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Total Syntheses of Festuclavine, Pyroclavine, Costaclavine, *epi*-Costaclavine, Pibocin A, 9-Deacetoxyfumigaclavine C, Fumigaclavine G, and Dihydrosetoclavine

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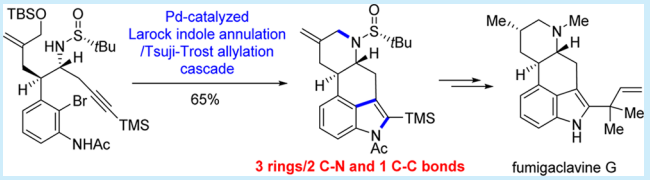
Supporting Information

ABSTRACT: A new approach for the divergent total synthesis of eight ergot alkaloids is reported. The approach allows the first total syntheses of pyroclavine, pibocin A, 9-deacetoxyfumigaclavine C, and fumigaclavine G and also enables the efficient synthesis of festuclavine, costaclavine, *epi*-costaclavine, and dihydrosetoclavine. The main feature of the synthesis is the use of an unprecedented Pd-catalyzed intramolecular Larock indole annulation/Tsuji−Trost allylation cascade to assemble the tetracyclic core in one step.



The ergot alkaloids produced by the fungus *Claviceps purpurea* are a diverse class of indole natural products with a broad spectrum of potent pharmacological activities (Figure 1).[1] They are among the most important groups of natural products since many of them are important pharmaceuticals and are also recognized as important natural toxins in human history. To date, two natural alkaloids and nine semisynthetic derivatives such as pergolide and cabergoline have been used clinically for the treatment of migraines, Parkinson's disease, and other ailments.[2] Structurally these molecules have a unique tetracyclic ergoline skeleton containing several chiral centers of various configurations. As a result, since the first total synthesis of lysergic acid by Woodward in 1956,[3] the total synthesis of the ergot alkaloids has been the subject of extensive study over the last six decades.[4,5] Interestingly, despite the many successful synthetic approaches already reported, recent efforts have shifted toward devising innovative and elegant approaches to construct the C/D rings or B/C rings in one step, thus improving their synthetic efficiency.[5a,b,e,f,j,l,m] However, no approach to construct the B/C/D rings in one step has been reported yet.

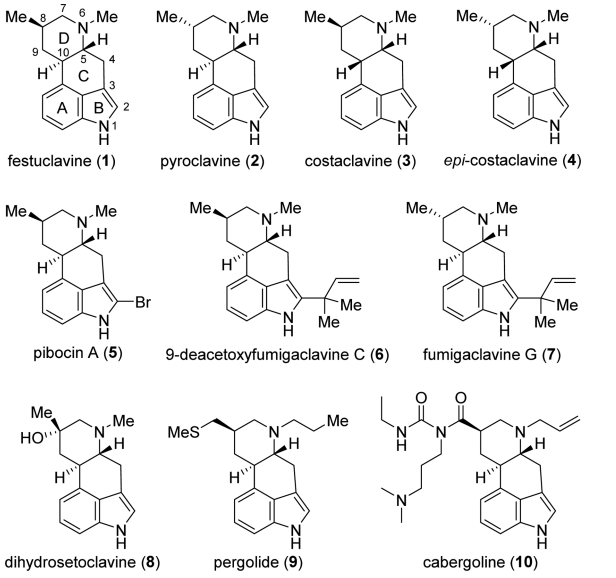


Figure 1. Structures of ergot alkaloids, pergolide, and cabergoline.

As part of our ongoing studies toward the concise and efficient synthesis of 3,4-indole alkaloids,[6] we have recently developed a novel strategy for the construction of 3,4-fused indoles and benzofurans through a palladium-catalyzed intramolecular Larock annulation.[7] We initiated further studies to demonstrate the utility of this method and facilitate the preparation of ergot alkaloid analogues bearing deep-seated structural changes and not readily accessible by conventional approaches.

Herein, we report an unprecedented palladium-catalyzed intramolecular Larock indole annulation/Tsuji−Trost allylation cascade, which allowed the assembly of the B/C/D rings of ergot alkaloids in one step and enabled the expedient synthesis of the advanced common intermediate. This approach could be used for the efficient and divergent total syntheses of festuclavine (**1**),[8,9] pyroclavine (**2**),[10,9c,d,11] costaclavine (**3**),[10,9a,b,12] *epi*-costaclavine (**4**),[12a,b] pibocin A (**5**),[13] 9-deacetoxyfumigaclavine C (**6**),[14] fumigaclavine G (**7**),[15] and dihydrosetoclavine (**8**) via late-stage manipulations.[16,17]

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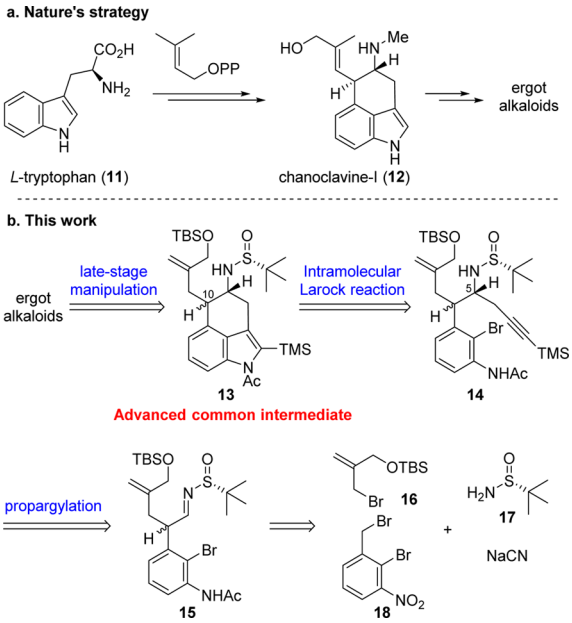
The biosynthesis of ergot alkaloid starts with the prenylation of L-tryptophan (**11**) followed by a series of transformations to give chanoclavine-I (**12**), which is the advanced common biosynthetic precursor of all ergot alkaloids.[18] Inspired by the biosynthetic sequence, we envisioned that the ergot alkaloids could be divergently synthesized from the advanced common intermediate **13** (relative to **12**) by late-stage manipulations (Scheme 1). Since both 10*R* and 10*S* configurations of natural

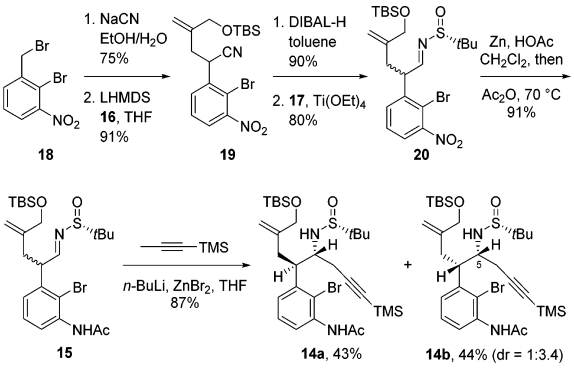
Scheme 1. Retrosynthetic Analysis



products are found in ergot alkaloids, two diastereoisomers of **13** at C(10) are welcomed. The tricycle **13** would be readily assembled by a Pd-catalyzed intramolecular Larock indole annulation of **14**.[7] The chemoselectivity of carbapalladation of acetylene versus olefin posed a significant challenge at this step.[19] The stereogenic center (5*R*) of **14** at the propargylic position, which was required and fixed in all the natural ergot alkaloids, was introduced by propargylation of chiral *N*-*tert*-butylsulfinylimine **15**.[20] In turn, **15** could be readily obtained from commercially available or known compounds.

Our synthesis commenced with bromide **18**, which was prepared in one step from commercially available 2-bromo-1-methyl-3-nitrobenzene following the reported procedure (Scheme 2).[21] Cyanidation of bromide **18** with NaCN followed

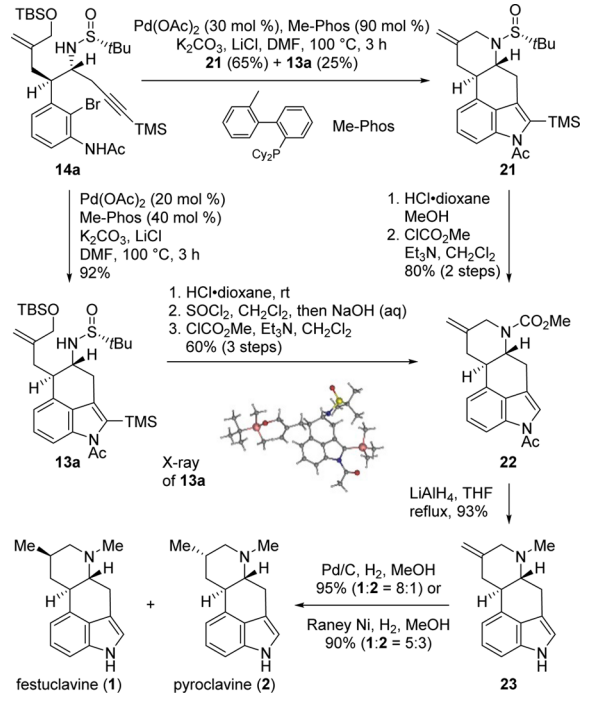
Scheme 2. Synthesis of Cyclization Precursors 14



by alkylation of the corresponding nitrile with the known allylic bromide **16** furnished **19**. Reduction of nitrile **19** with DIBAL-H followed by condensation of the resulting aldehyde with (S_R)-*N*-*tert*-butanesulfinamide (**17**) afforded a mixture of two inseparable diastereoisomers of **20** (dr = 1:1) in 80% yield. Reduction of **20** with Zn/HOAc followed by acetylation of the corresponding aniline with Ac_2O provided inseparable acetanilide **15** in 91% overall yield. Propargylation of *N*-*tert*-butylsulfinylimine **15** with 1-(trimethylsilyl)allenylzinc bromide proceeded smoothly to afford the homopropargylic amines **14a**,**b** and its C5 diastereoisomer in excellent overall yield (dr = 1:3.4).[20] The absolute configurations of **14a** and **14b** were determined by X-ray crystallographic analysis of downstream product or after completion of the synthesis of ergot alkaloids (vide infra).

With the desired cyclization precursors **14** in hand, the intramolecular Pd-catalyzed Larock indole annulation of **14a** was performed under our optimized catalyst system ($Pd(OAc)_2$ and Me-phos at 100 °C), giving the desired tricyclic indole **13a** in 92% yield (Scheme 3). The structure of **13a** was unequivocally

Scheme 3. Total Synthesis of Festuclavine and Pyroclavine



confirmed by X-ray crystallographic analysis.[22] Surprisingly, when the reaction was run on a gram scale, an unexpected tetracyclic compound **21** was isolated in a small amount. Compound **21** was produced most likely from Tsuji–Trost allylation of tricyclic indole **13a**.[23] To gain insights into such unprecedented reactions, the indole **13a** was subjected to the aforementioned reaction conditions. The allylation reaction did occur, and **21** was formed in 50% yield with recovery of **13a** in 35% yield. This result implied that **13a** was indeed the cyclization precursor of **21**, and an unprecedented Pd-catalyzed intramolecular Larock indole annulation/Tsuji–Trost allylation cascade occurred for **14a**. *Most importantly, this cascade reaction constructs three rings, two C–C bonds, and one C–N bond in one step, forming the tetracyclic skeleton of ergot alkaloids.* Since compound **21** could be used as the advanced intermediate to

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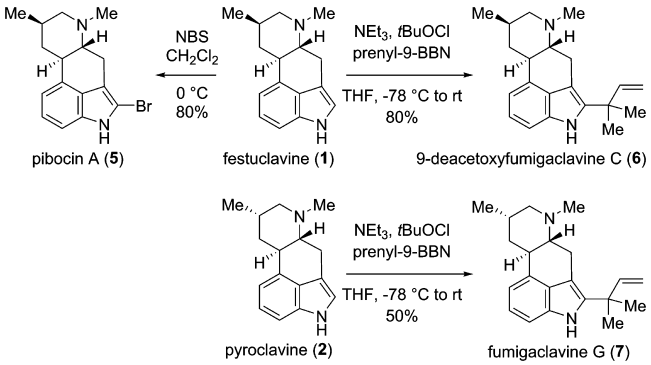
streamline the synthesis and shorten the synthetic route, further optimization of the cascade reaction of **14a** to improve the yield of **21** was investigated. Considering the Tsuji–Trost allylation also needs Pd catalyst and ligand, the optimal ratios of Pd catalyst and ligand were examined. When the reaction was conducted with 0.3 equiv of $Pd(OAc)_2$ and 0.9 equiv of Me-phos, the desired **21** was obtained in 65% yield accompanied by 25% of **13a**. An extensive literature search did not show any report on the use of such a TBS-protected allylic alcohol for the Tsuji–Trost reaction. Thus, this unprecedented Tsuji–Trost reaction of TBS-protected allylic alcohol to form a piperidine ring is reported for the first time.

Having constructed the requisite tetracyclic basic skeleton **21**, we sought to complete the synthesis of festuclavine (**1**) and pyroclavine (**2**) (Scheme 3). Removal of the *tert*-butanesulfinyl group and subsequent *N*-protection of the resulting secondary amine with $ClCO_2Me$ gave carbamate **22** in 80% overall yield. In addition, tricyclic indole **13a** could be also converted to **22** in a three-step sequence by removal of the silyl group and *tert*-butanesulfinyl group with HCl, chlorination of the resulting free hydroxyl group with $SOCl_2$ followed by treatment with NaOH, and subsequent N protection of the secondary amine. Reduction of the carbamate **22** with $LiAlH_4$ gave the desired olefin **23** in 93% yield. Finally, selective reduction of the olefin **23** with 5% Pd/C afforded **1** and **2** in 95% yield in a ratio of 8:1. In addition, reduction of the olefin **23** with Raney Ni furnished the target molecules **1** and **2** in 90% yield with a ratio of 5:3. The physical data of our synthesized products **1** and **2** are identical to those reported in the literature.[8−11] Thus, we have achieved the first asymmetric total synthesis of festuclavine and pyroclavine.

After the synthesis of **1** and **2**, we investigated the synthesis of pibocin A (**5**), 9-deacetoxyfumigaclavine C (**6**), and fumigaclavine G (**7**) by direct functionalization of **1** and **2** (Scheme 4).

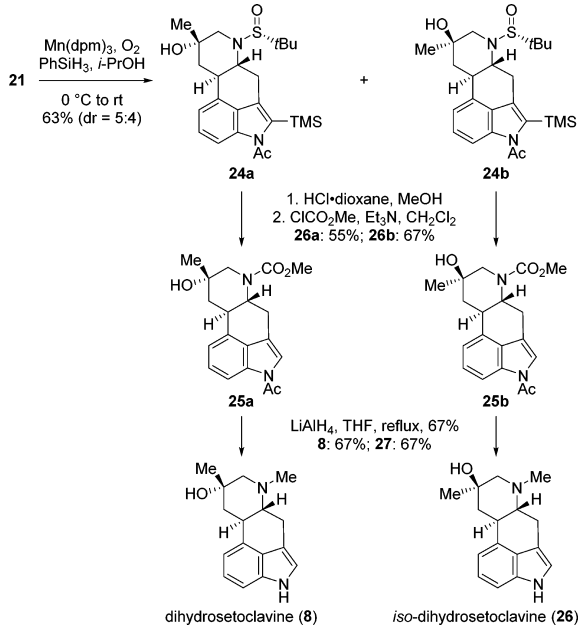
Scheme 4. Total Synthesis of Pibocin A, 9-Deacetoxyfumigaclavine C, and Fumigaclavine G



Chemoselective bromination of the 2-position of **1** with NBS provided pibocin A (**5**) in 80% yield. The synthesis of 9-deacetoxyfumigaclavine C (**6**) and fumigaclavine G (**7**) from **1** and **2** by formation of the C-2 reverse prenylated indole was carried out following the excellent procedure established by Danishefsky and co-workers.[24] Thus, chlorination of **1** with *t*BuOCl followed by treatment with prenyl-9-BBN in the presence of Et_3N provided 9-deacetoxyfumigaclavine C (**6**) in 80% yield. In the same manner, **2** was transformed to target molecule **7** in 50% yield. The physical data of our synthesized products **5**–**7** are identical to those reported in the literature.[13−15] Thus, we have achieved the first total synthesis of **5**–**7**.

Having successfully completed the total synthesis of **1**, **2**, and **5**–**7**, we next turned to the synthesis of dihydrosetoclavine (**8**) (Scheme 5). Initial attempts to the direct hydrofunctionalization

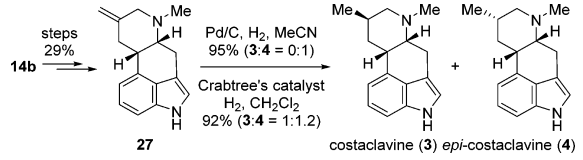
Scheme 5. Total Syntheses of Dihydrosetoclavine and Isodihydrosetoclavine



of advanced intermediate **22** under a variety of conditions failed. We thought that carbamate might affect this reaction.[25] Thus, hydrofunctionalization of **21** with $Mn(dpm)_3$ was further examined.[25b] This reaction proceeded smoothly and gave the desired alcohol **24a** accompanied by its diastereoisomer **24b** in 35% and 28% yield, respectively. Removal of the *tert*-butanesulfinyl group in **24a** and subsequent *N*-protection of the resulting secondary amine with $ClCO_2Me$ gave carbamate **25a** in 55% overall yield. Finally, reduction of **25a** with $LiAlH_4$ furnished the target molecule **8** in 67% yield. Using the same procedure as described for **24a**, **24b** was converted to isodihydrosetoclavine (**26**).

Having successfully completed the total synthesis of **1**, **2**, and **5**–**8** from intermediate **14a**, we then conducted the transformation of **14b** into **3** and **4** following the same sequence as described for **14a** (Scheme 6). Compound **14b** could be

Scheme 6. Total Syntheses of Costaclavine and *epi*-Costaclavine



smoothly converted to teracycle **27**. Finally, hydrogenation of the exocyclic C=C bond with Pd/C or Raney Ni in a variety of conditions gave *epi*-costclavine (**4**) as the sole product, but reduction with Crabtree's catalyst provided **3** and **4** in 92% with a ratio of 1:1.2.[26]

In summary, we have developed a unified strategy for the enantioselective synthesis of ergot alkaloids and accomplished the total syntheses of festuclavine (**1**), pyroclavine (**2**),

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costaclavine (**3**), *epi*-costaclavine (**4**), pibocin A (**5**), 9-deacetoxyfumigaclavine C (**6**), fumigaclavine G (**7**), and dihydrosetoclavine (**8**) in a collective manner. Among them, the total syntheses of **1** and **5**−**7** were achieved for the first time. The significant feature of this strategy is the tetracyclic skeleton of the ergot alkaloids are rapidly and efficiently constructed through an unprecedented Pd-catalyzed intramolecular Larock indole annulation/Tsuji−Trost allylation cascade.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01504.

Full experimental procedures and ^{1}H and ^{13}C NMR spectra of compounds **1**−**8**, **13**−**15**, and **19**−**27** (PDF)

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Notes

The authors declare no competing financial interest.

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