# SYNTHESIS OF MACROCYCLIC COMPOUNDS VIA CONSECUTIVE SONOGASHIRA – UGI – SONOGASHIRA REACTIONS

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## INTRODUCTION

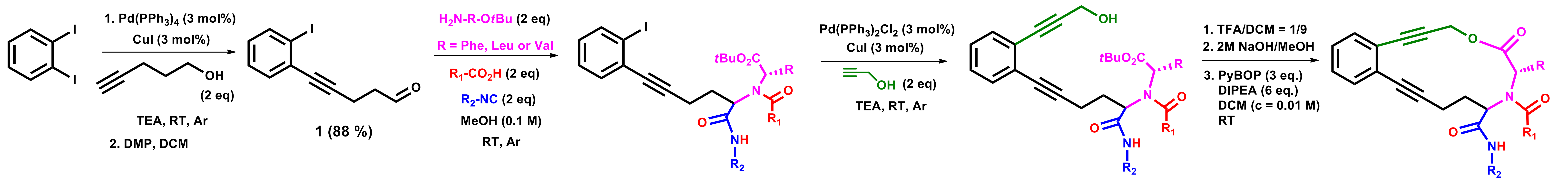
Multicomponent reactions (MCRs) are among the most important reactions in organic synthesis for introducing chemical diversity.[1,2] The main advantages of MCRs are rapid, cost-effective and sustainable access to chemical diverse small–molecule libraries from relatively simple and inexpensive components in a single reaction step. Isocyanide-based multicomponent reactions (IMCRs, i.e. Ugi and Passerini reaction) are the most important and the 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. Post-condensation methods can afford a wide variety of small cyclic mimics, medium sized cyclic and macrocyclic peptidomimetics.[3] Macrocyclic compounds represent a unique chemical structure bridging conventional small molecules and large biomolecules. Owing to their favored size, flexibility and complexity, macrocycles can engage previously undruggable biological targets, and thus play even more important roles in the future.

## AIM

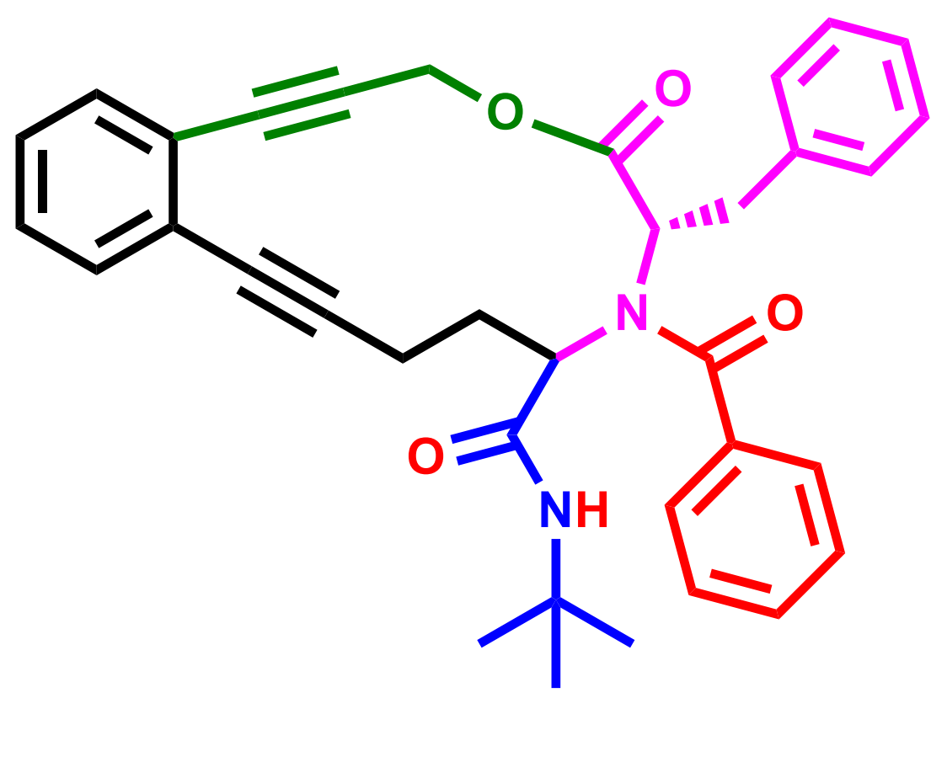
Naturally occurring compounds with enediyne motif show antitumor activity,[3] while their synthetic analogous can be used in catalysis[4a] or as *β*-turn structural mimics.[4b] To expend the pool of Nature-inspired macrocyclic compounds, here we describe synthesis of enediyne macrocyclic compounds utilizing the Sonogashira/Ugi reaction approach coupled with intramolecular cyclization.

## SYNTHESIS

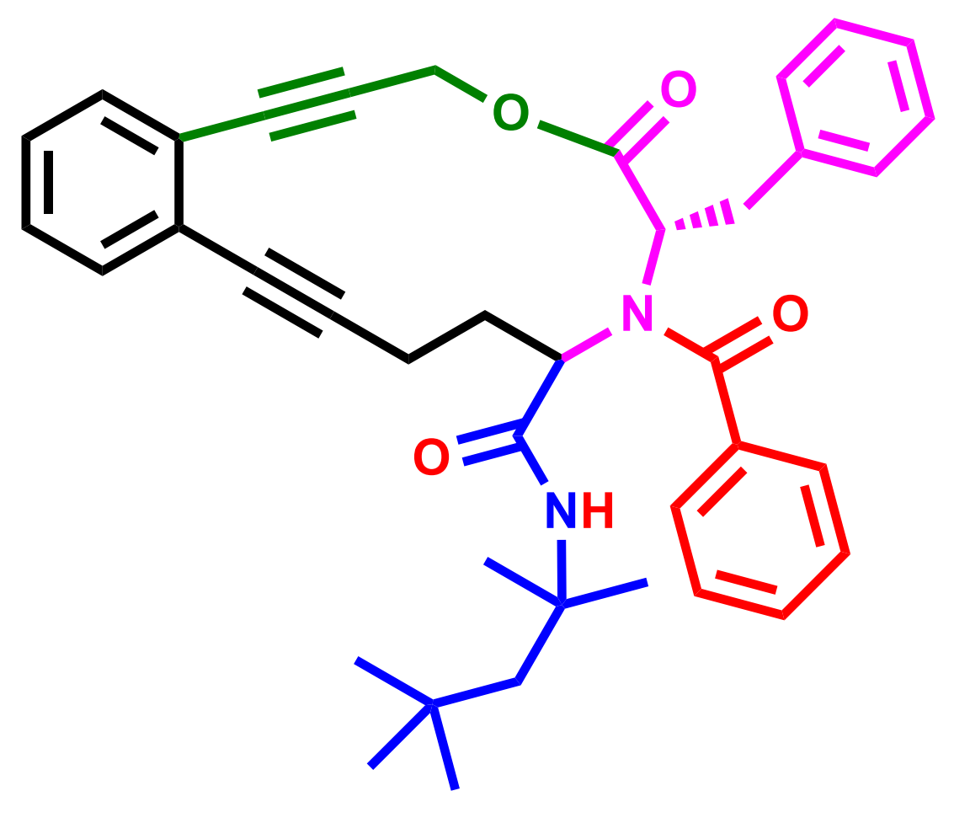
Synthesis of macrocyclic compounds started with preparation of aldehyde **1** by Sonogashira reaction from 1,2-diiodobenzene. After oxidation with Dess-Martin periodinane, aldehyde **1** was used in the Ugi reaction in combination with amino component ($H_2N$-Phe-O*t*Bu, $H_2N$-Leu-O*t*Bu or $H_2N$-Val-O*t*Bu), different commercially available isocyanides and aliphatic or aromatic carboxylic acid in methanol. Ugi products were isolated in 65 – 91 % yields. The second Sonogashira reaction was carried out with prop-2-yn-1-ol yielding acyclic structures in 44 – 98 % yields.



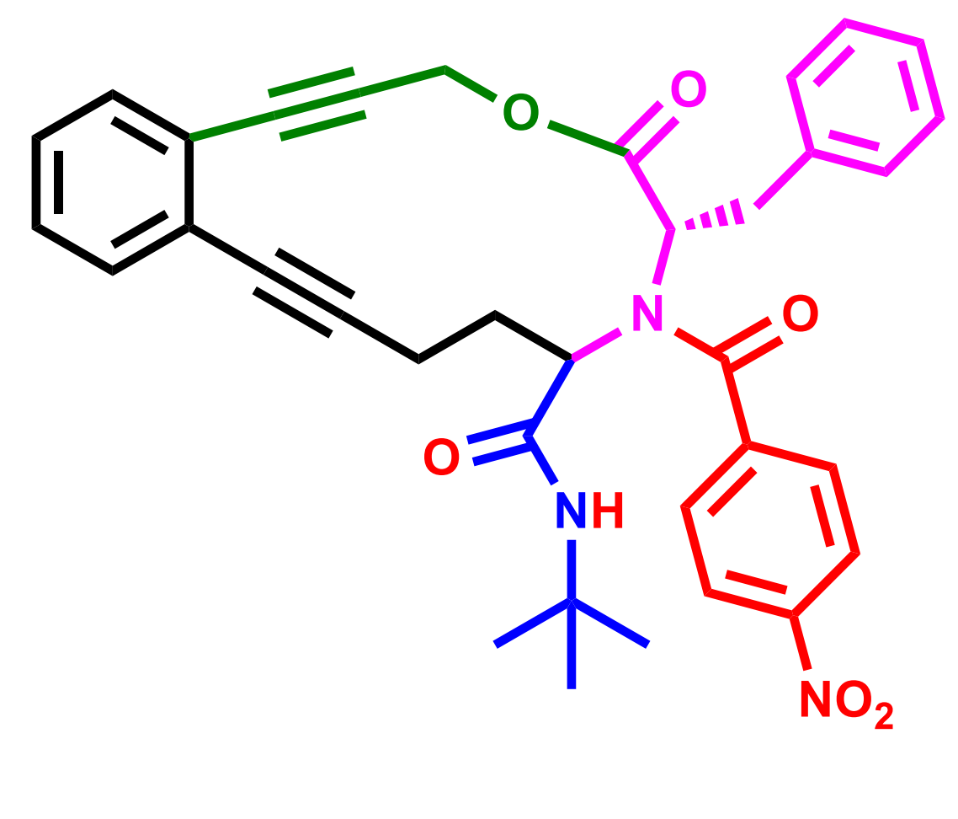
Macrocyclic compounds, with phenylalanine as an amino component (**1** – **12)** were synthesized by deprotection of *t*-Bu group followed by the intramolecular esterification and were obtained in up to 68 % yield. Products were isolated as a mixture of diastereoisomers, while in a five examples a single diastereoisomer was obtained.



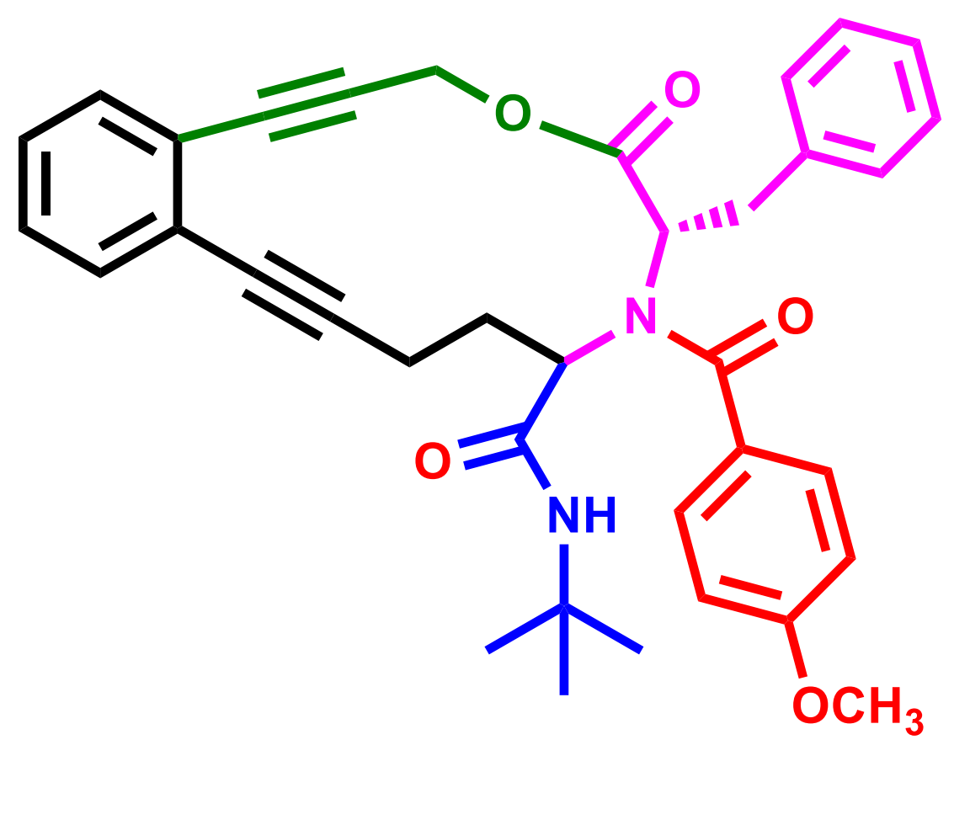
**1 (68 %)**
**d.r. = 76:26**



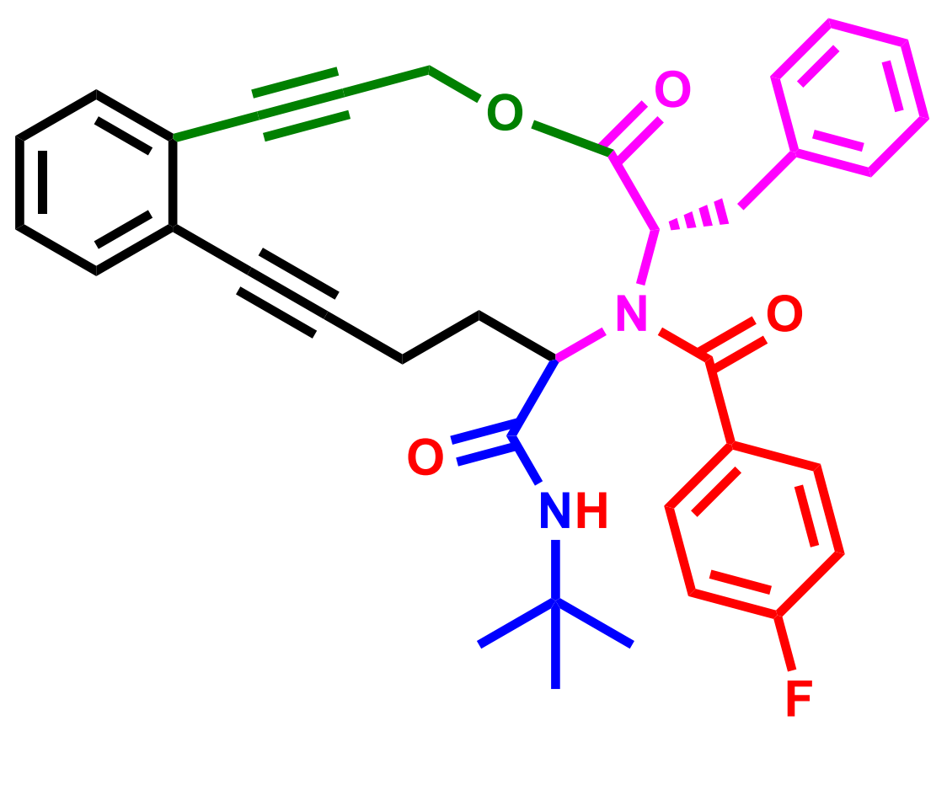
**2 (48 %)**
**d.r. = 55:45**



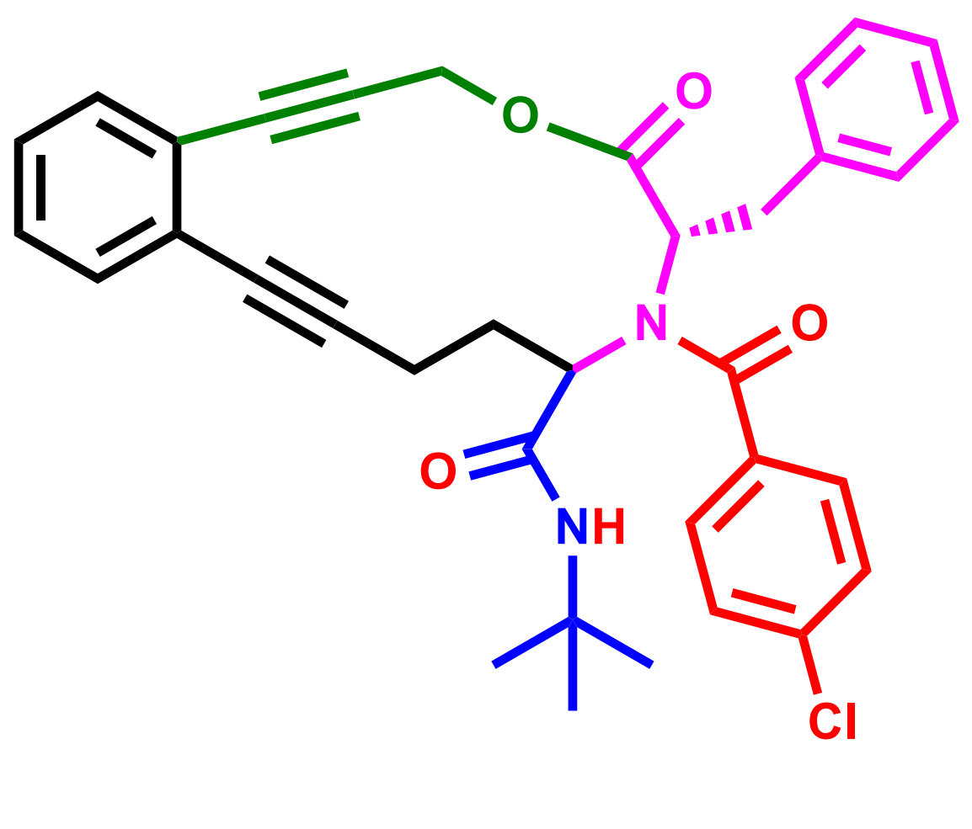
**3 (57 %)**
**d.r. = 78:22**



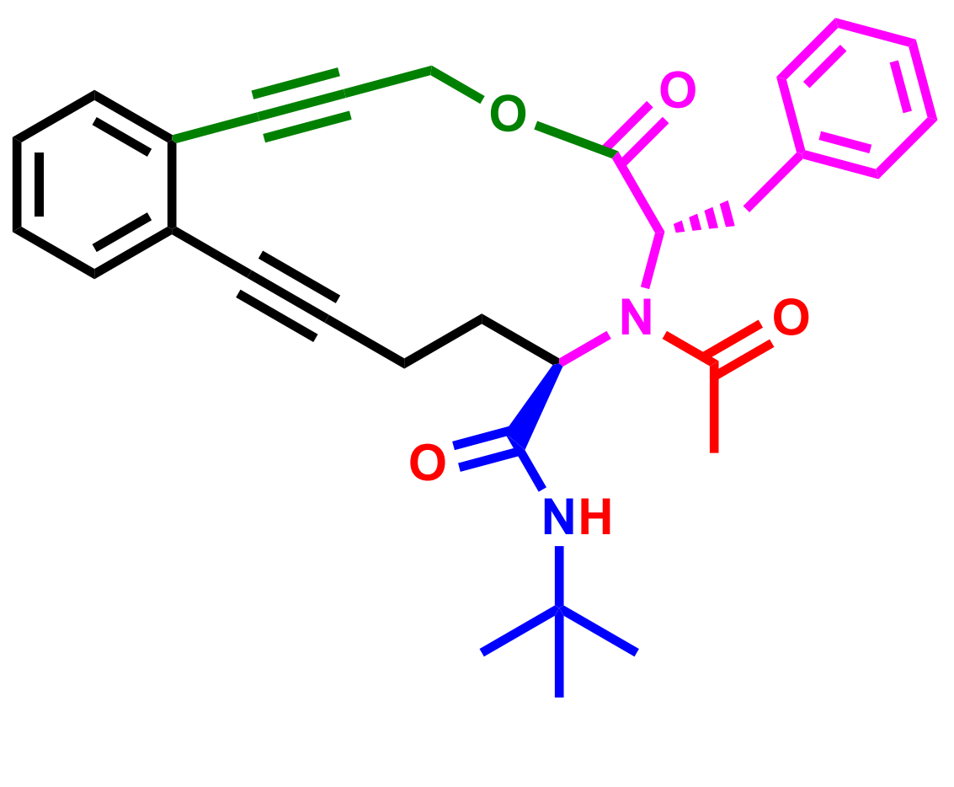
**4 (40 %)**
**d.r. = 50:50**



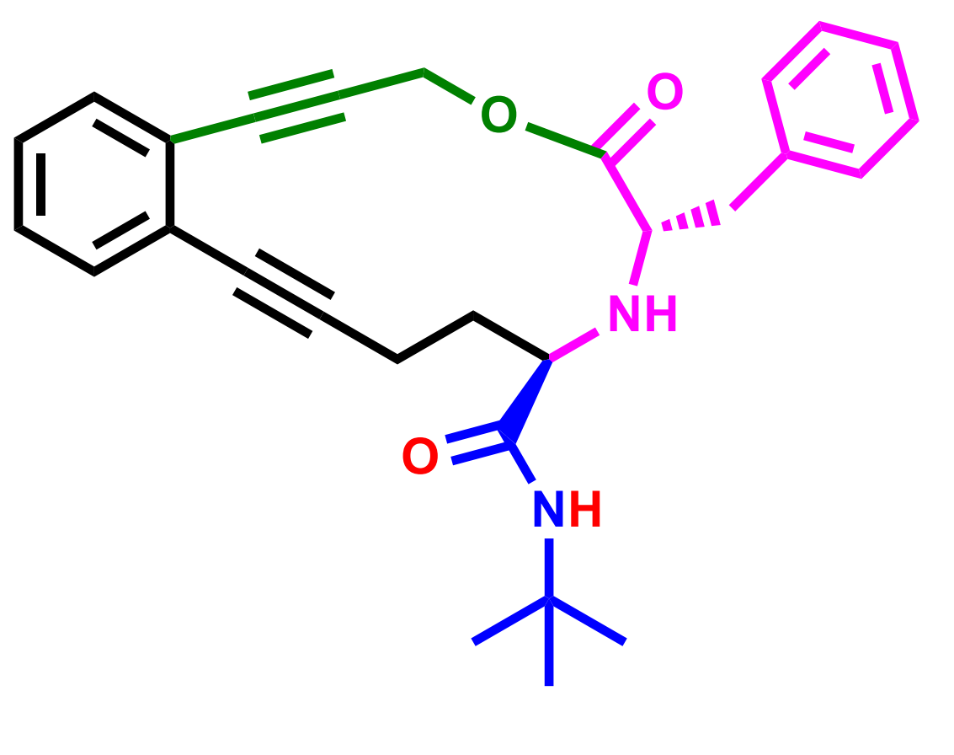
**5 (50 %)**
**d.r. = 62:38**



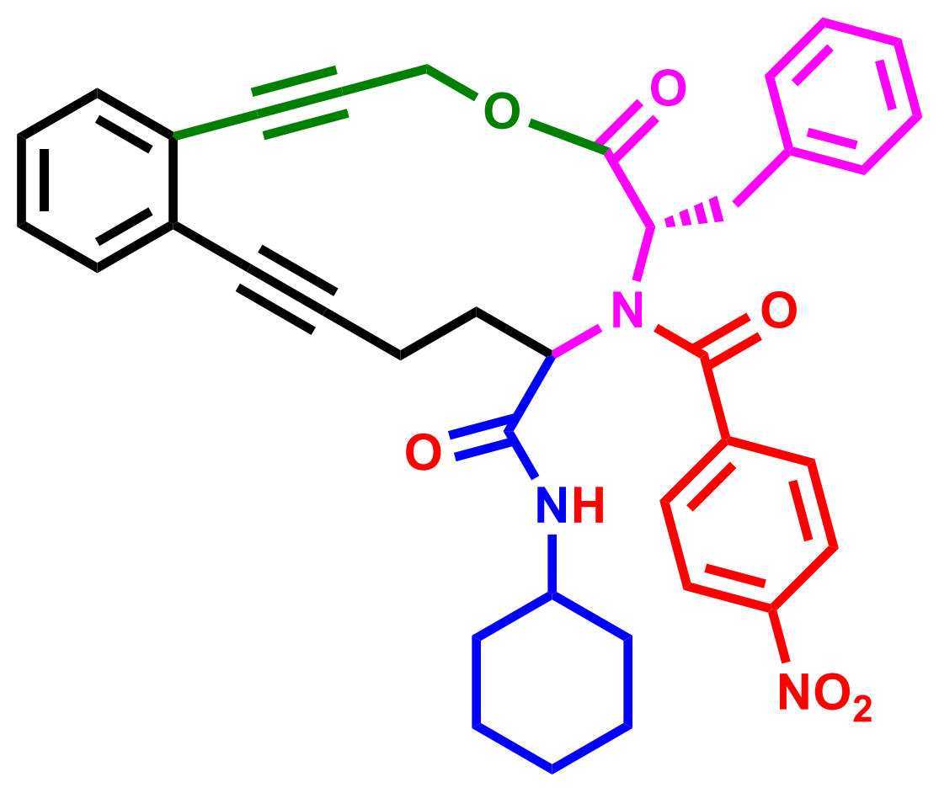
**6 (30 %)**
**d.r. = 85:15**



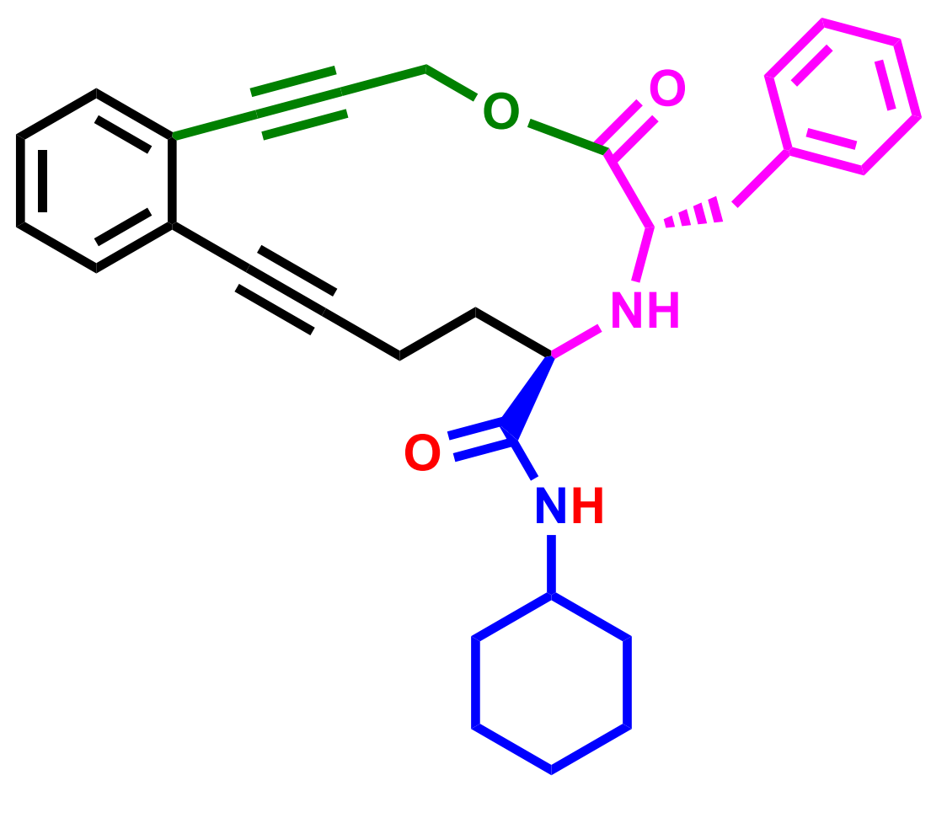
**7 (26 %)**
**d.r. > 98:2**



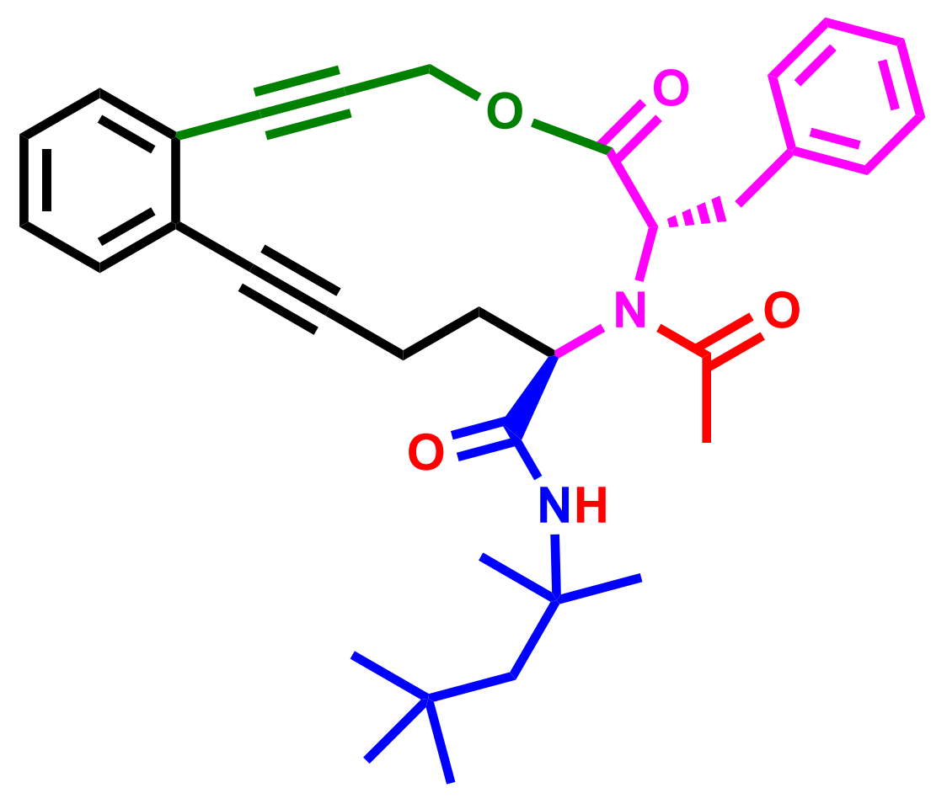
**8 (22 %)**
**d.r. > 98:2**



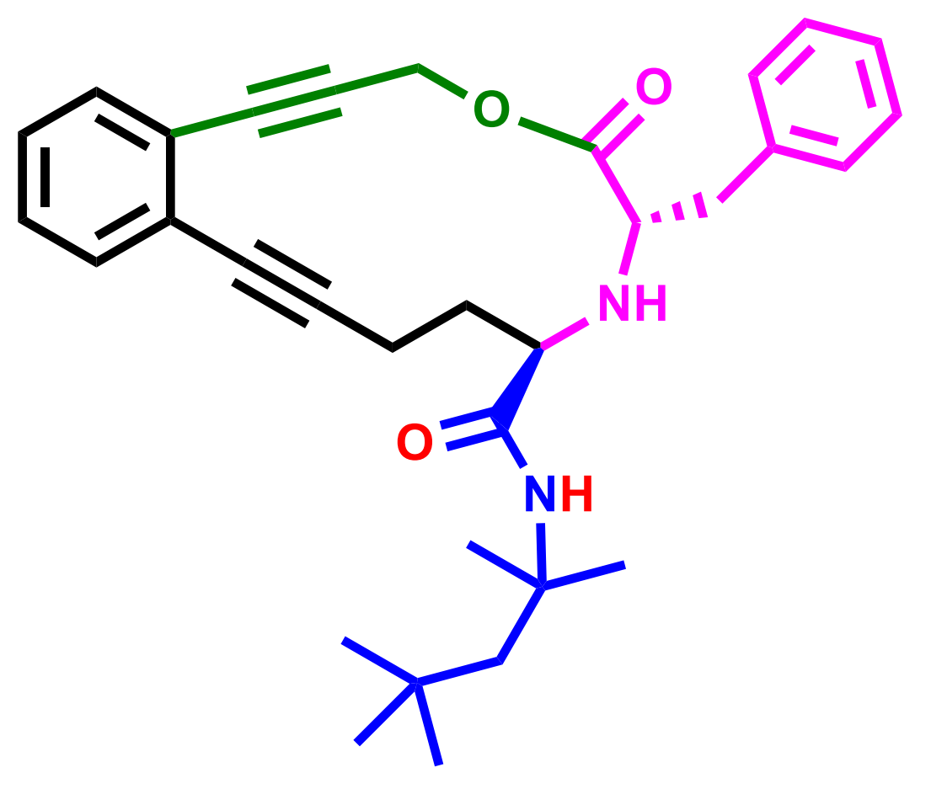
**9 (44 %)**
**d.r. = 50:50**



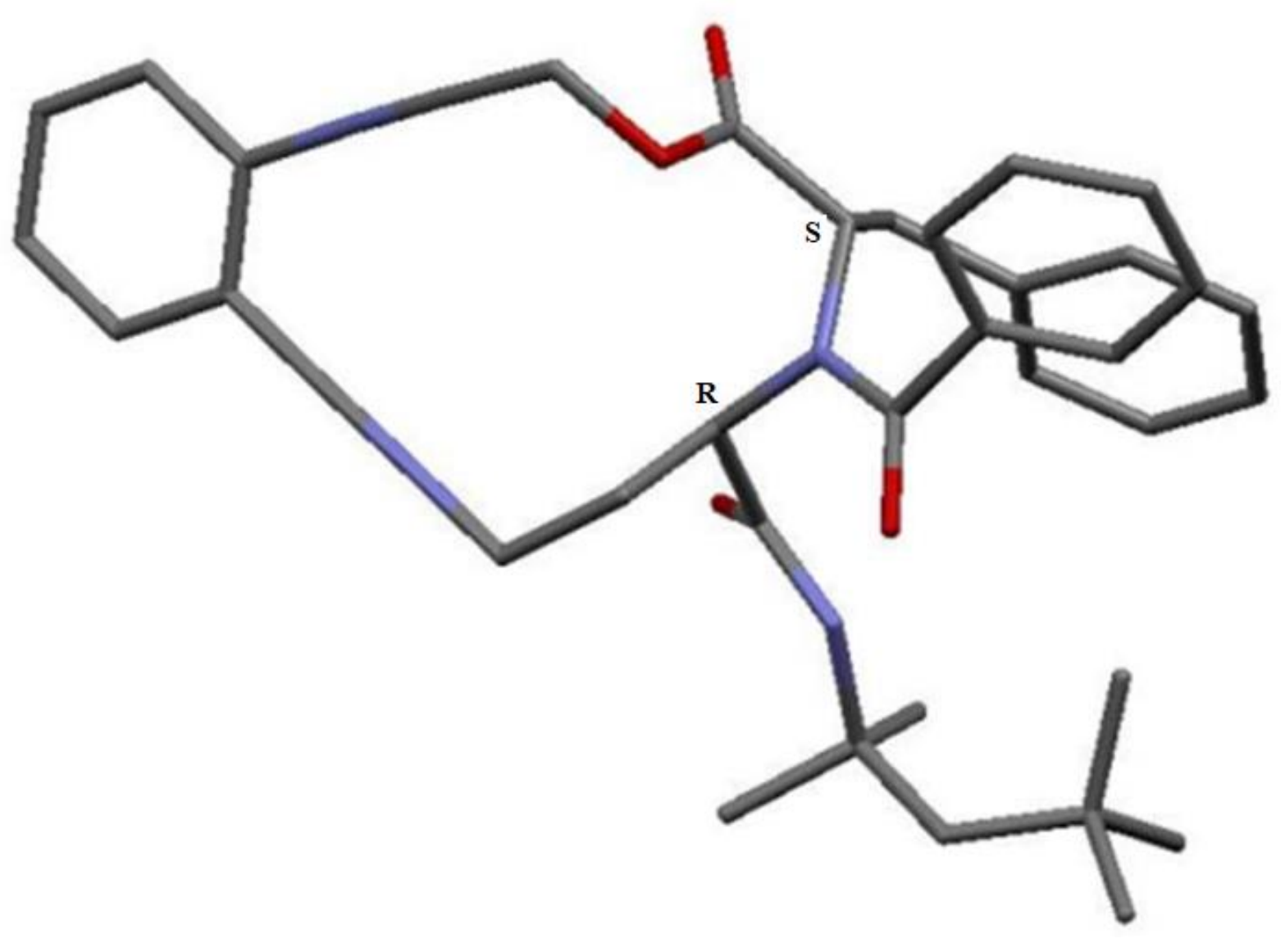
**10 (30 %)**
**d.r. > 98:2**



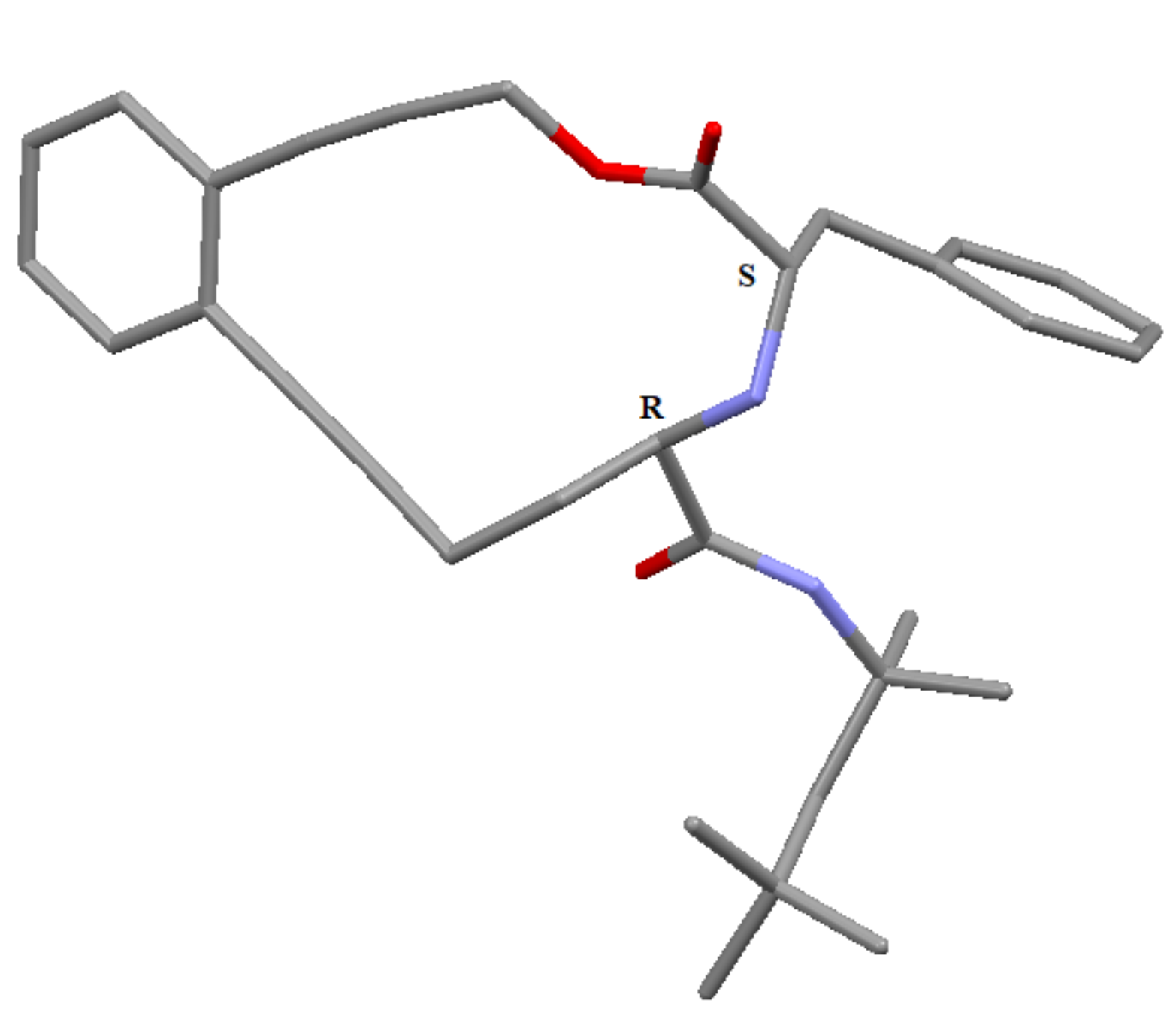
**11 (40 %)**
**d.r. > 98:2**



**12 (15 %)**
**d.r. > 98:2**



The absolute configuration of a major diastereoisomer of compound **2** and **12** was determined by the X-ray analysis and showed the **R** configuration at the newly created stereogenic center.



## CONCLUSION

- Ugi and Sonogashira reactions were carried out in up to 91 % and 98 % yield, respectively
- macrocycles **1** - **12** 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

[1] G. Koopmanschap, et al. *Beilstein J. Org. Chem.*, **10** (2014) 544–598.; [2] B. Westermann, et al. *Chem. Soc. Rev.* **42** (2013) 4948 – 49632.; [3] L. A. Wessjohann, et al. *Chem. Rev.*, 109 (2009) 796–814.; [3] K. C. Nicolaou, W.-M. Dai, *Angew. Chem. Int. Ed.* **30** (1991) 1387-1416.; [4] a) Z. Kokan, et al. *Organometallics*, **33** (2014) 4005–4015; b) M. Gredičak, et al. *J. Inorg. Biochem.*, **116** (2012) 45–52.