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Catalytic asymmetric formal total syntheses of (+)- and (−)-cycloclavine†

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We report an expeditious catalytic asymmetric approach to clavine alkaloids *via* a key Heck cyclization. This reaction sets the formation of vicinal stereocenters with excellent diastereoselectivity. Utilizing the aforementioned strategy, the formal total synthesis of cycloclavine (1) has been achieved *via* another key late-stage ester-aminolysis of 6.

Clavine alkaloids (**1** and **2**; Fig. 1) are a subclass of the ergot family of indole-containing alkaloids produced by several members of the *Clavicipitaceae* and *Trichocomaceae* families of filamentous fungi.[1,2] They have also been identified in plants of the families *Convolvulaceae*, *Poaceae* and *Polygalaceae*.[3] Ergot alkaloids (**1–4**; Fig. 1) primarily target serotonin (5-HT) receptors[4a] and α-adrenergic and dopamine receptors. Reportedly, some natural or semisynthetic ergoline derivatives are used as drugs, such as pergolide (**2d**) used as an anti-prolactin and anti-Parkinson's disease drug.[4,5]

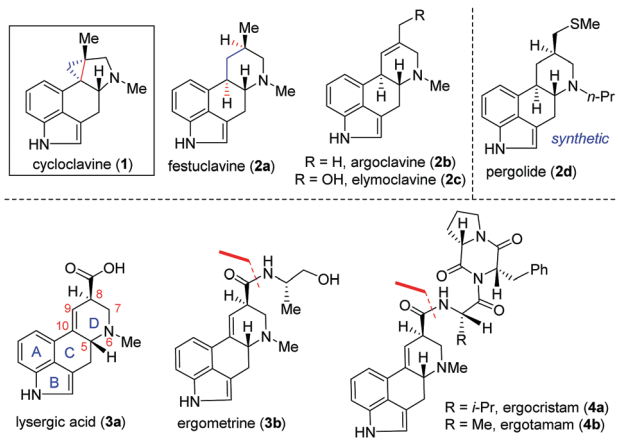

Fig. 1 Clavine alkaloids (**1** and **2**) and lysergic acid (**3** and **4**) family.

Therefore, significant progress has been made in the identification and characterization of genes responsible for the biosynthesis of clavine alkaloids (Fig. 1).[6] Structurally, clavine alkaloids can exist in pentacyclic [such as cycloclavine (**1**)] and tetracyclic [such as festuclavine (**2a–c**)] forms.[4b] Lysergic acid (**3a**) (and its derivatives such as ergometrine **3b** and ergopeptam alkaloids **4a–b**) differs from clavine alkaloids **2a–c** only in the oxidation state [see, **3a**].[7a,b]

Cycloclavine (**1**) was isolated from the seeds of the African morning glory shrub *Ipomoea hildebrandtii*, and later from a species of filamentous fungus, *Aspergillus japonicus*.[8a,b] Although smaller in size, structurally cycloclavine (**1**) poses a formidable challenge because of its complex architecture with a pyrrolidine ring linked with a strained cyclopropane ring with three contiguous stereocenters, out of which two are vicinal all-carbon quaternary stereocenters.[9] Despite the encouraging medicinal value of select clavine congeners, a comprehensive biological evaluation for the majority of these naturally occurring alkaloids has yet to be undertaken. From 2008 till 2016, only racemic syntheses of cycloclavine (**1**) have been reported, out of which three total syntheses[10–12] and two formal total syntheses[13,14] are reported. Interestingly, two consecutive coupling reactions such as selective alkylation of a dienolate and an intramolecular Heck reaction are utilized by Opatz and Netz for a racemic formal synthesis of cycloclavine (**1**).[14]

Recently, the first catalytic enantioselective total synthesis of unnatural (−)-cycloclavine (*ent*-**1**) has been achieved by Wipf and McCabe[15a] *via* Rh-catalyzed enantioselective cyclopropanation (up to 74% ee) of an unsubstituted allene to access a methylene-cyclopropane derivative. Very recently, Cao and co-workers have reported an elegant formal total synthesis of naturally occurring (+)-cycloclavine (**1**)[15b] while our manuscript was under preparation. This synthesis features a Zn-mediated asymmetrical nucleophilic addition of *N*-*tert*-butanesulfinimine, an intramolecular ester-aminolysis reaction followed by isomerization of an exocyclic double bond and a late-stage intramolecular Heck coupling reaction.[15b]

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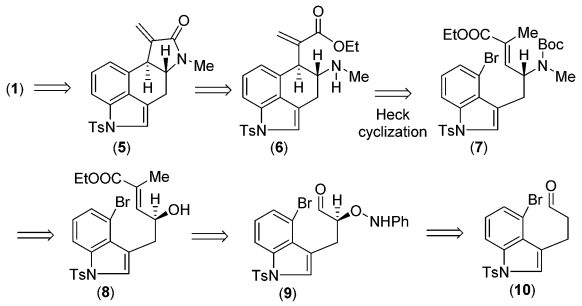
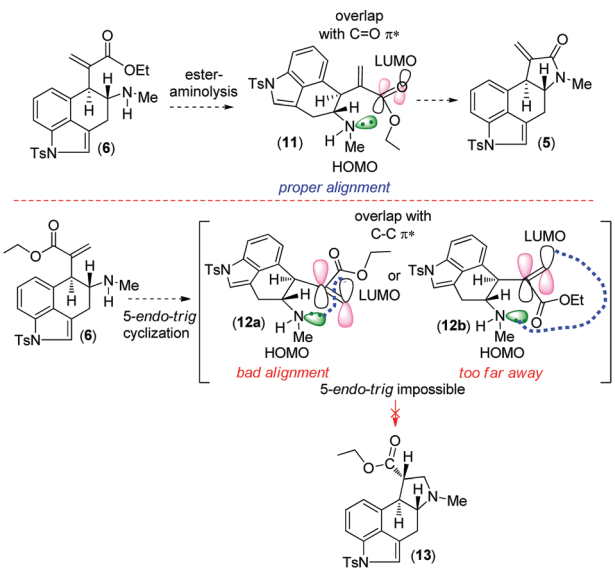


Scheme 1 Retrosynthetic analysis of cycloclavine (**1**).

In this context, a unified strategy for the synthesis of **1** and **2** in enantioenriched form would present opportunities to provide access to significant quantities of the natural products and related analogues.

Retrosynthetically, we envisioned that cycloclavine (**1**) can be synthesized from an advanced enantiopure intermediate α,β-unsaturated amide **5** (Scheme 1) *via* isomerization followed by reduction of the amide functionality and cyclopropanation.[10] Compound **5** can be accessed from α,β-unsaturated ester **6**, which could in fact be the advanced intermediate for clavine alkaloids **2a–d** sharing vicinal stereocenters (Fig. 1). We reasoned that ester **6** has the potential to afford two different tetracyclic intermediates such as **5** and **13** (Scheme 2). An ester-aminolysis of **6** can provide access to **5**, on the other hand **6** can also afford ester **13** following a 5-*endo-trig* cyclization (Scheme 2). We argued that as the secondary amine (HOMO) and C=O π* (LUMO) are in proper alignment (see the orbital representation in **11**), an ester-aminolysis of **6** would be facile to afford tetracyclic amide **5**. However, a 5-*endo-trig* cyclization of **6** would not be possible because of bad alignment of the secondary amine (HOMO) and C=C π* (LUMO) (see the orbital representation of intermediates **12a** and **12b**).

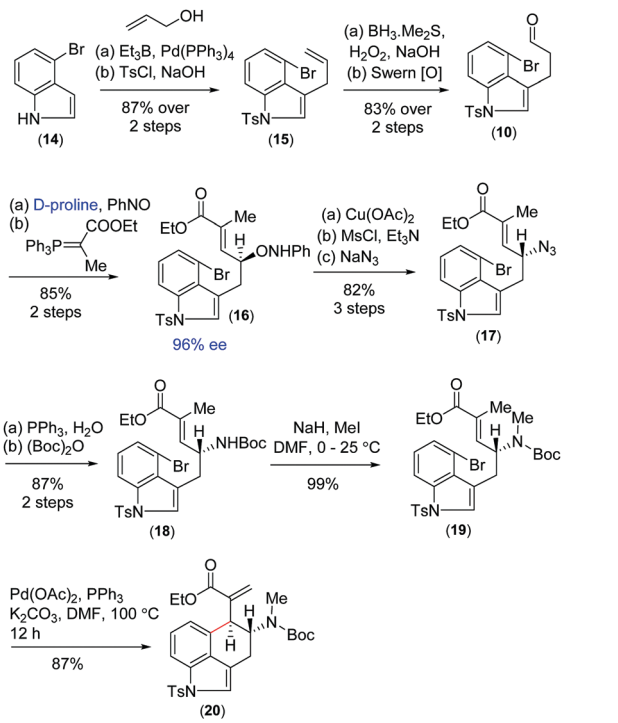


Scheme 2 An ester-aminolysis *versus* 5-*endo-trig* cyclization of α,β-unsaturated ester **6**.

Further, we thought that α,β-unsaturated ester **6** with an *exo*-double bond can be synthesized *via* a key intramolecular Heck cyclization of allylamine **7** (Scheme 1). Enantioenriched allylic amine **7** can be synthesized from allylic alcohol **8** *via* Mitsunobu type inversion using an azide nucleophile followed by synthetic manipulations. Non-racemic allyl alcohol **8** can be accessed from aldehyde **10** *via* a D-proline catalysed α-aminoxylation reaction with nitrosobenzene through the intermediate aldehyde **9** (Scheme 1). Importantly, since both enantiomers of proline are commercially available, one can synthesize both antipodes of allylic alcohols, *i.e.* **8** and *ent*-**8**.

On the basis of previous studies on the proline catalysed α-aminoxylation reaction of aliphatic aldehydes with nitrosobenzene,[16] we decided to investigate the potential of this process in the catalytic asymmetric total synthesis of clavine alkaloids (Fig. 1). Towards this direction, we synthesized 3-allyl-4-bromoindole **15** from the Pd(0)-catalyzed reaction of 4-bromoindole **14** with allyl alcohol in the presence of triethylborane using Tamaru's report.[17] This was then reacted with borane followed by oxidation with H_2O_2 in the presence of NaOH to afford a primary alcohol, which was then oxidized to obtain aldehyde **10** under Swern oxidation (Scheme 3). Having aldehyde **10** in hand, we then conducted a catalytic enantioselective α-aminoxylation reaction with nitrosobenzene in the presence of 10 mol% D-proline (Scheme 3). This reaction afforded an α-aminoxylated aldehyde, which was immediately reacted with a stabilized Wittig reagent prepared from 2-bromo ethylpropionate to afford compound *E*-ester **16** as the sole isomer in 85% yield over 2 steps with 96% enantioselectivity.[18]

With compound **16** in hand, our effort was thereafter to elaborate to allylic amine **19** for key Heck cyclization



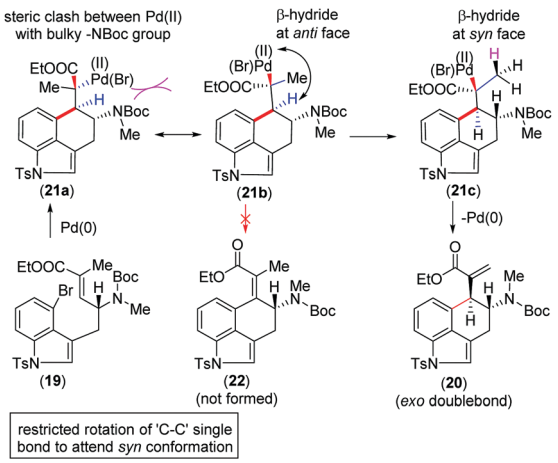
Scheme 3 Asymmetric synthesis of key α,β-unsaturated ester **20**.

(Scheme 3). Towards this, N–O bond cleavage was performed with anhydrous $Cu(OAc)_2$,[19,20] followed by mesylation and azide formation, affording **17** in 82% yield over 3 steps. The azide functionality was reduced under Staudinger conditions, followed by Boc-protection leading to intermediate **18** in 87% yield over 2 steps. The latter was *N*-methylated using methyl iodide to afford allyl amine **19** (Scheme 3). The intramolecular Heck cyclization of **19** was performed with 5 mol% $Pd(OAc)_2$ and 10 mol% PPh_3. Gratifyingly, this reaction afforded a single diastereomer of **20** in 87% yield (Scheme 3).[21]

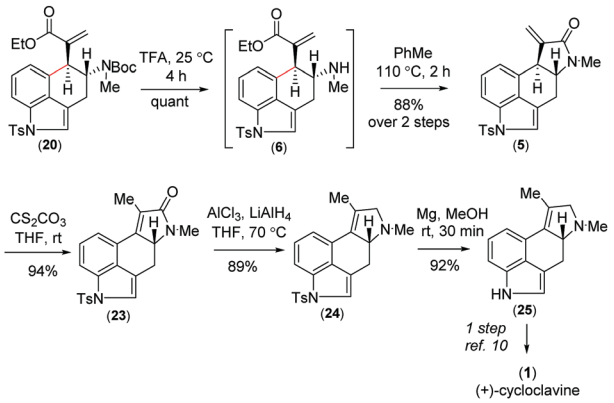
We urged that the Heck cyclization of **19** can proceed through the intermediate Pd(II)-species **21a** (Scheme 4). However, in order to minimize the steric clash, **21a** could immediately form **21b** *via* a C–C bond rotation. The formation of the tetra-substituted α,β-unsaturated ester **22** from this intermediate is not possible since Pd(II) and β-hydride are *anti*-position to each other (Scheme 4). At this situation, a β-hydride transfer from an adjacent methyl group in **21c** could afford **20** having vicinal stereogenic centers (Scheme 4).

Further, compound **20** was elaborated under a key cyclization in order to get the tetracyclic core of cycloclavine (**1**). Towards this, we deprotected the Boc group in the presence of trifluoroacetic acid at 25 °C to afford **6**, which under refluxing toluene afforded the ester-aminolysis product **5** with an exocyclic double bond in 88% isolated yield over 2 steps (Scheme 5).[22] To our delight, no trace of the 5-*endo-trig* cyclization (aza-Michael reaction) product was observed, as confirmed from ^{1}H-NMR analysis of the crude reaction mixture.

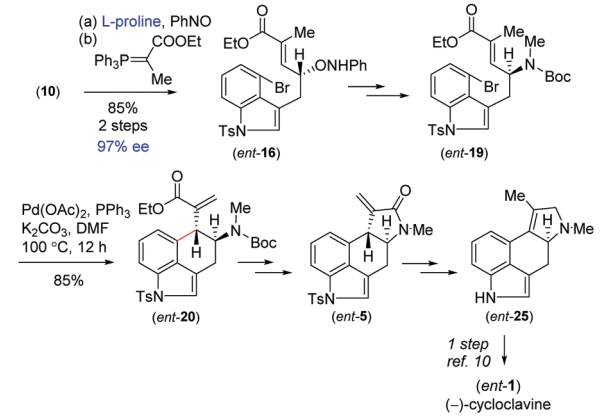
With the enantioenriched tetracyclic **5** in hand, we then isomerized to γ-lactam using cesium carbonate in THF to afford **23** in 94% yield (Scheme 5).[23] The latter was reduced using $LiALH_4$ in the presence of $AlCl_3$ to furnish the electron-rich tetrasubstituted double bonded product **24** in 89% yield.[24] Further, in order to access the antipode of **25**, we performed the catalytic enantioselective α-aminoxylation reaction of **10** with nitrosobenzene in the presence of 10 mol% L-proline, which afforded the product *ent*-**16** in 97% ee after a Wittig reaction (Scheme 6). This enantioenriched material was elaborated to *ent*-**25** *via* a similar reaction sequence as shown in Schemes 3 and 5. As the total synthesis of cycloclavine (**1**) from **25** is known, our effort culminated in the formal total synthesis of this alkaloid.



Scheme 4 Rationale of highly diastereoselective Heck cyclization.



Scheme 5 Asymmetric synthesis of (+)-cycloclavine (**1**).



Scheme 6 Asymmetric synthesis of (–)-cycloclavine (*ent*-**1**).

In summary, the catalytic enantioselective formal total synthesis of both antipodes of cycloclavine (**1**) has been achieved *via* a late stage ester-aminolysis of an α,β-unsaturated ester intermediate **6**. The vicinal stereocenters of this advanced intermediate were established following an intramolecular Heck cyclization of an enantioenriched α,β-unsaturated ester having allylamine **19**. Since both enantiomers of proline are inexpensive and commercially available, our strategy offers an expeditious approach to either enantiomer of cycloclavine (**1**). Further efforts for a rational extension of the strategy to other congeners of clavine alkaloids are underway and will be reported in due course.[25]

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Conflicts of interest

There are no conflicts to declare.

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