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Expanding the 'aplysinospin cascade' through DNA-templated [2+2] photocycloaddition†

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Inspired by the unique ability of nucleic acids to template chemical transformations that are otherwise impossible in solution, we embarked on the generalisation of our DNA-templated [2+2] photo-induced homo- and heterodimerization of aplysinopsins. Our process ensures a straightforward access to cyclobutane containing natural products and analogues thereof. Most importantly, this conceptual biomimetic achievement presents interesting arguments to build a biosynthetic scenario.

The importance of light-induced reactions in biosynthetic transformations is undisputable as showcased by the thousands of examples found in nature.[1] Photochemistry lies in the use of photons to displace a substrate of interest from its ground state to its excited states, where it can react and subsequently be transformed. Nevertheless, these highly energetic intermediates are particularly difficult to tame and can breed unusual and unforeseen reactivities. Various strategies have been developed to harness these transient species and guide photo-induced transformations.[2] Among them, the use of specific supramolecular interactions to template reactions has been regarded as a particularly appealing strategy.[3] Indeed, by providing a defined two- or three-dimensional environment, weak interactions such as electrostatic, H-bonding, π-stacking just to name a few, can template reactive molecules and induce regio- and stereoselectivity. This strategy has naturally been extended to the use of biomolecules as templating scaffolds.[4] For example, cyclodextrins[5] and cucurbiturils[6] have been reported to permit a guided organisation of reactants and control of the subsequent photochemical transformation. In this context, the emergence of DNA-catalysis has led to the development of various methodologies by several groups,[7] including ours[8] and, naturally, its use in photo-induced transformations has also been evaluated. For example, DNA templating effects were exploited to promote photo-induced ligations and cyclisations of modified oligonucleotides,[9] azobenzenes,[10] stilbenes,[11] dithienylethenes,[12] spiropyrans,[13] and other photoconvertible groups.[14] Surprisingly, however, the concept was never extended to synthetically relevant compounds, in particular in the context of natural product synthesis.

We recently demonstrated that under solvent-free conditions the (*E*)-aplysinopsin monomer could undergo a [2+2] photo-induced cycloaddition to produce the corresponding dictazole-type spiro-fused cyclobutane.[15] Structurally fascinating, these skeletons belong to the relatively broad family of indolic marine natural products which comprise three series: (i) the aplysinopsin-type which exhibit a monomeric structure [*e.g.* aplysinopsin (**1**) and its deimino and brominated analogues **2** and **3**],[16] (ii) the dictazoles,[17] which contain a spiranic cyclobutane framework [*e.g.* dictazole B (**5**)], and (iii) the tetrahydrocarbazole-type cycloaplysinopsins,[18] which are dimeric compounds [*e.g.* tubastrindole B (**6**) and dictazoline A (**7**)] (Fig. 1).

While successful, the fact that this [2+2] photo-induced cycloaddition only worked under solvent-free conditions came as a huge limitation as it annihilated any scale-up prospect or the development of an asymmetric variant. It also came across as counterintuitive as all the aforementioned natural products were isolated from marine sources. Nonetheless, in the absence of an established biosynthesis and considering that Williams and co-workers isolated the dictazoles from sponges residing in shallow waters (<5 m depths), a depth at which sunlight can still penetrate and promote a light-induced process, we decided to adopt a biomimetic approach and develop a photo-induced [2+2] cycloaddition, which could operate in solution. To circumvent the

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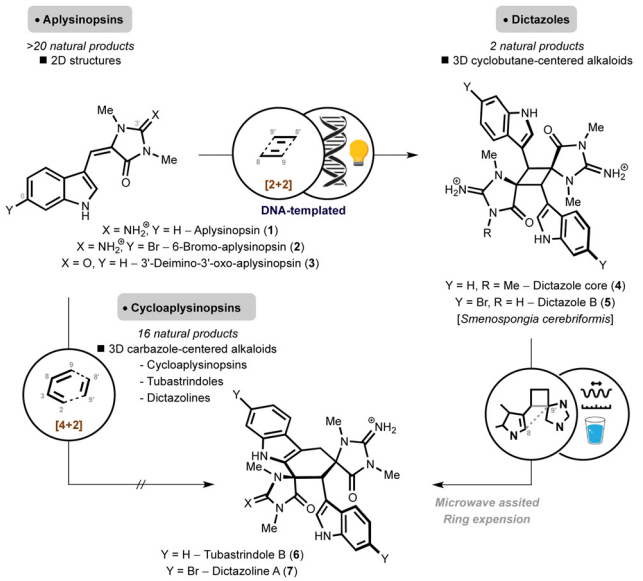

Fig. 1 The 'aplysinopsin cascade' *via* a DNA-templated [2+2] cycloaddition.

lack of reactivity and perhaps enlighten the 'aplysinopsin cascade', we envisioned a templated photochemical pathway using DNA as the key template. These considerations were guided by the advantageous structural features offered by the aplysinopsin monomers, which exhibit a positively charged guanidinium moiety and an electron-rich heteroaromatic core that can interact with the negatively charged phosphate backbone[19] and the nucleic bases of DNA respectively, which would ultimately allow the two monomers to be brought in close proximity for the cycloaddition to proceed (Fig. 1). We also opted for a UV-B enriched lamp (ZOOMED®, ReptiSun® 10.0, 10% UV-B), which exhibit an intense irradiation peak around 300 nm, to enables a proper excitation of our substrates while mimicking natural sunlight and its residual spectrum in shallow waters. Our initial incursion proved successful as after fine tuning the reaction conditions using (*E*)-aplysinopsin hydroiodide **1a** as our model substrate [**1a** (1.5 mM), salmon testes DNA (3 mM bp), MOPS (20 mM, pH 6.5)/DMSO (3 : 1)], we were able to obtain the corresponding pseudo-dictazole **4a** in 65% yield (40% isolated yield after preparative HPLC) along with 11% of the *syn* stereoisomer resulting from the dimerization of (*E*)-aplysinopsin with its (*Z*) isomer formed *in situ*.[20] The ability of DNA to promote the head-to-tail homo-dimerization was further supported by the formation of helical stacked aggregates of cationic aplysinopsin monomers evidenced by circular dichroism at low ionic strength. This strategy can be implemented to the synthesis of a variety of cyclobutane-containing natural product-like compounds at a synthetically relevant scale. We report here these results along with some additional mechanistic considerations.

To start off, the homodimerization of the iodinated analogue of (*E*)-aplysinopsin (**1b**) was attempted on a 0.15 mmol scale (Fig. 2B). Satisfyingly, the head-to-tail dimerization resulting from the topochemical control of the DNA-templated photodimerization was observed as confirmed by ^{1}H and ^{13}C NMR analysis. The homodimerized product **4b** was obtained in

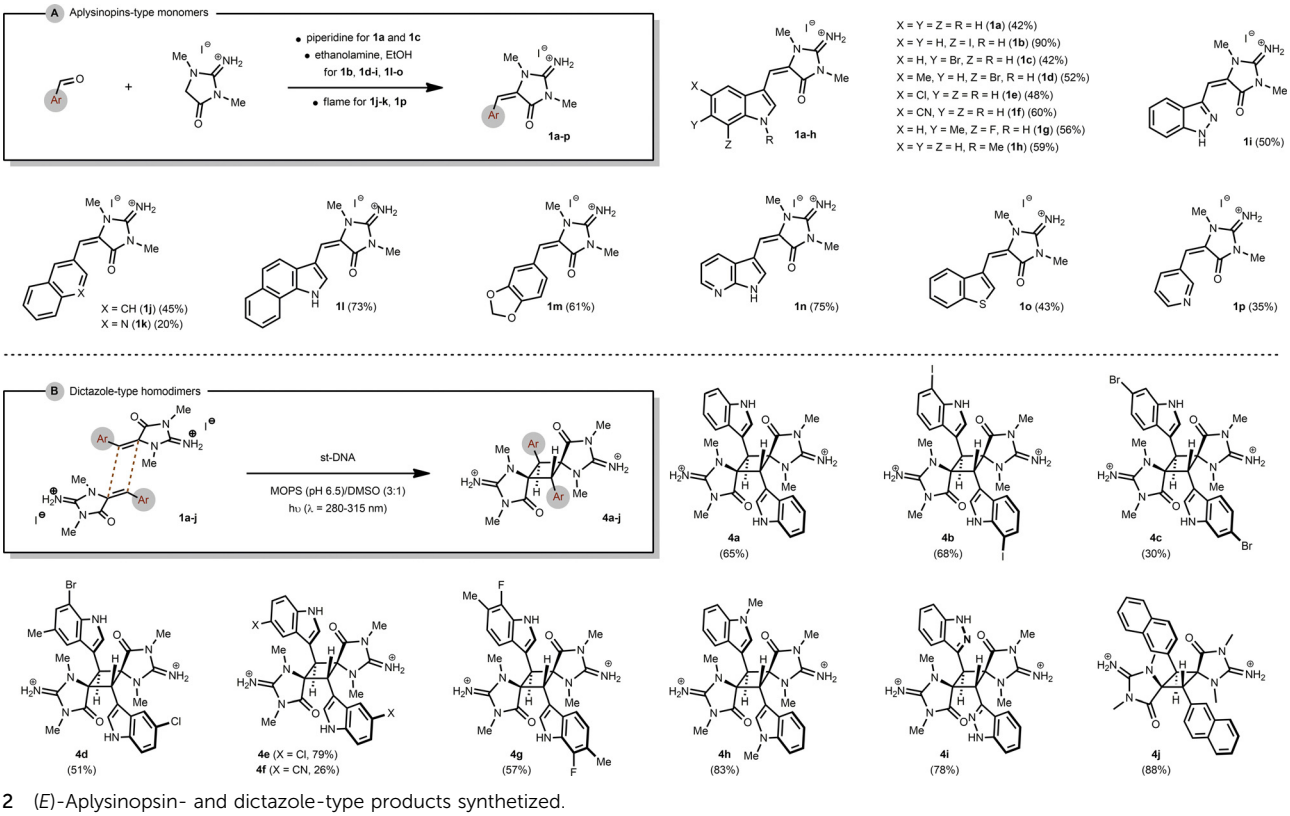

Fig. 2 (*E*)-Aplysinopsin- and dictazole-type products synthetized.

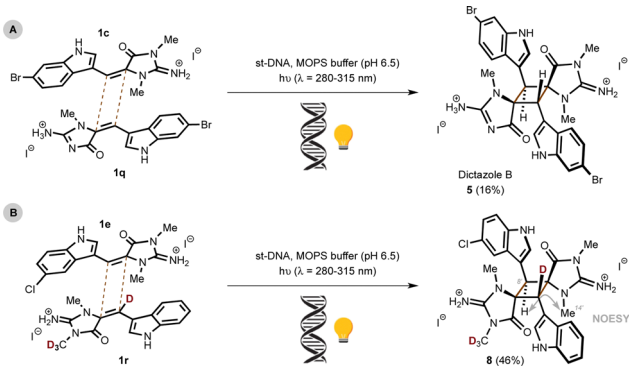

Fig. 3 (**A**) Synthesis of dictazole B (**5**). (B) Cycloaddition of 5-chloro-(*E*)-aplysinopsin (**1e**) and deutered-(*E*)-aplysinopsin (**1r**).

a very good 68% yield after running the reaction over a 24 h period. Following this result, we next explored the dimerization of the brominated analogue **1c**. Interestingly, our optimal conditions afforded the expected dictazole scaffold **4c**, albeit in only 12% yield. In this case, the reaction mainly led to the recovery of the starting monomer and traces of the brominated formyl indole resulting from the degradation of the starting aplysinopsin. This lower yield compared to the one previously obtained for the homodimerization of **1a** can be explained by the fast disassembly of the resulting cyclobutane product **4c** after a few hours in solution as experimentally observed on a pure sample. We pursued our scope with various synthetic aplysinopsins (**1d–1h**) all differing by their indolic core and all prepared in one step from the corresponding aldehydes (Fig. 2A). As a general trend, moderate to good yields were obtained ranging from 26% to 83%, confirming the potential sensitivity of the cyclobutane–dictazoles. The lower yields can also be attributed to the inherent physico-chemical properties of the substrates such as for example the low solubility of the fluorinated aplysinopsin **1f**, which truly hampers the conversion. We pushed the investigation further by replacing the indole moiety by an aromatic and a heteroaromatic group. Satisfyingly, the indazolyl- and the naphthyl-aplysinopsin analogues **1i** and **1j** behaved perfectly and afforded the corresponding dictazole-type cyclobutanes in 78% and 88% yield, respectively. The other substrates evaluated, **1k–1p**, led to only trace amounts of the desired products. Considering that all the control experiments run in the absence of DNA led to the exclusive formation of the corresponding formyl indoles, these results clearly prove the potency of our DNA-templated approach for the synthesis of structurally rich cyclobutane units.

To explore the possibility of applying our optimal conditions to the more challenging heterodimerization, we had previously run the reaction using a 1 : 1 mixture of the brominated (*E*)-aplysinopsin hydroiodide **1c** and the brominated *nor*-aplysinopsin **1q** (Fig. 3A). Satisfyingly, the cycloaddition had led to the formation of the naturally occurring heterodimer **5** as the major product (*i.e.* dictazole B) albeit in only 7% ee. The efficacy of the reaction was particularly striking as the natural product was obtained in 16% isolated yield on a 0.15 mmol scale, which compared favourably with the 3.4% yield previously obtained using the non-templated solvent-free approach that required running 28 batches, each on a 0.025 mmol scale. It is worth noting that the control experiment run without DNA was unproductive. To understand the nature of the reactive aplysinopsin diastereoisomer, we conducted a large scale heterodimerization using a 1 : 1 mixture of the 5-chloro-(*E*)-aplysinopsin **1e** and the deuterated (*E*)-aplysinopsin **1r** (Fig. 3B). Indeed, upon UV-light irradiation, an *in situ* photo-induced isomerisation of the (*E*)-isomer to the corresponding (*Z*)-aplysinopsin can occur and promote the homo and heterodimerization of the (*Z*)-aplysinopsin intermediates. Interestingly, heterodimer **8** was obtained in 46% yield along with 34% of the chlorinated homodimer and 15% of the deuterated homodimer. NOESY experiments allowed to clearly confirm the nature of the major reactive intermediates through the apparent correlation between the proton on 8′ and the 3 protons on methyl 14′ clearly advocating for a spatial arrangement where these nuclei are *syn* to each other (see ESI† for more details). This result also further illustrates the power of the DNA-templated approach as the same reaction attempted at the solid state led to only traces of the product.

To anchor this biomimetic approach to the postulated biosynthetic 'aplysinopsin cascade',[21] we selected five of the cyclobutane–dictazoles (**4a**, **4b**, **4d**, **4e** and **4h**) and subjected them to a TFA-mediated ionic rearrangement [H_2O/TFA, 150 °C under microwave irradiation for 90 s] to afford the corresponding vinylcyclobutane–cyclohexene ring-expansion products **6a**, **6b**, **6d**, **6e** and **6h** in yields ranging from 28 to 50% (Fig. 4).[22]

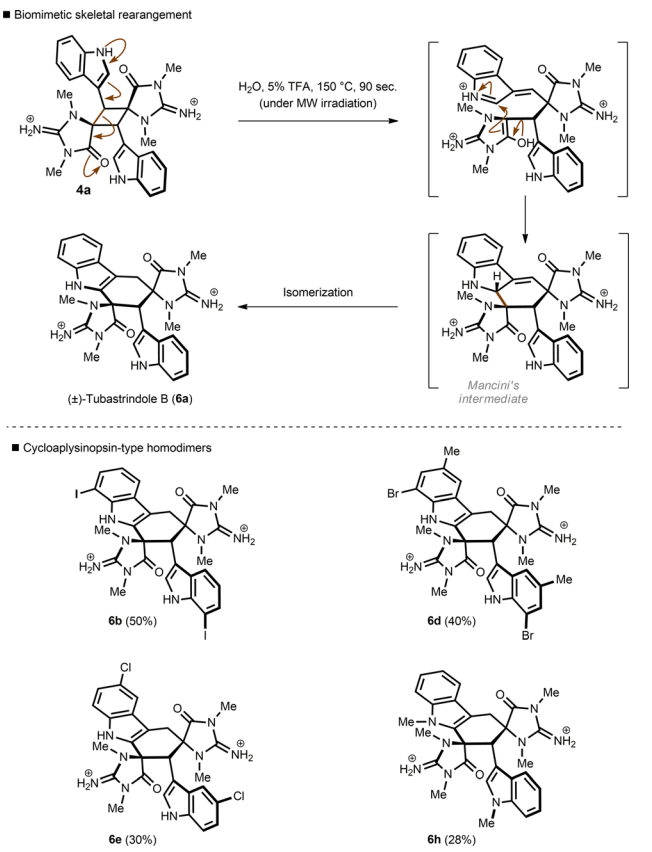

Fig. 4 Ring expansion of dictazole-type structures.

In summary, we were able to generalise our DNA-templated [2+2] photocycloaddition to the synthesis of a variety of cyclobutane-containing natural product analogues. This strategy not only allows to promote a reaction which is otherwise impossible in solution, it also offers interesting scale-up prospects as well as interesting arguments to build a biosynthetic scenario for a 'nature-like' synthesis of dictazoles.

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Conflicts of interest

There are no conflicts of interest to declare.

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