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 co-workers 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



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

was determined by both spectroscopic analysis and singlecrystal 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 palladiumcatalyzed cyclization of iodocarbamate 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 straightforward. Hydrogenolysis of the Cbz group of **7** afforded amino alcohol **9**, which was treated with silica gel in CH₂Cl₂ 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

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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 CH₂Cl₂ at 0–25 °C provided TES ether **11** in 80% yield (see Scheme 2).³ Hydrogenolysis with 1 atm of H₂ and 10% Pd/C afforded the desired amino ester **12** in only 56% yield, suggesting that cleavage of the TES group or hydrogenolysis of the OTES group 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 equiv of Et₃N 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 concentrated HF/CH₃CN⁷ for 7 h 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 ¹³C NMR, IR, CD, and mass spectra of synthetic **1** are identical to those reported by Tan.¹ H₁₄, H₁₉, H₂₅, C₁₃, C₁₄, C₁₇, C₁₈, and C₂₃ are very broad as noted by Tan. He attributed this to slow inversion of an sp³ nitrogen in the quinazolinone ring. We think that this is probably a result of slow rotation about the C₁₄–N bond. Similar broadening in the ¹H and ¹³C 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 h afforded a 1:1

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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 h. 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 support this analysis. The C₉-N₁-C₁₀=O and C₂-N₁-C₁₀=O torsion angles in **1** are 37.8 and 175.0°, respectively (see Figure 2).¹ In the simple tricyclic



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

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 h, 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 that of 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.

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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.

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