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Design and Synthesis of Cyclic RGD Pentapeptoids by Consecutive Ugi Reactions

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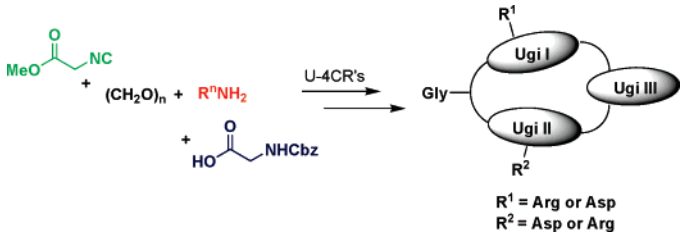
ABSTRACT



A new strategy for the synthesis of cyclic peptoids was developed. The approach is based on the use of consecutive Ugi reactions for the assembly of the acyclic peptoid and for the ring closure. Cyclopentapeptoid analogues of the RGD peptides were designed and synthesized using this methodology. The results confirm the versatility and efficiency of the method for the preparation of cyclic oligopeptoids.

Peptoids[1,2] are a class of oligomeric *N*-alkyl glycines that mimic the primary natural structure of peptides. They are attractive non-natural molecules for drug discovery approaches because of their many biological activities and proteolytic stability. Many peptoids have been shown to be capable of acting as protein ligands with high affinity.[3]

The Ugi four-component reaction (U-4CR)[4] is known to be one of the most versatile tools for the construction of peptoid and mixed peptoid−peptide backbones. Repetitive or consecutive Ugi reactions have been used in the synthesis of PNA oligomers[5] and also in the synthesis of hydantoin-imide and tetrazole derivatives.[6] U-4CRs also have been used in one-pot macrocyclizations.[7−9] However, these approaches did not allow the assembly of pure peptoid backbones in a consecutive fashion followed by formation of the macrocycle, as proposed in this study. In order to study sequential Ugi reactions for the construction of defined cyclopeptoid backbones, a convergent approach toward the synthesis of cyclic peptoids capable of mimicking the structural complexity of the cyclic RGD peptides is reported herein (RGD =

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arginine-glycine-aspartic acid). The RGD loop containing peptides are the molecular attachment points of many cellular and extracellular matrices. Along with the integrins, their receptors, they constitute a major system for cell adhesion,[10] which is crucial in many pathological processes, such as tumor metastasis, angiogenesis, osteoporosis, and thrombosis. Nearly half of the known integrins recognize the RGD sequence as ligands, giving this motif a central role in cell adhesion biology as the prototype adhesion signal.

The integrins became attractive targets for drug development, especially those involved in cancer treatment and in platelet aggregation. For instance, the inhibitors of the integrin $\alpha_{IIb}\beta_3$, involved in platelet aggregation, are used as antithrombotic agents,[11] and the cyclic peptide, c(RGDf-[NMe]V), an antagonist of integrin $\alpha_V\beta_3$, is in clinical tests as an anticancer drug.[12] Many cyclic RGD peptides and nonpeptidic mimetics have been developed as highly active and selective antagonists for different integrin receptors by tuning the conformational bias of the macrocycle.[11−17]

On the basis of the pharmacophore model proposed by Kessler and co-workers (**1**),[18] the structure−activity relationship (SAR) and docking studies on $\alpha_v\beta_3$ integrin ligands,[19,20] as well as synthetic feasibility, we designed cyclic pentapeptoid analogues of RGD peptides (Figure 1). Thus, the main

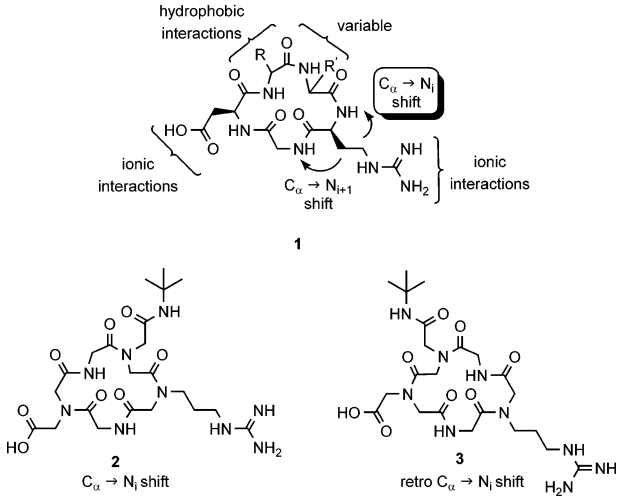
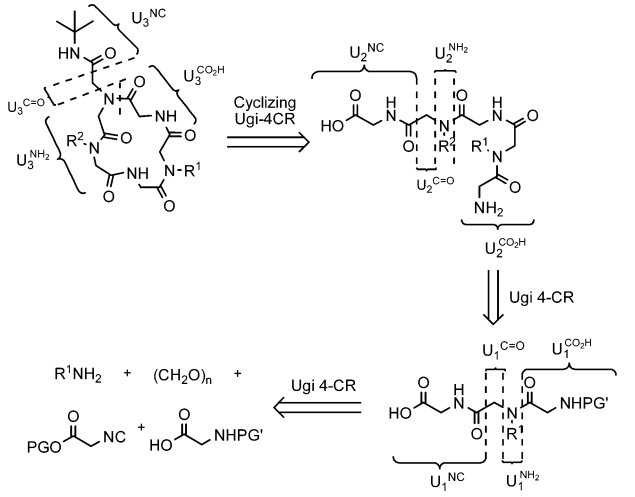


Figure 1. Structures of RGD peptide pharmacophore model (**1**) and of the cyclic pentapeptoid analogues. **2**: $C_\alpha \rightarrow N_i$ shifted peptoid; **3**: retro $C_\alpha \rightarrow N_i$ shifted peptoid. N_{i+1} shifted peptoids are not shown.

innovation in this approach is the rapid access to the cyclic skeleton, in principle, suitable to combinatorial extension, and the fact that the side chains are attached to the nitrogen of the amides and not to the α carbon as in peptides. The shift of the side chains to the amide nitrogen commonly results in increased metabolic stability. It can be done in two different directions: (1) toward the "N-terminus" direction, that is, to the nitrogen atom of the amino acid itself ($C_\alpha \rightarrow N_i$), or (2) to the "C-terminus" direction, that is, to the nitrogen atom of the next amino acid residue ($C_\alpha \rightarrow N_{i+1}$). As shown in Figure 1, for any given R and R′, a peptoid ("RGD") and a retro-peptoid ("DGR") can be formed within a cyclic peptide; that is, four different cyclopeptoid configurations with the side chain sequence of R-G-D are possible. For the targeted cyclopeptoids **2** and **3**, the $C_\alpha \rightarrow N_i$ shift had to be followed. Also, compared to classical peptoids, these compounds contain some amide−NH bonds that allow H-donor interaction, albeit less than in peptides.

The retrosynthetic analysis of the peptoids (Scheme 1) shows that the proposed compounds can be achieved

Scheme 1. Retrosynthesis



employing two consecutive Ugi four-component reactions (U-4CRs) for the construction of the acyclic amino acid precursor, and another Ugi three-component four-center reaction for the peptoid macrocyclization. A general route was developed in which the side chains of the peptoid backbone could be easily exchanged by varying the amine, leading to both kinds of target peptoids, the RGD- and the DGR-like compounds.

A special challenge was the introduction of the guanidinium group. Attempts to use ethyl or propylamine with

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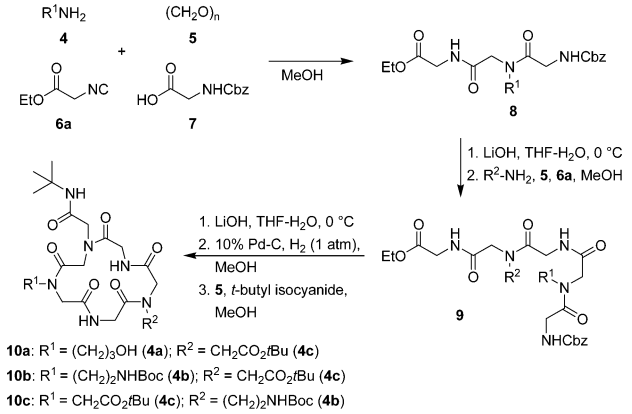
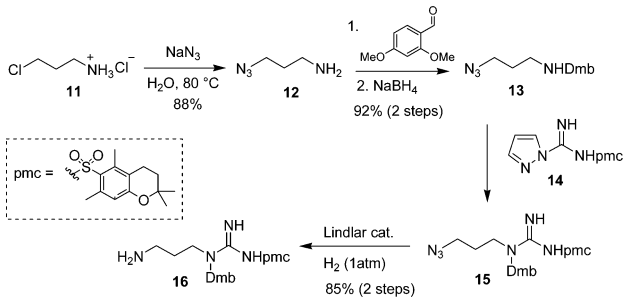
an ω-guanidinium group, unprotected or protected with either 2×Boc or 2×Cbz, were unsuccessful in the Ugi reactions. Some of the problems encountered were migration of the protecting group to the free amine or cyclization to a cyclic guanidinium, as observed previously in another context.[21−23] Therefore, monoprotected ethylene and propylene amino alcohols or diamines were used to synthesize SGD and KGD type peptoids that could allow the introduction of the guanidinium moiety after the synthesis of the central macrocycle (Scheme 2). Of many methods tried for the guanidi-

Scheme 2. Synthesis of Protected SGD-, KGD-, and DGK-like Peptoids



nylation, none was successful for these compounds.[21,24] Thus a new set of guanidinium protective groups had to be employed. For this purpose, amine **16** was synthesized from azide **12** after dimethoxybenzyl (Dmb) protection and introduction of the guanidinium moiety with the 2,2,5,7,8-pentamethyl-6-sulfonyl (pmc) protected 1*H*-pyrazole carboxamidine **14** (Scheme 3). This new set of mixed protecting

Scheme 3. Synthesis of Amine **16**



groups was suitable, and no migration or cyclization was observed.

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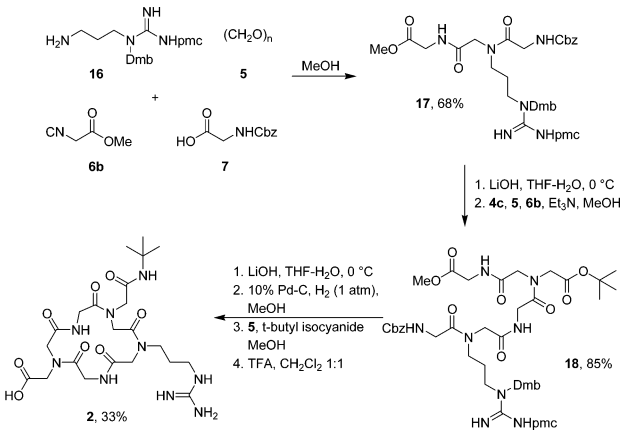
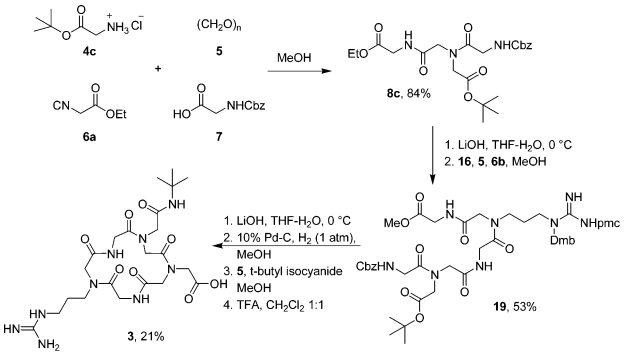
Scheme 4. Synthesis of Cyclopeptoid **2**



The first Ugi reaction (Scheme 4) was performed using amine **16** as the amino component, furnishing ester **17** in 68% yield. After hydrolysis of ester **17**, the resulting acid was used in a subsequent Ugi reaction to give ester **18** in high yield (85%). The amino acid precursor for the cyclization was obtained from **18** after ester hydrolysis and Cbz deprotection and was reacted with *tert*-butyl isocyanide and paraformaldehyde under pseudo-high-dilution conditions to avoid oligomerization, giving cyclopeptoid **2** in 33% yield (combined yield after four steps) after removal of the protecting groups with 1:1 TFA/CH_2Cl_2.

The retro-peptoid **3** was achieved likewise by changing the order of addition of the amines of the two initial Ugi reactions (Scheme 5). Glycine *tert*-butyl ester hydrochloride

Scheme 5. Synthesis of Retro-Cyclopeptoid **3**



(**4c**) was used in the first Ugi reaction (Scheme 5) to furnish ester **8c** (84% yield), followed by amine **16** in the second U-4CR to give ester **19** (53% yield). The cyclization of the amino acid, prepared from peptoid ester **19**, was carried out under the standard conditions to give peptoid **3** in 21% yield (four steps) after treatment with 1:1 TFA/CH_2Cl_2 to remove the protecting groups.

The approach proposed herein has been shown to be straightforward and opens the possibility for a combinatorial strategy toward a wide range of cyclic peptoids. By choosing

the proper amino and carbonyl components in the first two U-4CRs and isocyanide and carbonyl component in the Ugi three-component four-center reaction used for the cyclization, a variety of different peptoids can be obtained. We could demonstrate that even the most awkward amino acid side chain combination, carboxylate and guanidinium, can be achieved. The results confirm the versatility and efficiency of this method for the preparation of cyclic pentapeptoids but potentially also higher homologues.

It is noteworthy that this is the first report of peptoid synthesis where the peptoid backbone and the macrocycle closure are performed consecutively employing the Ugi four-component reaction. Further experiments to evaluate the biological activity of compounds **2** and **3** and their comparison with the activity of the known RGD peptides as well as studies to include a Passerini-3CR to form depsipeptoids[2] are in progress.

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

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