SEPTEMBER 23-27 2024
19BMOS
BRAZILIAN MEETING ON ORGANIC SYNTHESIS
BENTO GONÇALVES, RS - BRAZIL

Scaling up the Synthesis of *p*-mentha-2,8-dien-1-ol Under Continuous Photoflow Conditions

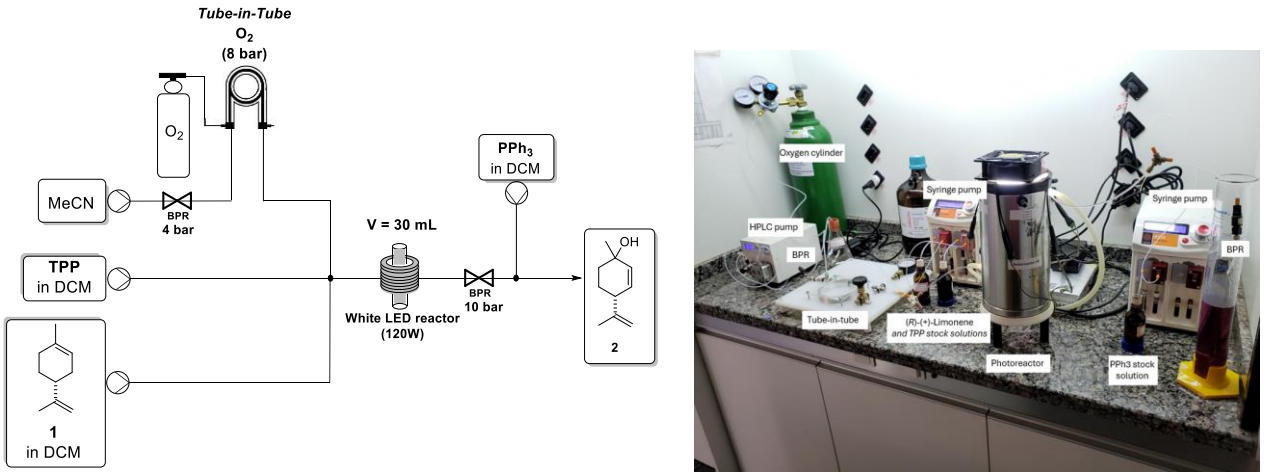
Tiago de O. Ramos[1], Felipe C. Braga[1], Rodrigo O. M. A. de Souza[2], Timothy J. Brocksom[1] and Kleber T. de Oliveira[1*]

1) Department of Chemistry, Federal University of São Carlos (UFSCar), 13565-905, São Carlos, SP, Brazil.
2) Institute of Chemistry, Federal University of Rio de Janeiro (UFRJ), 21941-909, Rio de Janeiro, RJ, Brazil
e-mail: kleber.oliveira@ufscar.br

Keywords: *Organic synthesis, continuous flow, photocatalysis*

ABSTRACT

We present the scale-up of the synthesis of *p*-mentha-2,8-dien-1-ol (**2**), a key intermediate for synthesizing cannabidiol and its derivatives.[1,2] Our methodology is based on the continuous flow photooxidation of (*R*)-(+)-limonene (**1**) to their hydroperoxide intermediates, followed by the *in-situ* reduction to the corresponding alcohols (Scheme 1). The setup consists of the saturation of acetonitrile with O_2 *via* a tube-in-tube reactor (8 bar) followed by the encounter of a stream of (*R*)-(+)-limonene (**1**) and another of *meso*-tetraphenylporphyrin in DCM. After mixing, the solution was irradiated by 120 W white LEDs in a 30 mL PFA photoreactor. Upon exiting the photoreactor, the resultant mixture was quenched with a stream of triphenylphosphine. The protocol was optimized to a 6-minute residence time with a maximum productivity of 6.5 g/day. A scale-up experiment was performed, processing 37.5 mmol of (*R*)-(+)-limonene (**1**) over 6 hours, resulting in 1.5 g of product.



Scheme 1: Scale-up protocol for *p*-mentha-2,8-dien-1-ol synthesis under continuous-flow conditions.[3]

ACKNOWLEDGEMENTS

The authors would like to thank the São Paulo Research Foundation FAPESP (grant numbers: 2020/06874-6 (K.T.O.), 2023/04020-8 (K.T.O.) and 2021/06110-9 (F.C.B.)) as well as the Conselho Nacional de Pesquisa - CNPq (K.T.O. research fellowship 303333/2022-7) and CAPES - Financial Code 001.

REFERENCES

(1) Devinsky, O.; Cross, J. H.; Laux, L.; Marsh, E.; Miller, I.; Nabbout, R.; Scheffer, I. E.; Thiele, E. A.; Wright, S. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. *New England Journal of Medicine* **2017**, *376* (21).

(2) Grotsch, K.; Fokin, V. V. Between Science and Big Business: Tapping Mary Jane's Uncharted Potential. *ACS Central Science*. **2022**.

(3) De Oliveira, K. T.; Braga, F. C.; Da Silva, F. L. N.; Ramos, T. O.; Rosa, J. G. H., Araujo, E. A.; Junior, N. F. C.; Wendler, E. D.; Beatriz, A.; de Souza R. O. M. A. and Brocksom, T. J. Batch and Continuous Flow Total Synthesis of Cannabidiol. *Chem. Asian J.* **2024**, e202400689