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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 cyclo-clavine (**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*-butanesulfinimine, an intramolecular ester-aminolysis reaction followed by isomerization of an exocyclic double bond and a late-stage intramolecular Heck coupling reaction.[15b]
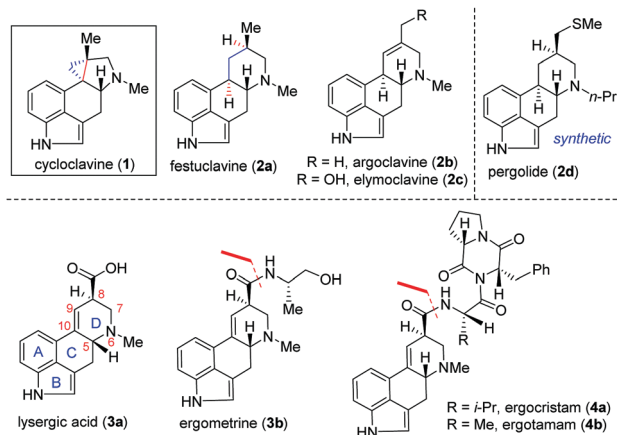

Fig. 1 Clavine alkaloids (**1** and **2**) and lysergic acid (**3** and **4**) family.

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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**).

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
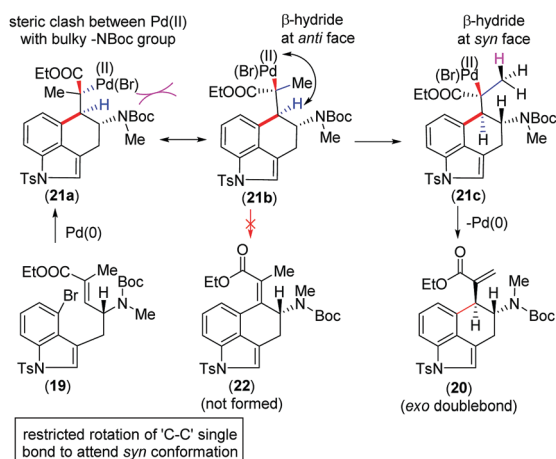

Scheme 2 An ester-aminolysis versus 5-endo-trig cyclization of α,β-unsaturated ester **6**.

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]
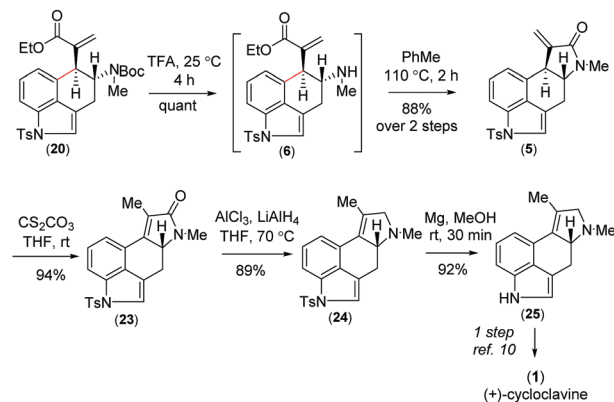
We urged that the Heck cyclization of **19** can proceed through the intermediate Pd(II)-species **21a** (Scheme 4). However, in order to minimize the steric clash, **21a** could immediately form **21b** *via* a C–C bond rotation. The formation of the tetra-substituted α,β-unsaturated ester **22** from 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.
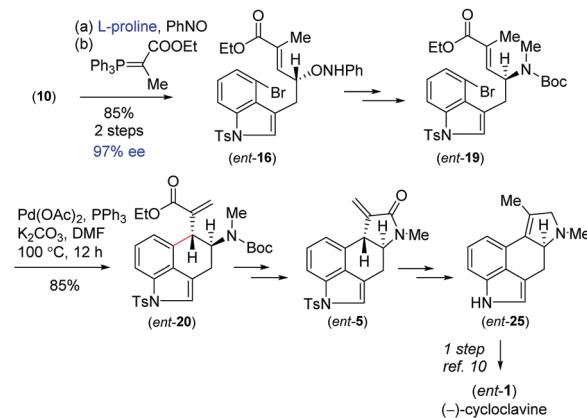
With the enantioenriched tetracyclic **5** in hand, we then isomerized to γ-lactam using cesium carbonate in THF to afford **23** in 94% yield (Scheme 5).[23] The latter was reduced using LiAlH$_4$ in the presence of AlCl$_3$ to furnish the electron-rich tetrasubstituted double bonded product **24** 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

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

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

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]

Conflicts of interest

There are no conflicts to declare.

Scheme 4   Rationale of highly diastereoselective Heck cyclization.

Notes and references

1 (*a*) A. Hofmann, in *Plants in the developments of modern medicine*, ed. T. Swain, Harvard University Press, Cambridge, Mass, 1972, pp. 235–260; (*b*) Review: S. R. McCabe and P. Wipf, *Org. Biomol. Chem.*, 2016, **14**, 5894.

2 (*a*) L. V. Boichenko, D. M. Boichenko, N. G. Vinokurova, T. A. Reshetilova and M. U. Arinbasarov, *Microbiology*, 2001, **71**, 306; (*b*) P. L. Schiff, *Am. J. Pharm. Educ.*, 2006, **70**, 98.

3 (*a*) D. Gröger and H. G. Floss, *Alkaloids: Chem. Biol.*, 1998, **50**, 171. Review; (*b*) C. Wallwey and S.-M. Li, *Nat. Prod. Rep.*, 2011, **28**, 496.

4 (*a*) A. Sinz, *Pharm. Unserer Zeit*, 2008, **37**, 306. Review; (*b*) H. Liu and Y. Jia, *Nat. Prod. Rep.*, 2017, **34**, 411.

5 (*a*) I. Ninomiya and T. Kiguchi, in *The Alkaloids*, ed. A. Brossi, Academic Press, San Diego, CA, 1990, vol. 38, pp 1–156; (*b*) M. Somei, Y. Yokoyama, Y. Murakami, I. Ninomiya, T. Kiguchi and T. Naito, in *The Alkaloids*, ed. G. A. Cordell, Academic Press, San Diego, CA, 2000, vol. 54, pp. 191–257.

6 (*a*) D. Jakubczyk, J. Z. Cheng and S. E. O'Connor, *Nat. Prod. Rep.*, 2014, **31**, 1328; (*b*) C. A. Young, C. L. Schardl, D. G. Panaccione, S. Florea, J. E. Takach, N. D. Charlton, N. Moore, J. S. Webb and J. Jaromczyk, *Toxins*, 2015, **7**, 1273.

7 (*a*) C. L. Schardl, D. G. Panaccione and P. Tudzynski, *Alkaloids: Chem. Biol.*, 2006, **63**, 45; (*b*) T. Haarmann, *et al.*, *Mol. Plant Pathol.*, 2009, **10**, 563 and references cited therein.

8 (*a*) D. Stauffacher, P. Niklaus, H. Tscherter, H. P. Weber and A. Hofmann, *Tetrahedron*, 1969, **25**, 5879; (*b*) T. Furuta, M. Koike and M. Abe, *Agric. Biol. Chem.*, 1982, **46**, 1921.

9 Biosynthesis of cycloclavine (**1**), see; (*a*) D. Jakubczyk, L. Caputi, A. Hatsch, C. A. F. Nielson, M. Diefenbacher, J. Klein, A. Molt, H. Schröder, J. Z. Cheng, M. Naesby and S. E. O'Conner, *Angew. Chem., Int. Ed.*, 2015, **54**, 5117; (*b*) D. Jakubczyk, L. Caputi, C. E. M. Stevenson, D. M. Lawson and S. E. O'Conner, *Chem. Commun.*, 2016, **52**, 14306.

10 M. Incze, G. Dörnyei, I. Moldvai, E. Temesvári-Major, O. Egyed and C. Szánty, *Tetrahedron*, 2008, **64**, 2924.

11 F. R. Petronijevic and P. Wipf, *J. Am. Chem. Soc.*, 2011, **133**, 7704.

12 N. D. Jabre, T. Watanabe and M. Brewer, *Tetrahedron Lett.*, 2014, **55**, 197.

13 W. Wang, J.-T. Lu, H.-L. Zhang, Z.-F. Shi, J. Wen and X.-P. Cao, *J. Org. Chem.*, 2014, **79**, 122.

14 N. Netz and T. Opatz, *J. Org. Chem.*, 2016, **81**, 1723.

15 (*a*) S. R. McCabe and P. Wipf, *Angew. Chem., Int. Ed.*, 2017, **56**, 324; (*b*) J.-Q. Chen, L.-L. Song, F.-X. Li, Z.-F. Shi and X.-P. Cao, *Chem. Commun.*, 2017, **53**, 12902.

16 (*a*) L-Proline catalyzed α-aminoxylation of aldehydes, see; G. Zhong, *Angew. Chem., Int. Ed.*, 2003, **42**, 4247; (*b*) L-proline catalyzed α-amination of aldehydes, see; (*c*) B. List, *J. Am. Chem. Soc.*, 2002, **124**, 5656; (*d*) A. Bøgevig, K. Juhl, N. Kumaragurubaran, W. Zhuang and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2002, **41**, 1790.

17 M. Kimura, M. Futamata, R. Mukai and Y. Tamaru, *J. Am. Chem. Soc.*, 2005, **127**, 4592.

18 For α-aminoxylation and Horner–Wadsworth–Emmons olefination of aldehydes, see, N. B. Kondekar and P. Kumar, *Org. Lett.*, 2009, **11**, 2611.

19 (*a*) Y. Hayashi, M. Shoji, H. Ishikawa, J. Yamaguchi, T. Tamura, H. Imai, Y. Nishigaya, K. Takabe, H. Kakeya and H. Osada, *Angew. Chem., Int. Ed.*, 2008, **47**, 6657; (*b*) J. S. Yadav, K. Ramesh, U. V. S. Reddy, B. V. S. Reddy and A. A. K. A. Ghamdi, *Tetrahedron Lett.*, 2011, **52**, 2943.

20 N–O bond cleavage using Pd/C under 1 atm H_2 led to a complex mixture of products.

21 For leading references for Pd-catalyzed intramolecular Heck cyclization for the synthesis of natural products, see; (*a*) M. Zhang, X. Huang, L. Shen and Y. Qin, *J. Am. Chem. Soc.*, 2009, **131**, 6013; (*b*) J. Wu, J. Becerril, Y. Lian, H. L. M. Davies, J. A. Porco Jr. and J. S. Panek, *Angew. Chem., Int. Ed.*, 2011, **50**, 5938; (*c*) J.-Q. Chen, J.-H. Xie, D.-H. Bao, S. Liu and Q.-L. Zhou, *Org. Lett.*, 2012, **14**, 2714; (*d*) W. Ren, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2014, **53**, 1818; (*e*) L.-Y. Pu, J.-Q. Chen, M.-L. Li, Y. Li, J.-H. Xie and Q.-L. Zhou, *Adv. Synth. Catal.*, 2016, **358**, 1229.

22 For references on intramolecular ester-aminolysis to from α-methylene-γ-lactam, see; (*a*) S. Bonazzi, B. Cheng, J. S. Wzorek and D. A. Evans, *J. Am. Chem. Soc.*, 2013, **135**, 9338; (*b*) J. A. Sirvent, F. Foubelo and M. Yus, *J. Org. Chem.*, 2014, **79**, 1356. Also, see ref. 14.

23 Other bases such as K_2CO_3, KHMDS, and DBU afforded isomerization products in 59–72% isolated yields along with some decomposition under heating.

24 Reduction using $LiAlH_4$ or Red-Al afforded a mixture of products as seen from TLC.

25 For a biomimetic approach to clavine alkaloids, see; S. Chaudhuri, S. Bhunia, A. Roy, M. K. Das and A. Bisai, *Org. Lett.*, 2018, **20**, 288.