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Diastereoselective access to hexahydro- and octahydrofuro[*f*]indolizines analogues of phenanthro[*f*]indolizidines alkaloids

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Abstract—Enantiospecific syntheses of furo[*f*]indolizines with different degrees of unstauration (**4a**,**b**, **8a**, **9a**, and **10a**) as analogues of phenanthro[*f*]indolizidine alkaloids have been completed from (*S*)-glutamic acid in a few-step sequence. This was achieved from the known optically active alcohol-lactams **2a** and **2b** by utilizing chemical and catalytic reduction processes. During these transformations, we have shown that partial furan ring reduction can be achieved conveniently. The resulting products **5a** and **8a** readily constituted platforms to access stereoselectively the partially **6a** and **7a** or totally **9a** and **9b** reduced furo[*f*]indolizines. The key step of the stereocontrolled reduction seems to be the catalytic hydrogenation of the furan nucleus in the (4a*S*,9a*S*)-(+)-**5a** product. Assignments of the absolute stereochemistry are made and some mechanistic aspects of these transformations also discussed.

1. Introduction

The octahydroindolizidine framework **A** and its oxidized and reduced forms are found in a wide array of alkaloids (up to 20% of all alkaloids) and other pharmaceutically important compounds (Chart 1). These latter are exemplified by phenanthroindolizidines[1,2] typified by tylocrebrine **C**, tylophorine **D**,[3] and antofine **E**,[4] which are known for their profound cytotoxic activity through the inhibition of protein and nucleic acid syntheses.[1,5] Polyhydroxylated indolizidines (often referred to as 'amino-sugars' or 'aza-sugars')[6] and analogues of pumiliotoxins,[7] as naturally occurring members of this class of alkaloids, show glycosidase inhibitory activities[6] and constitute metabolites, which serve as chemical defense compounds (numerous compounds of this family are found in skin secretions of amphibians; frogs notably),[7] respectively. As a consequence, in recent years there has been a great deal of interest not only in the synthesis of these natural products themselves but also in that of chemically modified analogues (**B**: Chart 1) with promising pharmaceutical properties and lower toxicity.[8]

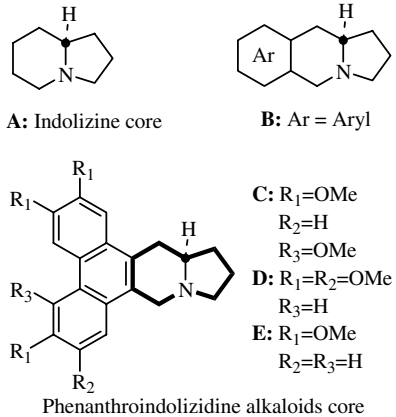

Chart 1. Representatives indolizidines and their aromatic homologues.

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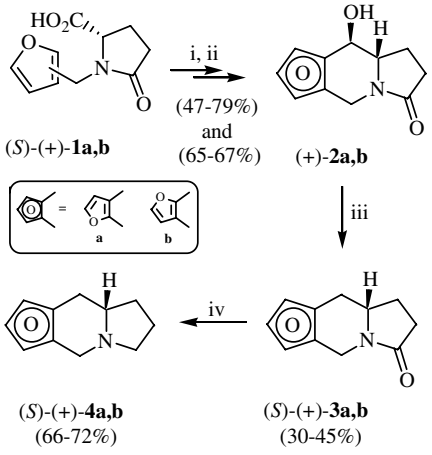
2. Results and discussion

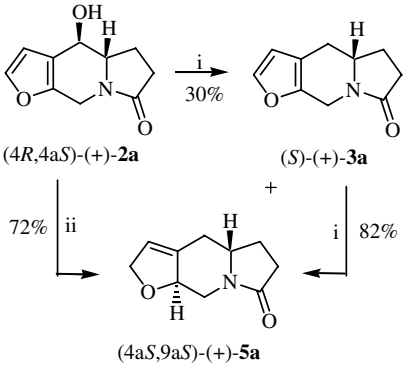
During our studies on the synthesis of diversely substituted polycyclic systems, we have previously reported indolizidines annulated to thiophene,[9,10] benzothiophene,[10,11] both benzene and thiophene,[12] and furan[13] rings.

Because of the lower stability of the furan ring in acidic medium allied to the fact that its diene character is more pronounced, such furo[*f*]indolizindiones skeletons **2a** and **2b** warrant additional investigations. In fact, these alcohol-lactams **2a** and **2b** could be valuable synthons for the synthesis of novel saturated tricyclic furo[*f*]indolizines, which could be considered analogous to dihydroxy indolizidines (polyhydroxylated indolizidines). We focused our attention on the reduction of the chiral alcohol and/or the lactam carbonyl to the corresponding alkanes **4a** and **4b**. These tertiary amine bases are able to activate electrophiles through hydrogen bonding, which should have an influence during the phase differentiation[14] and consequently make them promising candidates as catalysts in catalytic asymmetric synthesis. Herein, we report our findings in this area starting from enantiopure alcohols **2a** and **2b**.

The requisite alcohols **2a** and **2b** were obtained in a three-step sequence from (*S*)-glutamic acid as previously reported by us (Scheme 1).[13] In the next synthetic step we subjected the hydroxyhexahydroindolizines **2a** and **2b** to a 1 h reduction with 1.5 equiv of triethylsilane in trifluoroacetic acid at room temperature. The reduction of hydroxyindolizine **2a** afforded the desired (*S*)-hexahydrofuro[2,3-*f*]indolizinone **3a** albeit only in low yield (30%). In addition to (*S*)-(+)-hexahydrofuroindolizine-7-one **3a**, octahydrofuro[2,3-*f*]indolizine-7-one **5a** was also formed as a separable 1:1 mixture. Similarly, regioisomer (*S*)-hexahydrofuro[3,2-*f*]indolizinone **3b** was prepared in a comparable yield of 45%. In this particular case, the reduction did not affect the furan ring even after a longer reaction time (4 h) or using a large excess of triethylsilane as the hydride source. In the last step of



Scheme 1. Reagents and conditions to access furo[*f*]indolizinones **4a** and **b**: (i) (a) $(COCl)_2$, CH_2Cl_2; (b) $AlCl_3$, CH_2Cl_2; (ii) $NaBH_4$, MeOH; (iii) Et_3SiH, TFA; (iv) $LiAlH_4$, THF.



Scheme 2. Reagents and conditions: (i) Et_3SiH (1.5 equiv), TFA, rt, 1 h; (ii) Et_3SiH (5.0 equiv.), TFA, rt, 8 h.

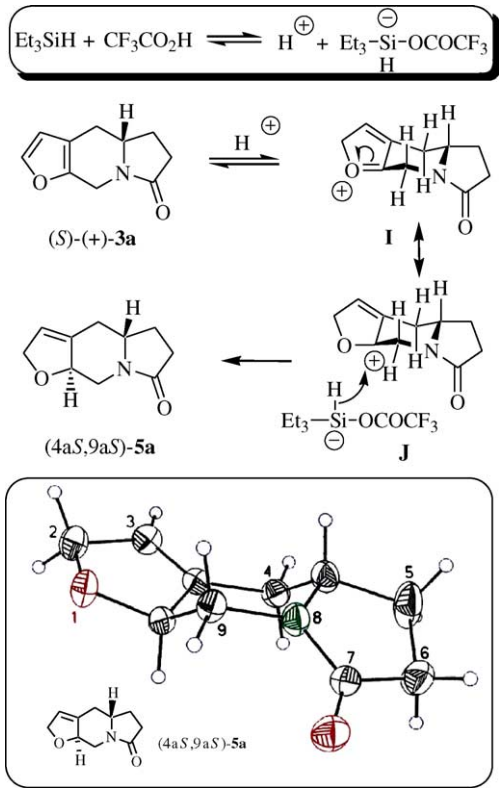
the reaction sequence, the lactam function of indolizines (*S*)-**3a** and **3b** was reduced classically with $LiAlH_4$ in THF at reflux to produce enantiopure (*S*)-hexahydrofuro[2,3-*f*]- and [3,2-*f*]indolizines (*S*)-**4a** and **4b** in 66% and 72% yields, respectively.

Intrigued by the above results and with the capability of the furo[2,3-*f*]indolizidinone **5a** to furnish saturated tricyclic systems bearing a strong tertiary amine base and two additional stereogenic centers, we directed our attention to examining the selectivity of the reduction process. Screening of reaction conditions (Scheme 2) revealed triethylsilane, in large excess (5.0 equiv) and prolonged reaction time (8 h), to be the most effective reducing protocol for total regioselective reduction in favor of the expected (4a*S*,9a*S*)-(+)-**5a**. Under these conditions the reaction proceeded cleanly with a good yield of 72%. Interestingly, this product was also obtained as the single isomer from the parent (4a*S*)-(+)-**3a** by partial reduction (82% yield). In this case, the reaction occurred under similar conditions. However, only a slight excess of Et_3SiH was necessary.

Semi-reduction of a furan nucleus into its 2,5-dihydro analogue is a well known useful transformation.[15] All contributions so far investigated in this field involve a single electron transfer (SET) process.[16] An impressive utilization of the so-called Birch reduction has been reported by Donohoe and co-workers.[17] Although an asymmetric variant could be implemented, thus allowing multiple accesses to structurally diverse natural products, this reaction suffers from some drawbacks such as low yields and use of both metallic lithium and liquid ammonia, naphthalene, or di-*tert*-butylbiphenyl (DBB). We believe that, under certain appropriate circumstances, this reaction may be a simpler alternative to the usual laborious Birch process.

The following mechanism has been proposed to account for both the structure and stereochemistry of **5a**. The furanic double bond is protonized at position 5 to give oxonium ion **I**, in resonance with tertiary carbcation **J**, which in turn undergoes a nucleophilic attack by a hydride anion. Due to the bulk of the anionic pentavalent silyl hydride species, attack is exclusively from the sterically less demanding *exo* side. This process, leading to

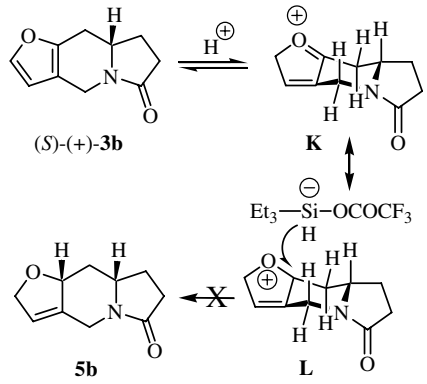
a *trans*-diaxial arrangement of hydrogens at positions 4a and 9a in a thermodynamically controlled fashion, gives rise to the more stable 1,4-*trans*-diaxial product **5a**. The structural determination of this product was based on an array of NMR considerations. Furthermore, our predictions were confirmed in the final stage by X-ray crystallography, which provided unequivocal proof of its absolute configuration (Scheme 3).[18,19] Finally, it is worth mentioning that reduction of such conjugated oxonium cations, either in the acyclic or the cyclic form, seems to have never been investigated.



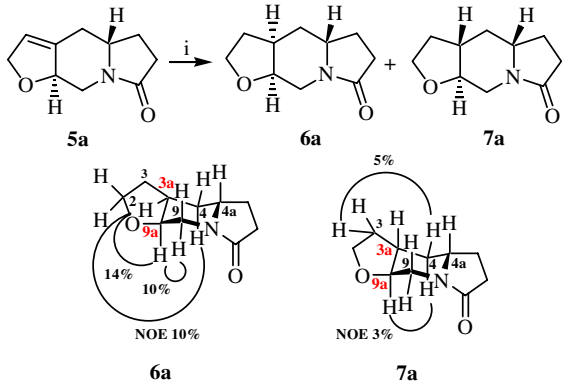
Scheme 3. Mechanism of the reduction of lactam **3a** with the tandem Et_3SiH/TFA and ORTEP plot of the obtained product **5a**.

From these results, we investigated the behavior of the regioisomer of **3a** toward this reduction protocol. Under identical conditions as above with starting material (*S*)-**3b**, the reaction surprisingly failed to give the corresponding dihydrofuro[3,2-*f*]indolizinone **5b**. This finding could be best explained by the bulk of the reducing agent (Scheme 4); the access of which is hindered by axial hydrogens at positions 4 and 8a. Another reason for the failed reduction of the furan ring may be the higher aromaticity of **3b** [(*S*)-**3a** has a more pronounced diene character] and hence better stabilization of the potentially formed carbocation **L**.

Taking into account that small modifications of the structure of indolizidines and its analogues, notably at the relative 6 and 7 positions of the indolizine ring, induces changes in their biological activity or their specificity,[20] it is interesting to consider the chemical and catalytic hydrogenation of the unsaturated furo[3,2-*f*]indolizidinone **5a** (Scheme 5).



Scheme 4. Mechanism of the nonreduction of lactam **3b**.



Scheme 5. Reduction of **5a** under various conditions: (i) H_2, cat., MeOH.

Catalytic hydrogenation of **5a** resulted in the creation of a third stereogenic center to afford the diastereomeric mixture in 93% yield. The product obtained was found to be a mixture of two diastereomers in a 1:1 ratio resulting from the *cis* addition of the dihydrogen molecule (Table 1, entry 1). As we can see when the reduction conditions were changed (entries 4–5), moderate to complete diastereoselectivities were achieved with best results being obtained (dr >95%) using 5% ruthenium on alumina and 50% Raney nickel as the catalysts. In both cases, the diastereoselectivity was in favor of lactam **6a** at the cost of its regioisomer **7a**.

The configuration of furolactams **6a** and **7a** was assigned by NOE difference measurements in $CDCl_3$ solution. In fact, for **6a** the experiments showed strong enhancement of the intensity of the H-3a signal ($\delta = 2.46$–2.58 ppm) by 14% when signal of H-9a signal ($\delta = 3.98$–4.08 ppm) was irradiated. Conversely, the signal of H-9a was enhanced by 12% when H-3a resonance was irradiated (Scheme 5). NOE experiments did not show any interaction between H-3a (or H-9a) and H-4a protons. Similarly for **7a**, no interactions were observed between H-3a, H-4a, and/or H-9a showing a *cis* relationship between the H-3a and H-9a protons in the major product **6a**. The observed high stereoselectivity during the reduction process and the configuration found at both C-3a and C-9a of **6a** (**7a** as minor

Table 1. Saturated furoindolizines **6a** and **7a** obtained by reduction of **5a**

Entry	Catalyst	Time (h)	Substrate/catalyst[a]	De (*cis*:**6a**, %)[b]	Yield (%)
1	10% Pd/C	20	1.0/0.2	50	93
2	5% Rh/Al_2O_3	12	1.0/0.2	74	89
3	5% Ru/C	15	1.0/0.2	83	91
4	5% Ru/Al_2O_3	2	1.0/0.2	>95	97
5	50% Ra-Ni	12	1.0/1.0	>95	96

[a] The ratio between substrate **5a** and the catalyst used.
[b] Determined by ^1H, ^{13}CNMR, and GC–MS spectroscopy.

reduction product) suggests that the origin for the stereoselection is likely to be the same as mentioned above for the synthesis of **5b**. This may result from a preferential hydrogen approach from the *exo* (convex) face to avoid 1,3-steric diaxial interactions. This is in agreement with both the model of **5a** rationalized by ChemDraw 3D (Chart 2) and the corresponding X-ray structure (see Scheme 4).

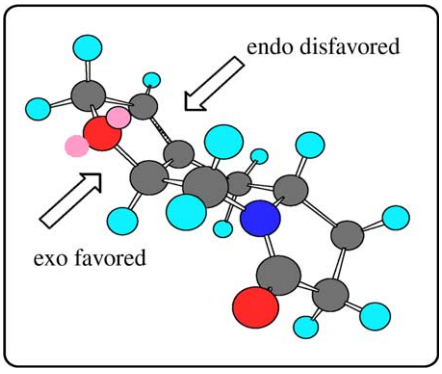
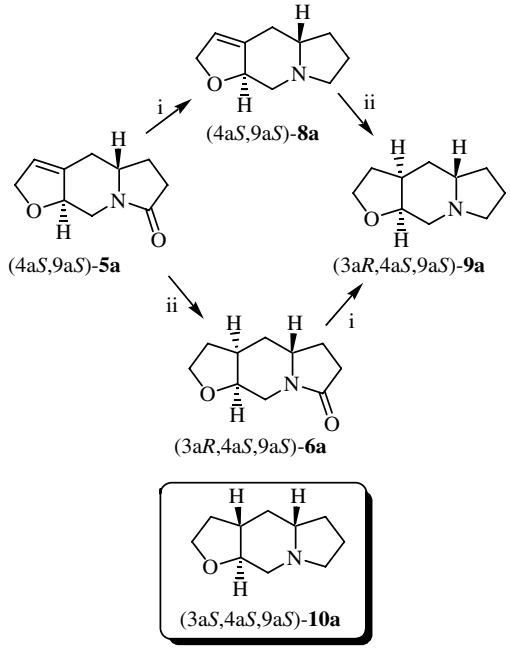


Chart 2. ChemDraw 3D plot of dihydrofuro[2,3-*f*]indolizinone **5a**.



Scheme 6. Reagents and conditions: (i) $LiAlH_4$, THF; (ii) Ra-Ni, MeOH.

In continuation of our experiments on the reduction of dihydrofuro[2,3-*f*]indolizinone **5a**, chemical reduction with LAH in THF at reflux furnished the optically active tricyclic amine (4a*S*,9a*S*)-**8a** as the sole reaction product in 82% yield. No trace of the totally reduced tricyclic amines **9a** and/or **10a** was detected (Scheme 6) thus showing that the dihydrofuranic double bond is inert in chemical reducing conditions. The compound (3a*R*,4a*S*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-decahydrofuro[2,3-*f*]indolizine **9a** was obtained in enantiopure form by catalytic hydrogenation using the well established protocol (i.e., 50% Ra-Ni, MeOH, 2 h, 96%). Interestingly, when reduction of **8a** was performed with 5% Pd–C in dry methanol, an inseparable mixture of two diastereomers **9a** and **10a** in a 7:1 ratio was obtained in 95% yield. Alternatively, compound **9a** can also be obtained as the sole product (in 75% yield) or in a mixture with **10a** (in 78% yield) in a two-step sequence, via **6a** or a mixture of **6a** and **7a** obtained by catalytic reduction of their congener octahydrofuro[2,3-*f*]indolizine **5a**. The reduction of the lactam function was performed in the final stage under standard conditions ($LiAlH_4$, THF, reflux).

From these results, it has been clearly established that in both sequences, the keystep of the process was the stereo-controlled hydrogenation of the C-3=C-3a double bond of octahydroindolizines **5a** and **8a** in the presence of Raney nickel. Furthermore, it is worth noting that **9a** could be synthesized with similar yield and stereoselectivity by inverting the order of reaction. This result minimized the role of nitrogen in the sense of stereo induction.

3. Conclusion

By means of new synthetic approaches involving regioselective and diasteroselective reduction processes, we have disclosed a concise and efficient synthesis of the enantiopure unsaturated dihydrofuro[2,3-*f*]indolizinone **5a**. This latter, which led by additional chemical and catalytic reductions to totally reduced chiral phenanthroindolizidines furo-analogues in good yields, could be considered as the virtually rare enantiopure 6(7)-hydroxy-7(6)-hydroxyethylindolizidines alkaloids homologues. Finally, owing to the efficiency and simplicity of these new transformations, the dihydrofuro[2,3-*f*]indolizidinone **5a** in particular shows a promising potential for further development, notably for the use independently of the dihydrofuran double bond and tetrahydrofuran ring as a diol surrogates. Investigations in this

sense are currently underway in our laboratory and the results to be published soon.

4. Experimental part

4.1. General

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Philips Analytical PV 9800 FT IR spectrometer. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) and Varian VXR-300 (300 MHz) instrument in deuteriochloroform unless otherwise indicated. Solvents and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. The assignment of 1H and 13C signals was supported by one- and two-dimensional ^1H–^1H COSY, DEPT, ^1H–^{13}C HMBC, and HSQC experiments. All the experiments were recorded using $CDCl_3$ as the solvent. Approximately 20 mg of the sample were dissolved with 0.5 mL of solvent. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualized using an ultraviolet lamp or iodine vapor. Mass spectra measurements were recorded on a AEI MS 902 S spectrophotometer. Optical rotations were determined with a Perkin–Elmer 241 MC instrument at 25 °C in the indicated solvent. Elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 at Mt. St. Aignan in France.

4.2. General procedure for the synthesis of the hexahydrofuro[*f*]indolizinones 3a and 3b

Triethylsilane (0.25 mL, 1.5 mmol) was added to a stirred solution of alcohols **2a** and **2b** (0.2 g, 1.0 mmol) in trifluoroacetic acid (2 mL) at 0 °C. The resulting yellow solution was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo, diluted with water (7 mL), made alkaline with 10% Na_2CO_3, and extracted with chloroform (3×10 mL). The combined extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column eluting with chloroform. Recrystallization of the solid from cyclohexane gave amides **3a** and **3b** as colorless crystals.

4.2.1. (4a*S*)-(+)-4,4a,5,6,7,9-Hexahydrofuro[2,3-*f*]indolizin-7-one 3a. This product was isolated in 30% yield; mp 71–73 °C; $[\alpha]_D^{25} = +1.4$ (*c* 0.1, EtOH); IR (ν cm^{-1}, KBr): 3092, 2910, 1677 (C=O), 1432; ^1H NMR (300 MHz, $CDCl_3$): δ 1.78–1.90 (m, 1H, H-5), 2.35–2.53 (m, 4H, H-5, H-4ax, $2 \times$ H-6), 2.71 (ddd, 1H, H-4eq, $J = 1.7$, 4.5 and 15.2 Hz), 3.79–3.87 (m, 1H, H-4a), 4.03 (d, 1H, H-9ax, $J = 16.5$ Hz), 4.85 (d, 1H, H-9eq, $J = 16.5$ Hz), 6.24 (d, 1H, H-3, $J = 1.8$ Hz), 7.32 (d, 1H, H-2, $J = 1.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8 (C-5), 29.5 (C-4), 30.4 (C-6), 38.9 (C-9), 54.9 (C-4a), 110.1 (C-3), 115.1 (C-3a), 142.1 (C-2), 145.5 (C-9a), 174.5 (C-7); MS (m/z (%)): 177 (M^+, 30), 95 (5), 94 (100), 66 (10), 65 (8), 39 (15). Anal. Calcd for $C_{10}H_{11}NO_2$ (177.08): C, 67.78; H, 6.26; N, 7.90. Found C, 67.61; H, 6.14; N, 7.79.

4.2.2. (8a*S*)-(+)-4,6,7,8,8a,9-Hexahydrofuro[3,2-*f*]indolizin-6-one 3b. This product was isolated in 45% yield; mp 99–101 °C; $[\alpha]_D^{25} = +116.7$ (*c* 1, EtOH); IR (ν cm^{-1}, KBr): 3110, 2914, 1680 (C=O), 1437, 1417; ^1H NMR (300 MHz, $CDCl_3$): δ 1.83–1.92 (m, 1H, H-8), 2.37–2.63 (m, 4H, H-8, H-9ax, $2 \times$ H-7), 2.93 (ddd, 1H, H-9eq, $J = 1.8$, 4.7, and 15.6 Hz), 3.87–3.96 (m, 2H, H-8a, H-4ax), 4.77 (dd, 1H, H-4eq, $J = 2.1$ and 16.1 Hz), 6.26 (d, 1H, H-3, $J = 1.8$ Hz), 7.30 (d, 1H, H-2, $J = 1.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.8 (C-8), 30.1 (C-7), 30.9 (C-9), 37.7 (C-4), 54.7 (C-8a), 108.3 (C-3), 113.8 (C-3a), 142.0 (C-2), 147.0 (C-9a), 174.1 (C-6); MS (m/z (%)): 177 (M^+, 26), 95 (6), 94 (100), 66 (7), 65 (5), 51 (4), 41 (4), 40 (4), 39 (11), 32 (10), 31 (11), 28 (43). Anal. Calcd for $C_{10}H_{11}NO_2$ (177.08): C, 67.78; H, 6.26; N, 7.90. Found C, 67.69; H, 6.08; N, 7.68.

4.3. General procedure for the synthesis of the hexahydrofuro[*f*]indolizines 4a and 4b

Lithium aluminum hydride (0.46 g, 12 mmol) was added to a solution of amides **3a** and **3b** (0.53 g, 3 mmol) in dry THF (20 mL) at room temperature and the mixture then heated under reflux for 1 h. The resulting mixture was cooled and water added cautiously until the lithium complex was destroyed. The mixture was then diluted with water (20 mL) and chloroform (40 mL). The chloroform layer was separated and the aqueous layer extracted with chloroform (2×40 mL). The combined extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue. Recrystallization of the solid from hexane gave pure amines **4a** and **4b**.

4.3.1. (4a*S*)-(−)-4,4a,5,6,7,9-Hexahydrofuro[2,3-*f*]indolizine 4a. This product was isolated in 66% yield; mp 40–41 °C; $[\alpha]_D^{25} = -20.5$ (*c* 0.1, EtOH); IR (ν cm^{-1}, KBr): 2970, 2933, 2793, 2774, 1504, 1376; ^1H NMR (300 MHz, $CDCl_3$): δ 1.54–1.65 (m, 1H, H-5), 1.80–2.11 (m, 3H, $2 \times$ H-6, H-5), 2.30–2.39 (m, 3H, H-7, H-4a, H-4ax), 2.66 (ddd, 1H, H-4eq, $J = 2.0$, 3.4, and 14.5 Hz), 3.25–3.31 (m, 2H, H-7, H-9ax), 4.04 (dd, 1H, H-9eq, $J = 4$ and 14.1 Hz), 6.21 (d, 1H, H-3, $J = 1.9$ Hz), 7.26 (d, 1H, H-2, $J = 1.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.3 (C-6), 28.6 (C-4), 29.8 (C-5), 50.1 (C-9), 54.1 (C-7), 61.2 (C-4a), 110.0 (C-3), 115.9 (C-3a), 141.1 (C-2), 148.5 (C-9a); MS (m/z (%)): 163 (M^+, 18), 95 (7), 94 (100), 66 (12), 65 (10), 51 (8), 42 (4), 41 (14), 39 (18). Anal. Calcd for $C_{10}H_{13}NO$ (163.10): C, 73.59; H, 8.03; N, 8.58. Found C, 73.48; H, 7.88; N, 8.39.

4.3.2. (8a*S*)-(+)-4,6,7,8,8a,9-Hexahydrofuro[3,2-*f*]indolizine 4b. This product was isolated in 72% yield; mp

51–54 °C; $[\alpha]_D^{25} = +110$ (*c* 0.1, EtOH); IR (ν cm^{-1}, KBr): 2962, 2925, 2773, 1501; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55–1.67 (m, 1H, H-8), 1.81–2.10 (m, 3H, 2 × H-7, H-8), 2.31 (q, 1H, H-6, $J = 9$ Hz), 2.48–2.53 (m, 2H, H-8a, H-9ax), 2.80–2.90 (m, 1H, H-9eq), 3.13 (dt, 1H, H-4ax, $J = 2.6$ and 13.4 Hz), 3.23 (ddd, 1H, H-6, $J = 2.3$ and 8.6 Hz), 3.88 (dd, 1H, H-4eq, $J = 1.2$ and 13.6 Hz), 6.18 (d, 1H, H-3, $J = 1.85$ Hz), 7.25 (d, 1H, H-2, $J = 1.85$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.4 (C-7), 30.3 (C-8), 30.6 (C-9), 48.9 (C-4), 53.6 (C-6), 61.0 (C-8a), 108.4 (C-3), 116.1 (C-3a), 141.2 (C-2), 149.4 (C-9a); MS (*m*/*z* (%)): 163 (M^+, 20), 162 (4), 95 (7), 94 (67), 66 (6), 39 (4), 32 (20), 28 (100). Anal. Calcd for $C_{10}H_{13}NO$ (163.10): C, 73.59; H, 8.03; N, 8.58. Found C, 73.50; H, 7.75; N, 8.40.

4.4. (4a*S*,9a*S*)-(−)-2,4,4a,5,6,7,9,9a-Octahydrofuro[2,3-*f*]indolizin-7-one 5a

Triethylsilane (3 g, 25.9 mmol) was added to a stirred solution of alcohol **2a** (1 g, 5.2 mmol) in trifluoroacetic acid (10 mL) at 0 °C. The resulting yellow solution was stirred under an argon atmosphere at rt for 8 h. The reaction mixture was concentrated in vacuo, diluted with water (10 mL), made alkaline with saturated solution of Na_2CO_3 (pH ≈ 9) and extracted with chloroform (3 × 25 mL). The combined extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was purified by flash chromatography on a silica gel column eluting with chloroform/acetone (10/1). Recrystallization of the solid from *n*-hexane/THF (20/1) gave amide **5a** as colorless crystals. Yield: 72%; mp 132–135 °C; $[\alpha]_D^{25} = -61.4$ (*c* 1, EtOH); IR (ν cm^{-1}, KBr): 2974, 2910, 2872, 2844, 1670 (C=O), 1442; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.66–1.78 (m, 1H, H-5), 2.00 (t, 1H, H-4ax, $J = 13.3$ Hz), 2.23–2.35 (m, 1H, H-5), 2.43–2.53 (m, 3H, 2 × H-6, H-9ax), 2.77 (dd, 1H, H-4eq, $J = 4$ and 13.3 Hz), 3.39–3.49 (m, 1H, H-4a), 4.47–4.53 (m, 2H, H-9eq, H-9a), 4.70 (m, 2H, 2 × H-2), 5.63 (t, 1H, H-3, $J = 1.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.0 (C-5), 30.3 (C-6), 34.2 (C-4), 46.4 (C-9), 57.3 (C-4a), 75.9 (C-2), 80.2 (C-9a), 118.9 (C-3), 137.3 (C-3a), 173.8 (C-7); MS (*m*/*z* (%)): 180 (17), 179 (M^+, 100), 151 (52), 150 (21), 136 (13), 98 (27), 97 (67), 96 (24), 95 (16), 94 (15), 84 (46), 69 (61), 68 (25), 67 (22), 55 (30), 54 (13), 53 (25), 41 (65). Anal. Calcd for $C_{10}H_{13}NO_2$ (179.09): C, 67.02; H, 7.31; N, 7.82. Found C, 66.89; H, 7.18; N, 7.69.

4.5. (4a*S*,3a*S*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-Decahydrofuro[2,3-*f*]indolizin-7-one 6a and (4a*S*,3a*R*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-decahydrofuro[2,3-*f*]indolizin-7-one 7a

Method A: A catalytic amount of 10% Pd/C was added to a solution of amide **5a** (0.46 g, 2.56 mmol) in anhydrous methanol (10 mL) and stirred at rt under a hydrogen atmosphere for 20 h. The solution was filtered through a Celite pad to remove the catalyst. After concentration in vacuo the residue was purified by flash chromatography on a silica gel column eluting with chloroform/acetone (20/1) to give a mixture of indolizinones **6a** and **7a** (93%) in a 3:1 ratio as pale yellow oil. ***Method B***: Activated Raney nickel (50% in water) (0.9 g) was added to a solution of amide **5a** (0.9 g, 5 mmol) in anhydrous methanol (10 mL) and stirred at room temperature under hydrogen atmosphere for 12 h. The solution was filtered through a Celite pad to remove the catalyst. After concentration in vacuo, the residue was purified by flash chromatography on a silica gel column eluting with chloroform/acetone (20/1) to give enantiomerically pure indolizinone (**6a**) (96%) as an colorless oil.

4.5.1. (4a*S*,3a*S*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-Decahydrofuro[2,3-*f*]indolizin-7-one 6a.

$[\alpha]_D^{25} = +32.6$ (*c* 1, $CHCl_3$); IR (ν cm^{-1}, KBr): 2929, 2880, 1686 (C=O), 1301; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.56–1.72 (m, 2H, H-5, H-4ax), 1.94–2.08 (m, 3H, H-4eq, 2 × H-3), 2.19–2.29 (m, 1H, H-5), 2.36–2.42 (m, 2H, 2 × H-6), 2.46–2.58 (m, 1H, H-3a), 2.83 (dd, 1H, H-9ax, $J = 8.1$ and 13.5 Hz), 3.65–3.73 (m, 1H, H-4a), 3.79 (dd, 1H, H-2, $J = 8.8$ and 16.4 Hz), 3.90 (dd, 1H, H-9eq, $J = 6.3$ and 13.2 Hz), 3.98–4.08 (m, 2H, H-9a, H-2); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.4 (C-5), 28.1 (C-3), 30.0 (C-6), 32.6 (C-4), 35.6 (C-3a), 39.7 (C-9), 50.6 (C-4a), 66.5 (C-2), 72.7 (C-9a), 173.2 (C-7);); MS (*m*/*z* (%)): 181 (M^+, 11), 180 (76), 166 (19), 153 (18), 150 (16), 138 (54), 137 (19), 136 (74), 98 (100), 84 (30), 70 (30), 55 (35), 41 (23). Anal. Calcd for $C_{10}H_{15}NO_2$ (181.11) C, 66.27; H, 8.34; N, 7.73. Found C, 66.09; H, 8.15; N, 7.40.

4.5.2. (4a*S*,3a*R*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-Decahydrofuro[2,3-*f*]indolizin-7-one 7a.

From the NMR spectra of the mixture; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.20 (q, 1H, H-4ax, $J = 12.9$ Hz), 1.54–1.80 (m, 3H, H-4eq, H-5, H-6), 2.10–2.30 (m, 3H, H-6, H-5, H-3a), 2.34–2.43 (m, 2H, 2 × H-3), 2.95 (dd, 1H, H-9ax, $J = 3.3$ and 14.7 Hz), 3.42–3.52 (m, 1H, H-4a), 3.77–3.81 (m, 1H, H-2), 3.85 (td, 1H, H-9a, $J = 3$ and 10 Hz), 3.93 (q, 1H, H-2, $J = 8.5$ Hz), 4.33 (d, 1H, H-9eq, $J = 14.8$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.5 (C-5), 29.4 (C-3), 31.8 (C-6), 33.9 (C-4), 35.8 (C-3a), 40.6 (C-9), 55.0 (C-4a), 65.6 (C-2), 74.2 (C-9a), 174.2 (C-7).

4.6. (4a*S*,9a*S*)-(−)-2,4,4a,5,6,7,9,9a-Octahydrofuro[2,3-*f*]indolizine 8a

Lithium aluminum hydride (0.74 g, 19.6 mmol) was added to a solution of amide **5a** (0.88 g, 4.9 mmol) in dry THF (60 mL) at room temperature and the mixture heated under reflux for 1 h. The resulting mixture was cooled and water added cautiously until the lithium complex was destroyed. The mixture was diluted with water (20 mL) and extracted with chloroform (3 × 15 mL). The combined extracts were washed with water, dried over $MgSO_4$ and concentrated in vacuo. The obtained residue was purified by flash chromatography on a silica gel column eluting with chloroform/acetone (10/1) to give pure **8a** as yellow oil. Yield: 82%; $[\alpha]_D^{25} = -1$ (*c* 1, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$): δ

1.40–1.53 (m, 1H, H-5), 1.71–1.82 (m, 1H, H-6), 1.85–1.94 (m, 5H, H-4ax, H-4a, H-5, H-6, H-9ax), 2.19 (q, 1H, H-7, $J = 8.9$ Hz), 2.68 (d, 1H, H-4eq, $J = 10.7$ Hz), 3.03 (td, 1H, H-7, $J = 2$ and 8.7 Hz), 3.42 (dd, 1H, H-9eq, $J = 5.8$ and 9.5 Hz), 4.63–4.67 (m, 2H, 2 × H-2), 4.68–4.76 (m, 1H, H-9a), 5.48 (s, 1H, H-3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.9 (C-6), 29.7 (C-5), 32.2 (C-4), 53.0 (C-7), 58.6 (C-9), 64.2 (C-4a), 75.6 (C-2), 82.2 (C-9a), 117.0 (C-3), 139.9 (C-3a). Anal. Calcd for $C_{10}H_{15}NO$ (165.12) C, 72.69; H, 9.15; N, 8.48. Found: C, 72.34; H, 9.00; N, 8.22.

4.7. (4a*S*,3a*S*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-Decahydrofuro[2,3-*f*]indolizine 9a and (4a*S*,3a*R*,9a*S*)-2,3,3a,4,4a,-5,6,7,9,9a-decahydrofuro[2,3-*f*]indolizine 10a

Method A: Decahydrofuro[2,3-*f*]indolizines **9a** and **10a** was prepared by the same procedure as octahydrofuro[2,3-*f*]indolizine **8a** from the mixture (3:1) of indolizinones **6a** and **7a**, in 78% yield as a pale yellow oil. Pure **9a** was prepared from **6a**, which was prepared by ***Method B***, in 75% yield as pale yellow oil. ***Method C***: A catalytic amount of 10% Pd/C was added to a solution of amine **8a** (0.5 g, 3 mmol) in anhydrous methanol (10 mL) and stirred at room temperature under hydrogen atmosphere for 10 h. The solution was filtered through Celite, concentrated in vacuo and the residue purified by flash chromatography on a silica gel column eluting with chloroform/acetone (20/1) to give an inseparable mixture of indolizinones **9a** and **10a** (95%) in a 7:1 ratio as pale yellow oil.

4.7.1. (4a*S*,3a*S*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-Decahydrofuro[2,3-*f*]indolizine 9a. $[\alpha]_D^{25} = +42.4$ (c 1, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33–1.43 (m, 1H, H-5), 1.60–2.06 (m, 10H, 2 × H-3, 2 × H-4, H-4a, H-5, 2 × H-6, H-7, H-9ax), 2.40–2.51 (m, 1H, H-3a, $J = 6$ Hz), 2.95–3.08 (m, 2H, H-7, H-9eq), 3.80 (q, 1H, H-2, $J = 8.4$ Hz), 3.99 (td, 1H, H-2, $J = 2.7$ and 8.5 Hz), 4.18–4.26 (m, 1H, H-9a); ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6 (C-6), 28.0 (C-3), 30.3 (C-5), 30.8 (C-4), 36.9 (C-3a), 54.2 (C-9, C-7), 58.4 (C-4a), 67.0 (C-2), 75.2 (C-9a); MS (m/z (%)): 168 (M^+, 31), 166 (19), 140 (19), 124 (21), 122 (19), 112 (23), 98 (10), 97 (19), 96 (26), 84 (38), 70 (64), 55 (33), 42 (19), 28 (100). Anal. Calcd for $C_{10}H_{17}NO$ (167.13) C, 71.81; H, 10.25; N, 8.37. Found: C, 71.50; H, 10.08; N, 8.21.

4.7.2. (4a*S*,3a*R*,9a*S*)-2,3,3a,4,4a,5,6,7,9,9a-Decahydrofuro[2,3-*f*]indolizine 10a. From the NMR spectra of the mixture; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22–1.35 (m, 1H, H-4ax), 1.48–1.58 (m, 1H, H-3), 1.60–1.82 (m, 6H, H-3, H-4eq, H-4a, H-5), 1.93–2.02 (m, 3H, H-3a, H-5, H-7), 2.18 (dd, 1H, H-9ax, $J = 2.5$ and 12.5 Hz), 2.95 (td, 1H, H-7, $J = 2.4$ and 8.5 Hz), 3.27 (dd, 1H, H-9eq, $J = 1.8$ and 12.5 Hz), 3.68–3.75 (m, 2H, H-2, H-9a), 3.89 (q, 1H, H-2, $J = 8.0$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$)1: δ 21.1 (C-6), 30.3 (C-3), 32.2 (C-5), 33.0 (C-4), 36.6 (C-3a), 53.9 (C-9), 54.2 (C-7), 62.5 (C-4a), 66.2 (C-2), 76.8 (C-9a).

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