Toward the Total Synthesis of *Daphniphyllum* Alkaloids: A fragment-based approach

Maxime VIGOUREUX[1], Zakaria MEFTAH[1], and Bastien NAY[1]

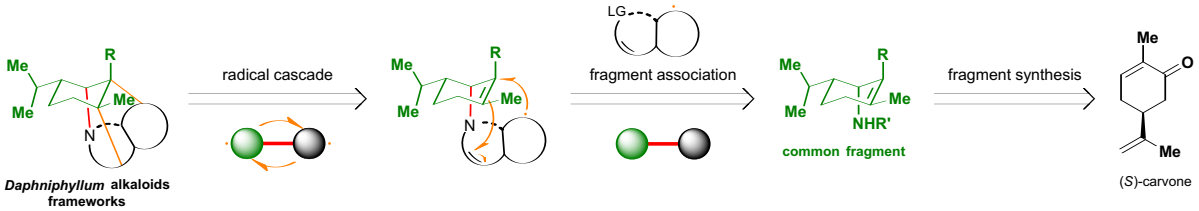
[1] *Ecole Polytechnique, Laboratoire de synthèse organique (LSO), 91120, Palaiseau, France*

E-mail: maxvig00@hotmail.com

The *Daphniphyllum* alkaloids are a large and structurally complex family of natural products, with more than 300 compounds. They became a classical target for synthetic chemists due to their structural complexity and their biological activities, including anticancer and anti-HIV properties.[1] Since the pioneer biomimetic work of Heathcock in 1986, more than forty total syntheses, as well as many studies toward their skeletons, have been reported.[2]

In this project, we are developing a unified fragment-based synthesis strategy that could be applied to one-third of these alkaloids, covering nine subfamilies, using a key radical cascade step. The strategy is based on the association of a common fragment, shared among the subfamilies, with a second part specific to each subfamily. The association will be followed by a radical cascade to build the molecular complexity.[3]

The common fragment has been designed and synthesized. It serves as a platform to access different *Daphniphyllum* frameworks. A preliminary study on a model system was carried out to better understand the key radical cyclization. Based on these results, the structure of the common fragment and the reaction conditions were adapted, allowing us to achieve the first radical cyclization. Current work is focused on exploring different skeletons through various radical cyclizations, radical cascades and on reaching the alkaloids. The synthesis of the common fragment, the radical study on models, and the key radical cyclization will be discussed in this presentation.



References

[1] S. Hanessian et al., *Chem. Rev.*, **2017**, *117*, 4104−4146 ; Zhong et al., *The Alkaloids*, **2021**, *85*, 113-176.

[2] (Heathcock bangers) C. H. Heathcock et al., *J. Am. Chem. Soc.* **1986**, *108*, 5650-5651 ; C. Heathcock et al., *Science*, **1990**, *248*, 1532−1534 ; (recent works) K. Namba et al., *Angew. Chem.*, **2025**, *137*, e202517671 ; A. Li et al., *J. Am. Chem. Soc*. **2025**, *147*, 31, 27137-27142 ; T. Sato et al., *Angew. Chem. Int. Ed.,* **2025**, 64, e202508062 ; X. She et al., *Org. Lett*. **2025**, *27*, 27, 7423-7427 ; D. Dixon et al., *Org. Lett*. **2025**, *27*, 11485−11490.

[3] S. Herzon et al, *Angew. Chem. Int. Ed*., **2021**, *60*, 1116–1150 ; K.C. Nicolaou et al., *Angew. Chem. Int. Ed.* **2006**, *45*, 7134 –7186 ; T. J. Maimone et al., *Nat. Prod. Rep*., **2018**, *35*, 174 ; P. S. Baran et al., *Angew. Chem. Novit*, **2026**, *2*, 1, e70017.