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Total Synthesis of the Putative Structure of Deoxypumiliotoxin 193H by an Ireland–Claisen Rearrangement

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A stereoselective total synthesis of one diastereomer of 8-deoxypumiliotoxin 193H is described. The concise total synthesis features the use of readily available natural amino acids as the starting materials and the Ireland–Claisen rearrangement as the key stereochemistry controlling step.

Introduction

Amphibians are a source for a broad range of unique and pharmacologically active compounds.[1] One notable source is in the skin secretions of frogs that are found in the rain forests of Columbia, Panama, and Madagascar, and it is these secretions that have been historically used for the preparation of poisoned arrows. Pumiliotoxins (PTX) is a class of dendrobatid alkaloids that have significant pharmacological activity.[2] PTX A and B were isolated in the late 1960s by Daly et al. from the Panamanian poison frog *Dendrobates pumilio* (Figure 1).[3] However, the structure of these toxins remained unclear until the 1980s, when the simpler alkaloid PTX 251D was isolated and its structure was elucidated by single-crystal X-ray analysis of its hydrochloride salt.[4] A common structural feature of the pumiliotoxins includes an octahydroindolizine core that has a stereochemically defined alkylidene substituent at C-6. The first total syntheses of PTX family members were reported by Overman et al.,[5] and new synthetic approaches towards these natural products continue to attract the attention of the scientific community.[6]

The exocyclic alkylidene unit is a structural motif of many natural products. However, efficient control of the geometry of the double bond during the syntheses of these systems is a considerable challenge. We have recently discovered an approach that allows efficient control of the geometry of the exocyclic double bond as well as the configuration of the chiral center in the 4-ethylidene proline moiety by using a boron enolate Ireland–Claisen[7–9] rearrangement.[10] We have continued to explore the applicability of this new approach towards the construction of bicyclic systems. Herein, we report the first total synthesis of a single diastereomer of the putative structure of 8-deoxypumiliotoxin 193H[11,12] (**4**) by using this synthetic approach. Compound **4** was found in the extracts of the *Scheloribates azumensis* species of mites, and its structure was proposed on the basis of GC–MS analysis and by analogy with related alkaloids.

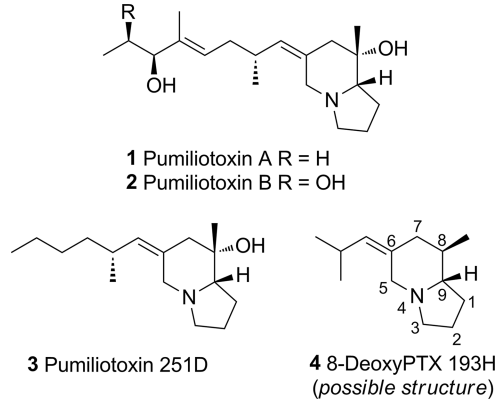

Figure 1. Structures of PTX A, B, and 251D as well as 8-deoxy-PTX 193H (**4**).

Results and Discussion

In the retrosynthetic analysis of 8-deoxypumiliotoxin 193H (**4**), isobutylidene-substituted indolizine intermediate **5** would come from an Ireland–Claisen rearrangement of eight-membered lactone **7**, which is derived from ketene actetal **6** (Scheme 1). We envisioned that intermediate **7** could be easily synthesized from chiral homoproline and allyl bromide **8**, which is derived from valine.

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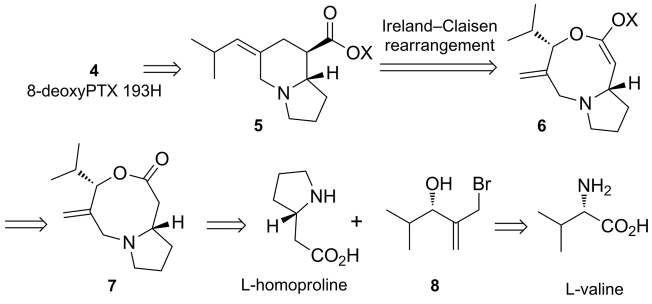
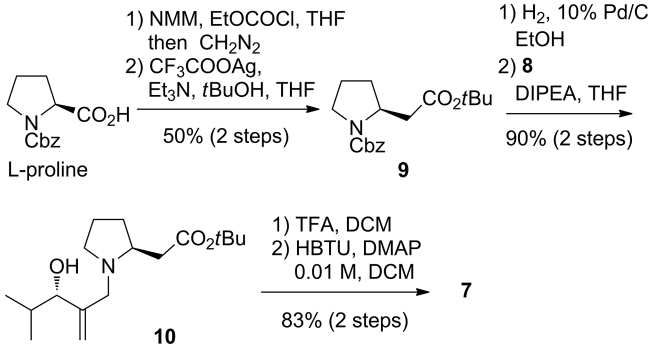


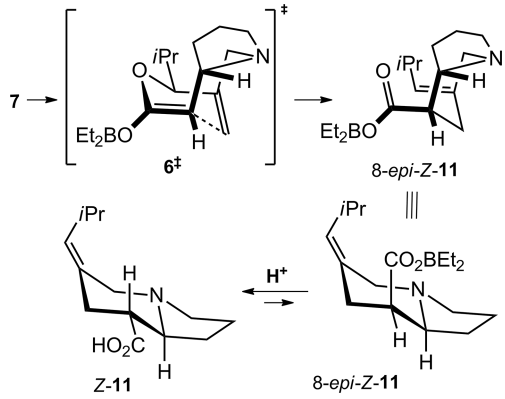
Scheme 1. Retrosynthetic analysis of 8-deoxypumiliotoxin 193H (**4**) (X = TMS, Bu_2B etc.).

We began the total synthesis with an Arndt–Eistert homologation sequence,[13] which smoothly transformed *N*-Cbz-protected proline (Cbz = benzyloxycarbonyl) into the desired homoproline *tert*-butyl ester **9** (Scheme 2). Cleavage of the Cbz protecting group followed by alkylation with the known bromide **8**[14] gave the necessary alcohol **10**. Finally, cleavage of the ester group and macrolactonization[15] under highly dilute conditions furnished eight-membered lactone **7** in good overall yield. In addition, compound **7** was easily accessible on a multigram scale.



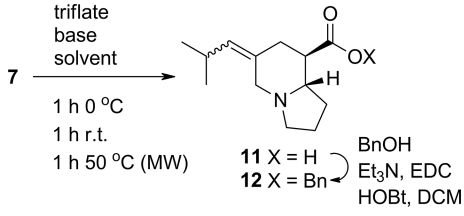
Scheme 2. Synthesis of eight-membered lactone **7** [NMM = *N*-methylmorpholine, DIPEA = *N*,*N*-diisopropylethylamine, TFA = trifluoroacetic acid, DCM = dichloromethane, HBTU = *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate, DMAP = 4-(dimethylamino)pyridine].

With the lactone **7** in hand, we turned our attention toward the Ireland–Claisen rearrangement (Scheme 3). This reaction is very sensitive to the combination of boron triflate and base that is employed in the transformation. A number of reaction conditions and reagents were screened (Table 1). To facilitate the isolation and analysis of the product, amino acid **11** was converted into the corresponding benzyl ester **12**, the (*E*) and (*Z*) isomers of which were readily separable by column chromatography. We began with our previously reported conditions for the transformation, which afforded poor yields and stereoselectivity (Table 1, Entry 1).[10] When toluene or tetrahydrofuran (THF) were used in the studies, the yields did not improve (Table 1, Entries 2 and 3). By screening commonly used bases, we found that the less bulky Me_2NEt afforded better results than the other bases (Table 1, Entries 4–8).



Scheme 3. Proposed transition states of Ireland–Claisen rearrangement step.

Table 1. Optimization of Ireland–Claisen rearrangement of lactone **7**.



Entry	Triflate	Base	Solvent	% Yield (*Z*)-**12** + (*E*)-**12**[a]	*Z*/*E*[b]
1	Bu_2BOTf	DIPEA	DCM	28	n.m.[c]
2	Bu_2BOTf	DIPEA	PhMe	2	n.m.
3	Bu_2BOTf	DIPEA	THF	0	n.m.
4	Bu_2BOTf	Me_2NEt	DCM	53	76:24
5	Bu_2BOTf	Et_3N	DCM	43	62:38
6	Bu_2BOTf	NMM	DCM	51	64:36
7	Bu_2BOTf	DABCO[c]	DCM	0	n.m.
8	Bu_2BOTf	2,6-lutidine	DCM	23	n.m.
9	Cy_2BOTf	Me_2NEt	DCM	45	54:46
10	Cy_2BOTf	Et_3N	DCM	28	74:26
11	Cy_2BOTf	NMM	DCM	21	n.m.
12	Cy_2BOTf	DIPEA	DCM	0	n.m.
13	Et_2BOTf	Me_3N	DCM	0	0
14	Et_2BOTf	Me_2NEt	DCM	69	82:18
15	Et_2BOTf	Et_3N	DCM	39	71:29

[a] Determined by HPLC–MS analysis. [b] Determined by ^1H NMR spectroscopic analysis. [c] n.m.: not measured, DABCO = 1,4-diazabicyclo[2.2.2]octane.

Next, we screened for other boron triflates instead of Bu_2BOTf. Employing Cy_2BOTf (Cy = cyclohexyl) did not increase the yields or the selectivity (Table 1, Entries 9–12). Fortunately, a combination of sterically less hindered reagents such as Et_2BOTf[16] and Me_2NEt gave the desired ester (*Z*)-**12** with fairly good stereoselectivity and in a reasonable yield (Table 1, Entry 14). Interestingly, the smallest tertiary amine base, that is, Me_3N, gave only trace amounts of the desired product.[17]

The Ireland–Claisen rearrangement most likely proceeds through chair-like transition state **6**‡ to provide **8**-*epi*-(*Z*)-**11** with the correct double-bond geometry but opposite configuration at the C-8 chiral center (Scheme 3). We further speculated that product **8**-*epi*-(*Z*)-**11** undergoes epimerization to the more thermodynamically stable isomer (*Z*)-**11** upon aqueous acidic workup. Subsequent derivatization of acid (*Z*)-**11** with benzyl alcohol gave ester (*Z*)-**12**, the stereochemistry of which was unambiguously assigned on the basis of 2D NOE experiments (Figure 2).

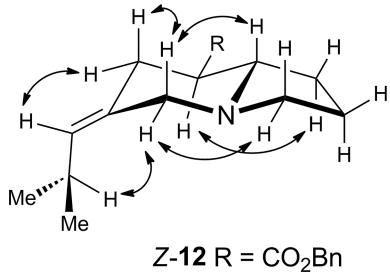
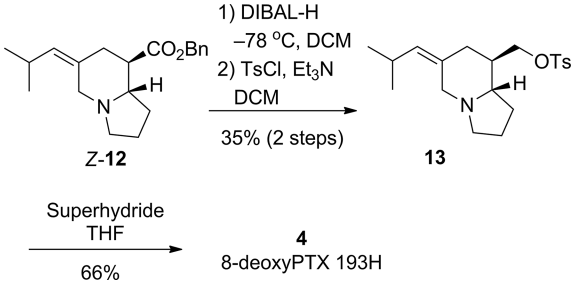


Figure 2. Observed NOE interactions for (*Z*)-**12**.

With the desired ester (*Z*)-**12** in hand, we proceeded to complete the total synthesis of 8-deoxypumiliotoxin 193H (**4**). The ester functionality was converted into the C-8 methyl group through a three-step sequence (Scheme 4). First, (*Z*)-**12** was reduced by treatment with diisobutylaluminum hydride (DIBAL-H) to give the corresponding alcohol, which then underwent tosylation to give the desired intermediate **13**. Finally, treatment of tosylate **13** with Superhydride® gave the target compound, 8-deoxypumiliotoxin 193H (**4**), in moderate yield.



Scheme 4. Completion of the total synthesis of 8-deoxyPTX 193H (**4**).

Conclusions

In summary, we have accomplished the first total synthesis of 8-deoxypumiliotoxin 193H (**4**) by starting from inexpensive and readily available amino acids. The total synthesis features an Ireland–Claisen rearrangement as the crucial transformation to control the olefin geometry and stereoselectively introduce a new chiral center in a single step. Further synthetic studies towards more complex PTX family members are now underway and will be reported in due course.

Experimental Section

General Methods: Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. Petroleum ether with a boiling range of 60–80 °C was used. Flash chromatography was carried out with Merck Kieselgel (230–400 mesh). Thin layer chromatography was performed on Merck Kieselgel 60F254. The NMR spectroscopic data were recorded with Bruker Fourier (300 MHz), Varian Mercury (400 MHz), and Varian Unity Inova (600 MHz) spectrometers. Chemical shift values are referenced against the residual solvent for ^{1}H NMR and the deuterated solvent for ^{13}C NMR. The multiplicity of each signal is reported by the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br. (broad). Infrared spectra were recorded as films in the range 4000–600 cm^{-1}. HRMS were obtained on a Micromass AutoSpec Ultima Magnetic sector mass spectrometer. Optical rotations were measured with a Rudolph Research Analytical Autopol VI polarimeter. LC–MS analyses were performed on a Shimadzu Prominence chromatograph that was connected to an Applied Biosystems API 2000 mass spectrometer [column: Phenomenex Gemini 5 μm C_{18}, 50 × 2 mm; eluent: MeCN (+0.1% HCOOH)/H_2O (+0.1% HCOOH)]. Purification by preparative LC–MS was performed by using a Waters 600 chromatograph that was connected to a Waters 3100 mass spectrometer [column: Xterra 10 μm C_{18}, 10 × 150 mm; eluent: MeOH (+0.1% HCOOH)/H_2O (+0.1% HCOOH)]. Microwave-assisted (MW = microwave) reactions were performed in a sealed tube by a Biotage Initiator apparatus using the external surface sensor to monitor the temperature.

(*S*)-Benzyl 2-[2-(*tert*-Butoxy)-2-oxoethyl]pyrrolidine-1-carboxylate (9): Ester **9** was prepared by following a slightly modified procedure to that reported by Clayden et al.[13] The intermediate diazoketone (8.60 g, 0.031 mol) was dissolved in a mixture of dry THF (30 mL) and dry *t*BuOH (50 mL), and the resulting mixture was then treated with CF_3COOAg. Compound **9** (525 mg, 50%) was isolated as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 5 H), 5.12 (d, J = 14.9 Hz, 2 H), 4.20–4.14 (m, 1 H), 3.41–3.37 (m, 2 H), 2.81 (AB m, 1 H), 2.22 (dd, J = 15.2, 10.2 Hz, 1 H), 2.09–2.01 (m, 1 H), 1.90–1.79 (m, 3 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, conformers): δ = 170.69, 154.52, 136.95, 128.39, 127.80, 127.59, 80.39, 66.52, 54.61, 54.16, 46.71, 46.38, 40.38, 39.27, 31.04, 30.34, 28.05, 23.50, 22.75 ppm. HRMS (ESI): calcd. for $C_{18}H_{26}NO_4$ $[M + H]^+$ 320.1856; found 320.1854. IR (film): $\tilde{\nu}$ = 2977, 1728, 1698, 1411, 1147, 1099 cm^{-1}. $[\alpha]_D^{20}$ = –36.2 (c = 1, $CHCl_3$).

***tert*-Butyl 2-{(*S*)-1-[(*S*)-3-Hydroxy-4-methyl-2-methylenepentyl]pyrrolidin-2-yl}acetate (10):** To a stirred solution of ester **9** (3.00 g, 9.39 mmol) in EtOH (20 mL) was added 10% Pd on carbon (50 mg), and the reaction flask was then purged with hydrogen (balloon, 3×). The reaction mixture was stirred at room temperature for 16 h. The catalyst was removed by filtration, and the solvent was carefully evaporated (100 mBar, 40 °C bath temperature). To the oily residue was added dry THF (10 mL) followed by a solution of DIPEA (3.64 g, 28.18 mmol) and allylbromide **8**[14] (1.81 g, 9.39 mmol) in dry THF (5 mL). The resulting solution was stirred for 16 h and then diluted with DCM followed by the addition of a saturated aqueous sodium hydrogen carbonate solution. The resulting mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography [petroleum ether/EtOAc, 9:1 (+2% Et_3N) to 6:1 (+2% Et_3N)] to give **10** (2.51 g, 90% in two steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.52 (s, 1 H), 4.98 (d, J =

19.9 Hz, 1 H), 3.83 (d, J = 7.0 Hz, 1 H), 3.24 (AB m, 1 H), 3.00–2.95 (m, 1 H), 2.94–2.87 (m, 1 H), 2.69 (AB m, 1 H), 2.35 (q, J = 8.2 Hz, 1 H), 2.17 (AB m, 1 H), 2.08–1.99 (m, 1 H), 1.85–1.78 (m, 1 H), 1.73–1.69 (m, 2 H), 1.55–1.52 (m, 1 H), 1.43 (s, 9 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.85 (d, J = 7.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.47, 146.06, 114.17, 81.04, 80.40, 61.39, 59.43, 54.07, 40.25, 32.33, 30.77, 28.06, 22.21, 19.58, 17.88 ppm. HRMS (ESI): calcd. for $C_{17}H_{32}NO_3$ $[M + H]^+$ 298.2384; found 298.2372. IR (film): $\tilde{\nu}$ = 3440, 2967, 1729, 1652, 1151 cm^{-1}. $[\alpha]_D^{20}$ = –66.8 (c = 1, $CHCl_3$).

(4*S*,10a*S*)-4-Isopropyl-5-methylenehexahydro-1*H*-pyrrolo[2,1-*d*]-[1,5]oxazocin-2(4*H*)-one (7): To a stirred solution of allylic alcohol **10** (2.83 g, 9.53 mmol) in DCM (25 mL) was added dropwise TFA (25 mL). The mixture was stirred for 4 h, as the color changed to black. The volatiles were removed in vacuo, and the residue was dissolved in dry DCM (10 mL). The resulting solution was added dropwise to a stirred solution of HBTU (14.45 g, 38.12 mmol) and DMAP (11.64 g, 95.28 mmol) in dry DCM (800 mL) over a period of 1 h. The obtained slurry was stirred for 16 h. The reaction was diluted with brine, and the mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography [petroleum ether/EtOAc, 9:1 (+2% Et_3N) to 4:1 (+2% Et_3N)] to give compound **7** (1.77 g, 83% in two steps) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.24 (s, 1 H), 5.03 (s, 1 H), 4.49 (d, J = 8.6 Hz, 1 H), 3.79 (d, J = 12.5 Hz, 1 H), 3.17 (s, 1 H), 2.93 (d, J = 12.5 Hz, 1 H), 2.81–2.77 (m, 2 H), 2.39–2.33 (m, 1 H), 2.29–2.23 (m, 1 H), 2.11–1.95 (m, 2 H), 1.87–1.76 (m, 2 H), 1.70–1.62 (m, 1 H), 1.10 (d, J = 6.6 Hz, 3 H), 0.86 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.19, 145.14, 119.24, 88.99, 59.33, 58.92, 56.76, 41.34, 32.11, 31.09, 22.62, 19.30, 19.06 ppm. HRMS (ESI): calcd. for $C_{13}H_{22}NO_2$ $[M + H]^+$ 224.1658; found 224.1644. IR (film): $\tilde{\nu}$ = 2962, 1743, 1642, 1457, 1146 cm^{-1}. $[\alpha]_D^{20}$ = –73.6 (c = 1, $CHCl_3$).

General Procedure for Ireland–Claisen Rearrangement of 7: Lactone **7** (50 mg, 0.224 mmol) was placed in a MW tube and then dried over P_2O_5 in a vacuum drying chamber overnight. The tube was tightly sealed and purged with argon (3×). Dry DCM (1 mL) and the freshly distilled (from sodium) tertiary amine[18] (2.015 mmol) were added, and the mixture was cooled to 0 °C and treated with the appropriate triflate (0.672 mmol).[19] After 1 h, the reaction mixture was warmed to ambient temperature, stirred for 1 h, and then heated in the MW at 50 °C for 1 h. The mixture was then diluted with water (approximately 1 mL), and 10% aqueous HCl (3 drops) was added. The biphasic mixture was stirred vigorously for 1 h and then evaporated. Benzyl alcohol (73 mg, 0.672 mmol), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 215 mg, 1.119 mmol), 1-hydroxybenzotriazole hydrate (HOBt·H_2O, 68 mg, 0.448 mmol), Et_3N (226 mg, 2.239 mmol), and dry *N*,*N*-dimethylformamide (DMF, 1 mL) were added, and the obtained slurry was stirred for 16 h. The reaction was diluted with brine, and the resulting mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo.[20] The residue was purified by preperative LC–MS. Fractions that contained (*Z*)-**12** and (*E*)-**12** were concentrated in vacuo, and the residue dissolved in MeOH. The solution was treated with Dowex® 1X8100 basic resin and then concentrated in vacuo again.[21] The residue was purified by flash column chromatography (petroleum ether/EtOAc, 9:1 to 3:2) to give the desired isomer (*Z*)-**12** as a pale yellow oil.

(8*R*,8a*S*,*Z*)-Benzyl 6-(2-Methylpropylidene)octahydroindolizine-8-carboxylate (*Z*-12): Lactone **7** (300 mg, 1.343 mmol) was placed in a MW tube and dried over P_2O_5 in a vacuum drying chamber overnight. The tube was tightly sealed and purged with argon (3×). Dry DCM (6 mL) and freshly distilled (from sodium) Me_2NEt (1.3 mL, 884 mg, 12.091 mmol) were added. The mixture was cooled to 0 °C and then treated with Et_2BOTf (878 mg, 4.030 mmol). After 1 h, the reaction mixture was warmed to ambient temperature, stirred for 1 h, and then heated in the MW at 50 °C for 1 h. The mixture was diluted with water (approximately 6 mL), and 10% aqueous HCl (20 drops) was added. The biphasic mixture was stirred vigorously for 1 h and then evaporated. Benzyl alcohol (435 mg, 4.030 mmol), EDC (772 mg, 4.030 mmol), HOBt·H_2O (411 mg, 2.686 mmol), Et_3N (1359 mg, 13.434 mmol), and dry DMF (6 mL) were added, and the obtained slurry was stirred for 16 h. The reaction was diluted with brine, and the resulting mixture was extracted DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by preperative LC–MS. Fractions that contained (*Z*)-**12** and (*E*)-**12** were concentrated in vacuo, and the residue was dissolved in MeOH. The solution was treated with Dowex® 1X8100 basic resin and then concentrated in vacuo again. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 9:1 to 3:2) to give the desired isomer (*Z*)-**12** (160 mg, 38%) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.32 (m, 5 H), 5.12 (s, 2 H), 5.09 (d, J = 9.0 Hz, 1 H), 3.84 (d, J = 12.1 Hz, 1 H), 3.05 (td, J = 6.6, 2.3 Hz, 1 H), 2.61–2.52 (m, 1 H), 2.47 (s, 1 H), 2.44 (s, 1 H), 2.39–2.26 (m, 2 H), 2.22–2.18 (m, 2 H), 1.95–1.77 (m, 2 H), 1.74–1.65 (m, 1 H), 1.53–1.43 (m, 1 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.90 (d, J = 6.6 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, rotamers): δ = 173.60, 135.93, 133.53, 129.45, 128.48, 128.12, 128.02, 127.43, 126.82, 66.08, 65.10, 53.63, 52.25, 48.11, 37.48, 28.74, 26.52, 23.44, 23.16, 21.01 ppm. HRMS (ESI): calcd. for $C_{20}H_{28}NO_2$ $[M + H]^+$ 314.2115; found 314.2114. IR (film): $\tilde{\nu}$ = 2962, 1734, 1641, 1457, 1238, 1166 cm^{-1}. $[\alpha]_D^{20}$ = +3.04 (c = 1, $CHCl_3$).

[(8*R*,8a*S*,*Z*)-6-(2-Methylpropylidene)octahydroindolizin-8-yl]methyl 4-Methylbenzenesulfonate (13): To a stirred solution of ester (*Z*)-**12** (230 mg, 0.734 mmol) in dry DCM (3 mL) at –78 °C was added DIBAL-H (1.2 M in toluene, 3.057 mL, 529 mg, 3.669 mmol), and the obtained solution was stirred for 5 h. The reaction mixture was quenched at the same temperature by the addition of MeOH and then warmed to ambient temperature. The mixture was treated with a saturated aqueous solution of sodium potassium tartrate, and the resulting mixture was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in DCM (3 mL), and pyridine (0.178 mL, 174 mg, 2.202 mmol) and 4-toluenesulfonyl chloride (TsCl, 210 mg, 1.101 mmol) were added. The obtained mixture was stirred for 16 h. The reaction was diluted with brine, and the mixture was extracted DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography (petroleum ether/EtOAc, 1:1 to 0:1) to give compound **13** (80 mg, 35% in two steps) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.78 (d, J = 8.4 Hz, 2 H), 7.35 (d, J = 8.0 Hz, 2 H), 5.03 (d, J = 9.0 Hz, 1 H), 3.97 (dd, J = 9.7, 4.6 Hz, 1 H), 3.88 (dd, J = 9.7, 6.0 Hz, 1 H), 3.83 (d, J = 12.3 Hz, 1 H), 3.05 (t, J = 8.6 Hz, 1 H), 2.60–2.48 (m, 1 H), 2.45 (s, 3 H), 2.35 (d, J = 12.1 Hz, 1 H), 2.22–2.09 (m, 2 H), 1.91–1.75 (m, 4 H), 1.71–1.55 (m, 4 H), 1.41–1.32 (m, 1 H), 0.95 (d, J = 6.6 Hz, 3 H), 0.88 (d, J = 6.7 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.78, 133.95, 133.43, 132.83, 129.83, 127.87, 72.01, 65.45, 53.78, 52.37, 41.67, 36.79, 28.32, 26.52, 23.47, 23.17, 21.62, 21.03 ppm. $[\alpha]_D^{20}$ = +3.0 (c = 1, $CHCl_3$).

8-Deoxypumiliotoxin 193H: A stirred solution of tosylate **13** (85 mg, 0.234 mmol) in dry THF (0.5 mL) was treated with Superhydride® (1 M in THF, 4.676 mL, 510 mg, 4.676 mmol). The obtained solution was stirred for 16 h and then poured into a vigorously stirred mixture of Et_2O and brine. The organic layer was separated, and the aqueous layer was extracted with DCM (2×). The combined organic layers were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by flash column chromatography ($CHCl_3$/MeOH, 15:1) to give 8-deoxypumiliotoxin 193H (30 mg, 66%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.06 (d, J = 9.0 Hz, 1 H), 3.87 (d, J = 12.2 Hz, 1 H), 3.09 (t, J = 9.03 Hz, 1 H), 2.62–2.50 (m, 1 H), 2.50–2.39 (m, 1 H), 2.28–2.15 (m, 2 H), 1.99–1.65 (m, 3 H), 1.53–1.38 (m, 2 H), 0.97 (d, J = 6.6 Hz, 3 H), 0.89 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.16, 131.64, 70.70, 54.12, 52.60, 43.05, 37.04, 28.54, 26.42, 23.61, 23.26, 20.91, 18.58 ppm. HRMS (ESI): calcd. for $C_{13}H_{24}N$ $[M + H]^+$ 194.1903; found 194.1917. $[a]_D^{20}$ = +12.2 (c = 1, $CHCl_3$).

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[18] DABCO was dried overnight over P_2O_5 in a vacuum drying chamber.
[19] Commercial nBu$_2$BOTf was distilled prior to use. Cy$_2$BOTf was dissolved in dry DCM (0.1 mL) and then added to the reaction mixture. Et$_2$BOTf was prepared according to the literature procedure.[16]
[20] At this point, a sample for was prepared to determine the combined yield of (*Z*)-**12** and (*E*)-**12** by LC–MS.
[21] At this point, a sample was prepared to determine the *E*/*Z* ratio by ^{1}H NMR spectroscopic analysis.

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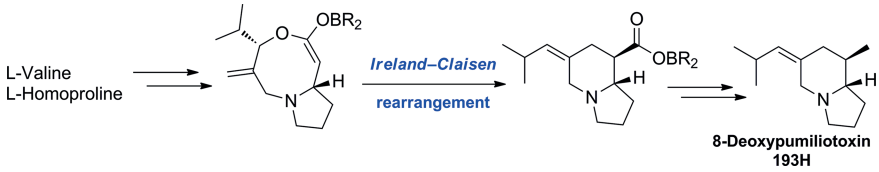
Total Synthesis



A stereoselective total synthesis of 8-deoxypumiliotoxin 193H is described. The concise total synthesis features the use of readily available starting materials, namely, natural amino acids and the Ireland–Claisen rearrangement as the key stereochemistry controlling step.

Keywords: Total synthesis / Natural products / Sigmatropic rearrangement / Amino acids / Boron

