Total Synthesis of (+)-Pumiliotoxin 251D[‡]

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Dedicated to Prof. Dr. E. Winterfeldt on the occasion of his 70th birthday

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The convergent total synthesis of pumiliotoxins by attachment of the side chain to a suitably functionalized core indolizidinone derivative has been achieved. The use of an aldol-type addition condensation strategy, intended to provide for the stereoselective generation of the exocyclic double bond, gave no satisfactory results. The method of choice was a Horner olefination. Initially, the reactant core indolizidinone was converted into an α phosphono amide by amide enolate formation, enol phosphate generation, and a final phosphate-phosphonate migration. The amido phosponates smoothly underwent Horner-type olefinations to allow successful introduction of the side chain with high *Z* selectivity in the exocyclic double bond. Similarly, the introduction of the phosphonate and the subsequent olefination could be run as a one-pot process. The final reductive removal of the lactam function provided (–)-8-*epi*-pumiliotoxin 209 F and (+)-pumiliotoxin 251 D. The structure of the pumiliotoxin 251 D was confirmed by X-ray analysis.

Introduction

Since Daly's isolation and structural determination of pumiliotoxins, and the initial investigations of some of their interesting biological properties, a number of total syntheses have been developed.[1] These alkaloids have been isolated from the skin secretions of some South and Central American arrow poison frogs.[2] Pumiliotoxin 251 D was reported as one major compound in an analysis of the alkaloid mixture secreted by *Dendrobates tricolor* (Ecuador).[3] All these compounds are thought to serve as chemical defense systems,[4] cardiotonic and myotonic properties having been reported for several species. Interaction with the charge-dependent ion channels of certain nerve cells influences signal transduction by induction of the opening of Na^+ ion channels.[5]

Examination of the structures of the pumiliotoxins (Figure 1) shows that all compounds are characterized by the bicyclic indolizidine system, with some stereogenic centers and an exocyclic trisubstituted double bond of defined configuration. In terms of the total syntheses of these alkaloids, the most convergent approach seemed to be retrosynthetic cleavage across the exocyclic double bond, dividing the molecule into a bicyclic core and a side chain **A**. The planning of such a convergent step requires an efficient coupling reaction, allowing introduction of the double bond in a stereoselective manner. In the case of the synthesis of allopumiliotoxin 267 A and related compounds, an aldol condensation of the 7-indolizidinone and (*R*)-2-methylhexanal was found to be the method of choice, always generating the thermodynamically more stable *E* olefin.[6] In contrast, the synthesis of pumiliotoxin 251 D implies the aldehyde **A** and the 5-indolizidinone, and an aldol condensation would now have to generate the less easily accessible *Z* olefin. Such a sequence was originally described by Gallagher.[7] The bicyclic core lactam and the aldehyde were coupled by means of an aldol-type reaction. The final dehydration introduced the exocyclic double bond, causing some problems concerning the stereoselective olefin formation. The *E*/*Z* ratio depended on the relative configuration of the aldol adduct and the reaction mechanism of the final H_2O elimination (*syn* or *anti* elimination).

With the goal of avoiding such problems, alternative strategies have been developed. Overman employed a vinylsilane iminium salt cyclization to generate the six-membered ring.[8] A more straightforward variant of the reaction is the simultaneous *anti* addition of an iminium salt and an iodide at an alkyne, stereoselectively generating the desired double bond.[9] Kibayashi described a Nozaki–Kishi coup-

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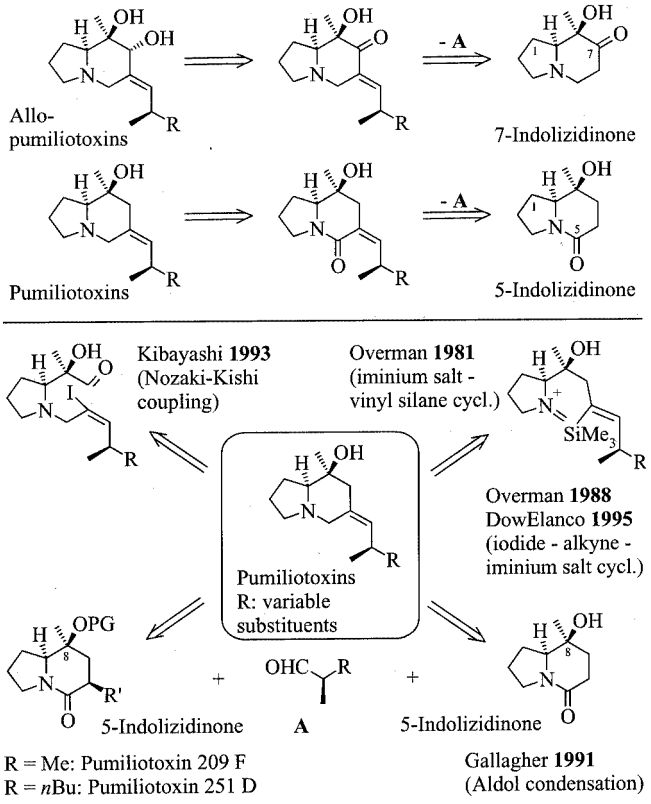


Figure 1. Retrosynthetic analyses of the pumiliotoxins

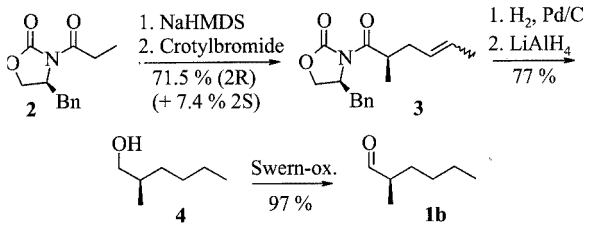
ling to generate allopumiliotoxins bearing the additional 7-OH function.[10] These attempts, however, required earlier introduction of the side chain, making the syntheses less convergent.

In the planning of a convergent total synthesis of (+)-pumiliotoxin 251 D starting from a 5-indolizidinone-type material,[11] the major challenge is the stereoselective generation of the exocyclic double bond (Figure 1). Two strategies seemed to be favorable. On one hand, optimized aldol-type condensations in the presence of a protected 8-OH function, requiring less harsh basic conditions in the coupling step, merited evaluation.[7] On the other hand, a Horner reaction might serve as a suitable key step. Indeed, the formation of *E* and *Z* olefins can be addressed selectively through variation of the ester substituents R^1 on the phosphonate [$R' = (R^1O)_2P(O)$].[12] Two side chain aldehydes **A** were chosen for preliminary investigations: the use of isobutyraldehyde (**1a**) being intended for the synthesis of pumiliotoxin 209 F, and that of (*R*)-2-methylhexanal (**1b**) to provide a new total synthesis of (+)-pumiliotoxin 251 D.

Results and Discussion

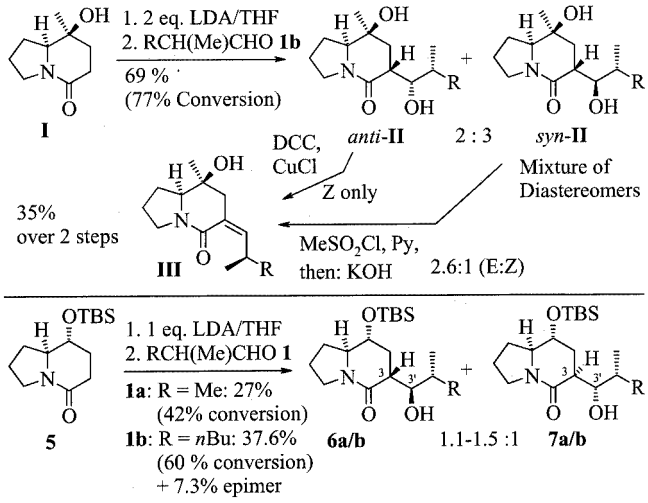
Some suitable indolizidinone core compounds had been synthesized in nine to eleven steps, starting from L-(−)-proline.[11] In principle, that sequence should allow one to generate the 5-indolizidinones and their corresponding enantiomers. Here, the natural series was used to generate the naturally configured pumiliotoxins.

(*R*)-2-methylhexanal (**1b**) was synthesized according to literature procedures by Evans' methodology (not optimized, Scheme 1).[13] The 3-propionoyloxazolidinone **2** derived from (*S*)-alaninol was treated subsequently with NaHMDS and crotyl bromide, the corresponding 2-methylhexenoates **3** being isolated in 71.5% (*2R*) and 7.4% (*2S*) yields.[14] The diastereomers could easily be separated by preparative HPLC. The double bond was then removed by hydrogenation and the (*R*)-2-methylhexanol (**4**) was obtained after $LiAlH_4$ reduction in 77% overall yield.[15] A final Swern oxidation generated the (*R*)-2-methylhexanal (**1b**) in 97% yield (crude product). To avoid any racemization, the aldehyde was always freshly prepared immediately before its employment in further transformations.[16]



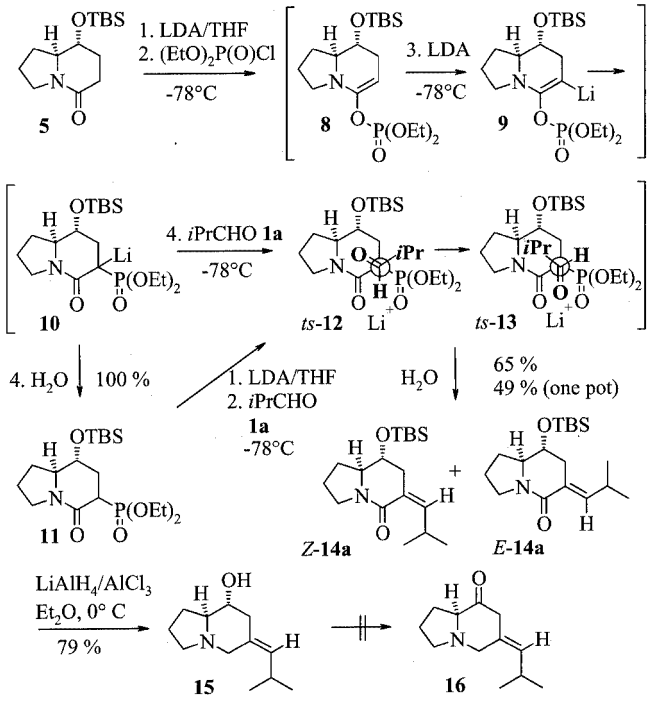
Scheme 1

Initial studies concerning the introduction of the side chain involved Gallagher's aldol condensation route (**I** to **III**, Scheme 2).[7] In contrast to the literature procedure, which required two equivalents of LDA to achieve complete deprotonation of the hydroxyindolizidinone **I**, only one equivalent of the base was enough to form the enolate starting from the protected indolizidinone **5**. The less harsh basic conditions held out the prospect of avoiding any racemization of the sensitive α-chiral hexanal **1b**. The TBS-indolizidinone **5** was deprotonated with one equivalent of LDA at −78 °C, and the thus formed enolate was treated with isobutyraldehyde **1a** (R = Me) and (*R*)-2-methylhexanal **1b** (R = *n*Bu) to yield mixtures of unchanged starting material **5** (40−60%) and about 27−43% aldol adducts **6/7**, respectively (64−72% if normalized to account for degree of conversion). Mixtures of the two major diastereomers **6a/b** and **7a/b** were always obtained, and these were separated by HPLC.[17] The relative configurations of the new stereogenic centers were determined by NOE analyses. A stable intramolecular hydrogen bond (O−H−O=C) fixed the conformation in such a way that the protons of C3 and C3′ of the side chain adopted defined positions, allowing correlation to the stereogenic centers of the indolizidinone ring.[18] Both major diastereomers of **6a/b** and **7a/b** showed *syn* configurations of the C3 proton and the C3′ OH group, which would require *anti* elimination to generate the *Z* olefin (in analogy to *syn*-**II** → **III**). The low degree of conversion of the reactant indolizidinone **5** and the predominantly *syn* arrangements of H and OH in **6a/b** and **7a/b**, requiring the difficult *anti* elimination with potential low diastereoselectivity, forced us to choose an alternative strategy to generate the exocyclic double bond with *Z* geometry.



Scheme 2

Wittig−Horner olefinations are powerful reactions for stereoselective generation of either *E* or *Z* olefins, depending on the substituents attached at the phosphorus.[12] With the intention to test such a method as a convergent key step in the pumiliotoxin synthesis, the smooth generation of a suitable β-amido phosphonate was a prerequisite (Scheme 3).[19] According a procedure published by Wiemer, ketones and carboxylic acid derivatives can be converted into the corresponding phosphonates by initial enol phosphate generation and a final phosphate to phosphonate rearrangement.[20] Such a strategy has been used by Savignac in cyclic systems to synthesize β-phosphonates of γ-lactams.[21] The TBS-indolizidinone **5** was deprotonated with one equivalent of LDA at −78 °C. The thus formed amide enolate was trapped with chloro diethyl phosphate to generate the corresponding enol phosphate **8**.[22] A second equivalent of LDA was then added in order to form the vinyl anion **9**, which underwent an immediate migration of the phosphorus. The enol phosphate β-amidophosphonate rearrangement occurred, producing the more stabilized enolate anion **10**. On one hand, aqueous workup provided the corresponding phosphono amide **11** in high yield (100% crude material) as a mixture of two C3 diastereomers, which were not separated. On the other hand, the β-amidophosphonate anion was treated with the isobutyraldehyde **1a** (R = Me) to induce the Horner reaction, the whole sequence performed as a one-pot procedure. Since all steps were carried out at −78 °C, the resulting α,β-unsaturated lactam (*Z*)-**14a** was isolated with high selectivity (*E*/*Z* 1:13) for the desired *Z* double bond. However, the one-pot procedure was characterized by a moderate yield (49%). In contrast, the two-step reaction through a worked-up β-amidophosphonate intermediate **11** and a subsequent deprotonation/Horner olefination with isobutyraldehyde **1a** succeeded in 65% yield and with high *Z* selectivity (*E*/*Z* 1:13) in the newly formed double bond in (*Z*)-**14a**. The diastereomers (*Z*)-**14** and (*E*)-**14a** were separated by column chromatography. The structures were established by NOE analyses.[23] In analysis of the ^{1}H NMR spectra of both compounds, the vinyl proton of the *Z* olefin was detected in a high-field position (δ = 5.6 ppm) while the side chain allyl proton was found downfield (δ = 3.9 ppm), because of the deshielding effect of the *syn* carbonyl oxygen. For the corresponding *E*-olefin (*E*)-**14a**, the reverse was found. The vinyl proton was found in downfield (δ = 6.6 ppm), the side chain allyl proton in a high-field position (δ = 2.6 ppm).

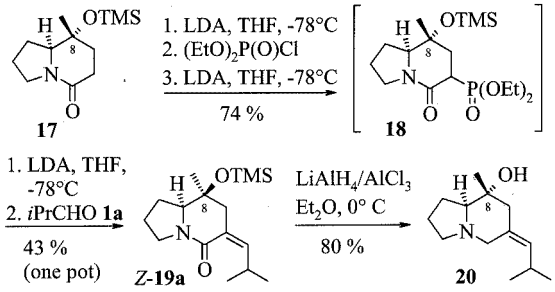


Scheme 3

The unsaturated lactam (*Z*)-**14a** seemed to be a suitable precursor for the total synthesis of pumiliotoxin 209 F (Scheme 3). With the intention to avoid potential low diastereoselectivity during the introduction of the missing C8 methyl group into a keto lactam,[11] the lactam carbonyl group was removed in a first step. The unsaturated lactam (*Z*)-**14a** was treated with a preformed mixture of $LiAlH_4$ and $AlCl_3$ in Et_2O at 0 °C.[24] The lactam CO function and the silyl ether protective group were removed in a single step to generate the corresponding amino alcohol **15** in 79% yield. It should be pointed out that careful preparation of the AlH_3 reagent was crucial to achieve a smooth reaction. On analysis of the crude product **15**, only traces of potential side products characterized by a reduced or an isomerized olefin sub-unit were detected. The chemoselective oxidation of the carbinol **15** to the corresponding ketone **16** failed completely. Swern-type oxidations suffered either from internal quenching of the sulfur reagent or from the migration of the double bond to yield an α,β-unsaturated ketone. Cr^{VI} oxidations caused re-oxidation, generating the lactam **14a**. Additionally, some migrated double bond was found. TEMPO, Dess−Martin, and TPAP oxidations either gave no conversion or the material was destroyed during the course of the reaction. Since intermediate protection of the

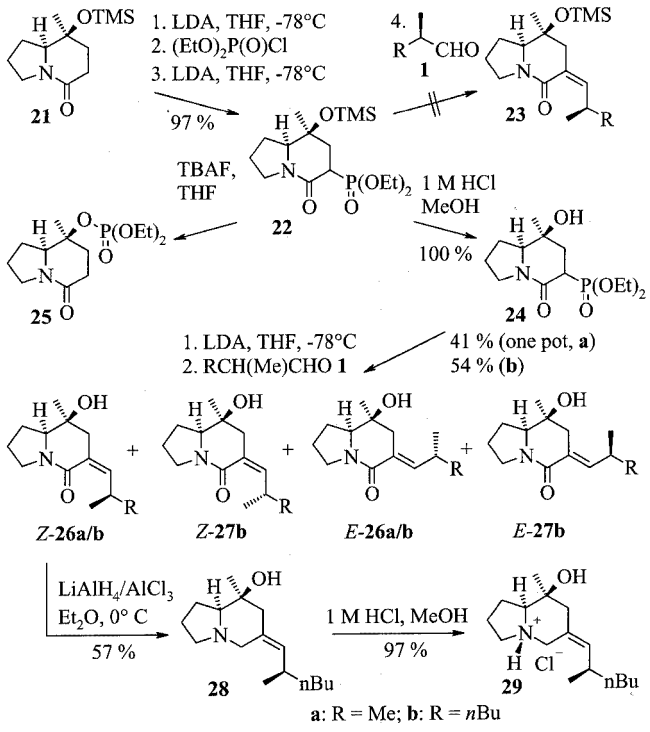
electron-rich amino function by protonation failed under various conditions, this path for a attempted total synthesis of the pumiliotoxins was abandoned (Scheme 3).[25]

For the purpose of pumiliotoxin syntheses, the phosphonate introduction and Horner olefination sequence was tested with the methyl indolizidinones **17** and **21** as suitable reactants. In investigation of the 8-*epi* series starting from bicycle **17**, a smooth reaction was found (Scheme 4). The one-pot procedure − consisting of initial deprotonation of indolizidinone **17**, trapping of the enolate with chloro phosphate, the vinyl anion formation, phosphate-phosphonate rearrangement to **18**, and the final olefination after addition of the isobutyraldehyde **1a** − gave the corresponding α,β-unsaturated lactam (*Z*)-**19a** in 43% overall yield, the *E*/*Z* ratio being about 1:15. An unoptimized two-step sequence allowed isolation of the intermediate β-phosphono amide **18** in 74% yield, and this could be subjected to the olefination conditions to yield the lactam (*Z*)-**19a**. The correct structure was determined by NMR and NOE analyses.[23] Finally, the total synthesis of the 8-*epi*-pumiliotoxin 209 F (**20**) was achieved by reduction of the amide with $AlCl_3/LiAlH_4$. The TMS protecting group was removed under the reaction conditions, and the indolizidine **20** (8-*epi*-pumiliotoxin 209 F) was isolated in 79.6% yield. Again, the suppression of the formation of any side products strongly depended on a high quality of the preformed AlH_3 reagent (Scheme 4).



Scheme 4

In contrast, the natural series starting from methyl indolizidinone **21** behaved completely differently (Scheme 5). The introduction of the phosphonate to **22** succeeded as described above. Enol phosphate formation/deprotonation/phosphate-phosphonate migration gave the corresponding β-phosphono amide **22** in 97.5% yield as a mixture of two C3 diastereomers (not separated). All attempts to use this material in Horner olefinations to give (*Z*)-**23** at low temperatures (< −30 °C, to avoid the formation of the *E* double bond) failed. Obviously, the bulky TMS protective group in **22** was preventing any attack of the aldehyde as the first step of the condensation. Neither the one-pot procedure nor the two-step sequence gave any of the desired product (*Z*)-**23**. Consequently, the TMS group was removed prior to the Horner olefination. The desilylation succeeded under acidic conditions by treatment of the phosphono amide **22** with HCl/MeOH. The carbinol **24** could be isolated in 100% yield as a mixture of the C3 diastereomers. In contrast, deprotection with TBAF in THF gave no desired hydroxy amide **24**, and the phosphate **25** was found as the major compound. This indicated a migration of the phosphonate to the tertiary hydroxyl function under the basic reaction conditions.[16]



Scheme 5

The potential migration of the phosphorus made the Horner olefination of the hydroxy indolizidinone **24** extremely tricky, because of the use of a base as the initial step for formation of the β-phosphono amide anion. With use of a single equivalent of LDA in THF at −78 °C, the phosphorus migration occurred as the predominant reaction (→ **25**), only traces of the olefins **26** being found after the addition of the aldehyde **1**. In contrast, the use of 2.3 to 2.5 equivalents of LDA in THF at −78 °C produced only small amounts of phosphate **25**. Obviously, the generation of the bis-anion was much faster than the rearrangement. Subsequent Horner olefination was then achieved by treatment of the intermediate with the isobutyraldehyde **1a** (R = Me). The α,β-unsaturated lactam (*Z*)-**26a** was isolated in 41% yield and with an *E*/*Z* ratio of about 1:10. The olefination with the chiral α-methylhexanal **1b** (R = *n*Bu) again turned out to be crucial, because of the potential racemization under the harshly basic reaction conditions. After a short reaction time of about 30 min at −78 °C, the desired α,β-unsaturated lactam (*Z*)-**26b** (R = *n*Bu) was isolated as the single diastereomer, but in a poor yield of only 20%. Prolongation of the reaction time increased the yield to about 54%, but a mixture of the diastereomers (*Z*)-**26b**, (*Z*)-**27b**, (*E*)-**26b**, and (*E*)-**27b** was now isolated in a ratio of 7:4:1:1. On analysis of this material, the double bond was found to have been generated predominantly with the *Z*

configuration ($E/Z \approx 1{:}6$). Furthermore, the side chain stereogenic center was not formed selectively, indicating partial racemization of the reactant aldehyde **1b**. Nevertheless, the diastereomers were separated by column chromatography and preparative HPLC. The relative configurations of the stereogenic centers and the double bond in (*E*/*Z*)-**26b** and (*E*/*Z*)-**27b** were unambiguously corroborated by NOE analyses.[23] All spectroscopic data were found to be in good accordance with those published by Gallagher in 1991, but the specific rotation of (*Z*)-**26b** differed (published: −28°, $CHCl_3$, found −67.6°, $CHCl_3$).[7] Surprisingly, the specific rotation of the 11′-*epi*-indolizidinone (*Z*)-**27b** was characterized by a positive sign (+55°, $CHCl_3$) whereas that of the naturally configured diastereomer (*Z*)-**26b** was negative (−67.6°, $CHCl_3$). Keeping in mind that the separation of both diastereomers required optimized HPLC techniques, the lower value published in the literature might have been the consequence of some racemization of the chiral α-methylhexanal **1b** (R = *n*Bu, *R*/*S* = 1.4:1) during the course of the aldol condensation used to introduce the side chain (Scheme 2). This is in good accordance with our findings, because both strategies needed the same harsh basic conditions (bis-anions of the reactant bicyclic indolizidinones **I** and **24**, respectively).

In completion of the total synthesis, the CO group of the major α,β-unsaturated lactam (*Z*)-**26b** was reduced with a preformed mixture of $LiAlH_4$ and $AlCl_3$ in Et_2O at 0 °C. The (+)-pumiliotoxin 251D (**28**) was obtained in 57% yield as a colorless oil. All data of the obtained material were identical with those published in the literature, and the correct structure was verified by NOE analyses. Finally, the indolizidine **28** was converted into the corresponding hydrochloride **29** by treatment with methanolic HCl. The material was crystallized from EtOAc/CH_2Cl_2, and an X-ray analysis of **29** confirmed the correct structure (Figure 2).[23,26]

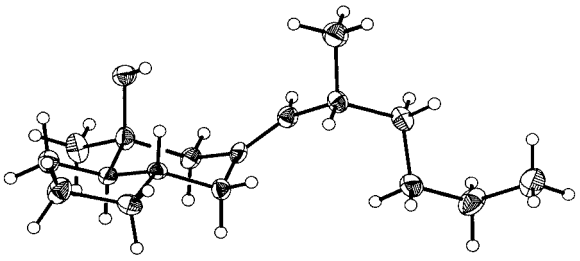


Figure 2. ORTEP plot of (+)-pumiliotoxin 251 D (·HCl) (**29**)

Mechanistic Conclusions

Horner olefination of the β-phosphonoamides **11**, **17**, and **24** has been found to serve as reliable method to produce the exocyclic double bond with a high *Z* selectivity (5−15:1, *Z*/*E*). A low reaction temperature was crucial to obtain satisfactory results with the standard diethyl phosphonate. The high selectivity could be explained as a result of a defined preorientation of the aldehyde attacking the deprotonated phosphonate (Scheme 3). Minimized repulsive interactions could be presumed, with adoption of a trajectory such as *ts*-**12**. The bulky side chain should be positioned next to the small CH_2 group of the indolizidinone. Alternatively, a lithium chelate complex *ts*-**13** might have been passed through, as theoretically postulated by ab initio calculations for open chain systems.[27] The carbon side chain should in this case be favorably positioned in an *anti* arrangement with respect to the bulky phosphonate substituent. However, open transition states (*ts*-**12** and *ts*-**13**) as described in Scheme 3 would always give rise to the same product independent of an α or a β addition of the aldehyde with respect to the indolizidinone ring plane. In instances of a fast and of an irreversible reaction, respectively, the nascent double bond would have to be *Z*-configured. The absence of additional nucleophiles should be ensured in order to prevent subsequent isomerization by a reversible Michael addition to the α,β-unsaturated indolizidinones.

On subjection of the indolizidinones **11**, **18**, **22**, and **24** to the Horner reaction conditions, the last two species were characterized by exceptional modified reactivity. The TMSO lactam **22** gave no reaction (sterically hindered lone pair in **B**?), and the hydroxylactam lactam **24** suffered from a migration of the phosphonate to give phosphate **25**. The phosphorus migration could be explained by intramolecular attack of the kinetically formed quasi-axial alkoxide at a 1,3-*syn*-oriented phosphonate **C**. The result was the final elimination of a more stabilized anion of the amide enolate **D** (in THF). After hydrolytic workup the phosphate **25** was isolated. In the presence of two equivalents of base, in contrast, the generation of the *bis*-anion **E** was much faster than the rearrangement. Presumably, the thus formed amido phosphonate anion in **E** was efficiently protected against any intramolecular nucleophilic attack of the alkoxide. Thus, the Horner reaction was favored, but the extremely basic bis-anion **E** might have caused some racemization of the (2*R*)-2-methylhexanal reactant **1b** (Figure 3).

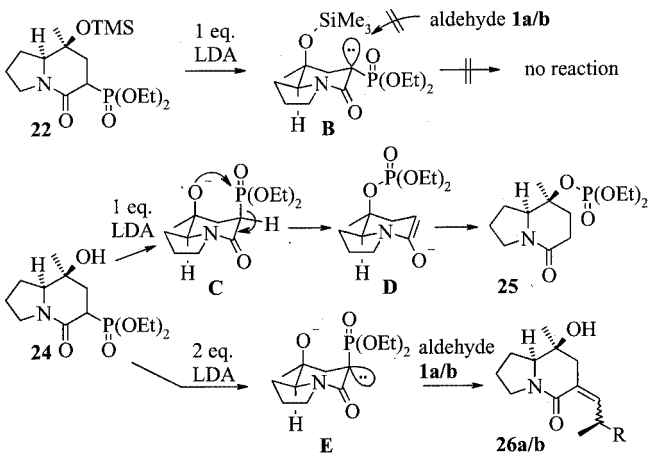


Figure 3. Reactions of phosphonates **22** and **24** with base and aldehydes **1**

Conclusion

A convergent total synthesis of enantiopure pumiliotoxins has been developed, the bicyclic core skeleton indolizidinones **5**, **17**, and **21** and the side chain aldehyde **1** being combined in the key step. An initial investigation to test the aldol strategy first described by Gallagher was found to be less efficient. The moderate level of conversion of the reactant lactam and the low diastereoselectivity of the addition made the selective generation of the exocyclic olefin extremely difficult. Alternatively, a Horner olefination could to be used as a reliable method to introduce the desired trisubstituted double bond with *Z* selectivity. Such strategy required an efficient route to the reactant β-amidophosphonates as a prerequisite. The phosphonate was introduced by a sequence developed by Wiemer and Savignac. The core indolizidinone was converted into the corresponding enol phosphate after deprotonation and phosphorylation. A second equivalent of base then generated the vinyl anion, which immediately underwent a phosphate-phosphonate migration. The thus formed β-amidophosphonate anion was treated with the aldehyde **1** to induce the Horner reaction. This one-pot procedure gave the α,β-unsaturated indolizidinones with a high *Z* selectivity and a moderate yield. However, the intermediate isolation of the β-amidophosphonates followed by a separate olefination gave higher yields, favoring this two-step procedure. The indolizidinones **5** and **17** smoothly gave the α,β-unsaturated indolizidinones (*Z*)-**14** and (*Z*)-**19**, while the analogous reaction with the 5-indolizidinone **21** failed. The phosphonate introduction to **22** caused no problems, but the subsequent olefination required the initial deprotection of the tertiary alcohol function prior to the Horner reaction. The hydroxyindolizidinone **24** was found to be very sensitive under the basic reaction conditions. However, the generation of the side chain to yield (*Z*)-**26a** and (*Z*)-**26b** succeeded, although the minor diastereomers had to be separated. In completion of the total syntheses, the amide functions of (*Z*)-**19a** and (*Z*)-**26b** were removed by AlH_3 reduction. The (−)-8-*epi*-pumiliotoxin 209 F (**20**) and the (+)-pumiliotoxin 251 D (**28**) were therefore synthesized in 12 to 14 steps overall. The structure of the latter (as the hydrochloride **29**) was confirmed by X-ray analysis.

Experimental Section

General Remarks: ^{1}H NMR,^{13}C NMR spectra, and NOE experiments were recorded on Bruker AM 270 or Bruker AC 550 (**11**, NOEDS analyses) spectrometers at room temp. unless specified otherwise. Tetramethylsilane was used as internal standard. For peak assignment, azabicyclononane numbering is used. IR spectra were obtained with a Perkin−Elmer 257 or 580B spectrophotometer. Optical rotations were measured with a Perkin−Elmer P 241 polarimeter in a 1 dm cell. Mass spectra were recorded on a Varian MAT 711 or 112S, The high-resolution mass spectra (HRMS) were obtained with a Varian MAT 711 spectrometer. PFK was used as reference, the results were determined by peak matching methods, resolution: > 10,000. The ion source temperature was 250 °C, the electron energy was 0.8 mA. The melting points (not corrected) were measured with a Büchi SMP 20. For HPLC, Knaur pumps UV and RI detectors and Rheodyne injection systems were used. Preparative amounts of the lactams were separated with a Macherey−Nagel & Co 32 mm × 120 mm column and 5 μm Nucleosil 50-5, with a flow of about 80 mL/min. Column chromatography was carried out with Merck silica gel (0.04−0.063 mm, 230−400 mesh A). Progress of reactions was monitored by thin layer chromatography (TLC) performed on aluminum sheets precoated with 60 silica gel (thickness 0.25 mm). All solvents were dried before use by standard procedures. X-ray analyses were performed with Mo-K_α radiation (λ = 0.71073 Å). The structure was determined by direct methods with the SHELXS program. The H atoms were taken from a difference Fourier synthesis and were refined with isotropic thermal parameters. The non-H atoms were refined with anisotropic thermal parameters. The structure was refined on *F* values with the weighting scheme: $\omega(F) = 4 \cdot F^2/[\sigma^2(F^2) + (0.03 \cdot F^2)^2]$. The final difference density was between −0.29 and +0.36 e/A^3.

(5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-(diethoxyphosphoryl)azabicyclo[4.3.0]nonan-2-one (11), (3*Z*)-(5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-isobutylideneazabicyclo[4.3.0]nonan-2-one [(*Z*)-14a], and (3*E*)-(5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-3-isobutylideneazabicyclo[4.3.0]nonan-2-one (*E*-14a). Two-Step Procedure: Phosphonate introduction: Under argon, LDA (1.53 mL, 3.07 mmol, 1.2 equiv., 2 M in THF) was diluted with dry THF (10 mL) and cooled to −78 °C. Indolizidinone **5** (690 mg, 2.56 mmol) in dry THF (3 mL) was added by syringe over a period of 5 min. After the mixture had been stirred at −78 °C for 30 min, diethyl chlorophosphate (0.74 mL, 883 mg, 5.12 mmol, 2 equiv.) in dry THF (2 mL) was added dropwise. The mixture was stirred for 2.5 h at −78 °C. A second portion of LDA (2 mL, 4 mmol, 2 M in THF) was then injected. After the mixture had been stirred for another 3.5 h at −78 °C, the cooling bath was removed and the excess of LDA was quenched with saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed to yield phosphonate **11** (1.13 g, 2.56 mmol, 100%) as a colorless oil pure enough for further transformations. Analytically pure **11** (mixture of C3 diastereomers) could be obtained by column chromatography on silica gel (EtOAc/*n*-hexane, 1:1, R_f = 0.1).

Horner Olefination: Under argon, phosphonate **11** (1.13 g, 2.56 mmol) in pre-cooled anhydrous THF 10 mL, −78 °C) was treated with LDA (1.66 mL, 3.32 mmol, 1.3 equiv., 2 M in THF, injection over a period of 5 min). After the mixture had been stirred for 1 h at −78 °C, isobutyraldehyde **1a** (0.93 mL, 738 mg, 10.2 mmol, 4 equiv., R = Me) was added and the mixture was stirred at −78 °C overnight. The cooling bath was removed and the excess of LDA was quenched with saturated aqueous NH_4Cl (30 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed. The crude oil was purified by column chromatography on silica gel (EtOAc/*n*-hexane 1:1, R_f = 0.55). Yield 0.54 g (1.67 mmol, 65.2%) isobutylideneindolizidinones **14a** as a colorless oil. The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy (*E*/*Z* = 1:13.5).

One-Pot Procedure: Phosphonate introduction was as described for the two-step procedure without workup: LDA (0.65 mL, 1.29 mmol, 1.2 equiv., 2 M in THF) in dry THF (50 mL), indolizidinone **5** (0.29 g, 1.08 mmol) in THF (1 mL), chloro phosphate (309 μL, 2.152 mmol, 2 equiv.), second portion of LDA (0.85 mL, 1.7 mmol, 1.2 equiv., 2 M in THF). Careful TLC monitoring was

essential in order to detect the complete formation of the intermediate phosphonate **11**. Isobutyraldehyde **1a** (0.39 mL, 4.3 mmol, 4 equiv.) was then added and the mixture was stirred at −78 °C overnight. The cooling bath was removed and the excess of LDA was quenched with saturated aqueous NH_4Cl (40 mL). The aqueous layer was extracted with Et_2O (4 × 30 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed. The crude oil was purified by column chromatography on silica gel (EtOAc/*n*-hexane 1:1, R_f = 0.55). Yield 0.17 g (0.53 mmol, 49%) isobutylidene indolizidinones **14a** as a colorless oil. The *E*/*Z* ratio was determined by ^{1}H NMR spectroscopy (*E*/*Z* = 1:12.8).

Data for Phosphonate 11:[28] ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.00 (s, 3 H, Si−CH_3), 0.01 (s, 3 H, Si−CH_3), 0.04 (s, 3 H, Si−CH_3), 0.06 (s, 3 H, Si−CH_3), 0.81 [s, 9 H, Si$(CH_3)_3$], 0.82 [s, 9 H, Si$(CH_3)_3$], 1.30−1.25 (m, 12 H, 2-H × CH_2−CH_3), 1.45−1.35 (m, 1 H, 7-H), 1.50−1.40 (m, 1 H, 7′-H), 1.75−1.60 (m, 2 H, 8-,8′-H), 1.95−1.85 (m, 3 H, 8-,8′-,4′-H), 2.07−1.95 (m, 2 H, 4-,4′-H), 2.23−2.10 (m, 2 H, 7-,7′-H), 2.37−2.29 (m, 1 H, 4-H), 3.05−2.90 (m, 2 H, 3-,3′-H), 3.20−3.15 (m, 1 H, 6-H), 3.37−3.30 (m, 1 H, 6′-H), 3.55−3.38 (m, 5 H, 9o-,9u-,9o′-,9u′-,5′-H), 4.00−3.93 (m, 1 H, 5-H), 4.25−4.00 (m, 8 H, 2-H × O−CH_2 and O−CH_2′) ppm. ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = −4.9 (q, Si−CH_3), −4.9 (q, Si−CH_3), −4.5 (q, Si−CH_3), −4.4 (q, Si−CH_3), 16.2 and 16.2 and 16.3 and 16.4 and 16.5 (multiple signals, no defined structure, O−CH_2−CH_3 and O−CH_2−CH_3′, 4 sets of doublets from quadruplets), 17.8 [s, Si-*C*$(CH_3)_3$], 22.0 (t, C-8′), 22.3 (t, C-8), 25.5 [q, Si−C(*C*$H_3)_3$], 25.6 [q, Si−C(*C*$H_3)_3$], 31.8 (t, C-4′), 32.2 (t, C-7 and C-7′ and C-4), 40.4 [dd, $^1J(^{31}P,^{13}C)$ = 138.9 Hz, C-3′], 40.5 [dd, $^1J(^{31}P,^{13}C)$ = 135.8 Hz, C-3], 45.9 (t, C-9′), 46.5 (t, C-9), 61.8 [dt, O−CH_2′, $^2J(^{31}P,^{13}C)$ = 7.5 Hz], 62.0 [dt, $^2J(^{31}P,^{13}C)$ = 7.5 Hz, O−CH_2′], 63.1 [dt, $^2J(^{31}P,^{13}C)$ = 6 Hz, O−CH_2], 63.2 [dt, $^2J(^{31}P,^{13}C)$ = 6 Hz, O−CH_2], 63.4 (d, C-6′), 64.4 (d, C-6), 69.1 (d, C-5), 72.0 [dd, $^3J(^{31}P,^{13}C)$ = 13 Hz, C-5′], 163.2 (s), 163.3 (s) ppm. ^{31}P NMR (202.5 MHz, $CDCl_3$): δ = 22.32, 22.72 ppm. IR ($CHCl_3$): ṽ = 3019 (m), 2982 (m), 2956 (m), 2931 (m), 1886 (m), 2858 (m), 1636 (s, C=O), 1462 (m), 1443 (m), 1389 (m), 1362 (m), 1252 (s), 1216 (s), 1128 (m), 1103 (m), 1028 (s), 965 (m) cm^{-1}. MS (80 eV, EI, 90 °C): *m*/*z* (%) = 405 (8) [$M^{+\cdot}$], 390 (5) [$M^+ - CH_3$], 348 (84) [$M^+ - C_4H_9$], 320 (26), 302 (4), 292 (10), 274 (15), 263 (10), 235 (7), 212 (96), 181 (35), 155 (18), 136 (100) [$PO(OEt)_2$], 129 (20), 109 (15), 99 (59), 84 (35), 75 (31), 73 (40), 70 (36). HRMS (80 eV, 80 °C): calcd. 405.21004 (for $C_{18}H_{36}N_1O_5PSi$ [M^+]), found 405.21331.

Data for (*Z*)-Isobutylideneindolizidinone (*Z*)-14a: $[\alpha]_D^{20}$ = −61.4 (*c* = 1.7, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.04 (s, 3 H, Si−CH_3), 0.05 (s, 3 H, Si−CH_3), 0.86 [s, 9 H, SiC$(CH_3)_3$], 1.00−0.90 (m, 6 H, 3c-H), 1.52−1.38 (m, 1 H, 7o-H), 1.80−1.60 (m, 1 H, 8u-H), 2.00−1.85 (m, 1 H, 8o-H), 2.25−2.15 (m, 1 H, 7u-H), 2.53−2.45 (m, 2 H, 4o-,4u-H), 3.33−3.23 [ddd, $^3J(H^{6u},H^{5o})$ = 10, $^3J(H^{6u},H^{7o})$ = 10, $^3J(H^{6u},H^{7u})$ = 5 Hz, 1 H, 6u-H], 3.60−3.40 (m, 3 H, 9o-,9u-,5o-H), 3.90−3.75 (m, 1 H, 3b-H), 5.60−5.55 [ddd, $^3J(H^{3a},H^{3b})$ = 9.5, $^4J(H^{3a},H^{4o})$ = 1.5, $^4J(H^{3a},H^{4u})$ = 1.5 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = −4.8 (q, Si−CH_3), −4.3 (q, Si−CH_3), 17.8 [s, Si*C*$(CH_3)_3$], 22.5 (t, C-8), 22.8 (q, C-3c′), 22.8 (q, C-3c), 25.6 [q, SiC(*C*$H_3)_3$], 27.2 (d, C-3b), 32.0 (t, C-4), 41.9 (t, C-7), 45.6 (t, C-9), 64.2 (d, C-6), 71.9 (d, C-5), 123.6 (s, C-3), 150.4 (d, C-3a), 163.7 (s) ppm. IR (KBr): ṽ = 2955 (s), 2860 (s), 1658 (s), 1620 (s), 1464 (m), 1472 (m), 1445 (s), 1423 (s), 1389 (m), 1378 (m), 1349 (m), 1258 (s), 1146 (m), 1115 (s), 1057 (w), 1023 (w), 1005 (m), 991 (m), 939 (m), 901 (m), 865 (s), 838 (s), 777 (s), 735 (m), 680 (m), 573 (w), 483 (w) cm^{-1}. MS (80 eV, EI, 90 °C): *m*/*z* (%) = 323 (100) [$M^{+\cdot}$], 308 (6) [$M^+ - CH_3$], 266 (34) [$M^+ - C_4H_9$], 192 (8), 183 (5), 156 (9), 148 (7), 136 (5), 96 (7), 81 (16), 75 (31), 73 (43), 70 (12). HRMS (80 eV, 90 °C): calcd. 323.228058 (for $C_{18}H_{33}N_1O_2Si$ [M^+]), found 323.22644.

Data for *E*-Isobutylidene Indolizidinone (*E*)-14a: $[\alpha]_D^{20}$ = −33.4 (*c* = 0.84, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, Si−CH_3), 0.08 (s, 3 H, Si−CH_3), 0.88 [s, 9 H, Si−C$(CH_3)_3$], 0.99 [d, $^3J(H^{3c'},H^{3b})$ = 5.5 Hz, 3 H, 3c′-H], 1.02 [d, $^3J(H^{3c},H^{3b})$ = 5.5 Hz, 3 H, 3c-H], 1.53−1.40 (m, 1 H, 7o-H), 1.80−1.65 (m, 1 H, 8u-H), 2.00−1.90 (m, 1 H, 8o-H), 2.31−2.18 (m, 2 H, 7u-,4u-H), 2.58−2.43 (m, 1 H, 3b-H), 2.83−2.73 [ddd, $^2J(H^{4o},H^{4u})$ = 15.5, $^3J(H^{4o},H^{5o})$ = 5, $^4J(H^{4o},H^{3a})$ = 1.5 Hz, 1 H, 4o-H], 3.40−3.28 (m, 1 H, 6u-H), 3.60−3.40 (m, 3 H, 5-,9o-,9u-H), 6.68−6.60 [ddd, $^3J(H^{3a},H^{3b})$ = 9, $^4J(H^{3a},H^{4u})$ = 2.5, $^4J(H^{3a},H^{4o})$ = 1.5 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = −4.7 (q, Si−CH_3), −4.2 (q, Si−CH_3), 17.9 [s, Si*C*$(CH_3)_3$], 21.8 (q, C-3c′), 22.0 (q, C-3c), 22.5 (t, C-8), 25.7 [q, SiC(*C*$H_3)_3$], 27.5 (d, C-3b), 32.2 (t, C-4), 34.6 (t, C-7), 46.1 (t, C-9), 63.6 (d, C-6), 72.0 (d, C-5), 125.0 (s, C-3), 145.5 (d, C-3a), 163.6 (s) ppm. IR (KBr): ṽ = 3409 (m), 2958 (s), 2929 (s), 2858 (s), 1664 (s), 1622 (s), 1443 (s), 1425 (s), 1384 (m), 1361 (m), 1337 (m), 1306 (w), 1257 (s), 1208 (m), 1190 (m), 1126 (s), 1102 (s), 1054 (m), 1030 (m), 1006 (m), 985 (m), 928 (m), 900 (m), 881 (m), 864 (m), 837 (s), 777 (s), 733 (s), 681 (m), 670 (s), 563 (m) cm^{-1}. MS (80 eV, EI, 80 °C): *m*/*z* (%) = 323 (14) [$M^{+\cdot}$], 308 (5) [$M^+ - CH_3$], 266 (100) [$M^+ - C_4H_9$], 237 (10), 222 (80), 194 (12), 180 (68), 155 (15), 124 (38), 99 (10), 75 (25), 73 (25). HRMS (80 eV, 90 °C): calcd. 323.228058 (for $C_{18}H_{33}N_1O_2Si$ [M^+]), found 323.22838.

(3*Z*)-(5*R*,6*S*)-5-Hydroxy-3-(isobutylidene)azabicyclo[4.3.0]nonane (15): Under argon, $LiAlH_4$ (80 mg, 2.1 mmol, 3.75 equiv.) in dry Et_2O (10 mL) was cooled to 0 °C and treated with $AlCl_3$ (93 mg, 0.7 mmol, 1.25 equiv.) in dry Et_2O (2 mL). The color of the suspension turned from deep gray to light gray (grainy suspension).[29] The cooling bath was removed and the resultant mixture was stirred at room temp. for 1 h. The mixture was then cooled to 0 °C, and indolizidinone (*Z*)-**14a** (180 mg, 0.56 mmol) in dry Et_2O (2 mL) was added by syringe. The mixture was stirred overnight at ambient temperature. Workup started with the dropwise addition of H_2O (0.3 mL) to form a white precipitate of aluminum salts. After the mixture had been stirred for a further 15 min, aqueous KOH (0.3 mL, 2.5 M) was added and the precipitate coagulated. The colorless organic solution was decanted and the solid residue was extracted with Et_2O (40 mL). The organic layers were dried (Na_2SO_4) and the solvent was removed. The crude indolizidine **15** was purified by column chromatography on silica gel (MeOH/EtOAc, 1:4, TLC: MeOH/EtOAc, 1:3 R_f = 0.25−0.37). Yield: 86.5 mg (0.44 mmol, 79.1%) of indolizidine **15** as a clear, colorless oil. $[\alpha]_D^{20}$ = −23.0 (*c* = 1.45, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.87 [d, $^3J(H^{3c'},H^{3b})$ = 6.5 Hz, 3 H, 3c′-H], 0.94 [d, $^3J(H^{3c},H^{3b})$ = 6.5 Hz, 3 H, 3c-H], 2.05−1.45 (m, 5 H, 8o-,8u-,6u-,7u-,7o-H), 2.24−2.13 [ddd, $^2J(H^{9u},H^{9o})$ = 8.5, $^2J(H^{9u},H^{8o})$ = 8.5, $^2J(H^{9u},H^{8u})$ = 8.5 Hz, 1 H, 9u-H], 2.35−2.30 [d, $^2J(H^{2u},H^{2o})$ = 12.5 Hz, 1 H, 2u-H], 2.60−2.40 (m, 2 H, 4o-,3b-H), 3.05−2.95 [ddd, $^2J(H^{9o},H^{9u})$ = 8.5, $^2J(H^{9o},H^{8})$ = 8.5, $^2J(H^{9o},H^{8})$ = 2 Hz, 1 H, 9o-H], 3.20−3.00 (s, 1 H, OH), 3.35−3.25 [ddd, $^3J(H^{5o},H)$ = 13, $^3J(H^{5o},H)$ = 8.5, $^3J(H^{5o},H)$ = 4 Hz, 1 H, 5o-H], 3.75−3.67 [d, $^2J(H^{2o},H^{2u})$ = 12.5 Hz, 1 H, 2o-H], 5.08−5.00 [d, $^3J(H^{3a},H^{3b})$ = 8.5 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 21.1 (t, C-8), 23.1 (q, C-3c′), 23.5 (q, C-3c), 26.7 (d, C-3b), 27.9 (t, C-7), 43.7 (t, C-4), 51.8 (t, C-9), 53.8 (t, C-2), 70.0 (d, C-6), 72.5 (d, C-5), 129.8 (s, C-3), 133.9 (d, C-3a) ppm. IR ($CHCl_3$): ṽ = 3618 (m), 2961 (s), 2935 (m), 2870 (m), 2804 (m), 1465 (m), 1447 (m), 1378 (m9, 1215 (w), 1153 (w), 1127 (w), 1095 (w), 1059 (w), 1020

(w) cm^{-1}. MS (80 eV, EI, 80 °C): *m/z* (%) = 195 (37) [$M^{+\cdot}$], 180 (18) [$M^+ - CH_3$], 152 (96) [$M^+ - C_3H_7$], 134 (12), 111 (12), 108 (17), 98 (16), 82 (17), 70 (100), 55 (31). HRMS (80 eV, 30 °C): calcd. 195.162314 (for $C_{12}H_{21}N_1O_1$ [M^+]), found 195.16433.

(5*R*,6*S*)-5-*tert*-Butyldimethylsilyloxy-3-(diethoxyphosphonyl)azabicyclo[4.3.0]nonan-2-one (18) and (3*Z*)-(5*R*,6*S*)-5-*tert*-Butyldimethylsilyloxy-3-(isobutylidene)azabicyclo[4.3.0]nonan-2-one (*Z*-19a). β-Amidophosphonate 18: Reaction of indolizidinone **17** (630 mg, 2.6 mmol) by following the procedure as described for phosphonate **11**. Enolate formation: 50 min, enol phosphate−phosphonate migration: 40 min. Purification by column chromatography on silica gel (MeOH/EtOAc 1:9, R_f = 0.3). Yield: 0.73 g (1.92 mmol, 74%) of β-amidophosphonate **18** as a colorless oil. $[\alpha]_D^{20}$ = −15.2 (*c* = 1.38, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.05 [s, 9 H, $Si(CH_3)_3$], 1.05 (s, 3 H, 5-CH_3), 1.30−1.20 (m, 6 H, H-PO-CH_2-CH_3), 1.60−1.46 (m, 1 H, 7u-H), 1.90−1.60 (m, 2 H, 8o-, 8u-H), 2.00−1.90 (m, 1 H, 7o-H), 2.20−2.00 (m, 2 H, 4o-,4u-H), 2.95−2.76 [ddd, $^2J(H^{3o},P)$ = 26.5, $^3J(H^{3o},H^{4u})$ = 11, $^3J(H^{3o},H^{4o})$ = 8 Hz, 1 H, 3o-H], 3.50−3.30 (m, 3 H, 9o-,9u-,6u-H), 4.28−3.93 (m, 4 H, PO-CH_2) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 2.43 (q, Si−CH_3), 16.1, 16.1, 16.2, 16.3, 16.35 and 16.4 (multiple signals, no defined structure, O−CH_2-CH_3, 2 sets of doublets from quadruplets), 19.5 (q, C-5−CH_3), 22.1 (t, C-8), 27.3 (t, C-7), 38.9 [dt, $^2J(^{13}C,^{31}P)$ = 3.5 Hz, C-4], 40.8 [dd, $^1J(^{13}C,^{31}P)$ = 139 Hz, C-3], 46.7 (t, C-9), 61.8 [dt, $^2J(^{13}C,^{31}P)$ = 7 Hz, PO-CH_2], 63.3 [dt, $^2J(^{13}C,^{31}P)$ = 6 Hz, PO-CH_2], 66.3 (d, C-6), 72.8 [d, $^3J(^{13}C,^{31}P)$ = 13 Hz, C-5], 163.1 [dd, $^2J(^{13}C,^{31}P)$ = 5 Hz, C-1] ppm. IR ($CHCl_3$): ṽ = 2996 (s), 2884 (m), 1634 (s), 1456 (m), 1441 (m), 1385 (m), 1296 (m), 1284 (m), 1252 (s), 1215 (s), 1161 (s), 1123 (m), 1028 (s), 974 (m), 909 (s), 876 (m), 843 (s) cm^{-1}. MS (80 eV, EI, 85 °C): *m/z* (%) = 377 (2) [$M^{+\cdot}$], 362 (4) [$M^+ - CH_3$], 332 (2), 288 (8), 280 (3), 251 (1), 240 (5), 237 (3), 219 (3), 198 (2), 170 (1), 150 (100), 110 (5), 73 (8). HRMS (80 eV, 80 °C): calcd. 377.17874 (for $C_{16}H_{32}N_1O_5PSi$ [M^+]), found 377.17645.

Indolizidinone (*Z*)-19a: Reaction of indolizidinone **17** (1.14 g, 4.72 mmol) by following the one-pot procedure as described for indolizidinone **5**. After addition of the isobutyraldehyde **1a**: stirring for 3 h at −65 °C and at −78 °C overnight. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 2:1, R_f = 0.45). Yield: 0.6 g (2.03 mmol, 43%) of indolizidinone (*Z*)-**19a** as a colorless oil, *E*/*Z* = 1:6 by NMR analysis. $[\alpha]_D^{20}$ = −35.9 (*c* = 1.56, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.12 [s, 9 H, $Si(CH_3)_3$], 0.96−0.94 [d, $^3J(H^{3c'},H^{3b})$ = 3.5 Hz, 3 H, 3c′-H], 0.98−0.96 [d, $^3J(H^{3c},H^{3b})$ = 3.5 Hz, 3 H, 3c-H], 1.08 (s, 3 H, 5-CH_3), 2.00−1.50 (m, 4 H, 7o-,7u-,8o-,8u-H), 2.40−2.34 [d, $^2J(H^{4o},H^{4u})$ = 14.5 Hz, 1 H, 4o-H], 2.70−2.65 [dd, $^2J(H^{4u},H^{4o})$ = 14, $^3J(H^{4u},H^{3a})$ = 2 Hz, 1 H, 4u-H], 3.55−3.43 (m, 3 H, 9o-,9u-,6u-H), 3.95−3.83 (m, 1 H, 3b-H), 5.57−5.53 [dd, $^3J(H^{3a},H^{3b})$ = 9.5, $^3J(H^{3a},H^{4o})$ = 2 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 2.6 [q, $Si(CH_3)_3$], 20.3 (q, 5-Me), 22.3 (t, C-8), 22.8 (q, C-3c′), 22.9 (q, C-3c), 27.1 (d, C-3b), 27.2 (t, C-7), 45.6 (t, C-4), 49.3 (t, C-9), 67.4 (d, C-6), 72.7 (s, C-5), 124.3 (s, C-3), 150.5 (d, C-3a), 163.6 (s) ppm. IR ($CHCl_3$): ṽ = 3019 (s), 2968 (w), 2863 (w), 1651 (w), 1602 (w), 1522 (w), 1429 (w), 1223 (s), 1210 (s), 1158 (w), 1125 (w), 1017 / w), 929 (w), 844 (w) cm^{-1}. MS (80 eV, EI, 50 °C): *m/z* (%) = 295 (100) [$M^{+\cdot}$], 280 (14) [$M^+ - CH_3$], 252 (40) [$M^+ - C_3H_7$], 224 (15), 223 (14), 183 (20), 155 (9), 143 (7), 142 (6), 96 (9), 81 (13), 75 (17), 73 (54), 70 (27). HRMS (80 eV, 90 °C): calcd. 295.19676 (for $C_{16}H_{29}N_1O_2Si$ [M^+]), found 295.19488.

(3*Z*)-(5*R*,6*S*)-3-Isobutylidene-5-methylazabicyclo[4.3.0]nonan-5-ol (20) (5-*epi*-pumiliotoxin 209 F): Reaction of indolizidinone (*Z*)-**19a** (342 mg, 1.15 mmol) and $LiAlH_4/AlCl_3$ (7.5:2.5 equiv.) by following the procedure as described for indolizidine **15**. Purification by column chromatography on silica gel (MeOH/EtOAc, 1:9, TLC: MeOH/EtOAc, 1:3 R_f = 0.25−0.37). Yield: 192.6 mg (0.92 mmol, 79.6%) of 5-*epi*-pumiliotoxin 209 F (**20**) as colorless crystals, m.p. 73−77 °C. $[\alpha]_D^{20}$ = −20.6 (*c* = 1.38, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.87−0.85 [d, $^3J(H^{3c'},H^{3b})$ = 6.5 Hz, 3 H, 3c′-H], 0.92−0.90 [d, $^3J(H^{3c},H^{3b})$ = 6.5 Hz, 3 H, 3c-H], 1.08 (s, 3 H, 5-CH_3), 1.85−1.50 (m, 5 H, 8o-,8u-,7o-,7u-,6u-H), 2.20−2.00 (m, 3 H, 9u-,4o-,4u-H), 2.37−2.30 [d, $^2J(H^{2u},H^{2o})$ = 12.5 Hz, 1 H, 2u-H], 2.58−2.42 (m, 1 H, 3b-H), 3.06−2.97 [ddd, $^2J(H^{9o},H^{9u})$ = 8.5, $^3J(H^{9o},H^{8u})$ = 8.5, $^3J(H^{9o},H^{8o})$ = 2 Hz, 1 H, 9o-H], 3.70−3.65 [d, $^2J(H^{2o},H^{2u})$ = 12.5 Hz, 1 H, 2o-H], 5.02−4.95 [d, $^2J(H^{3a},H^{3b})$ = 9.5 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 20.4 (d, C-3b), 20.9 (t, C-8), 23.3 (q, C-3c′), 23.4 (q, C-3c), 23.8 (t, C-7), 26.7 (q, 5-CH_3), 50.4 (t, C-4), 52.8 (t, C-9), 54.7 (t, C-2), 71.3 (s, C-5), 72.8 (d, C-6), 130.2 (s, C-3), 134.0 (d, C-3a) ppm. IR ($CHCl_3$): ṽ = 3019 (m), 2961 (m), 2880 (w), 2795 (w), 1637 (w), 1519 (w), 1464 (m), 1429 (w), 1382 (w), 1216 (s, C−O), 1149 (w), 1106 (m), 912 (s) cm^{-1}. MS (80 eV, EI, 30 °C): *m/z* (%) = 209 (42) [$M^{+\cdot}$], 194 (18) [$M^+ - CH_3$], 176 (10), 166 (99) [$M^+ - C_3H_7$], 148 (11), 136 (6), 108 (10), 96 (11), 84 (35), 70 (100), 55 (12). HRMS (80 eV, 30 °C): calcd. 209.177965 (for $C_{13}H_{23}N_1O_1$ [M^+]), found 209.17488.

***(5*S*,6*S*)-3-(Diethoxyphosphonyl)-5-methyl-5-(trimethylsilyloxy)-azabicyclo[4.3.0]nonan-2-one (22):** Reaction of indolizidinone **21** (350 mg, 1.45 mmol) in THF (100 mL) by following the procedure as described for phosphonate **11**. Enolate formation: 50 min. Purification by column chromatography on silica gel (MeOH/EtOAc 1:9, R_f = 0.25). Yield: 533.7 mg (1.41 mmol, 97.5%) of β-amidophosphonate **22** as a colorless oil. $[\alpha]_D^{20}$ = −10.7 (*c* = 1.58, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.02 [s, 9 H, $Si(CH_3)_3$], 1.30−1.15 (m, 9 H, 5-CH_3, $POCH_2-CH_3$), 1.85−1.45 (m, 4 H, 4′-,7′-,8-,8′-H), 2.05−1.93 (m, 2 H, 7-,4-H), 3.02−2.85 [ddd, $^2J(H^{3o},^{31}P)$ = 25.5, $^3J(H^{3o},H^{4u})$ = 10, $^3J(H^{3o},H^{4o})$ = 8 Hz, 1 H, 3o-H], 3.45−3.20 (m, 3 H, 9o-,9u-,6u-H), 4.23−3.98 (m, 4 H, PO-CH_2) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 2.00 [q, $Si(CH_3)_3$], 16.10 [qd, $^3J(^{13}C,^{31}P)$ = 6 Hz, $POCH_2-CH_3$], 16.24 [qd, $^3J(^{13}C,^{31}P)$ = 6 Hz, $POCH_2-CH_3$], 22.0 (t, C-8), 25.5 (q, 5-CH_3), 26.3 (t, C-7), 37.3 [dt, $^2J(^{13}C,^{31}P)$ = 3.5 Hz, C-4], 39.0 [dd, $^1J(^{13}C,^{31}P)$ = 139 Hz, C-3], 46.5 (t, C-9), 61.5 [dt, $^2J(^{13}C,^{31}P)$ = 6 Hz, PO-CH_2], 63.1 [dt, $^2J(^{13}C,^{31}P)$ = 7 Hz, PO-CH_2], 66.9 (d, C-6), 70.5 [d, $^3J(^{13}C,^{31}P)$ = 9.5 Hz, C-5], 163.9 [d, $^2J(^{13}C,^{31}P)$ = 4.5 Hz, C-1] ppm. IR ($CHCl_3$): ṽ = 2980 (s), 2953 (s), 2909 (m), 2881 (m), 1633 (s, C=O), 1460 (s), 1393 (m), 1378 /m), 1364 (m), 1340 (w), 1319 (w), 1295 (m), 1253 (s, C−O), 1217 (s, C−O), 1151 (m), 1130 (m), 1050 (s), 1028 (s), 979 (s), 969 (s) cm^{-1}. MS (80 eV, EI, 50 °C): *m/z* (%) = 377 (22) [$M^{+\cdot}$], 362 (10) [$M^+ - CH_3$], 288 (38), 286 (22), 241 (15), 240 (9), 219 (6), 198 (7), 170 (8), 153 (20), 150 (33), 126 (79), 109 (22), 98 (88), 80 (100), 75 (20), 73 (32), 70 (34). HRMS (80 eV, 40 °C): calcd. 377.17874 (for $C_{16}H_{32}N_1O_5PSi$ [M^+]), found 377.17682.

(5*S*,6*S*)-3-Diethoxyphosphonyl-5-hydroxy-5-methylazabicyclo[4.3.0]-nonan-2-one (24) and (3*Z*)-(5*S*,6*S*)-5-Hydroxy-3-isobutylidene-5-methylazabicyclo[4.3.0]nonan-2-one (*Z*)-26a: The amido phosphonate **22** (433.0 mg, 1.15 mmol) in HCl/MeOH (10 mL, 1 M) was stirred at room temp. for 1 h. The solvent was then removed under reduced pressure. The residue was dissolved in CH_2Cl_2 and passed through a short pad of silica gel, eluting with MeOH/EtOAc (1:3). The solvent was removed to give hydroxy phosphonate **24** (351 mg, 1.15 mmol, 100%) as a clear oil. In small-scale experiments, the crude hydroxy phosphonate **24** was dried by stirring in THF in the presence of molecular sieves (4 Å). The resulting material was used

without any further purification. ^{1}H NMR (270 MHz, $CDCl_3$, mixture of two C3 diastereomers, ratio: 1:3, marked with C′ and C): δ = 1.30−1.40 (m, 9 H, 5-CH_3 and $POCH_2-CH_3$), 1.60−2.40 (m, 6 H, 4-,7-,8-H), 3.05 and 3.40 (m, 2 × 3-H), 3.40−3.60 (m, 3 H, 9o-,9u-,6-H), 4.00−4.40 (m, 4 H, PO-CH_2) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 16.1, 16.2, 16.3, and 16.4 (q, 2 × $POCH_2-CH_3$ and 2 × $POCH_2'-CH_3'$), 21.8 (t, C-8′), 22.2 (t, C-8), 25.6 (q, 5-CH_3), 26.1 (t, C-7), 26.2 (q, 5-CH_3'), 26.3 (t, C-7′), 36.3 [dt, $^2J(^{13}C,^{31}P)$ = 3.5 Hz, C-4′], 36.6 [dt, $^2J(^{13}C,^{31}P)$ = 3 Hz, C-4], 38.3 [dd, $^1J(^{13}C,^{31}P)$ = 137.5 Hz, C-3], 39.3 [dd, $^1J(^{13}C,^{31}P)$ = 135.5 Hz, C-3′], 46.5 (t, C-9′), 47.7 (t, C-9), 62.2 [dt, $^2J(^{13}C,^{31}P)$ = 7 Hz, $POCH_2'$], 63.9 [dt, $^2J(^{13}C,^{31}P)$ = 7 Hz, $POCH_2$], 63.7 [dt, $^2J(^{13}C,^{31}P)$ = 7 Hz, $POCH_2$], 64.8 [dt, $^2J(^{13}C,^{31}P)$ = 6 Hz, $POCH_2'$], 66.8 (d, C-6), 67.0 (d, C-6′), 67.3 [dd, $^3J(^{13}C,^{31}P)$ = 8.5 Hz, C5 and C-5′], 166.3 (s, C=O). MS (80 eV, EI, 120 °C): *m/z* (%) = 305 (14) [$M^{+\cdot}$], 288 (6) [M^+ − OH], 265 (5), 260 (19), 234 (5), 222 (6), 208 (5), 195 (5), 168 (5), 155 (12), 151 (100), 136 (18), 127 (8), 111 (16), 99 (13), 96 (9), 83 (24), 70 (47). HRMS (80 eV, 120 °C): calcd. 305.139212 (for $C_{13}H_{24}N_1O_5P$ [M^+]), found 305.13687.

Indolizidinone (*Z*)-26a: Under argon, LDA (136 μL, 0.27 mmol, 2.5 equiv., 2 M in THF) was diluted with dry THF (2 mL) and cooled to −78 °C. Hydroxy phosphonate **24** (32.5 mg, 0.11 mmol) in dry THF (2 mL) was added over a period of 5 min. The mixture was stirred at −78 °C for 30 min, isobutyraldehyde **1a** (40 μL, 0.4 mmol, 4 equiv.) was then added, and stirring was continued for another 2.5 h. The cooling bath was removed and the excess of LDA was quenched with saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL), the combined organic layers were dried (Na_2SO_4), and the solvent was removed to yield crude indolizidinone (*Z*)-**26a** (10 mg, 0.045 mmol, 41%) as a colorless oil. The *E*/*Z* ratio was about 1:10 by ^{1}H NMR analysis. $[\alpha]_D^{20}$ = −68.7 (*c* = 0.91, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.00−0.95 (m, 6 H, 3c-,3c′-H), 1.24 (s, 3 H, 5-CH_3), 2.0−1.70 (m, 4 H, 8o-,8u-,7o-,7u-H), 2.42−2.37 [d, $^2J(H^{4o},H^{4u})$ = 14.5 Hz, 1 H, 4o-H], 2.65−2.60 [dd, $^2J(H^{4u},H^{4o})$ = 14.5, $^4J(H^{4u},H^{3a})$ = 2.5 Hz, 1 H, 4u-H], 3.43−3.37 [dd, $^3J(H^{6u},H^{7o})$ = 9.5, $^3J(H^{6u},H^{7u})$ = 5.5 Hz, 1 H, 6u-H], 3.55−3.45 (m, 2 H, 9o-,9u-H), 3.92−3.80 (m, 1 H, 3b-H), 5.65−5.60 [dd, $^3J(H^{3a},H^{3b})$ = 9.5, $^4J(H^{3a},H^{4u})$ = 2 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 22.1 (t, C-8), 22.7 (q, C-3c′), 22.9 (q, C-3c), 25.2 (q, 5-CH_3), 26.1 (t, C-7), 27.5 (d, C-3b), 45.5 (t, C-4), 46.9 (t, C-9), 66.5 (d, C-6), 67.7 (s, C-5), 122.3 (s, C-3), 152.8 (d, C-3a), 163.7 (s) ppm. IR ($CHCl_3$): ṽ = 2977 (m), 2932 (w), 2899 (w), 2866 (w), 1729 (w), 1653 (m), 1604 (m), 1468 (m), 1451 (m), 1437 (m), 1381 (m), 1295 (w), 1252 (w), 1099 (w), 919 (s), 899 (s), 751 (s), 718 (s), 651 (s) cm^{-1}.

(3*Z*)-(5*S*,6*S*)-5-Hydroxy-3-[(*R*)-2-methylhexylidene]-5-methylazabicyclo[4.3.0]nonan-2-one (*Z*)-26b, (3*Z*)-(5*S*,6*S*)-5-Hydroxy-3-[(*S*)-2-methylhexylidene]-5-methylazabicyclo[4.3.0]nonan-2-one (*Z*)-27b, (3*E*)-(5*S*,6*S*)-5-Hydroxy-3-[(*R*)-2-methylhexylidene]-5-methylazabicyclo[4.3.0]nonan-2-one (*E*)-26b, and (3*E*)-(5*S*,6*S*)-5-Hydroxy-3-[(*S*)-2-methylhexylidene]-5-methylazabicyclo[4.3.0]nonan-2-one (*E*)-27b: Reaction of hydroxy phosphonate **24** (351 mg, 1.15 mmol) by following the procedure as described for indolizidinone (*Z*)-**26a**, with LDA (1.15 mL, 2.3 mmol, 2.1 equiv., 2 M in THF) in dry THF (15 mL) and (*R*)-2-methylhexanal **1b** (648 μL, 4.5 mmol, 4 equiv.). After addition of the aldehyde: stirring for 4 h at −78 °C. Purification by column chromatography on silica gel (MeOH/EtOAc 1:9, R_f = 0.45). Separation of the diastereomers by preparative HPLC (10% *i*PrOH in *n*-hexane, 32 × 110 mm, Nucleosil 50−5, UV 254 nm, flow 64 mL/min. Yields: 56.3 mg (0.21 mmol, 18.4%) of (*Z*)-**27b**, retention time 2.7 min, 97.9 mg (0.37 mmol, 32.1%) of (*Z*)-**26b**, retention time 3.3 min, 14.2 mg (0.05 mmol, 4.7%) of (*E*)-**26b**, retention time 4.5 min; 16.2 mg (0.6 mmol, 5.3%) of (*E*)-**27b**, retention time 5.8 min.

Data for (*Z*)-Alkylideneindolizidinone (*Z*)-26b: $[\alpha]_D^{20}$ = −67.6 (*c* = 1.64, $CHCl_3$). M.p. 135−140 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.89−0.80 [t, $^3J(H^{3g},H^{3f})$ = 6.5 Hz, 3 H, 3g-H], 0.98−0.93 [d, $^3J(H^{3c},H^{3b})$ = 6.5 Hz, 3 H, 3c-H], 1.36−1.18 (m, 6 H, 3d-,3e-,3f-H), 2.04−1.65 (m, 4 H, 7o-,7u-,8o-,8u-H), 2.47−2.38 [d, $^2J(H^{4o},H^{4u})$ = 15 Hz, 1 H, 4o-H], 2.73−2.63 [dd, $^2J(H^{4u},H^{4o})$ = 14.5, $^3J(H^{4u},H^{3a})$ = 2 Hz, 1 H, 4u-H], 3.47−3.40 [dd, $^3J(H^{6u},H^{7o})$ = 9.5, $^3J(H^{6u},H^{7u})$ = 5.5 Hz, 1 H, 6u-H], 3.58−3.51 [dd, $^2J(H^{9o,9u},H^9)$ = 8.5, $^3J(H^{9o,9u},H^8)$ = 5 Hz, 2 H, 9o-,9u-H], 3.87−3.72 (m, 1 H, 3b-H), 5.64−5.60 [dd, $^3J(H^{3a},H^{3b})$ = 10, $^4J(H^{3a},H^4)$ = 2 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 14.08 (q, C-3 g), 20.8 (q, C-3c), 22.1 (t, C-8), 22.9 (t, C-3e), 25.2 (q, 5-CH_3), 26.1 (t, C-7), 29.6 (t, C-3d), 32.5 (d, C-3b), 37.2 (t, C-3c), 45.5 (t, C-4), 47.0 (t, C-9), 66.5 (d, C-6), 67.7 (s, C-5), 122.8 (s, C-3), 152.4 (d, C-3a), 163.7 (s, C=O) ppm. IR ($CHCl_3$): ṽ = 3019 (s), 1650 (w), 1600 (w), 1522 (w), 1472 (w), 1425 (w), 1215 (s), 1031 (w), 929 (w) cm^{-1}. MS (80 eV, EI, 50 °C): *m/z* (%) = 265 (73) [$M^{+\cdot}$], 250 (3) [M^+ − CH_3], 236 (10) [M^+ − C_2H_5], 222 (100) [M^+ − C_3H_7], 208 (6) [M^+ -C_4H_9], 180 (8), 169 (27), 153 (19), 126 (72), 109 (15), 108 (15), 98 (66), 80 (61), 70 (24). HRMS (80 eV, 50 °C): calcd. 265.204179 (for $C_{16}H_{27}N_1O_2$ [M^+]), found 265.20523.

Data for (*Z*)-Alkylideneindolizidinone (*Z*)-27b: $[\alpha]_D^{20}$ = + 55.0 (*c* = 1.79, $CHCl_3$). M.p. 85 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.85−0.79 [t, $^3J(H^{3g},H^{3f})$ = 6.5 Hz, 3 H, 3g-H], 0.95−0.90 [d, $^3J(H^{3c},H^{3b})$ = 6.5 Hz, 3 H, 3c-H], 1.30−1.15 (m, 6 H, 3d-,3e-,3f-H), 2.04−1.65 (m, 4 H, 7o-,7u-,8o-,8u-H), 2.43−2.38 [d, $^2J(H^{4o},H^{4u})$ = 15 Hz, 1 H, 4o-H], 2.65−2.60 [d, $^2J(H^{4u},H^{4o})$ = 14.5 Hz, 1 H, 4u-H], 3.43−3.35 [dd, $^3J(H^{6u},H^{7o})$ = 9.5, $^3J(H^{6u},H^{7u})$ = 5.5 Hz, 1 H, 6u-H], 3.53−3.45 (m, 2 H, 9o-,9u-H), 3.80−3.65 (m, 1 H, 3b-H), 5.60−5.54 [d, $^3J(H^{3a},H^{3b})$ = 10 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 13.9 (q, C-3 g), 20.4 (q, C-3c), 22.0 (t, C-8), 22.8 (t, C-3e), 25.1 (q, 5-CH_3), 26.0 (t, C-7), 29.6 (t, C-3d), 32.5 (d, C-3b), 37.2 (t, C-3c), 45.4 (t, C-4), 47.0 (t, C-9), 66.5 (d, C-6), 67.5 (s, C-5), 123.0 (s, C-3), 151.9 (d, C-3a), 163.7 (s, C=O) ppm. IR ($CHCl_3$): ṽ = 3019 (s), 2977 (m), 2929 (m), 1653 (m), 1604 (m), 1523 (w), 1450 (m), 1437 (m), 1426 (m), 1294 (m), 1265 (s), 1215 (s), 1046 (m), 929 (w) cm^{-1}. MS (80 eV, EI, 50 °C): *m/z* (%) = 265 (59) [$M^{+\cdot}$], 250 (3) [M^+ − CH_3], 236 (7) [M^+ − C_2H_5], 222 (100) [M^+ − C_3H_7], 208 (6) [M^+ − C_4H_9], 180 (4), 169 (29), 81 (7), 70 (22). HRMS (80 eV, 50 °C): calcd. 265.204179 (for $C_{16}H_{27}N_1O_2$ [M^+]), found 265.20733.

Data for (*E*)-Alkylideneindolizidinone (*E*)-26b: $[\alpha]_D^{20}$ = −65.1 (*c* = 1.40, $CHCl_3$). M.p. 150−153 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88−0.80 [t, $^3J(H^{3g},H^{3f})$ = 6.5 Hz, 3 H, 3g-H], 0.98−0.92 [d, $^3J(H^{3c},H^{3b})$ = 6.5 Hz, 3 H, 3c-H], 1.40−1.20 (m, 6 H, 3d-,3e-,3f-H), 2.04−1.70 (m, 4 H, 7o-,7u-,8o-,8u-H), 2.48−2.30 (m, 1 H, 3b-H), 2.43−2.38 [d, $^2J(H^{4u},H^{4u})$ = 16, $^4J(H^{4u},H^{3a})$ = 2.5 Hz, 1 H, 4u-H], 2.78−2.70 [d, $^2J(H^{4o},H^{4o})$ = 16 Hz, 1 H, 4o-H], 3.63−3.40 (m, 3 H, 9o-,9u-,6u-H), 6.81−6.73 [dd, $^3J(H^{3a},H^{3b})$ = 10, $^4J(H^{3a},H^{4u})$ = 2 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 14.0 (q, C-3g), 19.7 (q, C-3c), 22.2 (t, C-8), 22.8 (t, C-3e), 25.3 (q, 5-CH_3), 26.4 (t, C-7), 29.6 (t, C-3d), 32.7 (d, C-3b), 36.5 (t, C-3c), 39.5 (t, C-4), 46.1 (t, C-9), 65.7 (d, C-6), 67.7 (s, C-5), 124.3 (s, C-3), 147.3 (d, C-3a), 163.7 (s, C=O) ppm. IR ($CHCl_3$): ṽ = 3019 (s), 2976 (m), 2895 (w), 1601 (w), 1521 (w), 1476 (w), 1420 (w), 1215 (s), 1046 (m), 929 (w) cm^{-1}. MS (80 eV, EI, 80 °C): *m/z* (%) = 265 (53) [$M^{+\cdot}$], 236 (7) [M^+ − C_2H_5], 222 (100) [M^+ − C_3H_7], 208 (6) [M^+ − C_4H_9], 194 (5), 180 (20), 169 (17), 138 (15),

126 (8), 92 (13), 86 (23), 70 (88). HRMS (80 eV, 80 °C): calcd. 265.204179 (for $C_{16}H_{27}N_1O_2$ [M^+]), found 265.20654.

Data for (*E*)-Alkylideneindolizidinone (*E*)-27b: $[\alpha]_D^{20}$ = +38.1 (*c* = 1.63, $CHCl_3$). M.p. 105−110 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.88−0.80 [t, $^3J(H^{3g},H^{3f})$ = 6.5 Hz, 3 H, 3g-H], 1.01−0.97 [d, $^3J(H^{3c},H^{3b})$ = 6.5 Hz, 3 H, 3c-H], 1.40−1.10 (m, 6 H, 3d-,3e-,3f-H), 2.05−1.75 (m, 4 H, 7o-,7u-,8o-,8u-H), 2.43−2.28 (m, 1 H, 3b-H), 2.39−2.30 [d, $^2J(H^{4u},H^{4u})$ = 16, $^4J(H^{4u},H^{3a})$ = 2 Hz, 1 H, 4u-H], 2.79−2.70 [d, $^2J(H^{4o},H^{4o})$ = 16 Hz, 1 H, 4o-H], 3.62−3.42 (m, 3 H, 9o-,9u-,6u-H), 6.80−6.70 [ddd, $^3J(H^{3a},H^{3b})$ = 10, $^4J(H^{3a},H^{4u})$ = 3, $^4J(H^{3a},H^4)$ = 1.5 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 14.0 (q, C-3g), 20.3 (q, C-3c), 22.2 (t, C-8), 22.7 (t, C-3e), 25.3 (q, 5-CH_3), 26.4 (t, C-7), 29.7 (t, C-3d), 32.8 (d, C-3b), 36.5 (t, C-3c), 39.7 (t, C-4), 46.2 (t, C-9), 65.7 (d, C-6), 67.7 (s, C-5), 124.3 (s, C-3), 147.3 (d, C-3a), 163.8 (s, C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3390 (w), 3019 (s), 2976 (m), 2930 (m), 1658 (m), 1600 (m), 1522 (w), 1450 (m), 1439 (m), 1386 (w), 1296 (w), 1215 (s), 1046 (m), 929 (w) cm^{-1}. MS (80 eV, EI, 115 °C): *m*/*z* (%) = 265 (35) [$M^{+\cdot}$], 222 (100) [$M^+ - C_3H_7$], 208 (4) [$M^+ - C_4H_9$], 180 (20), 152 (3), 70 (30). HRMS (80 eV, 100 °C): calcd. 265.204179 (for $C_{16}H_{27}N_1O_2$ [M^+]), found 265.20822.

(3*Z*)-(5*S*,6*S*)-3-[(*R*)-2-Methylhexylidene]-5-hydroxy-5-methylazabicyclo[4.3.0]nonane (28) − Pumiliotoxin 251 D − and (3*Z*)-(5*S*,6*S*)-5-Hydroxy-3-[(*R*)-2-methylhexylidene]-5-methylazabicyclo[4.3.0]-nonane Hydrochloride (29). Pumiliotoxin 251 D ·HCl: Reaction of indolizidinone (*Z*)-**26b** (36.6 mg, 0.14 mmol) and $LiAlH_4/AlCl_3$ (7.5:2.5 equiv.) by following the procedure as described for indolizidine **15**. Purification by column chromatography on silica gel (MeOH/EtOAc 1:9, TLC: MeOH/EtOAc, 1:3 R_f = 0.05−0.15). Purification by preparative HPLC with 10% *i*PrOH in hexane (4 × 250 mm, Nucleosil 50−5, UV = 210 nm, flow 2 mL/min).[30] Yield: 19.7 mg (0.08 mmol, 56.8%) of **26**.

(+)-Pumiliotoxin 251 D Hydrochloride (29): The pumiliotoxin 251 D **28** (19.7 mg, 0.08 mmol) was dissolved in HCl/MeOH (4 mL, 1 M). The solvent was removed to give the pure hydrochloride **29** (21.8 mg, 0.076 mmol, 97%), which was recrystallized (CH_2Cl_2/EtOAc) to provide crystals appropriate for X-ray analysis.

Data for Pumiliotoxin 251 D (28): $[\alpha]_D^{20}$ = −8.5 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.87−0.80 [t, $^3J(H^{3g},H^{3f})$ = 6.5 Hz, 3 H, 3g-H], 0.96−0.93 [d, $^3J(H^{3c},H^{3b})$ = 6.5 Hz, 3 H, 3c-H], 1.11 (s, 3 H, 5-CH_3), 1.30−1.10 (m, 6 H, 3d-,3e-,3f-H), 1.78−1.60 (m, 4 H, 7o-,7u-,8o-,8u-H), 1.99−1.92 (m, 1 H, 6u-H), 2.12−2.08 (s, 2 H, 4o-,4u-H), 2.25−2.15 (m, 1 H, 9u-H), 2.35−2.29 [d, $^2J(H^{2u},H^{9o})$ = 12 Hz, 1 H, 2u-H], 2.43−2.40 (m, 1 H, 3b-H), 2.65 (s, 1 H, OH), 3.07−3.00 (m, 1 H, 9o-H), 3.78−3.73 [d, $^2J(H^{2o},H^{2u})$ = 12 Hz, 1 H, 2o-H], 5.04−4.97 [d, $^3J(H^{3a},H^{3b})$ = 9.5 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 14.1 (q, C-3 g), 21.0 (t, C-3f), 21.6 (q, C-3c), 22.8 (t, C-3e), 23.2 (t, C-3d), 24.2 (q, 5-CH_3), 29.9 (t, C-8), 32.0 (d, C-3b), 37.4 (t, C-7), 48.8 (t, C-4), 53.2 (t, C-9), 54.5 (t, C-2), 68.3 (s, C-5), 71.7 (d, C-6), 129.8 (s, C-3), 134.6 (d, C-3a) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2959 (m), 2929 (m), 2871 (w), 2857 (w), 2792 (w), 1794 (w), 1466 (m), 1382 (m), 1310 (w) cm^{-1}. MS (80 eV, EI, 30 °C): *m*/*z* (%) = 251 (26) [$M^{+\cdot}$], 236 (5) [$M^+ - CH_3$], 208 (17) [$M^+ - C_3H_7$], 206 (12), 194 (20) [$M^+ - C_4H_9$], 176 (5), 166 (100), 148 (7), 137 (9), 123 (9), 112 (12), 84 (18), 70 (76). HRMS (80 eV, 30 °C): calcd. 251.224915 (for $C_{16}H_{29}N_1O_1$ [M^+]), found 251.22622.

Data for Pumiliotoxin 251 D ·HCl (29): $[\alpha]_D^{20}$ = +28.0 (*c* = 1.09, MeOH; +28.0, *c* = 0.62, MeOH, ref.[8b]). M.p. 203−205 °C (205−206 °C ref.[8b]; 200−201 °C ref.[7a]). ^{1}H NMR (270 MHz, CD_3OD): δ = 0.91−0.84 [t, $^3J(H^{3g},H^{3f})$ = 6.5 Hz, 3 H, 3g-H], 1.05−1.01 [d, $^3J(H^{3c},H^{3b})$ = 5.5 Hz, 3 H, 3c-H], 1.28 (s, 3 H, 5-CH_3), 1.40−1.20 (m, 6 H, 3d-,3e-,3f-H), 2.20−1.95 (m, 6 H, 6u-,9u-,7o-,7u-,8o-,8u-H), 2.50−2.30 (m, 2 H, 4o-,4u-H), 3.20−3.05 (m, 1 H, 3b-H), 3.34 (s, 1 H, NH), 3.45−3.39 [d, $^2J(H^{2u},H^{2o})$ = 11 Hz, 1 H, 2u-H], 3.64−3.52 (m, 1 H, 9o-H), 4.42−4.33 [d, $^2J(H^{2o},H^{2u})$ = 13 Hz, 1 H, 2o-H], 5.35−5.28 [d, $^3J(H^{3a},H^{3b})$ = 9.5 Hz, 1 H, 3a-H] ppm. ^{13}C NMR (67.9 MHz, CD_3OD): δ = 14.7 (q, C-3 g), 20.8 (t, C-3f), 21.7 (q, C-3c), 23.0 (t, C-3e), 24.1 (t, C-3d), 26.3 (q, 5-CH_3), 31.0 (t, C-8), 33.7 (d, C-3b), 38.6 (t, C-7), 47.7 (t, C-4), 52.6 (t, C-9), 54.3 (t, C-2), 68.9 (s, C-5), 74.1 (d, C-6), 125.7 (s, C-3), 140.9 (d, 3a). For further data see ref. 3, 7 and 8.

Crystal Data of Pumiliotoxin 251 D Hydrochloride (29): Crystal data for pumiliotoxin 251 D hydrochloride (**29**:) colorless, transparent needles from ethyl acetate/*n*-hexane at room temperature. $C_{16}H_{30}ClNO$ (*M*r = 287.86); crystal dimensions 1.50 × 0.06 × 0.05 mm; monoclinic; $P2_1$, *a* = 10.2863(16), *b* = 6.9189(13), *c* = 11.959(2) Å, *Z* = 2, *V* = 842.9(3) Å^3, $\rho_{calcd.}$ = 1.134 g/cm^{-3}, *T* = 146 K, 2Θ max = 62°; of the 11,029 reflections measured, were 4707 independent reflections (R_{int} = 0.0880, ω*R* = 0.1092, and *S* = 0.973); Siemens−SMART diffractometer, Mo-K_α radiation (λ = 0.71073 Å). The structure was determined by direct methods with the program SHELXS. The H atoms were taken from a difference Fourier synthesis and were refined with isotropic thermal parameters. The non-H atoms were refined with anisotropic thermal parameters. The structure was refined on *F* values with the weighting scheme: $w(F) = 4{\cdot}F^2/[\sigma^2(F^2) + (0.03{\cdot}F^2)^2]$. The final difference density was between −0.278 and +0.386 e/A^3.
CCDC-172939 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

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[29] The quality of the $LiAlH_4$ was crucial for a successful reduction, because the exact molar ratio of $LiAlH_4$: $AlCl_3$ (3:1) must be maintained. If, after the addition of $AlCl_3$, no grainy suspension but a sticky precipitate was formed (no stirring possible), the reduction failed.

[30] The HPLC behavior of PTX 251 D **28** strongly depends on the injected concentration, the product was purified considering its tendency of a decreasing retention time when the column was overloaded.

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