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An Enantioselective Total Synthesis of (+)-Geissoschizine

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EXPERIMENTAL SECTION

General. All reagents obtained from commercial sources were used without further purification unless otherwise indicated. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium and benzophenone. Dichloromethane (CH_2Cl_2), benzene, toluene, diisopropylamine, 2,6-lutidine, acetonitrile (CH_3CN), and triethylamine were distilled from calcium hydride. All air and/or moisture sensitive reactions were run under an argon atmosphere in oven dried glassware. Flash chromatography was performed using Merck silica gel 60 (230-400 mesh ASTM). Percent yields are given for compounds that were ≥95% pure as judged by NMR or HPLC. Melting points are uncorrected. Infrared (IR) spectra were recorded on a salt plate unless noted otherwise and are reported in wavenumbers (cm^{-1}). ^1H and ^{13}C NMR spectra were obtained at the indicated field as solutions in deuteriochloroform ($CDCl_3$) unless otherwise indicated. Chemical shifts for ^1H and ^{13}C NMR spectra are reported in parts per million (ppm, δ) downfield relative to internal tetramethylsilane (TMS); for ^{13}C spectra TMS was referenced to the center line of the $CDCl_3$ triplet (δ 77.0). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; and br, broad.

[3*S-(3α, 5β)]-3,4,5,6-Tetrahydro-3-(methyl but-2'-enoate-4'-yl)-1*H*-pyrido[3,4-b]indole-5-carboxylate (5).** A mixture of imine hydrochloride **3** (5.12 g, 20.5 mmol) and the vinyl ketene acetal **4** (13.2 g, 61.5 mmol) in anhydrous MeCN (100 mL) was stirred at 0 °C for 30 min and then at rt for 4 h, during which time a clear yellow solution resulted. The solvent was removed under reduced pressure and then under vacuum (1 mm Hg) to give a thick yellow oil, which was purified by flash chromatography eluting with CH_2Cl_2 and then with 10, 20, and 40% MeOH/CH_2Cl_2 to

give **5** (6.5 g) as a yellow solid, which was used in the next reaction without further purification. An analytical sample was obtained by flash chromatography eluting with 15-20% MeOH/CH_2Cl_2 ^{1}H NMR (250 MHz, MeOH-d_4) δ 7.88 (s, 1 H), 7.46 (d, *J* = 7.7 Hz, 1 H), 7.32 (d, *J* = 8.1 Hz, 1 H), 7.16-6.89 (m, 3 H), 6.07 (d, *J* = 15.7 Hz, 1 H), 5.12-5.01 (m, 1 H), 4.12 (t, *J* = 7.6 Hz, 1 H), 3.70 (s, 3 H), 3.37-2.94 (m, 4 H); ^{13}C NMR (62 MHz, MeOH-d_4) δ 173.5, 167.9, 143.2, 138.5, 129.2, 127.4, 126.5, 123.5, 120.5, 119.2, 112.3, 107.7, 55.8, 52.2, 52.0, 36.4, 23.6; IR (neat) ν 3378, 2950, 1709, 1628 cm^{-1}; mass spectrum (CI) *m/z* 315.1333 (M+) ($C_{12}H_{19}N_2O_4$ requires 315.1345), 315, 169 (base).

***tert*-Butyl-[3*S**-(3α,5β)]-3,4,5,6-tetrahydro-3-(methyl but-2'-enoate-4'-yl)-1*H*-pyrido[3,4-*b*]indole-5-carboxylate (6).** The crude acid **5** (6.5 g) from the preceeding experiment was dissolved in *p*-dioxane (150 mL) containing concentrated H_2SO_4 (10 mL), and isobutylene gas was bubbled for 3 h at rt into the mixture through a dispersion tube fitted with a glass frit; the volume of the solution increased by about 20 mL during this period. The solution was maintained at rt overnight, and then isobutylene gas was bubbled into the mixture as before for 1 h. The mixture was again allowed to stand overnight, whereupon it was slowly poured into a mixture of ice (100 g), ammonium hydroxide (20 mL) and CH_2Cl_2 (300 mL). The pH of the aqueous phase was adjusted to 9 by the slow addition of additional ammonium hydroxide. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was purified by flash chromatography eluting with 30% EtOAc/hexane followed by 50% EtOAc/hexane to give 4.45 g (59% from **3**) of **6** as a yellow oil, which formed a solid foam under vacuum. ^{1}H NMR (250 MHz) δ 7.89 (s, 1 H), 7.50 (d, *J* = 7.3 Hz, 1 H), 7.30 (d, *J* = 7.4 Hz, 1 H), 7.19-7.01 (m, 3 H), 5.97 (d, *J* = 15.7 Hz, 1 H), 4.38 (t, *J* = 6.7 Hz, 1 H), 3.81 (dd, *J* = 7.8, 5.1 Hz, 1 H), 3.75 (s, 3 H), 3.07 (dd, *J* = 15.4, 5.0 Hz, 1 H), 2.89 (dd, *J* = 15.3, 6.9 Hz, 1 H), 2.67 (t, *J* = 6.8 Hz, 2 H), 2.15 (br s, 1 H), 1.46 (s, 9 H); ^{13}C NMR (62 MHz) δ 172.7, 166.6, 145.3, 136.0, 134.0, 127.0, 123.9, 121.9, 119.5, 118.2, 110.8, 108.0, 81.4, 52.9, 51.6, 49.7, 38.8, 28.0, 25.1; IR (neat) ν 3358, 2977, 1723, 1657 cm^{-1}; mass spectrum (CI) *m/z* 371.1965, ($C_{21}H_{27}N_2O_4$ requires 371.1971), 371, 315, 271 (base).

***tert*-Butyl-[3S*-(3α,5β,15α,20β)]-3,4,5,6,14,15,20-heptahydro-20-(ethan-1-one)-15-(methyl acetate)-21-oxo-indolo[2, 3-a]quinolizine-5-carboxylate (7).** A solution of the amino ester **6** (10.0 g, 27.0 mmol), DMAP (200 mg, 1.64 mmol), and diketene (2.80 mL, 36.3 mmol) in anhydrous toluene (200 mL) was stirred at rt for 2.5 h. The solution was diluted with toluene (150 mL) and cooled to -10 °C. Potassium *tert*-butoxide (5.80 g, 51.7 mmol) was added, and the resulting suspension was vigorously stirred at -10 °C to -5 °C for 70 min. The reaction was quenched by adding 0.5 N HCl (100 mL), and the resulting solution was diluted with EtOAc (300 mL) and water (100 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (2 x 200 mL). The combined organic fractions were dried ($MgSO_4$), and the solvents were evaporated under reduced pressure. The product was purified by flash chromatography eluting with CH_2Cl_2 and 30% EtOAc/hexane to give 10.5 g

(86%) of **7** as a yellow solid. m.p. 80-82 °C; ^{1}H NMR (250 MHz) δ 8.07 (s, 1 H), 7.52 (d, *J* = 7.1 Hz, 1 H), 7.31 (dd, *J* = 6.9, 1.1 Hz, 1 H). 7.22-7.09 (m, 2 H), 5.86 (dd, *J* = 6.1, 1.3 Hz, 1 H), 5.09 (d, *J* = 10.4 Hz, 1 H), 3.69 (s, 3 H), 3.46-3.38 (m, 2 H) 2.96 (ddd, *J* = 8.4, 6.1, 2.1 Hz, 2 H), 2.62 (dt, *J* = 12.9, 3.6 Hz, 1 H), 2.52-2.26 (m, 3 H), 2.40 (s, 3 H), 1.28 (s, 9 H); ^{13}C NMR (62 MHz) δ 204.0, 171.9, 169.2, 166.4, 136.5, 131.1, 126.7, 122.4, 119.4, 118.4, 110.9, 107.1, 82.2, 61.5, 51.9, 51.2, 51.1, 38.5, 34.8, 30.3, 29.7, 27.9, 22.6; IR (neat) ν 3312, 2976, 1731, 1633, 1621 cm^{-1}; mass spectrum (CI) *m/z* 455.2174 (M+) ($C_{25}H_{31}N_2O_6$ requires 455.2182), 399 (base), 381.

***tert*-Butyl-[3S*-(3α,5β,15α,19β,20β)]-3,4,5,6,14,15,20-heptahydro-20-(1'*S*-1'-ethan-1'-ol)-15-(methyl acetate)-21-oxo-indolo[2,3-*a*]quinolizine-5-carboxylate (8).** A mixture of **7** (1.70 g, 3.86 mmol) and $NaBH_4$ (293 mg, 7.72 mmol) in anhydrous MeOH (60 mL) was stirred at -10 °C for 25 min. Saturated $NaHCO_3$ (40 mL) and CH_2Cl_2 (80 mL) were added and the mixture was stirred at 0 °C for 5 min. The organic layer was removed and the aqueous layer was extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were dried (Na_2SO_4) and concentrated to give 1.68 g (95%) of **8** as an off white solid, m.p. 190-192 °C. ^{1} H NMR (250 MHz) δ 7.90 (s, 1 H), 7.52 (d, *J* = 7.2 Hz, 1 H), 7.31 (d, *J* = 7.4 Hz, 1 H). 7.21-7.09 (m, 2 H), 5.90 (d, *J* = 4.4 Hz, 1 H), 5.04 (d, *J* = 10.3 Hz, 1 H), 4.27 (br s, 1 H), 3.71 (s, 3 H), 3.44 (d, *J* = 15.7 Hz, 1 H), 3.28 (br s, 1 H), 2.98 (ddd, *J* = 15.7, 6.0, 3.8 Hz, 1 H), 2.81-2.31 (m, 5 H), 1.41 (d, *J* = 6.4 Hz, 3 H), 1.25 (s, 9 H); ^{13}C NMR (62 MHz) δ 172.6, 170.9, 170.0, 136.5, 131.5, 126.7, 122.3, 119.8, 118.3, 110.9, 107.1, 82.4, 70.7, 53.5, 51.7, 51.4, 50.6, 40.4, 36.7, 31.0, 27.8, 22.6, 21.3; IR (neat) ν 3295, 2977, 1732, 1716, 1614 cm^{-1}; mass spectrum (CI) *m/z* 457.2327 (M+) ($C_{25}H_{33}N_2O_6$ requires 457.2339), 457 (base), 401, 369, 313.

***tert*-Butyl-20*E*-[3S*-(3α,5β,15α)]-3,4,5,6,14,15-hexahydro-15-(methyl acetate)-20-ethylidene-21-oxo-indolo[2,3-*a*]quinolizine-5-carboxylate (9).** A 0 °C solution of freshly prepared 0.1 M NaOMe (20 mL, 2.09 mmol) was added to a flask containing crude alcohol **8** (288 mg, 0.63 mmol) at 0 °C. After 20 min the mixture was allowed to warm to rt and was heated to 50 °C for 1.5 h. The solution was recooled to 0 °C and acetyl chloride (0.54 mL, 7.6 mmol) was slowly added. After 30 min the mixture was allowed to warm to rt and stirred for a additional 2.5 h. Saturated $NaHCO_3$ (30 mL) and CH_2Cl_2 (30 mL) were added, and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried (Na_2SO_4) and concentrated. The crude concentrate was purified by flash chromatography eluting with 30% EtOAc/hexane to give 239 mg (89%) of **9** as a colorless oil which formed a foam under vacuum. ^{1}H NMR (300 MHz) δ 7.89 (s, 1H), 7.55 (d, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.15 (m, 2H), 6.87 (q, *J* = 6.1 Hz, 1H), 5.81 (d, *J* = 4.4 Hz, 1H), 4.88 (d, *J* = 10.5 Hz, 1H), 3.68 (s, 3H), 3.65 (d, *J*= 15.4 Hz, 1H), 3.45 (br s, 1H), 3.1 (dd, *J* = 5.9, 1.6 Hz), 2.81 - 2.74 (m, 1H), 2.63 (ddd, *J* = 16.3, 10.6, 3.5 Hz, 2H), 1.85 (d, *J* = 7.3 Hz, 3H), 1.75-1.65 (m, 1H), 1.24 (s, 9H); ^{13}C NMR (75 MHz) δ 172.3, 170.1, 168.5, 136.6, 135.9, 133.5, 132.2, 126.7, 122.0, 119.6, 118.0, 110.9, 106.6, 81.7,

52.0, 51.6, 49.5, 40.0, 36.8, 29.6, 27.8, 23.2, 14.0; IR (neat) ν 3268, 2976, 1732, 1652, 1608 cm^{-1}; mass spectrum (CI) *m/z* 439.2225 (M+) ($C_{25}H_{31}N_2O_5$ requires 439.2233), 439 (base), 383.

***tert*-Butyl-20*E*-[3*S**-(3α,5β,15α)]-3,4,5,6,14,15,21-heptahydro-15-(methylacetate)-20-ethylidene-indolo[2,3-a]quinolizine-5-carboxylate (10).** A slurry of **9** (0.843 g, 1.92 mmol) and trimethyloxonium tetrafluoroborate (0.752 g, 5.08 mmol) in CH_2Cl_2 (60 mL) was stirred at rt for 22 h during which time a homogeneous yellow solution was produced. The reaction mixture was cooled to 0 °C, and anhydrous MeOH (20 mL) was added. After 15 min, $NaBH_4$ (0.750 g, 19.8 mmol) was added, and the mixture was stirred at 0 °C for another 20 min. Saturated $NaHCO_3$ (50 mL) and CH_2Cl_2 (100 mL) were added and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic fractions were dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was purified by flash chromatography eluting with 20% (300 mL) and 30% (300 mL) EtOAc/hexane to give 0.75 g (92%) **10** as a solid foam. ^1H NMR (250 MHz) δ 8.37 (s, 1 H), 7.45 (d, *J* = 6.9 Hz, 1 H), 7.31-7.28 (m, 1 H), 7.13-7.02 (m, 2 H), 5.42 (q, *J* = 6.8 Hz, 1 H), 4.64 (br s, 1 H), 3.71 (dd, *J* = 6.7, 4.6 Hz, 1 H), 3.65 (s, 3 H), 3.45 (br d, *J* = 12.1 Hz, 1 H), 3.31-3.01 (m, 4 H), 2.36-1.99 (m, 4 H), 1.61 (d, *J* = 6.8 Hz, 3 H), 1.34 (s, 9 H); ^{13}C NMR (62 MHz) δ 173.7, 171.8, 136.0, 135.8, 134.1, 127.5, 121.3, 120.8, 119.2, 117.9, 110.9, 105.4, 81.8, 61.2, 55.1, 51.7, 49.0, 38.0, 32.4, 31.8, 28.1, 21.9, 12.7; IR (neat) ν 3377, 2975, 1729 cm^{-1}; mass spectrum (CI) *m/z* 425.2431 (M+) ($C_{25}H_{33}N_2O_4$ requires 425.2440), 425 (base), 397, 369, 323.

20*E*-[3*S-(3α,5β,15α)]-3,4,5,6,14,15,21-Heptahydro-15-(methyl acetate)-20-ethylidene-indolo[2,3-*a*]quinolizine-5-carboxylic acid (11)** To a solution of the ester **10** (0.709 g, 1.67 mmol) and thioanisole (3.5 mL) in CH_2Cl_2 (4.0 mL) at 0 °C was added trifluoroacetic acid (4.0 mL), and the solution was then stirred at rt for 5 h. The volatiles were removed under vacuum, and the residue was purified by flash chromatography eluting with 5% MeOH/CH_2Cl_2 and 20% MeOH/CH_2Cl_2 to give 0.752 g (93%) of **11** as a solid foam. ^1H NMR (250 MHz, MeOH-d_4) δ 7.47 (d, *J* = 7.7 Hz, 1 H), 7.35 (d, *J* = 9.7 Hz, 1 H), 7.19-7.03 (m, 2 H), 5.77 (q, *J* = 6.8 Hz, 1 H), 5.27 (br s, 1 H), 4.12 (br s, 1 H), 3.88 (AB q, *J* =13.5 Hz, 2 H), 3.60 (s, 3 H), 3.54-3.31 (m, 3 H), 2.49 (br s, 2 H), 2.36 (dd, *J* = 15.5, 7.6 Hz, 1 H), 2.10 (dd, *J* = 15.5, 7.9 Hz, 1 H), 1.70 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (62 MHz, MeOH-d_4) δ 173.6, 138.4, 131.0, 130.3, 128.5, 127.5, 123.6, 120.7, 119.2, 112.4, 105.5, 54.3, 53.6, 52.2, 37.4, 31.4, 28.0, 27.7, 21.6, 13.3; IR (neat) ν 3364, 3233, 2954, 1732, 1682, 1633 cm^{-1}; mass spectrum (CI) *m/z* 369.1799 (M+) ($C_{21}H_{25}N_2O_4$ requires 369.1814), 369 (base), 323.

20*E*-[3*S-(3α, 15α)]-3,4,5,6,14,15,21-Heptahydro-15-(methyl acetate)-20-ethylideneindolo[2,3-*a*]quinolizine (12)** To a solution of acid **11** (240 mg, 0.652 mmol) in anhydrous THF (25 mL) at -10 °C was added isobutyl chloroformate (0.10 mL, 0.771 mmol) and *N*-methylmorpholine (85 μL, 0.771 mmol). The reaction mixture was stirred at -10 °C for 15 min and at rt for 15 min, whereupon it was recooled to -10 °C. A solution of sodium phenylselenide in THF, which

was prepared by reaction of benzeneselenol (82 μL, 0.771 mmol) and sodium hydride (32 mg, 60% dispersion in mineral oil, 0.80 mmol) in THF (10 mL) at 0°C, was then added through a cannula. The resulting mixture was stirred at -10 °C for 20 min and at rt for 30 min. The volatiles were removed under reduced pressure, and the residue was dissolved in benzene (20 mL). Neat Bu_3SnH (0.70 mL, 2.60 mmol) and AIBN (20 mg, 0.12 mmol) were added, and the mixture was heated at 80 °C (oil bath temp) with stirring for 4 h. The solvents were removed under reduced pressure, and the residue was purified by flash chromatography eluting with 40% EtOAc/hexane to give 167 mg (79%) of **12**, which gave spectroscopic data (^{1}H and ^{13}C NMR, IR, and MS) identical to that reported in the literature.[6]