Diastereoselective Zwitterionic Aza-Claisen Rearrangement: Synthesis of Nine-Membered Ring Lactams and Transannular Ring Contraction

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Abstract: The zwitterionic aza-Claisen rearrangement of optically active 3-pyrrolidine acryl esters and various acid chlorides to generate optically active azoninones proceeds with high simple diastereoselectivity (internal asymmetric induction) and a complete 1,3-chirality transfer. The reaction path observed depends on the substitution pattern of the allylic system: while the more electron-rich alkylated allyl amine formed predominantly von Braun type products, the α,β-unsaturated esters could be rearranged with high yields. The azoninones thus obtained were treated with electrophiles, inducing regio- and diastereoselective transannular ring contractions. The resulting indolizidinones should be useful key intermediates in alkaloid synthesis.

Keywords
aza-Claisen rearrangement · azoninones · indolizidinones · ring contractions

Introduction

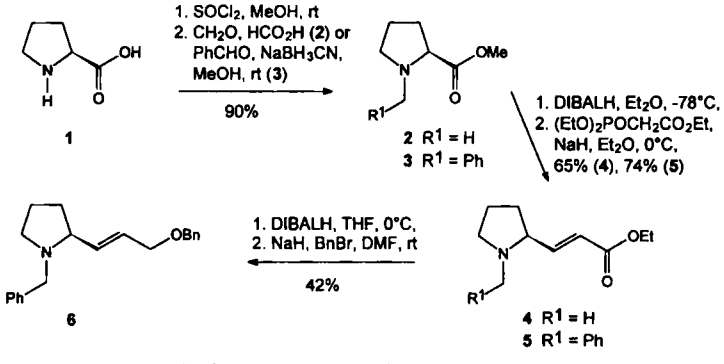
The complete 1,3-chirality transfer in ketene Claisen rearrangements of allyl thioethers is well known,[1] but the scope of the reaction is restricted to activated ketenes like chloro-, chloroalkyl- and dichloroketene.[2] Aza-ketene Claisen reactions involving ketenes generated in situ (especially dichloroketene) suffer from the same disadvantages. All rearrangements are accompanied by varying amounts of tarry by-products.[3] In contrast, treatment of *N*-allyl pyrrolidines with acid chlorides in the presence of trimethylaluminium in a two-phase system of solid K_2CO_3 in $CHCl_3$ produced the corresponding γ,δ-unsaturated lactams in high yields (zwitterionic variant).[4] Complete 1,3-chirality transfer was observed when reacting acetyl chloride with derivatives of proline and hydroxyproline. A highly efficient synthesis of the optically active nine-membered ring lactams was thus developed.[4]

The major competing reaction observed is a von Braun type process involving nucleophilic attack of a chloride ion on an intermediate acylammonium salt.[5] The von Braun type reaction path predominated whenever α,α-disubstituted acid chlorides (e.g., dichloroacetyl chloride) were used.[4, 6]

Results and Discussion

In the first part of this paper, the scope and limitations of the use of the zwitterionic aza-Claisen rearrangement to generate optically active 3,4-disubstituted azonin-2-ones is reported. The optically active pyrrolidines **4**–**6** were chosen for investigation.

The allyl amines **4** to **6** (Scheme 1) were synthesized in four to six steps starting from L-proline: after esterification of the L-proline with $SOCl_2$ in MeOH,[7] an *N*-protective group was introduced by reductive amination. The *N*-methylation to ester **2** was achieved by a Clarke–Eschweiler reaction in 90% yield overall,[8] the *N*-benzylation was carried out with benzaldehyde and $NaBH_3CN$ in MeOH, forming ester **3** in 90% yield.[9] The chain elongation to the allyl amines **4** and **5** was achieved by a one-pot procedure[10] of a DIBALH reduction of the ester function followed by a Horner reaction of the aldehyde formed in situ with sodium triethylphosphonoacetate in Et_2O; the corresponding allyl aminoesters **4** and **5** with electron-deficient double bonds were isolated in 65 and 74% yield.[4] The reduction of the ester group of **5** proved crucial because in most cases a DIBALH reduction[11] led to the formation of the saturated carbinol as a by-product.[12] The separation of allyl alcohol and saturated carbinol was difficult. The extensive variation of the reaction conditions (solvent, temperature, addition of Lewis acids) and the reducing reagent ($LiAlH_4$, Red-Al®, boranes, etc.)[13] led to a moderate yield of about 60% of the allylic alcohol. The final benzylation with BnBr in presence of NaH gave the allyl amine **6** with an electron-rich double bond in 70% yield.[14]



Scheme 1. Synthesis of the optically active allylamines.

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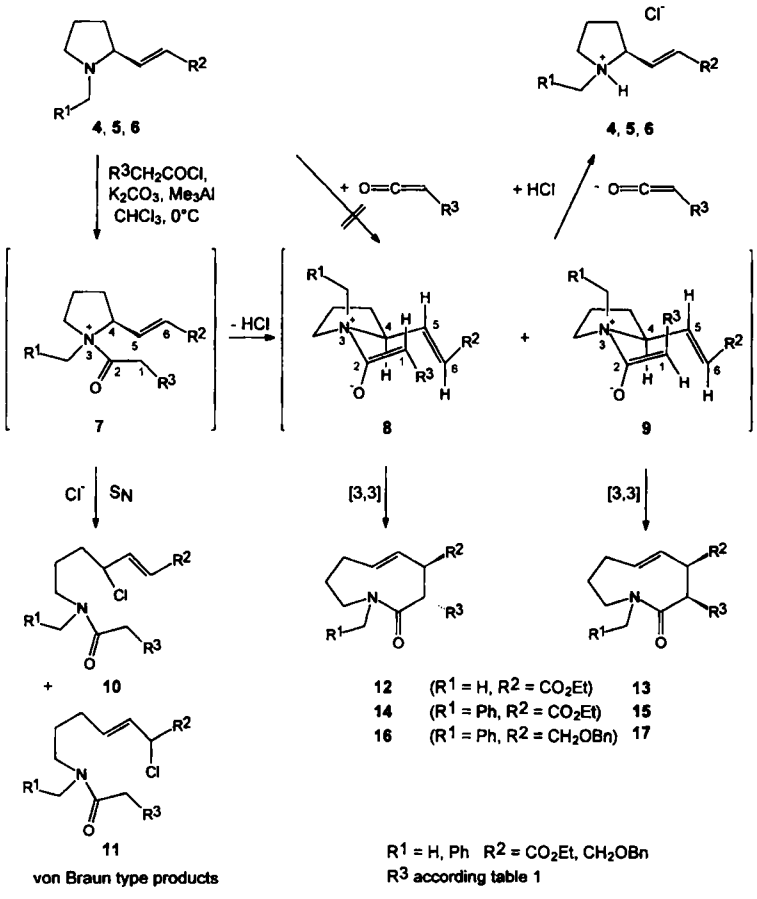
Diastereoselective aza-Claisen rearrangement: The allyl amines **4**–**6** were treated with several types of acid chlorides as listed in Table 1. All isolated amides **12** to **17** were, if operative, separated and purified by preparative HPLC. The relative stereochemistry of each lactam **12** to **17** was unequivocally proved by NOEDS (nuclear Overhauser effect difference spectroscopy) analysis.

In the first series, aminoester **4** (electron-deficient double bond, *N*-methyl protective group) was acylated with a range of acid chlorides and rearranged (Table 1, entries a–g). The corresponding *anti*-configurated azoninones **12** were generated diastereoselectively in high yields in the case of linear chains (entry a: ref. [4]; entries b, c). It should be pointed out that the β,γ-double bond of the lactam **12c** did not isomerize, and the α,β-unsaturated amide was not found. The rearrangement of phenylacetyl chloride (entry d) formed slightly higher amounts of the chlorides **10** and **11** (up to about 15%). In the rearrangement product **12/13d** the simple diastereoselectivity was found to be nonuniform. Possibly, the product **12** had partially epimerized during the extended reaction time, but it seemed to be more likely that the reaction passed unselectively through the competing zwitterionic intermediates **8** and **9**. *iso*-Butyric acid chloride and ethoxycarbonyl acetyl chloride did not give any rearrangement product. α-Heteroatom substituted acetyl chlorides could be efficiently rearranged (Table 1, entries e–g); only small amounts of the competing von Braun type products were formed. The reaction with chloroacetyl chloride (entry e) led to the diastereoselective formation of the *anti*-lactam **12e** in about 72% yield. No *syn*-lactam **13e** could be detected, even though the α-chlorocarbonyl function of **12e** was expected to undergo facile epimerization under the reaction conditions. After the selective generation of only one diastereomer in this case it seemed reasonable to assume that all unselective rearrangements resulted from the unselective formation of the zwitterionic intermediates **8** and **9** rather than from a diastereoselective reaction followed by an epimerization. Benzyloxyacetyl and *N*-phthaloylamidoacetyl chloride (entries f, g) were rearranged to the corresponding lactams **12/13f** in 68 and **12/13g** in 35% yield, respectively.[15] In the case of the benzyloxy substituent, two diastereomers **12f** and **13f** were isolated in a ratio of 4:1 (*anti*:*syn*). The reaction with the *N*-phthaloylamido group afforded a significantly longer reaction time, but the product **12g** was formed with a much higher diastereoselectivity (about 15:1, *anti* **12g**:*syn* **13g**). In contrast to the known aza-ketene Claisen rearrangements,[3] dichloroacetyl chloride did not yield any rearrangement product **12**, only von Braun type allylchlorides **10** and **11**.



Scheme 2. Diastereoselective zwitterionic aza-Claisen rearrangement: formation of nine-membered-ring lactams.

In the second series, rearrangements of the aminoester **5** (electron-deficient double bond, easily removable *N*-benzyl protective group) were investigated (Table 1, entries h–j). In all attempts, the reaction time increased compared with the corresponding rearrangements of the first series and higher amounts of von Braun type products **10** or **11** could be detected. Previously,[4] the reaction of aminoester **5** with acetyl chloride (entry h) formed exclusively the corresponding allylchlorides **10** and **11**, but a considerableprolongation of the reaction time (to about 3 weeks) and a higher concentration of the Lewis acid Me_3Al resulted in the generation of up to 60% of lactam **14**. All other attempts (entries i, j) suffered from the occurrence of a more or less efficient von Braun type process; only chloroacetyl and benzyloxyacetyl chloride led to the generation of the corresponding lactams **14/15** in 22–30% yield. The diastereoselectivities observed varied between *anti*:*syn* 9:1 (**14i**:**15i**) and 4:1 (**14j**:**15j**). Propionyl chloride, phenylacetyl chloride and hexadienoic acid chloride generated the allylchlorides **10** and **11** exclusively.

In the third series (Table 1, entry k), the allylamine **6**, with an electron-rich double bond, was treated with a range of acid chlorides. The results were disappointing, because most of the acid chlorides involved (acetyl, benzyloxyacetyl, crotyl, phenylacetyl and propionyl chloride) generated the allyl chlorides **10**

Table 1. Results of the zwitterionic aza-Claisen rearrangement.

Entry	Amine	R^1	R^2	R^3	Qual. yield [a] **10**, **11**	Yield (%) Lactams	Ratio **12,14,16**	**13,15,17**
a	**4**	H	CO_2Et	H	o	70	–	–
b	**4**	H	CO_2Et	CH_3	o	77	>95	<5
c	**4**	H	CO_2Et	$CH=CH_2$	o	80	>95	<5
d	**4**	H	CO_2Et	Ph	o	32 [a]	45	55
e	**4**	H	CO_2Et	Cl	o	72	>95	<5
f	**4**	H	CO_2Et	OBn	o	68	80	20
g	**4**	H	CO_2Et	NPht	o	35 [a]	>94	<6
h	**5**	Ph	CO_2Et	H	o	60	–	–
i	**5**	Ph	CO_2Et	Cl	+ +	22	90	10
j	**5**	Ph	CO_2Et	OBn	+	30	80	20
k	**6**	Ph	CH_2OBn	Cl	+ +	11	87	13

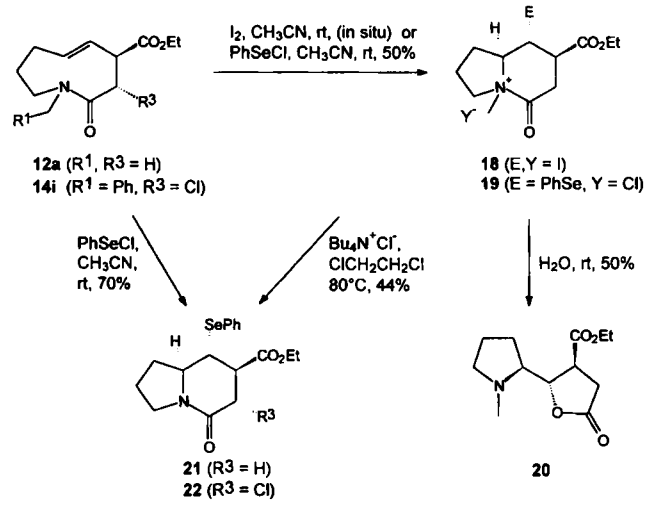
[a] o = ≤15%, + = ≥25%, + + = ≥50%. [b] About 50% aminoester **4** recycled.

and **11** exclusively. Only the attempt with the most reactive chloroacetyl chloride gave some rearrangement product **16/17k** in poor yields (about 10%). The diastereoselection observed was moderate: the *anti/syn* ratio of the lactams **16k** and **17k** was about 6.5:1 (entry k).[16]

Mechanistic conclusions: The different efficiency of the three series of rearrangements depended on the substitution pattern of the allylamines **4**–**6** involved: while the *N*-methyl aminoester **4** was rearranged to the corresponding lactams **12** (and **13**) in high yields, the reaction of the *N*-benzylated ester **5** led to the formation of significant amounts of von Braun type by-products **10** and **11**. It seems reasonable to conclude that the decreased nucleophilicity or the increased steric hindrance of the *N*-benzyl group disfavoured the generation of the azoninones **14** and **15**. In contrast to these rearrangements involving acceptor-substituted olefinic systems, the reactions of the allyl amine **6** (electron-rich double bond) formed von Braun type products nearly exclusively. It is known for Claisen rearrangements that, generally, an electron-withdrawing substituent in position 6 (as in **4**, **5**) decreases the reaction rate.[18] In the present examples, the ester group in position 6 of the acylammonium salt **7** (Scheme 2) protected the system. Obviously, the rate of the von Braun type process was decreased to a significantly greater degree than the Claisen rearrangements. A von Braun type reaction involving nucleophilic attack of the chloride ion at position 4 or 6 of the acylammonium salt **7** generated the allyl chlorides **10** and **11**, respectively. This process predominated for allylamine **6**. For the allylamines **4** and **5** the Michael acceptor position 5 (and the carbonyl carbon atom, reversible) and positions 4 and 6 (irreversible) of **7** competed to trap a nucleophile. Consequently, a less likely von Braun type process favoured the Claisen rearrangement to the lactams **12**–**15** as observed for the amines **4** and **5**.

The results of the first series are most expressive in stereochemical terms. The acyclic Claisen rearrangement is known to pass preferentially through a chair-like transition state[18] with the substituents in quasi-equatorial positions. According to the observations of Evans[19], Myers[20] and Sonnet[21] in their amide enolate chemistry, the deprotonation of an acylammonium salt should generate the *Z*-enolate structure **8** because of minimized steric (and 1,3-diaxial) repulsions. Obviously, the defined enolate geometry resulted in the high simple diastereoselectivity of the zwitterionic aza-Claisen rearrangement.[22] In contrast, the result of entry d (R^3 = Ph) was incompatible with these considerations. Epimerization under basic reaction conditions is not a satisfactory explanation in view of the results in entries c (R^3 = vinyl), e (R^3 = Cl) or g (R^3 = *N*-phthaloyl). It seems that the intermediates **8** and **9** were formed unselectively or the reaction passed through the corresponding boat-like transition state. Steric arguments cannot be exclusively responsible for the different behaviour (entry g); it is more likely that electronic aspects of the extensive π-system of the phenyl substituent are also involved.

The second part of this paper describes the investigation of the regio- and diastereoselective transannular reactions of azoninones **12** and **14** (Scheme 3). Initial experiments were carried out with lactam **12a** (R^3 = H) under the reaction conditions developed by Edstrom:[3c] after treating **12a** with I_2 in MeCN, the acylammonium salt **18** (E, Y = I) was formed in situ, but the subsequent demethylation to the corresponding indolizidinone type **21** failed. The hydrolysis of **18** generated the γ-lactone **20** in about 50% yield by formation of the corresponding carboxylic acid and intramolecular substitution of the iodide E by the carboxylate (S_N2). The relative stereochemistry



Scheme 3. Transannular ring contraction; formation of indolizidinones.

could be proved by NOEDS analysis. The reaction of **12a** with phenylselenyl chloride led to the acylammonium salt **19** (E = PhSe) in about 50% yield. The final demethylation to the indolizidinone **21** succeeded after treatment of **19** with tetrabutylammonium chloride in 1,2-dichloroethane at 80 °C in 44% yield.

The reaction of lactam **14i** (R^1 = Ph) and PhSeCl in MeCN led to the corresponding indolizidinone **22** in one step (70% yield); no acylammonium salt type **19** could be detected. Obviously, the debenzylation of the intermediate acylammonium salt was much more efficient than the demethylation steps of the *N*-methyl series.

The relative stereochemistry of the new chiral centres was unequivocally proved by NOEDS analysis. The transannular reaction proceeded as a regio- and diastereoselective *anti* addition of the electrophile (I^+ or $PhSe^+$) and the nucleophilic amide function to the double bond. The initial attack of the electrophile seemed to be efficiently directed by the ester group (β position) to the *Si* face of the olefin. The resulting indolizidinone **22** bears four consecutive chiral C atoms with defined configurations and should be a useful intermediate in indolizidine alkaloid synthesis.

Conclusion

A range of optically active nine-membered ring lactams have been generated from L-proline in 5–7 steps. The zwitterionic aza-Claisen rearrangement served as a key step. The restriction of the well-known Bellus–Malherbe ketene Claisen rearrangement to activated ketenes like dichloroketene was prevented by the use of common acid chlorides. The most efficient rearrangements were achieved with allylamine **4** (*N*-methyl group); in this series the competing von Braun type process was suppressed and the azoninones were generated in fairly high yields.

Stereochemically, we found complete 1,3 chirality transfer[4] and high simple diastereoselectivity (internal asymmetric induction). The high diastereoselectivity results from the enolate geometry in the hypothetical zwitterionic intermediate. The majority of our experiments generated a substitution pattern similar to an Eschenmoser-type rearrangement[23] corresponding to the preferentially quasi-equatorial position of the acid chloride substituent in a chair-like conformation. Any explanation of the different behaviour of phenylacetyl chloride is still

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speculative; further experiments concerning this problem are in progress.

First attempts at the use of azoninones in transannular reactions led regio- and diastereoselectively to the corresponding indolizidinones in moderate to high yields. The *N*-methyl lactams were cyclized in 2 steps: after the initial ring closure the demethylation could be initiated by the addition of tetraalkyl ammonium chlorides to increase the concentration of the nucleophilic chloride ions. In contrast, the ring closure and the consecutive dealkylation of the corresponding *N*-benzyl azoninones proceeded in a single diastereoselective step to form the indolizidinones in high yields.

The indolizidinones were synthesized from L-proline in 6 or 7 steps. The highly diastereoselective key steps of this synthesis make the method suitable for further applications.

Experimental Section

^{1}H NMR, ^{13}C NMR spectra and NOE experiments were recorded on Bruker AC250 or Bruker AC550 spectrometers; tetramethylsilane was used as internal standard. IR spectra were obtained on a Perkin Elmer 257 or 580 B spectrophotometer. Optical rotations were measured with a Perkin Elmer P241 polarimeter in a 1 dm cell. Mass spectra were recorded on a Varian MAT711 or 112S. The melting points (not corrected) were measured with a Büchi SMP20. Elemental analyses were performed on a Perkin Elmer 240 Elemental Analyser. For HPLC, Knaur pumps, UV and IR detectors and Waters Millipore injection systems were used. Preparative amounts of the lactams were separated with a 32 × 120 mm column and 5 μm nucleosil 50-5 obtained from Macherey & Nagel, with a flow of about 80 mL min^{-1}. Column chromatography was carried out with Merck silica gel 0.063–0.2 mm, 70–230 mesh A. Reactions were monitored by thin-layer chromatography (TLC) on aluminium sheets precoated with silica gel 60 (thickness 0.25 mm). All solvents were dried before use following standard procedures.

(1′*S*)-3-(2-*N*-Methylpyrrolidinyl)propenoic acid ethyl ester (4): Under argon the aminoester **2** (7.2 g, 50 mmol) was dissolved in dry Et_2O (50 mL) and cooled to −78 °C. DIBALH (54 mL, 65 mmol, 1.3 equiv, 1.2 M in toluene) was added carefully keeping the temperature below −75 °C. After 16 h at −78 °C, a solution of sodium triethyl phosphonoacetate (13.5 g, 12 mL, 60 mmol triethylphosphonoacetate and 0.72 g, 60 mmol NaH) in dry THF (100 mL) was added. The mixture was stirred for 5 h while the temperature rose to r.t. Then the reaction was quenched with MeOH (5 mL). After 15 min K/Na tartrate (10 g) was added; after a further 15 min the mixture was hydrolysed with 10% aqueous $NaHCO_3$ (30 mL). The organic layer was decanted and the residue was extracted with EtOAc (3 × 30 mL). After drying ($MgSO_4$), the crude material was purified by column chromatography on silica gel, eluent EtOAc/hexanes 2:1, R_f (EtOAc): 0.22. Yield: 5.96 g (32.5 mmol, 65%) of colourless oil. For spectral data see ref. [4].

(1′*S*)-3-(*N*-Benzyl-2-pyrrolidinyl)propenoic acid ethyl ester (5): Reaction with *N*-benzylproline ester **3** (14.1 g, 64.1 mmol) under the conditions described for aminoester **4**. Chromatography: EtOAc/hexanes, 1:12. R_f (EtOAc/hexanes 1:4): 0.26. Yield: 12.3 g (47.4 mmol, 74%). $[\alpha]_D^{20} = -48.8$ ($c = 4.0$, in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.3$ (m, 5H; CH), 6.9 (dd, ^3J(H,H) = 8 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 5.95 (d, ^3J(H,H) = 15 Hz, 1H; CH), 4.2 (q, ^3J(H,H) = 8 Hz, 2H; OCH_2), 3.9 (d, ^2J(H,H) = 13 Hz, 1H; CH_2), 3.2 (d, ^2J(H,H) = 13 Hz, 1H; CH_2), 3.0 (m, 2H; NCH, NCH_2), 2.2 (m, 1H; NCH_2), 1.95 (m, 1H; CH_2), 1.65 (m, 3H; CH_2), 1.3 (t, ^3J(H,H) = 8 Hz, 3H; CH_3); ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): $\delta = 166.0$ (C=O), 150.2, 138.7, 128.5, 127.9, 126.6, 121.7 (CH), 65.4 (OCH_2), 59.9 (NCH), 58.1 (NCH_2), 53.1 (NCH_2), 31.2 (CH_2), 29.0 (CH_2), 14.0 (CH_3); IR (KBr, film): $\tilde{\nu} = 1718$, 1653, 1493, 1451 cm^{-1}; MS (70 eV, EI, 60 °C): *m/z* (%): 259 (6) [M^+], 244 (2), 230 (19), 214 (12), 186 (18), 182 (7), 168 (79), 160 (44), 105 (4), 91 (100) [$C_7H_7^+$], 77 (4), 65 (8); $C_{16}H_{21}NO_2$ (259.35): calcd C 74.10, H 8.16, N 5.40; found C 74.03, H 7.95, N 5.18.

(2*S*)-*N*-Benzyl-2-(3-hydroxypropen-1-yl)pyrrolidine and **(2*S*)-*N*-benzyl-2-(3-benzyloxypropen-1-yl)pyrrolidine (6)**:

DIBALH reduction: Under argon, the aminoester **5** (9 g, 34.7 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and cooled to −78 °C. $BF_3 \cdot Et_2O$ (4.5 mL, 4.9 g, 34.7 mmol) was added and the mixture was stirred for 30 min. After warming to −10 °C, DIBALH (58 mL, 70 mmol, 1.2 M in toluene) was added dropwise while the temperature was kept ≤0 °C. After the mixture had been stirred for 4 h at 0 °C the reaction was stopped by the addition of a conc. solution of NaOH in MeOH (7 mL). Then saturated aqueous $NaHCO_3$ was added dropwise until the $Al_2O_3/B(OH)_3$ precipitated. The organic layer was decanted and the solid residue was extracted with Et_2O (3 × 50 mL). The organic layers were dried ($MgSO_4$) and after removal of the solvents the crude material was purified by column chromatography on silica gel, eluent: EtOAc/hexanes 1:2, yield: 5.1 g of a clear oil. Separation of the amines (ratio 9:1) by column chromatography. Allylamine: R_f (EtOAc) = 0.09, 4.52 g (20.8 mmol, 60%). Saturated amine: $R_f = 0.06$, 0.58 g (2.6 mmol, 7.6%). Data for the allyl alcohol: $[\alpha]_D^{20} = -59.3$ ($c = 3.8$, in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.25$ (m, 5H; CH), 5.75 (dt, ^3J(H,H) = 6.3 Hz, ^3J(H,H) = 15.2 Hz, 1H; CH), 5.6 (dd, ^3J(H,H) = 8.9 Hz, ^3J(H,H) = 15.2 Hz, 1H; CH), 4.05 (d, ^3J(H,H) = 6.3 Hz, 2H; OCH_2), 3.95 (d, ^2J(H,H) = 12.7 Hz, 1H; NCH_2), 3.15 (br s, 1H, OH), 3.1 (d, ^2J(H,H) = 12.7 Hz, 1H; NCH_2), 2.9 (dt, ^3J(H,H) = 2.5 Hz, ^3J(H,H) = 8.9 Hz, 1H; NCH), 2.75 (td, ^3J(H,H) = 9 Hz, ^2J(H,H) = 17 Hz, 1H; NCH_2), 2.1 (td, ^3J(H,H) = 9 Hz, ^2J(H,H) = 17 Hz, 1H; NCH_2), 1.9 (m, 1H; CH_2), 1.65 (m, 3H; CH_2); ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): $\delta = 139.1$, 133.7, 131.7, 129.0, 128.0, 126.7 (CH), 67.0 (OCH_2), 62.7 (NCH_2) 58.2 (NCH), 53.3 (NCH_2), 31.5 (CH_2), 21.8 (CH_2); IR (KBr, film): $\tilde{\nu} = 3370$, 1735, 1492, 1451 cm^{-1}; MS (70 eV, EI, 60 °C): *m/z* (%): 217 (15) [M^+], 200 (4), 186 (13), 160 (55), 126 (9), 92 (9), 91 (100) [$C_7H_7^+$], 65 (8); $C_{14}H_{19}NO$ (217.31): calcd C 77.38, H 8.81, N 6.45; found C 77.01, H 8.41, N 6.13.

Benzylation: Under argon, the allyl alcohol (4 g, 18.4 mmol) was dissolved in dry DMF (20 mL) and cooled to 0 °C. NaH (0.53 g, 22.1 mmol) was added and the mixture was stirred until the generation of H_2 was terminated (ca. 30 min). Then, benzyl bromide (3.9 g, 22.8 mmol) was added and the mixture was stirred at r.t. for 16 h. After quenching with saturated aqueous $NaHCO_3$ (50 mL), the aqueous layer was extracted with Et_2O (4 × 40 mL). After drying ($MgSO_4$) the solvent was evaporated and the crude material was purified by chromatography on silica gel, eluent: EtOAc/hexanes 1:4, $R_f = 0.17$. Yield: 3.96 g (12.8 mmol, 70%) benzylether **6** as a pale yellow oil. $[\alpha]_D^{20} = -40.5$ ($c = 2.6$, in $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.4$ (m, 10H; CH), 5.75 (m, 2H; CH), 4.5 (s, 2H; OCH_2), 4.03 (d, ^3J(H,H) = 6.2 Hz, 2H; OCH_2), 3.95 (d, ^2J(H,H) = 13 Hz, 1H; NCH_2), 3.1 (d, ^2J(H,H) = 13 Hz, 1H; NCH_2), 2.93 (m, 2H; NCH, NCH_2), 2.15 (brq, ^3J(H,H) = 9 Hz, ^2J(H,H) = 17 Hz, 1H; NCH_2), 1.95 (m, 1H; CH_2), 1.7 (m, 3H; CH_2); ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): $\delta = 139.2$, 138.2, 135.7, 128.7–126.6 (9 peaks, CH), 71.8 (OCH_2), 70.2 (OCH_2), 67.0 (NCH_2), 58.0 (NCH), 53.2 (NCH_2), 31.5 (CH_2), 21.9 (CH_2); IR (KBr, film): $\tilde{\nu} = 3082$, 1694, 1601, 1492, 1451 cm^{-1}; MS (70 eV, EI, 100 °C): *m/z* (%): 307 (2) [M^+], 216 (41), 200 (9), 186 (13), 173 (6), 160 (23), 134 (11), 91 (100) [$C_7H_7^+$], 70 (7); $C_{14}H_{19}NO$ (307.43): calcd C 82.05, H 8.19, N 4.56; found C 81.93, H 8.04, N 4.46.

Standard procedure for the zwitterionic Claisen rearrangement: Under argon, dry Na_2CO_3 (1.6 g, 11.6 mmol) was suspended in dry $CHCl_3$ (35 mL) and cooled to 0 °C. Aminoester **4** or **5** or *N*-allyl pyrrolidine **6** (5 mmol) and acid chloride (6 mmol) were added subsequently by means of a syringe. After about 30 min of stirring at 0 °C, a solution of Me_3Al (0.25 mL, 0.51 mmol, 2 M in toluene) was added from a syringe. The mixture was stirred at 0 °C. After 24 h, a second volume of Me_3Al was injected. After 2–5 d, the reaction was quenched dropwise with saturated aqueous $NaHCO_3$ (5–10 mL) at 0 °C until the Al_2O_3/Na_2CO_3 precipitated. Then the organic layer was decanted, the solid residue was extracted with CH_2Cl_2 (5 × 20 mL) and the combined organic layers were dried ($MgSO_4$). The solvent was removed and the crude mixture of diastereomeric amides and von Braun type products was purified by column chromatography. If necessary, diastereomers were separated by HPLC or column chromatography on silica gel. If the crude product contained more than 10% allyl amine (as occurred in several experiments), the mixture was subjected to these reaction conditions for a second cycle.

(4*S*)-Ethoxycarbonyl-1-methyl-2(6*H*)-azoninone (12a): Reaction with aminoester **4** (2.2 g, 12 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:1, $R_f = 0.11$. Yield: 1.89 g (8.4 mmol, 70%). Analysis: $C_{12}H_{19}NO_3$ (225.28): calcd C 63.98, H 8.49, N 6.22; found C 64.09, H 8.57, N 6.10. For spectral data see ref. [4].

(3*S*,4*R*)-1,3-Dimethyl-4-ethoxycarbonyl-2(6*H*)-azoninone (12b): Reaction with aminoester **4** (0.52 g, 2.84 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:1, $R_f = 0.22$. Yield: 523 mg (2.18 mmol, 77%). $[\alpha]_D^{20} = 47.7$ ($c = 8.1$, in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.65$ (dd, ^3J(H,H) = 10 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 5.15 (ddd, ^3J(H,H) = 5 Hz, ^3J(H,H) = 10 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 4.05 (m, 2H; OCH_2), 3.6 (dd, ^3J(H,H) = 11 Hz, ^3J(H,H) = 14 Hz, 1H; CH), 2.95 (m, 1H; CH_2), 2.9 (m, 1H; CH), 2.8 (m, 1H; CH), 2.6 (m, 1H; CH_3), 2.25 (m, 1H; CH_2), 2.0 (m, 1H; CH_2), 1.8 (m, 1H; CH_2), 1.7 (m, 1H; CH_2), 1.2 (t, ^3J(H,H) = 8 Hz, 3H; CH_3), 1.0 (d, 3H; CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$, 25 °C): $\delta = 174$ (C=O), 173 (C=O), 131.3, 130.4 (C=CH), 60.4 (CH_2), 51.9 (CH), 51.9 (CH), 47.6 (CH_2), 43.25 (NCH_3), 33.9 (CH), 30.9 (CH_2), 26.6 (CH_2), 15.2 (CH_3), 13.6 (CH_3); IR (KBr): $\tilde{\nu} = 1733$, 1630, 1439, 1397 cm^{-1}; MS (70 eV, EI, 40 °C): *m/z* (%): 239 (21) [M^+], 170 (15), 166 (100), 154 (22), 143 (17), 97 (77), 84 (50); $C_{13}H_{21}NO_3$ (239.31): calcd C 65.25, H 8.84, N 5.85; found C 65.31, H 8.79, N 5.78.

(3*S*,4*R*)-3-Ethenyl 4-ethoxycarbonyl-1-methyl-2(6*H*)-azoninone (12c): Reaction with aminoester **4** (0.5 g, 3.22 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:1, $R_f = 0.3$. Yield: 647 mg (2.58 mmol, 80%), m.p.: 81–83 °C. $[\alpha]_D^{20} = -12.4$ ($c = 3.5$, in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 6.0$ (m, 1H; CH), 5.7 (dd, ^3J(H,H) = 9 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 5.25 (ddd, ^3J(H,H) = 5 Hz, ^3J(H,H) = 9 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 4.9 (m, 2H; CH_2), 3.95 (m, 2H; OCH_2), 3.6 (dd, ^3J(H,H) = 15 Hz, ^3J(H,H) = 9 Hz, 1H; CH), 3.2 (m, 2H; CH_2), 3.0 (dd, ^3J(H,H) = 15 Hz, ^3J(H,H) = 5 Hz, 1H; CH), 2.7

(s, 3H; CH_3), 3.2 (m, 1H; CH_2), 2.3 (m, 1H; CH_2), 2.0 (m, 1H; CH_2), 1.8 (m, 1H; CH_2), 1.7 (m, 1H; CH_2), 1.1 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$, 25 °C): $\delta = 171.8$ (2 × C=O), 134.9, 130.7, 130.4 (3 × =CH), 117.0 (=CH_2), 60.2 (CH_2), 54.5 (NCH_3), 51.9 (CH), 47.6 (CH_2), 34.0 (CH), 31.0 (CH_2), 26.6 (CH_2), 13.6 (CH_3); IR (KBr): $\tilde{\nu} = 1726$, 1618, 1439, 1401 cm^{-1}; MS (70 eV, EI, 80 °C): *m/z* (%): 251 (19) [M^+], 223 (6), 206 (16), 178 (61), 154 (100), 138 (13), 110 (26), 97 (78), 84 (61); $C_{14}H_{21}NO_3$ (251.32): calcd C 66.91, H 8.42, N 5.57; found C 66.87, H 8.48, N 5.50.

(3*R*,4*R*)-4-Ethoxycarbonyl-1-methyl-3-phenyl-2(6*H*)-azoninone (12d) and (3*S*,4*R*)-4-ethoxycarbonyl-1-methyl-3-phenyl-2(6*H*)-azoninone (13d): Reaction with aminoester **4** (0.6 g, 3.3 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:1, $R_f = 0.39$. Yield: 316 mg (1.05 mmol, 32%; 324 mg, 1.77 mmol, 54% of **4** were recycled). Separation of the diastereomeric lactams **12d** and **13d** (ratio 45:55) by preparative HPLC: eluent, 4% 2-propanol in hexane. Minor diastereomer lactam **12d**: retention time, 4.12 min, 142 mg (0.47 mmol, 14.2%), m.p.: 127–128 °C. $[\alpha]_D^{20} = 87.8$ ($c = 4.6$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.4$–7.1 (m, 5H; CH), 5.8 (dd, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 16$ Hz, 1H; CH), 5.5 (ddd, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 16$ Hz, 1H; CH), 4.1 (d, $^3J(H,H) = 11$ Hz, 1H; CH), 3.9 (m, 1H; CH_2), 3.8 (q, $^3J(H,H) = 8$ Hz, 2H; CH_2), 3.7 (dd, $^3J(H,H) = 11$ Hz, 1H; CH), 3.2 (m, 1H; CH_2), 2.8 (s, 3H; CH_3), 2.5 (m, 1H; CH_2), 2.1 (m, 1H; CH_2), 2.0 (m, 1H; CH_2), 1.8 (m, 1H; CH_2), 0.9 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$, 25 °C): $\delta = 172$ (2 × C=O), 173.1 (s, C–Ar), 131.3, 131.0, 129.9, 127.6, 127.2 (C=C and C–Ar), 60.4 (OCH_2), 54.8 (CH_2), 52.2 (CH), 48.3 (CH), 34.4 (NCH_3), 31.2 (CH_2), 26.8 (CH_2), 13.6 (CH_3); IR (KBr): $\tilde{\nu} = 1735$, 1622, 1432, 1396 cm^{-1}; MS (70 eV, EI, 120 °C): *m/z* (%): 301 (29) [M^+], 228 (35), 183 (48), 154 (100), 118 (15), 110 (19), 97 (62); $C_{18}H_{23}NO_3$ (301.38): calcd C 71.73, H 7.69, N 4.65; found C 71.69, H 7.61, N 4.60. Major diastereomer lactam **13d**: retention time, 4.36 min, 174 mg (0.58 mmol, 17.6%), m.p.: 132–134 °C. $[\alpha]_D^{20} = -88.3$ ($c = 3.3$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.2$ (m, 5H; CH), 6.1 (dd, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH) 5.5 (ddd, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH), 5.0 (d, $^3J(H,H) = 5$ Hz, 1H; CH), 4.2 (q, $^3J(H,H) = 8$ Hz, 2H; CH_2), 3.7 (dd, $^3J(H,H) = 12$ Hz, $^3J(H,H) = 2$ Hz, 1H; CH_2), 3.0 (m, 1H; CH_2), 2.9 (s, 3H; NCH_3), 2.5 (m, 1H; CH_2), 2.0 (m, 2H; CH_2), 1.6 (m, 1H; CH_2), 1.5 (m, 1H; CH_2), 1.2 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 173.5$ (C=O), 172.5 (C=O), 136.3, 134.1, 128.8, 128.3, 127.0, 126.5 (C=C and C–Ar), 61.3 (CH), 59.2 (OCH_2), 48.6 (CH_2), 48.1 (CH), 35.1 (NCH_3), 31.6 (CH_2), 26.2 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1722$, 1627, 1435, 1401 cm^{-1}; MS (70 eV, EI, 100 °C): *m/z* (%): 301 (12) [M^+], 228 (15), 183 (36), 154 (100), 118 (12), 110 (15), 97 (27), 84 (41); $C_{18}H_{23}NO_3$ (301.38): calcd C 71.73, H 7.69, N 4.65; found C 71.70, H 7.71, N 4.72.

(3*S*,4*S*)-3-Chloro-4-ethoxycarbonyl-1-methyl-2(6*H*)-azoninone (12e): Reaction with aminoester **4** (0.5 g, 2.73 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:1, $R_f = 0.2$. Yield: 510 mg (1.96 mmol, 72%), m.p.: 134–136 °C. $[\alpha]_D^{20} = 3.9$ ($c = 10.1$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 5.6$ (dd, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 16$ Hz, 1H; =CH) 5.4 (ddd, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 16$ Hz, 1H; =CH), 4.6 (d, $^3J(H,H) = 12$ Hz 1H; CH), 4.2 (m, $^3J(H,H) = 8$ Hz, 2H; CH_2), 3.55 (m, 1H; NCH_2), 3.45 (dd, $^3J(H,H) = 11$ Hz, $^3J(H,H) = 12$ Hz, 1H; CH), 3.1 (m, 1H; NCH_2), 2.8 (s, 3H; NCH_3), 2.35 (m, 1H; CH_2), 2.05 (m, 1H; CH_2), 1.8 (m, 2H; CH_2), 1.2 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 170.6$ (C=O), 167.3 (C=O), 134.5, 127.5 (C=C), 61.0 (OCH_2), 57.3 (CH), 53.4 (CH), 48.0 (CH_2), 34.5 (NCH_3), 31.0 (CH_2), 25.1 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1731$, 1640, 1439, 1402 cm^{-1}; MS (70 eV, EI, 100 °C): *m/z* (%): 259 (18) [M^+], 224 (58), 186 (100), 178 (19), 97 (70), 84 (56); $C_{12}H_{18}ClNO_3$ (259.73): calcd C 55.49, H 6.99, N 5.39; found C 55.54, H 7.04, N 5.31.

(3*S*,4*R*)-3-Benzyloxy-4-ethoxycarbonyl-1-methyl-2(6*H*)-azoninone (12f) and (3*R*,4*R*)-3-Benzyloxy-4-ethoxycarbonyl-1-methyl-2(6*H*)-azoninone (13f): Reaction with aminoester **4** (0.5 g, 2.73 mmol) following the standard procedure. Chromatography: EtOAc, $R_f = 0.37$. Yield: 615 mg (1.86 mmol, 68%). Separation of the diastereomeric lactams **12f** and **13f** (ratio 4:1) by preparative HPLC: eluent, 12% 2-propanol in hexane. Major diastereomer lactam **12f**: retention time, 3.11 min, 492 mg (1.58 mmol, 57.9%). $[\alpha]_D^{20} = -35.4$ ($c = 11.8$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.3$ (m, 5H; CH), 5.45 (dd, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH), 5.25 (ddd, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH), 4.4 (d, $^2J(H,H) = 12$ Hz, 1H; OCH_2), 4.1 (d, $^3J(H,H) = 12$ Hz, 1H; OCH_2) 4.05 (d, $^2J(H,H) = 12$ Hz, 1H; CH_2O), 4.0 (m, 2H; OCH_2), 3.3 (m, 2H; CH_2), 2.85 (dd, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH), 2.7 (s, 1H; NCH_3), 2.25 (m, 1H; CH_2), 1.9 (m, 1H; CH_2), 1.6 (m, 2H; CH_2), 1.1 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 171.3$ (C=O), 168.9 (C=O), 136.6, 132.9, 127.6, 127.2, 127.3, 126.5 (C=C), 77.6 (OCH), 71.4 (OCH_2), 60.3 (OCH_2), 51.7 (CH), 46.7 (CH_2), 33.4 (NCH_3), 30.8 (CH_2), 24.9 (CH_2), 13.7 (CH_3); IR (KBr): $\tilde{\nu} = 1736$, 1640, 1440, 1402 cm^{-1}; MS (70 eV, EI, 120 °C): *m/z* (%): 331 (4) [M^+], 240 (12), 225 (21), 194 (25), 166 (24), 97 (21), 91 (100), 84 (22); $C_{19}H_{25}NO_4$ (331.41): calcd C 68.86, H 7.60, N 4.23; found C 68.93, H 7.71, N 4.32. Minor diastereomer lactam **13f**: retention time, 2.61 min, 123 mg (0.37 mmol, 13.6%). $[\alpha]_D^{20} = -21.9$ ($c = 7.4$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.3$ (m, 5H; CH), 5.9 (dd, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH), 5.4 (ddd, $^3J(H,H) = 5$ Hz, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH), 4.85 (d, $^3J(H,H) = 2$ Hz, 1H; CH), 4.55 (d, $^2J(H,H) = 11$ Hz, 1H; OCH_2), 4.45 (m, 1H; NCH_2), 4.1 (m, 2H; CH_2), 3.9 (d, $^2J(H,H) = 11$ Hz, 1H; OCH_2), 3.35 (dd, $^3J(H,H) = 1$ Hz, $^3J(H,H) = 10$ Hz, 1H; CH), 2.85 (m, 1H; NCH_2), 2.75 (s, 3H; NCH_3), 2.35 (m, 1H; CH_2), 2.1 (m, 2H; CH_2), 1.7 (m, 2H; CH_2), 1.2 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 182.2$ (C=O), 182.1 (C=O), 136.7, 133.0, 128.2, 127.9, 127.8, 127.5, 126.5 (C=C), 88.6 (OCH), 72.6 (OCH_2), 60.9 (OCH_2), 50.2 (CH), 46.8 (CH_2), 35.1 (NCH_3), 31.8 (CH_2), 27.0 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1737$, 1623, 1454, 1443, 1398 cm^{-1}; MS (70 eV, EI, 100 °C): *m/z* (%): 331 (8) [M^+], 240 (10), 225 (9), 194 (20), 166 (16), 107 (14), 97 (14), 91 (100), 84 (31); $C_{19}H_{25}NO_4$ (331.41): calcd C 68.86, H 7.60, N 4.23; found C 68.79, H 7.50, N 4.17.

(3*S*,4*R*)-4-Ethoxycarbonyl-1-methyl-3-phthalimido-2(6*H*)-azoninone (12g) and (3*R*,4*R*)-4-ethoxycarbonyl-1-methyl-3-phthalimido-2(6*H*)-azoninone (13g): Reaction with aminoester **4** (0.6 g, 3.3 mmol) following the standard procedure. Chromatography: EtOAc, $R_f = 0.39$. Yield: 424 mg (1.15 mmol, 35%), about 300 mg (50%) of **4** were recycled. Separation of the diastereomeric lactams **12g** and **13g** (ratio 15:1) by preparative HPLC: eluent, 15% 2-propanol in hexane. Major diastereomer lactam **12g**: retention time, 3.48 min, 398 mg (1.07 mmol, 32.4%), m.p.: 143–145 °C. $[\alpha]_D^{20} = 48.4$ ($c = 8.4$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.6$ (m, 4H; CH), 5.5 (m, 2H; HC=CH), 5.1 (m, 1H; CH), 4.4 (d, 1H), 4.2 (m, 4H; OCH_2), 3.95 (m, 2H; CH_2), 3.6 (m, 1H), 3.1 (m, 1H), 2.6 (s, 3H; NCH_3), 2.3 (m, 1H; CH_2), 2.0 (m, 1H; CH_2), 1.6 (m, 2H; CH_2), 0.9 (t, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 170.8$, 169.2, 167.4, 167.0 (C=O), 134.8, 133.5, 131.2, 127.7, 122.6 (CH), 60.3 (OCH), 54.2 (CH), 47.7 (NCH_3), 47.6 (CH_2), 33.6 (CH), 30.6 (CH_2), 25.1 (CH_2), 13.4 (CH_3); IR (KBr): $\tilde{\nu} = 1774$, 1732, 1716, 1632, 1402 cm^{-1}; MS (70 eV, EI, 150 °C): *m/z* (%): 370 (70) [M^+], 325 (24), 297 (89), 269 (22), 230 (17), 183 (19), 160 (30), 154 (86), 130 (24), 97 (100), 84 (91); $C_{20}H_{22}N_2O_5$ (370.40): calcd C 64.85, H 5.99, N 7.56; found C 64.76, H 6.08, N 7.45. Minor diastereomer lactam **13g**: retention time 2.58 min, 2.25 min, 26 mg (0.07 mmol, 2.1%), this material was contaminated with some von Braun type products and could not be isolated as a pure compound.

(3*S*)-1-Benzyl-4-ethoxycarbonyl-2(6*H*)-azoninone (14h): Reaction with aminoester **5** (2.3 g, 8.87 mmol) following the standard procedure, reaction time 5 weeks, 1 equiv Me_3Al. Chromatography: EtOAc/hexane 1:2, R_f (EtOAc) = 0.3. Yield: 1.6 g (5.32 mmol, 60%). $[\alpha]_D^{20} = 151.6$ ($c = 2.2$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.3$ (m, 5H; CH), 5.7 (dd, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 16$ Hz, 1H; CH), 5.5 (m, 1H; CH), 5.35 (d, $^2J(H,H) = 15$ Hz, 1H; CH_2), 4.2 (m, 2H; OCH_2), 3.9 (d, $^2J(H,H) = 15$ Hz, 1H; CH_2), 3.45 (m, 2H), 3.05 (m, 1H; CH_2), 2.75 (m, 2H; CH_2), 2.4 (m, 1H; CH_2), 2.05 (m, 2H; CH_2), 1.2 (m, 1H; CH_2), 1.25 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 172.9$ (C=O), 171.5 (C=O), 137.3, 132.1, 131.4, 128.5, 128.1, 127.2 (C=C), 61.0 (OCH_2), 47.1 (CH), 46.3 (CH), 45.5 (CH_2), 41.0 (CH_2), 31.5 (CH_2), 27.5 (CH_2), 14.1 (CH_3); IR (KBr): $\tilde{\nu} = 1733$, 1624, 1495, 1451, 1416 cm^{-1}; MS (70 eV, EI, 150 °C): *m/z* (%): 301 (12) [M^+], 228 (15), 210 (13), 136 (15), 91 (100); $C_{18}H_{23}NO_3$ (301.38): calcd C 71.73, H 7.69, N 4.65; found C 71.64, H 7.58, N 4.71.

(3*S*,4*S*)-1-Benzyl-3-chloro-4-ethoxycarbonyl-2(6*H*)-azoninone (14i) and (3*R*,4*S*)-1-benzyl-3-chloro-4-ethoxycarbonyl-2(6*H*)-azoninone (15i): Reaction with aminoester **5** (0.7 g, 2.7 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:4, $R_f = 0.11$. Yield: 200 mg (0.59 mmol, 22%). Separation of the diastereomeric lactams **14i** and **15i** (ratio 9:1) by preparative HPLC: eluent, 15% EtOAc in hexane. Major diastereomer lactam **14i**: retention time 2.54 min, 180 mg (0.54 mmol, 19.9%). $[\alpha]_D^{20} = 66.3$ ($c = 6.1$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.2$ (m, 5H; CH), 5.6 (m, 1H; CH), 5.5 (m, 1H; CH), 5.3 (d, $^2J(H,H) = 15$ Hz, 1H; CH_2Ph), 4.7 (d, $^3J(H,H) = 11$ Hz, 1H; CH), 4.2 (m, 2H; CH_2), 3.8 (d, $^2J(H,H) = 15$ Hz, 1H; CH_2Ph), 3.55 (dd, 1H; CH), 3.35 (dd, $^3J(H,H) = 15$ Hz, $^3J(H,H) = 10$ Hz, 1H; NCH_2), 3.0 (d, $^3J(H,H) = 15$ Hz, $^3J(H,H) = 5$ Hz, 1H; NCH_2), 2.4 (m, 1H; CH_2), 2.05 (m, 1H; CH_2), 2.05 (m, 1H; CH_2), 1.85 (m, 1H; CH_2), 1.6 (m, 1H; CH_2), 1.2 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 170.6$ (C=O), 168.3 (C=O), 136.4, 135.0, 128.6, 128.2, 128.0, 127.5, 126.5 (C=C), 61.3 (OCH_2), 57.9 (CH), 53.4 (CH), 47.9 (CH_2), 44.7 (NCH_2Ph), 31.2 (CH_2), 25.4 (CH_2), 14.1 (CH_3); IR (KBr): $\tilde{\nu} = 1737$, 1645, 1419 cm^{-1}; MS (70 eV, EI, 150 °C): *m/z* (%): 335 (8) [M^+], 300 (7), 262 (7), 244 (10), 136 (18), 91 (100); $C_{18}H_{22}ClNO_3$ (335.83): calcd C 64.38, H 6.60, N 4.17; found C 64.51, H 6.69, N 4.24. Minor diastereomer lactam **15i**: retention time 3.03 min, 20 mg (0.06 mmol, 2.2%). $[\alpha]_D^{20} = 1.9$ ($c = 4.2$, in $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.3$ (m, 5H; CH), 6.05 (dd, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 15$ Hz, 1H; CH), 5.4 (d, $^3J(H,H) = 2$ Hz, 1H; CH), 5.25 (d, $^2J(H,H) = 15$ Hz, 1H; CH_2Ph), 4.3 (m, 3H; CH_2), 3.9 (d, $^2J(H,H) = 15$ Hz, 1H; CH_2Ph), 3.75 (dd, $^3J(H,H) = 10$ Hz, $^3J(H,H) = 2$ Hz, 1H; CH), 3.1 (m, 1H; CH), 2.5 (m, 1H; CH_2), 2.2 (m, 1H; CH_2), 1.8 (m, 2H; CH_2), 1.2 (t, $^3J(H,H) = 8$ Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 169.5$ (C=O), 168.3 (C=O), 136.6, 135.5, 128.6, 127.4, 127.3, 126.2 (C=C), 65.7 (OCH_2), 61.6 (CH), 50.2 (CH), 49.3 (CH_2), 45.9 (NCH_2Ph), 32.2 (CH_2), 27.2 (CH_2), 14.1 (CH_3); IR (KBr): $\tilde{\nu} = 1738$, 1621, 1495, 1439, 1420 cm^{-1}; MS (70 eV, EI, 120 °C): *m/z* (%): 335 (4) [M^+], 300 (3), 262 (3), 244 (4), 136 (10), 91 (100); $C_{18}H_{22}ClNO_3$ (335.83): calcd C 64.38, H 6.60, N 4.17; found C 64.31, H 6.53, N 4.11.

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(3*S*,4*R*)-1-Benzyl-3-benzyloxy-4-ethoxycarbonyl-2(6*H*)-azoninone (14j) and (3*R*,4*R*)-1-benzyl-3-benzyloxy-4-ethoxycarbonyl-2(6*H*)-azoninone (15j): Reaction with aminoester **5** (0.75 g, 2.89 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:4, $R_f = 0.13$. Yield: 354 mg (0.87 mmol, 30%). Separation of the diastereomeric lactams **14j** and **15j** (ratio 4:1) by preparative HPLC: eluent, 2% 2-propanol in hexane. Major diastereomer lactam **14j**: retention time 2.79 min, 283 mg (0.69 mmol, 24%). $[\alpha]_D^{20} = -4.4$ ($c = 18.5$, in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.2$ (m, 10H; CH), 5.6 (dd, ^3J(H,H) = 10 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 5.55 (m, 1H; CH), 5.45 (m, 1H; OCH_2), 4.6 (m, 1H; NCH_2), 4.3 (m, 1H; CH_2), 4.25 (m, 1H; CH_2), 4.2 (m, 2H; OCH_2), 3.85 (m, 1H; CH_2), 3.45 (m, 1H; CH), 3.25 (m, 1H; CH_2), 2.95 (m, 1H; CH_2), 2.35 (m, 1H; CH_2), 2.0 (m, 1H; CH_2), 1.85 (m, 1H; CH_2), 1.6 (m, 1H; CH_2), 1.1 (t, ^3J(H,H) = 8 Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 171.5$ (C=O), 169.6 (C=O), 137.0, 136.8, 133.4, 128.5, 128.3, 128.2, 127.9, 127.8, 127.4, 127.0 (C=C), 78.1 (OCH), 71.3 (OCH_2), 60.6 (OCH_2), 51.8 (CH), 47.1 (NCH_2), 43.7 (NCH_2), 31.0 (CH_2), 25.2 (CH_2), 13.9 (CH_3); IR (KBr): $\tilde{\nu} = 1734$, 1640, 1496, 1454 cm^{-1}; MS (70 eV, EI, 150 °C): *m/z* (%): 407 (2) [M^+], 316 (4), 301 (6), 228 (5), 173 (2), 160 (7), 136 (4), 91 (100); $C_{25}H_{29}NO_4$ (407.51): calcd C 73.69, H 7.17, N 3.44; found C 73.77, H 7.21, N 3.51. Minor diastereomer lactam **15j**: retention time, 2.51 min, 71 mg (0.17 mmol, 6%). $[\alpha]_D^{20} = 15.9$ ($c = 7.0$, in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.2$ (m, 10H; CH), 5.9 (dd, ^3J(H,H) = 10 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 5.45 (ddd, ^3J(H,H) = 5 Hz, ^3J(H,H) = 10 Hz, ^3J(H,H) = 15 Hz, 1H; CH), 5.25 (d, 1H, ^2J(H,H) = 15 Hz, 1H; CH_2), 4.9 (d, ^3J(H,H) = 2 Hz, 1H; CH), 4.4 (m, 1H; CH_2), 4.3 (m, 2H; CH_2), 4.05 (m, 2H; CH_2), 3.75 (d, ^4J(H,H) = 15 Hz, 1H; CH_2), 2.9 (m, 1H; CH_2), 2.3 (m, 1H; CH_2), 2.05 (m, 1H; CH_2), 1.8 (m, 2H; CH_2), 1.6 (m, 2H; CH_2), 1.1 (t, ^3J(H,H) = 8 Hz, 3H; CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 171.5$ (C=O), 170.9 (C=O), 137.4, 136.7, 133.4, 128.5, 128.3, 128.26, 127.8, 127.7, 127.3 (C=C), 88.6 (OCH), 72.5 (OCH_2), 60.9 (OCH_2), 50.1 (CH), 48.5 (CH_2), 43.4 (CH_2), 31.9 (CH_2), 27.2 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1737$, 1622, 1496, 1455, 1423 cm^{-1}; MS (70 eV, EI, 150 °C): *m/z* (%): 407 (5) [M^+], 316 (8), 301 (4), 228 (4), 173 (4), 160 (8), 136 (4), 91 (100); $C_{25}H_{29}NO_4$ (407.51): calcd C 73.69, H 7.17, N 3.44; found C 73.59, H 7.07, N 3.56.

(3*S*,4*S*)-1-Benzyl-4-benzyloxymethyl-3-chloro-2(6*H*)-azoninone (16k) and (3*R*,4*S*)-1-benzyl-4-benzyloxymethyl-3-chloro-2(6*H*)-azoninone (17k): Reaction with allyl amine **6** (1.75 g, 5.69 mmol) following the standard procedure. Chromatography: EtOAc/hexane 1:4, $R_f = 0.17$. Yield: 240 mg (0.63 mmol, 11%). Separation of the diastereomeric lactams **16k** and **17k** (ratio 6.5:1) by preparative HPLC: eluent, 2% 2-propanol in hexane. Major diastereomer lactam **16k**: retention time 1.85 min, 208 mg (0.54 mmol, 9.5%). $[\alpha]_D^{20} = 58.0$ ($c = 2.6$, in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.3$ (m, 10H; CH), 5.7 (dd, ^3J(H,H) = 11 Hz, ^3J(H,H) = 16 Hz, 1H; CH), 5.55 (ddd, ^3J(H,H) = 5 Hz, ^3J(H,H) = 11 Hz, ^3J(H,H) = 16 Hz, 1H; CH), 5.35 (d, ^2J(H,H) = 16 Hz, 1H; NCH_2), 4.7 (d, ^3J(H,H) = 11 Hz, 1H; CHCl), 4.55 (s, 2H; OCH_2), 3.9 (d, ^2J(H,H) = 16 Hz, 1H; NCH_2), 3.7 (m, 1H; OCH_2), 3.4 (m, 1H; CH_2), 3.0 (m, 1H; CH_2), 2.35 (m, 1H; CH), 2.4 (m, 1H; CH_2), 2.1 (m, 1H; CH_2), 1.9 (m, 1H; CH_2), 1.6 (m, 1H; CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 170.3$ (C=O), 138.1, 136.1, 133.5, 130.2, 128.4, 128.2, 128.0, 127.5, 127.4, 127.2 (C=C), 73.3 (OCH_2), 68.9 (CH_2), 58.2 (CH), 47.5 (CH_2), 46.0 (CH), 44.6 (CH_2), 31.2 (CH_2), 25.1 (CH_2); IR (KBr): $\tilde{\nu} = 3029$, 1643, 1496, 1495, 1453, 1419 cm^{-1}; MS (70 eV, EI, 150 °C): *m/z* (%): 383 (1) [M^+], 292 (13), 242 (3), 186 (7), 160 (5), 136 (10), 91 (100); $C_{23}H_{26}NO_2Cl$ (383.92): calcd C 71.96, H 6.83, N 3.65; found C 72.07, H 6.96, N 3.77. Minor diastereomer lactam **17k**: retention time 1.34 min, 32 mg (0.08 mmol, 1.5%). $[\alpha]_D^{20} = 5.5$ ($c = 3.5$, in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.3$ (m, 10H; CH), 5.7 (m, 1H; CH), 5.65 (ddd, ^3J(H,H) = 4 Hz, ^3J(H,H) = 8 Hz, ^3J(H,H) = 14 Hz, 1H; CH), 5.55 (dd, ^3J(H,H) = 10 Hz, ^3J(H,H) = 14 Hz 1H; CH), 5.25 (d, ^2J(H,H) = 16 Hz, 1H; NCH_2), 5.2 (d, ^3J(H,H) = 3 Hz, 1H; CHCl), 4.55 (m, 2H; OCH_2), 4.3 (m, 1H; CH_2), 3.9 (d, ^2J(H,H) = 16 Hz, 1H; NCH_2), 3.7 (m, 2H; OCH_2), 3.15 (m, 1H; CH), 3.1 (m, 1H; CH_2), 2.45 (m, 1H; CH_2), 2.05 (m, 1H; CH_2), 1.75 (m, 2H; CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$, 25 °C): $\delta = 169.4$ (C=O), 168.3 (C=O), 137.9, 136.9, 135.0, 128.8, 128.5, 128.2, 127.5, 127.3, 127.0 (C=C), 72.9 (OCH_2), 68.6 (CH_2), 66.0 (CH), 49.1 (CH_2), 45.8 (CH_2), 44.8 (NCH_2), 32.3 (CH_2), 27.4 (CH_2); IR (KBr): $\tilde{\nu} = 3029$, 1720, 1618, 1496, 1495, 1453, 1419 cm^{-1}; MS (70 eV, EI, 150 °C): *m/z* (%): 383 (1) [M^+], 292 (14), 242 (2), 186 (12), 160 (4), 136 (8), 105 (4), 91 (100); $C_{23}H_{26}NO_2Cl$ (383.92): calcd C 71.96, H 6.83, N 3.65; found C 71.88, H 6.78, N 3.59.

(7*R*,8*R*,8a*S*)-7-Ethoxycarbonyl-4-methyl-8-phenylselenyl-5(8*H*)-indolizidinonium chloride (19): Under Ar, lactam **12a** (1.4 g, 6.2 mmol) was dissolved in dry MeCN (15 mL). PhSeCl (1.3 g, 6.8 mmol) was added and the mixture was heated to 60 °C. After the mixture had been stirred for 16 h, the solvent was evaporated and the crude solid material was purified by chromatography on silica gel, eluent: EtOAc/hexane 1:1, $R_f = 0.2$. Yield: 1.3 g (3.11 mmol, 50%) indolizidinium chloride **19** as a white crystalline material, m.p.: 135 °C. $[\alpha]_D^{20} = 39.0$ ($c = 2.6$, in $CHCl_3$); ^{1}H NMR (500.1 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.65$ (m, 2H; CH), 7.35 (m, 3H; CH), 4.2 (m, 2H; OCH_2), 3.45 (m, 2H; NCH_2), 3.45 (m, 1H; NCH), 3.4 (m, 1H; CHSe), 2.95 (m, 1H; CH), 2.85 (s, 3H; NCH_3), 2.65 (m, 2H; CH_2), 2.1 (m, 1H; CH_2), 1.8 (m, 1H; CH_2), 1.6 (m, 2H; CH_2), 1.3 (m, 3H; CH_3); ^{13}C NMR (67.93 MHz, $CDCl_3$, 25 °C): $\delta = 172.4$ (C=O), 168.0 (C=O), 135.9, 129.3, 128.8 (CH), 127.0 (CSe), 62.8 (CH), 61.3 (CH_2), 44.2 (CH_2), 43.6 (CH), 41.7 (CH), 34.2 (CH_2), 32.9 (CH), 28.7 (CH_2), 26.6 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1732$, 1650, 1437, 1399 cm^{-1}. MS (CH 5 DF, FAB pos, Xenon, DMSO/*m*NO_2-benzil-OH): *m/z* (%): 418 (64) [$C_{18}H_{25}NO_3SeCl^+$], 416 (35) [M^+], 340 (18), 262 (21), 260 (56), 215 (19), 214 (31), 210 (26), 188 (43), 186 (49), 157 (30), 154 (28), 136 (66), 120 (28), 110 (78), 107 (27), 99 (21), 91 (79) [$C_7H_7^+$], 89 (33), 81 (47), 55 (100); $C_{18}H_{24}ClNO_3Se$ (416.81): calcd C 51.87, H 5.8, N 3.36; found C 51.7, H 6.02, N 3.48.

(1′*S*,4*R*,5*S*)-4-Ethoxycarbonyl-5-(2-methyl-2-pyrrolidine)-2(3*H*)-furanone (20): Under Ar, lactam **12a** (0.2 g, 0.89 mmol) was dissolved in dry MeCN (5 mL). I_2 (224 mg, 0.88 mmol) was added and the mixture was stirred at 50 °C for 2 d. Aqueous saturated $Na_2S_2O_3$ was then added until the colour of I_2 disappeared. Aqueous saturated $NaHCO_3$ (5 mL) was added and the mixture was extracted with EtOAC (4 × 5 mL). The organic layers were dried ($MgSO_4$) and the crude material was purified by chromatography on silica gel, eluent: EtOAc/MeOH 20:1, $R_f = 0.06$. Yield: 107 mg (0.44 mmol, 50%) lactone **20** as a clear oil. $[\alpha]_D^{20} = -86.7$ ($c = 0.7$, in $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 4.7$ (dd, ^3J(H,H) = 4 Hz, ^3J(H,H) = 8 Hz, 1H; CH), 4.2 (q, ^3J(H,H) = 8 Hz, 3H; CH_3), 3.45 (m, 1H; CH), 3.05 (m, 1H; CH_2), 2.8 (m, 1H; CH_2), 2.7 (m, 1H; CH_2), 2.65 (m, 1H; CH), 2.35 (s, 1H; NCH_3), 2.25 (m, 1H; CH_2), 1.75 (m, 4H; CH_2), 1.3 (t, ^3J(H,H) = 8 Hz, 3H; CH_3); ^{13}C NMR (67.93 MHz, $CDCl_3$, 25 °C): $\delta = 175.0$ (C=O), 170.8 (C=O), 81.6 (CH), 65.0 (CH), 61.3 (CH_2), 57.1 (CH_2), 42.5 (CH), 41.9 (NCH_3), 32.8 (CH_2), 25.9 (CH_2), 23.3 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1786$, 1732, 1457 cm^{-1}; MS (70 eV, EI, 100 °C): *m/z* (%): 241 (3) [M^+], 196 (31), 116 (2), 110 (4), 94 (4), 83 (100); $C_{12}H_{19}NO_4$ (241.29): calcd C 59.73, H 7.94, N 5.80, found C 60.08, H 8.05, N 5.78.

(7*R*,8*R*,8a*S*)-7-Ethoxycarbonyl-8-phenylselenyl-5(8*H*)-indolizidinone (21): Under Ar, the indolizidinium chloride **19** (240 mg, 0.58 mmol) was dissolved in dry 1,2-dichloroethane (10 mL). Bu_4NCl (160 mg, 0.58 mmol) was added, and the mixure was stirred at 80 °C for 3 d. Then the reaction was quenched with saturated aqueous $NaHCO_3$ (15 mL) and the aqueous layer extracted with $CHCl_3$ (3 × 10 mL). After drying ($MgSO_4$) the solvent was removed and the crude material was purified by chromatography on silica gel, eluent: EtOAc, $R_f = 0.44$. Yield: 93 mg (0.25 mmol, 44%) indolizidinone **21** as a pale yellow oil. $[\alpha]_D^{20} = -27.9$ ($c = 2.6$, in $CHCl_3$); ^{1}H NMR (270.1 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.6$ (m, 2H; CH), 7.3 (m, 3H; CH), 4.3 (m, 2H; OCH_2), 4.1 (m, 1H; CH_2), 3.8 (dd, ^3J(H,H) = 6 Hz, ^3J(H,H) = 12 Hz, 1H; CHSe), 3.0 (m, 1H; CHN), 2.7 (m, 2H; CH_2), 2.6 (m, 1H; CH), 2.55 (m, 1H; NCH_2), 1.7 (m, 1H; CH_2), 1.6 (m, 1H; CH_2), 1.5 (m, 2H; CH_2), 1.3 (m, 3H; CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$, 25 °C): $\delta = 173.4$ (C=O), 170.3 (C=O), 136.4, 129.1, 128.5 (CH), 63.4 (CH), 61.5 (OCH_2), 46.2 (CH), 43.2 (CH), 39.6 (NCH_2), 34.5 (CH_2), 32.8 (CH_2), 25.8 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1732$, 1694, 1437, 1421 cm^{-1}; MS (70 eV, EI, 120 °C): *m/z* (%): 367 (11) [$C_{18}H_{25}NO_3SeCl^+ + H$], 366 (1) [$M^+$], 365 (5), 364 (2), 322 (2), 260 (29), 210 (100), 182 (9), 138 (6), 136 (30), 110 (8), 108 (12), 105 (23); $C_{17}H_{21}NO_3Se$ (366.31): calcd C 55.74, H 5.78, N 3.82; found C 55.79, H 5.68, N 3.71.

(6*S*,7*S*,8*R*,8a*S*)-6-Chloro-7-ethoxycarbonyl-8-phenylselenyl-5(8*H*)-indolizidinone (22): Under Ar, the lactam **14i** (300 mg, 0.89 mmol) was dissolved in dry MeCN (15 mL). PhSeCl (3 g, 15.7 mmol) was added and the mixture was stirred at r.t. for 16 h. Then the solvent was removed and the crude material was purified by chromatography on silica gel, eluent: EtOAc/hexanes 1:1, $R_f = 0.17$. Yield: 251 mg (0.63 mmol, 70%) indolizidinone **22** as a white solid material, m.p.: 134–136 °C. $[\alpha]_D^{20} = -102.5$ ($c = 2.8$, in $CHCl_3$); ^{1}H NMR (270.1 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 7.6$ (m, 2H; CH), 7.3 (m, 3H; CH), 4.3 (m, 2H; OCH_2), 4.1 (m, 1H; CH_2), 3.8 (dd, ^3J(H,H) = 6 Hz, ^3J(H,H) = 12 Hz, 1H; CHSe), 3.0 (m, 1H; CHN), 2.7 (m, 2H; CH_2), 2.6 (m, 1H; CH), 2.55 (m, 1H; NCH_2), 1.7 (m, 1H; CH_2), 1.6 (m, 1H; CH_2), 1.5 (m, 2H; CH_2), 1.3 (m, 3H; CH_3); ^{13}C NMR (67.9 MHz, $CDCl_3$, 25 °C): $\delta = 173.4$ (C=O), 170.3 (C=O), 136.4, 129.1, 128.5 (CH), 63.4 (CH), 61.5 (OCH_2), 46.2 (CH), 43.2 (CH), 39.6 (NCH_2), 34.5 (CH_2), 32.8 (CH_2), 25.8 (CH_2), 14.0 (CH_3); IR (KBr): $\tilde{\nu} = 1726$, 1647, 1438 cm^{-1}; MS (70 eV, EI, 150°): *m/z* (%): 401 (20) [M^+], 246 (33), 244 (100), 172 (20), 170 (50), 157 (14), 145 (15), 136 (27), 70 (20); $C_{17}H_{20}NO_3SeCl$ (400.76): calcd C 50.95, H 5.03, N 3.50; found C 51.06, H 5.12, N 3.41.

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[1] R. Öhrlein, R. Jeschke, B. Ernst, D. Bellus, *Tetrahedron Lett.* **1989**, *30*, 3517.
[2] a) R. Malherbe, D. Bellus, *Helv. Chim. Acta* **1978**, *61*, 3096; b) R. Malherbe, G. Rist, D. Bellus, *J. Org. Chem.* **1983**, *48*, 860.
[3] a) M. M. Cid, U. Eggnauer, H. P. Weber, E. Pombo-Villar, *Tetrahedron Lett.* **1991**, *32*, 7233; b) M. M. Cid, E. Pombo-Villar, *Helv. Chim. Acta* **1993**, *76*, 1591; c) E. D. Edstrom, *J. Am. Chem. Soc.* **1991**, *113*, 6690; d) M. Ishida, H. Muramaru, S. Kato, *Synthesis* **1989**, 562; e) S. M. Roberts, C. Smith, R. J. Thomas, *J. Chem. Soc. Perkin Trans. 1* **1990**, 1493.
[4] M. Diederich, U. Nubbemeyer, *Angew. Chem.* 1995, *107*, 1095; *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 1026.

  0947-6539/96/0207-0899 $ 15.00+.25/0

[5] H. A. Hagemann, *Org. React.* **1953**, *7*, 198.
[6] U. Nubbemeyer, *J. Org. Chem.* **1995**, *60*, 3773.
[7] L. F. Tietze, T. Eicher, *Reaktionen und Synthesen im organisch chemischen Praktikum*, 2nd ed., Thieme, Stuttgart, **1991**, p. 135.
[8] R. N. Icke, B. B. Wisegarver, G. A. Alles, *Org. Synth. Coll. Vol. 3* **1955**, 723. *N*-Methylproline methyl ester **2**: R. L. Elliott, H. Kopeka, N.-H. Lin, Y. He, D. S. Garvey, *Synthesis* **1995**, 772.
[9] L. F. Tietze, T. Eicher, *Reaktionen und Synthesen im organisch chemischen Praktikum*, 2nd ed., Thieme, Stuttgart, **1991**, p. 85. *N*-Benzylproline methyl ester **3**: E. J. Corey, J. O. Link, *J. Org. Chem.* **1991**, *56*, 442.
[10] a) J. M. Takacs, M. A. Helle, F. L. Seely, *Tetrahedron Lett.* **1986**, *27*, 1257; b) A. Krief, W. Dumant, P. Pasau, *ibid.* **1988**, *29*, 1079.
[11] a) E. Winterfeldt, *Synthesis* **1975**, 617; b) G. E. Keck, M. B. Andrus, D. R. Romer, *J. Org. Chem.* **1991**, *56*, 417.
[12] T. Moriwake, S.-I. Hamano, S. Saito, S. Torii, *Chem. Lett.* **1987**, 2085.
[13] J. Seyden-Penne, *Reductions by the Alumino- and Borohydrates in Organic Synthesis*, VCH, Weinheim, Paris, **1991**, p. 95.
[14] R. A. Houghten, A. Beckman, J. M. Ostresh, *Int. J. Pept. Protein Res.* **1986**, *27*, 653.
[15] The reaction was not complete after 3 weeks; about 50% of aminoester 4 was recycled. Only small amounts of allylchlorides **10** and **11** were formed. The second diastereoisomer could not be obtained in pure form (mixture with the von Braun type products).
[16] Similar results were achieved by replacing the terminal benzyloxy group by a hydrogen. Chloroacetyl chloride only generated the corresponding azoninone in poor yields (about 10%) and a disappointing diastereoselectivity (*anti*:*syn* = 1.2:1). Most of the allylamine employed generated the von Braun type products **10** and **11**.
[17] a) S. D. Kahn, W. J. Hehre, *J. Org. Chem.* **1988**, *53*, 301; b) J. J. Gajewski, K. R. Gee, J. Jurayj, *J. Org. Chem.* **1990**, *55*, 1813; c) D. P. Curran, Y.-G. Suh, *J. Am. Chem. Soc.* **1984**, *106*, 5002; d) D. P. Curran, Y.-G. Suh, *Carbohydr. Res.* **1987**, *171*, 161.
[18] a) W. S. Johnson, V. J. Bauer, J. L. Margrave, M. A. Frisch, L. H. Dreger, W. N. Hubbard, *J. Am. Chem. Soc.* **1961**, *83*, 606; b) P. Vittorelli, H.-J. Hansen, H. Schmid, *Helv. Chim. Acta* **1975**, *58*, 1293; c) R. L. Vance, N. G. Rondan, K. N. Houk, F. Jensen, W. T. Borden, A. Komornicki, E. Wimmer, *J. Am. Chem. Soc.* **1988**, *110*, 2314.
[19] D. A. Evans, J. M. Takacs, *Tetrahedron Lett.* **1980**, *21*, 4233.
[20] M. Larcheveque, E. Ignatova, T. Cuvigny, *Tetrahedron Lett.* **1978**, 3961.
[21] P. E. Sonnet, J. R. Heath, *J. Org. Chem.* **1980**, *45*, 3139.
[22] a) H. Frauenrath in *Methoden Org. Chem. (Houben–Weyl)*, Vol. E21d: *Stereoselective Synthesis*, Thieme, Stuttgart, New York, **1995**, 3301. b) P. Wipf, in *Comprehensive Organic Synthesis*; Pergamon Press, New York, **1991**, *5*, 827.
[23] D. Felix, K. Gschwend-Steen, A. E. Wick, A. Eschenmoser, *Helv. Chim. Acta* **1969**, *52*, 741.

0947-6539/96/0207-0900 $ 15.00+.25/0 Chem. Eur. J. 1996, 2, No. 7