



Strategic Optimization of Coupling Reactions and Green Solvents for Sustainable Peptide Manufacturing



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QVIT LAB

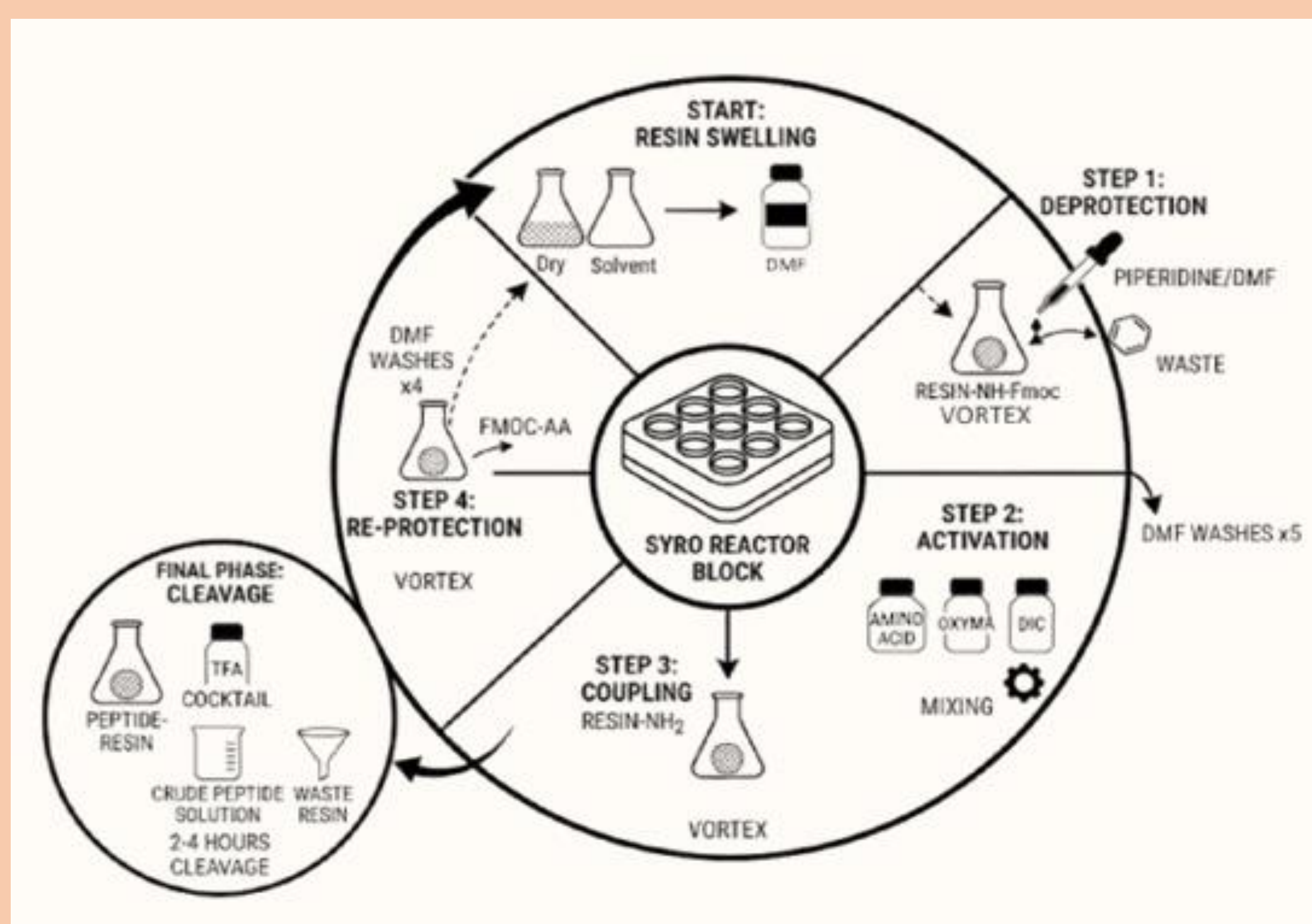
Abstract

Peptide synthesis is essential for biochemical and pharmaceutical research, yet achieving high efficiency and yield while reducing environmental impact remains a major challenge. This study evaluated a sustainable binary solvent system of dimethyl sulfoxide and ethyl acetate (1:1, v/v) to enhance performance and environmental compatibility. Peptides CVP-118 and CVP-127 were synthesized using a Syro-I automated synthesizer to compare coupling reagents, including diisopropylcarbodiimide and TBDC in its tosylate and hydrochloride forms. Utilizing TBDC with the green binary solvent system yielded higher purity and improved yields up to 100% by HPLC compared to conventional DIC in DMF. Furthermore, this sustainable approach significantly reduced cis-trans isomerization while maintaining high reaction efficiency and overall performance.

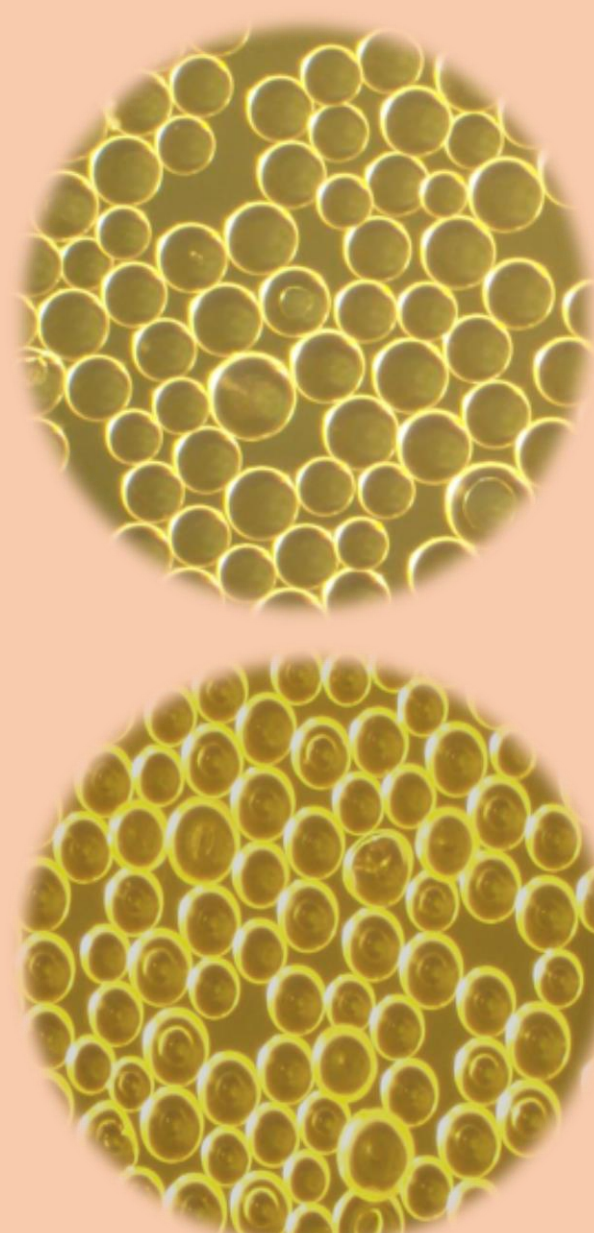
Methods



Conventional Solid Phase Peptide synthesis

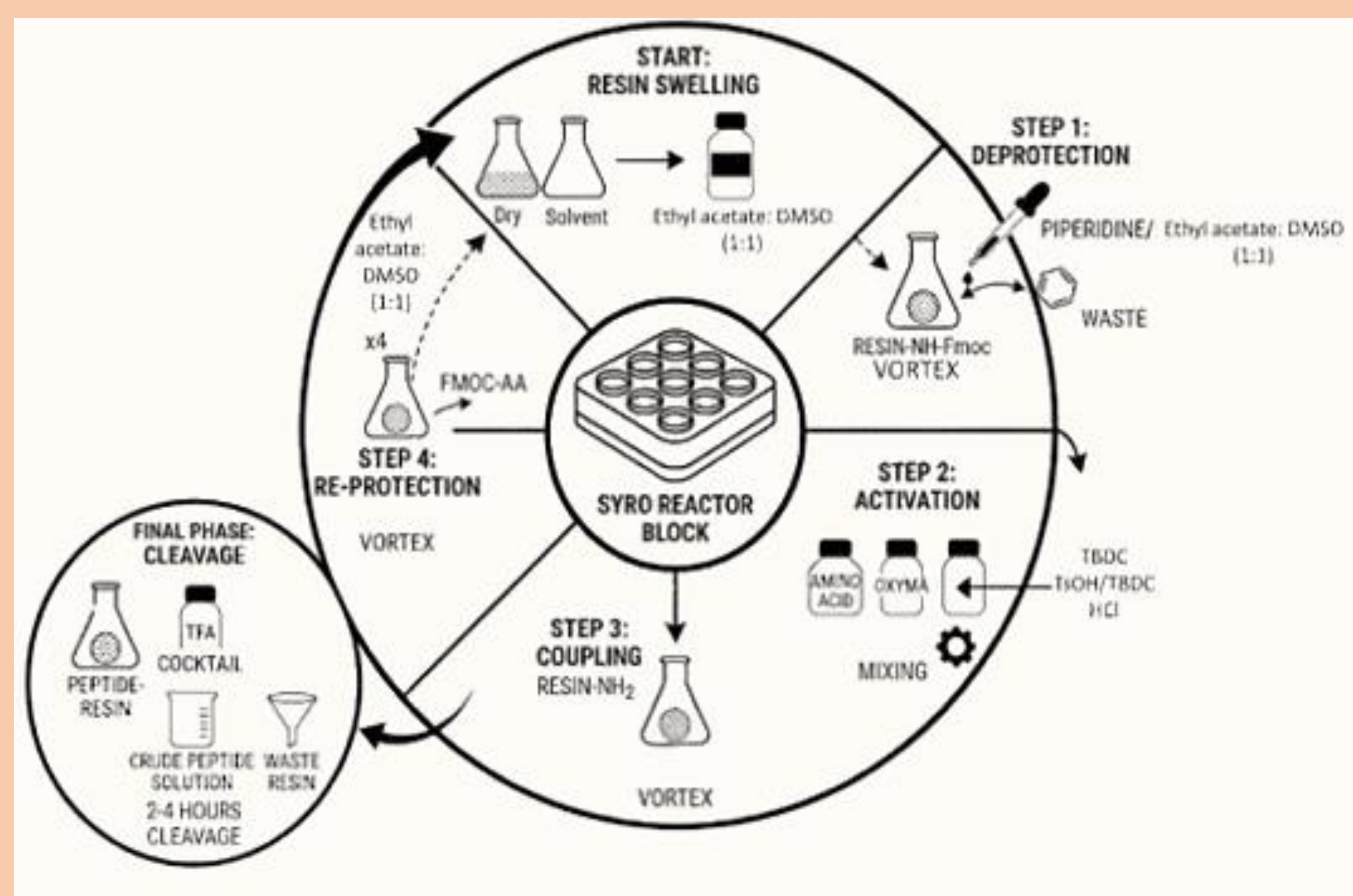


Resin Swelling in DMF / DMSO : Ethyl Acetate



Peptide load on the swelled resin before peptide cleavage.

Green Solid Phase Peptide synthesis



Results

CVP-118

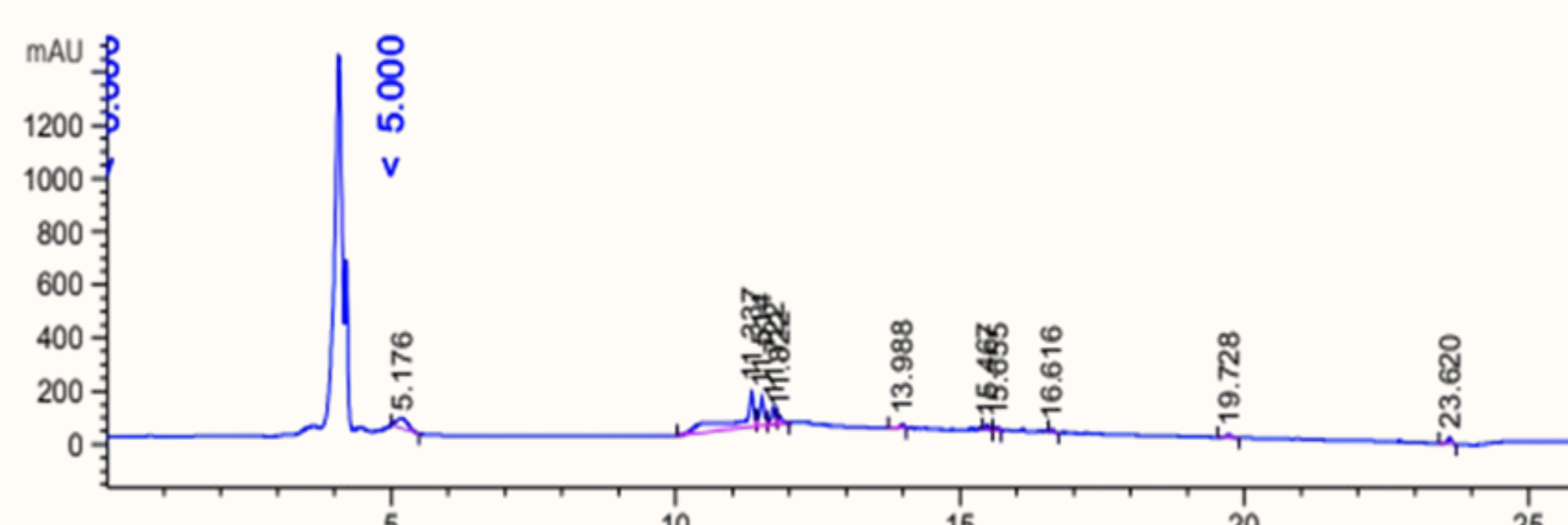


This is hydrophilic, serine rich short peptide presents significant synthesis hurdles, including resin-bound aggregation, aspartimide formation, and complex purification due to polar byproduct overlap.

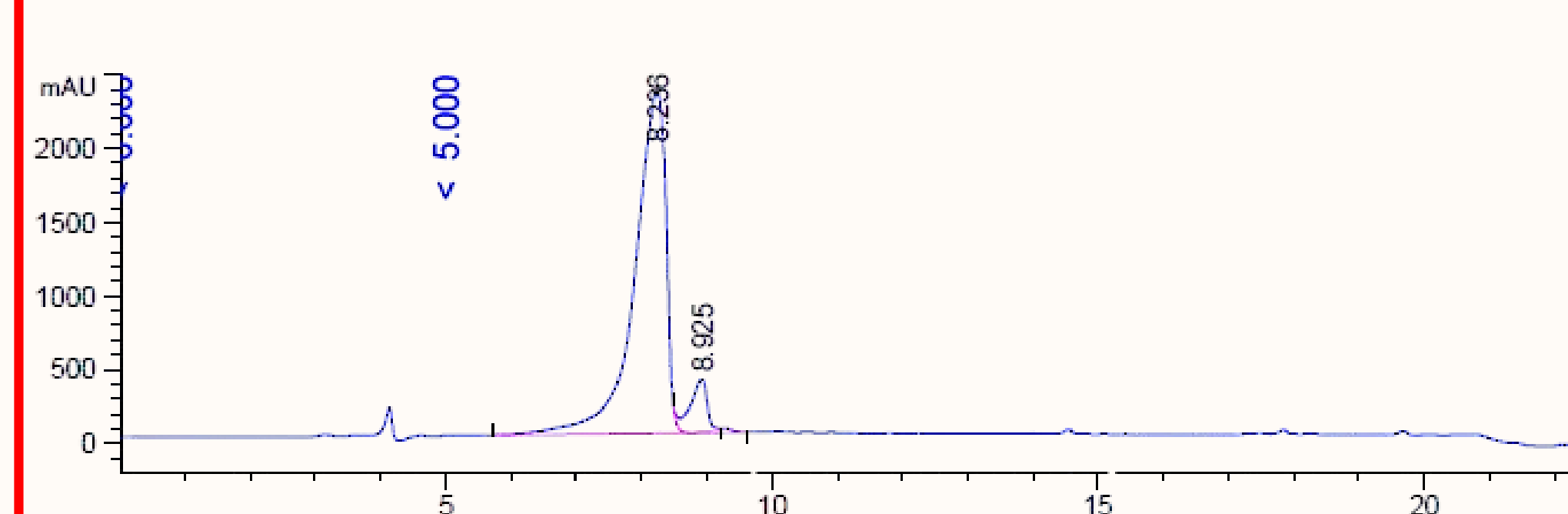
Green SPPS



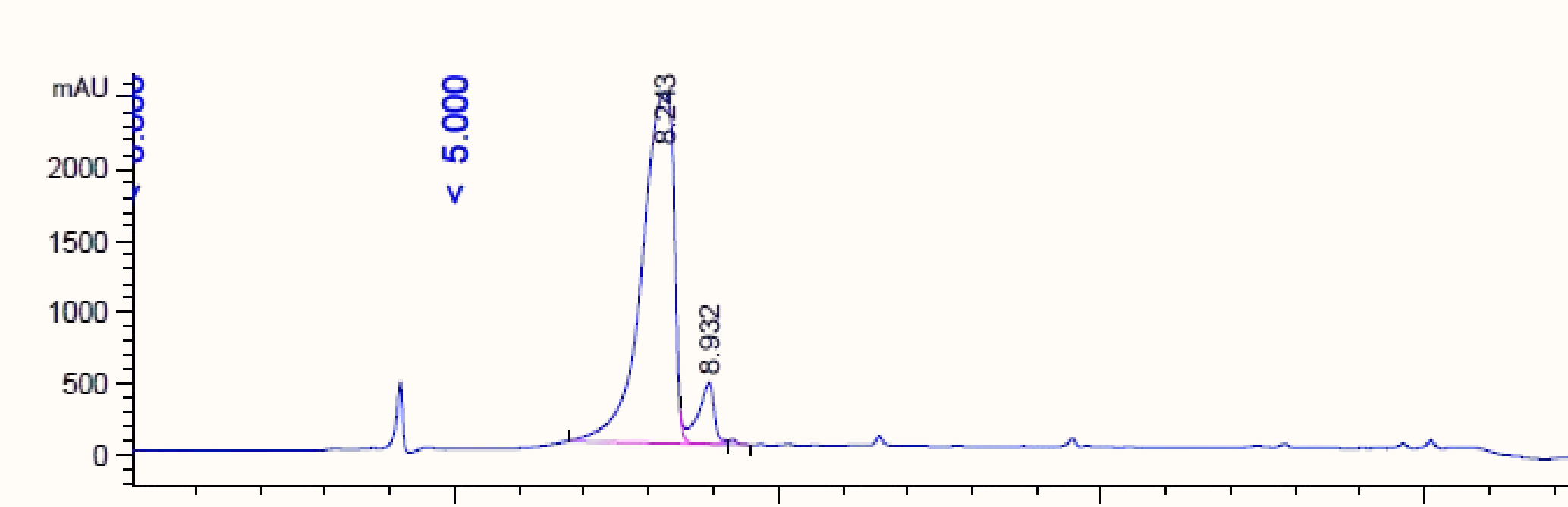
Conventional SPPS



TBDC HCl



TBDC TsOH



Compared to conventional SPPS (DMF/DIC), sustainable protocols utilizing **TBDC HCl** and **TBDC TsOH** significantly enhance coupling efficiency and crude purity, yielding sharp, well-defined product peaks at **8.236 min** and **8.243 min**, respectively.

CVP-127

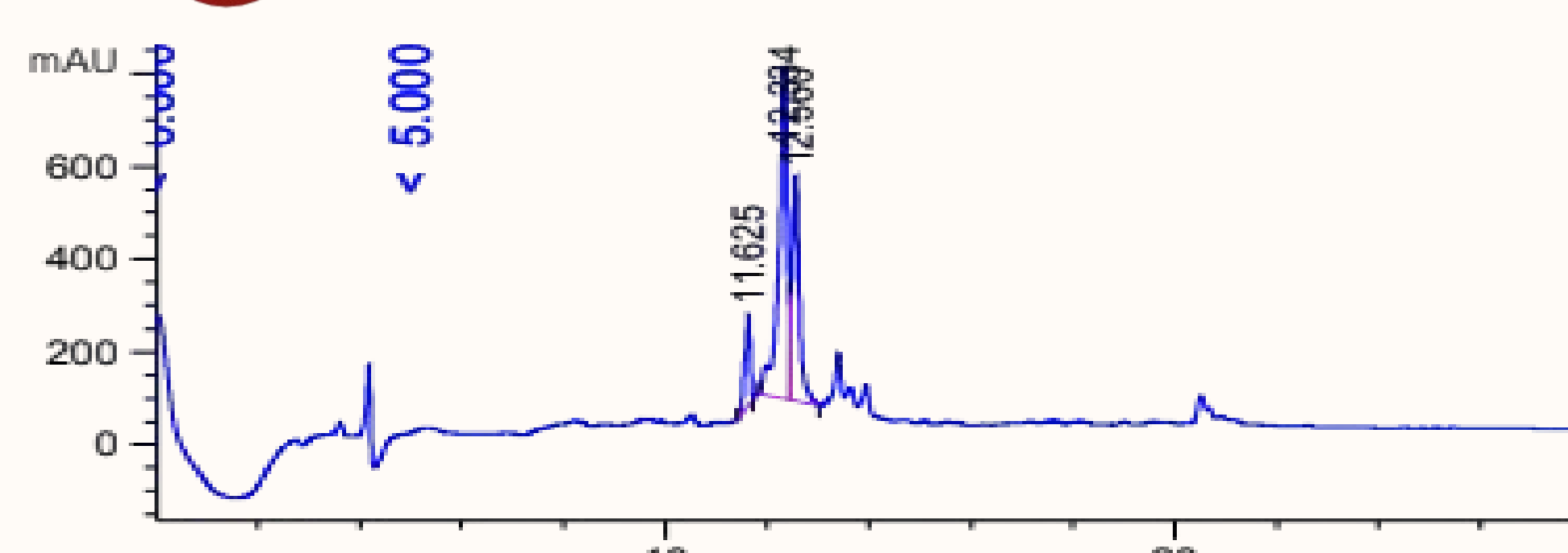


This is 29 amino acids long proline and serine rich peptide which significantly exacerbates proline-driven racemization risks due to prolonged coupling kinetics and extended base exposure caused by severe resin aggregation and steric hindrance.

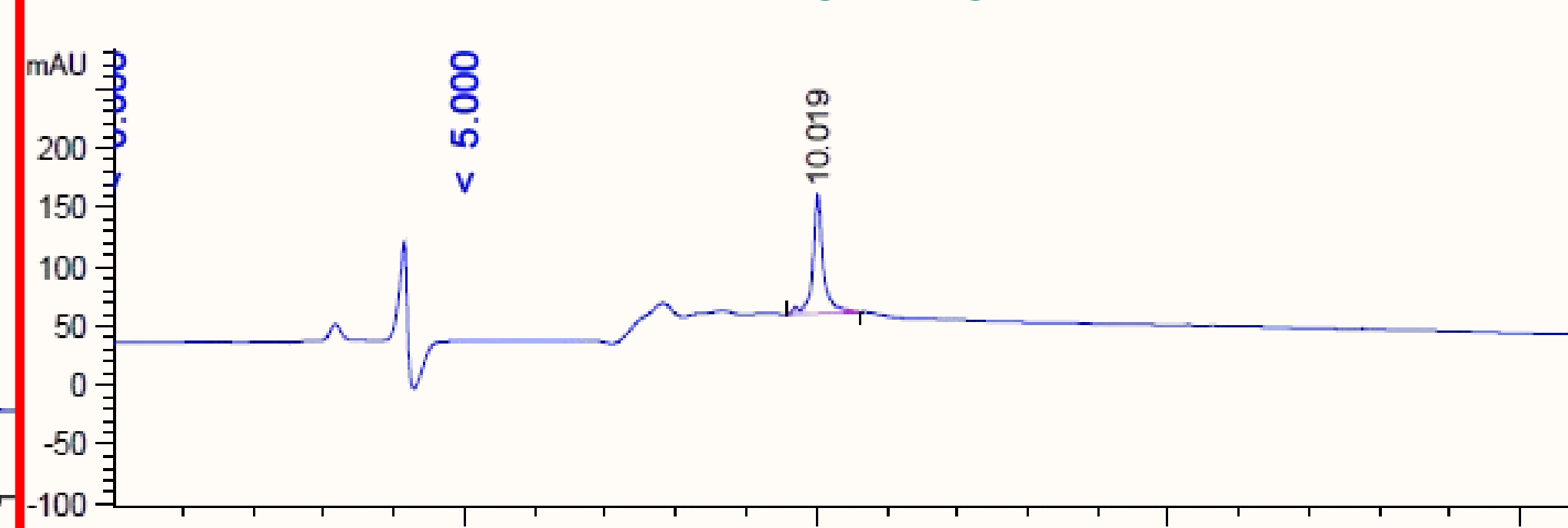
Green SPPS



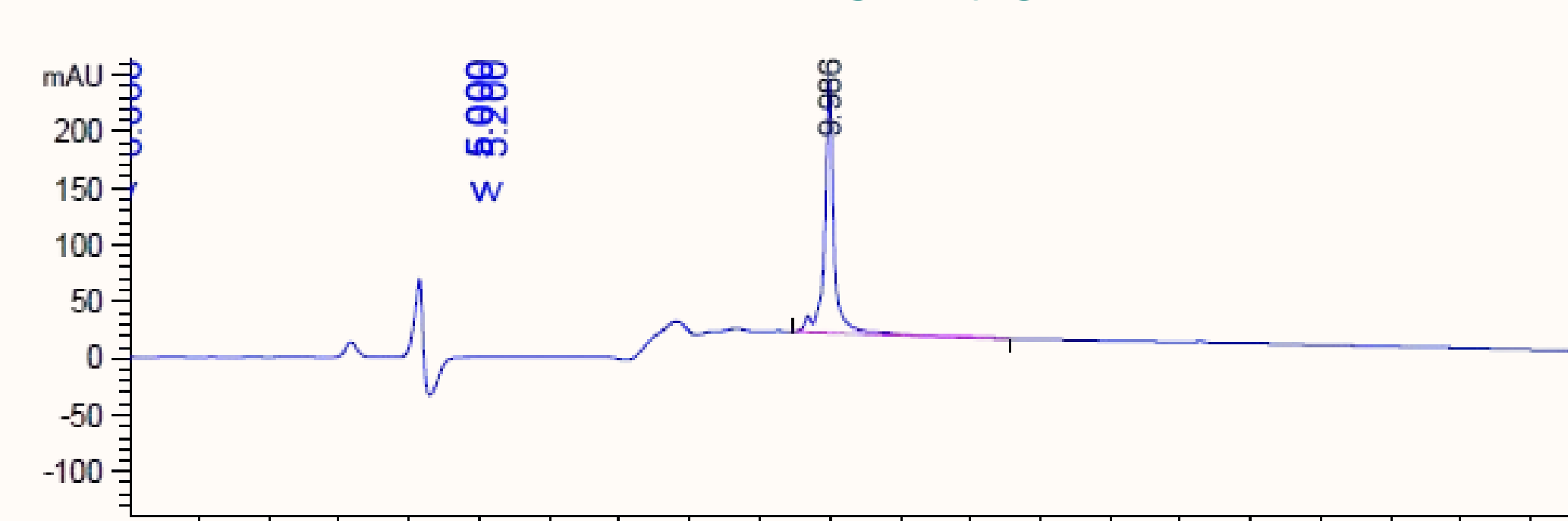
Conventional SPPS



TBDC HCl



TBDC TsOH



Synthesizing sterically demanding, proline-containing peptide sequences via conventional solid-phase peptide synthesis (SPPS) leads to severe epimerization, sluggish kinetics, and high byproduct formation, as evidenced by poorly resolved peaks between 11 and 13 minutes. Conversely, protocols utilizing **TBDC HCl** and **TBDC TsOH** effectively suppress proline-driven racemization and drive quantitative coupling, yielding sharp, high-purity single product peaks at approximately 10 minutes.

Conclusion

The implementation of sustainable green chemistry reagents, specifically **TBDC HCl** and **TBDC TsOH** overcomes the primary limitations of conventional SPPS. These modified protocols effectively suppress proline-driven epimerization, accelerate sluggish coupling kinetics, and eliminate complex byproduct profiles. Consequently, they provide a robust, high-purity, and eco-friendly alternative for both standard peptide assembly and challenging, sterically demanding sequences in automated peptide synthesis.