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Stereocontrolled and Efficient Total Synthesis of (−)-Stephanotic Acid Methyl Ester and (−)-Celogentin C

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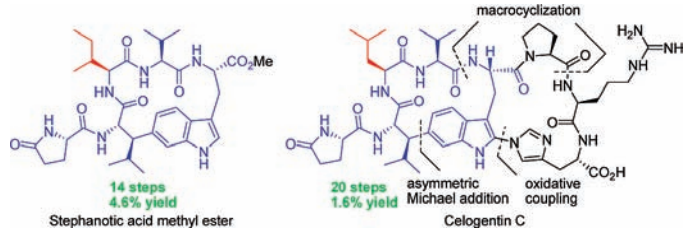
ABSTRACT



A highly stereocontrolled and efficient total synthesis of (−)-stephanotic acid methyl ester and (−)-celogentin C was accomplished in longest linear 14 steps (4.6% overall yield) and in 20 steps (1.6% overall yield) from L-tryptophan, respectively. Highlights of the synthesis include a tandem asymmetric Michael addition/bromination/azidation strategy for a ready access to the leucine-tryptophan moiety (Leu-Trp linkage) and an oxidative coupling reaction to form the indole-imidazole linkage.

A series of bicyclic peptide celogentins A-H and J, as well as moroidin were isolated by Kobayashi and co-workers from the seeds of *Celosia argentea*, which is one of Chinese herbal medicines used as a therapeutic drug for eye and hepatic diseases in China and Japan.[1,2] Stephanotic acid (Figure 1), corresponding to the left-hand part of this bicyclic peptide family, was isolated from *Stephanotis floribunda*.[3] Some bicyclic peptides of this family inhibit the tubulin polymerization, among which celogentin C (IC_{50} 0.8 μM) showed to be 4 times more potent than a known anticancer agent vinblastine (IC_{50} 3.6 μM) in a laboratory experiment. However, stephanotic acid did not show such inhibition. The unique structure of celogentin C contains an unusual direct C−C linkage between the tryptophan C-6 and the leucine β-carbon, and a C−N linkage between the tryptophan C-2 and the imidazole N-1 of histidine. The impressive biological properties coupled with their unprecedented molecular architectures made the celogentins and related compounds enticing targets for chemical synthesis.[4−8] In this context, Moody has reported the sole total synthesis of stephanotic acid methyl ester.[4a] Very recently, Castle and co-workers

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reported the first, and to date only, total synthesis of celogentin C.[5a] Herein, we report a short, stereocontrolled total synthesis of (−)-stephanotic acid methyl ester and (−)-celogentin C that would potentially be amenable to large-scale production of this important antitumor agent.

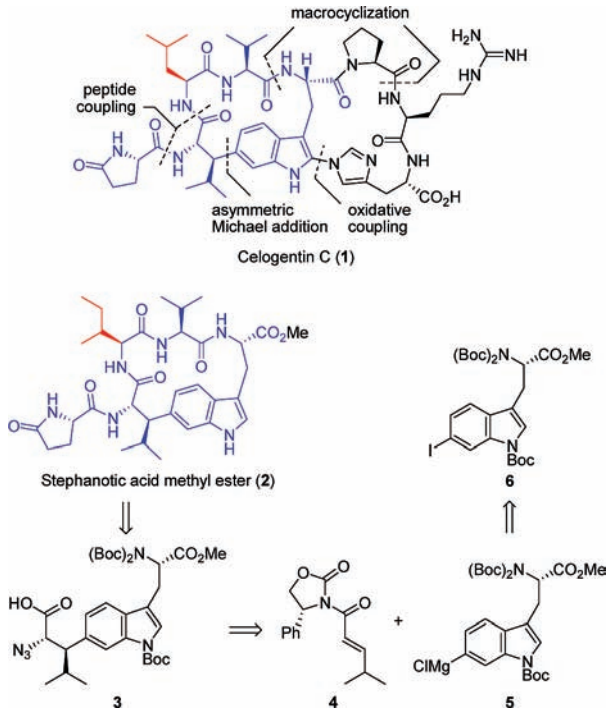

Figure 1. Structure of celogentin C and its retrosynthetic analysis.

To achieve the scalable and controllable total synthesis of celogentin C, two challenging issues (the two unusual cross-links) should be addressed. The first is to develop a method for the efficient, asymmetric synthesis of leucine-tryptophan moiety in the "left-hand" macrocycle of the celogentin/moroidin family, which has not been well resolved in previous reports. Moody and Castle both employed the diastereoisomers separation strategy. The second issue is how to generate the tryptophan-histidine cross-link in the "right-hand" macrocycle. Castle has reported an elegant method to construct the indole-imidazole linkage by using an intermolecular oxidative coupling, which also led them to complete the first synthesis of celogentin C.

A left-to-right sequence was adopted in our synthetic plan of celogentin C (**1**) as outlined in Figure 1. The final construction of the right-hand ring of **1** would follow the elegant sequence recently reported by Castle. The formation of the left-hand ring would be considered to be the total synthesis of stephanotic acid methyl ester **2**, which could be achieved by macrolactamization at the Val-Trp site. Accordingly, we envisioned that the key leucine-tryptophan moiety **3** could be obtained stereoselectively by using a tandem asymmetric Michael addition/bromination/azidation strategy, which employs Evans' oxazolidinone auxiliary to control the configuration.[9] Thus, the known (4S,2E)-3-(1-oxo-2-isohexenyl)-4-phenyl-2-oxazolidinone **4**[10] could be used as Michael reaction acceptor, and L-tryptophan C6-Grignard reagent **5** as the Michael reaction donor. The Grignard reagent **5** could be prepared by iodo/magnesium exchange from 6-iodo-L-tryptophan derivative **6**,[11] which would be assembled either from a known Pd-catalyzed annulation method developed by Zhu and Jia,[12] or from commercially available L-tryptophan.[13]

The total synthesis of **2** commenced with commercially available L-tryptophan as outlined in Scheme 1. Nitration of L-tryptophan **7** with fuming nitric acid in acetic acid following the literature process gave the nitrate of 6-nitro-L-tryptophan **8**.[13] Treatment of **8** with Me_3SiCl in dry MeOH followed by the addition of Et_3N and Boc_2O gave the mono-Boc product **9** in 81% overall yield (2 steps). Protection of **9** with Boc_2O in the presence of a catalytic amount of DMAP afforded **10** in 95% yield, which has been also prepared by Pd-catalyzed annulation method developed by Zhu and Jia.[12] However, the present method is advantageous because it can be easy to prepare hundreds gram of **10** without using any expensive reagents such as $Pd(OAc)_2$.

Reduction of the nitro group in **10** with Zn dust and HOAc in CH_2Cl_2 gave the 6-amino derivative **11** in quantitative

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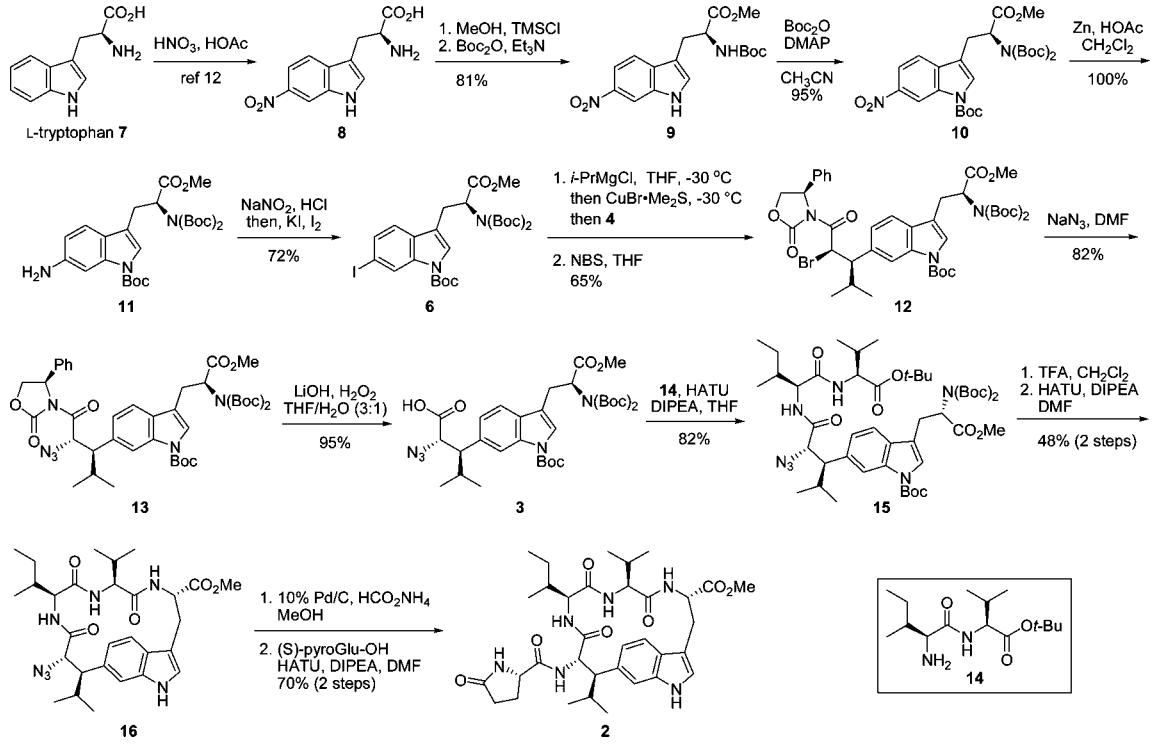
Scheme 1. Total Synthesis of Stephanotic Acid Methyl Ester **2**



yield. Diazotization of aniline followed by iodination under classical acidic conditions ($NaNO_2$, HCl then KI) was disappointing and led to substantial amounts of the reduced compound. After surveying a variety of conditions, we found that the addition of one equivalent of I_2 could decrease the reduced compound and gave the desired product **6** in 72% yield along with 10% reduced compound.[14]

With this material in hand, we were able to examine the pivotal conjugate addition/bromination cascade sequence in detail. The L-tryptophan C6-Grignard reagent was prepared by iodo/magnesium exchange following the literature's procedure.[11] To our disappointment, only a small amount of the expected product **12** (ca. 10% yield) was obtained according to the protocol developed by Hruby.[9] After surveying a variety of reaction conditions (catalysts, temperatures, and times), we eventually found that the amount of $CuBr{\bullet}SMe_2$ (20%) was crucial to get good yield.[9a] Under the optimized reaction conditions, compound **12** was obtained as a single detectable diastereomers in 65% yield! Since we could not get X-ray crystallography of **12**, a determination of its absolute configuration would have to await completion of the synthesis of **2** (*vide infra*). It is noteworthy that, to the best of our knowledge, this key reaction not only provides the amino acid precursor in superb stereoselectivity, but it also represents the first example that such tryptophan Grignard reagent is used as the Michael reaction donor.

Subsequently, S_N2 displacement of the bromo group with NaN_3 in DMF provided α-azido product **13** in 82% yield. As azide could be served as a "masked" amine, we did not reduce it at this stage. Selective removal of the chiral auxiliary of **13** seemed to be challenging under base conditions in the presence of base-sensitive amine di-Boc, indole-*N*-Boc and methyl ester. To our delight, chemoselective hydrolysis of azido compound **13** was effected exclusively by using LiOH in the presence of hydrogen peroxide to give the azido acid **3** in 95% yield, with simultaneous recovery of the chiral auxiliary. It is noteworthy that no epimerization at the α-carbon was detected in any case.

Coupling of azido acid **3** with the dipeptide Ile-Val-O*t*Bu (**14**) provided **15** in 82% yield. Simultaneous deprotection of the tryptophan *N*-Boc group and the valine *tert*-butyl ester by treatment with trifluoroacetic acid followed by macrolactamization under high-dilution conditions using HATU as coupling agent gave the macrocycles **16** in 48% overall yield without any epimerization. Initial attempt to reduce the azide under Staudinger condition failed to give the desired product. Gratefully, azide **16** was successfully converted to the desired amine with HCO_2NH_4 in the presence of 10% Pd/C. Finally, coupling the amine with pyroglutamic acid using HATU provided the stephanotic acid methyl ester **2**. The physical properties (^1H and ^{13}C NMR, MS data) of synthetic stephanotic acid methyl ester matched those reported for the natural material. Its optical rotation {$[\alpha]_D = -112$ (c = 0.50, MeOH)} was essentially identical to that of the natural substrate {$[\alpha]_D = -118$ (c = 1.7, MeOH)}.[3] These results also confirmed that the tandem conjugate addition/bromination sequence provided the desired stereochemistry.

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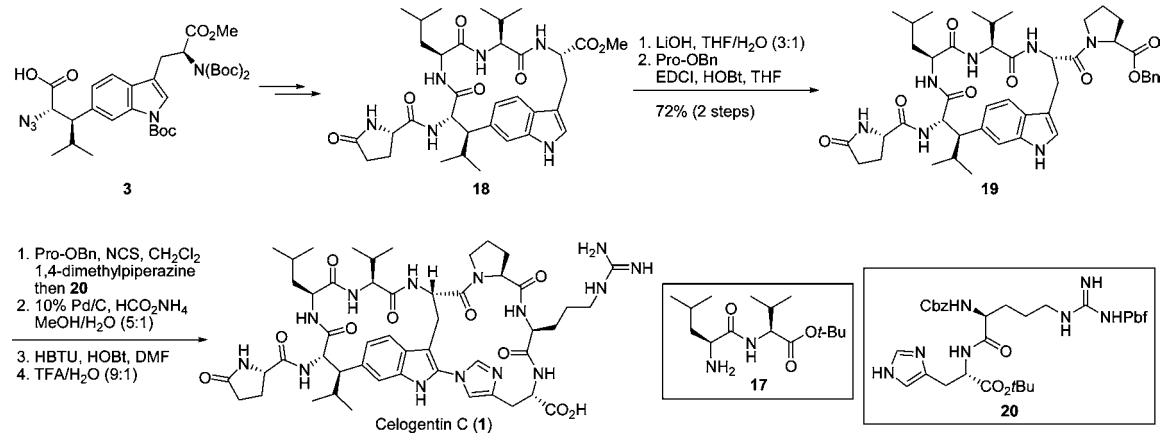
Scheme 2. Total Synthesis of Celogentin C **1**



With the practical method for the key azido acid **3** in hand, the synthesis of celogentin C was illustrated in Scheme 2. Thus, coupling of **3** with the dipeptide Leu-Val-O*t*Bu (**17**)[15] following the same synthetic scheme as described for stephanotic acid methyl ester gave monocycle compound **18**. As a testament to the practicality of this route, its utilization has allowed for the production of over 1 g of **18** to date! Saponification of the methyl ester of **18** (LiOH, THF/H_2O) followed by acidic treatment (HCl) afforded the free acid, which then coupled with Pro-OBn using EDCI and HOBt provided the known hexapeptide **19**, the key intermediate in the Castle's total synthesis of celogentin C, in 72% yield. The spectral data for **19** are in accord with those described in the literature.[5a] According to the protocol reported by Castle, compound **19** was readily converted to (−)-celogentin C in a four-step sequence.

In summary, a highly stereocontrolled and efficient total synthesis of (−)-stephanotic acid and (−)-celogentin C was accomplished in longest linear 14 steps (4.6% overall yield) and in 20 steps (1.6% overall yield) from L-tryptophan, respectively. The present synthesis features a tandem asymmetric Michael addition/bromination/azidation strategy for a ready access to the leucine-tryptophan moiety (Leu-Trp linkage), and an oxidative coupling reaction to form the indole-imidazole linkage. The described chemistry renders (−)-celogentin C readily available through chemical synthesis, and opens the way for the total synthesis of its naturally occurring siblings and designed analogues for chemical biology and medicinal chemistry studies directed toward the development of new anticancer drugs.

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Supporting Information Available: Detailed experimental procedures, compound characterization, and copies of spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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