Total Synthesis of Rhazinilam of Through Direct Arylation

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General. Tetrahydrofuran (THF) was distilled from Na/benzophenone. Triethylamine (Et_3N) was distilled from calcium hydride. Dichloromethane (CH_2Cl_2) was dried by passing through a column of activated alumina prior to use. Pyrrole-2-carboxylic acid methyl ester was made according to literature procedures.¹ All other starting materials and solvents are commercially available and were used without further purification. Chromatography was carried out with ICN SiliTech 32-63 D 60 Å silica gel. Reactions and chromatography fractions were analyzed with Merck silica gel 60 F_{254} plates. Extracts were dried over MgSO_4 , and solvents were removed with a rotary evaporator at aspirator pressure. Melting points were determined with an electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in CDCl_3 (7.27 ppm, 77.23 ppm) on a Bruker AM 400 MHz spectrometer.

11

Pyrrole 11. To a solution of pyrrole 2-carboxylic acid methyl ester (1.35 g, 10.8 mmol) in dry *N,N*-dimethylformamide (DMF, 36 mL) at 0 °C was added a 60% dispersion of NaH in mineral oil (432 mg, 10.8 mmol). After 10 min at 0 °C, the solution was allowed to warm to rt over 1 h. The mixture was cooled to 0 °C, and a solution of tosylate **9** (2.51 g, 7.69 mmol) in DMF (15 mL) was added dropwise via cannula. The flask containing the tosylate was rinsed with an additional 2 mL DMF. The solution was allowed to warm to rt over 18 h, and then poured into water (300 mL) and extracted with ether (3 x 200 mL). The combined organic extracts were washed with water (2 x 50 mL), brine (50 mL), dried, filtered, and concentrated. The product was purified by column chromatography (35% EtOAc in hexanes) to afford 2.02 g (94%) of **11** as a colorless oil: IR (film): 2948, 1767, 1712 cm^{-1} ; ^1H NMR: δ 6.92 (m, 1H), 6.84 (m, 1H), 6.12 (m, 1H), 4.32 (m, 2H), 3.81 (s, 3H), 2.56 (m, 2H), 2.07-1.91 (m, 2H), 1.89-1.76 (m, 2H), 1.73-1.59 (m, 4H), 0.90 (t, J = 7.6 Hz, 3H); ^{13}C NMR: δ 176.9, 161.7, 128.9, 121.6, 118.5, 108.4,

¹ Hong, F.; Zaidi, J.; Pang, Y.-P.; Cusack, B.; Richelson, E. *J. Chem. Soc., Perkin Trans. 1* **1997**, 20, 2997

88.9, 51.2, 49.1, 35.2, 31.4, 30.4, 29.2, 26.0, 8.0; HRMS (EI+): m/z (M^+) calcd for $C_{15}H_{21}NO_4$ 279.1471; found 279.1470.

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Acid 12. To a solution of pyrrole **11** (559 mg, 2.00 mmol) in nitromethane at 0 °C was added aluminum(III) chloride (1.07 g, 8.02 mmol). After 10 min at 0 °C, the mixture was allowed to warm to rt over 24 h. The reaction was then quenched with water (20 mL). The solution was stirred vigorously for 30 min, filtered through Celite with CH_2Cl_2 washings, diluted with water (100 mL), and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were dried, filtered, and concentrated. The product was purified by column chromatography (40% EtOAc in hexanes), on a short 20 cm column, to yield 310 mg (55%) of **12** as a colorless oil: IR (film): 3106 (br), 2945, 1693 cm^{-1} ; 1H NMR: δ 6.93 (d, J = 3.6 Hz, 1H), 5.92 (d, J = 3.6 Hz, 1H), 4.29 (m, 2H), 3.77 (s, 3H), 2.37-2.14 (m, 2H), 2.03-1.82 (m, 4H), 1.77-1.51 (m, 4H), 0.82 (t, J = 7.2 Hz, 3H); ^{13}C NMR: δ 180.0, 161.9, 142.7, 120.7, 117.9, 106.0, 51.0, 45.3, 38.2, 34.8, 33.6, 29.8, 29.1, 20.0, 8.7; HRMS (EI+): m/z (M^+) calcd for $C_{15}H_{21}NO_4$ 279.1471; found 279.1471.

14

Iodide 14. To a solution of acid **12** (300 mg, 1.07 mmol) in CH_2Cl_2 (5 mL) was added 2-chloro-1-methyl-pyridinium iodide (330 mg, 1.29 mmol) and 2-iodoaniline (1.29 g, 5.89 mmol). The mixture was heated at reflux for 1 h, and then allowed to cool. Et_3N (0.30 mL, 2.2 mmol) was added, and the mixture was heated at reflux for an additional 20 h, allowed to cool, poured into water (40 mL), and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were dried, filtered, and concentrated. The product was purified by column chromatography (25% EtOAc in hexanes) to furnish 387 mg (75%) of **14** as a foamy solid: IR (film): 3300, 2946, 1694 cm^{-1} ; 1H NMR: δ 8.05 (m, 1 H), 7.70 (d, J = 7.6 Hz, 1 H), 7.48 (br s, 1 H), 7.30-7.20 (m, 1 H), 6.95-6.88 (m, 1 H), 6.82-6.71 (m, 1 H), 5.95 (br s, 1 H), 4.27 (m,

2H), 3.73 (s, 3H), 2.40-2.15 (m, 2 H), 2.00-1.86 (m, 4 H), 1.75-1.52 (m, 4 H), 0.81 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR: δ 171.2, 161.5, 142.6, 138.7, 138.2, 129.0, 126.0, 122.6, 120.5, 117.7, 105.7, 90.6, 50.7, 45.1, 38.2, 35.4, 33.7, 33.1, 28.9, 19.9, 8.6; HRMS (EI⁺): m/z (M^+) calcd for $\text{C}_{21}\text{H}_{25}\text{IN}_2\text{O}_3$ 480.0910; found 480.0917. X-ray quality crystals were obtained by layering hexanes above a dilute solution of the iodide in CH_2Cl_2 , allowing for slow inter-diffusion of the two layers, and providing for gradual evaporation of the solvent mixture with a needle placed through the cap.

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Iodide 15. To a solution of iodide **14** (270 mg, 0.562 mmol) in THF (6.0 mL) at 0 °C was added a solution of sodium bis(trimethylsilyl)amide in THF (0.34 mL, 2.0 M, 0.68 mmol) dropwise via syringe. After 30 min at 0 °C, a solution of chloromethyl methyl ether in THF (6.0 mL, 0.10 M, 0.60 mmol) was added dropwise. After an additional 10 min, the mixture was allowed to warm to rt over 1 h, diluted with water (25 mL), and extracted with EtOAc (3 x 20 mL). The product was purified by column chromatography (30% EtOAc in hexanes) to yield 250 mg (85%) of **15** as a yellowish solid: IR (film): 1695 cm^{-1} ; ^1H NMR (mixture of rotamers): δ 7.91 (t, $J = 8.0$ Hz, 1H), 7.37 (t, $J = 8.0$ Hz, 1H), 7.16 (dd, $J = 8.0, 24.0$ Hz, 1H), 7.07 (t, $J = 7.5$ Hz, 1H), 6.80 (dd, $J = 4.0, 8.0$ Hz, 1H), 5.65 (dd, $J = 4.0, 12.0$ Hz, 1H), 5.57 (dd, $J = 4.0, 12.0$ Hz, 1H), 4.30 (d, $J = 10.2$ Hz, 1H), 4.24-4.07 (m, 2H), 3.76 (s, 3H), 3.41 (d, $J = 4.2$ Hz, 3H) 1.97-1.77 (m, 6H), 1.59-1.41 (m, 4H), 0.79 (m, 3H); ^{13}C NMR (mixture of rotamers): δ 174.2, 174.1, 162.0, 143.6, 143.0, 142.9, 140.2, 131.0, 130.3, 129.7, 120.5, 117.7, 105.9, 105.8, 100.6, 78.3, 57.1, 50.9, 45.2, 38.3, 38.2, 35.5, 35.2, 33.6, 33.1, 30.4, 30.3, 29.3, 29.1, 20.0, 19.9, 8.7, 8.6; HRMS (EI⁺): m/z (M^+) calcd for $\text{C}_{23}\text{H}_{29}\text{IN}_2\text{O}_4$ 524.1172; found 524.1170.

19: R = MOM

Lactam 19. Iodide **15** (12 mg, 0.023 mmol), potassium carbonate (6.4 mg, 0.046 mmol), 2-dicyclohexylphosphino-2'-(*N,N*-dimethylamino)biphenyl (**16**, 1 mg, 0.003 mmol), and palladium acetate (0.5 mg, 0.002 mmol) were placed in a flame-dried vial. The vial was flushed with nitrogen, *N,N*-dimethylacetamide (DMA, 0.4 mL) was added, and the solution was heated to 145 °C. After 12 h at 145 °C, the solution was allowed to cool, and the solvent was removed by rotary evaporation under high vacuum. The resulting black residue was dissolved in CH₂Cl₂ and passed through a plug of silica gel. The product was purified by column chromatography (25% EtOAc in hexanes) to afford 4.3 mg (47%) of **19** as a white solid: IR (film): 1704, 1668 cm⁻¹; ¹H NMR: δ 7.43-7.26 (m, 4H), 6.61 (s, 1 H), 5.21 (d, *J* = 12.0 Hz, 1H), 4.82 (m, 1H), 4.25 (d, *J* = 8.0 Hz, 1H), 3.90 (m, 1H), 3.74 (s, 3H), 3.28 (s, 3H), 2.47 (m, 2H), 2.17-2.04 (m, 2H), 1.95 (m, 1H), 1.74 (m, 1 H) 1.51-1.42 (m, 3 H), 1.19-1.14 (m, 1 H), 0.79 (m, 3H); ¹³C NMR: δ 175.7, 161.6, 142.9, 138.2, 137.9, 131.6, 129.0, 127.6, 127.3, 120.4, 119.5, 118.5, 79.1, 56.9, 51.1, 46.4, 39.9, 37.3, 32.3, 30.3, 29.7, 19.1, 8.4; HRMS (EI+): *m/z* (M⁺) calcd for C₂₃H₂₈N₂O₄ 396.2049; found 396.2054.

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Lactam 20. To a solution of lactam **19** (15 mg, 0.038 mmol) in CH₂Cl₂ (2.0 mL) at -78 °C was added boron trichloride (0.37 mL, 1.0 M, 0.37 mmol) dropwise via syringe over two minutes. After 2.5 h at -78 °C, the reaction was quenched with a saturated NaHCO₃ solution (5 mL), and the mixture was extracted with EtOAc (3 x 15 mL). The crude solid was dissolved in MeOH (2.0 mL), and Et₃N (0.10 mL, 0.72 mmol) was added, and the solution was heated at 50 °C for 2 h. The product was purified by column chromatography (30% EtOAc in hexanes) to give 8.0 mg (60%) of **20** as a white solid: IR (film): 1702, 1667 cm⁻¹; ¹H NMR: δ 7.40-7.30 (m, 3H), 7.22 (d, *J* = 7.6 Hz, 1 H), 6.66 (br s, 1H), 6.60 (s, 1H), 4.77 (dd, *J* = 14.0, 5.0 Hz, 1H), 3.90 (dt, *J* = 12.0, 5.0 Hz, 1H), 3.74 (s, 3H), 2.49-2.39 (m, 2H), 2.21-

2.17 (m, 1H), 2.04-1.93 (m, 2H), 1.74 (m, 1H), 1.53-1.47 (m, 3H), 1.20-1.26 (m, 1H), 0.69 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR: δ 177.0, 161.6, 139.2, 138.3, 137.8, 131.5, 128.4, 127.8, 127.3, 120.6, 119.4, 118.9, 51.1, 46.3, 39.8, 36.9, 32.2, 30.3, 28.3, 19.1, 8.4. HRMS (EI⁺): m/z (M⁺) calcd for $\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_3$ 352.1787; found 352.1784.

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Rhazinilam (7). To a solution of lactam **20** (4.0 mg, 0.011 mmol) in MeOH (0.7 mL) was added a 50 % aqueous NaOH solution (0.15 mL), and the mixture was heated under an argon atmosphere to 50 °C. After 30 min the solution was allowed to cool, acidified with an aqueous HCl solution to pH 2, and then heated to 50 °C. After another 4 h at 50 °C, the mixture was allowed to cool, extracted with CHCl_3 (3 x 2 mL), dried, filtered, and concentrated. The product was purified by column chromatography (1% MeOH in CHCl_3) to give 2.8 mg (85%) of racemic rhazinilam as a white solid: ^1H NMR: δ 7.44 (dd, $J = 1.5, 7.6$ Hz, 1H), 7.34 (dt, $J = 1.5, 7.6$ Hz, 1H), 7.30 (dt, $J = 1.5, 7.6$ Hz, 1H), 7.21 (d, $J = 7.6$ Hz, 1H), 6.57 (br s, 1H), 6.51 (d, $J = 5.0$ Hz, 1H), 5.75 (d, $J = 5.0$ Hz, 1H), 4.02 (dd, $J = 5.0, 14.0$ Hz, 1H), 3.76 (m, 1H), 2.45 (m, 2H), 2.23 (m, 1H), 1.95 (dd, $J = 13.0, 14.0$ Hz, 1H), 1.86 (m, 1H), 1.74 (dt, $J = 3.5, 13.1$ Hz, 1H), 1.53-1.41 (m, 3H), 1.26 (m, 1H), 0.69 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR: δ 177.6, 140.6, 138.2, 131.7, 130.8, 128.2, 127.5, 127.1, 119.4, 117.5, 109.8, 46.3, 39.1, 36.8, 33.3, 30.3, 28.3, 19.6, 8.4; MS (EI⁺): m/z (M+H) calc for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}$ 294; found 294.

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19: R = MOM

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EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$\text{IO}_3\text{N}_2\text{C}_{21}\text{H}_{25}$
Formula Weight	480.34
Crystal Color, Habit	colorless, bladelike
Crystal Dimensions	0.00 X 0.00 X 0.00 mm
Crystal System	monoclinic
Lattice Type	Primitive
Lattice Parameters	$a = 9.919(2)\text{\AA}$ $b = 21.430(4)\text{\AA}$ $c = 9.639(2)\text{\AA}$ $\beta = 105.614(3)^\circ$ $V = 1973.3(6)\text{\AA}^3$
Space Group	$P2_1/c$ (#14)
Z value	4
D_{calc}	1.617 g/cm ³
F_{000}	968.00
$\mu(\text{MoK}\alpha)$	16.47 cm ⁻¹

B. Intensity Measurements

Diffractometer	Bruker SMART CCD
Radiation	MoK α ($\lambda = 0.71069\text{\AA}$) graphite monochromated
Detector Position	60.00 mm
Exposure Time	10.0 seconds per frame.
Scan Type	ω (0.3 degrees per frame)
$2\theta_{\text{max}}$	49.4 $^\circ$
No. of Reflections Measured	Total: 8544 Unique: 3465 ($R_{\text{int}} = 0.051$)
Corrections	Lorentz-polarization Absorption (Tmax = 1.00 Tmin = 0.62)

C. Structure Solution and Refinement

Structure Solution	Direct Methods (SIR97)
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w(Fo - Fc)^2$
Least Squares Weights	$w = \frac{1}{\sigma_c^2(Fo)} = [\sigma_c^2(Fo) + \frac{v^2}{4}Fo^2]^{-1}$
p-factor	0.0300
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00\sigma(I)$)	2309
No. Variables	244

Reflection/Parameter Ratio	9.46
Residuals: R; Rw; Rall	0.037 ; 0.043; 0.062
Goodness of Fit Indicator	1.31
Max Shift/Error in Final Cycle	0.00
Maximum peak in Final Diff. Map	0.57 $\epsilon^-/\text{\AA}^3$
Minimum peak in Final Diff. Map	-0.93 $\epsilon^-/\text{\AA}^3$