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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.<sup>1,2</sup> These mycotoxins are characterized by a bridged polysulfide linkage across the cyclic dipeptide substructure.<sup>3,4,5,6,7</sup> Epipolythiodiketopiperazines with a 3'-indolyl substitution at the C3 position of a cyclotryptophan constitute an intriguing subset of this alkaloid family (Fig. 1).<sup>8,9</sup> (+)-Gliocladin B (**1**),<sup>10,11</sup> 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.<sup>10a</sup> In 2007, Overman reported the first enantioselective synthesis of (+)-gliocladin C (**4**) and confirmed its stereochemical assignment.<sup>12a</sup> Recently, Overman reported a concise and elegant second-generation synthesis of (+)-gliocladin C (**4**) and its utility in the synthesis of the related epidithiodiketopiperazine (+)-gliocladin C.<sup>12b</sup> The most recent synthesis of (+)-gliocladin C (**4**), reported by Stephenson, used photoredox catalysis to introduce an indolyl substructure as a key step.<sup>12c</sup> Although Usami and co-workers' studies allowed them to elucidate the molecular structure of (+)-gliocladins,<sup>10a</sup> limitations in spectroscopic techniques did not permit stereochemical assignments of (+)-gliocladins A (**2**) and B (**1**) at C15.<sup>11</sup> As an epipolythiodiketopiperazine alkaloids,<sup>7</sup> 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.

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†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of <sup>1</sup>H, <sup>13</sup>C and <sup>19</sup>F 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 C<sub>3</sub><sub>sp<sup>3</sup></sub>-C<sub>sp<sup>2</sup></sub><sup>13,14</sup> and C<sub>3</sub><sub>sp<sup>3</sup></sub>-C<sub>sp<sup>3</sup></sub><sup>7,15,16,17</sup> linkages as well as C<sub>3</sub><sub>sp<sup>3</sup></sub>-N<sup>18</sup> junctions in cyclotryptamine-based alkaloids. Inspired by seminal reports on the chemistry of functional hexahydropyrroloindoles<sup>19</sup> by Crich and Danishefsky,<sup>20</sup> several of our reported synthetic strategies have focused on the preparation and functionalization of 3-bromocyclotryptamine<sup>16a</sup> and 3-bromocyclotryptophan<sup>7,14,16b-c</sup> 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.<sup>21</sup> Recently, it was reported<sup>12c</sup> that 3-bromocyclotryptophans could be functionalized under basic conditions with a variety of nucleophiles.<sup>18e,i</sup> However, indole-nucleophiles exclusively led to *N*-alkylation to give C3-(*N*-indolyl)-products.<sup>18c</sup> Interestingly, free-radical based strategies for the derivatization of 3-bromocyclotryptophans have also been described for introduction of the 3'-indolyl substructure.<sup>12c,22</sup> 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 C<sub>3</sub><sub>sp<sup>3</sup></sub>-C<sub>3'</sub><sub>sp<sup>2</sup></sub> bond formation in conjunction with our methodologies for late-stage diketopiperazine dihydroxylation<sup>7</sup> and directed thiolation chemistry<sup>7b</sup> 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.<sup>8b-c,10a</sup> 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**)/(+)-bionectin A (**6**)}<sup>8e</sup> and {(+)-T988 B (**3**)/(+)-T988 C (**10**)}<sup>8b</sup>), 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.<sup>24</sup> 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**).<sup>10a</sup>

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<sub>3</sub><sub>sp<sup>3</sup></sub>-C<sub>sp<sup>2</sup></sub>

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

### 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),<sup>7,16b</sup> accessible in three steps from commercially available *N*-Boc-L-tryptophan and sarcosine methyl ester on greater than 10-gram scale.<sup>26</sup> 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)<sup>26</sup> 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<sup>27</sup> in nitromethane<sup>28</sup> 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 AgBF<sub>4</sub> 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,<sup>29</sup> we achieved the critical and challenging dihydroxylation of substrate (+)-**19a** with tetra-*n*-butylammonium permanganate<sup>30</sup> (*n*-Bu<sub>4</sub>NMnO<sub>4</sub>, 3.8 equiv) in dichloromethane,<sup>31</sup> 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- $\alpha$ -isomeric alcohol as the partial oxidation product, consistent with our observations regarding the reactivity profile of these diketopiperazines.<sup>7</sup>

Armed with the critical diol (–)-**20**, we proceeded from this strategic point of divergence with our planned stereoselective thiolation<sup>7b</sup> 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- $\beta$ -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,<sup>32</sup> 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.<sup>7b,33</sup>

Under optimal conditions, taking advantage of the high oxophilicity<sup>34</sup> and low thiophilicity<sup>35</sup> of hafnium trifluoromethanesulfonate (Hf(OTf)<sub>4</sub>), 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.<sup>7b</sup> Gratifyingly, exposure of intermediate (+)-**25** to Hf(OTf)<sub>4</sub> in acetonitrile provided (+)-12-deoxybionectin A (**11**) in 80% yield.<sup>36</sup> Ultimately, reduction of the bridgehead disulfide with NaBH<sub>4</sub> followed by *in situ* *S*-methylation<sup>37</sup> afforded (+)-gliocladin B (**1**) in 80% yield. All <sup>1</sup>H and <sup>13</sup>C NMR data<sup>26,38</sup> as well as the optical rotation {[α]<sub>D</sub><sup>24</sup> = +200 (*c* 0.062, CHCl<sub>3</sub>); for lit. [α]<sub>D</sub><sup>16</sup> = +200 (*c* 0.06, CHCl<sub>3</sub>)} for our synthetic (+)-gliocladin B (**1**) matched those provided in the isolation report,<sup>10a</sup> 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)<sup>26</sup> revealed the pseudoaxial and *cis* configuration of the two thiomethyl ethers.<sup>39</sup>

### 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 (C15β:C15α, ~7:1)<sup>26</sup> 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.<sup>40</sup> Overman's concise syntheses<sup>12a,b</sup> 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<sup>41</sup> provided fragile triketopiperazine **32**. Treatment with acetic acid in aqueous acetone gave (+)-gliocladin C (**4**) in 54% yield over three steps. All <sup>1</sup>H and <sup>13</sup>C NMR data<sup>26</sup> as well as the optical rotation {[Δ]<sub>D</sub><sup>25</sup> = +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.<sup>10a,12</sup>

## 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 C<sub>3</sub><sub>sp3</sub>–C<sub>3'</sub><sub>sp2</sub> 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.

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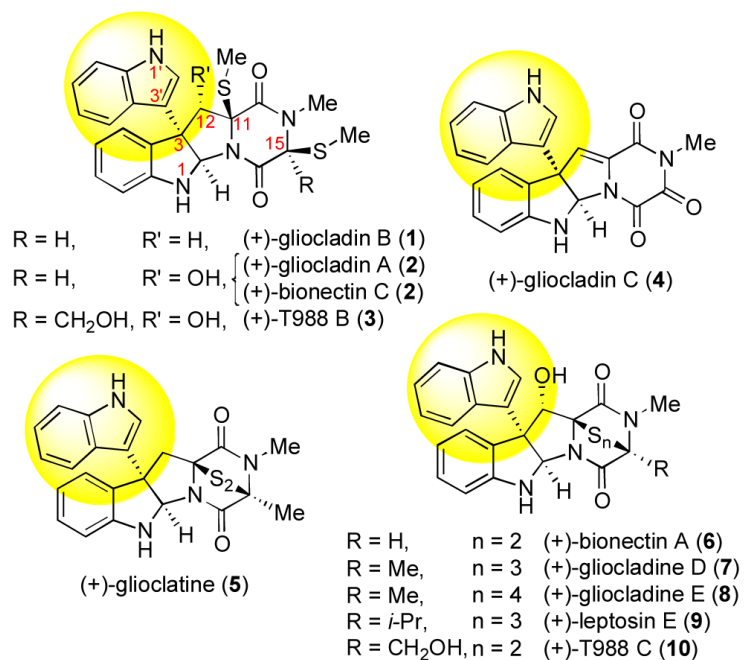


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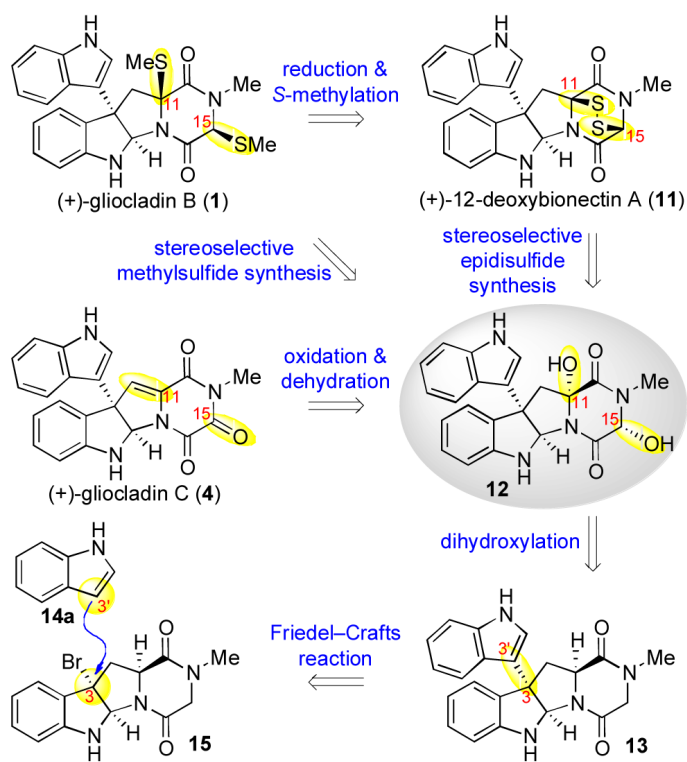
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26. See the ESI† for details.
27. While a variety of Lewis acids (*i.e.*, SnCl<sub>4</sub>, BF<sub>3</sub>•OEt<sub>2</sub>, AlCl<sub>3</sub>, TiCl<sub>4</sub>, SbCl<sub>5</sub>, InCl<sub>3</sub>) exclusively resulted in a Brønsted acid-catalyzed indole oligomerization, use of a stoichiometric amount of silver salts (*i.e.*, AgBF<sub>4</sub>, AgSbF<sub>6</sub>, AgOTf, AgOCOCF<sub>3</sub>) in MeNO<sub>2</sub> 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 Pyr<sub>2</sub>AgMnO<sub>4</sub> or other related oxidants (*e.g.*, SrMnO<sub>4</sub>, KMnO<sub>4</sub>•18-crown-6, [(Bipy)<sub>2</sub>Cu(MnO<sub>4</sub>)<sub>2</sub>]) in various solvents were not as effective.

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36. Ionization with  $\text{BF}_3 \cdot \text{OEt}_2$  in the presence of DTBMP in MeCN gave (+)-12-deoxybionectin A (**11**) in 37% yield (90% brsm).
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38. The reported (ref. 10a)  $^1\text{H}$  NMR signal at 7.04 ppm for  $\text{C}7' - \text{H}$  should be corrected to 7.16 ppm. The reported (ref. 10a)  $^{13}\text{C}$  NMR resonances at 122.6 and 120.2 ppm for  $\text{C}7'$  and  $\text{C}6'$ , respectively, should be inverted. For our complete NMR assignment of (+)-**1**, see ESI†.
39. Structural parameters for (+)-**1** are freely available from the Cambridge Crystallographic Data Center under CCDC 866659.
40. For another example of metabolized polythiodiketopiperazines, see: Yamada T, Iwamoto C, Yamagaki N, Yamanouchi T, Minoura K, Hagishita S, Numata A. *Heterocycles.* 2004; 63:641.
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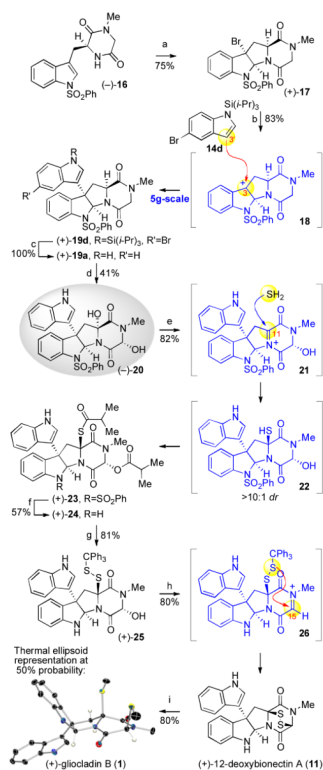




**Fig. 1.** Representative natural C3-(3'-indolyl)hexahydropyrroloindole alkaloids.<sup>11</sup>

**Scheme 1.**

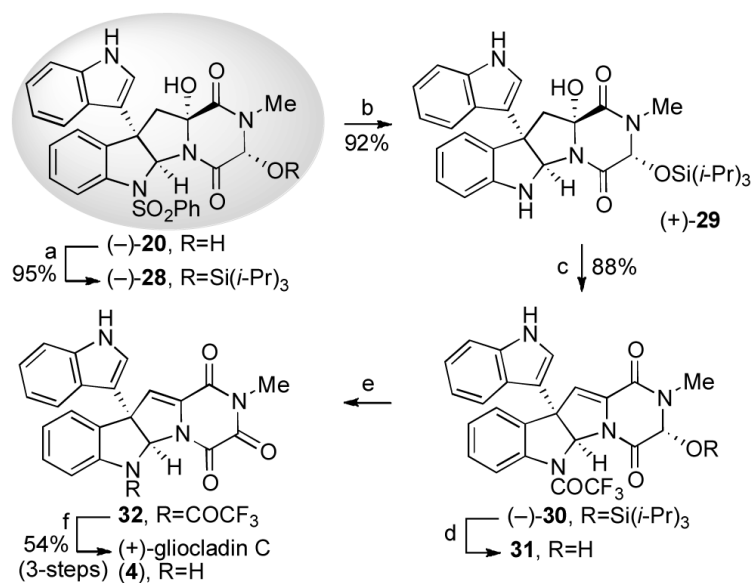
Retrosynthetic analysis of (+)-gliocladin B (**1**), (+)-gliocladin C (**4**), and (+)-12-deoxybionectin A (**11**).



### Scheme 2.

First-generation total synthesis of (+)-gliocladin B (**1**). Reagents and conditions: (a) Br<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C (75%); (b) AgBF<sub>4</sub>, DTBMP, EtNO<sub>2</sub>, 0 °C (83%, 5g-scale); (c) H<sub>2</sub>, Pd/C, NEt<sub>3</sub>, MeOH, EtOAc, 23 °C; Et<sub>3</sub>N•3HF, 23 °C (100%); (d) *n*-Bu<sub>4</sub>NMnO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, 23 °C (41%); (e) H<sub>2</sub>S, TFA-CH<sub>2</sub>Cl<sub>2</sub> (1:9 v/v), 0 °C; *i*-PrCOCl, pyr, CH<sub>2</sub>Cl<sub>2</sub>, 0→23 °C (82%, 2-steps); (f) hν (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H<sub>2</sub>O, MeCN, 25 °C (57%); (g) N<sub>2</sub>H<sub>4</sub>, THF, 0 °C; Ph<sub>3</sub>CSCl, NEt<sub>3</sub>, THF, 0 °C (81%, 2-steps); (h) Hf(OTf)<sub>4</sub>, MeCN, 23 °C (80%); (i) NaBH<sub>4</sub>, MeI, pyr, MeOH, 23 °C (80%); DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TFA = trifluoroacetic acid, *i*-PrCOCl = isobutryl chloride, pyr = pyridine.



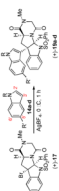
**Scheme 4.**

Total synthesis of (+)-gliocladin C (**4**). Reagents and conditions: (a) TIPSCl, DMAP,  $\text{CH}_2\text{Cl}_2$ , 23 °C (95%); (b)  $h\nu$  (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate,  $\text{H}_2\text{O}$ , MeCN, 25 °C (92%); (c) TFAA, DTBMP, MeCN, 23 °C (88%); (d)  $(\text{HF})\cdot\text{pyr}$ , THF, 23 °C; (e) IBX, DMSO, 23 °C; (f) AcOH,  $\text{H}_2\text{O}$ , 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 C3<sub>sp3</sub>-C3' sp<sub>2</sub> bond formation via stereoretentive Friedel-Crafts alkylation<sup>a</sup>



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

<sup>a</sup>Reactions conditions unless otherwise noted: AgBF<sub>4</sub> (2.5 equiv) and **14** (10.0 equiv) in nitromethane (0.1 M).

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

<sup>c</sup>Isolated yield of the desired 3'-indolyl (+)-**19**.

<sup>d</sup>AgBF<sub>4</sub> (3.1 equiv), DTBMP (1.2 equiv), and **14d** (4.0 equiv) in nitroethane (0.06 M).

<sup>e</sup>5-gram scale.