Published in final edited form as:
J Am Chem Soc. 2011 May 4; 133(17): 6549–6552. doi:10.1021/ja201789v.

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

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Abstract

A concise second-generation total synthesis of the fungal-derived alkaloid (+)-gliocladin C (**11**), in ten steps and 11% overall yield from isatin, is reported. In addition, the ETP natural product (+)-gliocladine C (**6**) is prepared in six steps and 29% yield from the di-(*tert*-butoxycarbonyl) precursor of **11**. The total synthesis of (+)-gliocladine C (**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 either can directly conjugate 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 selectivity towards both myeloma[3] and solid tumors[4] has been demonstrated and novel molecular targets have been identified.[5] The structure and chemical lability of epipolythiodioxopiperazines 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] with the chemistry developed in these investigations for incorporating an epidithiodioxopiperazine unit[7] being 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 was 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

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Supporting Information Available: Experimental details, characterization data, copies of ^{1}H and ^{13}C NMR spectra of new compounds, and full citation of reference 4b. This material is available free of charge via the Internet at http://pubs.acs.org.

hydroxyl substituent (e.g., **4**–**10**, Figure 1). Herein we disclose a general approach for preparing ETPs having this highly 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 (+)-gliocladine C (**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 by 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) disulfide bridge formation.

The opening phase of this endeavor was the development of an efficient second-generation total synthesis of (+)-gliocladin C (**11**), whose first total synthesis was reported from our laboratory in 2007.[12] Our plan was to assemble the tetracyclic core of (+)-gliocladin C from the union of enantioenriched dielectrophile **12** and dinucleophile **13**,[17] with the quaternary carbon stereocenter of the former arising from catalytic enantioselective Steglich-type rearrangement of indolyl carbonate **14**.[18,19]

The synthesis of (+)-gliocladin C 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 5 mol % 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 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 (er = 98:2).

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 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 (+)-gliocladin C (**11**) (Scheme 3). Aldol condensation of aldehyde **20** with the lithium enolate of piperazinedione **21**[25] in THF at −78 °C, followed by quenching the reaction with excess acetic acid and warming to room temperature delivered condensation product **22**, as exclusively 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. Alternately, coupled intermediate **22** could be transformed directly to (+)-gliocladin C (**11**), $[\alpha]^{23}_D$ +127 (*c* 0.23, pyridine),[27] in 60% yield upon reaction with excess $Sc(OTf)_3$ in acetonitrile at 0 °C to room temperature. Single-crystal X-ray diffraction of synthetic (+)-gliocladin C (**11**) confirmed the constitution and relative configuration of this natural product.[28]

With substantial quantities of trioxopiperazine-fused pyrrolidinoindoline **23** in hand, we turned to its transformation to (+)-gliocladine C (**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**, 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 epimers was highly substrate controlled yielding α diol **25** with 20:1 diasteroselectivity using OsO_4/NMO, AD-Mix-α or AD-Mix-β.[30] Although no diasteroselectivity was observed in 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. Employing this oxidant, the initially produced 3:2 mixture of siloxy epimers **24** was dihydroxylated and the crude diol products 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 at −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 stereoselection in this step is the result of initial iminium ion formation 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 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**, $[\alpha]^{23}_D$ +505 (*c* 0.47 pyridine), compared well with the value reported for the natural sample, $[\alpha]^{18.7}_D$ +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 (+)-gliocladine C (**6**) disclosed herein showcase two short synthetic sequences that we expect will find broader utility. First, the assembly of (+)-gliocladin C (**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 (+)-gliocladine C (**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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Support from the NIH National Institutes of General Medical Sciences (GM-30859) and postdoctoral fellowship support to JED (GM090473), SMM (GM082113), and FLZ (Swiss NSF) is gratefully acknowledged. NMR and mass spectra were determined at UC Irvine using instruments purchased with the assistance of NSF and NIH shared instrumentation grants. We thank Dr. Joseph Ziller and Dr. John Greaves, Department of Chemistry, UC Irvine, for their assistance with X-ray and mass spectrometric analyses.

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22. For example, global reduction of **18** could be accomplished with several reducing agents (i.e., $LiBH_4$, $NaBH_4$, $LiAlH_4$) to afford the 3-hydroxymethyl-2-hydroxyindoline intermediates. However, these reactions resulted in partial racemization of the quaternary carbon stereocenter, presumably at the stage of a 3-formyl-2-hydroxyindoline intermediate; see: (a) Dmitrienko GI, Denhart D, Mithani S, Prasad GKB, Taylor NJ. Tetrahedron Lett. 1992; 33:5705–5708.(b) Ziegler FE, Belema M. J Org Chem. 1997; 62:1083–1094.
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27. The reported optical rotation for the natural product is $[\alpha]^{16}_{D}$ +131.4 (*c* 0.07, $CHCl_3$).[15a] We observed limited solubility for synthetic crystalline (+)-gliocladin C in $CHCl_3$; as a result, we could obtain rotation data in this solvent only under dilute conditions: $[\alpha]^{23}_{D}$ +113 (c 0.0093, $CHCl_3$).
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31. After purification, this product contained approximately 5% of the β-diols.
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33. The relative configuration of this product was confirmed by single crystal X-ray diffraction of the corresponding racemate, CCDC 814557.
34. Preparation of gliocladine C directly from diol precursor **25** is problematic as a result of the acid sensitivity of C11-hydroxylated pyrrolidinoindolines.[12]
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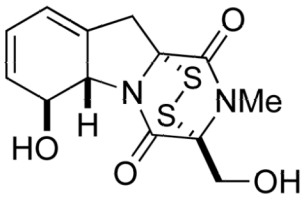
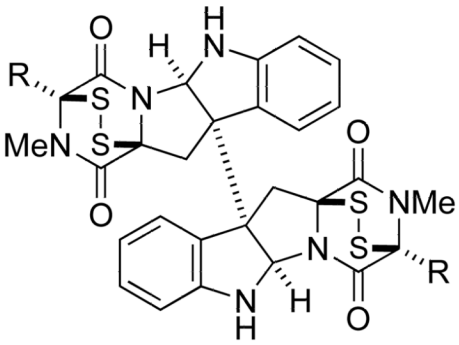
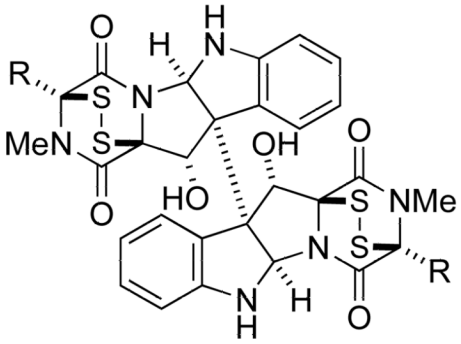


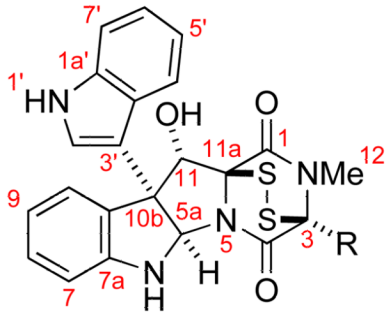
gliotoxin (**1**)



dideoxyverticillin A: R = Me (**2**)
chaetocin A: R = CH_2OH (**3**)

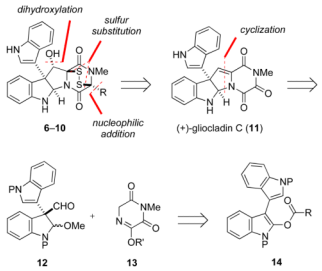


verticillin A: R = Me (**4**)
verticillin D: R = CH(OH)Me (**5**)

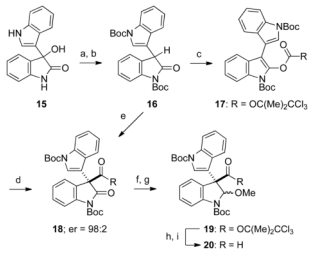


gliocladine C: R = Me (**6**)
bionectin A: R = H (**7**)
T988A: R = CH_2OH (**8**)
leptosin D: R = *i*-Pr (**9**)
bionectin B: R = CH(OH)Me (**10**)

Figure 1.
Some ETP natural products.



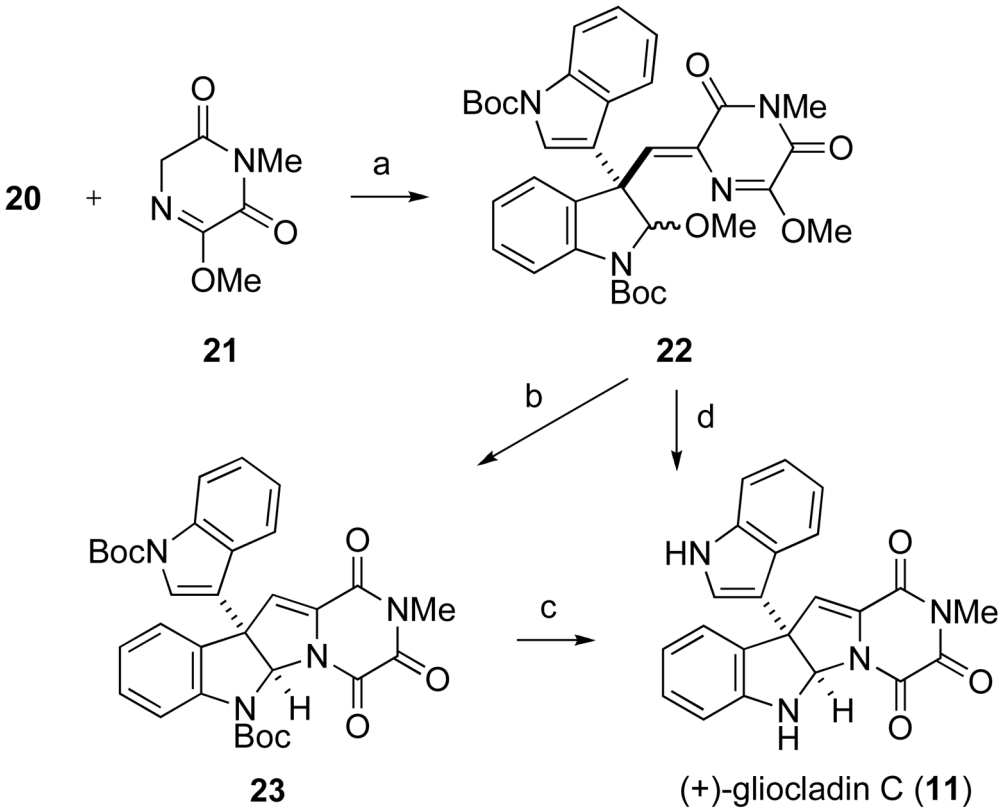
Scheme 1.
Retrosynthetic Analysis of ETPs **6–10**



Scheme 2.

Preparation of Enantioenriched Dielectrophile **20**[a]

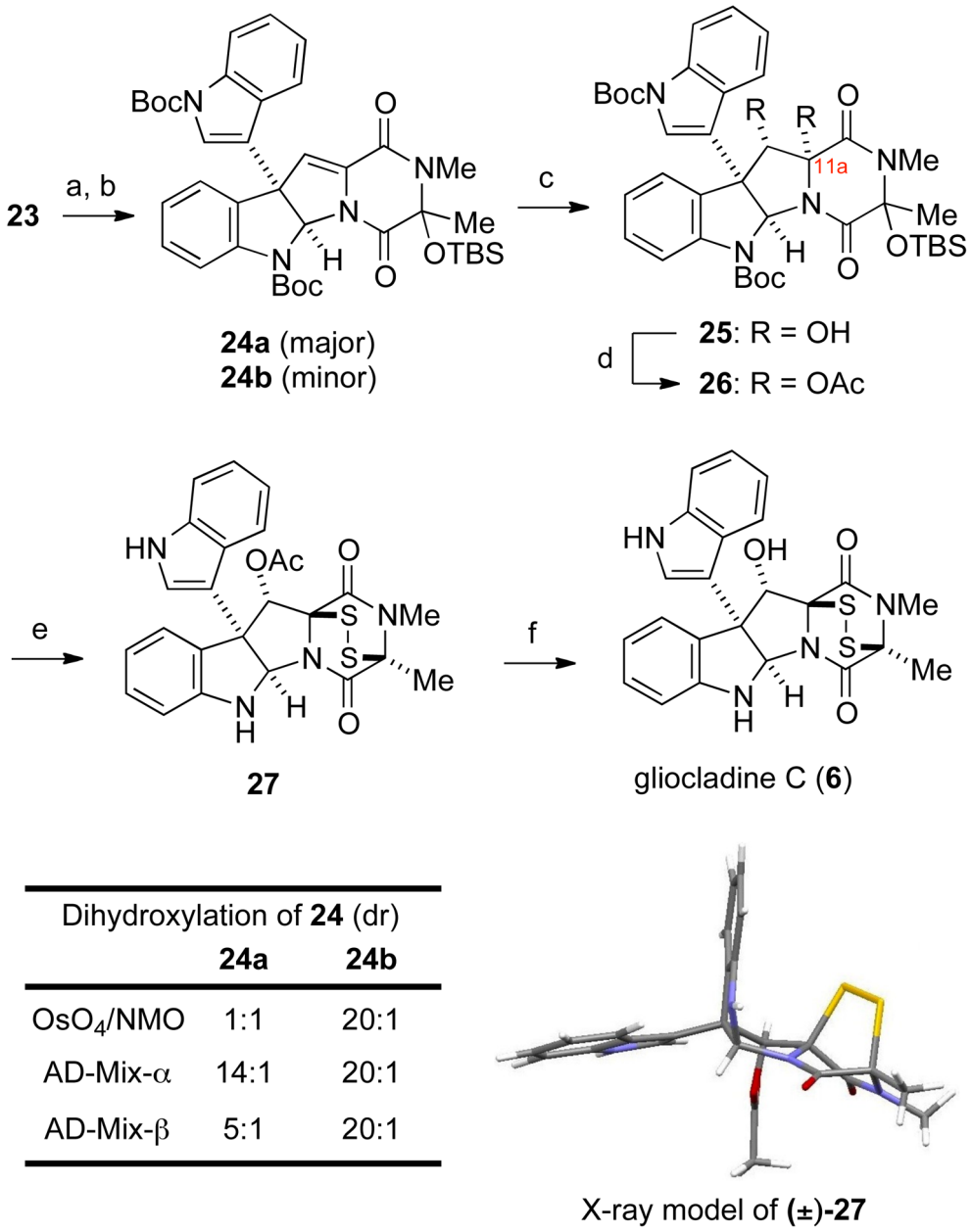
[a] Reaction conditions: (a) TFA, Et_3SiH, CH_2Cl_2, rt; (b) i. $(Boc)_2O$, 15 mol % DMAP, CH_2Cl_2, rt; ii. MeOH (68% from **15**); (c) 2,2,2-trichloro-1,1-dimethylethylchloroformate, Et_3N, THF, 0 °C (97%); (d) (*S*)-(−)-4-pyrrolidinopyridinyl(pentamethylcyclopentadienyl)-iron, THF, rt (96%, 98:2 er); (e) 2,2,2-trichloro-1,1-dimethylethylchloroformate, Et_3N, (*S*)-(−)-4-pyrrolidinopyridinyl(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%).



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**

Scheme 4.

Synthesis of (+)-Gliocladine C (**6**)[a]

[a] Reaction conditions: (a) MeMgCl, THF, −78 ºC (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 ºC to rt; ii. O_2, MeOH/EtOAc, rt (62%); (f) $La(OTf)_3$, MeOH, 40 ºC (75%).