Electronic Supplemental Information

Gold(I)-Catalysed Approach towards Harmalidine an Elusive Alkaloid from Peganum harmala

Solène Miaskiewicz, a Jean-Marc Weibel, a Patrick Pale a and Aurélien Blanc* a

*Corresponding Author: ablanc@unistra.fr

Laboratoire de Synthèse, Réactivité Organiques et Catalyse
Institut de Chimie, UMR 7177 - CNRS, Université de Strasbourg
4 rue Blaise Pascal, 67070 Strasbourg, France.

GENERAL INFORMATION .............................................................................................................................................. S1

EXPERIMENTAL AND PREDICTED 13C NMR DATA OF HARMALIDINE & COMPOUND 13 ................................ S2

CHARACTERIZATION OF ORGANIC COMPOUNDS........................................................................................................ S4

GENERAL PROCEDURE 1 FOR PREPARATION OF ALKYNYL ALDIMINES (GP1) ................................................................. S4

GENERAL PROCEDURE 2 FOR ENOLATE-IMINE CONDENSATION (GP2) ........................................................................ S5

GENERAL PROCEDURE 3 FOR AZETIDINONE REDUCTION (GP3) ................................................................................ S6

SYNTHESIS OF THE CHLOROETHYL 2,3-DIHYDROPYRROLO[1,2-a]INDOLE DERIVATIVE 6D ............................................. S7

GENERAL PROCEDURE 4 FOR THE GOLD-CATALYZED CONVERSION OF N-ARYL ALKYNYL AZETIDINES 3 TO PYRROLO[1,2-a]INDOLES 4 (GP4) ...................................................................................................................... S9

DERIVATIZATION OF PYRROLO[1,2-a]INDOLES 6B ........................................................................................................... S11

GENERAL PROCEDURE 5 FOR THE OXIDATION OF PYRROLO[1,2-a]INDOLES USING TFAA AND DPSO OR DMSO (GP5)......... S12

GENERAL PROCEDURE 6 FOR THE OXIDATION OF INDOLES USING OXALYL CHLORIDE AND DMSO (GP6) ......................... S14

GENERAL PROCEDURE 7 FOR THE STAUDINGER REACTION (GP7) ..................................................................................... S15

GENERAL PROCEDURE 8 FOR THE AMINATION OF 2,3-DIHYDROPYRROLO[1,2-a]INDOLE AT THE 2A POSITION (GP8) ........... S16

ANALYTICAL DATA....................................................................................................................................................... S19

X-RAY STRUCTURE .................................................................................................................................................. S19

NMR SPECTRA ....................................................................................................................................................... S20

HR-MS SPECTRA ...................................................................................................................................................... S76

1H & 13C NMR SPECTRA OF HARMALINE AND N-METHYLHARMALINE ........................................................................... S85
Proton ($^1$H NMR) and carbon ($^{13}$C NMR) nuclear magnetic resonance spectra were recorded on 300, 400 or 500 MHz instruments. The chemical shifts are given in parts-per-million (ppm) on the delta scale. The solvent peak was used as reference value. For $^1$H NMR: CDCl$_3$ = 7.26 ppm, Acetone-$d_6$ = 2.05 ppm, Benzene-$d_6$ = 7.16 ppm. For $^{13}$C NMR: CDCl$_3$ = 77.16 ppm, Acetone-$d_6$ = 29.84 ppm, Benzene-$d_6$ = 128.06 ppm. Data are presented as follows; chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, b = broad), coupling constants ($J$ in Hz) and integration and carbons with same chemical shift as follows: chemical shift (x carbons). Infrared spectra were recorded neat. Wavelengths of maximum absorbance ($\nu_{max}$) are quoted in wave numbers (cm$^{-1}$). High resolution mass spectra (HRMS) data were recorded on a microTOF spectrometer equipped with orthogonal electrospray interface (ESI). The parent ions [M]$^+$, [M+H]$^+$, [M+Li]$^+$, [M+K]$^+$ or [M+Na]$^+$ are quoted. Analytical thin layer chromatography (TLC) was carried out on silica gel 60 F$_{254}$ plates with visualization by ultraviolet light, cerium-ammonium-molybdate or potassium permanganate dip. Flash column chromatography was carried out using silica gel 60 (40–63 µm) and the procedure included the subsequent evaporation of solvents in vacuo. Reagents and solvents were purified using standard means. Dichloroethane (DCE) was distilled from CaH$_2$, triethylamine (Et$_3$N) and pyridine were distilled from KOH; tetrahydrofuran (THF), diethyl ether (Et$_2$O), acetonitrile (MeCN), toluene (PhMe) and dichloromethane (DCM) were dried by passing through activated alumina under argon atmosphere. K$_2$CO$_3$ was dried overnight in an oven at 110 °C. All other chemicals were used as received, all extractive procedures were performed using non-distilled solvents and all aqueous solutions were saturated unless details are given. AuCl (Premion grade, 99.99%), AuCl$_3$ (99.9%) and NaAuCl$_4$·2H$_2$O (Premion grade, 99.99%) were purchased from Alfa Aesar whereas AgSbF$_6$ (98%), AgOTf (99%), AgBF$_4$ (99%), Ag$_2$CO$_3$ (99%+) and AgCl (99.9%) were purchased from STREM Chemicals. AgNTf$_2$ was prepared from commercially available HNTf$_2$ (Aldrich) and Ag$_2$CO$_3$. Triphenylphosphine (PPh$_3$) was recrystallized from MeOH and dried under vacuum. All other phosphine or phosphite ligands were purchased from STREM Chemicals. All phosphinegold(I) chloride precatalysts were prepared by reduction of NaAuCl$_4$ with thiodiethanol followed by subsequent addition of the appropriate phosphine.$^1$ IPrAuCl was prepared following the procedure described by Nolan et al.$^2$ Silver-free preactivated catalysts were prepared either from the corresponding phosphine gold chloride and AgSbF$_6$ in acetonitrile or AgNTf$_2$ in CH$_2$Cl$_2$ followed by filtration over a short pad of celite. Silylated propargylic alcohols 1a$^3$ and 1b$^4$ and $\alpha$, $\beta$-acetylenic aldehydes 2a$^5$, 2b$^6$ and 2c$^7$ are known compounds and have been prepared according to reported procedures.

1. A. K. Al’Sa-Ady, C. A. McAuliffe, R. V. Parish and J. A. Sandeank, Inorg. Synth., 1985, 191.
2. P. De Frémont, N. M. Scott, E. D. Stevens and S. P. Nolan, Organometallics, 2005, 24, 2411.
3. S. F. Kirsch, P. Klahn and H. Menz, Synthesis, 2011, 22, 3592.
4. K. Nacro, M. Baltas and L. Gorrichon, Tetrahedron, 1999, 55, 14013.
5. N. Kern, M. Hoffmann, A. Blanc, J.-M. Weibel and P. Pale, Org. Lett., 2013, 15, 836.
6. T. Luu and R. R. Tykwinski, J. Org. Chem., 2006, 71, 8982.
7. Z.-L. Liu, C. Yang, Q.-Y. Xue, M. Zhao, C.-C. Shan, Y.-H. Xu and T.-P. Loh, Angew. Chem., Int. Ed., 2019, 58, 16538.
Table S1. Comparison of experimental and predicted $^{13}$C NMR data of harmalidine and experimental $^{13}$C NMR data pyrrolo[1,2-$\alpha$]indole 13.

![Diagram of harmalidine and 13](image)

| Position | harmalidine $^{13}$C | harmalidine Difference (Exp - Pred/ppm)$^a$ | $^{13}$C Neural Network Prediction$^b$ | $^{13}$C HOSE-Code Prediction$^c$ | $^{13}$C$_{exp}$ | $^{13}$C$_{Harmalidine Pred}$ Difference (Exp - Harmalidine Pred/ppm)$^a$ |
|----------|----------------------|--------------------------------------------|-----------------------------------|-------------------------------|----------------|--------------------------------------------------|
| 2        | 126.3                | 7.8                                        | 144.0                             | 134.1                         | 129.5         | 4.6                                              |
| 3        | 161.3/144.5$^d$      | 4.4/12.4                                   | 172.8                             | 156.9                         | 168.4         | 4.4                                              |
| 5        | 42.8                 | 2.7                                        | 46.7                              | 45.5                          | 56.1           | 9.1                                              |
| 6        | 19.0                 | 0.2                                        | 22.9                              | 19.2                          | 28.2           | 5.3                                              |
| 7        | 119.1                | 3.6                                        | 115.5                             | 133.8                         | 109.7         | 5.8                                              |
| 8        | 126.7/124.4$^e$      | 0.1/2.4                                    | 118                               | 126.8                         | 126.8         | 0.0                                              |
| 9        | 122.1                | 1.2                                        | 120.9                             | 119.2                         | 122.0         | 1.1                                              |
| 10       | 115.0                | 5.4                                        | 109.8                             | 109.6                         | 111.3         | 1.5                                              |
| 11       | 144.5/161.3$^d$      | 11.4/1.3                                   | 155.9                             | 160.0                         | 158.0         | 2.0                                              |
| 12       | 94.0                 | 0.2                                        | 92.2                              | 94.2                          | 91.6           | 0.6                                              |
| 13       | 124.4/126.7$^e$      | 10.9/9.1                                   | 136.6                             | 135.3                         | 134.2         | 1.1                                              |
| 14       | 39.7                 | 4.6                                        | 44.3                              | 46.4                          | 48.6           | 2.2                                              |
| 15       | 43.0                 | 9.7                                        | 57.6                              | 52.7                          | 53.9           | 1.2                                              |
| 16       | 27.0                 | 1.4                                        | 25.6                              | 26.5                          | 27.2           | 0.7                                              |
| 17       | 14.0                 | 11.6                                       | 25.6                              | 26.5                          | 27.2           | 0.7                                              |
| OMe      | 55.2                 | 0.3                                        | 56.0                              | 55.5                          | 55.6           | 0.1                                              |

$^a$NMR data from reference 1; $^b$Difference of experimental and the closest predicted value in ppm (green < 4 ppm; orange = 4-6 ppm; red > 6 ppm); $^c$Neural Network or HOSE-Code NMR predictions obtained from CSEARCH Robot-Referee at [https://nmrpredict.orc.univie.ac.at/c13robot/robot.php](https://nmrpredict.orc.univie.ac.at/c13robot/robot.php); $^d$Values may be reversed. $^e$Values may be reversed.
Table S2. Comparison of experimental $^{13}$C NMR data of harmalidine and predicted $^{13}$C NMR data of dimethyl isomer of harmaline.

| Position | harmalidine | dimethyl isomer of harmaline | Carbon $^{13}$C | Difference (Exp-Pred/ppm)$^b$ | $^{13}$C Neural Network Prediction | $^{13}$C HOSE-Code Prediction |
|----------|-------------|-----------------------------|----------------|-------------------------------|----------------------------------|-------------------------------|
| 2        | 126.3       | 156.1                       |                | 7.8                           |                                  | 134.1                         |
| 3        | 161.3/144.5$^e$ | 157.2                       | 4.4/12.4       | 156.9                         |                                  |
| 5        | 42.8        | 7.8                         | 0.2            | 47.5                          |                                  | 42.6                          |
| 6        | 19.0        | 22.9                        | 0.2            | 22.9                          |                                  | 19.2                          |
| 7        | 119.1       | 133.8                       | 14.7           | 133.8                         |                                  | 119.1                         |
| 8        | 126.7/124.4$^e$ | 119.3                       | 0.1/2.4        | 126.8                         |                                  | 126.8                         |
| 9        | 122.1       | 120.3                       | 1.8            | 119.2                         |                                  | 119.2                         |
| 10       | 115.0       | 107.5                       | 5.4            | 109.6                         |                                  | 109.6                         |
| 11       | 144.5/161.3$^e$ | 154.1                       | 9.6/3.5        | 155.8                         |                                  | 155.8                         |
| 12       | 94.0        | 98.0                        | 2.7            | 96.7                          |                                  | 96.7                          |
| 13       | 124.4/126.7$^e$ | 140.7                       | 10.9/9.1       | 135.3                         |                                  | 135.3                         |
| 14       | 39.7        | 43.2                        | 3.5            | 33.7                          |                                  | 33.7                          |
| 15       | 43.0        | 77.4                        | 19.6           | 62.6                          |                                  | 62.6                          |
| 16       | 27.0        | 27.2                        | 0.2            | 26.2                          |                                  | 26.2                          |
| 17       | 14.0        | 27.2                        | 12.2           | 26.2                          |                                  | 26.2                          |
| OMe      | 55.2        | 56.0                        | 0.3            | 55.5                          |                                  | 55.5                          |

$^a$NMR data from reference 1; $^b$Difference of experimental and the closest predicted value in ppm (green < 4 ppm; orange = 4-6 ppm; red > 6 ppm, black > 15 ppm); $^c$Neural Network or HOSE-Code predictions obtained from CSEARCH Robot-Referee at https://nmrpredict.orc.univie.ac.at/c13robot/robot.php; $^d$Values may be reversed. $^e$Values may be reversed.
Characterization of Organic Compounds

General Procedure 1 for preparation of alkylnyl aldimines (GP1)

\[
\begin{align*}
\text{ArNH}_2 & \quad \text{MgSO}_4 \\
\text{Et}_2\text{O, rt, 16 h} & \quad \text{NHAr}
\end{align*}
\]

The appropriate \(\alpha,\beta\)-acetylenic aldehyde (5 mmol, 1 equiv) was dissolved in dry \(\text{Et}_2\text{O}\) (10 mL) with \(\text{MgSO}_4\) (15 mmol, 3 equiv) and the appropriate aniline derivative (5 mmol, 1 equiv) and vigorously stirred at room temperature for 16 hours. The mixture was then filtered through a pad of celite before being concentrated under vacuum. The crude imine 3 was used in the next step without purification (yields were assumed quantitative).

\((E)-5-((\text{tert-Butyldimethylsilyl})\text{oxy})-N-(3\text{-methoxyphenyl})\text{pent-2-yn-1-imine (3a):}\) Prepared following the GP1 from 5-((\text{tert-butyldimethylsilyl})\text{oxy})\text{pent-2-ynal}^6 \text{ 2a} (2.33 g, 11 mmol) and 3-methoxyaniline (1.24 mL, 11 mmol, \(E/Z\) ratio 92/8). Yellowish oil; \(^1\text{H NMR (500 MHz, CDCl}_3\) \(\delta\) 0.09 (s, 6 H), 0.91 (s, 9 H), 2.66 (td, \(J = 1.7, 7.2 \text{ Hz, 2 H}\), 3.81 (s, 3 H), 3.83 (t, \(J = 7.2 \text{ Hz, 2 H}\), 6.69 (dd, \(J = 1.7, 2.4 \text{ Hz, 1 H}\), 6.71 (dd, \(J = 1.7, 7.8 \text{ Hz, 1 H}\), 7.00 (dd, \(J = 2.4, 8.3 \text{ Hz, 1 H}\), 7.25 (dd, \(J = 7.8, 8.3 \text{ Hz, 1 H}\), 7.69 (t, \(J = 1.7 \text{ Hz, 1 H}\); \(^{13}\text{C NMR (126 MHz, CDCl}_3\) \(\delta\) -5.2 (x2), 18.5, 24.0, 26.0 (x3), 55.4, 61.4, 80.5, 94.5, 106.8, 112.7, 112.8, 130.0, 144.3, 152.4, 160.4.

\((E)-5-((\text{tert-Butyldiphenylsilyl})\text{oxy})-N-(3\text{-methoxyphenyl})\text{pent-2-yn-1-imine (3b):}\) Prepared following the GP1 from 5-((\text{tert-butyldiphenylsilyl})\text{oxy})\text{pent-2-ynal}^6 \text{ 2b} (4.16 g, 12.36 mmol) and 3-methoxyaniline (1.4 mL, 12.36 mmol, \(E/Z\) ratio 92/8). Yellow oil; \(^1\text{H NMR (500 MHz, C}_6\text{D}_6\) \(\delta\) 1.17 (s, 9 H), 2.34 (td, \(J = 1.6, 6.6 \text{ Hz, 2 H}\), 3.24 (s, 3 H), 3.66 (t, \(J = 6.6 \text{ Hz, 2 H}\), 6.6–6.70 (m, 2 H), 6.71–6.74 (m, 1 H), 7.00 (dd, \(J = 8.0, 8.0 \text{ Hz, 1 H}\), 7.19–7.28 (m, 6 H), 7.49 (dd, \(J = 1.3, 1.8 \text{ Hz, 1 H}\), 7.74–7.81 (m, 4 H).

\((E)-N\text{-Phenylnon-2-yn-1-imine (3c):}\) Prepared following the GP1 from non-2-ynal\(^7\) \text{ 2c} (2.0 g, 14.5 mmol) and aniline (1.35 g, 14.5 mmol, \(E/Z\) ratio 89/11). Yellowish oil; \(^1\text{H NMR (500 MHz, CDCl}_3\) \(\delta\) 0.90 (t, \(J = 7.0 \text{ Hz, 3 H}\), 1.26–1.35 (m, 4 H), 1.41–1.47 (m, 2 H), 1.58–1.65 (m, 2 H), 2.44 (td, \(J = 1.7, 7.2 \text{ Hz, 2 H}\), 7.14 (d, \(J = 7.6 \text{ Hz, 2 H}\), 7.24 (dd, \(J = 7.6, 7.6 \text{ Hz, 1 H}\), 7.36 (dd, \(J = 7.6, 7.6 \text{ Hz, 2 H}\), 7.69 (t, \(J = 1.7 \text{ Hz, 1 H}\); \(^{13}\text{C NMR (126 MHz, CDCl}_3\) \(\delta\) 14.2, 19.7, 22.7, 28.2, 28.8, 31.4, 79.7, 98.0, 120.9 (x2), 127.0, 129.3 (x2), 144.5, 151.2.
**General Procedure 2 for enolate-imine condensation (GP2)**

To a cooled solution of DIPA (4.4 mmol, 2.2 equiv) in toluene (8 mL) at -78 °C under argon was added n-BuLi dropwise (1.6 M in hexanes, 4.4 mmol, 2.2 equiv). After 10 min of stirring, ethyl isobutyrate (4 mmol, 2 equiv) previously dissolved in 2 mL of toluene was added dropwise and the mixture was warmed to 0 °C. After 30 min of stirring, the imine 3 (2 mmol, 2 equiv) previously dissolved in 2 mL of toluene was added dropwise. The mixture was then warmed to room temperature and stirred overnight. The reaction was quenched with 1N HCl (10 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were washed with water, NaHCO₃, brine, and dried over MgSO₄. After filtration and evaporation, the crude product was purified by flash chromatography (SiO₂, Cyclohexane/EtOAc) to afford the title azetidinone 4.

4-(4-((tert-Butyldimethylsilyl)oxy)but-1-yn-1-yl)-1-(3-methoxyphenyl)-3,3-dimethylazetidin-2-one (4a): Prepared following the GP2 in 71 % yield over two steps (3.01 g, 7.77 mmol) from 2.33 g of the crude imine 3a. Yellow oil; TLC Rf 0.48 (Cyclohexane/EtOAc 20 %); IR (neat) νmax 663, 686, 734, 773, 809, 834, 915, 991, 1006, 1041, 1103, 1158, 1185, 1219, 1246, 1279, 1335, 1368, 1389, 1461, 1495, 1600, 1754, 2857, 2929, 2956; 1H NMR (500 MHz, CDCl₃) δ 0.04 (s, 6 H), 0.88 (s, 9 H), 1.40 (s, 6 H), 2.46 (td, J = 2.0, 7.0 Hz, 2 H), 3.70 (t, J = 7.0 Hz, 2 H), 3.81 (s, 3 H), 4.29 (t, J = 2.0 Hz, 1 H), 6.65 (dd, J = 2.4, 8.2 Hz, 1 H), 7.04 (dd, J = 1.7, 8.2 Hz, 1 H), 7.16 (dd, J = 1.7, 2.5 Hz, 1 H), 7.23 (dd, J = 8.2, 8.2 Hz, 1 H); 13C NMR (126 MHz, CDCl₃) δ -5.2 (x2), 18.4, 19.1, 21.8, 23.4, 26.0 (x3), 54.3, 54.6, 55.5, 61.8, 75.1, 87.2, 102.9, 109.2, 110.1, 130.0, 139.0, 160.3, 170.7; HR-MS 388.2306 (C₂₂H₃₃NO₃Si+H⁺) calcd 388.2302.

4-(4-((tert-Butydiphenylsilyl)oxy)but-1-yn-1-yl)-1-(3-methoxyphenyl)-3,3-dimethylazetidin-2-one (4b): Prepared following the GP2 in 90 % yield (5.70 g, 11.14 mmol) from 4.16 g of the crude imine 3b. Yellow oil; TLC Rf 0.48 (Cyclohexane/EtOAc 20 %); IR (neat) νmax 488, 503, 613, 686, 701, 735, 772, 822, 851, 938, 997, 1040, 1107, 1157, 1185, 1219, 1246, 1279, 1335, 1368, 1389, 1428, 1460, 1495, 1600, 1754, 2857, 2929, 2956; 1H NMR (500 MHz, CDCl₃) δ 1.03 (s, 9 H), 1.37 (s, 3 H), 1.39 (s, 3 H), 2.50 (td, J = 1.9, 6.8 Hz, 2 H), 3.75 (t, J = 6.8 Hz, 2 H), 3.78 (s, 3 H), 4.27 (t, J = 1.9 Hz, 1 H), 6.64 (dd, J = 2.0, 8.1 Hz, 1 H), 7.02 (dd, J = 1.5, 8.1 Hz, 1 H), 7.16 (dd, J = 2.0, 2.0 Hz, 1 H), 7.20 (dd, J = 8.1, 8.1 Hz, 1 H), 7.34–7.40 (m, 4 H), 7.42–7.46 (m, 2 H), 7.63–7.68 (m, 4 H); 13C NMR (126 MHz, CDCl₃) δ 19.1, 19.3, 21.8, 23.2, 26.8 (x3), 54.3, 54.6, 55.4, 62.3, 75.1, 87.3, 102.8, 109.1, 110.1, 127.8 (x4), 129.9 (x2), 130.0, 133.6 (x2), 135.7 (x4), 138.9, 160.2, 170.7; HR-MS 550.2170 (C₃₂H₃₇NO₃Si+K⁺) calcd 550.2174.
3,3-Dimethyl-4-(oct-1-yn-1-yl)-1-phenylazetidin-2-one (4c): Prepared following the GP2 in 85 % yield (3.51 g, 12.38 mmol) from the crude imine 3c. Colorless oil; TLC Rf 0.42 (Cyclohexane/EtOAc 10 %); IR (neat) νmax 476, 513, 652, 690, 751, 896, 985, 1049, 1082, 1118, 1179, 1278, 1332, 1367, 1388, 1459, 1501, 1598, 1753, 2869, 2927, 2959; 1H NMR (500 MHz, CDCl3) δ 0.87 (t, J = 6.8 Hz, 3 H), 1.21–1.31 (m, 4 H), 1.32–1.39 (m, 2 H), 1.40 (s, 3 H), 1.41 (s, 3 H), 1.46–1.52 (m, 2 H), 2.24 (td, J = 2.0, 7.0 Hz, 2 H), 4.31 (t, J = 2.0 Hz, 1 H), 7.09 (dd, J = 7.4, 7.4 Hz, 1 H), 7.34 (dd, J = 7.4, 8.5 Hz, 2 H), 7.53 (d, J = 8.5 Hz, 2 H); 13C NMR (126 MHz, CDCl3) δ 14.2, 18.9, 19.1, 21.8, 22.7, 28.6 (x2), 31.4, 54.2, 54.6, 74.1, 90.3, 117.1 (x2), 123.9, 129.1 (x2), 137.8, 170.7; HR-MS 284.1997 (C19H25NO+H+) calcd 284.2009.

General Procedure 3 for azetidinone reduction (GP3)

To a stirred solution of AlCl3 (6 mmol, 3 equiv) in Et2O (5 mL) at room temperature under argon was added a solution of LiAlH4 (6 mmol, 3 equiv) previously dissolved in Et2O (10 mL). The resulting mixture was refluxed for 30 min and the azetidinone 4 (2 mmol, 1 equiv) was added dropwise as a solution in Et2O (2 mL). After completion of the reaction (within a few minutes as monitored by TLC), the mixture was cooled to 0 °C, diluted with Et2O (at least 50 mL) and an aqueous sodium potassium tartrate solution (12 mmol, 6 equiv in 50 mL H2O) was added very carefully and dropwise until bubbling stopped. The mixture was then stirred vigorously for several hours until decantation was clean. After separation of the two layers, the aqueous layer was extracted with Et2O (3 x 10 mL), the combined organic layers were washed with water and brine, concentrated and the residue was stirred for 30 min in a 3:1 THF/water mixture (30 mL) in the presence of EDTA (4 mmol, 2 equiv). After partitioning the mixture between Et2O and brine (30 + 30 mL), layers were separated, and the aqueous layer was extracted again with Et2O (30 mL). The combined organic layers were dried over MgSO4, filtered and concentrated, and the residue was purified by flash chromatography (SiO2, Cyclohexane/EtOAc) to afford the title compound 5.

2-(4-((tert-Butyldimethylsilyl)oxy)but-1-yn-1-yl)-1-((3-methoxyphenyl)-3,3-dimethylazetidine (5a): Prepared following the GP3 in 77 % yield (1.10 g, 2.94 mmol) from azetidinone 4a (1.49 g, 3.84 mmol). Colorless oil; TLC Rf 0.44 (Cyclohexane/EtOAc 10 %); IR (neat) νmax 546, 584, 665, 687, 775, 832, 915, 1048, 1099, 1163, 1214, 1238, 1252, 1290, 1338, 1460, 1494, 1598, 1611, 2854, 2927, 2954; 1H NMR (500 MHz, CDCl3) δ 0.07 (s, 6 H), 0.90 (s, 9 H), 1.20 (s, 3 H), 1.42 (s, 3 H), 2.49 (td, J = 2.1, 7.2 Hz, 2 H), 3.35 (d, J = 6.5 Hz, 1 H), 3.58 (d, J = 6.5 Hz, 1 H), 3.74 (td, J = 0.9, 7.2 Hz, 2 H), 3.78 (s, 3 H), 4.16 (t, J = 2.1 Hz, 1 H), 6.22 (dd, J = 2.5, 2.5 Hz, 1 H), 6.29 (dd, J = 2.5, 8.0 Hz, 1 H), 6.35 (dd, J = 2.5, 8.0 Hz, 1 H), 7.12 (dd, J = 8.0, 8.0 Hz, 1 H); 13C NMR (126 MHz, CDCl3) δ -5.1 (x2),
18.5, 23.5, 24.7, 26.0 (x3), 26.9, 36.0, 55.2, 62.1, 63.1, 63.7, 78.6, 85.1, 98.8, 103.8, 105.6, 129.8, 153.2, 160.5; HR-MS 374.2496 (C\textsubscript{22}H\textsubscript{35}NO\textsubscript{2}Si\textsuperscript{+}H\textsuperscript{+}) calcd 374.2510.

2-(4-((tert-Butyldiphenylsilyl)oxy)but-1-yn-1-yl)-1-(3-methoxyphenyl)-3,3-dimethylazetidine (5b): Prepared following the GP3 in 79 % yield (4.09 g, 10.18 mmol) from azetidinone 4\textsubscript{b} (5.31 g, 10.38 mmol). Pale yellow oil; TLC \(R_f\) 0.52 (Cyclohexane/EtOAc 20 %); IR (neat) \(\nu_{\text{max}}\) 487, 504, 613, 687, 700, 736, 757, 821, 916, 1047, 1103, 1264, 1289, 1338, 1427, 1453, 1598, 1611, 2856, 2929, 2956; \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 1.08 (s, 9 H), 1.09 (s, 3 H), 1.41 (s, 3 H), 2.57 (td, \(J = 2.1, 7.0 \text{ Hz}, 2 \text{ H})\), 3.36 (d, \(J = 6.4 \text{ Hz}, 1 \text{ H})\), 3.58 (d, \(J = 6.4 \text{ Hz}, 1 \text{ H})\), 3.76 (t, \(J = 7.2 \text{ Hz}, 2 \text{ H})\), 4.17 (dd, \(J = 1.4, 2.1 \text{ Hz}, 1 \text{ H})\), 6.22 (dd, \(J = 1.5, 2.3 \text{ Hz}, 1 \text{ H})\), 6.30 (dd, \(J = 1.5, 8.0 \text{ Hz}, 1 \text{ H})\), 6.35 (dd, \(J = 2.3, 8.0 \text{ Hz}, 1 \text{ H})\), 7.12 (dd, \(J = 8.0, 8.0 \text{ Hz}, 1 \text{ H})\), 7.37–7.47 (m, 6 H), 7.69–7.72 (m, 4 H); \(^1\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 19.3, 23.3, 24.7, 26.8, 26.9 (x3), 36.0, 55.2, 62.7, 63.1, 63.7, 78.6, 85.1, 98.7, 103.8, 105.5, 127.8 (x4), 129.7, 129.8 (x2), 133.7 (x2), 135.7 (x4), 153.2, 160.5; HR-MS 498.2855 (C\textsubscript{32}H\textsubscript{39}NO\textsubscript{2}Si\textsuperscript{+}H\textsuperscript{+}) calcd 498.2823.

3,3-Dimethyl-2-((3-Oct-1-yn-1-yl)-1-phenylazetidine (5c): Prepared following the GP3 in 85 % yield (822 mg, 3.05 mmol) from azetidinone 4\textsubscript{c} (1.02 g, 3.6 mmol). Colorless oil; TLC \(R_f\) 0.49 (Pentane/Et\textsubscript{2}O 5 %); IR (neat) \(\nu_{\text{max}}\) 516, 692, 746, 786, 872, 989, 1032, 1096, 1112, 1156, 1177, 1294, 1336, 1461, 1473, 1500, 1598, 1857, 2927, 2955; \(^1\)H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 0.89 (t, \(J = 6.8 \text{ Hz}, 3 \text{ H})\), 1.21 (s, 3 H), 1.25–1.35 (m, 4 H), 1.38–1.45 (m, 2 H), 1.43 (s, 3 H), 1.51–1.57 (m, 2 H), 2.27 (td, \(J = 2.0, 7.0 \text{ Hz}, 2 \text{ H})\), 3.35 (d, \(J = 6.9 \text{ Hz}, 1 \text{ H})\), 3.60 (d, \(J = 6.9 \text{ Hz}, 1 \text{ H})\), 4.16 (t, \(J = 2.0 \text{ Hz}, 1 \text{ H})\), 6.66 (d, \(J = 8.8 \text{ Hz}, 2 \text{ H})\), 6.77 (dd, \(J = 7.4, 7.4 \text{ Hz}, 1 \text{ H})\), 7.21 (dd, \(J = 7.4, 8.8 \text{ Hz}, 2 \text{ H})\); \(^1\)C NMR (126 MHz, CDCl\textsubscript{3}) \(\delta\) 14.2, 19.1, 22.7, 24.7, 26.9, 28.7, 28.9, 31.5, 36.2, 63.1, 63.8, 77.6, 88.4, 112.7 (x2), 118.4, 128.9 (x2), 151.9; HR-MS 270.2199 (C\textsubscript{19}H\textsubscript{27}N\textsuperscript{+}H\textsuperscript{+}) calcd 270.2216.

Synthesis of the chloroethyl 2,3-dihydropyrrolo[1,2-a]indole derivative 6d

4-(1-((3-Methoxyphenyl)-3,3-dimethylazetidin-2-yl)but-3-yn-1-ol (I): To a stirred solution of azetidine 5a (20 mmol, 1 equiv) in THF (100 mL) at 0 °C was added a solution of TBAF (1.0 M in THF, 30 mmol, 1.5 equiv). After 30 minutes, the reaction was quenched by addition of satd aqueous NH\textsubscript{4}Cl (100 mL) and diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2 x 100 mL) and the combined organic layers were washed with H\textsubscript{2}O (100 mL) then brine (100 mL). The solution was dried over MgSO\textsubscript{4}, filtered and concentrated to yield the compound I in 92 % yield (4.69 g) from 7.33 g of 5a.
Yellow oil; TLC $R_f$ 0.21 (Cyclohexane/EtOAc 30 %); IR (neat) $\nu_{\text{max}}$ 457, 560, 688, 759, 823, 987, 1041, 1100, 1161, 1211, 1236, 1289, 1336, 1438, 1457, 1493, 1598, 2837, 2866, 2924, 2956, 3371; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.23 (s, 3 H), 1.42 (s, 3 H), 2.55 (td, $J = 2.0, 6.3$ Hz, 2 H), 3.37 (d, $J = 6.5$ Hz, 1 H), 3.59 (d, $J = 6.5$ Hz, 1 H), 3.73 (td, $J = 2.1, 6.3$ Hz, 2 H), 3.78 (s, 3 H), 4.19 (t, $J = 2.1$ Hz, 1 H), 6.21 (dd, $J = 1.5, 2.2$ Hz, 1 H), 6.27 (dd, $J = 2.2, 8.0$ Hz, 1 H), 6.35 (dd, $J = 2.2, 8.0$ Hz, 1 H), 7.13 (dd, $J = 8.0, 8.0$ Hz, 1 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 23.5, 24.7, 26.9, 36.0, 55.3, 61.3, 63.1, 63.5, 79.6, 84.8, 98.8, 103.8, 105.5, 129.9, 152.9, 160.6; HR-MS calcd 260.1664 (C$_{16}$H$_{21}$NO$_2$ + H$^+$).

4-[(1-(3-Methoxyphenyl)-3,3-dimethylazetidin-2-yl)but-3-yn-1-yl]4-methylbenzenesulfonate (II): Deprotected alcohol I was dissolved in CH$_2$Cl$_2$ (30 mL) and cooled to 0 °C. Et$_3$N (6.7 mmol, 1.2 equiv), DMAP (0.6 mmol, 0.1 equiv) and finally para-toluene sulfonyl chloride (6.7 mmol, 1.2 equiv) were then successively added to the stirring mixture before removal of the cooling bath. The mixture was stirred overnight at room temperature, quenched by addition of satd aqueous NH$_4$Cl and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with H$_2$O then brine. The solution was dried over MgSO$_4$, filtered and concentrated to yield tosylated azetidine derivative II in 87 % yield (2.00 g) from 1.44 g of alcohol I. Orange/brown oil; TLC $R_f$ 0.46 (Cyclohexane/EtOAc 30 %); IR (neat) $\nu_{\text{max}}$ 458, 499, 552, 662, 688, 728, 760, 815, 838, 903, 973, 1020, 1043, 1071, 1097, 1174, 1188, 1213, 1238, 1264, 1289, 1340, 1359, 1458, 1494, 1598, 2839, 2925, 2958; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.19 (s, 3 H), 1.36 (s, 3 H), 2.44 (s, 3 H), 2.65 (td, $J = 2.0, 7.1$ Hz, 2 H), 3.34 (d, $J = 6.6$ Hz, 1 H), 3.56 (d, $J = 6.6$ Hz, 1 H), 3.77 (s, 3 H), 4.08–4.14 (m, 3 H), 6.16 (dd, $J = 2.1, 2.1$ Hz, 1 H), 6.23 (dd, $J = 2.1, 8.0$ Hz, 1 H), 6.35 (dd, $J = 2.1, 8.0$ Hz, 1 H), 7.11 (dd, $J = 8.0, 8.0$ Hz, 1 H), 7.32 (d, $J = 8.2$ Hz, 2 H), 7.79 (d, $J = 8.2$ Hz, 2 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 20.1, 21.8, 24.6, 26.9, 36.0, 55.3, 63.1, 63.3, 67.8, 80.0, 82.0, 98.7, 103.8, 105.5, 128.1 (x2), 129.9, 130.1 (x2), 132.9, 145.1, 152.9, 160.5; HR-MS calcd 414.1734.

2-(4-Chlorobut-1-yn-1-yl)-1-(3-methoxyphenyl)-3,3-dimethylazetidine (5d): Tosyl derivative II (5 mmol, 1 equiv) was dissolved in DMF (25 mL) at room temperature with LiCl (15 mmol, 3 equiv) and stirred for 16 hours. The mixture was then dissolved in EtOAc (200 mL) and washed with H$_2$O then brine. Finally, the crude mixture was dried over MgSO$_4$, filtered and concentrated. After purification on column chromatography (SiO$_2$, Cyclohexane/EtOAc), chloride azetidine derivative 5d was obtained in 55 % yield (90 mg) from 245 mg of II. Colorless oil; TLC $R_f$ 0.60 (Cyclohexane/EtOAc 30 %); IR (neat) $\nu_{\text{max}}$ 458, 661, 688, 739, 758, 798, 821, 833, 987, 1044, 1072, 1101, 1123, 1162, 1212, 1237, 1264, 1297, 1337, 1370, 1457, 1493, 1597, 2837, 2924, 2957; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.43 (s, 3 H), 2.75 (td, $J = 2.0, 7.2$ Hz, 2 H), 3.36 (d, $J = 6.5$ Hz, 1 H), 3.59 (d, $J = 6.5$ Hz, 1 H), 3.61 (t, $J = 7.2$ Hz, 2 H), 3.78 (s, 3 H), 4.17 (t, $J = 2.0$ Hz, 1 H), 6.21 (dd, $J = 2.0, 2.5$ Hz, 1 H), 6.27 (dd, $J = 2.0, 8.3$ Hz, 1 H), 6.35 (dd, $J = 2.5, 7.8$ Hz, 1 H), 7.13 (dd, $J = 7.8, 8.3$ Hz, 1 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 20.1, 21.8, 24.6, 26.9, 36.0, 55.3, 63.1, 63.3, 67.8, 80.0, 82.0, 98.7, 103.8, 105.5, 128.1 (x2), 129.9, 130.1 (x2), 132.9, 145.1, 152.9, 160.5; HR-MS calcd 414.1761 (C$_{23}$H$_{27}$NO$_4$S+H$^+$).
General Procedure 4 for the gold-catalyzed conversion of N-aryl alkynylazetidines 3 to pyrrolo[1,2-α]indoles 4 (GP4)

To a solution of N-aryl 2-alkynylazetidine 5 (0.2 mmol, 1 equiv) in CH₂Cl₂ (1 mL) was added (Cy₂)JohnPhosAuSbF₆ (0.01 mmol, 5 mol %) at room temperature or at 60 °C (specified for each compound). The solution was stirred until completion of the reaction (as monitored by TLC), solvent was removed in vacuo, and the crude residue was purified by flash chromatography (SiO₂, cyclohexane/EtOAc) to yield the title compound 6 or 7.

9-((2-(tert-Butyldimethylsilyl)oxy)ethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole (6a): Prepared following the GP4 in 47 % yield (93 mg, 0.249 mmol) from 5a (197 mg, 0.527 mmol) after 2 minutes at 60 °C. White solid; mp 107 °C; TLC Rf 0.37 (Pentane/Et₂O 20 %); IR (neat) νmax 512, 570, 596, 628, 679, 740, 774, 800, 813, 938, 969, 1004, 1039, 1084, 1118, 1148, 1177, 1340, 1378, 1435, 1449, 1624, 2855, 2886, 2927, 2953; ¹H NMR (500 MHz, CDCl₃) δ 0.05 (s, 6 H), 0.90 (s, 9 H), 1.28 (s, 6 H), 2.73 (s, 2 H), 2.89 (t, J = 7.9 Hz, 2 H), 3.71 (s, 2 H), 3.80 (t, J = 7.9 Hz, 2 H), 3.85 (s, 3 H), 6.67 (d, J = 2.3 Hz, 1 H), 6.72 (dd, J = 2.3, 8.5 Hz, 1 H), 7.36 (d, J = 8.5 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ -5.1 (x2), 18.6, 26.2 (x3), 28.2 (x2), 29.0, 39.0, 44.1, 56.0, 56.9, 64.1, 93.4, 102.8, 108.0, 119.0, 126.6, 133.4, 140.2, 155.3; HR-MS 374.2531 (C₂₂H₃₅NO₂Si+H⁺) calcd 374.2510.

9-((2-(tert-Butyldimethylsilyl)oxy)ethyl)-8-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole (7a): Prepared following the GP4 in 43 % yield (85 mg, 0.227 mmol) from 5a (197 mg, 0.527 mmol) after 2 minutes at 60 °C. White solid; mp 86 °C; TLC Rf 0.54 (Pentane/Et₂O 20 %); IR (neat) νmax 558, 730, 773, 839, 1008, 1042, 1054, 1072, 1088, 1109, 1184, 1198, 1254, 1264, 1337, 1362, 1413, 1443, 1461, 1498, 1562, 1614, 2854, 2897, 2927, 2949; ¹H NMR (500 MHz, CDCl₃) δ 0.11 (s, 6 H), 0.96 (s, 9 H), 1.30 (s, 6 H), 2.77 (s, 2 H), 3.07 (t, J = 7.7 Hz, 2 H), 3.75 (s, 2 H), 3.86 (t, J = 7.7 Hz, 2 H), 3.94 (s, 3 H), 6.49 (d, J = 7.8 Hz, 1 H), 6.81 (d, J = 8.1 Hz, 1 H), 7.03 (dd, J = 7.8, 8.1 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ -5.0 (x2), 18.6, 26.2 (x3), 28.1 (x2), 30.4, 38.8, 44.0, 55.1, 57.2, 65.4, 98.9, 102.9 (x2), 120.8, 121.2, 134.4, 140.3, 154.3; HR-MS 374.2530 (C₂₂H₃₅NO₂Si+H⁺) calcd 374.2510.
9-(2-((tert-Butyldiphenylsilyl)oxy)ethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole (6b): Prepared following the GP4 in 54 % yield (1.40 g, 2.812 mmol) from 5b (2.55 g, 5.946 mmol) after 2 minutes at 60 °C. White solid; mp 95 °C; TLC Rf 0.38 (Pentane/EtO 20 %); IR (neat) v\textsubscript{max} 491, 503, 608, 699, 739, 796, 820, 967, 1005, 1042, 1065, 1080, 1110, 1149, 1176, 1220, 1243, 1360, 1382, 1405, 1461, 1568, 1588, 1625, 2855, 2896, 2930, 2953; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 1.08 (s, 9 H), 1.23 (s, 6 H), 2.60 (s, 2 H), 2.93 (t, J = 7.7 Hz, 2 H), 3.67 (s, 2 H), 3.85 (s, 3 H), 3.86 (t, J = 7.7 Hz, 2 H), 6.62–6.68 (m, 2 H), 7.11 (d, J = 9.3 Hz, 1 H), 7.32–7.48 (m, 6 H), 7.63–7.70 (m, 4 H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 19.3, 27.1 (x3), 28.1 (x2), 28.6, 38.8, 44.0, 55.9, 56.9, 64.7, 93.3, 102.6, 107.8, 119.1, 126.5, 127.7 (x4), 129.6 (x2), 133.4, 134.1 (x2), 135.8 (x4), 140.3, 155.3; HR-MS 497.2771 (C\textsubscript{32}H\textsubscript{39}NO\textsubscript{2}Si\textsuperscript{+}) calcd 497.2745.

9-(2-((tert-Butyldiphenylsilyl)oxy)ethyl)-8-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole (7b): Prepared following the GP4 in 37 % yield (945 mg, 1.90 mmol) from 5b (2.55 g, 5.946 mmol) after 2 minutes at 60 °C. White solid; mp 116 °C; TLC Rf 0.63 (Pentane/EtO 20 %); IR (neat) v\textsubscript{max} 476, 484, 495, 505, 558, 602, 682, 700, 729, 739, 762, 773, 997, 1005, 1031, 1058, 1112, 1132, 1196, 1281, 1303, 1364, 1375, 1426, 1446, 1567, 1587, 1617, 2861, 2927, 2956; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 1.06 (s, 9 H), 1.22 (s, 6 H), 2.64 (s, 2 H), 3.12 (t, J = 7.5 Hz, 2 H), 3.70 (s, 2 H), 3.75 (s, 3 H), 3.94 (t, J = 7.5 Hz, 2 H), 6.41 (d, J = 7.7 Hz, 1 H), 6.77 (d, J = 8.1 Hz, 1 H), 6.99 (dd, J = 7.7, 8.1 Hz, 1 H), 7.29–7.43 (m, 6 H), 7.62–7.69 (m, 4 H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 19.4, 27.1 (x3), 28.1 (x2), 30.1, 38.7, 43.9, 55.0, 57.2, 65.9, 99.0, 102.8, 103.1, 120.7, 121.3, 127.6 (x4), 129.4 (x2), 134.4, 134.5 (x2), 135.7 (x4), 140.5, 154.4; HR-MS 497.2740 (C\textsubscript{32}H\textsubscript{39}NO\textsubscript{2}Si\textsuperscript{+}) calcd 497.2745.

9-Hexyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole (6c): Prepared following the GP4 in 97 % yield (568 mg, 2.108 mmol) from 5c (588 mg, 2.182 mmol) in 2 h at room temperature. Colorless oil; TLC Rf 0.55 (Pentane/EtO 5 %); IR (neat) v\textsubscript{max} 453, 553, 733, 1010, 1166, 1242, 1336, 1368, 1378, 1410, 1458, 1479, 1619, 2859, 2823, 2955, 3050; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 0.94 (t, J = 7.0 Hz, 3 H), 1.34–1.45 (m, 6 H), 1.32 (s, 6 H), 1.71 (tt, J = 7.5, 7.5 Hz, 2 H), 2.74 (t, J = 7.5 Hz, 2 H), 2.80 (s, 2 H), 3.80 (s, 2 H), 7.09 (dd, J = 7.8, 7.8 Hz, 1 H), 7.15 (dd, J = 7.8, 7.8 Hz, 1 H), 7.21 (d, J = 7.8 Hz, 1 H), 7.57 (d, J = 7.8 Hz, 1 H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 14.3, 22.9, 24.8, 28.1 (x2), 29.4, 30.6, 31.9, 39.2, 44.2, 56.8, 107.0, 109.1, 118.2, 118.6, 120.0, 132.1, 132.9, 140.6; HR-MS 269.2125 (C\textsubscript{19}H\textsubscript{22}N\textsuperscript{+}) calcd 269.2138.

9-(2-Chloroethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-α]indole (6d): Prepared following the GP4 in 30 % yield (36 mg) from 171 mg of 5d after 1 h at 60 °C. Colorless oil; TLC Rf 0.37 (Cyclohexane/EtOAc 10 %); IR (neat) v\textsubscript{max} 436, 628, 646, 730, 810, 908, 1043, 1144, 1176, 1217, 1237, 1319, 1369, 1405, 1460, 1567, 1595, 1625, 2868, 2933, 2956; \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) δ 1.29 (s, 6 H), 2.77 (s, 2 H), 3.13 (t, J = 7.4 Hz, 2 H), 6.68 (s, 1 H), 7.04–7.13 (m, 3 H), 7.53–7.57 (m, 3 H), 7.62–7.70 (m, 4 H), 7.95 (m, 2 H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) δ 22.7, 28.0, 29.0, 30.6, 31.9, 39.2, 44.2, 56.8, 107.0, 109.1, 118.2, 118.6, 120.0, 132.1, 132.9, 140.6; HR-MS 269.2125 (C\textsubscript{19}H\textsubscript{22}N\textsuperscript{+}) calcd 269.2138.
Hz, 2 H), 3.71 (t, J = 7.4 Hz, 2 H), 3.74 (s, 2 H), 3.86 (s, 3 H), 6.69 (d, J = 2.4 Hz, 1 H), 6.75 (dd, J = 2.4, 8.5 Hz, 1 H); 13C NMR (126 MHz, CDCl3) δ 28.0 (x2), 28.9, 39.0, 44.2, 45.1, 55.9, 56.9, 93.5, 102.5, 108.3, 118.7, 125.9, 133.5, 140.7, 155.5; HR-MS 278.1275 (C16H20ClNO+H+) calcd 278.1261.

9-(2-Chloroethyl)-8-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole (7d): Prepared following the GP4 in 21 % yield (36 mg) from 171 mg of 5d after 1 h at 60 °C. Colorless oil; TLC Rf 0.51 (Cyclohexane/EtOAc 10 %); IR (neat) νmax 555, 605, 627, 653, 729, 770, 800, 905, 941, 1041, 1064, 1108, 1124, 1151, 1200, 1251, 1264, 1288, 1306, 1343, 1445, 1496, 1563, 1618, 2872, 2934, 2989; 1H NMR (300 MHz, CDCl3) δ 1.28 (s, 6 H), 2.77 (s, 2 H), 3.23 (t, J = 7.4 Hz, 2 H), 3.75 (s, 2 H), 3.79 (t, J = 7.4 Hz, 2 H), 3.92 (s, 3 H), 6.47 (d, J = 8.0 Hz, 1 H), 6.79 (d, J = 8.0 Hz, 1 H), 7.00 (dd, J = 8.0, 8.0 Hz, 1 H); 13C NMR (126 MHz, CDCl3) δ 28.0 (x2), 30.5, 38.8, 44.2, 46.5, 55.2, 57.3, 99.1, 102.9, 103.0, 120.8, 121.1, 134.5, 140.8, 154.1; HR-MS 277.1264 (C16H20ClNO) calcd 277.1228.

Derivatization of pyrrolo[1,2-a]indoles

2-(6-Methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethan-1-ol (8): To a stirred solution of pyrroloindole 6b (1.00 g, 2 mmol, 1 equiv) in THF (10 mL) at 0 °C was added a solution of TBAF (4 mL 1.0 M in THF, 4 mmol, 1.5 equiv). After 3 h, the reaction was quenched by addition of satd aqueous NH4Cl (10 mL) and diluted with EtOAc (10 mL). The aqueous layer was extracted with EtOAc (2 x 10 mL) and the combined organic layers were washed with H2O (10 mL) then brine (10 mL). The solution was dried over MgSO4, filtered, and concentrated to yield the alcohol 8 in 87 % yield (449 mg, 1.731 mmol) after flash chromatography. White solid; mp 98 °C; TLC Rf 0.16 (Cyclohexane/EtOAc 30 %); IR (neat) νmax 437, 512, 596, 627, 675, 740, 807, 823, 880, 968, 1002, 1036, 1147, 1174, 1222, 1241, 1337, 1379, 1410, 1455, 1488, 1563, 1592, 1623, 2867, 2927, 2954, 3299; 1H NMR (500 MHz, CDCl3) δ 1.26 (s, 6 H), 2.74 (s, 2 H), 2.91 (t, J = 6.3 Hz, 2 H), 3.72 (s, 2 H), 3.82 (t, J = 6.3 Hz, 2 H), 3.83 (s, 3 H), 6.66 (d, J = 2.1 Hz, 1 H), 6.71 (dd, J = 2.1, 8.7 Hz, 1 H), 7.37 (d, J = 8.7 Hz, 1 H); 13C NMR (126 MHz, CDCl3) δ 28.0 (x2), 28.5, 39.0, 44.2, 55.9, 57.0, 62.9, 93.4, 101.9, 108.2, 119.1, 126.3, 133.7, 140.9, 155.6; HR-MS 282.1442 (C16H21NO2+Na+) calcd 282.1465.

2-(6-Methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-9-yl)ethyl 4-methylbenzenesulfonate (8a): Para-toluene sulfonyl chloride (495 mg, 2.6 mmol, 1.5 equiv) was dissolved in toluene (5 mL) and added to a stirring mixture of TMEDA (0.4 mL, 2.6 mmol, 1.5 equiv) and alcohol
**8** (449 mg, 1.7 mmol, 1 equiv) in 1 mL of toluene. The mixture was stirred at 0 °C for 5 hours, quenched by addition of H₂O and diluted with EtOAc. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with H₂O. The solution was dried over MgSO₄, filtered, and concentrated to yield tosylated azetidine derivative **8a** used in the following step without purification. TLC Rₐ 0.48 (Cyclohexane/EtOAc 40 %); ¹H NMR (500 MHz, CDCl₃) δ 1.25 (s, 6 H), 2.40 (s, 3 H), 2.67 (s, 2 H), 2.99 (t, J = 7.2 Hz, 2 H), 3.68 (s, 2 H), 3.84 (s, 3 H), 4.19 (t, J = 7.2 Hz, 2 H), 6.63 (d, J = 2.2 Hz, 1 H), 6.67 (dd, J = 2.2, 8.6 Hz, 1 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.21 (d, J = 8.5 Hz, 2 H), 7.66 (d, J = 8.6 Hz, 1 H).

**9-(2-Azidoethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indole (4d):** Crude tosyl derivative **8a** (1.7 mmol, 1 equiv) was dissolved in DMF (9 mL) at room temperature. NaN₃ (338 mg, 5.2 mmol, 3 equiv) was then added as a solid in one portion to the mixture which was then stirred for 16 h. The reaction mixture was partitioned between H₂O (5 mL) and Et₂O (10 mL) and layers were separated. The organic layer was washed with H₂O (5 mL) then brine (5 mL). The solution was dried over MgSO₄, filtered, and concentrated to yield azide derivative **9** in 87 % yield (428 mg, 1.505 mmol) after flash chromatography over 2 steps from alcohol **8** (449 mg, 1.731 mmol). Orange solid; mp 49 °C; TLC Rₐ 0.58 (Cyclohexane/EtOAc 30 %); IR (neat) ν max 434, 511, 557, 592, 625, 643, 738, 792, 805, 815, 897, 968, 1063, 1169, 1197, 1238, 1274, 1336, 1355, 1368, 1379, 1405, 1434, 1456, 1488, 1566, 1594, 1622, 2077, 2837, 2873, 2940; ¹H NMR (500 MHz, CDCl₃) δ 1.29 (s, 6 H), 2.76 (s, 2 H), 2.95 (t, J = 7.2 Hz, 2 H), 3.48 (t, J = 7.2 Hz, 2 H), 3.73 (s, 2 H), 3.85 (s, 3 H), 6.68 (d, J = 2.2 Hz, 1 H), 6.74 (dd, J = 2.2, 8.6 Hz, 1 H), 7.35 (d, J = 8.7 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ 25.0, 28.1 (x2), 39.0, 44.2, 51.9, 56.0, 57.0, 93.6, 102.2, 108.3, 118.7, 126.0, 133.6, 140.6, 155.6; HR-MS 307.1565 (C₁₆H₂₀N₄O⁺Na⁺) calcd 307.1529.

**General Procedure 5 for the oxidation of pyrrolo[1,2-a]indoles using TFAA and DPSO or DMSO (GP5)**

Anhydrous DMSO or DPSO was dissolved in dry DCM and cooled to -78 °C. Freshly distilled trifluoroacetic anhydride was then carefully added via syringe to the solution, which was then stirred for 15 min at -78 °C. Pyrroloindole **6** (1 equiv) was dissolved in DCM in a second flask, cooled to -78 °C and finally added to the first flask via cannula. In each case, a strong coloration was immediately observed and the reaction reached full conversion within minutes. (All the pyrroloindol-1-ones synthesized in this section strongly revealed under the UV lamp). In some cases, the reaction mixture was quenched via classical workup conditions, or filtered through alumina to yield the crude product. Purification of the product by column chromatography

---

⁸ Y. Yoshida, *Synthesis*, 1999, 1633.
(SiO₂, cyclohexane/EtOAc) must be stored directly in the freezer to avoid degradation of the product.

**9-Hexyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-ol (10a):**
Product obtained following the GP5 with TFAA (3 equiv) and diphenylsulfoxide (DPSO, 3 equiv). The reaction was quenched after 45 min with NaHCO₃, extracted with DCM. The combined organic layers were washed with H₂O then brine, dried over MgSO₄ and concentrated under vacuum. After purification, 10a was obtained in 27 % yield (13.8 mg, 0.048 mmol) from pyrroloindole 6c (47.8 mg, 0.177 mmol). Colorless oil; TLC Rᵣ 0.15 (Cyclohexane/EtOAc 5 %); IR (neat) νmax 434, 734, 809, 1004, 1043, 1170, 1233, 1306, 1335, 1377, 1456, 2853, 2923, 2955, 3312; 1H NMR (500 MHz, CDCl₃) δ 0.89 (t, J = 7.0 Hz, 3 H), 1.12 (s, 3 H), 1.26–1.33 (m, 2 H), 1.32 (s, 3 H), 1.34–1.42 (m, 4 H), 1.58 (s, 1 H), 1.69–1.76 (m, 2 H), 2.82 (dd, J = 7.0, 8.1 Hz, 2 H), 3.73 (d, J = 9.8 Hz, 1 H), 3.90 (d, J = 9.8 Hz, 1 H), 4.67 (s, 1 H), 7.08 (dd, J = 1.5, 6.6, 8.0 Hz, 1 H), 7.16–7.22 (m, 2 H), 7.59 (d, J = 8.0 Hz, 1 H); 13C NMR (126 MHz, CDCl₃) δ 14.3, 20.9, 22.9, 24.6, 26.6, 29.5, 31.0, 31.9, 48.3, 54.7, 75.2, 109.7, 110.0, 118.6, 119.9, 121.5, 131.5, 132.9, 141.3; HR-MS 308.1985 (C₁₉H₂₇NO+Na⁺) calcd 308.1985.

**9-Hexyl-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-a]indol-1-one (11a):**
Product obtained following the GP5 with TFAA (3 equiv) and dimethylsulfoxide (DMSO, 3 equiv). The reaction was quenched after 1 min with NaHCO₃, extracted with DCM. The combined organic layers were washed with H₂O then brine, dried over MgSO₄ and concentrated under vacuum. After purification, 11a was obtained in 88 % yield (48.0 mg, 0.17 mmol) from pyrroloindole 6c (52.0 mg, 0.193 mmol). Colorless oil with blue reflection; TLC Rᵣ 0.25 (Cyclohexane/EtOAc 2.5 %); IR (neat) νmax 434, 484, 737, 944, 1004, 1044, 1109, 1131, 1147, 1184, 1245, 1311, 1342, 1374, 1399, 1463, 1562, 1701, 2855, 2925, 2957; 1H NMR (500 MHz, CDCl₃) δ 0.87 (t, J = 7.0 Hz, 3 H), 1.26–1.34 (m, 4 H), 1.36–1.43 (m, 2 H), 1.39 (s, 6 H), 1.72–1.79 (m, 2 H), 3.03 (dd, J = 7.7, 7.7 Hz, 2 H), 4.16 (s, 2 H), 7.13–7.19 (m, 1 H), 7.33–7.38 (m, 2 H), 7.76 (d, J = 8.2 Hz, 1 H); 13C NMR (126 MHz, CDCl₃) δ 14.3, 22.8, 24.3, 24.9 (x2), 29.3, 31.0, 31.8, 50.2, 54.5, 110.6, 118.9, 120.4, 122.5, 125.2, 131.1, 132.0, 135.1, 199.0; HR-MS 306.1823 (C₁₉H₂₅NO+Na⁺) calcd 306.1828.
3.87 (s, 3 H), 3.90–3.96 (m, 1 H), 4.65 (d, \(J = 4.4\) Hz, 1 H), 6.66–6.70 (m, 2 H), 7.20 (d, \(J = 9.3\) Hz, 1 H), 7.24 (dd, \(J = 7.2, 8.0\) Hz, 2 H), 7.30 (dd, \(J = 7.2, 8.0\) Hz, 2 H), 7.37 (dd, \(J = 7.0, 8.0\) Hz, 1 H), 7.40 (dd, \(J = 7.0, 8.0\) Hz, 1 H), 7.48 (d, \(J = 7.9\) Hz, 2 H), 7.57 (d, \(J = 7.9\) Hz, 2 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 19.2, 21.1, 26.5, 27.1 (x3), 27.7, 48.1, 55.0, 55.9, 64.8, 74.9, 93.2, 105.1, 108.7, 120.1, 126.0, 127.7 (x2), 127.8 (x2), 129.7, 129.8, 133.5 (x2), 133.6, 135.6 (x2), 135.7 (x2), 141.9, 156.2; HR-MS 536.2585 (C\(_{32}\)H\(_{39}\)NO\(_3\)Si+Na\(^+\)) calcd 536.2591.

**General Procedure 6 for the oxidation of indoles using oxalyl chloride and DMSO (GP6)**

Anhydrous DMSO (1.0 mmol, 6 equiv) was dissolved in dry DCM (0.6 mL) and cooled to -78 °C. Freshly distilled oxalyl chloride (0.5 mmol, 3 equiv) was then carefully added via syringe to the solution, which was then stirred for 15 min at -78 °C. Indole derivatives (0.17 mmol, 1 equiv) were dissolved in DCM (1 mL) in a second flask, cooled to -78 °C and finally added to the first flask via cannula. In each case, a strong coloration was immediately observed, and the reaction reached full conversion within minutes. (All the pyrroloindol-1-ones synthesized in this section strongly revealed under the UV lamp). The flask was then removed from the cooling bath but the mixture was directly filtered through a small pad of celite and finally evaporated without letting it reach room temperature. The delicious smell of Me\(_2\)S will tell you if the reaction is successful or not! Purification of the product by column chromatography (SiO\(_2\), cyclohexane/EtOAc) must be done immediately thereafter or the crude mixture must be stored directly in the freezer to avoid degradation of the product.

9-(2-((tert-Butyldiphenylsilyl)oxy)ethyl)-8-methoxy-2,2-dimethyl-3,5-dihydro-1H-pyrrolo[1,2-ajindol-1-ol (10c): Side-product obtained following the GP6 but with DMSO (6 equiv), (COCI\(_2\)) (3 equiv) and Et\(_3\)N (6 equiv) in 60 % yield (17.3 mg, 0.034 mmol) from pyrroloindole 7b (28.2 mg, 0.057 mmol). White solid; mp 128 °C; TLC \(R_f\) 0.15 (Cyclohexane/EtOAc 10 %); IR (neat) \(\nu_{max}\) 485, 503, 523, 645, 693, 965, 1008, 1064, 107, 1109, 1190, 1219, 1251, 1293, 1362, 1401, 1427, 1445, 1461, 1497, 1562, 2861, 2926, 2959, 3483; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 0.99 (s, 9 H), 1.12 (s, 3 H), 1.14 (s, 3 H), 2.86 (d, \(J = 4.6\) Hz, 1 H), 3.13 (ddd, \(J = 5.7, 8.9, 14.1\) Hz, 1 H), 3.28 (ddd, \(J = 4.3, 4.9, 14.1\) Hz, 1 H), 3.69 (d, \(J = 9.6\) Hz, 1 H), 3.71 (s, 3 H), 3.83 (d, \(J = 9.6\) Hz, 1 H), 3.87–3.99 (m, 2 H), 4.70 (d, \(J = 4.6\) Hz, 1 H), 6.42 (d, \(J = 7.8\) Hz, 1 H), 6.83 (d, \(J = 7.8\) Hz, 1 H), 7.07 (dd, \(J = 7.8, 8.3\) Hz, 1 H), 7.17 (dd, \(J = 6.8, 8.3\) Hz, 2 H), 7.27 (dd, \(J = 6.8, 8.3\) Hz, 2 H), 7.32 (dd, \(J = 6.8, 8.3\) Hz, 1 H), 7.37 (dd, \(J = 6.8, 8.3\) Hz, 1 H), 7.40 (d, \(J = 7.9\) Hz, 2 H), 7.55 (d, \(J = 7.9\) Hz, 2 H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 19.3, 21.1, 26.5, 27.1 (x3), 29.0, 48.1, 55.1, 55.5, 65.8, 74.8, 99.2, 103.1, 105.5, 121.1, 122.1, 127.6 (x2), 127.7 (x2), 129.5, 129.6, 133.5, 133.6, 134.6, 135.6 (x2), 135.7 (x2), 142.3, 155.2; HR-MS 552.2337 (C\(_{32}\)H\(_{39}\)NO\(_3\)Si+K\(^+\)) calcd 552.2331.
9-(2-((tert-Butyldiphenylsilyl)oxy)ethyl)-8-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-ajindol-1-one (11c): Prepared following the GP6 in 27 % yield (7.6 mg, 0.015 mmol) from pyrroloindole 7b (28.2 mg, 0.056 mmol). White solid; mp 127 °C; TLC Rf 0.33 (Cyclohexane/EtOAc 10 %); IR (neat) νmax 501, 616, 641, 655, 683, 781, 827, 857, 912, 926, 996, 1042, 1100, 1141, 1164, 1186, 1213, 1254, 1304, 1373, 1428, 1459, 1502, 1561, 1697, 2855, 2885, 2928; 1H NMR (400 MHz, CD6D6) δ 1.01 (s, 6 H), 1.15 (s, 9 H), 3.29 (s, 2 H), 3.30 (s, 3 H), 3.95 (t, J = 7.0 Hz, 2 H), 4.34 (t, J = 7.0 Hz, 2 H), 6.22 (d, J = 7.8 Hz, 1 H), 6.75 (d, J = 8.3 Hz, 1 H), 7.16–7.21 (m, 7 H), 7.74–7.79 (m, 4 H); 13C NMR (126 MHz, CD6D6) δ 19.5, 24.5 (x2), 27.1 (x3), 29.3, 49.5, 53.9, 54.7, 65.5, 99.9, 103.6, 114.9, 123.4, 125.8, 128.3 (x4), 129.6 (x2), 131.4, 134.6 (x2), 136.0 (x4), 136.9, 159.2, 198.0; HR-MS 550.2203 (C32H37NO3Si+K+) calcd 550.2174.

9-(2-Azidoethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-ajindol-1-one (11d): Prepared following the GP6 in 87 % yield (122 mg, 0.408 mmol) from pyrroloindole 9 (133 mg, 0.467 mmol). Orange solid; mp 76 °C; TLC Rf 0.20 (Cyclohexane/EtOAc 20 %); IR (neat) νmax 462, 642, 681, 734, 805, 1007, 1039, 1067, 1123, 1144, 1207, 1258, 1301, 1338, 1380, 1456, 1472, 1504, 1562, 1625, 1689, 2092, 2869, 2889, 2936; 1H NMR (500 MHz, CDCl3) δ 1.39 (s, 6 H), 3.26 (t, J = 7.2 Hz, 2 H), 3.69 (t, J = 7.2 Hz, 2 H), 3.89 (s, 3 H), 4.13 (s, 2 H), 6.70 (d, J = 2.3 Hz, 1 H), 6.87 (dd, J = 2.3, 9.0 Hz, 1 H), 7.62 (d, J = 9.0 Hz, 1 H); 13C NMR (126 MHz, CDCl3) δ 24.5, 24.9 (x2), 50.2, 51.6, 54.6, 55.7, 91.8, 113.5, 114.1, 122.9, 126.7, 130.8, 136.0, 159.2, 198.0; HR-MS 321.1316 (C16H18N4O2+Na+) calcd 321.1322.

**General Procedure 7 for the Staudinger Reaction (GP7)**

Azide derivative (1.30 mmol, 1 equiv) was dissolved in THF (8 mL) with an aqueous solution of NaOH [0.1M] (1 mL) at room temperature. A solution of trimethylphosphine [1M in THF] (3.9 mmol, 3 equiv) was then carefully and slowly added dropwise to the stirring mixture. The reaction was then stirred for 30 minutes even if the bubbling observed after PMe3 addition seems to indicate an immediate reaction. The mixture was then filtered through a small pad of celite and concentrated. Purification on reversed-phase flash column chromatography (H2O/MeCN) leads to protonated amine due to the presence of TFA in water during the purification process. A deprotonation of the ammonium species using Amberlyst-A resin yield the title amine compound.

9-(2-Aminoethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-ajindol-1-one (12): Prepared following the GP7 in 63 % yield (222 mg, 0.815 mmol) from azide 11d (388 mg, 1.3 mmol). Yellow solid; TLC Rf 0.10 (EtOAc/MeOH 5 %); IR (neat) νmax 437, 527, 627, 741, 767, 810, 855, 939, 1039, 1164, 1210, 1250, 1339, 1377, 1462, 1503, 1558, 1622, 1687, 2868,
2925, 2959, 3366; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.36 (s, 6 H), 3.01 (t, $J = 6.7$ Hz, 2 H), 3.09 (t, $J = 6.7$ Hz, 1 H), 6.67 (d, $J = 2.0$ Hz, 1 H), 6.81 (dd, $J = 2.0$, 9.0 Hz, 1 H), 7.59 (d, $J = 9.0$ Hz, 1 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 24.9 (x2), 28.9, 43.2, 50.1, 54.4, 55.6, 91.7, 113.0, 116.1, 123.1, 126.7, 130.8, 136.1, 159.0, 198.1; HR-MS 273.1586 (C$_{16}$H$_{20}$N$_2$O$_2$+H$^+$) calcd 273.1598.

Harmalidine dimer (13): Pyridinium para-toluenesulfonic acid (PPTS, 3 mg, 0.012 mmol) was added to a benzene solution (12 mL) of amine 12 (21.5 mg, 0.079 mmol) in round bottom flask equipped with a Dean-Stark apparatus. The reaction was stirred at 120°C for 6 days. Solvent was removed in vacuo and purification by flash chromatography afforded the harmalidine dimer 13 in 55% yield (11 mg, 0.022 mmol). White solid; TLC $R_f$ 0.41 (EtOAc/MeOH 5 %); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.42 (s, 12 H), 3.41 (dd, $J = 7.7$, 10.2 Hz, 4 H), 3.89 (s, 6 H), 3.95 (s, 4 H), 4.26 (dd, $J = 7.7$, 8.7 Hz, 4 H), 6.69 (d, $J = 2.1$ Hz, 2 H), 6.84 (dd, $J = 2.1$, 9.0 Hz, 2 H), 7.78 (d, $J = 9.0$ Hz, 2 H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 27.2 (x4), 28.2 (x2), 48.6 (x2), 53.9 (x2), 55.6 (x2), 56.1 (2x), 91.6 (x2), 109.7 (x2), 111.3 (x2), 122.0 (x2), 126.8 (x2), 129.5 (x2), 134.2 (x2), 158.0 (x2), 168.4 (x2); HR-MS 509.2920 (C$_{32}$H$_{36}$N$_4$O$_2$+H$^+$) calcd 509.2911.

General Procedure 8 for the Amination of 2,3-dihydropyrrolo[1,2-α]indole at the 2α position (GP8)

Anhydrous DMSO (1.0 mmol, 1 equiv) was dissolved in dry DCM (3 mL) and cooled to -78 °C. Freshly distilled oxalyl chloride (1.0 mmol, 1 equiv) was then carefully added via syringe to the solution, which was then stirred for 15 min at -78 °C. Pyrroloindole derivative 6 (1.0 mmol, 1 equiv) was dissolved in DCM (6 mL) in a second flask, cooled to -78 °C too and added to the first flask via cannula. In each case, a strong coloration was immediately observed. The amine was finally rapidly added to the reaction mixture via syringe, leading to a strong change of the coloration of the solution and the reaction reached full conversion within minutes. (All the pyrroloindol-1-ones synthesized in this section strongly revealed under the UV lamp). The flask was then removed from the cooling bath but the mixture was directly evaporated without letting it reach room temperature. Purification of the product by column chromatography (SiO$_2$, cyclohexane/EtOAc) has to be done immediately thereafter or the crude mixture has to be stored directly in the freezer to avoid degradation of the product.
N-Benzyl-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-\(\alpha\)]indol-1-amine (14a):
Prepared following the GP8 in 78% yield (25.0 mg) from 27.4 mg of 6b and 12 \(\mu\)L of benzylamine. It has to be noticed that 18% of the starting material has also been recovered in this case. Colorless oil; \(\text{TLC } R_f \ 0.42\) (Cyclohexane/EtOAc 30%); \(^1\text{H NMR (500 MHz, CDCl}_3\) \(\delta 1.03 \) (s, 3 H), 1.05 (s, 9 H), 1.22 (s, 3 H), 1.48 (bs, 1 H), 3.00–3.11 (m, 2 H), 3.56 (d, \(J = 9.6\) Hz, 1 H), 3.70 (s, 1 H), 3.77–3.92 (m, 5 H), 3.82 (s, 3 H), 6.60–6.64 (m, 2 H), 7.08 (d, \(J = 9.2\) Hz, 1 H), 7.22–7.27 (m, 1 H), 7.27–7.36 (m, 8 H), 7.36–7.42 (m, 2 H), 7.59–7.65 (m, 4 H); \(^{13}\text{C NMR (126 MHz, CDCl}_3\) \(\delta 19.3, 21.7, 27.1\) (x3), 27.7, 28.6, 52.7, 55.3, 55.9, 64.0, 65.0, 93.1, 104.6, 108.2, 119.9, 126.0, 127.1, 127.7 (x4), 128.3 (x2), 128.5 (x2), 129.6 (x2), 133.5, 134.0 (x2), 135.7 (x4), 140.7, 141.9, 155.8. \(\text{HR-MS } 602.3273\) (C\(_{30}\)H\(_{46}\)N\(_2\)O\(_2\)Si) calc 602.3223.

N- Allyl-9-(2-((tert-butyldiphenylsilyl)oxy)ethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-\(\alpha\)]indol-1-amine (14b):
Prepared following the GP8 in 25% yield (18 mg) from 68.4 mg of 6b and 20 \(\mu\)L of allylamine. Yellow oil; \(\text{TLC } R_f \ 0.30\) (Cyclohexane/EtOAc 30%); \(\text{IR ( neat) } v_{\text{max}}\) 488, 504, 611, 700, 729, 807, 821, 908, 1088, 1105, 1145, 1215, 1243, 1461, 1490, 1625, 2857, 2929, 2956; \(^1\text{H NMR (500 MHz, CDCl}_3\) \(\delta 1.02\) (s, 3 H), 1.06 (s, 9 H), 1.21 (s, 3 H), 2.98–3.10 (m, 2 H), 3.24 (ddt, \(J = 1.7, 5.7, 13.8\) Hz, 1 H), 3.31 (ddt, \(J = 1.7, 5.7, 13.8\) Hz, 1 H), 3.56 (d, \(J = 9.7\) Hz, 1 H), 3.64 (s, 1 H), 3.80 (d, \(J = 9.7\) Hz, 1 H), 3.83 (s, 3 H), 3.82–3.89 (m, 2 H), 5.08 (dq, \(J = 1.7, 10.2\) Hz, 1 H), 5.19 (dq, \(J = 1.7, 17.2\) Hz, 1 H), 5.88 (ddt, \(J = 5.9, 10.2, 17.2\) Hz, 1 H), 6.61–6.65 (m, 2 H), 7.09 (d, \(J = 9.3\) Hz, 1 H), 7.31–7.37 (m, 4 H), 7.39–7.44 (m, 2 H), 7.62–7.68 (m, 4 H); \(^{13}\text{C NMR (126 MHz, CDCl}_3\) \(\delta 19.3, 21.6, 27.1\) (x3), 27.7, 28.7, 48.2, 51.1, 55.2, 55.9, 63.7, 64.9, 93.1, 104.8, 108.2, 115.9, 119.9, 125.9, 127.7 (x4), 129.7 (x2), 133.5, 134.0, 134.1, 135.7 (x4), 137.2, 141.8, 155.8. \(\text{HR-MS } 575.3074\) (C\(_{35}\)H\(_{44}\)N\(_2\)O\(_2\)SiNa\(^+\)) calc 575.3064.

9-(2-Chloroethyl)-6-methoxy-2,2-dimethyl-2,3-dihydro-1H-pyrrolo[1,2-\(\alpha\)]indol-1-yl allylcarbamate (15):
Prepared following the GP8 in 20% yield (4.3 mg) from 13.0 mg of 6d and 7 \(\mu\)L of allylamine. It has to be noticed that 33% of the starting material has also been recovered in this case. Colorless oil; \(\text{TLC } R_f \ 0.10\) (Cyclohexane/EtOAc 10%); \(\text{IR ( neat) } v_{\text{max}}\) 533, 627, 731, 799, 917, 1017, 1092, 1144, 1167, 1258, 1300, 1379, 1458, 1492, 1530, 1626, 1650, 1724, 2853, 2923, 2958, 3296; \(^1\text{H NMR (500 MHz, CDCl}_3\) \(\delta 1.14\) (s, 3 H), 1.30 (s, 3 H), 3.16–3.35 (m, 2 H), 3.70 (d, \(J = 9.6\) Hz, 1 H), 3.75–3.87 (m, 3 H), 3.86 (s, 3 H), 3.90 (d, \(J = 9.6\) Hz, 1 H), 3.95 (dddd, \(J = 1.3, 1.3, 5.4, 6.7\) Hz, 1 H), 5.18 (dddd, \(J = 1.3, 2.7, 10.1\) Hz, 1 H), 5.22 (dddd, \(J = 1.3, 2.7, 17.2\) Hz, 2 H), 5.82 (ddt, \(J = 5.4, 10.1, 17.2\) Hz, 1 H), 6.67 (dd, \(J = 2.3\) Hz, 1 H), 6.74 (dd, \(J = 2.6, 8.4\) Hz, 1 H), 7.38 (d, \(J = 8.5\) Hz, 1 H), 7.53 (bs, 1 H); \(^{13}\text{C NMR (126 MHz, CDCl}_3\) \(\delta 20.7, 26.2, 28.2, 42.0, 45.4, 48.2, 54.7, 55.7, 74.7, 93.2, 104.7, 109.1, 117.3, 119.6, 125.1, 132.6, 133.5, 141.7, 156.3, 159.5.
7-Methoxy-1,9-dimethyl-4,9-dihydro-3H-pyrido[3,4-b]indole (N-methylharmaline): To a solution of commercially available harmaline (500 mg, 2.33 mmol) in anhydrous DMF (5 mL), NaH (60%, 233 mg, 5.83 mmol) was added under inert atmosphere at room temperature and heated at 55 °C for 3 h. Iodomethane (174 μL, 2.8 mmol) was then added at room temperature and the reaction was stirring for 24 h. The mixture was acidified with 1% HCl and washed with toluene (3x15 mL). The aqueous phase was basified to pH 8.5 and the product extracted with CH₂Cl₂ (3x30 mL). The organic phase was collected, dried over MgSO₄, filtered, and concentrated. Purification by flash chromatography afforded the N-methylharmaline in 47% (249 mg, 1.09 mmol). Pale yellow solid; TLC Rf 0.50 (EtOAc/MeOH 5 %); ¹H NMR (500 MHz, CDCl₃) δ 3.01 (t, J = 7.0 Hz, 2 H), 3.11 (s, 3 H), 3.64 (t, J = 7.0 Hz, 2 H), 3.89 (s, 3 H), 4.07 (s, 3 H), 6.75 (d, J = 2.2 Hz, 1 H), 6.81 (dd, J = 8.7, 2.2 Hz, 1 H), 7.43 (dd, J = 8.7, 0.6 Hz, 1 H); ¹³C NMR (126 MHz, CDCl₃) δ 20.7, 31.2, 34.1, 49.8, 55.5, 92.4, 111.0, 118.2, 118.9, 120.9, 125.6, 140.1, 158.4, 162.3.
Table S1. XRD image of amine 12 (trifluoracetic salt, hydrogens atoms have been omitted for clarity) and table of crystal data and refinement details:

| Identification Code | Compound 12 (CCDC 2111055) |
|---------------------|-----------------------------|
| Formula             | C_{16}H_{21}N_{2}O_{2}, C_{2}F_{3}O_{2} |
| Formula weight      | 386.37                      |
| Crystal system      | triclinic                   |
| Space group         | P - 1                       |
| a (Å)               | 8.790(5)                    |
| b (Å)               | 9.963(5)                    |
| c (Å)               | 10.845(5)                   |
| α (°)               | 88.953(5)                   |
| β (°)               | 89.952(5)                   |
| γ (°)               | 73.603(5)                   |
| V (Å³)              | 911.0(8)                    |
| Z                   | 2                           |
| Density (g cm⁻³)    | 1.409                       |
| μ (mm⁻¹)            | 0.119                       |
| F(000)              | 404                         |

**Data collection**

| Temperature (K)     | 173 (2)                     |
| Radiation (Å)       | MoK\(\alpha\) – 0.71069    |
| Theta min - max     | 0.9362 – 1.0225             |
| Dataset [h, k, l]   | -10/10, -12/12, -11/13     |
| Tot., sigmal/netl, R(int) | 8477, 0.0489, 0.0445 |

**Refinement**

| Nreflections, Nparameters, Nrestrains | 3574, 257, 18  |
| R2, R1, wR2, wR1, Goof              | 0.0961, 0.0704, 0.2326, 0.2019, 1.117 |
| Max. and Av. Shift/Error            | 0.000, 0.000    |
| Min, Max. Resd Dens. (e-/Å³)        | -0.700, 0.845   |
3a, E/Z 92:8
Crude $^1$H NMR, 500 MHz, CDCl$_3$
$^{3b}$, E/Z 89:11
Crude $^1$H NMR, 300 MHz, C$_6$D$_6$
3c, E/Z 89:11
Crude $^1$H NMR, 500 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$\text{C}_9\text{H}_{13}$

$4c$

$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$\text{tBuMe}_2\text{SiO}$

5a

$^{13}\text{C}$ NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$\text{C}_9\text{H}_{13}$

$5c$

$^{13}\text{C NMR, 125 MHz, CDCl}_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}\text{C NMR, 125 MHz, CDCl}_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
\[ \text{\textsuperscript{1}H NMR, 500 MHz, CDCl\textsubscript{3}} \]
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
Crude $^1$H NMR, 300 MHz, CDCl$_3$
-H NMR, 300 MHz, CDCl₃
$^{13}$C NMR, 500 MHz, CDCl$_3$
1H NMR, 500 MHz, CDCl₃
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^1$H NMR, 500 MHz, CDCl$_3$
\(^{13}\)C NMR, 126 MHz, CDCl\(_3\)
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, C$_6$D$_6$
$^{13}$C NMR, 126 MHz, C$_6$D$_6$
$^{1}\text{H NMR, 500 MHz, CDCl}_3$
1H NMR, 500 MHz, CDCl₃
$^{13}$C NMR, 126 MHz, CDCl$_3$
13

$^1$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 126 MHz, CDCl$_3$
**HR-MS Spectra**

Figure S1. Low- and high-resolution mass spectra for compound 13.
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^{1}$H NMR, 500 MHz, CDCl$_3$
$^{13}$C NMR, 125 MHz, CDCl$_3$
^1H NMR, 500 MHz, CDCl\textsubscript{3}
$^{13}$C NMR, 125 MHz, CDCl$_3$
$^1$H & $^{13}$C NMR Spectra of harmaline and $N$-methylharmaline

harmaline +
trace of harmine

$^1$H NMR, 500 MHz, CDCl$_3$
harmaline

$^{13}$C NMR, 125 MHz, CDCl$_3$
$N$-methylharmaline

$^1$H NMR, 500 MHz, CDCl$_3$
$N$-methylharmaline

$^{13}$C NMR, 125 MHz, CDCl$_3$