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Formal synthesis of (+)-gliocladin C

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ABSTRACT

An asymmetric synthesis of chiral intermediate **15** for (+)-gliocladin C has been accomplished from *N*-phthaloyl L-tryptophan methyl ester.

Secondary metabolites produced by marine organisms are the source of architecturally complex and pharmacologically important compounds. Gliocladins A–B (**1**–**2**, Fig. 1), two epidithiodi-ketopiperazines and gliocladin C (**3**), a non-thiolated triketopiperazine, were first isolated from a strain of *Gliocladium roseum* by Usami et al.[1a] Notably, among these three alkaloids, gliocladin C exhibited the most potent cytotoxic activity against P388 lymphocytic leukemia in cell culture (ED_{50} = 2.4 μg/mL). Interestingly, gliocladin C was also recently found in the terrestrial fungus *Gliocladium catenulatum*.[1b]

The structural complexity and high biological activities of gliocladin C, have attracted the attention of several research groups.[2] The first total synthesis was reported by Overman and Shin in 2007.[2a] Subsequently, they reported the second generation synthesis in 2011.[2b] Shortly after, Stephenson's synthesis highlighted a photoredox catalysis to install the indolyl group as a key step.[2c] The most recent synthesis of (+)-gliocladin C adopted a novel regioselective Friedel–Crafts strategy to introduce the key indolyl substructure, reported by Movassaghi and Boyer.[2d]

Our interest for syntheses of this class of alkaloids was initially aroused by studies toward the synthesis of trigololiimine C based on an oxidative rearrangement biogenetic hypothesis,[3] we observed that treatment of the hydroxyindolenine **4** with $Sc(OTf)_3$ in refluxed toluene provided a novel bistryptamine derivative **5** in 70% yield (Scheme 1).[3c] We considered that the migration of the indolyl group might be very significant for the synthesis of

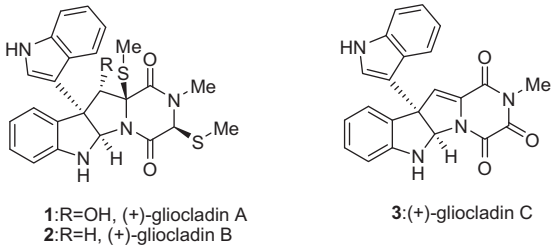
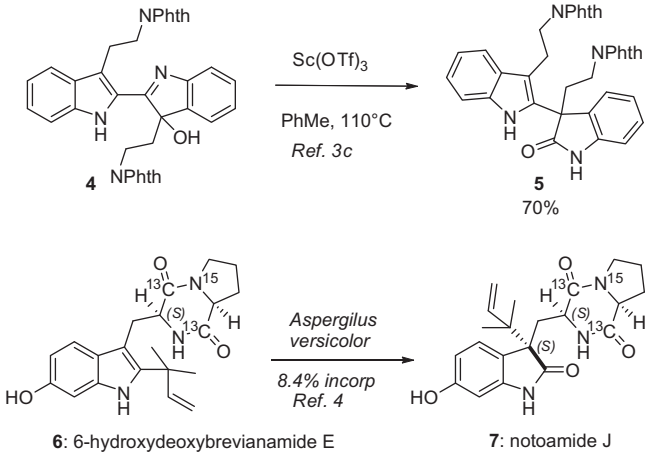


Figure 1. Gliocladins A–C.



Scheme 1. Initial inspiration.

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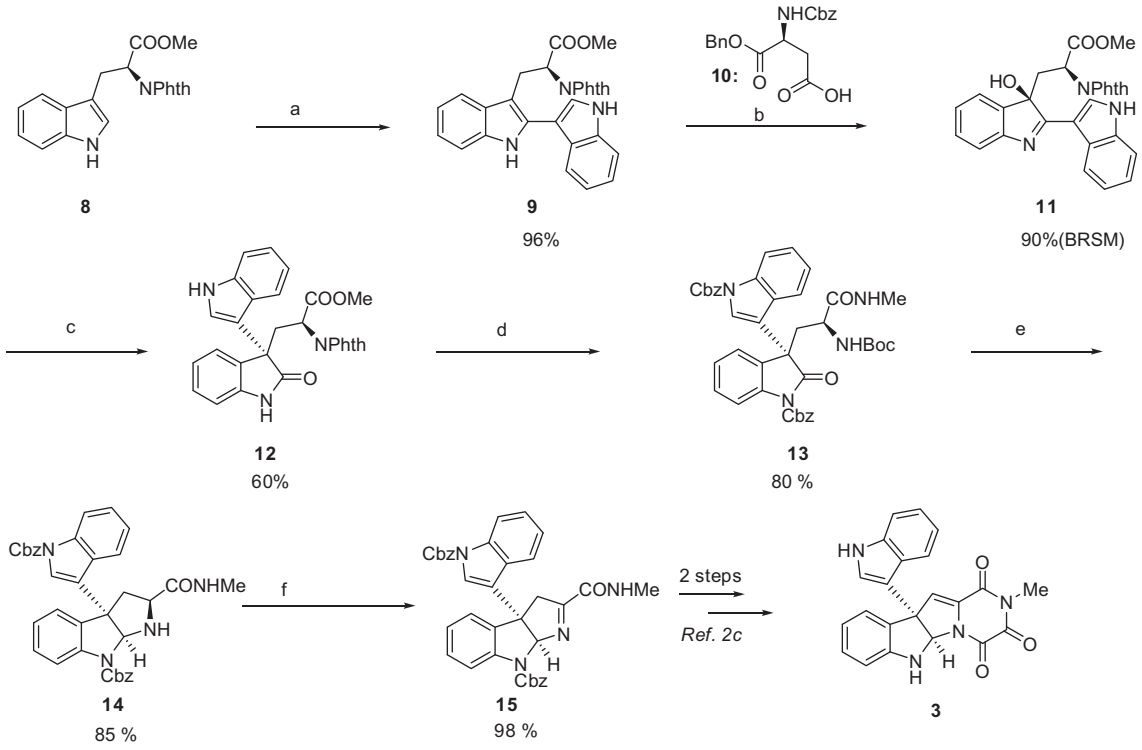
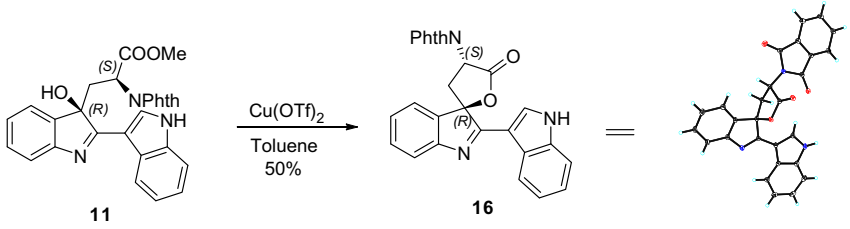


Scheme 2. Reagents and conditions: (a) *t*-BuOCl, Et_3N, THF, then indole, $BF_3{\cdot}Et_2O$; (b) **10**, 30% H_2O_2, DIC, DMAP, DCM, 0 °C; (c) $Sc(OTf)_3$, toluene, 110 °C; (d) (i) $MeNH_2$, MeOH, (ii) Boc_2O, satd $NaHCO_3$, (iii) CbzCl, Et_3N, DMAP, DCM; (e) (i) $NaBH_4$, MeOH, (ii) TFA, DCM; (f) NBS, DBU, DCM.



Scheme 3. Derivatization and stereochemical assignment of **11**.

dimeric indole alkaloids. Particularly, it provided a novel strategy to assemble gliocladin C. On the other hand, the leading study by Williams and co-workers (Scheme 1),[4] indicated the biogenesis of 3-prenylated indole alkaloid notoamide J should incorporate an oxidative rearrangement, enabled us to investigate whether a similar biomimetic step could be achieved in the synthesis of the class of 3-(3′-indolyl) indole alkaloids.[5] Intrigued by these considerations, we set out to develop a new approach to the chiral tetracyclic core of gliocladin C.

The synthetic work started from phthaloyl protected L-tryptophan methyl ester **8** (Scheme 2). It was reacted with *t*-butyl hypochloride in tetrahydrofuran at −78 °C to cleanly produce a 3-chloroindolenine intermediate, which could be nucleophilically attacked by indole in the presence of $BF_3{\cdot}Et_2O$ thus leading to *N*-phthaloyl-2-indolyl tryptophan methyl ester **9** in high yield.[6] As our plan is to provide a platform for the asymmetric synthesis of gliocladin C, the oxidative transformation of **9** should be realized with a high chemoselectivity and stereoselectivity. Although it was well precedented that good chemoselectivity and stereoselectivity of oxidation of indoles could be achieved in the bisindole system toward the synthetic studies of trigololiimine alkaloids[3] and Movassaghi's pioneer work,[7] it seemed risky to implement this particular transformation. Given the developed optimal conditions for oxidation in related derivatives,[7,8] we focused our attention on the use of aspartic peracids generated in situ. It was gratifying that the employment of a simple precatalyst **10** (Cbz-L-Asp-OBn) in the presence of 30% aqueous H_2O_2 and 1,3-diisopropylcarbodiimide (DIC) would lead the desired oxidative transformation. Under this favorable condition, our key intermediate **11** was obtained as the only diastereoisomer in 90% yield after recovering 5–10% of staring material **9** on a multigram scale, with no detectable amount of its epimer.

The absolute stereochemistry of hydroxybisindole **11** was confirmed by its chemical derivatization to lactone **16** (Scheme 3). Treatment of **11** with $Cu(OTf)_2$ led to the intramolecular esterification thus afforded the spirocycle **16**. The 3-(*R*) assignment of **16** was secured by X-ray crystallography.

With tertiary alcohol **11** in hand, using $Sc(OTf)_3$ mediated condition smoothly led to the desired rearrangement product **12** in 60% yield. Unveiling the amino group of imide **12** by $MeNH_2$ in MeOH with concurrent ammonolysis as a one pot two-step procedure provided the desired *N*-methyl amide. To avoid intramolecular transamidation, crude released amines were immediately blocked by Boc and Cbz groups, respectively, to afford **13** in 80% yield over three steps from **12**, without further purification. Subsequent selective reduction of the oxindole carbonyl moiety of **13**

was achieved with $NaBH_4$ (4.0 equiv) in MeOH at 25 °C for 15 min,[9] followed by treatment of the resulting hemiaminal with excess TFA in DCM to form the five-membered ring and deprotect the Boc group in one pot, thus gave desired secondary amine **14** in 85% yield (2 steps). Finally, the oxidation of **14** by sequential treatment with *N*-bromosuccinimide (NBS) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) provided a known imine **15**, whose analytical and spectral data[10] were in good agreement with the literature report.[2c] Having **15** been previously converted into (+)-gliocladin C in two steps,[2c] its obtainment constitutes a formal diastereoselective synthesis of the latter.

In conclusion, a formal synthesis of (+)-gliocladin C was accomplished and intermediate **15** was obtained in a 34.5% total yield in nine steps. A good efficiency combined with the fact that only cheap reagents and popular conditions were adopted in our procedures made the present synthesis practically and easily to handle, thus provided a useful starting point for the synthesis of gliocladin C-like library. Moreover, since epipolythiodiketo-piperazines with 3′-indolyl substitution at the C3 position of a cyclotryptophan constitute an intriguing subset of this alkaloid family,[5] the methodology described herein may be applied to these natural targets.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.12.007.

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10. $[\alpha]_D^{25}$ −38.9 (*c* 0.7, $CHCl_3$); IR (KBr) 3420, 3401, 3033, 2937, 1716, 1684, 1482, 1455, 1396, 1361, 1308, 1282, 1235, 1153, 1096, 1049, 1022, 752; ^1H NMR (500 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 7.98 (br s, 0.5H), 7.52–7.32 (br m, 12.5H), 7.26–7.10 (br m, 5H), 6.74 (br s, 0.5H), 6.63 (br s, 0.5H), 5.45–5.36 (m, 4H), 3.91 (dd, *J* = 17.5, 1.0 Hz, 1H), 3.71 (br d, *J* = 23.3 Hz, 1H), 2.89 (d, *J* = 5.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 171.7, 171.6, 161.9, 155.4, 152.3, 150.6, 140.3, 139.2, 136.4, 136.1, 135.5, 134.9, 134.7, 134.0, 129.5, 128.8, 128.5, 128.1, 127.9, 127.8, 125.3, 125.2, 124.9, 124.2, 123.3, 122.6, 119.2, 116.1, 115.9, 96.4, 96.1, 68.8, 68.5, 67.4, 52.8, 52.8, 48.0, 25.9; HRMS Calcd for $[C_{36}H_{30}N_4O_5+Na^+]$: 621.2108. Found: 621.2129.