Au(I)-Catalyzed Annulation of Enantioenriched Allenes in the Enantioselective Total Synthesis of (–)-Rhazinilam

Supporting Information

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General Information: Unless otherwise stated, all reactions were carried out in dry glassware under a nitrogen atmosphere using standard inert atmosphere (N₂) techniques for the manipulation of solvents and reagents. Proton NMR chemical shifts are reported relative to residual CHCl₃ (7.27 ppm) for ¹H and CDCl₃ (77.00 ppm) for ¹³C NMR spectra. Analytical high performance liquid chromatography (HPLC) was performed using a variable wavelength UV detector (deuterium lamp, 190-600 nm) using a Daicel ChiracelTM OD-H column (250 x 4.6 mm) (Daicel Inc.) and HPLC-grade isopropanol and hexanes as the eluting solvents. Anhydrous solvents (CH₂Cl₂, THF, diethyl ether, *N,N*-dimethylformamide, and toluene) were obtained by passage through successive alumina- and Q5 reactant-packed columns on a solvent purification system. *N,N*-Diisopropylethylamine, triethylamine, CH₃CN, benzene, and CHCl₃ were distilled under nitrogen from CaH₂. Commercially available (Aldrich Chemical Co.) acetyl bromide and propionyl chloride were redistilled under N₂. Anhydrous MgCl₂ was purchased from Aldrich Chemical Co. and weighed out in a N₂-filled glovebox. Pd₂(dba)₃ and SPhos¹ were purchased from Strem Chemical Co. and weighed out in a N₂-filled glovebox. Al(triamine) complex **7**,² *O*-trimethylsilylquinine (TMSQn),³ (CH₃CN)₂PdCl₂,⁴ and boronic ester **21**⁵ were prepared according to literature procedures. Ph₃P·AuOTf was prepared in situ from Ph₃P·AuCl and AgOTf as described.⁶ All other reagents were used as received from the supplier. Melting points are uncorrected. Flash chromatography was performed as previously described on EM silica gel 60 (230-240 mesh).⁷

(R)-4-(But-1-ynyl)oxetan-2-one (5): To a solution of the triamine ligand (988 mg, 1.83 mmol)² in 10 ml of CH₂Cl₂ at ambient temperature was slowly added a solution of AlMe₃ (0.96 ml, 2.0 M in hexane, 1.92 mmol). After stirring for 2 h, the resulting catalyst solution was diluted with CH₂Cl₂ (70 mL), cooled to –78 °C and *N,N*-diisopropylethylamine (10.8 mL, 62.1 mmol) and 2-pentynal (3.0 g, 35.56 mmol) were added consecutively. The resulting heterogeneous mixture was stirred 20 min at –78 °C whereupon a solution of acetyl bromide (4.86 mL, 65.77 mmol) in 20 mL of CH₂Cl₂ was added by syringe pump over 3 h and the reaction was stirred 12 h at –78 °C. The reaction was quenched at –78 °C by the addition of a saturated aqueous NH₄Cl solution (50 mL). The resulting mixture was extracted with ethyl ether (2 × 200 mL) and the combined organic extracts were washed with water and brine, dried (Na₂SO₄), and concentrated. The residue was purified by bulb-to-bulb distillation (40 °C, 0.1 mb) to afford **5** (3.48 g, 79%) as a colorless oil. Separation of the enantiomers by chiral GLC [ChiraldexTM G-TA column 20 m x 0.25 mm, flow rate 0.5 mL/min,

¹ Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685-4696.

² (a) Nelson, S. G.; Peelen, T. J.; Wan, Z. *J. Am. Chem. Soc.* **1999**, *121*, 9742-9743. (b) Nelson, S. G.; Mills, P. M. *Org. Synth.* **2005**, *82*, 170-174.

³ Calter, M. A. *J. Org. Chem.* **1996**, *61*, 8006-8007.

⁴ Wimmer, F. L.; Wimmer, S.; Castan, P.; Puddephatt, R. J. *Inorg. Synth.* **1992**, *29*, 185-187

⁵ Lamba, J. J. S.; Tour, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 11723-11736.

⁶ Preisenberger, M.; Schier, A.; Schmidbaur, H. *J. Chem. Soc., Dalton Trans.* **1999**, 1645-1650.

⁷ Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

method: 80 °C for 5.0 min, ramp @ 5.0 °C/min to 100 °C for 10.0 min, ramp @ 5.0 °C/min to 130 °C for 5.0 min, T_r: 19.38 min (S), T_r: 20.05 min (R)] provided the enantiomer ratio: 4(R):(S) = 98.5:1.5 (97% ee). [α]_D²³ +2.1 (c 2.0, CHCl₃); IR (neat, cm⁻¹): 2981, 2246, 1840, 1252; ¹H NMR (300 MHz, CDCl₃): δ 4.99 (ddt, *J* = 6.2, 4.6, 1.9 Hz, 1 H), 3.71 (dd, *J* = 16.2, 6.2 Hz, 1 H), 3.43 (dd, *J* = 16.2, 4.5 Hz, 1 H), 2.23 (qd, *J* = 7.4, 1.9 Hz, 2H), 1.12 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 167.1, 92.6, 74.4, 59.0, 46.0, 13.1, 12.3; HRMS (EI) *m/z*: calcd for C₇H₉O₂ (M⁺+H) 125.0602; found 125.0603.

5-Ethyl-8-(1*H*-pyrrol-1-yl)octa-3,4-dienoic acid (9): To a suspension of magnesium powder (50 mesh, 243 mg, 15 mmol) in THF (10 mL) was added dropwise 1, 2-dibromoethane (25 μ L, 0.3 mmol) and 5 drops of a solution of 1-(3-bromopropyl)-1*H*-pyrrole (567 mg, 3 mmol)⁸ in 30 mL of THF. The reaction was heated to reflux for 5 min to initiate Grignard reagent formation.

The reaction was then cooled to ambient temperature and the remainder of the 1-(3-bromopropyl)-1*H*-pyrrole solution was added dropwise over 30 min. Once addition was complete, the reaction was stirred an additional 30 min. The resulting Grignard reagent solution was added to a -78 °C solution of lactone **6** (266 mg, 2.14 mmol), copper cyanide (18 mg, 0.2 mmol) and anhydrous lithium bromide (40 mg, 0.46 mmol) in 30 mL THF. The reaction was stirred at -78 °C for 15 min then quenched by the addition of a saturated aqueous NH₄Cl solution (50 mL). The resulting mixture was extracted with ethyl acetate (2 $\times$ 200 mL) and the combined organic extracts were washed with H₂O and brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 4:1 to 1:1) to afford **9** (438 mg, 88%) as a colorless oil. [α]_D²³ +10.2 (c 2.1, CHCl₃); IR (neat, cm⁻¹) 3200, 2964, 2932, 1709, 1499, 1281, 1088, 722; ¹H NMR (300 MHz, CDCl₃): δ 6.67 (t, *J* = 2.0 Hz, 2H), 6.16 (t, *J* = 2.0 Hz, 2H), 5.36-5.32 (m, 1H), 3.91 (t, *J* = 6.5 Hz, 2H), 3.08 (d, *J* = 7.1 Hz, 2H), 2.01-1.90 (m, 6H), 1.01 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 201.8, 178.1, 120.5 (2C), 107.88, 107.81, 107.1, 85.6, 48.8, 35.2, 29.19, 29.10, 25.6, 12.1; MS (EI) *m/z*: 233 (20, M⁺), 218 (16), 204 (15), 188 (36), 174 (67), 160 (65), 120 (27), 92 (61), 80 (100), 67 (26); HRMS (EI) *m/z*: calcd for C₁₄H₁₉NO₂ (M⁺) 233.1416, found 233.1421.

(S)-6-[3-(1*H*-Pyrrol-1-yl)propyl]-6-ethyl-3*H*-pyran-2(6*H*)-one (9'): To a solution of allenic acid **9** (22.4 mg, 0.096 mmol) in acetonitrile (2 mL) was added *N,N*-diisopropylethylamine (0.8 μ L, 0.0048 mmol) and silver nitrate (1.6 mg, 0.0096 mmol) under N₂. The mixture was heated at reflux for 1 h then cooled to ambient temperature. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 4:1) to afford the title compound as a colorless oil (21 mg, 94%). [α]_D²³ +18.1 (c 0.8, CHCl₃); IR (neat, cm⁻¹): 3098, 3045, 2968, 2880, 1731, 1500, 1090, 1023, 962, 725; ¹H NMR (300 MHz, CDCl₃): δ 6.61 (t, *J* = 2.0 Hz, 2H), 6.12 (t, *J* = 2.0 Hz, 2H), 5.86 (dt, *J* = 10.3, 3.4 Hz, 1H), 5.56 (dt, *J* = 10.3, 2.3 Hz, 1H), 3.96-3.77 (m, 2H), 3.02-3.00 (m, 2H), 1.83-1.72 (m, 4H), 1.65-1.51 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 167.0, 128.1, 121.6, 120.4 (2C), 108.1 (2C), 88.1, 49.2, 37.2, 33.6, 29.1, 25.6, 7.6; MS (EI) *m/z*: 233 (45, M⁺), 218 (11), 204 (65), 186 (6), 174 (12), 160 (23), 148 (7), 125 (22), 93 (28), 81 (100), 67 (12); HRMS (EI) *m/z*: calcd for C₁₄H₁₉NO₂ (M⁺) 233.1416; found 233.1420.

(S)-6-[3-(1*H*-pyrrol-1-yl)propyl]-6-ethyl-5,6-dihydropyran-2-one (10): To a solution of (S)-6-[3-(1*H*-pyrrol-1-yl)propyl]-6-ethyl-3*H*-pyran-2(6*H*)-one (16 mg, 0.0686 mmol) in THF (2 mL) was added DBU (15 μ L, 0.103 mmol) and the mixture was heated at 50 °C for 1 h. After cooling the reaction to ambient temperature, a solution of 5% HCl (2 mL) was added and the resulting mixture was extracted with ethyl acetate (2 $\times$ 100 mL). The combined organic extracts were washed with H₂O and brine, dried (MgSO₄), and evaporated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 3:1) to afford **10** as a colorless oil (14 mg, 88%). Separation of enantiomers by Chiral HPLC [Daicel ChiracelTM OD-H column, flow rate 1.0 mL/min, 10% *i*PrOH in hexanes, T_r: 18.6 min (R), 22.9 min (S)] provided the enantiomer ratio: (R):(S) = 4.5:95.5 (91% ee). [α]_D²³ +15.5 (c 0.6, CHCl₃); IR (neat, cm⁻¹): 3098, 2930, 2801, 1712, 1500, 1091, 1008, 812, 727; ¹H NMR (300 MHz, CDCl₃): δ 6.72 (dt, *J* = 9.8, 4.3 Hz, 1H), 6.63 (t, *J* = 2.0 Hz, 2H), 6.13 (t, *J* = 2.0 Hz, 2H), 6.00 (dt, *J* = 9.8, 2.0 Hz, 1H),

⁸ Dehaen, W.; Hassner, A. *J. Org. Chem.* **1991**, 56, 896-900.

3.98-3.81 (m, 2H), 2.44-2.28 (m, 2H), 1.97-1.83 (m, 2H), 1.78-1.70 (m, 2H), 1.68-1.56 (m, 2H), 0.87 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 163.5, 143.3, 120.9, 120.3 (2C), 108.1 (2C), 84.1, 49.4, 34.2, 31.3, 30.2, 25.5, 8.1; MS (EI) m/z : 233 (29, M^+), 204 (60), 148 (11), 136 (10), 125 (9), 108 (8), 93 (26), 81 (100), 57 (33); HRMS (EI) m/z : calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ (M^+) 233.1416; found 233.1420.

Methyl 5-ethyl-8-(1H-pyrrol-1-yl)octa-3,4-dienoate (11): To a solution of allenic acid **9** (438 mg, 1.88 mmol) in benzene (25 mL) and absolute methanol (10 mL) was added TMSCHN_2 (2 M in Et_2O , 1.6 mL, 3.2 mmol). The reaction was stirred at ambient temperature for 30 min and the solvent was evaporated. The crude product mixture was purified by flash chromatography on silica gel (hexanes:ethyl ether 10:1) to afford **11** as a colorless oil (457 mg, 98%). $[\alpha]_{\text{D}}^{23} +11.8$ (c 0.8, CHCl_3); IR (neat, cm^{-1}): 2964, 1740, 1500, 1436, 1281, 1161, 1089, 723; ^1H NMR (300 MHz, CDCl_3): δ 6.64 (t, $J = 2.0$ Hz, 2H), 6.13 (t, $J = 2.0$ Hz, 2H), 5.35-5.29 (m, 1H), 3.89 (t, $J = 6.4$ Hz, 2H), 3.68 (s, 3H), 3.01 (d, $J = 7.1$ Hz, 2H), 1.94-1.87 (m, 6H), 0.98 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 201.3, 171.6, 120.1 (2C), 107.5 (2C), 106.5, 86.1, 51.4, 48.5, 34.9, 29.0, 28.8, 25.4, 11.8; MS (EI) m/z : 247 (6, M^+), 232 (2), 218 (4), 188 (12), 174 (13), 160 (36), 106 (6), 80 (18), 74 (61), 59 (100); HRMS (EI) m/z : calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ (M^+) 247.1572; found 247.1566.

(E)-Methyl 4-[(R)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl]but-3-enoate (12): To a solution of allenic ester **11** (944 mg, 3.81 mmol) in CH_2Cl_2 (380 mL) was added $\text{PdCl}_2(\text{CH}_3\text{CN})_2$ (198 mg, 0.76 mmol) under N_2 . The mixture was stirred at ambient temperature for 1 h and the reaction solution was loaded directly onto a silica gel column and eluted with hexanes:ethyl acetate (10:1) to afford **12** as a colorless oil (866 mg, 92%). Separation of enantiomers by Chiral HPLC [Daicel ChiralcelTM OD-H column, flow rate 1.0 mL/min, 1% i PrOH in hexanes, T_r : 11.2 min (R), 12.3 min (S)] provided the enantiomer ratio: (R):(S) = 68.5:31.5 (37% ee). $[\alpha]_{\text{D}}^{23} +3.2$ (c 0.62, CHCl_3); IR (neat, cm^{-1}): 2948, 2876, 1740, 1486, 1160, 1071, 974, 710; ^1H NMR (300 MHz, CDCl_3): δ 6.49 (t, $J = 2.0$ Hz, 1H), 6.13 (t, $J = 3.2$ Hz, 1H), 5.90 (dd, $J = 3.2, 2.0$ Hz, 1H), 5.56 (d, $J = 15.6$ Hz, 1H), 5.24 (dt, $J = 15.6, 7.0$ Hz, 1H), 3.95 (dt, $J = 11.9, 4.9$ Hz, 1H), 3.82 (ddd, $J = 11.9, 5.0, 4.5$ Hz, 1H), 3.65 (s, 3H), 3.01 (dd, $J = 7.0, 0.9$ Hz, 2H), 2.03-1.82 (m, 2H), 1.78-1.66 (m, 4H), 0.87 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 171.7, 141.6, 133.4, 120.1, 118.1, 106.9, 104.0, 51.0, 44.8, 41.2, 37.1, 33.6, 30.1, 19.5, 8.1; MS (EI) m/z : 247 (45, M^+), 218 (100), 186 (21), 158 (28), 144 (14), 130 (16), 104 (8), 91 (16), 75 (15); HRMS (EI) m/z : calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ (M^+) 247.1572; found 247.1575.

(3R,4R)-4-(But-1-ynyl)-3-methyloxetan-2-one (14): To a suspension of MgCl_2 (2.31 g, 24.3 mmol) in 25 mL of diethyl ether was added N, N -diisopropylethylamine (10.6 mL, 60.7 mmol) and a solution of O -trimethylsilylquinine (0.963 g, 2.43 mmol) in 75 mL of CH_2Cl_2 . The reaction mixture was cooled to -78°C and a solution of 2-pentynal (2.0 g, 24.3 mmol) in 20 mL CH_2Cl_2 was added. A solution of propionyl chloride (4.23 mL, 48.7 mmol) in 10 mL CH_2Cl_2 was then added over 3 h by syringe pump. The reaction mixture was stirred for 12 h at -78°C and then quenched by adding a saturated aqueous NH_4Cl solution (50 mL). The resulting mixture was extracted with ethyl ether (3 $\times$ 200 mL) and the combined organic extracts were washed successively with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (pentane:ethyl ether 10:1) to afford **16** as a colorless oil (2.4 g, 72%). Separation of the stereoisomers by chiral GLC [ChiraldexTM G-TA column 20 m $\times$ 0.25 mm, flow rate 0.5 mL/min, method: 80°C for 5.0 min, ramp @ $5.0^\circ\text{C}/\text{min}$ to 100°C for 10.0 min, ramp @ $5.0^\circ\text{C}/\text{min}$ to 130°C for 5.0 min, T_r : 21.3 min (3*S*,4*S*), T_r : 21.8 min (3*R*,4*R*)] provided the enantiomer and diastereomer ratios: (R,R):(S,S) = >99:1 (>99% ee), cis:trans = >99:1 (>99% de). $[\alpha]_{\text{D}}^{23} -18.6$ (c 0.63, CHCl_3); IR (neat, cm^{-1}): 2981, 2940, 2359, 2246, 1829, 1141, 1103, 972, 879; ^1H NMR (300 MHz, CDCl_3): δ 5.10 (dt, $J = 6.4, 1.9$ Hz, 1 H), 3.79 (qd, $J = 7.6, 6.4$ Hz, 1 H), 2.25 (qd, $J = 7.5, 1.9$ Hz, 2 H), 1.34 (d, $J = 7.6$ Hz, 3 H), 1.12 (t, $J = 7.5$ Hz, 3 H); ^{13}C NMR (75 MHz, CDCl_3): δ 171.4, 94.9, 71.8, 65.0, 49.3, 13.3, 12.4, 10.1; MS (EI) m/z : 94 ($\text{M}^+ - \text{CO}_2$), 79 ($\text{M}^+ - \text{CH}_3, \text{CO}_2$). HRMS (EI) m/z : calcd for C_7H_{10} ($\text{M}^+ - \text{CO}_2$) 94.0783; found 94.0776.

(2R)-5-Ethyl-2-methyl-8-(1H-pyrrol-1-yl)octa-3,4-dienoic acid (15): To a suspension of magnesium powder (50 mesh, 168 mg, 7 mmol) in THF (2 mL) was added dropwise 1, 2-dibromoethane (12 μ L, 0.14 mmol) and 5 drops of a solution of 1-(3-bromopropyl)-1H-pyrrole (264 mg, 3 mmol)⁸ in 5 mL of THF. The reaction was heated to reflux for 5 min to initiate Grignard reagent formation. The reaction was then cooled to ambient temperature and the remainder of the 1-(3-bromopropyl)-1H-pyrrole solution was added dropwise over 30 min.

Once addition was complete, the reaction was stirred an additional 30 min. The resulting Grignard reagent solution was added to a -78 °C solution of lactone **14** (138 mg, 1.0 mmol), copper cyanide (8.9 mg, 0.1 mmol) and anhydrous lithium bromide (20 mg, 0.23 mmol) in 10 mL of THF. After stirring at -78 °C for 10 min, the reaction was quenched by adding a saturated aqueous NH_4Cl solution (50 mL). The resulting mixture was extracted with ethyl acetate (2×200 mL) and the combined organic extracts were successively washed with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 4:1 to 1:1) to afford **15** as a colorless oil (220 mg, 89%). $[\alpha]_{\text{D}}^{23} +37.1$ (c 0.79, CHCl_3); IR (neat, cm^{-1}): 3120, 2966, 1708, 1499, 1457, 1281, 1088, 806, 722; ^1H NMR (300 MHz, CDCl_3): δ 6.65 (t, $J = 2.0$ Hz, 2H), 6.14 (t, $J = 2.0$ Hz, 2H), 5.43-5.38 (m, 1H), 3.90 (t, $J = 6.4$ Hz, 2H), 3.15 (pent, $J = 7.0$ Hz, 1H), 2.05-1.84 (m, 6H), 1.27 (d, $J = 7.0$ Hz, 3H), 0.99 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 200.1, 181.1, 120.3 (2C), 108.4, 107.7 (2C), 93.1, 48.8, 39.7, 29.2 (2C), 25.6, 16.3, 12.0; MS (EI) m/z : 247 (24, M^+), 232 (12), 218 (16), 202 (42), 186 (14), 174 (92), 160 (41), 106 (29), 93 (46), 91 (41), 80 (100), 67 (32); HRMS (EI) m/z : calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ (M^+) 247.1572; found 247.1559.

(2R)-Methyl 5-ethyl-2-methyl-8-(1H-pyrrol-1-yl)octa-3,4-dienoate (16): To a solution of allenic acid **15** (196 mg, 0.796 mmol) in benzene (12 mL) and absolute methanol (4 mL) was added TMSCHN_2 (2 M in Et_2O , 0.6 mL, 1.2 mmol). The reaction was stirred at ambient temperature for 30 min and the solvent was evaporated. The resulting crude product mixture was purified by flash chromatography on silica gel (hexanes:ethyl ether 10:1) to afford **16** as a colorless oil (196 mg, 94%). $[\alpha]_{\text{D}}^{23} +18.3$ (c 0.89, CHCl_3); IR (neat, cm^{-1}): 3099, 2966, 2876,

1733, 1500, 1455, 1169, 1089, 723; ^1H NMR (300 MHz, CDCl_3): δ 6.64 (t, $J = 2.0$ Hz, 2H), 6.13 (t, $J = 2.0$ Hz, 2H), 5.39-5.34 (m, 1H), 3.90 (t, $J = 6.5$ Hz, 2H), 3.67 (s, 3H), 3.11 (pent, $J = 7.0$ Hz, 1H), 1.98-1.83 (m, 6H), 1.24 (d, $J = 7.0$ Hz, 3H), 0.98 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 199.9, 174.8, 120.3 (2C), 108.0, 107.7 (2C), 93.7, 51.6, 48.8, 39.8, 29.20, 29.15, 25.6, 16.6, 11.9; MS (EI) m/z : 261 (52, M^+), 246 (12), 232 (11), 202 (64), 186 (24), 174 (90), 160 (100), 146 (12), 106 (28), 93 (47), 80 (84), 67 (12); HRMS (EI) m/z : calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2$ (M^+) 261.1732; found 261.1729.

(R,E)-Methyl 4-[(R)-8-ethyl-5,6,7,8-tetrahydroindolizin-8-yl]-2-methylbut-3-enoate (17): To a solution of allenic ester **16** (1.50 g, 5.75 mmol) in CH_2Cl_2 (480 mL) was added silver triflate (74 mg, 0.29 mmol) and $\text{Ph}_3\text{P}\cdot\text{AuCl}$ (142 mg, 0.29 mmol) under N_2 . The mixture was stirred at ambient temperature for 16 h, quenched with saturated NH_4Cl solution (50 mL), and extracted with ethyl acetate (3×200 mL). The combined organic extracts were washed successively with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica

gel (hexanes:ethyl acetate 10:1) to afford **17** as a colorless oil (1.39 g, 92%). $[\alpha]_{\text{D}}^{23} -22.5$ (c 1.8, CHCl_3); IR (neat, cm^{-1}): 3098, 2938, 2876, 1738, 1486, 1325, 1185, 1076, 972, 771, 711; ^1H NMR (300 MHz, CDCl_3): δ 6.13 (brs, 2H), 5.88 (brs, 1H), 5.55 (d, $J = 15.5$ Hz, 1H), 5.19 (dd, $J = 15.5, 8.0$ Hz, 1H), 3.92 (dt, $J = 11.9, 5.1$ Hz, 1H), 3.82 (ddd, $J = 11.9, 5.1, 4.7$ Hz, 1H), 3.65 (s, 3H), 3.11 (pent, $J = 7.0$ Hz, 1H), 1.97-1.81 (m, 2H), 1.77-1.64 (m, 4H), 1.20 (d, $J = 7.0$ Hz, 3H), 0.85 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 175.3, 139.6, 134.2, 127.5, 118.4, 107.2, 104.3, 51.6, 45.2, 42.6, 41.3, 34.1, 30.4, 19.7, 17.3, 8.5; MS (EI) m/z : 261 (16, M^+), 246 (38), 232 (100), 218 (12), 200 (14), 190 (37), 172 (34), 158 (38), 144 (29), 130 (28), 118 (23), 91 (33), 55 (38); HRMS (EI) m/z : calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2$ (M^+) 261.1732; found 261.1733.

(R)-Methyl 8-[(E)-3-(methoxycarbonyl)but-1-enyl]-8-ethyl-5,6,7,8-tetrahydroindolizine-3-carboxylate (18): To a solution of allenic ester **17** (135 mg, 0.517 mmol) in CH_2Cl_2 (15 mL) was added trichloroacetyl chloride (63 μL , 0.57 mmol). The mixture was stirred at ambient temperature for 1 h whereupon the volatiles were evaporated. The residue was dissolved in 15 mL of absolute methanol and a solution of sodium methoxide (150 mg, 2.79 mmol) in 8 mL of methanol was added and the reaction was stirred 30 min. The reaction was quenched with the addition of 50 mL saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3×200 mL). The combined organic extracts were washed successively with H_2O and brine, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 10:1) to afford the ester **18** as a mixture of C_2 epimers (158 mg, 99%). IR (neat, cm^{-1}): 2949, 2878, 1738, 1698, 1531, 1485, 1341, 1101, 973; ^1H NMR (300 MHz, CDCl_3): δ 6.88 (d, $J = 4.0$ Hz, 1H), 5.88 (d, $J = 4.0$ Hz, 1H), 5.47 (d, $J = 15.6$ Hz, 1H), 5.14 (dt, $J = 15.6, 7.8$ Hz, 1H), 4.49 (dt, $J = 13.7, 4.4$ Hz, 1H), 3.92 (dt, $J = 13.7, 7.0$ Hz, 1H), 3.70 (s, 3H), 3.57 (s, 3H), 3.03 (pent, $J = 7.2, 0.9$ Hz, 1H), 1.90-1.81 (m, 2H), 1.72-1.63 (m, 4H), 1.13 (d, $J = 7.2$ Hz, $1/2\text{CH}_3$), 1.12 (d, $J = 7.2$ Hz, $1/2\text{CH}_3$), 0.76 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 175.1, 161.7, 141.9, 138.91 (0.5 C), 138.69 (0.5 C), 128.53 (0.5 C), 128.48 (0.5 C), 120.5, 117.5, 106.37 (0.5 C), 106.31 (0.5 C), 51.7, 50.7, 45.5, 42.65 (0.5 C), 42.61 (0.5 C), 42.13 (0.5 C), 42.08 (0.5 C), 34.0, 29.2, 19.4, 17.6 (0.5 C), 17.3 (0.5 C), 8.4; MS (EI) m/z : 319 (18, M^+), 290 (100), 258 (16), 230 (12), 172 (25), 144 (15); HRMS (EI) m/z : calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_4$ (M^+) 319.1784; found 319.1778.

(S)-Methyl 8-ethyl-8-formyl-5,6,7,8-tetrahydroindolizine-3-carboxylate (18'): To a solution of ester **18** (158 mg, 0.517 mmol) in acetone (17 mL) and H_2O (4 mL) was added *N*-methyl morpholine-oxide (NMO, 250 mg, 2.06 mmol) and OsO_4 (2.5 wt % in *t*-BuOH, 0.65 mL, 0.0517 mmol) at 0 $^\circ\text{C}$. The reaction was then warmed to ambient temperature and stirred for 2 days. The reaction was quenched with 20% aqueous Na_2SO_3 (20 mL) and the resulting

mixture was extracted with ethyl acetate (3×100 mL). The combined organic extracts were washed successively with H_2O and brine, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 2:1) to afford the corresponding diol (168 mg, 92%) as a mixture of diastereomers. A 0 $^\circ\text{C}$ solution of diol (168 mg, 0.46 mmol) in THF (9 mL) and H_2O (3 mL) was treated with sodium periodate (305 mg, 1.42 mmol) and, once addition was complete, the reaction was warmed to ambient temperature and stirred for 16 h. The reaction mixture was extracted with ethyl acetate (3×100 mL) and the combined organic extracts were washed successively with H_2O and brine, then dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 10:1) to afford **18'** as a colorless oil (85 mg, 76%). Separation of enantiomers by Chiral HPLC [Daicel ChiracelTM OD-H column, flow rate 1.0 mL/min, 3% *i*-PrOH in hexanes, T_r : 7.38 min (*R*), 8.85 min (*S*)] provided the enantiomer ratio: (*R*):(*S*) = 3:97 (94% ee). $[\alpha]_D^{23} +22.3$ (*c* 1.15, CHCl_3); IR (neat, cm^{-1}): 2950, 1726, 1702, 1528, 1484, 1466, 1349, 1240, 1153, 1105, 754; ^1H NMR (300 MHz, CDCl_3): δ 9.43 (d, $J = 1.2$ Hz, 1H), 6.98 (d, $J = 4.0$ Hz, 1H), 6.12 (d, $J = 4.0$ Hz, 1H), 4.58 (dt, $J = 13.8, 4.4$ Hz, 1H), 4.00 (ddd, $J = 13.8, 10.5, 4.7$ Hz, 1H), 3.78 (s, 3H), 2.29 (ddd, $J = 13.7, 5.8, 3.0$ Hz, 1H), 1.97-1.91 (m, 1H), 1.88-1.77 (m, 3H), 1.61-1.53 (m, 1H), 0.79 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3): δ 199.2, 161.2, 134.8, 122.1, 117.5, 106.8, 51.7, 50.7, 44.8, 28.7, 23.3, 20.4, 7.8; MS (EI) m/z : 235 (26, M^+), 206 (100), 174 (8), 147 (9), 118 (7); HRMS (EI) m/z : calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_3$ (M^+) 235.1208; found 235.1165.

(R)-Methyl 8-[(E)-2-(methoxycarbonyl)vinyl]-8-ethyl-5,6,7,8-tetrahydroindolizine-3-carboxylate (18''): To a solution of aldehyde **18'** (235 mg, 1 mmol) in toluene (30 mL) was added methyl (triphenylphosphoranylidene)acetate (2.0 g, 6.0 mmol). The reaction was heated at 80 $^\circ\text{C}$ for 2 days. The reaction mixture was cooled to ambient temperature and was loaded directly onto a silica gel column and eluted with hexanes:ethyl acetate (10:1) to afford **18''** as an oil (276 mg, 95%). $[\alpha]_D^{23} -110.8$ (*c* 1.48, CHCl_3); IR (neat, cm^{-1}): 2950, 1724, 1703,

1649, 1484, 1434, 1341, 1272, 1235, 1165, 755; ^1H NMR (300 MHz, CDCl_3): δ 6.96 (d, $J = 15.7$ Hz, 1H), 6.95 (d, $J = 4.0$ Hz, 1H), 5.98 (d, $J = 4.0$ Hz, 1H), 5.50 (d, $J = 15.7$ Hz, 1H), 4.61 (dt, $J = 13.7, 4.7$ Hz, 1H), 3.97 (dt, $J = 13.7, 5.0$ Hz, 1H), 3.77 (s, 3H), 3.69 (s, 3H), 1.98-1.72 (m, 6H), 0.87 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz,

CDCl₃): δ 167.1, 161.6, 155.0, 139.4, 121.1, 120.6, 117.6, 106.7, 51.5, 50.8, 45.3, 42.8, 33.2, 28.9, 19.7, 8.4; HRMS (ES) m/z (M+Na)⁺: calcd for C₁₆H₂₁NNaO₄ 314.1368; found 314.1367.

(R)-Methyl 8-[2-(methoxycarbonyl)ethyl]-8-ethyl-5,6,7,8-tetrahydroindolizine-3-carboxylate (19): A 25 mL round-bottomed flask was charged with **18** (98 mg, 0.337 mmol) and 10% Pd/C (10 mg). The flask was evacuated under vacuum and the atmosphere was replaced with H₂ (1 atm, balloon). The mixture was suspended in MeOH (10 mL) and was stirred at ambient temperature for 16 h. The mixture was filtered through celite eluting with ethyl acetate. The filtrate was concentrated to afford **19** as an oil (99 mg, 100%). [α]_D²³ -45.2 (*c* 1.13, CHCl₃); IR (neat, cm⁻¹): 2949, 2879, 1738, 1698, 1530, 1484, 1352, 1236, 1174, 1108, 1033, 755; ¹H NMR (300 MHz, CDCl₃): δ 6.84 (d, *J* = 4.0 Hz, 1H), 5.83 (d, *J* = 4.0 Hz, 1H), 4.21 (t, *J* = 6.1 Hz, 2H), 3.67 (s, 3H), 3.53 (s, 3H), 2.23-2.05 (m, 2H), 1.93-1.81 (m, 4H), 1.66-1.49 (m, 4H), 0.73 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 173.7, 161.3, 142.3, 120.2, 117.3, 105.5, 51.2, 50.4, 44.8, 37.7, 34.7, 33.2, 29.3, 28.7, 19.6, 8.2; HRMS (ES) m/z (M+Na)⁺: calcd for C₁₆H₂₃NNaO₄ 316.1525; found 316.1556.

(R)-Methyl 8-[2-(methoxycarbonyl)ethyl]-8-ethyl-5,6,7,8-tetrahydro-1-iodoindolizine-3-carboxylate (20): To a 0 °C solution of **19** (99 mg, 0.337 mmol) in CHCl₃ (10 mL) was added silver trifluoroacetate (89 mg, 0.405 mmol) and iodine (103 mg, 0.405 mmol) whereupon the reaction was warmed to ambient temperature and stirred for 16 h. The reaction was quenched with 5 mL of 20% aqueous Na₂S₂O₅ and the resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed successively with saturated aqueous NaHCO₃ (20 mL) and brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 10:1) to afford **20** as an oil (125 mg, 89%). [α]_D²³ -17.0 (*c* 0.95, CHCl₃); IR (neat, cm⁻¹): 2951, 1737, 1705, 1509, 1435, 1353, 1233, 1201, 1166, 1095, 760; ¹H NMR (300 MHz, CDCl₃): δ 7.07 (s, 1H), 4.37 (dt, *J* = 13.8, 5.7 Hz, 1H), 4.24 (dt, *J* = 13.8, 6.3 Hz, 1H), 3.76 (s, 3H), 3.63 (s, 3H), 2.60 (ddd, *J* = 13.8, 6.3, 5.7 Hz, 1H), 2.22-2.03 (m, 3H), 1.94-1.84 (m, 3H), 1.82-1.71 (m, 1H), 1.68-1.54 (m, 2H), 0.78 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 173.6, 160.2, 139.5, 126.6, 122.3, 57.5, 51.3, 50.8, 45.9, 39.2, 33.0, 31.1, 29.4, 28.3, 20.0, 8.4; HRMS (ES) m/z (M+Na)⁺: calcd for C₁₆H₂₂INNaO₄ 442.0491; found 442.0507.

tert-Butyl 2-[(R)-3-(methoxycarbonyl)-8-(2-(methoxycarbonyl)ethyl)-8-ethyl-5,6,7,8-tetrahydroindolizin-1-yl]phenylcarbamate (22): A 25 mL round-bottomed flask was charged with **20** (125 mg, 0.30 mmol), *tert*-butyl-*N*-[2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-carbamate **21** (191 mg, 0.6 mmol), and K₃PO₄ (254 mg, 1.2 mmol). The flask was transferred to N₂-filled glovebox and Pd₂(dba)₃ (7 mg, 7.5 μ mol) and SPhos ligand (12 mg, 30 μ mol)¹ were added to the flask. The flask was sealed with a septum, removed from the glovebox, and THF (12 mL) and degassed H₂O (3 mL) were added. The resulting red solution was stirred at ambient temperature for 1 h then at 40 °C for 36 h. The reaction was quenched with saturated aqueous NH₄Cl (10 mL) and the resulting mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed successively with saturated aqueous NaHCO₃ (20 mL) and brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 10:1) to afford **22** as a 60:40 mixture of rotamers (124 mg, 86%). [α]_D²³ -10.3 (*c* 0.71, CHCl₃); IR (neat, cm⁻¹): 3411, 2950, 1732, 1706, 1583, 1512, 1470, 1435, 1221, 1156, 756; ¹H NMR (300 MHz, CDCl₃): (mixture of rotamers) δ 8.16 (d, *J* = 7.4 Hz, 1/3H), 8.08 (d, *J* = 7.4 Hz, 2/3H), 7.29 (t, *J* = 7.4 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.81 (s, 1/3H), 6.79 (s, 2/3H), 6.43 (s, 1/3H), 6.30 (s, 2/3H), 4.54-4.41 (m, 1H), 4.37-4.22 (m, 1H), 3.80 (s, 3H), 3.62 (s, 2/3 CH₃), 3.56 (s, 1/3 CH₃), 2.29-2.18 (m, 1H), 2.14-2.02 (m, 1H), 1.94-1.85 (m, 2H), 1.78-1.57 (m, 4H), 1.51-1.27 (m, 2H), 1.45 (s, 9H), 0.76 (d, *J* = 7.4 Hz, 1/3 CH₃), 0.72 (d, *J* = 7.4 Hz, 2/3 CH₃); ¹³C NMR (75 MHz, CDCl₃): (mixture of rotamers) δ 173.1 (0.6C), 173.0 (0.4C), 161.1, 152.4, 139.7 (0.4C), 139.2 (0.6C), 138.1, 131.7 (0.6C), 131.4 (0.4C), 129.0, 125.9 (0.6C), 125.7 (0.4C), 122.1 (0.6C), 121.77 (0.4C), 121.66 (0.4C), 121.53 (0.6C), 120.1 (0.6C), 119.8 (0.4C), 118.6 (0.6C), 118.3 (0.4C), 116.4 (0.6C), 116.2 (0.4C), 80.2 (0.4C), 79.9 (0.6C), 51.3 (0.4C), 51.1 (0.6C), 50.5, 45.7, 40.1, 36.4 (0.6C), 34.4

(0.4C), 33.7 (0.4C), 33.5 (0.6C), 30.3 (0.6C), 30.1 (0.4C), 28.7 (0.6C), 28.2 (3C), 28.0 (0.4C), 20.9 (0.6C), 20.1(0.4C), 9.5 (0.6C), 9.0 (0.4C); HRMS (ES) m/z (M+Na)⁺: calcd for C₂₇H₃₆N₂NaO₆ 507.2471; found 507.2447.

10-(Carbomethoxy)rhazinilam (23): To a solution of **22** (124 mg, 0.256 mmol) in methanol (12 mL) was added Ba(OH)₂·8H₂O (2.02 g, 6.41 mmol) and the resulting solution was stirred 2 h at ambient temperature. Aqueous 1 N HCl was added to the reaction mixture until pH 2 was obtained and this solution was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed successively with H₂O and brine, dried (Na₂SO₄), and concentrated. The residue was dried under high vacuum then dissolved in 12 mL of CH₂Cl₂ containing 8 mL of trifluoroacetic acid. The reaction was stirred at ambient temperature for 1 h whereupon the volatiles were evaporated to afford an oily residue (120 mg) that was used in next step without purification. A solution of the crude residue in CH₂Cl₂ (30 mL) was added via syringe pump over 12 h to a stirred solution of *O*-(7-azabenzotriazole-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU; 292 mg, 0.77 mmol) and *N,N*-diisopropylethylamine (0.22 mL, 1.28 mmol) in DMF (50 mL) and CH₂Cl₂ (20 mL). Once addition was complete, the reaction was stirred for an additional 4 h then the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic extracts were washed successively with aqueous 5% HCl (30 mL), aqueous 1 N NaOH (10 mL), saturated aqueous NaHCO₃ (20 mL), and brine, then dried (Na₂SO₄) and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 1:1) to afford **23** as a colorless solid (67 mg, 74% for three steps). mp 231-232 °C; [α]_D²³ -278 (c 0.46, CHCl₃); IR (neat, cm⁻¹): 3180, 1703, 1669, 1495, 1189, 761, 729; ¹H NMR (300 MHz, CDCl₃): δ 7.39-7.28 (m, 3H), 7.21 (d, J = 7.2 Hz, 1H), 6.97 (brs, 1H), 6.59 (s, 1H), 4.77 (dd, J = 13.7, 4.7 Hz, 1H), 3.91 (dt, J = 13.7, 5.1 Hz, 1H), 3.72 (s, 3H), 2.52-2.37 (m, 2H), 2.20-2.13 (m, 1H), 2.03-1.92 (m, 2H), 1.72 (dt, J = 13.4, 2.9 Hz, 1H), 1.54-1.44 (m, 3H), 1.27-1.16 (m, 1H), 0.69 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 177.0, 161.4, 138.8, 138.0, 137.5, 131.3, 128.6, 127.5, 127.0, 120.5, 119.2, 118.7, 50.8, 46.0, 39.6, 38.6, 32.0, 30.0, 28.0, 18.9, 8.1; MS (EI) m/z : 352 (19, M⁺), 323 (90), 295 (20), 291 (26), 267 (62), 69 (41), 55 (100); HRMS (EI) m/z : calcd for C₂₁H₂₄N₂O₃ (M⁺) 352.1787; found 352.1789.

(-)-Rhazinilam (2): A solution of **23** (6.3 mg, 0.0178 mmol) in methanol (1 mL) and 50% aqueous NaOH (0.23 mL) was heated at 50 °C for 30 min. Aqueous 1 N HCl was added to the reaction mixture until pH 2 was obtained and the resulting solution was heated at 50 °C for 4 h. The reaction mixture was cooled to ambient temperature and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed successively with saturated aqueous NaHCO₃ and brine, dried (Na₂SO₄), and concentrated. The residue was purified by flash chromatography on silica gel (hexanes:ethyl acetate 1:1) to afford synthetic (-)-rhazinilam (**2**) as a colorless solid (5.1 mg, 96%). mp 211-213 °C (lit. mp 213-215 °C);⁹ [α]_D²³ -406 (c 0.28, CHCl₃) [lit. [α]_D²³ -421 (c 1.0, CHCl₃)];¹⁰ IR (neat, cm⁻¹): 3173, 3054, 2923, 2856, 1671, 1601, 1500, 1454, 1396, 1222, 1195, 755, 740, 702; ¹H NMR (300 MHz, CDCl₃): δ 7.42 (dd, J = 7.3, 2.0 Hz, 1H), 7.34 (dt, J = 7.4, 2.0 Hz, 1H), 7.29 (dt, J = 7.4, 1.6 Hz, 1H), 7.19 (dd, J = 7.2, 1.6 Hz, 1H), 6.91 (brs, 1H), 6.50 (d, J = 2.7 Hz, 1H), 5.75 (d, J = 2.7 Hz, 1H), 4.01 (dd, J = 12.1, 5.2 Hz, 1H), 3.78 (dt, J = 12.1, 4.8 Hz, 1H), 2.41 (pent, J = 12.2 Hz, 2H), 2.23 (ddq, J = 13.6, 5.6, 2.8 Hz, 1H), 1.97 (dd, J = 11.8, 7.2 Hz, 1H), 1.89-1.81 (m, 1H), 1.71 (dt, J = 13.3, 3.0 Hz, 1H), 1.56-1.40 (m, 3H), 1.25 (dq, J = 14.4, 7.2 Hz, 1H), 0.71 (t, J = 7.4 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃): δ 177.5, 140.3, 137.9, 131.4, 130.5, 128.0, 127.2, 126.7, 119.1, 117.2, 109.6, 46.0, 38.9, 36.6, 33.1, 30.1, 28.0, 19.4, 8.1; MS (EI) m/z : 294 (21, M⁺), 265 (100), 237 (38), 209 (31), 69 (16); HRMS (EI) m/z : calcd for C₁₉H₂₂N₂O (M⁺) 294.1732; found 294.1724.

⁹ Johnson, J. A.; Li, N.; Sames, D. *J. Am. Chem. Soc.* **2002**, *124*, 6900-6903.

¹⁰ Linde, H. H. A. *Helv. Chim. Acta* **1965**, *48*, 1822.

13C NMR, CDCl₃, 300 MHz

¹H NMR Spectrum of Compound 19

¹³C NMR Spectrum of Compound 19

¹H NMR Spectrum of Compound 20

¹³C NMR Spectrum of Compound **20**

¹H NMR Spectrum of Compound **22**

¹³C NMR Spectrum of Compound **22**

¹H NMR Spectrum of Compound 23

¹³C NMR Spectrum of Compound **23**

¹H NMR Spectrum of Synthetic (-)-Rhazinilam (2)

¹³C NMR Spectrum of Synthetic (-)-Rhazinilam (**2**)