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Bidirectional Synthesis of the Central Amino Acid of Chloptosin

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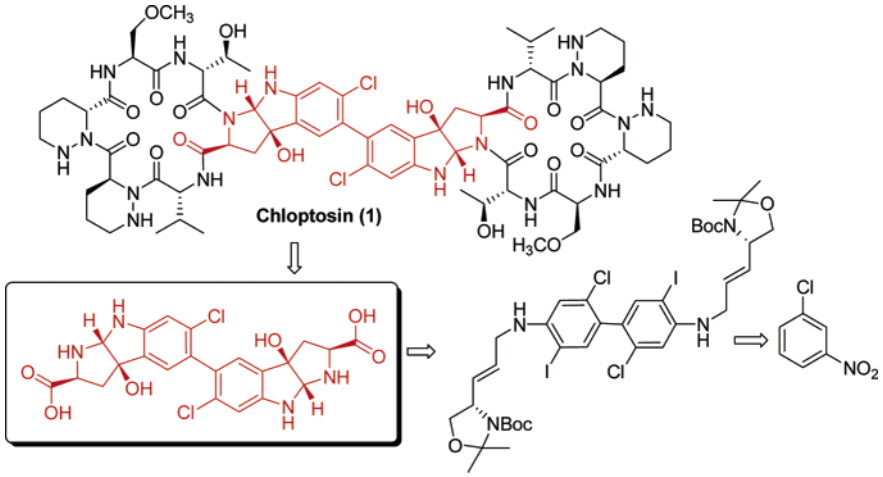
ABSTRACT



An efficient total synthesis of (2*S*,2′*S*,3a*R*,3′a*R*,8a*R*,8′a*R*)-6,6′-dichloro-3a,3′a-dihydroxy-1,1′,2,2′,3,3a,3′,3′a,8,8a,8′,8′a-dodecahydro-5,5′-bipyrrolo[2,3-*b*]indole-2,2′-dicarboxylic acid, the central amino acid component of chloptosin (1), is described. Starting from *m*-chloronitrobenzene, this C_2-symmetrical amino acid was synthesized by using a 14-step route, in which a Zinin benzidine rearrangement, intramolecular Heck reaction, and selenocyclization and oxidative deselenation served as key steps. The absolute stereochemistry of the target was confirmed by X-ray single-crystal studies on a key intermediate (17).

Adriamycin, paclitaxel, and many other anticancer agents are known to induce apoptosis in cultured neoplastic cells.[1] However, human carcinoma cells are often resistant to apoptosis, and this phenotype may partly explain the poor therapeutic effect of present cancer chemotherapies on most solid tumors. Chloptosin (**1**) was recently isolated as the third metabolite from the culture broth of the MK498-98F14 strain of *Streptomyces*.[2a] All three reported metabolites, chloptosin (**1**) and polyoxypeptins A (**2**) and B (**3**)[2b,c] (Figure 1), were found to induce apoptotic activity in the apoptosis-resistant human pancreatic adenocarcinoma cell line AsPC-1. In addition, chloptosin (**1**) shows strong antimicrobial activity against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. Structurally, chloptosin (**1**) consists of a biaryl linkage connecting two identical subunits. Although indole units are frequently found in a large number

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(1) (a) Ling, Y.-H.; Priebe, W.; Perez-Soler, R. *Cancer Res.* **1993**, *53*, 1845−1852. (b) Haldar, S.; Chintapalli, J.; Croce, C. M. *Cancer Res.* **1996**, *56*, 1253−1255.

(2) (a) Umezawa, K.; Ikeda, Y.; Uchihata, Y.; Naganawa, H.; Kondo, S. *J. Org. Chem.* **2000**, *65*, 459−463. (b) Umezawa, K.; Nakazawa, K.; Uemura, T.; Ikeda, Y.; Kondo, S.; Naganawa, H.; Kinoshita, N.; Hashizume, H.; Hamada, M.; Takeuchi, T.; Ohba, S. *Tetrahedron Lett.* **1998**, *39*, 1389−1392. (c) Umezawa, K.; Nakazawa, K.; Ikeda, Y.; Naganawa, H.; Kondo, S. *J. Org. Chem.* **1999**, *64*, 3034−3038.

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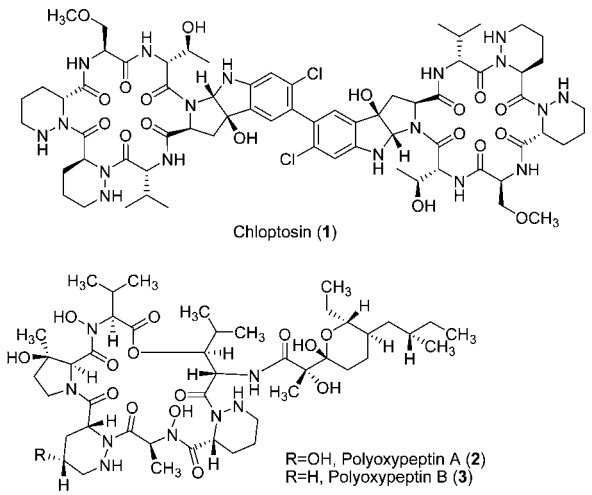

Figure 1. Structures of chloptosin (**1**) and polyoxypeptins A (**2**) and B (**3**).

of alkaloids,[3,5] the presence of a chlorine atom at the 6-position in chloptosin is apparently rare. Existing methods for generating similar structures such as 3a-hydroxypyrrolo-[2,3-*b*]indole have suffered from problems related to poor yields and stereocontrol.[4] One notable exception is the dimethyldioxirane (DMDO)-based oxidation of trytophan derivatives developed by Danishefsky and co-workers.[5] However, our initial efforts utilizing a similar strategy could not achieve satisfactory results when applied to the substrates having two chlorines. Recently, partial syntheses of this pyrroloindoline were reported by us[6a] and Han[6b] using a Davis silyl ether oxidation and Danishefsky's protocol, respectively. Unfortunately, these methods lacked satisfactory stereoselectivity and efficiency when applied to the synthesis of this dimeric amino acid. Very recently, important methodology was developed in Ley's lab[7] to elaborate similar hexahydropyrrolo[2,3-*b*]indol-3a-ols using a selenocyclization-oxidative deselenation sequence. This method presented itself as an alternative protocol that may avoid side reactions associated with the chlorines. Herein, we report our successful total synthesis of the challenging C_2-symmetrical amino acid **4** present in chloptosin (**1**) (Figure 2).

As shown in Figure 2, chloptosin (**1**) can be disconnected into one dimeric L-6-chloropyrroloindoline derivative **4** and two pentapeptides **5**. A bidirectional route was then designed to take advantage of the C_2 symmetry of the target.

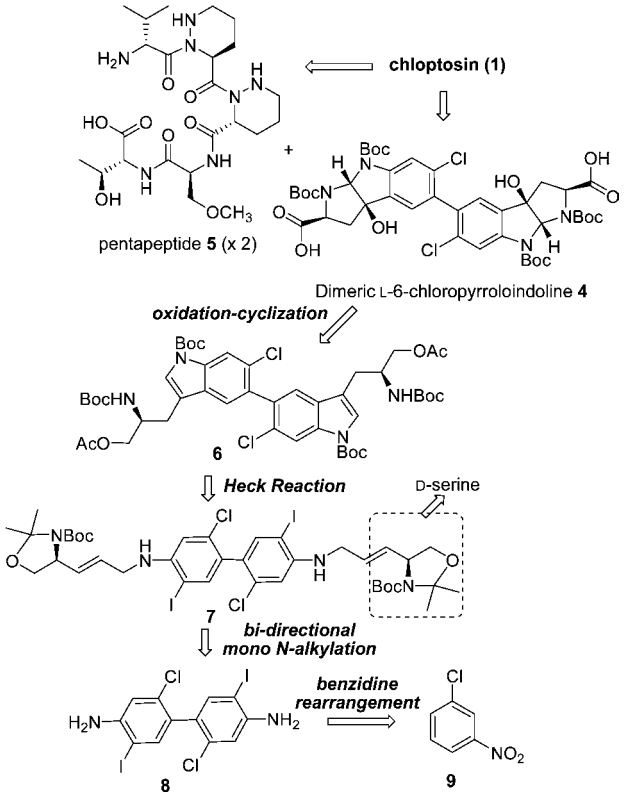

Figure 2. Retrosynthetic analysis of the dimeric amino acid **4** in chloptosin (**1**).

According to our synthetic plan, a Zinin benzidine rearrangement, intramolecular Heck reaction, and selenocyclization−oxidative deselenation were designed as the key reactions, and commercially available *m*-chloronitrobenzene (**9**) and D-serine were used as the starting materials. The intermediate diamine **8** could be prepared via a Zinin benzidine rearrangement[8] followed by regioselective iodination. Double mono *N*-akylations and intramolecular Heck reactions could achieve the indole derivative **6**. The final dimeric L-6-chloropyrroloindoline derivative **4** could be elaborated via Ley's protocol.[7]

The precursor **7** for the intramolecular Heck reactions was prepared first (Scheme 1). Treatment of *m*-chloronitrobenzene (**9**) with powdered zinc and sodium hydroxide under refluxing conditions afforded 1,2-bis(3-chlorophenyl)hydrazine (**10**), which was then efficiently rearranged to 2,2′-dichlorobiphenyl-4,4′-diamine (**11**) using hydrochloride acid[8] (70% yield in two steps). Regioselective iodination of **11** was carried out by treatment with H_2O_2 and iodine,[9] giving the desired iodide **8** in 62% yield. Next double mono *N*-alkylations were accomplished by reacting **8** with the bromide **12**[10] in water and acetone in the presence of $NaHCO_3$ and Bu_4NCl.[11] Optimization of this procedure finally afforded **7** in acceptable yield.

(3) Recent examples: (a) Depew, K. M.; Marsden, S. P.; Zatorska, D.; Zatorski, A.; Bornmann, W. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11953−11963. (b) Nishida, A.; Ushigome, S.; Sugimoto, A.; Arai, S. *Heterocycles* **2005**, *66*, 181−185. (c) Iwaki, T.; Yamada, F.; Funaki, S.; Somei, M. *Heterocycles* **2005**, *65*, 1811−1815. (d) Kawahara, M.; Nishida, A.; Nakagawa, M. *Org. Lett.* **2000**, *2*, 675−678. (e) Sun, W. Y.; Sun, Y.; Tang, Y. C.; Hu, J. Q. *Synlett* **1993**, 337−338.

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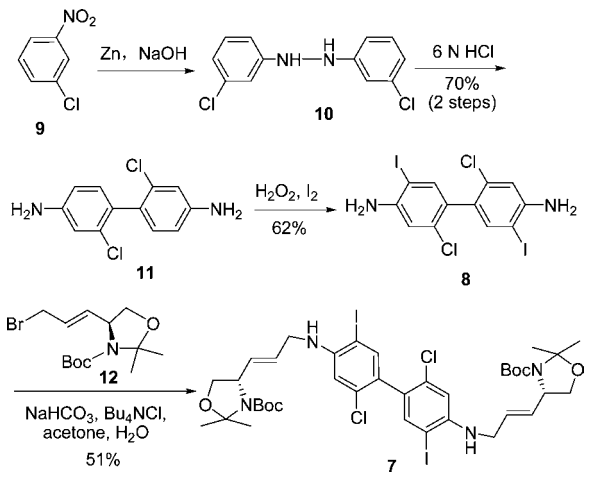
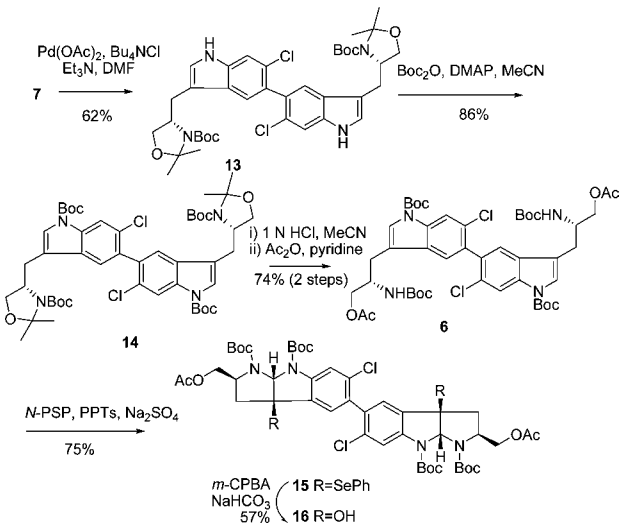
Scheme 1. Synthesis of Precursor **7** from *m*-Chloronitrobenzene

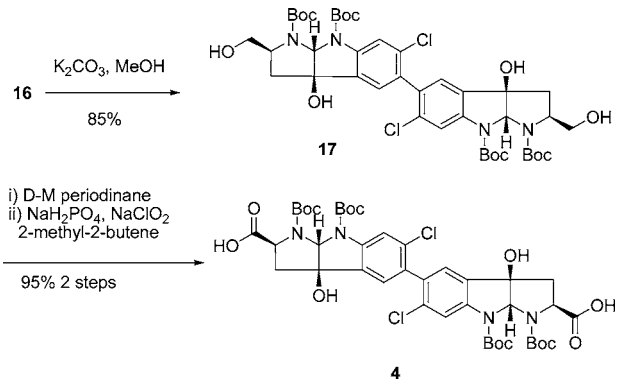


Intramolecular Heck reaction of compound **7** with $Pd(OAc)_2$ as a catalyst[12] afforded the dimeric indole derivative **13** in 62% yield (Scheme 2). This reaction involved the C=C bond migration from the exo position of a five-member ring to give the indole functionality. The disfavored dihydroquinoline Heck reaction product was not observed. After protection of the indole free nitrogens with Boc_2O,[13] two *O*,*N*-aminals were selectively removed under dilute HCl conditions.[14] The resulting primary alcohols were protected as their acetates.[15] Compound **6** was then subjected to selenocyclization.[16] Studies showed that the success of this selenocyclization reaction in terms of yield and stereocontrol (*exo* vs *endo* products) was dependent on the particular *N*-protecting groups employed, with the *N*-Boc derivative (**6**) being the best.[17] With **6** as substrate, the final optimized conditions provided the *exo* product **15** in 75% yield as a single diastereomer. Oxidative deselenation by treatment of **15** with an excess of wet *m*-CPBA[18] afforded the corresponding tertiary alcohol **16** in 57% yield. The stereochemistry of the alcohol is required to be the same as that of the parent selenide, owing to the necessary *syn*-[5,5] ring junction.[7] Our initial attempts to obtain the clear stereochemical assignment of **16** by nOe studies were not successful. Fortunately, an X-ray diffraction crystal study of alcohol **17** provided the absolute stereochemistry of this fused ring unambiguously following the removal of both acetates in **16** (Scheme 3).

Scheme 2. Synthesis of the Dimeric Indol Derivatives



Scheme 3. Completion of the Total Synthesis of Amino Acid Derivative **4**



Removal of the acetate protecting groups of **16** with K_2CO_3 in MeOH[19] smoothly afforded the alcohol **17** as crystals, whose three-dimensional structure was determined by X-ray crystallographic analysis (Figure 3, for details see the Supporting Information). Dess−Martin oxidation[20] of **17** followed by treatment with $NaClO_2$[21] afforded the desired dimeric L-6-chloropyrroloindoline acid **4** in 95% yield.

In conclusion, an enantioselective synthesis of the central amino acid component of chloptosin (**1**), dimeric L-6-chloropyrroloindoline derivative **4**, was efficiently accomplished bidirectionally starting from *m*-chloronitrobenzene (14 steps, 5% overall yield). The synthesis was designed to take advantage of the symmetrical characteristics of the target, and featured a Zinin benzidine rearrangement, intramolecular Heck reaction, and selenocyclization−oxidative

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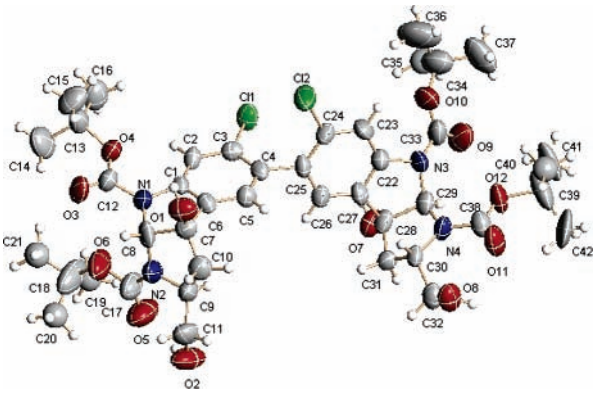

Figure 3. X-ray single-crystal structure of **17**.

deselenation as key steps. The X-ray crystallographic analysis of an advanced intermediate (**17**) indirectly confirmed the absolute stereochemistry of the final amino acid **4**. Further efforts toward the total synthesis of chloptosin are currently ongoing in our laboratory and will be reported in due course.

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Supporting Information Available: Experimental details and characteristics of compounds, ^{1}H NMR spectra of compounds **4**, **6**−**8**, and **13**−**17**, and ^{13}C NMR spectra of compounds **4** and **13**−**17**, as well as the X-ray structure of compound **17** (image in PDF and CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

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