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Total Synthesis of Celogentin C by Stereoselective C–H Activation**

*Yiqing Feng and Gong Chen**

Dedicated to Professor Samuel J. Danishefsky

Celogentin C (**1**) is a bicyclic nonribosomal peptide that was isolated from the seeds of *Celosia argentea* (Figure 1).[1] It is

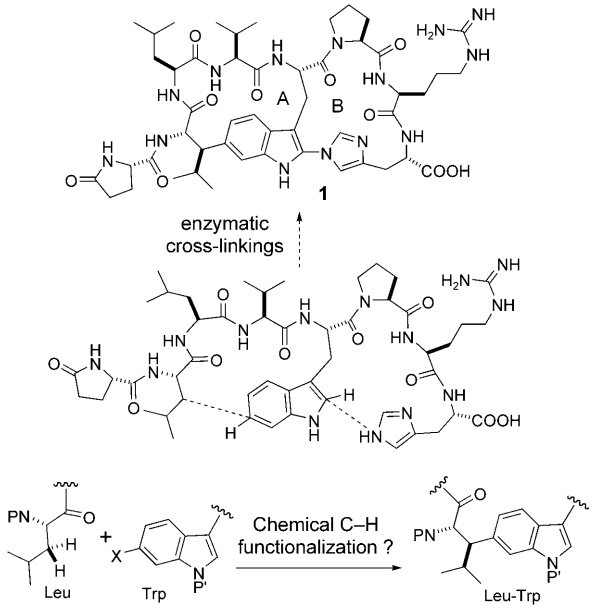

Figure 1. Celogentin C and our synthetic strategy.

the most potent isolate ($IC_{50} = 0.8\ \mu M$; IC = inhibitory concentration) from the celogentin/moroidin family, whose members possess inhibitory activity against tubulin polymerization. Its highly unusual architecture, which is characterized by the direct linkages of Trp C6 to Leu Cβ, and Trp C2 to His N1 (Figure 1), and its biological activity have prompted a number of synthesis studies.[2] Although N-linked His residues are known to occur in other macrocyclic peptides, the Leu-Trp linkage is extremely rare and poses a difficult synthetic challenge.[3] To access the key Leu-Trp motif, Moody and Bentley,[2c] and Campagne et al.,[2f] applied asymmetric hydrogenation conditions to dehydroamino acid precursors. Enantio- and/or diastereoselectivities ranged from 1:1 to 16:1 for these 10–14 step sequences. More recently, Castle and co-workers developed a novel Knoevenagel condensation/radical conjugate addition approach to the Leu-Trp linkage. They completed the first celogentin synthesis through an elegant NCS-mediated Trp-His C–N coupling by utilizing the major diastereomer product, albeit in modest enantio- and diastereoselectivity.[4] Herein, we report a highly stereoselective and efficient synthesis of celogentin C using a novel palladium-catalyzed C–H functionalization strategy.

The highly constrained structure of **1** is probably assembled in vivo from the much simpler linear peptide precursor through a series of enzymatic oxidative cross-links (Figure 1).[5] Inspired by these simple yet powerful transformations found in nature, we envisioned developing a synthetic equivalent of these processes in a direct approach to celogentin. Our synthetic strategy relied on the direct regio- and stereoselective activation of the β C–H bond of a Leu moiety and on the subsequent coupling of the derived C–Pd species with a suitable Trp partner.[6] The recent report by Corey et al.[7] of the carboxamide-directed β C–H functionalization of amino acids served as the starting point for our venture. Corey demonstrated that the β C–H bond of the *N*-phthaloyl amino acid 8-aminoquinoline amide can be efficiently activated and then arylated with simple aryl iodides under $Pd(OAc)_2$ catalysis, a procedure built on the seminal discovery of Daugulis and co-workers for the functionalization of inactivated sp^3 C–H bonds.[8] The quinoline moiety serves as a chelating auxiliary for palladium coordination, and promotes the formation of *trans*-palladacycle intermediate **4**. This palladium(II) intermediate presumably undergoes cross-coupling with an aryl iodide partner to provide the final arylated product which has an *erythro* stereochemical preference. To our delight, we were able to achieve the high-yielding and highly stereoselective 6-indolylation of *N*-phthaloyl leucine (Scheme 1a). Upon simple heating of precursors **2** (2.0 equiv) and **3** (1.0 equiv), with $Pd(OAc)_2$ (0.2 equiv), and AgOAc (1.5 equiv), at 110 °C in *t*BuOH, the desired diastereomer **5** was formed exclusively, and the slight excess of **2** could be largely recovered. About 3% of deiodinated side product **6** was also generated.

Although the quinoline carboxamide serves as an effective auxiliary in arylation chemistry, its efficient removal under mild conditions would be required for this process to become a useful tool for natural product synthesis. However, the cleavage of the amide linkage was particularly problematic, owing to both steric hindrance and the lability of the *N*-phthaloyl group.[9] This phthaloyl group, which provides both bis-protection of the α-amino group and steric bias, is critical

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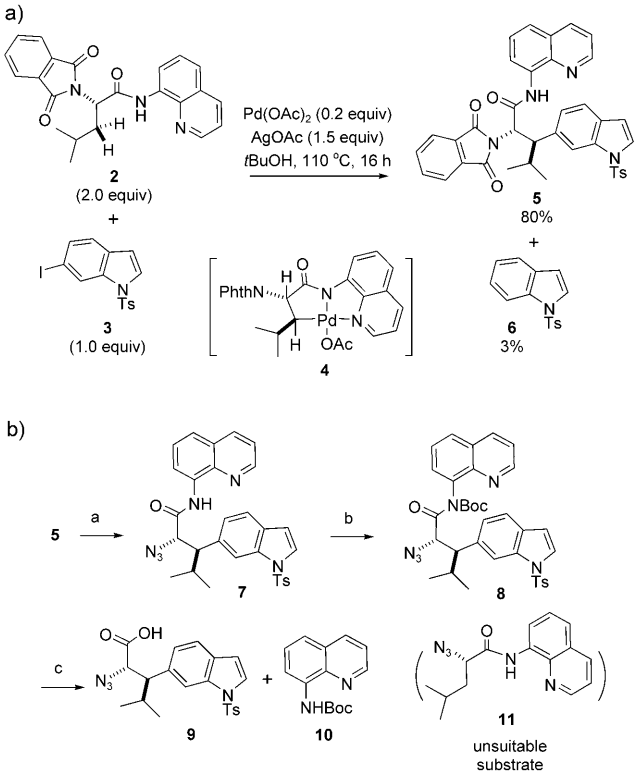
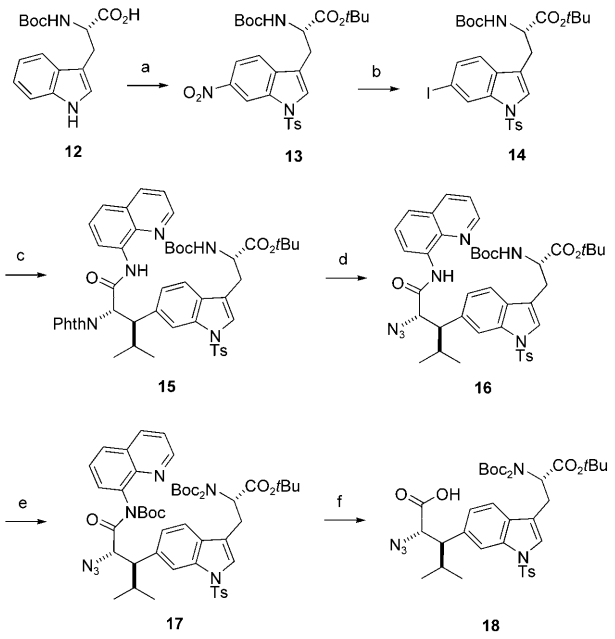


Scheme 1. C–H activation–indolylation and auxiliary removal. Reagents and conditions: a) Ethylenediamine, *n*BuOH, 90 °C; TfN_3, NEt_3, CH_2Cl_2, RT; 81 % yield over 2 steps; b) Boc_2O, DMAP, CH_3CN, RT; c) LiOH, H_2O_2, THF/H_2O, RT; 91 % yield over 2 steps. Ts = toluenesulfonyl, TfN_3 = triflic azide, Boc_2O = di-*tert*-butyl dicarbonate, DMAP = 4-dimethylaminopyridine.



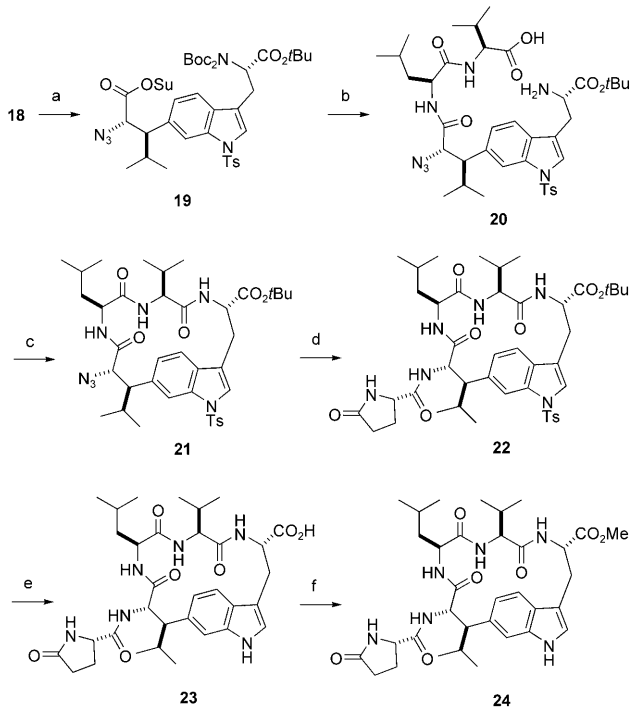
Scheme 2. Synthesis of the key Leu-Trp intermediate. Reagents and conditions: a) *t*BuBr, TEBAC, DMA, 55 °C, 89 %; HNO_3 (1.7 equiv), HOAc (5.0 equiv), CH_2Cl_2, RT; NaH, TsCl, DMF, 0 °C to RT; 24 % yield over 2 steps; b) H_2, 10 % Pd/C, MeOH, RT, 78 % yield; $NOBF_4$, KI, I_2, CH_3CN, −40 °C, 62 % yield; c) **14** (1.0 equiv), **2** (2.0 equiv), $Pd(OAc)_2$ (0.2 equiv), AgOAc (1.5 equiv), *t*BuOH, 110 °C, 36 h, 85 % yield; d) Ethylenediamine, *n*BuOH, RT; TfN_3, NEt_3, CH_2Cl_2, RT; 82 % yield over 2 steps; e) Boc_2O (15 equiv), DMAP (3.0 equiv), CH_3CN, 70 °C, 89 % yield; f) LiOH (1.2 equiv), H_2O_2 (5.0 equiv), THF/H_2O, 0 °C to RT, quantitative yield. *t*BuBr = *tert*-butyl bromide, TEBAC = triethyl benzyl ammonium chloride, DMA = *N*,*N*′-dimethylacetamide,.

to the arylation reaction; replacement with either a monocarbamate or a dibenzyl amine shuts down the reaction completely. Eventually, this dilemma was successfully addressed by converting the phthaloyl unit into a much smaller azido function. This transformation was conveniently achieved through the initial ethylenediamine deprotection of **5**, followed by a diazo transfer reaction with TfN_3.[10] Gratifyingly, Boc activation of the reformulated amide **7** proceeded smoothly with Boc_2O and DMAP (Scheme 1 b).[11] Upon treatment of **8** with the Evans hydrolytic conditions (LiOH/H_2O_2) at room temperature, the desired azido acid **9** was formed in quantitative yield, and with complete chiral integrity (Scheme 1 b).[12] Interestingly, the azido substrate **11** completely failed in the indolylation reaction.

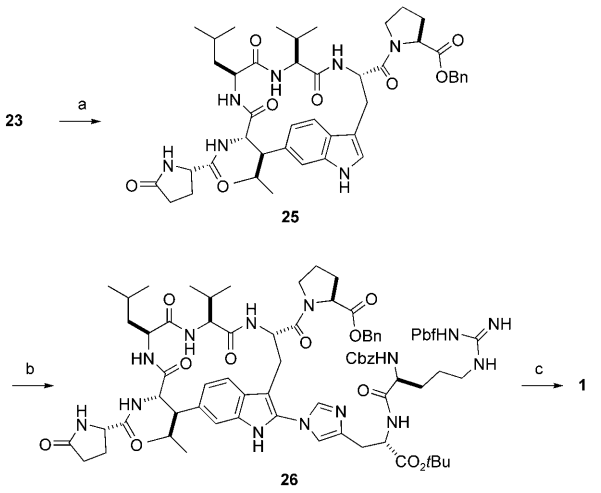
We then set out to apply the indolylation chemistry and auxiliary removal methodology to the total synthesis of celogentin C. The key iodotryptophan precursor **14** was rapidly prepared from commercially available compound **12** using a nitration–reduction–Sandmeyer reaction sequence (Scheme 2).[13,2f] The Trp C_α was protected as the *tert*-butyl ester for the anticipated construction of ring B (Figure 1). We were delighted to find that the indolylation reaction of **2** (2.0 equiv) with iodotryptophan **14** (1.0 equiv) worked extremely well under the $Pd(OAc)_2$/AgOAc/tBuOH conditions, affording an 85 % yield of isolated **15** (along with 3 % of the de-iodinated side product), and complete diastereoselectivity on a 4 gram scale. The *N*-Phth unit was then converted into the azido group using the same sequence as described for azide **9**. Boc-activation of amide **16** proceeded smoothly with concomitant di-Boc protection of Trp *N*α. The subsequent amide cleavage of **17** proceeded quantitatively upon treatment of LiOH and H_2O_2.

The resulting azido acid **18** was then converted into ester **19** using DCC and HOSu (Scheme 3). Upon coupling of **19** with the dipeptide NH_2Val-LeuOH and then Boc deprotection with HCl in dioxane, the cyclization precursor **20** was obtained in excellent yield. The macrolactamization of **20** was effected cleanly by EDCI/HOOBt to give **21** in 82 % yield without detectable epimerization. The azido group of **21** was then reduced and the resulting amine was coupled with pyroglutamic acid to furnish **22**. The *N*-toluenesulfonyl and *tert*-butyl protecting groups were then removed to yield acid **23**, which successfully intercepts the Castle synthesis. It is worth noting that the ^{1}H NMR spectroscopic chemical shifts (especially the Trp protons) of the protons in [D_4]methanol can be affected by residual trifluoroacetic acid. The methyl ester **24** was then prepared and matched the previously reported spectrum perfectly (see the Supporting Information).

Employing the elegant route developed by Castle et al., NH_2ProOBn was installed at the Trp Cα, and the His N1 of dipeptide CbzNHArg(Pbf)-HisOtBu was linked at the Trp C_2



Scheme 3. Synthesis of ring A. Reagents and conditions: a) HOSu, DCC, CH_2Cl_2, RT, 92% yield; b) NH_2Leu-ValOH, $NaHCO_3$, DMF/H_2O, RT, 84% yield; 4 mol L^{-1} HCl/dioxane, RT, 85% yield; c) EDCI, HOOBt, CH_2Cl_2, RT, 82% yield; d) H_2, 10% Pd/C, HOAc, EtOAc, RT, 85% yield; pyroglutamic acid, EDCI, HOOBt, CH_2Cl_2, RT, 92% yield; e) Magnesium, MeOH, sonication, RT, 87% yield; TFA/TIPS/H_20, RT, 96% yield; f) $SOCl_2$, MeOH, RT, 82% yield. HOSu = *N*-hydroxysuccinimide, DCC = dicyclohexylcarbodiimide, DMF = *N*,*N*-dimethylformamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOOBt = 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one, TFA = trifluoroacetic acid, TIPS = triisopropylsilane.



Scheme 4. Completion of the synthesis of **1**. Reagents and conditions: a) EDCI, HOBt, DIPEA, NH_2ProOBn·HCl, CH_2Cl_2, RT, 75% yield; b) NCS, DMP, NH_2ProOBn, CH_2Cl_2, then CbzNHArg(Pbf)-HisOtBu, RT; c) NH_4HCO_2, Pd/C, MeOH/H_2O, RT; HBTU, HOBt, DIPEA, DMF, RT; TFA/H_2O, RT; approx. 30% over 4 steps. DMF = *N*,*N*-dimethylformamide, EDCI = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOBt = *N*-hydroxybenzotriazole, DIPEA = diisopropylethylamine, NCS = *N*-chlorosuccinimide, DMP = 1,4-dimethylpiperazine, HBTU = *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate,, Pbf = 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl, Bn = benzyl, Cbz = carbobenzoxy.

by NCS-mediated oxidative coupling (Scheme 4).[4,14] Subsequently, the benzyl and carbobenzoxy protecting groups were removed from **26** by hydrogenolysis, and ring B was cyclized using a HBTU/HOBt-mediated coupling. The final deprotection steps with trifluoroacetic acid completed the total synthesis of **1** in a total of 23 steps from simple amino acid building blocks.

In summary, we have demonstrated a powerful methodology for the stereoselective indolylation of the β C–H of N-Phth Leu by $Pd(OAc)_2$ catalyzed C–H activation. The aminoquinoline auxiliary was effectively detached under mild conditions. A concise synthesis of celogentin C was accomplished using this methodology; the synthesis and biological studies of the other members of the celogentin family and analogues are currently under investigation.

Experimental Section

A typical C–H indolylation procedure (synthesis of compound **5**): A 4 mL glass vial with a PTFE lined cap was charged with compound **2** (63 mg, 0.16 mmol, 2.0 equiv), compound **3** (32 mg, 0.08 mmol, 1.0 equiv), $Pd(OAc)_2$ (Aldrich 98%, 3.7 mg, 0.016 mmol, 0.2 equiv), AgOAc (Aldrich 99%, 21 mg, 0.12 mmol, 1.5 equiv), and 0.3 mL of *t*BuOH (ACS grade). The reaction vial was capped with or without argon flushing, covered with aluminum foil, and heated at 110 °C for 16 h. The reaction mixture was then cooled to room temperature, diluted with 10 mL of dichloromethane, filtered through celite, concentrated under vacuum, and purified by flash chromatography (20–50% ethyl acetate in hexanes) to give compound **5** (43 mg, 80%), compound **6** (approx. 1 mg), and recovered compound **2** (28 mg); $[\alpha]_D^{23} = -49$ ($c = 1.4$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 9.72$ (s, 1H), 8.54 (dd, $J = 3.1$, 5.6 Hz, 1H,), 8.16 (s, 1H), 7.96 (m, 2H), 7.92 (d, $J = 8.9$ Hz, 1H,), 7.85 (d, $J = 2.6$ Hz, 1H), 7.78 (m, 2H), 7.63 (d, $J = 8.6$ Hz, 2H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.40–7.30 (m, 3H), 7.12 (m, 1H), 6.72 (d, 1H, $J = 3.4$ Hz), 6.65 (d, $J = 7.9$ Hz, 2H), 5.76 (d, $J = 12.3$ Hz, 1H), 4.34 (dd, $J = 2.8$, 12.1 Hz, 1H), 2.08 (m, 1H), 1.89 (s, 3H), 0.84 (d, $J = 6.7$ Hz, 3H), 0.74 ppm (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.7$, 166.2, 147.7, 144.6, 138.1, 135.3, 134.7, 134.3, 133.1, 132.0, 130.3, 129.3, 127.4, 126.9, 126.7, 126.6, 123.8, 121.6, 121.5, 121.2, 116.8, 108.8, 57.8, 48.9, 29.6, 21.6, 21.1, 16.1 ppm; IR (thin film): $\nu_{max} =$ 3281.0, 2953.2, 1709.3, 1527.6, 1381.5, 1172.2 cm^{-1}; HRMS (ESI^+) calcd. for $C_{38}H_{33}N_4O_5S$ $[M+H]^+$ 657.2166; found 657.2171.

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