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Total Synthesis of (+)-Lysergic Acid

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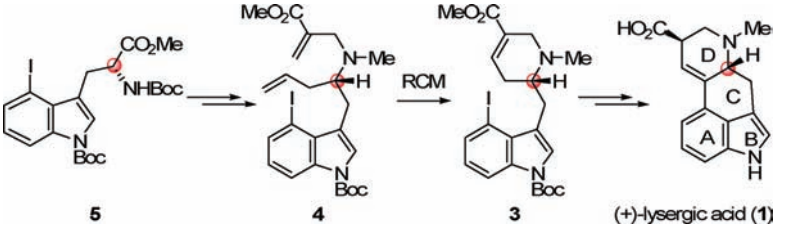
ABSTRACT



A stereocontrolled total synthesis of (+)-lysergic acid (1) is achieved using three metal-catalyzed methodologies for the construction of three key rings. Highlights of the synthesis include Pd-catalyzed indole synthesis to form the B ring, a RCM reaction to form the D ring, and an intramolecular Heck reaction to form the C ring.

The ergot family of alkaloids are pharmacologically important indole compounds because they possess various potent biological activities.[1] Indeed, several ergot alkaloids and their synthetic analogues are clinically used for treating a diverse array of human maladies (e.g., as a vasodilator, a prolactin inhibitor, and an anti-Parkinsonian's disease drug).[2] One of these compounds, the lysergic acid diethylamine (LSD), is strongly and notoriously psychoactive. Lysergic acid (**1**) is a typical representative of ergot alkaloids, and most congeners of ergot alkaloids are the amides of lysergic acid. Its characteristic structure features the unique tetracyclic ergoline skeleton, which contains the $\Delta^{9,10}$-double bond and chiral centers at C5 and C8 (Figure 1).

The interesting biological activities and unique structural features of ergot alkaloids have attracted considerable attention from the synthetic community.[3] Since the first total synthesis of racemic lysergic acid **1** by Woodward, 12 total syntheses have been accomplished. Most of the previous syntheses started from the reduced indole ring called Kornfeld's ketone and needed to reconstitute the indole form at the end. One was based on Uhle's ketone containing the intact indole ring, thus avoiding the reoxidation problem.[3j] The present sythetic studies have focused on utilizing a Pd-catalyzed reaction for the construction of the C/D ring system through 3,4-disubstitued indole derivatives. However, only three asymmetric syntheses were recently reported: (1) Szántay's synthesis in 2004 involving optical resolution of the tetracyclic indole

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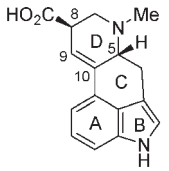
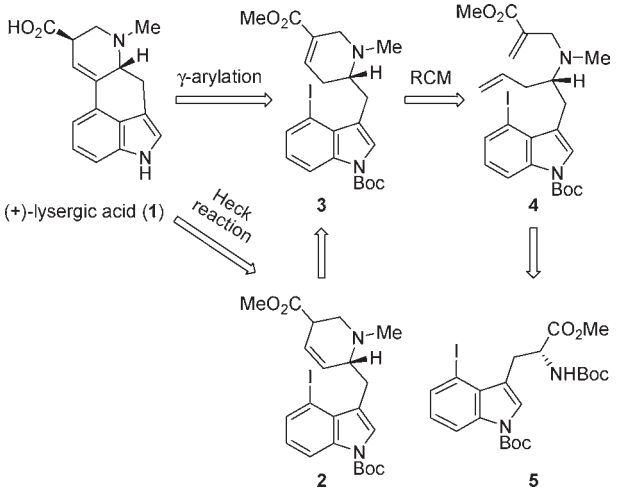


(+)-lysergic acid (**1**)

Figure 1. Structure of (+)-lysergic acid.

intermediate,[3j] (2) Fukuyama's synthesis in 2009 utilizing a double-cyclization strategy and an intramolecular Heck reaction,[3k] and (3) Ohno's synthesis in 2011 employing palladium-catalyzed domino cyclization of allenes.[3l]

Scheme 1. Retrosynthesis of (+)-Lysergic Acid



Recently, an appealing synthetic method for benzofuntionalized indoles, especially for optically pure tryptophan derivatives, through a Pd-catalyzed reaction of *o*-haloanilines and aldehydes has been developed by Jia and Zhu.[4] The method has already been applied in the synthesis of some natural products.[5−7] Taking advantage of this methodology for the assembly of 4-halotryptophan derivatives, we have accomplished the synthesis of clavicipitic acid, aurantioclavine, and indolactam V. In order to further define its application scope in the total synthesis of natural products, we describe herein the total synthsis of (+)-lysergic acid from (*R*)-4-iodotryptophan derivative **5**.

Retrosynthetic analysis of lysergic acid **1** is shown in Scheme 1. We envisioned that the C ring could be constructed by utilizing γ-arylation of α,β-unsaturated ester **3** or intramolecular Heck reaction of olefin **2**.[3k] Both compounds **2** and **3** already have the A/B/D ring system. The olefin **2** can be accessed from α,β-unsaturated ester **3** via isomerization of the double bond. The double bond in intermediate **3** could be formed by an intramolecular ring-closing metathesis reaction of **4**,[8] which could be readily obtained by a series of conversions of functional groups from (*R*)-4-iodotryptophan derivative **5**. (*R*)-**5**, possessing the C5 stereogenic center of lysergic acid **1**, could be synthesized starting from D-glutamic acid following the same procedures as described for its enantiomer (*S*)-**5** using the Pd-catalyzed indole synthesis as the key step.[5c]

Our synthesis of lysergic acid commenced with (*R*)-**5** (Scheme 2). Thus, *N*-methylation of **5** with MeI and Ag_2O in DMF provided **6** in 83% yield. Reduction of **6** with $LiBH_4$[9] followed by Swern oxidation gave aldehyde **7** in 83% overall yield. Wittig reaction of aldehyde **7** with the reagent derived from methoxymethylene phosphonium chloride yielded the desired methyl enol ether **8** (*trans*/*cis* = 4:5) in 86% yield. Hydrolysis of **8** with $Hg(OAc)_2$/KI provided the aldehyde **9** in 95% yield.[10] Witting reaction of aldehyde **9** afforded the terminal olefin **10** in 92% yield. Deprotection[5a] of the Boc group of **10** with TMSOTf followed by *N*-alkylation[11] with methyl 2-(bromomethyl)acrylate[12] afforded the diene **4** in 76% yield.

Following the synthesis of diene **4**, the key RCM reaction was exploited. It is well-known that the presence of basic amines in the metathesis reaction reduces the catalyst efficiency due to the interactions of the lone pair of electrons on nitrogen with the metal center.[13] Modifications of the reactant using the corresponding ammonium salts or addition of protic[14] or Lewis[15] acid have been widely used. Thus, **4** was first treated with Grubbs second-generation catalyst in the presence of Lewis acid Ti(O-*i*-Pr)$_4$

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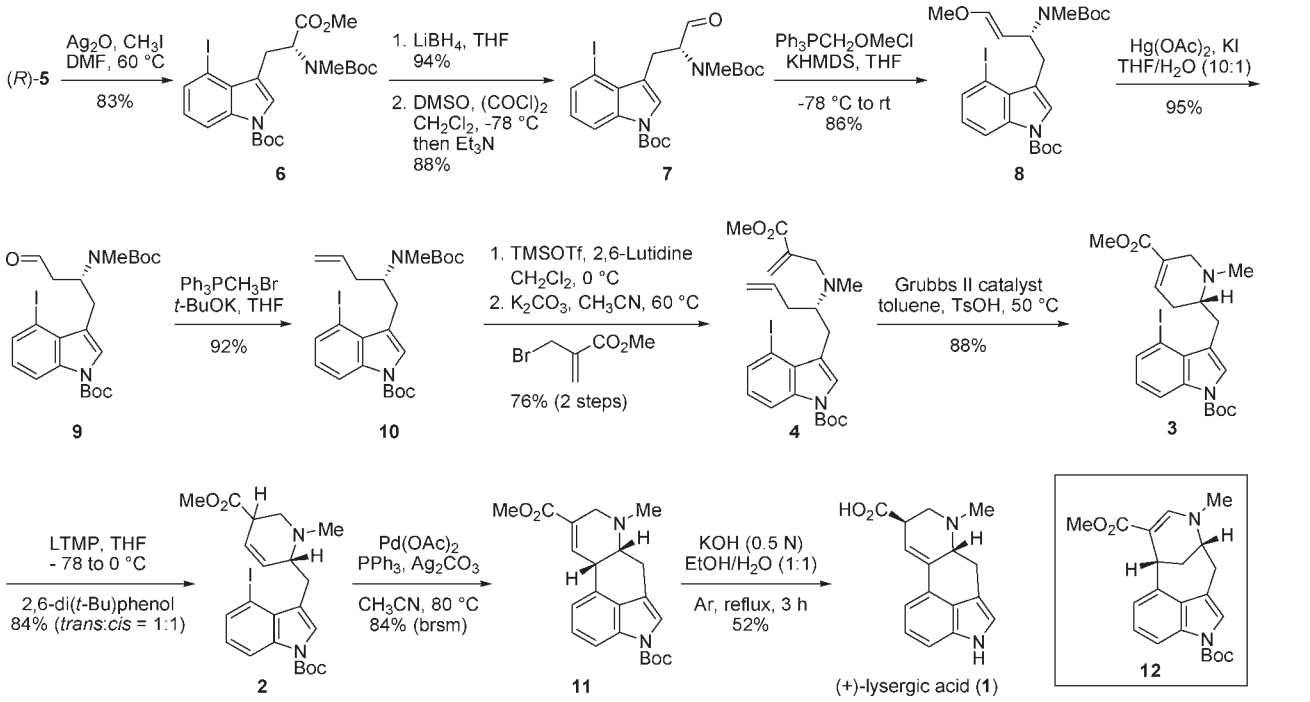
Scheme 2. Total Synthesis of (+)-Lysergic Acid



in CH_2Cl_2 at reflux.[15] No cyclization product was isolated, and the starting material was recovered. Alternatively, the ring-closing metathesis reaction was carried out using Grubbs second-generation catalyst in the presence of protic acid *p*-TsOH (1.1 equiv). We found that the solvent was cruical for the reaction. When CH_2Cl_2 was used as solvent and the reaction was carried out at 40 °C, no product was obtained. However, when toluene was used as the solvent and the reaction was carried out at 50 °C, the reaction proceeded smoothly and the desired product was obtained in 88% yield.[14] It is noteworthy that **4** could also be converted to **3** in the absence of *p*-TsOH under refluxing in toluene after 12 h, albeit in only 60% yield.[16]

After the preparation of the crucial intermediate **3**, we examined the key γ-arylation reaction. To the best of our knowledge, there are only a few γ-arylation reactions of α,β-unsaturated carbonyl compounds with haloarenes being reported,[17] and the intramolecular γ-arylation reactions of α,β-unsaturated esters have not been reported previously. Indeed, the γ-arylation reaction of the intermediate **3** proceeded poorly and no desired product was found, even after a wide variety of reaction conditions (catalysts, ligands, bases, additives, and solvents) were screened.[17,18] The attempt to prepare the silyl ketene acetals of α,β-unsaturated esters **3** led to the formation of isomer **2**.[17b] An exception was that when **3** was subjected to Jeffery's condition,[19] a bridged seven-membered ring product **12** of Heck reaction was obtained. In addition, the light-assisted $S_{RN}1$ reaction[20] was also investigated, and the starting material was recovered besides a small amount of deiodinated starting material.

After the γ-arylation reaction failed, we next focused on the intramolecular Heck reaction (Scheme 2). Isomerization of the double bond of **3** with lithium 2,2,6,6-tetramethylpiperidide (LTMP) followed by quenching with a bulky phenol, 2,6-di(*t*-Bu)phenol, provided a mixture of epimers **2** (*trans*/*cis* = 1:1) according to Fukuyama's procedure.[3k] The mixture **2** was impossible to be separated by preparative TLC. Initial attempt to perform the Heck reaction of **2** under Jeffery's conditions generated no desired product. Subsequently, a variety of reaction conditions were examined. When **2** was treated with 10 mol % of $Pd(OAc)_2$, 30 mol % of Ph_3P, and 2 equiv of Et_3N in refluxing acetonitrile for 5 h, the desired Heck product **11** was obtained in 27% yield together with **12** in 35% yield.[21] It was believed that **12** was formed from the Heck rection of **3**, which could be generated by the alkene isomerization of **2** that was formed from readdition−elimination of Pd−H species produced in Heck reaction. It is well

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established that the use of silver salts could suppress alkene isomerization in Heck reaction.[21,22] Thus, when 2 equiv of Ag_2CO_3 was used as the base and halide scavenger, Heck reaction of **2** generated **11** as the sole product. When the reaction was stopped after refluxing in CH_3CN for 2 h, **11** was obtained in 84% yield (brsm) and 34% of the starting material was recovered.[21] Prolonging the reaction time will reduce the yield because **11** is unstable under the Heck reaction conditions. The ratio of *trans* versus *cis* of the recovered **2** was still 1:1. It could be subjected to Heck reaction again. From the mechanism of the Heck reaction, only *trans*-epimer **2** could undergo the Heck reaction. From our observations, it is most like that **2** were epimerized under base conditions due to the acidity of the α-H of β,γ-unsaturated ester **2**, which resulted in an equilibrium ratio. Finally, the deprotection and hydrolysis of methyl ester of **11** with KOH, accompanied with the isomerization of the double bond, furnished (+)-lysergic acid **1** in 52% yield.[3d] All the spectroscopic data of **1** were in agreement with those of natural and synthetic lysergic acid reported in the literature.[3i,l]

In summary, we have completed the enantioselective synthesis of (+)-lysergic acid in 12 steps and 12.7% overall yield starting from (*R*)-4-iodotryptophan derivative **5**, which was prepared using the recently developed Pd-catalyzed indole synthesis procedure. The synthesis features an intramolecular RCM reaction to form the D ring and an intramolecular Heck reaction to form the C ring. The γ-arylation of α,β-unsaturated ester **3** was also studied. Further optimization of synthetic routes is in progress and the results will be reported in due course.

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Supporting Information Available. Full experimental procedures and ^1H and ^{13}C NMR spectra of compounds **1**–**4** and **6**–**14**. This material is available free of charge via the Internet at http://pubs.acs.org.