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Stereoselective Approach to Hydroxyindolizidines: Protection/Deprotection of the Nitrone Functionality Via Cycloaddition/Retrocycloaddition

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SUPPORTING INFORMATION

Experimental Section

General Remarks: All the reactions requiring anhydrous conditions were carried out under nitrogen and the solvents were appropriately dried before use. R_f values refer to TLC on 0.25 mm silica gel plates (Merck F_{254}). Melting points were determined on a RCH Kofler apparatus. Polarimetric measures were performed on a JASCO DIP-370 or on a Perkin–Elmer 241 polarimeter. NMR spectra were recorded on Varian Gemini (^{1}H 200 MHz), VXR 300 (^{1}H 300 MHz); or Bruker DRX-500 (^{1}H 500 MHz), with $CDCl_3$ as solvent, the NMR data are reported in δ(ppm) from TMS. IR spectra were recorded in $CDCl_3$ solution on a Perkin–Elmer 881 spectrophotometer. Mass spectra were recorded on a QMD 1000 Carlo Erba instrument by GC or direct injection; relative percentages are shown in brackets. Elemental analyses were performed with a Perkin–Elmer 240 C analyzer.

3-(4-Methoxybenzyloxy)-1-propanol (2):
The title compound was synthesized analogously to 3-benzyloxy-1-propanol[7] starting from 1,3-propanediol and using *p*-anisaldehyde in place of benzaldehyde:
2-(4-Methoxyphenyl)-1,3-dioxane: quantitative yield; R_f = 0.68 (petroleum ether/ethyl acetate, 2 : 1); ^{1}H NMR: δ = 7.44-7.41 (m, 2H), 6.92-6.87 (m, 2H), 5.47 (s, 1H), 4.25 (dd, *J* = 5.1, 1.5 Hz, 2H), 3.99 (dd, *J* = 9.5, 1.5 Hz, 2H), 3.80 (s, 3H), 2.35-2.10 (m, 1H), 1.50-1.40 (m, 1H).
2: R_f = 0.50 (petroleum ether/ethyl acetate, 9 : 1); ^{1}H NMR: δ = 7.28-7.24 (m, 2H), 6.92-6.86 (m, 2H), 4.46 (s, 2H), 3.81 (s, 3H), 3.78 (t, *J* = 5.8, 2H), 3.64 (t, *J* = 5.5 Hz, 2H), 1.86 (quintet, *J* = 5.7 Hz, 2H).

Methyl 5-(4-Methoxybenzyloxy)-pent-2-enoate (3):
Swern Oxidation: A solution of DMSO (20.3 mL, 286 mmol) in CH_2Cl_2 (42 mL) was added to a solution of oxalyl chloride (10.6 mL, 122 mmol) in CH_2Cl_2 (125 mL) cooled at –65 °C. After 5 min a solution of **2** (20.0 g, 102 mmol) in CH_2Cl_2 (83 mL) was added dropwise to the cold mixture during 5 min. After 20 min, NEt_3 (71 mL, 0.510 mol) was added, then the mixture was allowed to reach rt, and poured into water (125 mL). The organic phase was separated and the aqueous phase was extracted twice with CH_2Cl_2 (2x100 mL). The collected organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated to give the crude aldehyde (19.8 g, quantitative yield) as a yellow oil, that was used in the next step without further purification.
3-(4-Methoxybenzyloxy)-propionaldehyde: ^{1}H NMR: δ = 9.82-9.74 (t, *J* = 1.8 Hz,, 1H), 7.30-7.24 (m, 2H), 6.98-6.66 (m, 2H), 4.47 (s, 2H), 3.82 (s, 3H), 3.80 (t, *J* = 6.8 Hz, 2H), 2.70 (dt, *J* = 6.8, 1.8 Hz, 2H).
Wadsworth-Emmons reaction: Trimethyl phosphonoacetate (1.1 mL, 6.76 mmol) was added to a solution of K_2CO_3 (2.0 g, 13.5 mmol) in water (2 mL) cooled at 0°C. The reaction mixture was stirred for 15 min, then a solution of the crude aldehyde (1.0 g, 5.2 mmol) in diethyl ether (1.5 mL) was added. The heterogeneous mixture was stirred overnight at rt, then extracted with diethyl ether. The organic phase was dried over anhydrous Na_2SO_4 and concentrated to give **3** (1.28 g, 98%) sufficiently pure to be used in the next step without further purification. A sample purified by chromatography on silica gel (eluent petroleum ether/ethyl acetate, 5:1) afforded analytically pure **3**.

3: R_f = 0.33 (petroleum ether/ethyl acetate, 5:1); ^{1}H NMR: δ = 7.28-7.24 (m, 2H), 6.99 (dt, *J* = 15.7, 7.0 Hz, 1H), 6.91-6.87 (m, 2H), 5.90 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.45 (s, 2H), 3.81 (s, 3H), 3.73 (s, 3H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.50 (dq, *J* = 1.5, 6.6 Hz, 2H). ^{13}C NMR: δ = 166.7 (s), 159.2 (s), 145.9 (d), 130.1 (s), 129.2 (d, 2C), 122.3 (d), 113.7 (d, 2C), 72.6 (t), 67.8 (t), 55.1 (q), 51.3 (q), 32.5 (t). IR: ν = 3008, 2954, 2862, 1712, 1656, 1610, 1511, 1246, 1171, 1080 cm^{-1}. MS (EI): *m/z* = 250 (1, M^+), 190 (6), 135 (20), 121 (100), 114 (39). $C_{14}H_{18}O_4$ (250.29): calcd. C 67.18, H 7.25; found C 67.11, H 7.29.

5-(4-Methoxybenzyloxy)-pent-2-enoic acid (4):
A solution of **3** (12.0 g, 48 mmol) in THF (22.5 mL) was treated with NaOH 1M (72 mL). The resulting mixture was stirred at rt for 5 h and diluted with diethyl ether (60 mL). The layers were separated, and the aqueous layer acidified with 6M HCl and extracted twice with CH_2Cl_2 (6x90 mL). The organic extracts were combined, dried over Na_2SO_4, filtered and concentrated. The crude product was washed with diisopropyl ether to give **4** (8.15 g, 72%) as a pure colorless solid.
4: R_f = 0.18 (CH_2Cl_2/CH_3OH, 30:1); m.p. 65-67°C. ^{1}H NMR: δ = 7.29-7.24 (m, 2H), 7.09 (dt, *J* = 15.7, 7.0 Hz, 1H), 6.91-6.87 (m, 2H), 5.91 (dt, *J* = 15.7, 1.5 Hz, 1H), 4.46 (s, 2H), 3.82 (s, 3H), 3.58 (t, *J* = 6.6 Hz, 2H), 2.54 (dq, *J* = 6.6, 1.5 Hz, 2H). ^{13}C NMR: δ = 171.7 (s), 159.2 (s), 148.6 (d), 130.0 (s), 129.3 (d, 2C), 122.2 (d), 113.8 (d, 2C), 72.7 (t), 67.7 (t), 55.2 (q), 32.6 (t). IR: ν = 3001, 2940, 2865, 1695, 1512, 1246, 1171, 1086 cm^{-1}. MS (EI): *m/z* = 236 (5, M^+), 190 (4), 163 (3), 137 (27), 121 (100), 100 (22), 77 (20). $C_{13}H_{16}O_4$ (236.27): calcd. C 66.09, H 6.83; found C 66.15, H 6.99.

(3*S*)-3-[(Tetrahydropyran-2-yl)oxy]-1-pyrroline *N*-Oxide (7): A solution of **5** (15.0 g, 79 mmol) and 2*H*-dihydropyran (8.6 mL, 95 mmol) in pentane (22 mL) was added to a suspension of Amberlyst-15® (1.97 g) in pentane (10 mL). The reaction mixture was stirred at rt for 1.5 h, filtered through Celite and concentrated. The mixture of the two diastereoisomers was diluted in diethyl ether (80 mL) and added dropwise to a suspension of $LiAlH_4$ (6.84 g, 180 mmol) in diethyl ether (220 mL). The white suspension was vigorously stirred and refluxed for 6 h. An aqueous saturated Na_2SO_4 solution (80 mL) was slowly added to the reaction mixture. Then the suspension was filtered through Celite, the salts washed thoroughly with diethyl ether and the ethereal solution dried over Na_2SO_4. The solvent was removed and the crude product was dissolved in CH_2Cl_2 (85 mL) and NEt_3 (30.6 mL, 221 mmol). Methansulfonylchloride (MsCl, 14.2 mL, 184 mmol) was added dropwise to the solution at 0 °C, then the mixture was stirred at rt for 1 h, cooled to 0 °C and treated with ice (50 mL) and an aqueous saturated K_2CO_3 solution (50 mL). The two phases were separated and the aqueous phase extracted with CH_2Cl_2 (50 mL). The collected organic phases were washed with saturated Na_2CO_3 (50 mL) and brine (50 mL), dried over K_2CO_3 and filtered. The solvent was removed to give **6** as a mixture of two diastereoisomers. A suspension of crude **6** and hydroxylamine hydrochloride (21.0 g, 300 mmol) in NEt_3 (200 mL) was heated at reflux temperature for 5 h. The solvent was then evaporated and the resulting yellow solid was washed thoroughly with diethyl ether. Ethereal extracts were concentrated to give the crude *N*-hydroxypyrrolidine as a mixture of two diastereoisomers. The crude product was dissolved in CH_2Cl_2 (250 mL), cooled to 0 °C and reacted yellow mercury oxide (17.8 g, 82 mmol) added in little portions. The green suspension was stirred at rt for 3 h, filtered through Celite and concentrated. Purification and separation of the two regioisomeric nitrones (each of them as a mixture of two diastereoisomers) by chromatography on silica gel (eluent: ethyl acetate/MeOH, 10 : 1) gave **7** (6.46g, 44% of the starting **5**) and **8** (678 mg, 4%).
7: (mixture of two diastereoisomers in 1.3 molecular ratio) R_f = 0.20 and 0.13 (ethyl acetate/MeOH, 10 : 1); ^{1}H NMR: δ = 7.01-6.98 (m, 1H, =C*H*N), 4.98-4.96 (m, 1H, OC*H*O, major isomer), 4.87-4.84 (m, 1H, OC*H*O, minor isomer),4.75-4.68 (m, 1H, NCHC*H*O), 4.24-4.06 (m, 1H), 3.92-3.78 (m, 2H), 3.57-3.48 (m, 1H), 2.70-2.49 (m, 1H), 2.37-2.15 (m, 1H), 1.91-1.53 (m, 6H).^{13}C NMR: δ = (major isomer) 132.5 (d), 97.2 (d), 74.9 (d), 61.5(t), 60.4(t), 29.4 (t), 27.3 (t), 24.1 (t), 18.3 (t); (minor isomer) 133.9 (d), 97.6 (d), 76.1 (d), 61.2 (t), 59.8 (t), 29.4 (t), 26.5 (t), 24.1 (t), 18.2 (t). IR: ν = 2900, 1590, 1450, 1380, 1280

cm^{-1}. MS (EI): *m/z* = 185 (2,M^+), 179 (6), 169 (15), 85 (100). $C_9H_{15}NO_3$ (185.22): calcd. C 58.36, H 8.16, N 7.56; found C 58.07, H 8.20, N 7.29.

(2*R*,3a*R*,4*S*)- and (2*S*,3a*R*,4*S*)-4-Hydroxy-2-phenyl-2,3,3a,4,5,6-hexahydropyrrolo[1,2-*b*]isoxazole (15): A solution of **7** (2.23 g, 12 mmol) and freshly distilled styrene (2.77 mL, 24 mmol) in toluene (12 mL) was heated at 80 °C for 10 h and concentrated. Purification by chromatography on silica gel (eluent: ethyl acetate/petroleum ether, 2 : 3) gave a mixture of the four diastereoisomers **13** (2.76 g, 79%) that was diluted in MeOH (35 mL) and treated with Amberlyst 15® (860 mg). The mixture was stirred at 40 °C for 16 h, then filtered through Celite and the resin was washed with $MeOH/NEt_3$ 9 : 1. After concentration, purification by chromatography on silica gel (eluent: ethyl acetate) gave **13** (740 mg) and the two diastereoisomer **15** (1.294 g, 90% yield, 70% of conversion) in 1 : 5 ratio.

(2*R*,3a*R*,4*S*)-15: (major isomer) colorless solid; R_f = 0.16 (ethyl acetate); $[\alpha]_D^{19}$ = -6.9 (c = 1, $CHCl_3$); m.p.= 118-119 °C; ^{1}H NMR: δ = 7.40-7.30 (m, 5H), 4.98 (dd, *J*=8.2, 6.8 Hz, 1H), 4.26 (dt, *J*=5.8, 3.5 Hz, 1H), 3.78-3.71 (m, 1H), 3.59-3.45 (m, 1H), 3.40-3.30 (m, 1H), 2.50-2.45 (m, 2H), 2.37-2.20 (m, 1H, **e**), 1.88-1.74 (m, 1H); ^{13}C NMR: δ = 139.1 (s), 128.5 (d, 2C), 128.0 (d), 126.4 (d, 2C), 79.2 (d), 77.1 (d), 74.0 (d), 55.7 (t), 42.6 (t), 33.8 (t); IR: ν = 3658, 3323 br, 3071, 2949, 1491, 1445 cm^{-1}. MS (EI): *m/z* = 205 (7, M^+), 188 (8), 161 (5), 144 (30), 115 (15), 104 (100), 91 (11). $C_{12}H_{15}NO_2$ (205.26): calcd. C 70.22, H 7.37, N 6.82; found C 70.04, H 7.51, N 6.63.

(2*S*,3a*R*,4*S*)-15: (minor isomer) colorless solid; R_f = 0.27 (ethyl acetate); $[\alpha]_D^{19}$ = +18.3 (c = 1, $CHCl_3$); m.p.= 161-163 °C; ^{1}H NMR: δ = 7.42-7.26 (m, 5H), 5.03 (dd, *J*=9.4, 5.8 Hz, 1H), 4.31 (dt, *J*=5.5, 4.2 Hz, 1H), 3.82 (ddd, *J*=8.8, 5.5, 1.7 Hz, 1H), 3.32 (m, 2H), 2.95 (br s, 1H), 2.81 (ddd, *J*=12.2, 5.8, 1.8 Hz, 1H), 2.19 (ddd, *J*=12.2, 9.4, 8.8 Hz, 1H) 2.05-1.94 (m, 2H); ^{13}C NMR: δ = 139.8 (s), 128.3 (d, 2C), 127.7 (d), 126.5 (d, 2C), 79.3 (d), 71.4 (d), 69.5 (d), 53.5 (t), 38.4 (t), 34.1 (t); IR: ν = 3624, 3032, 2950, 1490, 1438 cm^{-1}. MS (EI): *m/z* = 205 (9, M^+), 188 (10), 161 (3), 144 (32), 115 (14), 104 (100), 77 (26). $C_{12}H_{15}NO_2$ (205.26): calcd. C 70.22, H 7.37, N 6.82; found C 70.42, H 7.45, N 6.66.

(2*R*,3a*R*,4*R*)- and (2*S*,3a*R*,4*R*)-5-(4-Methoxybenzyloxy)-pent-2-enoic acid 2-Phenyl-2,3,3a,4,5,6-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (17): A mixture of **4** (1.58 g, 6.69 mmol) and PPh_3 (polystyrene supported) (3.7 g, 3 mmol/g) in CH_2Cl_2 (14 mL) cooled at 0 °C was treated sequentially with a solution of **15** (1.143 g, 5.57 mmol) in CH_2Cl_2 (36 mL) and DEAD (1.35 mL, 8.36 mmol). The reaction mixture was stirred at 0 °C for 2 h, then at rt for 3 days and was filtered through Celite washing with ethyl acetate. The solvent was evaporated and the residue chromatographed on silica gel (eluent: ethyl acetate/petroleum ether, 1 : 1) to obtain the two diastereoisomers **17** (1.388 g, 59%).

(2*R*,3a*R*,4*R*)-17: Colorless oil, R_f = 0.40 (ethyl acetate); $[\alpha]_D^{22}$ = -20.8 (c = 0.467, $CHCl_3$); ^{1}H-NMR: δ = 7.40-7.21 (m, 7H), 7.06 (dt, *J*=15.8, 6.6 Hz, 1H), 6.90-6.80 (m, 2H), 5.95 (dt, *J*=15.8, 1.8 Hz, 1H), 5.35 (q, *J*=5.0 Hz, 1H), 5.03 (dd, *J*=9.1, 6.2 Hz, 1H), 4.50 (s, 2H), 4.04 (dt, *J*=6.6, 1.8 Hz, 1H), 3.77 (s, 3H), 3.58 (t, *J*=6.3 Hz, 2H), 3.38-3.32 (m, 2H), 2.59-2.50 (m, 3H), 2.30-2.20 (m, 3H).^{13}C-NMR: δ = 165.2 (s), 159.0 (s), 146.8 (d), 139.8 (s), 133.4 (s), 129.0 (d, 2C), 128.3 (d, 2C), 127.0 (d), 126.1 (d, 2C), 122.1 (d), 113.6 (d, 2C), 79.1 (d), 73.9 (d), 72.6 (t), 67.8 (d), 67.6 (t), 55.1 (q), 53.7 (t), 39.1 (t), 32.6 (t), 31.2 (t). IR: ν = 3013, 2936, 1714, 1649, 1611, 1506, 1246 cm^{-1}. MS (EI): *m/z* = 423 (3, M^+), 301 (4), 204 (8), 186 (11), 135 (17), 121 (100), 104 (38). $C_{25}H_{29}NO_5$ (423.51): calcd. C 70.90, H 6.90, N 3.31; found C 70.75, H 6.97, N 3.68.

(2*S*,3a*R*,4*R*)-17: Colorless oil, R_f = 0.35 (ethyl acetate/petroleum ether, 2 : 3); $[\alpha]_D^{19}$ = -4.0 (c = 0.875, $CHCl_3$); ^{1}H-NMR: δ = 7.41-7.21 (m, 7H), 7.02 (dt, *J*=15.7, 7.0 Hz, 1H), 6.91-6.86 (m, 2H), 5.89 (dt, *J*=15.7, 1.5 Hz, 1H), 5.11 (dt, *J*=6.6, 3.0 Hz, 1H), 5.03 (dd, *J*=7.9, 6.8 Hz, 1H), 4.44 (s, 2H), 4.38-4.22 (m, 1H), 3.78 (s, 3H), 3.55 (t, *J*=6.4 Hz, 2H), 3.60-3.50 (m, 2H), 3.46-3.37 (m, 1H), 2.70-2.30 (m, 4H), 2.00-1.90 (m, 1H).^{13}C-NMR: δ = 166.0 (s), 159.2 (s), 146.7 (d), 140.3 (s), 130.0 (s), 129.2 (d, 2C), 128.4 (d, 2C), 127.7 (d), 126.0 (d, 2C), 122.3 (d), 113.7 (d, 2C), 79.9 (d), 78.9 (d), 72.6 (t), 72.3 (d), 67.7 (t), 55.9 (t), 55.1 (q), 43.0 (t), 32.5 (t), 31.1 (t). IR: ν = 3020, 2953, 2862, 1709, 1611, 1510, 1301, 1244,

1170 cm^{-1}. MS (EI): *m/z* = 423 (2, M^+), 302 (8), 235 (4), 186 (53), 137 (42), 121 (100), 104 (100). $C_{25}H_{29}NO_5$ (423.51): calcd. C 70.90, H 6.90, N 3.31; found C 70.50, H 6.92, N 3.70.

(2*R*,3a*R*,4*S*)- and (2*S*,3a*R*,4*S*)-2-Ethoxycarbonyl-4-hydroxy-2,3,3a,4,5,6-hexahydro-pyrrolo[1,2-*b*]isoxazole (16): A solution of **7** (470 mg, 2.54 mmol) and ethyl acrylate (0.36 mL, 3.3 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 1 d and concentrated. Purification of the residue by chromatography on silica gel (eluent ethyl acetate/petroleum ether, 3 : 2) gave a mixture of the four diastereoisomers **14** (443 mg, 70%) that was diluted with EtOH (12 mL) and treated with Amberlyst 15® (240 mg). The mixture was stirred at 40 °C for 8 h, filtered through Celite and the resin was washed with a mixture of MeOH/NEt_3, 9 : 1 and the solvent evaporated. Purification by chromatography on silica gel (eluent: ethyl acetate) gave the two diastereoisomers **16** (166 mg, 53%) in 1.3 : 1 ratio.
(2*R*,3a*R*,4*S*)-16: (major isomer) R_f = 0.16 (ethyl acetate/petroleum ether, 8 : 1); ^{1}H NMR: δ = 4.52 (dd, *J* = 8.4, 4.4 Hz, 1H), 4.28-4.16 (m, 3H), 3.68-3.60 (m, 1H), 3.45-3.35 (m, 2H), 2.87 (ddd, *J* = 12.8, 8.8, 4.4 Hz,1H), 2.34 (ddd, *J* = 12.8, 8.1, 4.8 Hz, 1H), 2.33-2.22 (m, 1H), 1.80-1.70 (m, 1H), 1.30 (t, *J*=7.1 Hz, 3H); ^{13}C NMR: δ = 171.4 (s), 78.3 (d), 75.3 (d), 73.7 (d), 61.5 (t), 55.3 (t), 37.9 (t), 33.7 (t), 14.1 (q); IR: ν = 3615, 2945, 1730, 1263, 1205 cm^{-1}. MS (EI): *m/z* = 201 (4, M^+), 158 (3), 128 (3), 83 (100).

(2*R*,3a*R*,4*R*)-5-(4-Methoxybenzyloxy)-pent-2-enoic acid 2-Ethoxycarbonyl-2,3,3a,4,5,6-hexahydro-pyrrolo[1,2-*b*]isoxazol-4-yl ester (18): A mixture of **16** (60 mg, 0.30 mmol) and PPh_3 (236 mg, 0.9 mmol) in THF (1.5 mL) cooled at 0 °C was treated with **4** (85 mg, 0.36 mmol) and DEAD (0.14 mL, 0.90 mmol) and stirred for 2 h. The solvent was evaporated and the residue chromatographed on silica gel (eluent: ethyl acetate/petroleum ether, 8 : 1) to obtain **18** (50 mg, 82% yield, 50% conversion) in addition to unchanged **16** (30 mg, conversion: 50%).

(2a*R*,3*S*,7a*R*,7b*R*)-2a,3,6,7,7a,7b-Hexahydro-3-[2-(4-methoxybenzyloxy)-ethyl)-2-oxo-[2*H*]-furo[4,3,2-*c*,*d*]pyrrolo[1,2-*b*]isoxazole (20):
Method A: A solution of **17** (1.046 g, 2.47 mmol) in *o*-dichlorobenzene (40 mL) was heated at 190 °C for 64 h. The solution was filtered through silica gel eluting first with petroleum ether and then with MeOH. The alcoholic solution was evaporated and the residue chromatographated on silica gel (eluent: ethyl acetate/MeOH, 10 : 1) to give **20** (560 mg, 71%).
Method B: A solution of **18** (50 mg, 0.12 mmol) in *o*-dichlorobenzene (7 mL) was heated at 150°C for 3 h. The solution was filtered through silica gel eluting first with petroleum ether and then with MeOH. The alcoholic solution was evaporated and the residue chromatographated on silica gel (eluent: ethyl acetate/MeOH, 15 : 1) to give **20** (28 mg, 73%).
20: Pale yellow oil, R_f = 0.46 (ethyl acetate/MeOH, 10 : 1); $[\alpha]_D^{19}$ = -17.9 (c = 0.547, $CHCl_3$); ^{1}H NMR: δ = 7.28-7.24 (m, 2H), 6.92-6.86 (m, 2H), 5.03 (q, *J* = 5.9 Hz, 1H), 4.64 (dt, *J*=9.2, 2.6 Hz, 1H), 4.45 (s, 2H), 4.35 (dd, *J* = 8.8, 6.0 Hz, 1H), 3.81 (s, 3H), 3.61 (dd, *J* = 6.8, 5.3 Hz, 2H), 3.46 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.40-3.31 (m, 1H), 3.18-3.09 (m, 1H), 2.30-2.21 (m, 2H), 2.13-1.95 (m, 2H). ^{13}C-NMR: δ = 176.7 (s), 159.2 (s), 130.4 (s), 129.3 (d, 2C), 113.8 (d, 2C), 82.4 (d), 80.9 (d), 72.8 (t), 70.7 (d), 66.2 (t), 55.2 (d), 54.9 (q), 52.3 (t), 34.0 (t), 31.9 (t). IR: ν = 2934, 1770, 1510, 1245, 1173, 1085 cm^{-1}. MS (EI): *m/z* = 319 (0.1, M^+), 198 (5), 183 (4), 154 (10), 137 (18), 121 (100), 84 (16). $C_{17}H_{21}NO_5$ (319.36): calcd. C 63.94, H 6.63, N 4.39; found C 63.79, H 6.70, N 4.01.

(2a*R*,3*S*,8a*R*,8b*R*)-2a,3,4,5,7,8,8a,8b-Octahydro-3-hydroxy-2-oxo-[2*H*]-furo[4,3,2-*h*,*i*]indolizine (21):
Deprotection of PMB group: A solution of **20** (575 mg, 1.8 mmol) in TFA : CH_2Cl_2 10 : 90 (100 mL), was stirred at rt for 45 min, concentrated, diluted with CH_2Cl_2 and treated with Amberlyst A-21®. The mixture was stirred for 30 min., filtered through Celite and concentrated. The purification of the residue by chromatography on silica gel (eluent ethyl acetate/MeOH, 10 : 1) gave the deprotected alcohol as a yellow oil (250 mg, 70%).

(2a*R*,3*S*,7a*R*,7b*R*)-2a,3,6,7,7a,7b-Hexahydro-3-(2hydroxyethyl)-2-oxo-[2*H*]-furo[4,3,2-*c*,*d*]pyrrolo[1,2-*b*]isoxazole: Yellow oil, R_f = 0.16 (ethyl acetate/MeOH, 10 : 1); $[\alpha]_D^{19}$ = -15.5 (c = 0.98, $CHCl_3$); ^{1}H-NMR: δ = 5.07 (dt, *J*=6.2, 5.1 Hz, 1H), 4.67 (dt, *J*=6.2, 2.9 Hz, 1H), 4.23 (dd, *J*=8.6, 6.2 Hz, 1H), 3.83-3.77 (m, 2H), 3.45 (dd, *J*=8.6, 2.9 Hz, 1H), 3.44-3.33 (m, 1H), 3.22-3.11 (m, 1H), 2.36-2.24 (m, 2H), 2.09-1.92 (m, 1H). ^{13}C-NMR: δ = 176.9 (s), 82.6 (d), 82.0 (d), 70.9 (d), 59.3 (t), 54.8 (d), 52.0 (t), 36.6 (t), 31.83 (t). IR: ν = 3629 (br), 2931, 1770, 1357, 1180, 1053 cm^{-1}. MS (EI): *m/z* = 199 (5, M^+), 149 (5), 127 (27), 110 (5), 84 (100), 79 (16). $C_9H_{13}NO_4$ (199.21): calcd. C 54.26, H 6.58, N 7.03; found C 54.29, H 6.62, N 6.84.

Mesylation, intramolecular cyclization and hydrogenation: MsCl (0.152 mL, 1.98 mmol) was added dropwise to solution of the deprotected alcohol (246 mg, 1.23 mmol) and NEt_3 (0.293 mL, 2.12 mmol) in CH_2Cl_2 (13 mL) cooled at 0 °C. The reaction mixture was stirred for 2 h, diluted with THF concentrated. The residue was dissolved in MeOH treated with Pd/C 10% (26 mg) and maintained in H_2 atmosphere for 2 days. The mixture was filtered through Celite, stirred in presence of Amberlyst A26® for 30 min and filtered again through Celite. The solvent was removed and the crude product purified by chromatography on silica gel (eluent: ethyl acetate/MeOH/NEt_3, 8 : 1 : 0.01) to give **21** (45 mg, 20%) as colorless oil.

21: Colorless oil, R_f = 0.18 (ethyl acetate/MeOH/NEt_3, 8 : 1 : 0.01); $[\alpha]_D^{22}$ = -57.4 (c = 0.93, $CHCl_3$); ^{1}H-NMR: δ = 5.06 (t, *J* = 4.2 Hz, 1H), 3.97-3.95 (m, 1H), 3.93 (dd, *J*=6.3, 4.3 Hz, 1H), 3.13 (dt, *J* = 14.5, 3.2 Hz, 1H), 2.97-2.83 (m, 4H), 2.20 (dd, *J* = 13.6, 4.8 Hz, 1H), 2.05-1.97 (m, 1H), 1.75-1.72 (m, 1H), 1.67 (br s, 1H, OH), 1.55 (dq, *J* = 3.6, 12.6 Hz, 1H). ^{13}C-NMR: δ = 178.1 (s), 84.2 (d), 68.2 (d), 60.8 (d), 48.3 (t), 45.5 (t), 42.7 (d), 31.8 (t), 28.2 (t). IR: ν = 3493 (br), 2926, 1744, 1342, 1176 cm^{-1}. MS (EI): *m/z* = 183 (11, M^+), 164 (2), 136 (4), 120 (33), 112 (13), 95 (100), 84 (30). $C_9H_{13}NO_3$ (183.21): calcd. C 59.00, H 7.15, N 7.65; found C 58.89, H 7.35, N 8.02.