Tetrahedron: *Asymmetry* 20 (2009) 626–634

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Highly diastereoselective approach to novel phenylindolizidinols via benzothieno analogues of tylophorine based on reductive desulfurization of benzo[*b*]thiophene

Peter Šafář [a], Jozefína Žúžiová [a], Štefan Marchalín [a,*], Eva Tóthová [a], Nadežda Prónayová [b], Ľubomír Švorc [c], Viktor Vrábel [c], Adam Daïch [d,*]

[a] *Department of Organic Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, SK-81237 Bratislava, Slovak Republic*
[b] *Central Laboratories, Faculty of Chemical and Food Technology, Slovak University of Technology, SK-81237 Bratislava, Slovak Republic*
[c] *Department of Analytical Chemistry, Faculty of Chemical and Food Technology, Slovak University of Technology, SK-81237 Bratislava, Slovak Republic*
[d] *URCOM, EA 3221, UFRST, CNRS INC3M FR-3038 Université du Havre, 25 rue Philippe Lebon, BP: 540, F-76058 Le Havre Cedex, France*

ARTICLE INFO

Article history:
Received 23 January 2009
Accepted 10 February 2009
Available online 8 April 2009

ABSTRACT

Chiral tetra- and hexahydro[1]benzothieno[2,3-*f*]indolizines **3**–**5**, **9**, and **11** were synthesized easily from benzo[*b*]thiophene-2-carboxaldehyde (**1**) and (*S*)-glutamic acid (**2**) in good overall yields and both high enantio- and diastereomeric purities. Applying a diastereoselective reductive desulfurization of benzo[*b*]thiophene followed by lactam reduction, epimeric alcohols **4a** and **4b** were readily converted into (7*R* or *S*,8a*S*)-phenylindolizidinols **6a**,**c**. During these studies, the reduction of benzothienoindolizines **3**–**5**, **9**, **11**, and **12**, was investigated and the results obtained are also discussed.

1. Introduction

Bicyclic alkaloids such as azabicyclo[4.3.0]nonanes, commonly known as indolizidines, or their unsaturated analogues are amongst the most important structural motifs found abundantly in Nature. Their sources are extremely divers varying from marine and terrestrial materials to organisms, such as plants, bacteria, fungi, vertebrates, and invertebrates.[1]

The spectrum of biological activity displayed by these natural structures is remarkable in its diversity and efficacy. For example, polyhydroxylated indolizidine alkaloids represented by the so popular castanospermine **I** and swainsonine **II** (Fig. 1) are well-known for their ability to function as excellent inhibitors of biologically important pathways. These include the binding and processing of glycoproteins, potent glycosidase inhibitory activities,[2] activity against AIDS virus HIV, and some carcinogenic cells as well as against other important pathologies.[3] In addition, alkyl indolizidine alkaloids such as structures **IIIa**–**d**, also called gephyrotoxins, show significant biological activities as exemplified by the ability of many of them to act as non-competitive blockers of neuromuscular transmission by interacting with nAChRS (nicotinic acetylcholine receptors) of the CNS.[4]

More importantly, hybrids of these structures such as alkylindolizidinols of type **IVa** and **IVb** have shown in numerous cases an increase in glycosidase activity as demonstrated by Pearson et al.

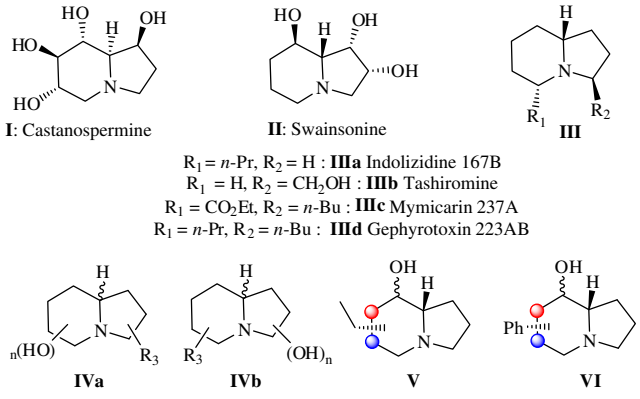


Figure 1. Representative natural products containing indolizidine unit.

and others.[5] This fact is similar to that observed in azasugars and is due to the enhancement of the interaction of these alkyl groups with the active site of the enzymes by providing favorable conformational flexibility to the molecules.[6]

Illustrative examples of our most recent efforts in this direction include: (1) the *cis*-dihydroxylation of the C_1–C_2 linkage to provide concise syntheses of benzoanalogues of lentiginosine and swainsonine;[7] and (2) the use of an uncommon strategy based on reductive desulfurization by Raney-nickel of the thiophene ring of chiral thienoindolizidinediones and the corresponding

* Corresponding authors. Tel.: +33 02 32 74 44 03; fax: +33 02 32 74 43 91 (A.D.).
E-mail address: adam.daich@univ-lehavre.fr (A. Daïch).

0957-4166/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2009.02.042

thienoindolizidinols.[8] More recently, we have described a concise and very efficient route to enantiopure tetrahydrofuran-fused indolizidinols, which could be considered as protected new indolizidindiols, in a two-step sequence starting from the known chiral furoindolizidinediones. The key-step of these reactions was the formation, in one operation, of THF indolizidinols containing a lactam functionality by simultaneous highly diastereoselective catalytic hydrogenation of carbonyl function and the furan ring.[9]

2. Results and discussion

2.1. Synthetic strategy

Our previous work in this area has illustrated that enantiopure (*S*)-glutamic acid and (hetero)aren-carboxaldehyde were extremely useful building blocks that allow the preparation in few steps of a wide range of enantiopure aromatic and heteroaromatic analogues[7,10] of tylophori(ni)nes **VIIa**,**b**,[11] the phenanthroindolizidine type of alkaloids. Further modifications, including regioselective reductions and/or a competitive new strategy based on the thiophene ring desulfurization, have led to a new class of alkyl indolizidinols.[8,9]

In this context, in order to reach the targeted compound **5**, we now selected optically active hexahydrobenzothieno[2,3-*f*]indolizine-3,11-dione **3** and the corresponding epimeric alcohols **4a**,**b** as key templates for further elaboration (Fig. 2). Ultimately, the benzothiophene ring of compounds **4a**,**b** could very well play the role of reservoir for the phenyl substituent at position 7 of the indolizidine ring following the well established reductive desulfurization protocol. The potential utility of this technique has been aptly illustrated in the literature by numerous examples in different fields of organic chemistry, notably including the field of total synthesis.[12,13]

2.2. Synthesis of benzothieno-analogues 11 and 5 of bioactive tylophorine alkaloids VIIa,b

The synthetic pathway for the novel benzothieno analogue **5** of tylophorine is detailed in Scheme 1. For this purpose, our synthesis began with the commercially available and cheap L-glutamic acid **2**, which was condensed with benzo[*b*]thiophene-2-carboxaldehyde **1** to give the expected Schiff base, which upon treatment with $NaBH_4$ for 2 h at room temperature and concentrated hydrochloric acid at same temperature gave the (*S*)-*N*-benzothienylmethyl glutamic acid **7** in an overall yield of 80% over two steps. The cyclization of carboxylic acid **7** in good yield (74%) was performed by refluxing in ethanol for 8 h. The resulting *N*-benzothien-2-ylmethyl-pyroglutamic acid **8** was conveniently converted to the corresponding acid chloride by treatment with thionyl chloride

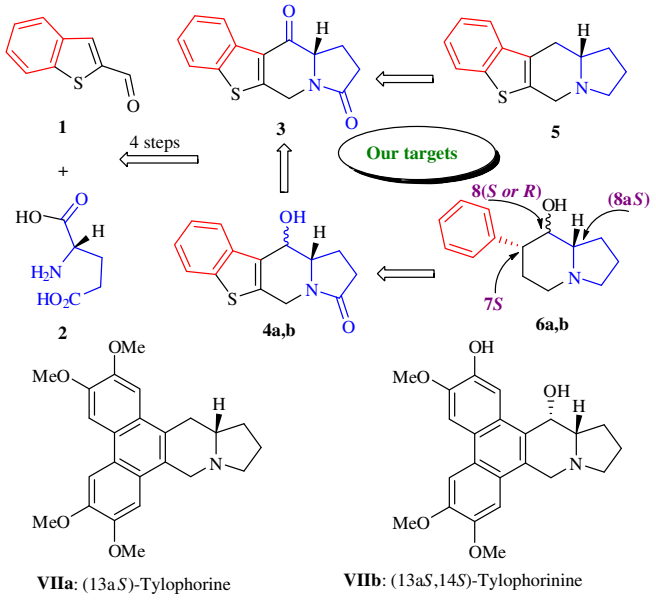
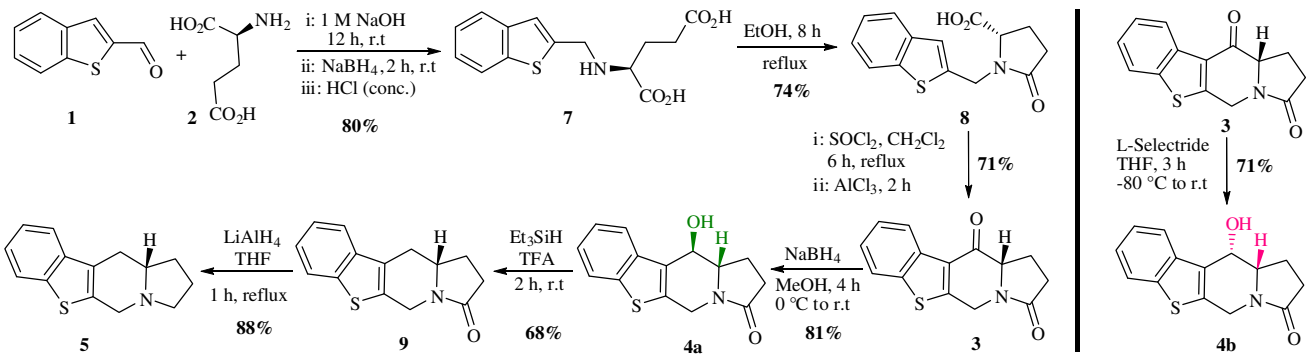


Figure 2. Scheme leading to benzothienoindolizidine **5** and arylated indolizidinols **6a**,**b** from benzothiophen-2-carboxaldehyde **1** and (*S*)-glutamic acid **2**.

in dichloromethane at reflux for 6 h. The resulting acid chloride, under conditions of Friedel–Crafts cyclization using aluminum trichloride of high quality as a catalyst (99.99%), gave the expected tricyclic keto-lactam **3** in good yield (71%). The $NaBH_4$ reduction of the ketone gave (11*R*)-alcohol **4a** in 81% yield as a single *trans*-diastereomer. This is similar to the result observed earlier by us with related structures.[7,10] The stereochemical assignments of this structure are based on analysis of the NMR spectra (HMBC, HSQC, and COSY experiment) and show that there is no evidence for the formation of the epimeric *cis*-alcohol **4b**.

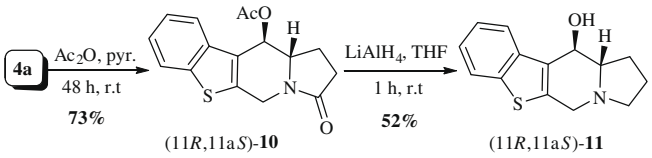
In order to reach both epimeric *cis and trans*-alcohols **4a**,**b**, required for our further investigations, the preparation of the epimeric alcohol (11*S*,11a*S*)-**4b** was also investigated. The selective reduction of the keto-lactam **3** with $NaBH_4$ reflects a preference for an *axial* hydride attack from the more hindered *endo* face of the tricyclic system. Thus, the stereoselectivity can be reversed by using a larger hydride reagent in which case severe hindrance to axial approach diverts the reaction to the equatorial face. Thus using L-Selectride as a reducing agent in THF at −80 °C gave enantiomerically pure alcohol (11*S*,11a*S*)-**4b** in 71% yield. On the other hand, attempts to convert alcohol (11*R*,11a*S*)-**4a** into the expected alcohol **4b** by alternative Mitsunobu inversion were not successful. Furthermore, treating of alcohol **4a** with triethylsilane in trifluoroacetic acid led to lactam **9** in 68% yield. Finally the synthesis of the



Scheme 1. Scheme for the synthesis of the tricyclic keto-lactam **3** and phenanthroindolizidinols **4a** and **4b**.

targeted benzothiophene analogue **5** of the tylophorine alkaloids **VIIa**,**b** was achieved with LAH reduction of the lactam (11a*S*)-**9** in refluxing THF. The reduction occurred cleanly within 1 h to provide the title compound (11a*S*)-hexahydro[1]benzothieno[2,3-*f*]-indolizine **5** in 88% yield.

For the preparation of the benzothieno analogue of the naturally occurring phenanthroindolizidinols, the *trans* alcohol **4a** was acetylated using standard conditions (Scheme 2). In fact, reaction with acetic anhydride in the presence of pyridine in CH_2Cl_2 at room temperature over 48 h led to the acetoxy derivative (11*R*,11a*S*)-**10** (73%). Ultimately, **10** was efficiently converted into the expected phenanthroindolizidinol (11*R*,11a*S*)-**11** using LAH reduction in refluxing THF for 1 h (52%) according to Green's protocol.[14]



Scheme 2. Synthesis of phenanthroindolizidinol (11*R*,11a*S*)-**11**.

2.3. Diastereoselective synthesis of 7-phenylindolizidin-ols 12a–d and 6a–d

In our previous work and as outlined also in the Introduction, an expedient synthesis of the prototypic alkyl-substituted indolizidinols, namely 7-ethyl and 6-ethyl-8-indolizidinols, is described.[7] The key step that creates the linkages between the C_7/ethyl group and the C_8/OH function is based on a reductive desulfurization of the thiophene ring. From these results we speculated that the benzothiophene ring of the compounds **3** and **4a**,**b**, by using the same sequence, could serve as building blocks for the preparation of new 7-phenyl indolizidinol derivatives.

In this sense, we have started the required study with Raney-nickel hydrogenolysis of both carbonyl group and benzothiophene ring in the keto-lactam **3** (Scheme 3). Interestingly, after screening the best experimental protocol turned out to be the reaction of enantiopure tricyclic keto-lactam (8a*S*)-**3** with activated Ra–Ni in anhydrous methanol under stirring and under one atmosphere of hydrogen gas at reflux for 75 h (90%).

As might be expected (Scheme 3), from the four possible diastereomers **12a–d**, only three were formed in a 77:0:3:20 ratio, albeit in very good overall yield (90%) and the repetition of reaction gave approximately the same stereoisomeric distribution. Importantly, by comparing this result with that obtained in the thiophene series (68:12:10:10 ratio for related ethyl-stereoisomers),[8] we found that the reduction processes in both cases have same profile, however, with a better diastereo- and regioselectivity in the case of the benzothiophene series. Furthermore, treatment of the crude mixture with a small amount of dry acetone provided the major stereoisomer **12a**, which crystallized out from the mixture in a synthetically useful yield of 71%. Further recrystallization from acetone upgraded the purity of this product and its structure **12a**, was unequivocally identified by means of ^1H and ^{13}C NMR (Table 1) spectroscopy as well as by single X-ray crystallography to be that of (7*R*,8*S*,8a*S*)-8-hydroxy-7-phenylhexahydroindolizin-3(5*H*)-one (see Fig. 3 for the X-ray of **12a**).[15] In order to learn more about the possible influence of the configuration of the hydroxy group at the C_8-position on the stereochemical course of the reductive desulfurization, a set of additional experiments was conducted.

Table 1
Chemicals shifts (δ in ppm) in the ^1H and ^{13}C NMR spectra of the three diastereomers **12a**, **12c**, and **12d** in CD_3OD solution

Proton/carbon	(7*R*,8*S*,8a*S*)-**12a**	(7*R*,8*R*,8a*S*)-**12c**	(7*S*,8*R*,8a*S*)-**12d**
H-5*ax*/C-5	2.90 ddt/40.9	2.82 dt/40.6	3.06 dt/37.2
H-5*eq*/C-5	4.17 ddd/40.9	4.05 ddd/40.6	3.86 ddd/37.2
H-6*ax*/C-6	2.05 dddd/24.3	1.69 dq/33.3	1.96 tt/29.5
H-6*eq*/C-6	1.59 ddtd/24.3	1.83 dtd/33.3	2.11 ddd/29.5
H-7/C-7	2.95 ddd/47.7	2.67 ddd/51.5	3.33 q/45.2
H-8/C-8	3.76 t/72.1	3.41 t/77.4	3.68 dd/76.4
H-8a/C-8a	3.85 ddd/63.8	3.42 ddd/64.3	3.83 td/59.5

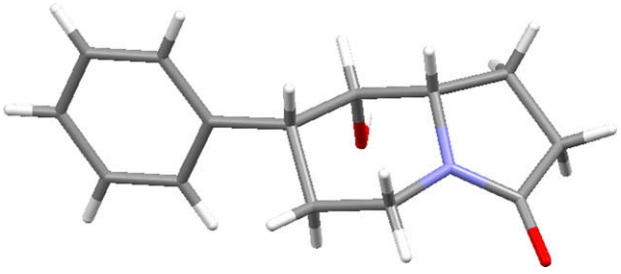
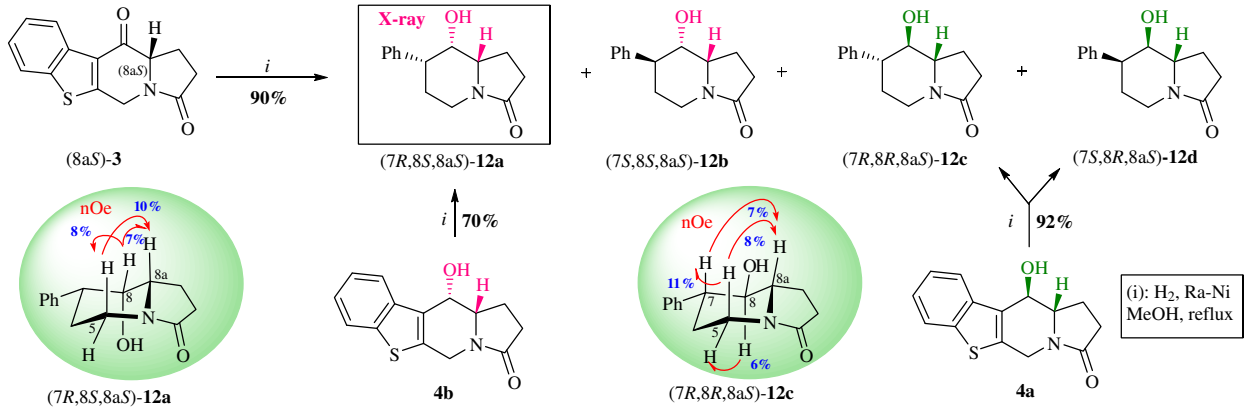
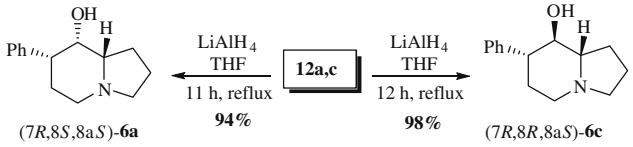


Figure 3. ORTEP drawing of the indolizinone, namely, (7*R*,8*S*,8a*S*)-8-hydroxy-7-phenylhexahydroindolizin-3(5*H*)-one **12a**. Thermal ellipsoids at 30% probability level.



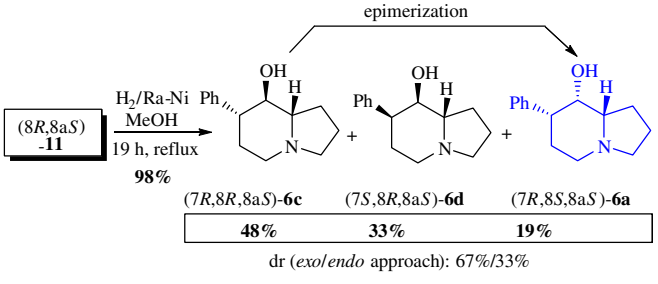
Scheme 3. Synthetic route to the 7(*S*)-phenyl-8(*S*)-indolizidinol target (7*R*,8*S*,8a*S*)-**12**. Three of the four possible diastereomers (7*R*,8*S*,8a*S*)-**12a**, (7*S*,8*S*,8a*S*)-**12b**, (7*R*,8*R*,8a*S*)-**12c**, and (7*S*,8*R*,8a*S*)-**12d** were obtained in a 77:0:3:20 ratio as determined by NMR analysis as well as X-ray analysis of (7*R*,8*S*,8a*S*)-**12a**. Selected 1D-NOE ^1H NMR experiments helped to establish the relative configuration in the 7-phenylindolizidinols **12a**,**c**.

In order to learn more, and to measure the impact of another C_8-substituent during the stereochemical course of benzothiophene reductive cleavage, a set of additional experiments was performed. First, the enantiopure *trans*-alcohol **4a** was subjected to the same protocol used for the reduction of its precursor **3** (Scheme 3). Interestingly, a mixture of two diastereomers (7*R*,8*R*,8a*S*)-**12c** and (7*S*,8*R*,8a*S*)-**12d** was obtained in an 85:15 ratio in very good yield (92%, Scheme 3). Once more, treating the crude mixture with dry acetone led to the major stereoisomer crystallizing out from the mixture in a synthetically useful 67% yield. The structure of this compound was confirmed to be (7*R*,8*R*,8a*S*)-**12c** by means of ^{1}H and ^{13}C NMR including HMBS, HSQC, and COSY experiments (see Scheme 3 for nOe measurements). Parallel experiments were also carried out starting from the *cis*-epimeric analogue **4b**. In this case (Scheme 3), highly diastereoselective reductive desulfurization was observed, leading to alcohol **12a** as single diastereoisomer identical to that obtained in 99.9% de (from HPLC) and only 70% yield. These results highlight, in line with those observed in the furan[7,9] and thiophene[8] series, the stereo-complementarities between the $NaBH_4$ and L-selectride reduction and the catalytic hydrogenation modes. Ultimately, the synthesis of target epimeric indolizidinols **6a**,**c** was completed by LAH reduction of the lactams (8a*S*)-**12a**,**c** in refluxing THF (Scheme 4). The reduction occurred cleanly within 4 h, to provide the title compounds 7(*S*)-phenyl-8(*R* or *S*)indolizidinols **6a**,**c** in almost 70% yield.



Scheme 4. Access to 7(*S*)-phenyl-8(*R* or *S*)-indolizidinols **6a**,**c** targets.

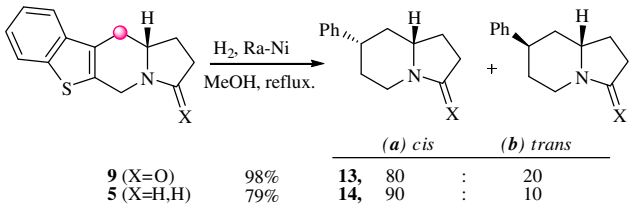
To access the indolizidinol target **6c** and other epimers such as **6d**, another route was explored starting from the C_3-deoxy analogue as **11**, easily obtainable from alcohol **4a** via the corresponding acetate derivative **10**, as outlined above (Scheme 2). In this case, treatment of benzothienoindolizidinol **11** under the well established reductive-desulfurization protocol led to an oily mixture of three inseparable diastereomers in a 48:33:19 ratio in favor of the product (7*R*,8*R*,8a*S*)-**6c** (see Scheme 5). The structure of all of these isomers, respectively, (7*R*,8*R*,8a*S*)-**6c** (48%), (7*S*,8*R*,8a*S*)-**6d** (33%), and (7*R*,8*S*,8a*S*)-**6a** (19%), was identified without ambiguity by NMR spectroscopy studies including notably nOe measurements. The formation of diastereomer **6a**, obtained to our surprise, can be explained by epimerization of the initially formed alcohol **6c** under the reaction conditions.



Scheme 5. Target 7(*S*)-phenyl-8(*R* or *S*)-indolizidinols **6a**,**c**,**d** by reduction of the C_3-deoxy analogue **11**.

Based upon this result, we believe that the lower degree of facial stereoselectivity of this reaction, in comparison with the *trans*-alcohol **4a**, is probably due to the more pronounced steric hindrance of the hexahydroindolizine skeleton in alcohol **11** making the *exo* (or top) face more difficult to access during the hydrogen attack.

As shown in Scheme 6, another parameter such as the absence of a substituent on the methylene group at position 3 (outlined in red in Scheme 6) of the benzo[*b*]thiophene ring in the tricyclic systems was considered. For this, two compounds **9**: (11a*S*)-1,5,11,11a-tetrahydro[1]benzothieno[2,3-*f*]indolizin-3(2*H*)-one and **5**: (11a*S*)-1,2,3,5,11,11a-hexahydro[1]benzothieno[2,3-*f*]indolizine described above in Scheme 1 were submitted to our reductive desulfurization protocol.



Scheme 6. Target 7(*R* or *S*)-phenylindolizidines **13a**,**b**, and **14a**,**b** by reduction of the tylophorine analogues **5** and **9**.

Under these conditions, starting from **9** and after 72 h reaction an oily mixture of inseparable two stereoisomers, arised as expected, favoring the diastereomer **13a** (the *cis*:*trans* ratio of **13** was determined as 80:20 by using HPLC measurements). This, in the case of non-hydroxylated lactam **9**, proceeded in an excellent 98% overall yield. This experiment revealed also a slightly better dr in favor of the *cis*-stereomer **13a** in comparison with the 7-ethyl-indolizinones obtained earlier by same protocol from the thienoindolizines.[8] In addition, the reductive-desulfurization of the final tylophorine analogue **5** provided, after 48 h of reaction, the two possible diastereomers (7*S*,8a*S*)-**14a** and (7*R*,8a*S*)-**14b** as well in only 79% yield, but preserving the usual course with the preferred 'exo-approach' and favorable level (90:10) of stereo-induction. In light of these results, it is important to notice that the lactam function present in substrate **9** probably induces an important electronic and steric rearrangement in the starting material making the catalytic hydrogenation more or less selective. To measure the impact of this parameter, additional investigations are actually under investigations in our group.

Finally, though the literature in this field is rather unconclusive regarding the stereoselectivity of hydrogenation, it is nevertheless generally accepted that addition of hydrogen occurs from the less hindered face of the double bond of the thiophene ring. However, the discrepancies in certain results observed herein, notably during the reduction of alcohols **4a**,**b**, **11**, and C_{11}-deoxygenated derivatives **5**, **9** could be ascribed in part to the so called haptophilic effect[8,9,17] operative in **4a**,**b**, and **11**, which causes H_2 to be added from the same side as a polar substituent such as an hydroxyl group.

3. Conclusion

In conclusion, this work constitutes an improvement of our strategy based on the reductive desulfurization of a thiophene ring of chiral thienoindolizidinediones and corresponding thienoindolizidinols with Raney-nickel. Herein, the application of a similar process to the benzo[*b*]thienoindolizidinedione and the corresponding benzo[*b*]thienoindolizidinols opens up an effective synthetic approach to various enantio- and diastereomerically pure

7-phenyl-8-indolizidinols using five or eight synthetic steps. This original strategy was in its key step based on the desulfurization process of the benzo[*b*]thiophene nucleus, which constitutes the phenyl group source. During these investigations, a synthesis of a benzothieno analogue of the bioactive alkaloid tylophorine was also described in only six-step-sequence and high global yield (20% starting from the cheap and easily available L-glutamic acid and benzo[*b*]thiophene-2-carboxaldehyde,[16] respectively). Finally, these structures deserve interest as analogous to a wide range of naturally occurring alkaloids and/or bioactive substances.

All these attributes make this strategy very interesting and quite attractive for the design and synthesis of a wide variety of novel polyhydroxylated indolizidines including alkaloids comprising different substituents, stereo-chemistry, and with promising pharmacological profiles. On the other hand, further functionalization of these ultimate scaffolds could constitute a crucial point of a structural modularity and diversity to access a large library of small molecules indispensable for the structure–activity relationship studies.

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; pyridine was distilled from calcium hydride and stored over dried 3 Å molecular sieves; acetic anhydride was distilled from P_2O_5. All other solvents were used as supplied (analytical or HPLC grade) without prior purification. 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 (230–400 mesh) and analytical thin-layer chromatography (TLC) was performed on aluminum plates pre-coated 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/methanesulfonic acid (1000/25/1), solvent B: water/acetonitrile/methane-sulfonic 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 30 m × 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 = 589 nm). 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 an 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 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.

4.2. (*S*)-*N*-(1-Benzo[*b*]thien-2-ylmethyl)glutamic acid 7

Commercially available (*S*)-glutamic acid **2** (7.36 g, 50 mmol) was added at room temperature to a freshly prepared solution of NaOH (2 M, 45 mL) and EtOH (8 mL). To the resulting mixture was added dropwise under stirring a solution of freshly distilled benzo[*b*]thiophene-2-carbaldehyde **1**[16] (9.73 g, 60 mmol) in EtOH (18 mL) during 12 h and the reaction was stirred overnight. Then, powder sodium borohydride (2.28 g, 60 mmol) was added at 5–10 °C in small portions during 10 min, stirred 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, colorless crystals (11.72 g, 80%); mp 174–175 °C; $[\alpha]_D = -31.8$ (*c* 1.0, MeOH); IR (ν, cm^{-1}, KBr): 3130, 3024, 2925, 2637, 2503, 1712, 1616, 1537, 1484, 1447, 1436, 1412, 1357m 1346, 1291, 1266, 1243, 1185, 1174, 1139, 1129, 1063, 1046, 1021, 953, 920, 899, 850, 819, 752, 730, 592, 552, 512, 467; UV (λ_{max}, nm (log ε)): 200 (3.71), 227 (3.77), 258 (3.3127), 263 (3.30), 290 (2.80), 300 (2.80). 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, 57.03; H, 5.11; N, 4.54; S, 10.84.

4.3. (*S*)-1-(Benzo[*b*]thien-2-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 to reflux for 6 h. The resulting solution was filtered and concentrated in vacuo to give a solid. Crystallization from a mixture of toluene/heptane (90:10, v/v) afforded carboxylic acid **8** (8.1 g, 73.5%) as colorless crystals; R_f = 0.56 (dichloromethane/acetone, 3:1); mp 170–172 °C; $[\alpha]_D$ = +53.8 (*c* 1.0, MeOH); IR (ν, cm^{-1}, KBr): 2927, 2906, 2719, 2609, 2522, 1737, 21643, 1469, 1458, 1434, 1419, 1342, 1325, 1279, 1254, 1225, 1212, 1197, 1167, 1074, 1014, 964, 949, 893, 835, 755, 729, 715, 677, 653, 609, 579, 559, 492, 474, 444; UV (λ_{max}, nm (log ε)): 200 (3.55), 228 (3.53), 258 (3.11), 263 (3.11), 290 (2.70), 299 (2.70); ^{1}H NMR (600 MHz, DMSO-d_6): δ 1.91–1.97 (m, 1H, H-3), 2.20–2.35 (m, 3H, 2 × H_4 and H_3), 3.31 (br s, 1H, COO*H*), 4.01 (dd, 1H, H_2; *J* = 3.9 and 8.8 Hz), 4.25 (d, 1H, N–*CH*, *J* = 15.6 Hz), 5.00 (d, 1H, N–*CH*, *J* = 15.6 Hz), 7.26 (s, 1H, $H_{3'}$), 7.28 (dt, 1H, H_{Ar}, *J* = 7.7 and 1.1 Hz), 7.30 (dt, 1H, H_{Ar}, *J* = 7.7 and 1.1 Hz), 7.33 (dd, 1H, H_{Ar}, *J* = 7.8 and 0.9 Hz), 7.85 (dd, 1H, H_{Ar}, *J* = 7.8 and 0.9 Hz); ^{13}C NMR (150 MHz, DMSO-d_6): δ 22.4 (t, C_3), 28.8 (t, C_4), 40.2 (t, N–CH_2), 58.1 (d, C_2), 122.4 (d, $C_{3'}$), 123.3, 123.4, 124.3 and 124.4 (d, $C_{4-7'}$), 139.1, 139.2 and 140.0 (s, $C_{2',3a',7a'}$), 173.0, 174.2 (COOH+NC=O). Anal. Calcd for $C_{14}H_{13}NO_3S$ (275.32): C, 61.07; H, 4.76; N, 5.09; S, 11.65. Found: C, 60.94; H, 4.55; N, 4.89; S, 11.22.

4.4. (11a*S*)-1,11a-Dihydro[1]benzothieno[2,3-*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 under reflux for 6 h, and then cooled to 0 °C. Under vigourous stirring, $AlCl_3$ (14 g, 105 mmoL) was added by small portions. The mixture was stirred for 1 h at 0 °C and then for additional 2 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 purifield by flash column chromatography (dichloromethane) to yield keto-lactam **3** as a yellow solid. Recrystallization from toluene/*n*-hexane (3:2) gave **3** (9.25 g, 71%) as a light yellow crystal; mp 184–185 °C; $[\alpha]_D = -64.5$ (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3346, 3313, 2958, 2881, 1680, 1562, 1525, 1463, 1427, 1417, 1385, 1360, 1299, 1259, 1206, 1189, 1151, 1110, 977, 929, 795, 781, 763, 732, 668, 633, 592, 567, 471, 432; UV (λ_{max}, nm ($\log\varepsilon$)): 218 (3.79), 242 (3.30), 302 (3.13); ^{1}H NMR (600 MHz, CD_3OD): δ 2.40–2.49 (m, 2H, 2 × H_1), 2.51–2.61 (m, 2H, 2 × H_2), 4.54 (ddd, 1H, H_{11a}; *J* = 1.5, 5.6 and 8.6 Hz), 4.61 (d, 1H, H_{5ax}; *J* = 18.2 Hz), 5.45 (d, 1H, H_{5eq}; *J* = 18.2 Hz), 7.43 (ddd, 1H, H_{Ar}; *J* = 1.3, 7.2 and 8.2 Hz), 7.49 (ddd, 1H, H_{Ar}; *J* = 1.1, 7.2 and 8.2 Hz), 7.90 (td, 1H, H_{Ar}; *J* = 1.1 and 8.0 Hz), 8.58 (td, 1H, H_{Ar}; *J* = 1.1 and 8.1 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 20.5 (t, C_1), 30.0 (t, C_2), 39.9 (t, C_5), 61.7 (d, C_{11a}), 122.1, 125.0, 126.0 and 126.3 (d, C_{7-10}), 128.5, 135.5, 137.7 and 155.1 (s, $C_{5a,6a,10a,10b}$), 173.9 (s, N–C=O, C_3), 189.7 (s, C=O, C_{11}). Anal. Calcd for $C_{14}H_{11}NO_2S$ (257.31): C, 65.35; H, 4.31; N, 5.44; S, 12.46. Found: C, 65.15; H, 4.19; N, 5.28; S, 12.32.

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

To a solution of a freshly crystallized keto-lactam **3** (8.26 g, 30 mmoL) in methanol (200 mL) was added in a small portions sodium borohydride (1.33 g, 35 mmoL) at 0–5 °C. The mixture was then stirred at 0 °C for 4 h, until total disappearance of starting materials was observed (TLC). The solution was carefully neutralized with 10% (v/v) dry HCl in dry EtOH, and the solvent was removed under vacuum. The obtained solution was then extracted with dichloromethane. The organic layer was dried over $MgSO_4$ and concentrated to afford a solid. Recrystallization from toluene/*n*-hexane gave the title compound **4a** (6.16 g, 79%) as colorless crystals; mp 203–204 °C; $[\alpha]_D = +56.8$ (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3341, 3060, 2980, 2884, 2835, 1664, 1577, 1450, 1434, 1415, 1379, 1351, 1311, 1293, 1271, 1242, 1200, 1152, 1076, 1068, 1052, 1020, 1001, 982, 940, 887, 862, 784, 753, 676, 635, 585, 571, 501, 433, 411; UV (λ_{max}, nm ($\log\varepsilon$)): 202 (3.52), 229 (3.48), 258 (3.02), 289 (2.71), 298 (2.72); ^{1}H NMR (600 MHz, CD_3OD): δ 2.20 (dddd, 1H, H_1; *J* = 5.5, 8.8, 12.0 and 14.7 Hz), 2.47–2.60 (m, 3H, 2 × H_2 and H_1), 3.74 (tt, 1H, H_{11a}; *J* = 2.3 and 8.3 Hz), 4.31 (d, 1H, H_{5ax}; *J* = 17.2 Hz), 4.74 (td, 1H, H_{11}; *J* = 2.0 and 8.5 Hz), 4.98 (dd, 1H, H_{5eq}; *J* = 1.7 and 17.2 Hz), 7.30 (ddd, 1H, H_{Ar}; *J* = 1.3, 7.2 and 8.2 Hz), 7.33 (ddd, 1H, H_{Ar}; *J* = 1.2, 7.2 and 8.2 Hz), 7.79 (ddd, 1H, H_{Ar}; *J* = 0.8, 1.2 and 7.8 Hz), 8.14 (ddd, 1H, H_{Ar}; *J* = 0.8, 1.2 and 7.8 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 21.8 (t, C_1), 29.1 (t, C_2), 39.3 (t, C_5), 59.8 (d, C_{11a}), 68.9 (d, C_4), 122.4, 2 × 124.0, 124.1 (d, C_{7-10}), 132.7, 133.2, 138.1 and 138.4 (s, $C_{5a,6a,10a,10b}$), 173.1 (s, C=O, C_3). Anal. Calcd for $C_{14}H_{13}NO_2S$ (259.32): C, 64.84; H, 5.05; N, 5.40; S, 12.36. Found: C, 64.66; H, 5.01; N, 5.27; S, 12.18.

4.6. (11*S*,11a*S*)-11-Hydroxy-1,5,11,11a-tetrahydro[1]-benzo- thieno[2,3-*f*]indolizin-3(2*H*)-one 4b

The freshly crystallized keto-lactam **3** (2.59 g, 10 mmol) was dissolved in dry THF (70 mL) and cooled to −78 °C with stirring. L-Selectride (20 mL of a 1.0 mol dm^{-3} solution in THF) was added (30 min) dropwise via a syringe and the reaction mixture was stirred for 4 h at −78 °C, then was quenched at the same temperature by addition of NaOH (4 mL, 3 mol dm^{-3}) and 30% aqueous H_2O_2 (4 mL) and stirred for 1 h. The mixture was filtered and the filtrate was evaporated and extracted with dichloromethane (3 × 20 mL). The combined organic solvents were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. Recrystallization of the solid from toluene gave **4b** (2.14 g, 71%) as a colorless crystal; mp 193–194 °C; $[\alpha]_D = -9.4$ (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3350, 2980, 2958, 2888, 2846, 1689, 1577, 1545, 1473, 1459, 1452, 1434, 1412, 1369, 1356, 1309, 1299, 1276, 1254, 1196, 1161, 1153, 1085, 1065, 1018, 1007, 985, 940, 815, 784, 766, 739, 715, 695, 678, 642, 615, 570, 476, 429; UV (λ_{max}, nm ($\log\varepsilon$)): 203 (3.55), 228 (3.51), 258 (3.01), 288 (2.57), 297 (2.60); ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.22 (dddd, 1H, H_1; *J* = 7.3, 8.8, 10.0 and 13.0 Hz), 2.42 (dddd, 1H, H_2; *J* = 1.2, 4.0, 10.3 and 17.0 Hz), 2.47 (tdd, 1H, H_1; *J* = 3.6, 10.0 and 13.1 Hz), 2.61 (ddd, 1H, H_2; *J* = 7.2, 9.8 and 17.0 Hz), 2.72 (d, 1H, OH, *J* = 8.7 Hz), 3.92 (td, 1H, H_{11a}; *J* = 2.9 and 8.8 Hz), 4.20 (d, 1H, H_{5ax}; *J* = 17.6 Hz), 4.86 (dd, 1H, H_{11}; *J* = 2.1 and 8.5 Hz), 5.13 (d, 1H, H_{5eq}; *J* = 17.6 Hz), 7.35 (ddd, 1H, H_{Ar}; *J* = 1.0, 7.2 and 8.0 Hz), 7.41 (ddd, 1H, H_{Ar}; *J* = 1.0, 7.2 and 8.0 Hz), 7.82 (td, 1H, H_{Ar}; *J* = 0.7 and 8.0 Hz), 7.83 (td, 1H, H_{Ar}; *J* = 0.7 and 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.2 (t, C_2), 30.7 (t, C_3), 40.2 (t, C_5), 59.1 (d, C_{11a}), 64.3 (d, C_{11}), 121.1, 122.6, 124.8 and 124.9 (d, C_{7-10}), 130.7, 136.2, 137.7 and 139.2 (s, $C_{5a,6a,10a,10b}$), 175.0 (s, C=O, C_3). Anal. Calcd for $C_{14}H_{13}NO_2S$ (259.32): C, 64.84; H, 5.05; N, 5.40; S, 12,36. Found: C, 64.59; H, 4.98; N, 5.29; S, 12.21.

4.7. (11*R*,11a*S*)-3-Oxo-1,2,3,5,11,11a-hexahydro[1]-benzothieno[2,3-*f*]indolizin-11-yl acetate 10

A solution of *trans*-alcohol **4a** (3.89 g, 15 mmol) and pyridine (30 mL) in dichloromethane (175 mL) was cooled to +5 °C. Acetic anhydride (28 mL) was added dropwise and the reaction stirred for 10 h at room temperature, when major product was formed ($R_f = 0.42$; dichloromethane/acetone, 3:1). The reaction mixture was diluted with dichloromethane (50 mL) and washed twice with 2 M hydrochloric acid (40 mL). The organic layer was further washed with water (3 × 50 mL), with brine (50 mL), dried with magnesium sulfate, and concentrated under reduced pressure. Recrystallization from toluene gave the acetate derivative **10** (3.30 g, 73%) as a colorless crystal; mp 141–142 °C; $[\alpha]_D = +24.0$ (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3460, 3365, 2970, 2877, 1735, 1702, 1687, 1572, 1462, 1454, 1432, 1402, 1380, 1371, 1350, 1319, 1292, 1272, 1240, 1201, 1152, 1128, 1105, 1066, 1044, 1031, 1022, 959, 852, 785, 769, 748, 727, 683, 629, 584, 546, 534, 471, 428; UV (λ_{max}, nm ($\log\varepsilon$)): 203 (3.50), 228 (3.49*), 259 (3.02), 288 (2.71), 297 (2.71); ^{1}H NMR (600 MHz, CD_3OD): δ 2.15–2.20 (m, 1H, H_1), 2.21 (s, 3H, CH_3CO), 2.40–2.52 (m, 2H, 2 × H_2), 2.55 (tdd, 1H, H_1; *J* = 5.4, 9.9 and 14.2 Hz), 3.93 (td, 1H, H_{11a}; *J* = 4.7 and 7.9 Hz), 4.31 (t, 1H, H_{5ax}; *J* = 17.2 Hz), 5.01 (dd, 1H, H_{5eq}; *J* = 1.5 and 17.2 Hz), 6.17 (td, 1H, H_{11}; *J* = 1.8 and 7.9 Hz), 7.31 (dt, 1H, H_{Ar}; *J* = 1.5 and 7.2 Hz), 7.34 (dt, 1H, H_{Ar}; *J* = 1.5 and 7.2 Hz), 7.41 (dd, 1H, H_{Ar}; *J* = 1.9 and 7.2 Hz), 7.81 (dd, 1H, H_{Ar}; *J* = 1.9 and 7.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1 (q, CH_3), 22.9 (t, C_1), 29.6 (t, C_2), 39.7 (t, C_5), 58.7 (d, C_{11a}), 70.1 (d, C_{11}), 121.6, 122.8, 124.6 and 124.7 (d, C_{7-10}), 127.0, 136.5, 136.9 and 139.0 (s, $C_{5a,6a,10a,10b}$), 171.0 and 173.8 (s, C=O). Anal. Calcd for $C_{16}H_{15}NO_3S$ (301.36): C, 63.77; H, 5.02; N, 4.65; S, 10.64. Found: C, 63.58; H, 4.91; N, 4.24; S, 10.52.

4.8. (11a*S*)-1,5,11,11a-Tetrahydro[1]benzothieno[2,3-*f*]-indolizin-3(2*H*)-one 9

Triethylsilane (2.5 mL, 15 mmol) was added dropwise to a stirred solution of alcohol **4a** (2.59 g, 10 mmol) in trifluoroacetic acid (20 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 (50 mL), made alkaline carefully with 10% Na_2CO_3, and extracted with dichloromethane (3 × 20 mL).

The combined extracts were washed with water, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue (2.28 g, 88%) was purified by flash chromatography on a silica gel column eluting with dichloromethane. Recrystallization of the solid from ethanol/water (3:1) gave product **9** as a colorless crystal (1.65 g, 68%); mp 125–127 °C; $[\alpha]_D$ = +73.8 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3557, 3357, 3053, 2969, 2922, 2835, 1686, 1582, 1462, 1449, 1431, 1415, 1381, 1363, 1313, 1291, 1267, 1246, 1195, 1162, 1146, 1125, 1036, 997, 854, 823, 761, 731, 721, 696, 656, 600, 561, 488, 451, 420; UV (λ_{max}, nm (log ε)): 200 (3.61), 231 (3.58), 260 (3.05), 289 (2.73), 298 (2.73); ^{1}H NMR (600 MHz, CD_3OD): δ 1.92–1.99 (m, 1H, H_1), 2.45–2.51 (m, 1H, $H_{\bar{1}}$), 2.52–2.56 (m, 2H, 2 × H_2), 2.61 (tdd, 1H, H_{11ax}; *J* = 2.4, 10.7 and 15.5 Hz), 3.18 (ddd, 1H, H_{11eq}; *J* = 1.5, 4.5 and 15.6 Hz), 3.98 (tdd, 1H, H_{11a}; *J* = 4.8, 6.6 and 12.3 Hz), 4.30 (d, 1H, H_{5ax}; *J* = 17.3 Hz), 5.05 (dd, 1H, H_{5eq}; *J* = 1.9 and 17.3 Hz), 7.29 (ddd, 1H, H_{Ar}; *J* = 1.1, 7.2 and 8.1 Hz), 7.34 (ddd, 1H, H_{Ar}; *J* = 1.1, 7.2 and 8.1 Hz), 7.58 (d, 1H, H_{Ar}; *J* = 7.9 Hz), 7.77 (d, 1H, H_{Ar}; *J* = 7.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.0 (t, C_1), 30.1 (t, C_2), 31.0 (t, C_{11}), 40.3 (t, C_5), 53.7 (d, C_{11a}), 120.6, 122.6, 124.3 and 124.4 (d, C_{7-10}), 127.4, 132.1, 138.3 and 139.0 (s, $C_{5a,6a,10a,10b}$), 174.0 (s, C=O). Anal. Calcd for $C_{14}H_{13}NOS$ (243.32): C, 69.11; H, 5.39; N, 5.76; S, 13.18. Found: C, 68.91; H, 5.14; N, 5.25; S, 13.01.

4.9. (11*R*,11a*S*)-1,2,3,5,11,11a-Hexahydro[1]benzothieno[2,3-*f*] indolizin-11-ol 11

Lithium aluminum hydride (0.38 g, 10 mmol) was added to a solution of acetyl derivative **10** (0.6 g, 2 mmol) in dry THF (20 mL) at room temperature and the mixture then heated at 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 dichloromethane (50 mL). The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue (0.46 g, 98%). Recrystallization of the solid from *n*-hexane gave pure indolizinol **11** as a colorless crystal (0.21 g, 52%); mp 182–183 °C; $[\alpha]_D$ = +140.4 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3146, 3059, 2986, 2929, 2874, 2823, 2789, 2742, 1572, 1477, 1458, 1432, 1364, 1311, 1285, 1256, 1180, 1145, 1123, 1109, 1097, 1075, 1013, 964, 929, 909, 850, 781m 741, 728, 708, 609, 513, 456; UV (λ_{max}, nm (log ε)): 202 (3.46), 229 (3.48), 260 (3.02), 289 (2.71), 298 (2.72); ^{1}H NMR (600 MHz, CD_3OD): δ 1.72 (dddd, 1H, H_1; *J* = 6.5, 9.4, 10.9 and 12.5 Hz), 1.87–1.97 (m, 2H, 2 × H_2), 2.31 (dddd, 1H, $H_{\bar{1}}$; *J* = 5.5, 7.2, 9.3 and 12.4 Hz), 2.39–2.45 (m, 2H, H_{11a} and H_3), 3.22 (ddd, 1H, $H_{\bar{3}}$; *J* = 3.0, 7.3 and 9.2 Hz), 3.49 (dd, 1H, H_{5ax}; *J* = 2.4 and 14.9 Hz), 4.13 (dd, 1H, H_{5eq}; *J* = 1.2 and 14.9 Hz), 4.72 (td, 1H, H_{11}; *J* = 2.0 and 8.6 Hz), 7.30 (ddd, 1H, H_{Ar}; *J* = 1.2, 7.2 and 8.1 Hz), 7.33 (ddd, 1H, H_{Ar}; *J* = 1.2, 7.2 and 8.1 Hz), 7.78 (d, 1H, H_{Ar}; *J* = 8.0 Hz), 8.06 (d, 1H, H_{Ar}; *J* = 8.0 Hz); ^{13}C NMR (75 MHz, CD_3OD): δ 22.8 (t, C_2), 29.5 (t, C_1), 53.0 (t, C_5), 55.1 (t, C_3), 69.8 (d, C_{11a}), 72.8 (d, C_{11}), 123.3, 124.6, 125.1 and 125.2 (d, C_{7-10}), 133.8, 137.4, 139.5 and 140.7 (s, $C_{5a,6a,10a,10b}$). Anal. Calcd for $C_{14}H_{15}NOS$ (245.34): C, 68.54; H, 6.16; N, 5.71; S, 13.07. Found: C, 68.31; H, 6.01; N, 5.56; S, 12.84.

4.10. (11a*S*)-1,2,3,5,11,11a-Hexahydro[1]benzothieno-[2,3-*f*] indolizine 5

Lithium aluminum hydride (0.75 g, 2 mmol) was added to a solution of the lactam **9** (0.73 g, 3 mmol) in dry THF (30 mL) at room temperature and the mixture then heated at 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 dichloromethane (50 mL). The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue (0.61 g, 88%). Recrystallization of the solid from *n*-hexane gave pure amine **5** as a colorless crystal (0.41 g, 59%); mp 86–88 °C; $[\alpha]_D$ = +118.4 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3433, 3055, 2963, 2902, 2796, 1460, 1435, 1392, 1369, 1332, 1211, 1288, 1271, 1258, 1165, 1144, 1120, 1103, 1019, 1003, 990, 930, 885, 787, 749, 727, 696, 577, 498, 426; UV (λ_{max}, nm (log ε)): 200 (3.47), 231 (3.51), 262 (2.99), 289 (2.71), 299 (2.68); ^{1}H NMR (600 MHz, CD_3OD): δ 1.60 (ddt, 1H, H_1; *J* = 6.6, 10.0 and 11.6 Hz), 1.84–1.97 (m, 2H, 2 × H_2), 2.11 (dddd, 1H, $H_{\bar{1}}$; *J* = 4.4, 6.8, 9.8 and 12.3 Hz), 2.31 (q, 1H, H_{3ax}; *J* = 9.1 Hz), 2.44 (ddt, 1H, H_{11a}; *J* = 3.7, 6.7 and 10.2 Hz), 2.52 (dddd, 1H, H_{11ax}; *J* = 1.6, 2.7, 10.7 and 15.4 Hz), 3.04 (ddd, 1H, H_{11eq}; *J* = 2.0, 3.7 and 15.4 Hz), 3.23 (dt, 1H, H_{3eq}; *J* = 2.4 and 8.8 Hz), 3.43 (td, 1H, H_{5ax}; *J* = 2.4 and 15.0 Hz), 4.16 (dd, 1H, H_{5eq}; *J* = 1.1 and 15.0 Hz), 7.29 (dt, 1H, H_{Ar}; *J* = 0.9, and 7.9 Hz), 7.34 (dt, 1H, H_{Ar}; *J* = 0.9 and 7.9 Hz), 7.60 (d, 1H, H_{Ar}; *J* = 7.9 Hz), 7.77 (d, 1H, H_{Ar}; *J* = 7.9 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 22.7 (t, C_2), 31.0 (t, C_1), 31.1 (t, C_{11}), 53.0 (t, C_5), 54.9 (t, C_3), 62.0 (d, C_{11a}), 121.7, 123.5, 125.2 and 125.3 (d, C_{7-10}), 130.1, 135.1, 140.0 and 140.5 (s, $C_{5a,6a,10a,10b}$). Anal. Calcd for $C_{14}H_{15}NS$ (229.34): C, 73.32; H, 6.59; N, 6.11; S, 13.98. Found: C, 73.11; H, 6.35; N, 6.01; S, 13.82.

4.11. General procedure for the desulfurization of benzothienoindolizinones 3–5, 9, and 11

Activated Raney-nickel was added to a solution of benzothienoindolizidine **3**–**5**, **9**, or **11** 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.

4.11.1. (7*R*,8*S*,8a*S*)-8-Hydroxy-7-phenylhexahydroindolizin-3 (5*H*)-one 12a

Method A: This product was obtained by the hydrogenation of benzothienoindolizine-dione **3** (1.0 g, 3.88 mmol) in methanol (90 ml) with activated Raney-nickel (6.6 g) at reflux for 75 h. After filtration through a Celite pad of the catalyst and concentration in vacuo, the crude product (0.85 g, 94%) was treated with acetone (2 mL). The resulting precipitate was filtered off. Recrystallization from acetone gave enantiomerically pure indolizinone **12a** (0.69 g, 71%) as a colorless solid; mp 195–198 °C;; $[\alpha]_D$ = −142.2 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3356, 3055, 2969, 2952, 2889, 1647, 1581, 1502, 1471, 1455, 1416, 1385, 1364, 1303, 1286, 1265, 1184, 1161, 1102, 1063, 1036, 994, 970, 941, 886, 850, 822, 768, 702, 661, 579, 522, 501, 410; UV (λ_{max}, nm (log ε)): 196 (3.26), 205 (3.23); ^{1}H NMR (600 MHz, CD_3OD): δ 1.59 (ddtd, 1H, H_{6eq}; *J* = 0.8, 1.5, 2.8 and 13.0 Hz), 2.05 (dddd, 1H, H_{6ax}; *J* = 5.1, 6.2, 10.4 and 13.0 Hz), 2.10 (dddd, 1H, H_1; *J* = 6.3, 8.6, 10.2 and 13.0 Hz), 2.19 (dq, 1H, $H_{\bar{1}}$; *J* = 5.1 and 13.0 Hz), 2.34 (dddd, 1H, H_2; *J* = 1.6, 6.3, 10.2 and 17.1 Hz), 2.43 (ddd, 1H, $H_{\bar{2}}$; *J* = 6.4, 10.5 and 17.0 Hz), 2.90 (ddt, 1H, H_{5ax}; *J* = 1.4, 3.5 and 13.0 Hz), 2.95 (ddd, 1H, H_7; *J* = 2.1, 3.3 and 13.0 Hz), 3.76 (t, 1H, H_8, *J* = 1.8 Hz), 3.85 (ddd, 1H, H_{8a}; *J* = 1.8, 5.1 and 8.5 Hz), 4.17 (ddd, 1H, H_{5eq}; *J* = 1.6, 5.1 and 13.1 Hz), 7.19 (tdd, 1H, H_{pAr}; *J* = 1.9, 6.8 and 7.3 Hz), 7.27–7.32 (m, 4H, H_{m+oAr}); ^{13}C NMR (150 MHz, CD_3OD): δ 20.5 (t, C_1), 24.3 (t, C_6), 31.6 (t, C_2), 40.9 (t, C_5), 47.7 (d, C_7), 63.8 (d, C_{8a}), 72.1 (d, C_8), 127.5 (d, C_{pAr}), 129.1 and 129.3 (d, C_{m+oAr}), 144.5 (s, C_{ipsoAr}), 177.0 (C=O, C_3). Anal. Calcd for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.49; H, 7.15; N, 5.91. *Method B*. This product was obtained by the hydrogenation

of *cis*-alcohol **4b** (0.49 g, 1.89 mmol) in methanol (90 ml) with activated Raney-nickel (6.6 g) at reflux for 75 h. Recrystallization from acetone gave enantiomerically pure indolizinone **12a** (0.68 g, 70%) as a colorless solid; mp 195–198 °C.

4.11.2. (7*R*,8*R*,8a*S*)-8-Hydroxy-7-phenylhexahydro-indolizin-3(5*H*)-ones 12c and 12d

These products were obtained by the hydrogenation of the *trans*-alcohol **4a** (0.49 g, 1.89 mmol) in methanol (70 ml) with activated Raney-nickel (3.5 g) at reflux for 70 h. After the filtration of the catalyst and concentration in vacuo, the crude product (0.42 g, 100%) was treated with acetone (2 mL). The resulting precipitate was filtered off and recrystallized from acetone to give enantiomerically pure indolizinone **12c** (0.29 g, 67%) as a colorless solid; mp 171–172 °C; $[\alpha]_D = -73.2$ (*c* 1.0, MeOH); IR (ν, cm^{-1}, KBr): 3295, 3082, 3030, 2960, 2944, 2919, 2851, 1650, 1494, 1466, 1454, 1447, 1425, 1371, 1352, 1334, 1294, 1272, 1259, 1177, 1154, 1097, 1084, 1064, 1030, 979, 888, 757, 698, 670, 627, 585, 556, 531; UV (λ_{max}, nm ($\log\varepsilon$)): 205 (3.16); ^{1}H NMR (600 MHz, CD_3OD): δ 1.69 (dq, 1H, H_{6ax}; J = 4.9 and 12.8 Hz), 1.83 (dtd, 1H, H_{6eq}; J = 1.7, 3.5 and 13.3 Hz), 1.93 (dddd, 1H, H_1; J = 5.4, 8.1, 9.6 and 13.3 Hz), 2.35 (dq, 1H, $H_{\acute{1}}$; J = 7.1 and 13.8 Hz), 2.41–2.46 (m, 2H, 2 × H_2), 2.67 (ddd, 1H, H_7; J = 3.6, 9.7 and 12.6 Hz), 2.82 (dt, 1H, H_{5ax}; J = 3.2 and 13.0 Hz), 3.41 (t, 1H, H_8; J = 9.5 Hz), 3.42 (ddd, 1H, H_{8a}; J = 5.6, 7.7 and 9.3 Hz), 4.05 (ddd, 1H, H_{5eq}; J = 1.5, 4.8 and 13.2 Hz), 7.03 (tt, 1H, H_{pAr}; J = 1.3 and 7.2 Hz), 7.27 (dd, 2H, H_{mAr}; J = 1.3 and 7.9 Hz), 7.31 (dt, 2H, H_{oAr}; J = 1.0 and 7.8 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 23.6 (t, C_1), 31.3 (t, C_2), 33.3 (t, C_6), 40.6 (t, C_5), 51.5 (d, C_7), 64.3 (d, C_{8a}), 77.4 (d, C_8), 127.7 (d, C_{pAr}), 129.1 and 129.5 (d, C_{m+oAr}), 143.7 (s, C_{ipsoAr}), 176.3 (C_3). Anal. Calcd for $C_{14}H_{17}NO_2$ (231.29): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.51; H, 7.18; N, 5.92.

4.11.3. (7*S*,8*R*,8a*S*)-8-Hydroxy-7-phenylhexahydroindolizin-3(5*H*)-one 12d

The characteristics of this product were extracted from a spectra of the mixture of two diastereomers **12c** and **12d** and are as follows: ^{1}H NMR (600 MHz, CD_3OD): δ 1.90–1.95 (m, 1H, H_1), 1.96 (tt, 1H, H_{6ax}; J = 5.8 and 12.8 Hz), 2.11 (ddd, 1H, H_{6eq}; J = 4.0, 6.7 and 14.1 Hz), 2.25–2.32 (m, 1H, $H_{\acute{1}}$), 2.36–2.41 (m, 2H, H_2), 3.06 (dt, 1H, H_{5ax}; J = 4.1 and 12.8 Hz), 3.33 (q, 1H, H_7, J = 4.7 Hz), 3.68 (dd, 1H, H_8; J = 5.3 and 9.4 Hz), 3.83 (td, 1H, H_{8a}; J = 7.2 and 9.2 Hz), 3.86 (ddd, 1H, H_{5eq}; J = 2.4, 6.2 and 13.7 Hz), 7.22 (dd, 1H, H_{pAr}; J = 1.3 and 7.6 Hz), 7.31 (t, 2H, H_{mAr}; J = 7.6 Hz), 7.48 (d, 2H, H_{oAr}; J = 7.6 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 24.6 (t, C_1), 29.5 (t, C_6), 31.2 (t, C_2), 37.2 (t, C_5), 45.2 (d, C_7), 59.5 (d, C_{8a}), 76.4 (d, C_8), 127.4 (d, C_{pAr}), 129.2 (d, C_{mAr}), 131.1 (d, C_{oAr}), 141.7 (s, C_{ipsoAr}), 176.6 (s, C=O, C_3).

4.11.4. (8a*S*)-7-Phenyloctahydroindolizin-8-ols 6a,c,d

These products were obtained by desulfurization of starting indolizinol **11** (0.75 g, 3 mmol) in methanol (80 ml) with activated Raney-nickel (1.5 g) at 60 °C for 19 h. After filtration of the catalyst and concentration in vacuo, the crude product obtained (0.65 g, 98%) constitutes a mixture of **6c** (48%), **6d** (33%), and **6a** (19%) determined from NMR spectra. The characteristics of diastereomer **6d** were extracted from a spectra of a mixture of three diastereomers **6a**,**c**,**d** and are as follows: ^{1}H NMR (600 MHz, CD_3OD): δ 2.73 (ddd, 1H, H_3; J = 11.4, 5.8 and 11.5 Hz), 2.92 (ddd, 1H, H_{5eq}; J = 2.8, 6.3 and 13.5 Hz), 3.75 (dd, 1H, H_8; J = 4.9 and 7.3 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 21.6 (t, C_2), 28.2 (t, C_1), 29.2 (t, C_6), 44.1 (d, C_7),49.7 (t, C_3), 55.4 (t, C_5), 66.2 (d, C_{8a}), 74.2 (d, C_8), 127.1 (d, C_{pAr}), 128.9 (d, C_{mAr}), 130.8 (d, C_{oAr}), 143.3 (s, C_{ipsoAr}).

4.11.5. (8a*S*)-7-Phenylhexahydroindolizin-3(5*H*)-ones 13a and 13b

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) under reflux for 72 h. After the filtration of the catalyst and concentration in vacuo, a crude product (0.39 g, 98%) as a colorless semisolid was obtained. The characteristics of these products were established from a mixture of two diastereomers 7-phenylindolizines **13a** and **13b** (80:20) and are as follows:

4.11.5.1. Product (8*S*,8a*S*)-13a. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.38 (dt, 1H, H_{8ax}; J = 11.4 and 12.5 Hz), 1.57 (dq, 1H, H_{6ax}; J = 4.9 and 12.6 Hz), 1.65 (dddd, 1H, H_1; J = 6.9, 9.0, 9.7 and 12.9 Hz), 1.88 (dddd, 1H, H_{6eq}; J = 1.9, 3.5, 5.3 and 13.2 Hz), 2.07 (dtd, 1H, H_{8eq}; J = 1.9, 3.2 and 12.8 Hz), 2.25 (dddd, 1H, H_1; J = 5.5, 7.6, 8.2 and 12.7 Hz), 2.39–2.44 (m, 1H, 2 × H_2), 2.74 (tt, 1H, H_7; J = 3.2 and 12.3 Hz), 2.79 (dt, 1H, H_{5ax}; J = 3.3 and 12.9 Hz), 3.60 (tt, 1H, H_{8a}; J = 3.7 and 10.8 Hz), 4.25 (ddd, 1H, H_{5eq}; J = 1.8, 4.9 and 13.3 Hz), 7.19 (dd, 1H, H_{oAr}; J = 1.3 and 7.7 Hz), 7.22 (tt, 1H, H_{pAr}; J = 1.3 and 7.7 Hz), 7.31 (tt, 1H, H_{mAr}; J = 1.6 and 7.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.0 (t, C_1), 30.3 (t, C_2), 31.9 (t, C_6), 39.8 (t, C_5),41.0 (t, C_8), 41.8 (d, C_7), 57.1 (d, C_{8a}), 126.5 (d, C_{pAr}), 126.6 (d, C_{oAr}), 128.5 (d, C_{mAr}), 144.9 (s, C_{ipsoAr}), 173.5 (C=O, C_3).

4.11.5.2. Product (7R,8aS)-13b. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.55–1.63 (m, 1H, H_1), 1.77 (ddd, 1H, $H_{\acute{8}}$; J = 5.1, 11.7 and 13.7 Hz), 1.91 (dtd, 1H, H_{6ax}; J = 1.5, 5.2 and 13.3 Hz), 2.18 (dddd, 1H, $H_{\acute{1}}$; J = 3.9, 7.3, 9.6 and 12.9 Hz), 2.24–2.27 (m, 1H, H_6), 2.32 (dtd, 1H, $H_{\acute{2}}$; J = 1.5, 9.3 and 17.0 Hz), 2.35–2.38 (m, 1H, H_2), 2.39–2.44 (m, 1H, H_8), 2.93 (ddd, 1H, H_{5ax}; J = 1.2, 3.5 and 13.1 Hz), 3.29 (tt, 1H, H_7; J = 5.0 and 5.8 Hz), 3.64 (tt, 1H, H_{8a}; J = 3.8 and 11.0 Hz), 3.99 (ddd, 1H, H_{5ax}; J = 2.6, 5.5 and 13.5 Hz), 7.19 (dd, 1H, H_{oAr}; J = 1.3 and 7.7 Hz), 7.22 (tt, 1H, H_{pAr}; J = 1.3 and 7.7 Hz), 7.31 (tt, 1H, H_{mAr}; J = 1.6 and 7.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.6 (t, C_1), 27.8 (t, C_6), 30.0 (t, C_2), 34.9 (d, C_7), 36.1 (t, C_5), 37.5 (t, C_8), 52.1 (d, C_{8a}), 126.5 (d, C_{pAr}), 126.6 (d, C_{oAr}), 128.5 (d, C_{mAr}), 144.9 (s, C_{ipsoAr}), 173.5 (C=O, C_3).

4.11.6. (8a*S*)-7-Phenyloctahydroindolizines 14a and 14b

These products were obtained by desulfurization process starting from indolizinone **5** (0.20 g, 0.87 mmol) in methanol (45 ml) with activated Raney-nickel (2.0 g) at 60 °C for 48 h. After the filtration of the catalyst and concentration of the solution in vacuo, the crude product (0.14 g, 79%) obtained as yellow oil was purified by flash column chromatography (SiO_2, *n*-hexane) to yield a mixture of **14a** (90%) and **14b** (10%) from HPLC as a light yellow oil (0.11 g, 64%). The characteristics of product **14a** are as follows: Product (7*S*,8a*S*)-**14a**: ^{1}H NMR (600 MHz, CD_3OD): δ 1.45 (dq, 1H, $H_{\acute{1}}$; J = 0.9, and 11.2 Hz), 1.46 (tq, 1H, H_8; J = 11.4 Hz), 1.74–1.81 (m, 2H, $H_{\acute{2}}$ and $H_{\acute{6}}$), 1.81–1.88 (m, 2H, H_2 and H_6), 1.93 (dddd, 1H, H_1; J = 3.5, 6.2, 9.7 and 12.2 Hz), 1.99 (tdd, 1H, H_{8eq}; J = 2.2, 3.6 and 12.7 Hz), 2.07 (ddt, 1H, H_{8a}; J = 2.5, 6.3 and 10.8 Hz), 2.18 (q, 1H, H_3; J = 9.2 Hz), 2.20 (dt, 1H, H_{5ax}; J = 3.2 and 11.6 Hz), 2.62 (tt, 1H, H_7; J = 4.1 and 12.1 Hz), 3.07 (dt, 1H, H_3; J = 2.3 and 8.9 Hz), 3.19 (ddd, 1H, H_{5eq}; J = 2.5, 4.1 and 11.2 Hz), 7.16 (tdd, 1H, H_{pAr}; J = 1.5 and 7.3 Hz), 7.23 (dd, 2H, H_{oAr}, J = 1.8 and 7.9 Hz), 7.27 (dt, 2H, H_{mAr}, J = 1.8 and 7.9 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 21.9 (t, C_2), 31.1 (t, C_1), 34.3 (t, C_6), 39.1 (t, C_8), 44.2 (d, C_7), 53.6 (t, C_5), 54.8 (t, C_3), 66.0 (d, C_{8a}), 127.3 (d, C_{pAr}), 127.9 (d, C_{oAr}), 129.5 (d, C_{mAr}), 147.4 (s, C_{ipsoAr}).

4.12. (7*R*,8*S*,8a*S*)-7-Phenyloctahydroindolizin-8-ol 6a

The product was obtained by reduction of **12a** (0.37 g, 1.6 mmol) with lithium aluminum hydride (0.47 g, 1.2 mmol) in dry THF (30 mL) at reflux for 11 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 dichloromethane (50 mL). The dichloromethane layer was separated and the aqueous layer extracted with dichloromethane (2 × 20 mL). The combined extracts were washed with water, brine, dried over $MgSO_4$, and concentrated in vacuo to give a residue (0.36 g, 94%). Recrystallization from *n*-heptane gave enantiomerically pure indolizinol **6a** (0.22 g, 64%) as a colorless solid; mp 110–112 °C; $[\alpha]_D$ = +0.9 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3183, 3054, 3027, 2967, 2948, 2933, 2883, 2796, 2785, 2742, 1942, 1599, 1498, 1458, 1450, 1443, 1381, 1347, 1325, 1278, 1236, 1198, 1161, 1147, 1099, 1085, 1041, 1028, 995, 926, 906, 881, 818, 757, 696, 655, 600, 503, 475; UV (λ_{max}, nm (log ε)): 205 (2.98); ^{1}H NMR (600 MHz, CD_3OD): δ 1.61 (ddd, 1H, H_{6eq}; *J* = 2.6, 6.1 and 12.9 Hz), 1.68–1.82 (m, 3H, 2 × H_2 and H_1), 1.87 (ddd, 1H, H_1; *J* = 5.3, 10.5 and 15.3 Hz), 2.10–2.19 (m, 2H, 2 × H_2), 2.20 (dd, 1H, H_{8a}; *J* = 6.6 and 10.6 Hz), 2.29 (dq, 1H, H_{6ax}; *J* = 4.1 and 12.8 Hz), 2.69 (td, 1H, H_7; *J* = 2.8 and 12.9 Hz), 3.05 (dt, 1H, H_3; *J* = 2.1 and 7.9 Hz), 3.17 (ddd, 1H, H_{5eq}; *J* = 2.4, 3.7 and 10.8 Hz), 3.81 (s, 1H, H_8), 7.17 (t, 1H, H_{pAr}; *J* = 7.3 Hz), 7.27 (t, 2H, H_{mAr}; *J* = 7.6 Hz), 7.33 (d, 2H, H_{oAr}; *J* = 8.3 Hz); ^{13}C NMR (150 MHz, CD_3OD): δ 22.0 (t, C_2), 26.1 (t, C_1), 26.5 (t, C_6), 49.2 (d, C_7), 53.5 (t, C_5), 55.1 (t, C_3), 69.8 (d, C_{8a}), 70.7 (d, C_8), 127.2 (d, C_{pAr}), 129.1 and 129.3 (d, C_{m+oAr}), 145.0 (s, C_{ipsoAr}). Anal. Calcd for $C_{14}H_{19}NO$ (217.31): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.26; H, 8.64; N, 6.22.

4.13. (7*R*,8*R*,8a*S*)-7-Phenyloctahydroindolizin-8-ol 6c

The product was obtained by reduction of **12c** (0.4 g, 1.8 mmol) with lithium aluminum hydride (0.35 g, 0.95 mmol) in dry THF (25 mL) at reflux for 12 h. After standard work-up, a residue was obtained (0.35 g, 98%). Recrystallization from *n*-heptane gave enantiomerically pure indolizidinol **6c** (0.32 g, 48%) as a white solid; mp 132–134 °C; $[\alpha]_D$ = +7.5 (*c* 1.0, MeOH); IR (*ν*, cm^{-1}, KBr): 3159, 3053, 3017, 2996, 2906, 2874, 2809, 1601, 1581, 1497, 1476, 1459, 1439, 1414, 1369, 1330, 1281, 1264, 1214, 1192, 1161, 1117, 1100, 1077, 1053, 1016, 996, 924, 900, 870, 846, 763, 702, 578, 546, 515, 443, 418; UV (λ_{max}, nm (log ε)): 206 (2.99); ^{1}H NMR (600 MHz, CD_3OD): δ 1.61 (ddt, 1H, H_1; *J* = 7.0, 10.6 and 11.8 Hz), 1.76–1.92 (m, 4H, 2 × H_2 and 2 × H_6), 2.00 (dt, 1H, H_{8a}; *J* = 6.5 and 9.6 Hz), 2.14 (dddd, 1H, H_1; *J* = 3.7, 6.5, 10.0 and 12.6 Hz), 2.19 (dt, 1H, H_{5ax}; *J* = 3.8 and 11.2 Hz), 2.27 (q, 1H, H_3; *J* = 9.2 Hz), 2.50 (ddd, 1H, H_7; *J* = 5.3, 10.2 and 11.8 Hz), 3.09 (ddd, 1H, H_{5eq}; *J* = 2.4, 4.1 and 11.2 Hz), 3.12 (dt, 1H, H_3; *J* = 2.3 and 8.8 Hz), 3.52 (t, 1H, H_8, *J* = 9.5 Hz), 7.19 (tdd, 1H, H_{pAr}; *J* = 1.8, 6.9 and 7.1 Hz), 7.26–7.32 (m, 4H, H_{m+oAr}); ^{13}C NMR (150 MHz, CD_3OD): δ 21.9 (t, C_2), 29.5 (t, C_1), 34.7 (t, C_6), 52.4 (d, C_7), 53.0 (t, C_5), 55.2 (t, C_3), 71.6 (d, C_{8a}), 77.0 (d, C_8), 127.5 (d, C_{pAr}), 129.2 and 129.4 (d, C_{m+oAr}), 144.5 (s, C_{ipsoAr}). Anal. Calcd for $C_{14}H_{19}NO$ (217.31): C, 77.38; H, 8.81; N, 6.45. Found: C, 77.22; H, 8.68; N, 6.25.

Acknowledgments

The authors thank the Grant Agency of Slovak Republic, Grant No. 1/0161/2008, the Scientific Council of University of Le Havre (France), and the Slovak Research and Development Agency under the Contract No. APVV-0210-07 for financial support for this research program. NMR measurements were performed on the equipment supported by the Slovak State Program Project No. 2003SP200280203. The authors also thank TAU-CHEM, Ltd Company and Dr. Pavel Čepec for HPLC and GC–MS analyses.

References

1. (a) Howard, A. S.; Michael, J. P. Simple Indolizidine and Quinolizidine Alkaloids. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1986; Vol. 28, p 183; (b) Takahata, H.; Momose, T. Simple Indolizidine Alkaloids. In *The Alkaloids*; Cordell, G., Ed.; Academic Press: San Diego, 1993; Vol. 44, p 189; (c) Michael, J. P. *Nat. Prod. Rep.* **2007**, *24*, 191. and references cited therein.
2. (a) Das, P. C.; Roberts, J. D.; White, S. L.; Olden, K. *Oncol. Res.* **1995**, *7*, 425; (b) Goss, P. E.; Reid, C. L.; Bailey, D.; Dennis, J. W. *Clin. Cancer Res.* **1997**, *3*, 1077; (c) Wang, S.; Panter, K. E.; Holyoak, G. R.; Molyneux, R. J.; Lui, G.; Evans, R. C.; Bunch, T. D. *Anim. Reprod. Sci.* **1999**, *56*, 19; (d) Heihtman, T. D.; Vasella, A. T. *Angew. Chem., Int. Ed.* **1999**, *38*, 750; (e) Michael, J. P. *Nat. Prod. Rep.* **2000**, *17*, 579; (f) Lillelund, V. H.; Jensen, H. H.; Liang, X. F.; Bols, M. *Chem. Rev.* **2002**, *102*, 515; (g) Michael, J. P. *Nat. Prod. Rep.* **2003**, *20*, 458; (h) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 603. and other references cited therein; (i) deMelo, E. B.; de Silveria Gomes, A.; Carvalho, I. *Tetrahedron* **2006**, *62*, 10277.
3. For selected recent reviews in this subject, see: (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (b) Watson, A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265; (c) Asano, N. *Glycobiology* **2003**, *13*, 93R; (d) Asano, N. *Curr. Top. Med. Chem.* **2003**, *3*, 471; (e) Cipolla, L.; Ferla, B. L.; Nicotra, F. *Curr. Top. Med. Chem.* **2003**, *3*, 485; (f) Greimel, P.; Spreitz, J.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Top. Med. Chem.* **2003**, *3*, 513; (g) Schramm, V. L.; Tyler, P. C. *Curr. Top. Med. Chem.* **2003**, *3*, 525; (h) Compain, P.; Martin, O. R. *Curr. Top. Med. Chem.* **2003**, *3*, 541; (i) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Curr. Top. Med. Chem.* **2003**, *3*, 561; (j) Gerber-Lemaire, S.; Juillerat-Jeanneret, L. *Mini-Rev. Med.Chem.* **2006**, *6*, 1043.
4. (a) Daly, J. W.; Sande, T. F. In *Alkaloids: Chemical and Biological Perspectives*, Vol. 4; Pelletier, S. W., Ed.; New York; **1986**, Chapter 1.; (b) Daly, J. W. *Cell Mol. Neurobiol.* **2005**, *25*, 513.
5. (a) Hembre, E. J.; Pearson, W. H. *Tetrahedron* **1997**, *53*, 11021; (b) Pearson, W. H.; Guo, L. *Tetrahedron Lett.* **2001**, *42*, 8267; (c) Pearson, W. H.; Hembre, E. J. *Tetrahedron Lett.* **2001**, *42*, 8273; (d) Pearson, W. H.; Guo, L.; Jewell, T. M. J. *Tetrahedron Lett.* **2002**, *43*, 2175; (e) Fujita, T.; Nagasawa, H.; Uto, Y.; Hashimoto, T.; Asakawa, Y.; Hori, H. *Org. Lett.* **2004**, *6*, 827; (f) Alam, M. A.; Kumar, A.; Vankar, Y. D. *Eur. J. Org. Chem.* **2008**, 4972. and references therein; (g) Shi, G.-F.; Li, J.-Q.; Jiang, X.-P.; Cheng, Y. *Tetrahedron* **2008**, *64*, 5005.
6. (a) Mors-Varas, F.; Qian, X. H.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7647; (b) Qian, X. H.; Mors-Varas, F.; Wong, C. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1117; (c) Shih, T. L.; Yang, R. Y.; Li, S. T.; Chiang, C. F.; Lin, C. H. *J. Org. Chem.* **2007**, *72*, 4258.
7. Kadlečíková, K.; Dalla, V.; Marchalín, Š.; Decroix, B.; Baran, P. *Tetrahedron* **2005**, *61*, 4743.
8. Marchalín, Š.; Žúžiová, J.; Kadlečíková, K.; Šafář, P.; Baran, P.; Dalla, V.; Daïch, A. *Tetrahedron Lett.* **2007**, *48*, 697.
9. Šafář, P.; Žúžiová, J.; Bobošíková, M.; Marchalín, Š.; Prónayová, N.; Dalla, V.; Daïch, A. *Tetrahedron: Asymmetry* **2008**, *19*, 467.
10. (a) Daïch, A.; Decroix, B. *J. Heterocycl. Chem.* **1996**, *33*, 873; (b) Marchalín, Š.; Kadlečíková, K.; Bar, N.; Decroix, B. *Synth. Commun.* **1998**, *28*, 3619; (c) Szemes, F.; Marchalín, Š.; Bar, N.; Decroix, B. *J. Heterocycl. Chem.* **1998**, *35*, 1371; (d) Marchalín, Š.; Szemes, F.; Bar, N.; Decroix, B. *Heterocycles* **1999**, *50*, 445; (e) Szemes, F.; Kadlečíková, K.; Marchalín, Š.; Bobošíková, M.; Dalla, V.; Daïch, A. *Tetrahedron: Asymmetry* **2004**, *15*, 1763.
11. For recent syntheses of tylophorine, see: (a) Chuang, T. H.; Lee, S. J.; Yang, Ch. W.; Wu, P. L. *Org. Biomol. Chem.* **2006**, *4*, 860; (b) Fürstner, A.; Kennedy, J. W. J. *Chem. Eur. J.* **2006**, *12*, 7398; (c) Gao, W.; Bussom, S.; Grill, S. P.; Gullen, E. A.; Hu, Y. C.; Huang, X.; Zhong, S.; Kaczmarek, C.; Gutierrez, J.; Francis, S.; Baker, D. C.; Yu, S.; Cheng, Y. C. *Biorg. Med. Chem. Lett.* **2007**, *17*, 4338.
12. For representative examples using this protocol, see: (a) Badger, G. M.; Rodda, H. J.; Sasse, W. H. F. *J. Chem. Soc.* **1954**, 4162; (b) Gol'Dfarb, Y. L.; Fabrichnyi, B. P.; Shalavina, I. F. *Tetrahedron* **1961**, *18*, 21; (c) Michelliza, S.; Al-Mourabit, A.; Gateau-Olesker, A.; Marazano, C. *J. Org. Chem.* **2002**, *67*, 6474.
13. For stereoselective reduction of 2,3-disubstituted and 2,3,4,5-tetrasubstituted thiophenes, see: (a) Crenshaw, R. R.; Luke, G. M.; Jenks, T. A.; Partyka, R. A.; Bialy, G.; Bierwagen, M. E. *J. Med. Chem.* **1973**, *16*, 813; (b) Jacobi, P. A.; Frechette, R. F. *Tetrahedron Lett.* **1987**, *28*, 2937; (c) Jacobi, P. A.; Egberston, M.; Frechette, R. F.; Miao, C. K.; Weiss, K. T. *Tetrahedron* **1988**, *44*, 3327; (d) Collins, M. A.; Neville-Jones, D. *Tetrahedron Lett.* **1995**, *36*, 4467.
14. Rasmussen, M. O.; Delair, P.; Greene, A. E. *J. Org. Chem.* **2001**, *66*, 5438.
15. Full crystallographic data have been deposited to the Cambridge Crystallographic Data Center; CCDC reference number 716573 for product (7*R*,8*S*,8a*S*)-**12a**. Copies of the data can be obtained free of charge at the following address: http://www.ccdc.cam.ac.uk.
16. Podea, P. V.; Tosa, M. I.; Paizs, C. P.; Irimie, F. D. *Tetrahedron: Asymmetry* **2008**, *19*, 500.
17. (a) MaGee, D. I.; Lee, M. L.; Decken, A. *J. Org. Chem.* **1999**, *64*, 2549; (b) Ranade, V. S.; Consiglio, G.; Prins, R. *J. Org. Chem.* **1999**, *64*, 8862; (c) Ranade, V. S.; Consiglio, G.; Prins, R. *J. Org. Chem.* **2000**, *65*, 1132.