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Synthesis of New Indolizidine Derivatives from 1-(2-Quinolyl)-2-propen-1-ol

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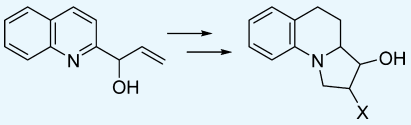
Supporting Information

ABSTRACT: The four-step procedure involving bromination, reduction, and nucleophilic substitution via elimination/addition previously applied to 1-(2-pyridyl)-2-propen-1-ol for the synthesis of indolizidine systems has now been extended to 1-(2-quinolyl)-2-propen-1-ol allowing a general access to benzo-fused derivatives. For instance, (±)-benzo[*e*]lentiginosine has been easily synthesized in an 18% overall yield.



INTRODUCTION

In 1988, Evans introduced the term "privileged structures" to define molecular frameworks "capable of providing useful ligands for more than one receptor," which upon modifications "could be a valuable alternative in the search for new receptor agonists and antagonists."[1] The principle of privileged structures has been widely applied for the design and synthesis of libraries of natural products and their analogues by planning diversity-oriented syntheses[2] to access molecules (often small molecules) with maximum structural diversity.

Heterocyclic systems and mainly six-membered aza-heterocycles, including pyridines,[3] quinolines,[4] and their reduced forms such as 1,2,3,4-tetrahydroquinolines,[5] are privileged structures because they are widely spread in nature and are well-known for their multifaceted biological activities as well as for their significant applications in the pharmaceutical and agrochemical domains.

Moreover, indolizidine alkaloids, and mainly polyhydroxylated derivatives, have been recognized as potent and selective inhibitors of glycosidases and have also been investigated as antibacterial, antiviral, antitumor, antiinflammatory, or antidiabetic agents.[6] In particular, from its isolation in 1990, a noteworthy attention has been devoted to natural (+)-lentiginosine [(1*S*,2*S*,8a*S*)-octahydroindolizine-1,2-diol][7] as well as to the non-natural enantiomer able to behave, respectively, as amyloglucosidase and Hsp90 inhibitor or apoptosis inducer on tumor cells of different lines.[8]

In this context, we recently reported a facile four-step synthesis of *rac*-lentiginosine from 1-(2-pyridyl)-2-propen-1-ol.[9] With the aim to synthesize different analogues to test their biological properties, we then decided to apply the same methodology to 1-(2-quinolyl)-2-propen-1-ol (**1**)[10] to access benzo[*e*]indolizidines with a tetrahydroquinoline skeleton (Figure 1), assessed as promising targets on the basis of computational studies.[11]

RESULTS AND DISCUSSION

1-(2-Quinolyl)-2-propen-1-ol (**1**) was synthesized in 94% yield from 2-quinolinecarboxaldehyde, but the easy isomerization into the corresponding ethyl ketone[10] made its purification impossible. After isolation, compound **1** was immediately subjected to bromination with a stoichiometric amount of bromine in dichloromethane at 0 °C, affording a mixture of diastereomeric *trans* and *cis* benzoindolizinium salts **2** and **3** (1:2−1:3 ratio), recovered in 97% yield by ensuing multiple filtrations (Scheme 1). The diastereomeric salts cannot be separated but simple stirring in water at room temperature allowed the total conversion of the *cis* isomer into *trans*-salt **2**, which was then isolated in a quantitative yield (Scheme 1). As previously observed for indolizinium salts,[9] in polar solvents, the solvent-separated ion pairs in **2** and **3** are likely able to evolve into the more stable *trans* isomer **2** through the nucleophilic attack of the bromide ion on C-2 carbon.[a]

Salt **2** was then subjected to reduction under different conditions. The use of $NaBH_4$ led to complex reaction mixtures, whereas no reduction was observed for hydrogenation

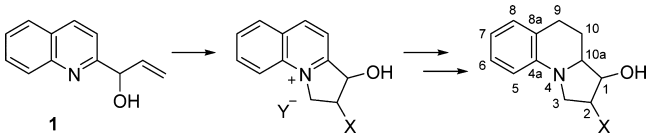
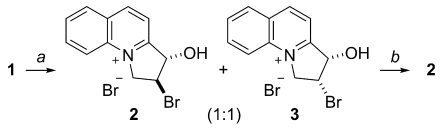


Figure 1. General approach to benzo[*e*]indolizidines from 1-(2-quinolyl)-2-propen-1-ol (**1**).

Scheme 1. Bromocyclization of 1-(2-Quinolyl)-2-propen-1-ol (1) and *Cis*/*Trans* Salt Isomerization



a: Br_2, CH_2Cl_2, 0 °C - rt, 24 h, 97%
b: H_2O, rt, 3 d, 100%

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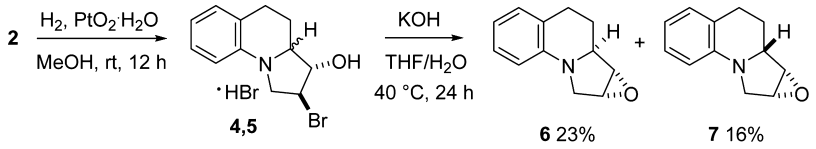
Scheme 2. Synthesis of Oxiranes 6 and 7 by Reduction of *Trans* Salt 2 and HBr Elimination



in the presence of Pd/C. On the other hand, hydrogenation in the presence of monohydrate PtO_2 as the catalyst afforded the formation of diastereomeric tetrahydroquinolines bromohydrates **4** and **5** (Scheme 2).[b] Compounds **4** and **5** are completely stable as hydrobromides, but attempts to isolate the bromohydrins as free bases were unsuccessful.[c]

The mixture of **4** and **5** was then subjected to treatment with aqueous KOH in tetrahydrofuran (THF) affording diastereomeric epoxides **6** and **7** isolated in 23 and 16% yields, respectively, by column chromatography (Scheme 2). It is worthy to note that epoxides **6** and **7** are the first products purified after four reaction steps, then involving an averaged 80% yield for any single step.

The *trans*-OH/Br relationship in **4** and **5** is certainly responsible for intramolecular S_N2 reactions leading to oxiranes **6** and **7**, respectively, via formal HBr elimination (Figure 2).

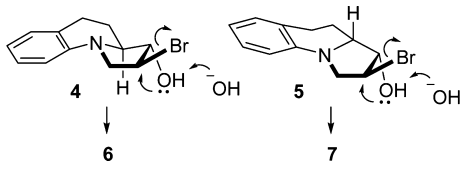


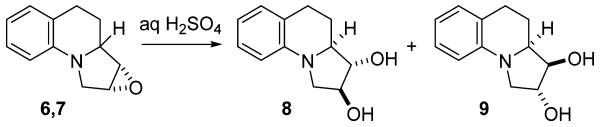
Figure 2. Intramolecular S_N2 reactions on bromohydrins **4** and **5**.

With oxiranes **6** and **7** in hand, ring opening reactions with different nucleophiles were studied.

When oxirane **6** was treated with aqueous H_2SO_4 in THF at 100 °C in a screw-cap tube (see Experimental Section) for 24 h, a 3:1 mixture of diols **8** and **9** was recovered in 35% yield (Table 1, entry 1).

The formation of the reaction products can be rationalized trough a totally *anti* diastereoselective and highly C-2 regioselective nucleophilic attack of water on epoxide **6** (activated by protonation at oxygen and/or nitrogen) (Scheme 3).

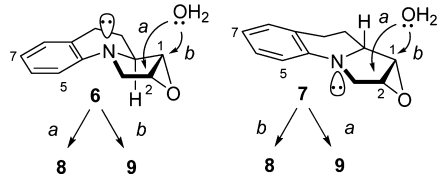
Table 1. Nucleophilic Attack of Water on Oxiranes 6 and 7



entry	oxirane	solvent	*T* (°C)	time	conversion[a] (%)	8:9 ratio[a]	yield[b] (%)
1	**6**	THF	100	24 h	100	3:1	35
2	**6**	D_2O	60	15 d	100	7:1	
3	**6**	D_2O	80	72 h	100	3.5:1	
4	**6**	D_2O	100	24 h	100	2.5:1	
5	**7**	THF	100	24 h	100	1:4	64
6	**7**	D_2O	40	24 h	100	1:4	
7	**7**	D_2O	60	24 h	100	1:4	
8	**7**	H_2O	40	60 h	100	1:3.5	72

[a]Determined via proton nuclear magnetic resonance (^{1}H NMR) spectroscopy. [b]Isolated yields.

Scheme 3. Formation of Diols 8 and 9 from Oxiranes 6 and 7

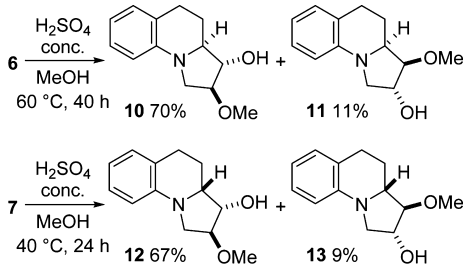


The separation of diols was however unsuccessful. The same reaction was then performed with D_2O as the solvent under different conditions to evaluate the selectivity of the process via ^{1}H NMR analyses. The formation of diol **8** indeed improved at 60 °C, but the reaction times were too long (Table 1, entry 2), whereas operating at 80 or 100 °C, the transformation was faster, but the selectivity decreased (Table 1, entries 3 and 4).

An analogous study was undertaken on oxirane **7**. Operating in THF at 100 °C, diols **8** and **9** were isolated in 64% yield as a 1:4 mixture (Scheme 3, Table 1, entry 5). ^{1}H NMR analyses of reactions performed in D_2O showed a higher reactivity for **7**, compared to **6**, that underwent a total conversion even at 40 or 60 °C (Table 1, entries 6 and 7). Operating in water at 40 °C, a 1:3.5 mixture of diols was recovered in 72% yield (Table 1, entry 8).[d]

Reactions of oxiranes **6** and **7** in dry MeOH, in the presence of conc. H_2SO_4 allowed to recover the methoxy derivatives **10**–**13** in 70 and 11% yields and 67 and 9% yields, respectively (Scheme 4). In this case, the selectivity is higher and the major isomer derives again from a totally *anti* diastereoselective and highly C-2 regioselective nucleophilic attack of methanol on activated epoxides **6** and **7**. Small amounts of diols **8** and **9** were also recovered (see Experimental Section).

Scheme 4. Formation of Methoxy Derivatives 10–13 from Oxiranes 6 and 7



Oxirane ring opening was then studied with acetic acid as the solvent. When heated at 60 °C for 3 days, compound **6** afforded only traces of monoacetates, whereas total decomposition of the starting material was observed for compound **6** after 48 and 24 h at 80 and 100 °C, respectively, and even for epoxide **7** when heated at 60 °C for 4 days.

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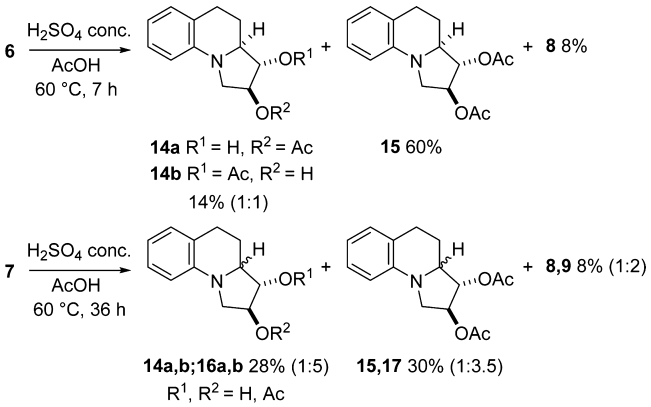
Accidentally, a different pathway was observed operating in AcOH in the presence of concentrated H_2SO_4.[e] Heating compound **6** for 7 h in glacial AcOH at 60 °C allowed to isolate diacetate **15** in 60% yield along with minor amounts of regioisomeric monoacetates **14a,b** (1:1 ratio, 14%) and diol **8** (8%) (Scheme 5).

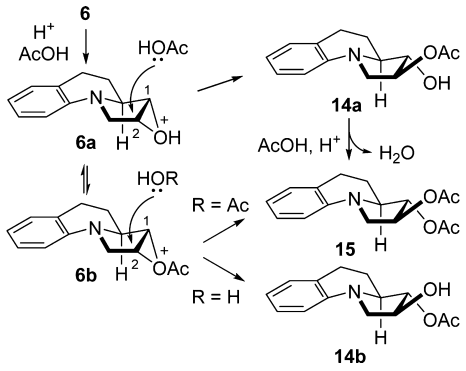
Scheme 5. Ring Opening of Oxiranes 6 and 7 with AcOH and H_2SO_4



By contrast, epoxide **7**, under the same conditions for 36 h, gave a complex reaction mixture of isomeric monoacetates, diacetates, and diols (^{1}H NMR). Careful chromatographic separation allowed to recover a 1:3.5 mixture of diacetates **15** and **17** in 30% yield along with monoacetates **14a,b** and **16a,b** (1:5 ratio, 28%) and diols **8** and **9** (1:2 ratio, 8%) (Scheme 5).

It is worth to note that in the case of oxirane **6**, all reaction products show the same relative stereochemistry on the three stereogenic centers as the fruit of totally *anti* diastereoselective and totally C-2 regioselective nucleophilic attacks on the epoxide ring. This result can be rationalized considering different nucleophilic attacks on suitably activated intermediates (Scheme 6).

Scheme 6. Ring Opening of Oxirane 6 with AcOH: Mechanistic Rational

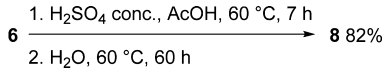


Anti diastereoselective attack of AcOH on the C-2 carbon of protonated oxirane **6a** affords monoacetate **14a**, easily converted into diacetate **15** by esterification. Compound **15** can also arise from acetylated epoxide **6b** via nucleophilic attack of AcOH at position 2, whereas nucleophilic attack of H_2O can give monoacetate **14b**. Hydrolysis of all reaction products can produce diol **8**.

The same mechanism can justify the results observed for epoxide **7**, invoking totally *anti* diastereoselective attacks, but in this case, only preferential regioselective attacks at position 2.

On the basis of these results, running a one-pot reaction for compound **6**, including oxirane ring opening in AcOH/H_2SO_4, followed by hydrolysis under the same conditions allowed to isolate *rac*-benzo[*e*]lentiginosine **8** as the sole reaction product in 82% yield (Scheme 7).

Scheme 7. One-Pot Formation of *rac*-Benzo[*e*]lentiginosine 8 from Oxirane 6



Concerning diol **8**, the relative stereochemistry of the stereogenic centers was unambiguously confirmed by nuclear Overhauser enhancement spectroscopy (NOESY)-one-dimensional (1D) experiments recorded in $CDCl_3$, evidencing dipolar couplings for proton H-10a at δ 3.32 with H-2 (pseudo quartet at 4.37 ppm) and H-3α (doublet-of-doublets at 3.68 ppm) (Figure 3).

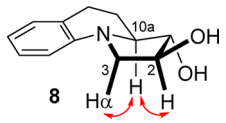


Figure 3. Dipolar couplings for compound **8** (from NOESY-1D experiments).

As previously evidenced, oxirane ring openings in acidic water or MeOH show a higher reactivity for **7** compared to **6**, probably because of a more difficult *anti* nucleophilic attack in the latter for the presence of the nitrogen lone pair (see Scheme 3). On the other hand, compound **6** showed a higher reactivity (with total regioselectivity) in AcOH after addition of H_2SO_4 (complete transformation at 60 °C in 7 h for **6** and in 36 h for **7**). This different behavior could be rationalized in terms of acid−base interactions between AcOH and the ring nitrogen. This coordination could favor the *anti* nucleophilic attack only in oxirane **6** because in compound **7** the nitrogen lone pair is on the same side with respect to the oxirane bridge (Figure 4). Likely for **6**, the same coordination is also able to direct the nucleophilic attack of AcOH exclusively at position 2.

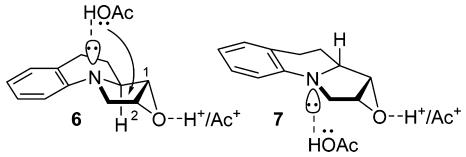


Figure 4. Ring openings of **6** and **7** in AcOH/H_2SO_4.

CONCLUSIONS

In conclusion, these results clearly show the possibility of a general application of this new methodology exploiting pyridine-2-carboxaldehyde derivatives as commercially available starting materials for the synthesis of pyridyl-2-propen-1-ol systems and conversion into various functionalized indolizidines through a four-step approach involving bromination/reduction/nucleophilic substitution via elimination/addition. In

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particular, the use of 2-quinolinecarboxaldehyde allowed the synthesis of polynuclear tetrahydroquinolines, well-recognized as privileged structures with many different applications. For instance, the tricyclic moiety of benzo[*e*]indolizidine is present in naturally occurring alkaloids, such as incargranine B isolated from *Incarvillea mairei* var. grandiflora, a member of the genus *Incarvillea,* from which several derivatives with a strong antinociceptive activity have been isolated (Figure 5).[12]

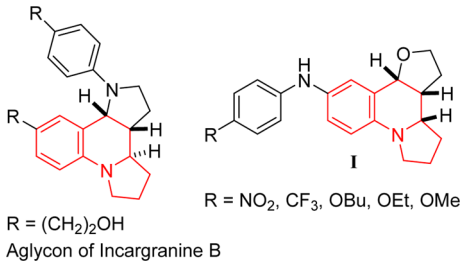

Figure 5. Benzo[*e*]indolizidine derivatives.

Moreover, synthetic tetracyclic derivatives of type **I** showed good in vitro inhibiting activity toward human lung cancer cells, human hepatoma cells, and acute myeloid leukemia cells (Figure 5).[13]

EXPERIMENTAL SECTION

General. Melting points were taken on a Stuart Scientific SIMP3 apparatus and are uncorrected. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230−400 mesh) were used for thin-layer chromatography and flash chromatography (FC), respectively; petroleum ether (PE) employed for chromatographic workup refers to the fraction of bp 40−70 °C. Infrared (IR) spectra were recorded with a Shimadzu FT-IR 84 00S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Mercuryplus 400 and Varian Inova instruments operating at 400 and 100 MHz, respectively. Elemental analyses were performed with a PerkinElmer 2400 analyzer. Accurate mass spectra were recorded on a LTQ-Orbitrap high-resolution mass spectrometer (Thermo, San Jose, CA, USA) equipped with a conventional electrospray ionization (ESI) source.

*(2SR,3SR)-2-Bromo-3-hydroxy-2,3-dihydro-1H-pyrrolo[1,2-a]quinolinium Bromide (**2**) and (2RS,3SR)-2-Bromo-3-hydroxy-2,3-dihydro-1H-pyrrolo[1,2-a]quinolinium Bromide (**3**).* In a typical procedure 2-quinolinecarboxaldehyde (1.000 g, 6.36 mmol) was dissolved in dry diethyl ether (80 mL), and 1.0 M solution of vinylmagnesium bromide in THF (8.26 mmol, 8.26 mL) was added at 0 °C.[10] After workup, 1-(2-quinolyl)-2-propen-1-ol (**1**) (1.108 g, 5.98 mmol, 94% yield) was recovered as an orange oil that was immediately dissolved in CH_2Cl_2 (24 mL), and a solution of bromine (0.956 g, 0.306 mL, 5.98 mmol) in the same solvent (12 mL) was added dropwise (ca. 1 h), keeping the reaction vessel at 0 °C under magnetic stirring. At the end of addition, the reaction mixture was stirred for 30 min at 0 °C and then maintained at room temperature overnight. An approximately 1:2 mixture (^{1}H NMR) of salts **2** and **3** (1.754 g, 85% with respect to **1**) as a dark green solid was recovered by filtration. ^{1}H NMR (CD_3OD):[f] δ [9.27 (d, J = 8.8 Hz, 1H)], 9.18 (d, J = 8.7 Hz, 1H), 8.54 (d, J = 8.1 Hz, 1H), [8.46 (d, J = 7.9 Hz, 1H)], 8.40−8.35 (m, 2H, **2** and **3**), [8.31 (m, 1H)], 8.25−8.16 (m, 3H, **2** and **3**), [8.08 (m, 1H)], 8.01 (m, 1H), 5.96 (d, J = 2.0 Hz, 1H), [5.87 (d, J = 6.8 Hz, 1H)], [5.80 (dd, J = 13.1 and 7.7 Hz, 1H)], [5.23 (dd, J = 13.0 and 7.8 Hz, 1H)], 4.96 (ddd, J = 10.2, 5.1 and 2.0 Hz, 1H), [4.81 (m, 1H)], 4.16−4.05 (m, 2H).[g] ^{13}C NMR (CD_3OD): δ [162.1 (s)], 162.0 (s), [149.7 (d)], 148.7 (d), 138.95 (s), [137.8 (s)], [137.5 (d)], 136.6 (d), [131.6 (d, 2x)], 131.45 (d), [131.0 (s)], 130.6 (d), 129.95 (s), 121.6 (d), 120.85 (d), [119.8 (d, 2x)], [82.4 (d)], 70.5 (d), [61.5 (t)], 55.6 (d), [46.0 (d)], 32.5 (t).[g]

Ensuing filtrations allowed to recover a second crop of salts **2** and **3** (0.248 g, 12% with respect to **1**).

*(2SR,3SR)-2-Bromo-3-hydroxy-2,3-dihydro-1H-pyrrolo[1,2-a]quinolinium Bromide (**2**).* The mixture of salts **2** and **3** (0.690 g, 2.00 mmol) was dissolved in water (100 mL) and stirred at room temperature for 3 days, affording compound **2** as a black solid (0.690 g, 100%): mp > 370 °C. IR, ν_{max} (KBr): 3134, 3076, 2990, 2966, 1620, 1596, 1527, 1055, 847, 779 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 9.34 (d, J = 8.5 Hz, 1H), 8.52 (d, J = 7.4 Hz, 1H), 8.44 (d, J = 8.5 Hz, 1H), 8.30 (m, 1H), 8.22 (d, J = 8.6 Hz, 1H), 8.06 (pseudo t, J = 7.6 Hz, 1H), 5.82 (d, J = 7.4 Hz, 1H), 5.76 (dd, J = 12.9 and 7.8 Hz, 1H), 5.14 (dd, J = 12.7 and 8.4 Hz, 1H), 4.83 (pseudo q, J = 7.8 Hz, 1H). ^{13}C NMR (DMSO-d_6): δ 160.7 (s), 147.9 (d), 135.7 (d), 135.6 (s), 130.1 (d), 130.0 (d), 128.6 (s), 118.9 (d), 118.6 (d), 80.0 (d), 59.45 (t), 45.6 (d). Anal. Calcd for $C_{12}H_{11}Br_2NO$: C, 41.77; H, 3.21; N, 4.06. Found: C, 42.22; H, 2.95; N, 4.01.

*(1aRS,9aSR,9bSR)-1a,2,8,9,9a,9b-Hexahydrobenzo[e]-oxireno[a]indolizine (**6**) and (1aRS,9aRS,9bSR)-1a,2,8,9,9a,9b-Hexahydrobenzo[e]oxireno[a]indolizine (**7**).* Compound **2** (0.345 g, 1.0 mmol) was added to a suspension of $PtO_2{\cdot}H_2O$ (0.023 g, 0.1 mmol) in MeOH (16 mL), and the mixture was stirred at room temperature under an atmospheric pressure of hydrogen for 12 h. The solution was filtered through a celite pad, washed with MeOH and CH_2Cl_2, and evaporated to dryness affording a mixture of **4** and **5** as the major compounds, which was dissolved in THF (12 mL) and water (4 mL), added with solid KOH (0.168 g, 3.0 mmol), and heated at 40 °C for 24 h. The reaction crude was extracted with ethyl acetate (4 × 10 mL), and the resulting organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Chromatographic resolution with CH_2Cl_2 as the eluent allowed to isolate compound **7** (R_f = 0.59, 0.030 g, 16%): mp 58−59 °C (ivory crystals from pentane/Et_2O). IR, ν_{max} (KBr): 3040, 2928, 2892, 2841, 1603, 1503, 1459 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.05 (t, J = 7.7 Hz, 1H), 6.97 (d, J = 7.4 Hz, 1H), 6.58 (td, J = 7.5, 1.0 Hz, 1H), 6.34 (d, J = 8.1 Hz, 1H), 3.74 (dd, J = 3.2, 1.3 Hz, 1H), 3.72 (ddd, J = 3.2, 1.2, 0.3 Hz, 1H), 3.66 (ddd, J = 11.3, 2.9, 1.2 Hz, 1H), 3.63 (d, J = 11.5 Hz, 1H), 3.34 (dd, J = 11.5, 1.2 Hz, 1H), 2.94−2.78 (m, 2H), 2.10 (ddt, J = 12.5, 5.3, 2.7 Hz, 1H), 1.77 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 144.3 (s), 128.6 (d), 127.1 (d), 120.5 (s), 115.6 (d), 110.0 (d), 58.5 (d), 57.2 (d), 54.5 (d), 48.9 (t), 27.3 (t), 21.9 (t). HRMS (ESI) m/z: calcd for $C_{12}H_{14}NO$ $[MH]^+$, 188.1070; found, 188.1074.

The slowest moving fraction afforded oxirane **6** (R_f = 0.27, 0.044 g, 23%) that was crystallized from pentane/Et_2O in ivory flakes: mp 63−64 °C. IR, ν_{max} (KBr): 3034, 2929, 2847, 1602, 1494, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 7.08 (t, J = 7.6 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.67 (td, J = 7.4, 0.8 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 3.96 (d, J = 11.4 Hz, 1H), 3.85 (dd, J = 2.9, 2.0 Hz, 1H), 3.71 (d, J = 3.1 Hz, 1H), 3.67 (dd, J = 12.6, 2.4 Hz, 1H), 3.26 (dd, J = 11.3, 1.8 Hz, 1H), 2.93−2.78 (m, 2H), 1.97 (ddt, J = 12.2, 5.0, 2.5 Hz, 1H), 1.39 (qd, J = 12.4, 5.5 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 145.2 (s), 129.1 (d), 127.0 (d), 122.2 (s), 117.4 (d), 114.8 (d), 60.3 (d), 58.8 (d), 56.7 (d),

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52.1 (t), 27.9 (t), 21.9 (t). HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{14}NO$ $[MH]^+$, 188.1070; found, 188.1069.

Ring Openings of Oxiranes 6 and 7: General Procedure. A solution of oxirane (0.094 g, 0.5 mmol) in the reported solvent (10 mL) was added with H_2SO_4 and heated at the reported temperature for the reported time in a screw-cap tube (Pyrex N. 22) under magnetic stirring. The resulting mixture was made basic by the addition of NH_4OH 30% (ca. 0.5 mL), evaporated to dryness under reduced pressure, and resolved by FC.

*(2SR,3SR,3aSR)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]-quinoline-2,3-diol (**8**) and (2RS,3RS,3aSR)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoline-2,3-diol (**9**).*

(A) Oxirane **6** and aqueous H_2SO_4 (1 M, 1.25 mL, 1.25 mmol) were heated in THF at 100 °C for 24 h. Chromatographic resolution (toluene/MeOH/AcOH 7:2:0.15 v/v) allowed to isolate a 3:1 mixture of **8** and **9** (R_f = 0.42, 0.036 g, 35%).

(B) Operating as above with oxirane **7**, a 1:4 mixture of **8** and **9** (R_f = 0.42, 0.066 g, 64%) was isolated.

(C) Operating in water as the solvent, a 1:3.5 mixture of **8** and **9** (R_f = 0.42, 0.074 g, 72%) was recovered by heating oxirane **7** at 40 °C for 60 h. A small amount of pure diol **9** was isolated by FC as a sticky solid. IR, ν_{max} (KBr): 3386, 3043, 2931, 2849, 1604, 1505 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (t, *J* = 7.4 Hz, 1H), 7.00 (d, *J* = 7.4 Hz, 1H), 6.60 (t, *J* = 7.4 Hz, 1H), 6.41 (d, *J* = 7.8 Hz, 1H), 4.33 (d, *J* = 4.8 Hz, 1H), 4.05 (d, *J* = 3.0 Hz, 1H), 3.79 (dt, *J* = 11.8, 3.3 Hz, 1H), 3.65 (dd, *J* = 11.1, 4.8 Hz, 1H), 3.18 (d, *J* = 11.1 Hz, 1H), 2.99−2.80 (m, 2H), 2.03−1.97 (m, 1H), 1.95−1.51 (vbr s, 2H), 1.79 (pseudo qd, *J* = 12.3, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 144.4 (s), 128.5 (d), 127.3 (d), 121.3 (s), 115.8 (d), 110.1 (d), 77.5 (d), 75.2 (d), 59.1 (d), 53.5 (t), 27.5 (t), 20.3 (t). HRMS (ESI) *m*/*z*: calcd for $C_{12}H_{16}NO_2$ $[MH]^+$, 206.1176; found, 206.1177.

*(2SR,3SR,3aSR)-2-Methoxy-1,2,3,3a,4,5-hexahydropyrrolo-[1,2-a]quinolin-3-ol (**10**) and (2RS,3RS,3aSR)-3-Methoxy-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolin-2-ol (**11**).* Concentrated H_2SO_4 (0.069 mL, 1.25 mmol) was added to a solution of **6** in dry MeOH (6 mL). After heating at 60 °C for 40 h, the reaction mixture was subjected to chromatographic separation, with CH_2Cl_2/EtOAc 5:1 v/v as the eluent. The first moving band gave a 4:1 mixture (^1H NMR) of methoxy derivatives **10** and **11** (R_f = 0.39, 0.060 g, 55%). ^1H NMR ($CDCl_3$): δ 7.12−7.02 (m, 2H), 7.01−6.96 (m, 2H), 6.62 (td, *J* = 7.4, 0.8 Hz, 1H), [6.57 (t, *J* = 7.3 Hz, 1H)], [6.38 (d, *J* = 7.9 Hz, 1H)], 6.37 (d, *J* = 8.0 Hz, 1H), [4.42 (d, *J* = 4.6 Hz, 1H)], 3.97 (pseudo q, *J* = 6.7 Hz, 1H), 3.86 (dd, *J* = 8.3, 7.0 Hz, 1H), [3.82 (dt, *J* = 11.7, 3.6 Hz, 1H)], 3.68−3.61 (m, 2H, **10** and **11**), [3.54 (dd, *J* = 10.9, 4.6 Hz, 1H)], 3.50 (s, 3H), [3.43 (s, 3H)], 3.30 (ddd, *J* = 11.4, 8.4, 3.1 Hz, 1H), [3.22 (d, *J* = 10.9 Hz, 1H)], 3.17 (dd, *J* = 9.6, 6.4 Hz, 1H), 2.95−2.75 (m, 4H), 2.61 (br s, 2H), 2.33−2.23 (m, 1H), [1.99−1.90 (m, 1H)], [1.82 (pseudo qd, *J* = 12.6, 4.9 Hz, 1H)], 1.58 (pseudo qd, *J* = 11.8, 6.0 Hz, 1H).[h] ^{13}C NMR ($CDCl_3$): δ [144.5 (s)], 143.9 (s), 128.7 (d), [128.3 (d)], 127.2 (d), [127.1 (d)], [121.5 (s)], 121.3 (s), 116.2 (d), [115.3 (d)], [109.9 (d)], 109.7 (d), [86.3 (d)], 84.5 (d), 80.6 (d), [72.0 (d)], 61.0 (d), [59.3 (d)], 58.2 (q), [58.1 (q)], [54.0 (t)], 49.6 (t), [27.8 (t)], 27.2 (t), 25.3 (t), [20.3 (t)].[h]

The following band afforded compound **10** (R_f = 0.29, 0.029 g, 26%) that was crystallized from Et_2O/pentane in pale yellow pearls: mp 109−110 °C. IR, ν_{max} (KBr): 3427, 3038, 2926, 2849, 1601, 1502 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.08 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.3 Hz, 1H), 6.61 (td, *J* = 7.4, 1.0 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 3.97 (pseudo q, *J* = 7.0 Hz, 1H), 3.86 (t, *J* = 7.4 Hz, 1H), 3.65 (dd, *J* = 9.6, 7.7 Hz, 1H), 3.50 (s, 3H), 3.30 (ddd, *J* = 11.3, 8.0, 3.1 Hz, 1H), 3.17 (dd, *J* = 9.6, 6.4 Hz, 1H), 2.90−2.76 (m, 2H), 2.33−2.25 (m, 1H), 1.64−1.52 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 143.9 (s), 128.7 (d), 127.2 (d), 121.3 (s), 116.0 (d), 109.7 (d), 84.7 (d), 80.7 (d), 61.0 (d), 58.1 (q), 49.6 (t), 27.2 (t), 25.3 (t).

HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{18}NO_2$ $[MH]^+$, 220.1332; found, 220.1334.

The slowest moving fraction gave diols **8** and **9** (R_f = 0.04, 0.013 g, 13%) in 1.5:1 ratio (^1H NMR).

*(2SR,3SR,3aRS)-2-Methoxy-1,2,3,3a,4,5-hexahydropyrrolo-[1,2-a]quinolin-3-ol (**12**) and (2RS,3RS,3aRS)-3-Methoxy-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolin-2-ol (**13**).* Operating as above on oxirane **7**, the reaction mixture was heated at 40 °C for 24 h and then resolved by FC (CH_2Cl_2/EtOAc 7:1 v/v). The first band afforded compound **12** (R_f = 0.44, 0.054 g, 49%) as an orange sticky product. IR, ν_{max} (KBr): 3422, 3039, 2930, 2849, 1604, 1502 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (t, *J* = 7.6 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 6.59 (td, *J* = 7.6, 1.0 Hz, 1H), 6.41 (d, *J* = 8.0 Hz, 1H), 4.15 (d, *J* = 3.0 Hz, 1H), 3.85 (d, *J* = 5.1 Hz, 1H), 3.65 (dt, *J* = 11.8, 3.2 Hz, 1H), 3.58 (dd, *J* = 11.0, 5.2 Hz, 1H), 3.42 (s, 3H), 3.21 (d, *J* = 11.0 Hz, 1H), 2.99−2.79 (m, 2H), 2.03−1.96 (m, 1H), 1.81−1.68 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 144.6 (s), 128.4 (d), 127.2 (d), 121.3 (s), 115.7 (d), 110.0 (d), 84.2 (d), 74.7 (d), 59.4 (d), 57.0 (q), 50.5 (t), 27.4 (t), 20.5 (t). HRMS (ESI) *m*/*z*: calcd for $C_{13}H_{18}NO_2$ $[MH]^+$, 220.1332; found, 220.1335.

The following band gave a mixture of methoxy derivatives **12** and **13** (R_f = 0.34, 0.030 g, 27%) in about 2:1 ratio (^1H NMR). ^1H NMR ($CDCl_3$): δ 7.11−7.03 (m, 2H), 6.99 (d, *J* = 7.3 Hz, 2H), 6.65−6.56 (m, 2H), 6.42 (d, *J* = 8.0 Hz, 1H), [6.38 (d, *J* = 8.1 Hz, 1H)], [4.39 (dt, *J* = 7.4, 5.7 Hz, 1H)], 4.15 (d, *J* = 2.6 Hz, 1H), 3.86 (d, *J* = 5.2 Hz, 1H), 3.66 (dt, *J* = 11.8, 3.1 Hz, 1H), 3.61−3.55 (m, 3H, **12** and **13**), [3.58 (s, 3H)], 3.42 (s, 3H), [3.27 (ddd, *J* = 11.0, 7.6, 3.0 Hz, 1H)], 3.22−3.17 (m, 2H), 3.00−2.77 (m, 4H), [2.34−2.28 (m, 1H)], 2.04−1.95 (m, 1H), 1.84 (br s, 2H), 1.82−1.61 (m, 2H, **12** and **13**).[i] ^{13}C NMR ($CDCl_3$): δ 144.6 (s), [144.1 (s)], [128.7 (d)], 128.5 (d), 127.2 (d), [127.1 (d)], [121.4 (s)], 121.3 (s), [116.2 (d)], 115.7 (d), [110.2 (d)], 110.1 (d), [91.3 (d)], 84.2 (d),[75.0 (d)], 74.7 (d), [60.9 (d)], 59.4 (d), [58.8 (q)], 57.1 (q), [52.4 (t)], 50.5 (t), 27.4 (t), [27.3 (t)], [26.3 (t)], 20.6 (t).[i]

The slowest moving fractions afforded diols **8** and **9** (R_f = 0.04, 0.009 g, 9%) in 1:1.5 ratio (^1H NMR).

*(2SR,3SR,3aSR)-3-Hydroxy-1,2,3,3a,4,5-hexahydropyrrolo-[1,2-a]quinolin-2-yl Acetate (**14a**), (2SR,3SR,3aSR)-2-Hydroxy-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinolin-3-yl Acetate (**14b**), and (2SR,3SR,3aSR)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoline-2,3-diyl Diacetate (**15**).* A solution of oxirane **6** and concentrated H_2SO_4 (0.138 mL, 2.5 mmol) in glacial AcOH was heated at 60 °C for 7 h. Basic workup by addition of NH_4OH 30% (ca. 20 mL), extraction with EtOAc (4 × 10 mL), and evaporation to dryness of the organic phase dried over anhydrous Na_2SO_4 led to a residue that was resolved by FC with PE/EtOAc 4:1 v/v as the eluent. The first band gave compound **15** (R_f = 0.61, 0.087 g, 60%) that was crystallized from pentane/Et_2O in white needles: mp

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71−72 °C. IR, ν_{max} (KBr): 3041, 2943, 2847, 1744, 1601, 1501, 1366, 1238 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.08 (t, J = 7.8 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.66 (td, J = 7.4, 1.0 Hz, 1H), 6.40 (d, J = 7.5 Hz, 1H), 5.31 (ddd, J = 7.3, 5.2, 4.2 Hz, 1H), 5.16 (dd, J = 7.3, 5.2 Hz, 1H), 3.71 (dd, J = 10.8, 7.3 Hz, 1H), 3.37 (dd, J = 10.7, 4.2 Hz, 1H), 3.35 (ddd, J = 11.3, 7.3, 2.9 Hz, 1H), 2.92−2.70 (m, 2H), 2.27−2.19 (m, 1H), 2.13 (s, 3H), 2.09 (s, 3H), 1.82−1.70 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 170.7 (s), 170.3 (s), 143.7 (s), 128.9 (d), 127.1 (d), 121.5 (s), 117.0 (d), 110.8 (d), 79.9 (d), 75.6 (d), 60.3 (d), 51.0 (t), 26.7 (t), 25.3 (t), 20.95 (q), 20.9 (q). Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.04; H, 6.89; N, 4.51.

The following band afforded an almost 1:1 mixture of monoacetates **14a,b** (R_f = 0.20, 0.017 g, 14%). ^1H NMR ($CDCl_3$): δ 7.11−7.06 (m, 2H), 7.03−6.97 (m, 2H), 6.67−6.61 (m, 2H), 6.44−6.36 (m, 2H), 5.05 (ddd, J = 8.2, 5.4, 4.8 Hz,, 1H, **14a**), 4.64 (dd, J = 8.2, 5.5 Hz, 1H, **14b**), 4.44−4.39 (m, 1H, **14b**), 3.90 (dd, J = 8.2, 5.6 Hz, 1H, **14a**), 3.66−3.59 (m, 2H), 3.46−3.35 (m, 3H, **14b** and **14a**), 3.28 (ddd, J = 11.1, 8.2, 2.9 Hz, 1H, **14a**), 2.95−2.76 (m, 4H), 2.40−2.32 (m, 1H, **14a**), 2.27−2.21 (m, 1H, **14b**), 2.17 (s, 3H, **14b**), 2.15 (s, 3H, **14a**), 1.77−1.62 (m, 4H). ^{13}C NMR ($CDCl_3$): δ 173.0 (s, **14a**), 172.8 (s, **14b**), 143.9 (s, **14a**), 143.8 (s, **14b**), 128.8 (d, **14b**), 128.7 (d, **14a**), 127.2 (d, **14b**), 127.1 (d, **14a**), 121.8 (s, **14a**), 121.4 (s, **14b**), 116.9 (d, **14a**), 116.8 (d, **14b**), 110.6 (d, **14b**), 110.4 (d, **14a**), 86.2 (d, **14a**), 81.1 (d, **14b**), 80.8 (d, **14b**), 74.8 (d, **14a**), 61.7 (d, **14a**), 59.9 (d, **14b**), 52.7 (t, **14b**), 50.0 (t, **14a**), 27.0 (t, 2x), 25.6 (t, **14a**), 25.5 (t, **14a**), 20.9 (q, 2x).

The slowest moving band led to diol **8** (R_f = 0.08, 0.008 g, 8%).

*Reaction of Oxirane **7** with AcOH/H_2SO_4: Synthesis of (2SR,3SR,3aSR)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoline-2,3-diyl Diacetate (**15**) and (2SR,3SR,3aRS)-1,2,3,3a,4,5-hexahydropyrrolo[1,2-a]quinoline-2,3-diyl Diacetate (**17**).* Operating as above, chromatographic resolution (PE/EtOAc 4:1 v/v) of the reaction mixture obtained from oxirane **7** after heating for 36 h led to a 1:3.5 mixture of diacetates **15** and **17** (R_f = 0.61, 0.043 g, 30%). ^1H NMR ($CDCl_3$): δ 7.13−7.05 (m, 2H), 7.01 (d, J = 7.3 Hz, 2H), [6.66 (td, J = 7.4, 1.0 Hz, 1H)], 6.61 (td, J = 7.4, 0.9 Hz, 1H), 6.42−6.36 (m, 2H), [5.34−5.28 (m, 1H)], 5.32 (d, J = 3.5 Hz, 1H), 5.24 (d, J = 5.1 Hz, 1H), [5.16 (dd, J = 7.3, 5.2 Hz, 1H)], 3.89 (dt, J = 11.6, 3.4 Hz, 1H), [3.75−3.66 (m, 1H)], 3.70 (dd, J = 11.5, 5.1 Hz, 1H), [3.41−3.32 (m, 2H)], 3.32 (d, J = 11.5 Hz, 1H), 2.97−2.76 (m, 4H), [2.26−2.18 (m, 1H)], [2.13 (s, 3H)], 2.10 (s, 3H), [2.09 (s, 3H)], 2.06 (s, 3H), 2.02−1.94 (m, 1H), [1.82−1.70 (m, 1H)], 1.65−1.53 (m, 1H).[j] ^{13}C NMR ($CDCl_3$): δ [170.8 (s)], [170.7 (s)], 169.9 (s, 2x), [143.7 (s)], 143.6 (s), [128.9 (d)], 128.5 (d), 127.4 (d), [127.1 (d)], [121.5 (s)], 121.0 (s), [117.0 (d)], 115.9 (d), [110.8 (d)], 109.9 (d), [79.8 (d)], 76.2 (d), [75.6 (d)], 74.8 (d), [60.3 (d)], 59.0 (d), 51.5 (t), [51.0 (t)], 27.3 (t), [27.0 (t)], [25.3 (t)], 21.0 (q), [20.9 (q, 2x)] (q), 20.6 (t).[j]

The following band afforded an almost 1:5 mixture of a couple of monoacetates **14a,b** and **16a,b** (R_f = 0.20, 0.035 g, 28%).

The slowest moving band led to a 1:2 mixture of diols **8** and **9** (R_f = 0.08, 0.008 g, 8%).

*(2SR,3SR,3aSR)-1,2,3,3a,4,5-Hexahydropyrrolo[1,2-a]quinoline-2,3-diol (**8**).* A solution of oxirane **6** and concentrated H_2SO_4 (0.138 mL, 2.5 mmol) in glacial AcOH was heated at 60 °C for 7 h. Then, water (10 mL) was added, and the resulting mixture was heated at the same temperature for 60 h. Basic workup by addition of NH_4OH 30% (ca. 20 mL), extraction with EtOAc (4 × 10 mL), and evaporation to dryness of the dried organic phase gave a residue that was subjected to FC, with CH_2Cl_2/MeOH 9.5:0.5 v/v as the eluent. Compound **8** (R_f = 0.37, 0.084 g, 82%) was recovered and crystallized from Et_2O in ivory crystals: mp 150−151 °C. IR, ν_{max} (KBr): 3360, 3304, 3212, 3074, 2957, 2916, 2839, 1602, 1505 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.07 (t, J = 7.7 Hz, 1H), 6.99 (d, J = 7.4 Hz, 1H), 6.61 (td, J = 7.4, 1.0 Hz, 1H), 6.36 (d, J = 7.8 Hz, 1H), 4.37 (pseudo q, J = 7.3 Hz, 1H), 3.79 (dd, J = 8.1, 7.3 Hz, 1H), 3.68 (dd, J = 9.6, 7.9 Hz, 1H), 3.32 (ddd, J = 11.4, 8.3, 3.2 Hz, 1H), 3.14 (dd, J = 9.7, 7.0 Hz, 1H), 2.89−2.74 (m, 2H), 2.49 (br s, 2H), 2.32−2.25 (m, 1H), 1.57 (pseudo qd, J = 11.4, 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 143.6 (s), 128.7 (d), 127.3 (d), 121.3 (s), 116.1 (d), 109.7 (d), 82.2 (d), 76.1 (d), 61.2 (d), 51.4 (t), 27.2 (t), 25.2 (t). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 69.83; H, 7.73; N, 6.60.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsomega.8b00167.

^1H and ^{13}C NMR spectra of all new compounds (PDF)

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

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■ ADDITIONAL NOTES

[a]The conversion was almost instantaneous in dimethyl sulfoxide (DMSO), but the use of water was preferred, being a green solvent and allowing an easier recovery of the product.
[b]Minor amounts of fully reduced products were also observed via ^1H NMR analyses.
[c]Likely, the presence of an aniline moiety in the reduction products is responsible for decomposition/polymerization processes.
[d]^1H NMR analyses of the reaction crudes with D_2O as the solvent, for both epoxides, clearly evidenced the total deuteration at positions 5 and 7, likely an aromatic electrophilic substitution activated by the aniline-type ring nitrogen in diols **8** and **9**.
[e]The reaction was performed with a 1:5 molar ratio epoxide/H_2SO_4 to favor the formation of diacetate **15** (see Experimental Section).
[f]The spectrum of the diastereomeric mixture has been recorded in CD_3OD because in DMSO-*d6*, the *cis* salt immediately isomerizes into the *trans* one.
[g]The data reported in square brackets refer to the *trans* indolizinium bromide **2**.

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[h]The data reported in square brackets refer to compound **11**.
[i]The data reported in square brackets refer to compound **13**.
[j]The data reported in square brackets refer to compound **15**.

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