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Asymmetric Synthesis of Lysergic Acid via an Intramolecular (3+2) Dipolar Cycloaddition/Ring-Expansion Sequence

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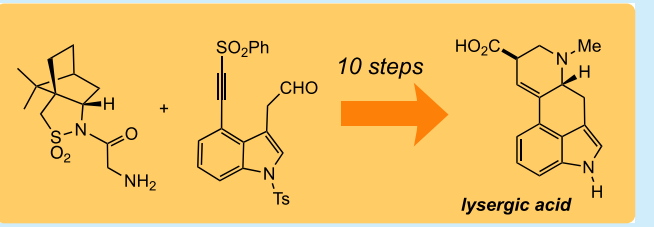
ABSTRACT: An effective, potentially scalable asymmetric synthesis of lysergic acid, a core component of the ergot alkaloid family, is reported. The synthesis features the strategic combination of an intramolecular azomethine ylide cycloaddition and Cossy−Charette ring expansion to assemble the target's C- and D-rings. Simple functional group manipulation produced a compound that had been converted to lysergic acid in four steps, thus constituting a formal synthesis of the natural product. The strategy may be used to prepare novel ergot analogues that include unnatural antipodes and may be more amenable to analogue generation relative to prior approaches.



The ergot alkaloid family is a rich source of bioactive natural products that is produced by *Claviceps* fungi.[1,2] Many of these natural products serve as drugs themselves or provide a starting point for the development of semisynthetic analogues. Although humankind's first experience with ergot alkaloids was probably negative (ergot poisoning resulting from eating moldy rye), ergot alkaloids can be used to treat a variety of human diseases. They are particularly useful for the treatment of neurological disorders such as Parkinson's disease, migraine headaches, and senile dementia and certain psychological conditions. Two examples of ergot alkaloids are shown in Figure 1, ergotamine (a naturally occurring ergot alkaloid used to treat migraines) and LSD (a synthetic compound known for its illicit recreational use but now being evaluated as a treatment for anxiety, depression, and addiction). Lysergic acid (Scheme 1) is a core constituent of these drugs. Although it is available on an industrial scale via hydrolysis of naturally occurring peptidic ergot alkaloids, this chiral tetracyclic molecule has remained a popular synthetic target ever since Woodward first reported its total synthesis in 1954.[3] It has been used to showcase both synthetic methodology and synthetic strategy. Seven of the resulting syntheses have delivered this natural product in enantiomerically pure form.[4−11] Herein, we report a novel asymmetric synthesis of lysergic acid.

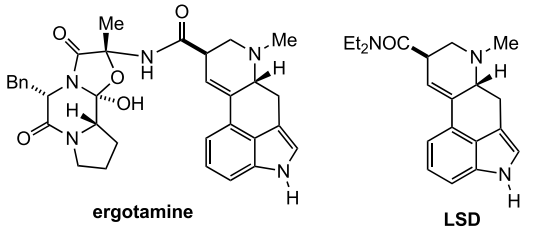
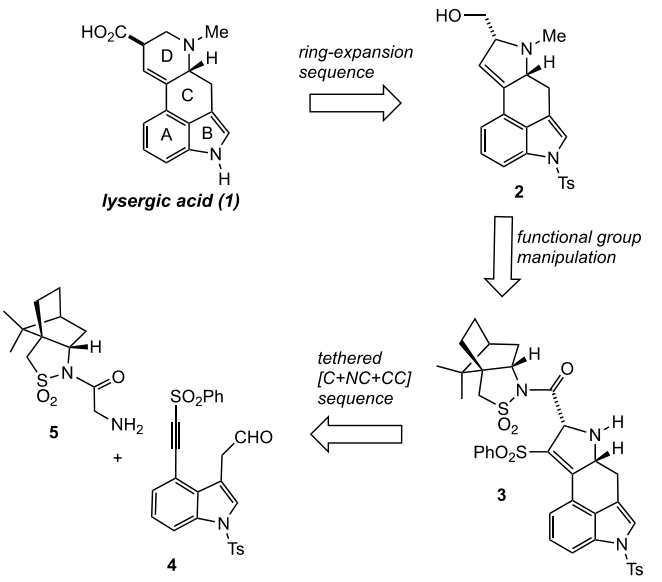


Figure 1. Structures of two representative ergot alkaloids.

Scheme 1. Retrosynthetic Plan



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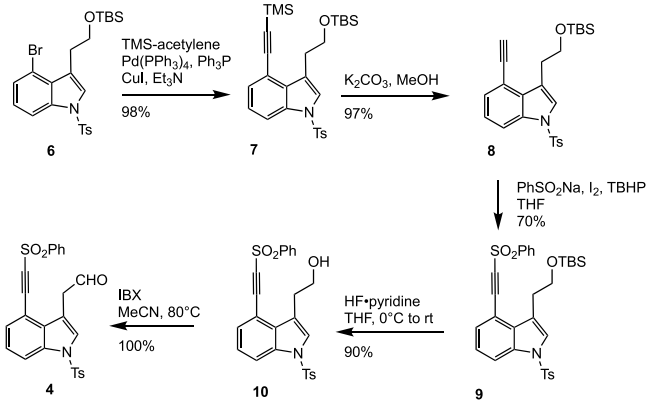
Our retrosynthetic analysis is shown in Scheme 1. The synthesis of **1** features the strategic use of two key reactions: an intramolecular azomethine ylide cycloaddition[12] that may also be described as a tethered asymmetric [C+NC+CC] cycloaddition paired with the ring expansion of a functionalized pyrroline to construct the target's C- and D-rings. The asymmetric [C+NC+CC] cycloaddition is a robust multicomponent reaction that enables the synthesis of highly functionalized pyrrolidines in enantiomerically pure form via the staged one-pot combination of an aldehyde (C-component), a chiral glycylsultam (NC-component), and a dipolarophile (CC-component) (a brief overview of this multicomponent reaction is provided in the Supporting Information). This application of the asymmetric [C+NC+CC] cycloaddition using an alkyne dipolarophile not only provides an enantiomerically pure pyrroline (the D-ring precursor) but also installs a synthetic handle for the subsequent ring-expansion reaction.

Significantly, the plan allows for potential structural modification of the ergoline core that would expand ergot alkaloid structural space. For example, the C-ring may be enlarged by simply modifying the tether connecting the "C" and "CC" components. Our strategy may also be applied to the synthesis of the antipode of **1** and related analogues. Such deep-seated variation in molecular structure is not found in the natural ergot alkaloids. The resulting diversification of three-dimensional structure space could prove useful for targeting specific receptor subtypes employing fragment-based drug design strategies. The use of an intramolecular azomethine ylide cycloaddition to construct the C-ring and (pre)D-ring of **1** was inspired by Brewer's synthesis of (±)-cycloclavine.[13] The ring-expansion reaction finds precedent in the work of Cossy[14] and Charette.[15]

The synthesis of **1** began with the known[16] trisubstituted indole **6** (Scheme 2), itself prepared in five steps from

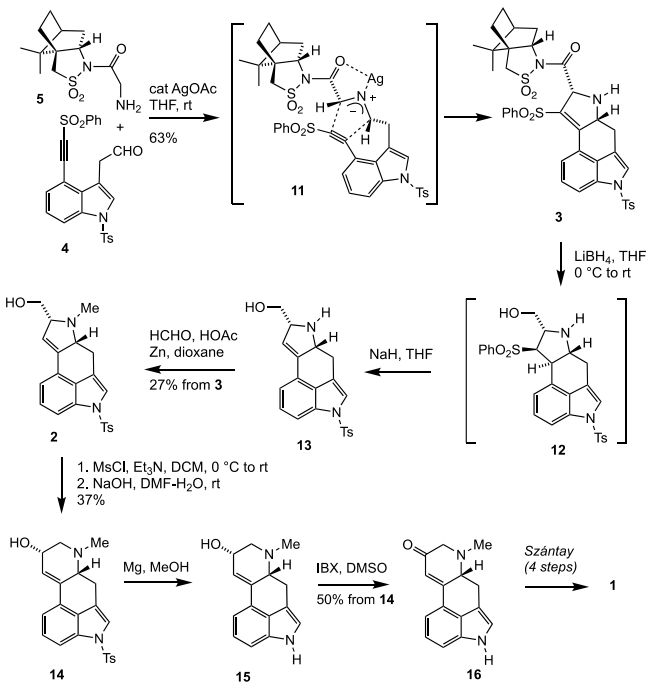
Scheme 2. Synthesis of Disubstituted Indole 9



commercially available 4-bromoindole (Supporting Information). Sonogashira coupling of trimethylsilyl acetylene and aryl bromide **6** gave alkyne-substituted indole **7** in excellent yield. Removal of the trimethylsilyl group produced terminal acetylene **8**, which reacted with the *in situ*-generated phenylsulfonyl radical to produce alkynyl sulfone **9**.[17] The sulfone moiety serves to activate the alkyne for the dipolar cycloaddition but is readily removed afterward. This three-step route from **6** to **9** was necessitated by the reluctance of **6** to couple directly with ethynyl phenyl sulfone. Removal of the TBS protecting group followed by oxidation of primary alcohol **10** using 2-iodoxybenzoic acid (IBX) gave aldehyde **4**, which served as the CC−tether−C construct. The overall yield of **4** from **6** was 60%.

Assembly of the ergoline structure (Scheme 3) commenced with the Ag(I)-catalyzed reaction of **4** and **5** to give

Scheme 3. Asymmetric Synthesis of Lysergic Acid



cycloadduct **3** in good yield on a multigram scale. On the basis of our prior experience, this reaction was expected to proceed through concerted pre-TS **11**. It is unlikely that a stepwise Michael addition/Mannich ring closure is involved because the observed regioselectivity would be disfavored in that case. The structure of **3** was confirmed by extensive NMR analysis of intermediate **12** (see the Supporting Information) as well as the eventual correlation with lysergic acid (**1**). It is worth noting that attempted cycloaddition using an alkynyl aldehyde structurally related to **4** but lacking the activating sulfonyl group failed. Treatment of **3** with lithium borohydride resulted in reductive removal of the auxiliary as well as conjugate reduction of the α,β-unsaturated sulfone to give a mixture of saturated sulfone **12** along with elimination product **13**. Intermediate **12** could be converted to **13** by treating the crude product with sodium hydride. The sulfonyl group thus not only activates the dipolarophile but also enables installation of the target's double bond. Presumably, both the conjugate reduction and sulfinate elimination reaction proceed with the help of the hydroxyl moiety. The removal of the sulfone group under nonreducing conditions was crucial because it allowed the retention of the toluenesulfonyl indole protecting group. At this point, the pyrroline was N-methylated via reductive amination to give β-aminoalcohol **2** in 27% overall yield from cycloadduct **3** (an average of 65% yield for each operation). Because the protons α to the acylsultam and γ to the sulfone in **3** are potentially epimerizable, we decided to assess the enantiomeric purity of **2**. The enantiomer of **2** (*ent*-**2**) was prepared by the same sequence of reactions but using *ent*-**5** as the NC component.

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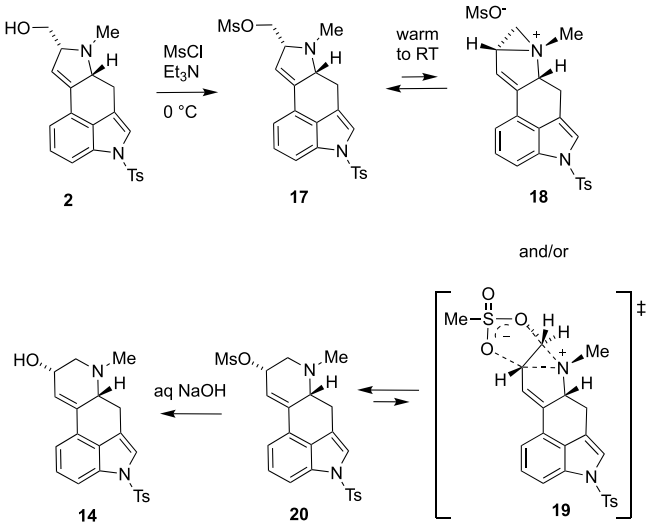
Chiral HPLC showed these antipodes to be >99% pure (see the Supporting Information).

Treatment of **2** with methanesulfonyl chloride followed by exposure to aqueous NaOH produced ring-expanded secondary alcohol **14**. The structure of this compound was based on NMR coupling data and conformational analysis (see the Supporting Information). The details of this pivotal transformation deserve further comment (Scheme 4). Mesylation of

Scheme 4. Proposed Ring-Expansion Mechanism



2 at 0 °C resulted in the clean formation of primary mesylate **17**, which appeared to be relatively stable at this temperature. However, when the compound was warmed to rt, a rapid equilibrium between **17** and **20** was established [followed by NMR (see the Supporting Information)], favoring **20**. On the basis of a literature precedent,[18] we believe that the rearrangement proceeds through aziridinium **18** or synchronized transition state **19**. Alkaline hydrolysis of the crude product resulted in alcohol **14**. The fact that mesylate hydrolysis occurred with retention of configuration suggests the intermediacy of **18**. It is also possible that hydroxide attacks the sulfonyl moiety in **20**.

Reductive removal of the indole protecting group (Mg/MeOH) gave compound **15**. Oxidation of the allylic alcohol to produce the enone proved to be delicate, presumably due to overoxidation leading to a 3-oxidopyridinium species.[19] However, IBX/DMSO cleanly produced the desired enone **16**, a compound that Szántay and co-workers had converted to lysergic acid (**1**) in four steps utilizing the van Leusen reaction.[4] Our NMR data for **16** matched those reported by Szántay (see the Supporting Information), thus constituting a formal synthesis of **1**.

The asymmetric synthesis of lysergic acid (**1**) described herein proceeds in 20 steps from commercially available 4-bromoindole (11 steps from keystone cycloadduct **3**). It extends the utility of the asymmetric [C+NC+CC] cycloaddition and features a novel application of the Cossy–Charette ring expansion. The strategic combination of a (3+2) dipolar cycloaddition and Cossy–Charette ring expansion may be more amenable to analogue generation relative to prior approaches. This synthesis of lysergic acid paves the way for the exploration of novel three-dimensional ergot alkaloid structural space that includes unnatural antipodes.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c02337.

General experimental information, detailed procedures, and NMR and MS data (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Schiff, P. L., Jr. Ergot and Its Alkaloids. *Am. J. Pharm. Educ.* **2006**, *70*, 98.

(2) Liu, H.; Jia, Y. Ergot Alkaloids: Synthetic Approaches to Lysergic Acid and Clavine Alkaloids. *Nat. Prod. Rep.* **2017**, *34*, 411−432.

(3) Kornfeld, E. C.; Fornefeld, E. J.; Kline, G. B.; Mann, M. J.; Jones, R. G.; Woodward, R. B. The Total Synthesis of Lysergic Acid and Ergonovine. *J. Am. Chem. Soc.* **1954**, *76*, 5256−5257.

(4) Moldvai, I.; Temesvári-Major, E.; Incze, M.; Szentirmay, É.; Gács-Baitz, E.; Szántay, C. Enantioefficient Synthesis of α-Ergocryptine: First Direct Synthesis of (+)-Lysergic Acid. *J. Org. Chem.* **2004**, *69*, 5993−6000.

(5) Inoue, T.; Yokoshima, S.; Fukuyama, T. Synthetic Studies toward (+)-Lysergic Acid: Construction of the Tetracyclic Ergoline Skeleton. *Heterocycles* **2009**, *79* (C), 373−378.

(6) Kurokawa, T.; Isomura, M.; Tokuyama, H.; Fukuyama, T. Synthesis of Lysergic Acid Methyl Ester via the Double Cyclization Strategy. *Synlett* **2009**, *2009*, 775−778.

(7) Inuki, S.; Iwata, A.; Oishi, S.; Fujii, N.; Ohno, H. Enantioselective Total Synthesis of (+)-Lysergic Acid, (+)-Lysergol, and (+)-Isolysergol by Palladium-Catalyzed Domino Cyclization of Allenes Bearing Amino and Bromoindolyl Groups. *J. Org. Chem.* **2011**, *76*, 2072−2083.

(8) Iwata, A.; Inuki, S.; Oishi, S.; Fujii, N.; Ohno, H. Formal Total Synthesis of (+)-Lysergic Acid via Zinc(II)-Mediated Regioselective Ring-Opening Reduction of 2-Alkynyl-3-Indolyloxirane. *J. Org. Chem.* **2011**, *76*, 5506−5512.

(9) Umezaki, S.; Yokoshima, S.; Fukuyama, T. Total Synthesis of Lysergic Acid. *Org. Lett.* **2013**, *15*, 4230−4233.

https://doi.org/10.1021/acs.orglett.1c02337
Org. Lett. XXXX, XXX, XXX−XXX

(10) Liu, Q.; Jia, Y. Total Synthesis of (+)-Lysergic Acid. *Org. Lett.* **2011**, *13*, 4810−4813.
(11) Liu, Q.; Zhang, Y. A.; Xu, P.; Jia, Y. Total Synthesis of (+)-Lysergic Acid. *J. Org. Chem.* **2013**, *78*, 10885−10893.
(12) Coldham, I.; Hufton, R. Intramolecular Dipolar Cycloaddition Reactions of Azomethine Ylides. *Chem. Rev.* **2005**, *105*, 2765−2809.
(13) Jabre, N. D.; Watanabe, T.; Brewer, M. Formal and Total Synthesis of (±)-Cycloclavine. *Tetrahedron Lett.* **2014**, *55*, 197−199.
(14) Métro, T. X.; Gomez Pardo, D.; Cossy, J. Highly Enantioselective Synthesis of Linear β-Amino Alcohols. *Chem. - Eur. J.* **2009**, *15*, 1064−1070. See also: Chavan, S. P.; Kawale, S. A.; Pisal, M. M.; Kadam, A. L.; Gonnade, R. G. Formal Synthesis of (−)-Quinagolide: Diastereoselective Ring Expansion via a Bicyclic Aziridinium Ion Strategy to Access the Octahydrobenzo[g]Quinoline Architecture. *J. Org. Chem.* **2021**, *86*, 9344−9352.
(15) Jarvis, S. B. D.; Charette, A. B. Synthesis of Enantiopure Substituted Piperidines via an Aziridinium Ring Expansion. *Org. Lett.* **2011**, *13*, 3830−3833.
(16) Zuo, Z.; Ma, D. Enantioselective Total Syntheses of Communesins A and B. *Angew. Chem., Int. Ed.* **2011**, *50*, 12008−12011.
(17) Meesin, J.; Katrun, P.; Pareseecharoen, C.; Pohmakotr, M.; Reutrakul, V.; Soorukram, D.; Kuhakarn, C. Iodine-Catalyzed Sulfonylation of Arylacetylenic Acids and Arylacetylenes with Sodium Sulfinates: Synthesis of Arylacetylenic Sulfones. *J. Org. Chem.* **2016**, *81*, 2744−2752.
(18) Picq, D.; Cottin, M.; Anker, D.; Pacheco, H. Transposition de l'atome d'azote de Dialkylaminopentopyranosides; Mise En Evidence de Sels d'aziridinium Intermediaires. *Tetrahedron* **1983**, *39*, 1797−1801.
(19) Szantay, C.; Moldvai, I.; Gacs-Baitz, E.; Termesvari-Major, E.; Incze, M.; Poppe, L. Chemistry of Indoles Carrying a Basic Function. Part IX. Unexpected Cyclizations of Diketones Derived from Uhle's Ketone. *Heterocycles* **2004**, *64*, 153−175.

https://doi.org/10.1021/acs.orglett.1c02337
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