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Synthesis and Conformational Analysis of β,β-Diaryl-α-Amino Acids: on the Way to Molecular Gearing

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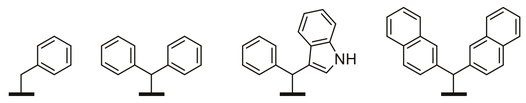
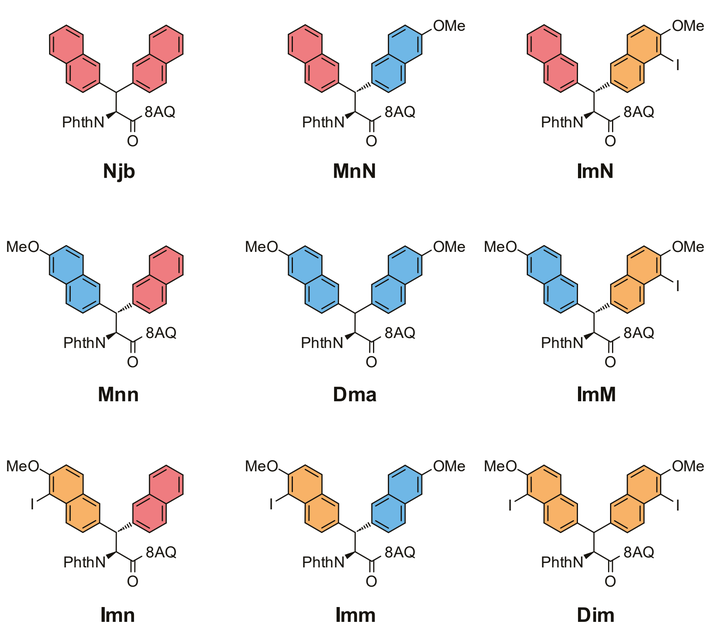
Introduction

Unnatural amino acids are useful building blocks for the synthesis of custom-made peptides and other complex molecules in drug discovery, medicinal, or material chemistry among other fields. β-branched-α-amino acids allow the conformational control of side chain orientation and thus can shape a peptide in a predictable way. We previously synthesized unsymmetric β,β-diaryl-α-amino acids, combining phenylalanine and tryptophan in one amino acid.[1] Depending on the side chain orientation the biologic function of short ghrelin peptides could be switched between agonism and antagonism towards its receptor.[2] We present the synthesis of even larger β,β-dinaphthyl-α-amino acids, their conformational analysis, and incorporation into peptides.



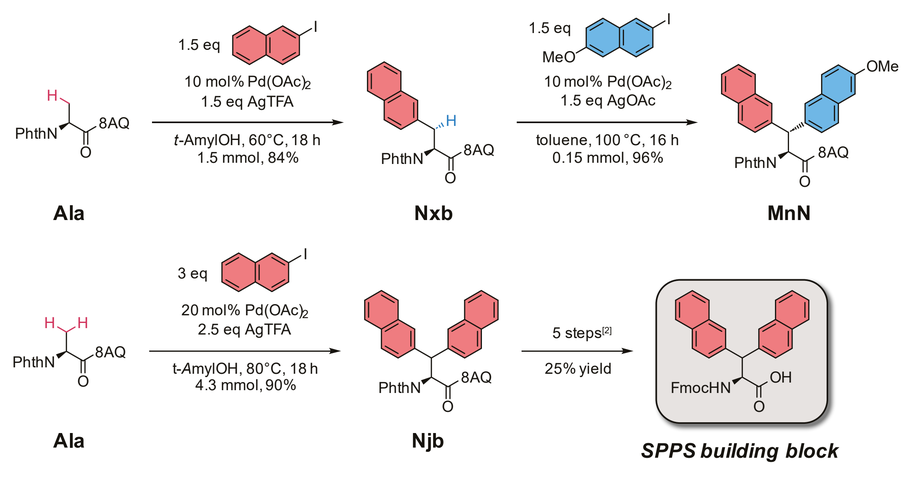
Design

Combining different aromatic groups leads to a squared number of possible substitution patterns. Shown is the combination of 3 different naphthyl moieties, resulting in 9 different amino acids, that have been synthesized.



Synthesis

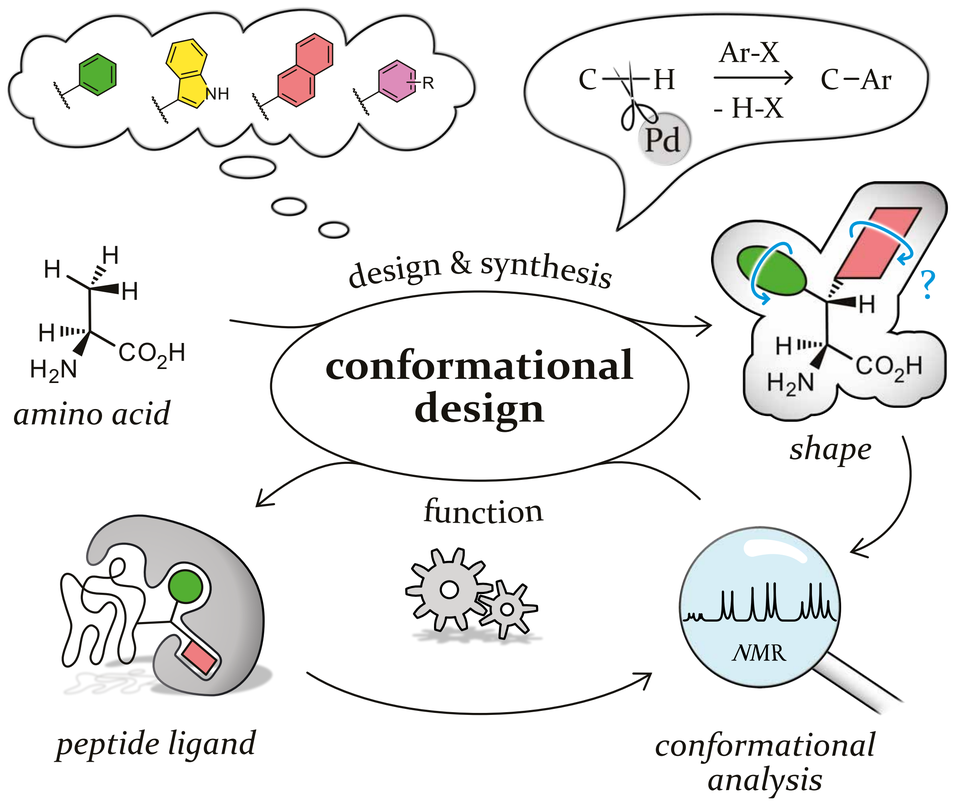
The amino acids are synthesized *via* palladium catalyzed, directed C-H activation. Therefore alanine is decorated with a phtalimide (Phth) protecting group on the nitrogen and the amide of 8-aminoquinoline (8AQ) at the *C*-terminus. Depending on the reaction conditions only one or two aryl groups are installed in β-position. In the former case a second aryl group can be incorporated stereoselectively, thus giving access to different diasteromers of the same amino acid. The amino acid can consecutively be transformed into a building block for solid phase peptide synthesis (SPPS), as prieviously reported by our group.[2]



Applications in SPPS

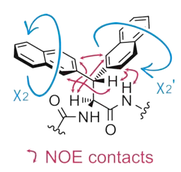
The dinaphthyl amino acids are incorporated into peptides via SPPS. Due to their high hydrophobicity and their distinct sidechain orientation they can shape a peptide in a specific way, while the mobility of each napthyl group allows for adaptation to the environment. Furthermore, a possibly cooperative conformational exchange between the naphthyl groups would allow the design of allosteric interactions in a complex environment.

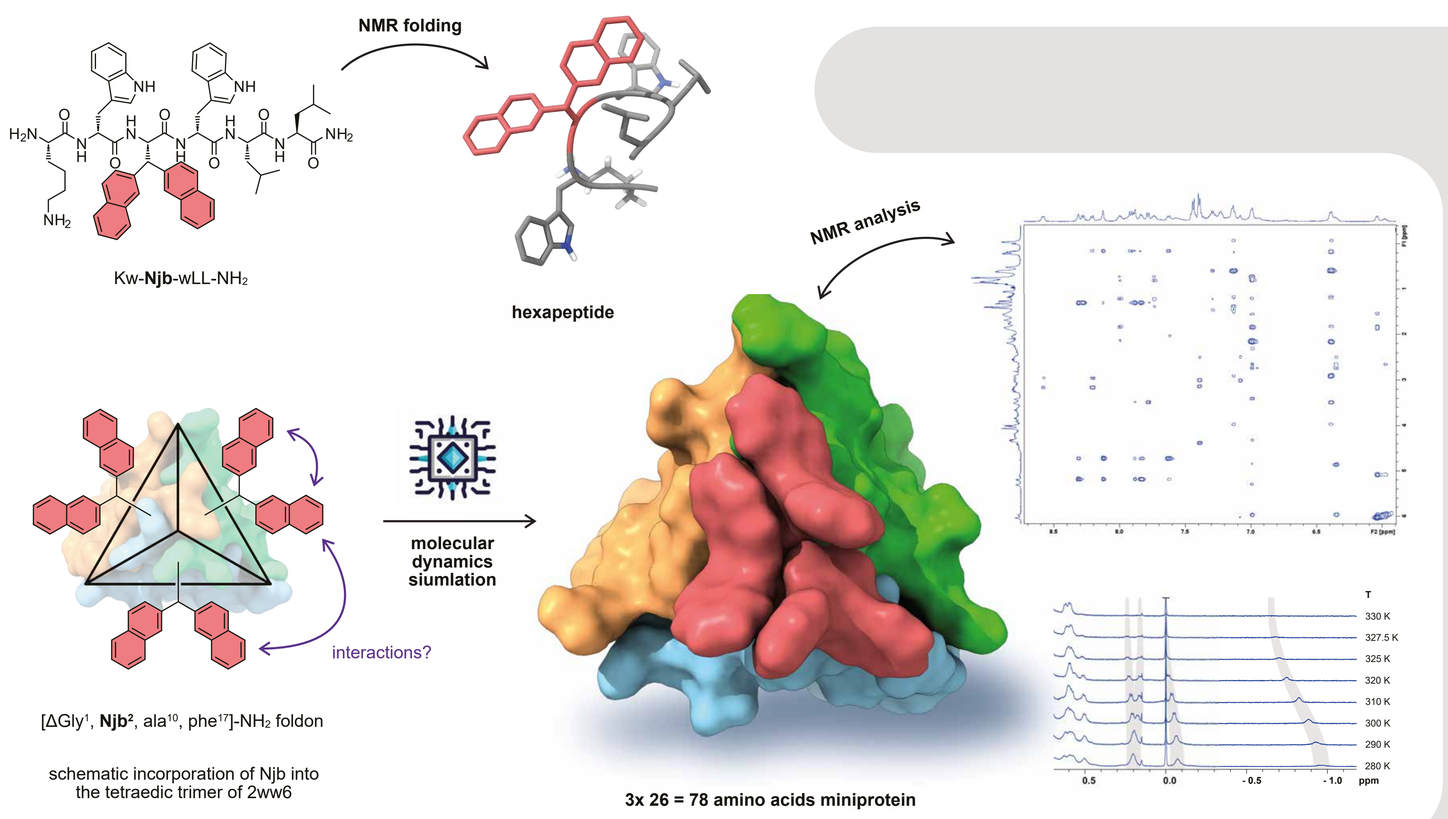
In the examples shown below the Njb amino acid (red) replaces phenylalanine in a short ghrelin receptor binding peptide. Structure determinaton based on NMR derived restraints reveal the helical structure of the peptide. Another example shows the incorporation of Njb into the foldon miniprotein, a well known trimeric structure. This way the interaction between three Njb residues can be studied, as they are brought into spatial proximity.

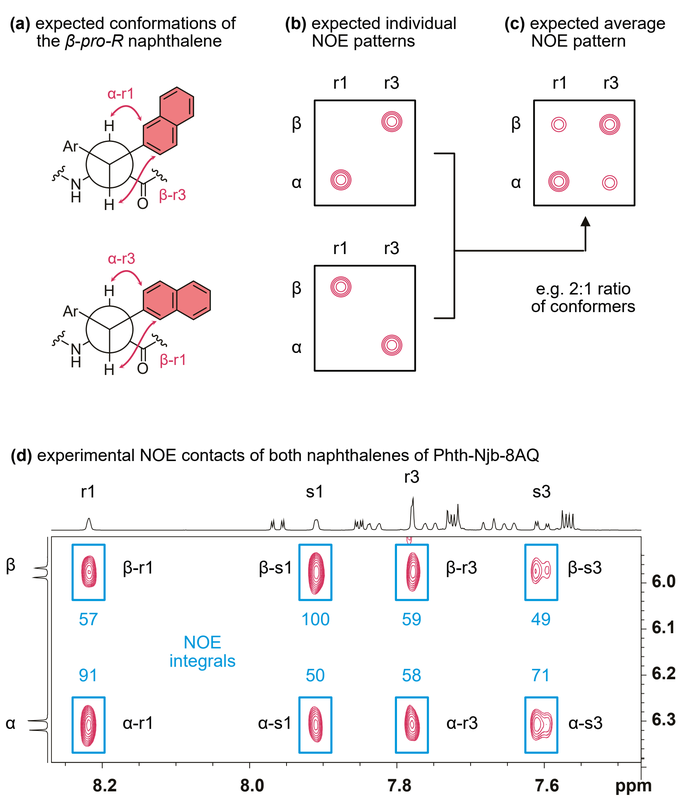


Analysis of Side Chain Conformation

The conformation of β,β-diaryl amino acids is usually restricted along the Cα-Cβ (χ1) axis due to steric reasons, with Hα and Hβ oriented anti-periplanar. The aromatic side chains may rotate along the χ2 and χ2' axis (indicated with blue arrows), although due to steric reasons the two conformations in which the aromatic ring is in the same plane as the Cβ-Hβ bond should be preferred (a). For each of those conformations a specific NOE pattern is expected (b). An analysis of the averaged pattern (c) indicates to what extent the conformations are populated and, more interestingly, if a correlation between the conformations exists. Such a gearing type interaction between the aromatic rotors, as observed for Phth-Njb-8AQ (d) can potentially be used for the design of allosteric interactions.







References

[1] L. Nicke, P. Horx, R. Müller, S. Els-Heindl, A. Geyer, *ChemBioChem* **2021**, *22*, 330-335.
[2] L. Nicke, P. Horx, K. Harms, A. Geyer, *Chem. Sci.* **2019**, *10*, 8634.
[3] B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391.

Conclusion and Outlook

The synthesis of a novel β,β-diaryl-α-amino acids featuring two naphthyl moieties was achieved by a palladium catalyzed C-H activation strategy with consecutive transformation into a SPPS building block[2]. The conformation of the Njb amino acid was studied in peptidic environment, showing promising first results on the way to molecular gearing.