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

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

To cite this version:
Dawei Zhang, Benjamin Bousquet, Jean-Christophe Jean, Delphine Pitrat, Marion Jean, et al.. Synthesis, Resolution, and Absolute Configuration of Chiral Tris(2-pyridylmethyl)amine-Based Hemicryptophane Molecular Cages. Journal of Organic Chemistry, American Chemical Society, 2017, 82 (12), pp.6082-6088. <10.1021/acs.joc.7b00559>. <hal-01682759>

HAL Id: hal-01682759
https://hal.archives-ouvertes.fr/hal-01682759
Submitted on 20 Apr 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L’archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d’enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.
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‡,†,‡

*Laboratoire de Chimie, École Normale Supérieure de Lyon, CNRS, UCBL, 46 allée d’Italie, F-69364 Lyon, France
†Aix Marseille Univ, CNRS, UCBL, 46 allée d’Italie, F-69364 Lyon, France
§Laboratoire de Chimie, École Normale Supérieure de Lyon, CNRS, UCBL, 46 allée d’Italie, F-69364 Lyon, France

ABSTRACT: The synthesis, characterization, and chiroptical properties of a new class of hemicryptophane cages combining a cyclotriveratrylene unit and a tris(2-pyridylmethyl)amine (TPA) moiety are reported. Changing the linksers 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. In particular, biomimetic chiral cages arouse a growing interest because of the important role of chirality in nature. One prominent example is substrate binding and transformation by enzymes, displaying high chemoselectivity, regioselectivity, and stereospecificity. Among the chiral cages, hemicryptophanes, which combine a cyclotriveratrylene (CTV) unit with another C3-symmetric moiety, exhibit remarkable properties in molecular recognition and supramolecular catalysis. 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 C3-symmetrical moiety.

To construct novel hemicryptophane scaffolds, tripod building blocks, such as tris(2-aminoethyl)-amine (tren) and trialkanolamine units, have been attached to the CTV unit. The usefulness and easy availability should be considered when choosing this C3-symmetric group. In this regard, the 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 Fe6, Cu6, Zn8, Co9, Mn10, Ru11, Rh12, Ni13, and Ln14. The resulting complexes have been extensively used in recognition15 catalysis,6,7,10a,11b,12 chiroptical molecular switches,16 and enantiomeric excess (ee) determination.4a,h,17 For instance, the [Fe(TPA)(MeCN)2]2−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.4a,h,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.18

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.

**RESULTS AND DISCUSSION**

The structures of the enantiomeric hemicryptophanes M-1 and P-1 (Figure 1) present the following features: (i) first, 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) 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 the TPA unit, i.e., two singlets for the aromatic protons, one singlet for the protons on aromatic TPA and linkers, and one singlet for the OCH2 linkers in each cage were observed with 1H NMR spectra of (±)-1 and (±)-16 indicate that the molecules are, on average, of C2 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 OCH2 linkers, and the multiplets for the OCH2 linkers in each cage were carefully assigned by 2D NMR experiments (see the Supporting Information).

In order to prepare the hemicryptophane precursor 13, the naphtol derivative 12 was synthesized according to the pathway described in Scheme 2. First, 2,6-dihydroxynaphthalene was monosilylated-protected via its reaction with 1.0 equiv of allyl bromide in acetonitrile in the presence of K2CO3 to give allyloxynaphthol 9 in 29% yield. Then, 9 reacted with compound 10, obtained in three steps as described previously, in the presence of Cs2CO3 in DMF at 80 °C to give 11 in 78% yield. Compound 11 was subsequently deprotected using Pd(II) complex in a H2O/THF mixture at 80 °C to generate the naphtol derivative 12 in 88% yield. Hemicytrophe 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 Cs2CO3 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 CH3CN at 65 °C provided racemic cryptophane (±)-1 with a yield of 49%.

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. 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 CH2Cl2/Et2O without the need for column chromatography purification. The preorganization of the precursor of cyclization in formic acid can account for the remarkable yield obtained. Moreover, the yields of the previous steps were relatively high, and 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.

The 1H NMR spectra of (±)-1 and (±)-16 indicate that the molecules are, on average, of C2 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 OCH2 linkers, and the characteristic AB system for the ArCH2 groups. The protons on aromatic TPA and linkers and the multiplets for the OCH2 linkers in each cage were carefully assigned by 2D NMR experiments (see the Supporting Information).

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(ClO₄)₂ in a CHCl₃/CH₃OH mixture (1/1, v/v) (Scheme 5). The pure Zn(II)@16 complex gradually precipitates within 4 h and was fully characterized in DMSO-d₆ by a series of NMR experiments (see the Supporting Information) and HRMS spectroscopy. The ¹H 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 rigidity of the whole structure induced by the metal complexation (Figure S11).

The heteroditopic character of the new complex prompted us to test its recognition properties toward zwitterionic guests. As shown in Figure 3, upon stepwise addition of zwitterionic G1 to a DMSO-d₆/D₂O (80/20, v/v) solution of Zn(II)@16, several signals in the ¹H 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 or choline G3 (Figure 3). However, in the present case, no obvious change of the ¹H 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, we optically resolved the hemicryptophane racemates (±)-1 and (±)-16 using chiral HPLC (see the Supporting Information). 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/CH₂Cl₂/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 was 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 CH₂Cl₂ at 298 K by comparison with already assigned hemicryptophanes. As shown in Figure 4, in both cases, the spectra of the first eluted enantiomers exhibit a characteristic positive—negative bisignate curve from 230 to 250 nm corresponding to the M-configuration. The second eluted enantiomers show mirrored ECD signals allowing the assignment of the P-configuration.

**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. ¹H and ¹³C 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\(^{-1}\) g\(^{-1}\)) 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.\(^{21,22}\)

Compound 9 was synthesized according to the published procedure.\(^{22}\)

**Synthesis of 11.** A solution of 9 (100 mg, 0.50 mmol), 10 (172 mg, 0.500 mmol), and Cs$_2$CO$_3$ (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$_2$SO$_4$. 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$_2$Cl$_2$:MeOH as eluent to give compound 11 as a light yellow solid (180 mg, 0.39 mmol, 78% yield).\(^{1}H\) NMR (CDCl$_3$, 298 K, 500.1 MHz): δ 7.65 (dd, $J = 8.9$, 1.9 Hz, 2H); 7.21−7.14 (m, 1H); 7.00−6.93 (m, 3H); 6.91−6.81 (m, 1H); 5.50 (dd, $J = 17.4$, 1.9 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); 3.93−3.91 (m, 1H); 3.90 (s, 3H); 3.60−3.56 (m, 1H); 1.93−1.62 (m, 6H) ppm.

$^{13}$C NMR (CDCl$_3$, 298 K, 125.7 MHz): δ 155.1, 152.0, 149.7, 146.9, 148.7, 136.8, 133.1, 132.0, 129.7, 129.6, 128.1, 128.0, 126.9, 119.1, 114.2, 107.8, 107.3, 97.6, 70.8, 68.7, 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$_{25}$H$_{28}$NaO$_6$ 447.1778; Found 447.1768. **Synthesis of Hemicryptophane (±)-1.** A solution of hemicryptophane precursor 13 (100 mg, 0.207 mmol, 90% yield).\(^{1}H\) NMR (CDCl$_3$, 298 K, 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$_3$, 298 K, 125.7 MHz): δ 159.1, 156.7, 153.5, 150.4, 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, 68.7, 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$_{28}$H$_{32}$NaO$_{14}$ 559.7262; Found 559.7249. Mp $>$ 64°C (decomp.).

**Resolution of Hemicryptophane (±)-1.** A solution of hemicryptophane 13 (100 mg, 0.63 mmol) in CH$_2$CN (18 mL) was added dropwise (4 h) under argon at 65°C to a solution of Sc(OT$_3$) (44 mg, 88 pmol) in CH$_2$CN (46 mL). The mixture was stirred under argon at 65°C for 24 h. The solvent was then evaporated. The crude product was purified by column chromatography on silica gel with a 20:0.5:1 mixture of CHCl$_3$:MeOH:triethylamine as eluent to give hemicryptophane (±)-1 as a light yellow solid (40 mg, 88 pmol, 49% yield). The crude product could be also used directly for the following resolution.

**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$_2$Cl$_2$/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, $\alpha = 1.52$, and Rs = 2.3.

**Resolution of Hemicryptophane (±)-1.** The crude product of (±)-1 (320 mg) was dissolved in 25 mL of CH$_2$CN. On a Chiralpak IA column (250 × 10 mm), with 5 mL·min$^{-1}$ as flow-rate, hexane/EtOH/CH$_2$Cl$_2$/TEA (20/40/40/0.1) as mobile phase, UV detection at 254 nm, 210 injections of 120 μL were stacked every 3.5 min. 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: [α]$_{D}^{25}$ = +38 (c = 0.114; CH$_2$Cl$_2$); M-1: [α]$_{D}^{25}$ = −35 (c = 0.114; CH$_2$Cl$_2$).\(^{1}H\) NMR (CDCl$_3$, 298 K, 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 (CDCl$_3$, 298 K, 125.7 MHz): δ 158.8, 156.6, 154.9, 148.7, 148.6, 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, 60.5, 56.0, 36.2 ppm. For COSY, HSOQC, and HMBC, see the Supporting Information. HRMS (ESI-TOF) m/z:
[M + H]+ Calcld for C41H32N4O12 1293.5220; Found 1293.5202. Mp > 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), C6H2O7 (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 rt, and DMF was removed under vacuum. Then 300 mL CH2Cl2 and 300 mL H2O were added. After thoroughly mixing, the organic layer was separated, and the aqueous phase was extracted with CH2Cl2 (2 × 100 mL). The combined organic layers were dried over Na2SO4 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 CH2Cl2:MeOH as eluent and eluted by the metal complexation that gives diastereoisomers, which is similar as the previously reported Zn(II)@Hemicryptophane complex. For the detailed spectra of 1H NMR, 13C NMR, COSY, HSQC, and HMBC, see the Supporting Information. HRMS (ESI-TOF) m/z: [M + HCOO]+ Calcld for C61H47N4O12Zn 1251.3940; Found 1251.3930; [M + Cl]+ Calcld for C61H46ClN4O12Zn 1241.3652; Found 1241.3640. Mp > 220 °C (decomp.).

Chiral HPLC Analysis for (±)-16. On Chiralpak ID column (250 × 10 mm), with 5 mL min−1 as flow-rate, hexane/EtOH/CH2Cl2/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 CH2Cl2. On a Chiralpak ID column (250 × 10 mm), with 5 mL min−1 as flow-rate, hexane/EtOH/CH2Cl2/TEA (20/40/40/0.1) as mobile phase, UV detection at 300 nm, 26 injections of 200 μL were made every 7.2 min. Both enantiomers were collected, and the solvent was then evaporated. The first eluted enantiomer ((−)-16, 46 mg) and the second one ((+)-16, 18 mg) were obtained with both ee values >99%. P-16: [α]25D +52 (c = 0.27; CH2Cl2); M-16: [α]25D = −52 (c = 0.25; CH2Cl2). 1H NMR (CDCl3, 300 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, 1H); 4.09–4.03 (m, 6H); 3.97–3.90 (m, 6H); 3.66 (s, 9H); 3.54 (d, J = 13.7 Hz, 3H). 13C NMR (CDCl3, 75 MHz): δ 158.7, 156.8, 152.6, 148.8, 146.7, 136.8, 135.1, 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 the Supporting Information. HRMS (ESI-TOF) m/z: [M + 2H]+ Calcld for C31H34N4O24Zn 646.7456; Found 646.7456. Rs = 0.98.

To a solution of (±)-16 (47 mg, 0.041 mmol) in 4 mL CH2Cl2, 12 μL triethylamine was added under argon followed by addition of the solution of Zn(C4H4O4)2.4H2O (15 mg, 0.041 mmol, 1 equiv) in 2.5 mL CH2Cl2. After stirring the reaction mixture at room temperature for 4 h, a large amount of precipitate appeared. The precipitate was collected, washed thoroughly with Et2O, and dried under vacuum to give the pure complex as a white solid (33 mg, 0.023 mmol, 57% yield). The 1H NMR spectrum of Zn(II)@16 exhibits complex and broad signals because of the conformational rigification of the whole structure induced by the metal complexation that gives different

**ACKNOWLEDGMENTS**

D.Z. acknowledges grants from the China Scholarship Council, the Région Auvergne-Rhône-Alpes, France, for an Accueil Doctoral Bursary, and ENS-Lyon for an Attractiveness Fellowship for Ph.D studies. A.M. thanks ANR OH-risque for funding, grant number ANR-14-OHRI-0015-01.

**REFERENCES**


