Organic Letters

Letter

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A Unified Bioinspired “Aplysinopsin Cascade”: Total Synthesis of (±)-Tubastrindole B and Related Biosynthetic Congeners

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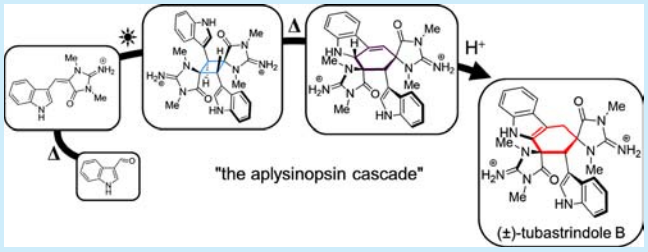
Ⓢ *Supporting Information*

ABSTRACT: Applying a biomimetic approach, the first total synthesis of (±)-tubastrindole B is reported herein. This work features a ring-expansion cascade of a dictazole-type precursor into cycloaplysinopsin-type congeners. Moreover, the isolation of a transient biogenetic intermediate represents a milestone in the biosynthetic understanding of this family of marine alkaloids.



A structurally diverse set of marine natural products isolated from several sponges and stony corals has been described in recent decades and collectively defined as the “aplysinopsins alkaloid family”.[1] Three types of natural skeletons, with clearly distinct levels of complexity, make up this broad family of unique indole- and creatinine-containing marine natural products: (i) aplysinopsin-type monomeric structures (e.g., aplysinopsin (**1**) and brominated analogs **2** and **3**, Figure 1);[2] (ii) tetrahydrocarbazole-type dimeric compounds, i.e., cycloaplysinopsins (e.g., tubastrindole C (**4**), tubastrindole E (**5**), dictazoline C (**6**), and tubastrindole B (**7**));[3,4] and (iii) the latest discovered skeleton of intriguing spiranic cyclobutanes (dictazole A (**8**), for which the relative configuration is not fully assigned, and dictazole B (**9**)).[5] Since the very first isolation of aplysinopsin (**1**) in 1977 by Wells et al.,[2a] the discovery of their tetrahydrocarbazole-type congeners in 2003[3a,4a] suggested an obvious Diels–Alder biosynthetic scenario, a possibility discussed by Mancini et al.[3a] However, the recent isolation (in 2010) of dictazole cyclobutanes by Williams et al.[5] identified a crucial puzzle piece that led to the proposed biosynthetic scenario being reformulated (Scheme 1). Indeed, rather reminiscent of the epic story of pyrrole–imidazole alkaloids[6] and the beautiful conversion of sceptrin into ageliferin reported by Baran et al.,[7] dictazoles may be presented as plausible intermediates toward their tetrahydrocarbazole counterparts by ring-expansion but with, up to now, piecemeal experimental evidence due to an obvious lack of natural dictazoles.[5,8]

In this paper, we report for the first time the total synthesis of a representative of the cycloaplysinopsin-type natural products namely tubastrindole B (**7**). We also disclose the total synthesis of a key biosynthetic intermediate and its spontaneous transformation which provide strong clues for a unified biosynthetic scenario.

In order to undertake the envisioned ring-expansion step, more than 1 g of cyclobutane **10** was produced by photochemical [2 + 2] homodimerization of aplysinopsin (**1**) under conditions similar to those previously reported for the biomimetic synthesis of (±)-dictazole B (**9**).[9,10] Taking advantage of this large-scale process, two minor compounds (**11**, **12**) of biosynthetic interest have also been accumulated, isolated, and characterized in addition to **10**, isolated by preparative HPLC in 16% yield (Scheme 2). Interestingly, resulting from a slight erosion of diastereoselectivity of the [2 + 2] process in the presence of CuOTf, compound **11**, isolated in variable but low ratios, appeared to be a diastereomer of **10** with a *syn* configuration for both indoles. This *syn* configuration is comparable to the one observed in dictazole A (**8**) and could suggest that such alkaloids are formed more or less spontaneously in confined compartments of living cells. This point has been further strengthened since compound **12** possesses a hydantoin in place of one of the creatinine moieties (such as found in tubastrindole C (**4**)) as the result of a spontaneous hydrolysis.

Starting from **10**, we then embarked on evaluating the missing biosynthetic link by considering dictazole-type cyclobutanic skeletons as penultimate precursors of tetrahydrocarbazole-containing cycloaplysinopsins. In that way, compound **10** indeed constituted an ideal precursor for studying such a ring-expansion and could permit an easy access to tubastrindole B (**7**).[11] Screening of temperature, duration, and additives

Received: July 25, 2014
Published: September 15, 2014

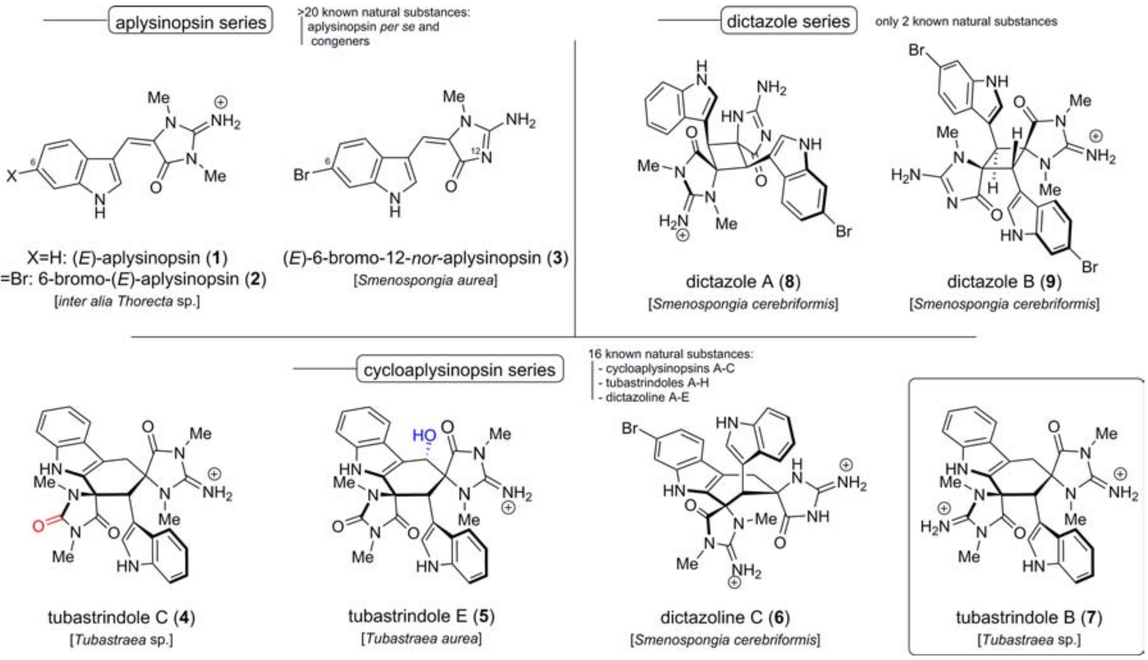
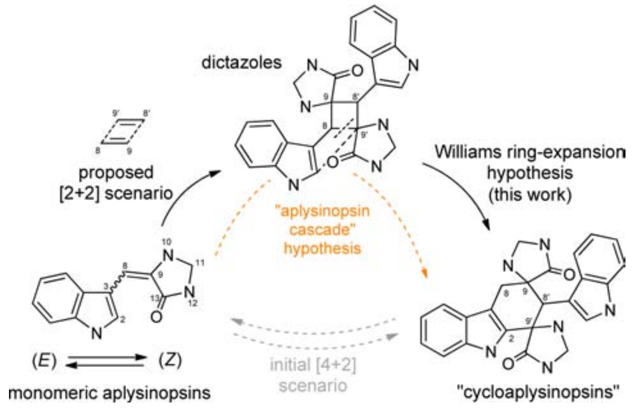
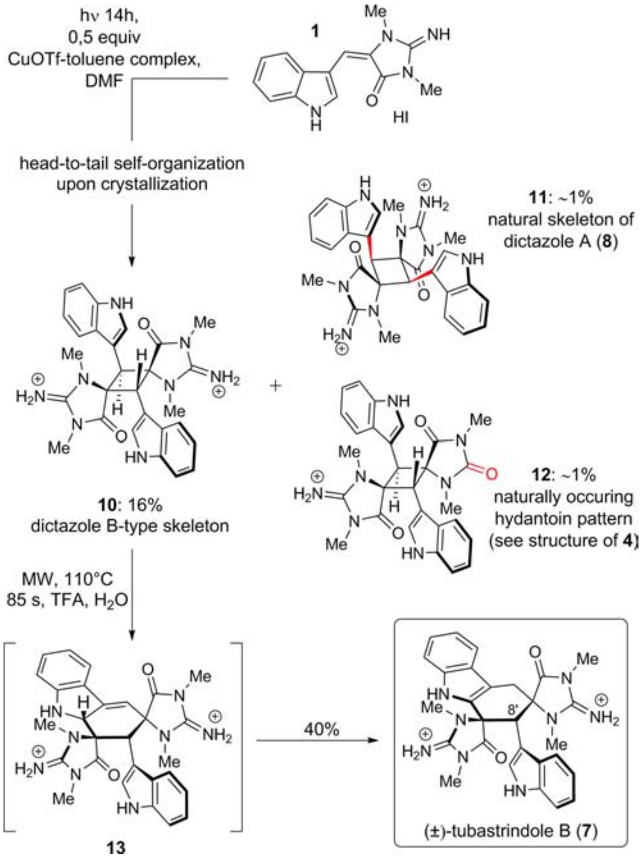


Figure 1. Overview of the existing aplysinopsin skeletons with selected examples.

Scheme 1. Biosynthetic Hypothesis of the "Aplysinopsin Cascade"



Scheme 2. Expeditious Synthesis of (±)-Tubastrindole B via Biosynthetically Relevant Precursors



including both Lewis and Brønsted acids were necessary to overcome initial disappointing results.[12] Ultimately, total conversion of cyclobutane **10** has been reached in water with TFA heated at 110 °C for 85 s under microwave irradiation (Scheme 2).

Satisfyingly, tubastrindole B (**7**) has been isolated in 40% yield along with cycloreversed monomeric **1**. Key NOESY correlations between H-8′/H-8β, H-14′, and H-8α/H-14 hydrogen atoms clearly established the relative configurations of C-9′, C-8′, and C-9 positions as awaited for **7** (Figure 2), confirming the first total synthesis of (±)-tubastrindole B (**7**) in only two steps (from aplysinopsin **1**) and also the first total synthesis of such natural products.[13] To our delight, the ring-expansion cascade also occurs with full retention of configuration as no other stereoisomer is formed during the process.

Given that this cascade only leads to one pair of enantiomers and in light of the experimental conditions, mechanistic hypotheses can be put forward and an ionic general mechanism appears plausible to us.[14] For this singular intramolecular rearrangement, two underlying selective processes are needed to reach that level of selectivity.

The precise outcome of the ring-opening step, in terms of regio- and stereoselectivity, seems to be driven by the *anti* relative 1,2-position of the indole heterocycle and the

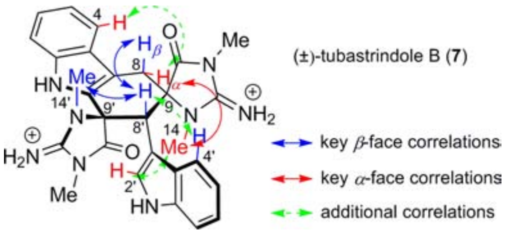
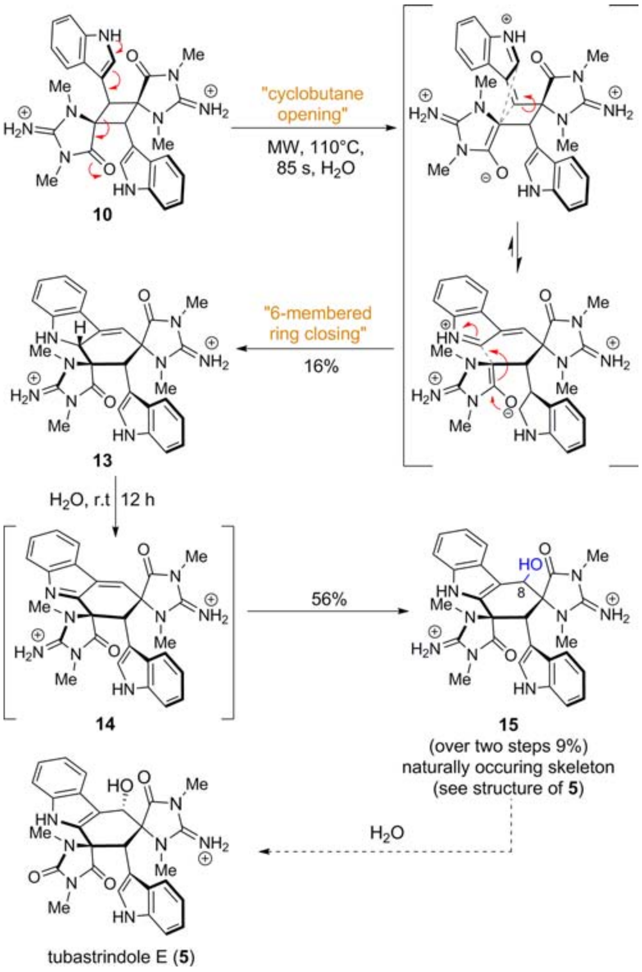


Figure 2. Key NOESY correlations of **7**.

Scheme 3. Synthesis of the Postulated Biosynthetic Intermediate 13 and Its Spontaneous Conversion into 15, Access to Another Naturally Occurring Skeleton



carboxamide group at each side of the bond undergoing the cleavage. Hence, no C-8′ epimer is formed during the ring expansion.[15] In a second event, the free methylcreatinine moiety is reacting with complete retention of configuration: the *anti* relative configuration of the creatinine nuclei is preserved and no *syn* isomer is observed. This final Mannich-type C–C bond formation could lead to the 1,2,3,9a-tetrahydro-9*H*-carbazole intermediate (**13**) signaling the entry into the cycloaplysinopsins subgroup. A final tautomerism restores the integrity of the indole nucleus of tubastrindole B (**7**).

The importance of TFA may be rationalized assuming at least two distinct roles: (i) it could activate the indole/carbonyl system in cyclobutane **10**, consequently lowering the activation energy of the bond-breaking step, and (ii) it could provide a proton source for the final isomerization of the double bond in intermediate **13** to **7**.[16] This last point was particularly important and had practical applications. Indeed, when the same reaction was performed under microwave conditions in water but without any addition of TFA, the postulated biosynthetic intermediate **13** was isolated and fully characterized (Scheme 3).[17]

The formation of this biosynthetic intermediate **13** further led to a crucial discovery that widened the scope of comprehension of the biosynthetic links between the different representatives. Indeed, performing HPLC/MS analysis of the reaction mixture of **13** (without TFA) after 12 h at room temperature revealed new outcomes. Whereas biosynthetic intermediate **13** mostly disappeared, its spontaneous conversion in water led to a new compound **15** which has been isolated and characterized.[18]

Structural determination revealed the formation of compound **15**, which displays a site-specific hydroxylation at position 8. Spontaneous oxidation of **13** into **14**, which now contains a suitable Michael acceptor motif for the straightforward addition of a water molecule, can be postulated for such an outcome. The formation of hydroxylated analogue **15** provides clear and tangible clues as to the biosynthetic pathway by which tubastrindole E (**5**) (for which synthetic access would consist in a selective hydrolysis of one guanidine subunit of **15** into the corresponding urea) and related 8-hydroxylated cycloaplysinopsins are formed. Noteworthy, intermediate **13** does not spontaneously evolve into tubastrindole B (**7**) without proton assistance.

In conclusion, the present work demonstrates, for the first time, by bioinspired total synthesis, the interlinkages in the aplysinopsin group of marine natural products. Under simple reaction conditions that may have all their biosynthetic pendants, we were able to chemically point out all types of skeletons in the metabolomic map of marine organisms displaying the "aplysinopsin cascade".[19] In terms of total synthesis, we have succeeded with a highly atom-economic strategy in the first total synthesis of (±)-tubastrindole B (**7**) as well as a direct precursor of tubastrindole E (**5**).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details, copies of all spectral and chromatographical data, and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Pr. Cyrille Kouklovsky, Dr. Guillaume Vincent, and Terry Tomakinian (ICMMO, Université Paris-Sud, France) for their help in the realization of microwave experiments. We also thank Jean-Christophe Jullian and Jean-François Gallard

(ICSN-CNRS, Gif-sur-Yvette, France) for NMR assistance. LabEx LERMIT (ANR-10-LABX-0033-LERMIT) is gratefully acknowledged for funding (grant to A.S.). Finally, the IT department from Université Paris-Sud is acknowledged for providing computing resources.

■ REFERENCES

(1) (a) Bialonska, D.; Zjawiony, J. *Mar. Drugs* **2009**, *7*, 166–183. (b) Boyd, E. M.; Sperry, J. *Chem. N. Z.* **2010**, *74*, 109–112.

(2) (a) Kazlauskas, R.; Murphy, P. T.; Quinn, R. J.; Wells, R. J. *Tetrahedron Lett.* **1977**, *18*, 61–64. (b) Cachet, N.; Loffredo, L.; Vicente, O. O.; Thomas, O. P. *Phytochem. Lett.* **2013**, *6*, 205–208.

(3) (a) Mancini, I.; Guella, G.; Zibrowius, H.; Pietra, F. *Tetrahedron* **2003**, *59*, 8757–8762. (b) Meyer, M.; Delberghe, F.; Liron, F.; Guillaume, M.; Valentin, A.; Guyot, M. *Nat. Prod. Res.* **2009**, *23*, 178–182.

(4) (a) Iwagawa, T.; Miyazaki, M.; Okamura, H.; Nakatani, M.; Doe, M.; Takemura, K. *Tetrahedron Lett.* **2003**, *44*, 2533–2535. (b) Iwagawa, T.; Miyazaki, M.; Yokogawa, Y.; Okamura, H.; Nakatani, M.; Doe, M.; Morimoto, Y.; Takemura, K. *Heterocycles* **2008**, *75*, 2023–2028. (c) Balansa, W.; Islam, R.; Gilbert, D. F.; Fontaine, F.; Xiao, X.; Zhang, H.; Piggott, A. M.; Lynch, J. W.; Capon, R. J. *Bioorg. Med. Chem.* **2013**, *21*, 4420–4425. (d) Dai, J.; Jiménez, J. I.; Kelly, M.; Barnes, S.; Lorenzo, P.; Williams, P. *J. Nat. Prod.* **2008**, *71*, 1287–1290.

(5) Dai, J.; Jiménez, J. I.; Kelly, M.; Williams, P. G. *J. Org. Chem.* **2010**, *75*, 2399–2402.

(6) Wang, X.; Ma, Z.; Wang, X.; De, S.; Ma, Y.; Chen, C. *Chem. Commun.* **2014**, *50*, 8628–8639.

(7) (a) Baran, P. S.; O'Malley, D. P.; Zografos, A. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2674–2677. (b) Baran, P. S.; Li, K.; O'Malley, D. P.; Mitsos, C. *Angew. Chem., Int. Ed.* **2006**, *45*, 249–252. (c) O'Malley, D. P.; Li, K.; Maue, M.; Zografos, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2007**, *129*, 4762–4775. (d) Northrop, B. H.; O'Malley, D. P.; Zografos, A. L.; Baran, P. S.; Houk, K. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 4126–4130. (e) Recent works of Molinski et al. led to crucial progress in the understanding of pyrrole–imidazole alkaloids biosynthesis: Stout, E. P.; Morinaka, B. I.; Wang, Y.-G.; Romo, D.; Molinski, T. F. *J. Nat. Prod.* **2012**, *75*, 527–530. Stout, E. P.; Wang, Y.-G.; Romo, D.; Molinski, T. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4877–4881.

(8) In ref 5, conversion of dictazole A into dictazoline C was attempted on a 100 μg scale in H_2O (200 °C, 1 min) and led to ε% formation of a compound comparable to dictazoline C by HPLC/MS analysis.

(9) For the one-step, multigram-scale synthesis of **1** from 3-formylindole and methylcreatinine, the procedure has been adapted from ref 4c and reported in ref 10a.

(10) (a) Skiredj, A.; Beniddir, M. A.; Joseph, D.; Leblanc, K.; Bernadat, G.; Evanno, L.; Poupon, E. *Angew. Chem., Int. Ed.* **2014**, *53*, 6419–6424. (b) Photodimerization conditions: a thin film of **1** in DMF is exposed to artificial UV-enriched light in the presence of copper(I) triflate–toluene complex. (c) Gutekunst, W. R.; Baran, P. S. *J. Org. Chem.* **2014**, *79*, 2430–2452.

(11) An example, to a certain extent comparable to the present work by Wenkert, McPhail et al., attracted our attention as a visibly fortuitous ring expansion of a cyclobutanic oxindole (CH_2Cl_2, $MgSO_4$ (300 equiv), room temperature, 110 h; see: Wenkert, E.; Moeller, P. D. R.; Piettre, S. R.; McPhail, A. T. *J. Org. Chem.* **1987**, *52*, 3404–3409.

(12) At the temperatures described by Baran et al. (195 °C for sceptrin, ref 7a,b) and Williams et al. (200 °C for dictazole A, ref 11), high degradation of **10** into monomer **1** was observed with minute amounts of rearranged products. Therefore, milder conditions had to be found.

(13) Additional NOESY correlations between H-2′/H-14 and H-4′/H-8′ also provided conformational data for the free indole nucleus orientation.

(14) Mostly in accordance with the mechanism suggested by Wenkert, McPhail et al. in the yuehchukene series, see ref 11.

(15) See the Supporting Information for detailed mechanistic hypotheses and DFT data.

(16) Tan, B.; Hernández-Torres, G.; Barbas, C. F. *J. Am. Chem. Soc.* **2011**, *133*, 12354–12357.

(17) See the Supporting Information for NMR ^4J coupling features concerning **13**.

(18) See the Supporting Information for comparative LC/MS chromatograms at $t = 0$ h and $t = 12$ h showing the conversion of **13** into **15**.

(19) See the full biosynthetic cascade realized (in this work) in the Supporting Information.