JOC The Journal of Organic Chemistry

Article

Synthesis, Resolution and Absolute Configuration of Chiral Tris(2-pyridylmethyl)amine-Based Hemicryptophane Molecular Cages

Dawei Zhang, Benjamin Bousquet, Jean-Christophe Mulatier, Delphine Pitrat, Marion Jean, Nicolas Vanthuyne, Laure Guy, Jean-Pierre Dutasta, and Alexandre Martinez

J. Org. Chem., **Just Accepted Manuscript** • Publication Date (Web): 08 May 2017

ACS Publications

The Journal of Organic Chemistry is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis, Resolution and Absolute Configuration of Chiral Tris(2-pyridylmethyl)amine-Based Hemicryptophane Molecular Cages

Dawei Zhang,[a] Benjamin Bousquet,[a] Jean-Christophe Mulatier,[a] Delphine Pitrat,[a] Marion Jean,[b] Nicolas Vanthuyne,[b] Laure Guy,[a] Jean-Pierre Dutasta,[a] Alexandre Martinez*[b]

[a] *Laboratoire de Chimie, École Normale Supérieure de Lyon, CNRS, UCBL, 46 allée d'Italie, F-69364 Lyon, France.*

[b] *Aix Marseille Univ, CNRS, Centrale Marseille, iSm2, Marseille, France.*

ABSTRACT: The synthesis, characterization and chiroptical properties of a new class of hemicryptophane cages combining a cyclotriveratrylene (CTV) unit and a tris(2-pyridylmethyl)amine (TPA) moiety are reported. Changing the linkers between these two units allows for the modification of the size and shape of the cavity. The synthesis is straightforward and efficient, providing gram-scale of cage compounds. The racemic mixture of each hemicryptophane host can be readily resolved by chiral HPLC, giving an easy access to the enantiopure molecular cages of which absolute configurations have been assigned by ECD spectroscopy. These new hemicryptophanes are available chemical platforms ready to use for various purposes due to the versatile metal complexation properties of the TPA unit. A Zn(II)@hemicryptophane complex has been obtained and used as a heteroditopic host for the selective recognition of zwitterionic guests.

INTRODUCTION

Molecular cages have attracted considerable attention in the last two decades, leading to important applications in recognition, catalysis, separation and reactive species stabilization.[1] In particular, biomimetic chiral cages arouse a growing interest because of the important role of chirality in nature.[2] One prominent example is substrate binding and transformation by enzymes, displaying high chemoselectivity, regioselectivity and stereospecificity.[3] Among the chiral cages, hemicryptophanes, which combine a cyclotriveratrylene (CTV) unit with another C_3-symmetric moiety, exhibit remarkable properties in molecular recognition and supramolecular catalysis.[1a] The promising applications of hemicryptophanes benefit from the rigid bowl shape of the inherently chiral CTV unit as well as the feature of variability and easy functionalization of the other C_3-symetrical moiety.

To construct novel hemicryptophane scaffolds, tripodal building blocks, such as tris(2-aminoethyl)-amine (tren)[4] and trialkanolamine units,[5] have been attached to the CTV unit. The usefulness and easy availability should be considered when choosing this C_3-symmetric group. In this regard, tris(2-

pyridylmethyl)amine (TPA) unit appears promising. Indeed, TPA ligand is widely used in coordination chemistry, and can bind with various metals, such as Fe,[6] Cu,[7] Zn,[8] Co,[9] Mn,[10] Ru,[11] Rh,[12] Ni,[13] and Ln.[14] The resulting complexes have been extensively used in recognition,[15] catalysis,[6-7,10b,11b,12] chiroptical molecular switches,[16] and enantiomeric excess (*ee*) determination.[8a,8b,17] For instance, the [Fe-(TPA)$(MeCN)_2$]$(ClO_4)_2$ complex combined with photocatalyst riboflavin tetraacetate has been used as a readily accessible and efficient catalytic system for the visible-light-driven aerobic C-H bond oxidation of alkyl benzene to ketones and carboxylic acids.[6a] The copper complexes of TPA derivatives have been widely used to catalyze the reactions of atom transfer radical cyclization (ATRC),[7a] atom transfer radical addition (ATRA),[7b] and atom transfer radical polymerization (ATRP).[7c] Moreover, Anslyn and Giulia *et al.* adopted Zn(II) or Cu(II) complexes of TPA derivatives for rapid determination of *ee* of alcohols, carboxylic acids, amines, and amino acids.[8a,8b,17] This application originates from the propeller-like arrangement of TPA ligands around the metal center. The handedness of the helicity of the TPA analogues can also be controlled by the presence of a stereogenic center in the ligand backbone, which realizes redox-triggered chiroptical switches, as reported by the group of Canary.[16]

In line with the versatile nature of TPA complexes and their potential applications, we hereby report on the design and synthesis of a class of TPA-based hemicryptophanes (Figure 1). A Zn(II)@hemicryptophane complex has also been obtained and used for the selective encapsulation of zwitterionic guest. The racemic hemicryptophane ligand can be readily resolved by chiral HPLC to give the enantiopure form in relatively large-scale. Electronic circular dichroism (ECD) spectroscopy was used to determine the absolute configuration of each hemicryptophane enantiomer. To the best of our knowledge, the synthesis of enantiopure TPA-based cage molecules is unprecedented and these enantiopure hemicryptophanes are promising chemical platforms capable of complexation of various metals for different purposes and applications.

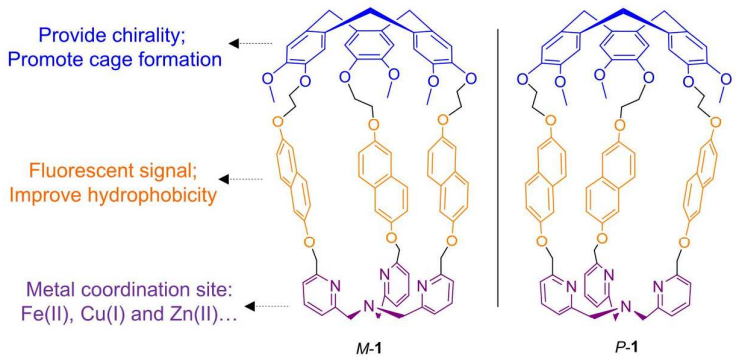
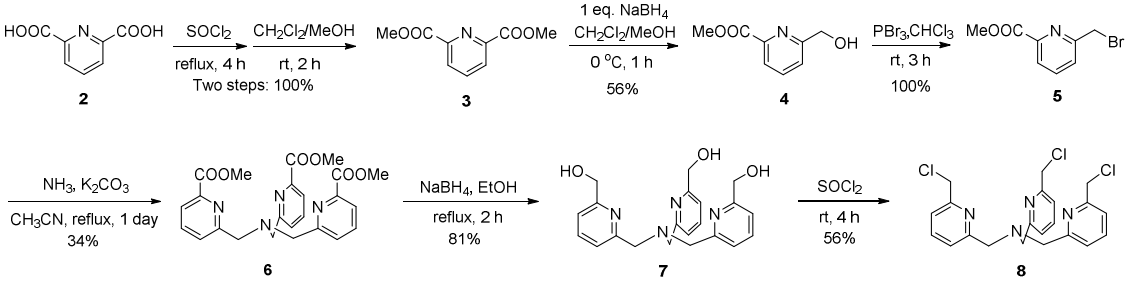


Figure 1. Structure of the new enantiopure TPA-based hemicryptophanes.

RESULTS AND DISCUSSION

The structures of the enantiomeric hemicryptophanes *M*-**1** and *P*-**1** (Figure 1) present the following features: (i) Firstly, the bowl-shaped CTV unit allows the formation of a well-defined chiral cavity; (ii) the naphthalene fluorophores, used as hydrophobic "walls" connecting the TPA and CTV units, confer fluorescence properties to the host; (iii) as mentioned above, the TPA moiety is able to coordinate with various metals giving rise to chemical platforms for further applications. Two synthesis routes can be followed to obtain hemicryptophane compounds: i) the [1+1] coupling reaction between a CTV moiety and another C_3 symmetrical unit to afford the expected cage, or ii) the triple macrocylization reaction to build the CTV core in the last step of the synthesis.[1a] We anticipated that the protonation of the TPA unit in formic acid could lead to some preorganization of the precursor for the cyclization, thus we decided to adopt the second strategy,[1a,1b,5a] and we first prepared the TPA-trichloride **8** (Scheme 1).[18]

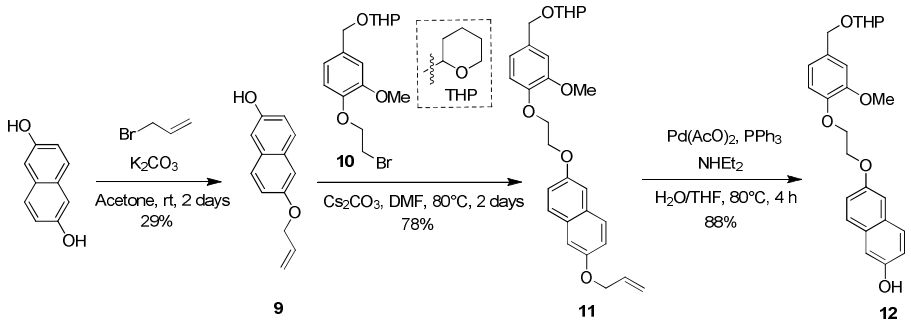


Scheme 1. Synthesis of TPA-trichloride **8**.

Starting from 2,6-pyridinedicarboxylic acid **2**, 2,6-pyridinedicarboxylate **3** was quantitatively prepared in two successive steps: chloroformylation with thionyl chloride under reflux followed by esterification with MeOH at room temperature. The reduction of one ester group in **3** by 1.0 equiv. of $NaBH_4$ in CH_2Cl_2/MeOH afforded alcohol **4** in 56% yield. Bromide **5** was then obtained quantitatively by bromination of **4** with PBr_3 at r.t.. The addition of an ammonia solution to **5** in the presence of K_2CO_3 under reflux for 1 day, gave the TPA-triester **6** in 34% yield. The synthesis of trichloride **8** was achieved by reduction of **6** with an excess of $NaBH_4$ followed by chlorination using thionyl chloride, with an overall yield of 45% (Scheme 1).

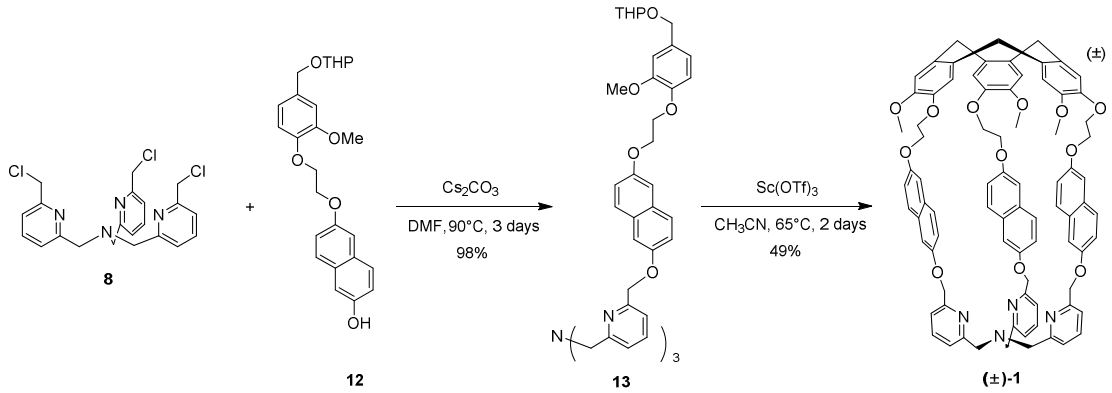
In order to prepare the hemicryptophane precursor **13**, the naphtol derivative **12** was synthesized according to the pathway described in Scheme 2. Firstly, 2,6-dihydroxynaphthalene was mono-allyl-protected via its reaction with 1.0 equiv. of allyl bromide in acetone in the presence of K_2CO_3 to give allyloxynaphtol **9** in 29% yield. Then, **9** reacted with compound **10**, obtained in 3 steps as described previously,[5a] in the presence of Cs_2CO_3 in DMF at 80 °C to give **11** in 78% yield. Compound **11** was subsequently deprotected using Pd(II) complex in a H_2O/THF mixture at 80 °C to generate the

naphtol derivative **12** in 88% Yield.



Scheme 2. Synthesis of phenol derivative **12**.

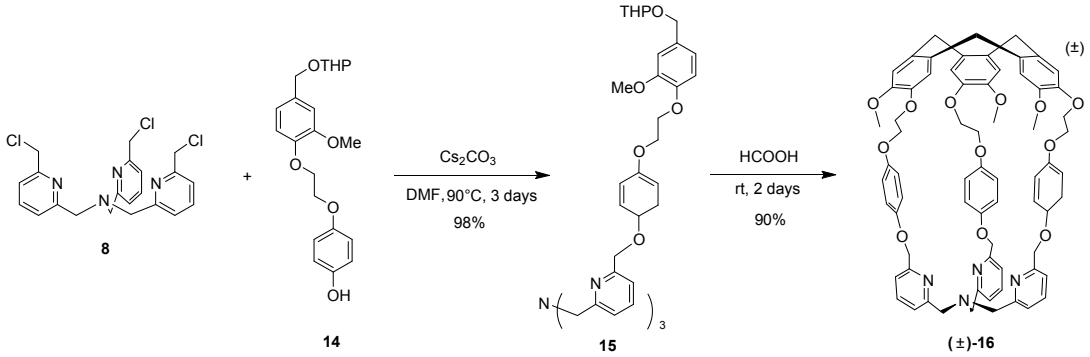
Hemicryptophane precursor **13** was prepared in one step (98% yield) by heating a solution of **8** and **12** in DMF at 90 °C for 3 days in the presence of Cs_2CO_3 as a base (Scheme 3). The intramolecular cyclization of **13**, first performed in formic acid, led to low yields because of purification issues: several side products were very difficult to separate from the cage compounds. Finally, the use of stoichiometric amounts of Lewis acid $Sc(OTf)_3$ in CH_3CN at 65 °C provided *rac*-hemicryptophane (±)-**1** with a yield of 49%.



Scheme 3. Synthesis of the racemic mixture of hemicryptophane (±)-**1**.

Given the modular feature of this synthetic pathway, we decided to change the naphtyl linkers to phenyl ones in order to prepare the hemicryptophane analogue (±)-**16** presenting a smaller cavity (Scheme 4). Compound **14** was first obtained following the known procedure.[5a] The hemicryptophane precursor **15** was synthesized from **14**, following a synthetic route similar to that used to get **13** from **12**. The macrocyclization of **15** in formic acid afforded the racemic mixture (±)-**16** in 90% yield. Remarkably, hemicryptophane **16** was easily isolated by simple precipitation in CH_2Cl_2/Et_2O without the need of column chromatography purification. The preorganization of the precursor of cyclization in formic acid can account for the remarkable yield obtained. Moreover, because the yields of the previous steps were relatively high, gram-scale synthesis of (±)-**16** could be

achieved. This constitutes an important step for the future development of this class of host compounds as sensors or catalysts, considering the common limitation related to the difficulty of accessing cage compounds on a large scale.[1a]



Scheme 4. Synthesis of the racemic mixture of hemicryptophane (±)-**16**.

The ^{1}H NMR spectra of (±)-**1** and (±)-**16** indicate that the molecules are, on average, of C_3 symmetry in solution (Figure 2). They display the usual features of the structure of the CTV unit, *i.e.* two singlets for the aromatic protons, one singlet for the OCH_3 groups, and the characteristic AB system for the $ArCH_2$ bridges.[1a,1b] The protons on aromatic TPA and linkers, and the multiplets for the OCH_2 linkers in each cage were carefully assigned by 2D NMR experiments (see SI).

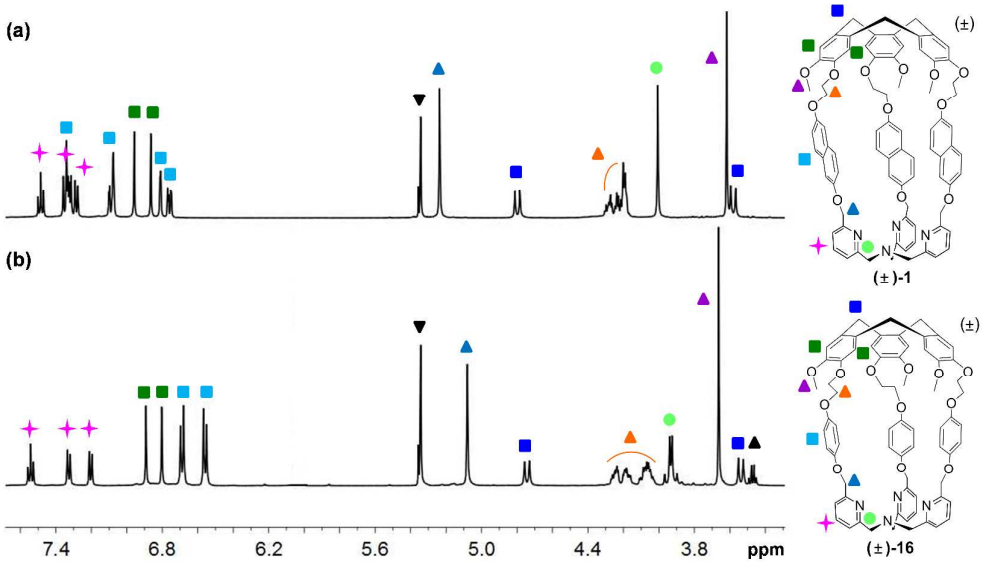
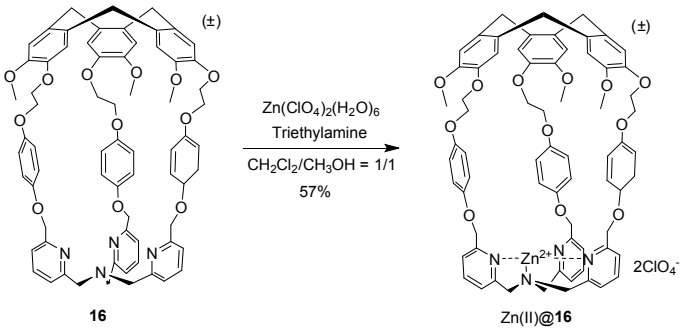


Figure 2. ^{1}H NMR spectra (500.1 MHz, CD_2Cl_2, 298 K) of hemicryptophanes (±)-**1** (a) and (±)-**16** (b) and their protons assignment. ▼ = $CHDCl_2$; ▲ = Et_2O.

To test the metal coordination ability of the TPA units of hemicryptophanes, we prepared the zinc complex Zn(II)@**16** by mixing the ligand **16** and $Zn(ClO_4)_2$ in a $CHCl_2/CH_3OH$ mixture (1/1, v/v) (Scheme 5). The pure Zn(II)@**16** complex gradually precipitates within four hours, and was fully

characterized in DMSO-d_6 by a series of NMR experiments (see SI) and HRMS spectroscopy. The ^{1}H NMR spectrum of Zn(II)@**16** is consistent with that of the previously reported Zn(II)@hemicryptophane complex bearing tren unit,[4b] and exhibits complicated and broad signals because of the conformational rigidification of the whole structure induced by the metal complexation (Figure S11).



Scheme 5. Synthesis of hemicryptophane complex Zn(II)@**16**.

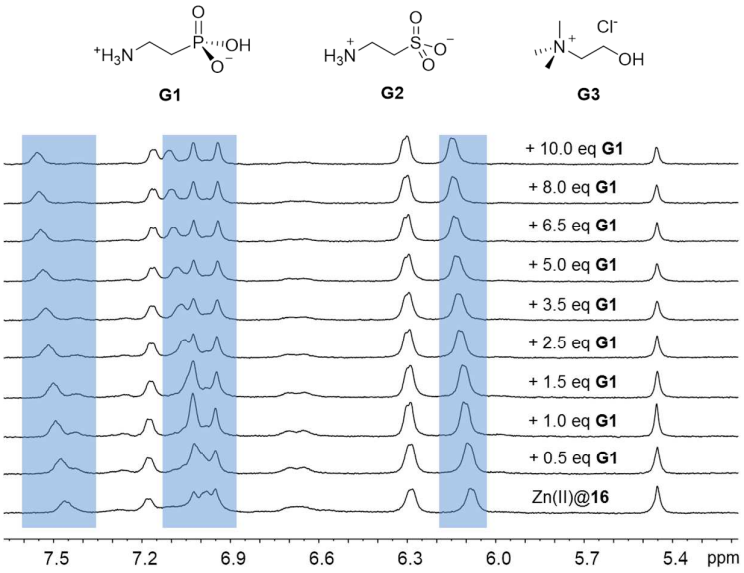


Figure 3. Zwitterionic guests **G1-G3** tested in this work and ^{1}H NMR titration spectra (500.1 MHz, 298 K) of **G1** with 1 mM hemicryptophane host Zn(II)@**16** in DMSO-d_6/D_2O (80/20, v/v).

The heteroditopic character of the new complex, prompted us to test its recognition properties toward zwitterionic guests.[19] As shown in Figure 3, upon stepwise addition of zwitterionic **G1** to a DMSO-d_6/D_2O (80/20, v/v) solution of Zn(II)@**16**, several signals in the ^{1}H NMR spectrum shifted gradually, indicating that the host-guest complexation is fast on the NMR time-scale. Previously, our group also reported three other heteroditopic hemicryptophanes which showed high selectivity toward either taurine **G2**[19a,b] or choline **G3**[19c] (Figure 3). However, in the present case, no obvious change of the ^{1}H NMR spectra of Zn(II)@**16** was observed after addition of **G2** or **G3**, highlighting the

selectivity of the new host and also the possibility to tune the structure of hemicryptophanes to encapsulate selectively a targeted zwitterionic guest of biological interest.

As enantiopure hosts are very helpful in chiral recognition, asymmetric catalysis, and chirality sensing,[2] we optically resolved the hemicryptophane racemates (±)-**1** and (±)-**16** using chiral HPLC (see SI). In the case of (±)-**1**, the two enantiomers were separated on a Chiralpak IA column (250 × 4.6 mm) with an enantioselectivity of 1.52 and a resolution of 2.3, using heptane/ethanol/CH_2Cl_2/triethylamine (20/40/40/0.1) as the mobile phase. At preparative scale, after multiple injections on a Chiralpak IA column (250 × 10 mm), around 80 mg of each enantiomer were obtained in 12 h with *ee* values of 99% and 90% for the first and second eluted compounds, respectively. For (±)-**16**, the same eluent used with a Chiralpak ID column, gave the two enantiomers with an enantioselectivity of 1.51 and a resolution of 4.6 for the analytical separation. Preparative scale separation afforded around 50 mg of each enantiomer with *ee* values > 99% in 3 h. The absolute configuration of each enantiopure hemicryptophane was determined by ECD spectroscopy recorded in CH_2Cl_2 at 298 K by comparison with already assigned hemicryptophanes.[20] As shown in Figure 4, in both cases, the spectra of the first eluted enantiomers exhibit a characteristic positive-negative bisignate curve from 230-250 nm corresponding to the *M*-configuration. The second eluted enantiomers show mirrored ECD signals allowing the assignment of the *P*-configuration.[20]

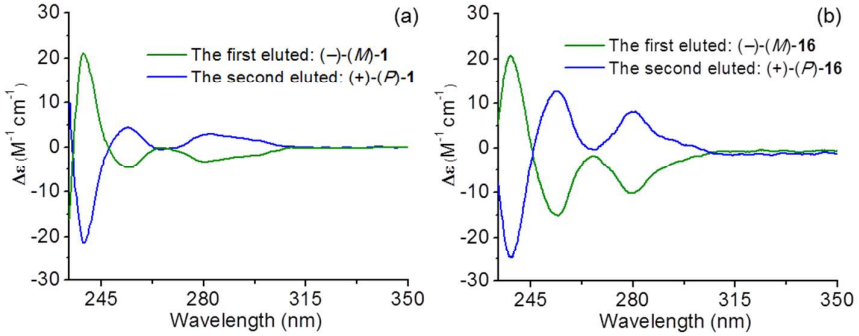


Figure 4. Experimental ECD spectra in CH_2Cl_2 at 298 K of: (a) (+)-(*P*)-**1** (blue) and (–)-*M*-**1** (green), and (b) (+)-(*P*)-**16** (blue) and (–)-*M*-**16** (green).

CONCLUSION

In summary, we have described the synthesis of two hemicryptophanes (**1** and **16**) belonging to a new class of TPA-based hemicryptophane cages. According to the metal binding abilities of the TPA units, these hemicryptophanes are chemical platforms available for various purposes and applications. This has been illustrated by the preparation of a Zn(II) complex and its subsequent use for the selective recognition of zwitterionic guests. Despite the 14 steps involved in the synthesis of each molecular cage, all the reactions are quite straightforward with relatively high yields. In

particular, benefiting from a remarkable 90% yield for a triple macrocyclization reaction, gram-scale synthesis of hemicryptophane **16** was achieved. The racemate of each hemicryptophane can be readily resolved by chiral HPLC to give the enantiopure cages of which absolute configurations have been assigned by ECD spectroscopy. Currently, the preparation of metal complexes for these new cages, such as Cu(I) and Fe(II), and their applications in molecular recognition and supramolecular catalysis are being investigated and will be reported in due course.

EXPERIMENTAL SECTION

Methods and Materials. All reactions were carried out under argon by means of an inert gas/vacuum double manifold and standard Schlenk techniques. Dichloromethane was dried and degassed on a solvent station by passage through an activated alumina column followed by argon flush. Other solvents were dried prior to use over molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded at 500.1 and 125.7 MHz, respectively, and δ chemical shifts are reported relative to the residual solvent signal. The HRMS-ESI mass spectra were recorded in positive-ion mode (or negative) on a hybrid quadrupole time-of-flight mass spectrometer with an electrospray ionization (ESI) ion source. Specific rotations (in deg cm^2g^{-1}) were measured in a 1 dm thermostated quartz cell on a Jasco-P1010 polarimeter. Circular dichroism spectra were recorded on a CD6 Jobin-Yvon dichrograph.

Synthesis of 8 and 9. Compound **8** was prepared starting from 2,6-pyridinedicarboxylic acid **2** according to the reported procedures.[18,21] Compound **9** was synthesized according to the published procedure.[22]

Synthesis of 11. A solution of **9** (100 mg, 0.500 mmol), **10** (172 mg, 0.500 mmol), and Cs_2CO_3 (244 mg, 0.750 mmol) in DMF (4 mL) was stirred for 2 days at 80 °C under argon. Then AcOEt (30 mL) and 10% aqueous NaOH (30 mL) were added. The organic layer was separated, and the aqueous phase was extracted with AcOEt (2 × 30 mL). The combined organic layers were washed with 10% aqueous NaOH (2 × 30 mL) and dried over Na_2SO_4. After filtration, the organic solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with a 400 : 3 mixture of CH_2Cl_2 : MeOH as eluent to give compound **11** as a light yellow solid (180 mg, 0.39 mmol, 78% yield). ^{1}H NMR ($CDCl_3$, 298K, 500.1 MHz): δ 7.65 (dd, J = 8.9, 1.9 Hz, 2H); 7.21-7.14 (m, 4H); 7.00-6.93 (m, 3H); 6.19-6.11 (m, 1H); 5.50 (dd, J = 17.3, 1.4 Hz, 1H); 5.35 (dd, J = 10.5, 1.2 Hz, 1H); 4.76 (d, J = 11.7 Hz, 1H); 4.72 (t, J = 3.6 Hz, 1H); 4.66 (d, J = 5.3 Hz, 1H); 4.50-4.47 (m, 5H); 3.98-3.91 (m, 1H); 3.90 (s, 3H); 3.60-3.56 (m, 1H); 1.93-1.62 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 298K, 125.7 MHz): δ 155.2(5), 155.1(9), 149.8, 147.7, 133.4, 131.9, 129.9, 129.8, 128.3, 128.2, 120.6, 119.3(1), 119.2(8), 117.7, 114.2, 112.1, 107.4, 107.3, 97.6, 69.0, 68.8, 68.0, 66.6, 62.4, 56.0, 30.7, 25.5, 19.5 ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{28}H_{32}NaO_6$ 487.2091; Found 487.2077. M.p. = 99 °C.

Synthesis of 12. In a 25 mL round bottom flask, **11** (750 mg, 1.62 mmol), $Pd(OAc)_2$ (7.3 mg, 0.033 mmol), PPh_3 (28.5 mg, 0.110 mmol), $NHEt_2$ (25.1 mmol), H_2O (2 mL) and THF (8 mL) were mixed and stirred at 80 °C under argon for 4 h. Then the mixture was cooled to r.t., and the solvents were removed under vacuum. AcOEt (10 mL) was first added and then removed under vacuum twice. AcOEt (200 mL) and H_2O (100 mL) were then added. After thoroughly mixing, the organic layer was separated, and the aqueous phase was extracted with AcOEt (2 × 30 mL). The combined organic layers were dried over Na_2SO_4, and the organic solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with a 20 : 3 mixture of CH_2Cl_2 : AcOEt as eluent to give compound **12** as a light yellow solid (600 mg, 1.41 mmol, 88% yield). ^{1}H NMR ($CDCl_3$, 298K, 500.1 MHz): δ 7.60 (dd, J = 15.1, 8.3 Hz, 2H); 7.18-7.08 (m, 4H); 7.00-6.93 (m, 3H); 5.10 (s, 1H); 4.76 (d, J = 11.7 Hz, 1H); 4.72 (t, J = 3.7 Hz, 1H); 4.50-4.43 (m, 5H); 3.99-3.94 (m, 1H); 3.90 (s, 3H); 3.61-3.57 (m, 1H); 1.93-1.63 (m, 6H) ppm. ^{13}C NMR ($CDCl_3$, 298K, 125.7 MHz): δ 155.1, 152.0, 149.7, 147.7, 131.8, 130.0, 129.6, 128.5, 127.8, 120.6, 119.6, 118.1, 114.1, 112.1, 109.7, 107.2, 97.7, 68.8, 67.9, 66.5, 62.4, 56.0, 30.7, 25.5, 19.5 ppm. HRMS (ESI-TOF) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{28}NaO_6$ 447.1778; Found 447.1763. M.p. > 70 °C (decomp.).

Synthesis of 13. In a 50 mL round bottom flask, **8** (100 mg, 0.230 mmol), **12** (321 mg, 0.757 mmol), Cs_2CO_3 (337 mg, 1.04 mmol), and DMF (10 mL) were mixed and stirred at 90 °C for 3 days. Then the mixture was cooled to r.t., and DMF was removed under vacuum. CH_2Cl_2 (200 mL) and H_2O (200 mL) were then added. After thoroughly mixing, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layers were dried over Na_2SO_4, and the organic solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with a 18 : 1 mixture of CH_2Cl_2 : MeOH as eluent to give hemicryptophane precursor **13** as a yellow solid (330 mg, 0.207 mmol, 90% yield). ^{1}H NMR ($CDCl_3$, 298K, 500.1 MHz): δ 7.72-7.65 (m, 6H); 7.61-7.56 (m, 6H); 7.46 (d, J = 7.7 Hz, 3H); 7.26 (dd, J = 8.9, 2.5 Hz, 3H); 7.20-7.16 (m, 9H); 6.99-6.92 (m, 9H); 5.31 (s, 6H); 4.75 (d, J = 11.7 Hz, 3H); 4.72 (t, J = 3.5 Hz, 3H); 4.49-4.44 (m, 15H); 4.01(s, 6H); 3.98-3.93 (m, 3H); 3.89 (s, 9H); 3.59-3.56 (m, 3H); 1.90-1.54 (m, 18H) ppm. ^{13}C NMR ($CDCl_3$, 298K, 125.7 MHz): δ 159.1, 156.7, 155.3, 155.0, 149.8, 147.7, 137.3, 131.9, 129.9, 129.8, 128.3, 121.8, 120.6, 119.6, 119.3, 119.1, 114.2, 112.1, 107.8, 107.3, 97.6, 70.8, 68.8, 67.9, 66.6, 62.4, 60.3, 56.0, 30.7, 25.5, 19.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{96}H_{103}N_4O_{18}$ 1599.7262; Found 1599.7249. M.p. > 64 °C (decomp.).

Synthesis of hemicryptophane (±)-1. A solution of hemicryptophane precursor **13** (100 mg, 63.0 µmol) in CH_3CN (18 mL) was added dropwise (4 hours) under argon at 65 °C to a solution of $Sc(OTf)_3$ (44 mg, 88 µmol) in CH_3CN (46 mL). The mixture was stirred under argon at 65 °C for 24 hours. The solvent was then evaporated. The crude product was purified by column chromatography on silica

gel with a 200 : 5 : 1 mixture of $CHCl_3$: MeOH : triethylamine as eluent to give hemicryptophane (±)-**1** as a light yellow solid (40 mg, 88 µmol, 49% yield). The crude product could be also used directly for the following resolution procedure.

Chiral HPLC analysis for (±)-1. On a Chiralpak IA column (250 × 4.6 mm), with 1 $mL.min^{-1}$ as flow-rate, heptane/EtOH/CH_2Cl_2/TEA (20/40/40/0.1) as mobile phase, UV detection at 254 nm, Rt(*M*-**1**) = 4.7 min, Rt(*P*-**1**) = 5.6 min, k(*M*-**1**) = 0.59, k(*P*-**1**) = 0.90, α = 1.52 and Rs = 2.3.

Resolution of hemicryptophane (±)-1. The crude product of (±)-**1** (320 mg) was dissolved in 25 mL of CH_2Cl_2. On a Chiralpak IA column (250 × 10 mm), with 5 mL min^{-1} as flow-rate, hexane/EtOH/CH_2Cl_2/TEA (20/40/40/0.1) as mobile phase, UV detection at 254 nm, 210 injections of 120 µL were stacked every 3.5 minutes. Both enantiomers were collected and the solvent was then evaporated. The first eluted enantiomer ((–), *M*-**1**, 84 mg) was obtained with 99% *ee*, and the second one ((+), *P*-**1**, 73 mg) with 90% *ee*. *P*-**1**: $[\propto]_D^{25}$: +38 (c = 0.114; CH_2Cl_2); *M*-**1**: $[\propto]_D^{25}$: -35 (c = 0.114; CH_2Cl_2). ^{1}H NMR (CD_2Cl_2, 298K, 500.1 MHz): δ 7.48 (t, *J* = 7.7 Hz, 3H); 7.36-7.28 (m, 12H); 7.10-7.08 (m, 6H); 6.96 (s, 3H); 6.86 (s, 3H); 6.81 (d, *J* = 2.3 Hz, 3H); 6.76 (dd, *J* = 8.9, 2.5 Hz, 3H); 5.24 (s, 6H); 4.80 (d, *J* = 13.7 Hz, 3H); 4.30-4.19 (m, 12H); 4.01 (s, 6H); 3.62 (s, 9H); 3.58 (d, *J* = 13.7 Hz, 3H) ppm. ^{13}C NMR (CD_2Cl_2, 298K, 125.7 MHz): δ 158.8, 156.6, 154.9, 154.6, 148.7, 146.9, 136.8, 133.1, 132.0, 129.7, 129.6, 128.1, 128.0, 122.2, 119.5, 119.2, 118.9, 118.7, 116.6, 113.9, 108.4, 107.4, 70.9, 68.2, 66.7, 60.6, 56.0, 36.2 ppm. For COSY, HSQC and HMBC, see SI. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{81}H_{73}N_4O_{12}$ 1293.5220; Found 1293.5202. M.p. > 250 °C (decomp.).

Synthesis of 15. In a 100 mL round bottom flask, **8** (225 mg, 0.516 mmol), **14** (638 mg, 1.70 mmol), Cs_2CO_3 (757 mg, 2.32 mmol), and DMF (22 mL) were mixed and stirred at 90 °C for 3 days. Then the mixture was cooled to r.t., and DMF was removed under vacuum. 300 mL CH_2Cl_2 and 300 mL H_2O were then added. After thoroughly mixing, the organic layer was separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, and the organic solvent was removed under vacuum. The crude product was purified by column chromatography on silica gel with a 25 : 1 mixture of CH_2Cl_2 : MeOH as eluent to give hemicryptophane precursor **15** as a white solid (728 mg, 0.504 mmol, 98% yield). ^{1}H NMR ($CDCl_3$, 298K, 500.1 MHz): δ 7.70 (t, *J* = 7.8 Hz, 3H); 7.55 (d, *J* = 7.7 Hz, 3H); 7.40 (d, *J* = 7.7 Hz, 3H); 6.96-6.88 (m, 21H); 5.15 (s, 6H); 4.75 (d, *J* = 11.8 Hz, 3H); 4.71 (t, *J* = 3.5 Hz, 3H); 4.47 (d, *J* = 11.8 Hz, 3H); 4.36 (t, *J* = 5.0 Hz, 6H); 4.30 (t, *J* = 5.0 Hz, 6H); 3.98-3.89 (m, 9H); 3.88 (s, 9H); 3.60-3.55 (m, 3H); 1.91-1.54 (m, 18H) ppm. ^{13}C NMR ($CDCl_3$, 298K, 125.7 MHz): δ 159.0, 156.9, 153.1, 152.9, 149.8, 147.7, 137.2, 131.8, 121.6, 120.6, 119.5, 116.1, 116.0, 115.8, 115.7, 114.1, 112.1, 97.6, 71.3, 68.8, 68.0, 67.2, 62.3, 56.0, 30.7, 25.5, 19.5 ppm. HRMS (ESI-TOF) m/z: $[M + H]^+$ Calcd for $C_{84}H_{97}N_4O_{18}$ 1449.6792; Found 1449.6768. M.p. > 70 °C (decomp.).

Synthesis of hemicryptophane (±)-16. In a 2 L round bottom flask, the hemicryptophane precursor **15** (1.45 g, 1.00 mmol), HCOOH (1 L) and CH_2Cl_2 (10 mL) were added. The mixture was stirred at r.t. for 2 days. Then HCOOH was removed under vacuum and yellow oil was obtained. CH_2Cl_2 (100 mL) and TEA (5 mL) were added and then evaporated. Finally CH_2Cl_2 (3 mL) was added to fully solubilize the crude product followed by the addition of Et_2O (300 mL) to precipitate the product. After filtration and washing with Et_2O, the pure (±)-**16** was obtained as a white solid (1.03 g, 0.900 mmol, 90% yield).

Chiral HPLC analysis for (±)-16. On Chiralpak ID column (250 × 4.6 mm), with 1 mL min^{-1} as flow-rate, heptane/EtOH/CH_2Cl_2/TEA (20/40/40/0.1) as mobile phase, UV detection at 254 nm, Rt(*M*-**16**) = 8.7 min, Rt(*P*-**16**) = 11.7 min, k(*M*-**16**) = 1.92, k(*P*-**16**) = 2.90, α = 1.51 and Rs = 4.6.

Resolution of hemicryptophane (±)-16. The pure product of (±)-**16** (100 mg) was dissolved in 5.2 mL of CH_2Cl_2. On a Chiralpak ID column (250 × 10 mm), with 5 mL min^{-1} as flow-rate, hexane/EtOH/CH_2Cl_2/TEA (20/40/40/0.1) as mobile phase, UV detection at 300 nm, 26 injections of 200 µL were stacked every 7.2 minutes. Both enantiomers were collected and the solvent was then evaporated. The first eluted enantiomer ((–), *M*-**16**, 46 mg) and the second one ((+), *P*-**16**, 48 mg) were obtained with both *ee* values > 99%. *P*-**16**: $[\propto]_D^{25}$: +52 (c = 0.27; CH_2Cl_2); *M*-**16**: $[\propto]_D^{25}$: -52 (c = 0.25; CH_2Cl_2). ^{1}H NMR (CD_2Cl_2, 298K, 500.1 MHz): δ 7.56 (t, *J* = 7.7 Hz, 3H); 7.34 (d, *J* = 7.4 Hz, 3H); 7.22 (d, *J* = 7.7 Hz, 3H); 6.90 (s, 3H); 6.82 (s, 3H); 6.70 (d, *J* = 9.0 Hz, 6H); 6.56 (d, *J* = 9.0 Hz, 6H); 5.08 (s, 6H); 4.75 (d, *J* = 13.7 Hz, 3H); 4.27-4.23 (m, 3H); 4.19-4.15 (m, 3H); 4.09-4.03 (m, 6H); 3.97-3.90 (m, 6H); 3.66 (s, 9H); 3.54 (d, *J* = 13.7 Hz, 3H) ppm. ^{13}C NMR (CD_2Cl_2, 298K, 125.7 MHz): δ 158.7, 156.8, 152.6, 148.8, 146.7, 136.8, 133.1, 131.9, 122.2, 119.4, 116.7, 115.7, 115.6, 113.8, 71.2, 68.2, 67.2, 60.5, 56.0, 36.1 ppm. For COSY, HSQC and HMBC, see SI. HRMS (ESI-TOF) m/z: $[M + 2H]^{2+}$ Calcd for $C_{69}H_{68}N_4O_{12}$ 572.2411; Found 572.2398. M.p. = 260 °C.

Synthesis of the racemic hemicryptophane complex Zn(II)@16. To a solution of (±)-**16** (47 mg, 0.041 mmol) in 4 mL $CHCl_2$, 12 µL triethylamine was added under argon followed by addition of the solution of $Zn(ClO_4)_2(H_2O)_6$ (15 mg, 0.041 mmol, 1 equivalent) in 2.5 mL CH_3OH. After stirring the reaction mixture at room temperature for 4 hours, a large amount of precipitate appeared. The precipitate was collected, washed thoroughly with Et_2O and dried under vacuum to give the pure complex as a white solid (33 mg, 0.023 mmol, 57% yield). The ^{1}H NMR spectrum of Zn(II)@**16** exhibits complex and broad signals because of the conformational rigidification of the whole structure induced by the metal complexation that gives different isomers, which is similar as the previously reported Zn(II)@Hemicryptophane complex.[4b] For the detailed spectra of ^{1}H NMR, ^{13}C NMR, COSY, HSQC and HMBC, see SI. HRMS (ESI-TOF) m/z: $[M + HCOO]^+$ Calcd for $C_{70}H_{67}N_4O_{14}Zn$ 1251.3940; Found 1251.3930; $[M + Cl]^+$ Calcd for $C_{69}H_{66}ClN_4O_{12}Zn$ 1241.3652; Found 1241.3640. M.p. > 220 °C

(decomp.).

SUPPORTING INFORMATION

^{1}H, ^{13}C, and 2D NMR spectra, chiral HPLC reports for resolution of (±)-**1** and (±)-**16**.

AUTHOR INFORMATION

E-mail: alexandre.martinez@centrale-marseille.fr

ACKNOWLEDGEMENT

D.Z. acknowledges grants from the China Scholarship Council, the Région Auvergne-Rhône-Alpes, France, for an Accueil Doc Bursary, and ENS-Lyon for an Attractiveness Fellowship for PhD studies. A.M. would like to thank ANR OH-risque for funding, grant number: ANR-14-OHRI-0015-01.

REFERENCES

(1) (a) Zhang, D.; Martinez, A.; Dutasta, J. P. *Chem. Rev.* **2017**, *117*, 4900. (b) Ajami, D.; Liu, L. J.; Rebek, J. *Chem. Soc. Rev.* **2015**, *44*, 490. (c) Zarra, S.; Wood, D. M.; Roberts, D. A.; Nitschke, J. R. *Chem. Soc. Rev.* **2015**, *44*, 419. (d) Brown, C. J.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. *Chem. Rev.* **2015**, *115*, 3012. (e) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1660. (f) Blanco, V.; Leigh, D. A.; Marcos V. *Chem. Soc. Rev.*, **2015**, *44*, 5341.

(2) Hembury, G. A.; Borovkov, V. V.; Inoue, Y. *Chem. Rev.* **2008**, *108*, 1.

(3) (a) Wiester, M. J.; Ulmann, P. A.; Mirkin, C. A. *Angew. Chem., Int. Ed.* **2011**, *50*, 114. (b) Jaeger, K. E.; Eggert, T. *Curr. Opin. Biotech.* **2004**, *15*, 305. (c) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2014**, *43*, 1734.

(4) (a) Chatelet, B.; Payet, E.; Perraud, O.; Dimitrov-Raytchev, P.; Chapellet, L. L.; Dufaud, V.; Martinez, A.; Dutasta, J. P. *Org. Lett.* **2011**, *13*, 3706. (b) Zhang, D. W.; Gao, G. H.; Guy, L.; Robert, V.; Dutasta, J. P.; Martinez, A. *Chem. Commun.* **2015**, *51*, 2679.

(5) (a) Gautier, A.; Mulatier, J. C.; Crassous, J.; Dutasta, J. P. *Org. Lett.* **2005**, *7*, 1207. (b) Zhang, D. W.; Mulatier, J. C.; Cochrane, J. R.; Guy, L.; Gao, G. H.; Dutasta, J. P.; Martinez, A. *Chem. Eur. J.* **2016**, *22*, 8038.

(6) (a) Muhldorf, B.; Wolf, R. *Angew. Chem., Int. Ed.* **2016**, *55*, 427. (b) Oloo, W. N.; Fielding, A. J.; Que, L. *J. Am. Chem. Soc.* **2013**, *135*, 6438.

(7) (a) Isse, A. A.; Visona, G.; Ghelfi, F.; Roncaglia, F.; Gennaro, A. *Adv. Synth. Catal.* **2015**, *357*, 782. (b) Eckenhoff, W. T.; Biernesser, A. B.; Pintauer, T. *Inorg. Chem.* **2012**, *51*, 11917. (c) Pan, X. C.; Malhotra, N.; Simakova, A.; Wang, Z. Y.; Konkolewicz, D.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2015**,

137, 15430.

(8) (a) Badetti, E.; Wurst, K.; Licini, G.; Zonta, C. *Chem. Eur. J.* **2016**, *22*, 6515. (b) Scaramuzzo, F. A.; Licini, G.; Zonta, C. *Chem. Eur. J.* **2013**, *19*, 16809. (c) Lei, Z. Q.; Polen, S.; Hadad, C. M.; RajanBabu, T. V.; Badjic, J. D. *J. Am. Chem. Soc.* **2016**, *138*, 8253.

(9) (a) Wang, H. Y.; Mijangos, E.; Ott, S.; Thapper, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 14499. (b) Woods, T. J.; Ballesteros-Rivas, M. F.; Ostrovsky, S. M.; Palii, A. V.; Reu, O. S.; Klokishner, S. I.; Dunbar, K. R. *Chem. Eur. J.* **2015**, *21*, 10302.

(10) (a) Chatelain, L.; Walsh, J. P. S.; Pecaut, J.; Tuna, F.; Mazzanti, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 13434. (b) Aratani, Y.; Yamada, Y.; Fukuzumi, S. *Chem. Commun.* **2015**, *51*, 4662.

(11) (a) Sawaki, T.; Ishizuka, T.; Kawano, M.; Shiota, Y.; Yoshizawa, K.; Kojima, T. *Chem. Eur. J.* **2013**, *19*, 8978. (b) Weisser, F.; Stevens, H.; Klein, J.; van der Meer, M.; Hohloch, S.; Sarkar, B. *Chem. Eur. J.* **2015**, *21*, 8926.

(12) (a) Kotani, H.; Sugiyama, T.; Ishizuka, T.; Shiota, Y.; Yoshizawa, K.; Kojima, T. *J. Am. Chem. Soc.* **2015**, *137*, 11222. (b) Desnoyer, A. N.; Behyan, S.; Patrick, B. O.; Dauth, A.; Love, J. A.; Kennepohl, P. *Inorg. Chem.* **2016**, *55*, 13.

(13) Saad, F. A.; Knight, J. C.; Kariuki, B. M.; Amoroso, A. J. *Dalton Trans.* **2016**, *45*, 10280.

(14) Andrez, J.; Bozoklu, G.; Nocton, G.; Pecaut, J.; Scopelliti, R.; Dubois, L.; Mazzanti, M. *Chem. Eur. J.* **2015**, *21*, 15188.

(15) Ngo, H. T.; Liu, X. J.; Jolliffe, K. A. *Chem. Soc. Rev*. **2012**, *41*, 4928.

(16) (a) Canary, J. W.; Mortezaei, S.; Liang, J. A. *Coordin Chem. Rev.* **2010**, *254*, 2249. (b) Canary, J. W. *Chem. Soc. Rev.* **2009**, *38*, 747.

(17) (a) You, L.; Berman, J. S.; Anslyn, E. V. *Nat. Chem.* **2011**, *3*, 943. (b) Joyce, L. A.; Maynor, M. S.; Dragna, J. M.; da Cruz, G. M.; Lynch, V. M.; Canary, J. W.; Anslyn, E. V. *J. Am. Chem. Soc.* **2011**, *133*, 13746. (c) Jo, H. H.; Edupuganti, R.; You, L.; Dalbyc, K. N.; Anslyn, E. V. *Chem. Sci.* **2015**, *6*, 158.

(18) Zeng, X. S.; Coquiere, D.; Alenda, A.; Garrier, E.; Prange, T.; Li, Y.; Reinaud, O.; Jabin, I. *Chem. Eur. J.* **2006**, *12*, 6393.

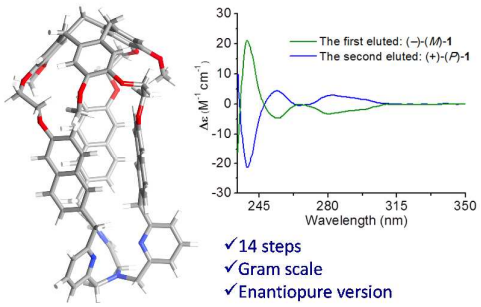
(19) (a) Perraud, O.; Robert, V.; Martinez A.; Dutasta, J. P. *Chem. Eur. J.*, **2011**, *17*, 13405. (b) Perraud, O.; Robert, V.; Gornitzka, H.; Martinez A.; Dutasta, J. P. *Angew. Chem.*, *Int. Ed.*, **2012**, *51*, 504. (c) Schmitt, A.; Robert, V.; Dutasta, J. P.; Martinez, A. *Org. Lett.*, **2014**, *16*, 2374.

(20) (a) Schmitt, A.; Perraud, O.; Payet, E.; Chatelet, B.; Bousquet, B.; Valls, M.; Padula, D.; Di Bari, L.; Dutasta, J. P.; Martinez, A. *Org. Biomol. Chem.* **2014**, *12*, 4211. (b) Perraud, O.; Dimitrov-Raytchev, P.; Martinez, A.; Dutasta, J. P. *Chirality* **2010**, *22*, 88. (c) Cochrane, J. R.; Schmitt, A.; Wille, U.; Hutton, C. A. *Chem. Commun.* **2013**, *49*, 8504. (d) Canceill, J.; Collet, A.; Gabard, J.; Gottarelli, G.; Spada, G. P. *J. Am. Chem. Soc.* **1985**, *107*, 1299. (e) Canceill, J.; Collet, A.; Gottarelli, G.; Palmieri, P. *J. Am. Chem. Soc.* **1987**, *109*, 6454.

(21) Liu, X.; Bouwman, E. *Polyhedron* **2016**, *118*, 25.

(22) Hau, S. C. K.; Cheng, P. S.; Mak, T. C. W. *Polyhedron* **2013**, *52*, 992.

TOC


The first eluted: (−)-(M)-1
The second eluted: (+)-(P)-1
Δε (M⁻¹ cm⁻¹)
Wavelength (nm)
✓14 steps
✓Gram scale
✓Enantiopure version