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Enantioselective Total Synthesis of (+)-Gliocladin C

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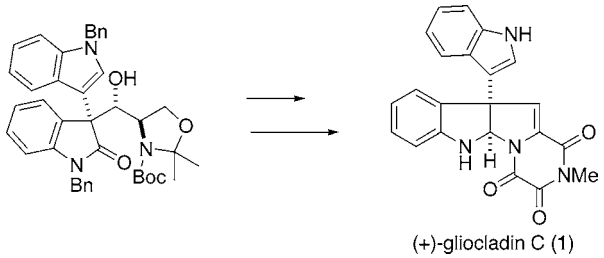
ABSTRACT



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

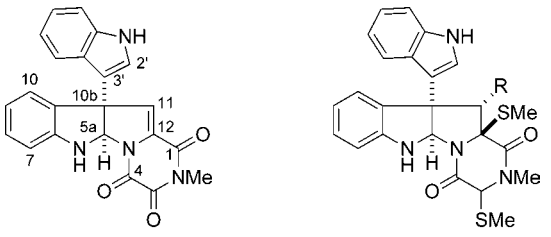


Figure 1. Gliocladins A (**2**), B (**3**), and C (**1**).

were the sulfur-containing analogues 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

(1) Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, M. R. *Nat. Prod. Rep.* **2006**, *23*, 26−78 and earlier reviews in this series.

(2) Usami, Y.; Yamaguchi, J.; Numata, A. *Heterocycles* **2004**, *63*, 1123−1129.

(3) Takahashi, C.; Numata, A.; Ito, Y.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1859−1864.

(4) Dong, J.−Y.; He, H.−P.; Shen, Y.−M; Zhang, K.−Q. *J. Nat. Prod.* **2005**, *68*, 1510−1513.

(5) Feng, Y.; Blunt, J. W.; Cole, A. L. J.; Munro, M. H. G. *J. Nat. Prod.* **2004**, *67*, 2090−2092.

(6) A trioxopiperazine ring is found in dithiosecoemestrin[7a] and neoechinulin.[7b]

(7) (a) Seya, H.; Nozawa, K.; Udagawa, S.; Nakajima, S.; Kawai, K. *Chem. Pharm. Bull.* **1986**, *34*, 2411−2416. (b) Casnati, G.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1973**, *103*, 141−151.

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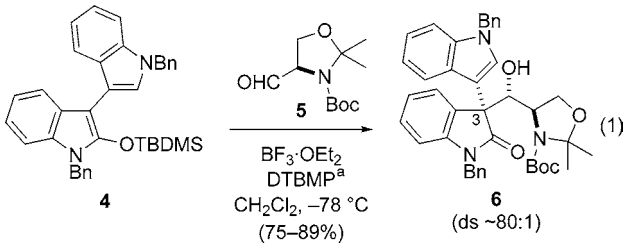
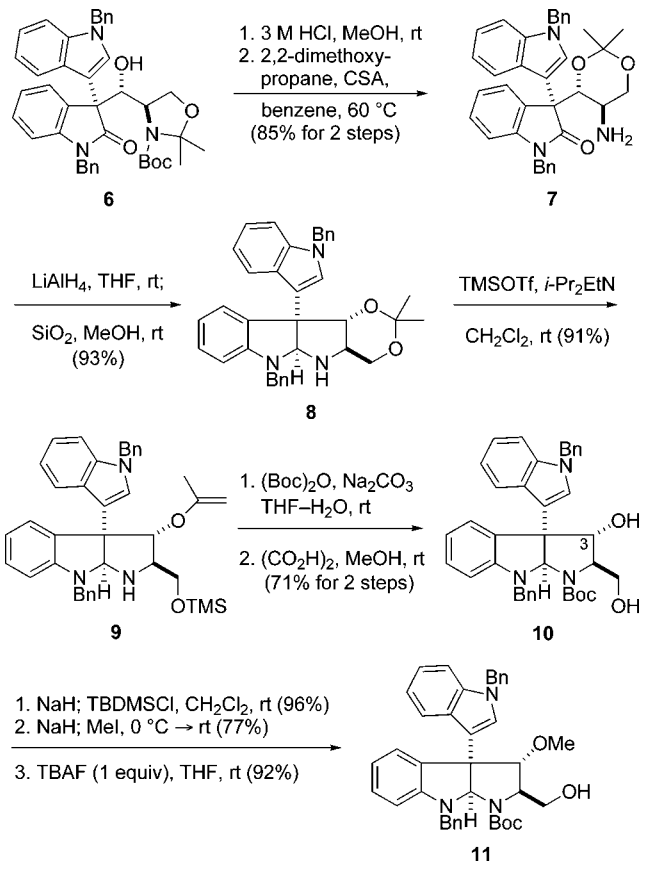
reported[9] that elaborate, enantiopure structures of this type containing an aryl or heteroaryl substituent at the quaternary C3 stereocenter could be quickly assembled by the Mukaiyama aldol reaction[10] of 2-siloxyindoles and the serine-derived aldehyde **5** (eq 1, DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine).[11] (+)-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**).



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

Scheme 1. Conversion of Aldol Product **6** to Pyrrolidinoindoline Alcohol **11**



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

(8) Julian, P. L.; Pikl, J.; Boggess, D. *J. Am. Chem. Soc.* **1934**, *56*, 1797–1801.

(9) Adhikari, S.; Caillé, S.; Hanbauer, M.; Ngo, V. X.; Overman, L. E. *Org. Lett.* **2005**, *7*, 2795–2798.

(10) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503–7509.

(11) Garner, P.; Park, J. M. *Organic Syntheses*; Wiley: New York, 1998; Collect. Vol. IX, pp 300–305.

(12) (a) The acid sensitivity of 3-hydroxypyrrolidinoindolines is believed to derive from acid-catalyzed ring opening of the aminal functionality. Iminium species generated in this way could degrade by multiple pathways, for example, by retroaldol-type cleavage. (b) Degradative studies of verticillin A[13a] and leptosin B[13b] demonstrated the instability of the 3-hydroxypyrrolidinoindoline subunit under strongly basic conditions or upon reaction with triphenylphosphine.

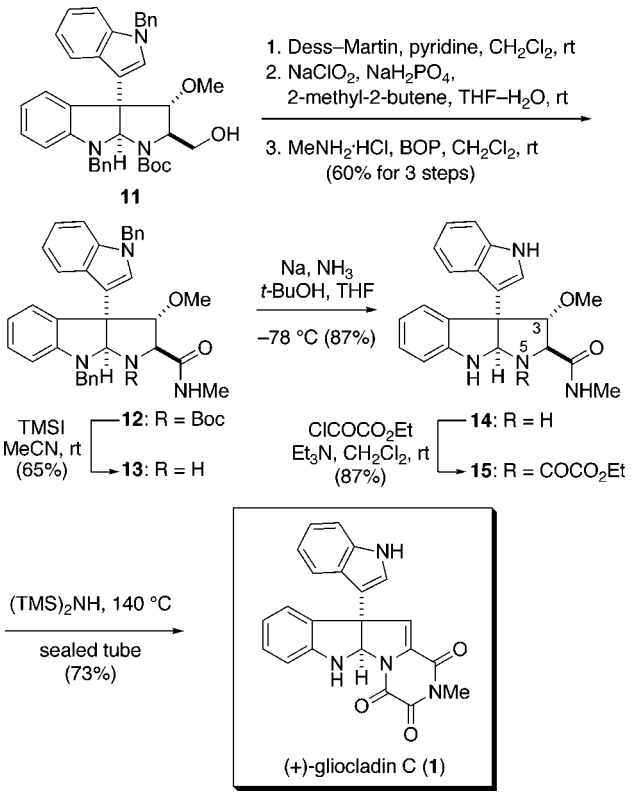
(13) (a) Minato, H.; Matsumoto, M.; Katayama, T. *J. Chem. Soc., Perkin Trans. 1* **1973**, 1819–1825. (b) Takahashi, C.; Numata, A.; Ito, Y.; Matsumura, E.; Araki, H.; Iwaki, H.; Kushida, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1859–1864.

(14) (a) Rychnovsky, S. D.; Hoye, R. C. *J. Am. Chem. Soc*. **1994**, *116*, 1753–1765. (b) Rychnovsky, S. D.; Kim, J. *Tetrahedron Lett.* **1991**, *32*, 7219–7222.

(15) The use of excess TBAF resulted in lower yields.

(16) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549–7552.

Scheme 2. Construction of the Trioxopiperazine Ring To Form (+)-Gliocladin C (**1**)



hydroxymethylpyrrolidinoindoline **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]

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Supporting Information Available: Experimental procedures, tabulated ^1H and ^{13}C NMR spectra of natural and synthetic (+)-gliocladin C, copies of ^1H and ^{13}C NMR spectra of new compounds, and the X-ray model of the C3 acetate analogue of **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) (a) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096. (b) Kraus, G. A.; Taschner, M. J. *J. Org. Chem.* **1980**, *45*, 1175−1176.

(18) BOP = benzotriazole-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate.

(19) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963.

(20) The C3 acetate analogue 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.

(22) (a) Makino, S.; Nakanishi, E.; Tsuji, T. *Synlett* **2003**, *6*, 817−820. (b) Bailey, P. D.; Bannister, N.; Bernad, M.; Blanchard, S.; Boa, A. N. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3245−3251.

(23) Mulliez, M.; Royer, J. *Tetrahedron* **1984**, *40*, 5143−5151.

(24) The small signal for the quaternary carbon C3′ at 116.7 ppm, which is seen in the ^{13}C NMR spectrum of natural gliocladin C, was not reported in ref 2. Assignments reported in this paper for signals at 122.7 and 120.11/120.13 ppm should be changed to C6′ and C4′/C5′.[25] A summary of peak assignments for synthetic gliocladin C, which were established by HMQC and HMBC experiments, can be found in the Supporting Information.

(25) Usami, Y. Personal communication, Aug 8, 2006.

(26) Anthoni, U.; Christophersen, C.; Nielsen, P. H. Naturally Occurring Cyclotryptophans and Cyclotryptamines. In *Alkaloids*: *Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 163−236.