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Construction of the tetracyclic core of (±)-cycloclavine and 4-amino Uhle's ketone†

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A rapid construction of the tetracyclic core (±)-**2** of (±)-cycloclavine (**1**) was accomplished in seven steps and 24% overall yield from commercially available aldehyde **7**. Key features include a domino Friedel–Crafts/nitro-Michael reaction to construct the C ring and an intramolecular ammonolysis of a diester to close the D ring. In addition, a versatile 4-amino Uhle's ketone (±)-**3** was afforded rapidly in five steps and 43% overall yield.

Introduction

Cycloclavine belongs to the clavine subset of ergot alkaloids, isolated from the seeds of the African morning glory shrub *Ipomea hildebrandtii* by Hofmann in 1969.[1] The unique structural features and biological properties of cycloclavine[2] have stimulated the synthesis[3] and biosynthesis[4] efforts of several research groups. To date, three total syntheses of cycloclavine (**1**) have been reported. In 2008, the first total synthesis of (±)-cycloclavine (**1**) was accomplished by Szántay *et al.*[5] in eight steps and 1% overall yield from a brominated Uhle's ketone derivative. Subsequently, Wipf *et al.* achieved the total synthesis[6] in fourteen steps and 1.2% overall yield, using an intramolecular Diels–Alder cycloaddition reaction[7] in 2011. They then went on to complete the first enantioselective total synthesis of the unnatural enantiomer (−)-cycloclavine[8] in eight steps and 7.1% overall yield in 2017. Brewer *et al.*[9] also achieved the total synthesis of (±)-cycloclavine (**1**) in fourteen steps and 1% overall yield using a ring fragmentation/intramolecular azomethine ylide 1,3-dipolar cycloaddition route in 2014. In addition, two formal synthesis approaches to (±)-cycloclavine (**1**) have been disclosed.[10] Our research group has had continued interest in the synthesis of cycloclavine. Recently, the first asymmetric formal synthesis of (+)-cycloclavine[11] was accomplished by our group in eleven steps and 19.7% overall yield through a tandem asymmetrical Barbier-type nucleophilic addition.[12] However, exploration of new versatile strategies to this unique pyrrolidine-fused structure still remains of significant interest. Inspired by cascade reactions and step-economical synthesis strategies,[13] herein, we present a direct and concise route to assemble the tetracyclic core (±)-**2** of (±)-cycloclavine (**1**), using a (±)-1,1′-binaphthyl-2,2′-diyl hydrogen-phosphate [(±)-PA]-catalyzed domino Friedel–Crafts/nitro-Michael reaction and an intramolecular ammonolysis of a diester as key steps to construct the C/D rings. Additionally, the synthesis of a versatile Boc-protected 4-amino Uhle's ketone (±)-**3**,[3a,7c,14] a framework shared by most ergot alkaloids[15] (Fig. 1), was attempted using the same phosphoric acid catalysis strategy.

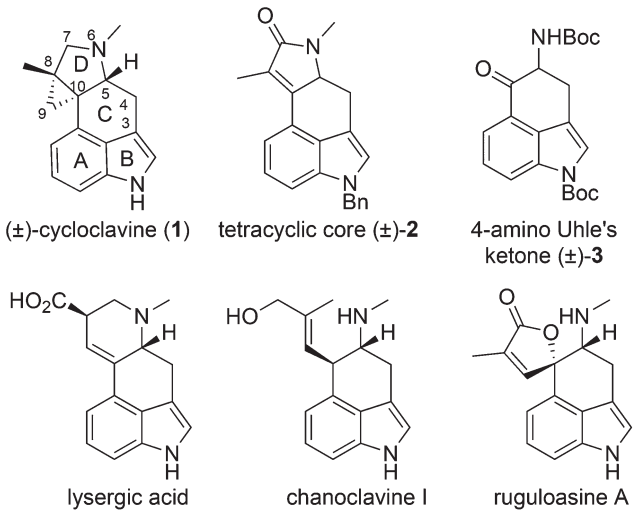

Fig. 1 Structures of (±)-cycloclavine (**1**), tetracyclic core (±)-**2**, 4-amino Uhle's ketone (±)-**3** and other ergot alkaloids.

Results and discussion

Our initial retrosynthesis analysis of tetracyclic core (±)-**2** is outlined in Scheme 1. We envisioned that tetracyclic core (±)-**2**

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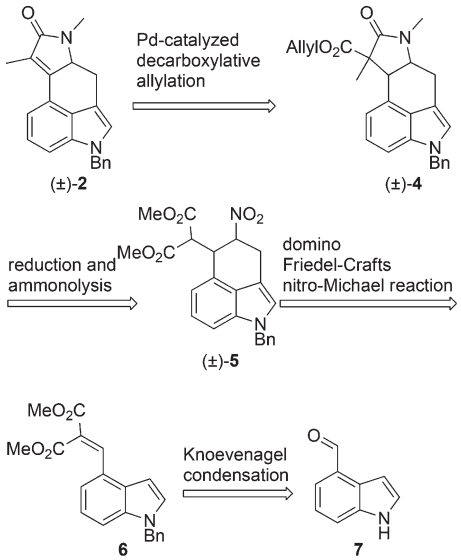
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of compounds **6**, (±)-**5**, (±)-**9**, (±)-**10**, (±)-**4**, (±)-**11**, (±)-**12**, (±)-**13**, (±)-**2**, (±)-**14**, (±)-**15**, (±)-**16** and (±)-**3**. CCDC 1569863 for (±)-**5**. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ob03067c

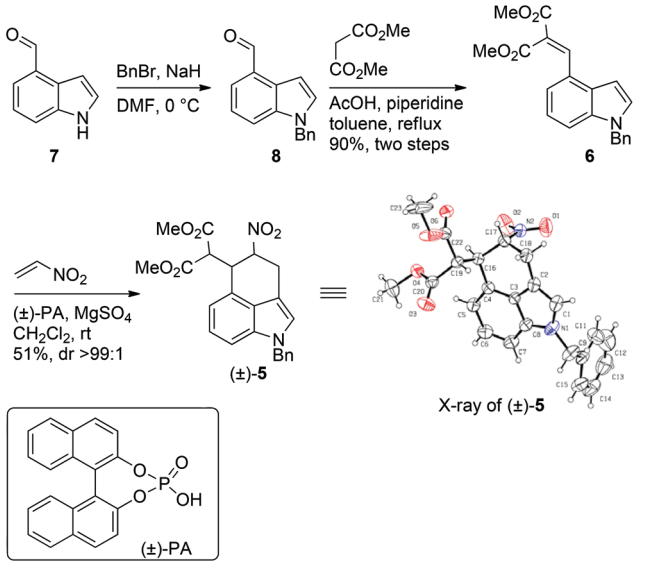


Scheme 1 Initial retrosynthesis analysis of tetracyclic core (±)-**2**.

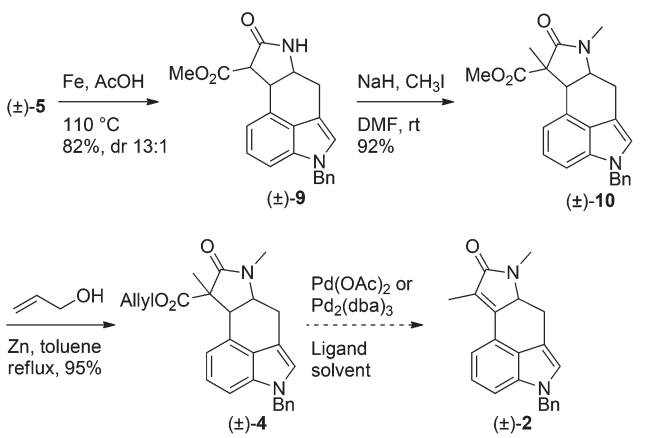
could be reached by palladium-catalyzed decarboxylative allylation[16] from allyl ester (±)-**4**, which could be constructed by nitro reduction followed by intramolecular ammonolysis of tricyclic diester (±)-**5**. The key tricyclic diester (±)-**5** could be obtained through a (±)-PA catalyzed domino Friedel–Crafts/nitro-Michael reaction between nitroethylene and α,β-unsaturated diester **6**, which could be prepared from the commercially available aldehyde **7** by a Knoevenagel condensation reaction.[17]

As shown in Scheme 2, the synthesis of tricyclic diester (±)-**5** started from commercially available aldehyde **7**. The nitrogen atom of aldehyde **7** was protected with a benzyl group under sodium hydride (NaH) as a base in *N*,*N*-dimethylformamide (DMF), followed by a Knoevenagel condensation with dimethyl malonate in toluene under reflux to afford α,β-unsaturated diester **6** in 90% overall yield. Next, a [(±)-PA]-catalyzed domino Friedel–Crafts/nitro-Michael addition reaction between diester **6** and nitroethylene was used to deliver the key tricyclic diester (±)-**5** in one pot on a gram scale with a moderate yield. The relative configuration of tricyclic diester (±)-**5** was shown to be *trans* by X-ray crystallographic analysis. The diastereomeric ratio of (±)-**5** is more than 99 : 1 which was determined by comparing the characteristic peak area of the crude ^{1}H NMR spectrum and precise spectrum.

Subsequent treatment of diester (±)-**5** with iron powder in glacial acetic acid at 110 °C afforded the *cis*, *trans*-tetracyclic lactam (±)-**9** in 82% yield (Scheme 3). The diastereomeric ratio of (±)-**9** is 13 : 1. With tetracyclic lactam (±)-**9** in hand, further derivatization and protection steps were carried out. Methylation of tetracyclic lactam (±)-**9** with excess iodomethane readily afforded the *cis*, *trans*-lactam (±)-**10** in 93% yield. The relative configuration of (±)-**10** was determined by using larger coupling constants and NOESY spectra. Zinc-promoted ester alcoholysis afforded the *cis*, *trans*-allyl ester (±)-**4** as a single product in 95% yield.[18] The relative configuration of (±)-**4** is the same as (±)-**10** because of the unvaried chiral centers as well as coupling constants in the transformation. Palladium-catalyzed decarboxylative allylation was then attempted to form the desired α,β-unsaturated tetracyclic core (±)-**2** of (±)-cycloclavine (**1**).[16] A variety of reaction conditions were screened, including catalysts [$Pd(OAc)_2$ and $Pd_2(dba)_3$], ligands (dppe and PPh_3), solvents (CH_3CN, toluene and THF) and temperature (room temperature to reflux). Firstly, the decarboxylative allylation did not take place in the presence of $Pd(OAc)_2$ without any additional ligands at room temperature. Subsequently, we attempted this reaction by raising the temperature or adding phosphorus ligands in different solvents; however, all attempts to install the α,β-unsaturated fragment by palladium-catalyzed reactions were unsuccessful and the starting material was recycled or decomposed. We speculated



Scheme 2 Synthesis of tricyclic diester (±)-**5** by domino Friedel–Crafts/nitro-Michael reaction.

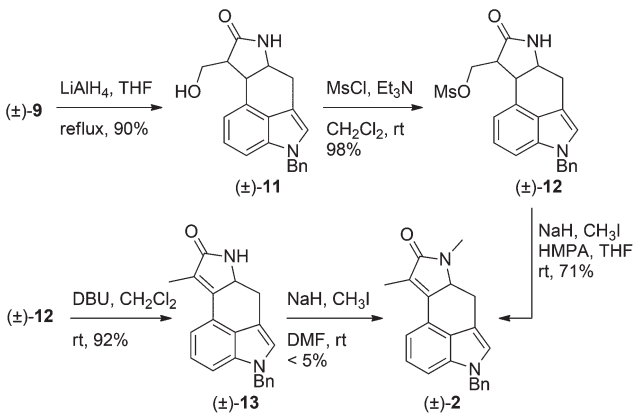


Scheme 3 Attempted synthesis of tetracyclic core (±)-**2** by palladium-catalyzed decarboxylative allylation.

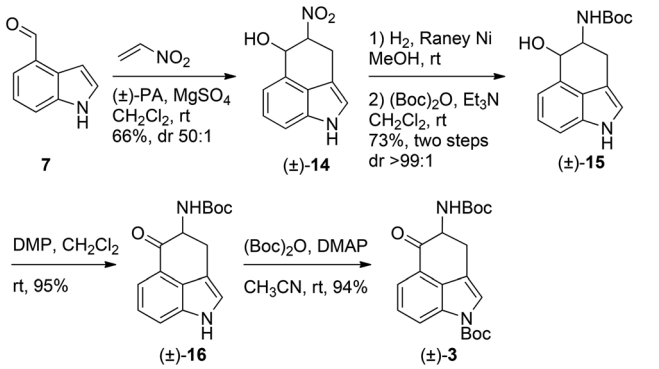
that the unsuccessful decarboxylative allylation reaction was not only due to the steric hindrance of the β-tertiary hydrogen but also because the hydrogen atom in allyl ester (±)-**4** was in a sub-optimal conformation for elimination. Therefore, this strategy of forming tetracyclic core (±)-**2** by palladium-catalyzed decarboxylative allylation of allyl ester (±)-**4** was not successful.

Because the desired tetracyclic core (±)-**2** could not be obtained by palladium-catalyzed decarboxylative allylation, we modified the route to tetracyclic core (±)-**2** through elimination of methanesulfonate (Scheme 4). Thus, selective reduction of the carboxylic ester of tetracyclic lactam (±)-**9** with $LiAlH_4$ afforded β-hydroxyl lactam (±)-**11** in 90% yield. Esterification with methanesulfonyl chloride (MsCl) using triethylamine (Et_3N) as a base in dichloromethane (CH_2Cl_2) afforded methanesulfonate (±)-**12** in excellent yield. So far, we could conjecture the relative configuration of these compounds by that of (±)-**5** and the invariable key chiral centers from (±)-**5**. The next step was the key elimination of methanesulfonate and isomerization of the double bond to construct the α,β-unsaturated lactam (±)-**13**. Treatment of methanesulfonate (±)-**12** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in CH_2Cl_2 afforded the unstable α,β-unsaturated lactam (±)-**13** directly in 92% yield in one pot. We did not observe the exocyclic double bond product, presumably owing to rapid elimination to form a more stable intra-annular α,β-unsaturated amide under the DBU conditions. However, methylation of α,β-unsaturated lactam (±)-**13** with sufficient iodomethane in the presence of NaH only afforded a small amount of tetracyclic core (±)-**2**, along with other unidentified side products. Unfortunately, it was difficult to isolate an analytically pure sample of tetracyclic core (±)-**2** by silica gel column chromatography, while it was detectable by HRMS.

As both elimination and isomerization reactions proceeded well under basic conditions, we treated methanesulfonate (±)-**12** directly with NaH and iodomethane in THF, along with a catalytic amount of HMPA. To our delight, the desired tetracyclic core (±)-**2** was obtained *via* a cascade methylation/elimination/isomerization reaction in 71% yield in one pot. Thus, the tetracyclic core (±)-**2** was achieved in 7 steps and 24% overall yield.



Scheme 4 Completed synthesis of tetracyclic core (±)-**2**.



Scheme 5 Synthesis of Boc-protected 4-amino Uhle's ketone (±)-**3**.

Having completed the synthesis of tetracyclic core (±)-**2**, we next attempted to assemble 4-amino Uhle's ketone (±)-**3**. The rapid synthesis of the 4-amino Uhle's ketone skeleton would be beneficial for expanding the construction of related ergot alkaloids. A similar strategy was used to prepare 4-amino Uhle's ketone (±)-**3** *via* (±)-PA catalysis between aldehyde **7** and nitroethylene (Scheme 5). The synthesis started from commercially available aldehyde **7**. Treatment with nitroethylene under (±)-PA catalysis afforded tricyclic alcohol (±)-**14** in 66% yield in one pot on a gram scale. The diastereomeric ratio of (±)-**14** is 50 : 1. Subsequent reduction of the nitro group of tricyclic alcohol (±)-**14** to an amino group with RANEY® Ni under a hydrogen atmosphere and protection with di-*tert*-butyl dicarbonate gave β-hydroxyl carbamate (±)-**15** in 73% yield (two steps). The compound (±)-**14** was obtained in accordance with the similar (±)-PA catalysis strategy to compound (±)-**5**, so the chiral centers were not changed and the relative configuration of (±)-**14** and (±)-**15** is *trans*. The diastereomeric ratio of (±)-**15** is more than 99 : 1. To complete the synthesis, β-hydroxyl carbamate (±)-**15** was subjected to a high-yielding two-step functionalization comprising oxidation with Dess–Martin periodinane (DMP) followed by protection with di-*tert*-butyl dicarbonate (95% and 94% yields, respectively). The Boc-protected 4-amino Uhle's ketone (±)-**3** was successfully prepared from aldehyde **7** in five steps and 43% overall yield.

Conclusions

In conclusion, a concise route for the rapid construction of the tetracyclic core (±)-**2** of (±)-cycloclavine (**1**) has been accomplished in 7 steps and 24% overall yield. The synthesis features include a [(±)-PA]-catalyzed domino Friedel–Crafts/nitro-Michael reaction and an intramolecular ammonolysis of a diester to construct the C/D rings of tetracyclic core (±)-**2**, respectively. In addition, a Boc-protected versatile 4-amino Uhle's ketone (±)-**3** was afforded effectively in five steps and 43% overall yield using a similar strategy, which is a key skeleton in a wide variety of ergot alkaloids, providing a valuable protocol for synthetic chemists.

Experimental

General procedures

All commercially available materials were used without further purification unless otherwise noted. Solvents were dealt with according to the standard methods. Petroleum ether (PE) used had a boiling range of 60–90 °C. Air- or moisture-sensitive reactions were carried out under an argon inert atmosphere. Flash chromatography was performed on silica gel (200–300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on Bruker AM 400 MHz and 100 MHz spectrometers, respectively. Chemical shifts (δ) are reported in parts per million, and coupling constants (J) are reported in Hz. The splitting abbreviations were used as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad, dd = doublet of doublets, and q = quartet. (±)-PA = (±)-1,1′-binaphthyl-2,2′-diyl hydrogen-phosphate. Reactions were monitored by thin layer chromatography (TLC). IR spectra were recorded on a Bruker Tensor 27 IR spectrometer. High-resolution mass spectrometry (HRMS) was performed by using a Bruker Daltonics APEX II 47e FT-ICR. Melting points were determined *via* microscope apparatus and are uncorrected.

Dimethyl 2-((1-benzyl-1*H*-indol-4-yl)methylene)malonate (6)

To a solution of aldehyde **7** (6.2 g, 1.0 equiv., 42.7 mmol) in anhydrous DMF (100 mL) was added 60% NaH (2.6 g, 1.5 equiv., 64.0 mmol). The mixture was stirred at 0 °C for 10 min and BnBr (6.1 mL, 1.2 equiv., 51.2 mmol) was added. The reaction was stirred at room temperature for 4 hours. Water was added dropwise and carefully at 0 °C. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product of **8** was dissolved in toluene (100 mL) and then dimethyl malonate (6.8 g, 1.2 equiv., 51.2 mmol), piperidine (0.21 mL, 5% equiv., 2.1 mmol), and acetic acid (0.5 mL, 20% equiv., 8.5 mmol) were added at room temperature. The reaction mixture was allowed to reflux and water was removed by using a Dean–Stark trap overnight. The organic solvent was evaporated under reduced pressure, and the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10 : 1, R_f = 0.12) to afford α,β-unsaturated diester **6** as a yellow solid (13.4 g, 90% yield, two steps): m.p. = 86–88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.37–7.29 (m, 4H), 7.27–7.26 (m, 2H), 7.19–7.11 (m, 3H), 6.75 (d, J = 3.2 Hz, 1H), 5.36 (s, 2H), 3.90 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6, 164.9, 141.0, 137.0, 136.4, 129.7, 129.3, 128.9, 127.8, 126.8, 125.0, 124.9, 121.8, 119.5, 112.4, 99.9, 52.7, 52.6, 50.3; IR (thin film, ν_{max}/cm^{-1}): 2951, 2847, 1727, 1621, 1602, 1363, 1269, 751; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{20}NO_4$ 350.1387, found 350.1379.

Dimethyl 2-(1-benzyl-4-nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-yl)malonate [(±)-5]

To a Schlenk tube equipped with a magnetic stirring bar was added anhydrous $MgSO_4$ (2.2 g, 300 mg per 1.0 mmol **6**). This salt was carefully thermally activated under vacuum with a heat-gun prior to the reaction for 5 min and then allowed to cool to room temperature. The α,β-unsaturated diester **6** (2.5 g, 1.0 equiv., 7.2 mmol) was added, followed by the (±)-PA catalyst (0.25 g, 0.1 equiv., 0.7 mmol) and CH_2Cl_2 (30 mL) as a solvent under an argon atmosphere. The mixture was stirred for 5 minutes at 0 °C, and then nitroethylene (1.2 mL, 2.5 equiv., 18.0 mmol,) was added in one portion. The mixture was then stirred at room temperature for 60 h. After concentration of the solvent, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1, R_f = 0.16) to afford tricyclic dister (±)-**5** as a pale yellow solid (1.54 g, 51% yield): m.p. 131–133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 3H), 7.16–7.11 (m, 4H), 6.93–6.91 (m, 2H), 5.27 (d, J = 2.8 Hz, 2H), 5.24–5.21 (m, 1H), 4.83 (dd, J = 10.6, 3.2 Hz, 1H), 3.90 (dd, J = 17.2, 3.1 Hz, 1H), 3.83 (s, 3H), 3.65 (s, 3H), 3.61 (d, J = 10.6 Hz, 1H), 3.40–3.34 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 167.4, 137.4, 134.7, 128.8, 127.8, 127.1, 125.7, 125.1, 123.3, 123.0, 117.5, 109.0, 105.8, 83.1, 55.8, 53.1, 52.7, 50.3, 40.2, 23.6; IR (thin film, ν_{max}/cm^{-1}): 2954, 2920, 1737, 1547, 1367, 1261, 783, 736; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{23}H_{23}N_2O_6$ 423.1551, found 423.1550.

Methyl 4-benzyl-8-oxo-6,6a,7,8,9,9a-hexahydro-4*H*-indolo[6,5,4-cd]indole-9-carboxylate [(±)-9]

To a solution of tricyclic dister (±)-**5** (0.10 g, 1.0 equiv., 0.24 mmol) in acetic acid (10 mL) was added iron powder (0.12 g, 8.8 equiv., 2.1 mmol), and the mixture was stirred for 8 hours at 110 °C. The mixture was cooled to room temperature and filtered with Celite, and washed with ethyl acetate. The organic solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 30 : 1, R_f = 0.16) to give tetracyclic lactam (±)-**9** as a colorless foamed solid (70 mg, 82% yield): m.p. 182–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.32–7.20 (m, 7H), 7.04–7.00 (m, 1H), 6.52 (d, J = 7.0 Hz, 1H), 5.35 (s, 2H), 3.79 (s, 3H), 3.68–3.66 (m, 1H), 3.64–3.58 (m, 2H), 3.21 (dd, J = 14.2, 4.1 Hz, 1H), 2.79 (t, J = 11.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 173.0, 171.1, 138.9, 134.0, 129.8, 129.0, 127.8, 127.6, 127.4, 124.5, 122.6, 112.7, 110.0, 109.4, 56.8, 52.7, 52.1, 49.8, 48.4, 27.9; IR (thin film, ν_{max}/cm^{-1}): 3394, 2920, 2850, 1742, 1703, 1453, 1317, 746; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{21}N_2O_3$ 361.1547, found 361.1548.

Methyl 4-benzyl-7,9-dimethyl-8-oxo-6,6a,7,8,9,9a-hexahydro-4*H*-indolo[6,5,4-*cd*]indole-9-carboxylate [(±)-10]

To a solution of (±)-**9** (60 mg, 1.0 equiv., 0.17 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) was added 60% NaH (68 mg, 10.0 equiv., 1.7 mmol) in ice water. The mixture was stirred for 10 min at this temperature and an excess of iodomethane (0.1 mL, 10.0 equiv., 1.7 mmol) was added. After being stirred for 10 hours, the reaction mixture was poured into a saturated aqueous NH_4Cl solution. The organic solvent was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated

under reduced pressure. Purification by silica gel column chromatography afforded *N*-protected (±)-**10** (60 mg, 92%) as a pale yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 3H). 7.18–7.14 (m, 4H), 6.93 (s, 1H), 6.83–6.82 (m, 1H), 5.30 (s, 2H), 4.06 (d, J = 10.4 Hz, 1H), 3.86 (s, 3H), 3.74 (ddd, J = 10.9, 10.9, 3.9 Hz, 1H), 3.44 (dd, J = 13.8, 4.2 Hz, 1H), 3.00 (s, 3H), 2.94 (dd, J = 12.8, 12.8 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (C), 173.1 (C), 137.6 (C), 134.4 (C), 128.8 (CH), 128.0 (C), 127.8 (CH), 127.4 (C), 126.9 (CH), 123.3 (CH), 122.8 (CH), 114.0 (CH), 109.4 (C), 108.4 (CH), 60.2 (CH), 53.5 (C), 52.8 (CH), 50.3 (CH_2), 49.9 (CH_3), 27.8 (CH_3), 27.0 (CH_2), 12.4 (CH_3); IR (thin film, ν_{max}/cm^{-1}): 2920, 2850, 1738, 1696, 1317, 1250, 747; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{24}H_{25}N_2O_3$ 389.1860, found 389.1857.

Allyl 4-benzyl-7,9-dimethyl-8-oxo-6,6a,7,8,9,9a-hexahydro-4*H*-indolo[6,5,4-*cd*]indole-9-carboxylate [(±)-4]

To a solution of *N*-protected (±)-**10** (0.12 g, 1.0 equiv., 0.3 mmol) in toluene (5 mL) were added zinc powder (4 mg, 0.2 equiv., 0.06 mmol) and an excess of allyl alcohol (0.1 mL, 5.0 equiv., 1.5 mmol). The reaction mixture was heated to reflux for 5 hours and then cooled to room temperature. The organic solvent was removed under reduced pressure, and the crude product was purified by silica gel column chromatography to give a single product allyl carboxylate (±)-**4** (0.122 g, 95%) as a pale yellow solid: mp = 49–52 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 3H), 7.19–7.13 (m, 4H), 6.92 (d, J = 1.1 Hz, 1H), 6.82–6.80 (m, 1H), 5.95–5.93 (m, 1H), 5.41–5.36 (m, 1H), 5.30 (s, 2H), 5.24 (dd, J = 10.4, 1.2 Hz, 1H), 4.79–4.76 (m, 2H), 4.07 (d, J = 10.0, 1H), 3.74–3.72 (m, 1H), 3.43 (dd, J = 13.8, 4.4 Hz, 1H), 3.0 (s, 3H), 2.97 (dd, J = 13.2, 13.2 Hz, 1H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3 (C), 172.3 (C), 137.6 (C), 134.4 (C), 131.9 (CH), 128.8 (CH), 128.0 (C), 127.8 (CH), 127.4 (C), 127.0 (CH), 123.3 (CH), 122.8 (CH), 118.4 (CH_2), 114.0 (CH), 109.4 (C), 108.4 (CH), 66.2 (CH_2), 60.2 (CH_3), 53.6 (C), 50.3 (CH_2), 49.9 (CH), 27.8 (CH), 27.0 (CH_2), 12.4 (CH_3); IR (thin film, ν_{max}/cm^{-1}): 3358, 3186, 2920, 2850, 1736, 1697, 1454, 1244, 747; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{26}H_{27}N_2O_3$ 415.2016, found 415.2017.

4-Benzyl-9-(hydroxymethyl)-4,6,6a,7,9,9a-hexahydro-8*H*-indolo[6,5,4-*cd*]indol-8-one [(±)-11]

To a suspension of $LiAlH_4$ (91.2 mg, 3.0 equiv., 2.4 mmol) in THF (10 mL) was added dropwise the solution of tetracyclic lactam (±)-**9** (0.3 g, 1.0 equiv., 0.8 mmol) in anhydrous THF (20 mL). The mixture was refluxed for 4 hours, and cooled to 0 °C. Water, sodium hydroxide solution (10%), and water (v/v/v = 1 : 2 : 3) were slowly added dropwise with vigorous stirring. The reaction mixture was filtered with Celite, washed with ethyl acetate, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 20 : 1, R_f = 0.10) to give β-hydroxyl lactam (±)-**11** as a colorless foamed solid (0.25 g, 90% yield): m.p. 257–260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (s, 1H), 7.33–7.19 (m, 7H), 7.04–6.96 (m, 2H), 5.34 (s, 2H), 4.80 (t, J = 5.1 Hz, 1H), 4.02–3.92 (m, 2H), 3.49–3.46 (m, 1H), 3.38–3.33 (m, 1H), 3.22–3.18 (dd, J = 14.1, 4.1 Hz, 1H), 2.72–2.68 (m, 1H), 2.60–2.56 (tt, J = 7.9, 3.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 177.8, 139.0, 134.0, 132.0, 129.0, 127.8, 127.7, 127.6, 124.0, 122.6, 113.8, 110.5, 108.8, 59.6, 57.1, 49.7, 48.2, 46.0, 28.6; IR (thin film, ν_{max}/cm^{-1}): 3385, 3214, 2920, 2849, 1693, 1503, 1027, 745; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{21}N_2O_2$ 333.1598, found 333.1595.

(4-Benzyl-8-oxo-6,6a,7,8,9,9a-hexahydro-4*H*-indolo[6,5,4-*cd*]indol-9-yl)methyl methanesulfonate [(±)-12]

To a solution of β-hydroxyl lactam (±)-**11** (0.4 g, 1.0 equiv., 1.2 mmol) in dry CH_2Cl_2 (20 mL) were added dry Et_3N (0.9 mL, 5.0 equiv., 6.0 mmol) and an excess of MsCl (0.9 mL, 10.0 equiv., 12.0 mmol). The reaction mixture was stirred for 4 hours and a saturated NH_4Cl solution was added into the reaction mixture. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 30 : 1, R_f = 0.14) to give methanesulfonate (±)-**12** as a colorless solid (0.48 g, 98% yield): m.p. 240–243 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.39 (br, 1H), 7.33–7.21 (m, 7H), 7.04 (t, J = 7.2 Hz, 1H), 6.95 (d, J = 7.1 Hz, 1H), 5.36 (s, 2H), 4.80–4.64 (m, 2H), 3.60–3.54 (m, 1H), 3.36–3.33 (m, 1H), 3.24–3.18 (m, 1H), 3.20 (s, 3H), 3.05–3.00 (m, 1H), 2.73 (t, J = 12.6 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 175.4, 139.0, 134.0, 130.7, 129.0, 127.8, 127.7, 127.6, 124.2, 122.7, 113.4, 110.2, 109.2, 68.6, 57.0, 49.8, 45.9, 45.3, 28.3; IR (thin film, ν_{max}/cm^{-1}): 3393, 2920, 2849, 1691, 1166, 1092, 1027, 751; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{23}N_2O_4S$ 411.1373, found 411.1368.

4-Benzyl-9-methyl-4,6,6a,7-tetrahydro-8*H*-indolo[6,5,4-*cd*]indol-8-one [(±)-13]

To a solution of methanesulfonate (±)-**12** (0.1 g, 1.0 equiv., 0.25 mmol) in dry CH_2Cl_2 (10 mL) was added DBU (0.5 mL, 14.0 equiv., 3.5 mmol) at room temperature. The reaction mixture was stirred for about 1 hour, and then a saturated NH_4Cl solution was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 30 : 1, R_f = 0.10) to give α,β-unsaturated tetracyclic lactam (±)-**13** as a pale claybank liquid (70 mg, 92% yield); ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H), 7.44 (d, J = 7.7 Hz, 1H), 7.34–7.19 (m, 8H), 5.39 (s, 2H), 4.36–4.31 (m, 1H), 3.45–3.35 (m, 1H), 2.52–2.50 (m, 1H), 2.04 (d, J = 1.6 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 174.2, 148.2, 138.8, 134.5, 129.0, 127.9, 127.9, 127.7, 126.7, 125.2, 124.1, 123.0, 115.6, 111.2, 109.2, 56.0, 49.8, 28.8, 9.8; IR (thin film, ν_{max}/cm^{-1}): 3389, 3204, 3061, 2921, 2850, 1676, 1606, 746; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{19}N_2O$ 315.1492, found 315.1489.

4-Benzyl-7,9-dimethyl-4,6,6a,7-tetrahydro-8*H*-indolo[6,5,4-*cd*]-indol-8-one [(±)-2]

To a solution of methanesulfonate (±)-**12** (30 mg, 1.0 equiv., 0.07 mmol) in anhydrous THF (10 mL) with a catalytic amount of HMPA was added 60% NaH (28 mg, 10.0 equiv., 0.7 mmol) at 0 °C. The mixture was stirred for 10 min at this temperature and an excess of iodomethane (43.6 μL, 10.0 equiv., 0.7 mmol) was added. The reaction mixture was stirred at room temperature for about 4 hours. Then the reaction mixture was poured into a saturated NH_4Cl solution. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2 : 1, R_f = 0.12) to give α,β-unsaturated tetracyclic core (±)-**2** as a slightly yellow liquid (17 mg, 71% yield); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.32 (m, 4H), 7.31–7.25 (m, 2H), 7.18–7.16 (m, 2H), 6.97 (d, J = 1.4 Hz, 1H), 5.33 (s, 2H), 4.29–4.24 (m, 1H), 3.56 (dd, J = 14.2, 6.5 Hz, 1H), 3.15 (s, 3H), 2.70–2.63 (m, 1H), 2.25 (d, J = 1.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8 (C), 146.0 (C), 137.4 (C), 134.6 (C), 128.8 (CH), 128.1 (C), 127.8 (CH), 127.4 (C), 126.9 (CH), 124.2 (C), 124.0 (CH), 123.2 (CH), 115.7 (CH), 110.1 (CH), 109.2 (C), 61.4 (CH), 50.4 (CH_2), 27.4 (CH_2), 26.9 (CH_3), 10.1 (CH_3); IR (thin film, ν_{max}/cm^{-1}): 2920, 2849, 1688, 1646, 1350, 750; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{22}H_{21}N_2O$ 329.1648, found 329.1649.

4-Nitro-1,3,4,5-tetrahydrobenzo[*cd*]indol-5-ol [(±)-14]

Tricyclic alcohol (±)-**14** was prepared according to the synthesis procedure of tricyclic diester (±)-**5**. Aldehyde **7** (2.0 g, 1.0 equiv., 13.8 mmol), anhydrous $MgSO_4$ (4.1 g, 300 mg per 1.0 mmol **7**), (±)-PA (0.5 g, 0.1 equiv., 1.4 mmol), and nitroethylene (2.9 mL, 3.0 equiv., 41.7 mmol) were used in this reaction. The product tricyclic alcohol (±)-**14** was obtained as a pale yellow solid (1.98 g, 66% yield): m.p. 155–157 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.92 (br, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.15–7.11 (m, 2H), 7.03 (d, J = 7.1 Hz, 1H), 6.18 (d, J = 7.9 Hz, 1H), 5.39 (t, J = 8.4 Hz, 1H), 4.93–4.87 (m, 1H), 3.54–3.39 (m, 2H); ^{13}C NMR (100 MHz, acetone-d_6) δ 133.9, 130.4, 125.3, 122.7, 119.5, 114.0, 110.2, 107.0, 90.1, 70.9, 27.0; IR (thin film, ν_{max}/cm^{-1}): 3393, 2919, 2849, 1646, 1545, 1469, 1450, 777; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{11}H_{10}N_2O_3Na$ 241.0584, found 241.0581.

***tert*-Butyl (5-hydroxy-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl)carbamate [(±)-15]**

To a solution of tricyclic alcohol (±)-**14** (0.7 g, 1.0 equiv., 3.2 mmol) in anhydrous MeOH (50 mL) was added RANEY® Ni (0.7 g) under a hydrogen atmosphere. The mixture was stirred at room temperature for about 5 hours and then filtered. The filtrate was concentrated under reduced pressure. The crude product was used in the next step without further purification. To a solution of the above crude product in CH_2Cl_2 (50 mL) were added $(Boc)_2O$ (1.4 g, 2.0 equiv., 6.4 mmol) and Et_3N (1.1 mL, 2.5 equiv., 8.0 mmol). The mixture was stirred at room temperature for 6 hours, and a saturated NH_4Cl solution was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 2 : 1, R_f = 0.12) to give β-hydroxyl carbamate (±)-**15** as a slightly yellow solid (0.675 g, 73% yield, two steps): m.p. 96–98 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (br, 1H), 7.30 (t, J = 8.0 Hz, 1H), 7.24 (t, J = 7.1 Hz, 1H), 7.18 (d, J = 7.0 Hz, 1H), 6.94 (s, 1H), 4.90 (d, J = 5.4 Hz, 1H), 4.59 (br, 1H), 4.31 (br, 1H), 3.34–3.30 (dd, J = 15.4, 3.4 Hz, 1H), 2.91–2.86 (dd, J = 15.6, 5.6 Hz, 1H), 2.54 (br, 1H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 134.0, 129.9, 125.6, 123.3, 119.6, 117.1, 110.6, 109.0, 79.7, 70.7, 52.4, 28.4, 24.9; IR (thin film, ν_{max}/cm^{-1}): 3415, 2931, 2853, 1688, 1345, 1165, 753, 738; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{20}N_2O_3Na$ 311.1366, found 311.1361.

***tert*-Butyl (5-oxo-1,3,4,5-tetrahydrobenzo[*cd*]indol-4-yl)carbamate [(±)-16]**

To a solution of β-hydroxyl carbamate (±)-**15** (0.7 g, 1.0 equiv., 2.4 mmol) in dry CH_2Cl_2 (50 mL) was added DMP (1.3 g, 1.3 equiv., 3.1 mmol). The mixture was stirred at room temperature for about 4 hours. Concentrated under reduced pressure, the crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1, R_f = 0.15) to give ketone (±)-**16** as a slightly yellow foamed solid (0.66 g, 95% yield): m.p. 195–198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (br, 1H), 7.61–7.56 (m, 2H), 7.31–7.27 (m, 1H), 7.08 (s, 1H), 5.87 (br, 1H), 4.78–4.72 (m, 1H), 3.93–3.88 (dd, J = 14.5, 6.5 Hz, 1H), 3.01 (t, J = 13.2 Hz, 1H), 1.53 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.4, 155.9, 134.6, 131.5, 124.8, 123.0, 121.2, 116.5, 116.2, 108.9, 79.8, 57.6, 28.9, 28.4; IR (thin film, ν_{max}/cm^{-1}): 3343, 2978, 2931, 2853, 1677, 1620, 1348, 1165, 768; HRMS (ESI) m/z: $[M + Na]^+$ calcd for $C_{16}H_{18}N_2O_3Na$ 309.1210, found 309.1206.

***tert*-Butyl 4-((*tert*-butoxycarbonyl)amino)-5-oxo-4,5-dihydrobenzo[*cd*]indole-1(3*H*)-carboxylate [(±)-3]**

To a solution of ketone (±)-**16** (0.3 g, 1.0 equiv., 1.0 mmol) in dry acetonitrile (50 mL) was added DMAP (0.2 g, 2.0 equiv., 2.0 mmol) at room temperature. The mixture was stirred for 5 min and $(Boc)_2O$ (0.3 g, 1.5 equiv., 1.5 mmol) was added. The mixture was stirred at room temperature for about 6 hours. Then, a saturated aqueous NH_4Cl solution was added. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 10 : 1, R_f = 0.34) to give 4-amino Uhle's ketone (±)-**3** as a colorless foamed solid (0.319 g, yield 94%): m.p. 125–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (br, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.48 (s, 1H), 7.43 (t, J = 7.8 Hz, 1H), 5.82 (s, 1H), 4.71–4.68 (m, 1H), 3.93–3.87 (dd, J = 15.2, 6.8 Hz,

1H), 2.94 (t, J = 13.8 Hz, 1H), 1.71 (s, 9H), 1.51 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.4, 155.7, 149.6, 133.9, 125.4, 125.2, 122.2, 120.7, 119.2, 113.3, 84.3, 79.9, 57.0, 28.5, 28.4, 28.2; IR (thin film, ν_{max}/cm^{-1}): 3373, 2926, 2851, 1736, 1697, 1354, 765; HRMS (ESI) m/z: $[M + H]^+$ calcd for $C_{21}H_{27}N_2O_5$ 387.1914, found 387.1917.

Conflicts of interest

There are no conflicts to declare.

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