A novel approach to the enantioselective formal synthesis of pumiliotoxin 251D

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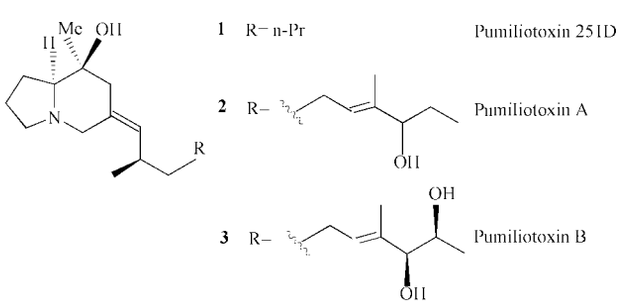
An efficient enantioselective synthesis of the indolizidine framework **9** of pumiliotoxin 251D in good yield by using a Lewis acid (cat.)-promoted diastereoselective addition of ethyl lithiopropiolate to ketone **7** derived from L-proline as a key step is reported. Hydrogenation of the addition product **8a** gave the desired lactam **9**. At the same time the 8-epimer of **9** was synthesized for the first time.

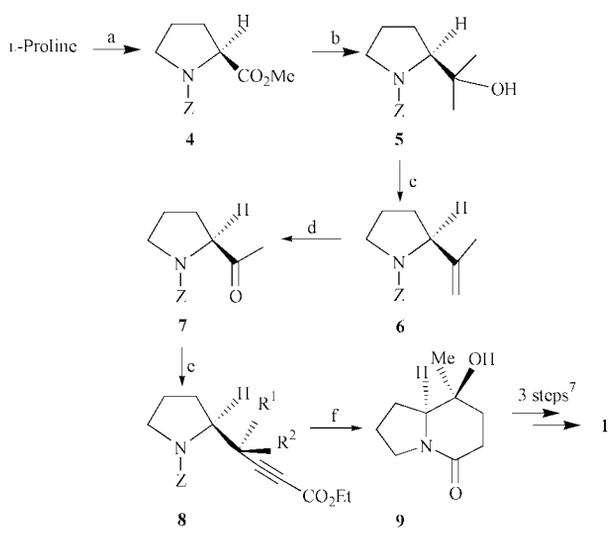
Introduction

The neotropical frogs of the family *Dendrobatidae* are a rich source of biologically significant alkaloids[1] with varied structure prototypes. These alkaloids are usually released onto the skin surface from cutaneous granular glands and many of them play a chemical defense role. Among them, pumiliotoxins A (**2**), B (**3**), and 251D (**1**) have shown ability to activate voltage-dependent sodium channels, therefore displaying in some cases cardiotonic and myotonic activity.[2] Pumiliotoxins A and B were first isolated from the Panamanian poisonous frog *Dendrobates pumilio* in 1967 by Daly and co-workers.[3] The structure of pumiliotoxin A among dendrobatid alkaloids was not defined until the structure and absolute configuration of pumiliotoxin 251D, a major component of the basic skin extracts of the Ecuadorean poisonous frog *Dendrobates tricolor*, were established by means of X-ray crystallographic analysis.[4] Since the natural source of these alkaloids is limited, it has stimulated the development of comprehensive synthetic programmes from the laboratories of Overman,[5] Trost,[6] and Gallagher.[7] In 1996, Cossy and co-workers presented an approach to the optically active pumiliotoxin 251D skeleton by using a 6-*exo*-*dig* radical cyclisation.[8] Recently, Barrett reported a formal synthesis of pumiliotoxin 251D *via* a highly diastereoselective addition of a titanium homoenolate to an L-proline derivative[9] and Martin described a formal synthesis of pumiliotoxin 251D by using a vinylogous Mannich reaction to construct the ring skeleton.[10]



Results and discussion

We report here a short novel synthesis of the lactam **9** with the basic pumiliotoxin 251D skeleton and correct stereochemistry, employing a diastereoselective addition of ethyl lithiopropiolate to ketone **7** as a key step, as shown in Scheme 1.



Scheme 1 *Reagents*, *conditions* (*and yields*): (a) (i) $SOCl_2$, MeOH, reflux; (ii) ZCl, K_2CO_3, CH_3CN (84%, 2 steps). (b) MeMgI, Et_2O (91%). (c) $SOCl_2$, Et_3N, THF, −45 °C (60%). (d) O_3, MeOH, Me_2S (90%). (e) Ethyl propiolate, LDA, THF, −78 °C. (f) H_2, Pd/C, MeOH (80%).

N-(Benzyloxycarbonyl)-L-proline methyl ester **4**, formed from L-proline in two steps, was converted to propenyl derivative **6** by the reaction with an excess of MeMgI in diethyl ether followed by regioselective dehydration of the resulting tertiary alcohol **5** with thionyl dichloride and Et_3N at low temperature. Ozonolysis of **6** with O_3 in MeOH gave the ketone **7**. Addition of ethyl lithiopropiolate to ketone **7** to elongate the side-chain by three carbon atoms with the terminal carboxylate group necessary for the next cyclisation should provide a most concise strategy. Garner and Park[11] reported highly diastereoselective addition of ethyl lithiopropiolate in hexamethylphosphonic triamide–tetrahydrofuran (HMPA–THF) to *N*-Boc-*N*,*O*-isopropylidene-L-serinal, and Chen and Fang[12] accomplished the diastereoselective addition of ethyl lithiopropiolate to a chiral α-keto ester in the presence of 1 equivalent of $MgCl_2$. Therefore, we investigated the effect of different Lewis, acids, including YCl_3, $TiCp_2Cl_2$, $Ti(OPr^i)_4$, $BF_3{\cdot}Et_2O$, $ZnCl_2$, $Ti(OPr^i)_3Cl$, $TiCl_4$–$Ti(OPr^i)_4$, and $SnCl_4$, on the addition of ethyl lithio-

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Table 1 The effect of different Lewis acids on the addition to ketone **7**[a]

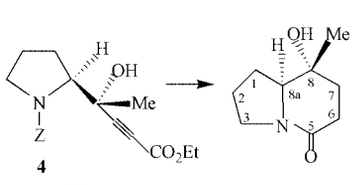
Entry	Lewis acid	Ratio to ketone **7**	Yield (%)[b]	**8a**:**8b**[c]
1	YCl_3	0.1 mol eq.	58	1:4.4[d]
		2 mol eq.	16	1:3.5
2	$TiCp_2Cl_2$	0.1 mol eq.	80	1:7.5[d]
		2 mol eq.	12	1:1.1
3	$Ti(OPr^i)_4$	0.1 mol eq.	55	4.6:1
		2 mol eq.	36	1:2.2
4	$BF_3{\cdot}Et_2O$	0.1 mol eq.	68.5	1:3.6
		2 mol eq.[e]		
5	$ZnCl_2$	0.1 mol eq.	77	1:1.7
		2 mol eq.[e]		
6	$Ti(OPr^i)_3Cl$	0.1 mol eq.	29.4	1.9:1
		2 mol eq.	12	4.3:1
7	$TiCl_4$–$Ti(OPr^i)_4$ (1:1)	0.1 mol eq.	81	1.3:1
		2 mol eq.[e]		
8[f]	$SnCl_4$	0.1 mol eq.	29	7.7:1
		2 mol eq.[e]		
9	None		86	1:2.7

[a] The ratio of ethyl lithiopropiolate to ketone **7** = 2:1. [b] Isolated yield. [c] The absolute configurations are determined according to those of their cyclo-products. [d] The ratio is decided by isolation yield (others by HPLC). [e] No analytical data due to complicated products. [f] The solvent is toluene (THF in cases with no indication otherwise).

propiolate to ketone **7** in detail. As the results show in Table 1 we found that the addition in the presence of only a catalytic amount of $TiCp_2Cl_2$ (10% mol) provided an 80% yield of the alcohols **8a** and **8b** in the ratio 1:7.5, while in the presence of $Ti(OPr^i)_4$ (10% mol) a 55% yield of the alcohols **8a** and **8b** in the ratio 4.6:1 was obtained, which is the best complementary promoters' combination among the tested Lewis acids for the preparation of the respective addition products **8b** and **8a**.

The diastereoselectivity of this addition in the presence of $Ti(OPr^i)_nCl_{4-n}$ is opposite to that in the case of $TiCp_2Cl_2$. It is interesting that 2 equivalents of Lewis acid reduced yields and diastereoselectivity dramatically. We think that the chelation of a catalytic amount of Lewis acid (10% mol) with the carbonyl group promoted the nucleophilic addition of ethoxycarbonylethynyl anion to the carbonyl group of ketone **7** and improved the diastereoselectivity, but the possible organotitanium or other organometallic compounds formed in the stoicheiometric reaction of an excess of Lewis acid with ethyl lithiopropiolate are less active in the addition to ketone **7** than is the ethoxycarbonylethynyl anion, resulting in poor yields and diastereoselectivity.

Hydrogenation of **8a** in MeOH at room temperature under 1 atm H_2 provided the desired lactam **9** in 80% yield. Thus we have constructed the pumiliotoxin 251D skeleton lactam **9** from L-proline in six steps with high diastereoselectivity and 18.2% overall yield. Furthermore, hydrogenation of **8b** under the same conditions gave an 80% yield of lactam **10**, which is the 8-epimer of lactam **9**.



Scheme 2

Indolizidine skeleton **9** could be converted to pumiliotoxin 251D in three steps as already described,[7] and pumiliotoxins A and B could be synthesized by the same strategy. Therefore we have found a shorter enantioselective approach (nine steps) to pumiliotoxin 251D, and are the first to have synthesised the 8-epimer of **9**.

Experimental

General

All reactions were conducted under nitrogen unless stated otherwise and followed by TLC on precoated silica gel HSGF254 plates (Yantai Chemical Co. Ltd). Column chromatography was performed on silica gel 300–400 μ (Yantai Chemical Co. Ltd) and columns were eluted with petroleum spirit (60–90 °C) (PS) and ethyl acetate (EA) mixtures. All solvents were refluxed and distilled under nitrogen from sodium benzophenone ketyl (THF, Et_2O) or CaH_2 (CH_2Cl_2, Pr^i_2NH).

All ^1H NMR spectra were recorded on a Bruker AMX-300 spectrometer and are reported in δ-units (ppm) and J-values (Hz) with Me_4Si as standard. Mass spectra (EI) were recorded on an HP-5985-A mass spectrometer. Infrared (IR) spectra were recorded on a Shimadzu IR-440 or a Digital FTIR and are reported in wavenumbers (cm^{-1}). Optical rotations were measured on a Perkin-Elmer 241 Autopol Polarimeter. $[\alpha]_D$-Values are reported in units of 10^{-1} deg cm^2 g^{-1}. Element analyses were performed on a Carlo Erba 1106.

Methyl benzyloxycarbonyl-L-prolinate 4

A solution of L-proline methyl ester (6.45 g, 50 mmol), containing K_2CO_3 (10.35 g, 75 mmol), in CH_3CN (60 ml) was stirred at 25 °C for 10 min. After the mixture was cooled to 0 °C in an ice-bath, benzyloxycarbonyl chloride (8.55 ml, 60 mmol) was added dropwise slowly within 20 min. The reaction mixture was stirred at 0 °C for 3 h and poured into ice-cooled, saturated aq. NH_4Cl, then extracted with Et_2O. The organic layer was washed with brine and dried over Na_2SO_4. After concentration, and purification of the residue by chromatography (PS–EA 5:1), the Z-protected methyl prolinate **4** (12.2 g, 92.8%) was given as a colorless liquid, $[\alpha]_D^{21}$ −55.6 (*c* 1.4 in CH_3OH) {lit.,[13] $[\alpha]_D^{25}$ −57.5 (*c* 5.03 in CH_3OH)}; ν_{max}(neat) 3034, 2980, 2955, 2883, 1749, 1706, 1499, 1448, 1416; *m*/*z* (EI) 264 (M^+ + 1, 1%), 218 (4), 204 ($M^+ - CO_2Me$, 11), 160 (15), 91 (100) (Found: C, 63.55; H, 6.53; N, 5.27. Calc. for $C_{14}H_{17}NO_4$: C, 63.85; H, 6.50; N, 5.32%).

(2*S*)-*N*-Benzyloxycarbonyl-2-(1′-hydroxy-1′-methylethyl)pyrrolidine 5

To a solution of MeMgI prepared in advance from Mg (360 mg, 15 mmol), MeI (1 ml, 16 mmol) and dry diethyl ether (12 ml) was added a solution of **4** (1.32 g, 5 mmol) in diethyl ether (5 ml) rapidly with vigorous stirring at room temperature. After being stirred for another 10 min the reaction mixture was refluxed for 3 h, cooled to room temperature, and stirred overnight, then quenched by addition of saturated aq. NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and dried (Na_2SO_4). Concentration *in vacuo* and purification of the residue by chromatography (PS–EA 4:1) gave the pyrrolidine **5** (1.2 g, 91%) as a colorless liquid, $[\alpha]_D^{22}$ −58.4 (*c* 4.5 in $CHCl_3$) {lit.,[14] $[\alpha]_D^{20}$ −69.3 (*c* 3.0 in $CHCl_3$)}; ν_{max}(neat) 3389, 3034, 2976, 2887, 1674, 1498, 1455, 1415; *m*/*z* (EI) 264 (M^+ + 1, 27%), 246 (M^+ − OH, 65), 204 (11), 202 (22), 160 (33), 91 (100) (Found: C, 67.95; H, 8.30; N, 5.25. Calc. for $C_{15}H_{21}NO_3$: C, 68.40; H, 8.04; N 5.32%).

(2*S*)-*N*-Benzyloxycarbonyl-2-(1′-methylethenyl)pyrrolidine 6

To a solution of **5** (132 mg, 0.5 mmol) in THF (5 ml) at −50 °C was added dropwise cold $SOCl_2$ (0.1 ml), followed by cold Et_3N (1.4 ml). The reaction temperature was kept between −45 and −50 °C. The reaction mixture was stirred at the same temperature for another 30 min and was then allowed to warm to room temperature, poured onto 5 g of ice and extracted with diethyl ether; the extract was washed (brine) and dried (Na_2SO_4). Purification on silica gel (PS–EA 10:1) gave **6** (73 mg, 60%) as a colorless liquid, $[\alpha]_D^{24}$ −24 (*c* 0.89 in $CHCl_3$) {lit.,[5b]

$[\alpha]_D^{25}$ −27.9 (*c* 6.05 in CH_3OH)}; ν_{max}(neat) 3034, 2972, 2879, 1705, 1654, 1541, 1498, 1449; *m/z* (EI) 245 (M^+, 0.2%), 204 (2), 186 (1), 160 (9), 154 (3), 139 (7), 114 (18), 91 (100) (Found: C, 73.03; H, 8.07; N, 6.16. Calc. for $C_{15}H_{19}NO_2$: C, 73.43; H, 7.80; N, 5.71%).

(2*S*)-2-Acetyl-*N*-(benzyloxycarbonyl)pyrrolidine 7

To a solution of **6** (389 mg, 1.58 mmol) in absolute MeOH (100 ml) at −78 °C was introduced O_3 until the reaction became blue (*ca*. 10 min), followed by introduction of O_2 to make the solution colorless again and then the reaction mixture was allowed to warm to room temperature. To the solution was added Me_2S (0.5 ml) and the mixture was stirred for 30 min. Concentration and purification by chromatography (PS–EA 3 : 1) gave **7** (351 mg, 90%) as a colorless oil, $[\alpha]_D^{20}$ −43.9 (*c* 2.1 in $CHCl_3$) {lit.,[9] $[\alpha]_D^{27}$ −42.2 (*c* 1.0 in $CHCl_3$)}; ν_{max}(neat) 3034, 2958, 2884, 1704, 1499, 1448, 1416; *m/z* (EI) 248 ($M^+ + 1$, 0.15%), 204 (13), 160 (18), 91 (100) (Found: C, 67.60; H, 7.12; N, 5.60. Calc. for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66%).

Ethyl 4-[(2′*S*)-*N*-(benzyloxycarbonyl)pyrrolidin-2′-yl]-4-hydroxypent-2-ynoate 8

To a solution of Pr^i_2NH (0.16 ml, 1.09 mmol) in THF (6 ml) was added dropwise 1.6 M *n*-BuLi (0.68 ml, 1.09 mmol) at 0 °C. The solution was then warmed to room temperature and stirred for 20 min. After it had been cooled to −78 °C and ethyl propiolate (0.12 ml, 1.09 mmol) had been added dropwise, the reaction mixture was stirred for 70 min. Then $TiCp_2Cl_2$ (14 mg, 0.055 mmol) was added and the mixture was stirred for another 20 min. A solution of **7** (135 mg, 0.546 mmol) in THF (1 ml) was added dropwise. Stirring at −78 °C was continued until the starting material had disappeared on TLC. The reaction mixture was treated dropwise with saturated aq. NH_4Cl, extracted with diethyl ether, and the extract was washed (brine) and dried (Na_2SO_4). Concentration, and purification by chromatography (PS–EA 4 : 1) gave **8a** and **8b** (150 mg, 80%) in the ratio 7.5 : 1 as a yellow liquid: **8a** $[\alpha]_D^{24}$ +217.4 (*c* 1.3 in $CHCl_3$); ν_{max}(neat) 3331, 3035, 2985, 2899, 2243, 1712, 1670, 1499, 1455, 1413; *m/z* (EI) 346 ($M^+ + 1$, 0.4%), 328 (0.8), 302 (1), 204 (13), 160 (39), 91 (100); δ_H (300 MHz; $CDCl_3$) 7.40 (m, 5H), 6.00 (br s, 1H), 5.15 (s, 2H), 4.30 (m, 1H), 4.23 (q, *J* 7.1, 2H), 3.71–3.79 (m, 1H), 3.36–3.44 (m, 1H), 1.67–2.26 (m, 4H), 1.41 (s, 3H), 1.30 (t, *J* 7.1, 3H) (Found: C, 66.22; H, 6.64; N, 4.13. Calc. for $C_{19}H_{23}NO_5$: C, 66.06; H, 6.71; N, 4.06%).

For **8b** $[\alpha]_D^{24}$ −108.8 (*c* 3.24 in $CHCl_3$); ν_{max}(neat) 3286, 2985, 2241, 1712, 1668, 1499, 1454, 1419; *m/z* (EI) 346 ($M^+ + 1$, 0.3%), 328 (0.5), 302 (0.4), 204 (13), 160 (39), 91 (100); δ_H (300 MHz; $CDCl_3$) 7.30 (m, 5H), 5.14 (s, 2H), 4.17 (q, *J* 7.1, 2H), 3.94 (t, *J* 7.5, 1H), 3.75 (dt, *J* 3.1 and 7.6, 1H), 3.35 (m, 1H), 1.64–2.15 (m, 4H), 1.42 (s, 3H), 1.24 (t, *J* 7.1, 3H) (Found: C, 65.94; H, 6.78; N, 4.33. Calc. for $C_{19}H_{23}NO_5$: C, 66.06; H, 6.71; N, 4.06%).

(8*S*,8a*S*)-8-Hydroxy-8-methylindolizidin-5-one 9 and (8*R*,8a*S*)-8-hydroxy-8-methylindolizidin-5-one 10

To a solution of **8a** (or **8b** for compound **10**) (49 mg, 0.142 mmol) in absolute MeOH (3 ml) was added 5% Pd/C (15 mg). The reaction mixture was stirred under H_2 (1 atm) for 10 h, then filtered through Celite and concentrated *in vacuo* to give a slightly yellow crude product, which was recrystallised to provide **9** (19 mg, 80%) as colorless needles, mp 88.3–91.1 °C (from *n*-hexane–diethyl ether) {lit.,[9] 89–91 °C; lit.,[7] 90–92 °C; lit.,[10] 94–95 °C}; $[\alpha]_D^{26}$–50.7 (*c* 0.55 in $CHCl_3$) {lit.,[7] $[\alpha]_D^{21}$ −47.0 (*c* 0.97 in $CHCl_3$); lit.,[9] $[\alpha]_D^{29}$ −53.0 (*c* 0.97 in $CHCl_3$); lit.,[10] $[\alpha]_D^{22}$ −55.0 (*c* 0.79 in $CHCl_3$)}; ν_{max}(KBr) 3370, 2971, 2881, 1616, 1475, 1412; *m/z* (EI) 170 ($M^+ + 1$, 26%), 169 (M^+, 41), 154 ($M^+ - CH_3$, 4), 126 (16), 112 (15), 111 (18), 99 (13), 98 (12), 83 (81), 70 (100); δ_H (400 MHz; $CDCl_3$) 3.45 (dd, *J* 4.4 and 9.5, 2H), 3.30 (dd, *J* 5.6 and 10, 1H), 3.15 (s, 1H, disappeared when exchanged with D_2O), 2.50 (ddd, *J* 7.2, 11.2 and 18.6, 1H), 2.35 (dd, *J* 7.2 and 18.2, 1H), 1.65–2.00 (m, 6H), 1.20 (s, 3H).

For **10**, mp 128.3–129.7 °C (from *n*-hexane–diethyl ether); $[\alpha]_D^{25}$ −57.8 (*c* 0.6 in $CHCl_3$); ν_{max}(KBr) 3279, 2952, 2885, 1610, 1483, 1450, 1413; *m/z* (EI) 170 ($M^+ + 1$, 11.5%), 169 (M^+, 32), 154 ($M^+ - CH_3$, 4), 136 (1), 112 (13), 111 (16), 99 (12), 98 (11), 83 (79), 70 (100); δ_H (300 MHz; $CDCl_3$) 3.50 (m, 3H), 2.50 (ddd, *J* 3.8, 6.0 and 17.5, 1H), 2.35 (dd, *J* 7.3 and 18.0, 1H), 2.30 (s, 1H), 1.60–2.15 (m, 6H), 1.20 (s, 3H).

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