Asymmetric [2+2] Cycloaddition: Total Synthesis of (–)-Swainsonine and (+)-6-Epicastanospermine

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SUPPORTING INFORMATION

Reactions were generally carried out under argon in oven-dried glassware at 110 °C. Standard inert atmosphere techniques were used in handling all air and moisture sensitive reagents. Dry THF was obtained by filtration through activated molecular sieves and dry toluene, diethyl ether, and CH₂Cl₂ by filtration through activated aluminium oxide. Hexamethylphosphoramide (HMPA) was distilled from calcium hydride. Thin-layer chromatography was performed on (0.2 mm) silica sheets, which were visualized under ultraviolet light and by heating the plate after treatment with phosphomolybdic acid in ethanol, a *p*-anisaldehyde staining solution (80 mL of 95% ethanol, 2.9 mL of sulfuric acid, 0.86 mL of acetic acid, 2.1 mL of *p*-anisaldehyde), ninhydrin in ethanol, ceric ammonium molybdate in ethanol, or basic, aqueous KMnO₄. Silica gel (0.040-0.063 mm) was employed for flash column chromatography. Melting points were obtained on a Büchi melting point apparatus and are uncorrected. Optical rotations were determined with a Perkin-Elmer 341 polarimeter. A Fourier transform infrared spectrometer (FTIR) was used to record IR spectra. ¹H NMR and ¹³C NMR spectra were recorded on either a Bruker AV 300 or a Varian 500 apparatus. All shifts for ¹H spectra were referenced to the residual solvent peak and are reported in ppm. When ambiguous, proton and carbon assignments were established using COSY, HMQC and/or DEPT experiments. Mass spectra were recorded using either DCI (ammonia/isobutane 63/37) or ESI techniques. Microanalyses were performed by the analytical service of the LEDSS.

(*S,E*)-2-(1-(1,2-Dichlorovinyl)oxyethyl)-1,3,5-triisopropylbenzene (5). An argon-flushed flask was charged with potassium hydride (30% suspension in mineral oil, 14.3 g, 107 mmol). The mineral oil was removed by washing with pentane (3×10 mL), and anhydrous THF (60 mL) was then added. A solution of (*S*)-1-(2,4,6-triisopropylphenyl)ethanol **4** (12.0 g, 48.3 mmol) in anhydrous THF (40 mL) was added dropwise at 0 °C. The mixture was stirred at room temperature for 2 h, cooled to –50 °C, and treated dropwise with a solution of trichloroethylene (4.8 mL, 53 mmol) in anhydrous THF (20 mL). The reaction mixture was allowed to warm to 0 °C, and stirred until TLC (eluent pentane) showed complete disappearance of starting material. The mixture was then carefully treated with methanol (6 mL) and water (12 mL). The crude product was extracted with pentane in the usual way and the combined extracts were washed with water, dried over Na₂SO₄, and concentrated under vacuum at 0 °C. The residue was purified by flash chromatography on silica gel (pretreated with 2.5% of triethylamine, v/v) (eluent pentane) to afford 13.0 g (79%) of dichloroenol ether **5**: mp 38–41 °C; $[\alpha]_D^{20}$ –16.2 (*c* 1.0, CHCl₃); IR (film) 3086, 1623, 1609, 1078, 1040 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 7.05 (s, 2H), 6.00 (q, *J* = 6.9 Hz, 1H), 5.60 (s, 1H), 3.75–3.15 (br s, 2H), 2.90 (sept, *J* = 6.9 Hz, 1H), 1.70 (d, *J* = 6.9 Hz, 3H), 1.35–1.20 (m, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 148.5 (C_q), 142.9 (C_q), 131.2 (C_q), 122.1 (CH), 98.3 (CH), 76.4 (CH), 34.1 (CH), 29.4 (CH), 24.7 (CH₃), 24.5 (CH₃), 23.9 (CH₃), 20.3 (CH₃); MS (EI⁺) *m/z* 343 and 341 (M⁺), 248, 231 (100%); Anal. Calcd. for C₁₉H₂₈ClO: C, 66.47; H, 8.22. Found: C, 66.63; H, 8.36.

(*S*)-1,3,5-Triisopropyl-2-(1-(pent-4-en-1-ynyl)oxyethyl)benzene (6a). To a solution of dichloroenol ether **5** (13.0 g, 37.7 mmol) in anhydrous THF (120 mL) at –78 °C was added dropwise a solution of *n*-BuLi (2.5 M in hexanes, 33 mL, 83 mmol). The reaction mixture

was allowed to warm to $-40\text{ }^{\circ}\text{C}$. Allyl iodide (7.0 mL, 77 mmol) (prefiltered through a pad of basic alumina) and distilled HMPT (12 mL) were then added slowly at $-60\text{ }^{\circ}\text{C}$. The resulting solution was allowed to warm to $-5\text{ }^{\circ}\text{C}$, stirred until TLC (eluent pentane) showed complete consumption of starting material, and then poured into cold saturated NH_4Cl . The aqueous layer was extracted three times with cold pentane. The combined organic phases were washed with cold water and brine, dried over Na_2SO_4 , filtered, and concentrated at $0\text{ }^{\circ}\text{C}$ to give the crude acetylenic enol ether **6a** as a yellow oil, which was used immediately without purification: IR (film) 3005, 2960, 2930, 2896, 2269, 1608, 1460, 1230 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.00 (s, 2H), 5.80-5.65 (m, 2H), 5.04 (dq, $J = 15.1, 1.9\text{ Hz}$, 1H), 4.95 (dq, $J = 11.8, 1.9\text{ Hz}$, 1H), 3.39 (br s, 2H), 2.89 (sept, $J = 6.9\text{ Hz}$, 1H), 2.83 (dt, $J = 5.0, 1.9\text{ Hz}$, 1H), 1.70 (d, $J = 6.9\text{ Hz}$, 3H), 1.35-1.20 (m, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 148.5 (C_q), 134.1 (CH), 130.9 (C_q), 122.0 (C_q), 120.4 (CH), 119.3 (CH), 114.8 (CH_2), 91.7 (C_q), 83.0 (CH), 34.1 (CH_2), 29.3 (CH), 24.5 (CH_3), 23.9 (CH_3), 23.9 (CH), 21.6 (CH_3); MS (EI^+) m/z 313 (M^+), 271, 231 (100%).

(*S,Z*)-1,3,5-Triisopropyl-2-(1-(penta-1,4-dienyloxy)ethyl)benzene (6b). A $0\text{ }^{\circ}\text{C}$ solution of the crude acetylenic enol ether **6a** (37.7 mmol, based on a 100% yield for the previous reaction) in anhydrous THF (50 mL) was added dropwise to a solution of Dibal-H (1.5 M in toluene, 57 mmol, 38 mL) in anhydrous THF (25 mL) at $50\text{ }^{\circ}\text{C}$. After TLC showed complete disappearance of starting material (ca. 45 min), the solution was quenched with $\text{Na}_2\text{SO}_4 \cdot 10\text{H}_2\text{O}$, diluted with pentane, and poured into a 1/1 mixture of saturated aqueous NH_4Cl and pentane at $0\text{ }^{\circ}\text{C}$. After elimination of the precipitate by filtration, the organic layer was separated, and the aqueous phase extracted twice with cold pentane. The combined organic phases were washed with cold water and brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated at $0\text{ }^{\circ}\text{C}$ to give the crude enol ether **6b** as a yellow oil, which was used without purification: IR (film) 2961, 2935, 2867, 1667, 1612, 1464, 1384 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.03 (s, 2H), 6.03 (dt, $J = 6.3, 1.4\text{ Hz}$, 1H), 5.85 (ddt, $J = 17.2, 10.1, 6.3\text{ Hz}$, 1H), 5.37 (q, $J = 6.9\text{ Hz}$, 1H), 5.05 (ddd, $J = 17.2, 3.7, 1.7\text{ Hz}$, 1H), 4.95 (ddd, $J = 10.1, 3.5, 1.4\text{ Hz}$, 1H), 4.31 (dt, $J = 7.3, 6.3\text{ Hz}$, 1H), 3.70-3.30 (m, 2H), 3.00-2.80 (m, 2

H), 1.63 (d, $J = 6.9$ Hz, 3 H), 1.35-1.20 (m, 18 H); ^{13}C NMR (75 MHz, CDCl_3) δ 147.7 (C_q), 144.5 (CH), 137.7 (CH), 133.0 (C_q), 121.9 (CH), 113.9 (CH_2), 103.3 (CH), 75.4 (CH), 34.0 (CH), 29.1 (CH), 28.5 (CH_2), 24.5 (CH_3), 23.9 (CH_3), 22.5 (CH_3).

(3*S*,4*R*)-4-Allyl-2,2-dichloro-3-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)cyclobutanone (7). To Zn-Cu (3.14 g, 48.2 mmol) in degassed Et_2O (50 mL) at 20 °C was added a solution of enol ether **6b** (30.2 mmol, based on an 80% yield for the previous reaction) in degassed Et_2O (70 mL), followed by trichloroacetyl chloride (4.0 mL, 36 mmol) dropwise over 1 h. The resulting mixture was then poured in cold hexane (300 mL), which was filtered over Celite[®] and partially concentrated at 0 °C. The solution was poured again into cold hexane (200 mL), which was filtered over Celite[®] and concentrated at 0 °C to give the crude cyclobutanone **7** as a yellow oil (dr = 95:5), which was used without purification: IR (film) 2956, 2930, 2872, 1809, 1455 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.09 (d, $J = 1.9$ Hz, 1H), 7.04 (d, $J = 1.9$ Hz, 1H), 5.86 (dddd, $J = 17.0, 10.1, 6.9, 6.9$ Hz, 1H), 5.47 (q, $J = 6.9$ Hz, 1H), 5.18-5.02 (m, 2H), 4.34 (d, $J = 9.5$ Hz, 1H), 3.85 (sept, $J = 6.9$ Hz, 1H), 3.55 (ddd, $J = 9.5, 9.5, 6.3$ Hz, 1H), 3.28 (sept, $J = 6.9$ Hz, 1H), 2.89 (sept, $J = 6.9$ Hz, 1H), 2.67-2.48 (m, 2H), 1.68 (d, $J = 6.9$ Hz, 3H), 1.40-1.10 (m, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 195.8 (C_q), 148.9 (C_q), 148.3 (C_q), 147.1 (C_q), 134.5 (CH), 123.4 (CH), 120.8 (CH), 117.1 (CH_2), 88.3 (C_q), 77.2 (CH), 73.4 (CH), 58.5 (CH), 34.0 (CH), 29.7 (CH_2), 29.2 (CH), 28.2 (CH), 25.4 (CH_3), 24.9 (CH_3), 23.9 (CH_3), 22.5 (CH_3); MS (DCI, NH_3 /isobutane) m/z 444, 429, 427, 425 (MH^+), 232, 231 (100%), 230.

(4*S*,5*R*)-5-Allyl-3,3-dichloro-4-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-one. To a solution of the crude dichlorocyclobutanone **7** (30.2 mmol, based on a 100% yield for the previous reaction) in anhydrous CH_2Cl_2 (100 mL) at 0 °C was added anhydrous Na_2SO_4 and Tamaru's reagent (3×7.82 g, 108.6 mmol) in 3 portions one hour apart. After

IR showed complete disappearance of the starting material, CH₂Cl₂ (150 mL) and toluene (20 mL) were added and the mixture was filtered and the filtrate was concentrated at 0 °C to afford a yellow oil. Toluene (10 mL) was added and the solution was filtered through a column of basic alumina (500 mL), eluting with methanol (500 mL). The solvents were evaporated under reduced pressure to afford the crude dichlorolactam, which was used without purification: mp 112-116 °C; IR (film) 3248, 2964, 2924, 2864, 1735, 1610, 1462 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.07 (d, *J* = 1.8 Hz, 1H), 6.96 (d, *J* = 1.8 Hz, 1H), 5.80-5.60 (m, 2H), 5.21-5.11 (m, 2H), 4.47 (d, *J* = 7.0 Hz, 1H), 3.91 (sept, *J* = 6.8 Hz, 1H), 3.64-3.55 (m, 1H), 3.25 (sept, *J* = 6.8 Hz, 1H), 2.87 (sept, *J* = 6.8 Hz, 1H), 2.65-2.55 (m, 1H), 2.40-2.15 (m, 1H), 1.71 (d, *J* = 6.8 Hz, 3H), 1.35-1.15 (m, 18H); ¹³C NMR (75 MHz, CDCl₃) δ 167.5 (C_q), 148.8 (C_q), 148.1 (C_q), 146.5 (C_q), 133.5 (CH), 123.4 (CH), 120.9 (CH), 119.0 (CH₂), 82.5 (C_q), 81.8 (CH), 73.6 (CH), 55.0 (CH), 34.4 (CH₂), 33.9 (CH), 28.9 (CH), 28.3 (CH), 25.5 (CH₃), 25.0 (CH₃), 23.9 (CH₃), 23.0 (CH₃); MS (DCI, NH₃/isobutane) *m/z* 461, 459, 457, 444, 442, 440 (M⁺, 100%), 406, 231, 230; Anal. Calcd. for C₂₄H₃₅Cl₂NO₂: C, 65.45; H, 8.01; N, 3.18; Cl, 16.10. Found: C, 65.43; H, 8.12; N, 3.15; Cl, 16.18.

(4*R*,5*R*)-5-Allyl-4-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-one (8).

The crude dichlorolactam (30.2 mmol, based on a 100% yield for the previous reaction) was dissolved in a solution of saturated NH₄Cl in methanol (300 mL), and Zn-Cu (5.89 g, 90.5 mmol) was added. The suspension was stirred for 18 h at room temperature. Cold Et₂O (350 mL) was added and the reaction mixture was filtered through a pad of Celite® and the filtrate was partially concentrated. Cold Et₂O (350 mL) was added again and the mixture was filtered through a pad of Celite® and the filtrate was concentrated. Purification of the crude product by flash chromatography on silica gel (eluent EtOAc/pentane, 3/7 to 10/0) afforded lactam **8** (4.77 g, 34% over 5 steps) as a white solid: mp 109-111 °C; [α]_D²⁰ -69.9 (*c* 1.0, CHCl₃); IR (film) 3214, 2960, 2926, 2868, 1697, 1455, 1385, 1108, 1077 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.05 (s, 1H), 6.95 (s, 1H), 5.88 (br s, 1H), 5.76 (dddd, *J* = 17.9, 9.7, 8.4, 6.0 Hz, 1H), 5.16-5.01 (m, 3H), 4.17 (q, *J* = 7.0 Hz, 1H), 3.87 (sept, *J* = 6.7 Hz, 1H), 3.64 (app. ddd, *J* = 9.9, 7.0, 3.1 Hz, 1H), 3.15 (sept, *J* = 6.8 Hz, 1H), 2.85 (sept, *J* = 6.9 Hz, 1H), 2.54 (dd, *J* =

16.6, 7.0 Hz, 1H), 2.47 (dd, $J = 16.6, 7.0$ Hz, 1H), 2.52-2.42 (m, 1H), 2.33-2.17 (m, 1H), 1.55 (d, $J = 6.8$ Hz, 3H), 1.29-1.17 (m, 18H); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9 (C_q), 148.7 (C_q), 147.6 (C_q), 145.8 (C_q), 134.6 (CH), 132.0 (C_q), 123.2 (CH), 120.6 (CH), 118.2 (CH_2), 72.3 (CH), 71.2 (CH), 57.2 (CH), 36.6 (CH_2), 34.7 (CH_2), 33.9 (CH), 29.1 (CH), 25.1 (CH_3), 24.9 (CH_3), 24.2 (CH_3), 23.8 (CH_3), 23.1 (CH_3); MS (DCI, $\text{NH}_3/\text{isobutane}$) m/z 389, 372 (MH^+ , 100%), 264, 231, 163; Anal. Calcd. for $\text{C}_{24}\text{H}_{37}\text{NO}_2$: C, 77.58; H, 10.04; N, 3.77. Found: C, 77.30; H, 10.05; N, 3.79.

(4*R*,5*R*)-5-((*RS*)-1-Hydroxyallyl)-4-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)-pyrrolidin-2-one (9a,b). *tert*-Butylhydroperoxide (5 M in decane, 1.8 mL, 9.0 mmol) was added to SeO_2 (254 mg, 2.27 mmol) in distilled 1,2-dichloroethane (10 mL). The mixture was vigorously stirred at 20 °C for 1.5 h and then lactam **8** (1.70 g, 4.58 mmol) in distilled 1,2-dichloroethane (20 mL) was added rapidly. The resulting mixture was warmed to 70 °C and stirred for 3.3 h. After being allowed to cool to 20 °C, the reaction mixture was treated with an aqueous solution of NaHCO_3 (50 mL), diluted with H_2O (30 mL), and extracted with EtOAc (3 $\times$ 120 mL). The combined organic extracts were washed with aqueous Na_2SO_3 (120 mL), water (120 mL), and brine (120 mL), dried over MgSO_4 , filtered, and concentrated. The resulting crude product was dissolved in EtOH (7 mL) and at 0 °C was treated with $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (171 mg, 0.46 mmol), followed by NaBH_4 (17.3 mg, 0.46 mmol), to reduce the 5-10% of enone. After 1 h at 0 °C, the reaction mixture was processed with EtOAc in the usual way and the crude product was purified by flash chromatography on silica gel (eluent EtOAc/ CH_2Cl_2 , 4/6 to 10/0) to afford 440 mg of recovered lactam **8**, followed by 988 mg (56%, 75% based on recovered starting material) of **9a,b** as a white foam. Extensive purification of this material over silica gel provided enriched samples of **9a** and **9b** for spectral data:

Compound 9a (cis-anti): IR 3380, 2957, 2926, 2869, 1693, 1455, 1383, 1103, 1073 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.09 (s, 1H, H_{R^*}), 7.00 (s, 1H, H_{R^*}), 5.86 (ddd, $J = 17.3, 10.5, 6.8$ Hz, 1H, H_7), 5.48 (br s, 1H, H_{NH}), 5.39 (app. dt, $J = 17.3, 1.2$ Hz, 1H, H_8), 5.32 (app. dt, $J = 10.5, 1.2$ Hz, 1H, H_8), 5.20 (q, $J = 6.8$ Hz, 1H, H_{R^*}), 4.45-4.35 (m, 2H, $\text{H}_{4,6}$), 3.72

(sept, $J = 6.9$ Hz, 1H, H_{R^*}), 3.56 (dt, $J = 7.1, 1.1$ Hz, 1H, H_5), 3.38 (d, $J = 2.3$ Hz, 1H, H_{OH}), 3.17 (sept, $J = 6.8$ Hz, 1H, H_{R^*}), 2.88 (sept, $J = 6.9$ Hz, 1H, H_{R^*}), 2.57 (s, 1H, H_3), 2.54 (s, 1H, H_3), 1.63 (d, $J = 6.8$ Hz, 3H, H_{R^*}), 1.34-1.18 (m, 18H, H_{R^*}); ^{13}C NMR (75 MHz, CDCl_3) δ 174.1 (C_q , C_2), 148.7 (C_q , C_{R^*}), 148.2 (C_q , C_{R^*}), 146.1 (C_q , C_{R^*}), 136.5 (CH, C_7), 123.4 (CH, C_{R^*}), 121.0 (CH, C_{R^*}), 118.4 (CH_2 , C_8), 73.2 (CH, C_4 et C_6), 72.6 (CH, C_{R^*}), 59.8 (CH, C_5), 36.1 (CH_2 , C_3), 34.0 (CH, C_{R^*}), 29.2 (CH, C_{R^*}), 28.5 (CH, C_{R^*}), 25.2 (CH_3 , C_{R^*}), 25.1 (CH_3 , C_{R^*}), 24.1 (CH_3 , C_{R^*}), 23.8 (CH_3 , C_{R^*}), 23.2 (CH_3 , C_{R^*}), 23.1 (CH_3 , C_{R^*}); MS (DCI, $\text{NH}_3/\text{isobutane}$) m/z 405, 388 ($\text{M}+\text{H}^+$, 50%), 231, 184 (100%).

Compound 9b (cis-syn): IR 3380, 2957, 2926, 2869, 1693, 1461, 1383, 1105, 1073 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.07 (s, 1H, H_{R^*}), 6.99 (s, 1H, H_{R^*}), 5.80 (ddd, $J = 17.3, 10.7, 4.4$ Hz, 1H, H_7), 5.70 (br s, 1H, H_{NH}), 5.42 (dt, $J = 17.3, 1.7$ Hz, 1H, H_8), 5.27 (dt, $J = 10.7, 1.7$ Hz, 1H, H_8), 5.18 (q, $J = 6.9$ Hz, 1H, H_{R^*}), 4.61 (m, 1H, H_6), 4.35 (dt, $J = 7.6, 6.8$ Hz, 1H, H_4), 3.82 (sept, $J = 6.7$ Hz, 1H, H_{R^*}), 3.65 (dd, $J = 7.6, 1.4$ Hz, 1H, H_5), 3.16 (sept, $J = 6.7$ Hz, 1H, H_{R^*}), 2.87 (sept, $J = 6.9$ Hz, 1H, H_{R^*}), 2.61 (dd, $J = 16.7, 6.8$ Hz, 1H, H_3), 2.54 (dd, $J = 16.7, 7.6$ Hz, 1H, H_3), 1.61 (d, $J = 6.9$ Hz, 3H, H_{R^*}), 1.31-1.18 (m, 18H, H_{R^*}); ^{13}C NMR (75 MHz, CDCl_3) δ 175.0 (C_q , C_2), 148.6 (C_q , C_{R^*}), 148.2 (C_q , C_{R^*}), 146.4 (C_q , C_{R^*}), 136.3 (CH, C_7), 123.4 (CH, C_{R^*}), 120.9 (CH, C_{R^*}), 116.6 (CH_2 , C_8), 72.3 (CH, C_4), 71.7 (CH, C_{R^*}), 70.4 (CH, C_6), 60.5 (CH, C_5), 37.3 (CH_2 , C_3), 34.0 (CH, C_{R^*}), 29.2 (CH, C_{R^*}), 28.2 (CH, C_{R^*}), 25.14 (CH_3 , C_{R^*}), 25.06 (CH_3 , C_{R^*}), 25.0 (CH_3 , C_{R^*}), 24.2 (CH_3 , C_{R^*}), 23.8 (CH_3 , C_{R^*}), 22.9 (CH_3 , C_{R^*}); MS (DCI, $\text{NH}_3/\text{isobutane}$) m/z 405, 388 ($\text{M}+\text{H}^+$, 70%), 231, 184 (100%).

(4R,5S)-5-Acryloyl-4-((S)-1-(2,4,6-triisopropylphenyl)ethoxy)pyrrolidin-2-one.

To a solution of alcohols **9a,b** (1.87 g, 4.82 mmol) in CH_2Cl_2 (35 mL) was added Dess-Martin reagent (15 wt % in CH_2Cl_2 , 27.2 g, 9.62 mmol). After 1 h, aqueous NaHCO_3 (60 mL) and aqueous $\text{Na}_2\text{S}_2\text{O}_3$ (10 wt %, 60 mL) were added, and the crude product was extracted with EtOAc (3 $\times$ 120 mL). The combined organic phases were washed with water and brine, dried over anhydrous MgSO_4 , and concentrated to afford the enone as a pale yellow solid, which was used without purification: IR (film) 3245, 2956, 2929, 2864, 1701, 1401, 1070 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.05 (s, 1H, H_{R^*}), 6.95 (s, 1H, H_{R^*}), 6.52 (dd, $J = 17.3, 10.5$ Hz, 1H, H_7), 6.25 (dd, $J = 17.3, 1.4$ Hz, 1H, H_8), 5.84 (s, 1H, H_1), 5.68 (dd, $J = 10.5, 1.4$ Hz, 1H,

H₈), 5.06 (q, $J = 6.8$ Hz, 1H, H_{R*}), 4.53-4.46 (m, 2H, H_{4,5}), 3.72 (sept, $J = 6.9$ Hz, 1H, H_{R*}), 3.12 (sept, $J = 6.8$ Hz, 1H, H_{R*}), 2.86 (sept, $J = 7.0$ Hz, 1H, H_{R*}), 2.55-2.52 (m, 2H, H_{3,3'}), 1.49 (d, $J = 6.8$ Hz, 3H, H_{R*}), 1.32-1.14 (m, 18H, H_{R*}); ¹³C NMR (75 MHz, CDCl₃) δ 196.0 (C_q, C₆), 175.6 (C_q, C₂), 148.7 (C_q, C_{R*}), 148.0 (C_q, C_{R*}), 145.9 (C_q, C_{R*}), 133.8 (CH, C₇), 131.0 (C_q, C_{R*}), 127.9 (CH₂, C₈), 123.2 (CH, C_{R*}), 120.8 (CH, C_{R*}), 73.9 (CH, C₄), 72.3 (CH, C_{R*}), 63.7 (CH, C₅), 36.3 (CH₂, C₃), 34.0 (CH, C_{R*}), 29.1 (CH, C_{R*}), 28.0 (CH, C_{R*}), 25.3 (CH₃, C_{R*}), 25.1 (CH₃, C_{R*}), 24.0 (CH₃, C_{R*}), 23.9 (CH₃, C_{R*}), 22.8 (CH₃, C_{R*}), 22.2 (CH₃, C_{R*}); MS (DCI, NH₃/isobutane) m/z 403 (M+NH₄⁺, 100%), 387, 245, 199, 182.

(4R,5R)-5-((R)-1-Hydroxyallyl)-4-((S)-1-(2,4,6-triisopropylphenyl)ethoxy)-pyrrolidin-2-one (9a). A solution of the above enone (4.82 mmol, based on a 100% yield for the previous reaction) in anhydrous THF (20 mL) was added dropwise to a suspension of LiAlH₄ (329 mg, 8.69 mmol) in anhydrous THF (5 mL) at -25 °C. The mixture was kept at -25 °C until TLC showed complete disappearance of the starting material (ca. 1 h), whereupon the reaction was quenched at -25 °C by addition of water (0.33 mL), aqueous NaOH (15 wt %, 0.33 mL), and water (1.0 mL). The suspension was stirred until a white solid was formed and then diluted with EtOAc and filtered over Celite[®]. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography on silica gel (eluent EtOAc/CH₂Cl₂, 4/6 to 10/0) to afford 1.53 g (82%) of **9a,b** (cis-anti: cis-syn = 92:8) as a white foam.

(1R,7R,7aS)-7-((S)-1-(2,4,6-Triisopropylphenyl)ethoxy)-1-vinyl-tetrahydro-pyrrolo[1,2-c]-oxazol-3(1H)-one (11). To a solution of LiAlH₄ (20 mg, 0.52 mmol) in THF (2 mL) was added pyrrolidinone **9a** (50.0 mg, 0.13 mmol) and the mixture refluxed for 2 h. The reaction was then quenched by addition of water (0.020 mL), NaOH (15% water, 0.020

mL), and water (0.020 mL) and the resulting suspension was filtered over Celite and the filtrate was concentrated. The crude oil was taken up in CH₂Cl₂ (2 mL), carbonyldiimidazole (26 mg, 0.16 mmol) was added, and the resulting solution was stirred for 12 h. After standard workup of the reaction mixture with EtOAc, the residue was purified by flash chromatography on silica gel (eluent pentane/ether, 1/1) to give oxazolidinone **11** (20.5 mg, 50% over 2 steps) as a white solid: mp 141-143 °C; IR 2960, 2926, 2866, 1755, 1461, 1383, 1067 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.06 (d, *J* = 2.0 Hz, 1H, H_{R*}), 6.95 (d, *J* = 2.0 Hz, 1H, H_{R*}), 6.07 (ddd, *J* = 17.4, 10.3, 8.2 Hz, 1H, H₈), 5.33 (dt, *J* = 17.4, 1.2 Hz, 1H, H₉), 5.14 (q, *J* = 6.9 Hz, 1H, H_{R*}), 5.13 (dt, *J* = 10.3, 1.2 Hz, 1H, H₉), 5.02 (app. t, *J* = 8.2 Hz, 1H, H₁), 3.95 (dt, *J* = 3.0, 1.1 Hz, 1H, H₇), 3.85-3.68 (m, 2H, H_{R*,5}), 3.75 (dd, *J* = 8.2, 3.0 Hz, 1H, H_{7a}), 3.33 (ddd, *J* = 11.0, 9.7, 1.6 Hz, 1H, H_{5'}), 3.24 (sept, *J* = 6.8 Hz, 1H, H_{R*}), 2.87 (sept, *J* = 6.9 Hz, 1H, H_{R*}), 2.35 (app. ddt, *J* = 13.8, 7.5, 1.3 Hz, 1H, H₆), 1.91 (app. dtd, *J* = 13.8, 9.7, 3.5 Hz, 1H, H_{6'}), 1.57 (d, *J* = 6.9 Hz, 3H, H_{R*}), 1.34-1.18 (m, 18H, H_{R*}); ¹³C NMR (75 MHz, CDCl₃) δ 161.9 (C_q, C₃), 148.8 (C_q, C_{R*}), 147.6 (C_q, C_{R*}), 144.4 (C_q, C_{R*}), 132.8 (CH, C₈), 123.3 (CH, C_{R*}), 120.6 (CH, C_{R*}), 119.9 (CH₂, C₉), 77.5 (CH, C₁), 77.2 (CH, C₇), 73.4 (CH, C_{R*}), 68.2 (CH, C_{7a}), 44.4 (CH₂, C₅), 34.0 (CH, C_{R*}), 32.7 (CH₂, C₆), 29.3 (CH, C_{R*}), 28.5 (CH, C_{R*}), 25.7 (CH₃, C_{R*}), 25.2 (CH₃, C_{R*}), 24.7 (CH₃, C_{R*}), 24.0 (CH₃, C_{R*}), 23.9 (CH₃, C_{R*}), 23.2 (CH₃, C_{R*}); MS (DCI, NH₃/isobutane) *m/z* 417 (M+NH₄⁺), 400 (MH⁺), 356, 264, 231 (100%).

(4*R*,5*S*)-4-((*S*)-1-(2,4,6-Triisopropylphenyl)ethoxy)-5-((*R*)-1-(triisopropylsilyloxy)-allyl)-pyrrolidin-2-one (12). To a solution of alcohol **9a** (1.61 g, 4.15 mmol) in anhydrous CH₂Cl₂ was added dropwise distilled *i*-Pr₂NEt (2.90 mL, 16.6 mmol) and TIPSOTf (3.00 mL, 11.2 mmol) and the reaction mixture was stirred for 1 h. Water (70 mL) was then added and the crude product was extracted with Et₂O (3 × 70 mL). The combined organic layers were washed with water and brine, dried over MgSO₄, and concentrated to afford the disilylated product as a colorless oil. This material was dissolved in THF (30 mL) and aqueous AcOH (1 N, 4.5 mL, 4.5 mmol) was added dropwise, followed by water (70 mL). The reaction mixture was processed with Et₂O in the usual way and the crude product was purified by flash

chromatography on silica gel (eluent Et₂O/pentane, 2/8 to 8/2) to afford silyl ether **12** (1.84 g, 81%) as a white foam: $[\alpha]_D^{20} -15.3$ (*c* 1.0, CHCl₃); IR 3212, 3107, 2965, 2867, 1706, 1466, 1107 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.05 (s, 1H, H_{R*}), 6.96 (s, 1H, H_{R*}), 6.10 (ddd, *J* = 17.4, 10.7, 5.0 Hz, 1H, H₇), 5.71 (s, 1H, H₁), 5.47 (dt, *J* = 17.4, 1.8 Hz, 1H, H₈), 5.29 (ddd, *J* = 10.7, 1.8, 1.1 Hz, 1H, H₈'), 5.05 (q, *J* = 6.8 Hz, 1H, H_{R*}), 4.65 (dd, *J* = 5.0, 3.3 Hz, 1H, H₆), 4.27 (q, *J* = 8.5 Hz, 1H, H₄), 3.88 (sept, *J* = 6.7 Hz, 1H, H_{R*}), 3.87 (dd, *J* = 8.5, 3.3 Hz, 1H, H₅), 3.14 (sept, *J* = 6.7 Hz, 1H, H_{R*}), 2.86 (sept, *J* = 6.9 Hz, 1H, H_{R*}), 2.46 (dd, *J* = 16.3, 8.5 Hz, 1H, H₃), 2.39 (dd, *J* = 16.3, 8.5 Hz, 1H, H₃'), 1.56 (d, *J* = 6.8 Hz, 1H, H_{R*}), 1.30-1.12 (m, 18H, H_{R*}), 1.07-1.04 (m, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 175.0 (C_q, C₂), 148.7 (C_q, C_{R*}), 147.9 (C_q, C_{R*}), 146.3 (C_q, C_{R*}), 136.5 (CH, C₇), 131.3 (C_q, C_{R*}), 123.2 (CH, C_{R*}), 120.8 (CH, C_{R*}), 118.2 (CH₂, C₈), 72.8 (CH, C₆), 71.4 (CH, C_{R*}), 71.2 (CH, C₄), 62.2 (CH, C₅), 36.4 (CH₂, C₃), 34.0 (CH, C_{R*}), 29.1 (CH, C_{R*}), 28.1 (CH, C_{R*}), 25.3 (CH₃, C_{R*}), 25.2 (CH₃, C_{R*}), 25.1 (CH₃, C_{R*}), 24.2 (CH₃, C_{R*}), 23.9 (CH₃, C_{R*}), 23.3 (CH₃, C_{R*}), 18.1 (CH₃, C_{TIPS}), 12.3 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) *m/z* 544 (M⁺, 100 %), 231, 166; Anal. Calcd. for C₃₃H₅₇NO₃Si: C, 72.87; H, 10.56; N, 2.58. Found: C, 72.62; H, 10.75; N, 2.55.

(4*R*,5*S*)-1-Allyl-4-((*S*)-1-(2,4,6-triisopropylphenyl)ethoxy)-5-((*R*)-1-(triisopropylsilyloxy)-allyl)pyrrolidin-2-one (13**).** Lactam **12** (1.84 g, 3.38 mmol) was added to CH₂Cl₂ (30 mL) and aqueous NaOH (40 wt %, 15 mL). Allyl bromide (3 × 1.20 mL, 3 × 13.9 mmol) and *n*-Bu₄N.HSO₄ (3 × 575 mg, 3 × 1.69 mmol) were added at room temperature, each in three portions, one every 2 h. The reaction mixture was then diluted with water (60 mL) and the product was extracted with Et₂O (3 × 70 mL). The combined organic phases were washed with water and brine, dried over anhydrous MgSO₄, and concentrated, and the crude product was purified by flash chromatography on silica gel (eluent Et₂O/pentane, 1/9 to 6/4) to afford **13** (1.89 g, 95%) as a colorless oil: $[\alpha]_D^{20} -3.2$ (*c* 1.0, CHCl₃); IR (film) 3390, 3083, 2959, 2866, 1695, 1457, 1106, 1065 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.05 (d, *J* = 1.6 Hz, 1H, H_{R*}), 6.97 (d, *J* = 1.6 Hz, 1H, H_{R*}), 5.99 (ddd, *J* = 17.0, 10.8, 6.5 Hz, 1H, H₇), 5.69 (dddd, *J* = 17.6, 9.8, 7.1, 4.5 Hz, 1H, H₁₀), 5.40 (app. d, *J* = 17.0 Hz, 1H, H₈), 5.26 (dd, *J* = 10.8, 1.1 Hz, 1H, H₈'), 5.11-5.03 (m, 3H, H_{11,11',R*}), 4.89 (d, *J* = 6.5 Hz, 1H, H₆), 4.47 (ddt, *J* = 15.4, 4.5,

1.7 Hz, 1H, H₉), 4.13 (dt, $J = 9.5, 8.4$ Hz, 1H, H₄), 3.97-3.82 (m, 3H, H_{5,9,R*}), 3.15 (sept, $J = 6.9$ Hz, 1H, H_{R*}), 2.86 (sept, $J = 6.9$ Hz, 1H, H_{R*}), 2.55 (dd, $J = 15.6, 9.5$ Hz, 1H, H₃), 2.37 (dd, $J = 15.6, 8.4$ Hz, 1H, H_{3'}), 1.55 (d, $J = 6.7$ Hz, 3H, H_{R*}), 1.30-1.13 (m, 18H, H_{R*}), 1.08 (app. s, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 171.9 (C_q, C₂), 148.6 (C_q, C_{R*}), 147.8 (C_q, C_{R*}), 146.3 (C_q, C_{R*}), 137.7 (CH, C₇), 132.6 (CH, C₁₀), 131.1 (C_q, C_{R*}), 123.2 (CH, C_{R*}), 121.0 (CH, C_{R*}), 117.9 (CH₂, C₈), 117.0 (CH₂, C₁₁), 74.4 (CH, C₆), 71.2 (CH, C_{R*}), 70.0 (CH, C₄), 65.2 (CH, C₅), 44.1 (CH₂, C₉), 36.8 (CH₂, C₃), 34.0 (CH, C_{R*}), 29.0 (CH, C_{R*}), 27.8 (CH, C_{R*}), 25.3 (CH₃, C_{R*}), 25.2 (CH₃, C_{R*}), 24.1 (CH₃, C_{R*}), 23.9 (CH₃, C_{R*}), 23.5 (CH₃, C_{R*}), 18.1 (CH₃, C_{TIPS}), 12.3 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) m/z 585, 584 (M⁺, 100%), 264, 231; Anal. Calcd. for C₃₆H₆₁NO₃Si: C, 74.04; H, 10.53; N, 2.40. Found: C, 74.26; H, 10.75; N, 2.45.

(1R,8R,8aS)-1-((S)-1-(2,4,6-Triisopropylphenyl)ethoxy)-8-(triisopropylsilyloxy)-8,8a-dihydroindolizin-3(1H,2H,5H)-one (14). Diene **13** (1.86 g, 3.18 mmol) was dissolved in anhydrous, degassed CH₂Cl₂ (160 mL) and Grubbs 2nd generation catalyst (270 mg, 0.32 mmol) was added. The mixture was refluxed for 2 h and then additional Grubbs catalyst (54 mg, 0.07 mmol) was added. Following an additional 1 h at reflux, the mixture was quenched with aqueous NaHCO₃ (50 mL) and water (20 mL). The aqueous layer was extracted with CH₂Cl₂ in the usual way and the combined organic phases were washed with water, dried, and concentrated. The crude product was purified by flash chromatography on silica gel (eluent Et₂O/pentane, 2/8) to afford indolizidinone **14** (1.45 g, 84%) as a light yellow oil: $[\alpha]_D^{20} -76.7$ (c 1.0, CHCl₃); IR (film) 2959, 2866, 1707, 1461, 1416, 1106, 1066 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.03 (s, 1H, H_{R*}), 6.93 (s, 1H, H_{R*}), 5.78 (dq, $J = 10.5, 1.9$ Hz, 1H, H₇), 5.70 (ddt, $J = 10.5, 3.0, 1.8$ Hz, 1H, H₆), 5.17 (q, $J = 6.8$ Hz, 1H, H_{R*}), 4.76 (app. dd, $J = 7.7, 1.9$ Hz, 1H, H₈), 4.33 (dt, $J = 5.3, 3.9$ Hz, 1H, H₁), 4.17 (dq, $J = 18.7, 3.0$ Hz, 1H, H₅), 3.84 (sept, $J = 6.8$ Hz, 1H, H_{R*}), 3.51-3.41 (m, 2H, H_{5',8a}), 3.18 (sept, $J = 6.6$ Hz, 1H, H_{R*}), 2.84 (sept, $J = 6.9$ Hz, 1H, H_{R*}), 2.60 (dd, $J = 16.5, 3.9$ Hz, 1H, H₂), 2.49 (dd, $J = 16.5, 5.3$ Hz, 1H, H_{2'}), 1.58 (d, $J = 6.8$ Hz, 3H, H_{R*}), 1.32-1.14 (m, 18H, H_{R*}), 0.99 (s, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 172.4 (C_q, C₃), 148.7 (C_q, C_{R*}), 147.4 (C_q, C_{R*}), 144.8 (C_q, C_{R*}), 133.0 (C_q,

C_R*), 130.5 (CH, C₇), 123.2 (CH, C_R*), 122.8 (CH, C₆), 120.6 (CH, C_R*), 72.8 (CH, C_R*), 72.1 (CH, C₁), 63.8 (CH, C₈ et C_{8a}), 39.3 (CH₂, C₅), 38.1 (CH₂, C₂), 34.0 (CH, C_R*), 29.2 (CH, C_R*), 28.4 (CH, C_R*), 25.5 (CH₃, C_R*), 25.3 (CH₃, C_R*), 24.7 (CH₃, C_R*), 24.0 (CH₃, C_R*), 23.9 (CH₃, C_R*), 23.4 (CH₃, C_R*), 18.2 (CH₃, C_{TIPS}), 13.2 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) *m/z* 557, 556 (M⁺, 100%), 212, 195; HRMS (FT, ESI) calcd for C₃₄H₅₈NO₃Si (MH⁺): 556.41805. Found: 556.41838.

(1*R*,8*R*,8a*S*)-1-((*S*)-1-(2,4,6-Triisopropylphenyl)ethoxy)-8-(triisopropylsilyloxy)-tetrahydroindolizidin-3(1*H*,2*H*,5*H*)-one (14a). To a solution of indolizidinone **14** (331 mg, 0.595 mmol) in EtOAc (10 mL) was added 10% Pd/C (63 mg, 0.060 mmol). The resulting suspension was stirred vigorously at 20 °C under a H₂ atmosphere for 2.5 h and then diluted with EtOAc, filtered over Celite[®], and concentrated. Purification of the crude product by flash chromatography on silica gel (eluent Et₂O/pentane, 4/6 to 8/2) afforded the reduced product **14a** (292 mg, 87%) as a colorless oil: [α]_D²⁰ -72.6 (*c* 1.0, CHCl₃); IR (film) 2959, 2863, 1701, 1463, 1419, 1124, 1068 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.00 (s, 1H, H_R*), 6.91 (d, *J* = 2.0 Hz, 1H, H_R*), 5.11 (q, *J* = 6.7 Hz, 1H, H_R*), 4.29 (dt, *J* = 5.0, 1.5 Hz, 1H, H₁), 4.07 (ddd, *J* = 10.2, 8.2, 4.7 Hz, 1H, H₈), 4.00 (dd, *J* = 14.4, 4.1 Hz, 1H, H₅), 3.78 (sept, *J* = 6.7 Hz, 1H, H_R*), 3.23 (dd, *J* = 8.2, 5.0 Hz, 1H, H_{8a}), 3.15 (sept, *J* = 6.8 Hz, 1H, H_R*), 2.83 (sept, *J* = 6.9 Hz, 1H, H_R*), 2.70 (dd, *J* = 16.7, 1.5 Hz, 1H, H₂), 2.60-2.50 (m, 1H, H₅'), 2.47 (ddd, *J* = 16.7, 5.0, 1.5 Hz, 1H, H₂'), 2.11-2.05 (m, 1H, H₇), 1.72-1.64 (m, 1H, H₆), 1.59 (d, *J* = 6.7 Hz, 3H, H_R*), 1.42-1.36 (m, 2H, H_{7',6'}), 1.32-1.13 (m, 18H, H_R*), 0.92-0.90 (m, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 172.7 (C_q, C₃), 148.3 (C_q, C_R*), 147.1 (C_q, C_R*), 144.0 (C_q, C_R*), 134.6 (C_q, C_R*), 123.1 (CH, C_R*), 120.3 (CH, C_R*), 73.8 (CH, C_R*), 73.1 (CH, C₁), 67.7 (CH, C_{8a}), 65.8 (CH, C₈), 39.4 (CH₂, C₂), 39.0 (CH₂, C₅), 34.0 (CH, C_R*), 33.1 (CH₂, C₇), 29.3 (CH, C_R*), 28.8 (CH, C_R*), 25.5 (CH₃, C_R*), 25.2 (CH₃, C_R*), 24.9 (CH₃, C_R*), 24.0 (CH₃, C_R*), 23.8 (CH₃, C_R*), 21.7 (CH₂, C₆), 18.1 (CH₃, C_{TIPS}), 13.0 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) *m/z* 559 (MH⁺), 558 (M⁺, 100%), 264, 231; Anal. Calcd. for C₃₄H₅₉NO₃Si: C, 73.19; H, 10.66; N, 2.51. Found: C, 73.07; H, 10.97; N, 2.49.

(1*R*,8*R*,8*aS*)-1-Hydroxy-8-(triisopropylsilyloxy)-tetrahydroindolizin-3(1*H*,2*H*,5*H*)-one (15). The above indolizidinone (1.21 g, 2.17 mmol) was dissolved in anhydrous CH₂Cl₂ (25 mL) at room temperature and TFA (2.50 mL, 32.5 mmol) was added dropwise. Toluene was added after 10 min and the reaction mixture was concentrated in vacuo. Purification of the crude mixture by flash chromatography on silica gel (eluent MeOH/EtOAc, 0/10 to 1/9) afforded **15** (687 mg, 97%) as a white solid: mp 112–116 °C; $[\alpha]_D^{20}$ –57.2 (*c* 1.0, CHCl₃); IR (film) 3372, 2943, 2865, 1682, 1463, 1125 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 4.59 (t, *J* = 5.2 Hz, 1H, H₁), 4.05–3.96 (m, 2H, H_{5,8}), 3.20 (dd, *J* = 9.1, 5.2 Hz, 1H, H_{8a}), 2.66 (ddd, *J* = 17.4, 6.5, 1.7 Hz, 1H, H₂), 2.58–2.50 (m, 1H, H_{5'}), 2.37 (d, *J* = 17.4 Hz, 1H, H_{2'}), 2.20–2.12 (m, 2H, H₇ et OH), 1.78–1.74 (m, 1H, H₆), 1.55–1.38 (m, 2H, H_{6',7'}), 1.15–1.04 (m, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 172.6 (C_q, C₃), 67.5 (CH, C_{8a}), 67.4 (CH, C₈), 40.7 (CH₂, C₂), 39.3 (CH₂, C₅), 33.6 (CH₂, C₇), 22.5 (CH₂, C₆), 18.1 (CH₃, C_{TIPS}), 12.8 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) *m/z* 345 (M+NH₄⁺), 329 (MH⁺), 328 (M⁺, 100%), 310, 284; Anal. Calcd. for C₁₇H₃₃NO₃Si: C, 62.34; H, 10.16; N, 4.28. Found: C, 62.65; H, 10.32; N, 4.22.

(1*R*,8*R*,8*aS*)-8-(Triisopropylsilyloxy)-octahydroindolizin-1-ol(15a). Indolizidinone **15** (670 mg, 2.05 mmol) in anhydrous THF (20 mL) was added to a suspension of LiAlH₄ (249 mg, 6.60 mmol) in anhydrous THF (5 mL). The mixture was refluxed for 1.3 h and then hydrolyzed at room temperature by addition of water (0.25 mL), aqueous NaOH (15 wt %, 0.25 mL), and water (0.75 mL). EtOAc was added to the mixture, the white suspension filtered over Celite[®], and the filtrate concentrated. Purification of the crude product by flash chromatography on silica gel (eluent MeOH/EtOAc, 0/10 to 2/8) afforded the tertiary amine **15a** (588 mg, 92%) as a white solid: mp 60–62 °C; $[\alpha]_D^{20}$ –57.7 (*c* 1.0, CHCl₃); IR (film) 3433, 3320, 2941, 2865, 2804, 1463, 1129 cm^{–1}; ¹H NMR (300 MHz, CDCl₃) δ 4.38–4.32 (m,

1H, H₁), 3.92 (ddd, $J = 10.7, 8.8, 4.5$ Hz, 1H, H₈), 3.17-3.11 (m, 1H, H₅), 2.99 (app. d, $J = 11.0$ Hz, 1H, H₃), 2.18-2.04 (m, 3H, H₂, H_{7,5'}), 1.89 (app. dt, $J = 11.0, 3.1$ Hz, 1H, H_{3'}), 1.80 (d, $J = 7.2$ Hz, 1H, OH), 1.75-1.53 (m, 4H, H_{2'}, H_{6,6',8a}), 1.34-1.21 (m, 1H, H_{7'}), 1.15-1.01 (m, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 75.0 (CH, C_{8a}), 71.1 (CH, C₁), 68.6 (CH, C₈), 52.6 (CH₂, C₅), 52.3 (CH₂, C₃), 34.3 (CH₂, C₇), 32.4 (CH₂, C₂), 24.2 (CH₂, C₆), 18.2 (CH₃, C_{TIPS}), 18.1 (CH₃, C_{TIPS}), 12.8 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) m/z 314 (MH⁺); Anal. Calcd. for C₁₇H₃₅NO₃Si: C, 65.12; H, 11.25; N, 4.47. Found: C, 65.04; H, 11.37; N, 4.23.

(8R,8aS)-8-(Triisopropylsilyloxy)-3,5,6,7,8,8a-hexahydroindolizine (16). Martin sulfurane (1.97 mg, 2.93 mmol) in anhydrous Et₂O (13 mL) was added dropwise to the above indolizidine (369 mg, 1.17 mmol) in Et₂O (13 mL) at 0 °C. After 30 min at 0 °C, the reaction mixture was allowed to warm to room temperature over 30 min. Water was added and the mixture was extracted three times with EtOAc. The combined organic layers were washed with brine, dried over anhydrous MgSO₄, and concentrated to afford the crude product as a colorless oil, which was used in the next step without purification. A sample was partially purified by flash chromatography on silica gel (eluent CH₂Cl₂/MeOH, 100/0 to 98/2): IR (film) 2941, 2866, 2779, 1464, 1115 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 6.17-6.13 (m, 1H, H₁), 5.87 (ddd, $J = 6.3, 4.0, 2.3$ Hz, 1H, H₂), 3.67-3.59 (m, 2H, H_{3,8}), 3.23 (dddd, $J = 12.8, 6.1, 2.3, 1.7$ Hz, 1H, H_{8a}), 2.95-2.87 (m, 2H, H_{3',5}), 2.45-2.36 (m, 1H, H_{5'}), 2.03 (m, 1H, H₇), 1.70-1.61 (m, 2H, H_{6,6'}), 1.35-1.18 (m, 1H, H_{7'}), 1.07 (br s, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 131.8 (CH, C₁), 128.4 (CH, C₂), 74.3 (CH, C_{8a}), 72.1 (CH, C₈), 57.9 (CH₂, C₃), 48.9 (CH₂, C₅), 34.7 (CH₂, C₇), 24.3 (CH₂, C₆), 18.2 (CH₃, C_{TIPS}), 18.1 (CH₃, C_{TIPS}), 12.6 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) m/z 296 (MH⁺, 100%), 252, 120.

Acetic Acid (1S,2R,8R,8aR)-1,2-Diacetoxyoctahydroindolizin-8-yl ester (17). AD-mix- α (3.10 g) and methylsulfonamide (334 mg, 3.51 mmol) were partially dissolved in water

(10 mL) and *t*-BuOH (5 mL) at 0 °C. Indolizidine **16** (1.17 mmol, based on a 100% yield for the previous reaction) in *t*-BuOH (15 mL) was added dropwise at 0 °C and the heterogeneous mixture was vigorously stirred for 9 days at 4 °C. Aqueous Na₂SO₃ (50 mL) was then added at 0 °C and the resulting solution was stirred for 1 h at the same temperature and extracted with AcOEt (4 × 50 mL). The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated and the resulting material was filtered through silica gel (eluent CH₂Cl₂/MeOH, 9/1). The crude product obtained on evaporation was dissolved in anhydrous THF (5 mL), TBAF (7 mL, 1.0 M solution in THF) was added dropwise, and the resulting solution was stirred at room temperature for 27 h. MeOH was then added and the reaction mixture was concentrated. The resulting product was dissolved in CH₂Cl₂ (5 mL) and dry pyridine (2.8 mL), and DMAP (29 mg, 0.24 mmol) and acetic anhydride (1.7 mL, 18 mmol) were added. After being stirred for 48 h, the reaction mixture was quenched with MeOH and concentrated. Flash chromatography of the crude product on silica gel (eluent AcOEt/hexane, 3/7 to 5/5) afforded a 20:1 mixture of the diastereomers as a light yellow oil. A second chromatography (eluent AcOEt/hexane, 2/8 to 4/6) gave the desired triacetate **17** (143 mg, 41%, 4 steps) and its diastereomer (7 mg). Triacetate **17**: $[\alpha]_D^{20} +6.3$ (*c* 1.0, MeOH); IR (film) 2946, 2802, 1747, 1434, 1374, 1256 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.51 (dd, *J* = 6.5, 4.3 Hz, 1H, H₁), 5.21 (app. ddd, *J* = 7.8, 6.4, 1.8 Hz, 1H, H₂), 4.95 (ddd, *J* = 11.0, 9.5, 4.7 Hz, 1H, H₈), 3.16 (dd, *J* = 11.1, 1.8 Hz, 1H, H₃), 3.04 (app. dt, *J* = 10.7, 3.0 Hz, 1H, H₅), 2.57 (dd, *J* = 11.1, 7.6 Hz, 1H, H_{3'}), 2.17-2.09 (m, 1H, H₇), 2.12 (dd, *J* = 9.6, 4.2 Hz, 1H, H_{8a}), 2.08 (s, 3H, H_{Ac}), 2.04 (s, 3H, H_{Ac}), 1.98 (s, 3H, H_{Ac}), 1.94-1.86 (m, 1H, H_{5'}), 1.78-1.69 (m, 2H, H_{6,6'}), 1.29-1.15 (m, 1H, H_{7'}); ¹³C NMR (75 MHz, CDCl₃) δ 170.2 (C_q, C_{Ac}), 170.0 (C_q, C_{Ac}), 169.9 (C_q, C_{Ac}), 70.2 (CH, C₂), 69.8 (CH, C₁), 69.2 (CH, C_{8a}), 68.0 (CH, C₈), 59.3 (CH₂, C₃), 51.8 (CH₂, C₅), 29.8 (CH₂, C₇), 23.3 (CH₂, C₆), 21.0 (CH₃, C_{Ac}), 20.6 (CH₃, C_{Ac}), 20.5 (CH₃, C_{Ac}); MS (DCI, NH₃/isobutane) *m/z* 300 (MH⁺, 100%), 240, 180; HRMS (FT, ESI) calcd for C₁₄H₂₂NO₆: 300.14416. Found: 300.14447.

(1*S*,2*R*,8*R*,8*aR*)-Octahydroindolizidine-1,2,8-triol **[(-)-Swainsonine]** **(1).**

Swainsonine triacetate **17** (54.6 mg, 0.182 mmol) in MeOH (3 mL) was shaken with Amberlite IRA-402 (OH) (100 mg) for 18 h. The reaction mixture was then diluted with

MeOH and filtered (MeOH wash), and the filtrate was concentrated to afford (–)-swainsonine (**1**) (30.6 mg, 97%) as a colorless solid: mp 143–144 °C; $[\alpha]_D^{20}$ –86.2 (*c* 1.0, MeOH); ^1H NMR (500 MHz, CDCl_3) δ 4.24 (ddd, *J* = 8.0, 5.9, 2.4 Hz, 1H, H_2), 4.14 (dd, *J* = 6.1, 3.7 Hz, 1H, H_1), 3.69 (ddd, *J* = 11.1, 9.5, 4.6 Hz, 1H, H_8), 2.80 (m, 1H, H_5), 2.77 (dd, *J* = 11.1, 2.4 Hz, 1H, H_3), 2.45 (dd, *J* = 11.1, 7.8 Hz, 1H, H_3'), 1.94 (app. dq, *J* = 11.8, 3.8 Hz, 1H, H_7), 1.88–1.83 (m, 1H, H_5'), 1.82 (dd, *J* = 9.5, 3.5 Hz, 1H, H_{8a}), 1.61 (app. ddd, *J* = 14.1, 4.3, 2.4 Hz, 1H, H_6), 1.40 (app. qt, *J* = 13.4, 4.2 Hz, 1H, H_6'), 1.17–1.08 (m, 1H, H_7'); ^{13}C NMR (75 MHz, CDCl_3) δ 72.8 (CH, C_{8a}), 69.7 (CH, C_1), 69.1 (CH, C_2), 66.4 (CH, C_8), 60.6 (CH_2 , C_3), 51.7 (CH_2 , C_5), 32.5 (CH_2 , C_7), 23.2 (CH_2 , C_6); MS (DCI, NH_3 /isobutane) *m/z* 174 (MH^+ , 100%), 156, 138; HRMS (FT, ESI) calcd for $\text{C}_8\text{H}_{16}\text{NO}_3$: 174.11247. Found: 174.11285.

(4*S*,5*R*)-4-((*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy)-5-((*S*)-1-(triisopropylsilyloxy)-allyl)-pyrrolidin-2-one (ent-12). Preparation as for **12**. **ent-12**: $[\alpha]_D^{20}$ +13.9 (*c* 1.0, CHCl_3).

(4*S*,5*R*)-1-Allyl-4-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-5-((*S*)-1-(triisopropylsilyloxy)-allyl)-pyrrolidin-2-one (ent-13). Preparation as for **13**. **ent-13**: $[\alpha]_D^{20}$ +2.6 (*c* 1.0, CHCl_3).

(1*S*,8*S*,8*aR*)-1-((*R*)-1-(2,4,6-Triisopropylphenyl)ethoxy)-8-(triisopropylsilyloxy)-8,8*a*-dihydroindolizin-3(1*H*,2*H*,5*H*)-one (ent-14). Preparation as for **14**. **ent-14**: $[\alpha]_D^{20}$ +72.5 (*c* 1.0, CHCl_3).

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(3a*R*,8*S*,8a*R*,9*R*,9a*R*)-2,2-Dimethyl-8-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-9-(triisopropylsilyloxy)-hexahydro-[1,3]dioxolo[4,5-*f*]indolizin-6(7*H*)-one (18). Me₃NO (190 mg, 1.71 mmol) and OsO₄ (2.5 wt % in *t*-BuOH, 0.086 mL, 0.0069 mmol) were added to a solution of indolizidinone **ent-14** (190 mg, 0.342 mmol) in *t*-BuOH (6 mL) and water (2 mL) at room temperature. The resulting solution was stirred for 24 h and then diluted with aqueous Na₂SO₃ (10 mL). The reaction mixture was extracted with EtOAc (4 × 20 mL) and the combined extracts were washed with water, dried over anhydrous MgSO₄, and concentrated. The resulting oil was dissolved in anhydrous toluene (4 mL), 2-methoxyprop-1-ene (0.165 mL, 1.72 mmol) and a catalytic amount of PTSA (8.0 mg, 0.042 mmol) were added, and the resulting solution was stirred for 3 h. A few drops of NEt₃ were then added and the reaction mixture was concentrated. Purification of the crude product by flash chromatography on silica gel (eluent Et₂O/pentane, 3/7 to 7/3) gave **18** (169 mg, 80%) as a white solid: mp 114-115 °C; [α]_D²⁰ +70.0 (*c* 1.0, CHCl₃); IR (film) 3443, 2960, 2867, 1710, 1454, 1096, 1066 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.04 (s, 1H, H_{R*}), 6.94 (d, *J* = 1.7 Hz, 1H, H_{R*}), 5.12 (q, *J* = 6.7 Hz, 1H, H_{R*}), 4.64 (app. t, *J* = 2.6 Hz, 1H, H₉), 4.32-4.22 (m, 3H, H_{3a,8,9a}), 4.10 (app. d, *J* = 14.4 Hz, 1H, H₄), 3.92 (sept, *J* = 6.7 Hz, 1H, H_{R*}), 3.75 (dd, *J* = 7.5, 2.4 Hz, 1H, H_{8a}), 3.18 (sept, *J* = 6.7 Hz, 1H, H_{R*}), 3.00 (dd, *J* = 14.2, 2.1 Hz, 1H, H_{4'}), 2.85 (sept, *J* = 6.9 Hz, 1H, H_{R*}), 2.57 (dd, *J* = 16.4, 5.5 Hz, 1H, H₇), 2.49 (app. dd, *J* = 16.4, 6.8 Hz, 1H, H_{7'}), 1.57 (d, *J* = 6.8 Hz, 1H, H_{R*}), 1.43 (s, 3H, H₁), 1.31-1.14 (m, 21H, H_{1',R*}), 1.00-0.96 (m, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 172.3 (C_q, C₆), 148.8 (C_q, C_{R*}), 147.6 (C_q, C_{R*}), 145.3 (C_q, C_{R*}), 132.5 (C_q, C_{R*}), 123.0 (CH, C_{R*}), 120.7 (CH, C_{R*}), 108.8 (C_q, C₂), 76.5, 72.0 and 70.5 (3 CH, C_{3a}, C₈ and C_{9a}), 72.5 (CH, C_{R*}), 66.7 (CH, C_{8a}), 65.0 (CH, C₉), 41.8 (CH₂, C₄), 38.7 (CH₂, C₇), 34.1 (CH, C_{R*}), 29.2 (CH, C_{R*}), 27.9 (CH, C_{R*}), 26.1 (CH₃, C_{R*}), 25.9 (CH₃, C₁), 25.4 (CH₃, C_{R*}), 25.0 (CH₃, C_{R*}), 24.5 (CH₃, C_{R*}), 24.0 (CH₃, C_{R*}), 23.4 (CH₃, C_{R*}), 18.0 (CH₃, C_{TIPS}), 12.4 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) *m/z* 631 (MH⁺), 630 (M⁺), 400, 264, 231; Anal. Calcd. for C₃₇H₆₃NO₅Si: C, 70.54; H, 10.08; N, 2.22. Found: C, 70.49; H, 10.25; N, 2.31.

(3a*R*,8*S*,8a*R*,9*R*,9a*R*)-2,2-Dimethyl-8-((*R*)-1-(2,4,6-triisopropylphenyl)ethoxy)-9-(triisopropylsilyloxy)-octahydro-[1,3]dioxolo[4,5-*f*]indolizine (19). Indolizidinone **18** (153 mg, 0.243 mmol) in THF (3.5 mL) was added to a suspension of LiAlH₄ (28 mg, 0.74 mmol) in THF (1.5 mL). The reaction mixture was refluxed for 2 h and then hydrolyzed at room temperature by addition of water (28 mL), aqueous NaOH (15 wt %, 28 mL), and water (84 mL). EtOAc was added and the white precipitate was removed by filtration over Celite®. The filtrate was concentrated and the crude product purified by flash chromatography on silica gel (eluent EtOAc/pentane, 5/95 to 2/8) to yield indolizidine **19** (135 mg, 90%) as a colorless oil: $[\alpha]_D^{20} +20.5$ (*c* 1.0, CHCl₃); IR (film) 2960, 2866, 2802, 1462, 1381, 1125, 1065 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.01 (s, 1H, H_{R*}), 6.89 (s, 1H, H_{R*}), 5.17 (q, *J* = 6.7 Hz, 1H, H_{R*}), 4.33 (dt, *J* = 6.7, 4.6 Hz, 1H, H_{3a}), 4.27-4.22 (m, 2H, H_{8,9}), 4.00-4.90 (m, 1H, H_{R*}), 3.96 (t, *J* = 6.9 Hz, 1H, H_{9a}), 3.26-3.17 (m, 1H, H_{R*}), 3.20 (dd, *J* = 12.1, 4.8 Hz, 1H, H₄), 3.12 (app. q, *J* = 7.7 Hz, 1H, H₆), 2.83 (sept, *J* = 6.9 Hz, 1H, H_{R*}), 2.54-2.46 (m, 1H, H_{6'}), 2.51 (dd, *J* = 11.9, 4.5 Hz, 1H, H_{4'}), 2.21-2.12 (m, 1H, H₇), 2.14 (dd, *J* = 9.2, 3.7 Hz, 1H, H_{8a}), 1.92-1.80 (m, 1H, H_{7'}), 1.57 (d, *J* = 6.7 Hz, 3H, H_{R*}), 1.46 (s, 3H, H₁), 1.32 (s, 3H, H_{1'}), 1.30-1.15 (m, 18H, H_{R*}), 0.97-0.89 (m, 21H, H_{TIPS}); ¹³C NMR (75 MHz, CDCl₃) δ 148.3 (C_q, C_{R*}), 146.6 (C_q, C_{R*}), 143.6 (C_q, C_{R*}), 136.4 (C_q, C_{R*}), 123.1 (CH, C_{R*}), 120.3 (CH, C_{R*}), 108.9 (C_q, C₂), 80.9 (CH, C_{9a}), 78.8, 71.5 and 71.4 (CH, C₈, C_{8a} and C₉), 74.1 (CH, C_{3a}), 72.5 (CH, C_{R*}), 53.2 (CH₂, C₄ and C₆), 34.0 (CH, C_{R*}), 30.6 (CH₂, C₇), 29.0 (CH, C_{R*}), 28.8 (CH, C_{R*}), 27.3 (CH₃, C₁), 25.5 (CH₃, C_{R*}), 25.4 (CH₃, C_{R*}), 25.3 (CH₃, C_{1'}), 25.1 (CH₃, C_{R*}), 24.8 (CH₃, C_{R*}), 24.0 (CH₃, C_{R*}), 24.0 (CH₃, C_{R*}), 23.7 (CH₃, C_{R*}), 18.3 (CH₃, C_{TIPS}), 18.2 (CH₃, C_{TIPS}), 12.7 (CH, C_{TIPS}); MS (DCI, NH₃/isobutane) *m/z* 617 (MH⁺), 616 (M⁺, 100%), 386, 384, 369, 231; Anal. Calcd. for C₃₇H₆₅NO₄Si: C, 72.14; H, 10.64; N, 2.27. Found: C, 71.94; H, 10.41; N, 2.41.

(1*S*,6*R*,7*R*,8*R*,8*aR*)-Octahydroindolizine-1,6,7,8-tetraol [(+)-6-Epicastanospermine] (2). Indolizidine **19** was dissolved in 95% EtOH (4 mL) containing HCl (1 wt %) and the resulting solution was refluxed for 10 h. After the addition of MeOH, the mixture concentrated and the residue passed down a column of Dowex 50W-X8 ion exchange resin (H⁺ form), eluting with water and then aqueous ammonia (2.0 N). Lyophilization then afforded 19 mg of (+)-6-epicastanospermine (**2**) (98%) as a colorless oil: $[\alpha]_D^{20} +2.3$ (*c* 0.7, MeOH); ¹H NMR (500 MHz, D₂O) δ 4.43 (m, 1H, H₁), 4.03 (br s, 1H, H₆), 3.91 (t, *J* = 9.7 Hz, 1H, H₈), 3.56 (dd, *J* = 9.7, 3.5 Hz, 1H, H₇), 3.23-3.14 (m, 2H, H_{3,5}), 2.45-2.25 (m, 3H, H_{5',2,3'}), 2.08 (br s, 1H, H_{8a}), 1.76 (app. dt, *J* = 13.8, 7.9 Hz, 1 H, H₂); ¹³C NMR (75 MHz, D₂O) δ 75.5 (CH, C₇), 72.1 (CH, C_{8a}), 70.2 (CH, C₁), 69.0 (CH, C₆), 67.3 (CH, C₈), 55.6 (CH₂, C₅), 52.2 (CH₂, C₃), 33.0 (CH₂, C₂); HRMS (FT, ESI) Calcd. for C₈H₁₆NO₄: 190.1074. Found 190.1077 (MH⁺).

juce075c1 exp3 20/10/05
PROTON AVANCE 300.13

juce084c1 exp1 31/10/05
PROTON AVANCE 300.13

jnce084c1 exp2 31/10/05
c13mult

juce088c1 exp1 03/11/05
HLR00

juc0091C2 exp2 08/11/05
PROTON AVANCE 300.13

juce091C2 exp10 08/11/05
C13mult

juc0097c1 exp7 17/11/05
PROTON AVANCE 300.13

juc0097c1 exp4 17/11/05
C13mult

jucei02c2 exp1 25/11/05
H1R00

jucel61c7 exp5 13/03/06
c13mult CDCl3 u l3 1

juce167C
RMN ¹H 500 MHz

juce167c exp3 16/03/06
C13mult

juce134c1 exp6 24/01/06
H1R00

jucel34c1 exp5 24/01/06
C13m1t

jucei135c1 exp20 07/02/06
PROTON AVANCE 300.13

jucel46c exp1 09/10/06
C13mult D20 u l3 1