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Supramolecular Compounds from Multiple Ugi Multicomponent Macrocyclizations: Peptoid-based Cryptands, Cages, and Cryptophanes

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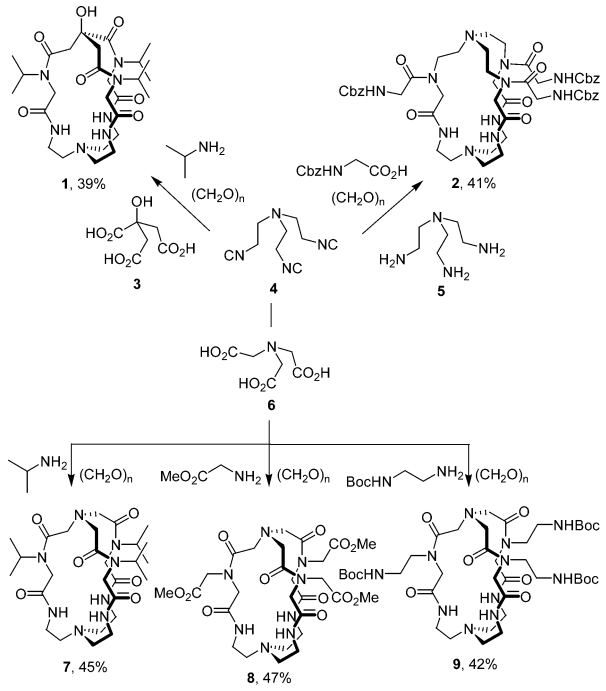
The design and synthesis of macrocycles capable of binding and encapsulating a target species has been recognized as a milestone in the development of supramolecular chemistry.[1] Cryptands[1] and cryptophanes[1,2] are among the most-studied types of macrocyclic receptors due to their recognized capability to include either ions or neutral molecules, depending on the size and nature of the cavity as well as the binding properties of the tether chains.

Herein, we report a very efficient and straightforward methodology for the synthesis of cryptands, cages, and cryptophanes containing multidimensional arrays of peptoid cores suitable for forming inclusion complexes. This approach features the one-pot assembly of complex molecular architectures by Ugi-type multiple multicomponent macrocyclizations[3] of trifunctional building blocks. The Ugi four-component reaction (Ugi-4CR) is a highly efficient process in which a primary amine, an oxo compound, a carboxylic acid, and an isocyanide react in one pot to form a peptoid.[4] The incorporation of Ugi-peptoid backbones into host-like macrocycles represents a completely new and promising outlook for molecular-recognition studies. The cyclic peptoid core may be seen as a binding motif capable of complexing with ions in a manner similar to cyclic peptides, where the amide bonds enable binding the guest on the basis of the π- and σ-donor behavior or the hydrogen-bonding pattern.

Scheme 1 summarizes the synthesis of cryptands by 3-fold Ugi-4CR-based macrocyclizations unifying 12 reaction steps of 8 components in one pot. All macrocyclizations were accomplished under pseudodilution conditions by slowly adding one of the components to a stirred mixture of the others. The simplicity of this procedure and the great complexity that can be achieved with minimized synthetic cost make this methodology an interesting candidate for the combinatorial generation of synthetic receptors. The syntheses of cryptands **2**, **8**, and **9** show the prospect of employing monoprotected amino acids and diamines to install appended functionalities with additional binding capacity, e.g., NH_2 and CO_2H. Other Ugi-compatible amino acids presenting chemical motifs of known catalytic or recognition relevance may also be incorporated to produce desired properties.

Another key feature of this strategy is the rapid variation of molecular topologies accessible by using constitutionally different scaffolds. This is properly illustrated in Schemes 2 and 3, where the synthetic planning is directed to demonstrate the possibility of easily creating upper and lower receptor poles highly diverse in shape and binding features. We focused also on the use of extended structures to be incorporated into the host cores, thus creating highly functionalized, cage-like structures with large interaction surfaces. Aryl groups are the simplest and most readily available rigid elements, albeit with two-dimensional functionalization. Additionally, steroids represent an amenable preorganized scaffold for three-

Scheme 1. Peptoid-Based Cryptands by 3-Fold Ugi-4CR-Based Macrocyclizations



dimensional functionalization with Ugi-reactive functional groups and binding motifs tailored for complementarity of target guests.[3a,5]

Scheme 2 shows the rapid construction of macrobicycles featured by a concave moiety on the northern pole of the cavity. For this, the umbrella-shaped cholic acid and the bowl-shaped cyclotriveratrylene (CTV)[6] were functionalized and submitted to 3-fold multicomponent macrocyclizations to assemble the cages **11** and **13** and the hemicryptophanes **15** and **17**. Compared to the, at this stage, simpler cryptands, these cages and cryptophanes offer enhanced possibilities to form inclusion complexes. For example, by substituting one bridgehead with an extended, rigid skeleton it is not only possible to enlarge and better define the interior of the cavity but also to impose differentiation of the three peptoid tethers and hence asymmetric interiors (e.g., cages **11** and **13**). Indeed, several trifunctionalized scaffolds with defined geometries can be incorporated into the host cavity, especially to gain selectivity based on differentiable recognition profiles and encapsulation properties.

Scheme 3 highlights the synthesis of nonrepetitive macromulticyclic skeletons by sequential multicomponent macrocyclizations of different multiplicity. Steroid−aryl hybrid macrocycles, produced by an initial double Ugi-4CR-based macrocyclization, behave after the corresponding deprotection as trifunctional building blocks for a consecutive 3-fold Ugi-4CR-based macrocyclization. Macrotet-

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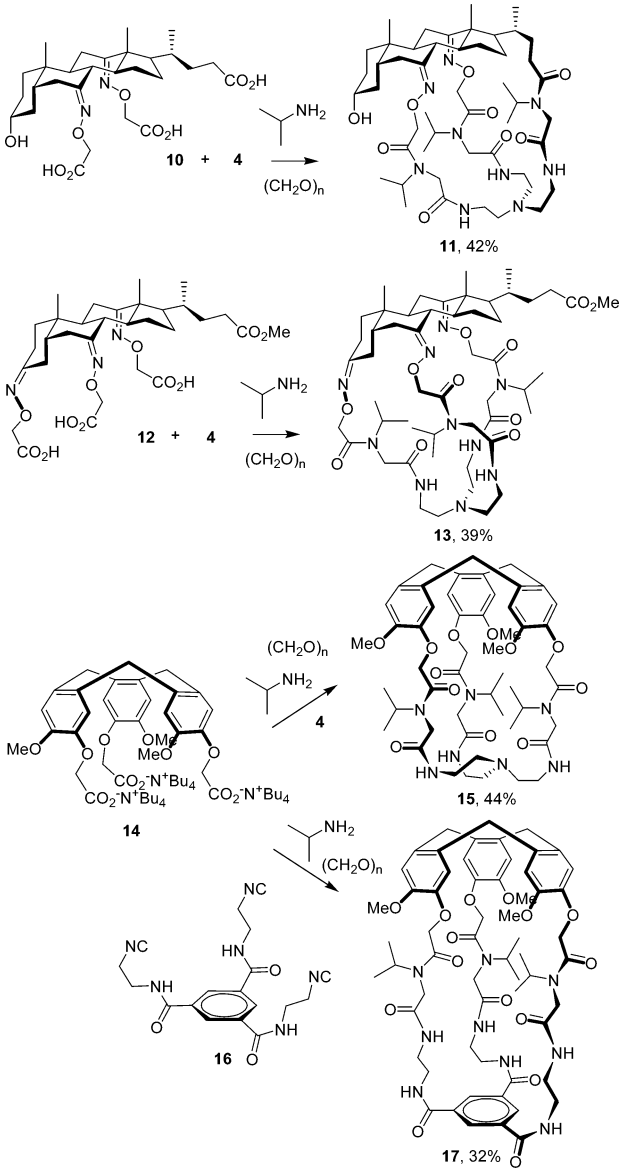
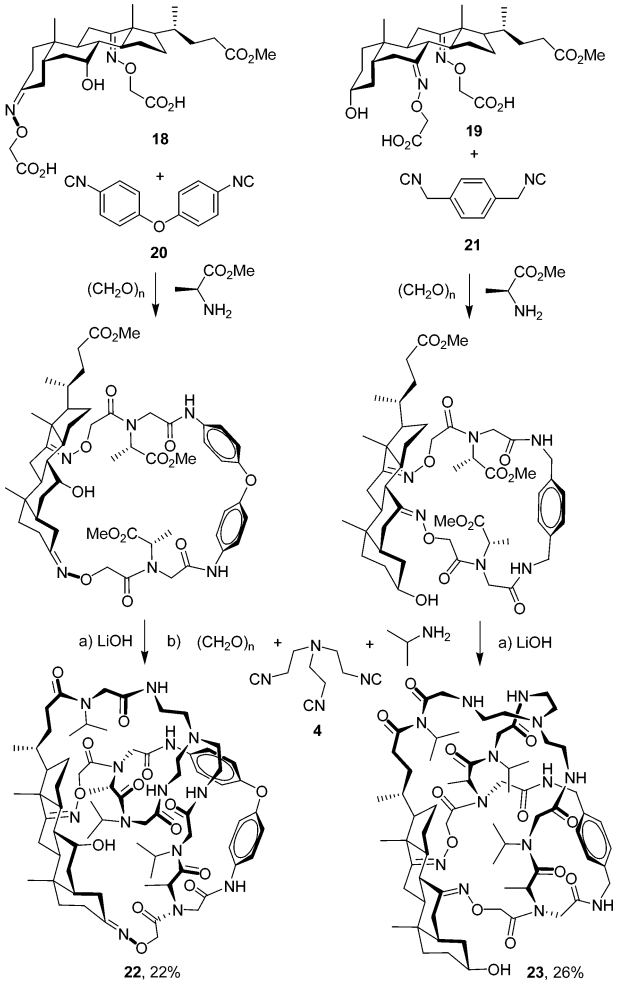
Scheme 2. Peptoid-Based Cages and Cryptophanes by 3-Fold Multicomponent Macrocyclizations



racycles **22** and **23** were thus achieved by the incorporation of 13 building blocks, forming 20 new bonds in a very short, one-pot reaction sequence that does not require isolation of the intermediates. This illustrates the formidable scope of the method to produce highly functionalized receptors featuring unusual shapes, e.g. the cross-linked igloo-shaped skeletons of cages **22** and **23**, tetramacrocyclo[XYZR] systems, not counting the aromatic and steroidal intrinsic rings. Indeed, the current procedure is suitable to produce large cyclic skeletons that may combine a binding pocket tailored for a target substrate with a catalytic site, just as in enzymes.

In conclusion, highly diverse, nonrepetitive macromulticycles can be assembled in one pot by Ugi-type multiple multicomponent macrocyclizations of polyfunctional building blocks. These host-like compounds contain peptoids as tethers which carry structural moieties of established recognition profiles, thus creating complex three-dimensional arrays of binding functionalities suitable to form inclusion complexes with various guests. We believe that this macrocyclization approach may emerge as one of the most valuable

Scheme 3. One-Pot Synthesis of Steroid−Aryl Hybrid Cages by Sequential 2- and 3-Fold Ugi-4CR-Based Macrocyclizations



strategies toward supramolecular receptors due to its efficient and diversity-oriented character.

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Supporting Information Available: Experimental and spectral data for all compounds; selected NMR and HR-FT-ICR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; Wiley-VCH: Weinheim, 1995. (b) Vögtle, F. *Supramolecular Chemistry*; Wiley & Sons: Chichester, 1991. (c) Cram, D. J.; Cram, M: J. *Container Molecules and Their* Guests; Royal Society of Chemistry: Cambridge, 1997.

(2) (a) Collet, A. In *Comprehensive Supramolecular Chemistry*; Vögtle, F., Ed.; Pergamon Press: New York, 1996; pp 325−365. (b) Dutasta, J.-P. *Top. Curr. Chem.* **2004**, *232*, 55.

(3) (a) Wessjohann, L. A.; Voigt, B.; Rivera, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4785. (b) Wessjohann, L. A.; Ruijter, E. *Mol. Diversity* **2005**, *9*, 159.

(4) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168.

(5) (a) Virtanen, E.; Kolehmainen, E. *Eur. J. Org. Chem.* **2004**, 3385. (b) Davis, A. P.; Joss. J.-B.; *Coord. Chem. Rev.* **2003**, *240*, 143. (c) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2979. (d) Wallimann, P.; Marti, T.; Fürer, A.; Diederich, F. *Chem. Rev.* **1997**, *97*, 1567.

(6) Vériot, G.; Dutasta, J.-P.; Matouzenko, G.; Collet, A. *Tetrahedron* **1995**, *51*, 389.

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