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Six-Step Synthesis of (±)-Lysergic Acid

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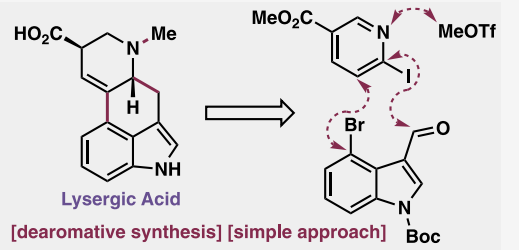
ABSTRACT: This article describes a concise synthesis of lysergic acid from simple aromatic precursors. The successful strategy relies on the coupling, dearomatization, and cyclization of a halopyridine with a 4-haloindole derivative in 6 total synthetic steps from commercial starting materials. In addition to highlighting the advantages of employing dearomative retrosynthetic analysis, the design is practical and anticipated to enable the synthesis of novel neuroactive compounds as exemplified by the synthesis of a novel natural product derivative, 12-chlorolysergic acid.



INTRODUCTION

Since Hofmann's discovery of lysergic acid diethylamide (LSD, **1**) in 1938, the medicinal wonders of this natural product derivative have proven both intriguing and controversial.[1,2] For instance, Sandoz Laboratories heralded LSD as "a cure for everything" in the 1940s, while the US congress, in partial response to the "counterculture" of the 1960s, made its possession and use illegal in 1968.[3] Despite this ongoing debate, some ergoline derivatives such as pergolide (**4**)[4] and lisuride (**5**)[5] have found their way to the clinic for the treatment of Parkinson's disease and migraines. These ergolines, in addition to the psychedelics ibogaine (**3**) and 2,5-dimethoxy-4-iodoamphetamine (**6**) are ligands for the 5-HT_{2A} GPCR, a key receptor responsible for many downstream neuropharmacological phenotypes.[6] Because of LSD's therapeutic potential, several X-ray crystallographic structures have recently been obtained that enable the design of 5-HT_{2A} ligands capable of novel neuropharmacology.[7−9] Thus, we maintained that a practical synthesis of diverse LSD (**1**) derivatives would aid this burgeoning realm of biomedical research.[10,11]

Recently, Olson and coworkers identified that **7**, bearing a simple substitution of the benzenoid ring of ibogaine (**3**), displayed similar psychoplastogenic effects without the psychedelic effects in **3** (Figure 1B).[12] This intriguing discovery, coupled with another study on dimethyltryptamine analogs,[13] spurred our curiosity regarding similar benzenoid substituent effects on the ergoline scaffold, which have been largely unexplored in the neuropharmacology of LSD.[14,15] Many ergoline derivatives have been accessed from natural isolates (e.g., **4**, **5**) via functionalization at chemically "available" sites.

As shown in Figure 1C, we reasoned that benzenoid substitution would require a short and modular synthesis in order to understand the potentially phenotypically beneficial substituent effects observed in other psychedelics.

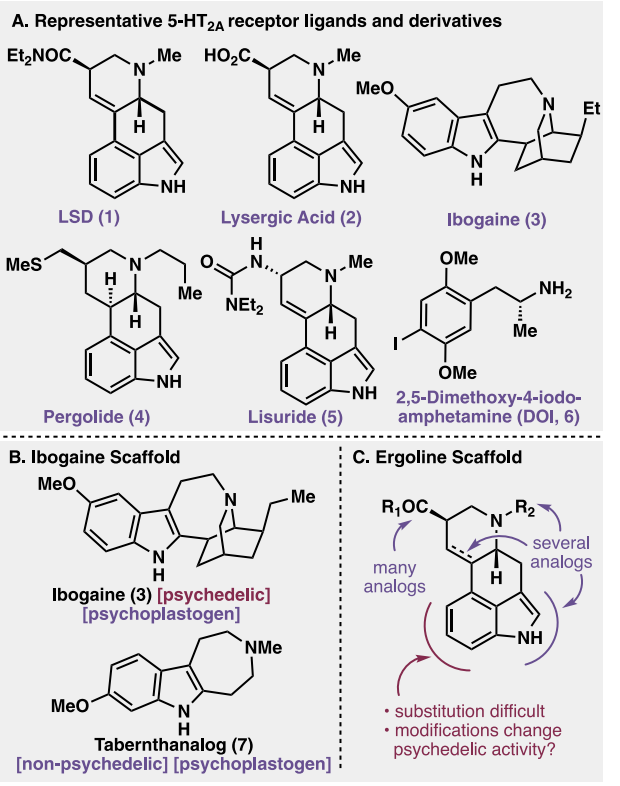


Figure 1. (A) 5-HT_{2A} ligands, (B) psychoplastogenic tryptamines, and (C) ergoline scaffold amenable for chemical modifications.

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Like many before us, targeting lysergic acid (**2**) was a starting point toward synthesizing and validating any psychoactive LSD derivatives.[16−35] Prior to our studies, the most concise approach was the controversial synthesis of **2** reported by Hendrickson[35] which was later disputed by both Nichols[36] and Boger.[37] Overall, we considered two retrosynthetic strategies to allow quick access to lysergic acid (**2**). In the first strategy (Figure 2), it was envisioned that the natural

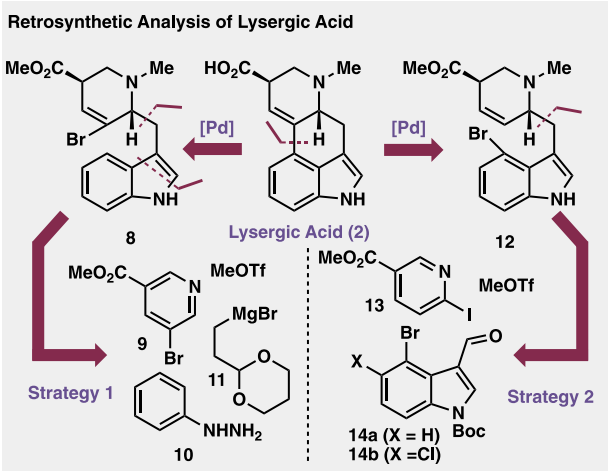


Figure 2. Lysergic acid retrosynthetic analyses.

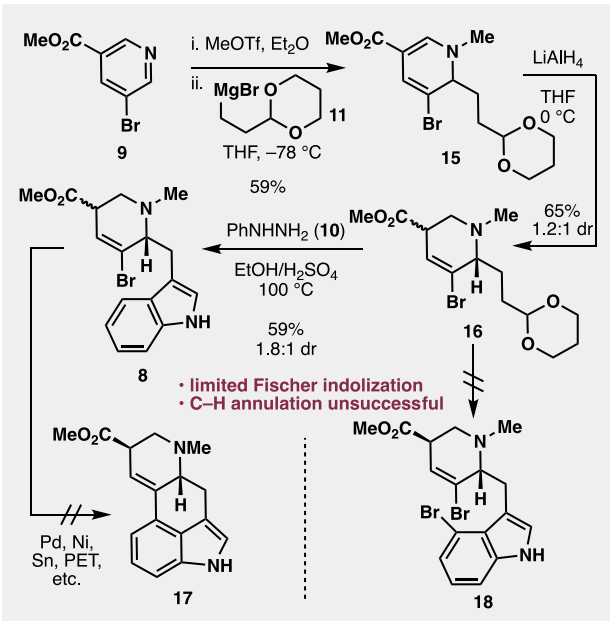
product would arise from a late-stage Pd-catalyzed annulation of vinyl bromide **8** via C−H vinylation of the C4 position of the pendant indole heterocycle.[38] Intermediate **8** would be the product of a Fischer indolization reaction with phenylhydrazine (**10**) and a tetrahydropyridine (not shown) synthesized from a dearomatization and reduction sequence between pyridine **9** and Grignard reagent **11**.[39] If the first strategy was inoperable (*vide infra*), it was also hypothesized that a Heck reaction, inspired by previous work from Fukuyama and Jia, could forge the scaffold of lysergic acid (**2**) from bromoindole **12** (Figure 2).[24−26] This tetrahydropyridine would be ultimately derived from pyridinium reduction following the coupling of iodide **13** and aldehyde **14a**, both of which are commercially available. While both approaches included attractive modularity and brevity, strategy 1 was pursued first.

RESULTS AND DISCUSSION

Scheme 1 depicts efforts toward **2** implementing strategy 1. Starting from bromopyridine **9**, methylation of the pyridine nitrogen with MeOTf generated an intermediate *N*-methylpyridinium that was trapped with Grignard reagent **11** to produce dihydropyridine **15** as the major regioisomer in a 2.6:1 C6/C4 ratio and in 82% overall yield (59% of **15**). From our previous studies on the regiochemistry of pyridinium dearomatizations, we predicted the combined directing effect of the ester and bromide substituents would increase addition at C6.[39]

Next, the reduction of the vinylogous carbamate in **15** with $LiAlH_4$ proceeded in 65% yield to deliver a 1:1 mixture of diastereomers of acetal **16**. This mixture was deemed inconsequential for the synthesis of **2**, as the alpha center to the ester is thermodynamically resolvable upon construction of the ergoline framework.[26,30] Acetal **16** was then treated with phenylhydrazine (**10**) and a 4% H_2SO_4/EtOH mixture at

Scheme 1. First-Generation Approach to Lysergic Acid



elevated temperature to afford indole **8** in 59% yield (1.8:1 dr). Notably, this Fischer indolization reaction was attempted with a variety of other phenylhydrazine derivatives that gave no observable indole products. This unexpected result impeded abilities to generate modified intermediates (e.g., **18**) in route to **2**.

With **8** in hand, our efforts focused on the C−H annulation to close the last six-membered ring found in lysergic acid (**2**). Initially, following prior precedent for this kind of transformation,[38] the only observable product was annulation at the C2 position of the indole heterocycle (not shown). Attempts to sterically deter this undesired cyclization were thwarted by the inability to properly functionalize or protect the indole nitrogen under basic conditions. Presumably, this was due to the base sensitivity of the tetrahydropyridine ring found in **8**, where attempts to deprotonate the indole nitrogen resulted in nonproductive decomposition pathways.[40] Further efforts to effect annulation of the vinyl bromide using Ni-catalysis or radical propagation[39,41] (e.g., PET, Bu_3SnH, and AIBN) also largely resulted in hydrodebromination of **8**. Additionally, while a reductive coupling tactic might have been possible through an intermediate such as **18**, the Fischer indolization of **16** was only operable with phenylhydrazine (**10**), disallowing access to benzenoid-functionalized indole congeners of **8**. With an unproductive annulation tactic and a limited Fischer indolization reaction, the second strategy outlined in Figure 1 became more attractive for the synthesis of **2**. As the same final ring-closing strategy would be needed, a tactical change in the placement of the halogen would likely allow for a more competent and reliable annulation.

Scheme 2 outlines the forward implementation of the second retrosynthetic strategy toward lysergic acid (**2**). Starting from iodopyridine **13**, magnesium−halogen exchange[42,43] generated a heterocyclic nucleophile that was trapped with commercial aldehyde **14a** to afford an intermediate alcohol (not shown) in 85% yield. Exposure of this intermediate to Et_3SiH and TFA cleaved the Boc protecting group and reduced benzylic alcohol to generate indole **19** in good yield on the gram scale. The next step in the

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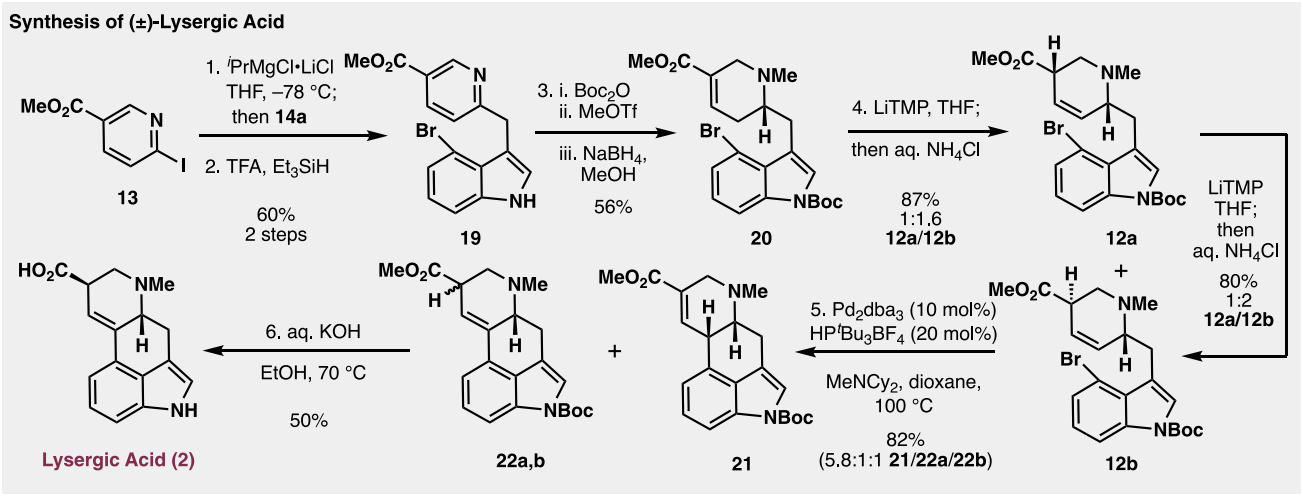
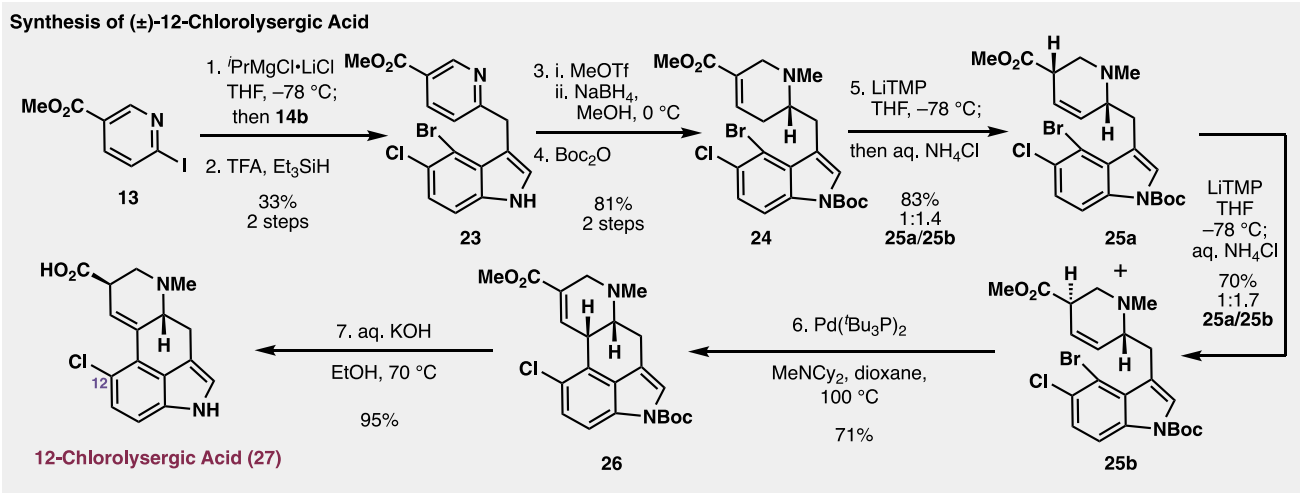
Scheme 2. Second-Generation Approach to Lysergic Acid



Scheme 3. Synthesis of 12-Chlorolysergic Acid



synthesis involved the key reductive dearomatization of the pyridine to a tetrahydropyridine. In the event, Boc protection of **19** followed by in situ methylation of the pyridine nitrogen resulted in an intermediate pyridinium salt. This nonisolated intermediate was treated with $NaBH_4$ to smoothly generate dihydropyridine **20** in 56% yield. Isomerization of the enoate with LiTMP gave a 1:1.6 diastereomeric mixture of **12a** and **12b**, among which the latter was poised for the key Heck annulation.[23,26] Conveniently, **12a** can be converted to **12b** upon its re-exposure to the isomerization conditions with a similar diastereomeric outcome. Treatment of **12b** with a catalytic amount of Fu's Pd^0 complex[44] (generated in situ) allowed for facile generation of **21** in excellent yield along with **22a** and **22b**, two diastereomeric alkene isomers, in a 5.8:1:1 ratio, respectively.

While similar transformations have been reported,[23,25,26] low yields and/or stoichiometric amounts of Pd have been required to affect this annulation, attesting to its challenging implementation. Simultaneous with our investigation, Wipf also reported a similar strategic implementation of this cyclization.[45] The stereochemistry of the center alpha to the ester in **12b** was crucial to the success of this reaction, allowing for *syn*-beta-hydride elimination to proceed following the migratory insertion of the putative arylpalladium(II) intermediate. Finally, saponification and isomerization of the mixture of **21**, **22a**, and **22b** was executed as previously reported to generate lysergic acid (**2**) in 50% yield.[30]

The successful generation of **2** encouraged the application of this synthetic platform toward the generation of new lysergic acid derivatives with novel benzenoid substitution. As a proof of principle, we adapted our synthesis to the generation of 12-chlorolysergic acid, which could potentially serve as a divergence point for exploring various C12 substituents (Scheme 3). Starting from iodopyridine **13**, magnesium-halogen exchange followed by the addition to aldehyde **14b** (see the Supporting Information for synthesis) resulted in an intermediate benzylic alcohol that was reduced to give biaryl **23** in the modest yield over 2 steps. Methylation and reduction of the intermediate was followed by the Boc protection of indole in 81% yield (over 2 steps) to afford **24**. This intermediate was subjected to base-mediated isomerization to give a 1:1.4 ratio of **25a**/**25b** in 83% yield. The minor undesired isomer (**25a**) could again be recycled to afford higher quantities of **25b**, which proceeded through the Heck cyclization to generate enoate **26** in 71% yield. Hydrolysis of this mixture gave 12-chlorolysergic acid (**27**) in good yield.

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CONCLUSIONS

In conclusion, a concise synthesis of lysergic acid (**2**) has been accomplished in 6 steps and 12% overall yield from commercially available materials (**13** and **14**). Central to the efficiency of this approach was the strategic and redox-economic utilization of heteroaromatic starting materials as functionalized precursors to the ergoline core. While our initial approach was initially thwarted by tactical limitations, the inversion of polar synthons enabled the construction of the final tetracyclic core. Furthermore, the synthesis of 12-chlorolysergic acid (**27**) was accomplished through the adaptation of the successful second-generation approach, demonstrating entry into novel molecular space unlocked by this synthetic blueprint. We contend that this synthetic advance holds great promise for the increased utilization of psychedelics and their derivatives as new neuropharmacological treatments.

EXPERIMENTAL SECTION

General. All reactions were performed using flame-dried round-bottom flasks or reaction vessels unless otherwise stated. Reactions were carried out under an inert atmosphere of nitrogen with dry solvents, unless otherwise stated. Dichloromethane (CH_2Cl_2), diethyl ether (Et_2O), 1,4-dioxane, methanol (MeOH), and tetrahydrofuran (THF) were obtained by passing the previously degassed solvents through activated alumina columns. Methyltriflate, 2,2,6,6-tetramethylpiperidine, and triethylsilane were purified via distillation prior to use. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin-layer chromatography carried out on Merck silica gel plates (glass-backed, 60G, F-254). Basic silica plates were prepared by treating commercial silica gel plates with 50:1 hexane−triethylamine followed by evaporation under reduced pressure. Thin layer chromatography (TLC) plates were visualized using ultraviolet light and an appropriate developing agent. NMR spectra were recorded on a Bruker Avance III 400, 500, 600, or 700 MHz NMR spectrometer and were calibrated using a residual solvent as an internal reference ($CDCl_3$: ^{1}H NMR δ = 7.26, ^{13}C{H} NMR δ = 77.16; CD_2Cl_2: ^{1}H NMR δ = 5.32; Pyr-d_5: ^{1}H NMR δ = 8.74, 7.58, 7.22, ^{13}C{H} NMR δ = 150.35, 135.91, 123.87.) The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, dq = doublet of quartets, dtt = doublet of triplets of triplets, m = multiplet, br = broad, app.d = apparent doublet, and app.t = apparent triplet. Flash column chromatography was performed using VWR silica gel (irregular, 60 Å, 40−60 μm). Basic silica gel was prepared by treating commercial silica gel with 50:1 hexane−triethylamine followed by evaporation under reduced pressure. Preparatory TLC was performed on Merck silica gel plates (glass-backed, 60G, F-254) and basic silica plates. High-resolution mass spectroscopy (HRMS) spectra were recorded on an Agilent 6230 TOF-MS spectrometer (DART) or a liquid chromatography−mass spectroscopy (LC−MS) spectrometer (ESI).

Methyl-6-(2-(1,3-dioxan-2-yl)ethyl)-5-bromo-1-methyl-1,6-dihydropyridine-3-carboxylate (15). This compound was prepared following the reported procedure:[39] in a 30 mL test tube, pyridine **9** (*AA Blocks*) (0.216 g, 1.00 mmol) was suspended in Et_2O (1.00 mL) and the mixture was placed under a N_2 atmosphere. The reaction vessel was placed in a water bath, and the mixture was stirred lightly. MeOTf (0.110 mL, 1.00 mmol) was added dropwise to the mixture, and the reaction was stirred for 1 h. After the disappearance of the starting material as determined by TLC, the thick, white mixture was concentrated under reduced pressure and redissolved in THF (4.00 mL) before being cooled to −78 °C. Grignard reagent **11** (0.219 mL, 1.00 M, 0.219 mmol) was added dropwise to the reaction, and the resulting yellow mixture was subjected to continuous stirring for 2 h. The reaction was then quenched with the addition of a sat. aqueous $NaHCO_3$ solution (4 mL), and the mixture was allowed to warm to rt. The product was extracted with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (gradient 4:1 → 7:3 → 3:2 → 1:1 hexanes:EtOAc, silica) to afford 203.9 mg (59% yield) of **15**. ^{1}H NMR (400 MHz, CD_2Cl_2): δ 7.26 (s, 1H), 6.71 (d, J = 1.1 Hz, 1H), 4.54−4.47 (m, 1H), 4.38 (t, J = 3.8 Hz, 1H), 4.05−4.00 (m, 2H), 3.75−3.67 (m, 2H), 3.60 (s, 3H), 2.96 (s, 3H), 2.02−1.94 (m, 1H), 1.85−1.65 (m, 3H), 1.65−1.55 (m, 1H), 1.29 (dtt, J = 13.4, 2.7, 1.4 Hz, 1H) ppm.

Methyl-6-(2-(1,3-dioxan-2-yl)ethyl)-5-bromo-1-methyl-1,2,3,6-tetrahydropyridine-3-carboxylate (16a,b). To a stirring suspension of acetal **15** (1.00 g, 2.89 mmol) in THF (15.00 mL) at 0 °C was added a suspension of $LiAlH_4$ (84.4 mg, 2.22 mmol) in THF (15.00 mL) over 5 min. The reaction mixture was stirred for 40 min. Upon completion of TLC, the mixture was cooled to −78 °C, and EtOAc (7 mL) was added in one portion. The mixture was then stirred at −78 °C for 5 min, warmed to 0 °C, and stirred for 5 min. A sat. solution of Rochelle salt (7 mL) was then added, and the mixture was stirred for 10 min. The mixture was diluted with water (20 mL), and the product was extracted with EtOAc (3 × 20 mL). The combined organic layer was washed with brine (20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (1:1 hexane−EtOAc eluent, silica) to afford 654 mg (65% yield) of tetrahydropyridine **16** as a yellow oil and a 1.2:1 mixture of diastereomers. R_f = 0.43 (1:1 hexane−EtOAc eluent, silica). ^{1}H NMR (**16a**) (500 MHz, $CDCl_3$): δ 6.21 (dt, J = 3.2, 1.0 Hz, 1H), 4.56−4.52 (m, 1H), 4.11−4.05 (m, 2H), 3.77−3.71 (m, 2H), 3.69(s, 3H), 3.42−3.36 (m, 1H), 3.19−3.09 (m, 1H), 2.90−2.78 (m, 2H), 2.44 (s, 3H), 2.12−1.99 (m, 1H), 1.99−1.84 (m, 1H), 1.82−1.72 (m, 1H), 1.71−1.53 (m, 2H), 1.35−1.28 (m, 1H) ppm. (**16b**) (500 MHz, $CDCl_3$): δ 6.31 (q, J = 1.5 Hz, 1H), 4.56−4.52 (m, 1H), 4.11−4.05 (m, 2H), 3.77−3.71 (m, 2H), 3.70 (s, 3H), 3.19−3.09 (m, 2H), 2.96−2.91 (m, 1H), 2.90−2.78 (m, 1H), 2.37 (s, 3H), 2.12−1.99 (m, 1H), 1.99−1.84 (m, 1H), 1.82−1.72 (m, 1H), 1.71−1.53 (m, 2H), 1.35−1.28 (m, 1H). ^{13}C{H} NMR (**16a** and **16b**) (126 MHz, $CDCl_3$): *(25 of 26 peaks observed)* δ 172.4, 172.1, 128.0, 126.9, 126.1, 124.6, 102.4, 102.4, 67.0, 67.0, 66.4, 66.2, 52.3, 52.3, 50.1, 46.5, 43.1, 42.5, 42.3, 39.8, 32.0, 30.2, 26.0, 25.9, 24.7 ppm. HRMS (DART-TOF) m/z: $[M + H]^+$ Calcd for $C_{14}H_{22}BrNO_4H$ 348.0805; found 348.0804.

Methyl-6-((1*H*-indol-3-yl)methyl)-5-bromo-1-methyl-1,2,3,6-tetrahydropyridine-3-carboxylate (8a,b). To a scintillation vial containing tetrahydropyridines **16a** and **16b** (155 mg, 0.444 mmol) and phenylhydrazine (131 μL, 1.33 mmol) was added a solution mixture of 22:1 MeOH/conc. H_2SO_4 (3.00 mL). Initially, a white solid and red solution formed. The vial was flushed with N_2 and sealed with a Teflon cap. The suspension was heated in an oil bath and stirred at 100 °C. After solubilizing, the reaction mixture turned deep red in color and stirred at 100 °C for additional 3 h. After this time, the reaction mixture was cooled to rt. and poured over a 1:1 mixture of a sat. aqueous Na_2CO_3 solution and ice (6 mL). The product was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (13:7 hexanes/EtOAc eluent, silica) to afford 94.7 mg (59% yield) of indoles **8a** and **8b** as a yellow oil and a mixture of diastereomers (1.8:1 dr). R_f = 0.39 (13:7 hexanes:EtOAc eluent, silica). ^{1}H NMR (**8a**) (600 MHz, $CDCl_3$): δ 8.10 (s, 1H), 7.70 (app. d, J = 7.7 Hz, 1H), 7.33 (app. d, J = 8.0 Hz, 1H), 7.18 (app. t, J = 7.5 Hz, 1H), 7.15−7.09 (m, 2H), 6.33 (s, 1H), 3.69 (s, 3H), 3.54−3.44 (m, 1H), 3.41−3.25 (m, 3H), 3.09−2.80 (m, 2H), 2.45 (s, 3H) ppm. (**8b**) (600 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.70 (app. d, J = 7.7 Hz, 1H), 7.33 (app. d, J = 8.0 Hz, 1H), 7.18 (app. t, J = 7.5 Hz, 1H), 7.15−7.09 (m, 2H), 6.39 (s, 1H), 3.71 (s, 3H), 3.54−3.44 (m, 1H), 3.41−3.25 (m, 3H), 3.09−2.8 (m, 2H), 2.45 (s, 3H) ppm. (**8a** and **8b**) ^{13}C{H} NMR (151 MHz, $CDCl_3$): *(27 of 34 peaks observed)* δ 172.2, 136.2, 136.2, 127.7, 125.8, 125.0, 122.9, 122.0, 121.9, 119.4, 119.4, 119.2, 119.1, 111.3, 111.2, 67.3, 67.3, 52.5, 52.3,

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48.7, 45.9, 43.3, 42.3, 41.7, 39.5, 27.5, 26.8 ppm. HRMS (DART-TOF) *m/z*: $[M-H]^+$ calcd for $C_{17}H_{19}BrN_2O_2H$ 361.0546; found 361.0515.

Methyl-6-((1*H*-indol-3-yl)methyl)nicotinate (19). To a solution of pyridyl iodide **13** (*AA Blocks*) (1.32 g, 5.00 mmol) in THF (5.00 mL) cooled in a $CHCl_3$/dry ice bath (−61 °C) was added a solution of *i*-PrMgCl·LiCl (5.00 mL, 1.00 M, 5.00 mmol) over 2 min. The mixture was stirred in the cooling bath for 1 h. Upon consumption of **13** as determined by TLC, a solution of indole **14a** (1.78 g, 5.50 mmol) in THF (3.00 mL) was added dropwise over 2 min. The resulting solution was stirred in the cooling bath for 1 h. After this time, the bath was removed, and the reaction mixture was slowly warmed to rt. The reaction mixture turned dark green upon warming and then amber after approximately 1 h at rt. The mixture was quenched with a sat. aqueous solution of NH_4Cl (10 mL), diluted with water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (1:1:0.05 hexanes−EtOAc: CH_2Cl_2 eluent, silica) to afford 1.95 g (85% yield) of an intermediate alcohol as beige wax (S-1, see the Supporting Information). R_f = 0.31 (4:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 8.28−8.18 (m, 2H), 7.46 (s, 1H), 7.42 (d, *J* = 7.8 Hz, 2H), 7.17 (t, *J* = 8.1 Hz, 1H), 6.75 (s, 1H), 3.95 (s, 3H), 1.61 (s, 9H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 165.6, 165.2, 149.6, 148.9, 138.0, 137.2, 127.6, 127.5, 126.5, 125.5, 125.1, 122.2, 121.4, 114.7, 113.5, 84.7, 67.9, 52.5, 28.1 ppm. HRMS (DART-TOF) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{21}BrN_2O_5H$ 461.0712; found 461.0735.

To a stirring solution of alcohol **S-1** (1.95 g, 4.23 mmol) in THF (4.20 mL) at 0 °C was added TFA (12.60 mL) in one portion turning the mixture dark amber. The mixture was warmed to rt., and after 30 min, Et_3SiH (4.05 mL, 25.4 mmol) was added and stirred for 14 h at 35 °C. Upon completion as determined by ^{1}H NMR analysis of aliquots from the reaction, the mixture was diluted with EtOAc (30 mL) and poured into a sat. aqueous solution of $NaHCO_3$ (100 mL). The mixture was then adjusted to pH 7 using $NaHCO_3$ and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (1:1 hexanes−EtOAc eluent, silica) to afford 1.02 g (70% yield) of **19** as beige wax. R_f = 0.35 (1:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.17 (s, 1H), 8.62 (s, 1H), 8.15 (dd, *J* = 8.2, 2.2 Hz, 1H), 7.28 (d, *J* = 7.7 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 8.2 Hz, 1H), 7.04−6.96 (m, 2H), 4.65 (s, 2H), 3.93 (s, 3H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 166.7, 166.0, 150.3, 137.8, 137.6, 125.4, 125.3, 124.1, 123.5, 123.1, 122.7, 114.2, 113.1, 110.7, 52.3, 35.1 ppm. HRMS (DART-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{13}BrN_2O_2H$ 345.0238; found 345.0257.

***tert*-Butyl-3-((5-(methoxycarbonyl)-1-methyl-1,2,3,6-tetrahydropyridin-2-yl)methyl)-1*H*-indole-1-carboxylate (20).** To a solution of indole **19** (85.0 mg, 246 μmol) and Boc_2O (57.1 mg, 0.262 mmol) in CH_2Cl_2 (12.00 mL), DMAP (1.6 mg, 52.0 μmol) was added and stirred at rt. After 1.5 h, the reaction was complete as determined by TLC. The mixture was cooled to 0 °C and MeOTf (28.7 μL, 262 μmol) was added in one portion. After 1.5 h at 0 °C, the reaction was complete, as determined by TLC. To this mixture, a solution of $NaBH_4$ (56.5 mg, 1.49 mmol) in MeOH (1.20 mL) was added to the pyridinium over 1 min, turning the reaction bright canary yellow. This combined mixture was stirred for 1 h at 0 °C and then quenched with a 1:1 mixture of a sat. aqueous solution of $NaHCO_3$ and acetone (2 mL). The mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (3:2 EtOAc−hexanes eluent, silica) to afford 63.3 mg (56% yield) of tetrahydropyridine **20** as a white foam. R_f = 0.40 (3:2 EtOAc−hexanes eluent, silica). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 (d, *J* = 8.3 Hz, 1H), 7.40 (s, 1H), 7.35 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 8.1 Hz, 1H), 6.96 (s, 1H), 3.73 (s, 3H), 3.52−3.31 (m, 3H), 3.17 (q, *J* = 4.6 Hz, 1H), 2.69 (dd, *J* = 14.2, 10.0 Hz, 1H), 2.54 (s, 3H), 2.20 (s, 2H), 1.65 (s, 9H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 166.4, 149.1, 137.2, 137.0, 128.4, 128.1, 127.3, 125.8, 125.1, 117.9, 114.5, 114.1, 84.3, 56.7, 51.6, 51.0, 40.8, 28.4, 28.2, 25.9 ppm. HRMS (DART-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{27}BrN_2O_4H$ 463.1232; found 463.1230.

***tert*-Butyl-3-((5-(methoxycarbonyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl)methyl)-1*H*-indole-1-carboxylate (12a,b).** To a stirring solution of HTMP (93.7 μL, 0.55 mmol) in THF (1.0 mL), *n*-BuLi (230 μL, 2.35 M, 0.54 mmol) was added at 0 °C. The solution was stirred for 50 min before cooling to −78 °C, after which tetrahydropyridine **20** (0.05 g, 0.108 mmol) was added dropwise in THF (1.00 mL). The mixture changed from light yellow to amber upon addition. The reaction mixture was stirred at −78 °C for 1 h, warmed to 0 °C, and then stirred for an additional 20 min. The reaction was quenched with a sat. aqueous solution of NH_4Cl (1.0 mL). This mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on neutralized silica (4:1 hexanes−EtOAc eluent, silica) to afford 27.2 mg (54% yield) of the major diastereomer **12b** and 16.6 mg (33% yield) of the minor diastereomer **12a** as yellow oils in a 1.6:1 ratio. (**12a**) R_f = 0.57 (1:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.53 (s, 1H), 7.37 (dd, *J* = 7.8, 0.9 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 5.89 (d, *J* = 10.3 Hz, 1H), 5.71 (d, *J* = 10.3 Hz, 1H), 3.70 (s, 3H), 3.59 (dd, *J* = 14.8, 4.6 Hz, 1H), 3.48−3.42 (m, 1H), 3.30−3.25 (m, 1H), 3.20 (dd, *J* = 11.7, 5.3 Hz, 1H), 2.86 (dd, *J* = 15.0, 9.6 Hz, 1H), 2.68 (t, *J* = 10.2 Hz, 1H), 2.56 (s, 3H), 1.66 (s, 9H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 173.0, 149.2, 136.9, 130.4, 128.7, 127.3, 126.3, 125.0, 123.1, 117.1, 114.5, 114.0, 84.2, 61.1, 54.0, 52.0, 43.0, 41.6, 29.3, 28.2 ppm. HRMS (DART-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{27}BrN_2O_4H$ 463.1232; found 463.1229.

(12b). R_f = 0.60 (1:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.6 Hz, 1H), 7.48 (s, 1H), 7.38 (d, *J* = 8.7 Hz, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 5.91 (d, *J* = 10.6 Hz, 1H), 5.75 (d, *J* = 10.3 Hz, 1H), 3.75 (s, 3H), 3.53−3.45 (m, 1H), 3.40−3.33 (m, 1H), 3.32−3.22 (m, 2H), 2.92−2.83 (m, 2H), 2.56 (s, 3H), 1.67 (s, 9H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 173.5, 149.2, 137.0, 130.4, 128.6, 127.2, 126.2, 124.9, 122.5, 117.5, 114.5, 114.0, 84.1, 60.3, 52.1, 50.3, 42.7, 38.5, 29.4, 28.2. HRMS (DART-TOF) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{27}BrN_2O_4H$ 463.1232; found 463.1226.

Recycling of 12a. To a stirring solution of HTMP (340 μL, 2.01 mmol) in THF (2.0 mL), *n*-BuLi (1.02 mL, 1.93 M, 1.97 mmol) was added at 0 °C. The solution was stirred for 50 min before cooling to −78 °C, after which tetrahydropyridine **12a** (0.183 g, 0.395 mmol) was added dropwise in THF (2.00 mL). The mixture changed from light yellow to amber upon addition. The reaction mixture was stirred at −78 °C for 1 h, warmed to 0 °C, and then stirred for an additional 20 min. The reaction was quenched with a sat. aqueous solution of NH_4Cl (1.0 mL). This mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on neutralized silica (4:1 hexanes−EtOAc eluent, silica) to afford 99 mg (54% yield) of the major diastereomer **12b** and 48 mg (26% yield) of the minor diastereomer **12a** with a 2:1 ratio.

Indoles 21 and 22a,b. In a reaction vial, $Pd_2(dba)_3$ (5.0 mg, 5.4 μmol) and $P(t\text{-}Bu)_3HBF_4$ (3.0 mg, 10.8 μmol) were charged with tetrahydropyridine **12a** (25.0 mg, 0.054 mmol) in degassed 1,4-dioxane (2.70 mL), followed by Cy_2NMe (13.9 μL, 64.8 μmol). The mixture was heated in an oil bath at 100 °C for 12 h. Upon completion as determined by TLC, the mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (1:2 hexanes−EtOAc eluent, silica) to afford 17.0 mg (82% yield) of an inconsequential

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5.8:1:1 mixture of tetracyclic compounds **21:22a:22b** as a yellow oil. (**21**) R_f = 0.23 (1:1 hexanes−EtOAc eluent, silica).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.37−7.27 (m, 2H), 7.13 (d, J = 7.3 Hz, 1H), 7.04 (s, 1H), 4.07 (s, 1H), 3.71 (s, 3H), 3.55−3.47 (m, 1H), 3.41−3.32 (m, 2H), 2.95 (dd, J = 15.4, 4.6 Hz, 1H), 2.73−2.65 (m, 1H), 2.60 (s, 3H), 1.66 (s, 9H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 166.0, 150.0, 140.4, 135.8, 131.5, 128.9, 126.9, 125.6, 120.0, 119.8, 115.4, 113.6, 83.4, 57.3, 51.7, 48.6, 42.2, 39.2, 36.7, 28.2 ppm.

(22a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.37−7.27 (m, 2H), 7.13 (d, J = 7.3 Hz, 1H), 6.60 (s, 1H), 3.78 (s, 3H), 3.55−3.47 (m, 2H), 3.41−3.32 (m, 2H), 2.73−2.65 (m, 2H), 2.58 (s, 3H), 1.66 (s, 9H) ppm *(Relative stereochemistry not determined)*. (**22b**) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.37−7.27 (m, 2H), 7.13 (d, J = 7.3 Hz, 1H), 6.55 (d, J = 4.0 Hz, 1H), 3.73 (s, 3H), 3.55−3.47 (m, 1H), 3.41−3.32 (m, 3H), 2.73−2.65 (m, 2H), 2.55 (s, 3H), 1.66 (s, 9H) ppm. *(Relative stereochemistry not determined)*. (**22a and 22b**) ^{13}C{H} NMR (151 MHz, $CDCl_3$): *(26 of 40 peaks observed)* δ 173.2, 172.5, 156.7, 125.5, 119.7, 119.0, 118.4, 116.2, 115.9, 114.2, 114.2, 62.2, 62.3, 54.6, 53.0, 52.2, 52.1, 43.5, 43.5, 41.9, 41.0, 29.0, 26.7, 26.7, 24.7, 23.5 ppm. Mixture of **21:22a:22b** HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}N_2O_4H$ 383.1970; found 383.1951.

Lysergic Acid (2). To a stirring solution of tetracyclic compounds **21:22a:22b** (19 mg, 0.049 mmol) in ethanol (0.625 mL) was added 1 N KOH (0.625 mL) and the mixture was heated in an oil bath at 70 °C for 3 h. Upon completion as determined by TLC, the mixture was allowed to cool to rt and acidified to pH 5.8 using 1 N HCl. The resulting solution was concentrated, and the residue was washed with cold water (3 × 1 mL) and acetone (1 mL) before being extracted with pyridine (1 mL). Evaporation of pyridine afforded 7.0 mg (50% yield) of lysergic acid **2** as a brown solid, in agreement with the reported data by Jia. ^{1}H NMR (500 MHz, pyr-D5) δ 11.69 (s, 1H), 7.45 (dd, J = 12.5, 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 4.09−4.03 (m, 1H), 3.64 (dd, J = 14.5, 5.5 Hz, 1H), 3.57−3.51 (m, 1H), 3.34−3.28 (m, 1H), 3.00−2.86 (m, 2H), 2.53 (s, 3H) ppm.

Methyl 6-((4-Bromo-5-chloro-1*H*-indol-3-yl)methyl)-nicotinate (23). To a solution of pyridyl iodide **13** (0.668 g, 2.54 mmol) in THF (12.5 mL) cooled in an acetone/dry ice bath (−78 °C) was added a solution of *i*-PrMgCl·LiCl (2.54 mL, 1.00 M, 2.54 mmol) dropwise over 2 min. The mixture was stirred in the cooling bath for 1 h. Upon consumption of **13** as determined by TLC, a solution of aldehyde **14b** (1.00 g, 2.79 mmol) in THF (12.5 mL) was added dropwise over 2 min. After 10 min, the resulting solution was warmed to 0 °C and stirred in the cooling bath for 9 h. After this time, the mixture was quenched with a sat. aqueous solution of NH_4Cl (10 mL), diluted with water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (4:1 hexanes−EtOAc eluent, silica) to afford 1.95 g (46% yield) of an intermediate alcohol as a light orange oil (S-3, see the Supporting Information). R_f = 0.67 (1:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.22 (s, 1H), 8.28 (dd, J = 8.2, 2.1 Hz, 1H), 8.17 (d, J = 8.9 Hz, 1H), 7.51 (s, 1H), 7.43 (d, J = 8.8 Hz, 1H), 7.39 (d, J = 8.2 Hz, 1H), 6.79 (s, 1H), 3.97 (s, 3H), 1.62 (s, 9H) ppm. ^{13}C{H} NMR (176 MHz, $CDCl_3$): δ 165.2, 164.8, 149.2, 148.7, 138.5, 135.2, 130.0, 129.2, 127.6, 126.0, 125.4, 122.0, 121.6, 115.5, 113.5, 85.1, 67.7, 52.6, 28.1 ppm. HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{21}H_{20}BrClN_2O_5H$ 495.0322; found 495.0317.

To a stirring solution of the above alcohol (**S-3**, 0.222 g, 0.448 mmol) in THF (1.35 mL) at 0 °C was added TFA (4.05 mL) in one portion turning the mixture dark amber. The mixture was warmed to rt., and after 1 h, Et_3SiH (0.690 mL, 4.31 mmol) was added and stirred for 9 h at 50 °C. Upon completion as determined by TLC, the mixture was diluted with EtOAc (30 mL) and poured into a sat. aqueous solution of $NaHCO_3$ (100 mL). The mixture was then adjusted to pH 7 using $NaHCO_3$ and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (6:4 hexanes−EtOAc eluent, silica) to afford 121 mg (71% yield) of indole **23** as a beige foam. R_f = 0.32 (1:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.14 (s, 1H), 8.65 (s, 1H), 8.17 (d, J = 2.2 Hz, 1H), 7.23−7.15 (m, 3H), 7.06 (s, 1H), 4.64 (s, 2H), 3.93 (s, 3H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$): δ 166.4, 165.9, 150.1, 137.8, 135.7, 126.9, 126.6, 126.3, 123.8, 123.7, 122.8, 113.8, 113.6, 111.5, 52.4, 35.2. HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{12}BrClN_2O_2H$ 378.9849; found 378.9852.

***tert*-Butyl 4-bromo-5-chloro-3-((5-(methoxycarbonyl)-1-methyl-1,2,3,6-tetrahydropyridin-2-yl)methyl)-1*H*-indole-1-carboxylate (24).** To a solution of indole **23** (271 mg, 0.714 mmol) in CH_2Cl_2 (7.14 mL) was added MeOTf (0.094 mL, 0.857 mmol) in one portion at 0 °C. After 1.5 h, the reaction was complete as determined by TLC. The mixture was concentrated under reduced pressure, and the residue was dissolved in MeOH (7.14 mL) and then cooled to 0 °C. To this solution, $NaBH_4$ (108 mg, 2.85 mmol) was added over 1 min turning the reaction bright canary yellow. This mixture was stirred at 0 °C for 6 h before the reaction was quenched with a 1:1 mixture of a sat. aqueous solution of $NaHCO_3$ and acetone (2 mL). The mixture was extracted with EtOAc (3 × 15 mL), the combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (9:1: CH_2Cl_2−MeOH eluent, silica) to afford 250 mg (88% yield) of an intermediate tetrahydropyridine **S-4** as an off-white foam (S-4, see the Supporting Information). R_f = 0.44 (9:1: CH_2Cl_2−MeOH eluent, silica). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.94 (s, 1H), 7.17 (d, J = 0.9 Hz, 1H), 7.12 (d, J = 0.8 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 6.99−6.96 (m, 1H), 3.75 (s, 3H), 3.56−3.51 (m, 1H), 3.49 (dd, J = 14.2, 4.9 Hz, 1H), 3.40−3.35 (m, 1H), 3.18 (dq, J = 10.5, 5.4 Hz, 1H), 2.77 (dd, J = 14.3, 9.5 Hz, 1H), 2.57 (s, 3H), 2.21−2.16 (m, 2H) ppm. ^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 166.5, 137.6, 135.7, 127.8, 126.8, 126.1, 126.1, 123.3, 114.0, 113.7, 111.4, 57.7, 51.7, 51.1, 40.6, 28.2, 26.1 ppm. HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{18}BrClN_2O_2H$ 397.0318; found 397.0311.

To a solution of the above tetrahydropyridine (**S-4**, 224 mg, 0.561 mmol) and Boc_2O (134 mg, 0.617 mmol) in CH_2Cl_2 (5.60 mL) was added DMAP (13.7 mg, 0.112 mmol) and stirred at rt. After 9 h, the reaction was complete as determined by TLC, and the reaction was concentrated under reduced pressure. The crude residue was purified by flash column chromatography silica (1:1 hexanes−EtOAc eluent, silica) to afford 247 mg (92%) of carbamate **24** as an off-white foam. R_f = 0.31 (1:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (400 MHz, $CDCl_3$) 8.09 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.35 (d, J = 8.9 Hz, 1H), 7.02−6.92 (m, 1H), 3.75 (s, 3H), 3.54−3.32 (m, 3H), 3.22−3.13 (m, 1H), 2.71 (dd, J = 14.2, 9.8 Hz, 1H), 2.55 (s, 3H), 2.24−2.18 (m, 2H), 1.66 (s, 9H) ppm.^{13}C{H} NMR (151 MHz, $CDCl_3$) δ 166.4, 148.8, 137.1, 135.0, 130.1, 129.5, 128.0, 126.8, 125.6, 118.1, 115.2, 114.6, 114.0, 84.7, 56.7, 51.6, 50.9, 40.7, 28.2, 26.2 ppm. HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}BrClN_2O_4H$ 497.0843; found 497.0823.

***tert*-Butyl-4-bromo-5-chloro-3-((5-(methoxycarbonyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl)methyl)-1*H*-indole-1-carboxylate (25a,b).** To a stirring solution of HTMP (309 μL, 1.81 mmol) in THF (3.55 mL), *n*-BuLi (756 μL, 2.35 M, 1.77 mmol) was added at 0 °C. The solution was stirred for 50 min before cooling to −78 °C, after which carbamate **24** (177 mg, 0.355 mmol) was added dropwise in THF (3.55 mL). The reaction mixture was stirred at −78 °C for 30 min, then quenched with a sat. aqueous solution of NH_4Cl (6 mL). This mixture was diluted with water (7 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on neutralized silica (2.5:1 hexanes−Et_2O eluent, silica) to afford 85.2 mg (48% yield) of the major diastereomer **25b** and 61.8 mg (35% yield) of the minor diastereomer **25a** in 1.4:1 ratio as yellow oils. (25a) R_f = 0.60 (1:1 hexanes−EtOAc eluent, silica). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.56 (s, 1H), 7.36 (d, J = 8.9 Hz, 1H), 5.90 (d, J = 10.2 Hz, 1H), 5.68 (dt, J = 10.2, 2.5 Hz, 1H), 3.71 (s, 3H), 3.58 (dd, J = 15.0, 4.2 Hz, 1H), 3.43 (s, 1H),

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3.28−3.16 (m, 2H), 2.89 (dd, J = 14.9, 9.3 Hz, 1H), 2.67 (t, J = 10.7 Hz, 1H), 2.55 (s, 3H), 1.66 (s, 9H) ppm. $^{13}C\{H\}$ NMR (25a) (151 MHz, $CDCl_3$) δ 173.0, 148.9, 134.8, 130.4, 130.4, 129.4, 127.2, 125.5, 123.2, 117.3, 115.1, 114.0, 84.5, 61.0, 54.0, 52.0, 43.0, 41.6, 29.5, 28.2 ppm. (**25a**) HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}BrClN_2O_4H$ 497.0843; found 497.0853.

(25b). R_f = 0.70 (1:1 hexanes−EtOAc eluent, silica). ^1H NMR (600 MHz, $CDCl_3$) δ 8.10 (s, 1H), 7.49 (s, 1H), 7.36 (d, J = 8.8 Hz, 1H), 5.94−5.88 (m, 1H), 5.78−5.71 (m, 1H), 3.74 (s, 3H), 3.46 (dd, J = 14.5, 5.5 Hz, 1H), 3.30−3.20 (m, 3H), 2.90−2.81 (m, 2H), 2.53 (s, 3H), 1.66 (s, 9H). $^{13}C\{H\}$ NMR (151 MHz, $CDCl_3$) δ 173.6, 148.9, 135.0, 130.3, 129.4, 127.2, 125.5, 122.7, 117.9, 115.2, 114.0, 84.5, 60.3, 52.1, 50.3, 42.7, 38.3, 29.8, 28.2. HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{26}BrClN_2O_4H$ 497.0843; found 497.0845.

Recycling of 25a. To a stirring solution of HTMP (57.5 μL, 0.338 mmol) in THF (650 μL), n-BuLi (140 μL, 2.35 M, 0.331 mmol) was added at 0 °C. The solution was stirred for 50 min before cooling to −78 °C, after which tetrahydropyridine **25a** (33 mg, 0.066 mmol) was added dropwise in THF (650 μL). The mixture changed from light yellow to amber upon addition. The reaction mixture was stirred at −78 °C for 30 min, quenched with a sat. aqueous solution of NH_4Cl (1.0 mL), and warmed to rt. This mixture was diluted with water (10 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on neutralized silica (2.5:1 hexanes−Et_2O eluent, silica) to afford 13.4 mg (41% yield) of the major diastereomer **25b** and 9.60 mg (29% yield) of the minor diastereomer **25a** in a 1.7:1 ratio.

Indole 26. In a reaction vial, tetrahydropyridine **25b** (69.0 mg, 0.139 mmol) and $Pd(t\text{-}Bu_3P)_2$ (69.0 mg, 0.139 mmol) in degassed 1,4-dioxane (6.90 mL) was charged with Cy_2NMe (89.0 μL, 0.416 mmol). The mixture was heated in an oil bath at 100 °C for 12 h. Upon completion as determined by TLC, the mixture was diluted with water (15 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (2:1 hexanes−EtOAc eluent, silica) to afford 41.3 mg (71% yield) of indole **26** as a yellow oil. R_f = 0.34 (2:1 hexanes−EtOAc eluent, silica). ^1H NMR (600 MHz, CD_2Cl_2) δ 7.76 (s, 1H), 7.33−7.26 (m, 2H), 6.94 (s, 1H), 4.25 (s, 1H), 3.68 (s, 3H), 3.57−3.49 (m, 1H), 3.37 (dt, J = 11.0, 4.9 Hz, 1H), 3.34−3.27 (m, 1H), 2.92 (dd, J = 15.2, 4.6 Hz, 1H), 2.61 (s, 3H), 1.64 (s, 9H) ppm. $^{13}C\{^1H\}$ NMR (176 MHz, CD_2Cl_2) δ 166.21, 150.06, 138.09, 130.85, 130.16, 128.95, 128.33, 125.95, 125.69, 121.42, 116.14, 115.10, 57.36, 51.87, 48.12, 42.62, 37.95, 28.30, 23.11, 14.29. HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{22}H_{25}ClN_2O_4H$ 417.1581; found 417.1577.

12-Chlorolysergic Acid (27). To a stirring solution of tetracyclic compound **26** (20.4 mg, 0.049 mmol) in ethanol (0.613 mL) was added 1 N KOH (0.613 mL), and the mixture was heated in an oil bath at 70 °C for 3 h. Upon completion as determined by TLC, the mixture was allowed to cool to rt. and acidified to pH 5.45 using 1 N HCl. The resulting solution was concentrated, and the residue was washed with cold water (3 × 1 mL) and acetone (1 mL) before being extracted with pyridine (2 × 1 mL). Evaporation of pyridine afforded 13.9 mg (95% yield) of 12-chlorolysergic acid **27** as brown wax. ^1H NMR (700 MHz, Pyr) δ 11.93 (s, 1H), 7.39−7.30 (m, 3H), 7.26 (s, 1H), 4.64 (s, 1H), 3.96 (d, J = 17.9 Hz, 1H), 3.66 (d, J = 17.7 Hz, 1H), 3.52−3.48 (m, 1H), 3.04−2.97 (m, 1H), 2.84 (t, J = 13.2 Hz, 1H), 2.62 (s, 3H) ppm. $^{13}C\{H\}$ NMR (176 MHz, Pyr) δ 168.7, 138.6, 134.1, 130.3, 129.5, 129.1, 121.8, 121.6, 111.8, 111.5, 58.5, 49.4, 43.1, 39.3, 15.8 ppm. HRMS (DART-TOF) m/z: $[M + H]^+$ calcd for $C_{16}H_{15}ClN_2O_2H$ 303.0900; found 303.0906.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its only supplementary material.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.2c02564.

General experimental procedures; references; and ^1H NMR and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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