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Amino-Acid Templated Assembly of Sucrose-Derived Macrocycles

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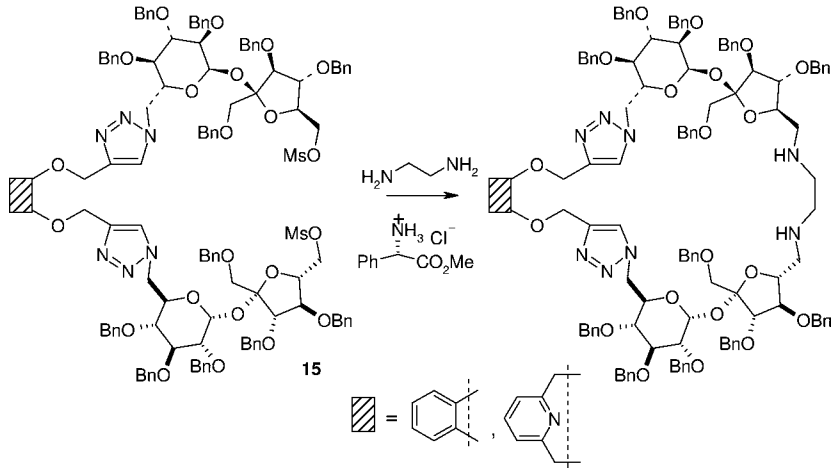
ABSTRACT



***C*$_2$-Symmetrical chiral macrocyles containing two sucrose units were prepared by an amino acid templated macrocyclization reaction between appropriate sucrose-based linear precursors and ethylenediamine.**

The ongoing quest for efficient and cheap synthetic methods that lead to large-sized rings is motivated by a wide variety of possible applications of natural and synthetic macrocyclic molecules (in medicine, material and supramolecular chemistry, and many others).[1] The classical high-dilution technique developed by Ziegler,[2] although still being applied especially in the synthesis of complex supramolecular assemblies, has two major limitations. Usually it does not provide the products in high yields and it is also very time-consuming. On the other hand, high-pressure techniques,[3] which require a special apparatus, impede the monitoring and control of the reaction. A more convenient methodology lays in metal-templated synthesis of crown ethers,[4] and there is increasing growth in the number of different templating methods available. This allows a wide variety of macrocycles to be obtained, possessing diverse structures and properties, it being devoid of the limitations mentioned above. Besides metal-templated macrocyclizations,[5] a considerable number of other synthetic approaches, which take advantage of nonmetallic templates, have also been discovered and studied. The most common methodologies utilize π-stacking, π-donor/π-acceptor interactions, and hydrogen bonding[6] as the

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templating motifs, and therefore, the molecules applied as templates are typically simple aromatic compounds, transition-metal complexes, amides, esters, and other simple hydrogen-bond acceptors and donors. So far, there have been no precedents for the application of amino acid derivatives or other simple biomolecules as templates for construction of macrocyclic skeleta.

In recent years, we have devoted considerable effort to the synthesis of chiral macrocycles based on the sucrose molecule. We have succeeded in preparing a series of crown[7] and aza-crown ether analogues[8,9] starting from the partially protected derivative 1′,2,3,3′,4,4′-hexa-*O*-benzylsucrose (**1**).[10] Such macrocycles containing nitrogen atoms in the ring (e.g., **2** and **3**) are promising chiral receptors for primary amine hydrochlorides (Figure 1).[11] Given our involvement in the

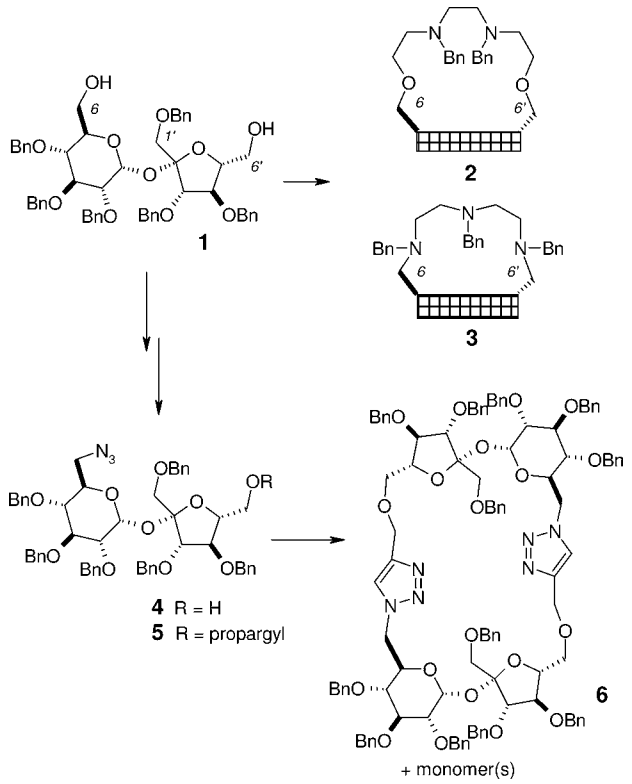
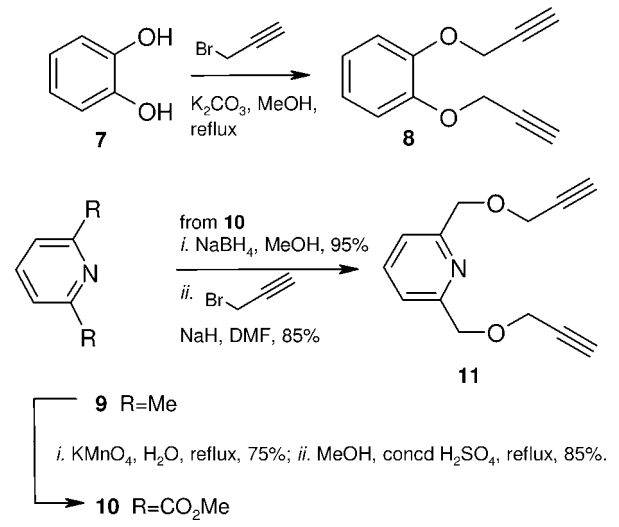


Figure 1. Synthesis of macrocyclic receptors containing a sucrose unit.

synthesis and application of "simple" sucrose-based crown-ether analogues, we became also interested in exploring C_2-symmetrical receptors that contain two sucrose units. The Cu(I)-catalyzed alkyne−azide cycloaddition (AAC)[12] of activated sucrose derivative **5** was used as the key macrocycle-forming step (Figure 1).[13] However, the product **6**, obtained from two molecules of **4**, did not show sufficient stability and, therefore, could not be applied as a macrocyclic receptor.

We changed, therefore, our approach to such symmetric targets and decided to connect two sucrose molecules via a dialkyne linker (**8** and **11**), which was obtained from catechol (**7**) or lutidine (**9**) according to the synthetic routes shown in Scheme 1. This linker might react efficiently with two

Scheme 1. Synthesis of Dialkyne Linkers



molecules of sucrose that were functionalized with an azide at one of the terminal positions.

The Cu−AAC reaction between the linker **8** and sucrose derivative **4** was carried out in acetonitrile with CuI as the catalyst and diisopropylethylamine as the base (the most effective conditions applied in the cyclization of **5**). It afforded the desired product **12** containing two sucrose units (Scheme 2).

These conditions could not, however, be applied for the efficient preparation of another C_2-symmetrical derivative **14**, which was obtained in very low yield. This resulted probably from the fact that copper cation was complexed by the pyridine unit of the linker, as well as that of the product formed, which effectively decreased the yield of the reaction. The unwanted formation of the complex was suppressed by applying the conditions of the CuAAC reaction first reported by Sharpless.[14] This invoved both the linker and the azide being dispersed in a 1:1 water−*t*-BuOH mixture containing copper sulfate and sodium ascorbate. These conditions proved to be ideal and allowed the desired

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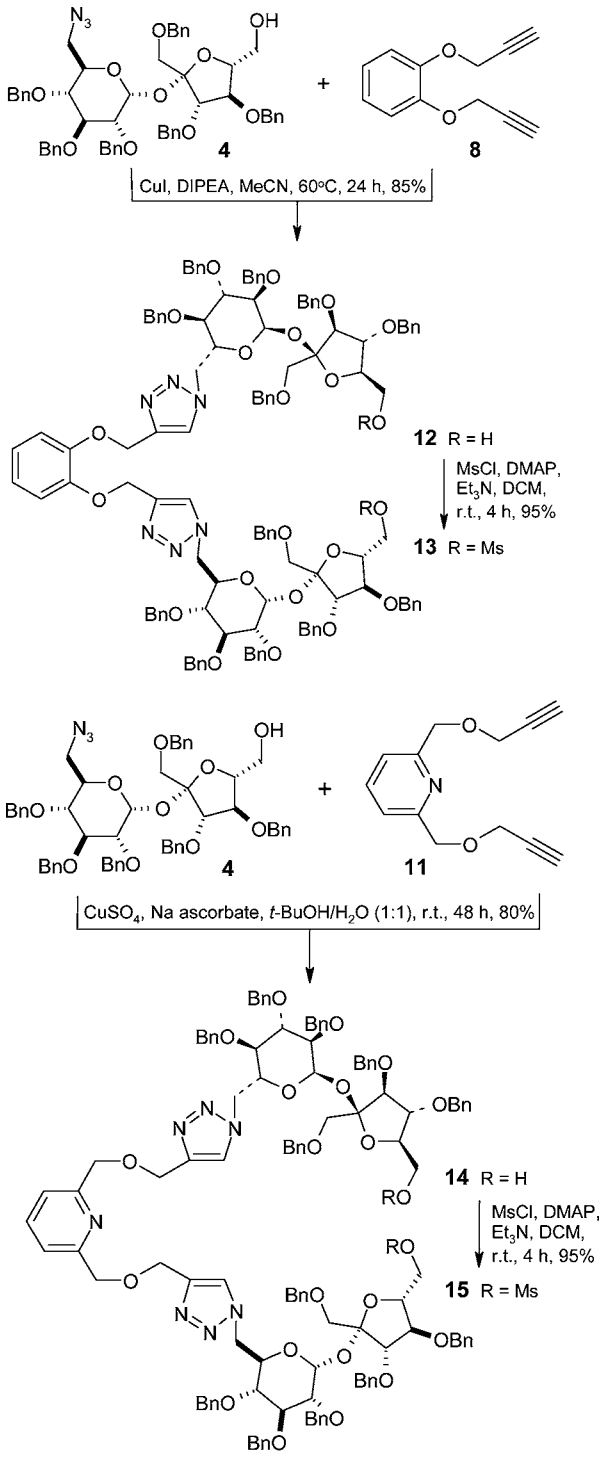
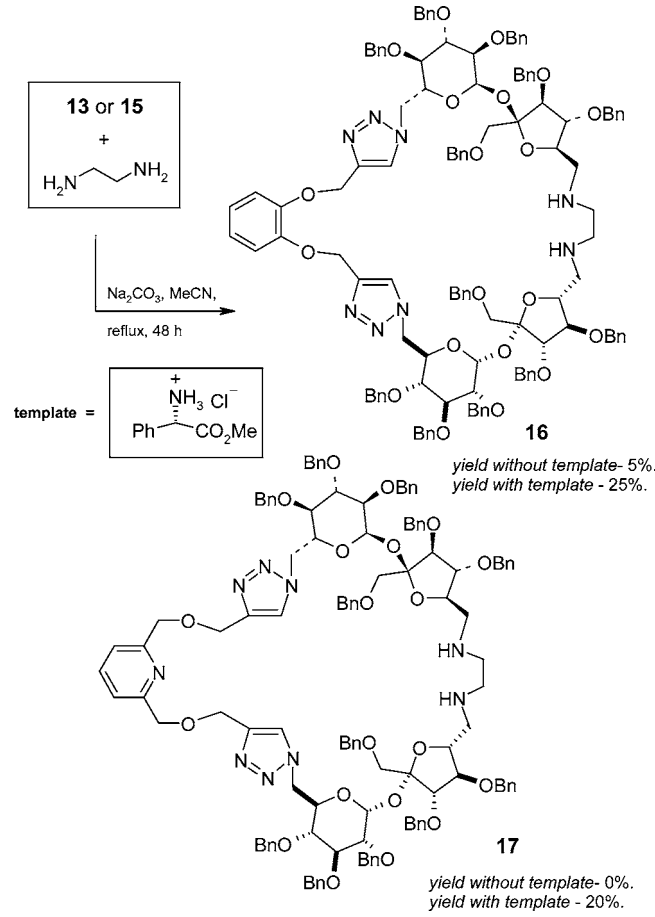
Scheme 2. Cu(I)−AAC Assembly of Derivatives Containing Two Sucrose Units



Scheme 3. Amino Acid Templated Macrocyclization



product **14** to be obtained in high yield (80%, Scheme 2). Mesylation of the hydroxyl groups in **12** and **14** led quantitatively to dimesylates **13** and **15**.

Macrocyclization was then performed using various diamines and diols (varying their chain length and rigidity). Ethylenediamine proved to be the best reagent to obtain the macrocycle in the reaction with dimesylate **13** (Scheme 3).

Unfortunately, the product **16** was obtained in very low yield (5%) and, moreover, proved to be quite unstable, decomposing within a few hours. The same reaction performed with dimesylate **15** did not afford any products. Therefore, we decided to find a template which would preorganize the reagents in solution and facilitate formation of the target macrocycle. Unfortunately, neither metal cations nor simple organic molecules (aromatic compounds and hydrogen bond donors and acceptors) were effective as templates. Finally, application of phenylglycine methyl ester hydrochloride allowed us to obtain the desired macrocycle **17** in 20% yield (Scheme 3).[15] What was even more impressive and surprising, only the L- enantiomer of the amino acid derivative proved to act efficiently as a template in this reaction. D-Methylphenylglycinate hydrochloride had almost no effect on formation of the product. This result prompted us to apply the chiral salt in the reaction between **13** and ethylenediamine. To our satisfaction the yield of **16** increased from

(15) The dimesylate **15** or **16** (0.1 mmol) was dissolved in acetonitrile (10 mL). Na_2CO_3 (500 mg), phenylglycine methyl ester hydrochloride HCl (25 mg) and ethylenediamine (0.02 mL) were added. The mixture was refluxed for 48 h. After being cooled to rt, the mixture was partitioned between water (5 mL) and ethyl acetate (15 mL), the layers were separated, the organic layer was dried and concentrated, and the product was isolated by column chromatography (toluene−methanol 15:1 for **16** or toluene−methanol 12:1 then 5:1 for **17**).

5% to 25%, once again proving the ability of the amino acid derivative to template formation of the large ring product (Scheme 3). The structure of the macrocyclic sucrose derivative **16** was unambiguously confirmed by the MS, ^{1}H, ^{13}C, ^{15}N, and 2D NMR spectra.

The proposed mechanism of the templated process is presented in Figure 2.

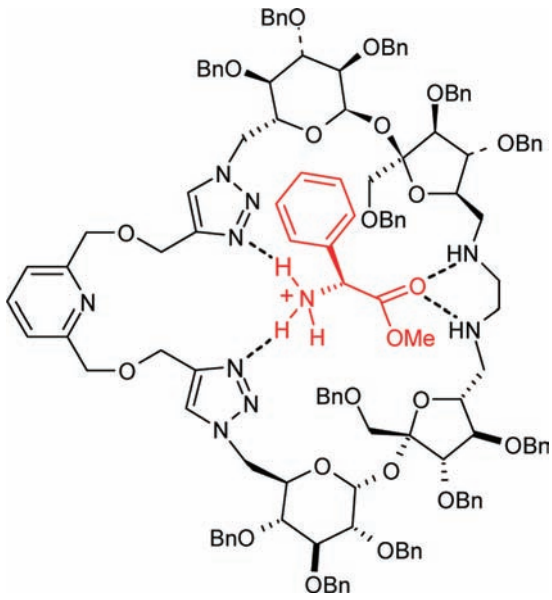


Figure 2. Proposed templation mechanism (origin of enantioselectivity).

The triazole nitrogen atoms (known to be good hydrogen bond acceptors)[16] form a hydrogen bond with the ammonium cation. Although the ester oxygen atom is a weak hydrogen bond acceptor and primary amines are weak hydrogen bond donors, the interaction of the two in the template and ethylenediamine brings all three molecules in close proximity, so the reaction of dimesylate with diamine can occur to provide the desired product. The importance of the ester motif is clearly proven by the lack of templating ability of phenylethylamine hydrochloride. The lack of templating effect for the D-enantiomer of the amino acid derivative is most likely due to steric reasons (the repulsion between the phenyl group and the OBn substituent in position 1′ of the disaccharide skeleton).

To our knowledge, this is the first example of an amino-acid templated macrocyclization reaction. This result opens interesting perspectives in the area of supramolecular chemistry and catalysis. A more precise study of the reaction, its scope, and its mechanism may provide interesting information for the development of new methodologies for large-ring molecule synthesis, even in a stereoselective fashion, as well as in the area of mechanically interlocked molecules (rotaxanes, catenanes etc.). In conclusion, a novel synthetic route toward sucrose-based C_2-symmetrical macrocycles has been developed. Application of an L-phenylglycine derivative as a template was crucial for the efficient formation of the large ring product. This approach is the first reported example of an amino acid templated reaction leading to a product of high added value. Further comprehensive study of the scope and limitations of this reaction may lead to the development of more general methodologies for amino acid templated organic reactions.

Supporting Information Available: Details on the synthesis and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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