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DIASTEREOSELECTIVE SYNTHESIS OF 3-ALKYLINDOLOQUINOLIZINE DERIVATIVES VIA REGIOSPECIFIC OXIDATIVE CYCLIZATION

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Abstract – 3-Alkylindoloquinolizine alkaloids were synthetized in two steps from enantiopure 3-alkylpiperidines through sequential *N*-alkylation and regiospecific and diastereoselective oxidative cyclization.

INTRODUCTION

The indoloquinolizine framework is widely distributed in both pharmaceuticals and natural products (e.g. Figure 1) showing a wide range of pharmacological activities such as analgesic,[1] anti-inflammatory,[2] antihypertensive,[3] anticancer,[4] apoptosis inducers,[5] anti-leishmanial,[6] among others.

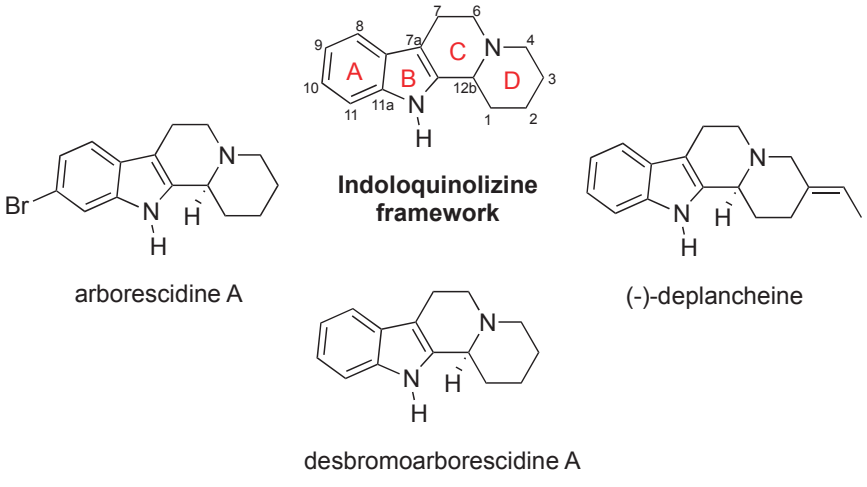
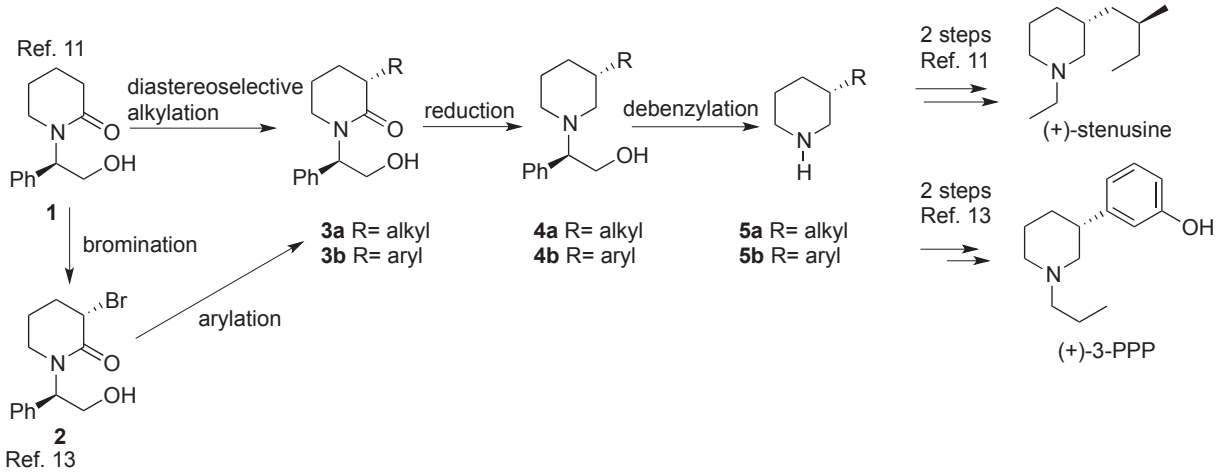


Figure 1. Indoloquinolizine framework present in natural products

Several synthetic strategies to afford them have been reported involving multistep processes with the use of chiral resources, non-catalytic sequences, and asymmetric metal- and organocatalysis.[7] Traditionally, the

majority of reported strategies for asymmetric total synthesis of indoloquinolizidine alkaloids have required multistep syntheses relying on starting materials from the chiral pool. These strategies often include several functional group transformations and tedious protection/deprotection steps, often providing low overall yields of target alkaloids.[7a] Based on the above, there is still a need to continue designing syntheses with high diastereoselectivity. In this way, we envisioned a diastereoselective synthetic strategy involving two key building blocks: enantiopure alkylpiperidines and tryptophyl derivatives. This methodology would require of the enantioselective functionalization of piperidine ring and the subsequent attachment to indole derivatives followed by known cyclization reactions through either Polonovski,[8] Bischler-Napieralski[9] or Fujii type reactions.[10] In this context, we have recently developed highly efficient diastereoselective methods to generate 3-alkyl- or 3-arylpiperidines (**5a-b**) from (*R*)-1-(2-hydroxy-1-phenylethyl)piperidin-2-one (**1**)[11-13] and we have applied these methodologies in syntheses of medicinally interesting alkaloids, such as (+)-stenusine[11] and (+)-3-PPP (preclamol)[13] (Scheme 1).



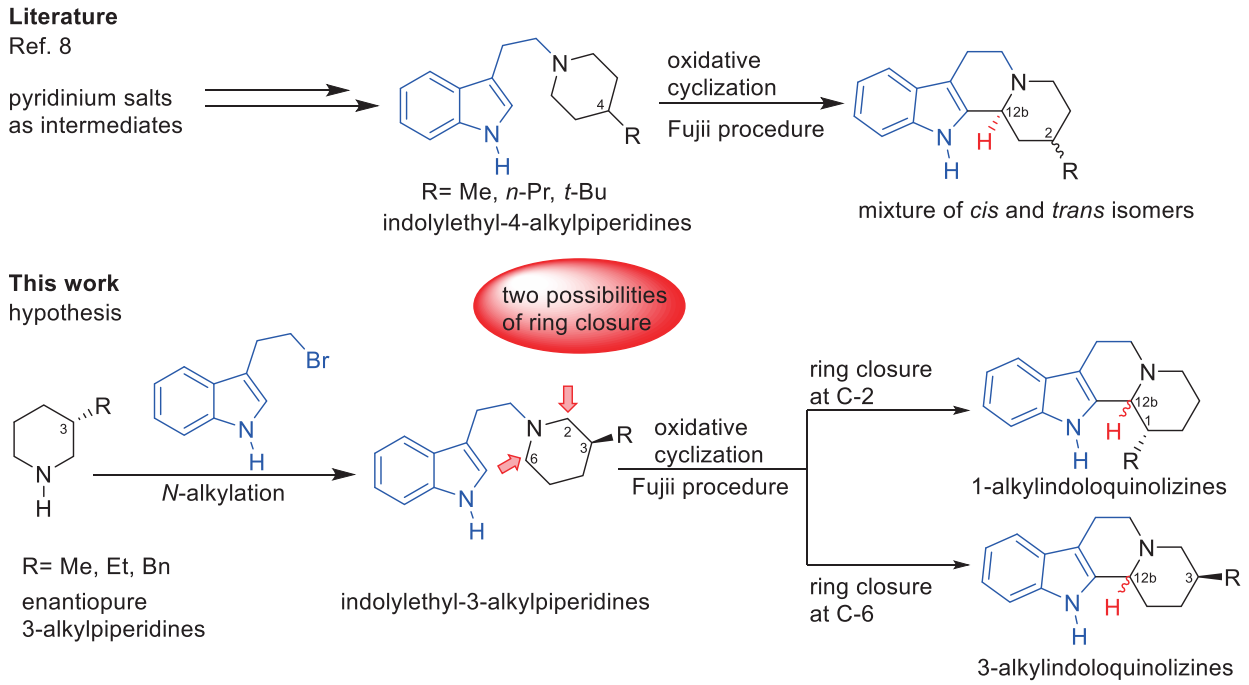
Scheme 1. Synthesis of (+)-stenusine and (+)-3-PPP (preclamol) from enantiopure alkyl- and arylpiperidines respectively

In the present work we want to report a diastereoselective synthesis of 3-alkylindoloquinolizines via regiospecific oxidative cyclization from enantiopure 3-alkyl-substituted piperidines (**5a**) (Scheme 1).

RESULTS AND DISCUSSION

According to our envisioned synthetic strategy and to the best of our knowledge there is only one report in literature applying alkylpyridines (instead of alkylpiperidines) and tryptophyl derivatives as building blocks by the oxidative cyclization strategy for the synthesis of indoloquinolizines through a modified Fujii procedure.[8] This methodology involves the condensation of 4-alkylpyridine derivatives with tryptophyl bromide, giving their respective pyridinium salts which after reduction produce the respective indolylethyl-alkylpiperidine derivatives. Subsequently, their oxidative cyclization produce mixture of *cis*

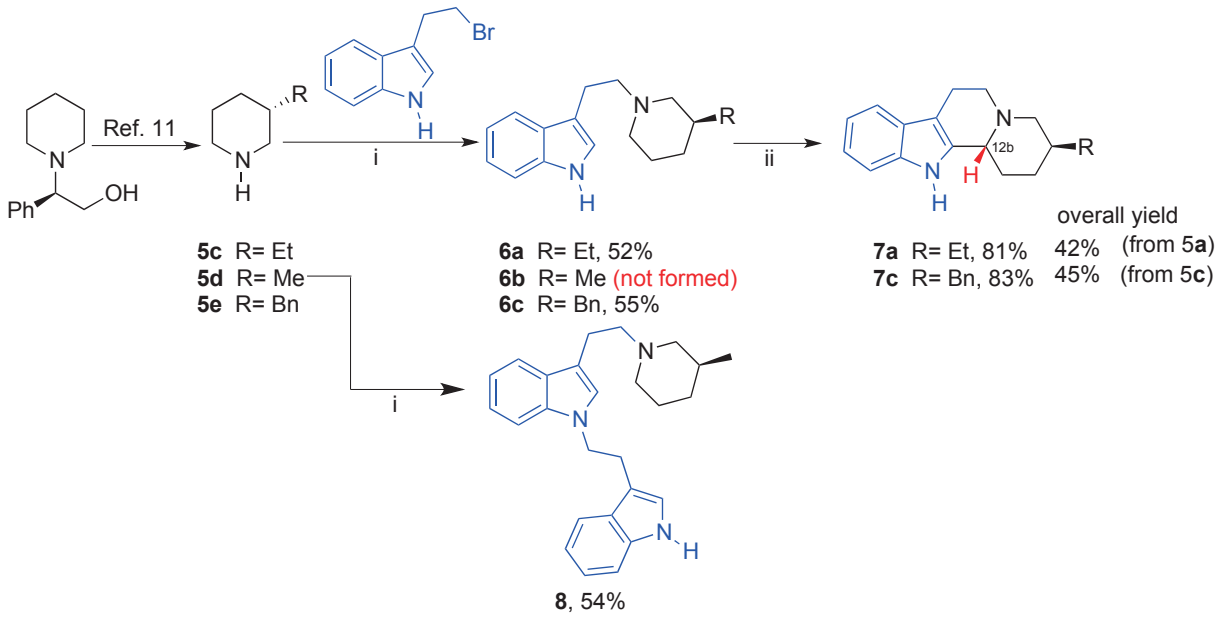
and *trans* indoloquinolizines[8] due to the indistinct attachment at C-2 or C-6 on the piperidine moiety of 1-indolylethyl-3-alkylpiperidine intermediates, resulting in low regio- and diastereoselectivities (Scheme 2).



Scheme 2. Hypothesis of the two possibilities during the attachment

Our hypothesis is that taken advantage of our experience synthesizing enantiopure 3-alkylpiperidines[11] it is possible to increase the regio- and diastereoselectivity during the ring closure using the Fujii procedure. For this purpose, we designed the synthesis of three indolylethyl-3-alkylpiperidine derivatives containing methyl, ethyl or benzyl an alkyl group to evaluate their effect during the ring closure. In this context, it would be possible to obtain two regioisomers; if the attachment occurs at C-2 or C-6 on the piperidine moiety of the indolylethyl-3-alkylpiperidine intermediates producing either 1-alkylindoloquinolizines or 3-alkylindoloquinolizines, respectively (Scheme 2).

First, the enantiopure (3*S*)-3-ethylpiperidine (**5c**) was prepared following our previously reported methodology[11] and then subjected to an *N*-alkylation with tryptophyl bromide giving the (*S*)-3-(2-(3-ethylpiperidin-1-yl)ethyl)-1*H*-indole (**6a**) in 52% yield.[14] The indole **6a** was treated under oxidative cyclization conditions (Fujii procedure for the synthesis of 4-alkyl-substituted indoloquinolizine[8]) affording an indoloquinolizine derivative as a sole regio- and diasteroisomer in 81% (42% overall yield from **5c**). The 2D NMR analysis (*vide infra*) provided us with strong evidence that the attachment during the ring closure was favored at C-6 producing the 3-ethylindoloquinolizine **7a** (Scheme 3).

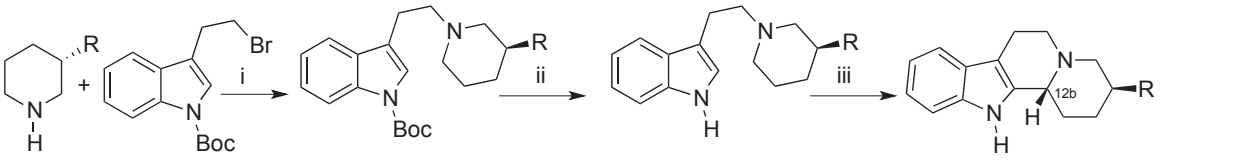


Reagents and conditions: (i) $NaHCO_3$, MeCN, reflux 30 h; (ii) a) $Hg(OAc)_2$-EDTA·2Na, $EtOH/H_2O$, reflux 3 h, b) $NaBH_4$, $CHCl_3$, rt, 4 h

Scheme 3. Synthesis of indololoquinolizines **7a** and **7c** and dimer **8** from enantiopure alkylpiperidines **5c-e**

Additionally, the NMR analysis also allowed us to identify the configuration of the new chiral center (C-12b) as *R* (*vide infra*). Continuing with the synthesis, the 3-alkylpiperidines (*S*)-3-methylpiperidine (**5d**) and (*R*)-3-benzylpiperidine (**5e**) were prepared and submitted to conditions toward the formation of 3-alkylindoloquinolizines (*vide supra*). When methylpiperidine **5d** was reacted with the tryptophyl bromide, the formation of the indolylethyl-3-methylpiperidine **6b** was not observed. Instead, we isolated the dimerization product **8** in 54% yield (Scheme 3). On the other hand, when we used the benzylpiperidine **5e** as starting material for the same sequential procedure, no dimerization during the *N*-alkylation was observed allowing the formation of **6c** in 55% yield. The subsequent oxidative cyclization of the indolylethyl-3-benzylpiperidine **6c** furnished 3-indoloquinolizine **7c** also as a sole regioisomer in 83% (45% overall yield form **5e**) (Scheme 3). Due to the low yields (for **6a** and **6c**) and dimerization product **8** during the *N*-alkylation, the tryptophyl bromide was *N*-protected with di-*tert*-butyl dicarbonate (Boc) previous to the *N*-alkylation giving **9b** in 82% yield (Scheme 4). Then, **9b** was unprotected affording the indolylethyl-3-methylpiperidine **6b** almost quantitatively and was submitted under oxidative cyclization conditions furnishing the 3-indoloquinolizine **7b** in 80% yield. These results confirmed that the attachment during the ring closure at C-6 is favored due to the steric effect of alkyl groups at C-3 position of the piperidine moiety in indolylethyl-3-alkylpiperidine derivatives **6(a-c)**, thus C-6 is the less hindered position. Interestingly, under the protection/deprotection conditions the overall yield for **7b** increased notably (63%) respect to previous entries (42% for **7a** in Scheme 3 and 45% **7c** in Scheme 5), in spite one step was added. Therefore, this sequential methodology was applied to the alkylpiperidines **5e** and **5c** showing the same

trend and hence an increase in overall yields was also observed for the expected 3-alkylindoloquinolizines **7c** and **7a** (69% and 67% overall yields, respectively) (Scheme 4).



5c R= Et
5d R= Me
5e R= Bn

9a R= Et, 85%
9b R= Me, 82%
9c R= Bn, 86%

6a R= Et, 96%
6b R= Me, 96%
6c R= Bn, 95%

7a R= Et, 82% overall yield: 67%
7b R= Me, 80% overall yield: 63%
7c R= Bn, 85% overall yield: 69%

Reagents and conditions: (i) $NaHCO_3$, MeCN, reflux 30 h; (ii) Me_2S, TFA, DCM anh.; (iii) $Hg(OAc)_2$-EDTA·2Na, EtOH-H_2O, reflux 3 h / $NaBH_4$, $CHCl_3$, rt 4 h.

Scheme 4. An increase in overall yields for indoloquinolizine derivatives **7(a-c)** were observed when the tryptophyl bromide was *N*-protected with Boc during the *N*-alkylation step

On the other hand, the 2D NMR analysis was fundamental to establish the position of alkyl groups and the configuration of the new chiral center in the indoloquinolizines **7(a-c)** (their total assignment is shown in Table S1 of Supplementary Information). For this purpose, we identified the diagnostic signals at C/D rings of **7(a-c)**. Initially, we used **7a** as a model for the 2D NMR analysis. Thus, the H-12b signal (δ_H 3.16) splits into a doublet of doublets of doublets (ddd, J = 12.0, 3.5, 2.5 Hz). The value of J = 12.0 indicates a *trans*-diaxial coupling with axial H-1 (δ_H 1.60), whereas the value of J = 3.5 indicates an axial-equatorial coupling with equatorial H-1 (δ_H 2.10). These two couplings were corroborated by the COSY experiment (Figures 2 and 3, Table S1).

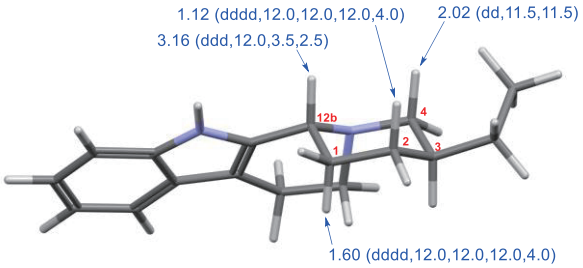
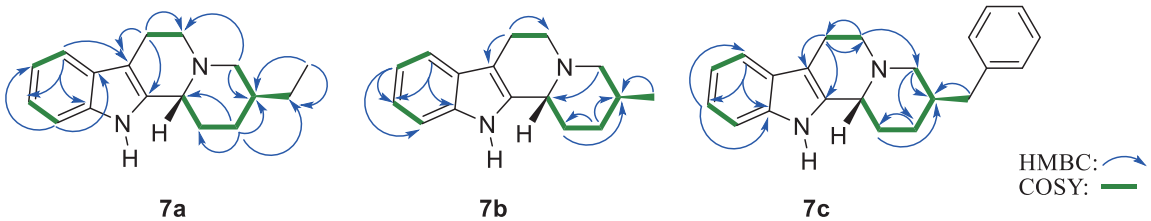


Figure 2. Diagnostic ^{1}H-NMR signals for the assignment of *R* configuration at C-12b in **7a**



7a **7b** **7c**

Figure 3. Key HMBC and COSY correlations of compounds **7(a-c)**

H-12b was simplified to a doublet of doublets signal (dd, J = 12.0, 3.5 Hz) by the addition of a few drops of deuterium oxide. This suggests the third J-value (2.5 Hz) of H-12b is due to a long range coupling with the N-H (δ_H 7.75); axial H-1 signal splits into a doublet of doublet of doublet of doublets (dddd, J = 12.0, 12.0, 12.0, 4.0 Hz) due to the geminal, two *trans*-diaxial (with axial H-2 and axial H-12b) and equatorial (with equatorial H-2) couplings. Additionally, axial H-1 showed HMBC correlations with C-2 (δ_C 30.9), C-12a (δ_C 135.1) and C-12b (δ_C 60.3) together with COSY correlation with axial H-2 (δ_H 1.12); axial H-2 signal also splits into a dddd signal due to the geminal, two *trans*-diaxial (with axial H-1 and axial H-3) and equatorial (with equatorial H-2) couplings. Axial H-2 exhibited HMBC correlations with C-1 (δ_C 29.9), C-3 (δ_C 37.8), C-4 (δ_C 61.8), C-12b, and with the methylene (δ_C 27.3) of the ethyl substituent attached to C-3. One of the most important diagnostic signals is the axial H-4 (δ_H 2.02), which splits into a dd (J = 11.5, 11.5 Hz) due to the geminal, and *trans*-diaxial (with axial H-3) couplings. This indicates the ethyl substituent is in equatorial orientation (Figures 2 and 3, Table S1). Additionally, 2D NOESY experiment showed the spatial interaction between axial H-4 and axial H-12b (Figure 4) confirming the *R* configuration for the new chiral center C-12b. Thus, based on the total and unequivocal assignment for **7a**, the regiospecific and diastereoselective cyclization was confirmed. Finally, 2D NMR analysis was performed for **7b** and **7c** which exhibited the same pattern as **7a** (Figures 3 and 4, Table S1), except for H-12b (δ_H 3.20) and axial H-4 (δ_H 2.12) of **7c**, which appear at slightly higher frequency than **7a** and **7b**, due to the influence of the benzyl substituent in **7c**.

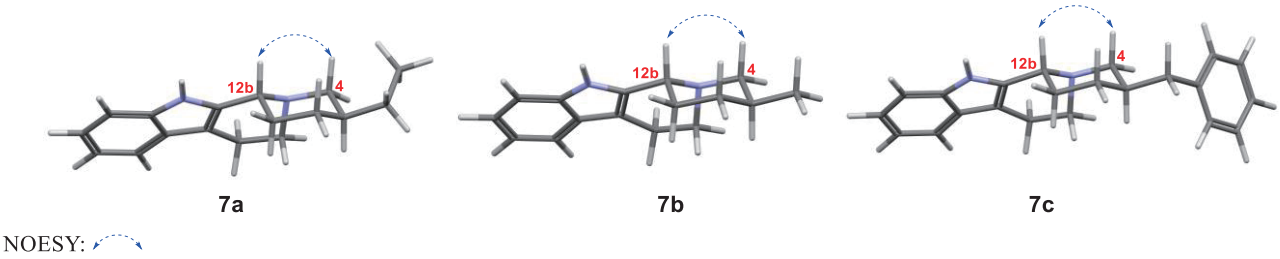


Figure 4. 2D NOESY correlations of compounds **7(a-c)**

EXPERIMENTAL

All reagents and solvents were purchased from commercial sources. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and 125 MHz, respectively, in $CDCl_3$ using a Bruker Avance III Spectrometer. Chemical shifts are given in ppm and reported to the residual solvent peak ($CHCl_3$ 7.26 ppm and 77.0 ppm). Data are reported as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), coupling constant(s) (J, Hz), and integration. Analytical TLC was performed on silica gel 60 F_{254} plates. Column chromatography was carried out on silica gel 60 (63-200 μm). Mass spectra were recorded on JEOL JMS-700 MStation Mass Spectrometer at a voltage of 70 eV. Optical rotations were

measured on the Perkin-Elmer 341 polarimeter at room temperature using a 1 dm cell with a total volume of 1 mL and are referenced to the D-line of sodium.

General procedure for preparation of 3-alkylpiperidines, 5(c-d)

A mixture of the compound **4** (200 mg, 0.855 mmol) in MeOH (2 mL) and containing 5% Pd/C (200 mg) was hydrogenated at rt for 0.5 h. The catalyst was removed by filtration, and the solvent was evaporated. The product was purified by chromatography (CH_2Cl_2-MeOH = 94:6).

(3*S*)-3-Methylpiperidine (5c). Colorless crystals, mp 166-165 ºC. Yield 0.069 g (77%). $[\alpha]_D^{20}$ –3.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.42 (br s, NH), 3.45 (d, 1H, *J* = 12.5 Hz), 3.36 (d, 1H, *J* = 12.5 Hz), 2.76 (dd, 1H, *J* = 12.5, 2.8 Hz), 2.47 (t, 1H, *J* = 12.2 Hz), 2.11 (m, 1H), 1.97 (m, 1H), 1.87 (m, 2H), 1.13 (m, 1H), 0.97 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.1, 43.8, 30.8, 28.3, 22.0, 18.8.

(3*S*)-3-Ethylpiperidine (5d). Colorless crystals, mp 160-161 ºC. Yield 0.060 g (62%). $[\alpha]_D^{20}$ –3.4 (*c* 1.0 EtOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.43 (br s, NH), 3.43 (m, 2H), 2.75 (dd, 1H, *J* = 12.7, 3.6 Hz), 2.47 (t, 1H, *J* = 12.2 Hz), 1.94 (m, 2H), 1.88 (m, 2H), 1.31 (m, 2H), 1.07 (m, 1H), 0.92 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 48.9, 44.3, 34.8, 28.5, 26.5, 22.1, 10.6.

(3*R*)-3-Benzylpiperidine (5e). Colorless oil. Yield: 0.097 g (82%). $[\alpha]_D^{20}$ –13.6 (*c* 1.0 $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (br s, NH), 7.28 (m, 2H), 7.20 (dd, 1H, *J* = 7.3, 1,2 Hz), 7.13 (d, 2H, *J* = 7.9 Hz), 3.36 (d, 1H, *J* = 12.7 Hz), 3.29 (d, 1H, *J* = 12.3 Hz), 2.71 (dd, 1H, *J* = 12.6, 3.0 Hz), 2.55 (m, 2H), 2.45 (m, 1H), 2.27 (m, 1H), 1.88 (m, 3H), 1.13 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.7, (129.0 x 2), (128.5 x 2), 126.5, 48.6, 44.1, 40.0, 34.7, 28.7, 21.9.

General procedure for *N*-alkylation

Compounds **6(a,c)** and **8** were obtained adapting the literature procedure.[14] A mixture of (*S*)-3-ethylpiperidine **5c** (50 mg, 0.442 mmol), 3-(2-bromoethyl)-1*H*-indole (99 mg, 0.442 mmol) and $NaHCO_3$ (155 mg, 1.85 mmol) in MeCN (5 mL) was heated at 80 °C for 30 h. The mixture was cooled at rt and Et_2O (5 mL) and water (5 mL) were added. The phases were separated, and the organic phase was dried and concentrated. The product was purified by column chromatography (petroleum ether-AcOEt = 96:4).

(3*S*)-3-(2-(3-Ethylpiperidino)ethyl)-1*H*-indole (6a). Colorless oil. Yield: 0.058 g (52%). $[\alpha]_D^{20}$ –5.9 (*c* 0.9, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (br s, NH), 7.62 (d, 1H, *J* = 7.5 Hz), 7.35 (d, 1H, *J* = 7.5 Hz), 7.18 (ddd, 1H, *J* = 7.5, 7.5, 1.0 Hz), 7.11 (ddd, 1H, *J* = 7.5, 7.5, 1.0 Hz), 7.01 (d, 1H, *J* = 2.2 Hz), 3.04 (m, 2H), 3.00 (m, 2H), 2.69 (m, 2H), 1.96 (ddd, 1H, *J* = 11.5, 11.5, 3.0 Hz), 1.81 (m, 1H), 1.70 (m, 2H), 1.66 (m, 1H), 1.52 (m, 1H), 1.24 (m, 2H), 0.91 (t, 3H, *J* = 7.5 Hz), 0.85 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 127.5, 121.9, 121.4, 119.1, 118.9, 114.6, 111.1, 60.4, 59.9, 54.3, 37.9, 30.8, 27.5, 25.5, 22.8, 11.4.

(3*R*)-3-(2-(3-Benzylpiperidino)ethyl)-1*H*-indole (6c). Colorless oil. Yield: 0.049 g (55%). $[\alpha]_D^{20}$ –17.9

(*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.32 (br s, NH), 7.49 (d, 1H, *J* = 7.5 Hz), 7.35 (d, 1H, *J* = 7.5 Hz), 7.28 (m, 2H), 7.22 (m, 1H), 7.15 (ddd, 1H, *J* = 8.0, 8.0, 1.5 Hz), 7.09 (m, 3H), 6.85 (s, 1H), 3.46 (m, 2H), 3.07 (m, 2H), 3.00 (m, 2H), 2.56 (dd, 1H, *J* = 13.5, 6.5 Hz), 2.41 (m, 3H), 2.29 (dd, 1H, *J* = 13.5, 7.5 Hz), 2.19 (m, 1H), 1.79 (m, 2H), 1.03 (ddd, 1H, *J* = 12.0, 12.0, 3.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.7, 136.3, (129.0 x 2), (128.5 x 2), 126.7, 126.6, 122.6, 122.1, 119.4, 118.1, 111.6, 109.9, 58.5, 57.5, 52.7, 40.0, 35.0, 29.7, 28.5, 22,4.

(3*S*)-1-(2-(1*H*-Indol-3-yl)ethyl)-3-(2-(3-methylpiperidino)ethyl)-1*H*-indole (8). Yellow oil. Yield: 0.105 g (54%). $[\alpha]_D^{20}$ +5.9 (*c* 1.0, MeOH). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.61-7.58 (m, 2H), 7.42-7.39 (m, 2H), 7.21 (s, 1H), 7.18-7.15 (m, 2H), 7.14 (s, 1H), 7.10-7.06 (m, 2H), 3.78 (m, 1H), 3.80-3.75 (m, 2H), 3.67-3.65 (m, 2H), 3.34-3.32 (m, 2H), 3.29 (m, 2H), 3.28 (d, 1H, *J* = 3.3 Hz), 3.22 (dd, 2H, *J* = 6.4, 9.8 Hz), 2.16-2.09 (m, 1H), 1.90 (t, 1H, *J* = 12.5 Hz), 1.25-1.22 (m, 1H), 0.98 (d, 3H, *J* = 6.5 Hz), ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.2, 138.1, 128.0, 128.0, 122.9, 122.9, 120.3, 120.2, 118.9, 118.7, 112.8, 112.7, 109.6, 109.5, 65.9, 65.4, 60.2, 58.3, 54.8, 31.1, 26.9, 21.0, 19.3, 19.1, 18.9. HRMS (FAB^+): calcd. for $C_{26}H_{32}N_3[M+H]^+$ 386.2518. Found: 386.2515.

***tert*-Butyl (3*S*)-3-(2-(3-ethylpiperidino)ethyl)-1*H*-indole-1-carboxylate (9a).** Colorless oil. Yield: 0.133 g (85%). $[\alpha]_D^{20}$ –5.2 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.54 (d, 1H, *J* = 7.7 Hz), 7.40 (br s, 1H), 7.30 (dd, 1H, *J* = 7.5, 1.0 Hz), 7.23 (dd, 1H, *J* = 7.5, 1.0 Hz), 3.00 (d, 2H, *J* = 10.0 Hz), 2.90 (m, 2H), 2.67 (m, 2H), 1.96 (ddd, 1H, *J* = 12.5, 11.5, 2.5 Hz), 1.87 (br s, 1H), 1.81 (m, 1H), 1.71 (m, 2H), 1.66 (br s, 9H), 1.60 (m, 1H), 1.51 (m, 1H), 1.25 (m, 1H), 0.91 (t, 3H, *J* = 7.4 Hz), 0.85 (ddd, 1H, *J* = 12.5, 12.5, 4.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 130.7, 124.2, 122.6, 122.3, 119.2, 119.0, 115.2, 83.3, 60.3, 58.9, 54.4, 37.9, 30.8, 29.7, (28.2 x 3), 27.4, 25.5, 22.5, 11.4.

***tert*-Butyl (3*S*)-3-(2-(3-methylpiperidino)ethyl)-1*H*-indole-1-carboxylate (9b).** White crystals, mp 172-174 °C. Yield: 0.141 g (82%). $[\alpha]_D^{20}$ –4.5 (*c* 0.8, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.54 (m, 1H), 7.40 (br s, 1H), 7.30 (ddd, 1H, *J* = 9.0, 7.5, 1.0 Hz), 7.23 (m, 1H), 2.97 (m, 2H), 2.90 (m, 2H), 2.66 (m, 2H), 1.941 (ddd, 1H, *J* = 12.0, 11.0, 3.0 Hz), 1.80 (br s, 1H), 1.72 (m, 3H), 1.65 (br s, 11H), 0.90 (d, 3H, *J* = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 130.7, 124.2, 122.6, 122.3, 119.2, 119.0, 115.2, 83.3, 62.1, 58.8, 54.0, 33.1, 31.2, 29.7, (28.2 x 3), 25.6. 22.6, 19.9. Crystal structure was deposited at the Cambridge Crystallographic Data Centre, deposit number: 1896055.

***tert*-Butyl (3*R*)-3-(2-(3-benzylpiperidino)ethyl)-1*H*-indole-1-carboxylate (9c).** Colorless oil. Yield: 0.102 g (86%). $[\alpha]_D^{20}$ -32.6 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.11 (br s, 1H), 7.51 (m, 1H), 7.38 (br s, 1H), 7.30 (m, 3H), 7.23 (d, 1H, *J* = 7.5 Hz), 7.20 (m, 1H), 7.15 (d, 2H, *J* = 7.5 Hz), 2.97 (d, 1H, *J* = 10.0 Hz), 2.91 (d,1 H, *J* = 10.0 Hz), 2.86 (m, 2H), 2.64 (m, 2H), 2.55 (dd, 1H, *J* = 12.5, 7.0 Hz), 2.50 (dd, 1H, *J* = 12.5, 7.0 Hz), 1.99 (m, 1H), 1.92 (m, 1H), 1.78 (t, 1H, *J* = 10.5 Hz), 1.70 (m, 3H), 1.65 (s, 9H), 0.96 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.7, 140.4, 135.4, 130.7, (129.0 x 2), (128.1 x 2),

125.8, 124.2, 122.5, 122.2, 119.1, 118.9, 115.2, 83.3, 60.2, 58.8, 54.1, 41.1, 38.0, 30.8, (28.2 x 3), 25.3, 22.6.

Deprotection of compounds 9(a-c)

To a solution of **9** (22 mg 0.052 mmol) in anhydrous CH_2Cl_2 (0.16 mL) under nitrogen atmosphere were added Me_2S (1.03 mL) and TFA (0.161 mL) and stirred for 30 min at rt. The mixture was neutralized with an aqueous $NaHCO_3$ solution. The phases were separated and aqueous phase was extracted with CH_2Cl_2 (4 x 5.0 mL) and the combined organic layer were dried over Na_2SO_4 and concentrated under reduced pressure to afford **6(a-c)** in 95-96% yields after purification by flash chromatography (CH_2Cl_2-MeOH = 95:5).

(3*S*)-3-(2-(3-Methylpiperidino)ethyl)-1*H*-indole (6b). Colorless oil. Yield: 0.0148 g (96%). $[\alpha]_D^{20}$ –1.1 (*c* 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.24 (br s, 1H) 7.62 (d, 1H, *J* = 7.9 Hz), 7.33 (d, 1H, *J* = 8.2 Hz), 7.18 (ddd, 1H, *J* = 7.5, 7.5, 1.0 Hz), 7.11 (ddd, 1H, *J* = 7.5, 7.5, 1.0 Hz), 6.99 (d, 1H, *J* = 2.5 Hz), 3.04 (m, 1H), 2.98 (m, 3H), 2.69 (m, 2H), 1.94 (m, 1H), 1.73 (m, 1H), 1.72 (m, 1H), 1.66 (m, 3H), 0.89 (d, 3H, *J* = 6.0 Hz), 0.85 (dd, 1H, 12.3, 5.4, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 136.2, 127.4, 121.8, 121.4, 119.1, 118.8, 114.4, 111.1, 62.0, 59.8, 54.0, 33.1, 31.1, 25.6, 22.7, 19.9.

General procedure for cyclization of compounds 6(a-c)

Compounds **7(a-c)**, were prepared adapting the literature procedure.[8] The compound **6** (30 mg, 123 mmol) was dissolved in EtOH (1.9 mL). A solution containing EDTA disodium salt dihydrate (138 mg 0.371 mmol) and mercuric acetate (118 mg, 0.371 mmol) in H_2O (3.7 mL) was added and the resulting mixture was refluxed for 3 h. After cooling, CH_2C1_2 was added, and then dilute with aqueous ammonia until the pH reached 9.0. Then, $NaBH_4$ (0.046 g, 1.23 mmol) was added and the reaction mixture was stirred at rt for 4 h. $CHCl_3$ was added and the mixture was filtered. Extraction, washing with brine, drying (Na_2SO_4), filtering and evaporation gave the crude product **7**, this was purified by flash chromatography column (petroleum ether-AcOEt = 90:10).

(3*S*,12b*R*)-3-Ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (7a). Yellow oil. Yield: 0.024 g (82%). $[\alpha]_D^{20}$ +7.0 (c 1.0, $CHCl_3$). HRMS (FAB^+): calcd. for $C_{17}H_{23}N_2[M+H]^+$ 255.1783. Found: 255.1803. ^{1}H NMR (500 MHz, $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) (See ***Table S1***).

(3*S*,12b*R*)-3-Methyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (7b). Yellow oil. Yield 0.023 g (80%). $[\alpha]_D^{20}$ +2.8 (*c* 1.0, $CHCl_3$). HRMS (FAB^+): calcd. for $C_{16}H_{21}N_2[M+H]^+$ 241.1626. Found: 241.1611. ^{1}H NMR (500 MHz, $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) (See ***Table S1***).

(3*R*,12b*R*)-3-Benzyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (7c). Colorless oil. Yield 0.025 g (85%). $[\alpha]_D^{20}$ +5.3 (*c* 1.0, $CHCl_3$). HRMS (FAB^+): calcd. for $C_{22}H_{25}N_2[M+H]^+$ 317.1939. Found: 317.1922. ^{1}H NMR (500 MHz, $CDCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$) (See ***Table S1***).

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