Targeted Exploration of Bioinspired Cascade Reactions: A One-Pot Total Synthesis of Nesteretal A

Axel Leblond*[1,2], Inès Houari[2], Yann Beauxis[3], Karine Leblanc[2], Erwan Poupon[2], and Mehdi Beniddir[2]

[1]Laboratoire d'Innovation Thérapeutique – université de Strasbourg, Centre National de la Recherche Scientifique – France

[2]Biomolécules : Conception, Isolement, Synthèse – Université Paris-Saclay, Centre National de la Recherche Scientifique – France

[3]Cibles Thérapeutiques et conception de médicaments – Centre National de la Recherche Scientifique, Université Paris Cité – France

Résumé

Nesteretal A, a representative of a novel class of cage-like metabolites, was isolated in 2019 by Yang *et al.* from the coral-derived actinomycete *Nesterenkonia halobia.*(1) This natural product exhibits an intriguing complex highly oxygenated structure including four intricated cycles and seven stereocenters, six of which are quaternary. The biosynthetic pathway proposed by the authors involving diacetyl as a plausible and unique precursor makes nesteretal A an interesting and challenging synthetic target for bioinspired total synthesis. From diacetyl, by a succession of self-aldolizations/hemiacetalizations catalyzed by (S)-proline mimicking an aldolase-type mechanism, we performed an expeditious one-pot total synthesis of nesteretal A.(2) In a context where atom, step, and redox economies are important, this single operation from costless diacetyl clearly competes with classical multistep total syntheses.(3, 4)

Versatility in the diacetyl auto-assembly prompted us to explore the "bioinspired metabolomes" generated "in the flask" using chemoinformatic tools such as MetWork.(5) This powerful *in silico* metabolization tool, based on a reaction toolbox and MS/MS spectra prediction, allowed us to illuminate the hypothetic biosynthetic pathway leading to nesteretal A, along with a wide chemical space including nesteretal A-like cage molecules. Among them, *iso*-nesteretal, a potentially not yet discovered natural product, was anticipated, targeted, and isolated.

This work falls within the scope of a trend where chemoinformatics and natural products chemistry are becoming closely linked(6) with an innovative and concrete application in total synthesis.

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Mots-Clés: total synthesis, natural products, chemoinformatics, cheminformatics, mass spectrometry, biosynthesis, biomimetic