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Synthesising Libraries of α,δ-Foldamers using Solid Phase Peptide Synthesis

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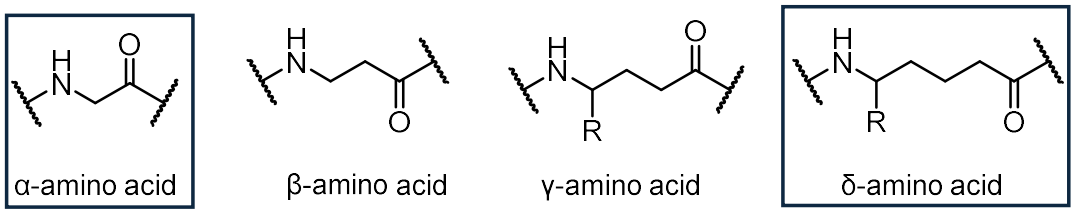
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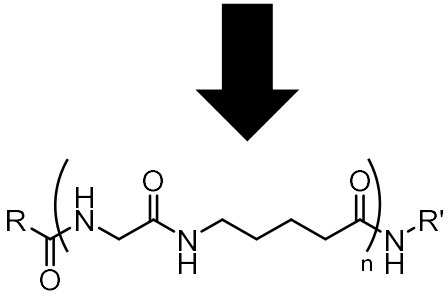
Introduction to Foldamers

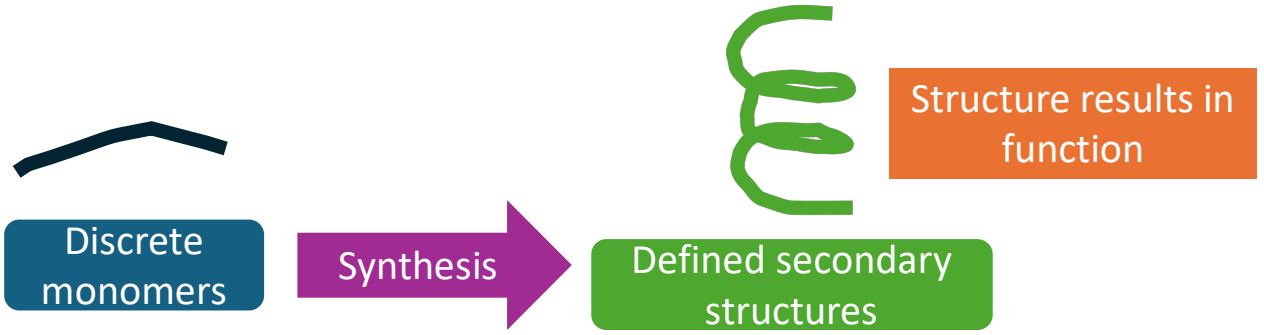
- Foldamer – oligomers that fold due to noncovalent interactions from non-adjacent units.

- Key subunits:
  - Amino acids
  - Ureas
  - Aromatic groups
  - Carbohydrates

- Applications:
  - Therapeutics
  - Materials
  - Catalysis



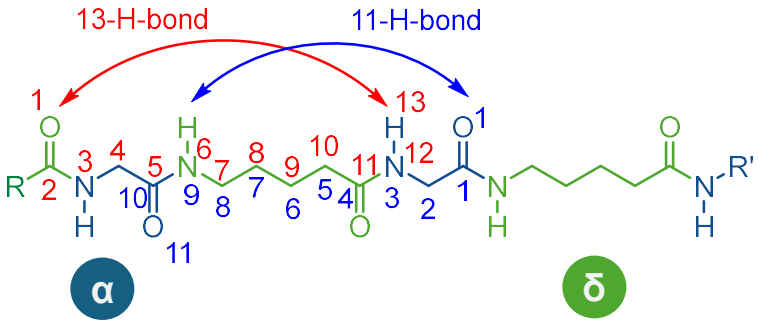


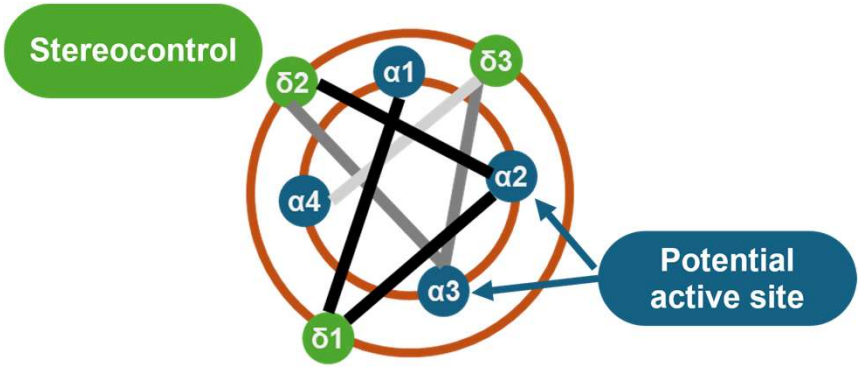


S. H. Gellman, *Acc. Chem. Res.,*1998, **31**, 173–180; D. J. Hill *et al.*, *Chem. Rev.,* 2001, **101**, 3893 – 4012;
R. Gopalakrishnan *et al.*, *J. Med. Chem.*, 2016, **59**, 9599–9621; Z. C. Girvin and S. H. Gellman, *J. Am. Chem. Soc.,* 2020, **142**, 17211–17223.

Hybrid α,δ-Foldamers

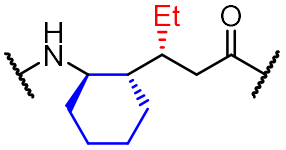
- Hybrid α,δ-foldamers form predictable 13/11 helix
  - δ-residues form a binding pocket + exposed α-residues – sites of interests
  - Potential catalyst scaffold



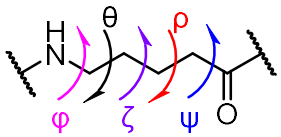


- Our δ-amino acid (AchPA) shows similar dihedral angles computed by Hofmann

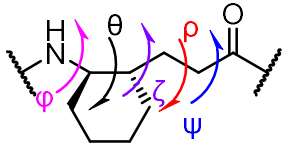
Stabilises helix through noncovalent interactions



Responsible for chiral environment during folding



Dihedral angles



AchPA

Dihedral angles	ϕ	θ	ζ	ρ	ψ
Predicted angles of 13/11 helix by Hofmann	137	-79	64	57	-143
Low energy conformation of AchPA	111	-64	73	49	-125

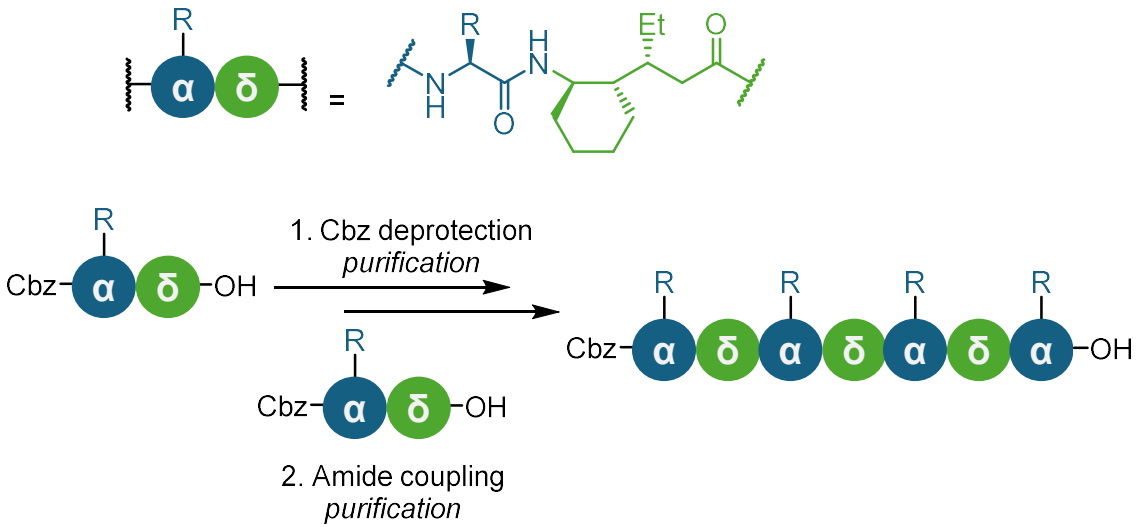
Q. Lin *et al.*, *Angew. Chem Int. Ed.*, 2023, **62**, e202305326. G. V. M. Sharma *et al.*, *Chemistry – A European Journal,* 2009, **15**, 5552–5566

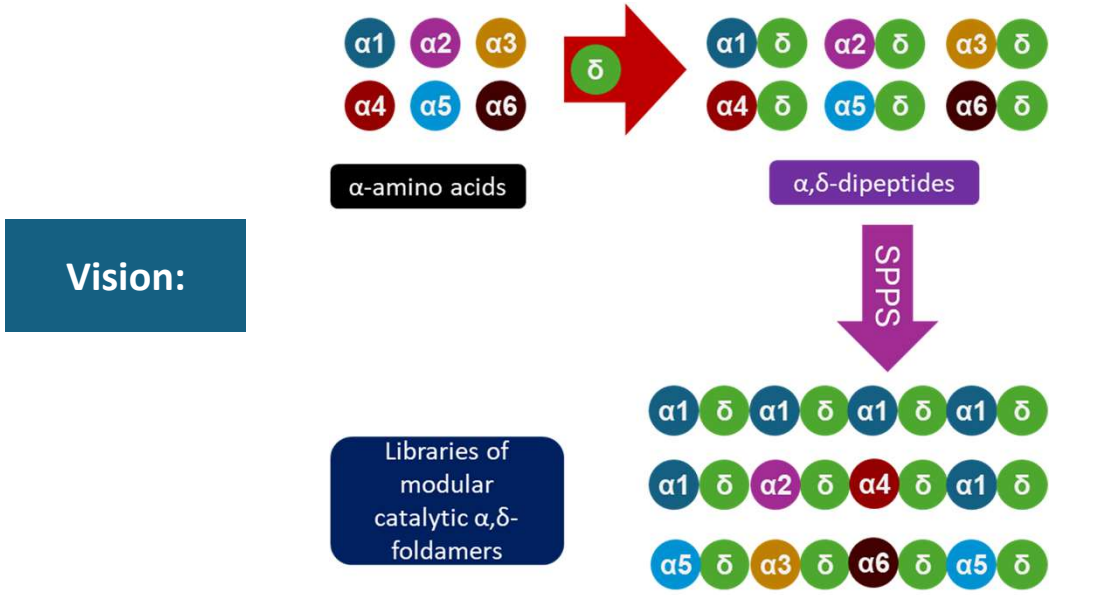
Aims and Objectives

- 1:1 α,δ-Foldamers synthesised by solution phase peptide synthesis
  - <50 mg produced after 20 steps

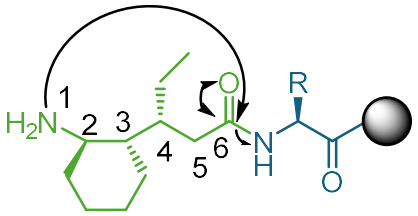
- SPPS methodologies for faster syntheses of diverse foldamers.
  - Libraries could be developed for catalytic studies

Solution phase synthesis developed by Cobb group (2023)

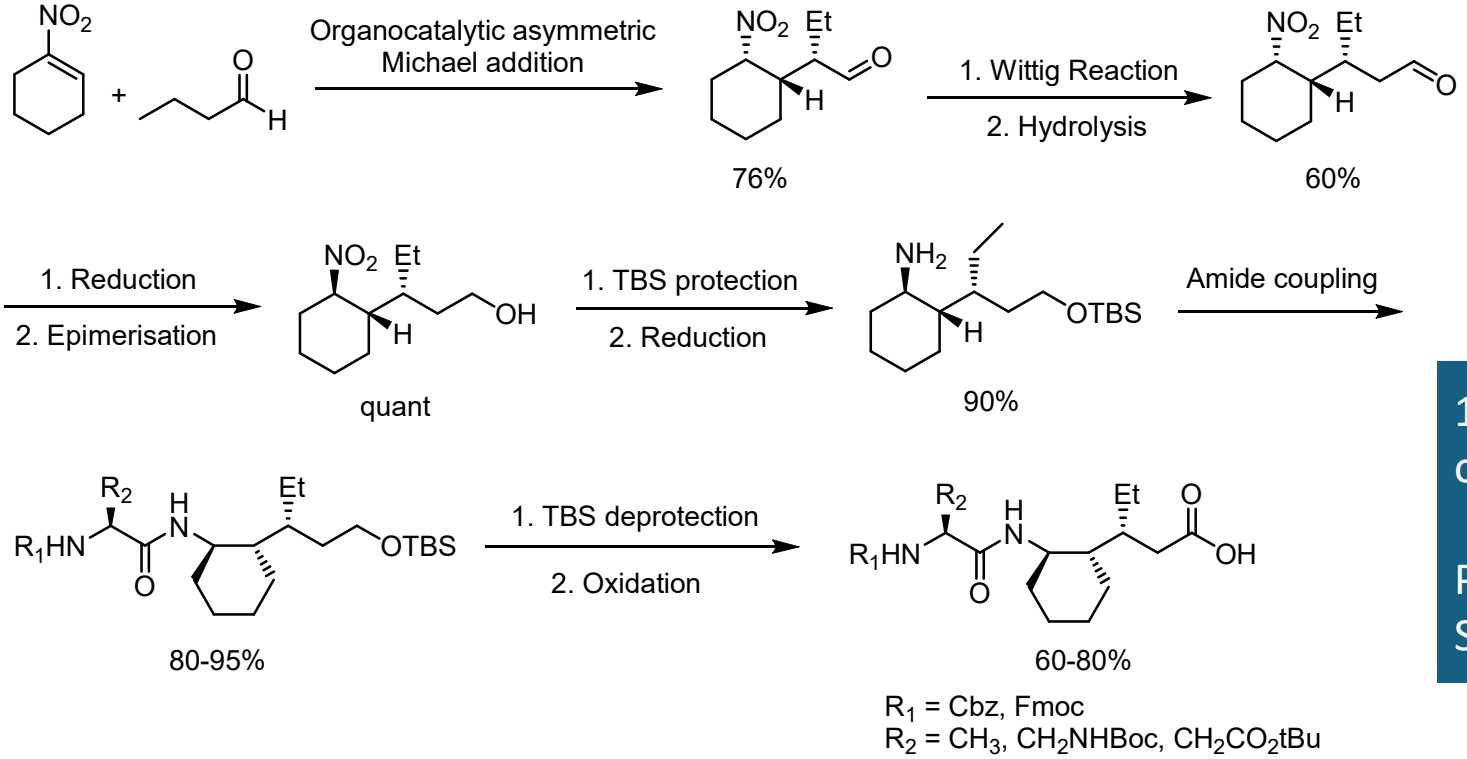




Synthesis of Dipeptide Building Blocks



Loading AchPA impossible -> 6-exo-trig cleavage

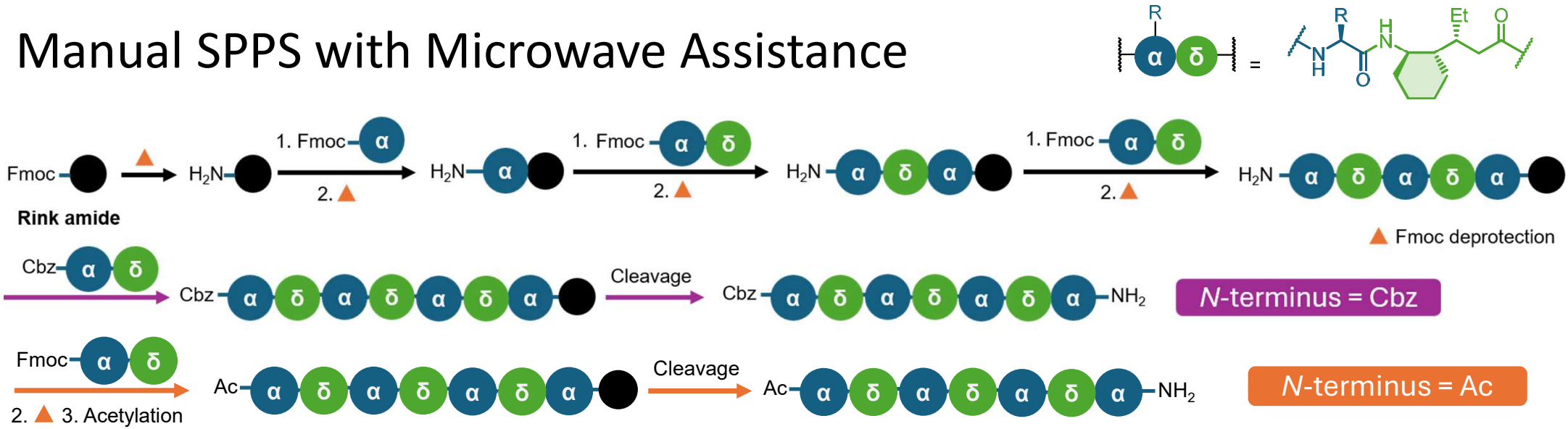


R_1 = Cbz, Fmoc
R_2 = CH_3, CH_2NHBoc, CH_2CO_2tBu

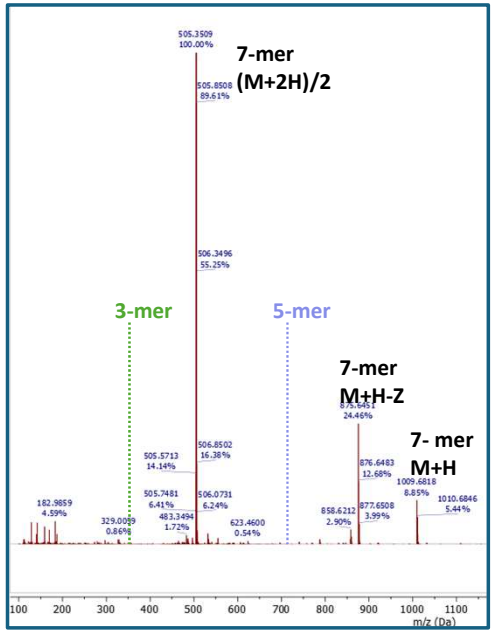
1-2 g scale of dipeptide from 3 mL of 1-nitro-cyclohexene SM

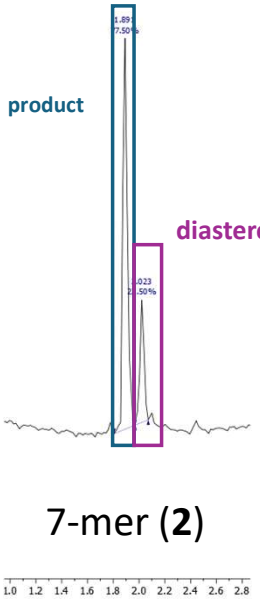
Purity assessed by HPLC before SPPS

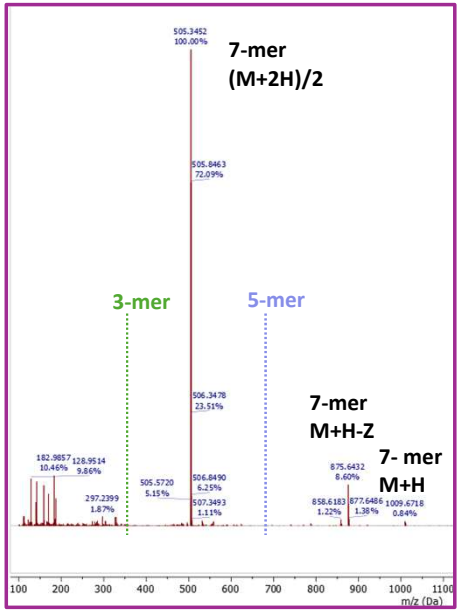
Manual SPPS with Microwave Assistance



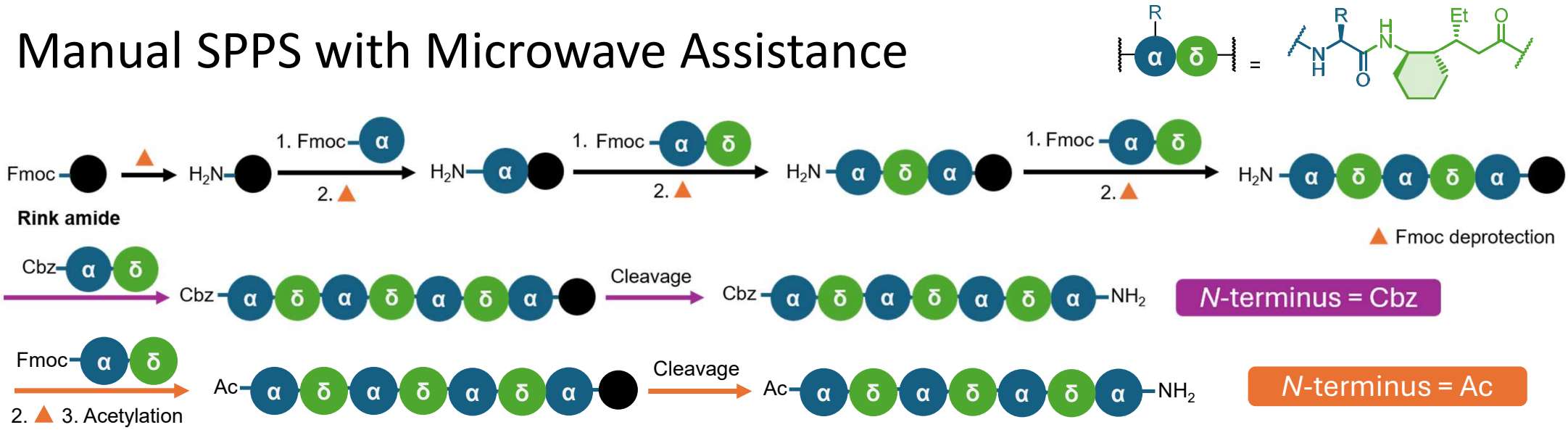
- 2.0 equiv. of dipeptide needed
- 15 min, 65 °C in microwave synthesiser
- High coupling efficiency – no capping required

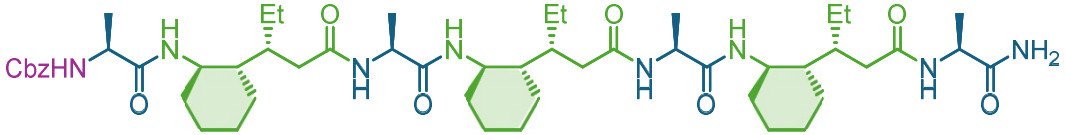




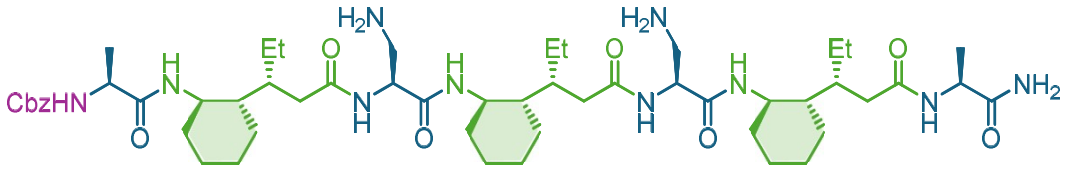


Manual SPPS with Microwave Assistance

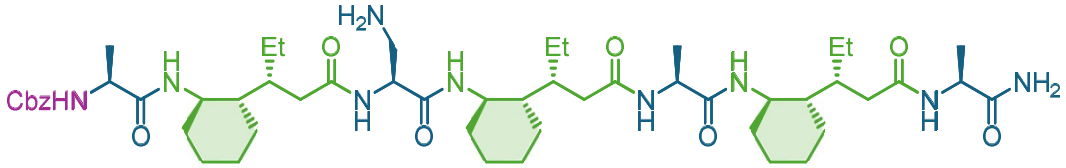




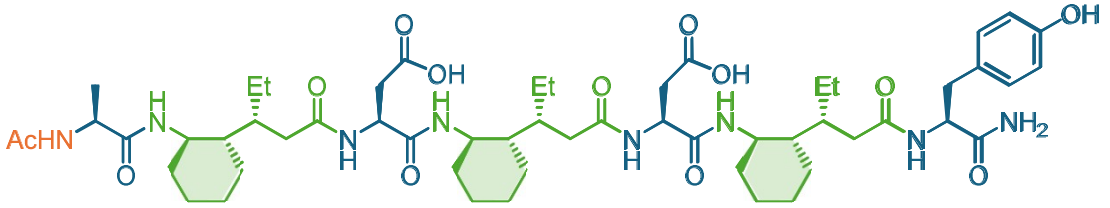
Z-Ala-AchPA-Ala-AchPA-Ala-AchPA-Ala-NH_2 (**1**), 70 mg (36% yield)



Z-Ala-AchPA-Dap(NH_2)-AchPA-Dap(NH_2)-AchPA-Ala-NH_2 (**2**), 68 mg (34% yield)

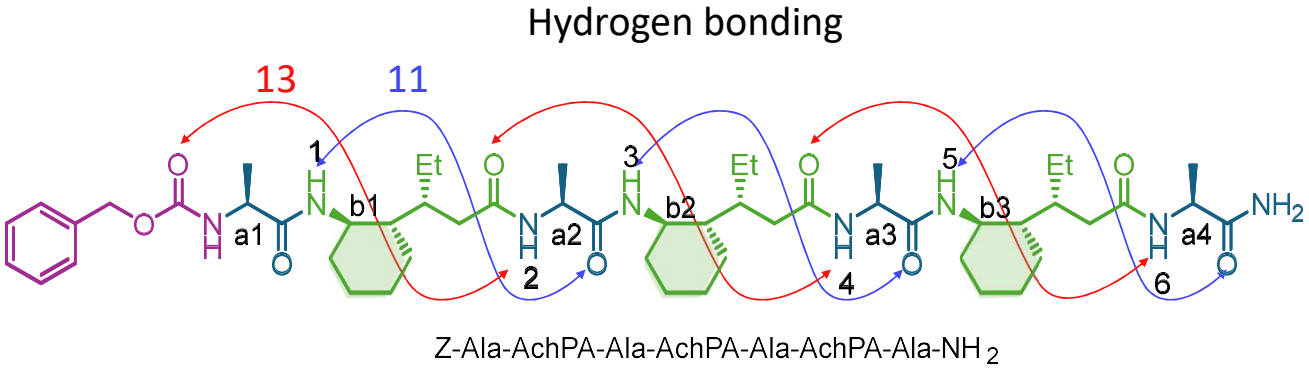


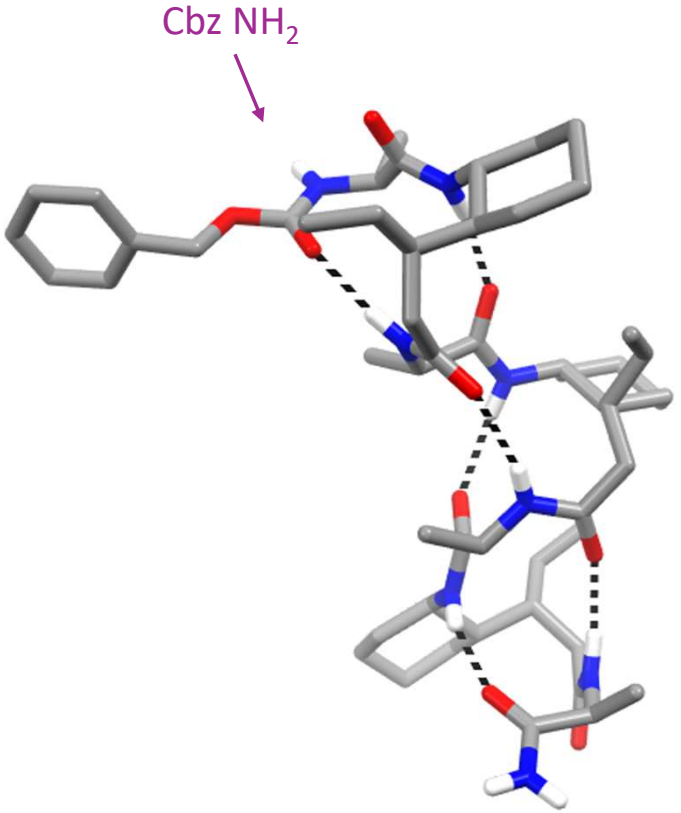
Z-Ala-AchPA-Dap(NH_2)-AchPA-Ala-AchPA-Ala-NH_2 (**3**), 173 mg (87% yield)



Ac-Ala-Asp(OH)-AchPA-Asp(OH)-AchPA-Tyr(OH)-NH_2 (**4**), 75 mg (35% yield)

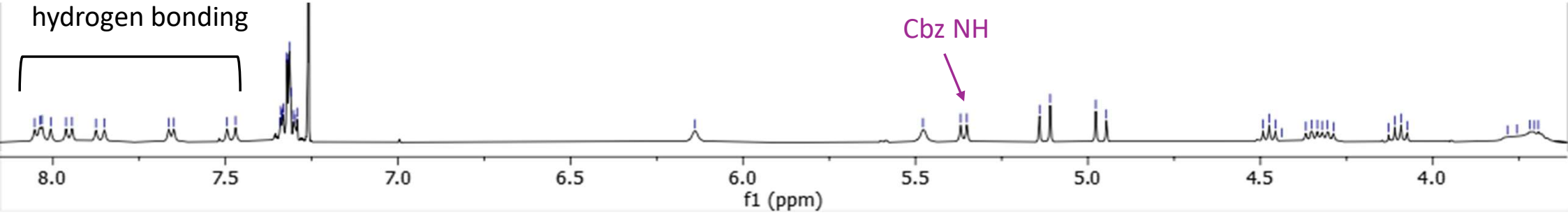
Do the SPPS Foldamers Fold?



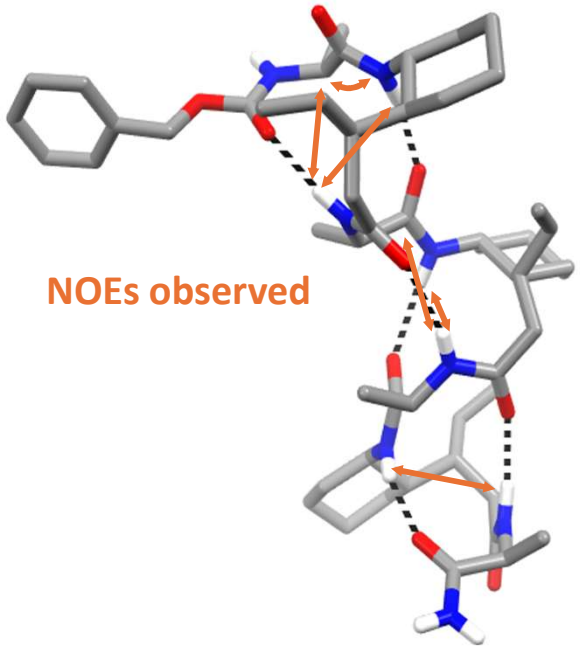


400 MHz, $CDCl_3$

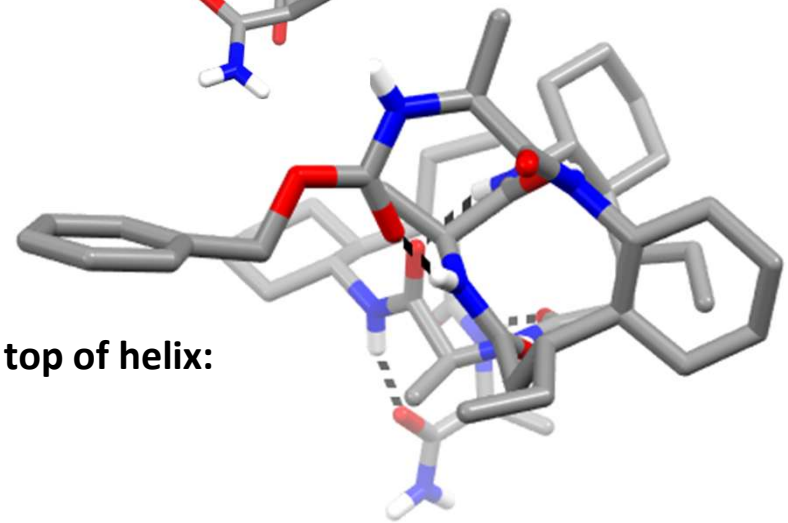
6 × NH involved in hydrogen bonding



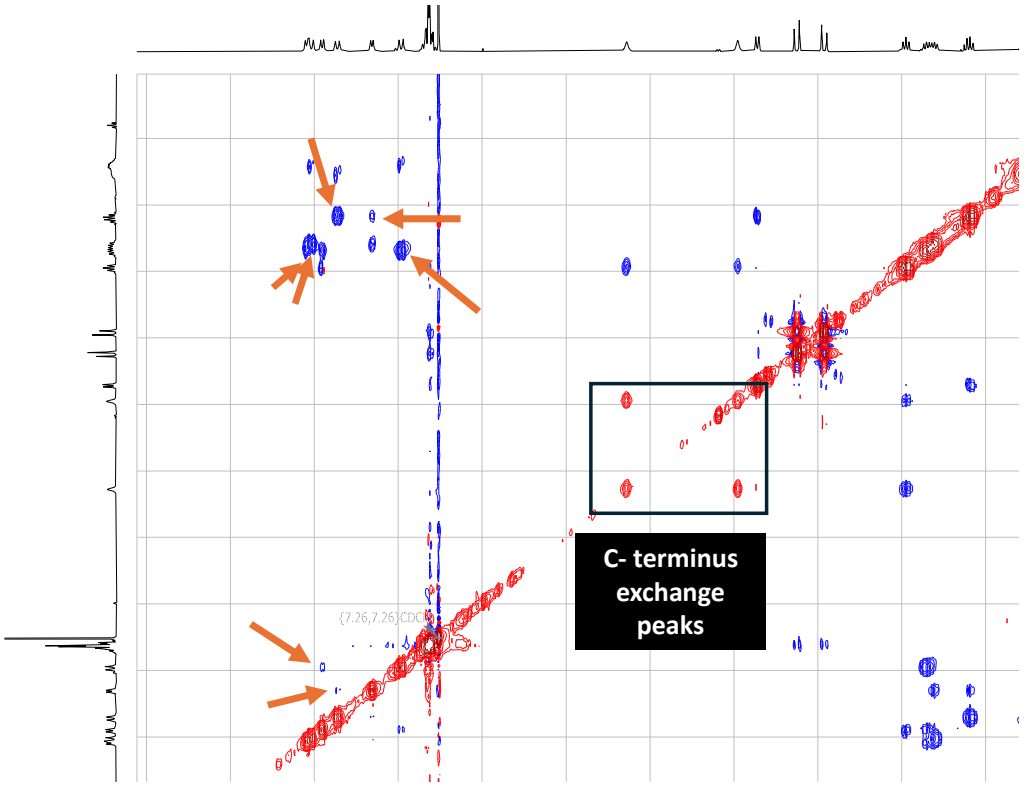
Structure in Solid vs Solution



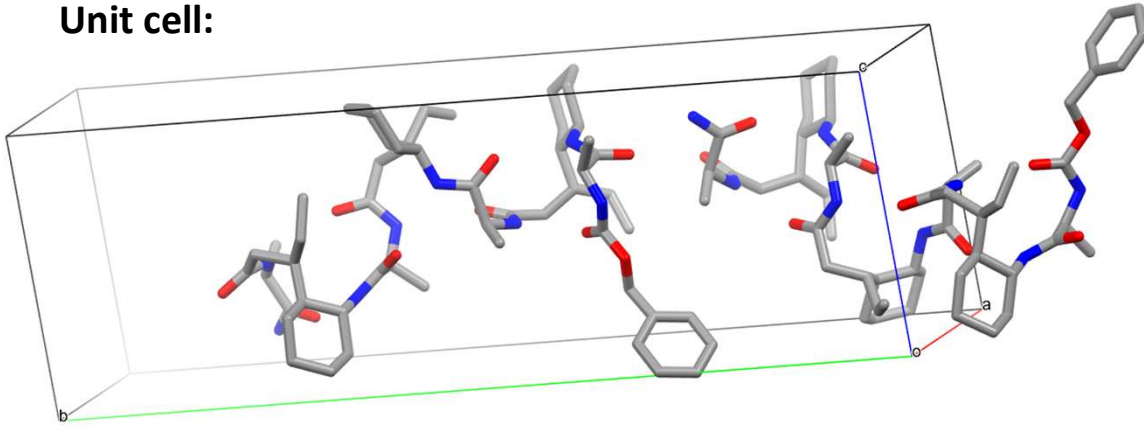
NOEs observed



View from top of helix:



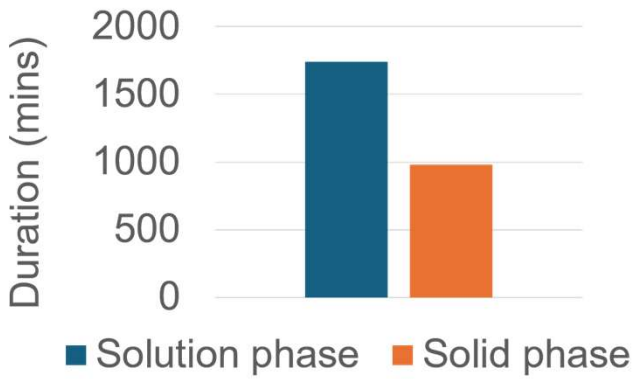
Unit cell:



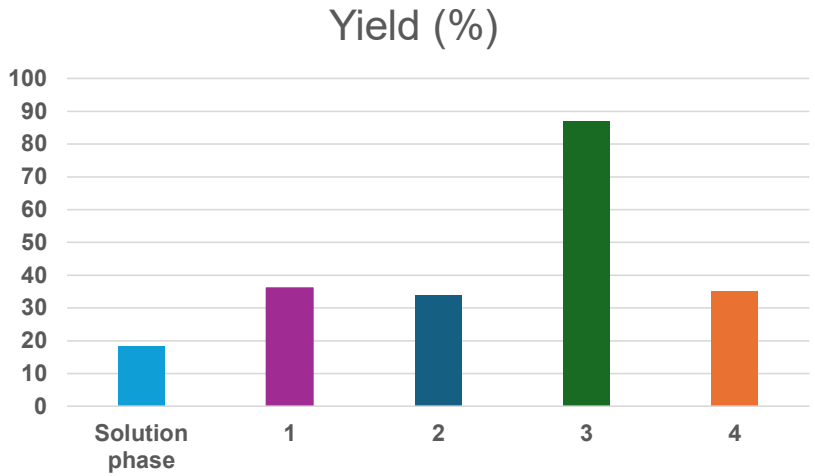
Conclusion

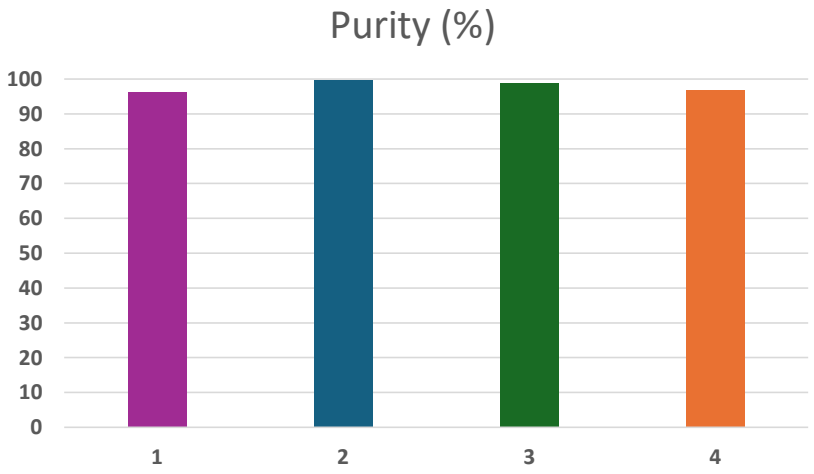
- Heteromers with different functionalities synthesised and characterised
- Solution (NMR) structure matches solid state structure (X-ray)

- Duration for synthesis of heteromers reduced



- Yield improved vs solution phase with good purities

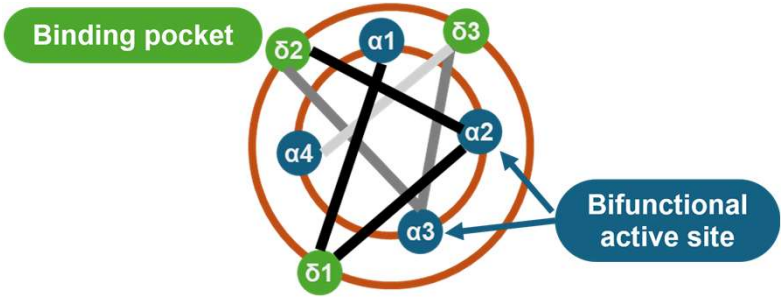




Outlook and Acknowledgement

Future work:

- Investigate synthesising libraries with new functional groups
  - Bifunctional catalytic active sites
- Synthesise longer chains of heteromers
- Greener SPPS methods.







Cobb group, KCL

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Junyan Xu
An-Jie Ler
Beth Clent
Inés Cruz Blanco

Müller Lab, KCL
Dr Manuel Müller
Lewis Picken

KCL NMES Faculty Studentship