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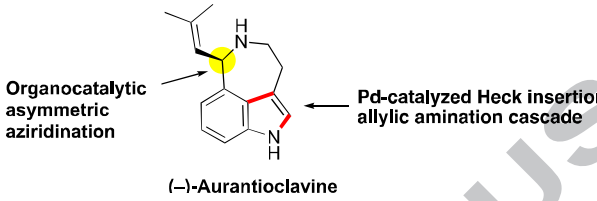

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Enantioselective formal synthesis of (–)-aurantioclavine using Pd-catalyzed cascade cyclization and organocatalytic asymmetric aziridination

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ABSTRACT

The enantioselective formal synthesis of (–)-aurantioclavine is described. The core tricyclic skeleton was synthesized using a Pd-catalyzed Heck insertion–allylic amination cascade. The stereocenter was constructed by a highly enantioselective organocatalytic asymmetric aziridination reaction.

The ergot alkaloid (–)-aurantioclavine (**1**) was isolated from *Penicillium aurantiovirens* by Kozlovskii and co-workers in 1981.[1] This natural product possesses an azepane ring bridging the C3- and C4-positions of the indole, and a stereogenic center on the benzylic position. The absolute stereochemistry was determined to be *R* by Stoltz and co-workers in 2008.[2] (–)-Aurantioclavine is a biosynthetic intermediate of the complex polycyclic alkaloid, communesins, which exhibit a variety of bioactivities.[3] Thus, (–)-aurantioclavine is an attractive synthetic target for organic chemists. In addition to the synthesis of racemic aurantioclavine, several enantioselective total syntheses of (–)-aurantioclavine have been reported.[4]

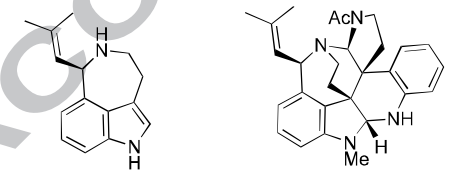
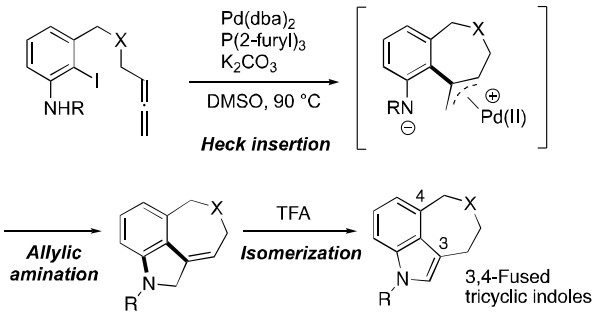


Figure 1. (–)-Aurantioclavine and communesin F.

Efficient synthetic methods of 3,4-fused tricyclic indole skeletons are in high demand in synthetic organic and medicinal chemistry because of the ubiquity of this tricyclic structure in bioactive molecules.[5,6] Recent efforts have focused on developing catalytic synthetic methods for this skeleton using easily prepared anilinic or aromatic substrates in place of expensive 4-haloindoles or their derivatives. Representative synthetic methods of this class are based on intramolecular Larock indole synthesis,[5a,b] Rh-catalyzed intramolecular dearomatizing [3+2] annulation of α-imino Rh-carbenoids,[5c,d] and Rh-catalyzed C-H activation.[5e–g] As part of our ongoing studies aimed at developing an efficient synthetic method for 3,4-fused tricyclic indole derivatives,[7] we reported a synthetic method based on a palladium-catalyzed Heck insertion to an allene–allylic amination cascade (Scheme 1).[7a] The reaction products, 3,4-fused 3-alkylidene indolines, could be transformed to the corresponding indole derivatives by treating them with acid. We hypothesized that the enantioselective total synthesis of (–)-aurantioclavine would be realized using the present palladium catalysis in combination with an organocatalytic asymmetric aziridination of α,β-unsaturated aldehydes developed by our group.[8] Herein we report the formal enantioselective total synthesis of (–)-aurantioclavine based on our synthetic methods.



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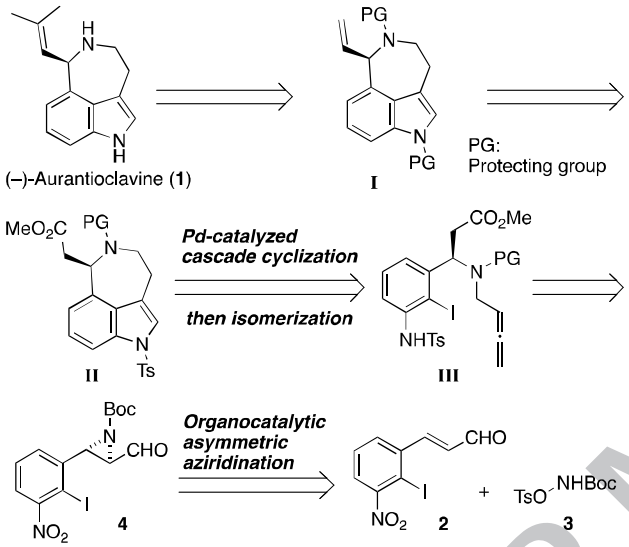
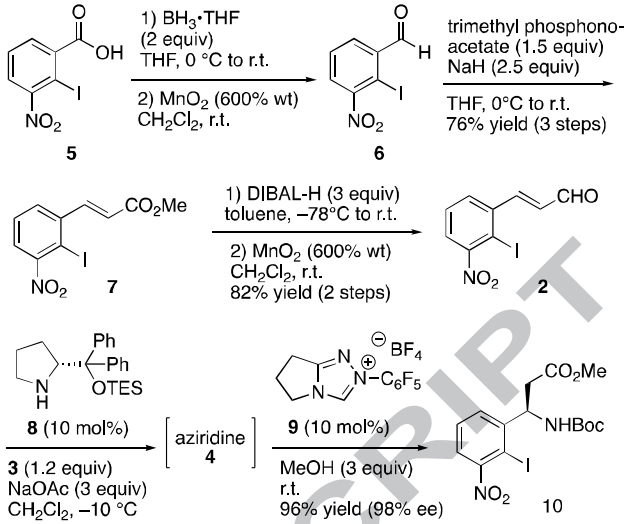
Scheme 1. Pd-catalyzed cascade cyclization to construct 3,4-fused tricyclic indole skeletons.

The retrosynthetic analysis is shown in Scheme 2. The prenyl moiety was constructed using the vinyl precursor in some previous syntheses. Therefore, compound **I** was set as the key intermediate for this work.[9] We envisioned that compound **I** would be accessible from 3,4-fused tricyclic indole derivative **II** bearing a side-chain at the benzylic position, which would be synthesized by Pd-catalyzed cascade cyclization using allene-tethered iodoaniline derivative **III**. We envisioned that chiral amine derivative **III** would be prepared from chiral aziridine **4**, which in turn could be synthesized by an organocatalytic asymmetric aziridination of α,β–unsaturated aldehyde **2** with *tert*-butyl *p*-toluenesulfonyloxy carbamate **3**.



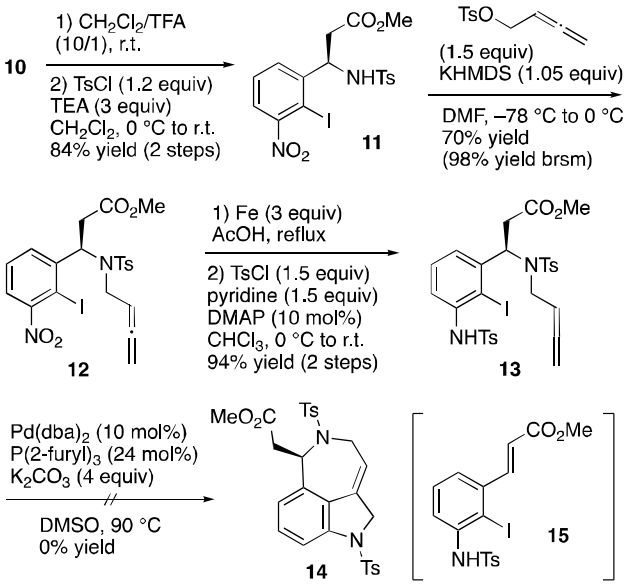
Scheme 2. Retrosynthetic analysis of (–)-aurantioclavine.

Our synthesis began with commercially available 2-iodo-3-nitrobenzoic acid **5** (Scheme 3). A carboxylic acid moiety was converted into aldehyde via a two-step process involving BH_3·THF reduction and MnO_2 oxidation. Aldehyde **6** was then reacted with trimethyl phosphonoacetate to give *trans*-α,β-unsaturated ester **7** in 76% overall yield. After conversion of the ester moiety to aldehyde (82% yield in 2 steps), the obtained α,β–unsaturated aldehyde **2** was applied to organocatalytic asymmetric aziridination.[10] The reaction proceeded in the presence of 10 mol % of (*S*)-L-proline-derived chiral amine catalyst **8**,[11] 1.2 equiv of **3**, and 3 equiv of sodium acetate, affording chiral aziridine derivative **4**. The subsequent transformation from **4** to β–amino ester derivative **10** could be performed in a single-pot reaction by adding 10 mol % of triazolium salt **9** and methanol to the reaction mixture, producing *N*-Boc protected amine **10** in 96% yield.[10d,12] Enantiomeric excess (98% ee) was determined by chiral HPLC analysis.



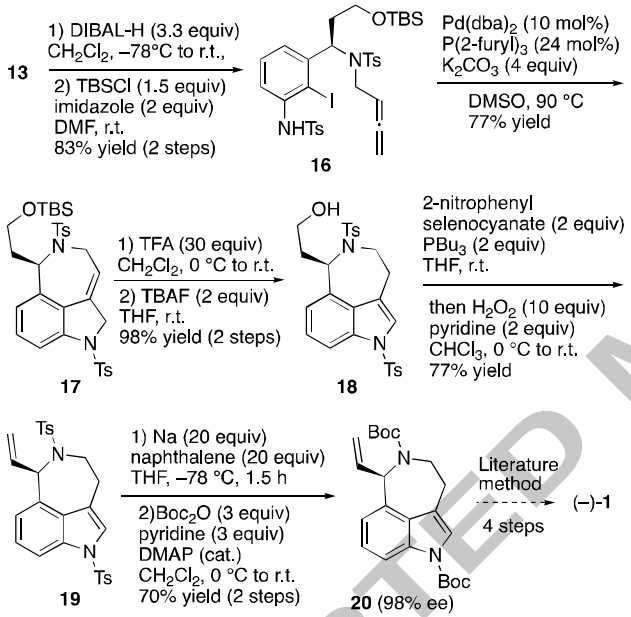
Scheme 3. Synthesis of *N*-Boc protected amine **10** using organocatalytic asymmetric aziridination.

We next examined the synthesis of a substrate for the Pd-catalyzed cascade cyclization (Scheme 4). Although direct allenylation of **10** with buta-2,3-dien-1-yl 4-methylbenzenesulfonate (allenyl tosylate) was examined first, the desired product was not obtained. Thus, the Boc group was converted into a tosyl group by standard protocols and compound **11** was obtained in 84% yield in two steps. Compound **11** was then treated with allenyl tosylate in DMF under basic conditions to furnish **12** in 70% yield (98% yield based on the recovered starting material). Reduction of the nitro group followed by protection of the resulting amine with a tosyl group afforded the cyclization precursor **13** in 94% yield (2 steps). The cascade cyclization was performed using 10 mol% of $Pd(dba)_2$, 24 mol% of P(2-furyl)$_3$, and 4 equiv of K_2CO_3 in DMSO at 90 °C. The corresponding tricyclic alkylidene indoline derivative **14** was not obtained at all, however, and elimination of the tosylamido moiety occurred to form compound **15** exclusively, probably due to acidity of the α-proton of the methyl ester.



Scheme 4. Synthesis of a substrate for the Pd-catalyzed cascade cyclization.

To prevent the observed side reaction, ester moiety in **13** was converted into the corresponding TBS-protected alcohol **16** via DIBAL-H reduction in 83% yield (2 steps) (Scheme 5). Pd-catalyzed cascade cyclization was then examined using the TBS-protected substrate under the optimum conditions and tricyclic alkylidene indoline derivative **17** was obtained in 77% yield.[13] Isomerization of **17** into the 3,4-fused tricyclic indole derivative was achieved by treatment with 30 equiv of TFA and subsequent removal of the TBS group by TBAF provided compound **18** in 98% yield (2 steps). Dehydration of **18** using 2-nitrophenyl selenocyanate followed by elimination under oxidative conditions afforded **19** in 77% yield. Both tosyl groups were removed by Birch reduction and protection of the two nitrogen atoms with a Boc group afforded Yang's known intermediate **20** in 70% yield (2 steps).[4h, 14] The NMR data were identical to those reported by Yang *et al.* The enantiomeric excess of **20** (98% ee) was determined by chiral HPLC analysis. Because the synthetic route from **20** to (–)-aurantioclavine **1** was established, we achieved a formal enantioselective synthesis.



Scheme 5. Formal enantioselective total synthesis of (–)-aurantioclavine.

In conclusion, we achieved a formal enantioselective synthesis of (–)-aurantioclavine. The core tricyclic skeleton was synthesized using a Pd-catalyzed Heck insertion–allylic amination cascade as the key step. The stereocenter was constructed by a highly enantioselective organocatalytic asymmetric aziridination reaction. This work successfully demonstrated the synthetic utility of our methods. Further studies on the application of these methods to the synthesis of bioactive natural products are underway.

Acknowledgments

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9. Dimethylation of **II**, followed by dehydration of the corresponding tertiary alcohol, can be a possible synthetic route for **1**. Stoltz and co-workers already reported that, however, dehydration of such tertiary alcohol gave a mixture of inseparable olefin isomers. See, reference 2a.
10. For representative examples of organocatalytic asymmetric aziridination of α,β–unsaturated aldehydes and ketones using **3** as a nucleophile, see: (a) Pesciaioli, F.; De Vincentiis, F.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew, Chem., Int. Ed.* **2008**, *47*, 8703; (b) Deiana, L.; Zhao, G.-L.; Lin, S.; Dziedzic, P.; Zhang, Q.; Leijonmarck, H.; Córdova, A. *Adv. Synth. Catal.* **2010**, *352*, 3201; (c) De Vincentiis, F.; Bencivenni, G.; Pesciaioli, F.; Mazzanti, A.; Bartoli, G.; Galzerano, P.; Melchiorre, P. *Chem. Asian J.* **2010**, *5*, 1652; (d) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rois, R.; Sun, J.; Córdova, A. *Chem. Eur. J.* **2011**, *17*, 7904; (e) Menjo, Y.; Hamajima, A.; Sasaki, N.; Hamada, Y. *Org. Lett.* **2011**, *13*, 5744.
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13. We also examined the cascade cyclization using a primary alcohol derivative. The reaction was very slow, however, and the target

molecule was obtained in only trace amount. We expected that coordination of the hydroxyl group to the palladium catalyst resulted in the low reactivity.

14. Although prenylation of the vinyl moiety in **19** was investigated using Yang's stepwise method, the desired product was obtained in only 7% yield.

Supplementary Material

Supplementary data associate with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet.

Highlights

The enantioselective formal synthesis of (−)-aurantioclavine was achieved.
The core skeleton was synthesized using a Pd-catalyzed cascade cyclization.
The stereocenter was constructed by a organocatalytic asymmetric aziridination.