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Insights into the Biosynthesis of Cyclic Guanidine Alkaloids from Crambeidae Marine Sponges

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Abstract: Among the outstanding chemical diversity found in marine sponges, cyclic guanidine alkaloids present in species of the family Crambeidae are particularly attractive, first because of unique chemical features but also due to a broad range of biological activities. Despite a growing interest for these natural products as therapeutic agents, their metabolic pathway has not been experimentally investigated, and a hypothesis based on the reactivity of free guanidines is still largely accepted. The first *ex situ* feeding experiments using radiolabelled precursors performed on the Mediterranean sponge *Crambe crambe* suggests arginine and fatty acids as precursors in the metabolic pathway of crambescins. A subsequent bio-inspired approach supported the change of paradigm in the metabolic pathway of cyclic guanidine alkaloids. A large part of the chemical diversity of this family would therefore originate from a tethered Biginelli-like reaction between C-2/C-3 activated fatty acids and a central guanidinylated pyrrolinium.

The marine environment is now well recognized as a source of unique metabolites produced through diverse and original metabolic pathways. While some pathways of microbial origin have been unravelled in the last decades mainly due to advances in genomics,[1] the biosynthesis of entire families of natural products found in marine invertebrates has not been addressed experimentally yet.[2] Marine alkaloids have been identified as metabolites with high pharmacological potential, as exemplified by the marketing of the anticancer drug ecteinascidin 743 (aka trabectedin).[3] Of particular interest, cyclic guanidine alkaloids (CGA) present in some groups of sponges have shown an outstanding range of bioactivities.[4] More precisely, sponges of the genera *Batzella*, *Crambe* and *Monanchora* (Family: Crambeidae) are rich in CGA with unique chemical architectures like the bicyclic crambescins (*e.g.* crambescin A2-448 (**1**)), tricyclic batzelladines (*e.g.* batzelladine A (**2**)) or pentacyclic crambescidins (*e.g.* crambescidin 800 (**3**)) endowed with a broad range of antitumoral and antimicrobial activities (Figure 1).[5] The therapeutic potential of this family of natural products has been supported by some patents especially on crambescidin analogues.[6]

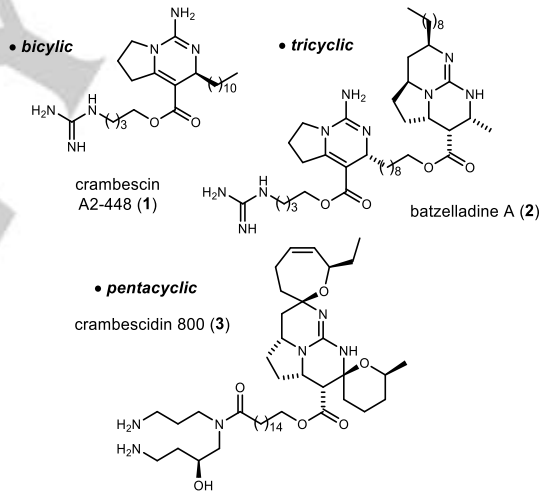

Figure 1. Illustrating the chemical complexity of key Cyclic Guanidine Alkaloids.

Yet, surprisingly, only hypotheses have been proposed for the metabolic pathways of these highly complex and bioactive CGA so far. The first hypothesis was put forward by the group of Snider in the 1990[ies] where a simple condensation of a guanidine on a polyketide chain might lead to the complex structures of ptilomycalin and crambescins (Scheme 1).[7] The success of efficient "biomimetic" total syntheses, especially from the groups of Snider and Overman, left no doubt on a "full polyketide origin" of these sponge alkaloids with a late condensation of a free guanidine onto a well suited oxidized carbon backbone.[8] This metabolic hypothesis has not been really questioned until recently, when an alternate proposition emerged from the isolation of unsaturated derivatives of crambescins from the sponge *C. crambe*.[9] Altogether, valuable clues led to reconsider the biosynthetic origin of these alkaloids and they include: i- the

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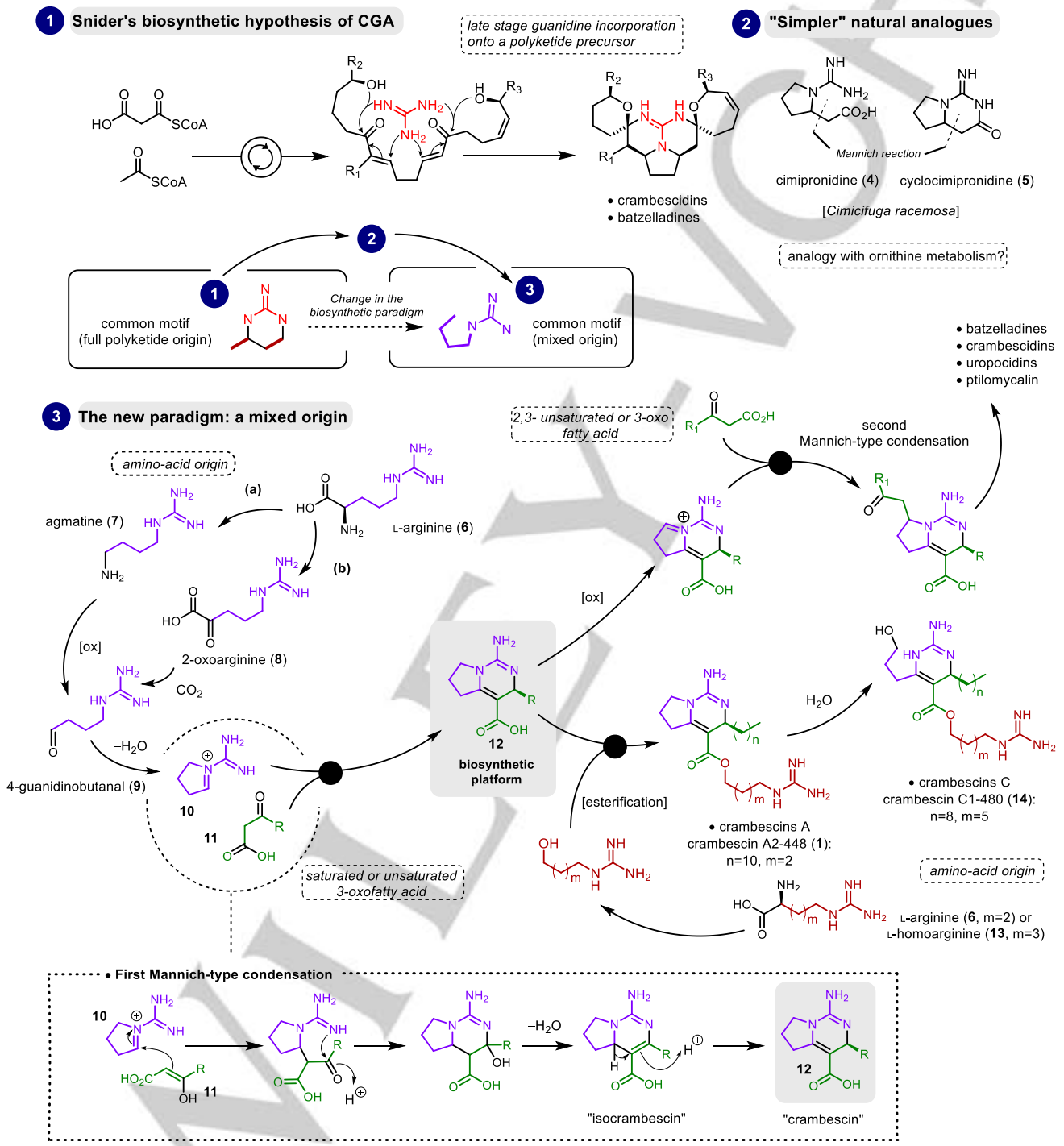
recurrent presence of a central and α-substituted guanidinopyrrolidine in CGA, ii- the inconsistency to establish the "Birch' C_2 patterning" of a classical polyketide origin in the Snider hypothesis and iii- the existence of simple and closely related guanidine alkaloids isolated from the plant *Cimicifuga racemosa*, cimipronidine (**4**), cyclocimipronidine (**5**).[10] Together with elegant total syntheses of batzelladines elaborated around key pyrrole/pyrrolidine scaffolds,[10] these observations set the scene for an alternative biosynthetic pathway closely related to the ornithine pathway of some alkaloids (Mannich-type α-alkylations of nitrogens).[11]



Scheme 1. Biosynthetic hypotheses for cyclic guanidine alkaloids from marine sponges: building of a new hypothesis.

The change of paradigm would thus consist in a mixed biosynthetic origin (Scheme 1): L-arginine as building block for a C4-guanidine unit connected to putative exogenous activated fatty acid precursors as depicted in scheme 1. In brief, L-arginine

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(**6**) may provide the central platform guanidinopyrrolinium **10** through a sequence of oxidative deamination decarboxylation cyclization steps, involving agmatine (**7**) or 2-oxoarginine (**8**) and 4-guanidinobutanal (**9**). This latter pyrrolinium salt may then represent a perfect electrophile for Mannich-type reactions involving C-2 activated oxo-fatty acids of type **11** (explaining thereby the observed diversity of side chains in the series). Subsequent cyclisation through a tethered Biginelli condensation[12] would ensure the formation of the central 1-amino-pyrrolo[1,2-*c*]pyrimidine (**12**) as a central biosynthetic platform of CGA. Final esterification with diverse guanidinylated alcohols that may also arise from L-arginine (**6**) or homoarginine (**13**) would provide crambescins A and then crambescins C (*e.g.* crambescin C1-480 (**14**)) after hydrolysis of the pyrrolinium. The transformation of crambescin A into C could arise from an oxidation of the nitrogen into an iminium followed by hydrolysis into an aldehyde and a final reduction into a primary alcohol. This transformation is supported by biotransformations of amino derivatives.[13]

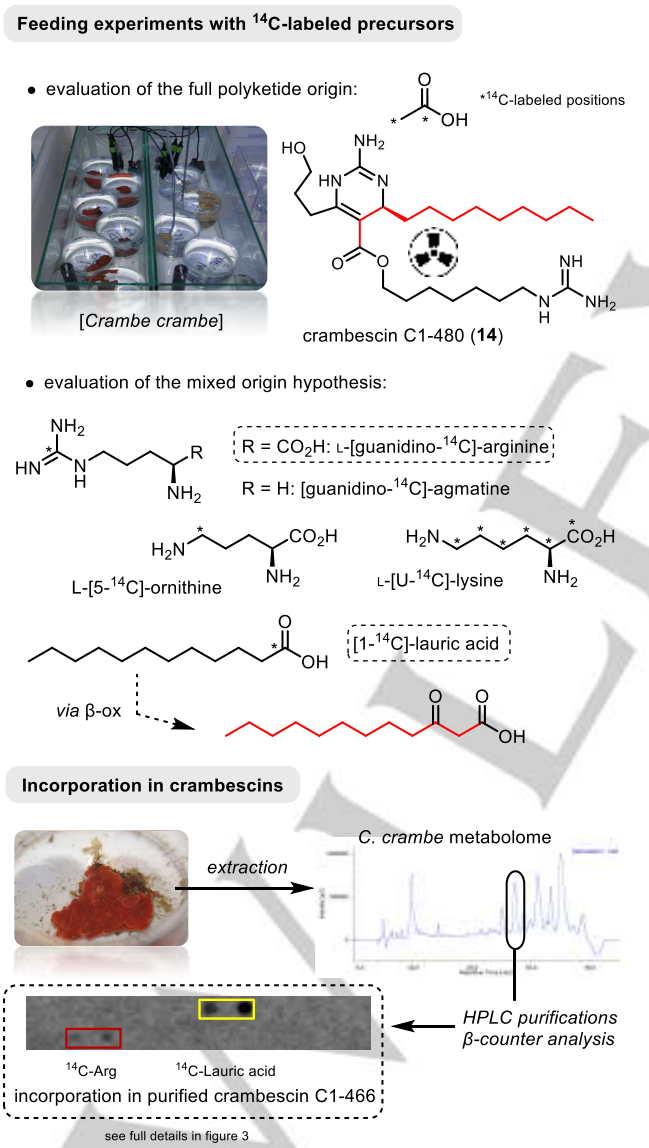

Figure 2. Design of the radiolabeled feeding experiments on *C. crambe*.

These two distinct hypotheses prompted us to design the first feeding experiments with labelled precursors on a sponge containing CGA (Figure 2).[2a, 14] The encrusting sponge *Crambe crambe* (Family: Crambeidae) was selected as an appropriate model to this end as it is widespread in the Western Mediterranean sea, and also well known to produce both crambescins and crambescidins CGA.[2a, 14] Crambescin C1-480 (**14**) was chosen as the targeted CGA to track in the complex alkaloid metabolome due to its high concentration and ease of HPLC purification. Specimens of *C. crambe* were collected with their substrate to avoid any stress and maintained healthy in open system aquaria. Radiolabelled precursors were selected for feeding experiments, as previous studies with sponge natural products demonstrated their suitability due to a much higher detection sensitivity compared to stable isotopes.[15] Inspired by current hypotheses but also the availability of radiolabelled precursors, the following ^{14}C labelled precursors were selected: L-[guanidino-^{14}C]arginine, [guanidino-^{14}C]agmatine, L-[U-^{14}C]lysine, L-[5-^{14}C]ornithine, [U-^{14}C]acetic acid, and [1-^{14}C]lauric acid. Briefly, lysine and ornithine were chosen as they represent the most common starting precursors of non-aromatic alkaloids. Arginine (**6**) was selected as a provider of the guanidine moieties of CGA, and agmatine (**7**) as a more advanced precursor even if two pathways are plausible to convert arginine into 4-guanidinobutanal (**9**) (Scheme 1, pathways a and b). Finally, acetic acid was tested according to the Snider route involving polyketides. In parallel, labelled lauric acid was chosen as the putative exogenous fatty acid precursor (12:0) of crambescin C1-480 following the mixed origin hypothesis. The use of beta-imager detection ensured the highest sensitivity for the detection of radiolabelled derivatives deposited on a TLC plate. Using two replicates for each precursor and two purification steps with different HPLC columns, radiolabelled lauric acid and arginine were unambiguously incorporated into the targeted crambescin C1-480 with specific activities of 36 and 11 Bq.nmol^{-1} respectively after the second HPLC purification (Figures 2 and 3). None of the other tested precursors disclosed a stable specific activity after the second purification therefore suggesting a low or no contribution to the metabolic pathway of CGA. The clear incorporation of lauric acid labelled at C-1 into **14** supports the mixed origin hypothesis in the biosynthesis of CGA as no radioactivity was evidenced with [U-^{14}C]acetic acid. Even if these two metabolites are biosynthetically linked, this result reveals a direct and exogenous incorporation of lauric acid into CGA and therefore supports our new hypothesis. The incorporation of arginine labelled at the guanidine part suggests a key role of this amino-acid in the metabolic pathway of CGA. Guanidine is not known to be produced directly from arginine as the hydrolysis of arginine releases urea. Therefore, the positive result with arginine i) rules out the Snider hypothesis where guanidine is proposed to condense directly on a polyketide chain; ii) supports the new hypothesis where arginine is the source of the guanidine moiety in CGA but also supplies some additional carbons to their structures. In addition, the diversity of fatty hydrocarbon chains of CGA can now be explained as a result of the diversity of surrounding fatty acids available.

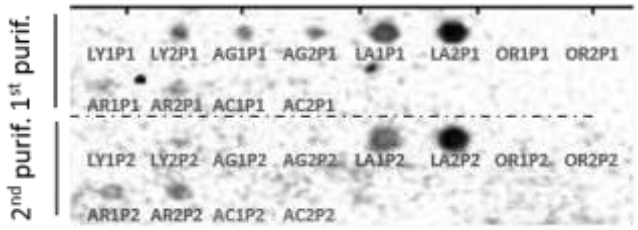

Figure 3. Beta-imager counting (36 h) of the radioactivity associated with Crambescin C1-466 after the first purification (Ending by P1) and the second purification (Ending by P2) for duplicate experiments using the ^{14}C-radiolabelled precursors: lysine (LY), agmatine (AG), lauric acid (LA), ornithine (OR), arginine (AR) and acetic acid (AC).

The contribution of ornithine and lysine in the metabolic pathways of CGA has not been evidenced even if the level of sensitivity can be responsible for a lack of radiodetection in **14** but it highlights the key role of arginine in the biochemical pathway of the nitrogenated parts of CGA. The absence of radioactivity detected with the more advanced precursor agmatine (**7**) also labelled at the guanidine part was not consistent with the first pathway (a) and would rather suggest the pathway (b) and the involvement of 2-oxoarginine (**8**) into the production of 4-guanidinobutanal (**9**) (Scheme 1).

With strong experimental evidence of a mixed origin for the CGA biosynthesis, we investigated the chemical feasibility of the hypothesis through a bio-inspired synthesis of crambescins. The appealing tethered Biginelli-type cascade reaction prompted us to investigate this key reaction to build the heterocyclic core of CGA. Crambescin A2-448 (**1**) was chosen as a convenient target with a rather simple 1-amino-pyrrolo[1,2-*c*]pyrimidine core (Figure 1). Lessons learnt from related works led us to envisage straightforward biomimetic approaches respecting as closely as possible the biosynthetic hypothesis.[16] Therefore, an oxidative decarboxylation of arginine (**6**) was investigated to generate the highly reactive pyrrolinium salt **10** *in situ* (Scheme 2). Silver(II) picolinate[17] was chosen according to Lee's procedure and permitted to perform three biomimetic transformations in a single pot: i- oxidative decarboxylation ii- deamination into aldehyde **9**, and iii- intramolecular dehydration into **10**. To achieve a convergent synthesis, the suitable fully functionalized *β*-keto ester **15** was concomitantly prepared. A bio-inspired homologation of lauric acid (**16**) was successfully envisaged: monobenzylester malonate **17** (as a surrogate of malonyl-CoA) was engaged in a Knoevenagel-Claisen-type reaction/decarboxylation sequence providing **18** in good yield. Hydrogenolysis of this latter provided an unstable *β*-ketoacid **19** which was esterified with the protected guanidino-alcohol **20** (prepared by guanidinylation of aminobutanol **21**). From the two entities **10** and **15**, the key step could be investigated. The projected cascade sequence proceeded smoothly under optimized buffered conditions (morpholine/acetic acid 1:1 mol/mol) in trifluoroethanol at reflux, allowing for the construction of the bicyclic system of crambescins in a single operation. Indeed, purification by preparative HPLC provided the expected isocrambescin A2-448 (**22**) validating thereby the entire cascade of reactions from L-Arg. The apparently trivial final isomerization into **1** was largely investigated using a set of diverse conditions (acidic, basic, ruthenium catalysis…) and was proven to be difficult to mimic. Anyhow, a slow oxidation process into didehydrocrambescin A2-448 (**23**) was observed that could be accelerated under air and light exposure.[18] Finally, a subsequent reduction of the aromatic analogue with a 5:1 TFA/Et_3SiH mixture led quantitatively to crambescin A2-448 (**1**, 60% after HPLC purification), gratifyingly confirming a higher thermodynamic stability for this isomer. A feedback from the experimental isomerization issue to biosynthetic considerations may let us consider that the real fatty acid precursor involved in the condensation would be a C2-C3 unsaturated fatty acid rather than the 3-oxo derivative (see Supplementary Information for a final slight modification of the scenario).

Based on this successful transformation, we propose to break down the chemical structure of more complex CGA in a similar manner. Indeed, the tricyclic baztelladines and pentacyclic crambescidins congeners might originate from a subsequent tethered Biginelli condensation on the other side of the pyrrolidine nitrogen affording the observed 5,6,9-triazaacenaphthylene as depicted on scheme 1 and as beautifully anticipated in Herzon total synthesis of batzelladine B.[11] These results give valuable insights into the metabolic pathway of an entire and bioactive family of sponge natural products suggesting a new construction of alkaloids through successive tethered Biginelli type reactions. They pave the way for the elucidation of an alternate pathway in non-aromatic alkaloids and will inspire biochemists and molecular biologists to target the genes and enzymes responsible for the key depicted transformations.

Acknowledgements

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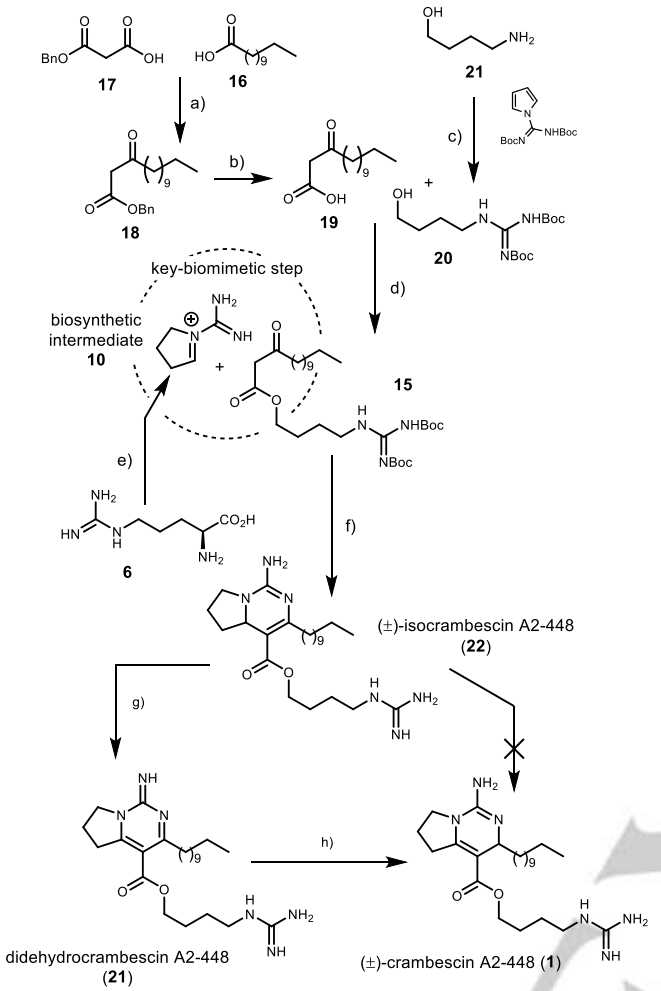

Scheme 2. Bio-inspired synthesis of crambescin A2-448 following the mixed biosynthetic origin chemical logic. Reaction conditions: a) CDI, *i*PrMgCl, THF, 0 °C then r.t., 63%; b) Pd/C, H_2, MeOH, r.t., quantitative; c) DIPEA, formamide, dioxane, r.t. 68%; d) DCC, DMAP, DCM, 0°C then r.t., 54%; e) $Ag(pic)_2$, H_2O, 70 °C, f) AcOH, morpholine, Na_2SO_4, TFE, reflux, 5 days, 16% (2 steps); g) aq. HCl (1 M), hν, 84 %; h) TFA : Et_3SiH (5:1 *v/v*), r.t. 60%.

Keywords: Biosynthesis • Marine Sponges • Cyclic Guanidine Alkaloids • Feeding experiments • Biomimetic synthesis

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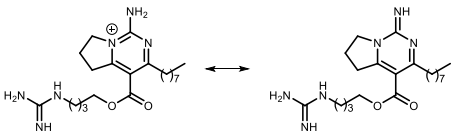

dehydrocrambescine A2-488 [*Monanchora* n. sp. 4696]

Following this, a close analysis of *C. crambe* metabolome, permitted us to isolate and fully characterized dehydro-crambescin A2-446 as also a "natural product". The artifactual character of such over-oxidized analogs is clearly to be envisaged.

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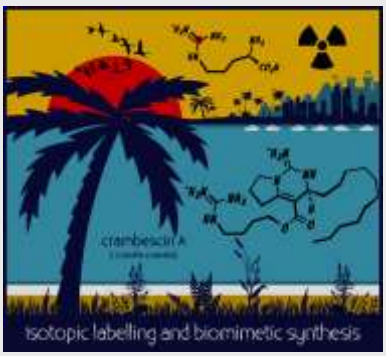
An unprecedented biosynthesis study on the marine sponge *Crambe crambe* permitted to suggest a mixed origin (fatty acid/arginine) for crambescins. The chemical logic of the new scenario was ascertained by a straightforward bio-inspired synthesis of crambescin A2 and could pave the way for a unified metabolic pathway of cyclic guanidine alkaloids.



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Changing the Paradigm in the Biosynthesis of Cyclic Guanidine Alkaloids from Crambeidae Marine Sponges