Conjugate Additions of Sulfur-stabilized Anions to Unsaturated Lactams. Synthesis of Polyfunctionalized benzo[*a*]quinolizinone systems

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General experimental methods: Melting points were determined in unsealed capillary tubes and are uncorrected. IR spectra were obtained on KBr pellets (solids) or CHCl₃ solution (oils). NMR spectra were recorded at 20-25 °C, running at 250 MHz or 500 MHz for ¹H and 62.8 MHz or 125.7 MHz for ¹³C in CDCl₃ solutions. Assignment of individual ¹³C resonances is supported by DEPT and HMQC experiments. Mass spectra were recorded under electron impact at 70 eV. GC-MS analyses were performed using a methyl polysiloxane column (30 m × 0.25 mm × 0.25 μm). HRMS analyses were performed under electron impact with a TOF analyzer. TLC was carried out with 0.2 mm thick silica gel plates. Visualization was accomplished by UV light. Flash column chromatography¹ on silica gel was performed with Kiesegel 60 (230-400 mesh). HPLC All solvents used in reactions were anhydrous and purified according to standard procedures.² Organolithium reagents were titrated with diphenylacetic acid periodically prior to use. All air- or moisture-sensitive reactions were performed under argon; the glassware was dried (130 °C) and purged with argon.

Synthesis of *N*-[2-(3,4-dimethoxyphenyl)ethyl]glutarimide (**1**).

A solution of glutaric anhydride (3 g, 26.3 mmol) and 2-(3,4-dimethoxyphenyl)ethylamine (1.0 g, 14.5 mmol) in glacial AcOH (30 mL) was heated under reflux for 16 h. The solvent was evaporated under vacuum and the resulting crude mixture was crystallized from MeOH to afford glutarimide **1** as a white solid (3 g, 75%): mp (MeOH) 111-112 °C (lit³ mp (MeOH) 111-113 °C); IR (KBr) 1725, 1690 cm⁻¹; ¹H NMR (CDCl₃) 1.83-1.94 (m, 2H), 2.61 (t, *J* = 6.5 Hz, 4H), 2.71-2.77 (m, 2H), 3.85 (s, 3H), 3.87 (s, 3H), 3.93-3.99 (m, 2H), 6.77 (broad s, 3H); ¹³C NMR (CDCl₃) 17.0, 32.7, 33.5, 40.7, 55.7, 110.9, 111.9, 120.8, 130.9, 147.3, 148.5, 172.3; MS (EI) *m/z* (rel intensity) 277 (M⁺, 8), 164 (100), 151 (25), 121 (4), 107 (6), 91 (6), 77, (4), 55 (20), 42 (8). Anal. Calcd for C₁₅H₁₉NO₄: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.88; H, 6.85; N, 5.12.

Synthesis of 9,10-dimethoxy-1,2,3,6,7,11b-hexahydrobenzo[a]quinolizin-4-one (2a).

Procedure A.

NaBH₄ (210 mg, 5.6 mmol) was added in portions to a solution of glutarimide **1** (393 mg, 1.4 mmol) in 10% EtOH/H₂O (20 mL) at 0 °C, maintaining pH = 8 by portion wise addition of 3 M HCl. The reaction mixture was stirred for 40 min. 3 M HCl was added to adjust pH to 4, and water was added (10 mL). The mixture was extracted with CH₂Cl₂ (3 × 20 mL). The combined organic extracts were washed with saturated NaHCO₃ (3 × 10 mL), and with brine (3 × 10 mL), dried (Na₂SO₄), and concentrated *in vacuo*. The tautomeric mixture of hydroxylactam and oxoamide was submitted to cyclization without further purification. Thus, TFA (1.5 mL, 9 mmol) was added over a solution of the crude reaction mixture in CH₂Cl₂ (30 mL), and the mixture was stirred at rt for 16 h. The reaction was quenched by addition of saturated NaHCO₃ (10 mL). The organic phase was separated, and the resulting aqueous phase was extracted with CH₂Cl₂ (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash column chromatography (silica gel, AcOEt) afforded benzoquinolizidone **2a** (302 g, 83%): mp (50 % hexane/AcOEt) 114-115 °C (lit.⁴ mp (EtO₂) 88-90 °C); IR (KBr) 1635 cm⁻¹; ¹H NMR (CDCl₃) 1.56-1.71 (m, 1H), 1.73-2.01 (m, 2H), 2.27-2.48 (m, 1H), 2.50-2.64 (m, 3H), 2.71-2.94 (m, 2H), 3.84 (s, 6H), 4.58 (dd, *J* = 10.3, 4.4 Hz, 1H), 4.81-4.88 (m, 1H), 6.59 (s, 1H), 6.65 (s, 1H); ¹³C NMR (CDCl₃) 19.2, 28.2, 30.6, 31.8, 39.6, 55.7, 55.9, 56.5, 107.9, 111.2, 127.0, 128.7, 147.4, 147.5, 169.6; MS (EI) *m/z* (rel intensity) 262 (M⁺+1, 21), 261 (M⁺, 100), 260 (47), 246 (30), 230 (34), 205 (7), 191 (72), 176 (20), 146 (4), 91 (5). Anal. Calcd for C₁₅H₁₉NO₃: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.98; H, 7.55; N, 4.91.

Procedure B.

Treatment of glutarimide **1** (3 g, 11 mmol) with NaBH₄ (2.87 g, 70 mmol) according to the procedure described in Procedure A gave the *N*-[2-(3,4-dimethoxyphenyl)ethyl]-5-hydroxypentanamide (**I**) (2.5 g, 82%): mp (Et₂O) 71-72 °C; IR (KBr) 3500, 1637cm⁻¹; ¹H NMR (CDCl₃) 1.46-1.57 (m, 2H), 1.61-1.73 (m, 2H), 2.15 (t, *J* = 7.1 Hz, 2H), 2.66 (broad s, 1H), 2.72 (t, *J* = 7.1 Hz, 2H), 3.45 (dd, *J* = 7.1, 6.7 Hz, 2H), 3.57 (t, *J* = 5.9 Hz, 2H), 3.8 (s, 3H), 3.84 (s, 3H), 5.82 (broad s, 1H), 6.68-6.76 (m, 3H); ¹³C NMR (CDCl₃) 21.6, 31.7, 34.9, 55.6, 55.7, 61.5, 111.1, 111.7, 120.4, 131.2, 147.3, 148.7, 173.2. MS (EI) *m/z* (rel intensity) 263 (M⁺ - H₂O, 7), 164 (11), 151 (6), 112 (100), 91 (2), 69 (10), 55 (11). HRMS calcd for C₁₅H₂₃NO₄: 218.1627. Found: 218.1621.

The hydroxypentanamide **I** was submitted to Swern oxidation without purification: DMSO (1.21 mL, 17.1 mmol) was added over a solution of oxalyl chloride (0.75 mL, 8.5 mmol) in dry CH₂Cl₂ (15 mL) at — 60 °C. After stirring for 10 min, a solution of **I** (2 g, 7.1 mmol) in dry CH₂Cl₂ (80 mL) was added drop wise, and the resulting solution was stirred at — 60 °C for 1 h. Et₃N (4.9 mL, 35.4 mmol) was added and, after 15 min, the reaction mixture was allowed to warm up to rt, and stirred at this temperature for 30 min. Water was added (50 mL), and the organic phase was separated. The resulting aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na₂SO₄), and concentrated *in vacuo* to afford *N*-[2-(3,4-dimethoxyphenyl)ethyl]-5-oxopentanamide (**II**) as a colorless oil, that was used without purification : ¹H NMR (CDCl₃) 1.87-1.96 (m, 2H), 2.15 (t, *J* = 7.1, 2H), 2.73 (t, *J* = 7.1 Hz, 2H), 3.45-3.67 (m, 4H), 3.83 (s, 3H), 3.84 (s, 3H), 5.61 (broad s, 1H); 6.59-6.80 (m, 3H); 9.71 (s, 1H). Oxopentanamide **II** was

submitted to cyclization with TFA, according to the procedure described in Procedure A, yielding benzoquinolizidone **2a** (1.7 g, 92 % two steps), whose data were identical to those reported above.

Synthesis of 9,10-dimethoxy-11b-methyl-1,2,3,6,7,11b-hexahydrobenzo[*a*]quinolizin-4-one (2b).

MeLi (4.5 mL of a 1 M solution, 4.5 mmol) was added drop wise over a solution of glutarimide **1** (418 mg, 1.50 mmol) in dry THF (15 mL) at -78°C , and the resulting solution was stirred at this temperature for 6 h. H_2O (10 mL) was added, and the mixture was allowed to reach rt. The organic phase was separated and the aqueous phase was extracted with Et_2O (10 mL) and with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (3×10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (silica gel, AcOEt) afforded *N*-[2-(3,4-dimethoxyphenyl)ethyl]-5-oxohexanamide (**III**) as a white solid (400 mg, 90%): mp (50% hexane/AcOEt); IR (KBr) 3400, 1730, 1650 cm^{-1} ; ^1H NMR (CDCl_3) 1.73 (q, $J = 7.1$ Hz, 2H), 1.99 (s, 3H), 2.04 (t, $J = 7.1$ Hz, 2H), 2.34 (t, $J = 7.1$ Hz, 2H), 2.64 (t, $J = 7.1$ Hz, 2H), 3.28-3.46 (m, 2H), 3.72, (s, 3H), 3.73 (s, 3H), 6.08-6.12 (m, 1H), 6.59-6.69 (m, 3H); ^{13}C NMR (CDCl_3) 19.5, 29.8, 35.1, 35.2, 40.5, 42.2, 55.7, 111.1, 111.6, 120.4, 131.2, 147.5, 148.7, 172.2, 208.5. MS (EI) m/z (rel intensity) 293 (M^+ , 2), 164 (100), 151 (17), 91 (5), 85 (10), 77 (5). Anal. Calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_4$: C, 65.50; H, 7.90; N, 4.77. Found: C, 65.08; H, 7.75; N, 4.70.

TFA (1 mL, 12 mmol) was added over a solution of oxoamide **III** (360 mg, 1.2 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred at rt for 16 h. The reaction was quenched by addition of saturated NaHCO_3 (10 mL). The organic phase was separated, and the resulting aqueous phase was extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine (3×10 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Flash column chromatography (silica gel, AcOEt) afforded

benzoquinolizidone **2b** (310 mg, 93%; overall yield from **1**, 84%): mp (50 % hexane/AcOEt) 92-93 °C (lit.⁵ mp 97-98 °C); IR (KBr) 1610 cm⁻¹; ¹H NMR (CDCl₃) 1.54 (s, 3H), 1.62-1.84 (m, 3H), 2.20-2.34 (m, 2H), 2.42-2.59 (m, 2H), 2.74-2.87 (m, 2H), 3.77 (s, 3H), 3.78 (s, 3H), 4.85 (dd, *J* = 13.0, 6.8 Hz, 1H), 6.50 (s, 1H), 6.56 (s, 1H); ¹³C NMR (CDCl₃) 16.7, 27.5, 28.6, 31.5, 35.4, 37.2, 55.7, 55.8, 58.4, 108.1, 111.1, 125.0, 134.6, 147.2, 147.3, 168.8; MS (EI) *m/z* (rel intensity) 275 (M⁺, 7), 260 (100), 244 (5), 216 (5), 190 (4), 131 (2), 91 (3), 77 (4), 55 (10). Anal. Calcd for C₁₆H₂₁NO₃: C, 69.79; H, 7.69; N, 5.08. Found: C, 69.45; H, 7.65; N, 4.90.

Synthesis of 9,10-dimethoxy-1,6,7,11b-tetrahydrobenzo[*a*]quinolizin-4-one (**3a**).

A solution of **2a** (1.04 g, 4 mmol) in THF (100 mL) was added drop wise over a solution of LDA [12 mmol, prepared from *i*-Pr₂NH (1.67 mL, 12 mmol) and *n*-BuLi (8 mL of a 1.5 M solution in hexanes, 12 mmol)] in THF (20 mL), at — 78°C. After 40 min, a solution of PhSeBr (1.3 g, 5.2 mmol) in THF (30 mL) was added drop wise, and the reaction mixture was stirred at — 78 °C for 1 h. The reaction was quenched by addition of 1 M HCl (40 mL). The organic phase was separated, and the resulting aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash column chromatography (silica gel, AcOEt) afforded a 2:1 diastereomeric mixture of selenides **IV** (1.13 g, 70%): Data of the major diastereomer are given: IR (KBr) 1652 cm⁻¹; ¹H NMR (CDCl₃) 1.60-1.76 (m, 1H), 1.93-2.20 (m, 2H), 2.41-2.59 (m, 1H), 2.64-2.66 (m, 1H), 2.76-2.99 (m, 2H), 3.83 (s, 3H), 3.85 (s, 3H), 4.06 (dd, *J* = 9.9, 6.7 Hz, 1H), 4.57 (dd, *J* = 9.9, 4.4 Hz, 1H), 4.79-4.86 (m, 1H), 6.58 (s, 1H), 6.60 (s, 1H), 7.28-7.31 (m, 3H), 7.67-7.70 (m, 2H); ¹³C NMR (CDCl₃) 27.9, 28.3, 30.5, 40.6, 42.1, 55.8, 56.0, 56.6, 107.9, 111.5, 127.3, 128.1, 128.5, 129.0, 135.6, 147.6, 147.8, 168.4. MS (EI) *m/z* (rel intensity) 259 (45), 244 (9), 191 (100), 176 (36), 103 (7), 91 (9), 77 (21).

A solution of the diastereomeric mixture of selenides **IV** (1.13 g, 2.7 mmol) in CH₃CN/H₂O (2:1, 80 mL) was treated with TFA (2.1 mL, 27 mmol) at rt. PIDA (1.1 g, 3.3 mmol) was added in portions, and the resulting mixture was stirred for 2 h. The reaction mixture was extracted with hexane (3 × 30 mL). The combined organic extracts were washed with saturated NaHCO₃ (3 × 20 mL), dried (Na₂SO₄), and concentrated *in vacuo*. Flash column chromatography (silica gel, 30% hexane/AcOEt) afforded tetrahydrobenzoquinolizidone **3a** (526 mg, 75%; overall yield from **2a**, 56%): mp (Et₂O) 128-130 °C; IR (KBr) 1665 cm⁻¹; ¹H NMR (CDCl₃) 2.15-2.30 (m, 1H), 2.56-2.88 (m, 4H), 3.80 (s, 6H), 4.63-4.77 (m, 2H), 5.99 (dd, *J* = 9.5, 2.8 Hz, 1H), 6.55 (s, 1H), 6.58-6.65 (m, 1H), 6.59 (s, 1H); ¹³C NMR (CDCl₃) 28.7, 33.4, 37.7, 55.6, 55.8, 56.7, 108.3, 111.2, 125.2, 126.8, 127.3, 138.8, 147.6, 147.7, 164.5; MS (EI) *m/z* (rel intensity) 260 (M⁺+1, 15), 259 (M⁺, 83), 244 (7), 228 (11), 191 (100), 176 (32), 164 (3), 91 (3). Anal. Calcd for C₁₅H₁₇NO₃: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.47; H, 6.77; N, 5.58.

Synthesis of 9,10-dimethoxy-11b-methyl-1,6,7,11b-tetrahydrobenzo[*a*]quinolizin-4-one (**3b**).

A solution of **2b** (248 mg, 0.9 mmol) in THF (10 mL) was added drop wise over a solution of LDA [2.2 mmol, prepared from *i*-Pr₂NH (0.32 mL, 2.2 mmol) and *n*-BuLi (3.14 mL of a 0.7 M solution in hexanes, 2.2 mmol)] in THF (2 mL), at — 78°C. After 40 min, a solution of PhSeBr (300 mg, 1.2 mmol) in THF (7 mL) was added drop wise, and the reaction mixture was stirred at — 78 °C for 1 h. The reaction was quenched by addition of 1 M HCl (40 mL). The organic phase was separated, and the resulting aqueous phase was extracted with CH₂Cl₂ (3 × 50 mL). The combined organic extracts were washed with brine (3 × 50 mL), dried (Na₂SO₄), and concentrated *in vacuo*. A solution of the diastereomeric mixture of selenides in CH₂Cl₂ (20 mL) was treated with pyridine (0.25 mL, 3.1 mmol) and H₂O₂ (0.45 mL, 6.2 mmol) at 0 °C. The resulting mixture was stirred for 1 h at this temperature, allowed to reach rt, and stirred 16 h. The reaction was quenched by addition of 1M HCl (10 mL). The aqueous phase was extracted with CH₂Cl₂ (3 × 15mL). The combined organic extracts were dried (Na₂SO₄), and concentrated *in vacuo*. Flash column chromatography (silica gel, 30%

hexane/AcOEt) afforded tetrahydrobenzoquinolizidone **3b** as a colorless oil (lit.⁶ mp (hexane) 115 °C) (151 mg, 61% overall yield from **2b**): IR (neat) 1654 cm⁻¹; ¹H NMR (CDCl₃) 1.55 (s, 3H), 2.5 (dd, *J* = 17.8, 2.4 Hz, 1H), 2.64-2.79 (m, 2H), 2.81-2.94 (m, 2H), 3.85 (s, 3H), 3.86 (s, 3H), 4.79-4.85 (m, 1H), 6.06 (dd, *J* = 9.9, 3.1 Hz, 1H), 6.51-6.57 (m, 1H), 6.58 (s, 1H), 6.59 (s, 1H); ¹³C NMR (CDCl₃) 24.8, 29.1, 34.1, 39.1, 55.8, 56.1, 57.5, 108.3, 111.2, 124.9, 125.9, 133.7, 137.3, 147.6, 147.8, 163.4; MS (EI) *m/z* (rel intensity) 273 (M⁺, 6), 259 (18), 258 (100), 242(6), 214 (4), 205 (3). Anal. Calcd for C₁₆H₁₉NO₃: C, 70.31; H, 7.06; N, 5.12. Found: C, 69.95; H, 6.86; N, 4.82.

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