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Synthesis of (–)-Chaetominine

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Abstract

The tricyclic hydroxy imidazolidinone was converted to chaetominine in seven steps in 22% overall yield. The key step was the construction of the δ -lactam by heating an amino ester with a catalytic amount of DMAP in toluene at reflux.

Tan and coworkers recently isolated chaetominine (**1**), an alkaloid with a novel skeleton from *Chaetomium* sp. IFB-E015, an endophytic fungus found on apparently healthy *Adenophora axilliflora* leaves (see Figure 1).¹ The structure was determined by both spectroscopic analysis and single-crystal X-ray diffraction analysis. The absolute stereochemistry was assigned as shown based on the release of L-alanine on acidic hydrolysis. Chaetominine is more active against human leukemia K562 (21 nM) and colon cancer SW1116 (28 nM) cell lines than 5-fluorouracil.

Chaetominine (**1**) is a modified tripeptide alkaloid containing D-tryptophan, L-alanine, anthranilic acid and formic acid. Chaetominine is very closely related to the fumiquinazoline alkaloids such as fumiquinazolines A (**2**) and B (**3**), which are tetrapeptide alkaloids containing D-tryptophan, L-alanine, anthranilic acid, and a second alanine instead of the formic acid of chaetominine. We recently reported efficient syntheses of (–)-fumiquinazolines A, B, C, E, H and I.² The key step in the syntheses is the Buchwald palladium-catalyzed cyclization of iodo carbamate **4**, which provided tricycle **5** in 64% yield (see Scheme 1). Oxidation of tricycle **5** with oxaziridine **6** in MeOH followed by reduction with NaBH₄ in HOAc afforded hydroxy imidazolidinone **7** in 51% yield. Treatment of **7** with silica gel resulted in cyclization to form lactone **8**, which was then elaborated to fumiquinazolines A, B, C and E.²

Deprotection of the Cbz group of **7**, formation of the δ -lactam, deprotection of the Troc group, and construction of the quinazolinone should provide a short synthesis of chaetominine (**1**). However, our earlier studies indicated that formation of the δ -lactam might not be

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Supporting Information **Available**. Full experimental details and copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

straightforward. Hydrogenolysis of the Cbz group of **7** afforded amino alcohol **9**, which was treated with silica gel in CH_2Cl_2 to give lactone **10** in 81% yield from **7**.² Hydrogenolysis of the Cbz group of **7** could be accomplished without hydrogenolysis of the tertiary benzylic alcohol, but hydrogenolysis of Cbz lactone **8**, resulted in reductive cleavage of the benzylic lactone as well as the Cbz group.²

We explored a variety of approaches to form the desired δ -lactam from amino alcohol **9**. These invariably led to complex mixtures or the undesired lactone **10**. Eventually, we concluded that protection of the alcohol was necessary. Reaction of **7** with TESOTf and 2,6-lutidine in CH_2Cl_2 at 0 to 25 °C provided TES ether **11** in 80% yield (see Scheme 2).³ Hydrogenolysis with 1 atm of H_2 and 10% Pd/C afforded the desired amino ester **12** in only 56% yield, suggesting that cleavage of the TES group or hydrogenolysis was occurring. Use of Pd(OH)₂ as catalyst or transfer hydrogenation did not improve the yield. We were unable to prepare more hindered silyl ethers of **7** in acceptable yield, so we proceeded with compound **12**.

Lactamization of amino ester **12** was also challenging, but was eventually accomplished to give **13** in 79% yield by heating **12** in toluene containing a catalytic amount of DMAP for 3 days at reflux in a sealed tube.⁴ Lactam **13** was contaminated with about 5% of two compounds that are probably diastereomers of **13**. Use of 6 equivalents of Et_3N instead of catalytic DMAP gave a lower yield of **13**.⁵

Deprotection of the Troc group of **13** without cleavage of the TES ether was accomplished with Zn in 1:1 MeOH/HOAc to give amine **14** in 88% yield. Reaction of amine **14** with isatoic anhydride in benzene at reflux⁶ afforded amino amide **15** in 82% yield. Reaction of **15** with excess triethyl orthoformate and a catalytic amount of TsOH in benzene at reflux⁶ provided TES-chaetominine (**16**) in 83% yield. Cleavage of the TES group in 1:19 conc. $\text{HF}/\text{CH}_3\text{CN}$ ⁷ for 7 hours at 25 °C provided chaetominine (**1**) in 89% yield. The yields were improved if intermediates were not purified. The four-step conversion of **13** to **1** proceeded in 62% overall yield when only amino amide **15** was purified.

The ^1H and ^{13}C NMR, IR, CD and mass spectra of synthetic **1** are identical to those reported by Tan.¹ $^1\text{H}_{14}$, $^1\text{H}_{19}$, $^1\text{H}_{25}$, $^{13}\text{C}_{14}$, $^{13}\text{C}_{17}$, $^{13}\text{C}_{18}$, and $^{13}\text{C}_{23}$ are very broad as noted by Tan. He attributed this to slow inversion of an sp^3 nitrogen in the quinazolinone ring. We think that this is probably a result of slow rotation about the $\text{C}_{14}\text{-N}$ bond. Similar broadening in the ^1H and ^{13}C NMR spectra of TES ether **16** also results from slow rotation about this bond.

Tan noted that chaetominine (**1**) was unstable in acid and recrystallized it from MeOH at room temperature.¹ We found that heating **1** in MeOH at reflux for 5 hours afforded a 1:1 mixture of **1** and amino ester **17** (see Scheme 3). Chromatography afforded a 6:1 mixture of **17** and **1**, which was converted to 1:1 mixture on heating in MeOH at reflux for 5 hours. The conversion of **17** back to **1** establishes that the reaction is reversible and that the 1:1 mixture is at equilibrium. There are two lactams in chaetominine (**1**) and either one could be opened by MeOH to give a methyl ester. The ^1H NMR spectrum of **17** shows two protons at δ 6.85 (dd, 1, $J = 7.6, 7.6$ Hz) and 6.74 (d, 1, $J = 7.6$ Hz), whereas the furthest upfield aromatic hydrogen of chaetominine absorbs at δ 7.24. The upfield shift establishes that the *N*-acylindoline was cleaved to give an indoline, which has the expected upfield absorptions⁸ for the protons ortho and para to the nitrogen.

The facile cleavage of the γ -lactam ring of **1** on heating in MeOH is not typical of γ -lactams and may result from the strain present in the tetracyclic core of chaetominine (**1**). The crystallographic data supports this analysis. The $\text{C}_9\text{-N}_1\text{-C}_{10}=\text{O}$ and $\text{C}_2\text{-N}_1\text{-C}_{10}=\text{O}$ torsion angles in **1** are 37.8° and 175.0°, respectively (see Figure 2).¹ In the simple tricyclic model **18**, the torsion angles are 21.9° and 177.2°, respectively.⁹ The torsion angles should be 0° and

180°, respectively, in an unstrained amide. The deformation from 21.9° in **18** to 37.8° in **1** suggests that the introduction of the δ -lactam significantly increases the strain. No reaction occurs on heating **11** in MeOH at reflux for 5 hours, which supports the hypothesis that the ring strain of the tetracyclic ring system of chaetominine makes the imidazolidinone much more susceptible to cleavage. Relief of ring strain in **1** could be achieved by opening either the δ -lactam or the γ -lactam with MeOH. The inherently greater reactivity of an *N*-aryl lactam than an *N*-alkyl lactam may be at least partially responsible for the selective opening of the γ -lactam. The enhanced reactivity of the strained γ -lactam ring of **1** likely plays a role in its biological activity.

The strain of the tetracyclic ring system is likely responsible for the cyclization of amino alcohol **9** with SiO₂ in CH₂Cl₂ to give amino lactone **10** rather than the desired hydroxy lactam. However, it is not clear whether this is a result of kinetic or thermodynamic control. We therefore cleaved the TES ether of **13** to give hydroxy lactam **19**, which is an isomer of amino lactone **10**. Unfortunately, both amino lactone **10** and hydroxy lactam **19** decomposed on heating in toluene containing a catalytic amount of DMAP so that we were unable to determine the relative stability of amino lactone **10** and hydroxy lactam **19** (see Scheme 4).

In conclusion, fumiquinazoline intermediate **7** has been converted to chaetominine (**1**) in seven steps in 22% overall yield. The key step is the cyclization of amino ester **12** with catalytic DMAP in toluene at reflux to give δ -lactam **13** in 79% yield.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

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Figure 1.
Structures of chaetominine (1) and fumiquinazolines A (2) and B (3).

Scheme 1.
Synthesis of Imidazolidinone **7**

Scheme 2.
Synthesis of (-)-Chaetominine (**1**)

Scheme 3.
Interconversion of Chaetominine (**1**) and Amino Ester **17**

Figure 2.
Torsion angles in the crystal structures of **1** and **18**.

Scheme 4.

Lactone **10** and Lactam **19** Do Not Interconvert with DMAP in Toluene at Reflux