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Highly diastereoselective approach to novel tetrahydrofuran-fused indolizidinols: a one-step formation of three contiguous stereocenters

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Abstract—A concise and very efficient route to enantiopure tetrahydrofuran-fused indolizidinols, which could be considered as protected new indolizidindiols, is described in two-steps sequence starting from the known furoindolizidindiones. The key-step of these transformations was the formation, in one operation, of THF indolizidinols containing a lactam function by simultaneous highly diastereoselective catalytic hydrogenation of the carbonyl function and the furan ring. During these investigations, numerous catalysts in different combinations were tested and the impact of substrates on the reduction profile is discussed.

1. Introduction

Indolizidine alkaloids occur widely in nature and are endowed with a wide range of potent biological activities.[1] These are exemplified by swainsonine (1,2,8-trihydroxyindolizidine) and castanospermine (1,6,7,8-tetrahydroxyindolizidine), which act mainly as glycosidase, mannosidase, and amylglycosidase inhibitors.[2] In addition, it is now well established that the number and spatial position of the hydroxyl groups determine the nature of the interaction between a particular enzyme and an iminosugar. These compounds and the related structures are also regarded as promising agents in the treatment of viral infections, cancer, and metabolic disorders, a fact that renders them valuable synthetic targets for the scientific community.[3]

Other, natural and unnatural indolizidinols and indolizidindiols are worth recording in view of the unabating interest in the therapeutic potential of polyhydroxylated indolizidines. The latter include, for example, the two (−)-indolizidin-6-ols **A1** and **A2**, their (+)-enantiomers, and their racemates.[4] An alcohol of a different kind, (1*R*,8a*S*)-indolizidinol **B**, has been designed as the biosynthetic congener of (−)-epilentiginosine and as a metabolite of the fungus *Rhizoctonia leguminicola*,[5] the locoweeds *Astragalus oxyphysus*[6] and *A. lentiginosus*.[7] Four new diols, (−)-(2*R*,8*S*,8a*S*)-indolizidine-2,8-diol **C1** and the (−)-(2*R*,8*R*,8a*S*)-, (−)-(2*R*,8*S*,8a*R*)- and (−)-(2*R*,8*R*, 8a*R*)-epimers **C2**, **C3** and **C4**, were assayed for activity against a suite of glycosidases; **C1**, **C2** and **C4** were moderately potent inhibitors of α-amylo-glycosidase, and the first two also inhibited α-glycosidase.[8]

To elaborate a new class of indolizidines with an original pharmacological profile, C_3-, C_6- and C_7-substituted analogues of swainsonine **D**, as a clinical candidate for cancer treatment were disclosed and their inhibition toward α-mannosidase first evaluated by Pearson et al. and by Nagasawa et al. (Fig. 1). During these studies, the incorporation for the first time of an hydroxymethyl, an arylalkylhydroxymethyl and a carbohydrate residue at the C_3 position[9] resulted in an increase of the α-mannosidase activity compared to that exhibited by swainsonine itself, whereas the introduction of C_6- or C_7-ethyl and benzyloxyethyl-substituents in either equatorial and axial orientations resulted in a loss of activity.[10] More recently, other structural diversity led to new 5α-substituted swainsonine analogues which were found to be more potent α-mannosidase inhibitors than swainsonine,[11] in contrast to Pearson's C_6- and C_7-substituted analogues.

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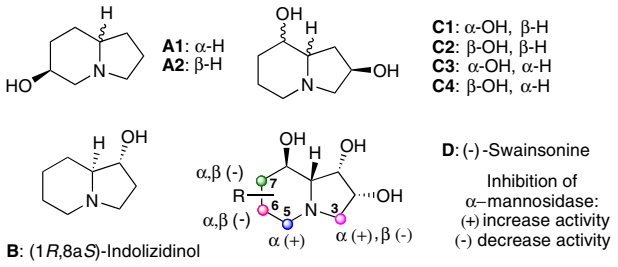


Figure 1. Representative indolizidinols **A** and **B**, indolizidindiols **C** and structural modifications of (−)-swainsonine **D**.

In light of the limitations encountered by the sugar-based methods generally used for the synthesis of these structures and taking into account the interesting biological profiles and potential of these structures as valuable candidates for novel therapeutic agents, the demand for straightforward, simple and low cost non-carbohydrate-based methods has become increasingly apparent, especially in the design of sparsely hydroxylated counterparts.

2. Results and discussion

We have previously described an effective, very convergent methodology that shortly provides ready access to enantiomerically pure tricyclic indolizidine diones **I** from (*S*)-glutamic acid.[12] We realized that such compounds, which are amenable to ready modifications at diverse positions, including the (hetero)-aromatic nucleus should constitute an attractive platform to a range of new alkyl/aryl substituted hydroxylated indolizidines.[13] An illustrative example of our most recent efforts in this direction includes the *cis*-dihydroxylation of the C_1–C_2 segment to provide concise syntheses of lentiginosine and swainsonine benzoanalogues **IIa**,**b** (Fig. 2).[14] We have also reported complementary low cost tactics based on simple, stereoselective (and stereoeconomic) hydrogenation processes that provide two-step access from ketone **I** to enantiopure 6-ethyl(or 7-ethyl-)-8-indolizidinols **IIIa** through the simultaneous creation of two stereocenters in one step. Alternatively, diastereomers **IIIb** with the inverted absolute configuration at C_8 were obtained with equal facility through reductive desulphurization of the 8*R*-alcohol, readily available in a complete

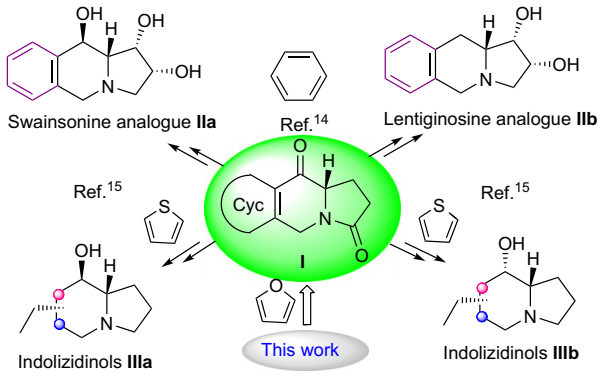
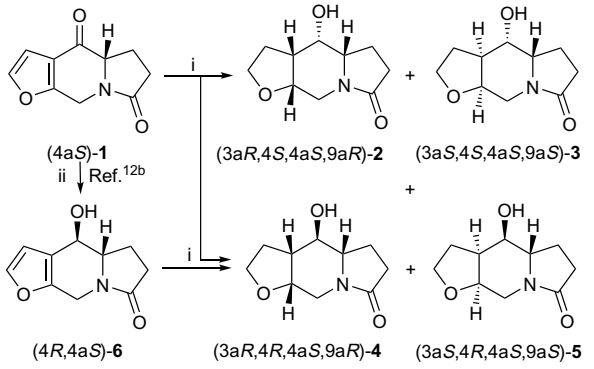


Figure 2. Fused polyhydroxyindolizidines **II** and alkylated indolizidinols **III** from ketone **I**.

stereocontrolled manner through $NaBH_4$ reduction of the tricyclic indolizidinedione **I** (Fig. 2).[15]

Pursuing these preliminary efforts, we herein report that the furan ring can also be addressed in this hydrogenation strategy in a highly efficient and stereoselective manner. The potential of this straightforward strategy for a general use in the indolizidine synthesis is illustrated by a specific application. This concerns the asymmetric synthesis of two novel enantiopure tricyclic octahydrofuroindolizinols that were produced in five steps from (*S*)-glutamic acid and with virtually complete stereocontrol of three stereogenic centers in the key hydrogenation step. Beyond their own interests as potentially pharmacological relevant candidates, these new indolizidine compounds could be regarded as precursors of more sophisticated alkyl-substituted indolizidinediols through opening of the tetrahydrofuran ring (see Scheme 1).



Scheme 1. The hydrogenation of furoindolizidine (4a*S*)-**1** and the corresponding alcohol (4*R*,4a*S*)-**6**. Reagents and condition: (i) H_2, catalyst, MeOH, reflux; (ii) $NaBH_4$, MeOH (see Ref. 12b).

The required regioisomeric furoindolizidinones **1** and **7** were readily prepared in multigram-scale and in enantiomerically pure forms in three steps from (*S*)-glutamic acid as previously described.[12b] With large quantities of **1** and **7** in hand, the stage was now set for surveying a range of conditions for their catalytic hydrogenation (Table 1). Little is known about the catalytic hydrogenation of compounds bearing a furan ring and hydrogenation of the furan ring itself. However, based on the recent disclosure of a number of papers in this area[16] documenting catalytic asymmetric processes,[17] we were confident that our project could be successfully developed.

Due to the moderate reactivity of the furan π system and the ketone function, elevated temperatures and relatively long reaction times were necessary with an operationally attractive low hydrogen pressure. All catalysts trialled in the hydrogenation of **1** gave a clean process providing the four expected 4-hydroxyoctahydrofuroindolizinones **2**–**5** as a result of the reduction of both the ketone function and the furan ring. Depending on the catalyst used, various ratios of compounds **2**–**5** were produced, the determination of which was easily established by HPLC analyses (Fig. 3). The stereochemistry of indolizidinol **4**, readily available in pure form from ketone **1** through its stereospecific reduc-

tion using $NaBH_4$ followed by hydrogenation on Pd/C of the resulting formed enantiopure alcohol **6** (see Table 1 for catalytic reduction conditions experienced) and the recrystallization from acetone, was unequivocally identified as (3a*R*,4*R*,4a*S*,9a*R*)-**4** by means of ^1H and ^{13}C NMR spectroscopy and single X-ray crystallography.[18] Structural determinations for the other diastereomers **2**, **3** and **5** were established by spectroscopic correlations by means of complementary NMR analyses, including COSY, NOESY, DIFFNOE, HSQC, HMQC, and TOCSY-1D techniques.

Table 1. The composition of diastereomers of 4-hydroxyfuro[2,3-*f*]indolizidinones in crude reaction mixture after catalytic hydrogenation of ketone **1** and the corresponding alcohol **6**

Entry	Reagent	Catalyst	Time (h)	Yield (%)	Products (%) **2**:**3**:**4**:**5**[a]
1	**1**	10% Pd/C	18	99	14:16:12:46
2	**1**	Ra-Ni	17	98	41:16:15:28
3	**1**	5% Ru/C	29	99	58:08:09:25
4	**1**[b]	5% Rh/Al_2O_3	22	82	87:04:03:06
5	**6**[c]	10% Pd/C	02	99	39:61
6	**6**	Ra-Ni	04	99	64:36
7	**6**	5% Ru/C	45	99	30:70
8	**6**	5% Rh/Al_2O_3	28	95	56:44
9	**6**	10% $Pd/CaCO_3$	04	97	53:47
10	**6**	10% $Pd/BaSO_4$	72	51	54:46
11	**6**	10% Pd/C AcOH	02	99	54:46
12	**6**	10% Pd/C NEt_3	03	99	73:27
13	**6**	10% Pd/C TMEDA	03	82	76:24

[a] Ratio of diastereomers was determined by HPLC analysis as shown in Figure 3.
[b] Major diastereomer **2** was isolated in 71% yield.
[c] Only two diastereomers **4** and **5** could be obtained from alcohol **6**.

Besides their synthetic interest, these results as well as the ensuing ones deserve the following comment regarding the mechanism. Since no products sharing a trans-relationship at the tetrahydofuran/piperidine ring junction were detected, it is assumed that both π bonds of the furan nucleus were hydrogenated simultaneously, since the involvement of a stepwise process leading to transient 2,5-dihydrofuran intermediates should have led to additional stereomers as previously observed by Liu[19] (see Fig. 4).

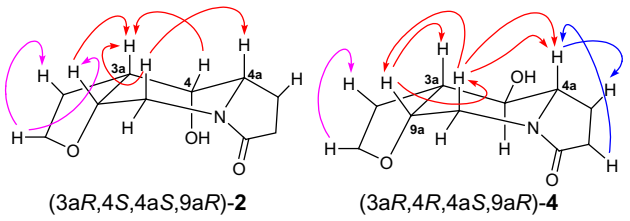


Figure 4. Selected NOEs for the determination of relative configuration in hydrogenated furoindolizidines **2** and **4**.

Except the catalysis on Pd/C (entry 1), all attempts displayed the same distribution profile favoring indolizidinols **2** and **4** (56–90% combined proportion) as the result of a preferential hydrogenation from the convex face of ketone **1**, and production of the (4*S*)-isomers **2** and **3** (57–91% combined proportion) (entries 2–4). Stereomer **2** was formed predominantly to various extents depending on the catalyst employed. Using the Rh/Al_2O_3 catalytic system furnished by far the best result giving **2** in high selectivity (entry 4). While the diastereomer ratios did not exactly match that previously obtained in the thiophene series,[15,20] the same trend resulting from inherent hydrogen approach from the *exo* (convex) face of the tricyclic skeleton was assessed. While we have no clear explanation for the spectacular effect exerted by the Rh/Al_2O_3 catalyst, this transformation clearly demonstrates, however, the synthetic advantage of catalyst-enforced induction possibilities versus strictly uniform substrate directed stereocontrol.

Encouraged by what seems to be a general feature for this class of tricyclic substrates, we then embarked on the hydrogenation study on the ancillary alcohol **6** (Table 1), readily obtained through the stereospecific $NaBH_4$ reduction of ketone **1**,[12b] in the belief that suitable conditions for the stereoselective preparation of **4** could be found. Hence, by using the same catalytic systems as above, quite different **4**/**5** distribution profiles were obtained (Table 1, entries 5–8). Unfortunately, disappointing stereoselectivities were

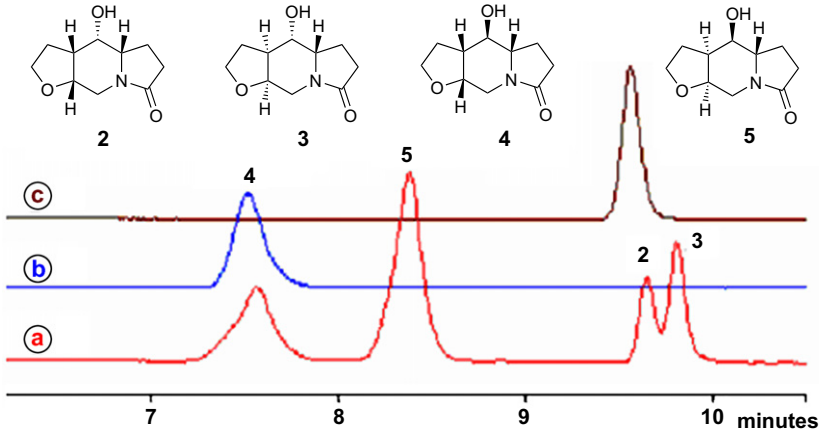
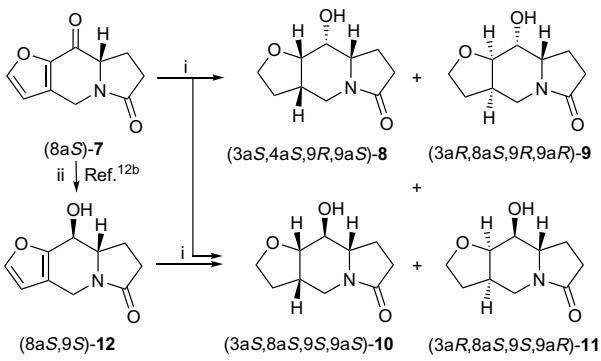


Figure 3. (a) Crude reaction mixture after hydrogenation of (4a*S*)-**1** in the presence of 10% Pd/C. (b) Isolated diastereomer (3a*R*,4*R*,4a*S*,9a*R*)-**4**. (c) Isolated diastereomer (3a*R*,4*S*,4a*S*,9a*R*)-**2**.

achieved reaching an optimal 30/70 ratio in favor of **5**. While a similar trend to the parent study was observed in the case of using a Pd/C or a Ru/C system regarding the **4/5** ratio (Table 1, entries 1, 5 and 3, 7), a reversed facial discrimination restoring the intended stereochemistry for **4** did not occur, albeit at a moderate level, when the hydrogenation was run on Ra/Ni or Rh/Al_2O_3 (Table 1, entries 2, 6 and 4, 8). While the subtle differences in reaction mechanisms may be involved with respect to the catalyst, these results roughly account for a ketone in first pathway during processing of **1** when using the two former catalysts (**4/5** ratio constant), while hydrogenation on Ra/Ni and Rh/Al_2O_3 seems to proceed through a furan first pathway (**4/5** ratio reversed), in accordance with what was proposed earlier in the thiophene series.[15] A brief solvent survey in the context of the Pd/C-catalyzed process was undertaken with the aim at improving the proportion of compound **4**. Although some significant changes in the **4/5** ratios were observed by varying the solvent from MeOH, this study did not reveal any clear preference for one or the other stereomer and a more satisfactory solution remained to be found.[21] Some efforts toward altering the Pd/C-catalyzed process were then pursued through the screening of various additives (Table 1, entries 9–13). Quite interestingly, all additives used, particularly those with a basic property, exerted a marked influence on the process by systematically reversing the original endo selectivity at the benefit to the desired *exo* one.[17,22] The best results were achieved with amines, with TMEDA giving an optimal 76:24 dr very similar to that obtained in the thiophene series, most likely due to better bonding of the partially negatively charged furan oxygen atom to the catalyst surface. It is worth noticing that even in this moderately diastereoselective reaction we were able to isolate compound **4** in a quite synthetically useful 51% yield by simple recrystallization. Overall, our ability to selectively obtain either isomers **2** or **4** by using simple and inexpensive chemistry based on $NaBH_4$ reduction and catalytic hydrogenation (component **5** cannot be obtained by applying this method) and secured them in pure forms without the need of chromatography illustrates further the stereo-complementarity and synthetic utility of this novel strategy (see Scheme 2).



Scheme 2. The hydrogenation of ketone (8a*S*)-**7** and the corresponding alcohol (8a*S*,9*S*)-**12**. Reagents and condition: (i) H_2, catalyst, MeOH, reflux; (ii) $NaBH_4$, MeOH (Ref. 12b).

To complete this study, we have also investigated the reduction of the regioisomeric ketone (8a*S*)-**7** and its hydroxyl derivative (8a*S*,9*S*)-**12** using the same catalysts as above. The reaction on **7** again took place cleanly to provide a mixture of the four tricyclic indolizidinols **8**–**11** as a result of the complete hydrogenation of the ketone function and the furan ring. As previously, the reaction could be monitored by HPLC by using the readily isolable **8**, **10** and **11** as pure standard references (Fig. 5).

In general, the diastereomer ratios were roughly comparable to those observed in the processing of ketone **1**, though some changes could be occasionally found, especially in the **10/11** versus **4/5** ratios (Table 2, entries 1 and 2 vs Table 1, entries 1 and 2). Except for the Pd/C-catalyzed process, a slightly better stereocontrol did occur regarding the *exo* face hydrogenation of the furan ring (**8** and **10** in 72–97% combined proportion versus 56–90% for **2** and **4**) and the production of the (9*R*)-isomers (**8** and **9** in 69–96% combined proportion versus 57–91% for the accordant (4*S*)-isomers **2** and **3**) (Table 2, entries 2–4 vs Table 1, entries 1–4). The Rh/Al_2O_3 catalyzed reaction even gave an outstanding selectivity with **8** being virtually the sole product formed (Table 2, entry 4). As a testament to the applicability of this reaction toward preparative scale synthesis, the hydrogenation of the keto-lactame **7** on Rh/Al_2O_3 catalyst was repeatedly performed on a one-gram scale to provide **8** in an excellent 76% isolated yield.

Having established the capacity of the enantiopure furo[3,2-*f*]indolizidindione **7** originating from furan-2-carbox-aldehyde to provide superior stereoselectivities in the catalytic hydrogenation processes, we sought to determine if this asymmetric paradigm might be extended to the related alcohol **12** (Table 2). The catalytic hydrogenations of **12** were immediately rewarded with a uniform preferential hydrogen delivery to the *exo* face of the substrate and selectivity enhancements relative to similar reactions of **6** (see the results in Table 1 for comparison purpose). The best result was obtained using Ra-Ni giving an excellent 86% de. The consistent *and unique* set of results obtained herein may be interpreted by the so called haptophilic effect, which generally causes H_2 to be added from the same side as a polar group as a hydroxyl group.[15,23] In these examples, the proximity of both the furan and the hydroxyl oxygen atoms should be the driving force favoring this phenomenon. In line with the above results, the **10/11** ratios in entries 6–8 clearly contrast with those observed from the hydrogenations of **7** and subsequently support a furan first hydrogenation mechanism for the experiments summarized in the entries 2–4 in Table 2.

As a preliminary application to these highly stereoselective hydrogenations of furo[3,2-*f*]indolizidindiones, we document the facile synthesis of two novel optically pure hydroxyindolizidines, namely (3a*R*,4*S*,4a*S*,9a*R*,)-furo[3,2-*f*]indolizidine **13** and (3a*S*,8a*S*,9*R*,9a*S*)-furo[3,2-*f*]-indolizidine **14** which were available in five steps from (*S*)-glutamic acid as a chiral source. The highly diastereoselective hydrogenation of indolizidindiones **1** and **7** catalyzed by Rh/Al_2O_3 (Scheme 3) as previously described allowed the isolation of the enantiopure hydroxyl-lactams **2** and **8** in very high yields. Finally, lactam reduction of these compounds

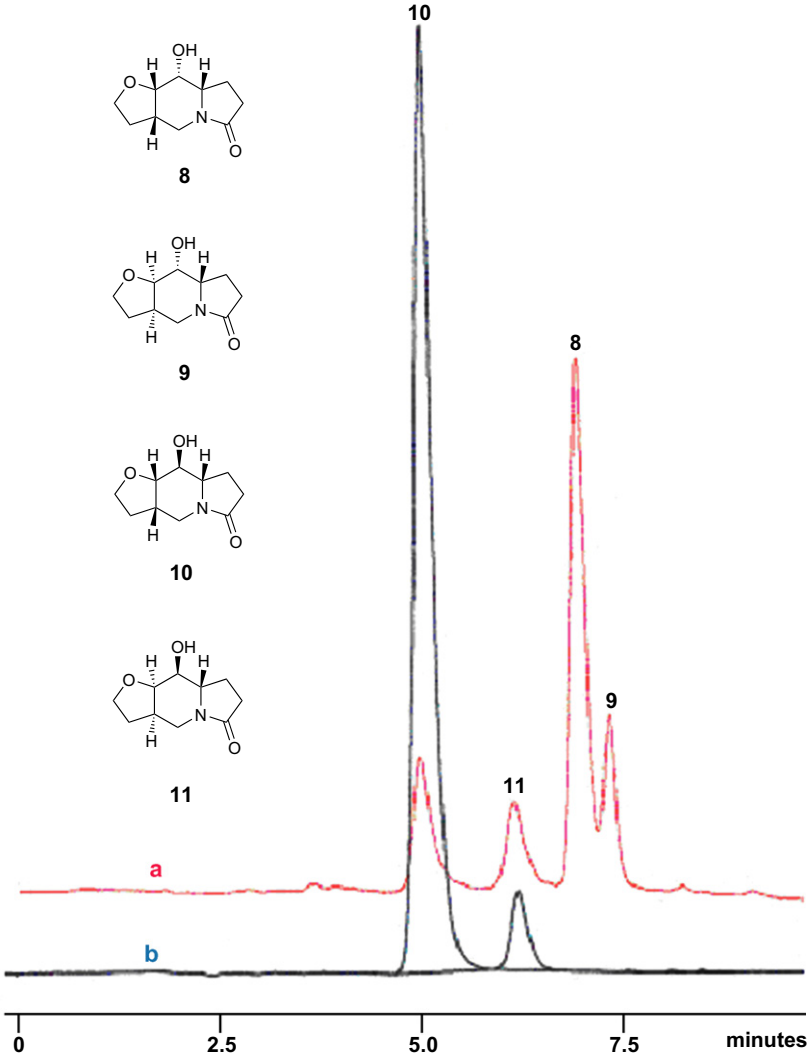
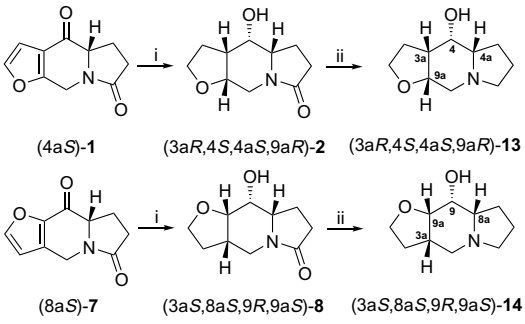


Figure 5. (a) Crude reaction mixture after hydrogenation of ketone (4a*S*)-**7** in the presence of Ra-Ni. (b) Crude reaction mixture after hydrogenation of furo[3,2-*f*]indolizindinol (8a*S*,9*S*)-**12** in the presence of Pd/C.

Table 2. The composition of diastereomers of 9-hydroxyfuro[3,2-*f*]indolizidinones in crude reaction mixture after the catalytic hydrogenation of ketone **7** and the corresponding alcohol **12**

Entry	Reagent	Catalyst	Time (h)	Yield (%)	Products (%) **8**:**9**:**10**:**11**[a]
1	**7**	10% Pd/C	01	90	12:04:63:21
2	**7**	Ra-Ni	20	99	56:16:17:11
3	**7**	5% Ru/C	46	85	60:09:12:20
4	**7**	5% Rh/Al_2O_3	46	82	96:00:01:03
5	**12**[b]	10% Pd/C	15	99	77:24
6	**12**	Ra-Ni	22	99	93:03
7	**12**	5% Ru/C	42	95	62:38
8	**12**	5% Rh/Al_2O_3	16	99	75:25

[a] Ratio of diastereomers **8**–**11** were determined by HPLC (see Supplementary data part for HPLC plot).
[b] Only diastereomers **10** and **11** could be obtained from alcohol **12**.



Scheme 3. Scheme leading to enantiopure hydroxyoctahydrofuroindolizidines **13** and **14**. Reagents and conditions: (i) H_2, 5% Rh/Al_2O_3, MeOH, 60 °C; (ii) $LiAlH_4$, THF, reflux, 4 h.

using $LiAlH_4$ readily occurred according to the protocol developed by Greene et al.[24] and already applied by our group[15] gave the targeted indolizidinols **13** and **14**. The pathways of these transformations are summarized in Scheme 3.

3. Conclusion

In conclusion, we have developed a very short and efficient route to novel enantiopure tetrahydrofuroindolizidinols, which add to the increasingly important stock of alkyl-substituted hydroxylated indolizidines. The salient features of this route includes: (1) operationally simple and low cost conditions; (2) high level of stereoselectivities; (3) cheap and modular chiral source [(*S*)- and (*R*)-glutamic acids are commercially available] as well as aldehydes in furan series needed; (4) structural modularity for further synthetic manipulations as for example, oxidation of the two carbons at the α- and β-positions to the lactam function in compound **2** and **8** followed by functionalization or opening of the furan ring. 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 and stereochemistry with promising pharmacological profiles.

4. Experimental

4.1. General

Melting points were obtained using a Boecius 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 lm, 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 (fy Macherey Nagel). Mobile phase: solvent A: water/acetonitrile/methanesulfonic acid (1000/25/1), solvent B: water/acetonitrile/methanesulfonic acid (25/1000/1), elution mode: gradient with 5–50% solvent B, flow rate: 0.65 ml/min, UV detection: 210 nm (DAD), 35 °C, 20 min. GC–MS analyses were performed on GC MS Varian Saturn 2100 T, ion trap MS detector, 70 eV. Column: Varian, Factor Four capillary column VF-5ms 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 10.000 cm cell at the wavelength of sodium line D ($\lambda = 589$ 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 FT-IR 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 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. The elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt. St. Aignan, France.

4.2. General procedure for the hydrogenation of furoindolizinones 1, 6, 7 or 12

A catalytic amount of catalyst was added to a solution of the hexahydrofuroindolizinone **1**, **6**, **7** or **12** (2.0 mmol) in dry methanol (20 mL). The solution was then stirred at 60 °C under a hydrogen atmosphere at 203 kPa for 1–46 h. After completion, the solution was filtered through a Celite pad to remove the catalyst and concentrated in vacuo. The crude product, as a mixture of diasteromeric hydroxyl-indolizidines **2**–**5** or **8**–**11**, was analyzed by HPLC, GC–MS and NMR spectroscopy.

4.2.1. (3a*R*,4*S*,4a*S*,9a*R*)-4-Hydroxyoctahydrofuro[2,3-*f*]-indolizin-7(2*H*)-one 2. This product was obtained by the hydrogenation of furoindol-izindione **1** (0.38 g, 2.0 mmol) in dry methanol (30 mL) with 5% Rh/Al_2O_3 (0.05 g) at 60 °C under 203 kPa for 22 h. After the filtration of the catalyst and the concentration of the filtrate, the residue was treated with acetone (5 mL) and the precipitate filtered off. Recrystallization from acetone gave enantiomerically pure indolizinone **2** (0.28 g, 71%) as colorless crystals; mp 165–170 °C; $[\alpha]_D = -0.6$ (*c* 1.0, EtOH); IR (*v*, cm^{-1}, KBr): 3385 (OH), 2981, 2967, 2925, 2869, 2583, 1651 (C=O), 1482, 1435, 1416; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.05–2.12 (m, 1H, H_5), 2.13–2.19 (m, 2H, H_3 and $H_{5'}$), 2.21 (ddt, 1H, $H_{3'}$; $J = 5.3$, 9.0 and 12.4 Hz), 2.28 (td, 1H, H_{3a}; $J = 3.5$ and 7.4 Hz), 2.33–2.42 (m, 2H, H_6 and OH), 2.52 (ddd, 1H, $H_{6'}$; $J = 6.0$, 10.7 and 17.0 Hz), 3.06 (dd, 1H, H_{9ax}; $J = 2.8$ and 14.9 Hz), 3.53 (d, 1H, H_4; $J = 3.4$ Hz), 3.57 (dd, 1H, H_{4a}; $J = 4.5$ and 8.3 Hz), 3.72 (t, 1H, H_{9a}; $J = 3.0$ Hz), 3.76 (ddd, 1H, H_2; $J = 5.4$, 8.8 and 10.3 Hz), 4.00 (dt, 1H, $H_{2'}$; $J = 6.2$ and 8.8 Hz), 4.49 (d, 1H, H_{9eq}; $J = 14.9$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.6 (C_5), 28.4 (C_3), 30.3 (C_6), 40.3 (C_9), 40.9 (C_{3a}), 59.9 (C_{4a}), 67.2 (C_2), 70.7 (C_4), 75.2 (C_{9a}), 175.7 (C_7); MS (*m*/*z*, (%)): 199 ([M+2]$^+$, 7), 198 ([M+1]$^+$, 70), 197 (M$^+$, 7), 180 (19), 179 (37), 169 (36), 168 (17), 154 (21), 152 (15), 151 (6), 150 (5), 139 (6), 138 (6), 136 (29), 124 (7), 113 (10), 112 (6), 110 (6), 100 (5), 99 (46), 98 (52), 97 (10), 96 (5), 86 (11), 85 (15), 84 (base). Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.81; H, 7.58; N, 6.97.

4.2.2. (3a*R*,4*R*,4a*S*,9a*R*)-4-Hydroxyoctahydrofuro[2,3-*f*]-indolizin-7(2*H*)-one 4. This product was obtained from 4-hydroxyfuroindolizinone **6** (0.39 g, 2.0 mmol) in dry methanol (30 mL), 10% Pd/C (0.05 g) and TMEDA (0.05 g) after hydrogenation at 60 °C and 203 kPa for 3 h. The catalyst was filtered through a Celite pad to remove the catalyst, washed with methanol and the filtrate concentrated to afford a solid which recrystallized from acetone to give enantiomerically pure indolizinone **4** (0.21 g, 51%) as colorless crystals; mp 171–173 °C; $[\alpha]_D = -44.8$ (*c* 1.0, EtOH); IR (*v*, cm^{-1}, KBr): 3253 (OH), 2967, 2923, 2874,

1660 (C=O), 1487, 1465, 1439, 1419; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.94 (dddd, 1H, H_5; $J = 5.1$, 7.3, 9.9 and 14.5 Hz), 2.04–2.12 (m, 2H, H_3 and H_{3a}), 2.18 (ddd, 1H, $H_{3'}$; $J = 3.8$, 8.0 and 11.6 Hz), 2.28 (tdd, 1H, $H_{5'}$; $J = 7.8$, 9.0 and 14.5 Hz), 2.35–2.46 (m, 2H, $2 \times H_6$), 2.96 (dd, 1H, H_{9ax}; $J = 2.3$ and 14.6 Hz), 3.10 (t, 1H, H_4; $J = 9.5$ Hz), 3.29 (ddd, 1H, H_{4a}; $J = 5.0$, 8.2 and 9.4 Hz), 3.38 (br s, 1H, OH), 3.85–3.93 (m, 3H, $2 \times H_2$ and H_{9a}), 4.30 (d, 1H, H_{9eq}; $J = 14.7$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.7 (C_5), 29.0 (C_3), 30.1 (C_6), 40.7 (C_9), 45.4 (C_{3a}), 60.8 (C_{4a}), 66.1 (C_2), 72.3 (C_4), 76.6 (C_{9a}), 174.9 (C_7); MS (*m*/*z*, (%)): 199 ([M+2]$^+$, 12), 198 ([M+1]$^+$, base), 197 (M$^+$, 6), 180 (14), 179 (32), 169 (23), 168 (13), 152 (8), 136 (19), 124 (5), 113 (8), 99 (25), 98 (32), 97 (11), 86 (6), 85 (14), 84 (52). Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.85; H, 7.52; N, 6.95.

4.2.3. (3a*S*,4*R*,4a*S*,9a*S*)-4-Hydroxyoctahydrofuro[2,3-*f*]-indolizin-7(2*H*)-one 5. The characteristics of this product were extracted from a spectra of two diastereomers **4** and **5** and are as following; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.86–1.93 (m, 1H, H_5), 2.04–2.12 (m, 2H, $2 \times H_3$), 2.28 (tdd, 1H, $H_{5'}$; $J = 7.8$, 9.0 and 14.5 Hz), 2.35–2.46 (m, 2H, $2 \times H_6$), 2.68 (dd, 1H, H_{9ax}; $J = 8.8$ and 13.3 Hz), 2.77 (tdd, 1H, H_{3a}; $J = 6.2$, 7.5 and 11.6 Hz), 2.92 (br s, 1H, OH), 3.50 (ddd, 1H, H_{4a}; $J = 5.3$, 7.8 and 9.6 Hz), 3.70 (dd, 1H, H_4; $J = 5.9$ and 9.8 Hz), 3.85–3.93 (m, 1H, H_2), 3.98 (dd, 1H, H_{9eq}; $J = 6.7$ and 13.3 Hz), 4.10 (dt, 1H, $H_{2'}$; $J = 2.5$ and 8.9 Hz), 4.10 (td, 1H, H_{9a}; $J = 6.9$ and 8.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.9 (C_5), 23.8 (C_3), 30.2 (C_6), 39.9 (C_9), 44.6 (C_{3a}), 56.3 (C_{4a}), 67.4 (C_2), 71.3 (C_4), 73.9 (C_{9a}), 174.3 (C_7).

4.2.4. (3a*S*,8a*S*,9*R*,9a*S*)-9-Hydroxyoctahydrofuro[3,2-*f*]-indolizin-6(2*H*)-one 8. This product was obtained by the hydrogenation of furoindolizindione **7** (0.38 g, 80%) in dry methanol (30 mL) with 5% Rh on Al_2O_3 (0.045 g) at 60 °C and 203 kPa for 46 h. The catalyst was filtered through a short column of Celite pad, washed twice with methanol (5 mL) and the filtrate concentrated under reduced pressure to afford a solid, which recrystallized from acetone to give enantiomerically pure indolizinone **4** (0.30 g, 76%) as colorless crystals; mp 183–185 °C; $[\alpha]_D = -31.8$ (*c* 1.0, EtOH); IR (*v*, cm^{-1}, KBr): 3223 (OH), 2980, 2938, 2894, 1659, 1639 (C=O), 1485, 1473, 1444, 1422, 1367, 1358; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.90–1.99 (m, 1H, H_3), 1.97–2.02 (m, 1H, H_3), 2.07–2.15 (m, 1H, H_8), 2.17 (ddd, 1H, $H_{8'}$; $J = 4.7$, 8.6 and 13.9 Hz), 2.32–2.44 (m, 2H, H_7 and H_{3a}), 2.57 (ddd, 1H, $H_{7'}$; $J = 7.1$, 10.1 and 17.0 Hz), 2.87 (br s, 1H, OH), 3.19 (dd, 1H, H_{4ax}; $J = 5.9$ and 13.7 Hz), 3.56 (ddd, 1H, H_{8a}; $J = 1.3$, 3.9 and 8.5 Hz), 3.83 (td, 1H, H_2; $J = 8.0$ and 8.3 Hz), 3.86 (dd, 1H, H_9; $J = 1.0$ and 3.1 Hz), 4.00 (dd, 1H, H_{4eq}; $J = 3.3$ and 13.6 Hz), 4.06 (dd, 1H, H_{9a}; $J = 4.7$ and 7.7 Hz), 4.10 (dt, 1H, $H_{2'}$; $J = 2.3$ and 8.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 20.2 (C_8), 30.5 (C_3), 30.7 (C_7), 36.0 (C_{3a}), 38.6 (C_4), 57.4 (C_{8a}), 69.2 (C_2), 69.4 (C_9), 77.2 (C_{9a}), 175.4 (C_6); MS (*m*/*z*, (%)): 199 ([M+2]$^+$, 9), 198 ([M+1]$^+$, 80), 197 (M$^+$, 6), 180 (18), 179 (5), 178 (9), 168 (13), 155 (9), 154 (base), 152 (8), 151 (15), 150 (10), 136 (10), 134 (6), 124 (5), 122 (7), 114 (6), 112 (6), 110 (7), 99 (10), 98 (33), 97 (19), 96 (7), 86 (6), 85 (5), 84 (24). Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.79; H, 7.54; N, 6.99.

4.2.5. (8a*S*,9*S*)-9-Hydroxyoctahydro[3,2-*f*]indolizin-6(2*H*)-ones 10 and 11. These products were isolated by the hydrogenation of 9-hydroxyfuroindolizinone **12** (0.39 g, 2.0 mmol) in dry methanol (30 mL) with 5% Rh on Al_2O_3 (0.04 g) at 60 °C and 203 kPa for 16 h. The obtained residue (after successive filtration of the solution through a Celite pad, washing with methanol and concentration in vacuo), was treated with acetone (10 mL) and the precipitate was filtered off. The filtrate was subjected to the same procedure for 3 times and finally concentrated in vacuo. The resulting crystals were collected and recrystallized from acetone to furnish optically pure indolizinone (minor diastereomer) **11** (0.035 g, 9%) as colorless crystals. Ultimately, the filtrates were collected and evaporated in vacuo to give the major diastereomer **10** as a thick colorless oil in 63% yield (m = 0.25 g).

4.2.6. (3a*S*,8a*S*,9*S*,9a*S*)-9-Hydroxyoctahydro[3,2-*f*]-indolizin-6(2*H*)-one 10. $[\alpha]_D = -35.6$ (*c* 1.0, EtOH); IR (*v*, cm^{-1}, KBr): 3373 (OH), 2887, 1769, 1667 (C=O), 1460, 1447, 1423, 1371, 1281; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.73 (tt, 1H, H_3; $J = 9.5$ and 12.3 Hz), 1.97 (dddd, 1H, H_8; $J = 4.5$, 7.1, 9.8 and 12.8 Hz), 2.03 (dtd, 1H, $H_{3'}$; $J = 2.6$, 7.7 and 12.5 Hz), 2.27 (tdd, 1H, $H_{8'}$; $J = 7.6$, 9.1 and 13.2 Hz), 2.42–2.48 (m, 2H, $2 \times H_7$), 2.49 (tdd, 1H, H_{3a}; $J = 5.1$, 7.0 and 12.1 Hz), 2.73 (br s, 1H, OH), 3.07 (dd, 1H, H_{4ax}; $J = 5.0$ and 14.0 Hz), 3.23 (dd, 1H, H_9; $J = 7.9$ and 10.0 Hz), 3.29 (ddd, 1H, H_{8a}; $J = 4.5$, 7.9 and 10.1 Hz), 3.89 (t, 1H, H_{9a}; $J = 7.7$ Hz), 3.92 (dd, 1H, H_2; $J = 7.7$ and 9.2 Hz), 3.99 (dt, 1H, $H_{2'}$; $J = 2.6$ and 9.2 Hz), 4.15 (d, 1H, H_{4eq}; $J = 13.9$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1 (C_8), 28.4 (C_3), 29.9 (C_7), 38.1 (C_{3a}), 38.3 (C_4), 58.7 (C_{8a}), 66.9 (C_2), 73.0 (C_9), 82.6 (C_{9a}), 174.9 (C_6); MS (*m*/*z*, (%)): 199 ([M+2]$^+$, 8), 198 ([M+1]$^+$, 66), 197 (M$^+$, 4), 196 (5), 180 (19), 179 (8), 178 (8), 168 (14), 166 (6), 155 (9), 154 (base), 152 (7), 151 (14), 150 (9), 148 (5), 136 (11), 134 (5), 124 (5), 122 (5), 114 (6), 112 (7), 110 (6), 99 (8), 98 (29), 97 (15), 96 (7), 86 (5), 84 (21). Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23): C, 60.90; H, 7.67; N, 7.10. Found: C, 60.73; H, 7.46; N, 6.85.

4.2.7. (3a*R*,8a*S*,9*S*,9a*R*)-9-Hydroxyoctahydro[3,2-*f*]-indolizin-6(2*H*)-one 11. This product melted at 190–193 °C; $[\alpha]_D = -17.8$ (*c* 1.0, EtOH); IR (*v*, cm^{-1}, KBr): 3449 (OH), 2951, 2923, 2867, 1681 (C=O), 1639, 1452, 1473, 1439, 1427, 1370, 1262; ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.75 (ddd, 1H, H_3; $J = 3.4$, 7.7 and 12.8 Hz), 1.92–1.99 (m, 1H, H_8), 2.05–2.13 (m, 1H, $H_{3'}$), 2.29 (qd, 1H, $H_{8'}$; $J = 8.2$ and 13.3 Hz), 2.35–2.47 (m, 4H, $2 \times H_7$, H_{4ax} and H_{3a}), 3.42 (dd, 1H, H_9; $J = 3.0$ and 9.7 Hz), 3.51 (ddd, 1H, H_{8a}; $J = 4.7$, 8.1 and 9.7 Hz), 3.93 (dt, 1H, H_2; $J = 3.4$ and 9.2 Hz), 3.96–4.02 (m, 2H, H_{9a} and H_{4eq}), 4.04 (q, 1H, $H_{2'}$; $J = 8.3$ Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.4 (C_8), 29.7 (C_3), 30.0 (C_7), 37.2 (C_{3a}), 38.9 (C_4), 56.5 (C_{8a}), 66.1 (C_2), 72.6 (C_9), 79.6 (C_{9a}), 173.7 (C_6); MS (*m*/*z*, (%)): 199 ([M+2]$^+$, 10), 198 ([M+1]$^+$, 82), 197 (M$^+$, 3), 196 (6), 181 (5), 180 (48), 179 (58), 178 (34), 169 (7), 168 (23), 166 (12), 155 (10), 154 (base), 152 (17), 151 (70), 150 (30), 148 (15), 141 (5), 138 (9), 137 (5), 136 (26), 135

(13), 134 (14), 126 (7), 125 (5), 124 (13), 123 (9), 122 (14), 114 (8), 113 (6), 112 (10), 110 (12), 99 (17), 98 (47), 97 (32), 96 (18), 95 (6), 86 (7), 85 (11), 84 (40). Anal. Calcd for $C_{10}H_{15}NO_3$ (197.23) C, 60.90; H, 7.67; N, 7.10. Found: C, 60.81; H, 7.57; N, 7.01.

4.3. (3a*R*,4*S*,4a*S*,9a*R*)-4-Hydroxyoctahydrofuro[2,3-*f*]-indolizine 13

To a suspension of 300 mg of $LiAlH_4$ (8.0 mmol) in THF (30 mL), 4-hydroxyfuroindolizinone **2** (0.39 g, 2.0 mmol) was added slowly at room temperature. The mixture was refluxed for 3 h, cooled to 5 °C and carefully treated with water (20 mL). The resulting mixture was stirred again for 1 h, filtered and the crude product was isolated with dichloromethane in the usual way. This gave enantiomerically pure indolizidine **13** as a colorless thick oil in 81% yield (0,30 g); $[\alpha]_D = +181$ (*c* 1.0, MeOH); IR (*v*, cm^{-1}, KBr): 3497 (OH), 2968, 2945, 2924, 2872, 2792, 1461, 1444, 1410; ^1H NMR (600 MHz, $CDCl_3$): δ 1.70–1.82 (m, 3H, $2 \times H_6$ and H_5), 1.88–1.97 (m, 1H, H_5), 2.05–2.14 (m, 3H, H_3, H_{3a} and H_{4a}), 2.14–2.20 (m, 2H, H_{7ax} and OH), 2.21 (ddd, 1H, H_3; $J = 4.8$, 9.0 and 10.8 Hz), 2.35 (d, 1H, H_{9ax}; $J = 12.6$ Hz), 3.09 (t, 1H, H_{7eq}; $J = 8.1$ Hz), 3.42 (d, 1H, H_{9eq}; $J = 12.6$ Hz), 3.54 (d, 1H, H_4; $J = 2.4$ Hz), 3.75–3.81 (m, 2H, H_{9a} and H_2), 4.04 (dt, 1H, $H_{2'}$; $J = 6.9$ and 8.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.8 (C_6), 24.9 (C_5), 28.5 (C_3), 42.1 (C_{3a}), 53.9 (C_9), 54.4 (C_7), 66.5 (C_{4a}), 67.6 (C_2), 68.6 (C_4), 76.7 (C_{9a}). Anal. Calcd for $C_{10}H_{17}NO_2$ (183.13): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.29; H, 9.11; N, 7.40.

4.4. (3a*S*,8a*S*,9*R*,9a*S*)-9-Hydroxyoctahydrofuro[2,3-*f*]-indolizine 14

In the same manner as above, the reduction of 9-hydroxyfuroindolizinone **8** (0.39 g, 2.0 mmol) gave enantiomerically pure indolizidine **14** after recrystallization from *n*-heptane (0.28 g, 77%) as colorless crystals; mp 116–119 °C; $[\alpha]_D = +34.0$ (*c* 1.0, EtOH); IR (*v*, cm^{-1}, KBr): 3382 (OH), 3076, 2961, 2889, 2869, 2727, 1481, 1456, 1446, 1380; ^1H NMR (600 MHz, $CDCl_3$): δ 1.73–1.80 (m, 2H, H-7 and H_8), 1.81–1.88 (m, 1H, $H_{7'}$), 1.92–2.02 (m, 2H, H_3 and H_8), 2.04 (tt, 1H, $H_{3'}$; $J = 9.8$ and 10.9 Hz), 2.16 (t, 1H, H_{8a}; $J = 7.8$ Hz), 2.24 (q, 1H, H_6; $J = 8.4$ Hz), 2.39–2.46 (m, 2H, H_{3a} and H_{4ax}), 2.54 (d, 1H, OH; $J = 6.0$ Hz), 2.99 (dt, 1H, $H_{6'}$; $J = 2.3$ and 8.6 Hz), 3.14 (td, 1H, H_{4eq}; $J = 4.6$ and 9.3 Hz), 3.86 (ddd, 1H, H_2; $J = 7.0$, 7.8 and 10.0 Hz), 3.89 (dd, 1H, H_{9a}; $J = 4.4$ and 7.6 Hz) 4.21 (dt, 1H, $H_{2'}$; $J = 2.1$ and 8.9 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.6 (C_7), 25.1 (C_8), 31.2 (C_3), 37.7 (C_{3a}), 52.1 (C_4), 54.8 (C_6), 64.3 (C_{8a}), 68.9 (C_9), 69.3 (C_2), 78.6 (C_{9a}). Anal. Calcd for $C_{10}H_{17}NO_2$ (183.13): C, 65.54; H, 9.35; N, 7.64. Found: C, 65.41; H, 9.26; N, 7.51.

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