RESPONSE SURFACE MODELLING OF MICROWAVE ASSISTED BISCHLER-NAPIERALSKI REACTION: SYNTHESIS OF EUDOSTOMIN H

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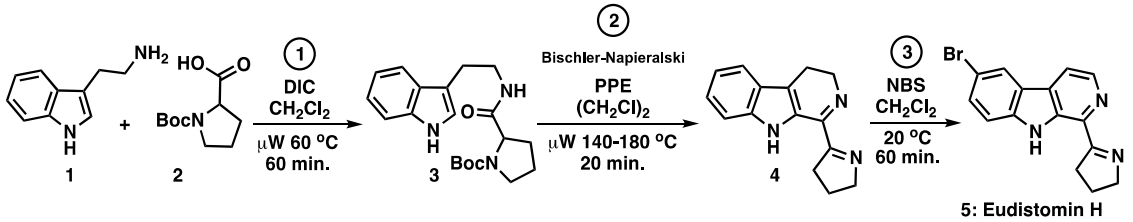
Eudistomin H emerged as a suitable synthon for a project in progress in our laboratory. For this project, we needed gram quantities of this compound. A total synthesis leading to the marine alkaloid Eudistomin H 5 has been previously disclosed[1], Scheme 1. The Bischler-Napieralski reaction[2], step 2, afforded a very low yield only. The other steps requested further development to reduce waste streams. In this context, we commenced a development and optimization study involving microwave irradiation as heating source. The introductory results spurred us to conduct a statistical experimental design for detailed investigation and first step optimization of reaction step 2. The obtained multivariate model was graphically presented as a contour map that was used to select optimal reaction conditions for the microwave assisted Bischler-Napieralski reaction. Overall, the total synthesis was substantially improved and optimized.



Scheme 1. Synthesis of Eudistomin H.

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[1] (a) Hino, T.; Ziping, L.; Seki, H.; Hara, R.; Kuramochi, T.; Nakagawa, M. *Chem. Pharm. Bull.* **1989**, *37*, 2596–2600. (b) Shemand, G. Q.; Baker, B. J. *Tetrahedron Lett.* **1994**, *35*, 4923-4926.

[2] (a) Bischler; A.; Napieralski, B. *Ber. Dtch. Chem. Ges.* **1893,** *26*, 1903. (b) Li, J.J. *Bischler–Napieralski reaction, Name Reactions, 4th ed.*, Springer: Heidelberg **2009**, 48-49.