DIASTEROSELECTIVE SYNTHESIS OF 3-ALKYINDOLOQUINOLIZINE 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, anti-inflammatory, antihypertensive, anticancer, apoptosis inducers, anti-leishmanial, among others.

![Figure 1. Indoloquinolizine framework present in natural products](image)

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. 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. 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, Bishler-Napieralski or Fujii type reactions. 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) and we have applied these methodologies in syntheses of medicinally interesting alkaloids, such as (+)-stenusine and (+)-3-PPP (preclamol) (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. 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 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 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-alkylindoloquinolizine or 3-alkylindoloquinolizines, respectively (Scheme 2).

First, the enantiopure (3S)-3-ethylpiperidine (5c) was prepared following our previously reported methodology and then subjected to an N-alkylation with tryptophyl bromide giving the (S)-3-(2-(3-ethylpiperidin-1-yl)ethyl)-1H-indole (6a) in 52% yield. The indole 6a was treated under oxidative cyclization conditions (Fujii procedure for the synthesis of 4-alkyl-substituted indoloquinolizine) affording an indoloquinolizine derivative as a sole regio- and diastereoisomer 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).
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 from 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 moieties 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).

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 (\( \delta_H 3.16 \)) 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 (\( \delta_H 1.60 \)), whereas the value of \( J = 3.5 \) indicates an axial-equatorial coupling with equatorial H-1 (\( \delta_H 2.10 \)). 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

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 ($\delta_H 7.75$); axial H-1 signal splits into a doublet of doublet of doublets 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 ($\delta_C 30.9$), C-12a ($\delta_C 135.1$) and C-12b ($\delta_C 60.3$) together with COSY correlation with axial H-2 ($\delta_H 1.12$); 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 ($\delta_C 29.9$), C-3 ($\delta_C 37.8$), C-4 ($\delta_C 61.8$), C-12b, and with the methylene ($\delta_C 27.3$) of the ethyl substituent attached to C-3. One of the most important diagnostic signals is the axial H-4 ($\delta_H 2.02$), 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 ($\delta_H 3.20$) and axial H-4 ($\delta_H 2.12$) 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 ($\delta$), 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 $\mu$m). Mass spectra were recorded on JEOL The MS station JMS-700 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$_2$Cl$_2$-MeOH = 94:6).

**3(S)-3-Methylpiperidine (5c).** Colorless crystals, mp 166-165 °C. Yield 0.069 g (77%). $[\alpha]_D^{20}$ = -3.4 (c 1.0, CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 50.1, 43.8, 30.8, 28.3, 22.0, 18.8.

**3(S)-3-Ethylpiperidine (5d).** Colorless crystals, mp 160-161 °C. Yield 0.060 g (62%). $[\alpha]_D^{20}$ = -3.4 (c 1.0 EtOH). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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$_3$): $\delta$ 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)-1H-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$_2$O (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)-1H-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$_3$): $\delta$ 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), 7.04 (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$_3$): $\delta$ 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)-1H-indole (6c).** Colorless oil. Yield: 0.049 g (55%). $[\alpha]_D^{20}$ = -17.9
(c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): 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.

(3S)-1-(2-(1H-Indol-3-yl)ethyl)-3-(2-(3-methylpiperidino)ethyl)-1H-indole (8). Yellow oil. Yield: 0.105 g (54%). [α]D²⁰ +5.9 (c 1.0, MeOH). ¹H NMR (500 MHz, CDCl₃): 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), ¹³C NMR (125 MHz, CDCl₃): 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 C₂₆H₃₂N₃[M+H]⁺ 386.2518. Found: 386.2515.

tert-Butyl (3S)-3-(2-(3-ethylpiperidino)ethyl)-1H-indole-1-carboxylate (9a). Colorless oil. Yield: 0.133 g (85%). [α]D²⁰ −5.2 (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): 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 (dd, 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); ¹³C NMR (125 MHz, CDCl₃): 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 (3S)-3-(2-(3-methylpiperidino)ethyl)-1H-indole-1-carboxylate (9b). White crystals, mp 172-174 °C. Yield: 0.141 g (82%). [α]D²⁰ −32.6 (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): δ 8.11 (br s, 1H), 7.51 (m, 1H), 7.54 (m, 1H), 7.40 br s, 1H), 7.30 (dd, 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); ¹³C NMR (125 MHz, CDCl₃): 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 (3R)-3-(2-(3-benzylpiperidino)ethyl)-1H-indole-1-carboxylate (9c). Colorless oil. Yield: 0.102 g (86%). [α]D²⁰ -32.6 (c 1.0, CHCl₃). ¹H NMR (500 MHz, CDCl₃): 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,l 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); ¹³C NMR (125 MHz, CDCl₃): δ 149.7, 140.4, 135.4, 130.7, (129.0 x 2), (128.1 x 2),
Deprotection of compounds 9(a-c)
To a solution of 9 (22 mg 0.052 mmol) in anhydrous CH$_2$Cl$_2$ (0.16 mL) under nitrogen atmosphere were added Me$_2$S (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$_2$Cl$_2$ (4 x 5.0 mL) and the combined organic layer were dried over Na$_2$SO$_4$ and concentrated under reduced pressure to afford 6(a-c) in 95-96% yields after purification by flash chromatography (CH$_2$Cl$_2$-MeOH = 95:5).

(3S)-3-(2-(3-Methylpiperidino)ethyl)-1H-indole (6b). Colorless oil. Yield: 0.0148 g (96%).

General procedure for cyclization of compounds 6(a-c)
Compounds 7(a-c), were prepared adapting the literature procedure. 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$_2$O (3.7 mL) was added and the resulting mixture was refluxed for 3 h. After cooling, CH$_2$Cl$_2$ 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$_2$SO$_4$), filtering and evaporation gave the crude product 7, this was purified by flash chromatography column (petroleum ether-AcOEt = 90:10).

(3S,12bR)-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).

(3S,12bR)-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).

(3R,12bR)-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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