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Total Synthesis of Chaetominine

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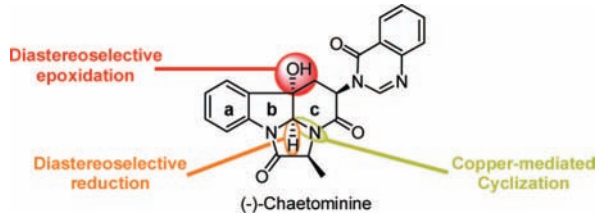
ABSTRACT



An efficient, asymmetric synthesis of the cytotoxic natural product chaetominine was achieved in 14 steps. The strategy employs a copper(I)-mediated cyclization reaction as a key step to install the abc-tricyclic ring system, which was further elaborated by diastereoselective oxidation and reduction reactions. This effort also documents the first example of an oxidative rearrangement yielding to homochiral spirocyclic pyrrolidinyloxindoles.

(−)-Chaetominine **1** (Figure 1) was isolated in 2006 by Tan and co-workers from the solid-substrate culture of *Chaetomium* sp. IFB-E015, an endophytic fungus on apparently healthy *Adenophora axilliflora* leaves.[1] A unique feature of this compact modified tripeptide is its strained tetracyclic framework which is only encountered in seven other metabolites, the kapakahines.[2] In vitro cytotoxic assays showed that chaetominine was highly potent against human leukemia K562 (21 nM) and colon cancer SW1116 (28 nM) cell lines with IC_{50} values smaller than the ones of 5-fluorouracil, which is one of the most frequently prescribed anticancer drugs.

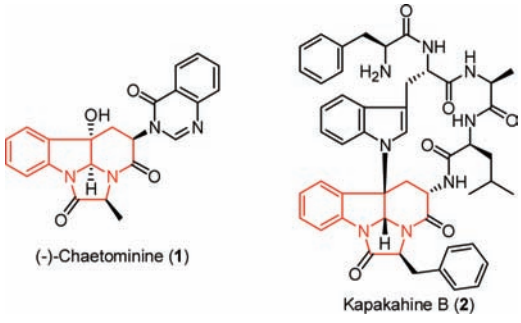


Figure 1. Structures of (−)-chaetominine and kapakahine B.

Due to its intriguing molecular architecture and its potential as a lead compound for anticancer drugs, chaetominine has attracted immediate interest from the synthetic community. This culminated in a total synthesis by the Snider group,[3] who smartly adapted their elegant synthesis of related alkaloids, the fumiquinazolines.[4]

Herein, we describe an efficient synthesis of (−)-chaetominine as part of our ongoing studies of cyclic peptide alkaloids and copper-mediated cyclizations.[5]

Our synthetic plan for the synthesis of (−)-chaetominine is shown in Scheme 1. We envisioned the exocyclic quinazolinone would be installed at the end of the synthesis starting from a phthalimide-protected precursor by using

(1) Jiao, R. H.; Xu, S.; Liu, J. Y.; Ge, H. M.; Ding, H.; Xu, C.; Zhu, H. L.; Tan, R. X. *Org. Lett.* **2006**, *8*, 5709.

(2) (a) Yeung, B. K. S.; Nakao, Y.; Kinnel, R. B.; Carney, J. R.; Yoshida, W. Y.; Scheuer, P. J.; Kelly-Borges, M. *J. Org. Chem.* **1996**, *61*, 7168. (b) Nakao, Y.; Kuo, J.; Yoshida, W. Y.; Kelly, M.; Scheuer, P. J. *Org. Lett.* **2003**, *5*, 1387.

(3) Snider, B. B.; Wu, X. *Org. Lett.* **2007**, *9*, 4913.

(4) Snider, B. B.; Zeng, H. *J. Org. Chem.* **2003**, *68*, 545.

(5) (a) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572. (b) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2007**, *72*, 9003. (c) Toumi, M.; Couty, F.; Evano, G. *Synlett* **2008**, 29.

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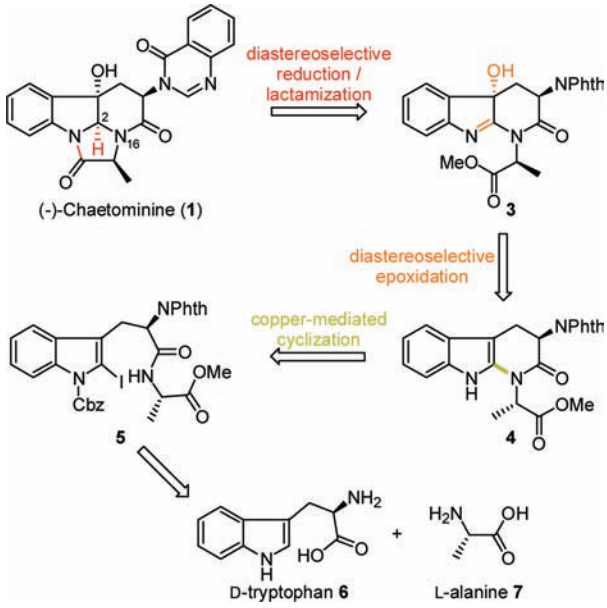
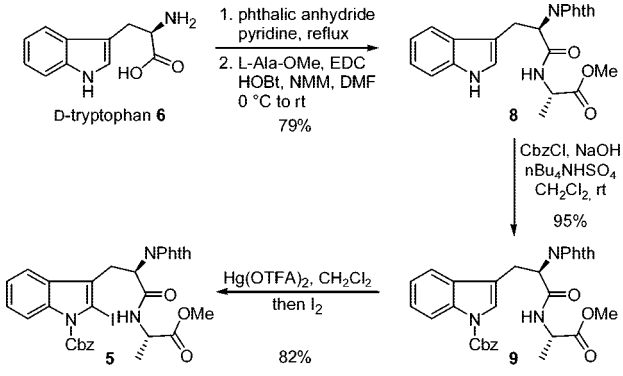
Scheme 1. Retrosynthetic Analysis of (−)-Chaetominine



Snider's strategy. To access the γ-lactam moiety in **1** together with the installation of its last stereocenter, we expected that a diastereoselective reduction of the imine in **3** would generate an amine that would hopefully react with the ester to give the corresponding lactam. The hydroxy imine **3** could be obtained by a substrate-controlled diastereoselective epoxidation of **4** followed by opening of the epoxide by the secondary amine. In this synthetic plan, the first key issue to be adressed is, therefore, the formation of tetrahydropyrido[2,3-*b*]indole **4**. Disconnection at the C2−N16 bond reveals iodo amide **5**, where the use of a copper-mediated cyclization reaction would enable formation of the tricyclic ring system.[6] This precursor **5** would itself be obtained from D-tryptophan **6** and L-alanine **7**. We expected that the use of a phthalimide protecting group for the exocyclic amine would allow for good levels of stereoselectivity during the installation of the oxygenated stereocenter together with masking the amine that could interfere during the copper-mediated cyclization.

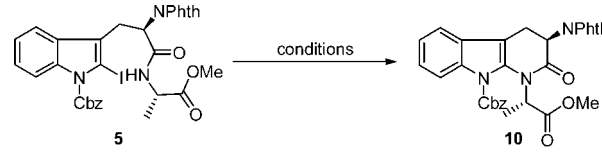
Scheme 2. Synthesis of Cyclization Precursor **5**

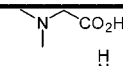
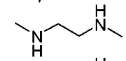
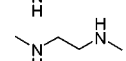
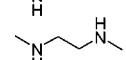
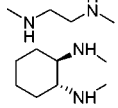
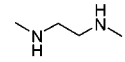


The synthesis of the precursor for the copper-catalyzed cyclization (Scheme 2) started with protection of D-tryptophan **6** by reaction with phthalic anhydride in refluxing pyridine followed by EDC-mediated coupling with alanine methyl ester. In order to install suitable functionalities for the cyclization reaction, the indole nitrogen was first selectively protected as a carbamate using phase-transfer conditions to give fully protected dipeptide **9**. Mercuration with mercury trifluoroacetate followed by workup with potassium iodide and reaction with iodine then allowed for a clean regioselective introduction of the iodide at C2 of the indole ring and set the stage for the key cyclization step.[4,7]

As expected, the cyclization proved to be challenging due to the formation of the six-membered ring, which involves formation of an intermediate seven-membered ring metallacycle, as well as the known low reactivity of hindered and/or acyclic secondary amides toward copper-mediated amidation. Selected examples of conditions assayed are shown in Table 1. After considerable experimentation, we eventually

Table 1. Optimization of Cyclization Conditions



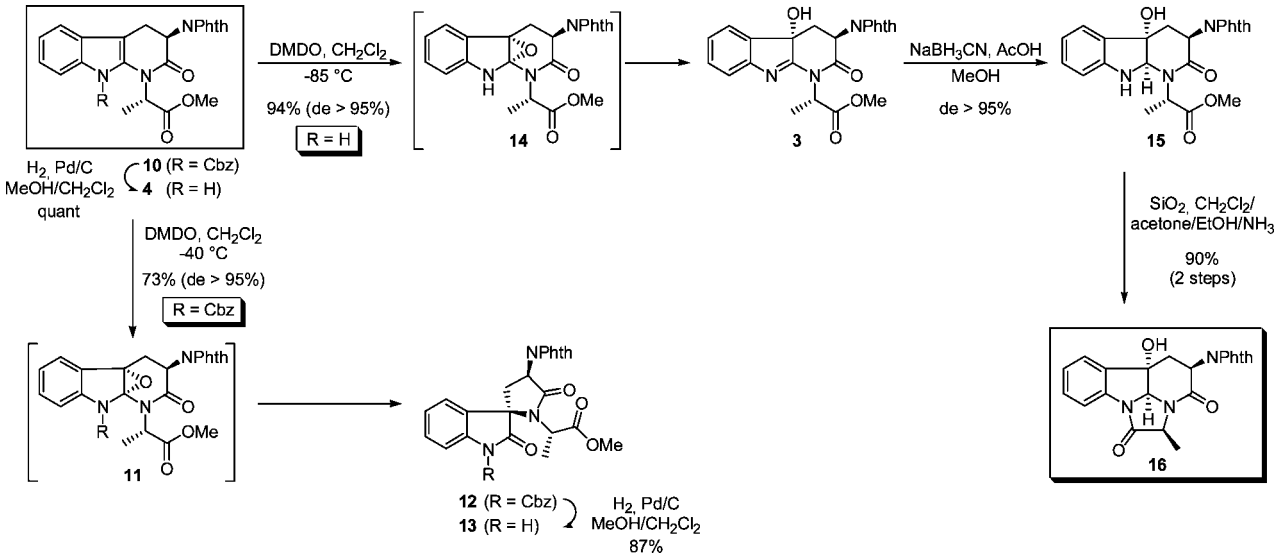
entry	catalyst	ligand	conditions	yield
1	CuI		K_2CO_3, dioxane, 110 °C	-[a]
2	CuI		K_2CO_3, THF, reflux	-[a]
3	CuI		K_3PO_4, toluene, 110 °C	33%
4	CuI		K_2CO_3, dioxane, 110 °C	57%
5	CuI		K_3PO_4, toluene, 110 °C	64%
6	$Pd_2(dba)_3$	$P(o\text{-tolyl})_3$	K_2CO_3, toluene, 110 °C	-[a]
7	$FeCl_3$		K_3PO_4, toluene, 135 °C	-[b]

[a] No reaction. [b] Degradation of starting material.

found that this reaction was best effected using a combination of copper iodide, *trans*-*N*,*N*′-dimethylcyclohexane-1,2-diamine, and potassium phosphate at 110 °C in toluene.[8,9] Using these conditions, cyclized compound **10** could be isolated in 64% yield, without epimerization and along with

(6) (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428. (c) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (d) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.
(7) Mingoia, Q. *Gazz. Chim. Ital.* **1930**, *60*, 509.
(8) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421.
(9) Coste, A.; Toumi, M.; Wright, K.; Razafimahaléo, V.; Couty, F.; Marrot, J.; Evano, G. *Org. Lett.* **2008**, *10*, 3841.

Scheme 3. Formation of the Tetracyclic Core



30% of reduced product **9** that could be resubmitted to the iodination−cyclization sequence (Table 1, entry 5).

While this system turned out to be quite similar to the one we used for the synthesis of pyrroloindoles starting from related 2-iodotryptophan derivatives,[9] the presence of an acyclic secondary amide and the formation of a six-membered ring required the use of a more efficient ligand in this case. Another striking difference is the proportion of reduction products which could be minimized for the formation of a five-membered ring but could not be completely avoided in this case. This combination, however, proved to be the most efficient one, and all other ligands, bases, and solvent systems gave inferior results. Other metals such as palladium(0)[10] (Table 1, entry 6) or iron(III)[11] (Table 1, entry 7) proved to be completely inefficient cyclization promoters.

Having useful quantities of tricyclic precursor **10** in hand, we next turned our attention to the installation of the two remaining stereocenters as well as the formation of the γ-lactam (Scheme 3). To this end, a diastereoselective epoxidation of **10** was first envisioned. Upon reaction with DMDO at low temperature in dichloromethane, we were delighted to note that **10** was smoothly oxidized and furnished a single compound which we expected to be epoxide **11**. Upon closer inspection, it however turned out that epoxide **11** was indeed formed within the reaction mixture but immediately underwent a rearrangement yielding spirolactam **12** as a single stereoisomer. Its structure and stereochemistry could be ascertained by X-ray diffraction after removal of the Cbz protecting group. This unprecedented rearrangement probably involves ring opening of the epoxide and migration of the amide at the benzylic position.[12,13]

Even if the oxidative rearrangement of **10** to spiro-oxindole **12** clearly is a quite interesting transformation, it did seriously compromise the formation of the tetracyclic ring system of chaetominine. In order to avoid this rearrangement, we decided to carry out the oxidation on a deprotected indole. Indeed, the presence of the secondary amine in **4** allowed for a clean isomerization of the intermediate amino epoxide **14** to hydroxy imine **3** before the undesired rearrangement could occur. Simple treatment of **4** with DMDO at −85 °C for 45 min allowed for the isolation of 94% of hydroxy imine **3** with complete diastereoselectivity. Steric interactions between the bulky phthalimide and DMDO in the spiro transition state usually invoked for related oxidations might account for the high level of diastereoselectivity observed in this epoxidation.[14]

Elaboration of the tetracyclic core then proceeded easily (Scheme 3). Reaction of imine **3** with sodium cyanoborohydride and acetic acid in methanol at room temperature provided compound **15** as a single diastereoisomer, most certainly through assistance of the free hydroxyl group.[15] This compound, however, proved to be relatively unstable upon purification on silica gel since it was isolated as a mixture with a newly formed compound which gratifyingly turned out to be the γ-lactam **16**. Pleased by this most

(10) Wolfe, J. P.; Rennels, R. A.; Buchwald, S. L. *Tetrahedron* **1996**, *52*, 7525.

(11) Correa, A.; Elmore, S.; Bolm, C. *Chem.—Eur. J.* **2008**, *14*, 3527.

(12) For oxidation of indoles with DMDO followed by epoxide opening/alkyl shift, see: (a) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867. (b) Adam, W.; Ahrweiler, M.; Peters, K.; Schmiedeskamp, B. *J. Org. Chem.* **1994**, *59*, 2733.

(13) For oxidation with DMDO followed by epoxide opening/oxygen shift, see: Konno, F.; Ishikawa, T.; Kawahata, M.; Yamaguchi, K. *J. Org. Chem.* **2006**, *71*, 9818.

(14) (a) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830. (b) Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Wong, M.-K. *J. Org. Chem.* **1999**, *64*, 1635. (c) Ouchi, H.; Mihara, Y.; Takahata, H. *J. Org. Chem.* **2005**, *70*, 5207.

(15) An equilibration of the *trans* isomer to the more stable *cis* isomer through opening of the aminal might also account for the high level of selectivity observed in this reduction. Basic AM1 calculations (MOPAC) show a difference in energy of ca. 10 kcal•mol^{-1} between the two isomers.

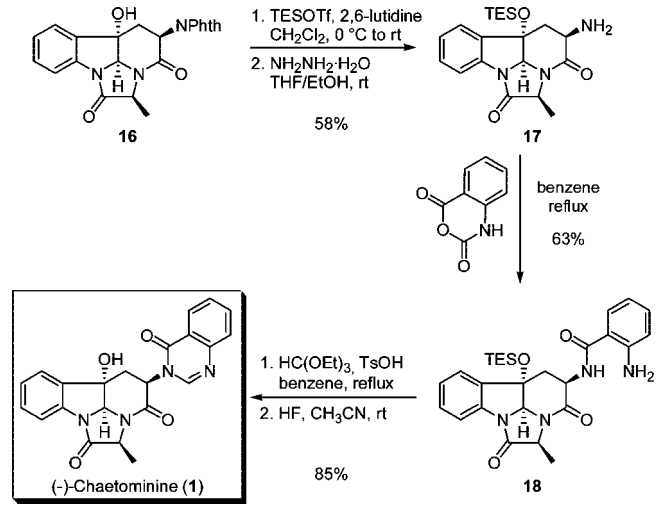
encouraging result, we tried to promote this lactamization by simply stirring the crude product **15** with silica gel in a mixture of dichloromethane, acetone, and ethanol together with small amounts of ammonia. Using these conditions, the desired tetracyclic compound **16**, whose stereochemistry was ascertained by NOESY experiments, could be isolated in 90% yield over the last two steps.

To avoid interaction of the free alcohol in **16** during the final steps of the synthesis, it was protected as a silyl ether by reaction with TESOTf and 2,6-lutidine in dichloromethane. Deprotection of the phthalimide proved to be an especially challenging task because of epimerization at the amino acid stereocenters and opening of the sensitive γ-lactam.[16] After considerable experimentation, it was found that treatment with hydrazine hydrate in a mixture of THF and ethanol cleanly cleaved the phthalimide and left the newly formed γ-lactam intact, affording free amine **17** in 58% overall yield (two steps). This material proved to be identical in all respects to Snider and Wu's intermediate.[3] Installation of the quinazolinone using their three-step sequence (reaction with isatoic anhydride and triethyl orthoformate followed by TES deprotection) finally provided synthetic (−)-chaetominine **1** in 54% over the last three steps.

In summary, we have developed an efficient synthesis of (−)-chaetominine in 14 steps and 10% overall yield starting from D-tryptophan and L-alanine as building blocks. Notable features of our synthetic approach include an efficient copper(I)-mediated cyclization of a sensitive, highly substituted iodotryptophanylalanine derivative. This effort also documents the first example of a diastereoselective oxidative rearrangement yielding highly substituted spirocyclic pyrrolidinyloxindoles. This oxidation could be controlled to access either tetrahydropyrido[2,3-*b*]indole or spirocyclic compounds by simply changing the protecting groups. The convergent approach reported here should be easily applied to the synthesis of analogues for further biological testing, which will be reported in due time.

(16) Snider and Wu noted that the γ-lactam in chaetominine was readily opened by simple heating in methanol. See ref 3 for details.

Scheme 4. Completion of the Synthesis of (−)-Chaetominine



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Supporting Information Available: Experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra for all for all intermediates and chaetominine. Chaetominine spectral data compared to reported data and X-ray structure of **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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