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Total Synthesis of Cladoniamide G

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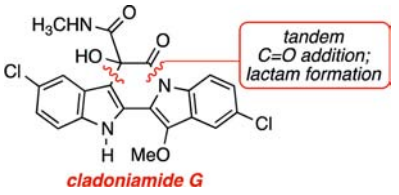
ABSTRACT

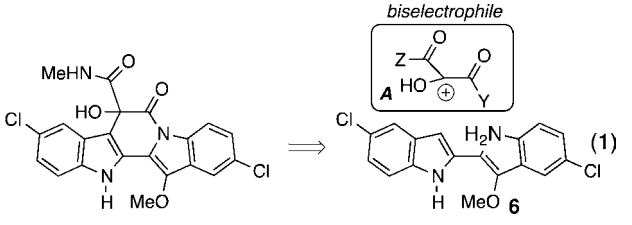


The total synthesis of cladoniamide G, a cytotoxic compound against MCF-7 breast cancer cells (10 μg/mL), was accomplished. Key steps in the sequence include oxidative dimerization of 3-acetoxy-5-chloroindole and a tandem process incorporating three steps: bimolecular carbonyl addition, lactam formation, and carbamate removal.

Natural products containing a 2,2′-bisindole skeleton are known to derive from a variety of marine and terrestrial organisms.[1] Recently, the Andersen group reported the isolation and structural elucidation of a new class of indolotrypoline alkaloids, the cladoniamides, from extracts of *Streptomyces uncialis* harbored within the lichen *Cladonia uncialis* found near the Pitt River, British Columbia (Figure 1).[2] Ryan has reported the biogenetic gene cluster for the cladoniamides that suggests they arise biosynthetically through a tryptophan dimer known as a biosynthetic precursor to the well-described indolocarbazole class of natural products (e.g., staurosporine and rebeccamycin).[3] A characteristic difference between the indolotryptoline and the indolocarbazole alkaloid classes is the relative orientation of the bisindole subunit—one of the indole fragments is flipped within the indolotryptoline.

Compounds within the cladoniamide family differ by the number of carbon atoms (21 or 22), the position of functional groups, oxidation level, and halogen substitution. The presence of chloride substituents has been suggested to be a critical prerequisite for biological activity, as cladoniamide G (**1**) is weakly cytotoxic against MCF-7 breast cancer cells (10 μg/mL in vitro) compared to the activity of cladoniamide F. Similarly, cladoniamide A (**3**), featuring an imide functional group, possesses potent activity (8.8 ng/mL) against human colon cancer HCT116 cells, while cladoniamide C (**5**) lacks this activity.[4]

We were interested in developing a synthetic approach to the cladioniamide set of natural products that would enable simple manipulations in order to generate a set of structural analogs with more significant biological potency. Cladoniamide G (**1**) was selected as a target to provide a context for an initial tactical approach. Cladoniamide G displayed, at the onset of the work, the most significant biological activity.[5] The lessons learned during this exercise would be utilized in second generation approaches to other, perhaps more structurally complicated natural and artificial compounds.



Our analysis of **1** involved establishing the central ring connecting the two indole partners at a late stage of the synthesis (eq 1). Condensation between a biselectrophilic

(1) Sanchez, C.; Mendez, C.; Salas, J. A. *Nat. Prod. Rep.* **2003**, *23*, 1007–1045.

(2) Williams, D. E.; Davies, J.; Patrick, B. O.; Bottriell, H.; Tarling, T.; Roberge, M.; Andersen, R. J. *Org. Lett.* **2008**, *10*, 3501–3504.

(3) (a) Ryan, K. *PLoSONE* **2011**, *6*, e23964. (b) Nakano, H.; Omura, S. *J. Antibiot.* **2009**, *62*, 17–26. (c) Ryan, K. S.; Drennan, C. L. *Chem. Biol.* **2009**, *16*, 351–364.

(4) Chang, F.-Y.; Brady, S. F. *J. Am. Chem. Soc.* **2011**, *133*, 9996–9999.

(5) The synthesis of **3** and its methylated analog BE-54017 has recently been achieved: Kimura, T.; Kanagaki, S.; Matsui, Y.; Imoto, M.; Watanabe, T.; Shibasaki, M. *Org. Lett.* **2012**, *14*, 4418–4421.

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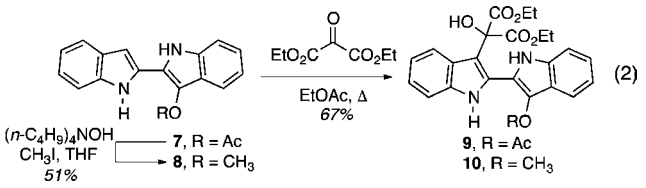
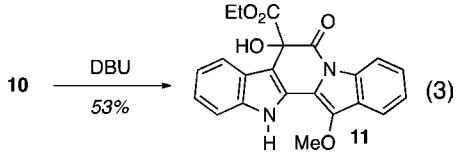
synthon as represented by ***A*** and the C2−C2′ bisindole **6** would generate the carbon skeleton of **1**. The key C2−C2′ bisindole **6** would be constructed using established indigo dye chemistry.[6] 5,5′-Dichloroindigo is a relatively expensive starting material,[7] and consequently some initial experiments to establish the feasibility of this approach were undertaken using indigo as the starting material.



Acetate **7** is readily available from the chemical reduction of indigo using tin metal, acetic anhydride, and acetic acid (eq 2). The acetate function could be converted to a methyl ether in 51% yield through saponification using tetrabutylammonium hydroxide in the presence of methyl iodide. Early experiments had demonstrated the high reactivity of electrophiles at C-3 of the desoxygenated indole. Thus, the reaction with **7** or **8** with diethyl 2-oxomalonate in ethyl acetate led to carbonyl addition product **9** or **10** in 82% and 90% yields respectively.



Attempts to construct the lactam ring of the indolotryptoline core using boron trifluoride etherate activation of **9** were unsuccessful.[8] Treatment of **10** with DBU, however, generated the desired β-ester lactam in 53% yield. The sequence of experiments in eqs 2 and 3 had provided us with (a) the means to convert the acetate within **7** to a methyl ether prior to lactam formation and (b) the apparent need for basic conditions to generate the lactam ring within **11**. With this information in hand, we were ready to utilize 5-chloroindole as a starting material.

Commercially available 5-chloroindole (**12**) was converted to 3-acetoxy-5-chloroindole (**13**) by initial iodination followed by a iodide−acetate exchange process promoted by silver(I) (Scheme 1). Subjecting **13** to sodium hydroxide in ethanol led, as precedented, to the formation of 5,5′-dichloroindigo (**14**).[6] The reduction of **14** using tin metal as precedented for indigo led to a disappointing 22% yield of bisindole **15**. Using the procedure used to process **7**, the saponification and methylation of **15** resulted in methyl ether **6**, but only in 21% yield. The attempts to improve the yields for each of these processes were uniformly unsuccessful. In response, a one-pot procedure was developed that utilizes the reduction of indigo compounds using

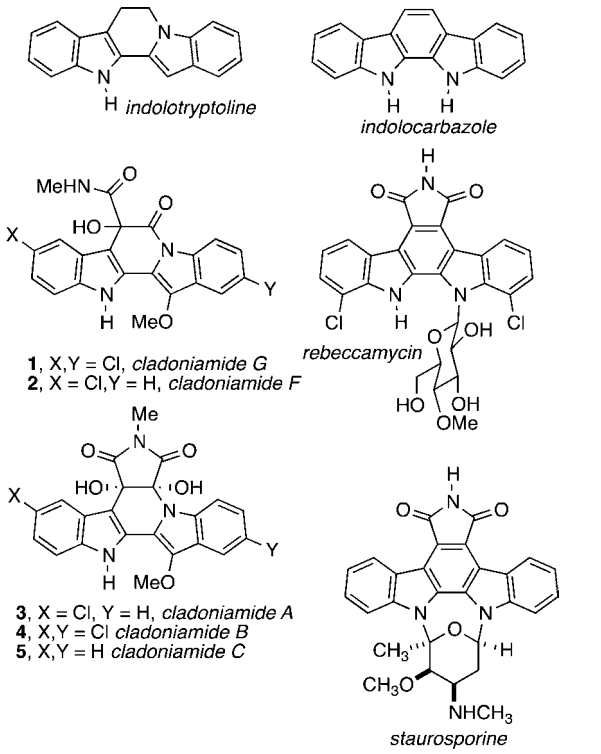


Figure 1. Cladoniamides and biosynthetic relatives.

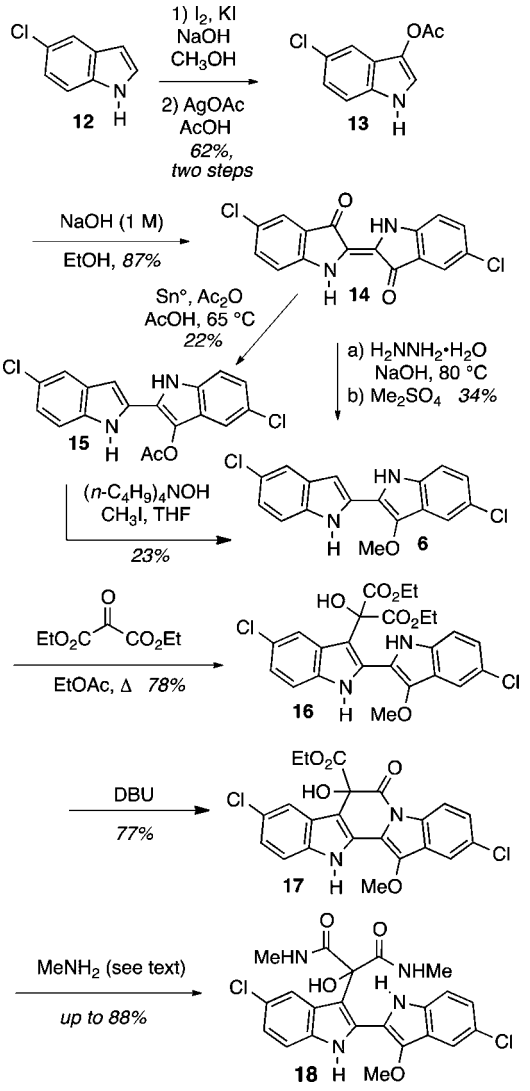
hydrazine and sodium hydroxide with a dimethyl sulfate quench.[9] This reaction converted **14** to **6** directly in 34% yield, a 7-fold improvement. Reaction of **6** with diethyl oxomalonate in hot ethyl acetate to give **16** was followed by its treatment with DBU to generate ethyl ester **17**.

Interestingly, the reaction of **17** with methylamine (5 equiv) generated diamide **18** in 88% yield. We surmised that limiting the amount of methylamine to 1 equiv or lower would allow for the formation of **1** regardless of the site selectivity of the nucleophilic attack of methylamine. In the event, limiting the quantity of methylamine to 1 equiv or lower still produced **18** and unreacted **17**. The use of a more hindered nucleophile such as *N*-methylbenzylamine or modifying solvents or temperatures was not successful. Diamide **18** or its *O*-*tert*-butyldimethylsilyl ether derivative could not be manipulated under a variety of conditions to afford the desired lactam.

At this point, we were forced to track backward to use a conjunctive electrophilic reagent with **6** that contained three distinct carbonyl functions. Diester **19**, produced through a Knoevenagel condensation between dimethyl malonate and benzaldehyde,[10] was carefully saponified to generate carboxylic acid **20** (Scheme 2).[11] Standard manipulations generated carbamate **21**. Oxidative cleavage of **21** with ozone in the absence of methanol as a cosolvent

(6) Tanoue, Y.; Sakata, K.; Hashimoto, M.; Hamada, M.; Kai, N.; Nagai, T. *Dyes Pigm.* **2004**, *62*, 101–105.
(7) 5,5′-Dichloroindigo: $200 CAD/gram; Indigo: $1.40 CAD/gram.
(8) Spectroscopic experiments on the reaction products suggest dehydrative cyclizations to form polycycles took place.
(9) (a) Borsche, W.; Meyer, R. *Ber.* **1921**, *54*, 2854–2856. (b) Bergman, J.; Egestad, B.; Eklund, N. *Tetrahedron Lett.* **1978**, *19*, 3147–3150.
(10) Smith, A. B.; Liu, Z. *Org. Lett.* **2008**, *10*, 4363–4365.
(11) Flipo, M.; Beghyn, T.; Lehoux, V.; Florent, I.; Deprez, B. P.; Deprez-Poulain, R. F. *J. Med. Chem.* **2007**, *50*, 1322–1334.

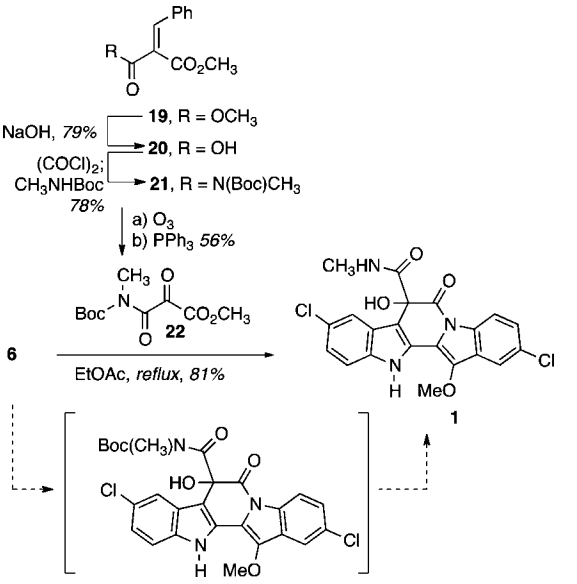
Scheme 1. Approach to **1**



generated, after workup with triphenylphosphine, linchpin reagent **22**. It is recommended that **22** (and similar compounds) be used promptly. During storage, these compounds were noted to convert to carbonyl hydrates.

The reaction of **6** with **22** proceeded efficiently in ethyl acetate at reflux. The examination of the reaction mixture after 12 h using NMR spectroscopy resulted in a gratifying observation—the target compound **1** was a significant product along with unreacted **6**. The carbonyl addition adduct formed in situ unexpectedly underwent additional spontaneous lactam formation and *tert*-butyl carbamate deprotection. Running the reaction between **6** and **22** for a longer reaction time, 72 h, led to essentially complete

Scheme 2. Successful Construction of **1**



conversion of starting materials to **1**, isolated in 81% yield. This synthetically prepared material shared all spectroscopic data with those of the natural compound.

Access to synthetic cladoniamide G has been achieved using a sequence with a low step count (9 steps, 5 in the longest linear sequence, 15% from 5-chloroindole, 27% from dimethyl malonate). The information gathered in this exercise will be useful in second generation approaches to structurally related natural products and their analogs that could display interesting medicinal and biological chemistry properties. Of specific interest to us for further study are *N*-glycosyl derivatives of **1**. We are also interested in examining the chemistry of other members of the cladoniamide family. These studies are underway, and results will be reported in due course.

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Supporting Information Available. Experimental procedures and characterization data for previously unreported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.