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Decarbonylation of α-Tertiary Amino Acids Application to the Synthesis of Polyhydroxylated Indolizidines from D,L-Pipecolic acid

María J. Martín-López, Rosa Rodriguez and Francisco Bermejo*

Departamento de Química Orgánica. Facultad de Químicas. Universidad de Salamanca. Pza de la Merced s.n. 37008. Salamanca, Spain.

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Abstract: The decarbonylation of the bicyclic α -tertiary carboxamido acid 11 led to the enamide 12, easily transformed into the indolizidine alkaloid 8,8a-*trans*-8-hydroxy-indolizidine 14. Likewise, the same process applied to the α -substituted pipecolic acid derivative 5 led to the unsaturated ester 6 which was easily transformed either into δ -coniceine 9 or to 14. The thermal fragmentation of the acyl derivative 22 led to the enamide 24 which has been transformed into (±)-swainsonine 26. © 1998 Elsevier Science Ltd. All rights reserved.

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Introduction

The fragmentation of activated acyl derivatives of α -tertiary amino acids has been first rationalized by Maksimov¹ in terms of a decarbonylation process: the α -amino acid derivatives with tertiary nitrogen atoms undergo clean decarbonylation through conveniently activated carboxy functionalities (acyl chlorides, acyl azides, acyl diazonium salts, mixed anhydrides and carbonates). The reaction is generally catalysed either by acids or bases and iminium salts are involved as intermediates in the process, yielding in part a secondary amine and an aldehyde after decomposition with water.

The α -amino acid chlorides with a tertiary nitrogen atom undergo decarbonylation at the moment of formation in an inert solvent (benzene, chloroform, ether) either without heating or by raising the temperature to 30-40 °C. This well known instability has been widely exploited in the synthetic work related to alkaloids²⁻¹⁰ via decarbonylation/iminium ion cyclization processes; furthermore, the thermal fragmentation of these derivatives has recently revealed a practicable and versatile method for the preparation of indolizidines. Based on the instability of activated acyl derivatives of DL-pipecolic acid we have developed a method to prepare hydroxylated indolizidine alkaloids: the syntheses of δ -coniceine,¹¹ trans-8,8a-8-hydroxy indolizidine¹² and swainsonine¹³ have recently been achieved. The activation of the carboxy functionality in derivatives of D,L-pipecolic acid (A) (Fig. 1) by treatment with diphenylphosphorazidate (DPPA) and triethylamine leads to the formation of the mixed anhydrides (B) which undergo clean decarbonylation to the acyl immonium intermediates (C). An autocatalytic process may be invoked to explain the formation of the

enamides (D) from the acyl immonium intermediates (Fig 1). In this paper we would like to provide full experimental data on the above mentioned synthetic processes.



Results and discussion

We have already reported the thermal fragmentations of 3-oxo-indolizidine-8a carboxylic acid 11, and the α -substituted pipecolic acid 5 promoted by diphenylphosphorazidate (DPPA). These decarbonylation processes have proved to be of general application to the synthesis of indolizidines starting from D,Lpipecolic acid.

Our first preparation of the indolizidine system is outlined in Scheme 1. Fully protected DL-pipecolic acid was alkylated with allyl bromide to give the α -allyl derivative 1 according to a procedure reported by Johnson.¹⁴ In this approach the hydroboration of the terminal olefin followed by treatment with alkaline hydroperoxide led to the primary alcohol 2 which was further oxidized with PDC in dimethyl formamide to yield the carboxylic acid 3. Treatment of 3 with an ethereal diazomethane solution led quantitatively to the methyl ester 4 (70% yield from 1). With the methyl ester 4 in our hands we have been able to access to the bicyclic methyl ester 10 by catalytic hydrogenation followed by treatment with trifluoroacetic acid in dichloromethane solution afforded the carboxylic acids 5 and 11 respectively, in quantitative yields. Treatment of 5 with diphenylphosphorazidate and triethylamine in toluene at 90 °C underwent clean decarbonylation to afford the enamine 6 with 85% yield after flash chromatography of the crude reaction product . Analogously, the bicyclic acid 11 led to the enamide 12 with 75% yield.¹¹⁻¹³

Catalytic hydrogenation of 6 followed by aminolysis of the resulting α -substituted pyrimidine ester in refluxing toluene led to the bicyclic amide 7. Amide reduction of 7 by reaction with borane-methyl sulfide complex at room temperature allowed us to isolate (\pm) - δ -coniceine 9 with 65% overall yield from 6 (Scheme 1).

Careful hydroboration of the double bonds present in 6 and 12 by treatment with $BH_3.SMe_2$ in THF at 0 °C followed by treatment with alkaline hydroperoxide led to the hydroxy derivatives 8 and 13 with 75% and 70% yields, respectively. Catalytic hydrogenation of the Cbz-protected hydroxy ester 8 followed by the methyl ester aminolysis led to the hydroxy bicyclic amide 13 with excellent yields.

Treatment of 13 with the borane-methyl sulfide complex afforded the 8,8a-trans-8-hydroxyindolizidine 14 quantitatively.



a: BH3.SMe2, THF, rt, 3h; **b**: H₂O₂, OH⁻, EtOH, 0^oC; **c**: PDC, DMF, rt, 24h.; **d**: CH₂N₂, ether; **e**: TFA, CH₂Cl₂, rt, 15h; **f**: TEA, DPPA, toluene, 90 ^oC, 1h.; **g**: H₂, 5% Pd(C), MeOH, Et₃N.

Scheme 1

The necessary introduction of the internal double bond in 18 (Scheme 2) to access to polyhydroxylated indolizidines was achieved by application of a two-step sequence. Treatment of bicyclic lactam 10 with LDA at -78 °C followed by addition of phenylselenenyl bromide and subsequent *syn* elimination of the corresponding selenoxide allowed us to isolate the α , β -unsaturated lactam 15 in 70% yield.

The syn dihydroxylation of 15 was successfully achieved by catalytic osmylation with Nmethylmorpholine N-oxide (NMO) in aqueous acetone.¹⁵ However, separation of the two diastereomeric diols 16 and 17 by conventional chromatographic methods was impossible to achieve at this stage. Treatment of the crude mixture of diols 16 and 17 with 2,2-dimethoxypropane and pyridinium p-toluenesulfonate (PPTS) followed by flash chromatographic separation on silica gel allowed us to isolate the two acetonides (18:19= 1: 2) with 85% yield. The *trans* stereochemistry of the major isomer 19 was tentatively assigned based on spectroscopic evidence.¹³

The planarity of the pyrrolinone ring in enamide 15 considerably diminishes the usual preference for attack at the convex face in comparison with the standard indolizidine arrangement. We assume that oxidation takes place preferably at the concave face of the enamide 15 (*anti* approach) because of the 1,2 interaction of the oxidising reagent with the t-butoxycarbonyl moiety at the convex face (*syn* approach). It has been shown that this type of interaction overwhelms the 1,3 steric interaction of the oxidising reagent with the axial H-8 in similar systems. ¹⁶



a: i: LDA, THF,-78°C; ii: PhSeCl; iii: H2O2, AcOH; **b**: OsO4, NMO, acetone, H2O, ¹BuOH; **c**: CH3C(OMe)₂CH3, PPTS, CH₂Cl₂; **d**: CF₃COOH, CH₂Cl₂, 0 °C; **e**: (COCl)₂; **f**: DPPA, Et₃N, toluene, 0°C; **g**: (from 22)1,2-DCE, xylene, reflux, 15h.; **h**: i: BH3. SMe₂; ii: H₂O₂, OH⁻; **i**: i: 6N HCl; ii: Dowex.

Scheme 2

Deprotection of tert-butyl esters 18 and 19 by treatment with trifluoroacetic acid led quantitatively to the carboxy derivatives 20 and 21, respectively. However, DPPA-promoted decarbonylation of both isomers under the above mentioned conditions led to disappointing results. The minor diastereomer 20 led to the enamide 24 with 15% yield and the major acetonide 21 afforded the isocyanate 23, which was isolated in 55% yield after flash chromatography on silica gel. We assume that the low yield obtained in the former case may be rationalized in terms of the steric hindrance encountered in the formation of the acyldiphenyl phosphate intermediate. The isolation of the isocyanate 23 is obviously explained by the competitive Curtius rearrangement.

However, the thermal fragmentation of the acyl chloride 22 allowed us to isolate the enamide 24 with 75% yield after flash chromatography. The enamide was obtained upon warming at the end of the acid chloride formation by treatment of the carboxy acetonide 21 with oxalyl chloride followed by evaporation of the excess of reagent and immersion of the solution of the rather stable acyl chloride 22 in a 1:2 mixture of 1,2-dichloromethane (DCE)/xylene in a preheated bath and stirring overnight under reflux in Argon atmosphere.

Treatment of enamide 24 with excess of the borane-methyl sulfide complex in THF followed by treatment with alkaline hydroperoxide led stereospecifically to the known acetonide 25 (85%), which was hydrolyzed to swainsonine 26 in 96% yield.¹⁷⁻¹⁹

Experimental

All the reactions were carried out using dry solvents under nitrogen or argon atmosphere. All the solvents and chemicals were commercially available and, unless otherwise indicated, were used as received. Tetrahydrofuran, diethyl ether and toluene were dried over sodium benzophenone ketyl. Methylene chloride was dried over CaH₂ under argon and kept over molecular sieves. ¹H-NMR and ¹³C-NMR spectra were

measured in a Bruker WP-200-SY spectrometer operating at 200 MHz and 50.3 MHz respectively; chemical shifts were reported in ppm (δ), and the coupling constants were indicated in Hz. ¹H-NMR spectra were referenced to either the residual proton in the deuterated solvent or TMS. ¹³C-NMR spectra were referenced to the chemical shifts of the deuterated solvent. The IR spectra were determined on a Bomen MB-100 IR-FT spectrophotometer as indicated in each case; the frequencies in the IR spectra were indicated in cm⁻¹. Microanalysis were realized by Dr. Benigno Macías-Sánchez (Inorganic Chemistry Dept. University of Salamanca) in a Perkin-Elmer 240-B analyzer. Unless otherwise indicated, all the preparative chromatographies were performed with silica gel (40-63 mm) using the technique of flash chromatography.²⁰

tert-Butyl N-(benzyloxycarbonyl)-2-(3-hydroxy-propyl)-pipecolate (2): To a solution of 1 (5.0 g, 13.9 mmol) in 75 ml of THF, was dropwise added a solution of borane-methyl sulfide complex (BMS) 2.0 M in THF (3.56 ml, 6.9 mmol) at 0°C and under nitrogen atmosphere. Following the addition of the hydride, the cooling bath was removed and the mixture was stirred for 3h at room temperature. Ethanol (2 ml) was then added followed by 2.5 ml of 3N aqueous sodium hydroxide. The reaction mixture was cooled to 0°C in an icewater bath, and 1 ml of hydrogen peroxide (40%) was added dropwise at such a rate that the mixture warmed to 25-35°C. Following the addition, the cooling was removed and the reaction mixture was heated at reflux for 1h. The reaction was poured into ice water and then extracted with ether, washed with brine and dried over Na₂SO₄. Evaporation of the solvent at reduced pressure afforded a crude wich was fractionated by flash chromatography on silica gel (hexane: AcOEt= 1:1) to give a colorless oil 2 (3.9 g, 75 %). IR v_{max} (film) 3393, 2942, 2876, 1730, 1703, 1456, 1410, 1368, 1339, 1267, 1159, 1130, 1084, 951, 847, 750, 698 cm⁻¹; ¹H NMR (CDCl₃) δ = 1.21 (t, J= 7 Hz, 2H), 1.32 (s, 9H), 1.44-1.77 (m, 5H), 1.52 (m, 2H), 2.1-2.31 (m, 1H), 3.18-3.35 (m, 1H), 3.51 (t, J= 7 Hz, 2H), 3.70-3.90 (m, 1H), 4.91-4.97 (d, J= 12 Hz, 1H), 5.09 (d, J= 1H), 7.23-7.29 (m, 5H) ppm; ¹³C NMR (CDCl₃) δ = 17.81 (t), 22.52 (t), 26.93 (t), 27.56 (q), 31.60 (t), 41.77 (t), 62.49 (t), 63.63 (s), 66.85 (t), 80.73 (s), 127.74-128.11 (d), 136.37 (s), 156.16 (s), 173.0 (s) ppm. Anal. Calcd for C₂₁H₃₁NO₅: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.25; H, 8.19; N, 3.65.

tert-Butyl N-(benzyloxycarbonyl)-2-(carboxyethyl)-pipecolate (3): Pyridinium dichromate (PDC) (4.1g, 10.9 mmol) was added to a solution of 2 (3.9 g, 10.3 mmol) in DMF (5 ml). The reaction mixture was stirred for 24h and then ice water was added. The mixture was acidulated to pH 2 with concentrated H₂SO₄. The water phase was saturated with NaCl and then extracted with ether. The combined organic layers were washed with brine, dried over Na₂SO₄ and evaporated to give 3 as a colorless oil (3.8 g, 95 %). IR (film): v_{max} : 3500-2850, 1745-1720, 1454, 1410, 1340, 1159, 960, 745 cm⁻¹. ¹H NMR (CDCl₃) δ = 1.30 (s, 9H), 1.51 (m, 6H), 1.72 (m, 2H), 2.37 (m, 2H), 3.20 (m, 1H), 3.71 (m, 1H), 4.95 (d, J= 16 Hz, 1H), 5.10 (d, J= 16 Hz, 1H), 7.25 (m, 5H) ppm; ¹³C NMR (CDCl₃) δ = 18.01 (t), 22.9 (t), 27.8 (q), 29.37 (t), 29.77 (t), 32.13 (t), 41.92 (t), 63.40 (s), 67.19 (t), 127.94-128.36 (d), 136.62 (s), 156.32 (s), 172.38 (s), 177.38 (s) ppm. Anal. Calcd for C₂₁H₂₉NO₆: C, 66.47; H, 7.47; N, 3.58. Found: C, 66.39; H, 7.45; N, 3.52.

tert-Butyl N-(benzyloxycarbonyl)-2-(methoxycarbonylethyl)-pipecolate (4): Treatment of 3 (3.8 g, 9.7 mmol) with an ethereal diazomethane solution followed by evaporation of the solvent afforded a crude

which was fractionated by flash chromatography on silica gel (hexane: AcOEt= 6:4) to give a colorless oil 4 (3.9 g, 100%). IR ν_{max} (film) 3451, 2951, 2874, 1728, 1709, 1454, 1408, 1368, 13331, 1263, 1159, 1069, 849, 735, 698 cm⁻¹; ¹H NMR (CDCl₃) δ = 1.38 (s, 9H), 1.57 (m, 6H), 1.78 (t, J= 6.5 Hz, 2H), 2.43 (m, 2H), 3.29 (m, 1H), 3.63 (s, 3H), 3.78 (dt, J₁= 13 Hz, J₂= 6 Hz, 1H), 5.04 (d, J= 12 Hz, 1H), 5.18 (d, J= 12 Hz, 1H), 7.33 (m, 5H) ppm; ¹³C NMR (CDCl₃) δ = 18.15 (t), 23.04 (t), 27.86 (q), 29.17 (t), 30.56 (t), 32.27 (t), 41.99 (t), 51.43 (q), 63.42 (s), 67.15 (t), 81.07 (s), 127.9 (d), 128.03 (d), 128.39 (d), 136.73 (s), 156.28 (s), 172.38 (s), 174.03 (s) ppm. Anal. Calcd for C₂₂H₃₁NO₆: C, 65.16; H, 7.71; N, 3.45. Found: C, 65.13; H, 7.65; N, 3.40.

N-(Benzyloxycarbonyl)-2-(methoxycarbonylethyl)-pipecolic acid (5): Trifluoroacetic acid (2.5 ml, 32.5 mmol) was added to a solution of 4 (3.9g, 9.6 mmol) in dichloromethane (2.5ml) at 0 °C. The mixture was stirred overnight at room temperature. Evaporation of the solvent afforded 5 as a colorless oil (3.4 g, 100%). IR v_{max} (film) 3414, 3021, 2955, 1786, 1713, 1678, 1422, 1352, 1267, 1217, 1171, 758 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ = 1.66-1.90 (m, 6H), 2.44 (m, 2H), 3.18 (m, 1H), 3.65 (s, 3H), 3.94 (m, 1H), 5.10 (m, 2H), 7.33 (m, 5H) ppm; ¹³C NMR (CDCl₃) δ = 18.02 (t), 23.11 (t), 28.70 (t), 29.30 (t), 32.27 (t), 41.54 (t), 51.63 (q), 67.68 (t), 86.81 (s), 128-128.43 (d), 138.04 (s), 156.46 (s), 174.09 (s), 176.58 (s) ppm. Anal. Calcd for C₁₈H₂₃NO₆: C, 61.88; H, 6.75; N, 4.00. Found: C, 61.80; H, 6.69; N, 4.10.

Methyl 3-(1'-benzyloxycarbonyl-1',4',5',6'-tetrahydropyridin-2'-yl)-propanoate (6): To a solution of 5 (3.4 g, 9.7 mmol) in toluene (45 ml) were successively added triethylamine (1.5 ml, 10.6 mmol) and diphenylphosphorazidate (2.27 ml, 10.6 mmol) at room temperature and under Argon atmosphere. The mixture was heated at 90°C for 1h. The reaction was then cooled to room temperature and poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine and dried on Na₂SO₄. Evaporation of the solvent at reduced pressure afforded a crude product which was fractionated by flash chromatography on silica gel (hexane: AcOEt= 8:2) to give a colorless oil 6 (2.5 g, 85%). IR v_{max} (film) 3395, 3055, 2949, 2172, 1738, 1709, 1659, 1441, 1402, 1344, 1265, 1190, 1051, 964, 737, 700 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ = 1.75 (m, 2H), 2.05 (m, 2H), 2.38 (t, J= 7 Hz, 2H), 2.81 (t, J= 7 Hz, 2H), 3.57 (t, J= 6.5 Hz, 2H), 3.63 (s, 3H), 5.05 (m, 1H), 5.15 (s, 2H), 7.35 (m, 5H) ppm; ¹³C NMR (CDCl₃) δ = 22.86 (t), 23.20 (t), 30.67 (t), 32.89 (t), 47.17 (t), 51.33 (q), 67.35 (t), 113.60 (d), 128.1-128.5 (d), 136.40 (s), 138.27 (s), 154.05 (s), 173.40 (s) ppm. Anal. Calcd for C₁₇H₂₁NO₄: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.36; H, 7.01; N, 4.57.

1,5,6,7,8,8a-Hexahydro-indolizin-3(2H)-one (7): A solution of 6 (2.5 g, 8.24 mmol) and triethylamine (1.15 ml, 8.2 mmol) in MeOH (25 ml) was added to a suspension of (10%) Palladium on charcoal (200 mg) previously activated under hydrogen atmosphere. After 4h of stirring under hydrogen atmosphere at room temperature, the catalyst was filtered off, and the solvent was removed in vacuo to give a crude which was disolved in toluene (25 ml) and refluxed for 3h. Evaporation of the solvent at reduce pressure afforded a colorless oil 7 (1 g, 87%). ¹H NMR (200 MHz, CDCl₃) δ = 1.0-1.8 (m, 6H), 2.07 (m, 2H), 2.24 (m, 2H), 2.5 (td, J₁= 14 Hz, J₂= 3.5 Hz, 1H), 3.28 (m, 1H), 4.0 (m, 1H) ppm; ¹³C NMR (CDCl₃) δ = 23.38 (t), 24.15 (t),

24.96 (t), 29.89 (t), 33.24(t), 39.89 (t), 56.96 (d), 173.14 (s) ppm. Anal. Calcd for C₈H₁₃NO: C, 69.03; H, 9.41; N, 10.06. Found: C, 69.07 H, 9.45; N, 10.10.

(2R*,3S*)-N-(Benzyloxycarbonyl)-2-(ethoxycarbonylethyl)-3-hydroxy-piperidine (8): To a solution of 6 (1.5 g, 4.9 mmol) in 10 ml of THF at 0°C and under nitrogen atmosphere was dropwise added a 2.0 M solution of borane-methyl sulfide in THF (2.5 ml, 5 mmol). Following the addition of the hydride, the cooling bath was removed and the mixture was stirred for 2h at room temperature. Then, ethanol (2ml) and 3N NaOH (1.6 ml, 5 mmol) were successively added. The reaction mixture was cooled to 0°C in an ice-water bath, and 0.81 ml of H₂O₂ (40%) were dropwise added at such a rate that the mixture warmed to 25-35°C. The cooling bath was removed and the reaction mixture was heated at reflux for 1h. The reaction was poured into ice water and then extracted with ether, washed with brine and dried over Na₂SO₄. Evaporation of the solvent at reduced pressure afforded a crude which was fractionated by flash chromatography on silica gel (hexane: AcOEt= 2:8) to afford 8 as a colorless oil (1.2 g, 75%). IR v_{max} (film) 3440, 2935, 1732, 1678, 1468, 1432, 1351, 1256, 1176, 1126, 1097, 1045, 992 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 1.17 (t, J= 7 Hz, 3H), 1.41-2.03 (m, 6H), 2.28 (t, J= 7 Hz, 2H), 2.83 (m, 1H), 3.58 (m, 1H), 3.78 (m, 1H), 4.05 (q, J= 7 Hz, 2H), 4.26 (m, 1H), 5.11 (s, 2H), 7.32 (m, 5H) ppm; ¹³C NMR (CDCl₃) δ = 14.13 (c), 19.04 (t), 24.12 (t), 24.(t), 26.09 (t), 31.01 (t), 38.77 (t), 57.55 (d), 60.40 (t), 67.25 (t), 67.73 (d), 127.75, 127.88, 128,43 (d), 136.87 (s), 156.70 (s), 172.67 (s) ppm. Anal. Calcd for C₁₇H₂₃NO₅: C, 63.53; H, 7.21; N, 4.36. Found: C, 63.48 H, 7.15; N, 4.42.

δ-Coniceine (9): A solution of 7 (1 g, 7.2 mmol) in THF (25 ml).was cooled to 0°C and then a 2.0M solution of borane-methyl sulfide complex in THF (10.3ml, 21.6 mmol) was dropwise added under Argon atmosphere. The reaction mixture was allowed to room temperature and stirred overnight. The reaction was quenched with ethanol (25 ml). Evaporation of the solvent at reduced pressure was followed by addition of water and extraction with ethyl acetate. The combined organic layers were washed with brine, dried on Na₂SO₄ to give, after evaporation of the solvent, a crude which was fractionated by flash chromatography on silica gel (hexane:AcOEt = 7:3) to give 9 as a colorless oil (0.67g, 75%). ¹H NMR (200 MHz, CDCl₃) δ= 1.3-1.6 (m, 6H), 1.74-2.05 (m, 4H), 2.55-3.3 (m, 5H) ppm; ¹³C NMR (CDCl₃) δ= 18.67 (t), 19.37 (t), 20.97 (t), 24.16 (t), 27.02 (t), 53.46 (t), 60.41 (t), 65.41 (d) ppm. Anal. Calcd for C₈H₁₅N: C, 76.74; H, 12.07; N, 11.18. Found: C, 76.70; H, 12.10; N, 11.10.

8a-(tert-Butoxycarbonyl)-1,2,5,6,7,8-hexahydro-indolizin-3-one (10): A solution of 4 (1.5 g, 3.7 mmol) and Et₃N (0.5 ml, 3.7 mmol) in MeOH (25 ml) was added to a suspension of Palladium on charcoal (10%) in methanol (20 ml) previously equilibrated on a hydrogen atmosphere. After 1h of stirring at room temperature the catalyst was filtered off and washed with CH₂Cl₂. The solvent was removed in vacuo to give a crude which was disolved in toluene (10 ml) and refluxed for 1h. Evaporation of the solvent at reduce pressure afforded a crude which was flash chromatographed on silica gel (Cl₃CH: MeOH= 95:5) to afford **10** as a colorless oil (0.9 g, 100%). IR v_{max} (film) 2973, 2939, 2860, 1733, 1699, 1464, 1411, 1363, 1313, 1249, 1154, 1082, 845 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 1.10-2.43 (m, 8H), 1.42 (s, 9H), 2.45 (m, 2H), 2.69 (td, J₁= 7 Hz, J₂= 14.6 Hz, 1H), 4.02 (dt, J₁= 2.5 Hz, J₂= 14.6 Hz, 1H) ppm; ¹³C NMR (CDCl₃) δ = 21.49 (t),

23.73 (t), 27.72 (t), 27.72 (t), 31.43 (t), 34.98 (t), 38.43 (t), 65.65 (s), 81.61 (s), 172, 02 (s), 173.79 (s) ppm. Anal. Calcd for C₁₃H₂₁NO₃: C, 65.24; H, 8.84; N, 5.85. Found: C, 65.20 H, 8.90; N, 5.79.

3-Oxo-1,2,5,6,7,8-hexahydro-indolizin-8a-carboxylic acid (11): Trifluoroacetic acid (4 ml, 27.7 mmol) was added to a solution of **10** (0.9 g, 3.7 mmol) in CH₂Cl₂ (4 ml). The mixture was stirred for 11h at room temperature. Evaporation of the solvent afforded **11** (0.7 g, 100%) as a white solid m.p. 148°C (hexane). IR v_{max} (film) (Cl₃CH): 3369, 3019, 2941, 1723, 1684, 1636, 1457, 1420, 1247, 1215, 1160 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 1.24-1.40 (m, 4H), 1.72 (m, 2H), 2.01 (m, 1H), 2.33 (m, 1H), 2.47 (m, 2H), 2.85 (td, J₁= 14.6 Hz, J₂= 7 Hz, 1H), 4.07 (dt, J₁= 14.6 Hz, J₂= 2.4 Hz, 1H), 8.19 (s, 1H) ppm; ¹³C NMR (CDCl₃) δ = 21.60 (t), 23.89 (t), 29.26 (t), 31.71 (t), 35.27 (t), 39.01 (t), 66.90 (s), 175.23 (s), 175.69 (s) ppm. Anal. Calcd for C₉H₁₃NO₃: C, 59.00; H, 7.15; N, 7.65. Found: C, 59.07 H, 7.09; N, 7.59.

1,2,6,7-Tetrahydro-indolizin-3(5H)-one (12): To a suspension of 11 (0.7 g, 3.8 mmol) in toluene (30 ml) were successively added triethylamine (0.62 ml, 3.8 mmol) and diphenylphosphorazidate (DPPA) (0.8 ml, 3.8 mmol) under nitrogen and at room temperature. The mixture was heated at 90°C for 1h. The reaction was then cooled to room temperature and poured into a saturated aqueous solution of sodium bicarbonate and extracted with ethyl acetate. The combined organic layers were washed with brine and dried on Na₂SO₄. Evaporation of the solvent at reduced pressure afforded a crude product which was fractionated by flash chromatography on silica gel (hexane: AcOEt= 4:6) to give 12 as colorless oil (0.4 g, 75%). IR v_{max} (film) 2944, 1689, 1559, 1507, 1457, 1420, 1364 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) &= 1.74 (m, 2H), 2.07 (m, 2H), 2.44 (m, 2H), 2.59 (m, 2H), 3.49 (t, J= 5.6 Hz, 2H), 4.68 (m, 1H) ppm; ¹³C NMR (CDCl₃) &= 20.58 (t), 21.44 (t), 22.66 (t), 29.12 (t), 39.02 (t), 97.38 (d), 138.27 (s), 174.23 (s) ppm. Anal. Calcd for C₈H₁₁NO: C, 70.04; H, 8.08; N, 10.21. Found: C, 69.99; H, 8.01; N, 10.15.

(8R*, 8aS*) 1,2,5,6-Tetrahydro-8-hydroxy-indolizin-3(7,8aH)-one (13): METHOD A: A solution of 8 (1.2 g, 3.7 mmol) and Et₃N (4.5 ml, 3.7 mmol) in MeOH (30 ml) was added to a suspension of Palladium on charcoal (5%) in 20 ml of methanol previously equilibrated under hydrogen atmosphere. After 1h of stirring, at room temperature the catalyst was filtered off and washed with CH₂Cl₂. The solvent was removed in vacuo to give a crude product which was disolved in toluene (25 ml) and refluxed for 2h. Evaporation of the solvent at reduced pressure afforded 13 (0.6g, 100%) as a white solid m.p. 82-84°C (hexane). IR v_{max} (film) 2944, 1689, 1559, 1507, 1457, 1420, 1364 cm⁻¹. ¹H NMR (200 MHz, CDCl₃) δ = 1.41 (m, 2H), 1.85 (m, 2H), 2.04-2.32 (m, 2H), 2.40 (m, 2H), 2.51 (td, J₁= 7 Hz, J₂= 13.2 Hz, 1H), 3.15-3.21 (m, 2H), 3.95 (dd, J₁= 2.6 Hz, J₂= 13.2 Hz, 1H) ppm; ¹³C NMR (CDCl₃) δ = 20.58 (t), 21.44 (t), 22.66 (t), 29.12 (t), 39.02 (t), 62.97 (d), 73.16 (d), 97.38 (s), 174.23 (s) ppm; MS (EI, 70 eV) m/z (rel. intensity): 155 (M⁺, 20), 138 (10), 98 (40), 91 (100); Anal. Calcd for C₈H₁₃NO₂: C, 61.91; H, 8.44; N, 9.02. Found: C, 61.85 H, 8.40; N, 8.90.

METHOD B: A solution of 12 (0.4 g, 2.9mmol) in THF (10 ml) was cooled at 0 °C and a 2M solution of borane-methyl sulfide in THF (1.5 ml, 3mmol) was dropwise added. The reaction mixture was brought to room temperature and stirred overnight. The reaction was quenched bith ethanol (5 ml) and then treated with an aqueous solution of 3N NaOH (1.1 ml, 3.3 mmol). The reaction was cooled at 0 °C and 2.1 ml of H_2O_2

(40%) were dropwise added. The cooling was removed and the reaction mixture was refluxed for 1h. The reaction mixture was brought to room temperature poured into ice water and extracted with ether. The combined organic layers were washed with brine and dried over Na_2SO_4 . The evaporation of the solvent at reduced pressure afforded a crude product which was further fractionated by flash chromatography on silica gel (hexane: AcOEt= 7:3) to give 13 (0.3 g, 70%) which exhibited analogous spectroscopical properties as those described above.

(8R*, 8aS*) 1,2,3,5,6,8a-Hexahydro-8-hydroxy-(7H)-indolizine (14): A solution of 13 (0.3g, 1.9 mmol) in THF (4 ml) was cooled to 0°C and then 3 ml (6 mmol) of a solution 2.0 M BH₃.SMe₂ in THF were dropwise added. The reaction mixture was allowed to room temperature and stirred overnight. The reaction was quenched with ethanol (5 ml). Evaporation of the solvent at reduced pressure was followed by addition of water and extraction with ethyl acetate. The combined organic layers were washed with brine, dried on Na₂SO₄ to give, after evaporation of the solvent, a crude product which was flash chromatographed on silica gel (hexane:AcOEt= 7:3) to give 14 as a colorless oil (0.3 g, 100%). IR ν_{max} : 3350-3150, 2996, 1460, 1414, 1350, 1280, 1263, 1100, 1042, 978 cm⁻¹; ¹H NMR (200 MHz, CDCl₃) δ = 1.08-2.17 9 (m, 8H), 2.78-3.08 (m, 4H), 3.36 (m, 1H), 3.62 (t, J= 5.7 Hz, 1H); ¹³C NMR (CDCl₃) δ = 20.79 (t), 24.37 (t), 28.31 (t), 33.87 (t), 51.77 (t), 54.15 (t), 70.36 (d), 73.4 (d). Anal. Calcd for C₈H₁₅NO: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.10; H, 10.63; N, 9.85.

tert-Butyl-3-oxo-5,6,7,8-tetrahydro-indolizin-8a-carboxylate (15): To a stirred solution of LDA (11 mmol) prepared by reaction of diisopropylamine (1.15 ml, 11.1 mmol) with 11 ml of a solution 1.15 M BuLi in THF (25 ml) was added dropwise at -78 °C a solution of 1 (2.4 g, 10. mmol) in THF (10 ml) under argon atmosphere and the reaction mixture was stirred for 1h at that temperature. A solution of phenylselenylchloride (1.9 g, 10 mmol) in THF (5 ml) was dropwise added to the enolate solution. After 2 h, the reaction mixture was quenched with sat. NH4Cl (15 ml) and extracted with EtOAc. The combined organic layers were washed with saturated brine and dried over Na₂SO₄. Evaporation of the solvent gave the crude selenide as a brown oil which was used for the next step without purification.

To a stirred solution of the above crude product in 100 ml of THF containing 2 ml of AcOH were gradually added 25 ml of H₂O₂ (30%) at 0 °C. Decoloration of the solution was observed and then the reaction mixture was poured into a saturated NaHCO₃ aqueous solution and extracted with EtOAc. The combined organic layers were washed with NaCl aq and dried (Na₂SO₄). Evaporation of the solvent afforded a crude product which was fractionated by flash chromatography on silica gel to give **15** as a colorless oil (1.7g, 70%). IR (film) v_{max} : 1738, 1699, 1452, 1398, 1370, 1248, 1155 cm⁻¹. ¹HNMR: δ (CDCl₃): 1.12-1.29 (m, 1H); 1.45 (s, 9H); 1.68-1.87 (m, 4H); 2.52-2.61 (dt, J₁= 12.8 Hz, J₂= 3.4 Hz, 1H); 2.95-3.10 (dt, J₁= 12.8 Hz, J₂= 3.9 Hz, 1H); 4.19-4.28 (dd, J₁= 13.3 Hz, J₂= 5.0 Hz, 1H); 6.13 (d, J= 5.7 Hz, 1H); 6.99 (d, J= 5.7 Hz, 1H) ppm. ¹³CNMR: δ (CDCl₃): 20.97(t), 24.68(t), 27.76(q), 33.84(t), 37.65(t), 71.46(s), 82.80(s), 127.36(d), 146.86(d), 167.91(s), 168.78(s) ppm. MS (EI, 70 eV) m/z (rel. intensity): 237 (M⁺, 3), 230 (5), 137 (65), 136 (100), 108 (25), 80 (5); Anal. Calcd for C₁₃H₁₉NO₃: C, 65.79; H, 8.07; N, 5.90. Found: C, 65.70; H, 8.00; N, 5.85.

 $(1R^*, 2R^*, 8aR^*)$ tert-Butyl-1,2-(isopropylidendioxy)-3-oxo-5,6,7,8-tetrahydro-indolizin-8acarboxylate (18) and $(1S^*, 2S^*, 8aR^*)$ tert-Butyl-1,2-(isopropylidendioxy)-3-oxo-5,6,7,8-tetrahydroindolizin-8a-carboxylate (19): To a stirred solution of 15 (1.7g, 7.1 mmol) in 10 ml of a mixture of water: acetone= 1:8 were successively added N-methylmorpholine N-oxide (1.7g, 14.4 mmol) and 4 ml of a 0.1M OsO₄ solution in ^tBuOH at 0 °C. The reaction is stirred for 48h at room temperature then, poured into a 10% NaHSO₃ solution an extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na₂SO4. The evaporation of the solvent aforded a crude mixture of diols 16 and 17 (1.7g) which was not possible to elucidate by conventional chromatographic methods.

A catalytic amount of p-toluenesulfonic acid (20 mg) was added to a solution of the diol mixture 16 + 17 (1.7 g, 6.22 mmol) and dimethoxy-propane (3 ml, 24.4 mmol) in 20 ml of CH₂Cl₂. The reaction was stirred overnight at room temperature and then, diluted with CH₂Cl₂ and washed with a saturated aqueous solution of NaHCO₃. The organic layer was washed with brine, separated and dried over Na₂SO₄. The solvent was removed at reduced pressure to afford a crude 18+19 (1.9g, 85%) which was fractionated by flash chromatography on silica gel. By elution with ether: EtOAc = 7/3 18 (0.6g) and 19 (1.2g) were obtained

18: as a white solid m.p. 70-72 °C (hexane); IR (film) v_{max} : 1715, 1456, 1418, 1371, 1290, 1248, 1154, 1101 cm⁻¹. ¹H NMR: δ (CDCl₃): 1.13-1.23 (m, 1H); 1.30 (s, 3H); 1.33 (s, 3H); 1.38 (s, 9H); 1.58-1.88 (m, 4H); 2.18 (m, 1H); 2.68 (dt, J₁= 12.9 Hz, J₂= 3.6 Hz, 1H); 4.08 (dd, J₁= 13.3 Hz, J₂= 4.6 Hz, 1H); 4.43 (d, J= 5.8 Hz, 1H); 4.63 (d, J= 5.8 Hz, 1H) ppm. ¹³C NMR: δ (CDCl₃): 20.69 (t); 23.34 (t); 26.20 (t); 26.05 (q); 26.84 (q); 27.56 (q); 38.47 (t); 68.28 (s); 76.33 (d); 77.22 (d); 82.87 (s); 112.61 (s); 170.00 (s); 170.20 (s) ppm. MS (EI, 70 eV) m/z (rel. intensity): 311 (M⁺, 2), 240 (5), 210 (100); 85 (5), 57 (6), 138 (10), 182 (33) ; Anal. Calcd for C₁₆H₂₅NO₅: C, 61.71; H, 8.09; N, 4.50. Found: C, 61.65; H, 8.15; N, 4.59.

19: as a white solid m.p. 120-122 °C (hexane); IR (film) v_{max} : 1738, 1703, 1452, 1371, 1314, 1254, 1215, 1159, 1113 cm⁻¹. ¹H NMR : δ (CDCl₃): 1.13 (dt, J₁= 13.1 Hz, J₂= 3.7 Hz, 1H); 1.36 (s, 3H); 1.39 (s, 3H); 1.51 (s, 9H); 1.53-1.66 (m, 4H); 1.78-1.85 (dt, J₁= 13.6 Hz, J₂= 3.6 Hz, 1H); 2.50 (dt, J₁= 13.2 Hz, J₂= 3.7Hz, 1H); 3.03 (dt, J₁= 13.2 Hz, J₂= 3.5 Hz, 1H); 4.15 (dd, J₁= 13.6 Hz, J₂= 5.8 Hz, 1H); 4.47 (d, J= 6.7Hz, 1H); 4.67 (d, J= 6.7 Hz, 1H) ppm. ¹³C NMR: δ (CDCl₃): 21.45 (t); 24.02 (t); 25.72 (q); 26.30 (q); 27.82 (q); 33.60 (t); 39.07 (t); 69.54 (s); 77.18 (d); 78.97 (d); 82.29 (s); 113.11 (s); 167.59 (s); 169.20 (s) ppm. MS (EI, 70 eV) m/z (rel. intensity): 311 (M⁺, 1), 296 (1), 270 (10), 253 (8), 240 (4), 210 (100), 182 (15), 140 (5); Anal. Calcd for C₁₆H₂₅NO₅: C, 61.71; H, 8.09; N, 4.50. Found: C, 61.68; H, 8.12; N, 4.57.

(1R*, 2R*, 8aR*) 1,2-(Isopropylidendioxy)-3-oxo-5,6,7,8-tetrahydro-indolizin-8a-carboxylic acid (20): To a solution of 18 (0.6g, 1.9 mmol) in 1.5 ml of CH₂Cl₂ was added freshly distilled trifluoroacetic acid (1.5 ml). The solution was stirred overnight at room temperature. Removal of solvent at reduced pressure afforded the acid 20 as a colorless oil (0.5g, 100%). IR (film) v_{max} : 3600-2845, 1734, 1684, 1452, 1215 cm⁻¹. ¹H NMR : δ (CDCl₃): 1.23 (s, 3H), 1.24 (s, 3H); 1.14-1.80 (m, 5H); 2.14 (dt, J₁= 16 Hz, J₂= 3 Hz, 1H); 2.65 (dt, J₁= 16 Hz, J₂= 6 Hz, 1H); 3.85 (dd, J₁= 16 Hz, J₂= 7 Hz, 1H); 4.47 (d, J= 5.7 Hz, 1H); 4.58 (d, J= 5.7Hz, 1H) ppm. ¹³C NMR: δ (CD₃OD): 22.62 (t); 25.10 (t); 26.00 (q); 26.73 (q); 34.29 (t); 40.55 (t); 71.30 (s); 78.55 (d); 80.15 (d); 114.50 (s); 171.69 (s); 171. 70 (s) ppm. Anal. Calcd for C₁₂H₁₇NO₅: C, 56.46; H, 6.71; N, 5.48. Found: C, 56.40; H, 6.65; N, 5.50.

(15*, 25*, 8aR*) 1,2-(Isopropylidendioxy)-30xo-5,6,7,8-tetrahydro-indolizin-8a-carboxylic acid (21): Analogously, the same treatment of acetonide 19 (1.2 g) allowed us to isolate the acid 21 as a colorless oil (1g, 100%). IR (film): v_{max} : 3600-2850, 1734, 1684, 1452, 1215 cm⁻¹. ¹H NMR: &CDCl₃): 1.35 (s, 3H); 1.37 (s, 3H); 1.23-1.96 (m, 5H); 2.61 (dd, J₁= 16 Hz, J₂= 8 Hz, 1H); 3.10 (dt, J₁= 16 Hz, J₂= 7 Hz, 1H); 4.20 (dd, J₁= 14.6 Hz, J₂= 7 Hz, 1H); 4.55 (d, J= 6.5 Hz, 1H); 4.81 (d, J= 6.5 Hz, 1H); 8.1 (s broad, 1H) ppm. ¹³C NMR: &(CD₃OD): 21.99 (t); 24.69 (t); 26.47 (q); 27.46 (q); 27.70 (t); 40.04 (t); 70. 10 (s); 78.83 (d); 78.98 (d); 114.16 (s); 173.21 (s); 173.91 (s) ppm. Anal. Calcd for C₁₂H₁₇NO₅: C, 56.46; H, 6.71; N, 5.48. Found: C, 56.38; H, 6.64; N, 5.53.

Acyl chloride (22): To a solution of 21 (0.5 g, 1.95 mmol) in 1,2-dichloroethane (DCE) (20 ml) at -10 °C was added dropwise oxalyl chloride (0.24 ml, 2.75 mmol) . After the addition freshly distilled DMF (0.5 ml) was added and the mixture was stirred at room temperature for 1 h. Toluene (15 ml) was added, and the solution was immersed in a preheated bath (60 °C) and stirred overnight under Ar atmosphere. The mixture was allowed to cool and then poured into saturated NaHCO3 and the aqueous phase was extracted with CHCl3. The combined organic phase was washed with brine, dried over Na₂SO4, and evaporated to give 22 as a white solid (0.52 g, 97%) m.p. 118-120 °C (hexane). IR (film) v_{max} : 1780, 1705, 1422, 1379; 1271, 1213, 1155, 1092, 907cm⁻¹. ¹H NMR: δ (CDCl₃): 1.36 (s, 3H); 1.39 (s, 3H); 1.44-1.91 (m, 4H); 2.74-3.06 (m, 3H); 4.16-4.23 (m, 1H); 4.59 (d, J= 6.5 Hz, 1H); 4.73 (d, J= 6.5 Hz, 1H) ppm. ¹³C NMR: δ (CDCl₃): 21.17 (t); 23.70 (t); 25.59 (q); 26.05 (q); 33.63 (t); 39.34 (t); 56.88 (s); 77.00 (d); 78.59 (d); 114.52 (s); 169.24(s); 174.40(s) ppm. Anal. Calcd for C₁₂H₁₆NO₄Cl: C, 52.65; H, 5.89; N, 5.11; Cl, 12.95. Found: C, 52.59; H, 5.95; N, 5.03; Cl, 12.87.

Isocyanate (23): To a solution of 21 (0.15 g, 0.6 mmol) in toluene (5 ml) were successively added at room temperature and under argon atmosphere, triethylamine (0.1 ml, 0.7 mml) and diphenylphosphorazidate (DPPA) (0.12 ml, 0.6 mmol) The reaction mixture was heated up to 90 °C and stirred at this temperature for 2h then is allowed to go to room temperature, poured into saturated NaHCO₃ and extracted with chloroform. The combined organic layers were washed with brine and dried over Na₂SO₄. Evaporation of the solvent at reduced pressure afforded a crude solid which was fractionated by flash chromatography on silica gel (hexane: AcOEt= 3:7) to afford 23 as a white solid (0.08g, 55%) m.p. 70-72 °C (hexane). IR (film) v_{max} : 2249, 1705, 1420, 1377, 1215, 1103 cm⁻¹. ¹H NMR: &CDCl₃): 1.20-1.40 (m, 1H); 1.43 (s, 3H); 1.52 (s, 3H); 1.62-1.88 (m, 4H); 1.90-2.10 (m, 1H); 2.89-3.04 (dt, J₁=13.3 Hz, J₂= 3.6 Hz, 1H); 4.07-3.98 (dd, J₁= 13.3 Hz, J₂= 5.0 Hz, 1H); 4.48 (d, J= 6.6 Hz, 1H); 4.70 (d, J= 6.6 Hz, 1H).¹³C NMR: &(CDCl₃): 20.19 (t); 24.06 (t); 25.61 (q); 26.24 (q); 37.60 (t); 38.28 (t); 53.32 (s); 77.00 (d); 79.18 (d); 114.99 (s); 126.92 (s); 166.86 (s) ppm. Anal. Calcd for C₁₂H₁₆N₂O₄: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.21; H, 6.47; N, 11.05.

Enamide (24):

<u>Method A</u>: A solution of **22** (0.52 g, 1.9 mmol) in xylene was refluxed for a period of 2 days. After cooling the mixture the solvent was removed under vacuo. Purification of the crude by column chromatography (hexanes: EtOAc= 3:7) afforded **24** (0.30g, 75%) as a white solid m.p. 68-70 °C (hexane); IR (film) v_{max} : 1732, 1688, 1410, 1377, 1317, 1252, 1209, 1152, 1096 cm⁻¹. ¹H NMR: δ (CDCl₃): 1.38 (s, 3H); 1.40 (s, 3H); 1.68-1.85 (m, 2H); 2.13-2.21 (m, 2H); 3.30-3.44 (m, 1H); 3.64-3.76 (m, 1H); 4.64 (d, J= 6.4 Hz, 1H); 4.93 (d, J= 6.4 Hz, 1H); 5.22 (t, J= 4 Hz, 1H) ppm. ¹³C NMR: δ (CDCl₃): 19.52 (t); 20.96 (t); 24.82 (q); 26.07 (q); 38.42 (t); 72.96 (d); 75.69 (d); 103.38 (d); 112.22 (s); 168.78 (s) ppm. MS (EI) (m/z, %): 210 (M⁺+1, 16), 209 (10), 152 (100), 99 (76), 85 (53), 71 (30). Anal. Calcd for C₁₁H₁₅NO₃: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.20; H, 7.15; N, 6.60.

<u>METHOD B:</u> To a stirred solution of 20 (0.25 g, 1 mmol) in freshly destilled toluene (10 ml) were added freshly distilled Et₃N (0.17 ml, 1.2 mmol) and diphenylphosphorazidate (DPPA) (0.24 ml, 1.1 mmol). The solution was immersed in a preheated bath (90 °C) and stirred for 3.5 h under Ar atmosphere. The mixture was allowed to cool and then poured into saturated NaHCO₃ and the aqueous phase were extracted with CHCl₃. The combined organic phases were washed with brine, dried over Na₂SO₄, and evaporated to give 24 (0.030g, 15 %) which exhibited identical spectroscopic characeristics to those described above.

(1S*,2R*,8R*,8aR*)-8-Hydroxy-1,2-(isopropylidenedioxy)-indolizidine (25): To a cold (0 °C) solution of enamide 24 (115 mg, 0.55 mmol) in anhydrous THF (1 ml) was added 0.9 ml of a 2M BH₃.SMe₂ solution in THF at room temperature under Argon atmosphere. The reaction was stirred for 5 h at room temperature then, ethanol (2.5 ml), 3N NaOH (1 ml) and of 30% H₂O₂ (1ml) were successively added. The reaction mixture was refluxed for 2 h, the ethanol was removed at reduced pressure and the residue dissolved in 2 ml of H₂O. The aqueous solution was saturated with solid NaCl and then extracted with dichloromethane. The combined organic extracts were dried over Na₂SO4 and concentrated in vacuo to give 25 as a white solid (0.12g, 85%) m.p. 90-92 °C (hexane); IR (film); v_{max} : 3451, 1466, 1381, 1215, 1148, 1123, 1071, 1028, cm-1; ¹H NMR: δ (CDCl₃): 1.17-1.27 (m, 1H); 1.33 (s, 3H); 1.49 (s, 3H); 1.54-1.70 (m, 4H); 1.78-1.91 (m, 1H); 2.00-2.03 (m, 1H); 2.10 (dd, J₁= 4 Hz, J₂= 11 Hz, 1H); 2.98 (dt, J₁= 11Hz, J₂= 3 Hz, 1H); 3.14 (d, J= 11 Hz, 1H); 3.76-3.86 (m, 1H); 4.60 (dd, J₁= 6Hz, J₂= 4 Hz, 1H); 4.69 (dd, J₁= 6 Hz, J₂= 4 Hz, 1H) ppm. ¹³C NMR: δ (CDCl₃): 23.93 (t); 24.86 (q); 25.86 (q); 32.90 (t); 51.41 (t); 59.94 (t); 66.68 (d); 73.62 (d); 78.10 (d); 79.15 (d); 111.18 (s) ppm. Anal. Calcd for C₁₅H₁₉NO₃: C, 68.94; ; H, 7.32; N, 5.36. Found: C, 68.87; H, 7.27; N, 5.40.

(1S*,2R*,8R*,8aR*)-1,2,8-Trihydroxyindolizidine: (\pm)-Swainsonine (26): Prepared according to a published procedure.¹⁷ A solution of 25 (0.12g, 0.5 mmol) in THF (1.5 ml) was treated with 6N HCl (0.1 ml) at room temperature for 15h. The solution was then concentrated and the residue was applied to an ion exchange column (Dowex 1 x 8 200 OH⁻, 3g) and eluted with water. The fractions with 26 were identified by TLC (iodine stain). These fractions were concentrated to give 26 (0.1g, 96%) IR: v_{max}: 3366, 2944, 2884, 2804, 2727, 1660, 1378, cm⁻¹. ¹H NMR δ (D₂O): 4.39 (ddd, J₁= 2.8 Hz, J₂= 5.9 Hz, J₃=8.0 Hz, 1H); 4.29

(dd, J_1 = 3.5, J_2 =5.8 Hz, 1H); 3.84 (dt, J_1 = 4.6 Hz, J_2 =10.3 Hz, 1H); 3.0 (m, 1H); 2.97 (dd, J_1 = 2.8 Hz, J_2 =11.3 Hz, 1H); 2.70 (dd, J_1 = 8.1 Hz, J_2 = 11.3 Hz, 1H); 2.04-2.15 (m, 3H); 1.76 (m, 1H); 1.55 (qt, J_1 = 4.1 Hz, J_2 = 13.2 Hz, 1H); 1.28 (qd, J_1 = 4.5, J_2 =12.3 Hz, 1H); ¹³C NMR: δ (D₂O): 72.6; 69.4; 68.9; 66.0; 60.3; 51.6; 32.2; 22.9; ppm. Anal calcd for C₈H₁₅NO₃: C: 55.47%, H: 8.73%, N: 8.09%; Found C: 55.41%, H: 8.78%, N: 8.13%.

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