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Enantioselective Total Synthesis of (+)-Gliocladine C: Convergent Construction of Cyclotryptamine-Fused Polyoxopiperazines and a General Approach for Preparing Epidithiodioxopiperazines from Trioxopiperazine Precursors

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Supporting Information

ABSTRACT: A concise second-generation total synthesis of the fungal-derived alkaloid (+)-gliocladin C (**11**) in 10 steps and 11% overall yield from isatin is reported. In addition, the epipolythiodioxopiperazine (ETP) natural product (+)-gliocladine C (**6**) has been prepared in six steps and 29% yield from the di-(*tert*-butoxycarbonyl) precursor of **11**. The total synthesis of **6** constitutes the first total synthesis of an ETP natural product containing a hydroxyl substituent adjacent to a quaternary carbon stereocenter in the pyrrolidine ring.

Epipolythiodioxopiperazine (ETP) toxins are fungal secondary metabolites that possess unique molecular structures and a wide range of biological activities (Figure 1).[1] The toxicity of these amino acid-derived natural products is attributed to the di- or polysulfide bridge of the dioxopiperazine subunit, which can either conjugate directly to cysteine residues or generate reactive oxygen species. A number of recent studies point to the potential utility of epidithiodioxopiperazines in cancer chemotherapy,[2] as impressive selectivities toward both myeloma[3] and solid tumors[4] have been demonstrated and novel molecular targets have been identified.[5] The structure and chemical lability of ETPs pose a number of challenges for chemical synthesis. In a remarkable accomplishment, Fukuyama and Kishi disclosed the total synthesis of gliotoxin (**1**) in 1976,[6] and the chemistry developed in those investigations for incorporation of an epidithiodioxopiperazine unit[7] was subsequently used for the synthesis of various other ETP natural products.[8] In an incisive total synthesis of dideoxyverticillin A (**2**) reported in 2009 by Movassaghi and co-workers, biosynthetically inspired oxidation of cyclotryptamine-fused dioxopiperazines and sulfidation were employed to elaborate epidithio bridges onto dimeric dioxopiperazine precursors.[9,10] Shortly thereafter, Sodeoka and co-workers reported the synthesis of (+)-chaetocin A (**3**) using a related strategy for forging the epidithiodioxopiperazine units.[11]

The largest group of ETP natural products is derived from tryptophan and contains an ETP ring fused to a cyclotryptamine fragment (Figure 1).[1] In many of these structures, the carbon of the pyrrolidine ring adjacent to the quaternary carbon stereocenter bears a hydroxyl substituent (e.g., **4**−**10** in Figure 1). Herein we disclose a general approach for preparing ETPs having this highly

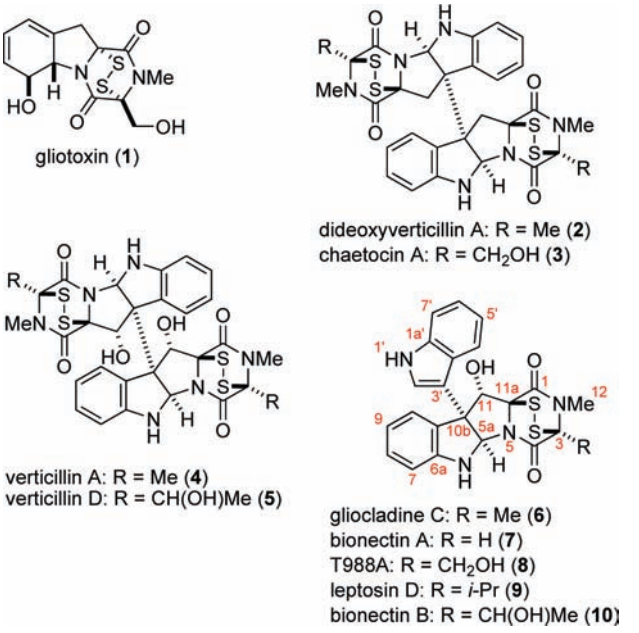

Figure 1. Some ETP natural products.

labile hydroxyl substituent,[12] which we illustrate by an enantioselective total synthesis of (+)-gliocladine C (**6**).[13,14] Critical to our success was the development of a new convergent method for constructing cyclotryptamine-fused polyoxopiperazines.

Our approach for preparing **6** and congeners is outlined in Scheme 1. We hypothesized that the simpler alkaloid (+)-gliocladin C (**11**)[15] might serve as a synthetic precursor of this family of ETPs through three potentially straightforward transformations: (i) nucleophilic addition of a C3 substituent[16] to the α-ketoimide carbonyl group, (ii) dihydroxylation of the alkylidene dioxopiperazine double bond, and (iii) formation of the disulfide bridge.

The opening phase of this endeavor was the development of an efficient second-generation total synthesis of **11**, the first total synthesis of which was reported by our laboratory in 2007.[12] Our plan was to assemble the tetracyclic core of **11** from the union of enantioenriched dielectrophile **12** and dinucleophile **13**,[17] with

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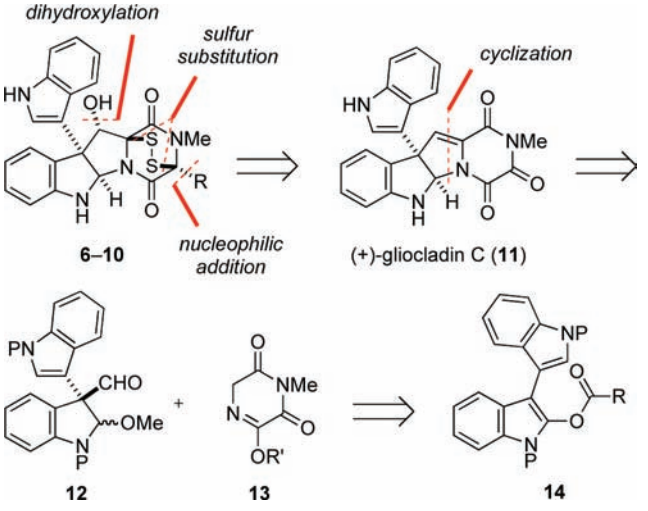
Scheme 1. Retrosynthetic Analysis of ETPs 6−10



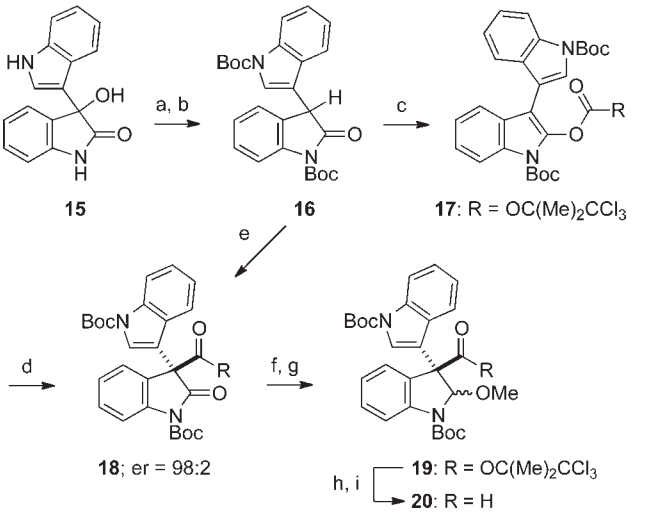
the quaternary carbon stereocenter of the former arising from a catalytic enantioselective Steglich-type rearrangement of indolyl carbonate **14**.[18,19]

The synthesis of **11** commenced with acid-promoted ionic reduction of readily available 3-hydroxy-3,3′-biindolin-2-one (**15**)[20] followed by Boc protection to give intermediate **16** (Scheme 2).[21] Reaction of oxindole **16** with 2,2,2-trichloro-1,1-dimethylethyl chloroformate and Et_3N delivered prochiral indolyl carbonate **17** in 66% overall yield from biindolinone **15**. Catalytic rearrangement of **17** took place efficiently and with high enantioselectivity at room temperature in the presence of a 5 mol % loading of Fu's (*S*)-(−)-4-pyrrolidinopyrindinyl(pentamethylcyclopentadienyl)iron catalyst[19a] to give 3,3-disubstituted oxindole **18** in 96% yield and a 98:2 enantiomer ratio (er) on scales of up to 15 g. In addition, direct reaction of oxindole **16** with 2,2,2-trichloro-1,1-dimethylethyl chloroformate, Et_3N, and 10 mol % of Fu's catalyst at 40 °C provided oxindole ester **18** in 88% yield and identical high enantioselectivity (98:2 er).

After several shorter approaches proved inefficient or resulted in partial racemization,[22] oxindole **18** was elaborated to indoline **20** in good yield as follows. The oxindole carbonyl group of **18** was reduced selectively with $NaBH_4$ at 0 °C, and the resulting 2-hydroxyindoline intermediate was exposed to a methanolic solution of trimethyl orthoformate and a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) at 65 °C to afford indoline *N*,*O*-acetal **19**, a 1.2:1.0 mixture of the α- and *β*-*N*,*O*-acetal epimers, in 67% overall yield. Sequential Soai reduction[23] and Dess−Martin oxidation[24] provided enantioenriched dielectrophile **20** in 80% yield from **19**.

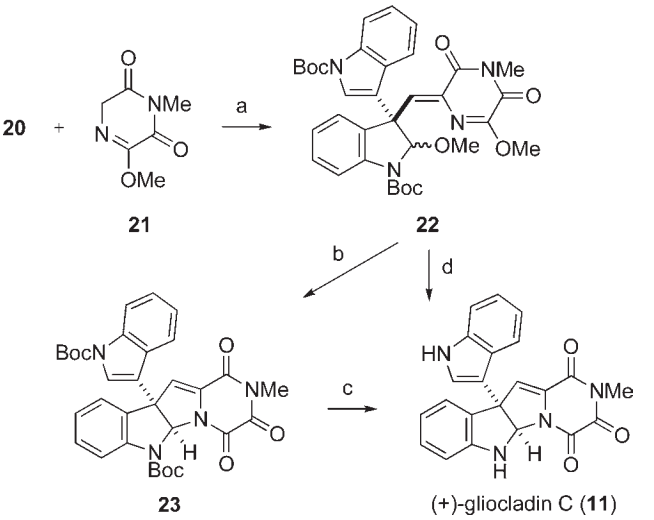
In two additional steps, indoline aldehyde **20** was united with trioxopiperazine derivative **21** to provide **11** (Scheme 3). Aldol condensation of aldehyde **20** with the lithium enolate of piperazinedione **21**[25] in THF at −78 °C followed by quenching of the reaction with excess acetic acid and warming to room temperature delivered condensation product **22** exclusively as the *Z* stereoisomer in 75% yield. Exposure of **22** to $BF_3\cdot OEt_2$ at −40 °C promoted cyclization and concomitant demethylation to provide trioxopiperazine-fused cyclotryptamine **23** in 80% yield. The Boc protecting groups of **23** were then removed thermolytically[26] to afford crystalline (+)-gliocladin C (**11**) in 89% yield. Alternatively, coupled intermediate **22** could be transformed directly to **11**

Scheme 2. Preparation of Enantioenriched Dielectrophile 20[a]



[a] Reaction conditions: (a) TFA, Et_3SiH, CH_2Cl_2, rt. (b) (i) $(Boc)_2O$, 15 mol % DMAP, CH_2Cl_2, rt; (ii) MeOH (68% from **15**). (c) 2,2,2-Trichloro-1,1-dimethylethyl chloroformate, Et_3N, THF, 0 °C (97%). (d) (*S*)-(−)-4-Pyrrolidinopyrindinyl(pentamethylcyclopentadienyl)iron, THF, rt (96%, 98:2 er). (e) 2,2,2-Trichloro-1,1-dimethylethyl chloroformate, Et_3N, (*S*)-(−)-4-pyrrolidinopyrindinyl(pentamethylcyclopentadienyl)iron, THF, 40 °C (88%, 98:2 er). (f) $NaBH_4$, MeOH, 0 °C (81%). (g) $HC(OMe)_3$, 10 mol % PPTS, MeOH, 65 °C (83%; 1.2:1.0 dr). (h) $LiBH_4$−MeOH, Et_2O, rt to 40 °C (84%). (i) Dess−Martin periodinane, pyridine, CH_2Cl_2, rt (95%).

Scheme 3. Second-Generation Synthesis of (+)-Gliocladin C (11)[a]



[a] Reaction conditions: (a) (i) LDA, **21**, THF, −78 °C; (ii) **20**, −78 °C; (iii) AcOH, −78 °C to rt (75% from **20**). (b) $BF_3\cdot OEt_2$, CH_2Cl_2, −78 to −40 °C (80%). (c) Neat, 175 °C (89%). (d) $Sc(OTf)_3$, MeCN, 0 °C to rt (60%).

$\{[\alpha]_D^{23}$ +127 (*c* 0.23, pyridine)$\}$[27] in 60% yield upon reaction with excess $Sc(OTf)_3$ in acetonitrile from 0 °C to room temperature. Single-crystal X-ray diffraction of the synthetic **11** confirmed the constitution and relative configuration of this natural product.[28]

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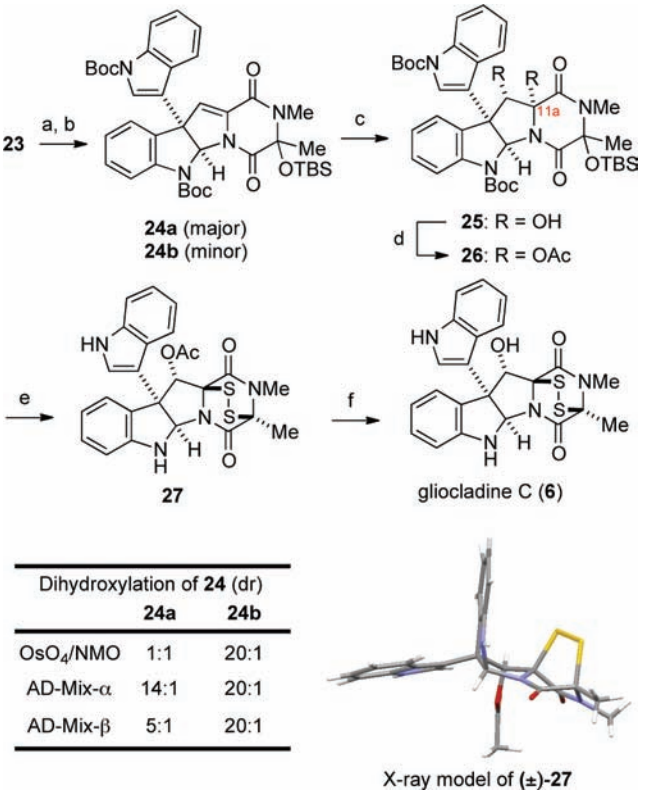
Scheme 4. Synthesis of (+)-Gliocladine C (6)[a]



Dihydroxylation of **24** (dr)	**24a**	**24b**
OsO_4/NMO	1:1	20:1
AD-Mix-α	14:1	20:1
AD-Mix-β	5:1	20:1

X-ray model of (±)-27

[a] Reaction conditions: (a) MeMgCl, THF, −78 °C (86%, 9:1 dr). (b) TBSOTf, DMAP, Et_3N, DMF, rt (94%, 3:2 dr). (c) Mixture of **24a** and **24b** (3:2), AD-Mix-α, H_2NSO_2Me, $K_2OsO_4 \cdot 2H_2O$, $(DHQ)_2PHAL$, *t*-BuOH/H_2O/acetone, rt (82%, >14:1 dr). (d) Ac_2O, DMAP, CH_2Cl_2, rt (93%). (e) (i) H_2S, $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C to rt; (ii) O_2, MeOH/EtOAc, rt (62%). (f) $La(OTf)_3$, MeOH, 40 °C (75%).

With substantial quantities of trioxopiperazine-fused pyrrolidinoindoline **23** in hand, we turned to its transformation into **6** (Scheme 4). Chemoselective addition[29] of methylmagnesium chloride to trioxopiperazine **23** at −78 °C provided a 9:1 mixture of epimeric tertiary alcohols, which was silylated to give dioxopiperazine **24** as a 3:2 mixture of siloxy epimers in 81% overall yield. Although it was most convenient to prepare ETP product **27** directly from this mixture of stereoisomers (see below), insight into the dihydroxylation step was obtained when epimers **24a** and **24b** were separated and individually examined. As summarized in Scheme 4, catalytic dihydroxylation of the minor siloxy epimer was highly substrate-controlled, yielding α-diol **25** with 20:1 diasteroselectivity when OsO_4/NMO, AD-Mix-α, or AD-Mix-*β* was used.[30] Although no diasteroselectivity was observed in the dihydroxylation of the major epimer **24a** with OsO_4, diastereoselection in forming the α-diol product was improved to 14:1 using AD-Mix-α. With this oxidant, the initially produced 3:2 mixture of siloxy epimers **24** was dihydroxylated, and the crude diol products were acetylated to provide diacetates **26** in 76% yield over the two steps.[30b,31] Reaction of this mixture of siloxy epimers with condensed hydrogen sulfide and $BF_3 \cdot OEt_2$ in CH_2Cl_2 from −78 °C to room temperature[32] followed by exposure of the product to oxygen delivered ETP product **27** in 62% yield.[33,34] We speculate that the stereoselection in this step is the result of initial formation of an iminium ion at C11a followed by kinetically controlled trapping with H_2S from the face opposite both the angular indolyl substituent and the adjacent acetate.

At this stage, all that remained was the removal of the acetate, and this transformation was accomplished by heating ETP intermediate **27** in a methanolic solution of $La(OTf)_3$ at 40 °C,[35] which gave (+)-gliocladine C (**6**) as a colorless amorphous solid in 75% yield. The optical rotation of synthetic **6** $\{[\alpha]_D^{23}$ +505 (*c* 0.47 pyridine)$\}$ compared well with the value reported for the natural sample $\{[\alpha]_D^{18.7}$ +513 (*c* 0.33, pyridine)$\}$, as did spectroscopic data.

In conclusion, the total synthesis of (+)-gliocladine C (**6**) constitutes the first total synthesis of an ETP natural product containing hydroxy substitution in the pyrrolidine ring. Moreover, the total syntheses of (+)-gliocladin C (**11**) and **6** disclosed herein showcase two short synthetic sequences that we expect will find broader utility. First, the assembly of **11** from enantioenriched aminal aldehyde **20** and dioxopiperazine derivative **21** illustrates a convergent construction of oxopiperazine-fused pyrrolidinoindolines that can be employed to access more widely distributed dioxopiperazine variants. Second, the construction of epidithiodioxopiperazine alkaloid **6** from trioxopiperazine precursor **23** illustrates a sequence wherein diversity in the dioxopiperazine unit of an ETP product can be introduced at a late stage in a synthetic sequence.

■ ASSOCIATED CONTENT

Supporting Information. Complete ref 4b, experimental details, characterization data, copies of ^1H and ^{13}C NMR spectra of new compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(28) These data have been deposited at The Cambridge Crystallographic Data Centre as entry CCDC 814556 and can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif.

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