Supporting information

**Concise enantioselective synthesis of 3,5-dialkylsubstituted indolizidine alkaloids
via sequential cross metathesis - double reductive cyclization**

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General methods. All reagents were obtained commercially and were used without further purification. All reactions were carried out under an inert atmosphere (N_2) unless otherwise indicated. 1H and ^{13}C spectra were recorded at 500 and 125.8 MHz or 400 and 100.6 MHz, respectively. Chemical shifts are expressed in ppm upfield relative to the internal solvent peak. Mass spectra were obtained at an ionizing potential of 70 eV. IR spectra were measured by attenuated total reflection (ATR). Optical rotations were determined on a polarimeter as solutions in a 10 cm unit cell at 589 nm. Melting points are uncorrected.

1-Bicyclo[2.2.1]hept-5-en-2-yl-octan-1,4-dione (12a). To a solution of 2.48 g (20.3 mmol) bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (**10**), 2.28 g (20.3 mmol) butyl vinyl ketone (**11a**) and 1.42 ml (10.2 mmol) triethylamine were added 0.27 g (1.0 mmol) of 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride. After stirring the reaction mixture for 18 h at 65 °C, 100 ml of dichloromethane were added. The organic phase was washed with 50 ml of 1N aqueous HCl, 50 ml of brine and then dried over Na_2SO_4 . After evaporation of the solvent under vacuum, the residue was purified by chromatography on silica gel using hexane/ethyl acetate (10:1) to yield 4.05 g (17.3 mmol, 85 %) of a mixture of *endo/exo*-isomers **12a**. The isomers were separated for NMR-spectroscopy. *Endo-12a*: 1H NMR (500 MHz, $CDCl_3$): δ 6.14 (dd, $J=5, 3$ Hz, 1H), 5.85 (dd, $J = 5, 3$ Hz, 1H), 3.28 (m, 1H), 3.07 (ddd, $J = 9, 4, 4$ Hz, 1H), 2.89 (m, 1H), 2.76-2.66 (m, 2H), 2.65-2.60 (m, 2H), 2.43 (t, $J = 8$ Hz, 2H), 1.75 (ddd, $J = 12, 9, 4$ Hz, 1H), 1.59-1.41 (m, 4H), 1.34-1.23 (m, 3H), 0.89 (t, $J = 8$ Hz, 3H). ^{13}C (125.8 MHz, $CDCl_3$): δ 209.8 (C_q), 209.5 (C_q), 137.6 (CH), 131.4 (CH), 51.4 (CH), 49.9 (CH₂), 46.0 (CH), 42.6 (CH₂), 42.6 (CH), 35.9 (CH₂), 35.3 (CH₂), 27.5 (CH₂), 25.9 (CH₂), 22.2 (CH₂), 13.8 (CH₃). *Exo-12a*: 1H NMR (500 MHz, $CDCl_3$): δ 6.17-6.10 (m, 2H), 3.03 (m, 1H), 2.89 (m, 1H), 2.83 (m, 1H), 2.76-2.65 (m, 3H), 2.46 (t, $J = 7$ Hz, 2H), 2.42 (dd, $J = 9, 5$ Hz, 1H), 1.90 (ddd, $J = 12, 4, 4$ Hz, 1H), 1.61-1.52 (m, 2H), 1.37-1.28 (m, 5H), 0.90 (t, $J = 7$ Hz, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 211.3 (C_q), 209.8 (C_q), 138.2 (CH), 135.8 (CH), 50.7 (CH), 45.9 (CH₂), 45.6 (CH), 42.6 (CH₂), 41.6 (CH), 36.1 (CH₂), 36.0 (CH₂), 29.3 (CH₂), 25.9 (CH₂), 22.3 (CH₂), 13.8 (CH₃). MS m/z (%) 234 (4), 169 (100), 141 (19), 111 (30), 66 (82). HR-MS calcd for $C_{15}H_{22}O_2$ [M^+] 234.1620, obsd 234.1622. IR (neat,

cm⁻¹) 2959, 2937, 1708, 1362, 1220, 721. Anal. calcd for C₁₅H₂₂O₂: C, 76.88; H, 9.46. Found C, 76.75; H, 9.48.

1-Bicyclo[2.2.1]hept-5-en-2-yl-hexan-1,4-dione (12b). This compound was prepared from 2.50 g (20.5 mmol) bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (**10**) and 1.72 g (20.5 mmol) ethyl vinyl ketone (**11b**) in 87 % yield as a mixture of endo/exo-isomers (3.67 g, 17.8 mmol) by a procedure analogous to that employed in the synthesis of **12a**. The isomers were separated for NMR-spectroscopy. *Endo-12b*: ¹H NMR (400 MHz, CDCl₃): δ 6.13 (dd, *J* = 6, 3 Hz, 1H), 5.84 (dd, *J* = 5, 3 Hz, 1H), 3.27 (br s, 1H), 3.06 (ddd, *J* = 9, 4, 3 Hz, 1H), 2.88 (br s, 1H), 2.75-2.66 (m, 2H), 2.63 (br t, *J* = 6 Hz, 2H), 2.45 (q, *J* = 8 Hz, 2H), 1.74 (ddd, *J* = 12, 9, 4 Hz, 1H), 1.47 (ddd, *J* = 12, 3, 3 Hz, 1H), 1.43 (br d, *J* = 8 Hz, 1H), 1.31 (br d, *J* = 9 Hz, 1H), 1.14 (t, *J* = 8 Hz, 3H). ¹³C (125.8 MHz, CDCl₃): δ 210.2 (C_q), 209.6 (C_q), 137.7 (CH), 131.5 (CH), 51.5 (CH), 49.9 (CH₂), 46.1 (CH), 42.6 (CH), 36.0 (CH₂), 35.6 (CH₂), 35.4 (CH₂), 27.5 (CH₂), 7.8 (CH₃). *Exo-12b*: ¹H NMR (400 MHz, CDCl₃): δ 6.14-6.08 (m, 2H), 3.00 (br s, 1H), 2.87 (br s, 1H), 2.82 (m, 1H), 2.72 (dd, *J* = 7, 5 Hz, 1H), 2.70-2.64 (m, 2H), 2.47 (q, *J* = 8 Hz, 2H), 2.39 (dd, *J* = 9, 5 Hz, 1H), 1.87 (ddd, *J* = 11, 4, 4 Hz, 1H), 1.34-1.22 (m, 3H), 1.03 (t, *J* = 8 Hz, 3H). ¹³C NMR (125.8 MHz, CDCl₃): δ 211.4 (C_q), 210.1 (C_q), 138.2 (CH), 135.9 (CH), 50.7 (CH), 46.0 (CH₂), 45.6 (CH), 41.7 (CH), 36.1 (CH₂), 35.9 (CH₂), 35.7 (CH₂), 29.3 (CH₂), 7.8 (CH₃). MS *m/z* (%) 206 (5), 141 (96), 113 (22), 66 (100), 55 (30). HR-MS calcd for C₁₃H₁₈O₂ [M⁺] 206.1307, obsd 206.1310. IR (neat, cm⁻¹) 2973, 2940, 1706, 1359, 1100, 714. Anal. calcd for C₁₃H₁₈O₂: C, 75.69; H, 8.79. Found C, 75.51; H, 8.63.

Dec-10-ene-3,6-dione (13a). 1.80 g (7.7 mmol) of norbornene **12a** were dropped slowly (ca. 1 drop/5 seconds) into a vertically arranged pyrolysis tube filled with Raschig-rings kept at 500 °C under vacuum (15 mbar). The crude product was collected in an ice-cooled U-tube. The cyclopentadiene formed was condensed in a second cooling trap kept at -78 °C. After Kugelrohrdestillation of the crude product (0.5 mbar, 120-140 °C), **13a** (1.05 g, 6.05 mmol, 81 %) was obtained as a colorless liquid. ¹H NMR (400 MHz, CDCl₃): δ 6.38 (dd, *J* = 18, 10 Hz, 1H), 6.26 (dd, *J*

= 18, 1 Hz, 1H), 5.86 (dd, $J = 10$, 1 Hz, 1H), 2.89 (t, $J = 7$ Hz, 2H), 2.74 (t, $J = 7$ Hz, 2H), 2.48 (t, $J = 7$ Hz, 2H), 1.58 (m, 2H), 1.32 (tq, $J = 8$, 8 Hz, 2H), 0.90 (t, $J = 8$ Hz, 3H). ^{13}C NMR (125.8 MHz, CDCl_3): δ 209.6 (C_q), 199.1 (C_q), 136.2 (CH), 128.2 (CH_2), 42.5 (CH_2), 35.8 (CH_2), 33.0 (CH_2), 25.8 (CH_2), 22.2 (CH_2), 13.7 (CH_3). MS m/z (%) 168 (0.4), 126 (80), 111 (97), 85 (66), 57 (83), 55 (100). HR-MS calcd for $\text{C}_{10}\text{H}_{16}\text{O}_2$ [M^+] 168.1150, obsd 168.1151. IR (neat, cm^{-1}) 2959, 2933, 1714, 1683, 1402, 1363, 964.

Oct-8-ene-3,6-dione (13b). This compound was prepared from 2.50 g (12.1 mmol) of norbornene **12b** in 76 % yield (1.29 g, 9.2 mmol) as a colorless liquid by a procedure analogous to that employed in the synthesis of **13a**. ^1H NMR (400 MHz, CDCl_3): δ 6.34 (dd, $J = 18$, 11 Hz, 1H), 6.22 (br d, $J = 18$ Hz, 1H), 5.82 (br d, $J = 10$ Hz, 1H), 2.86 (t, $J = 6$ Hz, 2H), 2.71 (t, $J = 6$ Hz, 2H), 2.47 (q, $J = 7$ Hz, 2H), 1.03 (t, $J = 7$ Hz, 3H). ^{13}C NMR (125.8 MHz, CDCl_3): δ 209.8 (C_q), 199.0 (C_q), 136.1 (CH_2), 128.2 (CH), 35.8 (CH_2), 35.3 (CH_2), 33.0 (CH_2), 7.6 (CH_3). MS m/z (%) 140 (1), 111 (100), 83 (25), 57 (74), 55 (87). HR-MS calcd for $\text{C}_8\text{H}_{12}\text{O}_2$ [M^+] 140.0837, obsd 140.0831. IR (neat, cm^{-1}) 2978, 2940, 1714, 1700, 1681, 1401, 1102, 988.

(R)-Toluene-4-sulfonic acid 1-methyl-but-3-enyl ester (7). A solution of vinyl magnesium bromide (1 M in THF, 37.5 ml, 37.5 mmol) was added to a suspension of 1.75 ml (25 mmol) (*R*)-methyloxirane (**6**) and 0.52 g (2.5 mmol) $\text{Cu}(\text{COD})\text{Cl}$ in 25 ml THF at -78°C . The mixture was allowed to warm to room temperature overnight. After the addition of 50 ml aq. sat. NH_4Cl , the aqueous layer was extracted three times with Et_2O (100ml each). The combined organic layers were dried over Na_2SO_4 and the solvent was carefully evaporated. Distillation using a Vigreux-column (b.p. $90\text{--}105^\circ\text{C}$) afforded crude (*R*)-4-penten-2-ol as a colorless liquid. 20 ml of CH_2Cl_2 were added followed by 2.2 ml (27 mmol) of pyridine, 4.77 g (25 mmol) of tosyl chloride and 0.30 g (2.5 mmol) of DMAP. The solution was stirred for 36 h at room temperature. The organic layer was washed with 20 ml of 1 N aq. HCl and 20 ml of aq. sat. NaHCO_3 . The organic phase was dried over Na_2SO_4 and the solvent was evaporated under vacuum. Chromatography on silica gel (hexane/ EtOAc 10/1) afforded **7** (3.91 g, 16.3

mmol, 65 %) as a colorless oil. ^1H NMR (400 MHz, CDCl_3): δ 7.79 (m, 2H), 7.33 (m, 2H), 5.60 (m, 1H), 5.05 (br d, $J = 5$ Hz, 1H), 5.01 (br s, 1H), 4.64 (ddq, $J = 7, 7, 7$ Hz, 1H), 2.44 (s, 3H), 2.38-2.27 (m, 2H), 1.26 (d, $J = 7$ Hz, 3H). ^{13}C NMR (125.8 MHz, CDCl_3): δ 144.4 (C_q), 134.3 (C_q), 132.1 (CH), 129.6 (CH), 127.7 (CH), 118.6 (CH_2), 79.3 (CH), 40.7 (CH_2), 21.5 (CH_3), 20.2 (CH_3). MS m/z (%) 199 (20), 155 (100), 91 (93), 65 (17). HR-MS calcd for $\text{C}_9\text{H}_{11}\text{O}_3\text{S}$ 199.0429, obsd 199.0429. IR (neat, cm^{-1}) 3079, 2981, 2926, 1353, 1176, 906. $[\alpha]_{\text{D}}^{20} = +11.8^\circ$ (c 1.35, CHCl_3). Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{S}$: C, 59.98; H, 6.71. Found C, 60.15; H, 6.64.

(S)-4-Azido-pent-1-ene (8). To a solution of 4.50 g (18.7 mmol) of tosylate **7** in 18 ml DMF were added 6.09 g (94 mmol) of sodium azide. The suspension was stirred at 40°C for 12 hours. 30 ml of diethyl ether and 30 ml of water were added. The organic phase was separated and the aqueous phase was extracted twice with 30 ml of diethyl ether. The combined organic layers were dried over Na_2SO_4 and the solvent was carefully evaporated under reduced pressure. The crude product was purified by Kugelrohr distillation ($90\text{--}100^\circ\text{C}$, 190 mbar) to yield **8** (1.92 g, 17.3 mmol, 92%) as a colorless liquid. ^1H -NMR (500 MHz, CDCl_3): δ 5.79 (m, 1H), 5.14 (dd, $J = 18$ Hz, 1 Hz, 1H), 5.12 (br d, $J = 10$ Hz, 1H), 3.51 (ddq, $J = 7, 7, 7$ Hz, 1H), 2.33-2.19 (m, 2H), 1.25 (d, $J = 6$ Hz, 3H). ^{13}C -NMR (125.8 MHz, CDCl_3): δ 133.8 (CH), 118.0 (CH_2), 57.2 (CH), 40.4 (CH_2), 18.9 (CH_3). MS m/z (%) 82 (25), 70 (89), 69 (84), 68 (61), 55 (65), 41 (100). HR-MS calcd for $\text{C}_5\text{H}_8\text{N}$ 82.0657, obsd 82.0681. IR (neat, cm^{-1}) 2974, 2933, 2105, 1380, 1240, 919. $[\alpha]_{\text{D}}^{20} = +33.4^\circ$ (c 0.78, CHCl_3).

(S)-(1-Methyl-but-3-enyl)-carbamic acid benzyl ester (9). To a solution of 1.51 g (13.6 mmol) azide **8** in 50 ml diethyl ether were added 1.03 g (27.1 mmol) lithium aluminium hydride at 0°C in small portions over a period of 20 minutes. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. The reaction was quenched by the addition of 10 % aqueous sodium hydroxide. The solution was filtered and the residue was washed three times with 20 ml of diethyl ether. The etherial solution was dried over Na_2SO_4 and the solution was carefully concentrated by distillation using a Vigreux column. 15 ml of THF were added, followed by 2.76 g (20 mmol)

K_2CO_3 and 2.14 ml (15 mmol) of carbobenzoxychloride. After stirring the reaction mixture for 12 hours, 10 ml of water and 20 ml of diethyl ether were added. The organic layer was separated and the aqueous phase was extracted twice with 20 ml of ether. The combined organic layers were washed with 20 ml of brine and dried over Na_2SO_4 . The solvents were removed under vacuum and the residue was purified on silica gel using hexane/ethyl acetate (6:1) to yield 2.65 g (12.1 mmol, 89 %) of **9** as a colorless oil. 1H NMR (400 MHz, $CDCl_3$): δ 7.42-7.30 (m, 5H), 5.77 (m, 1H), 5.15-5.04 (m, 4 H), 4.72 (br s, 1H), 3.82 (ddq, $J = 7, 7, 7$ Hz, 1H), 2.28-2.17 (m, 2H), 1.15 (d, $J = 7$ Hz, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 155.6 (C_q), 136.5 (CH), 134.1 (C_q), 128.4 (CH), 128.0 (CH), 128.0 (CH), 117.9 (CH_2), 66.4 (CH_2), 46.4 (CH), 41.0 (CH_2), 20.4 (CH_3). MS m/z (%) 178 (33), 134 (25), 91 (100), 65 (8). HR-MS calcd for $C_{13}H_{17}NO_2$ [M^+] 219.1259; obsd 219.1267. IR (neat, cm^{-1}) 3327, 3067, 2972, 2933, 1695, 1531, 1454, 1254, 1060. $[\alpha]_D^{20} = -13.0^\circ$ (c 1.09, $CHCl_3$). Anal Calcd for $C_{13}H_{17}NO_2$: C, 71.21; H, 7.81; N, 6.39. Found C, 71.03; H, 7.89; N, 6.13.

(S)-((E)-1-Methyl-5,8-dioxo-dec-3-enyl)-carbamic acid benzyl ester (14b). This compound was prepared from 0.45 g (2.1 mmol) of amine **9** and 0.29 g (2.1 mmol) of enone **13b** in 87 % yield (0.59 g, 1.8 mmol) as a colorless solid by a procedure analogous to that employed in the synthesis of **14a**. 1H NMR (500 MHz, $CDCl_3$): δ 7.38-7.27 (m, 5H), 6.79 (dt, $J = 18, 7$ Hz, 1H), 6.12 (d, $J = 18$ Hz, 1H), 5.10-5.03 (m, 2H), 4.74 (d br, $J = 6$ Hz, 1H), 3.90 (septett, $J = 6$ Hz, 1H), 2.84-2.78 (m, 2H), 2.69 (t, $J = 7$ Hz, 2H), 2.48 (q, $J = 7$ Hz, 2H), 2.39 (t br, $J = 7$ Hz, 2H), 1.17 (d, $J = 6$ Hz, 3H), 1.05 (t, $J = 7$ Hz, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 210.0 (C_q), 198.4 (C_q), 155.5 (C_q), 142.6 (CH), 136.3 (C_q), 132.4 (CH), 128.4 (CH), 128.0 (CH), 128.0 (CH), 66.5 (CH_2), 46.1 (CH), 39.7 (CH_2), 35.9 (CH_2), 35.5 (CH_2), 33.5 (CH_2), 20.5 (CH_3), 7.7 (CH_3). MS m/z (%) 224 (2), 207 (3), 178 (13), 154 (18), 134 (19), 91 (100). HR-MS calcd for $C_{12}H_{18}NO_3$ 224.1287, obsd 224.1293. IR (neat, cm^{-1}) 3331, 2971, 2937, 1712, 1696, 1671, 1526, 1243, 1055. $[\alpha]_D^{20} = -22.3^\circ$ (c 0.76, $CHCl_3$). Anal. Calcd for $C_{19}H_{25}NO_4$: C, 68.86; H, 7.60; N, 4.23. Found C, 68.80; H, 7.71; N, 4.28. Mp 55-56 $^\circ C$.

(3*R*,5*S*,9*S*)-3-Ethyl-5-methyl-indolizine (15b). This compound was prepared from 0.41 g (1.22 mmol) of enedione **14b** in 62 % yield (0.13 g, 0.76 mmol) as a colorless liquid by a procedure analogous to that employed in the synthesis of **15a**. Spectral data were in accordance with those previously reported.¹⁹ ¹H NMR (500 MHz, CDCl₃): δ 2.40 (t br, *J* = 10 Hz, 1H), 2.19 (m, 1H), 2.07 (m, 1H), 1.81 (m, 1H), 1.75-1.59 (m, 4H), 1.51 (d br, *J* = 9 Hz, 1H), 1.45-1.35 (m, 2H), 1.32-1.19 (m, 4H), 1.10 (d, *J* = 7 Hz, 3H), 0.83 (t, *J* = 8 Hz, 3H). ¹³C NMR (125.8 MHz, CDCl₃): δ 67.1 (CH), 64.4 (CH), 60.1 (CH), 35.8 (CH₂), 32.5 (CH₂), 30.9 (CH₂), 30.2 (CH₂), 29.1 (CH₂), 24.8 (CH₂), 22.8 (CH₃), 11.1 (CH₃). MS *m/z* (%) 167 (15), 166 (15), 152 (36), 138 (100), 124 (9), 95 (17), 55 (20). HR-MS calcd for C₁₁H₂₁N [M⁺] 167.1674, obsd 167.1669. IR (neat, cm⁻¹) 2959, 2928, 1718, 1455, 1378, 1200, 1131. $[\alpha]_D^{20} = +60.3^\circ$ (*c* 0.98, hexane).