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Total Synthesis of Lycogarubin C and Lycogalic Acid

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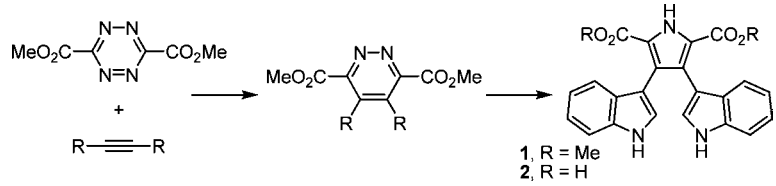
ABSTRACT



Two complementary concise total syntheses of lycogarubin C (1) and lycogalic acid (2, aka chromopyrrolic acid) are detailed utilizing a 1,2,4,5-tetrazine → 1,2-diazine → pyrrole Diels−Alder strategy and enlisting acetylenic dienophiles.

Lycogarubin C (**1**) and lycogalic acid (**2**) were first identified as natural products in 1994, having been isolated independently by Steglich[1] and Akazawa[2] from *Lycogala epidendrum*, a slime mold (Figure 1). More recently, lycogalic acid, also referred to as chromopyrrolic acid (CPA),[3] has been identified as a common intermediate in the biosynthesis of the indolo[2,3-*a*]carbazole alkaloids including rebeccamycin (**6**) and staurosporine (**7**) that exhibit broad spectrum activity as inhibitors of protein kinases as well as Topoisomerase I.[4] As the efforts to elucidate the details of this biosynthetic pathway have progressed, the oxidation of chromopyrrolic acid (**2**) to **4** via **3** has attracted considerable interest since it involves an unusual oxidative aryl−aryl coupling reaction.[3,5] Moreover, in exploration of the individual enzyme-catalyzed steps in the pathway, **5** was isolated as an aerobic product following the oxidative coupling of **2** effected by RebP/StaP.[6] As an off-pathway intermediate that does not lead to formation of **4**, it is likely that **5** and related compounds may well constitute the newest members of this class of natural products. As a result, we initiated efforts on the synthesis of **1** and **2** that in turn may serve as synthetic as well biosynthetic precursors to these potential newest members of this class of natural products.

Complementary to reports of the synthesis of **1** or **2**,[1,7−9] we anticipated that **1** and **2** would be readily accessible through use of a 1,2,4,5-tetrazine → 1,2-diazine → pyrrole Diels−Alder strategy that appears ideally suited for their preparation.[10] Thus, the inverse electron demand Diels−Alder reaction of a 1,2-bis(indol-3-yl)acetylene (**8**) with

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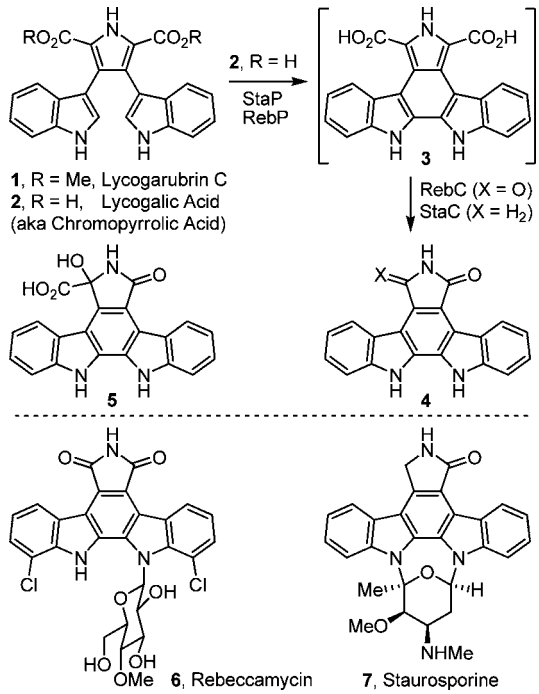


Figure 1. Natural products.

dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**9**)[11] followed by a reductive ring contraction reaction of the resulting 1,2-diazine[12] to a dimethyl pyrrole-2,5-dicarboxylate could directly provide **1** or a protected penultimate precursor (Figure 2). Moreover, the potential use of the mono methyl

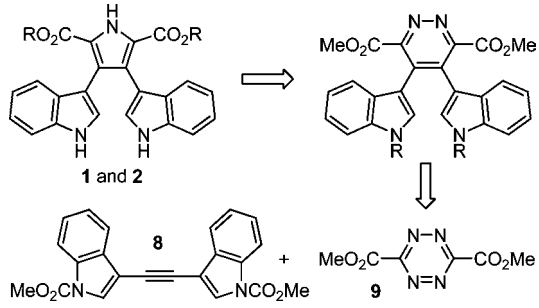
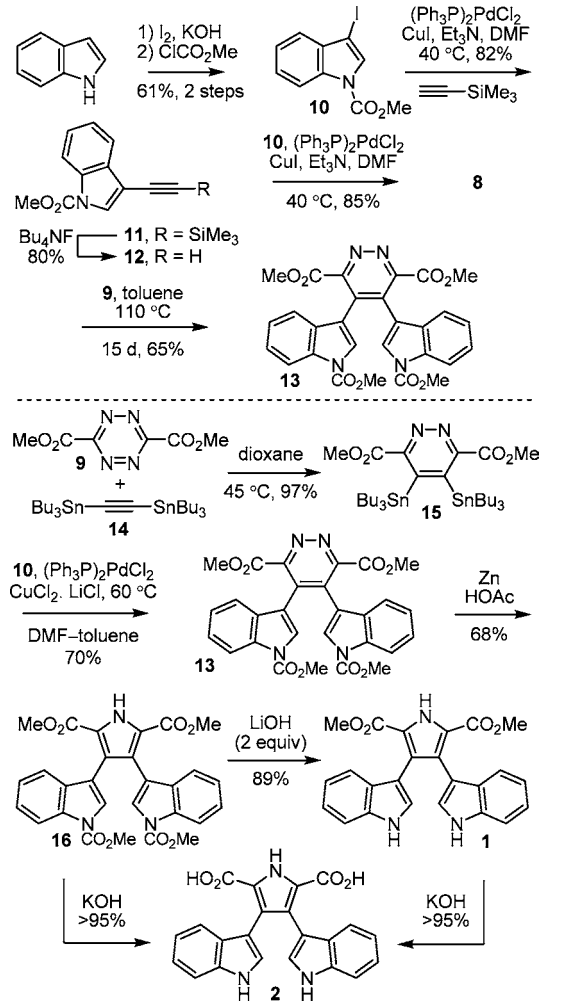


Figure 2. Initial synthetic strategy.

esters derived from such dimethyl pyrrole-2,5-dicarboxylates to directly access products such as **5** via a unique oxidative decarboxylation reaction[13] provided the additional incentive for us to pursue the synthesis of **1** and **2**. The recent disclosure of Fu and Gribble[9] reporting that this direct strategy was not successful and their development of a clever alternative, using an olefinic versus acetylenic dienophile, provided the incentive for us to disclose our related but more successful observations utilizing acetylenic dienophiles.

The initial route explored entailed implementing the Diels−Alder reaction of the 1,2-bis[(*N*-methoxycarbonyl)-indol-3-yl]acetylene (**8**) with 1,2,4,5-tetrazine **9**, Scheme 1. The preparation of the indole-substituted acetylene **8** began

Scheme 1. Two Syntheses of **1** and **2**



with iodination of indole followed by immediate methyl carbamate protection of the sensitive indole providing **10**. Stepwise Sonogashira coupling of **10** first with trimethylsilylacetylene (82%), TMS deprotection of **11** (Bu_4NF, THF, 80%), and subsequent coupling of the resulting acetylene **12** again with **10** provided **8** (85%).

The Diels−Alder reaction of acetylene **8** with **9** provided **13** (65%) in a reaction that proved sluggish, requiring 15 d in refluxing toluene (110 °C) with repetitive additions of the 1,2,4,5-tetrazine **9** every 3 d as it slowly decomposes at this temperature. Use of higher reaction temperatures simply accelerated the decomposition of the 1,2,4,5-tetrazine **9** and did not lead to improvements in the rate or conversions to **13**. Notably and although this result merits the examination of alternative approaches to the preparation of the 1,2-diazine **13**, it was not as unsuccessful as reported by Fu and Gribble.[9] In fact, such 1,2-diarylacetylenes exhibit a reactivity that is dependent on the electronic character of the aryl groups. For

example, although alkoxyphenyl substituents convey sufficient reactivity to such alkynes making their use synthetically attractive,[12d,e,g] the unsubstituted diphenylacetylene itself reacts with **9** only slowly. We found that **8** exhibits a reactivity that is slightly lower than that of diphenylacetylene and that it not as reactive as a number of more productive acetylenic dienophiles.

The acetylene adopted for an alternative approach to **13** was 1,2-bis(tributylstannyl)acetylene (**14**).[14] The reaction of **14** with dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (**9**) proceeded smoothly in dioxane under mild thermal conditions (45 °C, 24 h) and provided the Diels−Alder product **15** in exceptional conversions (97%). Subsequent Stille coupling of **10** with the resulting 1,2-diazine **15** proceeded effectively and twice providing the same key 4,5-bis(indol-3-yl)-1,2-diazine **13** in good yield (70%). In the optimization of this reaction, $(Ph_3P)_2PdCl_2$ proved more effective than $(Ph_3P)_4Pd$, the addition of CuI or $CuCl_2$ improved the initially modest conversions, and the additional inclusion of LiCl further improved the reaction eliminating a side reaction of proto deiodination.

Treatment of **13** with Zn/HOAc (30 equiv Zn, HOAc/CH_2Cl_2 1:1, 25 °C, 12 h) cleanly effected the reductive ring contraction reaction, providing pyrrole **16** (68%) and completing the 1,2,4,5-tetrazine → 1,2-diazine → pyrrole conversions originally envisioned. Selective removal of the indole *N*-methoxylcarbonyl groups under mild conditions (2 equiv of LiOH, MeOH/THF/H_2O 2:2:1, 24 °C, 12 h) provided lycogarubin C (**1**) in good to excellent conversion (65−89%), whereas exhaustive hydrolysis of **16** (7 equiv of KOH, THF/H_2O 1:1, 45 °C, 24 h) or hydrolysis of **1** (3.5 equiv of KOH, THF/H_2O 1:1, 45 °C, 16 h) afforded lycogalic acid (**2**) in superb conversion (95%).

Thus, two complementary syntheses of **1** and **2** based on a 1,2,4,5-tetrazine → 1,2-diazine → pyrrole Diels−Alder strategy using acetylenic dienophiles are disclosed that extend our use of heterocyclic azadiene Diels−Alder reactions[12,15] to a key biosynthetic precursor to the indolo[2,3-*a*]carbazole alkaloids.

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Supporting Information Available: Full experimental details and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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