DOI: 10.1002/ejoc.201402720

Flexible Synthesis of Planar Chiral Azoninones and Optically Active Indolizidinones

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Dedicated to Professor Dr. Johann Mulzer on the occasion of his 70th birthday

Keywords: Nitrogen heterocycles / Allylic compounds / Sigmatropic rearrangement / Ring expansion / Medium-ring compounds / Ring contraction

The flexible synthesis of defined substituted optically active indolizidinones starting from chiral pool (*S*)-proline and *trans* 4-hydroxy-(*S*)-proline is described. Several defined 2-vinylpyrrolidines were generated in short sequences. The aza-Claisen rearrangement using chloro and phenylketene equivalents delivered nine-membered-ring lactams with up to three stereogenic centres and *pS*-arranged *E* olefins. Depending on the substitution pattern, certain azoninones had a flexible conformation and showed *pS*/*pR* double-bond flipping. Treatment of the unsaturated lactams with the soft electrophile iodine induced diastereoselective transannular ring contractions. Here, the planar chiral arrangement of the azoninone double bond predetermined the bridgehead configuration of the product indolizidinones. Thus, the (*S*)-proline starting materials could be used to gain access to either one of the two antipodal series of indolizidinone products. The indolizidinone scaffolds should serve as versatile key intermediates in the synthesis of natural products and pharmaceutically important molecules.

Introduction

The synthesis of optically active indolizidine alkaloids and their analogues delivers various biologically active and structurally challenging compounds.[1] New natural products are still isolated from natural sources, and total synthesis helps to allow their chemical and biological investigation.[2]

A long-term research program in our group focusses on flexible access to defined substituted indolizidinone scaffolds as key intermediates for the synthesis of enantiomerically pure natural products and drugs.[3] This strategy has been used successfully in several examples. Starting from vinylpyrrolidine **I**, trihydroxyindolizidinones **II** and **III** were generated as useful precursors for the synthesis of castanospermine analogues.[4] Simple enantiopure 2-vinylpyrrolidine **IV** was converted into hydroxyindolizidinone **V**, and further steps allowed the completion of a total synthesis of pumiliotoxin 251D.[5] Furthermore, ester **VI** could be converted into lactam **VII**, which served as a key intermediate in the synthesis of dendroprimines (Figure 1).[6]

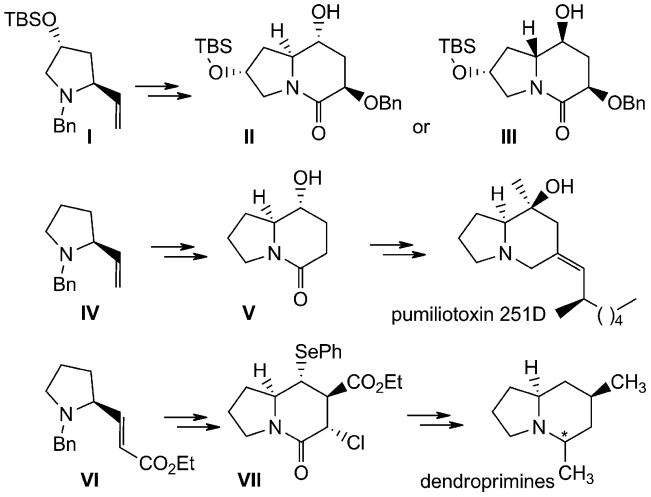

Figure 1. Syntheses using optically active indolizidinones as key intermediates; TBS = *tert*-butyldimethylsilyl.

Analysis of the reaction cascade that converts vinylpyrrolidines into indolizidinones reveals that stereochemical aspects need careful consideration. Starting from stereochemically defined 2-vinylpyrrolidine derivatives **VIII** and acid halides **IX**, a ring expansion by means of a zwitterionic aza-Claisen rearrangement gave unsaturated nine-membered ring lactams **X**, and a complete chirality transfer led

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201402720.

to a defined planar chiral arrangement of the 5,6 double bond (*pS*-**X** and *pR*-**X**). A complete 1,4 chirality transfer was found for vinylpyrrolidines **VIII** ($R^1 \neq H$, $R^2 = H$) and acid halides **IX** (X = Cl, F),[3a–3c,4] a complete 1,3 chirality transfer was observed for substrates **VIII** ($R^2 \neq H$) and acid chlorides **IX** (X = Cl),[3d,3e] and the same results were found in preliminary experiments involving less reactive acid fluorides **IX** (X = F).[3c] A smooth formation of defined stereogenic centres in the rearrangement delivered lactams **X**. Subsequent transformation of the double bond moiety allowed the planar chiral properties to be used for the diastereoselective synthesis of bicyclic systems. Running the olefin conversion as a transannular ring contraction, the configuration of the bridgehead carbon of the product indolizidinones could be chosen to be *R* or *S* (in **XI** and **XII**, respectively; Figure 2).[3–7]

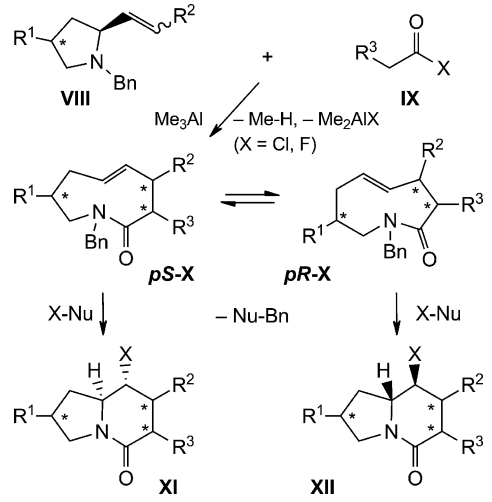


Figure 2. Concept: diastereoselective synthesis of optically active indolizidinones.

To gain deeper insight into the scope and limitations of this strategy, the interactions between the different stereochemical components (e.g., the relative configuration of R^1 and the vinyl group, and the olefin geometry in **VIII**) had to be investigated systematically. In this paper, we report the synthesis of protected *cis* and *trans* 4-hydroxy-2-vinylpyrrolidines with defined olefin geometries. Subsequent aza-Claisen rearrangements delivered the corresponding azoninones with several combinations of defined stereogenic centres and planar chiral arranged *E* olefins.[8] Next, *anti* addition across the double bond of an external soft electrophile and the intramolecular lactam nitrogen gave, after von Braun removal of the benzyl moiety, a set of target indolizidinones.[9] These indolizidinone scaffolds should serve as key intermediates for further synthetic applications.

Results and Discussion

Starting from commercially available *trans*-4-hydroxy-L-(–)-proline (**1**) and L-(–)-proline (**2**), ester formation with AcCl and MeOH,[10] and *N*-benzylation with BnCl and Et_3N gave amino esters **3** and **4a**, respectively, according to literature procedures.[5a,11] The OH group of hydroxy ester **3** could be protected as a TBS ether (to give **4b**) or as a MOM (methoxymethyl) ether (to give **4d**), as described earlier.[12] Phenyl ether **4c** was obtained in 38% yield by Buchwald coupling with PhI using catalytic amounts of CuI/1,10-phenanthroline in the presence of Cs_2CO_3.[13] The inversion of the 4-OH configuration was achieved under Mitsunobu conditions. Treatment of hydroxy ester **3** with DIAD, PPh_3, and PhOH led to 2,4-*cis* phenyl ether **5c** in 56% yield.[14] Mitsunobu inversion according a publication by Cossy using DEAD, PPh_3, and benzoic acid, and subsequent Zemplén transesterification with K_2CO_3 in MeOH delivered the *cis* 4-hydroxy proline ester derivative. A final silyl ether protection with TBSCl and imidazole gave *cis* silyl ether **5b** in 41% yield (over three steps).[15]

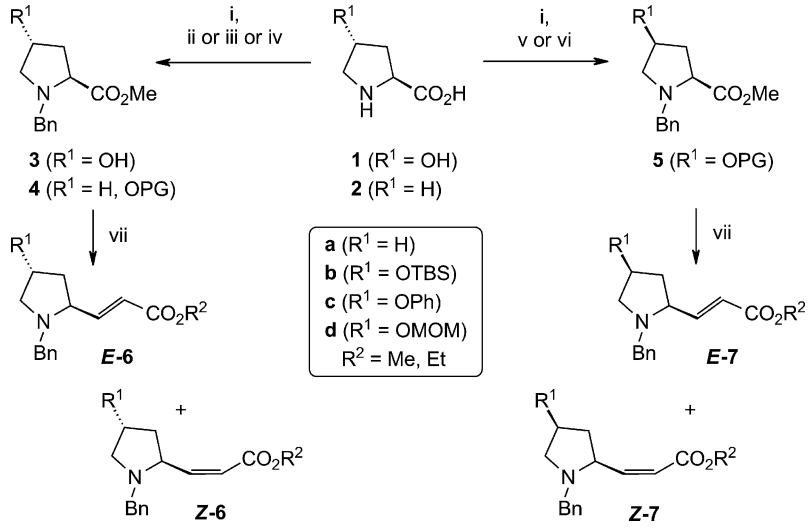
The introduction of the olefin moieties always followed a three-step sequence. After initial DIBAL-H reduction of esters **4** and **5**, and subsequent Swern oxidation,[16] the resulting aldehydes were immediately subjected to Horner olefinations to avoid any epimerisation of the 2-position under the basic reaction conditions. Typical Horner olefinations using trimethylphosphonoacetate and ethyl dimethylphosphonoacetate delivered predominantly *E* α,β-unsaturated γ-amino esters *E*-**6** and *E*-**7** in 48–87% yield (*E*/*Z* = 5–13:1).[17] *Z* isomers *Z*-**6** and *Z*-**7** were isolated as minor products. In contrast, Ando olefination using ethyldiphenylphosphonoacetate gave *Z*-**6** and *Z*-**7** *Z*/*E* ratios of 5:2 to >10:1, and yields of 48–90% (for details, see Table 1 and Scheme 1).[18]

Table 1. Results of Horner and Ando olefinations.[a]

Entry	Olefin	Method	R^1	Yield [%]	Ratio *E*/*Z*
1	*E*-**6a**	Horner	H	55	10:1
2	*Z*-**6a***	Ando	H	48	1:10
3	*E*-**6b**	Horner	OTBS	79	9:1
4	*E*-**6c**	Horner	OPh	58	5:1
5	*Z*-**6c***	Ando	OPh	54	1:10
6	*Z*-**6d***	Ando	OMOM	50	1:10
7	*E*-**7b**	Horner	OTBS	48	6:1
8	*E*-**7c**	Horner	OPh	70	13:1
9	*E*-**7c***	Horner	OPh	87	10:1
10	*Z*-**7c***	Ando	OPh	90	25:65

[a] Standard: methyl ester (R^2 = Me); * ethyl ester (R^2 = Et).

With a set of defined amino esters in hand, the zwitterionic aza-Claisen rearrangement[3–6] to induce ring expansion was investigated using chloroacetyl fluoride and phenylacetyl fluoride as the standard ketene sources.[19,20] Generally, allylamines **6** and **7** and an excess of acid fluoride were dissolved in dry dichloromethane in the presence of solid potassium carbonate, and trimethylaluminum was added at 23 °C. In most runs, the conversion was found to be complete after 12–16 h of stirring. After hydrolysis, product azoninones **8**–**21** could be isolated in 49–94% yield. Separation of the diastereomers (if necessary) was achieved by careful preparative HPLC. The temperatures at every stage of the process were kept at 23 °C or below to avoid any rotation of the olefin moiety within the ring and maintain the kinetic *pS* arrangement of azoninones *pS*-**8**–*pS*-**21**.



Scheme 1. Synthesis of 2-vinylpyrrolidines. Conditions: i) 1. AcCl, MeOH, reflux, 12 h; 2. BnCl, Et_3N, CH_2Cl_2, 23 °C, 12 h, yield **3**: 72%, **4a**: 53%; ii) TBSCl, imidazole, CH_2Cl_2, 23 °C, 12 h, **4b**: 88%; iii) PhI, CuI, 1,10-phenanthroline, K_2CO_3, solvent, 23 °C, **4c**: 38%; iv) MOMCl, EtN(*i*Pr)$_2$, CH_2Cl_2, 23 °C, 12 h, **4d**: ca. 70%; v) DIAD, PPh_3, PhOH, CH_2Cl_2, 23 °C, 12 h, **5c**: 56%; vi) 1. DEAD, PPh_3, BzOH, CH_2Cl_2, 23 °C, 12 h; 2. K_2CO_3, MeOH, 23 °C, 12 h; 3. TBSCl, imidazole, CH_2Cl_2, 23 °C, 12 h, **5b**: 41% (3 steps); vii) 1. DIBAL-H, THF, 0 °C, 12 h; 2. $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, –70 °C to 0 °C, 3 h; 3. $(MeO)_2P(O)CH_2CO_2Me$/NaH, THF, 0 °C, 12 h (Horner, procedure A); or $(PhO)_2P(O)CH_2CO_2Et$/NaH, THF, 0 °C, 12 h (Ando, procedure B), yield *E*-**6a**: 35% (*E*/*Z* = 10:1), *Z*-**6a**: 30% (ethyl ester *E*/*Z* = 1:10), *E*-**6b**: 54% (*E*/*Z* = 9:1), *E*-**6c**: 58% (*E*/*Z* = 5:1), *Z*-**6c**: 54% (*E*/*Z* = 1:10), *Z*-**6d**: ca. 40% (ethyl ester, *E*/*Z* = 1:10), *E*-**7b**: 32% (*E*/*Z* = 6:1), *E*-**7c**: 49% (*E*/*Z* = 13:1, R^2 = Me), *E*-**7c**: 87% (*E*/*Z* = 10:1, R^2 = Et), *Z*-**7c**: 90% (*E*/*Z* = 25:65), (always: three steps, for details concerning olefination see Table 1).

Furthermore, selected reactions were conducted in the absence of K_2CO_3 to avoid any base-promoted epimerisation of the α-chloro and α-phenyl substituents at the C-3 position. Details are given in Table 2 and Scheme 2.

Table 2. Results of the aza-Claisen rearrangement.

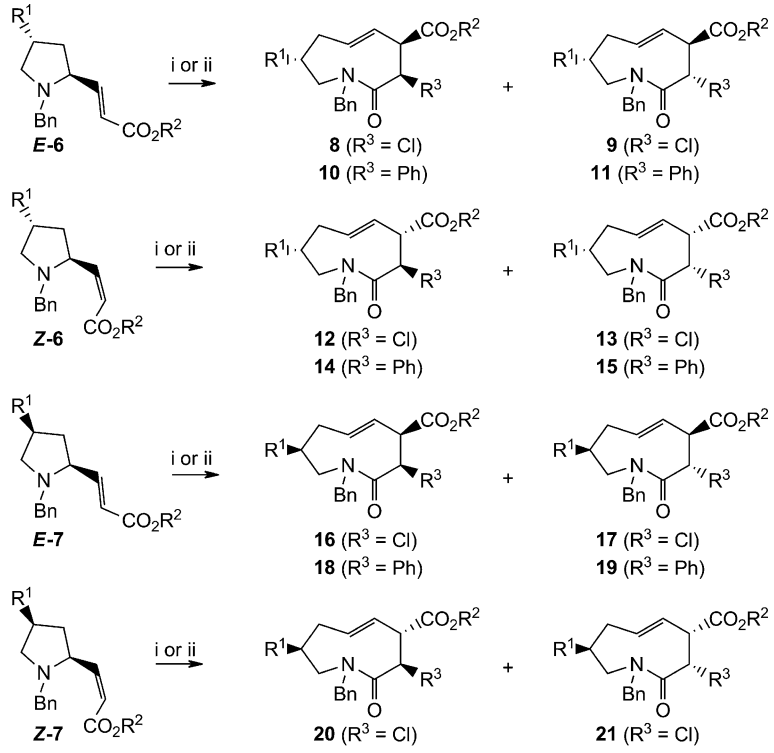
Entry	Olefin	Method	Products	R^2	Yield [%]	Ratio
1	*E*-**6a**	C	**8a/9a**	Cl	83	2:1[a]
2	*E*-**6a**	D	**8a/9a**	Cl	84	1.3:1
3*	*E*-**6a**	C	**10a/11a**	Ph	79	1:2[a]
4	*E*-**6b**	C	**8b/9b**	Cl	68	>10:1
5	*E*-**6c**	C	**8c/9c**	Cl	64	>10:1
6	*E*-**6c**	D	**10c/11c**	Ph	70	>10:1[b]
7*	*Z*-**6a**	C	**12a/13a**	Cl	77	>10:1
8*	*Z*-**6a**	D	**14a/15a**	Ph	92	>10:1[c]
9	*Z*-**6b**	C	**12b/13b**	Cl	58	>10:1
10*	*Z*-**6b**	C	**12b/13b**	Cl	69	>10:1
11*	*Z*-**6b**	C	**14b/15b**	Ph	81	>10:1[c]
12*	*Z*-**6c**	C	**12c/13c**	Cl	57	>10:1
13*	*Z*-**6c**	D	**14c/15c**	Ph	70	>10:1
14*	*Z*-**6d**	C	**12d/13d**	Cl	77	>10:1
15	*E*-**7b**	C	**16b/17b**	Cl	56	1:1.3
16	*E*-**7b**	D	**16b/17b**	Cl	94	1:6
17	*E*-**7c**	C	**16c/17c**	Cl	68	2:1
18	*E*-**7c**	D	**16c/17c**	Cl	89	1:10
19*	*E*-**7c**	C	**16c/17c**	Cl	49	1:1
20	*E*-**7c**	D	**18c/19c**	Ph	63	1:10
21*	*Z*-**7c**	C	**20c/21c**	Cl	78	68:10

[a] For details see ref.[3b] [b] 17:6 mixture of *pS* and *pR* diastereomers. [c] Mixture (potential equilibrium) of *pS* and *pR* diastereomers. Standard: methyl ester (R^2 = Me); * ethyl ester (R^2 = Et).

The first rearrangements using monosubstituted 2-vinylpyrrolidine *E*-**6a** (Table 2, entries 1–3) gave high yields (79–84%) of azoninones **8a/9a** and **10a/11a**. The reactions of *E* olefin **6a** proceeded with complete 1,3 chirality transfer, but the diastereoselectivity at the C-3 position was low (2:1 to 1:2), irrespective of whether any base was present, indicating an unselective reaction. It is unlikely that significant C-3 epimerisation of azoninones **8a/9a** and **10a/11a** occurred.[21] In contrast, the ring expansion of *cis* 2-vinylpyrrolidine *Z*-**6a** (Table 2, entries 7 and 8) succeeded, with complete 1,3 chirality transfer and high diastereoselectivity, to give *trans* azoninones **12a** and **14a** in 77 and 92% yield, respectively. None of the 3,4-*cis* lactams (i.e., **13a** and **15a**) were found.

For all of the 4-substituted vinylpyrrolidines (i.e., *E*/*Z*-**6b**–**6d** and *E*/*Z*-**7b**–**7c**), the C-4 configuration and the olefin geometry had a crucial influence on the diastereoselectivity of the aza-Claisen rearrangement.

Starting from 2,4-*trans*-configured allylamines *E*- and *Z*-**6** (with an α-C-4 substituent), all the reactions proceeded with complete 1,3 chirality transfer and a high diastereoselectivity to give the C-3 chloride and phenyl groups in the β position (β:α, >10:1). Azoninones **8b**, **8c**, **10b**, **12b**–**12d**, and **14b**–**14c** were isolated in 57–92% yield, and none of the 3α-chloride (i.e., **9** and **13**) or 3α-phenyl (i.e., **11** and **15**) configured diastereomers could be detected (Table 2, entries 4–6, 9–14). Some of the phenyl-derived compounds underwent partial facile flipping of the double bond to give mixtures of planar chiral diastereomers (Table 2, entries 6, 8, and 11; *pS*/*pR*-**10c**, *pS*/*pR*-**14b**, and *pS*/*pR*-**14c**). Initial rearrangements starting from 2,4-*cis* amino esters *E*-**7** (β-C-4 substituent) in the presence of K_2CO_3 delivered mixtures of diastereomers **16/17** (Table 2, entries 15, 17, and 19). Although complete 1,3 chirality transfer occurred, the diastereoselectivity **16/17** was low (β:α, 1:1–2:1), and the



Scheme 2. Aza-Claisen rearrangement to synthesise azoninones. Conditions: i[a]) (procedure C) $ClCH_2C(O)F$, Me_3Al, K_2CO_3, CH_2Cl_2, 23 °C, 12 h, yield **8a/9a**: 83% (2:1), **8b/9b**: 68% (>10:1), **8c/9c**: 64% (>10:1), **12a/13a**: 77% (>10:1), **12b/13b**: 58% (>10:1), **12b/13b**: 69% (>10:1, R^2 = Et), **12c/13c**: 57% (>10:1), **12d/13d**: 77% (>10:1), **16b/17b**: 56% (1:1.3), **16c/17c**: 68% (2:1, R^2 = Me), 49% (1:1, R^2 = Et), **20c/21c**: 78% (7:1); i[b]) (procedure C) $PhCH_2C(O)F$, Me_3Al, K_2CO_3, CH_2Cl_2, 23 °C, 12 h, yield **10a/11a**: 79% (2:1), **14b/15b**: 81% (>10:1); ii[a]) (procedure D) $ClCH_2C(O)F$, Me_3Al, CH_2Cl_2, 23 °C, 12 h, **8a/9a**: 84% (1.3:1), **16b/17b**: 94% (1:6), **16c/17c**: 89% (1:10); ii[b]) (procedure D) $PhCH_2C(O)F$, Me_3Al, CH_2Cl_2, 23 °C, 12 h, **10c/11c**: 70% (>10:1), mixture *pS*/*pR* 17:6, **14a/15a**: 92% (>10:1), **14c/15c**: 70% (1:>10), **18c/19c**: 63% (1:>10), see Table 2.

yields varied from 49 to 68%. When the ring-expansion reactions were run without K_2CO_3, the outcome changed (Table 2, entries 16, 18, and 20). The formation of 3α-chlorides **17** and 3α-phenyl derivative **19** predominated. Lactam **17b** was isolated in 94% yield with a *dr* of 6:1, lactam **17c** was obtained in 89% yield with a *dr* of >10:1, and lactam **19c** was formed in 63% yield with a *dr* of >10:1. A first rearrangement of 2,4-*cis* amino ester *Z*-**7c** (β-C-4 substituent) preferentially delivered 3β-chloride **20c** with a combined yield of **20c** and **21c** of 78%, and a *dr* of nearly 7:1 (Table 2, entry 21).

The structural determination of all the azononinones was achieved unequivocally by ^1H and ^{13}C NMR spectroscopic analysis. NOESY spectra gave decisive information about the relative configuration of the lactams. Most of the products (i.e., *pS*-**8**, *pS*-**10**, and *pS*-**16**) adopted a preferred conformation **A** (Figure 5) in which the lactam oxygen and the benzyl group were arranged *anti* with respect to the C-5 olefin proton. A second minor conformation **B** (Figure 5) was detected in the ^1H NMR spectra of *pS*-**8b** (ratio 1:2) and *pS*-**8c** (ratio 1:4) in which the lactam oxygen and the benzyl group were arranged *syn* with respect to the C-5 olefin proton. In contrast, a high preference for conformation **B** was found for lactams *pS*-**12**, *pS*-**14**, and *pS*-**20**.[22] X-ray analysis of lactam *pS*-**8b** supported the findings of the NMR spectra (Figure 3).[23] Lactams *pS*-**9a**, *pS*-**17**, and *pS*-**19** adopted a single conformation **A** in which all the substituents were arranged in quasi-equatorial positions. Additionally, *pS*-**21c** adopted a conformation **A** with a quasi-axial positioned ester group. For detailed information, see Figure 6 and NOE data.[22]

The stability of the *pS* arrangement of the double bond in the presence of the defined stereogenic centres was crucial for the planned diastereoselective transannular ring contractions.[3,4] With this in mind, selected azoninones *pS*-**8**–*pS*-**21** directly obtained from the rearrangement were heated to 40–65 °C, and the potential transformation from *pS* into *pR* arranged compounds was investigated using TLC and HPLC analysis as well as NMR spectroscopy. Heating 3,4-*trans* azoninone *pS*-**9a** gave no new conformer, even after prolonged heating to 65 °C, indicating a thermodynamic stability (Table 3, entry 3). In contrast, 3,4-*trans* azoninones *pS*-**12a** and *pS*-**14a** underwent a nearly complete double-bond flip to give *pR*-**12a** and *pR*-**14a** as more stable planar chiral diastereomers (Table 3, entries 5–10). Furthermore, all the 4β/8α-configured *pS* azoninones (i.e.,

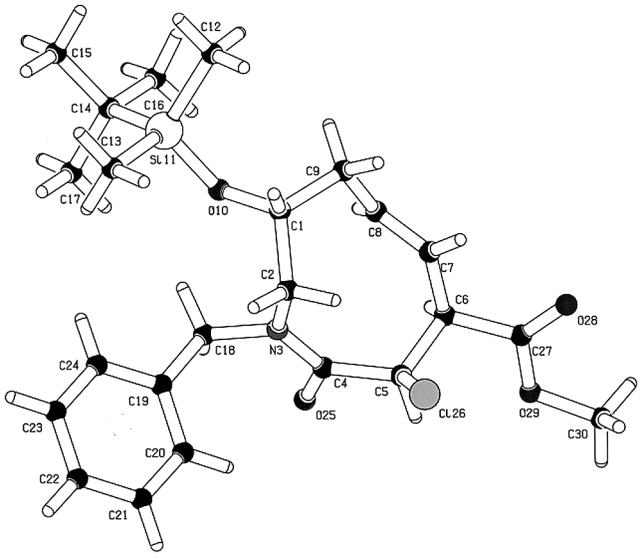


Figure 3. X-ray analysis of lactam *pS*-**8b** (lactam oxygen and benzyl group *anti* with respect to the C-5 olefin proton).

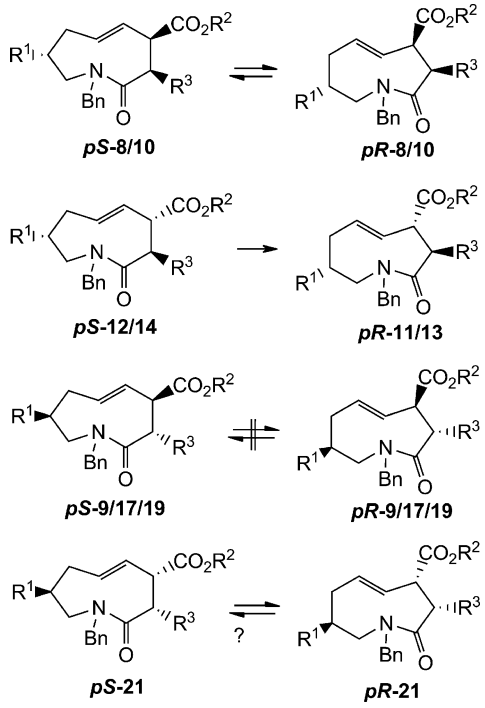
pS-**8** and *pS*-**10**) underwent at least a partial double-bond rotation from *pS* to *pR* with respect to the ring (Table 3, entries 1, 2, and 4). The heating of *pS*-**8b** to 65 °C for 12 h led to the formation of a 1.5:1 mixture of *pS*-**8b** and *pR*-**8b**, and this ratio remained the same even after prolonged heating (Table 3, entry 1). These diastereomers (i.e., *pS*-**8b** and *pR*-**8b**) were separated by preparative HPLC. Heating *pS*-**8c** to 65 °C for 12 h led to the formation of a 2:1 mixture of *pS*-**8c** and *pR*-**8c**, which could be separated by preparative HPLC (Table 3, entry 2). 3-Phenyllactam **10c** underwent *pS*/*pR* isomerisation at room temperature. Even though the diastereomers could be separated by preparative HPLC, a nearly 3:1 mixture of *pS*/*pR*-**10c** always regenerated from either isomer upon standing. Structural elucidation was achieved by analysing the spectra of the mixture (Table 3, entry 4).

Table 3. *pS*/*pR* epimerisation of selected azoninones.

Entry	Reactant	R^3	Product	Ratio *pS*/*pR*	Time
1	*pS*-**8b**	Cl	*pR*-**8b**	1.5:1	12 h to 5 d
2	*pS*-**8c**	Cl	*pR*-**8c**	2:1	12 h
3	*pS*-**9a**	Cl	*pR*-**9a**	>10:1	12 h
4	*pS*-**10c**	Ph	*pR*-**10c**	3:1	12 h[a]
5*	*pS*-**12a**	Cl	*pR*-**12a**	1:>10	24 h
6	*pS*-**12b**	Cl	*pR*-**12b**	1:3	12 h
7*	*pS*-**12b**	Cl	*pR*-**12b**	1:<5	12 h[c]
8*	*pS*-**12d**	Cl	*pR*-**12d**	1:>10	6 h
9*	*pS*-**14a**	Ph	*pR*-**14a**	1:>10	6 h[a]
10*	*pS*-**14b**	Ph	*pR*-**14b**	1:>10	6 h[a]
11	*pS*-**17b**	Cl	*pR*-**17b**	>10:1	12 h
12	*pS*-**17c**	Cl	*pR*-**17c**	>10:1	12 h
13*	*pS*-**19c**	Ph	*pR*-**19c**	5:1	12 h[b]
14*	*pS*-**21c**	Cl	*pR*-**21c**	1:1.6	12 h

[a] Rapid induction of epimerisation at 20 °C. [b] Inseparable mixture. [c] With some decomposition. Standard: methyl ester (R^2 = Me); * ethyl ester (R^2 = Et).

Heating 4α/8α-configured lactams *pS*-**12** and *pS*-**14** resulted in almost complete flipping of the double bond to give the *pR* diastereomers as stable products. After 12 h of heating, *pS*-**12b** gave a 1:3 mixture of *pS*-**12b** and *pR*-**12b**, which could be separated by preparative HPLC (Table 3, entry 6). Prolonged heating resulted in complete flipping of the double bond. Heating of azoninone *pS*-**12d** for a short time resulted in a nearly complete isomerisation to give *pR*-**12d** (Table 3, entry 8). Finally, 3-phenyllactam *pS*-**14b** underwent a complete double-bond flip from *pS* to *pR* within 6 h (Table 3, entry 10). In contrast, 4β/8β lactams *pS*-**17b/c** and *pS*-**19c** showed no significant isomerisation, indicating the thermodynamic stability of the starting planar diastereomer (Table 3, entries 11–13).[24] Lactam *pS*-**21c** underwent partial *pS*/*pR* flipping upon heating. After 12 h, a ratio of 1:1.6 of the two compounds was found (Table 3, entry 14). Separation was achieved by preparative HPLC. The structures of all the *pR* azoninones were determined by ^{1}H and ^{13}C NMR spectroscopy and NOESY analysis. For detailed information, see Table 3 and Scheme 3.[22]



Scheme 3. Epimerisation of selected azoninones. Conditions: $CHCl_3$, 65 °C, 12 h, quantitative yield, see Table 3.

To investigate transannular ring contractions, iodocyclisation was chosen. According to literature procedures,[3–7] azoninones **8**–**20** were treated portionwise with iodine in CH_2Cl_2 at 23 °C until the colour of unreacted iodine remained. After destruction of the excess iodine and removal of the benzyl iodide by-product, indolizidinones **22**–**32** (along with **33** and **34**) were isolated in 40–93% yield. The products were subjected to careful NMR spectroscopic analysis to determine the relative configurations of the new stereogenic centres.[22] Consistently with the literature, *pS* lactams **8**–**20** gave the corresponding indolizidinones with

α bridgehead C–H and α C–I configurations, indicating highly regioselective and diastereoselective conversions (Table 4, entries 1, 2, 4, 6, 9, and 12–21, Schemes 4 and 5). The relative and absolute configurations of iodolactams **22b** were unambiguously proved by X-ray analysis (Figure 4).[25]

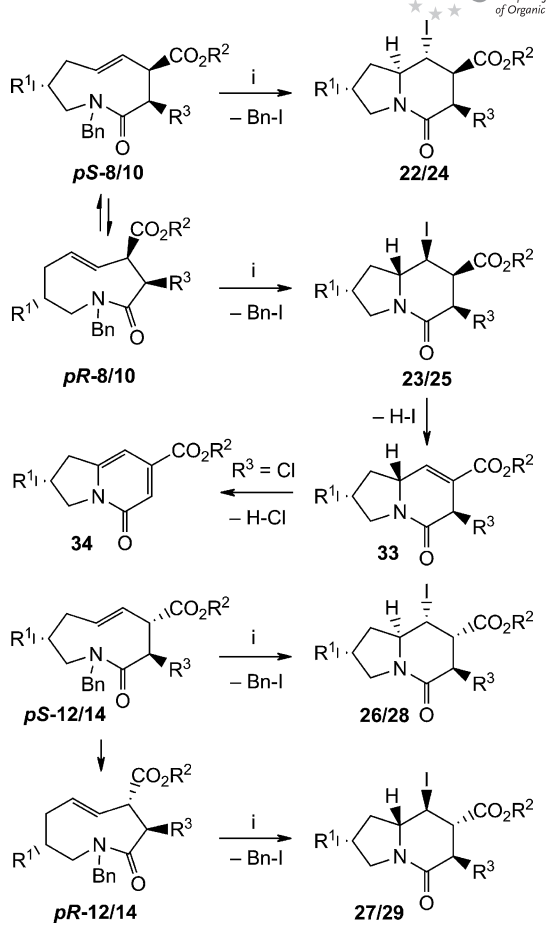
Table 4. Iodocyclisation of selected *pS*/*pR* azoninones to form indolizidinones.[a]

Entry	Reactant	Product	R^3	Yield [%]	Ratio
1	*pS*-**8a**	**22a**	Cl	60	>20:1
2	*pS*-**8b**	**22b**	Cl	68	>20:1
3	*pR*-**8b**	**22b/33b**	Cl	93	42:51
4	*pS*-**8c**	**22c**	Cl	52	>20:1
5	*pS*/*pR*-**8c** (2:1)	**22c/34**	Cl	51	37:14
6	*pS*-**9a**	**30a**	Cl	51	>20:1
7	*pS*/*pR*-**10c** (3:1)	**24/25c**	Ph	75	67:8
8	*pR*-**10c**	**24/25c**	Ph	71	38:33
9	*pS*-**12b**	**26b**	Cl	83	>20:1
10	*pS*/*pR*-**12b** (1:3)	**26b/27b**	Cl	67	15:52
11	*pR*-**12b**	**27b**	Cl	65	>20:1
12*	*pS*-**12c**	**26c**	Cl	65	>20:1
13*	*pS*-**14c**	**28c**	Ph	54	>20:1
14	*pS*-**16b**	**29b**	Cl	40	>20:1
15	*pS*-**16c**	**29c**	Cl	68	>20:1
16*	*pS*-**16c**	**29c**	Cl	62	>20:1
17	*pS*-**17b**	**30b**	Cl	68	>20:1
18	*pS*-**17c**	**30c**	Cl	49	>20:1
19*	*pS*-**17c**	**30c**	Cl	65	>20:1
20	*pS*-**19c**	**31c**	Ph	73	>20:1
21*	*pS*-**20c**	**32c**	Cl	62	>20:1

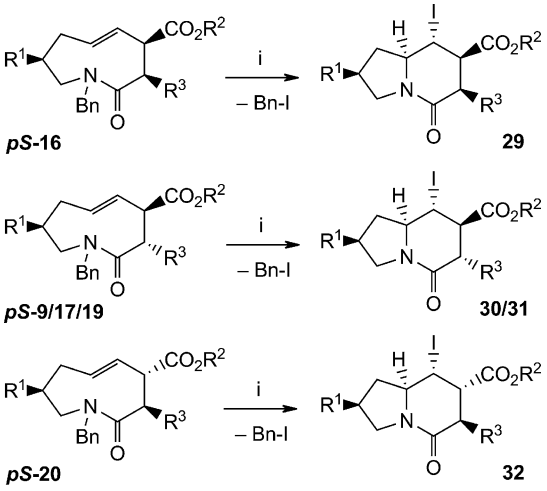
[a] Standard: methyl ester (R^2 = Me); * ethyl ester (R^2 = Et).

Surprisingly, the iodocyclisations starting from selected *pR* azoninones gave a somewhat different outcome (Table 4, entries 3, 5, 7, 8, 10, and 11). The reaction of azoninone *pR*-**8b** gave a 42:51 mixture of indolizidinones **22b** and **33b** in 93% yield (Table 4, entry 3). No lactam **25b** was detected, indicating that after its formation, it must have undergone rapid dehydroiodination to form the unsaturated ester moiety in **33b**. In contrast, 3-phenyllactam *pR*-**10c** delivered iodoindolizidinones **24c** and **25c** in 71% yield with a ratio of 38:33, and no HI elimination could be detected (Table 4, entry 8). Furthermore, transannular ring contractions starting from mixtures of *pS*/*pR*-**8c** (2:1) and *pS*/*pR*-**10c** (3:1) resulted in the formation of bicycles **22c**/**34** (51% yield, 37:14 ratio, complete dehydrohalogenation in **34**) and **24c**/**25c** (75% yield, 67:8 ratio), respectively (Table 4, entries 5 and 7). Despite the lower percentage of the *pS* lactam in the reactant mixtures, the proportion of the corresponding bicycles **22c**/**24c** in the product mixtures from the ring contraction were found to increase. Obviously, *pS*/*pR* flipping of the double bond and iodocyclisation could be assumed to be competing processes under the reaction conditions, and this could explain the formation of the observed diastereomeric mixture of indolizidinones (Scheme 4).

In contrast, ring contraction of a 1:3 mixture of azoninones *pS*/*pR*-**12b** delivered a 52:15 mixture of bicycles **27b** and **26b** in 67% yield, and no accompanying dehydroiodination could be observed (Table 4, entry 10). However, pure azoninone *pR*-**12b** underwent transannular ring contraction



Scheme 4. Transannular ring contraction to synthesise indolizidinones. Conditions: i) I_2, CH_2Cl_2, 23 °C, yield **22a**: 60%, **22b**: 68%, **22b/33b**: 93% (42:51), **22c**: 52%, **22c/34**: 51% (37:14 from *pS*/*pR*-**8c** 2:1), **24c/25c**: 75% (67:8), **24c/25c**: 71% (38:33 from *pR*-**10c**), **26b**: 83%, **26b/27b**: 67% (15:52 from *pS*/*pR*-**12b**, 1:3), **26c**: 65%, **27b**: 65%, **28c**: 54% see Table 4.



Scheme 5. Transannular ring contraction to synthesise indolizidinones. Conditions: i) I_2, CH_2Cl_2, 23 °C, yield: **29b**: 40%, **29c**: 68%, 62% (R^2 = Et), **30a**: 51%, **30b**: 68%, **30c**: 49%, 65% (R^2 = Et), **31c**: 73%, **32c**: 62% see Table 4.

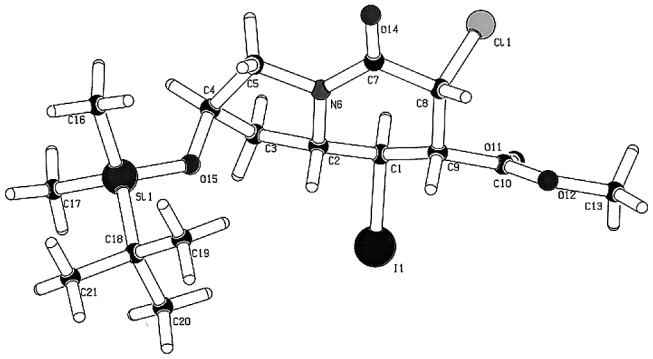


Figure 4. X-ray analysis of indolizidinone **22b**.

to give indolizidinone **27b** diastereoselectively in 65% yield (Table 4, entry 11). The *pS*/*pR* arrangements of the azoninone double bonds in the *pS*/*pR*-**12b** lactams were stable under the iodolactamization reaction conditions. Consequently, the ratio of the *pS*/*pR*-**12b** mixture was retained in the ratio of indolizidinone products **26b** and **27b** (Table 4, entry 10), and neat *pR*-**12b** was converted into indolizidinone **27b**. For detailed information, see Table 4 and Scheme 4.

Mechanistic Conclusions

The reaction mechanism and stereochemical outcome of the substrate-controlled zwitterionic aza-Claisen rearrangement have been rationalised (Figures 5 and 6). Initially, chloroacetyl fluoride or phenylacetyl fluoride and trimethylaluminium formed a Lewis-acid-activated ketene **35**.[26] The evolution of methane was always observed. Then, ketene **35** added to the nitrogen of *N*-benzylpyrrolidines **6** and **7**, respectively, to generate intermediate acylammonium enolates with complete selectivity for the *Z* enolate geometry.[27] All of the rearrangements were characterised by complete 1,3 chirality transfer to generate an *E* olefin in a *pS* arrangement.

Analysing the transformations of *E* alkenes *E*-**6** and *E*-**7**, the configuration of the R^1-substituted carbon (C-4) directed the diastereoselectivity of the acylation. The C-4-α-configured *E*-**6** delivered the 1,2-*syn* ketene adduct, which then rearranged via a boat-like conformation with minimised 1,3 repulsive interactions to form azoninones **8** and **10**, with β-configured C–Cl and C–Ph groups, respectively.[3a,4] In contrast, the 1,2-*anti* acylammonium enolate derived from C-4-β-configured *E*-**7** went via a favoured chair-like conformation to give lactams **17** and **19** with α-configured C–Cl and C–Ph groups.[3d] Simple *E*-configured 2-vinylpyrrolidine *E*-**6a** underwent a nearly equal ketene addition from either side to give both 1,2-*syn* and 1,2-*anti* zwitterions.[5a] Consequently, both pathways were active, and a product mixture of *pS*-**8a**/**10a** and *pS*-**9a**/**11a** was formed (Figure 5). The NMR spectra of lactams *pS*-**8**/**10** revealed that most of these products showed an equilibrium of at least two interconverting conformations **A** and **B**, indicating a non-ideal arrangement of the stereogenic centres

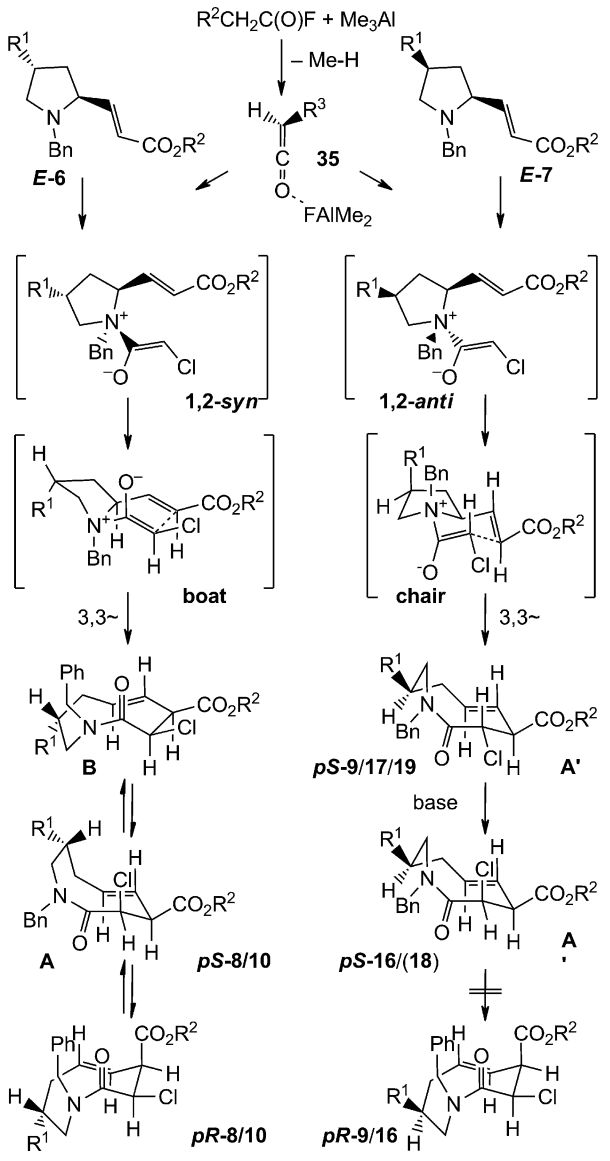


Figure 5. Mechanistic conclusions on the aza-Claisen rearrangement starting from *E* olefins *E*-**6** and *E*-**7**.

and the *pS*-*E*-olefin moiety, with repulsive interactions.[28] Furthermore, heating to about 60 °C for 12 h in an inert solvent induced a partial reversible flipping of the double bond to form *pR*-*E* diastereomers *pR*-**8**/**10**.[29] In contrast, the NMR spectra of lactams *pS*-**17**/**19** showed a single lactam conformation **A′** with a *pS* arrangement of the double bond, and further heating to 60 °C caused no *pS*-into-*pR* flipping of the olefin moiety.[24] Surprisingly, lactams *pS*-**17b** and *pS*-**17c** were sensitive to basic conditions. Obviously, if the C-3 C–Cl bond of lactams *pS*-**17** suffered from some epimerisation in the presence of potassium carbonate, the resulting *pS*-**16** diastereomers might be characterised by a decreased 3,4-*gauche* repulsive interaction within the nine-membered ring. When the rearrangement was run in the absence of potassium carbonate, the initially formed α-chlorides (i.e., *pS*-**17**) and α-phenyl derivative (i.e., *pS*-**19**) remained almost unchanged (Figure 5).

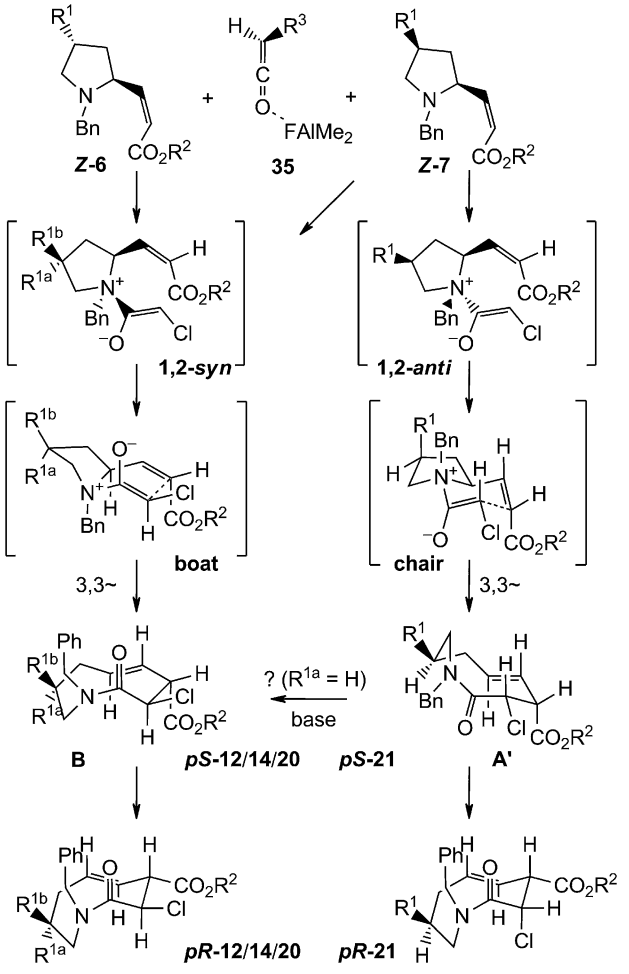


Figure 6. Mechanistic conclusions on the aza-Claisen rearrangement starting from *Z* olefins *Z*-**6** and *Z*-**7**.

In the transformations of *Z* alkenes *Z*-**6** and *Z*-**7**, the olefin geometry was more important for the diastereoselectivity of the ring enlargement. In contrast to the corresponding *E* series, the reaction of amino ester *Z*-**6a** delivered lactam *pS*-**12a** diastereoselectively. Obviously, the minimisation of the 1,3-allylic strain caused an efficient shielding of the α face of the pyrrolidine ring by the *Z*-configured double bond.[28] So amine acylation delivered the 1,2-*syn* adduct to give lactams *pS*-**12a/14a** ($R^{1a/b}$ = H, R^2 = CO_2Et). In addition, 2,4-*trans* disubstituted vinylpyrrolidines **6** ($R^{1a} \neq H$, R^{1b} = H) with matched stereodirecting substituents (α-R^1 and *Z* olefin) also underwent 1,2-*syn* ketene addition. Rearrangement via the boat-like transition state resulted in the generation of lactams *pS*-**12/14** with β-configured C–Cl and C–Ph groups. In most cases, the NMR spectra of these products showed an equilibrium of at least two interconverting conformations. The predominant form **B** indicated a non-ideal arrangement of stereogenic centres and the *pS*-*E* olefin moiety, with repulsive interactions/allylic strain.[29] Consequently, heating to about 30–40 °C (C–Ph) or 60 °C (C–Cl) induced flipping of the double bond to form the *pR*-*E* diastereomers, with significant relaxation of the steric repulsions in thermodynamically stable conformation **A**.[30] Ring enlargement of 2,4-*cis* disubstituted vinylpyrrolidines *Z*-**7c** (R^{1b} = OPh) should suffer from mismatched stereodirecting substituents (β-R^1 vs. *Z* olefin). A plausible mechanism to account for the preferred formation of lactam *pS*-**20c** involves 1,2-*syn* addition directed by the *Z* olefin, and subsequent rearrangement via a boat-shaped transition state to form conformer **B**. However, β-R^1-directed 1,2-*anti* addition, a subsequent rearrangement via a chair-shaped transition state to form conformer **A′**, and an efficient C-3 C–Cl epimerisation to form conformer **B** cannot be excluded (Figure 6).

In contrast to earlier experiments that generated 3,8-disubstituted azoninones, kinetically obtained 3,4,8-trisubstituted *pS* lactams *pS*-**8–21** are not characterised by a general instability with respect to the planar chiral arrangement of the double bond moiety.[3a,4] In fact, the entire substitution pattern had to be considered. In summary, kinetically obtained lactams *pS*-**9/16/17** remained stable, lactams *pS*-**8/10** were characterised by a reversible partial flipping *pS*↔*pR*, and lactams *pS*-**12/14/21** underwent complete *pS*→*pR* transformation.[31]

When azoninones **8**–**20** were subjectd to iodocyclisation, indolizidinones **22**–**34** were generated with selective *anti* additions to the planar chiral olefin moiety. Starting from *pS* azoninones, the iodine attacked the unshielded *Re* face of the double bond to form an intermediate iodonium ion. After transannular ring closure by the nitrogen lone pair of the amide functionality, the so-formed intermediate acylammonium salt underwent immediate degradation. Finally, benzyl iodide was removed in an S_N2 reaction to give lactams **22**, **24**, **26**, and **28**–**32**, respectively, with an α-configured bridgehead proton and an adjacent C–I bond. All other stereogenic centres remained untouched (Figure 7).

In contrast, *pR* lactam *pR*-**12b** suffered *Si* face attack by the iodine. Transannular ring contraction and S_N2 removal of benzyl iodide gave lactam **27b**, with a β-configured bridgehead proton and an adjacent C–I bond. When a mixture of *pR*-**12b**/*pS*-**12b** (ratio 52:15) was subjected to the ring-contraction conditions, a mixture of indolizidinones **27b/26b** (ratio 52:15) was obtained with complete transfer of planar chirality to central chirality.

Surprisingly, the conversion of pure azoninone *pR*-**8b** led to a mixture of indolizidinones **22b/33b** (via intermediate **23b**) (ratio 1.2:1), and *pR*-**10c** gave a mixture of indolizidinones **24c/25c** (ratio 2.3:2). Furthermore, mixtures of *pS*/*pR*-**8c** (2:1) and *pS*/*pR*-**10c** (3:1) resulted in indolizidinone mixtures **22c/34** (via intermediate **23c**) and **24c/25c**, respectively, showing an increased proportion of the *pS*-derived bicycles with an α-configured bridgehead proton. Such an outcome could be rationalised by assuming comparable (slower) rates of *pS*↔*pR* flipping of the olefin moiety and of the transannular ring contraction of the *pR* diastereomer under the reaction conditions, and a faster transannular ring closure of the *pS* azoninone. Consequently, ring contraction of lactam *pS*-**8b** led to indolizidinone **22b** diastereoselectively, the conversion of lactam *pR*-**8b** gave a mixture of indolizidinones **22b** and **23b**. Furthermore, the *anti* relationship of the iodide and the C-4 proton in lact-

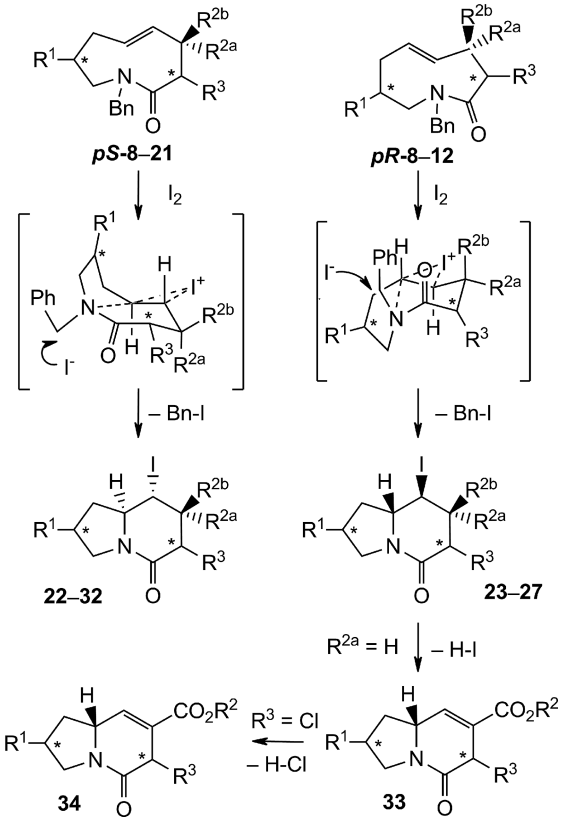


Figure 7. Mechanistic conclusions on the transannular ring contraction by iodocyclisation.

ams **23b** and **23c** allowed a facile (partial) dehydrohalogenation to generate unsaturated lactams **33b** (via indolizidinone **23b** as an intermediate) and **34** (via indolizidinones **23c** and **33c** as intermediates).

In summary, the activation energy for the *pS*↔*pR* flipping of the olefin moiety in most azoninones proved to be much higher than that for the transannular ring contraction. The planar chiral olefin moiety could be used to generate indolizidinones with complete chirality transfer. In contrast, the *pR*-**8**/**10** series was characterised by a low *pS*↔*pR* flipping activation barrier at room temperature that enabled both competing double bond rotation and iodocyclisation under the conditions used. Consequently, a mixture of diastereomers was generated (Figure 7).

Conclusions

A set of 2-vinylpyrrolidines with defined substitution patterns and with defined configurations of stereogenic centres and double bonds has been synthesised starting from *S*-proline and 4-*trans*-hydroxy-*S*-proline. Zwitterionic aza-Claisen rearrangements allowed the conversion of the unsaturated amino esters into azoninones with complete 1,3 chirality transfer and the formation of a *pS* arranged olefin moiety. The simple diastereoselectivity directing the configuration of the C–Cl or C–Ph bond (C-3) depended on the substitution pattern of the allylamine starting materials: *Z*-2-vinylpyrrolidines and 2,4-*trans*-disubstituted 2-vinylpyrrolidines *E*/*Z*-**6** and *Z*-**7** gave β-C–Cl- and β-C–Ph-configured azoninones **8**–**14** stereoselectively. Upon heating, the *pS* arranged olefin in azoninones **8** and **10** underwent partial flipping to generate the *pR* form, and azoninones **12**/**14** underwent complete *pS*-to-*pR* isomerisation. In contrast, the rearrangements starting from 2,4-*trans* disubstituted 2-vinylpyrrolidines *E*-**7** gave α-C–Cl- and α-C–Ph-configured azoninones **17** and **19** with high selectivity. Epimerisation of the C–Cl functionality could be induced under basic conditions. Even upon heating, azoninones *pS*-**16**, **17**, and **19** had a stable *pS* olefin arrangement. As an exception, the reaction of monosubstituted *E*-2-vinylpyrrolidine **6a** delivered azoninones **8a** and **9a** with low diastereoselectivity. Finally, indolizidinones **22**–**34** were synthesised by subjecting the azoninones to transannular iodocyclisation. Generally, the *anti*-additions meant that the planar chiral information of the double bond generated α-configured C–H bridgehead groups from *pS* reactants and β-C–H groups from *pR* azoninones, respectively. Azoninones *pR*-**8b/c** and *pR*-**10c** delivered a mixture of both indolizidinone series **22**/**23** (**33**/**34**) and **24**/**25**, indicating that the ring contraction and *pR*/*pS* olefin flipping have similar activation barriers.

Overall, the two-step generation of indolizidinones bearing up to five stereogenic centres from simple 2-vinylpyrrolidines (one or two stereogenic centres) is a major advantage of this sequence. In addition, the generation of the two indolizidinone series with each of the two bridgehead configurations starting from the same chiral pool starting material (i.e., *S*-proline) recommends the strategy for further applications in the total synthesis of natural products and drug molecules.

Experimental Section

General Remarks: When necessary, reaction solvents were dried following standard procedures before use. All reactions involving moisture- or air-sensitive reagents were carried out under an argon atmosphere. ^{1}H , ^{13}C, and 2D (COSY, HSQC, HMBC, NOESY) NMR spectra were recorded at room temperature with Bruker AM 300, ARX400, AV400, AC 250, AM 270, and AMX 500 spectrometers in $CDCl_3$ using the signal of residual $CHCl_3$ as internal standard. IR spectra were recorded with a Jasco FTIR 400 plus spectrometer, a Perkin–Elmer IR 257 or IR 580B spectrometer, or a Nicolet 5SXC, 55C or AVATAR 320 FTIR spectrometer. High-resolution mass spectra (HRMS) were recorded with a Waters Q-Tof Ultima 3 Micromass spectrometer, or a Varian-MAT MAT 711 or MAT 112S instrument. Optical rotations were recorded with a Perkin–Elmer P241 polarimeter, or a IBZ Messtechnik Polar-LμP polarimeter. Column chromatography was carried out on MN silica gel 60*M* from Macherey–Nagel (grain size: 0.040–0.063 mm). The progress of reactions was monitored by thin-layer chromatography (TLC) on aluminum sheets pre-coated with 60F254 silica gel from Merck. PE = petroleum ether, Hept = heptane, Hex = hexane, t_R = HPLC peak retention time.

2*S*,4*R*-(*N*-Benzyl)-4-phenoxyproline Methyl Ester (4c): Iodobenzene (0.19 mL, 1.70 mmol), CuI (20.0 mg, 0.09 mmol), Cs_2CO_3 (0.55 g, 1.70 mmol), and 1,10-phenanthroline (31.0 mg, 0.17 mmol) were

added to a solution of *N*-benzyl-*trans*-4-hydroxy-(*S*)-proline methyl ester (**3**; 0.20 g, 0.85 mmol) in dry toluene (5 mL). The mixture was heated at 125 °C for 24 h, then it was cooled to room temperature. The mixture was filtered through silica gel, which was then washed with EtOAc (20 mL). The filtrate was concentrated, and the resulting residue was purified by flash chromatography (PE/EtOAc, 6:1) to give phenyl ether **4c** (38%) as a colourless oil. R_f = 0.17 (PE/EtOAc, 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30–2.44 (m, 2 H, 3-H), 2.66 (dd, ^2J = 10.5, ^3J = 4.0 Hz, 1 H, 5a-H), 3.52 (dd, ^2J = 10.5, ^3J = 6.1 Hz, 1 H, 5b-H), 3.62 (t, ^3J = 7.9 Hz, 1 H, 2-H), 3.63 (d, ^2J = 12.8 Hz, 1 H, 8a-H), 3.68 (s, 3 H, 7-H), 3.95 (d, ^2J = 12.9 Hz, 1 H, 8b-H), 4.88 (ddd, ^3J = 10.2, ^3J = 6.9, ^3J = 3.7 Hz, 1 H, 4-H), 6.81 (dd, ^3J = 8.7, ^4J = 0.9 Hz, 2 H, 14-H), 6.93 (t, ^3J = 7.4 Hz, 1 H, 16-H), 7.24–7.35 (m, 7 H, 10-H, 11-H, 12-H, 15-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 36.9 (C-3), 51.9 (C-7), 58.6 (C-8), 58.9 (C-5), 64.2 (C-2), 75.0 (C-4), 115.2 (C-14), 120.9 (C-16), 127.3 (C-12), 128.3 (C-10), 129.1 (C-11), 129.5 (C-15), 137.8 (C-9), 157.3 (C-13), 173.6 (C-6) ppm. IR: $\tilde{\nu}$ = 3027, 2947, 1737, 1599, 1495, 1455, 1374, 1241, 1173, 1087, 913, 750, 692, 667 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{22}NO_3$ $[M]^+$ 312.1600; found 312.1595. $[a]_D$ = –58 (*c* = 1.00, CH_2Cl_2).

Standard Procedure A for Horner Olefination: Trimethylphosphonoacetate (11 mmol) in dry CH_2Cl_2 (5 mL) was slowly added to a suspension of NaH (60% dispersion in mineral oil; 11 mmol) in dry THF (50 mL) at 0 °C with stirring. After 1 h, a freshly prepared solution of the aldehyde (5 mmol) in dry THF (10 mL) was added. The reaction mixture was stirred for 12 h, during which time it was allowed to warm up to room temperature. The reaction was then stopped by the addition of water (70 mL), and the mixture was extracted with diethyl ether (3×). The combined organic phases were washed with brine (2×), dried ($MgSO_4$), and concentrated under vacuum. The crude unsaturated ester was purified by flash chromatography.

2*S*,4*R*-(*N*-Benzyl)-2-(*E*-methoxycarbonyl-ethenyl)-4-phenoxypyrrolidine (*E*-6c) and 2*S*,4*R*-(*N*-Benzyl)-2-(*Z*-methoxycarbonyl-ethenyl)-4-phenoxypyrrolidine (*Z*-6c): Reaction between *N*-benzyl-*trans*-4-phenoxy-(*S*)-prolinal (0.28 g, 1.00 mmol) and trimethylphosphonoacetate (0.30 mL, 2.09 mmol) following standard procedure A. Ratio *E*-**6c**/*Z*-**6c** about 5:1. Separation and purification by column chromatography (PE/EtOAc, 6:1) gave *E*-**6c** (41%) as a yellow oil. R_f = 0.37 (PE/EtOAc, 6:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.08 (ddd, ^2J = 13.7, ^3J = 10.0, ^3J = 7.1 Hz, 1 H, 3a-H), 2.21 (ddd, ^2J = 13.5, ^3J = 6.4, ^3J = 1.9 Hz, 1 H, 3b-H), 2.45 (dd, ^2J = 10.7, ^3J = 4.3 Hz, 1 H, 5a-H), 3.29 (d, ^2J = 13.1 Hz, 1 H, 6a-H), 3.46 (dd, ^3J = 13.1, ^3J = 5.7 Hz, 1 H, 2-H), 3.51 (dd, ^2J = 10.8, ^3J = 6.3 Hz, 1 H, 5b-H), 3.76 (s, 3 H, 18-H), 3.98 (d, ^2J = 13.1 Hz, 1 H, 6b-H), 4.80 (tdd, ^3J = 6.4, ^3J = 4.3, ^3J = 1.8 Hz, 1 H, 4-H), 6.08 (dd, ^3J = 15.7, ^4J = 0.6 Hz, 1 H, 16-H), 6.79 (dd, ^3J = 8.7, ^4J = 0.9 Hz, 2 H, 12-H), 6.90 (dd, ^3J = 16.3, ^3J = 8.5 Hz, 1 H, 15-H), 6.93 (t, ^3J = 7.4 Hz, 1 H, 14-H), 7.24–7.31 (m, 7 H, 8-H, 9-H, 10-H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.4 (C-3), 51.6 (C-18), 58.3 (C-6), 59.7 (C-5), 64.2 (C-2), 74.8 (C-4), 115.1 (C-12), 120.8 (C-14), 122.5 (C-16), 127.1 (C-10), 128.3 (C-8), 128.7 (C-9), 129.5 (C-13), 138.5 (C-7), 157.3 (C-11), 166.7 (C-17) ppm. IR: $\tilde{\nu}$ = 3025, 2946, 1724, 1599, 1495, 1454, 1362, 1240, 1169, 1085, 889, 770, 775, 693, 668 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{24}NO_3$ $[M]^+$ 338.1756; found 338.1759. $[a]_D$ = –72 (*c* = 1.10, CH_2Cl_2).

And *Z*-**6c** (8%) as a yellow oil. R_f = 0.27 (PE/EtOAc, 6:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94–2.02 (m, 1 H, 3a-H), 2.18–2.24 (m, 1 H, 3b-H), 2.42–2.49 (m, 1 H, 5a-H), 3.35 (d, ^2J = 13.0 Hz, 1 H, 6a-H), 3.45–3.52 (m, 1 H, 5b-H), 3.73 (s, 3 H, 18-H), 3.92 (d, ^2J = 13.0 Hz, 1 H, 6b-H), 4.77–4.82 (m, 1 H, 2-H), 4.88 (ddd, ^3J = 9.2, ^3J = 8.3, ^3J = 7.9 Hz, 1 H, 4-H), 5.88 (d, ^3J = 11.6 Hz, 1 H, 16-H), 6.21 (dd, ^3J = 11.5, ^4J = 8.6 Hz, 1 H, 15-H), 6.80 (t, ^3J = 7.5 Hz, 2 H, 13-H), 6.86–6.91 (m, 1 H, 14-H), 7.22–7.31 (m, 7 H, 8-H, 9-H, 10-H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.6 (C-3), 51.3 (C-18), 58.3 (C-6), 59.7 (C-5), 64.2 (C-2), 75.0 (C-4), 115.2 (C-12), 120.6 (C-14), 122.2 (C-16), 127.1 (C-10), 128.2 (C-8), 128.7 (C-9), 129.4 (C-13), 138.5 (C-7), 157.5 (C-11), 166.3 (C-17) ppm. IR: $\tilde{\nu}$ = 3027, 2948, 1723, 1599, 1495, 1455, 1373, 1240, 1169, 1085, 884, 754, 700, 669 cm^{-1}. HRMS (ESI): calcd. for $C_{21}H_{24}NO_3$ $[M]^+$ 338.1756; found 338.1763. $[a]_D$ = –67 (*c* = 1.20, CH_2Cl_2).

Standard Procedure B: Ando Reaction: Ethyl(diphenylphosphono) acetate (24 mmol) in dry THF (130 mL) was slowly added to a suspension of NaH (80% dispersion in mineral oil; 36 mmol) in dry THF (130 mL) at –78 °C with stirring. After 0.5 h, a freshly prepared solution of the aldehyde (26 mmol) in dry THF (50 mL) was added. The reaction mixture was stirred for 12 h, during which time it was allowed to warm up to room temperature. The reaction was then stopped by the addition of saturated aqueous NH_4Cl (170 mL), and the mixture was extracted with diethyl ether (3×). The combined organic phases were washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated under vacuum. The crude unsaturated ester was purified by flash chromatography (formation of the ethyl ester!).

2*S*,4*S*-(*N*-Benzyl)-2-(*E*-ethoxycarbonylethenyl)-4-phenoxy-pyrrolidine (*E*-7c Ethyl Ester) and 2*S*,4*S*-(*N*-Benzyl)-2-(*Z*-ethoxycarbonylethenyl)-4-phenoxypyrrolidine (*Z*-7c Ethyl Ester): Reaction between aldehyde **5c**′′ (6.0 g, 21.0 mmol) and ethyldiphenylphosphonoacetate (9.0 g, 28.0 mmol) following standard procedure B. Purification by column chromatography (PE/EtOAc, 5:1) gave a mixture (25:65) of *E*-**7c**/*Z*-**7c** ethyl esters (90%). The mixture was separated by HPLC [Nucleosil 50–5 (ID 32 × 238 mm), (Hex/EtOAc, 5.7:1), 100 mL/min, 16.2 MPa, t_R = 0.9 min (*Z*-**7c** ethyl ester), t_R = 1.4 min (*E*-**7c** ethyl ester)] to give *Z*-**7c** ethyl ester (65%) as a colourless solid.

Data for *Z*-**7c** ethyl ester: R_f = 0.5 (PE/EtOAc, 5:1), m.p. 104 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, ^3J = 7.1 Hz, 3 H, 19-H), 1.79–1.87 (m, 1 H, 3a-H), 2.53–2.60 (m, 1 H, 5a-H), 2.70–2.79 (m, 1 H, 3b-H), 3.20 (d, ^3J = 10.9 Hz, 1 H, 5b-H), 3.34 (d, ^2J = 13.0 Hz, 1 H, 6a-H), 3.94 (d, ^2J = 13.3 Hz, 1 H, 6b-H), 4.19 (q, ^3J = 7.1 Hz, 2 H, 18-H), 4.24 (m, 1 H, 2-H), 4.79 (dd, ^3J = 10.3, ^3J = 6.4 Hz, 1 H, 4-H), 5.86 (dd, ^3J = 11.6, ^4J = 0.9 Hz, 1 H, 16-H), 6.36–6.43 (m, 1 H, 15-H), 6.81 (d, ^3J = 7.8 Hz, 1 H, 12-H), 6.91 (t, ^3J = 7.4 Hz, 1 H, 14-H), 7.19–7.36 (m, 7 H, 8-H, 9-H, 10-H, 13-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (C-19), 39.0 (C-3), 58.7 (C-6), 59.6 (C-5), 60.3 (C-18), 61.5 (C-2), 75.5 (C-4), 115.4 (C-12), 120.7 (C-14), 121.4 (C-16), 127.2 (C-10), 128.4 (C-8), 129.1 (C-9), 129.5 (C-13), 138.5 (C-7), 151.6 (C-15), 157.8 (C-11), 166.3 (C-17) ppm. IR: $\tilde{\nu}$ = 2979, 2794, 1716, 1647, 1600, 1494, 1372, 1240, 1192, 1027, 825, 981, 753, 694 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{26}NO_3$ $[M + H]^+$ 352.1913; found 352.1901. $[a]_D$ = –72 (*c* = 1.0, CH_2Cl_2).

Standard Procedure C for an Aza-Claisen Rearrangement: K_2CO_3 (40 mmol) was suspended in dry CH_2Cl_2 (100 mL), and allylamine **6**/**7** (10 mmol) and a solution of freshly prepared chloroacetyl fluoride (50 mmol) in dry CH_2Cl_2 (75 mL) were added at 0 °C. Then, trimethylaluminium (2 M in heptane; 50 mmol) was added dropwise, with stirring. Methane was evolved, and the mixture was stirred for 12 h, during which time the temperature slowly reached 23 °C. The reaction was stopped by the careful dropwise addition of water until the remaining trimethylaluminium was hydrolysed.

The resulting suspension was dried ($MgSO_4$), and then filtered through $MgSO_4$. The filtrate was washed with saturated aqueous

$NaHCO_3$ (2×) and brine (1×). The combined aqueous phases were reextracted with diethyl ether (3×). The combined organic phases were dried ($MgSO_4$) and concentrated under vacuum. The crude azoninone **8**–**13** was purified by flash chromatography.

(*pS*) *E*-3*R*,4*S*,8*R*-*N*-Benzyl-3-chloro-4-methoxycarbonyl-8-(phenoxy)-2,3,4,7,8,9-hexahydro-1*H*-azonin-2-one (*pS*-8c): Reaction between allylamine *E*-**6c** (0.11 g, 0.33 mmol) and chloroacetyl fluoride (0.12 mL, 1.63 mmol) following standard procedure C. Purification by column chromatography (PE/EtOAc, 6:1) gave *pS*-**8c** (64%) as a yellow oil. R_f = 0.38 (PE/EtOAc, 4:1). ^{1}H NMR (400 MHz, $CDCl_3$, amide conformation **A**): δ = 2.51 (dd, ^2J = 11.4, ^3J = 6.0 Hz, 1 H, 7a-H), 2.77 (dd, ^2J = 13.5, ^3J = 4.1 Hz, 1 H, 7b-H), 3.59 (dd, ^2J = 15.4, ^3J = 5.0 Hz, 1 H, 9a-H), 3.81 (s, 3 H, 20-H), 3.89 (dd, ^3J = 9.5, ^3J = 2.3 Hz, 1 H, 4-H), 4.50 (d, ^2J = 15.4 Hz, 1 H, 10a-H), 4.69 (d, ^2J = 15.4 Hz, 1 H, 9b-H), 4.88 (t, ^3J = 5.3 Hz, 1 H, 8-H), 5.43 (d, ^3J = 2.5 Hz, 1 H, 3-H), 5.46 (d, ^2J = 15.6 Hz, 1 H, 10b-H), 5.99 (ddd, ^3J = 15.8, ^3J = 11.2, ^3J = 4.2 Hz, 1 H, 6-H), 6.15 (dd, ^3J = 16.0, ^3J = 9.6 Hz, 1 H, 5-H), 6.90 (d, ^3J = 7.9 Hz, 2 H, 16-H), 7.01 (t, ^3J = 7.4 Hz, 1 H, 18-H), 7.13 (d, ^3J = 7.0 Hz, 2 H, 17-H), 7.28–7.35 (m, 5 H, 12-H, 13-H, 14-H); (amide conformation **B**): 2.32–2.33 (m, 1 H, 7a-H), 2.47 (dd, ^2J = 11.4, ^3J = 6.2 Hz, 1 H, 7b-H), 3.38 (dd, ^2J = 15.2, ^3J = 4.1 Hz, 1 H, 9a-H), 3.79–3.80 (m, 1 H, 9b-H), 3.83–3.85 (m, 1 H, 4-H), 3.85 (s, 3 H, 20-H), 4.45 (d, ^2J = 14.6 Hz, 1 H, 10a-H), 4.61–4.65 (m, 1 H, 8-H), 4.94 (d, ^2J = 15.1 Hz, 1 H, 10b-H), 5.08 (d, ^3J = 7.9 Hz, 1 H, 3-H), 5.87–5.90 (m, 2 H, 5-H, 6-H), 6.76 (d, ^3J = 7.9 Hz, 2 H, 16-H), 6.99 (t, ^3J = 7.1 Hz, 1 H, 18-H), 7.22 (d, ^3J = 7.1 Hz, 2 H, 17-H), 7.29–7.32 (m, 5 H, 12-H, 13-H, 14-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, amide conformation **A**): δ = 38.0 (C-7), 48.2 (C-9), 50.0 (C-4), 52.7 (C-20), 53.4 (C-10), 66.5 (C-3), 79.4 (C-8), 115.6 (C-16), 121.6 (C-18), 127.2 (C-17), 128.3 (C-13), 128.5 (C-5), 129.5 (C-12), 129.5 (C-14), 133.3 (C-6), 137.4 (C-11), 156.5 (C-15), 169.3 (C-2), 169.7 (C-19); (amide conformation **B**): 34.1 (C-7), 50.1 (C-10), 50.5 (C-4), 50.6 (C-9), 52.3 (C-20), 56.1 (C-3), 71.9 (C-8), 115.8 (C-16), 121.8 (C-18), 127.0 (C-17), 127.9 (C-13), 128.7 (C-12), 128.8 (C-14), 129.4 (C-5), 131.5(C-6), 136.8 (C-11), 156.5 (C-15), 166.7 (C-2), 168.9 (C-19) ppm. IR: $\tilde{\nu}$ = 3031, 2953, 1739, 1657, 1621, 1597, 1494, 1231, 1169, 1028, 913, 750, 695, 640 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}NO_4NaCl$ [M + Na]$^+$ 436.1292; found 436.1290. $[\alpha]_D$ = –45 (c = 0.85, CH_2Cl_2).

Standard Procedure D: Same procedure as described for Standard Procedure C, but without K_2CO_3.

(*pS*) *E*-3*S*,4*S*,8*R*-*N*-Benzyl-4-ethoxycarbonyl-8-(phenoxy)-3-phenyl-2,3,4,7,8,9-hexahydro-1*H*-azonin-2-one (*pS*-14c): Reaction between allylamine *Z*-**6c** (ethyl ester; 300 mg, 0.85 mmol) and phenylacetyl fluoride (648 mg, 4.69 mmol) following standard procedure D. Purification by column chromatography (PE/EtOAc, 5:1) and HPLC [Nucleosil 50–5 (ID 32×250 mm), (Hex/EtOAc, 17:3), 64 mL/min, 68 bar, t_R = 4.56 min] gave *pS*-**19c** (70%) as a yellow solid. R_f = 0.3 (PE/EtOAc, 5:1), m.p. 113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 (t, ^3J = 7.1 Hz, 3 H, 21-H), 2.11 (ddd, ^2J = 13.8, ^3J = 11.8, ^3J = 5.9 Hz, 1 H, 7β-H), 2.58 (dd, ^2J = 13.8, ^3J = 3.4 Hz, 1 H, 7α-H), 3.46 (dd, ^2J = 14.9, ^3J = 4.7 Hz, 1 H, 9β-H), 3.83 (dd, ^3J = 10.7, ^3J = 7.3 Hz, 1 H, 4-H), 4.13 (td, ^3J = 7.2, ^3J = 3.4 Hz, 2 H, 20-H), 4.35 (dd, ^2J = 14.9, ^3J = 10.0 Hz, 1 H, 9α-H), 4.52 (d, ^2J = 14.7 Hz, 1 H, 10α-H), 4.67–4.74 (m, 1 H, 8-H) 4.71 (d, ^3J = 10.7 Hz, 1 H, 3-H), 4.84 (d, ^2J = 14.7 Hz, 1 H, 10β-H), 5.86 (dd, ^3J = 16.4, ^3J = 7.3 Hz, 1 H, 5-H), 6.18–6.28 (m, 1 H, 6-H), 6.75 (d, ^3J = 7.8 Hz, 2 H, 23-H), 6.96 (t, ^3J = 6.1 Hz, 1 H, 25-H), 7.19 (d, ^3J = 2.1 Hz, 2 H, 14-H, 18-H), 7.19–7.23 (m, 2 H, 12-H), 7.21–7.36 (m, 6 H, 13-H, 17-H, 24-H), 7.48 (d, ^3J = 7.1 Hz, 2 H, 16-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (C-21), 34.6 (C-7), 48.7 (C-4), 49.5 (C-10), 49.9 (C-9), 55.2 (C-3), 61.2 (C-20), 71.8 (C-8), 115.8 (C-23), 121.6 (C-25), 129.4 (C-6), 127.7 (C-14), 127.9 (C-18), 128.1 (C-12), 128.4 (C-13), 128.6 (C-17), 128.9 (C-24), 129.2 (C-16), 132.2 (C-5), 137.2 (C-11), 137.7 (C-15), 157.0 (C-21), 171.0 (C-19), 173.2 (C-2) ppm. IR: $\tilde{\nu}$ = 3029 (w), 2933 (w), 1729 (s), 1637 (s), 1597 (m), 1451 (m), 1225 (s), 1157 (s), 1033 (m), 942 (w), 752 (s), 695 cm^{-1}. HRMS (ESI): calcd. for $C_{30}H_{31}NO_4Na$ [M + Na]$^+$ 492.2151; found 492.2163. $[\alpha]_D$ = –115 (c = 1.03, CH_2Cl_2).

(*pS*) *E*-3*S*,4*R*,8*S*-*N*-Benzyl-3-chloro-4-ethoxycarbonyl-8-(phenoxy)-2,3,4,7,8,9-hexahydro-1*H*-azonin-2-one (*pS*-20c) and (*pS*) *E*-3*R*,4*R*,8*S*-*N*-Benzyl-4-ethoxycarbonyl-8-(phenoxy)-3-phenyl-2,3,4,7,8,9-hexahydro-1*H*-azonin-2-one (*pS*-21c): Reaction between allylamine *Z*-**7c** (4.0 g, 11.38 mmol) and chloroacetyl fluoride (4.8 mL, 79.6 mmol) following standard procedure C. Purification by column chromatography (PE/EtOAc, 8:1) gave *pS*-**20c** (68%) as a pale yellow oil, and *pS*-**21c** (10%) as a pale yellow oil.

Data for *pS*-**20c**. R_f = 0.3 (PE/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.31 (t, ^3J = 7.1 Hz, 3 H, 21-H), 2.31–2.42 (m, 1 H, 7-H$^\beta$), 3.07 (dd, ^2J = 13.2, ^3J = 7.6 Hz, 1 H, 7-H$^\alpha$), 3.57–3.62 (m, 1 H, 4-H), 3.65 (d, ^2J = 16.2 Hz, 1 H, 9-H$^\beta$), 3.81–3.95 (m, 2 H, 9-H$^\alpha$), 4.20–4.33 (m, 2 H, 20-H), 4.38 (d, ^2J = 14.2 Hz, 1 H, 10a-H), 4.63–4.70 (m, 1 H, 8-H), 5.14 (d, ^3J = 9.8 Hz, 1 H, 3-H), 5.60 (dd, ^2J = 14.2, ^4J = 1.1 Hz, 1 H, 10b-H), 5.78–5.91 (m, 2 H, 5-H, 6-H), 6.92 (d, ^3J = 7.8 Hz, 2 H, 16-H), 7.01 (t, ^3J = 7.4 Hz, 1 H, 18-H), 7.21–7.27 (m, 5 H, 12-H, 13-H, 14-H), 7.28–7.34 (m, 2 H, 17-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (C-21), 36.2 (C-7), 48.8 (C-9), 49.7 (C-10), 50.4 (C-4), 57.0 (C-3), 61.9 (C-20), 74.4 (C-8), 115.8 (C-16), 122.0 (C-18), 127.6 (C-14), 128.6 (C-13), 129.0 (C-12), 129.4 (C-5 or C-6), 129.9 (C-17), 130.2 (C-5 or C-6), 136.8 (C-11), 156.7 (C-15), 169.0 (C-2), 170.0 (C-19) ppm. IR: $\tilde{\nu}$ = 3030, 2935, 1732, 1647, 1597, 1492, 1422, 1374, 1222, 1172, 1063, 1013, 753, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{26}NO_4ClNa$ [M + Na]$^+$ 450.1448; found 450.1450. $[\alpha]_D$ = 19.0 (c = 1.0, CH_2Cl_2).

Data for *pS*-**21c**. R_f = 0.2 (PE/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, ^3J = 7.1 Hz, 3 H, 21-H), 2.18 (td, ^2J = 11.8, ^3J = 9.2 Hz, 1 H, 7-H$^\beta$), 3.07–3.15 (m, 1 H, 7-H$^\alpha$), 3.28 (d, ^2J = 14.4 Hz, 1 H, 9-H$^\alpha$), 3.70–3.80 (m, 2 H, 4-H, 9-H$^\beta$), 4.19–4.38 (m, 3 H, 10a-H, 20-H), 4.56 (dd, ^3J = 16.4, ^3J = 8.5 Hz, 1 H, 8-H), 4.82 (d, ^3J = 3.6 Hz, 1 H, 3-H), 5.03 (d, ^2J = 14.7 Hz, 1 H, 10b-H), 5.75 (dd, ^3J = 16.1, ^3J = 6.2 Hz, 1 H, 5-H), 6.31 (ddd, ^3J = 16.1, ^3J = 12.2, ^3J = 3.7 Hz, 1 H, 6-H), 6.85 (dd, ^3J = 8.7, ^4J = 0.9 Hz, 2 H, 16-H), 7.02–7.08 (m, 1 H, 18-H), 7.09–7.11 (m, 2 H, 13-H), 7.21–7.28 (m, 3 H, 12-H, 14-H), 7.28–7.34 (m, 2 H, 17-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.4 (C-21), 39.8 (C-7), 50.5 (C-10), 51.1 (C-4), 52.4 (C-9), 57.5 (C-3), 61.5 (C-20), 75.2 (C-8), 117.3 (C-16), 122.6 (C-18), 127.7 (C-5), 128.5 (C-12), 128.6 (C-13), 128.8 (C-14), 130.0 (C-17), 132.5 (C-6), 137.1 (C-11), 157.1 (C-15), 165.9 (C-2), 168.1 (C-19) ppm. IR: $\tilde{\nu}$ = 3029, 2930, 1736, 1650, 1597, 1492, 1415, 1222, 1179, 1043, 753, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{27}NO_4Cl$ [M + H]$^+$ 428.1629; found 428.1636. $[\alpha]_D$ = 107.0 (c = 0.5, CH_2Cl_2).

Standard Procedure E for a Transannular Ring Contraction: A solution of azoninone **8**–**20** (1.0 mmol) in dry CH_2Cl_2 (20 mL) was treated dropwise with a solution of iodine (1.1 mmol) in dry CH_2Cl_2 until the colour of unreacted iodine remained. The mixture was stirred for a further 15 min at 23 °C to achieve complete conversion. Then, the excess iodine was destroyed by adding saturated aqueous $Na_2S_2O_3$. The organic phase was dried ($MgSO_4$), and concentrated under vacuum. The residue was purified by flash chromatography.

2*R*,6*R*,7*S*,8*R*,8a*S*-6-Chloro-8-iodo-7-methoxycarbonyl-2-phenoxy-indolizidin-5-one (22c): Reaction between azoninone *pS*-**8c**

(75.0 mg, 0.18 mmol) and iodine (47.0 mg, 0.20 mmol) following standard procedure E. Purification by column chromatography (PE/EtOAc, 2:1) gave indolizidinone **22c** (52%) as a white solid. R_f = 0.16 (PE/EtOAc, 3:1), m.p. 175 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (ddd, ^2J = 13.3, ^3J = 11.3, ^3J = 4.9 Hz, 1 H, 7a-H), 2.84 (dd, ^2J = 13.2, ^3J = 4.5 Hz, 1 H, 7b-H), 3.64 (dd, ^3J = 11.3, ^3J = 4.9 Hz, 1 H, 4-H), 3.82 (s, 3 H, 15-H), 3.85 (d, ^2J = 14.2 Hz, 1 H, 9a-H), 4.13 (dd, ^2J = 13.5, ^3J = 7.9 Hz, 1 H, 9b-H), 4.18 (t, ^3J = 11.1 Hz, 1 H, 5-H), 4.26 (td, ^3J = 11.1, ^3J = 4.5 Hz, 1 H, 6-H), 4.57 (d, ^3J = 4.9 Hz, 1 H, 3-H), 4.94 (t, ^3J = 5.0 Hz, 1 H, 8-H), 6.84 (dd, ^3J = 8.7, ^4J = 0.9 Hz, 2 H, 11-H), 7.00 (t, ^3J = 7.0 Hz, 1 H, 13-H), 7.30 (dd, ^3J = 8.6, ^3J = 7.4 Hz, 2 H, 12-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.6 (C-5), 40.8 (C-7), 52.9 (C-15), 53.9 (C-9), 54.3 (C-3), 54. (C-4), 64.0 (C-6), 71.8 (C-8), 115.5 (C-11), 121.9 (C-13), 129.9 (C-12), 156.5 (C-10), 162.8 (C-2), 167.9 (C-14) ppm. IR: $\tilde{\nu}$ = 3083, 2978, 1742, 1664, 1488, 1289, 1230, 1099, 913, 751, 689, 652 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{17}NO_4NaClI$ $[M + Na]^+$ 338.1756; found 471.9789. $[\alpha]_D$ = 68 (c = 0.80, CH_2Cl_2).

2*R*,6*S*,7*S*,8*R*,8a*S*-8-Iodo-7-methoxycarbonyl-2-phenoxy-6-phenylindolizidin-5-one (28c): Reaction between azoninone *pS*-**14c** (141 mg, 0.30 mmol) and iodine (85.0 mg, 0.33 mmol) following standard procedure E. Purification by column chromatography (PE/EtOAc, 1:1) gave **28c** (54%) as a colourless oil. R_f = 0.16 (PE/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, ^2J = 7.1 Hz, 3 H, 16-H), 1.86 (ddd, ^2J = 13.2, ^3J = 11.6, ^3J = 5.1 Hz, 1 H, 7β-H), 2.75 (dd, ^2J = 13.1, ^3J = 4.8 Hz, 1 H, 7α-H), 3.90 (d, ^2J = 14.1 Hz, 1 H, 9α-H), 3.33 (dd, ^3J = 4.8, ^3J = 2.1 Hz, 1 H, 4-H), 4.12 (q, ^2J = 7.1 Hz, 2 H, 15-H), 4.05 (t, ^3J = 5.5 Hz, 1 H, 5-H), 4.28 (dd, ^3J = 7.2, ^3J = 1.9 Hz, 1 H, 3-H), 4.31 (dd, ^2J = 5.4, ^3J = 1.6 Hz, 1 H, 9β-H), 4.68 (td, ^3J = 11.3, ^3J = 4.8 Hz, 1 H, 6-H), 4.98 (t, ^3J = 5.3 Hz, 1 H, 8-H), 6.88 (d, ^3J = 7.6 Hz, 2 H, 18-H), 6.99 (t, ^3J = 7.4 Hz, 1 H, 20-H), 7.13 (d, ^3J = 5.3 Hz, 2 H, 11-H), 7.28–7.37 (m, 5 H, 12-H, 13-H, 19-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.4 (C-16), 41.8 (C-7), 50.9 (C-5), 53.4 (C-9), 55.6 (C-4), 60.2 (C-6), 60.5 (C-15), 61.8 (C-3), 72.0 (C-8), 115.6 (C-18), 121.6 (C-20), 127.7 (C-13), 128.1 (C-11), 129.2 (C-12), 129.8 (C-19), 139.8 (C-10), 156.8 (C-17), 166.5 (C-2), 171.1 (C-14) ppm. IR: $\tilde{\nu}$ = 2951, 1738, 1630, 1490, 1290, 1228, 1096, 905, 760, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{23}H_{24}NO_4I$ $[M + H]^+$ 506.0826; found 506.0892. $[\alpha]_D$ = –15 (1.04, CH_2Cl_2).

Supporting Information (see footnote on the first page of this article): Spectroscopic data, NOE data and copies of ^{1}H and ^{13}C NMR spectra for new compounds.

Acknowledgments

This work was supported by the Naturstoffzentrum Rheinland-Pfalz, University of Mainz, Germany. The authors are grateful for helpful discussions and financial aid.

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[21] A diastereoselective ring expansion, as reported earlier for an small-scale experiment (ref.[3b]) and using acid chlorides (ref.[3d]), was not reproduced in the larger scale experiments described here.

[22] For detailed NOESY data, see the Supporting Information.

[23] CCDC-985005 contains supplementary crystallographic data of *pS*-**8b** for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[24] The ^{1}H NMR spectrum of the mixture of lactams **19c** showed chemical shifts typical of the olefin protons for a *pS* arrangement (major) and a *pR* arrangement (minor). All attempts to induce complete isomerisation and to separate the potential planar diastereomers failed. The unambiguous assignment of the minor component structure failed because of (partial) overlap of crucial peaks in the NMR spectra.

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Received: June 8, 2014
Published Online: August 21, 2014

