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Total Synthesis of (+)-Gliocladin C Enabled by Visible-Light Photoredox Catalysis**

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Keywords

alkaloids; homogeneous catalysis; natural products; photoredox; total synthesis

Hexahydropyrroloindoline alkaloids are a large class of natural products that are formally derived from two molecules of tryptophan.[1] A subset of this class, the C3–C3′ indole alkaloids, contain the 3a-(3-indolyl)-hexahydropyrrolo-[2,3-b]indole skeleton and include compounds such as gliocladin C,[2] gliocladine C,[3] leptosin D,[4] and the bionectins[5] (Figure 1). Aside from their interesting structural features, they exhibit a broad range of potent biological activities. For example, gliocladin C[2] and leptosin D[4] are cytotoxic against P-388 lymphocytic leukemia cell lines with ED_{50} values of 240 ng mL^{-1} and 86 ng mL^{-1}, respectively, while bionectins A and B[5] exhibit antibacterial activity against MRSA (methicillin-resistant *S. aureus*) and QRSA (quinolone-resistant *S. aureus*) with MIC = 10–30 μ_M mL^{-1}.

The structural complexity and high biological activities of hexahydropyrroloindoline alkaloids,[7] have gained the attention of several research groups, thus resulting in total syntheses of natural products that incorporate C3–C3′ pyrroloindoline dimers,[8, 9] including work by the research groups of Hino,[9a] Danishefsky,[9b] Overman,[9c] Movassaghi,[9d–g] de Lera,[9h,i] Sodeoka,[9j] and Baran.[9k] Elegant approaches to the synthesis of C3–C7′ and C3–N1′ bisindole alkaloids have also been achieved by Overman and Govek (C3–C7′),[10] Baran and co-workers,[11a,c] and Rainier and Espejo (C3–N1′).[11b] However, the total syntheses of gliocladin C by Overman and co-workers, starting from isatin in 2007[12a] and the subsequent second generation synthesis in 2011,[12b] remain the only completed nondimeric C3–C3′ bisindole alkaloid syntheses. Moreover, the strategy by Overman and co-workers illustrated the importance of gliocladin C as a key intermediate for the preparation of other C3–C3′ bisindole alkaloids. For example, bis-Boc-protected **1** can be effectively converted into gliocladine C (**2**) in six steps. Two additional reports by Crich et al.,[13] and Somei and co-workers[14] were aimed at the synthesis of the core.[15, 16] Herein, we report the total synthesis of gliocladin C (10 steps total) which was enabled by a highly efficient radical coupling reaction that is mediated by visible-light photoredox catalysis (Scheme 1).[17–24]

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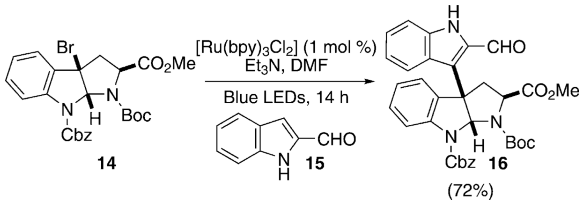
During our studies into the visible-light-mediated synthesis of indole alkaloid natural products using the photoredox catalyst tris(bipyridyl)ruthenium(II) chloride ([Ru-(bpy)$_3$Cl$_2$])[25] we serendipitously discovered an efficient method for the reductive dehalogenation of activated C–X bonds.[20a, 26] In the process, we were able to effectively access the tertiary benzylic radical **7** (Scheme 1) from bromopyrroloindolines **6** en route to the corresponding reduced compounds. By utilizing the method developed within our group, we envisioned that the trapping of **7** with an indole derivative would provide a direct approach to C3–C3′ bisindoles **8**, and thus efficient access to an entire class of natural products.

The key step in our synthetic strategy was evaluated by exposing simple bromopyrrolindoline **9**,[11b] which is derived from tryptamine in two steps on a large scale, to *N*-methylindole (**10**) under typical reductive quenching reaction conditions for photoredox catalysis (Scheme 2). As expected[27] only the C3–C2′ coupled product **11** was observed, with no detectable traces of products containing the desired C3–C3′ connectivity. However, by effectively blocking the indole C2′-position with a carboxylate group, we were able to direct the reactivity towards the preferred indole C3′-position. Indeed, coupling with methyl indole-2-carboxylate (**12**) led to 58% yield of the desired C3–C3′ coupling product **13** (Scheme 2). The visible-light-mediated coupling of indoles with bromopyrroloindolines now selectively enables the synthetic access to both the unnatural C3–C2′ and the natural C3–C3′ connectivity, depending on the indole substitution pattern.

Further model studies towards the total synthesis of gliocladin C were conducted with Boc-L-tryptophan-derived bromopyrroloindoline **14** [Eq. (1)]. We identified indole-2-carboxaldehyde (**15**) as the best coupling partner and the desired product **16** was obtained in 72% yield with only 1 mol% of [Ru(bpy)$_3$Cl$_2$] on up to a 2 g scale.[28] This strategy not only employs mild reaction conditions and low catalyst loading, but also provides rapid access to the C3–C3′ bisindole alkaloid core structure in high yield on a large scale.

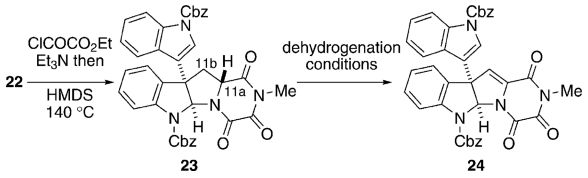


(1)

After securing a rapid and scalable route to the core structure of the C3–C3′ bisindole alkaloid framework, we initiated our synthesis of **1** by using an orthogonal nitrogen protection of Boc-D-tryptophan methyl ester (**17**) with CbzCl (Scheme 3). Bromocyclization using NBS and PPTS[29] yielded bromopyrroloindoline **18** in 91% yield over the two steps. Methylamidation of **18** with aqueous MeNH$_2$ in THF resulted in the formation of the corresponding methylamide **19** in 87%yield. Bromopyrroloindoline **19** was then subjected to the key indole coupling reaction using the previously optimized reaction conditions. Treatment of a mixture of amide **19** and aldehyde **15** (5.0 equiv)[30] with Et$_3$N (2.0 equiv) in the presence of 1 mol% of [Ru(bpy)$_3$Cl$_2$] in DMF under blue-light[31, 32] irradiation, successfully provided the desired coupling product **20** in 82% yield. During further optimization studies, we found that the use of an amine with a lower vapor pressure instead of Et$_3$N proved beneficial to the reaction conversion and the yield of the isolated product.[33] As a result, the use of *n*Bu$_3$N as the stoichiometric reducing agent resulted in the complete conversion of the starting material on a preparative scale (3.8 mmol) and provided **20** in 82% yield.

With a scalable and highly efficient synthetic route to the core structure established, catalytic decarbonylation of the aldehyde at the C2′-position of the indole was explored. Initial attempts using [$Rh(Ph_3P)_3Cl$] (20 mol%) and DPPA (2.0 equiv)[34] provided **21** in an unsatisfactory yield of 60%. Hence, we opted to complete the synthesis using a stoichiometric decarbonylation reaction by heating compound **20** in xylenes (140 °C) in the presence of [$Rh(Ph_3P)_3Cl$] to achieve the desired decarbonylation in 86% yield. Subsequent re-evaluation of the catalytic decarbonylation conditions led to improved results using 20 mol% of [$Rh(CO)(Ph_3P)_3Cl$], dppp[35] (44 mol%), and DPPA (2.0 equiv) in xylenes at 140 °C, and provided **21** in 85% yield.

At this stage, two challenges remained to complete an efficient synthesis of gliocladin C: 1) the formation of the triketopiperazine moiety and 2) the introduction of the α,β-unsaturated imide. Several attempts to complete the synthesis, first by conversion of **21** into bis-Cbz-protected dihydrogliocladin C [**23**; N-acylation with $ClCOCO_2Et/Et_3N$ then cyclization using hexamethyldisilazane (HMDS), 140 °C,[36] 56% yield over the two steps; Eq. (2)] followed by dehydrogenation to introduce the α,β-unsaturated imide (e.g. LiHMDS/NBS, DDQ) failed to provide **24** in an acceptable yield. Under unoptimized reaction conditions, treatment of **23** with Pd/C (20 mol%, toluene, reflux, 3 days) provided **24** in <50%yield.We reasoned that the orientation of the methine hydrogen at C11a inside the concave face of the ring prevented efficient conversion into **24**. Attempts to epimerize C11a resulted only in the ring opening of the triketopiperazine.



(2)

Inspired by the historical approach by Woodward and Ling to unnatural cyclic amino acids by using the acylation/elimination of cyclic oxime ethers,[37] we chose to pursue a one-pot *N*-acyliminium ion promoted enamine formation/intramolecular amidation to introduce the triketopiperazine and the α,β-unsaturated imide in a single transformation (Scheme 4; **25**→**24**).[38] Accordingly, the oxidation of the secondary amine by sequential treatment with NBS and DBU provided the requisite imine **25** in nearly quantitative yield. The acylation/cyclization step was then accomplished by microwave irradiation of a mixture of imine **25**, $ClCOCO_2Et$, and Et_3N in toluene at 150°C. Presumably, the imine reacts with $ClCOCO_2Et$ to provide acyliminium intermediate **26**, which upon deprotonation forms enamine **27**. Intramolecular amidation occurs by attack of the amide nitrogen atom on the ester carbonyl to close the ring, thus providing the desired triketopiperazine **24** in 76% yield (after one recycle). As a final step, global Cbz removal using BCl_3 in CH_2Cl_2 (−78°C to 23°C) provided gliocladin C (**1**) in 80% yield. Spectroscopic and optical rotation data for synthetic **1** were in agreement with the data reported for the natural sample.[39]

In summary, gliocladin C (**1**) was synthesized in 10 steps from commercially available Boc-D-tryptophan methyl ester in 30% overall yield. This study highlights photoredox catalysis not only as a viable method in the context of this particular synthesis, but also as a general, mild, and robust means to potentially access a wide variety of complex molecules. With the route to gliocladin C by photoredox catalysis established, we anticipate using imine **25** as a common intermediate for the preparation of other members of this important class of indole alkaloids by using the imine annulation sequence outlined in Scheme 4.

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28. We have not had occasion to test the limits of the scalability of this transformation, however, no noticeable difference in reaction rate has been observed on changing from a 50 mg to a 2 g scale. Further investigations into the generality of this radical cross-coupling reaction will be reported in due course.

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30. The use of excess **10** was necessary to preclude competitive reductive dehalogenation (see Ref. [20a]). Unreacted **10** was quantitatively recovered during reaction purification and subsequently reused.

31. Blue LED's were purchased at http//www.creativelightings.com (λ_{max} = 435 nm, 1 W).

32. The reaction temperature does not exceed 30°C upon irradiation with blue LEDs.

33. We observed that the headspace volume of the reaction flask correlated inversely with the reaction conversion when using Et_3N as the reductive quencher (stoichiometric reducing agent), wherein lower conversion was observed when there was a larger headspace volume. We hypothesized that the reductive quencher (Et_3N) was partitioning into the headspace of the reaction flask, thereby impeding the catalytic cycle. Switching to a trialkylamine with a lower vapor pressure, eg. *n*Bu_3N (0.3 mm Hg, 20°C) compared with Et_3N (51.8 mm Hg, 20°C) recovered the reactivity observed on a smaller scale.

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38. Alternative mechanisms are also possible, such as initial imide formation with the subsequent attack of the imine. However, based on observations made on similar systems, both in our studies and in the literature (e.g. Ref. [12a]), we believe imine acylation precedes imidation.

39. The measured optical rotation for synthetic 1 in two solvents ($[\alpha]_D$ = +128 deg $cm^3g^{-1}dm^{-1}$ (*c* = 0.04 g/100 mL, $CHCl_3$); +125 (*c* = 0.2 g/100 mL, C_5H_5N)) correlates well to the reported data for the natural product ($[\alpha]_D$ = +131.4 deg $cm^3g^{-1}dm^{-1}$ (*c* = 0.07 g/100 mL, $CHCl_3$))[2] as well as to that reported by Overman and Shin in 2007[12a] ($[a]_D$ = +116.4 deg $cm^3g^{-1}dm^{-1}$ (*c* = 0.02 g/100 mL, $CHCl_3$)). In their most recent synthesis,[12b] Overman and co-workers observed poor solubility of crystalline gliocladin C in chloroform ($[\alpha]_D$ = +113 deg $cm^3g^{-1}dm^{-1}$ (*c* = 0.0093 g/100 mL, $CHCl_3$)) and optical rotation data was also reported in pyridine ($[\alpha]_D$ = +127 deg $cm^3g^{-1}dm^{-1}$ (*c* = 0.23 g/100 mL, C_5H_5N)).

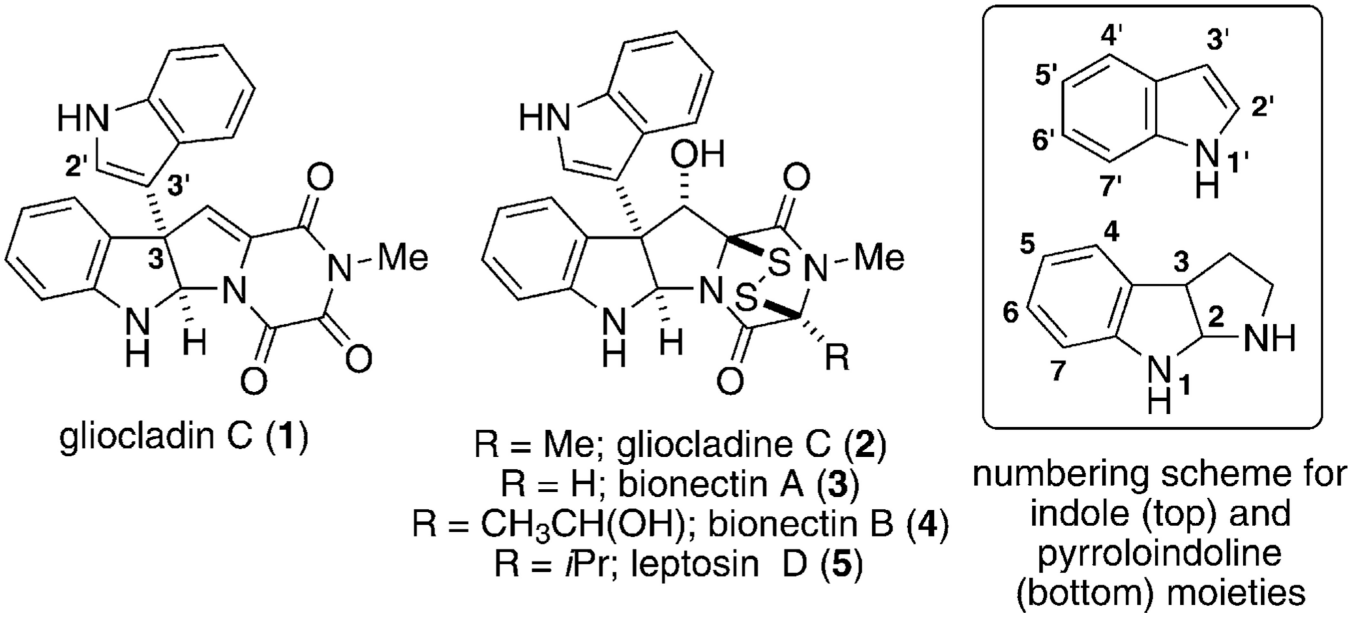
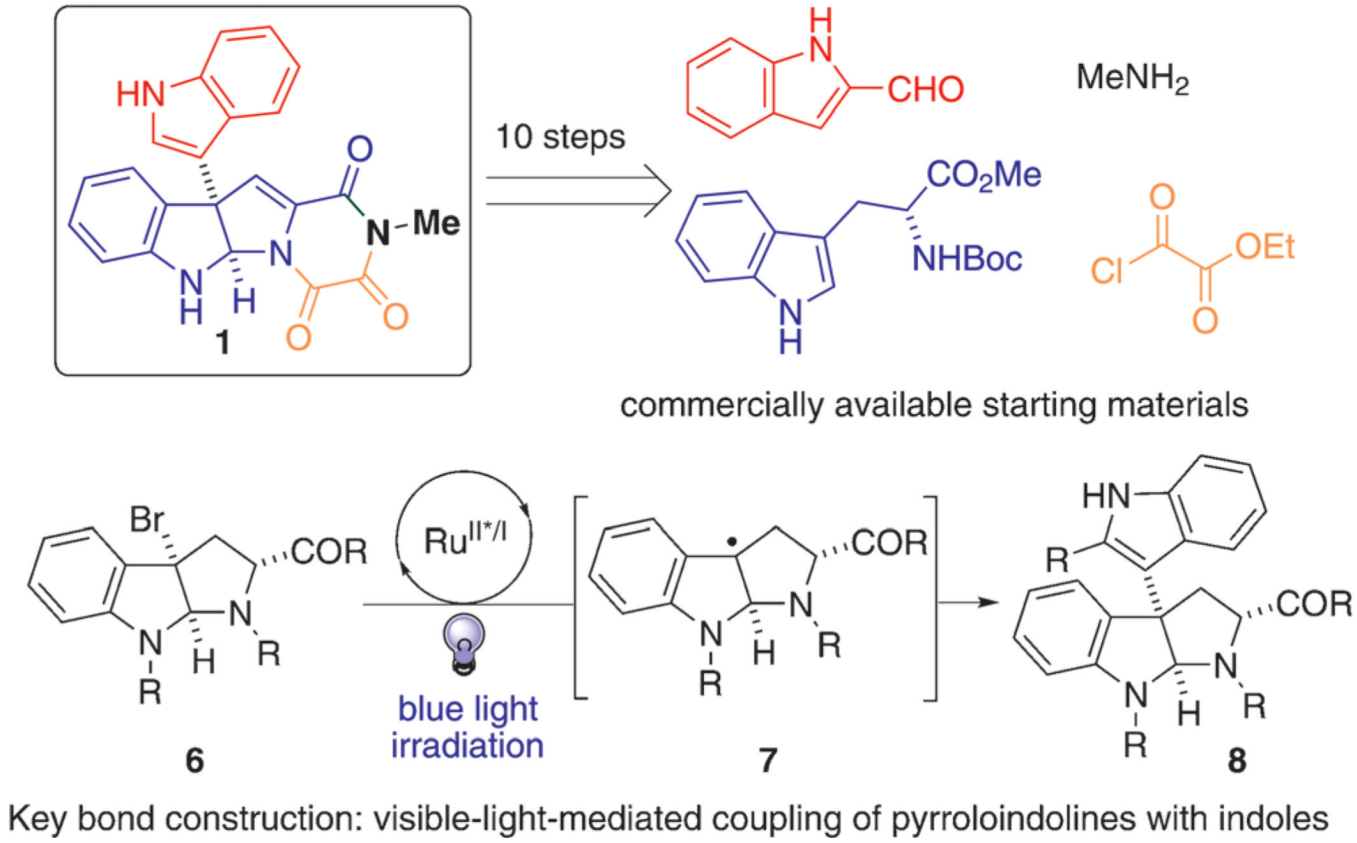
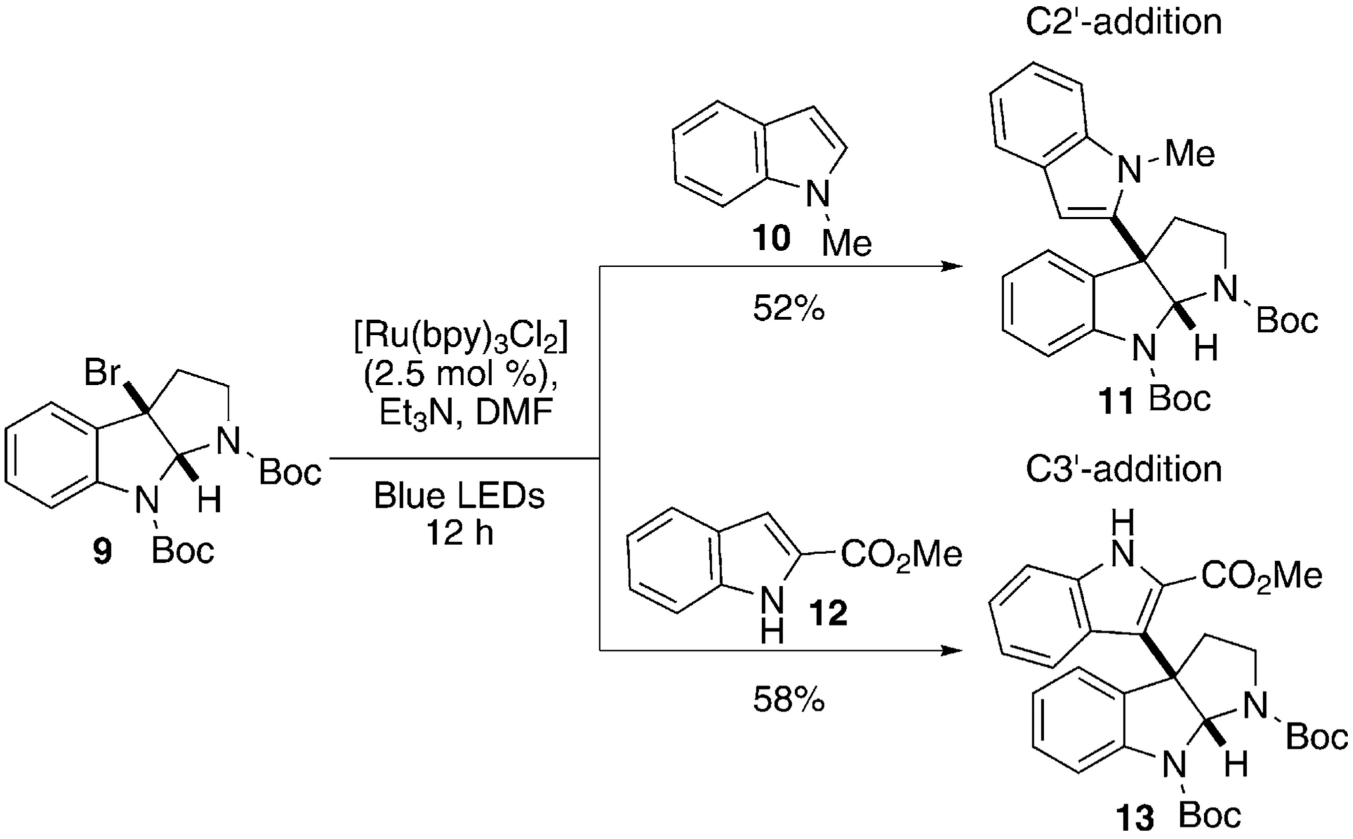


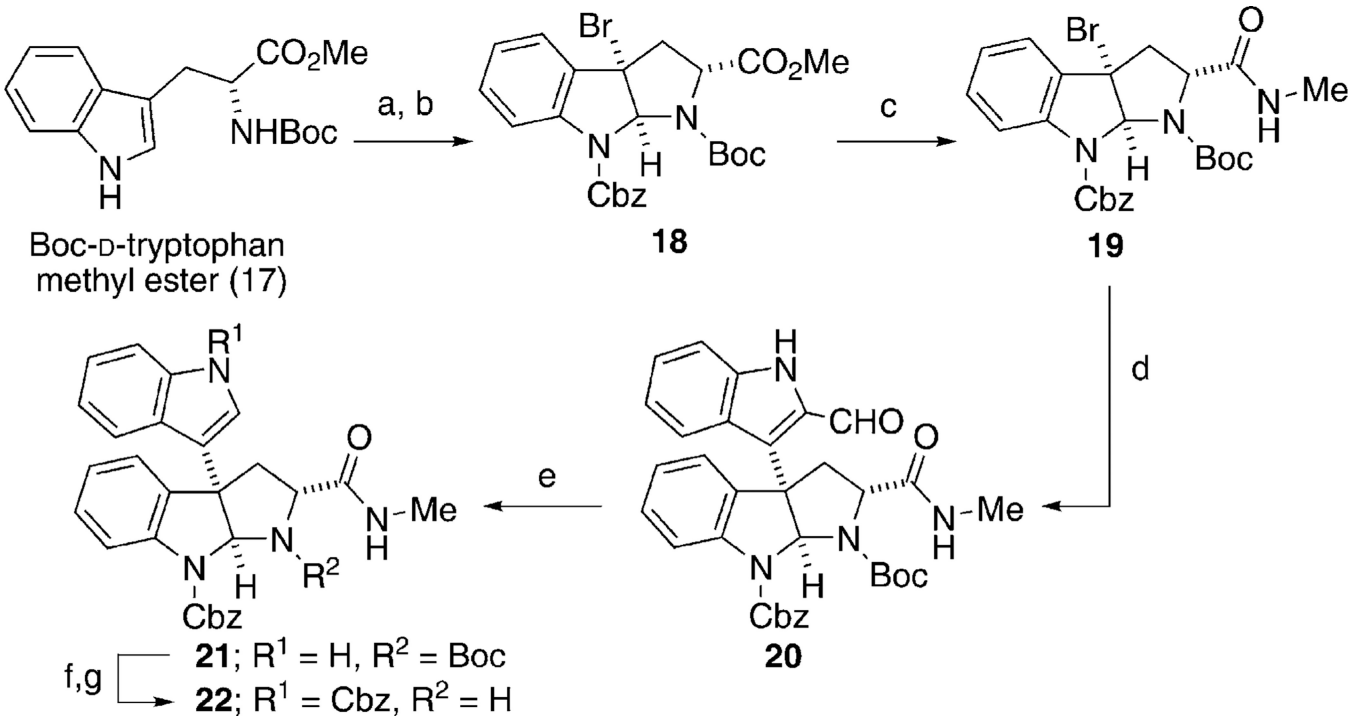
Figure 1.
Representative examples of cytotoxic and antibiotic C3–C3′ bisindole alkaloids.[6]



Scheme 1.
Retrosynthesis of gliocladin C (**1**; top) and visible-light-mediated C–C bond formation (bottom).

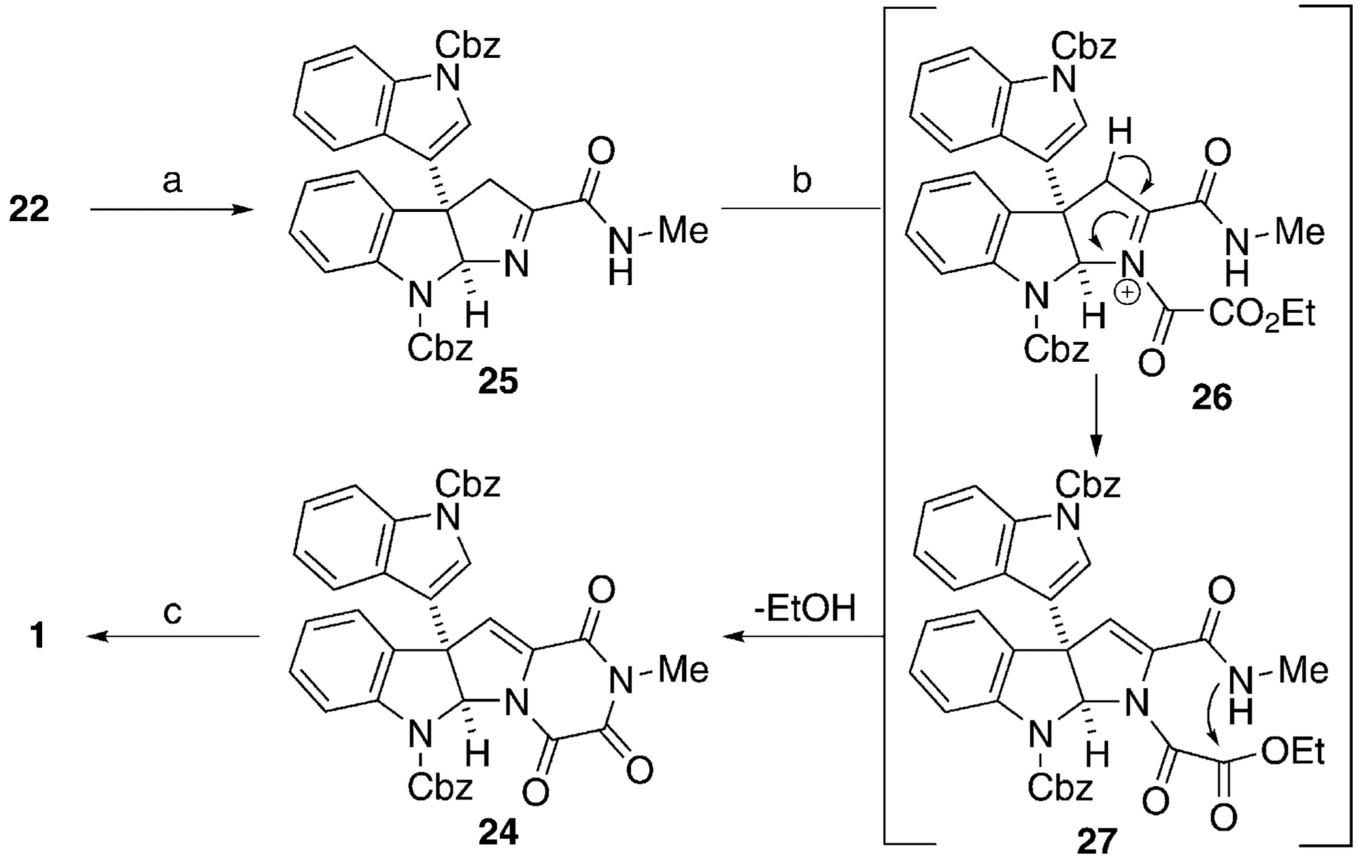


Scheme 2.
Visible-light-mediated coupling of bromopyrroloindoline **9** with indoles enables selective access to both C2′- and C3′-substituted bisindoles. Boc = *tert*-butyloxycarbonyl.



Scheme 3.

a) CbzCl, NaOH, Bu_4NHSO_4, CH_2Cl_2, 12 h; b) NBS, PPTS, CH_2Cl_2, 23°C, 12 h, 91% (two steps); c) $MeNH_2$, THF, 23°C, 3 d, 87%; d) $[Ru(bpy)_3Cl_2]$ (1.0 mol%), Bu_3N (2 equiv), **15** (5 equiv), DMF, blue LEDs, 12 h, 82%; e) $[Rh(Ph_3P)_3Cl]$ (1 equiv), xylenes, 140°C, 12 h, 86% or $[Rh(CO)(Ph_3P)_2Cl]$ (20 mol%), dppp (44 mol%), DPPA (2 equiv), xylenes, 140°C, 85%; f) CbzCl, NaOH, Bu_4NHSO_4, CH_2Cl_2, 12 h, 98%; g) TMSI, CH_3CN, 0°C, 1 h, 91%. Cbz = benzyloxycarbonyl; DMF = *N*,*N*′-dimethylformamide; DPPA = diphenylphosphoryl azide; dppp = 1,3-bis(diphenylphosphino)propane; LED = light-emitting diode; NBS = *N*-bromosuccinimide; PPTS = pyridinium *p*-toluenesulfonate; THF = tetrahydrofuran; TMS = trimethylsilyl.



Scheme 4.

a) NBS, CH_2Cl_2, DBU, 23°C, 99%; b) $ClCOCO_2Et$, Et_3N, 150°C, microwaves, 0.5 h, 76% (90% conversion, two cycles); c) BCl_3, CH_2Cl_2, −78 °C to 23°C, 12 h, 80%. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene.