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A Concise Synthesis of Lentiginosine Derivatives Using a Pyridinium Formation via the Mitsunobu Reaction

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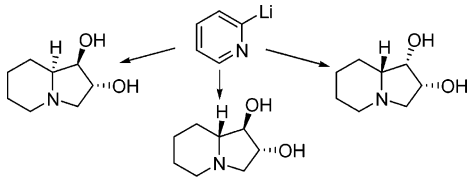

(4 step-synthesis)

A four-step synthesis of (−)-lentiginosine and its epimers is described starting from 2-bromopyridine. The key step consisted of a quaternarization of a fully unprotected pyridinium-polyol unit using Mitsunobu methodology. Subsequent PtO_2-catalyzed diastereoselective hydrogenation of the pyridinium ring proceeded smoothly and led to the expected dihydroxyindolizidines with excellent yields. This stereochemically flexible strategy has been illustrated by the concise total synthesis of non-natural products derivatives such as (−)-lentiginosine and its stereoisomers in high yields.

As a continuation of our studies concerning the chemistry of pyridines,[1] we were interested in investigating this heteroaromatic ring as the precursor of fully reduced 6-membered rings, present in numerous alkaloids. Consequently, the indolizidine scaffold was chosen for this study. Considering their biomedically relevant properties, the search for a versatile and straightforward route toward indolizidine alkaloids remains challenging. Ring-saturated nitrogen heterocycles are well-known components of the venoms of ants, as well as of amphibian skin.[2] These alkaloid structures, including indolizidines, are increasingly attractive because of their high potential in a wide range of biological applications. Therefore, numerous reports describing the syntheses of indolizidine and polyhydroxylated indolizidine alkaloids and their biological properties have been published.[3] Since 1965, more than 100 polyhydroxylated alkaloids have been isolated from plants and micro-organisms.[4] Due to their pharmacological potential as amyloglycosidase inhibitors,[5] polyhydroxylated indolizidine alkaloids, such as (+)-lentiginosine and its isomers,[6,7] have received considerable synthetic interest (Figure 1). These naturally occurring sugar mimics are potential therapeutic agents against many diseases such as cancer, diabetes, or viral infections including HIV.[8]

Despite their relatively simple structure, hydroxylated indolizidines represent challenging synthetic targets. A number of elegant routes toward these alkaloids have been reported.[3] Most of the synthetic routes to lentiginosine rely upon the construction of the pyrrolidine or piperidine unit, in numerous steps, featuring the appropriate functionalities able to secure the generation of the bicyclic skeleton.[6b,i−l,9] Surprisingly, synthesis of a hydroxylated indolizidine framework from pyridine is sparse.[10] For example, the shortest synthesis to date of natural (+)-lentiginosine was accomplished in five steps by Zhou starting from pyridine 2-carbaldehyde in 16% overall

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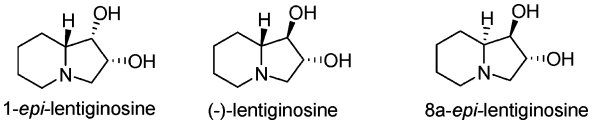
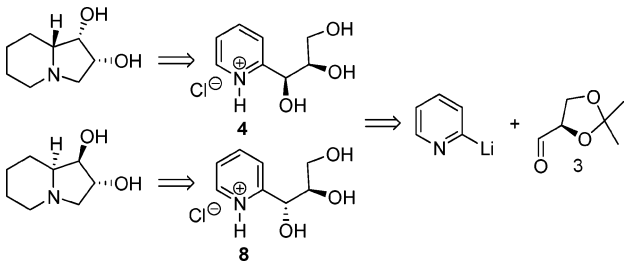


FIGURE 1. (−)-Lentiginosine and some epimeric structures.

SCHEME 1. Retrosynthetic Pathway

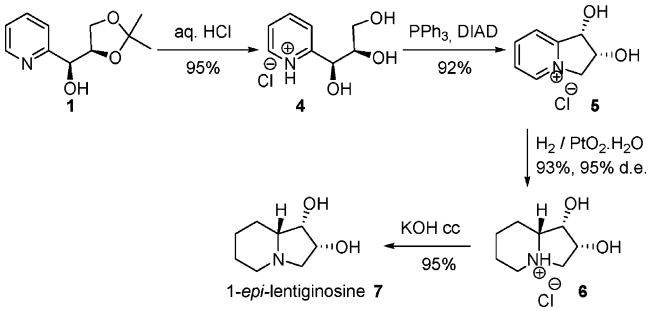


yield.[6m] This synthesis is closely related to Gurjar's approach starting from pipecolic acid.[11] Herein, we wish to describe a new and concise strategy based upon the exploitation of the ubiquitous Mitsunobu reaction[12] for the creation of the dihydroxylated five-membered ring included in the indolizidine framework.

Considering the Mitsunobu mechanism, we worked out the cyclization step using a pyridinium salt as NuH. To the best of our knowledge, there is no precedent for this approach.[13] This strategy does not require a protection−deprotection sequence of the alcohol moieties. Classically, this bicyclic pyridinium system was built using pyridyl propranol by treatment with mesyl chloride or triflic anhydride and a base.[14] If the cyclization step could be done via the Mitsunobu reaction, we believe that we would be able to generate a new approach to the synthesis of indolizidinium. In order to test this hypothesis, 2-(3-hydroxypropyl)pyridinium was subjected to Mitsunobu conditions (PPh_3-DIAD in acetonitrile). The bicyclic pyridinium was formed quantitatively and was extracted in water allowing easy discarding of Mitsunobu side products. Our general retrosynthetic approach for the synthesis of hydroxylated indolizidines is depicted in Scheme 1. In this strategy, pyridinium intermediates **4** and **8** are readily available in two steps from 2-bromopyridine and provide the dihydroxyindolizidine scaffold in a short and excellent carbon economy pathway.

Enantiomerically pure (*R*)-2,3-*O*-isopropylidene glyceraldehyde **3** was prepared from D-mannitol in two steps according to the literature.[15] 2-Bromopyridine was treated with *n*-BuLi at

SCHEME 2. Total Synthesis of 1-*epi*-Lentiginosine



−78 °C affording 2-lithiopyridine. The latter reacted smoothly with (*R*)-2,3-*O*-isopropylideneglyceraldehyde to give a 2.3:1 mixture of diastereoisomeric alcohols **1** and **2** in 63% yield, which is consistent with the results described by Moberg et al.[16] Since both stereoisomers could be easily separated by chromatography on silica gel using a solvent gradient and led to different targets, the diastereoisomeric excess was not improved. The alcohol **1** is presumably formed via a chelation-controlled addition of 2-lithiopyridine to the aldehyde. On the other hand, compound **2** could also be obtained as the major diastereoisomer by reducing the corresponding ketone with $LiAlH_4$[17] (in 99% yield with a 50% de as indicated by ^{1}H NMR). We first applied our synthetic route to the diastereoisomer **1**. As illustrated in Scheme 2, subsequent cleavage of acetonide under mild acidic conditions afforded the triol **4** in 95% yield. The indolizidine ring system was built by using an intramolecular cyclization under Mitsunobu conditions (PPh_3-DIAD in acetonitrile for 2 h), leading to pure pyridinium **5** in 92% yield. It is worth noting that these conditions were compatible with the fully unprotected triol and required no purification, the pyridinium being extracted in water.

The catalytic hydrogenation[18] of this *N*-alkylpyridinium **5** proceeded smoothly in ethanol at atmosphere pressure, in the presence of PtO_2 as catalyst to give **6** in 93% yield with more than 95% de as indicated by ^{1}H NMR. The high diastereoselectivity observed in the reduction of the pyridine ring of compound **5** could be explained by the formation of a rigid chiral pyridinium intermediate.[19] In absence of a base, the indolizidinium hydrochloride **6** resulting from the reduction prevents catalyst poisoning by the corresponding indolizidine. In addition, the protonated indolozidine leads to a stable compound that can be isolated. Finally, compound **6** was readily transformed into 1-*epi*-lentiginosine **7** in 95% yield through simple treatment with concentrated aqueous KOH.[20a] The obtained stereochemistry indeed corresponds to the less-hindered

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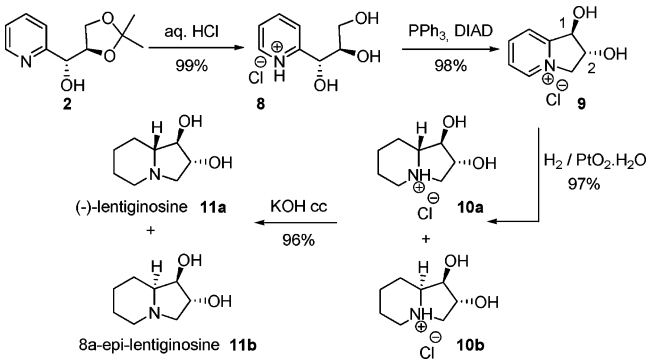
SCHEME 3. Total Synthesis of (−)-Lentiginosine and Its 8a-Epimer



side of the pyridinium salt. Using this strategy, 1-*epi*-lentiginosine **7** was synthesized in four steps from commercially available 2-bromopyridine in 36% overall yield.

As illustrated in Scheme 3, applying this synthetic approach to the diastereoisomer **2** gave access to (−)-lentiginosine. In this case, the platinum oxide-catalyzed hydrogenation of compound **9** produced a 0.8:1 mixture of diastereoisomers **10a** and **10b**, allowing an expedient 5-steps total synthesis of (−)-lentiginosine **11a** and its 8a-epimer **11b** in respectively 28% and 31% overall yield from 2-bromopyridine. A subtle balance of steric and torsional factors might be responsible for the loss of diastereoselectivity during the reduction step. For the structures **7**,[20] **11a**,[21] and **11b**,[21] the stereochemical assignment and absolute configurations were unequivocally established on the basis of published spectra.

In compound **9**, a hindered group introduced at C_1 should shield one face of the molecule during the reduction step. As a result, hydrogen atoms transferred stepwise to the unhindered side should enhance the diastereoselectivity. As depicted in Scheme 4, substrate **14** with an *O*-*p*-toluoyl group at C_1 was subjected to hydrogenation reaction. The increased steric hindrance at C_1 led to improved de value. The reduction proceeded in a substrate-controlled fashion and gave 95% yield of the expected diastereoisomer **15** with a 74% de as determined by ^{1}H NMR.

The present methodology has several advantages over classical published synthetic routes toward hydroxylated indolizidine alkaloids derivatives. First, subjecting the pyridinium salts to Mitsunobu conditions resulted exclusively in indolizidinium scaffold without purification. This approach illustrates an original use of Mitsunobu protocol applied to pyridinium compounds. Second, the dihydroxyindolizidine was obtained in a short and excellent carbon economy pathway in good yield. Finally, both cyclization and reduction steps are carried out under simple, mild and effective conditions allowing the synthesis of various nitrogen-bridgehead heterocycles containing a piperidine ring, a common scaffold in biologically active natural compounds.

In summary, we have demonstrated that the Mitsunobu reaction is viable as a new methodology for the formation of bridgehead azabicyclic compounds from pyridine derivatives. The concise and high-yielding total synthesis of non-naturals analogues of (+)-lentiginosine provided an interesting example of this reaction. In addition, such an alkylation−reduction sequence opens the way to shortened synthesis of numerous azabicyclic alkaloids, such as swainsonine and castanospermine. Studies are in progress in this area.

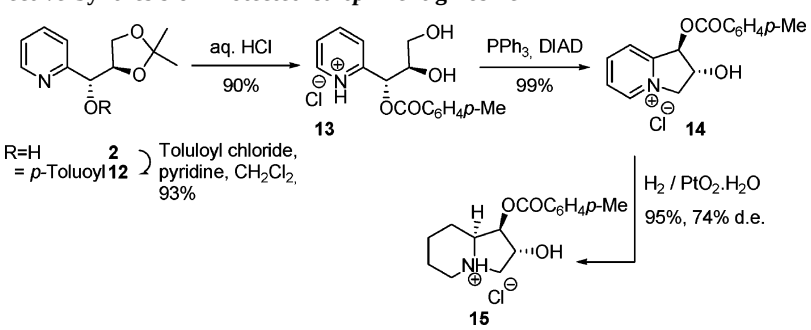
Experimental

General Methods. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. All reactions were monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminum plates (0.25 mm). Flash chromatography was performed with indicated solvents using silica gel (particle size 30−63 μm). ^{1}H and ^{13}C NMR spectra were recorded at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Chemical shifts are reported relative to TMS, calibrated with chloroform or deuterium oxide. Coupling constants *J* are in Hz and are reported as d (doublet), t (triplet), q (quartet).

Experimental Procedures and Data. 2-((1*S*,2*R*)-1,2,3-Trihydroxypropyl)pyridinium Chloride (4). Compound **1** (450 mg, 2.15 mmol) was taken up in dioxane (4 mL), and an equal volume of 2 M aq HCl was added. After the mixture was stirred at room temperature for 2 h, solvents were evaporated in vacuo, and the residue was dissolved in H_2O, washed with diethyl ether, and freeze-dried to afford pure (1*S*,2*R*)-1-(2′-pyridyl)-1,2,3-trihydroxypropane **4** (420 mg, 95%) as its hydrochloride salt. ^{1}H NMR (D_2O): δ 3.67 (m, 2H), 3.93 (dt, J = 6.0, 4.7, 1H), 5.1 (d, J = 6.0, 1H), 7.95 (t, J = 7.6, 1H), 8.03 (d, J = 7.6, 1H), 8.54 (t, J = 7.6, 1H), 8.69 (d, J = 5.8, 1H). ^{13}C NMR (D_2O): δ 61.9, 70.5, 73.9, 126.1, 126.5, 140.9, 147, 155.3. $[\alpha]_D$ = −4 (*c* 1, CH_3OH). IC(+)MS (MH^+) *m*/*z* = 170 (100), 154, 117, 108, 79. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 46.73; H, 5.88; N, 6.81. Found: C, 45.94; H, 5.79; N, 6.20.

(1*S*,2*R*)-1,2-Dihydroxy-2,3-dihydro-1*H*-indolizinium Chloride (5). To a solution of **4** (350 mg, 1.7 mmol) and triphenylphosphine (669 mg, 2.55 mmol) in anhydrous CH_3CN (30 mL) was added diisopropyl azodicarboxylate (DIAD) (0.51 mL, 2.55 mmol) dropwise at 0 °C. After the mixture was stirred at room temperature for 2 h, CH_3CN was evaporated, and the residue was dissolved in H_2O, washed with Et_2O, and freeze-dried to afford pure **5** (293 mg, 92%) as a white powder. ^{1}H NMR (D_2O): δ 4.8 (m, 1H), 4.87 (m, 2H), 5.53 (d, J = 4.5, 1H), 7.97 (t, J = 8, 1H), 8.11 (d, J = 8, 1H), 8.55 (t, J = 8, 1H), 8.8 (d, J = 6.2, 1H). ^{13}C NMR ($CDCl_3$): δ 63.5, 70.7, 74.5, 124.9, 127.5, 141.8, 146.7, 157.1. IC-(+) MS (MH^+) *m*/*z* = 190, 134 (100), 108, 73. Anal. Calcd for

SCHEME 4. Diastereoselective Synthesis of Protected 8a-*epi*-Lentiginosine



$C_8H_{10}ClNO_2$: C, 51.21; H, 5.37; N, 7.47. Found: C, 50.80; H, 5.65; N, 6.86.

(1*S*,2*R*,8a*R*)-1,2-Dihydroxyoctahydro-1*H*-indolizinium Chloride (6). A solution of (1*S*,2*R*)-1,2-dihydroxy-2,3-dihydro-1*H*-indolizinium chloride **5** (240 mg, 1.28 mmol) in ethanol (20 mL) was stirred overnight at room temperature in the presence of $PtO_2 \cdot H_2O$ (41.8 mg, 10% mol) under an atmospheric pressure of hydrogen. Filtration through a Celite pad and evaporation in vacuo afforded compound **6** (231 mg, 93% yield) as a white powder. ^{1}H NMR (D_2O): δ 1.4−2.1 (m, 6H), 2.9 (t, J = 11.8, 1H), 3.2 (d, J = 11.7, 1H), 3.6 (m, 1H), 3.4 (m, 2, 2H), 4.3 (t, J = 2.1, 2H), 4.6 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 21.6, 23, 23.1, 52.5, 57.8, 68.2, 69.3, 70.6. $[\alpha]_D = -25$ (*c* 1, CH_3OH). IC(+)MS (MH^+) m/z = 158 (100%). Anal. Calcd for $C_8H_{16}ClNO_2$: C, 49.61; H, 8.33; N, 7.23. Found: C, 49.12; H, 8.39; N, 6.96.

(1*S*,2*R*,8a*R*)-Indolizidine-1,2-diol (7).[20] The hydrochloride **6** (180 mg, 0.93 mmol) was dissolved in saturated KOH (10 mL) and extracted with THF (3 × 15 mL). Drying over K_2CO_3 followed by solvent evaporation afforded compound **7** (139 mg, 95%) as a white powder. ^{1}H NMR ($CDCl_3$): δ 1.20 (m, 1H), 1.51−1.89 (m, 7H), 2.26 (m, 1H), 2.91 (d, J = 10.7, 1H), 3.01 (d, J = 10.7, 1H), 3.60−3.90 (br s, 2H), 3.96 (s, 1H), 4.19 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 24.9, 25.0, 53.5, 62.8, 68.4, 69.4, 72.3. $[\alpha]_D$ = −36 (*c* 1, CH_3OH) (lit.[20a] $[\alpha]_D = -37.1$, *c* 0.55, CH_3OH).

2-((1*R*,2*R*)-1,2,3-Trihydroxypropyl)pyridinium Chloride (8). Applying the procedure described for compound **4**, acetonide **2** (200 mg, 0.96 mmol) afforded pure triol **8** (195 mg, 99%) as a white powder. ^{1}H NMR (D_2O): δ 3.66 (m, 1H), 3.79 (dd, J = 11.5, 5.5, 1H), 4.0 (dt, J = 5.6, 2.5, 1H), 5.28 (d, J = 2.25, 1H), 7.96 (t, J = 6.9, 1H), 8.04 (d, J = 8.28, 1H), 8.54 (dt, J = 7.9, 1.3, 1H), 8.68 (d, J = 5.6, 1H). ^{13}C NMR (D_2O): δ 62.2, 69.9, 74.2, 125.2, 126.3, 140.7, 147.1, 156.2. $[\alpha]_D = -19$ (*c* 1, CH_3OH). IC(+)MS (MH^+) m/z = 226, 212, 170 (100). Anal. Calcd for $C_{11}H_{15}NO_3$: C, 46.73; H, 5.88; N, 6.81. Found: C, 46.44; H, 5.92; N, 6.38.

(1*R*,2*R*)-1,2-Dihydroxy-2,3-dihydro-1*H*-indolizinium Chloride (9). Starting from triol **8** (160 mg, 0.78 mmol), the protocol described for compound **5** gave pure pyridinium **9** (143 mg, 98%) as a white powder. ^{1}H NMR ($CDCl_3$,): δ 4.62 (dd, J = 12.9, 5.9, 1H), 4.73 (dd, J = 11.9, 5.6, 1H), 5.08 (dd, J = 13, 6.3, 1H), 5.38 (d, J = 5.5, 1H), 8.0 (t, J = 6.7, 1H), 8.12 (d, J = 7.9, 1H), 8.55 (t, J = 7.8, 1H), 8.79 (d, J = 6.2, 1H). ^{13}C NMR ($CDCl_3$): δ 61.4, 74.6, 77.9, 125.2, 128, 141.7, 147, 156.5.$[\alpha]_D = -19$ (*c* 1, CH_3OH). IE (70 eV) (M^+) m/z = 152 (100), 131, 122, 114, 99. Anal. Calcd for $C_{11}H_{15}NO_3$: C, 51.21; H, 5.37; N, 7.47. Found: C, 50.98; H, 5.25; N, 7.06.

(1*R*,2*R*,8a*R*)-Octahydroindolizine-1,2-diol Hydrochloride (10a) and (1*R*,2*R*,8a*S*)-Octahydroindolizine-1,2-diol Hydrochloride (10b). Using the same procedure described for compound **6**, the pyridinium salt **9** (111 mg, 0.59 mmol) provided **10a** + **10b** (111 mg, 97%) as a white powder.

(1*R*,2*R*,8a*R*)-Octahydroindolizine-1,2-diol (11a) and (1*R*,2*R*,-8a*S*)-Octahydroindolizine-1,2-diol (11b).[21] The hydrochloride **10** (61 mg, 0.32 mmol) was dissolved in saturated KOH (5 mL) and extracted with THF (3 × 10 mL). Drying over K_2CO_3 followed by solvent evaporation afforded a mixture of diastereomers **11a** and **11b** in a 0.8:1 ratio (47 mg, 96%). **11a**. ^{1}H NMR (D_2O): δ 1.16−1.42 (m, 3H), 1.58−1.67 (m, 1 H), 1.76−1.82 (m, 1 H), 1.87−1.91 (m, 2 H), 1.95−2.08 (m, 1 H), 2.57 (dd, J = 11.2, 7.6, 1 H), 2.78 (dd, J = 11.2, 1.4, 1H), 2.91 (br d, J = 11.1, 1H), 3.61 (dd, J = 8.7, 4.0, 1H), 4.01 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 24.0, 24.8, 28.7, 53.5, 61.7, 70.0, 77.1, 84.8. **11b**. ^{1}H NMR ($CDCl_3$): δ 1.25−1.75 (m, 5 H), 1.80−1.89 (m, 1 H), 2.03−2.14 (m, 2H), 2.25 (m, 1H), 2.90−3.13 (m, 3H), 3.54 (dd, J = 9.6, 7.3, 1H), 3.83 (d, J = 4.1, 1H), 4.21 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 23.9, 24.5, 25.0, 53.5, 61.7, 66.7, 77.5, 80.5.

(1*R*)-1-[(4*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)(pyridin-2-yl)]methyl 4-Methylbenzoate (12). To a solution of compound **2** (113 mg, 0.54 mmol) and *p*-toluoyl chloride (94 μL, 0.7 mmol) in dichloromethane (15 mL) was added pyridine (0.13 mL, 1.62 mmol) at 0 °C, and then the mixture was stirred for 4 h at room temperature. The solution was evaporated, and the residue was purified by flash chromatography. Eluting with EtOAc/cyclohexane = 1/2 provided **12** (164 mg, 93%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.4 (s, 3H), 1.5 (s, 3H), 2.4 (s, 3H), 4 (m, 2H), 4.8 (q, J = 6.2, 1H), 6.1 (d, J = 5.6, 1H), 7.2 (dd, J = 5.2, 7.6, 1H), 7.24 (d, J = 8.2, 2H), 7.4 (d, J = 7.6, 1H), 7.7 (dt, J = 1.5, 7.7, 1H), 8.0 (d, J = 8.2, 2H), 8.6 (d, J = 5.2, 1H). ^{13}C NMR ($CDCl_3$): δ 21.8, 25.5, 26.6, 66, 76.9, 77, 110.1, 122.1, 123.2, 127.1, 129.2, 130, 136.8, 144.1, 149.4, 156.9, 166. IC(+)MS (MH^+) m/z = 328 (100), 270. HRMS for $C_{19}H_{22}NO_4$ (MH^+): 328.1549, found 328.1567.

2-[(1*R*,2*R*)-2,3-Dihydroxy-1-(4-methylbenzoyloxy)propyl]pyridinium Chloride (13). Applying the procedure described for compound **4**, acetonide **12** afforded pure diol **13** (139 mg, 90%) as a white powder. ^{1}H NMR (D_2O): δ 2.4 (s, 3H), 3.8 (m, 2H), 4.2 (d, J = 3.1, 1H), 6.3 (d, J = 3.1, 1H), 7.4 (d, J = 8.0, 2H), 7.9 (t, J = 6.6, 1H), 8.0 (d, J = 8.0, 2H), 8.1 (d, J = 7.9, 1H), 8.5 (t, J = 7.9, 1H), 8.7 (d, J = 4.9, 1H). ^{13}C NMR (D_2O): δ 21.2, 61.9, 72.7, 73.6, 125.2, 125.7, 126.8, 129.8, 130.3, 142.7, 146.6, 146.7, 152.1, 167. IC(+) MS (M^+ without chloride ion) m/z = 288 (100), 282. Anal. Calcd for $C_{16}H_{18}ClNO_4$: C, 59.35; H, 5.60; N, 4.33. Found: C, 59.01; H, 5.65; N, 4.21.

(1*R*,2*R*)-2-Hydroxy-1-(4-methylbenzoyloxy)-2,3-dihydro-1*H*-indolizinium Chloride (14). Starting from diol **13** (127 mg, 0.39 mmol), the protocol described for compound **5** gave pure pyridinium **14** (118 mg, 99%) as a white powder. ^{1}H NMR (D_2O): δ 2.4 (s, 3H), 3.8 (m, 2H), 4.2 (d, J = 3.7, 2H), 5.1 (m, 1H), 5.3 (dd, J = 5.9, 13.5, 1H), 6.6 (d, J = 3.1, 1H), 7.4 (d, J = 8.2, 2H), 7.9 (d, J = 8.3, 2H), 8.1 (dd, J = 6.6, 7.9, 1H), 8.3 (d, J = 7.9, 1H), 8.6 (t, J = 8.9, 1H), 9 (d, J = 6.6, 1H).

(1*R*,2*R*,8a*S*)-2-Hydroxy-1-(4-methylbenzoyloxy)octahydro-1*H*-indolizinium Chloride (15). Using the same procedure described for compound **6**, the pyridinium salt **14** (80 mg, 0.26 mmol) provided compound **15** (77 mg, 95% yield) as a white powder. ^{1}H NMR (D_2O): δ 1.4−2.1 (m, >6H, solvent impurities), 2.4 (s, 3H), 3.1 (m, 2H), 3.7 (m, 2H), 4.1 (dd, J = 6.9, 12.9, 1H), 4.5 (t, J = 12.6, 1H), 5.3 (d, J = 3.5, 1H), 7.3 (d, J = 8, 2H), 7.9 (d, J = 8, 2H). ^{13}C NMR (D_2O): δ 21.2, 21.7, 23, 23.3, 53.7, 58.8, 67.2, 72.1, 79.4, 125.5, 129.8, 130.1, 146.2, 167.1.

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Supporting Information Available: General experimental, details, detailed procedures for the preparation of **1**−**15**, and ^{1}H and ^{13}C NMR and MS spectra for each intermediate. This material is available free of charge via the Internet at http://pubs.acs.org.

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