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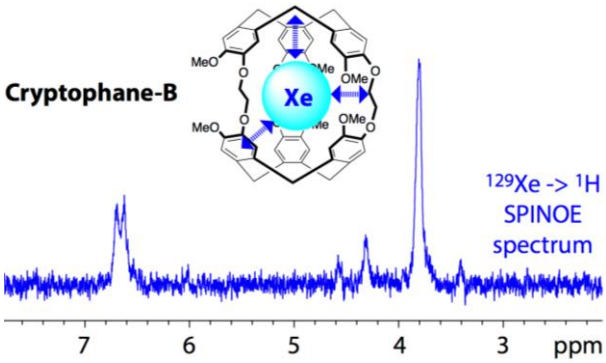


ABSTRACT: Whereas the synthesis of the *anti*-cryptophane-A (**1**) derivative is known for nearly 40 years, the preparation of its diastereomer (cryptophane-B according to Collet's nomenclature) has never been reported. Thus, the synthesis of the cryptophane-B derivative represents a real challenge for chemists interested in the preparation of these hollow molecules. Herein, we describe a synthetic route that allows us to prepare cryptophane-B (**2**), however in low yield. The X-ray crystallographic structure of this compound is described and it reveals the presence of an ethanol molecule inside the cavity of the host. Finally, the ability of cryptophane-B to bind xenon in 1,1,2,2-tetrachloroethane-d_2 is also studied via hyperpolarized ^{129}Xe NMR.

INTRODUCTION

The cryptophane derivatives represent an important class of hollow molecules with remarkable binding properties.[1] For instance, it has been shown that these host molecules have a very high affinity for xenon and they constitute, amongst other host systems, excellent candidates for biosensing applications.[2,3,4] To date, cryptophane-A and its congeners, which have a small cavity size, remain the most studied host derivatives with xenon (Chart 1). Collet and co-workers were the first to report the synthesis of cryptophane-A in 1981 via the *template method*.[5] Since then, different strategies aimed at preparing this host molecule have been described in the literature.[6] This compound exhibits an inherently chiral structure thanks to the presence of three ethylenedioxy bridges arranged in a helicoidal manner (D_3-symmetry; anti conformation). Thus, the two cyclotribenzylene (CTB) units that constitute its skeleton possess the same absolute configuration *M* or *P*. Several approaches have also been reported in the literature to prepare cryptophane-A in its enantiopure form.[7, 8, 9]

Surprisingly, the different synthetic routes used to prepare the cryptophane-A derivative did not result in the production of its diastereomer even in small quantities. Thus, to date, the *syn* diastereomer of cryptophane-A has never been isolated or even detected. Therefore, the access to this compound is not straightforward and it constitutes a real challenge since a new synthetic route has to be imagined. The *syn* diastereomer of cryptophane-A is also called cryptophane-B according to Collet's nomenclature and its structure is reported in Chart 1. Cryptophane-A (**1**) and cryptophane-B (**2**) only differ by the arrangement of the three linkers. In contrast to cryptophane-A, cryptophane-B presents a plane of symmetry (C_{3h}-symmetry) and is achiral. Consequently, the two CTB units that constitute the skeleton of the cryptophane-B derivative possess opposite absolute configuration (*MP*).

In this article, we report the formation of cryptophane-B from a multi-step synthesis. A known functionalized CTB derivative was used as a starting material for the preparation of

compound **2**. The approach described herein allows us to obtain cryptophane-B in small quantities, whereas the other classical approaches failed to produce this derivative. We also report the X-ray crystallographic structure of the ethanol@cryptophane-B complex. Finally, we examine the ability of cryptophane-B to bind xenon in organic solution using hyperpolarized ^{129}Xe NMR.

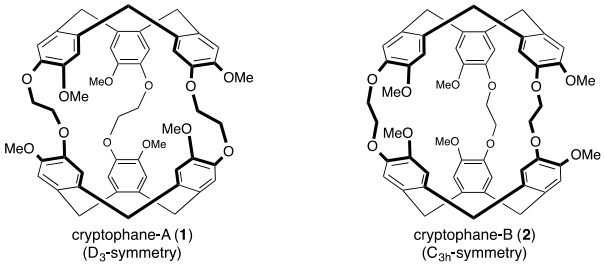


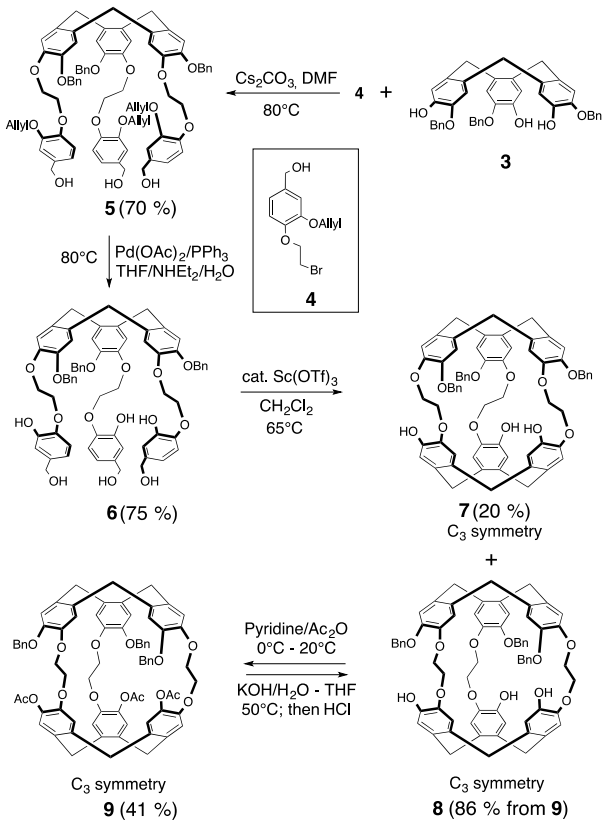
Chart 1: Structure of *PP-anti*-cryptophane-A (**1**) (chiral) and *syn*-cryptophane-B (**2**) (achiral).

RESULTS AND DISCUSSION

Synthesis of cryptophane-B: A known functionalized CTB (**3**) unit decorated with three benzyl groups has been used as a starting material to prepare cryptophane-B. Its synthesis has been reported in 2005.[10] In the past, this compound has been used for the synthesis of modified cryptophane-A congeners with C_3-symmetry thanks to the removal of the three benzyl moieties at a later stage.[9] For the synthesis of **2**, a SN_2 reaction between compound **3** and 4-(2-bromoethoxy)-3-(2-propen-1-yloxy)-benzenemethanol (**4**) in the presence of Cs_2CO_3 gave rise to the tris-functionalized CTB derivative (**5**) in moderate yield (57%) (Scheme 1; Supporting Information Figures S1-S2). Then, compound **5** was allowed to react under acidic conditions to perform the second ring closing reaction. Unfortunately, the formation of the second CTB unit does not take place under these conditions whatever the nature of the acid used for the cyclisation reaction. In the presence of a mixture of formic acid and chloroform (50/50) the reaction resulted in the formation of polymeric side-products and no ^{1}H NMR signals that could

be attributed to the formation of the second CTB unit was detected. Milder conditions gave similar results. For instance, scandium triflate $Sc(OTf)_3$ used in catalytic amount gave only polymeric materials as side-products.

In 2011, Dmochowski and co-workers successfully reported the one-step synthesis of a tris-hydroxycryptophane derivative from a functionalized CTB derivative bearing three vanillyl alcohol functions.[11] In this example, scandium triflate was used as a Lewis acid to promote the cyclization of the second CTB unit. Encouraged by this example, we decided to use a similar approach. Thus, prior to react under acidic conditions, the three allyl functions of compound **5** were removed with a palladium catalyst to give rise to compound **6** in good yield (75 %) (Supporting Information Figures S3-S4). Compound **6** was then allowed to react under diluted condition in the presence of a catalytic amount of $Sc(OTf)_3$. Interestingly, in contrast to what was previously observed with compound **5**, the ^1H NMR spectrum of the crude material has revealed the presence of two sets of signals in the aromatic region with a ratio close to 75/25. The presence of these signals suggests that derivatives *anti*-**7** and *syn*-**8** are formed simultaneously under these conditions. The concomitant formation of *syn* and *anti*-diastereomers is not new and has already been observed in the past. For instance, Collet and co-workers reported the formation of the two diastereomers cryptophane-C and D by reacting the cryptophane precursor in formic acid.[12]

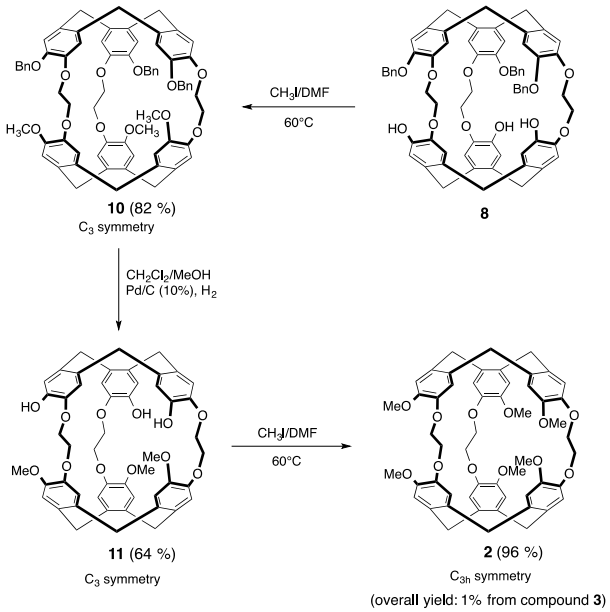


Scheme 1: Synthesis of anti-**7** and syn-**8** cryptophanes.

The derivative *anti*-**7** (C_3-symmetry) was isolated with a 20% yield (Supporting Information Figures S5 and S6). In order to confirm its stereochemistry, compound *anti*-**7** was allowed to react with methyl iodide. The ^{1}H NMR spectrum of this cryptophane was found identical to the one previously obtained for the *anti*-cryptophane decorated with three benzyl groups.[10] Compound *anti*-**7** has been recently used for the construction of a new pH-sensitive chemical platform.[13] Compound *syn*-**8** was found more difficult to isolate than *anti*-**8** and additional steps were necessary to complete its purification. Thus, the three phenol functions of *syn*-**8** were protected by acetate groups to give compound *syn*-**9** with a moderate yield (41 % based on the crude product) (Supporting Information Figures S7 and S8). Compound **8** was then recovered under basic conditions with a 86 % yield. The ^{1}H and ^{13}C NMR spectra of this derivative confirm that compound *syn*-**8** possesses a C_3-symmetry and the HRMS allows us to

assign this compound as the diastereomer of derivative *anti*-**7** (Supporting Information Figures S9 and S10).

Interestingly, compound *syn*-**8** possesses three protected and three unprotected phenol functions that can be used at a latter stage to conceive new *syn*-cryptophane derivatives with C_3 or C_{3h} symmetry. Up to date, cryptophane derivatives with C_3-symmetry are rare and the overwhelming majority of the cryptophane derivatives reported in the literature possesses the *anti*-configuration. New chiral scaffolds can thus be prepared from compound *syn*-**8** since cryptophane derivatives with two different CTB units possess an inherently chiral structure. It is noteworthy that only very few enantiopure cryptophanes of this kind have been isolated in the past.[14, 15, 16] Finally, the synthesis of compound *syn*-**8** allows us to prepare the cryptophane-B (**2**) derivative, which had never been isolated in the past.



Scheme 2: synthesis of cryptophane-B (**2**) (C_{3h} symmetry) from compound *syn*-**8**.

For the synthesis of this compound, the three phenol groups of compound *syn*-**8** were first allowed to react with methyl iodide to give rise to compound *syn*-**10** in good yield (82 %) (Supporting Information Figures S11 and S12). Then, the three benzyl groups of *syn*-**10** were removed by a catalytic hydrogenation reaction using palladium-on-charcoal (10%). Even

though the reaction has gone to completion, the compound *syn*-**11** was only isolated with a 64 % yield (Supporting Information Figures S13 and S14). Finally, the desired cryptophane-B (**2**) was obtained in a 96 % yield by reacting compound *syn*-**11** with an excess of methyl iodide. Compound **2** has been fully characterized by ^{1}H, ^{13}C NMR spectroscopy (Supporting Information Figures S15 and S16) and HRMS.

A comparison of the ^{1}H NMR spectra of compound **1** and **2** recorded in CD_2Cl_2 and $CDCl_3$ is reported (Supporting Information Figures S17 and S18). These two solvents can easily enter the cavity of hosts **1** and **2**. In CD_2Cl_2, the diastereotopic protons of the ethylenedioxy linkers show two sets of symmetrical signals for both compounds. The aromatic part is also different for these two compounds. A change of the nature of the solvent has a strong impact on the ^{1}H NMR signals of **1** whereas it leaves almost unchanged those of compound **2**. Thus, the replacement of CH_2Cl_2 (V_{vdw} = 54 Å^3) by the bigger $CHCl_3$ guest molecule (V_{vdw} = 72 Å^3) strongly modifies the NMR signals of the ethylenedioxy linkers of **1**. These spectral changes reflect the greater flexibility of **1** with respect to compound **2**. Indeed, the helicoidal arrangement of the three linkers, makes it easier for him to maximize interactions with the guest molecule.

The overall yield to prepare the cryptophane-B derivative is low (~ 1% from compound **3**) and the ring closing reaction of the second CTB unit is the limiting step. Unfortunately, a change of our experimental conditions is not expected to significantly improve the yield of this reaction or to modify the *syn*/*anti* ratio.

A simplification of the proposed synthetic procedure can be envisaged if we only focus on the synthesis of compound **2**. Thus, we can imagine to replace the CTB **3** unit by the more easily accessible cyclotriguaiacylene derivative.[17] This approach was also tested and was successful in a sense that a change of the nature of the CTB unit also resulted in the production of the two diastereomers with a similar ratio. However, we encountered a difficulty to isolate

and to purify properly the *syn*-intermediate. Thus, to date the synthetic route used in scheme **1** remains the only way to prepare cryptophane-B in a reproductive manner.

In the future new synthetic routes will have to be imagined to access to cryptophane-B with a better overall yield. For instance, we have reported that cryptophane precursors bearing additional substituents positioned from each side of the linkers can produce the *syn* diastereomers with better yields.[16] Of course, if successful this strategy will require additional synthetic steps to remove the extra substituents at the end of the synthesis.

X-ray crystallographic structure of cryptophane-B (2):

Single crystals of compound **2** have been grown from slow evaporation of a CH_2Cl_2/EtOH mixture. Under a microscope these crystals show a diamond-shaped structure. Compound **2** crystallizes in the triclinic system P_{-1} with two molecules par unit-cell. An ORTEP representation of compound **2** is reported in Figure 1 (see also Supporting Information Figure S19). Compared to the X-ray structure of its diastereomer **1**, the structure of **2** shows interesting features. Unlike cryptophane-A, cryptophane-B does not show any disorder and the three linkers adopt an all-trans conformation (dihedral angles OCH_2CH_2O: 171.8°, -167.1° and 167.8°) and the methoxy groups are also located out of the plane of the benzene rings. It is noteworthy that the X-ray structure of **2** also appears less spherical than the X-ray structure of the cryptophane-A derivative. For instance it can be easily seen from the ORTEP representation that the two CTB units are tilted with respect to each other. This spatial arrangement should be detrimental for molecular recognition but it is possible that compound **2** adopts another conformation in solution. From the ORTEP representation the internal volume of cryptophane-B was estimated to be $V_{vdw} \sim 100$ Å^3. This volume is slightly larger than the volume measured for the inner cavity of the cryptophane-A derivative ($V_{vdw} = 95$ Å^3) considering an all-trans conformation of the linkers.

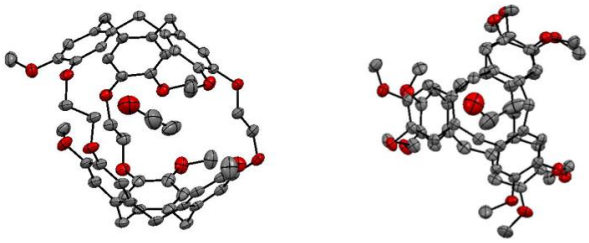


Figure 1: ORTEP representation of cryptophane-B (**2**). Two different views are shown. Hydrogen atoms have been removed for clarity. The cavity is filled with an ethanol molecule. The displacement ellipsoids were plotted at 30 % probability level.

However, the most interesting feature of this structure lies in the nature of the encapsulated guest. The binding properties of the cryptophane-A derivative have been thoroughly studied in the past and it is known that this derivative has a high affinity for tetrahedral molecules such as CH_2Cl_2 or $CHCl_3$.[18] Thus, the X-ray crystallographic structures of **1** have always displayed CH_2Cl_2 or $CHCl_3$ molecules within its cavity, when CH_2Cl_2/Ethanol or $CHCl_3$/Ethanol mixtures were used.[19] Interestingly, in the case of cryptophane-B (**2**), the ORTEP representation reveals that this host molecule prefers to accommodate an ethanol molecule even though CH_2Cl_2 molecules were initially present in the solution. Thus, the CH_2Cl_2 molecule (V_{vdw} = 54 Å^3) seems too small to be encapsulated within the cavity of this host. The lack of affinity of host **2** for CH_2Cl_2 probably originates from the higher rigidity of the linkers that cannot easily modify their conformations. Consequently, host **2** cannot adopt an optimal conformation to maximize its interaction with the CH_2Cl_2 guest molecule.

The xenon-cryptophane-B complex:

Cryptophane-A shows interesting binding properties toward xenon in 1,1,2,2-tetrachloroethane-d_2 and the ^{129}Xe NMR spectrum reveals a signal characteristic of the Xe@**1** complex at 70 ppm (reference xenon gas extrapolated at zero pressure).[2a] Considering that these

two compounds possess a very similar structure it seems natural to assess the ability of the cryptophane-B (**2**) diastereomer to bind xenon in the same conditions. Therefore ^{129}Xe NMR experiments with hyperpolarized xenon have been performed at various temperatures. A single broad ^{129}Xe peak has been detected in 1,1,2,2-tetrachloroethane-d_2 at room temperature (Supporting Information Figure S20). Experiments have been performed at lower temperature (until 260 K) but in no case a slow exchange phenomenon (two signals) has been observed. The ^{129}Xe full width at half maximum (FWMH) of this signal varies from ca. 340 Hz at 256 K to ca. 700 Hz at 279 K. Hence, the unique ^{129}Xe signal becomes sharper and sharper as the temperature decreases suggesting that encapsulation indeed takes place under a fast exchange regime. To ascertain that xenon enters the cavity of cryptophane-B, ^{129}Xe-^{1}H NMR SPINOE experiments have been performed using laser-polarized xenon. The ^{129}Xe-^{1}H NMR SPINOE sequence has been published earlier.[20] It allows us to witness the through-space interaction between hyperpolarized xenon and protons. The cross-relaxation rate between xenon and proton strongly depends on the inter-nuclear distance, and therefore, provided that the rotational correlation time of the pair of nuclei is not too long (i.e. that xenon is not buried in the cryptophane cavity) indicates the inclusion of xenon in the cryptophane cavity by the appearance of some cryptophane protons in the SPINOE difference experiment.[21] No SPINOE effect is expected in the absence of complexation. Thus, this approach appears very convenient way to ascertain that encapsulation takes place. Figure **2** shows the ^{1}H NMR spectra of a) ^{129}Xe@cryptophane-B complex recorded in $C_2D_2Cl_4$ (blue spectrum) and b) the ^{129}Xe-^{1}H NMR SPINOE sub-spectrum (red spectrum).

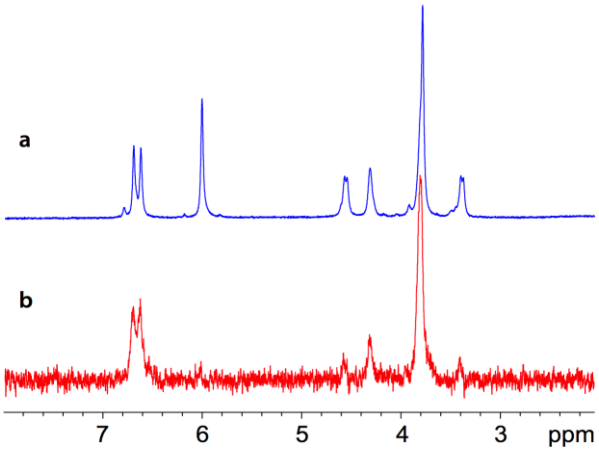


Figure 2: ^{1}H NMR spectra of cryptophane-B recorded in 1,1,2,2-tetrachloroethane-d_2 at 298 K and 11.7 T. a) after addition of xenon into the solution; b) ^{129}Xe-^{1}H NMR SPINOE spectrum (mixing time 700 ms). The signal at 6 ppm corresponds to the protons of the solvent.

In figure 2a, two sets of aromatic signals with different intensities can be distinguished in the aromatic region. This spectrum, which is different from that recorded in $CDCl_3$ (Supporting Information Figure S18), suggests that cryptophane-B shows some flexibility and can adopt at least two different conformations in slow exchange. It is worth noting that the population of the two conformations strongly depends on the experimental conditions (Supporting Information Figure S21). A similar effect was observed with other *syn*-cryptophane derivatives bearing nine or twelve methoxy substituents.[22] As can be observed on Figure 2b, the ^{129}Xe - ^{1}H NMR SPINOE difference sub-spectrum reveals the aromatic protons. This is an irrefutable proof that xenon reversibly enters the cavity of the cryptophane. It is noteworthy from figure 2b that the magnetization redistribution is larger for the aromatic protons and the methoxy groups, which is expected as some of these groups point toward the interior of the cavity, as observed in the ORTEP representation. In contrast the protons of the ethylenedioxy linkers are not clearly visible, which suggests that these protons are not in close contact with the encapsulated xenon.

CONCLUSION

For nearly 40 years the synthesis of cryptophane-B remained out of reach. The structure of cryptophane-B only differs from that of the cryptophane-A by the arrangement of the three ethylenedioxy linkers. Thus, in contrast to cryptophane-A, the cryptophane-B (**2**) is achiral (C_{3h} symmetry). We report for the first time a reproducible synthetic route that allows us to prepare cryptophane-B (**2**) in low yield. The synthetic route described in this article present several advantages. Indeed, the chemical intermediates described in this article show an inherently chiral structure that can be exploited in the future to prepare new chiral cryptophanes. For instance, compound *syn*-**8** possesses protected and unprotected chemical functions that can facilitate the preparation of new *syn*-cryptophanes. Thus, this work also paves the way to the synthesis of new chiral *syn*-cryptophane derivatives with C_3 symmetry.

An X-ray crystallographic structure of the cryptophane-B derivative was obtained from slow evaporation of a CH_2Cl_2/Ethanol mixture. The Structure reveals that the cavity of this compound is filled with an ethanol molecule. This contrasts with the solid-state structure of cryptophane-A that shows a preference for tetrahedral molecules (CH_2Cl_2 or $CHCl_3$).

Finally, thanks to ^{129}Xe-^{1}H NMR SPINOE experiments we show that cryptophane-B reversibly encapsulates xenon in 1,1,2,2-tetrachloroethane-d_2. Nevertheless, whatever the conditions used the binding process always occurs via an exchange dynamics fast at the NMR timescale. Thus, no signal characteristic of the Xe@**2** complex was observed even at low temperature. This situation may change in aqueous solution where a slowing down of the in-out exchange dynamics is usually observed with the cryptophane complexes. The synthesis of a water-soluble version of the cryptophane-B derivative would be of high interest for ^{129}Xe NMR-based biosensing applications where the in-out xenon exchange is of importance. Its synthesis is under way.[23]

EXPERIMENTAL DETAILS

X-ray Crystallography: A suitable crystal of cryptophane B was selected and mounted on a Gemini kappa-geometry diffractometer (Agilent Technologies UK Ltd) equipped with an Atlas CCD detector and using Cu radiation (λ= 1.5418 Å). X-ray data are summarized in Supporting Information (Table S1).

Intensities were collected at 150 K by means of the CrysalisPro software.[24] Reflection indexing, unit-cell parameters refinement, Lorentz-polarization correction, peak integration and background determination were also carried out with the CrysalisPro software. An analytical absorption correction was applied using the modeled faces of the crystal.[25] The resulting set of *hkl* was used for structure solution and refinement. The structures were solved by direct methods with SIR97 and the least-square refinement on F^2 was achieved with the CRYSTALS software.[26,27]. All non-hydrogen atoms were refined anisotropically. The hydrogen atoms were all located in a difference map, but those attached to carbon atoms were repositioned geometrically. The H atoms were initially refined with soft restraints on the bond lengths and angles to regularize their geometry (C---H in the range 0.93--0.98 Å, O--H = 0.82 Å) and U_{iso}(H) (in the range 1.2-1.5 times U_{eq} of the parent atom), after which the positions were refined with riding constraints. Residual electronic density in between the cryptophane cages was located but could not be modeled. The contribution of the disordered solvent molecules was removed using the SQUEEZE algorithm.[28]

The volume of the cryptophane cage was calculated using the VOID algorithm within the PLATON software.[29] The volume of the internal cryptophane cavity was calculated by removing the ethanol molecule. It was found to be 100 $Å^3$ with a probe size of 1.2 Å using the SQUEEZE procedure.**[28]** An Inter-molecular void was also evaluated using the same procedure. Its volume was found to be 93 $Å^3$ and the estimated electron count was 27, which is in agreement with the presence of an ethanol molecule. However, the ethanol molecule could not be modeled

due to heavy disorder. The contribution of the inter-molecular residual electronic density was then removed from the observed data.

CCDC 1864062 contains the supplementary crystallographic data for cryptophane-B (**2**). These data can be obtained free of charge from the Cambridge Crystallographic data Centre via www.ccdc.cam.ac.uk/data request/cif.

Production of hyperpolarized xenon. Hyperpolarized xenon was produced in the batch mode via SEOP (Spin Exchange Optical Pumping) using a home-built setup.[30] Rubidium is used as the alkali metal, and five minutes suffice to produce five millilitres of xenon at a polarization ranging from 15 to 20%. Frozen hyperpolarized xenon immersed in a bath of liquid nitrogen and subjected to a magnetic field of 3 kG provided by a solenoid is transported near the NMR magnet. There it is sublimated in the fringe field of the magnet and transferred thanks to a vacuum line to the NMR tube. A hollow spinner enabled us to condense it in the upper part of the NMR tube (screw capped Wilmad PP-528) without cooling the solution. The hyperpolarized ^{129}Xe NMR experiments were performed at 11.7 T (^{129}Xe resonance frequency 138.35 MHz) using a 5mm-broadband inverse probehead.

Mass spectra (HRMS LSIMS) were performed by the Centre de Spectrométrie de Masse, University of Lyon, on a Thermo-Finnigan MAT 95XL spectrometer. 1H and 13C NMR spectra were recorded at 300 and 75.5 MHz, respectively. Chemical shifts are referenced to Me4Si (1H, 13C). 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. The solvents were distilled prior to use: DMF and CH2Cl2 from CaH2, THF from Na/benzophenone and pyridine from KOH.

EXPERIMENTAL PROCEDURE

Synthesis of CTB 5: Compound **4** (5.5 g, 19.2 mmol) was added to a stirred solution of CTB **3** (3.5 g, 5.5 mmol) and Cs_2CO_3 (7.17 g, 22.0 mmol) in dry DMF (60 mL) under an argon atmosphere. The mixture was stirred for 48 hours at 80°C. The mixture was then poured in water and the product was extracted three times with AcOEt (300 mL). Then, the organic layer was washed three times with water (100 mL) to remove DMF and then dried over Na_2SO_4. The organic solvent was removed under reduced pressure to leave brown residue. Purification on silica gel (AcOEt/petroleum ether: 90/10 then ACOEt 100%) gives rise to compound **5** (4.85 g, 70 %) as white glassy product. ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.34 – 7.22 (m, 15 H), 6.89 – 6.83 (m, 12 H), 6.70 (dd, *J* = 3.0 Hz, *J* = 9.0 Hz, 3 H), 5.935 (m, 3 H), 5.22 (m, 6 H), 4.97 (m, 6 H), 4.66 (d, *J* = 15.0 Hz, 3 H), 4.50 (s, 6H), 4.48 (m, 6H), 4.24 (m, 12 H), 3.45 (d, *J* = 15.0 Hz, 3 H). ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25°C) δ = 148.8 (3 C), 148.1 (3 C), 147.9 (3 C), 147.7 (3 C), 137.5 (3 C), 134.6 (3 C), 133.3 (3 C), 132.9 (3 C), 132.8 (3 C), 128.4 (6 C), 127.7 (3 C), 127.2 (6 C), 119.8 (3 C), 117.5 (3 C), 117.2 (6 C), 115.0 (3 C), 113.3 (3 C), 71.8 (3 C), 69.8 (3 C), 68.5 (3 C), 68.2 (3 C), 65.0 (3 C), 36.3 (3 C). HRMS(ESI) *m/z* $[M + Na]^+$ calcd for $C_{78}H_{78}O_{15}Na$ 1277.5233, found 1277.5243.

Synthesis of CTB 6: CTB **5** (6.0 g, 47 mmol), triphenylphosphine (0.62 g, 2.36 mmol), THF (120 mL), diethylamine (36 mL), palladium acetate (0.26 g, 1.16 mmol) and water (16 mL) were introduced in a 500 mL three neck flask under an argon atmosphere. The mixture was heated at 80°C for 6 hours. The dark solution was concentrated under reduced pressure. Then water and AcOEt were added to the solution. The solution was extracted three times with AcOEt. The organic layer was washed once with water and then dried over Na_2SO_4.

Evaporation of the solvent leaves a residue, which was then purified on silica gel (AcOEt/petroleum ether: 80/20). The second spot detected on TLC was collected and the fractions evaporated under reduced pressure to give rise to compound **6** as a white glassy solid (4.1 g, 75 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.33 - 7.26 (m, 15H), 6.80 – 6.65 (m, 15 H), 6.20 (s, 3 H; OH), 4.98 (m, 6H), 4.63 (d, *J* = 14.4 Hz, 3 H), 4.46 (m, 6 H), 4.27 – 4.12 (m, 12 H), 3.43 (d, *J* = 14.4 Hz, 3 H), 1.84 (s, 3 H; CH_2OH). $^{13}C\{^{1}H\}$ NMR (75.5 MHz, $CDCl_3$, 25°C) δ = 148.2 (3C), 146.9 (3C), 146.8 (3C), 145.1 (3C), 137.1 (3C), 135.5 (3C), 133.8 (3C), 132.5 (3C), 128.5 (6C), 127.8 (3C), 127.2 (6C), 118.5 (6C), 116.3 (3C), 114.4 (3C), 114.0 (3C), 71.4 (3C), 69.0 (3C), 68.8 (3C), 64.9 (3C), 36.3 (3C). HRMS(ESI) *m/z* [M + K^+] calcd for $C_{69}H_{66}O_{15}K$ 1173.4033, found 1173.4028.

Synthesis of cryptophane (rac)-*anti*-7 and (rac)-*syn*-8: catalytic amount of scandium triflate (0.060 g; 0.12 mmol) was added at 40°C to a stirred solution of compound **6** (0.60 g; 0.51 mmol) in 500 mL of dry CH_2Cl_2. Then, the solution was stirred for 48 hours at 65°C under argon. Water was added to the purple solution and the organic phase was washed once with water. The organic phase was dried over sodium sulphate, filtrated and the solvent was evaporated under reduced pressure to give rise to a purple residue. A column chromatography on silica gel (CH_2Cl_2/EthylAcetate: 95/5) allows us to isolate compound **7** as a white glassy solid (0,115 g; 20%). ^{1}H NMR (300 MHz, DMSO-d_6, 25°C): δ = 8.24 (s, 3 H, OH), 7.62 - 7.35 (m, 15 H), 6.88 (s, 3 H), 6.79 (s, 3 H), 6.65 (s, 3 H), 6.63 (s, 3 H), 5.08 (m, 6 H), 4.50 (d, *J* = 13.1 Hz, 3 H), 4.45 (d, *J* = 13.1 Hz, 3 H), 4.18 (m, 12 H), 3,25 (d, *J* = 13.1 Hz, 3 H), 3.24 (d, *J* = 13.1 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (75.5 MHz, DMSO-d_6, 25°C) δ = 148.5 (3C), 146.3 (3C), 146.0 (3C), 144.4 (3C), 138.3 (3C), 133.9 (3C), 133.7 (3C), 131.9 (3C), 130.2 (3C), 128.3 (6C), 127.9 (6C), 127.5 (3C), 120.3 (3C), 119.2 (3C), 117.9 (3C), 116.3 (3C), 70.6 (3C), 68.7 (3C), 68.5 (3C), 35.0 (6C). HRMS(ESI) *m/z* [M+Na^+] calcd for $C_{69}H_{60}O_{12}Na$ 1103.3977, found

1103.3927. A second fraction that contains compound (**8**) was also isolated (0.073 g). Three independent experiments were performed and gave identical results.

Purification of compound 8: The solid (0.22 g of crude product) was dissolved in pyridine (7 ml) and the solution was cooled down to 0°C with an ice-bath under an argon atmosphere. Then, acetic anhydride (1.4 mL) was added with a syringe and the solution was then allowed to reach room temperature. Then, the solution was stirred for 16 hours at room temperature under an argon atmosphere. The solution was poured in a CH_2Cl_2 (20 mL)/H_2O (20 mL) mixture and extracted three times with CH_2Cl_2 (60 mL). Finally, the organic layer was dried over sodium sulphate. Purification (CH_2Cl_2/Acetone: 95/5) of the solid residue on silica gel gave the expected compound **9** as a white glassy solid (0.1 g, 41 % based on the crude product).

Compound 9: ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.55 – 7.30 (m, 15 H), 6.92 (s, 3 H), 6.98 (s, 3 H), 6.62 (s, 3 H), 6.38 (s, 3 H), 5.18 (d, *J* = 13.5 Hz, 3 H), 5.04 (d, *J* = 13.5 Hz, 3 H), 4.61 (d, *J* = 13.5 Hz, 3 H), 4.43 (d, *J* = 13.5 Hz, 3 H), 4.23 – 4.05 (m, 6 H), 4.00 – 3.80 (m, 6 H), 3.51 (d, *J* = 13.9 Hz, 3 H), 3.21 (d, *J* = 13.9 Hz, 3 H), 2.0 (s, 9 H). ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25°C) δ = 168.8 (3 C), 149.4 (3 C), 149.3 (3 C), 147.2 (3 C), 141.0 (3 C), 137.8 (6 C), 134.7 (3 C), 134.2 (3 C), 132.1 (3 C), 128.7 (6 C), 128.0 (3 C), 126.7 (6 C), 124.3 (3 C), 123.3 (3 C), 121.8 (3 C), 117.3 (3 C), 72.0 (3 C), 70.8 (3 C), 70.0 (3 C), 36.4(3 C), 36.3 (3 C), 20.4 (3 C). HRMS(ESI) *m/z* [M+H$^+$] calcd for $C_{75}H_{67}O_{15}$ 1207.4474, found 1207,4466.

Finally, the cryptophane *syn*-**8** was recovered by hydrolysis of the three acetate groups under basic conditions. Thus, a solution of KOH (0.5 M; 7 mL) was added to a stirred solution of compound **9** (0.10 g, 0.083 mmol) in THF (6 mL). The solution was stirred for 16 hours at 50°C under an argon atmosphere. Evaporation of the solvent followed by acidification of the solution with few drop of conc. HCl at 0°C gives rise to a white precipitate. This solid was dissolved in CH_2Cl_2 and the organic layer was then dried over Na_2SO_4. Filtration and evaporation of the

solvent give a residue, which was purified on silica gel (CH_2Cl_2/Acetone: 95/5) to give compound *syn*-**8** as a white glassy solid (0.076 g, 86 %). **Compound (8)**: ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.56 - 7.28 (m, 15H), 6.71 (s, 6H), 6.64 (s, 3H), 6.50 (s, 3H), 5.96 (s, 3H; OH), 5.05 (m, 6H), 4.50 (d, *J* = 13.7 Hz, 6H), 4.40 – 4.20 (m, 6H), 4.12 – 4.00 (m, 3H), 3.90 – 3.75 (m, 3H), 3.34 (d, *J* = 15.0 Hz; 3H), 3.245 (d, *J* = 15.0 Hz; 3H). ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25°C) δ = 148.4 (3 C), 146.8 (3 C), 146.3 (3 C), 147. 3 (3 C), 137.5 (3 C), 134.3 (3 C), 132.8 (3 C), 132.6 (3 C), 130.5 (3 C), 128.6 (6 C), 127.9 (3 C), 127.4 (6 C), 117.9 (3 C), 117.7 (3 C), 117.3 (3 C), 116.9 (3 C), 72.4 (3 C), 68.6 (3 C), 67.0 (3 C), 36.6 (3 C), 35.9 (3 C). HRMS(ESI) *m/z* [M+H$^+$] calcd for $C_{69}H_{61}O_{12}$ 1081.4158, found 1081.4126.

Synthesis of *syn*-cryptophane (10): methyl iodide (few drops) was added to a stirred solution of compound **8** (0.07 g; 0.065 mmol) and Cs_2CO_3 (0.10 g, 0.31 mmol) in DMF (3 mL). The mixture was stirred for 18 hours at 60°C under an argon atmosphere. Then, Water (10 mL) and CH_2Cl_2 (10 mL) were added to the solution. The organic layer was washed six times with water to remove the DMF and the organic layer was then dried over Na_2SO_4. Filtration and evaporation of the solvent gives a solid, which was purified on a small column chromatography (CH_2Cl_2/Acetone: 95/5). Evaporation of the fractions gives rise to a white glassy solid, which was identified as compound **10** (0.06 g, 82 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.55 – 7.30 (m, 15H), 6.79 (s, 3H), 6.72 (s, 3H), 6.65 (s, 3H), 6.64 (s, 3H), 5.14 (d, *J* = 13.6 Hz; 3 H), 4.97 (d, *J* = 13.6 Hz; 3 H), 4.55 (d, *J* = 13.6 Hz; 3 H), 4.49 (d, *J* = 13.6 Hz; 3 H), 4.36 - 4.16 (m, 6 H), 4.10 - 3.84 (m, 6 H), 3.44 (s, 9 H), 3.38 (d, *J* = 13.6 Hz; 3 H), 3.305 (d, *J* = 13.6 H; 3 H). ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25°C) δ = 150.4 (3 C), 149.6 (3 C), 147.5 (3 C), 146.7 (3 C), 137.6 (3 C), 135.1 (3 C), 134.9 (3 C), 132.7 (3 C), 131.6 (3 C), 128.7 (6 C), 127.9 (3 C), 127.0 (6 C), 123.3 (3 C), 123.1 (3 C), 117.9 (3 C), 114.4 (3 C), 72.1 (3 C), 71.0 (3 C), 70.6 (3

C), 55.8 (3 C), 36.3 (6 C). HRMS(ESI) *m/z* [M+H$^+$] calcd for $C_{72}H_{67}O_{12}$ 1123.4627, found 1123.4645.

Synthesis of cryptophane (11): a small amount of Pd/C (10%) was added to a stirred solution of cryptophane **10** (0.035 g, 0.031 mmol) in a mixture of CH_2Cl_2 (4 mL) and methanol (3 mL). Hydrogen gas was slowly bubbled for one hour. The mixture was then stirred for 18 hours at room temperature. The solution was filtrated over Celite and the solvents were evaporated under reduced pressure. A ^{1}H NMR spectrum showed complete removal of the benzyl groups under these conditions. A small silica column (CH_2Cl_2/Acetone: 80/20) and evaporation of the solvents gives cryptophane **11** as a white glassy solid (0.017 g, 64 %). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 7.52 (s, 3 H; OH), 6.97 (s, 3 H), 6.94 (s, 3 H), 6.73 (s, 3 H), 6.69 (s, 3 H), 4.54 (d, *J* = 12.0 Hz, 3 H), 4.425 (d, *J* = 12.0 Hz, 3 H), 4.24 - 4.00 (m, 8 H), 3.81 – 3.60 (m, 13 H), 3.34 (d, *J* = 12.0 Hz, 3 H), 3.23 (d, *J* = 12.0 Hz, 3 H). ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25°C) δ = 149.0 (3 C), 146.5 (3 C), 145.2 (3 C), 143.7 (3 C), 134.7 (3 C), 133.8 (3 C), 131.5 (3 C), 130.2 (3 C), 120.3 (3 C), 119.4 (3 C), 117.1 (3 C), 114.9 (3 C), 68.8 (3 C), 68.2 (3 C), 56.1 (3 C), 34.9 (6 C). HRMS(ESI) *m/z* [M+H$^+$] calcd for $C_{51}H_{49}O_{12}$ 853.3219, found 853.3222.

Synthesis of cryptophane B (2): methyl iodide (2 drops) was added to a stirred mixture of cryptophane **11** (0.035 g, 0.041 mmol) and Cs_2CO_3 (0.12 g, 0.37 mmol) in DMF (1 mL). The mixture was stirred for 18 hours at 60°C under an argon atmosphere. Then, CH_2Cl_2 (5 mL) and water (5 mL) were added to the solution. The aqueous phase was extracted twice with CH_2Cl_2 (10 mL) and the organic layer was dried over Na_2SO_4. The organic layer was filtrated and the solvent evaporated under reduced pressure to give a residue, which was purified on silica gel ($CHCl_3$/Acetone: 90/10 then $CHCl_3$/Acetone: 75/25). Evaporation of the solvent gives rise to cryptophane-B as a white solid (0.035 g, 96 %). This compound was then crystallized in a

mixture of CH_2Cl_2 and Ethanol. Mp: decomp 127-128 °C. UV-vis (CH_2Cl_2) λ_{max} (log ε) 233 (4.60), 289 (4.12). ^{1}H NMR (300 MHz, $CDCl_3$, 25°C): δ = 6.74 (s, 6 H), 6.67 (s, 6 H), 4.565 (d, *J* = 15.0 Hz; 6 H), 4.22 (m, 6 H), 3.87 (m, 6 H), 3.81 (s, 18 H), 3.39 (d, *J* = 15.0 Hz; 6 H). ^{13}C{^{1}H} NMR (75.5 MHz, $CDCl_3$, 25°C) δ = 150.6 (6 C), 146.6 (6 C), 135.2 (6 C), 132.0 (6 C), 121.8 (6 C), 114.3 (6 C), 70.3 (6 C), 56.3 (6 C), 36.6 (6 C). HRMS(ESI) *m/z* [M+H$^+$] calcd for $C_{54}H_{55}O_{12}$ 895.3688, found 895.3647.

Supporting Information. ^{1}H and ^{13}C spectra of compounds **2** and **5**-**12**. Comparison of ^{1}H spectra of cryptophane-A and B in CD_2Cl_2 and $CDCl_3$. ORTEP representation of compound **2** and X-ray crystallographic data of **2**. Hyperpolarized ^{129}Xe NMR spectrum of compound **2** recorded in 1,1,2,2-tetrachloroethane-d_2. ^{1}H NMR spectra of cryptophane-B (degassed solution and in presence of xenon) recorded in 1,1,2,2-tetrachloroethane-d_2. Crystallographic data of cryptophane-B.

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Notes

The authors declare no competing financial interest.

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