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Review

Chiral cyclotriveratrylene-based molecular cages: Synthesis and molecular recognition properties

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ABSTRACT

The synthesis of cyclotriveratrylene (CTV) – a rigid, bowl-shaped macrocyclic compound consisting of three veratrole units – and its derivatives, as well as the properties of these compounds are reported. Application of this synthon in the preparation of molecular cages is discussed. Special emphasis is put on the synthesis of hemicryptophanes: inherently chiral, covalently bound cage-type molecular receptors with ditopic cavity, consisting of a *C*3-symmetrical cyclotriveratrylene scaffold (existing in the *P* and *M* configuration) triply connected to another unit. Such cages are prepared in most cases as racemic mixtures resulting from the inherent chirality of CTV. Enantiomerically pure CTV-cages are rare; most typical examples of the synthesis of such derivatives are discussed in detail. Application of such supramolecular structures in chiral recognition is also discussed.

KEYWORDS: cyclotriveratrylene, chiral molecular cages, hemicryptophanes, molecular recognition, supramolecular chemistry.

INTRODUCTION

Supramolecular chemistry is an interdisciplinary research area across chemistry, biology, physics, nanotechnology, and materials science [1, 2]. In medicine, almost all interactions between a drug and a receptor are supramolecular in Nature. Two enantiomers of chiral compound often show significant differences in toxicity, biochemical activity, transport, mechanism, and pathways of metabolism [3]. The synthesis of compounds able to bind cations, anions, or neutral compounds in a highly selective fashion is an important challenge in supramolecular chemistry [4-6]. One of the interesting building blocks for creation of molecular cages is cyclotriveratrylene and its derivatives – inherently chiral C_3-symmetrical macrocyclic compounds – capable of binding small guest molecules [7, 8].

This review is related to the synthesis and properties of CTV itself, molecular cages with this scaffold, and the application of such supramolecular structures in chiral recognition.

Cyclotriveratrylene: Basic information

Cyclotriveratrylene (CTV, **1**) is a rigid, bowl-shaped macrocyclic compound consisting of three veratrole units. This comparatively shape-persistent C_{3v}-symmetrical compound with tribenzo[*a*,*d*,*g*] cyclononatriene core has two conformations: crown and saddle (Fig. 1).

The predominant crown conformation is more thermodynamically stable and adopts a pyramidal shape [9]. Its saddle conformation is unstable because of steric interactions of the methylene proton (H_{in}) with the aromatic ring [10]. Nevertheless, the crown-to-crown interconversion of CTV is possible through a pseudo-rotating saddle form [11]. The majority of the CTV derivatives engaged in molecular cages are C_3-symmetrical and thus – being inherently chiral – they exist as *M* and *P* enantiomers (Fig. 2)

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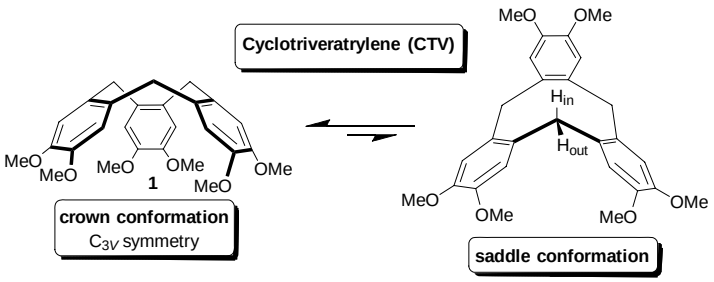


Fig. 1. Crown and saddle conformations of CTV.

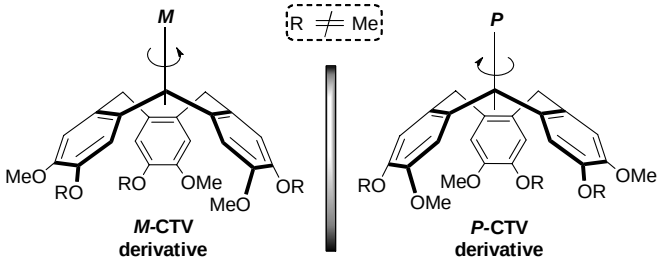


Fig. 2. Structures of two enantiomers (*M* and *P*) of CTV-derivatives separated by mirror.

Synthesis and functionalization of cyclotriveratrylene

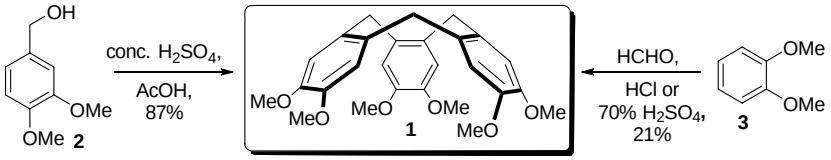
Cyclotriveratrylene derivatives can be synthesized *via* two main routes: 1) an acid-catalyzed condensation of formaldehyde with 1,2-disubstituted benzenes or - more commonly 2) an acid-catalyzed condensation of 3,4-disubstituted benzylic alcohols (Scheme 1).

Cyclotriveratrylene (**1**) was synthesized for the first time more than one century ago, but its structure was incorrectly assigned as a dimer [12]. The proper trimeric macrocyclic structure was confirmed in the 1960s [13]. Condensation of veratryl alcohol (**2**) leading to cyclotriveratrylene generally requires harsh acidic conditions; the cyclic products, however, could be usually effectively separated by crystallization.

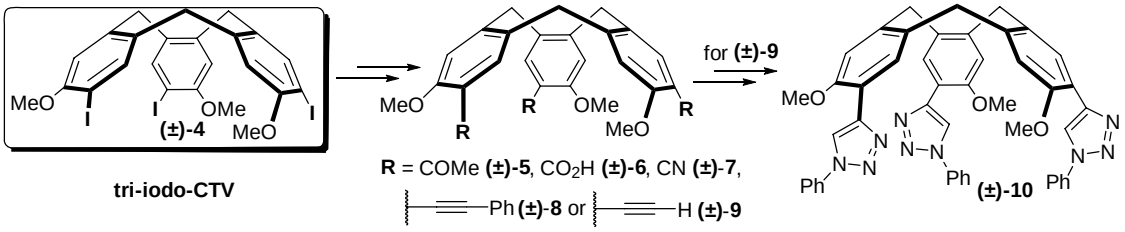
The cyclization of benzyl alcohol containing electron donating groups in the *para* and *meta* positions, leading to the CTV derivatives, is very efficient but the same strategy for benzyl alcohols with the aromatic or electron withdrawing groups is usually ineffective. Despite that, weak deactivating groups (I, Br) directly attached to the substrate at the *para* position could be used in a trimerization providing tri-halogenated CTV analogues in moderate yields. These compounds are attractive intermediates, in particular for the synthesis of CTV derivatives with the extended cavity. For example, tri-iodo-CTV derivative (±)-**4** is a key intermediate for the CTV analogues containing electron withdrawing groups (*e.g.* (±)-**5**–**10**; Scheme 2), which cannot be obtained *via* a typical trimerization [14-16].

The most important approach to CTV derivatives is a functionalization of hydroxy groups in cyclotricatechylene [CTC; **11** (obtained from **1**) [17] Scheme 3a] or cyclotriguaiacylene (CTG; **(±)-13**; prepared from (±)-**12** [18-20]). Reaction of **11** or (±)-**13** with alkyl or acid chlorides provided appropriate CTV structures with the ether- or ester-linked arms [**(±)-14**] [21-23].

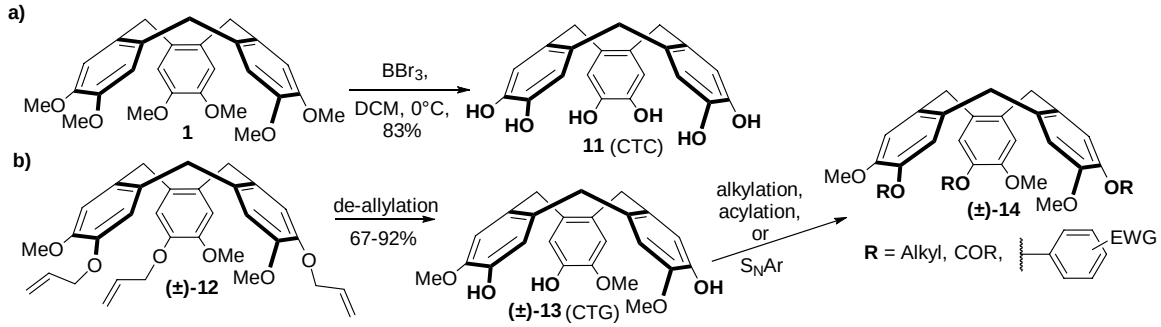
The CTV derivatives with the amino functional groups [*e.g.* aCTG; (±)-**16**] – an important class of macrocyclic compounds – can be prepared in a multi-step procedure shown in Scheme 4a [24]. They could be easily converted into various imines [*e.g.* (±)-**17**] [25]. The CTV derivatives with the thio-groups are also available [*e.g.* tCTG; (±)-**18**; Scheme 4b] [26].



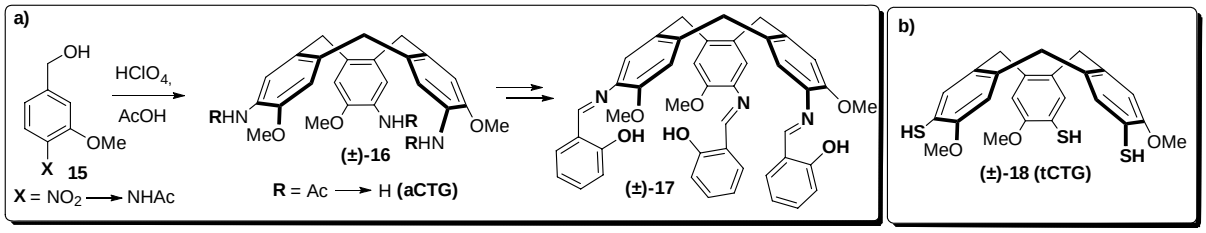
Scheme 1. The common routes to cyclotriveratrylene (CTV).



Scheme 2. The CTV analogues containing electron withdrawing groups obtained from tri-iodo-CTV.



Scheme 3. a) Synthesis of CTC *via* demethylation of CTV; **b)** Synthesis of (±)-CTG by de-allylation and its further conversion into a variety of derivatives [(±)-**14**].



Scheme 4. a) Synthesis of aCTG and its conversion into imines; **b)** Example of the thio-derivative of CTV.

Synthesis of C_1-symmetrical CTV derivatives

Most CTV derivatives are C_3-symmetrical; mono- or di-functionalized ones are relatively rare. Their synthesis is based on the selective cleavage of the methoxy group in hexa-*O*-methyl CTV (**1**) [27] or – more conveniently – on a mono-halogenation of cyclotriphenolene [CTP; (±)-**21**] with *N*-iodo- (→(±)-**22**; Scheme 5) or *N*-bromo-succinimide [28]. These mono-halogeno functionalized CTV analogues serve as a platform for further transformations towards novel C_1-symmetrical hosts.

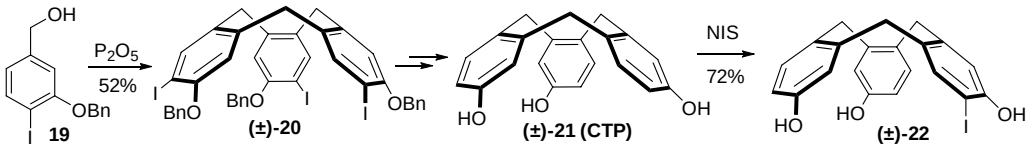
Recently, Martinez reported an efficient, gram scale synthesis of enantiopure C_1-symmetrical CTG with inverted spatial arrangement [29]. Treatment of a 1:1 mixture of regioisomers **23** and **24** with a catalytic amount of $Sc(OTf)_3$ afforded a 4:1 mixture of racemic C_1-derivative **25** + C_3-symmetrical CTV derivatives in 46% yield. Subsequent removal of the allyl groups provided the C_1-symmetrical (±)-CTGs ***M*-26** and ***P*-26** in 90% yield, which were separated into enantiomers by chiral high-performance liquid chromatography (HPLC) (Scheme 6).

Modification of CTV at the apex part

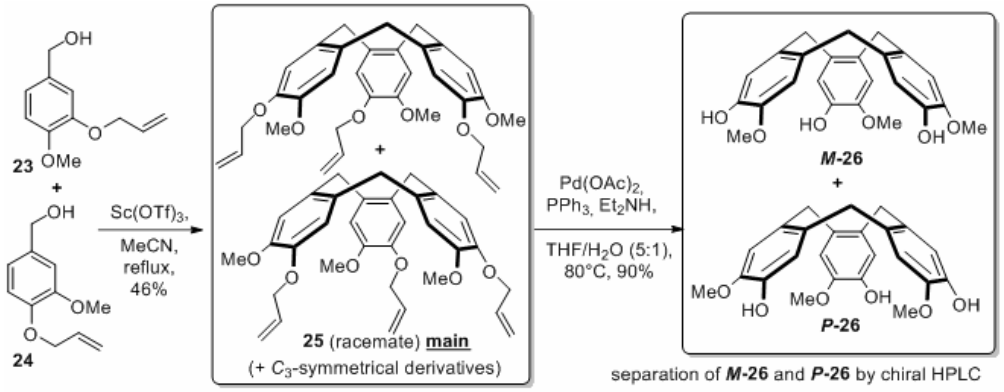
The functionalization of the CTV scaffold could be also carried out at the apex part (Scheme 7). While the common lower rim modification is very important in the preparation of CTV-based host molecules, rare and challenging apex part functionalization is particularly meaningful for the conformational aspects. Several groups reported, however, a number of CTV analogues modified at apex part [30-33].

Synthesis of molecular cages with CTV units

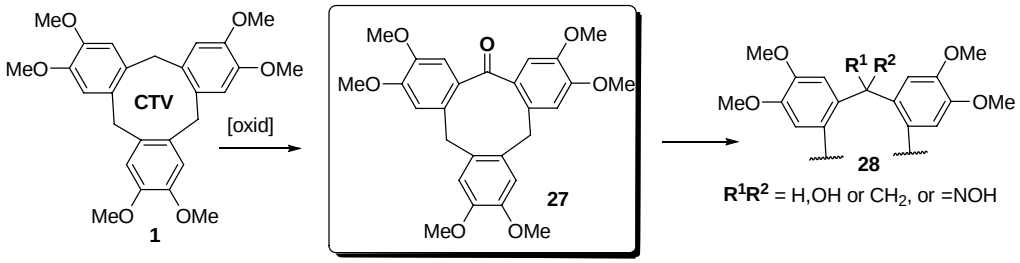
The C_3-symmetrical cyclotriveratrylene unit is effectively used in the synthesis of various host molecules such as cryptophanes - in which two CTV molecules are connected together [34] (this topic will not be discussed here) - and *hemicryptophanes*: inherently chiral, covalently



Scheme 5. Example of the synthesis of mono-halogenated CTV derivative.



Scheme 6. Synthesis of C_1-symmetrical (±)-CTGs.



Scheme 7. Synthetic pathways towards apex-functionalized CTV analogues

bound cage-type molecular receptors with ditopic cavity, consisting of a C_3-symmetrical cyclotriveratrylene scaffold (existing in the *P* and *M* configuration; see Fig. 2) triply connected to another unit [35]. Basically, hemicryptophanes differ from each other by the type and length of the linkers as well as the nature of the lower unit. Their most important advantage is, undoubtedly, the ability to recognize various neutral or charged guest molecules.

First synthesis of hemicryptophane was published in 1982 by Collet, Lehn *et al*. [36]. They described two molecular cages built of the CTV unit and aza-crown ether [**(±)-29** and **(±)-30**], which were named *speleands* (Fig. 3). However, there was almost no interest in this class of molecular hosts during the next two decades. Only a few articles, focused on hemicryptophane chemistry, were published before 2005 by Nolte's [37] and Dutasta's [38] groups (**31** and **(±)-32**; Fig. 3).

Since 2005 hemicryptophanes have attracted growing attention [35].

Three different strategies could be used to obtain hemicryptophanes (Scheme 8).

1) the cage-closing reaction to construct the CTV scaffold from veratryl precursors,
2) the cage-closing reaction at the lower part of appropriate CTV-based precursor,
3) the [1+1] coupling between the CTV unit and other C_3-symmetrical moiety.

The first pathway, commonly applied in the construction of numerous CTV derivatives, is based on an acid-catalyzed cyclization of veratryl

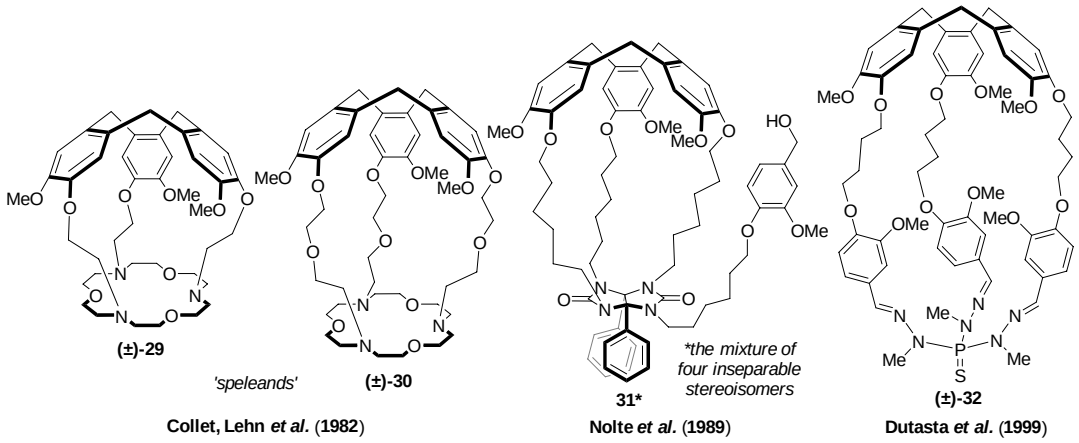
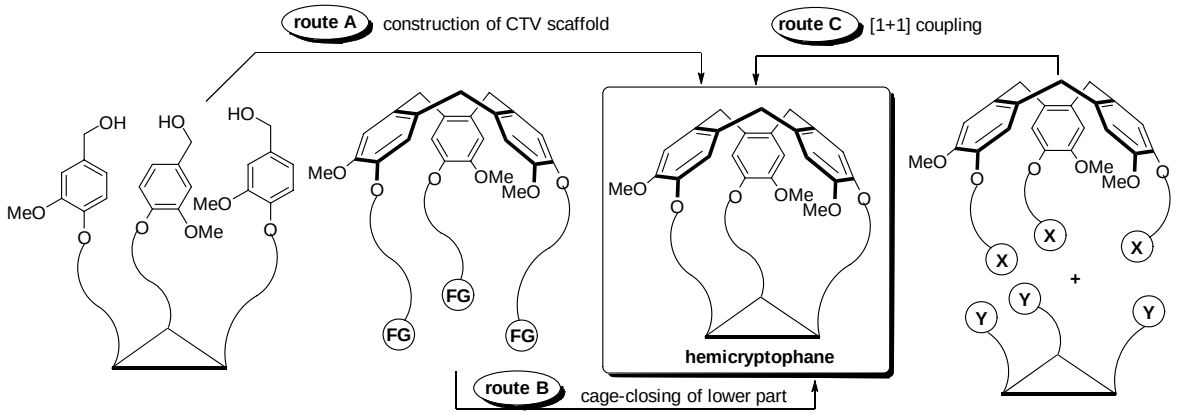


Fig. 3. Structures of first hemicryptophanes synthesized from 1982 to 2005.



Scheme 8. Three different synthetic routes for the synthesis of hemicryptophane.

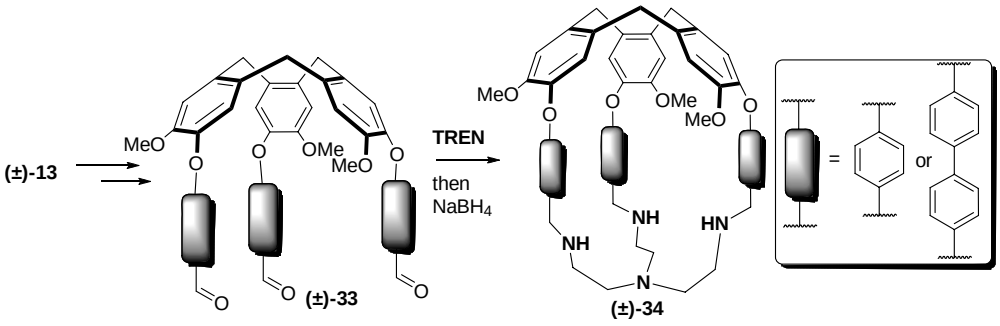
precursors; the CTV moiety is formed in the last step of hemicryptophane synthesis (Scheme 8, route A); this method cannot be used for acid-sensitive compounds. The second one (route B) involves the CTV unit containing three linkers with appropriate functional groups, engaged in the intramolecular reaction forming hemicryptophanes; this method is rarely used in practice.

The last approach, most widely used pathway leading to hemicryptophanes, deals with the [1+1] coupling of the CTV derivative with another C_3-symmetrical unit (route C). This strategy is very effective for the preparation of many CTV-based molecular cages due to the vast array of different molecules (crown ethers, cyclodextrins, calixarenes) as well as various types of reactions that could be used for a triple connection of both units (*e.g.* alkylation, reductive amination, amidation, *etc.*) [35, 39].

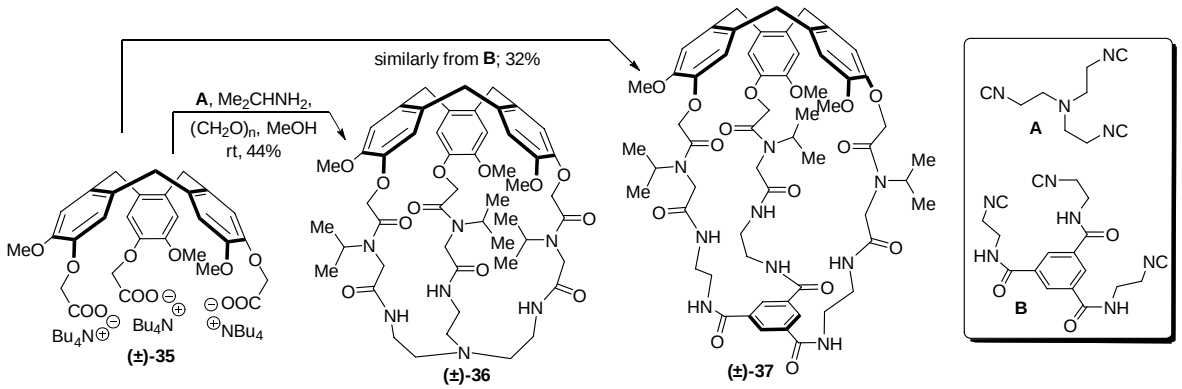
Interesting examples of the synthesis of racemic hemicryptophanes containing the CTV and TREN units were reported by Makita (Scheme 9) [40-42]. The racemic CTV-derivative **13** (shown in Scheme 3b) was elongated with phenylene or biphenylene units [→(±)-**33**] which – upon treatment with TREN and subsequent reduction of the resulting tri-imine – provided racemic hemicryptophanes (±)-**34**.

A one-pot multicomponent Ugi reaction was used by Rivera and Wessjohann in the synthesis of hemicryptophane containing TREN moiety [(±)-**36**] (Scheme 10). The simplicity of this method makes it interesting for the combinatorial generation of host macrocycles. The same methodology was used for the preparation of first hemicryptophane containing 1,3,5-tripodal benzene moiety [(±)-**37**] as shown in Scheme 10 [43].

In 2019, Martinez reported the synthesis of a water-soluble polytopic hemicryptophane consisting of the CTV unit triply connected to TREN *via* 2-hydroxyisophthalamide linkers [**(±)-38**, Fig. 4] [44].



Scheme 9. Synthesis of racemic hemicryptophanes (±)-**34**.



Scheme 10. Synthesis of hemicryptophanes with peptoid backbones *via* multicomponent Ugi reaction.

Recently, the same group reported two hemicryptophanes [(±)-**39** and (±)-**40**] containing three urea functions. The authors introduced additional urea groups to the cage structure, because of their well-known remarkable affinity for anions. Moreover, combining the CTV unit, capable of binding cationic species with the urea functions provided heteroditopic ion-pair receptors that could simultaneously recognize both anions and cations (Fig. 4) [45, 46].

In 2020 a different approach to hemicryptophanes with TREN motif was proposed by Pinet and Gosse [47]. They developed fluorescent hemicryptophane **(±)-41**, in which the methoxy groups of the CTV scaffold were replaced by phenylacetylene units (Fig. 4). This molecular cage, due to the introduced π-conjugated moieties, shows fluorescence properties with the red-shifted excitation and emission wavelengths.

In 2017 Martinez described the straightforward synthesis of two hemicryptophanes consisting of tris(2-pyridylmethyl)amine (TPA) and naphthyl or phenyl linkers [(±)-**45**; Scheme 11] [48]. Recently, the synthesis of the smallest TPA-based hemicryptophane **(±)-46** obtained by the coupling of (±)-CTG (**13**) with TPA-based trichloride **43** was reported. This molecular cage was then separated into individual enantiomers by HPLC on chiral column (Scheme 11) [49].

An efficient synthesis of hemicryptophane containing three 1,2,3-triazole rings was developed by Colomban *et al* [50]. Alkylation of (±)-CTG

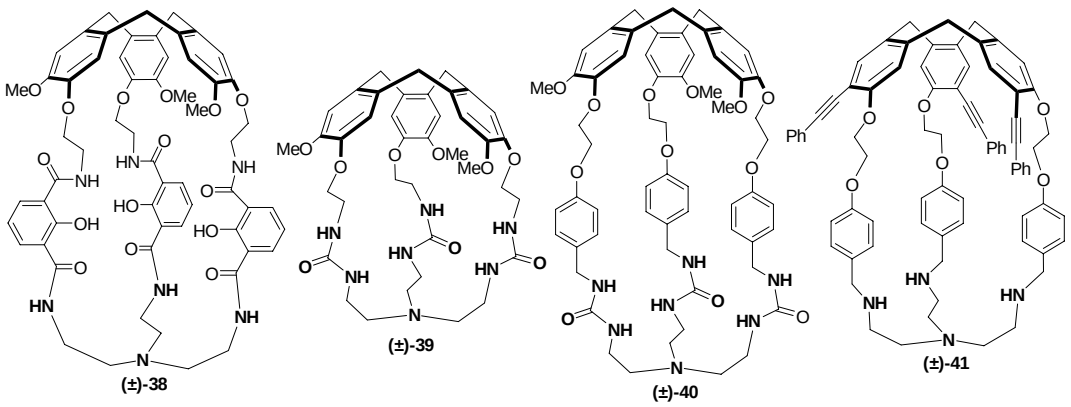
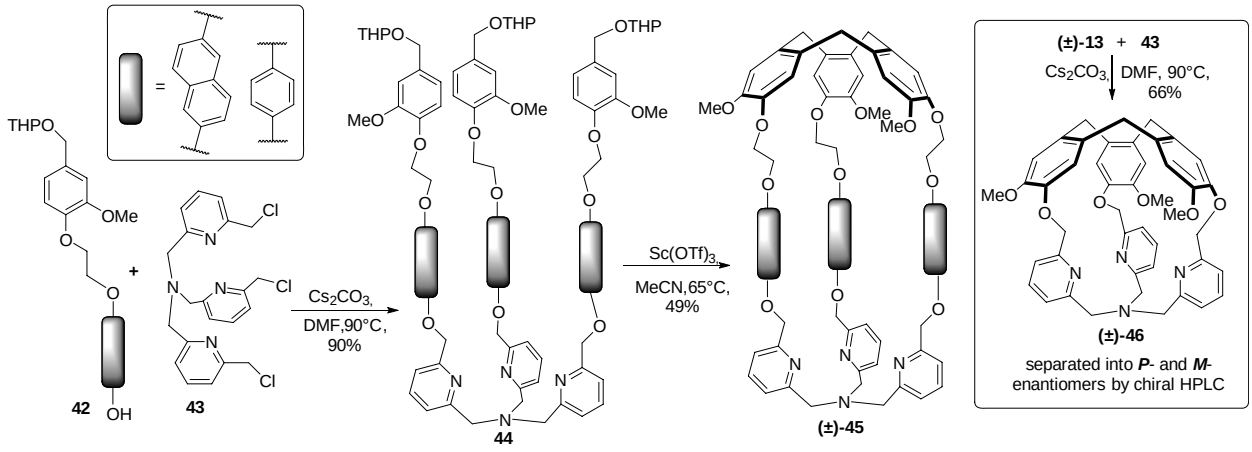


Fig. 4. Examples of highly functionalized hemicryptophanes.



Scheme 11. Synthesis of various TPA-based hemicryptophanes.

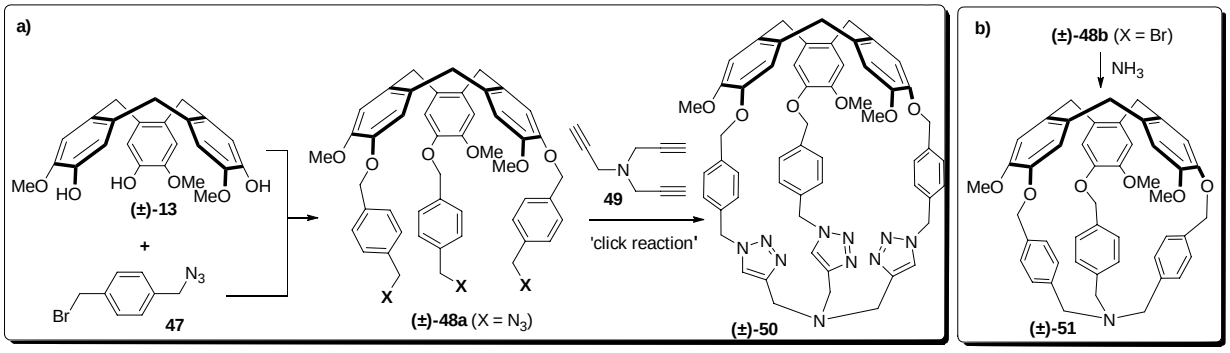
(**13**) with arene **47** provided triazido CTV derivative **(±)-48a**, which was reacted with tripropargylamine (**49**) to afford the target compound (±)-**50** in 22% yield (Scheme 12a).

A facile synthesis of tribenzylamine hemicryptophane **(±)-51** from the analog of substituted CTV **(±)-48b** was proposed by Dmochowski *et al*. (Scheme 12b) [51].

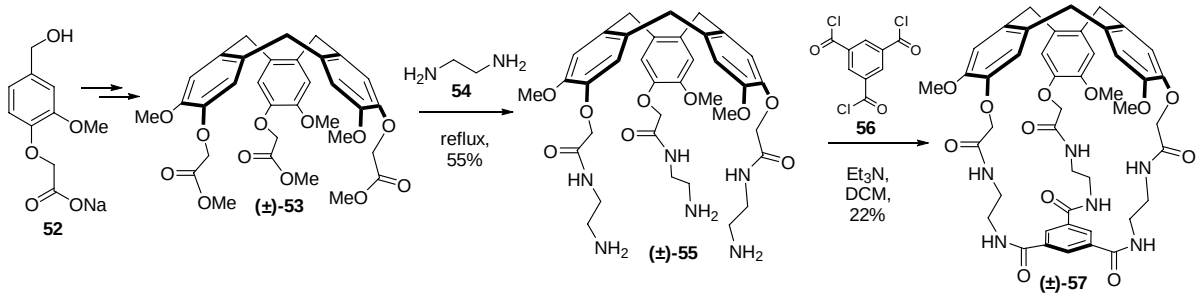
The commonly used moiety linked to cyclotriveratrylene unit is a 1,3,5-tripodal benzene scaffold [one example – (±)-**37**, is shown in Scheme 10]. This platform is an attractive cage closing unit due to the wide range of possibilities of its functionalization. Furthermore, the benzene ring itself can interact with neutral or charged guests by the CH-π, π-π, cation-π, or anion-π interactions. Additionally, the introduction of different type of substituents at the benzene ring (*e.g.* electron donating or withdrawing groups) could also improve its host-guest properties.

Dutasta and Martinez reported the four-step synthesis of hemicryptophane **(±)-57** (Scheme 13), in which the CTV unit was triply connected to a C_3-symmetrical aromatic ring *via* electron deficient linkers [52]. This cage contained three additional amide functions in its structure, which increased the number of hydrogen bonds that could be formed between the host and the guest. All intermediates in this synthesis, as well as the target product, were isolated by crystallization.

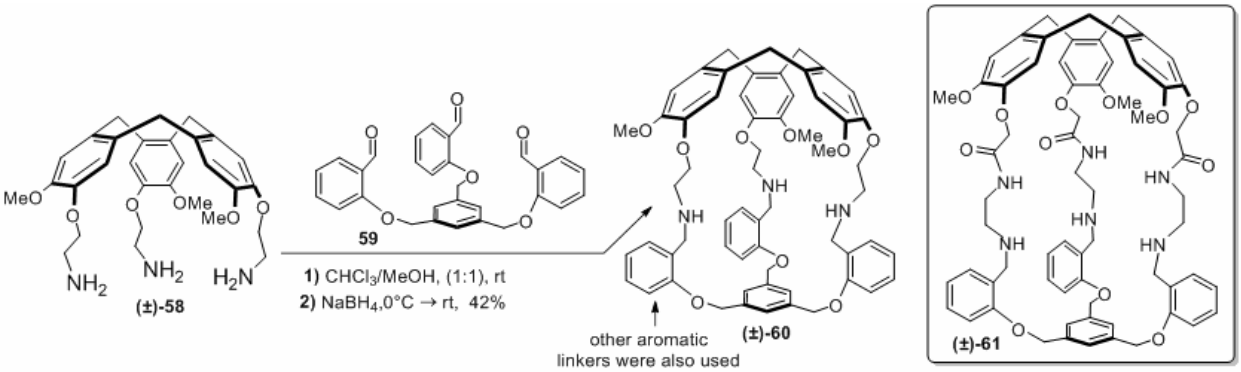
In 2018, Martinez described another synthesis of enantiopure hemicryptophanes bearing tripodal benzene moiety using the [1+1] macrocyclization strategy [53]. Reaction of CTV triamine **(±)-58** with trialdehyde **59** afforded racemic mixture of hemicryptophane **(±)-60** in 42% yield, which was resolved by chiral HPLC to optically pure cages ***M*-60** and ***P*-60** (Scheme 14). Recently, the same strategy was used for the synthesis of three fluorescent hemicryptophanes containing naphthalene, diphenylacetylene, and biphenyl groups in the linkers [54, 55]. Another example of hemicryptophane with tripodal benzene platform and longer linkers [(±)-**61**] is shown in Scheme 14 [56].



Scheme 12. Synthesis of hemicryptophane containing: **a)** three 1,2,3-triazole rings and **b)** tribenzylamine unit.



Scheme 13. Synthesis of hemicryptophane containing six amide functions and 1,3,5-tripodal benzene scaffold.



Scheme 14. Synthetic pathway towards hemicryptophanes bearing tripodal benzene moiety.

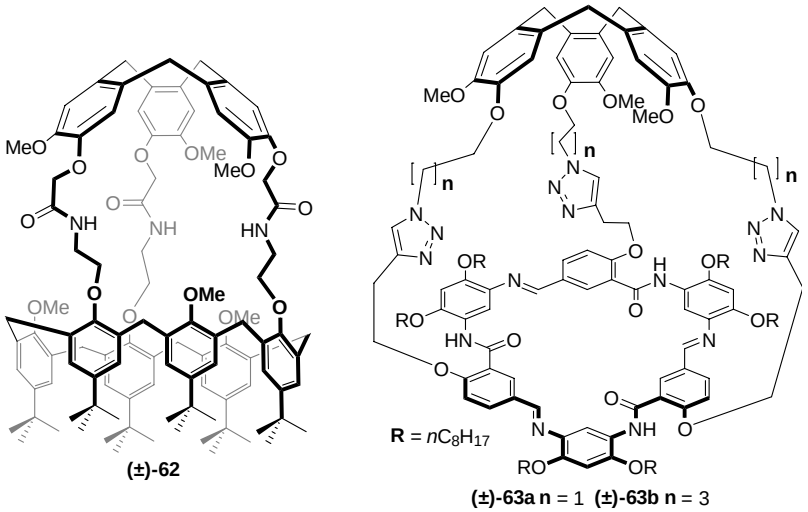


Fig. 5. Examples of hemicryptophanes with macrocyclic scaffold.

More complex hemicryptophanes bearing macrocyclic scaffold were not described until 2008, when Le Gac and Jabin presented the synthesis of bifunctional cages (called *calix[6]cryptamides*), composed of the CTV unit triply connected with calix[6]arene derivative [(±)-**62**; Fig. 5] [57]. Different type of macrocycle-based hemicryptophanes was presented by Zhao and Li [(±)-**63a**, **(±)-63b**; Fig. 5] [58].

This very short and absolutely not comprehensive review should introduce the reader to the complexity of the synthetic approaches to optically inactive hemicryptophanes. By application of various linkers and platforms, a number of configurationally different macrocyclic cages could be prepared in a *racemic* form.

Synthesis of optically pure hemicryptophanes with CTV unit

The connection of inherently chiral CTV unit with an achiral C_3-symmetrical scaffold leads to a *racemic* mixture of the *P* and *M* enantiomers of hemicryptophane; most such receptors have been synthesized so far as racemic mixtures. An efficient and easy preparation of enantiopure cages – due to their high complexity – is, therefore, very challenging. In general, the enantiopure cages could be prepared by three different methods: 1) resolution of a racemic mixture by chiral HPLC; this expensive method typically provides only small amounts of target compounds, 2) application of optically pure *M* and *P* stereoisomers of the CTV substrate. However, the racemization is possible during

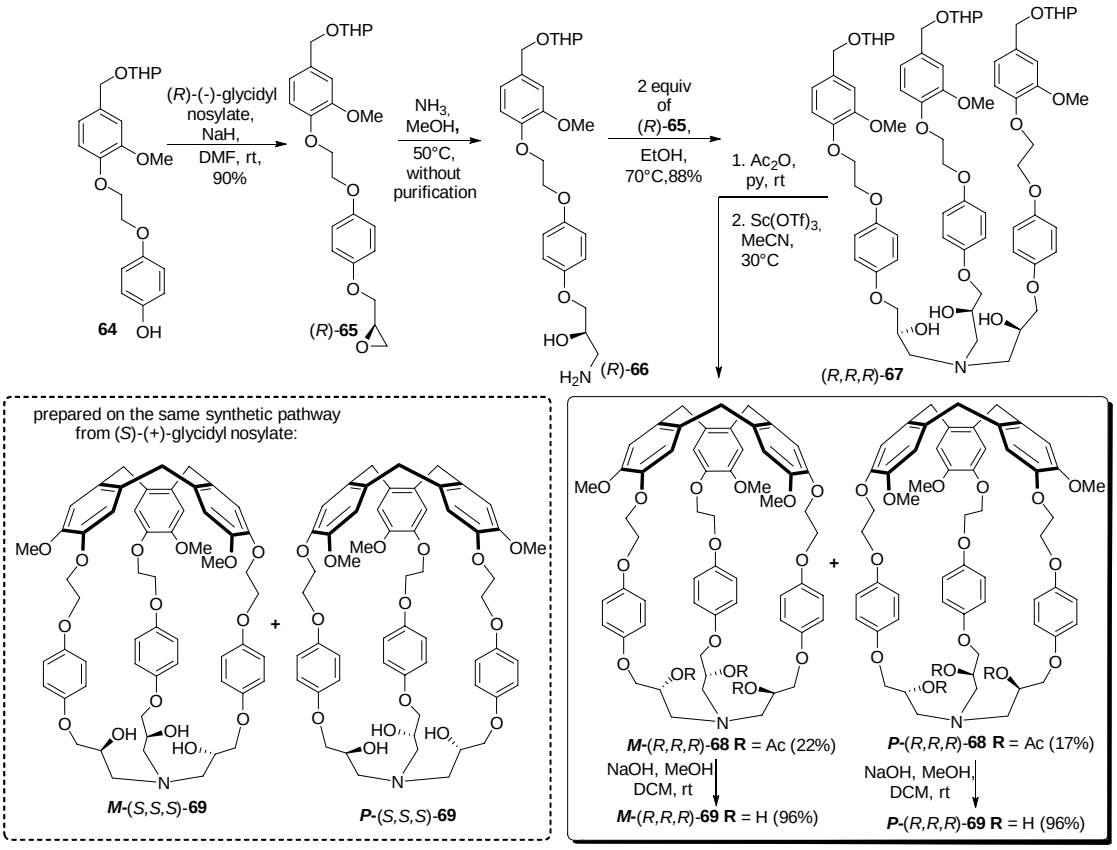
further synthetic steps (*via* a crown → saddle inversion shown in Fig. 1), and 3) introduction of *racemic* CTV unit to chiral platforms, which affords diastereoisomers that could be separated. There are only a few reports, in which the CTV scaffold is triply connected with such chiral molecule [39].

This part of the review will be dealing with the synthesis of optically pure compounds prepared according to method 3.

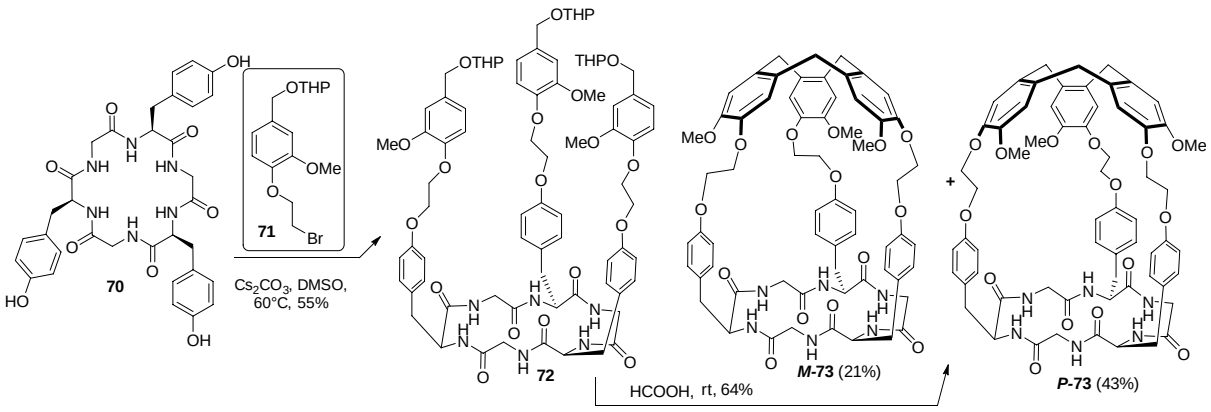
The cages built of CTV and optically pure C_3-symmetrical units

After a long break in hemicryptophane chemistry, Dutasta and co-workers reported the synthesis of four enantiopure CTV-based molecular cages containing triethanolamine moiety [59]. The synthesis of the first diastereoisomeric pair was initiated from veratryl precursor **64**. Its reaction with (*R*)-(–)-glycidyl nosylate afforded enantiopure epoxide (*R*)-**65** which - upon treatment with an excess of ammonia - provided aminoalcohol (*R*)-**66**. Subsequent reaction of this intermediate with epoxide (*R*)-**65** gave the C_3-symmetrical veratryl precursor (*R*,*R*,*R*)-**67**, which was acetylated and cyclized to afford diastereoisomeric hemicryptophanes ***M***-(*R*,*R*,*R*)-**68** and ***P***-(*R*,*R*,*R*)-**68** in 22% and 17% yields. Removal of the acetyl functions afforded hemicryptophanes ***M***-(*R*,*R*,*R*)-**69** and ***P***-(*R*,*R*,*R*)-**69** in quantitative yield (Scheme 15). The other pair of diastereoisomeric hemicryptophanes [***M***-(*S*,*S*,*S*)-**69** and ***P***-(*S*,*S*,*S*)-**69**] were similarly obtained using (*S*)-(+)-glycidyl nosylate.

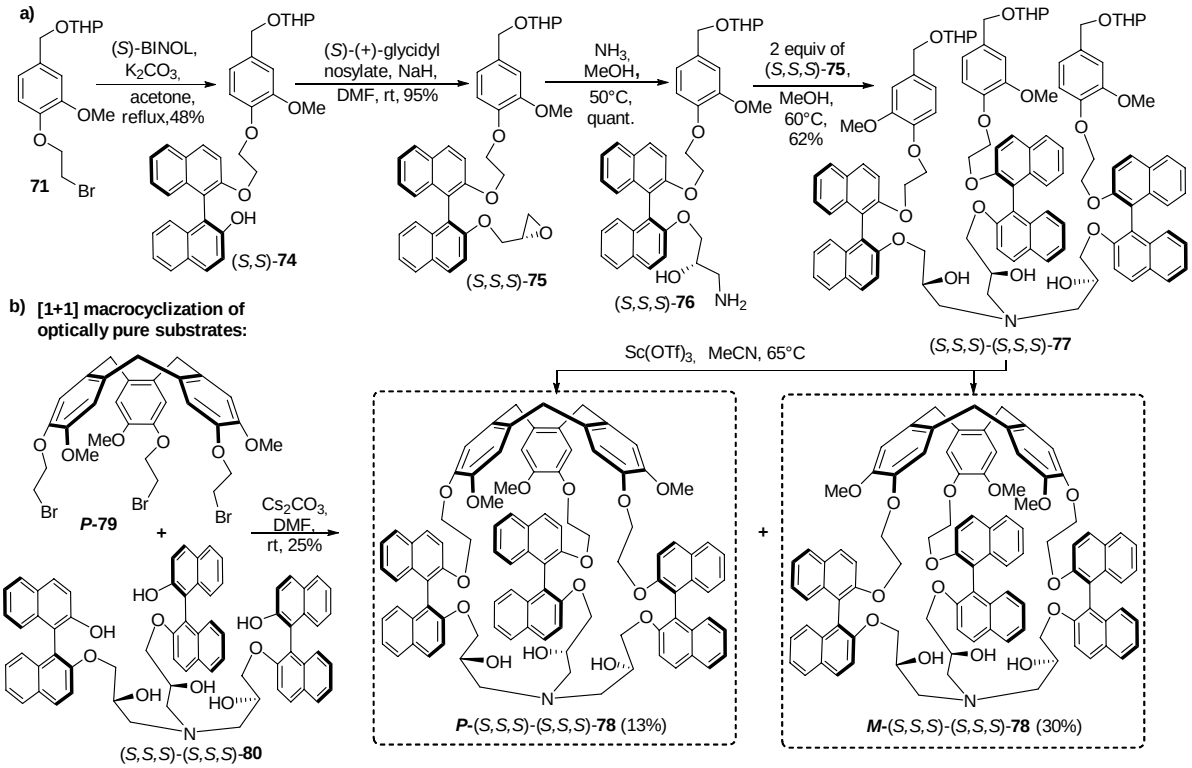
An interesting approach to C_3-symmetrical diastereoisomeric hemicryptophanes containing macrocyclic peptide was reported by Hutton *et al*. (Scheme 16) [60]. The C_3-symmetrical macrocyclic hexapeptide **70** (composed of three L-tyrosine and glycine amino acids) was reacted with bromide **71** to afford hemicryptophane precursor **72** in 55% yield. The final cage-formation step, realized by an intramolecular cyclodehydration induced by



Scheme 15. Synthetic pathway towards four optically pure diastereoisomeric hemicryptophanes.



Scheme 16. Synthesis of macrocyclic peptide-based hemicryptophanes.



Scheme 17. Synthetic pathways to hemicryptophanes with triethanolamine scaffold bearing multiple stereogenic elements.

formic acid, provided two diastereoisomeric hemicryptophanes ***P*-73** and ***M*-73** in 43% and 21% yield.

The synthesis of enantiopure hemicryptophanes containing different types of stereogenic elements has been reported [61]. This approach can be exemplified by the synthesis of cages **78** shown in Scheme 17 [62].

Target hemicryptophanes **78** contained a helically chiral CTV unit, axially chiral 1,1'-bi-2-naphthol linkers, and central chirality of the stereogenic centers located on carbon atoms on the triethanolamine moiety.

The first hemicryptophanes containing nitrilotriacetamide moiety were synthesized by Martinez, Dutasta *et al*. (Scheme 18) [63, 64, 65].

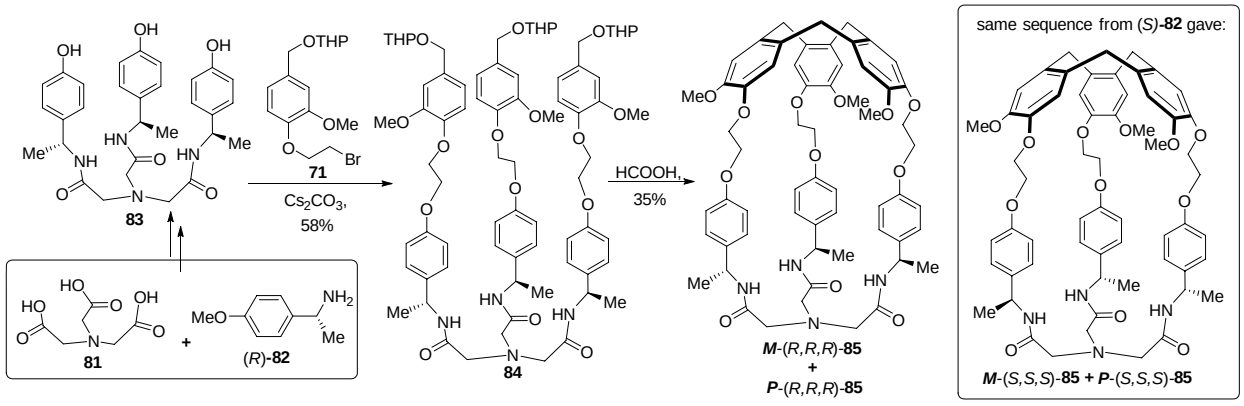
Nitrilotriacetic acid (**81**) was condensed with (*R*)-4-methoxybenzylamine (*R*-**82**) and subsequently demethylated with BBr_3 to triphenol derivative **83**. This intermediate was further reacted with bromide **71** under the basic conditions giving hemicryptophane precursor **84** in good yield. The final intramolecular macrocyclization of this tripodal precursor induced by HCOOH provided the mixture of *P*- and *M*-hemicryptophanes **85** in 35% yield [64]. Application of (*S*)-**83** in the same sequence of reactions afforded another mixture of diatereoisomeric, optically pure hemicrypotophanes **85**.

In 2015 Martinez described a convenient synthesis of enantiomerically pure cages with TREN moiety based on a thermodynamic resolution of a racemic CTV-based substrate [66]. They observed that the reductive amination of CTV trialdehyde **(±)-86** with enantiopure derivative of TREN: (*S*,*S*,*S*)-**87a** afforded only one diastereoisomer ***M***-(*S*,*S*,*S*)-**88a** in 15% yield (Scheme 19). This thermodynamic resolution is independent of the nature of the substituents located on tris(2-aminoethyl)amine's stereogenic centers, as both methyl and benzyl groups gave similar results and only one diastereoisomer (*M*) was obtained exclusively.

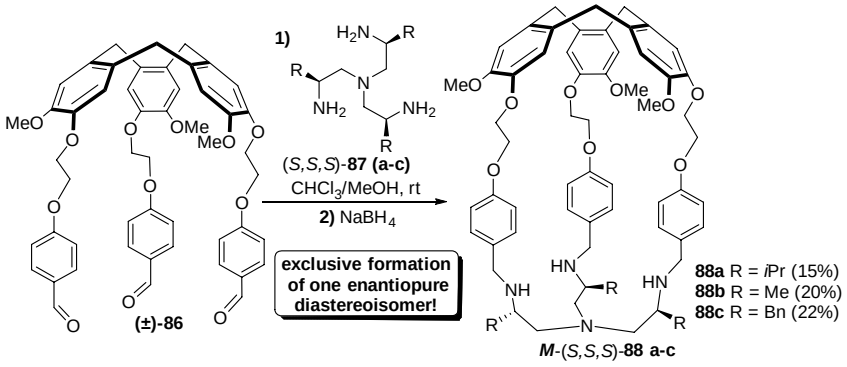
Reduction of the amide functions in hemicryptophane **85** provides another hemicryptophane based on TREN scaffold (**89**) with different character of the cavity (Scheme 20) [63, 67].

Molecular cages with carbohydrate scaffold

In this chapter, molecular cages composed of C_3-symmetrical CTV unit and carbohydrate part will be presented; the examples of such cages are very rare. In 2012 Chambron described the synthesis of two C_3-symmetrical diastereoisomeric



Scheme 18. Synthetic pathway towards hemicryptophanes bearing nitrilotriacetamide moiety.



Scheme 19. Synthesis of optically pure diastereoisomers ***M***-(*S*,*S*,*S*)-**88** *via* thermodynamic resolution.

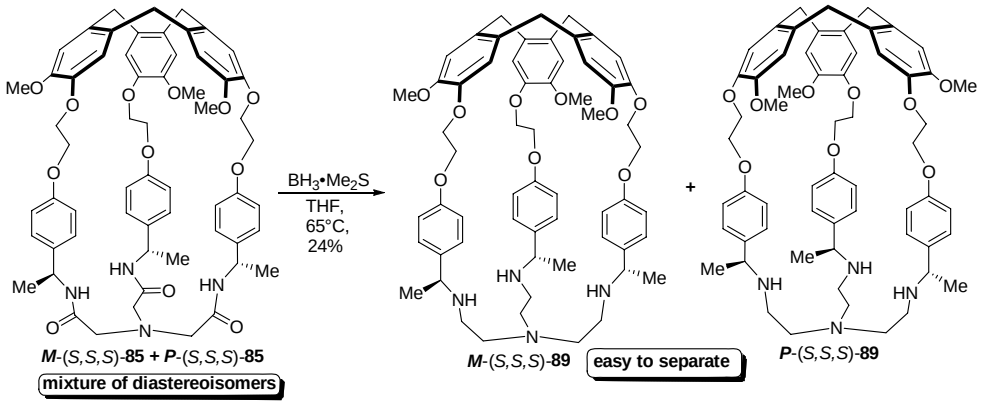
hemicryptophanes (***P*-90** and ***M*-90**), in which the CTV unit was triple-connected to permethylated α-cyclodextrin *via* ethylene bridges [68] (Fig. 6).

Permethylated α-cyclodextrin platform was also used for the preparation of macrocycle-based hemicryptophanes with disulfide bonds [69]. The [1+1] coupling between racemic cyclotrithiophenolene [**(±)-91**] and trithiol-α-cyclodextrin derivative **92** afforded an inseparable mixture of two diastereoisomers ***M*-93** and ***P*-93** in 11% yield in a 5:3 ratio (Scheme 21).

Another interesting molecule that can be applied as chiral platform for hemicryptophanes is the disaccharide – sucrose, which is most abundant in Nature (**94**). Being very well soluble in water, it offers a possibility to prepare water-soluble receptors, in which the geometry and chirality of the cavity would be controlled by nine stereogenic centers present in sucrose molecule.

We have used this raw material for the preparation of a number of complex macrocyclic receptors; selected examples (*e.g.* **95** or **96**) are shown in Fig. 7 [70]. This approach required a protection of six hydroxyl groups (five secondary and one primary at the C1'-position) and functionalization of the remaining ones at the C6,6'-positions. More interesting derivative of sucrose is, however, triol **97**, which should open a convenient route to sucrose-based cryptands and molecular cages.

We applied this triol in the synthesis of molecular cages containing the CTV unit; first results were reported by us in 2019. Sucrose triol **97** was elongated and activated to **98** which - upon reaction with a *racemic* cyclotriveratrylene **13** - afforded two macrocyclic cages ***P*-99a** and ***M*-99a** in a ~1:1 ratio and in 32% overall yield (Scheme 22) [71]. The benzyl blocks from the sucrose core could be removed by hydrogenolysis affording cages **99b** soluble in water.



Scheme 20. Preparation of TREN-hemicryptophanes *via* reduction of amide functions.

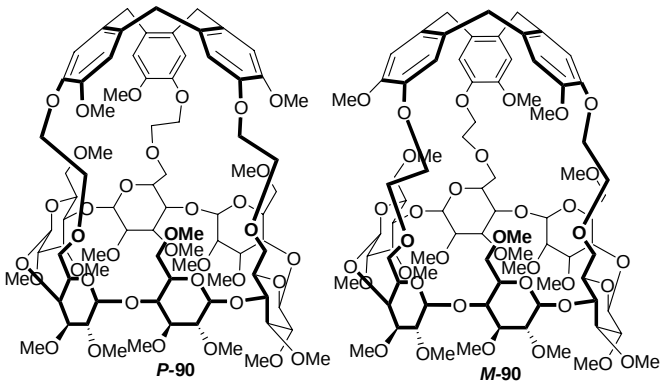
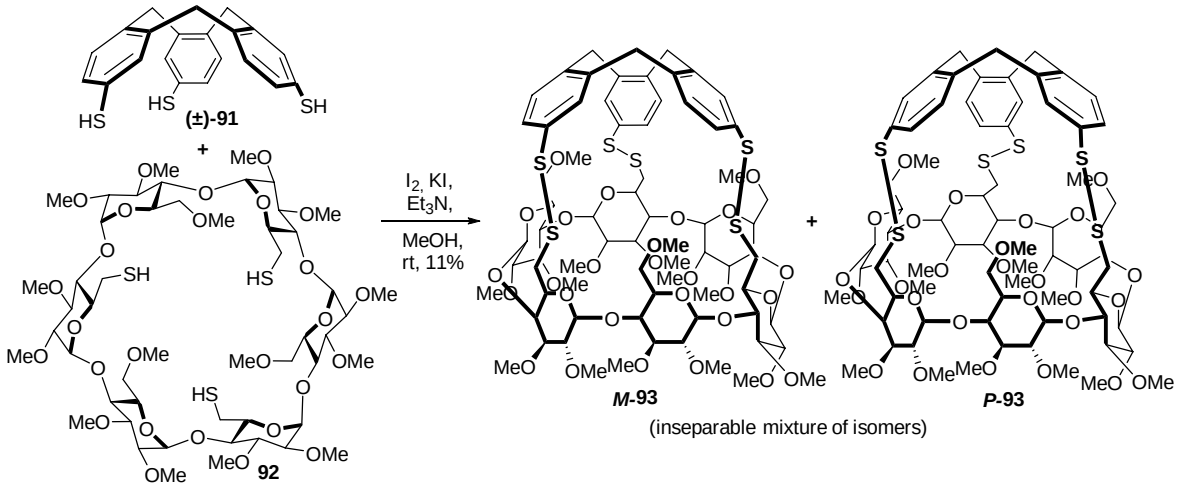


Fig. 6. α-Cyclodextrin-based molecular cages with ethylene bridges.



Scheme 21. Synthesis of α-cyclodextrin-based molecular cages with disulfide linkers.

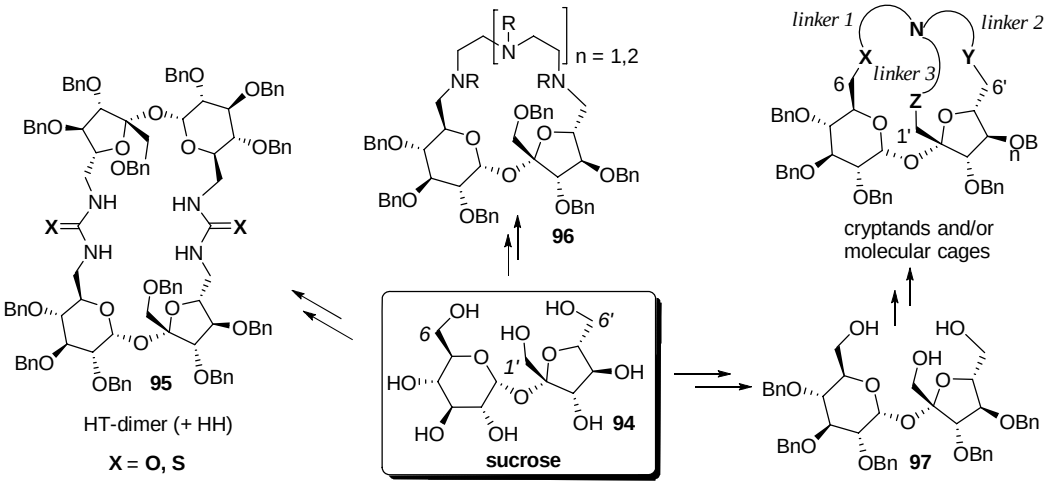
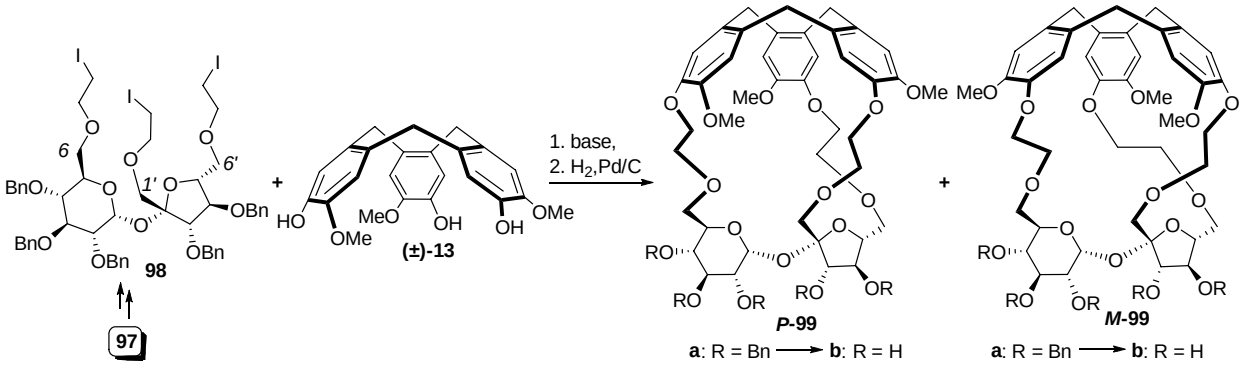


Fig. 7. Conversion of sucrose into macrocyclic receptors and possible route to sucrose-based cryptands.



Scheme 22. First synthesis of molecular cages composed of sucrose and cyclotriveratrylene units.

In this synthesis as many as four isomers can be formed: two 'normal' and two 'twisted'. However, only two products ('normal') were obtained, indicating that the ethylene linker connecting sucrose and CTV units is too short. Application of a longer phenylidene linker afforded all four possible stereoisomeric cages: ***P*-100**, ***M*-100**, ***P*-101**, and ***M*-101** in a 2:2:1:1 ratio in excellent yield (52%; Fig. 8, linker = L_1) showing moderate complexing ability towards imidazolium and pyridinium cations [72]. The application of a longer linker (naphtylidene) also resulted in the formation of four molecular cages: ***P*-102**, ***M*-102**, ***P*-103**, and ***M*-103** in 39% yield in a 2:2:1:1 ratio (Fig. 8, linker = L2); these receptors exhibited significant complexing selectivity of choline and acetylcholine [73].

Application of hemicryptophanes in the host-guest chemistry

In this section, the application of synthetic CTV-based receptors in selective recognition of biologically important compounds will be shortly described. While biologically important derivatives are well recognized by natural receptors, the application of synthetic receptors is still at the very early stage of knowledge.

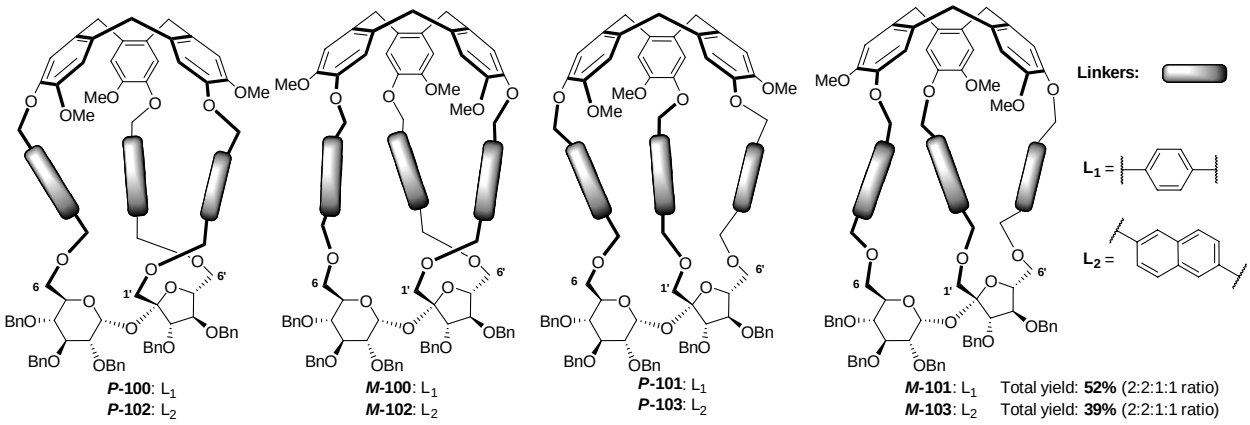


Fig. 8. Structures of molecular cages from sucrose and CTV units connected *via* phenylidene (L_1) and naphtylidene (L_2) linkers.

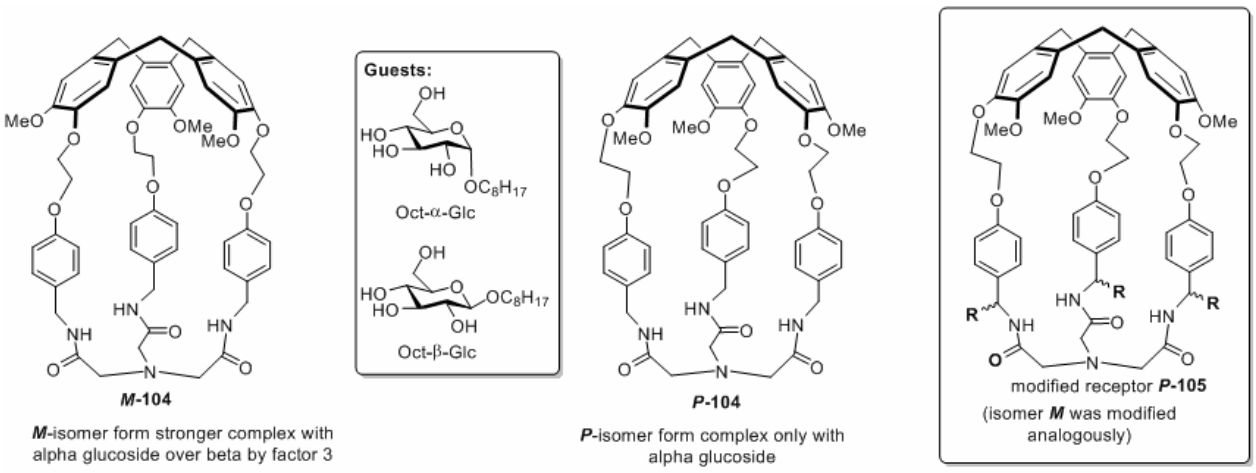


Fig. 9. Complexation of selected glucosides by hemicryptophane receptors.

Recognition of carbohydrates

The first recognition of carbohydrates by hemicryptophane receptors was reported in 2011 by Dutasta *et al.* who observed that the ***M*** enantiomer of receptor **104** forms stronger complexes with α-octyl glucoside than β-octyl glucoside by factor 3, while the ***P***-enantiomer of **104** forms complex only with the α-glucoside (Fig. 9) [74].

Modification of the structure of receptor **104** by an introduction of additional groups at the benzylic position in both enantiomers (→ **105**), as well as complexation of different monosaccharides (*e.g.* both alkyl mannosides) has been studied [62, 64].

Recognition of ammonium cations

Many neurotransmitters involved in key biological processes have the amino function(s) and exist in an ionic form (ammonium cations) at the physiological pH. One of the neurotransmitters of broad interest is acetylcholine (ACh) playing significant role in peripheral and central nervous systems [75]. Significant selective recognition of such neurotransmitter was already reported by us for hemicryptophanes **102** and **103** (shown in Fig. 8).

Makita *et al.* reported that hemicryptophane containing triamide moiety [(±)-**106a**] is able to complex various tetraalkylammonium salts (Me_4N^+, $Et_2Me_2N^+$, acetylcholine) with very good association constants (K_a) ranging between 10^3-10^4 M^{-1} [42]. Several primary alkylammonium cations of different size were effectively encapsulated by hemicryptophane bearing tris(2-aminoethyl)amine unit [(±)-**107**] [76]. Enantiomerically pure variants of hemicryptophane **(±)-107** were used in the recognition studies of chiral ammonium guest [77].

While host ***M*-107** could bind (1*R*,2*S*)-(–)-norephedrine with $K_a = 4.9 \times 10^7$ M^{-2}, its enantiomer ***P*-107** was able to recognize this ammonium guest with $K_a = 5.1 \times 10^6$ M^{-2}, assuming the 1:2 (H:G) stoichiometry. The recognition properties of water-soluble cage (±)-**108** (Fig. 10) towards structurally similar ammonium guest (choline, glycine betaine, and betaine aldehyde) in aqueous media have been reported [78]. It was found that only choline was effectively recognized by this receptor (K_a = 2300 M^{-1}).

Four enantiopure hemicryptophanes ***M*-**(*S*,*S*,*S*)-**88b** (shown in Scheme 19) and its diastereoisomers: ***P*-**(*S*,*S*,*S*)-**88b**, ***M*-**(*R*,*R*,*R*)-**88b**, and ***P*-**(*R*,*R*,*R*)-**88b** were successfully employed in the recognition of (1*R*,2*S*)-(–)-ephedrine and (1*R*,2*S*)-(–)-norephedrine picrates [79]. All four isomers proved to be efficient hosts in chiral recognition of both bioactive compounds. The higher binding constants were observed for (1*R*,2*S*)-(–)-norephedrine than (1*R*,2*S*)-(–)-ephedrine.

Recently, three different fluorescent hemicryptophanes: (±)-**109**, (±)-**110**, and (±)-**111** (Fig. 11) were used for the selective recognition of acetylcholine in the presence of choline [54, 55]. Hemicryptophanes (±)-**109** and (±)-**111** displayed a remarkable increase of the fluorescence intensity ("turn on" signal), while molecular cage (±)-**110** exhibited decrease of the fluorescence intensity ("turn off" signal) after each addition of the guest solutions.

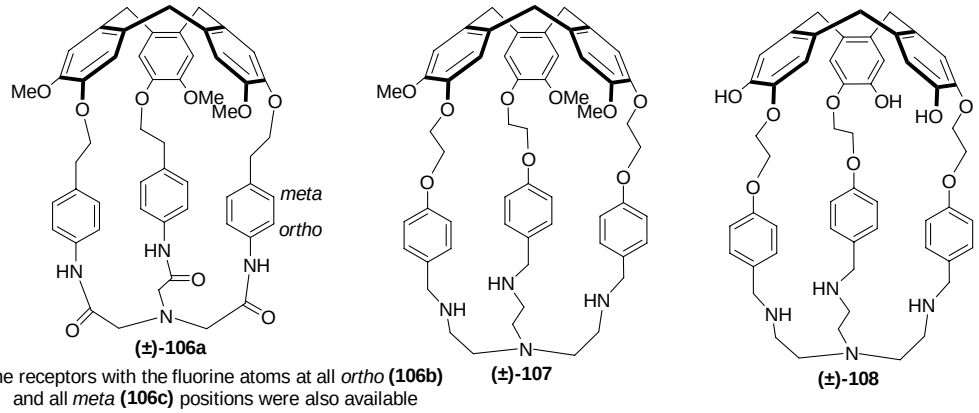


Fig. 10. Hemicryptophanes applied for the complexation of important ammonium guests.

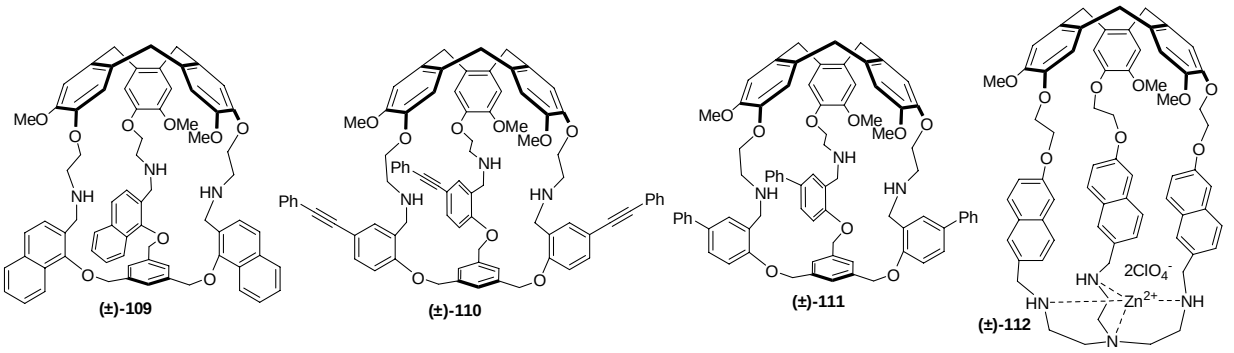


Fig. 11. Structures of fluorescent hemicryptophanes used for recognition of choline and acetylcholine [(±)-**109**–**111**] and choline phosphate [(±)-**112**].

The Zn(II)-based fluorescent racemic hemicryptophane **(±)-112** was used as a selective receptor for choline phosphate in polar media. It was found that choline (K_a = 1.2 × 10^2 M^{-1}) was much less recognized than its phosphorylated analogue (K_a = 4.1 × 10^3 M^{-1}) [80].

Recognition of zwitterions

In most cases, hemicryptophanes are heteroditopic, *i.e.* they have two different binding sites in their structure, capable of simultaneous binding of ion-pairs or zwitterions. In comparison to ammonium neurotransmitters, the selective recognition of biologically important zwitterionic guests by artificial receptors is much less explored. This is due to the fact that recognition of zwitterionic guests is often energetically unfavorable because these strongly solvated bifunctional molecules have to be removed from water to the solution of much lower dielectric constant, which is a huge barrier to cross. Thus, strong coordination bonds along with the ionic interactions are usually involved in the binding of zwitterionic species. Moreover, the distance between cationic and anionic binding sites in the receptor should be coordinated with the shape and size of bifunctional guest molecule [81].

Heteroditopic hemicryptophane **(±)-106a** with nitrilotriacetamide moiety (see Fig. 10) was successfully used as a selective receptor for the encapsulation of taurine over other related zwitterionic compounds in a competitive polar environment [81]. Another heteroditopic hemicryptophane **(±)-57** (see Scheme 13) with a modified cavity, able to simultaneously bind both negatively and positively charged parts of the zwitterionic guests by the anion-π and cation-π interactions, was used for complexation of four neurotransmitters: taurine, homotaurine, β-alanine, and GABA [52]. Compared to the previously described receptor **(±)-106a**, the complexation abilities of **(±)-57** were considerably improved.

The recognition properties of diastereoisomerically pure hemicryptophanes ***M*-73** and ***P*-73** (see Scheme 16) containing cyclic peptide moiety were investigated using L- and D-carnitine as guests [60]. Both hosts were selective towards L-carnitine (K_a = 4.1 × 10^3 M^{-1} and 9.1 × 10^2 M^{-1}); the association constant of ***M*-73** and ***P*-73** for L-carnitine was 1.5 and 1.3 times greater than for its D-enantiomer (K_a = 2.7 × 10^3 $M^{-1}$and 6.9 × 10^2 M^{-1}, respectively).

Recognition of anions

Sensing of anion by artificial receptors is one of the main goals of supramolecular chemistry. Transport of anions across the cell membranes, extraction of anions from complex mixtures, or their use in supramolecular catalysis are only a few examples demonstrating the great importance of such phenomenon [5]. Despite large progress in this field, the selective recognition of anions is still challenging, particularly in water, due to the fact that they are strongly solvated by polar solvents, they have more diffuse charge comparing to the corresponding isoelectronic cations, greater pH dependence, and a wide type of geometries [5, 82]. A few examples presented below will show the most significant achievements in sensing anions.

Martinez and Dutasta reported the study on the selective recognition of various anionic species with different geometry by hemicryptophane (±)**-106a** containing a tripodal amide moiety (shown in Fig. 10). They found that the affinity of this receptor for the spherical halide anions increased as follows: F– > Cl– > Br– > I–, and was compatible with its hydrogen-bond accepting capability. Second, more basic $H_2PO_4^-$ anion was better recognized than HSO_4^-. Finally, the most basic AcO^- anion displayed weaker affinity for host (±)**-106a** in relation to $H_2PO_4^-$ [83].

Two hemicryptophanes (±)**-106b** and (±)**-106c** containing differently fluorinated aromatic rings in the linkers (Fig. 12) has also been studied towards anionic guests [65]. The complexing ability was highly dependent on the position of the fluorine atoms; the K_a value was remarkably increased in case of host (±)**-106c**, whereas decreased in case of (±)**-106b**. Introduction of the urea units to the structure of the receptor resulted in the improvement of the complexing properties. For example, the association constants for receptor (±)**-40** (see Fig. 4) were remarkably higher than for other hemicryptophanes [45].

Recently, a small urea-based hemicryptophane (±)**-39** (see Fig. 4) has been studied towards selective recognition of halides [46]. Compared to its previously described analogue (±)**-40** with much larger cavity, receptor (±)**-39** displayed the exclusive recognition of the fluoride anion over other competing halides.

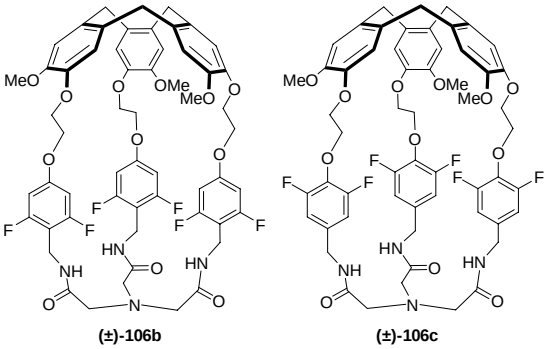


Fig. 12. Structures of hemicryptophanes with differently located fluorine atoms.

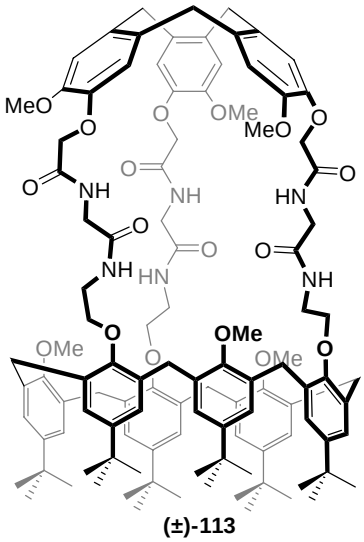


Fig. 13. Structure of calix[6]cryptamide.

Recognition of ion-pairs

Heteroditopic receptors capable to bind simultaneously both cationic and anionic guests have an important advantage, namely they could prevent the competitive pairing of the guest ions in solution. Most of the ion-pair receptors exhibit improved selectivity and binding affinity comparing to the analogous single ion hosts. In case of ion-pairs, the binding sites of the receptors responsible for complexation should be located close to each other to increase the electrostatic interactions; otherwise ion-pairs could associate outside the cage. Well-designed receptors allow for a positive cooperative effect, manifested in additional or more intensified long-range electrostatic interactions, which improve affinity to ion-pairs [6].

This is well demonstrated by complexation of calix[6]cryptamide (±)**-113** (Fig. 13) towards two ion-pairs: $EtNH_3^+Cl^-$ and $PrNH_3^+Cl^-$ [57]. This host acts as a heteroditopic receptor, in which the alkylammonium chain of the guest molecule occupies the calixarene cavity, whereas the chloride counterion is simultaneously bound by the three amide functions of the hosts's linkers through the strong hydrogen-bonding interactions.

Martinez and Dutasta also proposed hemicryptophane **(±)-106a** (shown in Fig. 10) with two properly located binding sites: 1) the CTV scaffold suitable for complexation of ammonium cations and 2) three amide groups able to coordinate anions

via hydrogen-bonding interactions, as a good receptor capable of simultaneously recognizing ion pairs [83]. They proved that tetramethylammonium guest was effectively bound by the CTV unit, while the anionic species interacted with the triamide moiety. Therefore, this bi-functional receptor exhibited a strong positive cooperativity effect for all studied ion-pairs.

Recently, the simultaneous complexation of ion-pairs employing hemicryptophane (±)-**40** (see Fig. 4) containing three urea groups was reported [45]. This receptor was also able to bind both cations and anions ($Me_4N^+F^-$, $Me_4N^+Cl^-$ and $Me_4N^+Br^-$) with much higher association constants, when compared to its complexation of individual ion.

Recognition of other guests

The selective recognition of various neutral molecules by artificial receptors through non-covalent interactions is of great importance. For example, the selective recognition of fullerenes from its crude fullerite mixture by synthetic receptors might be crucial in their isolation process, which usually is difficult and tedious, especially due to their poor solubility in most solvents. This separation process is of particular importance, as most of the spherical nanocarbons can find an application in multiple areas including catalysis, photovoltaics, or medicinal chemistry [84].

Recognition of persistent organic pollutants (*e.g.* chlordecone and its analogues) is equally important, as in most cases they are extremely hard to remove from environment [85].

The recognition properties of calix[6]cryptamide (±)-**113** (see Fig. 13) towards neutral molecules such as achiral pyrrolidin-2-one and imidazolidin-2-one as well as chiral (±)-4-methyl-imidazolidin-2-one have been studied [57]. The results showed that all three guests were fully encapsulated in the calixarene cavity instead of the CTV unit. The guest molecules are additionally stabilized by strong hydrogen bonds with the calixarene oxygen atoms of the host. These results demonstrated the specific complexation of neutral amide and urea type guests by hemicryptophane (±)-**113** involving both hydrogen bond acceptor and donor groups of the guests in the recognition process. When comparing the binding constants of calix[6]cryptamide (±)-**113** with both achiral guests, strong preference for imidazolidin-2-one (K_a = 12800 M^{-1}) than for pyrrolidin-2-one (K_a = 250 M^{-1}) can be noticed. It is noteworthy that in case of chiral recognition of (±)-4-methyl-imidazolidin-2-one guest, the formation of two diastereoisomeric host-guest complexes was observed (44% *de*).

The encapsulation abilities of two racemic macrocycle-based hemicryptophanes (±)-**63a** and (±)-**63b** (see Fig. 5) with two fullerenes (C_{60} and C_{70}) were investigated by Zhao and Li [58]. They confirmed the encapsulation of C_{60} and C_{70} inside the cavities of hosts (±)-**63a** and (±)-**63b**. Host (±)-**63b** showed better recognition properties than host (±)-**63a** which is related to its larger cavity. In addition, although these two hosts have different sized cavities, they both display better affinity for C_{60} than for C_{70}.

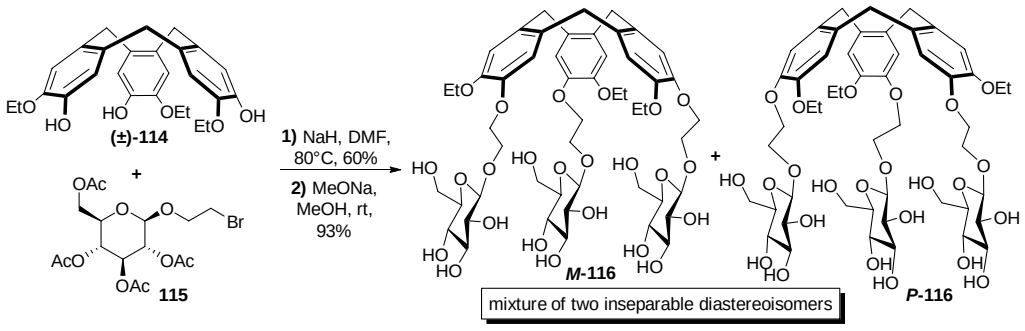
Miscellaneous

There are only very limited reports in the literature about the CTV unit combined with carbohydrates. Hemicryptophanes built of CTV and cyclodextrins or sucrose are already presented in Fig. 6 and 8, as well as in Schemes 21 and 22.

They are also a few other examples of derivatives, in which the CTV is connected with sugar moieties. Although they are not hemicryptophanes, they represent an interesting class of optically pure CTV derivatives. The first example concerning the connection of simple sugar with the CTV platform (→ ***P*-116** and ***M*-116**), reported in 1999, is shown in Scheme 23 [86].

The small library of trivalent CTV-based amino acid glycoconjugates (**117**; Fig. 14) was synthesized by Liskamp and Ameijde [87]. However, the biological activity of such prepared glycoconjugates has not been investigated.

Water-soluble CTV-based glycoconjugates containing peripheral glucose, glucosamine hydrochloride (***M*/*P*-118** and ***M*/*P*-119**), or lactose units were reported by Han and co-workers (Fig. 14), who also studied their binding properties with C_{60} in both organic and aqueous media [88, 89]. All hosts demonstrated very good binding abilities towards C_{60} with particular emphasis of the cationic receptor ***M*/*P*-119**, which displayed the best complexing properties.



Scheme 23. Synthesis of water-soluble CTV derivative with peripheral glycosyl residues.

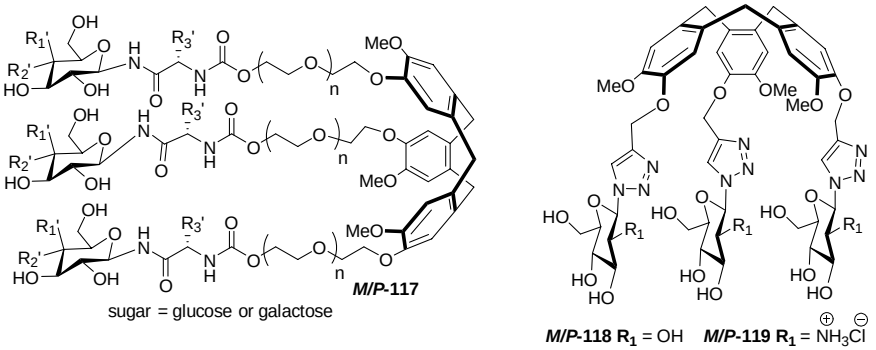


Fig. 14. CTV-based amino acid glycoconjugates.

Similar synthetic pathway involving the azide-alkyne cycloaddition towards trivalent and hexavalent CTV-based glucoconjugates were also reported by Vidal *et al.* [90].

CONCLUSIONS

Cyclotriveratrylene (CTV), a rigid, bowl-shaped macrocyclic compound consisting of three veratrole units, is an excellent platform for the preparation of chiral molecular cages. The methods of the synthesis of cyclotriveratrylene and the properties of this macrocycle were reviewed. The synthesis of derivatives of CTV was also described. Special emphasis was put on the synthesis of hemicryptophanes: inherently chiral, covalently bound cage-type molecular receptors with ditopic cavity, consisting of a C_3-symmetrical cyclotriveratrylene scaffold (existing in the *P* and *M* configuration) triply connected to another unit. Most of hemicryptophanes reported so far were prepared as racemic mixtures, which is a consequence of inherent chirality of the CTV unit with the C_3-symmetry. Much more interesting optically pure molecular cages are very rare. Their synthesis was reported in detail in this review. The application of the CTV-based hemicryptophanes in molecular recognition of various species (anions, cation, zwitterions, and neutral molecules) was discussed. Special attention was paid to enantioselective complexation of chiral species.

ACKNOWLEDGEMENTS

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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