

Enantioselective Total Synthesis of Plectosphaeroic Acid B

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Supporting Information

ABSTRACT: The first total synthesis of a member of the plectosphaeroic acid family of fungal natural products is reported. Key steps include the late-stage formation of the hindered N6–C9'' bond and stereoselective introduction of the two methylthio substituents.

In 2009, Mauk, Andersen, and co-workers reported the isolation of plectosphaeroic acids A–C (**1–3**) from cultured extracts of the fungus *Plectosphaerella cucumerina* collected in Barkley Sound, British Columbia, Canada (Figure 1).¹ These

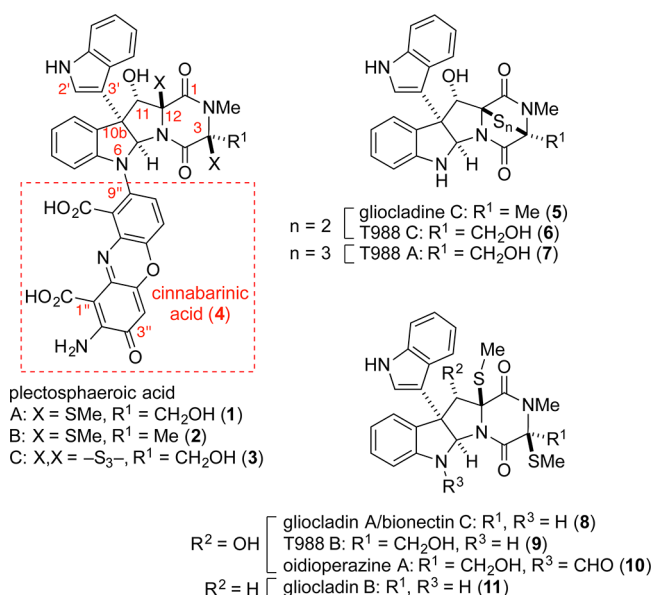


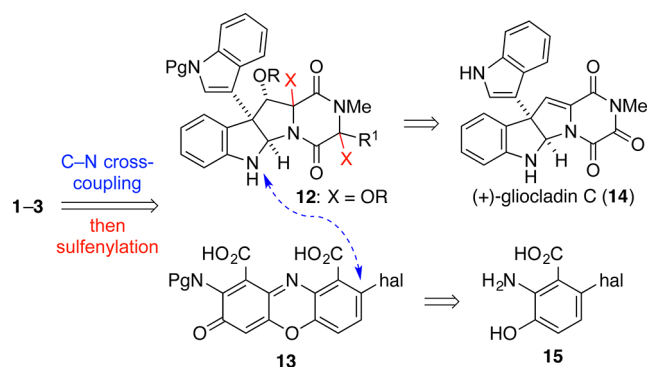
Figure 1. The plectosphaeroic acids and related metabolites.

highly functionalized, secondary metabolites are defined by the union of a tryptophan-derived epitrithiodioxopiperazine (or methylthio analogue)² and 2-aminophenoxazin-3-one fragments,³ structural motifs commonly found in natural products but never before seen in conjunction. A number of epipolythiodioxopiperazine (ETP) alkaloids and their methylthio congeners (e.g., **5–11**) share a polycyclic core that is homologous to the northern fragments of **1–3**.^{4,5} Naturally occurring cinnabaric acid (**4**) comprises the southern fragment of **1–3**. Molecules comprised of either structural motif display a broad spectrum of biological properties (e.g., antimicrobial, antiviral, antifungal, immunosuppressive, and anticancer activities),^{2,3} with numerous studies focusing on chemotherapeutic applications.^{6,7} In the isolation report, it was

disclosed that **1–3** were equipotent (IC₅₀ = 2 μM) against indoleamine 2,3-dioxygenase (IDO), a recently identified molecular target for the potential treatment of cancer. Although it was found that only the phenoxazinone subunit is required for this activity,⁸ we were intrigued by the potential utility of molecules that contain both anticancer motifs,⁹ as well as the considerable synthetic challenges^{10–12} posed by the complexity of **1–3**. Herein, we describe our recent efforts that culminated in the first total synthesis of (+)-plectosphaeroic acid B (**2**).

Our plan for preparing plectosphaeroic acids A–C (**1–3**) is outlined in Scheme 1. We envisaged stereoselectively

Scheme 1

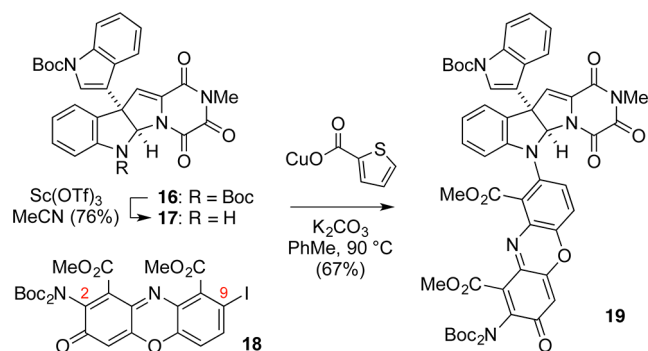


introducing the labile thioethers or bridging trisulfide functionalities of **1–3** after late-stage construction of the critical N6–C9'' bond between the indoline nitrogen atom of fragment **12** and a halogenated congener **13** of cinnabaric acid. Although efficient transition metal-catalyzed methods are known, the hindered nature and structural complexity of these intermediates would make the successful joining of fragments **12** and **13** one of the most challenging applications of C–N cross-coupling to date.^{13,14} Fragment **12** was seen arising from the simpler trioxopiperazine alkaloid (+)-gliocladiol C (**14**)^{4b,e,10a,15} using a general sequence our group disclosed in 2011 for the total synthesis of the ETP natural product (+)-gliocladiol C (**5**).¹⁰ Halide **13** was envisioned originating from the biomimetic, oxidative dimerization of 6-halo-3-hydroxyanthranilic acid **15**.¹⁶

In order to assess the feasibility of—and identify conditions for—the critical C–N bond-forming step, we began our efforts by examining *N*-arylation of a structurally simplified indoline fragment (Scheme 2). The di-(*tert*-butoxycarbonyl) derivative **16** of (+)-gliocladiol C, which is available on multigram scale by

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Scheme 2



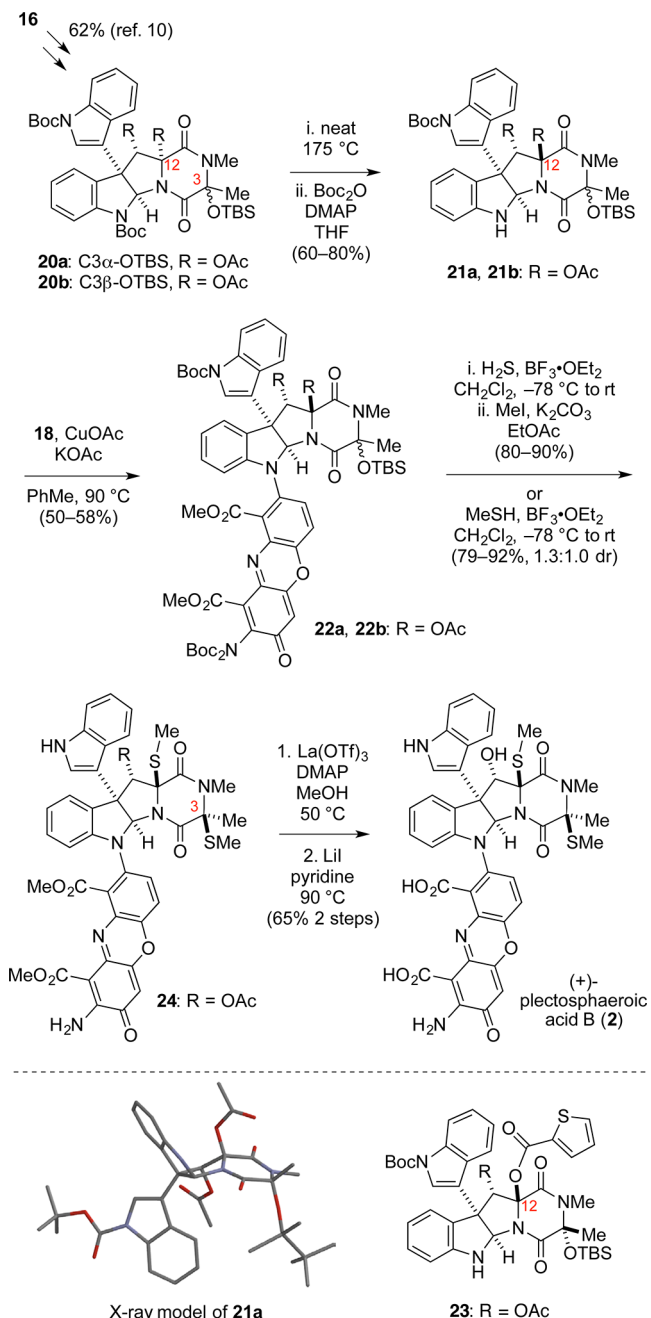
chemical synthesis,^{10a} was exposed to a catalytic amount of $\text{Sc}(\text{OTf})_3$, resulting in the selective deprotection of the indoline nitrogen atom. After a considerable screening effort,¹⁷ joining of the two fragments was realized in 67% yield when indoline 17 was allowed to react with 2.3 equiv of iodide 18,¹⁸ 3.0 equiv of copper(I) thiophene-2-carboxylate (CuTC),¹⁹ and excess K_2CO_3 in toluene at 90 °C. Other $\text{Cu}(\text{I})$ salts and ligand combinations that were screened gave poor conversions to 19 (0–20% yields). Reducing the amount of CuTC also resulted in low yields of 19. Additionally, it was found that double protection of the 2-amino group of iodide 18 was critical,²⁰ and that N -arylation of the corresponding bromide was much less efficient (8% yield of 19). Although the excess of iodide 18 was recoverable, minor amounts of the byproduct arising from undesired hydrodehalogenation of 18 were observed as well. Having discovered conditions to successfully unite the two fragments, we focused our attention on the synthesis of plectosphaeric acid B (2).

The total synthesis of (+)-plectosphaeric acid B (2) commenced with deprotection of the indoline nitrogen atoms of the individual epimers 20a and 20b, intermediates previously prepared en route to (+)-gliocladiene C (5) (Scheme 3).¹⁰ Attempts to chemoselectively remove the Boc group of 20a or 20b with Lewis or protic acids proved challenging because of the other acid-labile functionalities that were present, including the C3- and C12- N,O -acetals. For this reason, a two-step (single-pot) procedure was developed. Thermolytic cleavage of both Boc groups of 20a or 20b, followed by selective reprotection of the indole nitrogen atom by reaction with 1 equiv of Boc_2O and a catalytic amount of DMAP, afforded intermediates 21a and 21b in 60–80% yields. Complete inversion of the C12-stereocenter occurred during the thermolytic deprotection step.²¹

The potential to form an N -acyliminium ion by loss of the oxygen substituents at C3 or C12 also complicated the ensuing copper-mediated C–N cross-coupling reaction. In preliminary experiments, treatment of epimer 21a with iodide 18, CuTC , and K_2CO_3 resulted in inefficient conversion to the coupled product 22a (10–30% yields). In these reactions, some formation of the thiophene-2-carboxylate adduct 23 was observed. As in situ activation of the angular N,O -acetal appeared unavoidable, we explored substituting CuTC with CuOAc ²² in order to minimize the formation of byproducts. After some optimization, exposure of 21a or 21b to 3.0 equiv of iodide 18 and 6.0 equiv of CuOAc in toluene at 90 °C delivered 22a and 22b in 50–58% yields.

We turned our attention to the stereoselective installation of the methylthio substituents of 2.²³ Activation of the N,O -acetals

Scheme 3



of 22a and 22b by exposure to excess $\text{BF}_3 \cdot \text{OEt}_2$ and MeSH in CH_2Cl_2 at -78 °C with slow warming to room temperature led to the generation of a 1.3:1.0 mixture of di(methylthio)ethers 24 and C3-*epi*-24 in high yield (79% from 22a, 92% from 22b). Alternatively, it was found that transforming 22a or 22b by reaction with H_2S and $\text{BF}_3 \cdot \text{OEt}_2$, then methylation with MeI and K_2CO_3 , provided *cis*-di(methylthio)ether 24 in 80–90% yield as virtually a single stereoisomer. The difference in stereochemical outcomes for these sulfenylation procedures warrants further comment. Substantial precedent suggests that introduction of the sulfur nucleophile would occur first at C12, with high stereoselectivity from the concave face.^{2c,e,10,11} The factors governing the facial selectivity of the subsequent addition of the sulfur nucleophiles at C3 are less certain. The greater stereoselectivity we observe in forming 2 by the two-

step sequence could reflect the difference between directly forming configurationally stable thioether products and proceeding via configurationally less stable hemithioaminal intermediates, which could be equilibrating under the sulfenylation or methylation conditions to the more stable cis product.^{24–26}

Completion of the synthesis of (+)-plectosphaeroic acid B (2) required careful cleavage of the three remaining ester groups.²⁷ Methanolysis of the C11-acetate of 24 was achieved using excess La(OTf)₃ and 1 equiv of DMAP at 50 °C. Conversion of the methyl esters of the phenoxazinone subunit to carboxylic acids by the use of LiI in pyridine at 90 °C gave (+)-plectosphaeroic acid B (2) in 65% yield over two steps after HPLC purification. The optical rotation of synthetic 2, [α]_D²³ +228 (c 0.08, MeOH), was considerably higher than the value reported for the natural sample, [α]_D²³ +69.8 (c 0.27, MeOH). However, all other spectroscopic data, including CD spectra, compared well.

In conclusion, the first total synthesis of (+)-plectosphaeroic acid B (2) was achieved in seven steps from the known intermediates 20a and 20b. This total synthesis confirms the unique structure and absolute configuration of plectosphaeroic acid B, which had been assigned on the basis of NMR, MS, and CD data.¹ Introduction of the highly congested, central C–N bond of 2 by a late-stage copper-mediated process provides one of the most demanding examples of C–N cross-coupling reported to date. The convergence of this synthesis strategy should enable the synthesis of the remaining plectosphaeroic acids and analogues and allow for the pharmacological evaluation of these and related molecules containing multiple anticancer motifs.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental details, characterization data, ¹H and ¹³C NMR spectra of new compounds, complete ref 6c, and CIF file for 21a. 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.

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(17) Our early investigations focused on the *N*-arylation of indoline **17** with *o*-bromo(or iodo)benzoic acids and derivatives with Cu(I) and Pd(0) catalysts.¹³ Successful *N*-arylation was observed only using Cu(I) catalysts.

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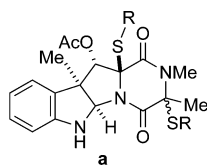
(20) For example, the corresponding mono-Boc derivative of **18** was cross-coupled in less than 20% yield.

(21) The relative and absolute configuration of **21a** was secured by single crystal X-ray diffraction. These data have been deposited at The Cambridge Crystallographic Data Centre as entry CCDC 922842 and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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(24) As observed computationally (and likely experimentally) for simple 2,5-dialkyl-3,6-di-(*p*-methoxybenzylthio)dioxopiperazines,²⁵ the lowest energy *cis*-disulfated stereoisomers of **a** are calculated (B3-LYP/def2-TZVP)²⁶ to be more stable by 2.5 kcal/mol (R = H) and 0.9 kcal/mol (R = Me).



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