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Synthesis of 1,2-Dihydroxyindolizidines from 1-(2-Pyridyl)-2-propen-1-ol

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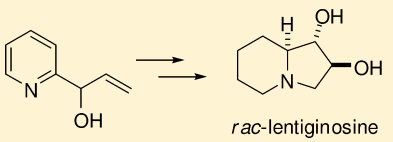
Supporting Information

ABSTRACT: 1-(2-Pyridyl)-2-propen-1-ol, obtained by vinylation of commercially available picolinaldehyde, resulted a good starting material for the synthesis of the indolizidine skeleton. In particular, a simple process involving bromination, reduction, and nucleophilic substitution (via elimination and addition) allowed an easy conversion of the starting material into (±)-lentiginosine in ~27% overall yield.



More than 100 polyhydroxylated alkaloids, mimicking the structures of monosaccharides, have been isolated from plants and microorganisms.[1] These sugar mimics can act as potent and selective glycosidase inhibitors with important effects on quality control, maturation, transport, and secretion of glycoproteins as well as on cell−cell and cell−virus/bacteria recognition processes. This latter aspect is the basis for their application as therapeutic agents in viral infections, cancer, and genetic disorders.[2] In particular, polyhydroxylated indolizidine alkaloids have received considerable attention[3] because of their biological activities. Then, intense synthetic work has been performed to afford these natural products and their nonnatural analogues to be tested in biological and structure−activity relation (SAR) studies. In this context, natural (+)-lentiginosine, isolated in 1990 from the leaves of *Astragalus lentiginosus*,[4] was found to be a potent and selective inhibitor of the fungal α-glucosidase, amyloglucosidase,[5] while recent results showed that the nonnatural enantiomer (−)-lentiginosine acts as an apoptosis inducer on tumor cells of a different origin.[6] On this ground, many syntheses of lentiginosine have been described, and apart from a few enantioselective procedures, most of them are based on chiral pool starting materials.[3,5b] Nevertheless, after the first approach of Shibasaki and co-workers[7] starting from a dihydropyridone derivative, some processes exploiting suitably functionalized nonchiral pyridines as precursors have been reported for the synthesis of natural (+)-lentiginosine,[8] swainsonines,[9] benzo-fused hydroxyindolizidines,[10] and more recently (−)-lentiginosine and its epimers.[11] On the whole, the synthesis of indolizidine derivatives from pyridines is quite sparse, and only a few examples have been reported.[12]

On the other hand, 1-(2-pyridyl)-2-propen-1-ol (**1**),[13] besides exhibiting a peculiar thermal reactivity toward different electrophiles,[14] could be a good candidate for achieving facile access to the indolizidine skeleton. The suitably activated double bond appears in fact to be promising for electrophilic additions. Then, as depicted in Figure 1, a retrosynthetic approach to 1-hydroxyindolizidines substituted at position 2 could involve halogenation of **1**, cyclization, and reduction of the pyridinium ring. Further synthetic elaboration could allow the synthesis of lentiginosine and its analogues in few steps and with high atom economy.

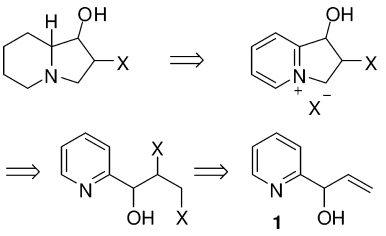


Figure 1. Retrosynthetic approach to 1-hydroxyindolizidines from alcohol **1**.

With this hypothesis in mind, bromination of alcohol **1** was studied first. When a slight excess of bromine (1.1 equiv) was added to **1**, the indolizinium salt **2** was isolated in 59% yield together with an inseparable mixture of diastereomeric salts **2** and **3** (~1:1 ratio, ^{1}H NMR) recovered in 40% yield (Table 1, entry 1). Operating with a stoichiometric amount of bromine to avoid the following treatment with sodium thiosulfate to destroy the excess of reagent,[15] we obtained the mixture of indolizinium salts **2** and **3** (~1:1 ratio, ^{1}H NMR) by filtration in 51% yield, while evaporation of the solvent allowed us to isolate the *trans* diastereomer **2** in 48% yield as a pearl gray solid (Table 1, entry 2).

Operating with an excess of *N*-bromosuccinimide (NBS) as a bromine source (2.5 equiv) in aqueous THF, we slowly and diastereoselectively converted alcohol **1** into the *trans* indolizinium salt **2**, isolated by filtration in 53% yield as a pure white solid that gradually became darker (Table 1, entry 3). Attempts to improve the conversion by changing the reaction conditions were unsuccessful.

The diastereoselective formation of indolizinium salts **2** and **3** (dr between 4:1 and 3:1, in favor of the *trans* diastereomer),

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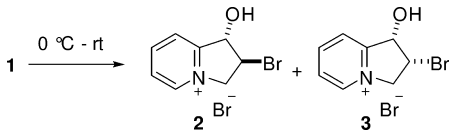
Table 1. Bromination of 1-(2-Pyridyl)-2-propen-1-ol (1)

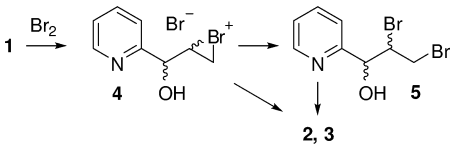


entry	reagent (equiv)	solvent	time (h)	yield[a] of **2** (%)	yield[a] of **2** and **3** (%) (ratio)[b]
1	Br_2 (1.1)[c]	CH_2Cl_2	3	59	40 (1:1)
2	Br_2 (1)	CH_2Cl_2	2	48	51 (1:1)
3	NBS (2.5)	THF and 10% H_2O	72	53	–

[a]Isolated yields. [b]Determined via ^{1}H NMR. [c]The excess of bromine was destroyed by treatment with an aqueous solution of $Na_2S_2O_3$.

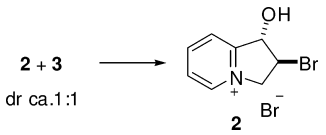
operating with Br_2, can be rationalized through a domino process involving electrophilic addition of bromine on the alkene moiety of **1** and cyclization of the bromonium ions **4** or the dibromo intermediates **5** (Scheme 1).[16]

Scheme 1. Reaction Pathways Leading to Salts 2 and 3



When the mixture of **2** and **3** was dissolved in highly polar solvents, such as DMSO, a quantitative conversion of **3** into **2** was observed after some days at room temperature (Table 2, entry 1). Nevertheless, the recovery of a clean indolizinium salt **2** from this high-boiling point solvent was quite difficult. In water, the thermal isomerization was performed by prolonged heating at 60 °C (Table 2, entry 2). When a less concentrated solution of **2** and **3** was heated at 80 °C, the conversion was complete after 5 days and the removal of the solvent allowed isolation of pure compound **2** as a black solid in 84% yield (Table 2, entry 3). Likely, in polar solvents, the solvent-separated ion pairs in **2** and **3** were able to evolve via S_N2 nucleophilic attack of the bromide ion on the C-2 atom, leading to the more stable *trans* isomer **2**. Then, the two-step bromination–isomerization sequence allowed the high-yield diastereoselective conversion of alcohol **1** to *trans* salt **2**.

Table 2. Conversion of the Mixture of Indolizinium Salts 2 and 3 (~1:1 ratio) into *trans* Salt 2



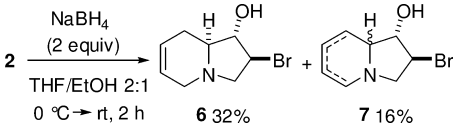
entry	solvent	T (°C)	concn (M)	time (days)	conversion[a] (%)	yield[b] (%)
1	DMSO	rt	0.30	4	100	–[c]
2	H_2O	60	0.15	11	100	88
3	H_2O	80	0.02	5	100	84

[a]Determined via ^{1}H NMR. [b]Isolated yields. [c]The recovery of pure **2** was difficult.

With the indolizinium salt **2** in hands, reduction to indolizidine derivatives was then studied.

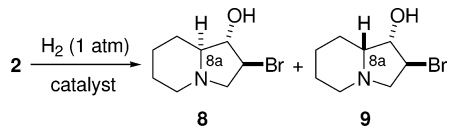
Operating with $NaBH_4$ in a THF/EtOH mixture, we isolated the tetrahydro derivative **6**[17] in 32% yield along with a complex mixture of regio- and diastereomers **7** (Scheme 2).[18]

Scheme 2. Reduction of 2 with Sodium Borohydride



Hydrogenation of **2** in the presence of Pd/C was unsuccessful, leading to a complex reaction mixture (Table 3, entry 1). On the other hand, the use of $PtO_2 \cdot H_2O$ (10 mol %) in EtOH[11] allowed after 6 h at room temperature isolation of the diastereomeric *trans* bromohydroxyindolizidines **8** and **9** in 43 and 29% yields, respectively (Table 3, entry 2). Longer reaction times led to lower yields of the reduction products (Table 3, entry 3).[19] The structures of **8** and **9**, which differ just for the configuration at position 8a, were confirmed by single-crystal X-ray diffraction analyses (see Figure 2 below).

Table 3. Catalytic Hydrogenation of Salt 2

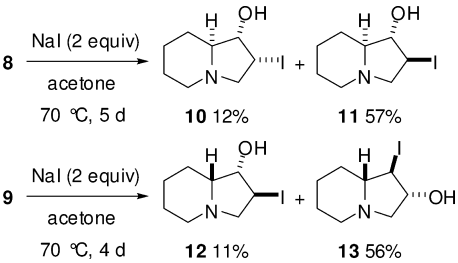


entry	catalyst	solvent	T (°C)	time (h)	yield[a] (%) 8	yield[a] (%) 9
1	Pd/C	MeOH	rt	24	–[b]	
2	$PtO_2 \cdot H_2O$ (10 mol %)	EtOH	rt	6	43	29
3	$PtO_2 \cdot H_2O$ (10 mol %)	EtOH	rt	16	33	20

[a]Isolated yields. [b]Complex reaction crude.

The presence of a good leaving group at position 2 of indolizidines **8** and **9** could open the way to the synthesis of variously functionalized hydroxyindolizidines. At first, we studied the behavior of iodide anion as a nucleophile. When compound **8** was heated with NaI in acetone at 70 °C, the *trans* iodo derivative **11** was isolated in 57% yield, along with a minor amount of the *cis* diastereomer **10** (12%), while indolizidine **9** gave the two regioisomers **12** and **13** in 11 and 56% yields, respectively (Scheme 3).

Scheme 3. Reactions of 8 and 9 with Sodium Iodide



The formation of both diastereomers **10** and **11** from **8** could be rationalized on the basis of an S_N1 mechanism, involving a preferential attack of I^- on the less hindered face of the carbocation intermediate, leading to *trans* iodoindolizidine **11** as the predominant product. However, the cyclic secondary

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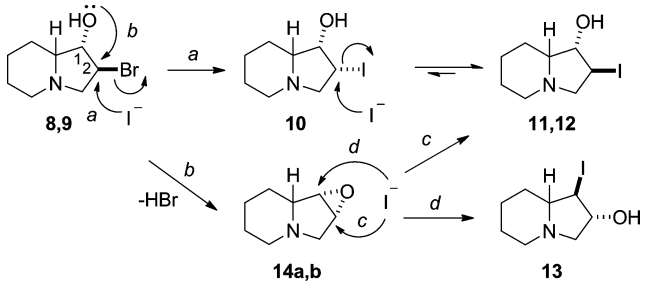
carbocation intermediate likely does not enjoy significant stabilization via hyperconjugation, and an S_N2 mechanism could be more plausible (Scheme 4, route a). In fact, a direct

Scheme 4. Mechanistic Hypothesis for the Reaction of 8 and 9 with Sodium Iodide



bimolecular nucleophilic substitution on **8** could give rise to **10**, through inversion of the configuration at C-2, followed by a second sterically and electronically favored S_N2 attack of I^- on **10** leading to the more stable *trans* isomer **11**. Then, the preferential formation of **11**, with retention of configuration at C-2, could be the result of a double-inversion process. On the other hand, as reported for nucleophilic substitutions of *trans* 3-bromo-4-hydroxypyrrolidines,[20] compound **11** could be the result of a diastereo- and regioselective ring opening of epoxide intermediate **14a**[21] (Scheme 4, routes b and c). In fact, the *trans* relationship of OH and Br groups in **8** and **9** supports an entropically assisted intramolecular S_N2 process leading to epoxides **14a** and **14b**. The formation of both *trans* regioisomers **12** and **13** from indolizidine **9** (Scheme 4, routes b–d) can then be rationalized with the ring opening of epoxide **14b** via S_N2 attack of iodide on C-1 or C-2.

Because of the exclusive formation of the *trans* derivatives **12** and **13**, the mechanism via the epoxide intermediate seems to be more favorable in the case of indolizidine **9** with respect to **8**. This assumption found support in studies of molecular modeling that provided evidence of HO–C-1–C-2–Br dihedral angles of 93° and 157° in the diastereomeric bromohydroxyindolizidines **8** and **9**, respectively.[22] Such a difference, clearly associated with the different stereochemistry at C-8a, makes the intramolecular S_N2 attack easier in compound **9**, characterized by an almost antiperiplanar arrangement of the Br/OH substituents. This observation was in reasonable agreement with the data obtained by single-crystal X-ray diffraction analyses of **8** and **9** providing evidence of solid state dihedral angles of 99° and 133°, respectively (Figure 2).

Then, with the aim of evaluating the strategy described above for the synthesis of lentiginosine, compound **8** was allowed to react with aqueous KOH, in THF. A smooth reaction took place leading to epoxide **14** as the only product. The structure of **14a**, as well as that of **14b** (see below), was unambiguously determined via in situ NMR experiments (see Experimental Section). Compound **14a** was directly converted, without isolation, by treatment with aqueous H_2SO_4[21] into *rac*-lentiginosine (**15**) and the diastereomeric 1,2-dihydroxyindolizidine (**16**) isolated in 69 and 5% yields, respectively (Scheme 5). The same procedure applied to bromoindolizidine **9** afforded compounds **15** and **16** in 10 and 71% yields, respectively (Scheme 5).

These results can be ascribed to a completely *anti* diastereoselective and highly C-2 regioselective ring opening

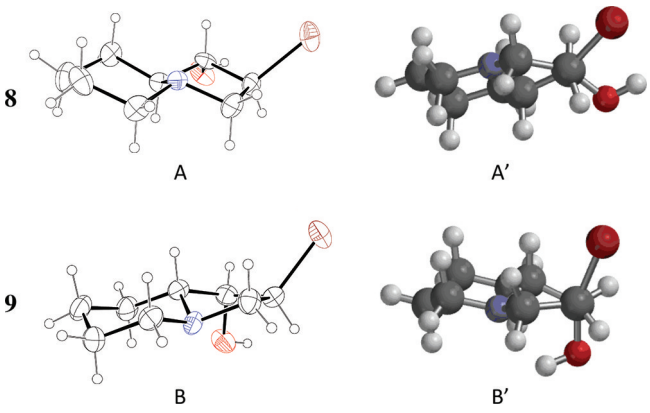
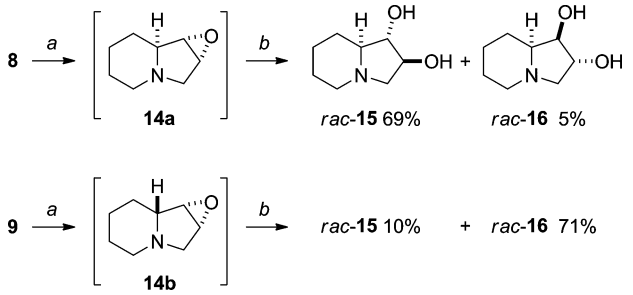


Figure 2. X-ray (A and B) and calculated (A′ and B′) structures of compounds **8** and **9**.

Scheme 5. Conversion of Bromoindolizidines 8 and 9 into *rac*-1,2-Dihydroxyindolizidines 15 and 16[a]



[a](a) Aqueous KOH, THF, 40 °C, 15 h; (b) aqueous H_2SO_4, 100 °C, 7 h.

of epoxides **14a** and **14b**. Simple steric reasons seem to be unable to explain the observed regioselectivity. On the other hand, in acidic medium, protonation of the epoxide oxygen has to be invoked, besides that of nitrogen, and nucleophilic attack on the secondary C-1 or C-2 atoms can be performed in a "quasi-carbocationic" transition state. In light of this hypothesis, stabilization via hyperconjugation, associated with the presence of the vicinal CH_2 group, could likely favor C-2 quasi-carbocationic transition states TS-I and TS-II (coming from epoxides **14a** and **14b**, respectively), responsible for the formation of the major products, with respect to the alternative ones involving a partial positive charge at C-1 (Figure 3).

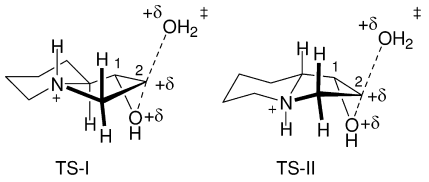


Figure 3. Preferred transition states involved in the epoxide ring openings.

In conclusion, 1-(2-pyridyl)-2-propen-1-ol (**1**), obtained by vinylation of commercially available picolinaldehyde, behaves as a good starting material for the synthesis of the indolizidine skeleton. In particular, a simple process involving bromination of allyl alcohol **1**, reduction of indolizinium salt **2**, and one-pot nucleophilic substitution of **8** (via elimination/addition) allowed an easy conversion of the starting material into

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(±)-lentiginosine (**15**), obtained in ~27% overall yield, as well as its diastereomer **16**. This new method appears on the whole to be very promising for the synthesis of variously functionalized indolizidines even in enantiomerically pure form starting from optically pure alcohol **1**,[13] in progress in our laboratories.

EXPERIMENTAL SECTION

General. Chemicals were purchased from commercial suppliers and used as received. Melting points were taken on a capillary melting point apparatus and are uncorrected. Silica gel plates and silica gel 60 (230−400 mesh) were used for TLC and flash chromatographies (FC), respectively. Petroleum ether (PE) employed for crystallizations and chromatographic workup refers to the fractions of bp 30−50 and 40−70 °C, respectively. ^{1}H and ^{13}C NMR spectra were recorded with instruments operating at 200 and 50 MHz and at 400 and 100 MHz, respectively. Accurate mass spectra were recorded on a high-resolution mass spectrometer, equipped with a conventional ESI source.

(1*SR*,2*SR*)-2-Bromo-1-hydroxy-1*H*,2*H*,3*H*-indolizinium Bromide (2) and (1*SR*,2*RS*)-2-Bromo-1-hydroxy-1*H*,2*H*,3*H*-indolizinium Bromide (3). (**A**) A solution of bromine (0.176 g, 0.056 mL, 1.1 mmol) in CH_2Cl_2 (1.5 mL) was added dropwise at 0 °C to a solution of alcohol **1** (0.135 g, 1 mmol) in the same solvent (2 mL). A white precipitate formed, and the reaction mixture was stirred at room temperature for 10 min. Then, an oversaturated solution of $Na_2S_2O_3$ was added to destroy the excess of Br_2, and the resulting mixture was dried over anhydrous Na_2SO_4. Filtration of the solution and evaporation of the solvent under reduced pressure led to indolizinium bromide **2** as a pearl gray solid (0.174 g, 59%): mp >350 °C; IR ν_{max} (KBr) 3122, 3050, 2980, 1628, 1499, 1121 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.12 (d, J = 6.2 Hz, 1H), 8.70 (pt, J = 7.6 Hz, 1H), 8.25 (d, J = 7.8 Hz, 1H), 8.18 (pt, J = 7.0 Hz, 1H), 7.29 (br s, 1H), 5.63 (d, J = 6.2 Hz, 1H), 5.43 (dd, J = 13.6 and 6.8 Hz, 1H), 5.04 (dd, J = 13.7 and 6.7 Hz, 1H), 4.77 (pq, J = 6.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.6 (s), 147.0 (d), 141.8 (d), 127.6 (d), 124.5 (d), 78.95 (d), 62.7 (t), 46.8 (d).

Extraction with acetone from the reaction residue gave, after evaporation to dryness, a gray solid consisting of an ~1:1 mixture (^{1}H NMR) of **2** and **3** (0.118 g, 40%). ^{1}H NMR (400 MHz, DMSO-d_6)[23] δ [9.14 (d, J = 5.5 Hz, 1H)], 9.11 (d, J = 6.1 Hz, 1H), 8.66 (pt, J = 7.8 Hz, 2H), 8.21 (d, J = 7.8 Hz, 1H), 8.16−8.11 (m, 3H), [5.69 (d, J = 4.7 Hz, 1H)], 5.59 (d, J = 6.1 Hz, 1H), 5.40 (dd, J = 13.6 and 6.9 Hz, 1H), [5.35−5.31 (m, 2H)], [5.19 (dd, J = 16.0 and 1.8 Hz, 1H)], 5.0 (dd, J = 13.6 and 6.8 Hz, 1H), 4.74 (pq, J = 6.5 Hz, 1H), 4.50−3.90 (vbr s, 2H); ^{13}C NMR (100 MHz, DMSO-d_6)[23] δ [157.1 (s)], 156.7 (s), 147.0 (d), [146.8 (d)], [142.2 (d)], 141.8 (d), 127.6 (d), [127.2 (d)], 124.5 (d), [124.4 (d)], 78.9 (d), [73.4 (d)], [64.2 (t)], 62.7 (t), [55.1 (d)], 46.8 (d).

(**B**) A solution of bromine (0.160 g, 0.051 mL, 1 mmol) in CH_2Cl_2 (2 mL) was slowly added dropwise (~1 h) at room temperature under magnetic stirring to a solution of pyridylpropenol **1** (0.135 g, 1 mmol) in the same solvent (3 mL). At the end of the addition, the reaction mixture was stirred for 30 min to allow the complete disappearance of the starting material. An ~1:1 mixture of **2** and **3** (0.151 g, 51%) as a pearl gray solid was recovered by filtration. Anal. Calcd for $C_8H_9Br_2NO$: C, 32.57; H, 3.08; N, 4.75. Found: C, 32.25; H, 2.91; N, 4.53.

Evaporation to dryness of the mother liquor led to compound **2** (0.141 g, 48%) as a pearl gray solid.

(**C**) To a solution of alcohol **1** (0.135 g, 1 mmol) in THF (7 mL) and 5% H_2O (0.35 mL), cooled to 0 °C, was added NBS (0.215 g, 1.2 mmol) in small portions over 40 min. Then, the resulting mixture was stirred for 24 h at room temperature. Filtration of the white solid precipitate gave salt **2** (0.059 g, 20%). Then, NBS (0.178 g, 1 mmol) and H_2O (0.35 mL) were added again to the solution, and the resulting mixture was stirred at room temperature for 24 h. A second amount of salt **2** (0.067 g, 23%) as a white solid was recovered by filtration. A third addition of NBS (0.089 g, 0.5 mmol) to the solution led, after 24 h, to a third crop of salt **2** (0.030 g, 10%), isolated in 53% overall yield, identical to the sample isolated before. An analytical sample was obtained by washing with THF and prolonged evacuation at room temperature. Anal. Calcd for $C_8H_9Br_2NO$: C, 32.57; H, 3.08; N, 4.75. Found: C, 32.19; H, 3.09; N, 4.44.

Isomerization of *cis* Isomer 3 into *trans* Isomer 2. A mixture of diastereomeric salts **2** and **3** (~1:1 ratio, 0.136 g, 0.46 mmol) in H_2O (23 mL) was heated at 80 °C in a screw-cap tube under magnetic stirring for 5 days. After filtration of a black residue, evaporation of the solvent under reduced pressure afforded salt **2** as a black solid (0.114 g, 84%).

(1*SR*,2*SR*,8a*SR*)-2-Bromo-1,2,3,5,8,8a-hexahydro-1-indolizinol (6). At 0 °C, while the solution was being stirred, $NaBH_4$ (0.076 g, 2 mmol) was added in 1 h, in small portions, to a solution of (1*SR*,2*SR*)-2-bromo-1-hydroxy-1*H*,2*H*,3*H*-indolizinium bromide (**2**) (0.295 g, 1 mmol) in dry THF (15 mL) and absolute EtOH (7.5 mL). After the addition, the reaction mixture was stirred at room temperature for 1.5 h. Then, the excess of hydride was destroyed by treatment with an oversaturated solution of anhydrous Na_2SO_4, and the dried mixture was filtered through a Celite pad. Chromatographic resolution (3:2 EtOAc/PE) gave compound **6** (R_f = 0.48; 0.070 g, 32%). An analytical sample was obtained by crystallization from a PE/Et_2O mixture: mp 91−92 °C (white needles); IR ν_{max} (KBr) 3121, 2970, 2808, 1462, 1339, 1209, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81−5.76 (m, 1H), 5.72−5.66 (m, 1H), 4.27 (dd, J = 7.2 and 4.1 Hz, 1H), 4.12 (ddd, J = 7.8, 4.1, and 2.6 Hz, 1H), 3.48−3.41 (m, 1H), 3.44 (dd, J = 11.5 and 2.6 Hz, 1H), 3.05 (dd, J = 11.5 and 7.8 Hz, 1H), 2.88 (m, 1H), 2.44−2.37 (m, 1H), 2.32−2.27 (m, 1H), 2.25−2.16 (m, 1H), 2.06 (vbr s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 124.6 (d), 124.4 (d), 86.5 (d), 65.1 (d), 62.4 (t), 51.9 (t), 50.8 (d), 29.5 (t). Anal. Calcd for $C_8H_{12}BrNO$: C, 44.06; H, 5.55; N, 6.42. Found: C, 43.99; H, 5.56; N, 6.42.

(1*SR*,2*SR*,8a*SR*)-2-Bromooctahydro-1-indolizinol (8) and (1*SR*,2*SR*,8a*RS*)-2-Bromooctahydro-1-indolizinol (9). Indolizinium salt **2** (0.147 g, 0.5 mmol) was added to a preactivated suspension of $PtO_2{\cdot}H_2O$ (0.011 g, 0.048 mmol) in EtOH (8 mL), and the mixture was stirred at room temperature under an atmospheric pressure of hydrogen for 6 h. The solution was filtered through a Celite pad, washed with EtOH and MeOH, and evaporated to dryness. After a quick chromatographic purification with a 1:1 EtOAc/MeOH mixture as the eluent to remove the inorganic materials, the reaction crude was resolved by flash chromatography with EtOAc. The first moving band gave compound **8** (R_f = 0.37; 0.047 g, 43%) that was crystallized from a PE/Et_2O mixture as white needles: mp 128−129 °C; IR ν_{max} (KBr) 3118, 2931, 2804, 1325, 1133, 1052 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.17 (dd, J = 8.1 and 4.3 Hz, 1H), 4.02 (ddd, J = 8.0, 4.2, and 2.1 Hz, 1H), 3.28 (dd, J = 11.5 and 2.0 Hz, 1H), 2.99 (dt, J = 10.7 and 3.0 Hz, 1H), 2.93 (dd, J = 11.3 and 8.0 Hz, 1H), 2.19 (br s, 1H), 2.04−1.94 (m, 2H), 1.85−1.80 (m, 2H), 1.60 (m, 2H), 1.38−1.28 (m, 1H), 1.27−1.15 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 86.0 (d), 69.8 (d), 62.8 (t), 52.8 (t), 51.4 (d), 28.4 (t), 24.6 (t), 23.7 (t). Anal. Calcd for $C_8H_{14}BrNO$: C, 43.65; H, 6.41; N, 6.36. Found: C, 43.64; H, 6.38; N, 6.04.

The slowest-moving fraction afforded indolizidine **9** (R_f = 0.14; 0.032 g, 29%) as a white solid: mp 122−123 °C (from PE/Et_2O); IR ν_{max} (KBr) 3127, 2942, 2827, 2788, 1138, 1097 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (br s, 1H), 4.02 (pt, J = 6.8 Hz, 1H), 3.69 (dd, J = 10.5 and 7.4 Hz, 1H), 3.06 (br d, J = 11.1 Hz, 1H), 2.60 (vbr s, 1H), 2.51 (dd, J = 10.5 and 6.2 Hz, 1H), 2.27 (dt, J = 11.3 and 3.1 Hz, 1H), 2.06 (td, J = 11.4 and 2.6 Hz, 1H), 1.89−1.61 (m, 3H), 1.54−1.43 (m, 2H), 1.35−1.19 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 81.3 (d), 65.1 (d), 63.3 (t), 52.8 (t), 49.4 (d), 25.1 (t), 24.6 (t), 23.6 (t). Anal. Calcd for $C_8H_{14}BrNO$: C, 43.65; H, 6.41; N, 6.36. Found: C, 43.91; H, 6.38; N, 6.21.

(1*SR*,2*RS*,8a*SR*)-2-Iodooctahydro-1-indolizinol (10) and (1*SR*,2*SR*,8a*SR*)-2-Iodooctahydro-1-indolizinol (11). A solution of indolizidine **8** (0.030 g, 0.136 mmol) and NaI (0.042 g, 0.28 mmol) in acetone (0.5 mL) was stirred at 70 °C in a screw-cap tube (Pirex N. 13) for 5 days. Filtration of the precipitate (NaBr) and evaporation of the solvent led to a crude that was purified by flash chromatography (20:1 EtOAc/PE). The first moving band gave compound **11** (R_f =

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0.50; 0.018 g, 50%) that crystallized in ivory needles from a PE/Et_2O mixture: mp 107−108 °C; IR ν_{max} (KBr) 3124, 2931, 2853, 2801, 1456, 1439, 1321, 1183, 1128, 1099, 1049 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.27 (dd, J = 8.0 and 5.3 Hz, 1H), 3.98 (ddd, J = 8.6, 5.1, and 2.7 Hz, 1H), 3.34 (dd, J = 11.4 and 2.6 Hz, 1H), 3.00−2.93 (m, 2H), 2.60 (vbr s, 1H), 2.07−1.93 (m, 2H), 1.83−1.77 (m, 2H), 1.62−1.55 (m, 2H), 1.36−1.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 87.5 (d), 69.55 (d), 64.2 (t), 52.7 (t), 28.3 (t), 25.2 (d), 24.6 (t), 23.8 (t); HRMS (ESI) m/z calcd for $C_8H_{15}INO$ $[MH]^+$ 268.0198, found 268.0196.

The following band (R_f = 0.20; 0.007 g, 19%) gave a mixture of **10** and **11** (1.7:1 ratio determined by ^1H NMR): ^1H NMR (400 MHz, $CDCl_3$)[24] δ 4.55 (pq, J = 7.6 Hz, 1H), [4.25 (dd, J = 8.2 and 5.1 Hz, 1H)], [3.98 (ddd, J = 8.6, 5.1, and 2.7 Hz, 1H)], 3.67 (dd, J = 10.1 and 7.4 Hz, 1H), [3.33 (dd, J = 11.3 and 2.6 Hz, 1H)], 3.30 (pt, J = 7.4 Hz, 1H), 3.00−2.91 (m, 4H), 2.10−1.77 (m, 10H), 1.64−1.44 (m, 4H), 1.35−1.20 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$)[24] δ [87.6 (d)], 73.9 (d), [69.5 (d)], 68.8 (d), 64.35 (t), [64.2 (t)], [52.6 (t)], 52.5 (t), 32.3 (d), 28.45 (t), [28.4 (t)], [25.1 (d)], 25.05 (t), [24.65 (t)], 23.9 (t), [23.8 (t)].

(1*SR*,2*SR*,8a*RS*)-2-Iodooctahydro-1-indolizinol (12) and (1*RS*,2*RS*,8a*RS*)-1-Iodooctahydro-2-indolizinol (13). A solution of indolizidine **9** (0.032 g, 0.145 mmol) and NaI (0.045 g, 0.30 mmol) in acetone (0.9 mL) was stirred at 70 °C in a screw-cap tube (Pirex N. 13) for 5 days. After filtration of the precipitate (NaBr) and evaporation of the solvent, the reaction crude was purified by flash chromatography (50:1:1 CH_2Cl_2/MeOH/30% aqueous NH_3). Compound **12** was isolated along with indolizidine **13** (R_f = 0.35; 0.011 g, 28%, 1:1.6 ratio determined by ^1H NMR): ^1H NMR (400 MHz, $CDCl_3$)[25] δ [4.44 (ddd, J = 6.3, 4.0, and 1.0 Hz, 1H)], 4.30 (br d, J = 3.1 Hz, 1H), 4.02 (pt, J = 7.5 Hz, 1H), 3.82 (dd, J = 10.5 and 7.7 Hz, 1H), [3.59 (dd, J = 9.7 and 3.8 Hz, 1H)], 3.17 (m, 1H), [3.08 (m, 1H)], [2.97 (d, J = 10.3 Hz, 1H)], 2.90 (vbr s, 2H), 2.76 (dd, J = 10.5 and 7.2 Hz, 1H), [2.56 (dd, J = 10.4 and 6.4 Hz, 1H)], 2.41 (m, 1H), [2.18 (m, 1H)], 2.14 (m, 1H), [2.04−1.94 (m, 2H)], 1.89−1.74 (m, 3H), 1.68−1.52 (m, 4H), 1.38−1.14 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$)[25] δ 82.8 (d), [80.1 (d)], [73.6 (d)], 65.75 (d), 64.7 (t), [62.1 (t)], 52.65 (t), [52.6 (t)], [34.3 (d)], [28.3 (t)], [25.0 (t)], 24.7 (t), 24.4 (t), [23.8 (t)], 23.4 (t), 22.7 (d).

The following band gave regioisomeric indolizidine **13** as a white solid (R_f = 0.21; 0.015 g, 39%): mp 125−126 °C (from PE/Et_2O); IR ν_{max} (KBr) 3118, 2935, 2825, 1449, 1338, 1155, 1027 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (ddd, J = 6.4, 3.9, and 1.0 Hz, 1H), 3.57 (dd, J = 9.7 and 3.7 Hz, 1H), 3.21, (vbr s, 1H), 3.05 (dt, J = 10.6 and 2.6 Hz, 1H), 2.94 (d, J = 10.1 Hz, 1H), 2.53 (dd, J = 10.3 and 6.4 Hz, 1H), 2.15 (td, J = 9.9 and 2.5 Hz, 1H), 2.01−1.94 (m, 2H), 1.87−1.82 (m, 1H), 1.62−1.50 (m, 2H), 1.29−1.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.1 (d), 73.5 (d), 62.2 (t), 52.7 (t), 34.7 (d), 28.4 (t), 25.1 (t), 23.9 (t); HRMS (ESI) m/z calcd for $C_8H_{15}INO$ $[MH]^+$ 268.0198, found 268.0194.

(1a*RS*,7a*SR*,7b*SR*)-Octahydrooxireno[2,3-*a*]indolizine (14a). A solution of KOH (0.018 g, 0.321 mmol) in CD_3OD (0.3 mL) was added to a solution of indolizidine **8** (0.024 g, 0.109 mmol) in the same solvent (0.6 mL) in an NMR tube and the mixture heated overnight at 40 °C. Compound **8** disappeared completely, and epoxide **14a**[21] was the only reaction product:[26] ^1H NMR (400 MHz, CD_3OD) δ 3.62 (br d, J = 3.3 Hz, 1H), 3.47 (d, J = 3.3 Hz, 1H), 3.11 (dd, J = 12.4 and 3.7 Hz, 1H), 2.94 (br s, 2H), 2.92−2.73 (m, 2H), 1.80 (m, 1H), 1.52−1.42 (m, 2H), 1.39 (dt, J = 12.6 and 3.2 Hz, 1H), 1.31 (m, 1H), 1.14 (qd, J = 12.6 and 3.8 Hz, 1H); ^{13}C NMR (50 MHz, CD_3OD) δ 59.8 (d), 57.6 (d), 55.1 (d), 48.85 (t), 46.8 (t), 24.3 (t), 24.2 (t), 21.1 (t).

(1a*RS*,7a*RS*,7b*SR*)-Octahydrooxireno[2,3-*a*]indolizine (14b). A solution of KOH (0.006 g, 0.107 mmol) in CD_3OD (0.3 mL) was added to a solution of indolizidine **9** (0.016 g, 0.073 mmol) in the same solvent (0.6 mL) in an NMR tube and the mixture heated overnight at 40 °C. The disappearance of compound **9** gave rise to epoxide **14b** as the only reaction product: ^1H NMR (400 MHz, CD_3OD) δ 3.52 (m, 2H), 3.18 (d, J = 10.9 Hz, 1H), 2.95 (m, 1H), 2.30 (d, J = 10.9 Hz, 1H), 2.21 (m, 1H), 2.14 (dd, J = 11.5 and 2.1 Hz, 1H), 1.87 (m, 2H), 1.58 (m, 2H), 1.51−1.30 (m, 2H); ^{13}C NMR (50 MHz, CD_3OD) δ 65.35 (d), 57.4 (d), 54.3 (t), 52.8 (d), 52.2 (t), 27.2 (t), 26.1 (t), 25.6 (t).

(1*SR*,2*SR*,8a*SR*)-1,2-Dihydroxyindolizidine (15) and (1*RS*,2*RS*,8a*SR*)-1,2-Dihydroxyindolizidine (16). **(A)** When a solution of KOH (0.042 g, 0.750 mmol) in H_2O (0.4 mL) was added to a solution of indolizidine **8** (0.055 g, 0.250 mmol) in THF (1 mL), two immiscible phases formed. The reaction mixture was heated overnight at 40 °C while being magnetically stirred in a screw-cap tube (Pirex N. 13). The aqueous phase was then separated and washed with THF (3 × 1 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4. The inorganic material was removed by filtration and washed with THF (2 × 1 mL). Then, aqueous H_2SO_4 (1 M solution, 0.37 mL, 0.370 mmol) was added to the organic phase. After the mixture had been heated at 100 °C while being stirred in a screw-cap tube (Pirex N. 20) for 7 h, evaporation of the solvent left a crude that was purified by flash chromatography (41:8:1 CH_2Cl_2/MeOH/30% aqueous NH_3). The first moving band gave compound **15**[5a,7,27] (R_f = 0.30; 0.027 g, 69%) as a white solid: ^1H NMR (400 MHz, D_2O) δ 4.11 (ddd, J = 7.6, 4.0, and 1.8 Hz, 1H), 3.69 (dd, J = 9.0 and 3.9 Hz, 1H), 2.98 (br d, J = 11.0 Hz, 1H), 2.87 (dd, J = 11.1 and 1.8 Hz, 1H), 2.68 (dd, J = 11.3 and 7.4 Hz, 1H), 2.10 (td, J = 11.7 and 3.0 Hz, 1H), 2.02−1.96 (m, 2H), 1.89−1.81 (m, 1H), 1.68 (br d, J = 13.6 Hz, 1H), 1.55−1.43 (m, 1H), 1.36−1.22 (m, 2H); ^{13}C NMR (100 MHz, D_2O) δ 81.35 (d), 74.1 (d), 67.0 (d), 58.7 (t), 51.1 (t), 26.0 (t), 22.4 (t), 21.5 (t); HRMS (ESI) m/z calcd for $C_8H_{16}NO_2$ $[MH]^+$ 158.1181, found 158.1179.

The slowest-moving band afforded 1,2-dihydroxyindolizidine **16**[7,27] (R_f = 0.18; 0.002 g, 5%) as a white solid: ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (t, J = 6.3 Hz, 1H), 4.02 (m, 2H), 3.86 (d, J = 4.7 Hz, 1H), 3.51 (m, 1H), 3.11 (br d, J = 11.0 Hz, 1H), 2.25 (m, 1H), 2.13−2.04 (m, 2H), 1.85 (br d, J = 12.9 Hz, 1H), 1.73−1.47 (m, 4H), 1.35−1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.0 (d), 77.1 (d), 66.8 (d), 61.4 (t), 53.3 (t), 24.7 (t), 24.3 (t), 23.6 (t); HRMS (ESI) m/z calcd for $C_8H_{16}NO_2$ $[MH]^+$ 158.1181, found 158.1177.

(B) As described above, a solution of KOH (0.021 g, 0.375 mmol) in H_2O (0.3 mL) was added to a solution of indolizidine **9** (0.055 g, 0.250 mmol) in THF (1 mL), and the resulting biphasic mixture was heated overnight at 40 °C while being magnetically stirred in a screw-cap tube (Pirex N. 13). After separation of the aqueous phase and anydrification, the organic solution was treated with aqueous H_2SO_4 (1 M solution, 0.28 mL, 0.280 mmol) and heated while being stirred at 100 °C in a screw-cap tube (Pirex N. 20) for 7 h. After evaporation of the solvent, the reaction crude was resolved by flash chromatography (41:8:1 CH_2Cl_2/MeOH/30% aqueous NH_3) to give 1,2-dihydroxyindolizidines **15**[5a,7,27] (R_f = 0.30; 0.004 g, 10%) and **16**[7,27] (R_f = 0.18; 0.028 g, 71%), which were identical with the samples previously obtained.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all new compounds and X-ray crystal data of **6**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) The treatment with $Na_2S_2O_3$ prevents the following reduction step (H_2, $PtO_2{\cdot}H_2O$), likely due to the poisoning of the catalyst.

(16) If the bromine addition was performed in $CDCl_3$, NMR analyses of the solution clearly provided evidence, after the disappearance of **1**, of a transient open chain dibromo derivative along with the predominant indolizinium salt **2**. The presence in the ^{1}H NMR spectrum of a quartet (J = 5.8 Hz) at δ 4.44 for the CHBr resonance supported the open chain structure **5**.

(17) The structure was unambiguously established by single-crystal X-ray diffraction analysis (see the Supporting Information).

(18) Attempts to improve this result under different reaction conditions and/or with other hydrides ($LiAlH_4$ and $NaBH_3CN$) were unsuccessful.

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(22) Dihedral angles were determined at the HF 3.21G* level of the theory using PC Spartan version 0.8 from Wave function, Inc.

(23) The data reported in square brackets are those of *cis*-indolizinium bromide **3**.

(24) The data in square brackets are the resonances of compound **11**.

(25) The data in square brackets are the resonances of compound **13**.

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