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Enantioselective Total Synthesis of (+)-Gliocladin C

Larry E. Overman* and **Youseung Shin**
Department of Chemistry, 1102 Natural Sciences II, University of California, Irvine, California 92697-2025

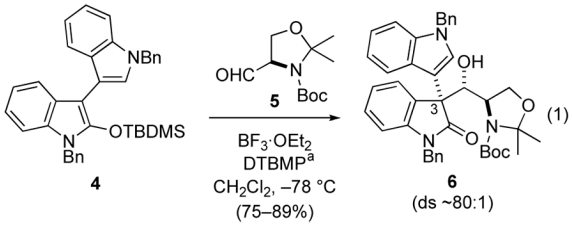
Abstract

The first total synthesis of gliocladin C, a fungal-derived marine alkaloid containing a rare trioxopiperazine fragment, is reported. This asymmetric synthesis establishes the absolute configuration of this structurally novel natural product.

Fungi found in marine organisms have proven to be a rich source of architecturally novel and biologically active natural products.[1] In 2004, Usami and co-workers reported the isolation of the indole alkaloid gliocladin C (**1**) from a strain of *Gliocladium roseum*, originally obtained from the sea hare *Aplysia kurodai* (Figure 1).[2] Coisolated with gliocladin C were the sulfur-containing analogs gliocladins A (**2**) and B (**3**), the former being related closely in structure to epidithiodiketopiperazine congeners leptosin D,[3] gliocladine A[4] and T988A.[5] Gliocladins A–C exhibited cytotoxic activity against P388 lymphocytic leukemia in cell culture, with gliocladin C (**1**) being most potent (2.4 μg/mL).[2]

The proposed gross structure and relative configuration of gliocladin C (**1**) was based on mass spectrometric and spectroscopic data, with the absolute configuration being undefined.[2] The most novel structural feature of gliocladin C is the trioxopiperazine ring, which is an extremely rare feature of natural products, never before seen in conjunction with a pyrrolidinoindoline fragment.[6,7] We report in this disclosure the first total synthesis of gliocladin C (**1**) and proof that its absolute configuration is as depicted in Figure 1.

Oxindoles having a β-aminoethyl substituent at C3 are time-tested precursors of pyrrolidinoindolines.[8] We recently reported[9] that elaborate, enantiopure structures of this type containing an aryl or heteroaryl substituent at the quaternary C3 stereocenter could be quickly assembled by the Mukaiyama aldol reaction[10] of 2-siloxyindoles and the serine-derived aldehyde **5** (equation 1).[11] (+)-Oxindole **6**, which can be prepared in this fashion on a large scale in five steps from isatin, was the starting point for our construction of (+)-gliocladin C (**1**).



[a]DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine

leoverma@uci.edu.

The conversion of Mukaiyama aldol adduct **6** to hydroxymethyl pyrrolidinoindoline **11** is summarized in Scheme 1. This seemingly straightforward elaboration was rendered challenging by the propensity of oxindole **6** to undergo retro-aldol fragmentation under basic conditions,[9] and the acid sensitivity of pyrrolidinolindolines having a hydroxyl substituent at C3.[12,13] The sequence that ultimately proved successful began by cleavage of the oxazoline and Boc substituents of aldol adduct **6** with 3 M HCl in MeOH, followed by reaction of the resulting amino diol with 2,2-dimethoxypropane, a sequence that delivered 1,3-dioxane **7** in 85% overall yield. The use of formic acid in the first step[9] resulted in partial retroaldolization in large-scale reactions when this less volatile acid was removed by evaporation. Reaction of amino oxindole **7** with excess $LiAlH_4$ at room temperature, followed by exposure of the crude product to a slurry of silica gel in MeOH provided pyrrolidinoindoline **8** in 93% yield.

We first became aware of the extreme acid sensitivity of pyrrolidinoindolines containing hydroxyl sustituents at C3 when all standard conditions we surveyed for cleaving the acetonide substituent of intermediate **8** resulted in extensive decomposition. However, using the method developed by Rychnovsky,[14] this group was transformed to silyloxy propenyl ether **9** in high yield by exposure to excess TMSOTf and diisopropylethylamine. After introducing a Boc group to protect the pyrrolidine nitrogen, reaction at room temperature with a catalytic amount of oxalic acid in MeOH delivered diol **10** in 71% yield for the two steps. As this intermediate was quite sensitive, all attempts to selectively oxidize the primary alcohol substituent were unsuccessful. Thus, diol **10** was transformed to methoxy derivative **11** by selective protection of the primary alcohol with a TBDMS group, followed by sequential reaction with excess NaH and MeI and then TBAF (1 equiv). This series of three reactions provided intermediate **11** in 68% overall yield from diol precursor **10**.[15] All steps of this sequence take place under basic conditions, which is likely key to its success.

The trioxopiperazine ring of (+)-gliocladin C was assembled, and the $\Delta^{11,12}$-unsaturation introduced, by the series of transformations summarized in Scheme 2. The primary alcohol substituent of alcohol **11** was first oxidized to give the corresponding acid without effecting the indole substituent by a two-step sequence involving initial reaction with Dess-Martin periodinane[16] to give the corresponding aldehyde, followed by sodium chlorite oxidation.[17] Coupling of the crude acid product with methylamine using the BOP reagent[18] then delivered amide **12** in 60% overall yield form hydroxymethyl pyrrolidinoindoline **11**. To set the stage for assembling the trioxopiperazine ring, the Boc group was cleaved by reaction of **12** with TMSI to give secondary amine **13** in 65% yield.[19,20] A preliminary survey of the reactivity of the pyrrolidine nitrogen of congeners of **13**[21] had shown that acylation of the hindered and inductively deactivated secondary amine was problematic; thus, the benzyl protecting group of the adjacent nitrogen and that of the indole substituent were removed at this stage by the reaction of **13** at −78 °C with excess Na and *t*-BuOH in THF–NH_3. This deprotection was remarkably clean, providing the secondary triamine **14** in 87% yield. Although several potential approaches for fashioning the trioxopiperazine ring in one step were unsuccessful,[22] reaction of **14** with ethyl chlorooxoacetate in the presence of Et_3N took place cleanly at N5 to give oxalyl half-ester half-amide **15** in 87% yield. To our initial dismay, attempts to cyclize this intermdiate by reaction with a variety of bases (e.g., DBU, *i*-Pr_2EtN, Et_3N, or NaH) led to extensive decomposition. Fortunately, a method developed by Mulliez to form peptide-derived trioxopiperazines proved successful.[23] Thus, when a solution of **15** and 1,1,1,3,3,3-hexamethyldisilazane was heated at 140 °C in a sealed tube, cyclization to form the trioxopiperazine and elimination of the methoxy group both took place to give (+)-gliocladin C (**1**), a pale yellow solid, in 73% yield. Comparison of ^1H and ^{13}C NMR data[24,25] of synthetic **1** with those of the natural product confirmed their identity. The optical rotation of synthetic **1**, $[\alpha]^{23}_D$ +116, (*c* 0.02 $CHCl_3$), compared well with that reported for the natural sample, $[\alpha]_D$ +131, (*c* 0.07 $CHCl_3$). Because the relative and absolute configuration of the Fmoc

derivative of synthetic precursor **7** had been determined by single-crystal X-ray analysis,[9] this comparison establishes the absolute configuration of (+)-gliocladin C (**1**) to be as depicted.

In summary, the first total synthesis of the structurally novel marine alkaloid (+)-gliocladin C (**1**) was completed in ~4% overall yield and 21 steps from isatin. A central step in this sequence is asymmetric construction of the quaternary carbon stereocenter by a Mukaiyama aldol reaction of siloxyindole **4** and enantiopure aldehyde **5**.[9] Knowledge gained during the latter stages of this synthesis could potentially allow the synthetic sequence to be streamlined. Of more importance, a better appreciation of the acid sensitivity of pyrrolidinoindolines containing oxygen substituents at C3 should assist in the design of synthetic approaches to related, more complex and biologically more potent, alkaloids.[26]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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20. The C3 acetate analog of **13** provided single crystals allowing the relative configuration of this intermediate to be confirmed by X-ray crystallography.

21. The substituent was OAc or OTIPS instead of OMe.

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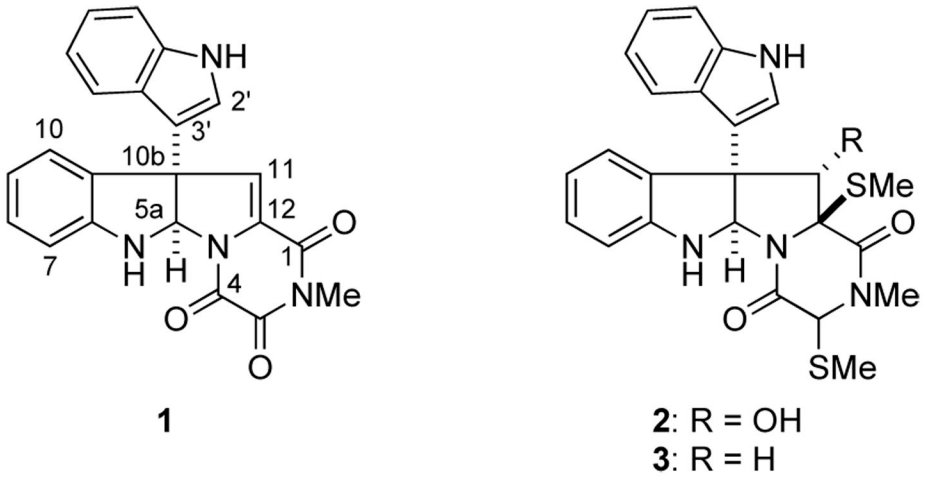
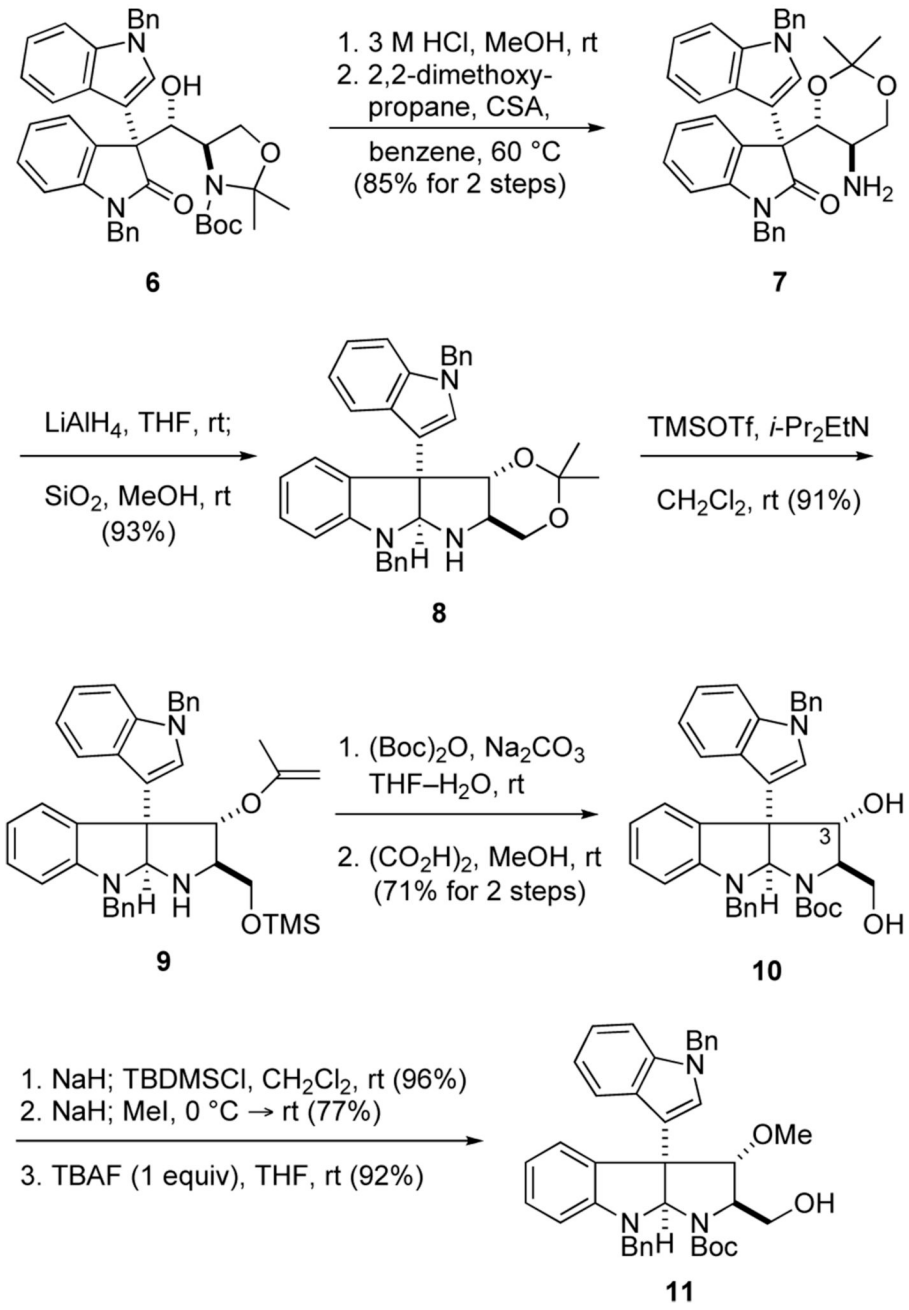
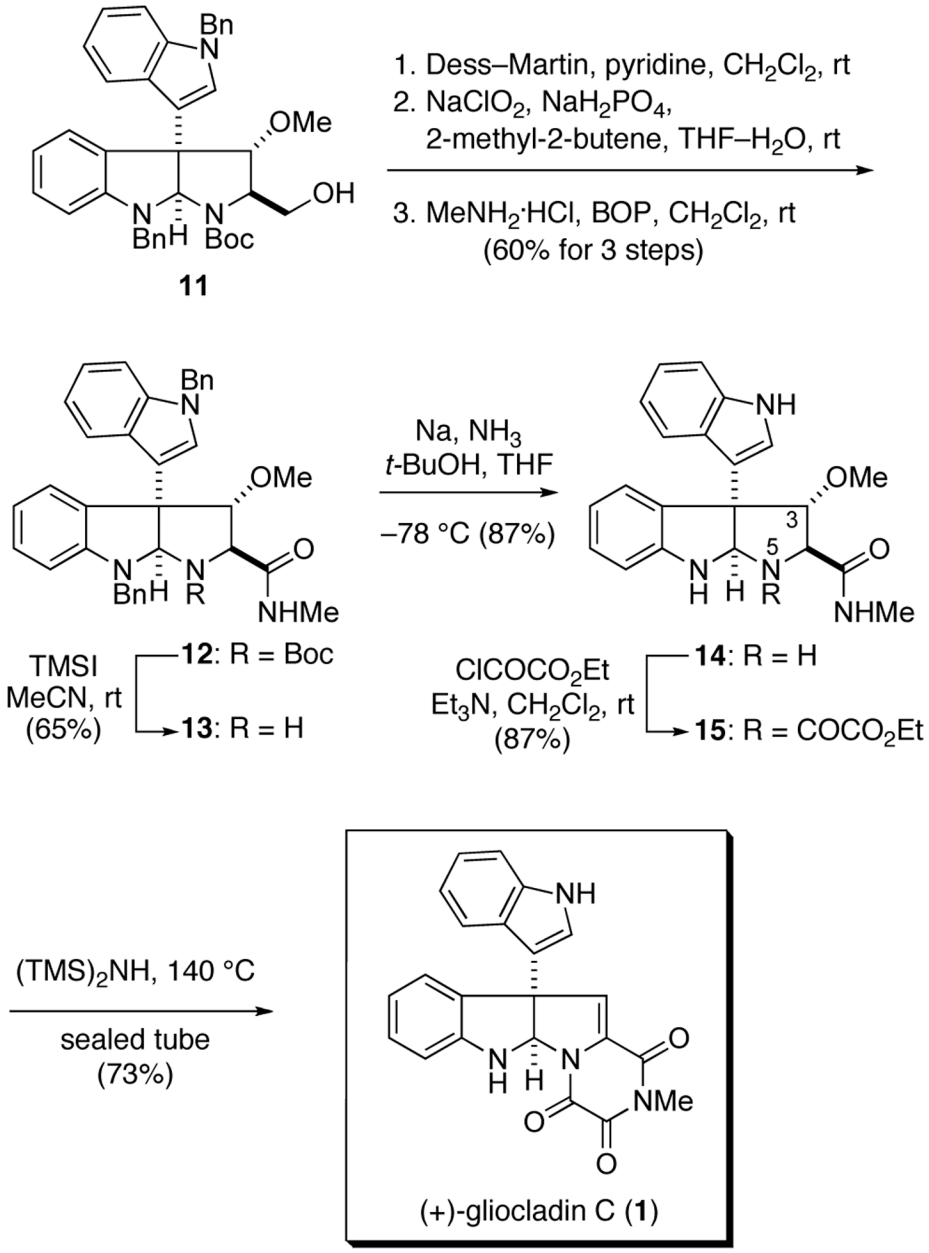


Figure 1.
Gliocladins A (**2**), B (**3**) and C (**1**).



Scheme 1.
Conversion of aldol product **6** to pyrrolidinoindoline alcohol **11**



Scheme 2.
Construction of the trioxopiperazine ring to form (+)-gliocladin C (**1**)