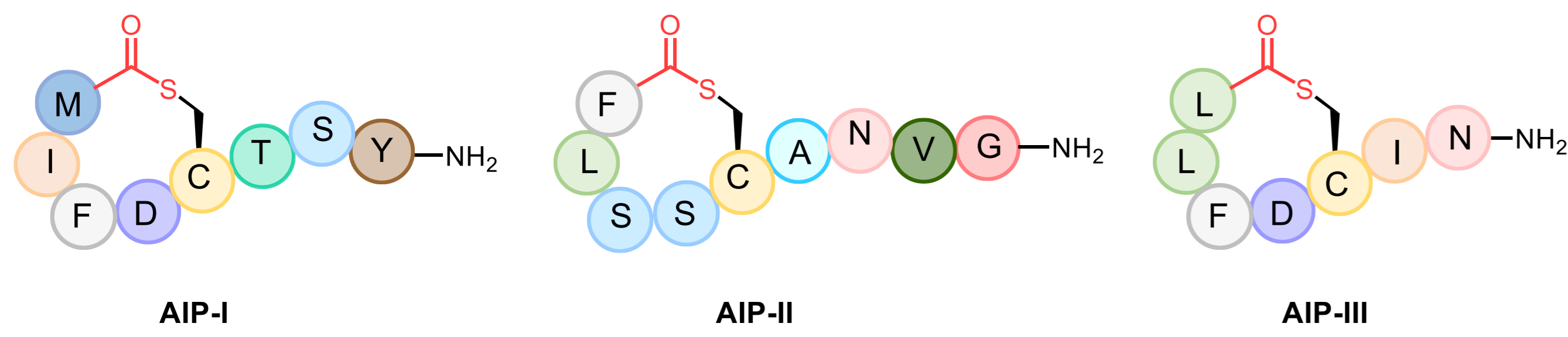


1. Peptide Thiolactones - AIPs

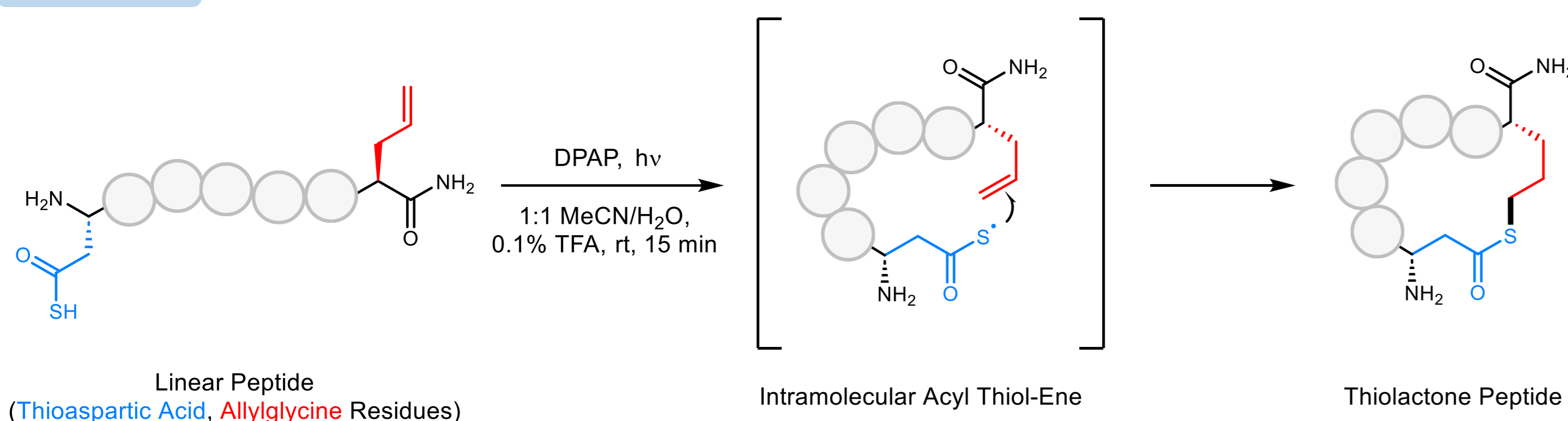
Thiolactones are found in several bioactive natural peptides, including the **autoinducing peptides (AIPs)** found in Gram-positive bacteria such as *Staphylococcus aureus*. AIPs play a key role in the regulation of the quorum sensing system.¹⁻² Thus, analogues of AIPs have been investigated as modulators of the quorum sensing system to attenuate and treat *S. aureus* infections.³⁻⁴



2. Peptide Thiolactone Synthesis

The traditional synthesis of peptide thiolactones has relied on the thiolactonisation of fully protected peptides using coupling reagents, or the displacement of activated groups (thioesters, Dbz, MeDbz) by Cys. Both require elevated temperature (50 °C) and extended reaction times (2–12 h).⁵ The aim of this project is to **develop a photochemical acyl thiol-ene method to rapidly synthesise peptide thiolactones**.

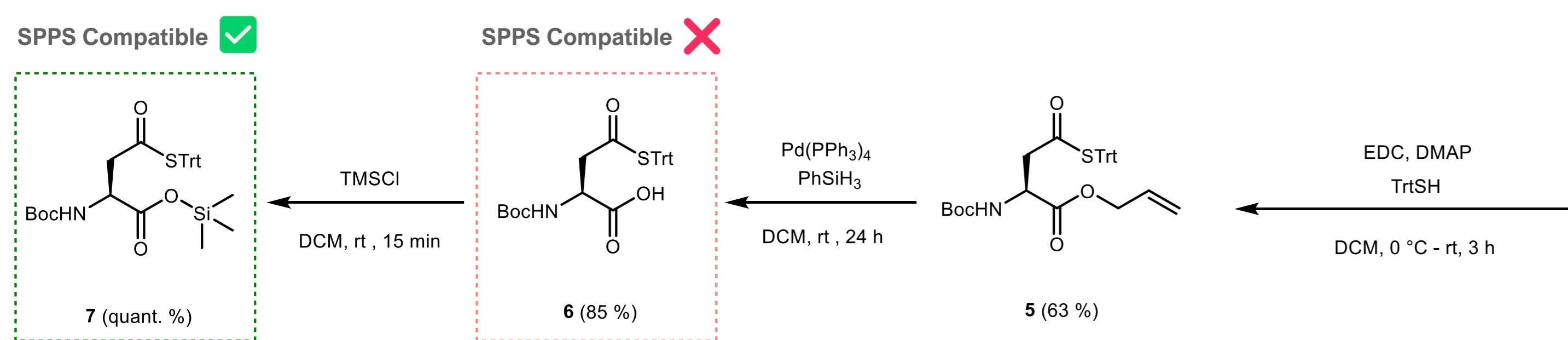
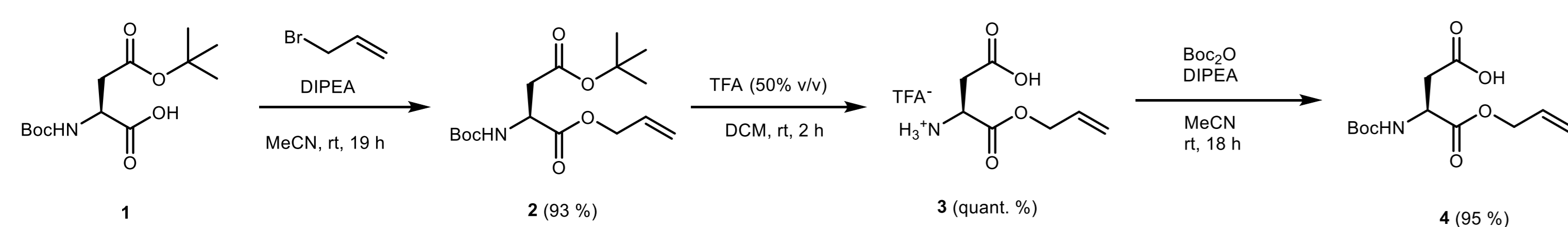
This work



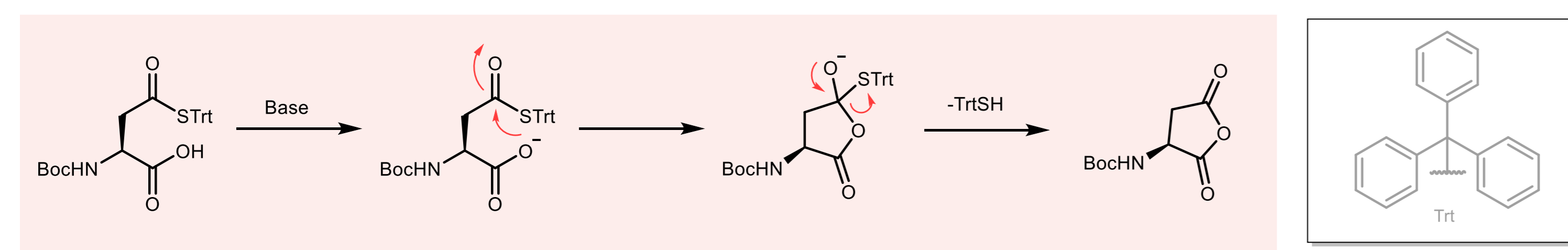
- ✓ Standard Fmoc SPPS synthesis of linear peptide.
- ✓ Compatible with fully unprotected peptides.
- ✓ Compatible with aqueous conditions.
- ✓ Rapid reaction time (15 min)

3. Thioaspartic Acid SPPS Monomer Synthesis

Thioacid was introduced during standard Fmoc SPPS as the **acid-labile S-trityl group**, which can be deprotected during global deprotection/resin cleavage. **Overall, 51% yield over 6 steps**, with two chromatographic purifications.



Carboxylic acid (**6**) prone to base catalysed lactonisation during amino acid activation. Silyl ester (**7**) masks carboxylic acid.⁶



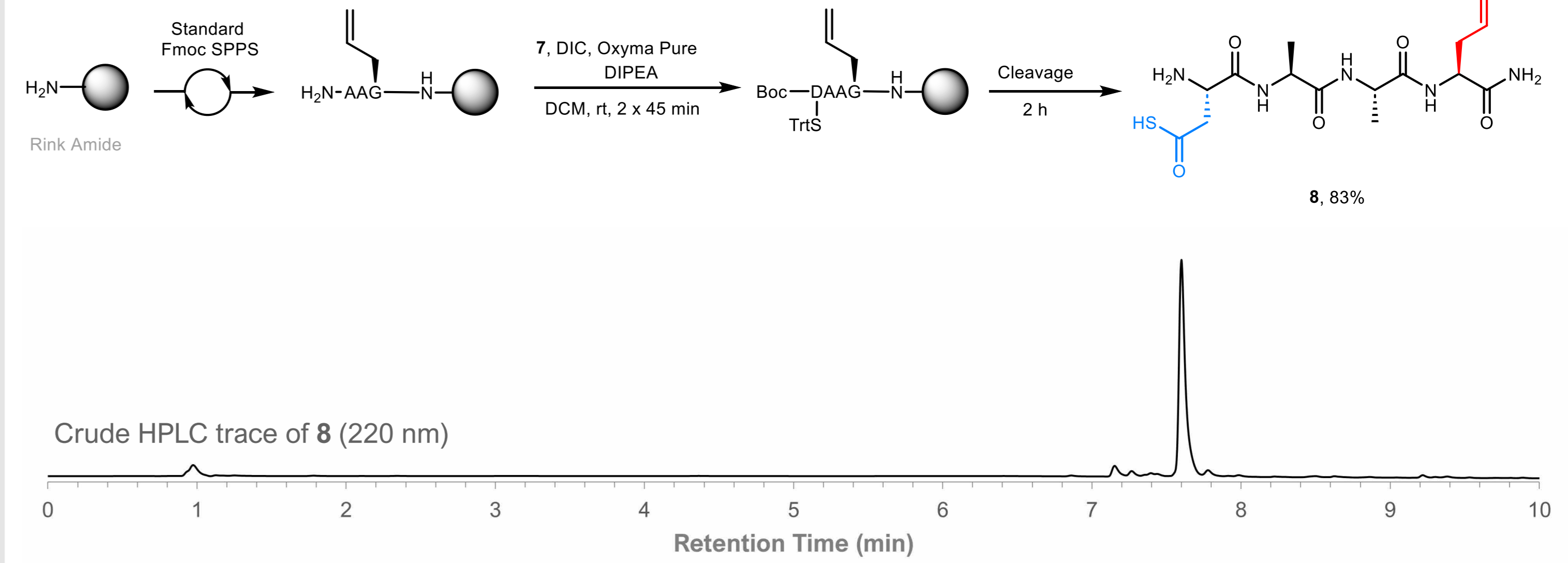
References and Acknowledgements

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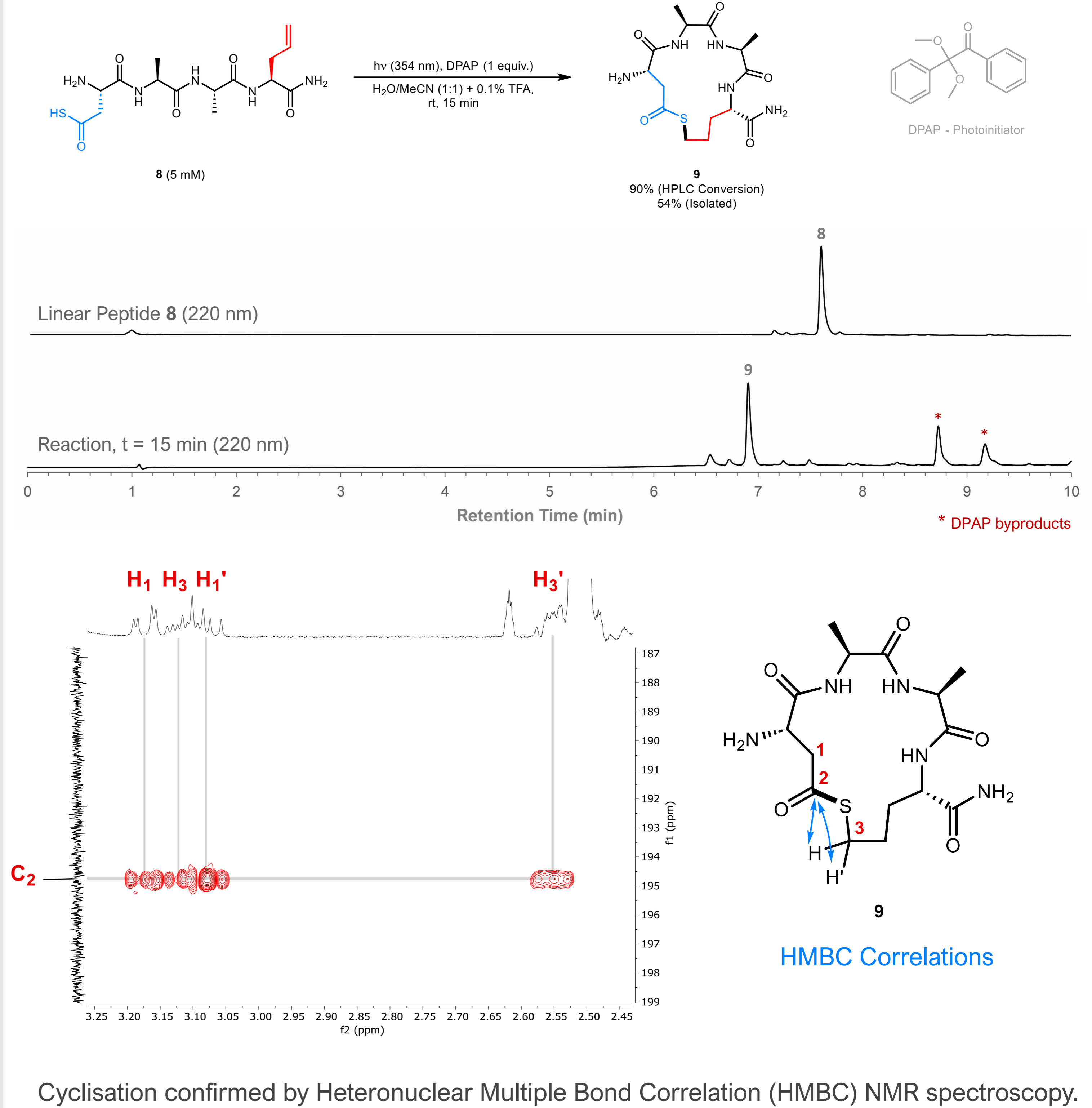
SCAN ME



4. SPPS of Linear Thioacid/Alkene Peptide

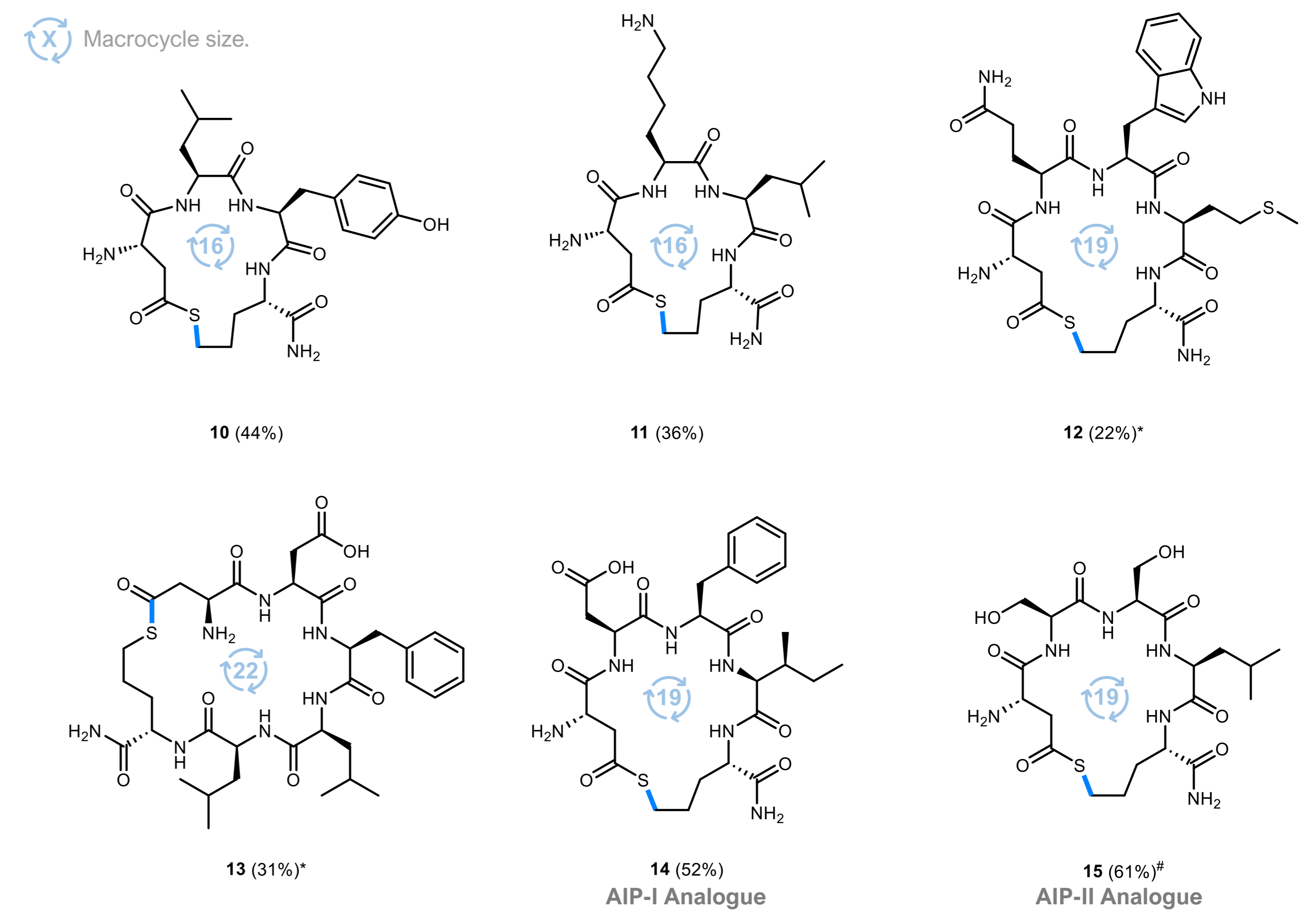


5. Model Acyl Thiol-Ene Thiolactonisation Reaction



6. Acyl Thiol-Ene Macrothiolactonisation Scope

Series of linear peptides were synthesised by SPPS and cyclised using the conditions above. Compatibility with various ring sizes and functional groups was demonstrated. All reported yields are isolated yields after semi-preparative HPLC purification.⁷



* 80% pure by ¹H NMR due to inseparable impurity. #6 M guanidinium hydrochloride added to reaction mixture.