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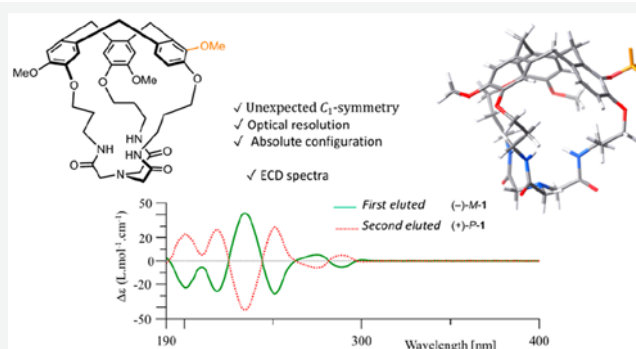
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Hemicryptophane Cages with a C_1 -Symmetric Cyclotrimeratrylene Unit

Chunyang Li, Anne-Doriane Manick, Marion Jean, Muriel Albalat, Nicolas Vanthuynne, Jean-Pierre Dutasta, Xavier Bugaut,* Bastien Chatelet,* and Alexandre Martinez*

ABSTRACT: Two new hemicryptophanes combining a cyclotrimeratrylene unit with either an aminotrisamide or a tris(2-aminoethyl)amine (tren) moiety have been synthesized. Although a conventional synthesis approach was used, the molecular cages obtained are devoid of the expected C_3 symmetry. NMR analyses and X-ray crystal structure determination showed that these hemicryptophanes exhibited C_1 symmetry due to the unusual arrangement of the substituents of the cyclotrimeratrylene unit. This unprecedented arrangement is related to a change in the regioselectivity of the Friedel–Crafts reactions that led to the CTV cap. This constitutes an original approach to access enantiopure chiral molecular cages with low symmetry.



INTRODUCTION

Cyclotrimeratrylenes (CTVs) are bowl-shaped molecules whose symmetry is related to the cone conformation and the arrangement of the six peripheral substituents (Figure 1a).¹ When R^1 is different from R^2 , CTVs become chiral² and present most of the time a C_3 symmetry, although some chiral CTVs with C_1 symmetry have been reported.³ Connecting two CTV units leads to cryptophane host molecules first synthesized by Collet in 1981 (Figure 1b).⁴ Cryptophanes have been widely used for their remarkable binding properties, with special emphasis on the enantiopure molecules that display interesting enantioselectivity in recognition and detection of chiral analytes such as epoxides or bromofluoroiodomethane.⁵ Cryptophanes were also used for the design of various covalent or self-assembled supramolecular architectures.⁶ In addition, the hemicryptophanes constitute another class of covalent cages based on the CTV unit bonded to a different entity making it possible to introduce functionalities at the molecular cavity (Figure 1c). Hemicryptophanes have found a wide range of applications from molecular switches to enantioselective receptors and supramolecular catalysts.⁷ The C_3 symmetrical CTV unit of the hemicryptophane structure can be connected to a moiety of C_3 or C_1 symmetry to vary the size and shape of the cavity.^{8–11} However, to date no hemicryptophane cages built from a C_1 symmetrical CTV have been reported. To access to such dissymmetric cages presents an increasing interest as they can exhibit remarkable properties for different issues in terms of molecular recognition, asymmetric catalysis, or chiroptical spectroscopy.¹²

Herein, we report on the synthesis of two chiral hemicryptophane cages that combine a CTV unit linked either to an aminotrisamide moiety (1) or to a tris(2-aminoethyl)amine (tren) moiety (2). These two hemicryptophanes present an unexpected C_1 arrangement of the substituents of the CTV unit as evidenced by NMR analyses and X-ray molecular structure of 2. Compound 1 was optically resolved by chiral HPLC to give the two enantiomers with ee >99%, and their absolute configurations were determined from ECD spectra and TD-DFT calculations.

RESULTS AND DISCUSSION

Synthesis. Scheme 1 shows the synthetic pathway used to obtain hemicryptophanes 1 and 2. The reaction of vanillyl alcohol with 1,3-dibromopropane in ethanol provides compound 3 in 72% yield. Then protection of the alcohol function of 3 by a THP group was achieved, leading to compound 4 in 98% yield. A subsequent nucleophilic substitution with sodium azide using DMF as solvent gives 5, which is then reduced under the Staudinger conditions to give 6 in 65% yield (two steps). Then nitrilotriacetic acid reacts at 50 °C with amine 6 in the presence of DCC/HOBt as coupling agent in THF to afford the aminotrisamide 7. Intramolecular Friedel–Crafts

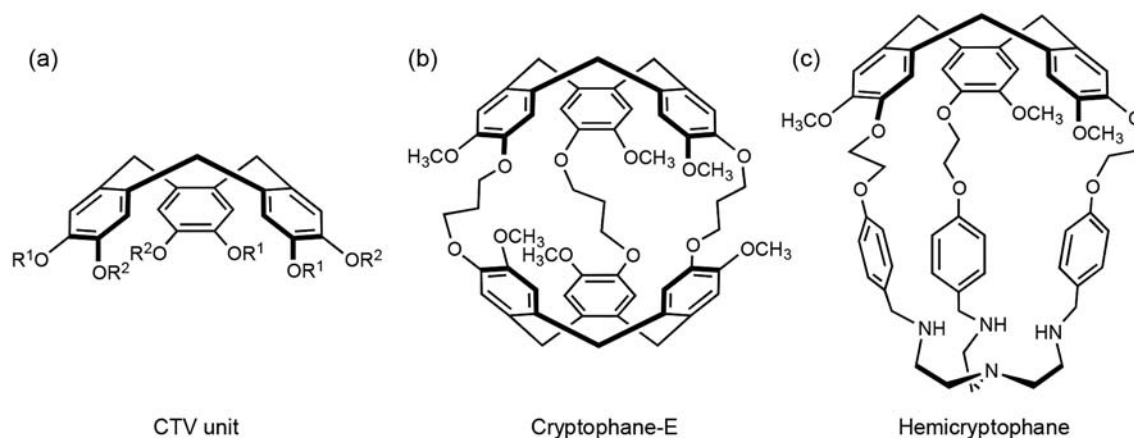
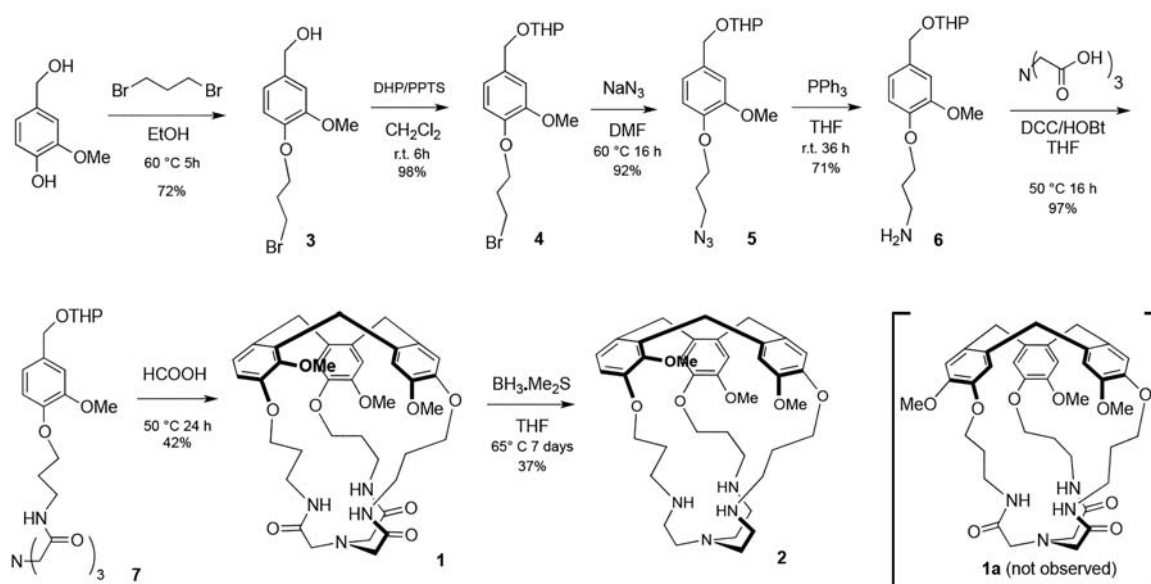


Figure 1. General structure of cyclotrimeratriylene derivatives (a) and selected examples of cryptophane (b) and hemicyptophane (c).

Scheme 1. Synthetic Pathway Leading to Hemicyptophanes 1 and 2^a



^aDHP = dihydropyrene; PPTS = pyridinium *p*-toluenesulfonate; DCC = dicyclohexylcarbodiimide; HOBt = hydroxybenzotriazole.

reactions of 7 carried out in formic acid lead to the C₁-symmetry molecular cages (±)-1 with a moderate yield of 42%. Although modest, the yield is in the same range of values to those usually obtained for the synthesis of hemicyptophane cages.^{7b} Indeed, this cyclization step involved the simultaneous formation of three macrocycles and side reactions, leading to oligomers or polymers, which are difficult to avoid. It is remarkable and important to note that the expected C₃-symmetry hemicyptophane 1a was not detected (Scheme 1). The reduction of the amide functions of (±)-1, performed with BH₃·Me₂S in THF, provides the tren-hemicyptophane racemate (±)-2 in 37% yield.

Characterization and Molecular Structure. Because of the unexpected outcome of this synthetic pathway, characterizations of the new hemicyptophanes were cautiously done by mass measurements and NMR analyses. While hemicyptophane 1 displays the expected exact mass (Figure S30), its ¹H NMR spectrum does not present the C₃ symmetry usually observed for hemicyptophanes in solution (Figure 2). Hemicyptophane 1 exhibits the characteristic signals of a CTV moiety but with a lack of the usual C₃ symmetry: three

singlets for the methoxy groups at 3.93, 3.80, and 3.79 ppm, three different AB systems for the diastereotopic H_a and H_c ArCH₂Ar protons (4.76, 4.72, 4.30 ppm and 4.12, 3.56, 3.51 ppm, respectively); four singlets (7.55, 6.91, 6.88, and 6.83 ppm) and two AB doublets (7.02 and 6.72 ppm; J_{AB} = 8.5 Hz) are assigned to the non equivalent aromatic protons. The OCH₂CH₂CH₂N methylene protons of the linkers give a complex pattern with a multiplet at 4.25 ppm and another one between 3.2 and 3.6 ppm. The CH₂ protons of the aminotrisamide core also reveal as diastereotopic leading to three AB systems between 1.7 and 2.8 ppm. Finally, three different signals can be observed for the NH at 5.77, 6.48, and 7.13 ppm. The ¹³C NMR spectrum also confirms the absence of C₃ symmetry for 1 (Figure S14) with, for instance, three peaks for the carbonyl carbons at 169.5, 169.4, and 169.2 ppm.

The presence of six different aromatic protons for the CTV unit, including one AB system between *ortho* protons of one aromatic ring, and the splitting of other sets of signals are consistent with the observed C₁ symmetry. This is a different situation compared to the loss of the C₃ symmetry due to intramolecular hydrogen bonding between the amide functions

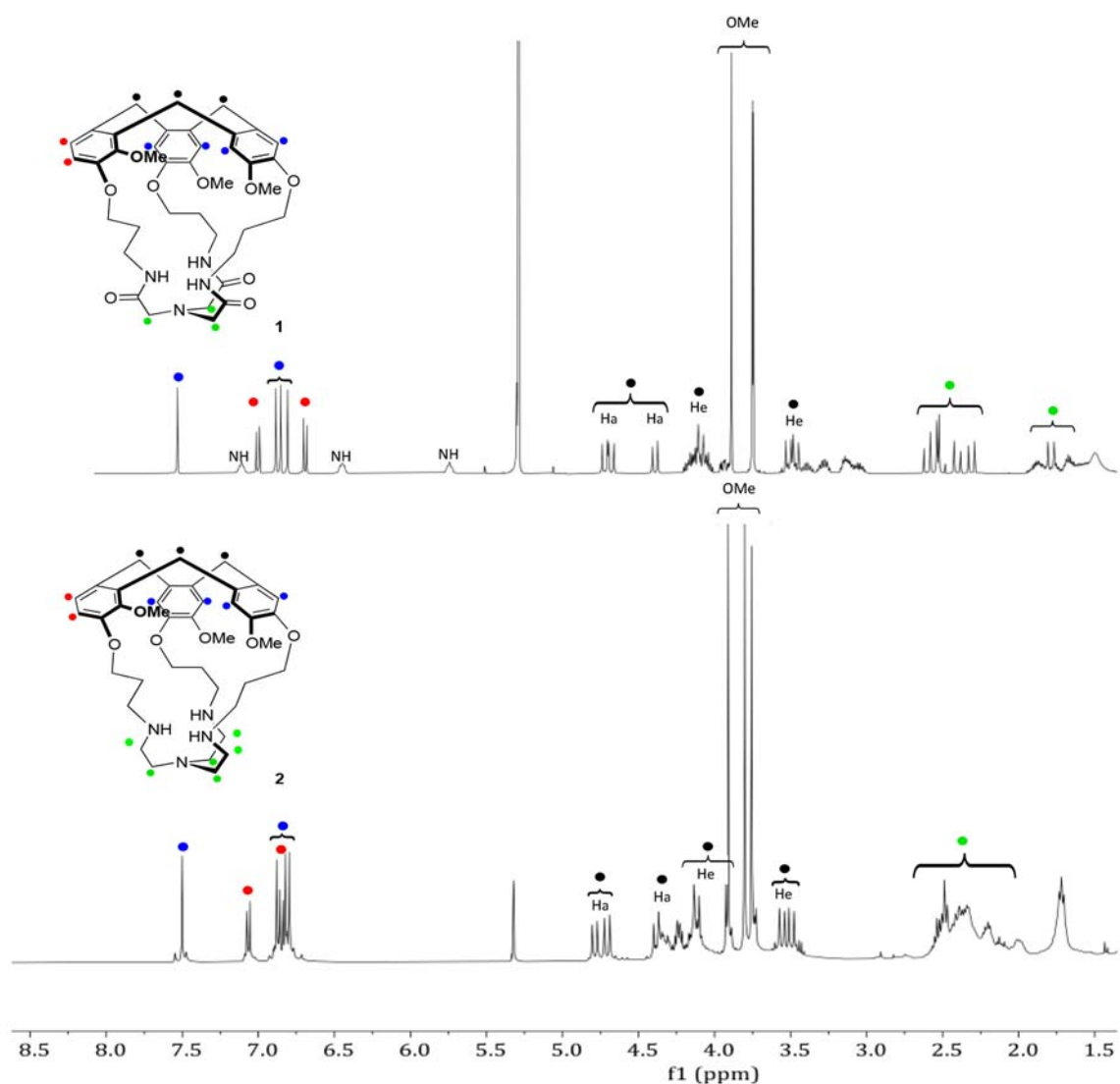


Figure 2. ^1H NMR spectra (400 MHz, CD_2Cl_2 , 298 K) of hemicyptophanes **1** and **2**.

as previously observed in the solid state for other hemicyptophane parents, where one linker was oriented inside the molecular cavity, breaking the C_3 -symmetrical conformation observed in solution.¹³ However, to rule out this possibility, the ^1H NMR spectrum of **1** has been also performed in $\text{DMSO}-d_6$ in order to break any intramolecular hydrogen bonds. The C_1 symmetry is again retained (Figure S13).

A decisive argument is brought by studying the hemicyptophane-tren **2** obtained by reduction of the amide functions of **1** (Scheme 1). The ^1H and ^{13}C NMR spectra of hemicyptophane **2** show patterns similar to those observed for **1** (Figures 2 and S18), proving the C_1 symmetry of hemicyptophane-tren **2** in solution. In particular, the aromatic protons of the CTV unit of **2** appear as four singlets and two AB doublets. The main differences are in the resonances of the protons of the tren unit (between 2.0 and 2.7 ppm compared to the amino-trisamide core (between 1.7 and 2.8 ppm)).

We hypothesize that these C_1 -symmetrical hosts result from an unusual regioselectivity of the last Friedel–Crafts reaction during the cyclization step from precursor **7** to afford host **1**. Although this regioselectivity has never been observed for CTVs, cryptophanes, or hemicyptophanes, this new structure

could arise from a specific arrangement of the amino-trisamide unit under acidic conditions that controls the relative position and orientation of the vanillyl aromatic rings. As Friedel–Crafts reactions can be either under thermodynamic or kinetic control,¹⁵ hemicyptophane **1** was heated at 50 °C in formic acid during 24 h to investigate if this unusual regioselectivity is thermodynamically driven. The ^1H NMR remains unchanged (Figure S22); no signals corresponding to other compounds, like the precursor of cyclization **7**, cage **1a**, oligomers, or polymers, can be observed, showing that this step is not reversible and, hence, that the kinetic control prevails. A molecular structure of the protonated cage **2**· $3[\text{H}^+\text{Cl}^-]$ was determined by X-ray diffraction on crystals obtained by slow evaporation from a CHCl_3 solution (Figure 3). Protonation of the cage probably occurs during the crystallization because of traces of HCl usually found in chloroform. This solid-state structure is consistent with the structure of **2** characterized by NMR, with a CTV unit presenting a C_1 symmetry induced by an unprecedented arrangement of the substituents on one of the aromatic rings. Indeed, two arms exhibit the expected position for their OMe group, whereas for the last one, the OMe group lies between the $-\text{OCH}_2\text{CH}_2\text{CH}_2\text{N}-$ linker and

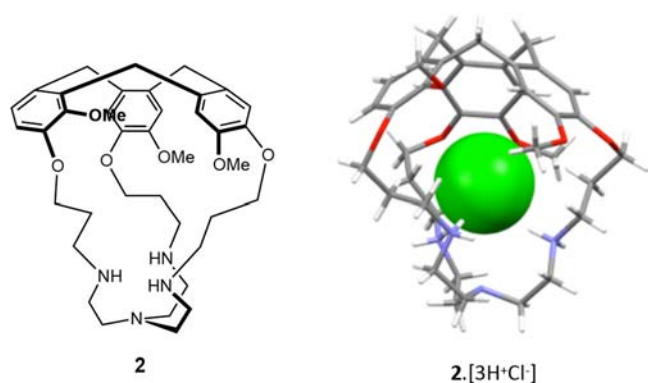


Figure 3. Hemicyptophane **2** and X-ray molecular structure of rac-(±)-**2**·[3H⁺Cl⁻].

the methylene bridge. Hemicyptophane **2** presents a well-defined cavity, with a chloride anion trapped inside. Hydrogen bonding between the three secondary ammonium functions of the linkers and the chloride anion (average distance $d_{N...Cl} = 2.247 \text{ \AA}$) can account for the formation of this host–guest complex. This constitutes only the second example of an X-ray structure of a hemicyptophane complex with an anion inside, confirming the ability of this class of hosts to complex ions both in solution and in the solid state.

Optical Resolution of (±)-1. Resolution of the racemic mixture (±)-**1** was performed by chiral HPLC on Chiralpak IF, a polysaccharide based chiral stationary phase (Figure 4). The two enantiomers were obtained with high purity (ee >99%, Figures S23).

The absolute configuration of the enantiopure compounds was established in two steps. First, the electronic circular dichroism (ECD) spectra of the two enantiomers of **1** were recorded (Figure 5). Indeed, Collet et al. have shown that the sign of the exciton pattern centers on the 1L_a transition ($\sim 240 \text{ nm}$) is weakly sensitive to the substituents grafted on the CTV unit.¹⁴ Thus, a direct comparison of this sign for one enantiomer with that of a CTV of known absolute configuration allows for a direct assignment of its absolute configuration. Thus, the (–)-*M*-**1** and (+)-*P*-**1** configurations were assigned to the first and second eluted enantiomers, respectively. Second, as the spatial arrangement of the CTV substituents in **1** differs from that of usual C_3 -symmetry derivatives, the simple comparison of the ECD spectra of enantiomers (+)-**1** and (–)-**1** with those of other C_3 CTV of known configuration might not be relevant. Therefore, to support our previously proposed stereochemical assignment, the ECD spectrum of *P*-**1** (second eluted) was calculated using the TD-DFT method. The results confirm our initial assignment: the first eluted peak corresponds to the CTV with an *M* configuration, while the second one is *P* (Figures 5 and S32; see the Supporting Information for the assignment of the stereodescriptor *M* or *P* for the CTV unit in this specific case).

CONCLUSION

Herein, we have reported an unexpected alternative to hemicyptophanes of low symmetry using a conventional synthetic pathway. The usual Friedel–Crafts cyclization in formic acid of an adequately tris-substituted nitrilotrisamide precursor **7** afforded C_1 -symmetric hemicyptophane **1** that

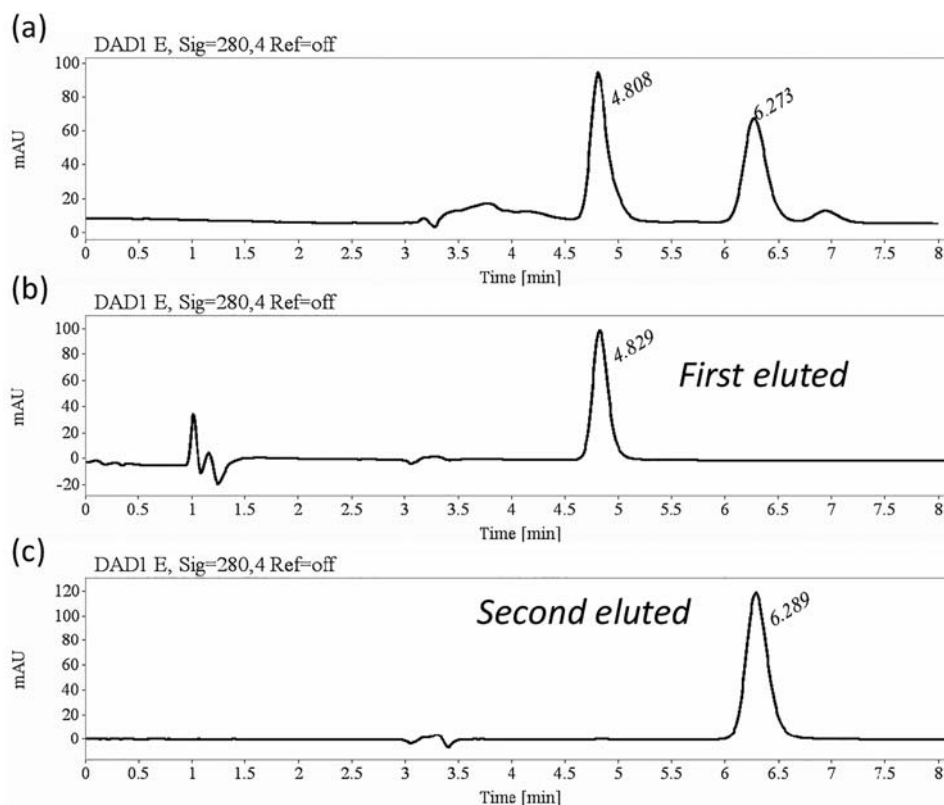


Figure 4. Chiral HPLC chromatograms of the mixture of (a) the two enantiomers of **1**; (b) the first eluted enantiomer of **1**; and (c) the second eluted enantiomer of **1**. Conditions: column Chiralpak IF. Eluent: heptane/ethanol + triethylamine 0.5%/dichloromethane (20/40/40).

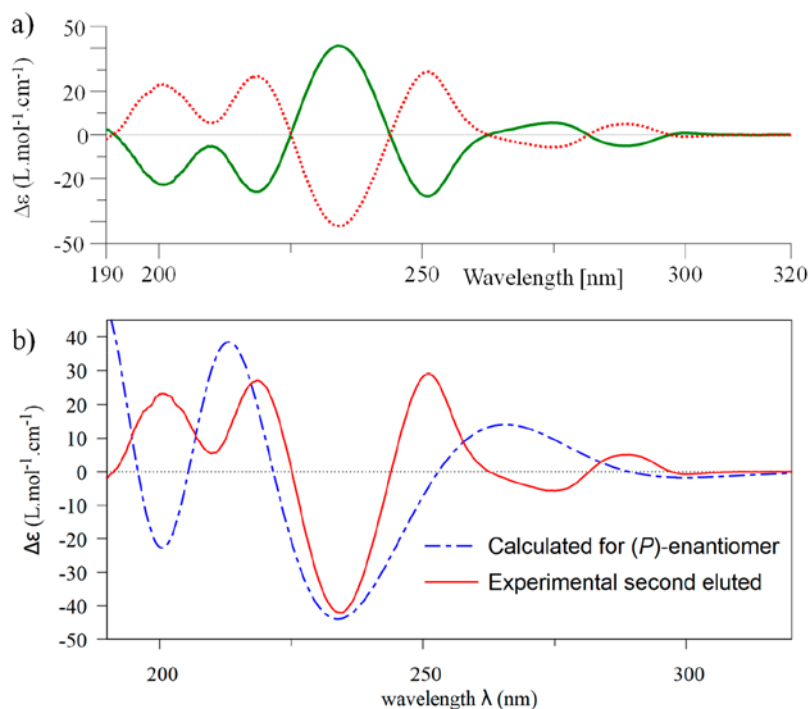


Figure 5. (a) Experimental ECD spectra of the enantiomers of **1**: the first eluted enantiomer is represented with a green solid line (0.229 mmol L⁻¹ in CH₃CN) and the second one by a red dotted line (0.233 mmol L⁻¹ in CH₃CN). (b) Comparison of calculated ECD spectrum for the (*P*) enantiomer with the experimental ECD spectrum of the second eluted enantiomer of **1**.

was then reduced to give the *tren* derivative **2**. The racemic mixture (\pm)-**1** was resolved by chiral HPLC. The absolute configuration of the resulting enantiomers was determined from their ECD spectra and corroborated by TD-DFT calculations. The hemicryptophane cages **1** and **2** display an unprecedented C₁ symmetry in solution, evidenced by the NMR analyses, and supported by the X-ray structure of the tetra-ammonium derivative **2**·4[H⁺Cl⁻]. The C₁ symmetry is due to the unusual arrangement of the substituents of the CTV moiety, leading to original hemicryptophane cages. These results open the way for the synthesis of cages presenting a CTV unit with lower symmetry for more tunable and specific properties. This approach is currently being carried out in our laboratory for applications in supramolecular catalysis and molecular recognition.

EXPERIMENTAL SECTION

General Information. Commercial reagents were used directly as received without further purification. Dichloromethane was dried prior to use through standard procedures or obtained from a solvent drying system (MB-SPS-800). The preparation of the compound **9** was performed under inert atmosphere of dry argon. ¹H and ¹³C NMR spectra were recorded on a Bruker AC 400 (400 MHz for ¹H NMR, 101 MHz for ¹³C NMR spectra in CDCl₃ or CD₂Cl₂). Chemical shifts are reported in ppm on the δ scale relative to residual CDCl₃ (δ = 7.26 for ¹H NMR and δ = 77.16 for ¹³C NMR), CD₂Cl₂ (δ = 5.32 for ¹H NMR and 53.84 for ¹³C NMR), and (CD₃)₂SO (δ = 2.50 for ¹H NMR and 39.52 for ¹³C NMR) as the internal references. Coupling constant (*J*) are reported in hertz (Hz). Multiplicities are described with the following standard abbreviations: s = singlet, br = broad, d = doublet, t = triplet, q = quadruplet, quint = quintuplet, m = multiplet. Structural assignments were made with additional information from COSY and NOESY experiments. Column chromatographies were performed with gel 60 (Macherey-Nagel Si 60, 0.040–0.063 mm). Analytical thin-layer chromatography (TLC) was carried out on MerckKieselgel 60 F254 plates and achieved under

254 nM UV light. High-resolution mass spectra (HRMS) were performed on a SYNAPT G2 HDMS (Waters) spectrometer equipped with an atmospheric pressure ionization source (API) pneumatically assisted. Spectra were obtained with TOF analysis. Measurements were realized with two internal standards. Single crystals of cage **2** were analyzed on a SuperNova, Dual, Cu at home/near, AtlasS2 diffractometer. The crystal was kept at 295 K during data collection.

(4-(3-Bromopropoxy)-3-methoxyphenyl)methanol 3. In a round-dried bottom flask, vanillyl alcohol (10.0 g, 64.86 mmol) and potassium carbonate (10.0 g, 72.36 mmol) were dissolved in ethanol (500 mL), and 1, 3-dibromopropane (16.45 mL, 162.08 mmol) was added dropwise. The mixture was vigorously stirred and heated at 70 °C (oil bath) for 5 h. The solvent was removed under reduced pressure, the crude residue was dissolved in CH₂Cl₂ (200 mL) and successively washed with 1 M NaOH solution (200 mL \times 3). After 2 h, the precipitate was filtered off on the sintered glass, the organic phase was dried by anhydrous Na₂SO₄ and CH₂Cl₂ was removed under reduced pressure to give brown oil. The crude compound was purified on silica gel by column chromatography using pure CH₂Cl₂ as eluent to give pure **3** (12.85 g, 72%). White solid. mp: 61 \pm 1 °C. ¹H NMR (400 MHz, CDCl₃): δ = 6.92 (d, *J* = 1.56 Hz, 1H), 6.90–6.83 (m, 2H), 4.60 (d, *J* = 4.8 Hz, 2H), 4.14 (t, *J* = 6.0 Hz, 2H), 3.85 (s, 3H), 3.62 (t, *J* = 6.5 Hz, 2H), 2.35 (quint, *J* = 6.2 Hz, 2H), 1.82 (t, *J* = 5.44 Hz, 1H). ¹³C{¹H} NMR (101 MHz, CDCl₃): δ = 149.9, 147.9, 134.5, 119.6, 113.9, 111.2, 67.1, 65.3, 56.1, 32.5, 30.2. IR: cm⁻¹ 3332, 2935, 2867, 2184, 1743, 1591, 1511, 1463, 1418, 1384, 1357, 1324, 1258, 1229, 1155, 1134, 1102, 1076, 1059, 1026, 915, 891, 653, 799, 761, 718, 761, 718, 646, 550. HRMS (ESI-TOF): *m/z* [M + Na]⁺ calcd for C₁₁H₁₅BrO₃Na, 297.0097; found at 297.0094.

2-((4-(3-Bromopropoxy)-3-methoxybenzyl)oxy)tetrahydro-2H-pyran 4. In a round-dried bottom flask, **3** (3.0 g, 10.91 mmol) was dissolved in CH₂Cl₂ (80 mL), and a catalytic amount of PPTS (274 mg, 1.09 mmol) was added. The mixture was vigorously stirred at room temperature for 16 h. A solution of 1 M NaOH in distilled water (80 mL \times 3) was added to extract the CH₂Cl₂. The combined organic phase was dried by anhydrous Na₂SO₄, and then the solvent was removed under reduced pressure to give the yellow oil. The crude

compound was purified by column chromatography on silica gel using pure CH_2Cl_2 as eluent to give the pure **4** (3.83 g, 98%). Colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 6.94–6.83 (m, 3H), 4.72 (d, J = 11.6 Hz, 1H), 4.69 (t, J = 3.5 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.15 (t, J = 5.9 Hz, 2H), 3.97–3.89 (m, 1H), 3.87 (s, 3H), 3.63 (t, J = 6.4 Hz, 2H), 3.58–3.47 (m, 1H), 2.35 (quint, J = 6.2 Hz, 2H), 1.93–1.49 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ = 149.8, 147.9, 131.7, 120.7, 113.9, 112.2, 97.8, 68.9, 67.1, 62.5, 56.1, 32.6, 31.0, 30.3, 25.7, 19.7. IR: cm^{-1} 2938, 2870, 1592, 1517, 1465, 1419, 1384, 1348, 1322, 1260, 1231, 1200, 1183, 1158, 1117, 1076, 1020, 975, 949, 931, 903, 868, 810, 766, 744, 547. HRMS (ESI-TOF): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{BrO}_4\text{Na}$, 381.0672; found at 381.0669.

2-((4-(3-Azidopropoxy)-3-methoxybenzyl)oxy)tetrahydro-2H-pyran 5. In a round-dried bottom flask, **4** (3.0 g, 8.35 mmol) was dissolved in DMF (50 mL), NaN_3 (1.09 g, 16.70 mmol) was added portionwise, and the mixture was vigorously stirred and heated at 60 °C (oil bath) for 16 h. The solvent was removed under reduced pressure, and the crude residue was dissolved in CH_2Cl_2 (80 mL), then washed by 1 M NaOH solution (80 mL \times 3). The combined organic layers were dried over anhydrous Na_2SO_4 and then concentrated under vacuum to give the pure **5** (2.47 g, 92%). Yellow oil. ^1H NMR (400 MHz, CDCl_3): δ = 6.97–6.79 (m, 3H), 4.72 (d, J = 11.6 Hz, 1H), 4.68 (dd, J = 3.1 Hz, 4.3 Hz, 1H), 4.44 (d, J = 11.7 Hz, 1H), 4.09 (t, J = 6.1 Hz, 2H), 3.99–3.89 (m, 1H), 3.86 (s, 3H), 3.54 (t, J = 6.7 Hz, 2H), 3.58–3.52 (m, 1H), 2.08 (quint, J = 6.2 Hz, 2H), 1.92–1.51 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ = 149.8, 147.8, 131.7, 120.7, 113.8, 112.1, 97.8, 68.9, 66.2, 62.4, 56.1, 48.4, 30.8, 28.9, 25.6, 19.6. IR: cm^{-1} 2940, 2871, 2093, 1746, 1677, 1592, 1513, 1465, 1420, 1385, 1347, 1321, 1200, 1183, 1159, 1117, 1076, 1054, 1021, 975, 949, 903, 868, 809, 731, 646, 584. HRMS (ESI-TOF): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{16}\text{H}_{23}\text{N}_3\text{O}_4\text{Na}$, 344.1581; found at 344.1578.

3-(2-Methoxy-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenoxy)propan-1-amine 6. In a round ice-cooled bottom flask, **5** (2 g, 6.22 mmol) was dissolved in THF (60 mL), and PPh_3 (2.45 g, 9.34) was carefully added portionwise. The mixture was allowed to warm at room temperature slowly for 36 h. The solvent was removed under reduced pressure, and the crude compound was dissolved in CH_2Cl_2 (70 mL), extracted by a solution of 1 M NaOH (70 mL \times 3) in distilled water. The organic phase was dried over anhydrous Na_2SO_4 and then concentrated under vacuum to give yellow oil. The crude compound was purified on silica gel by column chromatography using a mixture of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (10:1) as eluent to give pure **6** (1.31 g, 71%). Colorless oil. ^1H NMR (300 MHz, CDCl_3): δ = 6.94–6.66 (m, 3H), 4.65 (d, J = 11.7 Hz, 1H), 4.61 (dd, J = 1.2 Hz, 2.9 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.03 (t, J = 6.2 Hz, 2H), 3.90–3.81 (m, 1H), 3.79 (s, 3H), 3.52–3.43 (m, 1H), 2.86 (t, J = 6.6 Hz, 2H), 1.90 (quint, J = 6.4 Hz, 2H), 1.83–1.39 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3): δ = 149.4, 147.8, 131.0, 120.5, 113.0, 111.8, 97.4, 68.7, 67.4, 62.2, 55.8, 39.3, 32.6, 30.5, 25.4, 19.4. IR: cm^{-1} 2939, 2870, 2196, 1592, 1513, 1465, 1420, 1385, 1348, 1322, 1261, 1231, 1200, 1183, 1159, 1116, 1075, 1020, 975, 946, 903, 868, 748, 732, 645, 547. HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{26}\text{NO}_4$, 296.1856; found at 296.1857.

2,2',2''-Nitrilotris(N-(3-(2-methoxy-4-(((tetrahydro-2H-pyran-2-yl)oxy)methyl)phenoxy)propyl)acetamide) 7. In a round ice-cooled round-bottom flask, **6** (1.3 g, 4.40 mmol) was dissolved in THF (50 mL), DCC (1 g, 4.84 mmol) and HOBT (0.66 g, 4.84 mmol) were slowly added, and then the ligand nitrilotriacetic acid (255 mg, 1.33 mmol) was added. The mixture was vigorously stirred, warmed to room temperature, and heated at 50 °C (oil bath) for 16 h. After the precipitate was removed on sintered glass several times, the solvent was removed under vacuum. The crude compound was dissolved in CH_2Cl_2 (50 mL), extracted with 1 M NaOH solution (50 mL \times 3), and filtered, and the organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum to give the yellow oil. The crude compound was purified on silica gel column by chromatography using a mixture of $\text{CH}_2\text{Cl}_2/\text{EtOAc}$ (30:1) as eluent to give pure **7** (1.32 g, 97%). Light yellow oil. ^1H NMR (300 MHz, CDCl_3): δ = 7.68 (t, J = 5.5 Hz, 3H), 6.92–6.84 (m, 6H), 6.81 (d, J = 8.1 Hz, 3H), 4.70 (d, J

= 11.7 Hz, 3H), 4.67 (dd, J = 2.8 Hz, 4.3 Hz, 3H), 4.42 (d, J = 11.7 Hz, 3H), 4.04 (t, J = 6.0 Hz, 6H), 3.97–3.87 (m, 3H), 3.86 (s, 9H), 3.60–3.50 (m, 3H), 3.45 (q, J = 6.0 Hz, 6H), 3.36 (s, 6H), 1.99 (quint, J = 6.0 Hz, 6H), 1.91–1.47 (m, 18H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CDCl_3): δ = 170.7, 149.4, 147.7, 131.6, 120.7, 112.9, 111.9, 97.8, 68.9, 68.2, 62.5, 59.9, 56.1, 53.6, 37.8, 30.8, 29.0, 25.6, 19.7. IR: cm^{-1} 3296, 3007, 2943, 2874, 1750, 1658, 1592, 1513, 1465, 1452, 1384, 1348, 1262, 1232, 1215, 1201, 1159, 1135, 1118, 1075, 1022, 976, 950, 903, 868, 810, 744, 665, 596, 547. HRMS (ESI-TOF): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{34}\text{H}_{78}\text{N}_4\text{O}_{15}\text{Na}$, 1045.5356; found at 1045.5356.

Hemicryptophane 1. Precursor **7** (1.0 g, 0.98 mmol) was dissolved in formic acid (1 L). The mixture was stirred vigorously and heated at 50 °C (oil bath) for 1 day. Then the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 (50 mL) and was washed by 1 M NaOH solution (50 mL \times 3). The organic phase was dried over anhydrous Na_2SO_4 , then concentrated in vacuum to give yellow solid compound. The crude compound was purified on silica gel column by chromatography using a mixture solution of $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (15:1) as eluent to give the pure **1** (294 mg, 42%). White solid. Mp: 157 ± 1 °C. ^1H NMR (400 MHz, CD_2Cl_2): δ = 7.55 (s, 1H), 7.13 (t, J = 4.1 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.91 (s, 1H), 6.88 (s, 1H), 6.83 (s, 1H), 6.72 (d, J = 8.5 Hz, 1H), 6.48 (t, J = 4.1 Hz, 1H), 5.77 (t, J = 5.2 Hz, 1H), 4.74 (dd, J = 16.7, 13.6 Hz, 2H), 4.43 (d, J = 13.2 Hz, 1H), 4.26–4.04 (m, 5H), 4.02–3.94 (m, 1H), 3.93 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.54 (dd, J = 4.52 Hz, 19.2 Hz, 3H), 3.48–3.39 (m, 1H), 3.39–3.27 (m, 1H), 3.25–3.04 (m, 2H), 2.66 (d, J = 16.8 Hz, 1H), 2.58 (d, J = 5.5 Hz, 1H), 2.46 (d, J = 16.6 Hz, 1H), 2.37 (d; J = 16 Hz, 1H), 2.01–1.61 (m, 6H), 1.36–1.18 (m, 4H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, DMSO): δ = 169.5, 169.4, 169.2, 149.7, 148.6, 147.5, 145.5, 144.8, 133.9, 133.8, 133.7, 132.6, 132.4, 131.1, 124.9, 118.2, 114.5, 113.5, 67.4, 66.9, 66.6, 60.3, 58.6, 55.7, 55.2, 35.4, 35.3, 35.0, 34.7, 30.9, 28.6, 28.2, 27.9, 27.6, 13.9, 8.1. IR: cm^{-1} 3296, 2918, 2849, 2436, 2229, 2184, 2148, 2053, 2031, 1735, 1654, 1597, 1576, 1517, 1483, 1463, 1445, 1401, 1378, 1337, 1263, 1215, 1158, 1133, 1081, 1035, 988, 964, 880, 801, 740, 701, 615. HRMS (ESI-TOF): m/z $[\text{M} + \text{Na}]^+$ calcd for $\text{C}_{39}\text{H}_{48}\text{N}_4\text{O}_9\text{Na}$, 739.3314; found at 739.3312.

Hemicryptophane 2. Under an atmosphere of argon, hemicryptophane **1** (294 mg, 0.41 mmol) was placed in a two-neck round-bottom flask and dissolved in dry THF (10 mL), and then a 2 M BH_3SMe_2 solution in THF (2.05 mL) was added dropwise. The mixture was vigorously stirred and heated at 65 °C for 6 days. Then the reaction was cooled at room temperature, MeOH (7 mL) and 1 M HCl (1 mL) were added. Keeping the reaction mixture stirred and heated at 40 °C (oil bath) for another 1 day, the solvent was removed under reduced pressure. The crude was dissolved in CHCl_3 (10 mL), MeOH (7 mL) and 1 M HCl (1 mL) was added and the mixture was stirred at 60 °C (oil bath) for 2 days. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (30 mL), extracted by 1 M NaOH solution (30 mL \times 3), the organic phase was dried over anhydrous Na_2SO_4 , the solvent was removed under vacuum to give brown oil. The crude compound was purified on silica gel by column chromatography by using $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{TEA}$ (8:1:0.08) to give the pure hemicryptophane **2** (91 mg, 37%). White solid. Mp: 217 ± 1 °C. ^1H NMR (400 MHz, CD_2Cl_2): δ = 7.50 (s, 1H), 7.06 (d, J = 8.4 Hz, 1H), 6.87 (s, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.82 (s, 1H), 6.79 (s, 1H), 4.78 (d, J = 13.4 Hz, 1H), 4.70 (d, J = 13.7 Hz, 1H), 4.38 (d, J = 13.2 Hz, 1H), 4.27–4.01 (m, 6H), 3.91 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.55 (d, J = 13.8 Hz, 2H), 3.49 (d, J = 13.6 Hz, 2H), 2.55–1.91 (m, 20H), 1.82–1.59 (m, 6H). $^{13}\text{C}\{^1\text{H}\}$ NMR (101 MHz, CD_2Cl_2): δ = 149.6, 149.3, 149.0, 148.6, 145.3, 145.1, 135.6, 134.7, 133.9, 133.1, 132.7, 131.8, 124.9, 117.2, 116.9, 115.7, 115.3, 113.1, 67.8, 66.9, 60.7, 56.3, 56.2, 53.33, 47.1, 46.9, 46.8, 46.6, 46.1, 45.9, 36.5, 30.1, 29.7. IR: cm^{-1} 2917, 2849, 2691, 2431, 2105, 1992, 1742, 1642, 1597, 1516, 1481, 1461, 1446, 1378, 1337, 1262, 1214, 1158, 1134, 1082, 1031, 964, 885, 800, 724, 699. HRMS (ESI-TOF): m/z $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{39}\text{H}_{55}\text{N}_4\text{O}_6$, 675.4116; found at 675.4114.

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