**An efficient sequential reaction process to
polysubstituted indolizidines and quinolizidines and its
application to the total synthesis of indolizidine 223A**

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Experimental

General procedure for table 1: A mixture of **1** (0.22 mmol), **5** (0.23 mmol), anhydrous K₂CO₃ (0.7 mmol) and 4Å MS (40 mg) in 3 mL of MeCN was refluxed until the starting materials disappeared monitored by TLC. The cooled solution was concentrated and partitioned between brine and ether. The organic phase was concentrated and the residue was chromatographed eluting with 1:1 to 1:10 ethyl acetate/petroleum ether to afford **6**.

1,2,3,5,6,7-Hexahydroindolizine-8-carboxylic acid ethyl ester 6a^[1]: ¹H NMR (CDCl₃, 300 MHz) δ 4.11 (q, *J* = 7.2 Hz, 2H), 3.28 (t, *J* = 7.1 Hz, 2H), 3.14 (t, *J* = 5.8 Hz, 2H), 3.05 (t, *J* = 7.8 Hz, 2H), 2.35 (t, *J* = 6.5 Hz, 2H), 1.94 – 1.81 (m, 4H), 1.25 (t, *J* = 7.2 Hz, 3H); MS *m/z* 195 (M⁺).

8-(Toluene-4-sulfonyl)-1,2,3,5,6,7-hexahydroindolizine 6b: IR (film) 2847, 1592 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.72-7.68 (m, 2H), 7.28-7.23 (m, 2H), 3.28 (t, *J* = 7.2 Hz, 2H), 3.14-3.09 (m, 4H), 2.40 (s, 3H), 2.33 (t, *J* = 6.0 Hz, 2H), 1.98-1.88 (m, 2H), 1.86-1.78 (m, 2H); MS *m/z* 277 (M⁺); HRMS calcd for C₁₅H₁₉NSO₂ 277.1180 (M⁺), found 277.1158.

(1,2,3,5,6,7-Hexahydroindolizin-8-yl)phosphonic acid diethyl ester 6c: IR (film) 2979, 1610, 1238 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 4.04-3.90 (m, 4H), 3.22 (t, *J* = 6.9 Hz, 2H), 3.15 (t, *J* = 5.8 Hz, 2H), 2.90 (t, *J* = 7.4 Hz, 2H), 2.18 (q, *J* = 6.1 Hz, 2H),

1.92-1.81 (m, 4H), 1.29 (t, $J = 7.2$ Hz, 6H); MS m/z 259 (M^+); HRMS calcd for $C_{12}H_{23}NPO_3$, 260.1410 ($M + H$)⁺, found 260.1415.

3,4,6,7,8,9-Hexahydro-2H-quinolizine-1-carboxylic acid ethyl ester 6d^[1]: 1H NMR ($CDCl_3$, 300 MHz) δ 4.08 (q, $J = 7.2$ Hz, 2H), 3.13-3.06 (m, 4H), 3.01 (t, $J = 6.4$ Hz, 2H), 2.38 (t, $J = 12.9$ Hz, 2H), 1.80-1.73 (m, 4H), 1.63-1.59 (m, 2H), 1.24 (t, $J = 7.2$ Hz, 3H); MS m/z 209 (M^+).

9-(Toluene-4-sulfonyl)-1,3,4,6,7,8-hexahydro-2H-quinolizine 6e: IR (film) 2948, 1558, 1270 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ 7.71-7.68 (m, 2H), 7.27-7.24 (m, 2H), 3.12-3.04 (m, 4H), 2.84 (t, $J = 6.5$ Hz, 2H), 2.53 (t, $J = 6.2$ Hz, 2H), 2.40 (s, 3H), 1.83-1.77 (m, 2H), 1.74-1.68 (m, 2H), 1.60-1.55 (m, 2H); MS m/z 291 (M^+); HRMS calcd for $C_{16}H_{21}NSO_2$, 291.1315 (M^+), found 291.1304.

(3,4,6,7,8,9-Hexahydro-2H-quinolizin-1-yl)phosphonic acid diethyl ester 6f: IR (film) 2939, 1577, 1235 cm^{-1} ; 1H NMR ($CDCl_3$, 300 MHz) δ 4.06-3.96 (m, 4H), 3.07-3.01 (m, 4H), 2.80 (br s, 2H), 2.27-2.21 (m, 2H), 1.85-1.73 (m, 4H), 1.64-1.58 (m, 2H), 1.34-1.28 (m, 6H); MS m/z 273 (M^+); HRMS calcd for $C_{13}H_{25}NPO_3$, 274.1567 ($M + H$)⁺, found 274.1565.

2,3,4,6,7,8,9,10-Octahydropyrido[1,2-a]azepine-1-carboxylic acid ethyl ester 6g^[1]: 1H NMR ($CDCl_3$, 300 MHz) δ 4.10 (q, $J = 7.2$ Hz, 2H), 3.37-3.34 (m, 2H), 3.21 (t, $J = 5.8$ Hz, 2H), 3.15 (t, $J = 4.7$ Hz, 2H), 2.37 (t, $J = 6.3$ Hz, 2H), 1.81-1.77 (m, 2H),

1.65-1.57 (m, 6H), 1.25 (t, $J = 7.2$ Hz, 3H); MS m/z 223 (M^+).

(2R)-3,4,6,7,8,9-Hexahydro-2H-quinolizine-1-carboxylic acid ethyl ester 6h^[2]:

$[\alpha]_D^{30}$ -1.05 (c 1.2, EtOH); IR (film) 2932, 1680, 1593, 1282 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.11 (q, $J = 7.2$ Hz, 2H), 3.51 (dt, $J = 9.3, 7.0$ Hz, 1H), 3.24-3.14 (m, 2H), 3.10-3.04 (m, 2H), 2.44 (dt, $J = 15.8, 5.1$ Hz, 1H), 2.27-2.16 (m, 1H), 1.97-1.85 (m, 2H), 1.86-1.75 (m, 2H), 1.68-1.55 (m, 2H), 1.38-1.23 (m, 1H), 0.89 (t, $J = 7.2$ Hz, 3H); MS m/z 265 (M^+); HRMS calcd for $\text{C}_{16}\text{H}_{29}\text{NO}_2$ 266.2115, found 266.2119.

(2R,3S)-6-Ethyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylic acid ethyl

ester 6i: $[\alpha]_D^{17}$ +16.1 (c 1.2, CHCl_3); IR (film) 1678, 1593 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.11 (q, $J = 7.2$ Hz, 2H), 3.56 (dt, $J = 9.3, 7.1$ Hz, 1H), 3.24-3.17 (m, 1H), 3.09-3.01 (m, 3H), 2.39-2.19 (m, 2H), 1.97-1.86 (m, 2H), 1.65 (m, 1H), 1.53 (m, 1H), 1.40-1.23 (m, 6H), 1.17-1.10 (m, 2H), 0.95-0.86 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 169.3, 157.2, 84.6, 58.3, 58.0, 52.4, 35.4, 34.7, 32.7, 25.3, 22.3, 21.2, 19.2, 14.8, 14.1 12.0; MS m/z 265 (M^+); HRMS calcd for $\text{C}_{16}\text{H}_{28}\text{NO}_2$ 266.2115 ($M + \text{H}$)⁺, found 266.2113.

(2R,3S)-3-Ethyl-4-propyl-3,4,6,7,8,9-hexahydro-2H-quinolizine-1-carboxylic acid

ethyl ester 6j: $[\alpha]_D^{18}$ -139.2 (c 0.5, CHCl_3); IR (film) 1730, 1673, 1556 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.08 (q, $J = 7.0$ Hz, 2H), 3.35-3.10 (m, 3H), 2.90-2.81 (m, 2H), 2.37-2.23 (m, 2H), 1.74-1.64 (m, 3H), 1.57-1.52 (m, 4H), 1.34-1.16 (m, 7H), 0.94-0.88 (m, 6H); MS m/z 265 (M^+); HRMS calcd for $\text{C}_{17}\text{H}_{30}\text{NO}_2$ 280.2271 ($M +$

H)⁺, found 280.2277.

(2S)-4-(3,4-Dimethoxyphenyl)-3,4,6,7,8,9-hexahydro-2H-quinolizine-1-carboxylic acid ethyl ester 6k: $[\alpha]_D^{19} +44.3$ (*c* 1.4, CHCl₃); IR (film) 2939, 1669, 1549 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 6.83-6.81 (m, 1H), 6.72-6.69 (m, 2H), 4.20 (br s, 1H), 4.11-4.06 (m, 2H), 3.87 (s, 3H), 3.86 (s, 3H), 3.21-3.15 (m, 4H), 2.57-2.45 (m, 1H), 2.10-1.69 (m, 7H), 1.24 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 168.8, 156.4, 148.9, 147.9, 135.1, 118.3, 111.0, 109.3, 91.5, 62.9, 58.5, 55.9, 55.8, 49.6, 28.6, 27.6, 23.4, 20.4, 19.2, 14.7; ESI-MS *m/z* 346 (M + H)⁺; HRMS calcd for C₂₀H₂₈NO₄ 346.2013 (M + H)⁺, found 346.2013.

(2S)-[4-(3,4-Dimethoxyphenyl)-3,4,6,7,8,9-hexahydro-2H-quinolizin-1-yl]phenyl-methanone 6n: $[\alpha]_D^{21} +144.9$ (*c* 1.2, CHCl₃); IR (film) 2933, 1712, 1595, 1516 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.49-7.46 (m, 2H), 7.40-7.30 (m, 3H), 6.89-6.86 (m, 1H), 6.79-6.74 (m, 2H), 4.29 (t, *J* = 3.9 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 3.29-3.00 (m, 4H), 2.32-2.19 (m, 2H), 2.03-1.96 (m, 1H), 1.88-1.64 (m, 5H); ¹³C NMR (CDCl₃, 75 MHz) δ 194.7, 158.6, 149.1, 148.2, 143.9, 135.0, 129.3 (2C), 127.9 (2C), 127.6 (2C), 118.4, 111.1, 109.3, 102.5, 63.5, 55.9, 49.5, 29.4, 28.8, 23.2, 22.6, 20.4; ESI-HRMS calcd. for C₂₄H₂₈NO₃ 378.2070 (M + H)⁺, found 378.2064.

(2S,3R,1'R)-3-[Benzyl-(1-phenylethyl)amino]-2-ethylhexanoic acid *tert*-butyl ester 8. To a stirred solution of (+)-*N*-benzyl- α -methylbenzylamine (10.5 g, 50 mmol) in 30 mL of dry toluene was slowly added *n*-BuLi (1.6 M, 31 mL) at 0 °C. The

resultant solution was stirred for 1 h before been cooled to -78 °C. Then *tert*-butyl 2-ethyl-2-hexenoate (3.96 g, 20 mmol) in 20 mL dry toluene was added slowly. The mixture was stirred for 1 h at -78 °C, then warmed to -40 °C over 1 h and maintained for 1 h before it was re-cooled to -78 °C. After pre-cooled THF (-78 °C, 200 mL) was added quickly, the solution was stirred for another 30 min before a pre-cooled solution of 2,6-di-*tert*-butyl-4-methylphenol (18 g, 100 mmol) in THF (-78 °C, 20 mL) was added in one portion. After it was stirred for a further 10 min at -78 °C, the solution was warmed to room temperature over 1 h. Evaporation of the mixture left a residue which was partitioned between brine and Et₂O and the organic layer was dried over MgSO₄, removed in vacuum. The residue was purified via chromatograph to give 5.5 g (67%) of **8** as a colorless oil. $[\alpha]_D^{15} +43$ (*c* 1.25, CHCl₃); IR (film) 2966, 2874, 1725, 1455 cm⁻¹; ¹H NMR (CDCl₃, 300 MHz) δ 7.35-7.21 (m, 10H), 3.91 (dq, *J* = 14, 3.5 Hz, 3H), 2.82 (m, 1H), 2.21(m, 1H), 1.52-1.23 (m, 4H), 1.41 (s, 9H), 1.26 (d, *J* = 6.9 Hz, 3H), 0.94 (m, 2H), 0.81 (t, *J* = 7.2 Hz, 3H), 0.66 (t, *J* = 7.2 Hz, 3H); ¹³C NMR (CDCl₃, 75 MHz) δ 175.1, 144.8, 142.7, 128.2, 128.0, 127.9, 127.8, 127.0, 126.7, 126.3, 79.8, 60.1, 51.2, 32.7, 28.0, 24.9, 21.1, 20.0, 14.3, 11.9; EI-HRMS calcd. for C₂₇H₃₉NO₂ 409.2474 (M⁺), found 409.2455.

(2*S*,3*R*,1'*R*)-3-[Benzyl(1-phenylethyl)amino]-2-ethylhexan-1-ol 9. A mixture of **8** (5.5 g, 13.4 mmol) and LiAlH₄ (1.5 g) in dry THF (60 mL) was refluxed for 12 h. Then the reaction was quenched with 15% NaOH (1 mL) and filtered. The filtrate was concentrated and purified via chromatography to give **9** as a viscous oil. $[\alpha]_D^{20} -40.6$ (*c* 1.23, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 7.44-7.21 (m, 10H), 3.95-3.90 (m,

3H), 3.72 (d, $J = 13.5$ Hz, 1H), 3.43-3.39 (m, 1H), 3.00 (dt, $J = 10.2, 3.6$ Hz, 1H), 2.94-2.88 (m, 2H), 1.72-1.70 (m, 1H), 1.61-1.50 (m, 2H), 1.40-1.22 (m, 5H), 0.97 (t, $J = 7.1$ Hz, 3H), 0.86 (t, $J = 7.4$ Hz, 3H); ESI-HRMS calcd. for $C_{23}H_{34}NO$ 340.2635 ($M + H$)⁺, found 340.2639.

(1*R*,2*S*)-2-Chloromethyl-1-propylbutylamine 10. To a stirred solution of **9** (0.45 g, 1.33 mmol) in 4 mL dry $CHCl_3$ at 0 °C was added slowly $SOCl_2$ (0.2 mL, 2.66 mmol). Then the mixture was refluxed for 1 h. Evaporation of the solvent in vacuum gave the desired product as a hydrochloride salt, which was dissolved in MeOH (5 mL), and hydrogenated with 20% $Pd(OH)_2/C$ (200 mg) at 50 atm, 40 °C for 48 h. The solution was filtered, and the filtrate was concentrated in vacuum to give **10** as its hydrochloride salt, which was used directly for next step due to its instability.

(2*R*,3*R*)-6-Ethyl-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylic acid ethyl ester 11. Following the procedure for Table 1 as mentioned above, **11** was prepared from **1a** and **10** in 80% yield. $[\alpha]_D^{18}$ -40.3 (c 0.75, $CHCl_3$); 1H NMR ($CDCl_3$, 300 MHz) δ 4.22-4.04 (m, 2H), 3.60-3.52 (m, 1H), 3.39-3.00 (m, 5H), 2.79-2.77 (m, 1H), 2.06-1.89 (m, 2H), 1.46-1.23 (m, 10H), 0.97-0.91 (m, 6H); ESI m/z 266 ($M + H$)⁺; HRMS calcd for $C_{16}H_{28}NO_2$ 266.2115 ($M + H$)⁺, found 266.2113.

(2*R*,3*R*,5*R*)-6-Ethyl-5-propyloctahydroindolizine-8-carboxylic acid ethyl ester 12b. A mixture of **11** (40 mg, 0.15 mmol) in glacial acid (1 ml) was hydrogenated over platinum dioxide (8 mg) at room temperature and 1 atm for 2 h. After the

volatiles was removed, the residue was treated with aqueous NaHCO_3 , and extracted with CH_2Cl_2 , dried over MgSO_4 . The solution was concentrated to give the desired product as a mixture of two diastereoisomers **12a** and **12b**, which was dissolved in anhydrous EtOH containing catalytic amount of NaOEt, and refluxed for 5 h before it was quenched with aqueous NaHCO_3 . The aqueous layer was extracted with EtOAc, and dried over MgSO_4 . The solution was concentrated and the residue was chromatographed on silica gel to afford 32 mg (81%) of **12b** as a single isomer. $[\alpha]_{\text{D}}^{18} -27.3$ (*c* 0.5, CHCl_3); IR (film) 2962, 1734, 1261 cm^{-1} ; ^1H NMR (CDCl_3 , 300 MHz) δ 4.13-4.04 (m, 2H), 3.07 (d, $J = 11.4$ Hz, 1H), 2.90 (t, $J = 8.1$ Hz, 1H), 2.09-1.82 (m, 4H), 1.75-1.06 (m, 15H), 0.92-0.86 (m, 6H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 174.4, 67.1, 60.1, 54.5, 54.1, 50.9, 42.3, 37.3, 32.4, 28.9, 20.9, 19.8, 17.7, 14.4, 14.3, 12.8; ESI-HRMS calcd. for $\text{C}_{16}\text{H}_{29}\text{NO}_2$ 267.2193 (M^+), found 267.2190.

Indolizidine 223A 14. A mixture of **12b** (30 mg, 0.112 mmol) and LiAlH_4 (20 mg) in dry THF (1 mL) was stirred at room temperature for 1 h before it was quenched with 15% NaOH (0.15 mL). The mixture was filtered and the filtrate was dried over MgSO_4 and concentrated to give the crude alcohol **13** (91% yield), which was used directly in the next step.

To a solution of oxalyl chloride (0.23 mmol) in 1 mL dry CH_2Cl_2 was added dropwise a solution of DMSO (0.33 mmol) in 0.5 mL of CH_2Cl_2 at -78°C . After the solution was stirred for 15 min, a solution of the above alcohol in 0.5 mL of CH_2Cl_2 was added slowly, and stirred for another 15 min. After Et_3N (0.56 mmol) was added, the stirring was continued for 5 min and then the solution was allowed to warm to

room temperature. The mixture was partitioned between water and CH₂Cl₂. The combined organic layers were washed with water and dried over MgSO₄. Evaporation on vacuum gave the crude aldehyde.

To a solution of Ph₃P⁺CH₃I⁻ (132 mg, 0.33 mmol) in THF (2 mL) was added NaHMDS (2.0 M, 0.15 mL, 0.31 mmol) at -78 °C. After 30 min, a solution of the above crude aldehyde in 1 mL of THF was added. The solution was stirred for 1 h, then warmed up to 0 °C before water was added to quench the reaction. The mixture was extracted with Et₂O, washed with brine, and dried over MgSO₄. Flash chromatography on silica gel gave the crude olefin, which was directly hydrogenated on 10% Pd-C (5 mg) in 1 mL EtOAc at 1 atm and room temperature for 2 h. Removal of the solvent and purification on silica gel gave 11 mg (49% yield from **13**) of **Indolizidine 223A** as a volatile oil. Data for its DCl salt: $[\alpha]_D^{15} -38.0$ (*c* 0.30, CHCl₃); ¹H NMR (300 MHz, D₂O) δ 3.58 (dt, *J* = 9.6, 2.7 Hz, 1H), 3.15 (dt, *J* = 11.0, 3.6 Hz, 1H), 2.95 (q, *J* = 9.1 Hz, 1H), 2.86 (dt, *J* = 11.5, 6.0 Hz, 1H), 2.28 (m, 1H), 2.05 (dd, *J* = 13.2, 2.5 Hz, 1H), 1.97-1.88 (m, 3H), 1.74-1.37 (m, 7H), 1.22-1.12 (m, 4H), 0.88-0.80 (m, 9H).