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An efficient approach to new dihydroxyquinolizidines

Tony Tite, Feïmida Jacquelin, Laurent Bischoff *, Corinne Fruit, Francis Marsais

ECOFH-UMR 6014 COBRA, IRCOF-INSA Rouen Université de Rouen, Place Emile Blondel, 76130 Mont-Saint-Aignan, France

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ABSTRACT

Using D-glyceraldehyde acetonide as a starting material, a four-step synthesis of enantiomerically pure 3,4-dihydroxyquinolizidines is described. The key steps of the synthesis consist of a Mitsunobu ring-closing reaction and the subsequent reduction of a pyridinium ring.

1. Introduction

Since the discovery of swainsonine in 1973, considerable efforts have been made in isolating or synthesizing parent compounds.[1] This molecule, as well as other naturally occurring iminosugars (azasugars), in particular polyhydroxylated indolizidine alkaloids such as lentiginosine and castanospermine (Fig. 1) was found to be potent glycosidase inhibitors.[2] This activity makes them potential candidates for antidiabetic, antibacterial, immunosuppressive, or antiviral compounds.[3] Over the last 20 years, many structural modifications have been published, as well as the design of new stereocontrolled synthetic routes to such substances or their unnatural isomers,[4] which might be of interest for SAR studies. Thus, numerous stereochemically different and ring-expanded analogues of polyhydroxylated bicyclic iminosugars have been synthesized and evaluated.[5] Many of these compounds isolated from plants and microorganisms belong to the family of indolizidines. They have also been obtained through various synthetic pathways and the number of unnatural analogues is becoming increasingly important.

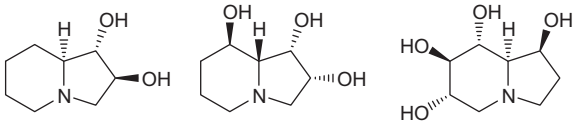

Figure 1. Naturally occurring polyhydroxyindolizidines.

However, ring-expanded analogues, such as quinolizidines still remain little explored, although they are interesting targets. As they differ from indolizidines, which are closely related to natural sugars, quinolizidines may lead to a better understanding of the mechanisms of action and their metabolism, further providing new classes of potent inhibitors. Since the first synthesis by Ganem et al. in 1987,[6] the synthesis of polyhydroxylated quinolizidines is scarcely reported, and has attracted much lesser interest. Indeed, although these compounds represent the formal homologation of the indolizidine scaffold, there has not been any discovered in Nature. Most of the approaches to date are based on those for quinolizidines/indolizidines and polyhydroxylated indolizidines. Many synthetic methods published to date often involve ring-closure metathesis using first and second generation Grubb's catalysts.[7] Some other elegant strategies using one or double-reductive amination,[8] hetero-Diels–Alder reaction,[9] intramolecular S_N2 reactions with a mesylate leaving group,[10] intramolecular 1,3-cycloaddition via nitrones and sulfones,[11] and double-Michael additions[12] have also been reported. The syntheses of hydroxylated quinolizidines with up to five hydroxyl groups have been achieved. Some derivatives including homocastanospermine and homonojirimycin were found to be potent inhibitors of α- and β-glucosidases, even if the introduction of several hydroxyl groups sometimes triggers lower selectivities. However, one limitation of many of these methodologies is the lower availability of carbohydrate precursors for such compounds. This consequently leads to the use of time-consuming protective and deprotective sequences. To the best of our knowledge, only two syntheses of dihydroxyquinolizidines have been reported before.[13] Marquart et al. have reported the synthesis of **I** and **II** (Fig. 2) in nine steps [0.80% and 0.92% overall yield, respectively, from a bromobutyl phtalimide]. Later, the derivative **II**, as well as **III** was synthesized by West and Vanecko using a stereoselective silyl-directed Stevens [1,2]-shift of ammonium ylides [six steps, 17% overall yield from Boc-pyrrolidine].

2. Results and discussion

Dihydroxyquinolizidines with the stereochemical patterns given in Scheme 1 have not been described in the literature and thus represent interesting targets. We have recently demonstrated how the Mitsunobu reaction can be successfully employed to readily

* Corresponding author. Fax: +33 2 35522962.
E-mail address: laurent.bischoff@insa-rouen.fr (L. Bischoff).

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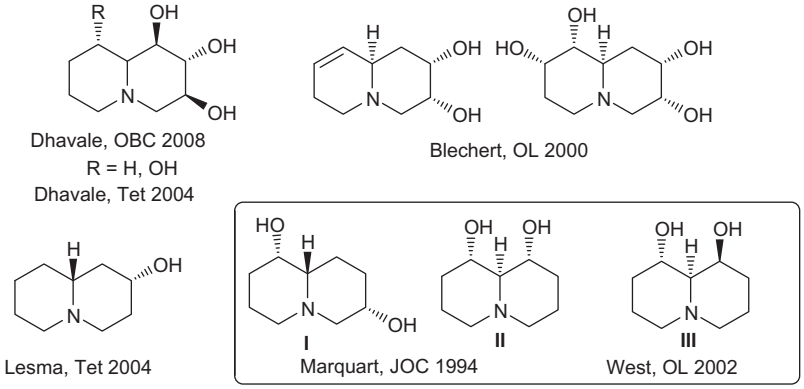
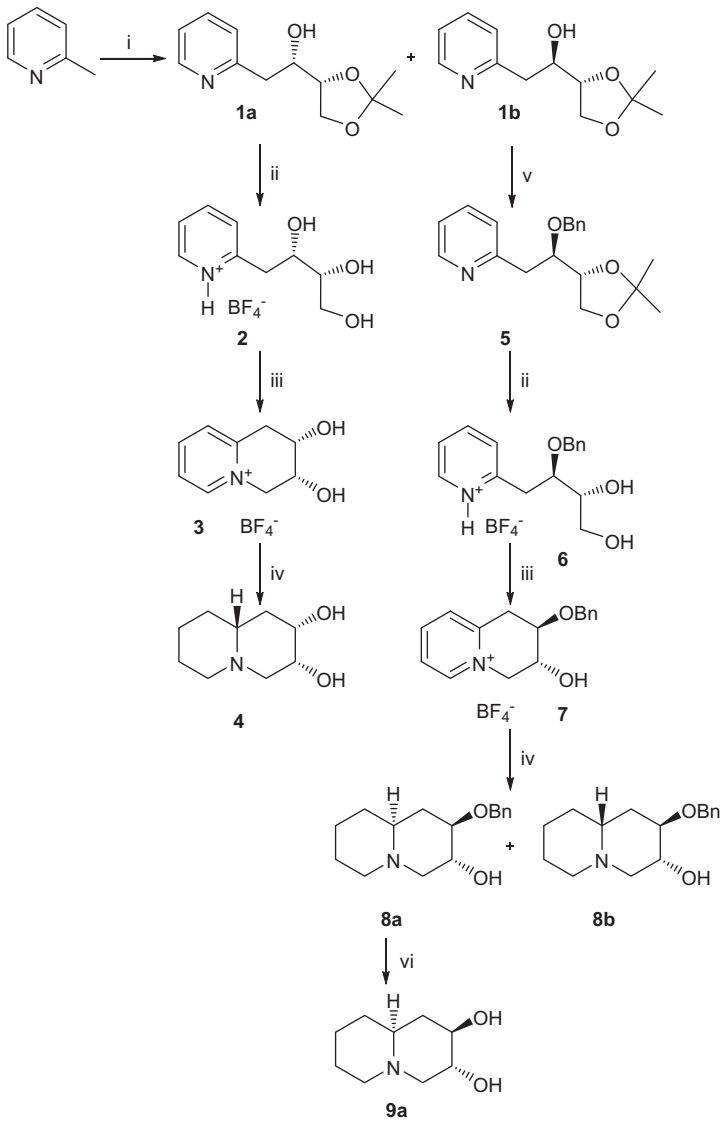


Figure 2. Synthetic polyhydroxyquinolizidines published in the literature.



Scheme 1. Reagents and conditions: (i) *n*-BuLi, THF, −78 °C then D-glyceraldehyde acetonide, −78 °C, overnight; (ii) $HBF_4(OCH_2CH_3)_2$ (1.1 equiv), CH_3OH, 20 h, rt; (iii) PPh_3 (1.1 equiv), DIAD (1.1 equiv), CH_3CN, 24 h, rt; (iv) (a) H_2, PtO_2, 1 atm, 22 h; (b) Et_3N; (v) NaH, BnBr, THF; (vi) H_2, $PdCl_2$, 1 atm, 3 h.

access 5/6 bicyclic azasugar lentiginosine derivatives using quaternarization of a pyridinium polyol as the key step.[14] As part of our ongoing efforts toward the synthesis of new azasugars using this methodology, we disclose a practical and diastereoselective synthesis of 6/6 bicyclic azasugar dihydroxyquinolizidine alkaloids. As this ring-closing step considerably differs when a (6+6) system is involved, we wished to examine the reactivity and stereochemical outcome of both pyridine alkylation and further

pyridinium reduction to illustrate this synthetic strategy with the obtention of new dihydroxyquinolizidines, namely homolentiginosine.

The usefulness of glyceraldehyde as a chiral-pool reagent has already been illustrated in many syntheses,[15] therefore this material was chosen as the chiral building block required for the construction of the dihydroxyl-substituted six-membered ring. Thus, the adjunction of a picoline subunit leads to the whole backbone of the target molecule. As depicted in Scheme 1, lithiation of picoline readily took place with *n*-BuLi and was followed by quenching with glyceraldehyde acetonide. Better yields were obtained when the reaction mixture was stirred at −78 °C overnight, as slow warming to room temperature resulted in some degradation. Both diastereomers **1a** and **1b** were obtained in a 3/1 ratio,[16] and were easily separated via chromatography through silica gel. The assignment of the absolute configuration of the new stereocenter was first postulated on the basis of previous results,[14] and confirmed with the NMR NOESY spectrum of compound **9a**. In the following steps, only the *cis*-diastereomer **1a** was used as a free alcohol, since we expected that in the case of the minor diastereomer **1b**, hardly any facial selectivity would be observed for the reduction step. Further hydrolysis of the acetonide was achieved upon treatment with 1 M equiv of aqueous tetrafluoroboric acid (Et_2O complex). Both HCl and HBF_4 resulted in quantitative deprotection, however the choice of the counterion was crucial for the following step. The ring closing was based on a Mitsunobu reaction, in which the acidic, nucleophilic component of the reaction consisted of the pyridinium itself, and relies on the highly selective activation of the primary alcohol. During this process, a non-nucleophilic counterion was required to avoid the transformation of the alcohol into the corresponding halide. Whereas in the case of a (6+5) ring system, the ring closing was considerably facilitated, in the present case much degradation occurred in our previously reported conditions (excess PPh_3/DIAD, rt, overnight). We believe that the alkaline conditions of the Mitsunobu reaction led to a retro-aldol-mediated loss of the hydroxylated part of the molecule, since the formation of a picolinium was observed. Thus, the ring-closure step required some optimization and better results were obtained when the tetrafluoroborate salt **2** was treated in the presence of triphenylphosphine (1.1 equiv) by slow addition of di-isopropyl azadicarboxylate (DIAD, 1.1 equiv) in an ice-cold bath.

Under these conditions, much less degradation compounds were observed, and the dihydroxyquinolizinium **3** was obtained as a 1:1 mixture together with **2** as indicated by ^{1}H NMR spectroscopy. We observed that **3** was difficult to be purified by chromatography on silica gel, subsequent catalytic hydrogenation of the crude material in the presence of PtO_2 proceeded with a 90% de as indicated by NMR spectroscopy and GC/MS, affording the ring-expanded analogue **4** of lentiginosine.

On the other hand, in order to both enhance the diastereoselectivity at the reduction step of the pyridinium bearing the *trans*-diol system and facilitate further separation of the stereoisomers, we carried out the benzylation of the free alcohol in compound **1b** prior to hydrolysis of the acetonide. The cyclization under Mitsunobu conditions was not improved for compound **6** versus **2**, however the purification of the resulting pyridinium **7** by flash chromatography was greatly facilitated. Bearing the benzyl group as a more hindered substituent at C-2 position, hydrogenation led to a 2:1 ratio of compounds **8a** and **8b**, respectively. Unfortunately, whatever the reaction conditions, the de could not be improved upon for this compound, probably due to the higher flexibility and different spatial orientation of substituents in a (6+6) ring system versus its (6+5) indolizinium analogue. In addition, we observed that even under atmospheric pressure, PtO_2-mediated debenzylation also led to the reduction of the aromatic ring of the benzyl group.

As far as the stereochemistries are concerned, the absolute (*S*)-configuration at C-2 corresponds to that of D-glyceraldehyde. It can be expected, according to the literature, that the major diastereomer obtained via the addition of lithiated picoline to the aldehyde had the (2*S*,3*R*) configuration. This is also in agreement with the good diastereoselectivity observed for the reduction of the pyridinium *cis*-diol **3**. The addition of hydrogen onto the pyridinium ring should occur at the less-hindered face, providing the (2*S*,3*R*,9a*R*) diastereomer from compound **3**. These structural features were confirmed by means of NOE experiments as depicted in Figure 3 for compound **4**, which allowed us to observe strong correlation peaks between H-9a/H-2 and H-9a/H-4_{ax} in agreement with a *cis* relationship between these protons. Moreover, the clear NOE cross-peaks between H-2_{ax}/H-3_{eq}; H-2_{ax}/H-4_{ax}; H-2_{ax}/H-1_{eq}; H-9a/H-4_{ax} support the *syn* relationship of these two protons and also confirm the structure depicted in **4**. In structure **8a** a clear NOE cross-peak between H-9a/H-2_{ax} was observed in accordance with a *cis* relationship between these protons. The strong NOE cross-peaks between H-2_{ax}/H-4_{ax}, H-3_{ax}/H-4_{eq}, support the (2*R*,3*R*,9a*S*) configuration for **8a**.

Finally, the benzyl group of **8a** was easily cleaved in the presence of palladium chloride to yield almost quantitatively the target derivative **9a**.

3. Conclusion

In conclusion, we have prepared two novel dihydroxyquinolizidines which could be viewed as homolentiginosine analogues. The synthetic approach was proven to be short, efficient, and stereoselective. Its application in the synthesis of mono-hydroxyquinolizidine through the reduction of a 2-benzyl-3-xanthate derivative using a Barton McCombie reaction is currently in progress.

4. Experimental

4.1. General experimental procedures

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly distilled solvents. All reactions

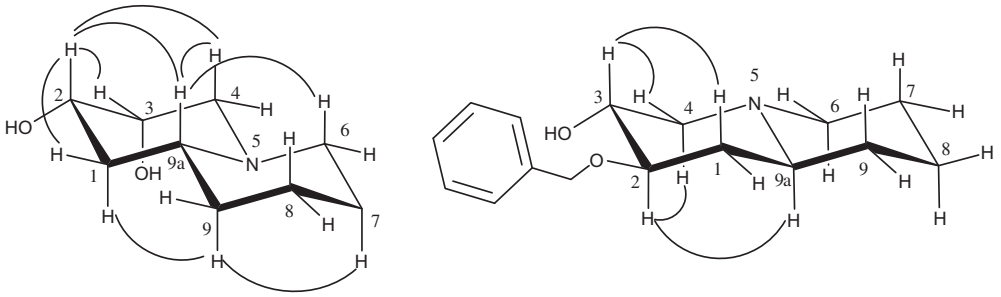


Figure 3. NOE experiments.

were monitored by thin-layer chromatography using aluminium-backed Silica Gel 60 F254 plates (0.25 mm). Flash chromatography was performed using silica gel (particle size 30–63 μm). Chromatography solvents were distilled prior to use. ^{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 $CDCl_3$, CH_3OD, or D_2O. Coupling constants *J* are in Hz and are reported as d (doublet), t (triplet), q (quartet). Melting points were determined on a Hot Kofler bench and are uncorrected.

4.2. Experimental procedures and data

4.2.1. (2*S*,3*R*)-3,4-*O*-Isopropylidene-1-(2′-pyridyl)-2,3,4-trihydroxy-butane 1a and (2*R*,3*R*)-3,4-*O*-isopropylidene-1-(2′-pyridyl)-2,3,4 trihydroxy-butane 1b

To a solution of freshly distilled 2-picoline (0.60 mL, 6.41 mmol) in dry THF (30 mL) at −78 °C was added under nitrogen *n*-BuLi (4.40 mL, 7.05 mmol, 1.6 M solution in hexane). The reaction mixture was stirred at −78 °C for 15 min and the temperature was allowed to rise gradually to −45 °C over 1 h 30 min. Then, the resulting red solution was cooled to −78 °C and a solution of the aldehyde (1 g, 7.69 mmol) in dry THF (5 mL) was added dropwise during 15 min. The reaction mixture was stirred at −78 °C for 15 h and then the reaction was quenched with a saturated solution of ammonium chloride (40 mL). After extraction with CH_2Cl_2 (4 × 30 mL) and then EtOAc (2 × 30 mL) the combined organic layers were dried (Na_2SO_4), filtrated, and evaporated under reduced pressure to give an orange oil. Flash chromatography on silica gel using [pet ether/EtOAc 2/1] as the eluent afforded first **1a** (470 mg, 36%) and then **1b** (160 mg, 12%) as a pale yellow oil. Data for **1a**: $[\alpha]_D^{20} = +24$ (*c* 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 3H), 1.42 (s, 3H), 2.85–2.89 (m, 1H, CH_2), 3.15 (dd, 1H, *J* = 2.07 Hz, *J* = 14.26 Hz), 3.90–4.17 (m, 4H), 5.64 (br s, 1H, OH), 7.14–7.23 (m, 2H), 7.64 (dt, 1H, *J* = 1.89 Hz, *J* = 7.72 Hz), 8.42–8.50 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.44, 26.85, 39.35, 67.26, 72.54, 78.12, 109.35, 121.74, 124.07, 137.02, 148.47, 159.91. HRMS: calcd 224.1287, found 224.1288 (MH^+) Data for **1b**: $[\alpha]_D^{20} = -12$ (*c* 1, CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 3H), 1.45 (s, 3H), 2.83–3.00 (m, 2H, CH_2), 3.86 (dd, 1H, CH_2, *J* = 6.59 Hz, *J* = 8.29 Hz), 4.00–4.20 (m, 3H), 4.57 (br s, 1H, OH), 7.11–7.21 (m, 2H), 7.61 (dt, 1H, *J* = 1.89 Hz, *J* = 7.72 Hz), 8.43–8.52 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.37, 26.59, 39.92, 65.79, 71.63, 78.42, 109.53, 121.77, 124.04, 136.86, 148.88, 159.27. HRMS: calcd 224.1287, found 224.1281 (MH^+).

4.2.2. 2-(2*S*,3*R*)-2,3,4-Trihydroxybutyl)pyridinium tetrafluoroborate 2

Compound **1a** (166 mg, 0.74 mmol) was taken up in methanol (4 mL) and a solution of tetrafluoroboric acid diethyl etherate (98%, 112 μL, 0.81 mmol) was added. After 20 h stirring at room temperature, solvents were evaporated in vacuo and the residue was dissolved in H_2O, freeze-dried to afford the pyridinium derivative **2** (192 mg, 95%) as its tetrafluoroborate salt. ^{1}H NMR (300 MHz, CH_3OD): δ 3.12 (dd, 1H, *J* = 8.83 Hz, *J* = 14.13 Hz), 3.41 (dd, 1H, *J* = 3.0 Hz, *J* = 14.13 Hz), 3.46–3.55 (m, 1H), 3.69 (dd, 1H, *J* = 5.66 Hz, *J* = 11.30 Hz), 3.75 (dd, 1H, *J* = 4.15 Hz, *J* = 11.30 Hz), 3.86–3.98 (m, 1H), 7.90 (t, 1H, *J* = 6.97 Hz), 7.99 (d, 1H, *J* = 7.91 Hz), 8.45–8.54 (m, 1H), 8.68 (d, 1H, *J* = 5.46 Hz). ^{13}C NMR (75 MHz, CH_3OD): δ 38.14, 64.12, 71.78, 75.61, 126.02, 129.50, 141.82, 147.50, 156.47. HRMS: calcd 184.0974, found 184.0961 (pyridinium M^+).

4.2.3. (2*S*,3*R*)-2,3-Dihydroxy-2,3-dihydro-1*H*-quinolizidinium tetrafluoroborate 3

To a solution of **2** (164 mg, 0.605 mmol) and triphenylphosphine (173 mg, 0.665 mmol) in anhydrous CH_3CN (6 mL) was added di-isopropyl azodicarboxylate (DIAD) (121.1 μL, 0.605 mmol) dropwise at 0 °C. After stirring for 24 h at room temperature, CH_3CN was evaporated and the residue was dissolved in H_2O, washed with Et_2O, and freeze-dried to afford an inseparable mixture of **2** and **3** (ratio 1:1, 160 mg). ^{1}H NMR (300 MHz, CH_3OD): δ 3.50–3.65 (m, 2H), 4.25–4.35 (m, 1H), 4.40–4.45 (m, 1H), 4.65–4.85 (m, 2H), 7.72–7.82 (m, 2H), 8.25 (t, 1H, *J* = 7.72 Hz), 8.50 (d, 1H, *J* = 6.21 Hz). ^{13}C NMR (75 MHz, CH_3OD): δ 33.09, 58.72, 70.31, 74.02, 125.52, 129.18, 144.75, 146.71, 154.10.

4.2.4. (2*S*,3*R*,9a*R*)-Octahydro-*1H*-quinolizine-2,3-diol 4

A solution of **2** and **3** (ratio 1:1, 153.8 mg, 0.587 mmol) in ethanol (16 mL) was stirred at room temperature in the presence of $PtO_2{\cdot}H_2O$ (20 mg, 10 mol %) under an atmospheric pressure of hydrogen. After 22 h under stirring, the solution was filtrated through a Celite pad, which was washed with MeOH, and the filtrate was evaporated in vacuo. The resulting yellow oil (160 mg) was redissolved with a mixture of CH_2Cl_2/MeOH/Et_3N (5/5/2, 12 mL) and the solution was stirred for 20 min at room temperature. Then, the solution was evaporated to dryness to give an orange oil. After purification by chromatography on silica gel using [CH_2Cl_2/MeOH/NH_3 5/1/0.12] as eluent, **4** was obtained as a white solid (43 mg, 0.251 mmol, 42%). $[\alpha]_D^{20} = -21$ (*c* 0.52, CH_3OH). Mp: 31 °C. ^{1}H NMR (300 MHz, CH_3OD): δ 1.26–1.41 (m, 2H, H-9, H-8), 1.52–1.74 (m, 4H, H-7, H-1), 1.76–1.88 (m, 1H, H-9a), 1.90–2.04 (m, 1H, H-6), 2.19 (dd, 1H, H-4_{ax}, *J* = 1.70 Hz, *J* = 12.62 Hz), 2.72–2.82 (m, 1H, H-6), 2.89 (dd, 1H, H-4_{eq}, *J* = 3.20 Hz, *J* = 12.62 Hz), 3.51–3.61 (m, 1H, H-2), 3.76–3.82 (m, 1H, H-3). ^{13}C NMR (75 MHz, CH_3OD): δ 24.98 (C-8), 26.27 (C-7), 33.55 (C-9), 36.56 (C-1), 56.73 (C-6), 61.39 (C-4), 61.95 (C-9a), 69.47 (C-3), 70.81 (C-2). HRMS: calcd 172.1338, found 172.1347 (MH^+).

4.2.5. (2*R*,3*R*)-2-Benzyloxy-3,4-*O*-isopropylidene-1-(2′-pyridyl)-2,3,4-trihydroxybutane 5

To a solution of **4** (160 mg, 0.71 mmol) in dry THF (15 mL) under nitrogen, was added cautiously NaH 95% (49.23 mg, 1.95 mmol) at 0 °C. After 1.5 h under stirring at room temperature, benzyl bromide (0.123 mL, 1.03 mmol) was added dropwise at 0 °C. Then, the resulting mixture was stirred at room temperature overnight, neutralized with a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2 (4 × 30 mL) and EtOAc (2 × 30 mL). The collected organic phases were dried over Na_2SO_4, and evaporated under reduced pressure. Purification by chromatography on silica gel of the residue using [pet ether/EtOAc 1/1] as eluent afforded pure **5** as a yellow oil (118 mg, 53%). $[\alpha]_D^{20} = +35$ (*c* 1, CH_2Cl_2), ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.37 (s, 3H), 1.44 (s, 3H), 2.88–3.02 (m, 2H, CH_2), 3.79–3.86 (m, 1H), 3.95–4.07 (m, 2H), 4.18–4.28 (m, 1H), 4.40 (d, 1H, *J* = 11.68 Hz), 4.58 (d, 1H, *J* = 11.68 Hz), 7.05, 7.27 (m, 7H), 7.57 (dt, *J* = 7.72 Hz, *J* = 1.70 Hz), 8.48–8.56 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 25.59, 26.62, 40.08, 65.99, 73.16, 78.18, 79.70, 109.48, 121.50, 124.63, 127.48, 127.86, 128.24, 136.23, 138.54, 149.33, 158.75. HRMS: calcd 314.1756, found 314.1759 (MH^+).

4.2.6. 2-(2*R*,3*S*)-3-(Benzyloxy)-2,3,4-trihydroxybutyl)pyridinium tetrafluoroborate 6

Applying the procedure described for compound **2**, acetonide **5** (116 mg, 0.37 mmol) afforded pure triol **6** as a pale yellow oil (97%). ^{1}H NMR (300 MHz, CH_3OD): δ 3.19 (dd, 1H, CH_2, *J* = 9.60 Hz, *J* = 13.94 Hz), 3.28–3.39 (m, 1H, CH_2), 3.65–3.86 (m, 3H), 3.94–4.05 (m, 1H), 4.25 (d, 1H, *J* = 11.68 Hz), 4.58 (d, 1H, *J* = 11.68 Hz), 6.99–7.24 (m, 5H), 7.78–7.91 (m, 2H), 8.39 (dt, *J* = 7.91 Hz, *J* = 1.51 Hz), 8.48–8.55 (m, 1H). ^{13}C NMR (75 MHz, CH_3OD): δ 36.59, 63.60, 74.28, 74.42, 79.55, 126.21, 128.87, 129.41, 129.45, 129.48, 138.78, 141.78, 147.49, 156.04.

4.2.7. (2*S*,3*S*)-2-*O*-Benzyl-3-hydroxy-3,4-dihydro-1*H*-quinolizidinium tetrafluoroborate 7

Applying the procedure described for compound **3**, triol **6** (101.1 mg, 0.28 mmol) purification by chromatography on silica gel using [CH_2Cl_2/CH_3OH 15/1] as eluent afforded 30 mg of **7** as a pale yellow oil (31%). $[\alpha]_D^{20} = -16$ (*c* 2.3, CH_3OH). ^1H NMR (300 MHz, CH_3OD): δ 3.47 (dd, 1H, CH_2, *J* = 3.20 Hz, *J* = 18.46 Hz), 3.67 (dd, 1H, CH_2, *J* = 4.71 Hz, *J* = 18.46 Hz), 4.00–4.06 (m, 1H), 4.40–4.48 (m, 1H), 4.61 (dd, 1H, CH_2, *J* = 3.01 Hz, *J* = 14.51 Hz), 4.71 (s, 2H, CH_2), 4.88 (dd, 1H, CH_2, *J* = 2.93 Hz, *J* = 14.51 Hz), 7.25–7.28 (m, 5H), 7.84–7.98 (m, 2H), 8.42 (dt, *J* = 7.91 Hz, *J* = 1.32 Hz), 8.74 (d, 1H, *J* = 6.40 Hz). ^{13}C NMR (75 MHz, CH_3OD): δ 32.27, 59.42, 65.81, 72.31, 73.59, 126.63, 128.99, 129.50, 130.38, 139.08, 146.00, 146.47, 155.52. HRMS: calcd 256.1338, found 256.1336 (pyridinium cation M^+).

4.2.8. (2*R*,3*R*,9a*S*)-2-(Benzyloxy)-octahydro-1*H*-quinolizin-3-ol 8a

Applying the same procedure described for compound **4**, the reduction of the pyridinium salt **7** (18.9 mg, 0.055 mmol) with 1.4 mg of PtO_2 followed by neutralisation of the crude material afforded a pale yellow oil. Purification by chromatography on silica gel using successively as the eluents [CH_2Cl_2/MeOH 15/1], then [CH_2Cl_2/MeOH 12/1] and finally [CH_2Cl_2/MeOH 9/1], afforded first compound **8a** as a pale yellow oil (6 mg, 40%), then a mixture of **8a** and **8b** (3 mg, 20%). ^1H NMR (300 MHz, CH_3OD): δ 1.10–1.37 (m, 5H, H-1, H-7, H-8, H-9), 1.42–1.80 (m, 2H, H-8, H-7), 1.81–1.94 (m, 1H, H-9a), 1.95–2.40 (m, 3H, H-6, H-4, H-1), 2.81–2.96 (m, 2H, H-6, H-4), 3.20–3.27 (m, 1H, H-2), 3.60–3.71 (m, 1H, H-3), 4.67 (br s, 2H, CH_2), 7.21–7.42 (m, 5H). ^{13}C NMR (75 MHz, CH_3OD): δ 24.81, 26.06, 33.19, 56.58, 61.77, 61.82, 72.01, 72.01, 72.65, 81.99, 128.53, 128.90, 129.27, 140.24.

4.2.9. (2*R*,3R,9a*S*)-Octahydro-1*H*-quinolizin-2,3-diol 9a

A solution of **8a** (6.5 mg, 0.024 mmol) in methanol (2 mL) was stirred at room temperature in the presence of $PdCl_2$ (1.5 mg) under an atmospheric pressure of hydrogen. After 3 h under stirring, the solution was filtrated through a Celite pad, which was washed with MeOH, and the filtrate evaporated in vacuo, affording a clear oil (4 mg, 97%). $[\alpha]_D^{20} = -6.5$ (*c* 0.38, CH_3OH). ^1H NMR (300 MHz, CH_3OD): δ 1.10–2.11 (m, 11H), 2.79–2.91 (m, 2H, H-6, H-4), 3.33–3.39 (m, 1H, H-2), 3.42–3.52 (m, 1H, H-3). ^{13}C NMR (75 MHz, CH_3OD): δ 24.92, 26.17, 33.27, 40.74, 56.65, 61.87, 61.89, 73.07, 74.41. HRMS: calcd 172.1338, found 172.1332 (MH^+).

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