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Application of the intramolecular PIFA-mediated amidation of alkynes to the synthesis of substituted indolizidinones

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ABSTRACT

The construction of the title compounds has been achieved from properly substituted linear alkynylamides through the suitable combination of two key cyclization steps. First, an intramolecular PIFA-mediated alkyne amidation protocol leads to the creation of the pyrrolidinone nucleus, which under proper manipulation of the generated keto–carbonyl group permits the assembling of the indolizidinone skeleton by the introduction of a subsequent ring closing olefin metathesis step. Finally, its transformation into a series of substituted mono- and trihydroxylated indolizidinone derivatives is achieved by manipulation of the remaining unsaturated fragment under hydrogenation and dihydroxylation conditions.

1. Introduction

Some years ago, our group demonstrated that the intramolecular amidation of properly substituted alkynes (**I**) can be performed in the presence of the hypervalent iodine reagent PIFA [bis(trifluoroacetoxy)phenyliodane] to render a series of 5-aroyl- and 5-alkenoyl-2-pyrrolidinones of type **II** (see Fig. 1).[1] As a constituent of the framework of a number of important heterocycles, we considered the construction of highly functionalized pyrrolidinone skeletons as a main object of our research. In this context, the subtle selection of different groups (*X* and *R* in **II**) would represent a new starting point for the synthesis of a number of nitrogen containing heterocycles and, in fact, we have recently confirmed the value of this approach in the preparation of pyrrolodiazepinone and pyrrolobenzodiazepinone derivatives from *N*-(3-aminopropyl)-, *N*-(2-aminomethylphenyl)-, and *N*-(2′-nitrobenzyl)-substituted pyrrolidinones,[2] and also in the synthesis of pyrrolo–pyrazinones from *N*-(2′-aminoethyl)pyrrolidinones[3] by the inclusion, in both cases, of an additional reductive amination step.

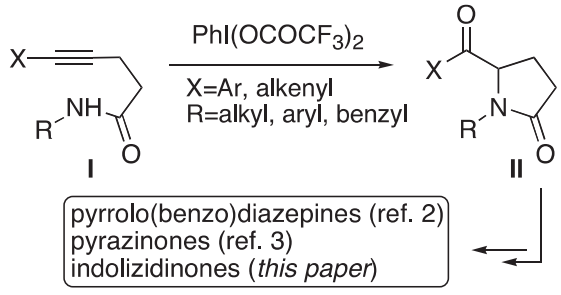

Fig. 1. PIFA-mediated construction of substituted pyrrolidinones.

With the aim of expanding the applicability of the proposed synthetic strategy, we show in this paper our efforts to prepare differently substituted indolizidinones of type **III** starting from 5-aryl- and 5-alkenyl-*N*-allylpentynamides **V**.[4] According to the retrosynthetic analysis shown Fig. 2, the success of our plan will rely on two key cyclization steps: (i) the PIFA-mediated alkyne amidation to render **IV**, in which the presence of the hydroxy group will be developed by the insertion of an additional reductive step or, alternatively, with the addition of an organometallic vinylic reagent to the previously generated keto–carbonyl group, and (ii) a ring closing metathesis step performed on the *N*-allyl group and the remaining olefin fragment. Manipulation of the resultant unsaturation—across C(6) and C(7) positions—under reductive and oxidative conditions will be also attempted as a source for higher structural diversity in the final mono- and trihydroxylated indolizidinones that will be eventually prepared, our final challenge.

Polyhydroxylated indolizidines have been the target of a myriad of well-established and novel synthetic approaches as a result of

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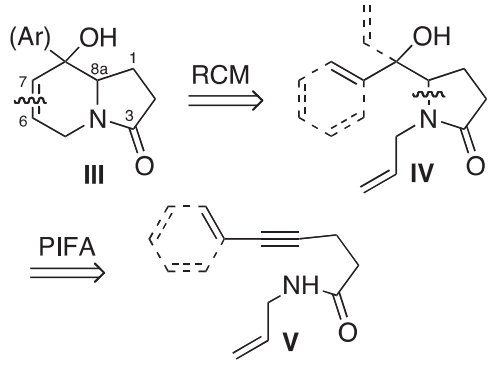


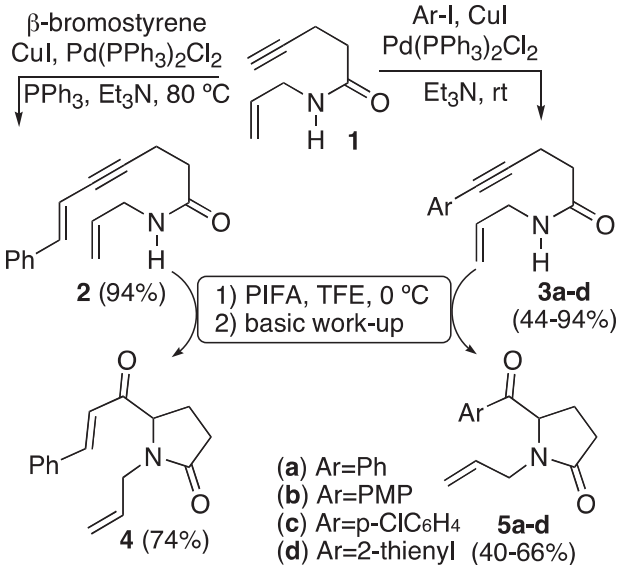
Fig. 2. Key retrosynthetic disconnections for the construction of the indolizidinone skeleton.

the relevant biological activity that these naturally occurring or synthetically-derived heterocycles display.[5] For this purpose, the selection of a number of carbohydrates, mainly D-mannitol, D-ribose, D-glucose or L-sorbose, among others, from the chiral pool has been a recurrent option to create the indolizidine skeleton.[6] These strategies benefit from the well defined stereochemistry that will be induced in the final compounds but, contrarily, they are occasionally limited by their lack of stereochemical flexibility and, in some cases, are usually longer than desired mainly because of the introduction of unavoidable protection and deprotection steps. Therefore, we show in this paper our efforts to design a new protecting-free non-sugar based route to the synthesis of racemic 8-hydroxyindolizidinones.[7]

2. Results and discussion

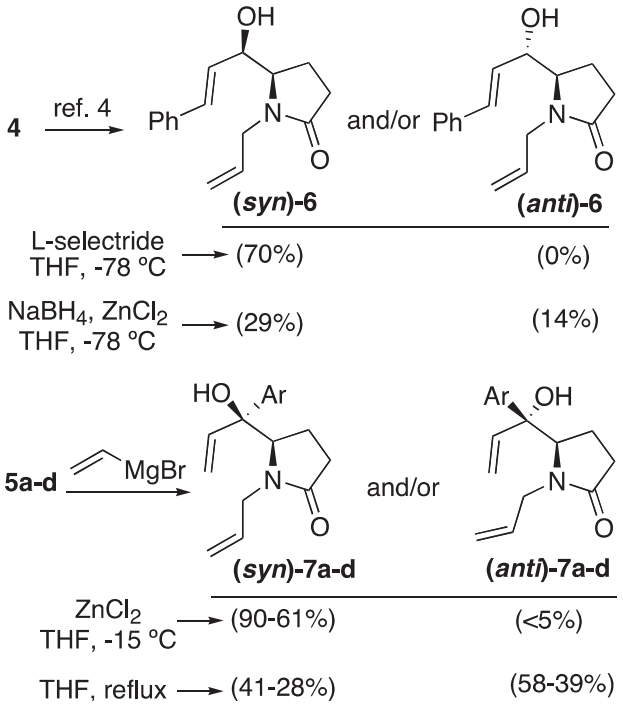
Looking for a high structural diversity in the final compounds, our synthetic design was conceived to incorporate a number of aryl and alkenyl groups at the terminal position of the starting *N*-allyl-5-pentynamide (**1**) in the first stage of the synthesis, as shown in Scheme 1. For that purpose, the required Sonogashira coupling process had to be optimized with respect to the nature of the halide component of the reaction.[8] Thus, the experimental conditions employed to obtain amides **3a**–**d**, which required a series of aryl iodides and the catalytic use of CuI and $Pd(PPh_3)_2Cl_2$ in triethylamine as solvent at room temperature, had to be modified with the additional participation of PPh_3 and working at solvent reflux temperature to prepare amide **2** from **1** and (*E*)-β-bromostyrene.[9] When all parts of substrates **2** and **3a**–**d** were assembled, they were submitted to the PIFA-mediated cyclization conditions. Thus, treatment of these alkynylamides **2** and **3** with a slight excess (1.5 equiv) of the hypervalent iodine reagent in trifluoroethanol (TFE) as solvent at room temperature, followed by a basic aqueous work up (aq K_2CO_3), rendered the corresponding 5-styryl- and 5-aroyl-2-pyrrolidinones **4** and **5a**–**d** in acceptable yields.

Prior to the planned ring closing metathesis step, we found that both types of pyrrolidinones **4** and **5** had to be manipulated. Considering that, in the case of pyrrolidinone **4**, all attempts to perform the projected cyclization didn't afford the expected results under a number of Ru-catalyzed conditions, a reductive step to generate the corresponding hydroxy group was introduced. Complementary, and with the same purpose, 5-aroylpyrrolidinones **5a**–**d** were submitted to the action of vinylmagnesium bromide in order to fix the olefin fragment and, at the same time, to develop the hydroxy group that eventually will be located at the C(8) position of the indolizidinone skeleton. In any case, both processes, the reduction of the keto group and the addition of the Grignard reagent, were studied with the aim to obtain pure samples of both possible *syn*/*anti* diastereoisomers, as it will be now disclosed.[10]



Scheme 1. Preparation of pyrrolidinones **4** and **5a**–**d**.

The survey to perform the diastereoselective reduction of **4** was carried out by combining a number of different reducing agents, solvents, and coordinating metal sources (see Scheme 2). In particular, when a sterically demanding reducing agent, such as L-Selectride was tested in THF at −78 °C, we were rewarded with a completely diastereoselective transformation leading to (***syn***)-**6**.[11] In contrast, we met only limited success in the preparation of (***anti***)-**6**. In fact, under the best circumstances, the use of $NaBH_4$ in combination with $ZnCl_2$, which was introduced with the aim to induce a chelation-controlled addition, produced a chromatographically separable mixture of both diastereoisomers. On the other hand, the selection of the adequate conditions to conduct the diastereodivergent addition of vinylmagnesium bromide to pyrrolidinones **5a**–**d** was also examined (see Scheme 2). Thus, it was found that



Scheme 2. Preparation of hydroxylated pyrrolidinones **6** and **7a**.

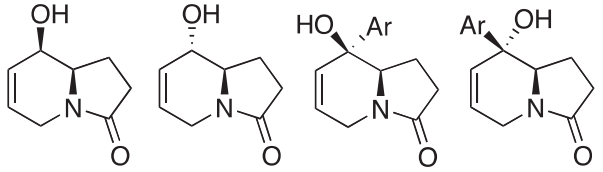
when the reaction was performed under chelation-controlled conditions, a series of pyrrolidinones (***syn***)-**7a–d** was obtained with complete diastereocontrol in good to excellent yields. Particularly, the behavior of $ZnCl_2$ resulted to be superior over other additives that were also studied, such as $Mg(ClO_4)_2$, 18-crown-6, $CeCl_3$, or CuI.[12] Contrarily, none of the experimental conditions that were tested with the aim to prepare pyrrolidinones (***anti***)-**7a–d** led to good levels of diastereocontrol (up to 66/34 for **7a**).[13]

With these materials in hand, we moved to our next synthetic step. In order to overcome a number of difficulties associated to the lack of reactivity and partial olefin isomerization[14] that were detected in our preliminary assays, a combination of several experimental parameters including the use of Grubbs I or Grubbs II catalysts (see Fig. 3), the use of different solvents (CH_2Cl_2 and toluene), and different temperatures (rt and solvent reflux) had to be optimized to perform the ring closing metathesis reaction on derivatives **6** and **7**.[15]

Fig. 3. First (**GI**) and second (**GII**) generation Grubbs' catalysts.

Such optimization process led to the conclusion (see Table 1) that whereas the transformation of either (***syn***)-**6** or (***anti***)-**6** into the corresponding indolizidinones **8** had to be performed under the assistance of **GII** catalyst in refluxing toluene (71 and 86% yield, respectively), the preparation of indolizidinones **9a–d** required the use of CH_2Cl_2 as solvent at room temperature with the aid of Grubbs' **GII** catalyst as well (58–66 yield).[16] The ^{1}H NMR-based stereochemical analysis of the crude samples revealed that the projected cyclization resulted to be successful in the absence of OH protection and with no detectable epimerization in none of the cases under study.[17]

Table 1
Preparation of a series of indolizidinones **8** and **9**[a,b]

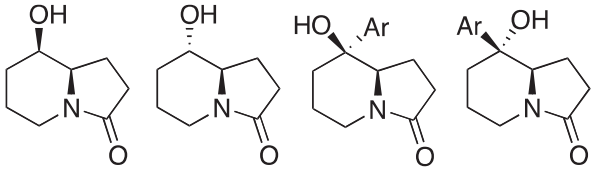


Entry	Ar	Substrate (*syn*/*anti*)	Product (*syn*/*anti*)	Yield (%)
1	—	**6** (100/0)	**8** (100/0)	71
2	—	**6** (0/100)	**8** (0/100)	86
3	Ph	**7a** (33/67)	**9a** (33/67)	66
4	Ph	**7a** (100/0)	**9a** (100/0)	65
5	PMP	**7b** (53/47)	**9b** (53/47)	60
6	PMP	**7b** (100/0)	**9b** (100/0)	65
7	p-ClC_6H_4	**7c** (41/59)	**9c** (41/59)	65
8	p-ClC_6H_4	**7c** (100/0)	**9c** (100/0)	58
9	2-Thienyl	**7d** (38/62)	**9d** (38/62)	65
10	2-Thienyl	**7d** (100/0)	**9d** (100/0)	58

[a] **GII** catalyst was employed in refluxing toluene for the transformation of compound **6**, and in CH_2Cl_2 at room temperature for the transformation of compounds **7a–d**.
[b] The diastereomeric composition was determined from the crude ^{1}H NMR.

To conclude our projected research, the resultant unsaturation generated on indolizidinones **8** and **9** was submitted to new manipulations, both under reductive and oxidative conditions, in order to extend the structural diversity of the series of indolizidinone derivatives that can be prepared. Firstly, (see Table 2) it was found that treatment of separated samples of both diastereoisomers **8** under an atmosphere of H_2 (70 psi) using Pd (C) as catalyst in MeOH rendered indolizidinones (***syn***)-**10** and (***anti***)-**10** in a moderate 46 and 43% yields, respectively. Similarly, when indolizidines **9** were submitted to the same reaction conditions, a series of indolizidinones **11a–d** was prepared in moderate to good yields.

Table 2
Preparation of a series of indolizidinones **10** and **11**[a,b]

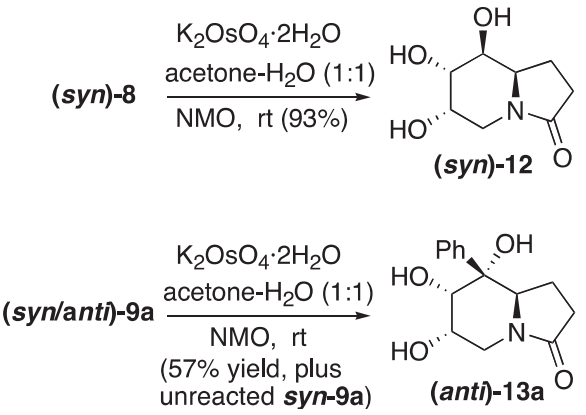


Entry	Ar	Substrate (*syn*/*anti*)	Product (*syn*/*anti*)	Yield (%)
1	—	**8** (100/0)	**10** (100/0)	46
2	—	**8** (0/100)	**10** (0/100)	43
3	Ph	**9a** (33/67)	**11a** (33/67)	69
4	Ph	**9a** (100/0)	**11a** (100/0)	60
5	PMP	**9b** (53/47)	**11b** (53/47)	67
6	PMP	**9b** (100/0)	**11b** (100/0)	63
7	p-ClC_6H_4	**9c** (41/59)	**11c** (41/59)	65
8	p-ClC_6H_4	**9c** (100/0)	**11c** (100/0)	53
9	2-Thyenyl	**9d** (38/62)	**11d** (38/62)	68
10	2-Thyenyl	**9d** (100/0)	**11d** (100/0)	56

[a] All reactions were performed under an atmosphere of H_2 in MeOH as solvent at room temperature, and in the presence of 10% Pd (C).
[b] The diastereomeric composition was determined from the crude ^{1}H NMR.

Finally, we found that the projected dihydroxylation step, that would render the desired trihydroxylated indolizidinone skeleton, resulted to be much more problematic.[18] In fact, although indolizidinone (***syn***)-**8** behaved as expected to render the 6,7,8-trihydroxyindolizidinone (***syn***)-**12** in an excellent 93% yield under modified Upjohn conditions,[19] for which the stereochemical outcome is the result of a stereoelectronic repulsion with the existing C(8)-hydroxy group,[20] indolizidinone (***anti***)-**8** resulted to be inexplicably unreactive under all different conditions that were tested. Similarly, none of all *syn* or *anti* indolizidinones **9** produced the desired trihydroxylated derivatives when submitted to an array of different dihydroxylation conditions, except for (***anti***)-**9a**. Thus, when a *syn*/*anti* mixture of (***syn***/***anti***)-**9a** was treated with $K_2OsO_4 \cdot 2H_2O$ under Upjohn conditions, pure (***anti***)-**13a** was obtained in 57% yield (86% based on consumed starting material) together with unreacted (***syn***)-**9a** (Scheme 3).

Although the explanation for the dramatic difference in the observed reactivity with respect to the nature of the aryl ring in the series of indolizidinones **9a–d** is out of our knowledge, —in fact, only **9a** appears to be reactive enough—, we can suggest (see Fig. 4) a possible explanation for the higher reactivity of (***anti***)-**9a** over its diastereoisomer (***syn***)-**9a**. If we assume that substrate **9a** is stabilized in a half-chair conformation, the allylic substituents at C(8) will occupy pseudoaxial and pseudoequatorial positions. Now, in the case of the *syn*-stereoisomer, the oxidative reagent will find opposition for its approach to both faces of the double bond, due to electronic repulsion with the hydroxy group located in the pseudoaxial position in combination with the nitrogen lone pair, in one case, and to the steric hindrance that the bulky phenyl group exerts in the opposite face. But, although the latter repulsion also exists for the phenyl group in the *anti*-stereoisomer, the electronic repulsion that the hydroxy group induces is diminished since it lies far from



Scheme 3. Preparation of hydroxylated pyrrolidinones (***syn***)-**12** and (***anti***)-**13a**.

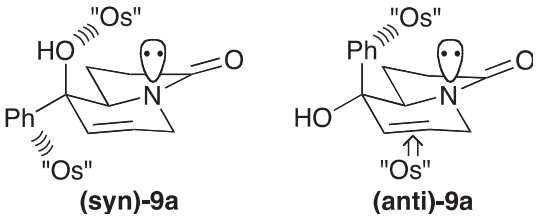


Fig. 4. Possible explanation for the different reactivity of (***syn***)- and (***anti***)-**9** toward the dihydroxylation reagent.

the double bond because of its pseudoequatorial location. Consequently, this situation is also in agreement with the all-*syn* relationships that the three hydroxy groups display in indolizidinone (***anti***)-**13a**.

3. Conclusions

In summary, the design of a new, short, and efficient strategy for the preparation of a series of unsaturated, saturated, and substituted indolizidinones has been achieved—in racemic fashion—from highly and properly functionalized linear alkynylamides. The combination of two key cyclization steps (PIFA-mediated alkyne amidation and a RCM step) allowed the creation of the required unsaturated bicyclic skeletons, on which the final hydrogenation and dihydroxylation processes were performed. It must be highlighted that all four continuous stereogenic centers in the final compounds are produced in a complete diastereoselective fashion and with no need of undesirable protection steps in any of the stages of the synthesis.

4. Experimental section

4.1. General procedures

All reagents were purchased and used as received. All solvents used in reactions were dried and purified according to standard procedures. All air- or moisture-sensitive reactions were performed under argon. The glassware was oven dried (140 °C) overnight and purged with argon prior to use. Melting points were measured using open glass capillaries and are uncorrected. Infrared spectra were recorded as thin films and peaks are reported in cm^{-1}. Only representative absorptions are given. Flash chromatography was carried out on SiO_2 (silica gel 60, 230–400 mesh ASTM). NMR spectra were recorded on a 300 instrument (300 MHz for ^1H and 75.4 MHz for ^{13}C) at 20–25 °C unless otherwise stated. Chemical shifts (δ) were measured in ppm relative to chloroform (δ=7.26 for ^1H or 77.0 for ^{13}C) as internal standard. Coupling constants, *J*, are reported in hertz. DEPT and several bidimensional NMR experiments (COSY, HSQC, NOESY) were used to assist with the assignation of the signals and structural and stereochemical determinations. Mass spectra were recorded under electron impact (EI, 70 eV) or chemical ionization conditions (CI).

4.2. Synthesis of *N*-allyl-4-pentynamide (1)

A solution of 4-pentynoic acid (640 mg, 6.5 mmol) in 5 mL of DCM was added to a magnetically stirred solution of EDC·HCl (1.9 g, 9.9 mmol) and HOBt (1.35 g, 9.9 mmol) in 30 mL of the same solvent followed by the addition of allylamine (0.75 mL, 9.9 mmol) dissolved in 10 mL of DCM. The mixture was cooled to 0 °C and Et_3N (1.4 mL, 9.9 mmol) was added dropwise and was left to react at rt overnight. Then, the reaction was diluted with DCM and water (30 mL), the mixture decanted, and the aqueous phase extracted with DCM (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. The resultant chromatographically pure colorless oil was triturated with cold Et_2O to afford amide **1** as a while solid (82%): mp 46–48 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 5.90–5.77 (m, 2H), 5.23–5.11 (m, 2H), 3.91–3.88 (m, 2H), 2.57–2.51 (m, 2H), 2.44–2.39 (m, 2H), 2.00 (t, *J*=2.0, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.7, 134.0, 116.4, 82.9, 69.3, 41.9, 35.3, 14.9; IR υ (cm^{-1}) 3295, 1648; MS [CI] *m*/*z*: 138 (100), 136 (8); HRMS calcd for $C_8H_{11}NO\cdot H^+$138.0919, found 138.0925.

4.3. Synthesis of (*E*)-*N*-allyl-5-(β-styryl)-4-pentynamide (2)

A solution of (*E*)-β-bromostyrene (500 mg, 3 mmol), $PdCl_2(PPh_3)_2$ (21 mg, 0.03 mmol), PPh_3 (23 mg, 0.09 mmol), and amide **1** (615 mg, 4.5 mmol) in Et_3N (20 mL) was stirred at 40 °C for 15 min. Then, CuI (17 mg, 0.09 mmol) was added and the stirring was continued at 80 °C until total consumption of the starting material (TLC, 6 h). Then, after cooling, the solvent was evaporated under vacuum and the residue purified by column chromatography (EtOAc) to afford amide **2** as a yellowish solid that was crystallized from Et_2O (54%): mp 68–70 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.37–7.29 (m, 5H), 6.87 (d, *J*=16.2, 1H), 6.11 (d, *J*=16.2, 1H), 5.91–5.80 (m, 1H), 5.74 (br s, 1H), 5.26–5.13 (m, 2H), 3.73 (t, *J*=5.6, 11.2, 2H), 2.73 (t, *J*=5.8, 12.7, 2H), 2.46 (t, *J*=7.1, 14.3, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.9, 140.8, 134.1, 128.7, 128.5, 126.1, 116.4, 108.2, 90.8, 80.8, 42.0, 35.7, 16.2; IR υ (cm^{-1}) 3295, 1638; MS [CI] *m*/*z*: 240 (100), 198 (32), 155 (23), 141 (25); HRMS calcd for $C_{16}H_{17}NO\cdot H^+$240.1388, found 240.1392.

4.4. Typical procedure for the Sonogashira coupling reaction

*4.4.1. Synthesis of N-allyl-5-phenyl-4-pentynamide (**3a**).* A solution of iodobenzene (0.5 mL, 4.05 mmol), $PdCl_2(PPh_3)_2$ (28 mg, 0.04 mmol), CuI (15 mg, 0.08 mmol), and amide **1** (555 mg, 4.05 mmol) in Et_3N (20 mL) was stirred at room temperature until total consumption of the starting material (TLC, 72 h). Then, water (30 mL) was added, the mixture was extracted with EtOAc (3×25 mL), and the combined organic extracts were dried over Na_2SO_4 (anh). Once the solvent was evaporated under vacuum, the whole crude was purified by column chromatography (hexanes/EtOAc, 1/1) to afford amide **3a** as a white solid that was crystallized from Et_2O (94%): mp 72–73 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.37–7.32 (m, 2H), 7.25–7.23 (m, 3H), 6.30 (br s, 1H), 5.89–5.74 (m, 1H), 5.22–5.06 (m, 2H), 3.90–3.86 (m, 2H), 2.76–2.70 (m, 2H), 2.51–2.45 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.1, 133.9, 131.4, 128.1, 127.7, 123.3, 116.1, 88.4, 81.4, 41.8, 35.4, 15.8; IR υ (cm^{-1}) 3301, 1631; MS [EI] *m*/*z*: 213 (15), 212 (41), 185 (45), 184 (98), 172 (100),

170 (31), 128 (67); HRMS calcd for $C_{14}H_{15}NO$ 213.1154, found 213.1149.

*4.4.2. N-Allyl-5-(4-methoxyphenyl)-4-pentynamide (**3b**).* According to the typical procedure, amide **3b** was prepared from amide **1** and 4-iodoanisole in 57% yield as a yellowish solid. It was purified by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from Et_2O: mp 82–83 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.28 (d, J=8.7, 2H), 6.77 (d, J=8.7, 2H), 6.10 (br s, 1H), 5.88–5.75 (m, 1H), 5.21–5.07 (m, 2H), 3.88 (t, J=5.6, 2H), 3.76 (s, 3H), 2.71 (t, J=7.2, 2H), 2.47 (t, J=7.2, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.2, 159.3, 134.4, 132.9, 115.5, 113.8, 116.2, 86.8, 81.4, 55.2, 41.9, 35.8, 15.9; IR υ (cm^{-1}) 3310, 1633; MS [CI] *m/z:* 244 (100), 243 (44), 202 (50), 145 (10); HRMS calcd for $C_{15}H_{17}NO_2 \cdot H^+$244.1337, found 244.1345.

*4.4.3. N-Allyl-5-(4-chlorophenyl)-4-pentynamide (**3c**).* According to the typical procedure, amide **3c** was prepared from amide **1** and 4-chlorophenyl iodide in 54% yield as a white solid. It was purified by column chromatography (hexanes/EtOAc, 2/8) followed by crystallization from Et_2O: mp 196–197 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.30–7.22 (m, 4H), 5.88–5.77 (m, 2H), 5.23–5.09 (m, 2H), 3.91 (t, J=5.7, 2H), 2.75 (t, J=7.2, 2H), 2.48 (t, J=7.2, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.9, 134.1, 133.8, 132.8, 128.5, 121.9, 116.4, 89.5, 80.5, 42.0, 35.5, 15.9; IR (film) υ (cm^{-1}) 3305, 1631; MS (CI) *m/z* (%) 248 (100), 247 (25), 206 (42), 149 (10); HRMS calculated for $C_{14}H_{14}^{35}ClNO \cdot H^+$248.0842, found 248.0839.

*4.4.4. N-Allyl-5-(2-thyenyl)-4-pentynamide (**3d**).* According to the typical procedure, amide **3d** was prepared from amide **1** and 2-iodothiophene in 44% yield as a brown solid. It was purified by column chromatography (hexanes/EtOAc, 1/1) followed by crystallization from Et_2O: mp 68–69 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.18–7.10 (m, 2H), 6.93–6.91 (m, 1H), 5.97 (br s, 1H), 5.90–5.77 (m, 1H), 5.23–5.09 (m, 2H), 3.91 (t, J=5.5, 2H), 2.77 (t, J=7.3, 2H), 2.48 (t, J=7.3, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 170.9, 134.0, 131.4, 126.3, 123.5, 116.4, 92.5, 74.8, 42.0, 35.4, 16.2; IR υ (cm^{-1}) 3305, 1633; MS [CI] *m/z*: 220 (100), 179 (47), 178 (96), 135 (10); HRMS calcd for $C_{12}H_{13}NOS \cdot H^+$220.0796, found 220.0790.

4.5. Typical procedure for the PIFA-mediated heterocyclization

*4.5.1. (±)-N-allyl-5-cinnamoyl-2-pyrrolidinone (**4**).* A solution of alkynylamide **2** (348 mg, 1.4 mmol) in CF_3CH_2OH (20 mL) was stirred at 0 °C and a solution of PIFA (940 mg, 2.2 mmol) in 12 mL of the same solvent was added dropwise. The reaction mixture was stirred at that temperature until total consumption of the starting material (TLC, 2 h). For the work up, aqueous Na_2CO_3 (20%) was added (30 mL) and the mixture extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone **4** as a chromatographically pure yellowish oil (74%): ^1H NMR ($CDCl_3$) δ (ppm) 7.70 (d, J=15.8, 1H), 7.54–7.39 (m, 5H), 6.76 (d, J=15.8, 1H), 5.75–5.62 (m, 1H), 5.15–5.08 (m, 2H), 4.53–4.41 (m, 2H), 3.46–3.38 (m, 1H), 2.48–2.33 (m, 3H), 2.00–1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 197.2, 175.2, 145.2, 133.9, 132.1, 131.2, 129.1, 128.6, 121.4, 118.8, 63.7, 44.5, 29.6, 21.4; IR 1692, 1609; MS [CI] *m/z*: 256 (89), 124 (100); HRMS calcd for $C_{16}H_{17}NO_2 \cdot H^+$256.1338, found 256.1335.

*4.5.2. (±)-N-allyl-5-benzoyl-2-pyrrolidinone (**5a**).* According to the typical procedure, pyrrolidinone **5a** was prepared from amide **3a** in 66% yield as a yellowish oil. It was purified by column chromatography (EtOAc): ^1H NMR ($CDCl_3$) δ (ppm) 7.91 (d, J=7.1, 2H), 7.63–7.45 (m, 3H), 5.78–5.55 (m, 1H), 5.15–5.02 (m, 3H), 4.51–4.45 (m, 1H), 3.39 (dd, J=15.0, 7.9, 1H), 2.42–2.39 (m, 3H), 2.01–1.96 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 196.8, 175.0, 134.0, 133.9, 132.3128.9, 128.2, 118.6, 60.6, 44.2, 29.4, 23.0; IR υ (cm^{-1}) 1690; MS [M] *m/z*: 229 (1), 124 (100), 105 (23); HRMS calcd for $C_{14}H_{15}NO_2$: 229.1103, found 229.1111.

*4.5.3. (±)-N-allyl-5-(4-methoxyphenyl)-2-pyrrolidinone (**5b**).* According to the typical procedure, pyrrolidinone **5b** was prepared from amide **3b** in 40% yield as a yellowish solid. It was purified by column chromatography (EtOAc) followed by crystallization from Et_2O: mp 72–73 °C (Et_2O); ^1H NMR ($CDCl_3$) δ (ppm) 7.86 (d, J=8.9, 2H), 6.91 (d, J=8.9, 2H), 5.72–5.59 (m, 1H), 5.10–4.99 (m, 3H), 4.45–4.38 (m, 1H), 3.82 (s, 3H), 3.37–3.30 (m, 1H), 2.44–2.33 (m, 3H), 1.96–1.90 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.4, 175.2, 164.2, 132.5, 130.6128.9, 118.5, 114.2, 60.4, 55.6, 44.3, 29.6, 23.4; IR υ (cm^{-1}) 1690; MS [CI] *m/z*: 260 (100), 124 (40); HRMS calcd for $C_{15}H_{17}NO_3 \cdot H^+$260.1287, found 270.1277.

*4.5.4. (±)-N-allyl-5-(4-chlorophenyl)-2-pyrrolidinone (**5c**).* According to the typical procedure, pyrrolidinone **5c** was prepared from amide **3c** in 54% yield as a yellowish oil. It was purified by column chromatography (EtOAc): ^1H NMR ($CDCl_3$) δ (ppm) 7.81 (d, J=8.6, 2H), 7.40 (d, J=8.6, 2H), 5.66–5.56 (m, 1H), 5.08–4.97 (m, 3H), 4.41–4.35 (m, 1H), 3.37–3.29 (m, 1H), 2.44–2.32 (m, 3H), 1.93–1.87 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 195.8, 175.0, 140.5, 132.5, 132.4, 129.7129.3, 118.7, 60.7, 44.3, 29.4, 23.1; IR υ (cm^{-1}) 1697; MS [CI] *m/z*: 266 (34), 264 (100), 124 (47); HRMS calcd for $C_{14}H_{14}^{35}ClNO_2 \cdot H^+$264.5791, found 264.0785.

*4.5.5. (±)-N-allyl-5-(2-thyenyl)-2-pyrrolidinone (**5d**).* According to the typical procedure, pyrrolidinone **5d** was prepared from amide **3d** in 64% yield as a yellowish oil. It was purified by column chromatography (EtOAc): ^1H NMR ($CDCl_3$) δ (ppm) 7.71–7.67 (m, 2H), 7.13–7.10 (m, 1H), 5.65–5.56 (m, 1H), 5.06–4.90 (m, 3H), 4.39–4.32 (m, 1H), 3.37–3.29 (m, 1H), 2.46–2.31 (m, 3H), 2.03–1.93 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 190.5, 175.1, 140.9, 135.1, 132.6132.2, 128.6, 118.8, 61.7, 44.3, 29.5, 23.7; IR υ (cm^{-1}) 1690; MS [CI] *m/z*: 237 (12), 236 (100), 124 (48); HRMS calcd for $C_{12}H_{13}NO_2S \cdot H^+$236.0745, found 236.0734.

4.6. (±)-(5*R*,1′*R*)-*N*-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (*syn*-6)

A solution of L-Selectride® (1.8 mL, 1.0 M in THF) was added dropwise to a cold (−78 °C) solution of pyrrolidinone **4** (230 mg, 0.9 mmol) in 4.5 mL of the same solvent. After 30 min, temperature was raised to room temperature and 2 mL of an aqueous solution of NaOH (10%) was added. The whole mixture was extracted with CH_2Cl_2 (3×10 mL), the combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone (***syn*-6** as a chromatographically pure yellowish oil (70%): ^1H NMR ($CDCl_3$) δ (ppm) 7.30–7.17 (m, 5H), 6.59 (d, J=15.9, 1H), 6.10 (dd, J=15.9, 6.00, 1H), 5.72–5.65 (m, 1H), 5.14 (d, J=4.5, 1H), 5.10 (s, 1H), 4.39–4.25 (m, 2H), 3.76–3.64 (m, 2H), 2.88 (br s, 1H), 2.36–1.98 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.9, 136.2, 132.8, 132.3, 128.7, 128.0, 127.5, 126.5, 117.8, 73.4, 61.6, 44.7, 30.2, 20.5; IR υ (cm^{-1}) 3374, 1670; HRMS calculated for $C_{16}H_{19}NO_2 \cdot H^+$258.1494, found 258.1507.

4.7. (±)-(5*R*,1′*S*)-*N*-allyl-5-(1-hydroxy-3-phenylallyl)-pyrrolidin-2-one (*anti*-6)

Solid $NaBH_4$ (68 mg, 1.8 mmol) was added in one portion to a cold (-78 °C) solution of pyrrolidinone **4** (230 mg, 0.9 mmol) in MeOH (5 mL). After 30 min, H_2O (2 mL) was added and temperature was raised to rt. The whole mixture was extracted with CH_2Cl_2

(3×10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (MeCN) rendered, independently, pyrrolidinones (***syn***)-**6** and (***anti***)-**6** as chromatographically pure yellowish oils in a 68:32 ratio (46% combined yield). Only the data for (***anti***)-**6** is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.40–7.25 (m, 5H), 6.73 (d, J=16.0, 1H), 6.14 (dd, J=16.0, 5.5, 1H), 5.87–5.74 (m, 1H), 5.27 (d, J=9.2, 1H), 5.23 (s, 1H), 4.63 (s, 1H), 4.36 (dd, J=15.5, 4.8, 1H), 3.72 (dd, J=16.2, 6.9, 2H), 2.92 (br s, 1H), 2.59–2.47 (m, 1H), 2.32–2.26 (m, 1H), 2.14–1.87 (m, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.1, 136.4, 132.8, 132.1, 128.7, 127.3, 126.5, 118.2, 70.7, 61.9, 43.6, 30.6, 18.2; HRMS calculated for $C_{16}H_{19}NO_2\cdot H^+$258.1494, found 258.1500.

4.8. Typical procedure for the nucleophilic addition of vinylmagnesium bromide to pyrrolidinones 5 (method A)

*4.8.1. Synthesis of (±)-(5R,1′S)-N-allyl-5-(1-hydroxy-1-phenylallyl)-pyrrolidin-2-one (**syn-7a**).* $ZnCl_2$ (30 mg, 0.22 mmol) was added to a solution of pyrrolidinone **5a** (50 mg, 0.2 mmol) in THF (2 mL). After 30 min, the mixture was cold to -20 °C and vinylmagnesium bromide (0.8 mL, 1.0 M in THF) was added. After 5 h, 4 mL of a saturated solution of NH_4Cl were added, and the whole mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone (***syn***)-**7a** as a chromatographically pure yellowish oil (90%): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.26–7.13 (m, 5H), 6.29–6.20 (m, 1H), 5.57–5.51 (m, 1H), 5.45 (d, J=17.2, 1H), 5.27 (d, J=10.8, 1H), 5.08 (d, J=10.2, 1H), 4.90 (d, J=17.1, 1H), 4.26–4.19 (m, 1H), 4.09–4.05 (m, 1H), 2.98–3.90 (m, 1H), 2.28–1.86 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.9, 143.4, 140.0, 132.6, 128.5127.6, 125.7, 117.5, 115.5, 79.3, 64.5, 44.5, 30.0, 21.3; IR υ (cm^{-1}) 3368, 1670; MS [CI] m/z: 258 (100), 240 (23), 124 (54); HRMS calculated for $C_{16}H_{19}NO_2\cdot H^+$258.1494, found 258.1501.

*4.8.2. Synthesis of (±)-(5R,1′S)-N-allyl-5-[1-hydroxy-1-(4-methoxyphenyl)allyl]-pyrrolidin-2-one (**syn-7b**).* According to the typical procedure pyrrolidinone (***syn***)-**7b** was obtained from **5b** in 86% yield. It was purified by column chromatography (EtOAc) as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.34 (d, J=8.8, 2H), 6.88 (d, J=8.8, 2H), 6.30–6.21 (m, 1H), 5.67–5.54 (m, 1H), 5.45 (d, J=17.1, 1H), 5.31 (d, J=10.8, 1H), 5.12 (d, J=10.2, 1H), 4.99 (d, J=17.1, 1H), 4.31–4.27 (m, 1H), 4.05–4.02 (m, 1H), 3.80 (s, 3H), 3.20–3.12 (m, 1H), 2.32–1.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.9, 159.1, 139.3, 135.0, 132.7, 127.0, 117.5, 115.7, 113.9, 79.3, 64.7, 55.3, 44.7, 30.1, 21.3; IR (film) υ (cm^{-1}) 3394, 1668; MS (CI) m/z (%) 288 (100), 272 (13), 270 (23), 163 (17); HRMS calculated for $C_{17}H_{21}NO_3\cdot H^+$288.1599, found 288.1605.

*4.8.3. Synthesis of (±)-(5R,1′S)-N-allyl-5-[1-(4-chlorophenyl)-1-hydroxyallyl]-pyrrolidin-2-one (**syn-7c**).* According to the typical procedure pyrrolidinone (***syn***)-**7c** was obtained from **5c** in 81% yield. It was purified by column chromatography (EtOAc) as a yellowish oil: ^{1}H NMR (MeOD) δ (ppm) 7.50 (d, J=8.7, 2H), 7.35 (d, J=8.7, 2H), 6.41–6.31 (m, 1H), 5.65–5.52 (m, 1H), 5.46 (d, J=17.2, 1H), 5.31 (d, J=10.5, 1H), 5.09 (d, J=10.5, 1H), 4.96 (d, J=17.2, 1H), 4.21 (br s, 1H), 4.15–4.11 (m, 2H), 3.14–3.04 (m, 1H), 2.10–1.96 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 179.4, 144.2, 134.3, 141.8, 133.4, 129.3, 129.1, 117.8, 116.0, 80.0, 66.5, 45.8, 30.9, 22.3; IR (film) υ (cm^{-1}) 3354, 1668; MS (M+1, CI) m/z (%) 292 (100), 276 (15), 234 (10), 167 (12); HRMS calculated for $C_{16}H_{18}^{35}ClNO_2\cdot H^+$292.1104, found 292.1107.

*4.8.4. Synthesis of (±)-(5R,1′S)-N-allyl-5-[1-hydroxy-1-(2-thyenyl) allyl]-pyrrolidin-2-one (**syn-7d**).* According to the typical procedure pyrrolidinone (***syn***)-**7d** was obtained from **5d** in 61% yield. It was purified by column chromatography (EtOAc) as a brownish oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.28–7.26 (m, 1H), 6.99–6.95 (m, 2H), 6.29–6.20 (m, 1H), 5.76–5.63 (m, 1H), 5.54 (d, J=17.2, 1H), 5.37 (d, J=10.6, 1H), 5.16 (d, J=10.2, 1H), 5.04 (br s, 1H), 4.36 (d, J=17.2, 1H), 4.04–3.97 (m, 1H), 3.53–3.41 (m, 1H), 2.92 (s, 1H), 2.22–1.91 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.7, 148.0, 138.6, 132.8, 127.1, 125.4, 124.5, 117.6, 116.8, 79.0, 65.6, 45.0, 29.9, 21.4; IR (film) υ (cm^{-1}) 3339, 1670; MS [EI] m/z (%) 246 (20), 124 (93); HRMS calculated for $C_{14}H_{17}^{32}SNO_2$ 263.0980, found 263.0957.

4.9. Typical procedure for the nucleophilic addition of vinylmagnesium bromide to pyrrolidinones 5 (method B)

*4.9.1. Synthesis of (±)-(5R,1′R)-N-allyl-5-(1-hydroxy-1-phenylallyl)-pyrrolidin-2-one (**anti-7a**).* A vinylmagnesium bromide solution (0.35 mL, 1.0 M in THF) was added to a solution of pyrrolidinone **5a** (50 mg, 0.2 mmol) in THF (2 mL) and the temperature was raised to 40 °C. After 5 h, 4 mL of a saturated solution of NH_4Cl were added and the whole mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4, and the solvent evaporated. Purification of the crude by flash chromatography (EtOAc) gave pyrrolidinone (***anti***)-**7a** and (***syn***)-**7a** in an inseparable 67/33 ratio (86% combined yield). Only the data for the (***anti***)-**7a** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.46–7.26 (m, 5H), 6.49–6.40 (m, 1H), 5.60–5.44 (m, 1H), 5.47 (d, J=17.2, 1H), 5.23 (d, J=10.8, 1H), 5.18 (d, J=10.2, 1H), 5.07 (d, J=17.1, 1H), 4.50–4.45 (m, 1H), 4.12–4.06 (m, 1H), 3.58–3.50 (m, 1H), 2.28–1.80 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.2, 143.7, 141.9, 132.8, 128.5, 127.3125.7, 117.9, 114.1, 78.9, 64.4, 45.1, 30.0, 21.4; GC-HRMS calculated for $C_{16}H_{19}NO_2\cdot H^+$258.1494, found 258.1599.

*4.9.2. Synthesis of (±)-(5R,1′R)-N-allyl-5-[1-hydroxy-1-(4-methoxyphenyl)allyl]-pyrrolidin-2-one (**anti-7b**).* According to the typical procedure pyrrolidinones (***anti***)-**7b** and (***syn***)-**7b** were obtained from **5b** in an inseparable 47/53 ratio (80% combined yield) as yellowish oils after purification by column chromatography (EtOAc). Only the data for the (***anti***)-**7b** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.34 (d, J=8.8, 2H), 6.88 (d, J=8.8, 2H), 6.49–6.36 (m, 1H), 5.94–5.80 (m, 1H), 5.45 (d, J=17.1, 1H), 5.31 (d, J=10.8, 1H), 5.19–5-15 (m, 1H), 4.99 (d, J=17.1, 1H), 4.46–4.41 (m, 1H), 4.15–4.10 (m, 1H), 3.79 (s, 3H), 3.56–3.48 (m, 1H), 2.32–1.68 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 177.2, 159.1, 139.9, 132.7, 126.8, 117.9, 115.7, 113.4, 78.9, 64.6, 55.3, 44.5, 30.1, 21.3; GC-HRMS calculated for $C_{17}H_{21}NO_3\cdot H^+$288.1599, found 288.1600.

*4.9.3. Synthesis of (±)-(5R,1′R)-N-allyl-5-[1-(4-chlorophenyl)-1-hydroxyallyl]-pyrrolidin-2-one (**anti-7c**).* According to the typical procedure pyrrolidinones (***anti***)-**7c** and (***syn***)-**7c** were obtained from **5c** in an inseparable 59/41 ratio (73% combined yield) as yellowish oils after purification by column chromatography (EtOAc). Only the data for the (***anti***)-**7c** isomer is now reported: ^{1}H NMR (MeOD) δ (ppm) 7.51–7.35 (m, 4H), 6.53–6.45 (m, 1H), 5.88–5.72 (m, 1H), 5.47 (d, J=17.2, 1H), 5.31 (d, J=10.5, 1H), 5.19 (d, J=10.5, 1H), 4.96 (d, J=17.2, 1H), 4.21 (br s, 1H), 4.40–4.35 (m, 2H), 3.14–3.04 (m, 1H), 2.10–1.96 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 179.4, 142.6, 142.1, 134.3, 134.0, 129.3, 129.1, 117.4, 116.0, 80.0, 65.3, 45.1, 30.8, 23.4; GC-HRMS calculated for $C_{16}H_{18}^{35}ClNO_2\cdot H^+$292.1104, found 292.1107.

*4.9.4. Synthesis of (±)-(5R,1′R)-N-allyl-5-[1-hydroxy-1-(2-thyenyl) allyl]-pyrrolidin-2-one (**anti-7d**).* According to the typical procedure pyrrolidinones (***anti***)-**7d** and (***syn***)-**7d** were obtained from **5d** in an inseparable 38/62 ratio (83% combined yield) as yellowish oils after purification by column chromatography (EtOAc). Only the data for the (***anti***)-**7d** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.28–7.26 (m, 1H), 6.99–6.95 (m, 2H), 6.44–6.35 (m, 1H),

5.80–5.62 (m, 1H), 5.58 (d, *J*=17.2, 1H), 5.34 (d, *J*=10.6, 1H), 5.16 (d, *J*=10.2, 1H), 5.04 (br s, 1H), 4.46 (d, *J*=17.2, 1H), 4.04–3.97 (m, 1H), 3.53–3.41 (m, 1H), 2.95 (s, 1H), 2.22–1.91 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 176.7, 148.0, 140.0, 135.8, 126.9, 125.6, 124.7, 117.4, 116.9, 68.2, 65.6, 45.2, 29.8, 21.4; GC-HRMS calculated for $C_{14}H_{17}^{32}SNO_2$ 263.0980, found 263.0966.

4.10. Typical procedure for the olefin metathesis reaction on pyrrolidinones 7

*4.10.1. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-phenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**syn**)-**9a**.* Grubbs II catalyst (5 mg, 10% wt) was added in one portion onto a solution of pyrrolidinone (***syn***)-**7a** (50 mg, 0.2 mmol) in CH_2Cl_2 (10 mL) at rt. After 12 h, the solvent was eliminated under vacuum and the resulting residue was column chromatographed (EtOAc) to afford indolizidinone (***syn***)-**9a** as a white solid that was triturated in Et_2O (65%): mp 162–165 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ (ppm) 7.41–7.26 (m, 5H), 5.97 (d, *J*=10.3, 1H), 5.82 (d, *J*=10.3, 1H), 4.48 (d, *J*=18.8, 1H), 3.79 (d, *J*=7.7, 1H), 3.63 (d, *J*=18.8, 1H), 2.79 (br s, 1H), 2.02–1.75 (m, 3H), 1.41–1.27 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.9, 139.0, 133.5, 128.2127.8, 126.5, 123.7, 73.9, 63.0, 40.0, 29.2, 18.8; IR (film) υ (cm^{-1}) 3359, 1670; MS (CI) *m*/*z* (%) 230 (100), 212 (83), 211 (53), 146 (34); HRMS calculated for $C_{14}H_{15}NO_2\cdot H^+$230.1181, found 230.1191.

*4.10.2. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**syn**)-**9b**.* According to the typical procedure indolizidinone (***syn***)-**9b** was obtained from (***syn***)-**7b** in 65% yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.23 (d, *J*=8.7, 2H), 6.85 (d, *J*=8.7, 2H), 5.94 (d, *J*=10.2, 1H), 5.79 (d, *J*=10.2, 1H), 4.46 (d, *J*=18.9, 1H), 3.77 (br s, 4H), 3.61 (d, *J*=18.9, 1H), 2.57 (br s, 1H), 1.97–1.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.8, 159.3, 133.7, 133.5, 131.4, 127.7, 123.5, 73.6, 63.0, 55.2, 39.9, 29.2, 18.8; IR (film) υ (cm^{-1}) 3389, 1670; MS (CI) *m*/*z* (%) 260 (100), 242 (99), 241 (77), 240 (41), 223 (11), 176 (53); HRMS calculated for $C_{15}H_{17}NO_3\cdot H^+$260.1286, found 260.1285.

*4.10.3. Synthesis of (±)-(8S,8aR)-8-(4-chlorophenyl)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**syn**)-**9c**.* According to the typical procedure indolizidinone (***syn***)-**9c** was obtained from (***syn***)-**7c** in 58% yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.36–7.27 (m, 4H), 6.00 (d, *J*=10.6, 1H), 5.80 (d, *J*=10.6, 1H), 4.51 (d, *J*=19.2, 1H), 3.78 (d, *J*=8.3, 1H), 3.63 (d, *J*=19.2, 1H), 2.33 (br s, 1H), 1.98–1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.6, 159.3, 133.1, 131.4, 128.3, 128.0, 124.3, 63.0, 40.0, 29.1, 18.7; IR (film) υ (cm^{-1}) 3387, 1670; MS (CI) *m*/*z* (%) 264 (100), 248 (36), 246 (40); HRMS calculated for $C_{14}H_{14}^{35}ClNO_2\cdot H^+$264.0791, found 264.0804.

*4.10.4. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-thyenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**syn**)-**9d**.* According to the typical procedure indolizidinone (***syn***)-**9d** was obtained from (***syn***)-**7d** in 60% yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.31–7.25 (m, 1H), 7.00–6.93 (m, 1H), 6.81–6.77 (m, 1H) 6.04–5.88 (m, 2H), 4.45 (d, *J*=19.3, 1H), 3.87–3.82 (m, 1H), 3.61 (d, *J*=19.3, 1H), 3.12 (br s, 1H), 2.11–2.00 (m, 3H), 1.41–1.31 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.0, 144.8, 133.7, 127.3, 126.2, 125.4, 123.6, 73.3, 62.6, 39.9, 29.0, 19.0; IR (film) υ (cm^{-1}) 3330, 1670; MS (CI) *m*/*z* (%) 236 (100), 218 (89), 217 (64), 152 (60); HRMS calculated for $C_{12}H_{13}NO_2S\cdot H^+$236.0745, found 236.0741.

*4.10.5. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-phenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**anti**)-**9a**.* According to the typical procedure indolizidinone (***anti***)-**9a** and (***syn***)-**9a** were obtained from a *syn*/*anti* (33/67) mixture of **7a** in 66% combined yield. It was purified by column chromatography (EtOAc) as a brown oil to give an inseparable diastereomeric mixture. Only the data for the (***anti***)-**9a** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.43–7.30 (m, 5H), 6.01 (s, 2H), 3.79 (d, *J*=7.7, 1H), 3.73–3.69 (dd, *J*=3.7, 2H), 3.42 (br s, 1H), 2.58–2.14 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.5, 142.8, 132.6, 128.0127.6, 126.6, 123.3, 71.6, 64.0, 40.1, 30.3, 17.3; GC-HRMS calculated for $C_{14}H_{15}NO_2\cdot H^+$230.1181, found 230.1191.

*4.10.6. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-(4-methoxyphenyl)-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**anti**)-**9b**.* According to the typical procedure indolizidinone (***anti***)-**9b** and (***syn***)-**9b** were obtained from a *syn*/*anti* (53/47) mixture of **7b** in 60% combined yield. It was purified by column chromatography (EtOAc) as a brown oil to give an inseparable diastereomeric mixture. Only the data for the (***anti***)-**9b** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.23 (d, *J*=8.7, 2H), 6.85 (d, *J*=8.7, 2H), 5.98 (s, 2H), 4.46 (d, *J*=18.9, 1H), 3.80 (br s, 4H), 3.61 (d, *J*=18.9, 1H), 2.57 (br s, 1H), 1.97–1.77 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.4, 158.8, 134.9, 133.7, 132.9, 126.8, 126.5, 71.5, 63.9, 55.3, 40.0, 30.3, 17.4; GC-HRMS calculated for $C_{15}H_{17}NO_3\cdot H^+$260.1286, found 260.1280.

*4.10.7. Synthesis of (±)-(8R,8aR)-8-(4-chlorophenyl)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**anti**)-**9c**.* According to the typical procedure indolizidinone (***anti***)-**9c** and (***syn***)-**9c** were obtained from a *syn*/*anti* (41/49) mixture of **7c** in 65% combined yield. It was purified by column chromatography (EtOAc) as a brown oil to give an inseparable diastereomeric mixture. Only the data for the (***anti***)-**9c** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.36–7.27 (m, 4H), 6.09 (s, 2H), 4.51 (d, *J*=19.2, 1H), 3.78 (d, *J*=8.3, 1H), 3.63 (d, *J*=19.2, 1H), 2.33 (br s, 1H), 1.98–1.54 (m, 4H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.4, 159.6, 134.9, 133.6, 132.9, 129.1, 128.3, 123.2, 63.9, 40.0, 30.2, 18.7; GC-HRMS calculated for $C_{14}H_{14}^{35}ClNO_2\cdot H^+$264.0791, found 264.0800.

*4.10.8. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-thyenyl-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**anti**)-**9d**.* According to the typical procedure indolizidinone (***anti***)-**9d** and (***syn***)-**9d** were obtained from a *syn*/*anti* (38/62) mixture of **7c** in 69% combined yield. It was purified by column chromatography (EtOAc) as a brown oil to give an inseparable diastereomeric mixture. Only the data for the (***anti***)-**9d** isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.31–7.25 (m, 1H), 7.00–6.93 (m, 1H), 6.81–6.77 (m, 1H) 6.92 (s, 2H), 4.45 (d, *J*=19.3, 1H), 3.87–3.82 (m, 1H), 3.61 (d, *J*=19.3, 1H), 3.12 (br s, 1H), 2.11–2.00 (m, 3H), 1.41–1.31 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 175.4, 147.4132.71, 127.1, 126.8, 125.1, 123.4, 71.3, 63.7, 40.0, 29.5, 18.0; GC-HRMS calculated for $C_{12}H_{13}NO_2S\cdot H^+$236.0745, found 236.0746.

4.11. Typical procedure for the olefin metathesis reaction on pyrrolidinones 6

*4.11.1. Synthesis of (±)-(8R,8aR)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**syn**)-**8**.* Grubbs II catalyst (3 mg, 10% wt) was added in one portion onto a solution of pyrrolidinone (***syn***)-**6** (90 mg, 0.35 mmol) in toluene (10 mL) and temperature was raised to reflux. After 4 h, the mixture was cooled to rt and solvent was eliminated under vacuum. The resulting residue was column chromatographed (EtOAc) to afford indolizidinone (***syn***)-**8** as a white solid that was triturated in hexanes (71%): mp 111–113 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ (ppm) 6.83 (d, *J*=7.0, 1H), 4.96 (dd, *J*=11.9, 5.9, 1H), 3.98 (s, 1H), 3.76 (dd, *J*=16.1, 8.0, 1H), 2.51–1.95 (m, 7H); ^{13}C NMR ($CDCl_3$) δ (ppm) 172.7, 121.8, 105.0, 63.4, 58.9, 31.6, 30.7, 20.1; IR υ (cm^{-1}) 3359, 1670; MS [CI] *m*/*z* (%) 154 (100), 153 (37), 136 (12); HRMS calculated for $C_8H_{11}NO_2\cdot H^+$154.0868, found 154.0866.

*4.11.2. Synthesis of (±)-(8S,8aR)-8-hydroxy-1,2,8,8a-tetrahydroindolizin-3(5H)-one (**anti**)-**8**.* According to the typical procedure indolizidinone (***anti***)-**8** was obtained from (***anti***)-**6** in 86%

combined yield. It was purified by column chromatography (EtOAc) as a brown oil: ^{1}H NMR ($CDCl_3$) δ (ppm) 6.72 (d, J=7.5, 1H), 5.05–5.00 (m, 1H), 3.68–3.60 (m, 1H), 3.54–3.45 (m, 1H), 2.97 (br s, 1H), 2.45–1.39 (m, 4H), 2.20–2.11 (m, 1H), 1.83–1.76 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 171.9, 121.2, 107.2, 70.4, 60.4, 32.5, 31.1, 24.3; HRMS calculated for $C_8H_{11}NO_2\cdot H^+$154.0868, found 154.0863.

4.12. Typical procedure for the hydrogenation reaction

*4.12.1. Synthesis of (±)-(8R,8aR)-8-hydroxy-hexahydroindolizin-3(5H)-one (**syn**)-**10**.* A solution of indolizidine (***syn***)-**8** (37 mg, 0.24 mmol) in MeOH (5 mL) was hydrogenated (70 psi) in the presence of Pd/C (4 mg, 10% weight) until total consumption of the starting material (TLC, 8 h). Then, the mixture was filtered through Celite, the solvent evaporated, and the resulting residue was column chromatographed (EtOAc) to yield indolizidinone (***syn***)-**10** as a colorless oil (46%): ^{1}H NMR (MeOD) δ (ppm) 4.11 (d, J=12.6, 1H), 3.81 (s, 1H), 3.53 (t, J=12.6, 6.3, 1H), 2.65 (t, J=22.9, 10.2, 1H), 2.40–1.24 (m, 9H); ^{13}C NMR (MeOD) δ (ppm) 174.7, 66.5, 60.9, 39.9, 30.8, 30.4, 19.3, 17.7; IR υ (cm^{-1}) 3379, 1660; MS [CI] m/z: 156 (100), 155 (17), 138 (13); HRMS calculated for $C_8H_{13}NO_2\cdot H^+$156.1025, found 156.1024.

*4.12.2. Synthesis of (±)-(8S,8aR)-8-hydroxy-hexahydroindolizin-3(5H)-one (**anti**)-**10**.* According to the typical procedure indolizidinone (***anti***)-**11a** was obtained from (***anti***)-**9a** in 43% yield. It was identified on the basis of the disappearance of the olefinic protons in the crude NMR spectrum. However, all efforts to isolate it by column chromatography resulted in a complete decomposition of the material.

*4.12.3. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-phenyl-hexahydroindolizin-3(5H)-one (**syn**)-**11a**.* According to the typical procedure indolizidinone (***syn***)-**11a** was obtained from (***syn***)-**9a** in 60% yield. It was purified as a white solid by column chromatography (MeOH) followed by crystallization from Et_2O: mp 144–148 °C (Et_2O): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.47 (d, J=7.4, 2H), 7.35–7.26 (m, 3H), 4.22 (d, J=13.1, 1H), 3.71 (t, J=8.3, 1H), 2.85–2.77 (m, 1H), 2.74 (s, 1H), 2.41–2.04 (m, 4H), 1.92–1.64 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 184.5, 143.7, 128.0, 127.9, 126.3, 73.6, 67.4, 40.8, 40.4, 31.1, 21.4, 19.8; IR (film) υ (cm^{-1}) 3379, 1663; MS (CI) m/z (%) 232 (100), 214 (47), 213 (28); HRMS calculated for $C_{14}H_{17}NO_2\cdot H^+$232.1337, found 232.1343.

*4.12.4. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-(4-methoxyphenyl)-hexahydroindolizin-3(5H)-one (**syn**)-**11b**.* According to the typical procedure indolizidinone (***syn***)-**11b** was obtained from (***syn***)-**9b** in 63% yield. It was purified as a yellowish oil by column chromatography (EtOAc): ^{1}H NMR (MeOD) δ (ppm) 7.37 (d, J=8.9, 2H), 6.88 (d, J=8.9, 2H), 4.10 (d, J=13.2, 1H), 3.77–3.71 (m, 4H), 2.91–2.81 (m, 1H), 2.40–1.69 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.6, 160.0, 136.6, 128.8, 114.4, 73.7, 67.7, 56.7, 41.0, 40.5, 31.1, 21.6, 19.7; IR (film) υ (cm^{-1}) 3379, 1660; MS (CI) m/z (%) 262 (67), 244 (100), 243 (49); HRMS calculated for $C_{15}H_{19}NO_3\cdot H^+$262.1443, found 262.1455.

*4.12.5. Synthesis of (±)-(8R,8aR)-8-(4-chlorophenyl)-8-hydroxy-hexahydroindolizin-3(5H)-one (**syn**)-**11c**.* According to the typical procedure indolizidinone (***syn***)-**11c** was obtained from (***syn***)-**9c** in 53% yield. It was purified as a brownish oil by column chromatography (EtOAc): ^{1}H NMR (MeOD) δ (ppm) 7.44 (d, J=8.7, 2H), 7.33 (d, J=8.7, 2H), 4.14–4.10 (m, 1H), 3.80–3.73 (m, 1H), 2.90–2.83 (m, 1H), 2.39–1.69 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.7, 144.8, 134.0, 129.4, 129.1, 73.6, 67.4, 40.8, 40.5, 31.1, 21.4, 19.8; IR (film) υ (cm^{-1}) 3379, 1660; MS (CI) m/z (%) 266 (100), 250 (10), 248 (19); HRMS calculated for $C_{14}H_{16}^{35}ClNO_2\cdot H^+$266.0948, found 266.0948.

*4.12.6. Synthesis of (±)-(8R,8aR)-8-hydroxy-8-(2-thyenyl)-hexahydroindolizin-3(5H)-one (**syn**)-**11d**.* According to the typical procedure indolizidinone (***syn***)-**11d** was obtained from (***syn***)-**11d** in 56% yield. It was purified as a yellowish oil by column chromatography (EtOAc): ^{1}H NMR ($CDCl_3$) δ (ppm) 7.26–7.18 (m, 1H), 6.95–6.87 (m, 1H), 4.17–4.13 (m, 1H), 3.61–3.56 (m, 1H), 3.75–2.67 (m, 1H), 2.28–1.66 (m, 9H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.8, 146.3, 126.8, 124.3, 123.7, 73.9, 66.0, 39.4, 39.1, 30.1, 21.0, 18.1; IR (film) υ (cm^{-1}) 3334, 1660; MS (CI) m/z (%) 238 (100), 222 (14), 220 (48), 219 (23); HRMS calculated for $C_{12}H_{15}^{32}SNO\cdot H^+$238.0902, found 238.0913.

*4.12.7. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-phenyl-hexahydroindolizin-3(5H)-one (**anti**)-**11a**.* According to the typical procedure indolizidinone **11a** was obtained as a diastereomeric mixture from (33/67) (***syn/anti***)-**9a** in 69% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the *anti* isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.47 (d, J=7.4, 2H), 7.33–7.25 (m, 3H), 4.21 (d, J=13.1, 1H), 3.70 (t, J=8.3, 1H), 2.86–2.76, 2.74 (s, 2H), 2.41–2.04 (m, 4H), 1.90–1.63 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 184.4, 143.7, 128.1, 127.9, 126.8, 73.6, 67.5, 40.9, 40.3, 31.3, 21.4, 19.8.

*4.12.8. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-(4-methoxyphenyl)-hexahydroindolizin-3(5H)-one (**anti**)-**11b**.* According to the typical procedure indolizidinone **11b** was obtained as a diastereomeric mixture from (53/47) (***syn/anti***)-**9b** in 67% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the *anti* isomer is now reported: ^{1}H NMR (MeOD) δ (ppm) 7.36 (d, J=8.9, 2H), 6.89 (d, J=8.9, 2H), 4.11 (d, J=13.2, 1H), 3.75–3.71 (m, 4H), 2.91–2.83 (m, 1H), 2.38–1.65 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.5, 160.0, 135.6, 128.8, 114.3, 73.6, 67.5, 56.7, 40.9, 40.5, 32.1, 21.6, 19.7.

*4.12.9. Synthesis of (±)-(8S,8aR)-8-(4-chlorophenyl)-8-hydroxy-hexahydroindolizin-3(5H)-one (**anti**)-**11c**.* According to the typical procedure indolizidinone **11c** was obtained as a diastereomeric mixture from (41/59) (***syn/anti***)-**9c** in 65% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the *anti* isomer is now reported: ^{1}H NMR (MeOD) δ (ppm) 7.44 (d, J=8.7, 2H), 7.33 (d, J=8.7, 2H), 4.14–4.10 (m, 1H), 3.80–3.73 (m, 1H), 2.90–2.83 (m, 1H), 2.39–1.69 (m, 8H); ^{13}C NMR (MeOD) δ (ppm) 176.7, 143.7, 134.0, 129.3, 128.1, 73.8, 67.5, 40.9, 40.4, 31.1, 21.4, 19.8.

*4.12.10. Synthesis of (±)-(8S,8aR)-8-hydroxy-8-(2-thyenyl)-hexahydroindolizin-3(5H)-one (**anti**)-**11d**.* According to the typical procedure indolizidinone **11d** was obtained as a diastereomeric mixture from (38/62) (***syn/anti***)-**9d** in 68% combined yield. It was purified as a yellowish oil by column chromatography (EtOAc). Data for the *anti* isomer is now reported: ^{1}H NMR ($CDCl_3$) δ (ppm) 7.40–7.37 (m, 1H), 6.93–6.90 (m, 1H), 6.87–6.83 (m, 1H), 3.85–3.80 (m, 1H), 3.39–3.23 (m, 2H), 2.23–1.43 (m, 9H); ^{13}C NMR ($CDCl_3$) δ (ppm) 174.8, 146.2, 126.6, 124.3, 123.7, 74.0, 66.1, 39.3, 39.2, 30.1, 21.0, 18.1.

4.13. Typical procedure for the dihydroxylation reaction

*4.13.1. Synthesis of (±)-(6S,7S,8R,8aR)-6,7,8-trihydroxy-hexahydroindolizidin-3-one (**syn-12**).* $K_2OsO_4\cdot 2H_2O$ (7 mg, 0.015 mmol) and *N*-methylmorpholine-*N*-oxide (70 mg, 0.6 mmol) were sequentially added to 2 mL of an acetone/water (1/1) solution of indolizidinone (***syn***)-**8** (50 mg, 0.3 mmol). The mixture was stirred at room temperature for 18 h, and then filtered through Celite. The volatiles were eliminated and the residue was column chromatographed (EtOAc) to render trihydroxyindolizidinone (***syn***)-**12** as a colorless oil (93%): ^{1}H NMR (MeOD) δ (ppm) 5.48 (d, J=3.7, 1H), 3.94–3.64 (m, 3H), 2.49–2.29 (m, 2H), 2.11–1.87 (m, 4H); ^{13}C NMR (MeOD) δ (ppm) 177.5, 74.5, 68.2, 65.0, 57.2, 35.2, 32.5, 19.6; IR υ

(cm^{-1}) 3408, 1660; HRMS calculated for $C_8H_{13}NO_4 \cdot H^+$: 188.0923, found: 188.0915.

*4.13.2. Synthesis of (±)-(6R,7S,8S,8aR)-6,7,8-trihydroxy-8-phenylhexahydroindolizidin-3-one (**anti-13a**).* According to the typical procedure, indolizidine (***anti***)-**13a** was obtained from a 0.5/1.0 diastereomeric mixture of (***syn***/***anti***)-**9a** in 57% yield. It was purified by column chromatography (EtOAc) followed by crystallization from Et_2O: mp 183–184 °C (Et_2O); ^1H NMR (MeOD) δ (ppm) 7.50–7.47 (m, 2H), 7.37–7.27 (m, 3H), 4.21–4.17 (m, 1H), 4.04–3.98 (m, 1H), 3.89–3.83 (m, 1H), 3.71 (s, 1H), 3.06–2.99 (m, 1H), 2.55–2.09 (m, 3H), 1.87–1.75 (m, 1H); ^{13}C NMR (MeOD) δ (ppm) 176.6, 142.7, 129.2, 128.5, 128.3, 78.0, 76.3, 65.4, 60.8, 40.9, 31.7, 18.6; IR (film) υ (cm^{-1}) 3408, 1658; MS (CI) *m*/*z* (%) 264 (100), 246 (33), 230 (33), 228 (61), 212 (26), 210 (17), 190 (12), 140 (17), 115 (13), 84 (11); HRMS calculated for $C_{14}H_{17}NO_4 \cdot H^+$264.1236, found 264.1244.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.03.033.

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