




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

Cite this: *Chem. Commun.*, 2018, 54, 940

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Received 24th November 2017,
Accepted 2nd January 2018

DOI: 10.1039/c7cc09045e

rsc.li/chemcomm

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}

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-butanefulfinimine, an intramolecular ester-aminolysis reaction followed by isomerization of an exocyclic double bond and a late-stage intramolecular Heck coupling reaction.^{15b}

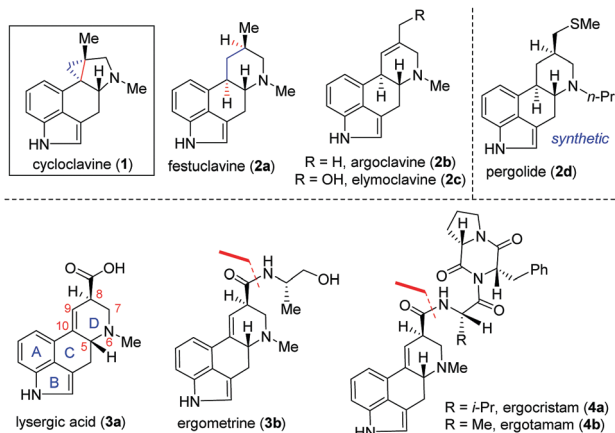
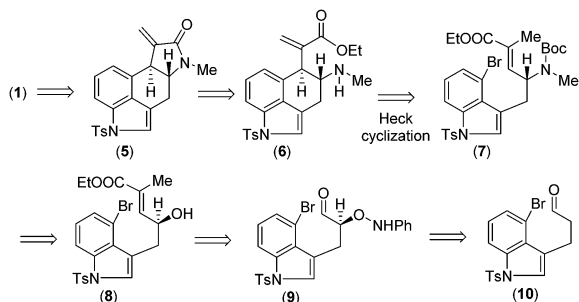


Fig. 1 Clavine alkaloids (1 and 2) and lysergic acid (3 and 4) family.

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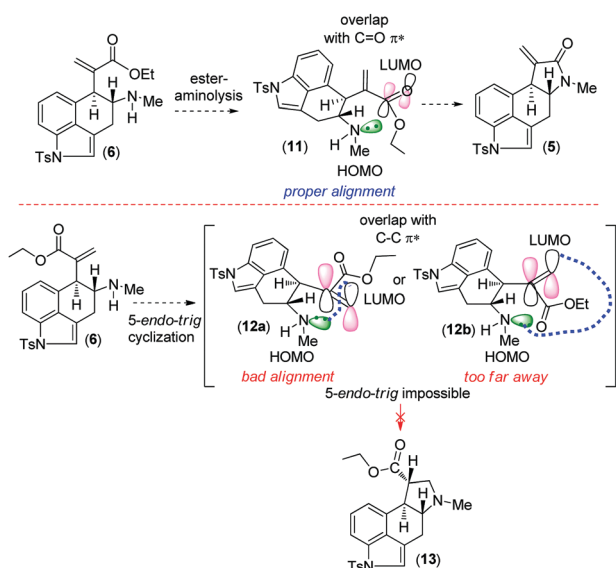
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† Electronic supplementary information (ESI) available: Experimental procedures, additional reaction optimization, spectroscopic data for all new compounds. See DOI: 10.1039/c7cc09045e

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.

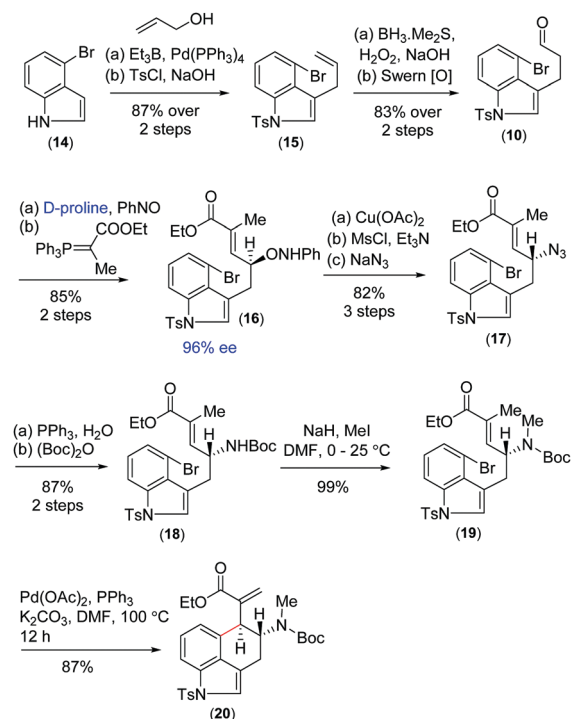
Retrosynthetically, we envisioned that cycloclavine (**1**) can be synthesized from an advanced enantiopure intermediate α,β -unsaturated amide **5** (Scheme 1) *via* isomerization followed by reduction of the amide functionality and cyclopropanation.¹⁰ Compound **5** can be accessed from α,β -unsaturated 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 H₂O₂ 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 -aminoxylation 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 $\text{Cu}(\text{OAc})_2$,^{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% $\text{Pd}(\text{OAc})_2$ and 10 mol% PPh_3 . Gratifyingly, this reaction afforded a single diastereomer of **20** in 87% yield (Scheme 3).²¹

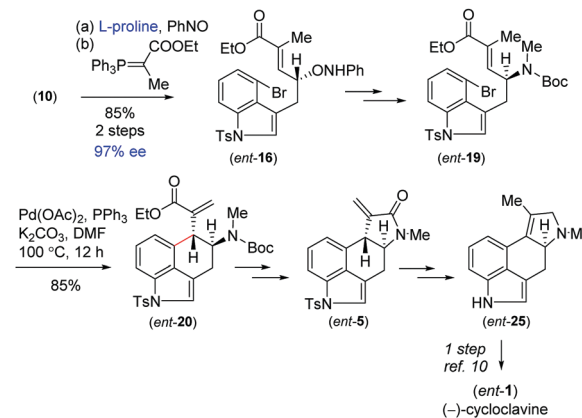
We urged that the Heck cyclization of **19** can proceed through the intermediate $\text{Pd}(\text{II})$ -species **21a** (Scheme 4). However, in order to minimize the steric clash, **21a** could immediately form **21b** via a C–C bond rotation. The formation of the tetra-substituted α,β -unsaturated ester **22** from this intermediate is not possible since $\text{Pd}(\text{II})$ 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 ¹H-NMR analysis of the crude reaction mixture.

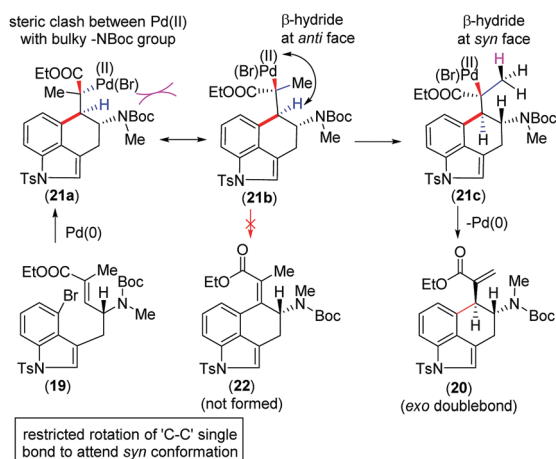
With the enantioenriched tetracyclic **5** in hand, we then isomerized to γ -lactam using cesium carbonate in THF to afford **23** in 94% yield (Scheme 5).²³ The latter was reduced using LiAlH_4 in the presence of AlCl_3 to furnish the electron-rich tetrasubstituted double bonded product **24** in 89% 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



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



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



Scheme 4 Rationale of highly diastereoselective Heck cyclization.

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.

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

Financial support from the SERB, DST [EMR/2016/000214] and CSIR [02(0295)/17/EMR-II], Govt. of India, is gratefully acknowledged. S. C. and S. B. thank the UGC and CSIR, respectively, for predoctoral fellowships. S. G. thanks IISER Bhopal for a post-doctoral fellowship.

Conflicts of interest

There are no conflicts to declare.

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