30 min at the given temperature before starting a new experiment. In order to follow the evolution of the rate constants with temperature and thus to obtain a better fit, a different set of mixing times was chosen for each temperature. A Gaussian pulse was used for the 180° selective pulse (pw = 556.2 μs). A relaxation delay of 35 s was used for each increment. Each spectrum was recorded with 32 scans for each mixing time. The length of the 90° pulse was 25 μs. Prior to Fourier transform an exponential apodization (line broadening lb = 20) was applied.

Syntheses

[3-Allyloxy-4-(2-bromoethoxy)phenyl]methanol (27). *General procedure A:* to a stirred solution of dry potassium carbonate (2.08 g, 15 mmol) and 3-allyloxy-4-hydroxybenzyl alcohol (2.72 g, 15 mmol) in acetone (35 mL), 1,2-dibromoethane (11.32 g, 60 mmol) was added. The solution was refluxed 18 h under argon. The solvent was removed by rotary evaporation and the residue extracted twice with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent led a residue that was treated with diethyl ether to precipitate the unreacted phenol, which can be reused for another experiment. Filtration on fritted glass and evaporation of the mother liquor led an oily residue, which was purified by chromatography on silica gel (AcOEt–CH_2Cl_2 30:70) to give derivative **27** as a white solid (1.2 g, 28%). M.p. 56 °C; ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.92–6.87 (m, 3H; Ar), 6.06 (m, 1H), 5.41 (m, 1H), 5.26 (m, 1H), 4.57 (m, 4H; OCH_2), 4.30 [t, ^3J(H,H) = 6.5 Hz, 2H; OCH_2], 3.62 [t, ^3J(H,H) = 6.5 Hz, 2H; CH_2Br], 1.82 (s, 1H; OH). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.03, 147.40, 135.26, 133.17, 117.64, 119.86, 115.68, 113.58, 69.94, 69.59, 64.95, 29.12. Anal. calcd (%) for $C_{12}H_{15}O_3Br$ (287.15): C 50.19, H 5.27; found C 50.46, H 5.30.

[3-Allyloxy-4-(2-bromo-[D$_4$]ethoxy)phenyl]methanol (28). According to general procedure A, potassium carbonate (2.3 g, 16.7 mmol), 3-allyloxy-4-hydroxybenzyl alcohol (3.0 g, 16.7 mmol) and 1,2-dibromoethane-[D$_4$] in acetone (40 mL) gave derivative **28** as a white solid (2.0 g, 41%). M.p. 56 °C; ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.94–6.86 (m, 3H; Ar), 6.06 (m, 1H), 5.41 (m, 1H), 5.27 (m, 1H), 4.595 (m, 4H; 2 CH_2), 1.57 [t, ^3J(H,H) = 6.0 Hz, 1H; OH]; ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 148.96, 147.33, 135.17, 133.14, 119.83, 117.68, 115.49, 113.46, 69.82, 68.60 [h, ^1J(C,D) = 22.0 Hz; OCD_2], 64.81, 28.42 [h, ^1J(C,D) = 23.6 Hz; CD_2I]. HRMS (LSIMS): calcd for $C_{12}H_{11}O_3D_4Br$ $[M]^{+\bullet}$ 290.0456; found 290.0454.

[3-Allyloxy-4-(3-bromopropoxy)phenyl]methanol (29). According to general procedure A, potassium carbonate (0.7 g, 5 mmol), 3-allyloxy-4-hydroxybenzyl alcohol (0.9, 5.0 mmol) and 1,3-dibromopropane (5.0 g, 25 mmol) in acetone (15 mL) gave derivative **29** as a white solid (1.3 g, 86%). M.p. 47 °C (diisopropyl ether); ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.93–6.86 (m, 3H; Ar), 6.06 (m, 1H), 5.40 (m, 1H), 5.26 (m, 1H), 4.59 [d, ^3J(H,H) = 6.0 Hz, 2H; CH_2O], 4.58 (m, 2H; CH_2O), 4.13 [t, ^3J(H,H) = 6.5 Hz, 2H; OCH_2], 3.63 [t, ^3J(H,H) = 6.5 Hz, 2H; CH_2Br], 2.33 [q, ^3J(H,H) = 6.5 Hz, 2H; CH_2], 1.54 [t, ^3J(H,H) = 6.0 Hz, 1H; OH]. ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 148.69, 148.14, 134.24, 133.27, 119.91, 117.50, 114.17, 113.25, 69.81, 66.85, 65.12, 32.35, 30.20. Anal. calcd (%) for $C_{13}H_{17}O_3Br$ (301.18): C 51.84, H 5.69; found C 51.84, H 5.75.

[3-Allyloxy-4-(2-iodoethoxy)phenyl]methanol (30). *General procedure B:* sodium iodide (4.36 g, 29 mmol) was added in one portion to a stirred solution of **27** (1.67 g, 5.8 mmol) in acetone (40 mL). The solution was stirred for 18 h at 80 °C under argon. The solvent was removed by rotary evaporation and the residue extracted twice with ethyl acetate. The combined organic layers were washed with brine and then dried over Na_2SO_4. After evaporation of the solvent under reduced pressure the residue was purified by chromatography on silica gel (AcOEt–CH_2Cl_2 30:70) to give derivative **30** as a white solid (1.67 g, 86%). M.p. 59 °C; ^{1}H NMR (200.13 MHz, $CDCl_3$, 20 °C) δ 6.70–6.63 (m, 3H, Ar), 5.82 (m, 1H), 5.09 (m, 2H), 4.35 (m, 4H, $CH_2OH + CH_2O$), 4.04 [t, 2H, ^3J(H,H) = 6.7 Hz, CH_2O], 3.17 [t, 2H, ^3J(H,H) = 6.7 Hz, CH_2I], 1.29 [d, 1H, ^3J(H,H) = 4.89 Hz; OH]. ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.06, 147.32, 135.19, 133.21, 117.70, 119.91, 115.65, 113.59, 70.46, 69.99, 65.08, 1.33 (1C; CH_2I). Anal. calcd (%) for $C_{12}H_{15}O_3I$ (334.15): C 43.13, H 4.52; found C 43.51, H 4.62.

[3-Allyloxy-4-(2-iodoethoxy-[D$_4$])phenyl]methanol (31). According to general procedure B: derivative **31** (0.51 g, 78%) was prepared from compound **28** (0.5 g, 1.93 mmol) and sodium iodide (1.45 g, 3.65 mmol) in acetone (15 mL). M.p. 59 °C; ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.94–6.87 (m, 3H; Ar), 6.06 (m, 1H), 5.42 (m, 1H), 5.27 (m, 1H), 4.60 (m, 4H), 1.545 [t, ^3J(H,H) = 6.5 Hz, 1H; OH]. ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 148.92, 147.18, 135.05, 133.14, 119.85, 117.74, 115.36, 113.41, 69.89, 69.46 [q, ^1J(C,D) = 22.0 Hz, 1C; OCD_2], 65.05, 0.86 [p, ^2J(C,D) = 22.0 Hz, 1C; CD_2I]. HRMS (LSIMS): calcd for $C_{12}H_{11}O_3D_4I$ $[M]^{+\bullet}$ 338.0317; found 338.0319.

[3-Allyloxy-4-(3-iodopropoxy)phenyl]methanol (32). According to general procedure B: compound **32** (4.74 g, 91%) was obtained from **29** (4.5 g, 14.9 mmol) and sodium iodide (11.2 g, 74.7 mmol) in acetone (50 mL). M.p. 49.0 °C (diisopropyl ether); ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.93–6.88 (m, 3H; Ar), 6.06 (m, 1H), 5.40 (m, 1H), 5.26 (m; 1H), 4.59 [d, ^3J(H,H) = 6.0 Hz, 2H; CH_2O], 4.58 (m, 2H; OCH_2), 4.07 [t, ^3J(H,H) = 6.5 Hz, 2H; OCH_2], 3.39 [t, ^3J(H,H) = 6.5 Hz, 2H; CH_2I], 2.28 [q, ^3J(H,H) = 6.5 Hz, 2H; CH_2], 1.55 [t, ^3J(H,H) = 6.0 Hz, 1H; OH]. ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ: 148.75, 148.17, 134.25, 133.29, 119.94, 117.54, 114.25, 113.31, 69.86, 68.81, 65.18, 32.96, 2.78 (1C; CH_2I). Anal. calcd (%) for $C_{13}H_{17}O_3I$ (348.18): C 44.85, H 4.92; found C 44.86, H 5.02.

2-[3-Allyloxy-4-(2-iodoethoxy)benzyloxy]tetrahydropyran (18). *General procedure C:* PPTS (0.126 g; 0.5 mmol) in CH_2Cl_2 (3 mL) was added in one portion to a stirred solution of **30** (1.67 g, 5 mmol) and dihydropyran (DHP) (0.63 g, 7.5 mmol) in THF (20 mL). The solution was stirred 18 h at room temperature under argon. The solvent was removed under reduced pressure and the residue extracted twice with diethyl ether. The combined organic layers were washed with brine and then dried over Na_2SO_4. The solvent was then removed by rotary evaporation to leave a residue, which was purified by chromatography on silica gel (Et_2O–pentane 50:50). Compound **18** was collected as an oily colorless product (1.7 g, 81%). ^{1}H

NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.93–6.85 (m, 3H, Ar), 6.06 (m, 1H), 5.41 (m, 1H), 5.26 (m, 1H), 4.68 [d, ^2J(H,H) = 12.0 Hz, 1H; CH_2O], 4.66 (m, 1H), 4.585 (m, 2H; CH_2O), 4.40 [d, ^2J(H,H) = 12.0 Hz, 1H; CH_2O], 4.27 [t, ^3J(H,H) = 7.0 Hz, 2H; CH_2O], 3.90 (m, 1H), 3.53 (m, 1H), 3.41 [t, ^3J(H,H) = 7.0 Hz, 2H; CH_2I], 1.88–1.78 (m, 1H), 1.76–1.66 (m, 1H), 1.64–1.46 (m, 4H). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 148.77, 147.13, 133.24, 132.34, 120.87, 117.60, 115.35, 114.35, 97.50, 70.30, 69.89, 68.46, 62.15, 30.50, 25.38, 19.36, 1.41 (1C; *C*H_2I). Anal. calcd (%) for $C_{17}H_{23}O_4I$ (418.27): C 48.82, H 5.54; found C 49.04, H 5.79.

2-[3-Allyloxy-4-(2-iodoethoxy-[D_4])benzyloxy]tetrahydropyran (19). According to general procedure C: compound **19** (1.47 g, 84%) was obtained as a colorless oil from **31** (1.4 g, 4.1 mmol) and DHP (0.42 g, 5.0 mmol) in THF (20 mL), and PPTS (0.1 g, 0.41 mmol) in CH_2Cl_2 (3 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.92–6.85 (m, 3H; Ar), 6.06 (m, 1H), 5.41 (m, 1H), 5.26 (m, 1H), 4.68 [d, ^2J(H,H) = 11.5 Hz, 1H; CH_2O], 4.65 (m, 1H), 4.58 (m, 2H; CH_2O), 4.40 [d, ^2J(H,H) = 11.5 Hz, 1H; CH_2O], 3.90 (m, 1H), 3.52 (m, 1H), 1.90–1.78 (m, 1H), 1.76–1.66 (m, 1H), 1.64–1.46 (m, 4H). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 148.76, 147.11, 133.24, 132.31, 120.87, 117.62, 115.30, 114.34, 97.51, 69.88, 70.0–69.0 [q, 1C, ^1J(C,D) = 22.0 Hz, *C*H_2O], 68.47, 62.16, 30.50, 25.38, 19.36, 1.08 [q, 1C, ^1J(C,D) = 22.0 Hz, *C*H_2I]. HRMS (LSIMS): calcd for $C_{17}H_{19}O_4D_4I$ $[M]^{+\bullet}$ 422.0892; found 422.0889.

2-[3-Allyloxy-4-(3-iodopropoxy)benzyloxy]tetrahydropyran (20). According to general procedure C: PPTS (0.18 g, 0.7 mmol) in CH_2Cl_2 (5 mL) and DHP (0.89 g, 10.6 mmol) and compound **32** (2.45 g, 7.0 mmol) in THF (35 mL) gave compound **20** as a oily colorless product (2.6 g, 85%). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.91–6.84 (m, 3H; Ar), 6.05 (m, 1H), 5.39 (m, 1H), 5.25 (m, 1H), 4.68 [(d, ^2J(H,H) = 11.5 Hz, 1H], 4.66 (m, 1H), 4.565 (m, 2H; CH_2O), 4.40 [d, ^2J(H,H) = 11.5 Hz, 1H; CH_2O], 4.06 [t, ^3J(H,H) = 6.0 Hz, 2H, OCH_2], 3.90 (m, 1H), 3.53 (m, 1H), 3.38 [t, ^3J(H,H) = 6.0 Hz, 2H; CH_2I], 2.28 [q, ^3J(H,H) = 6.0 Hz, 2H; CH_2], 1.88–1.78 (m, 1H, THP), 1.76–1.66 (m,1H, THP), 1.64–1.46 (m, 4H, THP). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ: 148.56, 148.10, 133.39, 131.45, 120.99, 117.44, 114.24, 114.12, 97.47, 69.87, 68.74, 68.57, 62.18, 32.97, 30.54, 25.41, 19.39, 2.79 (1C; *C*H_2I). Anal. calcd (%) for $C_{18}H_{25}O_4I$ (432.30): C 50.01, H 5.83; found C, 50.20; H, 5.86.

Cryptophane 33. 1,10-Diiododecane (0.134 g, 0.34 mmol) was added to a solution of cryptophanol **1** (0.2 g, 0.227 mmol) and cesium carbonate (0.15 g, 0.458 mmol) in a CH_2Cl_2–acetone mixture (30 mL, 1:5 v/v). The solution was stirred overnight at 70–80 °C under argon and then poured into water. The crude product was extracted twice with ethyl acetate. The combined organic layers were washed with brine and then dried over Na_2SO_4. The solvent was removed by rotary evaporation to leave a residue, which was purified by chromatography on silica gel (CH_2Cl_2–acetone 9:1). Compound **33** (0.1 g, 38%) was isolated as a white glassy solid. ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.77 (s, 1H; Ar), 6.75 (s, 1H; Ar), 6.735 (s, 1H; Ar), 6.73 (s, 2H; Ar), 6.71 (s, 1H; Ar), 6.65 (s, 6H; Ar), 4.62–4.52 (m, 6H; CH_a), 4.24–4.04 (m, 12H; CH_2O), 3.86 (m, 2H; CH_2O), 3.78 (s, 9H; OCH_3), 3.77 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 3.42–3.34 (m, 6H; CH_e), 3.18 ([t, ^3J(H, H) = 7.0 Hz, 2H; CH_2I], 1.86–1.68 (m, 4H; CH_2), 1.47 (m, 2H; CH_2), 1.40–1.28 (m, 10H; CH_2). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.93, 149.91, 149.83, 149.77, 149.75, 149.67, 147.31, 146.87, 146.84, 146.78 (3C), 134.57, 134.53, 134.47, 134.34, 134.28, 134.24, 132.21, 132.14, 131.76, 131.71, 131.66, 131.61, 122.47, 121.53 (2C), 120.64 (3C), 116.56, 114.72, 113.86, 113.81 (2C), 113.74, 69.75 (2C; O*C*H_2), 69.60 (2C; O*C*H_2), 69.47 (2C; O*C*H_2), 69.37 (1C; O*C*H_2), 56.22 (1C; O*C*H_3), 55.94 (1C; O*C*H_3), 55.87 (1C; O*C*H_3), 55.84 (1C; O*C*H_3), 55.78 (1C; O*C*H_3), 36.42 (6C; *C*$H_{a,e}$), 33.73, 30.69, 29.90, 29.72 (2C), 29.60, 28.74, 26.30, 7.64 (1C; *C*H_2I). HRMS (LSIMS): calcd for $C_{63}H_{71}0_{12}I$ $[M]^{+\bullet}$ 1146.3990; found 1146.3988.

Cryptophane 34. 1,10-Diiododecane (0.154 g, 0.39 mmol) was added to a solution of cryptophanol **3** (0.180 g, 0.195 mmol) and cesium carbonate (0.127 g, 0.39 mmol) in a mixture of acetone (6 mL) and CH_2Cl_2 (7 mL). The solution was heated at 60 °C for 18 h and then poured into water. The crude product was extracted twice with CH_2Cl_2. The combined organic layers were washed with brine and then dried other Na_2SO_4. After evaporating the solvent under reduced pressure the crude product was purified by chromatography on silica gel (CH_2Cl_2–acetone 9:1) to give compound **34** (0.1 g, 43%) as a white glassy product. ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.68–6.52 (m, 12H; Ar), 4.63 (m, 6H; CH_a), 4.04 (m, 6H; CH_2O), 3.88 (m, 8H; CH_2O), 3.81 (s, 12H; CH_3O), 3.75 (s, 3H; CH_3O), 3.40 (m, 6H; CH_e), 3.18 [t, ^3J(H,H) = 6.5 Hz, 2H; CH_2I], 2.28 (m, 6H; CH_2), 1.90–1.70 (m, 4H; CH_2), 1.50–1.30 (m, 12H; CH_2). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 148.45, 147.26, 147.11, 146.99 (3C), 146.97 (2C), 146.94 (2C), 146.91, 146.54, 132.01, 131.14, 131.11, 131.00 (2C), 130.97, 130.91, 130.89, 130.77, 130.68 (3C), 116.87, 112.95, 112.72, 112.29, 112.25, 112.16 (2C), 112.00 (2C), 111.88 (2C), 111.84, 70.19 (1C; O*C*H_2), 63.76 (1C; O*C*H_2), 63.64 (1C; O*C*H_2), 63.50 (3C; O*C*H_2), 63.34 (1C; O*C*H_2), 56.19 (1C; O*C*H_3), 55.55 (1C; O*C*H_3), 55.49 (3C; O*C*H_3), 36.02 (6C; *C*$H_{a,e}$), 33.42, 30.40, 29.74, 29.67, 29.55, 29.46, 29.38 (2C), 29.30, 28.45, 25.90, 7.53 (1C, *C*H_2I). HRMS (LSIMS): calcd for $C_{66}H_{77}O_{12}I$ $[M]^{+\bullet}$ 1188.4460; found 1188.4457.

7,12-Bis[2-(4-hydroxymethyl-2-methoxyphenoxy)ethoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononen-2ol (15). *General procedure D:* compound **30** (1.5 g, 4.9 mmol) was added to a stirred solution of cyclotriveratrylene (**10**; 1.0 g, 2.45 mmol) and cesium carbonate (3.2 g, 9.8 mmol) in DMF (50 mL). The solution was stirred overnight at 80 °C under argon. The dark solution was then poured into water and extracted three times with ethyl acetate. The combined organic layers were washed several times with brine and then dried over Na_2SO_4. After evaporating the solvent a residue was collected, which was then purified by chromatography on silica gel on a short column (AcOEt–EtOH 98:2). The third spot detected by TLC plates was collected and identified as the expected derivative **15** (0.49 g, 26%). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.98–6.77 (m, 12H; Ar), 5.42 (s, 1H; OH), 4.72 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.71 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.70 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.60 [d, ^3J(H,H) = 6.5 Hz, 2H; CH_2O)], 4.59 [d, ^3J(H, H) = 6.5 Hz, 2H; CH_2O], 4.38–4.30 (m, 8H; OCH_2), 3.82 (s, 3H; OCH_3), 3.78 (s, 3H; OCH_3), 3.755 (s, 3H; OCH_3), 3.72 (s, 3H; OCH_3), 3.66 (s, 3H; OCH_3), 3.50 [d, ^2J(H, H) = 13.5 Hz, 2H; CH_e], 3.49 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_e], 1.78 [t, ^3J(H, H) = 6.5 Hz, 1H; OH], 1.67 [t, ^3J(H, H) = 6.5 Hz, 1H; OH]). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.59 (2C), 148.455, 148.375, 147.47, 147.41, 146.66, 146.63, 145.255, 144.09, 134.46, 134.38, 133.06, 132.98, 132.27, 132.04, 131.68, 131.17, 119.35 (2C), 116.63 (2C), 115.62, 113.72 (3C), 113.69, 112.10, 110.89 (2C). 68.13 (1C; O*C*H_2), 68.05 (1C, O*C*H_2), 67.68 (1C; O*C*H_2), 67.65 (1C; O*C*H_2), 65.15 (2C; *C*H_2OH), 56.11 (1C; O*C*H_3), 56.06 (1C; O*C*H_3), 55.96 (1C; O*C*H_3), 55.71 (2C; O*C*H_3),

36.34 (2C; $CH_{a,e}$), 36.20 (1C; $CH_{a,e}$). HRMS (LSIMS): calcd for $C_{44}H_{47}O_{12}$ $[M-H]^-$ 767.3068; found 767.3059.

7,12-Bis{2-(4-hydroxymethyl-2-methoxy-[D_3]phenoxy)-ethoxy-[D_4]}-3,8,13-trimethoxy-[D_3]-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononen-2-ol (16). According to general procedure D: compound **16** (0.63 g, 33%) was obtained from **11** (1.01 g, 2.42 mmol), compound **13** (1.3 g, 4.85 mmol) and cesium carbonate (3.16 g, 9.68 mmol) in DMF (50 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.98–6.76 (m, 12H; Ar), 5.41 (s, 1H; OH), 4.72 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.71 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.70 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.60 [d, ^3J(H, H) = 6.5 Hz, 2H; CH_2O], 4.59 [d, ^3J(H,H) = 6.5 Hz, 2H; CH_2O], 3.50 [d, ^2J(H, H) = 13.5 Hz, 2H; CH_e], 3.49 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 1.70 [t, ^3J(H, H) = 6.5 Hz, 1H; OH], 1.63 [t, ^3J(H, H) = 6.5 Hz, 1H; OH]. ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.36 (2C), 148.23, 148.17, 147.23, 147.20, 146.47, 146.46, 145.22, 144.00, 134.40, 134.35, 132.93, 132.86, 132.11, 131.96, 131.59, 131.05, 119.16 (2C), 116.39, 116.33, 115.64, 113.58, 113.52 (3C), 112.07, 110.74 (2C), 77.4–66.2 (m, 4C; O*C*D_2), 64.81 (2C; *C*H_2OH), 54.91 [h, ^1J(C,D) = 23.0 Hz, 5C; O*C*D_3], 36.13 (2C, *C*$H_{a,e}$), 35.99 (1C, *C*$H_{a,e}$). HRMS (LSIMS): calcd for $C_{44}H_{25}D_{23}0_{12}$ $[M]^{+\bullet}$ 791.4590; found 791.4565.

7,12-Bis[3-(4-hydroxymethyl-2-methoxyphenoxy)propoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononen-2-ol (17). According to general procedure D: compound **17** (0.62 g, 32%) was obtained from **10** (1.0 g, 2.45 mmol), compound **14** (1.34 g, 4.90 mmol) and cesium carbonate (3.19 g, 9.79 mmol) in DMF (50 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.90–6.73 (m, 12H; Ar), 5.40 (s, 1H; OH), 4.72 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.71 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.69 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_a], 4.56 [d, ^3J(H, H) = 5.5 Hz, 4H; CH_2O], 4.25–4.12 (m, 8H; OCH_2), 3.78 (s, 3H; OCH_3), 7.775 (s, 3H; OCH_3), 3.725 (s, 6H; OCH_3), 3.68 (s, 3H; OCH_3), 3.49 [d, ^2J(H, H) = 13.5 Hz, 3H; CH_e], 2.27 [q, ^3J(H, H) = 6.0 Hz, 4H; CH_2], 1.71 [t, ^3J(H, H) = 6.0 Hz, 1H; OH], 1.69 [t, ^3J(H, H) = 6.0 Hz, 1H; OH]. ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.39, 149.37, 148.08, 148.04, 147.73, 147.65, 146.79, 146.66, 145.21, 143.99, 133.85, 133.82, 132.31, 132.22, 132.08, 131.89, 131.65, 131.22, 119.32, 119.30, 115.60, 115.16 (2C), 113.45 (2C), 112.96 (2C), 112.10, 110.69 (2C). 65.87 (1C; O*C*H_2), 65.76 (1C; O*C*H_2), 65.59 (2C; CH_2O), 65.13 (1C, O*C*H_2), 65.09 (1C, O*C*H_2), 56.03 (1C; O*C*H_3), 55.91 (1C; O*C*H_3), 55.83 (1C; O*C*H_3), 55.66 (1C; O*C*H_3), 55.61 (1C; O*C*H_3), 36.30 (2C; *C*$H_{a,e}$), 36.12 (1C, *C*$H_{a,e}$), 29.05 (1C; *C*H_2);29.00 (1C; *C*H_2). HRMS (LSIMS): calcd for $C_{46}H_{51}O_{17}$ $[M-H]^-$ 795.3381; found 795.3381.

[4-(2-{7-{2-[2-Allyloxy-4-(tetrahydropyran-2-yloxymethyl)-phenoxy]ethoxy}-12-[2-(4-hydroxymethyl-2-methoxyphenoxy)-ethoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]-cyclononen-2-yloxy}ethoxy)-3-methoxyphenyl]methanol (21). According to general procedure D: compound **21** (0.48 g, 81%) was obtained from starting materials **15** (0.43 g, 0.56 mmol), compound **18** (0.28 g, 0.67 mmol) and cesium carbonate (0.37 g, 1.1 mmol) in DMF (20 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.99–6.80 (m, 15H; Ar), 6.01 (m, 1H), 5.36 (m, 1H), 5.21 (m, 1H), 4.72 [d, ^2J(H, H) = 13.5 Hz, 3H; CH_a], 4.67 [d, ^2J(H, H) = 12.0 Hz, 1H], 4.65 (m, 1H), 4.58 (m, 6H), 4.40 [d, ^2J(H, H) = 12.0 Hz, 1H], 4.38–4.28 (m, 12H; CH_2O), 3.89 (m, 1H), 3.755 (s, 3H; OCH_3), 3.75 (s, 3H; OCH_3), 3.73 (s, 3H; OCH_3), 3.68 (s, 3H; OCH_3), 3.67 (s, 3H; OCH_3), 3.52 [d, ^2J(H, H) = 13.5 Hz, 1H; CH_e], 3.52 (1H, m), 3.51 [d, ^2J(H, H) = 13.5 Hz, 2H; CH_e], 1.88–1.80 (m, 1H), 1.78 [t, ^3J(H,H) = 6.0 Hz, 2H; OH], 1.74–1.66 (m, 1H), 1.64–1.46 (m, 4H). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.58 (2C), 148.50, 148.44, 148.38 (2C), 147.97, 147.35 (2C), 146.73, 146.71 (2C), 134.53, 134.52, 133.38, 132.97, 132.92, 132.88, 131.83, 131.76 (2C), 131.62, 120.94, 119.29 (2C), 117.55, 116.64, 116.56, 116.31, 114.36, 114.28, 113.76 (2C), 113.73, 113.66 (2C), 110.84 (2C), 97.48, 69.91, 68.53, 68.05 (3C), 67.72, 67.69, 67.66, 65.06 (2C), 62.18, 56.12 (1C; O*C*H_3), 56.11 (1C; O*C*H_3), 56.05 (1C; O*C*H_3), 55.68 (2C; O*C*H_3), 36.32 (3C; $CH_{a,e}$), 30.51, 25.38, 19.36. HRMS (LSIMS): calcd for $C_{61}H_{70}O_{16}$ $[M]^{+\bullet}$ 1058.4664; found 1058.4660.

[4-(2-{7-{2-[2-Allyloxy-4-(tetrahydropyran-2-yloxymethyl)phenoxy]ethoxy-[D_4]}-12-[2-(4-hydroxymethyl-2-methoxy-[D_3]phenoxy)ethoxy-[D_4]]-3,8,13-trimethoxy-[D_3]-10,15-dihydro-5*H*-tribenzo[a,d,g]cyclononen-2-yloxy}ethoxy-[D_4])-3-methoxy-[D_3]phenyl]methanol (22). According to general procedure D: compound **22** (0.63 g, 73%) was obtained from **16** (0.63 g, 0.79 mmol), compound **19** (0.385 g, 0.91 mmol) and cesium carbonate (0.52 g, 1.58 mmol) in DMF (20 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.99–6.78 (m, 15H; Ar), 6.03 (m, 1H), 5.37 (m, 1H), 5.21 (m, 1H), 4.70 [d, ^2J(H,H) = 13.0 Hz, 3H; CH_a], 4.66 (m, 2H), 4.56 (m, 6H; CH_2O), 4.40 [d, ^2J(H,H) = 11.5 Hz, 1H], 3.89 (m, 1H), 3.51 (m, 1H), 3.50 [d, ^2J(H,H) = 13.0 Hz, 3H; CH_e], 2.38 (s, 1H; OH), 2.30 (s, 1H; OH), 1.85–1.51 (m, 6H; THP). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.47 (2C), 148.43, 148.34, 148.28 (2C), 147.91, 147.22 (2C), 146.64, 146.61 (2C), 134.52 (2C), 133.32, 132.89, 132.84, 132.81, 131.75, 131.68 (2C), 131.53, 120.88, 119.16 (2C), 117.46, 116.53, 116.45, 116.22, 114.27, 114.23, 113.70, 113.64, 113.61 (2C), 113.58, 110.75 (2C), 97.43, 69.84, 68.46, 67.80–66.40 (m, 6C; O*C*D_2), 64.87 (2C), 62.11, 56.0–55.0 (m, 5C; O*C*D_3), 36.23 (s, 3C; *C*$H_{a,e}$), 30.44, 25.31, 19.28. HRMS (LSIMS): calcd for $C_{61}H_{43}D_{27}O_{16}$ $[M]^{+\bullet}$ 1085.6359; found 1085.6357.

[4-(3-{7-{3-[2-Allyloxy-4-(tetrahydropyran-2-yloxymethyl)-phenoxy]propoxy}-12-[3-(4-hydroxymethyl-2-methoxyphenoxy)-propoxy]-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g]-cyclononen-2-yloxy}propoxy)-3-methoxyphenyl]methanol (23). According to general procedure D: compound **23** (0.415 g, 60%) was obtained from **17** (0.5 g, 0.63 mmol), compound **20** (0.30 g, 0.70 mmol) and cesium carbonate (0.41 g, 1.26 mmol) in DMF (15 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.90–6.76 (m, 15 H; Ar), 6.00 (m, 1H); 5.35 (m, 1H), 5.19 (m, 1H), 4.71 [d, ^2J(H,H) = 13.5 Hz, 3H; CH_a], 4.66 [d, ^2J(H,H) = 12.0 Hz, 1H], 4.64 (m, 1H), 4.56 [d, ^3J(H,H) = 6.0 Hz, 4H; CH_2O], 4.53 (m, 2H), 4.39 [d, ^2J(H,H) = 12.0 Hz, 1H], 4.25–4.13 (m, 12H; CH_2O), 3.89 (m, 1H), 3.76 (s, 3H; OCH_3), 3.755 (s, 3H; OCH_3), 3.70 (s, 3H; OCH_3), 3.68 (s, 3H; OCH_3), 3.675 (s, 3H; OCH_3), 3.50 (m, 1H), 3.49 [d, ^2J(H,H) = 13.5 Hz, 3H; CH_e)], 2.27 [q, ^3J(H,H) = 6.0 Hz, 6H; CH_2], 1.86–1.78 (m, 1H), 1.77 [(t, ^3J(H,H) = 6.0 Hz, 1H; OH], 1.75 [t, ^3J(H,H) = 6.0 Hz, 1H; OH], 1.72–1.66 (m, 1H), 1.62–1.48 (m, 4H). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.39 (2C), 148.36, 148.24, 148.08, 148.07, 148.05, 147.69 (2C), 146.80, 146.77, 146.75, 133.91, 133.89, 133.40, 132.14 (3C), 131.78, 131.76, 131.74, 131.01, 120.96, 119.30, 119.28, 117.41, 115.10 (3C), 114.05, 113.61, 113.48 (3C), 112.92 (2C), 110.67 (2C), 97.42, 69.76 (1C; O*C*H_2), 68.57 (1C; O*C*H_2), 65.89 (1C; O*C*H_2), 65.78 (2C; O*C*H_2), 65.56 (2C; O*C*H_2), 65.10 (2C; O*C*H_2), 62.20 (1C; O*C*H_2), 56.01 (1C; O*C*H_3), 55.94 (1C; O*C*H_3), 55.92 (1C; O*C*H_3), 55.67 (2C; O*C*H_3), 36.32 (3C; $CH_{a,e}$), 30.50, 29.10, 29.06 (2C), 25.37, 19.36. HRMS (LSIMS): calcd for $C_{64}H_{76}O_{16}$ $[M]^{+\bullet}$ 1100.5133; found 1100.5135.

Cryptophane 1. *General procedure E:* cryptophane **4** (1.3 g, 1.41 mmol), triphenylphosphine (0.185 g, 0.71 mmol), THF

(50 mL), diethylamine (22 mL), palladium acetate (0.079 g, 0.35 mmol) and water were added together in a three-neck flask equipped with a reflux condenser. The solution was refluxed for 5 h and then the solvent was removed by rotary evaporation. The crude product was extracted three times with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporating the solvent the crude product was purified by chromatography on silica gel (CH_2Cl_2–acetone 9:1). Compound **1** was collected and washed with a few milliliters of diethyl ether on a glass frit. Further purification by chromatography on silica gel (CH_2Cl_2–acetone 9:1) afforded **1** (0.95 g, 77%) as a white glassy solid. ^{1}H NMR (499.83 MHz, CD_2Cl_2, 20 °C) δ 6.81 (s, 1H; Ar), 6.75 (s, 1H; Ar), 6.73 (s, 1H; Ar), 6.68 (s, 2H; Ar), 6.675 (s, 1H; Ar), 6.66 (s, 1H; Ar), 6.65 (s, 1H; Ar), 6.64 (s, 1H; Ar), 6.62 (s, 1H; Ar), 6.59 (s, 1H; Ar), 6.55 (s, 1H; Ar), 5.76 (s, 1H; OH), 4.625 ([d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.60 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.55 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.52 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.49 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.46 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.42–4.08 (m, 10H; OCH_2), 3.95 (m, 2H; OCH_2), 3.92 (s, 3H; OCH_3), 3.79 (s, 6H; OCH_3), 3.75 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 3.38 [d, ^2J(H,H) = 13.5 Hz, 2H; CH_e], 3.37 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 3.36 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 3.35 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 3.33 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e]. ^{13}C NMR (125.66 MHz, CD_2Cl_2, 20 °C) δ 150.32, 150.18, 150.09, 150.02, 149.36, 147.22, 146.63 (2C), 146.36, 145.73, 145.12, 144.04, 135.28, 135.10, 134.84, 134.76, 133.27, 132.87, 132.83, 132.51, 132.38, 131.74, 131.54, 131.36, 122.47, 121.99, 121.81, 121.56, 118.87, 116.40, 116.16, 114.72, 114.56, 114.43, 114.18, 113.95, 69.78 (1C; O*C*H_2), 69.68 (1C; O*C*H_2), 69.54 (1C; O*C*H_2), 69.48 (1C; O*C*H_2), 69.00 (1C; O*C*H_2), 67.87 (1C; O*C*H_2), 57.74 (1C; O*C*H_3), 56.25 (2C; O*C*H_3), 56.04 (1C; O*C*H_3), 56.02 (1C; O*C*H_2), 36.65 (1C; *C*$H_{a,e}$), 36.51 (1C; *C*$H_{a,e}$), 36.37 (2C; *C*$H_{a,e}$), 36.28 (1C; *C*$H_{a,e}$), 36.04 (1C; *C*$H_{a,e}$). HRMS (LSIMS): calcd for $C_{53}H_{51}O_{12}$ $[M-H]^-$ 879.3381; found 879.3372.

Cryptophane 4. *General procedure F:* formic acid (300 mL) was added in one portion to a solution of **21** (0.7 g, 0.66 mmol) in chloroform (300 mL). The solution was slowly stirred at 55 °C for 2.5 h. The solvent was then evaporated under reduced pressure and the residue purified by chromatography on silica gel (CH_2Cl_2–acetone 9:1) to give a white glassy compound. This compound was then washed on a fritted glass with a mixture of diethyl ether and pentane (1:1), purified by chromatography on silica gel (CH_2Cl_2–acetone 9:1) and then recrystallized from a chloroform–ethanol mixture to yield pure cryptophane **4** (0.33 g, 49%). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.77–6.65 (m, 12H; Ar), 6.00 (m, 1H), 5.40 (m, 1H), 4.55 (m, 1H), 4.61–4.48 (m, 8H; CH_a and CH_2O), 4.15 (m, 12H; CH_2O), 3.78–3.72 (m, 15 H; OCH_3), 3.42–3.35 (m, 6H; CH_e). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ: 149.74, 149.70, 149.60, 149.57, 149.54, 148.93, 147.18, 146.64 (2C), 146.59 (2C), 146.56, 134.36, 134.23, 134.15, 134.13, 134.09, 133.96, 133.79, 132.29, 131.69, 131.60, 131.53, 131.43,122.00, 121.22 (2C), 120.52, 120.47 (2C), 116.97, 116.59, 114.17, 113.70, 113.62, 113.61 (2C), 70.01, 69.55, 69.49, 69.42, 69.29, 69.25, 69.17, 56.21 (1C; O*C*H_3), 55.73 (1C; O*C*H_3), 55.67 (1C; O*C*H_3), 55.64 (1C; O*C*H_3);55.57 (1C; O*C*H_3), 36.20 (6C; *C*$H_{a,e}$). HRMS (LSIMS): calcd for $C_{56}H_{56}O_{12}$ $[M]^{+\bullet}$ 920.3772; found 920.3773.

Cryptophane 5. According to general procedure F: cryptophane **5** (0.27 g, 49%) was obtained from compound **22** (0.62 g, 0.58 mmol) in a mixture of formic acid (300 mL) and chloroform (300 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.775 (s, 1H; Ar), 6.74 (s, 1H; Ar), 6.735 (s, 1H; Ar), 6.72 (s, 1H; Ar), 6.70 (s, 2H; Ar), 6.65 (s, 6H; Ar), 6.015 (m, 1H; O-allyl), 5.45 (m, 1H; O-allyl), 4.32 (m, 1H; O-allyl), 4.58 [d, ^2J(H,H) = 13.5 Hz, 5H; CH_a)], 4.56 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.48 (m, 2H; O-allyl), 3.39 [d, ^2J(H,H) = 13.5 Hz, 5H; CH_e], 3.36 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.63, 149.59, 149.49, 149.46, 149.44, 148.82, 147.04, 146.51 (2C), 146.46 (2C), 146.42, 134.27, 134.12, 134.05, 134.03, 133.98, 133.84, 133.71 (2C), 132.19, 131.57, 131.48, 131.41, 131.31, 121.90, 121.13 (2C), 120.41, 120.35, 120.33, 116.87, 116.45, 114.03, 113.55, 113.48, 113.46 (2C), 69.87 (1C, O*C*H_2), 68.52 (m, 6C; O*C*D_2), 54.80 (m, 5C; O*C*D_3), 36.08 (s, 6C; *C*$H_{a,e}$). HRMS (LSIMS) calcd for $C_{56}H_{29}D_{27}O_{12}$ $[M]^{+\bullet}$ 947.5467; found 947.5464.

Cryptophane 2. Using experimental procedure E, compound **2** (0.19 g, 80%) was obtained from cryptophane **5** (0.25 g, 0.26 mmol), triphenylphosphine (0.034 g, 0.13 mmol), THF (8 mL), diethylamine (3 mL), palladium acetate (0.017 g, 0.065 mmol) and water (1.5 mL). ^{1}H NMR (499.83 MHz, CD_2Cl_2, 20 °C) δ 6.80 (s, 1H; Ar), 6.72 (s, 2H; Ar), 6.67 (s, 3H; Ar), 6.65 (s, 2H; Ar), 6.63 (s, 1H; Ar), 6.61 (s, 1H; Ar), 6.58 (s, 1H; Ar), 6.54 (s, 1H; Ar), 5.82 (s, 1H; OH), 4.61 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.58 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.53 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.505 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.48 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.45 ([d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 3.36 [d, ^2J(H,H) = 13.5 Hz, 2H; CH_e], 3.355 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 3.34 [d, ^2J(H,H) = 13.5 Hz, 2H; CH_e], 3.31 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e]. ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 150.31, 150.17, 150.07, 149.99, 149.38, 147.20, 146.61 (2C), 146.35, 145.70, 145.13, 144.05, 135.25, 135.08, 134.83, 134.72, 133.28, 132.85, 132.81, 132.48, 132.36, 131.73, 131.54, 131.35, 122.42, 121.97, 121.79, 121.52, 118.93, 116.39, 116.07, 114.69, 114.58, 114.40, 114.17, 113.94, 69.0–68.0 (m; 5C; O*C*D_2), 67.0 (m, 1C; O*C*D_2), 55.21 [h, ^1J(C,D) = 22.0 Hz, 5C; O*C*D_3], 36.65 (1C; *C*$H_{a,e}$), 36.50 (1C, *C*$H_{a,e}$), 36.37 (2C; *C*$H_{a,e}$), 36.28 (1C; *C*$H_{a,e}$), 36.04 (1C; *C*$H_{a,e}$), HRMS (LSIMS): calcd for $C_{53}H_{25}D_{27}O_{12}$ $[M]^{+\bullet}$ 907.5181; found 907.5181.

Cryptophane 3. Compound **3** (0.18 g, 66%) was obtained using the experimental procedure E with cryptophane **6** (0.285 g, 0.296 mmol), triphenylphosphine (0.040 g, 0.148 mmol), THF (12.5 mL), diethylamine (5 mL), palladium acetate (0.017 g, 0.074 mmol) and water (2.5 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.735 (s, 1H; Ar), 6.675 (s, 1H; Ar), 6.67 (s, 2H; Ar), 6.65 (s, 1H; Ar), 5.63 (s, 1H; Ar), 6.585 (s, 2H; Ar), 6.57 (s, 4H; Ar), 5.03 (s, 1H; OH), 4.65 [d, ^2J(H,H) = 13.5 Hz, 3H; CH_a], 4.63 [d, ^2J(H,H) = 13.5 Hz, 2H; CH_a], 4.57 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_a], 4.12–3.96 (m, 6H; OCH_2), 3.96–3.88 (m, 2H; OCH_2), 3.86–3.80 (m, 4H; OCH_2), 3.80 (s, 12H; OCH_3), 3.74 (s, 3H; OCH_3), 3.41 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 3.395 [d, ^2J(H,H) = 13.5 Hz, 4H; CH_a], 3.36 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 2.40–2.15 (m, 6H; CH_2). ^{13}C NMR (125.66 MHz, CD_2Cl_2, 20 °C) δ 148.36, 147.88, 147.84 (2C), 147.76, 147.70, 147.66 (3C), 147.59, 145.36, 143.88, 132.72, 132.06, 131.80, 131.77, 131.68, 131.54 (2C), 131.51 (3C), 131.36, 131.20, 115.48, 114.78, 113.25, 113.06, 112.99 (2C), 112.77, 112.62, 112.48 (2C), 112.44, 112.11, 64.48 (1C; O*C*H_2), 64.07 (1C, O*C*H_2), 64.03 (2C; O*C*H_2), 63.91 (1C; O*C*H_2), 63.53 (1C; O*C*H_2), 57.83 (1C; O*C*H_3), 56.49 (2C; O*C*H_3), 56.41 (2C; O*C*H_3), 36.41 (5C; *C*$H_{a,e}$), 36.24 (1C; *C*$H_{a,e}$), 30.47 (1C; CH_2), 30.40 (1C; CH_2), 30.34 (1C; CH_2). HRMS (LSIMS): calcd for $C_{56}H_{57}O_{12}$ $[M]^{+\bullet}$ 921.3850; found 921.3859.

Cryptophane 6. According to general procedure F, cryptophane **6** (0.29 g, 30%) was obtained from **23** (1.0 g, 1.0 mmol) in a mixture of formic acid (550 mL) and chloroform (550 mL). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.75 (s, 1H; Ar), 6.68

(s, 1H; Ar), 6.67 (s, 4H; Ar), 6.60 (s, 2H; Ar), 6.59 (s, 1H; Ar), 6.58 (s, 2H; Ar), 6.50 (s, 1H; Ar), 6.12 (m, 1H), 5.40 (m, 1H), 5.26 (m, 1H), 4.64 [d, ^2J(H,H) = 13.5 Hz, 4H; CH_a], 4.635 [d, ^2J(H,H) = 13.5 Hz, 2H; CH_a], 4.58 (m, 2H), 4.06–4.00 (m, 6H; CH_2O), 3.90–3.80 (m, 6H; OCH_2), 3.82 (s, 6H; OCH_3), 3.81 (s, 3H; OCH_3), 3.80 (s, 3H; OCH_3), 3.73 (s, 3H; OCH_3), 3.41 [d, ^2J(H,H) = 13.5 Hz, 2H; CH_e], 3.40 [d, ^2J(H,H) = 13.5 Hz, 3H; CH_e], 3.35 [d, ^2J(H,H) = 13.5 Hz, 1H; CH_e], 2.29 (m, 6H; CH_2). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 147.83, 147.17, 147.12, 147.10–147.04 (8C), 146.53, 135.60, 131.73, 131.18, 131.08, 131.05, 130.97 (2C), 130.95, 130.92, 130.89, 130.87, 130.82, 130.77, 116.22, 115.69, 112.69, 112.36, 112.25 (2C), 112.22, 112.18, 112.14, 112.03, 112.00, 111.97, 111.86, 70.55 (1C; O*C*H_2), 63.76 (1C; O*C*H_2), 63.66 (2C; O*C*H_2), 63.59 (1C; O*C*H_2), 63.55 (1C; O*C*H_2), 63.45 (1C; O*C*H_2), 55.88 (1C; O*C*H_3), 55.62 (2C; O*C*H_3), 55.57 (1C; O*C*H_3), 55.55 (1C; O*C*H_3), 36.09 (6C; $CH_{a,e}$), 29.72 (2C; O*C*H_2), 29.61 (1C; O*C*H_2). HRMS (LSIMS): calcd for $C_{59}H_{62}O_{12}$ $[M]^{+\bullet}$ 962.4241; found 962.4246.

Cryptophane 7. 1,10-Diiododecane (0.026 g, 0.066 mmol) was added to a solution containing cesium carbonate (0.086 g, 0.27 mmol) and cyptophanol **1** (0.117 g, 0.13 mmol) in DMF (5 mL). The solution was stirred for 18 h at 80 °C under argon. The solution was then poured into water and extracted twice with CH_2Cl_2. The combined organic layers were washed three times with brine and then dried over Na_2SO_4. After evaporating the solvent under reduced pressure an oily residue was collected, which was then purified twice by chromatography on silica gel (CH_2Cl_2–acetone 9:1) to give dimer **7** (85 mg, 34%). Compound **7** was then washed with a few milliliters of diethyl ether on a fritted glass. ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.77 (s, 2H, Ar), 6.75 (s, 2H; Ar), 6.73 (s, 8H; Ar), 6.65 (s, 12H; Ar), 4.59–4.56 (m, 12H; CH_a), 4.25–4.11 (m, 24H; CH_2), 3.90 (m, 4H; OCH_2), 3.78 (s, 24 H; OCH_3), 3.74 (s, 6H; OCH_3), 3.38 [d, ^2J(H,H) = 13.5 Hz, 12H; CH_e], 1.77 (m, 4H; CH_2), 1.50–1.40 (m, 12H; CH_2). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.71 (2C), 149.67 (2C), 149.58 (2C), 149.54 (2C), 149.51 (2C), 149.45 (2C), 147.08 (2C), 146.64 (2C), 146.60 (2C), 146.57 (2C), 146.54 (4C), 134.33 (2C), 134.28 (2C), 134.12 (4C), 134.06 (2C), 134.02 (2C), 131.98 (2C), 131.90 (2C), 131.52 (2C), 131.47 (2C), 131.43 (2C), 131.38 (2C), 122.24 (2C), 121.31 (2C), 121.29 (2C), 120.40 (2C), 120.37 (4C), 116.34 (2C), 114.47 (2C), 113.63 (2C), 113.56 (4C), 113.50 (2C), 69.52 (4C; O*C*H_2), 69.37 (4C; O*C*H_2), 69.24 (4C; O*C*H_2), 69.14 (2C; O*C*H_2), 55.99 (2C; O*C*H_3), 55.70 (2C; O*C*H_3), 55.64 (2C; O*C*H_3), 55.59 (2C; O*C*H_3), 55.54 (2C; O*C*H_3), 36.18 (12C; *C*$H_{a,e}$), 29.68 (2C; *C*H_2), 29.62 (2C; *C*H_2), 29.55 (2C; *C*H_2), 26.11 (2C; *C*H_2). HRMS (LSIMS): calcd for $C_{116}H_{122}O_{24}$ $[M]^{+\bullet}$ 1898.8326; found 1898.8362.

Cryptophane 8. Cryptophane **33** (0.245 g, 0.214 mmol) was added in one portion to a stirred solution of cesium carbonate (0.133 g, 0.396 mmol) and cryptophanol **2** (0.175 g, 0.193 mmol) in DMF (10 mL). The solution was stirred for 40 h at 80 °C under argon and then poured into water. The solution was extracted three times with CH_2Cl_2 and the combined organic layers were washed with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure leaves a residue, which was purified twice by chromatography on silica gel (CH_2Cl_2–acetone 9:1) to yield compound **8** as a white glassy solid (0.29 g, 77%). ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.77 (s, 2H; Ar), 6.75 (s, 2H; Ar), 6.72 (s, 6H; Ar), 6.71 (s, 2H; Ar), 6.655 (s, 6H; Ar), 6.645 (s, 6H; Ar), 4.575 [(d, ^2J(H,H) = 13.5 Hz, 6H; CH_a], 4.56 [d, ^2J(H,H) = 13.5 Hz, 4H; CH_a], 4.55 [d, ^2J(H,H) = 13.5 Hz, 2H; CH_a], 4.22–4.04 (m, 12H; OCH_2), 3.88 (m, 4H; OCH_2), 3.78 (s, 9H; OCH_3), 3.77 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 3.38 [d, ^2J(H,H) = 13.5 Hz, 12H; CH_e], 1.77 (m, 4H; CH_2), 1.50 (m, 4H; CH_2), 1.40 (m, 8H; CH_2). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.73 (2C), 149.69 (2C), 149.61 (2C), 149.54 (4C), 149.47 (2C), 147.12, 147.10, 146.65, 146.64 (2C), 146.60 (2C), 146.57 (3C), 146.54 (2C), 134.34 (2C), 134.29 (2C), 134.13 (4C), 134.06 (2C), 134.03 (2C), 132.00 (2C), 131.92, 131.88, 131.55, 137.52, 131.50, 131.47, 131.45, 131.41 (2C), 131.38, 122.25 (2C), 121.34 (2C), 121.30 (2C), 120.40 (6C), 116.38 (2C), 114.51, 114.46, 113.66 (2C), 113.55 (4C), 113.49 (2C), 69.54 (2C; O*C*H_2), 69.39 (2C; O*C*H_2), 69.27 (2C; O*C*H_2), 69.17 (2C; O*C*H_2), 69.0–68.0 (m, 6C; O*C*D_2), 56.01 (1C; O*C*H_3), 55.72 (1C; O*C*H_3), 55.66 (1C; O*C*H_3), 55.60 (1C; O*C*H_3), 55.55 (1C; O*C*H_3), 55.5–54.5 (m, 5C; O*C*D_3), 36.19 (12C; $CH_{a,e}$), 29.70 (2C; *C*H_2), 29.63 (2C; *C*H_2);29.57 (2C; *C*H_2), 26.12 (2C; *C*H_2). HRMS (LSIMS): calcd for $C_{116}H_{95}D_{27}O_{24}$ $[M]^{+\bullet}$ 1926.0021; found 1926.0011.

Cryptophane 9. A solution of **34** (0.1 g, 0.084 mmol), cesium carbonate (0.065 g, 0.2 mmol) and cryptophanol **1** (0.088 g, 0.1 mmol) in DMF (4 mL) was heated overnight at 80 °C under argon. The solution was then poured into water and extracted twice with CH_2Cl_2. The combined organic layers were washed with brine and dried over Na_2SO_4. The solvent was then removed by rotary evaporation to leave a residue, which was purified by chromatography on silica gel (CH_2Cl_2–acetone 9:1) to give a glassy solid. This compound was then washed on a fritted glass with diethyl ether. A further chromatography on silica gel (CH_2Cl_2–acetone 9:1) afforded dimer **9** (0.1 g, 61%) as a white glassy solid. ^{1}H NMR (499.83 MHz, $CDCl_3$, 20 °C) δ 6.77 (s, 1H; Ar), 6.75 (s, 1H; Ar), 6.74 (s, 1H; Ar), 6.73 (s, 1H; Ar), 6.72 (s, 1H; Ar), 6.71 (s, 1H; Ar), 6.68 (s, 2H; Ar), 6.665 (s, 5H; Ar), 6.66 (s, 3H; Ar), 6.65 (s, 2H; Ar), 6.59 (s, 3H; Ar), 6.575 (s, 2 H; Ar), 6.51 (s, 1 H; Ar), 4.70–4.52 (m; 12H CH_a), 4.22–3.80 (m, 28H; OCH_2), 3.81 (s, 6H; OCH_3), 3.80 (s, 6H; OCH_3), 3.785 (s, 6 H; OCH_3), 3.780 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.75 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 3.41–3.37 (m, 12H; CH_e), 2.28 (m, 6H; CH_2), 1.76 (m, 4H; CH_2), 1.50–1.35 (m, 12H; CH_2). ^{13}C NMR (125.66 MHz, $CDCl_3$, 20 °C) δ 149.70, 149.66, 149.57, 149.52, 149.50, 149.42, 148.52, 147.32, 147.18, 147.1–146.95 (9C), 146.63–145.52 (6C), 134.32, 134.28, 134.11 (2C), 134.04, 134.00, 132.08, 131.98, 131.90, 131.52, 131.48, 131.41, 131.38, 131.18 (2C), 131.07 (2C), 131.04, 130.97, 130.95, 130.84, 130.76 (3C), 122.23, 121.29 (2C), 120.38 (3C), 116.92, 116.32, 114.46, 113.62, 113.55 (2C), 113.495, 113.01, 112.78, 112.35, 112.31, 112.22 (2C), 112.06 (2C), 111.935 (3C), 70.25 (1C; O*C*H_2), 69.51 (2C; O*C*H_2), 69.36 (2C; O*C*H_2), 69.22 (2C; O*C*H_2), 69.13 (1C; O*C*H_2), 63.84 (1C; O*C*H_2), 63.71 (1C; O*C*H_2);63.58 (3C, O*C*H_2);63.40 (1C; O*C*H_2), 56.25 (1C; O*C*H_3), 55.98 (1C; O*C*H_3), 55.70 (1C; O*C*H_3), 55.60 (4C; O*C*H_3), 55.54 (3C; O*C*H_3), 36.18–36.12 (12C; *C*$H_{a,e}$), 29.79–29.50 (9C; *C*H_2), 26.11 (1C; *C*H_2), 26.01 (1C; *C*H_2). HRMS (LSIMS): calcd for $C_{119}H_{128}O_{24}$ $[M]^{+\bullet}$ 1940.8795; found 1940.8790.

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26 The $\boldsymbol{L}$ matrix may be calculated numerically by solving the following system: $\boldsymbol{R} = -(\ln \mathbf{A}_{ij})/\tau_{\mathrm{m}}$, where $\mathbf{A}_{ij} = \boldsymbol{I}_{ij}(\tau_{\mathrm{m}})/M_j^0$ is the experimental matrix that contains all the intensities for each site and for the three selective irradiations.