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A short enantioselective access to pumiliotoxin 251D from L-proline

Janine Cossy*, Manuel Cases, Domingo Gomez Pardo

Laboratoire de chimie organique, associé au CNRS, ESPCI, 10, rue Vauquelin,
75231 Paris cedex 05, France

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Summary — The indolizidine framework of pumiliotoxin 251D with the appropriate functionalities for incorporation of the tertiary hydroxyl at the C-8 and the alkylidene side chain at C-6 has been accessed from L-proline by using a 6-exo-dig radical cyclization.

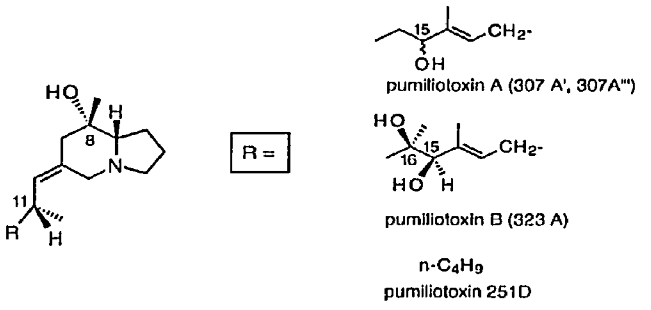
pumiliotoxin 251D / L-proline / radical cyclization

Résumé — Synthèse formelle énantiosélective de la pumiliotoxine 251D à partir de la L-proline. Le squelette indolizidinique de la pumiliotoxine 251D possédant les fonctionnalités nécessaires à l'introduction de l'alcool tertiaire en C-8 et de la chaîne latérale alkylidène en C-6 a été synthétisé à partir de la L-proline via une réaction de cyclisation radicalaire 6-exo-dig.

pumiliotoxine 251D / L-proline / cyclisation radicalaire

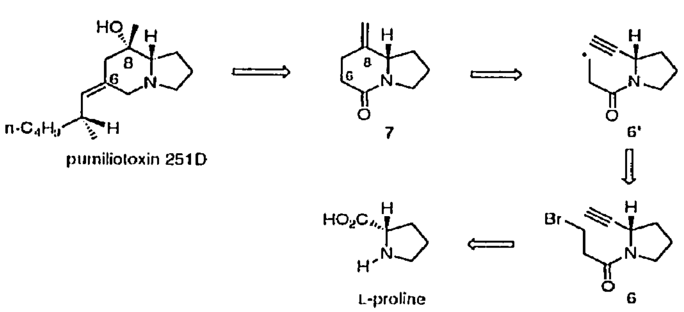
Introduction

Neotropical frogs of the family *Dendrobatidae* produce an array of more than 200 alkaloids [1]. Some of them serve as a 'chemical defense' against predators. They have high pharmacological activities on nerves and muscles [2]. Pumiliotoxin B was first isolated by Daly and coworkers [3] from the Panamanian frog *Dendrobates pumilio* together with the close analog pumiliotoxin A. The key to the structure of the pumiliotoxin A class of dendrobatid alkaloids was obtained through X-ray analysis of a relatively simple member, pumiliotoxin 251D, isolated from the Ecuadorean frog, *Dendrobates tricolor* [4].



The first synthesis of pumiliotoxin 251D was reported in 1981 [5]. It relied on an iminium ion-vinylsilane cyclization step that generated the indolizidine ring system. Another synthesis used an electrophilic cyclization of an allenic amine induced by $PdCl_2$ [6]. Furthermore, an enantioselective formal synthesis of pumiliotoxin 251D was carried out in 23 steps from 5-(trimethylsilyl)pent-4-yn-1-ol [7]. The key steps were a Sharpless kinetic resolution of a (2-furyl)methanol derivative and a selective radical cyclization of a thiocarbonyl imidazolide derivative.

We present here [8] a short approach to the optically active pumiliotoxin 251D skeleton that features a chemically and a photochemically induced radical cyclization of the unsaturated bromide **6** (scheme 1). Through this method, the indolizidine framework **7** has been constructed in eight steps from L-proline with functionalities appropriate to the incorporation of the tertiary hydroxyl group at C-8 and the alkylidene side chain at C-6. The key intermediate is the bromopropanamide



Scheme 1. Retrosynthetic analysis.

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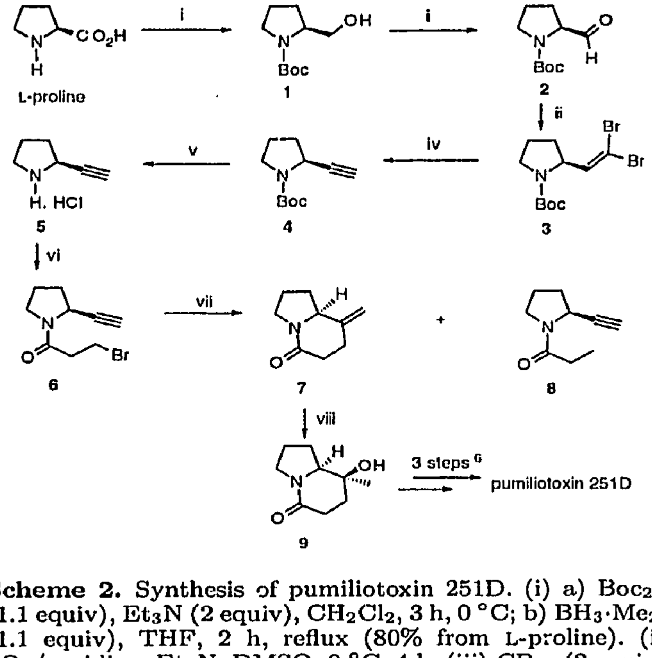
* Correspondence and reprints

6, which generates the corresponding radical 6′ which undergoes a 6-exo-dig cyclization.

The sequence begins with the protection of the amino moiety of L-proline as a carbamate (Boc_2O, Et_3N, CH_2Cl_2) [9]. The transformation of the *N*-Boc proline to the corresponding primary alcohol was achieved by using $BH_3{\cdot}Me_2S$ in refluxing THF for 2 h [10]. The overall yield for the two steps was 80%. Oxidation of the alcohol **1** (SO_3-pyr, DMSO, NEt_3) [11] gave the aldehyde **2**, which was reacted with CBr_4, zinc powder and triphenylphosphine [12], affording dibromide **3**. Treatment of **3** with 2 equiv of *n*-BuLi (−78 °C, 2 h) gave alkyne **4** without epimerization [13, 14]. Deprotection of the amine under acidic conditions (EtOH, HCl 8 N) afforded the corresponding ammonium salt **5**, which was treated directly with 3-bromopropanoyl chloride in the presence of NEt_3 (2 equiv). This furnished **6** (yield = 68%; $[\alpha]_D^{20} = -51.4$; $c = 1.6$, MeOH) which was heated with Bu_3SnH in the presence of AIBN (PhH, 80 °C, 12 h). The desired cyclized product **7** [6] was obtained with a yield of 40% ($[\alpha]_D^{20} = -102.1$; $c = 1.2$, $CHCl_3$) together with the product of reduction **8** which was isolated with a yield of 35% ($[\alpha]_D^{20} = -82.7$; $c = 2.0$, $CHCl_3$). When a solution of **6** in acetonitrile (5×10^{-2} M) was irradiated in the presence of triethylamine (10 equiv) at 254 nm [15], **7** (10% yield) and **8** (10% yield) were also formed concurrently but it appears that the photochemical process is somewhat lower yielding than the corresponding chemical process.

As previously described [6], the reductive hydroxymercuration of **7** provided a mixture of epimeric tertiary alcohols (95% yield) in a ratio 5:1 [16]. The major expected product **9** is the (8*S*,8a*R*)-isomer obtained pure by recrystallization from light petroleum ether and ether. Compound **9** can be converted to pumiliotoxin 251D in three steps [6]. Our work describes therefore the shortest enantioselective access (12 steps) to this alkaloid.



Scheme 2. Synthesis of pumiliotoxin 251D. (i) a) Boc_2O (1.1 equiv), Et_3N (2 equiv), CH_2Cl_2, 3 h, 0 °C; b) $BH_3{\cdot}Me_2S$ (1.1 equiv), THF, 2 h, reflux (80% from L-proline). (ii) SO_3/pyridine, Et_3N, DMSO, 0 °C, 4 h. (iii) CBr_4 (2 equiv), Zn (2 equiv), PPh_3 (3 equiv), CH_2Cl_2, 2 h, RT (65% from **1**). (iv) *n*-BuLi (2 equiv), THF, −78 °C (80%). (v) HCl/EtOH 8 N, reflux. (vi) $Br(CH_2)_2COCl$ (1.1 equiv), Et_3N (2 equiv), 10 min, 0 °C (60% from **4**). (vii) Bu_3SnH (1.2 equiv), AIBN (10% by weight), benzene, reflux 12 h, $c = 2 \times 10^{-2}$ M (40%). (viii) $Hg(OAc)_2$ (1.3 equiv), 3 h, RT, NaOH/$NaBH_4$ (95%).

Experimental section

General methods

All experiments were run under an Ar atmosphere. ^1H NMR and ^{13}C NMR spectra were obtained with a Bruker AC 300 instrument at 300 and 75 MHz respectively in $CDCl_3$. IR spectra were recorded on a Perkin-Elmer Infrared 137 spectrophotometer. Mass spectra (GC-MS) were run on a Hewlett-Packard 5971 (EI mode at 70 eV) and high-resolution mass spectra (HRMS) were recorded on a ZAB-HSQ VG Analytical. Specific rotations, $[\alpha]_D^{20}$, were recorded on a Polartronic I Schmitt-Haensch polarimeter. Flash chromatography was accomplished with Merck silica gel 0.043–0.063 mm.

(S)-1-(tert-Butoxycarbonyl)pyrrolidine-2-methanol **1**

Borane-methyl sulfide complex ($BH_3{\cdot}Me_2S$) (2.7 mL, 28.4 mmol, 1.1 equiv) was added dropwise to a solution of Boc-(L)-proline (5.5 g, 25.6 mmol) [9] in THF (38 mL). The $BH_3{\cdot}Me_2S$ was added at a rate to maintain a gentle reflux (the total addition time is 30 min). The reaction mixture was then refluxed for an additional period of 2 h. After cooling, ice (20 g) was added and the aqueous mixture was extracted with CH_2Cl_2 (100 mL). After filtration through a short pad of silica gel (CH_2Cl_2 as eluent) and evaporation of the solvent in vacuo, the alcohol **1** was obtained (4.6 g, 80% from L-proline).

Mp 59-60 °C; lit 55-56 °C [14].

$[\alpha]_D^{20} = -50.37$ ($c = 1.1$, MeOH); lit $[\alpha]_D^{20} = -46$ ($c = 0.85$, CH_2Cl_2) [14].

IR (film): 3 420, 1 695, 1 670 cm^{-1}.

^1H NMR ($CDCl_3$, 300 MHz) δ: 1.41 (s, 9H), 1.45–1.59 (m, 1H), 1.64–1.82 (m, 2H), 1.83–1.99 (m, 1H), 3.18–3.30 (m, 1H), 3.32–3.41 (m, 1H), 3.49–3.61 (m, 2H), 3.82–3.97 (m, 1H), 4.76 (ls, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.8 (t), 28.3 (q), 28.5 (t), 47.3 (t), 59.9 (d), 67.4 (t), 80.0 (s), 156.9 (s).

MS (EI, 70 eV) *m/z*: 201 ($M^{+\cdot}$, 02), 170 (20), 128 (22), 114 (74), 70 (100), 57 (86).

(S)-1-(tert-Butoxycarbonyl)pyrrolidine-2-carbaldehyde **2**

To a solution of alcohol **1** (8 g, 39.8 mmol) in DMSO (55 mL) was added Et_3N (19 mL, 136 mmol, 3.4 equiv). Sulfur trioxide-pyridine complex (22 g, 137.7 mmol, 3.5 equiv) was added at 0 °C over a 1 h period. The reaction mixture was maintained at 0–10 °C for 2.5 h. Ice (50 g) was added and the aqueous mixture was extracted with CH_2Cl_2 (3 × 200 mL). The organic phase was washed successively with a 50% citric acid solution (100 mL), water (200 mL), saturated sodium bicarbonate solution (100 mL), and water (200 mL). The organic phases were dried and removed in vacuo. Aldehyde **3** was obtained as a dense oil which was used immediatly in the next step. An analytical sample was purified by filtration through a short pad of silica gel (CH_2Cl_2 as eluent).

IR (film): 1 735, 1 700 cm^{-1}.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.31–1.36 (m, 9H), 1.78–2.01 (m, 4H), 3.21–3.42 (m, 2H), 3.73–4.08 (m, 1H), 9.34–9.44 (m, 1H).

^{13}C NMR (CDCl$_3$, 75 MHz) δ: 23.7 (t), 27.7 (t), 28 (q), 46.5 (t), 64.8 (d), 80.3 (s), 153.7 (s), 200.1 (d).

MS (EI, 70 eV) m/z: 199 ($M^{+\cdot}$, 2), 170 (18), 142 (12), 114 (100), 70 (92), 57 (80).

(S)-1-(tert-Butoxycarbonyl)-2-(2,2-dibromoethenyl)-pyrrolidine **3**

To a mixture of triphenylphosphine (31 g, 118 mmol, 3 equiv), Zn dust (5.14 g, 78.7 mmol, 2 equiv) and carbon tetrabromide (26.1 g, 78.7 mmol, 2 equiv), CH$_2$Cl$_2$ (126 mL) was added *carefully* (very exothermic process) at 0 °C. After 4 h, a solution of aldehyde **2** (7.9 g, 39.5 mmol) in dichloromethane (50 mL) was added at room temperature. The reaction mixture was stirred for 3 h then diluted with a mixture of EtOAc/cyclohexane (1:1) (100 mL), filtered through basic alumina/silica gel (1:1). The filter cake was washed with a mixture of dichloromethane/EtOAc/cyclohexane (1:1:1) (100 mL). The filtrate was concentrated and the residue was taken up in EtOAc/cyclohexane (1:1) (50 mL). After filtration and concentration of the filtrate, the residual oil was purified by flash chromatography (eluent: EtOAc/cyclohexane 30:70) to afford **3** as a white solid (9.2 g, 65% from **1**).

Mp 61–62 °C; lit 58–59 °C [14].

$[\alpha]_D^{20} = +22$ ($c = 1.6$, MeOH); lit $[\alpha]_D^{20} = +24$ ($c = 0.89$, CH$_2$Cl$_2$) [14].

IR (film): 1 670 cm^{-1}.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.45 (s, 9H), 1.68–1.76 (m, 1H), 1.79–1.88 (m, 2H), 2.10–2.21 (m, 1H), 3.35–3.47 (m, 2H), 4.32–4.35 (m, 1H), 6.33–6.35 (m, 1H).

^{13}C NMR (CDCl$_3$, 75 MHz) δ: 23.5 (t), 28.3 (q), 31.6 (t), 46.2 (t), 59.3 (d), 79.6 (s), 88 (s), 140.2 (d), 154 (s).

MS (EI, 70 eV) m/z: 299 (14), 220 (98), 218 (100), 57 (70).

(S)-1-(tert-Butoxycarbonyl)-2-ethynylpyrrolidine **4**

To a solution of **3** (9 g, 25.3 mmol) in THF (270 mL) cooled at −78 °C, an n-BuLi solution in hexanes (20.8 mL, 51.9 mmol, 2 equiv) was added dropwise over a period of 40 min. After stirring at −78 °C for 1 h, the reaction was quenched with an aqueous NH$_4$Cl saturated solution (10 mL). The extraction was achieved with Et$_2$O (3 × 20 mL) and the solvent was evaporated in vacuo. The crude reaction mixture was purified by flash chromatography (Et$_2$O/cyclohexane 2:8) and provided **4** (4 g, 80%) as a clear oil.

$[\alpha]_D^{20} = -99{,}0$ ($c = 1$, MeOH); lit $[\alpha]_D^{20} = +84$ ($c = 1.05$, CH$_2$Cl$_2$) [14].

IR (film): 3 310, 3 250, 1 695 cm^{-1}.

^{1}H NMR (C$_7$D$_8$, 90 °C, 300 MHz) δ: 1.64 (s, 9H), 1.76–2.00 (m, 4H), 2.14 (d, J = 2.2 Hz, 1H), 3.30–3.38 (m, 1H), 3.44–3.52 (m, 1H), 4.51–4.53 (m, 1H).

^{13}C NMR (C$_7$D$_8$, 90 °C, 75 MHz) δ: 24.9 (t), 29.6 (q), 34.6 (t), 46.8 (t), 49.4 (d), 70.7 (d), 80.2 (s), 86.0 (s), 154.7 (s).

MS (EI, 70 eV) m/z: 195 ($M^{+\cdot}$, 02), 139 (21), 57 (100).

(S)-2-Ethynylpyrrolidine hydrochloride **5**

A solution of **4** (4 g, 20.5 mmol) in dry HCl ethanolic solution (150 mL, 8 N) was refluxed under an inert atmosphere. After 30 min the solvent was evaporated in vacuo . The resulting hydrochloride **5** was used without further purification in the next step.

^{1}H NMR (D$_2$O, 300 MHz) δ: 2.01–2.31 (m, 3H), 2.33–2.42 (m, 1H), 3.07 (d, J = 2.2 Hz, 1H), 3.31–3.49 (m, 2H), 4.37–4.48 (m, 1H).

^{13}C NMR (D$_2$O, 75 MHz) δ: 25.6 (t), 34.2 (t), 47.7 (t), 52.2 (d), 79.7 (d).

(S)-1-(3-Bromopropanoyl)-2-ethynylpyrrolidine **6**

To a suspension of **5** (0.5 g, 3.8 mmol) in CH$_2$Cl$_2$ (15 mL) at 0 °C was added Et$_3$N (1.1 mL, 7.7 mmol, 2 equiv) and 3-bromopropanoyl chloride (0.43 mL, 4.2 mmol, 1.1 equiv). After stirring for 10 min at 0 °C, the reaction mixture was poured into a 1 N HCl aqueous solution and extracted with CH$_2$Cl$_2$. The organic phases were dried over MgSO$_4$ and evaporated in vacuo. The residue was purified by flash chromatography (Et$_2$O/cyclohexane 1:9) to give **6** as a colorless oil (0.52 g, 60% from **4**).

$[\alpha]_D^{20} = -51.4$ ($c = 1.6$, MeOH).

IR (film): 3 290, 2 110, 1 635 cm^{-1}.

^{1}H NMR (CDCl$_3$, 300 MHz) (two rotamers in a ratio 1.2:1) δ: 1.70–2.30 (m, 4H), 2.20 (m, 0.55 H), 2.40 (m, 0.45 H), 2.82–2.87 (m, 1.1 H), 2.93–2.98 (m, 0.45 H), 3.09–3.19 (m, 0.45 H), 3.40–3.80 (m, 4H), 4.47–4.51 (m, 0.55 H), 4.74–4.75 (m, 0.45 H).

^{13}C NMR (CDCl$_3$, 75 MHz) major rotamer δ: 24.5 (t), 26.9 (t), 34.0 (t), 37.6 (t), 45.7 (t), 48.1 (d), 72.1 (d), 82.4 (s), 168.7 (s); minor rotamer δ: 22.8 (t), 26.6 (t), 32.1 (t), 37.7 (t), 46.1 (t), 47.3 (d), 70.0 (d), 82.9 (s), 168.2 (s).

MS (EI, 70 eV) m/z: 230 ($M^{+\cdot}$, 47), 229 (45), 67 (100).

HRMS: calc for C$_9$H$_{12}$BrNO 229.010223, found 229.0101247.

(8aS)-8-Methylideneoctahydroindolizin-5-one **7**

A solution of **6** (0.4 g, 1.7 mmol) in dry benzene (85 mL), containing a catalytic amount of AIBN (0.04 g, 10% by weight) and Bu$_3$SnH (0.55 mL, 2.04 mmol, 1.2 equiv), was refluxed under an inert atmosphere. The solvent was evaporated and the residue purified twice by flash chromatography (cyclohexane/EtOAc 1:1) to afford **7** as a yellow oil (0.1 g, 40%).

$[\alpha]_D^{20} = -102.1$ ($c = 1.2$, CHCl$_3$); lit $[\alpha]_D^{20} = -98.3$ ($c = 1.2$, CHCl$_3$) [6].

IR (film): 1 630, 1 450 cm^{-1}.

^{1}H NMR (CDCl$_3$, 300 MHz) δ: 1.60–2.05 (m, 3H), 2.10–2.22 (m, 1H), 2.32–2.52 (m, 4H), 3.42–3.50 (m, 1H), 3.55–3.65 (m, 1H), 3.96–4.01 (m, 1H), 4.89–4.90 (m, 1H), 4.95–4.96 (m, 1H).

^{13}C NMR (CDCl$_3$, 75 MHz) δ: 22.1 (t), 29.3 (t); 30.8 (t), 32.4 (t), 44.5 (t), 60.7 (d), 109.0 (t), 143.3 (s); 169.3 (s).

MS (EI, 70 eV) m/z: 151 ($M^{+\cdot}$, 100), 136 (75), 122 (45), 95 (78), 67 (51).

HRMS: calc for C$_9$H$_{13}$NO 151.099713, found 151.0997391.

(S)-2-Ethynyl-1-propanoylpyrrolidine **8**

Compound **8** was obtained as a colorless oil (0.087 g, 35%).

$[\alpha]_D^{20} = -82.7$ ($c = 2$, CHCl$_3$).

IR (film): 3 210, 2 105, 1 640 cm^{-1}.

^{1}H NMR (CDCl$_3$, 300 MHz) (two rotamers in a ratio 1.2:1) δ: 1.11–1.18 (m, 3H), 1.92–2.37 (m, 7H), 3.32–3.68 (m, 2H), 4.43–4.47 (m, 0.55 H), 4.74–4.76 (m, 0.45 H).

^{13}C NMR (CDCl$_3$, 75 MHz) major rotamer δ: 8.8 (q), 22.7 (t), 27.4 (t), 32.0 (t), 45.8 (t), 48.1 (d), 71.4 (d), 82.9 (s), 172.5 (s); minor rotamer δ: 8.5 (q), 24.6 (t), 27.6 (t), 34.0 (t), 45.5 (t), 47.1 (d), 69.5 (d), 83.5 (s), 171.9 (s).

MS (EI, 70 eV) m/z: 151 ($M^{+\cdot}$, 37), 150 (45), 136 (14), 122 (19), 96 (23), 94 (100), 80 (16), 77 (38), 67 (83), 57 (52).

HRMS: calc for $C_9H_{13}NO$ 151.099713, found 151.099739.

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