Synthesis of Lysergic Acid Methyl Ester via the Double Cyclization Strategy

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Abstract: An asymmetric synthesis of (+)-lysergic acid methyl ester was accomplished through construction of the tetracyclic ergoline skeleton by double cyclization consisting of intramolecular aromatic amination and Heck reaction.

Key words: allylations, aminations, Heck reaction, tandem reaction, alkaloids

Ergot alkaloids are a pharmacologically highly important class of natural products, since they possess a wide spectrum of biological activities.[1] Currently, a variety of synthetic analogues have been clinically used as a vasodilator, a prolactin inhibitor, an anti-Parkinsonian, and other therapeutics to mention a few. These compounds have been attractive targets for synthetic chemists because of the unique tetracyclic ergoline skeleton containing a tetrahydropyridine and a [*cd*]-fused indole.[2] Among ergot alkaloids, lysergic acid (**1**) is pivotal for the synthesis of variety of its congeners, and numerous synthetic approaches have been reported to date (Figure 1).[3] After the first total synthesis of racemic **1** by Woodward and Kornfeld,[4a] nine total syntheses have so for been achieved[4b–4k] including the one in optically active form by Szántay using optical resolution of a racemic intermediate.[4k] A crucial issue to be addressed in an optically active synthesis of **1** should be stereoselective construction of the tetrahydropyridine moiety and incorporation to the ergoline skeleton while preserving the C5 stereochemistry. Herein, we report a synthesis of lysergic acid methyl ester featuring a double-cyclization strategy.

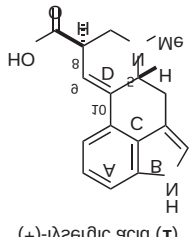
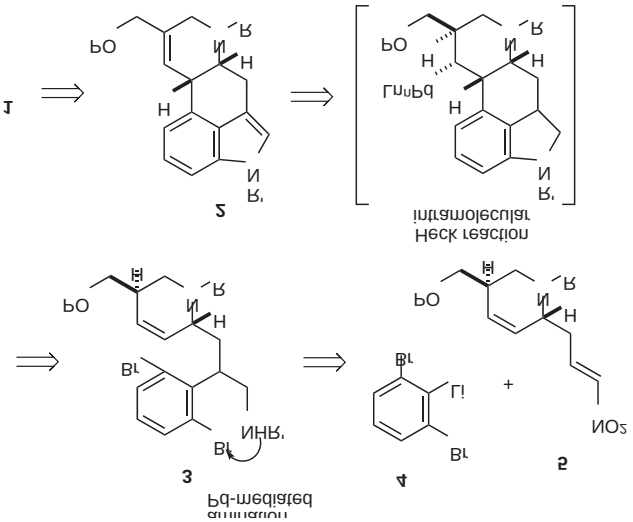


Figure 1

Our synthetic plan is illustrated in Scheme 1. We planned to construct the tetracyclic ergoline framework by utilizing the palladium(0)-mediated double-cyclization strategy consisting of intramolecular aromatic amination[5] and Heck reaction of dibromobenzene derivative **3** in one pot.[6] To secure the requisite regioselective β-elimination in the Heck reaction, it is necessary to set up *trans* relationship of the two substituents of the tetrahydropyridine moiety. The double-cyclization precursor **3** would be synthesized through a conjugate addition of (2,6-dibromophenyl)lithium species **4** to a fully functionalized optically active nitroolefin **5**. Lithium salt **4** could be generated by iodine-selective lithiation of 1,3-dibromo-2-iodobenzene.[7]



Scheme 1 Retrosynthetic analysis

The synthesis of the optically active nitroolefin **6** commenced with desymmetrization of *meso*-1,3-diol **7** (Scheme 2). Lipase PS-mediated acetylation at –15 °C afforded the optically active monoacetate,[8] which was immediately converted into BocNs-imide **8**[9] (95% ee) under the Mitsunobu conditions[10] to prevent racemization of the diol monoacetate. After removal of the Boc group, ozonolysis of the terminal olefin **9**, followed by dehydration of the resulting hemiaminal gave cyclic enamide **10**. To obtain an optically pure compound, acetate **10** was converted into the corresponding *p*-nitrobenzoate **11**, which was recrystallized from methanol to give **11** in optically pure form. Enamide **11** was then treated with NIS in methanol and subsequent dehydroiodination with DBU gave **12**. The next task was a stereoselective construction of the nitroolefin side chain. To this end, we investigated a diastereoselective allylation and a subsequent transformation

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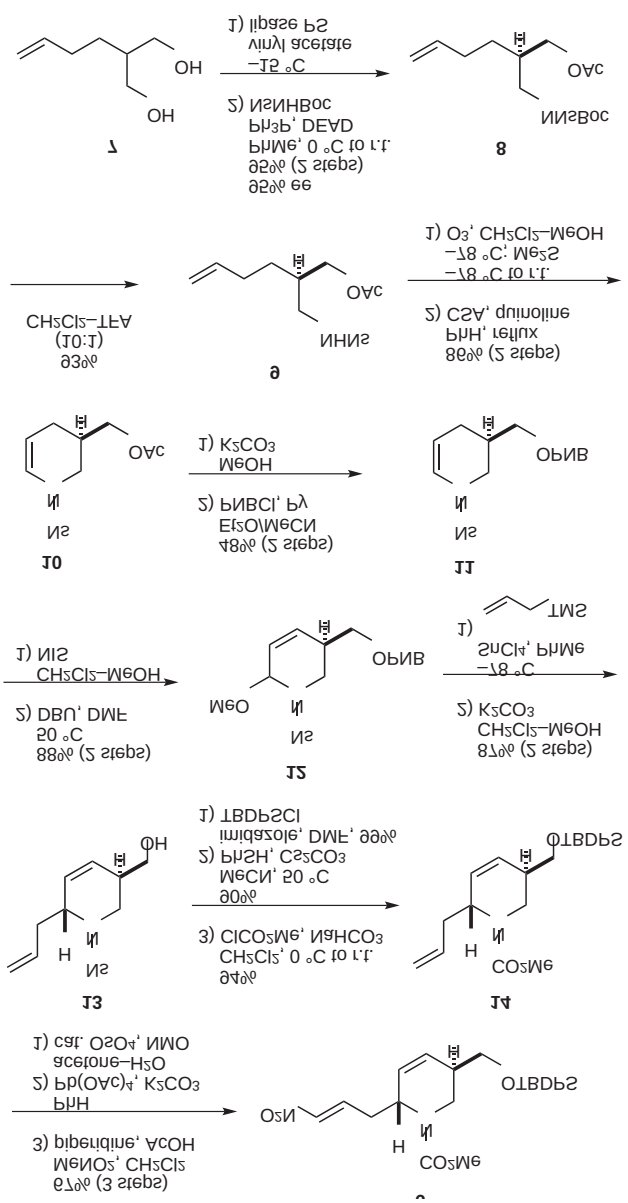
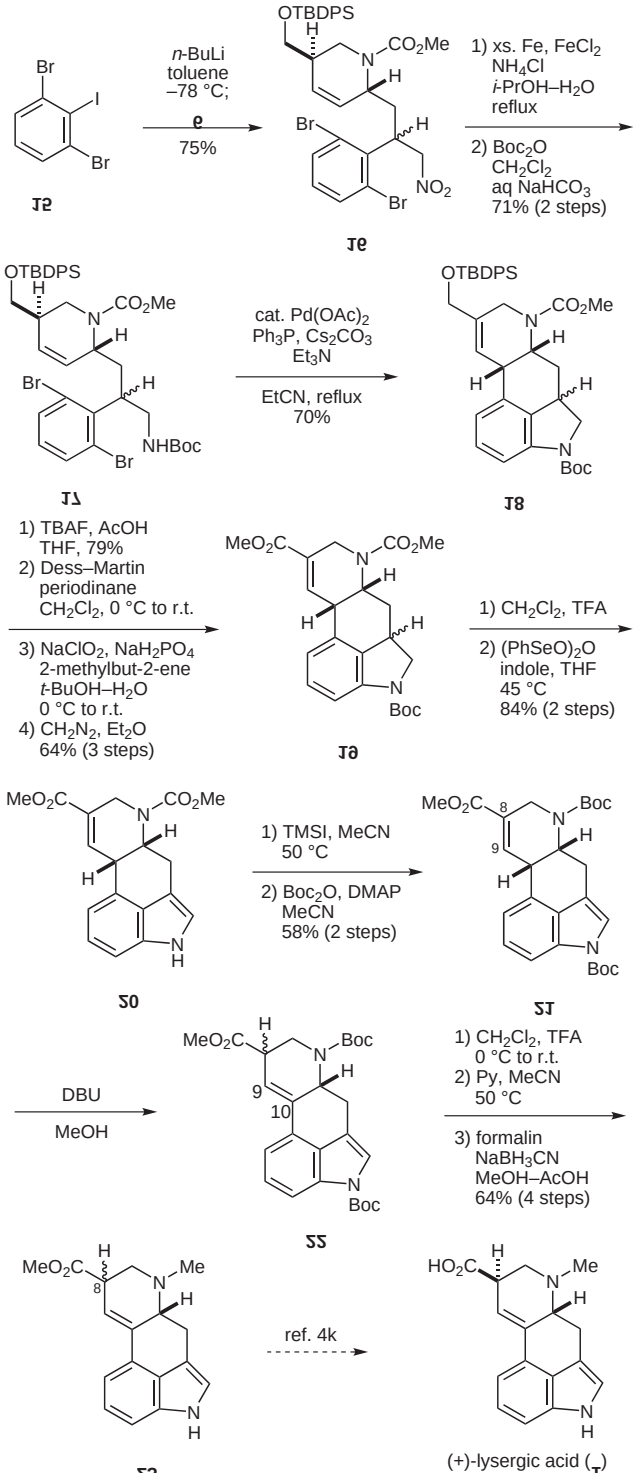


Scheme 2 Synthesis of the nitroolefin **6**

to the nitroolefin. After extensive screening, we have established the allylation conditions (allyltrimethylsilane, $SnCl_4$, toluene, –78 °C) providing the desired compound **13** in high *trans*-selectivity (dr = 13:1).[11] Judicious choice of the protective group on the alcohol was crucial to achieve the highly diastereoselective allylation. We speculate that the high selectivity could be attributed to the remote participation of the ester carbonyl group to form the cyclic oxonium ion, which blocked the nucleophilic attack from the β-face.[12] After manipulation of the protecting groups, the terminal olefin **14** was cleaved in two steps followed by condensation of the resultant aldehyde with nitromethane to afford nitroolefin **6**.

With the requisite nitroolefin **6** in hand, we then examined the crucial double cyclization for the construction of the tetracyclic ergoline framework (Scheme 3). (2,6-Dibromophenyl)lithium (**4**), generated by treatment of 1,3-dibromo-2-iodobenzene (**15**) with *n*-BuLi in toluene,[7] was added to the nitroolefin **6** to give conjugate addition product **16** as a mixture of diastereomers (the ratio was not determined). After chemoselective reduction of the nitro group, the resulting primary amine was protected with a Boc group to give the double cyclization precursor **17**. Upon heating at reflux with catalytic $Pd(OAc)_2$ and Ph_3P in propionitrile, **17** underwent the intramoleclar aromatic



Scheme 3 Synthesis of lysergic acid methyl ester (**23**)

amination and Heck reaction quite smoothly to furnish the desired tetracyclic ergoline skeleton **18** in good yield.[13]

Having successfully constructed the tetracyclic ergoline skeleton, we then executed the functional group manipulations. After deprotection of the TBDPS group in **18**, stepwise oxidation of the resulting alcohol to carboxylic acid followed by treatment with diazomethane gave methyl ester **19**. Indoline moiety was then converted into indole by removal of the Boc group and the subsequent oxidation with benzeneselenic anhydride in the presence of indole.[14] For smooth migration of the C8–C9 double bond to C9–C10 position, deprotection of the methyl carbamate and protection of the two nitrogen atoms with Boc groups were necessary at this stage. The double bond migration[4d,15] of the di-Boc compound **21** was effected by treatment with DBU to afford **22** as a mixture of diastereomers.[4f] Finally, stepwise deprotection of the both Boc groups and reductive methylation of the dehydropiperidine furnished lysergic acid methyl ester (**23**) as a mixture of diastereomers, whose spectroscopic data were identical to those reported in the literature.[4k] Since a mixture of **23** and 8-*epi*-**23** has been converted into (+)-lysergic acid (**1**) with epimerization of 8-*epi*-**23**,[4k] a formal total synthesis of (+)-lysergic acid was achieved.

In conclusion, we have achieved an asymmetric synthesis of (+)-lysergic acid methyl ester featuring highly diastereoseleticive allylation reaction and the efficient palladium-mediated double-cyclization strategy.

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(11) Synthesis of Compound **13**: To a solution of **12** (663.0 mg, 1.389 mmol) in toluene (15 mL) was added allyltrimethylsilane (0.33 mL, 2.08 mmol) at –78 °C. To this solution was added $SnCl_4$ (0.19 mL, 1.67 mmol) for 5 min at –78 °C. After completion, the reaction was quenched by addition of sat. $NaHCO_3$, and the mixture was extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to give the crude product, which was used in the next step without further purification. To a solution of crude product in MeOH (15 mL) and CH_2Cl_2 (15 mL) was added K_2CO_3 and stirred at r.t. After completion of the reaction, H_2O was added to the reaction mixture, and the resulting solution was extracted with EtOAc. The organic extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. Purification of the residue by flash chromatography (*n*-hexane–EtOAc, 1:1) afforded the title compound **13** (407.9 mg, 87% in 2 steps): $[\alpha]_D^{24}$ –343 (*c* 0.95, $CHCl_3$). IR (film): 3563, 3421, 2929, 1543, 1373, 1337, 1165, 1138, 1028, 925, 852, 781, 746, 678 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.12 (m, 1 H), 7.64–7.74 (m, 3 H), 5.82 (dd, *J* = 10.6, 3.2 Hz, 1 H), 5.77 (dd, *J* = 10.6, 4.8 Hz, 1H), 5.53–5.64 (m, 1 H), 4.92 (ddd, *J* = 17.2, 1.2, 1.2 Hz, 1 H), 4.86 (dd, *J* = 10.0, 0.8 Hz, 1 H), 4.37–4.44 (br m, 1 H), 4.09 (d, *J* = 14.4 Hz, 1 H), 3.53 (ddd, *J* = 17.6, 11.2, 6.0 Hz, 1 H), 3.30–3.37 (m, 2 H), 2.19–2.35 (m, 3 H), 2.04 (t, *J* = 1.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.9, 134.6, 133.5, 133.2, 131.7, 131.0, 129.1, 125.5, 124.3, 118.2, 61.9, 53.9, 40.2, 38.7, 37.6. HRMS–FAB: *m/z* calcd for $C_{15}H_{35}NO_3Si$ [M^+]: 338.0936; found: 338.0919.

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(13) Synthesis of Compound **18**: To a stirred solution of **17** (44.1 mg, 0.055 mmol) in EtCN (0.94 mL) was added successively Cs_2CO_3 (26.9 mg, 0.082 mg), $Pd(OAc)_2$ (3.7 mg, 0.0017 mmol), and Ph_3P (10.8 mg, 0.041 mmol). The reaction mixture was evacuated and quickly backfilled with argon for several times. Et_3N (23 μL, 0.165 mmol) was added to this solution, then allowed to warm to 110 °C, and the mixture was stirred for an additional 1 h. The reaction mixture was cooled to r.t. and filtrated through a pad of Celite. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by PTLC (*n*-hexane–EtOAc, 4:1) to give **18** (24.6 mg, 70%) as a mixture of diastereomers.
The more polar diastereomer: $[\alpha]_D^{24}$ –56 (*c* 0.59, $CHCl_3$). IR (film): 3047, 2931, 2857, 1704, 1616, 1456, 1390, 1354, 1238, 1170, 1113, 1082, 1006, 910, 737, 702, 615 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, *J* = 6.4 Hz, 4 H), 7.24–7.44 (m, 7 H), 7.16 (br m, 1 H), 6.80 (br dd, *J* = 7.6, 4.0 Hz, 1 H), 5.45 (br d, *J* = 7.6 Hz, 1 H), 4.79 and 4.63 (br s each, 1 H), 4.42 and 4.32 (d each, *J* = 18.2 Hz, 1 H), 4.24 (br s, 1 H), 4.07 (s, 2 H), 3.76 (s, 3 H), 3.67 (br s, 1 H), 3.48 (br d, *J* = 18.2 Hz, 1 H), 3.32–3.43 (br m, 2 H), 1.90 (br m, 1 H), 1.50–1.68 (br m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 152.6, 135.6, 135.5, 132.3, 131.8, 129.7, 129.7, 128.6, 127.6, 127.6, 125.0, 121.0, 112.2, 81.6, 65.7, 55.1, 52.8, 49.7, 40.0, 36.5, 36.1, 28.4, 27.4, 26.8, 19.2. HRMS–FAB: *m/z* calcd for $C_{38}H_{46}N_2O_5Si$ [M^+]: 638.3176; found: 638.3162.
The less polar diastereomer: $[\alpha]_D^{24}$ –47 (*c* 0.25, $CHCl_3$). IR (film): 3052, 2930, 2857, 1700, 1623, 1449, 1390, 1351, 1310, 1237, 1163, 1137, 1113, 998, 910, 824, 789, 737, 702, 615 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.68 (m, 4 H), 7.30–7.44 (m, 7 H), 7.14 (dd, *J* = 7.2, 7.2 Hz, 1 H), 6.78 (d, *J* = 7.2 Hz, 1 H), 5.36 (s, 1 H), 4.77 (br s, 1 H), 4.10 (s, 2 H), 4.04–4.60 (br m, 2 H), 3.73 (s, 3 H), 3.68–3.77 (br m, 1 H), 3.65 (br s, 1 H), 3.41 (br s, 1 H), 3.21 (quintet-like, *J* = 9.2 Hz, 1 H), 1.94–2.11, 1.76–1.88, and 1.46–1.70 (br m each, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 152.7, 135.6, 135.5, 134.4, 133.2, 132.2, 129.7, 128.7, 128.4, 127.6, 122.7, 120.4, 113.0, 80.5, 65.6, 56.3, 52.7, 47.8, 40.0, 38.7, 32.4, 31.9, 28.4, 26.8, 19.2. HRMS–FAB: *m/z* calcd for $C_{38}H_{46}N_2O_5Si$ [M^+]: 638.3176; found: 638.3146.

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