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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

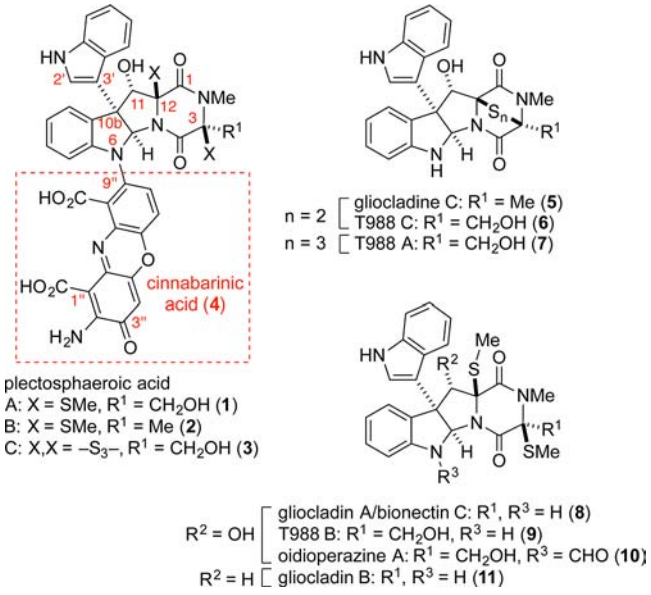
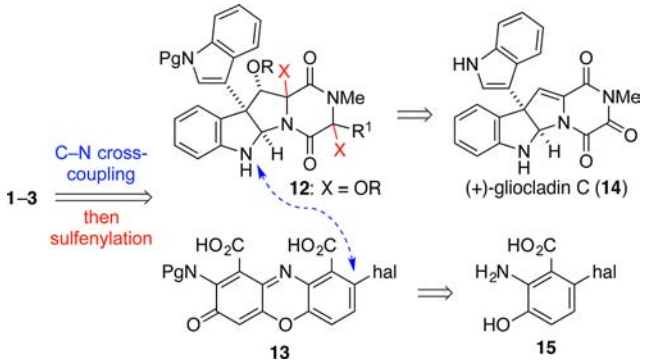


Figure 1. The plectosphaeroic acids and related metabolites.

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 cinnabarinic 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 (IC_{50} = 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 cinnabarinic 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 (+)-gliocladin C (**14**)[4b,e,10a,15] using a general sequence our group disclosed in 2011 for the total synthesis of the ETP natural product (+)-gliocladine 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 (+)-gliocladin C, which is available on multigram scale by

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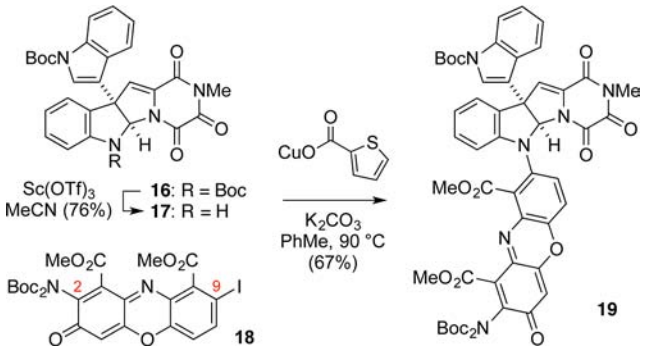
Scheme 2



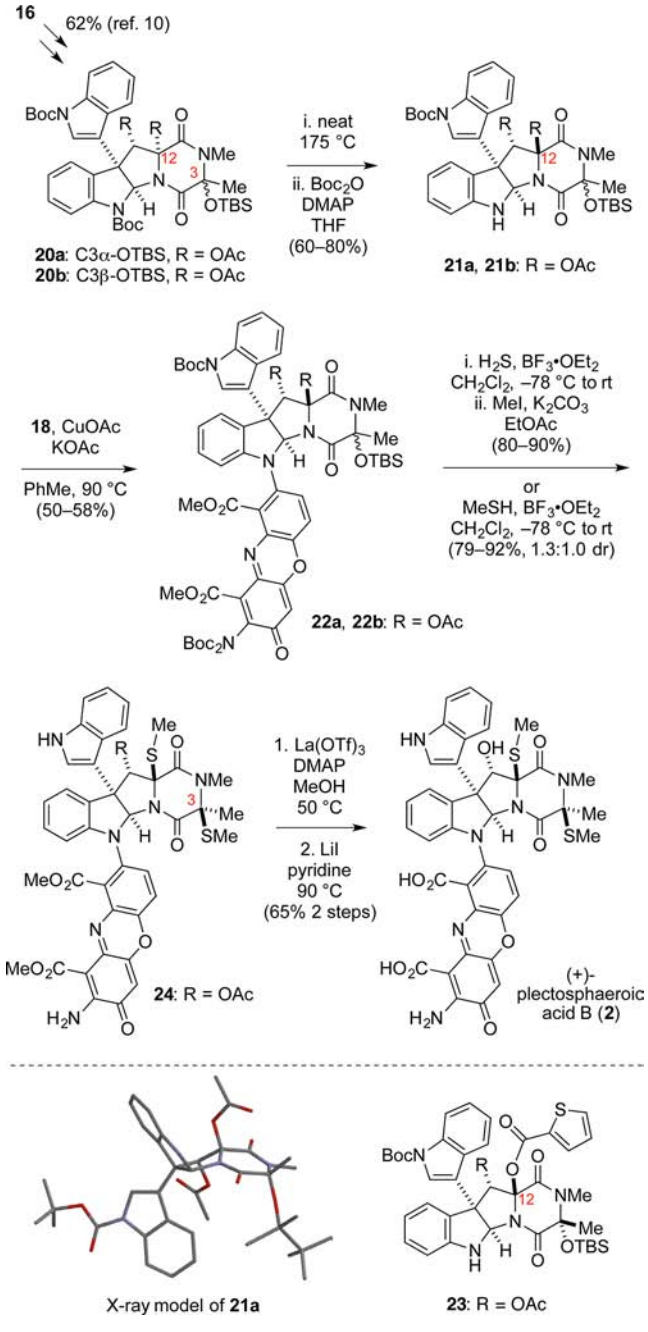
chemical synthesis,[10a] was exposed to a catalytic amount of $Sc(OTf)_3$, resulting in the selective deprotection of the indoline nitrogen atom. After a considerable screening effort,[17] joining of the two fragments was realized in 67% yield when indoline **17** was allowed to react with 2.3 equiv 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 Cu(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 plectosphaeroic acid B (**2**).

The total synthesis of (+)-plectosphaeroic acid B (**2**) commenced with deprotection of the indoline nitrogen atoms of the individual epimers **20a** and **20b**, intermediates previously prepared en route to (+)-gliocladine 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 $BF_3{\cdot}OEt_2$ 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 $BF_3{\cdot}OEt_2$, 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-

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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**, $[\alpha]_D^{23}$ +228 (*c* 0.08, MeOH), was considerably higher than the value reported for the natural sample, $[\alpha]_D^{23}$ +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 ^{13}C 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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(18) See Supporting Information for details of the preparation of **18**.

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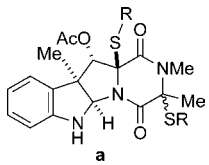
(24) As observed computationally (and likely experimentally) for simple 2,5-dialkyl-3,6-di-(*p*-methoxybenzylthio)dioxopiperazines,[25] the lowest energy *cis*-disulfated stereoisomers of **a** are calculated (B3-LYP/def2-TZVP)[26] to be more stable by 2.5 kcal/mol (R = H) and 0.9 kcal/mol (R = Me).



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