Synthesis of (±)-Desethylrhazinol using a tandem radical addition-cyclization process.

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General Information

Unless otherwise stated, all reactions were carried out in dry glassware under an argon atmosphere using standard techniques for the manipulation of solvents and reagents. CH₂Cl₂, triethylamine and DMF were distilled from CaH₂, THF was distilled from Na/Benzophenone. All other starting materials and solvents are commercially available and were used without further purification. Chromatography was performed on Macherey – Nagel silica gel 230 – 400.

¹H-NMR and ¹³C-NMR were recorded in CDCl₃ (7.27 ppm and 77.23 ppm respectively) in a 300MHz spectrometer employing (CH₃)₄Si as internal standard.

1-(pent-4-enyl)-1H-pyrrole-2-carbaldehyde (5b): To a suspension at 60% of NaH (0.684 g, 17.35 mmol) in N,N-dimethylformamide at 0 °C, a solution of pyrrole-2-carboxaldehyde (0.75 g, 7.89 mmol) in DMF was added. The reaction was then warmed to room temperature and stirred for 40 minutes. The reaction mixture was then cooled to 0 °C and 5-bromopentene (8b) (1.29 g, 8.68 mmol) was added slowly. The reaction was then warmed to room temperature and was further stirred for 30 minutes. The reaction was quenched with saturated NH₄Cl and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous NaHCO₃ and brine, dried with Na₂SO₄ and concentrated in vacuo. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 6:1) to afford the product as a yellow oil in 85% yield (2.4 g, 14.74 mmol). ¹H-NMR δH (300 MHz, CDCl₃) 2.13 – 1.78 (4 H, m), 4.38 – 4.25 (2 H, m), 5.12 – 4.94 (2 H, m), 5.79 (1 H, ddt, J 16.8, 10.2, 6.5), 6.21 (1 H, dd, J 3.8, 2.7), 6.98 – 6.86 (2 H, m), 9.53 (1 H, d, J 0.9). ¹³C-NMR δC (75 MHz, CDCl₃) 179.19, 137.42, 131.27, 124.79, 115.38, 109.45, 77.42, 77.00, 76.58, 48.44, 30.45. IR (CHCl₃, cm⁻¹) νmax: 3077, 2928, 2854, 2805, 2767, 1664 (CO), 1405, 1322, 763, 747. m/z (EI) 163 (M⁺, 22%), 146 (10), 134 (100), 108 (32), 97 (30), 81 (42), 41 (30), 28 (12). HRMS (FAB+) m/z Calculated for: C₁₃H₁₃NO (M⁺) 163.0997, (found) 163.0990.
**Ethyl 3-(3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (4b):** In a round bottom flask, 1-(pent-4-enyl)-1H-pyrrole-2-carbaldehyde (0.65 g, 3.98 mmol) and the ethyl 2-(ethoxycarbonothioylthio) acetate (0.99 g, 4.77 mmol), prepared as previously reported, were dissolved in 1,2-dichloroethane. The mixture was degassed with argon in an ultrasound bath. The reaction was heated to reflux temperature and the lauroyl peroxide (2.06 g, 5.18 mmol) was added portionwise every hour, for 7 hours. The reaction mixture was concentrated in vacuo and purified by flash column chromatography on basic alumina (hexanes:ethyl acetate 4:1) to afford the product as a brown oil in 69% yield (0.683 g, 2.74 mmol).

\[ \text{\textsuperscript{1}H-NMR } \delta (300 \text{ MHz, CDCl}_3) 1.26 (3 \text{ H, t, } J 7.1), 1.47 (1 \text{ H, m}), 2.46 – 1.8 (6 \text{ H}), 2.41 (2 \text{ H, m}), 2.9 (1 \text{ H, m}), 4.15 (2 \text{ H, m}), 4.54 (1 \text{ H, m}), 6.11 (1 \text{ H, m}), 6.89 (1 \text{ H, m}), 9.42 (1 \text{ H, s}). \text{\textsuperscript{13}C-NMR } \delta (75 \text{ MHz, CDCl}_3) 178.44, 173.08, 143.33, 130.89, 124.3, 107.35, 107.35, 60.35, 45.47, 33.7, 31.32, 29.55, 25.11, 21.47, 14.02. \text{IR (CHCl}_3 \text{ cm}^{-1} \nu_{\text{max}}: 2977, 2933, 2862, 1732 (\text{CO}), 1658 (\text{CO}), 1489, 1321, 1177, 1037, 784. \text{m/z (El)} 249 (M^+, 70\%), 220 (15), 176 (25), 161 (100), 148 (95), 134 (20), 120 (22), 118 (15), 83 (10), 55 (11), 41 (18). \text{HRMS (FAB+)} \text{m/z Calculated for: C}_{14}H_{20}NO_3 (M+1) 250.1443, (found) 250.1448.**

**Ethyl 3-(3-formyl-1-ido-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (11):** To a solution of 4b (0.5 g, 2.008 mmol), in CHCl\textsubscript{3} at 0 °C, silver trifluoroacetate (0.488 g, 2.21 mmol) and iodine (0.561 g, 2.21 mmol) were added, after that, the reaction was warmed to room temperature and stirred for 16 h. The reaction was then quenched with 5 mL of 20% aqueous Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5} and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated NaHCO\textsubscript{3} and brine, dried with Na\textsubscript{2}SO\textsubscript{4} and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 4:1) to afford the product as a yellow oil in 83% yield (0.62 g, 1.66 mmol).

\[ \text{\textsuperscript{1}H-NMR } \delta (300 \text{ MHz, CDCl}_3) 1.27 (3 \text{ H, t, } J 7.16), 2.24 – 1.72 (6 \text{ H}), 4.45 (2 \text{ H, m}), 2.93 (1 \text{ H, m}), 4.04 (1 \text{ H, m}), 4.15 (2 \text{ H, q, } J 7.2), 4.66 (1 \text{ H, m}), 7.02 (1 \text{ H, s}), 9.41 (1 \text{ H, s}). \text{\textsuperscript{13}C-NMR } \delta (75 \text{ MHz, CDCl}_3) 178.08, 172.88, 143.32, 132.64, 130.76, 62.53, 60.54, 46.18, 32.63, 32.29, 29.67, 28.15, 22.73, 18.31, 14.25. \text{IR (CHCl}_3 \text{ cm}^{-1} \nu_{\text{max}}: 2977, 2866, 2789, 1731 (\text{CO}), 1660 (\text{CO}), 1468, 1396, 1312, 1171, 1036, 871, 660. \text{m/z (El)} 375 (M^+, 15\%), 302 (20), 287 (25), 274 (75), 248 (100), 220 (10), 174 (55), 146 (22), 118 (20), 97 (15), 85 (18), 57 (30), 43 (15). \text{HRMS (FAB+)} \text{m/z Calculated for: C}_{14}H_{17}INO_3I (M+1) 376.0410, (found) 376.0413.**
Ethyl 3-(1-(2-(tert-butoxycarbonylamino)phenyl)-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (13): In a round bottom flask 11 (0.55 g, 1.466 mmol), tert-butyl-N-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-carbamate (12) (0.71 g, 2.2 mmol), K$_3$PO$_4$ (1.246 g, 5.87 mmol), Pd$_2$(dba)$_3$ (0.068 g, 0.074 mmol) and SPhos (0.054 g, 0.132 mmol) ligand, were dissolved in THF and degassed H$_2$O as solvent system. The resulting solution was stirred at room temperature for 1 h and then at 40 °C for 36 h. The reaction was quenched with saturated aqueous NH$_4$Cl and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed consecutively with saturated aqueous NaHCO$_3$ and brine, dried with Na$_2$SO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 4:1) to afford the product as a pale yellow oil in 86% yield (0.554 g, 1.26 mmol).

$^1$H-NMR $\delta$H (300 MHz, CDCl$_3$) 1.15 (3 H, t, J 7.2), 1.49 (9 H, s), 1.76 – 1.55 (3 H), 1.92 (1 H, m), 2.14 – 2.01 (3 H), 3.05 (1 H, m), 3.97 (2 H, m), 4.41 (2 H, m), 6.48 (1 H, bs), 6.87 (1 H, s), 7.04 (1 H, dt, J 7.6, 1.6), 7.14 (1 H, dd, J 7.8, 1.8), 7.31 (1 H, dt, J 8.4, 1.5), 8.09 (1 H, d, J 8.4), 9.51 (1 H, s). $^{13}$C-NMR $\delta$C (75 MHz, CDCl$_3$) 178.81, 172.72, 152.72, 140.9, 136.3, 131.01, 130.42, 124.85, 124.95, 124.27, 122.81, 119.4, 118.58, 80.53, 60.32, 45.99, 32.05, 31.46, 28.57, 28.31, 24.24, 19.73, 14.07. IR (CHCl$_3$ cm$^{-1}$) $\nu$max: 3227 (NH), 3105, 2979, 2940, 1722 (CO), 1653 (CO), 1526, 1446, 1308, 1237, 1156, 756. m/z (El) 440 (M$^+$, 30%), 384 (100), 339 (40), 297 (31), 253 (90), 237 (47), 211 (43), 209 (20), 181 (15), 57 (75), 41 (20), 28 (18). HRMS (FAB+) m/z Calculated for: C$_{25}$H$_{33}$N$_2$O$_5$ (M+1) 441.2389, (found) 441.2394.

Des-ethylrhazinal (3): To a solution of 13 (0.15 g, 0.341 mmol) in methanol, Ba(OH)$_2$·8H$_2$O (2.16 g, 6.82 mmol) was added. The resulting solution was stirred for 3 h at room temperature. Aqueous 1N HCl was added to the reaction mixture until pH 2, and the resulting solution was extracted with ethyl acetate. The combined organic extracts were washed consecutively with H$_2$O and brine, dried with Na$_2$SO$_4$ and concentrated. The residue was dried under high vacuum and then dissolved in CH$_2$Cl$_2$ (50 mL) containing trifluoroacetic acid (6 mL). The reaction was stirred at room temperature for 1 h, following that time, the volatiles were evaporated in vacuo to afford an oily residue that was used in the next step without further purification. A solution of latter crude residue in CH$_2$Cl$_2$ (50 mL) was added via syringe pump over 12 h to a stirred solution of O-(7-azabenzotriazole-1-yl)-N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.389 g, 1.023
mmol); and N, N-diisopropylethylamine (0.191 mL, 1.364 mmol) in DMF (100 mL) and CH₂Cl₂ (50 mL). Once the addition was completed, the reaction was stirred for additional 4 h and then extracted with ethyl acetate. The combined organic extracts were washed consecutively with aqueous 5% HCl, aqueous 1 N NaOH, saturated aqueous NaHCO₃, brine and then dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 1:1) to afford the product as pale yellow solid in 29% yield (0.029 g, 0.099 mmol). ¹H-NMR δH (300 MHz, CDCl₃) 2.02 – 1.66 (4 H, m), 2.38 – 2.09 (4 H, m), 2.74 (1 H, m), 3.98 (1H, ddd, J 14.2, 12.0, 2.1), 4.78 (1H, dd, J 14.7, 5.7), 6.63 (1 H, s), 6.92 (1 H, bs), 7.48 – 7.2 (4 H), 9.43 (1 H, s). ¹³C-NMR δC (75 MHz, CDCl₃) 178.89, 176.62, 139.99, 137.68, 136.69, 131.88, 130.97, 129.25, 128.18, 127.86, 124.05, 120.49, 45.96, 33.53, 32.44, 32.06, 29.69, 27.04. IR (CHCl₃ cm⁻¹) νmax: 3207 (NH), 2976, 1718 (CO), 1661 (CO), 1442, 1248, 1031, 758. m/z (EI) 294 (M⁺, 100%), 265 (25), 251 (40), 237 (85), 223 (45), 209 (31), 181 (30), 168 (15), 154 (18), 72 (22), 57 (25), 28 (45). HRMS (FAB+) m/z Calculated for: C₁₈H₁₉N₂O₂ (M⁺1) 295.1447, (found) 295.1436.

**1-(4-methylenehexyl)-1H-pyrrole-2-carbaldehyde (5a):** To a suspension of NaH (0.46 g, 11.46 mmol) in N,N-dimethylformamide at 0 °C, a solution of pyrrole-2-carboxaldehyde (0.545 g, 5.73 mmol) in DMF, was added. The reaction was then warmed to room temperature and stirred for 40 minutes. The reaction mixture was then cooled to 0 °C and a solution of the corresponding mesylate (8a) (1.21 g, 6.3 mmol) in DMF was slowly added. The reaction was then warmed to room temperature and was stirred for additional 30 minutes. The reaction was quenched with saturated NH₄Cl and the resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous NaHCO₃ and brine, dried with Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 6:1) to afford the product as an orange oil in 89% yield (0.97 g, 5.1 mmol). ¹H-NMR δH (300 MHz, CDCl₃) 1.01 (3 H, t, J 7.5), 1.01 (3 H, t, J 7.5), 1.85 – 1.65 (2 H, m), 2.1 – 1.9 (4 H, m), 4.3 (2 H, t, J 7.2), 4.73 (2 H, m), 6.22 (1 H, m), 6.94 – 6.91 (2 H, m), 9.53 (1 H, d, J 0.9). ¹³C-NMR δC (75 MHz, CDCl₃) 179.22, 150.09, 131.31, 124.81, 109.45, 108.3, 48.75, 32.88, 29.69, 29.24, 28.67, 12.28. IR (CHCl₃ cm⁻¹) νmax: 2965, 2931, 1662 (CO), 1481, 1405, 1369, 1241, 1074, 894. m/z (EI) 191 (M⁺, 18%), 162 (25), 149 (45), 111 (25), 71 (62), 57 (100), 55 (70), 43 (60), 29 (25).
**Ethyl 3-(8-ethyl-3-formyl-5,6,7,8-tetrahydroindolizin-8-yl)propanoate (4a):** In a round bottom flask, 1-(4-methylenehexyl)-1H-pyrrole-2-carbaldehyde (5a) (0.2 g, 1.045 mmol) and ethyl 2-(ethoxycarbonothioylthio) acetate (0.24 g, 1.15 mmol) were dissolved in 1,2-dichloroethane. This mixture was degassed with argon in an ultrasound bath. The reaction was heated to reflux temperature and the lauroyl peroxide (0.54 g, 1.36 mmol) was added portionwise every hour for 7 hours. The reaction mixture was concentrated and purified by flash column chromatography on basic alumina (hexanes:ethyl acetate 4:1) to afford the product as yellow oil in 71% yield (0.205 g, 0.74 mmol). $^1$H-NMR $\delta$ (300 MHz, CDCl$_3$), 0.83 (3 H, t, $J$, 7.5), 1.22 (3 H, t, $J$, 6.9), 1.67 (4 H, m), 1.96, (4 H, m), 2.2 (2 H, m), 4.09 (4 H, q, $J$, 6.9), 4.34 (2 H, t, $J$, 4.2), 6.04 (1 H, d, $J$, 4.2), 9.4 (1 H, s). $^{13}$C-NMR $\delta$ (75 MHz, CDCl$_3$) 178.45, 173.51, 130.79, 124.59, 107.59, 60.46, 45.4, 38.13, 34.81, 33.26, 29.8, 26.69, 28.89, 19.6, 14.16, 8.53. IR (CHCl$_3$ cm$^{-1}$) $\nu$$_{max}$: 2935, 2872, 1733 (CO), 1658 (CO), 1487, 1440, 1322, 1176, 1040, 783. $m/z$ (EI) 277 (M$^+$, 28%), 248 (40), 204 (15), 176 (100), 146 (28), 132 (18), 118 (12), 80 (10), 29 (18).
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