SYNTHESIS OF MACROCYCLIC COMPOUNDS WITH ENEDIYNE MOTIF

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INTRODUCTION

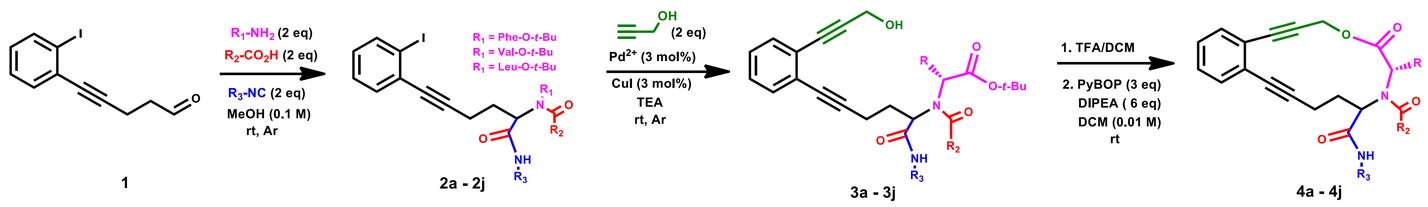
Multicomponent reactions (MCRs) are powerful tool for introducing chemical diversity and the rapid generation of small-molecule libraries.[1] Basic principle of MCRs is that relatively complex structure is generated from simple starting compounds in a single reaction step. Isocyanide-based multicomponent reactions (IMCRs, i.e. Ugi and Passerini reaction) are one of 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.[2]

Enediyne compounds are discovered at the end of 20th century in some species of microorganisms and showed antitumor activity.[3] Additionally, they can be used in asymmetric hydrogenation reactions,[4a] for inducing β-turn conformations and in metal complexation. [4b]

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

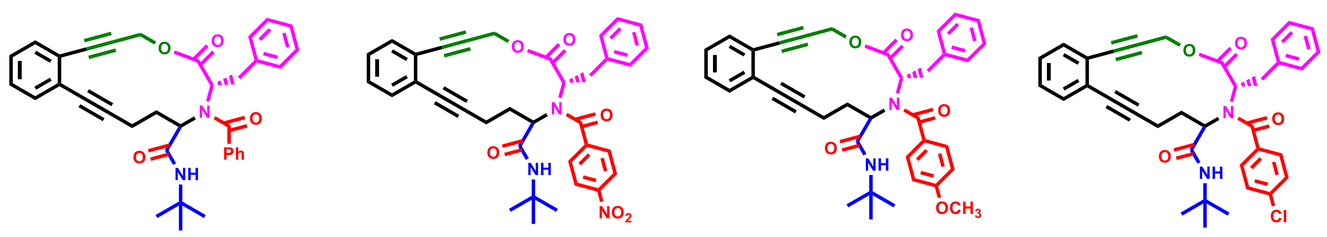
SYNTHESIS

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

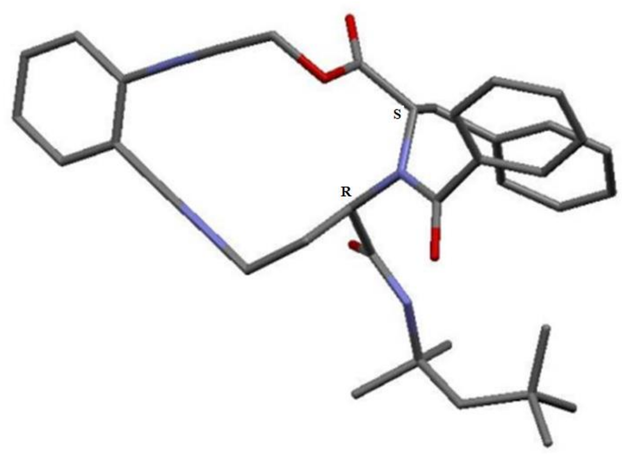


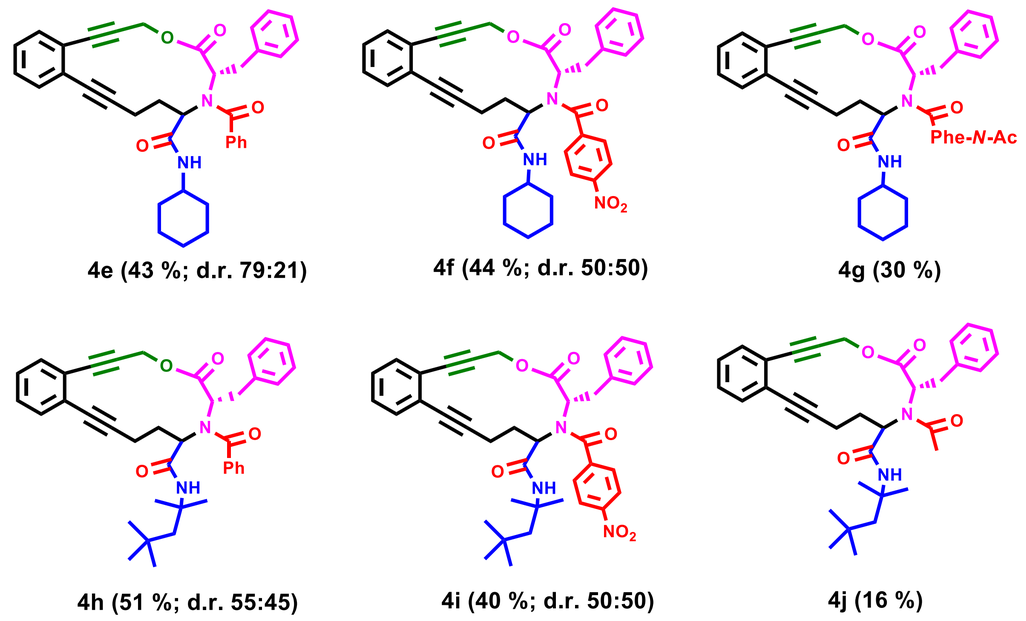
1 — 2a - 2j — 3a - 3j — 4a - 4j

Macrocyclic compounds with enediyne motif **4a - 4j** were synthesized by deprotection of *t*-Bu group and intramolecular esterification. Cyclization of Sonogashira products **3** comprising valine and leucine failed, but macrocyclic compounds comprising phenylalanine were isolated in up to 68 % yields. Products were isolated as a mixture of diastereomers, while in two examples a single diastereomer was obtained.



4a (68 %; d.r. 76:24) — 4b 57 %; d.r. 50:50) — 4c (40 %; d.r. 50:50) — 4d (30 %; d.r. 85:15)





4e (43 %; d.r. 79:21) — 4f (44 %; d.r. 50:50) — 4g (30 %)

4h (51 %; d.r. 55:45) — 4i (40 %; d.r. 50:50) — 4j (16 %)

The absolute configuration of a major diastereomer of compound **4h** was determined with the X-ray analysis and showed the R confuguration of the new chiral center.

CONCLUSIONS

- Ugi and Sonogashira reactions were carried out in up to 91 % and 98 % yield, respectively.
- macrocyclic compounds with valine and leucine haven't been obtained.
- macrocycles with phenylalanine, different isocyanides and carboxyl acids were isolated in up to 68 %
- the success of cyclization depends primarily on amino acid structure, but isocyanide and carboxyl acid also have some impact.

REFERENCES

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