Supplemental Material

An Aza-Achmatowicz Approach Toward the Hydroxylated Piperidine Alkaloids (±)-Azimic Acid and (±)-Deoxocassine

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Experimental Section

Melting points are uncorrected. Mass spectra were determined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame-dried glassware under an atmosphere of dry argon. The microwave reactor and reaction vessels were purchased from CEM Corporation. All solids were recrystallized from ethyl acetate/hexane for analytical data.

6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridin-3-ol (12). To a solution of 4.7 g (12.5 mmol) of cerium trichloride heptahydrate in 100 mL of MeOH was added 3.7 g (12.5 mmol) of *N*-tosyl aminal **10**. The solution was chilled to -40°C, and 0.5 g (14 mmol) of NaBH₄ was added. The solution was stirred for 10 min at -40°C, and then quenched with a saturated NaHCO₃ solution. The solution was extracted with CH₂Cl₂ and the combined extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to give 2.2 g (60% yield) of the title compound **12** as a colorless oil; IR (thin film) 2939, 1332, and 1167 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.20 (d, 3H, *J* = 6.8 Hz), 1.68 (d, 1H, *J* = 7.6 Hz), 2.42 (s, 3H), 3.49 (s, 3H), 3.87 (m, 1H), 4.03 (dq, 1H, *J* = 7.2 and 7.2 Hz), 5.37 (m, 1H), 5.62 (ddd, 1H, *J* = 10.8, 3.2 and 1.6 Hz), 5.81 (ddd, 1H, *J* = 10.4, 3.6 and 2.4 Hz), 7.28 (d, 2H, *J* = 8.0 Hz), and 7.69 (d, 2H, *J* = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ 13.2, 21.7, 49.8, 56.3, 65.5, 80.9, 125.3, 127.2,

129.9, 130.7, 138.1, and 143.9; HRMS Calcd. for $C_{14}H_{19}NSO_4$: 297.1035. Found: 297.1033.

3-(*tert*-Butyl-dimethyl-silanyloxy)-6-methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,2,3,6-tetrahydropyridine (13). To a solution of 0.7 g (2.3 mmol) of **12** in 25 mL of CH_2Cl_2 was added 0.3 g (4.6 mmol) of imidazole and a catalytic amount of 4-(dimethylamino)pyridine followed by 0.4 g (2.8 mmol) of *tert*-butyldimethylchlorosilane. The resulting solution was stirred at rt for 30 min, water was added, and the solution was extracted with ether and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the crude product was purified by silica gel chromatography to give 0.82 g (86% yield) of the title compound **13** as a colorless oil; IR (thin film) 2935, 1469, 1382, 1159 and 1073 cm^{-1} ; 1H -NMR (400 MHz, $CDCl_3$) δ -0.12 (d, 6H, J = 5.6 Hz), 0.80 (s, 9H), 1.17 (d, 3H, J = 7.2 Hz), 2.42 (s, 3H), 3.49 (s, 3H), 3.69 (m, 1H), 3.84 (dq, 1H, J = 6.8 and 6.8 Hz), 5.36 (m, 1H), 5.50 (dd, 1H, J = 10.8 and 1.6 Hz), 5.72 (ddd, 1H, J = 10.0, 7.2 and 7.2 Hz), 7.29 (d, 2H, J = 8.4 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C -NMR (100 MHz, $CDCl_3$) δ -5.01, -4.85, 13.2, 18.2, 21.7, 25.8, 50.3, 56.1, 65.6, 80.9, 124.2, 127.3, 129.9, 132.0, 138.5, and 143.8; HRMS Calcd. for $C_{20}H_{33}NSiSO_4$: 411.1899. Found: 411.1903.

5-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentanoic Acid Methyl Ester (11). To a solution of 0.8 g of **13** (1.9 mmol) in 20 mL of CH_2Cl_2 at $-78^\circ C$ was added 0.6 g (2.9 mmol) of methyl-3-(trimethylsilyl)-4-pentenonate (**14**) followed by 4 drops of $BF_3 \cdot OEt_2$. The reaction was stirred at -78° for 3 h and then quenched with a saturated sodium bicarbonate solution. After warming to room temperature, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 . The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude unsaturated ester **15** was dissolved in 20 mL of methanol and a catalytic amount of platinum (IV) oxide was added. The flask was purged with hydrogen gas three times before being allowed to stir under a

hydrogen balloon for 15 h. The solution was filtered through a pad of Celite, concentrated under reduced pressure and subjected to flash silica gel chromatography to give 0.6 g (57%) of the title compound **11** as a white solid, mp 68-71°C; IR (thin film) 2957, 1733, 1469, 1337, and 1100 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ - 0.08 (d, 6H, *J* = 3.6 Hz), 0.80 (s, 9H), 1.22 (d, 3H, *J* = 7.2 Hz), 1.30-1.70 (m, 10H), 2.32 (t, 2H, *J* = 7.2Hz), 2.41, (s, 3H), 3.19 (m, 1H) 3.67 (s, 3H), 3.96 (m, 3H), 7.28 (d, 2H, *J* = 6.8 Hz), and 7.69 (d, 2H, *J* = 8.0 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.6, 14.9, 18.1, 21.6, 23.6, 24.9, 25.9, 26.9, 27.5, 34.1, 34.9, 51.7, 51.9, 53.1, 69.4, 126.9, 129.8, 139.0, 143.0, and 174.3; HRMS Calcd. for C₂₅H₄₃NSiSO₅: 497.2631. Found: 497.2627.

5-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentanoic Acid Methoxymethylamide (16). To a solution of 0.3 g (0.6 mmol) of piperidino ester **11** in THF (1.2 mL) was added methoxymethylamine hydrochloride. The resulting slurry was chilled to approximately -20°C, and *iso*-propylmagnesium chloride (0.9 mL of a 2M solution in THF (1.8 mmol)) was added. The solution was stirred at this temperature for 20 min and was then quenched by addition of a saturated ammonium chloride solution. The reaction mixture was extracted with CH₂Cl₂, dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.27 g (85% yield) of the title compound **16** as a white solid, mp 77-78°C; IR (thin film) 2947, 2848, 1663, 1461, 1161, and 999 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.10 (d, 6H, *J* = 3.6 Hz), 0.79 (s, 9H), 1.21 (d, 3H, *J* = 7.2 Hz), 1.29-1.73 (m, 10H), 2.40 (s, 3H), 2.43 (m, 2H), 3.16 (m, 4H), 3.67 (s, 3H), 3.95 (m, 2H), 7.26 (d, 2H, *J* = 8.0 Hz), and 7.67 (d, 2H, 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.9, -4.7, 14.8, 18.0, 21.6, 23.5, 24.6, 25.8, 27.2, 27.4, 31.9, 32.2, 35.0, 51.9, 53.1, 61.4, 69.3, 126.8, 129.7, 139.0, 143.0, and 174.7; HRMS Calcd. for C₂₆H₄₆N₂SiSO₅: 526.2897. Found: 526.2889.

1-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-dodec-11-en-5-one (17). To a solution of 0.1 g (0.6 mmol) of 1-iodo-6-heptene in 0.5 mL of heptane at -78°C was added 1.6 mL of a 1.4 M solution of *tert*-butyllithium in pentane. The mixture was stirred for 5 min and then a solution of 0.17 g (0.3 mmol) of Weinreb amide **16** was added slowly. After warming to 0°C over 30 min, the reaction was quenched by the addition of a saturated NH₄Cl solution. The mixture was extracted with ether, dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.1 g (56%) of the title compound **17** as a colorless oil; IR (thin film) 2932, 2857, 1712, 1337, and 1162 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.12 (d, 6H, *J* = 4.0 Hz), 0.77 (s, 9H), 1.18 (d, 3H, *J* = 7.2 Hz), 1.23-1.72, (m, 16H), 2.00 (q, 2H, *J* = 6.8 Hz), 2.36 (t, 2H, *J* = 7.6 Hz), 2.38 (m, 5H), 3.14 (m, 1H), 3.92 (m, 2H), 4.92 (m, 2H), 5.75 (m, 1H), 7.24 (d, 2H, *J* = 8.0 Hz), and 7.65 (d, 2H, *J* = 7.6 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.6, 14.2, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 25.9, 27.0, 27.5, 28.8, 28.9, 33.8, 35.1, 42.8, 42.9, 51.9, 53.1, 69.4, 114.5, 126.9, 129.8, 139.1, 143.0, and 211.6; HRMS Calcd. for C₃₁H₅₃NSiSO₄: 563.3464. Found: 563.3472.

3-(*tert*-Butyl-dimethyl-silanyloxy)-6-dodec-11-enyl-2-methyl-1-(toluene-4-sulfonyl)-piperidine (18). To a solution of 0.1 g (0.18 mmol) of ketone **17** in 1.5 mL of absolute ethanol was added 0.037 g (0.19 mmol) of *p*-toluenesulfonylhydrazide. The solution was stirred for 15 h at room temperature and then was concentrated under reduced pressure. To the residue was added 1.5 mL of CH₂Cl₂ and the resulting solution was cooled to 0°C. To this solution was added 0.35 mL (0.34 mmol) of diisobutylaluminum hydride solution (1 M in hexane). The solution was warmed to rt over 30 min and was quenched with a 3 M solution of NaOH. The solution was extracted with ether, dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.04 g (40% yield) of the title compound **18** as a colorless oil; IR (thin film) 2852, 1640, 1598,

and 1163 cm^{-1} ; ^1H -NMR (400 MHz, CDCl_3) δ -0.07 (d, 6H, J = 4.0 Hz), 0.82 (s, 9H), 1.22 (d, 3H, J = 7.6 Hz), 1.27-1.72, (m, 22H), 2.04 (q, 2H, J = 7.6 Hz), 2.42 (s, 3H), 3.23 (m, 1H), 3.98 (m, 2H), 4.96 (m, 2H), 5.82 (m, 1H), 7.28 (d, 2H, J = 8.0 Hz), and 7.70 (d, 2H, J = 7.6 Hz); ^{13}C -NMR (100 MHz, CDCl_3) δ -4.8, -4.6, 14.2, 14.9, 18.1, 21.6, 23.6, 23.7, 23.9, 25.9, 26.5, 27.0, 27.5, 28.8, 28.9, 33.8, 35.1, 52.0, 53.1, 69.4, 114.3, 126.9, 129.8, 139.2, 139.5, and 142.9; HRMS Calcd. for $\text{C}_{31}\text{H}_{55}\text{NSiSO}_3$: 549.3672. Found: 549.3661.

6-Dodecyl-2-methyl-1-(toluene-4-sulfonyl)-piperidin-3-ol. To a solution of 0.03 g (0.06 mmol) of alkene **18** in 0.1 mL of methanol was added a catalytic amount of platinum (IV) oxide. After purging the reaction vessel 3 times with hydrogen gas, the mixture was stirred for 1 h under a hydrogen balloon. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The crude reaction mixture was taken up in 0.6 mL of THF and a solution of tetrabutylammonium fluoride (66 μL of a 1M solution in THF) was added at 0 $^\circ\text{C}$. After warming to rt over 30 min, water was added and the reaction mixture was extracted with ether. The ether extracts were dried over MgSO_4 , and concentrated under reduced pressure. The crude product was subjected to preparative thin-layer chromatography to give 0.024 g (92%) of the titled compound as a clear oil; IR (thin film) 3444, 2923, 2852, and 1460 cm^{-1} ; ^1H -NMR (600 MHz, CDCl_3) δ 0.89 (t, 3H, J = 7.2 Hz), 1.25-1.66, (m, 30H), 2.42 (s, 3H), 3.40 (m, 1H), 3.95 (q, 1H, J = 6.6 Hz), 4.18 (dq, 1H, J = 6.6 and 6.6 Hz), 7.28 (d, 2H, J = 9.0 Hz), and 7.70 (d, 2H, J = 8.4 Hz); ^{13}C -NMR (150 MHz, CDCl_3) δ 14.3, 14.7, 21.7, 22.9, 23.2, 27.3, 27.7, 29.6, 29.7, 29.8, 29.9, 32.1, 35.3, 52.1, 52.4, 69.2, 126.9, 129.9, 139.1, and 143.1; HRMS Calcd. for $\text{C}_{25}\text{H}_{43}\text{NSO}_4$: 453.2913. Found: 453.2924.

6-Dodecyl-2-methyl-piperidin-3-ol (8). To a solution of 0.05 g of the above alcohol in 0.5 mL of THF at -78°C was condensed 2 mL of NH_3 using a dry ice condenser. To this mixture was added lithium chips (approximately 2 mg) and the solution

immediately turned a deep blue color. The reaction mixture was allowed to stir at -78°C for 30 min and then 0.5 mL of isoprene was added to quench the reaction. The mixture was warmed to rt and water was added followed by a drop of 50% NaOH solution and CHCl₃. After extracting the aqueous layer with additional CHCl₃, the combined organic layer was dried over MgSO₄ and concentrated under reduced pressure to give 0.03 g (100%) of deoxocassine (**8**); IR (thin film) 3394, 2916, 2848, and 1455 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 0.89 (t, 3H, *J* = 7.2 Hz), 1.15, (d, 3H, *J* = 6.8 Hz), 1.22-1.36 (m, 22H), 1.46 (m, 2H), 1.90 (m, 2H), 2.50 (m, 2H), 2.72 (qd, 1H, *J* = 6.8 and 1.2 Hz), and 3.52 (d, 1H, *J* = 4.8 Hz); ¹³C-NMR (150 MHz, CDCl₃) δ 14.3, 18.9, 22.9, 26.0, 26.4, 29.6, 29.8, 29.9, 30.0, 32.1, 32.3, 37.2, 56.0, 57.5, and 68.3; FAB HRMS Calcd. for [(C₁₈H₃₇NO)+H⁺]: 284.2953. Found: 284.2941.

5-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-pentan-1-ol (19**).** To a solution of 0.13 g (0.26 mmol) of piperidino ester **11** at 0°C was slowly added 0.3 mL of a solution of lithium aluminum hydride (1M in THF). After the addition was complete, the reaction was quenched by the careful addition of Na₂SO₄·10H₂O. After stirring for 30 min at rt, MgSO₄ was added and the solution was filtered. The solution was concentrated under reduced pressure and the crude product was subjected to flash silica gel chromatography to give 0.12 g (97%) of the title compound **19** as a clear oil; IR (thin film) 3418, 2855, 1462, and 1095 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.08 (d, 6H, *J* = 3.6 Hz), 0.82 (s, 9H), 1.23 (d, 3H, *J* = 7.2 Hz), 1.30-1.80 (m, 13H), 3.43 (s, 3H), 3.19 (m, 1H), 3.66 (dt, 2H, *J* = 2.8 and 6.8 Hz), 3.98 (m, 2H), 7.28 (d, 2H, *J* = 8.0 Hz), and 7.70 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.6, 14.9, 18.2, 21.7, 23.6, 25.6, 25.9, 27.0, 27.5, 32.8, 35.2, 51.9, 53.1, 63.0, 69.4, 126.9, 129.8, 139.1, and 143.0; HRMS Calcd. for C₂₄H₄₃NSiSO₄: 469.2682. Found: 469.2675.

6-[5-(*tert*-Butyl-dimethyl-silanyloxy)-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanenitrile (20**).** To a solution of 0.26 g (0.6 mmol) of alcohol **19** in 5.5 mL of

CH₂Cl₂ was added methanesulfonyl chloride (0.09 g, 0.8 mmol). The solution was cooled to 0 °C and 0.09 g of triethylamine was added dropwise. After warming to rt over 30 min, the reaction was quenched by the addition of water. The solution was extracted with CH₂Cl₂, dried over MgSO₄, and concentrated under reduced pressure. The crude product was dissolved in 2 mL of DMF, and 0.05 g of sodium cyanide was added. The reaction mixture was heated at 50 °C for 15 h. After cooling to rt, water was added, and the mixture was extracted with ether. The ether extracts were washed three time with brine, dried over MgSO₄, and concentrated under reduced pressure. The crude product was subjected to flash silica gel chromatography to give 0.18 g (68%) of the title compound **20** as a clear oil; IR (thin film) 2943, 2242, 1592, 1150 and 1104 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ -0.08 (d, 6H, *J* = 3.6 Hz), 0.82 (s, 9H), 1.24 (d, 3H, *J* = 7.2 Hz), 1.30-1.74 (m, 12H), 2.36 (t, 2H, *J* = 7.2 Hz), 2.43 (s, 3H), 3.17 (m, 1H), 3.96 (m, 1H), 7.29 (d, 2H, *J* = 8.4 Hz), and 7.70 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (100 MHz, CDCl₃) δ -4.8, -4.6, 14.9, 17.3, 18.1, 21.7, 23.6, 25.5, 25.9, 26.4, 27.6, 28.6, 35.0, 51.8, 53.2, 69.3, 120.0, 126.9, 129.8, 139.0, and 143.1; HRMS Calcd. for C₂₅H₄₂N₂SiSO₃: 478.2685. Found: 478.2677.

6-[5-Hydroxy-6-methyl-1-(toluene-4-sulfonyl)-piperidin-2-yl]-hexanoic Acid (21).

To a solution of 0.09 g (0.188 mmol) of nitrile **20** in 2 mL of methanol was added 2 mL of a 50% NaOH solution. The mixture was heated at reflux for 3 h and cooled to rt. The solution was extracted once with ether and then the aqueous portion was acidified to pH 2 using a 6 N HCl solution. The acidified solution was extracted with CHCl₃ and the combined extracts were dried over MgSO₄ and concentrated under reduced pressure. The crude product contained 0.06 g (89%) of the title compound **21** as a clear oil; IR (thin film) 3453, 2934, 2871, 1705, 1328 and 1155 cm⁻¹; ¹H-NMR (400 MHz, CDCl₃) δ 1.25 (d, 4H, *J* = 7.2 Hz), 1.35-1.64 (m, 13H), 2.36 (t, 2H, *J* = 7.6Hz), 2.42 (s, 3H), 3.37 (m, 1H), 3.94 (q, 1H, *J* = 6.8Hz), 4.17 (dq, 1H, *J* = 6.8 and 6.8 Hz), 7.28 (d, 2H, *J* = 8.4 Hz), and 7.70 (d, 2H, *J* = 8.4 Hz); ¹³C-NMR (100 MHz,

CDCl_3) δ 14.7, 21.7, 23.0, 24.7, 27.1, 27.3, 29.0, 34.1, 35.0, 51.9, 52.4, 69.1, 126.9, 129.9, 138.9, 143.2, and 179.2; HRMS Calcd. for $\text{C}_{19}\text{H}_{29}\text{NSO}_5$: 383.1766. Found: 383.1772.

6-(5-Hydroxy-6-methyl-piperidin-2-yl)-hexanoic Acid (5). To a solution of 0.002 g (0.044 mmol) of carboxylic acid **21** in 0.6 mL of THF at -78°C was condensed 3 mL of NH_3 using a dry ice condenser. To this solution was added lithium chips which resulted in the formation of a deep blue color. The mixture was allowed to stir at -78°C for 30 min, and then 0.5 mL of isoprene was added to quench the reaction. The solution was warmed to rt and water was added to the resulting residue. The solution was brought to pH 7 by the addition of 6N HCl, and the solvent was subsequently removed under reduced pressure. Methanol was added to precipitate any inorganic salts, and the resulting solution was filtered and concentrated under reduced pressure to give 0.007 g (70%) of azimic acid (**5**) as a white solid mp $217\text{--}218^\circ\text{C}$; IR (thin film) 3344 , 1633 , and 1551 cm^{-1} ; $^1\text{H-NMR}$ (400 MHz, CD_3OD) δ 1.33 (d, 2H, $J = 6.8\text{ Hz}$), 1.22-1.81 (m, 11H), 1.96 (m, 1H), 2.17 (t, 2H, $J = 7.4\text{ Hz}$), 3.03 (bs, 1H), 3.21 (q, 1H, $J = 6.4\text{ Hz}$), and 3.83 (bs, 1H) $^{13}\text{C-NMR}$ (150 MHz, CDCl_3) δ 16.4, 24.0, 26.1, 27.3, 30.4, 31.4, 35.0, 39.0, 57.6, 58.7, 66.3, and 182.9; FAB HRMS Calcd. for $[(\text{C}_{12}\text{H}_{23}\text{NO}_3)+\text{H}^+]$: 230.1756. Found: 230.1759.