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Biomimetic Total Syntheses of Clavine Alkaloids

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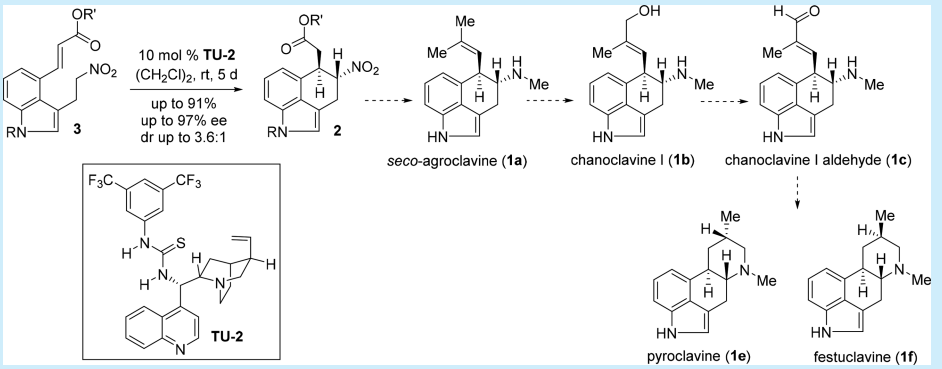
Supporting Information



ABSTRACT: Biomimetic total syntheses of either enantiomers of a number of ergot alkaloids, chanoclavine I (**1b**), chanoclavine I aldehyde (**1c**), pyroclavine (**1e**), festuclavine (**1f**), pibocin A (**1g**), 9-deacetoxyfumigaclavine C (**1h**), and fumigaclavine G (**1i**), have been achieved from *seco*-agroclavine (**1a**). The advanced intermediate for *seco*-agroclavine (**1a**) was synthesized via a key thiourea-catalyzed intramolecular nitronate addition onto α,β-unsaturated ester.

Because of their striking physiological properties, the clavine alkaloids of the ergot family (**1a**−**l**, Figure 1) have been the subject of longstanding interest.[1] Most of these alkaloids have been derived from the fungus *Claviceps purpurea* on rye grain. Biosynthetically derived from tryptophan through intriguing enzymatic pathways,[2] total syntheses of several members of this class of natural compounds have been reported.[3]

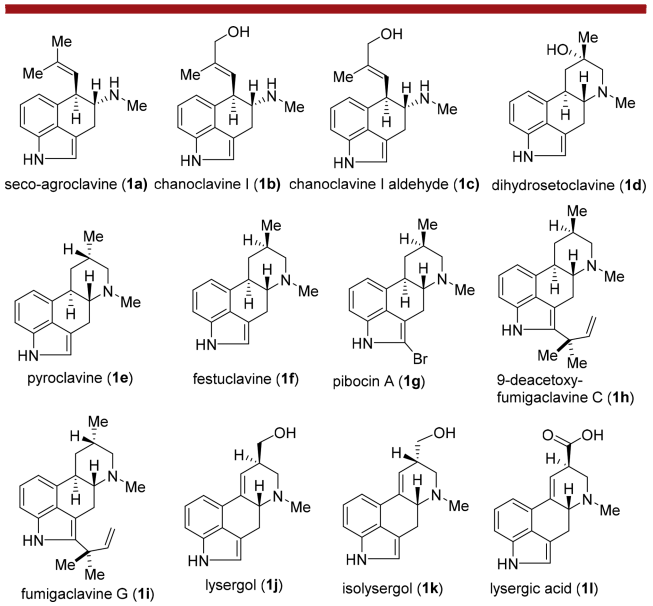


Figure 1. Selected naturally occurring clavine alkaloids **1a**−**l**.

They act as agonists or antagonists toward neuroreceptors for dopamine, serotonin, and adrenaline. Therefore, they are considered as potential drug candidates. Ergot alkaloids exhibit a broad spectrum of pharmacological effects and have already been extensively used as medicines over the centuries. Consequently, total synthesis of ergot alkaloids has recently received considerable attention, even in its racemic forms.[4] The majority of these alkaloids have the characteristic structure of a tetracyclic ring system (ergoline), which is believed to rise from *seco*-agroclavine (**1a**) via a series of oxidation reduction sequence (Figure 1). Herein, we report biomimetic collective total syntheses of either enantiomers of clavine alkaloids from simplest congener, *seco*-agroclavine (**1a**).

Retrosynthetically, we envisioned that vicinal stereocenters of *seco*-agroclavine (**1a**) can be accessed from tricyclic γ-nitroester derivative **2**, which in turn can be synthesized from a key organocatalytic enantioselective Michael addition of nitronate[5] onto conjugated esters (see **3**) in an intramolecular fashion.[6] The asymmetric Michael reaction of conjugated enone, enal, or nitroalkene variant[7,8] remains an important challenge for the construction of vicinal stereogenic centers.[9,10] We argued that the use of nitronates in the catalytic intramolecular Michael addition to conjugated esters could afford γ-nitroester derivative **2** sharing a vicinal stereogenic center (Scheme 1).

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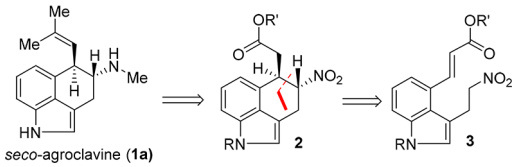
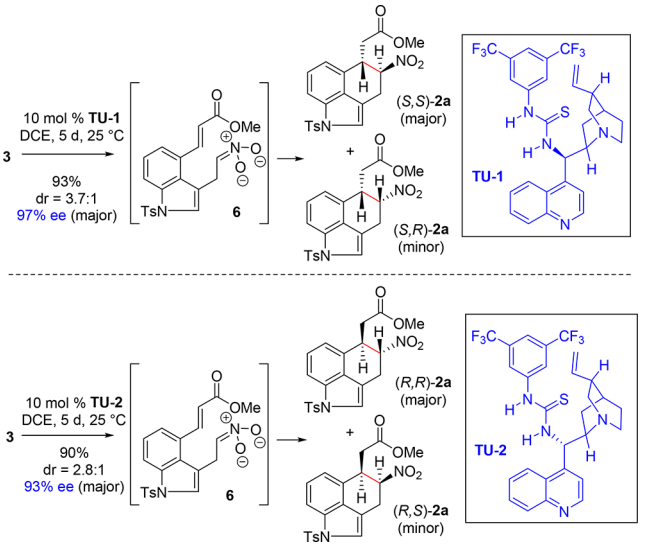
Scheme 1. Retrosynthetic Analysis of Clavine Alkaloids 1



Toward this end, encouraged by Cobb's report,[6a,11] recently, we have investigated the catalytic intramolecular nitronate Michael addition in the presence of bifunctional organocatalysts such as thiourea[12] and squaramide catalysts[13] to synthesize compounds (*S*,*S*)-**2a** and (*R*,*R*)-**2a** (Scheme 2).[14]

Scheme 2. Thiourea Catalyzed Nitronate Michael Reactions



It was hypothesized that the thiourea needs to coordinate to both the nitro group (essentially a nitronate generated in situ by abstraction of α-proton by quinuclidine base) and the ester (electrophile here) in order to proceed the reaction efficiently.[15] In fact, this can only occur effectively with the "*E* ester" and stabilizes **TS-I** (**4**) as a favored transition state (Figure 2) through H-bonding via three acidic N−H groups of the protonated catalyst.[15]

On the other hand, the geometry of the "*Z* ester" prevents such an H-bonding interaction, leading to the disfavored transition state **TS-II** (**5**) (Figure 2). It was also argued that a balance between steric and electronic effects should be maintained in order to have optimum results. In fact, a bulky ester might disturb the H-bonding (see, **TS-I**), whereas an electron-withdrawing group at the indole nitrogen might ease the reaction by pulling electrons toward it and create proper electronics (Figure 2).

In practice, we were delighted to obtain cyclized product **2** in dichloromethane in the presence of **TU-1** to afford 93% yields with 3.7:1 dr and 97% ee in favor of (*S*,*S*)-**2a** (Scheme 2).[16] Later, in our search for a flexible route to naturally occurring ergot alkaloids, (*R*,*R*)-**2a** was synthesized in 90% yield (dr = 2.8:1) with 93% ee from **3** using by using **TU-2** catalyst (synthesized from cinchonidine).[17] To our delight, the intramolecular nitronate Michael reaction can be performed on 1 g scale of compound **3** using 5 mol % of **TU-1** and **TU-2** at 25 °C (20 mL dichloroethane, ∼7 d), which afforded

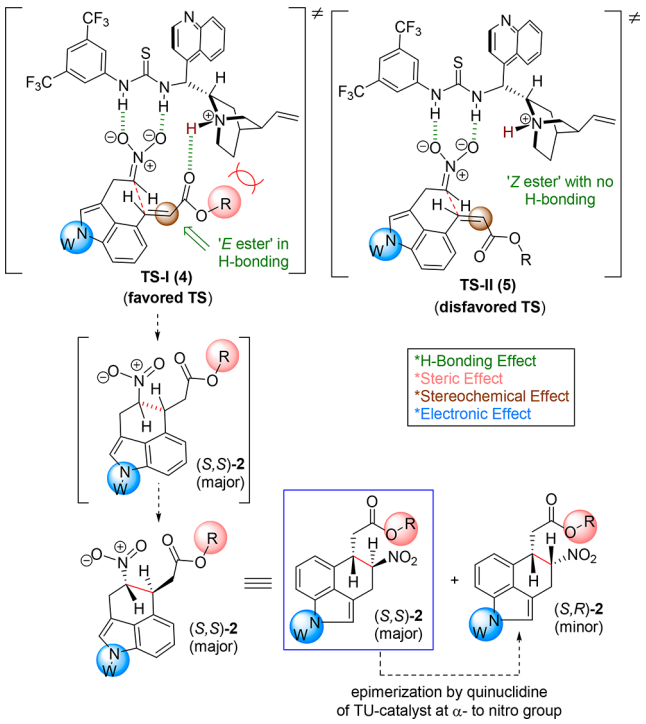
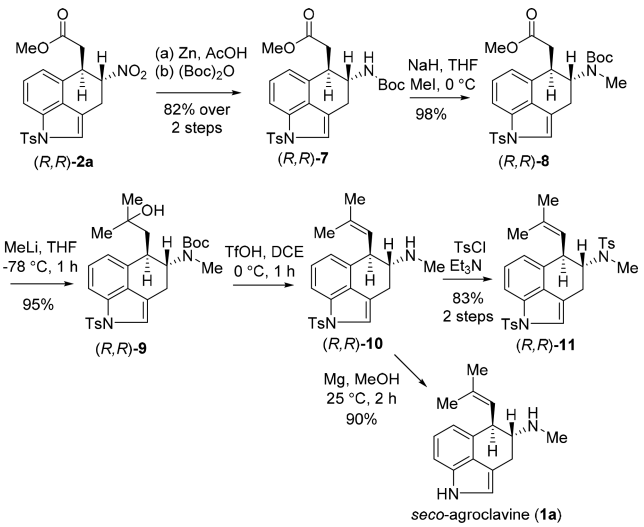


Figure 2. Stereochemical rational using thiourea.

product (*S*,*S*)-**2a** in 86% yield with 93% ee (dr = 3:1) and (*R*,*R*)-**2a** in 84% yield with 92% ee (dr = 2.8:1). More importantly, minor products (*S*,*R*)-**2a** and (*R*,*S*)-**2a** can be converted to (*S*,*S*)-**2a** and (*R*,*R*)-**2a** in 72% and 69% yields, respectively, by epimerization in the presence of 6 equiv of Et_3N in refluxing toluene (6−7 h). This ensures the overall efficiency of our strategy.

Having Michael product (*R*,*R*)-**2a** in hand, our effort was focused thereafter on its utilization for the synthesis of *seco*-agroclavine (**1a**) (Scheme 3). Toward this, we reduced the nitro functionality in the presence of Zn-AcOH followed by Boc protection to afford γ-aminoester (*R*,*R*)-**7** in 82% over two steps (Scheme 3). The latter was then *N*-methylation [see, (*R*,*R*)-**8**] followed by reaction with MeLi to furnish tertiary alcohol (*R*,*R*)-**9** in 93% over two steps. Further, compound

Scheme 3. Total Synthesis of Natural *seco*-Agroclavine (1a)



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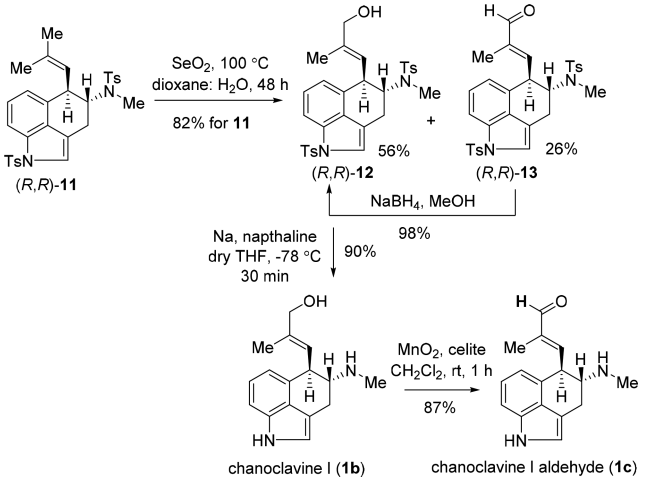
(*R*,*R*)-**9** was treated with triflic acid to give (*R*,*R*)-**10**, which was further treated with Mg in MeOH, without further purification, to complete the total synthesis of *seco*-agroclavine (**1a**) (90% over two steps) (Scheme 3). Further utilizing a similar strategy, total synthesis of unnatural *seco*-agroclavine (*ent*-**1a**) has been accomplished from (*S*,*S*)-**2a** (see the Supporting Information for details).

For further synthetic elaboration, the secondary amine of (*R*,*R*)-**10** was protected with tosyl group to furnish (*R*,*R*)-**11** (Scheme 3). Bistosylated compound (*R*,*R*)-**11** was reacted under the condition of allylic oxidation to afford a mixture of allylic alcohol (*R*,*R*)-**12** and aldehyde (*R*,*R*)-**13** in 56% and 26% yields, respectively (Scheme 4). We could obtain 81% yield of

Scheme 4. Total Syntheses of Chanoclavine I (1b) and Chanoclavine I Aldehyde (1c)

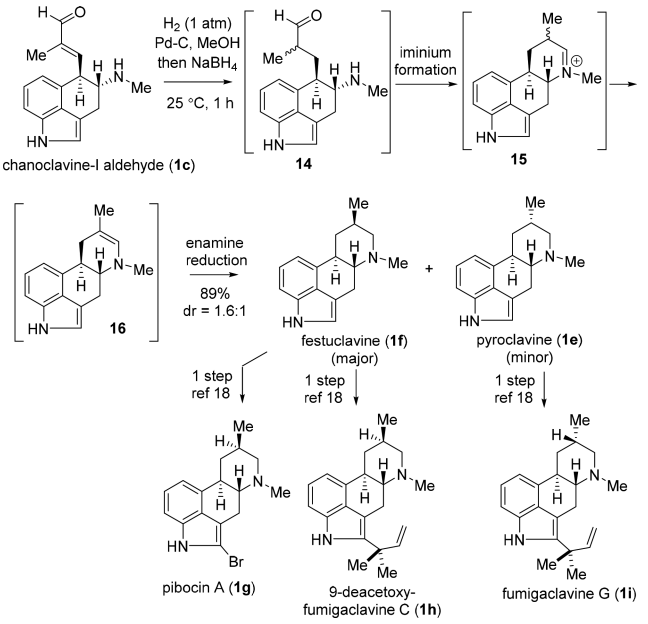


alcohol (*R*,*R*)-**12** when a crude mixture was reduced with $NaBH_4$, from where total synthesis of chanoclavine I (**1b**) was completed by treatment of Na-naphthalide at −78 °C (90% yield). Further oxidation of chanoclavine I (**1b**) to chanoclavine I aldehyde (**1c**) was performed using MnO_2 oxidation (Scheme 4). Along a similar line, total syntheses of unnatural chanoclavine I (*ent*-**1b**) to chanoclavine I aldehyde (*ent*-**1c**) have been accomplished from *ent*-**1a** (see the SI for details).

With the synthesis of chanoclavine I aldehyde (**1c**) secured, it was hydrogenated to access festuclavine (**1f**) and pyroclavine (**1e**) following a biomimetic proposal in a one-pot fashion (Scheme 5). This one-pot cascade featured a hydrogenation (**14**) and iminium (**15**)−enamine (**16**) tautomerization followed by reduction using $NaBH_4$ which afforded a pair of diastereomers in 1.6:1 ratio (Scheme 5). Chromatographic separation of these diastereomers ensures total syntheses of pyroclavine (**1e**) (35% yield) and festuclavine (**1f**) (54% yield) (Scheme 5). Further utilizing a similar reaction sequence, the total synthesis of unnatural festuclavine (*ent*-**1f**) and pyroclavine (*ent*-**1e**) have also been accomplished from *ent*-**1c** (see the SI for details). Since the total syntheses of pibocin A (**1g**) and 9-deacetoxyfumigaclavine C (**1h**) are reported from festuclavine (**1f**) in one step,[18] our effort culminated in the total syntheses of **1g**,**h** (Scheme 5). Further, as the total synthesis of fumigaclavine G (**1i**) is reported from pyroclavine (**1e**),[18] we have also shown formal total synthesis of **1i** (Scheme 5).

In conclusion, biomimetic total syntheses of tetracyclic clavine alkaloids pyroclavine (**1e**) and festuclavine (**1f**) have been achieved from *seco*-agroclavine (**1a**) via the intermediacy

Scheme 5. Biomimetic Total Syntheses of Naturally Occurring Pyroclavine (1e) and Festuclavine (1f)



of chanoclavine I (**1b**), and chanoclavine I aldehyde (**1c**). A reduction cascade involving a hydrogenation, iminium−enamine tautomerization, and imine reduction from chanoclavine I aldehyde (**1c**) ensures total syntheses of **1e**,**f**. Further utilizing a similar strategy, biomimetic total syntheses of unnatural (+)-festuclavine (*ent*-**1f**) and (+)-pyroclavine (*ent*-**1e**) have also been accomplished from unnatural *seco*-agroclavine (*ent*-**1a**) via chanoclavine I (*ent*-**1b**) and chanoclavine I aldehyde (*ent*-**1c**). Further efforts toward a rational extension of this strategy to access medicinally important drug molecules sharing ergoline scaffolds are currently under active investigation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b03683.

General experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(16) The *syn*-stereochemistry of minor product (*S*,*R*)-**2a** was confirmed by NOE experiments. See ref 14.

(17) The stereochemistry of (*R*,*R*)-**2a** was confirmed by the total synthesis of unnatural (+)-chanoclavine I (*ent*-**1a**) and (+)-chanoclavine I aldehyde (*ent*-**1b**). See the Supporting Information for details.

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