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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.[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] (+)-Gliocladin B (**1**),[10,11] 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.[10a] In 2007, Overman reported the first enantioselective synthesis of (+)-gliocladin C (**4**) and confirmed its stereochemical assignment.[12a] 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.[12b] The most recent synthesis of (+)-gliocladin 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 (+)-gliocladins,[10a] limitations in spectroscopic techniques did not permit stereochemical assignments of (+)-gliocladins 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 (+)-gliocladin B (**1**) and its complete stereochemical assignment.

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†Electronic supplementary information (ESI) available: Experimental procedures, spectroscopic data, copies of ^{1}H, ^{13}C and ^{19}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 $C3_{sp3}$–C_{sp2}[13,14] and $C3_{sp3}$–C_{sp3}[7,15,16,17] linkages as well as $C3_{sp3}$–N[18] 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′-indoyl)-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*-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 $C3_{sp3}$–$C3'_{sp2}$ 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**)}[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 epidisulfide 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 tetrafluoroborate[27] in nitromethane[28] 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 $AgBF_4$ 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 permanganate[30] (*n*-Bu_4NMnO_4, 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 triphenylmethanesulfenyl chloride gave the sensitive disulfide (+)-**25** in 81% yield over two steps.[7b,33]

Under optimal conditions, taking advantage of the high oxophilicity[34] and low thiophilicity[35] 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.[7b] Gratifyingly, exposure of intermediate (+)-**25** to $Hf(OTf)_4$ 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*-methylation[37] afforded (+)-gliocladin B (**1**) in 80% yield. All ^1H and ^{13}C NMR data[26,38] as well as the optical rotation {$[\alpha]_D^{24}$ = +200 (*c* 0.062, $CHCl_3$); for lit. $[\alpha]_D^{16}$ = +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 (C15β:C15α, ~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 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 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 DMSO[41] 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 data[26] as well as the optical rotation {$[\Delta]_D^{25}$ = +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 $C3_{sp3}$–$C3'_{sp2}$ 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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26. See the ESI† for details.

27. While a variety of Lewis acids (*i.e.*, $SnCl_4$, BF_3•OEt_2, $AlCl_3$, $TiCl_4$, $SbCl_5$, $InCl_3$) exclusively resulted in a Brønsted acid-catalyzed indole oligomerization, use of a stoichiometric amount of silver salts (*i.e.*, $AgBF_4$, $AgSbF_6$, AgOTf, $AgOCOCF_3$) in $MeNO_2$ 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_2AgMnO_4 or other related oxidants (*e.g.*, $SrMnO_4$, $KMnO_4$•18-crown-6, $[(Bipy)_2Cu(MnO_4)_2]$) in various solvents were not as effective.

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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.

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

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36. Ionization with BF_3•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}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 **C**7′ and **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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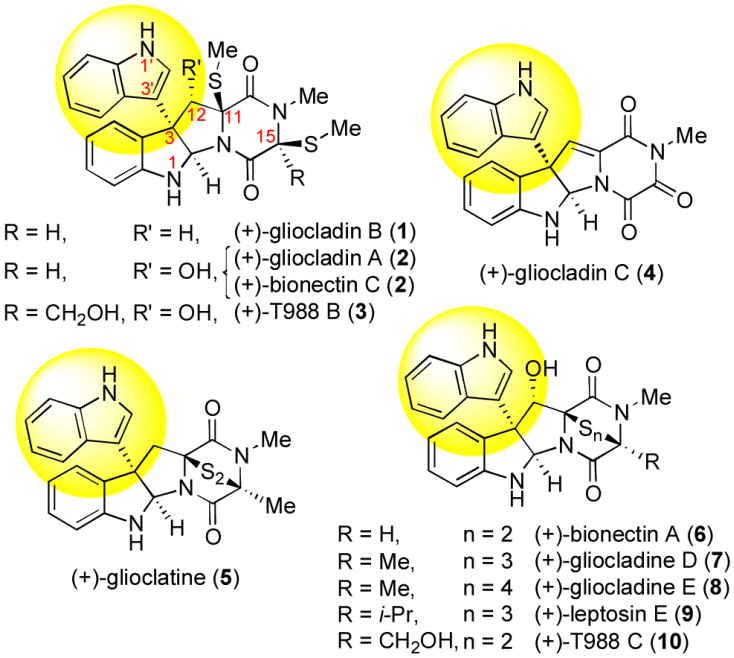
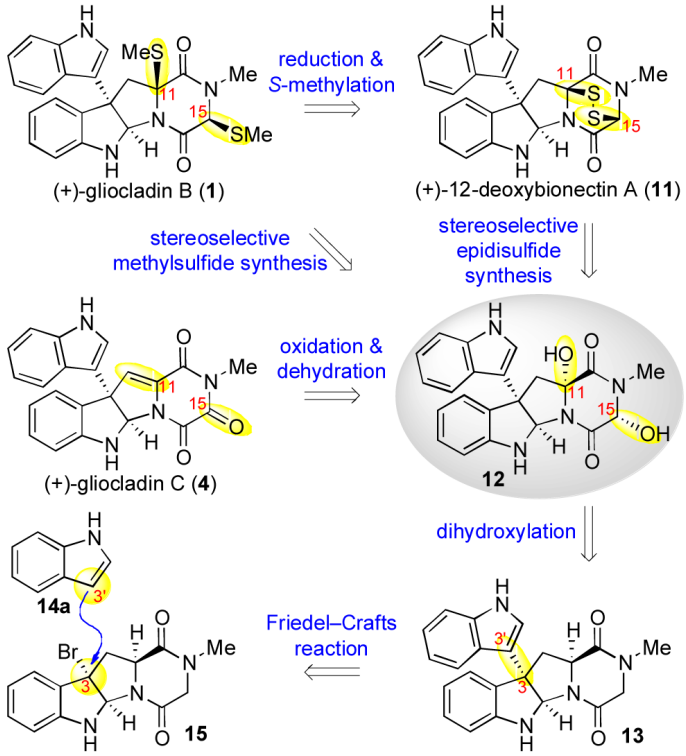
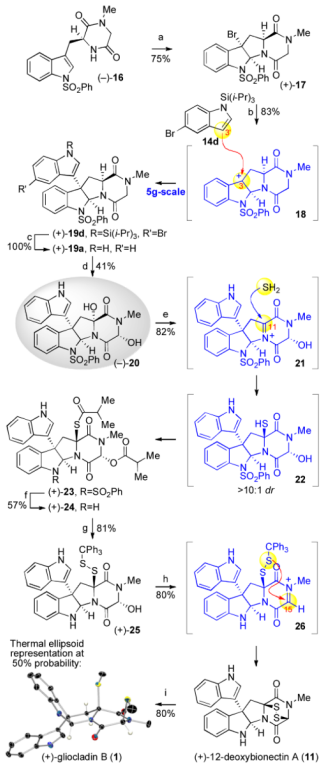


Fig. 1.
Representative natural C3-(3′-indolyl)hexahydropyrroloindole alkaloids.[11]

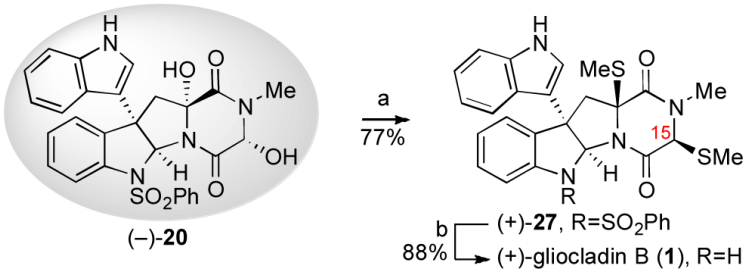


Scheme 1.
Retrosynthetic analysis of (+)-gliocladin B (**1**), (+)-gliocladin C (**4**), and (+)-12-deoxybionectin A (**11**).



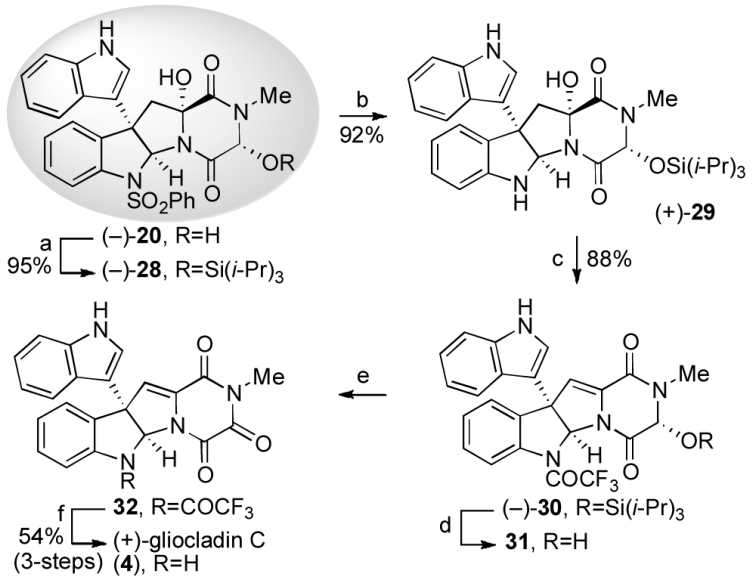
Scheme 2.

First-generation total synthesis of (+)-gliocladin B (**1**). Reagents and conditions: (a) Br_2, CH_2Cl_2, 0 °C (75%); (b) $AgBF_4$, DTBMP, $EtNO_2$, 0 °C (83%, 5g-scale); (c) H_2, Pd/C, NEt_3, MeOH, EtOAc, 23 °C; $Et_3N{\bullet}3HF$, 23 °C (100%); (d) *n*-Bu_4NMnO_4, CH_2Cl_2, 23 °C (41%); (e) H_2S, TFA–CH_2Cl_2 (1:9 v/v), 0 °C; *i*-PrCOCl, pyr, CH_2Cl_2, 0→23 °C (82%, 2-steps); (f) hν (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H_2O, MeCN, 25 °C (57%); (g) N_2H_4, THF, 0 °C; Ph_3CSCl, NEt_3, THF, 0 °C (81%, 2-steps); (h) $Hf(OTf)_4$, MeCN, 23 °C (80%); (i) $NaBH_4$, MeI, pyr, MeOH, 23 °C (80%); DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, TFA = trifluoroacetic acid, *i*-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→23 °C (77%); (b) hν (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H_2O, MeCN, 25 °C (88%).

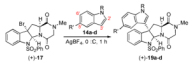


Scheme 4.

Total synthesis of (+)-gliocladin C (**4**). Reagents and conditions: (a) TIPSCl, DMAP, CH_2Cl_2, 23 °C (95%); (b) hν (350 nm), 1,4-dimethoxynaphthalene, ascorbic acid, sodium ascorbate, H_2O, 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_2O, acetone, 23 °C (54%, 3-steps); TIPSCl = triisopropylsilyl chloride, DMAP = 4-(dime-thylamino)pyridine, TFAA = trifluoroacetic anhydride, IBX = *o*-iodoxybenzoic acid.

Table 1

Optimization of the $C3_{sp3}$–$C3'_{sp2}$ bond formation *via* stereoretentive Friedel–Crafts alkylation[a]



Entry	19	R	R'	n[b] C2′:C3′:C5′:C6′	Yield[c] (%)
1	**19a**	H	H	17 : **38** : 22 : 23	37
2	**19b**	Si(*i*-Pr)$_3$	H	0 : **45** : 55 : 0	30
3	**19c**	H	Br	29 : **71** : 0 : 0	57
4	**19d**	Si(*i*-Pr)$_3$	Br	16 : **84** : 0 : 0	72
5[d]	**19d**	Si(*i*-Pr)$_3$	Br	10 : **90** : 0 : 0	83[e]

[a] Reactions conditions unless otherwise noted: $AgBF_4$ (2.5 equiv) and **14** (10.0 equiv) in nitromethane (0.1 M).

[b] Determined by ^{1}H NMR and/or HPLC analysis of the crude product mixture.

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

[d] $AgBF_4$ (3.1 equiv), DTBMP (1.2 equiv), and **14d** (4.0 equiv) in nitroethane (0.06 M).

[e] 5-gram scale.