OL | Organic Letters

Letter

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

pubs.acs.org/OrgLett

Enantioselective Formal Synthesis of (+)-Cycloclavine and Total Synthesis of (+)-5-*epi*-Cycloclavine

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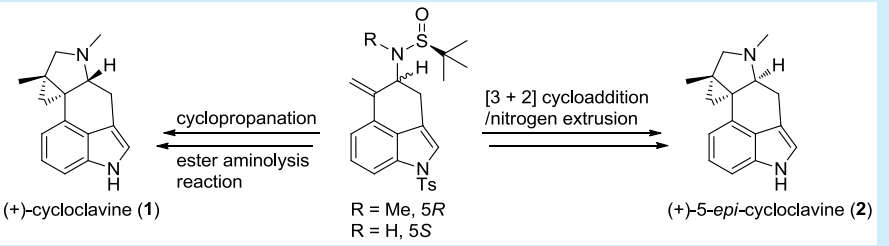
Supporting Information



ABSTRACT: Starting from the commercially available 4-bromoindole, a concise and efficient enantioselective formal synthesis of (+)-cycloclavine (**1**) in 13 steps with 2.0% overall yield and a total synthesis of (+)-5-*epi*-cycloclavine (**2**) in 14 steps with 3.3% overall yield were achieved. Key features of the syntheses include the addition of a Grignard reagent to the C═N/Heck reaction sequence to construct the fused 6−5−6 ring systems, cyclopropanation, an ester aminolysis reaction, and the first example of the construction of a 3-azabicyclo[3,1,0]hexane through an intramolecular [3 + 2] cycloaddition/nitrogen extrusion.

Ergot alkaloids comprise one of the largest classes of indole alkaloids, which are a significant and abundant source of pharmaceuticals.[1] Ergot alkaloids possess the characteristics of 3,4-fused tricyclic indole skeletons. Several typical ergot alkaloids are shown in Figure 1.[2] Cycloclavine was isolated in 1969 from the seeds of *Ipomea hildebrandtii* and was published by Hofmann and coworkers.[3] Cycloclavine is a highly congested polycyclic ring system that contains a cyclopropane moiety. Because of its inspiring architecture and high potency on the serotonin 5-HT_{2C} receptor,[4a] cycloclavine has attracted significant attention from the synthetic community. In 2008, Szántay's group reported the first total synthesis of (±)-cycloclavine, in which intramolecular aldol condensation and cyclopropanation of the tetrasubstituted olefin were employed.[4b] More reports were accomplished by Wipf,[4a,c,h] Brewer,[4d] Opatz,[4f] Bisai,[4i] Dong,[4j] and our group.[4e,g] Of particular note is Wipf's landmark first enantioselective total synthesis of (−)-cycloclavine and (+)-cycloclavine in eight steps by means of a Rh-catalyzed asymmetric allene cyclopropanation and intramolecular Diels−Alder cycloaddition to assemble the fused cycloclavine.[4a,h] In addition, Dong's group disclosed an asymmetric total synthesis of (−)-cycloclavine in 2018.[4j] The key feature included a Pd-catalyzed C−N bond coupling, followed by allylic alkylation, a highly enantioselective Rh-catalyzed C−C activation, and a late stage cyclopropanation of the disubstituted olefin.

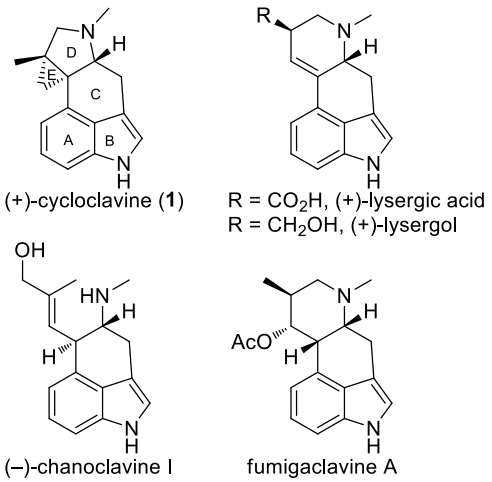


Figure 1. Selected natural ergot alkaloids.

In our previous work, we achieved an efficient formal synthesis of (±)-cycloclavine via an iron-catalyzed aza-Cope−Mannich cyclization and a self-terminating 6-*exo*-*trig* aryl radical-alkene cyclization.[4e] As an extension of this work, we published the first asymmetric synthesis of Szántay's amine utilizing a tandem asymmetrical Barbier-type nucleophilic addition/intramolecular ester aminolysis reaction and Ru-catalyzed isomerization.[4g] Although numerous cyclopropanation strategies in total syntheses have been developed,[5] the cyclopropanation of Szántay's amine presents significant challenges. Rh-catalyzed cyclopropanation and the intramolecular [3 + 2] cycloaddition of olefinic tosylhydrazone

Received: June 12, 2019

DOI: 10.1021/acs.orglett.9b02015
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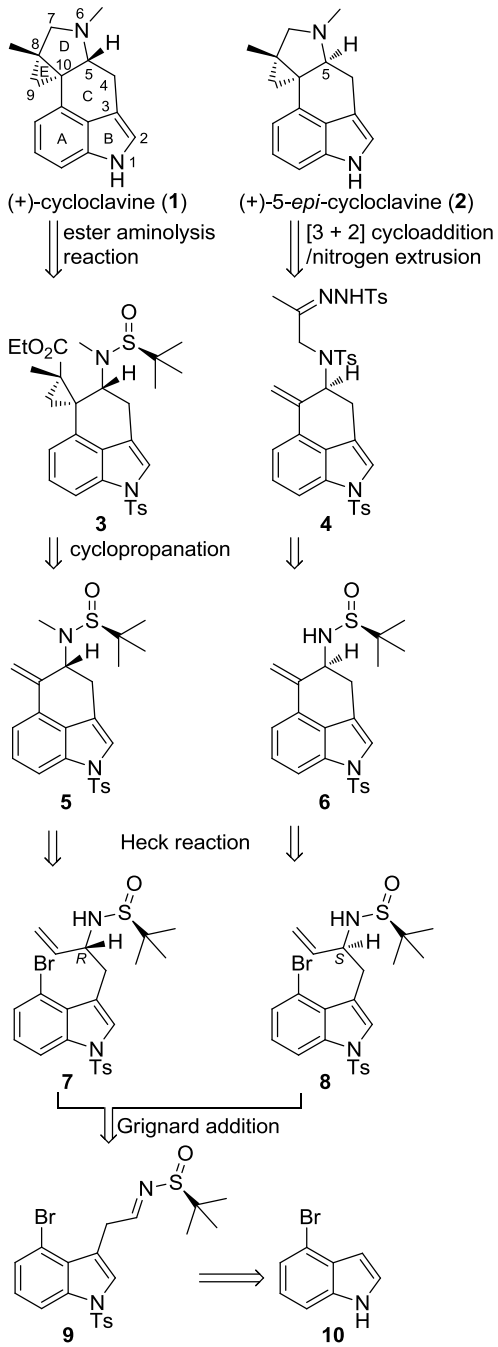
have been used as a key step in the construction of cyclopropane natural product skeletons.[6] With the above method in mind, the retrosynthetic analyses of (+)-cycloclavine (**1**) and (+)-5-*epi*-cycloclavine (**2**) are outlined in Scheme 1. We envisioned that (+)-cycloclavine (**1**) could be

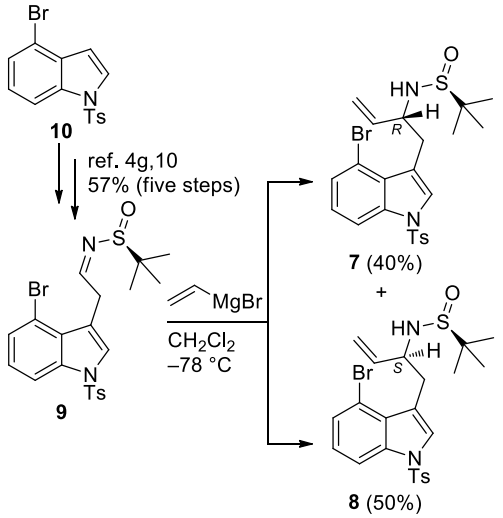
Scheme 1. Retrosynthetic Analyses of (+)-Cycloclavine (1) and (+)-5-*epi*-Cycloclavine (2)



synthesized through ester aminolysis and the reduction of tetracyclic compound **3**.[4a] The ABCE-tetracyclic compound **3** was accomplished from intermediate **5** via Rh-catalyzd cyclopropanation.[7] The fused A−B−C skeleton of disubstituted olefin compound **5** could be built by an intramolecular Heck reaction of **7**. The precursor **7** could be generated by Grignard addition and the methylation of **9**.[8] On the contrary, (+)-5-*epi*-cycloclavine (**2**) could be realized through the ABC-tricyclic olefin compound **4** via an intramolecular [3 + 2] cycloaddition, followed by nitrogen extrusion. The crucial compound **4** was anticipated to be derived from intermediate **6** by a series of functional group manipulations. Compound **6** could be accessed by an intramolecular Heck reaction of chiral compound **8**, which would be further divided in half via asymmetric Grignard addition to deliver the known compound **9** and vinylmagnesium bromide.[9]

We planned to explore the enantioselective synthesis of (+)-cycloclavine (**1**) by utilizing known Ellman (*S*)-*N*-*tert*-butanesulfinyl imine **9**, which was prepared from the commercially available 4-bromoindole **10** in five steps and 57% overall yield by us.[4g,10] Thus chiral imine **9** (>99% ee was determined by chiral HPLC; see the SI, p S39) was prepared by C3-selective allylation, *N*-protection, oxidative cleavage of the double bond, and condensation with (*S*)-2-methylpropane-2-sulfinamide. Then, as outlined in Scheme 2, the treatment of

Scheme 2. Asymmetric Synthesis of Compounds 7 and 8



chiral imine **9** on a 20 g scale with 2 equiv of vinylmagnesium bromide in CH_2Cl_2 for 8 h at −78 °C afforded olefinic sulfenamines **7** and **8** in 40 and 50% yields, respectively. The reaction on a 0.5 g scale gave compounds **8** and **7** with a diastereomeric ratio (dr) of 1.5:1 (see the SI, p S38).

Compound **7** (Scheme 3) was treated with potassium bis(trimethylsilyl)amide (KHMDS), followed by reaction with MeI to afford compound **11** in 80% yield. The desired product **5** by Heck reaction was found in 32% yield, together with the 7-*endo*-*trig* cyclization product in 64% yield (see the SI, p S26), which could be separated by flash column chromatography.[4e−g,i,11] To the best of our knowledge, a Rh-catalyzed cyclopropanation of an alkene with an α-alkyl-α-diazoester has been previously described.[7] Therefore, compound **3** could be constructed by the Rh-catalyzed protocol for the cyclopropanation of compound **5** with ethyl 2-diazopropanoate in CH_2Cl_2 at room temperature in 55% yield with recovered starting material in 27% yield. According to the nuclear Overhauser effect (NOE) experiments (see the SI, p S25), the hydrogen of position five and the hydrogen of the *t*-butanesulfinyl group are a little correlative, and they are far away. Meanwhile the *t*-butanesulfinyl group is in close proximity to the double bond of compound **5** from the back. As shown in ChemBio 3D (see the SI, p S38), cyclo-

DOI: 10.1021/acs.orglett.9b02015
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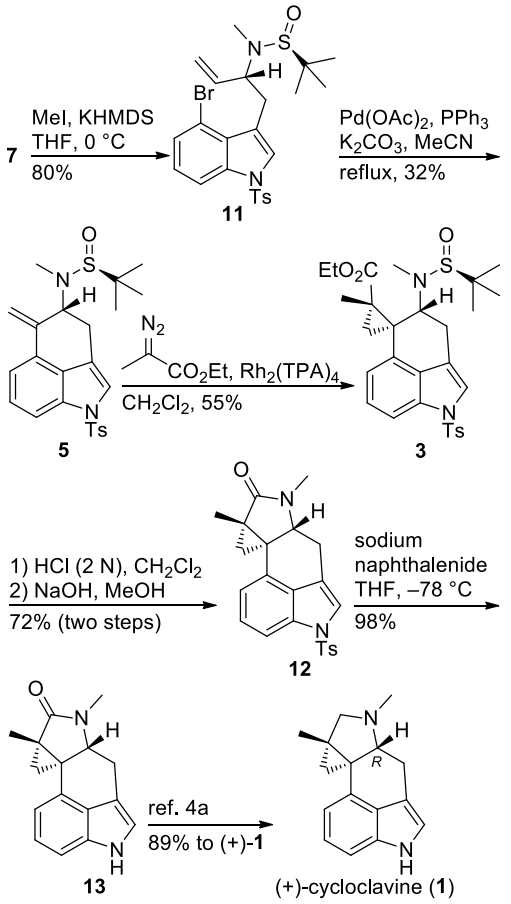
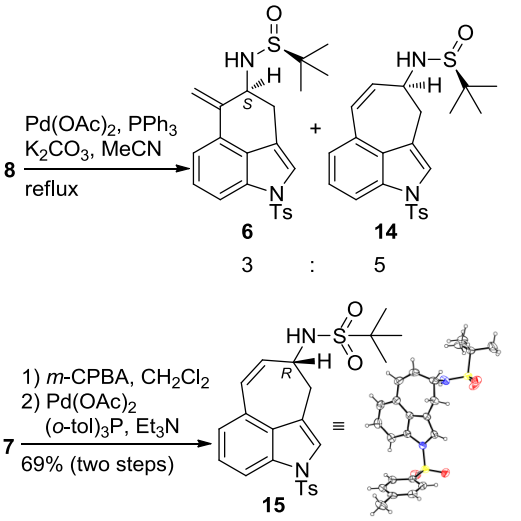
Scheme 3. Asymmetric Synthesis of Compound 13



propanation occurred from the front, less sterically hindered, double bond of compound **5**, leading to good selectivity. Other diastereomers were not detected. Compared with the cyclopropanation strategies that have been previously used in cycloclavine synthesis,[4a−d,h,j] not only did we use an achiral Rh catalyst but also we obtained compound **3** as a single diastereomer. Its stereochemistry was supported by the NOE experiments (see the SI, p S28 and S29). The removal of the *tert*-butylsulfinyl group with 2 N HCl (in MeOH) in CH_2Cl_2 and the subsequent intramolecular ester aminolysis cyclization in MeOH at room temperature led to the formation of lactam **12** in 72% yield by a two-step process without the isolation of any intermediates. The cleavage of the tosyl groups from compound **12** by the treatment with sodium naphthalenide in THF at −78 °C led to compound **13** in 98% yield, which was converted to (+)-cycloclavine (**1**) by reduction by Wipf and coworkers.[4a] The spectroscopic data (^1H and ^{13}C NMR) of (+)-cycloclavine (**1**) were in agreement with the compound reported by Wipf and coworkers (see the SI, p S2).[4a,c]

The intramolecular [3 + 2] cycloaddition reaction could be regarded as a powerful tool for the formation of the cycloclavine core.[6] On the basis of this, we developed a route for the synthesis of (+)-5-*epi*-cycloclavine (**2**) from monosubstituted olefin **8** (Scheme 4). The Heck reaction was previously employed in the cycloclavine synthesis.[4e−g,i] A variety of catalysts ($Pd(OAc)_2$, $Pd(PPh_3)_4$, $Pd_2(dba)_3$) combined with various ligands (PPh_3, $Ph_2PCH_2CH_2PPh_2$) and bases (K_2CO_3, Cs_2CO_3) in the presence of different solvents (MeCN, DMF, THF) were screened for the assembly of the tricyclic skeleton by means of an intramolecular Heck

Scheme 4. Attempted Heck Reaction of Compounds 8 and 7



reaction.[11] To our delight, Heck reaction of the olefin using $Pd(OAc)_2/PPh_3$ and K_2CO_3 in refluxing MeCN gave the products **6** and **14** in a proportion of 3:5, which could not be separated by flash column chromatography (see the SI, p S15). As with the preparation of compound **5** from compound **11**, we hypothesized that the reaction was likely due to its sterically hindered environment, as a bulky *tert*-butylsulfinamide was in close proximity to the olefin, thus favoring the undesired 7-*endo-trig* cyclization product over the 6-*exo-trig* cyclization product, whether the nitrogen was methylated or not. A *m*-CPBA-mediated oxidation reaction of compound **7** yielded a sulfonamide intermediate. Then, the Heck reaction of the sulfonamide intermediate, which used $Pd(OAc)_2$ and $(o\text{-tol})_3P$ in Et_3N at 100 °C, gave the undesired 7-*endo-trig* cyclization product **15** in 69% yield, whose structure was confirmed by single-crystal X-ray diffraction. The C-5 stereochemistry of compound **7** is the same as that of compound **15**. This result indicated that the C-5 stereocenter of compound **8** was in the S configuration because of the opposite configuration at the C-5 position.

Next, the removal of the *tert*-butylsulfinyl group of the inseparable mixture of compounds **6** and **14** with 4 N HCl resulted in the corresponding primary amine products, which were converted without further purification to the corresponding other inseparable sulfamide compounds by treatment with TsCl in the presence of Et_3N in CH_2Cl_2 (Scheme 5). The mixture was allowed to react with bromoacetone in acetone to give the separable product **16**. At this time, we focused our efforts on constructing the critical DE rings. The treatment of ketone **16** with H_2NNHTs and HCl in $MeOH/CH_2Cl_2$ afforded tosylhydrazone **4**. The stage was set for the key installation of the DE rings by an intramolecular [3 + 2] cycloaddition of olefinic tosylhydrazone, along with nitrogen extrusion in a cascading manner. To our delight, the intramolecular formal [3 + 2] cycloaddition reaction of compound **4** went smoothly,[6] and the ABCDE pentacyclic product **17** was achieved as a single isomer in an overall yield of 60% with a trace amount of pyrazoline **18** detected. We think that it is favorable to form a *cis* configuration for the 6−5 highly congested ring system. Thus the cyclopropane is in a *cis* configuration. This is the first example of constructing 3-azabicyclo[3,1,0]hexane by means of an intramolecular [3 + 2]

DOI: 10.1021/acs.orglett.9b02015
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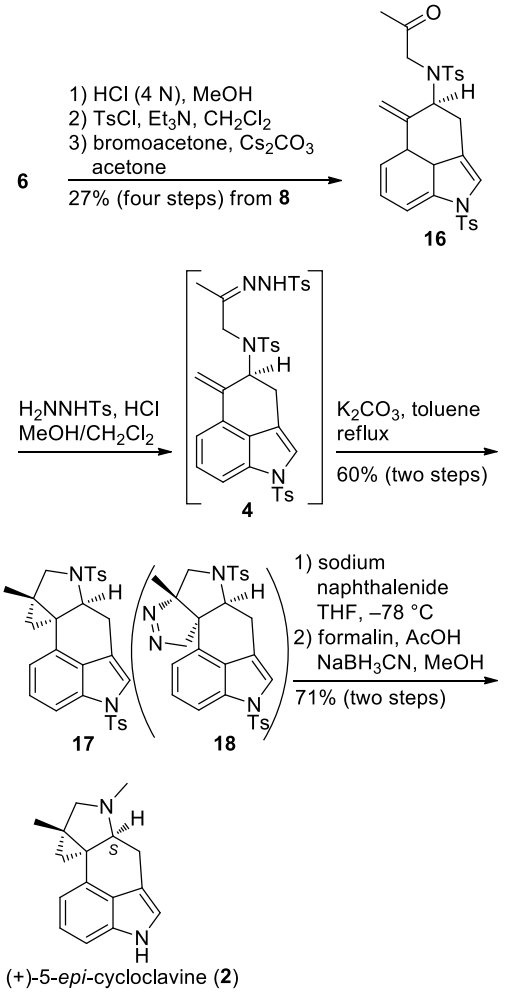
Scheme 5. Asymmetric Synthesis of (+)-5-*epi*-Cycloclavine (2)



cycloaddition reaction. The subsequent cleavage of two tosyl groups of **17** by treatment with sodium naphthalenide in THF at −78 °C and *N*-methylation afforded (+)-5-*epi*-cycloclavine (**2**) in 71% yield (97% ee was determined by chiral HPLC; see the SI, p S40). The spectroscopic data (^{1}H and ^{13}C NMR) of (+)-5-*epi*-cycloclavine (**2**) were consistent with those of (±)-5-*epi*-cycloclavine reported by Wipf (see the SI, p S5).[4c]

In summary, the enantioselective formal synthesis of (+)-cycloclavine (**1**) in 13 steps with 2.0% overall yield and the total synthesis of (+)-5-*epi*-cycloclavine (**2**) in 14 steps in 3.3% overall yield were accomplished from the commercially available 4-bromoindole. The key steps in the formal synthesis of (+)-cycloclavine (**1**) included an addition reaction of a Grignard reagent, an intramolecular Heck reaction, cyclopropanation, and an ester aminolysis reaction. Two *cis*-configured all-carbon quaternary chiral centers of (+)-5-*epi*-cycloclavine (**2**) were constructed by means of an intramolecular [3 + 2] cycloaddition reaction of olefinic tosylhydrazone, followed by nitrogen extrusion. Further investigation of the use of analogous strategies toward the total synthesis of other ergot alkaloids is in progress in our laboratory, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02015.

^{1}H and ^{13}C NMR spectra for compounds (**7**, **8**, **11**, **5**, NOE spectra of **5**, **7-*endo*-trigcyclization product**, **3**, NOE spectra of **3**, **12**, **13**, **1**, **15**, **16**, **18**, and **2**) along with X-ray crystallographic data for **15** and HPLC spectra of **2** and **9** (PDF)

Accession Codes

CCDC 1882003 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This paper is dedicated to Lanzhou University on the occasion of its 110th anniversary. We are grateful for financial support from the National Natural Science Foundation of China (21572085, 21272098, and 21572086); the Program for Changjiang Scholars and Innovative Research Team in University (PCSIRT: IRT_15R28), the Fundamental Research Funds for the Central Universities (FRFCU: lzujbky-2016-ct02), and the 111 Project of MOE (111-2-17). We thank Yong-Liang Shao of Lanzhou University for X-ray crystallographic analyses.

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DOI: 10.1021/acs.orglett.9b02015
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