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Enantioselective Approach to Indolizidine and Quinolizidine Scaffolds. Application to the Synthesis of Peptide Mimics

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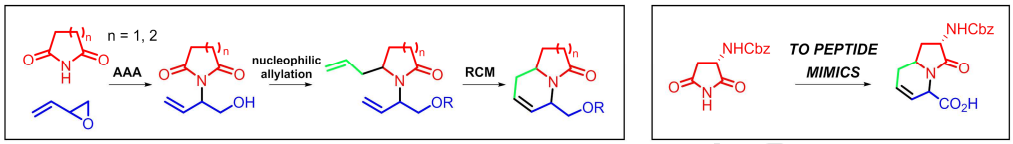

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ABSTRACT

An enantioselective approach to substituted indolizidine and quinolizidine frameworks has been developed. Key steps of the synthesis are the enantioselective, palladium-catalyzed *N*-allylation of an imide, the nucleophilic allylation of an acyliminium ion and a ring closing metathesis. This general strategy has been applied to the synthesis of indolizidine peptide mimics, starting from a chiral imide derived from L-aspartic acid. It was observed that the preexisting stereogenic center of this substrate has a moderate influence on the stereoselectivity of the electrophilic allylation, which is mainly determined by the sense of chirality of the catalyst.

1. Introduction

Indolizidine and quinolizidine are prominent heterobicyclic compounds containing a bridgehead nitrogen atom (Figure 1). These frameworks are often present in alkaloids isolated from diverse natural sources, frequently as part of a more complicated polyheterocyclic structure.[1] The polyhydroxylated indolizidines derived from plants and fungi, which function as potent glycosidase inhibitors, and the alkylindolizidines isolated from the skin of amphibians are among the most investigated groups of simple indolizidines. Prototypical examples of the first group are swainsonine and castanospermine, which have demonstrated activity against the HIV and other viruses,[2] stimulating considerable research on the synthesis of related structures and their mode of action. For instance, the castanospermine derivative known as celgosivir is currently in clinical trials as an anti-AIDS agent and for the treatment of dengue infections.[3] (−)-Lupinine and (−)-sparteine, isolated from plants, are probably the most representative examples among simple quinolizidines,[4] while 1,4- and 4,6-disubstituted quinolizidines are the more common structural patterns found in amphibian skin.[5] Bioactivity studies on quinolizidine alkaloids are relatively scarce, although some promising findings have been reported. For example, clavepictines A and B, isolated from a marine invertebrate, exhibit antimicrobial, antifungal, and antitumor activity.[6] The detailed structural assignment and biological evaluation of some isolated indolizidine and quinolizidine alkaloids is often constrained by affordability problems and, therefore, many investigations have been devoted to developing synthetic approaches to these systems.[7] In the last years, the interest in these heterobicycles has been expanded to the field of peptidomimetics. The replacement of a dipeptide motif with a

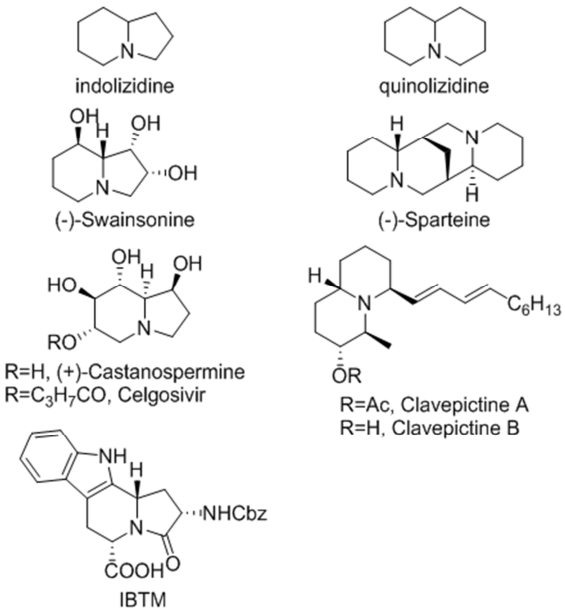
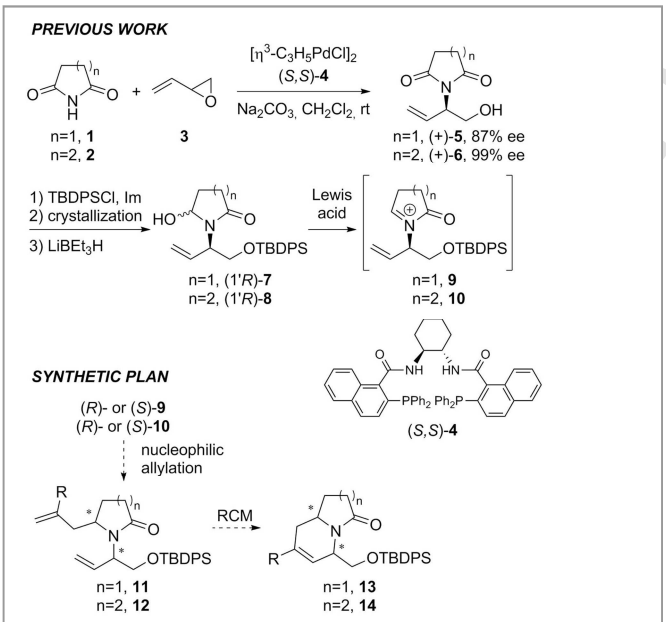


Figure 1. Some representative examples of indolizidines and quinolizidines.

constrained or rigidified counterpart that simulates a *β*-turn in the packaging of polypeptides has become a useful strategy for developing new therapeutic agents.[8] For instance, IBTM is an indolizidine dipeptide surrogate widely used to generate conformationally constrained *β*-turn mimics[9] and several analogs of it have been synthesized and investigated, showing diverse biological activities.[10] In this context, innovative methodologies for the synthesis of indolizidine and quinolizidine systems have been described,[11] wherein the regio- and stereochemical control of the substituent attachment is a main issue. Some of the described syntheses include alkylation reactions of cyclic iminium ions, mainly intramolecular,[12] and other encompass a ring closing metathesis (RCM) reaction.[13] However, there are only a few examples wherein these two processes were combined to generate one of these azabicycles,[14] and the asymmetric versions rely on chiral pool starting materials.[14a,c]

In former investigations, we adapted the palladium-catalyzed asymmetric allylic alkylation (AAA) of phtalimide developed by Trost[15] to the preparation of the *N*-subtituted succinimide (+)-**5** and glutarimide (+)-**6** (Scheme 1), which were used as starting materials for the synthesis of polycyclic alkaloids of the *Securinega* family.[16] Along these investigations, the *tert*-butyldiphenylsilylsilyl ethers derived from (+)-**5** and (+)-**6** were respectively reduced to the corresponding acylaminals (1'*R*)-**7** and (1'*R*)-**8**, as precursors of the acyliminium ions **9** and **10** that were then involved in a vinylogous Mannich reaction. Herein we describe how the AAA of succinimide and glutarimide can be an efficient entry to the enantioselective synthesis of indolizidine and quinolizidine frameworks, respectively, the *N*-acyliminium ions **9** and **10** acting as templates for the construction of these azabicyclic systems. An application of our strategy to the synthesis of indolizidine dipeptides is also reported.

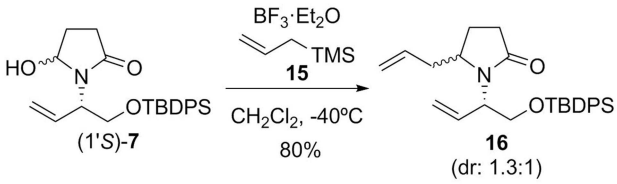


Scheme 1. AAA of **1** and **2** and preparation of acylaminals (1'*R*)-**7** and (1'*R*)-**8**[16] and synthetic plan for the stereoselective preparation of indolizidine and quinolizidine frameworks.

2. Results and discussion

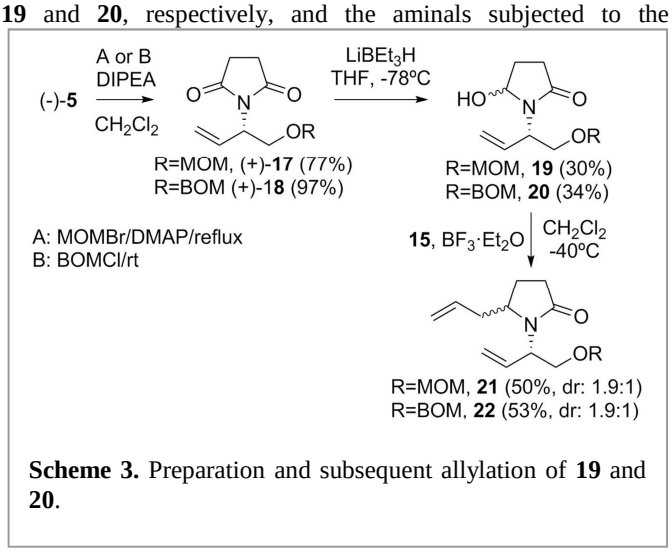
Our plan consisted on generating the *N*-acyliminium ions **9** or **10**, with a specific configuration of its stereogenic center, in the presence of an allylating reagent. This operation should furnish the dienes **11**/**12** containing a second stereogenic center. Then, a ring closing metathesis (RCM) reaction would provide the second ring.

The study was initiated by using the *N*-acylaminal (1'*S*)-**7**, readily prepared from succinimide through the sequence in Scheme 1 employing (*R*,*R*)-**4** as the chiral ligand. In the allylation of aminals, the Lewis acid exerts a fundamental effect on the formation of the electrophilic *N*-acyliminium ion and it also promotes the nucleophilic attack of the allylating reagent to this cation.[17] After exploring several combinations of Lewis acid/solvent/temperature, we found that treatment of (1'*S*)-**7** with 1.2 molar equivalents of allyltrimethylsilane, **15**, in the presence $BF_3 \cdot Et_2O$, in CH_3CN as solvent at –40°C afforded, after chromatographic purification, the allylated product **16** in 80% yield as a 1.3:1 mixture of diastereomers (Scheme 2).



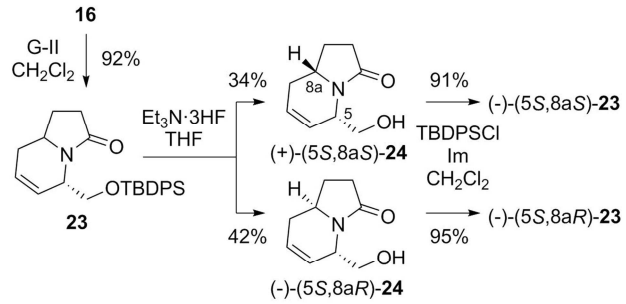
Scheme 2. Nucleophilic allylation of (1'*S*)-**7**.

Although the lack of diastereofacial selectivity of the nucleophilic allylation was not a drawback because it opened the access to different stereoisomeric indolizidines, we decided to investigate if the protecting group of the oxygen side chain exerted any influence on the stereoselectivity of the allylation reaction. To this aim, the methoxymethyl (MOM), (+)-**17**, and benzyloxymethyl (BOM), (+)-**18**, derivatives of alcohol (–)-**5** were prepared, converted into the corresponding *N*-acylaminals **19** and **20**, respectively, and the aminals subjected to the allylation reaction under identical conditions (Scheme 3). We observed that the allylation of both the MOM and BOM derivatives gave higher facial selectivity compared to the TBDPS analogue. However, the previous reduction of imides (+)-**17** and (+)-**18** proceeded in modest yields and no attempts were made to improve them. The studies were continued with the TBDPS derivative **16**.



Scheme 3. Preparation and subsequent allylation of **19** and **20**.

The RCM of **16**, performed with the mixture of diastereomers, in the presence of 5% molar second generation Grubbs catalyst (G-II) in CH_2Cl_2 at the reflux temperature, delivered the expected indolizidinone **23**, which was isolated as a mixture of diastereomers in 92% yield (Scheme 4). This mixture was desilylated by treatment with $Et_3N{\cdot}3HF$ in THF and the free alcohols **24** were separately isolated through purification by



Scheme 4. Preparation of indolizidinones **23** and **24**.

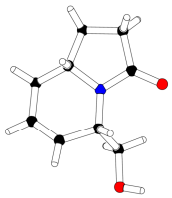
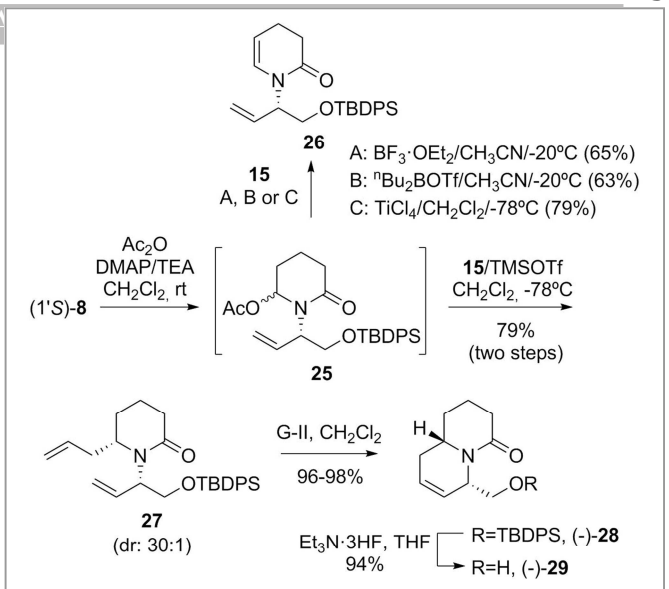


Figure 2. X-ray structure of alcohol (+)-(5*S*,8a*S*)-**24**.

column chromatography on silica gel, furnishing the less polar isomer (+)-(5*S*,8a*S*)-**24** in 34% yield and the more polar isomer (–)-(5*S*,8a*R*)-**24** in 42% yield. The relative configuration of these alcohols was established by X-ray diffraction analysis of the less polar isomer (Figure 2) that revealed the *cis* relationship between protons H-5 and H-8a. Each diastereomer of **24** was then separately re-silylated to afford (–)-(5*S*,8a*S*)-**23** and (–)-(5*S*,8a*R*)-**23**, in in 91% and 95% yield, respectively.

Then, the allylation of the glutarimide derivative (1'*S*)-**8** was undertaken (Scheme 5). In previous studies where (1'*R*)-**8** participated as the acceptor in a vinylogous Mannich reaction, we found that it was necessary to acetylate the hydroxyl group before generating the corresponding *N*-acyliminium ion, in order to circumvent the competitive elimination reaction leading to the enamide **26**.[16a] Hence, (1'*S*)-**8** was converted into the acetate **25** by treatment with acetic anhydride in CH_2Cl_2, in the presence of dimetyhlaminopyridine (DMAP), and an excess triethylamine (TEA),[18] which contributed to avoid the formation of the enamide **26** in parallel with the desired acetylation. The acetate **25** was isolated and rapidly subjected to the allylation reaction under the above conditions. Unexpectedly, we observed the predominant formation of the enamide **26** instead of the desired allylation product **27**. In view of that, we assayed other Lewis acids and conditions and found that the use of TMSOTf in CH_2Cl_2 at −40°C produced diene **27** as a 30:1 mixture of diastereomers in 79% overall yield for the two steps (acetylation/allylation).

The RCM of **27**, performed in the presence of 1% molar G-II in CH_2Cl_2 at the reflux temperature, after chromatographic purification, delivered the quinolizidine **28** as a unique isomer in 96% yield. This yield may be raised up to 98% by increasing the catalyst amount to 10%. As before, the azabicycle **28** was treated with $Et_3N{\cdot}3HF$ in THF to get the corresponding free alcohol **29**,



Scheme 5. Preparation of quinolizidinones **28** and **29**.

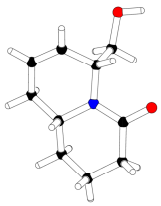
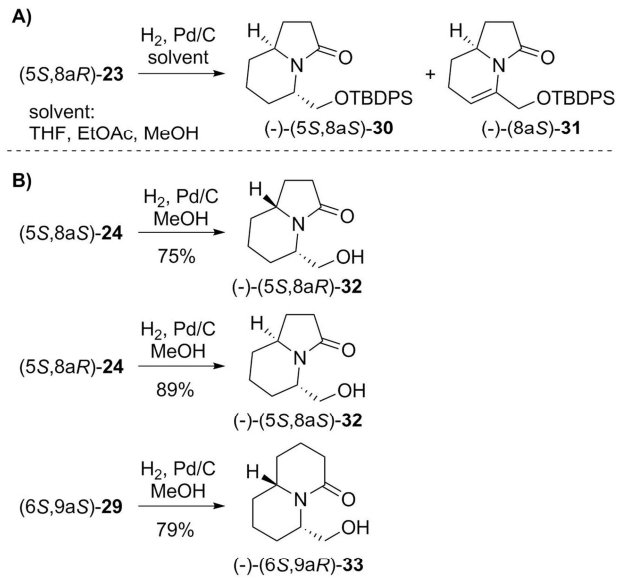


Figure 3. X-Ray structure of alcohol (–)-(6*S*,9a*S*)-**29**.

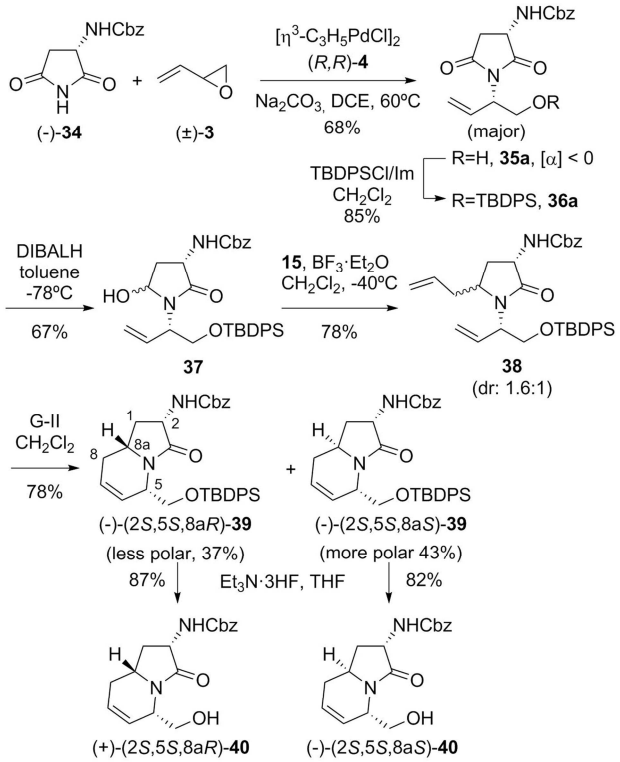
which relative configuration was established as 6*S*,9a*S* through an X-ray diffraction analysis (Figure 3).

Among other possibilities, the new alcohols **24** and **29** were visualized as suitable intermediates for the preparation of azabicyclic dipeptide mimics. To this purpose it would be necessary to accomplish an electrophilic amination at the α-carbonyl position and the oxidation of the primary alcohol to a carboxylic acid. Since the amination required the formation of an enolate under strongly basic conditions, we anticipated that it could be complicated by the presence of the relatively acidic allylic and α-nitrogen proton. Hence, we decided to hydrogenate the carbon-carbon double bond. The initial experiments with the TBDPS derivative (5*R*,8a*R*)-**23**, under 1 atm of H_2 in the presence of Pd/C in THF or EtOAc, showed that this substrate was very sluggish to react and that the migration of the carbon-carbon double bond leading to (8a*S*)-**31** was a competitive process (Scheme 6, A). In methanol as the solvent, the hydrogenation was much faster but concomitant with partial desilylation. Luckily, the hydrogenation in MeOH using as starting substrates the two isomeric alcohols **24** instead of their TBDPS derivatives **23** (Scheme 6, B) furnished the corresponding indolizidones **32** in good yields. Then, the same conditions were applied to prepare quinolizidone (6*S*,9a*R*)-**33** from the corresponding alkene precursor. The α-amination of alcohols **24**, **32** and **33** and silyl ether **30** was intended by treatment with three different sets of reagents: $Bu^tOK/^nBuONO$,[19] LDA/trisyl azide[20] and LDA/di-*tert*-butyl azodicarboxylate,[21] leading to recovery of the starting material in the first case and to unidentified decomposition products in the other cases.



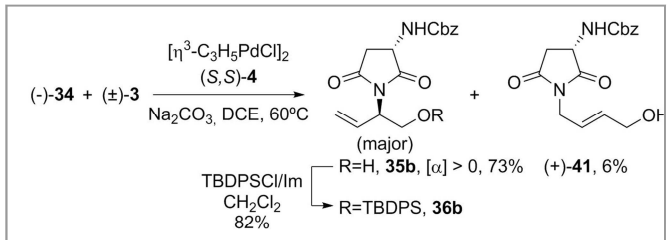
Scheme 6. Hydrogenation of **23** and preparation of azabicycles **32** and **33**.

As an alternative, we decided to explore the application of the sequence developed for preparing indolizidines starting from the simple succinimide **1** to the amino-substituted substrate (–)-**34** (Scheme 7), commercially available and readily prepared in three steps from L-aspartic acid.[22] This parallel sequence should thus involve the following consecutive steps: i) palladium catalyzed AAA, ii) *O*-silylation, iii) reduction to the acylaminal, iv) nucleophilic allylation, and v) RCM to form the indolizidine framework. Contrary to succinimide **1**, the starting substrate (–)-**34** is a chiral compound lacking any kind of symmetry. Consequently, it was particularly interesting to study the influence of the preexisting stereogenic centre on the stereoselectivity of the first allylation step, as well as on the regioselectivity of the reduction to the acylaminal from the imide. If the sequence could be successfully adapted to (–)-**34**, desilylation and subsequent oxidation of the primary alcohol should furnish the targeted peptide.



Scheme 7. Adjustment of the synthetic sequence to the preparation of azabicycles **40**.

Initially, the AAA of (–)-**34** with butadiene monoxide (±)-**3** was assayed under the same conditions used for succinimide, namely with 0.4 mol% Pd (II), 1.2 mol% (1*R*,2*R*)-**4** and 5 mol% Na_2CO_3 in dichloromethane at room temperature, but, surprisingly, in this case the starting material was recovered unchanged. The addition of DMF to the reaction medium, working at refluxing CH_2Cl_2, furnished the expected allylated product in a low 30% yield. Neither THF nor toluene as solvent, in both cases at the reflux temperature, led to any conversion of the substrate, but, when the reaction was performed in 1,2-dichloroethane (DCE) at 60°C, after purification by column chromatography on silica gel, the desired olefin **35a** was isolated in 68% yield, $[\alpha]_D$ −15.6 (*c* 1.04, CH_2Cl_2), apparently as a single diastereomer according to NMR analysis. Hence, the ^{1}H-NMR spectrum of compound **35a**, which was performed at 50°C to improve the resolution, showed only one set of signals, while the ^{13}C-NMR spectrum presented splitting of some signals, which was attributed to slow conformational equilibria related to the carbamate group and intramolecular hydrogen bonding. Since **35a** contains two stereogenic centres, the diastereomeric product ratio directly correlates with the stereoselectivity of the process. At this point, it was not possible to establish the relative configuration of **35a** and we assumed that the absolute configuration of the new stereogenic centre was governed by the sense of chirality of the catalyst ligand and, hence, we tentatively assigned it as *S*. Considering that the parallel reaction with the parent succinimide **1** under optimized conditions proceeded in 87% ee, we were intrigued by the apparent benefit that the pre-existing stereogenic centre in succinimide (–)-**34** exerts on the stereoselectivity of the reaction and decided to investigate if this improvement was due to a matching effect between the sense of chirality of the catalyst and the substrate, or it was a consequence of the lower reactivity of (–)-**34**, compared to the parent unsubstituted succinimide. To this aim, we assayed the reaction of (–)-**34** with (±)-**3** under identical conditions except for the use of the other enantiomer (1*S*,2*S*)-**4** of the catalyst ligand (Scheme 8). From this experiment, after chromatographic purification, we isolated the expected allylation product **35b** in 73% yield, $[\alpha]_D$ +14.6 (*c* 1.04, CH_2Cl_2), along with a minor quantity of the regioisomer (+)-**41** (6%). To our surprise, despite the opposite sign of the optical rotation, both ^{1}H- and ^{13}C-NMR spectra of **35b** showed identical signals to those of the former product **35a**, isolated from the reaction in the presence of the other enantiomer of the catalyst ligand.



Scheme 8. Palladium catalyzed AAA of (-)-**34** using the ligand (*S*,*S*)-**4**.

This finding led us to consider the possibility that both isolated products **35a** and **35b** were actually mixtures of two diastereomers in different proportions, a hypothesis which was reinforced when the samples were analyzed by CHPLC. Thus, both chromatograms presented at least four peaks, some of which

seemed to be common, in different relative intensities, but the complexity of these chromatograms prevented to infer the composition of the mixtures. In an attempt to solve this problem, the alcohols **35a** and **35b** were separately converted into the corresponding silyl ethers **36a** and **36b**, with the aim of suppressing the conformational complexity generated by the intramolecular hydrogen bonding. The silyl derivatives **36a** and **36b** presented also identical NMR spectra, with splitting of some ^{13}C signals, but showed simpler chromatograms, each one consisting in three peaks with different relative intensities (Figure 4). Analysis of these chromatograms, along with one of a mixture of **36a** and **36b** in equal amounts, made evident that the two diastereomers (3*S*,1'*R*)-**36** and (3*S*,1'*S*)-**36** were present in both samples and that each diastereomer displays two peaks, attributable to the two rotational carbamate conformers, with a close retention time for one rotamer of each isomer.

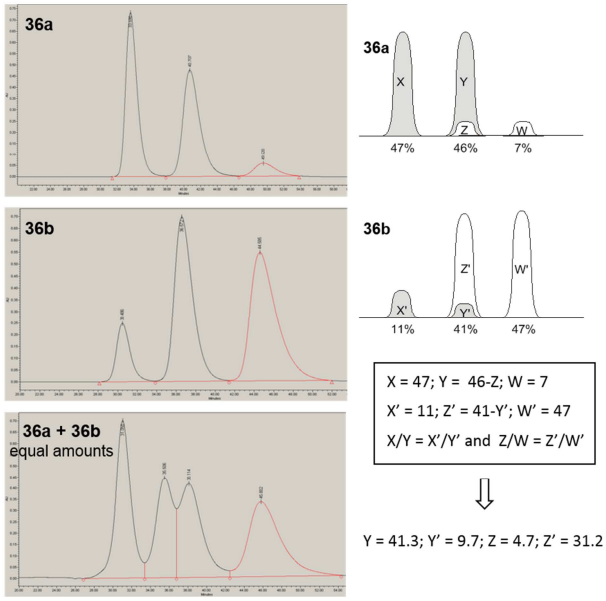


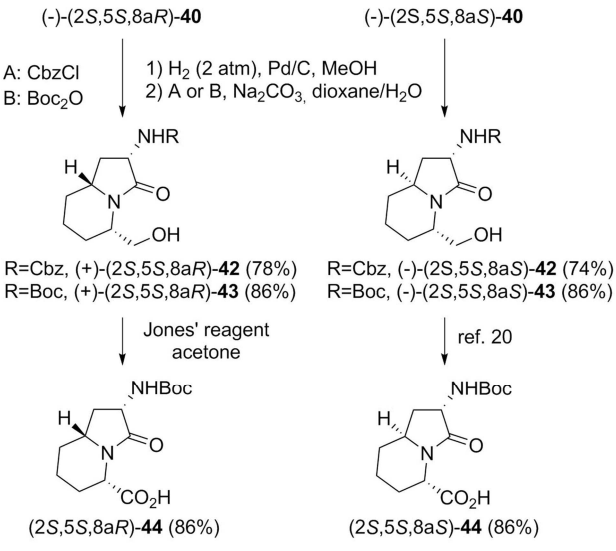
Figure 4. CHPLC analysis of **36a** and **36b**, derived from the AAA of (–)-**34**, in the presence of the ligand catalyst (1*R*,2*R*)-**4** and (1*S*,2*S*)-**4**, respectively. CHPLC analyses of the synthetic samples **36a**, **36b** and their mixture in equal amounts remain constant over time.

Since the conformational equilibrium of each diastereomer should not be affected by the presence of the other one, comparing the relative intensities of the peaks for each sample, it was possible to deduce its composition, which was roughly 88/12 (*de* 76%) for **36a**, coming from the reaction in the presence of the ligand (1*R*,2*R*)-**4** and 21/79 (*de* 58%) for **36b**, coming from the reaction in the presence of the ligand (1*S*,2*S*)-**4**. We can therefore conclude that the chirality of the substrate exerts a moderate influence on the stereochemical course of the reaction and that the stereoselectivity is mainly dictated by the sense of chirality of the catalyst ligand.

The synthesis was continued from the silyl ether **36a** (Scheme 7). The regioselective reduction of the imide was accomplished by treatment with DIBALH in toluene at –78°C.[23] The acylaminal **37**, isolated in 67% yield as a mixture of isomers, was treated with allyltrimethylsilane in the presence of $BF_3 \cdot Et_2O$, furnishing a 1.6:1 mixture of epimeric dienes **38** in 78% overall yield. Any diene eventually derived from the minor diastereomer (12%) present in the starting material **36a** could not be detected.

The RCM of **38** was performed in refluxing CH_2Cl_2 in the presence of 5% G-II catalyst and, after chromatographic purification, afforded the two azabicyles (–)-(2*S*,5*S*,8a*R*)-**39** (less polar) and (–)-(2*S*,5*S*,8a*S*)-**39** (more polar) in 37% and 43% yield, respectively. NMR experiments on these compounds confirmed their connectivity, since in their 2D-COSY spectra the signal of H-8a is related to four saturated hydrogens (2H-1 and 2H-8), but not to the proton next to the amino group (H-2). Their relative configuration was established after converting each isomer of **39** into the corresponding alcohol **40**. Thus, a NOESY experiment with the alcohol **40** derived from the less polar isomer of the silyl ether **39** in C_6D_6 showed crossed peaks between the three protons attached to the stereogenic centres, evidencing that H-2 (δ 4.25), H-5 (δ 4.04) and H-8a (δ 3.22) were in the same face of the bicyclic system, namely in a relative all *cis* configuration. Since the absolute configuration at C-2 was known to be *S*, according to the starting aspartic acid derivative, the absolute configuration of the new compounds **39** and **40** could be unambiguously established, confirming the tentative configuration assigned to the major diastereomer of alkene **35a**, formed in the AAA of imide (–)-**34**.

With the two diastereomers of **40** in hands, the only remaining step to the target peptides was the oxidation of the primary alcohol to the corresponding carboxylic acid. This transformation was attempted with several reagents, including DMP, PCC, Swern reagent, Jones reagent,[24] and $NaIO_4/RuCl_3 \cdot 3H_2O$,[25] under different conditions, leading always to decomposition products. Hence, we decided to undertake the hydrogenation of the carbon-carbon double bond prior to the oxidation (Scheme 9). This transformation was accomplished in MeOH solution, under 2 atm of hydrogen, using Pd/C as the catalyst, and proceeded with concomitant hydrogenolysis of the carbamate, as expected. Without isolation of the intermediate, the amino group was re-protected either as the benzyl- (Cbz) or the *tert*-butyloxycarbamate (Boc), furnishing the corresponding alcohols **42** and **43**, respectively, in good overall yields. Alcohol (2*S*,5*S*,8a*S*)-**43** has been previously described and converted into the peptide mimic (2*S*,5*S*,8a*S*)-**44** and its methyl ester.[20] The alcohol oxidation of the Cbz derivatives **42**, intended under various standard methods, revealed problematic, leading mainly to decomposition products instead of the expected carboxylic acids. However, the oxidation of the Boc derivative (2*S*,5*S*,8a*R*)-



Scheme 9. Palladium catalyzed AAA of (-)-**34** using the ligand (*S*,*S*)-**4**.

43 by treatment with Jones' reagent delivered the known peptide surrogate (2*S*,5*S*,8a*R*)-**44**,[26] in good yield.

3. Conclusions

We have developed an enantioselective approach to substituted indolizidine and quinolizidine frameworks, based on the introduction of two allylic residues over an imide substrate at a suitable distance, followed by a ring closing metathesis of the diene. The first allylic fragment is attached by means of a palladium mediated asymmetric *N*-alkylation and the second one through a nucleophilic addition to an acyliminium ion. By using the chiral succinimide (–)-**34** derived from aspartic acid, the general strategy has been applied to the synthesis of an indolizidine peptide mimic. It was observed that the preexisting stereogenic center of this substrate has a moderate influence on the stereoselectivity of the first allylation step, which is mainly determined by the sense of chirality of the catalyst.

4. Experimental section

4.1. General remarks

Commercially available reagents were used as received. The solvents were dried by distillation over the appropriate drying agents. All reactions were performed avoiding moisture by standard procedures and under nitrogen atmosphere. Flash column chromatography was performed using silica gel (230-400 mesh). High-Performance Liquid Chromatography (HPLC) analyses were performed using a chromatograph coupled to a UV-visible array detector (at 214 nm) with a Daicel Chiralcel OD (25 x 0.46 cm) with a flow of 1 ml/min and 97:03 hexane:isopropanol as mobile phase. ^{1}H NMR and ^{13}C NMR spectra were recorded at 250 and 62.5 MHz, 360 and 90 MHz, or 400 and 101 MHz. Proton and carbon chemical shifts are reported in ppm (δ) ($CDCl_3$, δ 7.26 for ^{1}H; $CDCl_3$, δ 77.2 for ^{13}C; C_6D_6 δ 7.16 for ^{1}H; δ 128.4 for ^{13}C). NMR signals were assigned with the help of COSY, HSQC, HMBC, and NOESY experiments. Melting points were determined on hot stage and are uncorrected. Optical rotations were measured at 22 ± 2°C.

*4.2. (S)-1-(1-Hydroxybut-3-en-2-yl)pyrrolidine-2,5-dione ((–)-**5**)*

A mixture of π-allylpalladium chloride dimer (11.8 mg, 0.03 mmol), (1*R*,2*R*)-**4** (81 mg, 0.10 mmol), sodium carbonate (43 mg, 0.40 mmol) and succinimide, **1**, (797 mg, 8.05 mmol) was purged with nitrogen for 1 h. Dry CH_2Cl_2 (100 mL) was added and the mixture was stirred at room temperature for 10 min. Then, butadiene monoepoxide, **3**, (640 µL, 8.00 mmol) was added and the resulting mixture was efficiently stirred under nitrogen for 14 h. After that time, the reaction mixture was filtered through Celite®, washing with ethyl acetate, and the filtrate concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 5:1 to 2:1) to give (−)-**5** (1.14 g, 6.76 mmol, 84% yield) as a clear oil in 83% enantiomeric excess (determined by CHPLC analysis, ^{i}PrOH/hexane, 10:90): $[\alpha]_D$ −32.8 (*c* 1.90, CH_2Cl_2). Other physical and spectroscopic data of (−)-**5** were identical to those previously described for (+)-**5**.[16]

*4.3. (5RS)-1-[(S)-1-(tert-Butyldiphenylsilyloxy)but-3-en-2-yl]-5-hydroxypyrrolidin-2-one ((1'S)-**7**)*

*4.3.1. Silylation of (−)-**5***

In a 250 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, alcohol (−)-**5** (1.35 g, 7.98 mmol) was dissolved in anhydrous CH_2Cl_2 (60 mL). After cooling to 0°C, imidazole (2.72 g, 39.90 mmol) was added, followed by TBDPSCl (4.1 mL, 15.96 mmol). The cooling bath was removed and the mixture was stirred at room temperature overnight. The solvent was evaporated under vacuum and replaced by ethyl acetate (50 mL). The resulting mixture was stirred vigorously for 1 h and the insoluble fine white powder (imidazole·HCl) filtered through Celite®. The filtrate was concentrated under vacuum and then purified by flash column chromatography (hexanes/ethyl acetate, from 9:1 to 3:2) to give a residue, which was crystallized from 2-propanol, furnishing the expected silylated derivative (2.18 g, 5.35 mmol, 67% yield) of >98% ee (determined by CHPLC analysis, ^{i}PrOH/hexane, 10:90): $[\alpha]_D$ +14.4 (*c* 1.30, CH_2Cl_2). The physical and spectroscopic data of this compound were identical to those previously described for its enantiomer.[16]

4.3.2. Reduction

A solution of $LiBEt_3H$ in THF (1M, 7.3 mL, 7.30 mmol) was added dropwise to a solution of the previous intermediate (1.99 g, 4.88 mmol) in dry THF (25 mL), under nitrogen atmosphere at −78°C, and the reaction mixture, monitored by TLC (hexanes/ethyl acetate, 1:1), was stirred at the same temperature for 45 min. Keeping the temperature at −78°C saturated aqueous $NaHCO_3$ (40 mL) and H_2O_2 (30%, 10 mL) were added, and the mixture was allowed to warm slowly to room temperature and then stirred for one additional hour. After filtration through Celite®, the solution was extracted with CH_2Cl_2 (4x30 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The oily residue was purified by flash chromatography (hexanes/ethyl acetate, from 4:1 to 1:1) to give a mixture of epimers (1'*S*)-**7** (1.70 g, 4.15 mmol, 85% yield) as a colourless oil. The physical and spectroscopic data of this product were identical to those previously described for (1'*R*)-**7**.[16]

*4.4. (5RS)-5-Allyl-1-[(S)-1-(tert-butyldiphenylsilyloxy)but-3-en-2-yl]pyrrolidin-2-one (**16**)*

In a 250 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of (1'*S*)-**7** (982 mg, 2.40 mmol) in anhydrous CH_3CN (50 mL) was cooled down to −40°C. To the cold solution was added allyltrimethylsilane (420 µL, 2.64 mmol) and then, dropwise, $BF_3{\cdot}Et_2O$ (610 µL, 4.80 mmol). The reaction, monitored by TLC (hexanes/ethyl acetate, 3:2), was finished in 1 h. Then, saturated aqueous $NaHCO_3$ (100 mL) was added and the mixture was allowed to warm up to room temperature. After the extraction with CH_2Cl_2 (4x50 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 4:1 to 1:2) to give a 1.3:1 mixture of (5*R*)- and (5*S*)-**16** (832 mg, 1.92 mmol, 80% yield) as a yellow oil: *Rf* = 0.4 (hexanes/ethyl acetate, 3:2); IR (ATR) 3073, 2932, 2858, 1687, 1428, 1259, 1110 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) Isomer A (5*R*) and B (5*S*) δ 7.67 (m, $4H_A$ + $4H_B$), 7.40 (m, $6H_A$ + $6H_B$), 6.11 (ddd, *J* = 17.4, 10.5, 7.1 Hz, $1H_B$), 5.90 (ddd, *J* = 17.1, 10.5, 6.6 Hz, $1H_A$), 5.66 (m, $1H_A$ + $1H_B$), 5.12 (m, $4H_A$ + $4H_B$), 4.55 (m, $1H_A$), 4.21 (dd, *J* = 10.2, 8.4 Hz, $1H_B$), 4.08 (m, $1H_B$), 3.97 (m, $1H_A$ + $1H_B$), 3.75 (m, $2H_A$ + $1H_B$), 2.49-1.98 and 1.75 (m) ($6H_A$ + $6H_B$), 1.07 (s, $9H_B$), 1,06 (s, $9H_A$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 175.0, 135.5, 134.4, 133.5, 133.4, 133.2, 129.7, 127.7, 127.6, 118.4, 118.2, 118.0, 117.6, 63.7, 62.9, 59.5, 59.3, 57.0, 39.4, 38.7, 30.4, 30.1, 26.8, 26.7, 23.9, 23.8, 19.1; HRMS m/z (ESI+) calcd for [$C_{27}H_{35}NO_2SiNa^+$]: 456.2335, found: 456.2326.

*4.5. (S)-1-(1-Methoxymethoxybut-3-en-2-yl)pyrrolidine-2,5-dione ((+)-**17**)*

In a 25 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, alcohol (−)-**5** (246 mg, 1.45 mmol) was dissolved in anhydrous CH_2Cl_2 (3.8 mL). After cooling to 0°C, DIPEA (1.6 mL, 9.2 mmol), DMAP (57 mg, 0.47 mmol) and MOMBr (185 μL, 2.27 mmol) were consecutively added. The cooling bath was removed, the mixture was allowed to warm to room temperature, and then it was heated at reflux overnight. The solvent was evaporated under vacuum and replaced by Et_2O (10 mL). The solution was washed with brine (10 mL), the organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum and the residue (278 mg) was purified by flash column chromatography (ethyl acetate) to furnish (+)-**17** (238 mg, 1.12 mmol, 77% yield) as oil: *Rf*= 0.3 (hexanes/ethyl acetate, 1:1); $[\alpha]_D$ +15 (*c* 0.01, CH_2Cl_2); IR (ATR) 2922, 2852, 1697, 1383, 1193, 1147, 1107 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.05 (ddd, *J* = 17.5, 10.2, 7.6 Hz, 1H), 5.24 (m, 2H), 4.85 (m, 1H), 4.55 (m, 2H), 4.09 (t, *J* = 10.1 Hz, 1H); 3.72 (dd, *J* = 10.6, 5.7 Hz, 1H), 3.30 (s, 3H), 2.68 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.7, 131.4, 119.6, 96.4, 65.7, 55.6, 54.4, 28.0; HRMS (ESI+) calcd for $[C_{10}H_{15}NO_4Na^+]$: 236.0899, found: 236.0887.

*4.6. (S)-1-(1-Benzyloxymethoxybut-3-en-2-yl)pyrrolidine-2,5-dione ((+)-**18**)*

In a 25 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, alcohol (−)-**5** (144 mg, 0.85 mmol) was dissolved in anhydrous CH_2Cl_2 (5 mL). After cooling to 0°C, BOMCl (240 μL, 173 mmol) and DIPEA (220 μL, 1.26 mmol) were added. The cooling bath was removed and the mixture, monitored by TLC (hexanes/ethyl acetate, 1:1), was stirred at room temperature overnight. The solution was diluted with Et_2O (10 mL) and washed with water (3x30 mL) and brine (30 mL). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum and the residue (276 mg) was purified by flash column chromatography (ethyl acetate) to furnish (+)-**18** (240 mg, 0.83mmol, 97% yield) as oil: *Rf*= 0.5 (hexanes/ethyl acetate, 1:1); $[\alpha]_D$ +12 (*c* 0.01, CH_2Cl_2); IR (ATR) 2920, 1774, 1698, 1383, 1254, 1195, 1111, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5H), 6.07 (ddd, *J* = 17.9, 10.3, 7.7 Hz, 1H), 5.27 (m, 2H), 4.88 (m, 1H), 4.70 (m, 2H), 4.55 (s, 2H); 4.17 (t, *J* = 10.1 Hz, 1H), 3.80 (dd, *J* = 10.3, 5.6 Hz, 1H), 2.66 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 137.6, 131.4, 128.4, 127.8, 127.7, 119.6, 94.5, 69.9, 66.0, 54.1, 28.1; HRMS (ESI+) calcd for $[C_{16}H_{19}NO_4Na^+]$: 312.1212, found: 312.1204.

*4.7. (5RS)-5-Hydroxy-1-[(S)-1-methoxymethoxybut-3-en-2-yl]pyrrolidin-2-one (**19**)*

A solution of $LiBEt_3H$ in THF (1M, 3.8 mL, 3.80 mmol) was added dropwise to a solution of (+)-**17** (490 mg, 2.30 mmol) in dry THF (20 mL), under nitrogen atmosphere at −78°C, and the reaction mixture, monitored by TLC (hexanes/ethyl acetate, 1:1), was stirred at the same temperature for 2 h. Keeping the temperature at −78°C, saturated aqueous $NaHCO_3$ (24 mL) and H_2O_2 (30%, 5.5 mL) were added, and the mixture was allowed to warm slowly to room temperature and then stirred for one additional hour. The solution was concentrated and then filtered through a small pad of silica gel, washing with ethyl acetate. The solvent was removed under vacuum, water (50 mL) was added to the residue and then extracted with CH_2Cl_2 (4x40 mL). The organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (hexanes/ethyl acetate, from 1:1 to 1:9) to give a 1.6:1 mixture of epimers (1'*S*)-**19** (146 mg, 0.68 mmol, 30% yield) as a colourless oil: *Rf* = 0.1 (hexanes/ethyl acetate, 1:1); IR (ATR) 3348, 2934, 1663, 1419, 1280, 1148, 1108, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) Isomer A (major) and B (minor) δ 6.03 (ddd, *J* = 17.4, 10.5, 6.9 Hz, $1H_B$), 5.89 (ddd, *J* = 16.9, 10.6, 6.0 Hz, $1H_A$), 5.23 (m, $3H_A + 3H_B$), 4.82 (m, $1H_A$), 4.63 (m, $2H_A + 2H_B$), 4.51 (br s, $1H_A$), 4.42 (m, $1H_B$), 3.96 (m, $1H_B$), 3.77 (m, $2H_A$), 3.70 (dd, *J* = 10.2, 4.0 Hz, $1H_B$), 3.35 (s, $3H_A$), 3.33 (s, $3H_B$), 2.63 (m, $2H_A$), 2.28 (m, $2H_B$), 2.23 (m, $2H_B$), 2.10 (m, $2H_A$); ^{13}C NMR (101 MHz, $CDCl_3$) Isomer A (major) and B (minor) δ 175.5 (A) and 174.9 (B), 133.9 (B) and 132.5 (A), 118.8 (A) and 118.0 (B), 96.7 (A) and 96.5 (B), 83.6 (B) and 80.5 (A), 68.5 (A) and 66.8 (B), 55.8 (A+B), 55.6 (B) and 52.7 (A), 29.2 (B) and 28.7 (A), 28.1 (B) and 27.8 (A); HRMS m/z (ESI+) calcd for $[C_{10}H_{16}NO_4Na^+]$: 237.0977, found: 237.0983.

*4.8. (5RS)-1-[(S)-1-Benzyloxymethoxybut-3-en-2-yl]-5-hydroxypyrrolidin-2-one (**20**)*

A solution of $LiBEt_3H$ in THF (1M, 5.2 mL, 5.20 mmol) was added dropwise to a solution of (+)-**18** (798 mg, 2.76 mmol) in dry THF (50 mL), under nitrogen atmosphere at −78°C, and the reaction mixture, monitored by TLC (hexanes/ethyl acetate, 1:1), was stirred at the same temperature for 1.5 h. Keeping the temperature at −78°C, saturated aqueous $NaHCO_3$ (25 mL) and H_2O_2 (30%, 5.5 mL) were added, and the mixture was allowed to warm slowly to room temperature and then stirred for one additional hour. The solution was concentrated and then filtered through a small pad of silica gel, washing with ethyl acetate. The solvent was removed under vacuum, water (70 mL) was added to the residue, and then it was extracted with CH_2Cl_2 (4x50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude product was purified by flash column chromatography (hexanes/ethyl acetate, from 1:1 to 1:4) to give a 1.5:1 mixture of epimers (1'*S*)-**20** (273 mg, 0.94 mmol, 34% yield) as a colourless oil: *Rf* = 0.1 (hexanes/ethyl acetate, 1:1); IR (ATR) 3342, 2921, 1663, 1453, 1418, 1279, 1164, 1107, 1039 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) Isomer A (major) and B (minor) δ 7.34 (m, $5H_A + 5H_B$), 6.06 (ddd, *J* = 17.0, 10.4, 6.7 Hz, $1H_B$), 5.91 (ddd, *J* = 17.5, 10.9, 6.4 Hz, $1H_A$), 5.26 (m, $3H_A + 3H_B$), 4.86 (m, $1H_A$), 4.79 (m, $2H_A + 2H_B$), 4.60 (s, $2H_A + 2H_B$), 4.49 (s, $1H_A$), 4.39 (m, $1H_B$), 4.06 (m, $1H_B$), 3.85 (m, $2H_A$), 2.66 (m, $2H_A$), 2.28 (m, $2H_A$), 2.07 (m, $4H_B$); ^{13}C NMR (101 MHz, $CDCl_3$) Isomer A (major) and B (minor) δ 175.5/174.9 (A/B), 133.3 (A+B), 137.0 (A+B), 133.8 (B) and 132.5 (A), 128.5 (A+B), 127.8 (A+B), 119.0 (A) and 118.2 (B), 94.8 (A+B), 83.8 (B) and 80.4 (A), 70.1 (A+B), 68.7 (A) and 67.2 (B), 56.0 (B) and 52.9 (A), 29.3 (B) and 28.8 (A), 28.0 (B) and 27.8 (A); HRMS m/z (ESI+) calcd for $[C_{16}H_{21}NO_4Na^+]$: 314.1363, found: 314.1363.

*4.9. (5RS)-5-Allyl-1-[(S)-1-methoxymethoxybut-3-en-2-yl]pyrrolidin-2-one (**21**)*

In a 25 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of (1'*S*)-**19** (16 mg, 0.07 mmol) in anhydrous CH_3CN (1.5 mL) was cooled down to −40°C. To the cold solution was added allyltrimethylsilane (14.5 μL, 0.09 mmol) and then, dropwise, $BF_3{\cdot}Et_2O$ (24.5 μL, 0.19 mmol). The reaction, monitored by TLC (hexanes/ethyl acetate, 2:3), was finished in 4 h. Then, saturated aqueous $NaHCO_3$ (5 mL) was added and the mixture was allowed to warm up to room temperature. After the extraction with CH_2Cl_2 (4x5 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 3:7 to 1:9) to give a 1.9:1 mixture of (5*R*)- and (5*S*)-**21** (9 mg, 0.04 mmol, 50% yield) as a yellow oil: *Rf* = 0.2 (hexanes/ethyl acetate, 2:3); IR (ATR) 3079, 2931, 1681, 1417, 1257, 1151, 1111, 1039 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) Isomer A (major) and B (minor) δ 6.07 (ddd, *J* = 16.5, 10.5, 6.9 Hz, $1H_B$), 5.93

(ddd, *J* = 17.0, 10.4, 6.6 Hz, $1H_A$), 5.71 (m, $1H_A$ + $1H_B$), 5.18 (m, $4H_A$ + $4H_B$), 4.61 (m, $2H_A$ + $2H_B$), 4.50 (m, $1H_A$), 4.32 (m, $1H_B$), 3.89 (m, $2H_A$ + $2H_B$), 3.35 (s, $3H_A$ + $3H_B$), 2.49-1.72 (complex, $6H_A$ + $6H_B$); ^{13}C NMR (90 MHz, $CDCl_3$) δ 175.7, 175.2, 134.5, 133.4, 118.5, 117.5, 96.4, 67.9, 66.8, 58.7, 57.3, 56.4, 55.4, 55.1, 39.2, 38.9, 30.3, 30.1, 23.8; HRMS m/z (ESI+) calcd for $[C_{13}H_{21}NO_3Na^+]$: 262.1419, found: 262.1412.

*4.10. (5RS)-5-Allyl-1-[(S)-1-benzyloxymethoxybut-3-en-2-yl]pyrrolidin-2-one (**22**)*

In a 25 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of (1'*S*)-**20** (42 mg, 0.15 mmol) in anhydrous CH_3CN (2.7 mL) was cooled down to −40°C. To the cold solution was added allyltrimethylsilane (28 µL, 0.18 mmol) and then, dropwise, $BF_3{\cdot}Et_2O$ (49 µL, 0.39 mmol). The reaction, monitored by TLC (hexanes/ethyl acetate, 2:3), was finished in 4 h. Then, saturated aqueous $NaHCO_3$ (9 mL) was added and the mixture was allowed to warm up to room temperature. After the extraction with CH_2Cl_2 (4x9 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 3:2 to 3:7) to give a 1.9:1 mixture of (5*R*)- and (5*S*)-**22** (24 mg, 0.08 mmol, 53% yield) as a yellow oil: *Rf* = 0.3 (hexanes/ethyl acetate, 2:3); IR (ATR) 2927, 2879, 1681, 1414, 1255, 1167, 1110, 1040 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) Isomer A (major) and B (minor) δ 7.34 (m, $5H_A$ +$5H_B$), 6.08 (ddd, *J* = 17.3, 10.6, 7.0 Hz, $1H_B$), 5.95 (ddd, *J* = 17.2, 10.4, 6.7 Hz, $1H_A$), 5.72 (m, $1H_A$ + $1H_B$), 5.19 (m, $4H_A$ + $4H_B$), 4.77 (m, $2H_A$ + $2H_B$), 4.60 (m, $2H_A$ + $2H_B$), 4.51 (m, $1H_A$), 4.30 (m, $1H_B$), 3.97 (m, $2H_A$ + $1H_B$), 3.74 (m, $1H_A$ + $2H_B$), 2.49-1.72 (complex, $6H_A$ + $_{6H_B}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 175.2, 134.5, 137.8, 134.5, 133.3, 128.6, 127.8, 118.5, 117.8, 94.7, 69.7, 68.0, 67.1, 58.8, 57.3, 56.5, 55.1, 39.2, 38.9, 30.3, 30.1, 23.9; HRMS m/z (ESI+) calcd for $[C_{19}H_{25}NO_3Na^+]$: 338.1732, found: 338.1727.

*4.11. (5S,8aRS)-5-(tert-Butyldiphenylsilyloxy)methyl-1,5,8,8a-tetrahydroindolizin-3(2H)-one (**23**)*

In a 250 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of **16** (654 mg, 1.51 mmol) in anhydrous CH_2Cl_2 (150 mL) was warmed up to the reflux temperature and, then, 2nd generation Grubbs catalyst (65 mg, 0.075 mmol) was added in 3 portions (one per hour). The mixture was heated at reflux overnight. After cooling down to room temperature, the resulting mixture was filtered through a small pad of silica gel, washing with ethyl acetate. The filtrate was concentrated under vacuum and the residue purified by flash column chromatography (hexanes/ethyl acetate, from 3:2 to 1:9) to give a 1.2:1 mixture of (5*S*,8a*R*)- and (5*S*,8a*S*)-**23** (563 mg, 1.39 mmol, 92% yield): *Rf* = 0.3 (hexanes/ethyl acetate, 1:1); IR (ATR) 3070, 3044, 2929, 2856, 1684, 1421, 1109 cm^{-1}; HRMS m/z (ESI+) calcd for $[C_{25}H_{31}NO_2SiNa]$: 428.2022, found: 428.2015. Other characterization data of these compounds are given below.

*4.12. (5S,8aR)- and (5S,8aS)-5-Hydroxymethyl-1,5,8,8a-tetrahydroindolizin-3(2H)-one (**24**)*

In a 250 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of a mixture of (5*S*,8a*R*)- and (5*S*,8a*S*)-**23** (360 mg, 0.89 mmol) in anhydrous THF (15 mL) was heated to the reflux temperature. After the addition of $Et_3N{\cdot}3HF$, (0.87 mL, 5.34 mmol), the mixture was stirred under reflux overnight. After cooling, the mixture was diluted with CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) was added. The layers were separated and the aqueous one extracted with CH_2Cl_2 (4x20 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum, and the residue was purified by flash column chromatography (from hexanes/ethyl acetate, 1:1, to ethyl acetate and then chloroform/methanol, 9:1) to give (5*S*,8a*S*)-**24** (51 mg, 0.31 mmol, 34% yield), which was less polar, and (5*S*,8a*R*)-**24** (63 mg, 0.38 mmol, 42% yield), which was more polar. (5*S*,8a*S*)-**24**: *Rf* = 0.2 (ethyl acetate); $[\alpha]_D$ +62.3 (*c* 1.35, CH_2Cl_2); IR (ATR): 3352, 3050, 2930, 2857, 1700, 1669, 1648, 1417, 1268, 1105 cm^{-1}; ^{1}H NMR (360 MHz, C_6D_6) δ 6.50 (m, 1H), 5.32 (ddt, *J* = 10.4, 6.4, 2.1 Hz, 1H), 5.08 (m, 1H), 4.00 (m, 1H), 3.80 (m, 2H), 2.71 (m, 1H), 1.94 (ddd, *J* = 10.3, 6.0, 2.0 Hz, 1H), 1.77 (m, 1H), 1.52-1.25 (m, 3H), 0.80 (m, 1H); ^{13}C NMR (90 MHz, C_6D_6) δ 177.5, 126.6, 125.9, 67.7, 60.2, 56.3, 32.7, 31.2, 26.7; HRMS (ESI+) calcd for $[C_9H_{13}NO_2Na^+]$: 190.0844, found: 190.0840. (5*S*,8a*R*)-**24**: *Rf* = 0.1 (ethyl acetate); $[\alpha]_D$ −211.4 (*c* 1.20, CH_2Cl_2); IR (ATR): 3355, 2926, 1662, 1644, 1423, 1265, 1079 cm^{-1}; ^{1}H NMR (360 MHz, C_6D_6) δ 5.39 (m, 2H), 4.59 (m, 1H), 3.70 (m, 2H), 3.58 (m, 1H), 3.17 (m, 1H), 1.98 (m, 2H), 1.52 (m, 2H), 1.31 (m, 1H), 0.87 (m, 1H); ^{13}C NMR (90 MHz, C_6D_6) δ 175.8, 126.2, 125.7, 66.1, 54.0, 51.4, 32.8, 30.5, 25.9; HRMS (ESI+) calcd for $[C_9H_{13}NO_2Na^+]$: 190.0844, found: 190.0843.

*4.13. (5S,8aR)-5-(tert-Butyldiphenylsilyloxy)methyl-1,5,8,8a-tetrahydroindolizin-3(2H)-one ((5S,8aR)-**23**)*

In a 10 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, (5*S*,8a*R*)-**24** (50 mg, 0.30 mmol) was dissolved in anhydrous CH_2Cl_2 (2 mL). After cooling to 0°C, imidazole (82 mg, 1.20 mmol) and TBDPSCl (0.16 mL, 0.6 mmol) were added. The cooling bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was concentrated under vacuum and the residue dissolved in ethyl acetate (5 mL). After vigorous stirring for 1 h, the mixture was filtered through Celite®, washing with ethyl acetate. The filtrate was concentrated under vacuum and the residue purified by flash column chromatography (from hexanes/ethyl acetate, 1:1, to ethyl acetate) to give (5*S*,8a*R*)-**23** (115 mg, 0.30 mmol, 95% yield): *Rf* = 0.3 (hexanes/ethyl acetate, 1:1); $[\alpha]_D$ −161 (*c* 0.94, CH_2Cl_2); ^{1}H NMR (400 MHz, C_6D_6) δ 7.74 (m, 4H), 7.23 (m, 6H), 5.59 (m, 2H), 4.63 (m, 1H), 3.90 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.71 (dd, *J* = 9.8, 4.3 Hz, 1H), 3.40 (m, 1H), 2.01 (m, 2H), 1.75-1.25 (m, 3H), 1.13 (s, 9H), 0.98 (m, 1H); ^{13}C NMR (101 MHz, C_6D_6) δ 173.4, 136.6, 134.7, 134.4, 130.7, 127.1, 126.2, 65.9, 52.4, 52.0, 32.8, 30.3, 27.8, 25.9, 20.1.

*4.14. (5S,8aS)-5-(tert-Butyldiphenylsilyloxy)methyl-1,5,8,8a-tetrahydroindolizin-3(2H)-one ((5S,8aS)-**23**)*

The same procedure starting from (5*S*,8a*S*)-**24** (50 mg, 0.30 mmol) furnished (5*S*,8a*S*)-**23** (110 mg, 0.27 mmol, 91% yield): *Rf* = 0.3 (hexanes/ethyl acetate, 1:1); $[\alpha]_D$ −64 (*c* 1.45, CH_2Cl_2); ^{1}H NMR (250 MHz, C_6D_6) δ 7.93 (m, 4H), 7.35 (m, 6H), 5.83 (m, 2H), 4.43 (m, 2H), 4.24 (m, 1H), 2.98 (m, 1H), 2.14 (ddt, *J* =16.7, 9.3, 1.2 Hz, 1H), 1.96 (m, 1H) 1.84 (m, 2H), 1.52 (m, 1H), 1.29 (s, 9H), 1.12 (m, 1H); ^{13}C NMR (101 MHz, C_6D_6) δ 174.3, 135.6, 133.7, 129.5, 125.0, 63.9, 54.4, 54.2, 31.8, 30.6, 26.7, 26.5, 19.2.

*4.15. (S)-1-(1-Hydroxybut-3-en-2-yl)piperidine-2,6-dione ((–)-**6**)*

A mixture of π-allylpalladium chloride dimer (72 mg, 0.20 mmol), (1*R*,2*R*)-**4** (474 mg, 0.57 mmol), sodium carbonate (246 mg, 2.32 mmol) and glutarimide, **2**, (2.60 g, 22.99 mmol) was purged with nitrogen for 1 h. Dry CH_2Cl_2 (180 mL) was added and the mixture was stirred at room temperature for 10 min. Then, butadiene monoepoxide, **3**, (1.8 mL, 22.37 mmol) was added and the resulting mixture was efficiently stirred under

nitrogen for 14 h. After that time, the reaction mixture was filtered through Celite®, washing with CH_2Cl_2 (120 mL) and then ethyl acetate (250 mL), and the filtrate concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 1:1 to 2:3) to give (−)-**6** (4.03 g, 22.00 mmol, 99% yield) as a clear oil in 95% enantiomeric excess (determined by CHPLC analysis, ^{i}PrOH/hexane, 3:1): $[\alpha]_D$ −23.3 (*c* 1.40, CH_2Cl_2). Other physical and spectroscopic data of (−)-**6** were identical to those previously described for (+)-**6**.[16]

*4.16. (6RS)-1-[(S)-1-(tert-Butyldiphenylsilyloxy)but-3-en-2-yl]-6-hydroxypiperidin-2-one ((1'S)-**8**)*

*4.16.1. Silylation of (+)-**6***

In a 250 mL Schlenk flask equipped with magnetic stirring, under nitrogen atmosphere, alcohol (−)-**6** (1.90 g, 10.37 mmol) was dissolved in anhydrous CH_2Cl_2 (100 mL). After cooling to 0°C, imidazole (3.54 g, 52.06 mmol) was added, followed by TBDPSCl (3.2 mL, 12.31 mmol). The cooling bath was removed and the mixture was stirred at room temperature overnight. The solvent was evaporated under vacuum and replaced by ethyl acetate (70 mL). The resulting mixture was stirred vigorously for 1 h and the insoluble fine white powder (imidazole·HCl) filtered through Celite®. The filtrate was concentrated under vacuum and then purified by flash column chromatography (hexanes/ethyl acetate, from 9:1 to 3:2) to give a residue, which was crystallized from 2-propanol, furnishing the expected silylated derivative (3.99 g, 9.46 mmol, 91% yield): $[\alpha]_D$ +16.7 (*c* 1.00, CH_2Cl_2). The physical and spectroscopic data of this compound were identical to those previously described for its enantiomer.[16]

4.16.2. Reduction

A solution of $LiBEt_3H$ in THF (1M, 11.5 mL, 11.5 mmol) was added dropwise to a solution of the previous intermediate (3.02 g, 7.17 mmol) in dry THF (28 mL), under nitrogen atmosphere at −78°C, and the reaction mixture, monitored by TLC (hexanes/ethyl acetate, 1:1), was stirred at the same temperature for 45 min. Keeping the temperature at −78ºC saturated aqueous $NaHCO_3$ (60 mL) and H_2O_2 (30%, 12 mL) were added, and the mixture was allowed to warm slowly to room temperature and then stirred for one additional hour. After filtration through Celite®, the solution was extracted with CH_2Cl_2 (4x30 mL), and the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The oily residue was purified by flash chromatography (hexanes/ethyl acetate, from 3:1 to 1:1) to give a mixture of epimers (1'*S*)-**8** (2.65 g, 6.27 mmol, 87% yield) as a colourless oil. The physical and spectroscopic data of this product were identical to those previously described for (1'*R*)-**8**.[16]

*4.17. (6R)- and (6S)-6-Allyl-1-[(S)-1-(tert-butyldiphenylsilyloxy)but-3-en-2-yl]piperidin-2-one (**27**)*

In a 50 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of (1'*S*)-**8** (1.375 g, 3.25 mmol) was dissolved in anhydrous CH_2Cl_2 (17 mL). After cooling to 0°C, DMAP (198 mg, 1.62 mmol), acetic anhydride (0.77 mL, 8.12 mmol) and Et_3N (1.13 mL, 8.12 mmol) were added. The cooling bath was removed and the mixture was stirred at room temperature overnight. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ solution (15 mL) and water (15 mL) and then extracted with CH_2Cl_2 (4x15 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The remaining crude product **25** was used in the next step without further purification. To this end, in a 50 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of the crude ester **25** in anhydrous CH_2Cl_2 (17 mL) was cooled to −40°C, followed by the addition of allyltrimethylsilane (1.0 mL, 6.5 mmol) and then, dropwise, TMSOTf (0.90 mL, 4.88 mmol). The reaction, monitored by TLC (hexanes/EtOAc, 1:1) was finished in 1.5 h. After that time, the reaction mixture was cooled to −78°C, saturated aqueous $NaHCO_3$ (30 mL) was added and the mixture was allowed to warm up to room temperature. After extraction with CH_2Cl_2 (4x30 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 4:1 to 1:2) to give a 30:1 mixture of (6*S*)- and (6*R*)-**27** (1.05 g, 2.34 mmol, 79% yield) as a yellow oil: *Rf* = 0.7 (hexanes/ethyl acetate, 1:1); IR (ATR) 3071, 2931, 2857, 1637, 1427, 1107 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) (6*S*)-**27** (major) δ 7.68 (m, 4H), 7.41 (m, 6H), 6.22 (ddd, *J* = 17.4, 10.6, 6.8 Hz, 1H), 5.68 (m, 1H), 5.11 (m, 4H), 4.29 (td, *J* = 10.0, 4.0 Hz, 1H), 3.86 (m, 2H), 3.43 (m, 1H), 2.55-2.10 (complex, 4H), 1.87-1.59 (complex, 4H), 1.08 (s, 9H); (6*R*)-**27** (minor) significant signals δ 6.06 (m, 1H), 5.18 (m, 4H), 4.01 (m, 2H); ^{13}C NMR (63 MHz, $CDCl_3$) (6*S*)-**27** δ 169.9, 135.7, 135.3, 134.6, 133.7, 133.5, 129.8, 127.8, 117.9, 117.1, 66.0, 64.2, 59.0, 37.7, 32.6, 27.0, 25.7, 19.2, 16.3; HRMS m/z (ESI+) calcd for $[C_{28}H_{37}NO_2SiNa^+]$: 470.2491, found: 470.2491.

*4.18. (6S,9aS)-6-[(tert-Butyldiphenylsilyloxy)methyl]-1,2,3,6,9,9a-hexahydroquinolizin-4(4H)-one (**28**)*

To a solution of a 30:1 mixture of (6*S*)- and (6*R*)-**27** (2.74 g, 6.12 mmol) in anhydrous and previously degassed CH_2Cl_2 (227 mL), 2nd generation Grubbs catalyst (51 mg, 0.06 mmol) was added and the mixture was heated at reflux overnight. After cooling down to room temperature, the reaction mixture was filtered through a short pad of silica gel, washing with Et_2O. The filtrate was concentrated under vacuum and the crude material was purified by flash column chromatography (hexanes/Et_2O, from 9:1 to 1:1) to furnish **28** (2.47 g, 5.88 mmol, 96% yield) as a unique isomer: *Rf* = 0.38 (3:1, Et_2O/hexanes); $[\alpha]_D$ = -85.8 (*c* 1.00, $CHCl_3$); IR (ATR) 2928, 2854, 1668, 1612, 1406, 1095 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67(m, 4H), 7.39 (m, 6H), 6.06 (ddd, *J* = 9.8, 6.7, 2.4 Hz, 1H), 5.98 (ddd, *J* = 9.8, 5.0, 2.7 Hz, 1H), 4.65 (m, 1H), 3.89 (m, 2H), 3.30 (tt, *J* = 11.0, 3.1 Hz, 1H), 2.41 (m, 2H), 2.16 (m, 2H), 1.89 (m, 2H), 1.75 (m, 1H), 1.51 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.3, 135.7, 133.9, 133.8, 129.6, 128.0, 127.7, 127.6, 127.0, 65.3, 55.0, 53.9, 32.9, 32.0, 31.1, 27.0, 20.8, 19.4; HRMS (ESI+) calcd for $[C_{26}H_{33}NO_2Si^+]$: 419.2281, found: 419.2287.

*4.19. (6S,9aS)-6-Hydroxymethyl-1,2,3,6,9,9a-hexahydroquinolizin-4(4H)-one (**29**)*

In a 50 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of **28** (264 mg, 0.63 mmol) in anhydrous THF (10 mL) was heated to the reflux temperature. After the addition of $Et_3N·3HF$, (0.62 mL, 5.34 mmol), the mixture was stirred under reflux overnight. The resulting cold mixture was diluted with CH_2Cl_2 (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) was added. The layers were separated and the aqueous one extracted with CH_2Cl_2 (4x8 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under vacuum, and the residue was purified by flash column chromatography (from hexanes/ethyl acetate, 1:1, to ethyl acetate) to give **29** (107 mg, 0.59 mmol, 94% yield): *Rf* = 0.1 (ethyl acetate); $[\alpha]_D$ −35.5 (*c* 1.30, CH_2Cl_2); IR (ATR) 3339, 2983, 1612, 1410, 1265, 1034 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.03 (m, 1H), 5.80 (m, 1H), 4.64 (m, 1H), 3.78 (dd, *J* = 11.3, 2.5 Hz, 1H), 3.55 (dd, *J* = 11.5, 6.1 Hz, 1H), 3.36 (m, 1H), 2.53

(dd, *J* = 8.3, 5.5 Hz, 2H), 2.15 (m, 2H), 1.93 (m, 2H), 1.79 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 126.9, 126.6, 67.2, 56.7, 55.6, 32.5, 31.3, 30.5, 20.0; HRMS (ESI+) calcd for [$C_{10}H_{15}NO_2Na^+$]: 204.1000, found: 204.0995.

*4.20. (5S,8aS)-5-(tert-Butyldiphenylsilyloxymethyl)hexahydroindolizin-3(2H)-one ((5S,8aS)-**30**) and (S)-5-(tert-butyldiphenylsilyloxymethyl)-1,7,8,8a-tetrahydroindolizin-3(2H)-one ((8aS)-**31**)*

In a 10 mL Schlenk flask equipped with magnetic stirring, (6*S*,8a*R*)-**23** (136 mg, 0.34 mmol) was dissolved in THF (5 mL) and Pd/C (15 mg) was added. The flask was sealed up by a septum, connected to a balloon filled with H_2 and the mixture was stirred at room temperature overnight. After that time, the solution was filtered through Celite®, washing with ethyl acetate, and then concentrated under vacuum. The residue was filtered through a short pad of silica gel, to furnish two fractions, one containing pure (8a*S*)-**31** (28 mg, 0.07 mmol, 20% yield) and another one containing a mixture (69 mg) of the starting material, (6*S*,8a*R*)-**23**, and (5*S*,8a*S*)-**30**. Repeated chromatography allowed the isolation of an analytical pure sample of (5*S*,8a*S*)-**30** (11 mg). (5*S*,8a*S*)-**30**: *Rf* = 0.6 (ethyl acetate); $[\alpha]_D$ −34.1 (*c* 0.55, CH_2Cl_2); IR (ATR) 2929, 2855, 1684, 1426, 1109 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.43 (m, 6H), 4.39 (m,1H), 3.67 (dd, *J* = 10.4, 6.7 Hz, 2H), 3.40 (dtd, *J* = 10.9, 7.2, 3.5 Hz, 1H), 2.31 (m, 2H), 2.10 (m, 1H), 2.00-1.37 (complex,7H), 1.07 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 135.6, 133.4, 133.2, 129.6, 127.6, 61.7, 54.2, 48.9, 33.5, 30.2, 26.8, 25.7, 24.1, 19.2, 19.1; HRMS (ESI+) calcd for [$C_{25}H_{33}NO_2SiNa^+$]: 430.2178, found: 430.2176. (8a*S*)-**31**: *Rf* = 0.3 (hexanes/ethyl acetate, 1:1); $[\alpha]_D$ −17.9 (*c* 1.40, CH_2Cl_2); IR (ATR) 2928, 2855, 1694, 1657, 1405, 1261, 1111 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.41 (m, 6H), 5.43 (br s, 1H), 4.96 (br d, *J* = 14.9 Hz, 1H), 4.79 (br d, *J* = 14.9 Hz, 1H), 3.62 (m, 1H), 2.41 (ddd, *J* = 17.0, 11.0, 9.7 Hz, 1H), 2.25 (m, 3H), 2.04 (br d, *J* =12.5 Hz, 1H), 1.58 (m, 3H), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5, 136.9, 135.5, 133.6, 129.5, 127.6, 105.9, 62.4, 57.1, 31.2, 29.9, 26.9, 25.9, 22.7, 19.3; HRMS (ESI+) calcd for [$C_{25}H_{31}NO_2SiNa^+$]: 428.2022, found: 428.2016.

*4.21. (5S,8aR)-5-Hydroxymethylhexahydroindolizin-3(2H)-one ((5S,8aR)-**32**)*

In a 10 mL Schlenk flask equipped with magnetic stirring, (6*S*,8a*S*)-**24** (50 mg, 0.30 mmol) was dissolved in methanol (2 mL) and Pd/C (5 mg) was added. The flask was sealed up by a septum, connected to a balloon filled with H_2 and the mixture was stirred at room temperature overnight. After that time, the solution was filtered through Celite®, washing with ethyl acetate, and then concentrated under vacuum. The residue was filtered through a short pad of silica gel, to furnish (5*S*,8a*R*)-**32** (38 mg, 0.22 mmol, 75% yield): *Rf* = 0.2 (ethyl acetate); $[\alpha]_D$ −7.0 (*c* 1.40, CH_2Cl_2); IR (ATR) 3306, 2936, 2859, 1655, 1420, 1267, 1061 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.33 (dd, *J* = 8.9, 6.2 Hz, 1H), 3.85 (m, 2H), 3.44 (m, 1H), 3.15 (m, 1H), 2.42 (m, 2H), 2.22 (m, 1H), 2.00-1.22 (complex, 7H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.5, 63.7, 60.8, 60.4, 33.1, 31.4, 27.9, 25.1, 23.5; HRMS (ESI+) calcd for [$C_9H_{15}NO_2Na^+$]: 192.1000, found: 192.0992.

*4.22. (5S,8aS)-5-Hydroxymethylhexahydroindolizin-3(2H)-one ((5S,8aS)-**32**)*

The same procedure starting from (6*S*,8a*R*)-**24** (20 mg, 0.12 mmol), furnished (5*S*,8a*S*)-**32** (18 mg, 0.11 mmol, 89% yield): *Rf* = 0.1 (ethyl acetate); $[\alpha]_D$ −31.5 (*c* 1.00, CH_2Cl_2); IR (ATR) 3365, 2937, 2854, 1657, 1420, 1265, 1056 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.31 (m, 1H), 3.70 (dd, *J* = 11.0, 9.0 Hz, 1H), 3.61 (m, 2H), 2.76 (br s, 1H), 2.37 (m, 2H), 2.21 (m, 1H), 1.97-1.40 (complex, 6H), 1.15 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.6, 61.6, 53.9, 49.9, 33.3, 30.3, 25.8, 24.2, 19.4; HRMS (ESI+) calcd for [$C_9H_{15}NO_2Na^+$]: 192.1000, found: 192.0996.

*4.23. (6S,9aR)-6-Hydroxymethyloctahydroquinolizin-4(4H)-one ((6S,9aR)-**33**)*

The same procedure starting from (6*S*,9a*S*)-**29** (50 mg, 0.27 mmol), furnished (6*S*,9a*R*)-**33** (39 mg, 0.21 mmol, 79% yield): *Rf* = 0.2 (ethyl acetate); $[\alpha]_D$ −80.0 (*c* 0.60, CH_2Cl_2); IR (ATR) 3371, 2940, 2872, 1603, 1410, 1343, 1050 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 4.94 (dd, *J* = 7.5, 5.8 Hz, 1H), 3.82 (m, 2H), 3.52 (m, 1H), 3.39 (m, 1H), 2.42 (m, 2H), 2.08-1.38 (complex, 10H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.1, 65.3, 62.0, 57.5, 33.3, 31.7, 29.7, 25.9, 21.3, 18.5; HRMS (ESI+) calcd for [$C_{10}H_{17}NO_2H^+$]: 184.1338, found: 184.1360.

*4.24. Benzyl {(S)-1-[(RS)-1-hydroxybut-3-en-2-yl]-2,5-dioxopyrrolidin-3-yl}carbamate (**35**) and benzyl (S,E)-[1-(4-hydroxybut-2-en-1-yl)-2,5-dioxopyrrolidin-3-yl]carbamate (**41**)*

A mixture of π-allylpalladium chloride dimer (6.4 mg, 0.02 mmol), (1*R*,2*R*)-**4** (44 mg, 0.05 mmol), sodium carbonate (25 mg, 0.05 mmol) and (−)-(3*S*)-**34** (720 mg, 2.90 mmol) was purged with nitrogen for 1 h. Dry 1,2-dichloroethane (20 mL) was added and the mixture was stirred at room temperature for 10 min. Then, butadiene monoepoxide, **3**, (230 µL, 2.90 mmol) was added and the resulting mixture was warmed up to 60ºC and stirred under nitrogen overnight. After that time, the reaction mixture was filtered through Celite®, washing with ethyl acetate, and concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 3:1 to 1:2) to give **35a** (627 mg, 1.97 mmol, 68% yield) as a clear oil: *Rf* = 0.6 (ethyl acetate); $[\alpha]_D$ −15.6 (*c* 1.04, CH_2Cl_2); IR (ATR) 3343, 3058, 2949, 1696, 1518, 1391, 1263, 1196 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, 323K) δ 7.37-7.28 (m, 5H), 6.10-5.97 (m, 1H), 5.80 (br s, 1H), 5.31-5.22 (m, 2H), 5.10 (br s, 2H), 4.87-4.74 (m, 1H), 4.33-4.16 (m, 1H), 4.15-4.07 (m, 1H), 3.78-3.67 (m, 1H), 3.21 (m, 1H), 3.08-2.72 (complex, 3H); ^{13}C NMR (101 MHz, $CDCl_3$, 323K) δ 176.1/176.0, 174.5/174.4, 156.0, 135.7/135.6, 130.9/130.8, 128.5, 128.3, 128.2, 128.0, 119.3, 67.5, 61.5, 57.2/56.9, 49.9/49.8, 35.6; HRMS (ESI+) calcd for [$C_{16}H_{18}N_2O_5$]: 318.1216, found: 318.1207. The same reaction starting from (−)-(3*S*)-**34** (190 mg, 0.77 mmol) in the presence of (1*S*,2*S*)-**4** (2 mg, 2.5 µmol) furnished **35b** (178 mg, 0.60 mmol, 73% yield) and **41** (14.5 mg, 0.05 mmol, 6% yield). **35b**: $[\alpha]_D$ +14.6 (*c* 1.04, CH_2Cl_2); the rest of physical and spectroscopic data are identical to those described for **35a**, isolated from the previous reaction. The optical rotation values of **36a** and **36b** remain constant over time. **41**: *Rf* = 0.35 (ethyl acetate); $[\alpha]_D$ +5.1 (*c* 0.39, CH_2Cl_2); IR (ATR) 3333, 2924, 2854, 2362, 2343, 1703, 1528, 1401, 1263, 1172 cm^{-1}; (400 MHz, $CDCl_3$, 323K) major conformer δ 7.32 (m, 5H), 5.85 (m, 1H), 5.48 (br s, 2H), 5.10 (m, 2H), 4.34-4.21 (complex, 5H), 4.11 (m, 1H), 3.10 (m, 1H), 2.80 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 323K) δ 175.0, 173.6, 155.5, 134.2, 128.8, 128.6, 128.4, 124.0, 123.7, 67.5, 58.0, 50.3, 35.5; HRMS (ESI+) calcd for [$C_{16}H_{18}N_2O_5H^+$]: 319.1294, found: 319.1286.

*4.25. Benzyl {(S)-1-[(RS)-1-(tert-butyldiphenylsilyloxy)but-3-en-2-yl]-2,5-dioxopyrrolidin-3-yl}carbamate (**36**)*

Imidazole (65.4 mg, 0.96 mmol) and TBDPSCl (130 µL, 0.51 mmol) were added to a solution of the alcohol **35a** (100 mg, 0.32 mmol), obtained in the presence of (1*R*,2*R*)-**4**, in anhydrous CH_2Cl_2 (3 mL) at 0°C. The resulting mixture was stirred

overnight at room temperature. After that time, it was concentrated under vacuum and the residue dissolved in ethyl acetate (2 mL). Then, the solution was filtered through Celite®, washing with ethyl acetate. The filtrate was concentrated under vacuum and the residue was purified by flash column chromatography (hexanes/ethyl acetate, from 4:1 to 1:1) to afford **36a** (150 mg, 0.27 mmol, 85% yield): *Rf* = 0.26 (hexanes/ethyl acetate, 3:1); IR (ATR) 2929, 2856, 1709, 1510, 1390, 1264, 111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 323 K) δ 7.65 (m, 4H), 7.40 (m, 11H), 6.02 (m, 1H), 5.38 (m, 1H), 5.24 (m, 2H), 5.14 (s, 2H), 4.89 (m, 1H), 4.29 (m, 2H), 3.86 (ddd, *J* = 10.4, 5.9, 2.8 Hz, 1H), 3.06 (m, 1H), 2.69 (m, 1H), 1.05 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$, 323 K) δ 175.3/175.2, 173.7/173.6, 156.0, 136.1, 135.7, 135.7, 133.5, 133.4, 133.3, 131.3/131.1, 130.0, 128.7, 128.5, 128.3, 127.9, 119.8/119.7, 67.6, 62.7/62.3, 57.0/56.9, 50.4/50.3, 36.6, 27.0, 19.3; HRMS (ESI+) calcd for $[C_{32}H_{36}N_2O_3SiNa^+]$: 579.2291, found: 579.2286. The same reaction starting from the alcohol **35b** (110 mg, 0.35 mmol), obtained in the presence of (1*S*,2*S*)-**4**, furnished **36b** (158 mg, 0.28 mmol, 82% yield): the spectroscopic data of this sample were identical to those described for **36a**. CHPLC analysis showed that **36a** and **36b** were mixtures of (3*S*,2'*S*)-**36** and (3*S*,2'*R*)-**36**, in 88:12 and 21:79 ratio, respectively.

*4.26. Benzyl {(3S,5RS)-1-[(S)-[(1-(tert-butyldiphenylsilyloxy)but-3-en-2-yl]-5-hydroxy-2-oxopyrrolidin-3-yl}carbamate (**37**)*

In a 100 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, (−)-**36a** (1.42 g, 2.55 mmol) was dissolved in anhydrous toluene (15 mL). The solution was cooled down to −78°C, DIBAL-H (1M in toluene, 3.8 mL, 3.8 mmol) was added dropwise and the reaction mixture, monitored by TLC (hexanes/ethyl acetate, 1:1), was stirred at the same temperature for 1 h. Keeping the temperature at −78°C, saturated aqueous potassium sodium tartrate (15 mL) was added, the mixture was allowed to warm slowly to room temperature, and then stirred for 30 min. After filtration through Celite®, the solution was extracted with CH_2Cl_2 (4x25 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The oily residue was purified by flash column chromatography (hexanes/ethyl acetate, from 4:1 to 1:1) to give a mixture of isomers **37** (953 mg, 1.71 mmol, 67% yield) as a colourless oil: *Rf* = 0.5 (hexanes/ethyl acetate, 1:1); IR (ATR) 3309, 2930, 2856, 1685, 1521, 1427, 1264, 1109 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.42 (m, 11H), 6.30-5.87 complex, 2H), 5.40-4.90 (complex, 6H), 4.57 (m, 1H), 4.07 (m, 1H), 3.89 (m, 2H), 2.76 (m, 1H), 1.95 (br d, *J* = 14.4 Hz,1H), 1.09 (s) and 1.07 (s) (9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 171.9, 156.9, 156.7, 136.1, 136.0, 134.6, 130.4, 129.0, 128.6, 128.5, 128.3, 119.3, 118.6, 81.7, 81.4, 67.6, 60.8, 58.3, 57.9, 51.6, 27.3, 27.2, 21.5, 19.7, 19.6; HRMS (ESI+) calcd for $[C_{32}H_{38}N_2O_5SiNa^+]$: 581.2448, found: 581.2445.

*4.27. Benzyl {(3S,5RS)-5-allyl-1-[(S)-1-(tert-butyldiphenylsilyloxy)but-3-en-2-yl]-2-oxopyrrolidin-3-yl}carbamate (**38**)*

In a 100 mL Schlenk flask equipped with magnetic stirring and nitrogen atmosphere, a solution of **37** (1.30 g, 2.33 mmol) in anhydrous CH_2Cl_2 (30 mL) was cooled down to −40°C. To the cold solution was added allyltrimethylsilane (450 μL, 2.80 mmol) and then, dropwise, $BF_3 \cdot Et_2O$ (740 μL, 5.82 mmol). The reaction, monitored by TLC (hexanes/ethyl acetate, 3:2), was finished in 1.5 h. Then, saturated aqueous $NaHCO_3$ (25 mL) was added and the mixture was allowed to warm up to room temperature. After the extraction with CH_2Cl_2 (4x20 mL), the combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. The residue was purified by flash column chromatography (hexanes/ethyl acetate, from 4:1 to 1:1) to give an 1.6:1 mixture of epimers **38** (1.06 g, 1.82 mmol, 78% yield) as a yellow oil: *Rf* = 0.8 (hexanes/ethyl acetate, 1:1); IR (ATR) 2930, 2856, 1686, 1499, 1239, 1109 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ Isomer A (major) and B (minor) δ 7.66 (m, 4H), 7.40 (m, 11H), 6.07 (ddd, *J* = 17.4, 10.4, 7.1 Hz, $1H_B$), 5.89 (ddd, *J* = 17.3, 10.5, 6.9 Hz, $1H_A$), 5.67 (m, 1H), 5.27-5.05 (complex, 7H), 4.52-3.60 (complex, 4H), 2.68-1.80 (complex, 4H), 1.08 (s) and 1,07 (s) (9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.2, 171.7, 156.4, 136.3, 135.5, 133.4, 133.2, 133.1, 133.0, 132.9, 132.4, 129.9, 129.8, 128.5, 128.0, 127.7, 119.1, 118.9, 118.6, 118.4, 66.8, 63.8, 62.7, 57.9, 57.3, 51.6, 51.4, 38.5, 38.0, 33.3, 26.8, 19.1; HRMS (ESI+) calcd for $[C_{35}H_{41}N_2O_4Si^+]$: 581.2836, found: 581.2852.

*4.28. Benzyl [(2S,5S,8aR)- and [(2S,5S,8aS)-5-(tert-butyldiphenylsilyloxy)methyl-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-2-yl]carbamate (**39**)*

In a 250 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of the mixture of epimers **38** (700 mg, 1.20 mmol) in anhydrous CH_2Cl_2 (100 mL) was warmed up to the reflux temperature and, then, 2nd generation Grubbs catalyst (51 mg, 0.06 mmol) was added in 3 portions (one per hour). The mixture was heated at reflux overnight. After cooling down to room temperature, the resulting mixture was filtered through a small pad of silica gel, washing with ethyl acetate. The filtrate was concentrated under vacuum and the residue purified by flash column chromatography (hexanes/ethyl acetate, from 4:1 to 1:2) to give by elution order (2*S*,5*S*,8a*R*)-**39** (246 mg, 0.44 mmol, 37% yield) and (2*S*,5*S*,8a*S*)-**39** (283 mg, 0.51 mmol, 43% yield). (2*S*,5*S*,8a*R*)-**39**: *Rf* = 0.6 (hexanes/ethyl acetate, 1:1); $[\alpha]_D$ −31 (*c* 1.95, CH_2Cl_2); IR (ATR) 3296, 2930, 2889, 1683, 1528, 1427, 1256, 1109 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (m, 4H), 7.38 (m, 11H), 6.01 (m, 1H), 5.85 (m, 1H), 5.28 (br s, 1H), 5.12 (m, 2H), 4.32 (dd, *J* = 9.6, 5.6 Hz, 1H), 4.22 (m, 1H), 4.10 (m, 2H), 3.74 (m, 1H), 2.31 (m, 2H), 2.08 (m, 2H), 1.04 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.4, 156.2, 136.1, 135.5, 133.5, 133.4, 129.6, 128.5, 128.1, 128.0, 127.5, 127.3, 125.8, 66.9, 62.5, 54.9, 53.5, 52.0, 31.7, 29.6, 26.7, 19.3; HRMS (ESI+) calcd for $[C_{33}H_{37}N_2O_4SiH^+]$: 554.2601, found: 554.2620. (2*S*,5*S*,8a*S*)-**39**: *Rf* = 0.4 (hexanes/ethyl acetate, 1:1); $[\alpha]_D$ −69 (*c* 2.10, CH_2Cl_2); IR (ATR) 3304, 2929, 2856, 1685, 1513, 1427, 1239, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 11H), 5.92 (ddd, *J* =10.1, 5.2, 2.9 Hz, 1H), 5.75 (m, 1H), 5.39 (br s, 1H), 5.15 (s, 2H), 4.53 (m, 1H), 4.31 (m, 1H), 3.90-3.70 (complex, 3H), 2.40 (m, 1H), 2.20 (m, 1H), 2.03 (complex, 2H), 1.09 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.5, 156.4, 136.3, 135.6, 135.5, 133.2, 133.1, 129.8, 129.7, 128.5, 128.1, 128.0, 127.7, 126.1, 125.8, 66.9, 65.0, 52.2, 51.8, 49.4, 30.5, 29.6, 26.8, 19.2; HRMS (ESI+) calcd for $[C_{33}H_{37}N_2O_4SiH^+]$: 554.2601, found: 554.2612.

*4.29. Benzyl [(2S,5S,8aR)-5-hydroxymethyl-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-2-yl]carbamate ((2S,5S,8aR)-**40**)*

In a 50 mL Schlenk flask, equipped with magnetic stirring and nitrogen atmosphere, a solution of (2*S*,5*S*,8a*R*)-**39** (283 mg, 0.51 mmol) in anhydrous THF (15 mL) was heated to the reflux temperature. After the addition of $Et_3N \cdot 3HF$, (500 μL, 3.06 mmol), the mixture was stirred under reflux overnight. After cooling, the resulting mixture was diluted with CH_2Cl_2 (10 mL) and aqueous saturated aqueous $NaHCO_3$ (10 mL), the layers were separated and the aqueous one extracted with CH_2Cl_2 (4x10 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated under vacuum, and the residue was purified by flash column chromatography (hexanes/ethyl acetate, from 3:1 to 1:2) to give (2*S*,5*S*,8a*R*)-**40** (140 mg, 0.44 mmol,

87% yield): *Rf* = 0.4 (ethyl acetate); $[\alpha]_D$ +16.8 (*c* 1.35, CH_2Cl_2); IR (ATR) 3295, 2924, 1675, 1645, 1533, 1454, 1242, 1040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.37 (m, 5H), 5.90 (m, 1H), 5.59 (m, 1H), 5.51 (d, *J* = 9.5 Hz, 1H), 5.12 (s, 2H), 4.35 (m, 1H), 4.22 (m, 1H), 3.83 (d, *J* = 5.1 Hz, 2H), 3.75 (m, 1H), 2.38-2.10 (complex, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, 323K) δ 172.8, 156.8, 136.7, 129.0, 128.6, 128.5, 127.1, 126.2, 67.6, 64.6, 60.3, 54.5, 52.6, 33.3, 31.9; HRMS (ESI+) calcd for $[C_{17}H_{20}N_2O_4^+]$: 316.1423, found: 316.1403.

*4.30. Benzyl [(2S,5S,8aS)-5-hydroxymethyl-3-oxo-1,2,3,5,8,8a-hexahydroindolizin-2-yl]carbamate ((2S,5S,8aS)-**40**)*

The same procedure starting from (2*S*,5*S*,8a*S*)-**39** (90 mg, 0.21 mmol) furnished (2*S*,5*S*,8a*S*)-**40** (54 mg, 0.17 mmol, 82% yield): *Rf* = 0.2 (ethyl acetate); $[\alpha]_D$ −67.5 (*c* 1.10, CH_2Cl_2); IR (ATR) 3297, 2923, 1673, 1649, 1531, 1454, 1255, 1057 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 323K) δ 7.32 (m, 5H), 6.12 (m, 1H), 5.87 (m,1H), 5.62 (m, 1H), 5.10 (s, 2H), 4.46 (m, 1H), 4.23 (m, 1H), 3.79 (m, 2H), 3.57 (m, 1H), 3.38 (m, 1H: OH), 2.28-1.85 (complex, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, 323K) δ 171.7, 156.3, 136.3, 128.3, 127.9, 126.4, 124.5, 124.4, 66.9, 63.6, 53.2, 52.1, 49.2, 32.9, 31.5; HRMS (ESI+) calcd for $[C_{17}H_{20}N_2O_4^+]$: 316.1423, found: 316.1413.

*4.31. Benzyl [(2S,5S,8aR)-5-hydroxymethyl-3-oxooctahydroindolizin-2-yl]carbamate, ((2S,5S,8aR)-**42**)*

A solution of (2*S*,5*S*,8a*R*)-**40** (38 mg, 0.12 mmol) in MeOH (2 mL) stirring at room temperature was hydrogenated in the presence of Pd/C (10%, 4 mg) at 2 atm for 20 h. After that time, the solution was filtered through Celite®, washing with ethyl acetate, and the filtrate concentrated under vacuum. To the residue were added K_2CO_3 (33 mg, 0.24 mmol) and 1,4-dioxane/H_2O (1:1, 2 mL). The mixture was cooled down to 0ºC, CbzCl (19 μL, 0.13 mmol) was added and the resulting solution was stirred at room temperature overnight. Then, the solution was diluted with H_2O (5 mL) and extracted with CH_2Cl_2 (4x3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash column chromatography (from hexane/ethyl acetate, 3:1 to ethyl acetate) furnished (2*S*,5*S*,8a*R*)-**42** (30 mg, 0.09 mmol, 78% yield): *Rf* = 0.3 (ethyl acetate); $[\alpha]_D$ +3.7 (*c* 1.65, CH_2Cl_2); IR (ATR) 3289, 2938, 2869, 1672, 1534, 1454, 1262, 1055 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 323K) δ 7.37 (m, 5H), 5.28 (br s, 1H), 5.14 (s, 2H), 4.31 (m, 1H), 3.91 (m, 2H), 3.46 (m, 1H), 3.23 (m, 1H), 2.32 (br t, *J* = 12.3 Hz, 1H), 2.15 (dt, *J* = 12.3, 8.9 Hz, 1H), 1.97 (m, 1H), 1.82 (m, 1H), 1.67-1.23 (complex, 4H); ^{13}C NMR (101 MHz, $CDCl_3$, 323K) δ 170.8, 156.1, 136.2, 128.4,128.0, 127.9, 67.0, 62.9, 61.3, 57.9, 52.7, 32.9, 31.9, 27.56, 23.84; HRMS (ESI+) calcd for $[C_{17}H_{22}N_2O_4^+]$: 318.1580, found: 318.1586.

*4.32. Benzyl [(2S,5S,8aS)-5-hydroxymethyl-3-oxooctahydroindolizin-2-yl]carbamate, ((2S,5S,8aS)-**42**)*

The same procedure starting from (2*S*,5*S*,8a*S*)-**40** (20 mg, 0.06 mmol), furnished (2*S*,5*S*,8a*S*)-**42** (14 mg, 0.04 mmol, 74% yield): *Rf* = 0.1 (ethyl acetate); $[\alpha]_D$ −13.7 (*c* 0.70, CH_2Cl_2); IR (ATR) 3306, 2936, 2858, 1712, 1665, 1533, 1454, 1239, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, 323K) δ 7.36 (m, 5H), 6.46 (br s) and (5.98 br s) (1H), 5.12 (m, 2H), 4.40-4.25 (complex), 4.17 (m), 3.90-3.60 (complex) and 3.59 (dt, *J* = 11.8, 5.1 Hz) (5H), 2.92 (m, 1H), 2.17 (m, 2H), 1.86-1.48 (complex, 5H), 1.16 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, 323K) δ 171.7, 156.3, 136.3, 128.3, 127.9, 66.9, 61.1, 60.8, 52.1, 51.6, 50.9, 33.3, 33.2, 32.9, 24.4, 19.8; HRMS (ESI+) calcd for $[C_{17}H_{22}N_2O_4^+]$: 318.1580, found: 318.1577.

*4.33. tert-Butyl [(2S,5S,8aR)-5-hydroxymethyl-3-oxooctahydroindolizin-2-yl]carbamate, ((2S,5S,8aR)-**43**)*

A solution of (2*S*,5*S*,8a*R*)-**40** (38 mg, 0.12 mmol) in MeOH (2 mL) stirring at room temperature was hydrogenated in the presence of Pd/C (10%, 4 mg) at 2 atm for 20 h. After that time, the solution was filtered through Celite®, washing with ethyl acetate, and the filtrate concentrated under vacuum. To the residue were added K_2CO_3 (25 mg, 0.18 mmol) and 1,4-dioxane/H_2O (1:1, 2 mL). The mixture was cooled down to 0°C, $(Boc)_2O$ (30 μL, 0.13 mmol) was added and the resulting solution was stirred at room temperature overnight. Then, the solution was diluted with H_2O (3 mL) and extracted with CH_2Cl_2 (4x2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum. Purification of the residue by flash column chromatography (from hexane/ethyl acetate, 3:1 to ethyl acetate) furnished (2*S*,5*S*,8a*R*)-**43** (29 mg, 0.10 mmol, 86% yield): *Rf* = 0.3 (ethyl acetate); $[\alpha]_D$ +13.0 (*c* 1.00, CH_2Cl_2); IR (ATR) 3399, 2938, 2106, 1679, 1450, 1055 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.04 (br s, 1H), 4.28 (m, 1H), 3.91 (dd, *J* = 9.4, 7.8 Hz, 1H), 3.86 (dd, *J* = 9.4, 3.9 Hz, 1H), 3.43 (m, 1H), 3.25 (m, 1H), 2.29 (m. 1H), 2.12 (m, 1H), 1.92 (dm, *J* = 12.5 Hz, 1H), 1.78 (dm, *J* = 12.5 Hz, 1H), 1.63-1.22 (complex) and 1.44 (s) (13H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 156.0, 80.2, 63.1, 61.4, 58.1, 52.6, 33.3, 32.0, 28.5, 27.7, 24.1; HRMS (ESI+) calcd for $[C_{14}H_{24}N_2O_4^+]$: 284.1736, found: 284.1732.

*4.34. tert-Butyl [(2S,5S,8aS)-5-hydroxymethyl-3-oxooctahydroindolizin-2-yl]carbamate, ((2S,5S,8aS)-**43**)*

The same procedure starting from (2*S*,5*S*,8a*S*)-**40** (38 mg, 0.06 mmol), furnished (2*S*,5*S*,8a*S*)-**43**[20] (29 mg, 0.10 mmol, 86% yield): *Rf* = 0.3 (ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.60 (br s) and 5.46 (br s (1H), 4.35 (m, 1H), 4.02 (m, 1H), 3.88 (m, 1H), 3.79 (m, 1H), 3.58 (m, 1H), 2.16 (m, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.74-1.50 (complex, 6H), 1.42 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$)) δ 172.2, 156.3, 80.4, 61.5, 52.3, 52.0, 51.0, 33.8, 33.3, 29.8, 28.6, 24.7, 20.2.

*4.35. (2S,5S,8aR)-2-(tert-Butoxycarbonylamino)-3-oxooctahydroindolizine-5-carboxylic acid, ((2S,5S,8aR)-**44**)*

Jones reagent was prepared by dissolving 2 g of chromium trioxide in 2 mL of concentrated sulfuric acid and adding distilled water to bring the total volume to 10 mL. In a 10 mL Schlenk flask equipped with magnetic stirring, alcohol (2*S*,5*S*,8a*R*)-**43** (11 mg, 0.04 mmol) was dissolved in acetone (1 mL). Then, Jones reagent was added (0.5 mL) and the mixture was stirred at room temperature for 2 h. After that time, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ (2 mL) and extracted with CH_2Cl_2 (3x2 mL). Then, the aqueous layer was acidified with 10% HCl to pH = 1 and extracted again with CH_2Cl_2 (4x2 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated under vacuum to furnish (2*S*,5*S*,8a*R*)-**44**[26] (10 mg, 0.03 mmol, 86% yield): *Rf* = 0.2 (ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (m, 1H), 4.78 (m, 1H), 4.23 (m, 1H), 3.90 (m, 1H), 3.62 (m, 1H), 2.20 (m, 2H), 2.07 (m, 1H), 1.97 (dt, *J* = 13.2, 3.2 Hz, 1H), 1.89 (m, 1H), 1.72 (m, 1H), 1.56 (m, 1H), 1.45 (s, 9H), 1.36 (dd, *J* = 12.4, 3.8 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.9 , 172.2 , 156.0 , 80.3 , 58.2 , 56.9 , 51.9 , 33.5 , 31.0 , 28.5 , 27.9 , 22.6; HRMS (ESI+) calcd for $[C_{14}H_{22}N_2O_5Na^+]$: 321.1426, found: 321.1421.

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