>20 known natural substances:

aplysinopsin and congeners

Spontaneous Biomimetic Formation of (\pm) -Dictazole B under Irradition with Artificial Sunlight^{**}

Adam Skiredj, Mehdi A. Beniddir, Delphine Joseph, Karine Leblanc, Guillaume Bernadat, Laurent Evanno,* and Erwan Poupon*

Abstract: Guided by biosynthetic considerations, the total synthesis of dictazole B is reported for the first time. Experimental evidence for an easy access to challenging cyclobutane alkaloids of marine origin, which are often postulated to be biosynthetic precursors of more complex structures, is provided.

The aplysinopsins, a family of indolic marine natural products with a common biosynthetic origin, were isolated from several sponges and stony corals.^[1] Three types of skeletons are encountered in nature (Figure 1): 1) aplysinopsin-type monomeric structures (see the structures of aplysinopsin (1) and its brominated analogues 2 and 3 in Figure 1),^[2] 2) cycloaplysinopsins, which are tetrahydrocarbazole-type dimeric compounds (see cycloaplysinopsin A (4) and dictazoline C (5),^[3,4] and 3) intriguing spiro-fused cyclobutanes (dictazoles A (6) and B (7)).^[5] These compounds mainly differ in the bromination state of the indole moiety and the Nmethylation patterns of the creatinine heterocycle. A stereochemical analysis also revealed interesting facts, as variable E/Z ratios were observed for the monomeric aplysinopsins.^[6] Furthermore, the cycloaplysinopsins were found to be of low enantiopurity, and the substituents in the polycyclic structures displayed various spatial arrangements.^[7] Interestingly, most of these compounds were isolated from samples that were collected in shallow waters (see below).^[8]

Despite being highly appealing at first sight, the previously postulated Diels–Alder cycloaddition^[9] was questioned when dictazoles, which may arise from an initial [2+2] reaction, were isolated and presented as plausible intermedi-

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aplysinopsin series

 $\textit{Figure 1.}\ Overview of the structural diversity of the aplysinopsin family.^{[14]}$

ates towards their tetrahydrocarbazole counterparts by ring expansion with piecemeal experimental evidence (Scheme 1).^[10] Recently, the key [2+2] photocycloaddition step was thoroughly discussed by Baran and co-workers.^[11] Such processes have remained a challenge in total synthesis, in particular, when the resulting cyclobutane structures have been postulated as biosynthetic intermediates on the way to even more complex rearranged structures.^[10]

Our interest in biomimetic strategies has led us to investigate particular cases of "molecular" self-assembly,^[12] which allowed us to observe the spontaneous formation of natural substances from simple reactive intermediates.^[13]





Scheme 1. Biosynthetic hypothesis.

Hence, the "aplysinopsin cascade" process also attracted our attention.

Therefore, the three monomeric aplysinopsins 1-3 were prepared in a single step from 3-formylindole derivatives (8 or 9) and the suitable creatinine (10 or 11)^[14] to set the stage for the dimerization studies (Scheme 2). At first, the abovementioned Diels-Alder cycloaddition was investigated with monomer 1 under different conditions, including heating for



Scheme 2. Synthesis of monomeric aplysinopsin derivatives. Reaction conditions: a) MeI, EtOH (>95%); b) Bunsen flame, neat (59%); c) piperidine, reflux (41%).

several days in DMF, use of $SbCl_3^{[15]}$ and the Ledwith–Weitz aminium salt $(SbCl_6N(p-BrPh)_3)$,^[16] or ultra-high pressures, but the desired transformation was not observed.^[17,18]

Despite several words of warning from the literature, we embarked on studying the alternative [2+2] photocycloaddition reaction. We rapidly confirmed the results of previous investigations,^[4c,6] as E/Z isomerization was observed when a solution of **1** was exposed to irradiation. Taken together, these results could have appeared discouraging, but a subtle detail markedly influenced the outcome of this project.

In fact, when running a routine LC/MS analysis of a solid sample of **1** (that had stood for several weeks under sunlight in the laboratory), we observed for the first time a small peak in the chromatogram that is related to both a doubly charged $[M+2H]^{2+}$ ion and a monocharged $[M+H]^+$ ion, excluding the possibility of a mass-source dimer (In situ generated MS ions corresponding to $[2M+H]^+$ not related to real dimers).^[19] This peak could correspond to a new dimeric entity, but was barely isolable at this stage. Several months were needed to clarify and finally propose suitable conditions to obtain a small amount of conversion in the solid state and identify the new compound, even though the substrate/product ratio was hardly reproducible, especially upon scale-up.^[20] Gratifyingly, the structure appeared to be cyclobutane 12, which was confirmed by NMR spectroscopy (see below), and the best conditions entailed the use of artificial light that recreates the irradiation with intense sunlight.[21] Many experimental details had to be resolved to provide a reliable procedure towards 12 and, as anticipated, its congeners, including dictazole B (7). Another fortuitous observation rapidly turned into a crucial discovery. Highly concentrated solutions of 1, which mimic the high concentrations that may arise when precursors are sequestered in confined compartments or enzyme active sites in living cells, were studied. Monomeric 1 was dissolved in DMF (5 mm), placed in a crystallizing dish as a thin film, and irradiated with the artificial light for one night. To our delight, one day later, the solution had evaporated to dryness, and analysis of the solid residue revealed a reproducible 20% conversion into 12.^[22] Solvents, concentrations, additives, and illumination time were among the parameters that had to be optimized. DMF appeared to be the only suitable solvent for the dimerization.^[23] Among many additives, copper(I) triflate^[24] satisfyingly improved the dimerization up to 40% conversion. The most intriguing experimental aspect resides in the fact that as long as 1 is in solution in DMF very little dimerization occurs, whereas it immediately takes place in the solid state, which suggests a crucial self-organization step upon crystallization. A finely tuned and reproducible method was devised that also avoids the degradation of 12 by retro-dimerization when it is irradiated in the solid state for longer periods of time. The process was then extended to the synthesis of brominated analogue 13, for which a similar ratio of dimerization was observed. Formylindoles 8 and 9 were also formed in the course of both reactions: Interestingly, they are also known as natural products and have already been co-isolated with aplysinopsins from sponges^[25] (see LC/MS chromatogram in Scheme 3).

One of the expected drawbacks of a [2+2] photocyclization^[26] is the lack of selectivity, which has been extensively discussed in the literature, for example, by Baran and coworkers.^[11] Templated processes, including topochemical, supramolecular, and biocatalytic approaches, to overcome this major issue therefore constitute a currently appealing topic of research.^[27] In our case, the photochemical [2+2]cycloaddition of the *N*-methylcreatinine containing *E* monomers **1** and **2** stereoselectively yielded the *anti* head-to-tail photodimers **12** and **13**, respectively, when high local concentrations were achieved by sunlamp-assisted solvent evaporation. The predominant formation of *anti* head-to-tail diastereomers is in accordance with the hypothesis that topochemical control of the photodimerization occurs through the stacking of a centrosymmetric pair of neighboring monomers.

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Scheme 3. Solid-state dimerization under irradiation with artificial sunlight. Reaction conditions: A solution of the starting material in DMF (5 mM) was allowed to concentrate, CuOTf toluene complex (0.5 equiv), 14 h (**12**: 40%; **13**: 35%). LC/MS chromatogram of the described reaction (see the Supporting Information).

An investigation of the effects of the Lewis acid complexation upon photodimerization showed that irradiation of a 2:1 monomer CuOTf complex significantly enhanced the efficiency of the [2+2] cycloaddition without modifying the regio- and stereoselectivities. In fact, complexation with CuOTf may move the head-to-tail stacked pair of monomers closer together, thereby shortening the distance between the reactive double bonds. Finally, close analysis of a previous crystallographic study of two synthetic aplysinopsin analogues not only mirrored our findings, but also opened the way to an improved understanding of the process.^[28] In short, first, crystals were obtained from crystallization in DMF with a molecule of DMF incorporated into the lattice; second, a perfect head-to-tail anti arrangement between two adjacent sheets imposes a geometry that is highly favorable for the light-induced [2+2] reaction.

The total synthesis of dictazole B (7) was the next challenge. Because of its pseudodimeric structure ([2+2] cycloaddition between 2 and 3), statistical couplings will be

observed, and unfavorable self-organization could be feared. The heterodimerization process was first evaluated with the fully methylated derivatives 1 and 2 with CuOTf as the additive and gave the expected statistical distribution in favor of 14 over 12 and 13 (Scheme 4). The relative *anti* configuration of the indole moieties that are appended to the cyclobutane framework was clearly demonstrated in the course of the structure determination of 14. Subsequent



Scheme 4. Heterodimerization reactions. Reaction conditions: a) DMF, *hν*, **1** (1 equiv), **2** (1 equiv), CuOTf toluene complex (1 equiv), 14 h; **14**: 19%; **12**: 11%; **13** co-eluted with **8**. b) DMF, *hν*, **2** (1 equiv), **3** (1 equiv), Bi(OTf)₃ (1 equiv), 14 h; dictazole B (7): 14%; **13**: 19%.

exposure of a 1:1 mixture of 2 (N,N-dimethylated) and 3 (Nmonomethylated) to light led to new challenges. At first sight, CuOTf was found to only allow the dimerization of fully methylated aplysinopsins, as the conversion of 2 and 3 into 7 was minute (in fact not better than for the same reaction without CuOTf). Therefore, new reaction conditions had to be established. An understanding of the inherent topology and innate reactivity of 3 was needed. The pseudo-aromatic character of the α,β -unsaturated creatinine moiety may explain the failure of the photodimerization of 3. In fact, a particular mesomeric form of the imidazoline moiety illustrates that for the [2+2] cycloaddition, **3** is the least reactive precursor of the series because of deconjugation of the C8/C9 double bond and facile E/Z photoisomerization.^[29] Hence, some other Lewis acids were evaluated, and the weak Lewis acid bismuth(III) triflate significantly enhanced the conversion into 7 and was thus selected as the best additive to initiate the regio- and stereoselective cross-dimerization.^[30,31] With these conditions in hand, condensation of 2 and 3 was finally possible and delivered dictazole B with 14% conversion along with 13. Analysis of the ROESY NMR spectrum clearly established the relative configurations of the C8, C8', C9, and C9' positions based on correlations between the H8' and H14' hydrogen atoms and between the H8 and H14 hydrogen atoms. No correlation was observed between the H8 and H8' hydrogen atoms. The ROESY spectrum therefore

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confirmed the *trans* configuration, which is the same as for natural dictazole B (7).^[32]

In an attempt to rationalize our results and to understand the difference in reactivity between monomers **1**, **2**, and **3** in terms of their *N*-methylation patterns, we first calculated their π/π^* orbital energies and corresponding atomic coefficients.^[33] HOMO and LUMO energies of the *N*,*N*-dimethylated monomers **1** and **2** are drastically lower than those of the *N*-monomethylated **3**. The atomic orbital coefficients of the HOMO for **1** and **2** revealed an "allyl-like" nonbonding orbital, which might be detrimental for the π orbital overlap that is required for the direct formation of the six-membered ring of the cycloaplysinopsin framework (Figure 2). This fact may explain the failure of all of our experiments that targeted a thermal Diels–Alder reaction.



Figure 2. HOMO and LUMO energies and "isodensity surfaces" of 1 and 2. Not shown: HOMO of 3: -5.18 eV; LUMO of 3: -1.47 eV.

Concerning the [2+2] photocyclization reaction, both singlet and triplet states can be involved in the process. Nevertheless, in the presence of triplet photosensitizers, significant dimer formation was not observed.^[34] This finding could indicate that the reaction occurs under solid-state conditions and involves short-lived singlet states because of the high proximity of the monomers.^[35] Furthermore, according to Schmidt's topochemical postulate, the precise packing of molecules (i.e., with properly placed reactive centers) also controls the outcome of [2+2] photodimerization reactions in the solid state.^[36] In line with this hypothesis, the aforementioned crystallographic structures^[28] gave us valuable indications concerning both the spatial arrangement of structures such as 3 in the solid state and the electronic structure of the creatinine moiety, which may preclude their direct dimerization.[37]

The effectiveness of Bi(OTf)₃ to enhance the stereoselective cross-photodimerization between **2** and **3**, which is needed for the synthesis of dictazole B (**7**), may thus be attributed to an increase in electrophilicity and singlet-state lifetimes combined with lowered orbital energies for complexed **3**, which restores the properties of the *N*,*N*-dimethylated monomers **1** and **2** to a certain extent.^[38] The higher propensity of dimethylated aplysinopsin derivatives to dimerize is corroborated by the fact that all dictazole- or cycloaplysinopsin-type natural products contain at least one such dimethylated imidazolidinone. It is thus proposed that during biosynthesis, demethylation reactions may occur after the cycloaddition step.

To understand and synthetically reproduce the whole metabolism from formylindoles to cycloaplysinopsins, the next step, which is currently under investigation, will be to provide a reliable procedure for the conversion of dictazoles into the corresponding cycloaplysinopsins. Meanwhile, the herein described first total synthesis of dictazole B once again highlights the long-lasting value of biosynthetic considerations in the design of synthetic routes to natural substances, especially when they exhibit densely functionalized structures.

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Odomari area, Kagoshima prefecture, Japan (Ref. [3a] and [4b]) and for the sponge *Ianthella cf. flabelliformis*, which was collected at Lonsdale wall, Port Phillip, Australia (38°17'55''S, 144°37'76''E). For the penetration of light into (tropical) sea water, see for example: R. P. Dunne, B. E. Brown, *Mar. Ecol. Prog. Ser.* **1996**, *144*, 109–118; E. M. Fleischmann, *Limnol. Oceanogr.* **1989**, *34*, 1623–1629.

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- [19] See the Supporting Information for an analysis of the mass spectrum of **12** ($R_{\rm T}$ = 8.08 min), which shows the [M+2H]²⁺ ion at m/z = 255.1194 along with the [M+H]⁺ ion at m/z = 509.2409.

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- [32] See the Supporting Information for in-depth analysis of 2D NMR data.
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Communications

Biomimetic Synthesis

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Spontaneous Biomimetic Formation of (\pm) -Dictazole B under Irradition with Artificial Sunlight



Always the sun? Biosynthetic considerations guided the first total synthesis of dictazole B. Furthermore, insights into the biosynthetic pathway towards the aplysinopsin family were gained, and an easy access to challenging cyclobutane alkaloids of marine origin, which are often postulated to be biosynthetic precursors of more complex structures, was developed.