Biomimetic Synthesis Hot Paper

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# Spontaneous Biomimetic Formation of (±)-Dictazole B under Irradiation with Artificial Sunlight**

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***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 *N*-methylation 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 intermediates 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] Hence, the "aplysinopsin cascade" process also attracted our attention.

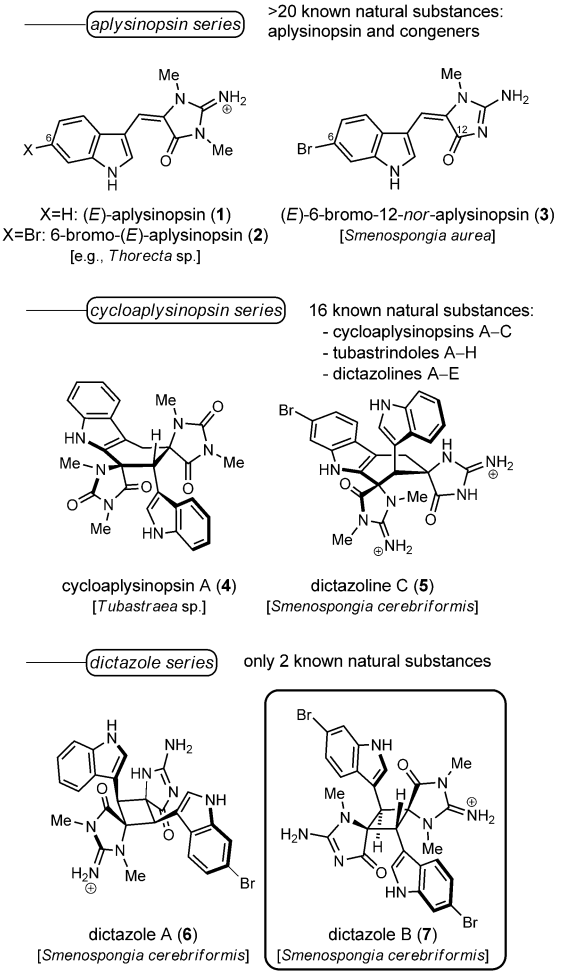


***Figure 1.*** Overview of the structural diversity of the aplysinopsin family.[14]

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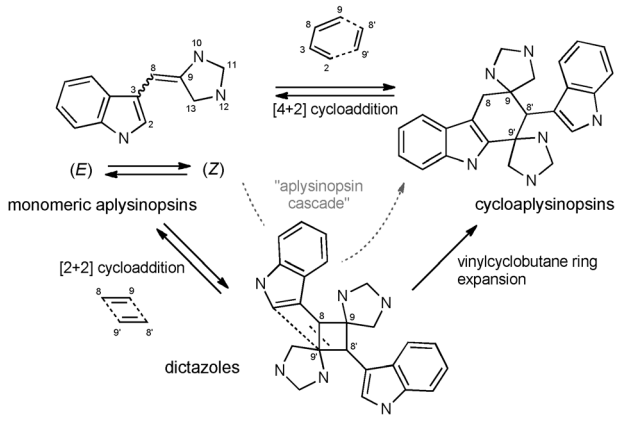
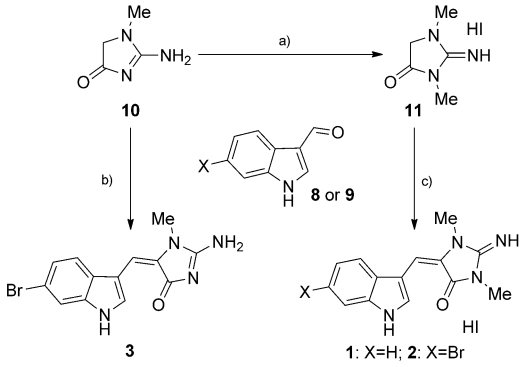



***Scheme 1.*** Biosynthetic hypothesis.

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 above-mentioned Diels–Alder cycloaddition was investigated with monomer **1** under different conditions, including heating for several days in DMF, use of $SbCl_3$[15] and the Ledwith–Weitz aminium salt ($SbCl_6N(p\text{-}BrPh)_3$),[16] or ultra-high pressures, but the desired transformation was not observed.[17,18]



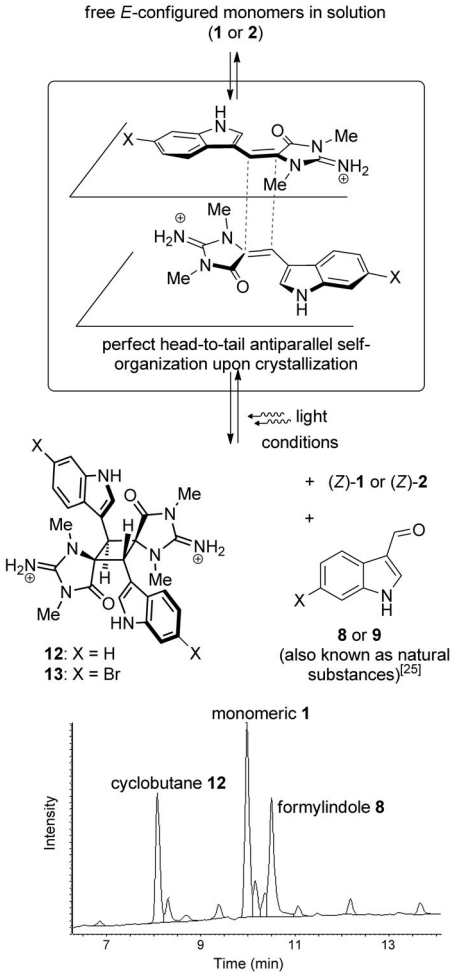

***Scheme 2.*** Synthesis of monomeric aplysinopsin derivatives. Reaction conditions: a) MeI, EtOH (>95%); b) Bunsen flame, neat (59%); c) piperidine, reflux (41%).

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. 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 effi-

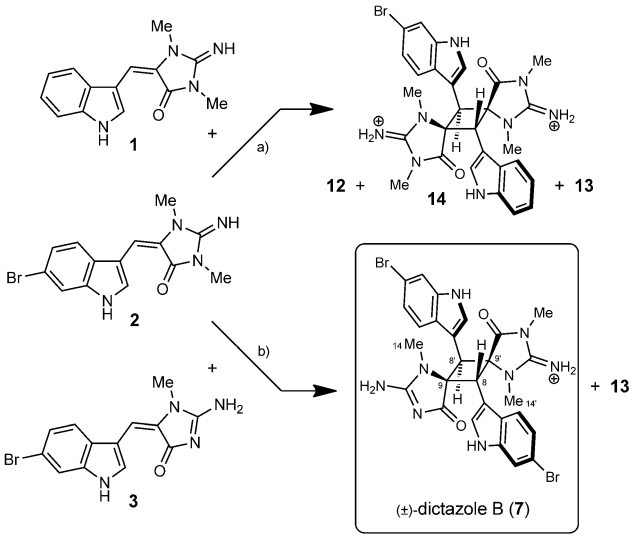
  




***Scheme 3.*** Solid-state dimerization under irradiation with artificial sunlight. Reaction conditions: A solution of the starting material in DMF (5 mM) was allowed to concentrate, CuOTf toluene complex (0.5 equiv), 14 h (**12**: 40%; **13**: 35%). LC/MS chromatogram of the described reaction (see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

ciency 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




***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%.

course of the structure determination of **14**. Subsequent exposure of a 1:1 mixture of **2** (*N*,*N*-dimethylated) and **3** (*N*-monomethylated) 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 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.

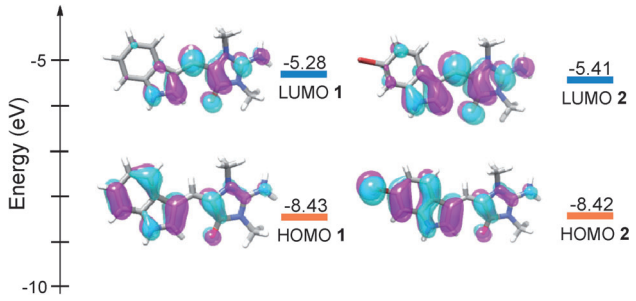



***Figure 2.*** HOMO and LUMO energies and "isodensity surfaces" of **1** and **2**. Not shown: HOMO of **3**: −5.18 eV; LUMO of **3**: −1.47 eV.

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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[1] For reviews, see: a) D. Bialonska, J. K. Zjawiony, *Mar. Drugs* **2009**, *7*, 166–183; b) E. M. Boyd, J. Sperry, *Chem. N. Z.* **2010**, *74*, 109–112.

[2] For the first isolation and description of aplysinopsin (**1**), see: R. Kazlauskas, P. T. Murphy, R. J. Quinn, R. J. Wells, *Tetrahedron Lett.* **1977**, *18*, 61–64. For the isolation of its congeners, see Ref. [1]; for a recent example, see: N. Cachet, L. Loffredo, O. O. Vicente, O. P. Thomas, *Phytochem. Lett.* **2013**, *6*, 205–208.

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[4] For a description of tubastrindoles A–C, see: a) T. Isagawa, M. Miyazaki, H. Okamura, M. Nakatani, M. Doe, K. Takemura, *Tetrahedron Lett.* **2003**, *44*, 2533–2535; for a description of tubastrindoles D–H, see: b) T. Isagawa, M. Miyazaki, Y. Yokogawa, H. Okamura, M. Nakatani, M. Doe, Y. Morimoto, K. Takemura, *Heterocycles* **2008**, *75*, 2023–2028; for a description of tubastrindole B, see also: c) W. Balansa, R. Islam, D. F. Gilbert, F. Fontaine, X. Xiao, H. Zhang, A. M. Piggott, J. W. Lynch, R. J. Capon, *Bioorg. Med. Chem.* **2013**, *21*, 4420–4425.

[5] For a description of dictazolines A and B, see: a) J. Dai, J. I. Jiménez, M. Kelly, S. Barnes, P. Lorenzo, P. G. Williams, *J. Nat. Prod.* **2008**, *71*, 1287–1290; for a description of dictazolines C–E and dictazoles A and B, see: b) J. Dai, J. I. Jiménez, M. Kelly, P. G. Williams, *J. Org. Chem.* **2010**, *75*, 2399–2402.

[6] Mancini et al. studied the changing *E*/*Z* ratio of aplysinopsins especially when they are exposed to light; see: a) G. Guella, I. Mancini, H. Zibrowius, F. Pietra, *Helv. Chim. Acta* **1988**, *71*, 773–782; b) G. Guella, I. Mancini, H. Zibrowius, F. Pietra, *Helv. Chim. Acta* **1989**, *72*, 1444–1450. See also Ref. [4c] for sunlight-induced *E*/*Z* interconversion.

[7] The enantiomeric excess of cycloaplysinopsin A (**4**) was found to be poor by using the chiral shift reagent $Eu(tfc)_3$; the relevant signals in the NMR spectrum were split in a ratio of approximately 65:35 (see Ref. [3a]).

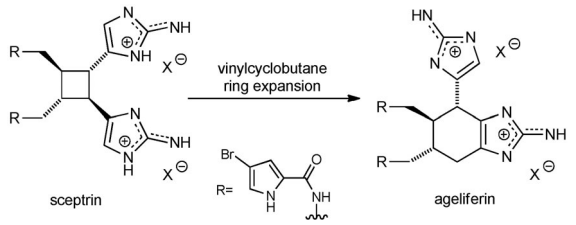
[8] The sponge *S. cerebriformis* was collected at the northwest coast of Panama from a depth of 2–3 m (Ref. [5a,b]); stony-coral *Tubastraea* sp. samples were collected in a reef environment from a depth of 3 m at Comoro Islands (Ref. [3a]), from a depth of ca. 3 m at Capsalon Island, Philippines (Ref. [6a] and [3a]), and from a depth of 12 m depth in the Hanish Islands archipelago, Yemen (Ref. [3b]). The depth was not mentioned in the description of the collection of *Tubastraea* sp. in the 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.

[9] The putative Diels–Alder cycloaddition was particularly investigated and discussed by Mancini et al. (see Ref. [3a]): Spontaneous formation during the extraction was rapidly set aside, and the existence of a putative Diels–Alderase was discussed.

[10] Indeed, preliminary results (LC/MS traces, see Ref. [5b]) indicated a conversion of dictazole A into dictazoline C under microwave activation in water, following the seminal and beautiful conversion of sceptrin into ageliferin under such conditions; see: B. H. Northrop, D. P. O'Malley, A. L. Zografos, P. S. Baran, *Angew. Chem.* **2006**, *118*, 4232–4236; *Angew. Chem. Int. Ed.* **2006**, *45*, 4126–4130, and references therein. In the particular case of pyrrole aminoimidazole alkaloids, Molinski and co-workers recently disclosed a crucial step forward in understanding the biosynthesis of this highly diverse family of natural substances; see: E. P. Stout, Y.-G. Wang, D. Romo, T. Molinski, *Angew. Chem.* **2012**, *124*, 4961–4965; *Angew. Chem. Int. Ed.* **2012**, *51*, 4877–4881; E. P. Stout, B. I. Morinaka, Y.-G. Wang, D. Romo, T. F. Molinski, *J. Nat. Prod.* **2012**, *75*, 527–530.




[11] a) W. R. Gutekunst, P. S. Baran, *J. Org. Chem.* **2014**, *79*, 2430–2452. This paper also features a synthetic approach towards dictazole A (**6**). The special [2+2] photochemical origin of sceptrin has also been discussed, but attempts to realize this [2+2] dimerization have previously been unsuccessful; see: b) R. P. Walker, D. J. Faulkner, D. Van Engen, J. Clardy, *J. Am. Chem. Soc.* **1981**, *103*, 6772–6773.

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[13] See, for example: a) E. Gravel, A. Harfouche, R. Salame, K. Leblanc, A. Maciuk, E. Poupon, *Chem. Eur. J.* **2013**, *19*, 14515–14519, and references therein; b) F. Senejoux, L. Evanno, E. Poupon, *Eur. J. Org. Chem.* **2013**, 453–455.

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[15] G. Maiti, P. Kundu, *Tetrahedron Lett.* **2006**, *47*, 5733–5736.

[16] a) S. L. Drew, A. L. Lawrence, M. S. Sherburn, *Angew. Chem.* **2013**, *125*, 4315–4318; *Angew. Chem. Int. Ed.* **2013**, *52*, 4221–4224; b) H. N. Lim, K. A. Parker, *Org. Lett.* **2013**, *15*, 398–401.

[17] W. G. Dauben, C. R. Kessel, K. H. Takemura, *J. Am. Chem. Soc.* **1980**, *102*, 6893–6894.

[18] Diels–Alder reaction with **1**: 1) heating in DMF for 5 days; 2) DMF, RT, 24 h; 3) $SbCl_6N(p\text{-}BrPh)_3$ (10 mol%), $CH_2Cl_2$ (low solubility) or DMF, RT, 12 h; 4) DMF/THF (1:1), 1.2 GPa, RT, 15 h. Reaction conditions 1–3 resulted in no reaction, conditions 4 mainly afforded a retro-aldol reaction.

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

[20] The reaction, which takes place at the surface of powdered **1**, necessitated daily fine grinding for the renewal of the surface.

[21] Artificial sunlight restitutes high UV-B quanta; see the Supporting Information for details.

[22] See the Supporting Information for details concerning the expression of the results in terms of conversion percentages.

[23] DMF was chosen because it appeared to be the best solvent to solubilize **1** and **2**. DMSO afforded a small dimer peak in the HPLC chromatogram but mainly provided the retro-aldol products **8** and **9**.

[24] For the use of copper triflate, see: a) R. G. Salomon, *Tetrahedron* **1983**, *39*, 485–575; b) R. G. Salomon, K. Folting, W. E. Streib, J. K. Kochi, *J. Am. Chem. Soc.* **1974**, *96*, 1145–1152.

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[26] a) T. Bach, J. P. Hehn, *Angew. Chem.* **2011**, *123*, 1032–1077; *Angew. Chem. Int. Ed.* **2011**, *50*, 1000–1045; b) J. Iriondo-Alberdi, M. F. Greaney, *Eur. J. Org. Chem.* **2007**, 4801–4815.

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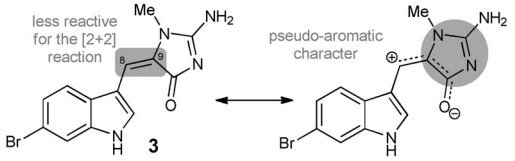
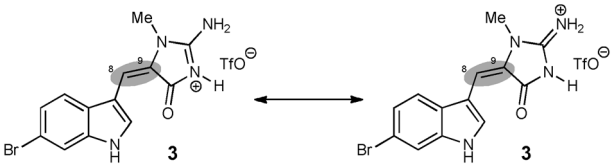
[29] The existence of particular pseudo-aromatic mesomeric forms may explain the following:




[30] Evaluated Lewis acids include $La(OTf)_3$, $Sc(OTf)_3$, $Y(OTf)_3$, $Yb(OTf)_3$, $MgCl_2$, and $ZnCl_2$, which mainly provided retro-aldol products, that is, formylindoles **8** and **9**. $Bi(OTf)_3$ was selected. For the use of $Bi(OTf)_3$ in organic synthesis, see: J. M. Bothwell, S. W. Krabbe, R. S. Mohan, *Chem. Soc. Rev.* **2011**, *40*, 4649–4707.

[31] Activation by a mild oxophilic Lewis acid in conjunction with activation by protonation, which arises from the catalytic liberation of triflic acid, may explain the outcome of the reaction. Protonation of the creatinine moiety of **3** indeed enables the loss of its pseudo-aromatic character, which renders the C8/C9 double bond more reactive for the [2+2] photocycloaddition.




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

[33] See the Supporting Information, p. 21 for the calculation method and a Figure showing orbital energies and atomic coefficients of **1**, **2**, and **3**.

[34] Evaluated photosensitizers include benzophenone and salcomine, which fully or partially inhibited the dimerization reaction.

[35] H. Gonçalves, G. Robinet, M. Barthelat, A. Lattes, *J. Phys. Chem. A* **1998**, *102*, 1279 – 1287.
[36] a) M. D. Cohen, G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 1996 – 2000; b) M. D. Cohen, G. M. J. Schmidt, F. I. Sonntag, *J. Chem. Soc.* **1964**, 2000 – 2013; c) G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 2014 – 2021.
[37] Whereas a 3′-exocyclic imine and a perfect stacking between the indole and the imidazolinone heterocycle was observed with superposed *N*-1,*N*-10′-dimethylated monomers **A** (see Ref. [28]), an endocyclic imine and different stacking may explain the differences in reactivity.
[38] a) F. D. Lewis, S. L. Quillen, P. D. Hale, J. D. Oxman, *J. Am. Chem. Soc.* **1988**, *110*, 1261 – 1267; b) F. D. Lewis, J. E. Elbert, A. L. Upthagrove, P. D. Hale, *J. Org. Chem.* **1991**, *56*, 553 – 561.