Studies Towards the Construction of Alkylidene Quinolizidines. The Total Synthesis of Homopumiliotoxin 223G

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The addition of 5-methyl-2-triisopropylsilyloxyfuran (5) to N-carbobenzyloxy-2-methoxypiperidine (6a) afforded a mixture of the corresponding erythro and threo isomers 7a and 8a, respectively, in moderate to good yields (42-85%) and diastereoisomeric ratio (7a : 8a) ranging from 1.1:1 – 6:1 depending on the solvent system and the Lewis acid employed. The threo isomer 8a was eventually converted to (+/-)-homopumiliotoxin 223G (1) which was prepared in 5 steps and 13% overall yield from 6a.

Keywords: homopumiliotoxin 223G, N-acyliminium ions, silyloxyfuran, vinylogous addition

Introduction

A wide range of biologically active compounds is found in the skin secretions of amphibians. Many of these alkaloids have unique profiles of pharmacological activities and therapeutic potential. A remarkable variety of alkaloids have been isolated from skin extracts of the frogs of the Dendrobatidae family, which are used as antimicrobial agent and chemical defense against predators. It appears likely that all of the frog skin alkaloids are taken up from diet, which for such amphibians consists mainly of small arthropods.1 Homopumiliotoxins 223G (1), 235C, 319A, 319B and 321B (Figure 1) featuring a quinolizidine core have been isolated in such minute amounts from Dendrobatidae frogs which precluded the structural elucidation of several representatives to be carried out.2

Prior to our efforts in this area, a single synthetic route to homopumiliotoxin 223G (1) had been reported by Kibayashi and coworkers3 along the synthetic scheme depicted in Figure 2. The construction of the quaternary

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This paper is dedicated to Prof. Albert J. Kascheres on occasion of his 60th birthday

Figure 1. Representative homopumiliotoxins isolated from Dendrobatidae frogs.
Results and Discussion

As previously reported by Morimoto for the addition of silyloxyfurans to 5-membered ring N-acyliminium ions, we also observed that the diastereoselectivity was not significantly affected by the nature of the Lewis acid, except when TMSOTf was employed which afforded the best erythro/threo ratio (6:1) in 80% yield in CH$_2$Cl$_2$/THF.\(^4\)-\(^6\)

Additionally, the hitherto not observed regioisomer 9b (relative configuration not determined) was formed when N-Boc precursor of the N-acyliminium ion was employed due to increased steric hindrance involving the methyl group at C-5 in silyloxyfuran 5 and the N-Boc group (Table 1).

The relative configuration at the two newly generated stereogenic centers was established after catalytic hydrogenation of 7a,b and 8a,b, followed by methanolyis, to give quinolizidinones 12 and 13, as illustrated below for 7a and 8a (Scheme 1). Comparison of the nOe experiments performed with quinolizidinones 12 (no increment on H-9a upon irradiation of the methyl group at C-1) and 13 (3.4% increment of the signal of H-9a upon

![Figure 2. Synthetic approach to homopumiliotoxin 223 G (1) by Kibayashi and coworkers.](image)

![Figure 3. Synthetic approach to homopumiliotoxin 223G (1) based on vinylogous Michael addition to N-acyliminium ions.](image)

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*Diastereoisomeric ratio determined by GC and confirmed by $^1$H-NMR analyses; \(^\ast\) Yields determined after column chromatography on silica gel of the crude product.

![Scheme 1. Conversion of butenolides 7a and 8a to the corresponding quinolizidinones 12 and 13.](image)
irradiation of the methyl group at C-1) allowed us to establish the erythro relative configuration for the major diastereoisomer 7a formed in the coupling reaction of 6a and silyloxyfuran 5.

The stereochemical outcome of the above reaction came to us as a surprise as previous results from our laboratory and elsewhere with 1-silyloxyfurans led us to predict the preferential formation of the threo isomer. Additionally, theoretical calculations of the transition state geometries associated with the addition of 5-methylsilyloxyfuran 5 to the N-acyliminium ion precursors at DFT level (B3LYP/3-21G*) showed that array A (relative energy: 1.52 kcal mol\(^{-1}\)) displaying an antiperiplanar approach of the \(\pi\) systems of the nucleophile and N-acyliminium ion leads to the lowest energy transition state for the erythro isomer while array E (relative energy: 0 kcal mol\(^{-1}\)) with a synclinal arrangement is preferred for the transition state leading to the threo isomer. Martin and coworkers have found a similar result for the transition state calculations (RHF/3-21G*) in the addition of 2-methoxyfuran to 5-membered N-carbomethoxy-N-acyliminium ion. Although at this point, we are not able to rationalize the reversal of the stereochemical outcome observed when 5-methyl-2-silyloxyfuran 5 was employed, the unexpected preference for the erythro isomer may be due to the steric hindrance posed by the methyl group at C-5 which has not being properly taken into account in the DFT calculations.

The addition of 5-methylsilyloxyfuran 5 to the N-acyliminium ion derived from chiral 2-methoxypiperidine carbamate 6c (Scheme 2) afforded butenolide 7c as the major diastereoisomer (diastereoisomeric ratio 12:1 determined by capillary GC analysis). Surprisingly, the regioisomer 9c (relative configuration not determined) was formed upon changing the order of addition of the reagents: whereas none of regioisomer 9c was observed when TiCl\(_4\) was added to a solution of methoxycarbamate 6c in dichloromethane, followed by the addition of silyloxyfuran 5, significant amounts were formed when the Lewis acid was added to a mixture of 6c and 5.

The relative configuration at the two newly generated stereogenic centers was established after catalytic hydrogenation to 10c, followed by methanolysis to give quinolizidinone 12 and the recovery of the chiral auxiliary. However, the absolute configuration has not being unambiguously established yet. The Si-face selectivity of the chiral N-acyliminium ion derived from 6c was proposed based on our previous results with 8-phenylmenthyl chiral auxiliaries and was rationalized through the kinetically preferred attack of the nucleophile to the \(s\)-cis conformation of N-acyliminium ions (Scheme 2), that might be enforced by \(\pi\)-stacking interactions involving

![Scheme 2. Proposed facial discrimination in the addition of 5 to the N-acyliminium ion derived from 2-methoxycarbamate 6c (**the absolute configuration may be the opposite as shown**).](image-url)
the low-lying LUMO of the carbamoyl group and HOMO of the phenyl substituent.

Assembly of quinolizidinone 13, the requisite precursor for the preparation of homopumiliotoxin 223G (1), was achieved from butenolide 8a in 76% overall yield (Scheme 1) which was best prepared through the reaction of 2-methoxycarbamate 6a and 2-triisopropylsilyloxy-5-methylfuran (5) in CH₂Cl₂ at –78 °C promoted by TiCl₄ (Table 1, entry 2). Under these conditions, a mixture (1.2:1.0) of butenolides 7a:8a (70% combined yield) was formed which afforded 8a in 32% yield, after separation by column chromatography on silica gel.

The construction of the (Z)-alkylidene side chain and the synthesis of homopumiliotoxin 223G (1)

With an access to the heterocyclic core of homopumiliotoxin 223G secured, we focused on the aldol reaction as the central strategy to install the (Z)-alkylidene side chain characteristic of this family of alkaloids. In order to evaluate the stereochemical outcome of the aldol reaction of lithium enolates derived from six-membered lactams, we first examined the addition of the lithium enolate of readily available N-ethyl-δ-valerolactam, (prepared in 96% yield from δ-valerolactam and ethyl iodide) to isobutyraldehyde. The reaction of its lithium enolate (generated in THF at –78 °C with LDA or LiHMDS) with isobutyraldehyde afforded two aldol products 14a:14b in 3.9:1 ratio and 75% yield when LDA was employed and 4.4:1 ratio and 60% yield with LiHMDS. The determination of diastereoisomeric ratio was achieved by GC and confirmed by ¹H-NMR. The relative configuration of the major diastereoisomer was tentatively assigned at this point as anti-14a based on the magnitude of the coupling constant (9.2 Hz) between H-3 and H-1’ and the relative shielding of C-3 and C-1’ (δ 44.0 and 76.3, respectively) in the major adduct as compared to the minor one (δ 44.8 and 76.6, respectively). The deshielding of the hydroxylic hydrogen in the ¹H-NMR spectrum of 14a (δ 5.90) and the lower stretching frequencies of the hydroxyl and carbonyl groups (3338 and 1610 cm⁻¹, respectively) in 14a as compared to 14b (3423 and 1622 cm⁻¹, respectively) are consistent with a hydrogen-bonded hydroxyl group in 14a.

The relative stereochemistry was eventually established after syn elimination carried out under the conditions described by Corey and coworkers. Treatment of the major diastereoisomer 14a with dicyclohexyl-carbodiimide (DCC) and cuprous chloride in refluxing toluene stereospecifically provided (E)-isobutylidene piperidinone 15a in 88% yield, while under the same conditions (Z)-isobutylidene piperidinone 15b was formed in 87% yield from the minor aldol adduct 14b.

The relative configuration of the isobutylidene piperidinones 15a and 15b could be straightforwardly assigned by inspection of the corresponding ¹H-NMR spectra, particularly from the H-1’ signal which appeared deshielded in 15a (δ 6.65) in comparison with 15b (δ 5.49) as the result of the anisotropic effect of the carbonyl group.

Next we evaluated the reaction of the preformed lithium enolate of quinolizidinone 13 with isobutyraldehyde which produced a 20:1 mixture of two aldol adducts 16a:16b in 85% yield, as depicted in Scheme 5. Only two out of the four possible stereoisomers were formed. The syn and anti stereochemistries were assigned by analogy to the above results. Moreover, an outstanding selectivity was observed: the diastereoisomeric ratio was determined by GC and ¹H-NMR to be 20:1 and 32:1 for the lithium- and titanium (IV)-mediated reactions, respectively.

The relative configuration of the two newly created stereogenic centers was unequivocally established after syn elimination to the corresponding isobutylidene derivatives. Treatment of the major aldol product anti-16a with DCC and cuprous chloride in refluxing toluene afforded (E)-17 in 95% yield while (Z)-17 was formed in 95% yield from the minor aldol adduct syn-16b. The assignment of the configuration of the double bond was
possible upon inspection of the $^1$H-NMR spectra which displayed H-1’ deshielded in \((E)-17\) (δ 6.81) when compared to \((Z)-18\) (δ 5.60). Alternatively, Mukaiyama aldol reaction of the \(N,O\)-silylketene acetal derived from 13 led to a reversal in the stereochemical outcome and aldol \(syn\)-16b was formed as the major isomer (3:1 mixture of \(syn\)-16b: \(anti\)-16a) in 70% yield, Scheme 5.

The high diastereoselection observed in the aldol reactions with lithium and titanium (IV) enolates led us to consider that these metal enolates provided highly selective aldol reaction under chelation control according to a Zimmerman-Traxler model (Scheme 7). The formation of diastereoisomers \(anti\)-16a and \(syn\)-16b was accounted for based on the approach of the aldehyde cis to the lithiated hydroxyl group of quinolizidinone 13.

Thus, the relative stereochemistry of the aldol adduct lactam at C-3 and C1’ was generated by the attack of the enolates into the aldehyde through its concave face. These results could be rationalized by the preformed quaternary lithium alkoxide in the enolate formation step, stabilizing the quinolizidinone enolate through a possible lithium dimer interaction, affording \(anti\)-16a preferentially due to the relief of the steric hinderance involving the isopropyl group which is axially positioned in the transition state model leading to \(syn\)-16b (Scheme 7). Theoretical analysis through geometry optimization of the possible conformers of \(anti\)-16a using DFT method (B3LYP/STO-3G, Gaussian98 program), as well as the semi empirical methods PM3 and AM1, showed an increase in the stability ranging from 1.8 to 4 kcal/mol when a hydrogen bond involving the carbonyl and hydroxyl groups is present. Additionally, geometry optimization using semi-empirical and \(ab\ initio\)
(DFT) methods showed that anti-16a is more stable by 0.39 (using PM3), 2.18 (using AM1) and 8.39 kcal mol\(^{-1}\) (using DFT) than its corresponding epimer at C-3 and C-1’ which would require cis approach of the aldehyde to the methyl group at the quaternary center through a Zimmerman-Traxler transition state.

The preferential formation of syn-16b when the N,O-silylketeneacetal from quinolizidinone 13 was employed (Mukaiyama conditions) may be rationalized through a preferential open transition state model with antiperiplanar approach of the N,O-silylketeneacetal to the aldehyde so as to relieve the steric strain between the isopropyl group of the aldehyde and the quinozilidine ring (Scheme 7).

At this point, we needed to secure an efficient and stereospecific anti elimination methodology in order to benefit from the highly stereoselective formation of anti-16a when the lithium or titanium(IV) enolates were employed (Scheme 5) and we that goal in mind several reaction conditions were investigated.

Initially, we employed anti-14a as our model compound and the results are summarized in Scheme 8. The conversion of anti-14a to the corresponding mesylate 19, followed by elimination in refluxing pyridine provided only (E)-15a. The same stereochemical outcome was observed by Gallagher 16 (1.Me\(_2\)SO\(_2\)Cl, py, 0 °C to rt; 2. HCl; 3. MeOH/ KOH, reflux) (Scheme 8, equation 2). Reasoning that the preferential formation of (E)-15a resulted from a competitive E2cB mechanism which would be enforced over the expected E2 by polar solvents, we decided to investigate elimination of 19 in hexane with DBU as base. Compared to bases such as pyridine, this amidine base (DBU) is particularly effective in promoting elimination reactions. 14 In fact, under these conditions a 3:1 mixture of stereoisomers 15a:15b was formed in 88% yield (Scheme 8, equation 3). The exclusive formation of
stereoisomer 15b was eventually achieved using Stork protocol, suggesting that only E2 mechanism was operative under these experimental conditions (Scheme 8, equation 4).

The preference for the formation of (E)-isobutylidene side chain was also observed when anti-16a was submitted to the conditions described by Gallagher et al. which provided (E)-17 in 83% yield. However, as observed above for anti-14a, under Stork conditions only the desired (Z)-isomer 18 was formed in 80% yield (Scheme 9).

(Z)-Alkylidenelactam 18 was then reduced with alane and after acidification with methanolic HCl, homopumiliotoxin 223G (1) was isolated as the corresponding hydrochloride salt in 82% yield (Scheme 10).

Experimental

General

All experiments were carried out under an argon atmosphere except for hydrolysis under acid conditions. Dichloromethane was distilled from CaH₂, tetrahydrofuran previously treated with CaH₂ and distilled from sodium, methanol was distilled from Mg tunnings. The normal extracts consisted of drying over MgSO₄, filtration and concentration under reduced pressure with a rotatory evaporator. The compounds were purified by column chromatography on silica gel (70-230 mesh). The H-NMR and ¹³C-NMR spectra were recorded on a Varian Gemini (7.05T), Varian Inova (11.7T) spectrometers. Chemical shifts (δ) are recorded in ppm with the solvent resonance as the internal standard and coupling constants (J) recorded in Hz. Signals for rotational and/or configuration isomers are denoted inside brackets. The infrared spectra were recorded as films in KBr cells on a Nicolet Impact 410 (FTIR). High resolution mass spectroscopy (HRMS) were performed on a Autoespec-Micromass-EBE. Optical rotations were measured on a polarimeter Polamat A Carl Zeiss Jena using a quartz cell and a mercury or sodium lamp. The melting points were measured on an Eletrothermal 9100 apparatus. The gas chromatography analyses (FID detector) were performed using a HP-5890-II equipment. Gas chromatography-mass spectrometry (GC-MS) analyses were performed on a Hewlett Packard 5890/ Hewlett Packard 5970 MSD.

Benzyl (2R*)-2-[(2S*)-2-methyl-5-oxo-2,5-dihydro-2-furanyl]hexahydro-1-pyridinecarboxylate (7a) and benzyl (2R*)-2-[(2R*)-2-methyl-5-oxo-2,5-dihydro-2-furanyl]hexahydro-1-pyridinecarboxylate (8a)

To a solution of metoxycarbamate 6a (0.18 mmol, 0.045 g) in anhydrous CH₂Cl₂ (1.00 mL) at −78 °C was added TiCl₄ (0.18 mmol, 0.020 mL) and the black mixture was stirred for 30 min. under argon atmosphere, followed by slow addition of 2-(5-methyl)-triisopropylsilyloxyfuran 5 (0.18 mmol, 0.046 g) in CH₂Cl₂ (0.10 mL). After 30 min saturated aqueous NH₄Cl (1.00 mL) was added and the layers were separated. The aqueous phase was extracted with CH₂Cl₂ (2x 5 mL), and the combined organic phase was dried over MgSO₄ and concentrated under reduced pressure. The crude was submitted to flash column chromatography purification (hexane/ethyl acetate, 2:1) affording 7a (0.022 g, 0.069 mmol) and 8a (0.018 g, 0.057 mmol) in a 1:2:1 diastereoisomeric mixture, in 70% combined yield. 7a. ¹H-NMR (500 MHz, CDCl₃) δ 1.20-1.26 (1H, m), 1.43 (3H, s),
The same procedure described for 7a was employed, affording 7e in 91% yield. mp 136.4-137.3 °C. IR (KBr) v max/cm -1: 3087, 3057, 3016, 2959, 2870, 1768, 1689, 1670, 1423, 1379, 1338(m), 1263(m), 1161(m), 1034, 957, 926, 822, 760, 700. 1H-RMN (500 MHz, CDCl3) δ: 0.81 (6H, d, J = 6.6 Hz), 0.84-0.91 (1H, m), 1.13 (1H, t, J = 2.20 Hz), 1.37 (1H, s), 1.32-1.54 (3H, m), 1.57-1.72 (3H, m), 1.81-1.89 (1H, m), 1.93-2.11 (3H, m), 2.52 (1H, dt, J = 2.4, 13.7 Hz), 2.91-2.98 (2H, m), 4.04-4.07 (1H, m), 4.37 (1H, d, J = 5.4 Hz), 4.69 (1H, ddd, J = 20.0, 9.0, 3.9, 3.9 Hz), 5.98 (1H, d, J = 5.6, 28.1 Hz), 7.03-7.10 (1H, m), 7.20 (3H, bd, J = 5.6 Hz), 7.18-7.27 (1H, m), 7.32 (1H, d, J = 5.6 Hz). 13C-RMN (125 MHz, CDCl3) δ: 20.4 (CH), 21.6 (CH3), 23.6 (CH), 24.9 (CH), 40.0 (CH), 53.7 (CH), 67.5(CH), 93.2 (C), 121.0 (CH), 127.7(2xCH), 128.1 (CH), 128.5(2xCH), 136.8 (C), 159.8 (C), 160.2(1H, CH2), 172.5 (C). IR (NaCl film) v max/cm -1: 177.5 (C). HRMS (EI): found 342.2431; calcd. for C22H32NO2 (M+ - C5H5O2): 342.2433.

(tet-Butyl (2R*)-2-[(2R*)-2-methyl-5-oxo-2,5-dihydro-2-furanyl]hexahydro-1-pyridinecarboxylate (7b))

IR (KBr) v max/cm -1: 3365, 3086, 3064, 2976, 2937, 2871, 1768, 1689, 1452, 1414, 1369, 1275, 1250, 1152, 1034, 957, 822, 768. 1H-RMN (300 MHz, CDCl3) δ: 1.41 (3H, d, J = 2.5 Hz), 1.46 (9H, s), 1.24-1.53 (4H, m), 1.52-1.67 (1H, m), 1.98 (0.2H, dt, J = 1.5, 7.0 Hz), 2.70-3.12 (1H, m), 3.48-3.88 (0.2H, m), 3.99 (0.6H, bd, J = 13.6 Hz), 4.09-4.13 (0.2H, m), 4.31 (0.4H, m), 4.50 (0.6H, m), 6.07 (1H, d, J = 5.5 Hz), 7.39 (1H, d, J = 5.5 Hz). 13C-RMN (75 MHz, CDCl3) δ: 20.5 (CH), 24.0 (CH3), 24.9 (CH), 28.3 (CH), 28.3 (3XCH3), 40.9 (CH3), 52.7 (CH), 79.9 (C), 93.4 (C), 120.9 (CH), 160.4 (C), 160.8 (CH), 172.2 (C). HRMS (EI): found 224.0924; calcd. for C11H14NO4 (M+ - Bu): 224.0923.

tert-Butyl 2-[(5-methyl-2-oxo-2,3-dihydro-3-furanyl)-1-piperidinecarboxylate (9b)

IR (KBr) v max/cm -1: 3105, 2974, 2937, 2864, 1795, 1697, 1452, 1412, 1367, 1162. 1H-RMN (300 MHz, CDCl3) δ: 1.34-1.38 (9H, m), 1.48-1.59 (5H, m), 1.70 (0.5H, m), 1.89 (0.9H, d, J = 1.5 Hz), 1.90 (0.9H, d, J = 1.5 Hz), 1.91 (0.6H, d, J = 1.5 Hz), 1.92 (0.6H, d, J = 1.5 Hz), 2.19 (0.5H, bd, J = 9.2 Hz), 2.66 (1H, m), 3.46 (0.3H, dt, J = 1.5, 7.7 Hz), 3.58 (0.7H, dt, J = 2.2, 7.7 Hz), 4.00 (1H, m), 4.25 (1H, m), 4.88 (0.32H, s), 5.01 (0.68H, t, J = 1.5 Hz). 13C-RMN (75 MHz, CDCl3) δ: 18.7 (CH), 18.9 (CH), 24.9 (CH), 27.1 (CH), 28.2 (3xCH3), 30.4 (CH), 44.8 (CH), 52.5 (CH), 80.4 (C), 102.1 (CH), 153.1 (C), 154.6 (C), 177.5 (C). HRMS (EI): found 224.0921; calcd. for C11H14NO4 (M+ - Bu): 224.0923.

(1R, 2S, 5R) - 5-M ethyl-2 - (1-m ethyl-1-phenylethyl)cyclohexyl (2R*)-2-[(2S*)-2-methyl-5-oxo-2,5-dihydro-2-furanyl]hexahydro-1-pyridinecarboxylate (7c)

mp 136.4-137.3 °C. IR (KBr) v max/cm -1: 3087, 3057, 3016, 2959, 2870, 1768, 1689, 1670, 1423, 1379, 1338(m), 1263(m), 1161(m), 1034, 957, 926, 822, 760, 700. 1H-RMN (500 MHz, CDCl3) δ: 0.81 (6H, d, J = 6.6 Hz), 0.84-0.91 (1H, m), 1.13 (1H, t, J = 2.20 Hz), 1.37 (1H, s), 1.32-1.54 (3H, m), 1.57-1.72 (3H, m), 1.81-1.89 (1H, m), 1.93-2.11 (3H, m), 2.52 (1H, dt, J = 2.4, 13.7 Hz), 2.91-2.98 (2H, m), 4.04-4.07 (1H, m), 4.37 (1H, d, J = 5.4 Hz), 4.69 (1H, ddd, J = 20.0, 9.0, 3.9, 3.9 Hz), 5.98 (1H, d, J = 5.6, 28.1 Hz), 7.03-7.10 (1H, m), 7.20 (3H, bd, J = 5.6 Hz), 7.18-7.27 (1H, m), 7.32 (1H, d, J = 5.6 Hz). 13C-RMN (125 MHz, CDCl3) δ: 20.4 (CH), 21.6 (CH3), 24.9 (CH), 24.5 (CH), 24.5 (CH), 26.6 (CH2), 28.1 (CH3), 31.3 (CH3), 34.6 (CH3), 39.5 (CH3), 39.8 (C), 42.1 (CH), 50.5 (CH3), 53.5 (CH), 75.9 (CH), 93.1 (CH), 120.8 (CH), 125.0 (CH), 125.1 (CH), 128.0 (CH), 128.1 (CH), 152.1 (C), 155.3 (C), 160.3 (CH), 172.6 (C). HRMS (EI): found 342.2431; calcd. for C22H32NO2 (M+ - C5H5O2): 342.2433.
Benzyl (2R*)-2-[(2S*)-2-methyl-5-oxotetrahydro-2-furanyl]hexahydro-1-pyridinecarboxylate (10a)

To a solution of 7a (0.019 g, 0.060 mmol) in ethyl acetate (0.60 mL) was added Pd/C (10%) (0.0019 g) and the mixture was stirred under H₂ (1 atm) for 4 h. The mixture was then filtered through Celite, and the pad was rinsed with EtOAc/MeOH (4:1, 10 mL). The organic layer was concentrated under reduced pressure to furnish pure 10a as a colorless oil in 99% yield (0.011 g, 0.059 mmol). ¹H-RMN (300 MHz, CDCl₃) δ 1.02-1.41 (2H, m), 1.30 (3H, s), 1.49-1.57 (2H, m), 1.64-1.70 (1H, m), 1.72-1.84 (1H, m), 2.43-2.60 (5H, m), 2.68 (1H, dd, J 11.4, 2.0 Hz), 3.04 (1H, dt, J 11.4, 2.0 Hz), 3.25 (1H, m), 3.32 (1H, m), 3.42 (1H, bs), 4.69 (1H, dddd, J 11.4, 2.0 Hz), 2.62 (1H, ddd, J 11.4, 2.0 Hz), 1.67 (1H, ddd, J 11.4, 2.0 Hz), 1.76 (1H, ddd, J 11.4, 2.0 Hz), 1.82 (1H, m), 1.13-1.17 (1H, m), 1.71-1.80 (1H, m), 1.82-2.06 (1H, m), 2.10-2.17 (1H, m), 2.41 (1H, dt, J 13.7, 2.4 Hz), 2.43-2.61 (2H, m), 2.91 (1H, bd, J 20.1 Hz), 4.04-4.12 (1H, m), 4.66 (1H, ddd, J 20.1, 10.7, 4.3 Hz), 4.75-4.88 (1H, m), 7.05-7.08 (1H, m), 7.17-7.25 (4H, m). ¹³C-RMN (75 MHz, CDCl₃) δ: 23.7 (CH₃), 24.3 (CH₂), 25.5 (CH₂), 26.2 (CH₂), 27.6 (CH₂), 29.0 (CH₂), 46.6 (CH₃), 63.0 (CH), 89.0 (C), 176.8 (C). IR (KBr film) νmax/cm⁻¹: 1777. HRMS (EI): found 183,1112; calcd. for C₁₀H₁₇NO₂ (M⁺): 183.1259.

(IS*,9aR*)-1-Hydroxy-1-methylperhydro-4-quinolizinone (12)

A solution of MeONa/MeOH (1.1 mol L⁻¹, 2.7 mL) was added to 10a (0.083 g, 0.45 mmol) at 0 °C, and the mixture was stirred at room temperature. After 2 h, 1.0 mL of HCl/MeOH solution (2 mol L⁻¹) was carefully added. The organic layer was concentrated under reduced pressure, providing 12 in 93% yield as a white solid (0.077 g, 0.42 mmol), mp 133.2-134.3 °C. ¹H-RMN (500 MHz, CDCl₃), δ 1.14 (1H, dq, J 12.5, 3.9 Hz), 1.20 (3H, s), 1.36 (1H, dt, J 12.7, 3.9 Hz), 1.47 (1H, t, J 12.9, 3.9 Hz), 1.57 (1H, bd, J 9.0 Hz), 1.67 (1H, ddd, J 11.7, 3.4, 1.5 Hz), 1.76 (1H, ddd, J 12.7, 2.7 Hz), 1.82 (1H, ddd, J 11.5, 6.1 Hz), 1.88 (1H, bd, J 10.5 Hz), 2.29 (1H, ddd, J 18.0, 6.1, 4.0 Hz), 2.35 (1H, dt, J 13.0, 2.9 Hz), 2.54 (1H, ddd, J 18.0, 11.5, 7.09 Hz), 3.08 (1H, bd, J 2.2 Hz), 3.42 (1H, bs), 4.69 (1H, dddd, J 13.0, 2.0, 2.0, 2.0 Hz). ¹³C-RMN (125 MHz, CDCl₃), δ: 25.1 (CH₃), 25.3 (CH₃), 26.0 (CH₃), 28.4 (CH₂), 29.6 (CH₂), 31.4 (CH₂), 44.4 (CH₂), 68.1 (CH), 69.5 (C), 168.1 (C). IR (KBr film) νmax/cm⁻¹: 1614. HRMS (EI): found 183,1259; calcd. for C₁₀H₁₇NO₂ (M⁺): 183.1259.

(1R*,9aR*)-1-Hydroxy-1-methylperhydro-4-quinolizinone (13)

The same procedure was employed from 11a, affording 13 in 78% yield, as a yellow sirup. ¹H-RMN (500 MHz, CDCl₃), δ: 1.33 (3H, s), 1.36 (2H, br, J 14.4 Hz), 1.44 (1H, dq, J 13.2, 3.2 Hz), 1.64 (1H, dd, J 11.9, 2.5 Hz), 1.76 (1H, ddd, J 16.6, 10.7, 5.6 Hz), 1.89 (2H, m), 1.95 (1H, m), 2.34 (1H, t, J 5.4 Hz), 2.41 (1H, dt, J 11.5, 4.2 Hz), 2.62 (1H, ddd, J 16.1, 10.7, 5.6 Hz), 3.07 (1H, bd, J 11.3, 2.5 Hz), 3.45 (1H, sl), 4.79 (1H, dddd, J 17.1, 2.0, 2.0, 2.0 Hz). ¹³C-RMN (125 MHz, CDCl₃), δ: 24.3 (CH₃), 25.0 (CH₃), 26.2 (CH₂), 27.4 (CH₂), 28.5 (CH₃), 33.3 (CH₃), 43.2 (CH₂), 65.5 (CH), 67.9 (C), 169.1 (C). IR (KBr film) νmax/cm⁻¹: 1614. HRMS (EI): found 183,1255; calcd. for C₁₀H₁₇NO₂ (M⁺): 183.1259.

(3S*)-1-Ethyl-3-[1(3S*)-1-hydroxy-2-methylpropyl]hexahydro-2-pyridinone (14a) and (3S*)-1-ethyl-3-[1(3R*)-1-hydroxy-2-methylpropyl]hexahydro-2-pyridinone (14b)

The same procedure described for 10a was employed using 8a, affording 11a in 98% yield. ¹H-RMN (300 MHz, CDCl₃) δ 1.11-1.29 (1H, m), 1.32 (3H, s), 1.53-1.57 (2H, m), 1.79-1.90 (2H, m), 2.08-2.18 (1H, m), 2.45-2.66 (6H, m), 3.08 (1H, m), 21.1 (CH₃), 24.6 (CH₂), 25.7 (CH₃), 26.5 (CH₂), 28.8 (CH₃), 31.1 (CH), 46.9 (CH₂), 64.8 (CH), 88.8 (C), 176.5 (C). IR (KBr film) νmax/cm⁻¹: 1770. HRMS (EI): found 183,1112; calcd. for C₁₀H₁₇NO₂ (M⁺): 183.1259.

n-Butyllithium (0.751 mL, 2.2 mol L⁻¹ solution in
hexane) was added to a solution of diisopropylamine (0.167 g, 1.65 mmol) in dry THF (14.5 mL) at –78 °C under argon atmosphere. The mixture was stirred for 30 min. at 0 °C, then cooled to –78 °C, followed by slow addition of N-ethylvalerolactam (0.100 g, 0.787 mmol) in 3.0 mL of dry THF. The mixture was warmed to 0 °C and stirred for 1 h. Isobutyraldehyde (0.0624 g, 0.866 mmol) was added at –78 °C and warmed to 0 °C. After 30 min, NH4Cl (2.0 mL) was added. The organic layer was separated, and the aqueous phase was extracted with AcOEt (3x 30 mL). The combined organic layer was dried over MgSO4, filtered and concentrated under reduced pressure, affording a 3.9:1 mixture of 14a:14b in 75% yield. The mixture of diastereoisomers was separated by flash chromatography (hexane:AcOEt, 1:1) providing pure 14a (0.0935 g, 0.470 mmol, 60%) and 14b (0.0239 g, 0.120 mmol, 15%) as white crystals. 14a. mp: 34.3-35.4 °C. 1H-RMN (CDCl3, 300 MHz) δ 0.88 (3H, d, J 6.6 Hz), 1.05 (3H, d, J 6.6 Hz), 1.13 (3H, t, J 7.3 Hz), 1.34-1.47 (1H, m), 1.72-1.83 (4H, m), 1.84-1.96 (2H, m), 2.26 (1H, ddd, J 11.4, 9.5, 5.9 Hz), 3.28-3.33 (2H, m), 3.39 (2H, dq, J 7.3, 3.6 Hz), 3.58 (1H, dd, J 9.2, 2.6 Hz), 5.90 (1H, s). 13C-RMN (CDCl3, 75 MHz) δ: 12.0 (CH3), 13.6 (CH2), 20.1 (CH2), 22.1 (CH2), 23.7 (CH3), 29.0 (CH), 42.1 (CH2), 44.0 (CH2), 47.1 (CH2), 76.3 (CH), 173.5 (C). IR (KBr film) νmax/cm−1: 3338, 1610. 14b. mp 63.8-64.4 °C. 1H-RMN (CDCl3, 300 MHz) δ 0.87 (3H, d, J 6.6 Hz), 1.02 (3H, d, J 6.6 Hz), 1.12 (3H, t, J 7.3 Hz), 1.11 mmol. 13C-RMN (CDCl3, 75 MHz) δ: 12.3 (CH3), 19.1 (CH2), 19.4 (CH2), 20.1 (CH2), 22.4 (CH2), 30.0 (CH), 42.1 (CH2), 44.8 (CH2), 46.9 (CH), 76.6 (CH), 171.7 (C). IR (KBr film) νmax/cm−1: 3423, 1622. The same procedure was performed using LiHMDS (LiHMDS was prepared employing HMDS instead of DIPA) as base affording a 4:4:1 diastereoisomeric mixture of 14a:14b in 60% combined yield.

(1R*,3R*,9aR*)-1-Hydroxy-3-[(1S*)-1-hydroxy-2-methylpropyl]-1-methylperhydro-4-quinolizinone (16b)

The lithium enolate of 13 was generated as described for δ-valerolactam. At –78 °C, TBSOTf (1.0 equiv.) was added dropwise with stirring and warmed to 0 °C. After 2 h at 0 °C, isobutyraldehyde (1.1 equiv.) and TMSOTf (1.1 equiv.) were added providing a 1:3 diastereoisomeric ratio mixture of anti-16a:syn-16b in 70% yield. 16b. mp: 148.7-149.5 °C. 1H-RMN (CDOD3, 300 MHz) δ 0.87 (3H, d, J 6.6 Hz), 1.02 (3H, d, J 6.6 Hz), 1.30 (3H, s), 1.35-1.51 (3H, m), 1.55-1.74 (4H, m), 1.79-1.89 (3H, m), 2.48 (1H, dt, J 13.2, 2.6 Hz), 2.74 (1H, ddd, J 12.5, 5.9, 1.8 Hz), 3.14 (1H, dd, J 11.4, 2.6 Hz), 3.30 (1H, quint., J 1.5 Hz), 3.94 (1H, dd, J 9.9, 1.8 Hz), 4.71 (1H, bd, J 13.2 Hz). 13C-RMN (CDOD3, 75 MHz) δ 19.3 (CH2), 20.6 (CH2), 24.8 (CH2), 26.0 (CH3), 26.9 (CH2), 27.7 (CH2), 31.9 (CH), 33.9 (CH), 41.3 (CH2), 44.0 (CH2), 65.8 (CH), 68.8 (C), 77.4 (CH), 173.4 (C). IR (KBr film) νmax/cm−1: 3400, 3370, 1691. HRMS (EI): found 255,1833; calcd. for C14H25NO3 (M+): 255,1834.

(1R*,3R*,9aR*)-1-Hydroxy-3-[(1S*)-1-hydroxy-2-methylpropyl]-1-methylperhydro-4-quinolizinone (16b)

To a solution of the aldol adduct 16a (47 mg, 0.18 mmol) in dry toluene (4.5 mL) was added DCC (46 mg, 0.22 mmol) and CuCl (34 mg, 0.34 mmol), and the resulting mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield. The mixture was heated to reflux in a Pyrex tube for 24 h. After this time, dilute aqueous ammonia (10 mL) was added, and the mixture was extracted with AcOEt (3x 20 mL). The organic layer was dried with MgSO4 and concentrated under reduced pressure. The crude was purified through flash chromatography (petroleum ether:AcOEt, 3:1) to give 16a in 75% yield.
The same procedure described for 17 was performed employing 16b to furnish 15b as the sole product in 87% yield, after column chromatography eluting with hexane:AcOEt (1:1). H-RMN (CDCl₃, 300 MHz) δ 0.98 (6H, d, J 6.6 Hz), 1.14 (3H, t, J 7.3 Hz), 1.82-1.90 (2H, m), 2.38 (2H, ddd, J 6.2, 6.2, 1.5 Hz), 3.29 (2H, t, J 6.6 Hz), 3.43 (2H, q, J 7.3 Hz), 3.66 (1H, dq, J 6.5, 2.9 Hz), 5.49 (1H, bd, J 9.5 Hz). ¹³C-RMN (CDCl₃, 75 MHz) δ 12.2 (CH₃), 22.9 (2xCH₃), 23.8 (CH₂), 27.6 (CH₂), 32.5 (CH₃), 41.7 (CH₂), 47.2 (CH₂), 126.5 (C), 148.0 (CH), 164.8 (C). IV (KBr film) vₙₐₜ / cm⁻¹: 1660, 1620. HRMS (EI): found 181,1466; calcd. for C₁₁H₁₉NO (M⁺) : 181.1467.

Preparation of lithium aluminum hydride solution in THF

Solution of LiAlH₄ (5.0 g, 0.125 mol) in THF (80.0 mL) was added a solution of aluminum hydride (3.0 equiv., previously prepared by mixing 1 equiv. of AlCl₃ and 3 equiv. of LiAlH₄ in THF) to furnish 1 as the sole product in 87% yield, after column chromatography eluting with hexane:AcOEt (1:1). ¹³C-RMN (CDCl₃, 75 MHz) δ 0.98 (6H, d, J 6.6 Hz), 1.14 (3H, t, J 7.3 Hz), 1.82-1.90 (2H, m), 2.38 (2H, ddd, J 6.2, 6.2, 1.5 Hz), 3.29 (2H, t, J 6.6 Hz), 3.43 (2H, q, J 7.3 Hz), 3.66 (1H, dq, J 6.5, 2.9 Hz), 5.49 (1H, bd, J 9.5 Hz). ¹³C-RMN (CDCl₃, 75 MHz) δ 12.2 (CH₃), 22.9 (2xCH₃), 23.8 (CH₂), 27.6 (CH₂), 32.5 (CH₃), 41.7 (CH₂), 47.2 (CH₂), 126.5 (C), 148.0 (CH), 164.8 (C). IV (KBr film) vₙₐₜ / cm⁻¹: 1660, 1620. HRMS (EI): found 181,1466; calcd. for C₁₁H₁₉NO (M⁺) : 181.1467.

Homopumiliotoxin 223G hydrochloride (1)

To a solution of 18 (30 mg, 0.13 mmol) in THF (1.0 mL) was added a solution of lithium aluminum hydride (3.0 equiv., previously prepared by mixing 1 equiv. of AlCl₃ and 3 equiv. of LiAlH₄ in THF) at room temperature. After 10 min, the reaction was quenched with saturated aqueous sodium sulfite solution and filtered. The solids were washed with CH₂Cl₂ and acetylated with HCl/MeOH (10%) to result in complete conversion to hydrochloride salt, and evaporation in reduced pressure afforded the crude 1 which was purified through flash chromatography eluting with CHCl₃/MeOH:NH₄OH (200:90:1). Recrystallization with HCl/MeOH afforded pure 1 HCl (0.029 g, 0.11 mmol) 82% yield as pale crystal. ¹HCl mp: 183-184 °C. ¹H-RMN (CD₂OD, 500 MHz) δ 0.86 (3H, d, J 6.7 Hz), 0.96 (3H, d, J 6.7 Hz), 1.15 (3H, s), 1.18-1.25 (1H, m), 1.48 (1H, tt, J 13.1, 3.7 Hz), 1.57-1.67 (2H, m), 1.77-1.86 (2H, m), 1.98 (1H, bd, J 14.3 Hz), 2.19 (1H, dd, J 14.3, 1.8 Hz), 2.34 (1H, bd, J 14.0 Hz), 2.53-2.58 (1H, m), 2.93 (1H, dt, J 13.1, 3.4 Hz), 3.05 (1H, dd, J 11.9,
3.1 Hz), 3.21 (1H, q, J 1.8 Hz), 3.33 (1H, tt, J 13.1, 1.8 Hz), 4.02 (1H, dd, J 13.4, 1.5 Hz), 5.24 (1H, bd, J 9.8 Hz).

$^{13}$C-RMN (CDCl$_3$, 75 MHz) $\delta$ 23.1 (CH$_2$), 23.2 (CH$_3$), 23.6 (CH$_3$), 24.3 (CH$_2$), 24.3 (CH$_2$), 26.0 (CH$_3$), 27.9 (CH), 47.8 (CH$_2$), 55.8 (CH$_2$), 56.5 (CH$_2$), 70.0 (C), 71.0 (CH), 124.1 (C), 140.7 (CH). HRMS (EI): found 223,1941; calcd. for C$_{14}$H$_{25}$NO (M$^+$ - HCl) : 223,1936.

(E)-I Hydrochloride

The same procedure was employed to 17 affording (E)-I in 80% yield as a colorless crystal. (E)-I. mp:203-204 °C.

1H-RMN (CDCl$_3$, 500 MHz) $\delta$ 0.93 (3H, d, J 6.2 Hz), 0.95 (3H, d, J 6.2 Hz), 1.26 (3H, s), 1.11-2.00 (5H, m), 2.25-2.62 (2H, m), 2.58-2.70 (1H, d, J 13.0 Hz), 2.99-3.05 (2H, m), 3.18-3.24 (1H, m), 3.43 (1H, bd, J 13.1 Hz), 3.63 (1H, dd, J 13.1, 9.8 Hz), 5.54 (1H, d, J 9.8 Hz). $^{13}$C-RMN (CDCl$_3$, 75 MHz) $\delta$ 21.1 (CH$_2$), 22.9 (CH$_3$), 23.0 (CH$_3$), 23.4 (CH$_3$), 24.6 (CH$_2$), 24.7 (CH$_2$), 27.9 (CH), 43.1 (CH$_3$), 57.1 (CH$_3$), 62.4 (CH$_2$), 70.7 (C), 71.8 (CH), 124.8 (C), 141.6 (CH). HRMS (EI): found 223,1940; calcd. for C$_{14}$H$_{25}$NO (M$^+$ - HCl) : 223,1936.

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