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Use of chiral-pool approach into *epi*-thieno analogues of the scarce bioactive phenanthroquinolizidine alkaloids

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ABSTRACT

The stereoselective synthesis of *epi*-thieno analogues of the phenanthroquinolizidine bioactive alkaloids (−)-Cryptopleurine and (−)-(15*R*)-Hydroxycryptopleurine was achieved in five steps starting from easily available enantiopure (*S*)-2-aminoadipic acid used as chiral pool and nitrogen atom source. During these investigations, both π-cationic cyclization of chiral *N*-thienylmethyl-6-oxopipecolinic acids into pure (*S*)-keto-lactams and theirs regioselective and diastereoselective reduction, considered as key steps of this sequence, were studied. Of particular interest, the Friedel–Crafts cyclization using $(CF_3CO)_2O/BF_3{\cdot}Et_2O$ show that near the expected keto-lactams, enamides and enamidones containing trifluoromethyl residue were isolated. A mechanism leading to the latter products with high synthetic potential was discussed.
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1. Introduction

2,3-Fused quinolizidine framework is an important motif which is found in numerous compounds among which the scarce phenanthroquinolizidines extract from three plants families.[1] The small family of pentacyclic alkaloids (Scheme 1), is represented by the bioactive (−)-Cryptopleurine (R=H, **1**),[1a] (−)-(15*R*)-Hydroxycryptopleurine (R=OH, **2**),[1a,b] Cryptopleuridine (**3**),[1c] Boehmeriasin-A (R=OMe, **4**),[1d] and Boehmeriasin-B (R=OH, **5**).[1d]

Based on the success of similar alkaloids with simpler skeleton, the phenanthroindolizidines, most of which demonstrate remarkable biological and pharmacological profiles, anticancer notably. In the light of these results, numerous efforts were undertaken to carry out quantitative structure–activity relationship (QSAR) studies (Scheme 1). The results of certain phenanthroquinolizidine derivatives show inhibitory activity in three human cancer cell lines with appreciable IC_{50} (104–130 nM),[2] the potential to treat coronavirus infection,[3] good to excellent in vivo antiviral activity against tobacco mosaic virus (TMV)[4] and anti-proliferative and selective antitumor properties.[5] While these studies were based essentially on Cryptopleurine (**1**) as the alkaloid model, the more recent Boehmeriasin-A (**4**) based compounds have shown in in vitro study anti-proliferative activity in three cancer cell lines (CEM, HeLa, and L1210) and in two endothelial cell lines (HMEC-1, BAEC) at concentration near the nanomolar range. Interestingly, during these studies, topoisomerases and SIRT2 were identified to be biological targets of these structures.[6]

Out of such considerations, the synthesis of these natural products and derivatives has been an appealing area of research. Most of the hitherto reported approaches into these types of compounds rely on a small number of strategies; the majority of which centers on the construction of the aza-six-membered ring **E** from cheap educts, which used subsequently as a chiral pool and a nitrogen atom source (Scheme 1). The ring closure of the central ring **D** proceeded then by Friedel–Crafts cyclization as pioneered by Rapoport et al.,[6,7] the Parham-type cycloacylation[8] and intramolecular aldol-type condensation.[6,9] Beyond other racemic experimental protocols[10] an alternative and interesting approach based on the construction first of chiral polycyclic systems containing piperidine-2-methanol (**A**–**D**) was also developed.[11] These key intermediates, when involved in a ring-closing metathesis afford a way to vary the nature and the size of the cycle at the end of

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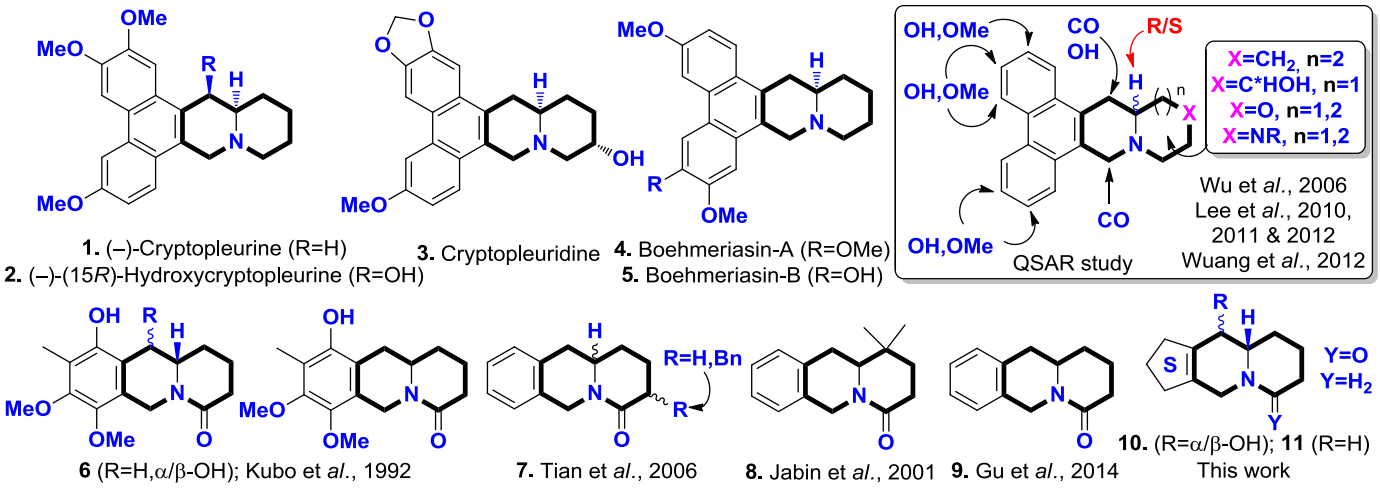


Scheme 1. Structure of the phenanthroquinolizidine alkaloids, their aromatic analogues and our targeted products **10** and **11**.

the targets enchainment **E** and are used to produce the molecular diversity.[5]

Curiously, no QSAR studies based on the modulation at the aromatic phenanthrene residue of these alkaloids have been described to this day. Along this line of reasoning, small aromatic analogues of these described phenanthroquinolizidines have been used as intermediates in the synthesis of the potent anticancer Saframycin-A (**6**)[7b] and precursors of enantiopure and non-proteogenic aromatic-δ-amino acids (**7**).[12]

Other structures, exemplified by compounds **8** and **9** were also found procreative. Their preparation is based on an imine Michael reaction followed by a radical cyclization[13] and intramolecular Schmidt reaction of acyl chlorides with alkyl azides, the last proceeding via *N*-acyliminium species as intermediates.[14]

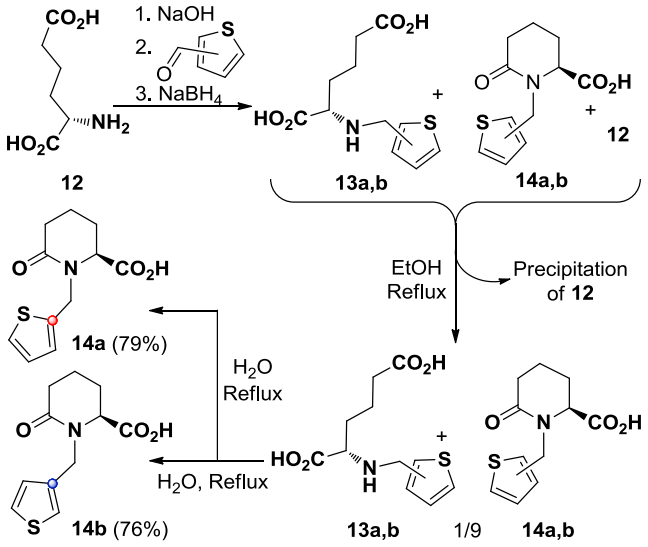
In keeping with our longstanding interest in the synthesis of indolizidinones and quinolizidinones fused to sulfur heterocyclic systems,[15] and their use for the elaboration of alkyl(or aryl) bicyclic iminosugars and their salts,[16] we herein report our findings on synthesis and properties of chiral thienoquinolizidindiones starting from chiral 6-oxopiperidine-carboxylic acid (6-oxopipecolinic acid). Their sequential stereoselective reduction led to the targeted thieno analogues of the bioactive phenanthroquinolizidine alkaloids **10** (R=OH) and **11** (R=H) (Scheme 1).

2. Results and discussion

2.1. Preparation of *N*-thienylmethyl-6-oxopipecolinic acids 14a,b

We firstly planned access to the requisite *N*-thienylmethyl-6-oxopipecolinic acids **14a**,**b** for the Rapoport cyclization by the known protocol.[7,17] This comprises *N*-reductive amination by mixing commercially available (*S*)-2-aminoadipic acid (**12**) and 2(or 3)-thienaldehyde in aqueous alkaline media (NaOH 2 M), addition of sodium borohydride to the same media, followed by intramolecular N-acylation of the resulting *N*-thienylmethyl-aminoadipic acids **13a**,**b** (Scheme 2).

The cyclization of dicarboxylic acids **13a**,**b** was performed by refluxing in ethanol for 8 h. To our surprise and contrary to the reaction profile obtained in the literature for similar sequences,[7,17] the reaction was incomplete (after cooling a small amount of unreacted (*S*)-2-aminoadipic acid (**12**) was obtained) and we observed after processing of the reaction mixture the expected carboxylic acids **14a**,**b** (in 79% and 76% isolated yields, respectively) in



Scheme 2. Synthesis scheme of oxopipecolinic acids **14a**,**b** precursors of the π-cationic cyclization.

addition to N-substituted amino acids **13a**,**b** in 9/1 ratio. Complete cyclization of **13a**,**b** to **14a**,**b** was carried out by heating in water at reflux for 4 h.

Interestingly, the structure of both carboxylic acids **14a** and **14b** was secured by an X-ray crystallographic analysis[18] (see also the ORTEP drawing of **14a**,**b** in the ESI part). Hence the possible epimerisation at the α-position of the cyclic lactam-acid under alkaline and thermal conditions can be excluded.

2.2. π-Cyclization of *N*-thienylmethyl-6-oxopipecolinic acids 14a,b

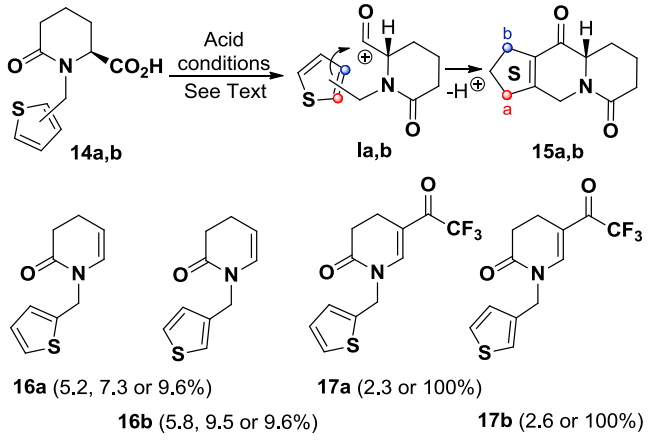
In the first set of Friedel–Crafts cyclization attempts of *N*-thienylmethyl-6-oxopipecolinic acids **14a**,**b**, standard Rapoport conditions were used.[7a] In stereospecific syntheses of the bioactive alkaloids (+)-Tylophorine and the piperidine analogue (−)-Cryptopleurine the reaction conditions were optimized. To our surprise, no reaction occurred, rather a complete polymerization of the reactants was observed under all reaction conditions tried.

Standard Rapoport conditions[7] having failed to produce the expected tricyclic keto-lactams **15a**,**b**, other cyclization conditions

of **14a**,**b** were then investigated in the hope to gain some insights in this cyclization and optimize the process for further general applications.

Thus under similar conditions (Method **A**) starting from carboxylic acid **14a**, but with $AlCl_3$ instead of $SnCl_4$ as catalyst at 10–40 °C then 0–40 °C for 2 h after the addition of the catalyst, the cyclization reaction yields the expected tricyclic product **15a** in 32% yield. Similarly, the carboxylic acid **14b** led to the keto-lactam **15b** in a yield up to 42%. The change of oxalyl chloride for thionyl chloride resulted in the erosion of the reaction yield both in the case of **15a** (29%) and **15b** (31%). It is worth mentioning that these cyclization conditions are effective in producing thienoindolizidindiones[17a,c] and benzothienoindolizidindiones[15b,19] in high yields (of ≈75%), which is absolutely not the case in the thienoquinolizidindiones series.

For the above reason, another method **B** based on the use of the combination of $(CF_3CO)_2O$ and $BF_3{\cdot}Et_2O$ to promote the Friedel–-Crafts cyclization was attempted.[20] Interestingly, under these cyclization conditions (rt, 12 days), two compounds **15a**,**b** (55.5 and 59.4%, respectively) and **16a**,**b** (7.3 and 9.6%, respectively) were detected in a better result than method **A** (Scheme 3). Similar yields of **16a**,**b** and **15a**,**b** were obtained when the reaction was carried out without solvent in clean TFAA and BF_3-etherate. In fact, when the reaction was carried out at reflux, except for keto-lactams of **15a** (53.0%), **15b** (57.3%) and enamides **16a** (5.2%) and **16b** (5.8%), unexpected trifluoroenamidones **17a**,**b** were also isolated in very low yields (Scheme 3). Under various reaction conditions the acids **14a**,**b** led in addition to ketones **15a**,**b** also to enamides **16a**,**b** with yields culminated at 9.6% in both cases; the yields of trifluoroenamidones **17a**,**b** were not affected. Apparently, **17a**,**b** are formed from **16a**,**b** at higher temperature by an independent reactions with TFAA (Scheme 4), as demonstrated experiments at 60 °C in a pressurized tube, **16a**,**b** both giving a near quantitative yield of **17a**,**b**.



Scheme 3. π-Cationic cyclization of *N*-thienylmethyl-6-oxopipecolinic acids **14a**,**b**.

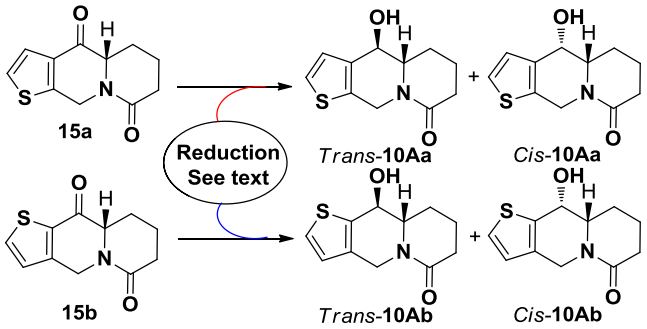
Furthermore, with polyphosphoric acid (PPA) at 100–105 °C under conditions **C**,[15,17] carboxylic acids **14a**,**b** provided the thienoquinolizidindiones **15a**,**b** as sole reaction products in yields of 41% and 52%, respectively. In addition to the best yields observed in the cyclization reaction, the latter is easy to implement, the reaction time being very short, but continuation of the reaction resulted in drastic decrease of reaction yields. Ultimately, the use of Eaton's reagent (P_2O_5/$MeSO_3H$: 1/10 w/w) at 90 °C for **14a** and 75 °C for **14b** according to the conditions **D** used by Rigo et al.,[21] afforded the cyclized products **15a** and **15b** after 1 or 1.5 h of the reaction in good yields of 71% and 78%, respectively.

The formation of the N-substituted lactams **16a**,**b** can be explained by the formation of the acylium cations **Ia**,**b**, followed by the elimination of CO and the deprotonation of the stable *N*-acyliminium species **IIa**,**b**. Trifluoroacetylen-amidones **17a**,**b** were then formed by the nucleophilic substitution reaction of the trifluoroacetic anhydride with enamides **16a**,**b** (Scheme 4).

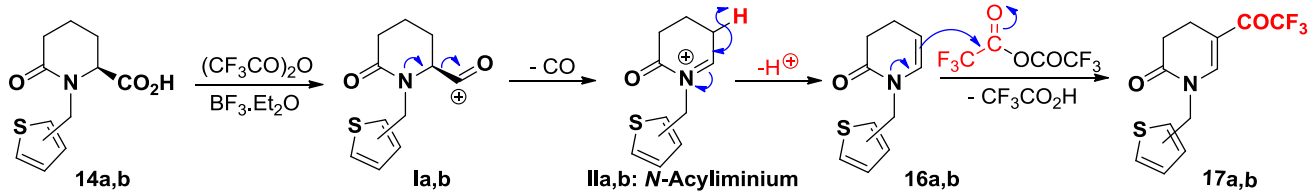
Interestingly, when the carboxylic acid **14a** was subjected to trifluoroacetic anhydride alone at 60 °C for 16 h, only keto-lactam **15a** and enamidone **17a** were isolated in 55.4% and 18.6%, respectively. Finally, the chiral integrity of the stereogenic centre during the Friedel–Crafts cyclization was secured by checking the ^1H and ^{13}C NMR spectra of the enantiopure (*S*)-**15a** and corresponding racemate (±)-**15a** in the presence of the chiral shift reagent Eu(hfc)$_3$.

2.3. Diastereoselective reduction of thienoquinolizidindiones 15a,b

According to previous reports on the stereoselective reduction of indolizidindiones containing thiophene[17a,c] or benzothiophene[19] ring into corresponding enantiopure alcohols, reduction of ketones **15a** and **15b** was examined by using a variety of hydride reagents (Scheme 5).



Scheme 5. Diastereoselective reduction of tricyclic ketones (*S*)-**15a**,**b**. Hydride reagents used are $NaBH_4$ with or without additive ($NiCl_2$, $CeCl_3$), $LiBH_4$, Red-Al, DIBAL, L-Selectride or K-Selectride at different reaction temperatures.



Scheme 4. A plausible mechanism of the formation of enamides **16a**,**b** and enamidones **17a**,**b** from carboxylic acid **14a**,**b**.

Thus, we assume that in each case the simple borohydride and aluminohydride reductions of the ketones **15a** and **15b** afforded diastereomeric mixture of alcohols *trans*-**10Aa**,**b** and *cis*-**10Aa**,**b** although *trans*-alcohols **10A** were largely favored.

It is clear that the selective reduction of the ketones **15a**,**b** with borohydride reagents reflects a preference for an axial hydride attack from the more hindered *endo* face of the tricyclic system. For instance, the $NaBH_4$ reduction at 0 °C in methanol gave a mixture of *trans*-**10Aa**,**b** and *cis*-**10Aa**,**b** diastereoisomers in the ratio of 90/10 with 73% yield for **10Aa** and 81% yield for **10Ab**. The same reaction but conducted at −80 °C, afforded a 95/5 mixture of *trans*/*cis*, while an addition of complexing agents such as $CeCl_3$ (Luche reagent) resulted in the same 95/5 ratio, thus demonstrating the ineffectiveness of the Lewis acid such as $CeCl_3$ used herein. A high diastereospecificity (*trans*/*cis*=99/1) in favor of the *trans*-**10Aa** diastereoisomer was reached when $NaBH_4$ was combined with $NiCl_2$ at −80 °C.

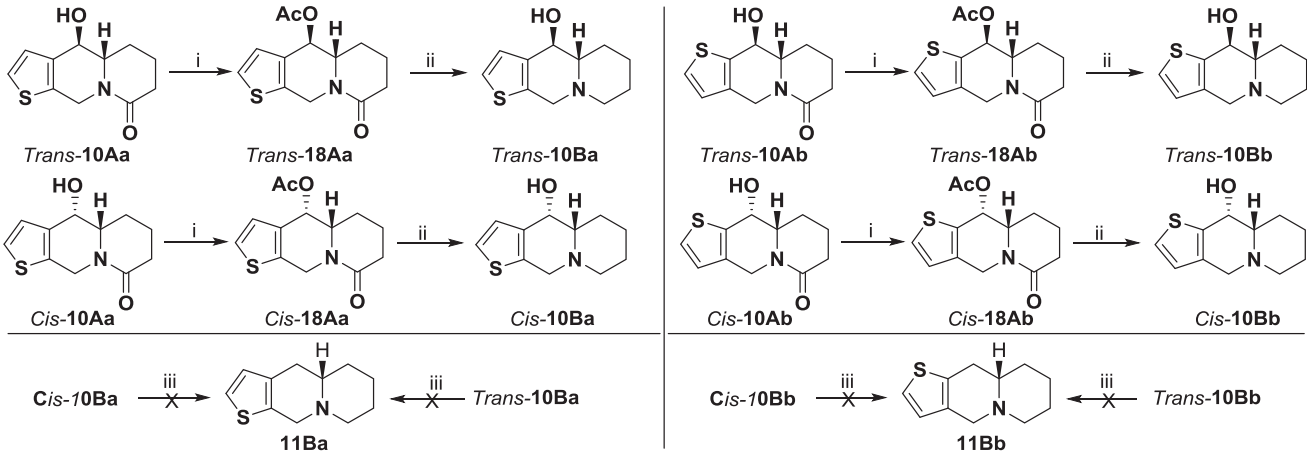
Conversely, the use of Red-Al or DIBAL at the same temperature of −75 °C gave a mixture of *trans*/*cis* diastereoisomers in the ratio of 90/10 in both cases, but in lower yields not exceeding 51% in the best case. While the stereochemistry distributions was in accord with our earlier investigations in indolizidindiones containing thiophene and benzothiophene nucleus,[15,17,19] it was significantly different with that reported by Rapoport during the synthesis of (−)-Cryptopleurine (**1**), with only one exception.[7a] The stereochemical assignments of these alcohols are based on analysis of the ^{1}H NMR spectra which show the interaction constants of J=9.3 Hz for the *trans*-isomer **10Aa** and J=9.5 for the *trans*-isomer **10Ab**.

The stereoselectivity can be reversed by using a bulkier hydride reagent that can block axial approach of the hydride to the benefit of the equatorial one, thus being more in line with the results obtained during the investigations of Rapoport.[7a] Thus, use of bulkier hydride reagents such as L-Selectride and K-Selectride solution in THF afforded alcohols *cis*-**10Aa** and *cis*-**10Ab** as major products. In both cases, the reaction conducted at −80 °C is more stereoselective (18/82 and 10/90) compared to the reaction taking place at −40 °C (29/71 and 19/81).

Ultimately, pure diastereomers *cis*-**10Aa** and *cis*-**10Ab** were isolated by simple crystallization from EtOAc in the yields of 62% and 60%, respectively. Further, the stereochemical assignments of these *cis*-alcohols are based on analysis of their ^{1}H NMR spectra which show the interaction constants for *cis*-**10Aa** isomer J=1.1 Hz and J=1.8 Hz for *cis*-**10Ab** isomer. Elsewhere, attempts to convert alcohol *trans*-**10Aa** into the expected alcohol *cis*-**10Aa** by alternative Mitsunobu inversion were unsuccessful.

2.4. Accessing the targeted thienoquinolizidinols 10 and thienoquinolizidines 11

With the ultimate objective to prepare enantiopure thieno analogues **11Ba**,**b**[15a] of the naturally occurring (−)-Cryptopleurine (**1**) and (−)-(15*R*)-Hydroxycryptopleurine (**2**), the formal reduction of lactam carbonyl group and/or OH function into corresponding alkane was envisioned as highlighted in Scheme 6.



Scheme 6. Synthesis of quinolizidinols *trans*-**10Ba**,**b** and *cis*-**10Ba**,**b**. Reagents and conditions: (i) Ac_2O, Et_3N, DAMP, CH_2Cl_2, rt, TLC. (ii) LAH, THF, reflux, 2.5 h. (iii) ET_3SiH, TFA.

In this perspective, the amido-alcohols *trans*-**10Aa**,**b** were acetylated using standard conditions (Scheme 6). Thus, reaction with acetic anhydride in the presence of dry triethylamine and catalytic amounts of DMAP led to the acetoxy derivatives *trans*-**18Aa**,**b** in yields of 74% ((4*R*,4*aS*)-**18Aa**) and 72% ((9*aS*,10*S*)-**18Ab**), respectively. The structure of *trans*-**18Ab** was learned from crystallographic analysis thus confirming the structure integrity during this transformation (See Fig. 1 for the ORTEP drawing).[22] Ultimately, these *trans*-derivatives were efficiently converted into the expected quinolizidinols *trans*-**10Ba**,**b** in good yields (71% and 74%) by using LAH reduction in refluxing THF for 1 h according to Green's protocol. The latter was developed for stereoselective synthesis of the alkaloids (−)-2-Epilentiginosine and (+)-Lentiginosine.[23] With this sequence in hand, alcohols *cis*-**10Aa**,**b** were then converted to acetoxy derivatives *cis*-**18Aa**,**b** in yields of 72% ((4*S*,4*aS*)-**18Aa**) and 71% ((9*aS*,10*R*)-**18Ab**), respectively, which finally provided quinolizidinols *cis*-**10Ba**,**b** in 71.7% and 71.5% yield, respectively.

The first attempts to remove the OH function from enantiopure *cis*- and *trans*-**10Ba**,**b** substrates with triethylsilane in TFA have failed to provide the targeted quinolizidines (*S*)-**11Ba**,**b** (Scheme 6). Taking into account these unsatisfactory results, we turned then our attention first to reduce the OH function into corresponding alkane residue in the presence of the lactam function followed by its reduction in the ultimate stage (Scheme 7).

Thus, treating of alcohols *trans*-**10Aa**,**b** with TFA in the presence of triethylsilane hydride led to the lactams **11Aa** and **11Ab** in 72% and 87% yield, respectively, after flash chromatography purification and recrystallization. Finally, the synthesis of the thieno analogues of the naturally occurring cryptopleurines **1** and **2** was achieved with LAH reduction of the lactam function in refluxing THF. The reduction reaction occurred cleanly within only 1 h to provide the optically pure title compounds (*S*)-4*a*,5,6,7,8,10-hexahydro-4*H*-

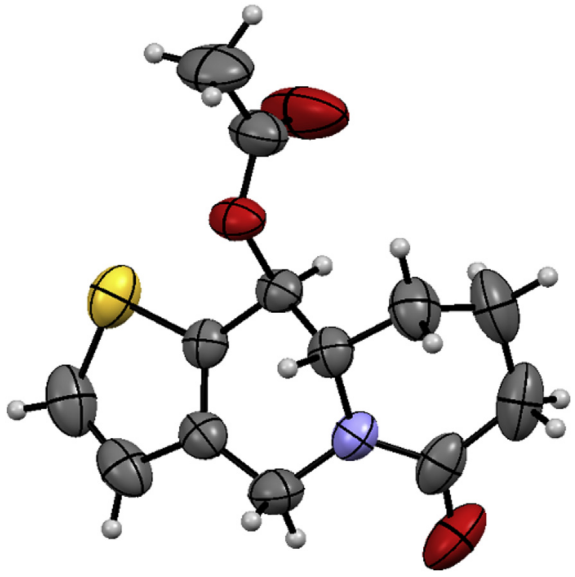
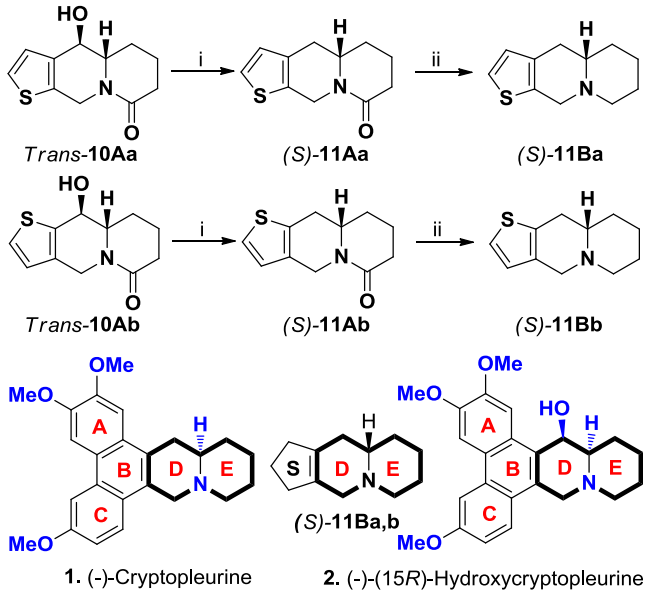


Fig. 1. ORTEP drawing of *trans*-**18Ab**.



Scheme 7. Synthesis of the targeted quinolizidines (*S*)-**11Ba**,**b**. Reagents and conditions: (i) TFA, Et_3SiH, rt, 12 h. (ii) LAH, THF, reflux, 2.5 h.

thieno[3,2-*b*]quinolizine (**11Ba**) in 65% yield and its regioisomer (*S*)-6,7,8,9,9*a*,10-hexahydro-4*H*-thieno[2,3-*b*]-quinolizine (**11Bb**) in 71% yield after recrystallization from dry *i*-hexane.

The formation of racemic thieno analogues (±)-**11Ba** and (±)-**11Bb** of the bioactive alkaloids Cryptopleurine (**1**) and Boehmeriasin-A (**4**), were reported from our laboratory in high yilelds.[24] The sequence used consisted of dehydration of thienoquinolizidinols (±)-**10Ba**,**b** in refluxing mixture of acetic acid/perchloric acid, followed by borohydride reduction of the resulting and non-isolated thienoquinol-izidinium salts.

3. Conclusions

We carried out stereoselective synthesis of *epi*-thieno analogues of the phenanthroquinolizidine bioactive alkaloids (−)-Cryptopleurine and (−)-(15*R*)-Hydroxycryptopleurine in five steps starting from available enantiopure (*S*)-2-aminoadipic acid used as chiral pool and nitrogen atom source. During these investigations, we envisaged both π-cationic cyclization of chiral *N*-thienylmethyl-6-oxopipecolinic acids into pure (*S*)-keto-lactams and their regioselective and diastereoselective reduction. The latter reductions, considered as key steps of this sequence, were investigated in order to get some insights necessary for further applications in the syntheses of these types of compounds. The overall yield of these transformations of approximately 19% in the series **a** and 27% in the series **b** outlines the higher reactivity at the C_2-position of the thiophene ring (series **a**) compared to its C_3-position (series **b**) during the important cyclization step.

In particular, during Friedel–Crafts reaction, we have shown that the protocol using Eaton's reagent is superior in terms of yields. On the other hand, the approach using the combination of $(CF_3CO)_2O/BF_3\cdot Et_2O$ is also very interesting since apart from expected keto-lactams, enamides and enamidones containing trifluoromethyl residue were isolated. A mechanism leading to the latter products, which have high synthetic potential, was discussed.

After screening of different reducing agents, the diastereoselective reduction of the ketone function of the pure tricyclic keto-lactams **15** was achieved to provide both *cis*-**10Aa**,**b** and *trans*-**10Aa**,**b** alcohol-lactams in good yields. Thienoquinolizidinols *cis*-**10Ba**,**b** and *trans*-**10Ba**,**b** were reached by lactamic carbonyl reduction in tandem with the acetate deprotection, but their transformation into the targeted *epi*-thienoquinolizidine analogues (*S*)-**11Ba**,**b** using various reducing agents failed in all attempts. However, this operation could be conducted efficaciously starting from alcohol-lactams *cis*-**10Aa**,**b** and *trans*-**10Aa**,**b** by first reducing the alcohol into enantiopure tricyclic lactams (*S*)-**11Aa**,**b** followed by their reduction at the lactamic ketone.

4. Experimental section

4.1. General remarks

Melting points were obtained using a Boetius apparatus and are corrected. Commercial reagents were used without further purification. All solvents were distilled before use. Flash column liquid chromatography (FLC) was performed on silica gel Kieselgel 60 (40–63 μm, 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). The compounds were visualized by UV fluorescence 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 (Macherey Nagel). Mobile phase: solvent A: water/acetonitrile/methanesulfonic acid (1000/25/1), solvent B: water/aceto-nitrile/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, FactorFour capillary column VF -5 ms 30mx0.25 mm ID, DF=0.25. Optical rotations were measured with a POLAR L-lP polarimeter (IBZ Messtechnik) with a water-jacketed 10.000 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. Infrared spectra were recorded on a Nicolet 5700 FTIR spectrometer as KBr discs (KBr) or as thin films on KBr plates (film). NMR spectra were recorded on an Inova 600 Varian spectrometer in $CDCl_3$. Chemical shifts (δ) are quoted in ppm and are referenced to the tetramethylsilane (TMS) as internal standard. The qCOSY, NOESY and DIFFNOE techniques were used in

assignment of $^1H-^1H$ relationships and the determination of relative configuration. The qHSQC and qHMBC techniques were used throughout for the assignment of the $^1H-^{13}C$ relationships. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt. St. Aignan, France. High-resolution spectrometry was performed on Micromass Q-Tof Micro MS system with ESI^+ ionization (measured mass represents $M+H^+$).

4.2. (*S*)-4*a*,5,6,7-Tetrahydro-4*H*-thieno[3,2-*b*]quinolizine-4,8(10*H*)-dione (15a)

4.2.1. Method A. Oxalyl chloride (1.74 mL, 2.1 mmol) was added at 10 °C to a solution of a freshly crystallized piperidine-carboxylic acid **14a** (2.39 g, 10 mmol) in dry dichloromethane (50 mL). The mixture was stirred at 40 °C for 30 min, cooled with an ice bath, and then $AlCl_3$ (3.33 g, 2.5 mmol) was added slowly by keeping temperature below 0 °C. After stirring at 20 °C for 2 h dichloromethane was added (20 mL), and then ice (20 g) and water (20 mL) were added to quench $AlCl_3$. The two phases were separated and the aqueous layer was extracted with dichloromethane (2×20 mL), then was dried with $MgSO_4$ and concentrated. The resulting crude yellow product (0.98 g, 44.3%) was purified by flash column chromatography (dichloromethane) to yield keto-lactam **15a**. Recrystallization from cyclohexane gave pure **15a** (0.71 g, 32%) as a light yellow crystal; mp 120.2–120.7 °C; $[\alpha]_D^{22}=+2.73$ (*c* 1.06, MeOH); R_f=0.53 (CH_2Cl_2/Acetone, 3/1); IR (ν, cm^{-1}, KBr): 3078, 2952, 2873, 1677, 1628, 1523, 1459, 1402, 1328, 1249, 1180, 1153, 1095, 1042, 964, 910, 889, 866, 833, 814, 739, 725, 655, 626, 612, 496, 491, 427. ^1H NMR (600 MHz, CD_3OD): δ 7.36 (s, 2H), 5.96 (d, 1H, *J*=17.4 Hz), 4.31 (t, 1H, *J*=5.9 Hz), 4.28 (d, 1H, *J*=17.5 Hz), 2.17 (dddd, 2H, *J*=13.7, 9.7, 6.0 and 3.2 Hz), 1.80 (ddt, 2H, *J*=10.5, 6.0 and 3.6 Hz), 1.76–1.69 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): δ 189.84, 171.79, 153.67, 136.62, 126.26, 125.30, 63.64, 42.13, 33.21, 23.34, 19.75. HRMS calcd for $C_{11}H_{11}NO_2S$ (221.28) $[M+1]^+$: 222.0510, found 222.0504.

4.3. (*S*)-7,8,9,9*a*-Tetrahydro-4*H*-thieno[2,3-*b*]quinolizine-6,10-dione (15b)

This product was obtained from **14b** (3.58 g, 15 mmol), oxalyl chloride (2.61 mL, 3.15 mmol) and $AlCl_3$ (5.0 g, 3.75 mmol) in the same way as for **15a**, yield 1.39 g, 42%; mp 120.5–121.4 °C, $[\alpha]_D^{22}=-3.97$ (*c* 1.0, MeOH); R_f=0.42 (CH_2Cl_2/Acetone, 3/1); IR (ν, cm^{-1}, KBr): 3124, 2962, 2860, 1670, 1636, 1537, 1447, 1427, 1414, 1326, 1314, 1237, 1213, 1172, 1095, 1020, 922, 840, 741, 629, 524, 490, 415. ^1H NMR (600 MHz, CD_3OD): δ 7.93 (d, 1H, *J*=5.0 Hz), 7.17 (d, 1H, *J*=5.0 Hz), 5.84 (d, 1H, *J*=17.3 Hz), 4.35 (t, 1H, *J*=5.8 Hz), 4.12 (d, 1H, *J*=17.3 Hz), 2.41 (tdq, 3H, *J*=17.5, 11.9 and 5.8 Hz), 2.18 (dddd, 1H, *J*=13.7, 10.0, 6.1 and 3.3 Hz), 1.80 (ddt, 1H, *J*=10.5, 6.2 and 3.7 Hz), 1.77–1.72 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD): δ 188.86, 172.01, 151.07, 137.15, 135.21, 127.51, 63.86, 43.08, 33.24, 23.47, 19.74. HRMS calcd for $C_{11}H_{11}NO_2S$ (221.28) $[M+1]^+$: 222.0510, found 222.0506.

4.4. 1-(Thien-2-ylmethyl)-3,4-dihydropyridin-2(1*H*)-one (16a) and 1-(thien-3-ylmethyl)-3,4-dihydropyridin-2(1*H*)-one (16b)

4.4.1. Method B (i, room temperature). A stirred mixture of a freshly crystallized acid **14a** (1.0 g, 4.18 mmol) and trifluoroacetic anhydride (1.2 mL, 8.35 mmol) in dry 1,2-dichloroethane (20 mL) was stirred for 45 min, then cooled with an ice bath and boron trifluoride etherate (4.75 mL, 38.4 mmol) was added. After stirring at 20 °C for 12 days under nitrogen atmosphere solvents were evaporated, then a saturated solution of K_2CO_3 in water (150 mL) was added and the mixture was stirred at room temperature for 2 h. The aqueous phase was extracted with dichloromethane; the organic phase was washed with water, dried (Na_2SO_4). Evaporation of the solution afforded a dark oil as a mixture of **15a** and **16a**, which was purified by chromatography (20 mm×30 cm, 80 g, CH_2Cl_2/acetone 20/1) on silica gel column to provide finally **16a** 59 mg (7.3%) as a light yellow oil and **15a** (510 mg, 55.5%) as a pale powder.

*4.4.2. 1-(Thien-2-ylmethyl)-3,4-dihydropyridin-2(1H)-one (**16a**).* IR (ν, cm^{-1}, KBr): 3305, 2951, 1616, 1472, 1441, 1412, 1363, 1329, 1272, 1187, 1078, 1039, 1010, 956, 849, 701, 553. ^1H NMR (600 MHz, CD_3OD): δ 7.38–7.13 (m, 1H), 6.96 (ddd, 1H, *J*=7.7, 3.6 and 1.7 Hz), 6.10 (dd, 1H, *J*=7.8 and 1.4 Hz), 5.16 (dt, 1H, *J*=8.1 and 4.2 Hz), 2.55 (t, 2 H, *J*=8.0 Hz), 2.32 (qt, 2H, *J*=6.9 and 1.9 Hz). ^{13}C NMR (150 MHz, CD_3OD): δ 169.10, 139.69, 128.89, 126.72, 126.41, 125.46, 106.74, 43.82, 31.30, 20.31. HRMS calcd for $C_{10}H_{11}NOS$ (193.27) $[M+1]^+$: 194.0561, found 194.0539.

*4.4.3. 1-(Thien-3-ylmethyl)-3,4-dihydropyridin-2(1H)-one (**16b**).* This product was obtained from **14b** (1.0 g, 4.18 mmol), trifluoroacetic anhydride (1.2 mL, 8.35 mmol) and boron trifluoride etherate (4.75 mL, 38.4 mmol) in dry 1,2-dichloroethane (20 mL) at room temperature for 12 days in the same way as for **16a**. Two compounds were isolated, **15b** (550 mg, 59.4%) and compound **16b** as light yellow oil (77.5 mg, 9.6%). IR (ν, cm^{-1}, KBr): 3305, 3097, 2949, 1613, 1471, 1441, 1410, 1329, 1268, 1229, 1170, 1077, 1013, 961, 891, 847, 830, 793, 759, 723, 694, 628, 573, 552, 481. ^1H NMR (600 MHz, CD_3OD): δ 7.29 (ddt, 1H, *J*=4.9, 3.0 and 0.4 Hz), 7.13 (1H, ddt, *J*=3.0, 1.3 and 0.8 Hz), 7.00 (ddt, 1H, *J*=4.9, 1.3 and 0.4 Hz), 6.06 (dt, 1H, *J*=7.7 and 1.6 Hz), 5.15 (dtt, 1H, *J*=7.7, 4.4 and 0.5 Hz), 4.67 (dd, 2H, *J*=0.9 and 0.4 Hz), 2.63–2.32 (m, 2H), 2.32 (dtdd, 2H, *J*=7.9, 4.4, 1.6 and 0.9 Hz). ^{13}C NMR (150 MHz, CD_3OD): δ 168.71, 137.73, 128.67, 127.14, 126.01, 122.03, 105.99, 43.83, 30.91, 19.91. HRMS calcd for $C_{10}H_{11}NOS$ (193.27) $[M+1]^+$: 194.0561, found 194.0541.

4.5. 1-(Thiophen-2-ylmethyl)-5-(2,2,2-trifluoroacetyl)-3,4-dihydropyridin-2(1*H*)-one (17a) and 1-(thiophen-3-ylmethyl)-5-(2,2,2-trifluoroacetyl)-3,4-dihydropyridin-2(1*H*)-one (17b)

4.5.1. Method B (ii, reflux). This reaction was carried out starting from carboxylic acid **14a** (1.0 g, 4.18 mmol), trifluoroacetic anhydride (1.2 mL, 8.35 mmol) and boron trifluoride etherate (4.75 mL, 38.4 mmol) in dry 1,2-dichloroethane (35 mL) at reflux for 6 h. Three compounds **17a** (27 mg, 2.3%), **16a** (42 mg, 5.2%) and **15a** (490 mg, 53.0%) were isolated from the reaction mixture via silica gel chromatography eluting with a gradient of 0–20 percent of acetone in DCM.

*4.5.2. 1-(Thiophen-2-ylmethyl)-5-(2,2,2-trifluoroacetyl)-3,4-dihydropyridin-2(1H)-one (**17a**).* This compound was isolated as colorless oil. ^1H NMR (600 MHz, $CDCl_3$): δ 7.55 (q, 1H, *J*=1.0 Hz), 7.30 (dd, 1H, *J*=5.1 and 1.3 Hz), 7.05 (ddt, 1H, *J*=3.5, 1.4 and 0.7 Hz), 6.99 (dd, 1H, *J*=5.1 and 3.5 Hz), 4.97 (d, 2H, *J*=0.8 Hz), 2.77–2.59 (m, 4H). ^{19}F NMR (600 MHz, $CDCl_3$): δ −69.89 (s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 178.22 (q, $^2J_{C,F}$=34.3 Hz, $CF_3-C=O$), 168.87, 144.92 (q, $^3J_{C,F}$=4.6 Hz), 137.32, 127.71, 127.22, 126.67, 116.66 (q, $^1J_{C,F}$=291.1 Hz, $CF_3-C=O$), 111.98, 45.35, 30.21, 18.71. HRMS calcd for $C_{12}H_{10}F_3NO_2S$ (289.27) $[M+1]^+$: 290.0384, found 290.0359.

*4.5.3. 1-(Thiophen-3-ylmethyl)-5-(2,2,2-trifluoroacetyl)-3,4-dihydropyridin-2(1H)-one (**17b**).* This product was obtained from **14b** (1.0 g, 4.18 mmol), trifluoroacetic anhydride (1.2 mL, 8.35 mmol) and boron trifluoride etherate (4.75 mL, 38.4 mmol) in dry 1,2-dichloroethane (35 mL) at reflux for 6 h. Three compounds **17b** (31 mg, 2.6%), **16b** (47 mg, 5.8%) and **15b** (530 mg, 57.3%) were isolated via silica gel chromatography eluting with a gradient of 0–20 percent of acetone in CH_2Cl_2. *1-(Thiophen-3-ylmethyl)-5-(2,2,2-trifluoro-acetyl)-3,4-dihydropyridin-2(1H)-one (**17b**).* This compound was isolated as pale yellow oil. ^1H NMR (600 MHz,

$CDCl_3$): δ 7.50 (d, 1H, *J*=1.5 Hz), 7.30 (dd, 1H, *J*=5.0 and 2.9 Hz), 7.20 (td, 1H, *J*=5.0, 2.9 and 0.8 Hz), 6.96 (dd, 1H, *J*=5.0 and 1.4 Hz), 4.78 (s, 2H), 3.10–2.27 (m, 4H). ^{19}F NMR (600 MHz, $CDCl_3$): δ −69.92 (s); ^{13}C NMR (150 MHz, $CDCl_3$): δ 177.43 (q, $^2J_{C,F}$=34.3 Hz, CF_3–C=O), 169.12, 145.42 (q, $^3J_{C,F}$=4.4 Hz), 136.06, 127.27, 126.96, 123.95, 116.66 (q, $^1J_{C,F}$=291.1 Hz, CF_3–C=O), 111.66, 45.82, 30.19, 18.68. HRMS calcd for $C_{12}H_{10}F_3NO_2S$ (289.27) $[M+1]^+$: 290.0384, found 290.0348.

4.5.4. Method B (iii, without solvent). To a stirred mixture of a freshly crystallized acid **14a** or **14b** (0.5 g, 2.09 mmol) and trifluoroacetic anhydride (3.0 mL, 20.9 mmol, 10 equiv) was added in one portion boron trifluoride etherate (2.84 mL, 23 mmol). After stirring at 20 °C for 20 h under nitrogen atmosphere the solid was filtered (^{1}H NMR indicated formation of pure ketone **15a**, 260 mg, 56.1% or **15b**, 260 mg, 56.2%), the remaining solvents were evaporated and saturated solution of K_2CO_3 in water (60 mL) added and the mixture stirred at room temperature for 10 min. The aqueous phase was extracted with dichloromethane (3×35 mL); the organic phase was washed with water, dried (Na_2SO_4). Evaporation of the solution afforded a dark oil as a mixture of **15a** and **16a** or **15b** and **16b** which was purified by chromatography (15 mm×30 cm, 80 g, CH_2Cl_2, CH_2Cl_2/acetone 20/1) on silica gel column to provide finally **16a** (39 mg, 9.7%) as a light yellow oil and **15a** (67 mg, 14.5%, total yield of **15a** was 297 mg, 70.6%) or **16b** (39 mg, 9.7%) as a colorless oil and **15b** (84 mg, 18.2%, total yield of **15b** 344 mg, 74.4%).

*4.5.5. Method B (**16a,b** to **17a,b**).* A stirred mixture of a freshly chromatographed **16a** or **16b** (250 mg, 1.29 mmol) and trifluoroacetic anhydride (2 mL, 15.18 mmol) was heated in a sealed tube at 60 °C. After stirring for 20 h sealed tube was cooled to room temperature, the solvent was evaporated, saturated solution of K_2CO_3 in water (10 mL) was added and the mixture stirred at room temperature for 10 min. The aqueous phase was extracted with dichloromethane (3×10 mL); the organic phase was washed with water, dried (Na_2SO_4). Evaporation of the solution afforded a yellow oil (310 mg), which was purified by chromatography (10 mm×30 cm, 50 g, CH_2Cl_2) on silica gel column to provide finally **17a** (299 mg, 80%) as a pale yellow oil or **17b** (310 mg, 83%) as colorless oil.

4.5.6. Method C. A mixture of freshly crystallized carboxylic acid **14a** (1.5 g, 6.27 mmol) and freshly prepared PPA (30 g) was heated at 105 °C for 45 min. The reaction mixture was cooled, neutralized with satd $NaHCO_3$ solution and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined extracts were washed with H_2O (3×30 mL), brine (30 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give crude products **15a** (0.86 g, 62%) which were purified on a small silica gel column using CH_2Cl_2 as eluent (0.69 g, 50%). Recrystallization from cyclohexane gave pure **15a** (0.56 g, 40.4%); R_f=0.52 (CH_2Cl_2/Acetone, 3/1).

4.6. Thieno[2,3-*b*]quinolizine-6,10-dione (15b)

This product was obtained from **14b** (1.5 g, 6.27 mmol) and PPA (30 g) at 110 °C for 1.5 h in the same way as for **14a**, yield 0.73 g, 52.6% (cyclohexane); R_f=0.42 (CH_2Cl_2/Acetone, 3/1).

4.6.1. Method D. A mixture of freshly prepared carboxylic acid **14a** (5.0 g, 20.9 mmol) and Eaton's reagent (P_2O_5/CH_3SO_3H/1/10 w/w) (15 mL) was heated at 90 °C for 1 h. The reaction mixture was cooled and ice (20 g) and water (80 mL) were added carefully. The aqueous phase was extracted with CH_2Cl_2 (3×60 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (50 mL), H_2O (30 mL), brine (20 mL), dried (Na_2SO_4) and evaporated under reduced pressure to give crude **15a** (4.11 g, 89%) as a yellow semi-crystalline solid which was purified on a small silica gel (120 g) column using CH_2Cl_2, CH_2Cl_2/acetone 25/1 as eluent gave pure **15a** (3.6 g, 78%). The analytically pure compound **15a** was obtained by crystallization from cyclohexane; R_f=0.52 (CH_2Cl_2/Acetone, 3/1).

4.7. Thieno[2,3-*b*]quinolizine-6,10-dione (15b)

This product was obtained from acid **14b** (5.0 g, 20.9 mmol) and Eaton's reagent (P_2O_5/CH_3SO_3H: 1/10 w/w) (30 mL) at 75 °C for 90 min in the same way as for **15a**, yield 3.28 g (71%), R_f=0.42 (CH_2Cl_2/Acetone, 3/1).

4.8. (4*R*,4a*S*)-4-Hydroxy-4*a*,5,6,7-tetrahydro-4*H*-thieno[3,2-*b*]quinolizin-8(10*H*)-one (*trans*-10Aa)

To a solution of a freshly crystallized ketone **15a** (2.21 g, 10 mmol) in methanol (80 mL) was added in a small portions sodium borohydride (0.45 g, 12 mmol) at −45 °C. The mixture was then stirred at −45 °C during 4 h, until total disappearance of starting materials was observed (TLC). The solution was carefully neutralized with concentrated HCl 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 as a mixture of two diastereomers *trans*-**10Aa** and *cis*-**10Aa** (2.13 g, 95.5%) in 9/1 ratio (from ^{1}H NMR spectra). Recrystallization from toluene gave single alcohol *trans*-**10Aa** (1.64 g, 73.5%) as colorless crystals; mp 171.6–172.4 °C (decomposition); $[\alpha]_D^{21}$=+75.2 (*c* 1.04, MeOH); R_f=0.32 (CH_2Cl_2/Acetone, 3/1); IR (ν, cm^{-1}, KBr): 3338, 3282, 3093, 2958, 2893, 1605, 1468, 1434, 1410, 1329, 1304, 1235, 1181, 1145, 1059, 1022, 951, 835, 806, 714, 672, 660, 618, 598, 581, 534, 504, 453, 414. ^{1}H NMR (600 MHz, CD_3OD): δ 7.26 (d, 1H, *J*=5.2 Hz), 7.06 (d, 1H, *J*=5.2 Hz), 5.50 (d, 1H, *J*=16.7 Hz), 4.57 (d, 1H, *J*=9.3 Hz), 4.07 (d, 1H, *J*=16.8 Hz), 3.43 (tt, 1H, *J*=8.6 and 3.7 Hz), 2.41 (t, 2H, *J*=6.3 Hz), 2.23 (ddt, 1H, *J*=13.5, 6.7 and 3.5 Hz), 2.07 (dtt, 1H, *J*=14.1, 9.9 and 4.5 Hz), 1.92 (ttd, 1H, *J*=11.2, 7.6 and 3.3 Hz), 1.82–1.72 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD): δ 172.06, 140.18, 133.38, 126.87, 124.87, 68.81, 60.86, 42.86, 33.29, 24.46, 18.13. HRMS calcd for $C_{11}H_{13}NO_2S$ (223.29) $[M+1]^+$: 224.0667, found 224.0661.

4.9. (9a*S*,10*S*)-10-Hydroxy-8,9,9*a*,10-tetrahydro-4*H*-thieno[2,3-*b*]quinolizin-6(7*H*)-one (*trans*-10Ab)

This product was obtained from freshly crystallized keto-lactam **15b** (2.21 g, 10 mmol), methanol (80 mL) and sodium borohydride (0.45 g, 12 mmol) in the same way as for 5a as a mixture of two diastereomers *trans*-**10Ab** and *cis*-**10Ab** (2.05 g, 94.4%) in 9/1 ratio (from ^{1}H NMR spectra). Yield 1.81 g (81.2%), colorless crystals (toluene); mp 190.5–191.4 °C (decomposition); $[\alpha]_D^{22}$=+ 94.2 (*c* 1.0, MeOH); R_f=0.27 (CH_2Cl_2/Acetone, 3/1); IR (ν, cm^{-1}, KBr): 3514, 3316, 3066, 2881, 2667, 1616, 1471, 1457, 1437, 1410, 1344, 1328, 1308, 1230, 1174, 1100, 1074, 1036, 1022, 987, 870, 856, 839, 800, 738, 690, 656, 632, 596, 568, 532, 504, 482. ^{1}H NMR (600 MHz, CD_3OD): δ 7.33 (dd, 1H, *J*=5.2 and 0.9 Hz), 6.83 (d, 1H, *J*=5.1 Hz), 5.37 (dd, 1H, *J*=16.7 and 1.5 Hz), 4.71 (dd, 1H, *J*=9.5 and 2.2 Hz), 3.94 (dd, 1H, *J*=16.8 and 2.3 Hz), 3.44 (ddd, 1H, *J*=9.4, 5.8 and 3.7 Hz), 2.45–2.38 (m, 2H), 2.23 (ddd, 1H, *J*=13.2, 6.5 and 3.2 Hz), 2.08 (dddd, 1H, *J*=13.8, 10.9, 5.8 and 3.4 Hz), 1.92 (ddt, 1H, *J*=14.1, 7.0 and 3.2 Hz), 1.84–1.72 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD): δ 172.31, 140.34, 133.84, 126.54, 125.40, 68.68, 61.39, 43.79, 33.29, 24.42,

18.09. HRMS calcd for $C_{11}H_{13}NO_2S$ (223.29) $[M+1]^+$: 224.0667, found 224.0658.

4.10. (4*S*,4*aS*)-4-Hydroxy-4*a*,5,6,7-tetrahydro-4*H*-thieno[3,2-*b*]quinolizin-8(10*H*)-one (*cis*-10Aa)

The freshly crystallized ketone **15a** (884 mg, 4 mmol) was dissolved in dry THF (80 mL) and cooled to −85 °C with stirring. 1 M solution of L-Selectride in THF (12 mL, 12 mmol) was added (90 min) dropwise via a syringe and the reaction mixture was stirred for 12 h at −80 °C, then was quenched with sodium hydroxide aqueous solution (1 M, 5 mL) and hydrogen peroxide (5 mL, 30% in water) at −40 °C. The reaction mixture was then stirred 1 h at 0 °C, concentrated under vacuum and extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with water, brine (2×20 mL) and dried over anhydrous $MgSO_4$. After filtration, the filtrate was concentrated in vacuo to afford a solid as a mixture of two diastereomers *trans*-**10Aa** and *cis*-**10Aa** (632 mg, 71%) in 18/82 ratio (from ^{1}H NMR spectra). Recrystallization of the solid from AcOEt (85 mL, to the 65 °C hot solution of AcOEt was added a few crystals of pure *cis*-diastereomer and during 1 h, cooled slowly to 45 °C, allowed for an additional hour at the same temperature and then cooled to 0 °C for 24 h) gave *cis*-**10Aa** (552 mg, 61%) as a colorless crystals; mp 177.5–179.1 °C; $[\alpha]_D^{23}$=+7.8 (*c* 1.06, MeOH); R_f=0.21 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3311, 3217, 3006, 2872, 2652, 1602, 1458, 1448, 1426, 1402, 1352, 1336, 1312, 1225, 1172, 1098, 1071, 1029, 1021, 983, 8762, 852, 834, 798, 732, 686, 605, 591, 562, 522, 498, 471. ^{1}H NMR (600 MHz, CD_3OD): δ 7.29 (dd, 1H, *J*=5.1 and 0.5 Hz), 7.01 (d, 1H, *J*=5.1 Hz), 5.53 (d, 1H, *J*=17.3 Hz), 4.54 (d, 1H, *J*=1.1 Hz), 4.14 (d, 1H, *J*=17.3 Hz), 3.72 (td, 1H, *J*=6.7 and 1.9 Hz), 2.43 (t, 2H, *J*=6.4 Hz), 2.21 (dddd, 1H, *J*=12.4, 9.3, 6.4 and 2.9 Hz), 2.18–2.12 (m, 1H), 2.11–1.78 (m, 1H), 1.76 (ddt, 1H, *J*=16.6, 9.7 and 3.6 Hz). ^{13}C NMR (150 MHz, CD_3OD): δ 173.67, 137.89, 135.42, 127.91, 124.89, 67.65, 58.88, 43.10, 33.61, 26.14, 19.83. HRMS calcd for $C_{11}H_{13}NO_2S$ (223.29) $[M+1]^+$: 224.0667, found 224.0659.

4.11. (9*aS*,10*R*)-10-Hydroxy-8,9,9*a*,10-tetrahydro-4*H*-thieno[2,3-*b*]quinolizin-6(7*H*)-one (*cis*-10Ab)

This product was obtained from freshly crystallized keto-lactam **15b** (1.33 g, 6 mmol), dry THF (100 mL) and L-Selectride (18 mL of a 1.0 mol dm^{-3} solution in THF) in the same way as for *cis*-10Aa as a mixture of two diastereomers and *trans*-**10Ab** and *cis*-**10Ab** (1.22 g, 91%) in 14/86 ratio (from ^{1}H NMR spectra). Recrystallization of the solid from AcOEt (120 mL) gave optically pure *cis*-**10Ab** (797 mg, 59.4%) as a colorless crystals; mp 196.8–198.5 °C (decomposition); $[\alpha]_D^{21}$=+ 27.3 (*c* 1.13, MeOH); R_f=0.24 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3313, 3086, 3066, 2887, 2841, 1615, 1472, 1457, 1437, 1410, 1344, 1329, 1308, 1262, 1230, 1174, 1101, 1074, 1035, 1022, 987, 970, 912, 901, 872, 856, 839, 800, 738, 690, 659, 631, 596, 568, 532, 504, 482, 460. ^{1}H NMR (600 MHz, CD_3OD): δ 7.38 (d, 1H, *J*=5.1 Hz), 6.87 (dd, 1H, *J*=5.2 and 0.5 Hz), 5.38 (d, 1H, *J*=17.3 Hz), 4.63 (d, 1H, *J*=1.8 Hz), 4.03 (d, 1H, *J*=17.3 Hz), 3.76 (td, 1H, *J*=6.6 and 2.2 Hz), 2.42 (t, 2H, *J*=6.4 Hz), 2.28–2.04 (m, 3H), 1.85–1.65 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD): δ 173.89, 136.55, 134.73, 127.13, 125.75, 66.98, 59.34, 44.19, 33.64, 26.33, 19.78. HRMS calcd for $C_{11}H_{13}NO_2S$ (223.29) $[M+1]^+$: 224.0667, found 224.0661.

4.12. (4*R*,4*aS*)-8-Oxo-4*a*,5,6,7,8,10-hexahydro-4*H*-thieno[3,2-*b*]quinolizin-4-yl acetate (*trans*-18Aa)

To a solution of a freshly crystallized *trans*-**10Aa** (1.56 g, 7.0 mmol) in 35 mL of dry CH_2Cl_2 was added acetic anhydride (1.43 g, 1.31 mL, 14 mmol), 4-(dimethylamino)pyridine (DMAP, 85 mg, 0.7 mmol), and triethylamine (1.42 g, 1.95 mL). The reaction mixture was stirred until disappearance of the starting material (monitored by TLC). The mixture was quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with diethyl ether and the organic layers were washed with a saturated aqueous $CuSO_4$ solution and water, dried over $MgSO_4$, and concentrated under vacuum. The yellow oil was purified by flash chromatography on silica gel column (20 mm×25 cm, 80 g, cyclohexane/CH_2Cl_2). An oil, which quickly crystallized on standing in a fridge, was obtained in the yield of 1.63 g (88%). Recrystallization from a mixture of cyclohexane/*i*-hexane (1/50) gave 1.33 g (71.6%) an analytical sample of *trans*-**18Aa**; mp 95.3–96.5 °C; $[\alpha]_D^{21}$=−22.6 (*c* 1.31, MeOH); R_f=0.53 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3101, 2947, 2877, 1731, 1635, 1454, 1413, 1373, 1333, 1233, 1178, 1141, 1022, 961, 942, 833, 787, 704, 667, 613, 521, 465, 449. ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.28 (d, 1H, *J*=5.2 Hz), 6.81 (t, 1H, *J*=5.1 Hz), 5.96 (dt, 1H, *J*=9.6 and 1.6 Hz), 5.55 (d, 1H, *J*=16.7 Hz), 4.10 (d, 1H, *J*=16.7 Hz), 3.73 (ddd, 1H, *J*=9.3, 5.8 and 3.3 Hz), 2.46–2.39 (m, 2H), 2.16 (s, CH_3), 2.09–2.00 (m, 1H), 1.98–1.88 (m, 2H), 1.77 (tdd, 1H, *J*=10.2, 7.5 and 5.3 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ 171.09, 170.54, 134.34, 133.98, 125.01, 124.02, 68.56, 56.69, 41.26, 31.71, 23.09, 19.45, 16.67. HRMS calcd for $C_{13}H_{15}NO_3S$ (265.33) $[M+1]^+$: 266.0773, found 266.0768.

4.13. (9*aS*,10*S*)-6-Oxo-6,7,8,9,9*a*,10-hexahydro-4*H*-thieno-[2,3-*b*]quinolizin-10-yl acetate (*trans*-18Ab)

This product was obtained from freshly crystallized *trans*-**10Ab** (1.56 g, 7.0 mmol), CH_2Cl_2 (40 mL), acetic anhydride (1.43 g, 1.31 mL, 14 mmol), 4-dimethylaminopyridine (DMAP, 85 mg, 0.7 mmol) and triethylamine (1.42 g, 1.95 mL) in the same way as for *trans*-**18Aa**, yield 1.37 g, 73.7% (DME/*i*-hexane 1:60), colorless crystals; R_f=0.49 (CH_2Cl_2/acetone, 3/1); mp 100.6–102.4 °C; $[\alpha]_D$=−39.6 (*c* 1.05, MeOH); IR (ν, cm^{-1}, KBr): 2941, 2844, 1734, 1645, 1458, 1434, 1414, 1366, 1339, 1245, 1222, 1177, 1101, 1017, 967, 953, 899, 839, 791, 710, 686, 617, 598, 528, 417. ^{1}H NMR (600 MHz, CD_3OD): δ 7.26 (d, 1H, *J*=5.2 Hz), 6.81 (d, 1H, *J*=5.1 Hz), 5.99 (d, 1H, *J*=9.3 Hz), 5.55 (d, 1H, *J*=16.4 Hz), 3.91 (d, 1H, *J*=16.6 Hz), 3.78–3.64 (m, 1H), 2.50 (ddd, 1H, *J*=10.8, 6.9 and 2.9 Hz), 2.47–2.40 (m, 1H), 2.18 (s, CH_3), 2.08–2.00 (m, 1H), 1.98–1.91 (m, 2H), 1.84–1.77 (m, 1H). ^{13}C NMR (150 MHz, CD_3OD): δ 170.74, 169.50, 135.21, 133.36, 126.41, 124.49, 69.07, 57.07, 42.55, 32.47, 24.13, 20.97, 17.40. HRMS calcd for $C_{13}H_{15}NO_3S$ (265.33) $[M+1]^+$: 266.0773, found 266.0766.

4.14. (4*S*,4*aS*)-8-Oxo-4,4*a*,5,7,8,10-hexahydro-6*H*-thieno[3,2-*b*]quinolizin-4-yl acetate (*cis*-18Aa)

To a solution of a freshly crystallized *cis*-**10Aa** (1.12 g, 5.0 mmol) in 35 mL of dry CH_2Cl_2 was added acetic anhydride (1.02 g, 0.94 mL, 10 mmol), 4-dimethylaminopyridine (DMAP, 61 mg, 0.5 mmol), and triethylamine (1.02 g, 1.41 mL). The reaction mixture was stirred until disappearance of the starting material (the reaction was monitored by TLC). The mixture was diluted with CH_2Cl_2 (50 mL) and quenched with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted with CH_2Cl_2 (50 mL) and the organic layers were washed with a saturated aqueous $CuSO_4$ solution, HCl (10%, 25 mL), Na_2CO_3 (25%, 30 mL) and water, dried over $MgSO_4$, and concentrated under vacuum. An oil, which quickly crystallized on standing, was obtained in the yield of (1.27 g, 96%). Recrystallization from a mixture of cyclohexane/*i*-hexane (1/50) gave 0.95 g (71.7% calculated on starting *cis*-**10Aa**) of an analytical sample of *cis*-**18Aa** as colorless crystals; R_f=0.47 (CH_2Cl_2/acetone, 3/1); mp 102.3–103.8 °C; $[\alpha]_D^{23}$=−2.65 (*c* 1.08, MeOH); IR (ν, cm^{-1}, KBr): 3446, 3246, 2952, 1732, 1635, 1624, 1436, 1416, 1372, 1365, 1304, 1224, 1167, 1142, 1064, 1036, 1017, 942, 912, 833, 738, 714, 662, 647, 615, 602, 519, 463, 433. ^{1}H NMR (600 MHz, $CDCl_3$): 7.33 (d, 1H, *J*=5.1 Hz), 6.97 (d, 1H, *J*=5.1 Hz), 5.82 (d, 1H, *J*=2.4 Hz), 5.55 (d, 1H, *J*=17.6 Hz), 4.11 (d, 1H, *J*=17.6 Hz), 3.95 (td, 1H, *J*=7.0 and 2.2 Hz),

2.83 (d, 1H, *J*=19.2 Hz), 2.35 (t, 1H, *J*=6.4 Hz), 2.11 (dtd, 1H, *J*=13.8, 6.9 and 3.4 Hz), 2.04 (s, 3H, OCH_3), 2.00 (qd, 1H, *J*=7.0 and 4.3 Hz), 1.92 (dddd, 1H, *J*=13.4, 10.3, 7.0 and 3.5 Hz), 1.74 (dtq, 1H, *J*=13.6, 6.9 and 3.7 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): 170.87, 170.25, 138.00, 133.94, 128.06, 124.65, 68.42, 56.28, 42.20, 33.53, 25.87, 20.95, 19.73. HRMS calcd for $C_{13}H_{15}NO_3S$ (265.33) $[M+1]^+$: 266.0773, found 266.0768.

4.15. (9*aS*,10*R*)-6-Oxo-6,7,8,9,9*a*,10-hexahydro-4*H*-thieno-[2,3-*b*]quinolizin-10-yl acetate (*cis*-18Ab)

This product was obtained from freshly crystallized *cis*-**11Ab** (1.56 g, 7.0 mmol), CH_2Cl_2 (45 mL), acetic anhydride (1.43 g, 1.31 mL, 14 mmol), 4-dimethylaminopyridine (DMAP, 85 mg, 0.7 mmol) and triethylamine (1.42 g, 1.95 mL) in the same way as for *cis*-**18Aa**, yield 1.33 g, (71.5%), colorless crystals; R_f=0.42 (CH_2Cl_2/acetone, 4/1); mp 162.2–163.1 °C (cyclohexane/*i*-hexane, 1/40); $[\alpha]_D^{22}$=+ 0.58 (*c* 1.12, MeOH); R_f=0.39 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3431, 3255, 3116, 3072, 2951, 1732, 1639, 1445, 1417, 1371, 1334, 1293, 1227, 1186, 1161, 1089, 1084, 1063, 1020, 954, 910, 887, 862, 794, 716, 692, 674, 644, 604, 528, 512, 457, 432. ^{1}H NMR (600 MHz, CD_3OD): δ 7.42 (d, 1H, *J*=5.2 Hz), 6.89 (d, 1H, *J*=5.2 Hz), 5.84 (d, 1H, *J*=2.2 Hz), 5.37 (d, 1H, *J*=17.4 Hz), 4.08 (d, 1H, *J*=17.4 Hz), 3.97 (td, 1H, *J*=6.8 and 2.2 Hz), 2.44 (t, 2H, *J*=6.4 Hz), 2.12 (ddt, 1H, *J*=13.8, 6.9 and 3.7 Hz), 2.08–2.01 (m, 1H), 2.06 (s, CH_3), 1.98 (ddd, 1H, *J*=9.8, 8.0 and 4.9 Hz), 1.77 (dtq, 1H, *J*=13.3, 6.7 and 3.5 Hz). ^{13}C NMR (150 MHz, CD_3OD): δ 173.55, 172.23, 136.69, 131.87, 128.84, 125.55, 68.90, 57.33, 44.09, 33.55, 26.23, 20.88, 19.67. HRMS calcd for $C_{13}H_{15}NO_3S$ (265.33) $[M+1]^+$: 266.0773, found 266.0766.

4.16. (4*R*,4*aS*)-4*a*,5,6,7,8,10-Hexahydro-4*H*-thieno[3,2-*b*]-quinolizin-4-ol (*trans*-10Ba)

Lithium aluminum hydride (0.38 g, 10 mmol) was added to a solution of a freshly crystallized acetyl thienoderivative *trans*-**18Aa** (530 mg, 2 mmol) in dry THF (20 mL) at room temperature and the mixture then heated under reflux for 2.5 h. The slurry was then warmed to ambient temperature and after an additional 40 min was carefully quenched with 2/1 w/w $NaSO_4 \cdot 10H_2O$/Celite (10 g). Gas Evolution! A dry diethyl ether (20 mL) was then added to a solution and after 30 min, the suspension was dried over $MgSO_4$ (3 g), filtered and concentrated in vacuo to give a residue (393 mg, 94%). Recrystallization of the solid twice from anhydrous *n*-hexane gave pure thienoquindolizinol *trans*-**10Ba** as a pale cream crystals (301 mg, 72%); mp 127.6–128.4 °C; $[\alpha]_D^{23}$=+31.7 (*c* 1.08, MeOH); R_f=0.16 (CH_2Cl_2:acetone, 3:1); IR (ν, cm^{-1}, KBr): 3072, 2933, 2854, 2781, 1454, 1435, 1408, 1325, 1293, 1271, 1205, 1190, 1173, 1136, 1114, 1098, 1076, 1045, 1028, 1009, 947, 847, 792, 772, 720, 692, 604, 531, 486, 436. ^{1}H NMR (600 MHz, CD_3OD): δ 7.15 (d, 1H, *J*=5.1 Hz), 6.96 (d, 1H, *J*=5.1 Hz), 4.34 (dd, 1H, *J*=8.1 and 1.5 Hz), 3.90 (d, 1H, *J*=8.1 Hz), 3.43 (d, 1H, *J*=15.0 Hz), 3.04 (d, 1H, *J*=11.5 Hz), 2.32–2.26 (m, 2H), 2.15–2.07 (m, 1H), 1.90–1.81 (m, 1H), 1.77–1.69 (m, 1H), 1.66–1.56 (m, 1H), 1.42–1.26 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): δ 137.39, 132.79, 125.51, 122.78, 70.33, 65.68, 55.46, 53.27, 29.67, 25.08, 23.50. HRMS calcd for $C_{11}H_{15}NOS$ (209.31) $[M+1]^+$: 210.0874, found 210.0868.

4.17. (9*aS*,10*S*)-6,7,8,9,9*a*,10-Hexahydro-4*H*-thieno[2,3-*b*]-quinolizin-10-ol (*trans*-10Bb)

This product was obtained from freshly crystallized acetyl derivative *trans*-**18Ab** (796 mg, 3.0 mmol) and lithium aluminum hydride (570 mg, 1.5 mmol) in dry THF (35 mL) in the same way as for *trans*-**10Aa**, yield 477 mg, 76% (1,2-dimethoxyethane), colorless crystals; mp 191.2–193.8 °C (decomposition); $[\alpha]_D^{21}$=+5.1 (*c* 1.02, MeOH); R_f=0.17 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3072, 2932, 2781, 1435, 1408, 1327, 1293, 1204, 1189, 1173, 1114, 1090, 1077, 1044, 1029, 1009, 989, 947, 847, 791, 772, 720, 692, 605, 532, 437. ^{1}H NMR (600 MHz, CD_3OD): δ 7.29 (d, 1H, *J*=5.1 Hz), 6.76 (d, 1H, *J*=5.1 Hz), 4.47 (d, 1H, *J*=8.1 Hz), 3.03 (dd, 1H, *J*=11.3 and 4.1 Hz), 3.02 (dt, 1H, *J*=14.3 and 5.3 Hz), 2.34 (dt, 1H, *J*=12.9 and 2.7 Hz), 2.29 (td, 1H, *J*=12.2 and 2.9 Hz), 2.12 (ddd, 1H, *J*=10.9, 8.2 and 3.1 Hz), 1.89–1.81 (m, 1H), 1.72 (dq, 1H, *J*=13.2 and 3.0 Hz), 1.60 (qt, 1H, *J*=12.8 and 3.7 Hz), 1.42–1.25 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): δ 139.31, 135.06, 126.04, 125.36, 71.83, 67.05, 56.83, 55.92, 30.87, 26.23, 24.70. HRMS calcd for $C_{11}H_{15}NOS$ (209.31) $[M+1]^+$: 210.0874, found 210.0866.

4.18. (4*S*,4*aS*)-4,4*a*,5,7,8,10-Hexahydro-6*H*-thieno[3,2-*b*]-quinolizin-4-ol (*cis*-10Ba)

Lithium aluminum hydride (0.323 g, 8.5 mmol) was added to a solution of a freshly crystallized acetyl derivative *cis*-**18Aa** (450 mg, 1.7 mmol) in dry THF (20 mL) at room temperature and the mixture then heated under reflux for 1.5 h. The resulting mixture was cooled and saturated NH_4Cl added cautiously until the lithium complex was destroyed. The mixture was then diluted with water (20 mL) and dichloromethane (50 mL) and stirred 2 h at 30 °C. 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 (341 mg). Recrystallization of the solid from *i*-hexane gave pure quindolizinol *cis*-**10Ba** as a *white* crystals (252 mg, 71%); mp 154.2–156.1 °C; $[\alpha]_D^{23}$=–5.86 (*c* 1.06, MeOH); R_f=0.19 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3219, 2939, 2895, 2848, 2763, 1446, 1414, 1392, 1348, 1295, 1277, 1240, 1138, 1109, 1086, 1076, 1038, 987, 974, 879, 845, 831, 775, 758, 689, 632, 578, 480, 416. ^{1}H NMR (600 MHz, CD_3OD): δ 7.21 (dd, 1H, *J*=5.1 and 0.9 Hz), 6.98 (d, 1H, *J*=5.1 Hz), 4.35 (d, 1H, *J*=2.1 Hz), 3.96 (d, 1H, *J*=15.1 Hz), 3.29 (d, 1H, *J*=15.0 Hz), 3.11 (dt, 1H, *J*=11.3, 2.7 Hz), 2.29 (dt, 1H, *J*=11.5, 3.1 Hz), 2.23 (ddd, 1H, *J*=12.6, 11.4, 2.9 Hz), 1.96–1.82 (m, 2H), 1.71–1.62 (m, 2H), 1.59 (ddd, 1H, *J*=12.9, 9.4 and 3.5 Hz), 1.42 (qt, 1H, *J*=13.0 and 3.6 Hz). ^{13}C NMR (150 MHz, CD_3OD): δ 137.91, 135.87, 128.10, 124.05, 67.14, 64.37, 57.46, 55.34, 28.65, 26.53, 25.33. HRMS calcd for $C_{11}H_{15}NOS$ (209.31) $[M+1]^+$: 210.0874, found 210.0868.

4.19. (9*aS*,10*R*)-6,7,8,9,9*a*,10-Hexahydro-4*H*-thieno[2,3-*b*]-quinolizin-10-ol (*cis*-10Bb)

This product was obtained from freshly crystallized acetyl derivative *cis*-**18Ab** (795 mg, 3.0 mmol) and lithium aluminum hydride (570 mg, 1.5 mmol) in dry THF (35 mL) in the same way as for *cis*-**18Ba**, yield 426 mg, 68% (*i*-hexane), colorless crystals; mp 161.8–163.6 °C; $[\alpha]_D^{21}$=–12.9 (*c* 1.02, MeOH); R_f=0.16 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3205, 2937, 2882, 2781, 1454, 1398, 1330, 1285, 1274, 1238, 1160, 1110, 1092, 1078, 1034, 1012, 987, 894, 847, 830, 798, 747, 723, 694, 635, 592, 582, 517, 459, 405. ^{1}H NMR (600 MHz, CD_3OD): δ 7.32 (d, 1H, *J*=5.1 Hz), 6.75 (d, 1H, *J*=5.1 Hz), 4.45 (d, 1H, *J*=2.9 Hz, OH), 3.80 (d, 1H, *J*=15.0 Hz), 3.14 (d, 1H, *J*=15.1 Hz), 3.08 (dq, 1H, *J*=11.6, 2.0 Hz), 2.34 (dt, 1H, *J*=11.5 and 3.0 Hz), 2.21 (ddd, 1H, *J*=14.3, 11.7 and 2.9 Hz), 1.96–1.79 (m, 2H), 1.69 (dq, 2H, *J*=14.1, 3.3 and 2.9 Hz), 1.61 (qt, 1H, *J*=12.9 and 3.5 Hz), 1.41 (qt, 1H, *J*=13.1 and 3.7 Hz). ^{13}C NMR (150 MHz, CD_3OD): δ 135.96, 134.53, 125.12, 124.03, 65.25, 63.36, 55.94, 55.06, 27.33, 25.02, 23.86. HRMS calcd for $C_{11}H_{15}NOS$ (209.31) $[M+1]^+$: 210.0874, found 210.0866.

4.20. (*S*)-4*a*,5,6,7-Tetrahydro-4*H*-thieno[3,2-*b*]quinolizin-8(10*H*)-one ((*S*)-11Aa)

Triethylsilane (1.3 mL, 8 mmol) was added dropwise to a stirred solution of alcohol *trans*-**10Aa** (1.17 g, 5.2 mmol) in trifluoroacetic acid (10 mL) at 0 °C. The resulting yellow solution was stirred at room temperature for 12 h. The reaction mixture was concentrated in vacuo, diluted with water (20 mL), made alkaline carefully with 10% Na_2CO_3, and extracted with dichloromethane (3×25 mL). The combined extracts were washed with water (2×15 mL), dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue (1.01 g, 93%) was purified by flash chromatography on a silica gel column eluting with dichloromethane gave a white solid (783 mg, 72%), which after recrystallization from *i*-hexane gave (*S*)-**11Aa** as a colorless crystals (680 mg, 62%); mp 101.4–102.3 °C; $[\alpha]_D^{21}$=+98.5 (*c* 1.0, MeOH); R_f=0.44 (CH_2Cl_2/acetone, 3/1); IR (*ν*, cm^{-1}, KBr): 3060, 2947, 2829, 1623, 1463, 1440, 1417, 1355, 1342, 1331, 1308, 1235, 1175, 1138, 1097, 1009, 899, 831, 750, 698, 651, 608, 651, 608, 511, 489, 472, 437. ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.22 (d, 1H, *J*=5.0 Hz), 6.79 (d, 1H, *J*=5.0 Hz), 5.34 (d, 1H, *J*=17.8 Hz), 4.00 (d, 1H, *J*=16.7 Hz), 3.78 (dd, 1H, *J*=10.2 and 5.1 Hz), 2.98–2.85 (m, 2H), 2.43 (t, 2H, *J*=6.4 Hz), 2.18 (dddd, 1H, *J*=15.2, 9.0, 5.9 and 2.8 Hz), 1.93 (dtd, 1H, *J*=13.3, 10.0, 9.3 and 6.5 Hz), 1.89–1.76 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): *δ* 172.2, 134.9, 131.8, 127.8, 124.4, 54.9, 49.4, 43.1, 33.7, 33.6, 29.4, 18.9. HRMS calcd for $C_{11}H_{13}NOS$ (207.29) $[M+1]^+$: 208.0718, found 208.0712.

4.21. (*S*)-8,9,9*a*,10-Tetrahydro-4*H*-thieno[2,3-*b*]quinolizin-6(7*H*)-one ((*S*)-11Ab)

This product was obtained from freshly crystallized alcohol *trans*-**10Ab** (1.50 g, 6.7 mmol), triethylsilane (2.2 mL, 13.5 mmol) and trifluoroacetic acid (25 mL) in the same way as for (*S*)-**11Aa**, yield 1.21 g, 87% (*n*-hexane), colorless crystals; mp 82.4–84.2 °C; $[\alpha]_D^{21}$=+29.2 (*c* 1.01, MeOH); R_f=0.38 (CH_2Cl_2/acetone, 3/1); IR (*ν*, cm^{-1}, KBr): 3255, 3086, 2945, 2850, 1633, 1574, 1461, 1445, 1434, 1411, 1334, 1303, 1285, 1364, 1234, 1175, 1152, 1092, 1082, 1020, 980, 889, 836, 751, 741, 707, 671, 654, 586, 537, 493, 461, 438. ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.21 (d, 1H, *J*=5.1 Hz), 6.82 (d, 1H, *J*=5.1 Hz), 5.34 (d, 1H, *J*=16.4 Hz), 4.00 (dd, 1H, *J*=16.8 and 2.6 Hz), 3.78 (dq, 1H, *J*=10.3 and 5.2 Hz), 2.98–2.84 (m, 2H), 2.43 (t, 2H, *J*=6.4 Hz), 2.18 (dddd, 1H, *J*=15.3, 9.0, 5.9 and 2.8 Hz), 1.94 (ddt, 1H, *J*=12.9, 6.3 and 2.8 Hz), 1.88–1.76 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): *δ* 171.1, 132.2, 131.3, 124.5, 123.2, 53.9, 42.7, 32.2, 31.5, 28.1, 17.5; HRMS calcd for $C_{11}H_{13}NOS$ (207.29) $[M+1]^+$: 208.0718, found 208.0710.

4.22. (*S*)-4*a*,5,6,7,8,10-Hexahydro-4*H*-thieno[3,2-*b*]quinolizine ((*S*)-11Ba)

Lithium aluminum hydride (0.75 g, 2 mmol) was added to a solution of the lactam (*S*)-**11Aa** (628 mg, 3 mmol) in dry THF (30 mL) at room temperature and the mixture then heated under reflux for 1 h. The resulting mixture was cooled, NH_4Cl 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 (553 mg, 89%). Recrystallization of the solid from *n*-hexane gave pure tricyclic amine (*S*)-**11Ba** as a colorless crystals (404 mg, 65%); mp 51–54 °C; $[\alpha]_D^{22}$=+110.4 (*c* 1.08, MeOH); R_f=0.23 (CH_2Cl_2/acetone, 3/1); IR (*ν*, cm^{-1}, KBr): 3377, 3113, 3084, 2928, 2850, 2762, 1566, 1444, 1402, 1342, 1289, 1242, 1185, 1132, 1110, 1075, 1031, 1017, 982, 915, 868, 833, 746, 699, 609, 521, 474, 455. ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.16 (dd, 1H, *J*=5.1, 1.0 Hz), 6.75 (d, 1H, *J*=5.0 Hz), 3.93 (dd, 1H, *J*=14.9 and 1.2 Hz), 3.39 (ddd, 1H, *J*=15.0, 3.2 and 1.7 Hz), 3.07 (dtd, 1H, *J*=11.7, 3.4 and 1.7 Hz), 2.76 (ddd, 1H, *J*=16.2, 4.4 and 1.7 Hz), 2.49 (dddd, 1H, *J*=16.4, 10.6, 2.7 and 1.3 Hz), 2.34 (tt, 1H, *J*=10.3 and 3.6 Hz), 2.25 (td, 1H, *J*=12.1 and 3.0 Hz), 1.92–1.84 (m, 1H), 1.82–1.77 (m, 1H), 1.76–1.70 (m, 1H), 1.63 (qt, 1H, *J*=14.1 and 4.0 Hz), 1.46–1.33 (m, 2H). ^{13}C NMR (150 MHz, CD_3OD): *δ* 134.38, 132.25, 127.53, 123.62, 59.49, 57.00, 55.06, 34.29, 34.15, 26.59, 25.09. HRMS calcd for $C_{11}H_{15}NS$ (193.31) $[M+1]^+$: 194.0925, found 194.0920.

4.23. (*S*)-6,7,8,9,9*a*,10-Hexahydro-4*H*-thieno[2,3-*b*]quinolizine ((*S*)-11Bb)

This product was obtained from freshly crystallized lactam (*S*)-**11Ab** (829 mg, 4 mmol) and lithium aluminum hydride (1.13 g, 3 mmol) in dry THF (40 mL) in the same way as for (*S*)-**11Ba**, yield 548 mg, 71% (*n*-hexane), colorless crystals; mp 55.6–57.8 °C; $[\alpha]_D^{23}$=+26.8 (*c*=1.05, MeOH); R_f=0.20 (CH_2Cl_2/acetone, 3/1); IR (ν, cm^{-1}, KBr): 3109, 3068, 2955, 2780, 1556, 1441, 1373, 1319, 1286, 1213, 1148, 1131, 1083, 1036, 999, 939, 838, 762, 693, 671, 622, 596, 557, 505, 469. ^{1}H NMR (600 MHz, CD_3OD): *δ* 7.14 (d, 1H, *J*=5.1 Hz), 6.74 (d, 1H, *J*=5.1 Hz), 3.85 (d, 1H, *J*=14.7 Hz), 3.24 (dd, 1H, *J*=14.9 and 2.4 Hz), 3.09–3.02 (m, 1H), 2.87 (dd, 1H, *J*=16.6 and 4.2 Hz), 2.68–2.59 (m, 1H), 2.37 (tt, 1H, *J*=7.4 and 4.0 Hz), 2.24 (td, 1H, *J*=11.9, 11.5 and 2.4 Hz), 1.90 (dt, 1H, *J*=9.6 and 3.1 Hz), 1.79 (dd, 1H, *J*=9.7 and 3.5 Hz), 1.76–1.69 (m, 1H), 1.68–1.56 (m, 1H), 1.39 (qd, 2H, *J*=12.0, 11.0 and 3.4 Hz). ^{13}C NMR (150 MHz, CD_3OD): *δ* 133.81, 133.51, 125.76, 123.84, 59.76, 56.92, 56.16, 34.19, 33.38, 26.52, 25.06. HRMS calcd for $C_{11}H_{15}NS$ (193.31) $[M+1]^+$: 194.0925, found 194.0919.

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Supplementary data

Supplementary data (Experimental procedures for the known starting carboxylic acids **14a**,**b**, ORTEP drawing of both acids, ORTEP drawing of the chiral tricyclic acetate *trans*-**18Ab** as well as copies of the ^{1}H NMR and ^{13}C NMR for all key intermediates and final products were attached as an ESI part) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2016.04.047.

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