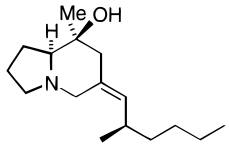
A Formal Synthesis of Pumiliotoxin 251D, via a Highly Diastereoselective Addition of a Titanium Homoenolate to an L-Proline Derivative

Anthony G. M. Barrett* and Federica Damiani

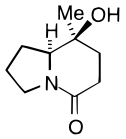
Department of Chemistry, Imperial College of Science, Technology and Medicine, South Kensington, London, UK, SW7 2AY

Received October 19, 1998

Pumiliotoxin A, B, and 251D (**1**), alkaloids isolated from skin secretion of neotropical dendrobatid frogs, have shown ability to activate voltage-dependent sodium channels, therefore displaying in some cases cardiotonic and myotonic activity.[1] Since the natural source of these alkaloids is limited, they have been subject to considerable synthetic investigations including the total syntheses of Overman, Trost, and Gallagher.[2,3] Lactam **2** is a key intermediate in the Gallagher synthesis of pumiliotoxin 251D and has alternatively been prepared from L-proline in nine steps with an overall yield of 9%.[3,4] Since the conversion of lactam **2** into pumiliotoxin 251D required only three steps,[3] a concise synthesis of this compound would be of value in the elaboration of libraries of analogues. Herein we report a concise, six-step, highly stereoselective synthesis of lactam **2** from L-proline, which therefore represents a formal total synthesis of pumiliotoxin 251D (**1**).



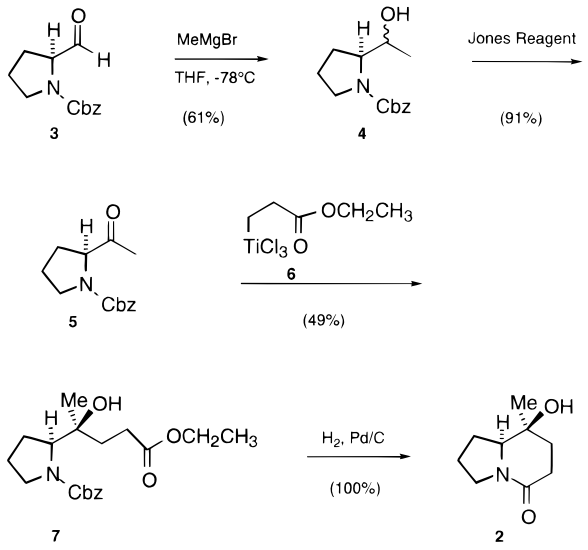
pumilitoxin 251D (**1**)



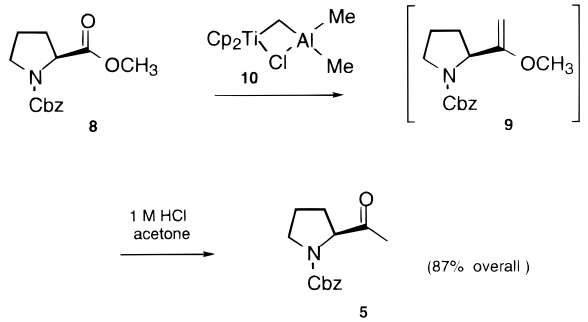
2

Grignard reaction of aldehyde **3** with methylmagnesium bromide gave a diastereoisomeric mixture of alcohols **4**, although some addition of the Grignard reagent to the carbamate did occur. The best yields of the desired alcohols **4** were achieved when the reaction was conducted for 1 h at −78 °C using 5 equiv of methylmagnesium bromide (61% isolated yield). Alcohols **4** were oxidized to the ketone **5** (91%) using Jones reagent[5] at 0 °C.[6] Reaction of the titanium homoenolate **6**, prepared in situ from titanium tetrachloride and 1-ethoxy-1-(trimethylsilyloxy)cyclopropane following the procedure of Nakamura and Kuwaijma,[7] with ketone **5** gave alcohol

Scheme 1



Scheme 2



7 in 49% yield as a single diastereoisomer.[8] Hydrogenation of **7** in MeOH gave the desired lactam **2** in quantitative yield (Scheme 1). This procedure afforded lactam **2** with complete diastereoselectivity, in 19% overall yield and in seven steps from L-proline.

Although this method provides a shorter and higher yielding access to pumiliotoxin 251D (**1**), it involved an undesirable sequence of redox steps. Therefore we sought a more direct approach to ketone **5**. Treatment of commercially available Cbz-protected proline methyl ester[9] with the Tebbe reagent (**10**)[10] afforded, after filtration through a short path of silica gel, a mixture of enol ether **9** and ketone **5**. Hydrolysis of this mixture in acetone with a catalytic amount of 1 M HCl gave ketone **5**,[6] which was obtained as a pure compound without chromatography, in 89% yield over the two steps (Scheme 2). This final improvement allows the synthesis of lactam **2** in six steps and in 41% overall yield from L-proline.

(1) For recent reviews, see (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. *The Alkaloids* **1993**, *43*, 185. (b) Daly, J. W.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, Chapter 1.

(2) For review on total synthesis of pumiliotoxin alkaloids, see Overman, L. E.; Franklin, S. A. *Chem. Rev.* **1996**, *96*, 505−522.

(3) Fox, D. N. A.; Lathbury, D.; Mahon, M. F.; Molloy, K. C.; Gallagher, T. *J. Am. Chem. Soc.* **1991**, *113*, 2652.

(4) Cossy, J.; Cases, M.; Gomez Pardo, D. *Synlett* **1996**, 909.

(5) Paquette, L. A. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: New York, 1995; Vol. 2, p 1261.

(6) The enantiomeric purity of ketone **5** was determined by chiral HPLC analysis which showed that no racemization had occurred [Chiralpak-AD column; eluant 10% EtOH/hexanes]. This system clearly resolved a racemic modification of the ketone **5**.

(7) Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, *108*, 3745.

(8) Analysis of the crude reaction product showed the presence of only one diastereoisomer.

(9) Compound **8** is also available in two steps from L-proline (95% yield): (a) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861. (b) Nakayama, K.; Thompson, W. J. *J. Am. Chem. Soc.* **1990**, *112*, 6936.

(10) Pine, S. H.; Shen, G. S.; Hoang, H. *Synthesis* **1991**, 165.

10.1021/jo9820972 CCC: $18.00
Published on Web 01/22/1999

Experimental Section

General. Solvents were dried by distillation under N_2, from sodium benzophenone ketyl (THF, Et_2O) or CaH_2 (CH_2Cl_2). Hexanes refers to the petroleum fraction bp 40−60 °C. All other reagents were used as commercially supplied. Air- and/or moisture-sensitive reactions were performed in oven-dried (110 °C) glassware under N_2. TLC was carried out on E. Merck precoated silica gel 60 F_{254} plates. Chromatography refers to flash chromatography on E. Merck silica gel 60, 40−60 μm.

(2*S*)-Benzyl 2-(1-Hydroxyethyl)-1-pyrrolidinecarboxylate (4). MeMgBr in Et_2O (3 M; 2.1 mL, 6.57 mmol, 5 equiv) was added to freshly prepared aldehyde **3**[11] (350 mg, 1.3 mmol) in dry THF (4 mL). The reaction mixture was stirred at −78 °C for 1 h, warmed to 0 °C over 30 min, and quenched with saturated $NaHCO_3$. The aqueous layer was extracted with Et_2O (3 × 30 mL), and the combined organic phases were washed with brine and dried (Na_2SO_4). Filtration, evaporation, and chromatography (hexanes:Et_2O 1:1) gave alcohol **4** (197 mg, 61%) as a mixture of two diastereoisomers: IR (neat) 3427, 2973, 2934, 2883, 1680, 1696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3−7.4 (m, 5 H), 5.16 (d, 1 H, J = 12.6 Hz), 5.13 (d, 1 H, J = 12.4 Hz), 4.0 (s, 1 H), 3.77−3.82 (m, 1 H), 3.70−3.74 (m, 1 H), 3.57−3.63 (m, 1 H), 3.3−3.4 (m, 1H), 1.94−2.02 (m, 1 H), 1.72−1.90 (m, 2 H), 1.61−1.69 (m, 1 H), 1.16; 1.10 (2d, 3 H, J = 5.9 Hz, J = 6.4 Hz, ratio = 2:1); ^{13}C NMR (100 MHz, $CDCl_3$) δ major diastereoisomer: 158.1, 136.4, 128.5, 128.1, 127.9, 72.0, 67.4, 64.9, 47.3, 28.8, 24.1, 20.8, minor diastereoisomer: 158.1, 136.6, 128.5, 128.1, 127.9, 69.4, 67.2, 64.0, 47.9, 27.6, 24.1, 17.6; HRMS (CI) [M + H$^+$] calcd 250.1443, found 250.1426. Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.50; H, 7.81; N, 5.58.

(2*S*)-Benzyl 2-Acetyl-1-pyrrolidinecarboxylate (5). Jones reagent was added dropwise to alcohol **4** (640 mg, 2.57 mmol) in Me_2CO (100 mL) at 0 °C to a permanent orange end-point. The reaction mixture was stirred for 30 min at room temperature when 2-propanol (50 mL) was added at 0 °C and stirring continued for 15 min. Filtration through a short plug of silica gave ketone **5** (580 mg, 91%) which by ^{1}H NMR resulted to be pure enough for the next step: $[\alpha_D]^{27} = -42.2°$ (c = 1, $CHCl_3$); IR (neat) 3033, 2956, 2926, 2884, 2855, 1705 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6, 95 °C) δ 7.0−7.2 (m, 5 H), 5.09 (d, 1 H, J = 12.5 Hz), 5.05 (d, 1 H, J = 12.5 Hz), 4.13 (br. s, 1 H), 3.31 (br. s, 2 H), 1.79 (s, 3 H), 1.51−1.6 (m, 1 H), 1.39−1.46 (m, 2 H), 1.2−1.3 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ mixture of rotamers 207.8, 207.5, 155.0, 154.4, 136.6, 136.3, 128.6, 128.5, 128.1, 128.0, 127.8, 67.15, 67.03, 65.5, 65.4, 47.2, 46.7, 30.3, 29.7, 24.3, 23.6; HRMS (CI) [M + H$^+$] calcd 248.1287, found 248.1278. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 67.87; H, 6.81; N, 5.61.

(4*S*)-Ethyl 4-[1-[(Benzyloxy)carbonyl]-2*S*-pyrrolidinyl]-4-hydroxypentanoate (7). 1-Ethoxy-1-(trimethylsilyloxy)-cyclopropane (8.5 mmol, 1.7 mL) was added at 21 °C over 20 s to $TiCl_4$ in CH_2Cl_2 (1 M, 8.5 mL, 8.5 mmol). The homoenolate (8.5 mmol) was diluted with dry CH_2Cl_2 (8 mL) at −78 °C, and ketone **5** (340 mg; 1.38 mol) was added. After 1 h, the reaction mixture was allowed to warm to 0 °C and then slowly to room-temperature overnight. The mixture was poured into water and extracted with Et_2O (3 × 10 mL), and the organic phase was washed with saturated aqueous $NaHCO_3$ (10 mL) and brine, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (hexanes:Et_2O 3:2) gave ester **7** (237 mg, 49%): $[\alpha_D]^{27} = -49.9°$ (c = 1.1, $CHCl_3$), IR (neat) 3364, 2977, 2940, 2896, 1732, 1671 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.4 (m, 5 H), 5.17 (s, 2 H), 4.14 (q, 2 H, J = 7.1 Hz), 3.9−4.0 (m, 1 H), 3.7−3.8 (m, 1 H), 3.2−3.3 (m, 1 H), 2.5−2.6 (m, 2 H), 2.07−2.11 (m, 1 H), 1.84−1.90 (m, 1 H), 1.6−1.81 (m, 4 H), 1.27 (t, 3 H, J = 7.1 Hz), 1.06 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.4, 158.4, 136.3, 128.6, 128.2, 128.0, 74.8, 67.7, 66.8, 60.3, 48.2, 35.1, 28.6, 28.5, 24.4, 21.2, 14.2; HRMS (CI) [M + H$^+$] calcd 350.1967, found 350.1953. Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.59; H, 7.84; N, 4.00.

(5*S*,6*S*)-5-Hydroxy-5-methyl-1-azabicyclo[4.3.0]nonan-2-one (2). To ester **7** (155 mg, 0.44 mmol) in MeOH (100 mL) was added 10% Pd/C (100 mg), and the mixture was evacuated and stirred under H_2 (1 atm) overnight. The solution was filtered through Celite and concentrated in vacuo to give **2** (75 mg, 100%), as a pure compound. Recrystallization from hexanes/Et_2O gave **2**: mp 89−91 °C; $[\alpha_D]^{29} = -53.0°$ (c = 0.97, $CHCl_3$); IR (neat) 3328, 2971, 2952, 2928, 2884, 1616 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.45 (dd, 2 H, J = 4.4, 9.3 Hz), 3.30 (dd, 1 H, J = 5.5, 10.3 Hz), 2.94 (s, 1 H), 2.49 (ddd, 1 H, J = 18.7, 11.4, 7.8 Hz), 2.32 (dd, 1 H, J = 18.1, 7.4 Hz), 1.6−2.2 (m, 6 H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 67.3, 66.3, 45.7, 34.9, 28.1, 26.4, 26.2, 21.9; HRMS (CI) [M + H$^+$] calcd 170.1181, found 170.1176. All data were identical with those reported.[3]

(2*S*)-Benzyl 2-(1-Methoxy-1-propenyl)pyrrolidinecarboxylate (9). To ester **8** (224 mg, 0.85 mmol) in dry THF (2.5 mL) at 0 °C was added Tebbe reagent **10** in PhMe (0.5 M, 1.7 mL) (Aldrich). The mixture was allowed to warm to room temperature and, after 30 min, Et_2O (10 mL) was added, followed by the slow addition of aqueous NaOH (0.1 M) while stirring the mixture. After gas evolution ceased, the mixture was dried (Na_2SO_4) and filtered through Celite. Evaporation and chromatography (hexanes:Et_2O 7:3−1:1) gave enol ether **9** (175 mg, 79%) and ketone **5** (36 mg, 17%). Data for enol ether **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.3−7.4 (m, 5 H), 5.1−5.2 (m, 2 H), 4.3−4.4 (m, 1 H), 3.9−4.0 (m, 2 H), 3.4−3.6 (m, 5 H), 1.8−2.1 (m, 4 H); HRMS (CI) [M + H$^+$] calcd 262.1443, found 262.1443. This crude mixture was used directly in the next step, and no further characterization was possible to obtain on the unstable **9**, which easily hydrolyzed to ketone **5**.

(2*S*)-Benzyl 2-Acetyl-1-pyrrolidinecarboxylate (5). Aqueous 1 M HCl (5 drops) was added to **9** (175 mg, 0.67 mmol) in Me_2CO (30 mL). After 30 min, saturated $NaHCO_3$ was added to reach neutral pH, and the solution was evaporated and the residue extracted with EtOAc (3 × 20 mL). The organic layer was washed with brine and dried (Na_2SO_4). Evaporation of the solvent gave ketone **5** (151 mg, 91%) which by NMR was pure enough for the next step: $[\alpha_D]^{27} = -43°$ (c = 1, $CHCl_3$), all data was identical with previous sample.

Acknowledgment. We thank Zeneca, Chiroscience, the EPSRC, and the DTI for generous support under the Link Asymmetric Scheme; Glaxo-Wellcome Research Ltd for the most generous endowment (to A.G.M.B.); the Wolfson Foundation for establishing the Wolfson Centre for Organic Chemistry in Medical Science at Imperial College; and George A. O'Doherty, Oswy Pereira, and D. Christopher Braddock for helpful discussions.

JO9820972

(11) Aldehyde **3** has been synthesized in a three-step sequence from L-proline via $LiAlH_4$ reduction (85%), Cbz protection (87%), and Swern oxidation (95%): (a) Enders, D.; Eichenauer, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 549. (b) St-Denis, Y.; Chan, T.-H. *J. Org. Chem.* **1992**, *57*, 3078. (c) Shi, X.; Attygalle, A. B.; Xu, S.-C.; Ahmad, V. U.; Meinwald, J. *Tetrahedron* **1996**, *52*, 6859.