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A chemoenzymatic-RCM strategy for the enantioselective synthesis of new dihydroxylated 5-hydroxymethyl-indolizidines and 6-hydroxymethyl-quinolizidines

Giordano Lesma,* Alessia Colombo, Nicola Landoni, Alessandro Sacchetti and Alessandra Silvani*

Dipartimento di Chimica Organica e Industriale, Università degli Studi di Milano, via G. Venezian 21, 20133 Milano, Italy

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Abstract—A direct method for the synthesis of new azasugars-like compounds has been developed, which involves a new biocatalytic protocol based on the use of a lipase from *Candida Cylindracea* and of a ionic liquid as reaction medium, to prepare the key C_1-symmetric piperidine precursor. By subsequent application of RCM reactions and OsO_4-catalyzed double bond *syn*-dihydroxylation, the synthesis of the target compounds could be accomplished in a straightforward and stereocontrolled manner.

1. Introduction

Azabicyclic ring skeletons, such as quinolizidines and indolizidines, are important structural subunits present in numerous biologically active natural products.[1] In this family, polyhydroxylated alkaloids have attracted much attention due to the ability of some of them to act as selective glycosidase inhibitors.[2] Glycosidases are involved in several metabolic pathways and the development of inhibitors is an important challenge towards the treatment of diseases, such as diabetes, cancer and viral infections, including AIDS.[3] The high therapeutic potential of these alkaloids, also called azasugars, has prompted considerable efforts towards their structural modification and towards the design of new stereocontrolled synthetic routes to these compounds, or to their unnatural isomers,[4] which might be of interest for SAR studies. In fact, small structural modifications have often been proven to induce very significant changes in terms of inhibiting potency and selectivity of the glycosidase enzymes. On the basis of these considerations, the development of novel synthetic strategies to expand upon the repertoire of available analogues constitutes as an area of considerable current interest.[5]

We have recently demonstrated how chemoenzymatically derived chiral synthons can be successfully employed, in combination with metathesis reactions, to readily access various classes of naturally occurring piperidine, pyrrolidine and quinolizidine alkaloids.[6]

Herein, we report a non-carbohydrate based approach to dihydroxylated 5-hydroxymethyl-indolizidines **1** and 6-hydroxymethyl-quinolizidines **2**, starting from the key building block *N*-carbobenzyloxy-*cis*-(2*S*)-acetoxymethyl-(6*R*)-hydroxymethylpiperidine **3**, already described by Chenevert (Fig. 1).[7,8] An improved access to **3** has been secured by means of a new biocatalytic protocol based on the use of lipase from *Candida Cylindracea* and the ionic

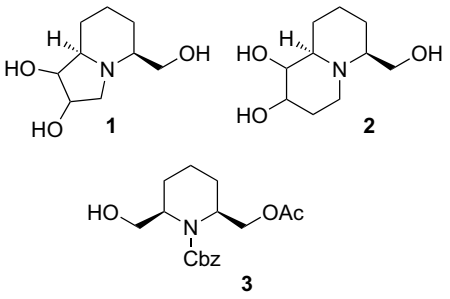

Figure 1.

* Corresponding authors. Tel.: +39 0250314080; fax: +39 0250314078; e-mail: alessandra.silvani@unimi.it

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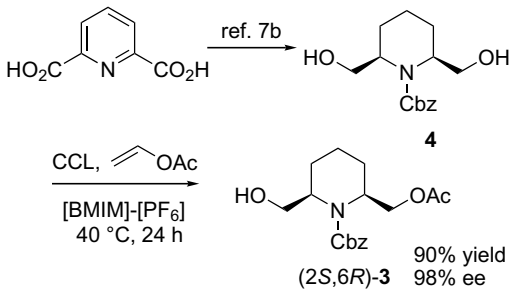
liquid [BMIM]PF_6 as a reaction medium. From **3**, obtained on a multigram scale in high ee, we developed a versatile RCM-based strategy for constructing the second heterocyclic ring, found in the aforementioned hydroxylated azabicyclic compounds, which are not naturally occurring, to the best of our knowledge.

2. Result and discussion

The requisite substrate **4** (Scheme 1) for the enzymatic desymmetrization was easily prepared from commercial pyridine-2,6-dicarboxylic acid, according to the literature.[7b] Diol **4** is known[8] to undergo enzyme-catalyzed transesterification by treatment with *Candida Antarctica* lipase in vinyl acetate to give optically active ester **3** in 80% yield and 95% ee. As part of our ongoing project on the enzyme-mediated asymmetric synthesis of nitrogen compounds, we became interested in ionic liquids[9] as alternative solvents for biotransformations using cell-free enzymes. Room-temperature ionic liquids, are attracting growing interest as novel replacements for volatile organic solvents in industrial organic synthesis and are particularly promising as solvents for catalysis. Moreover, ionic liquids are simple and inexpensive to manufacture, environmentally benign and easy to recycle; their properties can be fine-tuned by changing the anion or the R group of the cation. A number of publications[10] have recently shown the potential of carrying out enzymatic bioconversions in ionic liquids, but, no examples of desymmetrization of C_S-symmetric compounds have been reported until now.



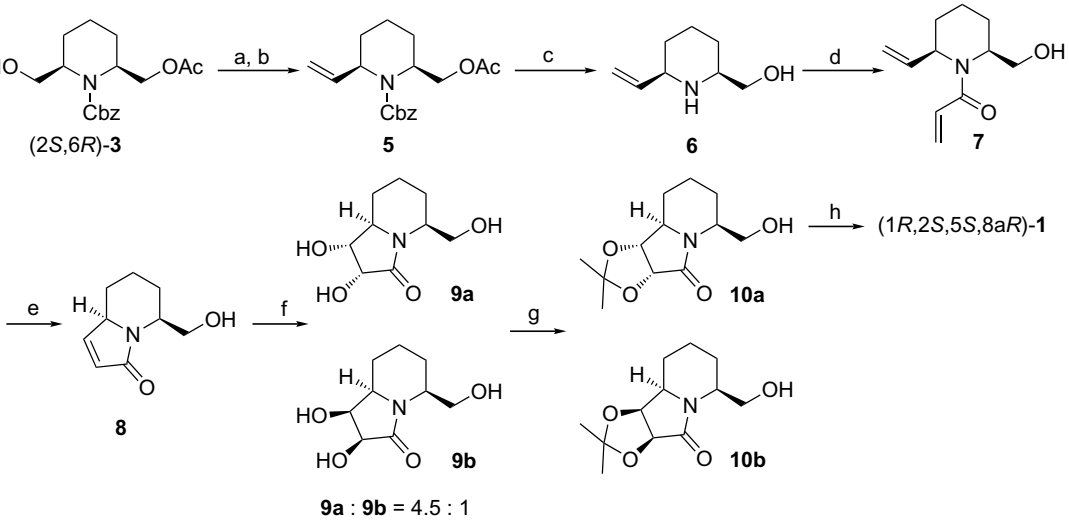
Scheme 1.

Two ionic liquids, [EMIM]–[BF_4] ([EMIM]$^+$ = 1-ethyl-3-methylimidazolium) and [BMIM]–[PF_6] ([BMIM]$^+$ = 1-butyl-3-methylimidazolium), were tested as media for lipase-catalyzed transesterification and two different enzymes were chosen, namely a lipase from *Candida Antarctica* and a lipase from *C. Cylindracea*, in order to compare their activity and enantioselectivity.

Under identical conditions, the acylation of **4** in [BMIM]–[PF_6] with vinyl acetate, proceeded promptly with both enzymes, but not in [EMIM]–[BF_4]. In particular, when lipase from *C. Cylindracea* was employed in [BMIM]–[PF_6], the best result of 90% yield and 98% ee[11] was achieved in around an half of the time with respect to the standard acylation conditions.

With the common precursor **3** in hand on a multigram scale, we pursued the synthetic sequence reported in Scheme 2. Swern oxidation of **3** gave the corresponding aldehyde, which, after work up and ^{1}H NMR verification of the lack of epimerisation, was immediately added to the methyl Wittig ylide to give alkene **5** in good yield. By treatment with KOH 1 M in MeOH at reflux, amino alcohol **6** was achieved in high yield and after which it was selectively N-acylated to give **7**, by reaction with acryloyl chloride in aqueous acetone, in the presence of Na_2CO_3.

We next examined ring-closing metathesis (RCM) conditions in order to prepare bicyclic compound **8**. Unlike first generation Grubbs's ruthenium catalyst, the second gener-



Scheme 2. Reagents and conditions: (a) $(COCl)_2$, DMSO, TEA, DCM, 94%; (b) Ph_3PCH_3Br, *t*-BuOK, toluene, 77%; (c) KOH 1 M, MeOH, 86%; (d) acryloyl chloride, Na_2CO_3, acetone/water, 73%; (e) 2nd generation Grubbs's ruthenium catalyst, toluene, MW irradiation, 180 °C, 72%; (f) OsO_4, trimethylamine *N*-oxide, *t*-BuOH, 70%; (g) (i) ADA, Dowex 50W × 8 (H^+ form); (ii) chromatographic separation, 64% for **10a** and 14% for **10b**; (h) (i) $Me_2S{\cdot}BH_3$, THF; (ii) 3 M HCl, 50 °C, 10 h, 85%.

ation one proved to be very suitable for RCM reaction of α,β-unsaturated amide **7**. Moreover, the use of microwave irradiation[12] in this step allowed us to complete the reaction in 30 min compared with the 20 hrs required under conventional oil bath heating. The presence of a carbonyl group and a double bond in the five-membered ring adds versatility to the chiral building block **8**. In our plan, dihydroxylation of olefin **8** was then easily achieved by oxidation with catalytic OsO_4 and trimethylamine *N*-oxide, affording the desired products **9a** and **9b** in good yield as an inseparable diastereoisomeric mixture. The reaction took place with good diastereoselectivity and **9a** and **9b** were obtained in a 4.5:1 ratio, as determined by ^{1}H NMR. In order to separate the two diastereoisomers, **9a** and **9b** were converted into the respective acetonide derivatives, which could be easily separated by usual flash chromatography. The *exo*-configuration of the diol formed was unambiguously assigned to the major diastereoisomer **10a**, by means of NOESY analysis, as outlined in Figure 2. Compound **10a** was then submitted to the reduction of the amide function by treatment with borane dimethylsulfide complex, followed by deprotection of the acetonide, to afford the desired final product (1*R*,2*S*,5*S*,8a*R*)-**1**.

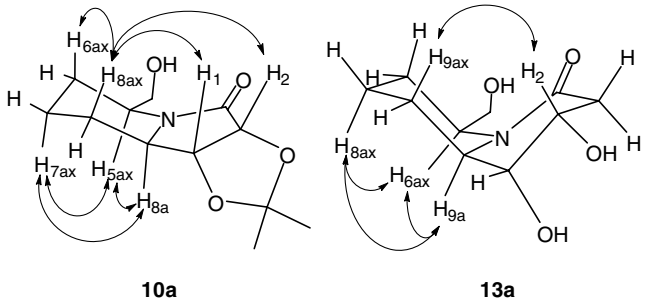


Figure 2. Diagnostic NOE contacts in **10a** and **13a.**

The intermediate **6** was also used as a starting material for the synthesis of the quinolizidine derivative **2** (Scheme 3). Acylation with 3-butenoic acid in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) cleanly afforded amide **11**, which was cyclised by RCM in the previously described reaction conditions (2nd generation Grubbs's ruthenium catalyst, toluene, microwave irradiation). Bicyclic olefin **12** was then dihydroxylated with the OsO_4/trimethylamine *N*-oxide system to produce a separable mixture of **13a** and **13b** in a 3:1 diastereoisomeric ratio, as determined by ^{1}H NMR. After chromatographic separation, the *exo*-configuration of the diol moiety was attributed to the major diastereoisomer **13a**, by means of NOESY analysis (Fig. 2). Compound **13a** was then reacted with borane dimethylsulfide complex, affording the final product (1*R*,2*S*,6*S*,9a*R*)-**2** in good yield.

For both **8** and **12** molecular modelling calculations[13] show the *endo*-face to be effectively more sterically hindered when compared to the *exo* one, thus precluding an efficient, high scale preparation of the 1,2-di-*epi* isomers of **1** and **2**.

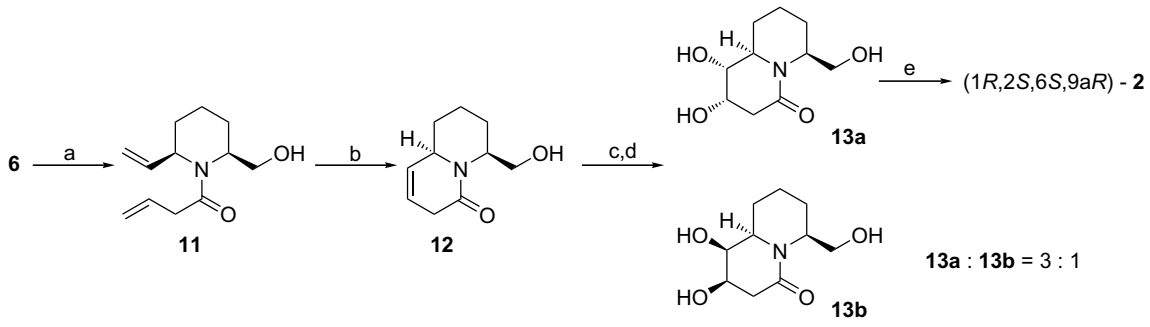
3. Conclusion

In conclusion, this work provides a straightforward procedure to prepare enantiopure dihydroxylated 5-hydroxymethyl-indolizidines and 6-hydroxymethyl-quinolizidines, by means of a chemoenzymatic-RCM approach. Aiming to give a synthetic contribution in gaining more insights about the mechanism by which these unnatural alkaloids act on glycosidase enzymes, further application of this strategy is currently under investigation, particularly for the synthesis of pyrrolizidine-based compounds.

4. Experimental

4.1. General

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254 (Merck); spots were visualized with UV light or by treatment with 1% aqueous $KMnO_4$ solution. Products were purified by flash chromatography on Merck silica gel 60 (230–400 mesh). ^{1}H and ^{13}C NMR spectra were recorded with Bruker AC 300 (^{1}H, 300 MHz; ^{13}C, 75.4 MHz) and 400 MHz Avance (^{1}H, 400 MHz; ^{13}C, 100 MHz) NMR spectrometers. Chemical shifts are reported in parts per million downfield from $SiMe_4$ ($\delta = 0.0$). HRMS spectra were measured on a Jeol SX 102 instrument equipped with its standard sources. Optical rotations were measured with a Perkin–Elmer 241 polarimeter.



Scheme 3. Reagents and conditions: (a) 3-butenoic acid, EDC, DMAP, DMF, 79%; (b) 2nd generation Grubbs's ruthenium catalysts, toluene, MW irradiation, 180 °C, 87%; (c) (i) OsO_4, trimethylamine *N*-oxide, *t*-BuOH; (ii) chromatographic separation, 48% for **13a** and 16% for **13b**; (d) $Me_2S{\cdot}BH_3$, THF, 85%.

4.2. Synthesis

4.2.1. (2*S*,6*R*)-2-Acetoxymethyl-6-hydroxymethyl-piperidine-1-carboxylic acid benzyl ester 3. Compound **4** (100 mg, 0.4 mmol), vinyl acetate (110 μL, 1.2 mmol), and lipase from *C. Cylindracea* (10 mg) were mixed with 1 mL of ionic liquid [BMIM]–[PF_6] ([BMIM]$^+$ = 1-butyl-3-methylimidazolium), and the resulting heterogeneous mixture was stirred at 40 °C for 24 h. The reaction was diluted with 3 mL of water and the enzyme was filtered through a pad of Celite. The aqueous phase was extracted three times with AcOEt and the combined organic fractions were dried and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 3:4) to yield **3** as a colorless oil (115 mg, 90% yield). Spectroscopical data are in agreement with the previously reported ones (see Ref. 8).

4.2.2. (2*S*,6*R*)-2-Acetoxymethyl-6-vinyl-piperidine-1-carboxylic acid benzyl ester 5. To a stirred solution of oxalyl chloride (0.105 mL, 1.24 mmol) in 1.8 mL of anhydrous CH_2Cl_2 at −78 °C under N_2, was added DMSO (0.130 mL, 1.42 mmol) in 1 mL of anhydrous CH_2Cl_2 dropwise and the mixture allowed to react for 5 min at −78 °C. Alcohol **3** (200 mg, 0.62 mmol) in 1 mL of anhydrous CH_2Cl_2 was added, and the reaction mixture was stirred for 1 h at −78 °C. On addition of anhydrous Et_3N (0.345 mL, 2.48 mmol), the dry ice/acetone bath was removed, and the reaction temperature left to go to rt. The reaction was diluted with 4 mL of CH_2Cl_2 and then poured into 10 mL of CH_2Cl_2 and 10 mL of 5% H_3PO_4 solution. The aqueous phase was extracted twice with CH_2Cl_2 and the combined CH_2Cl_2 fractions were dried and evaporated to give the crude aldehyde (2*S*,6*R*)-2-acetoxymethyl-6-formyl-piperidine-1-carboxylic acid benzyl ester (185 mg, 94% yield) sufficiently pure to proceed to the next synthetic step without purification. $R_f = 0.72$ (hexane/ethyl acetate, 1:3). $[\alpha]_D^{25} = -20.9$ (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.6 (s, 1H) 7.40–7.32 (m, 5H), 5.12 (s, 2H), 4.58–4.50 (m, 1H), 4.40–4.30 (m, 1H), 4.13 (dd, $J = 10.9$, 8.0 Hz, 1H), 3.95 (dd, $J = 10.9$, 6.9 Hz, 1H), 1.93 (s, 3H), 1.81–1.45 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.2, 170.6, 158.7, 137.6, 128.5–128.0 (5C), 67.61, 63.9, 59.5, 48.9, 24.6, 22.4, 20.7, 17.5. HRMS-FAB m/z calcd 319.1420. Found: 319.1424. Anal. Calcd for $C_{17}H_{21}NO_5$: C, 63.94; H, 6.63; N, 4.39; O, 25.05. Found: C, 63.89; H, 6.64; N, 4.38.

Anhydrous toluene (4 mL) and *t*-BuOK (107 mg, 0.952 mmol) were mixed at rt under N_2, and $Ph_3P(CH_3)Br$ (340 mg, 0.952 mmol) was added to the mixture. After the mixture was stirred for 1.5 h, (2*S*,6*R*)-2-acetoxymethyl-6-formyl-piperidine-1-carboxylic acid benzyl ester (100 mg, 0.313 mmol) was added with 2 mL of anhydrous toluene to the reaction mixture, and it was refluxed for 3 h. The reaction mixture was then partitioned between 10 mL of AcOEt and 6 mL of 10% $Na_2S_2O_3$ solution, and the aqueous phase was extracted 3 times with AcOEt. The organic fractions were dried and evaporated. The crude product was purified by flash chromatography (hexane/ethyl acetate, 2:1) to yield compound **5** as a colorless oil (76 mg, 77% yield). $R_f = 0.55$ (hexane/ethyl acetate, 2:1). $[\alpha]_D^{25} = -2.3$ (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): ^{1}H NMR (400 MHz, CDCl3) δ 7.35 (m, 5H), 5.88 (ddd, 1H, $J = 17.5$, 10.7, 4.8), 5.17 (m, 4H), 4.86 (m, 1H), 4.56 (dd, 1H, $J = 12.3$, 6.6), 4.20 (dd, 1H, $J = 10.8$, 8.1), 4.00 (dd, 1H, $J = 10.8$, 7.2), 1.98 (s, 3H), 1.95 (m, 1H), 1.77–1.65 (m, 5H), 1.52 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.2, 156.7, 139.9, 137.6, 129.1 (5C), 116.2, 67.9, 64.7, 52.2, 49.8, 28.2, 25.8, 21.3, 15.4. HRMS-FAB m/z calcd 317.1627. Found: 317.1628. Anal. Calcd for $C_{18}H_{23}NO$: C, 68.12; H, 7.30; N, 4.41; O, 20.16. Found: C, 68.17; H, 7.27; N, 4.39.

4.2.3. ((2*S*,6*R*)-6-Vinyl-piperidin-2-yl)-methanol 6. To a solution of **5** (600 mg, 3.59 mmol) in MeOH (30 mL) were added KOH 2 M (18 mL, 36 mmol). The resulting mixture was stirred at 80 °C for 40 h and the aqueous phase extracted 3 times with CH_2Cl_2. The combined organic phases were dried and evaporated to yield product **6** pure without other purification (440 mg, 86% yield). $R_f = 0.21$ (hexane/ethyl acetate, 1:2). $[\alpha]_D^{25} = -3.3$ (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.87 (ddd, $J = 17.1$, 10.4, 6.5 Hz, 1H), 5.19 (dt, $J = 17.1$, 1.5 Hz, 1H), 5.06 (ddd, $J = 10.4$, 1.5, 1.0 Hz, 1H), 3.66 (dd, $J = 10.6$, 3.6 Hz, 1H), 3.48 (dd, $J = 10.6$, 7.6 Hz, 1H), 3.16 (m, 1H), 2.79 (m, 1H), 1.98 (br s, 2H), 1.87 (m, 1H), 1.72 (m, 1H), 1.56 (m, 1H), 1.45 (m, 1H), 1.20 (m, 1H), 1.15 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 141.6, 114.3, 66.3, 59.4, 57.9, 32.1, 27.9, 24.0. HRMS-FAB m/z calcd 141.1154. Found: 141.1157. Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92; O, 11.33. Found: C, 68.05; H, 10.72; N, 9.89.

4.2.4. 1-((2*S*,6*R*)-2-Hydroxymethyl-6-vinyl-piperidin-1-yl)-propenone 7. To a solution of **6** (600 mg, 4.25 mmol) in acetone (20 mL) was added 9 mL of a saturated Na_2CO_3 aqueous solution and acryloyl chloride (0.6 mL, 7.43 mmol). The resulting mixture was stirred for 4 h and the aqueous phase was extracted 3 times with CH_2Cl_2. The combined organic phases were dried and evaporated to yield the product **7** pure without further purification (590 mg, 73% yield). $R_f = 0.49$ (ethyl acetate). $[\alpha]_D^{25} = +10.4$ (c 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.65 (dd, $J = 16.6$, 10.7 Hz, 1H), 6.30 (dd, $J = 16.6$, 1.6 Hz, 1H), 5.93 (ddd, $J = 17.3$, 10.9, 4.4 Hz, 1H), 5.67 (dd, $J = 10.7$, 1.6 Hz, 1H), 5.35 (d, $J = 17.3$, 1H), 5.21 (d, $J = 10.9$, 1.5 Hz, 1H), 4.88–4.55 (br m 2H), 3.75 (t, $J = 9.9$ Hz, 1H), 3.65 (dd, $J = 9.9$, 7.2 Hz, 1H), 2.43 (br s, 1H), 1.95 (br d, $J = 11.9$ Hz, 1H), 1.85–1.50 (m, 5H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.8, 140.1, 129.5, 128.0, 116.8, 65.7, 52.4, 50.2, 29.7, 25.9, 16.0. HRMS-FAB m/z calcd 195.1259. Found: 195.1257. Anal. Calcd for $C_{11}H_{17}NO_2$: C, 67.66; H, 8.78; N, 7.17; O, 16.39. Found: C, 67.64; H, 8.75; N, 7.13.

4.2.5. (5*S*,8a*R*)-5-Hydroxymethyl-6,7,8,8a-tetrahydro-5*H*-indolizin-3-one 8. To a stirred solution of **7** (300 mg, 1.54 mmol) in 50 mL of toluene was added the Grubbs catalyst 2nd generation (65 mg, 0.076 mmol). The reaction mixture was heated by microwave irradiation at 180 °C for 30′ and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography (ethyl acetate) to afford **8** (185 mg, 72%). R_f = 0.31 (ethyl acetate). $[\alpha]_D^{25} = -4.5$ (c 1, $CHCl_3$). ^{1}H NMR

($CDCl_3$, 400 MHz): δ 7.05 (dd, $J = 6.0$, 1.0 Hz, 1H), 6.12 (dd, 6.0, 1.0 Hz, 1H), 5.24 (t, $J = 7.8$ Hz, 1H), 3.97 (m, 1H), 3.85 (br d, $J = 12.4$ Hz, 1H), 3.72 (br s, 1H), 3.41 (ddt, $J = 13.4$, 6.5, 3.4 Hz 1H), 2.12 (dqd, $J = 12.8$, 3.4, 1.0 Hz, 1H), 2.09 (dt, $J = 13.5$, 3.3 Hz, 1H), 1.70 (m, 1H), 1.60 (dt, $J = 13.5$, 3.3 Hz, 1H), 1.37 (qd, $J = 12.8$, 4.2 Hz, 1H), 1.09 (qd, $J = 12.8$, 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.6, 147.7, 128.8, 64.9, 63.9, 60.9, 31.0, 30.4, 24.4. HRMS-FAB *m/z* calcd 167.0946. Found: 167.0941. Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38; O, 19.14. Found: C, 64.69; H, 7.81; N, 8.32.

4.2.6. (1*S*,2*S*,5*S*,8a*R*)-1,2-Dihydroxy-5-hydroxymethyl-hexahydro-indolizin-3-one 9a and (1*R*,2*R*,5*S*,8a*R*)-1,2-dihydroxy-5-hydroxymethyl-hexahydro-indolizin-3-one 9b. A 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (0.350 mL, 6.86 mg, 0.027 mmol) was added to a solution of 90 mg (0.539 mmol) of indolizidinone **8** and 100 mg (0.875 mmol) of trimethylamine *N*-oxide dihydrate in 2.5 mL of *tert*-butyl alcohol–water (3:1). The resulting solution was stirred at 35–40 °C for 3.5 h. After being allowed to cool to 25 °C, the reaction mixture was treated with sodium bisulfite (181 mg, 1.74 mmol), and the resulting mixture was stirred for 30 min, partially concentrated under reduced pressure, and then filtered through Celite with ethyl acetate. The filtrate was dried over sodium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by column chromatography (dichloromethane/methanol, 95:5) to afford 75 mg (70% yield) of a 4.5:1 inseparable mixture of **9a** and **9b**. ^1H NMR ($CDCl_3$, 400 MHz, major diastereoisomer **9a**): δ 7.05 (dd, $J = 6.0$, 1.0 Hz, 1H), 6.12 (dd, 6.0, 1.0 Hz, 1H), 5.24 (t, $J = 7.8$ Hz, 1H), 3.97 (m, 1H), 3.85 (br d, $J = 12.4$ Hz, 1H), 3.41 (ddt, $J = 13.4$, 6.5, 3.4 Hz 1H), 2.12 (dqd, $J = 12.8$, 3.4, 1.0 Hz, 1H), 2.09 (dt, $J = 13.5$, 3.3 Hz, 1H), 1.70 (m, 1H), 1.60 (qt, $J = 13.5$, 3.3 Hz, 1H), 1.37 (qd, $J = 12.8$, 4.2 Hz, 1H), 1.09 (qd, $J = 12.8$, 4.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.4, 147.7, 128.8, 64.9, 63.9, 60.9, 31.0, 30.4, 24.4. HRMS-FAB *m/z* calcd 201.1001. Found: 201.1004. Anal. Calcd for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; N, 6.96; O, 31.80. Found: C, 53.75; H, 7.56; N, 7.00.

4.2.7. (3a*R*,6*S*,9a*R*,9b*R*)-6-Hydroxymethyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*a*]indolizin-4-one 10a and (3a*S*,6*S*,9a*R*,9b*S*)-6-hydroxymethyl-2,2-dimethyl-hexahydro-[1,3]dioxolo[4,5-*a*]indolizin-4-one 10b. A mixture of 35 mg (0.174 mmol) of the **9a** and **9b** and 103 mg of Dowex 50W × 8 (H^+ form) in 5 mL of 2,2-dimethoxypropane (ADA) was stirred at 40 °C for 3.5 h, after which it was partially concentrated, filtered through Celite, and evaporated to dryness. Purification of the resulting crude product by column chromatography (hexane/ethyl acetate, 2:1) gave 31 mg (64% yield) of **10a** and 7 mg (14% yield) of **10b**.

Compound **10a**: $R_f = 0.25$ (ethyl acetate). $[\alpha]_D^{25} = +6.4$ (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ 4.72 (br s, 1H), 4.66 (d, $J = 6.4$ Hz, 1H), 4.37 (d, $J = 6.4$ Hz, 1H), 3.92 (m, 2H), 3.46 (dd, $J = 12.9$, 2.6 Hz, 1H), 3.25 (m, 1H), 2.00 (m, 1H), 1.65 (m, 2H), 1.57 (m, 1H), 1.49 (s, 3H), 1.44 (m, 1H), 1.39 (s, 3H), 1.16 (dq, $J = 13.1$, 4.6 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 112.7, 78.1, 77.1, 64.6, 62.7, 61.3, 30.6, 29.7, 27.6, 26.7, 23.8. HRMS-FAB *m/z* calcd 241.1314. Found: 241.1318. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81; O, 26.52. Found: C, 59.69; H, 7.91; N, 5.72.

Compound **10b**: $R_f = 0.14$ (ethyl acetate). $[\alpha]_D^{25} = -2.0$ (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ ppm 4.97 (br s, 1H), 4.66 (br s, 2H), 3.92 (dd, $J = 12.9$, 6.9 Hz, 1H), 3.85 (dd, $J = 12.9$, 2.4 Hz, 1H), 3.50 (m, 1H), 3.19 (m, 1H), 2.00 (m, 1H), 1.84–1.61 (m, 2H), 1.54 (m, 1H), 1.49 (s, 3H), 1.42 (s, 3H), 1.40 (m, 1H), 1.28 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.5, 112.7, 78.3, 74.1, 63.7, 61.1, 60.1, 27.9, 27.0, 26.0, 25.4, 23.1. HRMS-FAB *m/z* calcd 241.1314. Found: 241.1313. Anal. Calcd for $C_{12}H_{19}NO_4$: C, 59.73; H, 7.94; N, 5.81; O, 26.52. Found: C, 59.66; H, 7.58; N, 5.82.

4.2.8. (1*R*,2*S*,5*S*,8a*R*)-5-Hydroxymethyl-octahydro-indolizine-1,2-diol 1. Lactam **10a** (20 mg, 0.084 mmol) in dry THF (3.8 mL) was treated with a solution of $Me_2S{\cdot}BH_3$ (2 M in THF, 0.39 mL, 0.78 mmol) under N_2. After 2 h at RT and 1 h at reflux conditions, the excess reducing reagent was decomposed by the careful addition of EtOH (0.77 mL) at −5 °C. After evaporation, the resulting residue was stirred in 5 mL of 1M aqueous HCl at reflux for 1 h. The reaction mixture was then concentrated under reduced pressure, and the resulting residue was passed through a column of 5 g of Dowex 1 × 8-200 resin (OH^- form) with water. The oil obtained was purified by flash column chromatography on silica gel (methanol/ethyl acetate/triethylamine, 10:89:1) to give **1** (13 mg, 85% yield). $R_f = 0.35$ (dichloromethane/methanol, 95:5). $[\alpha]_D^{25} = -5.1$ (c 1, MeOH). ^1H NMR ($CDCl_3$, 400 MHz): δ ppm 4.08 (m, 1H), 3.72 (br s, 3H), 3.59 (m, 2H), 3.41 (m, 1H), 3.19 (m, 1H), 3.02 (m, 1H), 2.65–2.20 (m, 2H), 1.99 (m, 2H), 1.80–1.65 (m, 3H), 1.33 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 83.7, 77.1, 68.8, 63.7, 63.2, 56.2, 27.9, 26.8, 23.5. HRMS-FAB *m/z* calcd 187.1208. Found: 187.1205. Anal. Calcd for $C_9H_{17}NO_3$: C, 57.73; H, 9.15; N, 7.48; O, 25.64. Found: C, 57.69; H, 9.11; N, 7.51.

4.2.9. 1-((2*S*,6*R*)-2-Hydroxymethyl-6-vinyl-piperidin-1-yl)-but-3-en-1-one 11. To an ice cooled solution of EDC (150 μL, 0.85 mmol) in 4 mL of dry DMF under N_2, **6** (100 mg, 0.71 mmol), 3-butenoic acid (67 μL, 0.78 mmol) and DMAP (104 mg, 1.78 mmol) were added with stirring. The cooling bath was removed and the solution stirred at room temperature for 11 h. After evaporation of the solvent, the residue was dissolved in 10 mL of AcOEt and washed with 15 mL of solution. The aqueous phase was extracted twice with AcOEt (10 mL). The combined organic phases were washed with 5% aqueous HCl (10 mL), saturated aqueous $NaHCO_3$(10 mL) and then brine (10 mL). The organic phase was dried and evaporated to yield the product **11** (117 mg, 79% yield) pure without further purification. $R_f = 0.44$ (ethyl acetate). $[\alpha]_D^{25} = -2.5$ (c 1, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ ppm 5.86 (m, 2H), 5.20 (m, 4H), 4.82 (br m, 1H), 4.49 (br m, 1H), 4.09 (br s, 1H), 3.65 (m, 2H), 3.21 (m, 2H), 1.98–1.43 (br m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 168.3, 139.2, 131.7, 117.6, 116.2, 65.0, 53.9, 50.6, 38.8, 29.3,

24.9, 15.1. HRMS-FAB *m/z* calcd 209.1416. Found: 209.1421. Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69; O, 15.29. Found: C, 68.83; H, 9.14; N, 6.66.

4.2.10. (6*S*,9a*R*)-6-Hydroxymethyl-3,6,7,8,9,9a-hexahydroquinolizin-4-one 12. To a stirring solution of **11** (80 mg, 0.38 mmol) in 12 mL of dry toluene was added the Grubbs catalyst 2nd generation (16 mg, 0.088 mmol). The reaction mixture was heated by microwave irradiation at 180 °C for 30 min and the solvent was removed under reduced pressure. The resulting oil was purified by column chromatography (ethyl acetate) to afford **12** (59 mg, 87%). $R_f =$ 0.31 (ethyl acetate). $[\alpha]_D^{25} = -4.5$ (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.66 (m, 2H), 3.95 (dd, $J = 12.0$, 3.0 Hz, 1H), 3.81 (m, 2H), 3.14 (m, 1H), 2.94 (m, 2H, H_3), 2.61 (br s, 1H), 1.98 (m, 1H), 1.89 (m, 1H), 1.71 (m, 1H), 1.67 (m, 1H), 1.63 (m, 1H), 1.32 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 167.7, 125.8, 120.9, 65.3, 63.7, 60.3, 34.1, 33.2, 30.4, 24.4. HRMS-FAB *m/z* calcd 181.1103. Found: 181.1109. Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.34; N, 7.73; O, 17.66. Found: C, 66.29; H, 7.77; N, 8.28.

4.2.11. (1*R*,2*S*,6*S*,9a*R*)-1,2-Dihydroxy-6-hydroxymethyl-octahydro-quinolizin-4-one 13a and (1*S*,2*R*,6*S*,9a*R*)-1,2-dihydroxy-6-hydroxymethyl-octahydro-quinolizin-4-one 13b. A 2.5% solution of osmium tetraoxide in *tert*-butyl alcohol (0.700 mL, 13.7 mg, 0.054 mmol) was added to a solution of 180 mg (1.0 mmol) of **12** and trimethylamine *N*-oxide dihydrate (180 mg, 1.62 mmol) in 2.5 mL of *tert*-butyl alcohol/water (3:1). The resulting solution was stirred at 40 °C for 3 h. After cooling to 25 °C, the reaction mixture was treated with sodium bisulfite (400 mg, 3.84 mmol), and the resulting mixture was stirred for 30 min, partially concentrated under reduced pressure, and then filtered through Celite with ethyl acetate. The filtrate was dried over sodium sulfate and concentrated under reduced pressure to afford the crude product, which was purified by silica gel column chromatography with 5% methanol in dichloromethane to afford **13a** (104 mg, 48% yield) and **13b** (34 mg, 16% yield).

Compound **13a**: $R_f = 0.44$ (dichloromethane/methanol, 95:5). $[\alpha]_D^{25} = +8.6$ (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 4.13 (m, 1H), 3.89 (dd, $J = 12.2$, 2.7 Hz, 1H), 3.77 (dd, $J = 12.2$, 6.6 Hz, 1H), 3.73 (m, 1H), 3.48 (m, 2H), 2.72 (dd, $J = 17.4$, 7.3 Hz, 1H), 2.63 (dd, $J = 17.4$, 5.3 Hz, 1H), 2.39 (br s, 1H), 2.01 (m, 1H), 1.91 (m, 1H), 1.75–1.60 (m, 3H), 1.38–1.25 (m, 3H), 0.86 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 71.5, 65.7, 64.8, 62.7, 60.9, 37.6, 29.7, 26.3, 21.9. HRMS-FAB *m/z* calcd 215.1158. Found: 215.1149. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51; O, 29.73. Found: C, 55.86; H, 7.94; N, 6.53.

Compound **13b**: $R_f = 0.25$ (dichloromethane/methanol, 95:5). $[\alpha]_D^{25} = -6.6$ (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 4.21 (m, 1H), 3.91 (dd, $J = 12.3$, 2.8 Hz,1H), 3.81 (dd, $J = 12.4$, 6.8 Hz, 1H), 3.78 (m, 1H), 3.57 (m, 1H, $H_{9a'}$), 3.49 (m, 1H), 2.71 (m, 2H), 2.11 (m, 3H), 2.07 (m, 1H), 1.88 (m, 2H), 1.79 (m, 1H), 1.76 (m, 1H), 1.64 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.6, 70.3, 66.9, 66.8, 62.5, 55.4, 36.9, 24.5, 23.0, 16.8. HRMS-FAB *m/z* calcd 215.1158. Found 215.1151. Anal. Calcd for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; N, 6.51; O, 29.73. Found: C, 55.77; H, 7.98; N, 6.48.

4.2.12. (1*S*,2*R*,6*S*,9a*R*)-6-Hydroxymethyl-octahydro-quinolizine-1,2-diol 2. Lactam **13a** (40 mg, 0.186 mmol) in dry THF (6 mL) was treated with a solution of $Me_2S{\cdot}BH_3$ (2 M in THF, 0.930 mL, 1.86 mmol) under N_2. After 2 h at rt and 1 h under reflux conditions, the excess reducing reagent was decomposed by careful addition of EtOH (2 mL) at −5 °C. After evaporation, the residue was purified by flash column chromatography on silica gel (methanol/ethyl acetate/triethylamine, 10:89:1) to give **2** (31 mg, 85% yield). $R_f = 0.37$ (methanol/ethyl acetate/triethylamine, 10:89:1). $[\alpha]_D^{25} = -7.9$ (*c* 1, MeOH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 4.03 (m, 1H), 3.94 (dd, $J = 11.2$, 3.7 Hz, 1H), 3.40 (m, 2H), 2.98 (m, 1H), 2.47–2.27 (m, 3H), 1.83 (m, 2H), 1.79–1.90 (m, 6H), 1.35 (m, 1H), 1.23 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 73.9, 66.8, 62.8, 62.5, 61.3, 43.9, 30.1 (2C), 29.0, 23.4. HRMS-FAB *m/z* calcd 201.1365. Found: 201.1361. Anal. Calcd for $C_{10}H_{19}NO_3$: C, 59.68; H, 9.52; N, 6.96; O, 23.85. Found: C, 59.61; H, 9.41; N, 6.82.

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