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Total Synthesis of (+)-Lysergic Acid

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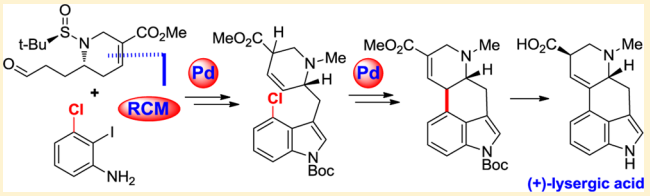
Supporting Information

ABSTRACT: We report the enantioselective total synthesis of (+)-lysergic acid using two different strategies, which featured three metal-catalyzed reactions for the construction of the BCD three rings, involving Pd-catalyzed indole synthesis for the construction of the B ring, a ring-closing metathesis reaction for the formation of the D ring, and an intramolecular Heck reaction to forge the C ring. In synthetic strategy I, the synthesis was achieved in 20 steps following the ring construction sequence of BDC. In synthetic strategy II, the synthetic route was shortened to only 12 steps by following the ring construction sequence of DBC and using a 4-chlorotryptophan derivative for the intramolecular Heck reaction. Moreover, we also discussed an unsuccessful synthetic strategy.



INTRODUCTION

Lysergic acid (**1**) is a representative natural product of the ergot alkaloid family, which are particularly important because they possess a wide spectrum of biological activities (Figure 1).[1]

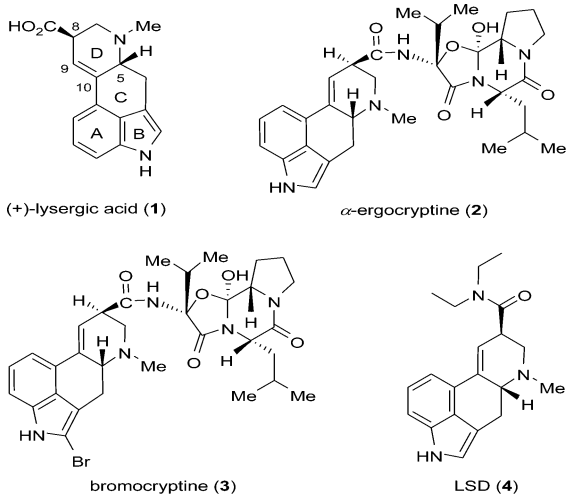


Figure 1. Structures of (+)-lysergic acid and other ergot alkaloids.

One of the most biologically important ergot alkaloids is α-ergocryptine (**2**). Its semisynthetic derivative bromocryptine (**3**) is clinically used as a prolactin inhibitor. The lysergic acid diethylamide (LSD) (**4**), another representative ergot alkaloid, is strongly and notoriously psychoactive. From a structural perspective, lysergic acid (**1**) possesses a unique tetracyclic ergoline skeleton that contains the $\Delta^{9,10}$-double bond and two chiral centers. Intrigued by the biological activities and unique structural features of ergot alkaloids, a number of total syntheses of lysergic acid (**1**) have been reported to date.[2]

The first synthesis of racemic lysergic acid was achieved by Woodward and Kornfeld in 1956.[2a] So far, its total synthesis has been achieved by 13 groups.[2a−u] Most previous syntheses have relied on a stepwise linear approach using Kornfeld's ketone, except for Oppolzer's intramolecular imino-Diels−Alder strategy.[2e] In recent years, palladium-catalyzed reactions of 3,4-disubstitued indole derivatives provide an attractive approach for the construction of the C ring of lysergic acid. However, only four asymmetric syntheses are recently reported: Szántay's synthesis in 2004 involved optical resolution of the tetracyclic indole intermediate;[2n] Fukuyama, Ohno, and our group employed palladium-catalyzed methodologies for the construction of the key C ring.[2o−u]

4-Halotryptophan derivatives containing a chiral center are useful intermediates for the synthesis of 3,4-disubstituted indole alkaloids. However, their synthesis is arduous.[3] Recently, Zhu and Jia have developed a useful method for the synthesis of 4-halotryptophan derivatives via a Pd-catalyzed annulation reaction.[4] In our previous work, we validated the efficiency of this methodology by successfully accomplishing the asymmetric synthesis of clavicipitic acid, aurantioclavine, indolactam V, lysergic acid, and rugulovasine A.[2u,5] Herein, we describe another successful example toward the total synthesis of (+)-lysergic acid (**1**) from an (*R*)-4-halotryptophan derivative.

RESULTS AND DISCUSSION

Unsuccessful Attempts for the Synthesis of (+)-Lysergic Acid. As shown in the retrosynthetic analysis outlined in

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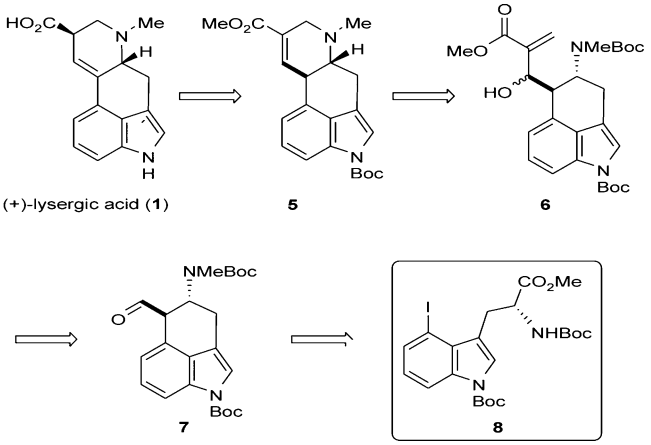
Scheme 1, we envisioned that (+)-lysergic acid (**1**) could be obtained by simple transformation of compound **5**. The

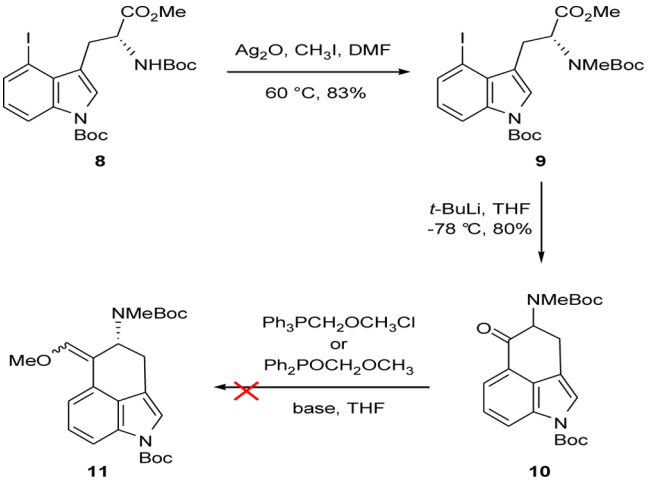
Scheme 1. Initial Retrosynthetic Analysis of (+)-Lysergic Acid (1)



piperidine ring of **5** could be constructed by means of an intramolecular S_N2' displacement of alcohol **6**, which could be readily accessed by Morita–Baylis–Hillman reaction of tricyclic aldehyde **7** with methyl acrylate.[6] The tricyclic aldehyde **7** could be obtained starting from (*R*)-4-iodotryptophan derivative **8**. For the synthesis of **8**, the same procedures could be used as its enantiomer (*S*)-**8** including the Pd-catalyzed annulation reaction as the key step.[5b]

Our synthesis of compound **7** commenced with (*R*)-4-iodotryptophan derivative **8** as shown in Scheme 2. Thus, N-

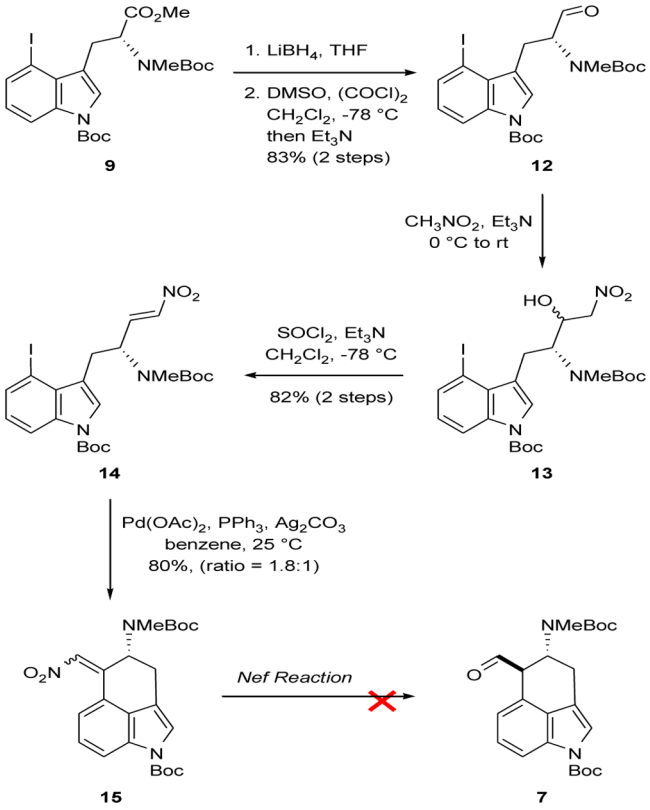
Scheme 2. Attempted Synthesis of Tricyclic Aldehyde 7 by Hydrolysis of Methyl Enol Ether 11



methylation of (*R*)-**8** with MeI and Ag_2O in DMF provided **9** in 83% yield. Treatment of compound **9** with *t*-BuLi afforded the desired tricyclic ketone **10** in 80% yield, which was described recently in the synthesis of Rugulovasine A by us.[5d] However, Wittig reaction of ketone **10** was unsuccessful. A variety of reaction conditions were screened, including using $Ph_2POCH_2OCH_3$ and ylide $Ph_3PCH_2OCH_3Cl$ as olefin reagents.[7] The reaction proceeded poorly, and no desired product **11** was found. Therefore, our original idea that tricyclic aldehyde **7** could be obtained by hydrolysis of methyl enol ether **11** had failed.

Next, we planned to synthesize the aldehyde **7** by utilizing the Nef reaction of a nitro compound (Scheme 3).[8] Reduction

Scheme 3. Attempted Synthesis of Tricyclic Aldehyde 7 by Nef Reaction



of **9** with $LiBH_4$, followed by Swern oxidation, gave aldehyde **12** in 83% overall yield. Henry reaction of aldehyde **12** with nitromethane provided a diastereomeric mixture of the expected *β*-nitro alcohol **13**, which was subsequently dehydrated to afford nitroalkene **14** in 82% overall yield solely as the *E* isomer.[9] With the nitroalkene **14** in hand, we next explored the intramolecular Heck reactions. Surprisingly, an extensive literature search showed that there are only a few reported intramolecular Heck reactions of nitroalkenes. Denmark reported that intramolecular Heck reaction of iodoaryl nitroalkene needed 1.0 equiv of $Pd(OAc)_2$.[10] Gratefully, when nitroalkene **14** was treated with 0.1 equiv of $Pd(OAc)_2$, 0.2 equiv of Ph_3P, and 2 equiv of Ag_2CO_3 in benzene at 25 °C, the intramolecular Heck reaction proceeded smoothly and gave *Z*/*E* isomers of **15** in 80% yield. The isomers of **15** were unstable, and *Z*/*E* isomerization of the double bond would occur on silica gel. Attempts were made to transform the mixture of **15** to the tricyclic aldehyde **7** by Nef reaction using oxidative, reductive, and neutral conditions.[8] Unfortunately, either the reaction was inert or complex products were formed, and no desired product **7** was found.

We next examined the construction of the skeleton of the tricyclic aldehyde **7** via the palladium-catalyzed *α*-arylation of aldehyde **17** directly (Scheme 4). Wittig reaction of aldehyde **12** yielded the desired methyl enol ether **16** (*trans*:*cis* = 5:4) in 86% yield. Hydrolysis of **16** with $Hg(OAc)_2$/KI gave the aldehyde **17** in 95% yield.[6,11] According to the reported

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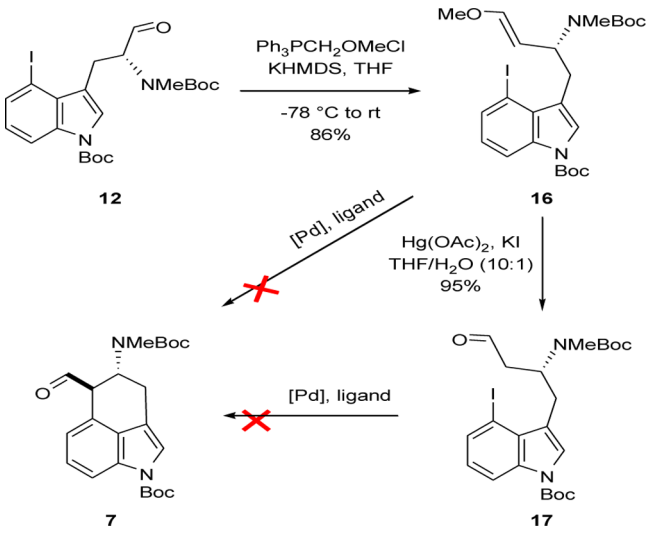
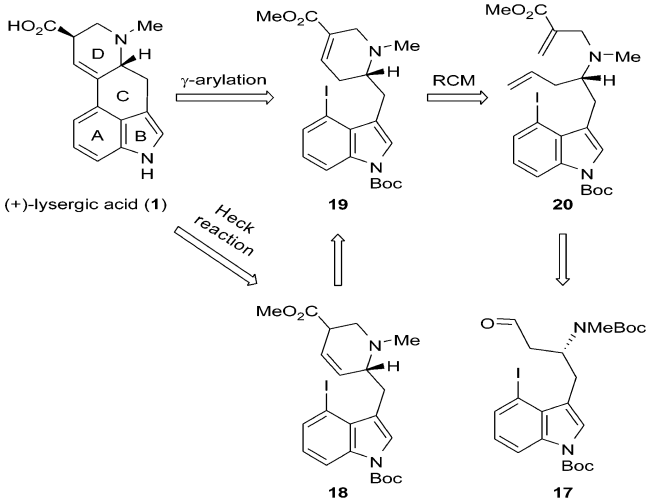
Scheme 4. Attempted Synthesis of Tricyclic Aldehyde 7 by Pd-Catalyzed α-Arylation of Aldehyde 17



protocol, a variety of intramolecular α-arylation conditions were investigated.[12] However, the reaction normally formed several unidentified side products and no desired product **7** was obtained. In addition, the intramolecular Heck reaction of methyl enol ether **16** was also investigated, and no desired product was observed.

Strategy I for the Successful Synthesis of (+)-Lysergic Acid. Having realized that the tricyclic aldehyde **7** was difficult to prepare, we turned our attention to the development of an efficient alternative strategy for the synthesis of (+)-lysergic acid (**1**) (Scheme 5). Instead of constructing C ring first, we

Scheme 5. Retrosynthetic Analysis of (+)-Lysergic Acid (1) of Strategy I



proceeded to investigate a new ring-closing sequence. The D ring of **18** would be first synthesized via ring-closing metathesis reaction of **20**, followed by isomerization of the double bond of **19**.[13] The C ring could be sequentially constructed by utilizing intramolecular Heck reaction of β,γ-unsaturated ester **18** or γ-arylation of α,β-unsaturated ester **19**.[2o] The diene **20** should be readily accessible from aldehyde **17** through a sequence of conversions of functional groups.

Starting from Wittig reaction of aldehyde **17**, the terminal olefin **21** was obtained in 92% yield (Scheme 6). Deprotection[5a] of the Boc group of **21** with TMSOTf, followed by N-alkylation[14] with methyl 2-(bromomethyl)acrylate,[15] afforded the diene **20** in 76% overall yield. The ring-closing metathesis reaction of the diene **20** proceeded smoothly when using Grubbs II catalyst in the presence of protic acid *p*-TsOH (1.1 equiv) in toluene at 50 °C.[16] The desired product **19** was obtained in 88% yield. It was presumed that the presence of protic acid inhibited the interactions of the lone pair of electrons on nitrogen with the metal center.[17] With the crucial intermediate **19** in hand, the γ-arylation reaction of α,β-unsaturated ester **19** was examined first. To the best of our knowledge, there is no literature report on the intramolecular γ-arylation reaction of α,β-unsaturated esters. Indeed, a variety of conditions screening failed to give the desired product **22**.[18] Alternatively, the α,β-unsaturated ester **19** was subjected to isomerization of the double bond according to Fukuyama's procedure.[2o] An inseparable mixture of epimers of **18** (*trans*/*cis* = 1:1) was afforded in 84% yield. For the intramolecular Heck reaction of **18**, a variety of reaction conditions were examined. We found that Ag_2CO_3 was necessary as the base and halide scavenger to suppress alkene isomerization in the reaction.[19] When **18** was treated with 0.1 equiv of $Pd(OAc)_2$, 0.3 equiv of Ph_3P, and 2 equiv of Ag_2CO_3 in CH_3CN at refluxing for 2 h, the desired Heck product **22** was obtained in 84% yield (brsm) and 34% of the starting material **18** was recovered. Surprisingly, the ratio of *trans* versus *cis* of the recovered **18** was still 1:1. Because the D ring of **18** should be a *trans*-2,5-disubstituted 1,2,5,6-tetrahydropyridine for smooth β-H elimination, **18** was probably epimerized under basic conditions. Finally, the deprotection of Boc and hydrolysis of methyl ester of **22** with KOH, accompanied with the isomerization of the double bond, furnished (+)-lysergic acid (**1**) in 52% yield.[2e] Thus, our first-generation enantioselective total synthesis of (+)-lysergic acid (**1**) was achieved in 12 steps and 12.7% overall yield starting from (*R*)-4-iodotryptophan derivative **8**, or 20 steps and 4.5% overall yield starting from readily available glutamic acid.

Strategy II for the Successful Synthesis of (+)-Lysergic Acid. Although we have accomplished the total synthesis of (+)-lysergic acid (**1**), the synthetic route was not convergent due to several redundant conversions of functional groups. For instance, conversion of the 4-nitro-tryptophan derivative to the 4-iodotryptophan derivative **8** required two more steps and carbon chain extension from ester **9** to olefin **21** needed five steps. To overcome these shortcomings effectively, we postulated that (1) the stereocenter of the D ring could be generated by the enantioselective addition of chiral imine and (2) using 3-chloro-2-iodoaniline instead of 3-nitro-2-iodoaniline to undergo Pd-catalyzed indole synthesis; the product could be subjected to the subsequent intramolecular Heck reaction directly. The retrosynthetic analysis of common intermediate **22** is illustrated in Scheme 7. The C ring could be constructed by utilizing intramolecular Heck reaction of 4-chlorotryptophan derivative **23**, which was regarded as an inert substrate and rarely used in the intramolecular Heck reaction. Compound **23** can be accessed from α,β-unsaturated ester **24** via isomerization of the double bond. The ester **24** containing the A/B/D ring system could be synthesized by the Pd-catalyzed indole synthesis from 3-chloro-2-iodoaniline (**25**) and aldehyde **26**, which already contains the D ring of (+)-lysergic acid (**1**). The tetrahydropyridine in aldehyde **26** could be

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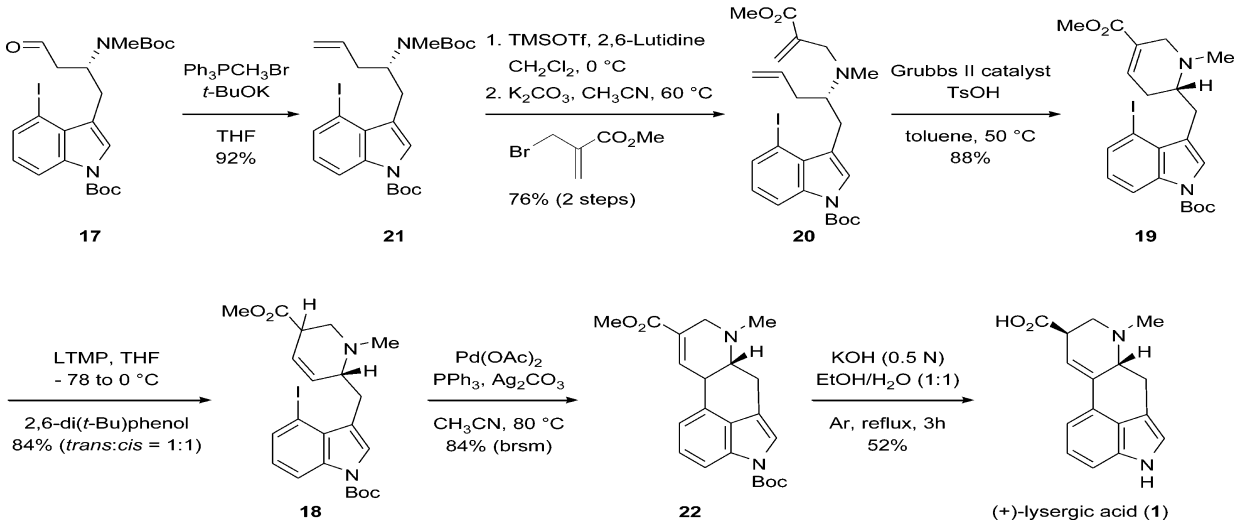
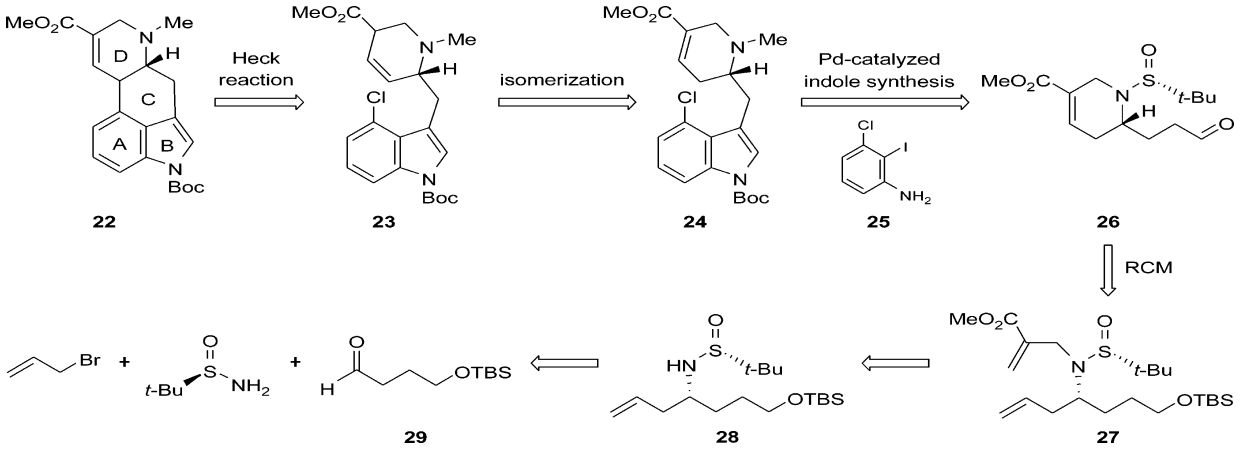
Scheme 6. Total Synthesis of (+)-Lysergic Acid (1) by Strategy I



Scheme 7. Retrosynthetic Analysis of Common Intermediate 22



formed by ring-closing metathesis reaction of diene **27**, which could be prepared by N-alkylation of **28**. The chiral allylamine **28** could be readily obtained by one-pot reaction of aldehyde **29**, allylic bromide, and *tert*-butanesulfinamide in the presence of indium metal and titanium tetraethoxide.[20]

Preparation of the precursor **23** for intramolecular Heck reaction is outlined in Scheme 8. When a mixture of aldehyde **29**, (S_R)-*N*-*tert*-butanesulfinamide, allyl bromide, indium powder, and $Ti(OEt)_4$ was heated in THF at 60 °C for 5 h, a mixture of two inseparable diastereoisomers of **28** (*dr* = 7:1) was obtained in 79% yield.[20] N-Alkylation of **28** with methyl 2-(bromomethyl)acrylate afforded the major diene product **27** in 74% yield together with its diastereoisomer in 10% yield.[21] The diastereoisomers could be separated by careful column chromatography in this step. The ring-closing metathesis reaction of **27** proceeded smoothly in refluxing CH_2Cl_2 for 12 h, and the desired product **30** was isolated in 90% yield.[21] Subsequent deprotection of the TBS group with TBAF, followed by Dess–Martin oxidation, gave aldehyde **26** in 78% overall yield.[22]

With the key chiral aldehyde **26** in hand, the stage was set for the Pd-catalyzed indole synthesis to construct B ring. Direct annulation of 3-chloro-2-iodoaniline (**25**) and aldehyde **26** under standard conditions provided the desired product in around 20% yield.[4] After screening a variety of conditions, it was found that the yield could be improved by shortening the reaction time. The optimized conditions were 40 mol % of $Pd(OAc)_2$ and 3 equiv of $DABCO{\cdot}6H_2O$ at 80 °C for 6 h. Since compound **32** was difficult to be purified by flash column chromatography, it was subjected to Boc protection without further purification, affording the product **33** in 39% overall yield for two steps. Removal of the *tert*-butanesulfinyl group and subsequent reductive methylation gave **24** in 72% overall yield.[23,24] Isomerization of the double bond of **24** with lithium 2,2,6,6-tetramethylpiperidide (LTMP), followed by quenching with saturated aqueous NH_4Cl solution, provided a mixture of epimers **23** (2:1).[2o]

Having succeeded in the preparation of the key intermediate **23**, we explored the intramolecular Heck reaction. Unexpectedly, the intramolecular Heck reaction of 4-chlorotryptophan derivative **23** was a formidable task. A variety of reaction conditions (palladium sources, ligands, bases, and solvents) were examined, and some of the representative ones are shown in Table 1. All the catalyzed conditions did not give any desired cyclized product (Table 1, entries 1–2).[25a] However, under Fu's reaction conditions, the starting material was recovered in 52% yield (Table 1, entry 2).[25b] When the reaction was conducted with 0.5 equiv of $Pd_2(dba)_3CHCl_3$, the desired product **22** was obtained in 20% yield with recovery of 35% of the starting material (Table 1, entry 3). Therefore, further

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Scheme 8. Synthesis of Intermediate 23

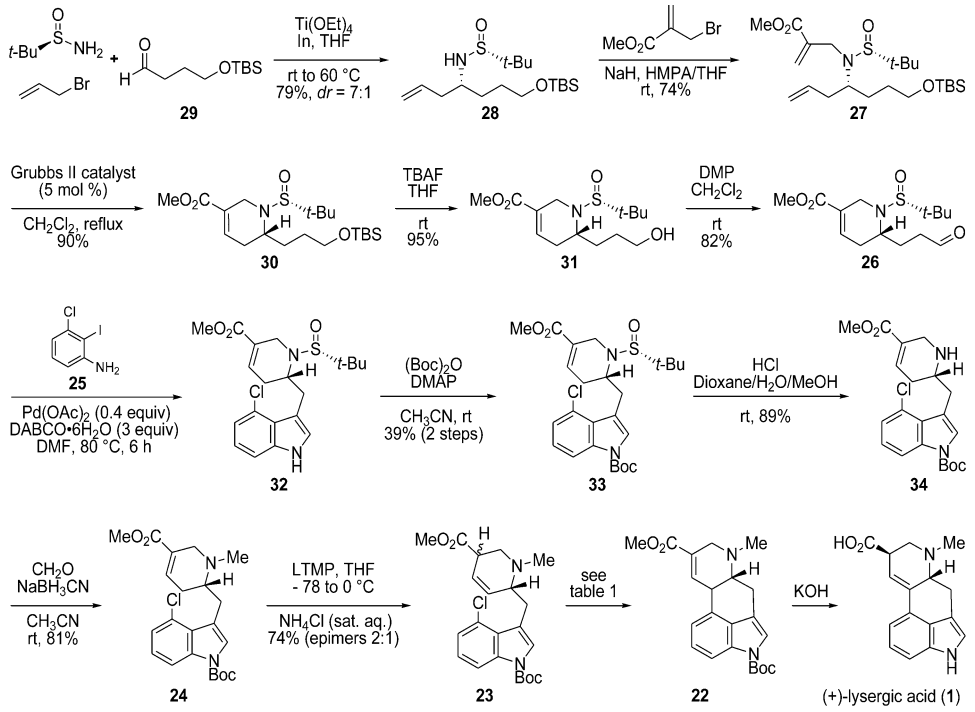
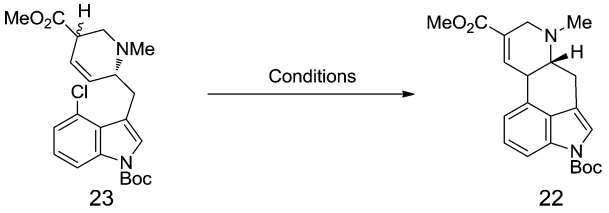


Table 1. Optimization of the Reaction Conditions for the Intramolecular Heck Reaction



							yield (%)	
entry	catalyst	ligand	base	solvent	T (°C)	t (h)	**23**[a]	product **22**[b]
1	$Pd(OAc)_2$ (0.2 equiv)	dppp (0.2 equiv)	Cs_2CO_3 (1.5 equiv)	EG[c]	140	2	0	0
2	$Pd_2(dba)_3CHCl_3$ (0.1 equiv)	$P(t\text{-}Bu)_3HBF_4$ (0.2 equiv)	Cy_2MeN (3 equiv)	dioxane	80	1.5	52	0
3	$Pd_2(dba)_3CHCl_3$ (0.5 equiv)	$P(t\text{-}Bu)_3HBF_4$ (1 equiv)	Cy_2MeN (3 equiv)	dioxane	80	1.5	35	20
4	$Pd_2(dba)_3CHCl_3$ (0.5 equiv)	$P(t\text{-}Bu)_3HBF_4$ (1 equiv)	Cy_2MeN (3 equiv)	dioxane	80 (MW)	0.25	59	0
5	**$Pd_2(dba)_3CHCl_3$ (0.5 equiv)**	**$P(t\text{-}Bu)_3HBF_4$ (1 equiv)**	**Cy_2MeN (3 equiv)**	**dioxane**	**100**	**1.5**	**27**	**25**
6	$Pd_2(dba)_3CHCl_3$ (0.5 equiv)	$P(t\text{-}Bu)_3HBF_4$ (1 equiv)	Cy_2MeN (3 equiv) Cs_2CO_3 (1.5 equiv)	dioxane	80	1.5	65	22
7	$Pd_2(dba)_3CHCl_3$ (0.5 equiv)	*John*-Phos (1 equiv)	Cy_2MeN (5 equiv)	dioxane	80	1.5	43	0
8	$Pd_2(dba)_3CHCl_3$ (0.5 equiv)	*Dave*-Phos (1 equiv)	Cy_2MeN (3 equiv)	dioxane	80	1.5	79	0
9	$Pd_2(dba)_3CHCl_3$ (0.5 equiv)	*X*-Phos (1 equiv)	Cy_2MeN (3 equiv)	dioxane	80	1.5	0	0

[a]Isolated yield. [b]Yield based on recovered starting material. [c]EG = ethylene glycol.

optimization of the reaction conditions was carried out in the presence of 0.5 equiv of $Pd_2(dba)_3CHCl_3$. The microwave treatment could not improve the reaction efficiency (Table 1, entry 4). When the reaction was conducted at a higher temperature, more starting material **23** was converted to the desired product **22** without the loss of yield (Table 1, entry 5). When Cs_2CO_3 was used as the co-base, the conversion of the starting material was significantly inhibited (Table 1, entry 6).[25c] Further optimization of the reaction conditions was carried out in the presence of different ligands. Unfortunately, no desired product **22** was found under these conditions (Table 1, entries 7–9). Therefore, the intramolecular Heck reaction of 4-chlorotryptophan derivative **23** was performed in the presence of 0.5 equiv of $Pd_2(dba)_3CHCl_3$, 1.0 equiv of $P(t\text{-}Bu)_3HBF_4$, and 3.0 equiv of Cy_2MeN in dioxane at 100 °C.

Finally, following the same above procedure for **22** furnished (+)-lysergic acid (**1**).[2e] Thus, our second-generation enantioselective total synthesis of (+)-lysergic acid (**1**) was achieved in only 12 steps and 1% overall yield starting from readily available and known aldehyde **29**. Although the overall yield was not satisfactory, which was mainly due to the challenge of the intramolecular Heck reaction of chlorosubstituted substrate, the present synthesis represented the shortest sequence for the asymmetric total synthesis of (+)-lysergic acid (**1**). In addition, the challenge of the Heck reaction using aryl chloride as the reaction partner underscores the need to develop more

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powerful catalytic systems for the Heck reaction with complex aryl chlorides.

CONCLUSIONS

In summary, we have achieved the enantioselective total synthesis of (+)-lysergic acid (**1**) by utilizing two different strategies, which both featured three metal-catalyzed reactions for the construction of three key rings, involving Pd-catalyzed indole synthesis for the construction of the B ring, a ring-closing metathesis (RCM) reaction for the formation of the D ring, and an intramolecular Heck reaction to forge the C ring. In strategy I, the synthesis of (+)-lysergic acid (**1**) has been achieved in 20 steps starting from D-glutamic acid as the chiral pool and the ring construction order was BDC. In strategy II, the synthetic route was shortened to only 12 steps by adjusting the ring construction order to DBC and using 4-chlorotryptophan derivative **23** as the intramolecular Heck reaction partner.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all experiments were carried out under an Ar atmosphere. Dichloromethane was distilled over CaH_2. Toluene was distilled over sodium, and tetrahydrofuran was distilled over Na−K alloy. The other reagents and solvents were directly used from the supplier without further purification unless noted. Reactions at −78 °C employed a dry ice−acetone bath. Chemical shifts were reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR). ^{1}H NMR spectra were tabulated as follows: chemical shift, multiplicity (br s = broad singlet, s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant (Hz). Infrared spectra were recorded with a thin layer of the product on a KBr disk and reported in frequency of absorption (cm^{-1}). High-resolution mass spectra (HRMS) were acquired on an FT-MS (7.0 T) equipped with an ESI source in positive mode.

Compound 14. To an ice-cooled solution of compound **12** (300 mg, 0.57 mmol) in CH_3NO_2 (3.8 mL) was added Et_3N (103 μL, 0.74 mmol), and the mixture was stirred for 12 h at room temperature, and then the mixture was concentrated in vacuo. To a solution of the residue **13** in CH_2Cl_2 (3.8 mL) was added $SOCl_2$ (61 μL, 0.85 mmol) at −78 °C, and the mixture was stirred for 1 h at the same temperature. After Et_3N (285 μL, 2.05 mmol) was added, the reaction mixture was allowed to warm to 0 °C and quenched with saturated aqueous NH_4Cl, followed by addition of CH_2Cl_2 (5 mL). The organic layer was separated, and the aqueous phase was further extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by FCC (PE-EtOAc, 10:1) afforded the product **14** (266 mg, 82% yield) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 7.5 Hz, 1 H), 7.69 (d, J = 7.5 Hz, 1 H), 7.48 (s, 0.4 H), 7.40 (s, 0.6 H), 7.34 (d, J = 12.0 Hz, 1 H), 7.08 (d, J = 12.0 Hz, 1 H), 6.98 (t, J = 7.5 Hz, 1 H), 5.25−5.38 (m, 1 H), 3.54−3.57 (m, 1 H), 3.34 (m, 0.4 H), 2.94 (m, 0.6 H), 2.81 (s, 1.8 H), 2.73 (s, 1.2 H), 1.64 (s, 9 H), 1.40 (s, 4 H), 1.05 (s, 5 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3, 154.9, 148.6, 140.4, 136.5, 134.4, 130.3, 126.6, 126.3, 125.7, 115.5, 84.5, 84.3, 80.4, 55.3, 55.0, 31.7, 30.0, 28.0, 27.7, 26.8; IR (KBr) 2978, 2931, 1738, 1696, 1530, 1416, 1369, 1282, 1254, 1157, 1092, 1052, 964, 861, 845, 775, 747 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{30}IN_3O_6Na$ $(M + Na)^+$ 594.1077; found 594.1074.

Compound 15. Compound **14** (110 mg, 0.19 mmol) and Ag_2CO_3 (106 mg, 0.38 mmol) were suspended in freshly distilled benzene (10 mL). $Pd(OAc)_2$ (4.3 mg, 0.019 mmol) was added to the solution, followed by the addition of triphenylphosphine (10 mg, 0.038 mmol). The mixture was stirred at rt for 24 h and quenched with saturated aqueous NH_4Cl, followed by the addition of EtOAc (5 mL). The organic layer was separated, and the aqueous phase was further extracted with EtOAc (2 × 15 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by FCC (PE-EtOAc, 10:1) afforded the isomers **15** (68 mg, 80% yield, ratio = 1.8:1): major isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (br s, 1 H), 7.75 (s, 1 H), 7.45 (d, J = 7.6 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 1 H), 7.29 (t, J = 7.5 Hz, 1 H), 6.41 (d, J = 4.6 Hz, 1 H), 5.22 (m, 1 H), 3.07−3.25 (m, 2 H), 2.33 (s, 3 H), 1.68 (s, 9 H), 1.51 (s, 9 H); minor isomer ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1 H), 7.48 (d, J = 7.8 Hz, 1 H), 7.44 (s, 1 H), 7.37 (d, J = 7.8 Hz, 1 H), 7.31 (t, J = 7.8 Hz, 1 H), 6.91 (d, J = 1.4 Hz, 1 H), 5.22 (m, 1 H), 3.07−3.25 (m, 2 H), 2.89 (s, 3 H), 1.66 (s, 9 H), 1.48 (s, 9 H); mixture of isomers ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 149.5, 140.6, 139.1, 135.1, 132.9, 130.5, 129.7, 126.0, 125.2, 123.9, 122.0, 121.8, 120.9, 118.1, 117.6, 117.0, 114.3, 113.7, 84.2, 84.1, 81.0, 80.5, 47.8, 36.6, 30.6, 30.4, 28.3, 28.1, 26.5; IR (KBr) 2977, 2930, 1734, 1695, 1523, 1442, 1392, 1366, 1331, 1301, 1282, 1255, 1147, 1122, 1049, 851, 767 cm^{-1}; HRMS (ESI) m/z calcd for $C_{23}H_{29}N_3O_6Na$ $(M + Na)^+$ 466.1954; found 466.1952.

Compound 28. A mixture of indium powder (1.48 g, 12.9 mmol), (S_R)-*N*-*tert*-butanesulfinamide (1.04 g, 8.6 mmol), compound **29** (2.00 g, 9.9 mmol), and $Ti(OEt)_4$ (3.6 mL, 17.2 mmol) in THF (18 mL) was stirred under argon for 1 h at 23 °C. At this time, allylic bromide (2.08 g, 17.2 mmol) was added and the reaction mixture was heated for 5 h at 60 °C. The mixture was cooled to room temperature, quenched with brine (18 mL), and diluted with EtOAc. The resulting suspension was filtered through a short pad of Celite and concentrated in vacuo. The residue was purified by FCC (PE-EtOAc, 4:1) to afford the epimers **28** (2.36 g, 79% yield, dr = 7:1) as a colorless liquid: ^{1}H NMR (400 MHz, $CDCl_3$) mixture of epimers δ 5.79−5.69 (m, 1 H), 5.13−5.09 (m, 1.75 H), 5.06−5.02 (m, 0.25 H), 3.60−3.55 (m, 2 H), 3.30−3.28 (m, 1 H), 3.21−3.12 (m, 1 H), 2.40−2.24 (m, 2 H), 1.56−1.50 (m, 4 H), 1.15 (s, 9 H), 0.84 (s, 9 H), −0.01 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) mixture of epimers δ 134.3, 134.0, 118.8, 117.7, 62.8, 62.6, 55.6, 55.6, 54.7, 40.4, 39.9, 31.7, 31.3, 28.8, 28.6, 25.8, 22.6, 18.2, −5.4; HRMS (ESI) m/z calcd for $C_{34}H_{74}N_2O_4S_2Si_2Na$ (2M + Na)$^+$ 717.4527; found 717.4498.

Compound 27. Epimers **28** (2.04 g, 5.9 mmol) and ethyl α-(bromomethyl)acrylate (4.55 g, 25.7 mmol) were dissolved in anhydride THF (60 mL) and HMPA (6 mL) with stirring under argon at 0 °C. NaH (0.62 g, 25.7 mmol) was added in 1 h. Then the mixture was stirred at room temperature for another 1 h. The mixture was cooled to 0 °C and quenched with brine carefully. The aqueous phase was extracted with EtOAc (3 × 50 mL). The organic layer was combined, washed with brine and dried over Na_2SO_4, filtered, and evaporated. The residue was purified by FCC (PE-EtOAc, 7:1) to afforded compound **27** as a colorless liquid (1.93 g, 74% yield): $[\alpha]_D^{20}$ + 18.5 (c 0.4, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, J = 1.2 Hz, 1 H), 5.90 (d, J = 1.2 Hz, 1 H), 5.78 (m, 1 H), 5.08−5.03 (m, 2 H), 4.25 (d, J = 18.4 Hz, 1 H), 3.75 (s, 3 H), 3.58 (m, 2 H), 3.41 (d, J = 18.4 Hz, 1 H), 2.94 (m, 1 H), 2.39 (m, 2 H), 1.82 (m, 1 H), 1.73 (m, 1 H), 1.59 (m, 2 H), 1.17 (s, 9 H), 0.87 (s, 9 H), 0.02 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 137.6, 136.0, 126.3, 117.2, 62.9, 57.9, 51.9, 44.1, 39.4, 30.6, 29.2, 25.9, 23.5, 18.3, −5.3, −5.4; IR (KBr) 2953, 2928, 2857, 1724, 1639, 1472, 1438, 1388, 1361, 1296, 1258, 1195, 1155, 1095, 835, 776 cm^{-1}; HRMS (ESI) m/z calcd for $C_{22}H_{44}NO_4SSi$ $(M + H)^+$ 446.2755; found 446.2753.

Compound 30. To a degassed solution of compound **27** (800 mg, 1.79 mmol) in DCM (600 mL) was added Grubbs II catalyst (76 mg, 0.09 mmol). The mixture was heated to reflux and stirred for 12 h. The solution was concentrated in vacuo, and the residue was purified by FCC (PE-EtOAc, 4:1) to afford compound **30** (674 mg, 90% yield) as a brown liquid: $[\alpha]_D^{20}$ − 12.1 (c 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 4.4 Hz, 1 H), 4.13 (d, J = 18.4 Hz, 1 H), 3.70 (s, 3 H), 3.59 (t, J = 5.6 Hz, 2 H), 3.48 (d, J = 18.4 Hz, 1 H), 3.42 (m, 1 H), 2.66 (d, J = 16.4 Hz, 1 H), 2.10 (dd, J = 3.6, 16.4 Hz, 1 H), 1.69−1.46 (m, 4 H), 1.17 (s, 9 H), 0.86 (s, 9 H), 0.01 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 136.5, 128.1, 62.6, 58.7, 55.7, 51.5, 35.6, 30.0, 28.8, 28.7, 25.8, 23.3, 18.2, −5.4; IR (KBr) 3510, 2922, 2855, 1638, 1431, 1375, 1321, 1161, 1062 cm^{-1}; HRMS (ESI) m/z calcd for $C_{40}H_{79}N_2O_8S_2Si_2$ $(2M + H)^+$ 835.4811; found 835.4789.

Compound 31. To a solution of compound **30** (1.36 g, 3.3 mmol) in anhydrous THF (33 mL) was added the TBAF·3H_2O (2.05 g, 6.5

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mmol). The solution was stirred for 2 h at room temperature, quenched with brine, and concentrated in vacuo, and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with brine (3 × 50 mL), dried over Na_2SO_4, filtered, and evaporated. The residue was purified by FCC (DCM-MeOH, 30:1) to afford compound **31** as a colorless liquid (935 mg, 95% yield): $[\alpha]_D^{20}$ − 24.4 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (d, *J* = 4.8 Hz, 1 H), 4.07 (d, *J* = 18.0 Hz, 1 H), 3.71 (s, 3 H), 3.64 (br s, 2 H), 3.57 (d, *J* = 18.8 Hz, 1 H), 3.54 (m, 1 H), 2.65 (dd, *J* = 3.2, 19.6 Hz, 1 H), 2.19−2.09 (m, 2 H), 1.72−1.49 (m, 4 H), 1.17 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 136.6, 128.1, 62.3, 58.8, 54.1, 51.6, 37.2, 29.5, 28.9, 28.8, 23.2; IR (KBr) 3411, 2949, 2870, 1712, 1658, 1436, 1384, 1362, 1265, 1186, 1061, 926 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{50}N_2O_8S_2Na$ (2M + Na)$^+$ 629.2901; found 629.2918.

Compound 26. To a solution of compound **31** (765 mg, 2.5 mmol) in anhydrous DCM (50 mL) was added the Dess−Martin periodinane (1.14 g, 2.7 mmol). The solution was stirred for 1 h at room temperature and quenched with saturated aqueous Na_2CO_3 solution. The aqueous phase was extracted with DCM. The organic layer was combined, dried over Na_2SO_4, filtered, and evaporated. The residue was purified by FCC (DCM-EtOAc, 3:1) to afford compound **26** (628 mg, 82% yield) as a pale yellow liquid: $[\alpha]_D^{20}$ − 11.6 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1 H), 6.98 (dd, *J* = 1.6, 6.0 Hz, 1 H), 4.11 (d, *J* = 18.4 Hz, 1 H), 3.71 (s, 3 H), 3.52−3.47 (m, 2 H), 2.70 (dd, *J* = 3.2, 19.6 Hz, 1 H), 2.57 (t, *J* = 7.6 Hz, 2 H), 2.11 (m, 1 H), 1.92 (m, 1 H), 1.75 (m, 1 H), 1.17 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.1, 165.4, 136.1, 128.0, 58.8, 54.0, 51.6, 40.9, 36.4, 28.9, 24.5, 23.3; IR (KBr) 3401, 2952, 2927, 1714, 1658, 1435, 1385, 1361, 1266, 1075, 1023, 918 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{28}H_{47}N_2O_8S_2$ (2M + H)$^+$ 603.2768; found 603.2779.

Compound 33. To a solution of compound **26** (400 mg, 1.3 mmol) in anhydrous DMF (4.8 mL) were added the 3-chloro-2-iodoaniline (**25**) (676 mg, 2.66 mmol) and DABCO·6H_2O (876 mg, 4.0 mmol) successively under an argon atmosphere. After oxygen was discharged with argon for 0.5 h, $Pd(OAc)_2$ (119.4 mg, 0.52 mmol) was added, and then the solution was heated at 80 °C for 6 h. The mixture was then filtered through a pad of Celite, extracted with EtOAc, washed with brine, dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by FCC (DCM-EtOAc, 3:1) to afford crude compound **32** (267 mg) as a yellow liquid.

The yellow liquid **32** mentioned above was dissolved in anhydrous CH_3CN. To the solution were added Boc_2O (170 mg, 0.78 mmol) and DMAP (16 mg, 0.13 mmol), and the mixture was stirred for 6 h. The solution was concentrated in vacuo, and the residue was purified by FCC (PE-EtOAc, 3:1) to afford compound **33** (272 mg, 39% yield two steps) as a white foam: $[\alpha]_D^{20}$ + 20.0 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 2.4 Hz, 1 H), 7.36 (s, 1 H), 7.21−7.19 (m, 2 H), 7.08 (d, *J* = 4.4 Hz, 1 H), 4.28 (d, *J* = 18.4 Hz, 1 H), 3.96 (dd, *J* = 7.2, 14.0 Hz, 1 H), 3.77 (s, 3 H), 3.64 (d, *J* = 18.4 Hz, 1 H), 3.18 (dd, *J* = 7.2, 14.4 Hz, 1 H), 3.04 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.61 (dd, *J* = 2.8, 18.8 Hz, 1 H), 2.24 (dd, *J* = 4.0, 18.8 Hz, 1 H), 1.67 (s, 9 H), 1.02 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 149.0, 137.1, 136.4, 128.0, 126.7, 125.9, 125.7, 125.0, 123.8, 117.0, 114.0, 84.4, 58.4, 56.7, 51.6, 35.3, 29.0, 28.1, 27.2, 23.0; IR (KBr) 2980, 2951, 1737, 1660, 1424, 1372, 1355, 1255, 1153, 1101, 1080 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{25}H_{34}ClN_2O_5S$ (M + H)$^+$ 509.1877; found 509.1881.

Compound 34. Compound **33** (360 mg, 0.71 mmol) was dissolved in a 1:1 mixture of anhydrous 1,4-dioxane and anhydrous MeOH (4.3 mL), and anhydrous HCl in dioxane (4 M solution in dioxane, 0.7 mL) was added. After the mixture was stirred at room temperature for 1 h, all volatiles were removed in vacuo, and the residue was dissolved in water and extracted with EtOAc. The water layer was basified to pH 8 with aqueous saturated $NaHCO_3$ and extracted with EtOAc. Combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by FCC (EtOAc) to afford compound **34** as a yellow liquid (255 mg, 89% yield): $[\alpha]_D^{20}$ − 45.0 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.4 Hz, 1 H), 7.47 (s, 1 H), 7.23−7.18 (m, 2 H), 7.02 (bs, 1 H), 3.72−3.69 (m, 4 H), 3.47 (dd, *J* = 2.4, 16.8 Hz, 1 H), 3.24 (dd, *J* = 4.4, 14.4 Hz, 1 H), 3.15−3.08 (m, 1 H), 2.82 (dd, *J* = 8.0, 14.4 Hz, 1 H), 2.37 (dd, *J* = 4.0, 19.2 Hz, 1 H), 2.17−2.10 (m, 1 H), 1.66 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 149.1, 137.9, 137.3, 129.6, 126.8, 126.2, 125.5, 125.0, 123.8, 116.9, 114.0, 84.2, 51.9, 51.5, 44.4, 32.8, 32.4, 28.1; IR (KBr) 3307, 2979, 2947, 2818, 1733, 1656, 1424, 1372, 1283, 1256, 1155, 1102, 1042 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{26}ClN_2O_4$ (M + H)$^+$ 405.1576; found 405.1563.

Compound 24. To a stirred mixture of compound **34** (180 mg, 0.45 mmol) and aqueous formaldehyde (0.18 mL, 2.25 mmol, 37%) in acetonitrile (11 mL) was added sodium cyanoborohydride (56 mg, 0.90 mmol). After being stirred for 20 min, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The aqueous layer was basified by addition of saturated aqueous Na_2CO_3. The aqueous solution was extracted with EtOAc. The organic layer was then dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by FCC (PE-EtOAc, 1:1) to afford compound **24** (152 mg, 81% yield) as a yellow liquid: $[\alpha]_D^{20}$ + 4.3 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1 H), 7.39 (s, 1 H), 7.20−7.19 (m, 2 H), 7.00−6.98 (m, 1 H), 3.76 (s, 3 H), 3.52−3.35 (m, 3 H), 3.17 (m, 1 H), 2.70 (dd, *J* = 10.0, 14.0 Hz, 1 H), 2.58 (s, 3 H), 2.24 (br s, 2 H), 1.67 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 149.2, 137.2, 137.1, 128.1, 127.1, 126.2, 125.4, 124.8, 123.7, 117.6, 114.0, 84.2, 56.8, 51.6, 50.8, 41.0, 28.6, 28.2, 25.7; IR (KBr) 2959, 2931, 2792, 2343, 2178, 1738, 1704, 1424, 1369, 1354, 1279, 1262, 1145, 1095 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}ClN_2O_4$ (M + H)$^+$ 419.1732; found 419.1719.

Compound 23. To a stirred solution of 2,2,6,6-tetramethylpiperidine (123 μL, 0.72 mmol) in THF (1 mL) was added *n*-BuLi (425 μL, 0.68 mmol, 1.6 M in hexanes) at 0 °C. After stirring for 30 min at room temperature, the mixture was cooled to −78 °C. Compound **24** (56.7 mg, 0.14 mmol) was dissolved in dried THF (1.5 mL), and added dropwise to the former mixture solution via syringe. After stirring for 40 min, saturated aqueous NH_4Cl solution was added. The reaction mixture was then allowed to warm to 0 °C and stirred for 20 min. The organic layer was separated, and the aqueous phase was further extracted with EtOAc (2 × 15 mL). The combined organic phases were dried over Na_2SO_4. Purification by FCC (PE-EtOAc, 3:1) afforded the mixed epimers **23** (42 mg, 74% yield, ratio = 2:1) as a yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (br s, 1 H), 7.48 (s, 0.7 H), 7.44 (s, 0.3 H), 7.18−7.17 (m, 2 H), 5.90−5.87 (m, 1 H), 5.78−5.70 (m, 1 H), 3.74 (s, 0.9 H), 3.70 (s, 2.1 H), 3.58−3.53 (m, 0.7 H), 3.47−3.41 (m, 1 H), 3.26−3.16 (m, 2.3 H), 2.84−2.76 (m, 1.3 H), 2.67−2.62 (m, 0.7 H), 2.54−2.52 (m, 3 H), 1.66 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 172.9, 149.2, 136.9, 130.6, 130.4, 127.3, 127.2, 126.1, 125.8, 125.8, 124.7, 124.6, 123.7, 123.6, 122.9, 122.3, 117.2, 116.7, 113.9, 84.0, 84.0, 61.2, 60.5, 54.0, 52.0, 51.9, 50.7, 43.0, 42.7, 41.6, 38.8, 29.6, 29.5, 28.1; HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}ClN_2O_4$ (M + H)$^+$ 419.1732; found 419.1721.

Compound 22. Compound **23** (30 mg, 0.072 mmol) dissolved in dry dioxane (3.6 mL) was degassed for 30 min. P(*t*-Bu)$_3$·HBF_4 (21 mg, 0.072 mmol), $Pd_2(dba)_3$·$CHCl_3$ (37 mg, 0.036 mmol), and Cy_2MeN (42 mg, 0.22 mmol) were added to the reaction, and the resulting reaction mixture was heated at 100 °C under an argon atmosphere for 1.5 h. After cooling, the reaction was quenched with saturated aqueous NH_4Cl, followed by addition of EtOAc (5 mL). The organic layer was separated, and the aqueous phase was further extracted with EtOAc (2 × 30 mL). The combined organic phases were washed with brine and dried over Na_2SO_4. Purification by FCC (PE-EtOAc, 3:1) afforded the starting material **23** (8.1 mg, 27% yield) and the product **22** (5.0 mg, 25% yield brsm) as a yellow solid: $[\alpha]_D^{20}$ − 163 (*c* 1.23, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1 H), 7.29−7.33 (m, 2 H), 7.13 (d, *J* = 7.28 Hz, 1 H), 7.05 (s, 1 H), 4.06 (s, 1 H), 3.71 (s, 3 H), 3.50 (d, *J* = 17.4 Hz, 1 H), 3.35−3.39 (m, 2 H), 2.95 (m, 1 H), 2.70 (m, 1 H), 2.60 (s, 3 H), 1.66 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 150.1, 140.4, 133.5, 131.6, 129.0, 127.1, 125.6, 120.0, 119.8, 115.4, 113.5, 83.4, 57.3, 51.6, 48.8, 42.3, 39.3, 37.4, 28.2; IR (KBr) 3434, 2922, 1730, 1257, 1116, 802 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{44}H_{53}N_4O_8$ (2M + H)$^+$ 765.3858; found 765.3856.

(+)-Lysergic Acid (1). To a solution of compound **22** (31 mg, 0.08 mmol) in ethanol (1 mL) was added 1 N KOH (1 mL). The reaction

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was heated at 70 °C for 3 h. The hot solution was treated with charcoal and filtered. The organic solvent was removed by evaporation. HCl (1 N) solution was used to carefully adjust the pH to 5.8 at 0 °C until a solid was formed. The aqueous solution was removed and the precipitate was washed with cold water and acetone to give (+)-lysergic acid (**1**) as a pale brown amorphous solid (11.2 mg, 52% yield), in agreement with the reported data by Hendrickson and Ohno: $[\alpha]_D^{20}$ + 40 (*c* 0.50, pyridine); ^{1}H NMR (400 MHz, pyridine-d_5) δ 11.66 (s, 1 H), 7.42 (d, *J* = 8.0 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.27 (t, *J* = 8.0 Hz, 1 H), 7.22 (s, 1 H), 7.15 (s, 1 H), 4.04 (m, 1 H), 3.61 (dd, *J* = 5.5, 14.5 Hz, 1 H), 3.52 (dd, *J* = 5.0, 11.2 Hz, 1 H), 3.29 (m, 1 H), 2.92 (m, 2 H), 2.51 (s, 3 H); ^{13}C NMR (100 MHz, pyridine-d_5) δ 175.1, 136.8, 136.1, 129.1, 127.4, 120.0, 119.8, 112.3, 110.6, 110.5, 63.8, 56.0, 43.9, 43.5, 27.9 (one of the sp^2 carbons was overlapped with C_5D_5N solvent peaks); IR (KBr) 3400, 1595, 1453 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{16}H_{17}N_2O_2$ $(M + H)^+$ 269.1285; found 269.1285.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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