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A General Method for Synthesis of Unclosed Cryptands via H-Bond Templated Macrocyclization and Subsequent Mild Postfunctionalization

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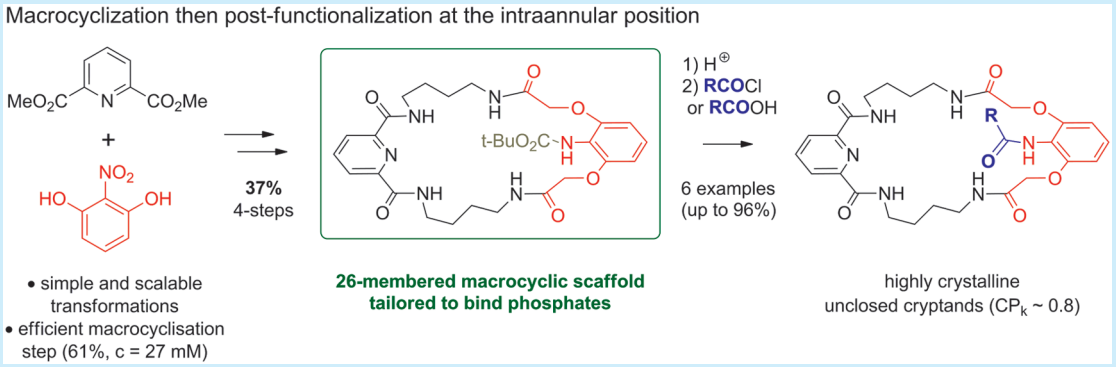
Supporting Information



ABSTRACT: A practical four-step synthesis of a model 26-membered N-Boc-protected macrocycle, starting from commercially available and inexpensive materials, is reported. The crucial macrocyclization step does not require high-dilution conditions and is completed in a short time (8 h). The high yield of macrocyclization (61%) is achieved owing to templation by intramolecular H-bonds and a chloride anion, which both help to adopt a favorable folded conformation of the open-chain intermediate. Finally, mild, selective, and efficient incorporation of intraannular amide function leading to five diversely functionalized unclosed cryptands (UCs) is described.

From its very beginnings, supramolecular chemistry has been based on macrocyclic compounds.[1] The geometrical constraints produced by the cyclic scaffold ensure a high level of preorganization leading to a well-defined spatial arrangement of substituents, in particular those capable of binding neutral and ionic guests. Crown ethers,[2] cyclodextrins,[3] calixarenes,[4,5] calixpyrroles,[6] cucurbiturils,[7] and pillararenes[8] are commonly utilized as host molecules. Very recently, drug-like macrocycles have started to be exploited in medicinal chemistry mainly due to their increased bioactivity and improved biostability.[9] Preparation of macrocyclic compounds, however, is often challenging as it requires multistep syntheses.[10] Moreover, the yield of the crucial step, i.e. formation of the desired macroring, is generally low for both steric and entropic reasons. This is a particularly serious issue when the corresponding intermediates are expensive due to low-yielding and difficult preparation procedures. For this reason, a number of attempts have been made to favor ring-closure over linear oligomerization; of these methods incorporation of an appropriate rigid scaffold[11] and templation by cationic[12] or anionic species[13] are used. The latter is of particular interest because it provides access to geometrically disfavored macrocycles.[13b] Moreover, in dynamic covalent systems, tuning of the macroring size has been reported to be strongly influenced by application of an appropriate cation[14] or anion.[15] These strategies greatly enhance macrocyclization; however, further functionalization of the resulting macrocycles is not always straightforward. In fact, few methods solving the latter problem have been reported.[16] Nevertheless, such an approach is highly desirable since it would allow for construction of a broad array of macrocycle structures with tailored chemical and physical properties from just one macrocyclic precursor.

In our previous work on anion receptors, we developed a simple one-step procedure for the preparation of macrocyclic tetralactams from appropriate α,ω-diamines and methyl esters of α,ω-dicarboxylic acids in methanol, in the presence of sodium methoxide.[17] Very recently, we have extended this research to more complex macrocycles—unclosed cryptands (UCs),[18] having a suitably functionalized and flexible substituent (lariat arm) connected directly to the interior of the macroring. Although optimized conditions to favor their macrocyclization were developed, the previous methodology did not allow for *a posteriori* functionalization of the lariat arm. Therefore, when one would like to synthesize an appropriately

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functionalized UC, the intraannular substituent (lariat arm) has to be introduced at the very beginning of the multistep synthesis. This methodology proved to be highly inconvenient when a very large lariat substituent is introduced and completely failed for a base-labile function due to the presence of a very strong base (MeONa) in the macrocyclization step.

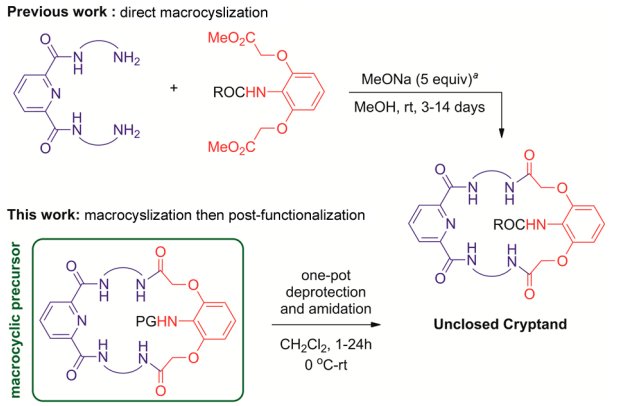
In this letter, we report a novel synthetic methodology that overcomes these limitations and allows efficient preparation of diversely substituted UCs employing simple and high-yielding chemical transformations (Schemes 1–3). Based on our preliminary studies, we decided to use UCs with a 26-membered ring as a synthetic target, owing to their potential binding compatibility with tetrahedral anions as well as their ability to stabilize transient water clusters in the solid state.[18,19] As an amine protecting group, we chose *tert*-butyloxycarbonyl (Boc) as the best one. The macrocyclization substrates **2** and **5** were prepared in three high-yielding steps in multigram quantities, without employing column chromatography, from either commercially available and inexpensive 2,6-pyridinedicarboxylic derivative **1a** (R = Cl) or **1b** (R = OMe) and 2-nitroresorcinol (Scheme 2).

Briefly, the dihydrochloride salt **2** was obtained by amidation of **1** in neat 1,4-diaminobutane and subsequent acidification of the resulting diamine using hydrochloride in methanol. Alternatively, **2** can be synthesized by the reaction of 2,6-pyridine dicarbonyl dichloride with a N-Boc-1,4-butanediamine followed by acid hydrolysis. The nitro-group reduction and subsequent protection using Boc_2O in a water–acetone mixture yielded **4** which, after double O-alkylation, delivered the second partner for macrocyclization, i.e. α,ω-diester **5**. In the next step, these two intermediates were subjected to macrocyclization, which does not require high-dilution conditions (c = 27 mM) and was completed in just 8 h, leading to macrocyclic product **6** in good yield (61%).

Finally, one-pot postfunctionalization of the lariat arm was achieved by amine function deprotection and subsequent amidation under mild conditions (Scheme 3). Near-quantitative yield of incorporation of the lariat arm was observed within 15 min for acyl chlorides, regardless of the type of chloride employed.[20] Application of carboxylic acids, however, led to lower yields and a longer reaction time. This can be rationalized more readily in terms of the low activity of the coupling reagent employed, namely 1-ethyl-3-(3-(dimethylamino)propyl)-carbodiimide (EDC), than in terms of the steric demands of the intermediate macrocyclic amine, since 1-pyreneacetic and benzoic acids gave comparable yields of macrocyclic products. The previous route,[18] by comparison, produced **7c**, with 23% overall yield after three tedious column chromatography stages, whereas under the present approach compound **7c** was synthesized with 35% overall yield after two simple column chromatography stages. The compounds **4**–**7** were characterized by NMR, ESI-MS, and elemental analysis. Furthermore, the structures of products **7c** and **7d** were additionally confirmed by single crystal X-ray diffraction (Figure 1). Despite differences in macrocycle and crystal composition, both macrocycles adopt a similar conformation with a molecule of DMSO entrapped in the macrocyclic cavity.

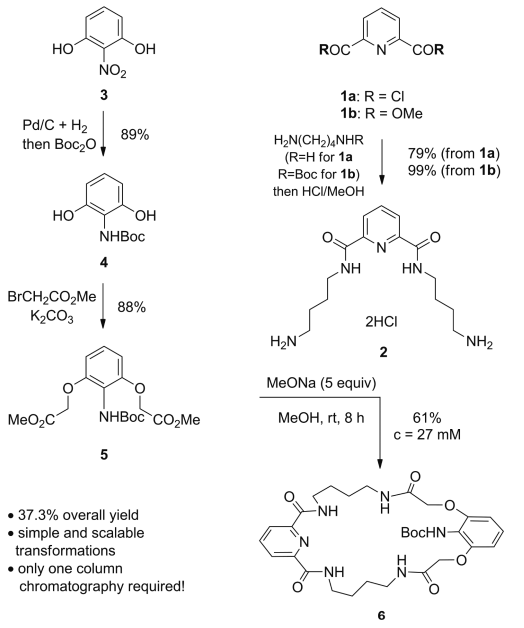
Interestingly, in-depth analysis of the crystal structure of macrocycle **7c**-DMSO solvate reveals an absence of any intramolecular H-bond (Figure S13). In the second solvate, however, the crystal is stabilized by multiple intramolecular H-bonds originating from amide groups and water molecules. Despite these differences, crystal packing efficiencies CP_k are high for both solvates (0.79 and 0.83 for **7c** and **7d**, respectively). All of these findings confirm the unusual, yet to some extent predictable, packing properties of this class of macrocycles in the solid state, as have been previously highlighted.[18,19] It is worth stressing that the high yield and

Scheme 1. Synthetic Methodologies toward Unclosed Cryptands (lariat arm shown in black color; PG = protection group)[a]

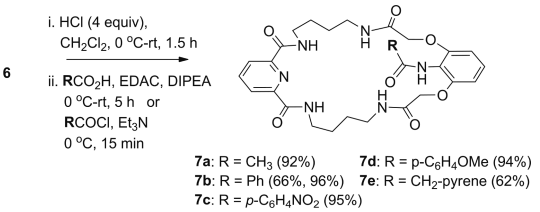


[a]Not effective for base-labile and large lariat substituents.

Scheme 2. Route to Macrocyclic N-Boc-Protected Macrocycle 6



Scheme 3. One-Pot Deprotection and Post-Functionalization of Lariat Arm of the N-Boc-Protected Macrocycle 6



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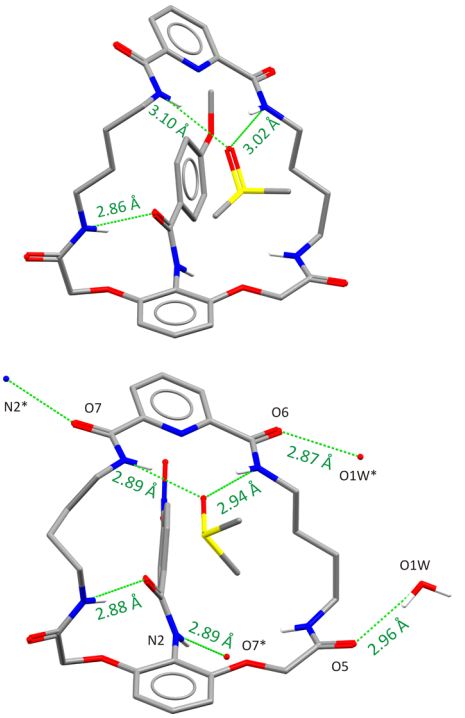
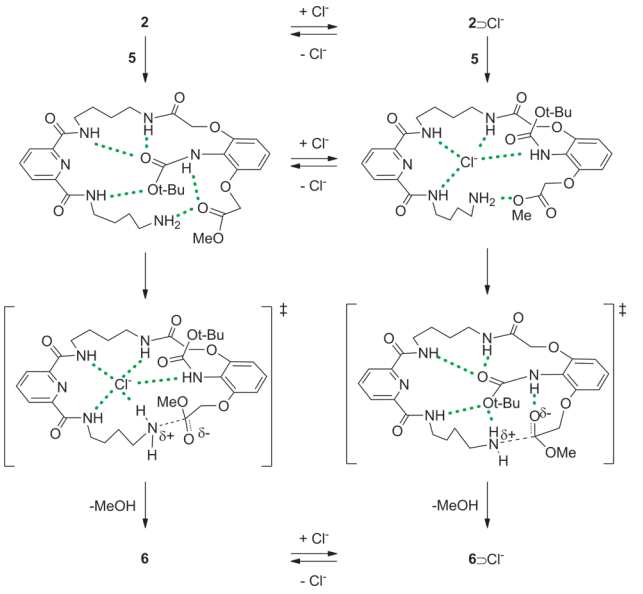


Figure 1. X-ray structures of **7c**·DMSO (top) and **7d**·H_2O·DMSO (bottom); nonacidic protons and disorder of DMSO molecule in **7c** were omitted for clarity, and asterisks within atom labels denote symmetry-equivalent atoms.

rate of macrocyclization leading to **6**, with a 26-membered macroring incorporating two flexible 1,4-butanediamine spacers, indicates that the folded conformation required for the ring closure is considerably stabilized by intramolecular H-bonds and/or templation by the guest, presumably anionic, present in the examined system (MeO^- and Cl^- anions). As a result, the reactive amine and ester groups are brought into close proximity, highly accelerating the rate of the second lactamization leading to the final macrocyclic product over the oligomerization byproducts (Scheme 4).

To experimentally determine how template (internal H-bonds vs chloride anion) influences macrocyclization yield, we conducted test reactions using free α,ω-diamine **2**, instead of its hydrochloride salt, without and with addition of 2 equiv of very well grounded NaCl or LiCl salts. The yield in the former case was considerably smaller (47%) in comparison with the chloride salt added (63% for NaCl and 67% for LiCl). These results clearly demonstrate that the chloride anion plays an essential role in the stabilization of the folded conformation whereas the inorganic cation has only a small impact. Based on our previous studies[19] indicating that chloride complexes with this type of macrocyclic scaffold are rather weak (e.g., $K < 10$ M^{-1} for **7c** in DMSO + 0.5% water), we envisioned that the chloride anion could act as a kinetic template which stabilizes the transition state ($TS^{‡}$) leading to product **6**. A similar observation was recently reported by Luis and co-workers[13c] in studies of macrocyclization of C_2-symmetric pseudopeptides, where using spherical halogens greatly enhanced macrocyclization rates and yields. To gain deeper insight into the nature of these interactions we decided to carry out *ab initio* calculations (see Supporting Information for details). The representative results of the conformational analysis for the lowest energy structures of the pure ligand and its chloride

Scheme 4. Proposed Mechanism of Intramolecular H-Bond (left) and Chloride Anion (right) Stabilization of TS‡ Leading to 6[a]



[a]H-bonds are marked with green dotted lines.

complex of the linear intermediate are shown in Figure 2. Analysis of the structures suggests that the intraannular alkyl-

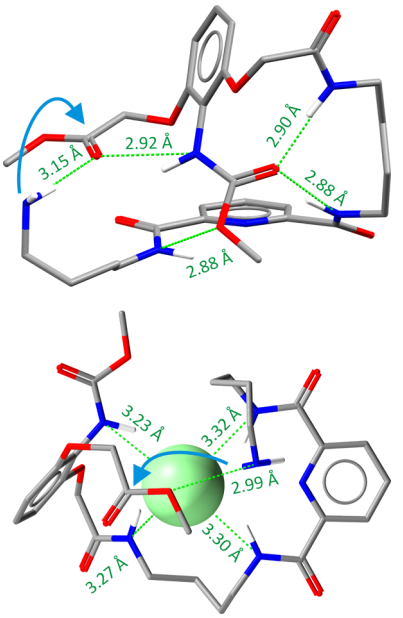


Figure 2. Energy-minimized structures (DFT/M062X/6-31G*) of the folded conformations templated by intramolecular H-bonds (top) and chloride anion (bottom); second lactamization (indicated by blue arrows) gives macrocycle; methyl group was used instead of Boc in order to reduce computational cost.

carbamoyl group participated strongly in the stabilization of both open-chain intermediates. In the first structure (Figure 2, top), the carbamoyl group is tightly bound by its oxygen atoms in the cleft created by two near-perpendicular aromatic rings connected by an aliphatic linker. The remaining carbamoyl NH proton bonded to the carbonyl oxygen atom of the ester group, placing it in close proximity to the free amine group. In the

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second structure (Figure 2, bottom), binding of the chloride anion by all available NH amide protons stabilizes the folded conformation.

The reactive groups are then brought into close proximity by H-bond formation between the amine and oxygen atom of the ester group. Interestingly, computational calculations for complexes of the linear intermediate with either water and methanol suggest that they are more conducive to the formation of oligomers than the desired macrocycle (Figure S15 and Tables S3–S4).

In summary, 26-membered N-Boc-protected macrocycle **6** was prepared in a four-step synthesis (37% overall yield) starting from commercially available and cheap precursors utilizing only single column chromatography. Its subsequent deprotection and site-selective postfunctionalization paves the way for the preparation of diversely functionalized UCs in high yields and under mild conditions. Moreover, installation of base-sensitive groups in the lariat arm, previously infeasible due to the presence of a strong base in the macrocyclization step, is now unlocked. Studies toward rationally functionalized UCs tailored to bind salts and chiral anions are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02324.

Detailed experimental procedures for the compounds synthesis and NMR (^{1}H, ^{13}C) spectra, calculation procedure, and Cartesian coordinates of calculated structures (PDF)

X-ray crystallographic information for **7c**·DMSO and **7d**·H_2O·DMSO (CIF)

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Notes

The authors declare no competing financial interest.

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(20) Note that during purification by column chromatography, host **7b** and **7c** left the column as pure 1:1 complexes with a TEA hydrochloride. Free macrocycles were then quantitatively liberated by the addition of water, subsequent short sonification (~2 min), and filtration (see Figures S5–S6). The reverse approach, i.e. extraction of the host and subsequent column chromatography, resulted in significantly lower yields of macrocycles (~60%).

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