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Shorter and Modular Synthesis of Hemicryptophane-tren Derivatives

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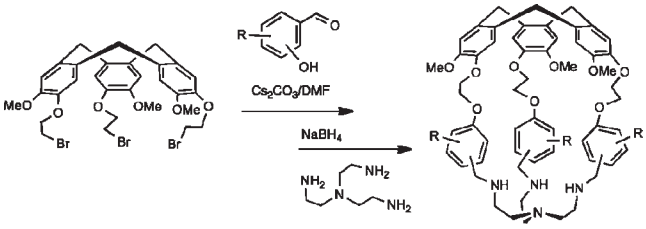
ABSTRACT



Hemicryptophanes are host molecules with many applications as supramolecular catalysts or in ion selective recognition. A very convenient and efficient modular approach for the synthesis of hemicryptophane-tren (tren, tris(2-aminoethyl)-amine) derivatives has been developed. For instance, hemicryptophane 1 was synthesized at the gram scale in four steps from vanillyl alcohol compared to the previous seven-step procedure. The size, shape, and functionalities of the molecular cavity were also easily modified.

The efficient and versatile synthesis of molecular containers is one of the key aspects of supramolecular chemistry.[1] The cryptophane hosts, which are constructed from two cyclotriveratrylene (CTV) units, can encapsulate a wide variety of guests and have remarkable binding properties toward neutral or charged guests and efficient chiral recognition properties.[2] Recently improved synthetic routes for cryptophanes, involving fewer steps and higher yields, have been reported. In particular Rousseau et al.[3] and Dmochowski et al.[4] developed respectively a scalable synthesis of cryptophane-111 and a shorter synthesis of tribsubstituted cryptophane-A derivatives. The hemicryptophanes[5] are ditopic host molecules and were found to be a novel class of efficient supramolecular catalysts,[6] selective hosts for ammonium,[5a] ion pairs,[7] C_{60} fullerene,[8] and enantioselective carbohydrate receptors.[9] They led to the design of novel molecular mechanical components as propellers[10] or gyroscopes.[11] We have previously described the synthesis of hemicryptophane **1** (Scheme 1), which contains a CTV unit, providing a rigid scaffold with a lipophilic cavity, and a C_3-symmetrical ligand derived from tris(2-aminoethyl)-amine (tren).[12] Supramolecular ligands combining these two features have been used to complex

(1) (a) Kirby, A. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 707–724. (b) Sanders, J. K. M. *Chem.—Eur. J.* **1998**, *4*, 1378–1383. (c) Lehn, J.-M. *Rep. Prog. Phys.* **2004**, *67*, 245–249. (d) Yoshizawa, M.; Klosterman, J. K.; Fujita, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 3418–3438.

(2) Brotin, T.; Dutasta, J.-P. *Chem. Rev.* **2009**, *109*, 88–130.

(3) Traoré, T.; Delacour, L.; Garcia-Argote, S.; Berthault, P.; Cintrat, J.-C.; Rousseau, B. *Org. Lett.* **2010**, *12*, 960–962.

(4) Taratula, O.; Hill, P. A.; Bai, Y.; Khan, N. S.; Dmochowski, I. J. *Org. Lett.* **2011**, *13*, 1414–1417.

(5) (a) Canceill, J.; Collet, A.; Gabard, J.; Kotzyba-Hibert, F.; Lehn, J.-M. *Helv. Chim. Acta* **1982**, *65*, 1894–1897. (b) Smeets, J. W. H.; Coolen, H. K. A. C.; Zwikker, J. W.; Nolte, R. J. M. *Recl. Trav. Chim. Pays-Bas* **1989**, *108*, 215–218. (c) Rapenne, G.; Crassous, J.; Collet, A.; Echegoyen, L.; Diederich, F. *Chem. Commun.* **1999**, 1121–1122. (d) Gosse, I.; Dutasta, J.-P.; Perrin, M.; Thozet, A. *New J. Chem.* **1999**, *23*, 545–548. (e) Gautier, A.; Mulatier, J.-C.; Crassous, J.; Dutasta, J.-P. *Org. Lett.* **2005**, *7*, 1207–1210.

(6) Martinez, A.; Dutasta, J.-P. *J. Catal.* **2009**, *267*, 188–192.

(7) (a) Le Gac, S.; Jabin, I. *Chem.—Eur. J.* **2008**, *14*, 548–557. (b) Perraud, O.; Robert, V.; Martinez, A.; Dutasta, J.-P. *Chem.—Eur. J.* **2011**, *17*, 4177–4182.

(8) Wang, L.; Wang, G.-T.; Zhao, X.; Jiang, X.-K.; Li, Z.-T. *J. Org. Chem.* **2011**, *76*, 3531–3535.

(9) Perraud, O.; Martinez, A.; Dutasta, J.-P. *Chem. Commun.* **2011**, *47*, 5861–5863.

(10) (a) Martinez, A.; Robert, V.; Gornitzka, H.; Dutasta, J.-P. *Chem.—Eur. J.* **2010**, *16*, 520–527. (b) Martinez, A.; Guy, L.; Dutasta, J.-P. *J. Am. Chem. Soc.* **2010**, *132*, 16733–16734.

(11) Khan, N. S.; Perez-Aguilar, J. M.; Kaufmann, T.; Hill, P. A.; Taratula, O.; Lee, O.-S.; Carroll, P. J.; Saven, J. G.; Dmochowski, I. J. *J. Org. Chem.* **2011**, *76*, 1418–1424.

(12) Dimitrov Raytchev, P.; Perraud, O.; Aronica, C.; Martinez, A.; Dutasta, J.-P. *J. Org. Chem.* **2010**, *75*, 2099–2102.

(13) Makita, Y.; Sugimoto, K.; Furuyoshi, K.; Ikeda, K.; Fujiwara, S.; Shin-ike, T.; Ogawa, A. *Inorg. Chem.* **2010**, *49*, 7220–7222.

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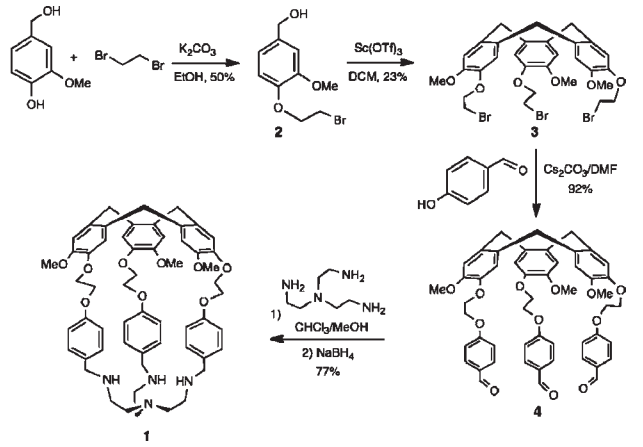
zinc[13] and phosphorus[14] leading to original compounds with unexpected reactivities. Host **1** was also found to be an efficient ammonium receptor, providing high association constants for the dopamine neurotransmitter.[15] Nevertheless, its synthesis involved seven steps with a 3% overall yield and a final time-consuming reduction step. Herein, we wish to report a shorter four-step synthesis of host **1** from commercially available vanillyl alcohol. The modular character of the synthesis provides an easy way to access variable molecular cavity sizes and to change the functional groups present in the linkers.

Scheme 1. Four-Step Synthesis of Hemicryptophane **1**



We investigated the new synthetic pathway for hemicryptophane **1** as shown in Scheme 1. Starting from the commercially available vanillyl alcohol and 1,2-dibromoethane reagents to give compound **2**, the alkyl-brominated CTV **3** was synthesized in two steps according to the procedure described by Dmochowski et al.[4] The preparation of the hemicryptophane precursor **4** was then conducted under standard conditions by reacting **3** with 4-hydroxybenzaldehyde in DMF in the presence of Cs_2CO_3. Compound **4** was isolated with excellent yields without the need for column chromatography purification. The condensation of **4** with tris(2-aminoethyl)-amine diluted in a $CHCl_3/CH_3OH$ mixture, followed by a reduction step with sodium borohydride, afforded **1** in 77% yield. Hemicryptophane **1** has thus been obtained in 8% overall yield via a four-step synthetic route, which improves our seven-step procedure previously published (3% overall yield). Moreover, this pathway was applied to larger quantities of starting materials allowing the production of host **1** at the gram scale. This strategy also avoids the time-consuming reduction step, which required nearly one week of reaction time.

Given the potential of this synthetic pathway, we investigated the possible functions within this structure, and we opted to vary the linkers to prepare different analogues of hemicryptphane **1** starting from the same alkyl-brominated CTV precursor **3**. This should allow synthetic development of new hosts with different shapes and functions and variation in the volume of the inner molecular cavity, while retaining the tren and CTV key moieties. We first envisioned modifying the cavity size by changing the relative position of the aldehyde and the hydroxy groups on the aromatic linker. The corresponding hemicryptophanes **5** and **6** were prepared in respectively 50% and 49% overall yields from precursor **3** via the two-step sequence that involved nucleophilic substitution followed by reductive amination (Figure 2b–c). Single crystals of host **5** suitable for X-ray diffraction analysis were obtained by slow evaporation from a CH_2Cl_2/diethyl ether solution.

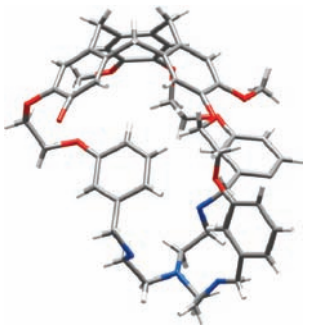


Figure 1. X-ray molecular structure of host **5**.

The molecule adopts a compact structure with the molecular cavity occupied by one of the linkers so that the tren moiety is significantly deviated from the inner cavity (Figure 1). This is an unexpected form of the molecular host, which generally exists as solvate with an encapsulated guest solvent inside the cavity. For instance, the crystal structure of molecule **1**, previously published, has revealed the C_3-symmetry of the host and the presence of a well-preorganized cavity imprisoning a molecule of *n*-pentane.[12] This highlights the significantly different behavior in the solid state of these two compounds, since both the cavity size and its shape are remarkably affected by the nature of the linkers. Second, an electron-donating group was incorporated in the aromatic part of the linker at different positions, leading to hosts **7** and **8** (Figure 2d–e). Interestingly, compound **8** presents a cavity including six methoxy groups, thus closer to that of cryptophane-A than **1**. Therefore, it could combine the complexation properties of cryptophanes toward small neutral molecules and the catalytic activities of hemicryptophane complexes. Third, the chlorine electron-withdrawing group was also successfully integrated in the host's aromatic walls to give compound **9** (Figure 2f). Nevertheless, the cyclization steps failed when fluorine or nitro groups were present in the hemicryptophane precursors (**17** and **18**, respectively) (Figure 2g–h). The introduction of these strong electron-withdrawing substituents on the benzaldehyde moiety can lead to more stable

(14) Dimitrov Raytchev, P.; Martinez, A.; Gornitzka, H.; Dutasta, J.-P. *J. Am. Chem. Soc.* **2011**, *133*, 2157–2159.

(15) Perraud, O.; Lefevre, S.; Robert, V.; Martinez, A.; Dutasta, J.-P. Unpublished results.

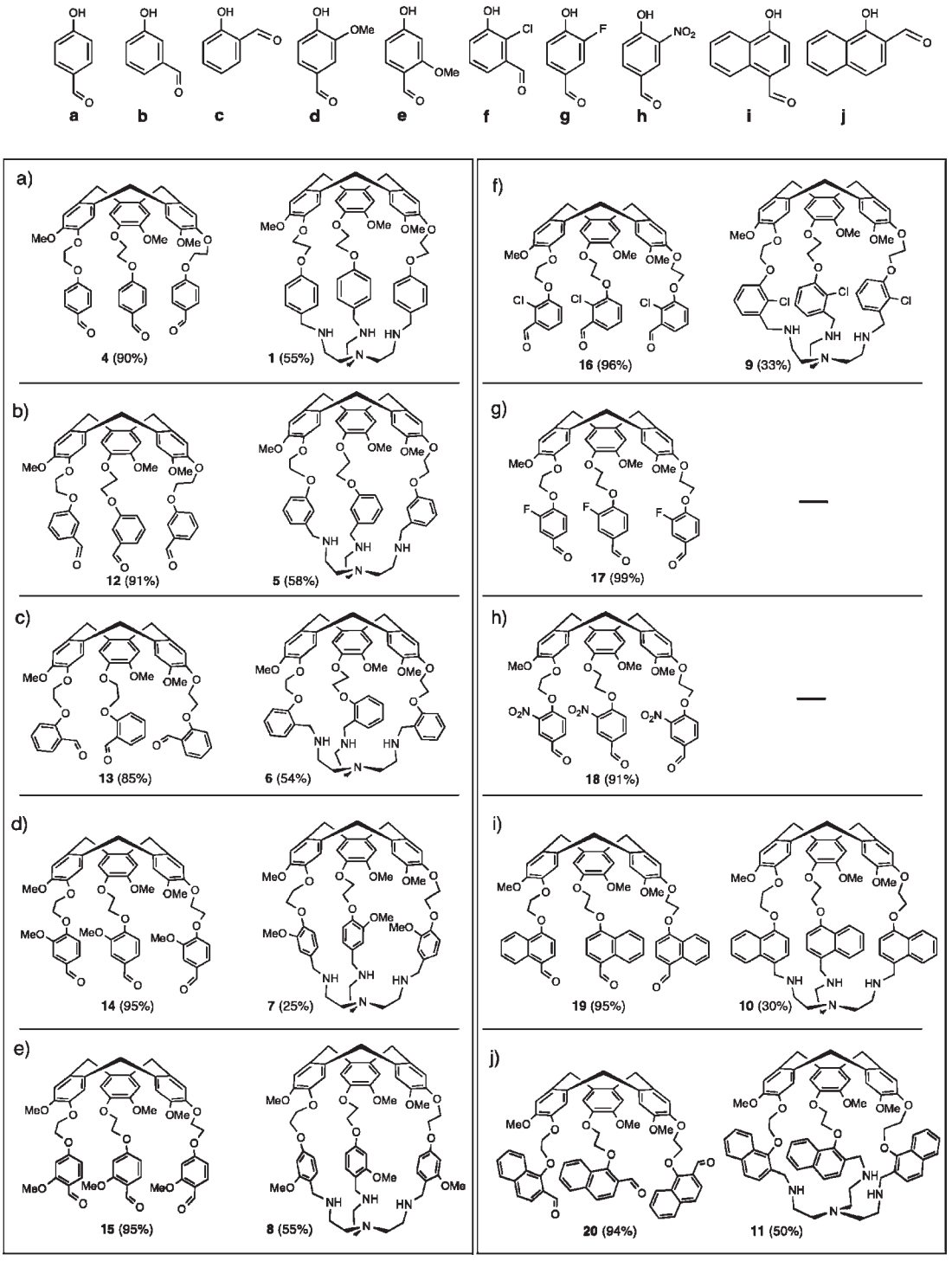


Figure 2. Hemicryptophanes and precursors synthesized from the alkyl-brominated CTV **3** and the corresponding starting compounds **a**–**j**.

imine bonds,[16] preventing the reversibility of the imine bonds formation, thus avoiding the thermodynamic control of the reaction which could account for the unsuccessful results.

Fourthly, hemicryptophanes with larger aromatic walls were obtained when naphthyl moieties were included in the linkers, and compounds **10** and **11** were synthesized in 29% and 47% overall yields from the brominated CTV **3** (Figure 2i–j). Note that these hosts could lead to optical chemosensors by giving a fluorescence response when bound to a suitable guest.[17]

(16) Godoy-Alcantar, C.; Yatsimirsky, A. K.; Lehn, J.-M. *J. Phys. Org. Chem.* **2005**, *18*, 979–985.

(17) Bell, T. W.; Hext, N. M. *Chem. Soc. Rev.* **2004**, *33*, 589–598.

In summary, a short synthesis of hemicryptophane **1** has been developed. Improvement of the overall yield was also achieved allowing the isolation of host **1** on the gram scale. Moreover, the size, shape, and function in the aromatic walls of the cavity can be modified through this synthetic pathway, whereas the key CTV and tren moieties are maintained in the host structure. Therefore, seven new hemicryptophane hosts have been prepared. This procedure should conceivably allow synthesis of a large number of CTV-based hemicryptophane-tren molecules with various functionalities and an inner cavity of modulable size.

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Supporting Information Available. Experimental procedures and full spectroscopic data; X-ray diffraction analysis. This material is available free of charge via the Internet at http://pubs.acs.org.