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Synthesis of the Celogentin C Right-Hand Ring

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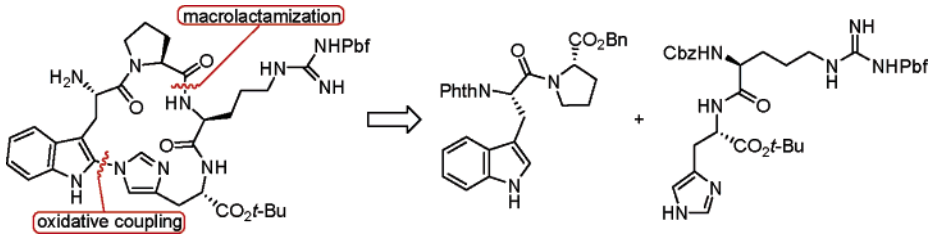
ABSTRACT



Synthesis of the cyclic tetrapeptide comprising the right-hand ring of celogentin C, a potent inhibitor of tubulin polymerization, has been accomplished. A mild oxidative coupling reaction permitted construction of the indole–imidazole linkage via a convergent union of two fully functionalized dipeptides. A high-yielding macrolactamization and subsequent deprotection of the *N*-terminus furnished the target compound.

Celogentin C (**1**, Figure 1) is a bicyclic octapeptide isolated by Kobayashi from the seeds of *Celosia argentea*.[1] It is a member of a growing family of structurally similar bicyclic peptides including moroidin[2] and celogentins A−J[3] as well as the related monocyclic peptides celogentin K[4] and stephanotic acid.[5] Many of these natural products inhibit the polymerization of tubulin,[6] with **1** ranking as the most potent agent of this class of compounds. The unusual architecture of **1** is derived from two cross-links, one joining the leucine β-carbon with the indole C-6 of tryptophan, and the other connecting the tryptophan indole C-2 with the imidazole N-1 of histidine. Despite the combination of complex structural features with useful biological activity, published synthetic studies of the celogentin family are scarce. Moody has disclosed syntheses of the moroidin right-hand ring[7] and the central tryptophan residue of stephanotic acid.[8] Our efforts toward the construction of **1** commenced with the asymmetric preparation of a suitably functionalized tryptophan subunit.[9] Herein, we report the synthesis of the right-hand ring of **1** which relies on a mild intermolecular oxidative coupling of

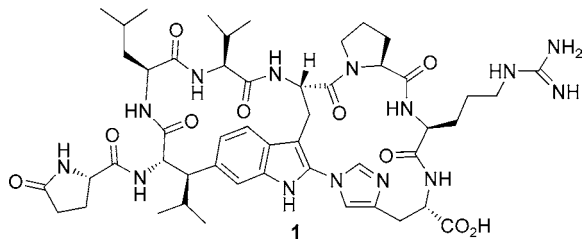


Figure 1. Celogentin C.

(1) Kobayashi, J.; Suzuki, H.; Shimbo, K.; Takeya, K.; Morita, H. *J. Org. Chem.* **2001**, *66*, 6626.
(2) (a) Leung, T.-W. C.; Williams, D. H.; Barna, J. C. J.; Foti, S.; Oelrichs, P. B. *Tetrahedron* **1986**, *42*, 3333. (b) Kahn, S. D.; Booth, P. M.; Waltho, J. P.; Williams, D. H. *J. Org. Chem.* **1989**, *54*, 1901.
(3) Celogentins A−C: ref 1. Celogentins D−J: Suzuki, H.; Morita, H.; Iwasaki, S.; Kobayashi, J. *Tetrahedron* **2003**, *59*, 5307.
(4) Suzuki, H.; Morita, H.; Shiro, M.; Kobayashi, J. *Tetrahedron* **2004**, *60*, 2489.
(5) Yoshikawa, K.; Tao, S.; Arihara, S. *J. Nat. Prod.* **2000**, *63*, 540.
(6) Morita, H.; Shimbo, K.; Shigemori, H.; Kobayashi, J. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 469; see also refs 1 and 3.
(7) (a) Harrison, J. R.; Moody, C. J. *Tetrahedron Lett.* **2003**, *44*, 5189. (b) Comber, M. F.; Moody, C. J. *Synthesis* **1992**, 731.
(8) Bentley, D. J.; Moody, C. J. *Org. Biomol. Chem.* **2004**, *2*, 3545.
(9) Castle, S. L.; Srikanth, G. S. C. *Org. Lett.* **2003**, *5*, 3611.

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two fully functionalized dipeptides to form the indole−imidazole linkage. A subsequent high-yielding macrolactamization creates the 17-membered ring.

The oxidative coupling process is illustrated in conceptual fashion in Figure 2. We postulated that exposure of a

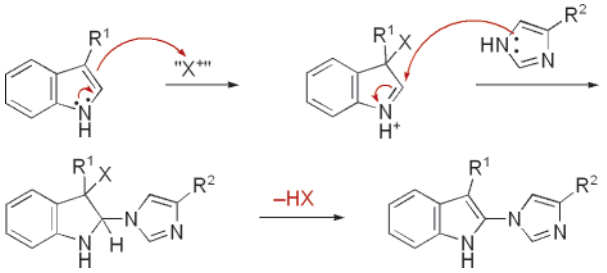
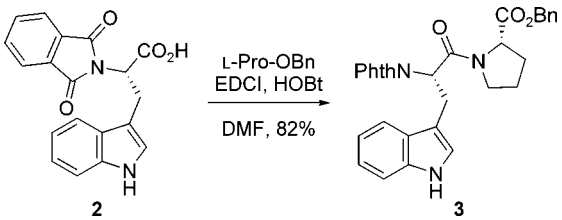


Figure 2. Proposed oxidative coupling process.

tryptophan derivative to a suitable electrophile would result in formation of a transient iminium ion. Trapping of this intermediate by the histidine imidazole and subsequent elimination would generate the desired link between the two heterocycles. Similar reactions have been performed by Booker-Milburn with alcohol nucleophiles[10] and by Bergman with anilines,[11] phenols, and thiophenols.[12] However, two potential problems concerned us. First, we questioned whether imidazole could function as a competent nucleophile in this process. Second, we feared that the ability of the product to react with the electrophilic reagent could complicate matters. Accordingly, we decided to examine the coupling of a tryptophan-containing dipeptide with imidazole prior to employing more complex histidine-containing nucleophiles.

Synthesis of the requisite dipeptide **3** was straightforward and is depicted in Scheme 1. We elected to protect the

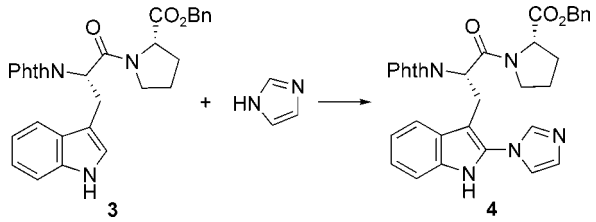
Scheme 1. Synthesis of Dipeptide **3**



N-terminus of tryptophan as a phthalimide due to concerns that the more commonly employed carbamate protecting groups might not prevent the nitrogen atom from engaging the chloroindolenine intermediate of the oxidative coupling reaction. Accordingly, *N*-phthaloyltryptophan (**2**)[13] was joined with proline benzyl ester under standard peptide-coupling conditions. With dipeptide **3** in hand, we commenced our exploration of its oxidative coupling with imidazole.

The results of these investigations of the oxidative coupling process are collected in Table 1. Of the oxidants examined,

Table 1. Oxidative Coupling of **3** and Imidazole



entry	oxidant[a]	solvent	*T* (°C)	yield (%)
1	NCS	EtOAc	−78	54
2	NBS	EtOAc	−78	37
3	NIS	EtOAc	−78	sm[b]
4	*t*-BuOCl	EtOAc	−78	sm[b]
5	NCS	EtOAc	0	73
6	NCS	CH_2Cl_2	0	72
7	NCS	EtOAc	rt	69
8	NCS	CH_2Cl_2	rt	77

[a] 1 equiv of oxidant was used in each reaction, and 1,4-dimethylpiperazine was used as base. [b] Complete recovery of starting material.

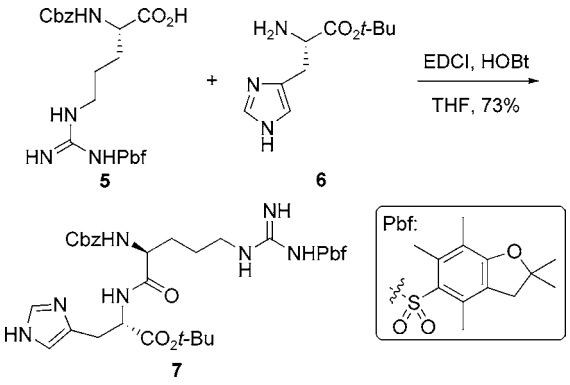
N-chlorosuccinimide proved the most effective (entry 1 vs entries 2−4). Use of dimethyldioxirane[14] afforded the oxindole derived from **3** presumably due to rearrangement of the intermediate epoxide (data not shown). Screening of solvents and reaction temperatures established the conditions given in entry 8 (NCS, CH_2Cl_2, rt) as optimal for the production of **4**. Although EtOAc was also a viable solvent, others examined were less effective.[15] In all reactions, recovered **3** accounted for the balance of the material. Attempts to drive the reaction to completion by using excess NCS were unsuccessful; lower yields of **4** were obtained, presumably due to the ability of **4** to react with the oxidant. Finally, we observed that very pure samples of the starting dipeptide **3** were essential to obtaining reproducible results. We speculate that impurities present in the starting material may react with the sensitive chloroindolenine intermediate, thereby reducing the yield of **4**.

With optimal oxidative coupling conditions established, we next prepared the histidine-containing dipeptide necessary for synthesis of the celogentin C right-hand ring. Coupling of N^{α}-Cbz-N^{G}-Pbf-arginine (**5**)[16] with histidine *tert*-butyl ester

(10) Booker-Milburn, K. I.; Fedouloff, M.; Paknoham, S. J.; Strachan, J. B.; Melville, J. L.; Voyle, M. *Tetrahedron Lett.* **2000**, *41*, 4657.
(11) Bergman, J.; Engqvist, R.; Stålhandske, C.; Wallberg, H. *Tetrahedron* **2003**, *59*, 1033.
(12) Engqvist, R.; Bergman, J. *Tetrahedron* **2003**, *59*, 9649.
(13) Casimir, J. R.; Guichard, G.; Briand, J.-P. *J. Org. Chem.* **2002**, *67*, 3764.
(14) Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964.
(15) Yields for reactions with other solvents: acetone, 52%; THF, 45%; Et_2O, <10%; CH_3CN, <10%; DMF, no product observed.
(16) Carpino, L. A.; Shroff, H.; Triolo, S. A.; Mansour, E.-S. M. E.; Wenschuh, H.; Albericio, F. *Tetrahedron Lett.* **1993**, *34*, 7829.

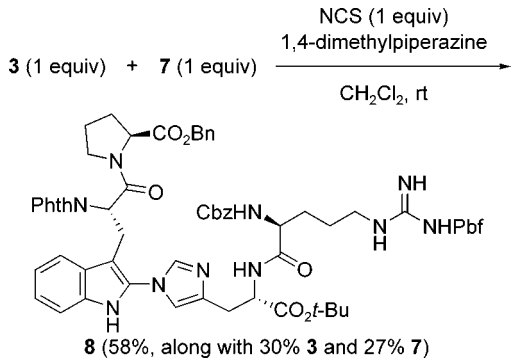
(**6**)[17] under standard conditions provided dipeptide **7** (Scheme 2). We chose the 2,2,4,6,7-pentamethyldihydrobenzofuran-5-sulfonyl (Pbf) moiety as our guanidine protecting group due to reports that it can be cleanly and rapidly removed under acidic conditions from tryptophan-containing peptides.[16]

Scheme 2. Synthesis of Dipeptide **7**



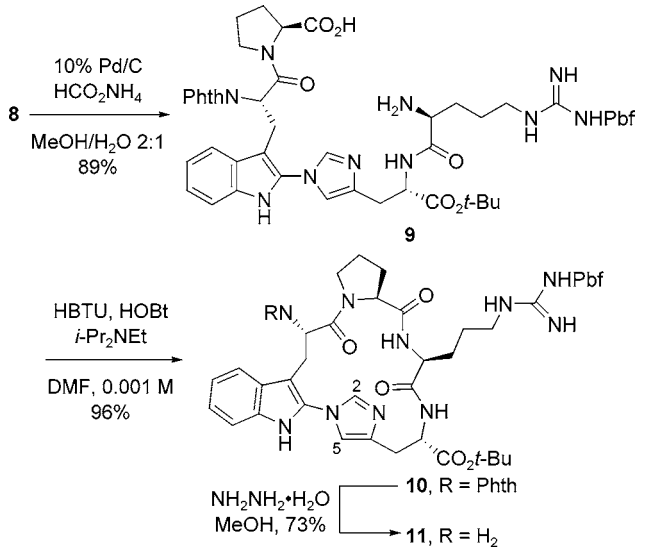
When dipeptides **3** and **7** were subjected to the previously developed oxidative coupling conditions, the desired product **8** containing the required indole−imidazole linkage emerged in 58% yield (Scheme 3). As before, the reaction could not be driven to completion, presumably due to the propensity of **8** to react with NCS. However, both starting materials could be easily recovered, as **3**, **7**, and **8** were readily separable by flash chromatography.

Scheme 3. Oxidative Coupling of Dipeptides **3** and **7**



Intermediate **8** was successfully elaborated into the right-hand ring of celogentin C as portrayed in Scheme 4. Transfer hydrogenation resulted in cleavage of both the benzyl ester and carbamate groups, providing macrocyclization substrate **9** in high yield. Notably, attempts to employ standard catalytic hydrogenation conditions were plagued by incomplete scission of the *N*-Cbz moiety, even when high pressures of H_2 (100 psi) were used. Then, exposure of a dilute solution of **9** to HBTU, HOBt, and *i*-Pr_2NEt afforded smooth macrolactamization, as cyclic peptide **10** was isolated in 96% yield. HATU was as effective as HBTU in mediating cyclization; however, we chose to utilize the less expensive reagent.[18] Reactions employing EDCI·HCl as peptide coupling agent were slightly less effective (86% yield).

Scheme 4. Completion of Celogentin C Right-Hand Ring



In contrast to all acyclic proline-containing intermediates which existed as mixtures of conformational isomers in solution, cyclic tetrapeptide **10** adopted a single detectable conformation in DMSO-d_6. Interestingly, the free amine **11**, generated by hydrazinolysis of **10**,[19] adopted two distinct conformations in DMSO-d_6 (1.4:1 ratio). Apparently, the bulky phthalimide moiety locks the macrocycle of **10** into a single orientation, whereas the absence of substitution on the amine in **11** allows slow rotation about either the tertiary amide bond or the indole−imidazole axis to occur. In the natural product itself, such rotation is precluded by the presence of the left-hand ring, since **1** exists as a single conformer in solution.[1]

The ROESY spectrum of **10** exhibits correlations between indole NH and imidazole H-2 as well as Trp β-H and imidazole H-5. These and other diagnostic through-space correlations are shown in Figure 3 superimposed on an MM2-minimized model of **10**. The spectroscopic data are consistent with the minimized structure. Interestingly, the NOESY spectrum of **1** shows the opposite correlations (i.e., indole NH/imidazole H-5 and Trp β-H/imidazole H-2),[1] indicating that the configuration about the indole−imidazole bi(hetero)-aryl axis is reversed for the two compounds. Apparently, the presence of the left-hand macrocycle in **1** causes the indole moiety to change its orientation relative to the

(17) Gibson, F. S.; Bergmeier, S. C.; Rapoport, H. *J. Org. Chem.* **1994**, *59*, 3216. The *tert*-butylating reagent used herein, *N*,*N*-diisopropyl-*O*-*tert*-butylisourea, is difficult to prepare due to the requirement for strictly anhydrous *t*-BuOH. Accordingly, we developed a more convenient preparation of **6** which is given in Supporting Information.

(18) For a review of peptide coupling reagents, see: Albericio, F.; Chinchilla, R.; Dodsworth, D. J.; Nájera, C. *Org. Prep. Proced. Int.* **2001**, *33*, 203.

(19) Sasaki, T.; Minamoto, K.; Itoh, H. *J. Org. Chem.* **1978**, *43*, 2320.

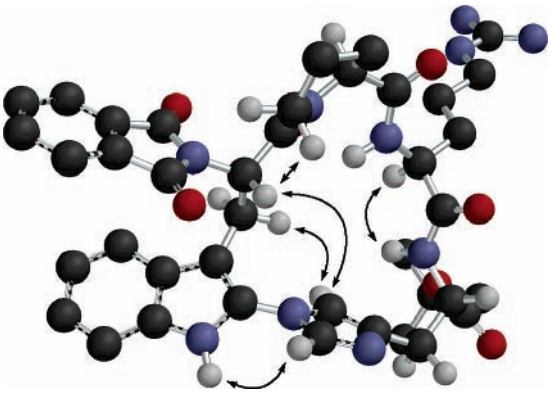


Figure 3. Selected ROESY correlations of **10** (Pbf group and some hydrogens removed for clarity).

imidazole. Our observations are supported by molecular modeling, as an MM2-minimized representation of **1** possesses the opposite configuration about the bi(hetero)aryl axis when compared to **10** due to a change in the position of the indole.

In conclusion, we have constructed the right-hand ring of the antimitotic bicyclic peptide celogentin C. The mild conditions employed in the oxidative coupling reaction permitted us to form the crucial indole−imidazole linkage by joining two highly functionalized dipeptides.[20] Additionally, our approach does not require activation of the indole C-2 with a halogen or other substituent, thereby increasing the efficiency of the route. Application of this process to the total synthesis of **1** itself is ongoing and will be reported in due course.

Acknowledgment. We thank Brigham Young University (startup funds to S.L.C., Cancer Research Center Fellowship to L.Y.) and the National Institutes of Health (GM70483) for support of this work. We also thank Professor Paul A. Wender of Stanford University for helpful discussions.

Supporting Information Available: Details of the synthesis of **6**; experimental procedures, characterization data, and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL060016F

(20) The S_NAr-type reaction employed by Moody to fashion the analogous linkage in the synthesis of the moroidin right-hand ring (see ref 7a) required both strong base (NaHMDS) and heat. Consequently, this transformation, although high-yielding (89%), was performed with relatively simple compounds that were later elaborated into amino acids and peptides.