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A Modular Formal Total Synthesis of (±)-Cycloclavine

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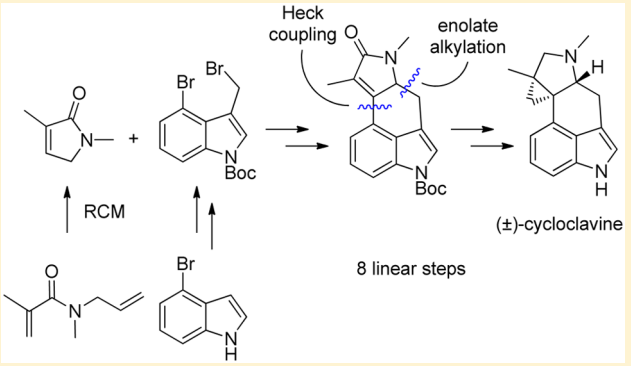
Supporting Information

ABSTRACT: Cycloclavine is a clavine-type *Ergot* alkaloid noteworthy for its unique pentacyclic skeleton featuring a 3-azabicyclo[3.1.0]hexane substructure. A short convergent route to the racemic alkaloid is described which comprises only eight linear steps and requires only four chromatographic purifications. The two key building blocks can be prepared in high yield from commercially available starting materials. Two consecutive coupling reactions, namely a selective alkylation of a dienolate and a Heck reaction, are the key steps of the reaction sequence.



The *Ergot* alkaloids are an important group of indole-derived mycotoxins which exhibit strong biological activities illustrated, for example, by St. Anthony's fire or ergotism, a life-threatening disease caused by chronic ingestion of toxic foodborne fungal secondary metabolites. *Ergot* alkaloids primarily target serotonin (5-HT) receptors but also α-adrenergic and dopamine receptors, and some natural or semisynthetic ergoline derivatives are used as drugs against migraine or Parkinson's disease.[1] Cycloclavine (**1**) belongs to the subclass of clavine-type alkaloids and was first isolated in 1969 from seeds of *Ipomoea hildebrandtii VATKE* by Hofmann, who also determined the absolute configuration as 5*R*,8*S*,10*S*.[2] Cycloclavine is an isomer of agroclavine, but instead of having an 8,9-double bond, the metabolite contains a cyclopropane ring formed by the C atoms 8, 9, and 10 and represents the only fused pentacyclic clavine alkaloid known to date (Figure 1).

The biosynthetic pathway for cycloclavine was investigated by Naesby and O'Connor[3] who identified chanoclavine-1 as an intermediate and the oxidase EasH as the key enzyme responsible for the formation of the cyclopropyl moiety. Besides their action on receptors for biogenic amine neurotransmitters, biological activities of clavine alkaloids also include antimicrobial and cytostatic effects.[4−10] The first total synthesis of cycloclavine was published in 2008 by Szántay;[11] further reports came from Wipf,[12] Cao,[13] and Brewer.[14]

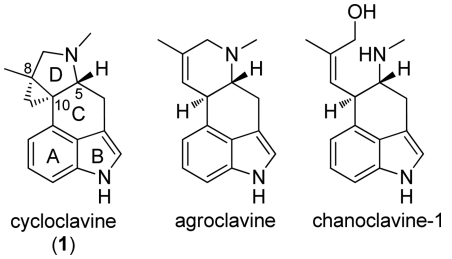
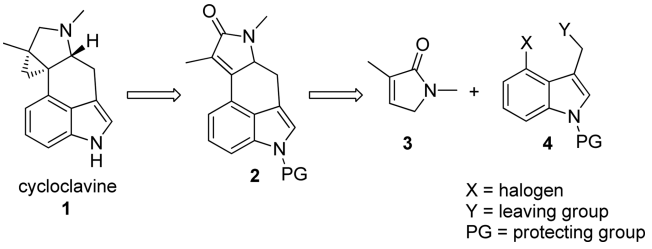


Figure 1. Structures of clavine alkaloids.

The construction of the ergoline skeleton is often effected using Uhle's ketone[15] as it already contains three of the required rings. However, to avoid problems emerging from the oxidative sensitivity of the 1,3,4,5-tetrahydrobenzo[*cd*]indole framework,[16] we chose a modular approach to (±)-cycloclavine (**1**) using indole and pyrrolinone-type building blocks and to connect them to establish ring C at a late stage (Scheme 1).

Scheme 1. Retrosynthesis of (±)-Cycloclavine



The pyrrolinone unit was chosen to be 1,3-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (**3**), while the bifunctional indole building block **4** was derived from gramine (Y = $N(CH_3)_3^+$) or another 3-methyleneindolenine precursor bearing a halogen substituent at C-4.

The synthesis of building block **3** started from allylamine (**5**) by an N-formylation using neat ethyl formate (Scheme 2). Lithium aluminum hydride reduction of **6** yielded *N*-allyl-methylamine, which was directly transformed into the

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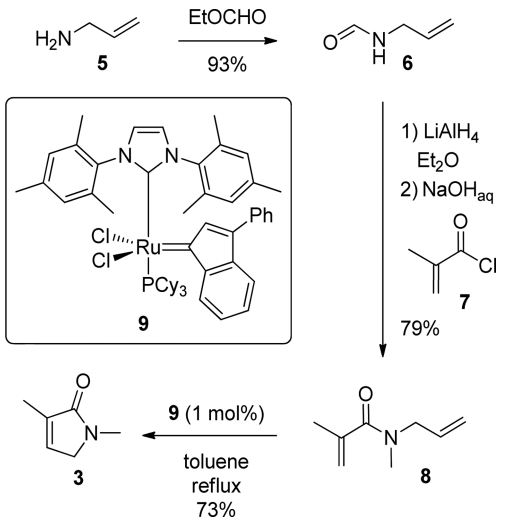
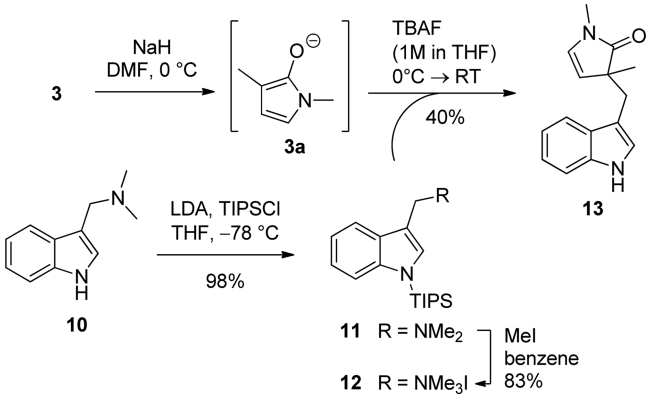
Scheme 2. Three-Step Synthesis of Pyrrolinone 3



methacryloyl amide **8** without isolation. Subsequent ring closing metathesis of **8** using catalyst **9** (catMETium RF1)[17] afforded pyrrolinone **3** in 54% yield over three steps.

At first, we attempted coupling **3** with *N*-triisopropylsilyl-protected gramine methiodide (**12**),[18] which is easily prepared from gramine (**10**) via reaction with lithium diisopropylamide (LDA) and triisopropylsilyl chloride (TIPSCl), followed by treatment with iodomethane (Scheme 3). Unfortunately,

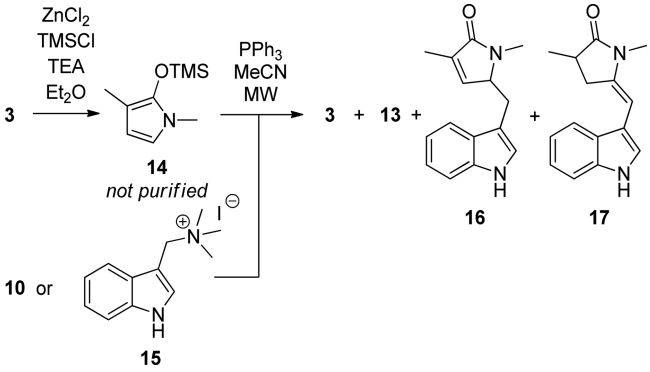
Scheme 3. TBAF Induced Coupling of 3 with Gramine Methiodide 12



deprotonation of pyrrolinone **3** with sodium hydride and reaction with methiodide **12** in the presence of tetrabutylammonium fluoride (TBAF) through the reactive 3-methyleneindolenine intermediate did not afford the desired γ-alkylation product. The isomeric α-coupling product **13** was formed instead. The deprotonation of **3** was also carried out with LDA, but the same unfavorable regioselectivity was observed.

To form the desired γ-isomer, the synthesis of silyl dienol ethers of **3** was attempted. However, reaction with various bases (2,6-lutidine, triethylamine, sodium hydride, and LDA) and TMS and TBDMS chlorides and triflates did not afford the desired silyloxypyrroles. On the other hand conversion to the trimethylsilyloxypyrrole **14** could be effected with the combination of zinc(II) chloride, triethylamine, and TMSCl (Scheme 4).[19,20] The highly moisture-sensitive compound **14** was not isolated but rather immediately reacted with gramine

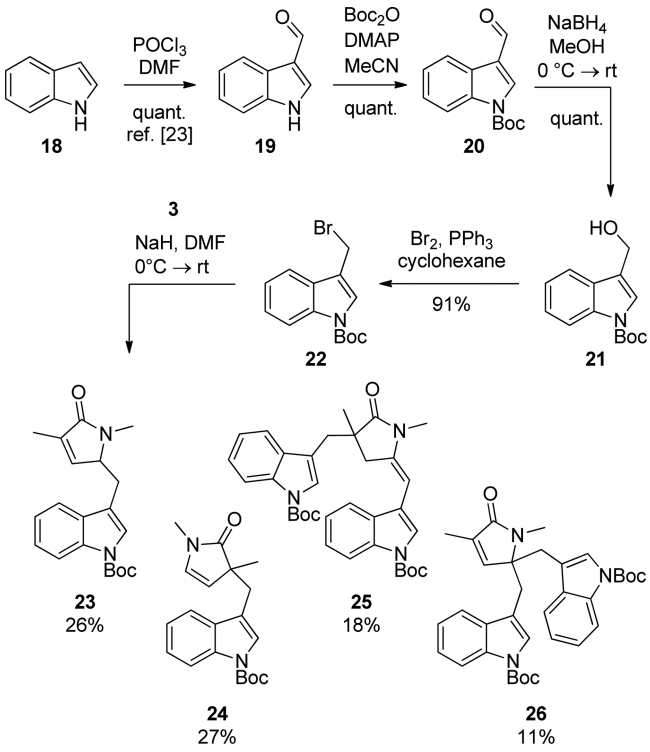
Scheme 4. Coupling of Silyl Dienolether 14 under Microwave Conditions



(**10**) or gramine methiodide (**15**) and triphenylphosphine under microwave irradiation (300 W, 125 °C)[21,22] to give the desired γ-isomer **16** along with the α-isomer **13** and regenerated pyrrolinone **3**. Remarkably, compound **16** was found to isomerize to enamide **17** during workup and purification. Compound **16** and the rearranged γ-isomer **17** were both isolated in up to 17% yields (multiple runs).

Since a γ-selective coupling of **3** with the gramine derived indole building block did not seem viable, a protected 3-bromomethyl-1*H*-indole was synthesized as an alternative electrophile. It was anticipated that the less reactive and "softer" bromide would show a larger preference for the sterically less hindered γ-position in the alkylation compared to the reactive 3-methyleneindolenine. 3-Bromomethyl-1*H*-indole **22** could be readily prepared from indole (**18**) in 91% overall yield through Vilsmeier formylation, Boc-protection, $NaBH_4$-reduction, and bromination (Scheme 5).[23−25] Its reaction with

Scheme 5. Coupling of Model Electrophile 22 with Pyrrolinone 3



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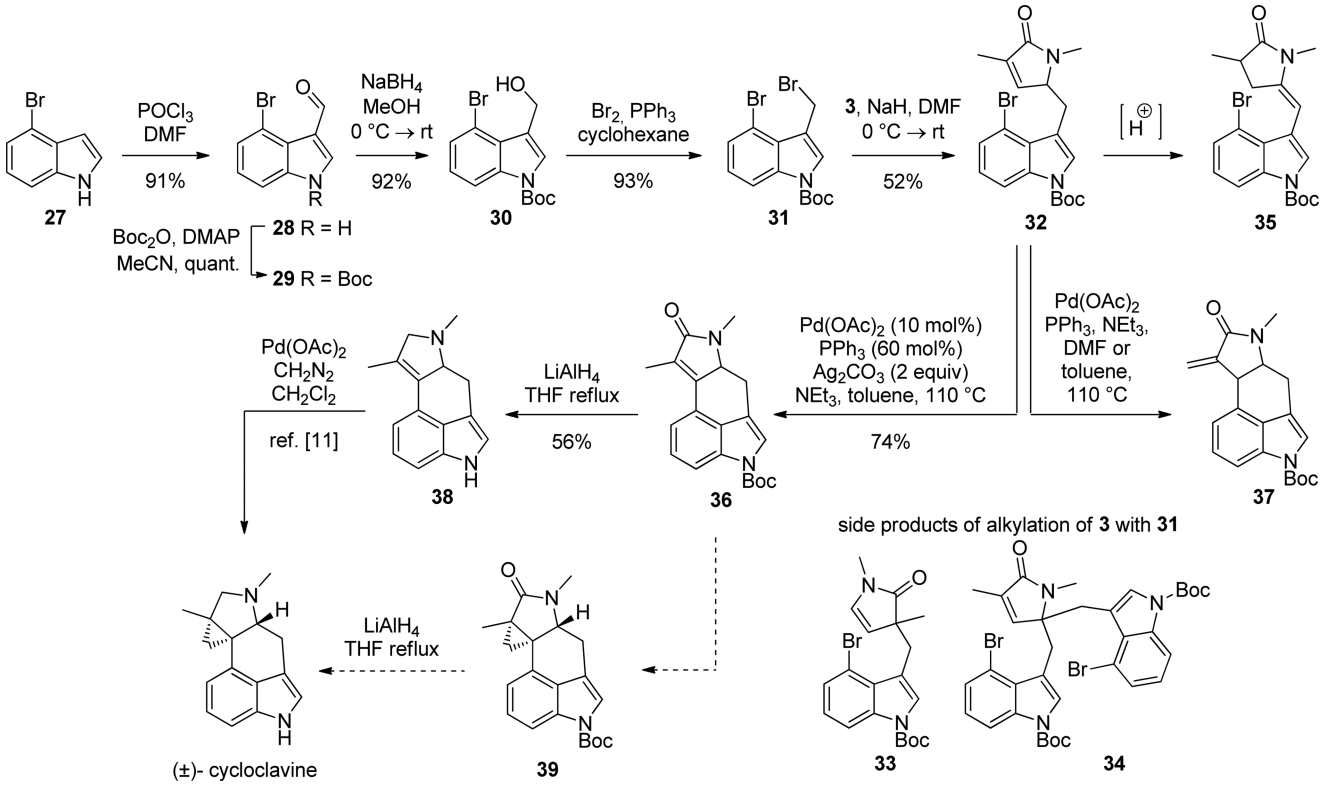
Scheme 6. Route to (±)-Cycloclavine



deprotonated pyrrolinone **3** led to a mixture of both isomers **23** and **24** in a 1:1 ratio (as judged by ^{1}H NMR, isolated yields 26% and 27%). Furthermore, the doubly alkylated compounds **25** and **26** were obtained in 18% and 11% yield, respectively. The application of KHMDS as an alternative base led to an identical product distribution.

Since this was the most promising result obtained so far, the 4-bromo-compound **31** was prepared from commercially available 4-bromoindole (**27**) over four steps in 78% overall yield (Scheme 6).[24,26] Reaction of **31** with deprotonated pyrrolinone **3** led to a surprisingly high selectivity for the desired γ-isomer **32**. Presumably, the γ-position receives a higher preference due to the steric demand of the bromine substituent in the S_N2 transition state. From experiments on larger scales, α-isomer **33** and the doubly alkylated byproduct **34** were identified (yields of 5% and 3%, respectively). The varying percentages of side products formed are probably due to minor variations of base equivalents and different batch sizes. Double bond isomerization on lactam **32** led to the conjugated isomer **35** and was found to take place under slightly acidic conditions (coevaporation with $CHCl_3$ containing traces of HCl). Further transformation of **32** via intramolecular Heck reaction led to tetracyclic lactam **36** in 74% yield. Notably, the exomethylene isomer **37** was formed as the major product next to **36** when palladium(II) acetate/triphenylphosphine with triethylamine in DMF or toluene was used as the catalytic system. Addition of silver(I) carbonate led to the desired selectivity (as reported by Cao)[13] in the β-hydride elimination step. Exomethylene compound **37** was difficult to separate from **36**; attempts to isomerize **37** to **36** were unsatisfactory, although partial isomerization could be achieved (see Experimental Section).

Lactam **36** was easily reduced to amine **38** by lithium aluminum hydride, completing the formal total synthesis of (±)-cycloclavine (**1**) as the final cyclopropanation step has previously been reported by Szántay.[11] Since the Szántay group[11] had reported low yields for this step (32%, brsm), we tried to cyclopropanate amide precursor **36** instead of the free amine. However, treatment of **36** with diazomethane did not give any conversion to **39** while trimethylsulfoxonium ylide only led to undesired oxidative side reactions. Reaction of **36** with diazomethane and several transition metal catalysts ($Pd(OAc)_2$, $Rh_2(OAc)_4$, CuCl, $Cu(OTf)_2$, $[[CH_3(CH_2)_6CO_2]_2Rh]_2$) in diethyl ether or dichloromethane either gave unidentified side products or no conversion, while Simmons–Smith conditions ($ZnEt_2$, CH_2I_2, THF or Zn/Cu, CH_2I_2, THF) led to the loss of the Boc protecting group. Application of the aforementioned conditions to the deprotected compound resulted in a low conversion (HPLC-MS) which could not be improved, and reproducibility was low.

The samarium/diiodomethane system, which was demonstrated to cyclopropanate α,β-unsaturated amides,[27] gave the best results to date, but the reaction rate was very low. The activation of samarium with mercury(II) chloride resulted in an improved conversion (HPLC-MS) while the addition of TMS chloride[28] or the use of chromium(II) chloride/diiodomethane[29] or samarium/iodoform under ultrasonication[30] showed no improvement. A gradual increase in the conversion was observed by addition of the carbene precursor with a syringe pump and by replacing diiodomethane with chloroiodomethane. Higher reaction temperatures also appeared to be beneficial in terms of conversion although the selectivity was reduced (HPLC-MS). Nevertheless, an analytically pure sample of the cyclopropane derivative **39** could not be obtained.

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In summary, a convergent formal total synthesis of (±)-cycloclavine was developed which involves eight steps in the longest linear sequence. Both key building blocks, pyrrolinone **3** and 3-(bromomethyl)indole **31**, were prepared from simple, commercially available starting materials. Intermediates **6**, **8**, and **3** could easily be purified by distillation while intermediates **28**−**31** were obtained in high purity and were used without further purification.

EXPERIMENTAL SECTION

All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in oven-dried glassware. All reagents and solvents were obtained from commercial suppliers and used without further purification, if not mentioned otherwise. Anhydrous toluene, THF, and diethyl ether were distilled from sodium/benzophenone under argon. Triethylamine was distilled from calcium hydride under argon. NMR spectra were recorded with a 300 MHz (300 MHz ^{1}H and 75.5 MHz ^{13}C), 400 MHz (400 MHz ^{1}H and 100.6 MHz ^{13}C), or 600 MHz spectrometer (600 MHz ^{1}H and 151 MHz ^{13}C) with digital architecture equipped with 5 mm probes. The δ values were referenced to the residual solvent signal ($CHCl_3$, 7.26 ppm).[31] IR spectra were recorded using a diamond ATR. ESI-HRMS spectra were recorded on a Q-TOF instrument with a dual source and a suitable external calibrant. Thin-layer chromatography (TLC) was carried out on 0.25 mm silica gel plates with a fluorescence indicator. Flash chromatography was performed on 35−70 μm silica gel using the solvent systems indicated.

Allylformamide (6). A protocol of Christensen[32] was applied to yield **6** as a colorless liquid (93%): bp 102 °C (22 mbar) (Lit.[33] 104−107 °C, 14 Torr); R_f = 0.10 (CH_2Cl_2/MeOH, 1:2); IR (ATR) ν (cm^{-1}) = 3282, 3086, 2872, 1655, 1643, 1532, 1383, 1232, 992, 919, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.10 (s, 1H, C*H*O), 7.94 (dd, J = 12.0, 2.2 Hz, 0.14H, C*H*O), 6.81 (s_{br}, 1H, N*H*), 6.44 (s_{br}, 0.14H, N*H*), 5.83−5.68 (m, 1.14H, C*H*=CH$_2$), 5.20−5.01 (m, 2.3H, =C*H*$_2$), 3.80 (t, J = 4.6 Hz, 2H, C*H*$_2$), 3.78−3.73 (m, 0.3H, C*H*$_2$); FD-MS (C_4H_7NO): 85.2. The analytical data are in accordance with the literature.[33,34]

1,3-Dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (3). Lithium aluminum hydride (9.0 g, 0.24 mol) was added to dry diethyl ether (500 mL). A solution of **6** (20.0 g, 0.235 mol) in dry diethyl ether (100 mL) was slowly added within 30 min. The reaction mixture was heated at reflux for 1 h. The reaction mixture was cooled to 0 °C and carefully quenched with (9.0 mL) water, 15% NaOH (9.0 mL), and water (27 mL). The resulting colorless solid was removed by filtration and thoroughly washed with diethyl ether. To the resulting solution of *N*-allyl-*N*-methylamine in diethyl ether (ca. 700 mL) was added an aqueous sodium hydroxide solution (17.0 g, 425 mmol in 170 mL). The reaction mixture was cooled to 0 °C, and methacryloyl chloride (27 mL, 0.28 mol) was slowly added within 10 min. The mixture was stirred for 30 min at 0 °C and for 1.5 h at rt. The organic layer was separated, and the aqueous layer was extracted with diethyl ether (3 × 50 mL). The combined organic layers were washed with a saturated $NaHCO_3$ solution and brine and dried over $MgSO_4$. Diethyl ether was removed by distillation, and further distillation of the residue yielded *N*,*N*-allyl-methyl-2-methacryloylamide (**8**, 25.71 g, 79%) as a colorless liquid: bp 60 °C (2.9 mbar); R_f = 0.49 (cyclohexane/EtOAc, 1:2); IR (ATR) ν (cm^{-1}) = 3083, 2922, 1684, 1647, 1617, 1456, 1396, 1296, 1204, 1088, 991, 914; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 5.75 (ddt, J = 16.1, 10.4, 5.4 Hz, 1H, C*H*=CH$_2$), 5.27−5.10 (m, 3H, CH=C*H*$_2$, C$_q$=C*H*$_{2A}$), 5.04 (s_{br}, 1H, C$_q$=C*H*$_{2B}$), 3.97 (s, 2H, C*H*$_2$), 2.93 (s, 3H, NC*H*$_3$), 1.95 (t, J = 1.4 Hz, 3H, C*H*); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 172.9, 172.1 (C=O), 140.6 (C$_q$=CH$_2$), 133.2, 132.6 (CH=CH$_2$), 117.3 (CH=CH$_2$), 115.4, 114.8 (C$_q$=CH$_2$), 53.3, 49.1 (CH$_2$), 35.9, 32.2 (NCH$_3$), 20.6, 20.3 (CH$_3$); FD-MS ($C_8H_{13}NO$): 139.2. Amide **8** (5.0 g, 36 mmol) and catMETium (**9**, 340 mg, 0.036 mmol, 1 mol %) were put in a Schlenk flask, dry and degassed toluene (250 mL) was added, and the reaction mixture was degassed (three freeze−pump−thaw cycles) and heated at reflux for 45 min. The solvent was removed *in vacuo*, and distillation of the residue afforded **3** (3.15 g, 79%) as a colorless liquid: bp 60 °C (0.4 mbar); R_f = 0.09 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 2923, 1709, 1670, 1642, 1450, 1400, 1247, 1072, 1021, 976, 814; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = δ 6.62 (dq, J = 1.8 Hz, 1H, *H*-4), 3.81−3.78 (m, 2H, *H*-5), 3.04−3.00 (m, 3H, NC*H*$_3$), 1.88 (dd, J = 3.1, 1.8 Hz, 3H, C*H*$_3$); ^{13}C NMR, COSY, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 172.6 (*C*=O), 136.4 (C$_q$3), 135.0 (*C*4), 53.0 (*C*5), 29.8 (NCH$_3$), 11.8 (CH$_3$); FD-MS (C_6H_9NO): 111.2. The analytical data are in accordance with the literature.[35−37]

1-(*N*-Triisopropylsilyl-1*H*-indol-3-yl)-*N*,*N*-dimethylmethanamine (11). Gramine (4.75 g, 27.3 mmol) was dissolved in dry THF (40 mL) under an argon atmosphere and cooled to −78 °C. LDA (2 M in THF/heptane/ethylbenzene; 15 mL, 30 mmol) was added. After stirring for 30 min at −78 °C, triisopropylsilyl chloride (6.4 mL, 30 mmol) was added. The cooling bath was removed, and the reaction was stirred overnight. The reaction mixture was quenched with saturated $NaHCO_3$ solution (100 mL) and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to afford 10.84 g crude of **11**. Thereof 8.89 g were purified by flash column chromatography (cyclohexane/EtOAc, 3:1 → 1:1 + 1% TEA) to yield **11** (7.22 g, 98%) as a yellow oil: R_f = 0.51 (cyclohexane/EtOAc, 1:1 + 1% TEA); IR (ATR) ν (cm^{-1}) = 2945, 2866, 1450, 1150, 1137, 1015, 963, 882, 738, 688, 660, 645; ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) = 7.70−7.66 (m, 1H, *H*-7), 7.50−7.45 (m, 1H, *H*-4), 7.17−7.09 (m, 3H, *H*-2, *H*-5, *H*-6), 3.63 (s, 2H, C*H*$_2$), 2.28 (s, 6H, NC*H*$_3$), 1.70 (h, J = 7.5 Hz, 3H, C*H*(CH$_3$)$_2$), 1.21 (d, J = 7.5 Hz, 18H, CH(C*H*$_3$)$_2$). The analytical data are in accordance with the literature.[38]

(*N*-Triisopropylsilyl-1*H*-indol-3-yl)-*N*,*N*,*N*-trimethylmethanaminium Iodide (12).[18] Methyl iodide (0.45 mL, 7.2 mmol) was added to a solution of **11** (1.19 g, 3.60 mmol) in benzene (20 mL). After 21 h of stirring at rt, diethyl ether was added and the resulting precipitate was filtered and washed with diethyl ether to yield **12** (1.4 g, 83%) as an off-white solid: mp 178.2−179.4 °C; R_f = 0.38 (CH_2Cl_2/MeOH, 9:1); IR (ATR) ν (cm^{-1}) = 3455, 2948, 2868, 1469, 1454, 1170, 1154, 960, 882, 749, 691, 659; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 7.89−7.84 (m, 1H, *H*-4), 7.80 (s, 1H, *H*-2), 7.53 (dd, J = 5.8, 3.3 Hz, 1H, *H*-7), 7.21 (dd, J = 6.0, 3.0 Hz, 2H, *H*-5,6), 5.17 (s, 2H, C*H*$_2$), 3.43 (s, 9H, N$^+$(C*H*$_3$)$_3$), 1.73 (sept, J = 7.5 Hz, 3H, C*H*(CH$_3$)$_2$), 1.13 (d, J = 7.5 Hz, 18H, CH(C*H*$_3$)$_2$); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 141.1 (C$_q$7a), 137.1 (*C*2), 130.4 (C$_q$3a), 122.6 (*C*6), 121.5 (*C*5), 119.2 (*C*4), 114.5 (*C*7), 104.7 (C$_q$3), 62.2 (CH$_2$), 52.7 (N$^+$(CH$_3$)$_3$), 18.1 (CH(CH$_3$)$_2$), 12.6 (CH(CH$_3$)$_2$).

3-[(1*H*-Indol-3-yl)methyl]-1,3-dimethyl-1,3-dihydro-2*H*-pyrrol-2-one (13). Compound **3** (33 mg, 0.30 mmol) was placed in a Schlenk flask under argon, dissolved in DMF (2 mL), and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 14 mg, 0.35 mmol) was added under an argon counter flow. After stirring at 0 °C for 30 min, a 1 M solution of TBAF in THF (0.35 mL, 0.35 mmol) and a solution of **12** (140 mg, 0.30 mmol) in DMF (1.1 mL) were simultaneously added within 5 min. After stirring at 0 °C for 5 min the cooling bath was removed and the reaction mixture was stirred for 2.5 h at rt. The mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (cyclohexane/EtOAc, 2:1 + 0.5% TEA) yielded **13** (28 mg, 40%) as a colorless oil: R_f = 0.21 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 3265, 2960, 2927, 1673, 1454, 1395, 1332, 1248, 1231, 1055, 743; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.12 (s, 1H, N*H*), 7.60−7.57 (m, 1H, *H*-4′), 7.33 (*app.*-dt, J = 8.1, 1.0 Hz, 1H, *H*-7′), 7.19−7.14 (m, 1H, *H*-6′), 7.10 (ddd, J = 8.0, 7.1, 1.1 Hz, 1H, *H*-5′), 7.00 (d, J = 2.4 Hz, 1H, *H*-2′), 6.16 (d, J = 4.9 Hz, 1H, *H*-5), 5.32 (d, J = 4.9 Hz, 1H, *H*-4), 3.00 (AB-system, J_{app} = 14.1 Hz, 2H, C*H*$_2$), 2.95 (s, 3H, NC*H*$_3$), 1.24 (s, 3H, C*H*$_3$); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 182.7 (*C*=O), 136.0 (C$_q$7′a), 131.2 (*C*5), 128.3 (C$_q$3′a), 123.4 (*C*2′), 121.8 (*C*6′), 119.5 (*C*4′), 119.3 (*C*5′), 116.4 (*C*4), 111.9 (C$_q$3′), 111.1 (*C*7′), 51.9 (C$_q$3), 32.6 (CH$_2$),

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29.0 (NCH_3), 21.8 (CH_3); ESI-HRMS calcd for $[C_{15}H_{16}N_2O + Na]^+$ 263.1160, found 263.1161.

Gramine Methiodide (15). The title compound was prepared in 89% yield from gramine (**10**) according to the protocol of Lown and Weir.[39] Colorless solid: mp 157.6−157.9 °C (Lit.[39] 168−170 °C); IR (ATR) ν (cm^{-1}) = 3208, 1483, 1460, 1428, 1416, 1342, 1104, 979, 873, 750, 674, 619; ^{1}H NMR (400 MHz, DMSO) δ (ppm) = 11.64 (s, 1H, N*H*), 7.83 (d, *J* = 7.7 Hz, 1H, *H*-7), 7.69 (d, *J* = 2.5 Hz, 1H, *H*-2), 7.48 (d, *J* = 7.9 Hz, 1H, *H*-4), 7.20−7.11 (m, 2H, *H*-5,6), 4.69 (s, 2H, CH_2), 3.04 (s, 9H, $N^+(CH_3)_3$). The analytical data are in accordance with the literature.[39]

5-[(1*H*-Indol-3-yl)methyl]-1,3-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (16). Following the protocol of Danishefsky and Kitahara[19] **3** was transformed into crude **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 6.09 (d, *J* = 3.2 Hz, 1H), 5.77 (d, *J* = 3.2 Hz, 1H), 3.34 (s, 3H, NCH_3), 1.91 (s, 3H, CH_3), 0.24 (s, 9H, $Si(CH_3)_3$). Since the TMS ether **14** showed high moisture sensitivity it was not purified, but the crude product was immediately subjected to the subsequent transformation. Gramine (222 mg, 1.27 mmol) and triphenylphosphine (134 mg, 0.511 mmol) were placed in a microwave reaction vessel (10 mL volume) under an argon atmosphere and dissolved in MeCN (2 mL). A solution of silyl enol ether **14** (crude, from 140 mg of **3**, 1.26 mmol) in MeCN (0.9 mL) was added, and the tube was put in the microwave at 140 °C and 300 W for 2 × 1 h. Dichloromethane and saturated $NaHCO_3$ solution were added. The organic layer was washed with $NaHCO_3$ solution and brine and dried over $MgSO_4$. The crude product contained **3** as well as the α- and γ-substitution product (ratio 3:0.4:1.6). Purification of the mixture by flash column chromatography (cyclohexane/EtOAc, 1:1 + 1% TEA) yielded the title compound (50 mg, 17%) as a light yellow oil: R_f = 0.10 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 3273, 2922, 1668, 1642, 1457, 1436, 1402, 1342, 1236, 1102, 1070, 745; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.55 (s, 1H, N*H*), 7.54 (d, *J* = 8.1 Hz, 1H, *H*-7′), 7.38 (d, *J* = 8.1 Hz, 1H, *H*-4′), 7.26−7.16 (m, 1H, *H*-6′), 7.14 (ddd, *J* = 8.1, 7.0, 1.1 Hz, 1H, *H*-5′), 7.00 (d, *J* = 2.3 Hz, 1H, *H*-2′), 6.58 (dq, *J* = 1.8 Hz, 1H, *H*-4), 4.15 (ddt, *J* = 9.0, 4.5, 1.8 Hz, 1H, *H*-5), 3.36 (dd, *J* = 14.2, 4.5 Hz, 1H, CH_{2A}), 3.07 (s, 3H, NCH_3), 2.74 (dd, *J* = 14.2, 9.0 Hz, 1H, CH_{2B}), 1.83 (t, *J* = 1.8 Hz, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 172.3 (*C*═O), 140.7 (*C*4), 136.3 (C_q7a′), 135.0 (C_q3), 127.5 (C_q3a′), 122.7 (*C*2′), 122.2 (*C*6′), 119.6 (*C*5′), 118.5 (*C*4′), 111.5 (*C*7′), 110.5 (C_q3′), 63.0 (*C*5), 27.7 (NCH_3), 27.2 (CH_2), 11.4 (CH_3); ESI-HRMS calcd for $[C_{15}H_{16}N_2O + Na]^+$ 263.1160, found 263.1172.

***N*-Methyl-3-methyl-5-(3-methinyl-indolyl)-pyrrolidin-2-one (17).** Gramine (42 mg, 0.24 mmol) and triphenylphosphine (25 mg, 0.095 mmol) were placed in a microwave reaction vessel (10 mL volume) under an argon atmosphere and dissolved in acetonitrile (1 mL). A solution of silyl enol ether **14** (crude, from 25 mg of **3**, 0.22 mmol) in acetonitrile (0.5 mL) was added, and the tube was put in the microwave at 140 °C and 300 W for 1 h. Dichloromethane and saturated $NaHCO_3$ solution were added. The organic layer was washed with $NaHCO_3$ solution and brine and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield a crude product (101 mg, yellow oil) which contained **3** as well as rearranged γ-product **17**, together with traces of the α- and γ-substitution product. Purification by flash column chromatography (cyclohexane/EtOAc, 2:1) yielded the title compound (9.0 mg, 17%) as a yellow oil: R_f = 0.24 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 3272, 2967, 2928, 1698, 1650, 1457, 1429, 1327, 1227, 1011, 740, 697; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.23 (s_{br}, 1H, N*H*), 7.70−7.66 (m, 1H, *H*-4′), 7.39 (*app.*-dt, *J* = 8.1, 0.9 Hz, 1H, *H*-7′), 7.27−7.20 (m, 1H, *H*-6′), 7.17 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H, *H*-5′), 7.10 (d, *J* = 2.5 Hz, 1H, *H*-2′), 5.96 (t, *J* = 2.3 Hz, 1H, = C*H*), 3.21−2.12 (m, 1H, CH_{2A}), 3.15 (s, 3H, NCH_3), 2.79−2.69 (m, 1H, *H*-3), 2.50 (ddd, *J* = 16.5, 5.8, 2.3 Hz, 1H, CH_{2B}), 1.32 (d, *J* = 7.3 Hz, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 178.3 (*C*═O), 139.6 (C_q5), 135.7 (C_q7a′), 127.2 (C_q3a′), 122.7 (*C*6′), 120.1 (*C*2′), 119.8 (*C*5′), 118.8 (*C*4′), 113.0 (C_q3′), 111.2 (*C*7′), 92.8 (═CH), 35.5 (*C*3), 33.1 (*C*4), 27.1 (NCH_3), 17.5 (CH_3); ESI-HRMS calcd for $[C_{15}H_{16}N_2O + Na]^+$ 263.1160, found 263.1159.

1*H*-Indole-3-carbaldehyde (19). The title compound was prepared from 1*H*-indole according to the protocol of Cuny.[23] Light brown solid: mp 193.9−196.2 °C (Lit.[40] 196−197 °C); R_f = 0.49 (CH_2Cl_2/MeOH, 9:1); IR (ATR) ν (cm^{-1}) = 3166, 1631, 1613, 1576, 1520, 1443, 1393, 1243, 1124, 787, 759, 640; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 9.91 (s, 1H, C*H*O), 8.14 (s, 1H), 8.12 (s, 1H), 8.09 (dd, *J* = 6.9, 1.5 Hz, 1H, *H*-7), 7.47 (dd, *J* = 7.5, 1.4 Hz, 1H, *H*-4), 7.23−7.15 (m, 2H, *H*-5,6). The analytical data are in accordance with the literature.[41]

***tert*-Butyl 3-Formyl-1*H*-indole-1-carboxylate (20).** The title compound was prepared from **19** according to the protocol of Pelcman[24] (quantitative yield). Off-white solid: mp 123.4−124.8 °C (decomposition) (Lit.[42] 121−123 °C); R_f = 0.34 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2980, 2816, 1743, 1679, 1398, 1359, 1242, 1155, 1134, 1102, 760, 751; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 10.10 (s, 1H, C*H*O), 8.29 (dd, *J* = 7.0, 1.3 Hz, 1H, *H*-7), 8.24 (s, 1H, *H*-2), 8.15 (d, *J* = 8.0 Hz, 1H, *H*-4), 7.42 (ddd, *J* = 8.3, 7.8, 1.6 Hz, 1H), 7.37 (*app.*-td, *J* = 7.5, 1.3 Hz, 1H), 1.71 (s, 9H, Boc). The analytical data are in accordance with the literature.[43]

***tert*-Butyl 3-(Hydroxymethyl)-1*H*-indole-1-carboxylate (21).** The title compound was prepared from **20** according to the protocol of Pelcman[24] (quantitative yield). Light brown oil: R_f = 0.60 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 3377, 2979, 1733, 1453, 1369, 1308, 1269, 1257, 1159, 1088, 767, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.14 (d, *J* = 7.8 Hz, 1H, *H*-7), 7.65 (ddd, *J* = 7.8, 1.2, 0.8 Hz, 1H), 7.58 (s, 1H, *H*-2), 7.34 (ddd, *J* = 8.5, 7.2, 1.2 Hz, 1H), 7.28−7.24 (m, 1H), 4.84 (d, *J* = 0.8 Hz, 2H, CH_2), 1.67 (s, 9H, Boc). The analytical data are in accordance with the literature.[43]

***tert*-Butyl 3-(Bromomethyl)-1*H*-indole-1-carboxylate (22).** The title compound was synthesized from **21** by a modification of the protocol of Schöllkopf.[25] Triphenylphosphine (3.21 g, 12.2 mmol) was dissolved in cyclohexane (90 mL), and bromine (0.67 mL, 13 mmol) was slowly added. After stirring for 15 min, **21** (3.03 g, 12.3 mmol) was added, and the reaction mixture was stirred overnight. Filtration over Celite and concentration of the filtrate yielded **22** (3.43 g, 91%) as a light yellow solid: mp 116.0−116.3 °C (decomposition) (Lit.[44] 106−107 °C); R_f = 0.56 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2979, 1735, 1453, 1366, 1271, 1258, 1205, 1154, 1114, 1083, 764, 746; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 8.16 (d, *J* = 8.1 Hz, 1H, *H*-7), 7.71−7.68 (m, 2H), 7.41−7.30 (m, 2H), 4.69 (s, 2H, CH_2), 1.68 (s, 9H, Boc). The analytical data are in accordance with the literature.[44]

Alkylation of Pyrrolinone 3 with 3-Bromomethylindole 22. In a Schlenk flask, compound **3** (38 mg, 0.34 mmol) was dissolved in DMF (2 mL) under an argon atmosphere and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 14 mg, 0.35 mmol) was added under an argon counter flow. After stirring at 0 °C, a solution of **22** (100 mg, 0.322 mmol) in DMF (1 mL) was added. After 15 min, the cooling bath was removed, and the reaction mixture was left to stir at ambient temperature for 21 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were thoroughly washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to afford the crude product (101 mg) as a light yellow oil, from which the γ-substitution product **23** (28 mg, 26%), the α-substitution product **24** (29 mg, 27%), and compounds **25** (13 mg, 18%) and **26** (8 mg, 11%) were isolated by repeated flash chromatography (vide infra).

***tert*-Butyl 3-[(1,4-Dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)methyl]-1*H*-indole-1-carboxylate (23).** Purification by flash column chromatography (cyclohexane/EtOAc, 3:1 + 1% TEA) yielded the title compound as a colorless oil (28 mg, 26%): R_f = 0.22 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 2978, 2928, 1730, 1683, 1453, 1369, 1256, 1156, 1085, 768, 746; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.14 (d, *J* = 8.2 Hz, 1H, *H*-7), 7.48−7.45 (m, 1H, *H*-4), 7.43 (s_{br}, 1H, *H*-2), 7.34 (ddd, *J* = 8.4, 7.2, 1.3 Hz, 1H, *H*-6), 7.29−7.24 (m, 1H, *H*-5), 6.58 (dq, *J* = 1.7 Hz, 1H, *H*-4′), 4.17−4.11 (m, 1H, *H*-5′), 3.29 (ddd, *J* = 14.3, 4.9, 1.0 Hz, 1H, CH_{2A}), 3.06 (s, 3H, NCH_3), 2.63 (ddd, *J* = 14.3, 9.7, 0.7 Hz, 1H, CH_{2B}), 1.86 (t, *J* = 1.7 Hz, 3H, CH_3), 1.68 (s, 9H, Boc); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 172.0 (*C*═O), 149.7 (COO^tBu),

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140.0 (*C*4′), 135.5 (2C: C_q8, C_q3′), 130.4 (C_q3a), 124.8 (*C*6), 123.9 (*C*2), 122.8 (*C*5), 118.8 (*C*4), 115.6 (*C*7), 115.5 (C_q3), 84.0 ($C(CH_3)_3$), 62.2 (*C*5′), 28.4 ($C(CH_3)_3$), 27.7 (NCH_3), 27.2 (CH_2), 11.4 (CH_3); ESI-HRMS calcd for $[C_{20}H_{24}N_2O_3 + H]^+$ 341.1865, found 341.1870.

***tert*-Butyl 3-[(1,3-Dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrol-3-yl)methyl]-1*H*-indole-1-carboxylate (24).** Purification by flash column chromatography (cyclohexane/EtOAc, 10:1 + 1% TEA) yielded the side product **24** as a colorless oil (29 mg, 27%): R_f = 0.26 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2962, 2926, 2854, 1731, 1703, 1453, 1369, 1258, 1158, 1078, 767, 747; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.09 (d, *J* = 7.5 Hz, 1H, *H*-7), 7.52 (ddd, *J* = 7.7, 1.2, 0.7 Hz, 1H, *H*-4), 7.35 (s, 1H, *H*-2), 7.31−7.25 (m, 1H, *H*-6), 7.24−7.19 (m, 1H, *H*-5), 6.21 (d, *J* = 4.9 Hz, 1H, *H*-5′), 5.29 (d, *J* = 4.9 Hz, 1H, *H*-4′), 2.97 (s, 3H, NCH_3), 2.93 (AB-system, J_{app} = 14.2, 0.9 Hz, 2H, CH_2), 1.66 (s, 9H, Boc), 1.25 (s, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 182.3 (*C*═O), 149.9 (COO^{t}Bu), 135.2 (*C*7a), 131.67 (*C*5′), 131.31 (C_q3a), 124.4 (*C*2), 124.2 (*C*6), 122.4 (*C*5), 119.7 (*C*4), 116.6 (C_q3), 115.7 (*C*4′), 115.1 (*C*7), 83.7 ($C(CH_3)_3$), 51.0 (C_q3′), 32.2 (CH_2), 29.1 (NCH_3), 28.4 ($C(CH_3)_3$), 22.0 (CH_3); ESI-HRMS calcd for $[C_{20}H_{24}N_2O_3 + Na]^+$ 363.1685, found 363.1694.

***tert*-Butyl 3-[(4-{[1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl]-methyl}-1,4-dimethyl-5-oxopyrrolidin-2-ylidene)methyl]-1*H*-indole-1-carboxylate (25).** Purification by flash column chromatography (cyclohexane/EtOAc, 10:1 + 1% TEA) yielded the side product **25** as a colorless oil (13 mg, 18%): R_f = 0.41 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2976, 2930, 1724, 1656, 1453, 1369, 1255, 1154, 1081, 762, 745; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.13−8.01 (m, 2H, *H*-7/7″), 7.52−7.49 (m, 1H, *H*-4), 7.46 (ddd, *J* = 7.8, 1.2, 0.7 Hz, 1H, *H*-4″), 7.35−7.27 (m, 3H, *H*-2/2″, *H*-6″), 7.25−7.20 (m, 2H, *H*-6, *H*-5″), 7.12 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H, *H*-5), 5.59 (s, 1H, = *CH*), 3.15−3.10 (m, 1H, CH_{2A}), 3.02 (dd, *J* = 16.3, 1.9 Hz, 1H, *H*-3$_A$), 2.95 (s, 3H, NCH_3), 2.85 (d, *J* = 14.5 Hz, 1H, CH_{2B}), 2.62 (dd, *J* = 16.3, 1.9 Hz, 1H, *H*-3$_B$), 1.68 (s, 9H, Boc), 1.53 (s, 9H, Boc), 1.39 (s, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 179.8 (*C*═O), 150.0, 149.6 (2 × COO^{t}Bu), 141.6 (C_q2′), 135.3, 134.8 (C_q7a, C_q7a″), 131.1 (C_q3a), 130.5 (C_q3a″), 124.8 (*C*6″), 124.4 (2C, *C*6, *C*2″), 122.7 (*C*5″), 122.5 (*C*5), 120.7 (*C*2), 119.3 (*C*4), 118.8 (*C*4″), 116.8 (C_q3a), 116.1 (C_q3a″), 115.3 (*C*7″), 115.2 (*C*7), 91.1 (═*C*H), 83.9, 83.5 (2 × $C(CH_3)_3$), 44.9 (C_q4′), 37.6 (*C*3′), 33.5 (CH_2), 28.4, 28.2 (2 × $C(CH_3)_3$), 27.1 (NCH_3), 24.9 (CH_3); ESI-HRMS calcd for $[C_{34}H_{39}N_3O_5 + Na]^+$ 592.2787, found 592.2773.

5,5-Bis[(1-*tert*-butyloxycarbonyl-1*H*-indol-3-yl)methylene]-1,3-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (26). Purification by flash column chromatography (cyclohexane/EtOAc, 3:1 + 1% TEA) yielded the side product **26** as a colorless oil (8 mg, 11%): R_f = 0.38 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 2978, 2927, 1732, 1682, 1453, 1369, 1309, 1257, 1157, 1086, 768, 746; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.09 (d, *J* = 7.3 Hz, 2H, *H*-7), 7.37 (ddd, *J* = 7.8, 1.2, 0.7 Hz, 2H, *H*-4), 7.33−7.27 (m, 4H, *H*-2, *H*-6), 7.24−7.19 (m, 2H, *H*-5), 6.59 (q, *J* = 1.6 Hz, 1H, *H*-2′), 3.27 (dd, *J* = 14.6, 1.0 Hz, 2H, CH_{2A}), 3.08−3.03 (m, 2H, CH_{2B}), 3.00 (s, 3H, NCH_3), 1.66 (s, 18H, 2 × Boc), 1.65 (d, *J* = 1.6 Hz, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 171.5 (*C*═O), 149.7 (COO^{t}Bu), 143.7 (*C*3′), 135.2 (2C, C_q4′, C_q7a), 130.9 (C_q3a), 124.6, 124.5 (*C*2, *C*6), 122.6 (*C*5), 118.9 (*C*4), 115.5 (*C*7), 114.4 (C_q3), 84.0 ($C(CH_3)_3$), 68.2 (C_q2′), 31.2 (2 × CH_2), 28.4 ($C(CH_3)_3$), 25.0 (NCH_3), 10.9 (CH_3); ESI-HRMS calcd for $[C_{34}H_{39}N_3O_5 + Na]^+$ 592.2787, found 592.2786.

4-Bromo-1*H*-indole-3-carbaldehyde (28). The title compound was prepared from **27** in 91% yield according to the protocol of Dixon.[26] Off-white solid: mp 178.4−182.2 °C (MeOH/H_2O) (Lit.[45] 185−187 °C); R_f = 0.18 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3212, 3170, 2936, 2872, 1639, 1512, 1487, 1388, 1333, 1295, 1190, 775, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 10.93 (s, 1H, *CH*O), 9.20 (s, 1H, N*H*), 8.11 (d, *J* = 3.2 Hz, 1H, *H*-2), 7.51 (dd, *J* = 7.7, 0.8 Hz, 1H), 7.45 (dd, *J* = 8.2, 0.8 Hz, 1H), 7.15 (*app.*-t, *J* = 7.9 Hz, 1H, *H*-5). The analytical data are in accordance with the literature.[26,45]

***tert*-Butyl 4-Bromo-3-formyl-1*H*-indole-1-carboxylate (29).** The title compound was prepared from **28** in quantitative yield according to the protocol of Pelcman.[24] Off-white solid: mp 118.0−118.6 °C (Lit.[46] 117−119 °C); R_f = 0.51 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2980, 1747, 1672, 1529, 1424, 1364, 1252, 1139, 1090, 1017, 854, 777, 735; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 10.93 (s, 1H, *CH*O), 8.36 (s, 1H, *H*-2), 8.25 (dd, *J* = 8.4, 0.7 Hz, 1H, *H*-7), 7.52 (dd, *J* = 7.8, 0.7 Hz, 1H, *H*-5), 7.22 (*app.*-t, *J* = 8.1 Hz, 1H, *H*-6), 1.68 (s, 9H, Boc); ^{13}C NMR, COSY, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 186.9 (*CH*O), 148.4 (*C*═O), 137.3 (C_q7a), 132.0 (*C*2), 128.6 (*C*5), 126.9 (C_q3a), 126.1 (*C*6), 121.1 (C_q3), 114.9 (*C*7), 113.5 (C_q4), 86.2 ($C(CH_3)_3$), 28.1 (3 × CH_3). Anal. Calcd for $C_{14}H_{14}BrNO_3$: C, 51.87; H, 4.35; N, 4.32. Found: C, 51.76; H, 4.50; N, 4.43. The analytical data are in accordance with the literature.[46]

***tert*-Butyl 4-Bromo-3-(hydroxymethyl)-1*H*-indole-1-carboxylate (30).** The title compound was prepared from **29** in 92% yield according to a protocol by Pelcman.[24] Off-white solid: mp 107.5−108.7 °C; R_f = 0.22 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 3372, 2979, 2933, 1732, 1421, 1367, 1278, 1253, 1152, 1095, 772, 736; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.17 (d, *J* = 8.3 Hz, 1H, *H*-7), 7.64 (s, 1H, *H*-2), 7.38 (dd, *J* = 7.8, 0.8 Hz, 1H, *H*-5), 7.15 (*app.*-t, *J* = 8.1 Hz, 1H, *H*-6), 4.96 (s, 2H, CH_2), 1.65 (s, 9H, Boc); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 149.2 (*C*═O), 137.4 (C_q7a), 128.0 (C_q3a), 126.9 (*C*5), 126.0 (*C*2), 125.5 (*C*6), 120.7 (C_q3), 114.7 (*C*7), 113.5 (C_q4), 84.4 ($C(CH_3)_3$), 57.3 (CH_2), 28.2 (3 × CH_3); ESI-HRMS calcd for $[C_{14}H_{16}{}^{79}BrNO_3 + Na]^+$ 348.0211, found 348.0210. Anal. Calcd for $C_{14}H_{16}BrNO_3$: C, 51.55; H, 4.94; N, 4.29. Found: C, 51.82; H, 4.74; N, 4.32.

***tert*-Butyl 4-Bromo-3-[(1,4-dimethyl-5-oxo-2,5-dihydro-1*H*-pyrrol-2-yl)methyl]-1*H*-indole-1-carboxylate (32).** Triphenylphosphine (3.35 g, 12.8 mmol) was dissolved in cyclohexane (100 mL), and bromine (0.68 mL, 13 mmol) was slowly added. After stirring for 15 min, **30** (4.11 g, 12.6 mmol) was added, and the reaction mixture was stirred overnight. Filtration over Celite and concentration of the filtrate *in vacuo* yielded *tert*-butyl 4-bromo-3-(bromomethyl)-1*H*-indole-1-carboxylate (**31**) (4.53 g, 93%) as a light red oil: R_f = 0.38 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2979, 2933, 1740, 1420, 1370, 1354, 1295, 1256, 1158, 1123, 1091, 744; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.18 (d, *J* = 8.3 Hz, 1H, *H*-7), 7.74 (s, 1H, *H*-2), 7.44 (dd, *J* = 7.8, 0.8 Hz, 1H, *H*-5), 7.18 (*app.*-t, *J* = 8.1 Hz, 1H, *H*-6), 4.94 (d, *J* = 0.5 Hz, 2H, CH_2), 1.66 (s, 9H, Boc); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 148.7 (*C*═O), 137.0 (C_q7a), 127.8 (*C*2), 127.7 (*C*5), 126.6 (C_q3a), 125.9 (*C*6), 117.8 (C_q3), 114.7 (*C*7), 113.9 (C_q4), 84.8 ($C(CH_3)_3$), 28.2 (3 × CH_3), 25.8 (CH_2); FD-MS ($C_{14}H_{15}Br_2NO_2$): 389.0. Pyrrolinone **3** (159 mg, 1.43 mmol) was placed in a Schlenk flask under argon, dissolved in DMF (6 mL), and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 56 mg, 1.4 mmol) was added under an argon counter flow. After stirring at 0 °C for 30 min, a solution of bromide **31** (500 mg, 1.29 mmol) in DMF (4 mL) was added. After 10 min, the cooling bath was removed and the reaction mixture was left to stir at ambient temperature for 1 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic layers were thoroughly washed with brine, dried over $MgSO_4$, and concentrated *in vacuo*. Purification by flash column chromatography (cyclohexane/EtOAc, 9:1 + 1% TEA) yielded **32** (276 mg, 52%) as a light yellow oil; R_f = 0.19 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 2980, 2927, 1736, 1687, 1421, 1370, 1278, 1256, 1148, 1094, 846, 776, 732. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.19 (d, *J* = 8.3 Hz, 1H, *H*-7), 7.44 (s, 1H, *H*-2), 7.41 (dd, *J* = 7.8, 0.8 Hz, 1H, *H*-5), 7.16 (*app.*-t, *J* = 8.1 Hz, 1H, *H*-6), 6.63 (dq, *J* = 1.7 Hz, 1H, *H*-4′), 4.41−4.22 (m, 1H, *H*-5′), 3.78 (dd, *J* = 13.8, 4.5 Hz, 1H, CH_{2A}), 3.08 (s, 3H, N−CH_3), 2.58 (dd, *J* = 13.8, 10.3 Hz, 1H, CH_{2A}), 1.89 (t, *J* = 1.7 Hz, 3H, CH_3), 1.68 (s, 9H, Boc); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 172.0 (*C*═O), 149.1 (COO^{t}Bu), 139.8 (*C*4′), 137.1 (C_q7a), 135.4 (C_q3′), 128.1 (C_q3a), 127.5 (*C*5), 126.4 (*C*2), 125.6 (*C*6), 116.1 (C_q3), 114.8 (*C*7), 113.9 (C_q4), 84.7 ($C(CH_3)_3$), 62.5 (*C*5′), 28.4 (CH_2), 28.3 ($C(CH_3)_3$), 27.8

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(NCH_3), 11.5 (CH_3). ESI-HRMS calcd for $[C_{20}H_{23}N_2O_3{}^{79}Br + H]^+$ 419.0970, found 419.0971. *tert*-Butyl 4-bromo-3-[(*E*)-(1,4-dimethyl-5-oxopyrrolidin-2-ylidene)methyl]-1*H*-indole-1-carboxylate (**35**) was obtained by rearrangement of compound **32** during coevaporation with $CHCl_3$ containing traces of acid. ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.14 (d_{br}, J = 8.1 Hz, 1H, *H*-7), 7.47 (s_{br}, 1H, *H*-2), 7.40 (d, J = 7.7 Hz, 1H, *H*-5), 7.13 (*app.*-t, J = 8.1 Hz, 1H, *H*-6), 6.50 (s_{br}, 1H, =C*H*), 3.17−3.05 (m, 1H, CH_{2A}), 3.12 (s, 3H, NCH_3), 2.75−2.64 (m, 1H, *H*-3′), 2.45 (ddd, J = 16.5, 6.0, 2.0 Hz, 1H, CH_{2B}), 1.68 (s, 9H, Boc), 1.29 (d, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 178.4 (*C*=O), 149.3 (*C*OO^{t}Bu), 141.4 (C_q5′), 136.5 (C_q7a), 128.2 (C_q3a), 127.7 (*C*5), 125.4 (*C*6), 123.4 (*C*2), 117.2 (C_q3), 114.7 (*C*7), 114.6 (C_q4), 93.6 (=CH), 84.6 ($C(CH_3)_3$), 35.3 (*C*3′), 32.6 (CH_2), 28.3 ($C(CH_3)_3$), 27.1 (NCH_3), 17.2 (CH_3).

***tert*-Butyl 4-Bromo-3-[(1,3-dimethyl-2-oxo-2,3-dihydro-1*H*-pyrrol-3-yl)methyl]-1*H*-indole-1-carboxylate (33).** The title compound was obtained as a side product of the reaction of **32** and **3** (7.2 mmol scale) as a colorless solid (160 mg, 5%): mp 121.7−126.2 °C; R_f = 0.31 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2977, 1734, 1694, 1419, 1369, 1356, 1276, 1255, 1157, 1088, 1055, 730; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.15 (d, J = 8.2 Hz, 1H, *H*-7), 7.35 (dd, J = 7.8, 0.9 Hz, 1H, *H*-5), 7.31 (s, 1H, *H*-2), 7.08 (*app.*-t, J = 8.1 Hz, 1H, *H*-6), 6.07 (d, J = 4.9 Hz, 1H, *H*-5′), 5.54 (d, J = 4.9 Hz, 1H, *H*-4′), 3.71 (d, J = 14.6 Hz, 1H, CH_{2A}), 3.10 (d, J = 14.6 Hz, 1H, CH_{2B}), 2.95 (s, 3H, N−CH_3), 1.63 (s, 9H, Boc), 1.31 (s, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 182.4 (*C*=O), 149.14 (*C*OO^{t}Bu), 136.7 (C_q7a), 131.6 (*C*5′), 128.7 (C_q3a), 127.7 (*C*5), 125.7 (*C*2), 124.8 (*C*6), 117.0 (*C*3), 115.1 (*C*4′), 114.5 (*C*7), 114.2 (C_q4), 84.1 ($C(CH_3)_3$), 51.8 (C_q3′), 32.0 (CH_2), 28.9 (NCH_3), 28.3 ($C(CH_3)_3$), 22.56 (CH_3); ESI-HRMS calcd for $[C_{20}H_{23}{}^{79}BrN_2O_3 + H]^+$ 419.0970, found 419.0980.

5,5-Bis[(4-bromo-1-*tert*-butyloxycarbonyl-1*H*-indol-3-yl)-methylene]-1,3-dimethyl-1,5-dihydro-2*H*-pyrrol-2-one (34). The title compound was obtained as a side product of the reaction of **32** and **3** (7.9 mmol scale) as a colorless oil (180 mg, 3%): R_f = 0.15 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2979, 2931, 1738, 1687, 1421, 1370, 1278, 1256, 1156, 1098, 1056, 733; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.15 (d, J = 8.3 Hz, 2H, *H*-7′), 7.35 (dd, J = 7.8, 0.8 Hz, 2H, *H*-5′), 7.28 (s, 2H, *H*-2′), 7.09 (*app.*-t, J = 8.1 Hz, 2H, *H*-6′), 6.84 (q, J = 1.6 Hz, 1H, *H*-4), 3.92 (d, J = 15.0 Hz, 2H, CH_{2A}), 3.31 (d, J = 15.0 Hz, 2H, CH_{2B}), 3.08 (s, 3H, N−CH_3), 1.65 (s, 18H, Boc), 1.58 (d, J = 1.6 Hz, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 171.9 (*C*=O), 149.0 (*C*OO^{t}Bu), 143.3 (*C*4), 136.7 (C_q7a′), 135.5 (C_q3), 128.2 (C_q3a′), 127.9 (*C*5′), 126.4 (*C*2′), 125.2 (*C*6′), 114.7 (2C, C_q3′, *C*7′), 113.9 (C_q4′), 84.6 ($C(CH_3)_3$), 68.6 (C_q5), 30.1 (2xCH_2), 28.3 ($C(CH_3)_3$), 25.0 (NCH_3), 11.0 (CH_3); ESI-HRMS calcd for $[C_{34}H_{37}{}^{79}Br_2N_3O_5 + Na]^+$ 748.0998, found 748.1006.

***tert*-Butyl 7,9-Dimethyl-8-oxo-6,6a,7,8-tetrahydro-4*H*-indolo[6,5,4-*cd*]indole-4-carboxylate (36).** Palladium(II) acetate (45.5 mg, 0.20 mmol), triphenylphosphine (173 mg, 0.66 mmol), and silver(I) carbonate (677 mg, 2.46 mmol) were placed in a Schlenk flask under an argon atmosphere. A solution of bromoarene **32** (460 mg, 1.10 mmol) in dry toluene (40 mL) and dry triethylamine (40 mL) were added. The reaction mixture was degassed (three freeze−pump−thaw cycles) and then heated to 110 °C (oil bath) for 13 h. After cooling to rt, the reaction mixture was filtered over Celite and concentrated *in vacuo*. Purification by flash column chromatography (cyclohexane/EtOAc, 3:1 + 1% TEA) yielded the title compound (274 mg, 74%) as a light yellow oil: R_f = 0.10 (cyclohexane/EtOAc, 2:1); IR (ATR) ν (cm^{-1}) = 2978, 2936, 1730, 1684, 1438, 1388, 1353, 1300, 1147, 1116, 784, 752; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 7.91 (s_{br}, 1H, *H*-3), 7.43−7.34 (m, 3H, *H*-1, *H*-2, *H*-5), 4.13 (ddd, J = 12.1, 6.3, 1.8 Hz, 1H, *H*-6a), 3.49 (dd, J = 14.5, 6.3 Hz Hz, 1H, *H*-6_A), 3.10 (s, 3H, N−CH_3), 2.52 (ddd, J = 14.5, 12.1, 2.2 Hz, 1H, *H*-6_B), 2.20 (dd, J = 1.8, 0.9 Hz, 1H, CH_3), 1.67 (s, 9H, Boc); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 172.6 (*C*=O), 149.8 (*C*OO^{t}Bu), 145.0 (C_q9a), 133.6 (C_q3a), 129.7 (C_q9c), 128.2 (C_q9), 125.7 (*C*2), 124.3 (C_q9b), 121.4 (*C*5), 119.1 (*C*1), 115.7 (*C*3), 114.2 (C_q5a), 84.1 ($C(CH_3)_3$), 60.9 (*C*6a), 28.3 ($C(CH_3)_3$), 27.5 (NCH_3), 26.7 (*C*6), 10.1 (CH_3); ESI-HRMS calcd for $[C_{20}H_{22}N_2O_3 + Na]^+$ 361.1528, found 361.1526.

***tert*-Butyl 7-Methyl-9-methylidene-8-oxo-6,6a,7,8,9,9a-hexahydro-4*H*-indolo[6,5,4-*cd*]indole-4-carboxylate (37).** Palladium(II) acetate (1.3 mg, 5.8 μmol, 12 mol %) and triphenylphosphine (2.6 mg, 9.9 μmol, 21 mol %) were placed in a Schlenk flask under an argon atmosphere. A solution of bromoarene **32** (20 mg, 0.048 mmol) in dry dimethylformamide (0.3 mL) and dry triethylamine (50 μL) were added. The medium was degassed (four freeze−pump−thaw cycles) and then heated to 100 °C (oil bath) for 7 h to yield **37** and **36** in a 1:0.15 ratio (^{1}H NMR). Purification by repeated column chromatography (cyclohexane/EtOAc, 3:1) yielded an analytically pure sample. Orange oil, R_f = 0.17 (cyclohexane/EtOAc, 1:1); IR (ATR) ν (cm^{-1}) = 2928, 1728, 1692, 1441, 1392, 1349, 1301, 1258, 1149, 1117, 757, 732; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) = 7.86 (s_{br}, 1H, *H*-3), 7.38−7.31 (m, 2H, *H*-2, *H*-5), 7.18 (d, J = 7.4 Hz, 1H, *H*-1), 6.06 (d, J = 2.8 Hz, 1H, =CH_{2A}), 5.34 (d, J = 2.8 Hz, 1H, =CH_{2B}), 4.27 (dt, J = 6.3, 2.8 Hz, 1H, *H*-9a), 4.02 (ddd, J = 8.8, 6.3, 5.6 Hz, 1H, *H*-6a), 3.34 (ddd, J = 15.8, 5.6, 1.0 Hz, 1H, *H*-6_A), 3.05 (s, 3H, NCH_3), 2.58 (ddd, J = 15.8, 8.8, 1.9 Hz, 1H, *H*-6_B), 1.67 (s, 9H, Boc); ^{13}C NMR, COSY, HSQC, HMBC (151 MHz, $CDCl_3$) δ (ppm) = 168.0 (C=O), 142.1 (C_q9), 133.7 (C_q3a, resonance located by HBMC), 128.2 (C_q9c), 127.3 (C_q9b), 125.6 (*C*2), 121.6 (*C*1), 120.2 (*C*5), 116.1 (=CH_2), 113.9 (*C*3), 113.4 (C_q5a), 83.8 ($C(CH_3)_3$), 57.4 (*C*6a), 41.5 (*C*9a), 28.4 (NCH_3), 28.3 ($C(CH_3)_3$), 24.6 (*C*6); the resonance of COO^{t}Bu could not be found; ESI-HRMS calcd for $[C_{20}H_{22}N_2O_3 + H]^+$ 339.1709, found 339.1703. Partial isomerization to **36** occurred by treatment with toluene/triethylamine (1:1) at 110 °C or with palladium(II) acetate in toluene at 110 °C.

7,9-Dimethyl-6,6a,7,8-tetrahydro-4*H*-indolo[6,5,4-*cd*]indole (38). Lactam **36** (41 mg, 0.12 mmol) was placed in a Schlenk flask, lithium aluminum hydride (2 M solution in THF, 2 mL, 4 mmol) was added, and the reaction mixture was heated to reflux for 17 h. The reaction mixture was cooled to 0 °C, and a 1 N NaOH solution was carefully added. The resulting colorless solid was removed by filtration, and the filtrate was extracted with ethyl acetate. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated. Purification by flash column chromatography ($CHCl_3$/MeOH, 6:1 + 1% TEA) yielded **38** (15 mg, 56%) as an off-white to light brown oil; R_f = 0.21 ($CHCl_3$/MeOH, 5:1); IR (ATR) ν (cm^{-1}) = 3199, 2934, 2854, 2769, 1590, 1575, 1446, 1380, 1364, 1337, 786, 752; ^{1}H NMR, COSY (400 MHz, $CDCl_3$) δ (ppm) = 8.17 (s, 1H, N*H*), 7.28−7.15 (m, 3H, *H*1,2,3), 6.91 (t, J = 1.8 Hz, 1H, *H*-5), 3.99 (ddd, J = 13.8, 3.6, 1.2 Hz, 1H, *H*-8_A), 3.82−3.73 (m, 1H, *H*-6a), 3.59−3.526 (m, 1H, *H*-8_B), 3.36 (dd, J = 14.4, 6.2 Hz, 1H, *H*-6_A), 2.78 (ddd, J = 14.4, 11.0, 1.8 Hz, 1H, *H*-6_B), 2.66 (s, 3H, NCH_3), 2.14 (s_{br}, 3H, CH_3); ^{13}C NMR, HSQC, HMBC (100.6 MHz, $CDCl_3$) δ (ppm) = 134.2 (C_q3a), 130.0 (C_q9b), 129.9 (C_q9), 127.4 (C_q9c), 125.4 (C_q9a), 123.2 (*C*2), 118.7 (*C*5), 115.0 (*C*1), 111.6 (C_q5a), 109.7 (*C*3), 72.7 (*C*6a), 67.7 (*C*8), 40.5 (NCH_3), 28.5 (*C*6), 13.7 (CH_3); ESI-HRMS calcd for $[C_{15}H_{16}N_2 + H]^+$ 225.1392, found 225.1383. The analytical data are in accordance with the literature.[11]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02815.

^{1}H and ^{13}C NMR spectra of all synthesized compounds (PDF)

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Notes

The authors declare no competing financial interest.

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