Concise total synthesis of (+)-gliocladins B and C

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

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Abstract

The first total synthesis of (+)-gliocladin 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 (+)-gliocladin B involved the stereoselective formation of (+)-12-deoxybionectin A, a plausible biosynthetic precursor. Our synthesis clarified the C15 stereochemistry of (+)-gliocladin B and allowed its full structure confirmation. Further studies of a versatile dihydroxylated diketopiperazine provided a concise and efficient synthesis of (+)-gliocladin B as well as access to (+)-gliocladin 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. These mycotoxins are characterized by a bridged polysulfide linkage across the cyclic dipeptide substructure. Epipolythiodiketopiperazines with a 3′-indolyl substitution at the C3 position of a cyclotryptophan constitute an intriguing subset of this alkaloid family (Fig. 1). (+)-Gliocladin B (1), a new epidithiodiketopiperazine, and (+)-gliocladin C (4), an atypical non-thiolated triketopiperazine, were first isolated by Usami in 2004 from a strain of Gliocladium roseum OUPS-N132. (+)-Gliocladins exhibit significant cytotoxic activity against the murine P388 lymphocytic leukemia cell line. In 2007, Overman reported the first enantioselective synthesis of (+)-gliocladin C (4) and confirmed its stereochemical assignment. Recently, Overman reported a concise and elegant second-generation synthesis of (+)-gliocladin C (4) and its utility in the synthesis of the related epidithiodiketopiperazine (+)-gliocladine C. The most recent synthesis of (+)-gliocladin C (4), reported by Stephenson, used photoredox catalysis to introduce an indolyl substructure as a key step. Although Usami and co-workers’ studies allowed them to elucidate the molecular structure of (+)-gliocladins, limitations in spectroscopic techniques did not permit stereochemical assignments of (+)-gliocladins A (2) and B (1) at C15. As an epipolythiodiketopiperazine alkaloid, we initiated a program to develop a broadly applicable strategy toward C3-(3′-indolyl)hexahydropyrroloindoles, an endeavor culminating in the first total synthesis of (+)-gliocladin B (1) and its complete stereochemical assignment.
Exciting progress has been made toward the concise construction of C$_3$sp$^3$–C$_{sp^2}$ linkages as well as C$_3$sp$^3$–N$_1$ junctions in cyclotryptamine-based alkaloids. Inspired by seminal reports on the chemistry of functional hexahydropyrroloindoles$^{19}$ 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 alkylation 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-indoyl)-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 indolylation of C3-bromopyrrolidino-indoline fused to a diketopiperazine. The versatility of this new C3–C3′ bond formation in conjunction with our methodologies for late-stage diketopiperazine dihydroxylation$^7$ 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 epidisulfides (i.e., {(+)-bionectin C (2)$^{23}$/(+)-bionectin A (6)}$^{8c}$ 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 C$_3$sp$^3$–C$_{sp^2}$
linkages, we sought a general solution to C3-(3'-indolyl)diketopiperazine alkaloids (Fig. 1) via a stereoretentive Friedel–Crafts alkylation of endo-tetracyclic bromide 15. 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), accessible in three steps from commercially available N-Boc-L-tryptophan and sarcosine methyl ester on greater than 10-gram scale. 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) 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 tetrafluoroborate in nitromethane 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, we achieved the critical and challenging dihydroxylation of substrate (+)-19a with tetra-n-butylammonium permanganate (n-Bu4NMnO4, 3.8 equiv) in dichloromethane, 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 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 desulfonilation of the sensitive intermediate (+)-23 to give aniline (+)-24 proved
capricious, 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 triphenylmethanesulfenyl chloride gave the sensitive disulfide (+)-25 in 81% yield over two steps.

Under optimal conditions, taking advantage of the high oxophilicity and low thiophilicity of hafnium trifluoromethanesulfonate (Hf(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. Gratifyingly, exposure of intermediate (+)-25 to Hf(OTf)₄ in acetonitrile provided (+)-12-deoxybionectin A (11) in 80% yield. Ultimately, reduction of the bridgehead disulfide with NaBH₄ followed by in situ S-methylation afforded (+)-gliocladin B (1) in 80% yield. All ¹H and ¹³C NMR data as well as the optical rotation [α]D₂₄ = +200 (c 0.062, CHCl₃) for our synthetic (+)-gliocladin B (1) matched those provided in the isolation report, 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) revealed the pseudoaxial and cis configuration of the two thiomethyl ethers.

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 sulfonylation 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 (C15β:C15α, ~7:1) 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-Benzensulfonyl photodeprotection gave (+)-gliocladin B (1) in 68% yield over two steps. Not only did the nucleophilic bisthiolation 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 metabolism of the epipolythiodiketopiperazine motif. Overman’s concise syntheses 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 DMSO provided fragile triketopiperazine 32. Treatment with acetic acid in aqueous acetone gave (+)-gliocladin C (4) in 54% yield over three steps. All ¹H and ¹³C NMR data as well as the optical rotation [Δ]D₂₅ = +126 (c 0.08, MeOH); for lit.
[α]D\textsuperscript{16} = +115 (c 0.6, MeOH)\textsuperscript{12a} for our synthetic (+)-gliocladin C (4) were identical in all respects with literature data.\textsuperscript{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\(_{sp3}\)–C3′\(_{sp2}\) 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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**Notes and references**


11. The C15 stereochemistry of (+)-gliocladins A (2) and B (1) was not assigned in ref. 10a. The C15 stereochemistry shown in Fig. 1 for (+)-1 is based on our assignment and that for (+)-2 and (+)-3 is predicted.


14. For a general solution to C3′ sp3−C bond formation, see: Kim J, Movassaghi M. J. Am. Chem. Soc. 2011; 133:14940. [PubMed: 21875056];


23. The structure of (+)-bionectin C (ref. 8e) has been previously reported as (+)-gliocladin A (ref. 10a). The similitude of their spectroscopic data supports a similar structure.


26. See the ESV† for details.

27. While a variety of Lewis acids (i.e., SnCl4, BF3•Et2O, 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 indolylation 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•18-crown-6, [(Bipy)2Cu(MnO4)2]) in various solvents were not as effective.

31. The choice of solvent was critical: acetone, chloroform or 1,2-dichloroethane gave lower yields; benzene led to poor conversion, pyridine caused immediate decomposition; addition of acetic acid or hexafluoroisopropanol as additive resulted in immediate oxidant disproportionation.


33. This can be combined as a one-pot two-step procedure in 74% yield.


36. Ionization with BF$_3$•OEt$_2$ in the presence of DTBMP in MeCN gave (+)-12-deoxybionectin A (11) in 37% yield (90% brsm).


38. The reported (ref. 10a) $^1$H NMR signal at 7.04 ppm for C7′–H should be corrected to 7.16 ppm. The reported (ref. 10a) $^{13}$C NMR resonances at 122.6 and 120.2 ppm for C7′ and C6′, respectively, should be inverted. For our complete NMR assignment of (+)-(1), see ESI†.

39. Structural parameters for (+)-I are freely available from the Cambridge Crystallographic Data Center under CCDC 866659.


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) Br₂,
CH₂Cl₂, 0 °C (75%); (b) AgBF₄, DTBMP, EtNO₂, 0 °C (83%, 5g-scale); (c) H₂, Pd/C,
NEt₃, MeOH, EtOAc, 23 °C; Et₃N•3HF, 23 °C (100%); (d) n-Bu₄NMnO₄, CH₂Cl₂, 23 °C
(41%); (e) H₂S, TFA–CH₂Cl₂ (1:9 v/v), 0 °C; i-PrCOCl, pyr, CH₂Cl₂, 0—23 °C (82%, 2-
steps); (f) hν (350 nm), 1,4-dimethoxy-naphthalene, ascorbic acid, sodium ascorbate, H₂O,
MeCN, 25 °C (57%); (g) N₂H₄, THF, 0 °C; Ph₃CSCl, NEt₃, THF, 0 °C (81%, 2-steps); (h)
Hf(OTf)₄, MeCN, 23 °C (80%); (i) NaBH₄, MeI, pyr, MeOH, 23 °C (80%); DTBMP = 2,6-
di-tert-butyl-4-methylpyridine, TFA = trifluoroacetic acid, i-PrCOCl = isobutryl chloride,
pyr = pyridine.
Scheme 3.
Second-generation total synthesis of (+)-gliocladin B (1). Reagents and conditions: (a) MeSNa, TFA–MeNO₂ (1:1 v/v), 0→23 °C (77%); (b) hν (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H₂O, MeCN, 25 °C (88%).
Scheme 4.
Total synthesis of (+)-gliocladin C (4). Reagents and conditions: (a) TIPSCl, DMAP, CH$_2$Cl$_2$, 23 °C (95%); (b) hν (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H$_2$O, MeCN, 25 °C (92%); (c) TFAA, DTBMP, MeCN, 23 °C (88%); (d) (HF)•pyr, THF, 23 °C; (e) IBX, DMSO, 23 °C; (f) AcOH, H$_2$O, acetone, 23 °C (54%, 3-steps); TIPSCl = triisopropylsilyl chloride, DMAP = 4-(dimethylamino)pyridine, TFAA = trifluoroacetic anhydride, IBX = o-iodoxybenzoic acid.
Table 1

Optimization of the C3sp3–C3′sp2 bond formation *via* stereoretentive Friedel–Crafts alkylation

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Yieldc (%)</th>
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<tr>
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<td>19b</td>
<td>Si(i-Pr)3</td>
<td>H</td>
<td>0 : 45 : 55 : 0</td>
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<tr>
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<td>19c</td>
<td>H</td>
<td>Br</td>
<td>29 : 71 : 0 : 0</td>
</tr>
<tr>
<td>4</td>
<td>19d</td>
<td>Si(i-Pr)3</td>
<td>Br</td>
<td>16 : 84 : 0 : 0</td>
</tr>
<tr>
<td>5d</td>
<td>19d</td>
<td>Si(i-Pr)3</td>
<td>Br</td>
<td>10 : 90 : 0 : 0</td>
</tr>
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</table>

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

*b*Determined by 1H NMR and/or HPLC analysis of the crude product mixture.

*c*Isolated yield of the desired 3′-indolyl (+)-19.

*d*AgBF4 (3.1 equiv), DTBMP (1.2 equiv), and 14d (4.0 equiv) in nitroethane (0.06 M).

*e*5-gram scale.