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Concise synthesis of (±)-rhazinilam

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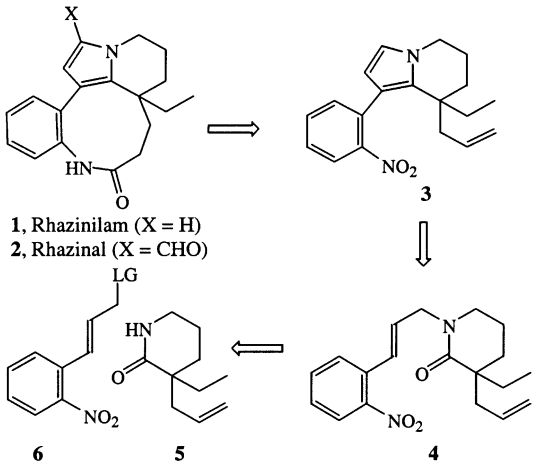
Abstract—2-Piperidone has been converted into (±)-rhazinilam in nine steps in 8% overall yield. The key transformation involves the conversion of the lactam **5** into the annulated pyrrole derivative **3** via the thiophenyl imine **8**. © 2001 Published by Elsevier Science Ltd.

(−)-Rhazinilam **1** has been isolated from a number of plant sources such as *Rhazya stricta* Decaisne,[1] *Melodinus australis*[2] and *Kopsia singapurensis*., Scheme 1.[3] Since the original elucidation of structure[4,5] and synthesis[6] of **1** there has been increasing interest in this alkaloidal structural type because of its ability to mimic the cellular effects of paclitaxel.[7] Much synthetic work has been devoted to structural analogs of **1**,[8] although recently Sames reported a new synthesis of (±)-**1**[9] that involves the use of a stoichiometric platinum complex dehydrogenation reaction to functionalize a *gem*-diethyl group. The synthesis of (±)-rhazinal **2** has also been recently described.[10]

The strategy depicted in Scheme 1 has the *gem*-alkyl groups on the piperidine ring differentiated early in the synthesis as **5**, and introduced by alkylation of the corresponding piperidone. *N*-Alkylation of **5** with **6** leads to **4** which is in the correct oxidation state to be directly converted into **3**. Conversion of the terminal alkene of **3** into a carboxyl group, followed by reduction of the nitro group to an amine and lactamization provides rhazinilam. While the synthesis of **5** described here is that of the racemate, reported adaptations of chiral oxazolidinone technology[11] could be used to synthesize **5** in an enantioenriched form.[12]



Scheme 1.

The *gem*-dialkyl piperidone **5** was synthesized by stepwise alkylation of 2-piperidone, Scheme 2. Treatment of 2-piperidone with *n*-BuLi (2.01 equiv., to form the dianion), followed by excess ethyl iodide gave **7** (90%).[13] It was found that this same protocol did not work satisfactorily for the allylation, and in situ protection of the amide was needed. Treatment of **7** with *n*-BuLi/Me_3SiCl, followed by $LiNPr^i_2$ and a large excess of allyl bromide gave **5** (61%) in reasonable reproducible yields.

The next step requires annulation of a pyrrole ring onto an amide. While the Grigg methodology[14] is applicable to this problem (see Ref. 9), it would involve reduction of the amide to an imine. Consequently, we examined the direct conversion of the lactam **5** into the pyrrole **3** without changing the oxidation state of **5**. After unsuccessfully experimenting with various iminoethers derived from **5**, it was found that treatment of the thiophenyl imino ether **8** with 2-nitrocinnamyl bromide, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave **3** (71%) as a yellow crystalline solid. This sequence of transformations provided **3** in four steps in an overall yield of 32%.

To complete the synthesis, **3** was converted into the alcohol **9** using standard hydroboration reaction conditions followed by oxidative work-up. Oxidation of **9** to the aldehyde **10** was accomplished with pyridine/sulfur trioxide/dimethylsulfoxide.[15] Attempts to oxidize **10** to the acid **11** using sodium chlorite also caused oxidation of the

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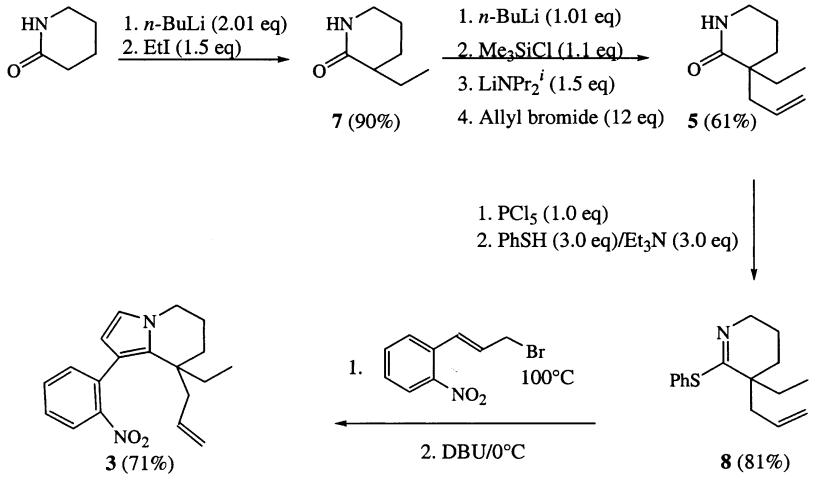
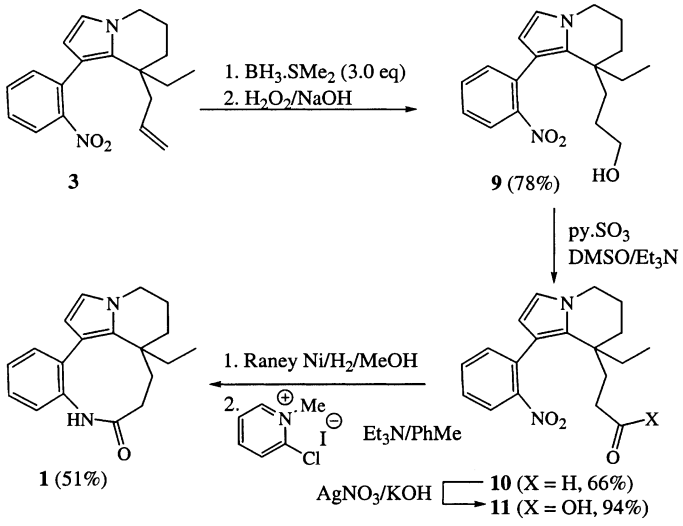


Scheme 2.



Scheme 3.

pyrrole ring,[16] whereas silver nitrate under alkaline conditions (Fehling's solution) converted **10** into **11** without any complications. Finally, Raney nickel reduction of the nitro group in **11** and treatment of the crude amino acid with 2-chloro-1-methylpyridinium iodide/NEt_3/PhMe (Mukaiyama conditions)[17] gave (±)-rhazinilam **1** in 51% yield from **11** (Scheme 3).

The synthesis of **1** proceeds through nine steps in 8% overall yield.

1. Experimental

1.1. General

Melting points were taken on a Thomas–Hoover capillary tube apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet FT-IR spectrophotometer neat unless otherwise indicated. ^{1}H NMR spectra were recorded on a General Electric QE-300 spectrometer at 300 MHz in the indicated solvent and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. ^{13}C NMR spectra were recorded on a General Electric QE-300 spectrometer at 75 MHz in the solvent indicated and are reported in ppm relative to tetramethylsilane and referenced internally to the residually protonated solvent. Mass spectra were obtained on a VG ZAB2E or a Finnigan TSQ70. Routine monitoring of reactions was performed using Merck 60 F_{254} silica gel, aluminum-backed TLC plates. PLC was performed using Merck 60 F_{254} silica gel, glass supported plates. Flash column chromatography was performed with the indicated eluents on Merck 60H F_{254} silica gel.

Solvents and commercial reagents were purified in accordance with Perrin and Armarego or used without further purification.

1.1.1. (±)-3-Ethyl-2-piperidone 7. A solution of *n*-butyl lithium (2.14 M in hexanes, 21.4 mL, 45.7 mmol) was added to a degassed solution of freshly distilled 2-piperidone

(2.25 g, 22.7 mmol) in anhydrous THF (50 mL) at −78°C under an atmosphere of argon. The resulting pale yellow solution was warmed to 0°C and stirred for 1 h, and ethyl iodide (2.73 mL, 34.1 mmol) was added dropwise. After stirring the solution for a further 45 min. at 0°C the mixture was quenched with saturated aqueous ammonium chloride (10 mL), and extracted with $CHCl_3$ (3×20 mL). The combined extracts were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), and evaporated in vacuo to give a yellow oil. The crude oil was purified by flash column chromatography (SiO_2, 100% EtOAc) to yield a pale yellow crystalline solid. R_f 0.3 (100% EtOAc). Bulb to bulb distillation (125°C, 0.5 mmHg) afforded **7** as a white crystalline solid (2.60 g, 90%.). Mp 62–63°C (hexanes). IR (thin film) 3287, 3203, 3074, 2957, 2873, 1672 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (1H, br s), 3.28–3.21 (2H, m), 2.20–2.11 (1H, m), 1.95–1.41 (6H, m), 0.90 (3H, t, J=7.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.2, 42.2, 25.4, 24.3, 21.2, 11.2 ppm. HRMS calcd for $C_7H_{14}NO$ (MH^+) 128.1075. Found 128.1076.

1.1.2. (±)-3-Ethyl-3-allyl-2-piperidone 5. A solution of *n*-butyl lithium (1.41 M in hexanes, 14.6 mL, 20.6 mmol) was added to a degassed solution of **7** (2.60 g, 20.4 mmol) in anhydrous THF (60 mL) at −78°C under an atmosphere of argon. The resulting canary yellow solution was warmed to 0°C and stirred for 1.25 h, and freshly distilled trimethylsilyl chloride (3.77 mL, 22.5 mmol) was added in one portion. After stirring the mixture for a further 1.75 h at 0°C a solution of lithium diisopropylamide [prepared by the addition of a solution of *n*-butyl lithium in hexanes (1.41 M, 21.6 mL, 30.4 mmol) to a solution of distilled diisopropylamine (4.29 mL, 30.6 mmol) in THF (15 mL) at −78°C, followed by stirring at 0°C for 20 min] was added in one portion, and the resulting solution stirred at 0°C for 45 min. After cooling the mixture to −78°C, freshly distilled allyl bromide (21 mL, 250 mmol) was added dropwise. The mixture was warmed to 0°C and stirred for a further 1.25 h. The mixture was quenched with saturated aqueous NH_4Cl (20 mL), extracted with $CHCl_3$ (3×150 mL), and the combined extracts washed with 1 M aqueous HCl (2×15 mL), water (20 mL), and saturated aqueous NaCl (20 mL), and dried (Na_2SO_4). Evaporation of the extracts in vacuo gave a yellow oil. Purification of the oil by flash column chromatography (SiO_2, 50% EtOAc in hexanes) gave **5** as a pale yellow oil (2.09 g, 61%). R_f 0.2 (50% EtOAc in hexanes.). IR (neat) 3204, 3071, 2939, 2869, 1650 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 6.48 (1H, br s), 5.82–5.69 (1H, m), 5.06–5.00 (2H, m), 3.24–3.20 (2H, m), 2.45 (1H, dd, J=13.7, 8.1 Hz), 2.15 (1H, dd, J=13.7, 6.6 Hz), 1.79–1.63 (5H, m), 1.52–1.40 (1H, m), 0.86 (3H, t, J=7.6 Hz.). ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7, 134.6, 117.8, 44.8, 42.8, 42.7, 31.0, 28.6, 19.7, 8.6 ppm. HRMS calcd for $C_{10}H_{18}NO$ (MH^+) 168.1388. Found 168.1397.

1.1.3. (±)-3-Ethyl-3-allyl-2-thiophenyl-2-piperideine 8. Phosphorous pentachloride (0.743 g, 3.57 mmol) was added to a solution of **5** (0.587 g, 3.51 mmol) in anhydrous toluene (3.5 mL) under an atmosphere of argon. The resulting pale yellow solution was heated at reflux for 3 h, after which time it was cooled to room temperature and concentrated in vacuo. The dark yellow colored residue was redissolved in anhydrous toluene (5 mL) and solution evaporated in vacuo. The resulting residue was dissolved in anhydrous THF (3.5 mL), to which was subsequently added distilled triethylamine (2.44 mL, 17.5 mmol) and distilled thiophenol (1.8 mL, 18 mmol.). After stirring the mixture for 2.5 h. at room temperature the solution was cooled to 0°C, saturated aqueous $NaHCO_3$ (5 mL) was added, and the mixture extracted with EtOAc (3×15 mL). The combined extracts were washed with 1.25 M aqueous NaOH (4×10 mL), water (15 mL), and saturated aqueous NaCl (15 mL.), and dried (Na_2SO_4). Evaporation of the extracts in vacuo gave a green oil, which was purified by flash column chromatography (SiO_2, 5% EtOAc in hexanes) to give **8** as a pale yellow oil (0.733 g, 81%). R_f 0.63 (25% EtOAc in hexanes). IR (neat) 2964, 2934, 2855, 1627 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.51–7.48 (2H, m), 7.41–7.34 (3H, m), 5.97–5.85 (1H, m), 5.23–5.15 (2H, m), 3.53–3.48 (2H, m), 2.67 (1H, dd, J=14.0, 6.3 Hz), 2.32 (1H, dd, J=14.0, 8.3 Hz), 1.96–1.86 (1H, m), 1.75–1.56 (5H, m), 1.04 (3H, t, J=7.4 Hz.). ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7, 135.3, 134.2, 130.6, 128.6, 128.0, 118.0, 51.2, 45.2, 44.7, 32.5, 29.1, 20.0, 8.7 ppm. HRMS calcd for $C_{16}H_{22}NS$ (MH^+) 260.1473. Found 260.1478.

1.1.4. 2-Nitrocinnamyl bromide. Triphenylphosphine (5.53 g, 21.1 mmol) and carbon tetrabromide (7.00 g, 21.1 mmol) were added sequentially to a solution of 2-nitrocinnamyl alcohol (2.52 g, 14.0 mmol) in anhydrous CH_2Cl_2 (50 mL) at 0°C. The dark brown solution was stirred for one hour at 0°C, at which time it was concentrated in vacuo, and adsorbed onto SiO_2 for purification. Flash column chromatography (SiO_2, 5% EtOAc in hexanes) gave 2-nitrocinnamyl bromide (3.06 g, 90%) as a pale green oil which solidified upon cooling. R_f 0.51 (25% EtOAc in hexanes). Mp 34–35°C. IR (thin film) 2960, 2920, 2850, 1521 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, d, J=8.3 Hz), 7.62–7.56 (2H, m), 7.46–7.40 (1H, m), 7.14 (1H, d, J=15.4 Hz), 6.41–6.31 (1H, m), 4.18–4.14 (2H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 147.8, 133.2, 131.5, 130.3, 129.3, 128.8, 128.7, 124.7, 32.0 ppm. HRMS calcd for $C_9H_9NO_2Br$ (MH^+) 241.9817. Found 241.9819.

1.1.5. (±)-8-Ethyl-8-allyl-1-(2-nitrophenyl)-5,6,7,8-tetrahydroindolizine 3. A mixture of **8** (0.743 g, 2.87 mmol) and 2-nitrocinnamyl bromide (1.32 g, 5.46 mmol) in dry toluene was azeotroped in vacuo three times (3×1 mL), and the mixture was heated at 100°C under an atmosphere of argon for 15 min. The dark brown colored mixture was subsequently cooled to room temperature, dissolved in anhydrous THF (10 mL), and cooled further to 0°C. Distilled 1,8-diazabicyclo[5.4.0]undec-7-ene (2.14 mL, 14.3 mmol) was added dropwise to the mixture, and the solution allowed to warm to room temperature. The mixture was poured into 5% aqueous $NaHCO_3$ (30 mL) and extracted with EtOAc (3×15 mL). The combined extracts were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. The residue was passed through a plug of SiO_2 (5% EtOAc in hexanes), and the crude product was purified by recrystallization from hexanes to give **3** (0.631 g, 71%) as yellow crystalline solid. Mp 105–107°C. R_f 0.6 (25% EtOAc in hexanes). IR (thin film) 2961, 2875, 1527 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.80–7.78 (1H, m), 7.52–7.38 (3H, m), 6.55 (1H, d, J=2.7 Hz), 6.06 (1H, d, J=2.7 Hz), 5.68–

5.56 (1H, m), 4.99–4.92 (2H, m), 3.90 (2H, t, J=5.4 Hz), 2.33–2.27 (1H, m), 2.05–1.72 (3H, m), 1.69–1.66 (2H, m), 1.50–1.32 (2H, m), 0.75 (3H, t, J=7.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 135.7, 133.8, 133.7, 131.2, 130.9, 127.5, 123.5, 118.5, 117.0, 114.1, 110.6, 46.3, 46.1, 39.4, 33.8, 29.9, 20.8, 9.1 ppm. HRMS calcd for $C_{19}H_{23}N_2O_2$ (MH^+) 311.1760. Found 311.1763.

1.1.6. (±)-8-Ethyl-8-(3-hydroxypropyl)-1-(2-nitrophenyl)-5,6,7,8-tetrahydroindolizine 9. Borane–THF complex (1.0 M in THF, 4.0 mL, 6.0 mmol) was added in one portion to a solution of **3** (0.622, 2.00 mmol) in anhydrous THF (13.5 mL) at 0°C under an atmosphere of argon. After stirring the mixture at 0°C for 1 h, NaOH (3.0 M aqueous, 6.0 mL, 18 mmol) was added dropwise, resulting in the vigorous evolution of gas. Hydrogen peroxide (30% aqueous, 2.1 mL, 18 mmol) was added to the mixture, and the resulting solution stirred for a further 30 min. The mixture was warmed to room temperature, poured into water (50 mL), and extracted with EtOAc (4×20 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (25–50% EtOAc in hexanes) to give **9** as a yellow oil (0.513 g, 78%). R_f 0.10 (25% EtOAc in hexanes). IR (neat) 3378, 2940, 2873, 1522 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (1H, d, J=7.3 Hz), 7.51–7.36 (3H, m), 6.53 (1H, d, J=2.6 Hz), 6.05 (1H, d, J=2.6 Hz), 3.89 (2H, t, J=5.9 Hz), 3.42–3.41 (2H, m), 1.95–1.87 (2H, m), 1.76–1.61 (2H, m), 1.51–1.25 (7H, m), 0.75 (3H, t, J=7.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.7, 133.7, 133.6, 131.4, 130.9, 127.4, 123.4, 118.5, 113.8, 110.7, 63.4, 46.1, 39.3, 37.6, 34.7, 30.1, 28.1, 21.2, 9.1 ppm. HRMS calcd for $C_{19}H_{25}N_2O_3$ (MH^+) 329.1865. Found 329.1868.

1.1.7. (±)-3-[1-(2-Nitrophenyl)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl]-propionaldehyde 10. Pyridine–sulfur trioxide complex (0.765 g, 4.80 mmol) was added in one portion to a solution of **9** (0.513 g, 1.61 mmol) in a mixture of DMSO (10 mL), THF (1.6 mL), and triethylamine (1.6 mL) under an atmosphere of argon. After stirring the mixture for 45 min the solution was poured into water (30 mL) and extracted with $CHCl_3$ (4×15 mL). The combined extracts were dried (Na_2SO_4), filtered, and the solvent evaporated in vacuo. Purification by flash column chromatography (10–25–50% EtOAc in hexanes) gave **10** as a crystalline yellow solid (0.334 g, 66%). Mp 102–103°C. R_f 0.52 (50% EtOAc in hexanes). IR (thin film) 2960, 2876, 2721, 1721, 1526 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.58 (1H, s), 7.73 (1H, d, J=7.7 Hz), 7.51–7.36 (3H, m), 6.54 (1H, d, J=2.7 Hz), 6.01 (1H, d, J=2.7 Hz), 3.90 (2H, t, J=5.6 Hz), 2.36–2.31 (2H, m), 1.98–1.80 (2H, m), 1.78–1.38 (6H, m), 0.79 (3H, t, J=6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 150.5, 133.3, 131.0, 130.3, 127.6, 123.4, 118.9, 114.2, 110.5, 45.9, 39.9, 39.0, 35.0, 32.6, 30.0, 21.0 9.0 ppm. HRMS calcd for $C_{19}H_{23}N_2O_3$ (MH^+) 327.1709. Found 327.1704.

1.1.8. (±)-3-[1-(2-Nitrophenyl)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl]-propionic acid 11. A solution of silver nitrate (0.282 g, 1.66 mmol) in water (1 mL) was added to a solution **10** (0.334 g, 1.02 mmol) in absolute ethanol (10 mL), followed by the dropwise addition of an aqueous solution of potassium hydroxide (1.0 M, 6.1 mL, 6.1 mmol). After stirring the mixture for 30 min the solution was filtered through Celite®, washing the filter cake with EtOAc (50 mL) and water (20 mL). The EtOAc layer of the filtrate was extracted with 1.5 MNaOH (4×10 mL) and the combined aqueous extracts subsequently acidified (pH 3) with the slow addition of a 2 M solution of H_2SO_4. The solution was extracted with $CHCl_3$ (3×10 mL) and the combined extracts washed with water (15 mL), followed by saturated aqueous NaCl (10 mL), and dried (Na_2SO_4). The extract was evaporated in vacuo to give **11** (0.329 g, 94%) as a yellow crystalline solid, which was used without further purification. R_f 0.45 (50% EtOAc in hexanes). Mp 174–175°C. IR (thin film) 2951, 2876, 1706, 1526 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.50 (1H, br s), 7.78 (1H, dd, J=1.0, 8.0 Hz), 7.61–7.37 (3H, m), 6.54 (1H, d, J=2.6 Hz), 6.02 (1H, d, J=2.6 Hz), 3.93–3.88 (2H, m), 2.27 (2H, t, J=8.1 Hz), 1.97–1.82 (2H, m), 1.75–1.38 (6H, m), 0.77 (3H, m). ^{13}C NMR (75 MHz, CH_3OD) δ 177.7, 152.2, 134.8, 134.5, 132.2, 131.4, 128.8, 124.5, 120.0, 115.7, 111.5, 47.1, 40.5, 37.8, 36.3, 31.5, 31.0, 22.7, 9.5 ppm. HRMS calcd for $C_{19}H_{23}N_2O_4$ (MH^+) 343.1658. Found 343.1649.

1.1.9. (±)-Rhazinilam 1. Raney nickel (ca. 0.5 g, washed with methanol) was added to a solution of **11** (0.329 g, 0.961 mmol) in anhydrous methanol (15 mL), followed by hydrogenation at 20 psi H_2 pressure in a Parr shaker until complete by TLC (ca. 1.5 h). The mixture was filtered through Celite® and concentrated in vacuo to give the crude amino acid as a yellow foam (0.295 g, 98%). A solution of the crude amino acid in a mixture of toluene (28.5 mL), THF (19 mL), and triethylamine (1.7 mL, 12 mmol) was added via syringe pump to a solution of triethylamine (2.5 mL, 18 mmol) and 2-chloro-1-methylpyridinium iodide (2.549 g, 9.98 mmol) in anhydrous toluene (47 mL) over a period of 5 h. After stirring the mixture for a further 2 h at room temperature, the solution was filtered and the filtrate concentrated in vacuo. Purification of the residue by flash column chromatography (SiO_2, 50% EtOAc in hexanes) gave **1** (0.145 g, 51%) as a white crystalline solid. Mp 215.5–216.5°C. R_f 0.18 (50% EtOAc in hexanes). IR (thin film) 3169, 3047, 2957, 2920, 1670 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, dd, J=2.1, 6.8 Hz), 7.36–7.28 (2H, m), 7.19 (1H, dd, J=1.3, 7.0 Hz), 6.83 (1H, s), 6.49 (1H, d, J=2.6 Hz), 5.74 (1H, d, J=2.6 Hz), 4.01 (1H, dd, J=5.1, 11.9 Hz), 3.78 (1H, dt, J=4.7, 11.9 Hz), 2.49–2.32 (2H, m), 2.27–2.20 (1H, m), 1.98–1.82 (2H, m), 1.71 (1H, dt, J=3.0, 13.3 Hz), 1.56–1.40 (3H, m), 1.30–1.21 (2H, m), 0.71 (3H, t; J=7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 140.3, 138.1, 131.3, 130.5, 127.9, 127.1, 126.7, 119.0, 117.3, 109.5, 46.0, 38.8, 36.5, 33.0, 30.1, 28.1, 19.4, 8.1 ppm. HRMS calcd for $C_{19}H_{23}N_2O$ (MH^+) 295.1810. Found 295.1814. Identical (mp, IR, ^{1}H NMR, ^{13}C NMR , HRMS, tlc) with a synthetic sample. The spectral data are in good agreement with literature data for the natural product.

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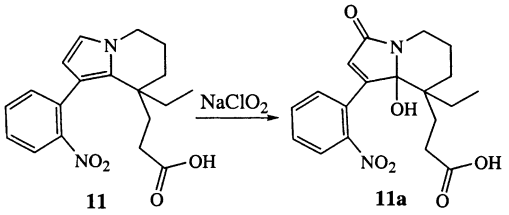
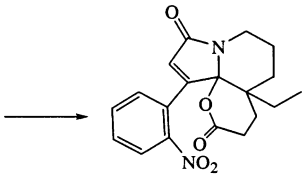
16. The sodium chlorite procedure caused oxidation of the pyrrole ring to give **11a**, which readily lactonized to give **11b**.





11b

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