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A chiral hexahydroindolizine as key intermediate in the synthesis of tri- and tetrahydroxyindolizidines

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Abstract—The highly stereoselective functionalization of hexahydro-3-oxo-indolizine **6** has been examined. The bishydroxylated product can be transformed successfully into the trihydroxyindolizidine **11** in 57% overall yield. In addition, a simple elimination process to give the α,β-unsaturated lactam **13** and a second highly stereoselective bishydroxylation can be used to synthesise the tetrahydroxyindolizidine **19** in 30% overall yield. © 2001 Published by Elsevier Science Ltd.

1. Introduction

Due to the ability of hydroxylated indolizidine alkaloids such as swainsonine (**1**), castanospermine (**2**) and lentiginosine (**3**) (Fig. 1) to inhibit glycosidases and glycosyl transferases,[1] this type of compound has been the subject of substantial synthetic efforts.[2]

In particular, it is important to develop a synthetic route to various bicyclic azasugars in a flexible and efficient way. As outlined in Scheme 1, hexahydro-3-oxo-indolizine **6**, which can be synthesised on a large scale in only five steps by a combined electrochemical oxidation- *N*-acyliminium ion coupling reaction[3] and subsequent ring closing olefin metathesis[4] starting from (*R*)-4-hydroxy-2-pyrrolidone (**4**), seems to be an ideal precursor for the synthesis of tri- and tetrahydroxyindolizidines. In this paper, we report the highly stereoselective functionalization of **6** and the application of these products to the synthesis of azasugars **11** and **17**.

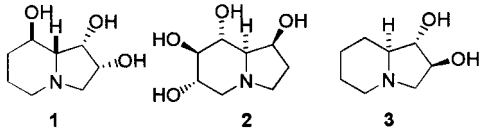
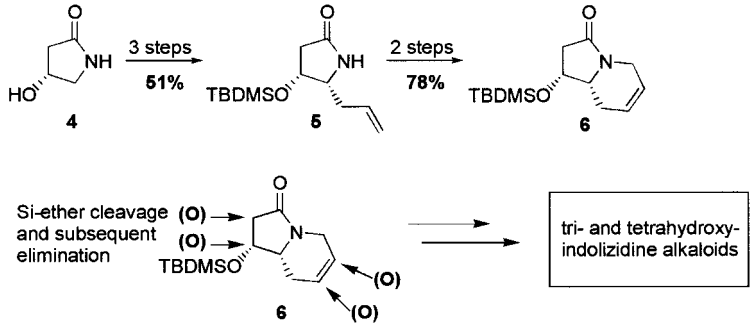


Figure 1.

2. Results and discussion

The stereoselective bishydroxylation of the 6,7-double bond was examined first (Scheme 2). Under modified *Upjohn* conditions[5] treatment of **6** with a catalytic amount of $K_2OsO_4{}^*2\ H_2O$ (1 mol%) and NMMO (1.5 equiv.) as cooxidant gave diol **7** in high yield of 91% and high diastereoselectivity (ds: 91%). The dihydroxylation occurred from the less hindered convex side of the bicyclic



Scheme 1. Synthesis of hexahydro-3-oxo-indolizine **6** and general synthetic strategy.

Keywords: azasugars; nitrogen heterocycles; asymmetric synthesis; dihydroxylations.

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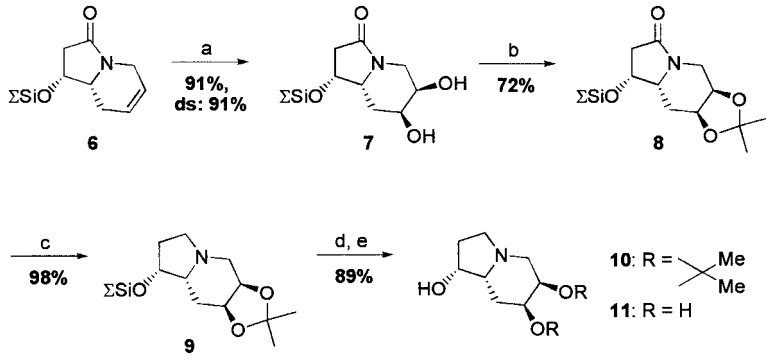


Scheme 2. SiΣ=TBDMS; (a) $K_2OsO_4{}^*2\ H_2O$, NMMO; (b) 2,2-dimethoxypropane, PPTS; (c) $BH_3{}^*$DMS, THF, 0°C; (d) TBAF, THF; (e) *p*-TsOH, MeOH.

compound and the stereochemistry of the product was confirmed by an X-ray structure determination (Fig. 2).[6] The ^{1}H NMR spectrum showed that the same conformation also prevailed in solution as indicated by large coupling constants J(H-5_{ax},H-6_{ax}) of 11.7 Hz and J(H-8_{ax},H-$8a_{ax}$) of 11.0 Hz.

After protection of the diol as acetonide **8** the lactam was reduced by treatment with borane-dimethylsulfide in almost quantitative yield. Reduction of the unprotected diol resulted in poor yield of the corresponding indolizidine derivative. To elaborate the trihydroxyindolizidine **11** we chose a two-step procedure. After quantitative cleavage of the TBDMS ether with TBAF in THF the completely deprotected azasugar was obtained by stirring the acetonide **10** with *p*-TsOH in methanol overnight.

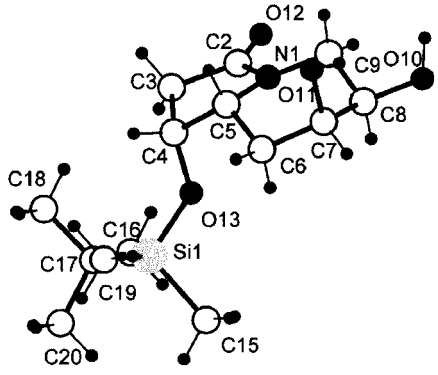
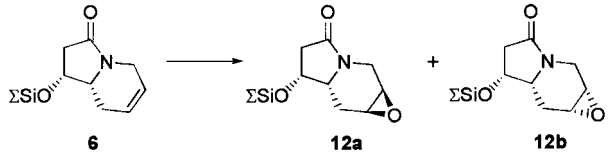
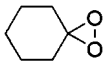


Figure 2. X-Ray crystal structure analysis of **7**.[6]

Table 1. Stereoselective epoxidation of hexahydroindolizine **6** under different conditions (SiΣ=TBDMS)

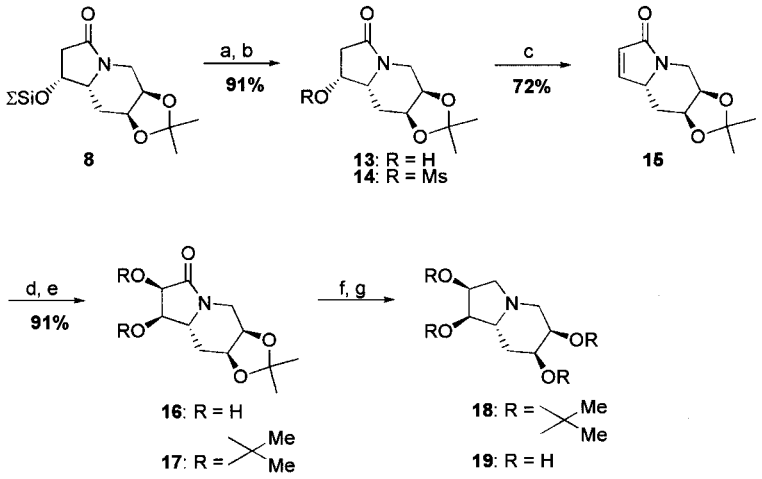


Reagent	Yield [%]	Ratio of **12a**:**12b**
MCPBA	65	66:34
	58	89:11
	62	92:8

In order to study the usefulness of **6** in other stereoselective conversions of the double bond we introduced the epoxy-functionality as an attractive key intermediate for further transformations (Table 1). The MCPBA oxidation of **6** gave an unsatisfying 66:34 mixture of diastereomers **12a** and **12b** in 65% yield. Higher stereoselectivities were obtained by using dioxiranes as epoxidizing reagents. The dioxiranes generated in situ from cyclohexanone and acetone according to a recent procedure[7] reacted with **6** to give **12a** and **12b** in ratios between 89:11 and 92:8. The yield of 62% in case of dimethyldioxirane in combination with the high diastereoselectivity offers perspectives for a broader synthetic application.

Compound **8** is an ideal intermediate for further synthetic manipulation at C-1 and C-2 (Scheme 3). For this purpose the TBDMS ether was quantitatively cleaved by TBAF in THF. Mesylation of the resulting hydroxy derivative by treatment with methanesulfonyl chloride and triethylamine led to compound **14** in 89% yield. Elimination of methanesulfonic acid under the influence of DBU as base resulted in the formation of the α,β-unsaturated lactam **15**. Under the same conditions mentioned above for **6** but now applying 10 mol% of Osmium catalyst[8] the electron deficient double bond was bishydroxylated in 70% yield and again in high diastereoselectivity (ds: 88%). Once more protection of the resulting diol as acetonide before the reduction of the lactam was advantageous and treatment of **17** with borane–dimethylsulfide led to the diprotected indolizidine **18** in 91% yield. By stirring **18** with *p*-TsOH in methanol the deprotected tetrahydroxyindolizidine **19** was quantitatively elaborated.

The stereochemical assignment of the relative configuration of the bishydroxylated product **16** was determined from ^{1}H NMR coupling constants of its derivative **17**. No coupling between protons H-1 and H-8a was observed indicating a *trans* relationship between these protons. This conclusion is based on comparison with known compounds with a similar substitution pattern.[3,8] On the other hand, in the *cis* configurated derivatives **8** and **13**–**14** typical coupling constants between H-1 and H-8a are around 4.1–4.7 Hz. The face-selectivity in the osmylation of **15** may be rationalized in terms of 1,2- and 1,3-interactions. In the most stable conformation there is an axially orientated allylic hydrogen H-8a but also an axial H-8 projecting to the opposite face. In fact, the oxidizing reagent approaches to the double bond in order to avoid 1,3-steric interaction with H-8.



Scheme 3. SiΣ=TBDMS; (a) TBAF, THF; (b) Ms-Cl, NEt_3, 0°C→rt; (c) DBU, THF, 0°C; (d) K_2OsO_4*2 H_2O, NMMO; (e) 2,2-dimethoxypropane, PPTS; (f) BH_3*DMS, THF, 0°C→rt; (g) *p*-TsOH, MeOH.

In conclusion, we were able to show that the hexahydro-3-oxo-indolizine **6** is a useful chiral building block for the synthesis of indolizidine alkaloids and of tri- and tetrahydroxyindolizidine azasugars.

3. Experimental

3.1. General

^{1}H NMR spectra were determined in the reported solvent using a Bruker AC 400 (400 MHz) spectrometer. The same instrument was also used for the measurements of ^{13}C NMR spectra (100.6 MHz). Chemical shifts are given in ppm downfield from tetramethylsilane. Mass or FABMS spectra were obtained using A.E.I. MS-50 and MS-30 or Kratos MS-50 spectrometers. R_f values were obtained by using thin-layer chromatography (TLC) on silic gel-coated plastic sheets (Merck silica gel F_{254}). All solvents were distilled before using. The diastereomeric ratios were determined by analysis of the ^{1}H NMR spectra of the crude products and/or by gas chromatography (GC).

3.1.1. (1*R*,6*R*,7*S*,8a*R*)-1-*tert*-Butyldimethylsilyloxy-6,7-dihydroxy-3-oxo-indolizidine (7). To a solution of **6** (500 mg, 1.95 mmol) in 24 ml of acetone and 3 ml of H_2O *N*-methylmorpholine *N*-oxide (391 mg, 2.94 mmol) and K_2OsO_4*2 H_2O (7.4 mg, 0.02 mmol) were added at 10°C. The solution was stirred at rt overnight. Then 20 ml of sat. Na_2SO_3 were added and the mixture was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (ethyl acetate/cyclohexane 9:1) afforded **7** as a colourless solid (510 mg, 91% (ds: 91%)). Mp: 177–179°C (colourless crystals). R_f: 0.23 (ethyl acetate/cyclohexane 9:1). $[\alpha]_{25}^{D}$=+9.8° (*c*=2.15, EtOH). ^{1}H NMR (CD_3OD): δ=0.00 (s, 6H, $2CH_3$), 0.80 (s, 9H, $C(CH_3)_3$), 1.67 (dt, *J*=14.0, 4.2 Hz, 1H, CH_2), 1.79 (ddd, *J*=14.0, 11.8, 2.2 Hz, 1H, CH_2), 2.12 (dd, *J*=17.2, 1.7 Hz, 1H, CH_2), 2.62 (ddd, *J*=17.2, 6.2, 1.7 Hz, 1H, CH_2), 2.79 (td, *J*=11.7, 1.7 Hz, 1H, CH_2N), 3.42 (ddd, *J*=11.0, 5.8, 2.5 Hz, 1H, CHN), 3.78 (dd, *J*=12.3, 5.7 Hz, 1H, CH_2N), 3.75–3.82 (m, 1H, CHO), 3.99 (ddd, *J*=4.1, 2.5, 2.1 Hz, 1H, CHO), 4.37 (td, *J*=5.8, 1.7 Hz, 1H, CHO). ^{13}C NMR (CD_3OD): δ=−4.9, −4.7, 19.0, 26.3, 31.7, 41.2, 43.1, 57.3, 67.9, 68.9, 69.0, 174.7. MS (FAB, mNBA) *m/z*=302.2 (M^++H).). HRMS calculated for $C_{13}H_{24}NO_4Si$ (M^+-CH_3) 286.1468, found 286.1475. Anal. found C, 54.18; H, 8.71; N, 3.88. Calculated for $C_{14}H_{27}NO_4Si$×0.5 H_2O: C, 54.16; H, 9.09; N, 4.51.

Crystal Structure Analysis of **7**:[6] A colourless crystal of **7** with the dimensions 0.30 mm×0.30 mm×0.18 mm was obtained by dissolving this substance in methanol. The crystal was measured on a CAD 4 diffractometer using CuKα radiation (λ=1.54178 Å). Crystal data: $C_{14}H_{27}NO_4Si$, *M*=301.46 g/mol, monoclinic space group *P* 2(1), *a*=7.926(1) Å, *b*=6.269(1) Å, *c*=16.976(3) Å, *V*=828.3(2) Å^3, *Z*=2, D_c=1.209 g/cm^3, *F* (328), μ (CuKα)=1.361 mm^{-1}. At 203 (2) K in the range of 2.65°<θ<75.85° 1864 reflections were measured with $R_1[I>2\sigma(I)]$=0.0342, wR_2 (F^2)=0.0874 and Goof=0.991. The structure was solved by direct methods and refined by least squares procedure within the SHELX program system.

3.1.2. (1*R*,6*R*,7*S*,8a*R*)-1-*tert*-Butyldimethylsilyloxy-6,7-(isopropylidene)dioxy-3-oxo-indolizidine (8). To a solution of **7** (205 mg, 0.68 mmol) in 10 ml of acetone 2,2-dimethoxypropane (0.74 ml, 6.2 mmol) and pyridinium *p*-toluenesulfonate (14 mg, 0.05 mmol) were added at rt. The mixture was stirred for 2 h and the solvent was evaporated in vacuo. Flash chromatography (ethyl acetate/cyclohexane 3:1) afforded **8** as a colourless solid (166 mg, 72%). Mp: 95–97°C (colourless crystals). R_f: 0.40 (ethyl acetate/cyclohexane 3:1). $[\alpha]_{25}^{D}$=+17.7° (*c*=0.77, EtOH). ^{1}H NMR ($CDCl_3$): δ=−0.01, 0.00 (2s, 6H, $2CH_3$), 0.81 (s, 9H, $C(CH_3)_3$), 1.30, 1.43 (2s, 6H, $2CH_3$), 1.79 (ddd, *J*=14.8, 4.0, 2.2 Hz, 1H, CH_2), 1.84 (ddd, *J*=14.8, 11.1, 3.7 Hz, 1H, CH_2), 2.19 (dd, *J*=16.7, 1.7 Hz, 1H, CH_2), 2.59 (dd, *J*=16.7, 5.9 Hz, 1H, CH_2), 3.48 (d, *J*=4.4 Hz, 2H, CH_2N), 3.75 (dt, *J*=11.1, 4.1 Hz, 1H, CHN), 4.32 (dt, *J*=6.4, 4.4 Hz, 1H, CHO), 4.35 (ddd, *J*=6.1, 3.7, 1.7 Hz, 1H, CHO), 4.45 (ddd, *J*=6.4, 3.6, 2.5 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ=−5.0, −4.7, 18.1, 24.5, 25.7, 27.1, 28.6, 39.9, 41.7, 55.1, 68.1, 70.8, 71.7, 108.2, 172.7. MS (FAB, mNBA) *m/z*=342.2 (M^++H).). HRMS calculated for

$C_{16}H_{28}NO_4Si$ (M^+-CH_3) 326.1780, found 326.1785. Anal. found C, 59.41; H, 8.93; N, 4.11. Calculated for $C_{17}H_{31}NO_4Si$: C, 59.79; H, 9.15; N, 4.10.

3.1.3. (1*R*,6*R*,7*S*,8a*R*)-1-*tert*-Butyldimethylsilyloxy-6,7-(isopropylidene)dioxy-indolizidine (9). Borane–dimethyl sulfide (0.15 ml, 1.5 mmol) was added to a cool (0°C) solution of **8** (103 mg, 0.3 mmol) in 10 ml of THF. The mixture was stirred at rt overnight. The reaction was quenched by addition of sat. Na_2SO_4 and the solvent was evaporated in vacuo. Flash chromatography (ethyl acetate/cyclohexane 1:4) afforded **9** as a colourless solid (96 mg, 98%). Mp: 126–127°C (colourless crystals). R_f: 0.65 (ethyl acetate/cyclohexane 1:4). $[\alpha]_{25}^{D}=+6.0°$ (c=0.2, EtOH). ^{1}H NMR ($CDCl_3$): $\delta=-0.003$, 0.00 (2s, 6H, $2CH_3$), 0.80 (s, 9H, $C(CH_3)_3$), 1.18, 1.32 (2s, 6H, $2CH_3$), 1.63 (dd, J=13.0, 5.4 Hz, 1H, CH_2), 1.97 (dt, J=15.0, 7.1 Hz, 1H, CH_2), 2.09 (ddd, J=15.0, 8.1, 2.2 Hz, 1H, CH_2), 2.14 (ddt, J=13.0, 12.6, 3.7 Hz, 1H, CH_2), 2.66 (dd, J=13.5, 12.1 Hz, 1H, CH_2N), 2.87 (dd, J=13.5, 4.4 Hz, 1H, CH_2N), 3.06–3.19 (m, 2H, CH_2N), 3.43 (ddd, J=6.7, 4.4, 2.2 Hz, 1H, CHN), 4.15 (m, 1H, CHO), 4.18 (dd, J=11.8, 4.7 Hz, 1H, CHO), 4.45 (dt, J=7.4, 7.1 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): $\delta=-5.0$, −4.8, 17.9, 25.4, 25.5, 25.8, 27.6, 33.1, 56.8, 58.8, 69.3, 70.0, 70.1, 75.7, 108.9. MS (EI) m/z=327 (M^+), 312 (M^+-CH_3), 270 ($M^+-C_4H_9$). HRMS calculated for $C_{17}H_{33}NO_3Si$ 327.2229, found 327.2223.

3.1.4. (1*R*,6*R*,7*S*,8a*R*)-1-Hydroxy-6,7-(isopropylidene)-dioxy-indolizidine (10). To a solution of **9** (70 mg, 0.21 mmol) in 10 ml of THF tetrabutylammonium fluoride in THF (1 M, 0.53 ml, 0.53 mmol) was added, and the mixture was stirred overnight. After evaporation of the solvent, purification by flash chromatography (ethyl acetate/cyclohexane 1:1) afforded **10** as a white solid (46 mg, quant.). Mp: 110–112°C. R_f: 0.35 (ethyl acetate/cyclohexane 1:1). $[\alpha]_{25}^{D}=+54.6°$ (c=0.4, EtOH). ^{1}H NMR ($CDCl_3$): δ=1.33, 1.44 (2s, 6H, $2CH_3$), 1.76 (dt, J=13.0, 2.7 Hz, 1H, CH_2), 1.82 (brs, 1H, OH), 2.09 (dt, J=15.0, 7.4 Hz, 1H, CH_2), 2.29 (m, 1H, CH_2), 2.31 (ddd, J=15.0, 7.6, 2.2 Hz, 1H, CH_2), 2.79 (dd, J=13.5, 11.8 Hz, 1H, CH_2N), 3.00 (dd, J=13.5, 4.7 Hz, 1H, CH_2N), 3.25–3.31 (m, 2H, CH_2N), 3.57 (m, 1H, CHN), 4.32 (ddd, J=11.8, 7.6, 4.9 Hz, 1H, CHO), 4.38 (t, J=3.2 Hz, 1H, CHO), 4.62 (td, J=7.4, 7.1 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ=25.3, 25.5, 27.6, 33.3, 56.9, 58.9, 69.4, 69.5, 70.0, 74.7, 108.9. MS (EI) m/z=213 (M^+), 1982 (M^+-CH_3), 195 (M^+-H_2O). HRMS calculated for $C_{11}H_{19}NO_3$ 213.1360, found 213.1361.

3.1.5. (1*R*,6*R*,7*S*,8a*R*)-1,6,7-Trihydroxy-indolizidine (11). To a solution of **10** (25 mg, 0.12 mmol) in 10 ml of methanol *p*-toluenesulfonic acid (46 mg, 0.24 mmol) was added, and the mixture was stirred overnight. The solution was neutralised by addition of K_2CO_3 and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH 4:1) afforded **11** as a colourless oil (18 mg, 89%). R_f: 0.08 (CH_2Cl_2/MeOH 4:1). $[\alpha]_{25}^{D}=+4.1°$ (c=0.77, EtOH). ^{1}H NMR (CD_3OD): δ=1.61 (dtd, J=13.8, 8.9, 2.0 Hz, 1H, CH_2), 1.68 (ddd, J=14.0, 11.3, 2.7 Hz, 1H, CH_2), 1.75 (dt, J=14.0, 3.2 Hz, 1H, CH_2), 2.03 (q, J=9.1 Hz, 1H, CH_2N), 2.12–2.28 (m, 3H, CH_2/ CH_2N), 2.82 (dd, J=10.1, 4.9 Hz, 1H, CH_2N), 2.96 (td, J=9.1, 2.0 Hz, 1H, CHO), 3.63 (ddd, J=10.8, 4.9, 3.0 Hz, 1H, CHN), 3.92 (q, J=2.9 Hz, 1H, CHO), 4.01 (ddd, J=7.1, 4.7, 2.0 Hz, 1H, CHO). ^{13}C NMR (CD_3OD): δ=31.1, 34.5, 53.3, 54.3, 63.4, 68.8, 70.1, 72.3. MS (EI) m/z=173 (M^+), 155 (M^+-H_2O). HRMS calculated for $C_8H_{15}NO_3$ 173.1048, found 173.1050.

3.1.6. (1*R*,6*R*,7*S*,8a*R*)-1-*tert*-Butyldimethylsilyloxy-6,7-epoxy-3-oxo-indolizidine (12a). To a solution of **7** (90 mg, 0.34 mmol) in 2.5 ml of dichloromethane, 10 ml of methanol and 3 ml of buffered H_2O (pH 11.0, 0.5 M phosphate buffer) 0.25 ml of acetone were added. After that a solution of oxone (1.06 g, 1.69 mmol) in H_2O was added dropwise under careful control of the pH. After 5 days stirring at rt the reaction was worked up by the addition of water and extraction with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (ethyl acetate/cyclohexane 1:1) afforded **12a** as a colourless solid (59 mg, 62% (ds: 92%)). Mp: 42–43°C (colourless crystals). R_f: 0.29 (ethyl acetate/cyclohexane 1:1). $[\alpha]_{25}^{D}=+21.6°$ (c=0.4, EtOH). ^{1}H NMR ($CDCl_3$): $\delta=-0.004$, 0.00 (2s, 6H, $2CH_3$), 0.82 (s, 9H, $C(CH_3)_3$), 2.01 (dt, J=14.5, 3.7 Hz, 1H, CH_2), 2.12 (ddd, J=14.5, 11.3, 1.2 Hz, 1H, CH_2), 2.18 (dd, J=17.0, 3.5 Hz, 1H, CH_2), 2.48 (dd, J=17.0, 6.6 Hz, 1H, CH_2), 3.23 (dd, J=3.9, 3.4 Hz, 1H, CHO), 3.38 (dd, J=3.7, 3.2 Hz, 1H, CHO), 3.45 (d, J=15.5 Hz, 1H, CH_2N), 3.65 (ddd, J=11.3, 5.7, 4.4 Hz, 1H, CHN), 4.05 (dd, J=15.5, 3.4 Hz, 1H, CH_2N), 4.32 (ddd, J=6.4, 5.9, 3.2 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): $\delta=-5.1$, −4.7, 18.1, 25.2, 25.7, 39.0, 40.2, 49.5, 52.4, 55.1, 66.9, 172.5. MS (FAB, mNBA) m/z=284.1 (M^++H). HRMS calculated for $C_{13}H_{22}NO_3Si$ (M^+-CH_3) 268.1368, found 268.1376.

3.1.7. (1*R*,6*R*,7*S*,8a*R*)-1-Hydroxy-6,7-(isopropylidene)-dioxy-3-oxo-indolizidine (13). To a solution of **8** (584 mg, 1.7 mmol) in 30 ml of THF tetrabutylammonium fluoride in THF (1 M, 4.3 ml, 4.3 mmol) was added, and the mixture was stirred overnight. After evaporation of the solvent, purification by flash chromatography (ethyl acetate/ethanol 5:1) afforded **13** as a colourless solid (389 mg, quant.). Mp: 68–70°C (colourless crystals). R_f: 0.30 (EtOAc/EtOH 5:1). $[\alpha]_{25}^{D}=+42.5°$ (c=0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.30, 1.42 (2s, 6H, $2CH_3$), 1.86–1.95 (m, 2H, CH_2), 2.26 (d, J=17.2 Hz, 1H, CH_2), 2.67 (dd, J=17.2, 4.7 Hz, 1H, CH_2), 3.32 (dd, J=14.3, 3.7 Hz, 1H, CH_2N), 3.62 (dd, J=14.3, 3.4 Hz, 1H, CH_2N), 3.77 (td, J=7.4, 4.4 Hz, 1H, CHN), 4.32 (t, J=4.7 Hz, 1H, CHO), 4.37 (dt, J=6.9, 3.5 Hz, 1H, CHO), 4.49 (dt, J=6.6, 2.7 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ=24.2, 26.8, 28.2, 39.8, 41.7, 54.9, 67.9, 70.9, 71.3, 108.1, 173.4. MS (EI) m/z=227 (M^+), 212 (M^+-CH_3), 209 (M^+-H_2O). HRMS calculated for $C_{11}H_{17}NO_4$ 227.1170, found 227.1161.

3.1.8. (1*R*,6*R*,7*S*,8a*R*)-6,7-(Isopropylidene)dioxy-1-methanesulfoxy-3-oxo-indolizidine (14). To a solution of **13** (67 mg, 0.3 mmol) in 5 ml of CH_2Cl_2 methanesulfonyl chloride (27 μl, 0.36 mmol) and triethylamine (57 μl, 0.42 mmol) were added at 0°C. The solution was stirred at 0°C for 1 h, and then allowed to warm to rt overnight. Water was added and the mixture was extracted with

CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (EtOAc) afforded **14** as a colourless solid (80 mg, 89%). Mp: 122–124°C (colourless crystals). R_f: 0.30 (EtOAc). $[\alpha]_{25}^{D}$=+39.1° (c=0.5, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.30, 1.42 (2s, 6H, $2CH_3$), 1.80 (ddd, J=14.5, 12.1, 3.5 Hz, 1H, CH_2), 2.02 (ddd, J=14.5, 2.5, 2.0 Hz, 1H, CH_2), 2.54 (d, J=17.7 Hz, 1H, CH_2), 2.79 (dd, J=17.7, 5.7 Hz, 1H, CH_2), 2.99 (s, 3H, SO_2CH_3), 3.34 (dd, J=14.8, 3.4 Hz, 1H, CH_2N), 3.71 (dd, J=14.8, 3.2 Hz, 1H, CH_2N), 3.98 (ddd, J=12.1, 4.4, 2.7 Hz, 1H, CHN), 4.40 (dt, J=6.9, 3.4 Hz, 1H, CHO), 4.48 (ddd, J=6.9, 3.4, 2.0 Hz, 1H, CHO), 5.24 (dd, J=5.4, 4.7 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ=24.0, 26.8, 29.2, 38.8, 39.0, 39.7, 53.5, 70.7, 70.9, 76.6, 108.2, 170.6. MS (EI) m/z=306 (M^++H), 290 (M^+-CH_3), 209 (M^+−MsOH). HRMS calculated for $C_{12}H_{20}NO_6S$ (M^++H) 306.1013, found 306.1003; calculated for $C_{11}H_{16}NO_6S$ (M^+-CH_3) 290.0697, found 290.0693.

3.1.9. (6*R*,7*S*,8a*R*)-6,7-(Isopropylidene)dioxy-3,5,6,7,8,8a-hexahydro-3-oxo-indolizine (15). To a solution of **14** (300 mg, 0.98 mmol) in 30 ml of THF DBU (0.25 ml, 1.08 mmol) was added at 0°C. The solution was stirred at 0°C for 2 h, and then quenched with 10 ml of water. The mixture was extracted with EtOAc, the combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (ethyl acetate/cyclohexane 3:1) afforded **15** as a colourless oil (189 mg, 92%). R_f: 0.14 (ethyl acetate/cyclohexane 3:1). $[\alpha]_{25}^{D}$=+56.0° (c=0.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.31 (ddd, J=14.3, 12.3, 3.4 Hz, 1H, CH_2), 1.33, 1.48 (2s, 6H, $2CH_3$), 2.32 (ddd, J=14.3, 3.2, 2.2 Hz, 1H, CH_2, 3.28 (dd, J=14.0, 5.7 Hz, 1H, CH_2N), 3.93 (dd, J=14.0, 5.9 Hz, 1H, CH_2N), 4.19 (dm, J=12.3 Hz, 1H, CHN), 4.29 (q, J=5.7 Hz, 1H, CHO), 4.36 (ddd, J=5.4, 3.2, 2.2 Hz, 1H, CHO), 6.09 (dd, J=5.9, 1.7 Hz, 1H, =CH), 7.03 (dd, J=5.9, 1.7 Hz, 1H, =CH). ^{13}C NMR ($CDCl_3$): δ=25.2, 27.5, 32.0, 40.5, 55.3, 70.9, 71.4, 109.0, 128.0, 147.8, 170.4. MS (EI) m/z=209 (M^+), 194 (M^+-CH_3). HRMS calculated for $C_{11}H_{15}NO_3$ 209.1048, found 209.1052.

3.1.10. (1*R*,2*R*,6*R*,7*S*,8a*R*)-1,2-Dihydroxy-6,7-(isopropylidene)dioxy-3-oxo-indolizidine (16). To a solution of **15** (160 mg, 0.77 mmol) in 64 ml of acetone and 8 ml of H_2O *N*-methylmorpholine *N*-oxide (160 mg, 1.21 mmol) and K_2OsO_4*2 H_2O (27 mg, 0.08 mmol) were added at 10°C. The solution was stirred at rt for 2 days. Then 10 ml of sat. Na_2SO_3 were added and the mixture was extracted with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (ethyl acetate/ethanol 10:1) afforded **16** as a colourless oil (130 mg, 70% (ds: 88%)). R_f: 0.39 (ethyl acetate/ethanol 10:1). $[\alpha]_{25}^{D}$=+2.4° (c=0.4, MeOH). ^{1}H NMR (CD_3OD): δ=1.28, 1.39 (2s, 6H, $2CH_3$), 2.00 (m, 1H, CH_2), 2.26 (dd, J=13.3, 10.1 Hz, 1H, CH_2), 2.34 (dd, J=10.1, 3.7 Hz, 1H, CHN), 2.57 (m, 1H, CHO), 3.21 (ddd, J=15.0, 3.7, 1.0 Hz, 1H, CH_2N), 3.55 (d, J=6.7 Hz, 1H, CHO), 4.12 (dd, J=15.0, 1.0 Hz, 1H, CH_2N), 4.18 (dd, J=6.6, 5.6 Hz, 1H, CHO), 4.26 (ddd, J=5.4, 3.7, 1.2 Hz, 1H, CHO). ^{13}C NMR (CD_3OD): δ=25.8, 29.4, 31.6, 36.9, 60.4, 72.6, 74.6, 77.7, 88.9, 109.3, 174.7. MS (FAB, mNBA) m/z=244.1 (M^++H). HRMS calculated for $C_{10}H_{14}NO_5$ (M^+-CH_3) 228.0882, found 228.0880; calculated for $C_{11}H_{15}NO_4$ (M^+-H_2O) 225.1012, found 225.1006.

3.1.11. (1*R*,2*R*,6*R*,7*S*,8a*R*)-1,2,6,7-Bis[(isopropylidene)-dioxy]-3-oxo-indolizidine (17). To a solution of **16** (45 mg, 0.19 mmol) in 25 ml of acetone 2,2-dimethoxypropane (0.23 ml, 1.93 mmol) and pyridinium *p*-toluenesulfonate (4.5 mg, 0.02 mmol) were added at rt. The mixture was stirred for 2 days and the solvent was evaporated in vacuo. Flash chromatography (ethyl acetate/cyclohexane 9:1) afforded **17** as a colourless solid (45 mg, 86%). Mp: 178–180°C (colourless crystals). R_f: 0.41 (ethyl acetate/cyclohexane 9:1). $[\alpha]_{25}^{D}$=+29.8° (c=0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.30, 1.31 (2s, 6H, $2CH_3$), 1.39, 1.47 (2s, 6H, $2CH_3$), 1.44 (ddd, J=14.5, 12.8, 3.7 Hz, 1H, CH_2), 2.32 (ddd, J=14.5, 3.4, 2.2 Hz, 1H, CH_2), 2.82 (dd, J=13.5, 8.1 Hz, 1H, CH_2N), 3.73 (dd, J=12.8, 3.4 Hz, 1H, CHN), 4.03 (td, J=7.6, 4.9 Hz, 1H, CHO), 4.13 (dd, J=13.5, 7.4 Hz, 1H, CH_2N), 4.27 (m, 1H, CHO), 4.32 (d, J=6.2 Hz, 1H, CHO), 4.58 (d, J=6.2 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ=25.4, 26.0, 26.8, 28.2, 31.6, 41.5, 55.5, 69.6, 72.1, 76.9, 77.4, 109.4, 112.9, 168.7. MS (EI) m/z=283 (M^+), 268 (M^+-CH_3), 225 ($M^+-C_3H_6O$). HRMS calculated for $C_{14}H_{21}NO_5$ 283.1420, found 283.1428.

3.1.12. (1*R*,2*R*,6*R*,7*S*,8a*R*)-1,2,6,7-Bis[(isopropylidene)-dioxy]-indolizidine (18). Borane–dimethyl sulfide (0.08 ml, 0.72 mmol) was added to a cool (0°C) solution of **17** (40 mg, 0.14 mmol) in 10 ml of THF. The mixture was stirred at rt overnight. The reaction was quenched by addition of sat. Na_2SO_4 and the solvent was evaporated in vacuo. The residue was dissolved in water and the solution was extracted with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography (ethyl acetate/ethanol 5:1) afforded **18** as a colourless solid (34 mg, 91%). Mp: 109–110°C (colourless crystals). R_f: 0.47 (ethyl acetate/ethanol 5:1). $[\alpha]_{25}^{D}$=+78.5° (c=0.4, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ=1.25, 1.28 (2s, 6H, $2CH_3$), 1.44, 1.45 (2s, 6H, $2CH_3$), 1.59 (ddd, J=14.5, 10.6, 4.2 Hz, 1H, CH_2), 2.15 (t, J=10.3 Hz, 1H, CH_2N), 2.29 (dd, J=9.4, 5.2 Hz, 1H, CH_2N), 2.31 (m, 1H, CH_2N), 2.39 (ddd, J=14.5, 3.0, 2.0 Hz, 1H, CH_2), 2.94 (dd, J=10.8, 6.9 Hz, 1H, CHN), 3.23 (dd, J=9.6, 6.4 Hz, 1H, CH_2N), 4.06 (ddd, J=9.6, 6.9, 4.7 Hz, 1H, CHO), 4.10 (t, J=6.9 Hz, 1H, CHO), 4.21 (td, J=4.4, 2.0 Hz, 1H, CHO), 4.62 (td, J=6.9, 5.4 Hz, 1H, CHO). ^{13}C NMR ($CDCl_3$): δ=25.2, 26.3, 27.2, 28.3, 30.4, 54.9, 59.8, 63.1, 71.8, 72.3, 77.9, 84.6, 108.6, 114.2. MS (EI) m/z=269 (M^+), 254 (M^+-CH_3). HRMS calculated for $C_{14}H_{23}NO_4$ 269.1627, found 269.1620.

3.1.13. (1*R*,2*R*,6*R*,7*S*,8a*R*)-1,2,6,7-Tetrahydroxy-indolizidine (19). To a solution of **18** (34 mg, 0.13 mmol) in 5 ml of methanol *p*-toluenesulfonic acid (51 mg, 0.27 mmol) was added, and the mixture was stirred overnight. The solution was neutralised by addition of K_2CO_3 and concentrated in vacuo. Purification by flash chromatography (CH_2Cl_2/MeOH 4:1) afforded **19** as a colourless oil (23 mg, quant.). R_f: 0.06 (CH_2Cl_2/MeOH 4:1). $[\alpha]_{25}^{D}$=+34.0° (c=0.1, MeOH). ^{1}H NMR (CD_3OD): δ=1.30 (ddd, J=13.8, 11.6, 2.5 Hz, 1H, CH_2), 2.04 (dt, J=13.5, 3.0 Hz, 1H, CH_2), 2.15 (dd, J=10.1, 5.2 Hz, 1H,

CH_2N), 2.26–2.36 (m, 2H, CHN/CH_2N), 2.73 (dd, J=10.3, 4.9 Hz, 1H, CH_2N), 3.29 (dd, J=10.1, 6.9 Hz, 1H, CH_2N), 3.38 (dd, J=8.6, 7.1 Hz, 1H, CHO), 3.57 (ddd, J=10.6, 4.9, 3.0 Hz, 1H, CHO), 3.89 (q, J=3.0 Hz, 1H, CHO), 4.03 (td, J=6.9, 5.2 Hz, 1H, CHO). ^{13}C NMR (CD_3OD): δ=34.7, 54.0, 61.7, 62.1, 68.4, 68.9, 70.0, 75.7. MS (EI) m/z=189 (M^+), 172 (M^+-OH), 154 (M^+-H_2O-OH). HRMS calculated for $C_8H_{15}NO_4$ 189.1001, found 189.1000.

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