Supporting Information

Unified Total Synthesis of Pyrroloazocine Indole Alkaloids Sheds Light on Their Biosynthetic Relationship

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General information

All solvents and other chemicals were used as received, unless otherwise stated. Methyl (±)-1-cyclohexylprop-2-en-1-ol,\textsuperscript{1} 5-(allyloxy)-4-oxopentanoate \textsuperscript{13a},\textsuperscript{2} dimethyl (1-diazo-2-oxopropyl)phosphonate,\textsuperscript{3} [(dpdmAuCl)\textsubscript{2}],\textsuperscript{4} 4-MeC\textsubscript{6}H\textsubscript{4}SOCl\textsuperscript{5} were prepared according to literature procedures. Analytical thin layer chromatography was carried out using TLC-aluminum sheets with 0.2 mm of silica gel (Merck 60 F\textsubscript{254}) using UV light as the visualizing agent and an acidic solution of vanillin in ethanol or basic solution of KMnO\textsubscript{4} in water as the developing agent. Chromatographic purifications were carried out using flash grade silica gel (PanReac AppliChem 60, 40-63\textmu m), preparative TLC plates (Silica Gel GF UV254, 20×20 cm, 1000/2000\textmu m) or alumina TLC plates (UV254, 20×20 cm, 60 Å medium pore diameter). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

NMR spectra were recorded at 298 K (unless otherwise stated) on BrukerAvance Ultrashield NMR spectrometers (300, 400, 500 and 500 with CryoProbe). The signals are given as \( \delta \) / ppm (multiplicity, coupling constant (Hertz), number of protons) downfield from tetramethylsilane, with calibration on the residual protio-solvent used (\( \delta_H = 7.27 \text{ ppm and} \delta_C = 77.0 \text{ ppm for CDCl}_3, \delta_H = 5.32 \text{ ppm and} \delta_C = 53.8 \text{ ppm for CD}_2\text{Cl}_2, \delta_H = 3.31 \text{ ppm for CD}_3\text{OD} \)). 2D NMR correlations (HMQC and HMBC) are shown when signals were not observed in \( ^{13}\text{C} \) NMR because of rotamerism. Mass spectra were recorded on MicroTOF Focus or Maxis Impact spectrometers (both from Bruker Daltonics). Melting points were determined using a Mettler Toledo MP70 melting point apparatus. Circular Dichroism (CD) and UV-Vis spectra were obtained with an Applied Photophysics Chirascan Circular Dichroism spectrometer equipped with a photomultiplier detector, dual polarizing prism design monochromator, photo-elastic modulator (PEM) and 150W Xenon light source, using 10 mm pathlength quartz cuvette. Specific optical rotation measurements were carried out on a Jasco P-1030 model polarimeter equipped with a PMT detector using the sodium line at 589 nm, and 1 mL (10 mm pathlength) or 2 mL (100 mm pathlength) cells. Cyclic voltammograms were recorded on a potentiostat PARSTAT 2273. HPLC-grade solvents were used for UV, CD, optical rotation and electrochemical measurements. CHCl\textsubscript{3} was additionally filtered through basic Al\textsubscript{2}O\textsubscript{3} prior to its use for optical rotation measurements of tertiary amine substrates.
All compounds were obtained in pure form (≥ 98% wt purity by $^1$H NMR), unless otherwise stated, and characterized with $^1$H, $^{13}$C NMR and mass spectra. The structures of the following racemic compounds were confirmed by single crystal X-ray diffraction studies:

Chiral HPLC analyses were carried out on an Agilent Technologies instrument HPLC 1100 series with VWD detector or HPLC 1200 series with DAD detector. The ee values were obtained by chiral HPLC for the following compounds:
For other chiral compounds the ee values were assumed to be the same, as for their direct precursors or derivatives, and for every batch the measurement was repeated separately to ensure their enantiomeric purity.

The synthesized enantiopure natural products had the same sign of optical rotation as previously reported ones isolated from natural sources, with the exception of lapidilectam (4), for which our data strongly suggests to reconsider the sign of the optical rotation from previously reported (+) to (–), see below. The absolute configuration was established by single crystal X-ray diffraction studies for the following compounds:

Details of single crystal X-ray diffraction studies are presented in the section “Crystallographic data”, page S117.

It is important to note that Kopsia grandifolia species was previously called Kopsia lapidilecta. In the modern classification, Kopsia lapidilecta describes another plant, which is endemic to Natuna island, Indonesia. The previous proposal of biosynthetic relationship between pyrroloazocine indole alkaloids is depicted below.

The nomenclature of the compounds follows the names as given by ChemDraw however for practical reasons, we decided to use the numbering as defined in the initial isolation report to compare the NMR data of our synthetic grandilodines/lapidilectines.
Experimental procedures and compounds characterization in the total synthesis of lapidilectines and grandilodines

\((S)-1\text{-Cyclohexylprop-2-en-1-ol}\)

<化学结构式>

Racemic 1-cyclohexylprop-2-en-1-ol was synthesized according to a literature procedure,\(^1\) and distilled before use (b.p. 92-95 °C, 17-18 mbar). Enantiopure \((S)-1\text{-cyclohexylprop-2-en-1-ol}\) was obtained by enzymatic kinetic resolution using novozyme 435, according to our previously reported procedure.\(^2,11\) In a dry 1L round-bottom flask under argon, powdered 4Å molecular sieves (10.7 g) were activated by heating (heat gun) under high vacuum (ca. 0.1 mbar) for 10 minutes. The flask was allowed to cool to room temperature under argon and novozyme 435 resin (2.29 g, >5000 U/g) was added under argon. The solids were suspended in anhydrous toluene (730 mL) and isoprenyl acetate (53.5 mL, 486 mmol, ca. 4.5 equiv) was added immediately followed by addition of racemic 1-cyclohexylprop-2-en-1-ol (15.0 g, 107 mmol, 1 equiv) in anhydrous toluene (10 mL). The resulting suspension was stirred vigorously and heated at 40 °C for 40 hours. The mixture was then loaded on silica gel column (ca. 500 g of silica gel pre-packed with pentane/diethyl ether 95:5) and purified by chromatography eluting with pentane/diethyl ether 100:0 to 3:1 to afford the enantiopure alcohol as a colorless oil (7.0 g, 50 mmol, yield = 47%, ee >99% was determined by chiral HPLC of hydrocinamate derivative, and absolute configuration and ee value were confirmed by \(^1\)H NMR of Mosher ester derivative, see below). Spectral data in agreement with the ones previously reported.\(^1,12\)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 5.86 (ddd, \(J = 17.1, 10.4, 6.6\) Hz, 1H), 5.20 (dt, \(J = 17.2, 1.5\) Hz, 1H), 5.14 (dt, \(J = 10.4, 1.4\) Hz, 1H), 3.85 (t, \(J = 6.5\) Hz, 1H), 1.89 – 1.81 (m, 1H), 1.80 – 1.63 (m, 4H), 1.57 (br s, 1H, OH), 1.40 (ddd, \(J = 15.1, 11.7, 6.4, 3.4\) Hz, 1H), 1.29 – 1.08 (m, 3H), 1.06 – 0.94 (m, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 139.8, 115.4, 77.7, 43.4, 28.7, 28.3, 26.5, 26.1, 26.1. HRMS (ESI+) \(m/z\) calc. for \(C_9H_{15}[\text{M-OH}]^+\): 123.1168, found: 123.1170. \(\alpha_D\)\(^{589}\) (CHCl\(_3\), c 2.00, 299 K) = −17.9 deg.cm\(^2\).g\(^{-1}\) (>99% ee). Lit.\(^12\): \(\alpha_D\) (CHCl\(_3\), c 1.17) = −17.1 deg.cm\(^2\).g\(^{-1}\) (95% ee).
(S)-1-Cyclohexylallyl-3-phenylpropanoate. (S)-1-Cyclohexylprop-2-en-1-ol (25 mg, 0.18 mmol, 1 equiv) was placed in a dry 10 mL round-bottom flask and dissolved in CH$_2$Cl$_2$ (0.3 mL). Triethylamine (37 µL, 0.27 mmol, 1.5 equiv) was added followed by addition of a crystal of DMAP and hydrocinnamic anhydride$^{13}$ (55 mg, 0.20 mmol, 1.1 equiv) as a solution in CH$_2$Cl$_2$ (0.2 mL). The solution was stirred at 25 ºC for 1 hour, whereupon TLC indicated full consumption of the starting alcohol. The mixture was loaded on silica gel column and purified by chromatography eluting with pentane then pentane/diethyl ether 95:5 to afford the title compound as a colorless oil (39 mg, yield = 80%).

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.32 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 5.78 – 5.69 (m, 1H), 5.22 – 5.14 (m, 2H), 5.07 (t, $J$ = 6.7 Hz, 1H), 2.98 (t, $J$ = 7.8 Hz, 2H), 2.70 – 2.64 (m, 2H), 1.78 – 1.62 (m, 5H), 1.52 (dddd, $J$ = 15.0, 11.7, 6.5, 3.3 Hz, 1H), 1.26 – 1.07 (m, 3H), 1.02 – 0.90 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.1, 140.5, 135.1, 128.4 (2C), 128.3 (2C), 126.2, 117.4, 78.9, 41.4, 36.1, 31.0, 28.5, 28.3, 26.3, 25.9, 25.9. HRMS (ESI+) m/z calc. for C$_{18}$H$_{24}$O$_2$Na$^+$ [M+Na]$^+$: 295.1669, found: 295.1673. $\alpha_D^{589}$ (CHCl$_3$, c 1.08, 300 K) = –9.9 deg.cm$^2$.g$^{-1}$ (>99% ee). HPLC (Chiralpak OD-H (250 mm x 4.6 mm), hexane/MTBE 90:10, 1 mL/min) $t_{R1}$ 7.9 – 8.0 min, $t_{R2}$ 8.4 – 8.6 min, >99% ee.

**HPLC trace of racemic sample**

Sample Info : ChiralCel OD-H 250x4.6mm, 5µm
Hex/MTBE 90:10
1mL/min
Sample in Hex / IPA

![HPLC trace of racemic sample](image-url)
HPLC trace of enantioenriched sample

\[ \text{(S,R)-Mosher ester derivative} \]

was obtained as a colorless oil from (S)-alcohol and (S)-Mosher acid chloride, following a literature procedure reported for a similar cyclopentyl derivative. \(^{(14)}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.56 – 7.51\) (m, 2H), 7.43 – 7.36 (m, 3H), 5.80 (ddd, \(J = 17.2, 10.4, 7.8\) Hz, 1H), 5.38 – 5.22 (m, 3H), 3.56 (q, \(J = 1.2\) Hz, 3H), 1.75 – 1.54 (m, 6H), 1.29 – 1.03 (m, 3H), 1.02 – 0.86 (m, 2H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 165.9, 133.9, 132.5, 129.5, 128.3\) (2C), 127.4 (2C), 123.4 (q, \(J = 288\) Hz), 119.7, 84.5 (q, \(J = 28\) Hz), 81.8, 55.5 (q, \(J = 1.5\) Hz), 41.2, 28.3, 28.0, 26.2, 25.8, 25.7. \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -71.05\). HRMS (ESI+) \(m/z\) calc. for C\(_{19}\)H\(_{23}\)F\(_3\)O\(_3\)Na\(^+\) [M+Na\(^+\)]: 379.1492, found: 379.1499. \(\alpha_d^{589}\) (CHCl\(_3\), c 1.25, 300 K) = +31.1 deg.cm\(^2\).g\(^{-1}\) (>99% ee).

\(\text{(S,S)-Mosher ester derivative}\) was obtained as a colorless oil from (S)-alcohol and (R)-Mosher acid chloride, following a literature procedure reported for a similar cyclopentyl derivative. \(^{(14)}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.55 – 7.49\) (m, 2H), 7.43 – 7.38 (m, 3H), 5.75 – 5.65 (m, 1H), 5.28 – 5.21 (m, 3H), 3.56 (q, \(J = 1.2\) Hz, 3H), 1.85 – 1.58 (m, 6H), 1.33 – 0.94 (m, 5H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\), 298 K) \(\delta 165.9, 133.7, 132.3, 129.5, 128.3\) (2C), 127.5 (2C), 123.4 (q, \(J = 288\) Hz), 119.1, 84.7 (q, \(J = 28\) Hz), 81.9, 55.5 (q, \(J = 1.5\) Hz), 41.3, 28.5, 28.3, 26.2, 25.8, 25.8. \(^{19}\)F NMR (376 MHz, CDCl\(_3\)) \(\delta -71.13\). HRMS (ESI+) \(m/z\) calc. for C\(_{19}\)H\(_{23}\)F\(_3\)O\(_3\)Na\(^+\) [M+Na\(^+\)]: 379.1492, found: 379.1499. \(\alpha_d^{589}\) (CHCl\(_3\), c 1.175, 300 K) = –43.2 deg.cm\(^2\).g\(^{-1}\) (>99% ee).

\(\text{Note: (S,R)-Mosher ester derivative shows shielding of the cyclohexyl CH and deshielding of the vinyl CH compared to (S,S)-Mosher ester derivative, this is consistent with the S configuration of the alcohol.}\)^{(15)}
Enantiopure (S)-1-cyclohexylprop-2-en-1-ol (14.4 g, 103 mmol, 3 equiv) was placed in a dry Schlenk flask and cooled to 0 °C. In(OTf)₃ (575 mg, 1.02 mmol, 3 mol %) was added and the mixture stirred for 2 minutes before addition of methyl 5-diazo-4-oxopentanoate² (5.33 g, 34 mmol, 1 equiv) slowly dropwise over 1.5 hours at 0 °C. The mixture was then slowly allowed to warm to room temperature and stirred for additional 5 hours (overall ca. 8 hours between beginning of addition of diazo and stopping the reaction). The mixture was then filtered through a short pad of silica gel eluting with pentane/Et₂O 4:1 and the relevant fractions combined and concentrated. The crude mixture was diluted with CH₂Cl₂ (60 mL) and Et₃N (30 mL, ca. 2 equiv based on starting alcohol), DMAP (250 mg, 2 mol % based on starting alcohol) and Ac₂O (15 mL, ca. 1.5 equiv based on starting alcohol) were added and the resulting mixture stirred for 1.5 hours at 25 °C. Purification by column chromatography on silica gel (mixture loaded directly on packed column) eluting with pentane/diethyl ether 20:1 to 2:1 afforded 4.90 g of colorless oil (18.3 mmol, 54%, ee >99%)² and (S)-1-cyclohexylallyl acetate.

The latter was redissolved in methanol (60 mL) and K₂CO₃ (58.7 g, 425 mmol, ca. 5 equiv of the excess unreacted alcohol [2.5 equiv]) was added and the suspension stirred vigorously at 25 °C for 2 hours. TLC indicated full conversion of the acetate. The mixture was poured on brine (750 mL) and extracted with diethyl ether (3 × 250 mL). The combined ethereal extracts were washed with brine (200 mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with pentane/diethyl ether 9:1 to 3:1 to afford the recycled enantiopure alcohol (9.67 g, contains 4 wt% of pentane, 66.2 mmol, 78% of excess alcohol, ee >99% was confirmed via Mosher ester derivative).  

Note: Although the cyclopentyl oxoester-derivative gave higher ee values in the Claisen rearrangement,² we chose to develop the gram-scale enantioselective synthesis using the cyclohexyl traceless group, as the commercial availability and price of starting cyclohexanecarboxaldehyde were advantageous in comparison with its cyclopentyl analogue. In addition, cyclohexyl derivatives have higher boiling point, and are thus easier to handle.
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.64 (ddd, $J = 17.3$, 10.3, 8.3 Hz, 1H), 5.26 (ddd, $J = 10.3$, 1.8, 0.6 Hz, 1H), 5.15 (ddd, $J = 17.3$, 1.9, 0.8 Hz, 1H), 4.08 (d, $J = 17.0$ Hz, 1H), 3.90 (d, $J = 17.0$ Hz, 1H), 3.68 (s, 3H), 3.40 (app. t, $J = 7.5$ Hz, 1H), 2.83 (t, $J = 6.6$ Hz, 2H), 2.61 (t, $J = 6.6$ Hz, 2H), 1.98 – 1.91 (m, 1H), 1.79 – 1.61 (m, 4H), 1.52 (ddd, $J = 14.9$, 11.5, 6.7, 3.3 Hz, 1H), 1.29 – 1.09 (m, 3H), 1.07 – 0.93 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 208.1, 173.1, 136.6, 119.0, 87.1, 73.7, 51.8, 42.2, 34.0, 29.0, 28.8, 27.2, 26.5, 26.1, 26.0. HRMS (ESI+) $m/z$ calc. for C$_{13}$H$_{24}$O$_4$Na$^+$ [M+Na$^+$]: 291.1567, found: 291.1573. $\alpha$D$^5$89 (CHCl$_3$, c 1.00, 300 K) = +26.4 deg.cm$^2$.g$^{-1}$ (>99% ee).

(±)-1-(2-(1H-Indol-3-yl)ethyl)-2-allyl-5-oxopyrrolidine-2-carbaldehyde (14a)

![Chemical Structure](image)

Tryptamine (2.40 g, 15.0 mmol, 3 equiv), methyl 5-(allyloxy)-4-oxopentanoate 13a$^2$ (0.93 g, 5.0 mmol, 1 equiv) and a mixture of triethylamine and toluene (HPLC-grade, 2:1 v/v, 50 mL) were placed in a 100 mL round-bottom flask equipped with a Dean-Stark head (filled with triethylamine/toluene 2:1). The resulting mixture was placed under argon atmosphere and gently stirred and heated at reflux for 4 hours. Concentration of the reaction mixture on rotary evaporator produced an orange gum, which was dissolved in EtOAc (100 mL), transferred into a separating funnel and washed with 0.1 M HCl (2 × 100 mL). The aqueous washings were combined and extracted with EtOAc (2 × 75 mL), and the combined organic layers were washed with NaHCO$_3$ (75 mL) and brine (75 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The obtained crude compound was redissolved in EtOAc and filtered through silica gel column (200 g of SiO$_2$, washed with 1.8 L of EtOAc). Concentration and purification by flash column chromatography on silica gel (EtOAc/cyclohexane 2:1 to 4:1) gave the title compound as a brown gum (1.28 g, contains 4 wt% of EtOAc, 4.15 mmol, yield = 83% -calculated according to the amount of solvent present in the gum-).

**Note 1:** The use of excess of tryptamine (3 equivalents) was important to reproducibly obtain high yields in this step, running the reaction on several gram-scale. Excess of tryptamine facilitates the reaction and leads to the formation of the Schiff base adduct.
of aldehyde product 14a (with tryptamine), which is then hydrolyzed during the acidic work-up and column chromatography. The aldehyde product is acid-sensitive, thus the acidic workup was fast (within 30 minutes). Alternatively, the product can be isolated after workup with 0.5 M HCl (2 × 50-200 mL) with subsequent column chromatography, circumventing the filtration through silica gel prior to chromatography. Employing this protocol in a similar experiment on 32.5 mmol scale the aldehyde product was isolated in 74% yield (7.72 g, contains 8 wt% of EtOAc).

**Note 2:** Because 14a slowly decomposes even at room temperature, the concentration of organic solvents was performed at 30 °C and the isolated product was stored in the fridge (6 °C).

**Note 3:** Complete removal of EtOAc from the obtained gum was found to be inconvenient (foamy gum) and had no influence on the efficiency of the next step. The amount of the residual EtOAc was calculated based on $^1$H NMR.

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.22 (s, 1H), 8.25 (br s, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 8.0$ Hz, 1H), 7.23 – 7.11 (m, 2H), 7.04 (d, $J = 2.2$ Hz, 1H), 5.73 – 5.61 (m, 1H), 5.26 – 5.17 (m, 2H), 3.69 (dt, $J = 13.9$, 7.7 Hz, 1H), 3.37 – 3.27 (m, 1H), 3.07 (t, $J = 7.9$ Hz, 2H), 2.58 – 2.38 (m, 4H), 2.11 – 1.93 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 198.8, 176.1, 136.2, 130.4, 127.3, 122.1, 122.1, 120.9, 119.5, 118.7, 112.6, 111.2, 71.7, 42.3, 35.9, 29.3, 24.6, 24.1. HRMS (ESI–) $m/z$ calc. for C$_{18}$H$_{19}$N$_2$O$_2^–$ [M–H]: 295.1452, found: 295.1454.

**(S,E)-1-(2-(1H-Indol-3-yl)ethyl)-2-(3-cyclohexylallyl)-5-oxopyrrolidine-2-carbaldehyde (14b)**

![Structure of 14b](image)

Tryptamine (1.87 g, 11.7 mmol, 3 equiv) was placed in a dry 50 mL round-bottom flask and suspended in NEt$_3$ (HPLC-grade, 25 mL). Enantiopure oxoester 13b (1.1 g, 95 wt% purity, 3.89 mmol, 1 equiv) was added as a solution in toluene (HPLC-grade, 12 mL), the flask was fitted up with a Dean-Stark apparatus filled with triethylamine/toluene 2:1 and the system left under argon atmosphere. The mixture was then heated at 115 °C (reflux) for 3 hours, upon which time TLC indicated disappearance of the oxoester. The volatiles were removed under reduced pressure.
and the resulting oil redissolved in EtOAc (25 mL), 0.5 M aqueous HCl (25 mL) was added and the mixture stirred for 5 minutes. It was then poured on 0.5 M aqueous HCl (100 mL), shaken vigorously and the organic layer collected. The aqueous phase was re-extracted with EtOAc (4 × 70 mL) and the combined organic extracts washed with 0.5 M aqueous HCl (3 × 100 mL), dried over Na₂SO₄, filtered and concentrated. Purification by flash column chromatography on silica gel eluting with cyclohexane/EtOAc 1:1 gave the title product as a pale brown foamy gum (1.21 g, 3.20 mmol, yield = 82%, ca. 20:1 mixture of E/Z olefin isomers, ee 70% was determined by HPLC for 15b, see below). In a similar experiment on 18.3 mmol scale the product 14b was isolated in 83% yield (6.01 g, contains 4 wt% of EtOAc).

**¹H NMR** (500 MHz, CDCl₃) δ 9.24 (s, 1H), 8.13 (br s, 1H), 7.66 (d, J = 7.9 Hz, 1H), 7.37 (dt, J = 8.2, 0.9 Hz, 1H), 7.20 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.14 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H), 7.05 (d, J = 2.3 Hz, 1H), 5.55 (dd, J = 15.4, 7.0 Hz, 1H), 5.25 – 5.16 (m, 1H), 3.68 (dt, J = 13.9, 7.4 Hz, 1H), 3.31 (dt, J = 13.8, 8.0 Hz, 1H), 3.08 (t, J = 7.9 Hz, 2H), 2.47 – 2.40 (m, 4H), 2.07 – 1.87 (m, 3H), 1.74 – 1.60 (m, 5H), 1.31 – 0.97 (m, 5H). **¹³C NMR** (126 MHz, CDCl₃) δ 199.3, 176.1, 143.1, 136.2, 127.3, 122.1, 122.0, 119.5, 118.8, 118.8, 112.8, 111.2, 72.1, 42.3, 40.8, 34.8, 32.8, 32.8, 29.4, 26.0, 25.9 (2C), 24.7, 24.0. **HRMS** (ESI+) m/z calc. for C₂₅H₂₄N₂O₃Na⁺ [M+MeOH+Na]⁺: 433.2462, found: 433.2464 (also observed m/z calc. for C₂₄H₂₄N₂O₂Na⁺ [M+Na]⁺: 401.2199, found: 401.2195). α''⁻⁵⁸⁹ (CHCl₃, c 0.78, 299 K) = −45.2 deg.cm².g⁻¹ (70% ee).

(±)-1-(2-(1H-Indol-3-yl)ethyl)-5-allyl-5-ethynylpyrrolidin-2-one (15a)

K₂CO₃ (1.01 g, 7.31 mmol, 2 equiv) was added to a solution of 14a (1.13 g, contains 4 wt% of EtOAc, 3.66 mmol, 1 equiv) in methanol (HPLC grade, 19 mL) and dimethyl (1-diazo-2-oxopropyl)phosphonate⁴ (Bestmann-Ohira reagent, 0.81 g, 4.22 mmol, 1.15 equiv) was added slowly dropwise at 25 °C as a solution in MeOH (3 mL). The mixture was stirred at 25 °C for 3.5 hours, then the volatiles were evaporated, and the resulting crude material was partitioned between CH₂Cl₂ (100 mL) and a saturated aqueous ammonium chloride solution (100 mL). The organic
layer was collected and the aqueous phase extracted with CH$_2$Cl$_2$ (4 × 25 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with EtOAc/cyclohexane 2:1 gave the title compound as a white crystalline solid (978 mg, 3.35 mmol, yield = 91%). In a similar experiment on 24.0 mmol scale the alkyne product 3 was isolated in 87% yield (6.07 g).

**M.p.** (EtOAc) 136-137 ºC. **$^1$H NMR** (300 MHz, CDCl$_3$) δ 8.38 (br s, 1H), 7.75 (d, $J = 7.6$ Hz, 1H), 7.38 (d, $J = 7.9$ Hz, 1H), 7.25 – 7.11 (m, 2H), 7.06 (d, $J = 2.0$ Hz, 1H), 5.82 (ddt, $J = 15.8$, 11.2, 7.1 Hz, 1H), 5.25 – 5.16 (m, 2H), 3.71 – 3.49 (m, 2H), 3.32 – 3.07 (m, 2H), 2.70 – 2.35 (m, 5H), 2.34 – 2.11 (m, 2H). **$^{13}$C NMR** (75 MHz, CDCl$_3$) δ 174.7, 136.2, 131.4, 127.4, 122.1, 121.8, 120.1, 119.2, 118.9, 113.1, 111.2, 84.6, 73.2, 60.5, 44.1, 42.1, 31.7, 29.5, 24.4. **HRMS** (ESI+) m/z calc. for C$_{19}$H$_{21}$N$_2$O$^+$ [M+H]$^+$: 293.1648, found: 293.1656.

**(S,E)-1-(2-(1H-Indol-3-yl)ethyl)-5-(3-cyclohexylallyl)-5-ethynylpyrrolidin-2-one (15b)**

Aldehyde 14b (1.21 g, 3.20 mmol, 1 equiv) was dissolved in HPLC grade methanol (10 mL) and the solution stirred vigorously at 25 ºC while K$_2$CO$_3$ (0.885 g, 6.40 mmol, 2 equiv) and a solution of Ohira-Bestmann reagent (0.705 g, 3.67 mmol, 1.15 equiv) in methanol (2 mL) were added sequentially. The flask was left under positive pressure of argon and stirred vigorously at 25 ºC for 3 hours upon which time TLC indicated full consumption of the aldehyde. The mixture was then poured on brine (150 mL), and extracted with EtOAc (5 × 60 mL). The combined organic extracts were washed with brine (150 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with cyclohexane/EtOAc 1:1 gave the title product as a white solid (1.10 g, 2.94 mmol, yield = 92%, ca. 20:1 mixture of E/Z olefin isomers, 70% ee). In a similar experiment on 15.25 mmol scale (6.01 g of 14b, contains 4% of EtOAc) the product 15b was isolated in 92% yield (5.27 g).
M.p. (CH$_2$Cl$_2$/pentane) 114-117 °C (70% ee). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.17 (br s, 1H), 7.75 (d, $J$ = 7.9 Hz, 1H), 7.37 (dt, $J$ = 8.1, 0.9 Hz, 1H), 7.20 (ddd, $J$ = 8.2, 7.0, 1.2 Hz, 1H), 7.14 (ddd, $J$ = 8.0, 7.1, 1.1 Hz, 1H), 7.08 (d, $J$ = 2.3 Hz, 1H), 5.53 (ddt, $J$ = 15.3, 6.8, 1.2 Hz, 1H), 5.33 (dtd, $J$ = 15.5, 7.2, 1.3 Hz, 1H), 3.63 (ddd, $J$ = 13.7, 11.3, 5.7 Hz, 1H), 3.52 (ddd, $J$ = 13.7, 11.4, 5.2 Hz, 1H), 3.24 (dddd, $J$ = 14.0, 11.4, 5.3, 0.9 Hz, 1H), 3.13 (ddd, $J$ = 13.8, 11.4, 5.6, 0.8 Hz, 1H), 2.58 – 2.44 (m, 3H), 2.43 – 2.35 (m, 2H), 2.25 (dd, $J$ = 12.9, 9.8, 6.6 Hz, 1H), 2.17 (dd, $J$ = 12.8, 9.3, 6.3 Hz, 1H), 1.99 – 1.90 (m, 1H), 1.75 – 1.60 (m, 5H), 1.31 – 0.99 (m, 5H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.7, 142.5, 136.3, 127.5, 122.0, 121.9, 119.9, 119.3, 119.0, 113.4, 111.1, 85.2, 72.9, 60.8, 43.1, 42.0, 40.8, 32.8, 32.8, 31.5, 29.6, 26.1, 25.9 (2C), 24.5. HRMS (ESI+) m/z calc. for C$_{25}$H$_{31}$N$_2$O $^+$ [M+H$^+$]: 375.2431, found: 375.2436. 

HPLC (Chiralpak IA (250 mm × 4.6 mm), hexane/IPA 90:10, 0.8 mL/min) $t_R$1 16.1 – 16.3 min, $t_R$2 19.6 – 19.7 min, 70% ee. $\alpha_D$ $^{589}$ (CHCl$_3$, c 0.92, 299 K) = +0.73 ± 0.11 deg.cm$^2$.g$^{-1}$ (70% ee).
(±)-(Z)-13a-Allyl-1,2,5,6,11,13a-hexahydro-3H-pyrrolo[1’,2’:1,8]azocino[5,4-b]indol-3-one (16a)

In the glovebox, alkyne 15a (588 mg, 2.01 mmol, 1 equiv) was placed in a dry screw-cap vial and dissolved in anhydrous CH$_2$Cl$_2$ (4 mL, ca. 0.5 M solution). The solution was stirred at 25 ºC and acetic acid (2.3 mL, 40.2 mmol, 20 equiv) was added followed by addition of AuCl (23.2 mg, 0.10 mmol, 5 mol %) in one portion. The vial was sealed with a screw-cap and the resulting mixture stirred at 25 ºC for 1 h. A second portion of AuCl (9.3 mg, 0.04 mmol, 2 mol %) was added and stirring was continued at 25 ºC for 1 h whereupon TLC indicated full consumption of the starting material. The vial was removed from the glovebox and the mixture slowly added to a saturated solution of NaHCO$_3$ (150 mL) in a separating funnel. The vial was washed with CH$_2$Cl$_2$ (2 × 10 mL) and the biphasic mixture shaken vigorously, evacuating the CO$_2$ formed. This operation was continued until vigorous effervescence had ceased. The biphasic mixture was diluted with CH$_2$Cl$_2$ (50 mL) and the organic layer was separated. The aqueous layer was re-extracted with CH$_2$Cl$_2$ (70 mL) and the combined organic layers washed with a saturated solution of NaHCO$_3$ (2 × 100 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with cyclohexane/EtOAc 2:1 gave the title product as a colorless solid (484 mg, 1.66 mmol, 82%). In a similar experiment on 16 mmol scale the cyclized product 16a was isolated in 79% yield (3.7 g).

**Note 1:** Unlike its 5-OMe derivative, 2 15a was a more difficult substrate for the Au-catalyzed cyclization. Additive of acetic acid was crucial to avoid the deactivation of the catalytic system and to reach full conversion. The origin of acid additive effect in Au-catalyzed alkyne hydroarylation with indole has previously been discussed. 16

**Note 2:** Alternatively, in the presence of ligand-stabilized cationic gold complex [IPrAu(NCCH$_3$)]SbF$_6$ (2 mol %), 15a undergoes the gold-catalyzed cyclization with a satisfactory ca. 20:1 8-endo/7-exo selectivity. After subsequent reaction with methyl chloroformate and crystallization, 17a was obtained in 65% yield over two steps, see below.
M.p. (EtOAc) 174-175 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.06 (br s, 1H), 7.55 (d, \(J = 7.6\) Hz, 1H), 7.20 – 7.16 (m, 1H), 7.15 – 7.05 (m, 2H), 6.30 (d, \(J = 12.4\) Hz, 1H), 5.85 (dddd, \(J = 16.9, 10.5, 8.0, 6.3\) Hz, 1H), 5.51 (d, \(J = 12.4\) Hz, 1H), 5.30 – 5.23 (m, 2H), 4.18 – 4.08 (m, 1H), 3.19 – 3.07 (m, 2H), 2.80 – 2.56 (m, 3H), 2.30 – 1.98 (m, 3H), 1.89 (ddd, \(J = 12.1, 8.0, 1.4\) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 174.9, 136.3, 133.4, 131.8, 131.6, 127.4, 122.3, 119.9, 119.5, 118.3, 117.6, 110.7, 110.6, 66.2, 43.6, 37.6, 33.7, 29.0, 22.5. HRMS (ESI+) \(m/z\) calc. for C\(_{19}\)H\(_{21}\)N\(_2\)O\(_2\)^+ [M+H]^+: 293.1648, found: 293.1656.

(±)-Methyl (Z)-13a-allyl-3-oxo-1,2,3,5,6,13a-hexahydro-11H-pyrrolo[1′,2′:1,8]azocino[5,4-b]indole-11-carboxylate (17a)

**Procedure A:** Pure tetracycle 16a (5.20 g, 17.8 mmol, 1 equiv) was dissolved in anhydrous THF (120 mL) and treated with a solution of NaHMDS (1.0 M in THF, 19.5 mL, 19.5 mmol, 1.1 equiv) at 0 °C (ice-bath) under argon atmosphere. After stirring at 0 °C for 45 minutes, methyl chloroformate (1.57 mL, 20.3 mmol, 1.15 equiv) was slowly added, the ice-bath was removed, and the resulting mixture was stirred for 1 hour at 25 °C. Then the mixture was quenched by addition of a saturated aqueous solution of NH\(_4\)Cl (100 mL), diluted with EtOAc (200 mL) and brine (100 mL). The aqueous layer was extracted with EtOAc (2 × 150 mL), and the combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with EtOAc/cyclohexane 1:1 to 3:1 gave the title product as a white solid (5.74 g, 16.4 mmol, 92%).

**Procedure B:** In the glovebox, 15a (877 mg, 3.0 mmol, 1 equiv), [(IPr)Au(NCCH\(_3\))]SbF\(_6\) \(^{17}\) (52 mg, 0.06 mmol, 2 mol %) and anhydrous 1,2-dichloroethane (2 mL) were sealed in a microwave vial. The reaction mixture was placed in a preheated oil bath, at 80 °C, and the obtained yellow-colored solution was stirred at this temperature for 1 hour. After this time, complete conversion of starting material was observed (TLC), and the reaction was cooled down to room temperature and filtered through a short pad of silica gel washing thoroughly with ethyl acetate.
The solution was transferred into a 250 mL flask, and the volatiles were removed on a rotary evaporator. The obtained white foamy solid was dissolved in THF (50 mL) and concentrated again to completely remove residual EtOAc (repeated two times). Thus obtained crude 16a was dissolved in anhydrous THF (30 mL) and treated with a solution of NaHMDS (1.0 M in THF, 3.6 mL, 3.6 mmol, 1.2 equiv) at 0 ºC (ice-bath) under argon atmosphere. After stirring at 0 ºC for 30 minutes, methyl chloroformate (290 µL, 3.75 mmol, 1.25 equiv) was slowly added, the ice-bath was removed, and the resulting mixture was stirred for 1 hour at 25 ºC. The mixture was then quenched by addition of a saturated aqueous solution of NH₄Cl (50 mL), diluted with EtOAc (100 mL) and brine (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL), and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with EtOAc/cyclohexane 1:1 to 3:1 gave the title product as a white solid (872 mg, ca. 95% purity by ¹H NMR). Dissolving this material in boiling EtOAc (8.7 mL) with subsequent crystallization at room temperature gave colorless block crystals, which were separated, washed with EtOAc/cyclohexane (1:1, 3 mL × 2) and dried under high vacuum. The residue after crystallization was purified by preparative silica gel TLC eluting with EtOAc/cyclohexane 2:1. Subsequent crystallization gave a second crop of the pure colorless crystalline product. The yield of 17a was 65% (687 mg: 594 mg + 93 mg, 1.96 mmol).

Note: In a similar experiment the yield of the crude 16a was ca. 87%, and it contained ca. 5% of exo-cyclization isomer, that was separated in protection/crystallization sequence.

M.p. (EtOAc) 169-170 ºC. ¹H NMR (400 MHz, CDCl₃) δ 8.04 – 7.97 (m, 1H), 7.56 – 7.49 (m, 1H), 7.31 – 7.22 (m, 2H), 6.58 (d, J = 12.4 Hz, 1H), 5.85 (dddd, J = 16.8, 10.3, 7.7, 6.5 Hz, 1H), 5.55 (d, J = 12.4 Hz, 1H), 5.32 – 5.22 (m, 2H), 4.08 – 3.98 (m, 4H), 3.10 – 2.99 (m, 2H), 2.71 – 2.57 (m, 3H), 2.34 (dd, J = 15.8, 11.6, 8.5 Hz, 1H), 2.16 – 1.91 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 175.1, 152.4, 135.8, 133.6, 131.4, 130.8, 128.9, 124.7, 123.1, 119.9, 119.2, 118.2, 117.4, 115.6, 65.6, 53.4, 43.4, 36.2, 33.2, 28.9, 22.2. HRMS (ESI+) m/z calc. for C₂₁H₂₅N₂O₃⁺ [M+H]⁺: 351.1703, found: 351.1709.
In the glovebox, alkyne 15b (5.30 g, 14.15 mmol, 1 equiv) was placed in a dry 100 mL flask and dissolved in anhydrous CH₂Cl₂ (28.7 mL, ca. 0.5 M solution). The solution was stirred at 25 ºC and acetic acid (16.2 mL, 283 mmol, 20 equiv) was added followed by addition of AuCl (161 mg, 0.69 mmol, 5 mol%) in one portion. The flask was sealed and the resulting mixture stirred at 25 ºC for 30 min, then another portion of AuCl (64.5 mg, 0.28 mmol, 2 mol%) was added and stirring was continued for 1 h, whereupon TLC indicated full consumption of the starting material. The flask was removed from the glovebox and the mixture slowly added to a saturated aqueous solution of NaHCO₃ (300 mL) in a separating funnel. The flask was washed with CH₂Cl₂ (2 × 50 mL) and the biphasic mixture shaken vigorously, evacuating the CO₂ formed. This operation was continued until vigorous effervescence had ceased. The biphasic mixture was diluted with CH₂Cl₂ (150 mL) and the organic layer was separated. The aqueous layer was re-extracted with CH₂Cl₂ (100 mL) and the combined organic layers washed with a saturated solution of NaHCO₃ (2 × 100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with cyclohexane/EtOAc 2:1 gave the title product 16b as a colorless solid (4.03 g, 10.8 mmol, yield = 76%, ca. 20:1 mixture of E/Z olefin isomers, ee 70%).

Note: The product can be recrystallized to enantiopurity via a series of crystallizations, however we found that depending on the enantiomeric excess of the material, the crystallization from EtOAc/pentane systems gave low ee solid (ca. 5-20% ee, if parting from <75-80% ee material) or enantiopure solid (99% ee, if parting from ≥80% ee material). This allowed us to obtain enantiopure material, however crystallization at this stage was impractical for the large-scale synthesis.

M.p. (amorphous) 100-103 ºC (99% ee). ¹H NMR (500 MHz, CDCl₃) δ 8.15 (br s, 1H), 7.54 (d, J = 6.8 Hz, 1H), 7.20 – 7.04 (m, 3H), 6.25 (dd, J = 12.4, 2.0 Hz, 1H), 5.61 (dd, J = 15.4, 6.8 Hz, 1H), 5.48 (d, J = 12.4 Hz, 1H), 5.40 (dt, J = 14.8, 7.1 Hz, 1H).
Hz, 1H), 4.11 (td, J = 13.5, 4.8 Hz, 1H), 3.19 – 3.07 (m, 2H), 2.80 – 2.67 (m, 1H), 2.56 (app. d, J = 7.1 Hz, 2H), 2.29 – 1.95 (m, 4H), 1.85 (ddd, J = 12.0, 8.1, 1.7 Hz, 1H), 1.79 – 1.63 (m, 5H), 1.36 – 1.06 (m, 5H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 175.1, 142.1, 136.2, 133.7 (2C), 131.9, 127.4, 122.2, 120.1, 119.4, 118.2, 117.3, 110.6, 110.5, 66.6, 42.4, 40.9, 37.6, 33.6, 33.0, 33.0, 29.1, 26.1, 25.9, 22.5. HRMS (ESI+) m/z calc. for C$_{25}$H$_{31}$N$_{2}$O$^+$ [M+H$^+$]: 375.2431, found: 375.2427. HPLC (Chiralpak IA (250 mm × 4.6 mm), hexane/CH$_2$Cl$_2$/ethanol 78:20:2, 1 mL/min) $t_{R1}$ 10.7 – 10.9 min, $t_{R2}$ 12.9 – 13.1 min, 70% ee (or 99% ee after crystallization). $\alpha_D$$_{589}$ (CHCl$_3$, c 0.49, 299 K) = $+168.0 \text{deg.cm}^2\cdot\text{g}^{-1}$ (99% ee).

**HPLC trace of racemic sample of tetracycle 16b**

**HPLC trace of enantioenriched sample of tetracycle 16b**

**HPLC trace of enantioenriched sample of tetracycle 16b for $\alpha_D$**
Methyl (S,Z)-13a-((E)-3-cyclohexylallyl)-3-oxo-1,2,3,5,6,13a-hexahydro-11H-pyrrolo[1',2':1,8]azocino[5,4-b]indole-11-carboxylate (17b)

A solution of NaHMDS (1.0 M in THF, 11.8 mL, 11.8 mmol, 1.1 equiv) was added to a solution of indole 16b (4.00 g, 10.7 mmol, 1 equiv, 70% ee) in anhydrous THF (110 mL) at 0 °C under argon atmosphere, forming a white suspension. After stirring at 0 °C for 30 minutes, methyl chloroformate (0.99 mL, 12.8 mmol, 1.2 equiv) was slowly added at 0 °C and the resulting mixture was allowed to warm to 25 °C and stirred for 1 hour. Then the mixture was quenched by addition of a saturated aqueous solution of NH₄Cl (75 mL), diluted with EtOAc (100 mL) and brine (50 mL). The aqueous layer was extracted with EtOAc (2 × 80 mL) and the combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. Purification by flash column chromatography on silica gel eluting with cyclohexane/EtOAc 1:1 gave the title product as a white foamy solid (4.30 g, 9.94 mmol, yield = 93%, ca. 20:1 mixture of E/Z olefin isomers, ee 70%).

Note: A similar transformation with enantiopure 16b (99% ee, obtained after crystallization, see above) on 0.75 mmol scale gave 17b as a white foamy solid (286 mg, 0.66 mmol, yield = 88%, ca. 20:1 mixture of E/Z olefin isomers). This compound was crystallized from hot EtOAc/pentane (1:3) to give small colorless needles (99% ee was assumed).

M.p. (EtOAc/pentane) 141-143 °C (99% ee). ¹H NMR (400 MHz, CDCl₃) δ 8.05 – 7.98 (m, 1H), 7.56 – 7.50 (m, 1H), 7.32 – 7.22 (m, 2H), 6.56 (d, J = 12.3 Hz, 1H), 5.62 (dd, J = 15.3, 6.8 Hz, 1H), 5.54 (d, J = 12.4 Hz, 1H), 5.39 (dt, J = 15.4, 7.0, 1.2 Hz, 1H), 4.06 – 3.96 (m, 4H), 3.10 – 2.98 (m, 2H), 2.64 (td, J = 13.8, 5.5 Hz, 1H), 2.55 (d, J = 7.2 Hz, 2H), 2.33 (ddd, J = 15.7, 11.7, 8.4 Hz, 1H), 2.15 – 1.87 (m, 4H), 1.80 – 1.63 (m, 5H), 1.36 – 1.03 (m, 5H). ¹³C NMR (101 MHz, CDCl₃) δ 175.2, 152.3, 142.1, 135.8, 133.6, 131.1, 128.9, 124.6, 123.0, 119.9, 118.9, 118.1, 117.3, 115.5, 65.9, 53.3, 42.2, 40.8, 36.2, 33.1, 33.0, 32.9, 28.9, 26.0, 25.9 (2C), 22.1. HRMS (ESI+) m/z calc. for C₂₇H₃₃N₂O₃⁺ [M+H]⁺: 433.2486, found: 433.2487. αD⁵⁸⁹ (CHCl₃, c 0.55, 299 K) = + 171.3 deg.cm².g⁻¹ (99% ee).
Methyl (S,Z)-3-oxo-13a-(2-oxoethyl)-1,2,3,5,6,13a-hexahydro-11H-pyrrolo[1', 2':1,8]azocino[5,4-b]indole-11-carboxylate (12)

(±)-12: In a round-bottom flask, 17a (500 mg, 1.43 mmol, 1 equiv) and NMO (201 mg, 1.72 mmol, 1.2 equiv) were suspended in acetone (6.0 mL, HPLC grade) and the suspension stirred vigorously at 25 °C while an aqueous solution of OsO₄ (5 mg/mL, 2.20 mL, 0.043 mmol, 3 mol %) was added. The reaction mixture was left under argon and stirred at 25 °C for 6 hours upon which time only traces of starting material were observed (TLC). The volatiles were then removed in vacuo and the resulting solid dried under high vacuum (<1 mbar) for 15 minutes. It was then suspended in acetone (8 mL, HPLC grade) and deionized water (4 mL) was added followed by addition of NaIO₄ (977 mg, 4.57 mmol, 3.2 equiv). The reaction mixture was stirred vigorously at 25 °C for 20 minutes upon which time all diol had been consumed (TLC). The mixture was poured onto brine (200 mL) and the obtained suspension was extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated and the crude aldehyde purified by flash column chromatography on silica gel eluting with cyclohexane/EtOAc 1:1 to 1:3 to give the title product (±)-12 as a white solid (458 mg, yield = 91%). In a similar experiment on 5.71 mmol scale the aldehyde product (±)-12 was isolated in 87% yield (1.75 g).

M.p. (CH₂Cl₂/Et₂O/pentane) 172-174 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.92 (t, J = 2.0 Hz, 1H), 8.04 – 8.00 (m, 1H), 7.55 – 7.51 (m, 1H), 7.34 – 7.24 (m, 2H), 6.65 (d, J = 12.2 Hz, 1H), 5.65 (d, J = 12.3 Hz, 1H), 4.12 (td, J = 13.7, 4.7 Hz, 1H), 4.04 (s, 3H), 3.07 – 2.95 (m, 3H), 2.87 (dd, J = 16.2, 1.9 Hz, 1H), 2.67 (td, J = 14.1, 5.5 Hz, 1H), 2.48 – 2.30 (m, 2H), 2.24 – 2.05 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 198.6, 174.6, 152.3, 135.9, 133.1, 129.3, 128.8, 125.1, 123.3, 120.4, 118.3, 117.6, 115.6, 63.9, 53.6, 51.9, 36.4, 34.7, 28.7, 22.3. HRMS (ESI+) m/z calc. for C₂₀H₂₀N₂O₄Na⁺ [M+Na]⁺: 375.1315, found: 375.1326.
(+)-12: In a round-bottom flask, 17b (376 mg, 0.87 mmol, 1 equiv) and NMO (123 mg, 1.05 mmol, 1.2 equiv) were suspended in acetone (3.8 mL, HPLC grade) and the suspension stirred vigorously at 25 °C while an aqueous solution of OsO₄ (5 mg/mL, 1.38 mL, 0.027 mmol, 3 mol %) was added. The reaction mixture was left under argon and stirred at 25 °C for 6 hours upon which time only traces of starting material were observed (TLC). The volatiles were then removed in vacuo and the resulting solid dried under high vacuum (<1 mbar) for 30 minutes. It was then redissolved in acetone (5.6 mL, HPLC grade) and deionized water (2.8 mL) was added followed by addition of NaIO₄ (596 mg, 2.79 mmol, 3.2 equiv). The suspension was stirred vigorously at 25 °C for 20 minutes upon which time all diol had been consumed (TLC). The mixture was poured onto brine (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated and the crude aldehyde purified by flash column chromatography on silica gel eluting with cyclohexane/EtOAc 1:1 to 1:3 to give the title product (+)-12 as a white solid (236 mg, yield = 77%, 70% ee, measured by chiral HPLC for alcohol derivative, see below).

Note 1: E-olefin isomer reacts much faster than Z-isomer under these conditions.

Note 2: In a similar experiment on 6.05 mmol scale and 4 hours reaction for the dihydroxylation step, product (+)-12 was isolated in 67% yield (1.43 g). In another experiment on 9.29 mmol scale and 2 hours reaction for the dihydroxylation step, product (+)-12 was isolated in 68% yield (2.23 g).

M.p. (EtOAc/CH₂Cl₂) 186-187 °C (>99% ee). αₛₐ₅⁸⁹ (CHCl₃, c 1.0, 300 K) = + 133.0 deg.cm².g⁻¹ (>99% ee).

Crystallization to enantiopurity (2 crystallizations):
The purified solid (1.43 g, 70% ee) was dissolved in 30 mL of hot acetone and the solution left at room temperature for 24 hours then placed in the fridge (4 °C) for 48 hours. The solid (700 mg) was separated by decantation, washed with 2 mL of acetone and showed >99% ee (40% ee for the mother liquor). The mother liquor was concentrated in vacuo and the remaining solid (710 mg) was redissolved in 10 mL of hot acetone and the solution left at room temperature for 24 hours then placed in the fridge (4 °C) for 16 hours (slow crystallization). The solid (239 mg) was separated by decantation and showed >99% ee (8% ee for the mother liquor). The obtained white solid (939 mg) showed >99% ee (94% yield of crystallization); 44% yield over dihydroxylation/diol cleavage and 2 crystallizations.
Methyl (S,Z)-13a-(2-hydroxyethyl)-3-oxo-1,2,3,5,6,13a-hexahydro-11H-pyrrolo [1',2':1,8]azocino[5,4-b]indole-11-carboxylate (S1)

NaBH₄ (7.2 mg, 0.19 mmol, ca. 2 equiv) was added to a solution of aldehyde (±)-12 (35.2 mg, 0.1 mmol, 1 equiv) in HPLC grade CH₂Cl₂ (1 mL) and methanol (1 mL). The resulting mixture was stirred vigorously at 25 °C for 15 min upon which time all aldehyde had been consumed (TLC). The mixture was poured onto brine (100 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated and the crude alcohol was purified by flash column chromatography on silica gel eluting with EtOAc to give the title product (±)-S1 as a white solid (34.3 mg, yield = 97%).

(±)-S1: M.p. (CH₂Cl₂/cyclohexane) 190-192 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.03 – 7.98 (m, 1H), 7.55 – 7.51 (m, 1H), 7.33 – 7.22 (m, 2H), 6.58 (d, J = 12.3 Hz, 1H), 5.60 (d, J = 12.4 Hz, 1H), 4.10 – 4.00 (m, 4H), 3.93 – 3.80 (m, 2H), 3.05 – 2.95 (m, 2H), 2.65 (td, J = 13.7, 5.2 Hz, 1H), 2.37 (ddd, J = 15.8, 11.6, 8.5 Hz, 1H), 2.25 (dt, J = 14.2, 7.2 Hz, 1H), 2.17 – 1.97 (m, 4H), 1.66 (br s, 1H, OH). ¹³C NMR (101 MHz, CDCl₃) δ 175.2, 152.4, 135.9, 133.6, 130.7, 128.9, 124.9, 123.2, 119.5, 118.2, 117.6, 115.6, 65.2, 57.9, 53.5, 41.1, 36.3, 33.8, 29.0, 22.3. HRMS (ESI+) m/z calc. for C₂₀H₂₂N₂O₄Na⁺ [M+Na]⁺: 377.1472, found: 377.1470.

(+)-S1: M.p. (CH₂Cl₂/cyclohexane) 105-107 °C (>99% ee). α₀⁺⁸⁹ (CHCl₃, c 0.50, 299 K) = + 44.7 deg.cm².g⁻¹ (>99% ee). HPLC (Chiralpak IA (250 mm × 4.6 mm), hexane/CH₂Cl₂/ethanol 70:27:3, 1 mL/min) tᵣ₁ 20.0 – 20.1 min, tᵣ₂ 25.1 – 25.9 min.

Note: The reaction was performed on 0.025 mmol scale for the determination of enantiomeric excess.
HPLC trace of racemic sample of alcohol S1

Sample Info: Method: Hex-DCM-EtOH 70-27-3
1A, 1 ml/min
aldehyde racemic

HPLC trace of enantioenriched sample of alcohol S1

Sample Info: Method: Hex-DCM-EtOH 70-27-3
1A, 1 ml/min

Before crystallization (70% ee)

1st crystallization
Crystals (>99% ee)

1st crystallization
Mother liquor (40% ee)

2nd crystallization
Crystals (>99% ee)

2nd crystallization
Mother liquor (8% ee)
Methyl (S)-3-oxo-13a-(2-oxoethyl)-1,2,3,5,6,12,13,13a-octahydro-11H-pyrrolo[1',2':1,8]azocino[5,4-b]indole-11-carboxylate (18)

(±)-18: Pd/C (10 wt% palladium, 85 mg, 0.08 mmol, 8 mol %) was placed in a sealed 25 mL microwave vial under argon atmosphere. HPLC grade ethyl acetate (17.5 mL) was added and the resulting suspension and system were sequentially placed under vacuum and charged with hydrogen (3 cycles), then a solution of aldehyde (±)-12 (352 mg, 1.00 mmol, 1 equiv) in HPLC grade CH₂Cl₂ (3.5 mL) was added. The mixture was stirred vigorously at 25 ºC for 90-120 min. The system was placed under vacuum and charged with argon. The reaction mixture was filtered through a pad of silica, washed with a 1:1 mixture of CH₂Cl₂/acetone (140 mL) and concentrated. The crude residue was loaded on silica gel column and purified by chromatography eluting with EtOAc/CH₂Cl₂ 1:1 to afford the product as an off-white solid (274 mg, 0.77 mmol, 77%) as well as recovered starting material (55 mg, 0.16 mmol, 16%; yield of (±)-18 based on recovered starting material = 92%).

Note 1: The reaction should be carefully monitored by TLC to minimize over hydrogenation and the formation of indoline byproducts.

Note 2: The product readily crashes out from EtOAc, which should be taken into account during column chromatography.

M.p. (CH₂Cl₂/pentane) 130-132 ºC. ¹H NMR (400 MHz, CDCl₃) δ 9.73 (t, J = 2.2 Hz, 1H), 8.03 – 7.97 (m, 1H), 7.47 – 7.42 (m, 1H), 7.30 – 7.21 (m, 2H), 4.25 (ddd, J = 13.7, 9.4, 3.8 Hz, 1H), 4.05 (s, 3H), 3.41 (ddd, J = 17.0, 7.1, 2.6 Hz, 1H), 3.16 – 2.85 (m, 4H), 2.64 (d, J = 2.3 Hz, 2H), 2.59 – 2.48 (m, 1H), 2.46 – 2.35 (m, 1H), 2.30 (ddd, J = 15.2, 10.7, 2.6 Hz, 1H), 2.25 – 2.10 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 199.1, 175.2, 152.6, 136.9, 135.1, 129.6, 124.1, 122.9, 117.3, 116.7, 115.6, 64.0, 53.5, 51.7, 40.2, 38.2, 30.7, 29.6, 22.9, 22.6. HRMS (ESI⁺) m/z calc. for C₂₀H₂₂N₂O₄Na⁺ [M+Na]⁺: 377.1472, found: 377.1465.
(−)-18: Pd/C (10 wt% palladium, 85 mg, 0.08 mmol, 8 mol %) was placed in a sealed 25 mL microwave vial under argon atmosphere. HPLC grade ethyl acetate (17.5 mL) was added and the resulting suspension and system were sequentially placed under vacuum and charged with hydrogen (3 cycles), then a solution of aldehyde (+)-12 (352 mg, 1.00 mmol, 1 equiv, >99% ee) in HPLC grade CH₂Cl₂ (3.5 mL) was added. The mixture was stirred vigorously at 25 °C for 90-120 min. The system was placed under vacuum and charged with argon. The reaction mixture was filtered through a pad of silica, washed with a 1:1 mixture of CH₂Cl₂/acetone (140 mL) and concentrated. The crude residue was loaded on silica gel column and purified by chromatography eluting with EtOAc/CH₂Cl₂ 1:1 to afford the product as an off-white solid (229 mg, 0.65 mmol, 65%) as well as recovered starting material (101 mg, 0.29 mmol, 29%; yield of (−)-18 based on recovered starting material = 92%).

M.p. (acetone) 123-124 °C (>99% ee). αD 589(CHCl₃, c 1.0, 300 K) = −98.9 deg.cm².g⁻¹ (>99% ee).

Methyl (13aS)-13a-(2-hydroxy-3-methoxy-3-oxopropyl)-3-oxo-1,2,3,5,6,12,13,13a-octahydro-11H-pyrrolo[1',2':1,8]azocino[5,4-b]indole-11-carboxylate (19)

(±)-19: In a glovebox, (±)-18 (354 mg, 1.00 mmol, 1 equiv) was placed in a 25 mL flame-dried microwave vial and dissolved in 2.0 mL of a 0.075 M solution of pyridine N-oxide in anhydrous CH₂Cl₂ (0.15 mmol, 15 mol %). The reaction mixture was sealed with a septum, removed from the glovebox and connected to an argon line through a needle. The vial was placed in a cooling bath (−40 °C), and SiCl₄ (0.5 mL, 738 mg, 4.35 mmol, 4.35 equiv) was injected immediately into the reaction mixture. A solution of t-BuNC (250 µL) in CH₂Cl₂ (1.5 mL) was prepared in the glovebox, and 1.27 mL of this solution was injected with a syringe pump within 10 hours at −40 °C, (t-BuNC: 180 µL, 125 mg, 1.50 mmol, 1.5 equiv). Then the reaction mixture was stirred for 6 hours at −40 °C. Anhydrous MeOH (1.67 mL) was slowly injected into the solution. The reaction mixture was warmed to 0 °C within 2.5 hours and then slowly added via syringe to a stirred ice-cold mixture of saturated aqueous NaHCO₃.
(35 mL) and CH₂Cl₂ (17 mL) in a beaker. The resulting biphasic mixture was stirred at 25 °C for 1 hour, and it was then filtered, applying external pressure. The filtered solids were washed with CH₂Cl₂ (30 mL), acetone (30 mL), and CH₂Cl₂-acetone (1:1, 20 mL × 8), and the filtrates were combined and partitioned between CH₂Cl₂ (150 mL) and brine (150 mL). The organic phase was separated and the aqueous layer was washed with CH₂Cl₂ (75 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, concentrated under reduced pressure and dried under high vacuum. Purification by column chromatography on silica gel eluting with CH₂Cl₂/MeOH 30:1 gave the title product as a white solid (367 mg, 2:1 mixture of diastereomers, yield = 89%). In a similar experiment on 2.87 mmol scale, product (+)-19 was isolated in 86% yield (1.02 g).

**Note 1:** Pyridine N-oxide was dried and stored in the glovebox as a crystalline solid.

**Note 2:** The density of t-BuNC (obtained from Aldrich) was found to be 0.70 g/mL.

**Note 3:** α-Halo esters are useful and versatile intermediates in organic synthesis. However, the current methods to access such compounds by aldehyde homologation are essentially limited to cyanohydrins synthesis. Those are far from modern synthetic standards and feature many steps and harsh conditions. Thus, seeking an alternative, our attention turned to the work of Denmark et al., where α-hydroxy methyl esters were synthesized from aldehydes and t-BuNC, in a Passerini-type reaction, with an exceptional functional group tolerance. To apply this transformation to compound 18, we had to account for the presence of several Lewis-basic centers in the molecule, and increase the amount of SiCl₄ (4.35 equiv instead of 1.1 equiv) and raise the reaction temperature (from –74 °C to –40 °C).

**M.p.** (amorphous) 159-175 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.04 – 7.97 (m, 1H major, 1H minor), 7.47 – 7.41 (m, 1H major, 1H minor), 7.30 – 7.20 (m, 2H major, 2H minor), 4.29 – 4.12 (m, 2H major, 1H minor), 4.11 – 4.02 (m, 3H major, 4H minor), 3.74 (s, 3H minor), 3.72 (s, 3H major), 3.51 – 3.37 (m, 1H major, 1H minor), 3.16 – 2.85 (m, 5H major, 5H minor), 2.56 – 2.35 (m, 2H major, 3H minor), 2.32 – 1.88 (m, 5H major, 4H minor), 1.81 – 1.70 (m, 1H major, 1H minor). **¹³C NMR** (101 MHz, CDCl₃) δ 176.3, 175.9, 175.3, 175.1, 152.7, 152.7, 137.8, 137.6, 135.2 (2C), 129.9, 129.8, 123.9 (2C), 122.9, 122.8, 117.7, 117.4, 117.3, 116.7, 115.6, 115.5, 67.8, 67.2, 65.6, 65.5, 53.5. 53.4, 52.9, 52.9, 43.0, 41.9, 40.8, 40.0, 39.2, 37.4, 30.4, 29.9 (2C), 29.1, 22.9, 22.8, 22.6, 22.3. **HRMS** (ESI+) m/z calc. for C₂₂H₂₇N₂O₆⁺ [M+H]⁺: 415.1864, found: 415.1861.
(-)-19: The above described procedure for racemic 19 on 1.60 mmol scale of (-)-18 gave the enantiopure product (-)-19 as a white foamy solid (623 mg, contains 6.5 wt% of CH₂Cl₂, 88% yield).

M.p. (amorphous, CH₂Cl₂) 74-76 °C (>99% ee). [α]D<sup>589</sup> (CHCl₃, c 0.92, 300 K) = -57.2 deg.cm<sup>2</sup>.g<sup>-1</sup> (>99% ee).

Methyl (13aS)-13a-(2-bromo-3-methoxy-3-oxopropyl)-3-oxo-1,2,3,5,6,12,13,13a-octahydro-11H-pyrrolo[1',2':1,8]azocino[5,4-b]indole-11-carboxylate (11)

(±)-11: In a glovebox, (±)-19 (360 mg, 0.87 mmol, 1 equiv), Ph₃PBr₂ (439 mg, 1.04 mmol, 1.2 equiv), imidazole (71 mg, 1.04 mmol, 1.2 equiv) and NBu₄Br (560 mg, 1.74 mmol, 2 equiv) were dissolved in 4.3 mL of anhydrous CH₂Cl₂ and the resulting solution stirred at 25 °C for 5 hours, upon which time complete conversion was observed (TLC). The reaction mixture was diluted with CH₂Cl₂ (50 mL) and EtOAc (15 mL) and evaporated with Florisil<sup>®</sup> absorbent (15 g). Purification by column chromatography on silica gel eluting with EtOAc/CH₂Cl₂ 1:1, concentration, evaporation from EtOAc and drying under high vacuum gave (±)-11 as a white solid (374 mg, ca. 3:2 mixture of two diastereomers, 0.78 mmol, yield = 90%). In a similar experiment on 2.46 mmol scale, product (±)-11 was isolated in 90% yield (1.06 g).

Note: Ph₃PBr₂ reagent is convenient to handle and in the presence of NBu₄Br as additional bromide source, the observed yields were consistently higher.

M.p. (amorphous) 148-152 °C. <sup>1</sup>H NMR (400 MHz, CDCl₃) δ 8.01 – 7.93 (m, 1H major, 1H minor), 7.48 – 7.38 (m, 1H major, 1H minor), 7.30 – 7.19 (m, 2H major, 2H minor), 4.27 – 4.16 (m, 1H major, 2H minor), 4.05 (s, 3H minor), 3.95 (ddd, J = 14.2, 8.4, 2.8 Hz, 1H major), 3.78 (s, 3H minor), 3.76 (s, 3H major), 3.48 (ddd, J = 16.3, 8.7, 2.3 Hz, 1H major), 3.41 (ddd, J = 16.9, 7.7, 2.2 Hz, 1H minor), 3.15 – 3.02 (m, 1H major, 1H minor), 3.01 – 2.82 (m, 1H major, 3H minor), 2.80 – 2.59 (m, 3H major, 1H minor), 2.54 – 2.42 (m, 2H major, 1H minor), 2.42 – 2.30 (m, 1H minor), 2.26 (dd, J = 15.2, 5.0 Hz, 1H minor), 2.20 – 1.90 (m, 5H major, 4H minor). <sup>13</sup>C NMR (101 MHz, CDCl₃) δ 175.1, 175.0, 170.4, 169.9, 152.7
(2C), 137.8, 137.2, 135.0, 135.0, 129.8, 129.7, 124.0, 123.9, 122.9 (2C), 117.7, 117.4, 117.3, 116.9, 115.5, 115.5, 66.0, 65.8, 53.5 (2C), 53.4, 53.3, 44.9, 43.0, 40.9, 40.4, 39.8, 39.0, 29.8, 29.7, 29.0, 28.2, 22.5 (2C), 22.5, 21.4. **HRMS** (ESI+) m/z calc. for C_{22}H_{26}BrN_{2}O_{5}^+ [M+H]^+: 477.1020, found: 477.1020.

(−)-11: In a glovebox, (−)-19 (485 mg, 1.17 mmol, 1 equiv), Ph_3PBr_2 (588 mg, 1.39 mmol, 1.2 equiv), imidazole (99 mg, 1.45 mmol, 1.25 equiv) and NBu_4Br (751 mg, 2.33 mmol, 2 equiv) were dissolved in 5.8 mL of anhydrous CH_2Cl_2 and the resulting solution stirred at 25 °C for 5 hours, upon which time complete conversion was observed (TLC). The reaction mixture was diluted with CH_2Cl_2 (75 mL) and EtOAc (25 mL) and evaporated with florisil® absorbent (30 g). Purification by column chromatography on silica gel eluting with EtOAc/CH_2Cl_2 1:1, concentration, evaporation from 1:3 mixture of EtOAc/cyclohexane and further drying under high vacuum gave (−)-11 as a white solid (575 mg, contains 9 wt% of residual solvents, ca. 3:2 mixture of diastereomers, 1.10 mmol, yield = 94%).

**M.p.** (EtOAc/cyclohexane) 140-142 °C (>99% ee). \( \alpha_D^{589} \) (CHCl_3, c 0.91, 300 K) = −46.1 deg.cm^2·g^−1 (>99% ee).

**Dimethyl (11aR,12R,13aS,Z)-3-oxo-2,3,12,13-tetrahydro-1H-11a,13a-ethanopyrrrolo[1′,2′:1,8]azocino[5,4-b]indole-11,12(5H)-dicarboxylate (10)**

(±)-10, **Procedure A:** For convenience two identical experiments were performed in parallel. They were combined after reaction and the isolation of the material was carried out on the combined crude mixtures. In a glovebox, (±)-11 (47.7 mg, 0.10 mmol, 1 equiv), Na_2CO_3 (21.2 mg, 0.20 mmol, 2 equiv), a magnetic stirbar, a solution of [(dpmmAuCl)_2]^4 in CH_3CN (1 mM, 2.0 mL, 2 mol %) and CH_3CN (anhydrous, oxygen-free, 3.0 mL) were placed in a 12 mL vial (Ø = 2.3 cm) and the vial was sealed. This was repeated (identically) for the second vial, and both were removed from the glovebox, and irradiated with a 365 nm UV light in a specific setup designed for this purpose (Note 1, Figure S1), stirring for 5 hours (25-35 °C). After this time, full conversion was observed (TLC). The reaction mixtures were combined, the
volatiles were removed, and the obtained residue was purified on a 2000 µm preparative silica gel TLC using EtOAc/CH₂Cl₂ 9:1 as eluent and acetone/CH₂Cl₂ 1:1 to separate the compound from the silica. Concentration of an EtOAc solution and further drying under high vacuum gave the title product (±)-10 as a white solid in 91% yield (72.5 mg, dr >50:1).

Note 1: Six OSA Opto Light UV LEDs (EOLD-365-525) were connected in 2 parallel lines of 3 diodes in each, and assembled in a PTFE setup with four sockets, with one or two diode(s) mounted at the bottom of each socket (Ø = 1.6 cm and 2.6 cm; Figure S1). In the abovementioned experiments, the vials were placed in two-diode-sockets. The irradiance at 365 nm in the two-diode-socket, measured at the vial distance of reaction (ca. 2 mm) was found to be 2.6 mW/cm² (voltage = 26V, current = 0.07 A in our setup). A high intensity UV irradiation was found to be important to achieve high yield in this transformation.

Note 2: Product 10 was found to be air-sensitive, presumably because of a possible autooxidation at the allylic position. Thus, the isolation was performed within two to three hours with particular precautions (the compound was kept under Ar atmosphere, the preparative TLC chamber was purged with argon). After isolation, 10 was placed under inert atmosphere and stored in the freezer.

Note 3: Crystals suitable for single-crystal X-ray diffraction studies were obtained by evaporation from EtOAc.

Figure S1. Setup used for UV light-mediated photoredox cyclization.
(±)-10, Procedure B: In a glovebox, a solution of (±)-11 (117 mg, 0.245 mmol, 1 equiv), 4-MeOC₆H₄NPh₂ (135 mg, 0.49 mmol, 2 equiv) and [Ru(bpy)₃]Cl₂·6H₂O (9.4 mg, 0.012 mmol, 5 mol %) in DMF (anhydrous, oxygen-free, 3.7 mL) was placed in a vessel designed for photochemical reactions (Figure S2). The vessel was sealed, removed from the glovebox and the resulting orange solution was irradiated with blue light (LEDs) for 12 hours (an air flow was applied for external cooling). After this time, catalyst decomposition was clearly observed (deep purple color of the reaction mixture). The reaction mixture was poured onto CH₂Cl₂-H₂O (50 mL:50 mL). The organic phase was separated and the aqueous layer was extracted with CH₂Cl₂ (25 mL × 2). The combined organic layers were washed with brine (25 mL), dried over Na₂SO₄, filtered, concentrated, and the obtained residue was purified on a 2000 µm preparative silica gel TLC using EtOAc as eluent. The title product (±)-10 was isolated as a pale yellow solid in 40% yield (39.0 mg, dr >50:1).

Note 1: Ledxon LED stripe (1.0 m, 60 blue LEDs, λ = 470 nm) coiled outside of a crystallizing dish (Ø = 11 cm) was used for blue-light irradiation (Figure S2). The irradiance at 470 nm of our setup, at the distance of the reaction vessel, was found to be 6.8 mW/cm² (calibrated photodiode).

Note 2: The starting material was recovered as an inseparable mixture with, presumably, the chloride derivative of (±)-11 arising from Br-Cl exchange (46 mg, ca. 40%).

Note 3: Deep purple block crystals deposited on the vessel walls in the course of the photochemical reaction. These crystals were analyzed by single-crystal X-ray diffraction, and the structure [(bpy)₂RuBr₂]Br was obtained. This deep-colored compound presumably interferes with the blue-light mediated photoredox process, and is responsible for the deactivation of the catalytic system.

Note 4: The following photoredox reaction conditions were screened without improvement over procedure B:

Catalyst: [Ru(bpy)₃]Cl₂·6H₂O or [(ppy)₂Ir(dtbbpy)]PF₆

Amine: 4-MeOC₆H₄NPh₂, NEt₃, PhNMe₂ or TMEDA; Solvent: DMF or CH₃CN.

In addition, the thermal catalytic transformation with CuI/TPMA²⁰ showed low selectivity toward the formation of 10.
Note 5: Compound 11H was the main identifiable side-product in the scouting photoredox experiments (1H NMR and TLC). It was isolated from combined reaction mixtures as a colorless oil (ca. 85 wt% purity after preparative silica gel TLC with EtOAc as eluent). 1H NMR (400 MHz, CDCl3) δ 8.00 – 7.95 (m, 1H), 7.46 – 7.42 (m, 1H), 7.26 – 7.22 (m, 2H), 4.15 (ddd, J = 14.0, 10.2, 3.9 Hz, 1H), 4.05 (s, 3H), 3.68 (s, 3H), 3.42 (ddd, J = 17.2, 7.5, 1.9 Hz, 1H), 3.17 – 2.87 (m, 4H), 2.48 (ddd, J = 17.2, 9.8, 7.2 Hz, 1H), 2.42 – 2.19 (m, 4H), 2.09 – 1.88 (m, 5H). 13C NMR (101 MHz, CDCl3) δ 175.4, 173.3, 152.8, 137.3, 135.1, 130.0, 123.9, 122.9, 117.3, 116.4, 115.6, 65.5, 53.4, 51.9, 39.8, 38.2, 33.8, 29.9, 28.8, 28.6, 23.1, 22.4. HRMS (ESI+) m/z calc. for C22H26N2O5 [M+Na]+: 421.1734, found: 421.1720.

Figure S2. a) Hollow cylinder-shaped reaction vessel (Ø int. = 26 mm; Ø ext. = 36 mm). b) Blue LED setup used for visible light photoredox transformation.

M.p. (EtOAc) 201-204 ºC. 1H NMR (500 MHz, CDCl3, 328 K) δ 7.65 (br s, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.17 (ddd, J = 8.5, 7.4, 1.3 Hz, 1H), 6.96 (td, J = 7.5, 1.0 Hz, 1H), 6.21 (ddd, J = 7.3, 4.7 Hz, 1H), 4.53 (dd, J = 18.8, 7.3 Hz, 1H), 4.35 (ddd, J = 18.8, 4.7 Hz, 1H), 4.08 – 3.88 (m, 4H), 3.21 – 2.91 (m, 4H), 2.54 (ddd, J = 15.4, 11.4, 1.7 Hz, 1H), 2.44 (td, J = 7.6, 2.4 Hz, 2H), 2.20 (td, J = 13.0, 7.0 Hz, 1H), 2.13 – 2.00 (m, 2H), 1.96 – 1.86 (m, 3H). 13C NMR (126 MHz, CDCl3, 328 K) δ 174.1, 171.9, 153.3, 141.8 (2C), 129.4, 128.6, 123.3, 119.3, 115.5, 113.9, 69.8, 60.6, 52.5, 51.7, 41.4, 38.7, 38.4, 34.3, 31.6, 29.8, 29.3. HRMS (ESI+) m/z calc. for C22H26N2O5 [M+H]+: 397.1758, found: 397.1766.

(--)-10: The above described procedure A applied to (--)-11 gave the enantiopure product (--)-10 as a white solid (71.8 mg, dr >50:1, 91% yield).

M.p. (EtOAc) 175-176 ºC (>99% ee). \( \alpha_D^{589} \) (CHCl3, c 1.08, 300 K) = – 73.6 deg.cm².g⁻¹ (>99% ee).
**General note on the dr estimation:**

The diastereoselectivity of the photoredox transformation was estimated after careful examination of the \(^1\)H NMR spectra of crude reaction mixtures and isolated products. It was noticed that all samples of isolated 10 still contained a minute amount of an inseparable impurity that could be observed in the \(^1\)H NMR as signals at 3.80 (s) and 3.60 (s) ppm. This impurity was assumed to be the \textit{exo}-isomer of 10, due to the similarity of its chemical shifts with those observed in related compounds, containing the \textit{exo}-CO\(_2\)Me-group, such as 7 (3.81, 3.61 ppm); 6 (3.79, 3.58 ppm); and dihydroisolapildilactine A (3.79, 3.57 ppm). The signal at 3.80 ppm was assigned to NCO\(_2\)Me and the signal at 3.60 ppm to the \textit{exo}-CO\(_2\)Me group. The careful integration of these signals in the \(^1\)H NMR spectra provided the following \textit{endo}/\textit{exo} ratios: for (\(\pm\))-10 isolated through procedure A – ca. 90:1; for (\(-\))-10 isolated through procedure A – ca. 110:1; for (\(\pm\))-10 isolated through procedure B – ca. 90:1. Similarly, a ca. 80:1 \textit{endo}/\textit{exo} ratio was observed in the crude reaction mixture before purification following procedure A and a ca. 85:1 ratio employing procedure B. It is also worth noting that the crude reaction mixture obtained via procedure A is rather clean, and in the area of 3.0 ppm – 4.2 ppm no significant amount of compounds other than \textit{endo}-10, 11H or \textit{exo}-10 could be observed. These results allowed us to estimate the \textit{endo}/\textit{exo} diastereoselectivity of the transformation to be >50:1.

\(^1\)H NMR (400 MHz, CDCl\(_3\), 298K) of crude reaction mixture after procedure A.

\(^1\)H NMR (500 MHz, CDCl\(_3\), 298K) of isolated (\(-\))-10 after procedure A.
Methyl \((6aR,11aR,12R,13aS)-3,16\text{-dioxo-2,3,5,6,12,13\text{-hexahydro-1H,11H-6a,12-}}\text{(epoxymethano)-11a,13a-ethanopyrrolo[1',2':1,8]azocino[5,4-}b\text{]indole-11-carboxylate}\) (8)

\((\pm)-8:\) A 50% (v/v) aqueous \(\text{H}_2\text{SO}_4\) (1.5 mL) was added dropwise to a solution of alkene (±)-10 (95.0 mg, 0.240 mmol, 1 equiv) in HPLC grade \(\text{CH}_2\text{Cl}_2\) (1.5 mL) at 25 °C, resulting in the formation of a purple biphasic mixture. After stirring at 25 °C for 3 hours, the reaction mixture was cooled to 0 °C, diluted with \(\text{CH}_2\text{Cl}_2\) (10 mL), and deionized water (15 mL) was slowly added at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred for 30 minutes. Then the layers were separated, the aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (3 × 10 mL) and the combined organic layers were washed with a saturated aqueous solution of \(\text{NaHCO}_3\) (20 mL), dried over \(\text{Na}_2\text{SO}_4\), filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with \(\text{CH}_2\text{Cl}_2/\text{acetone}\) 10:1 gave the title product as an off-white foamy solid (80.5 mg, 0.211 mmol, yield = 88%).

**M.p.** (Ethyl acetate/pentane) 251-252 °C. \(^1\text{H NMR}\) (500 MHz, \(\text{CDCl}_3\), 328 K) \(\delta\) 7.67 (br s, 1H), 7.43 – 7.32 (m, 2H), 7.11 (t, \(J = 7.5\), Hz, 1H), 4.47 (ddd, \(J = 16.0, 6.0, 2.2\) Hz, 1H), 3.97 – 3.85 (m, 4H), 2.98 (dd, \(J = 16.0, 12.1\) Hz, 1H), 2.80 (dd, \(J = 16.1, 5.9\) Hz, 1H), 2.55 – 2.30 (m, 3H), 2.23 – 2.08 (m, 3H), 2.03 – 1.75 (m, 5H). \(^{13}\text{C NMR}\) (126 MHz, \(\text{CDCl}_3\), 328 K) \(\delta\) 177.9, 175.2, 153.0, 141.9, 131.6, 127.2, 123.9, 123.6, 115.6, 92.5, 72.4, 60.5, 53.0, 41.1, 36.3, 34.5, 33.9, 31.6, 31.1, 29.8, 24.1. \(\text{HRMS}\) (ESI+) \(m/z\) calc. for \(\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_5\text{Na}^+ [\text{M+Na}]^+\): 405.1421, found: 405.1422. \(\text{UV-Vis}\) (MeOH) \(\lambda_{\text{max}}\) nm = 242, 283, 290 (sh).

\((+)-8:\) A 50% (v/v) aqueous \(\text{H}_2\text{SO}_4\) (2.8 mL) was added dropwise to a solution of alkene (–)-10 (178 mg, 0.449 mmol, 1 equiv) in HPLC grade \(\text{CH}_2\text{Cl}_2\) (2.8 mL) at 25 °C, resulting in the formation of a purple biphasic mixture. After stirring at 25 °C for 3 hours, the reaction mixture was cooled to 0 °C, diluted with \(\text{CH}_2\text{Cl}_2\) (19 mL), and deionized water (28 mL) was slowly added at 0 °C. The resulting mixture was allowed to warm to 25 °C and stirred for 30 minutes. Then the layers were separated, the aqueous layer was extracted with \(\text{CH}_2\text{Cl}_2\) (3 × 20 mL) and the combined organic
layers were washed with a saturated aqueous solution of NaHCO$_3$ (40 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with CH$_2$Cl$_2$/acetone 10:1 gave the title product as an off-white solid (161 mg, 0.421 mmol, yield = 94%).

**M.p.** (EtOAc) 226-228 °C (>99% ee, starts turning brown >215 °C). $\alpha^p_{D}^{589}$ (CHCl$_3$, c 0.70, 300 K) = +21.7 deg.cm$^2$.g$^{-1}$ (>99% ee).

Methyl (6aR,11aR,12R,13aS)-16-oxo-3-thioxo-2,3,5,6,12,13-hexahydro-1H,11H-6a,12-(epoxymethano)-11a,13a-ethanopyrrolo[1′,2′:1,8]azocino[5,4-b]indole-11-carboxylate (8S1)

(±)-8S1: A solution of (±)-8 (78.6 mg, 0.206 mmol, 1 equiv) and Lawesson’s reagent (2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide, 83.2 mg, 0.206 mmol, 1 equiv) in anhydrous toluene (2.0 mL) in a sealed microwave vial was stirred at 90 °C until full conversion of starting material was achieved (typically 1 hour). The volatiles were removed under reduced pressure and the resulting crude product was purified by preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 20:1 to afford the title compound as an amorphous pale pink solid (79.4 mg, 0.199 mmol, yield = 97%).

**M.p.** (CH$_2$Cl$_2$/pentane) 241-244 °C (starts turning brown at >232 °C). $^1$H NMR (500 MHz, CDCl$_3$, 328 K) $\delta$ 7.68 (br s, 1H), 7.45 – 7.38 (m, 2H), 7.15 (td, $J = 7.5, 1.0$ Hz, 1H), 5.21 (ddd, $J = 16.1, 6.1, 2.1$ Hz, 1H), 4.00 – 3.90 (m, 4H), 3.33 (ddq, $J = 16.2, 12.1, 1.3$ Hz, 1H), 3.05 (ddd, $J = 8.7, 5.5, 1.1$ Hz, 2H), 2.92 (ddd, $J = 16.3, 6.2, 1.5$ Hz, 1H), 2.54 (dd, $J = 15.7, 13.0$ Hz, 1H), 2.39 – 2.26 (m, 2H), 2.25 – 2.16 (m, 1H), 2.13 – 2.06 (m, 1H), 2.05 – 1.84 (m, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$, 328 K) $\delta$ 204.3, 177.6, 153.1, 141.8, 131.9, 126.9, 124.1, 123.8, 115.7, 92.3, 72.4, 68.3, 53.1, 42.4, 40.8, 40.6, 38.1, 33.6, 30.7, 30.1, 23.7. HRMS (ESI+) $m/z$ calc. for C$_{21}$H$_{23}$N$_2$O$_4$S$^+$ [M+H]$^+$: 399.1373, found: 399.1375.

(+)-8S1: A solution of (+)-8 (134 mg, 0.350 mmol, 1 equiv) and Lawesson’s reagent (148 mg, 0.366 mmol, 1.05 equiv) in anhydrous toluene (4.0 mL) in a sealed microwave vial was stirred at 90 °C until full conversion of starting material was achieved (typically 1 hour). The volatiles were removed under reduced pressure and
the resulting crude product was purified by preparative silica gel TLC eluting with CH₂Cl₂/acetone 20:1 to afford the title compound as an amorphous pale pink solid (136 mg, 0.341 mmol, yield = 97%).

**M.p.** (EtOAc/cyclohexane) 271-273 °C (>99% ee, starts turning brown >265 °C). \( \delta \text{H}^{589} \) (CHCl₃, c 1.0, 299 K) = + 97.9 deg.cm².g⁻¹ (>99% ee).

**Methyl (6aR,11aR,12R,13aR)-16-oxo-3-thioxo-5,6,12,13-tetrahydro-3H,11H-6a,12-(epoxymethano)-11a,13a-ethanopyrrolo[1′,2′:1,8]azocino[5,4-b]indole-11-carboxylate (8S2)**

(±)-8S2: A solution of (±)-8S1 (68.2 mg, 0.171 mmol, 1 equiv) in anhydrous CH₂Cl₂ (3.4 mL) was placed in a sealed microwave vial and cooled at –20 °C. N,N-Diisopropylethylamine (Hünig’s base, 360 µL, 2.07 mmol, 12 equiv) and para-toluenesulfinyl chloride\(^5\) (181 mg, 1.04 mmol, 6 equiv) were injected via two separate syringes and simultaneously. The reaction mixture was stirred at –20 °C until full conversion of starting material was observed by TLC (30 min). The mixture was then heated at 80 °C and stirred for additional 6 h. The brown solution was allowed to cool to 25 °C, the volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with CH₂Cl₂/acetone 40:1 to afford the title product as a yellow foamy solid (43.3 mg, 0.109 mmol, yield = 64%).

**M.p.** (CH₂Cl₂/pentane) 252-255 °C dec. (starts turning brown >235 °C). \(^1\text{H}\) NMR (500 MHz, CDCl₃, 328 K) \( \delta \) 7.72 (br s, 1H), 7.49 – 7.40 (m, 2H), 7.17 (td, \( J = 7.5, 1.0 \) Hz, 1H), 6.75 (d, \( J = 5.5 \) Hz, 1H), 6.39 (d, \( J = 5.5 \) Hz, 1H), 5.33 (ddd, \( J = 16.8, 6.7, 2.0 \) Hz, 1H), 4.04 – 3.91 (m, 4H), 3.44 (ddd, \( J = 16.8, 12.2, 1.4 \) Hz, 1H), 3.03 (ddd, \( J = 16.5, 6.7, 1.4 \) Hz, 1H), 2.69 (dd, \( J = 15.5, 12.0 \) Hz, 1H), 2.59 – 2.45 (m, 1H), 2.44 – 2.33 (m, 2H), 2.14 (ddd, \( J = 15.6, 2.4, 1.1 \) Hz, 1H), 1.91 – 1.75 (m, 2H). \(^{13}\text{C}\) NMR (126 MHz, CDCl₃, 328 K) \( \delta \) 196.7, 177.3, 152.8, 151.6, 141.9, 133.3, 132.0, 126.6, 124.2, 123.8, 116.0, 91.0, 72.8, 72.5, 53.1, 40.7, 39.5, 30.8, 28.7, 26.5, 20.7. HRMS (ESI+) \( m/z \) calc. for C₂₁H₂₀N₂O₄SNa\(^+\) [M+Na\(^+\)]: 419.1036, found: 419.1030.
(+)-8S2: A solution of (+)-8S1 (127 mg, 0.319 mmol, 1 equiv) in anhydrous CH₂Cl₂ (6.6 mL) was placed in a sealed microwave vial and cooled at –20 °C. N,N-Diisopropylethylamine (Hünig’s base, 0.70 mL, 4.0 mmol, ca. 12 equiv) and para-toluenesulfinyl chloride⁵ (352 mg, 2.0 mmol, ca. 6 equiv) were injected via two separate syringes and simultaneously. The reaction mixture was stirred at –20 °C until full conversion of starting material was observed by TLC (30 min). The mixture was then heated at 80 °C and stirred for additional 6 h. The brown solution was allowed to cool to 25 °C, the volatiles were removed under vacuum and the crude mixture was purified by column chromatography on silica gel eluting with CH₂Cl₂/acetone (100:1 to 30:1) to afford the title product as a yellow foamy solid (91 mg, 0.230 mmol, yield = 72%).

M.p. (CH₂Cl₂/cyclohexane) 252-254 °C (>99% ee, starts turning brown >200 °C). αD²⁸⁹ (CHCl₃, c 1.0, 300 K) = + 231.7 deg.cm²·g⁻¹ (>99% ee).

Grandilodine C (2)

(±)-2: A solution of (±)-8S2 (17.8 mg, 0.045 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1.1 mL) was placed in a dry Schlenk tube under argon. The solution was cooled to –78 °C and a freshly prepared solution of m-CPBA (ca. 75% purity, 100 mg in 5 mL anhydrous CH₂Cl₂, 1.15 mL, 0.1 mmol, 2.2 equiv) was added dropwise at –78 °C. The solution was stirred at this temperature for 30 minutes, upon which time full conversion of the starting material was observed by TLC. The mixture was filtered through a short pad of basic alumina (10 cm high, 1.5 cm diameter), first flushing with CH₂Cl₂ (70 mL) then CH₂Cl₂/acetone (1:1, 200 mL). The fractions containing the product were concentrated in vacuo to afford analytically pure (±)-grandilodine C as a white solid (15.7 mg, 0.041 mmol, yield = 92%).

Note 1: Crystals suitable for single-crystal X-ray diffraction studies were obtained from acetone/pentane solvent system by diffusion method.

M.p. (CH₂Cl₂/pentane) 279-281 °C dec. (starts turning brown >265 °C). ¹H NMR (500 MHz, CDCl₃) δ 7.61 (br s, 1H), 7.48 – 7.39 (m, 2H), 7.16 (t, J = 7.5 Hz, 1H), 6.86 (d, J = 5.8 Hz, 1H), 6.11 (d, J = 5.8 Hz, 1H), 4.58 (ddd, J = 16.2, 6.7, 1.9 Hz, 1H), 2.16 (s, 3H).
Hz, 1H), 4.05 – 3.87 (m, 4H), 3.20 (dd, \( J = 16.0 \), 12.1 Hz, 1H), 2.95 (dd, \( J = 16.1 \), 6.5 Hz, 1H), 2.75 – 2.58 (m, 1H), 2.50 – 2.21 (m, 3H), 2.08 (d, \( J = 15.4 \) Hz, 1H), 1.90 (br s, 1H), 1.68 – 1.58 (m, 1H). \(^1\)H NMR (500 MHz, CDCl\(_3\), 328 K) \( \delta \) 7.71 (br s, 1H), 7.47 – 7.40 (m, 2H), 7.16 (td, \( J = 7.5 \), 1.0 Hz, 1H), 6.84 (d, \( J = 5.8 \) Hz, 1H), 6.11 (d, \( J = 5.8 \) Hz, 1H), 4.59 (ddd, \( J = 16.2 \), 6.6, 2.0 Hz, 1H), 4.01 – 3.93 (m, 4H), 3.20 (ddd, \( J = 16.2 \), 6.7, 1.3 Hz, 1H), 2.95 (ddd, \( J = 16.2 \), 1.3 Hz, 1H), 2.71 – 2.61 (m, 1H), 2.46 – 2.36 (m, 1H), 2.32 – 2.22 (m, 2H), 2.08 (ddd, \( J = 15.3 \), 2.9, 1.6 Hz, 1H), 1.92 (ddd, \( J = 15.2 \), 10.4, 5.5 Hz, 1H), 1.63 (ddddd, \( J = 15.0 \), 10.5, 4.6, 2.8 Hz, 1H).

\(^13\)C NMR (126 MHz, CDCl\(_3\), 328 K) \( \delta \) 177.8, 171.4, 154.8, 152.9, 141.9, 131.9, 127.0, 125.0, 124.2, 123.7, 115.9, 91.6, 72.8, 64.2, 53.0, 39.9, 34.8, 31.5, 29.5, 29.1, 21.8.

HRMS (ESI+) \( m/z \) calc. for C\(_{21}\)H\(_{20}\)N\(_2\)O\(_5\)Na\(^+\) [M+Na\(^+\)]: 403.1264, found: 403.1265.

\((-\)-8S\(_2\)): A solution of \((-\)-8S\(_2\)) (70.1 mg, 0.177 mmol, 1 equiv) in anhydrous CH\(_2\)Cl\(_2\) (4.3 mL) was placed in a dry Schlenk tube under argon. The solution was cooled to –78 °C and a freshly prepared solution of \( m \)-CPBA (ca. 75% purity, 100 mg in 5 mL anhydrous CH\(_2\)Cl\(_2\), 4.7 mL, 0.41 mmol, 2.3 equiv) was added dropwise at –78 °C. The solution was stirred at this temperature for 30 minutes, upon which time full conversion of the starting material was observed by TLC. The mixture was filtered through a short pad of basic alumina (10 cm high, 3 cm diameter), first flushing with CH\(_2\)Cl\(_2\) (100 mL) then CH\(_2\)Cl\(_2\)/acetone (1:1, 300 mL). The fractions containing the product were concentrated in vacuo. The crude mixture was purified by silica gel chromatography eluting with CH\(_2\)Cl\(_2\)/EtOAc/EtOH (20:80:0 to 18:80:2) to afford analytically pure \((-\)-grandilodine C as white solid (60.9 mg, 0.160 mmol, yield = 90%).

M.p. (EtOAc/cyclohexane) 254-256 °C (>99% ee). \( \alpha_D^{589} \) (CHCl\(_3\), c 0.55, 300 K) = + 80.4 deg.cm\(^2\).g\(^{-1}\) (>99% ee), lit.\(^8\) \( \alpha_D \) (CHCl\(_3\), c 0.55, 298 K) = + 61 deg.cm\(^2\).g\(^{-1}\), lit.\(^{21}\) \( \alpha_D \) (CHCl\(_3\), c 0.08, 299 K) = + 60.4 deg.cm\(^2\).g\(^{-1}\). HPLC (Chiralpak IA (250 mm \( \times \) 4.6 mm), hexane/CH\(_2\)Cl\(_2\)/ethanol 80:15:5, 1 mL/min) \( t_R1 \) 22.2 – 22.6 min, \( t_R2 \) 40.0 – 40.6 min, >99% ee. UV-Vis (MeOH) \( \lambda_{max} \) nm = 241, 281, 290 (sh). CD (MeOH) \( \lambda_{ext} \) nm (\( \Delta \varepsilon \)) 231 (–8.1), 261 (+1.1), 289 (–1.7).

Note 2: Crystals suitable for single-crystal X-ray diffraction studies were obtained from acetone/pentane solvent system by diffusion method.
HPLC trace of racemic sample of grandilodine C

Sample Info:
Method: Hex-EtOH-DCM 80-15-5
IA, 1 ml/min

Grandilodine C racemic

HPLC trace of enantioenriched sample of grandilodine C
**Table S1.** Comparison of $^{13}$C NMR data of isolated,\(^8\) previously synthesized\(^{21}\) and our synthetic sample of grandilodine C.

| Position | $^{13}$C NMR of isolated\(^8\) grandilodine C, δ ppm | $^{13}$C NMR of synthetic\(^{21}\) grandilodine C, δ ppm | $^{13}$C NMR at 328K of our synthetic grandilodine C, δ ppm (Δδ\(_{ppm}\) with isolated)\(^8\) |
|----------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| NCO\(_2\)Me | 153.1 | 153.1 | 152.9 (−0.2) |
| NCO\(_2\)Me | 52.8 | 53.2 | 53.0 (+0.2) |
| 2 | 72.8 | 72.7 | 72.8 (0.0) |
| 3 | 171.6 | 171.5 | 171.4 (−0.2) |
| 5 | 34.9 | 34.7 | 34.8 (−0.1) |
| 6 | 29.2 | 29.3 | 29.5 (0.3) |
| 7 | 91.5 | 91.5 | 91.6 (0.1) |
| 8 | 126.9 | 126.9 | 127.0 (0.1) |
| 9 | 124.4 | 124.3 | 124.2 (−0.2) |
| 10 | 123.8 | 123.8 | 123.7 (−0.1) |
| 11 | 132.0 | 132.1 | 131.9 (−0.1) |
| 12 | 115.9 | 115.8 | 115.9 (0.0) |
| 13 | 142.0 | 141.4 | 141.9 (−0.1) |
| 14 | 124.9 | 124.9 | 125.0 (0.1) |
| 15 | 155.1 | 155.0 | 154.8 (−0.3) |
| 16 | 39.6 | 39.5 | 39.9 (0.3) |
| 17 | 31.4 | 31.3 | 31.5 (0.1) |
| 18 | 21.2 | 21.2 | 21.8 (0.6) |
| 19 | 28.7 | 28.8 | 29.1 (0.4) |
| 20 | 64.2 | 64.1 | 64.2 (0.0) |
| CO\(_{lactone}\) | 178.2 | 178.0 | 177.8 (−0.4) |
Lapidilectine B (1)

(±)-1: Procedure similar to the previously reported one. To a suspension of (±)-grandilodine C (10.0 mg, 0.0263 mmol, 1 equiv) and activated molecular sieves (4Å, 30 mg) in anhydrous CH₂Cl₂ (2.5 mL) was added Me₂OBF₄ (19.0 mg, 0.128 mmol, ca. 5 equiv). The mixture was stirred at 23 ºC for 3.5 hours, and then cooled to 0 ºC. Methanol (5.0 mL) and NaBH₄ (18.7 mg, 0.49 mmol, ca. 20 equiv) were added to this mixture and the resulting suspension was stirred for additional 40 min. The reaction was quenched by addition of saturated aqueous NaHCO₃ (10 mL). The mixture was then filtered through Na₂SO₄ and concentrated in vacuo. The residue was purified by preparative silica gel TLC eluting with CH₂Cl₂/acetone 5:1 to afford a mixture of (±)-lapidilectine B and (±)-dihydranolapidilectine B (6.4 mg of mixture), and unreacted (±)-grandilodine C (3.2 mg, 0.0084 mmol, 32%). The mixture of (±)-lapidilectine B and (±)-dihydranolapidilectine B was separated on alumina TLC eluting with cyclohexane/EtOAc 4:1 to afford 4.5 mg of (±)-lapidilectine B (1) as a white solid (contains 10 wt% of residual EtOAc and silicon grease, 0.0111 mmol, yield 42%) and 1.7 mg of (±)-dihydranolapidilectine B (26) as a gum (contains 3 wt% of residual EtOAc, 0.0045 mmol, yield ca. 17%).

Note 1: Crystals suitable for single-crystal X-ray diffraction studies were obtained from CH₂Cl₂/cyclohexane solvent system by slow evaporation method under argon atmosphere.

Note 2: The title product undergoes rapid decomposition when exposed to air, silica, chloroform or acidic media. For storage lapidilectine B should be concentrated from cyclohexane or EtOAc and kept at – 30 ºC under inert atmosphere.

M.p. (CH₂Cl₂/cyclohexane) 201-203 ºC dec. (starts turning brown >160 ºC).

¹H NMR (500 MHz, CDCl₃) δ 8.04 (br s, 0.4H minor rotamer), 7.57 (br s, 0.6H major rotamer), 7.45 – 7.32 (m, 2H), 7.10 (t, J = 7.5 Hz, 1H), 5.74 (d, J = 5.8 Hz, 1H), 5.53 (ddd, J = 5.8, 2.8, 1.5 Hz, 1H), 3.91 (s, 3H), 3.83 (ddd, J = 16.4, 2.9, 1.6 Hz, 1H), 3.47 – 3.14 (m, 3H), 2.92 (td, J = 13.1, 9.5 Hz, 1H), 2.76 (dd, J = 15.7, 9.2 Hz, 1H), 2.71 – 2.40 (m, 1H), 2.30 – 1.97 (m, 5H), 1.68 (br s, 1H, overlapping with H₂O peak).

¹H NMR (500 MHz, CDCl₃, 323 K) δ 7.67 (br s, 1H), 7.43 – 7.34 (m, 2H), 7.10 (td, J
Careful examination of our $^1$H NMR spectral data revealed that the integration of

**(+)-1:** Procedure similar to the previously reported one.$^{21}$ To a suspension of (+)-grandilodine C (17.0 mg, 0.0447 mmol, 1 equiv) and activated molecular sieves (4Å, 50 mg) in anhydrous CH$_2$Cl$_2$ (4.2 mL) was added Me$_3$OBF$_4$ (34.2 mg, 0.231 mmol, ca. 5 equiv). The mixture was stirred at 23 °C for 5.5 hours, and then cooled to 0 °C. Methanol (8.5 mL) and NaBH$_4$ (34.8 mg, 0.92 mmol, ca. 20 equiv) were added to this mixture and the resulting suspension was stirred for additional 40 min. The reaction was quenched by addition of saturated aqueous NaHCO$_3$ (25 mL). The mixture was then filtered through Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 5:1 to afford a mixture of (+)-lapidilectine B and (+)-dihydrolapidilectine B (10.4 mg of mixture), and unreacted (+)-grandilodine C (5.3 mg, 0.0139 mmol, 31%). The mixture of (+)-lapidilectine B and (+)-dihydrolapidilectine B was separated on alumina TLC eluting with cyclohexane/EtOAc 4:1 to afford 8.3 mg of (+)-lapidilectine B (1) as a white solid (contains 7 wt% of residual EtOAc, 0.0211 mmol, yield 47%) and 2.5 mg of (+)-dihydrolapidilectine B (26) as a white solid (contains 4 wt% of residual EtOAc, 0.0065 mmol, yield 15%).

**M.p.** (CH$_2$Cl$_2$/cyclohexane) 238-239 °C dec. (>99% ee, starts turning brown >215 °C). $\alpha_D^{589}$ (CHCl$_3$, c 0.64, 299 K) = + 59.6 deg.cm$^2$.g$^{-1}$ (>99% ee). lit.$^6$ $\alpha_D$ (CHCl$_3$, c 0.9) = + 7.6 deg.cm$^2$.g$^{-1}$, lit.$^{21}$ $\alpha_D$ (CHCl$_3$, c 0.5, 299 K) = + 35.6 deg.cm$^2$.g$^{-1}$). UV-Vis (MeOH) $\lambda_{\text{max}}$ nm = 242, 284, 290 (sh). CD (MeOH) $\lambda_{\text{cut}}$ nm ($\Delta\varepsilon$) 216 (−15.7), 241 (−5.0), 286 (−2.0).

*Note 3:* Nishida et al.$^{21}$ previously reported the reduction of (+)-grandilodine C into (+)-lapidilectine B with Me$_3$OBF$_4$/NaBH$_4$. We performed the reduction of (+)-grandilodine C according to their procedure, and isolated a product mixture with a $^1$H NMR spectrum nearly identical to the one reported$^{21}$ for lapidilectine B (see below).
aromatic protons in comparison to olefinic ones was off (higher) by ca. 20%. Moreover, HRMS(ESI+) analysis showed the presence of two molecular ions with 2H difference. All these data suggest that a 5:1 mixture of lapidilectine B and its dihydro-analogue 26 was obtained, and it is inseparable by standard silica gel chromatography. After extensive studies, we found that this mixture can be separated on alumina TLC plates after multiple (10-12) runs eluting with cyclohexane/EtOAc 4:1. Comparison of our and previously reported21 NMR data strongly suggests that Nishida et al. also obtained a mixture of lapidilectine B and 26 (for example signals at 3.1, 2.4 and 1.9 ppm of 26 are clearly observable in their reported NMR). However, this fact went unnoticed, and this mixture was characterized as the natural compound.

**Comparison of the $^1$H NMR data (CDCl₃, 298 K).**

Lapidilectine B reported²¹ by Nishida et al.: 

Our sample of 5:1 mixture of lapidilectine B (1) and dihydrolapidilectine B (26):

Lapidilectine B (1):

Dihydr lapidilectine B (26):
HRMS of our mixture of lapidilectine B / 26 before separation

Table S2. Comparison of $^{13}$C NMR data of isolated$^6$ and our synthetic sample of lapidilectine B.

| Position | $^{13}$C NMR of isolated$^6$ lapidilectine B, $\delta$ ppm | $^{13}$C NMR at 323K of our synthetic lapidilectine B, $\delta$ ppm (Δ$\delta_{ppm}$ with isolated)$^6$ |
|----------|-------------------------------------------------------|------------------------------------------------------|
| NCO$_2$Me | 152.9                                                  | 152.8 ($-0.1$)                                       |
| NCO$_2$Me | 53.0                                                   | 52.7 ($-0.3$)                                        |
| 2         | 73.3                                                   | 74.1 (+0.8)                                          |
| 3         | 62.4                                                   | 61.9 ($-0.5$)                                        |
| 5         | 47.1                                                   | 47.4 (+0.3)                                          |
| 6         | 29.6                                                   | 30.2 (+0.6)                                          |
| 7         | 91.2                                                   | 90.8 ($-0.4$)                                        |
| 8         | 128.1                                                  | 129.0 (+0.9)                                         |
| 9         | 124.6                                                  | 124.6 (0.0)                                          |
| 10        | 123.6                                                  | 123.4 ($-0.2$)                                       |
| 11        | 131.4                                                  | 131.2 ($-0.2$)                                       |
| 12        | 115.7                                                  | 115.8 (+0.1)                                         |
| 13        | 141.2                                                  | 141.6 (+0.4)                                         |
| 14        | 124.6                                                  | 126.9 (+2.3)                                         |
| 15        | 135.7                                                  | 136.0 (+0.3)                                         |
| 16        | 43.3                                                   | 45.1 (+1.8)                                          |
| 17        | 35.9                                                   | 38.5 (+2.6)                                          |
| 18        | 26.3                                                   | 25.4 ($-0.9$)                                        |
| 19        | 22.3                                                   | 22.4 (+0.1)                                          |
| 20        | 68.4                                                   | 67.3 ($-1.1$)                                        |
| CO$_{lactone}$ | 177.2                                                  | 177.3 (+0.1)                                         |
Dihydrolapidilectine B (26)

(+)-26: In a dry 10 mL flask under argon, a solution of BH₃·SMe₂ (2 M in THF, 145 µL, 0.29 mmol, 10 equiv) was added to a solution of (+)-8 (11.0 mg, 0.0289 mmol, 1 equiv) in anhydrous THF (1 mL) at 25 ºC. The resulting colorless solution was stirred vigorously at 25 ºC for 4 hours. The solution was cooled to 0 ºC and acetic acid (115 µL, 2.0 mmol, ca. 70 equiv) was added and stirring was continued for 30 minutes at 25 ºC until effervescence had ceased. The reaction was quenched by addition of a saturated aqueous solution of NaHCO₃ (ca. 5 mL, caution: very vigorous effervescence) and basified until pH ≈ 10 by addition of solid NaHCO₃. It was then diluted with EtOAc (10 mL) and the aqueous layer was re-extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified on neutral alumina TLC eluting with cyclohexane/EtOAc 3:1 to afford (+)-26 as a white solid (8.7 mg, contains 5 wt% of residual EtOAc and grease, 0.0224 mmol, yield = 78%).

M. p. (CH₂Cl₂/pentane) 256-258 ºC dec. (>99% ee, starts turning brown >245 ºC. αD 589 (CHCl₃, c 0.8, 300 K) = +24.9 deg.cm⁻¹.g⁻¹ (>99% ee). ¹H NMR (500 MHz, CDCl₃) δ 8.03 (br s, 0.4H minor rotamer), 7.56 (br s, 0.6H major rotamer), 7.44 – 7.31 (m, 2H), 7.09 (t, J = 7.5 Hz, 1H), 3.90 (s, 3H), 3.40 – 3.22 (m, 1H), 3.14 (dd, J = 13.2, 8.7 Hz, 1H), 3.08 (ddd, J = 10.6, 7.9, 2.7 Hz, 1H), 2.90 (dt, J = 13.2, 9.8 Hz, 1H), 2.75 – 2.58 (m, 1H + 0.6H major rotamer), 2.54 – 2.35 (m, 1H + 0.4H minor rotamer), 2.25 – 1.57 (m, 10H). ¹H NMR (500 MHz, CDCl₃, 323 K) δ 7.65 (br s, 1H), 7.42 – 7.33 (m, 2H), 7.09 (td, J = 7.5, 1.0 Hz, 1H), 3.90 (s, 3H), 3.34 (br s, 1H), 3.20 – 3.06 (m, 2H), 2.92 (dt, J = 13.1, 9.8 Hz, 1H), 2.76 – 2.48 (m, 2H), 2.42 (td, J = 10.0, 8.3 Hz, 1H), 2.23 (dt, J = 13.1, 2.3 Hz, 1H), 2.16 (ddd, J = 15.6, 10.0, 8.7 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.98 – 1.88 (m, 2H), 1.86 – 1.72 (m, 2H), 1.68 – 1.60 (m, 3H). ¹³C NMR (126 MHz, CDCl₃, 323 K) δ 176.6, 152.7, 141.6, 131.1, 129.0, 124.7, 123.3, 115.8, 90.3, 74.6, 60.4, 55.2, 52.6, 47.1, 45.1, 38.3, 37.8, 29.8, 25.8, 22.6 (2C). HRMS (ESI+) m/z calc. for C₂₁H₂₅N₂O₄⁺ [M+H]⁺: 369.1809, found: 369.1819. UV-Vis (MeOH) λmax nm = 242, 283, 291 (sh). CD (MeOH) λε, nm (Δε) 217 (−13.6), 244 (−5.9), 286 (−1.7).
Dimethyl (6aS,11aR,12R,13aS)-6a-hydroxy-3-oxo-2,3,6,6a,12,13-hexahydro-1H-11a,13a-ethanopyrrolo[1',2':1,8]azocino[5,4-b]indole-11,12(5H)-dicarboxylate (20)

(±)-20: Alkene (±)-10 (79.3 mg, 0.200 mmol, 1 equiv) was dissolved in EtOH/CH$_2$Cl$_2$ (1:1, 8.0 mL, HPLC grade solvents) at 23 °C in the presence of activated molecular sieves (4Å, 300 mg). NaBH$_4$ (36 mg, 0.95 mmol, ca. 5 equiv) and Mn(dpm)$_3$ (6.0 mg, 0.01 mmol, 5 mol %) were added sequentially (each in one portion). Air was then vigorously bubbled through a long needle (0.80 × 120 mm). After 1.5 h, full conversion was observed by TLC. Deionized water (100 µl) and CH$_2$Cl$_2$ (10 ml) were added to the reaction mixture and stirring was continued for 15 minutes. The resulting solution was slowly filtered through a pad of silica gel (5 g) and the pad was washed with acetone/CH$_2$Cl$_2$ mixture (1:1, 50 mL × 6). The volatiles were removed under reduced pressure and the crude mixture was used in the following step without further purification.

**Note 1:** The title compound is sensitive to elevated temperatures and undergoes fast degradation in acidic media (to alkene 10 and lactone 8).

**Note 2:** The sample for characterization was purified by preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 8:1 to afford the desired alcohol as a pale yellow solid (ca. 80% yield). Crystals suitable for single-crystal X-ray diffraction studies were obtained from CH$_2$Cl$_2$/CDCl$_3$/EtOAc solvent system by slow evaporation method.

**M.p.** (CDCl$_3$) 195-197 °C dec. (starts turning brown >185 °C). **$^1$H NMR** (500 MHz, CD$_2$Cl$_2$) δ 7.69 (br s, 1H), 7.28 (ddd, $J$ = 8.4, 7.4, 1.4 Hz, 1H), 7.20 (d, $J$ = 7.6 Hz, 1H), 7.03 (t, $J$ = 7.5 Hz, 1H), 4.15 (dd, $J$ = 15.3, 7.3 Hz, 1H), 3.89 (s, 3H), 3.79 – 3.64 (m, 2H), 2.96 – 2.86 (m, 1H), 2.84 (s, 3H), 2.75 (dd, $J$ = 15.9, 12.1 Hz, 1H), 2.71 – 2.62 (m, 1H), 2.53 – 2.44 (m, 2H), 2.38 – 2.23 (m, 2H), 2.09 (br s, 1H), 1.99 (dd, $J$ = 15.8, 10.4 Hz, 1H), 1.95 – 1.79 (m, 4H). **$^{13}$C NMR** (126 MHz, CD$_2$Cl$_2$) δ 174.9, 173.7, 154.5, 142.5, 134.5, 130.0, 123.6, 122.1, 116.3, 78.0, 75.5, 61.6, 52.9, 51.9, 40.7, 38.0, 37.4, 37.2, 32.2, 29.7, 29.3, 21.3. **HRMS** (ESI+) $m/z$ calc. for C$_{22}$H$_{26}$N$_2$O$_6$Na$^+$ [M+Na$^+$]: 437.1683, found: 437.1691.
(--)-20: Alkene (--)-10 (79.3 mg, 0.200 mmol, 1 equiv) was dissolved in EtOH/CH$_2$Cl$_2$ (1:1, 8.0 mL, HPLC grade solvents) at 23 °C in the presence of activated molecular sieves (4Å, 300 mg). NaBH$_4$ (36 mg, 0.95 mmol, ca. 5 equiv) and Mn(dpm)$_3$ (tris(2,2,6,6-tetramethyl-3,5-heptanedionato)manganese(III), 6.0 mg, 0.01 mmol, 5 mol %) were added sequentially (each in one portion). Air was vigorously bubbled through a long needle (0.80 × 120 mm). After 1.5 h, full conversion was observed by TLC. Deionized water (100 µl) and CH$_2$Cl$_2$ (10 mL) were added to the reaction mixture and stirring was continued for 15 minutes. The resulting solution was slowly filtered through a pad of silica gel (5 g) and the pad was washed with acetone/CH$_2$Cl$_2$ mixture (1:1, 50 mL × 6). The volatiles were removed under reduced pressure and the crude mixture was used in the following step without further purification.

*Note:* The sample for characterization was obtained by purification on preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 8:1, affording the desired alcohol as a pale yellow solid (ca. 80% yield).

**M.p.** (acetone/CH$_2$Cl$_2$) 263-265 °C dec. (>99% ee, starts turning brown >240 °C). $\alpha_d^{589}$ (CHCl$_3$, c 0.85, 300 K) = -169.9 deg.cm$^2$.g$^{-1}$ (>99% ee).

**Preliminary studies on the construction of benzylic C–C bond.**

Initial experiments on benzylic C–C bond construction were performed on alkene 10, alcohol 20 as well as their easily accessible 18,19-unsaturated analogues as sources for carbocation A (or $\Delta^{18,19}$-A) upon treatment with Brønsted/Lewis acids. Benzylic halide derivatives 20X could not be accessed, presumably because of the facile elimination of HX. Compound 20 easily dehydrates in the presence of Brønsted or Lewis acids. Arenes (anisole, 1,3-dimethoxybenzene), t-BuNC, CO, TMSCN were employed as nucleophiles, but without success.

![Chemical structures](image)

The oxidation of 10 into its corresponding $N$-acyliminium cation was accomplished with CAN or DDQ, but the subsequent attack of C-nucleophiles (TMSCN, allylTMS) proceeded at the position 5, not 7.  

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We also attempted to perform a one-pot radical cyclization / benzylic C–C bond construction on substrate 11 or Δ^{18,19}-11, but without success. The [(dppmAuCl)_2]-catalyzed photoredox cyclization of 11 in the presence of nucleophiles (TMSCN, allylTMS, 2-methylfuran, butyl vinyl ether) in place of Na_2CO_3 led to the same elimination product 10. The same outcome was observed for 1-methyl-1H-benzo[d]imidazole/CF_3CO_2H system as a radical trap. With allylSnBu_3 (10 equiv) instead of Na_2CO_3 the photoredox cyclization gave a mixture of 9 and 10 in ca. 1:2 ratio.

**Dimethyl (6aR,11aR,12R,13aS)-6a-allyl-3-oxo-2,3,6,6a,12,13-hexahydro-1H-11a,13a-ethanopyrrolo[1’,2’:1,8]azocino[5,4-b]indole-11,12(5H)-dicarboxylate (9)**

(±)-9: Crude (±)-20 obtained as mentioned above (ca. 0.16 mmol) was transferred into a 50 mL flask as a solution in CH_2Cl_2. The solution was concentrated, the residue was dried under high vacuum, and the flask was placed under argon. Anhydrous, oxygen-free CH_2Cl_2 (3.2 mL) and a magnetic stirbar were then added in the flask. Stirring was initiated. Once a homogeneous solution had been obtained, allyltributylstannane (0.50 mL, 1.6 mmol, 10 equiv) was added, and BF_3·Et_2O (1.0 mL, 8.1 mmol, 50 equiv) was injected fast, in one portion, in the vigorously stirred mixture, at 0 ºC. After stirring for 5 minutes at room temperature, the reaction mixture was poured onto a mixture of CH_2Cl_2 (50 mL) and saturated aqueous NaHCO_3 (50 mL). After stirring this biphasic mixture for 30 minutes, the organic phase was separated, and the aqueous layer was washed with CH_2Cl_2 (25 mL × 2). The combined organic extracts were dried over Na_2SO_4, filtered and evaporated with florisil® absorbent (15 g). The solid was placed on a pad of silica gel (3 g), washed with cyclohexane (100 mL, to remove the excess of allyltributylstannane), purged with air,
and washed with acetone/CH$_2$Cl$_2$ mixture (150 mL). The volatiles were removed, and
the residue was purified on 2000 μm silica gel preparative TLC using EtOAc/CH$_2$Cl$_2$
10:1 as eluent and acetone/CH$_2$Cl$_2$ 1:1 to collect the compound from the silica.
Evaporation of solvents and drying under high vacuum gave the title product (±)-9 as
a white foamy solid in 73% yield over two steps (76.3 mg, 84 wt% purity: 3% of
alkene (±)-10 and 12% of residual solvents). The obtained material was used in the
next step without further purification.

**Note 1:** Evaporation from cyclohexane/CH$_2$Cl$_2$ (10:1) and drying under high vacuum
gave the title product as a white solid, that was more convenient to handle.

**Note 2:** Fast injection of BF$_3$·Et$_2$O in one portion (all at once) is crucial to minimize
the amount of byproduct 10.

**Note 3:** The use of allylSnBu$_3$ as nucleophile was crucial to suppress the undesired
dehydration to 10 (ca. 30:1 ratio). With a number of allylsilanes$^{26}$ tested under similar
conditions the ratio of allylated product:10 varied from 1:2 to 3.5:1 (see Scheme 5 of
manuscript).

**M.p.** (Et$_2$O) 155-157 ºC. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.56 (br s, 1H), 7.16
(td, $J = 7.8$, 1.1 Hz, 1H), 6.96 (t, $J = 7.4$ Hz, 1H), 6.91 (d, $J = 7.5$ Hz, 1H), 5.23 (dddd,
$J = 16.9$, 10.1, 8.4, 5.9 Hz, 1H), 4.97 (d, $J = 10.1$ Hz, 1H), 4.84 (d, $J = 16.9$ Hz, 1H),
4.17 (dd, $J = 15.5$, 6.5 Hz, 1H), 3.95 (s, 3H), 3.71 (br t, $J = 9.8$ Hz, 1H), 3.50 (br t, $J =
14.2$ Hz, 1H), 3.05 (br s, 1H), 2.87 (s, 3H), 2.73 (br t, $J = 14.5$ Hz, 1H), 2.64 – 2.54
(m, 2H), 2.49 – 2.35 (m, 2H), 2.33 – 2.22 (m, 2H), 2.19 (dd, $J = 13.5$, 6.0 Hz 1H),
2.06 – 1.85 (m, 5H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 174.9, 174.1, 154.6, 141.4,
134.5, 133.0, 127.8, 123.4, 122.4, 119.1, 115.2, 75.7, 61.0, 52.6, 52.0, 51.6, 41.4,
39.2, 38.1, 37.7, 37.6, 31.2, 29.7, 25.1, 22.8. HRMS (ESI+) m/z calc. for
C$_{28}$H$_{39}$O$_5$Na$^+$ [M+Na]$^+$: 461.2047, found: 461.2042.

(−)-9: Crude (−)-20 obtained as mentioned above (ca. 0.16 mmol) was
transferred into a 50 mL flask as a solution in CH$_2$Cl$_2$. The solution was concentrated,
the residue was dried under high vacuum, and the flask was placed under argon.
Anhydrous, oxygen-free CH$_2$Cl$_2$ (3.2 mL) and a magnetic stirbar were then added in
the flask. Stirring was initiated. Once a homogeneous solution had been obtained,
allyltributylstannane (0.50 mL, 1.6 mmol, 10 equiv) was added, and BF$_3$·Et$_2$O (1.0
mL, 8.1 mmol, 50 equiv) was injected fast, in one portion, in the vigorously stirred
mixture, at 0 ºC. After stirring for 5 minutes at room temperature, the reaction mixture
was poured onto a mixture of CH₂Cl₂ (50 mL) and saturated aqueous NaHCO₃ (50 mL). After stirring this biphasic mixture for 30 minutes, the organic phase was separated, and the aqueous layer was washed with CH₂Cl₂ (25 mL × 2). The combined organic extracts were dried over Na₂SO₄, filtered and evaporated with Florisil® absorbent (15 g). The solid was placed on a pad of silica gel (3 g), washed with cyclohexane (100 mL, to remove the excess of allyltributylstannane), purged with air, and washed with acetone/CH₂Cl₂ mixture (150 mL). The volatiles were removed, and the residue was purified on 2000 µm silica gel preparative TLC using EtOAc/CH₂Cl₂ 10:1 as eluent and acetone/CH₂Cl₂ 1:1 to collect the compound from the silica. Evaporation from acetone/CH₂Cl₂ (1:1) and drying under high vacuum gave the title product (−)-9 as a white solid in 72% yield over two steps (68.5 mg, 92 wt% purity: 4% of alkene (−)-10 and 3% of residual solvents). The obtained material was used in the next step without further purification.

\[ \text{M.p. (CH₂Cl₂/acetone) 86-88 °C (>99% ee)} \]

\[ \alpha_\text{D}^{589} (\text{CHCl}_3, c 0.90, 299 K) = -112.6 \text{ deg.cm}^2\text{g}^{-1} (>99% ee) \]

**Dimethyl (6aS,11aR,12R,13aS)-6a-formyl-3-oxo-2,3,6,6a,12,13-hexahydro-1H-11a,13a-ethanopyrrolo[1′,2′:1,8]azocino[5,4-b]indole-11,12(5H)-dicarboxylate (23)**

(±)-23: Allyl (±)-9 (78.8 mg, 80 wt% purity, 0.144 mmol, 1 equiv) was dissolved in CH₂Cl₂ (150 µL, HPLC grade) at 23 °C and t-BuOH (1.5 mL, HPLC grade) and deionized water (1.5 mL) were added. The resulting emulsion was stirred vigorously, NMO (33.6 mg, 0.287 mmol, 2 equiv) and NaIO₄ (69.0 mg, 0.323 mmol, 2.25 equiv) were added together in one portion, followed by addition of an aqueous solution of OsO₄ (5 mg/mL, 0.76 mL, 0.015 mmol, 10 mol %). The reaction mixture was stirred at 23 °C for 1-1.5 h, upon which time full conversion of starting material was observed (TLC). The reaction mixture was then diluted with t-BuOH (1.5 mL) and deionized water (1.5 mL). Na₂CO₃ (93 mg, 0.88 mmol, 6 equiv), pyrrolidine (23 µL, 0.280 mmol, 2 equiv) and NaIO₄ (189 mg, 0.88 mmol, 6 equiv) were sequentially added. After stirring for 3 h, the reaction mixture was diluted with CH₂Cl₂ (30 mL)
and brine (20 mL). The layers were then separated, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 50 mL) and the combined organic layers were washed with 0.5 M NaHSO$_3$ (50 mL) and brine (50 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 8:1 to afford the title product as a white foamy solid (45.4 mg, contains 4 wt% of residual acetone and grease, 0.102 mmol, yield = 71%).

**Note:** Crystals suitable for single-crystal X-ray diffraction studies were obtained from CH$_2$Cl$_2$/acetone/pentane solvent system by diffusion method.

M.p. (CH$_2$Cl$_2$/acetone) 220-222 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 9.25 (d, $J$ = 2.3 Hz, 1H), 7.60 (br s, 1H), 7.29–7.24 (m, 1H), 7.05 (td, $J$ = 7.5, 1.0 Hz, 1H), 6.96 (dd, $J$ = 7.6, 1.4 Hz, 1H), 4.43 (ddd, $J$ = 16.1, 7.7, 1.7 Hz, 1H), 4.00 (s, 3H), 3.80 (br s, 1H), 3.45–3.30 (m, 2H), 3.01–2.91 (m, 4H), 2.78–2.70 (m, 1H), 2.62 (ddd, $J$ = 15.9, 11.1, 1.9 Hz, 1H), 2.47–2.34 (m, 2H), 2.08–1.83 (m, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 193.8, 174.8, 173.0, *154.2*, *142.4*, 129.9, 125.9, 124.8, 123.5, 115.8, 73.0, 66.0, 61.0, 53.0, 51.9, *40.4*, 39.3, 38.1, 37.1, 31.6, 29.3, *28.5*, 21.8.

**Note:** the signals between “*” were confirmed by 2D $^{13}$C-$^1$H correlation (HMQC, HMBC), see below. HRMS (ESI+) $m/z$ calc. for C$_{23}$H$_{26}$N$_2$O$_6$Na$^+$/[M+Na]$^+$: 449.1683, found: 449.1682.

(+)-23: Allyl (−)-9 (118.7 mg, 88 wt% purity, 0.238 mmol, 1 equiv) was dissolved in CH$_2$Cl$_2$ (240 µL, HPLC grade) at 23 °C and t-BuOH (2.4 mL, HPLC grade) and deionized water (2.4 mL) were added. The resulting emulsion was stirred vigorously, NMO (55.6 mg, 0.475 mmol, 2 equiv) and NaIO$_4$ (114.7 mg, 0.536 mmol, 2.25 equiv) were added together in one portion, followed by addition of an aqueous solution of OsO$_4$ (5 mg/mL, 1.26 mL, 0.025 mmol, ca. 10 mol %). The reaction mixture was stirred at 23 °C for 1-1.5 h, upon which time full conversion of starting material were observed (TLC). The reaction mixture was then diluted with t-BuOH (2.4 mL) and deionized water (2.4 mL). Na$_2$CO$_3$ (154 mg, 1.45 mmol, ca. 6 equiv), pyrrolidine (39 µL, 0.475 mmol, 2 equiv) and NaIO$_4$ (313 mg, 1.46 mmol, ca. 6 equiv) were sequentially added. After stirring for 3 h, the reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL) and brine (40 mL). The layers were then separated, the aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 75 mL) and the combined organic layers were washed with 0.5 M NaHSO$_3$ (75 mL) and brine (75 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude mixture was purified by
preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 8:1 to afford the title product as a white foamy solid (73.8 mg, 0.173 mmol, yield = 73%).

**M.p.** (CH$_2$Cl$_2$/pentane) 118-120 °C (>99% ee). $\alpha_B^{589}$ (CHCl$_3$, c 0.95, 299 K) = + 219.8 deg. cm$^2$.g$^{-1}$ (>99% ee).

**HMOC** correlation ($^1$H 500 MHz, $^{13}$C 126 MHz, CDCl$_3$):

**HMBC** correlation ($^1$H 500 MHz, $^{13}$C 126 MHz, CDCl$_3$):
Intermediates in double cleavage of allyl substrate 9: two-carbon aldehyde (21) and its enamine adduct with pyrrolidine (22)

(±)-21: Allyl (±)-9 (77.5 mg, 80 wt% purity, 0.141 mmol, 1 equiv) was dissolved in acetone (0.5 mL, HPLC grade) at 23 °C and deionized water (0.5 mL) was added. The resulting solution was stirred vigorously, NMO (16.4 mg, 0.140 mmol, 1 equiv) and NaIO₄ (92 mg, 0.43 mmol, 3 equiv) were added together in one portion, followed by addition of an aqueous solution of OsO₄ (5 mg/mL, 360 µL, 0.0071 mmol, 5 mol %). The reaction mixture was stirred at 23 °C for 1-1.5 h, upon which time full conversion of starting material was observed (TLC). The reaction mixture was diluted with CH₂Cl₂ (10 mL) and brine (10 mL). The layers were then separated, the aqueous layer was extracted with CH₂Cl₂ (3 × 15 mL) and the combined organic layers were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude mixture was purified by preparative silica gel TLC eluting with CH₂Cl₂/acetone 8:1 to afford the title product as a colorless gum (57.5 mg, ca. 85 wt% purity, 0.111 mmol, yield = 79%).

¹H NMR (500 MHz, CD₂Cl₂) δ 9.17 (t, J = 3.0 Hz, 1H), 7.60 (d, J = 8.3 Hz, 1H), 7.22 (ddd, J = 8.3, 6.6, 2.2 Hz, 1H), 7.07 – 6.99 (m, 2H), 4.20 (ddd, J = 15.8, 6.7, 2.0 Hz, 1H), 3.91 (s, 3H), 3.69 (t, J = 10.1 Hz, 1H), 3.51 – 3.42 (m, 1H), 3.03 (ddd, J = 14.2, 8.1, 4.9 Hz, 1H), 2.95 – 2.82 (m, 4H), 2.78 (dd, J = 13.9, 3.2 Hz, 1H), 2.55 – 2.26 (m, 5H), 2.16 – 1.82 (m, 6H). ¹³C NMR (126 MHz, CD₂Cl₂) δ 201.3, 174.9, 174.2, 154.7, 142.0, 133.9, 128.9, 123.6, 122.7, 116.0, 75.9, 60.9, 53.0, 52.4, 51.9, 49.3, 41.5, 38.4, 37.9, 37.8, 31.2, 29.9, 27.8, 23.9. HRMS (ESI+) m/z calc. for C₂₄H₂₈N₂O₆Na⁺ [M+Na]⁺: 463.1840, found: 463.1855 (also observed m/z calc. for C₂₅H₃₂N₂O₇Na⁺ [M+MeOH+Na]⁺: 495.2102, found: 495.2105).
Formation of (±)-22: A solution of (±)-21 (13.2 mg, 0.03 mmol) in CD$_2$Cl$_2$ (0.6 mL) was placed in an NMR tube and was treated with pyrrolidine (13 µL, 0.16 mmol, ca. 5 equiv). The tube was shaken and the $^1$H NMR spectrum of the mixture was recorded after 10 minutes, showing complete conversion of the starting aldehyde into the corresponding enamine (characteristic olefin signals at 5.69 (d, $J = 14.2$ Hz, 1H), 4.17 (d, $J = 14.2$ Hz, 1H) ppm, highlighted with *).

Comparison of the $^1$H NMR data (CD$_2$Cl$_2$).

Aldehyde 21:

![Aldehyde 21 NMR spectrum]

Pyrrolidine:

![Pyrrolidine NMR spectrum]

Reaction mixture between aldehyde 21 and pyrrolidine, showing formation of 22:

![Reaction mixture NMR spectrum]
**Note 1:** The reaction conditions employed for the synthesis of 21 resemble those used in the first step of the two-carbon cleavage of 9 into 23 (see above). This step proceeds under acidic conditions, and in the presence of a base (Na₂CO₃), the process slows down and becomes impractical. At the same time, the second C=C cleavage event requires basic conditions to efficiently generate the enamine intermediate and suppress the retro-Stork enamine alkylation reaction, which results in the formation of alkene 10 and/or alcohol 20 byproducts (Scheme S1).

**Note 2:** The direct one-carbon cleavage of aldehyde (±)-21 via enol,²⁷ without formation of an enamine intermediate was not successful.

**Scheme S1.** Proposed main and side pathways for the two-carbon cleavage in 9.
Reaction under acidic conditions, showing the formation of 20 ([H NMR, CDCl$_3$]):

\[
\text{Crude reaction mixture}
\]

(6aS,11aR,12R,13aS)-11,12-bis(Methoxycarbonyl)-3-oxo-2,3,5,6,12,13-hexahydro-1H-11a,13a-ethanopyrrolo[1’,2’:1,8]azocino[5,4-b]indole-6a(11H)-carboxylic acid (24)

\[
\text{Crude reaction mixture}
\]

\[
\text{Crude reaction mixture}
\]

(±)-24: Aldehyde (±)-23 (25.6 mg, 0.060 mmol, 1 equiv) was dissolved in CH$_2$Cl$_2$ (60 µL, HPLC grade) at 23 ºC and t-BuOH (1.2 mL, HPLC grade) and deionized water (1.2 mL) were added. The resulting emulsion was stirred vigorously, K$_2$CO$_3$ (49.6 mg, 0.359 mmol, 6 equiv) and NaIO$_4$ (26.2 mg, 0.122 mmol, ca. 2 equiv) were added together in one portion, followed by addition of KMnO$_4$ (38.0 mg, 0.240 mmol, 4 equiv). After 10 min, full conversion was observed by TLC. The reaction mixture was diluted with CH$_2$Cl$_2$ (50 mL) and brine (50 mL). The layers were then separated, the aqueous layer was washed with CH$_2$Cl$_2$ (3 × 20 mL) and the excess of oxidants in the aqueous layer was quenched with a saturated aqueous solution of NaHSO$_3$ (10 mL). pH 3 was achieved by slow addition of a 10% aqueous solution of HCl and the
aqueous layer was extracted with CH₂Cl₂ (5 × 50 mL). The combined extracts were washed with brine (50 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The obtained white solid (24.2 mg) was used in the next step without further purification.

**Note 1:** Crystals suitable for single-crystal X-ray diffraction studies were obtained from CH₂Cl₂/MeOH solvent system by slow evaporation method.

**Note 2:** Longer reaction times lead to a decrease in the yield due to over oxidation. Excess of oxidants (KMnO₄ and NaIO₄) was employed to minimize the side decarboxylation, presumably mediated by reduced manganese species.

**M.p.** (CH₂Cl₂/MeOH) 234-237 °C dec. (starts turning brown >226 °C). ¹H NMR (400 MHz, CD₂Cl₂) δ 7.51 (br s, 1H), 7.23 (ddd, J = 8.4, 7.4, 1.4 Hz, 1H), 7.05 (ddd, J = 7.5, 1.4 Hz, 1H), 6.98 (td, J = 7.4, 1.0 Hz, 1H), 4.18 – 4.10 (m, 1H), 3.99 – 3.46 (m, 5H), 3.22 (br s, 1H), 3.04 – 2.86 (m, 5H), 2.52 (dd, J = 15.5, 11.2 Hz, 1H), 2.45 – 2.33 (m, 1H), 2.21 (dd, J = 16.7, 8.3 Hz, 1H), 2.12 – 1.76 (m, 5H). ¹³C NMR (126 MHz, CD₂Cl₂) δ 177.7, 173.9, 173.5, *153.9*, *142.8*, 130.5, 129.5, 123.5, 123.1, 116.0, 73.6, 64.0, 63.7, 52.9, 52.1, 43.2, *41.2*, 38.1, 36.3, 32.3, 30.1, *29.4*, 24.3. **Note:** the signals between “*” were confirmed by 2D ¹³C-¹H correlation (HMBC), see below. **HRMS** (ESI+) m/z calc. for C₂₃H₂₆N₂O₇Na⁺ [M+Na]⁺: 465.1632, found: 465.1641.

(--)-24: Aldehyde (+)-23 (72.5 mg, 0.170 mmol, 1 equiv) was dissolved in CH₂Cl₂ (170 µL, HPLC grade) at 23 °C and t-BuOH (3.5 mL, HPLC grade) and deionized water (3.5 mL) were added. The resulting emulsion was stirred vigorously, K₂CO₃ (141 mg, 1.02 mmol, 6 equiv) and NaIO₄ (74.4 mg, 0.348 mmol, ca. 2 equiv) were added together in one portion, followed by addition of KMnO₄ (107.5 mg, 0.680 mmol, 4 equiv). After 10 min, full conversion was observed by TLC. The reaction mixture was diluted with CH₂Cl₂ (100 mL) and brine (100 mL). The layers were then separated, the aqueous layer was washed with CH₂Cl₂ (3 × 30 mL) and the excess of oxidants in the aqueous layer was quenched with a saturated aqueous solution of NaHSO₃ (30 mL). pH 3 was achieved by slow addition of a 10% aqueous solution of HCl and the aqueous layer was extracted with CH₂Cl₂ (5 × 100 mL). The combined extracts were washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The obtained white solid (62.6 mg) was used in the next step without further purification.
M.p. (CH$_2$Cl$_2$/pentane) 227-229 °C (>99% ee, starts turning brown >210 °C).

$\alpha_D^{589}$ (CHCl$_3$, c 0.68, 299 K) = −27.6 deg.cm$^2$.g$^{-1}$ (>99% ee).

HMBC correlation ($^1$H 500 MHz, $^{13}$C 126 MHz, CD$_2$Cl$_2$):

![Chemical spectrum diagram]
Trimethyl (6aS,11aR,12R,13aS)-3-oxo-2,3,5,6,12,13-hexahydro-1H-11a,13a-ethanopyrrolo[1′,2′:1,8]azocino[5,4-b]indole-6a,11,12-tricarboxylate (25)

(±)-25: The obtained white solid (±)-24 (24.2 mg, ca. 0.055 mmol) was dissolved in MeOH/CH$_2$Cl$_2$ (2:1, 6 mL, HPLC grade solvents) at 23 °C. TMSCHN$_2$ (2 M solution in diethyl ether, 138 µL, 0.276 mmol, 5 equiv) was added dropwise. The reaction mixture was stirred for 20 min and the volatiles were removed under vacuum. The crude mixture was purified by preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 7:1 to afford the title product as a foamy solid (23.2 mg, contains 4 wt% of residual acetone and grease, 0.049 mmol, yield = 81% over 2 steps).

M.p. (CH$_2$Cl$_2$/cyclohexane) 200-202 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.48 (br s, 1H), 7.21 (t, $J = 8.0$ Hz, 1H), 7.09 (d, $J = 7.6$ Hz, 1H), 6.96 (td, $J = 7.5, 1.0$ Hz, 1H), 4.35 – 4.27 (m, 1H), 3.96 (s, 3H), 3.79 (br s, 1H), 3.52 (s, 3H), 3.42 (dd, $J = 15.9, 11.5$ Hz, 1H), 3.27 (br s, 1H), 3.10 – 2.95 (m, 2H), 2.92 (s, 3H), 2.55 (dd, $J = 15.7, 10.8$ Hz, 1H), 2.45 (dt, $J = 18.7, 9.5$ Hz, 1H), 2.34 (ddd, $J = 16.8, 8.1, 3.5$ Hz, 1H), 2.13 – 1.83 (m, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 175.2, 173.6, 171.9, *153.9*, *142.3*, 129.7, 129.3, 123.4, 122.8, 115.7, 73.5, 64.1, 61.9, 52.6, 52.5, 51.9, 42.2, *40.9*, 38.1, 36.4, 32.2, 29.4, *28.5*, 24.3. Note: the signals between “*” were confirmed by 2D $^{13}$C-$^1$H correlation (HMQC, HMBC), see below. HRMS (ESI+) m/z calc. for C$_{24}$H$_{28}$N$_2$O$_7$Na$^+$ [M+Na$^+$]: 479.1789, found: 479.1793.

(–)-25: The obtained white solid (–)-24 (62.6 mg, ca. 0.14 mmol) was dissolved in MeOH/CH$_2$Cl$_2$ (2:1, 10 mL, HPLC grade solvents) at 23 °C. TMSCHN$_2$ (2 M solution in diethyl ether, 340 µL, 0.68 mmol, ca. 5 equiv) was added dropwise. The reaction mixture was stirred for 20 min and the volatiles were removed under vacuum. The crude mixture was purified by preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 7:1 to afford the title product as a foamy solid (61.5 mg, 0.1353 mmol, yield = 80% over 2 steps).

M.p. (CH$_2$Cl$_2$/pentane) 110-112 °C (>99% ee). $\alpha$$_D$ $^{589}$ (CHCl$_3$, c 0.95, 299 K) = – 29.6 deg.cm$^2$.g$^{-1}$ (>99% ee).
HMQC correlation ($^1$H 500 MHz, $^{13}$C 126 MHz, CDCl$_3$):

![HMQC correlation graph](image)

HMBC correlation ($^1$H 500 MHz, $^{13}$C 126 MHz, CDCl$_3$):

![HMBC correlation graph](image)
Trimethyl \((6aS,11aR,12R,13aS)-3\text{-thioxo-}2,3,5,6,12,13\text{-hexahydro-}1H-11a,13a\text{-ethanopyrrolo[1',2':1,8]azocino[5,4-b]indole-6a,11,12\text{-tricarboxylate}}\) (25S1)

(±)-25S1: A solution of (±)-25 (37.8 mg, 0.0828 mmol, 1 equiv) and Lawesson’s reagent (33.5 mg, 0.0828 mmol, 1 equiv) in anhydrous toluene (0.85 mL) in a sealed microwave vial was stirred at 90 °C until full conversion of starting material was achieved (typically 1 hour). The volatiles were removed under reduced pressure and the resulting crude product was purified by preparative silica gel TLC eluting with CH2Cl2/acetone 40:1 to afford the title compound as an amorphous pale yellow solid (37.5 mg, contains 4 wt% of residual acetone and grease, 0.0762 mmol, yield = 92%).

M.p. (CH2Cl2/cyclohexane) 211-213 °C. H NMR (500 MHz, CDCl3) δ 7.49 (br s, 1H), 7.22 (t, J = 7.9 Hz, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.98 (td, J = 7.5, 1.0 Hz, 1H), 4.82 – 4.68 (m, 1H), 3.97 (s, 3H), 3.92 – 3.63 (m, 2H), 3.54 (s, 3H), 3.36 – 3.07 (m, 3H), 3.04 – 2.98 (m, 2H), 2.93 (s, 3H), 2.69 (dd, J = 16.1, 10.9 Hz, 1H), 2.10 – 1.93 (m, 6H). C NMR (126 MHz, CDCl3) δ 202.0, 173.3, 171.7, *154.0*, *142.3*, *129.5*, 129.4, 123.5, 122.9, 115.7, 73.1, 70.5, *63.9*, 52.7, 52.6, 52.0, 49.3, 42.1, *40.8*, 38.2, 36.4, 31.3, *28.4*, 24.5. Note: the signals between “**” were confirmed by 2D 13C-H correlation (HMOC, HMBC), see below. HRMS (ESI+) m/z calc. for C24H28N2NaO6S+ [M+Na]+: 495.1560, found: 495.1572.

(−)-25S1: A solution of (−)-25 (56.1 mg, 0.123 mmol, 1 equiv) and Lawesson’s reagent (49.7 mg, 0.123 mmol, 1 equiv) in anhydrous toluene (1 mL) in a sealed microwave vial was stirred at 90 °C until full conversion of starting material was achieved (typically 1 hour). The volatiles were removed under reduced pressure and the resulting crude product was purified by preparative silica gel TLC eluting with CH2Cl2/acetone 40:1 to afford the title compound as an amorphous pale yellow solid (56.0 mg, 0.1185 mmol, yield = 96%).

M.p. (CH2Cl2/pentane) 194-196 °C (>99% ee). α589 (CHCl3, c 1.0, 297 K) = −61.4 deg.cm²·g⁻¹ (>99% ee).
HMOC correlation ($^1$H 500 MHz, $^{13}$C 126 MHz, CDCl$_3$):

HMBC correlation ($^1$H 500 MHz, $^{13}$C 126 MHz, CDCl$_3$):
Trimethyl (6aS,11aR,12R,13aR)-3-thioxo-5,6,12,13-tetrahydro-3H-11a,13a-ethanopyrrolo[1',2':1,8]azocino[5,4-b]indole-6a,11,12-tricarboxylate (25S2)

(±)-25S2: A solution of (±)-25S1 (36.0 mg, 0.0762 mmol, 1 equiv) in anhydrous CH₂Cl₂ (1.5 mL) was placed in a sealed microwave vial and cooled to –20 °C. N,N-Diisopropylethylamine (Hünig’s base, 159 µL, 0.91 mmol, 12 equiv) and para-toluenesulfinyl chloride (79.9 mg, 0.46 mmol, 6 equiv) were injected via two separate syringes and simultaneously. The reaction mixture was stirred at –20 °C until full conversion of starting material was observed by TLC (30 min). The mixture was then heated at 80 °C and stirred for additional 16 hours. The brown solution was allowed to cool to 25 °C, the volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with CH₂Cl₂/acetone 40:1 to afford the title product as a yellow foamy solid (26.3 mg, contains 3 wt% of residual acetone and grease, 0.0542 mmol, yield = 71%).

M.p. (CH₂Cl₂/cyclohexane) 237-239 °C. ¹H NMR (500 MHz, CDCl₃, 323 K) δ 7.60 (br s, 1H), 7.22 (ddd, J = 8.4, 7.4, 1.4 Hz, 1H), 7.11 (dd, J = 7.6, 1.3 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 6.72 (d, J = 5.5 Hz, 1H), 6.39 (d, J = 5.5 Hz, 1H), 5.55 (dd, J = 16.6, 8.1 Hz, 1H), 3.98 (s, 3H), 3.89 – 3.80 (m, 1H), 3.56 (s, 3H), 3.51 – 3.41 (m, 2H), 3.23 (dd, J = 16.4, 8.1 Hz, 1H), 3.01 – 2.92 (m, 4H), 2.48 – 2.29 (m, 4H), 1.73 (ddt, J = 14.3, 6.8, 2.4 Hz, 1H). ¹³C NMR (126 MHz, CDCl₃, 323 K) δ 195.5, 172.9, 172.0, 153.8, 151.4, 142.7, 132.8, 129.7, 129.4, 123.5, 122.9, 116.0, 73.6, 73.5, 64.2, 52.7, 52.6, 52.0, 45.2, 41.0, 31.7, 28.7, 26.5, 25.2. HRMS (ESI+) m/z calc. for CₙH₂₈N₂O₆Na⁺ [M+Na⁺]: 493.1404, found: 493.1414.

(–)-25S2: A solution of (–)-25S1 (51.9 mg, 0.110 mmol, 1 equiv) in anhydrous CH₂Cl₂ (2.5 mL) was placed in a sealed microwave vial and cooled to –20 °C. N,N-Diisopropylethylamine (Hünig’s base, 230 µL, 1.32 mmol, 12 equiv) and para-toluenesulfinyl chloride (115 mg, 0.66 mmol, 6 equiv) were injected via two separate syringes and simultaneously. The reaction mixture was stirred at –20 °C until full conversion of starting material was observed by TLC (30 min). The mixture was then heated at 80 °C and stirred for additional 16 hours. The brown solution was
allowed to cool to 25 ºC, the volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with CH$_2$Cl$_2$/acetone 40:1 to afford the title product as a yellow foamy solid (37.2 mg, 0.079 mmol, yield = 72%).

Note: Crystals suitable for single-crystal X-ray diffraction studies (yellow needles) were obtained from CH$_2$Cl$_2$/cyclohexane/acetone solvent system by slow evaporation method.

**M.p.** (CH$_2$Cl$_2$/cyclohexane/acetone) 204-206 ºC (>99% ee). $\alpha_0^{589}$ (CHCl$_3$, c 1.00, 299 K) = −227.4 deg.cm$^2$.g$^{-1}$ (>99% ee).

**Lapidilectam (4)**

(±)-4: A solution of (±)-25S2 (24.0 mg, 0.051 mmol, 1 equiv) in anhydrous CH$_2$Cl$_2$ (1.5 mL) was placed in a dry Schlenk tube under argon. The solution was cooled to −78 ºC and a freshly prepared solution of m-CPBA (ca. 75% purity, 100 mg in 5 mL of anhydrous CH$_2$Cl$_2$, 1.29 mL, 0.112 mmol, 2.2 equiv) was added dropwise at −78 ºC. The solution was stirred at this temperature for 30 minutes, upon which time full conversion of the starting material was observed by TLC. The mixture was filtered through a short pad of basic alumina (10 cm high, 1.5 cm diameter), flushing with EtOAc/EtOH (10:1, 200 mL). The fractions containing the product were concentrated in vacuo. The crude mixture was purified by preparative silica gel TLC eluting with EtOAc/EtOH 50:1 to afford (±)-lapidilectam (20.4 mg, contains 3 wt% of residual acetone and grease, 0.044 mmol, yield = 86%).

Note: Crystals suitable for single-crystal X-ray diffraction studies (colorless plates) were obtained from CH$_2$Cl$_2$/EtOAc solvent system by slow evaporation method.

**M.p.** (CH$_2$Cl$_2$/EtOAc) 251-253 ºC. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.51 (br s, 1H), 7.25 – 7.18 (m, 1H), 7.10 (d, J = 7.6 Hz, 1H), 6.98 (td, J = 7.5, 1.0 Hz, 1H), 6.78 (d, J = 5.8 Hz, 1H), 6.07 (d, J = 5.8 Hz, 1H), 4.80 (dd, J = 15.8, 8.1 Hz, 1H), 3.97 (s, 3H), 3.85 (br s, 1H), 3.54 (s, 3H), 3.42 (br s, 1H), 3.26 (dd, J = 15.9, 11.0 Hz, 1H), 3.16 (dd, J = 16.1, 8.2 Hz, 1H), 2.93 (s, 3H), 2.83 (dd, J = 16.1, 11.0 Hz, 1H), 2.41 – 2.17 (m, 4H), 1.71 – 1.63 (m, 1H). $^1$H NMR (500 MHz, CDCl$_3$, 323K) δ 7.59 (br s,
1H), 7.21 (ddd, $J = 8.4, 7.5, 1.4$ Hz, 1H), 7.10 (dd, $J = 7.5, 1.1$ Hz, 1H), 6.97 (td, $J = 7.5, 1.0$ Hz, 1H), 6.77 (d, $J = 5.8$ Hz, 1H), 6.07 (d, $J = 5.8$ Hz, 1H), 4.80 (dd, $J = 15.9, 8.3$ Hz, 1H), 3.98 (s, 3H), 3.88 – 3.79 (m, 1H), 3.54 (s, 3H), 3.43 (dd, $J = 15.6, 7.8$ Hz, 1H), 3.28 (dd, $J = 15.9, 11.0$ Hz, 1H), 3.16 (dd, $J = 16.1, 1.2$ Hz, 1H), 2.94 (s, 3H), 2.84 (ddd, $J = 16.1, 11.1, 1.2$ Hz, 1H), 1.67 (ddt, $J = 13.9, 7.0, 2.2$ Hz, 1H).

$^{13}$C NMR (126 MHz, CDCl$_3$, 323K) $\delta$ 173.2, 172.2, 170.5, 154.2, 153.8, 142.7, 129.9, 129.3, 124.2, 123.4, 122.9, 115.9, 73.6, 64.8, 64.6, 52.6, 52.4, 51.8, 41.1, 39.6, 33.7, 29.6, 27.0, 25.3.

HRMS (ESI+) $m/z$ calc. for $C_{24}H_{26}N_{2}O_{7}Na^{+}$ [M+Na$^+$]: 477.1632, found: 477.1630.

\((-\text{-})4\): A solution of \((-\text{-})25S2 (40.1$ mg, $0.0852$ mmol, 1 equiv) in anhydrous CH$_2$Cl$_2$ (2.5 mL) was placed in a dry Schlenk tube under argon. The solution was cooled to $-78$ °C and a freshly prepared solution of $m$-CPBA (ca. 75% purity, 100 mg in 5 mL of anhydrous CH$_2$Cl$_2$, 2.15 mL, 0.187 mmol, 2.2 equiv) was added dropwise at $-78$ °C. The solution was stirred at this temperature for 30 minutes, upon which time full conversion of the starting material was observed by TLC. The mixture was filtered through a short pad of basic alumina (15 cm high, 3 cm diameter), flushing with EtOAc/EtOH (1:10, 250 mL). The fractions containing the product were concentrated in vacuo. The crude mixture was purified by preparative silica gel TLC eluting with EtOAc/EtOH 50:1 to afford \((-\text{-})$-lapidilectam (34.7 mg, $0.0763$ mmol, yield = 90%).

M.p. (EtOAc) 222-223 °C (>99% ee). $\alpha_D^{589}$ (CHCl$_3$, c 1.05, 299 K) = $-122.2$ deg.cm$^2$.g$^{-1}$ (>99% ee), lit.$^7$ $\alpha_D$ (CHCl$_3$, c 0.55) = $+77$ deg.cm$^2$.g$^{-1}$. 

HPLC (Chiralpak IA (250 mm × 4.6 mm), hexane/CH$_2$Cl$_2$/ethanol 80:15:5 1 mL/min) $t_R1$ 9.7 – 9.9 min, $t_R2$ 13.2 – 13.4 min, >99% ee. UV-Vis (MeOH) $\lambda_{max}$ nm = 228, 255, 289. CD (MeOH) $\lambda_{ext}$ nm ($\Delta\varepsilon$) 219 (–47.6), 228 (–51.0), 256 (+42.0), lit.$^7$ CD (MeOH) $\lambda_{ext}$ nm ($\Delta\varepsilon$) 228 (–25), 257 (+21).

Note: Our synthetic lapidilectam has a negative optical rotation (levogyre), while a positive rotatory power (dextrogyre) was previously reported for lapidilectam isolated from plant material.$^7$ This discrepancy in reported and obtained data may be ascribed to a typing mistake; in the same report, on page 1139, this compound is described as “\((-\text{-})$-lapidilectam [5]”. Other closely related members of the family, lapidilectine A, grandilodine A, as well as our synthetic intermediates \((-\text{-})\text{-24, \(-\text{-})\text{-25, \(-\text{-})\text{-25S1, \(-\text{-})\text{-25S2, all have a negative optical rotation. The absolute configuration of \((-\text{-})-}
HPLC trace of racemic sample of lapidilectam

Sample Info

Method: Hex-EtOH-DCM 80-15-5
IA, 1 ml/min

Lapidilectam racemic

HPLC trace of enantioenriched sample of lapidilectam

HPLC trace of racemic sample of lapidilectam

All others natural compounds obtained in the course of the synthesis have the same sign of optical rotation, as previously reported, including the sample of lapidilectine A obtained directly from our synthetic (−)-lapidilectam. Moreover, while the sign of optical rotation was different from the reported one, our CD spectrum for (−)-4 showed exactly the same sign, position and relative intensity of signals as the one reported previously. All these data strongly suggests correcting the sign of the optical rotation for lapidilectam from the previously reported (+) to (−).

HPLC trace of enantioenriched sample of lapidilectam

lapidilectam was confirmed by single crystal X-ray diffraction studies for (−)-25S2, which is the direct precursor to (−)-4 in our synthesis, and whose absolute configuration corresponds to the one previously proposed for the natural compound.7
Table S3. Comparison of $^{13}$C NMR data of isolated\textsuperscript{7} and our synthetic sample of lapidilectam.

![Diagram of lapidilectam structure]

| Position | $^{13}$C NMR of isolated\textsuperscript{7} | $^{13}$C NMR at 323K of our synthetic lapidilectine B, δ ppm (\(\Delta\delta_{ppm}\) with isolated)\textsuperscript{7} |
|----------|---------------------------------------------|----------------------------------------------------------------------------------|
| NCO\textsubscript{2}Me | 154.4 | 153.8 (−0.6) |
| NCO\textsubscript{2}Me | 52.8 | 52.6 (−0.2) |
| 2 | 73.6 | 73.6 (0.0) |
| 3 | 170.7 | 170.5 (−0.2) |
| 5 | 39.8 | 39.6 (−0.2) |
| 6 | 25.3 | 25.3 (0.0) |
| 7 | 64.7 | 64.6 (−0.1) |
| 8 | 129.9 | 129.9 (0.0) |
| 9 | 123.0 | 122.9 (−0.1) |
| 10 | 123.7 | 123.4 (−0.3) |
| 11 | 129.9 | 129.3 (−0.6) |
| 12 | 116.0 | 115.9 (−0.1) |
| 13 | -not reported- | 142.7 |
| 14 | 124.1 | 124.2 (+0.1) |
| 15 | 154.4 | 154.2 (−0.2) |
| 16 | 41.1 | 41.1 (0.0) |
| 17 | 33.7 | 33.7 (0.0) |
| 18 | 27.1 | 27.0 (−0.1) |
| 19 | 29.8 | 29.6 (−0.2) |
| 20 | 65.0 | 64.8 (−0.2) |
| 21 | 172.4 | 172.2 (−0.2) |
| 21-OMe | 52.7 | 52.4 (−0.3) |
| CO\textsubscript{2}Me | 173.4 | 173.2 (−0.2) |
| CO\textsubscript{2}Me | 52.1 | 51.8 (−0.3) |
(±)-3: To a suspension of (±)-lapidilectam 4 (9.2 mg, 0.020 mmol, 1 equiv) and activated molecular sieves (4Å, 30 mg) in a 1:1 mixture of anhydrous CH₂Cl₂ and THF (2.0 mL) was added Me₃OBF₄ (29.2 mg, 0.20 mmol, 10 equiv). The mixture was stirred at 45 ºC for 2 h, and then cooled to 0 ºC. Methanol (2.0 mL) and NaBH₄ (14.4 mg, 3.8 mmol, ca. 20 equiv) were added and the resulting mixture was stirred for additional 30 min at 25 ºC. The reaction was quenched by addition of saturated aqueous NaHCO₃ (20 mL) and basified until pH ≈ 10 by addition of 1 M aqueous NaOH solution. The aqueous layer was extracted with CH₂Cl₂ (3 × 50 mL) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was redissolved in EtOAc (10 mL), AcOH (100 µL) was added and the resulting solution was stirred for 15 min. Water (10 mL) was added to the mixture, the layers were separated and the organic layer was washed with water (3 × 5 mL). The combined aqueous layers were basified to pH ≈ 10 with 5% aqueous NaOH and saturated with solid NaCl. The aqueous layer was then extracted with CH₂Cl₂ (5 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by alumina TLC eluting with cyclohexane/EtOAc 4:1 to afford (±)-lapidilectine A (6.4 mg, contains 6 wt% of residual solvents and grease, 0.0137 mmol, yield = 68%) and (±)-grandilodine A (1.3 mg, 0.003 mmol, yield = 15%).

**Note 1:** Crystals suitable for single-crystal X-ray diffraction studies (colorless plates) were obtained from CH₂Cl₂/cyclohexane/pentane solvent system by diffusion method.

**Note 2:** The use of THF as a co-solvent was essential to achieve the desired reactivity. In the absence of THF no conversion of lapidilectam or only traces of 1,4-reduction were observed. We think that the lack of reactivity is related to the low solubility of Me₃OBF₄ or forming O-methylated lactam salt in CH₂Cl₂. It is known that the polymerization of THF initiated by trialkyloxonium tetrafluoroborate salts proceeds via O-alkylation of THF²⁸ and results in the formation of more soluble oxonium species, which might facilitate the lactam alkylation in our case.
M.p. (CH₂Cl₂/cyclohexane/pentane) 180-182 °C (starts turning brown >165 °C). ¹H NMR (500 MHz, CDCl₃) δ 7.60 (br s, 1H), 7.18 (ddd, J = 8.4, 7.4, 1.4 Hz, 1H), 7.04 (dd, J = 7.7, 1.4 Hz, 1H), 6.92 (td, J = 7.5, 1.0 Hz, 1H), 5.71 (ddd, J = 5.8, 2.4, 1.6 Hz, 1H), 5.49 (ddd, J = 5.9, 2.6, 1.5 Hz, 1H), 4.00 – 3.79 (m, 4H), 3.75 (dt, J = 16.0, 2.1 Hz, 1H), 3.56 (s, 3H), 3.42 (dt, J = 15.6, 1.9 Hz, 1H), 3.21 (ddd, J = 12.5, 5.9, 4.0 Hz, 1H), 3.13 (dt, J = 12.7, 8.4 Hz, 1H), 3.09 – 2.95 (m, 4H), 2.87 – 2.75 (m, 2H), 2.67 – 2.56 (m, 2H), 2.03 (dd, J = 15.5, 10.5 Hz, 1H), 1.80 – 1.70 (m, 1H), 1.65 – 1.55 (m, 1H). ¹H NMR (500 MHz, CDCl₃, 323K) δ 7.65 (br s, 1H), 7.17 (ddd, J = 8.4, 7.4, 1.4 Hz, 1H), 7.04 (dd, J = 7.7, 1.4 Hz, 1H), 6.91 (td, J = 7.5, 1.0 Hz, 1H), 5.71 (dt, J = 5.8, 2.0 Hz, 1H), 5.51 – 5.47 (m, 1H), 3.95 (s, 3H), 3.87 (t, J = 9.9 Hz, 1H), 3.75 (dt, J = 15.7, 1.8 Hz, 1H), 3.56 (s, 3H), 3.44 (d, J = 15.4 Hz, 1H), 3.25 – 3.10 (m, 2H), 3.10 – 2.95 (m, 4H), 2.87 – 2.78 (m, 2H), 2.71 – 2.57 (m, 2H), 2.04 (dd, J = 15.3, 10.6 Hz, 1H), 1.76 (dt, J = 13.7, 8.9 Hz, 1H), 1.62 – 1.57 (m, 1H). ¹³C NMR (126 MHz, CDCl₃, 323K) δ 174.2, 173.0, 154.1, 143.1, 138.4, 132.1, 128.9, 125.8, 122.9, 122.8, 115.5, 75.7, 67.0, 62.5 (2C), 52.3, 51.9, 51.7, 49.2, 41.0, 32.5, 31.3, 30.0, 29.5. HRMS (ESI+) m/z calc. for C₂₄H₂₉N₂O₆⁺ [M+H]⁺: 441.2020, found: 441.2027.
(-)-3: To a suspension of (-)-lapidilectam (15.9 mg, 0.0350 mmol, 1 equiv) and activated molecular sieves (4 Å, 60 mg) in a 1:1 mixture of anhydrous CH₂Cl₂ and THF (3.8 mL) was added Me₃OBF₄ (51.1 mg, 0.35 mmol, 10 equiv). The mixture was stirred at 45 °C for 2 h, and then cooled to 0 °C. Methanol (2.0 mL) and NaBH₄ (25.2 mg, 0.67 mmol, ca. 20 equiv) were added and the resulting mixture was stirred for additional 30 min at 25 °C. The reaction was quenched by addition of saturated aqueous NaHCO₃ (30 mL) and basified until pH ≈ 10 by addition of 1 M aqueous NaOH solution. The aqueous layer was extracted with CH₂Cl₂ (3 × 80 mL) and the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was redissolved in EtOAc (15 mL), AcOH (150 µL) was added and the resulting solution was stirred for 15 min. Water (15 mL) was added to the mixture, the layers were separated and the organic layer was washed with water (3 × 7.5 mL). The combined aqueous layers were basified to pH ≈ 10 with 5% aqueous NaOH and saturated with solid NaCl. The aqueous layer was then extracted with CH₂Cl₂ (5 × 20 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by alumina TLC eluting with cyclohexane/EtOAc 4:1 to afford (-)-lapidilectine A as a colorless gum (11.1 mg, contains 9 wt% of residual solvents and grease 0.02 29 mmol, yield = 65%) and (-)-grandilodine A (2.5 mg, 0.0055 mmol, yield = 16%).

αD 589 (CHCl₃, c 0.55, 299 K) = −42.0 deg.cm².g⁻¹ (>99% ee). lit.⁶ αD (CHCl₃, c 0.8)=−33 deg.cm².g⁻¹. UV-Vis (MeOH) λmax nm = 226 (sh), 255, 288. CD (MeOH) λexc nm (Δε) 224 (−38.8), 257 (+36.6), 291 (−1.0), lit.⁷ CD (MeOH) λext nm (Δε) 220 (−27), 257 (+27), 290 (−0.43).
Table S4. Comparison of $^{13}$C NMR data of isolated$^6$ and our synthetic sample of lapidilectine A.

| Position | $^{13}$C NMR of isolated$^6$ lapidilectine A, δ ppm | $^{13}$C NMR at 323K of our synthetic lapidilectine A, δ ppm (Δδ<sub>ppm</sub> with isolated)$^6$ |
|----------|--------------------------------------------------|--------------------------------------------------|
| NCO<sub>2</sub>Me | 154.0 | 154.1 (+0.1) |
| NCO<sub>2</sub>Me | 52.4 | 52.3 (–0.1) |
| 2 | 75.7 | 75.7 (0.0) |
| 3 | 62.4 | 62.5 (+0.1) |
| 5 | 49.2 | 49.2 (0.0) |
| 6 | 29.8 | 30.0 (+0.2) |
| 7 | 62.4 | 62.5 (+0.1) |
| 8 | 132.0 | 132.1 (+0.1) |
| 9 | 123.0 | 122.9 (–0.1) |
| 10 | 122.8 | 122.8 (0.0) |
| 11 | 129.1 | 128.9 (–0.2) |
| 12 | 115.6 | 115.5 (–0.1) |
| 13 | 143.1 | 143.1 (0.0) |
| 14 | 125.7 | 125.8 (+0.1) |
| 15 | 138.4 | 138.4 (0.0) |
| 16 | 41.0 | 41.0 (0.0) |
| 17 | 32.5 | 32.5 (0.0) |
| 18 | 31.0 | 31.3 (+0.3) |
| 19 | 29.3 | 29.5 (+0.2) |
| 20 | 67.3 | 67.0 (–0.3) |
| 21-OMe | 51.6 | 51.7 (+0.1) |
| CO<sub>2</sub>Me | 174.2 | 174.2 (0.0) |
| CO<sub>2</sub>Me | 52.1 | 51.9 (–0.2) |
Grandilodine A (5)

(±)-5: In a dry 10 mL flask under argon, a solution of BH$_3$·SMe$_2$ (1 M in THF, 0.30 mL, 0.30 mmol, 10 equiv) was added to a solution of (±)-25 (14.0 mg, 0.0307 mmol, 1 equiv) in anhydrous THF (1.0 mL) at 25 ºC. The resulting colorless solution was stirred vigorously at 25 ºC for 4 hours. The solution was cooled to 0 ºC and acetic acid (120 µL, 2.10 mmol, 70 equiv) was added and stirring was continued for 30 minutes at 25 ºC until effervescence had ceased. The reaction was quenched by addition of a saturated aqueous solution of NaHCO$_3$ (ca. 5 mL, caution: very vigorous effervescence) and basified until pH ≈ 10 by addition of solid NaHCO$_3$. It was then diluted with EtOAc (10 mL) and the aqueous layer was re-extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by neutral alumina TLC eluting with cyclohexane/EtOAc 3:1 to afford (±)-grandilodine A as a colorless gum (12.0 mg, contains 4 wt% of residual solvents and grease, 0.0260 mmol, yield = 85%).

*Note 1:* Crystals suitable for single-crystal X-ray diffraction studies (colorless needles) were obtained from CH$_2$Cl$_2$/cyclohexane/pentane solvent system by diffusion method.

**M.p.** (CH$_2$Cl$_2$/cyclohexane/pentane) 160-162 ºC. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.53 (br s, 1H), 7.17 (ddd, $J = 8.5, 7.4, 1.4$ Hz, 1H), 7.03 (d, $J = 7.6$ Hz, 1H), 6.91 (td, $J = 7.5, 1.0$ Hz, 1H), 4.02 – 3.77 (m, 4H), 3.54 (s, 3H), 3.23 – 2.66 (m, 10H), 2.56 (t, $J = 13.0$ Hz, 1H), 2.50 – 2.39 (m, 1H), 1.87 (dd, $J = 15.3, 10.1$ Hz, 1H), 1.81 – 1.50 (m, 6H). $^1$H NMR (500 MHz, CDCl$_3$, 323K) δ 7.64 (br s, 1H), 7.16 (ddd, $J = 8.4, 7.4, 1.4$ Hz, 1H), 7.03 (dd, $J = 7.6, 1.4$ Hz, 1H), 6.91 (td, $J = 7.4, 1.0$ Hz, 1H), 3.95 (s, 3H), 3.86 (br s, 1H), 3.54 (s, 3H), 3.21 – 3.09 (m, 2H), 3.09 – 2.94 (m, 5H), 2.94 – 2.84 (m, 1H), 2.83 – 2.68 (m, 2H), 2.58 (t, $J = 13.0$ Hz, 1H), 2.47 (ddd, $J = 14.7, 11.4, 6.9$ Hz, 1H), 1.87 (dd, $J = 15.3, 10.1$ Hz, 1H), 1.83 – 1.50 (m, 6H). $^{13}$C NMR (126 MHz, CDCl$_3$, 323K) δ 174.3, 173.0, 154.2, 143.1, 132.0, 128.8, 122.9, 122.8, 115.5, 75.7, 63.0, 56.4, 52.3, 51.8, 51.7, 49.5, 40.9, 40.0, 33.0, 31.9, 29.5, 29.1, 22.3. HRMS (ESI+) m/z calc. for C$_{24}$H$_{31}$N$_2$O$_6$ $^+$ [M+H]$^+$: 443.2177, found: 443.2181.
In a dry 10 mL flask under argon, a solution of BH$_3$·SMe$_2$ (1 M in THF, 0.43 mL, 0.43 mmol, 10 equiv) was added to a solution of (-)-25 (19.6 mg, 0.0429 mmol, 1 equiv) in anhydrous THF (1.5 mL) at 25 ºC. The resulting colorless solution was stirred vigorously at 25 ºC for 4 hours. The solution was cooled to 0 ºC and acetic acid (172 µL, 3.01 mmol, 70 equiv) was added and stirring was continued for 30 minutes at 25 ºC until effervescence had ceased. The reaction was quenched by addition of a saturated aqueous solution of NaHCO$_3$ (ca. 8 mL, caution: very vigorous effervescence) and basified until pH ≈ 10 by addition of solid NaHCO$_3$. It was then diluted with EtOAc (15 mL) and the aqueous layer was re-extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by neutral alumina TLC eluting with cyclohexane/EtOAc 3:1 to afford (-)-grandilodine A as a white solid (15.9 mg, 0.0359 mmol, yield = 84%).

**M.p.** (CH$_2$Cl$_2$/cyclohexane) 132-134 ºC (>99% ee). $\alpha_D^{589}$ (CHCl$_3$, c 1.46, 298 K) = $-1.5 \pm 0.6$ deg.cm$^2$.g$^{-1}$ (>99% ee), lit.$^8$ $\alpha_D$ (CHCl$_3$, c 1.46) = $-76$ deg.cm$^2$.g$^{-1}$. **HPLC** (Chiralpak IC (250 mm × 4.6 mm), hexane/ethanol/CH$_2$Cl$_2$ 85:5:10 with 0.1% of diethylamine, 1 mL/min) $t_{R1}$ 8.8 – 9.1 min, $t_{R2}$ 10.1 – 10.4 min, >99% ee. **UV-Vis** (MeOH) $\lambda_{\text{max}}$ nm = 226 (sh), 255, 288. **CD** (MeOH) $\lambda_{\text{ext}}$ nm ($\Delta\varepsilon$) 226 (–58.4), 256 (+63.1), 291 (–1.2). **Note 2:** The error on measurement of the optical rotation is given in this case, because of the low value observed. The value of the optical rotation of our (-)-5 (– 1.5) significantly differs from the reported value for the (-)-5, isolated from plant material (– 76). We confirmed the enantiopurity of our compound by chiral HPLC (>99% ee, see below).

**HPLC trace of racemic sample of grandilodine A**

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(-)-5: In a dry 10 mL flask under argon, a solution of BH$_3$·SMe$_2$ (1 M in THF, 0.43 mL, 0.43 mmol, 10 equiv) was added to a solution of (-)-25 (19.6 mg, 0.0429 mmol, 1 equiv) in anhydrous THF (1.5 mL) at 25 ºC. The resulting colorless solution was stirred vigorously at 25 ºC for 4 hours. The solution was cooled to 0 ºC and acetic acid (172 µL, 3.01 mmol, 70 equiv) was added and stirring was continued for 30 minutes at 25 ºC until effervescence had ceased. The reaction was quenched by addition of a saturated aqueous solution of NaHCO$_3$ (ca. 8 mL, caution: very vigorous effervescence) and basified until pH ≈ 10 by addition of solid NaHCO$_3$. It was then diluted with EtOAc (15 mL) and the aqueous layer was re-extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by neutral alumina TLC eluting with cyclohexane/EtOAc 3:1 to afford (-)-grandilodine A as a white solid (15.9 mg, 0.0359 mmol, yield = 84%).

**M.p.** (CH$_2$Cl$_2$/cyclohexane) 132-134 ºC (>99% ee). $\alpha_D^{589}$ (CHCl$_3$, c 1.46, 298 K) = $-1.5 \pm 0.6$ deg.cm$^2$.g$^{-1}$ (>99% ee), lit.$^8$ $\alpha_D$ (CHCl$_3$, c 1.46) = $-76$ deg.cm$^2$.g$^{-1}$. **HPLC** (Chiralpak IC (250 mm × 4.6 mm), hexane/ethanol/CH$_2$Cl$_2$ 85:5:10 with 0.1% of diethylamine, 1 mL/min) $t_{R1}$ 8.8 – 9.1 min, $t_{R2}$ 10.1 – 10.4 min, >99% ee. **UV-Vis** (MeOH) $\lambda_{\text{max}}$ nm = 226 (sh), 255, 288. **CD** (MeOH) $\lambda_{\text{ext}}$ nm ($\Delta\varepsilon$) 226 (–58.4), 256 (+63.1), 291 (–1.2). **Note 2:** The error on measurement of the optical rotation is given in this case, because of the low value observed. The value of the optical rotation of our (-)-5 (– 1.5) significantly differs from the reported value for the (-)-5, isolated from plant material (– 76). We confirmed the enantiopurity of our compound by chiral HPLC (>99% ee, see below).

**HPLC trace of racemic sample of grandilodine A**

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(-)-5: In a dry 10 mL flask under argon, a solution of BH$_3$·SMe$_2$ (1 M in THF, 0.43 mL, 0.43 mmol, 10 equiv) was added to a solution of (-)-25 (19.6 mg, 0.0429 mmol, 1 equiv) in anhydrous THF (1.5 mL) at 25 ºC. The resulting colorless solution was stirred vigorously at 25 ºC for 4 hours. The solution was cooled to 0 ºC and acetic acid (172 µL, 3.01 mmol, 70 equiv) was added and stirring was continued for 30 minutes at 25 ºC until effervescence had ceased. The reaction was quenched by addition of a saturated aqueous solution of NaHCO$_3$ (ca. 8 mL, caution: very vigorous effervescence) and basified until pH ≈ 10 by addition of solid NaHCO$_3$. It was then diluted with EtOAc (15 mL) and the aqueous layer was re-extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude product was purified by neutral alumina TLC eluting with cyclohexane/EtOAc 3:1 to afford (-)-grandilodine A as a white solid (15.9 mg, 0.0359 mmol, yield = 84%).

**M.p.** (CH$_2$Cl$_2$/cyclohexane) 132-134 ºC (>99% ee). $\alpha_D^{589}$ (CHCl$_3$, c 1.46, 298 K) = $-1.5 \pm 0.6$ deg.cm$^2$.g$^{-1}$ (>99% ee), lit.$^8$ $\alpha_D$ (CHCl$_3$, c 1.46) = $-76$ deg.cm$^2$.g$^{-1}$. **HPLC** (Chiralpak IC (250 mm × 4.6 mm), hexane/ethanol/CH$_2$Cl$_2$ 85:5:10 with 0.1% of diethylamine, 1 mL/min) $t_{R1}$ 8.8 – 9.1 min, $t_{R2}$ 10.1 – 10.4 min, >99% ee. **UV-Vis** (MeOH) $\lambda_{\text{max}}$ nm = 226 (sh), 255, 288. **CD** (MeOH) $\lambda_{\text{ext}}$ nm ($\Delta\varepsilon$) 226 (–58.4), 256 (+63.1), 291 (–1.2). **Note 2:** The error on measurement of the optical rotation is given in this case, because of the low value observed. The value of the optical rotation of our (-)-5 (– 1.5) significantly differs from the reported value for the (-)-5, isolated from plant material (– 76). We confirmed the enantiopurity of our compound by chiral HPLC (>99% ee, see below).

**HPLC trace of racemic sample of grandilodine A**

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HPLC trace of enantioenriched sample of grandilodine A

Table S5. Comparison of $^{13}$C NMR data of isolated$^8$ and our synthetic sample of grandilodine A.

| Position | $^{13}$C NMR of isolated$^8$ | $^{13}$C NMR at 323K of our synthetic grandilodine A, grandilodine A, $\delta$ ppm | $\delta$ ppm ($\Delta\delta_{ppm}$ with isolated)$^8$ |
|----------|-------------------------------|---------------------------------------------------------------------------------|-----------------------------------------------|
| NCO$_2$Me | 154.0 | 154.2 (+0.2) |
| NCO$_2$Me | 52.4 | 52.3 (-0.1) |
| 2        | 75.5 | 75.7 (+0.2) |
| 3        | 56.3 | 56.4 (+0.1) |
| 5        | 49.4 | 49.5 (+0.1) |
| 6        | 28.8 | 29.1 (+0.3) |
| 7        | 62.4 | 63.0 (+0.6) |
| 8        | 131.7 | 132.0 (+0.3) |
| 9        | 122.9 | 122.9 (0.0) |
| 10       | 122.7 | 122.8 (+0.1) |
| 11       | 128.8 | 128.8 (0.0) |
| 12       | 115.4 | 115.5 (+0.1) |
| 13       | 144.0 | 143.1 (-0.9) |
| 14       | 22.1 | 22.3 (+0.2) |
| 15       | 39.8 | 40.0 (+0.2) |
| 16       | 39.8 | 40.9 (+1.1) |
| 17       | 32.8$^a$ | 29.5 (-3.3)$^a$ |
| 18       | 31.5 | 31.9 (+0.4) |
| 19       | 32.8$^a$ | 33.0 (+0.2)$^a$ |
| 20       | 60.3 | 60.4 (+0.1) |
| 21       | 173.0 | 173.0 (0.0) |
| 21-OMe  | 51.9 | 51.8 (-0.1) |
| CO$_2$Me | 174.3 | 174.3 (0.0) |
| CO$_2$Me | 51.7 | 51.7 (0.0) |

$^a$ There is an obvious typo in the original isolation report.$^8$ Both $^1$H and $^{13}$C NMRs for positions 17 and 19 were reported to be identical (with the same multiplicity in $^1$H NMR), which is clearly not the case.
Grandilodine B (7)

(±)-7: To a solution of (±)-lapidilectam (28.0 mg, 0.0616 mmol, 1 equiv) in a 1:2 mixture of t-BuOH and THF (1.5 mL, HPLC grade solvents) was added t-BuOK (33.6 mg, 0.30 mmol, 5 equiv). The mixture was stirred at 40 °C for 30 min, and then concentrated under reduced pressure. The residue was purified by preparative silica gel TLC eluting with EtOAc/EtOH 50:1 to afford (±)-grandilodine B (6.4 mg, contains 6 wt% of residual solvents and grease, 0.0135 mmol, 22%, 79% based on recovered starting material) and (±)-lapidilectam (20.4 mg, 0.0449 mmol, 73% yield).

Note: Crystals suitable for single-crystal X-ray diffraction studies (colorless plates) were obtained from CH$_2$Cl$_2$/EtOAc solvent system by slow evaporation method.

M.p. (CH$_2$Cl$_2$/EtOAc) 238-239 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.56 (d, $J =$ 8.1 Hz, 1H), 7.30 (ddd, $J =$ 8.3, 7.4, 1.3 Hz, 1H), 7.20 (d, $J =$ 7.7 Hz, 1H), 7.08 (td, $J =$ 7.5, 1.0 Hz, 1H), 7.01 (d, $J =$ 5.7 Hz, 1H), 6.04 (d, $J =$ 5.7 Hz, 1H), 4.51 (dd, $J =$ 15.8, 6.8 Hz, 1H), 3.81 (s, 3H), 3.61 (s, 3H), 3.56 (s, 3H), 3.54 – 3.44 (m, 1H), 3.33 (dd, $J =$ 15.7, 11.6 Hz, 1H), 3.19 (dd, $J =$ 16.0, 6.5 Hz, 1H), 3.07 (t, $J =$ 8.9 Hz, 1H), 2.79 (dd, $J =$ 14.9, 9.3 Hz, 1H), 2.50 (dd, $J =$ 15.0, 6.8 Hz, 1H), 2.35 (ddd, $J =$ 15.9, 8.7, 2.5 Hz, 1H), 1.94 (ddd, $J =$ 16.2, 11.9, 2.0 Hz, 1H), 1.71 (ddd, $J =$ 15.8, 12.6, 6.8 Hz, 1H), 1.47 (dd, $J =$ 14.9, 8.4 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 172.8, 172.5, 171.6, 156.1, 153.2, 142.9, 131.8, 129.4, 124.1, 123.8, 123.2, 117.8, 74.0, 62.7, 61.5, 52.6, 52.5, 52.0, 42.8, 36.5, 33.6, 30.8, 23.6, 23.4. HRMS (ESI+) m/z calc. for C$_{24}$H$_{26}$N$_2$O$_7$Na$^+$ [M+Na]$^+$: 477.1632, found: 477.1609 (also observed m/z calc. for C$_{24}$H$_{27}$N$_2$O$_7$Na$^+$ [M+H]$^+$: 455.1813, found: 455.1798).

(+)-7: To a solution of (−)-lapidilectam (59.9 mg, 0.132 mmol, 1 equiv) in a 1:2 mixture of t-BuOH and THF (6.0 mL, HPLC grade solvents) was added t-BuOK (37.0 mg, 0.330 mmol, 2.5 equiv). The mixture was stirred at 40 °C for 30 min, and then concentrated under reduced pressure. The residue was purified by preparative silica gel TLC eluting with EtOAc/EtOH 50:1 to afford (+)-grandilodine B (12.0 mg, 0.0264 mmol, 20%, 80% based on recovered starting material) and (−)-lapidilectam (44.9 mg, 0.099 mmol, 75%).
**M.p.** (CH$_2$Cl$_2$/pentane) 201-203 °C (>99% ee). $\alpha_D^{589}$ (CHCl$_3$, c 0.55, 298 K) = + 68.9 deg.cm$^2$.g$^{-1}$ (>99% ee). lit.$^8$ $\alpha_D$ (CHCl$_3$, c 0.39, 298K) = + 66 deg.cm$^2$.g$^{-1}$. UV-Vis (MeOH) $\lambda_{\text{max}}$ nm = 226 (sh), 252, 287, 320 (sh). CD (MeOH) $\lambda_{\text{ext}}$ nm ($\Delta$e) 229 (−20.8), 256 (+12.0), 290 (+2.9).

Table S6. Comparison of $^{13}$C NMR data of isolated,$^8$ previously synthesized,$^{29}$ and our synthetic sample of grandilodine B.

![Chemical structure of grandilodine B](image)

| Position | $^{13}$C NMR of isolated$^8$, grandilodine B, δ ppm | $^{13}$C NMR of synthetic$^{29}$ (±)-grandilodine B, δ ppm | $^{13}$C NMR of our synthetic grandilodine B, δ ppm (Δδ ppm with isolated)$^8$ |
|----------|-------------------------------------------------|-------------------------------------------------|-------------------------------------------------|
| NCO$_2$Me | 153.3                                           | 153.4                                           | 153.2 (−0.1)                                    |
| NCO$_2$Me | 52.7                                            | 52.8                                            | 52.6 (−0.1)                                    |
| 2        | 74.1                                            | 74.2                                            | 74.0 (−0.1)                                    |
| 3        | 172.8                                           | 172.7                                           | 172.5 (−0.3)                                   |
| 5        | 36.6                                            | 36.7                                            | 36.5 (−0.1)                                    |
| 6        | 30.8                                            | 30.9                                            | 30.8 (0.0)                                     |
| 7        | 61.5                                            | 61.7                                            | 61.5 (0.0)                                     |
| 8        | 131.8                                           | 131.9                                           | 131.8 (0.0)                                   |
| 9        | 123.3                                           | 123.4                                           | 123.2 (−0.1)                                   |
| 10       | 123.9                                           | 124.0                                           | 123.8 (−0.1)                                   |
| 11       | 129.5                                           | 129.6                                           | 129.4 (−0.1)                                   |
| 12       | 117.9                                           | 118.0                                           | 117.8 (−0.1)                                   |
| 13       | 143.0                                           | 143.1                                           | 142.9 (−0.1)                                   |
| 14       | 124.1                                           | 124.2                                           | 124.1 (0.0)                                    |
| 15       | 156.3                                           | 156.3                                           | 156.1 (−0.2)                                   |
| 16       | 42.9                                            | 43.0                                            | 42.8 (−0.1)                                    |
| 17       | 33.6                                            | 33.7                                            | 33.6 (0.0)                                     |
| 18       | 23.6                                            | 23.7                                            | 23.6 (0.0)                                     |
| 19       | 23.5                                            | 23.6                                            | 23.4 (−0.1)                                    |
| 20       | 62.8                                            | 62.8                                            | 62.7 (−0.1)                                    |
| 21       | 171.7                                           | 171.8                                           | 171.6 (−0.1)                                   |
| 21-OMe   | 52.6                                            | 52.6                                            | 52.5 (−0.1)                                    |
| CO$_2$Me | 172.9                                           | 172.9                                           | 172.8 (−0.1)                                   |
| CO$_2$Me | 52.1                                            | 52.1                                            | 52.0 (−0.1)                                    |
(±)-6: To a suspension of (±)-grandilodine B (6.4 mg, 0.014 mmol, 1 equiv) and activated molecular sieves (4Å, 20 mg) in a 1:1 mixture of anhydrous CH₂Cl₂ and THF (1.4 mL) was added Me₂OBF₄ (20.4 mg, 0.14 mmol, 10 equiv). The mixture was stirred at 45 °C for 3 h, and then cooled to 0 °C. Methanol (2.0 mL) and NaBH₄ (10.1 mg, 0.27 mmol, ca. 20 equiv) were added and the resulting mixture was stirred for additional 30 min at 25 °C. The reaction was quenched by addition of saturated aqueous NaHCO₃ (10 mL) and basified until pH ≈ 10 by addition of 1 M aqueous NaOH solution. The aqueous layer was extracted with CH₂Cl₂ (3 × 35 mL) and the combined organic layers were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was redissolved in EtOAc (10 mL), AcOH (70 µL) was added and the resulting solution was stirred for 15 min. The mixture was diluted with water (10 mL) and the layers were separated, the organic layer was washed with water (3 × 5 mL). The combined aqueous layers were basified to pH ≈ 10 with 5% aqueous NaOH and saturated with solid NaCl. The aqueous layer was then extracted with CH₂Cl₂ (5 × 10 mL). The combined extracts were washed with brine (10 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by alumina TLC eluting with cyclohexane/EtOAc 4:1 to afford (±)-isolapidilectine A as a colorless gum (4.4 mg, ca. 85 wt% purity, 0.0085 mmol, yield = 60%) and (±)-dihydroisolapidilectine A as a colorless gum (1.2 mg, ca. 85 wt% purity, 0.0023 mmol, yield = 16%).

¹H NMR (500 MHz, CDCl₃) δ 7.58 (br d, J = 6.5 Hz, 1H), 7.28 – 7.25 (m, overlapping with CHCl₃ peak, 1H), 7.14 (d, J = 7.7 Hz, 1H), 7.05 (t, J = 7.5 Hz, 1H), 5.62 (dt, J = 6.0, 1.8 Hz, 1H), 5.54 (d, J = 5.9 Hz, 1H), 3.87 (d, J = 14.1 Hz, 1H), 3.79 (s, 3H), 3.58 (s, 3H), 3.50 (s, 3H), 3.37 – 3.28 (m, 3H), 3.25 (dd, J = 11.3, 7.3 Hz, 1H), 3.10 – 2.95 (m, 2H), 2.60 (dd, J = 13.9, 11.4 Hz, 1H), 2.25 – 2.17 (m, 1H), 2.13 – 1.97 (m, 2H), 1.69 – 1.57 (m, 2H, overlapping with H₂O peak). ¹³C NMR (126 MHz, CDCl₃) δ 173.2, 172.7, 153.5, 143.5, 139.0, 132.9, 129.0, 123.5 (2C), 122.9, 117.5, 74.4, 64.3, 63.5, 61.0, 52.3 (2C), 51.5, 46.9, 43.0, 37.2, 33.3, 24.7, 22.2. HRMS (ESI+) m/z calc. for C₂₄H₂₉N₂O₆⁺ [M+H]⁺: 441.2020, found: 441.2026.
(+)-6: To a suspension of (+)-grandilodine B (15.9 mg, 0.035 mmol, 1 equiv) and activated molecular sieves (4Å, 60 mg) in a 1:1 mixture of anhydrous CH₂Cl₂ and THF (3.8 mL) was added Me₃OBF₄ (51.1 mg, 0.35 mmol, 10 equiv). The mixture was stirred at 45 °C for 2 h, and then cooled to 0 °C. Methanol (2.0 mL) and NaBH₄ (25.2 mg, 0.67 mmol, ca. 20 equiv) were added and the resulting mixture was stirred for additional 30 min at 25 °C. The reaction was quenched by addition of saturated aqueous NaHCO₃ (30 mL) and basified until pH ≈ 10 by addition of 1 M aqueous NaOH solution. The aqueous layer was extracted with CH₂Cl₂ (3 × 80 mL) and the combined organic layers were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was redissolved in EtOAc (15 mL), AcOH (150 µL) was added and the resulting solution was stirred for 15 min. The mixture was diluted with water (15 mL) and the layers were separated, the organic layer was washed with water (3 × 7.5 mL). The combined aqueous layers were basified to pH ≈ 10 with 5% aqueous NaOH and saturated with solid NaCl. The aqueous layer was then extracted with CH₂Cl₂ (5 × 20 mL). The combined extracts were washed with brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by alumina TLC eluting with cyclohexane/EtOAc 4:1 to afford (+)-isolapidilectine A as a white solid (10.9 mg, ca. 85 wt% purity, 0.021 mmol, yield = 60%) and (+)-dihydroisolapidilectine A as a white solid (2.7 mg, ca. 90 wt% purity, 0.0055 mmol, yield = 15%).

**M.p.** (CH₂Cl₂/pentane) 128-131 °C (>99% ee). αD⁵⁸⁹ (CHCl₃, c 0.51, 300 K) = +107.5 deg.cm².g⁻¹ (>99% ee). lit.⁷ αD (CHCl₃, c 0.72) = +54 deg.cm².g⁻¹. **UV-Vis** (MeOH) λmax nm = 226 (sh), 253, 283. **CD** (MeOH) λ₅₃ nm (Δε) 233 (-14.7), 257 (+3.7), 287 (+4.6), lit.⁷ **CD** (MeOH) λ₅₃ nm (Δε) 233 (-6.5), 257 (+3.7), 289 (+1.4).
Table S7. Comparison of $^{13}$C NMR data of isolated$^7$ and our synthetic sample of isolapidilectine A.

![Diagram of isolapidilectine A]

| Position | $^{13}$C NMR of isolated$^7$ isolapidilectine A, δ ppm | $^{13}$C NMR of our synthetic isolapidilectine A, δ ppm (Δδppm with isolated)$^7$ |
|----------|--------------------------------------------------------|----------------------------------------------------------------------------------|
| NCO$_2$Me | 153.4                                                  | 153.5 (+0.1)                                                                     |
| NCO$_2$Me | 52.3                                                   | 52.3 (0.0)                                                                         |
| 2         | 74.5                                                   | 74.4 (−0.1)                                                                         |
| 3         | 63.5                                                   | 63.5 (0.0)                                                                         |
| 5         | 49.2                                                   | 46.9 (−2.3)                                                                         |
| 6         | 33.0                                                   | 33.3 (+0.3)                                                                         |
| 7         | 60.8                                                   | 61.0 (+0.2)                                                                         |
| 8         | 132.3                                                  | 132.9 (+0.6)                                                                         |
| 9         | 122.9                                                  | 122.9 (0.0)                                                                         |
| 10        | 123.4                                                  | 123.5 (+0.1)                                                                         |
| 11        | 129.0                                                  | 129.0 (0.0)                                                                         |
| 12        | 117.6                                                  | 117.5 (−0.1)                                                                         |
| 13        | 142.4                                                  | 143.5 (+1.1)                                                                         |
| 14        | 123.6                                                  | 123.5 (−0.1)                                                                         |
| 15        | 138.9                                                  | 139.0 (+0.1)                                                                         |
| 16        | 42.9                                                   | 43.0 (+0.1)                                                                         |
| 17        | 36.9                                                   | 37.2 (+0.3)                                                                         |
| 18        | 24.6                                                   | 24.7 (+0.1)                                                                         |
| 19        | 22.4                                                   | 22.2 (−0.2)                                                                         |
| 20        | 65.4                                                   | 64.3 (−1.1)                                                                         |
| 21        | 171.9                                                  | 172.7 (+0.8)                                                                         |
| 21-OMe    | 52.3                                                   | 52.3 (0.0)                                                                         |
| CO$_2$Me  | 172.6                                                  | 173.2 (+0.6)                                                                         |
| CO$_2$Me  | 51.5                                                   | 51.5 (0.0)                                                                         |
Dihydroisolapidilectine A (epi-grandilodine A)

(±)-Dihydroisolapidilectine A: Was isolated in the course of the reduction of (±)-grandilodine B with Me$_3$OBF$_4$ / NaBH$_4$ (see above) as a colorless gum.

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.58 (br s, 1H), 7.28 – 7.23 (m, 1H, overlapping with CHCl$_3$ peak), 7.09 (d, $J = 7.6$ Hz, 1H), 7.03 (t, $J = 7.5$ Hz, 1H), 3.79 (s, 3H), 3.57 (s, 3H), 3.51 – 3.25 (m, 6H), 3.04 (br s, 2H), 2.89 (dd, $J = 15.7$, 6.0 Hz, 1H), 2.62 (br s, 1H), 2.37 (br s, 1H), 2.24 – 1.93 (m, 4H), 1.80 – 1.53 (m, 5H, overlapping with H$_2$O peak). $^1$H NMR (500 MHz, CDCl$_3$, 323K) $\delta$ 7.59 (d, $J = 8.2$ Hz, 1H), 7.28 – 7.23 (m, 1H, overlapping with CHCl$_3$ peak), 7.09 (d, $J = 7.7$ Hz, 1H), 7.02 (t, $J = 7.5$ Hz, 1H), 3.79 (s, 3H), 3.57 (s, 3H), 3.51 – 3.25 (m, 6H), 3.15 – 2.94 (m, 2H), 2.90 (dd, $J = 15.7$, 6.0 Hz, 1H), 2.62 (br s, 1H), 2.37 (br s, 1H), 2.20 (td, $J = 14.3$, 6.6 Hz, 1H), 2.15 – 1.94 (m, 3H), 1.80 – 1.47 (m, 5H, overlapping with H$_2$O peak). $^{13}$C NMR (126 MHz, CDCl$_3$, 323K) $\delta$ 173.3, 173.2, 153.6, 144.0, 133.2, 128.8, 123.3, 122.6, 117.2, 74.7, 61.6, 58.6, 57.3, 52.1, 51.3, 46.8, 46.2, 43.3, 38.6, 33.9, 25.4, 25.3, 23.3. HRMS (ESI+) $m/z$ calc. for C$_{24}$H$_{31}$N$_2$O$_6$ $^{+}[M+H]^{+}$: 443.2177, found: 443.2198.

(+)-Dihydroisolapidilectine A: Was isolated in the course of the reduction of (+)-grandilodine B with Me$_3$OBF$_4$ / NaBH$_4$ (see above) as a white solid.

M.p. (CH$_2$Cl$_2$/pentane) 130-132 ºC (>99% ee). $\alpha_d^{589}$ (CHCl$_3$, c 0.6, 299 K) = + 136.5 deg.cm$^2$.g$^{-1}$ (>99% ee). UV-Vis (MeOH) $\lambda_{\max}$ nm = 226 (sh), 253, 283, 324 (sh). CD (MeOH) $\lambda_{\text{ext}}$ nm ($\Delta\varepsilon$) 215 (+2.2), 234 (–6.2), 257 (+3.8), 288 (+3.5).
Biosynthetic relationship of pyrroloazocine indole alkaloids

Studies of oxidative decarboxylation of carboxylic acid 24 and diester 25

Oxidative decarboxylation of acid 24 with CAN. Step 1: A 3 mL vial was charged with carboxylic acid (±)-24 (4.4 mg, as it was obtained after oxidation of aldehyde 23, contains ca. 10% of inorganic impurities, 9 µmol) and Na₂CO₃ (5.0 mg, 0.047 mmol, ca. 5 equiv). The vial was placed in the glovebox, where anhydrous, oxygen-free CH₂Cl₂ (0.25 mL) and MeOH (0.25 mL) were added. The reaction mixture was stirred for 5 minutes, after which, a solution of CAN (cerium ammonium nitrate) in MeOH (freshly prepared in the glovebox, 0.09 M, 0.25 mL, 0.0225 mmol, 2.5 equiv) was added dropwise. The orange color of CAN faded and after 5 minutes stirring, the reaction mixture was removed from the glovebox and transferred into a mixture of CH₂Cl₂ (20 mL), brine (5 mL), and NaHCO₃ (5 mL). The organic phase was separated and the aqueous phase was washed with CH₂Cl₂ (15 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was dissolved in CDCl₃ with 1,3,5-tribromobenzene as internal standard (1.0 mL, 0.010 M) and the ¹H NMR spectrum was recorded showing the formation of alkene 10 and MeO-derivative (20Me) in ca. 30% and 32% NMR yields respectively (comparison of NMR spectra see below).

Step 2: The NMR sample was transferred into a 3 mL vial, concentrated, dried under high vacuum, redissolved in CH₂Cl₂ (0.10 mL) and treated with 50% (v/v) aqueous H₂SO₄ (0.10 mL). The purple reaction mixture was stirred for 3 hours, diluted with CH₂Cl₂ (1.0 mL) and water (1.0 mL) and stirred for additional 20 minutes. The layers were then separated, the aqueous layer was extracted with CH₂Cl₂ (3 × 2 mL) and the combined organic layers were washed with NaHCO₃ (3 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was dissolved in CDCl₃.
(0.6 mL) and a solution of 1,3-benzodioxole in CDCl$_3$ (0.10 mL, 0.10 M) was added as internal standard. The $^1$H NMR spectrum was recorded showing the formation of lactone 8 in ca. 62% NMR yield (comparison of NMR spectra see below).

**Attempt of oxidative decarboxylation of diester 25 with CAN.** A 3 mL vial was charged with methyl ester (±)-25 (2.5 mg, 5.5 µmol) and Na$_2$CO$_3$ (2.8 mg, 0.026 mmol, ca. 5 equiv). The vial was placed in the glovebox, where anhydrous, oxygen-free CH$_2$Cl$_2$ (0.15 mL) and MeOH (0.15 mL) were added. The reaction mixture was stirred for 5 minutes, whereupon a solution of CAN (cerium ammonium nitrate) in MeOH (freshly prepared in the glovebox, 0.09 M, 0.15 mL, 0.0135 mmol, 2.5 equiv) was added dropwise. The orange color of CAN slowly faded and after 30 minutes stirring, the reaction mixture was removed from the glovebox and transferred into a mixture of CH$_2$Cl$_2$ (10 mL) and brine (5 mL). The organic phase was separated and the aqueous phase was washed with CH$_2$Cl$_2$ (5 mL × 2). The combined organic layers were dried over Na$_2$SO$_4$, filtered and concentrated. The residue was dissolved in CDCl$_3$ (0.5 mL), a solution of 1,3,5-tribromobenzene in CDCl$_3$ (0.5 mL, 0.010 M) was added as internal standard and the $^1$H NMR spectrum was recorded showing the complete recovery of starting material 25 and no traces of alkene 10, MeO-derivative 20Me or lactone 8 (comparison of NMR spectra see below).
Comparison of $^1$H NMR data (CDCl$_3$, 298K):

**Alkene 10:**

**Lactone 8:**

Reaction mixture after oxidative decarboxylation of acid 24 with CAN (step 1, signals corresponding to 20Me are highlighted with *):

Reaction mixture after oxidative decarboxylation of acid 24 with CAN (step 2):
Diester 25:

Reaction mixture after treatment of diester 25 with CAN:

**CV measurements.** Cyclic voltammograms were obtained using a 5 mL voltammetry cell, NBu₄PF₆ 0.1 M in DMF (*ca.* 2 mL) as supporting electrolyte, Pt electrode (6 mm OD, 3 mm ID) as working electrode, Ag/AgCl (KCl 3 M, 6 mm OD) as reference electrode, and Pt wire as an auxiliary electrode with starting potential of 0.0 V and a range +2.0 V to −0.5 V with scan rate 100 mV/s at 28 ± 2 °C.

Crude carboxylic acid (±)-24 was prepared as mentioned above, and treated with CH₂Cl₂ (15 mL for 10 mg of acid). The suspension was filtered through a PTFE syringe filter (0.45 µm pore size), and the clear solution thus obtained was evaporated and the residue dried under high vacuum, providing acid (±)-24 as a white solid, free from inorganic impurities.

1. CV curves were obtained first for blank electrolyte solution in DMF and then in the presence of Na₂CO₃ (25 mg) and NaHCO₃ (5 mg) after 2 minutes of sonication in ultrasound bath.

2. CV curves for diester (±)-25 (4 mg) were obtained, showing no oxidation process up to 2.0 V range (see the plot below). The same was observed in the presence of Na₂CO₃ (25 mg).

3. CV curves for purified carboxylic acid (±)-24 (4 mg) were obtained showing oxidation process at *ca.* 1.8 V (see the plot below). Na₂CO₃ (25 mg) was added, the voltammetry cell was sonicated for 2 minutes, and the CV curves were measured again, showing an oxidation peak at *ca.* 0.9 V (see the plot below).
CV curves of blank (DMF) and diester 25:

CV curves of blank (DMF), and carboxylic acid 24 (2 mg and 4 mg):

CV curves of blank (DMF), and carboxylic acid 24 in the presence of Na$_2$CO$_3$:

- ca. 1.8V, oxidation
- ca. 0.9V, oxidation
As an example, the previously reported\textsuperscript{30} CV curves for carboxylic acid naproxen and its sodium salt are shown in Figure S3:

Figure S3. Previously reported\textsuperscript{30} CV curves of a) naproxen Na-salt in water; b) naproxen Na-salt in MeOH; c) CV of naproxen in MeOH. Starting potential of 0.0V; sweep rate, 200 mV/s; S.C.E. stands for “saturated calomel electrode”.
Studies of decarboxylation of lactone 8 into cyclopropane 27.

Lactone 8, UV-Vis spectrum:

Methyl \((5aR,5bS,6aS,12aR)-9\text{-oxo-5b,6,8,9,11,12-hexahydro-5H,7H-5a,6a-ethanopyrrolo[1\''',2\'':1',7']azepino[4',5':2,3]cyclopropa[1,2-b]indole-5-carboxylate}\) (27)

\((\pm)-27\): The reaction mixtures from lactone 8 decarboxylation experiments (see below) were combined and purified by preparative silica gel TLC eluting with EtOAc/CH\(_2\)Cl\(_2\) 10:1 affording product \((\pm)-27\) as a white solid (contains 7 wt% of residual grease).

**M.p.** (CDCl\(_3\)) 184-186 °C. \(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.58 (br d, \(J = 6.4\) Hz, 1H), 7.20 − 7.13 (m, 2H), 7.02 (td, \(J = 7.5\) Hz, 0.7 Hz, 1H), 3.96 − 3.85 (m, 4H), 3.67 − 3.59 (m, 1H), 2.82 (dd, \(J = 15.0\) Hz, 7.8 Hz, 1H), 2.73 − 2.63 (m, 1H), 2.53 − 2.35 (m, 4H), 2.25 − 2.16 (m, 2H), 1.89 − 1.76 (m, 4H), 1.06 (dd, \(J = 4.7, 1.4\) Hz, 1H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 174.9, 154.8, 141.8, 137.8, 126.8, 123.0, 122.5, 115.8, 61.2, 53.0, 49.2, 37.3, 35.1, 33.7 (2C, from comparison with 5-OMe derivative),\(^2\) 32.6, 29.9, 27.8, 26.6, 22.0. \textbf{HRMS} (ESI+) \(m/z\) calc. for C\(_{20}\)H\(_{23}\)N\(_2\)O\(_3\)\(^+\) [M+H]\(^+\): 339.1703, found: 339.1692.
Irradiation of lactone 8 with UVc light (254 nm). Lactone (±)-8 (4.0 mg, 0.01 mmol) was placed in a quartz NMR tube, dissolved in CD$_3$OD (0.6 mL) and the tube was sealed with a rubber septum. The initial $^1$H NMR spectrum was recorded. The NMR tube was placed inside a quartz vessel (ca. 3 cm OD) filled with water (to prevent overheating of the reaction mixture), the vessel was placed at the center of a Rayonet RPR-200 photochemical chamber reactor equipped with RPR-2537Å lamps (see Figure S4 for specifications), and it was irradiated for 20 minutes, whereupon a $^1$H NMR spectrum was recorded. The NMR tube containing the reaction mixture was irradiated for additional 25 minutes, and a final $^1$H NMR spectrum was recorded. Our results are summarized in the Table S8.

Figure S4. Specifications of our Rayonet reactor equipped with RPR-2537Å lamps.
Comparison of NMR data (CD$_3$OD, 298K):

Lactone 8 before irradiation:

Isolated cyclopropane 27:

Reaction mixture after 20 minutes of irradiation (254 nm):

Reaction mixture after 45 minutes of irradiation (254 nm):
Irradiation of lactone 8 with UVb light (300 nm). Lactone (±)-8 (4.0 mg, 0.01 mmol) was placed in a quartz NMR tube, dissolved in CD$_3$OD (0.6 mL) and the tube was sealed with a rubber septum. The NMR tube was then placed inside a quartz vessel (ca. 3 cm OD) filled with water (to prevent overheating of the reaction mixture), the vessel was placed at the center of a Rayonet RPR-200 photochemical chamber reactor equipped with RPR-3000Å lamps (see Figure S5 for specifications) and it was irradiated for 20 minutes, whereupon a $^1$H NMR spectrum was recorded. The NMR tube containing the reaction mixture was irradiated for additional 45 minutes and a second $^1$H NMR spectrum was recorded. Irradiation was continued for an additional hour and a final $^1$H NMR spectrum was recorded. Our results are summarized in Table S8.

Figure S5. Specifications of our Rayonet reactor equipped with RPR-3000Å lamps.

Comparison of NMR data (CD$_3$OD, 298K):

Lactone 8:

Cyclopropane 27:
Irradiation of lactone 8 with UVa light (350 nm). Lactone (±)-8 (4.0 mg, 0.01 mmol) was placed in a quartz NMR tube, dissolved in CD$_3$OD (0.6 mL) and the tube was sealed with a rubber septum. The NMR tube was then placed inside a quartz vessel (ca. 3 cm OD) filled with water (to prevent overheating of the reaction mixture), the vessel was placed at the center of a Rayonet RPR-200 photochemical chamber reactor equipped with RPR-3500Å lamps (see Figure S6 for specifications) and it was irradiated for 20 minutes, whereupon a $^1$H NMR spectrum was recorded. The NMR tube containing the reaction mixture was irradiated for additional 2.5 hours, and a final $^1$H NMR spectrum was recorded. Our results are summarized in Table S8.
Comparison of NMR data (CD$_3$OD, 298K):

Lactone 8:

Cyclopropane 27:

Reaction mixture after 20 minutes of irradiation (350 nm):

Reaction mixture after 170 minutes of irradiation (350 nm):
Figure S6. Specifications of our Rayonet reactor equipped with RPR-3500Å lamps.

Table S8. NMR yields in the UV-mediated photodecarboxylation of lactone 8 into cyclopropane 27.

| Entry | UV-light | Time (min) | Unreacted 8, %<sup>a</sup> | Yield of 27, %<sup>b</sup> | Yield<sup>b</sup> of 27 |
|-------|----------|------------|--------------------------|--------------------------|--------------------------|
| 1     | 254 nm   | 20         | 46                       | 14                       | 26                       |
| 2     | 254 nm   | 45         | 16                       | 12                       | 14                       |
| 3     | 300 nm   | 20         | 65                       | 23                       | 66                       |
| 4     | 300 nm   | 65         | 27                       | 34                       | 47                       |
| 5     | 300 nm   | 125        | 13                       | 27                       | 31                       |
| 6     | 350 nm   | 20         | 97                       | –                        | –                        |
| 7     | 350 nm   | 170        | 93                       | –                        | –                        |

<sup>a</sup> Approximate value, integrations are relative to the residual D₂HCOD signal (δ<sub>H</sub> = 3.31 ppm). <sup>b</sup> Based on conversion.

Irradiation of lactone 8 with sunlight. Lactone (±)-8 (6.3 mg, 0.0165 mmol) was dissolved in CH₂Cl₂ (125 µL), and the solution was placed between two rectangular quartz plates (54 mm × 22 mm × 1 mm; cut from 150 mm × 150 mm × 1 mm mechanically polished quartz glass plate, Vidrasa). Evaporation of CH₂Cl₂ gave a thin film of lactone between two quartz plates. The thus obtained thin film (Figure S7) was placed at the center of a Dewar dish (for sunlight concentration, Ø = 14 cm; depth = 9 cm), and kept on the roof of ICIQ in Tarragona, Spain at ambient temperature for 10 sunny days (10 hours each day) during the period from 8.05.2017 to 2.06.2017 (when the sample was not irradiated, it was stored in the laboratory). The quartz plates were
separated and thoroughly washed with CH\textsubscript{2}Cl\textsubscript{2}. The combined washings were concentrated, the residue was dissolved in CDCl\textsubscript{3}, and a solution of 1,3-benzodioxole in CDCl\textsubscript{3} (50 µL, 0.1 M, 0.005 mmol) was added as internal standard. The \textsuperscript{1}H NMR spectrum was measured showing unreacted 8 (ca. 45%) and the cyclopropane product 27 (ca. 6%, 11% based on conversion).

**Comparison of NMR data (CDCl\textsubscript{3}, 298K):**

**Lactone 8:**

![Lactone 8 NMR spectrum](image1)

**Cyclopropane 27:**

![Cyclopropane 27 NMR spectrum](image2)

**Reaction mixture:**

![Reaction mixture NMR spectrum](image3)
Figure S7. Thin films of lactone 8 between rectangular quartz plates in the course of sunlight irradiation experiments.

Attempt of Krapcho-type decarboxylation of lactone 8. An HPLC vial was charged with lactone (±)-8 (3.8 mg, 0.01 mmol), KCl (7.5 mg, 0.1 mmol, 10 equiv) and DMSO (HPLC grade, 50 µL), sealed under argon and heated at 85 °C for 17 hours (reaction conditions are similar to the ones in ref. 31). After this time, the reaction mixture was cooled to room temperature, treated with CH₂Cl₂ (3 mL) and water (3 mL). The organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂ (2 × 3 mL). The combined organic layers were washed with brine (5 mL), and the aqueous phase was washed with CH₂Cl₂ (2 × 5 mL). The combined organic phases were dried over Na₂SO₄, filtered, concentrated and the residue was dissolved in CDCl₃ with 1,3,5-tribromobenzene as internal standard (1.0 mL, 0.010 M). A ¹H NMR spectrum was recorded showing >95% recovery of starting material 8 and no traces of cyclopropane 27.

NMR spectrum of crude reaction mixture (CDCl₃, 298K):

![NMR spectrum image]
Autoxidation of (–)-Lundurine B into (–)-Lundurine A.

An HPLC-sample of (–)-lundurine B\(^2\) (ca. 2 mg) was concentrated and kept under air for 16 months. The sample was then dissolved in CDCl\(_3\) and its \(^1\)H NMR spectrum was recorded showing ca. 50% conversion of lundurine B into lundurine A.

Comparison of NMR data (CDCl\(_3\), 298K):

Lundurine B:

[HPLC diagram]

Lundurine A:

[HPLC diagram]

HPLC-sample of lundurine B after 16 months:
DFT Calculations

General comment
All DFT calculations were carried out using the Gaussian09 suite of programs. The geometries were fully optimized without any constraints with B3LYP functional and ultrafine integration grid. Solvent effects were taken into account by means of the implicit polarizable continuum model (PCM) and water (for A-C and 29, ε=78.3553) or acetonitrile (for radical cyclization, ε=35.688) as a solvent. Standard full electron Pople’s basis set 6-31+G(d,p) was used for all atoms. The stationary points were characterized by vibrational analysis at standard conditions. Transition states were identified by the presence of a single imaginary frequency while intermediates had a full set of real frequencies. The connectivity of the transition states was confirmed by relaxing each transition state towards both the reactant and the product. Additional single-point calculations based on optimized geometries were performed with the same B3LYP functional and a larger basis set 6-311+G(2d,2p). These single-point energies (E) modified by the thermal correction to Gibbs free energy from initial calculations were used to describe the reaction energies (G) throughout the study. For key stationary points, various rotamers of methyl carbamate and methyl ester were routinely calculated and the lowest in energy are presented below and used to calculate ΔG⁰ and ΔG‡ values (see below).

Radical cyclization
DFT calculations for radical cyclization were performed with acetonitrile as a solvent. First, the cyclized benzylic radicals were calculated for both C16-CO₂Me epimers: endo (R2a) and exo (R2b). For each epimer four orientations of the CO₂Me groups (two for the carbamate and two for the ester) were considered. For both R2a and R2b, the rotamers featuring the carbamate OMe-groups and the C16-CO₂Me pointing toward the aromatic ring were found to be slightly lower in energy than others (up to 2 kcal/mol). The same rotameric configuration was favored in the corresponding transition states of the radical cyclization leading to R2a and R2b (up to 1.5 kcal/mol), so it was selected to compute the full reaction profile. The most stable form of open α-CO₂Me radical R1 undergoes rotation around C20-C17 bond with the formation of its rotamer R1a, that in turn bends into conformer Inta via TS₆R1a (14.7
The radical cyclization toward endo-isomer goes from Inta through \( \text{TS}_{\text{R2a}} \) (20.2 kcal/mol). Alternatively, the low-barrier rotation around C16-C17 bond in Inta provides Intb (13.0 kcal/mol), the direct precursor to an exo-isomer R2b. Subsequent radical attack proceeds with a 23.2 kcal/mol barrier, which is 3.0 kcal/mol higher than that of the endo-pathway. This value correlates well with the observed >50:1 endo/exo ratio. Obtained barriers of 20.2 kcal/mol and 23.2 kcal/mol can be converted, through Eyring equation, into rate constants \( k \) of ca. \( 1 \cdot 10^{-2} \) and \( 6 \cdot 10^{-5} \text{ s}^{-1} \) (25 °C), which are, respectively, \( 5 \cdot 10^{5} \) and \( 9 \cdot 10^{7} \) times slower than the experimental \( k \) value for the standard 6-exo-trig cyclization of 6-hepten-1-yl radical (\( 5 \cdot 10^{3} \text{ s}^{-1} \)), ca. 12.4 kcal/mol barrier). A 13.9 kcal/mol barrier (\( k = 4 \cdot 10^{2} \text{ s}^{-1} \)) was calculated for the 6-hepten-1-yl radical cyclization by DFT employing our standard computational method, which is similar to the above-mentioned experimental value.
Cartesian coordinates (Å) and absolute energies (Hartrees) for stationary points:

R1

\begin{align*}
E & = -1339.448882 \\
G & = -1339.065740
\end{align*}

R1a

\begin{align*}
E & = -1339.446852 \\
G & = -1339.063287
\end{align*}
6  -0.979114  1.507350  1.210024
1  -1.265026  2.421773  1.742946
1  -1.340716  0.687480  1.831443
6  0.559171  1.489183  1.166663
6  0.918583  2.309547  0.536709
1  0.912163  1.749273  2.170108
6  1.24447  0.211053  0.745554
6  1.872940  0.447916  0.895956
1  3.050542  0.226941  1.892296
6  3.277821  1.537315  0.081090
1  3.503509  2.491791  0.586016
6  3.771576  1.572714  -0.894036
1  3.528905  1.241037  0.852580
6  5.749699  2.030878  0.667480
1  6.681939  1.641179  0.262273
1  5.467595  2.955791  0.161687
1  5.838254  2.203440  1.741354
6  5.042907  0.284117  0.450827
6  -6.629537  -1.954769  1.046839
1  -6.808301  -2.595971  1.908716
1  -7.489592  -1.304993  0.868806
6  -6.434913  -2.556512  0.156035

TS_R1a

E = -1339.428082
G = -1339.042362
Imag Freq = -27.80 cm⁻¹

7  2.389808  0.616164  0.175124
7  -2.271356  1.408585  -0.970031
8  -2.680451  2.979184  -2.612915
8  2.566519  1.957214  2.061939
6  4.405705  1.324700  0.910888
8  -3.944584  -2.849178  0.746144
8  -1.890731  -3.584856  1.391824
6  2.884175  -0.517363  -0.512229
6  4.155594  -1.101196  -0.548270
1  4.993343  -0.671723  -0.017784
1  4.315590  -2.263014  -1.306812
1  5.295469  -2.728813  -1.352991
1  3.240298  -2.833565  -0.201036
1  3.397711  -3.736379  -2.593676
1  1.975693  -2.250904  -1.964140
1  1.146261  -2.699336  -2.502588
1  1.791021  -1.081880  -1.207993
6  0.624757  -0.258503  -0.961648
6  -0.727825  -0.608466  -1.521775
1  -1.228276  -1.302191  -0.833790

Inta

E = -1339.432384
G = -1339.046429

7  -1.545896  1.327690  0.354814
7  3.129758  -0.083875  0.651256
8  4.946796  0.292653  2.019481
8  -1.188292  3.044346  -1.169518
8  -3.211563  2.753158  -0.198247
8  0.239853  -3.356627  -1.196213
8  -1.498903  -2.141556  -2.019277
6  -2.394475  0.302828  0.837994
6  -3.787352  0.174520  0.848767
1  -4.432476  0.949450  0.460569
6  -4.327061  -0.993924  1.392918
Imag Freq = - 11.51 cm⁻¹

TS

\[ E = -1339.429095 \]
\[ G = -1339.042543 \]

TSint

E = -1339.429095
G = -1339.042543
Imag Freq = -11.51 cm⁻¹
Intb

\[
E = -1339.431070 \\
G = -1339.045068
\]

TS\textsubscript{R2a}

\[
E = -1339.421587 \\
G = -1339.033612
\]

 Imag Freq = -400.41 cm\textsuperscript{-1}
1  -1.383499  -0.481048  2.225056
6  0.096692  -0.208259  0.736471
6  -0.321678  -0.711551  -1.418273
1  -0.068604  -1.749450  -1.299712
1  -1.773428  -0.372914  -1.613071
1  -2.118466  -0.979425  -2.464127
1  -1.887788  0.664972  -1.931817
6  1.938665  -1.863246  0.876215
6  3.813308  -3.275940  1.156549
1  4.863292  -3.132927  1.405461
6  3.326936  -3.916437  1.894091
6  3.708144  -3.705628  0.159087
6  0.661580  0.012205  -2.205482
6  2.914251  0.007327  -2.984882
6  3.764588  -0.671740  -2.931130
6  2.621623  0.168055  -4.025232
6  3.164489  0.965336  -2.523313

R2a

E = -1339.453562
G = -1339.063149

7  -1.590628  0.228728  0.721139
7  3.274982  -0.561917  0.114398
8  5.268288  -1.615862  0.623251
8  -1.477532  2.438907  1.346461
8  -3.446271  1.320455  1.426291
8  -0.398161  0.079873  -2.880249
8  -1.654854  1.754991  -2.043241
8  -2.241851  -1.011245  0.514981
8  -3.570099  -1.383907  0.691324
8  -4.311351  -0.680551  1.039171
8  -3.935701  -2.712258  0.404460
8  -4.970575  -3.010724  0.539795
8  -2.993077  -3.648373  -0.050960
8  -1.304677  -4.666178  -0.266067
8  -1.663533  -3.280079  -0.230095
8  -0.938036  -4.004804  -0.585051
8  -1.265143  -1.949171  0.053238
8  -0.007894  -1.327096  -0.040861
8  1.237784  -1.988838  -0.546391
8  1.426999  -1.712147  -1.592380
8  1.049418  -3.066718  -0.564703
8  2.531096  -1.820326  0.268770
8  3.227305  -2.599276  -0.047757
8  2.326345  -2.004773  1.331210
8  4.612599  -0.590437  0.394469
8  5.152387  0.825623  0.418766
8  5.345598  1.095318  1.464126

6  1.103078  0.887029  -0.116066
6  4.026246  1.647174  -0.206346
6  3.931728  2.655612  0.203850
6  4.194733  1.739141  -1.284101
6  2.726394  0.828322  0.033387
6  2.031340  1.237191  1.346577
6  2.725288  1.139726  2.188539
6  1.785706  2.302559  1.264411
6  0.747328  0.444816  1.648300
6  0.981628  -0.497366  2.148547
6  0.145615  1.027839  2.345348
6  -0.126518  0.123780  0.382362
6  0.250213  1.120947  -0.773306
6  0.025257  2.117634  -0.391878
6  1.747992  1.046850  -1.150698
6  1.998080  2.008681  1.610172
6  1.919253  0.291546  -1.918683
6  -2.126257  1.410550  1.177456
6  -4.081652  2.522848  1.914561
6  -5.126759  2.251425  2.055733
6  -3.634666  2.831247  2.861361
6  -3.990044  3.325540  1.180678
6  -0.611117  0.908211  -2.010518
6  -2.555803  1.633338  -3.169031
6  -3.312771  2.400515  -3.015435
6  -2.016696  1.805971  -4.102555
6  -3.010564  0.640926  -3.182153

TSR2b

E = -1339.417822
G = -1339.028803
Imag Freq = -416.43

7  1.601777  0.160793  0.736994
7  -3.253395  0.698784  0.121149
8  -5.239987  1.557280  0.929555
8  1.569571  -2.029517  1.471132
8  3.478618  -0.816713  1.534803
8  2.272011  1.280834  0.195022
8  3.631057  1.555769  0.024075
8  4.395296  0.863885  0.345628
8  3.980689  2.771165  -0.573771
8  5.032754  3.003987  -0.707515
8  3.006608  3.692703  -1.000967
8  3.315493  4.626251  -1.461162
8  1.654065  3.411295  -0.843060
8  0.901052  4.116106  -1.181069
8  1.276480  2.194964  -0.238342
8  -0.005846  1.637676  0.048040
8  -1.290127  2.304648  -0.349413
8  -1.451250  2.175518  -1.429409

S105
R2b

$$E = -1339.445560$$
$$G = -1339.053828$$

Hept1

$$E = -274.584904$$
$$G = -274.442325$$
|   |      |      |      |      |      |      |      |      |      |      |      |      |      |
|---|------|------|------|------|------|------|------|------|------|------|------|------|------|
|   |      |      |      |      |      |      |      |      |      |      |      |      |      |
|   | 1.238822 | 1.214817 | -0.931306 | 1.219849 | -0.396706 | 0.003423 | 1.337590 | -1.071594 | 0.863006 | 1.200642 | -1.033417 | -0.890889 | -0.111351 | 0.354809 | 0.125203 |
|   | -0.230242 | 1.033635 | -0.730337 | -0.091180 | 0.988294 | 1.023252 | -1.331065 | -0.584628 | 0.194885 | -1.189361 | -1.274027 | 1.040680 | -1.377461 | -1.200817 | -0.712193 |
|   | -2.630939 | 0.151474 | 0.375243 | -3.667434 | 0.115241 | -0.470438 | -2.707449 | 0.765757 | 1.274588 | -4.578267 | 0.676689 | -0.280431 | -3.638604 | -0.480729 | -1.380785 |
|   | 1.623543 | 0.297327 | -0.572752 | 1       | 2.263878 | 1.328814 | 1.001937 | 1       | 2.940842 | 1.544750 | 1       | 2.344390 | 0.600102 | 1       | 0.425892 |
|   | 1       | 0.864824 | 2.154086 | 1       | 0.956002 | 0.600102 | 1       | 1.337590 | 1.544750 | 1       | 1.212235 | 1.194315 | 1       | 1.298541 | 1.274588 |
|   | 1       | 0.765757 | 1.274588 | -2.681920 | 1.028894 | -0.713308 | -1.847630 | -0.593397 | 1.200881 | -2.519615 | -1.213103 | -0.295111 | 1.536857 | -1.986315 | 0.652953 |
|   | 0.573648 | 2.687227 | -0.043271 | -1.133058 | 0.731095 | -1.465043 | -0.82086 | -1.559669 | -0.114296 | -0.926574 | -1.087227 | 0.480142 | 1.732653 | -0.169368 | -0.402135 |
|   | -2.861920 | 1.028894 | -0.713308 | -1.847630 | -0.593397 | 1.200881 | -2.519615 | -1.213103 | -0.295111 | 1.536857 | -1.986315 | 0.652953 | 0.773365 | -0.626109 | 1.463976 |
|   | -0.296073 | -1.722235 | -1.194315 | -0.651120 | -2.545227 | 0.310385 | -1.164113 | 1.764648 | 1.460167 | 1.842867 | -0.496394 | -1.438333 | 2.344390 | 0.956002 | -0.016857 |
|   | 2.940842 | 1.544750 | -0.708880 | 2.263878 | 1.328814 | 1.001937 | 1       | 2.263878 | 1.328814 | 1.001937 | 1       | 2.263878 | 1.328814 | 1       | 2.263878 | 1.328814 | 1.001937 |
|   | 1.826621 | -0.257903 | -0.283405 | 1.445723 | 1.138065 | 0.236882 | 0.976655 | 1.593061 | -0.235523 | 1.001937 | 2.154086 | -0.283405 | 0.908044 | -1.377609 | 0.225530 | -0.392120 | 2.409516 | 0.289107 |
|   | 1.480355 | 1.142649 | 1.335459 | 2.172871 | 1.859655 | -0.087162 | 1.813559 | -0.248165 | -1.383110 | 2.859162 | -0.481984 | 0.012915 | 1.068725 | -2.202675 | 0.096163 | -0.634801 | -1.232739 | -1.300493 |
|   | 0.956696 | -1.411567 | 1.323988 | 1.298541 | -2.340792 | -0.126208 | -1.04129 | 1.549186 | -1.304231 | 1.097571 | 0.138425 | 1.423717 | -2.568905 | 0.272372 | -0.079339 | -3.183296 | 0.987130 | 0.460668 | -2.926929 | -0.048182 | -1.055513 |

**Hept2**

\[ E = -274.576160 \]

\[ G = -274.433690 \]

**Hept3**

\[ E = -274.610279 \]

\[ G = -274.459754 \]

**TS\textsubscript{Hept}**

\[ E = -274.567720 \]

\[ G = -274.420208 \]

Imag. Freq. = -401.86
**N-acyl ammonium cations 29**

*N-acyl ammonium cations 29* might be generated from kopsijasminilam- or pauciflorine-type compounds by protonation / dehydration or directly from kopsidasine- and lahadinine-type intermediates by oxidative C20-C21 fragmentation.37

DFT calculations of cations 29 were performed with water as a solvent. For both *endo*- and *exo*-CO₂Me epimers four orientations of the CO₂Me (two for the carbamate and two for the ester) were considered, and the most stable isomers for each are presented below. The *endo*-29 isomer features the ester CO₂Me group in an equatorial position of a boat-like cyclohexane ring, and it is 3.8 kcal/mol more stable than the *exo*-29 isomer featuring an axial CO₂Me. Both *endo*-29 and *exo*-29 cations have short C20–N distances (1.620 and 1.616 Å respectively), non-planar nitrogen atoms and elongated amide C21–N bonds (1.518 Å for *exo*-29 and 1.524 Å for *endo*-29), which are similar to N-alkylated twisted amides (1.535-1.554 Å).38 For *exo*-29, an additional open-form of N-acyl ammonium cation could be located (*exo*-29open), which was found to be 6.3 kcal/mol less stable than the corresponding cyclized form *exo*-29a.
Cartesian coordinates (Å) and absolute energies (Hartrees) for stationary points:

**endo-29**

![Image of endo-29 molecule]

Numbers in parenthesis are $\Delta G^0$ values in kcal/mol, relative to endo-29 (0.0)

**exo-29**

![Image of exo-29 molecule]

exo-29 and exo-29a are opposite rotamers at C25

exo-29a and exo-29open have same orientation at C25

E = -1377.355066
G = -1376.954598

| 6   | 1.989742 | -3.898955 | 1.264085 |
| 1   | 2.021187 | -4.877722 | 1.731256 |
| 6   | 3.147573 | -3.341060 | 0.712863 |
| 1   | 4.082696 | -3.891416 | 0.754395 |
| 6   | 3.138605 | -2.082361 | 0.102850 |
| 1   | 4.045804 | -1.674233 | -0.314186 |
| 6   | 1.928651 | -1.377606 | 0.049869 |
| 6   | 2.506867 | 0.767471  | -1.127257 |
| 8   | 2.155854 | 1.793674  | -1.698280 |
| 6   | 3.789510 | 0.389048  | -1.006145 |
| 8   | 4.767148 | 1.259119  | -1.623171 |
| 1   | 5.725966 | 0.777727  | -1.438221 |
| 8   | 4.578099 | 1.341099  | -2.694688 |
| 6   | 4.737914 | 2.247118  | -1.160841 |
| 6   | 0.504623 | 2.227684  | 1.067521  |
| 8   | 1.288011 | 1.668278  | 1.813785  |
| 8   | 0.179106 | 3.524783  | 1.168923  |
| 6   | 0.802939 | 4.274980  | 2.240634  |
| 6   | 3.999974 | 5.282296  | 2.155402  |
| 1   | 5.44570 | 3.835803  | 3.205771  |
| 1   | 1.886572 | 4.280327  | 2.110622  |
| 8   | -1.775873 | -2.646082 | -0.798729 |
| 1   | 0.094355 | 2.219495  | -0.959768 |
| 1   | -2.452586 | -0.441745 | -2.598722 |
| 1   | -5.942165 | 0.050777  | -0.837752 |
| 1   | -4.301309 | 2.029600  | -1.307913 |

**exo-29**

![Image of exo-29 molecule]

E = -1377.350409
G = -1376.948491
\[ G = \begin{bmatrix} 
E = \begin{bmatrix} 
-1377.348768 
\end{bmatrix} 
\end{bmatrix} 
\]
|   | E     | G     |
|---|-------|-------|
| 1 | 0.404467 | 0.213263 | 2.462569 |
| 6 | 0.468500 | 2.612477 | 0.925285 |
| 8 | 1.285135 | 2.987853 | 1.748221 |
| 8 | -0.020751 | 3.384556 | -0.052037 |
| 6 | 0.556322 | 4.703149 | -0.189753 |
| 1 | 1.622444 | 4.615872 | -0.405165 |
| 1 | 0.029159 | 0.556322 | -0.189753 |
| 1 | -2.199074 | 1.173515 | 1.957292 |
| 6 | 0.556322 | 4.703149 | -0.189753 |
| 1 | 1.622444 | 4.615872 | -0.405165 |
| 1 | 0.029159 | 0.556322 | -0.189753 |
| 1 | -2.199074 | 1.173515 | 1.957292 |
| 6 | 0.556322 | 4.703149 | -0.189753 |
| 1 | 1.622444 | 4.615872 | -0.405165 |
| 1 | 0.029159 | 0.556322 | -0.189753 |
| 1 | -2.199074 | 1.173515 | 1.957292 |

**exo-29open**

\[ E = -1377.335897 \]
\[ G = -1376.936937 \]
Open and cyclized forms of carbocations A-C

DFT calculations of cations A-C and A’-C’ were performed with water as a solvent. For all cations two different orientations of the carbamate NCO\textsubscript2Me were considered. For cations A-C two opposite orientations of ester CO\textsubscript2Me were calculated, and for cations A’-C’ two orientations of the OMe on the charged furan ring were taken into account. The most stable rotamers are presented below.

\[
\Delta G^0 = 5.3 \text{ kcal/mol}
\]

\[
\Delta G^0 = -5.6 \text{ kcal/mol}
\]

\[
\Delta G^0 = -6.9 \text{ kcal/mol}
\]
Cartesian coordinates (Å) and absolute energies (Hartrees) for stationary points

**A**

![Cartesian coordinates diagram for A]

E = -1339.291801
G = -1338.898853

**A’**

![Cartesian coordinates diagram for A']

E = -1339.28690
G = -1338.89047
\[ C' = \begin{array}{c}
\text{E} = -1265.223346 \\
\text{G} = -1264.802110
\end{array}
\]

\[
\begin{array}{cccc}
7 & 1.783425 & 0.781348 & -0.130969 \\
7 & -2.326439 & -0.793076 & -0.153512 \\
8 & -0.229715 & -1.524710 & 0.910655 \\
8 & 3.360130 & 2.394393 & 0.343680 \\
8 & 1.167348 & 2.934042 & 0.101868 \\
6 & 2.641892 & -0.344106 & -0.122241 \\
6 & 4.033954 & -0.392989 & 0.008986 \\
6 & 4.612730 & 0.510612 & 0.130904 \\
6 & 4.650550 & -1.649387 & -0.024530 \\
1 & 5.730908 & -1.702214 & 0.072848 \\
1 & 3.912992 & -2.821115 & -0.183771 \\
1 & 4.417543 & -3.788530 & -0.206578 \\
6 & 2.521618 & -2.764188 & -0.314906 \\
6 & 1.940168 & -3.673349 & -0.433716 \\
6 & 1.897550 & -1.520406 & -0.281036 \\
6 & 0.437757 & -1.201005 & -0.360390 \\
6 & -0.382145 & -1.960294 & -1.402498 \\
1 & -0.054759 & -3.002997 & -1.408764 \\
1 & -0.207060 & -1.576575 & -2.406679 \\
6 & -1.871282 & -1.964585 & -1.014474 \\
6 & -2.520630 & -1.920748 & -1.889559 \\
6 & -2.087385 & -2.845685 & -0.410294 \\
6 & -3.757491 & -1.122277 & 0.317117 \\
1 & -3.716327 & -1.475005 & 1.340097
\end{array}
\]
Crystallographic data

General comment
Two machines were used for single crystal diffraction analysis, Rigaku and Bruker.

Bruker device:
Full sphere single crystal X-ray diffraction data were collected at 100K on a Bruker Kappa APEX II DUO diffractometer equipped with an APEX II 4K CCD area detector, a Microsource with Mo Ka radiation and an Oxford Cryostream 700 low temperature device. Was used for racemic compounds 1-4, 7, 10, 23 and 24.

Programs:
- Data collection: APEX2
- Data reduction: SAINT
- Absorption correction: SADABS, TWINABS
- Structure solution: SIR2014, SHELXT
- Structure refinement: SHELXL

Rigaku device:
Full sphere single crystal X-ray diffraction data were collected at 100K on a Rigaku XtaLAB P200 Mo Ka rotating anode equipped with a Pilatus 200K detector and an Oxford Cryostream 700 low temperature device. Was used for (±)-5, (±)-20, (+)-12, (+)-2, (–)-25S2 and [(bpy)2RuBr2]Br.

Programs:
- Data collection, data reduction and absorption correction: CrysAlis PRO
- Structure solution: SIR2014, SHELXT
- Structure refinement: SHELXL

The obtained crystallographic information files (cif) were routinely examined with IUCr checkcif test, that showed no A- or B-level alerts for all structures with the only exception of [(bpy)2RuBr2]Br, for which two B-level alerts were rationalized (see below). More detailed information on the devices and programs used can be found in the corresponding cif files, that were deposited at the Cambridge Crystallographic Data Centre (CCDC numbers 1567826-1567839).
Crystallographic data for compound (±)-10, CCDC 1567829

The carbon atom C9 is disordered in two orientations (ratio 85:15).

| Identification code       | mo_KMS_G677_0m       |
|---------------------------|----------------------|
| Empirical formula         | C22 H24 N2 O5        |
| Formula weight            | 396.43               |
| Temperature               | 100(2) K             |
| Wavelength                | 0.71073 Å            |
| Crystal system            | Monoclinic           |
| Space group               | P2(1)/n              |
| Unit cell dimensions      | a = 8.7314(3) Å, b = 18.8210(7) Å, c = 11.6512(4) Å |
|                           | a = 90°, b = 102.3671(11)°, g = 90° |
| Volume                    | 1870.25(11) Å³       |
| Z                         | 4                    |
| Density (calculated)      | 1.408 Mg/m³          |
| Absorption coefficient    | 0.100 mm⁻¹           |
| F(000)                    | 840                  |
| Crystal size              | 0.51 x 0.35 x 0.10 mm³ |
| Theta range for data collection | 2.091 to 30.415°   |
| Index ranges              | -7<=h<=11,-26<=k<=26,-16<=l<=9 |
| Reflections collected     | 19546                |
| Independent reflections   | 5440[R(int) = 0.0303]|
| Completeness to theta =30.415° | 95.8%               |
| Absorption correction     | Empirical            |
| Max. and min. transmission| 0.990 and 0.955      |
| Refinement method         | Full-matrix least-squares on F² |
| Data / restraints / parameters | 5440/ 22/ 273         |
| Goodness-of-fit on F²     | 1.041                |
| Final R indices [I>2sigma(I)] | R1 = 0.0437, wR2 = 0.1072 |
| R indices (all data)      | R1 = 0.0571, wR2 = 0.1156 |
| Largest diff. peak and hole | 0.406 and -0.256 e.Å⁻³ |
Crystallographic data for compound (±)-grandilodine C (2), CCDC 1567827

![Crystal structure diagram](image)

| Identification code          | mo_KMSG688_05   |
|-----------------------------|---------------|
| Empirical formula           | C21 H20 N2 O5 |
| Formula weight              | 380.39        |
| Temperature                 | 100(2) K      |
| Wavelength                  | 0.71073 Å     |
| Crystal system              | Triclinic     |
| Space group                 | P-1           |
| Unit cell dimensions        |               |
| a = 7.2219(15) Å           | a = 84.894(4)°|
| b = 9.354(2) Å             | b = 85.225(4)°|
| c = 13.497(3) Å            | g = 68.613(4)°|
| Volume                      | 844.3(3) Å³   |
| Z                           | 2             |
| Density (calculated)        | 1.496 Mg/m³   |
| Absorption coefficient      | 0.108 mm⁻¹    |
| F(000)                      | 400           |
| Crystal size                | 0.40 x 0.10 x 0.05 mm³ |
| Theta range for data collection | 2.343 to 33.517° |
| Index ranges                | -10≤h≤10, -14≤k≤14, 0≤l≤20 |
| Reflections collected       | 10379         |
| Independent reflections     | 10379 [R(int) =?] |
| Completeness to theta =33.517° | 91.5%       |
| Absorption correction       | Empirical     |
| Max. and min. transmission  | 0.995 and 0.58|
| Refinement method           | Full-matrix least-squares on F² |
| Data / restraints / parameters | 10379/ 0/ 255 |
| Goodness-of-fit on F²       | 1.029         |
| Final R indices [I>2sigma(I)] | R1 = 0.0590, wR2 = 0.1550 |
| R indices (all data)        | R1 = 0.0751, wR2 = 0.1679 |
| Largest diff. peak and hole | 0.611 and -0.407 e.Å⁻³ |
This compound crystallized as a dichloromethane solvate. The main molecule is disordered in two orientations with a ratio of 80:20. The dichloromethane molecule is disordered in four orientations (Ratio 60:25:10:5).

| Property                        | Value                          |
|---------------------------------|--------------------------------|
| Identification code             | mo_KMS_G840_0m                 |
| Empirical formula               | C22 H24 Cl2 N2 O4              |
| Formula weight                  | 451.33                         |
| Temperature                     | 100(2) K                       |
| Wavelength                      | 0.71073 Å                      |
| Crystal system                  | Triclinic                      |
| Space group                     | P-1                            |
| Unit cell dimensions            | a = 7.3663(5) Å, b = 11.4058(8) Å, c = 12.1822(8) Å |
| Volume                          | 1005.43(12) Å³                 |
| Z                               | 2                              |
| Density (calculated)            | 1.491 Mg/m³                    |
| Absorption coefficient          | 0.357 mm⁻¹                     |
| F(000)                          | 472                            |
| Crystal size                    | 0.25 x 0.20 x 0.06 mm³         |
| Theta range for data collection | 2.382 to 32.513°.              |
| Index ranges                    | -10<=h<=10, -10<=k<=16, -16<=l<=18 |
| Reflections collected           | 13998                          |
| Independent reflections         | 6458[R(int) = 0.0175]           |
| Completeness to theta =32.513°  | 88.8%                          |
| Absorption correction           | Multi-scan                     |
| Max. and min. transmission      | 0.979 and 0.926                |
| Refinement method               | Full-matrix least-squares on F² |
| Data / restraints / parameters  | 6458/ 1.469/ 594               |
| Goodness-of-fit on F²           | 1.031                          |
| Final R indices [I>2sigma(I)]   | R1 = 0.0704, wR2 = 0.2224      |
| R indices (all data)            | R1 = 0.0786, wR2 = 0.2340      |
| Largest diff. peak and hole     | 0.404 and -1.638 e.Å⁻³         |
Crystallographic data for compound (±)-20, CCDC 1567826

This compound crystallized as a chloroform solvate. The measured sample is formed by at least two crystals with a ratio of 73:27. The collected data were processed with TWINABS taking into account overlapping reflections.

| Identification code                        | KMS-G791-OHtwin1_hklf5 |
|--------------------------------------------|-------------------------|
| Empirical formula                          | C23 H27 Cl3 N2 O6       |
| Formula weight                             | 533.81                  |
| Temperature                                | 100(2) K                |
| Wavelength                                 | 0.71073 Å               |
| Crystal system                             | Monoclinic              |
| Space group                                | P2(1)                   |
| Unit cell dimensions                       | a = 11.2210(8) Å        |
|                                            | b = 7.2383(5) Å         |
|                                            | c = 29.137(3) Å         |
|                                            | a = 90°.                |
|                                            | b = 96.855(7)°.         |
|                                            | g = 90°.                |
| Volume                                     | 2349.6(3) Å³            |
| Z                                          | 4                       |
| Density (calculated)                       | 1.509 Mg/m³             |
| Absorption coefficient                     | 0.434 mm⁻¹              |
| F(000)                                     | 1112                    |
| Crystal size                               | 0.15 x 0.06 x 0.03 mm³  |
| Theta range for data collection            | 2.817 to 28.345°        |
| Index ranges                               | -14<=h<=14,-9<=k<=9,-38<=l<=36 |
| Reflections collected                      | 5915                    |
| Independent reflections                    | 5915[R(int) =?]         |
| Completeness to theta =28.345°             | 90.9%                   |
| Absorption correction                      | Empirical               |
| Max. and min. transmission                 | 0.987 and 0.759         |
| Refinement method                          | Full-matrix least-squares on F² |
| Data / restraints / parameters             | 5915/ 0/ 311            |
| Goodness-of-fit on F²                      | 1.066                   |
| Final R indices [I>2sigma(I)]              | R1 = 0.0623, wR2 = 0.1451|
| R indices (all data)                       | R1 = 0.0984, wR2 = 0.1645|
| Largest diff. peak and hole                | 0.470 and -0.525 e.Å⁻³  |
Crystallographic data for compound (±)-23, CCDC 1567834

Identification code: mo_KMS_G747_0m
Empirical formula: C23 H26 N2 O6
Formula weight: 426.46
Temperature: 100(2) K
Wavelength: 0.71073 Å
Crystal system: Monoclinic
Space group: P2(1)/n
Unit cell dimensions:
- a = 12.0865(5) Å
- b = 13.2673(5) Å
- c = 13.6282(5) Å
- α = 90°
- β = 115.2341(8)°
- γ = 90°
Volume: 1976.81(13) Å³
Z: 4
Density (calculated): 1.433 Mg/m³
Absorption coefficient: 0.104 mm⁻¹
F(000): 904
Crystal size: 0.30 x 0.10 x 0.10 mm³
Theta range for data collection: 1.891 to 35.067°
Index ranges: -19 <= h <= 19, -21 <= k <= 21, -15 <= l <= 21
Reflections collected: 43441
Independent reflections: 8043 [R(int) = 0.0239]
Completeness to theta = 35.067°: 92.0%
Absorption correction: Empirical
Max. and min. transmission: 0.990 and 0.946
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 8043 / 0 / 282
Goodness-of-fit on F²: 1.051
Final R indices [I>2sigma(I)]: R1 = 0.0404, wR2 = 0.1133
R indices (all data): R1 = 0.0457, wR2 = 0.1178
Largest diff. peak and hole: 0.552 and -0.273 e.Å⁻³
Crystallographic data for compound (±)-24, CCDC 1567830

Identification code: mo_KMS_G850c_0m
Empirical formula: C23 H26 N2 O7
Formula weight: 442.46
Temperature: 100(2) K
Wavelength: 0.71073 Å
Crystal system: Triclinic
Space group: P-1
Unit cell dimensions:
- a = 8.161(6) Å
- b = 10.276(7) Å
- c = 13.734(8) Å
θ = 102.45(2)°
- g = 97.861(19)°
- k = 112.29(2)°
Volume: 1009.8(12) Å³
Z: 2
Density (calculated): 1.455 Mg/m³
Absorption coefficient: 0.108 mm⁻¹
F(000): 468
Crystal size: 0.12 x 0.06 x 0.03 mm³
Theta range for data collection: 1.565 to 34.930°.
Index ranges: -10 ≤ h ≤ 12, -15 ≤ k ≤ 13, -18 ≤ l ≤ 18
Reflections collected: 14595
Independent reflections: 6447 [R(int) = 0.0673]
Completeness to theta = 34.930°: 73.0%
Absorption correction: Empirical
Max. and min. transmission: 0.997 and 0.637
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 6447/0/292
Goodness-of-fit on F²: 1.074
Final R indices [I>2σ(I)]: R1 = 0.0669, wR2 = 0.1652
R indices (all data): R1 = 0.1000, wR2 = 0.1872
Largest diff. peak and hole: 0.402 and -0.352 e Å⁻³
Crystallographic data for (±)-lapidilectam (4), CCDC 1567833

Table 1. Crystal data and structure refinement for KMS-G838_Aba2.

| Property                                      | Value                                      |
|-----------------------------------------------|--------------------------------------------|
| Identification code                           | KMS-G838_Aba2                              |
| Empirical formula                             | C24 H26 N2 O7                              |
| Formula weight                                | 454.47                                     |
| Temperature                                   | 100(2) K                                   |
| Wavelength                                    | 0.71073 Å                                  |
| Crystal system                                | Orthorhombic                               |
| Space group                                   | Aba2                                       |
| Unit cell dimensions                          | a = 13.6713(13) Å                         |
|                                              | b = 37.374(4) Å                            |
|                                              | c = 8.2094(7) Å                            |
|                                              | a = 90°.                                   |
|                                              | b = 90°.                                   |
|                                              | g = 90°.                                   |
| Volume                                        | 4194.6(7) Å                                |
| Z                                             | 8                                          |
| Density (calculated)                          | 1.439 Mg/m³                                 |
| Absorption coefficient                        | 0.107 mm⁻¹                                 |
| F(000)                                        | 1920                                       |
| Crystal size                                  | 0.15 x 0.15 x 0.06 mm³                     |
| Theta range for data collection               | 1.090 to 25.438°.                          |
| Index ranges                                  | -16<=h<=16,-44<=k<=44,-9<=l<=9              |
| Reflections collected                         | 28913                                      |
| Independent reflections                       | 3605[R(int) = 0.0693]                      |
| Completeness to theta =25.438°                | 99.7%                                      |
| Absorption correction                         | Empirical                                  |
| Max. and min. transmission                    | 0.994 and 0.765                            |
| Refinement method                             | Full-matrix least-squares on F²            |
| Data / restraints / parameters                | 3605/ 1/ 301                               |
| Goodness-of-fit on F²                         | 1.077                                      |
| Final R indices [I>2sigma(I)]                 | R1 = 0.0396, wR2 = 0.0954                  |
| R indices (all data)                          | R1 = 0.0461, wR2 = 0.1002                  |
| Flack parameter                               | x =0.3(6)                                  |
| Largest diff. peak and hole                   | 0.303 and -0.211 e.Å⁻³                    |

Table 2. Bond lengths [Å] and angles [°] for KMS-G838_Aba2.

| Bond                          | Length [Å] |
|-------------------------------|------------|
| N1-C19                        | 1.374(4)   |
| N1-C1                         | 1.425(4)   |
| C19-N1-C1                    | 124.4(3)   |
| C19-C1-C1                    | 126.9(3)   |
| C1-C1-C1-C19                 | 119.7(3)   |

(±)-Lapidilectam (4)
Crystallographic data for (±)-lapidilectine A (3), CCDC 1567835

Identification code: mo_KMS_G866_0m
Empirical formula: C24 H28 N2 O6
Formula weight: 440.48
Temperature: 100(2) K
Wavelength: 0.71073 Å
Crystal system: Triclinic
Space group: P-1
Unit cell dimensions:
- a = 7.9625(13) Å
- b = 10.842(2) Å
- c = 12.972(3) Å
- α = 74.540(6)°
- β = 74.559(6)°
- γ = 87.974(6)°
Volume: 1039.6(3) Å³
Z: 2
Density (calculated): 1.407 Mg/m³
Absorption coefficient: 0.102 mm⁻¹
F(000): 468
Crystal size: 0.15 x 0.12 x 0.04 mm³
Theta range for data collection: 1.950 to 29.781°
Index ranges: -10 ≤ h ≤ 9, -15 ≤ k ≤ 15, -17 ≤ l ≤ 17
Reflections collected: 12823
Independent reflections: 5186[R(int) = 0.0328]
Completeness to theta = 29.781°: 87.2%
Absorption correction: Empirical
Max. and min. transmission: 0.996 and 0.95
Refinement method: Full-matrix least-squares on F²
Data / restraints / parameters: 5186 / 0 / 292
Goodness-of-fit on F²: 1.023
Final R indices [I>2σ(I)]: R1 = 0.0444, wR2 = 0.1003
R indices (all data): R1 = 0.0628, wR2 = 0.1113
Largest diff. peak and hole: 0.300 and -0.281 eÅ⁻³

Table 1. Crystal data and structure refinement for mo_KMS_G866_0m.

| Parameter                          | Value                        |
|------------------------------------|------------------------------|
| Identification code                | mo_KMS_G866_0m               |
| Empirical formula                  | C24 H28 N2 O6                |
| Formula weight                     | 440.48                       |
| Temperature                        | 100(2) K                     |
| Wavelength                         | 0.71073 Å                    |
| Crystal system                     | Triclinic                    |
| Space group                        | P-1                          |
| Unit cell dimensions               |                               |
|  a                                 | 7.9625(13) Å                 |
|  b                                 | 10.842(2) Å                  |
|  c                                 | 12.972(3) Å                  |
|  α                                 | 74.540(6)°                   |
|  β                                 | 74.559(6)°                   |
|  γ                                 | 87.974(6)°                   |
| Volume                             | 1039.6(3) Å                  |
| Z                                  | 2                            |
| Density (calculated)               | 1.407 Mg/m³                  |
| Absorption coefficient             | 0.102 mm⁻¹                   |
| F(000)                             | 468                          |
| Crystal size                       | 0.15 x 0.12 x 0.04 mm³       |
| Theta range for data collection    | 1.950 to 29.781°             |
| Index ranges                       | -10 ≤ h ≤ 9, -15 ≤ k ≤ 15, -17 ≤ l ≤ 17 |
| Reflections collected              | 12823                        |
| Independent reflections            | 5186[R(int) = 0.0328]        |
| Completeness to theta = 29.781°    | 87.2%                        |
| Absorption correction              | Empirical                    |
| Max. and min. transmission         | 0.996 and 0.95               |
| Refinement method                  | Full-matrix least-squares on F² |
| Data / restraints / parameters      | 5186 / 0 / 292               |
| Goodness-of-fit on F²              | 1.023                        |
| Final R indices [I>2σ(I)]          | R1 = 0.0444, wR2 = 0.1003    |
| R indices (all data)               | R1 = 0.0628, wR2 = 0.1113    |
| Largest diff. peak and hole        | 0.300 and -0.281 eÅ⁻³        |

(±)-Lapidilectine A (3)
Crystallographic data for (±)-grandilodine A (5), CCDC 1567837

Identification code: KMSG862LT
Empirical formula: C$_{24}$H$_{30}$N$_2$O$_6$
Formula weight: 442.50
Temperature: 100(2) K
Wavelength: 0.71073 Å
Crystal system: Monoclinic
Space group: P2(1)/n
Unit cell dimensions:
- $a = 10.9813(3)$ Å
- $b = 8.0063(2)$ Å
- $c = 24.4059(7)$ Å

Volume: 2119.73(11) Å$^3$
Z: 4
Density (calculated): 1.387 Mg/m$^3$
Absorption coefficient: 0.100 mm$^{-1}$
F(000): 944
Crystal size: 0.20 x 0.08 x 0.04 mm$^3$
Theta range for data collection: 2.681 to 37.357°
Index ranges: -18 <= h <= 18, -13 <= k <= 13, -41 <= l <= 40
Reflections collected: 50822
Independent reflections: 10582 [R(int) = 0.0260]
Completeness to theta = 37.357°: 95.8%
Absorption correction: Empirical
Max. and min. transmission: 0.996 and 0.766
Refinement method: Full-matrix least-squares on F$^2$
Data / restraints / parameters: 10582/ 0/ 292
Goodness-of-fit on F$^2$: 1.037
Final R indices [I>2sigma(I)]: $R_1 = 0.0366$, $wR_2 = 0.1007$
R indices (all data): $R_1 = 0.0460$, $wR_2 = 0.1056$
Largest diff. peak and hole: 0.586 and -0.232 e.Å$^{-3}$
Crystallographic data for (±)-grandilodine B (7), CCDC 1567832

Identification code: mo_KMS_G865_0m

| Property                        | Value                                      |
|--------------------------------|--------------------------------------------|
| Empirical formula              | C24 H26 N2 O7                              |
| Formula weight                 | 454.47                                     |
| Temperature                    | 100(2) K                                   |
| Wavelength                     | 0.71073 Å                                  |
| Crystal system                 | Triclinic                                  |
| Space group                    | P-1                                        |
| Unit cell dimensions           | a = 6.8694(3) Å, b = 10.0331(4) Å, c = 15.3665(7) Å |
| Volume                         | 1046.28(8) Å³                             |
| Z                              | 2                                          |
| Density (calculated)           | 1.443 Mg/m³                                |
| Absorption coefficient         | 0.107 mm⁻¹                                 |
| F(000)                         | 480                                        |
| Crystal size                   | 0.40 x 0.15 x 0.03 mm³                     |
| Theta range for data collection| 2.275 to 35.126°.                         |
| Index ranges                   | -10<=h<=8, -16<=k<=16, -24<=l<=24           |
| Reflections collected          | 23783                                      |
| Independent reflections        | 8308|R(int) = 0.0361|                          |
| Completeness to theta =35.126° | 89.3%                                      |
| Absorption correction          | Empirical                                  |
| Max. and min. transmission     | 0.997 and 0.79                             |
| Refinement method              | Full-matrix least-squares on F²            |
| Data / restraints / parameters | 8308/ 0/ 301                               |
| Goodness-of-fit on F²          | 1.046                                      |
| Final R indices [I>2sigma(I)]  | R1 = 0.0417, wR2 = 0.1146                  |
| R indices (all data)           | R1 = 0.0485, wR2 = 0.1202                  |
| Largest diff. peak and hole    | 0.669 and -0.282 e.Å⁻³                     |
Crystallographic data for [(bpy)$_2$RuBr$_2$]Br, CCDC 1567828

The asymmetric unit contains a half molecule of a metal complex and a half of a bromide anion. Both show $C_i$-symmetry. The measured sample is formed by at least four crystals with a ratio of 43:21:20:16. The collected data were processed with TWINABS$^\text{40}$ taking into account overlapping reflections. The structure has no A-level alerts in the checkcif test, and B-level alerts were commented.

Table 1. Crystal data and structure refinement for FM22_twin1_hklf5.

| Identification code          | FM22_twin1_hklf5 |
|----------------------------|------------------|
| Empirical formula           | C$_{20}$H$_{16}$Br$_3$Cl$_0$N$_4$Ru |
| Formula weight              | 653.17           |
| Temperature                 | 100(2) K         |
| Wavelength                  | 0.71073 Å        |
| Crystal system              | Triclinic        |
| Space group                 | $P-1$            |
| Unit cell dimensions        | $a = 7.2777(3) \text{Å}$ $a^* = 77.686(4)^\circ$, $b = 8.2938(4) \text{Å}$ $b^* = 83.158(3)^\circ$, $c = 9.0157(3) \text{Å}$ $g^* = 69.733(4)^\circ$. |
| Volume                      | 498.14(4) Å$^3$ |
| Z                           | 1                |
| Density (calculated)        | 2.177 Mg/m$^3$   |
| Absorption coefficient      | 6.817 mm$^{-1}$  |
| F(000)                      | 313              |
| Crystal size                | 0.20 x 0.20 x 0.15 mm$^3$ |
| Theta range for data collection | 2.315 to 32.737$^\circ$. |
| Index ranges                | $-10 \leq h \leq 11, -12 \leq k \leq 12, -13 \leq l \leq 13$ |
| Reflections collected       | 10035            |
| Independent reflections     | 10035[R(int) =$?$] |
| Completeness to theta       | 96.3%            |
| Absorption correction       | Empirical        |
| Max. and min. transmission  | 0.727 and 0.559  |
| Refinement method           | Full-matrix least-squares on $F^2$ |
| Data / restraints / parameters | 10035/ 0/ 133  |
| Goodness-of-fit on $F^2$    | 1.019            |
| Final R indices [$I>2\sigma(I)$] | $R1 = 0.0603$, $wR2 = 0.1769$ |
| R indices (all data)        | $R1 = 0.0734$, $wR2 = 0.2071$ |
| Largest diff. peak and hole | 4.464 and -0.794 e Å$^{-3}$ |
Crystallographic data for (+)-12, CCDC 1567836

The sample crystallized in the orthorhombic chiral space group $P_2_12_12_1$ and the absolute structure could be determined reliably with a Flack value based on Parsons’ quotients of 0.06(7) (the Flack parameter value for the correct absolute structure determination should be 0; the inverted structure would give 1). The determination was performed on high resolution data collected with Molybdenum-radiation using the previously described methodology. The absolute configuration based on the absolute structure of this compound was determined to be $S$ (C13).

| Identification code | FM-KMS691LT |
|---------------------|--------------|
| Empirical formula   | C20 H20 N2 O4 |
| Formula weight      | 352.38       |
| Temperature         | 100(2) K     |
| Wavelength          | 0.71073 Å    |
| Crystal system      | Orthorhombic |
| Space group         | $P_2_12_12_1$ |
| Unit cell dimensions| $a = 9.64769(5)$Å, $a = 90^\circ$.
|                     | $b = 11.43518(7)$Å, $b = 90^\circ$.
|                     | $c = 15.03401(9)$Å, $g = 90^\circ$.
| Volume              | 1658.598(17) Å³ |
| Z                   | 4            |
| Density (calculated)| 1.411 Mg/m³  |
| Absorption coefficient | 0.099 mm⁻¹ |
| F(000)              | 744          |
| Crystal size        | 0.30 x 0.20 x 0.15 mm³ |
| Theta range for data collection | 2.508 to 70.147°. |
| Index ranges        | 25<h<25, 25<k<29, 39<l<38 |
| Reflections collected | 163294       |
| Completeness to theta | 70.147°      |
| Absorption correction | Multi-scan   |
| Max. and min. transmission | 0.985 and 0.758 |
| Refinement method   | Full-matrix least-squares on F² |
| Data / restraints / parameters | 28685/ 0/ 236 |
| Goodness-of-fit on F² | 1.044        |
| Final R indices [I>2sigma(I)] | R1 = 0.0258, wR2 = 0.0691 |
| R indices (all data) | R1 = 0.0294, wR2 = 0.0705 |
| Flack parameter     | x =0.06(7)   |
| Largest diff. peak and hole | 0.482 and -0.295 e.Å⁻³ |

Table 1. Crystal data and structure refinement for FM-KMS691LT.
Crystallographic data for (+)-grandilodine C (2), CCDC 1567838

This compound crystallized as a monohydrate. The methoxy group (O2, C20) is disordered in two orientations (ratio 90:10). The sample crystallized in the orthorhombic chiral space group $P_{2_1}2_12_1$ and the absolute structure could be determined reliably with a Flack value based on Parsons’ quotients of 0.04(10) (the Flack parameter value for the correct absolute structure determination should be 0; the inverted structure would give 1). The determination was performed on high resolution data collected with Molybdenum-radiation using the previously described methodology. The absolute configuration based on the absolute structure of this compound was determined to be $R$ (C7), $R$ (C13), $R$ (C16), $R$ (C17).

### Table 1. Crystal data and structure refinement for KMS-G-875.

| Property                        | Value               |
|---------------------------------|---------------------|
| Identification code             | KMS-G-875           |
| Empirical formula               | C$_{21}$ H$_{20.18}$ N$_2$ O$_{5.09}$ |
| Formula weight                  | 382.01              |
| Temperature                     | 100(2) K            |
| Wavelength                      | 0.71073 Å           |
| Crystal system                  | Orthorhombic        |
| Space group                     | $P_{2_1}2_12_1$     |
| Unit cell dimensions            |                     |
| $a$                             | 7.84898(8) Å        |
| $b$                             | 14.47011(18) Å      |
| $c$                             | 15.52093(16) Å      |
| Volume                          | 1762.80(3) Å$^3$    |
| $Z$                             | 4                   |
| Density (calculated)            | 1.439 Mg/m$^3$      |
| Absorption coefficient          | 0.103 mm$^{-1}$     |
| F(000)                          | 804                 |
| Crystal size                    | 0.20 x 0.20 x 0.03 mm$^3$ |
| Theta range for data collection | 2.625 to 42.008°    |
| Index ranges                    | -14<=h<=14, -27<=k<=27, -27<=l<=29 |
| Reflections collected           | 41770               |
| Independent reflections         | 12010| $R(int) = 0.0231$ |
| Completeness to theta =42.008°  | 98.5%               |
| Absorption correction           | Empirical           |
| Max. and min. transmission      | 0.997 and 0.767     |
| Refinement method               | Full-matrix least-squares on F$^2$ |
| Data / restraints / parameters  | 12010/ 35/ 283      |
| Goodness-of-fit on F$^2$        | 1.071               |
| Final R indices [|$>2\sigma(I)$] | R1 = 0.0296, wR2 = 0.0798 |
| R indices (all data)            | R1 = 0.0330, wR2 = 0.0815 |
| Flack parameter                 | x =0.04(10)         |
| Largest diff. peak and hole     | 0.415 and -0.214 e.Å$^3$ |
The asymmetric unit contains two molecules of **25S2**, one of them disordered over two positions with an occupation ratio of 75:25 while the other one has a disordered fragment with a 90:10 occupation ratio, and a half molecule of acetone, which is disordered over three positions with a 25:15:10 occupation ratio. The absolute structure could be determined reliably with a Flack value based on Parsons' quotients of –0.013(8) (the Flack parameter value for the correct absolute structure determination should be 0; the inverted structure would give 1). The absolute configuration of both molecules of **25S2** in the asymmetric unit is the same in all disordered positions and was determined to be R (C4), R (C7), R (C8), S (C12).
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$^1$H NMR (500 MHz, CDCl$_3$) spectrum of (S)-1-cyclohexylprop-2-en-1-ol

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of (S)-1-cyclohexylprop-2-en-1-ol
$^{1}$H NMR (500 MHz, CDCl$_3$) spectrum of (S)-1-cyclohexylallyl-3-phenylpropanoate

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of (S)-1-cyclohexylallyl-3-phenylpropanoate
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of (S,R)-Mosher ester product of (S)-1-cyclohexylprop-2-en-1-ol and (S)-Mosher acid chloride

$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of (S,R)-Mosher ester product of (S)-1-cyclohexylprop-2-en-1-ol and (S)-Mosher acid chloride
$^1$H NMR (376 MHz, CDCl$_3$) spectrum of (S,R)-Mosher ester product of (S)-1-cyclohexylprop-2-en-1-ol and (S)-Mosher acid chloride

$^1$F NMR (376 MHz, CDCl$_3$) spectrum of (S,R)-Mosher ester product of (S)-1-cyclohexylprop-2-en-1-ol and (S)-Mosher acid chloride

$^1$H NMR (400 MHz, CDCl$_3$) spectrum of (S,S)-Mosher ester product of (S)-1-cyclohexylprop-2-en-1-ol and (R)-Mosher acid chloride
$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of (S,S)-Mosher ester product of (S)-1-cyclohexylprop-2-en-1-ol and (R)-Mosher acid chloride

$^{19}$F NMR (376 MHz, CDCl$_3$) spectrum of (S,S)-Mosher ester product of (S)-1-cyclohexylprop-2-en-1-ol and (R)-Mosher acid chloride
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 13b

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 13b
^1H NMR (400 MHz, CDCl₃) spectrum of compound 14a (with EtOAc)

^13C NMR (101 MHz, CDCl₃) spectrum of compound 14a (with EtOAc)
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 14a (without EtOAc)

$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of compound 14a (without EtOAc)
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 14b

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 14b
\(^1\)H NMR (300 MHz, CDCl\(_3\)) spectrum of compound 15a

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) spectrum of compound 15a
$^{1}$H NMR (500 MHz, CDCl$_3$) spectrum of compound 15b

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 15b
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 16a

$^1$C NMR (101 MHz, CDCl$_3$) spectrum of compound 16a
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 17a

$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of compound 17a
\(^1\)H NMR (500 MHz, CDCl\(_3\)) spectrum of compound 16b

\[^{13}\text{C} \text{NMR} \ (126 \text{ MHz, CDCl}\text{)}\) spectrum of compound 16b
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 17b

$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of compound 17b
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 12

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 12
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound S1

$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of compound S1
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 18

$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of compound 18
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 19

$^{13}$C NMR (101 MHz, CDCl$_3$) spectrum of compound 19
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of compound 11H

$^1$C NMR (101 MHz, CDCl$_3$) spectrum of compound 11H
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 10
1H Experiment 328 K

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 10
13C[1H] Experiment 328 K
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 8
1H Experiment 328 K

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 8
13C[1H] Experiment 328 K
UV-Vis spectrum of compound 8
**$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 8S1**

$^1$H Experiment 328 K

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0

**$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 8S1**

$^{13}$C[1H] Experiment 328 K

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 8S2

1H Experiment 328 K

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 8S2

13C[1H] Experiment 328 K
The first image shows an NMR spectrum of grandilodine C (2) in CDCl₃ at 500 MHz. The spectrum contains various peaks at different chemical shifts, indicating the presence of different proton environments in the molecule.

The second image also shows an NMR spectrum of grandilodine C (2) in CDCl₃ at 500 MHz. However, this spectrum is taken at 328 K, which is lower than room temperature. The peaks are shifted due to the lower temperature, indicating changes in the chemical shifts of the protons. The spectra are used to assign the proton chemical shifts and to understand the molecular structure and dynamics of grandilodine C (2).
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of grandilodine C (2)

CD spectrum of (+)-grandilodine C (2)

UV-Vis spectrum of grandilodine C (2)
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of lapidilectine B (1)

1H Experiment

$^1$H NMR (500 MHz, CDCl$_3$) spectrum of lapidilectine B (1)

1H Experiment 323 K

Silicone grease
$^1$H NMR (400 MHz, CDCl$_3$) spectrum of lapidilectine B (1), without EtOAc

$^1$C NMR (126 MHz, CDCl$_3$) spectrum of lapidilectine B (1)

13$^C$(1H) Experiment 323 K
CD spectrum of (+)-lapidiletine B (1)

UV-Vis spectrum of lapidiletine B (1)
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of dihydrolapidilectine B (26)

1H Experiment 298 K

$^1$H NMR (500 MHz, CDCl$_3$) spectrum of dihydrolapidilectine B (26)

1H Experiment 323 K
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of dihydrolapidilectine B (26)

CD spectrum of (+)-dihydrolapidilectine B (26)

UV-Vis spectrum of dihydrolapidilectine B (26)
\[ ^{1}H \text{ NMR (500 MHz, CD}_{2}\text{Cl}_{2}) \text{ spectrum of compound 20} \]

\[ ^{13}C \text{ NMR (126 MHz, CD}_{2}\text{Cl}_{2}) \text{ spectrum of compound 20} \]
$^{1}H$ NMR (500 MHz, CDCl$_3$) spectrum of compound 9

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 9
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 23

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 23
$^1$H NMR (500 MHz, CD$_2$Cl$_2$) spectrum of compound 21

$^{13}$C NMR (126 MHz, CD$_2$Cl$_2$) spectrum of compound 21
$^1$H NMR (400 MHz, CD$_2$Cl$_2$) spectrum of compound 24

$^1$C NMR (126 MHz, CD$_2$Cl$_2$) spectrum of compound 24
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 25

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 25
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 25S1

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 25S1
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 25S2
1H Experiment 323 K

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 25S2
13C[1H] Experiment 323 K
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of lapidilectam (4)

1H Experiment 298 K

$^1$H NMR (500 MHz, CDCl$_3$) spectrum of lapidilectam (4)

1H Experiment 323 K
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of lapidilectam (4)

13C[1H] Experiment 323 K

CD spectrum of (−)-lapidilectam (4)

UV-Vis spectrum of lapidilectam (4)
1H NMR (500 MHz, CDCl₃) spectrum of lapidilectine A (3), with residual solvents

1H Experiment 298 K

1H NMR (500 MHz, CDCl₃) spectrum of lapidilectine A (3), with residual solvents

1H Experiment 323 K
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of lapidilectine A (3), with residual solvents

13C[1H] Experiment 323 K

$^1$H NMR (500 MHz, CDCl$_3$) spectrum of lapidilectine A (3), without residual solvents

1H Experiment 298 K
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of lapidilectine A (3), without residual solvents

1H Experiment 323 K

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of lapidilectine A (3), without residual solvents

$^{13}$C{1H} Experiment 323 K
CD spectrum of (-)-lapidilectine A (3)

UV-Vis spectrum of lapidilectine A (3)
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of grandilodine A (5)

1H Experiment 298 K

$^1$H NMR (500 MHz, CDCl$_3$) spectrum of grandilodine A (5)

1H Experiment 323 K
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of grandilodine A (5)

CD spectrum of (−)-grandilodine A (5)

UV-Vis spectrum of grandilodine A (5)
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of grandilodine B (7)

![NMR spectrum of grandilodine B](image)

$^1$C NMR (126 MHz, CDCl$_3$) spectrum of grandilodine B (7)

![NMR spectrum of grandilodine B](image)
CD spectrum of (+)-grandilodine B (7)

UV-Vis spectrum of grandilodine B (7)
^1H NMR (500 MHz, CDCl₃) spectrum of isolapidilectine A (6), additionally purified (less grease and H₂O)

MeO₂C₂N

CO₂Me

CDCl₃

H grease

CDCl₃

H grease
$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of isolapidilectine A (6)

CD spectrum of (+)-isolapidilectine A (6)

UV-Vis spectrum of isolapidilectine A (6)
\(^1\)H NMR (500 MHz, CDCl\(_3\)) spectrum of dihydroisolapidilectine A

1H Experiment 298 K

1H NMR (500 MHz, CDCl\(_3\)) spectrum of dihydroisolapidilectine A

1H Experiment 323 K
$^{13}$C NMR (126 MHz, CDCl₃) spectrum of dihydroisolapidilectine A

13C[1H] Experiment 323 K

CD spectrum of (+)-dihydroisolapidilectine A

UV-Vis spectrum of dihydroisolapidilectine A
$^1$H NMR (500 MHz, CDCl$_3$) spectrum of compound 27

$^{13}$C NMR (126 MHz, CDCl$_3$) spectrum of compound 27