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Synthesis of Highly Substituted Cryptophane Derivatives

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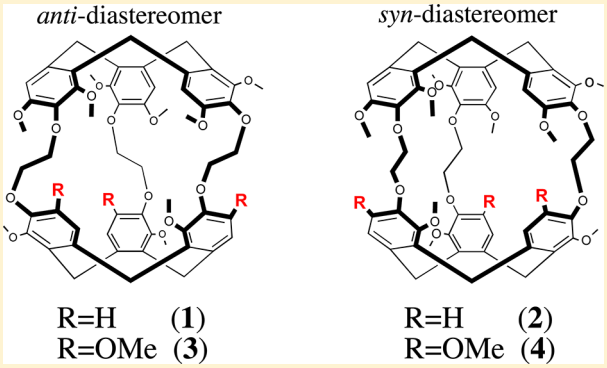
Supporting Information

ABSTRACT: We report the synthesis of new cryptophane derivatives **1**−**4** bearing nine (**1**, **2**) and twelve (**3**, **4**) methoxy substituents. These compounds represent the first examples of cryptophane derivatives bearing more than six substituents attached on the benzene rings. The preparation of these highly substituted cryptophanes was achieved due to the synthesis of a new cyclotrisyringyl derivative obtained from the reaction of a protected syringyl alcohol in the presence of a catalytic amount of scandium triflate $Sc(OTf)_3$. This reaction also provides the protected cyclotetrasyringyl derivative in low yield (7%), which was fully characterized by ^1H NMR, IR, and X-ray crystallography. In contrast to what is observed for the cryptophane-A congener, the synthesis of these highly substituted cryptophanes gives rise to the two *anti*- and *syn*-diastereomers. These compounds have been fully characterized, and their X-ray structures have been obtained to ascertain the stereochemistry of these new cryptophane derivatives.



INTRODUCTION

Since the first synthesis of the cryptophane-A derivative, described in the early 1980s by Collet and co-workers,[1] a large range of cryptophane derivatives bearing different substituents have been reported in the literature.[2] The synthetic procedure used to prepare cryptophanes requires strongly activated benzyl alcohol derivatives to give rise to functionalized cyclotribenzylene (CTB) compounds, which in turn can be modified to provide the desired cryptophane derivatives, using the so-called *template* method. Thus, vanillin alcohol and its relative compounds have generally been used to build up functionalized CTB skeletons, allowing the preparation of cryptophane derivatives bearing six substituents located in the *ortho*-position of the three linkers.

To our knowledge, attempts to synthesize cryptophane derivatives bearing more than six substituents attached on the benzene rings have never been reported in the literature. This requires adding supplementary substituents in the *ortho*-position of the linkers connecting the two CTB caps. 3,4,5-Trimethoxybenzyl alcohol has been used in the past to prepare the 5*H*-tribenzo[*a*,*d*,*g*]cyclononene-10,15-dihydro-1,2,3,6,7,8,11,12,13-nonamethoxy derivative, a molecule congener of the well-known cyclotriveratrylene (CTV) derivative.[3] This compound has been the object of many studies, and it has been extensively studied by several spectroscopic techniques in its racemic or enantiopure forms.[4] Nevertheless, no cryptophane derivative derived from this interesting molecular platform has been reported in the literature. Syringyl alcohol, which possesses one phenol function and two methoxy groups located in the *meta*-postion of the benzylic alcohol function, can be envisaged to introduce three or six additional substituents on the benzene rings of cryptophanes.

In this article, we report the synthesis of a new modified cyclotrisyringyl (CTS) derivative, whose hydroxyl group has been replaced by an allyl moiety. The removal of this protecting group, followed by subsequent chemical transformations, gives access to the new cryptophane derivatives bearing nine (**1**, **2**) or twelve (**3**, **4**) methoxy substituents (Scheme 1). In contrast to cryptophane-A, where only the *anti*-diastereomer has been isolated, the synthesis of these new cryptophanes gives rise to the *anti*-(**1**, **3**) and *syn*-diastereomers (**2**, **4**). These cryptophanes have been fully characterized by several spectroscopic techniques, and their X-ray structures have been determined to provide an unambiguous determination of their stereochemistry.

RESULTS AND DISCUSSION

Synthesis of Cyclotrisyringyl (CTS) and Cyclotetrasyringyl (CTTS) Derivatives. The commercially available 3,5-dimethoxy-4-hydroxy-benzylalcohol (syringyl alcohol, **5**) has been used as the starting material for the construction of

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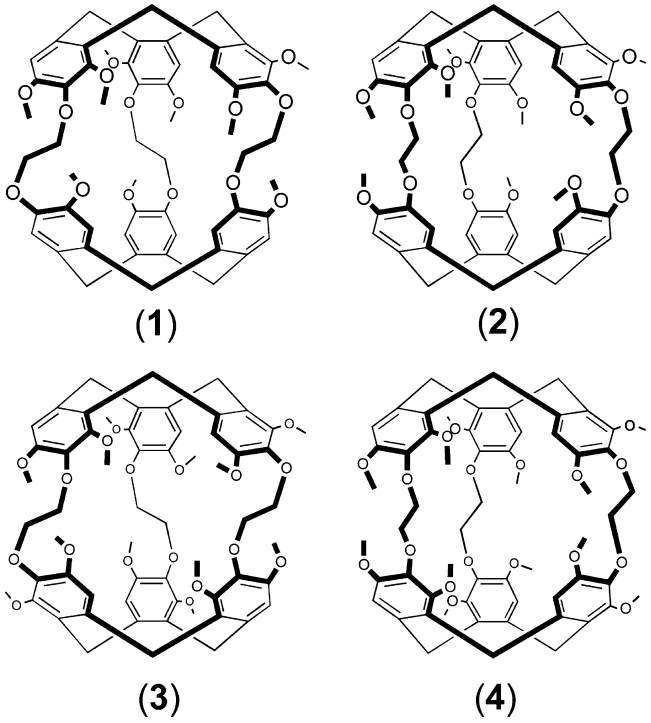
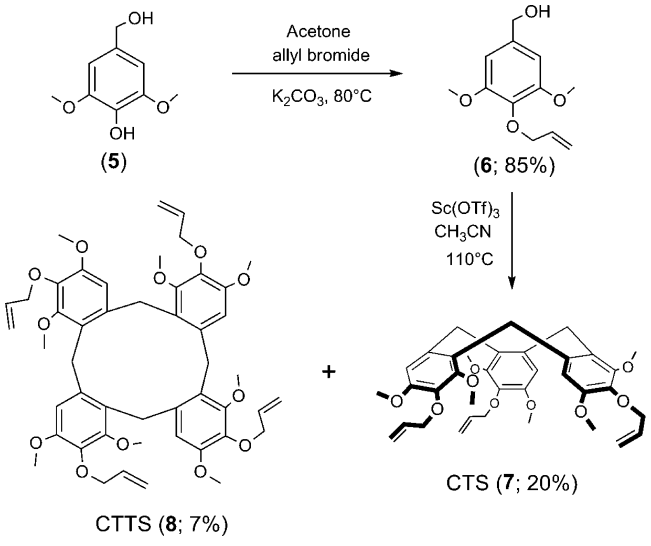
Scheme 1. Chemical Structure of *anti*-(1, 3) and *syn*-Diastereomers (2, 4) of Cryptophanes Bearing Nine and Twelve Methoxy Substituents



compounds **1**−**4**. Protection of the phenol moiety with an allyl group gives rise to the benzyl alcohol derivative (**6**).[5] This compound, isolated as a pale yellow solid (mp 47−48 °C), was used to build up both the CTS skeleton and tentacles needed for the construction of the four cryptophane derivatives. In a first attempt to prepare the CTS derivative (**7**) from the autocondensation of **6**, this compound was allowed to react in an $HClO_4$/MeOH mixture as a solvent. These experimental conditions are the usual ones to prepare the functionalized cyclotribenzylene (CTB) derivative needed for the construction of cryptophane-A via the so-called *template* method.[6] Unfortunately, this reaction resulted in an oily residue with no detectable amount of the desired product. Tin tetrachloride, a Lewis acid used to promote the formation of the nonamethoxy-cyclotriveratrylene,[3b] also failed to give rise to the expected cyclotrisyringyl (CTS) derivative. Then, the use of scandium triflate $Sc(OTf)_3$ has been considered because it has been employed in the past to prepare a large range of cyclotriveratrylene, hemicryptophane, or cryptophane derivatives in rather good yields.[7] We found that the reaction, performed with a catalytic amount of scandium triflate $Sc(OTf)_3$ (1%) in the presence of compound **6**, provided the expected CTS derivative (**7**) in moderate yield (Scheme 2). The best experimental conditions were found when acetonitrile was used as a solvent at a temperature of 110 °C. Under these conditions, the CTS derivative (**7**) was collected as a crystalline product with a 20% yield after purification. Performing the reaction at 60 °C led to a lower yield (11%) of **7**. A change of the solvent (dichloromethane or dimethylformamide) also resulted in lower yield (CH_2Cl_2, 2.6%) or the absence of a reaction (DMF).

An X-ray structure determination of compound **7** is reported in Figure 1. The crystals were obtained by slow evaporation of an ethyl acetate solution. This compound crystallizes in a

Scheme 2. Synthesis of CTS (7) and CTTS (8)



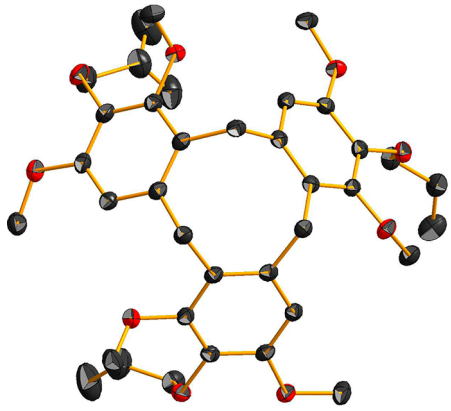


Figure 1. View of the structure of the CTS derivative with displacement ellipsoids plotted at the 30% probability level (hydrogen atoms were omitted for clarity).

triclinic $P\bar{1}$ space group with four molecules per unit cell (Supporting Information, S1). This X-ray structure is very similar to that previously reported by Salmon et al. for the (+,−)-5*H*-tribenzo[*a*,*d*,*g*]cyclononene-10,15-dihydro-1,2,3,6,7,8,11,12,13-nonamethoxy.[8] It is noteworthy that all the methoxy groups are not coplanar with benzene rings, and that the four CTS molecules present in the unit cell face each other to yield a very compact system with no possibility to accommodate solvent molecules (Supporting Information, S2).

The formation of **7** also resulted in the formation of a crystalline precipitate, whose ^1H NMR spectrum was found to be solvent-dependent and particularly difficult to interpret. The HRMS spectroscopy gives a peak of molecular mass $[M + H]^+$ m/z = 824.3776 that corresponds to the raw formula $C_{48}H_{57}O_{12}$. This result is in good agreement with the formation of the tetrabenzo[*a*,*d*,*g*,*j*]cyclododecene-5,10,15,20-tetrahydro-1,3,6,8,11,13,16,18-octamethoxy-2,7,12,17-tetrakis(allyloxy) derivative (CTTS, **8**) reported in Scheme 2. X-ray quality crystals allowed us to ascertain the chemical structure of compound **8** (vide infra). Even though the simultaneous formation of cyclotribenzylene and cyclotetrabenzylene derivatives has been previously observed in the past, the formation of compound **8** was not expected because, under similar experimental conditions, the 4-allyloxy-3-methoxybenzylalcohol in the

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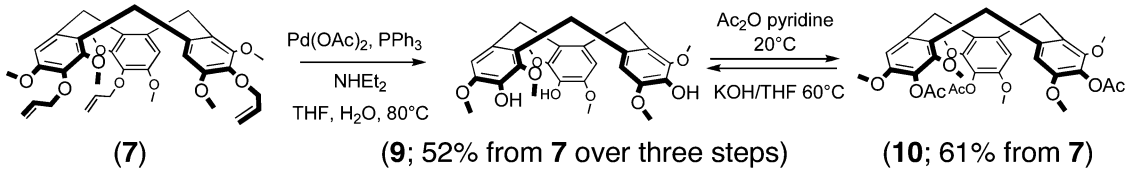
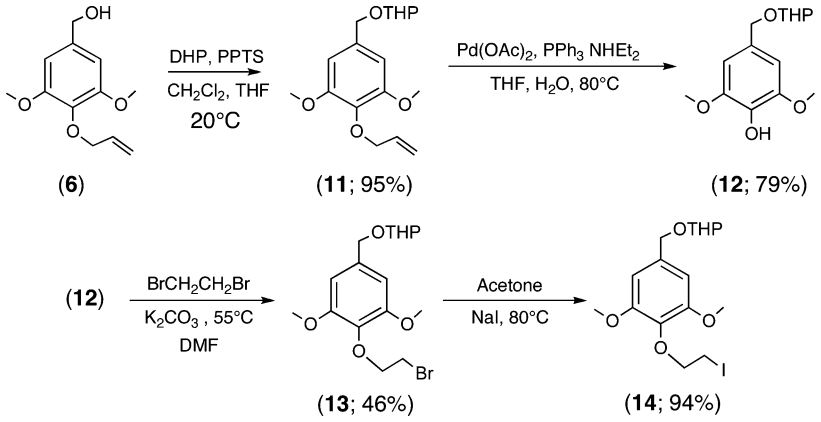
Scheme 3. Synthesis of the Tris-phenol CTS (9)



Scheme 4. Synthesis of Compound 14



presence of scandium triflate leads exclusively to the corresponding CTB derivative. The synthesis of compound **8** is interesting because only very few examples of cyclotetraveratrylene derivatives have been reported in the literature.[9] This new functionalized derivative represents a novel interesting chemical platform, and its characterization has been thoroughly examined in the last section of this article.

The deprotection of the three allyl moieties of compound **7** was then carried out using a palladium catalyst as previously described for its CTB congeners (Scheme 3). This reaction led to the tris-phenol derivative (**9**), which is very difficult to purify due to its extremely low solubility in organic solvents. An additional purification step has been necessary, consisting of the acylation of the three phenolic moieties with acetic anhydride in a CH_2Cl_2/pyridine mixture. Purification of the compound **10** was easily achieved by column chromatography on silica gel, and the tris-phenol derivative (**9**) was then recovered as a white solid with moderate yield (52%, from **7** over three steps) by hydrolysis in a KOH/H_2O/THF mixture. Compound **9** appears as an original chemical platform to design new cryptophane derivatives using the *template* approach.

Synthesis of *anti*- and *syn*-Diastereomers of Cryptophanes Bearing Nine and Twelve Methoxy Substituents. Compound **5** was also used to build up the tentacles needed for the construction of cryptophanes **1**−**4**. The benzylic alcohol function of **6** was first protected with a tetrahydropyranyl group to give rise to compound **11** in very good yield (95%). The introduction of this protecting group is necessary to facilitate the purification of cryptophane precursors on silica gel.[6] The removal of the allyl function was then performed using a palladium catalyst according to a procedure previously reported for the synthesis of functionalized CTB or cryptophane derivatives (Scheme 4).[10] This procedure gives rise to compound **12** in good yield (79%), which was then allowed to react with an excess of 1,2-dibromoethane to provide derivative **13** in moderate yield (46%).[11] Compound **14** was then obtained in quantitative yield by reacting compound **13** with an excess of sodium iodide in acetone.

All the compounds **6**−**14** have been fully characterized by ^{1}H NMR and ^{13}C NMR spectroscopy (Supporting Information, S3−S20), as well as elemental analysis. It is noteworthy that, in contrast to what is observed for **13**, the ^{1}H NMR spectrum of compound **14** displays an unusual ^{1}H NMR spectrum (Supporting Information, S19). Instead of the two triplet signals detected for the OCH_2 and the CH_2Br groups in compound **13**, a second-order AA′BB′ system is observed with compound **14**. This result is certainly associated with the loss of the free rotation around the CH_2−CH_2 bond when two bulky substituents are present on both sides of the ethylene group. Indeed, we have found (Supporting Information, S21−S23) that the potential barrier between the *trans* and the *gauche* conformations of the O−CH_2−CH_2−X (X = Br or X = I) side chain is significantly higher for compound **14** ($\Delta H \approx 17$ kJ/mol) than for compound **13** ($\Delta H \approx 8$ kJ/mol). This observation is important because it can explain our difficulties to easily interpret the ^{1}H NMR spectra of the cryptophane precursors described below.

From the different starting molecules described above and by using the so-called *template* method, we have prepared a series of cryptophane molecules bearing nine or twelve methoxy substituents. For instance, the cryptophane precursor **15** can be easily prepared in good yield (85%) by reacting the CTS derivative (**9**) with 3 equiv of compound **16**, as reported in Scheme 5. As is usually observed, compound **15** was obtained as a glassy product after purification and gives an ^{1}H NMR spectrum that is difficult to interpret (Supporting Information, S24). For instance, six singlet signals with different intensities can be observed in the methoxy region (4.2−3.6 ppm). The presence of these signals cannot be attributed to impurities because another purification step or a repetition of this experiment leads to the same ^{1}H NMR spectrum. Therefore, these signals indicate the presence of at least two conformers present in solution. Additional NMR signals in the aromatic region support this assumption.

Cryptophanes bearing nine substituents can also be prepared by reacting the tris-phenol CTB (**17**) with 3 equiv of

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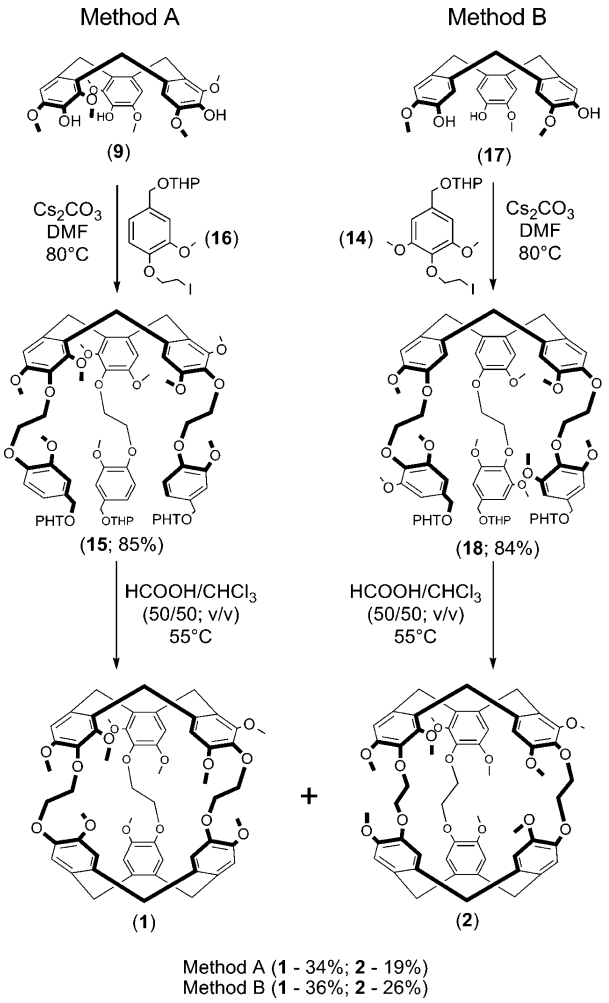
Scheme 5. Synthesis of Cryptophanes *anti*-1 and *syn*-2 Bearing Nine Methoxy Substituents

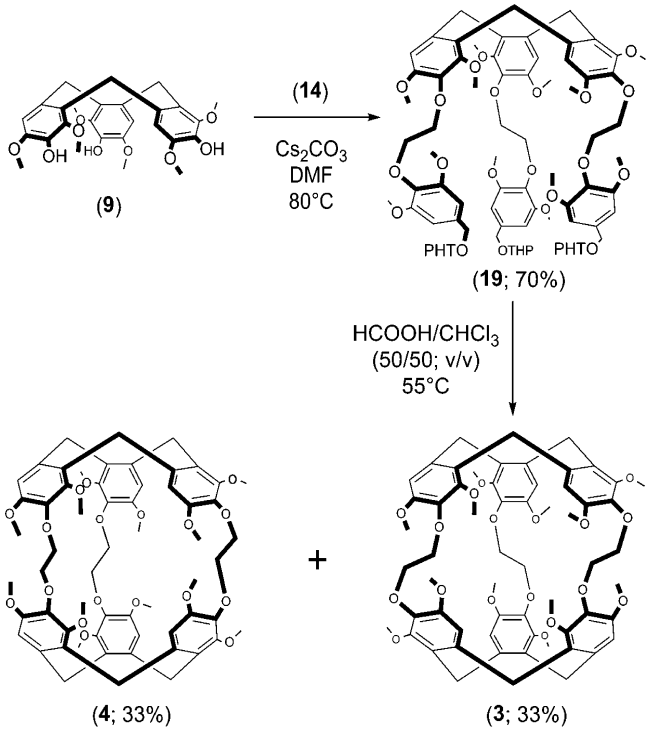


compound **14**, which gives rise to compound **18** in good yield (84%). The ^{1}H NMR spectrum of **18** can be more easily interpreted (Supporting Information, S26) because only a single major conformer is observed.

The cryptophane precursors (**15** and **18**) were then allowed to react in a mixture of chloroform/formic acid (50/50) according to the procedure previously described for the synthesis of cryptophane-A congeners.[12] Both routes A and B, described in Scheme 5, are expected to give rise to the same derivatives. A thin-layer chromatography (TLC) shows the presence of two major spots. The separation of these two derivatives on silica gel, followed by crystallization in a $CHCl_3$/ethanol mixture, led to two derivatives: **1** (34% route A, 36% route B) and **2** (19% route A, 26% route B). The ^{1}H and ^{13}C NMR spectra of these two derivatives are characteristic of the cryptophane backbone (Supporting Information, S28−S31). Indeed, the four AB systems of the two inequivalent caps are clearly visible in both cases. Moreover, the aromatic region displays three singlets compatible with the formation of a cryptophane derivative. The two derivatives, **1** and **2**, obtained from routes A and B, are consistent with the *anti*- and *syn*-diastereomers of this new cryptophane.[13] While the top and bottom cups differ with respect to their peripheral substituents, the *anti*- and *syn*-diastereomers are both chiral and possess a C_3 symmetry. The determination of their stereochemistry still arises, even though we previously noticed for cryptophane-C and -D that the *anti*-stereoisomer is always associated with the first eluted compound on silica gel (eluent: CH_2Cl_2/acetone).[14] In turn, the second spot visible on TLC was associated with the *syn*-stereoisomer. The determination of the stereochemistry of compounds **1** and **2** will be discussed in details in the following section.

The reaction of the CTS derivative (**9**) with 3 equiv of compound **14** leads to the cryptophane precursor (**19**) in good yield (70%), as reported in Scheme 6. As observed for

Scheme 6. Synthesis of Cryptophanes *anti*-3 and *syn*-4 Bearing Twelve Methoxy Substituents



compound **15**, additional signals are present in the methoxy region (4.2−3.6 ppm) of the ^{1}H NMR spectrum of compound **19** (Supporting Information, S32). Once again, these signals cannot be attributed to impurities because an additional purification step or a repetition of this experiment leaves the ^{1}H NMR spectrum unchanged and are certainly due to different conformations of compound **19** in solution.

Reacting compound **19** in a mixture of $CHCl_3$/formic acid leads to a crude product, whose TLC layer is dominated by two spots having the same intensities. Thus, the purification by column chromatography, followed by a recrystallization step in $CHCl_3$/ethanol, gives rise to two compounds having the characteristics of a cryptophane (Supporting Information, S34−S37). This result indicates that, as previously observed for compounds **15** and **18**, the reaction of **19** carried out under acidic condition gives rise to the two diastereomers *anti*-**3** and *syn*-**4** in similar quantities (33%). The *syn*-stereoisomer **4** is achiral with C_{3h} symmetry, whereas the *anti*-stereisomer **3** is chiral possessing D_3 symmetry. At this stage, the identification of the two spots is still incomplete and further investigations are necessary to ascertain the stereochemistry of these two compounds.

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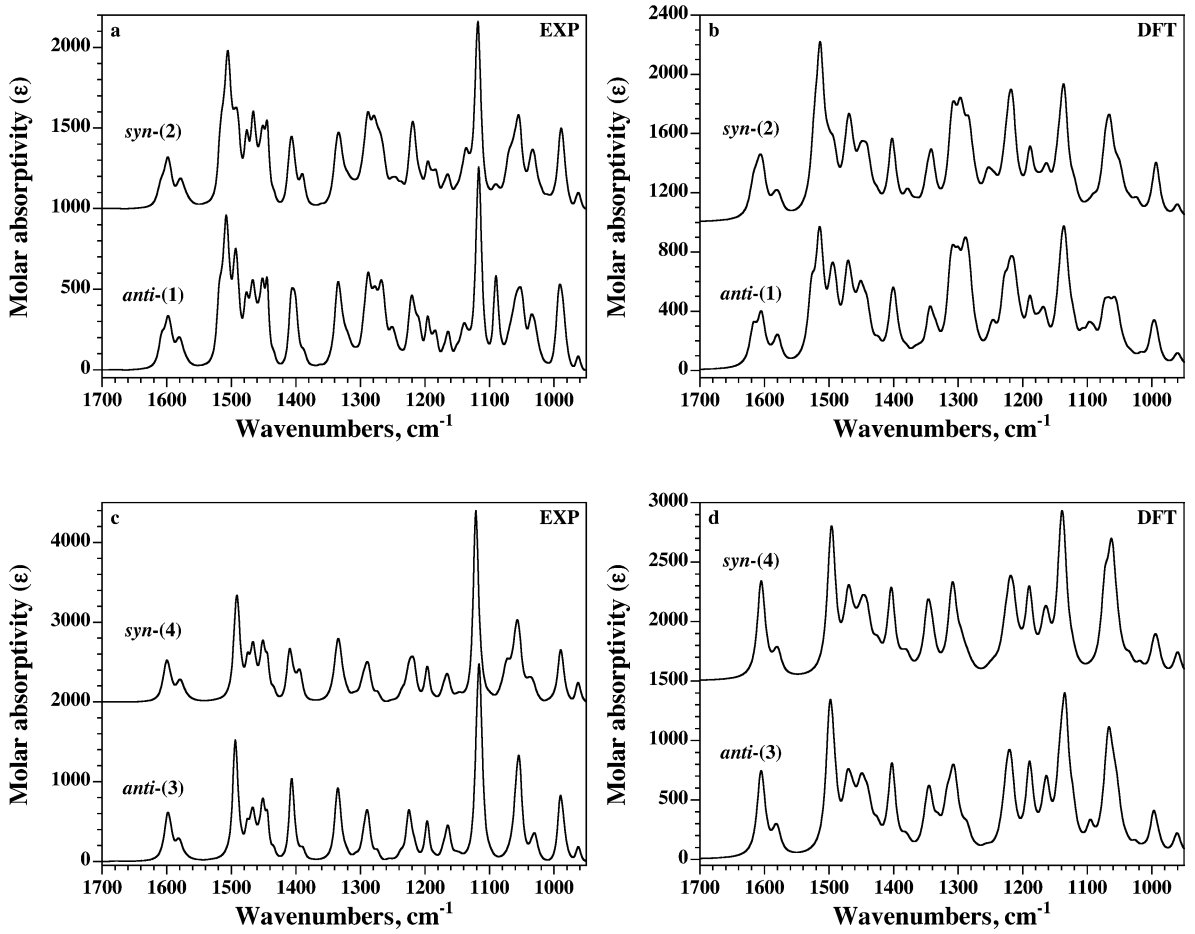

Figure 2. Experimental IR spectra of (a) *anti*-**1** and *syn*-**2** and (c) *anti*-**3** and *syn*-**4** in $CDCl_3$ solution (15 mM, 250 μm path length). Calculated IR spectra of (b) *anti*-**1** and *syn*-**2** and (d) *anti*-**3** and *syn*-**4** at the B3PW91/6-31G** level for the *GTT* conformation of the dioxyethylene linkers.

It is noteworthy that the HRMS spectrum of cryptophane precursor **19** shows the formation of the cryptophanes **3** and **4**. Indeed, the expected molecular peak $[M + Na]^+$ m/z = 1403.6 of **19** is also accompanied with an additional peak at m/z = 1075.4, corresponding to compounds **3** and **4**. The formation of cryptophane derivatives from their precursors has already been observed in the past and seems to occur in the liquid matrix before desorption.[15]

Determination of the Stereochemistry of Compounds 1−4. Additional experiments have been performed to assign unambiguously the stereochemistry of the four cryptophanes **1**−**4**. First, infrared (IR) spectroscopy has been used to identify cryptophanes **1**−**4**. Infrared spectroscopy may provide pertinent information on the stereochemistry because this technique is sensitive to the conformation of alkyl chains.

The IR spectra of *anti*- and *syn*-diastereomers of cryptophane bearing nine and twelve methoxy substituents are reported in Figure 2a,c, respectively. These experimental IR spectra are compared with those calculated at the B3PW91/6-31G** level for the *GTT* conformation of the dioxyethylene linkers (Figure 2b,d). The DFT calculations have been performed for this conformation of the linkers because we have shown, in previous articles,[16] that cryptophane-A derivatives exhibit a preferential *gauche, trans, trans* (*GTT*) conformation of the dioxyethylene linkers in $CDCl_3$ solution. Moreover, it is noteworthy that the IR spectrum of *anti*-**1** bearing nine methoxy substituents is approximately the half-sum of the IR spectra of *anti*-cryptophane-A and *anti*-**3**, bearing six and twelve methoxy substituents, respectively (Supporting Information, S38). This feature indicates that the conformation of the dioxyethylene linkers seems to be unmodified by the number of methoxy substituents attached on the benzene rings. On the whole, the calculated spectra for all the diastereomers reproduce, with a rather good agreement, the corresponding spectra measured experimentally.

The experimental IR spectra of *anti*-**1** and *syn*-**2** diastereomers exhibit small spectral differences in the 1700−900 cm^{-1} spectral range (see Figure 2a). These spectral modifications concern an increase in the intensity for the 1607 (shoulder), 1493, 1267, and 1090 cm^{-1} bands for the *anti*-diastereomer and of the 1390 cm^{-1} band for the *syn*-diastereomer. All of these modifications are perfectly reproduced by the DFT calculations (Figure 2b), allowing the discrimination between the two diastereomers of cryptophane bearing nine methoxy substituents using IR spectroscopy. On the other hand, no significant spectral changes have been observed in the experimental IR spectra of *anti*-**3** and *syn*-**4** diastereomers (Figure 2c). The IR spectra calculated for these two diastereomers confirm that no spectral modification was expected (Figure 2d). Thus, it is not possible to differentiate the two diastereomers of cryptophane bearing twelve methoxy substituents using IR spectroscopy.

Considering that the IR spectroscopy reveals very low (or no) spectral modifications for the two diastereomers of cryptophanes bearing nine (or twelve) methoxy substituents, single crystals of the four compounds have been prepared to determine their structure by X-ray crystallography. X-ray quality

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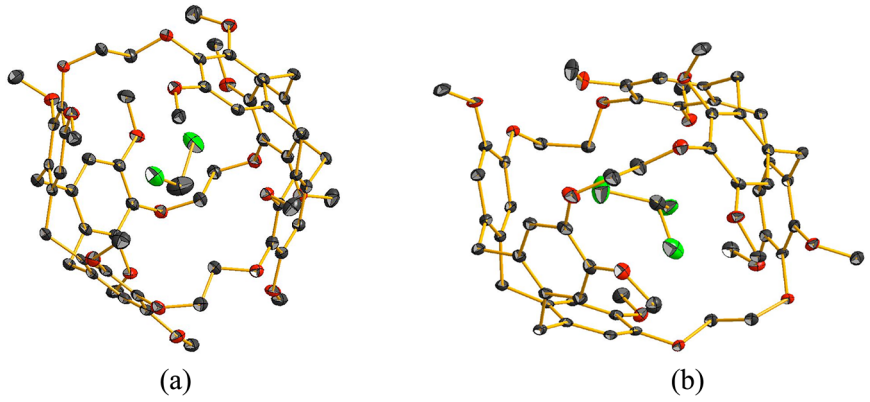

Figure 3. View of the structures of (a) CH_2Cl_2@*anti*-**1** and (b) $CHCl_3$@*syn*-**2** complexes with displacement ellipsoids plotted at the 30% probability level (hydrogen atoms have been removed for clarity).

crystals can be obtained from crystallization of compounds **1**−**4** in chloroform−ethanol or dichloromethane−ethanol mixtures. Thus, X-ray single crystals have been obtained for compounds **1** and **2** (Figure 3a,b), allowing the assignment of their stereochemistry. The *anti*-stereoisomer was assigned to compound **1** (i.e., first eluted compound) and the *syn*-stereoisomer to the less soluble compound **2** (i.e., second eluted compound). Single crystals of *anti*-**1** were obtained from a CH_2Cl_2/EtOH mixture, giving rise to block colorless crystals. This compound crystallizes in a monoclinic $P2_{1/c}$ space group, with four molecules per unit cell (Supporting Information, S1). Each molecule present in the lattice contains a CH_2Cl_2 molecule filling the cavity (Supporting Information, S39). The *syn*-diastereomer was crystallized in a $CHCl_3$/EtOH mixture to give rise to plate colorless crystals. This compound crystallizes in a monoclinic $P2_{1/n}$ space group with four molecules per unit cell (Supporting Information, S1). The X-ray crystals show the presence of $CHCl_3$ molecules filling the cavities of cryptophanes and the presence of interstitial $CHCl_3$ molecules located between cryptophanes (Supporting Information, S40).

Good quality single-crystals were more difficult to obtain with the highly substituted cryptophane derivatives **3** and **4**. Indeed, compound **3** leads to the formation of thin hexagonal-plate crystals by slow evaporation of a $CHCl_3$/EtOH mixture. Unfortunately, these crystals had a very low diffracting power, and the diffraction spots showed that their mosaicity was quite high. We were able to determine that **3** crystallizes in the $R\bar{3}$ space group with cell parameters $a = b = 45.8526(9)$ Å and $c = 32.4239(6)$ Å, but we were unable to solve its structure. Hopefully, the X-ray determination of compound **4** was made possible thanks to the formation of quality crystals in a CH_2Cl_2/EtOH mixture (Figure 4). This compound crystallizes in the triclinic $P\bar{1}$ space group with two cryptophane molecules per unit cell (Supporting Information, S1). This structure allows the assignment of the stereochemistry of compound **4** as the *syn*-diastereomer (Supporting Information, S41). In turn, the assignment of cryptophane **3** can be easily deduced and corresponds to the *anti*-diastereomer.

Characterization of the Cyclotetrasyringyl Derivative (8). As mentioned above, the synthesis of the CTS derivative (**7**) also results in the formation in small quantities of the cyclotetrasyringylic (CTTS) derivative (**8**). Only a few parent molecules of this compound have been reported in the literature.[9] The cyclotetraveratrylene (CTTV) derivative, bearing eight methoxy substituents, is the best-known example,

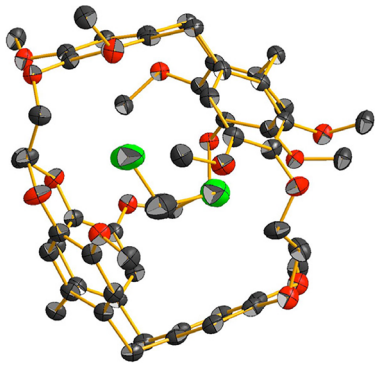

Figure 4. View of the structure of CH_2Cl_2@*syn*-**4** diastereomer with displacement ellipsoids plotted at the 30% probability level (hydrogen atoms have been removed for clarity).

and it has been thoroughly investigated in the past. This compound attracted attention because it can adopt several conformations in solution. Thus, it has been clearly established that the CTTV molecule and its derivatives exist under two main conformations: a C_{2h} symmetry "sofa" conformation and a C_{2v} symmetry "boat" conformation. In contrast, the concave "crown" conformation was never detected in solution because it is postulated to be unstable due to steric hindrances between the aromatic rings.

The characterization of compound **8** by NMR spectroscopy is not easy as the ^{1}H NMR spectra were found to be solvent-dependent. In $CDCl_3$ solution, the ^{1}H NMR spectrum reveals four singlets in the methoxy region and the presence of two independent sets of signals corresponding to the allyl moieties (Supporting Information, S7). These features indicates that only one main conformation of the CTTS molecule is present in $CDCl_3$ solution. White and Gesner also reported a major conformation for the CTTV derivative, which was consistent with the "sofa" conformation.[9b] On the other hand, in DMSO solution,[17] the ^{1}H NMR spectrum of **8** is more complex (Supporting Information, S42). Indeed, it reveals eight singlets in the methoxy region, as well as the presence of additional signals in the aromatic region of the spectrum. This result suggests the presence of at least two different conformations in slow exchange. To obtain information on the most favorable conformation of CTTS (**8**) in the solid state, single crystals were prepared from AcOEt solution. The structure reported in Figure 5 reveals that compound **8** crystallizes in the triclinic $P\bar{1}$ space group (Supporting Information, S1) with two independ-

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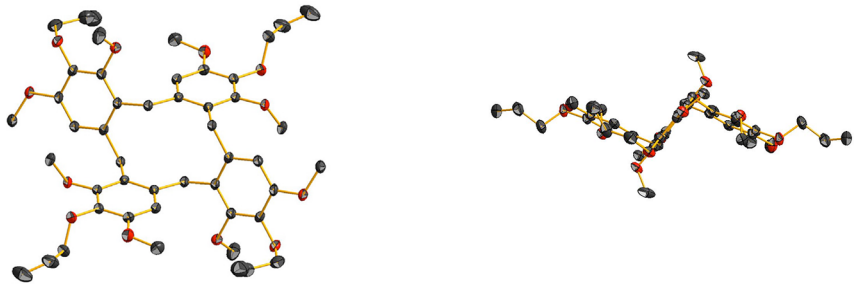

Figure 5. Two different views of the structure of CTTS (**8**) in the "sofa" conformation with displacement ellipsoids plotted at the 30% probability level (hydrogen atoms have been removed for clarity).

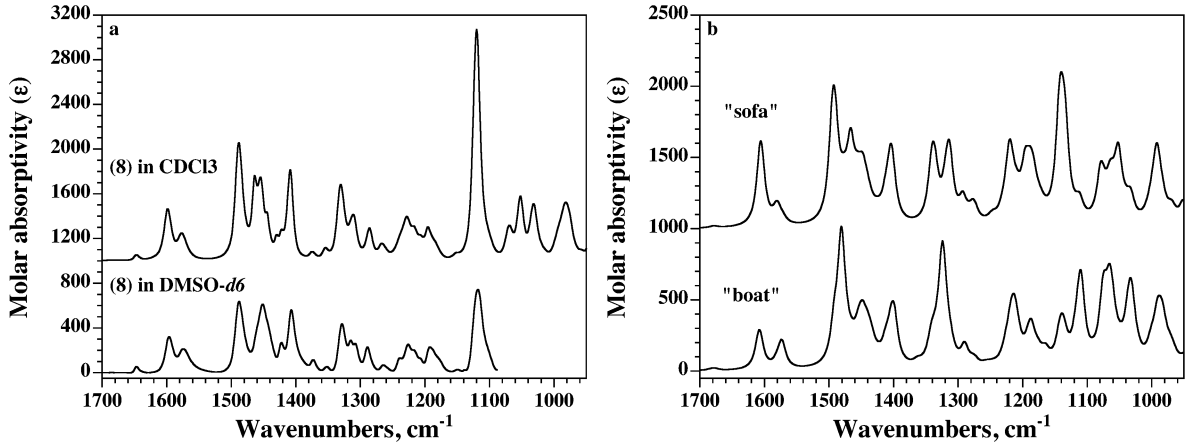

Figure 6. (a) Experimental IR spectra of **8** in $CDCl_3$ and DMSO-d_6 solutions (50 mM, 100 μm path length). (b) Calculated IR spectra of **8** at the B3PW91/6-31G** level for the "sofa" and "boat" conformations.

ent molecules in the lattice (Supporting Information, S43). As shown in Figure 5, CTTS (**8**) adopts the "sofa" conformation in the solid state, which is also the privileged conformation observed for CTTV derivatives in their crystalline state.[9f]

In order to confirm that the "sofa" conformation corresponds to the main conformation observed in $CDCl_3$ solution, IR spectroscopy and DFT calculations have been performed. The IR spectra of **8** in $CDCl_3$ and DMSO-d_6 solutions are reported in Figure 6a. For the DMSO-d_6 solution, the IR spectrum is not presented in the 950−1080 cm^{-1} region, due to the strong absorptions of the solvent in this spectral range. As shown in Figure 6a, noticeable differences are observed between the two IR spectra, in particular for the bands located at 1599 cm^{-1}, assigned to the νC=C vibration of aromatic rings, and at 1120 cm^{-1}, assigned to the νC−O vibration of the methoxy groups coupled with the rocking $r_{//}CH_3$. Indeed, the intensities of these two bands are significantly lower in the IR spectrum recorded in DMSO-d_6 solution. To interpret these spectral differences, the IR spectrum of **8** has been calculated at the B3PW91/6-31G** level for the "sofa" and "boat" conformations (Figure 6b). It is clear from these DFT calculations that the 1599 and 1120 cm^{-1} bands display higher intensities for the "sofa" conformation. Therefore, we conclude that the CTTS derivative exhibits a preferential "sofa" conformation in $CDCl_3$ solution, whereas the contribution of the "boat" conformation is relatively important in DMSO-d_6 solution.

CONCLUSION

We have reported in this article the synthesis of highly substituted cryptophanes **1**−**4** bearing nine and twelve methoxy substituents on the benzene rings. Both *anti*-(**1** and **3**) and *syn*-(**2** and **4**) diastereomers have been isolated. This result contrasts with the synthesis of cryptophane-A for which only the *anti*-diastereomer has been isolated. The stereochemistry of compounds **1**−**4** has been unambiguously determined thanks to the determination of the X-ray structures of cryptophanes **1**, **2**, and **4**. These new derivatives represent interesting new molecular hosts for xenon encapsulation and MRI application in biological media.[27] Indeed, the presence of additional methoxy substituents on the aromatic rings give us the opportunity to introduce, after suitable chemical transformations, additional functional groups to improve the solubility of the cryptophane backbone.

To obtain cryptophanes **1**−**4**, we have synthesized the new functionalized cyclotrisyringyl derivative (**7**) by autocondensation of a protected syringyl benzyl alcohol in the presence of a catalytic amount of scandium triflate. This compound represents a new chemical platform to build up highly substituted cryptophane derivatives. The formation of **7** was also accompanied by the presence a crystalline compound obtained in low yield, which has been identified as the corresponding tetracyclosyringyl CTTS derivative (**8**).

EXPERIMENTAL SECTION

General Information. ^1H NMR spectra were recorded at 500 MHz using a 5 mm liquid probe (nonspinning). ^{13}C NMR spectra were recorded at 126.7 MHz on the same apparatus. Melting points were measured with temperature step (5 °C/min). Column chromatographic separation was carried out over Acrös organic silica gel 60 (0.035−0.070 mm). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel TLC plates F254. The high- and low-resolution mass spectra were recorded in a positive and/or negative ion mode on a hybrid quadrupole time-of-flight mass

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spectrometer with an electrospray ionization (ESI) ion source. The gas flow of the spray gas is 0.6 bar, and the capillary voltage is 4−5 kV. The solutions are infused at 180 μL/h. The masse range of the analysis is 50−3000 *m*/*z*, and the calibration was done with tuneMix.

Single-Crystal X-ray Diffraction. Suitable crystals were selected and mounted on a Gemini kappa-geometry diffractometer equipped with an Atlas CCD detector and using Cu radiation (λ = 1.5416 Å). Intensities were collected at low temperature using the CrysalisPro software.[18] Reflection indexing, unit-cell-parameters refinement, Lorentz-polarization correction, peak integration, and background determination were carried out with the CrysalisPro software.[18] An analytical absorption correction was applied using the modeled faces of the crystal.[19] The structures were solved by direct methods with SIR97,[20] and the least-squares refinement on F^2 was achieved with the CRYSTALS software.[21] 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) 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.

IR Measurements. IR spectra were recorded with an FTIR spectrometer at a resolution of 4 cm^{-1}. Samples were held in a variable path length cell with BaF_2 windows. IR spectra of cryptophanes **1**−**4** were measured in $CDCl_3$ solvent at a concentration of 15 mM and at a path length of 250 μm. IR spectra of CTTS derivative **8** were measured in $CDCl_3$ and DMSO-d_6 solvents at a concentration of 50 mM and at a path length of 100 μm. In the presented absorption spectra, the solvent absorption was subtracted out.

Theoretical Calculations. The calculation of the IR spectra of **8** for the "sofa" and "boat" conformations began with a thorough analysis of the conformational freedom of the methoxy and allyl substituents of the CTTS molecule. This involved exploring the entire conformational energy surface of the molecule for the two "sofa" and "boat" conformations and carrying out semiempirical RM1[22] calculations with the simulated annealing technique,[23] as both are implemented in the package Ampac,[24] of the relative energies of conformers found in the various local minima of this surface. The search for energetic minima was performed in two stages: (i) a nonlocal search focused on 56 dihedral angles corresponding to methoxy and allyl groups, and (ii) a local energetic relaxation of the whole degrees of freedom, for each of the minima collected at stage (i). All conformers within roughly 3 kcal/mol of the lowest energy conformer were kept for further DFT calculations.

The geometry optimizations, vibrational frequencies, and absorption intensities were calculated by the Gaussian 09 program[25] on the DELL cluster of the MCIA computing center of the University Bordeaux I. Calculations of the optimized geometry of 10 conformers of both the "sofa" and "boat" conformations of **8** were performed at the density functional theory level using the B3PW91 functional and 6-31G** basis set. Vibrational frequencies and IR intensities were calculated at the same level of theory for the isolated molecule in vacuo. For comparison to experiment, the calculated frequencies were scaled by 0.968, and the calculated intensities were converted to Lorentzian bands with a half-width of 7 cm^{-1}. For the cryptophanes **1**−**4**, calculations were performed at the density functional theory level using the B3PW91 functional and 6-31G** basis set, considering the *GTT* conformations of the dioxyethylene linkers.

Synthesis of Benzenemethanol, 3,5-dimethoxy-4-(2-propenyloxy) (6). Allyl bromide (15.3 mL, 177 mmol, 1.3 equiv) was added in one portion to a stirred mixture of **5** (25 g, 136 mmol) and potassium cabonate (18.8 g, 136 mmol) in acetone (100 mL). The mixture was stirred for 16 h under an argon atmosphere at 80 °C. Then, the solvent was removed under an argon atmosphere. AcOEt and water were added to the solid residue. The product was extracted three times with AcOEt. The combined extracted layers were then washed two times with brine and dried over Na_2SO_4. Evaporation of the solvent gives rise to a residue, which was purified by column chromatography on silica gel (AcOEt/petroleum ether: 50/50). The second spot was collected, and evaporation of the solvent gives rise to an oily product, which rapidly recrystallizes as a pale yellow solid (26g, 85%): mp 237−238 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.56 (s, 2H), 6.07 (m, 1H), 5.21 (m, 2H), 4.60 (m, 2H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.825 (s, 6H), 1.77 (t, *J* = 6.0 Hz, 1H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 153.4, 136.7, 135.6, 134.4, 117.7, 103.7, 74.1, 65.3, 55.95. Anal. Calcd for $C_{12}H_{16}O_4$ (224.2560): C, 64.27; H, 7.19. Found: C, 64.00; H, 7.38.

Synthesis of 5*H*-Tribenzo[*a,d,g*]cyclononene-10,15-dihydro-1,3,6,8,11,13-hexamethoxy-2,7,12-triallyloxy (7). Scandium triflate (0.22 g, 0.45 mmol) was added in one portion to a solution of **6** (10.0 g, 44.6 mmol) in acetonitrile (40 mL). The solution was stirred and heated at 110 °C for 16 h. The white crystalline compound (0.61g, 7%), corresponding to the tetrabenzo[*a,d,g,j*]cyclododecene-5,10,15,20-tetrahydro-1,3,6,8,11,13,16,18-octamethoxy-2,7,12,17-tetrakis(allyloxy) **8** derivative, was isolated by suction filtration and washed several times with diethyl ether: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.91 (s, 2H), 6.10 (m, 2H), 6.03 (m, 2H), 5.90 (s, 2H), 5.30−5.10 (m, 8H), 4.55 (m, 4H), 4.37 (m, 4H), 4.03 (d, *J* = 10.0 Hz, 2H), 3.95 (s, 6H), 3.87 (d, *J* = 10.0 Hz, 2H), 3.77 (s, 6H), 3.66 (d, *J* = 10.0 Hz, 2H), 3.63 (d, *J* = 10.0 Hz, 2H), 3.52 (s, 6H), 3.10 (s, 6H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 153.0, 152.75, 151.9, 151.55, 139.4, 138.1, 137.2, 135.6, 134.4, 134.35, 124.9, 123.7, 117.5, 117.1, 112.1, 105.5, 73.9, 73.7, 61.4, 59.7, 55.9, 55.5, 33.13, 27.6. Anal. Calcd for $C_{48}H_{56}O_{12}$ (824,9632): C, 69.90; H, 6.84. Found: C, 69.70; H, 6.89. HRMS calcd for $C_{48}H_{57}O_{12}$ $[M + H]^+$ 825.3845, found 825.3847.

The solvent of the filtrate was then removed under reduced pressure to leave a dark residue. CH_2Cl_2 and water were added, and the product was extracted three times with CH_2Cl_2. Then, the combined organic layers were washed two times with brine and dried over Na_2SO_4. Filtration followed by evaporation of the solvent under reduced pressure leaves a dark residue. Purification by column chromatography on silica gel (AcOEt/petroleum ether: 10/90, *L* = 22 cm) gives rise to a white crystalline compound (1.8 g, 20%), which was identified as compound **7**: mp 163−164 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.2 (s, 3H), 6.06 (m, 3H), 5.2 (m, 6H), 4.385 (d, *J* = 15.0 Hz, 3H, H_a and m, 6H), 4.0 (d, *J* = 15.0 Hz, 3H; H_e), 3.96 (s, 9H), 3.77 (s, 9H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 151.7, 151.6, 139.2, 136.3, 134.65, 125.5, 116.85, 110.2, 74.0, 60.7, 55.7, 30.0. Anal. Calcd for $C_{36}H_{42}O_9$ (618,7224): C, 69.89; H, 6.84. Found: C, 70.0; H, 7.01.

Synthesis of 5*H*-Tribenzo[*a,d,g*]cyclononene-2,7,12-triol,10,15-dihydro-1,3,6,8,11,13-hexamethoxy (9). In a three-neck flask, a solution containing compound **7** (3.57 g, 5.8 mmol), triphenylphosphine (0.3 g, 1.14 mmol), diethylamine (30 mL), palladium acetate (0.128 g, 0.57 mmol), water (15 mL), and THF (80 mL) was stirred and warmed to 80 °C under an argon atmosphere for 4 h. During the reaction, a white precipitate is formed and the solution takes a green color. The THF and diethylamine were removed under reduced pressure. CH_2Cl_2 and water were added to the mixture to give three phases (a very insoluble solid compound, the aqueous, and the organic phases). The solid was then collected on a frit by suction filtration. This solid (3.0 g) was washed successively with water, acetone, and CH_2Cl_2 and dried in air. This solid contains the expected derivative **9**, but it requires an additional purification step. Thus, this solid was placed in a 100 mL flask. Pyridine (40 mL) was added to the solid under an argon atmosphere and cooled to 0 °C. At this temperature, acetic anhydride (10 mL) was added dropwise via syringe, and then the mixture was allowed to reach room temperature. After 3 h, the dark solution was poured in a flask containing CH_2Cl_2 and water. The product was extracted three times with CH_2Cl_2, and the organic phase was separated from the remaining solid residue by filtration over filter paper. The organic layer was dried over Na_2SO_4. After filtration, the solvents (CH_2Cl_2 and pyridine) were removed under reduced pressure to give an oily product that rapidly solidifies. This solid was washed several times with AcOEt on a frit to give 5*H*-tribenzo[*a,d,g*]cyclononene-2,7,12-triol,10,15-dihydro-1,3,6,8,11,13-hexamethoxy-2,7,12-triacetate (**10**) (2.2 g, 61%) as a white crystalline compound: mp 197−198 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.2 (s, 3H), 4.4 (d, *J* = 13.7 Hz, H_a), 4.05 (d, *J* = 13.7 Hz, H_e), 3.9 (s, 9H), 3.75 (s, 9H), 2.3 (s, 9H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C)

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δ 168.75, 150.6, 150.2, 138.6, 131.45, 125.2, 110.5, 60.85, 56.0, 30.1, 20.6; Anal. Calcd for $C_{33}H_{36}O_{12}$ + 0.5 H_2O (633,6478): C, 62.55; H, 5.89. Found: C, 62.43; H 5.82. These data are identical to those reported in the literature.[26]

Compound **9** was recovered by reacting derivative **10** (2.3 g, 3.7 mmol) in a mixture of KOH/H_2O (30 mL, 0.5 M) and THF (20 mL). The solution was heated at 60 °C for 16 h under an argon atmosphere. Then, the THF was removed under reduced pressure, and CH_2Cl_2 was added to the aqueous solution. The aqueous solution was acidified, and the solid residue corresponding to the expected product was collected on a frit. To remove the sticky solid from the walls of the glassware, THF and diethyl ether were added. This operation was also applied to the solid present on the frit to give a thin white powder (1.6 g), which was identified by NMR spectroscopy as compound **9**. This solid was then introduced in a 100 mL flask to the presence of CH_2Cl_2 (15 mL), THF (15 mL), and acetone (5 mL). The mixture was stirred at room temperature for 2 days. Filtration on a frit gives rise to compound **9** (1.5 g, 52% from compound **7**) as a white solid: mp (decomp.) ≈ 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 8.35 (s, 3H), 7.07 (s, 3H), 4.39 (d, *J* = 13.5 Hz, 3H), 3.83 (s, 9H), 3.81 (d, *J* = 13.5 Hz, 3H), 3.70 (s, 9H); ^{13}C NMR (126.7 MHz, DMSO-d_6, 25 °C) δ 146.6, 146.0, 137.4, 130.5, 125.9, 110.0, 59.55, 55.8, 29.1; Anal. Calcd for $C_{27}H_{30}O_9$ + 1.0 H_2O (516.5438): C, 62.78; H, 6.24. Found: C, 62.99; H 6.05.

Synthesis of 2-[4-(Allyloxy)-3,5-dimethoxybenzyloxy]tetrahydro-2*H*-pyran (11). PPTS (1,12 g, 4.46 mmol) in CH_2Cl_2 (10 mL) was added in one portion to a stirred solution of **6** (10.0 g, 44.6 mmol) and DHP (5.6 g, 66.6 mmol) in THF (100 mL). The solution was stirred for 16 h under an argon atmosphere at room temperature. Solvents were then removed under reduced pressure. Diethyl ether and water were added, and the product was extracted three times with diethyl ether. The combined organic layers were dried over Na_2SO_4. Filtration and evaporation of the solvent gives rise to an oily residue, which was purified by column chromatography on silica gel (Et_2O/petroleum ether: 50/50). Evaporation of the fractions gives an oily residue (13.0 g, 95%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.57 (s, 2H), 6.10 (m, 1H), 5.30−5.15 (m, 2H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.68 (m, 1H), 4.49 (m, 2H), 4.41 (d, *J* = 12.0 Hz, 1H), 3.91 (m, 1H), 3.83 (s, 6H), 3.54 (m, 1H), 1.90−1.40 (m, 6H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 153.3, 135.9, 134.5, 133.75, 117.55, 104.8, 97.7, 74.1, 69.0, 62.3, 56.0, 30.5, 25.4, 19.4; Anal. Calcd for $C_{17}H_{24}O_5^+$ 0.25 H_2O (312.8774): C, 65.5; H, 7.82. Found: C, 65.26; H, 7.89.

Synthesis of 2,6-Dimethoxy-4-((tetrahydro-2*H*-pyran-2-yloxy)methyl)phenol (12). A solution of compound **11** (12.3 g, 39.9 mmol), triphenylphosphine (1.05 g, 4.0 mmol), diethylamine (80 mL), and palladium acetate (0.44 g, 2.0 mmol) in a mixture of THF (200 mL) and water (40 mL) was stirred and heated to 80 °C under an argon atmosphere for 4 h. Rapidly, the solution turns black. The solvents (THF, $NHEt_2$) were removed under reduced pressure. Water and AcOEt were added, and the product was extracted three times with AcOEt. The combined organic layers were dried over Na_2SO_4, and the solvent was removed under reduced pressure. This leaves an oily residue, which was purified by column chromatography (AcOEt/petroleum ether: 70/30). Evaporation of the solvents gives rise to yellow oil, which solidifies upon cooling (8.5 g, 79%): mp 63 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.59 (s, 2H), 5.47 (s, 1H), 4.68 (d, *J* = 11.5 Hz, 1H), 4.66 (m, 1H), 4.41 (d, *J* = 11.5 Hz, 1H), 3.90 (m, 1H), 3.86 (s, 6H), 3.53 (m, 1H), 1.90−1.40 (m, 6H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 146.9, 134.1, 129.0, 104.9, 97.4, 69.1, 62.3, 56.2, 30.5, 25.4, 19.4; Anal. Calcd for $C_{14}H_{20}O_5$ (268,3090): C, 62.67; H, 7.45. Found: C, 62.89; H, 7.68.

Synthesis of 2-(4-(2-Bromoethoxy)-3,5-dimethoxybenzyloxy)tetrahydro-2*H*-pyran (13). 1,2-Dibromoethane (26.1 mL, 303 mmol) was added in one portion to a solution containing compound **12** (8.14 g, 30.3 mmol) and K_2CO_3 (20.7 g, 150 mmol) in dry DMF (80 mL). The mixture was stirred for 16 h at 60 °C under an argon atmosphere. Water and AcOEt were added to the mixture, and the desired product was extracted three times with AcOEt. Then, the combined organic layers were washed five times with water to remove the maximum amount of DMF. The organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure to give an oily residue. Purification on silica gel (AcOEt/petroleum ether: 70/30) gives the expected compound **13** (5.2 g, 46%) as an oily product: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.57 (s, 2H), 4.70 (d, *J* = 12.0 Hz, 1H), 4.68 (m, 1H), 4.41 (d, *J* = 12.0 Hz, 1H), 4.22 (t, *J* = 7.0 Hz, 2H), 3.91 (m, 1H), 3.89 (m, 6H), 3.57 (t, *J* = 7.0 Hz, 2H), 3.53 (m, 1H), 1.90−1.40 (m, 6H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 153.1, 135.5, 134.4, 104.7, 97.8, 72.5, 69.0, 62.3, 56.0, 30.55, 29.5, 25.4, 19.46; Anal. Calcd for $C_{16}H_{23}O_5Br$ (375,2587): C, 51.21; H, 6.18. Found: C, 50.88; H, 6.29. HRMS calcd for $C_{16}H_{23}BrO_5Na$ $[M + Na]^+$ 397.0621, found 397.0607.

Synthesis of 2-(4-(2-Iodoethoxy)-3,5-dimethoxybenzyloxy)-tetrahydro-2*H*-pyran (14). Sodium iodide (20.8 g, 139 mmol) was added in one portion to a stirred solution of compound **13** (5.2 g, 13.9 mmol) in dry acetone (60 mL). The mixture was stirred for 16 h at 80 °C under an argon atmosphere. The solvent was removed under reduced pressure. Water and Et_2O were added, and the product was extracted three times with Et_2O. The combined organic layers were dried over Na_2SO_4. Filtration and evaporation of the solvent gives rise to an oily residue, which was purified by column chromatography on silica gel (Et_2O/petroleum ether: 50/50). Evaporation of the fractions gives compound **14** (5.5 g, 94%) as an oily product: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 6.57 (s, 2H), 4.70 (d, *J* = 10.0 Hz, 1H), 4.67 (m, 1H), 4.41 (d, *J* = 10.0 Hz, 1H), 4.19 (m, 2H), 3.90 (m, 1H), 3.83 (s, 6H), 3.55 (m, 1H), 3.36 (m, 2H), 1.90−1.40 (m, 6H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 153.1, 135.3, 134.3, 104.7, 97.8, 73.5, 68.95, 62.3, 56.0, 30.5, 25.4, 19.4, 2.29; Anal. Calcd for $C_{16}H_{23}O_5I$ (422,2592): C, 45.51; H, 5.49. Found: C, 45.69; H, 5.73. HRMS calcd for $C_{16}H_{23}IO_5Na$ $[M + Na]^+$ 445.0482, found 445.0475.

Synthesis of Cryptophane Precursor (15). Compound **16**[10] (1.25 g, 3.6 mmol) was added in one portion to a stirred mixture of compound **9** (0.5 g, 1.0 mmol) and Cs_2CO_3 (1.30 g, 4.0 mmol) in dry DMF (10 mL). The mixture was heated at 80 °C for 16 h under an argon atmosphere. Then, the mixture was poured in water. The product was extracted three times with AcOEt. The combined extract layers were washed five times with brine and dried over Na_2SO_4. Filtration, followed by evaporation of the solvent under reduced pressure, leaves a residue, which was purified on silica gel (AcOEt/petroleum ether: 80/20). The second spot was collected, and an oily residue was obtained after evaporation of the solvent. A treatment with diethyl ether (several times), followed by evaporation of the solvent under reduced pressure, gives compound **15** (1.1 g, 85%) as a white glassy product: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (*main conformation*) δ 7.19 (s, 3H), 6.90−6.80 (m, 9H), 4.695 (d, *J* = 15.0 Hz, 3H), 4.66 (m, 3H), 4.415 (d, *J* = 15.0 Hz, 3H), 4.395 (d, *J* = 15.0 Hz, 3H), 4.30−4.19 (m, 12H), 4.015 (d, *J* = 15.0 Hz, 3H), 4.00 (s, 9H), 3.91 (m, 3H), 3.82 (s, 9H), 3.70 (s, 9H), 3.52 (m, 3H), 1.90−1.45 (m, 18H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) (*main conformation*) δ 151.8, 151.6, 149.5, 147.9, 139.1, 136.45, 131.2, 125.4, 120.5, 113.4, 112.0, 110.3, 97.6, 71.1, 68.8, 68.2, 62.3, 60.8, 55.9, 55.7, 30.6, 30.0, 25.4, 19.5; HRMS calcd for $C_{72}H_{90}NaO_{21}$ $[M + Na]^+$ 1313.5867, found 1313.5831.

Synthesis of Cryptophane Precursor (18). Compound **14** (1.69 g, 4.0 mmol) was added to a mixture of CTB (**17**)[10] (0.45 g, 1.1 mmol) and Cs_2CO_3 (1.45 g, 4.4 mmol) in dry DMF (18 mL). The mixture was heated at 80 °C for 16 h under an argon atmosphere. The solution was then poured into water. The product was extracted four times with AcOEt. The combined extract layers were washed five times with brine and dried over Na_2SO_4. Filtration, followed by evaporation of the solvent, leaves an oily residue, which was purified by column chromatography on silica gel (AcOEt/petroleum ether: 75/25 then AcOEt/petroleum ether: 90/10). The second spot was collected after the evaporation of the solvent leaves an oily residue. Treatment with diethyl ether (several times), followed by evaporation of the solvent under reduced pressure, gives compound **18** as a white glassy product (1.2 g, 84%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (*main conformation*) δ 6.95 (s, 3H), 6.79 (s, 3H), 6.55 (s, 6H), 4.725 (d, *J* = 15.0 Hz, 3H), 4.695 (d, *J*= 12.0 Hz, 3H), 4.67 (m, 3H), 4.405 (d, *J* = 12.0 Hz, 3H), 4.28 (m, 12H), 3.90 (m, 3H), 3.76 (s, 18H), 3.71 (s, 9H), 3.53 (m, 3H), 3.505 (d, *J* = 15.0 Hz, 3H), 1.90−1.45 (m, 18H);

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^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) (*main conformation*) δ 153.2, 148.25, 147.0, 136.2, 134.0, 132.4, 131.7, 115.85, 113.8, 104.8, 97.8, 71.1, 69.05, 68.15, 62.35, 56.2, 56.0, 36.5, 30.6, 25.4, 19.5; HRMS calcd for $C_{72}H_{90}NaO_{21}$ $[M + Na]^+$ 1313.5867, found 1313.5830.

Synthesis of Cryptophane Precursor (19). In a three-neck flask, compound **14** (2.06 g, 4.9 mmol) was added in one portion to a mixture of compound **9** (0.67 g, 1.3 mmol) and Cs_2CO_3 (1.74 g, 5.4 mmol) in dry DMF (25 mL). The mixture was heated at 80 °C for 16 h under an argon atmosphere. The mixture was then poured into water, and the product was extracted four times with AcOEt. The combined organic layers were washed fives times with brine and then dried over Na_2SO_4. Filtration, followed by evaporation of the solvent under reduced pressure, leaves an oily residue. Purification on silica gel (AcOEt/petroleum ether: 75/25) gives rise to compound **19** as an oily product. Addition of diethyl ether (this operation was repeated several times), followed by evaporation of the solvent under reduced pressure, gives compound **19** as a white glassy product (1.25 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) (*main conformation*) δ 7.18 (s, 3H), 6.55 (s, 6H), 4.695 (d, *J* = 12.0 Hz, 3H), 4.67 (m, 3H), 4.40 (d, *J* = 12.0 Hz, 3H), 4.385 (d, *J* = 13.5 Hz, 3H), 4.20 (m, 12H), 4.015 (d, *J* = 13.5 Hz, 3H), 4.00 (s, 9H), 3.90 (m, 3H), 3.80 (s, 3H), 3.77 (s, 9H), 3.76 (s, 9H), 3.72 (s, 3H), 3.71 (s, 3H), 3.54 (m, 3H), 1.90−1.45 (m, 18H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) (*main conformation*) δ 153.3, 151.6, 151.55, 139.5, 136.77, 136.2, 133.6, 125.4, 110.3, 105.1, 97.8, 72.0, 71.9, 69.1, 62.3, 60.8, 56.1, 55.7, 30.6, 30.0, 25.4, 19.5; HRMS calcd for $C_{75}H_{96}NaO_{24}$ $[M + Na]^+$ 1403.6184, found 1403.6149.

Synthesis of Cryptophanes *anti*-1 and *syn*-2 (Method A). Compound **15** (0.7 g, 0.54 mmol) was dissolved in a mixture of $CHCl_3$ (300 mL) and formic acid (300 mL). The solution was heated at 55−60 °C for 4 h. Then, the solvents were evaporated under reduced pressure to leave a yellow solid residue. Traces of formic acid were removed (azeotropic distillation) by addition of $CHCl_3$. A thin-layer chromatography (CH_2Cl_2/acetone: 90/10) shows two spots. A column chromatography on silica gel (CH_2Cl_2/acetone: 90/10) allows the separation of these two spots, which were identified as the *anti*-**1** and the *syn*-**2** diastereomers. The *anti*-**1** diastereomer was washed on a frit with diethyl ether and purified again on silica gel (CH_2Cl_2/acetone: 90/10). Evaporation of the solvents gives rise to a white solid, which was then recrystallized in a mixture of $CHCl_3$/EtOH. The crystals were filtrated on a frit and then washed with diethyl ether to give compound **1** (0.18 g, 34%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.08 (s, 3H), 6.75 (s, 3H), 6.65 (s, 3H), 4.6 (d, *J* = 13.5 Hz, 3H), 4.3 (d, *J* = 13.5 Hz, 3H), 4.25 (m, 3H), 4.1 (m, 6H), 4.0 (m, 3H), 3.9 (s, 9H), 3.85 (d, *J* = 13.5 Hz, 3H), 3.8 (s, 9H), 3.7 (s, 9H), 3.4 (d, *J* = 13.5 Hz, 3H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 151.4, 150.9, 149.95, 147.0, 139.3, 135.7, 134.4, 131.6, 125.2, 121.4, 113.6, 110.4, 70.3, 70.2, 60.3, 55.7, 55.3, 36.3, 30.1; mp > 260 °C; HRMS calcd for $C_{57}H_{61}O_{15}$ $[M + H]^+$ 985.4005, found 985.3990. The *syn*-**2** diastereomer was washed on a frit with diethyl ether and purified again on silica gel (CH_2Cl_2/acetone: 90/10) to give compound **2** as a white solid. It was recrystallized in a mixture of $CHCl_3$/EtOH. The crystals were filtrated on a frit and then washed with diethyl ether to give the *syn*-**2** diastereomer (0.10 g, 19%) as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.08 (s, 3H), 6.68 (s, 3H), 6.65 (s, 3H), 4.55 (d, *J* = 13.5 Hz, 3H), 4.31−4.15 (d, *J* = 13.5 Hz, 3H + m, 9H), 3.9 (s, 9H), 3.8 (d, *J* = 13.5 Hz, 3H), 3.75 (s, 9H), 3.7 (s, 9H), 3.65 (m, 3H), 3.35 (d, *J* = 13.5 Hz, 3H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 152.0, 151.3, 149.6, 146.2, 138.9, 136.0, 134.1, 131.6, 125.0, 121.3, 114.35, 110.5, 70.1, 69.4, 60.3, 55.9, 55.3, 36.2, 30.35; mp > 260 °C; HRMS calcd for $C_{57}H_{60}O_{15}Na_2$ $[M + 2Na]^+$ 515.1858, found 515.1872.

Synthesis of Cryptophanes *anti*-1 and *syn*-2 (Method B). Compound **18** (0.7 g, 0.54 mmol) was dissolved in a mixture of $CHCl_3$ (300 mL) and formic acid (300 mL). The solution was heated at 55−60 °C for 4 h. The same purification procedure was applied as described previously for the method A. This gives the *anti*-**1** (0.19 g, 36%) and the *syn*-**2** (0.14 g, 26%) diastereomers.

Synthesis of Cryptophanes *anti*-3 and *syn*-4. Compound **19** (0.6 g, 0.43 mmol) was dissolved in a mixture of $CHCl_3$ (300 mL) and formic acid (300 mL). The solution was heated at 55−60 °C for 4 h. Then, the solvents were evaporated under reduced pressure. $CHCl_3$ was added to the solid residue, and the solvent was evaporated to remove traces of formic acid (azeotropic distillation). This operation was repeated three times. A thin-layer chromatography (CH_2Cl_2/acetone: 90/10) shows two strong spots having the same intensities. These two spots were separated by column chromatography on silica gel (CH_2Cl_2/acetone: 90/10). The first spot, identified as the *anti*-**3** diastereomer, was purified one more time on silica gel (CH_2Cl_2/acetone: 95/5). The solid, obtained after evaporation of the solvents, was then recrystallized in a mixture of $CHCl_3$ and EtOH. The crystalline product was collected on a frit and washed several times with diethyl ether to give compound **3** as a white crystalline solid (0.15 g, 33%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.09 (s, 6H), 4.3 (d, *J* = 13.5 Hz, 6H), 4.2−4.1 (m, 6H), 4.0−3.9 (m, 6H), 3.9 (s, 18 H), 3.85 (d, *J* = 13.5 Hz, 6H), 3.7 (s, 18H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 151.55, 151.1, 139.7, 135.8, 125.2, 110.2, 70.9, 60.1, 55.3, 30.1; mp > 260 °C; HRMS calcd for $C_{60}H_{67}O_{18}$ $[M + H]^+$ 1075.4332, found 1075.4302.

The second spot, identified as the *syn*-**4** diastereomer, was also purified one more times on silica gel (CH_2Cl_2/acetone: 95/5). The collected fractions were evaporated, and the resulting solid was recrystallized in a mixture of $CHCl_3$ and EtOH to give compound **4** as a white crystalline solid (0.15 g, 33%): ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C) δ 7.06 (s, 6H), 4.3−4.25 (d, *J* = 13.5 Hz, 6H + m, 6H), 3.95−3.90 (m, 6H), 3.86 (s, 18H), 3.80 (d, *J* = 13.5 Hz, 6H), 3.75 (s, 18H); ^{13}C NMR (126.7 MHz, $CDCl_3$, 25 °C) δ 151.4, 150.9, 138.8, 135.4, 125.0, 110.65, 70.04, 60.4, 55.4, 30.4; mp > 260 °C; HRMS calcd for $C_{60}H_{67}O_{18}$ $[M + H]^+$ 1075.4332, found 1075.4308.

■ ASSOCIATED CONTENT

Supporting Information

Views of crystal structures of compounds **1**, **2**, **4**, **7**, and **8**. ^{1}H NMR (500 MHz) and ^{13}C NMR (126.7 MHz) spectra of compounds **1**−**4**, **6**−**15**, **18**, and **19**. IR spectra of compounds *anti*-**1**, *anti*-**3**, and *anti*-cryptophane-A in $CDCl_3$ solution. Number of imaginary frequencies, Gibbs energies, and Cartesian coordinates of the optimized geometries of compounds **1**−**4** and **8**. Electronic energies and dihedral angles of the O−CH_2−CH_2−X side chain of the different conformers found for compounds **13** and **14**. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 926796, 926797, 926798, 926799, and 926800 contain the supplementary crystallographic data related to this paper. These data can be obtained free of charge via the Internet at http://www.ccdc.cam.ac.uk/conts/retrieving.html or from The Cambridge Crystallographic Data Centre (12, Union Road, Cambridge CB21EZ, UK; Tel: (+44) 1223 336 408; E-mail: deposit@ccdc.cam.ac.uk).

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Notes

The authors declare no competing financial interest.

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