

C–H Activation

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

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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

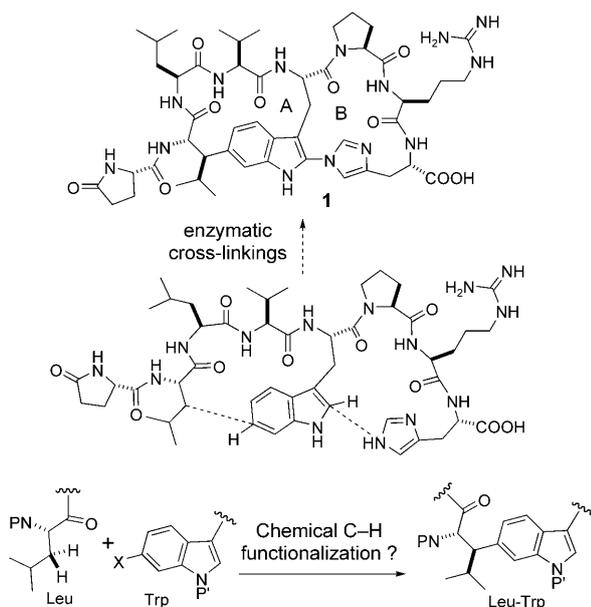


Figure 1. Celogentin C and our synthetic strategy.

the most potent isolate ($IC_{50} = 0.8 \mu\text{M}$; 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 C β , 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-indolylolation 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

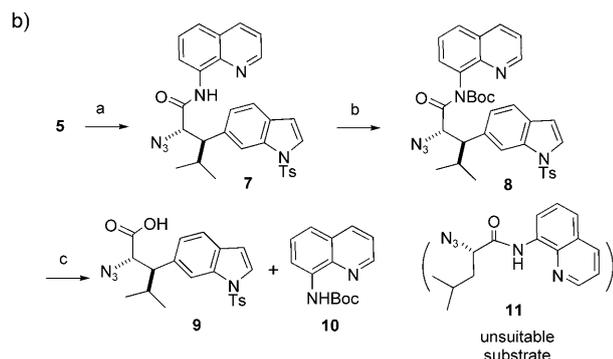
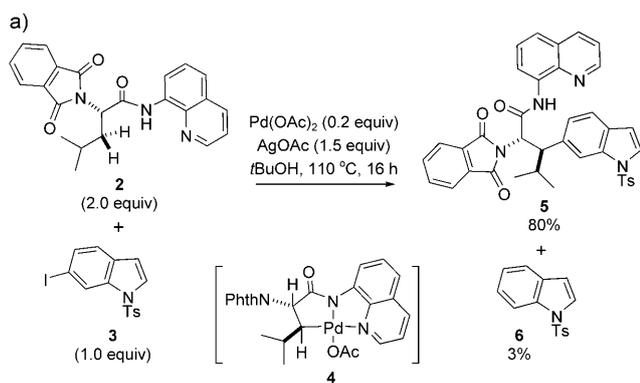
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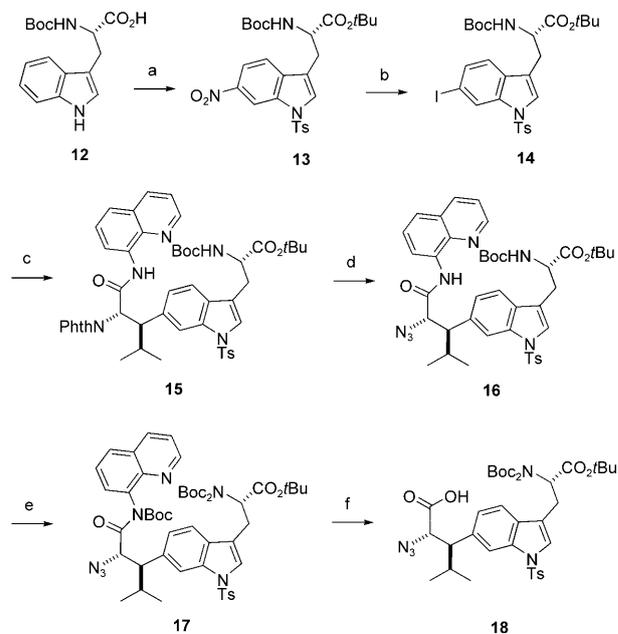
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.200905134>.



Scheme 1. C–H activation–indoloylation and auxiliary removal. Reagents and conditions: a) Ethylenediamine, *n*BuOH, 90 °C; TfN₃, NEt₃, CH₂Cl₂, RT; 81% yield over 2 steps; b) Boc₂O, DMAP, CH₃CN, RT; c) LiOH, H₂O₂, THF/H₂O, RT; 91% yield over 2 steps. Ts = toluenesulfonyl, TfN₃ = triflic azide, Boc₂O = di-*tert*-butyl dicarbonate, DMAP = 4-dimethylaminopyridine.

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 TfN₃.^[10] Gratifyingly, Boc activation of the reformulated amide **7** proceeded smoothly with Boc₂O and DMAP (Scheme 1b).^[11] Upon treatment of **8** with the Evans hydrolytic conditions (LiOH/H₂O₂) at room temperature, the desired azido acid **9** was formed in quantitative yield, and with complete chiral integrity (Scheme 1b).^[12] Interestingly, the azido substrate **11** completely failed in the indoloylation reaction.

We then set out to apply the indoloylation 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).^[13,21] 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 indoloylation reaction of **2** (2.0 equiv) with iodotryptophan **14** (1.0 equiv) worked extremely well under the Pd(OAc)₂/AgOAc/*t*BuOH conditions, affording an 85% yield of isolated **15** (along with 3% of the de-iodinated side product), and complete diastereoselec-

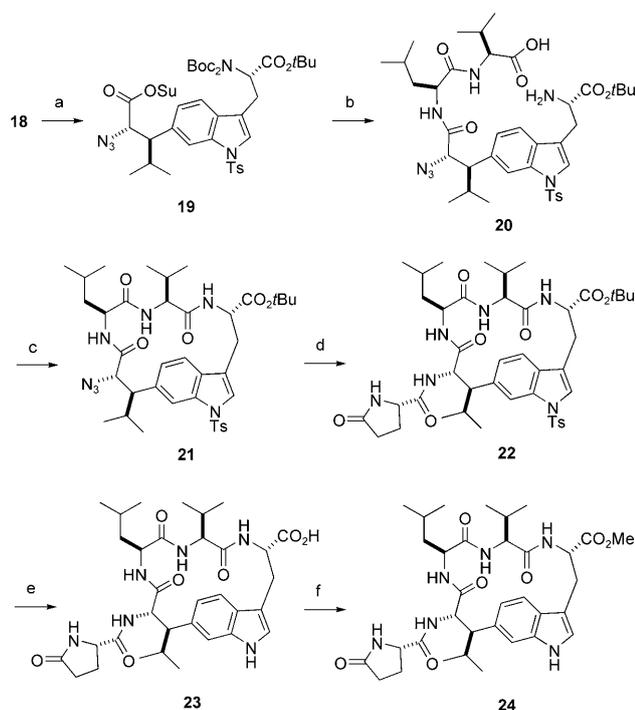


Scheme 2. Synthesis of the key Leu-Trp intermediate. Reagents and conditions: a) *t*BuBr, TEBAc, DMA, 55 °C, 89%; HNO₃ (1.7 equiv), HOAc (5.0 equiv), CH₂Cl₂, RT; NaH, TsCl, DMF, 0 °C to RT; 24% yield over 2 steps; b) H₂, 10% Pd/C, MeOH, RT, 78% yield; NOBF₄, KI, I₂, CH₃CN, –40 °C, 62% yield; c) **14** (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; TfN₃, NEt₃, CH₂Cl₂, RT; 82% yield over 2 steps; e) Boc₂O (15 equiv), DMAP (3.0 equiv), CH₃CN, 70 °C, 89% yield; f) LiOH (1.2 equiv), H₂O₂ (5.0 equiv), THF/H₂O, 0 °C to RT, quantitative yield. *t*BuBr = *tert*-butyl bromide, TEBAc = triethyl benzyl ammonium chloride, DMA = *N,N*-dimethylacetamide.

tivity 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 H₂O₂.

The resulting azido acid **18** was then converted into ester **19** using DCC and HOSu (Scheme 3). Upon coupling of **19** with the dipeptide NH₂Val–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 ¹H NMR spectroscopic chemical shifts (especially the Trp protons) of the protons in [D₄]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., NH₂ProOBn was installed at the Trp C_α, and the His N1 of dipeptide CbzNHArg(Pbf)–HisOtBu was linked at the Trp C₂



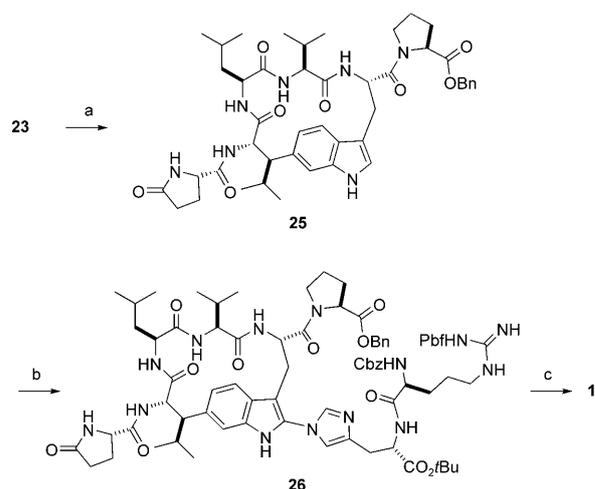
Scheme 3. Synthesis of ring A. Reagents and conditions: a) HOSu, DCC, CH₂Cl₂, RT, 92% yield; b) NH₂Leu-ValOH, NaHCO₃, DMF/H₂O, RT, 84% yield; 4 mol L⁻¹ HCl/dioxane, RT, 85% yield; c) EDCl, HOObt, CH₂Cl₂, RT, 82% yield; d) H₂, 10% Pd/C, HOAc, EtOAc, RT, 85% yield; pyroglutamic acid, EDCl, HOObt, CH₂Cl₂, RT, 92% yield; e) Magnesium, MeOH, sonication, RT, 87% yield; TFA/TIPS/H₂O, RT, 96% yield; f) SOCl₂, MeOH, RT, 82% yield. HOSu = *N*-hydroxysuccinimide, DCC = dicyclohexylcarbodiimide, DMF = *N,N*-dimethylformamide, EDCl = 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, HOObt = 3-hydroxy-1,2,3-benzotriazin-4(3*H*)-one, TFA = trifluoroacetic acid, TIPS = triisopropylsilane.

by NCS-mediated oxidative coupling (Scheme 4).^[4,14] Subsequently, the benzyl and carbobenzyloxy 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



Scheme 4. Completion of the synthesis of **1**. Reagents and conditions: a) EDCl, HOBt, DIPEA, NH₂ProOBn-HCl, CH₂Cl₂, RT, 75% yield; b) NCS, DMP, NH₂ProOBn, CH₂Cl₂, then CbzNHArg(Pbf)-HisOtBu, RT; c) NH₄HCO₂, Pd/C, MeOH/H₂O, RT; HBTU, HOBt, DIPEA, DMF, RT; TFA/H₂O, RT; approx. 30% over 4 steps. DMF = *N,N*-dimethylformamide, EDCl = 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-pentamethylidihydrobenzofuran-5-sulfonyl, Bn = benzyl, Cbz = carbobenzyloxy.

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); [α]_D²³ = –49 (*c* = 1.4, CHCl₃); ¹H NMR (300 MHz, CDCl₃): δ = 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); ¹³C NMR (75 MHz, CDCl₃): δ = 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): ν_{max} = 3281.0, 2953.2, 1709.3, 1527.6, 1381.5, 1172.2 cm⁻¹; HRMS (ESI⁺) calcd. for C₃₈H₃₃N₄O₅S [M+H]⁺ 657.2166; found 657.2171.

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