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Concise Total Synthesis of (+)-Glioclادins B and C

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Abstract

The first total synthesis of (+)-glioclادin B is described. Our concise and enantioselective synthesis takes advantage of a new regioselective Friedel–Crafts-based strategy to provide an efficient multigram-scale access to the C3-(3'-indolyl)hexahydropyrroloindole substructure, a molecular foundation present in a significant subset of epipolythiodiketopiperazine natural alkaloids. Our first-generation solution to (+)-glioclادin B involved the stereoselective formation of (+)-12-deoxybionectin A, a plausible biosynthetic precursor. Our synthesis clarified the C15 stereochemistry of (+)-glioclادin B and allowed its full structure confirmation. Further studies of a versatile dihydroxylated diketopiperazine provided a concise and efficient synthesis of (+)-glioclادin B as well as access to (+)-glioclادin C.

Introduction

Epipolythiodiketopiperazine alkaloids are a structurally diverse class of secondary fungal metabolites that display a wide spectrum of biological activity including antibiotic, antifungal, antiviral, and cytotoxic effects.^{1,2} These mycotoxins are characterized by a bridged polysulfide linkage across the cyclic dipeptide substructure.^{3,4,5,6,7} Epipolythiodiketopiperazines with a 3'-indolyl substitution at the C3 position of a cyclotryptophan constitute an intriguing subset of this alkaloid family (Fig. 1).^{8,9} (+)-Glioclادin B (**1**),^{10,11} a new epidithiodiketopiperazine, and (+)-glioclادin C (**4**), an atypical non-thiolated triketopiperazine, were first isolated by Usami in 2004 from a strain of *Glioclادium roseum* OUPS-N132. (+)-Glioclادins exhibit significant cytotoxic activity against the murine P388 lymphocytic leukemia cell line.^{10a} In 2007, Overman reported the first enantioselective synthesis of (+)-glioclادin C (**4**) and confirmed its stereochemical assignment.^{12a} Recently, Overman reported a concise and elegant second-generation synthesis of (+)-glioclادin C (**4**) and its utility in the synthesis of the related epidithiodiketopiperazine (+)-glioclادine C.^{12b} The most recent synthesis of (+)-glioclادin C (**4**), reported by Stephenson, used photoredox catalysis to introduce an indolyl substructure as a key step.^{12c} Although Usami and co-workers' studies allowed them to elucidate the molecular structure of (+)-glioclادins,^{10a} limitations in spectroscopic techniques did not permit stereochemical assignments of (+)-glioclادins A (**2**) and B (**1**) at C15.¹¹ As an epipolythiodiketopiperazine alkaloids,⁷ we initiated a program to develop a broadly applicable strategy toward C3-(3'-indolyl)hexahydropyrroloindoles, an endeavor culminating in the first total synthesis of (+)-glioclادin B (**1**) and its complete stereochemical assignment.

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[†]Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of ¹H, ¹³C and ¹⁹F NMR spectra, crystal structure of (+)-**1** (CIF), and reassignment of several resonances for (+)-**1** and (+)-**4**. CCDC 866659. For ESI and crystallographic data in CIF or other electronic format. See DOI: 10.1039/b000000x/

Exciting progress has been made toward the concise construction of C₃_{sp3}–C_{sp2}^{13,14} and C₃_{sp3}–C_{sp3}^{7,15,16,17} linkages as well as C₃_{sp3}–N¹⁸ junctions in cyclotryptamine-based alkaloids. Inspired by seminal reports on the chemistry of functional hexahydropyrroloindoles¹⁹ by Crich and Danishefsky,²⁰ several of our reported synthetic strategies have focused on the preparation and functionalization of 3-bromocyclotryptamine^{16a} and 3-bromocyclotryptophan^{7,14,16b-c} derivatives. Intrigued by the molecular structure of C3-(3'-indolyl)hexahydropyrroloindole alkaloids, we sought a versatile synthetic strategy for the introduction of the C3-(3'-indolyl)-substituent into complex polycyclic diketopiperazines. Notably, the direct alkylative cyclization of tryptamine derivatives with indole was described by Somei to result in a mixture of regioisomers.²¹ Recently, it was reported^{12c} that 3-bromocyclotryptophans could be functionalized under basic conditions with a variety of nucleophiles.^{18e,i} However, indole-nucleophiles exclusively led to *N*-alkylation to give C3-(*N*-indolyl)-products.^{18c} Interestingly, free-radical based strategies for the derivatization of 3-bromocyclotryptophans have also been described for introduction of the 3'-indolyl substructure.^{12c,22} Herein, we report a direct, scalable regio- and stereoselective Friedel–Crafts-based indoylation of C3-bromopyrrolidino-indoline fused to a diketopiperazine. The versatility of this new C₃_{sp3}–C_{3'}_{sp2} bond formation in conjunction with our methodologies for late-stage diketopiperazine dihydroxylation⁷ and directed thiolation chemistry^{7b} allowed for a concise and stereocontrolled route to (+)-gliocladin B (**1**) in addition to offering access to (+)-gliocladin C (**4**, Scheme 1).

Results and discussion

Retrosynthetic analysis

To date, four monomeric bis(thiomethylether)diketopiperazines with a C 3-(3'-indolyl)-substituent have been isolated from different fungi.^{8b-c,10a} In each case, due to the absence of solid-state structure data or critical nOe correlations, the stereochemistry of the C15-methyl sulfide remained undefined. In two cases, the bis(thiomethyl)ethers were isolated from the same fungal strain alongside their corresponding episulfides (i.e., {(+)-bionectin C (**2**)}²³/(+)-bionectin A (**6**)}^{8e} and {(+)-T988 B (**3**)/(+)-T988 C (**10**)}^{8b}), prompting the authors to postulate a *cis* configuration. We envisioned the sulfides might arise from irreversible trapping of the corresponding epipolysulfides by reductive *S*-methylation along the biosynthetic pathway.²⁴ Thus, we postulated that (+)-gliocladin B (**1**) could biosynthetically arise from the corresponding bridged epidithiodiketopiperazine, namely (+)-12-deoxybionectin A (**11**, Scheme 1). This approach would enable stereoselective introduction of the *cis*-configured bis(thiomethyl) ethers for comparison with the spectroscopic data for natural (+)-gliocladin B (**1**).^{10a}

In deference to our desire for a maximally concise and unified strategy en route to (+)-gliocladin B (**1**), (+)-gliocladin C (**4**) and (+)-12-deoxybionectin A (**11**), and consistent with our hypothesis for their biogenesis, our retrosynthetic plan was designed as illustrated in Scheme 1. Recognizing the potential versatility of hexacyclic diol **12** as a common precursor to these three alkaloids, we planned to access the episulfide and the corresponding methylsulfides *via* late-stage stereoselective thiolation. This approach would also offer a chance to examine the conversion of (+)-12-deoxybionectin A (**11**) into (+)-gliocladin B (**1**), a transformation of plausible biogenetic relevance. Furthermore, we envisioned the conversion of diol **12** into (+)-gliocladin C (**4**) using an oxidation-dehydration sequence. The synthesis of the key hexacyclic diol **12** was predicated on application of our dihydroxylation chemistry to hexacyclic diketopiperazine **13**. In view of the inherent nucleophilicity of indoles and grounded on our previous studies on the formation of related C₃_{sp3}–C_{sp2}

linkages,¹⁴ we sought a general solution to C3-(3'-indolyl)diketopiperazine alkaloids (Fig. 1) *via* a stereoretentive Friedel–Crafts alkylation of *endo*-tetracyclic bromide **15**.²⁵

First-generation total synthesis of (+)-gliocladin B

Our unified synthesis of (+)-gliocladins B (**1**) and C (**4**) commenced with the bromocyclization of diketopiperazine (–)-**16** (Scheme 2),^{7,16b} accessible in three steps from commercially available *N*-Boc-L-tryptophan and sarcosine methyl ester on greater than 10-gram scale.²⁶ Exposure of diketopiperazine (–)-**16** to molecular bromine in dichloromethane at 0 °C afforded *endo*-tetracyclic bromide (+)-**17** with a high level of diastereoselection (*endo:exo*, ~97:3)²⁶ in 75% yield (*endo*-diastereomer). After significant experimentation, we discovered that exposure of bromide (+)-**17** to indole (**14a**, Table 1, entry 1) in the presence of silver tetrafluoroborate²⁷ in nitromethane²⁸ at 0 °C yielded the desired *cis*-fused 3'-indolyl adduct in 37% yield along with three undesired regioisomers (i.e., 2'-, 5'-, 6'-indolyl). We next investigated the influence of the steric and electronic properties of the nucleophile on the efficiency of the indolylation reaction. While the use of various *N*-alkyl or *N*-carbamate indole derivatives had minimal effect on the outcome of the indolylation, a marked increase in regioisomeric ratio (*rr*) was observed with *N*-triisopropylsilylindole (**14b**, Table 1, entry 2). Addition of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a Brønsted acid scavenger prevented undesired protodesilylation. Notably, the use of 5-bromoindole (**14c**, Table 1, entry 3) further enhanced the desired regioselectivity as well as the isolated yield. Ultimately, 5-bromo-1-triisopropylsilylindole (**14d**, Table 1, entry 4) proved to be an excellent nucleophile for the desired regio- and stereoselective Friedel–Crafts-type coupling. Significantly, coupling of bromide (+)-**17** with indole **14d** promoted by AgBF₄ in nitroethane readily afforded the desired 3-(3'-indolyl)hexahydropyrroloindole (+)-**19d** in 83% yield on a 5-gram scale (Scheme 2).

Having established an expeditious synthetic solution to the 3-(3'-indolyl)hexahydropyrroloindole intermediate (+)-**19d**, we proceeded to evaluate our planned unified synthetic strategy to alkaloids (+)-**1**, (+)-**4**, and (+)-**11** (Scheme 1). Accordingly, a quantitative single-flask conversion of adduct (+)-**19d** to the corresponding derivative (+)-**19a** set the stage for chemoselective oxidation and access to the branching point diol (–)-**20** (Scheme 2). The desired dihydroxylation of (+)-**19a** at C11-methine and C15-methylene positions to give diol (–)-**20** proved exceptionally challenging. Ultimately,²⁹ we achieved the critical and challenging dihydroxylation of substrate (+)-**19a** with tetra-*n*-butylammonium permanganate³⁰ (*n*-Bu₄NMnO₄, 3.8 equiv) in dichloromethane,³¹ providing diol (–)-**20** in 41% yield as a single diastereomer. Interestingly, the use of substoichiometric amount of oxidant typically resulted in the isolation of the C11- α -isomeric alcohol as the partial oxidation product, consistent with our observations regarding the reactivity profile of these diketopiperazines.⁷

Armed with the critical diol (–)-**20**, we proceeded from this strategic point of divergence with our planned stereoselective thiolation^{7b} en route to (+)-gliocladin B (**1**, Scheme 2). Exposure of diol (–)-**20** to trifluoroacetic acid in hydrogen sulfide-saturated dichloromethane solution at 0 °C generated the corresponding thiohemiaminal **22** in a highly diastereoselective fashion (>10:1 *dr*) *via* trapping of iminium ion **21** from its less hindered concave face. Removal of the volatiles followed by addition of isobutyryl chloride and pyridine in dichloromethane afforded hexacyclic thioisobutyrate (+)-**23** in 82% yield over two steps. The regio- and diastereoselective monothiolation of diol (–)-**20** to afford C11- β -thiol **22** is consistent with the anticipated innate preference for faster iminium ion formation at C11 as compared to C15. Exceptional control in the thiolation was achieved by stereoinduction from the proximal C3-stereocenter. While our initial conditions for desulfonylation of the sensitive intermediate (+)-**23** to give aniline (+)-**24** proved

capricious,³² the use of an aqueous sodium ascorbate–ascorbic acid mixture in combination with UV irradiation at 350 nm reliably afforded the desired aminothioisobutyrate (+)-**24** in 57% yield. Hydrazinolysis of both thioester and ester functional groupings followed by chemoselective *S*-sulfenylation with triphenylmethanesulfonyl chloride gave the sensitive disulfide (+)-**25** in 81% yield over two steps.^{7b,33}

Under optimal conditions, taking advantage of the high oxophilicity³⁴ and low thiophilicity³⁵ of hafnium trifluoromethanesulfonate ($\text{Hf}(\text{OTf})_4$), we accomplished the critical cyclization of triphenylmethanedisulfide (+)-**25** (Scheme 2) to the corresponding epidisulfide *via* the putative C15 iminium ion **26** and concomitant loss of triphenylmethyl cation.^{7b} Gratifyingly, exposure of intermediate (+)-**25** to $\text{Hf}(\text{OTf})_4$ in acetonitrile provided (+)-12-deoxybionectin A (**11**) in 80% yield.³⁶ Ultimately, reduction of the bridgehead disulfide with NaBH_4 followed by *in situ* *S*-methylation³⁷ afforded (+)-gliocladin B (**1**) in 80% yield. All ^1H and ^{13}C NMR data^{26,38} as well as the optical rotation $\{[\alpha]_{\text{D}}^{24} = +200$ (c 0.062, CHCl_3); for lit. $[\alpha]_{\text{D}}^{16} = +200$ (c 0.06, CHCl_3) $\}$ for our synthetic (+)-gliocladin B (**1**) matched those provided in the isolation report,^{10a} confirming the molecular structure of this mycotoxin. Furthermore, the relative and absolute configurations of (+)-**1** were proven by X-ray crystallographic analysis, and its thermal ellipsoid representation (Scheme 2)²⁶ revealed the pseudoaxial and *cis* configuration of the two thiomethyl ethers.³⁹

Second-generation total synthesis of (+)-gliocladin B

Our original strategy toward (+)-gliocladin B (**1**), based on the regio- and stereospecific thiolation of key diol (–)-**20** followed by sulfenylation and ring closure, resulted in bridgehead disulfide (+)-**11**, thus confirming the *cis* configuration and chemically hinting at the viability of its biosynthetic connection with (+)-12-deoxybionectin A (**11**). With an unambiguous structural confirmation of (+)-gliocladin B (**1**) through our synthetic study, we next sought to develop a more streamlined route to (+)-**1**. Relying on the versatility of diol (–)-**20**, exposure to sodium thiomethoxide and trifluoroacetic acid in nitromethane resulted in the formation of bis(thiomethyl)ether (+)-**27** (Scheme 3) with a good level of diastereoselection ($\text{C15}\beta\text{:C15}\alpha$, ~7:1)²⁶ in 77% yield (single diastereomer), consistent with the steric bias imposed by the C3-(3'-indolyl)-substituent. Interestingly, this approach can be extended to related alkyl thiols. N1-Benzenesulfonyl photodeprotection gave (+)-gliocladin B (**1**) in 68% yield over two steps. Not only did the nucleophilic bithiolation proceed with good diastereoselection, but this second-generation route also provided an expedient route to (+)-**1** in 10% yield over nine steps.

Total synthesis of (+)-gliocladin C

The atypical triketopiperazine (+)-gliocladin C (**4**) likely arose from further metabolization of the epipolythiodiketopiperazine motif.⁴⁰ Overman's concise syntheses^{12a,b} of (+)-(**4**) established its stereochemical assignment and optical activity. Recognizing diol (–)-**20** as a strategic intermediate in the synthesis of C3-(3'-indolyl)hexahydropyrroloindole alkaloids, we next aimed to exploit its potential as a precursor of (+)-gliocladin C (**4**) through C11-dehydration followed by selective C15-oxidation (Scheme 4). Accordingly, site-selective silylation of the more accessible C15 hemiaminal followed by photolytic desulfonylation gave aniline (+)-**29** in 87% yield over two steps. Interestingly, exposure of aminoalcohol (+)-**29** to trifluoroacetic anhydride and 2,6-di-*tert*-butyl-4-methylpyridine in acetonitrile resulted in N1-tri-fluoroacetylation concomitant with C11-dehydration to generate 65 enamide (–)-**30** in 88% yield. Removal of the silyl ether followed by oxidation with *o*-iodoxybenzoic acid in DMSO⁴¹ provided fragile triketopiperazine **32**. Treatment with acetic acid in aqueous acetone gave (+)-gliocladin C (**4**) in 54% yield over three steps. All ^1H and ^{13}C NMR data²⁶ as well as the optical rotation $\{[\Delta]_{\text{D}}^{25} = +126$ (c 0.08, MeOH); for lit.

$[\alpha]_D^{16} = +115$ (c 0.6, MeOH) $\}^{12a}$ for our synthetic (+)-gliocladin C (**4**) were identical in all respects with literature data.^{10a,12}

Conclusions

We have developed an effective synthetic strategy to access the 3-(3'-indolyl)hexahydropyrroloindole substructure, a motif present in several complex epipolythiodiketopiperazine alkaloids. Our mild and highly regioselective Friedel–Crafts-based coupling strategy led to the efficient construction of the desired C₃_{sp3}–C_{3'}_{sp2} linkage on multi-gram scale, affording the first concise and enantioselective synthesis of (+)-gliocladin B (**1**). Our first-generation solution resulted in the stereoselective synthesis of epidithiodiketopiperazine (+)-12-deoxybionectin A (**11**), a plausible biosynthetic precursor to (+)-gliocladin B (**1**), culminating in its structure confirmation and stereochemical assignment. Relying on the versatility of dihydroxylated diketopiperazine (–)-**20**, we also developed a highly concise and unified strategy resulting in a second-generation synthesis of (+)-gliocladin B (**1**, nine steps, 10% overall yield) as well as access to (+)-gliocladin C (**4**). This new synthetic strategy that allows an advanced stage union between an indole and a cyclotryptamine fused to a diketopiperazine combined with our methods for stereoselective sulfuration is expected to provide access to other 3-(3'-indolyl)-epipolythiodiketopiperazines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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26. See the ESI† for details.
27. While a variety of Lewis acids (*i.e.*, SnCl₄, BF₃•OEt₂, AlCl₃, TiCl₄, SbCl₅, InCl₃) exclusively resulted in a Brønsted acid-catalyzed indole oligomerization, use of a stoichiometric amount of silver salts (*i.e.*, AgBF₄, AgSbF₆, AgOTf, AgOCOCF₃) in MeNO₂ led to the desired ionization and indolylolation chemistry.
28. Nitroalkane and nitrobenzene solvents proved particularly effective compared to DMSO, DMF, or acetonitrile.
29. The use of Pyr₂AgMnO₄ or other related oxidants (*e.g.*, SrMnO₄, KMnO₄•18-crown-6, [(Bipy)₂Cu(MnO₄)₂]) in various solvents were not as effective.

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Fig. 1. Representative natural C3-(3'-indolyl)hexahydropyrroloindole alkaloids.¹¹

Scheme 1.

Retrosynthetic analysis of (+)-gliocladin B (**1**), (+)-gliocladin C (**4**), and (+)-12-deoxybionectin A (**11**).

Scheme 2.

First-generation total synthesis of (+)-gliocladin B (1). Reagents and conditions: (a) Br_2 , CH_2Cl_2 , $0\text{ }^\circ\text{C}$ (75%); (b) AgBF_4 , DTBMP, EtNO_2 , $0\text{ }^\circ\text{C}$ (83%, 5g-scale); (c) H_2 , Pd/C, NEt_3 , MeOH , EtOAc , $23\text{ }^\circ\text{C}$; $\text{Et}_3\text{N}\cdot 3\text{HF}$, $23\text{ }^\circ\text{C}$ (100%); (d) $n\text{-Bu}_4\text{NMnO}_4$, CH_2Cl_2 , $23\text{ }^\circ\text{C}$ (41%); (e) H_2S , $\text{TFA}-\text{CH}_2\text{Cl}_2$ (1:9 v/v), $0\text{ }^\circ\text{C}$; $i\text{-PrCOCl}$, pyr, CH_2Cl_2 , $0\rightarrow 23\text{ }^\circ\text{C}$ (82%, 2-steps); (f) $h\nu$ (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H_2O , MeCN , $25\text{ }^\circ\text{C}$ (57%); (g) N_2H_4 , THF, $0\text{ }^\circ\text{C}$; Ph_3CSOCl , NEt_3 , THF, $0\text{ }^\circ\text{C}$ (81%, 2-steps); (h) $\text{Hf}(\text{OTf})_4$, MeCN , $23\text{ }^\circ\text{C}$ (80%); (i) NaBH_4 , MeI, pyr, MeOH , $23\text{ }^\circ\text{C}$ (80%); DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TFA = trifluoroacetic acid, $i\text{-PrCOCl}$ = isobutyryl chloride, pyr = pyridine.

Scheme 3.

Second-generation total synthesis of (+)-gliocladin B (**1**). Reagents and conditions: (a) MeSNa , TFA-MeNO_2 (1:1 v/v), $0 \rightarrow 23^\circ\text{C}$ (77%); (b) $h\nu$ (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H_2O , MeCN , 25°C (88%).

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Table 1

Optimization of the C3_{sp3}–C3’_{sp2} bond formation *via* stereoretentive Friedel–Crafts alkylation^a

Entry	19	R	R'	^{a,b} C2':C3':C5':C6'	Yield ^c (%)
1	19a	H	H	17 : 38 : 22 : 23	37
2	19b	Si(<i>i</i> -Pr) ₃	H	0 : 45 : 55 : 0	30
3	19c	H	Br	29 : 71 : 0 : 0	57
4	19d	Si(<i>i</i> -Pr) ₃	Br	16 : 84 : 0 : 0	72
5 ^d	19d	Si(<i>i</i> -Pr) ₃	Br	10 : 90 : 0 : 0	83 ^e

^aReactions conditions unless otherwise noted: AgBF₄ (2.5 equiv) and **14** (10.0 equiv) in nitromethane (0.1 M).

^bDetermined by ¹H NMR and/or HPLC analysis of the crude product mixture.

^cIsolated yield of the desired 3'-indolyl (+)-**19**.

^dAgBF₄ (3.1 equiv), DTBMP (1.2 equiv), and **14d** (4.0 equiv) in nitroethane (0.06 M).

^e5-gram scale.