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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 Steglich¹ and Akazawa² 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 dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate (9)¹¹ followed by a reductive ring contraction reaction of the resulting 1,2-diazine¹² 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 esters derived from such dimethyl pyrrole-2,5-dicarboxylates to directly access products like 5 via a unique oxidative decarboxylation reaction¹³ provided the additional incentive for us to pursue the synthesis of 1 and 2. The recent disclosure of Fu and Gribble⁹ reporting that this direct strategy was not successful and their development of a clever alternative, using an olefinic versus

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Supporting Information Available. Full experiment details and compound characterizations are provided. This material is available free of charge via the internet at <http://pubs.acs.org>.

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 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** (Bu₄NF, 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, (Ph₃P)₂PdCl₂ proved more effective than (Ph₃P)₄Pd, the addition of CuI or CuCl₂ 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–CH₂Cl₂ 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*-methoxycarbonyl groups under mild conditions (2 equiv of LiOH, MeOH/THF/H₂O 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/H₂O 1:1, 45 °C, 24 h) or hydrolysis of **1** (3.5 equiv of KOH, THF/H₂O 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Natural products.

Figure 2.
Initial synthetic strategy.

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