Concise total syntheses of lysergene, lysergine, isolysergine and festuclavine

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In honor of Professor Samir Zard and in celebration of his exceptional creative contributions to organic synthesis

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Abstract

A streamlined synthesis of the tetracyclic ergot alkaloid scaffold enabled the preparation of several clavine alkaloids, including lysergol, isolysergol, lysergine, isolysergine, lysergene, and festuclavine. The mesylation and subsequent elimination or reduction of lysergol and isolysergol building blocks complements and expands previous total syntheses of these natural products. In the course of the preparation of isolysergine, an interesting new cascade process was discovered that led to the formation of a cyclopropanated ergolin-2(3H)-one as a spontaneous oxidation product of an intermediate 1,3-dihydrobenzo[cd]indole.

Keywords: Ergot alkaloids, lysergol, lysergine, isolysergine, lysergene, festuclavine
Introduction

The ergot alkaloid family continues to attract vivid interest from synthetic chemists for its structural diversity and complexity as well as for its broad range of physiological effects, often paired with exceptional potency at CNS receptors. Historically, ergot alkaloids have been associated with outbreaks of ergotism and mass hysteria in the middle ages (dancing plague, Salem witch trials) in the West, and, in the East, with livestock poisonings (drunken horse disease), longevity, and spiritual transcendence. More recently, there is a surge of interest in the medical psychedelic properties of ergot alkaloids, in conjunction with their clinical success in the treatment of depression, anxiety, substance abuse, and obsessive-compulsive disorders. In October 2023, there were 71 active clinical trials with psilocybin, 25 with N,N-dimethyltryptamine (DMT) and 5-hydroxytryptophan (5-HTP), and 14 trials with lysergic acid diethylamide (LSD).

The first total synthesis of lysergic acid and ergonovine by Woodward in 1954, followed by numerous reports on the total syntheses of these and other ergot metabolites, clearly established the feasibility of a nature-independent access to these alkaloids that could be used for analog preparation and biological testing. However, the medicinal chemistry field was slow to transfer these advances to medical breakthroughs in the development of psychedelic drugs with attractive pharmacokinetic (PK) and ADME/Tox profiles, undoubtedly in part due to major legal and societal hurdles after lysergic acid and its analogs were removed from circulation in 1966. Furthermore, the accomplished total syntheses were frequently mainly of academic significance and lacked practical value due to their linear nature, number of steps, and limited scope and robustness. Synthetic advances in this field therefore remain highly significant. Clinical research and development of psychedelics is currently mainly limited to legacy compounds, i.e. nature-derived or structurally simple synthetic products from the public domain. In fact, the “paucity of structure—activity data for ergolines principally results from the synthetic difficulty attendant to chemical transformations of the ergolines”.

Based on a new approach to indole synthesis and the application of novel strategic disconnections, our group has developed a rapid access to ergot alkaloids, including the synthesis of unnatural stereoisomers, enabling iterative structure-activity relationship (SAR) investigations. Initially, both enantiomers of cycloclavine were prepared in eight steps with two sequential Diels-Alder reactions. Their CNS receptor profiles were compared to the three main agonist chemotypes at the serotonin (5-HT) receptor: tryptamines (and inverse tryptamines), ergolines related to LSD (essentially rigidified tryptamines), and phenethylamines (Fig. 1), showcasing the strong stereoselectivity and a distinct structure-activity relationship of the cycloclavines. For example, this work demonstrated for the first time the increased selectivity for serotonin receptors (5-HTRs) of the clavine alkaloid subclass that lacks the carboxyl group that is typical for lysergic acid and LSD derivatives. A key aspect of our synthetic approach was the rapid access to the tetracyclic scaffolds of these natural products. For example, an unprecedented Rh-catalyzed asymmetric cyclopropanation of allene with the pentafluorodiло diazoester was used, followed by aminolysis with vinylogous amide to generate the precursor for a novel intramolecular Diels-Alder reaction of a methylene cyclopropane (IMDAMC) to yield tricyclic indolinone (Scheme 1). (+)-Cycloclavine was obtained in overall 8 steps after a Stahl dehydrogenation of the novel lithium reagent to the resulting enone, an intramolecular furan Diels-Alder reaction (IMDAF), and LiAlH reduction of lactam.
**Fig. 1.** Panel A: Serotonin, 5-hydroxytryptophan (5-HTP) and synthetic 5-HTR ligands. Panel B: Lysergic acid and representative ergot (lysergic acid, lysergol) and clavine (cycloclavine, agroclavine, lysergene, festuclavine, lysergine) natural products.
Scheme 1. Overview of an 8-step asymmetric total synthesis of (+)-cycloclavine.\textsuperscript{16}

Our recent 5-step synthesis of lysergol and isolysergol enables the production of both natural products and synthetic analogs.\textsuperscript{17} This process takes advantage of a transition metal-free hydrogen autotransfer (HA) alkylation reaction with commercially available 10 and 4-bromoindole 9 to generate intermediate 11 (Scheme 2).\textsuperscript{18} Further optimization of this reaction led to a 79\% yield on a 4-g reaction scale. After N-alkylation of 11 and reduction of the resulting pyridinium salt, 12 proved to be a valuable intermediate for scaffold variation.\textsuperscript{17} Isomerization of the alkene results in 13 that is subjected to an intramolecular Heck coupling to provide both methyl lysergate (14) and isolysergat (15) configurations at C(8). Reduction with LiAlH\textsubscript{4} then generates lysergol 16 and isolysergol 17. The latter two compounds are valuable precursors for the synthesis of other ergot alkaloids 18 (\textit{vide infra}).
Scheme 2. Overview of a 5-step total synthesis of lysergols that serves as a segue to the preparation of other clavine alkaloids 18.17

A panel of 13 pertinent CNS GPCRs was profiled at 10 μM and 1 μM concentration for a comparison of the properties of cycloclavine (CCV), lysergol, and isolysergol enantiomeric pairs (Table 1).16 The cycloclavines were significantly more selective in this panel than D-LSD, the bioactive LSD stereoisomer, as well as psilocin, the active substance derived from the natural phosphate prodrug psilocybin that is currently being investigated clinically as a treatment for anxiety and depression in cancer care, as well as for enhancement of cognitive flexibility and creativity.19 (+)-Cycloclavine ((+)-CCV) proved considerably more potent at 5-HT1A than (−)-cycloclavine (EC50=0.14 μM vs ca. 5 μM for (−)-cycloclavine ((−)-CCV); Table 1). Both CCV stereoisomers are poor activators at 5-HT2A, suggesting that hallucinogenic or strongly euphoric effects in humans might be significantly reduced in comparison to D-LSD. (+)-CCV also displays a potent activation (EC50=16 nM) at 5-HT2C, a receptor that is thought to contribute to the desirable mental effects of psychedelics. None of these agents activated 5-HT2B, a subtype that has been associated with cardiotoxicity. Overall, the 5-HTR profile of (+)-CCV mirrors that of psilocin with the exception of agonist effects at 5-HT2A and is substantially different from the strongly hallucinogenic D-LSD, which bodes well for future therapeutic investigations of the clavine compound class. Substitution at the indole ring, or stereochemical variations in the scaffold of the clavine alkaloid (+)-lysergol can further enhance the selectivity among 5-HT receptors compared to D-LSD. Strong stereochemical preferences are also apparent in the receptor profile of the (iso)lysergols (Table 1), and the data confirm that further structural modifications to decrease 5-HT2C binding and increase 5-HT1A affinity are feasible. These and
other structure-activity relationships are currently being investigated, and the potential utility of these compounds in an exploratory disease model will be reported in due course.

**Table 1.** Effects of cycloclavines (CCVs), lysergols, isolysergols, psilocin, and D-LSD as a function of specific agonist radioligand binding to selected 5-HTRs [μM]^{a,b,16}

<table>
<thead>
<tr>
<th>Receptor</th>
<th>(+) / (-)-CCV^{b}</th>
<th>(+) / (-)-Lysergol^{b}</th>
<th>(+) / (-)-Isolysergol^{b}</th>
<th>Psilocin^{b,c}</th>
<th>D-LSD^{b,c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT_{1A}</td>
<td>0.14 / 5</td>
<td>0.1 / &gt;2</td>
<td>0.1 / &gt;2</td>
<td>0.123^{c,d}</td>
<td>0.003^{c,d}</td>
</tr>
<tr>
<td>5-HT_{2A}</td>
<td>10 / &gt;50</td>
<td>1.5 / &gt;2</td>
<td>&gt;2 / &gt;2</td>
<td>0.721</td>
<td>0.261</td>
</tr>
<tr>
<td>5-HT_{2B}</td>
<td>&gt;20 / &gt;20</td>
<td>&gt;5 / &gt;2</td>
<td>&gt;2 / &gt;2</td>
<td>&gt;20</td>
<td>12</td>
</tr>
<tr>
<td>5-HT_{2C}</td>
<td>0.016 / 3.2</td>
<td>0.005 / 1</td>
<td>0.1 / &gt;2</td>
<td>0.094^{c,d}</td>
<td>0.015^{c,d}</td>
</tr>
</tbody>
</table>

^{a}Assays were performed in duplicate at human receptors (5-point CRCs); ^{b}activation potency EC_{50} values [μM], unless otherwise specified; ^{c}literature data; ^{d}K_{i}.

**Results and Discussion**

The efficient synthesis of ergolines 14-17 allowed the possibility to extend the preparation of lysergols to other clavine alkaloids with the general structure 18. Specifically, mesylation of lysergol 16 provided 19 in quantitative yield, and subsequent elimination with KO-t-Bu led to lysergene (20) in 61% yield (Scheme 3). The mesylate 19 could also be reduced with LiAlH_{4} in THF at reflux to furnish lysergine (21) in 56% yield. This alkaloid was converted to festuclavine (22) by treatment with Pd/C and H_{2} gas, selectively installing the favored trans-ring junction in 93% yield.

**Scheme 3.** Syntheses of (±)-lysergene (20), (±)-lysergine (21), and (±)-festuclavine (22) from (±)-lysergol (16).

Previous preparations of lysergene,^{20} lysergine^{21} and festuclavine^{22} used different precursors and reaction protocols, and access to these ergot alkaloids was mainly accomplished by means of formal syntheses from
more readily available, isolated natural products. Lysergene, f. ex., has been prepared by a dehydration of the tertiary alcohol in setoclavine\textsuperscript{23} and by a Wittig methylenation of a lysergic acid derivative.\textsuperscript{24} The reduction of agroclavine with sodium metal and \textit{n}-butanol yielded pyroclavine, costaclavine, festuclavine, and lysergine.\textsuperscript{25,26} Festuclavine was also obtained from chanoclavine-I aldehyde,\textsuperscript{27} and through total syntheses using nitroaldol,\textsuperscript{28,29} Larock indole,\textsuperscript{30} and Giese coupling\textsuperscript{31} approaches as key steps. Finally, Vollhardt et al.\textsuperscript{32} and Ninomiya et al. used, respectively, a \textit{CpCo}(CO)\textsubscript{2} catalyzed cocyclization of two alkynes and a nitrile, and reductive enamide photocyclization to prepare racemic lysergene.

Analogous to the mesylation of 16, mesylation of isolysergol (17)\textsuperscript{17} proceeded smoothly before workup and concentration of the reaction mixture; however, the resulting mesylate 23 was surprisingly unstable compared to the epimeric 19, complicating its purification and characterization (Scheme 4). Without purification, the mesylate was therefore subjected to nucleophilic displacement with LiAlH\textsubscript{4} in THF at reflux, and the desired clavine alkaloid isolysergine (24) was isolated in 32\% overall yield from 17. Interestingly, the reaction mixture also contained the novel benzo[cd]indol-2(1\textit{H})-one 25, which was isolated in 12\% yield based on 17. A \textit{1}H,\textit{1}H-NOESY experiment was critical to support the structural assignment of 25. Namely, there were through-space correlations between the characteristic aromatic C(4) singlet and the N-Me group as well as between the C(12) proton and the cyclopropane methine hydrogen at C(9). The cyclopropane hydrogen were slightly shifted downfield in the \textit{1}H NMR, likely due to the conjugation to the benzo[cd]indol-2(1\textit{H})-one. The oxindole carbonyl carbon typically appears at ca. 171±2 ppm in the \textit{13}C NMR, and product 25 also showed this characteristic carbon resonance at 170.2 ppm.


Mechanistically, the formation of ergolin-2(3\textit{H})-one 25 could be rationalized by a deprotonation of indole 23 with LiAlH\textsubscript{4}, followed by a vinylogous intramolecular displacement of the pendant pseudo-axial mesylate in 26 to provide 28 (Scheme 4).\textsuperscript{14,33} Upon workup and exposure to air,\textsuperscript{34} the 1,3-dihydrobenzo[cd]indole is expected to be oxidized to the oxindole 25. Structurally related oxindole products have previously been observed as spontaneous air oxidation products and are also obtained from LSD and other lysergates through metabolic or chemical oxidation.\textsuperscript{32,35} In addition to the interesting structural similarity of the cyclopropane-containing scaffold of 25 to cycloclavine and the general relevance of the oxidative conversion of the putative...
intermediate 28 to 25 for the chemistry of ergot alkaloids, substituted benzo[cd]indol-2(1H)-ones have also emerged as potent pharmacological agents, f. ex. in the discovery of BET bromodomain inhibitors, and could therefore be of broader medical significance.36 Furthermore, the indolo[4,3-fg]quinolin-5(4H)-one scaffold of 25 has been found in isolates from the medicinal fungus Xylaria nigripes (KL.) SACC.37

Similarly to the prior synthetic work toward festuclavine and lysergine, isolysergine21 has previously been prepared from agroclavine by treatment with Na in n-BuOH, which also yielded pyroclavine and costaclavine.26 The latter work also explored the use of methyl lysergate as a source of lysergene, lysergine and isolysergine by LiAlH₄ reduction, treatment with sodium butoxide, and catalytic hydrogenation. Finally, Ninomiya et al. used a reductive enamide photocyclization to prepare racemic lysergene and isolysergine, as well as agroclavine and fumigaclavine B through multi-step procedures.38 In comparison, our routes to lysergine, isolysergine, lysergene, and festuclavine from lysergol and isolysergol are considerably more concise due to the rapid preparation of the precursor alkaloids from readily available starting materials by the hydrogen autotransfer alkylation of 4-bromoindole.

Conclusions

Ergot alkaloids are of high interest for their historical significance, structural complexity and inspiration for organic synthesis strategic and tactical development studies. Their therapeutic potential for the treatment of mental health challenges as well as cancer co-morbidities is under active re-investigation in many biotech companies. We were able to leverage our recent streamlined synthesis of all four stereoisomers of lysergol and isolysergol to establish new approaches to the ergot alkaloids lysergene, lysergine, isolysergine and festuclavine. This pathway complements and expands previous total syntheses of these natural products. In the course of the preparation of isolysergine, we also discovered an interesting new cascade process leading to formation of a cyclopropanated ergolin-2(3H)-one as a spontaneous oxidation product of an intermediate 1,3-dihydrobenzo[cd]indole that was formed in an intramolecular SN2-reaction. After chiral resolution of these compounds, we plan to characterize the pharmacological properties of the resulting ten products in comparison to the cycloclavine and lysergol stereoisomers, and further develop a structure-activity relationship that might support the development of non-hallucinogenic ergot alkaloid analogs as alternatives to psilocin and LSD.

Experimental Section

General. Unless stated otherwise, all reactions were performed under an atmosphere of N₂ that was passed through a column (10 × 2 cm) of Drierite®. Prior to use, THF was freshly distilled over sodium/benzophenone, and CH₂Cl₂ was freshly distilled over CaH₂. Et₃N and i-PrNET₂ were distilled over CaH₂ and stored over KOH. All glassware and stir bars were dried in an oven for 3 h prior to use. When necessary, degassed solvents were prepared by sparging with N₂ for 1 h. Reactions were monitored by TLC analysis (pre-coated silica gel 60 F254) and spots were visualized (UV lamp 254 nm and 395 nm). Purifications by chromatography were performed on SiO₂. ¹H/¹³C NMR spectra were recorded on Bruker Avance 300/75 MHz, Bruker Avance 400/100 MHz, Bruker Avance 500/125, or Bruker 600/150 MHz instruments. High resolution mass spectra were obtained on a Micromass UK Limited, Q-TOF Ultima API or a Thermo Scientific Exactive Orbitrap LC-MS. Chemical shifts were reported in parts per million (ppm) with the residual solvent peak (CDCl₃: 7.26 ppm for ¹H NMR, 77.16 ppm for
13C; CD3OD: 3.31 ppm for 1H NMR, 49.00 ppm for 13C NMR) used as the internal standard. Chemical shifts were tabulated as follows: chemical shift, multiplicity (s singlet, d doublet, t triplet, q quartet, dd doublet of doublet, dt doublet of triplet, td triplet of doublets, dq doublet of quartets, ddd doublet of doublet of doublet, m multiplet, br s broad singlet), coupling constant(s), and integration. IR spectra were obtained using neat samples on a PerkinElmer 100 IR-ATR spectrometer. Melting points were obtained using a Mel-Temp instrument and are uncorrected. The spectral information of all natural products was checked against the literature references in the isolation papers, and was consistent with this information.

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\text{Methanesulfonyl chloride (0.0460 mL, 0.590 mmol) was added to a solution of 16 (0.0300 g, 0.118 mmol) in pyridine (1.2 mL) at 0 °C. The reaction mixture was stirred for 1 h. Upon completion (TLC control), 1 M NaOH (3 mL) was added, and the solution was extracted with CH2Cl2 (3 x 10 mL). The combined organic extracts were washed with H2O (10 mL) and brine (10 mL), dried (MgSO4), filtered, and concentrated. After removal of pyridine under high-vacuum, the residue was reconcentrated from Al2O3-filtered CHCl3 (3x) and dried to remove residual pyridine, providing mesylate 19 (0.0390 g, 0.117 mmol, 99%) as a yellow powder: Mp >150 °C (dec.); IR (ATR) \text{3039, 2938, 2844, 2796, 1602, 1468, 1445, 1384, 1347, 1227, 1168, 1116, 988, 971, 916 cm}^{-1}; 1H NMR (500 MHz, CDCl3) \delta 7.96 (br s, 1 H), 7.25 (d, J 10.5 Hz, 1 H), 7.18 (t, J 7.20, 1 H), 7.15 (d, J 6.5 Hz, 1 H), 6.92 (s, 1 H), 6.28 (s, 1 H), 4.30 (dd, J 9.8, 5.3 Hz, 1 H), 4.22 (dd, J 9.5, 7.5 Hz, 1 H), 3.52 (dd, J 14.5, 5.5 Hz, 1 H), 3.21 – 3.17 (m, 1 H), 3.16 – 3.11 (m, 2 H), 3.07 (s, 3 H), 2.73 – 2.67 (m, 1 H), 2.59 (s, 3 H), 2.39 – 2.35 (m, 1 H); 13C NMR (125 MHz, CDCl3) \delta 137.8, 134.2, 128.2, 126.4, 123.5, 118.8, 118.5, 112.5, 111.1, 110.0, 71.3, 63.2, 55.9, 43.9, 37.7, 36.5, 27.0; HRMS (ESI+) m/z for C17H21O3N2S [M+H]^+: calcd 333.1267; found 333.1260.

(±)-Lysergene (20). Potassium t-butoxide (0.0672 g, 0.587 mmol) was added in one portion to a solution of 19 (0.0390 g, 0.117 mmol) in DMSO (2 mL) at rt. The reaction mixture was stirred at rt for 2 h, diluted with EtOAc (30 mL) and washed with ice cold brine (3 x 15 mL). The organic layer was dried (MgSO4), filtered, and concentrated. Purification by chromatography on SiO2 (3:7–2:3 acetone:hexanes with 1% Et3N) afforded 20 (0.0170 g, 0.0719 mmol, 61%) as a white solid: Mp >200 °C (dec.); IR (ATR) \text{V}_{\text{max}} \text{3033, 2938, 2844, 2796, 1602, 1468, 1445, 1384, 1347, 1227, 1168, 1116, 988, 971, 916 cm}^{-1}; 1H NMR (400 MHz, CDCl3) \delta 7.99 (br s, 1 H), 7.27 – 7.23 (m, 2 H), 7.20 (t, J 7.4 Hz, 1 H), 6.98 (s, 1 H), 6.93 (s, 1 H), 5.07 (s, 1 H), 4.96 (s, 1 H), 3.53 (t, J 6.8 Hz, 1 H), 3.51 (d, J 12.8 Hz, 1 H), 3.30 (dd, J 10.8, 5.6 Hz, 1 H), 3.23 (d, J 13.2 Hz, 1 H), 2.76 (ddd, J 14.4, 11.2, 1.2 Hz, 1 H), 2.59 (s, 1 H); 13C NMR (100 MHz, CDCl3) \delta 140.8, 136.5, 134.1, 128.1, 126.6, 123.5, 122.0, 118.6, 112.8, 111.22, 111.18, 110.0, 62.6, 59.0, 43.9, 37.7, 36.5, 27.0; HRMS (ESI+) m/z for C16H17N2 [M+H]^+: calcd 237.1386; found 237.1389.
(±)-Lysergine (21). A solution of 19 (0.039 g, 0.12 mmol) in THF (1.2 mL) was cooled to 0 °C, and LiAlH₄ in THF (0.15 mL, 0.35 mmol, 2.4 M) was added dropwise. The solution was stirred at reflux for 1 h, followed by dropwise addition of EtOAc (3 mL). H₂O (2 mL) was added, and the solution was vigorously stirred for 10 min. The organic layer was separated, and the aq. phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification by chromatography on SiO₂ (3:7 to 2:3 acetone:hexanes with 1% Et₃N) afforded 21 (0.0161 g, 0.0671 mmol, 56% over 2 steps from 16) as a fluffy white solid: Mp >200 °C (dec); IR (ATR) 3139, 3094, 3042, 2955, 2925, 2858, 2796, 2762, 1604, 1546, 1463, 1447, 1372, 1341, 1333, 1312, 1300, 1287, 1225, 1167, 1135 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.89 (br s, 1 H), 7.21–7.17 (m, 3 H), 6.90 (s, 1 H), 6.32 (s, 1 H), 3.53 (dd, J 14.5, 5.5 Hz, 1 H), 3.11–3.08 (m, 1 H), 3.00 (dd, J 11.0, 5.0 Hz, 1 H), 2.82–2.74 (m, 1 H), 3.69 (app t, J 7.5 Hz, 1 H), 2.57 (s, 3 H), 2.16 (t, J 10.8 Hz, 1 H), 1.07 (d, J 7.0 Hz, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ 134.2, 133.7, 128.9, 127.4, 126.4, 123.5, 118.1, 112.2, 111.5, 109.3, 63.3, 61.8, 44.1, 30.8, 27.6, 18.9; HRMS (ESI+) m/z for C₁₆H₁₉N₂[M+H]⁺: calcd 239.1543; found 239.1539.

(±)-Festuclavine (22). To a suspension of 21 (0.015 g, 0.063 mmol) in N₂-sparged MeOH (3 mL) was added 10% Pd/C (0.010 g). The reaction mixture was bubbled with H₂ for 10 min. The mixture was stirred at room temperature under H₂ (1 atm, balloon) for 16 h. Upon completion, the mixture was filtered over Celite®, and the filtrate was concentrated. Purification of the residue by chromatography on SiO₂ (3:7 acetone:hexanes) afforded 22 (0.014 g, 0.058 mmol, 93%) as a white solid: Mp >200 °C (dec); IR (ATR) 3191, 2925, 28851, 2498, 1616, 1441, 1374, 1350, 1291, 1279, 1227, 1154, 1093, 1032, 961 cm⁻¹; ¹H NMR (400 MHz, CD₃OD) δ 7.18 (d, J 8.0 Hz, 1 H), 7.07 (t, J 7.5 Hz, 1 H), 6.99 (s, 1 H), 6.88 (d, J 7.2 Hz, 1 H), 3.57 (app q, J 10.4 Hz, 1 H), 3.38–3.34 (m, 1 H), 3.16 (app t, J 9.0 Hz, 1 H), 2.90–2.85 (m with an app s at 2.86, 5 H), 2.75 (ddd, J 13.2, 5.6, 2.4 Hz, 1 H), 2.56 (t, J 18.0 Hz, 1 H), 2.22–2.15 (m, 1 H), 1.29–1.19 (m, 1 H), 1.09 (d, J 6.4 Hz, 3 H); ¹³C NMR (100 MHz, CD₃OD) δ 133.7, 130.1, 125.6, 122.3, 118.5, 112.3, 108.9, 108.0, 67.2, 62.0, 40.7, 39.5, 34.0, 29.3, 25.1, 17.7; HRMS (ESI+) m/z for C₁₆H₂₁N₂[M+H]⁺: calcd 241.1699; found 241.1702.

(±)-Isolysergine (24) and (±)-(1aSR,9cRS)-3-methyl-1,1a,2,3,6,9c-hexahydro-5H-cyclopropa[c]indolo[4,3-fg]quinolin-5-one (25). Methanesulfonyl chloride (0.046 mL, 0.59 mmol) was added to a solution of isolysergol (17) (0.030 g, 0.12 mmol) in pyridine (1.2 mL) at 0 °C. The reaction mixture was stirred for 1 h. Upon completion (TLC control), 0.5 M NaOH (5 mL) was added, and the solution was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were washed with H₂O (10 mL) and brine (10 mL), dried (MgSO₄), filtered, and concentrated. The residue was dried under high-vacuum until a dark film was obtained. Subsequent dissolution and reconcentration from Al₂O₃-filtered CHCl₃ (3 x 5 mL) afforded 23 which was used immediately in the next
step. A solution of 23 (0.039 g, 0.12 mmol) in THF (1.2 mL) was cooled to 0 °C, and LiAlH₄ in THF (0.15 mL, 0.35 mmol, 2.4 M) was added dropwise. The reaction mixture was stirred at reflux for 1 h, followed by dropwise addition of EtOAc (3 mL). H₂O (2 mL) was added slowly, and the solution was vigorously stirred for 10 min. The organic layer was separated, and the aq. phase was extracted with EtOAc (2 x 5 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated. Purification by chromatography on SiO₂ (3:7 to 2:3 Acetone:Hexanes with 1% Et₃N) afforded 24 (0.0091 g, 0.038 mmol, 32% over 2 steps) as a white solid and 25 (0.0035 g, 0.014 mmol, 12% over 2 steps) as a yellow solid. 24: ¹H NMR (500 MHz, CDCl₃) δ 7.86 (br s, 1 H), 7.19 (d, J 8.0 Hz, 1 H), 7.16 (app t, J 7.3 Hz, 1 H), 7.12 (d, J 6.5 Hz, 1 H), 6.90 (s, 1 H), 6.39 (dd, J 4.0, 1.0 Hz, 1 H), 3.44 (dd, J 8.5, 4.0 Hz, 1 H), 3.30–3.23 (m, 1 H), 2.78–2.73 (m, 2 H), 2.64 (dd, J 3.5, 1.5 Hz, 1 H), 2.57 (s, 3 H), 2.55–2.49 (m, 1 H), 1.20 (d, J 7.0 Hz, 3 H). Spectroscopic data were identical to those reported in a literature reference. 25: Mp >200 °C; IR (ATR) νmax 3221, 2923, 1686, 1634, 1505, 1482, 1447, 1405, 1303, 1188, 1067 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.67 (d, J 8.5 Hz, 1 H), 7.55 (s, 1 H), 7.53 (br s, 1 H), 7.38 (dd, J 8.5, 7.0 Hz, 1 H), 6.75 (d, J 7.0 Hz, 1 H), 3.89 (dd, J 10.5, 1.5 Hz, 1 H), 3.16 (dd, J 10.5, 2.0 Hz, 1 H), 2.96 (s, 3 H), 2.64 (td, J 8.7, 4.3 Hz, 1 H), 2.66–2.62 (m, 1 H), 1.55 (app q overlapping with residual H₂O peak, J 4.7 Hz, 1 H), 1.11 (app q, J 4.2 Hz, 1 H); ¹³C NMR (125 MHz, CDCl₃) δ 170.2, 145.2, 137.0, 128.8, 128.3, 127.2, 123.4, 120.6, 116.5, 111.3, 103.4, 48.6, 40.0, 20.9, 11.0, 9.3; HRMS (ESI⁺) m/z for C₁₆H₁₅ON₂ [M+H⁺]: calcd 251.1179; found 251.1177.

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Supplementary Material

Copies of ¹H and ¹³C NMR spectra are available in the supplementary material file associated with this manuscript.

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