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Cu(I)- and Ru(II)-Mediated "Click" Cyclization of Tripeptides Toward Vancomycin-Inspired Mimics

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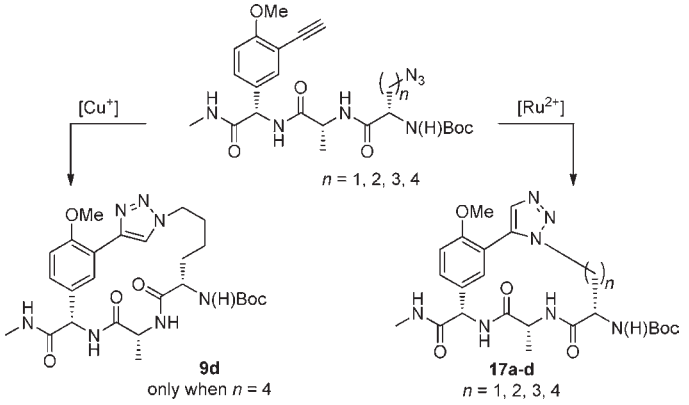
ABSTRACT



Structural mimics comprising 1,4- and 1,5-disubstituted triazole-containing cyclic tripeptides with excellent resemblance toward the DE-ring of vancomycin are conveniently accessible using Cu(I)- or Ru(II)-assisted "click" cyclization.

Reduction of conformational flexibility is important to increase the affinity of a peptide for its natural receptor.[1] A first convenient approach toward achieving this goal is head-to-tail cyclization. However, Nature has found many other covalent constraints to reduce the flexibility of a peptide and even beyond this in the creation of cavity or shell-like structures. The cavity of the vancomycin antibiotics induced by the biaryl ether bridge is an outstanding example in this respect.[2]

There is a great challenge in the development of approaches to control the conformation and shape of peptides, which are usually very flexible. Therefore, next to our goal toward the synthetic accessibility of small cyclic peptides, the presented work is also central in our ongoing quest toward uncovering promising alternatives for the biaryl ether bridge in the vancomycin antibiotics possibly leading to attractive mimics.

In our previous approaches we have used ring-closing metathesis for a side-chain knotted pentapeptide **1**[3a] inspired by vancomycin as well as the Sonogashira reaction for the preparation of alkyne bridged cyclic tripeptides like **2**[3b] toward constrained mimics of vancomycin (Figure 1).

As a new attractive alternative for the biaryl ether bridge in vancomycin, we report here on the successful introduction of the triazole ring system in cyclic tripeptides[4] toward the synthesis of vancomycin-inspired peptidomimetics.

In principle, this triazole ring can be introduced very conveniently by the Cu(I)-catalyzed azide–alkyne cycloaddition (CuAAC) reaction.[5] However, one has to realize that the resulting cyclic peptides are (highly) constrained, and

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(2) Williams, D. H.; Bardsley, B. *Angew. Chem., Int. Ed.* **1999**, *38*, 1172.

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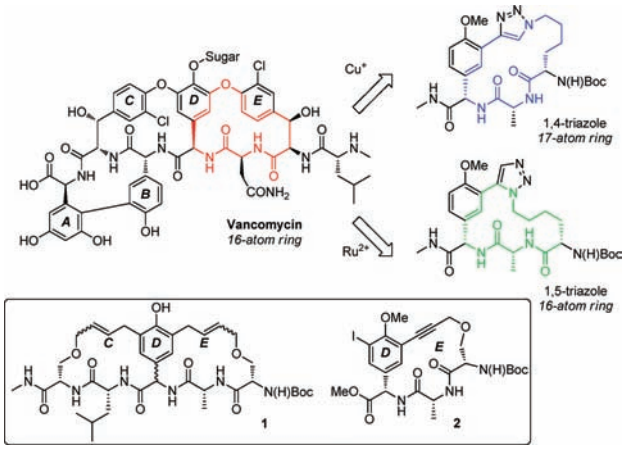
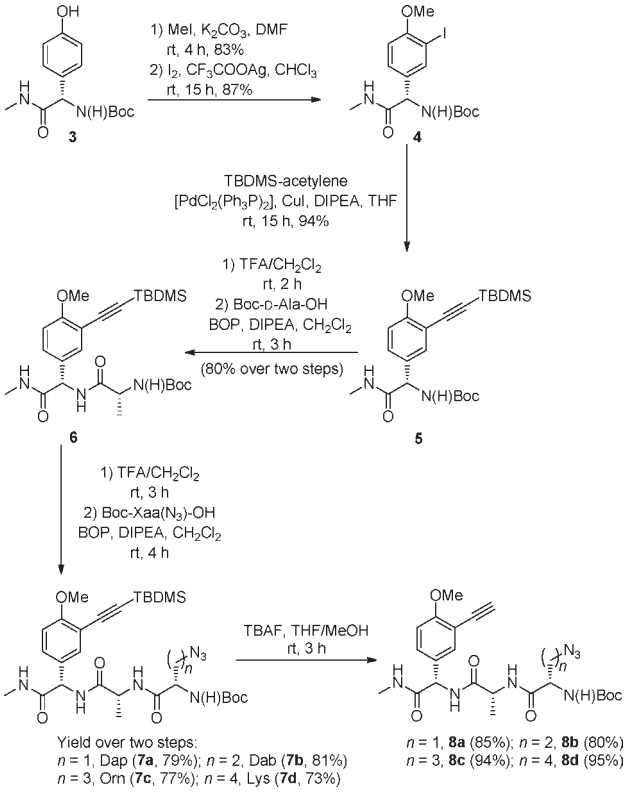


Figure 1. Design of triazole-containing vancomycin mimics.

therefore, dimers or oligomers may be formed as side products.[6] The triazole ring can be introduced intramolecularly as the final macrocyclization step or intermolecularly at the beginning of the synthesis, followed by a macrolactamization step by means of peptide coupling reagents.[7]

In the synthesis of the required precursors for both routes, the sensitivity toward racemization of the hydroxyphenyl glycine core is a critical issue. Therefore, after introduction of the Boc group, the carboxylic acid was converted to the methyl amide to give **3** instead of an ester to suppress racemization during subsequent peptide coupling steps (Scheme 1).[8] Methylation of the phenolic hydroxyl group in **3** with methyl iodide in DMF led to the methyl ether and was followed by iodination to **4** using iodine in the presence of silver trifluoracetate.[9] Next, the desired alkyne moiety was introduced via a Pd-catalyzed Sonogashira cross-coupling using TBDMS-protected acetylene to afford **5** in an excellent yield (94%). Originally, we used TMS-protected acetylene, but it was found that the TMS group was not completely impervious toward acid treatment needed for removal of the Boc group.[10] Dipeptide **6** was obtained after treatment with TFA, followed by BOP-mediated coupling with Boc-D-Ala-OH in a good yield (80%). At this point, the optimal length of the side chain of the azido-amino acid needed for cyclization by CuAAC was not known. Therefore, after removal of the Boc-group, four different azido-amino acids were introduced, which were conveniently accessible in a diazotransfer reaction using imidazole-1-sulfonyl azide.[11] Finally, the TBDMS group was removed by TBAF and the click precursors **8a**–**d** were obtained in high yields (Scheme 1).

Scheme 1. Synthesis of the Linear Precursor Peptides **8a**–**d**[a]



[a] Xaa: Dap, (*S*)-2,3-diaminopropanoic acid; Dab, (*S*)-2,4-diaminobutanoic acid; Orn, ornithine; Lys, lysine.

In the CuAAC reactions, 1.5 equiv of the soluble Cu(I) catalyst $Cu(CH_3CN)_4PF_6$ was used at a diluted (1 mM)

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(10) Treatment with TFA/CH_2Cl_2, HCl/Et_2O, or *p*-TosOH/toluene led to removal of the TMS group and/or addition of the conjugated base to the triple bond.

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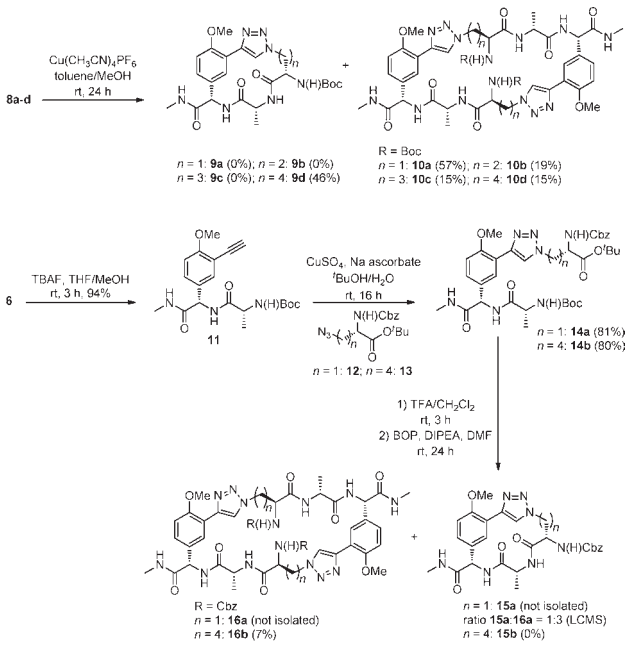
substrate concentration (Scheme 2). Under these conditions, the "click" macrocyclization proceeded with complete conversion after 24 h at room temperature. Not unexpectedly, cyclization of the precursor containing the shortest azido side chain **8a** led to formation of dimer **10a** as a major product and even its trimer (not shown), was obtained in an appreciable yield as was judged by HPLC and MALDI-TOF (Table 1). Apparently, the length of the ornithine azide was not sufficient for formation of the desired click macrocycle **9c**, but now the corresponding cyclic trimer was not formed and dimer **10c** was only obtained in a low yield (15%), partly due to its poor solubility. Gratifyingly, the precursor containing the lysine derived azide **8d** led to formation of the desired macrocycle **9d** as the major product (46%) together with dimer **10d** as the minor product (15%).

As was found previously in the preparation of alkyne bridged cyclic tripeptides toward constrained mimics of vancomycin, macrolactamization after introduction of triazole ring might be an attractive alternative,[3b,7] since a variety of coupling reagents are available. To evaluate this approach, the precursors with the shortest azide containing side chain **14a** and with the longest azide containing side chain **14b** were prepared (Scheme 2). After this, BOP-mediated cyclizations were carried out at diluted (0.5 mM) conditions in DMF. Different from the results above, the macrocyclization precursor with the shortest azide chain led to the formation of the dimer **16a**, but also the desired monocycle **15a** was obtained albeit present in a complex reaction mixture. The ratio between **15a**:**16a** was found to be 1:3 based on LCMS analysis. However, macrocyclization of **14b** gave only the cyclic dimer **16b** (in an isolated yield of 7%) as judged by HPLC, ^{1}H NMR, and MALDI-TOF analysis.

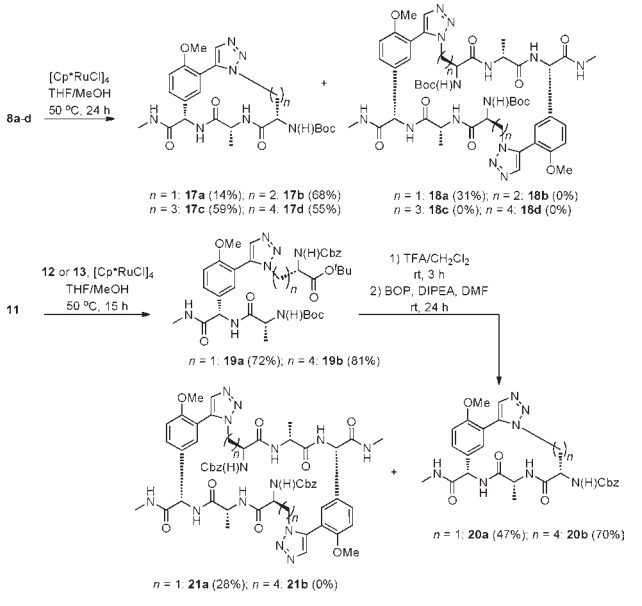
These results are indicative of the scope of the preparation of small cyclic peptides containing the 1,4-disubstituted triazole ring system (Scheme 2). Access to a 1,5-disubstituted triazole system via RuAAC[12] in which the substituents are positioned under a smaller angle, might be beneficial for obtaining a more easily obtainable bent site in the said macrocycles. Fortunately, Marcaurelle and coworkers recently described the Ru(II)-catalyzed synthesis of 1,5-disubstituted triazole *N*-methyl lactams,[13] which

Scheme 2. Cu(I)-Catalyzed Cyclization and Macrolactamization of the 1,4-Triazoles



seemed a very attractive for application on click precursors **8a**–**d** (Scheme 3).

Scheme 3. Ru(II)-Catalyzed Cyclization and Macrolactamization of the 1,5-Triazoles



[Cp*RuCl]$_4$ was selected as a catalyst since it leads to a good regioselectivity of formation of the 1,5-disubstituted triazole moiety. Attempts with the cyclization precursor containing the shortest azide-containing side chain **8a** were already successful after some optimization. Indeed, complete conversion was achieved after 24 h at 50 °C using a

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(14) The crystal structure of balhimycin (a vancomycin-related glycopeptide antibiotic) in complex with Lys-D-Ala-D-Ala (Protein Data bank accession code: 1GO6) was used, see:Lehmann, G.; Bunkóczi, G.; Vértesy, L.; Sheldrick, G. M. *J. Mol. Biol.* **2002**, *318*, 723.

substrate concentration of 5 mM in the presence of 15 mol % catalyst. In addition to the dimer **18a** (31%) and trimer (not shown, 8%), the desired monocycle **17a** was obtained in an encouraging yield of 14% (Table 1). Using this protocol, precursors **8b**–**d** were subjected to Ru(II)-catalyzed cyclization, which resulted in exclusive formation of the desired monocycles **17b**–**d** in attractive yields for these relatively small macrocyclic tripeptides, without the detection of any dimers **18b**–**d** (Table 1).

Table 1. Macrocycles Containing the 1,4- and 1,5-Disubstituted Triazole by CuAAC and RuAAC, Respectively

compd	approach	*c* (mM)	yield[a] (%)	monomer/dimer/trimer[b] (%)
8a	CuAAC	1	76	**9a** (0)/**10a** (57)/19
8b	CuAAC	1	27	**9b** (0)/**10b** (19)/8
8c	CuAAC	1	15	**9c** (0)/**10c** (15)/0
8d	CuAAC	1	61	**9d** (46)/**10d** (15)/0
14a	Cu(I)/ML[c]	0.5		**15a** (–)/**16a** (–)/0[d]
14b	Cu(I)/ML	0.5	7	**15b** (0)/**16b** (7)/0
8a	RuAAC	5	53	**17a** (14)/**18a** (31)/8
8b	RuAAC	5	68	**17b** (68)/**18b** (0)/0
8c	RuAAC	5	59	**17c** (59)/**18c** (0)/0
8d	RuAAC	5	55	**17d** (55)/**18d** (0)/0
19a	Ru(II)/ML	0.5	75	**20a** (47)/**21a** (28)/0
19b	Ru(II)/ML	0.5	70	**20b** (70)/**21b** (0)/0

[a] Isolated yield. [b] Yield as determined by LCMS. [c] ML: macrolactamization. [d] Ratio of **15a**:**16a** was 1:3 as determined by LCMS.

For completion of this study, macrocyclization of precursors derived from the shortest azide **19a** and longest azide-containing chain **19b** was carried out. It was found that BOP-mediated coupling of the shortest side chain containing precursor also gave 28% dimer **21a** next to the desired monocycle **20a** (47%). The precursor with the longest side chain even led to a slightly higher yield of the monocycle **20b** (70%) as compared to formation of the 1,5-triazole as the "click" cyclization step to give **17d** (55%), while formation of dimer **21b** was completely absent. These results demonstrated clearly that the geometry of the triazole moiety determines to a large extent the outcome of both cyclization approaches. Since the 1,4-disubstituted triazole moiety is extended, predominantly cylic dimers were formed. Only when the ring size is 17 atoms, a cyclic monomer was formed. Because of its β-turn-like conformation, the 1,5-disubstituted triazole moiety favored the formation of cyclic monomers and allowed the formation of a highly constrained ring structure of 13 atoms (**17a** and **20a**).

Cyclic monomer **9d** which was obtained by CuAAC was superimposed with the right half of the vancomycin-related balhimycin antibiotic[14] comprising the DE-ring system (Figure 2). Modeling of the structures was accomplished using the YASARA Structure 10.5.2.1 software package. Structures **9d** and **17d** were energy minimized using the simulated annealing protocol employing the AMBER99 force field. Molecules were superimposed by minimizing the rmsd between the five selected atoms in the ring. Although all 1,5-disubstituted triazole-containing cyclic monomers **17a**–**d** were accessible by Ru(II)-catalyzed cycloaddition, only **17d** was superimposed on balhimycin (Figure 2) since the number of atoms in its ring system equals that of the DE-ring (16 atoms, Figure 1). This superimposition indicated a high structural resemblance of **17d** with the DE-ring system, while superimposition of **9d** showed a more distorted appearance.

(15) Modeling has been performed with the YASARA software (www.yasara.org).

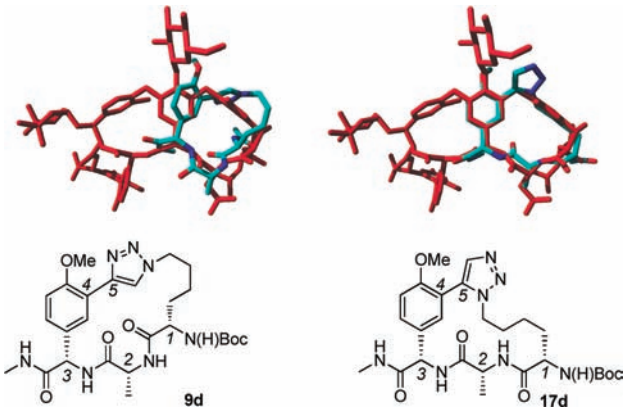

Figure 2. Superimposition of balhimycin (in red) with 1,4-triazole **9d** (left) and 1,5-triazole **17d** (right).[15] The carbon atoms αC^1, αC^2, αC^3, arom-C^4, and triazole-C^5 have been used as fixed coordinates for superimposition. Note: the atom coordinates of balhimycin have been mirror-imaged, since **9d** and **17d** represent the enantiomers of vancomycin's backbone stereochemistry.

In conclusion, the aim of this research was the development of a versatile approach toward the synthesis of relatively small (and constrained) cyclic peptide systems as are especially prominent in the vancomycin structure. Although this aim was achieved successfully using RuAAC, since the CuAAC click cyclization mostly led to the formation of cyclic dimers. These peptide derivatives are also of considerable interest, since symmetrical relatively small dimeric peptides form the backbone of potent antibiotic peptides like gramicidin.

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Supporting Information Available. Experimental procedures, spectroscopic data, and HPLC and MALDI-TOF analysis for compounds **8a**–**d**, **9d**, **10a**–**d**, **14a**,**b**, **16a**,**b**, **17a**, **b**, **18a**, **19a**,**b**, **20a**,**b**, and **21a**. This material is available free of charge via the Internet at http://pubs/acs.org.