Synthesis of the Bicyclic Core of Pumiliotoxins[‡]

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

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The bicyclic core of the pumiliotoxins was synthesized in nine to eleven steps starting from L-(–)-proline. This chiral pool starting material was initially converted into an optically active 2-vinylpyrrolidine by standard operations. The first key step allowed the generation of a nine-membered ring lactam by means of a zwitterionic aza-Claisen rearrangement. The 1,4 chirality transfer was found to be low, but the double bond of the azoninone was generated with an exclusive *trans* configuration in a planar-*S* arrangement. The mixture of diastereomers thus obtained was immediately epoxidized; the planar chiral information could be completely used to build up new stereogenic centers. Subsequent ring closure under hydrogenolytic conditions resulted in the formation of the bicyclic core with a bridgehead of defined configuration. The hydroxyl group of that material could be protected as a TBS ether, or alternatively a sequence of a Swern oxidation and subsequent methyl Grignard addition gave the complete bicyclic framework with low C8 diastereoselectivity.

Introduction

A number of total syntheses of pumiliotoxins have been developed since the isolation, the structure determination, and first investigations of some interesting biologically properties by Daly opened the goal to this class of alkaloids.[1] Since the natural source of these alkaloids is limited, synthetic approaches have to provide sufficient material for extensive tests. Convergent syntheses seem to be the method of choice, because slight modifications of a sequence can potentially allow a variety of important target molecules to be produced.

Analysis of the structure of the pumiliotoxins shows most compounds characterized by the bicyclic indolizidine system, with some stereogenic centers and an exocyclic trisubstituted double bond of defined configuration. A retrosynthetic cut through the double bond splits the skeleton into a side chain (aldehyde) and a bicyclic 5- and 7-indolizidinone core. The 7-indolizidinone unit has served as key intermediate in several allopumiliotoxin syntheses (R = *n*Bu: allopumiliotoxin 267 A, Figure 1).[2]

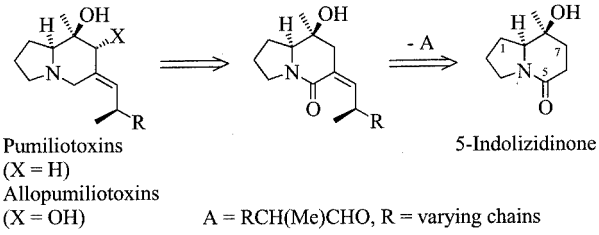

Figure 1. Retrosynthetic analyses of the pumiliotoxins

For the synthesis of pumiliotoxin 251 D (R = *n*Bu), several preparations of optically pure 5-indolizidinone precursors have been described in the literature (Figure 2). The shortest sequences have been published by Barrett[3] and by Ding,[4] by addition of C3 building blocks to the pyrrolidinyl ketone derived in four to six steps from L-proline. While Barrett introduced a titanium homoenolate, Ding succeeded in adding 3-metalated esters of propiolic acid. The synthesis of the bicyclic core was always completed by two further steps (seven to nine steps overall). However, both sequences solely allow the synthesis of the natural series. Martin started from L-pyroglutamate.[5] The key step in building up the target was described as a vinylogous Mannich reaction between the furan unit and the 2-methoxypyrrolidine in the presence of a Lewis acid. Finally, the stereodirecting hydroxymethyl group of the five-membered ring was removed by Raney Ni-mediated reduction. The bicyclic

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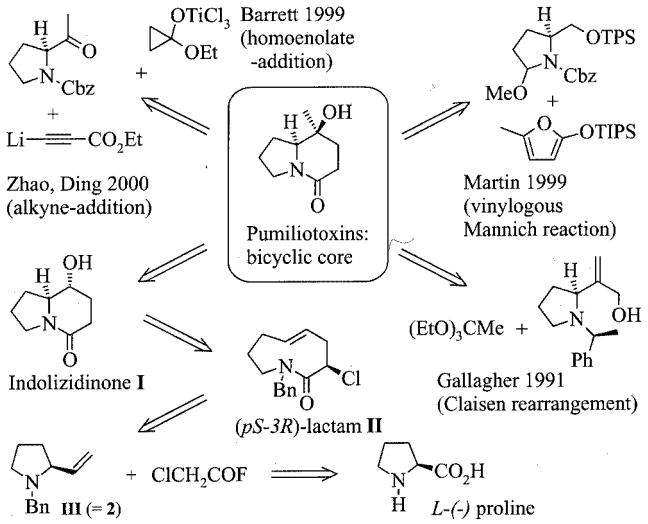


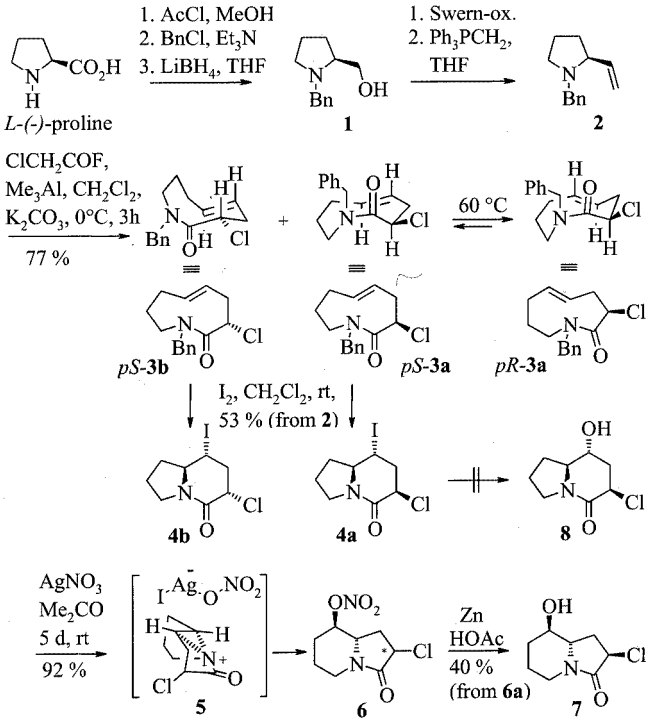
Figure 2. Retrosynthetic analyses of the pumiliotoxin bicyclic core

core (natural series) was generated in nine steps overall. Gallagher[6] described a reasonably flexible route to synthesize the 5-indolizidinone. The pyrrolidine ring was formed by a Pd-mediated intramolecular amino metallation, followed by CO insertion and methanolysis. The enantiomers were separated with the aid of a chiral phenylethylamine substituent. After generation of the allyl alcohol, the missing C2 unit was introduced by means of a Johnson orthoester rearrangement and, after lactam formation, the C8 OH group was added by a stereoselective oxymercuration. Overall, nine steps were used to generate the bicyclic core, and both enantiomers could be obtained (quasi-resolution during the first cyclization).

With the intention to develop a new flexible synthesis of the pumiliotoxin core, our retrosynthesis involved removal of the methyl group, resulting in an indolizidinone **I**. Such bicycles can be generated from nine-membered ring lactams **II** by a stereoselective transannular ring closure,[7] while the planar chiral properties of the azoninones **II** should allow the generation, from the same optically active material, both of the natural series **I** and of the unnatural series *ent*-**I**. Unsaturated nine-membered ring lactams **II** have been easily generated from vinylpyrrolidines **III** and carboxylic acid fluorides by means of a zwitterionic aza-Claisen rearrangement.[8] The synthesis of the allylamines **III** appeared achievable by a short ex-chiral pool synthesis starting from commercially available L-(−)-proline (Figure 2).

Results and Discussion

With the intention of testing several strategies to generate the bicyclic core we carried out the synthesis of the vinylpyrrolidine **2** on a 50 to 70 g scale (Scheme 1). L-(−)-Proline was treated with MeOH/HCl, and the resulting ester[9] was then subjected to *N*-benzylation with benzyl chloride and an excess of Et_3N.[10] The ester group was reduced with $LiBH_4$ to give alcohol **1**.[11] After a Swern oxidation of **1**,[12] a final methylene Wittig olefination allowed completion of



Scheme 1

the synthesis of the chiral vinylpyrrolidine **2**.[13] No chromatographic purification to obtain pure material was required for any of these steps, and the overall yield was about 40−50%.[14]

The zwitterionic aza-Claisen rearrangement of the vinylpyrrolidine **2** was regarded as the first crucial step of the synthesis (Scheme 1). Chloroacetyl fluoride was chosen as the reagent, in order to provide the best yields. Furthermore, it was anticipated that the resulting 3-chloroazoninones **3** should allow reliable information concerning the stereochemical outcome of the reaction to be obtained. The vinylpyrrolidine **2** was thus treated with freshly prepared chloroacetyl fluoride[15] and Me_3Al in the presence of K_2CO_3 in CH_2Cl_2 at 0 °C to give a mixture of two diastereomer azoninones − *pS*-**3a** and *pS*-**3b** − in 77% yield and a ratio of 1.4:1. These could be separated by column chromatography and preparative HPLC. These compounds were handled carefully, any warming to 30−40 °C being avoided in order to maintain the planar chiral properties (*pS*) of the diastereomers resulting from the ring expansion.[16] To test the conformational stability of both compounds, the separated diastereomers *pS*-**3a** and *pS*-**3b** were heated to about 60 °C.[17] From *pS*-**3a**, a second diastereomer − *pR*-**3a** − appeared after 3 to 10 h, indicating flipping of the double bond with respect to the ring. All spectroscopic data for the new diastereomer *pR*-**3a** were identical to those determined for lactam *pS*-**3b**, except for the specific rotation, corroborating the formation of the enantiomer.[18] Lactam *pS*-**3b** underwent the analogous process, generating *pR*-**3b** (enantiomer of *pS*-**3a**), but conversion was found to be incomplete. The relative arrangement of the double bond and the stereogenic center of the diastereomers was established

by NOE analyses.[19] While the lactam *pS*-**3b** was characterized by a single set of peaks (almost rigid conformation), the spectroscopic data for lactam *pS*-**3a** indicated the coexistence of two conformers (double set of peaks in ^{1}H and ^{13}C spectra) potentially originating from some mobility of the lactam function.[20]

The synthesis of the pumiliotoxin core **8** now required a transannular ring contraction to generate the indolizidinone framework. First tests were conducted by treatment of the azoninone *pS*-**3** with I_2 in MeCN.[7] Smooth formation of the iodoindolizidinones **4a** and **4b** in satisfactory yield (53% from **2**, ratio ≈ 1.4:1) was observed. An analytical sample was separated by HPLC to provide the pure diastereomers **4a** and **4b**. The relative configurations of all stereogenic centers were determined by NOE analyses (Scheme 1).[19]

Substitution of the iodide by a hydroxyl group failed: the direct S_N2 process gave the corresponding elimination products as the major compounds. Furthermore, clear differentiation between α chloride and γ iodide was tricky, depending on the reactant diastereomer **4** (α- or β-Cl). Obviously, the open book shape of the bicycles **4** bearing the *exo* iodides dictated a disfavored *endo* attack of any nucleophile, preventing smooth introduction of the oxygen. Thus, an alternative route involving an S_Ni reaction mechanism was tested.[21] Treatment of iodoindolizidinones **4a/b** with silver nitrate in acetone resulted in smooth substitution of the *exo* halide by the corresponding *exo* nitrate to build up **6a/b** in high yield (92%, ratio ≈ 1.4:1).[22] Again, separation of the diastereomers by HPLC successfully provided pure diastereomers. The deprotection of the OH function of **6a** was achieved by a final hydrogenolytic cleavage to give bicycle **7**.[23] Preliminary spectroscopic analyses of **6a** and **6b**, including NOE experiments,[19] gave no safe assignment concerning the generation of the skeletons **7** or **8**, respectively, except for the IR carbonyl peak at about 1710 cm^{-1} (→ **7**). Finally, an X-ray analysis of nitrate **6a** established the formation of the indolizidinone bearing a γ-butyrolactam unit (Figure 3).[24] Clearly, the ring junction had migrated during the course of the S_N1-type substitution of the iodide. The hypothetical Wagner−Meerwein-type reaction mechanism involved an intermediate acyl aziridinium salt **5**.[25] Initially, the Ag^+ removed the 8-iodide to form AgI and the secondary cation, which might have been stabilized as a hypothetical (quasi-symmetric) *N*-acylaziridinium salt **5** by transannular interactions with the lone pair of the lactam nitrogen. Then, the weakly nucleophilic nitrate attacked the former 8a-position of the highly reactive cation to generate the rearranged indolizindinone **6** as a single regioisomer. The high selectivity of the reaction might have been the consequence of efficient shielding of the original C-8 by the eliminated iodide, dissociation of the intermediate ions being slow with respect to the trapping rate of the cation by the nucleophilic nitrate. The process seemed to be regio- and stereospecific. Further investigations concerning its scope and limitations are in progress.

Recent investigations had shown that planar chiral azoninones underwent smooth cycloadditions to the double bond, the planar chiral information of the *E* olefin being completely transferred into the new stereogenic centers of the cycloadduct.[7] The pure diastereomers *pS*-**3a** and *pS*-**3b** lactams were therefore treated with *m*CPBA/buffer at 5 °C.[26] Similarly, the *pS*-**3a/b** mixture was used immediately after completion of the workup of the aza-Claisen rearrangement, to avoid any flipping of the double bond. The corresponding epoxides **9a** and **9b** were isolated in about 90−100% yield. The separation of the diastereomers was

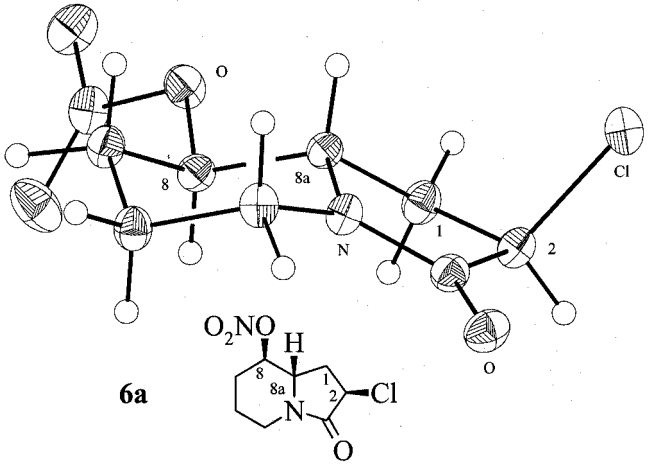


Figure 3. ORTEP plot of nitrate **6a**

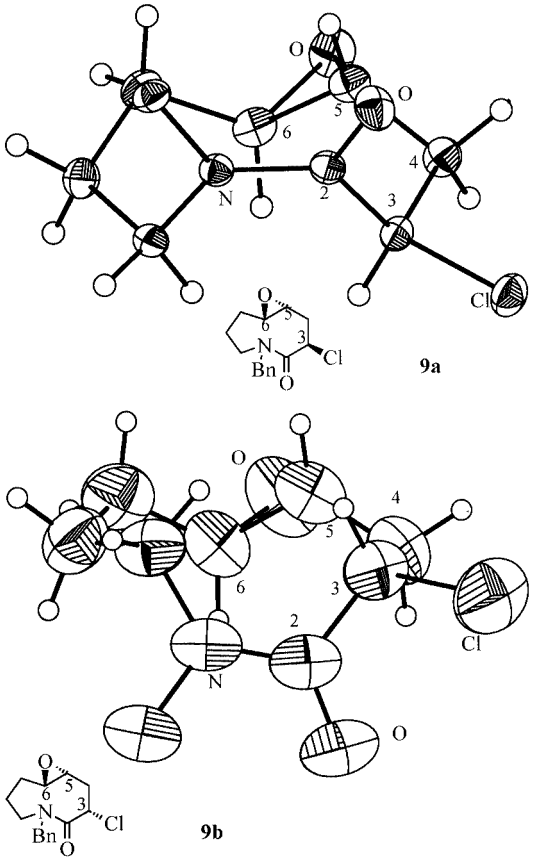
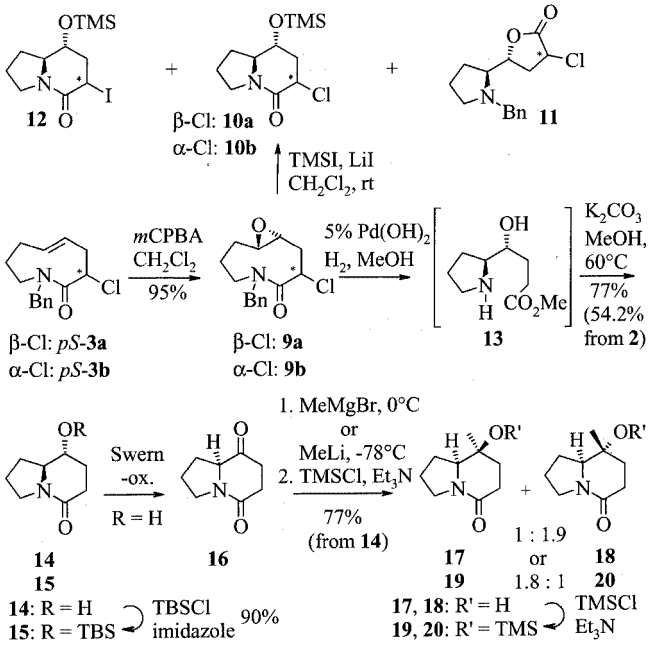


Figure 4. ORTEP plots of the epoxides **9a** and **9b** (the Ph substituents of the N-Bn groups have been omitted for clarity); for complete structures see supplementary material

successfully achieved by preparative HPLC, and NOE analyses validated the relative arrangement of the stereogenic centers. Spectra of epoxy-azonanone **9a** were characterized by a doubled set of peaks originating from some flexibility of the lactam unit: the lactam of the major species could be determined as a quasi-*Z* system (see Figure 4) with respect to the arrangement of amide oxygen and benzyl group at the partial C=N double bond, whereas the minor conformer displayed the corresponding *E* geometry.[19] In contrast, the epoxy-azonanone **9b** was found to adopt a single conformation.[19] Finally, X-ray analyses of both epoxides **9a** and **9b** confirmed the correct assignment of the absolute and the relative configuration of all stereogenic centers (Scheme 2, Figure 4).[24]



Scheme 2

The epoxy-azonanones were found to be unstable. Storage in solution at room temp. or treatment with acids or bases resulted in rapid conversion into the corresponding pyrrolidino lactones **11**.[14] Generally, such lactones **11** can be used as intermediates to generate the desired indolizidinones **8/10** − after hydrogenolytic removal of the *N*-benzyl function, a subsequent lactone lactam conversion should provide the desired bicyclic products **8/10** and **14**, respectively − but such a strategy requires at least two steps and suffers from difficulties in reaction monitoring. Conversions of **9a/b** in the presence of LiCl or LiI and TMSCl afforded some type **8/10/12** indolizidinones, but the isolated yields were low.[27] Obviously, the removal of the benzyl group by von Braun-type degradation of an intermediate acyl ammonium salt was the crucial step.[28] The competing lactonization (→ **11**) was the major reaction path, especially when handling more than 1 mmol quantities of the epoxides **9a/b**. Hence, hydrogenolytic cleavage of the *N*-benzyl group prior to the ring closure promised to be the strategy of choice. The best results were obtained by conducting the hydrogenolysis with H_2 in the presence of a $Pd(OH)_2$ catalyst (Pearlman's catalyst) in MeOH at 5 °C to room temp., the 3-chloride being removed simultaneously.[29] The resulting complex mixture of hydroxy lactam **14** and some amino ester **13** was treated with K_2CO_3 and heated to complete the cyclization. After non-aqueous workup, the hydroxy lactam **14** was isolated in 77% yield (54%, in 3−4 steps, starting from **2**, without any extensive chromatographic purification of intermediates on a 10 g scale), and was immediately converted into the corresponding TBS ether **15**.[30] Indolizidinone **15** was less polar than the reactant hydroxyindolizidinone **14**, and easily soluble in organic solvents. Alternatively, the bicyclic core of the pumiliotoxins could be obtained after a three-step sequence consisting of a Swern oxidation, a methyl Grignard addition, and a final OH protection as a TMS ether, in about 77% yield. While a smooth oxidation was achieved, generating the intermediate ketone **16**, the subsequent methylation was found to be unselective. Treatment of the ketone **16** with MeMgBr or MeMgI at −78 °C or 0 °C resulted predominantly in β-methyl addition (up to 1:2, **17/18**), giving the lactam **20** after the final protection of the alcohol function.[31] In contrast, MeLi addition at −78 °C gave a 1.8:1 (**17/18**) mixture in favor of the desired lactam **19** after the final silylation step.[32] However, the diastereomers had to be separated by preparative HPLC.[33] At present, no further efforts to optimize the diastereoselectivity of the process are being undertaken, because a suitable solution for this problem has been already published by Gallagher.[6] Replacement of the ketone by an *exo*-methylene function and sequential oxymercuration and reductive workup afforded the desired β-hydroxy lactam **17** with a 10:1 selectivity and in 60% yield.

Mechanistic Conclusions

The zwitterionic aza-Claisen rearrangement served as a first key step to generate the optically active azoninones. The stereochemical outcome of the reaction could be interpreted as follows (Figure 5).[8] Initially, the activated carboxylic acid fluoride attacked the 2-vinylpyrrolidine **2** *anti* and *syn* with respect to the adjacent vinyl substituent to give two hypothetical diastereomeric zwitterions (stereogenic ammonium center, low 1,2-induction) with *Z*-enolate geometry, as known for amide and acylammonium enolates, respectively. The rearrangement of the *syn* adduct then proceeded via a boat-like transition state (ts-boat) to give the 3β-lactam *pS*-**3a**. In contrast, the *anti* adduct rearranged through a chair-like transition state (ts-chair), resulting in the 3α-lactam *pS*-**3b**. Since both adducts passed through transition state conformations with minimized repulsive interactions, the 2*S* configuration of the reactant vinylpyrrolidine **2** initially effected the formation of the medium-sized ring, with a *pS* arrangement of the *E* double bond (complete chirality transfer − central-*S* into planar-*S*). This planar diastereomer was stable when the material was kept at room temp. or below. Heating (40−60 °C) of *pS*-**3a** resulted in a rapid flipping of the double bond with

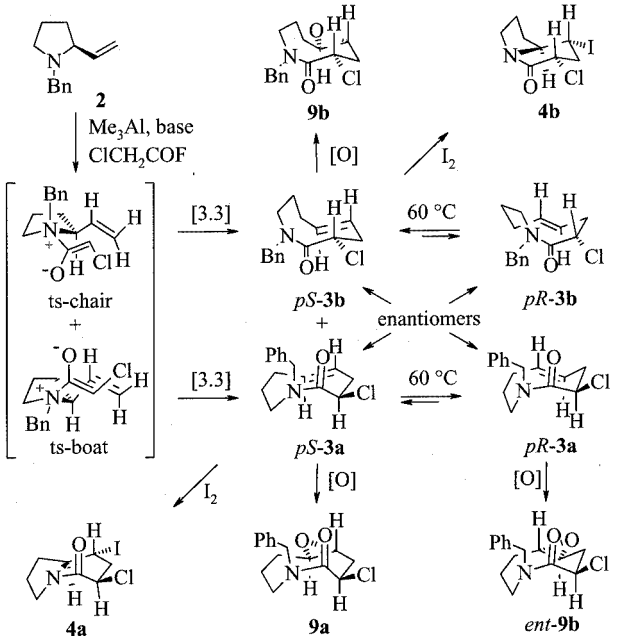


Figure 5. Formation and reactions of the planar chiral azoninones **3**

respect to the ring, generating *pR*-**3a** as the enantiomer of *pS*-**3b**. A high activation barrier had to be overcome to achieve the change of the planar chiral information. This allowed planar chiral information to be used to generate new stereogenic centers, depending on the conformation of the medium-sized ring. An electrophile would always be forced to attack the unshielded face of the double bond. Complete chirality transfer was observed in the transannular ring contraction generating the iodoindolizidinones **4a** and **4b**, respectively. Furthermore, the conversion was found to be highly regioselective. The epoxidation of the double bond yielded the epoxy-azonanones **9a** and **9b**, again with complete chirality transfer. This step determined the absolute configuration of the target 5-indolizidinone **15**, **19**, and **20**: starting from the *pS*-**3a/b** azoninones, the sequence gave the bicyclic core indolizidinones as reported (via epoxides **4a/b**). From the *pR*-**3a/b** series, the enantiomers *ent*-**15**, *ent*-**19**, and *ent*−**20** would have been generated (via epoxide ent-**9b**, see ref.[7]). In summary, the sequence can selectively provide either the natural bicyclic core skeleton or the enantiomer by selection of the suitable planar chiral intermediate, always starting from the same enantiopure L-(−)-proline.

Summary

A flexible sequence to generate the bicyclic core skeleton indolizidinone **19** (8-epi: **20**) has been developed, and should serve as a key intermediate for enantiopure pumiliotoxin total syntheses. Five standard steps starting from L-(−)-proline allowed the formation of the 2-vinylpyrrolidine (**2**) on a 50 g scale, without any need for chromatographic purification. A zwitterionic aza-Claisen rearrangement converted the allylamine **2** into the ring-enlarged azoninones *pS*-**3a/b**, bearing *E* double bonds. These nine-membered ring lactams were characterized by defined arrangements of the olefin unit with respect to the ring, indicating almost complete chirality transfer from the initially present stereogenic center (in **2**) to the planar chiral information of the medium-sized ring (in **3**). In contrast, the 1,4-chirality transfer on formation of the C3 position in the azoninones **3** was low. The planar chiral information of **3** could be used to generate new stereogenic centers. A transannular ring contraction in the presence of iodine, producing the iodoindolizidinone **4a/b**, and the epoxidation of the double bond to **9a/b** proceeded with complete chirality transfer from the stereogenic plane to the new stereogenic centers. Generally, these specific conversions allowed one to choose either a total synthesis of the natural series (starting from *pS*-**3**) or of the enantiomers (starting from *pR*-**3**). The epoxides *pS*-**9a/b** (structure determination by X-ray analyses) were found to be the precursors of choice for synthesis of the desired target **17/19**. After hydrogenolytic cleavage of the benzyl group and the 3-chloride the indolizidinone **14** was obtained. Both C3 diastereomers were converted into a single product. The OH function of the hydroxyindolizidinone **14** was protected as a TBS ether **15**. Alternatively, the missing C8 methyl group could be introduced with low diastereoselectivity by a Swern oxidation/Grignard addition sequence. After protection of the tertiary alcohol, the diastereomers **19** and **20** were separated by column chromatography or HPLC. In view of the fact that this final separation is the first necessary chromatography, the sequence is quite workable in spite of the use of about ten steps starting from L-(−)-proline. The 5-indolizidinones **15**, **19**, and **20** were used as key building blocks in enantiopure pumiliotoxin syntheses.

Experimental Section

General Remarks: ^{1}H NMR and ^{13}C NMR spectra and NOE experiments were recorded on Bruker AM 270 or Bruker AC 550 (**3a**, NOEDS analyses of **4a/b**, **9a/b**) spectrometers at room temp. unless specified otherwise. Tetramethylsilane was used as internal standard. For peak assignment, azabicyclononane numbering has been used. IR spectra were obtained with Perkin−Elmer 257 or 580B spectrophotometers. Optical rotations were measured with a Perkin−Elmer P 241 polarimeter in a 1 dm cell. Mass spectra were recorded on Varian MAT 711 or 112S spectrometers; high-resolution mass spectra (HRMS) were obtained on the Varian MAT 711. PFK was used as reference, and the results were determined by the peak matching method, 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 and UV- and RI-detectors and Rheodyne injection systems were used. Preparative amounts of the lactams were separated with a 32 mm × 120 mm column and 5 μm Nucleosil 50−5 (Macherey & Nagel), 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. Reaction progress was monitored by thin layer chromatography (TLC) performed on aluminium sheets pre-coated with silica gel 60 (thickness 0.25 mm). All solvents were dried by standard procedures before use. X-ray analyses were performed with Mo-K_α radiation (λ = 0.71073 Å). The

structure was determined by direct methods by use of the SHELXS program. The H atoms were taken from difference Fourier synthesis and were refined with isotropic thermal parameters. The nonH atoms were refined with anisotropic thermal parameters. The structure was refined on F values using 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.

(*pS*)*E*-(3*R*)-1-Benzyl-3-chloro-1,3,4,7,8,9-hexahydro-2*H*-azonin-2-one (3a) and (*pS*)*E*-(3*S*)-1-Benzyl-3-chloro-1,3,4,7,8,9-hexahydro-2*H*-azonin-2-one (3b): Under argon, a solution of vinylpyrrolidine (**2**) (5.1 g, 27.2 mmol) and K_2CO_3 (1.88 g, 0.5 eq, 13.6 mmol) in dry CH_2Cl_2 (100 mL) was cooled to −10 °C. Chloroacetyl fluoride (10.51 g, 4 equiv., 7.62 mL, 0.108 mol, d = 1.3788) was added dropwise. Me_3Al (27.3 mL, 54.5 mmol, 2 equiv, 2 M in heptane) was then added slowly, the internal temperature being maintained below 0 °C. After stirring overnight at 4 °C the orange-brown suspension was slowly poured into Et_2O (300 mL) to precipitate the aluminum salts. The mixture was filtered through a short silica gel column. The clear orange solution was then washed thoroughly with saturated aqueous $NaHCO_3$ and brine, and dried (Na_2SO_4). The solvent was removed at 20 °C to suppress any epimerization of the planar chiral information of the E olefin ($pS \rightarrow pR$). The crude orange oil was purified by flash chromatography on silica gel (EtOAc/*n*-hexane 1:1), all distillation processes being performed below 20 °C! Separation of the diastereomers by preparative HPLC (15% EtOAc in *n*-hexane, flow 64 mL/min; 32 × 110 Nucleosil 50−5, UV 254 nm) gave two major fractions: *pS*-**3a** (retention time 5 min, 3.22 g, 12.2 mmol, 44.8%) and *pS*-**3b** (retention time 6 min, 2.34 g, 8.84 mmol, 32.5%). For a 130 mmol scale preparation, see supplementary material.

Azoninone *pS*-3a was characterized by the coexistence of two conformers that could not be separated by HPLC. $[\alpha]_D^{20} = -44.3$ (c = 1.7, $CHCl_3$).^{1}H NMR (major conformer *pS*-**3a**, 500 MHz, $CDCl_3$): δ = 1.80−1.70 (m, 2 H, 8o-,8u-H), 2.18−2.00 (m, 1 H, 7o-H), 2.45−2.35 (m, 1 H, 7u-H), 2.75−2.58 [ddd, $^2J(H^{4o},H^{4u})$ = 13, $^3J(H^{4o},H^{5o})$ = 4, $^3J(H^{4o},H^{3u})$ = 4 Hz, 1 H, 4o-H], 2.82−2.72 [ddd, $^2J(H^{4u},H^{4o})$ = 13, $^3J(H^{4u},H^{5o})$ = 13, $^3J(H^{4u},H^{3u})$ = 2.5 Hz, 1 H, 4u-H], 3.10−3.00 (m, 1 H, 9u-H), 3.95−3.88 [d, $^2J(H^{N-Bn2},H^{N-Bn1})$ = 15 Hz, 1 H, H−N-Bn2], 4.38−4.25 (m, 1 H, 9o-H), 5.04−5.00 [dd, $^3J(H^{3u},H^{4o})$ = 4, $^3J(H^{3u},H^{4u})$ = 2.5 Hz, 1 H, 3u-H], 5.28−5.18 [d, $^2J(H^{N-Bn1},H^{N-Bn2})$ = 15.5 Hz, 1 H, H−N-Bn1], 5.62−5.50 [ddd, $^3J(H^{6u},H^{5o})$ = 15, $^3J(H^{6u},H^{7o})$ = 9, $^3J(H^{6u},H^{7u})$ = 4 Hz, 1 H, 6u-H], 5.98−5.85 [ddd, $^3J(H^{5o},H^{6u})$ = 15, $^3J(H^{5o},H^{4u})$ = 10, $^3J(H^{5o},H^{4o})$ = 5 Hz, 1 H, 5o-H], 7.40−7.20 (m, 5 H) ppm. ^{1}H NMR (minor conformer *pS*-**3a**, 500 MHz, $CDCl_3$): δ = 1.60−1.50 (m, 1 H, 8′-H) 2.00−1.90 (m, 2 H, 7o-,8-H), 2.40−2.28 (m, 1 H, 7u-H), 2.55−2.50 (m, 1 H, 4o-H), 2.90−2.80 (m, 1 H, 4u-H), 3.10−3.00 (m, 1 H, 9o-H), 3.75−3.60 (m, 1 H, 9u-H), 4.05−4.00 [d, $^2J(H^{N-Bn2},H^{N-Bn1})$ = 15 Hz, 1 H, H−N-Bn2], 4.86−4.80 [dd, $^3J(H^{3u},H^{4o})$ = 10, $^3J(H^{3u},H^{4u})$ = 8 Hz, 1 H, 3u-H], 5.28−5.18 [d, $^2J(H^{N-Bn1},H^{N-Bn2})$ = 15.5 Hz, 1 H, H−N-Bn1], 5.50−5.38 (m, 1 H, 5o-H), 5.70−5.55 (m, 1 H, 6u-H), 7.40−7.20 (m, 5 H) ppm. ^{13}C NMR (both conformers, peaks are partly overlapping. 62.9 MHz, $CDCl_3$): δ = 21.9, 27.8, 32.3, 35.7, 36.6, 44.2, 45.9, 47.1, 49.1, 55.4, 64.8, 127.1, 127.3, 127.5, 128.4, 128.5, 129.8, 132.8, 135.2, 136.9, 169.2 (s). For NOE analysis see Supplementary Material.

Azoninone *pS*-3b: $[\alpha]_D^{20} = -121.9$ (c = 1.9, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.75−1.65 (m, 1 H, 8o-H), 2.00−1.88 (m, 1 H, 8u-H), 2.15−2.00 (m, 1 H, 7u-H), 2.46−2.36 (m, 1 H, 7o-H), 2.67−2.57 [ddd, $^2J(H^{4o},H^{4o})$ = 12, $^3J(H^{4o},H^{5o})$ = 5, $^3J(H^{4o},H^{3o})$ = 3 Hz, 1 H, 4o-H], 2.84−2.70 [ddd, $^2J(H^{4u},H^{4o})$ = 11.5, $^3J(H^{4u},H^{5o})$ = 11.5, $^3J(H^{4u},H^{3o})$ = 9 Hz, 1 H, 4u-H], 3.12−3.02 [dd, $^2J(H^{9u},H^{9o})$ = 14.5, $^3J(H^{9u},H^{8o})$ = 5 Hz, 1 H, 9u-H], 3.45−3.33 [dd, $^2J(H^{9o},H^{9u})$ = 14.5, $^3J(H^{9o},H^{8u})$ = 10 Hz, 1 H, 9o-H], 3.95−3.88 [d, $^2J(H^{Bn-2},H^{Bn1})$ = 14.5 Hz, 1 H, H-Bn-2], 4.62−4.55 [dd, $^3J(H^{3o},H^{4u})$ = 11.5, $^3J(H^{3o},H^{4o})$ = 2 Hz, 1 H, 3o-H], 5.45−5.35 [d, $^2J(H^{Bn-1},H^{Bn2})$= 14.5 Hz, 1 H, H-Bn-1], 5.55−5.45 (m, 1 H, 6u-H), 5.65−5.50 (m, 1 H, 5o-H), 7.40−7.20 (m, 5 H) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 26.0 (t), 31.6 (t), 39.3 (t), 44.7 (t), 47.6 (t, C-9), 56.3 (d, C-3), 127.4 (d), 128.2 (d), 128.5 (d), 134.8 (d), 136.7(s), 169.5 (s) ppm. IR (KBr, mixture of *pS*-**3a** and *pS*-**3b**): $\tilde{\nu}$ = 3054 (m), 3031 (w), 2986 (m), 2940 (m), 2866 (m), 1643 (s), 1495 (w), 1453 (m), 1436 (m), 1421 (s), 1265 (s), 1185 (m), 994 (w), 896 (m) cm^{-1}. MS (80 eV, EI, 70 °C, mixture of *pS*-**3a** and *pS*-**3b**): *m/z* (%) = 263 (8) [M$^+$], 228 (4) [M$^+$ − Cl], 172 (14) [M$^+$ − C_7H_7], 136 (3), 91 (100) [$C_7H_7^+$], 65 (5), 55 (3). HRMS (80 eV, 120 °C, mixture of *pS*-**3a** and *pS*-**3b**): calcd. 263.107692 (for $C_{15}H_{18}ClNO$), found 263.10934.

(3*R*,5*R*,6*S*)-3-Chloro-5-iodo-1-azabicyclo[4.3.0]nonan-2-one (4a) and (3*S*,5*R*,6*S*)-3-Chloro-5-iodo-1-azabicyclo[4.3.0]nonan-2-one (4b): Two-step sequence starting from vinylpyrrolidine **2** without intermediate purification of the azoninones *pS*-**3** (efficient suppressing of any epimerization $pS \rightarrow pR$). *Rearrangement*: Reaction of vinylpyrrolidine **2** (5.0 g, 26.7 mmol), K_2CO_3 (3.7 g, 1 equiv., 26.7 mmol), chloroacetyl fluoride (10.3 g, 4 equiv., 7.4 mL, 0.106 mol), and Me_3Al (26.6 mL, 53.4 mmol, 2 equiv., 2 M in heptane) in CH_2Cl_2 (100 mL) by following the procedure as described for *pS*-**3a/b**. Yield: 7.71 g of the crude mixture of *pS*-**3a/b**. *Transannular reaction*: The crude azoninones *pS*-**3a/b** were dissolved in dry CH_2Cl_2 (300 mL) at 20 °C, with stirring. A solution of I_2 (3.39 g, 26.7 mmol, 1 equiv.) in dry CH_2Cl_2 (50 mL) was then added dropwise by syringe until the color of unchanged I_2 remained (quasi-titration). The reaction was found to be complete immediately after the end of the addition (TLC monitoring). The mixture was stirred for a further 15 min at room temperature. The solvent was then evaporated, and the crude material was purified by column chromatography on silica gel (hexane/EtOAc 1:1, R_f = 0.14). Yield: 4.23 g (14.15 mmol, 53%, 2 steps) of a mixture of diastereomers **4a/b**. An analytical sample was separated by HPLC (32 × 250, Nucleosil 50-5, 122 mL/min flow, UV = 254 nm, 30% EtOAc/*n*-hexane) to yield pure **4b** (retention time 20 min) and **4a** (retention time 23 min).

Data for Indolizidinone 4a: M.p. 103−105 °C. $[\alpha]_D^{20} = -11.9$ (c = 1.56, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.65−1.50 (m, 1 H, 7o-H), 1.85−1.70 (m, 1 H, 8u-H), 2.05−1.92 (m, 1 H, 8o-H), 2.45−2.35 (m, 1 H, 7u-H), 2.75−2.03 [ddd, $^2J(H^{4u},H^{4o})$ = 14.5, $^3J(H^{4u},H^{5o})$ = 14.5, $^3J(H^{4u},H^{3u})$ = 4 Hz, 1 H, 4u-H], 2.86−2.77 [ddd, $^2J(H^{4o},H^{4u})$ = 14.5, $^3J(H^{4o},H^{5o})$ = 3, $^3J(H^{4o},H^{3u})$ = 1.5 Hz, 1 H, 4o-H], 3.72−3.58 (m, 3 H, 6u-,9o-,9u-H), 4.18−4.08 [ddd, $^3J(H^{5o},H^{4u})$ = 10, $^3J(H^{5o},H^{6u})$ = 10, $^3J(H^{5o},H^{4o})$ = 3.5 Hz, 1 H, 5o-H], 4.28−4.25 [dd, $^3J(H^{3u},H^{4u})$ = 4, $^3J(H^{3u},H^{4o})$ = 1.5 Hz, 1 H, 3u-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 17.6 (d, C-5), 20.6 (t, C-8), 34.1 (t, C-7), 44.2 (t, C-4), 46.9 (t, C-9), 54.6 (d, C-6), 66.7 (d, C-3) ppm. IR (KBr): $\tilde{\nu}$ = 3426 (s), 2945 (s), 2868 (s), 1673 (m), 1645 (s), 1448 (m), 1370 (w), 1321 (w), 1290 (m), 1250 (m), 1221 (w), 1192 (w), 1152 (w), 1110 (w), 657 (m) cm^{-1}. MS (80 eV, EI, 80 °C, mixture of **4a** and **4b**): *m/z* (%) = 299 (12) [M$^+$], 264 (5) [M$^+$ − Cl], 172 (100) [M$^+$ − I], 145 (15), 136 (14), 108 (10), 82 (13), 80 (13), 70 (25), 67 (10), 55 (14), 53 (10). HRMS (80 eV, 80 °C, mixture of **4a** and **4b**): calcd. 298.957394 (for $C_8H_{11}{}^{35}Cl^{127}INO_2$), found 298.95721.

Data for Indolizidinone 4b: M.p. 144−146 °C. $[\alpha]_D^{20} = -45.6$ (c = 1.44, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.60−1.45 (m, 1

H, 7o-H), 1.90−1.70 (m, 1 H, 8u-H), 2.05−1.95 (m, 1 H, 8o-H), 2.48−2.38 (m, 1 H, 7u-H), 2.70−2.55 [ddd, $^2J(H^{4u},H^{4o})$ = 14, $^3J(H^{4u},H^{3o})$ = 12.5, $^3J(H^{4u},H^{5o})$ = 11 Hz, 1 H, 4u-H], 3.13−3.04 [ddd, $^2J(H^{4o},H^{4u})$ = 13, $^3J(H^{4o},H^{3o})$ = 6.5, $^3J(H^{4o},H^{5o})$ = 3 Hz, 1 H, 4o-H], 3.90−3.78 [ddd, $^3J(H^{5o},H^{4u})$ = 10, $^3J(H^{5o},H^{6u})$ = 10, $^3J(H^{5o},H^{4o})$ = 4 Hz, 1 H, 5o-H], 4.40−4.30 [dd, $^3J(H^{3o},H^{4u})$ = 10, $^3J(H^{3o},H^{4o})$ = 7 Hz, 1 H, 3o-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 19.5 (d, C-5), 21.3 (t, C-8), 34.8 (t, C-7), 45.2 (t, C-4), 47.5 (t, C-9), 53.4 (d, C-6), 66.3 (d, C-3) ppm. IR (KBr): ṽ = 3425 (s), 2939 (s), 2873 (s), 1736 (w), 1709 (w), 1636 (s), 1459 (m), 1441 (m), 1381 (w), 1332 (w), 1274 (m), 1192 (w), 1153 (w), 660 (m) cm^{-1}.

(3*R*,5*R*,6*S*)-8-Chloro-5-nitro-1-azabicyclo[4.3.0]nonan-9-one (6a) and (3*S*,5*R*,6*S*)-8-Chloro-5-nitro-1-azabicyclo[4.3.0]nonan-9-one (6b): The iodoindolizidinones **4a/b** (1.00 g, 3.34 mmol) in acetone (50 mL) were treated with carefully powdered $AgNO_3$ (1.13 g, 2 equi., 6.68 mmol) and stirred at 20 °C for 3 days. The precipitated silver iodide was then filtered off and another equivalent of $AgNO_3$ (0.57 g, 1 equiv., 3.34 mmol) was added. After the mixture had been stirred overnight the precipitates were filtered off and the solvent was removed. The crude product was purified by column chromatography on silica gel (EtOAc/*n*-hexane 1:1, R_f = 0.27 and R_f = 0.13). Yield: 0.72 g (92%, 3.07 mmol) of a mixture of the nitrate indolizidinones **6a** and **6b**. An analytical sample was separated by preparative HPLC (20% EtOAc/*n*-hexane, 32 × 110 mm, Nucleosil 50-5, flow 122 mL/min, UV =220 nm) to provide **6a** (retention time 9.9 min) and **6b** (retention time 16.7 min) as pure compounds.

Data for Nitrate Indolizidinone 6a: Colorless crystals, m.p. 75 °C. $[\alpha]_D^{20}$ = −54.9 (*c* = 1.56, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.68−1.50 (m, 2 H, 3′-,4o-H), 1.98−1.85 (m, 1 H, 3-H), 2.40−2.30 (m, 1 H, 4u-H), 2.42−2.30 [ddd, $^2J(H^{7u},H^{7o})$ = 14, $^3J(H^{7u},H^{6o})$ = 6.5, $^3J(H^{7u},H^{8u})$ = 6.5 Hz, 1 H, 7u-H], 2.61−2.50 [ddd, $^2J(H^{7o},H^{7u})$ = 14.5, $^3J(H^{7o},H^{6o})$ = 6.5, $^3J(H^{7o},H^{8u})$ = 2 Hz, 1 H, 7o-H], 2.77−2.63 (m, 1 H, 2o-H), 3.68−3.56 [ddd, $^3J(H^{6o},H^{5u})$ = 10.5, $^3J(H^{6o},H^{7o})$ = 6.5, $^3J(H^{6o},H^{7u})$ = 6.5 Hz, 1 H, 6o-H], 4.17−4.07 [ddd, $^2J(H^{2u},H^{2o})$ = 13, $^3J(H^{2u},H^{8})$ = 2.5, $^3J(H^{2u},H^{8'})$ = 1 Hz, 1 H, 2u-H], 4.42−4.37 [dd, $^3J(H^{8u},H^{7u})$ = 7, $^3J(H^{8u},H^{7o})$ = 2 Hz, 1 H, 8u-H], 4.65−4.54 [ddd, $^3J(H^{5u},H^{6o})$ = 10, $^3J(H^{5u},H^{4o})$ = 10, $^3J(H^{5u},H^{4u})$ = 3.5 Hz, 1 H, 5u-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 22.6 (t, C-3), 28.5 (t, C-4), 34.8 (t, C-7), 39.7 (t, C-2), 53.4 (d, C-8), 55.9 (d, C-6), 82.5 (d, C-5), 168.9 (s) ppm. IR (KBr): ṽ = 2965 (w), 2917 (w), 1701 (s, CO), 1697 (s), 1639 (s, NO), 1426 (m), 1318 (m), 1271 (s), 1196 (w), 1160 (w), 1109 (w), 1054 (w), 1018 (m), 978 (m), 897 (s), 884 (s), 959 (s), 755 (m), 692 (m), 650 (m) cm^{-1}. MS (80 eV, EI, 100 °C): *m*/*z* (%) = 236 (0.2) [$M^{+\cdot}$], 234 (0.8) [$M^{+\cdot}$], 190 (15), 188 (45) [$M^+ - NO_2$], 172 (17) [$M^+ - NO_3$], 160 (13), 132 (10), 124 (13), 97 (12), 71 (100), 43 (20). HRMS (80 eV, 120 °C): calcd. 234.040735 (for $C_8H_{11}{}^{35}Cl_1N_2O_4$ [M^+]), found 234.04344.

Data for Nitrate Indolizidinone 6b: Colorless crystals, m.p. 153 °C. $[\alpha]_D^{20}$ = −117.8 (*c* = 1.25, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.72−1.48 (m, 2 H, 3-,4o-H), 1.95−1.80 (m, 1 H, 3-H), 2.20−2.10 [ddd, $^2J(H^{7u},H^{7o})$ = 14, $^3J(H^{7u},H^{6o})$ = 5.5, $^3J(H^{7u},H^{8})$ = 5.5 Hz, 1 H, 7u-H], 2.40−2.31 (m, 1 H, 4u-H), 2.73−2.60 (m, 1 H, 2o-H), 2.03−2.10 [ddd, $^2J(H^{7o},H^{7u})$ = 13.5, $^3J(H^{7o},H^{6o})$ = 8, $^3J(H^{7o},H^{8})$ = 6 Hz, 1 H, 7o-H], 3.48−3.40 [ddd, $^3J(H^{6o},H^{5u})$ = 9.5, $^3J(H^{6o},H^{7o})$ = 7, $^3J(H^{6o},H^{7u})$ = 5 Hz, 1 H, 6o-H], 4.15−4.05 (m, 1 H, 2u-H), 4.45−4.35 [ddd, $^3J(H^{8o},H)$ = 7, $^3J(H^{8o},H)$ = 6, $^5J(H^{8o},H)$ = 0.5 Hz, 1 H, 8o-H], 4.85−4.75 [ddd, $^3J(H^{5u},H^{6o})$ = 9.5, $^3J(H^{5u},H^{4o})$ = 9.5, $^3J(H^{5u},H^{4u})$ = 3.5 Hz, 1 H, 5u-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 22.8 (t, C-3), 28.8 (t, C-4), 33.4 (t, C-7), 39.9 (t, C-2), 53.1 (d, C-8), 56.3 (d, C-6), 82.2 (d, C-5), 168.9 (s) ppm. IR (KBr): ṽ = 2963 (w), 2935 (w), 2864 (m), 1702 (s, CO), 1621 (s, NO), 1447 (m), 1431 (m), 1318 (m), 1304 (m), 1277 (s), 1260 (s), 1189 (w), 1153 (m), 1118 (w), 1018 (m), 975 (m), 894 (s), 885 (s), 865 (s), 806 (m), 762 (m), 737 (m), 657 (m) cm^{-1}. MS (80 eV, EI, 90 °C): *m*/*z* (%) = 236 (0.05) [$M^{+\cdot}$], 234 (0.1) [$M^{+\cdot}$], 190 (8), 188 (24) [$M^+ - NO_2$], 172 (6) [$M^+ - NO_3$], 160 (9), 132 (6), 124 (8), 97 (16), 71 (100), 43 (51), 41 (38). HRMS (80 eV,120 °C): calcd. 234.04735 (for $C_8H_{11}N_2O_4$ $^{35}Cl_1$ [M^+]), found 234.04522.

(3*R*,5*R*,6*S*)-8-Chloro-5-hydroxy-1-azabicyclo[4.3.0]nonan-9-one (7): The nitrate indolizidinone **6a** (100 mg, 0.43 mmol) was dissolved in MeOH (10 mL) and HOAc (2 mL). At 0 °C, zinc (powder, 100 mg, 1.72 mmol, 4 equiv.) was slowly added. The cooling bath was then removed and the mixture was stirred overnight at room temperature. Workup started with quenching with aqueous $NaHCO_3$ and extraction with CH_2Cl_2 (3 ×). The organic layers were then dried (Na_2SO_4) and the solvent was evaporated to give hydroxyindolizidinone **7** (32.3 mg, 0.17 mmol, 40%) as a colorless oil. $[\alpha]_D^{20}$ = −49.3 (*c* = 1.61, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.50−1.30 (m, 2 H, 3′-,4o-H), 1.85−1.70 (m, 1 H, 3-H), 2.15−2.00 (m, 1 H, 4u-H), 2.40−2.30 [ddd, $^2J(H^{7u},H^{7o})$ = 13.5, $^3J(H^{7u},H^{8u})$ = 7, $^3J(H^{7u},H^{6o})$ = 6 Hz, 1 H, 7u-H], 2.60−2.50 [ddd, $^2J(H^{7o},H^{7u})$ = 14.5, $^3J(H^{7o},H^{6o})$ = 6, $^3J(H^{7o},H^{8u})$ = 2 Hz, 1 H, 7o-H], 2.70−2.60 (m, 1 H, 9o-H), 3.25−3.15 [ddd, $^3J(H^{5u},H^{6o})$ = 9.5, $^3J(H^{5u},H^{4o})$ = 9.5, $^3J(H^{5u},H^{4u})$ = 3.5 Hz, 1 H, 5u-H], 3.43−3.32 [ddd, $^3J(H^{6o},H^{5u})$ = 9, $^3J(H^{6o},H^{7u})$ = 6.5, $^3J(H^{6o},H^{7o})$ = 6.5 Hz, 1 H, 6o-H], 4.05−3.95 [dd, $^2J(H^{2u},H^{2o})$ = 13, $^3J(H^{2u},H^{8})$ = 3.5 Hz, 1 H, 2u-H], 4.40−4.35 [dd, $^3J(H^{8u},H^{7u})$ = 7, $^3J(H^{8u},H^{7o})$ = 2 Hz, 1 H, 8u-H], 4.60−4.40 (s, 1 H, OH) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 22.9 (t, C-3), 32.9 (t, C-7), 34.8 (t, C-4), 39.9 (t, C-2), 54.5 (d, C-8), 60.4 (d, C-6), 72.9 (d, C-5), 69.3 (s) ppm. IR ($CHCl_3$): ṽ = 3395 (m, br), 2929 (m), 2861 (m), 1697 (s, C=O), 1441 (m), 1372 (m), 1272 (m), 1075 (m), 916 (s), 898 (s), 750 (s), 718 (s), 650 (s) cm^{-1}. MS (80 eV, EI, 90 °C): *m*/*z* (%) = 189 (27) [$M^{+\cdot}$], 172 (6) [$M^+ - OH$], 154 (100) [$M^+ - Cl$], 126 (32), 98 (11), 84 (25), 71 (35). HRMS (80 eV,120 °C): calcd. 189.055656 (for $C_8H_{12}N_1O_2$ $^{35}Cl_1$ [M^+]), found 189.05392.

(3*R*,5*R*,6*R*)-1-Benzyl-3-chloro-5,6-epoxyazonan-2-one (9a): The azoninone *pS*-**3a** (3.05 g, 11.56 mmol, 1 mol equiv.) was dissolved in a 1:1 mixture of CH_2Cl_2 and phosphate buffer (pH = 7). *m*-Chloroperbenzoic acid (2.64 g, 13.87 mmol, 1.2 equiv., mono hydrate) was then added and the mixture was stirred at 4 °C for 3−5 h (TLC monitoring). The mixture was then poured into saturated aqueous $NaHCO_3$/$NaHSO_3$. The organic layer was washed (saturated aqueous $NaHCO_3$ and brine) and dried (Na_2SO_4). After evaporation of the solvent, the product was purified by recrystallization from CH_2Cl_2/*n*-hexane. The remaining mother liquor was purified by HPLC (15% EtOAc/*n*-hexane, 32 × 250 mm Nucleosil 50-5, flow 64 mL/min).[34] Yield: 2.92 g (10.4 mmol, 90%) of epoxide **9a** as colorless crystals The epoxide was found to be heat-sensitive, suffering from rearrangement to the more stable lactone **11a**. In contrast, no decomposition was observed while storing at −20 °C for several months. M.p. 139−140 °C. $[\alpha]_D^{20}$ = −148.6 (*c* = 1.4, $CHCl_3$). The NMR spectra were characterized by the coexistence of two conformers:[35] ^{1}H NMR (270 MHz, $CDCl_3$, major conformer, 60%): δ = 0.90−0.70 (m, 1 H, 7o-H), 1.90−1.80 (m, 1 H, 4u-H), 2.20−2.10 (m, 2 H, 8-,7u-H), 2.50−2.40 [ddd, $^3J(H^{5o},H^{6u})$ = 8.5, $^3J(H^{5o},H^{4u})$ = 5, $^3J(H^{5o},H^{4o})$ = 2.5 Hz, 1 H, 5o-H], 2.80−2.60 (m, 2 H, 6-,4o-H), 3.30−3.15 (m, 1 H, 9o-H), 4.00−3.80 [ddd, $^2J(H^{9u},H^{9o})$ = 15, $^3J(H^{9u},H^{8})$ = 12, $^3J(H^{9u},H^{8})$ = 3.5 Hz, 1 H, 9u-H], 4.14−4.06 [d, $^2J(H^{N-Bn2},H^{N-Bn1})$ = 14.5 Hz, 1 H, H−N-Bn2], 5.15−5.10 [dd, $^3J(H^{3u},H^{4o})$ = 7, $^3J(H^{3u},H^{4u})$ =

3 Hz, 1 H, 3u-H], 5.18−5.13 [d, $^2J(H^{N-Bn1},H^{N-Bn2})$ = 15 Hz, 1 H, H−N-Bn1], 7.40−7.20 (m, 5 H, Ph-H) ppm. ^{1}H NMR (270 MHz, $CDCl_3$, minor conformer, 40%): δ = 1.20−1.10 (m, 1 H, 7o-H), 1.90−1.50 (m, 2 H, 8-,4u-H), 2.15−2.05 (m, 1 H, 7u-H), 2.30−2.20 (m, 1 H, 8-H), 2.80−2.60 (m, 2 H, 4o-,6u-H), 3.30−3.10 (m, 2 H, 5o-,9u-H), 4.13−4.05 [d, $^2J(H^{Bn2},H^{Bn-1})$ = 15 Hz, 1 H, H-Bn2], 4.65−4.53 [dd, $^2J(H^{9o},H^{9u})$ = 15, $^3J(H^{9o},H^{8})$ = 9 Hz, 1 H, 9o-H], 5.08−5.03 [dd, $^3J(H^{3u},H^{4o})$ = 4.5, $^3J(H^{3u},H^{4u})$ = 2.5 Hz, 1 H, 3u-H], 5.30−5.20 [d, $^2J(H^{N-Bn1},H^{N-Bn2})$ = 15 Hz, 1 H, H−N-Bn1], 7.40−7.20 (m, 5 H, Ph-H) ppm. ^{13}C NMR (125.7 MHz, $CDCl_3$):[36] δ = 21.4 (t, C-8), 22.2 (t, C-8′), 26.0 (t, C-7), 29.8 (t, C-7′), 35.4 (t, C-4′), 37.4 (t, C-4), 44.2 (t, C-9), 45.1 (t, C-9′), 47.6 (t, N-Bn), 49.2 (t, N-Bn′), 50.6 (d, C-3), 54.2 (d, C-6), 56.2 (d, C-6′), 56.5 (d, C-5′), 57.1 (d, C-5), 59.2 (d, C-3′), 127.4 (d), 127.8 (d), 128.4 (d), 128.7 (d), 136.4 (s), 168.2 (s, C-2′), 169.1 (s, C-2) ppm. IR (KBr): ṽ = 3039 (w), 3015 (m), 2976 (m), 2940 (m), 2885 (m), 1638 (s, C=O), 1495 (m), 1475 (m), 1461 (m), 1449 (m), 1429 (m), 1366 (m), 1298 (w), 1259 (m), 1238 (w), 1210 (m), 1202 (s), 1157 (w), 1127 (w), 1107 (m), 1081 (m), 1064 (w), 971 (m), 922 (m), 908 (m), 825 (m), 796 (m), 765 (m), 792 (w), 708 (m), 634 (w), 610 (w) cm^{-1}. MS (80 eV, EI, 120 °C): *m*/*z* (%) = 281 (12) [M$^{+\cdot}$], 279 (35) [M$^{+\cdot}$], 244 (49) [M$^+$ − Cl], 204 (10), 188 (8) [M$^+$ − C_7H_7], 160 (23), 120 (65), 91 (100), 70 (13). HRMS (80 eV, 120 °C): calcd. 279.1020607 (for $C_{15}H_{18}{}^{35}ClNO_2$), found 279.10409.

(3*S*,5*R*,6*R*)-1-Benzyl-3-chloro-5,6-epoxyazonan-2-one (9b): This compound was produced from *pS*-**3b** (2.55 g, 9.6 mmol) and *m*-CPBA following the procedure described for epoxy azonanone **9a**. After workup the product **9b** was recrystallized from CH_2Cl_2/*n*-hexane. Yield 2.70 g (100%) of **9b**, initially as a colorless oil, which slowly crystallized at −20 °C, mp: 92−95 °C. $[\alpha]_D^{20}$ = +5.5 (*c* = 1.39, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.20−1.00 (m, 1 H, 7o-H), 1.80−1.65 (m, 1 H, 8′-H), 1.95−1.80 [ddd, $^2J(H^{4u},H^{4o})$ = 12.5, $^3J(H^{4u},H^{3o})$ = 12.5, $^3J(H^{4u},H^{5o})$ = 10 Hz, 1 H, 4u-H], 2.15−1.95 (m, 1 H, 8-H), 2.30−2.18 (m, 1 H, 7u-H), 2.73−2.60 (m, 2 H, 4o-,6u-H), 2.80−2.73 [ddd, $^3J(H^{5o},H^{4u})$ = 10, $^3J(H^{5o},H^{6u})$ = 4, $^3J(H^{5o},H^{4o})$ = 2 Hz, 1 H, 5o-H], 3.25−3.15 [dd, $^2J(H^{9u},H^{9o})$ = 15, $^3J(H^{9u},H^{8})$ = 5.5 Hz, 1 H, 9u-H], 3.70−3.58 [dd, $^2J(H^{9o},H^{9u})$ = 15, $^3J(H^{9o},H^{8})$ = 11 Hz, 1 H, 9o-H], 4.07−4.02 [d, $^2J(H^{N-Bn2},H^{N-Bn1})$ = 14.5 Hz, 1 H, N-Bn2], 5.03−4.94 [dd, $^3J(H^{3o},H^{4u})$ = 12.5, $^3J(H^{3o},H^{4o})$ = 1.5 Hz, 1 H, 3o-H], 5.40−5.30 [d, $^2J(H^{N-Bn1},H^{N-Bn2})$ = 14.5 Hz, 1 H, N-Bn1], 7.40−7.20 (m, 5 H, Ph-H) ppm. ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.6 (t, C-8), 29.4 (t, C-7), 38.9 (t, C-4), 44.6 (t, C-9), 47.9 (t, N-Bn), 52.0 (d, C-3), 55.2 (d, C-6), 57.0 (d, C-5), 127.6 (d), 128.1 (d), 128.6 (d), 136.1 (s), 169.5 (s, C-2) ppm. MS (80 eV, EI, 120 °C): *m*/*z* (%) = 281 (11) [M$^{+\cdot}$], 279 (30) [M$^{+\cdot}$], 244 (40) [M$^+$ − Cl], 188 (5) [M$^+$ − C_7H_7], 160 (24), 158 (18), 156 (52), 141 (18), 139 (57), 120 (15), 111 (25), 91 (100), 75 (12). HRMS (80 eV,120 °C): calcd. 279.10206 (for $C_{15}H_{18}NO_2{}^{35}Cl$), found 279.10434.

(5*R*,6*S*)-5-Hydroxyazabicyclo[4.3.0]nonan-2-one (14): A mixture of the epoxy-azonanones **9a/b** (22.3 g, 80 mmol)[37] and Pearlman's catalyst (10% $Pd(OH)_2$/C, 2 g, 1.42 mmol) in MeOH (500 mL) was cooled to 5 °C. The flask was then evacuated (70−80 mbar) and refilled with nitrogen (2 ×) and hydrogen (3 ×). The mixture was vigorously stirred for 5 h at 5 °C and for another 7 days at room temperature until the ^{1}H NMR spectrum of an analytical sample showed no remaining peak originating from α-chlorolactam proton [dd at δ = 4.63 ppm (3-H)]. Additionally, all peaks of the aromatic section (8−7 ppm in ^{1}H NMR) should have disappeared. The hydrogen was then replaced by nitrogen, solid K_2CO_3 (26 g, 0.19 mol) was added, and the mixture was heated to about 45 °C for 6 h to bring about the recyclization of potentially cleaved indolizidinones. The methanol was removed and the black residue was dissolved in CH_2Cl_2 (300 mL). A black solid was removed by filtration and washed with CH_2Cl_2 (2 × 200 mL). The solvent of the combined clear extracts was evaporated to give 9.7 g of crude hydroxyindolizidinone **14**. The crude solid was finely powdered and washed with cold Et_2O (200 mL). Yield: 7.29 g (47.2 mmol, 59%, crude reactant **9**) and 9.64 g (62.4 mmol, 78%, pure reactant **9**) of hydroxyindolizidinone **14** as nearly colorless crystals. Optional: Purification by column chromatography on silica gel (EtOAc/MeOH 6:1). M.p. 99−101 °C). $[\alpha]_D^{20}$ = −37.7 (*c* = 1.27, EtOH). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 1.60−1.45 (m, 1 H, 7o-H), 1.85−1.70 (m, 2 H, 4u-,8u-H), 2.00−1.91 (m, 1 H, 8o-H), 2.13−2.00 (m, 1 H, 4o-H), 2.47−2.28 (m, 2 H, 3o-,7u-H), 2.60−2.48 [ddd, $^2J(H^{3u},H)$ = 18, $^3J(H^{3u},H)$ = 7, $^3J(H^{3u},H)$ = 2 Hz, 1 H, 3u-H], 3.32−3.21 [ddd, $^3J(H^{6u},H)$ = 14, $^3J(H^{6u},H)$ = 8.5, $^3J(H^{6u},H)$ = 3.5 Hz, 1 H, 6u-H], 3.60−3.43 (m, 3 H, 5o-,9o-,9u-H) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 22.1 (t, C-8), 29.9 (t, C-4 and C-7), 31.6 (t, C-3), 45.5 (t, C-9), 63.9 (d, C-6), 70.7 (d, C-5), 168.7 (s) ppm. IR (KBr): ṽ = 3267 (s, OH), 2969 (m), 2952 (m), 2885 (m), 1601 (s, C=O), 1479 (m), 1454 (m), 1442 (m), 1412 (m), 1339 (m), 1320 (w), 1287 (m), 1265 (s), 1224 (w), 1209 (w), 1167 (w), 1142 (w), 1132 (w), 1093 (m), 1063 (m), 990 (w), 960 (m), 843 (w), 770 (w), 667 (m) cm^{-1}. MS (80 eV, EI, 130 °C): *m*/*z* (%) = 155 (36) [M$^{+\cdot}$], 138 (3) [M$^+$ − OH], 127 (6), 111 (21), 99 (11), 83 (100), 70 (81), 55 (26), 41 (24). HRMS (80 eV, 130 °C): calcd. 155.094629 (for $C_8H_{13}N_1O_2$ [M$^+$]), found 155.09567.

(5*R*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)azabicyclo[4.3.0]nonan-2-one (15): The hydroxyindolizidinone **14** (500 mg, 3.22 mmol) in CH_2Cl_2 (50 mL) was treated consecutively with imidazole (395 mg, 5.79 mmol, 1.8 equiv.) in CH_2Cl_2 (50 mL) and with TBSCl (534 mg, 3.54 mmol, 1.1 equiv.). The mixture was stirred overnight at ambient temperature. The excess TBSCl was quenched with MeOH (10 mL). After a further 30 min stirring, the solvent was evaporated at temperatures below 30 °C. The residue was dissolved in Et_2O (150 mL), and the organic phase was extracted with saturated aqueous NH_4Cl to remove the imidazole and dried (Na_2SO_4). The solvent was removed and indolizidinone **15** was isolated as a colorless oil pure enough for further transformations. Optional: final extraction with CH_2Cl_2 and purification by column chromatography on silica gel. Yield: 780 mg (2.90 mmol, 90%). $[\alpha]_D^{20}$ = −36.2 (*c* = 0.85, $CHCl_3$). ^{1}H NMR (270 MHz, $CDCl_3$): δ = 0.00 (s, 6 H, Si−CH_3), 0.81 [s, 9 H, Si−C(CH_3)$_3$], 1.45−1.30 (m, 1 H, 7o-H), 1.75−1.60 (m, 2 H, 4u-,8u-H), 1.95−1.85 (m, 2 H, 4o-,8o-H), 2.35−2.10 (m, 2 H, 3o-,7u-H), 2.50−2.35 [ddd, $^2J(H^{3u},H)$ = 18, $^3J(H^{3u},H)$ = 7, $^3J(H^{3u},H)$ = 2 Hz, 1 H, 3u-H], 3.23−3.13 [ddd, $^3J(H^{6u},H)$ = 14, $^3J(H^{6u},H)$ = 8.5, $^3J(H^{6u},H)$ = 3.5 Hz, 1 H, 6u-H], 3.50−3.30 (m, 3 H, 5o-,9o-,9u-H) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = −4.9 (q, Si−CH_3), −4.5 (q, Si−CH_3), 17.6 [Si−*C*(CH_3)$_3$], 21.9 (t, C-8), 25.4 [Si−C(CH_3)$_3$], 29.9 (t, C-7), 30.6 (t, C-4), 31.9 (t, C-3), 45.4 (t, C-9), 63.9 (d, C-6), 72.0 (d, C-5), 168.0 (s) ppm. IR ($CHCl_3$): ṽ = 3018 (s), 1956 (s), 1930 (s), 2885 (m), 2858 (m), 1624 (m), 1470 (m), 1463 (m), 1416 (m), 1387 (w), 1361 (m), 1273 (m), 1257 (m), 1221 (s), 1210 (s), 1128 (m), 1104 (m). 867 (m), 837 (m) cm^{-1}. MS (80 eV, EI, 50 °C): *m*/*z* (%) = 269 (1) [M$^{+\cdot}$], 254 (3) [M$^+$ − CH_3], 212 (100) [M$^+$ − C_4H_9], 156 (4), 138 (18), 129 (19), 115 (9), 101 (7), 83 (18), 73 (12).

(6*S*)-Azabicyclo[4.3.0]nonan-2,5-dione (16), (5*R*,6*S*)-5-Methyl-5-(trimethylsilyloxy)azabicyclo[4.3.0]nonan-2-one (19), and (5*R*,6*R*)-5-Methyl-5-(trimethylsilyloxy)azabicyclo[4.3.0]nonan-2-one (20): ***Swern Oxidation*:** Freshly distilled oxalyl chloride (2.81 mL, 4.09 g, 0.032 mol, 2 equiv.) in dry CH_2Cl_2 (100 mL) was cooled under argon to −78 °C and treated dropwise with DMSO (2.34 mL,

2.58 g, 0.033 mol, 2.05 equiv.) in dry CH_2Cl_2 (5 mL), the internal temperature being kept below −70 °C. After stirring for 1 h at about −70 °C, the mixture was cooled again to −78 °C and hydroxyindolizidinone **14** (2.5 g, 0.016 mol) in dry CH_2Cl_2 (50 mL) was added slowly. After the mixture had been further stirred at −55 to −60 °C, Et_3N (11.0 mL, 0.08 mol, 5 equiv.) was injected slowly at about −65 °C. The cooling bath was removed and the mixture was stirred for 1 h until the temperature reached 20 °C. The solvent was then removed under reduced pressure and the residue was suspended in EtOAc. The white precipitate of $Et_3N{\cdot}HCl$ was filtered off and remaining impurities of the salt fraction were removed by passing the EtOAc solution through a short silica gel column. After evaporation of the solvent at temperatures below 30 °C, the crude ketone **16** was obtained as a colorless oil, which was used without further purification. Yield: 2.5 g (0.016 mol, 100%) of ketone **16**. (remark: aqueous workup caused severe decreases in the yield because of the great solubility of **16** in H_2O). $[\alpha]_D^{20} = -245$ (c = 1.56, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$, showed some minor impurities of the side product O-MTM ether): δ = 2.00−1.70 (m, 3 H, 7′-, 8o-,8u-H), 2.20−2.10 (m, 1 H, 7-H), 2.70−2.40 (m, 4 H, 3o-,3u-, 4o-,4u-H), 3.60−3.30 (m, 2 H, 9o-,9u-H), 3.98−3.90 [dd, $^3J(H^6,H^{7o})$ = 8, $^3J(H^6,H^{7u})$ = 8 Hz, 1 H, 6-H] ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 22.6 (t), 27.4 (t), 30.5 (t), 34.4 (t), 45.0 (t), 64.5 (d, C-6), 168.7 (s), 207.0 (s, C=O) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2983 (m), 2970 (m), 2916 (m), 2891 (m), 1732 (s, C=O), 1653 (s, N−C=O), 1450 (s), 1381 (m), 1346 (m), 1330 (m), 1321 (m), 1290 (m), 1203 (m), 1177 (m), 1132 (m), 1103 (m) cm^{-1}. MS (80 eV, EI, 30 °C): m/z (%) = 153 (100) [$M^{+\cdot}$], 141 (12), 125 (77), 110 (16), 97 (50), 91 (34), 84 (44), 78 (30), 75 (14), 70 (20). HRMS (80 eV, 30 °C): calcd. 153.078979 (for $C_8H_{11}NO_2$ [M^+]), found 153.07655.

Grignard Addition with Methylmagnesium Iodide: MeI (10.6 mL, 0.161 mol) was added dropwise from a dropping funnel to magnesium (5.1 g, 0.193 mol, turnings) in Et_2O (10 mL) under argon. The mixture began to boil under reflux, and subsequent addition of further portions of Et_2O allowed the temperature of the halide/metal exchange to be controlled. Heating at reflux was continued for another 30 min after the complete addition of the MeI to give a gray solution (remaining traces of Mg). The crude ketone **16** (2.5 g, 16.3 mmol) in dry THF (250 mL) was cooled under argon to −78 °C. The freshly prepared methylmagnesium iodide solution was added to this by double-ended needle, while the mixture was stirred by a mechanical stirrer. The internal temperature was kept below −60 °C, and a white precipitate of the magnesium salts appeared. After stirring at −78 °C overnight, the mixture was allowed to warm up to room temperature. The excess of methylmagnesium iodide was quenched by addition of saturated aqueous NH_4Cl (100 mL). All solvents (incl. H_2O!) were then removed under reduced pressure at temperatures below 40 °C. The remaining solid material was extracted carefully with CH_2Cl_2 (5 × 250 mL). The solvent was removed and the crude product was purified by passing through a short silica gel column (EtOAc/MeOH 3:1) and by preparative HPLC to separate remaining reactant ketone **16** (25% *i*PrOH/hexane, 32 × 110 mm Nucleosil 50-5, UV = 220 nm, flow 64 mL/min). The pure carbinols **17** and **18** were obtained as an inseparable mixture of diastereomers, yield 4.21 g (12.55 mmol, 77%) For spectroscopic data see supplementary material. (Retention time **16**: 2 min, carbinols **17/18**: 7−9 min). Some analogous reactions were carried out with MeLi (−78 °C, **17/18**: 1.8:1), MeMgBr (4 °C, **17/18**: 1:1.1), and MeMgI (0 °C, **17/18**: 1:1.9) as methylation reagents. All reactions were conducted as described for the MeMgI addition described above.

The mixture of C5 diastereomer carbinols **17/18** (1.85 g, 11 mmol) in dry CH_2Cl_2 (50 mL) was subsequently treated with imidazole (1.48 g, 22 mmol, 2 equiv.) and TMSCl (1.76 mL, 13 mmol, 1.2 equiv.) and stirred overnight at ambient temperature. The excess of TMSCl was quenched with MeOH (5 mL) and the solvent was removed at temperatures below 30 °C. The residue was dissolved in Et_2O (150 mL), extracted with saturated aqueous NH_4Cl to remove the imidazole, and dried (Na_2SO_4). After evaporation of the solvent, 2.14 g of the products **19/20** was obtained as a colorless oil. The diastereomers were separated by preparative HPLC (10% *i*PrOH/*n*-hexane, 32 × 110 mm Nucleosil 50-5, UV = 220 nm, flow 95 mL/min). Yield: 1.23 g (5.13 mmol, 46.6%; retention time 2.8 min) of indolizidinone **20** (colorless oil) and 0.54 g (2.26 mmol, 20.5%; retention time 5.5 min) of indolizidinone **19** (colorless oil).

Data for indolizidinone 19: $[\alpha]_D^{20} = -35.1$ (c = 1.08, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.05 [s, 9 H, H−Si$(CH_3)_3$], 1.25 (s, 3 H, 5-H−CH_3), 1.90−1.60 (m, 6 H, 8o-,8u-,7o-,7u-,4o-,4u-H), 2.35−2.21 (m, 1 H, 3u-H), 2.48−2.35 (m, 1 H, 3o-H), 3.21−3.14 [dd, $^3J(H^{6u},H^{7o})$ = 10, $^3J(H^{6u},H^{7u})$ = 5.5 Hz, 1 H, 6u-H], 3.48−3.38 (m, 2 H, 9o-,9u-H) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 2.2 [q, Si$(CH_3)_3$], 21.9 (t, C-8), 26.2 (t, C-4), 26.3 (q, 5-CH_3), 28.3 (t, C-7), 35.2 (t, C-3), 45.7 (t, C-9), 67.4 (d, C-6), 70.4 (s, C-5), 168.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2975 (m), 2955 (m), 2880 (w), 1621 (s, C=O), 1470 (m), 1413 (m), 1378 (m), 1316 (w), 1273 (m), 1265 (m), 1253 (m), 1224 (w), 1134 (m), 1068 (m), 1021 (m) cm^{-1}. MS (80 eV, EI, 30 °C): m/z (%) = 241 (100) [$M^{+\cdot}$], 226 (30) [$M^+ - CH_3$], 198 (28), 178 (7), 171 (13), 144 (43), 143 (42), 130 (16), 129 (25), 111 (65), 83 (76), 75 (29), 73 (47), 70 (50). HRMS (80 eV, 30 °C): calcd. 241.149808 (for $C_{12}H_{23}N_1O_2Si$ [M^+]), found 241.14755.

Data for indolizidinone 20: $[\alpha]_D^{20} = -38.2$ (c = 1.30, $CHCl_3$). ^1H NMR (270 MHz, $CDCl_3$): δ = 0.07 [s, 9 H; H−Si$(CH_3)_3$], 1.12 (s, 3 H, 5-H−CH_3), 1.60−1.50 (m, 1 H, 7o-H), 1.75−1.60 (m, 1 H, 8u-H), 1.90−1.80 (m, 3 H, 4o-,4u-,8o-H), 2.00−1.90 (m, 1 H, 7u-H), 2.33−2.18 (m, 1 H, 3o-H), 2.52−2.40 (m, 1 H, 3u-H), 3.50−3.30 (m, 3 H, 9o-,9u-,6u-H) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$): δ = 2.54 [q, Si$(CH_3)_3$], 19.8 (q, CH_3), 22.1 (t, C-8), 27.3 (t, C-4), 30.2 (t, C-7), 37.2 (t, C-3), 45.8 (t, C-9), 66.9 (d, C-6), 72.7 (s, C-5), 167.9 (s) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2976 (m), 2951 (m), 2884 (m), 1624 (s, C=O), 1649 (m), 1417 (m), 1382 (m), 1299 (w), 1282 (w), 1252 (m), 1216 (m), 1159 (s), 1127 (m), 1072 (m), 1023 (m), 995(w) cm^{-1}. MS (80 eV, EI, 30 °C): m/z (%) = 241 (100) [$M^{+\cdot}$], 226 (20) [$M^+ - CH_3$], 206 (8), 198 (28), 144 (43), 143 (44), 130 (18), 129 (28), 111 (64), 83 (75), 75 (48), 73 (59), 70 (48). HRMS (80 eV, 30 °C): calcd. 241.149808 (for $C_{12}H_{23}N_1O_2Si$ [M^+]), found 241.14787.

X-ray Crystallographic Studies

Indolizidinone 6a (CCDC-172938): Colorless, transparent prism from CH_2Cl_2/*n*-hexane at room temp. $C_8H_{11}ClN_2O_4$ (M_r = 234.64); crystal dimensions 0.64 × 0.64 × 0.14 mm; monoclinic; $P2_1$, a = 8.8883(18), b = 9.1550(14), c = 12.5246(18) Å, Z = 4, V =1006.9(3) Å^3, $\rho_{calcd.}$ = 1.548 g/cm^3, T = 146 K, 2Θ max = 66.3°; of the 20,797 reflections measured 6262 were independent reflections (R_{int} = 0.0248, ωR = 0.0632, and S = 1.325); Siemens−SMART-diffractometer, Mo-K_α radiation (λ = 0.71073 Å). The structure was determined by direct methods by 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 by using 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 −0.175 and +0.228 e/A^3.

The structure contains two crystallographically independent molecules. The dimensions of both molecules are very similar. A small

difference of 6° is found for the torsion angle about the N−O single bond of the nitrate side chains. The conformation of the 1-azabicyclo[4.3.0]nonan-9-one group is similar to the conformation of this group as found in other crystal structures (CSD ref-codes: GONJEY, HIHKAK, and PAWTAI): the six-membered ring has a chair conformation, the five-membered ring has a 7-envelope conformation. The nitrate group is in an equatorial position with respect to the six-membered ring. The Cl atoms is in a pseudo-axial position with respect to the five-membered ring. The nitrogen atoms are almost planar. The molecules show no significant intramolecular interactions. The crystal packing shows three intermolecular C−H···Cl interactions with H···Cl distances of between 2.93 and 3.03 Å and six intermolecular C−H···O interactions with H···O distances of between 2.48 and 2.61 Å.

Epoxy-azonanone 9a (CCDC-172936): Colorless, transparent prism from CH_2Cl_2/*n*-hexane at −20 °C. $C_{15}H_{18}ClNO_2$ (M_r = 275.75); crystal dimensions 0.50 × 0.40 × 0.19 mm; orthorhombic; $P2_12_12_1$, a = 9.5482 (16), b = 9.56918 (8), c = 15.0739 (17) Å, Z = 4, V = 1377.3(3) Å^3, $\rho_{calcd.}$ = 1.349 g/cm^3, T = 144 K, 2Θ max = 60°; of the 25,245 reflections measured 4509 were independent reflections (R_{int} = 0.0377, ωR = 0.0719, and S = 1.203); Siemens-SMART diffractometer, Mo-K_α radiation(λ = 0.71073 Å). The structure was determined by direct methods by 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 by using 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 −0.178 and +0.270 e/A^3.

The conformation of the nine-membered ring is very similar to that found in the corresponding compound with a TBSO group attached to C7. Differences are only found for the torsion angles about the C6−C7 and C7−C8 bonds (about 10°) and for the torsion angles about the N−C9 and C9−C10 bonds (about 5°). The molecule shows a short repulsive intramolecular distance of 2.04 Å between H2 and H8B. The intramolecular O1···H9B distance of 2.28 Å approaches the van der Waals contact distance. The crystal packing only shows very weak, intermolecular electrostatic interactions: H4···Cl: 2.88 Å (1/2 + x, 1/2 − y, 1 − z), H6b···Cl: 2.99 Å (1/2 − x, −y, z − 1/2), H14···Cl: 3.01 Å (1/2 − x, 1 − y, z − 1/2), H15···Cl: 3.07 Å (1/2 − x, 1 − y, z − 1/2), H7B···O2: 2.62 Å (1 − x, 1/2 + y, 1/2 − z), and H13···O1: 2.69 Å (x − 1/2, 3/2 − y, 1 − z).

Epoxy-azonanone 9b (CCDC-172937): Colorless, transparent block from product oil at −20 °C. $C_{15}H_{18}NO_2Cl$ (M_r = 275.75); crystal dimensions 1.00 × 0.80 × 0.43 mm; orthorhombic; $P2_12_12_1$, a = 8.9639(16), b = 11.9771(13), c = 13.5890(15) Å, Z = 4, V = 1458.9(3) Å^3, $\rho_{calcd.}$ = 1.247 g/cm^3, T = 202 K, 2Θ max = 62°; of the 30,222 reflections measured 4621 were independent reflections (R_{int} = 0.0268, ωR = 0.1522, and S = 1.049); Siemens-SMART-diffractometer, Mo-K_α radiation(λ = 0.71073 Å). The structure was determined by direct methods by 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 by using 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 −0.349 and +0.252 e/A^3.

CCDC-172938 (**6a**), CCDC-172936 (**9a**), and CCDC-172937(**9b**) contain 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 Center, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44−1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

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[18] $[\alpha]_D^{20}$, $CHCl_3$: *pS*-**3a**: −44.8; *pR*-**3a**: −147.5; *pS*-**3b**: +121.9 (enantiomer of *pR*-**3a**).

[19] For detailed information on NOE data see supporting information

[20] Azoninone *pS*-**3a** was characterized by the coexistence of two conformers that could not be separated by means of HPLC. However, in the ^{1}H NMR spectrum the signals could be assigned and the nature of the conformational change was determined by NOE measurements.

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[35] The position of the protons of the two conformers **9a-major** and **9a-minor** in the ^{1}H NMR spectrum could be determined from a magnetization transfer during the NOE experiment on **9a** resulting from a fast chemical equilibration between **9a-major** and **9a-minor**. The assignment of the three-dimensional structure is from the structural correlation of the protons with the change of the characteristic ^4J coupling between the first H-9/N-Bn pair and the second during the course of the isomerization.

[36] Peak assignment based on ^{13}C-^{1}H-HMQC spectrum (500 MHz) in combination with DEPT and ^{1}H-^{1}H-COSY spectra (Peaks of the minor conformer are marked as C-3′)

[37] The pure mixture of **9a/b** could also be used instead of the crude epoxy-azonanones **9a/b** immediately after the workup of the epoxidation step. The yield was somewhat higher in this case.

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