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Chiral Trialkanolamine-Based Hemicryptophanes: Synthesis and Oxovanadium Complex

Arnaud Gautier, Jean-Christophe Mulatier, Jeanne Crassous, and Jean-Pierre Dutasta*

Laboratoire de Chimie, École Normale Supérieure de Lyon, UMR CNRS 5182, 46, Allée d'Italie, F-69364 Lyon 07, France

jean-pierre.dutasta@ens-lyon.fr

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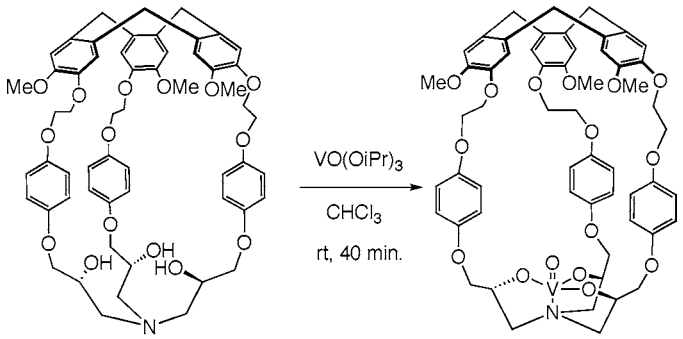
ABSTRACT



M-(*R*,*R*,*R*)-**1a** **11**

A novel class of chiral hemicryptophane hosts has been synthesized in diastereoisomerically pure form, namely, *M*-(*R*,*R*,*R*)-1a/*P*-(*S*,*S*,*S*)-1a and *M*-(*S*,*S*,*S*)-1b/*P*-(*R*,*R*,*R*)-1b. The C_3-symmetrical precursor 9 was prepared, using either (*R*)- or (*S*)-glycidyl nosylate, repectively, as the chiral pool reactant and subsequently cyclized (trimerized) in the presence of $Sc(OTf)_3$. The four stereoisomers were fully characterized and displayed two pairs of mirror-image CD spectra, which were used to determine their absolute configuration. The formation of the oxovanadium-(V) complex of hemicryptophane 1a is also reported.

The use of molecular containers for the design of metalloreceptors is very attractive, as they can act as supramolecular catalysts for important organic reactions. This is of current interest in supramolecular chemistry because they can mimic biological entities such as enzymes.[1] Cryptophanes, which possess a lipophilic molecular cavity, have remarkable binding properties toward neutral or charged guests[2] and are efficient in chiral recognition.[3] The related hemicryptophanes,[4] introducing dissymmetry at the molecular cavity level, can give access to ditopic host molecules, with all ingredients for catalytic and recognition properties.[5] Indeed, they can combine a potential catalytic site and a binding pocket for a given substrate and might favor a chemical reaction to occur inside the molecular cavity. Furthermore, the guest activation by molecular encapsulation,

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the close packing by accommodation of both reactants in the close cavity space, or the host activation by incorporation of the guest might bring both reaction acceleration and selectivity enhancement. In this context, two model hemicryptophanes displaying complexation properties toward iron and gallium ions have already been described but not in an enantiomerically enriched form.[6]

We wish to report herein the synthesis of the first members of a new family of enantiomerically pure chiral C_3-symmetric hemicryptophanes (Figure 1). These host molecules contain

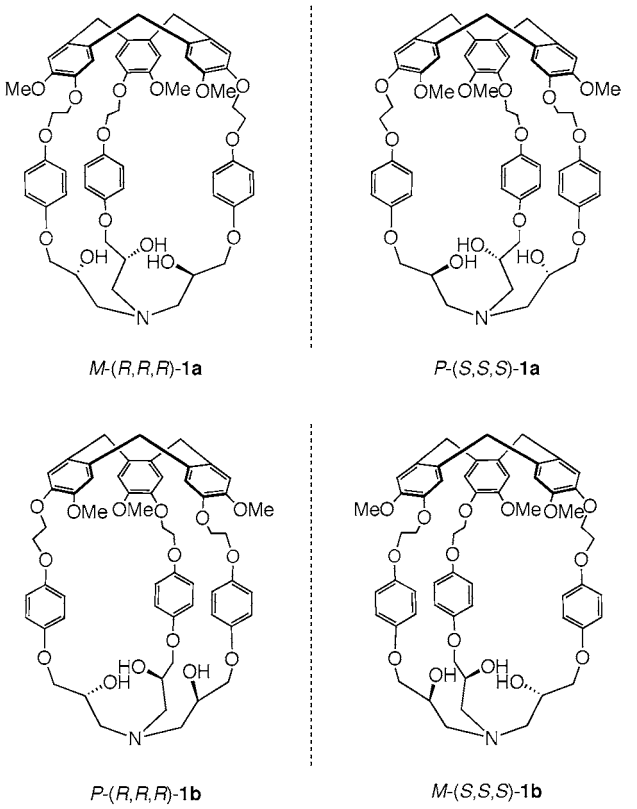
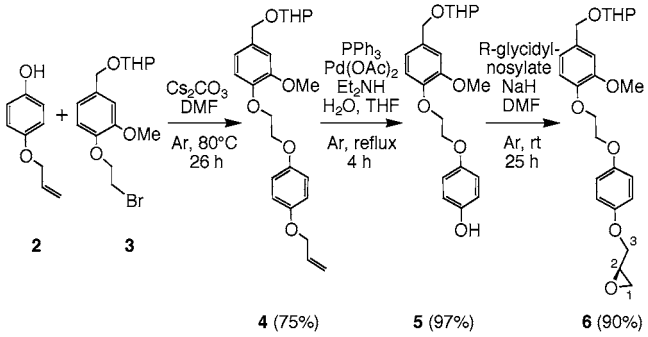


Figure 1. Four diastereoisomers (two pairs of enantiomers) of trialkanolamine-based hemicryptophanes.

a C_3-symmetric cyclotriveratrylene (CTV), which is used to provide both a shaping unit and a lipophilic chiral cavity, together with a chiral C_3-symmetric trialkanolamine moiety that is potentially a metalloreceptor with catalytic properties if proper metal and reactant(s) are used. Chiral C_3-symmetric trialkanolamine ligands are known to form efficient titanium(IV) and zirconium(IV) complexes that catalyze asymmetric sulfoxidation reactions when hydroperoxides are used as oxidants.[7] The trialkanolamine moiety was also known to form stable vanadium(V) complex.[8] In the present work, an oxovanadium complex was obtained from **1a** and characterized by ^{1}H NMR and mass spectrometry.

The diastereoisomeric hemicryptophanes *M*-(*R*,*R*,*R*)-**1a** and *P*-(*R*,*R*,*R*)-**1b**, together with their enantiomers (Figure 1), were synthesized by an intramolecular acid-catalyzed cyclization (trimerization) reaction of the chiral acetylated trialkanolamine **9**, which was obtained from the enantiopure epoxide **6**. Two diastereoisomers were expected, as the ring-closure reaction led to cyclotriveratrylene unit with *M* or *P* stereochemistry.[9] Chiral epoxide **6** was prepared according to Scheme 1: allyloxyphenol **2** was added to [4-(2-bromo-

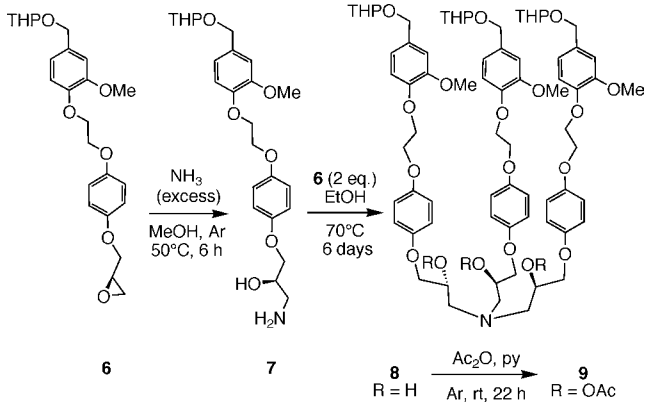
Scheme 1. Synthesis of Enantiopure Epoxide **6**



ethoxy)-3-methoxybenzyloxy]-tetrahydropyrane **3**, prepared following the literature procedure,[10] to give compound **4**. The latter was subsequently deprotected to give the phenol derivative **5** using $Pd(OAc)_2/PPh_3/Et_2NH/H_2O$.[11] The enantiopure epoxide **6** was finally synthesized by a regioselective nucleophilic substitution reaction of phenol **5** on commercially available (*R*)-(−)-glycidyl nosylate (overall yield 65% starting from allyloxyphenol **2**). It was previously shown by Sharpless et al. that such nucleophilic displacement proceeded without racemization.[12]

For the subsequent trimerization, the acetylated trialkanolamine precursor **9** was prepared in three steps from **6** (Scheme 2). In the first step, an excess of ammonia was

Scheme 2. Synthesis of Precursor **9**[a]



[a] Overall yield (three steps) = 88%.

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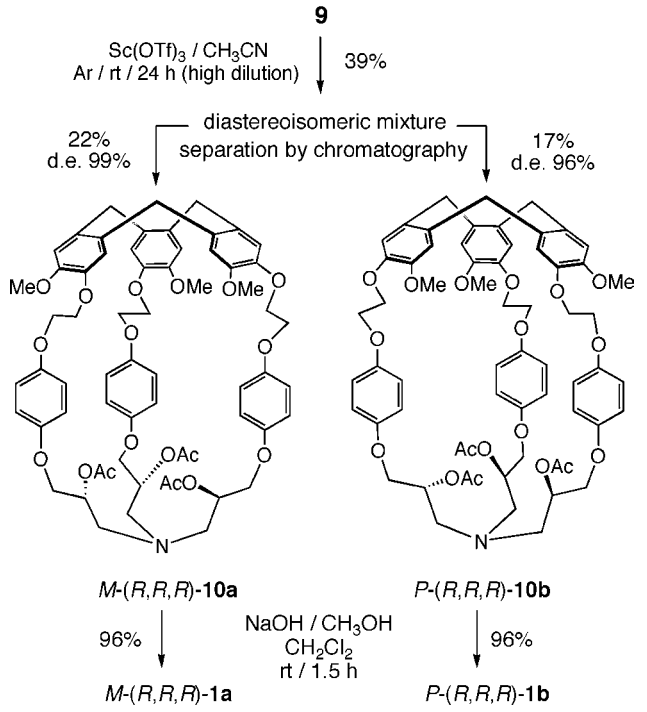
reacted with **6** in methanol to give the primary amine **7**. In the second step, 2 equiv of epoxide **6** was reacted with **7** in ethanol at 70 °C for 6 days to give the C_3-symmetric compound **8**. Finally, **8** was acetylated with acetic anhydride in pyridine to give the precursor **9**. This acetylation reaction was performed in order to decrease the polarity and to improve the solubility of the compound, to facilitate further purification. The overall yield for the three steps was 88%.

Intramolecular cyclization of trialkanolamine **9** was accomplished by using stoichiometric quantities of Lewis acid $Sc(OTf)_3$ in acetonitrile (Scheme 3).[13] The reaction conditions

Scheme 3. Synthesis and Separation of Diastereoisomeric Acetylated Hosts **10a** and **10b** and Their Saponification to Hosts **1a** and **1b**



were chosen to favor intramolecular reactions, and diastereoisomeric pairs *M*-(*R*,*R*,*R*)-**10a** and *P*-(*R*,*R*,*R*)-**10b** were obtained in 39% overall yield. Column chromatography on silica gel gave *M*-(*R*,*R*,*R*)-**10a** and *P*-(*R*,*R*,*R*)-**10b** in 22 and 17% yields, respectively. The diastereoisomeric excess (de) values were determined by ^{1}H NMR and found to be, respectively, 99 and 96%. Diastereoisomeric hemicryptophanes *M*-(*R*,*R*,*R*)-**1a** and *P*-(*R*,*R*,*R*)-**1b** were obtained quantitatively from *M*-(*R*,*R*,*R*)-**10a** and *P*-(*R*,*R*,*R*)-**10b**, respectively, by hydrolysis with methanolic NaOH. Starting from the (*S*)-(+) enantiomer of glycidyl nosylate, the other diastereoisomeric pairs *P*-(*S*,*S*,*S*)-**1a** and *M*-(*S*,*S*,*S*)-**1b** were similarly prepared and obtained with de ≥ 98%. The C_3-symmetry of the hemicryptophanes was ascertained by NMR spectroscopy (Figure 2). The ^{1}H NMR spectrum of **1a**

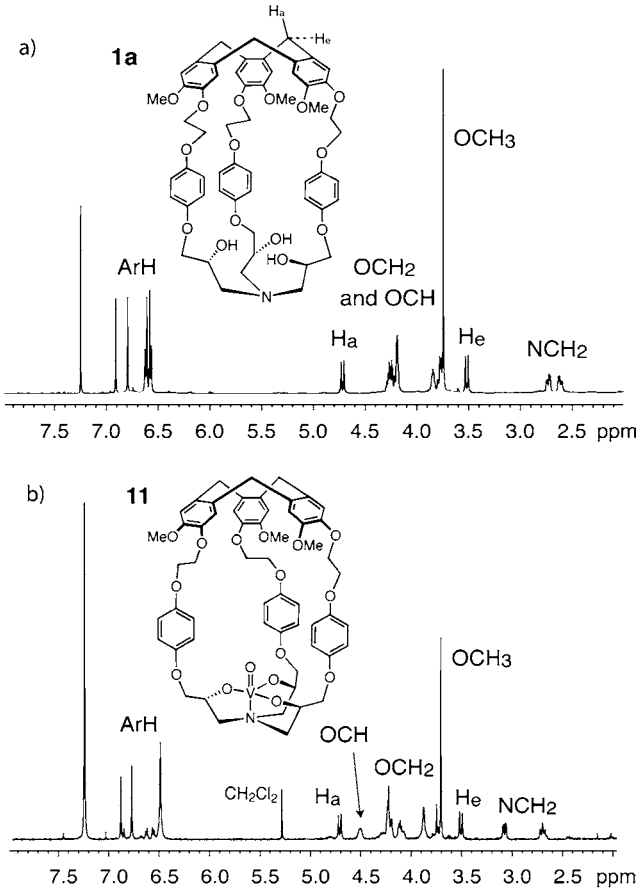


Figure 2. 500 MHz NMR spectra in $CDCl_3$ at 300 K of (a) **1a** and (b) its oxovanadium complex **11**.

displays the usual features for a C_3-CTV unit, i.e., two singlets for the aromatic protons, one singlet for the OMe groups, and the characteristic AB system for the CH_2 bridges. The spectrum also displays two shielded doublets for the protons of the aromatic chain, two doublets of doublets for the NCH_2 protons, and multiplets in the 3.5−4.5 ppm region for OCH_2 and OCH protons.

The absolute configurations of **1a** and **1b** were derived from the study of their circular dichroism spectra. The CD

(9) For the use of the *P* and *M* stereodescriptors in cyclotriveratrylenes, see the comment by Prof. V. Prelog in: Collet, A.; Gabard, J.; Jacques, J.; Cesario, M.; Guilhem, J.; Pascard, C. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1630−1638.

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spectra of the four stereoisomers, *M*-(*R*,*R*,*R*)-**1a**/*P*-(*S*,*S*,*S*)-**1a** and *M*-(*S*,*S*,*S*)-**1b**/*P*-(*R*,*R*,*R*)-**1b**, are depicted in Figure 3. As shown previously by Collet and co-workers,[14] the CD

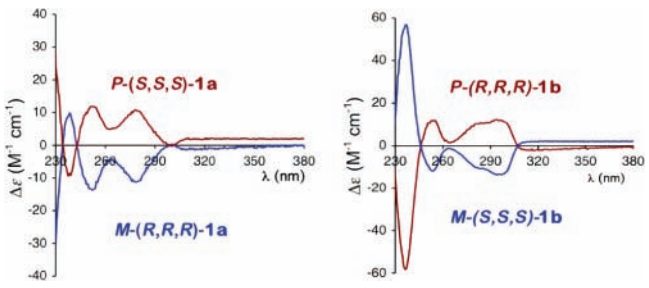

Figure 3. CD spectra in CH_2Cl_2 at 20 °C of the enantiomeric pairs of **1a** and **1b** (see Supporting Information for concentrations).

spectra of chiral C_3 derivatives of cyclotriveratrylene can be analyzed in terms of exciton coupling between the transition moments of the three aryl chromophores.[15] The CD spectra of **1a** and **1b** consist of two exciton patterns, roughly centered on the isotropic absorptions of the ^1L_B (290 nm) and ^1L_A (239 nm) transitions.

The ^1L_A transition pattern was used to determine the absolute configuration of **1a** and **1b** by comparison with other chiral CTVs bearing two different alkoxy groups (OR and OR′, with R and R′ ≠ H),[14] for which the so-called spectroscopic moment of the bulkier group is greater than that of the smaller one, which implies that the *P* stereoisomer (respectively, *M*) displays in the ^1L_A region two oppositely signed bands with a negative−positive sequence (respectively, positive−negative), from high to lower energies. Indeed, in the ^1L_A region, **1a** shows two oppositely signed CD bands between ca. 230 and 260 nm; from high to low energy, the sequence of signs is negative−positive for the *P*-(*S*,*S*,*S*) enantiomer and the opposite (positive−negative) for the *M*-(*R*,*R*,*R*) enantiomer. The same conclusions could be drawn from the ^1L_A region for host *M*-(*S*,*S*,*S*)-**1b**/*P*-(*R*,*R*,*R*)-**1b**.

Vanadium complexes are known to be efficient in oxidation of allylic alcohols to epoxides,[16] in oxidation of sulfides to sulfoxides,[17] and in oxidation of disulfides.[18] Vanadium is also present in haloperoxidase enzymes that catalyze oxidation of halide ions by hydrogen peroxide.[19−21] The complexation properties of enantiomerically pure **1a** were studied by way of their vanadium(V) complexes. Indeed, hemicryptophane **1a** reacted with 1 equiv of vanadium(V) oxytriisopropoxide to give rise to the C_3-symmetric compound **11**, which was characterized by high-resolution (ESI-TOF) mass spectrometry peaks at *m*/*z* 1066.3440 and by 500 MHz ^{1}H NMR spectroscopy shown in Figure 2b.[22] This preliminary result demonstrates clearly the feasibility of the metal insertion. The second step to be considered is the association of the hemicryptophane complex with a substrate of interest. Using molecular mechanics, we performed the modeling of the encapsulation of the methyl *p*-tolyl sulfide inside the cavity of **11** (see Supporting Information).[23] Methyl *p*-tolyl sulfide, which is a model substrate for the catalytic oxidation of sulfide to sulfoxide, is indeed encapsulated inside the molecular cavity of the vanadyl host, whose volume was approximated to 110 Å^3. This preliminary work is encouraging, and we are currently investigating the encapsulation process, which will be of prime importance to investigate the potential catalytic activity of the hemicryptophane complexes.

In conclusion, a novel series of chiral metalloreceptors has been prepared. Considering the already existing hemicryptophanes displaying complexation properties, these are the first enantiomerically pure ones. They display CD spectra, which were used to determine their absolute configuration. Host **1a** efficiently forms an oxovanadium complex and can be considered as an artificial model of an enzyme.[19] This new family of hemicryptophanes is promising, and supramolecular asymmetric catalytic properties are expected. These studies are in progress.

Acknowledgment. We warmly thank Jérôme Joubert for his skillful assistance in modeling the complexes.

Supporting Information Available: Experimental procedures and characterization for **2**, **4**−**10**, **1a**, **1b**, and complex **11**; ^{1}H NMR spectra of Figure 2; HR ESI-TOF MS of **11**; and structures of free **11** and thioether containing **11** obtained from molecular mechanics. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) See the special issue on vanadium: *Coord. Chem. Rev*. **2003**, *237* (1−2).

(22) In the case of hemicryptophane **1b**, we observed complexation, but two different compounds were detected from the ^{1}H NMR spectrum. This might be due a less favorable configuration of the complex with respect to the other, leading to the formation of different species.

(23) *MOPAC* with AM1/d. Commercial package CAChe 5.0; Fujitsu, Ltd.: Japan, 2000−2002.