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.† 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-HT₂A 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-HT₂A ligands capable of novel neuropharmacology.⁶,⁷ 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-HT₂A receptor ligands and derivatives, (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 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 indolation reaction with phenylhydrazine (10) and a tetrahydropyridine (not shown) synthesized from a deamortization 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 cleaved with Grignard reagent 11 to produce dihydropyridine 15 as the major regiosomer 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 deamortizations, 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 LiAlH4 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% H2SO4/CH3OL mixture at elevated temperature to afford indole 8 in 59% yield (1.8:1 dr). Notably, this Fischer indolation 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,$^{18}$ 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, Bu3SnH, and AIBN) also largely resulted in hydrodebrmination 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 isopyridine 13, magnesium–halogen exchange$^{33,43}$ 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 Et3SiH 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
synthesis involved the key reductive deamidation 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 NaBH₄ to smoothly generate dihydropyridine 20 in 56% yield. Isomerization of the enolate with LiTMP gave a 1:1.6 diastereomeric mixture of 12a and 12b, among which the latter was poised for the key Heck annulation. 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 Pd⁰ complex (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, 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. 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.

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 enone 26 in 71% yield. Hydrolysis of this mixture gave 12-chlorolysergic acid (27) in good yield.
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 synths 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 (CH₂Cl₂), diethyl ether (Et₂O), 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 (1H NMR) homogenous 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 (CDCl₃: 1H NMR δ = 7.26, 13C(H) NMR δ = 77.16; CD₂Cl₂: 1H NMR δ = 5.32; Pyr-d₅: 1H NMR δ = 8.74, 7.58, 7.22, 13C(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-(1H-indol-3-yl)-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 of 2:1 MeOH/conc. H₂SO₄ (3.00 mL). Initially, a white solid and red solution formed. The vial was flushed with N₂ 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 NaHCO₃ 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 MgSO₄, 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. §H NMR (400 MHz, CDCl₃): 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).

aqueous NaHCO₃ 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 MgSO₄, 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. §H NMR (400 MHz, CDCl₃): 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-((1H-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 CHCl₃/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 0 °C. The reaction mixture was then warmed upon warming and then amber after approximately 1 h at rt. The mixture was quenched with a sat. aqueous solution of NH₄Cl (10 mL), dilute with water (10 mL), and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried over MgSO₄, and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography (1:1:0.05 hexanes–EtOAc:CH₂Cl₂, eluent, silica) to afford 1.95 g (85% yield) of an intermediate alcohol as a beige solid (S-1, see the Supporting Information). Rf = 0.31 (4:1 hexanes–EtOAc eluent, silica). ¹H NMR (400 MHz, CDCl₃) δ 9.20 (s, 1H), 8.28–8.18 (m, 1H), 7.46 (s, 1H), 7.42 (d, J = 7.8 Hz, 2H), 7.17 (d, J = 8.1 Hz, 1H), 6.75 (s, 1H), 5.85 (s, 3H), 1.61 (s, 9H) ppm. ¹³C NMR (151 MHz, CDCl₃) δ 165.6, 165.2, 149.6, 148.9, 138.0, 137.2, 127.6, 127.5, 125.6, 125.5, 125.1, 122.1, 121.4, 114.7, 113.5, 84.7, 67.9, 52.5, 28.1 ppm. HRMS (DART-TOF) m/z: [M + H]⁺ calcd for C₂₃H₂₀BrN₂O₄H 461.0712; found 461.0735.

To a stirred 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, Et₃SiH (4.05 mL, 25.44 mmol) was added and stirred for 14 h at 35 °C. Upon completion as determined by ¹H NMR analysis of aliquots from the reaction, the mixture was diluted with EtOAc (30 mL) and poured into a sat. aqueous solution of NaHCO₃ (100 mL). The mixture was then adjusted to pH 7 using NaHCO₃ and extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (15 mL), dried with MgSO₄, 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 solid. Rf = 0.35: (1:1 hexanes–EtOAc eluent, silica). ¹H NMR (400 MHz, CDCl₃) δ 9.17 (s, 1H), 8.62 (s, 1H), 8.15 (dd, J = 8.2, 2.2, 1.1 Hz), 7.78 (d, J = 7.7, 1.1 Hz), 7.23 (d, J = 7.8, 1H), 7.18 (d, J = 8.2, 1H), 7.04–6.96 (m, 2H), 4.65 (s, 2H), 3.93 (s, 3H) ppm. ¹³C NMR (151 MHz, CDCl₃) 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 C₂₁H₁₈BrNO₄H 345.0238; found 345.0257.

tert-Butyl-3-((5-(methoxycarbonyl)-1-methyl-1,2,5,6-tetrahydro-pyridin-2-yl)methyl)-1H-indole-1-carboxylate (12b). To a stirring solution of THF (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 tetrahydroxypiridine 20 (0.05 g, 0.108 mmol) was added dropwise in THF (1.0 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 NH₄Cl (1.0 mL). This reaction 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 MgSO₄, 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 the minor diastereomer 12a as a light yellow oil in a 1:16.1 ratio. (12a) Rf = 0.57: (1:1 hexanes–EtOAc eluent, silica). ¹H NMR (600 MHz, CDCl₃) δ 8.16 (s, 1H), 7.53 (s, 1H), 7.37 (d, 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 (d, J = 14.8, 4.6 Hz, 1H), 3.48–3.42 (m, 1H), 3.30–3.25 (m, 1H), 3.20 (d, J = 11.7, 5.3 Hz, 1H), 2.86 (d, J = 15.0, 9.6 Hz, 1H), 2.68 (t, J = 10.2 Hz, 1H), 2.56 (s, 3H), 1.66 (s, 9H) ppm. ¹³C NMR (151 MHz, CDCl₃) 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 C₂₂H₂₂BrN₂O₄H 463.1229; found 463.1229.

Recovery of 12a. To a stirring solution of THF (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 tetrahydroxypiridine 12a (0.183 g, 0.395 mmol) was added dropwise in THF (2.0 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 NH₄Cl (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 MgSO₄, 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, Ph₂P(O)(dba) (5.0 mg, 5.4 μmol) and P(η5-C₅H₅)BF₆ (3.0 mg, 10.8 μmol) were charged with tetrahydroxypiridine 12a (25.0 mg, 0.054 mmol) in degassed 1,4-dioxane (2.70 mL), followed by Cy₃NMe (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 MgSO₄, 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 fraction.
5.8:1:1 mixture of tetracyclic compounds 21:22a:22b as a yellow oil. (21) Rf = 0.23 (1:1 hexanes–EtOAc eluent, silica). 1H NMR (400 MHz, CDCl3) 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. 13C(H) NMR (151 MHz, CDCl3) 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. 13C(N) NMR (400 MHz, CDCl3) 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, 1H), 2.58 (s, 3H), 1.66 (s, 9H) ppm. (Relative stereochemistry not determined). (22b) 1H NMR (400 MHz, CDCl3) 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, 2H), 2.73–2.65 (m, 2H), 2.55 (s, 3H), 1.66 (s, 9H) ppm. (Relative stereochemistry not determined).

11b-tert-Butyl 4-bromo-5-chloro-3-((5-methoxy carbonyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl)methyl-1H-indole-1-carboxylate (24). To a solution of indole 23 (271 mg, 0.714 mmol) in CH2Cl2 (7.14 mL) was added MeOTf (0.094 mL, 0.857 mmol) in one portion at 0 °C. After 1 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, NaBH4 (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 NaHCO3 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 MgSO4, and 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. Rf = 0.31 (1:1 hexanes–EtOAc eluent, silica). 1H NMR (400 MHz, CDCl3) δ 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), 7.34–3.32 (m, 3H), 3.27–3.13 (m, 1H), 2.71 (d, J = 14.2, 9.8 Hz, 1H), 2.55 (s, 2H), 2.24–2.18 (m, 2H), 1.66 (s, 9H) ppm. 13C(N) NMR (151 MHz, CDCl3) δ 166.4, 156.8, 137.6, 135.7, 127.8, 126.8, 126.1, 126.3, 114.0, 113.7, 111.4, 57.7, 51.7, 51.1, 40.6, 28.2, 26.2 ppm. HRMS (DART-TOF) m/z: [M + H]+ calc for C21H19BClNO4H 397.0318; found 397.0311.

11a-tert-Butyl 4-bromo-5-chloro-3-((5-methoxy carbonyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl)methyl-1H-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 NH4Cl (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 MgSO4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography silica (1:1 hexanes–EtOAc eluent, silica) to afford 121 mg (71% yield) of indole 23 as a beige foam. Rf = 0.32 (1:1 hexanes–EtOAc eluent, silica). 1H NMR (600 MHz, CDCl3): 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 (3H) ppm. 13C(N) NMR (151 MHz, CDCl3) δ 166.4, 165.9, 150.1, 137.8, 135.7, 126.9, 126.6, 126.3, 123.8, 127.2, 113.8, 113.6, 111.5, 52.4, 35.2. HRMS (DART-TOF) m/z: [M + H]+ calc for C10H13BrClNO3 378.8949; found 378.8952.

11b-tert-Butyl 4-bromo-5-chloro-3-((5-methoxy carbonyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-yl)methyl-1H-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 NH4Cl (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 MgSO4 and concentrated under reduced pressure. The crude residue was purified by flash column chromatography silica (1:1 hexanes–EtOAc eluent, silica) to afford 121 mg (71% yield) of indole 23 as a beige foam. Rf = 0.32 (1:1 hexanes–EtOAc eluent, silica). 1H NMR (600 MHz, CDCl3): 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 (3H) ppm. 13C(N) NMR (151 MHz, CDCl3) δ 166.4, 165.9, 150.1, 137.8, 135.7, 126.9, 126.6, 126.3, 123.8, 127.2, 113.8, 113.6, 111.5, 52.4, 35.2. HRMS (DART-TOF) m/z: [M + H]+ calc for C10H13BrClNO3 378.8949; found 378.8952.
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. 13C (H) NMR (25a) (151 MHz, CDCl3) δ 173.0, 148.9, 134.8; 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]+ calc’d for C21H23BrCl2N3O4H 497.0843; found 497.0853.

Recycling of 25a. 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 saturated aqueous solution of NH2Cl (1.0 mL), and warmed to rt. This mixture was diluted with water (3 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (15 mL), dried with MgSO4, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on neutralized silica (2:1 hexanes–EtOAc, 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 ratio.

Indole 26. In a reaction vial, tetrahydropyridine 25b (69.0 mg, 0.139 mmol) and Pd(t-Bu2P)3 (69.0 mg, 0.139 mmol) in degassed 1,4-dioxane (6.90 mL) was charged with Cu2NMe2 (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 MgSO4, 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. Rf = 0.34 (2:1 hexanes–EtOAc eluent, silica).

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

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Notes

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