

# MACROCYCLIC COMPOUNDS WITH ENEDIYNE MOTIF

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## INTRODUCTION

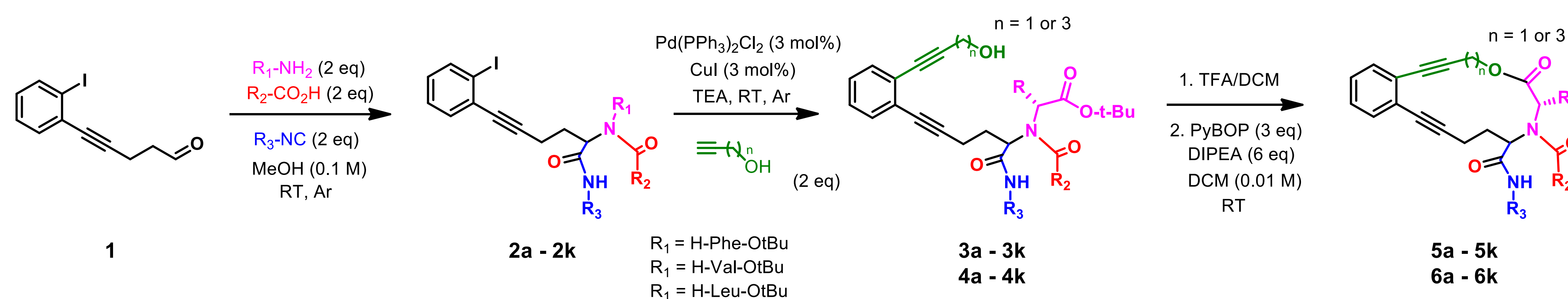
Multicomponent reactions (MCRs) are powerful tool for introducing chemical diversity and the rapid generation of small-molecule libraries.<sup>1</sup> Basic principle of MCRs is that relatively complex structure is generated from simple starting compounds in a single reaction step. Isocyanide-based multicomponent reactions (IMCRs, i.e. Ugi and Passerini reaction) are the most important and most used MCRs for the synthesis of peptide-like compounds. The starting reagents are carbonyl, carboxyl and isocyanide components in the Passerini reaction, and additionally, amino component in the Ugi reaction. The sequential IMCR-cyclization reactions can afford a wide variety of small cyclic mimics, medium sized cyclic and macrocyclic peptidomimetics.<sup>2</sup>

Enediyne compounds are discovered at the end of 20<sup>th</sup> century in some species of microorganisms and showed antitumor activity.<sup>3</sup> Additionally, they can be used as ligands in asymmetric hydrogenation reactions,<sup>4a</sup> for inducing  $\beta$ -turn conformations and in metal complexation reactions.<sup>4b</sup>

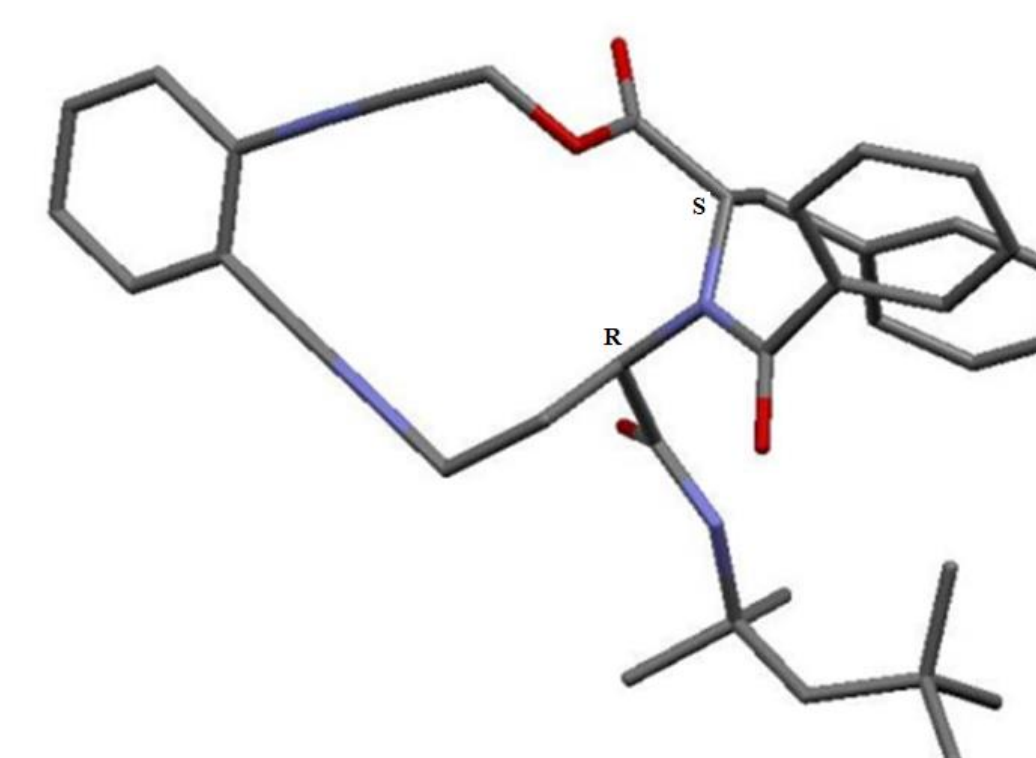
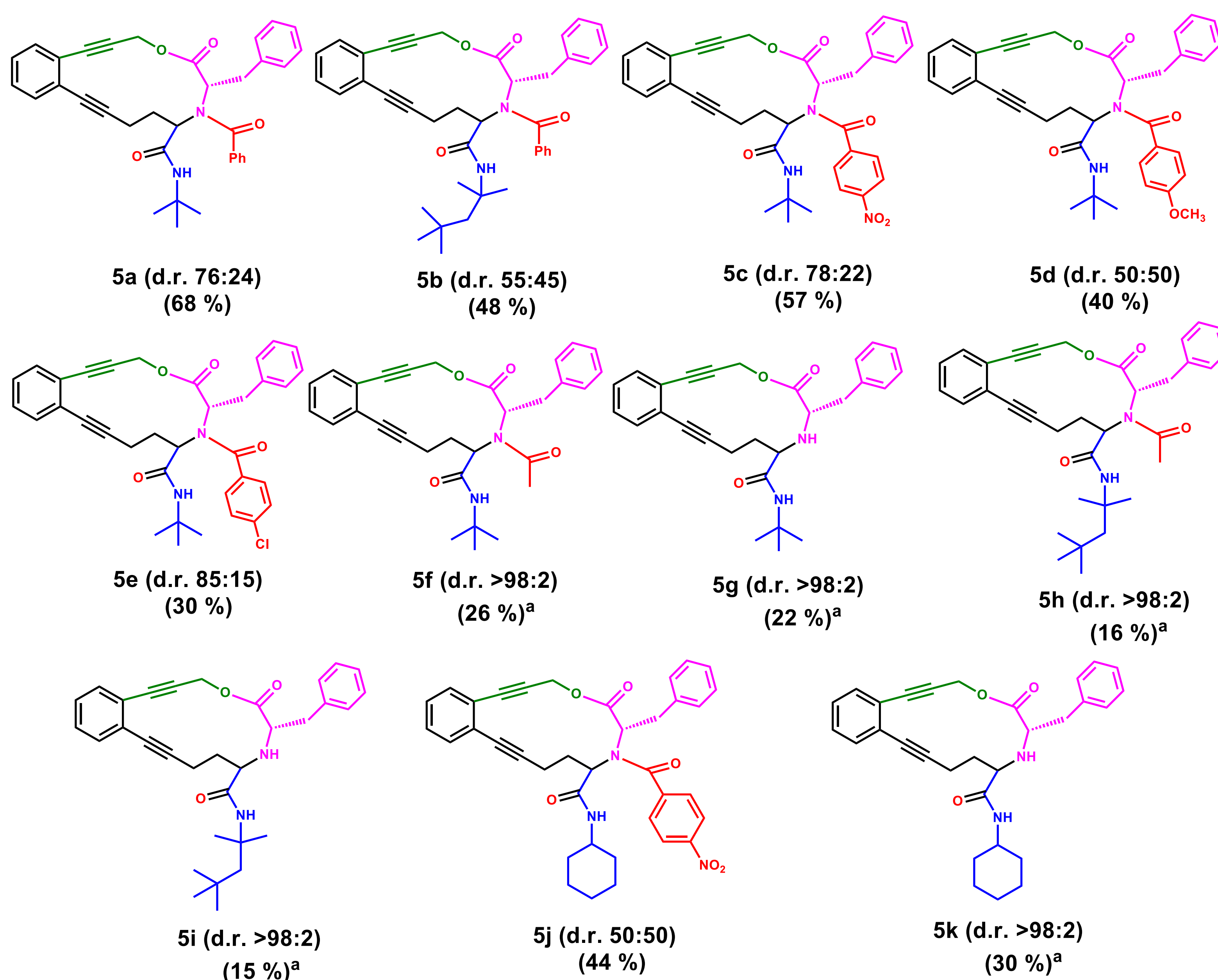
The aim of this study was synthesis of enediyne macrocyclic compounds with different size utilizing the Ugi reaction/Sonogashira reaction approach coupled with intramolecular cyclization.

## SYNTHESIS

Synthesis of macrocyclic compounds started with preparation of Ugi products obtained from aldehyde **1**, different amines (C-protected phenylalanine, valine and leucine), commercially available isocyanides and aliphatic or aromatic carboxylic acids in methanol. Ugi products **2a–2k** were isolated in 65–91 % yields. The Sonogashira reaction was carried out with two different unsaturated alcohols yielding acyclic structures **3a–3k** and **4a–4k** in 44–98 % yields.



Macrocyclic compounds with enediyne motif **5a–5k** were synthesized by deprotection of *t*-Bu followed by intramolecular esterification. Cyclization of Sonogashira products with valine and leucine failed, but macrocyclic compounds comprising phenylalanine were isolated in up to 68 % yields. Products were isolated as a mixture of diastereoisomers, while in five examples a single diastereoisomer was obtained.



The absolute configuration of a major diastereoisomer of compound **5b** was determined with the X-ray analysis and showed the R configuration at the newly created stereogenic center.

## CONCLUSIONS

- Ugi and Sonogashira reactions were carried out in up to 91 % and 98 % yield, respectively.
- macrocycles **5a–5k** were isolated in up to 68 % yield.
- the success of cyclization depends primarily on amino acid structure, but isocyanide and carboxylic acid also have some impact.

<sup>a</sup>Only one diastereoisomer was detected by <sup>1</sup>H NMR analysis.