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

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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**.

Keywords: alkaloids; amino acids and derivatives; decarbonylation; indolizidines

Introduction

The fragmentation of activated acyl derivatives of α-tertiary amino acids has been first rationalized by Maksimov[1] 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 alkaloids[2-10] 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 indolizidine[12] and swainsonine[13] 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

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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.

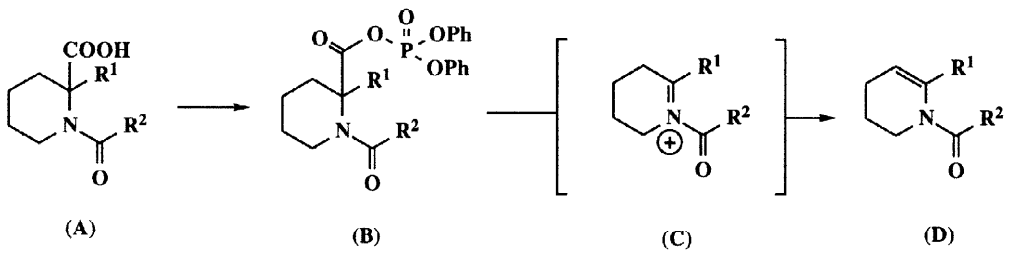


Fig.1

Results and discussion

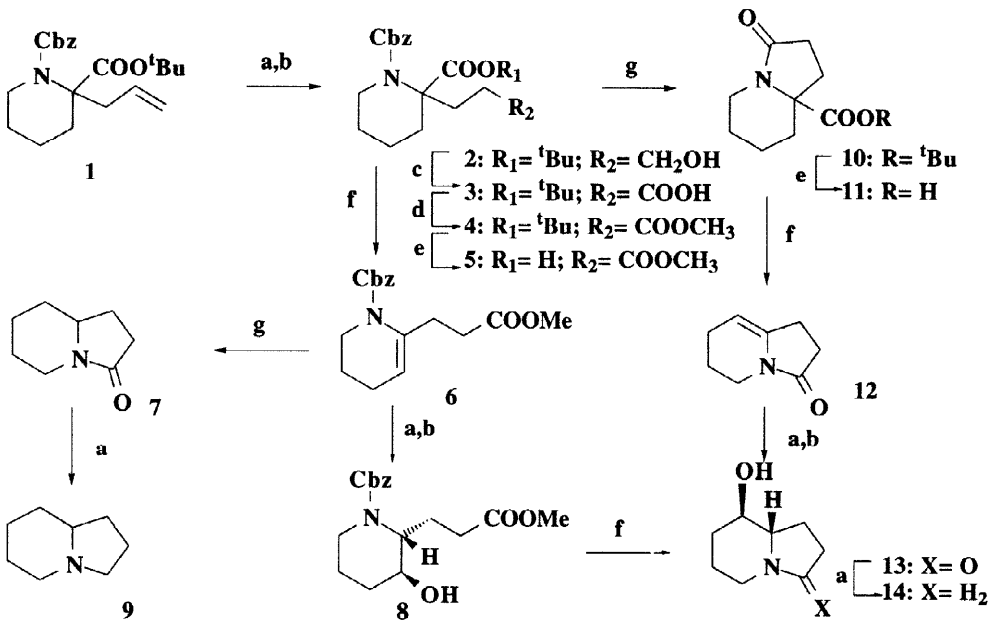
We have already reported the thermal fragmentations of 3-oxo-indolizidine-8a carboxylic acid **11**, and the α-substituted pipecolic acid **5** promoted by diphenylphosphorazidate (DPPA). These decarbonylation processes have proved to be of general application to the synthesis of indolizidines starting from D,L-pipecolic 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 internal aminolysis of the ester functionality with excellent yield. Removal of the tert-butyl esters **4** and **10** 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 (±)-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-hydroxy-indolizidine **14** quantitatively.



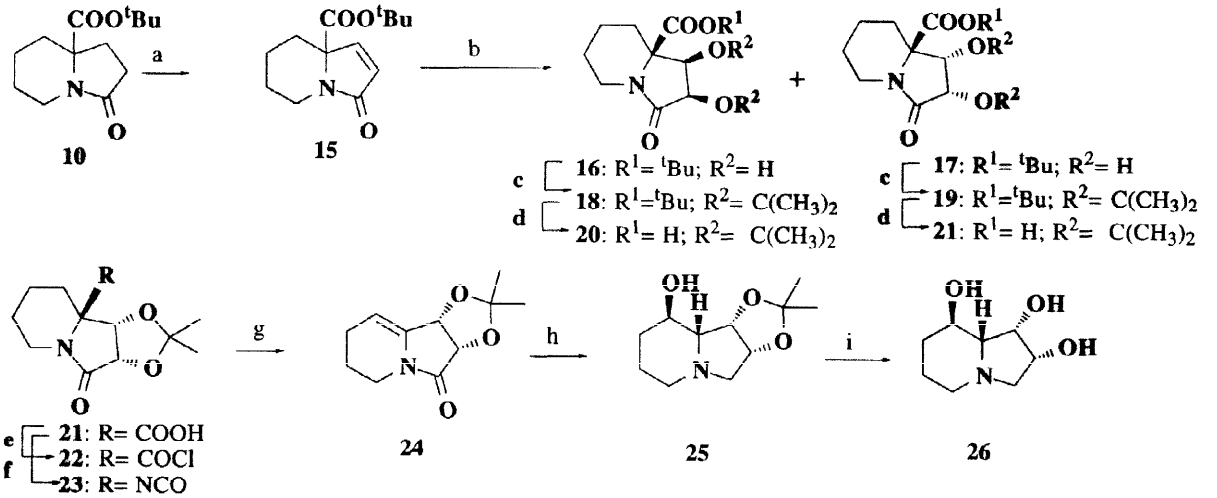
a: $BH_3.SMe_2$, THF, rt, 3h; **b:** H_2O_2, OH^-, EtOH, 0°C; **c:** PDC, DMF, rt, 24h.; **d:** CH_2N_2, ether; **e:** TFA, CH_2Cl_2, rt, 15h; **f:** TEA, DPPA, toluene, 90 °C, 1h.; **g:** H_2, 5% Pd(C), MeOH, Et_3N.

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 N-methylmorpholine 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: H_2O_2, AcOH; **b**: OsO_4, NMO, acetone, H_2O, ^{t}BuOH; **c**: $CH_3C(OMe)_2CH_3$, PPTS, CH_2Cl_2; **d**: CF_3COOH, CH_2Cl_2, 0 °C; **e**: $(COCl)_2$; **f**: DPPA, Et_3N, toluene, 0°C; **g**: (from **22**)1,2-DCE, xylene, reflux, 15h.; **h**: i: BH_3. SMe_2; ii: H_2O_2, 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 CaH_2 under argon and kept over molecular sieves. ^{1}H-NMR and ^{13}C-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. ^{1}H-NMR spectra were referenced to either the residual proton in the deuterated solvent or TMS. ^{13}C-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 ice-water 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 Na_2SO_4. 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 ν_{max} (film) 3393, 2942, 2876, 1730, 1703, 1456, 1410, 1368, 1339, 1267, 1159, 1130, 1084, 951, 847, 750, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$) 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= 12 Hz, 1H), 7.23-7.29 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) 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 $C_{21}H_{31}NO_5$: 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 H_2SO_4. The water phase was saturated with NaCl and then extracted with ether. The combined organic layers were washed with brine, dried over Na_2SO_4 and evaporated to give **3** as a colorless oil (3.8 g, 95 %). IR (film): ν_{max}: 3500-2850, 1745-1720, 1454, 1410, 1340, 1159, 960, 745 cm^{-1}. ^{1}H NMR ($CDCl_3$) 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; ^{13}C NMR ($CDCl_3$) 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 $C_{21}H_{29}NO_6$: 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 ($CDCl_3$) 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, J_1= 13 Hz, J_2= 6 Hz, 1H), 5.04 (d, J= 12 Hz, 1H), 5.18 (d, J= 12 Hz, 1H), 7.33 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) 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 $C_{22}H_{31}NO_6$: 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 ν_{max} (film) 3414, 3021, 2955, 1786, 1713, 1678, 1422, 1352, 1267, 1217, 1171, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 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; ^{13}C NMR ($CDCl_3$) 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 $C_{18}H_{23}NO_6$: 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 Na_2SO_4. 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 ν_{max} (film) 3395, 3055, 2949, 2172, 1738, 1709, 1659, 1441, 1402, 1344, 1265, 1190, 1051, 964, 737, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) 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; ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{21}NO_4$: 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, $CDCl_3$) δ= 1.0-1.8 (m, 6H), 2.07 (m, 2H), 2.24 (m, 2H), 2.5 (td, J_1= 14 Hz, J_2= 3.5 Hz, 1H), 3.28 (m, 1H), 4.0 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) 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 $C_8H_{13}NO$: 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 H_2O_2 (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 Na_2SO_4. 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 ν_{max} (film) 3440, 2935, 1732, 1678, 1468, 1432, 1351, 1256, 1176, 1126, 1097, 1045, 992 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 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; ^{13}C NMR ($CDCl_3$) 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 $C_{17}H_{23}NO_5$: 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 Na_2SO_4 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, $CDCl_3$) δ= 1.3-1.6 (m, 6H), 1.74-2.05 (m, 4H), 2.55-3.3 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) 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 $C_8H_{15}N$: 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 Et_3N (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 CH_2Cl_2. 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 (Cl_3CH: MeOH= 95:5) to afford **10** as a colorless oil (0.9 g, 100%). IR ν_{max} (film) 2973, 2939, 2860, 1733, 1699, 1464, 1411, 1363, 1313, 1249, 1154, 1082, 845 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ= 1.10-2.43 (m, 8H), 1.42 (s, 9H), 2.45 (m, 2H), 2.69 (td, J_1= 7 Hz, J_2= 14.6 Hz, 1H), 4.02 (dt, J_1= 2.5 Hz, J_2= 14.6 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) 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 $C_{13}H_{21}NO_3$: 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 CH_2Cl_2 (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 ν_{max} (film) (Cl_3CH): 3369, 3019, 2941, 1723, 1684, 1636, 1457, 1420, 1247, 1215, 1160 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) 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, J_1= 14.6 Hz, J_2= 7 Hz, 1H), 4.07 (dt, J_1= 14.6 Hz, J_2= 2.4 Hz, 1H), 8.19 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) 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 $C_9H_{13}NO_3$: 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 Na_2SO_4. 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 ν_{max} (film) 2944, 1689, 1559, 1507, 1457, 1420, 1364 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ= 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; ^{13}C NMR ($CDCl_3$) δ= 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 $C_8H_{11}NO$: 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 Et_3N (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 CH_2Cl_2. 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 ν_{max} (film) 2944, 1689, 1559, 1507, 1457, 1420, 1364 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ= 1.41 (m, 2H), 1.85 (m, 2H), 2.04-2.32 (m, 2H), 2.40 (m, 2H), 2.51 (td, J_1= 7 Hz, J_2= 13.2 Hz, 1H), 3.15-3.21 (m, 2H), 3.95 (dd, J_1= 2.6 Hz, J_2= 13.2 Hz, 1H) ppm; ^{13}C NMR ($CDCl_3$) 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 $C_8H_{13}NO_2$: 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 $BH_3.SMe_2$ 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 Na_2SO_4 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, $CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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 $C_8H_{15}NO$: 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. NH_4Cl (15 ml) and extracted with EtOAc. The combined organic layers were washed with saturated brine and dried over Na_2SO_4. 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 H_2O_2 (30%) at 0 °C. Decoloration of the solution was observed and then the reaction mixture was poured into a saturated $NaHCO_3$ aqueous solution and extracted with EtOAc. The combined organic layers were washed with NaCl aq and dried (Na_2SO_4). 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) ν_{max} : 1738, 1699, 1452, 1398, 1370, 1248, 1155 cm^{-1}. ^{1}HNMR: δ($CDCl_3$): 1.12-1.29 (m, 1H); 1.45 (s, 9H); 1.68-1.87 (m, 4H); 2.52-2.61 (dt, J_1= 12.8 Hz, J_2= 3.4 Hz, 1H); 2.95-3.10 (dt, J_1= 12.8 Hz, J_2= 3.9 Hz, 1H); 4.19-4.28 (dd, J_1= 13.3 Hz, J_2= 5.0 Hz, 1H); 6.13 (d, J= 5.7 Hz, 1H); 6.99 (d, J= 5.7 Hz, 1H) ppm. ^{13}CNMR: δ($CDCl_3$): 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 $C_{13}H_{19}NO_3$: 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-8a-carboxylate (18) and (1S*,2S*,8aR*) *tert*-Butyl-1,2-(isopropylidendioxy)-3-oxo-5,6,7,8-tetrahydro-indolizin-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 OsO_4 solution in ^tBuOH at 0 °C. The reaction is stirred for 48h at room temperature then, poured into a 10% $NaHSO_3$ solution an extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO4. 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 CH_2Cl_2. The reaction was stirred overnight at room temperature and then, diluted with CH_2Cl_2 and washed with a saturated aqueous solution of $NaHCO_3$. The organic layer was washed with brine, separated and dried over Na_2SO_4. 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) ν_{max} : 1715, 1456, 1418, 1371, 1290, 1248, 1154, 1101 cm^{-1}. ^1H NMR: $\delta(CDCl_3)$: 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, J_1= 12.9 Hz, J_2= 3.6 Hz, 1H); 4.08 (dd, J_1= 13.3 Hz, J_2= 4.6 Hz, 1H); 4.43 (d, J= 5.8 Hz, 1H); 4.63 (d, J= 5.8 Hz, 1H) ppm. ^{13}C NMR: $\delta(CDCl_3)$: 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 $C_{16}H_{25}NO_5$: 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) ν_{max}: 1738, 1703, 1452, 1371, 1314, 1254, 1215, 1159, 1113 cm^{-1}. ^1H NMR : $\delta(CDCl_3)$: 1.13 (dt, J_1= 13.1 Hz, J_2= 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, J_1= 13.6 Hz, J_2= 3.6 Hz, 1H); 2.50 (dt, J_1= 13.2 Hz, J_2= 3.7Hz, 1H); 3.03 (dt, J_1= 13.2 Hz, J_2= 3.5 Hz, 1H); 4.15 (dd, J_1= 13.6 Hz, J_2= 5.8 Hz, 1H); 4.47 (d, J= 6.7Hz, 1H); 4.67 (d, J= 6.7 Hz, 1H) ppm. ^{13}C NMR: $\delta(CDCl_3)$: 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 $C_{16}H_{25}NO_5$: 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 CH_2Cl_2 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) ν_{max}: 3600-2845, 1734, 1684, 1452, 1215 cm^{-1}. ^1H NMR : $\delta(CDCl_3)$: 1.23 (s, 3H), 1.24 (s, 3H); 1.14-1.80 (m, 5H); 2.14 (dt, J_1= 16 Hz, J_2= 3 Hz, 1H); 2.65 (dt, J_1= 16 Hz, J_2= 6 Hz, 1H); 3.85 (dd, J_1= 16 Hz, J_2= 7 Hz, 1H); 4.47 (d, J= 5.7 Hz, 1H); 4.58 (d, J= 5.7Hz, 1H) ppm. ^{13}C NMR: $\delta(CD_3OD)$: 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 $C_{12}H_{17}NO_5$: C, 56.46; H, 6.71; N, 5.48. Found: C, 56.40; H, 6.65; N, 5.50.

(1S*, 2S*, 8aR*) 1,2-(Isopropylidendioxy)-3oxo-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): ν_{max}: 3600-2850, 1734, 1684, 1452, 1215 cm^{-1}. ^1H NMR: $\delta(CDCl_3)$: 1.35 (s, 3H); 1.37 (s, 3H); 1.23-1.96 (m, 5H); 2.61 (dd, J_1= 16 Hz, J_2= 8 Hz, 1H); 3.10 (dt, J_1= 16 Hz, J_2= 7 Hz, 1H); 4.20 (dd, J_1= 14.6 Hz, J_2= 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. ^{13}C NMR: $\delta(CD_3OD)$: 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 $C_{12}H_{17}NO_5$: 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 $NaHCO_3$ and the aqueous phase was extracted with $CHCl_3$. The combined organic phase was washed with brine, dried over Na_2SO_4, and evaporated to give **22** as a white solid (0.52 g, 97%) m.p. 118-120 °C (hexane). IR (film) ν_{max} : 1780, 1705, 1422, 1379; 1271, 1213, 1155, 1092, 907cm^{-1}. ^1H NMR: $\delta(CDCl_3)$: 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. ^{13}C NMR: $\delta(CDCl_3)$: 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 $C_{12}H_{16}NO_4Cl$: 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 $NaHCO_3$ and extracted with chloroform. The combined organic layers were washed with brine and dried over Na_2SO_4. 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) ν_{max} : 2249, 1705, 1420, 1377, 1215, 1103 cm^{-1}. ^1H NMR: $\delta(CDCl_3)$: 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, J_1=13.3 Hz, J_2= 3.6 Hz, 1H); 4.07-3.98 (dd, J_1= 13.3 Hz, J_2= 5.0 Hz, 1H); 4.48 (d, J= 6.6 Hz, 1H); 4.70 (d, J= 6.6 Hz, 1H).^{13}C NMR: $\delta(CDCl_3)$: 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 $C_{12}H_{16}N_2O_4$: C, 57.13; H, 6.39; N, 11.10. Found: C, 57.21; H, 6.47; N, 11.05.

Enamide (24):

Method A: 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) ν_{max}: 1732, 1688, 1410, 1377, 1317, 1252, 1209, 1152, 1096 cm^{-1}. ^1H NMR: $\delta(CDCl_3)$: 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. ^{13}C NMR: $\delta(CDCl_3)$: 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 $C_{11}H_{15}NO_3$: C, 63.14; H, 7.22; N, 6.69. Found: C, 63.20; H, 7.15; N, 6.60.

METHOD B: To a stirred solution of **20** (0.25 g, 1 mmol) in freshly destilled toluene (10 ml) were added freshly distilled Et_3N (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 $NaHCO_3$ and the aqueous phase were extracted with $CHCl_3$. The combined organic phases were washed with brine, dried over Na_2SO_4, 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 $BH_3.SMe_2$ 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% H_2O_2 (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 H_2O. The aqueous solution was saturated with solid NaCl and then extracted with dichloromethane. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo to give **25** as a white solid (0.12g, 85%) m.p. 90-92 °C (hexane); IR (film); ν_{max}: 3451, 1466, 1381, 1215, 1148, 1123, 1071, 1028, cm-1; ^1H NMR: $\delta(CDCl_3)$: 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, J_1= 4 Hz, J_2= 11 Hz, 1H); 2.98 (dt, J_1= 11Hz, J_2= 3 Hz, 1H); 3.14 (d, J= 11 Hz, 1H); 3.76-3.86 (m, 1H); 4.60 (dd, J_1= 6Hz, J_2= 4 Hz, 1H); 4.69 (dd, J_1= 6 Hz, J_2= 4 Hz, 1H) ppm. ^{13}C NMR: $\delta(CDCl_3)$: 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 $C_{15}H_{19}NO_3$: 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: (±)-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: ν_{max}: 3366, 2944, 2884, 2804, 2727, 1660, 1378, cm^{-1}. ^1H NMR $\delta(D_2O)$: 4.39 (ddd, J_1= 2.8 Hz, J_2= 5.9 Hz, J_3=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); ^{13}C NMR: δ (D_2O): 72.6; 69.4; 68.9; 66.0; 60.3; 51.6; 32.2; 22.9; ppm. Anal calcd for $C_8H_{15}NO_3$: C: 55.47%, H: 8.73%, N: 8.09%; Found C: 55.41%, H: 8.78%, N: 8.13%.

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