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Synthesis and reductive desulfurization of chiral non-racemic benzothienoindolizines. An efficient approach to a novel bioactive tylophorine alkaloid analogue and 6-phenylindolizidine

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ABSTRACT

Enantiopure di- and tetrahydro[1]benzothieno[3,2-*f*]indolizines **3**,**4**,**9** and the benzothieno analogue **5** of the bioactive alkaloid tylophorine **10** were synthesized easily from the readily available benzo[*b*]thiophene-3-carboxaldehyde **1** and (*S*)-glutamic acid **2** in good overall yields. Applying a diastereoselective reductive desulfurization of benzo[*b*]thiophene **3**,**4** and **5** were readily converted into the enantiopure alcohols **11a–d,** alcohols **11c,d** and the target 6(*R*)-phenyl-8a(*R*)-indolizidine **6** (7 steps, 14%). During these reduction studies, the results obtained including the stereoinduction of the reaction are also discussed.

1. Introduction

Synthetic work and structure–activity studies on natural polyhydroxylated indolizidines have now revealed that these compounds are of increased pharmacological significance. This is due to their participation in biologically important pathways as excellent inhibitors of glycosidases, for example, against the AIDS virus HIV and some carcinogenic cells as well as against other important pathologies.[1,2]

Interestingly, alkylindolizidinols of types **Ia** and **Ib** have shown in numerous cases an increase of glycosidase activity as demonstrated by Pearson et al. and others.[3] This fact is similar to that observed with the popular azasugar scaffolds and is generally due to the enhancement of the interaction of the alkyl groups with the enzymes activated sites by providing favourable conformational flexibility to the molecules.[4]

In this line, research in our laboratories has focused on the synthesis of enantiopure benzoanalogues of lentiginosine and swainsonine[5] and enantiopure tetrahydrofuran-fused indolizidinols, which could be considered as protected new indolizidinediols.[6] More recently, we have described a concise and very efficient route to enantiopure 7-ethylindolizidinols of type **II**[7] using an uncommon strategy based on reductive desulfurization by Raney-nickel of thiophene ring of chiral thienoindolizidinediones and the corresponding thienoindolizidinols. Extension of this strategy to the benzo[*b*]thiophene series allowed to successfully obtain enantiopure 7-phenylindolizidinols of type **III**[8] in better diastereoselectivities.

Another important, scarce and emerging class of alkaloids that have been identified as challenging targets are the nitrogen heterocyclic systems **V** and **VI** containing an aryl group at the C_6-position of the indolizidine ring (Fig. 1). The alkaloid ipalbidine **V**[9] in particular, which was found to possess virtually no optical activity[1e] was obtained using various strategies.[10] The most frequently applied method was based on the elaboration of α-diazoimide derivatives via a [3+2]-cycloaddition of a phenylsulfonyl-substituted isomünchnone intermediate with an alkene, followed by a subsequent elimination of phenylsulfinic acid.[10c–f] Elsewhere, only two enantioselective total synthesis of (+)-ipalbidine were also achieved and the most

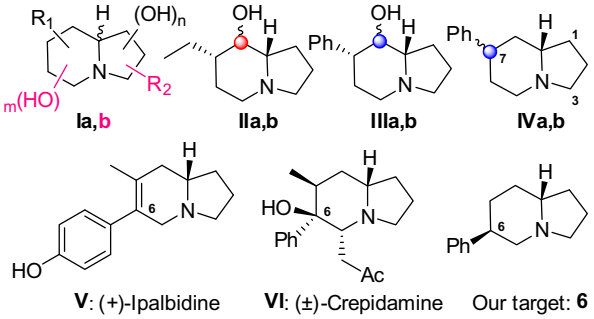

Figure 1. Representative natural and unnatural products **I**–**VI** containing an indolizidine unit and one **6** of our targets.

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important one of them starts with (*S*)-pyroglutamic acid by employing an intramolecular McMurry coupling reaction with a low-valent titanium, as a key and pivotal step.[11]

Herein in a full account and in continuation of our interest in the synthesis of polysubstituted indolizidines, we extend our work to reductive desulfurization by Raney-nickel (Fig. 2) of an aromatic ring containing-sulfur atom. In this sense, we duly report an easy and efficient approach to novel benzo[*b*]thieno-analogue of the bioactive tylophorine alkaloid **5** and the corresponding 6-phenylindolizidine **6** in highly diastereoselective manner.

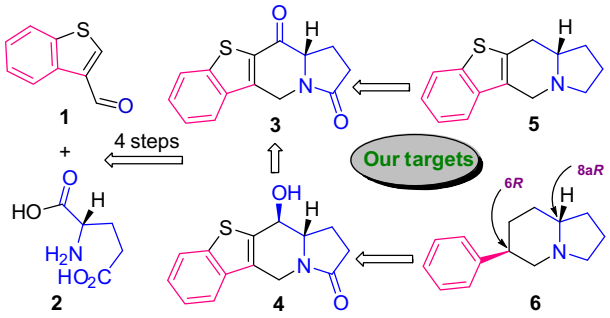


Figure 2. Scheme leading to benzo[*b*]thienoindolizidine **5** and 6-phenylindolizidine **6** from carboxaldehyde **1** and (*S*)-glutamic acid **2**.

2. Results and discussion

2.1. Synthetic strategy

The selection of enantiopure products **5** and **6** was influenced by our recent proposal starting from heteroaromatic carboxaldehydes and enantiopure (*S*)-glutamic acid to provide, in few steps, a wide range of enantiopure aromatic and heteroaromatic analogues[5,12] of tylophorine alkaloids.[13] During these investigations, additional manipulations based on a regioselective reduction and/or desulfurization of an aromatic sulfur-containing ring have led to a new class of alkyl indolizidinols[6,7] including the two regioisomers **IVa,b** (Fig. 1) of the targeted product **5**.[8]

Retrosynthetically (Fig. 2), the targeted compound **5** can be envisioned as coming from keto-amide **3** via a double ketone and lactam reduction. The asymmetry, as well as the nitrogen atom source, could be effectively derived from the same chiral pool approach using (*S*)-glutamic acid **2** as the starting substrate. Thus, in turn the tricyclic keto-lactam **3** may be reached by a concatenation of amino-carboxaldehyde condensation, imine reduction, amino-acid cyclodehydration and Friedel–Crafts reaction.

2.2. Synthesis of the benzothieno analogue 5 of the bioactive tylophorine alkaloid 10

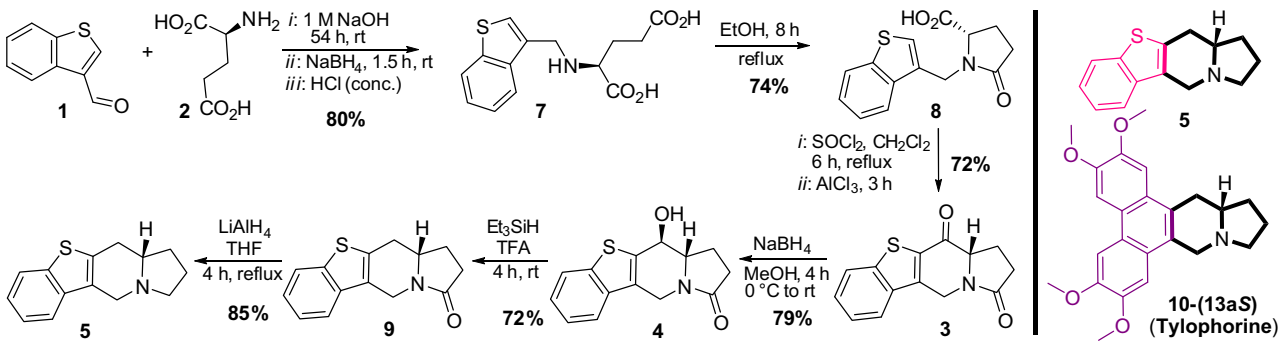
As highlighted in Scheme 1, our synthesis began with the amino-carboxaldehyde condensation, between the well known benzo[*b*]thiophene-3-carboxaldehyde **1**[14] and the commercially available and inexpensive L-glutamic acid **2**, to provide the expected Schiff base. A subsequent in situ reduction of the imine intermediate formed with $NaBH_4$ taking 1.5 h at room temperature followed by treatment with concentrated hydrochloric acid at the same temperature gave the (*S*)-*N*-benzothienylmethyl glutamic acid **7** in an overall yield of 80% in two steps. Ethanolic treatment of the amino-dicarboxylic acid at reflux for 8 h formed the *N*-benzothien-3-ylmethyl-pyroglutamic acid **8** in 74% yield. The latter pure acid **8** was subjected to thionyl chloride in dichloromethane at reflux for 6 h followed by treatment with aluminium trichloride of high analytical quality (99.99%) according to the Friedel–Crafts reaction for 3 h to supply the expected tricyclic keto-lactam **3** in 72% yield. Reduction of the ketone function of the lactam **3** (e.g., $NaBH_4$, MeOH, 0 °C to rt, 16 h) gave (11*S*)-alcohol **4** as a single *trans*-diastereomer (79%). The stereochemical assignments of this structure are based on the analysis of the NMR spectra including HMBC, HSQC and COSY experiments. In addition, these analyses show that there is no evidence for the formation of the epimeric *cis*-alcohol-(11*R*) for (11*S*)-alcohol **4**. It is believed that this result reflects a preference for *axial* hydride attack from the more hindered *endo* face of the tricyclic system **3**.[15]

In a final effort to reach our first target **5**, the reduction of (11*S*)-alcohol **4** was conducted with the triethylsilane/trifluoroacetic acid couple at room temperature for 4 h. Under these conditions, the lactam **9** was isolated in 94% yield and 72% isolated yield. The reduction of the (11a*S*)-lactam **9** with LAH in refluxing THF was unsuccessful and the starting material was recovered. Ultimately, reduction with $BH_3{\cdot}Me_2S$ in THF provided the title compound (11a*S*)-hexahydro[*b*]benzothieno[3,2-*f*]indolizine **5** in 85% yield.

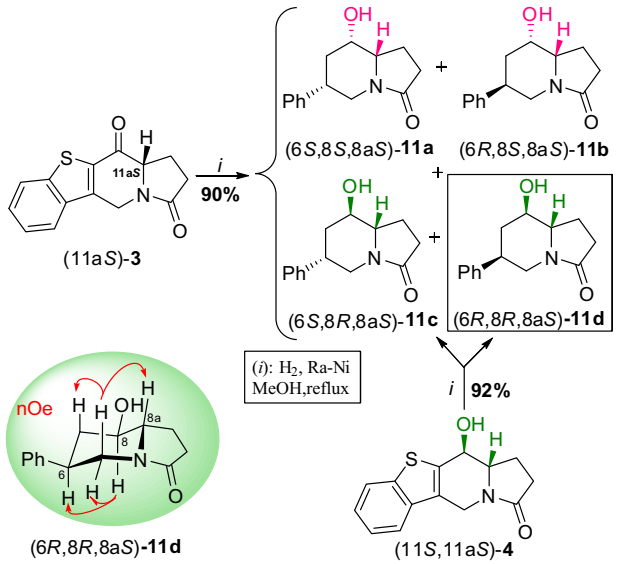
2.3. Diastereoselective synthesis of 6-phenylindolizidinols 11a–d

Based on the reductive desulfurization technique of heterocyclic sulfur-containing rings, which is well known,[7,8] we anticipated that by the same procedure benzo[*b*]thieno[3,2-*f*]indolizines **3–5** and **9** (Scheme 1) could serve as a phenyl reservoir more suitable for the preparation of novel 6-phenylindolizidine and 6-phenylindolizidinol derivatives.

Thus, as highlighted in Scheme 2, we began our study with our well-established protocol using the Raney-nickel hydrogenolysis of both carbonyl functions and the benzothiophene ring to the enantiopure keto-lactam **3**. As might be expected, compound **3** with activated Ra–Ni in anhydrous methanol under stirring and under



Scheme 1. Schematic of the synthesis of the tricyclic keto-lactam **3** and phenanthroindolizidinol **10**.



Scheme 2. All four possible diastereomers (6*S*,8*S*,8a*S*)-**11a**, (6*R*,8*S*,8a*S*)-**11b**, (6*S*,8*R*,8a*S*)-**11c** and (6*R*,8*R*,8a*S*)-**11d** were obtained in a 17:40:19:24 ratio determined by HPLC and NMR essays. Selected NOEs for the determination of relative configuration in the 6-phenylindolizidinol **11d** established by 1D-NOE ^{1}H NMR experiments.

203 kPa of hydrogen gas at reflux for 60 h provided the four possible diastereomers **11a–d**. These inseparable products were obtained in very good yield (90%) in a 17:40:19:24 ratio in which the couple of both *cis*-alcohols (6*S*,8*S*,8a*S*)-**11a**, (6*R*,8*S*,8a*S*)-**11b** represent 57% of the mixture.

For further comparison, the enantiopure *trans*-(11*S*)-alcohol **4** was obtained easily from (11a*S*)-keto-lactam **3** (Scheme 1) and then submitted to the reductive cleavage of the benzothiophene ring according to the same protocol used for (11a*S*)-keto-lactam **3** (Scheme 2). Under these conditions (i.e., H_2, Ra–Ni, MeOH, reflux, 72 h), a solid mixture of inseparable stereoisomers (6*S*,8*R*,8a*S*)-**11c** and (6*R*,8*R*,8a*S*)-**11d** in a 65:35 ratio favouring the alcohol (6*S*,8*R*,8a*S*)-**11c** was obtained in excellent (92%) yield. Interestingly, by triturating the reaction residue in dry acetone, the resulting precipitate was filtered off and then recrystallized from dry THF to provide the enantiopure alcohol (6*R*,8*R*,8a*S*)-**11d** as a minor stereoisomer (see the resulting attributions from NOE measurements of this isomer in Scheme 2).

These results were compared to those obtained in a thiophene series from both enantiopure (8a*S*)-hexahydrothieno[3,2-*f*]indolizine-6,9-dione and its ancillary alcohol, namely, (8a*S*,9*R*)-9-hydroxyhexahydrothieno[3,2-*f*]indolizine-6-one,[7] which were readily accessible from thiophene-3-carboxaldehyde. Thus, it became clear that there are no similar stereoisomeric distributions when keto-lactams in benzothiophene **3** and the thiophene nucleus were reduced. In the latter case, only three stereoisomers were obtained (90% yield) and the distribution was of 24:69:0:7 ratio for related ethyl-stereoisomers largely in favour of *cis*-alcohols (93% instead of 57% in the case given herein as shown in Scheme 2). Despite the general preference for *cis*-hydrogenation with respect to the angular pyrrolidone carbon stereogenicity, these first results made the rationalization of the reductive-cleavage cascade of the benzothiophene ring of (11a*S*)-**3** more difficult. In contrast, the reductive-cleavage of the enantiopure *trans*-(11*S*)-alcohol **4** and its thiophene analogue[7] seems to be operative in the same sense as well during the hydride deliverance (exo-approach) as the level of the stereo-induction (*trans*-alcohols **11c:11d** were obtained in a 65:35 ratio in the case of (11*S*)-alcohol **4** while *trans*-alcohols in the case of the thiophene analogue were obtained in a 77:23 ratio[7]). Finally, in light of these reductive-cleavage investigations from both ketone **3** and alcohol **4** the benzothiophene ring was probably opened first under the conditions used as suggested in the thiophene series.[7] This fact was corroborated by the reductive-desulfurization resulting from the (11*S*)-alcohol **4** showing that if the ketone function of (11a*S*)-**3** was reduced first, the stereoisomer distribution obtained for alcohols (6*S*,8*R*,8a*S*)-**11c** and (6*R*,8*R*,8a*S*)-**11d** (19:24) in the mixture of the four stereoisomers **11a–d** (17:40:19:24) would be approximately the same as the one obtained from the reduction of (11*S*)-alcohol **4** (Scheme 2; 65:35 in percent or 28:15 instead of 19:24).

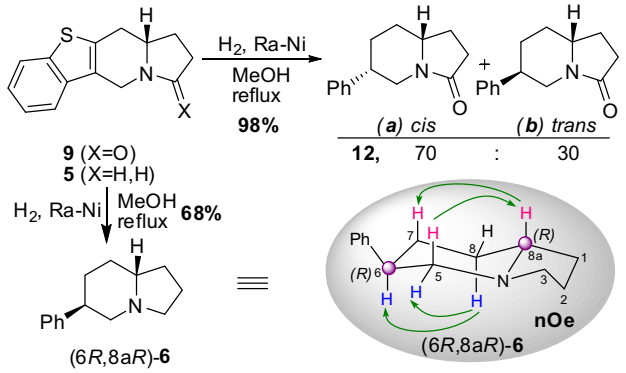
The structure of alcohol derivatives **11a–d** was confirmed by means of ^{1}H and ^{13}C NMR including HMBC, HSQC and COSY experiments. Their configuration aspects were studied by using ^{1}H NMR data, including NOE measurements. In the case of alcohols **11a–d**, the appearance of a doublet of doublet for H_8 for **11c** at $\delta = 3.14$ ppm ($J = 9.2$ and 11.5 Hz) and for **11d** at $\delta = 3.40$ ppm ($J = 9.4$ and 9.4 Hz), respectively. This clearly indicated the *trans*-diaxial relationship between H_{7ax}, H_8 and H_{8a}. Similarly, in the case of diastereomers (6*R*)-**11**, the appearance of a triplet of triplets for H_6 for **11b** at $\delta = 3.11$ ($J = 4.4$ and 12.2 Hz) and **11d** at $\delta = 2.75$ ($J = 3.3$ and 12.0 Hz), respectively, was observed. The large coupling constants indicated the *trans*-diaxial orientation between H_5, H_6 and H_7 with a phenyl group in the *equatorial* position at C_6-carbon (See ^{1}H and ^{13}C NMR details in Table 1).

In order to measure the impact of the absence of a substituent at the C_8-position as well as the presence or the absence of the carbonyl group at the α-position of the nitrogen atom on the reductive desulfurization process and the stereochemical course, a set of additional experiments was carried out.

Table 1
Chemicals shifts (δ in ppm) and coupling constants (J in Hz) in the ^{1}H and ^{13}C NMR spectra of the four diastereomers **11a–d** in CD_3OD solution

Proton/carbon	(6*S*,8*S*,8a*S*)-**11a**	(6*R*,8*S*,8a*S*)-**11b**	(6*S*,8*R*,8a*S*)-**11c**	(6*R*,8*R*,8a*S*)-**11d**
H-5_{eq}/C-5	3.97 dd/45.1	4.10 ddd/47.4	4.43 td/42.8	4.05ddd/46.9
J (Hz)	7.0, 13.1	1.4, 4.7, 12.7	1.7, 13.9	1.6, 3.5, 12.0
H-5_{ax}/C-5	3.36 dd/45.1	2.82 t/47.4	3.09 ddd/42.8	2.71 tt/46.9
J (Hz)	4.6, 12.7	12.4	1.5, 4.5, 13.9	1.5, 12.0
H-6/C-6	3.15 q/37.3	3.11 tt/36.4	3.31–3.29 m/38.4	2.75 tt/42.3
J (Hz)	6.7	4.4, 12.2	–	3.3, 12.0
H-7_{eq}/C-7	2.38–2.31 m/39.1	2.20–2.05 m/39.3	2.40–2.31 m/40.5	2.19 dddd/41.4
J (Hz)	–	–	–	1.9,2.9, 3.8, 12.5
H-7_{ax}/C-7	2.20–2.05 m/39.1	2.01 t/39.3	1.95 ddd/40.5	1.77 ddt/41.4
J (Hz)	–	13.1	4.8, 11.6, 13.2	1.9, 10.5, 12.3
H-8/C-8	3.95–3.88 m/68.1	3.95–3.88 m/67.7	3.14 ddd/70.3	3.40 dt/73.5
J (Hz)	–	–	3.9, 9.2, 11.5	3.9, 9.4
H-8a/C-8a	3.95–3.88 m /60.9	3.77 dt/62.3	3.34 tt /64.6	3.36 ddd/64.1
J (Hz)	–	1.8, 7.2	2.5, 7.7	5.4, 7.4, 9.2

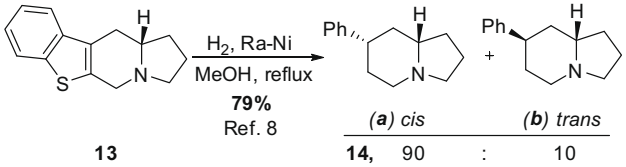
Firstly, the enantiopure indolizidinone **9** was subjected to the same protocol outlined above for the reduction of **3** and **4** (Scheme 2). Under these conditions (i.e., H_2, Ra–Ni, MeOH, reflux, 72 h), lactam **9** provided a mixture of two inseparable diastereomers (6*S*,8*aR*)-**12a** and (6*R*,8*aR*)-**12b** in an excellent yield (98%, Scheme 3) and in a 70:30 ratio. This result is comparable to that observed during the reduction of alcohol (11*S*,11*aS*)-**4** in the benzothiophene series which gives alcohols (6*S*,8*R*,8a*S*)-**11c** and (6*R*,8*R*,8a*S*)-**11d** in similar ratio (65:35). These observations indicated that in all probability, the presence or absence of a substituent at the C_8-position had no effect on the reduction-cleavage process.



Scheme 3. Target 6*R*,8a*R*-phenyloctahydroindolizidine **6** by reduction of the tylophorine analogue **5**.

The structure of these inseparable compounds was, in this case, established from the mixture of diastereomeric 6-phenylindolizines **12a** and **12b** by means of ^1H and ^{13}C NMR including HMBS, HSQC and COSY experiments.

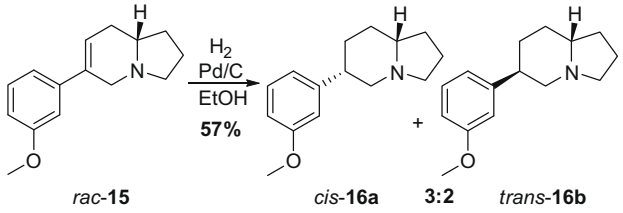
Secondly, because all attempts at separation of lactams **12a** and **12b** as excellent precursors for the targeted *cis*- and *trans*-6-phenylindolizidine derivatives failed, the reduction of the benzothieno analogue **5** of the tylophorine alkaloid **10** was considered. In this line, treatment of **5** under the well-established reductive-desulfurization protocol (Scheme 4) led to a product which seems to be the (6*R*,8*aR*)-**6** as the sole reaction stereoisomer in 68% yield. The structure of this isomer was identified without ambiguity by NMR studies including NOE measurements (Scheme 3). The formation of this unique diastereomer **6** can be explained in terms of the high basicity of the nitrogen atom of the starting indolizine **5**, which interacts favourably with the reducing support, thus rendering the hydrogen deliverance exclusively from the exo-face.



Scheme 4. Target (7*S* or 7*R*,8a*R*)-phenyloctahydroindolizine **14a**,**b** by reduction of the tylophorine analogue **13**.

In addition, when the regioisomer of indolizine **5**, namely, (11a*S*)-1,2,3,5,11,11*a*-hexahydrobenzothieno[2,3-*f*]indolizine **13**, was reduced under the same conditions,[8] two stereoisomers **14a,b** were obtained (79%, Scheme 4) in a 90:10 ratio in favour of the *cis*-phenylindolizidine isomer **14a** with exactly the opposite stereoinduction. This result suggests also that the relative position of the sulfur atom towards the nitrogen atom plays a pivotal role in the reductive desulfurization process. Thus, we believe that when the sulfur and the nitrogen atoms of the benzothienoindolizine structure are on the same side, both heteroatoms interact favourably with the reductant support but by the sulfur atom poisoned Ra–Ni rendered the reductive desulfurization non exclusive.

Interestingly, as reported in Scheme 5 a catalytic hydrogenation (i.e., H_2, Pd/C, EtOH) of hexahydro-6-(3-methoxyphenyl)indolizine *rac*-**15** provided a mixture of two 6-(3-methoxyphenyl)indolizidine derivatives *cis*-**16a** (axial isomer) and *trans*-**16b** (equatorial isomer) in favour of the *cis*-**16a** one (dr = 3:2 only).[16] This result indicates that in our case a highly diastereoselective reductive desulfurization of the tylophorine analogue **5** can proceed simultaneously, affording a new very effective approach to *trans*-6-phenylindolizidine derivatives with synthetic and biological interest notably for dopamine auto-receptor activity 3-PPP.



Scheme 5. Result of the catalytic hydrogenation of (S)-6-(3-methoxyphenyl)-1,2,3,5,8,8a-hexahydroindolizine *rac*-**15**.

3. Conclusion

Herein, we have improved our strategy which uses a reductive desulfurization of the chiral heterocyclic sulfur systems with a Raney-nickel as a reducing agent to provide various alkylindolizidine, arylindolizidines and corresponding indolizidinols related to alkaloids.

During the investigations shown, the diastereoselective desulfurization of benzo[3,2-*f*]thienoindolizinone and the corresponding benzo[3,2-*f*]thienoindolizinol was studied and its utility as a key step in the synthesis of indolizidines fused to benzothiophenes and phenylindolizidines related to alkaloids was confirmed. In fact, as an application of this strategy, we have successfully synthesized the novel enantiopure benzothieno analogue **5** of the bioactive alkaloid tylophorine in six steps (21% yield) starting from readily available benzo[*b*]thiophene-3-carboxaldehyde **1** and (*S*)-glutamic acid **2**. Also, by using the same strategy we have described a new (6*R*)-phenyl-(8a*R*)-indolizidine alkaloid core **6** in seven steps in an overall yield of 14%. The last step closing this sequence consists of the sensitive Ra-Ni reductive-desulfurization of the tylophorine benzothieno analogue **5** which occurred, in a diastereospecific manner. In all these studies, Ra–Ni was used as a catalyst and the benzothiophene ring as the phenyl group source.

Finally, these structures deserve interest as they are analogous to naturally occurring and/or bioactive substances with different degrees of substitution. Further investigations using these attributes aiming at preparing a small library of novel alkyl- and arylindolizidinediols are currently underway in our group, and the results will be published in the near future in a full account.

4. Experimental

4.1. General

Melting points were recorded on a Boetius hot block and are corrected. Tetrahydrofuran was distilled under an atmosphere of dry nitrogen from sodium benzophenone ketyl or purchased dry from the Aldrich Chemical Company in Sure/Seal bottles; dichloromethane was distilled from calcium hydride. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. The reactions performed under an atmosphere of

argon gas were maintained by an inflated balloon. Ascending Flash column liquid chromatography (FLC) was performed on Silica Gel Kieselgel 60 (40–63 ml, 230–400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminium plates precoated with either 0.2 mm (DC-Alufolien, Merck) or 0.25 mm Silica Gel 60 F254 (ALUGRAM-SIL G/UV254, Macherey-Nagel) and by dipping the plates in an aqueous H_2SO_4 solution of cerium sulfate/ammonium molybdate followed by charring with a heat gun. HPLC analyses were performed on Varian system 9012 with diode array Varian 9065 polychrom UV detector: column CC 250/3 Nucleosil 120-5 C18, 250 × 3 mm (fy Macherey Nagel). Mobile phase: solvent A: water/acetonitrile/methane-sulfonic acid (1000/25/1), solvent B: water/acetonitrile/ methanesulfonic acid (25/1000/1), elution mode: gradient with 5–50% solvent B, flow rate: 0.65 mL/min, UV detection: 210 nm (DAD), 35 °C, 20 min. GC–MS analyses were performed on GC–MS Varian Saturn 2100 T, ion trap MS detector, 70 eV. Column: Varian, Factor Four capillary column VF -5 ms 30m × 0.25 mm ID, DF = 0.25. Optical rotations were measured with a POLAR L-lP polarimeter (IBZ Messtechnik) with a water-jacketed 10 cm cell at the wavelength of sodium line D (λ = 6 589 nm). The specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 mL.

The infrared spectra were recorded on a Nicolet 5700 FT-IR spectrometer as KBr disc (KBr) or as thin films on KBr plates (film). The ^{1}H and ^{13}C NMR spectra were recorded on a VXR 300 and Inova 600 Varian spectrometer instrument in CD_3OD or $CDCl_3$. Solvents and chemical shifts (δ) are quoted in ppm and are referenced to the tetramethylsilane (TMS) as the internal standard. The COSY, NOESY and DIFFNOE techniques were used in the assignment of ^{1}H–^{1}H relationships and the determination of relative configuration. The HSQC and HMBC techniques were used throughout for the assignment of the ^{1}H–^{13}C relationships. High-resolution spectrometry was performed using waters UPLC system on Micromass Q-Tof Micro MS system with ESI$^+$ ionization (measured mass represents M+H$^+$).

4.2. (*S*)-*N*-(1-Benzo[*b*]thien-3-ylmethyl)glutamic acid 7

(*S*)-Glutamic acid **1** (7.36 g, 50 mmol) was added at room temperature to a freshly prepared solution of NaOH (2 M, 45 mL) and EtOH (10 mL). To the resulting mixture was added dropwise a solution of freshly distilled benzo[*b*]thiophene-3-carbaldehyde[14] **1** (9.73 g, 60 mmol) in EtOH (18 mL) over 14 h and the reaction mixture was then stirred for 40 h. Then, sodium borohydride (2.28 g, 60 mmol) was added at 0 °C in small portions, and stirred for 90 min allowing the temperature to rise to room temperature. The resulting clear solution was extracted with ether (3 × 50 mL). The aqueous layer was acidified to pH 3 at 0–5 °C with HCl (1:1). The crystalline precipitate was collected, washed with cooled water (50 mL) and dried to give a solid. The analytically pure compound **7** was obtained by crystallization from dioxane as colourless crystals (11.72 g, 80%); mp 141–146 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.98 (t, 2H, 2 × H_{Ar}; J = 5.9 Hz), 7.69 (s, 1H, $H_{2'}$), 7.40 (t, 2H, 2 × H_{Ar}; J = 5.9 Hz), 4.15 (d, 1H, N–C*H*; J = 13.9 Hz), 4.02 (d, 1H, N–C*H*; J = 13.9 Hz), 3.57 (br s, 2H, 2 × CO_2H), 3.32 (t, 1H, H_1; J = 6.5 Hz), 2.42–2.28 (m, 2H, 2 × H_3), 1.97–1.81 (m, 2H, 2 × H_2); ^{13}C NMR (75 MHz, DMSO-d_6): δ 174.0 (s, 2 × *C*O$_2$), 173.0 (s, *C*ON), 139.6, 138.0, 132.0 (s, $C_{3',3a',7a'}$), 125.5, 124.4, 124.0, 122.7, 122.2 (d, $C_{2',4'-7'}$), 59.9 (d, C_1), 44.1 (t, N-*C*H$_2$), 30.6 (t, CH_2, C_3), 26.7 (t, CH_2, C_2). Anal. Calcd for $C_{14}H_{15}NO_4S$ (293.34): C, 57.32; H, 5.15; N, 4.77; S, 10.93. Found: C, 57.06; H, 5.05; N, 4.56; S, 10.81.

4.3. (*S*)-1-(Benzo[*b*]thien-3-ylmethyl)-5-oxopyrrolidine-2-carboxylic acid 8

The suspension of crude *N*-substituted-(*S*)-glutamic acid **7** (11.72 g, 40 mmol) in EtOH (450 mL) was heated at reflux for 8 h. The resulting solution was filtered and concentrated in vacuo to give a solid. Crystallization from a mixture of toluene/heptane (9:1) afforded acid **8** (8.1 g, 74%) as colourless crystals; R_f = 0.56 (dichloromethane/acetone 3:1); mp 156–158 °C; $[\alpha]_D$ = +42.4 (*c* 1.0, MeOH); IR (ν, cm^{-1}, KBr): 3060, 2871, 2598, 1721, 1693, 1633, 1452, 1441, 1417, 1393, 1353, 1325, 1298, 1261, 1228, 1191, 1151, 1084, 1047, 1018; UV (λ_{max}, nm (log ε)): 298 (2.68), 289 (2.65), 263 (2.83), 259 (2.85), 227 (3.45), 200 (3.40); ^{1}H NMR (600 MHz, CD_3OD): δ 7.88 (dd, 1H, H_{Ar}; J = 2.1 and 7.5 Hz), 7.81 (dd, 1H, H_{Ar}; J = 2.1 and 7.5 Hz), 7.48 (s, 1H, $H_{2'}$), 7.37 (dt, 1H, H_{Ar}; J = 2.1 and 7.4 Hz), 7.36 (dt, 1H, H_{Ar}; J = 2.1 and 7.4 Hz), 5.22 (d, 1H, N–C*H*; J = 14.9 Hz), 4.35 (d, 1H, N–C*H*; J = 14.9 Hz), 3.91 (dd, 1H, H_2; J = 3.3 and 9.2 Hz), 2.52 (tt, 1H, H_4; J = 9.1 and 16.9 Hz), 2.41 (ddd, 1H, H_4; J = 4.0, 9.4 and 16.9 Hz), 2.23 (tdd, 1H, H_3; J = 9.0, 9.2 and 13.1 Hz), 2.05 (tdd, 1H, $H_{3'}$; J = 3.7, 9.4 and 13.1 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 177.8 (s, *C*O$_2$), 174.9 (s, *C*O), 142.1, 139.2, 131.6 (s, $C_{3',3a',7a'}$), 127.6 (d, $C_{2'}$), 125.9, 125.5 (d, $C_{5',6'}$), 123.9, 122.8 (d, $C_{4',7'}$), 60.3 (d, C_2), 40.2 (t, N–*C*H$_2$), 30.8 (t, C_4), 23.9 (t, C_3); HRMS calcd for $C_{14}H_{13}NO_3S$ [M+1]$^+$:275,0616, found 276.0661.

4.4. (11a*S*)-1,11a-Dihydro[1]benzothieno[3,2-*f*]indolizine-3,11(2*H*,5*H*)-dione 3

To a solution of a freshly crystallized carboxylic acid **8** (13.76 g, 50 mmoL) in dichloromethane (300 mL) was added thionyl chloride (4.7 mL, 6.5 mmol) at 0–5 °C. The mixture was stirred at reflux for 6 h, and then cooled to 0 °C. Under vigorous stirring, $AlCl_3$ (14 g, 105 mmol) was added in small portions. The mixture was stirred for 1 h at 0 °C and then for an additional 2.5 h at room temperature. After cooling to 0 °C, water (220 mL) and 15% HCl (5 mL) were added carefully. The two phases were separated and the aqueous layer was extracted twice with dichloromethane (50 mL). After washing with brine, the dichloromethane phase was dried with $MgSO_4$ and concentrated. The resulting product was purified by flash column chromatography (dichloromethane) to yield ketone **3** as a pale yellow solid. Recrystallization from toluene/*n*-hexane (10:1) gave **3** (9.25 g, 72%) as light yellow crystals; mp 181–183 °C; $[\alpha]_D$ = +73.6 (*c* 1.0, MeOH); IR (ν, cm^{-1}, KBr): 3342, 3319, 3057, 1666, 1641, 1594, 1563, 1528, 1469, 1460, 1423, 1415, 1391, 1333, 1297, 1276, 1255, 1239, 1217, 1192, 1145, 1084, 1065, 1020; UV (λ_{max}, nm (log ε)): 300 (3.29), 249 (3.11), 236 (3.15), 204 (3.45); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92 (d, 1H, H_9; J = 8.1 Hz), 7.84 (d, 1H, H_6; J = 8.1 Hz), 7.56 (dt, 1H, H_8; J = 1.0 and 7.7 Hz), 7.49 (dt, 1H, H_7; J = 0.7 and 7.7 Hz), 5.58 (d, 1H, H_{5eq}; J = 18.0 Hz), 4.48 (tt, 1H, H_{11a}; J = 1.5 and 6.8 Hz), 4.41 (d, 1H, H_{5ax}; J = 18.0 Hz), 2.63–2.55 (m, 2H, H_2 and H_1), 2.54–2.45 (m, 2H, H_2 and H_1); ^{13}C NMR (150 MHz, $CDCl_3$): δ 189.6 (s, CO), 174.3 (s, *N*CO), 143.7, 143.2, 136.0 and 134.0 (s, $C_{5a,5b,9a,10a}$), 128.9, 125.5, 123.8 and 123.7 (d, C_{6-9}), 62.3 (d, C_{11a}), 39.2 (t, C_5), 30.1 (t, C_2), 20.7 (t, C_1); HRMS calcd for $C_{14}H_{11}NO_2S$ [M+1]$^+$: 257.0510, found 258.0566.

4.5. 4.5.(11*S*,11a*S*)-11-Hydroxy-1,5,11,11a-tetrahydro[1]benzothieno[3,2-*f*]indolizin-3(2*H*)-one 4

To a solution of freshly crystallized ketone **3** (7.72 g, 30 mmol) in methanol (200 mL) was added in a small portion sodium borohydride (1.33 g, 35 mmol) at 0–5 °C. The mixture was then stirred at 0 °C for 16 h until total disappearance of the starting materials was observed. The solution was carefully neutralized with dry 10% (v/v) HCl in ethanol, and the solvent was removed under vacuum. The solution obtained was extracted twice with dichloromethane. The organic layers were dried over $MgSO_4$ and concentrated to afford a solid. Recrystallization from toluene/*n*-hexane (15:1) gave the title compound **4** (6.16 g, 79.9%) as colourless

crystals; mp 247–250 °C; $[\alpha]_D$ = +128.6 (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3188, 2860, 2475, 1645, 1612, 1494, 1455, 1466, 1421, 1376, 1349, 1334, 1292, 1267, 1231, 1176, 1151, 1138, 1096, 1063; UV (λ_{max}, nm (log ε)): 299 (2.63), 289 (2.64), 266 (2.95), 261 (2.95), 231 (3.49), 201 (3.42); ^{1}H NMR (600 MHz, CD_3OD): δ 7.78 (d, 1H, H_9; *J* = 7.8 Hz), 7.53 (d, 1H, H_6; *J* = 7.8 Hz), 7.34 (dt, 1H, H_8; *J* = 0.9 and 7.7 Hz), 7.31 (dt, 1H, H_7; *J* = 0.9 and 7.7 Hz), 4.95 (dd, 1H, H_{5eq}; *J* = 1.6 and 16.7 Hz), 4.61 (td, 1H, H_{11}; *J* = 1.9 and 8.7 Hz), 4.18 (dd, 1H, H_{5ax}; *J* = 1.3 and 16.7 Hz), 3.70 (dt, 1H, H_{11a}; *J* = 4.6 and 8.2 Hz), 2.55–2.47 (m, 2H, 2 × H_2), 2.46 (tdd, 1H, H_1; *J* = 8.0, 8.2 and 12.3 Hz), 2.15 (tdd, 1H, H_1; *J* = 3.7, 9.4 and 13.1 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 175.8 (s, CO), 140.6, 140.0, 137.1 and 125.9 (s, $C_{5a,5b,9a,10a}$), 124.9, 124.7, 123.0, 121.1 (d, C_{6-9}), 70.3 (d, C_{11}), 61.6 (d, C_{11a}), 39.8 (t, C_5), 30.2 (t, C_2), 22.3 (t, C_1); HRMS calcd for $C_{14}H_{13}NO_2S$ $[M+1]^+$: 259.0667, found 260.0719.

4.6. (11a*S*)-1,5,11,11a-Tetrahydro[1]benzothieno[3,2-*f*]-indolizin-3(2*H*)-one 9

Triethylsilane (2.5 mL, 15 mmol) wad added dropwise to a stirred solution of alcohol **4** (2.59 g, 10 mmol) in trifluoroacetic acid (20 mL) at 0 °C. The resulting yellow solution was stirred at room temperature for 4 h. The reaction mixture was concentrated in vacuo, after which the crude yellow mixture was diluted with ether (50 mL), and washed twice with 10% Na_2CO_3 (2 × 25 mL). The water phase was extracted twice with ether (2 × 10 mL). The combined ether extracts were washed with water (25 mL), 5% Na_2CO_3 (2 × 25 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuo. The weakly green residue (2.28 g, 94%) was purified by crystallization from a mixture of toluene/*n*-hexane (10:1) and gave **9** as a colourless crystal (1.74 g, 71.8%); mp 125–127 °C; $[\alpha]_D$ = +285.1 (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3438, 3057, 2823, 1672, 1583, 1461, 1429, 1413, 1360, 1338, 1308, 1260, 1248, 1189, 1146, 1122, 1058, 1022; UV (λ_{max}, nm (log ε)): 298 (2.41), 289 (2.41), 265 (2.82), 261 (2.83), 230 (3.46), 201 (3.45); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.78 (d, 1H, H_9; *J* = 7.9 Hz), 7.56 (d, 1H, H_6; *J* = 7.9 Hz), 7.37 (dt, 1H, H_8; *J* = 1.1 and 8.0 Hz), 7.32 (dt, 1H, H_7; *J* = 1.1 and 8.0 Hz), 5.09 (dd, 1H, H_{5eq}; *J* = 2.0 and 16.7 Hz), 4.27 (ddd, 1H, H_{5ax}; *J* = 1.3, 2.0 and 16.7 Hz), 3.96 (dddd, 1H, H_{11a}; *J* = 4.5, 5.0, 7.7 and 10.2 Hz), 3.11 (ddd, 1H, H_{11eq}; *J* = 1.1, 4.1 and 15.9 Hz), 2.81 (tdd, 1H, H_{11ax}; *J* = 2.3, 10.6 and 15.8 Hz), 2.61–2.50 (m, 2H, 2 × H_2), 2.46 (ddd, 1H, H_1; *J* = 7.6, 12.7 and 14.8 Hz), 1.90 (dddd, 1H, H_1; *J* = 5.4, 7.2, 9.3 and 13.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.4 (s, C=O), 138.7, 137.1, 133.3 and 125.2 (s, $C_{5a,5b,9a,10a}$), 124.5, 124.4 (d, $C_{7,8}$), 122.5 and 120.3 (d, $C_{6,9}$), 54.7 (d, C_{11a}), 39.8 (t, C_5), 32.8 (t, C_{11}), 30.3 (t, C_2), 25.0 (t, C_1); HRMS calcd for $C_{14}H_{13}NOS$ $[M+1]^+$: 243.0718, found 244.0803.

4.7. (11a*S*)-1,2,3,5,11,11a-Hexahydro[1]benzothieno[3,2-*f*]indolizine 5

To a solution of amide **9** (250 mg, 1.03 mmol) in THF (19 mL) was added dropwise a commercially available solution of $BH_3{\cdot}Me_2S$ 1 M in THF (8.7 mL, 8.7 mmol). The mixture was stirred at room temperature for 72 h, then EtOH (45 mL) was added slowly and the solution was refluxed for 5 h. After removal of the solvents, the crude product was obtained as a solid. Recrystallization of the solid from *n*-hexane gave amine **5** as colourless crystals (200 mg, 85%); mp 103–105 °C; $[\alpha]_D$ = +166.0 (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3381, 3053, 2967, 2938, 2920, 2872, 2792, 2740, 1460, 1431, 1392, 1355, 1330, 1294, 1261, 1254, 1219, 1159, 1144, 1136, 1097, 1062, 1046; UV (λ_{max}, nm (log ε)): 299 (2.34), 289 (2.38), 266 (2.79), 262 (2.80), 232 (3.39), 200 (3.33); ^{1}H NMR (600 MHz, CD_3OD): δ 7.77 (d, 1H, H_9; *J* = 8.0 Hz), 7.56 (d, 1H, H_6; *J* = 8.0 Hz), 7.34 (dt, 1H, H_8; *J* = 1.0 and 8.0 Hz), 7.28 (dt, 1H, H_7; *J* = 1.0 and 8.0 Hz), 4.30 (dd, 1H, H_{5eq}; *J* = 1.5 and 14.4 Hz), 3.38 (ddd, 1H, H_{5ax}; *J* = 2.1, 2.9 and 14.4 Hz), 3.30 (dt, 1H, H_{3peq}; *J* = 2.7 and 8.9 Hz), 3.11 (ddd, 1H, H_{11eq}; *J* = 1.9, 3.8 and 16.2 Hz), 2.76 (dddd, 1H, H_{11ax}; *J* = 1.9, 2.6, 10.5 and 16.2 Hz), 2.61 (ddt, 1H, H_{11a}; *J* = 3.9, 6.9 and 10.1 Hz), 2.43 (q, 1H, H_{3pax}; *J* = 9.2 Hz), 2.17 (dddd, 1H, $H_{1'}$; *J* = 4.7, 6.9, 9.6 and 12.4 Hz), 2.02–1.89 (m, 2H, 2 × H_2), 1.62 (dddd, 1H, H_1; *J* = 6.7, 10.2, 11.3 and 12.5 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 140.8, 138.8, 136.7 and 129.2 (s, $C_{5a,5b,9a,10a}$), 125.3, 125.1, 123.5 and 121.3 (d, C_{6-9}), 62.7 (d, C_{11a}), 54.9 (t, C_3), 52.1 (t, C_5), 33.0 (t, C_{11}), 31.1 (t, C_1), 22.7 (t, C_2); HRMS calcd for $C_{14}H_{15}NS$ $[M+1]^+$: 229.0925, found 230.1000.

4.8. General procedure for the desulfurization of benzothienoindolizines 3, 4, 5 and 9

Activated Raney-nickel was added to a solution of benzothienoindolizinone **3**, **4**, **5** and **9** in methanol and the mixture was stirred at reflux under hydrogen (203 kPa) for 35–75 h. The solution was filtered through a Celite pad to remove the catalyst. The crude product as a mixture of diastereomeric hydroxyindolizidines was analyzed by HPLC, GC–MS and NMR spectroscopy.

4.8.1. (8*R* or *S*,8a*S*)-8-Hydroxy-6-phenylhexahydroindolizin-3(5*H*)-ones 11a–d

This product was obtained by the hydrogenation of benzothienoindolizinedione **3** (1.0 g, 3.88 mmol) in methanol (150 mL) with activated Raney-nickel (6.6 g) at reflux (203 kPa) for 60 h. After filtration of the catalyst through a Celite pad and concentration in vacuo, the composition of four diastereomers in a colourless crude product (0.81 g, 90%) was analyzed by NMR and HPLC measurements. A mixture of four diastereomers **11a–d** was obtained when the crude product (0.90 g) was treated with acetone (2 mL) and the solid obtained was filtered off.

4.8.1.1. (6*S*,8*S*,8a*S*)-8-Hydroxy-6-phenylhexahydroindolizin-3-(5*H*)-one 11a. The characteristics of this product were extracted from spectra of four diastereomers **11a–d** and are as follows: ^{1}H NMR (600 MHz, CD_3OD): δ 7.32 (t, 2H, 2 × H_{mAr}; *J* = 7.6 Hz), 7.28 (d, 2H, 2 × H_{oAr}; *J* = 7.6 Hz), 7.17 (t, 1H, H_{pAr}; *J* = 7.2 Hz), 3.97 (dd, 1H, H_{5eq}; *J* = 7.0 and 13.1 Hz), 3.95–3.88 (m, 2H, H_{8eq} and H_{8a}), 3.36 (dd, 1H, H_{5ax}; *J* = 4.6 and 12.7 Hz), 3.15 (q, 1H, H_{6eq}; *J* = 6.7 Hz), 2.52–2.40 (m, 2H, 2 × H_2), 2.38–2.31 (m, 1H, H_{7eq}), 2.20–2.05 (m, 3H; H_{7ax} and 2 × H_1); ^{13}C NMR (150 MHz, CD_3OD): δ 177.5 (s, CO), 145.1 (s, C_{ipsoAr}), 129.5 (d, C_{mAr}), 128.3 (d, C_{oAr}), 127.4 (d, C_{pAr}), 68.1 (d, C_8), 60.9 (d, C_{8a}), 45.1 (t, C_5), 39.1 (t, C_7), 37.3 (d, C_6), 31.9 (t, C_2), 20.2 (t, C_1).

4.8.1.2. (6*R*,8*S*,8a*S*)-8-Hydroxy-6-phenylhexahydroindolizin-3-(5*H*)-one 11b. The characteristics of this product were extracted from spectra of four diastereomers **11a–d** and are as follows: ^{1}H NMR (600 MHz, CD_3OD): δ 7.32 (t, 2H, 2 × H_{mAr}; *J* = 7.7 Hz), 7.28 (d, 2H, 2 × H_{oAr}; *J* = 7.6 Hz), 7.22 (t, 1H, H_{pAr}; *J* = 7.2 Hz), 4.10 (ddd, 1H, H_{5eq}; *J* = 1.4, 4.7 and 12.7 Hz), 3.95–3.88 (m, 1H, H_{8eq}), 3.77 (dt, 1H, H_{8a}; *J* = 1.8 and 7.2 Hz), 3.11 (tt, 1H, H_{6ax}; *J* = 4.4 and 12.2 Hz), 2.82 (t, 1H, H_{5ax}; *J* = 12.4 Hz), 2.52–2.40 (m, 1H, H_2), 2.39–2.32 (m, 1H, $H_{2'}$), 2.20–2.05 (m, 3H; 2 × H_1 and H_{7eq}), 2.01 (t, 1H, H_{7ax}; *J* = 13.1 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 176.9 (C_3), 143.8 (s, C_{ipsoAr}), 129.7 (d, C_{mAr}), 128.3 (d, C_{oAr}), 127.9 (d, C_{pAr}), 67.7 (d, C_8), 62.3 (d, C_{8a}), 47.4 (t, C_5), 39.3 (t, C_7), 36.4 (d, C_6), 31.8 (t, C_2), 20.2 (t, C_1).

4.8.2. (6*R*,8*R*,8a*S*)-8-Hydroxy-6-phenylhexahydroindol-izin-3(5H)-ones 11d

These products were obtained by the hydrogenation of *trans*-alcohol **4** (1.0 g, 3.86 mmol) in methanol (150 mL) with activated Raney-nickel (4.5 g) at reflux for 72 h. After filtration of the catalyst

and concentration in vacuo, the crude product obtained as a mixture of **11c** and **11d** (0.82 g, 92%) was treated with acetone (2 mL). The resulting precipitate was filtered off. Recrystallization from dry THF gave enantiomerically pure (6*R*,8*R*,8a*S*)-8-hydroxy-6-phenylhexahydroindolizin-3(5*H*)-one **11d** (0.18 g, 20%) as a colourless solid; mp 181–183 °C; $[\alpha]_D$ = +14.2 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3327, 2860, 2475, 1645, 1612, 1494, 1455, 1466, 1421, 1376, 1349, 1334, 1292, 1267, 1231, 1176, 1151, 1138, 1096, 1063, 976, 961, 893, 857, 833, 758, 699, 672, 621, 612, 570, 550, 529, 516, 480, 458; UV (λ_{max}, nm (log *ε*)): 195 (3.31), 201 (3.28); ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.33 (tt, 2H, 2 × H_{mAr}; *J* = 1.6 and 7.7 Hz), 7.29 (td, 2H, 2 × H_{oAr}; *J* = 1.7 and 7.2 Hz), 7.24 (tt, 1H, H_{pAr}; *J* = 1.4 and 7.2 Hz), 4.05 (ddd, 1H, H_{5eq}; *J* = 1.6, 3.5 and 12.0 Hz), 3.40 (dt, 1H, H_{8ax}; *J* = 3.9 and 9.4 Hz), 3.36 (ddd, 1H, H_{8a}; *J* = 5.4, 7.4 and 9.2 Hz), 2.75 (tt, 1H, H_{6ax}; *J* = 3.3 and 12.0 Hz), 2.71 (tt, 1H, H_{5ax}; *J* = 1.5 and 12.0 Hz), 2.46–2.42 (m, 2H, 2 × H_2), 2.35 (ddd, 1H, H_1; *J* = 7.5, 13.1 and 15.0 Hz), 2.19 (dddd, 1H, H_{7eq}; *J* = 1.9, 2.9, 3.8 and 12.5 Hz), 1.96 (dddd, 1H, H_1; *J* = 5.3, 8.1, 9.4 and 13.4 Hz), 1.77 (ddt, 1H, H_{7ax}; *J* = 1.9 and 10.5 and 12.3 Hz); ^{13}C NMR (150 MHz, CD_3OD): *δ* 176.3 (s, CO), 143.0 (s, C_{ipsoAr}), 129.8 (d, C_{mAr}), 128.2 (d, C_{oAr}), 128.1 (d, C_{pAr}), 73.5 (d, C_8), 64.1 (d, C_{8a}), 46.9 (t, C_5), 42.3 (d, C_6), 41.4 (t, C_7), 31.3 (t, C_2), 23.0 (t, C_1); HRMS calcd for $C_{14}H_{17}NO_2$ $[M+1]^+$: 231.1259, found 232.1319.

4.8.2.1. (6*S*,8*R*,8a*S*)-8-Hydroxy-6-phenylhexahydroindolizin-3(5*H*)-one 11c.

The characteristics of this product were extracted from a spectra of two diastereomers **11c** and **11d** and are as follows: ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.28–7.26 (m, 4H, 2 × H_{mAr} and 2 × H_{oAr}), 7.18 (dddd, 1H, H_{pAr}; *J* = 0.8, 2.5, 5.8 and 7.8 Hz), 4.43 (td, 1H, H_{5eq}; *J* = 1.7 and 13.9 Hz), 3.34 (tt, 1H, H_{8a}; *J* = 2.5 and 7.7 Hz), 3.31–3.29 (m, 1H, H_{6eq}), 3.14 (ddd, 1H, H_{8ax}; *J* = 3.9, 9.2 and 11.5 Hz), 3.09 (ddd, 1H, H_{5ax}; *J* = 1.5, 4.5 and 13.9 Hz), 2.48–2.41 (m, 1H, H_2), 2.40–2.31 (m, 3H; H_1, H_2 and H_7), 1.95 (ddd, 1H, H_{7ax}; *J* = 4.8, 11.6 and 13.2 Hz), 1.75–1.68 (m, 1H, H_1); ^{13}C NMR (150 MHz, CD_3OD): *δ* 176.8 (s, CO), 143.7 (s, C_{ipsoAr}), 129.5 (d, C_{mAr}), 128.1 (d, C_{oAr}), 127.3 (d, C_{pAr}), 70.3 (d, C_8), 64.6 (d, C_{8a}), 42.8 (t, C_5), 40.5 (d, C_7), 38.4 (d, C_6), 31.4 (t, C_2), 24.2 (t, C_1).

4.8.3. (8a*R*)-6-Phenylhexahydroindolizin-3(5*H*)-one 12a and 12b

These products were obtained by desulfurization of starting indolizinone **9** (0.45 g, 1.85 mmol) in methanol (70 mL) with activated Raney-nickel (4.0 g) at reflux (203 kPa) for 72 h. After filtration of the catalyst and concentration in vacuo, the crude product (0.39 g, 98%) was obtained as a colourless semi-solid. The characteristics of these products established from the mixture of diastereomeric 6-phenylindolizines **12a** and **12b** are as follows: Selected data for product (6*S*,8a*R*)-**12a**: ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.29–7.25 (m, 4H, 2 × H_{mAr} and 2 × H_{oAr}), 7.19–7.14 (m, 1H, H_{pAr}), 4.45 (dd, 1H, H_{5eq}; *J* = 0.8 and 13.7 Hz), 3.62 (tdd, 1H, H_{8a}; *J* = 3.8, 7.7 and 11.3 Hz), 3.16 (dd, 1H, H_{6eq}; *J* = 4.6 and 8.4 Hz), 3.13 (ddd, 1H, H_{5ax}; *J* = 1.5, 4.5 and 13.5 Hz), 2.42–2.36 (m, 1H, H_2), 2.36–2.30 (m, 1H, $H_{2'}$), 2.26 (dddd, 1H, H_1; *J* = 2.6, 7.2, 9.8 and 12.6 Hz), 2.15 (tdd, 1H, H_{7eq}; *J* = 3.3, 5.3 and 13.9 Hz), 2.06 (tt, 1H, H_{7ax}; *J* = 3.9 and 13.8 Hz), 1.69 (qd, 1H, H_{8eq}; *J* = 3.6 and 13.1 Hz), 1.52 (ddt, 1H, $H_{1'}$; *J* = 8.2, 10.0 and 12.8 Hz), 1.15 (ddt, 1H, H_{8ax}; *J* = 3.5, 11.5 and 13.3 Hz); ^{13}C NMR (150 MHz, CD_3OD): *δ* 176.6 (s, CO), 144.0 (s, C_{ipsoAr}), 129.4 (d, C_{mAr}), 128.5 (d, C_{oAr}), 127.2 (d, C_{pAr}), 59.1 (d, C_{8a}), 43.5 (t, C_5), 37.3 (d, C_6), 31.4 (t, C_2), 31.2 (t, C_7), 29.2 (t, C_8), 26.7 (t, C_1).

Selected data for product (6*R*,8a*R*)-**12b**: ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.31 (tt, 2H, 2 × 2 × H_{mAr}; *J* = 1.6 and 7.4 Hz), 7.29–7.25 (m, 2H, 2 × H_{oAr}), 7.22 (tt, 1H, H_{pAr}; *J* = 1.4 and 7.3 Hz), 4.09 (ddd, 1H, H_{5eq}; *J* = 1.7, 4.5 and 12.9 Hz), 3.62 (tdd, 1H, H_{8a}; *J* = 3.8, 7.7 and 11.3 Hz), 2.76 (t, 1H, H_{5ax}; *J* = 12.4 Hz), 2.61 (tt, 1H, H_{6ax}; *J* = 3.9 and 12.1 Hz), 2.44–2.36 (m, 2H, 2 × H_2), 2.29 (dddd, 1H, H_1; *J* = 2.6, 7.2, 9.8 and 12.6 Hz), 2.03 (qd, 1H, H_{8eq}; *J* = 3.6 and 13.1 Hz), 2.00 (dddd, 1H, H_{7eq}; *J* = 2.0, 3.4, 6.5 and 13.4 Hz), 1.81 (dq, 1H, H_{7ax}; *J* = 3.2 and 12.8 Hz), 1.72–1.66 (m, 1H, $H_{1'}$), 1.40 (ddt, 1H, H_{8ax}; *J* = 3.3, 11.6 and 12.9 Hz); ^{13}C NMR (150 MHz, CD_3OD): *δ* 176.1 (s, C_3), 144.2 (s, C_{ipsoAr}), 129.7 (d, C_{mAr}), 128.2 (d, C_{oAr}), 127.9 (d, C_{pAr}), 58.6 (d, C_{8a}), 47.6 (t, C_5), 43.4 (d, C_6), 34.4 (t, C_8), 32.2 (t, C_7), 31.5 (t, C_2), 25.7 (t, C_1).

4.8.4. (6*R*,8a*R*)-6-Phenyloctahydroindolizine 6

This product was obtained by desulfurization of the starting benzothieno analogue of tylophorine **5** (0.20 g, 0.87 mmol) in methanol (50 mL) with activated Raney-nickel (2.0 g) (203 kPa) at 60 °C for 48 h. After the filtration of the catalyst, the reaction mixture was passed through a short pad of Celite and the solvent was removed under reduced pressure to afford the corresponding *cis*-diastereomer **6**. The resulting product was purified by flash column chromatography (dichloromethane) to yield a pure *cis*-diastereomer as a slightly yellow oil (0.12 g, 68%). The characteristics of product **6** are as follows: $[\alpha]_D$ = −2.0 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3060, 3028, 2962, 2929, 2783, 2475, 1603, 1495, 1452, 1383, 1349, 1228, 1165, 1132, 1111, 1068, 1030; UV (λ_{max}, nm (log *ε*)): 205 (3.03), 197 (3.06); ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.28 (tt, 1H, H_{mAr}; *J* = 1.4 and 7.3 Hz), 7.24 (dd, 1H, H_{oAr}; *J* = 1.4 and 7.2 Hz), 7.18 (tt, 1H, H_{pAr}; *J* = 1.3 and 7.2 Hz), 3.15 (ddd, 1H, H_{5eq}; *J* = 1.3, 4.0 and 11.0 Hz), 3.05 (dt, 1H, H_{3peq}; *J* = 2.3 and 8.8 Hz), 2.84 (tt, 1H, H_{6ax}; *J* = 3.8 and 11.9 Hz), 2.20 (t, 1H, H_{3pax}; *J* = 9.1 Hz), 2.17 (t, 1H, H_{5ax}; *J* = 11.2 Hz), 2.03–1.92 (m, 4H; H_1, H_{7eq}, H_{8eq} and H_{8a}), 1.88–1.74 (m, 2H, 2 × H_2), 1.60 (dq, 1H, H_{7ax}; *J* = 3.9 and 12.9 Hz), 1.44 (dq, 1H, $H_{1'}$; *J* = 6.9 and 11.2 Hz), 1.39 (ddt, 1H, H_{8ax}; *J* = 4.3, 10.8 and 13.4 Hz); ^{13}C NMR (150 MHz, CD_3OD): *δ* 145.3 (s, C_{ipsoAr}), 129.5 (d, C_{mAr}), 128.3 (d, C_{oAr}), 127.6 (d, C_{pAr}), 65.5 (d, C_{8a}), 60.6 (t, C_5), 54.9 (t, C_3), 44.0 (d, C_6), 33.3 (t, C_7), 31.3 (t, C_8), 30.2 (t, C_1), 21.8 (t, C_2); HRMS calcd for $C_{14}H_{19}N$ $[M+1]^+$: 201.1517, found 201,1586.

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