

Drop in solvents derived from glycerol can increase sustainability and efficiency of peptide synthesis

Vincent Freiburghaus^{1,§}, Tom Nelis^{2,§}, Tom Sorgius², Hidde Kolmeijer³, Javier Fernández-González³, Patrick Molliet², Étienne L.M. Vermeirssen⁴, Marie J. Jones², Antoine Brunel², Shasha Zheng², Gonzalo Guillén-Gosálbez⁴, Nina Hartrampf^{1,*}, Jeremy S. Luterbacher^{2,*}

¹ Department of Chemistry, University of Zürich, 8057 Zürich, Switzerland.

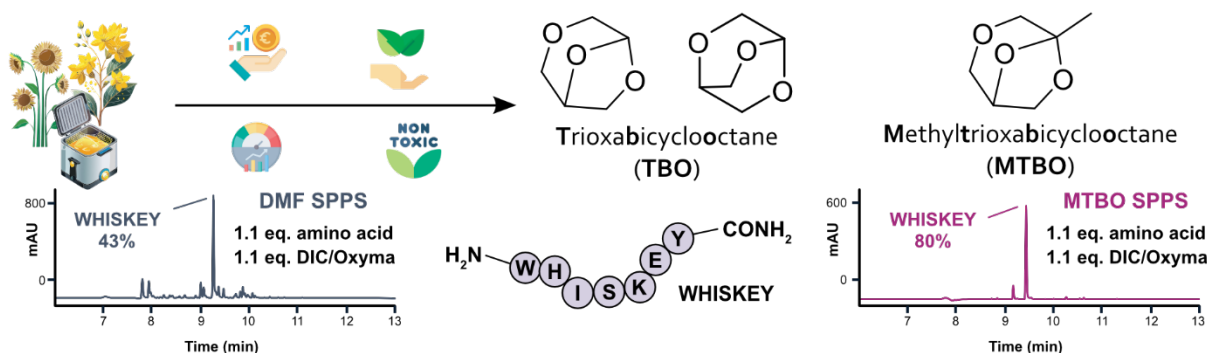
² Laboratory of Sustainable and Catalytic Processing (LPDC), Institute of Chemical Sciences and Engineering (ISIC), School of Basic Sciences (SB), École Polytechnique Fédérale de Lausanne (EPFL), Lausanne, Switzerland.

³ Institute for Chemical and Bioengineering, Department of Chemistry and Applied Biosciences, ETH Zürich, Vladimir-Prelog-Weg 1, 8093 Zürich, Switzerland.

⁴ Swiss Centre for Applied Ecotoxicology, Überlandstrasse, 133, 8600 Dübendorf, Switzerland.

Email: vincent.freiburghaus@chem.uzh.ch

Increasing demand for therapeutic peptides necessitates more sustainable manufacturing.¹ Solid-phase peptide synthesis (SPPS), the primary production method, has a high process mass intensity (PMI) due to heavy solvent consumption.² *N,N*-Dimethylformamide (DMF), the standard SPPS solvent,³ is classified as carcinogenic and reprotoxic, leading to EU restrictions since December 2023 and driving the search for alternatives.⁴ We present trioxabicyclooctanes (TBOs), bio-based, tunable, dipolar aprotic solvents derived scalably from glycerol. Following physicochemical and toxicological evaluations, TBO and methyltrioxabicyclooctane (MTBO) were identified as the best DMF replacements for SPPS. Both are fully compatible with standard workflows. MTBO allowed for efficient synthesis of short- and medium-length peptides while reducing Fmoc amino acid equivalents by up to 90% without compromising crude purity. Compatibility was also confirmed using automated flow SPPS on a PeptiPilot system. Life-cycle and techno-economic assessments verify the platform's sustainability and cost-competitiveness. These findings establish TBOs as practical, bio-based DMF alternatives and a major advancement toward green peptide manufacturing.



[1] Mullard, A. *Nature Reviews Drug Discovery*, **2023** <https://www.nature.com/articles/d41573-024-00001-x> (accessed 2024-01-18).

[2] Ivy Kekessie et al., *J. Org. Chem.*, **2024**, 89, 4261-4282.

[3] Merrifield, B. *J Am Chem Soc*, **1963**, 85 (14), 2149-2154.

[4] Sherwood, J.; Albericio, F.; de la Torre, B. G., *ChemSusChem*, **2024**, 17 (8), e202301639.