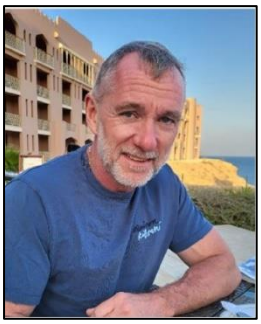

TOWARDS THE TOTAL SYNTHESIS OF ENACYLOXINE IIA

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The crisis of antibiotic drug discovery, combined with the increasing prevalence of bacterial antibiotic resistance, poses a significant threat to contemporary medicine. In this context, identifying new antibiotics that interact with new biological targets and providing access to them and their analogues through chemical synthesis, have become absolutely crucial.

The enacyloxins' antibiotic family gathers structurally unique polyketides first isolated in 1982 from the soil aerobe xanthomonadaceae Frateuria sp. W-315 (Figure 1),[1] and they were isolated again more recently from other sources.[2,3] In samples, enacyloxin-IIa (ENX-IIa, 2) is the most abundant of this family of natural products and only in 2007 was its exotic structure finally fully elucidated.[4] Most enacyloxins present an easily isomerizable chlorinated pentaenoic ester chain which bonds a cyclohexane head, variations in the structure concerning the C11-C19 zone.[5] ENX-IIa (2) displays antibiotic activity against both Gram-positive bacteria (S. aureus) and Gram-negative (B. multivorans, B. dolosa, A. baumannii, and N. gonorrhea) some being pan-resistant pathogens.[6] Remarkably ENX-IIa (2) is also active on Plasmodium falciparum.[7]

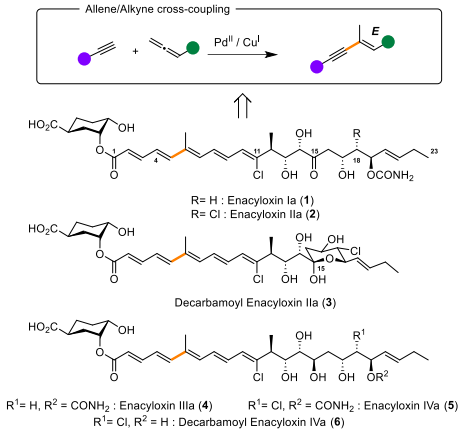

Figure 1. The enacyloxins' family, and the key allene/alkyne cross coupling

In 2021; our group embarked in the study of the total synthesis of ENX-IIa (2) resulting in an access towards most of the members of the ENX tribe. Of note that despite numerous previous efforts provided by other teams, no total synthesis within this family has ever been reported. The construction of the chlorinated polyene chain proved particularly challenging and significantly influenced the synthetic strategy. Among the key steps, we chose to implement the cross coupling of an allene with an alkyne using a palladium/copper dual catalysis which stereoselectively yielded an (*E*)-enyne under mild conditions with complete atom economy. This prompted use to investigate on the mechanism of this reaction, revealing an original catalytic cycle involving a palladium (IV) species, and an Pd-Cu heterodinuclear complex as the catalyst.[8] Notably, this reaction also enabled the total synthesis of other natural products of interest, including the antibiotic tiacumicin B. [9]

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